Catalytic Asymmetric Synthesis of Chiral Halogenated Compounds and Their Stereospecific Transformation

（キラルハロゲン化合物の触媒的不斉合成法および立体特異的変換反応の開発）

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Doctor of Philosophy (Engineering)

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Abstract（Doctor）

Title of Thesis	Catalytic Asymmetric Synthesis of Chiral Halogenated Compounds and Their Stereospecific Transformation （キラルハロゲン化合物の触媒的不斉合成法および立体特異的変換反応の開発）

Approx. 800 words

Stereoselective synthesis of halogenated small organic molecules is highly important in synthetic organic chemistry because resulting chiral organohalides can be easily converted into various chiral molecules by S_N2 reaction. Furthermore, recently, not only fluorinated compounds but also chiral chlorinated and brominated compounds are expected as potent drugs because biologically active natural compounds often contain chlorine or bromine atoms on stereogenic carbon centers. Despite the extraordinary interest in practical synthetic methodologies towards chiral halogenated compounds, the methodology for the construction of chiral halogenated stereogenic carbon center have not established well. Introduction of halogen atoms onto tertiary carbon center have been mostly limited to halogenation of active methylene compounds such as β-keto esters. In this research, highly enatioselective synthesis of tertiary halides was carried out. Furthermore, synthetic utility of resulting tertiary halides was explored by subsequent stereospecific derivatizations.

First, enantioselective synthesis of tertiary fluoride was achieved by fluorination of α-branched aldehydes with a newly developed chiral primary amine catalyst. Enantioselective fluorination of aldehydes with chiral secondary amine catalyst is a highly useful method to introduce a fluorine atom on a stereogenic carbon center. Although this method yields α-fluoroaldehydes with high enantioselectivity when α-alkylaldehydes were employed as substrates, fluorination of α,α-dialkylaldehydes (α-branched aldehydes) with secondary or primary amine catalysts exabits unsatisfactory results. According to these situations, a new chiral primary amine catalyst was developed and used for enantioselective fluorination of α-branched aldehydes. As a result, various tertiary fluorides were synthesized in good yield with high enantioselectivity (up to 95% ee). Resulting tertiary fluorides were converted into chiral 3-fluoropropenes and fluorinated analogue of bioactive compounds such as Flurbiprofen. Furthermore, α-fluoroaldehydes were converted into α-hydrxyacetal *via* Carbon-Fluorine bond cleavage on a stereospecitic manner [up to >99% es, es = enantiospecificity which is calculated by (ee of product)/(ee of substrate)]. After the confirmation of stereochemistry, it was confirmed that this reaction proceeded *via* S_N2 type reaction.

Second, enantioselective synthesis of tertiary chloride was achieved by decarboxylative chlorination of β-keto carboxylic acids in the presence of chiral primary amine catalyst and electrophilic chlorinating reagent. Although there is no asymmetric halogenation has been achieved, several enantioselective decarboxylative Carbon-Carbon bond formation reactions of β-oxo carboxylic acids have reported till date. According to these successful examples, β-oxo carboxylic acids can work as an enolate equivalent by decarboxylation of carboxylic acid moiety. Herein, enantioselective halogenation was developed by using β-keto carboxylic acids with chiral amine catalyst and electrophilic chlorinating reagent. This reaction afforded various secondary and tertiary α-chloroketones with high enantioselectivity (up to 98% ee). Furthermore, resulting tertiary chloroketone was subjected to S_N2 reactions and this reaction afforded corresponding α-surfenyl or α-azide ketones without loss of enantiopurity (up to >99% es). The absolute configuration of the substrate and the product were determined by X-ray crystallography and it was confirmed that inversion of stereochemistry surely occurred. Decarboxylative chlorination was also applicable to asymmetric synthesis of α-chloro-α-fluoroketones by asymmetric decarboxylative chlorination of α-fluoro-β-keto carboxylic acids in the presence of chiral amine catalyst. This reaction afforded some products with high enantioselectivity (up to 90% ee). However, moderate to low enantioselectivity was observed with indanone-derived and acyclic substrates. Then, resulting α-chloro-α-fluoroketone was subjected to S_N2 reaction and it yielded the corresponding chiral α-functionalized-α-fluoroketones with almost retained enantiopurity (up to >99% es).

Finally, asymmetric synthesis of chiral fluoroalkenes was achieved by S_N2’ reaction of chiral 3-chloro-3-fluropropenes. Fluoroalkene is an important substructure especially in medicinally-relevant chemistry because fluoroalkenes sometime act as peptide bioisosters. Therefore, development of efficient methods for the preparation of fluoroalkenes have attracted attention in recent years. Paquin’s research group recently reported an efficient synthetic method of chiral fluoroalkenes by S_N2’ reaction of 3,3-difluoropropene. On the other hand, our research group previously reported enantioselective synthesis of α-chloro-α-fluoroaldehydes by organocatalytic enantioselective fluorination of α-chloroaldehydes. Inspired by these works, novel synthetic route for chiral fluoroalkenes was designed by using S_N2’ reaction of 3-chloro-3-fluoropropens which are prepared by Horner-Wadsworth-Emmons reaction of chiral α-chloro-α-fluoroaldehydes. After screening of reaction conditions, it was revealed that S_N2’ reaction afforded the desired chiral fluroalkene in good yield with almost retained enantiopurity (up to >99% es).

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Table of contents

Chapter 1: Introduction

Chapter 3: Enantioselective fluorination of α-branched aldehydes and subsequent conversion into α-hydroxyacetals

Chapter 4: Enantioselective decarboxylative chlorination of β-keto carboxylic acids

Chapter 5: Enantioselective synthesis of chiral fluoroalkene by S_N2’ reaction

Chapter 1: Introduction

1.1 Importance of asymmetric synthesis of chiral compounds

Enantiolselective synthesis of chiral organic molecules is significantly important in pharmaceutical science because human body can recognize the difference between enantiomers. In many cases, chiral small organic molecules serve as useful treatment for various disease. However, because of the specific recognition of chiral small organic molecules, some a pair of enantiomers exhibit different biological activity each other. For example, although a enantiomer shows highly useful biological activity, another enantiomer cause side effects or it has less useful biological activity. Selected examples of useful and toxic/less useful pairs of enantiomers were shown in Figure 1. Recently, the number of chiral organic molecules which is used for pharmaceuticals have been increasing[1]. Thus, development of efficient enantioselective synthetic method for chiral organic molecules is highly desired in pharmaceutical science.

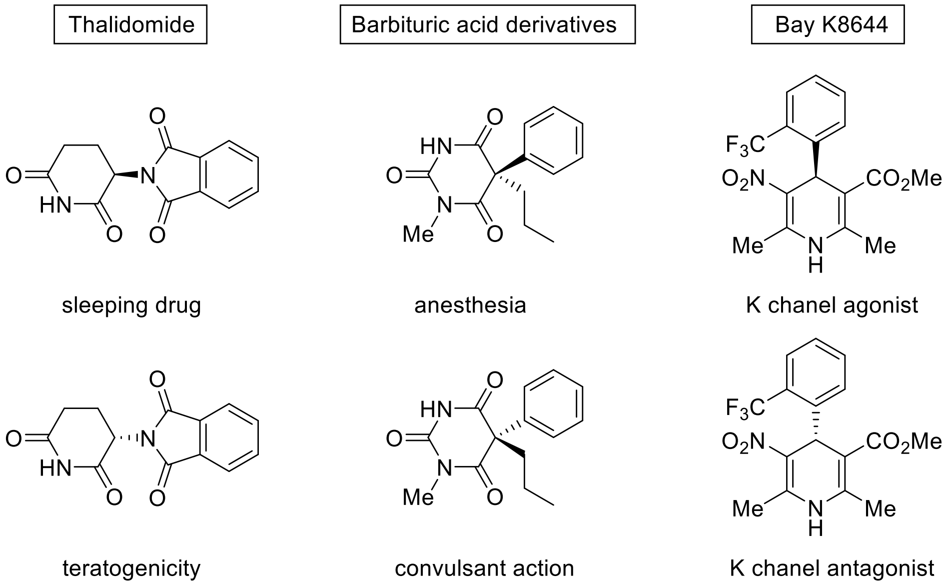


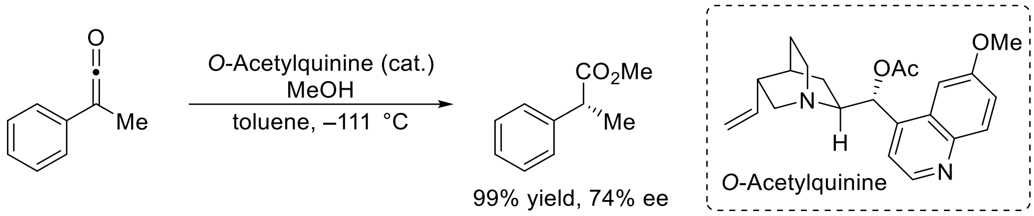
Figure 1. Examples of phamaceuticals which have different bioactivity between enantiomers.

Several synthetic strategies for the enantioselective synthesis of chiral compounds have been developed till date. From a long time ago, isolation of pure enantiomers have been carried out by using “optical resolution” or “chiral column”. However, in these processes, unnecessary another enantiomer is disposed, and it causes increase in the production cost. Furthermore, optical resolution requires relatively expensive stoichiometric amount of chiral sources and chiral column can not process large amount of samples.

Nowadays, catalytic asymmetric synthesis of chiral compounds have been attracting interest interest because they require only catalytic amount of chiral sources (eg. 0.01 mol% ~30 mol%). Furthermore, the chiral source is reusable after recovering from the reaction mixture and it can greatly decrease production cost of chrial compounds. However, to achieve high enantioselectivity, development of tailored chiral catalyst is required depend on target reactions.

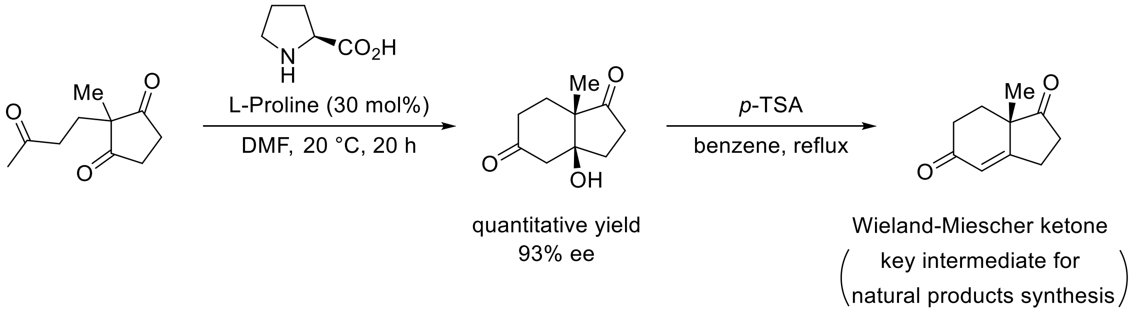
Compared to chiral transition metal catalysts, organocatalyst have been less studied although practical asymmetric organocatalytic reaction have already been reported in late 1950s. Organocatalyst have some features such as less toxicity compared to transition metal catalyst because organocatalyst is mostly consisted of carbon, nitrogen, oxygen and hydrogen atoms. This is highly advantageous in pharmaceutical science because contamination of pharmaceuticals with transition metals may cause significant side-effect even order of ppm. Furthermore, some chiral organocatalysts such as amino acid and cinchona alkaloids are relatively easily available with more affordable price compared to transition metals.

In 1960, Pracejus reported enantioselective synthesis of phenyl methylpropionate in the presence of *O*-acetylquinoline as a catalyst in 99% yield with 74% of enantioselectivity[2] (Scheme 1). This reaction was the first practical enantioselective organocatalytic reaction.



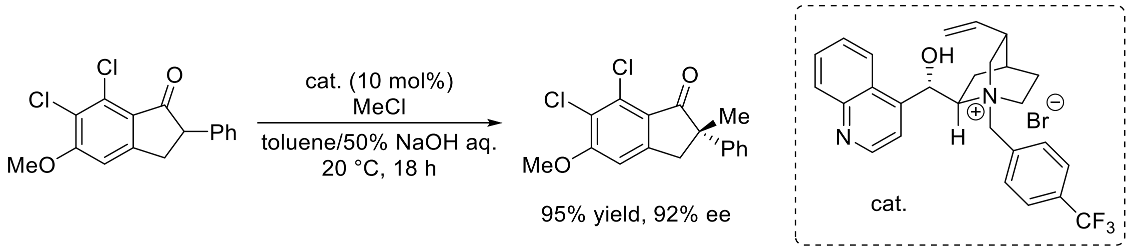
Scheme 1. Enantioselective organocatalytic reaction reported by Pracejus.

Then, Robinson found annulation reaction between carbonyl compounds and α,β-unsaturated ketones (Robinson annulation). Later, enantioselective version was achieved by using L-Proline as a catalyst (Hajos-Parrish-Eder-Sauer-Wiechert Reaction) as shown in Scheme 2. This reaction yielded corresponding cyclic product with high enantioselectivity (93% ee) and subsequent treatment by acid enabled readily access to Wieland-Miescher ketone which is known as a key intermediate for the synthesis of natural products[3].



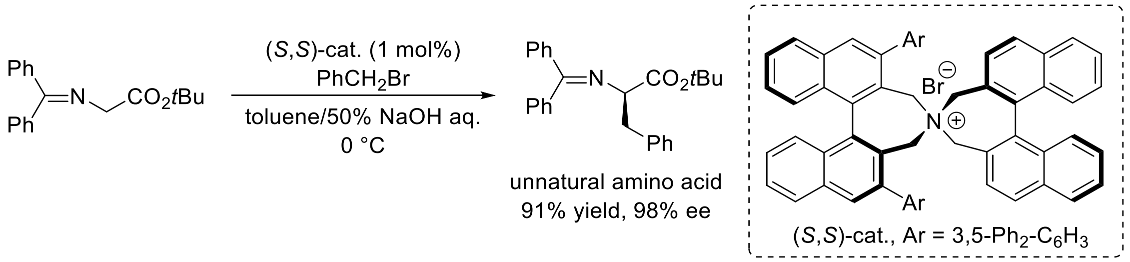
Scheme 2. Hajos-Parrish-Eder-Sauer-Wiechert Reaction and subsequent transformation into Wieland-Miescher ketone.

Afterwards, Dolling developed new cinchona alkaloid-derived chiral ammonium phase transfer catalyst and it was employed for enantioselective alkylation of a indanone derivative (Scheme 3). As a result, alkylated product was obtained in 95% yield with 92% of enantioselectivity[4].



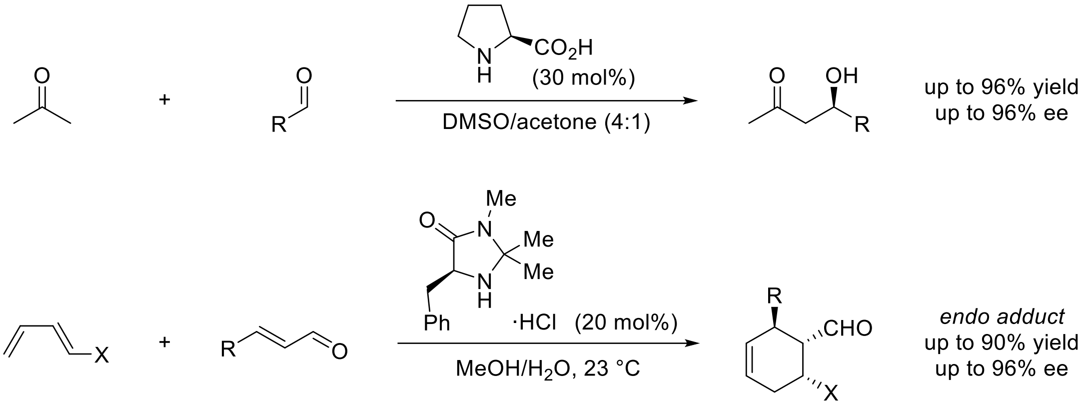
Scheme 3. Enantioselective alkylation with a chiral ammonium phase transfer catalyst.

Although cinchona alkaloid-derived chiral ammonium phase transfer catalyst demonstrated high enantioselectivity in alkylation reaction, the preparation of the catalyst has limitations. Because Hoffman elimination of ammonium catalyst easily occurs under basic condition. On the other hand, Maruoka and co-workers designed and synthesized novel chiral ammonium phase transfer catalysts which has two binaphtyl backbones. Maruoka's catalyst afforded the desired products with high enantioselectivity and yield (Scheme 4)[5].



Scheme 4. Enantioselective alkylation with Maruoka's chiral ammonium phase transfer catalyst.

On the other hand, the research group of List and Barbas III discovered chiral secondary amine catalyzed aldol reaction (Scheme 5). Furthremore, MacMillan also reported enantioselective Diels-Alder reaction by using imidanolidinone-derived chiral secondary amine catalyst[6].



Scheme 5. Enantioselective transformations with chiral secondary amine catalysts.

Nowadays, various organocalysts such as prolinol-derived catalysts, chiral ammonium catalysts, chiral phospholic acid catalysts have been developed to achieve high enantioselectivity in a lot of transformations. Especially, the chemistry of enamine catalysis have made remarkable progress and it enabled serious of α-functionalization of carbonyl compounds, which is characteristic transformation of organocatalyst because it is impossible by using chiral transition metal catalysts[7]. The selected examples of chiral organocatalysts were described in Figure 2.

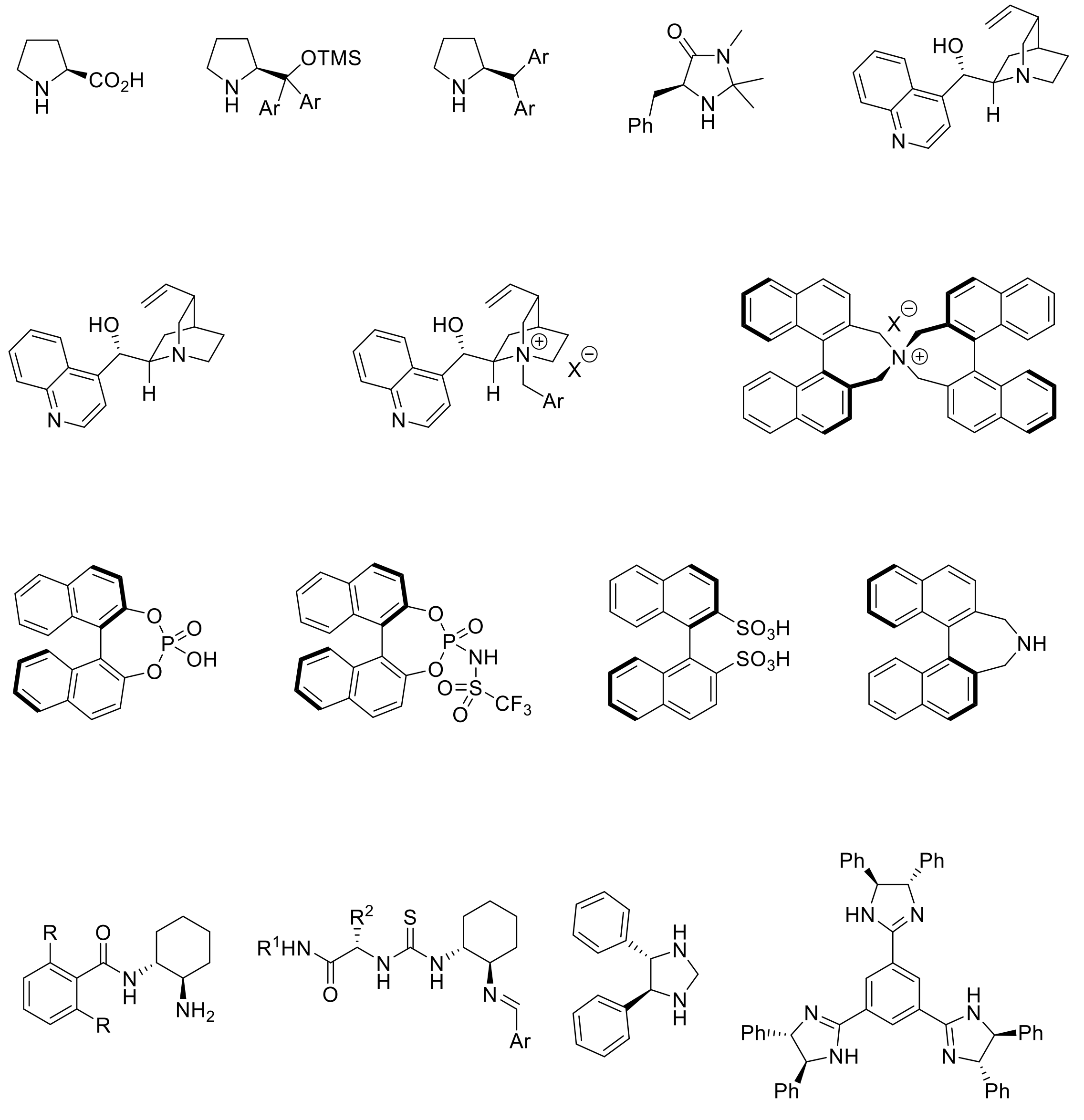
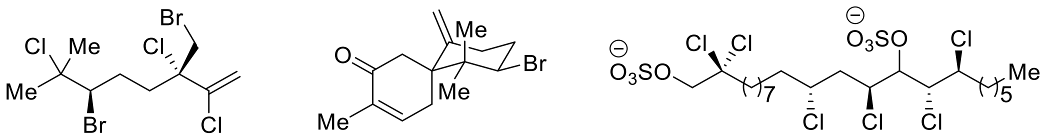


Figure 2. Selected examples of chiral organocatalysts.

1.2 Utility and importance of halogenated compounds

Halogen atoms such as bromine, chlorine and fluorine atoms are often found in biologically active compounds. For example, many bioactive natural compounds contain bromine and chlorine atoms in its structure[8]. Among then, some bromine and chlorine atoms locate on one or several chiral carbon centers (Figure 3). This is why, development of easy and convenient method for stereoselective construction of one or several halogenated chiral carbon centers has been required for the development of effective natural product-based artificial pharmaceuticals.

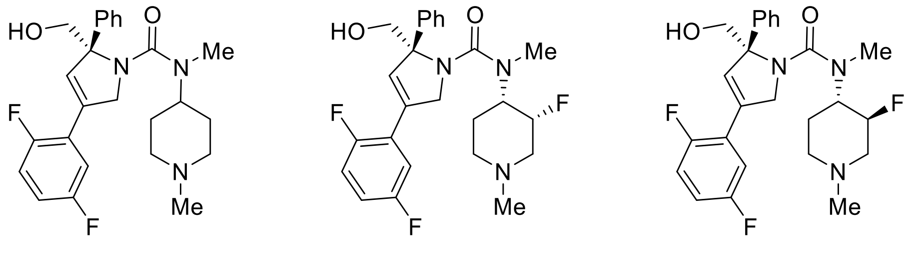


(+)-Halomon (–)-Dactylone (–)-Danicalipin A

Figure 3. Examples of chiral chlorinated or brominated natural products.

Although currently very few fluorinated natural products were discovered, large numbers of artificial fluorinated pharmaceuticals have been developed till date. This is considered as due to the characteristic features of fluorine atom such as small atom radius with high electron negativity. Furthermore, Carbon-Fluorine bond is known as more covalent than Carbon-Hydrogen bond. Thus, replacement of hydrogen atom into fluorine atom sometime enables improvement of metabolic stability of pharmaceuticals. Due to these characteristic features, fluorinated compounds sometime demonstrate better pharmacological effect compared to non-fluorinated compounds.

An example of improvement of biological activity in kinesin spindle protein (KSP) inhibitor was shown in Figure 4[9]. KSP inhibitor targeting the KSP with potential antineoplastic activity. When the lead compounds (pKa = 8.8) was introduced a fluorine atom on its structure, the pKa was slightly decreased to be 7.6 (MK-0731). In addition, pKa of fluorinated diastereomer of MK-0731 was further decreased to 6.6. As a result, MK-0731 was found to be potent agent as KSP inhibitor.



Lead compound
pKa = 8.8

MK-0731
pKa = 7.6

pKa = 6.6

Figure 4. Improvement of biological activity by introduding fluorine atom.

Nowadays, a report says fluorine containing pharmaceuticals accounts for 16% of newly developed pharmaceuticals on the market during 1991 to 2017 (143 items out of 878 items)[10]. Some examples of fluorinated pharmaceuticals were described in Figure 5.

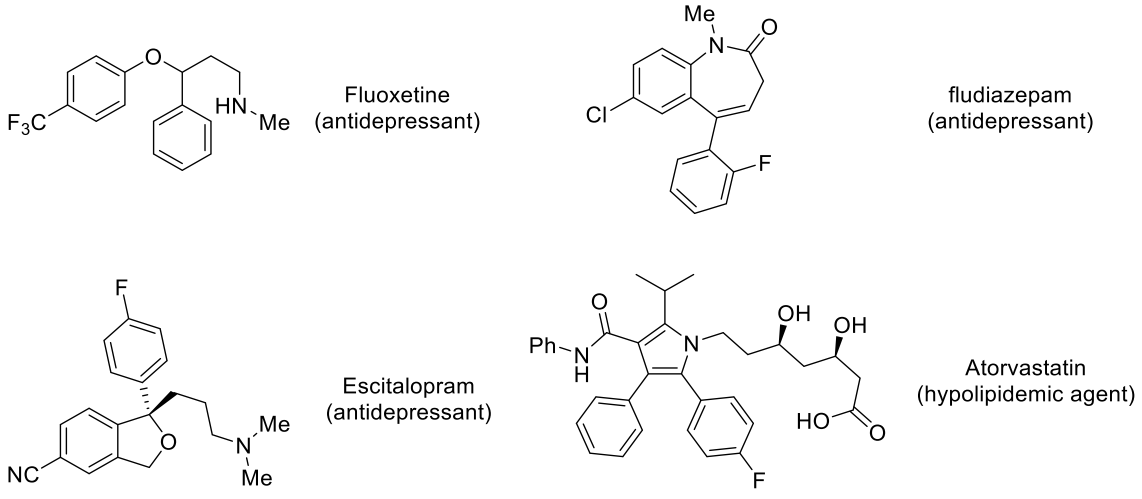


Figure 5. Examples of fluorine-containing pharmaceuticals.

However, mostly fluorine atom locates on sp^2 or achiral sp^3 carbon as shown Figure 5, and there are very few chiral fluorinated pharmaceuticals that has fluorine atom on chiral carbon centers have been reported (Figure 6). This is probably because synthetic methods for chiral fluorinated molecules have not been established well.

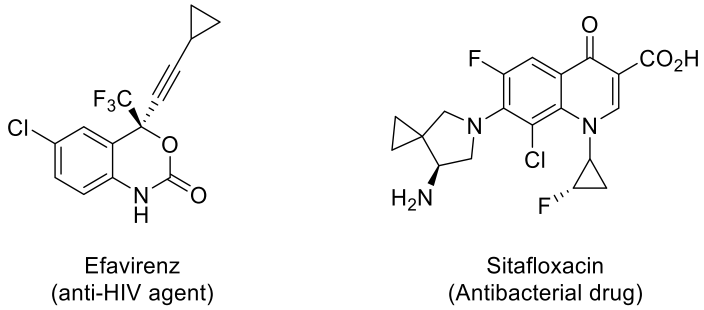
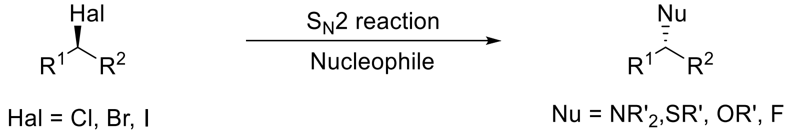


Figure 6. Examples of chiral fluorinated bioactive compounds.

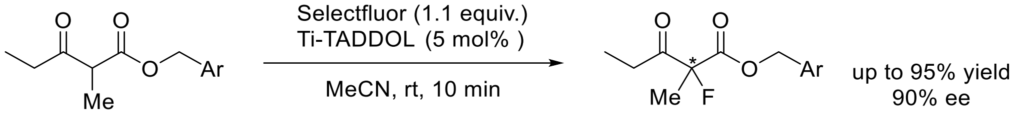
Furthermore, because of the good leaving ability of iodine, bromine and chlorine atoms, halogenated compounds are frequently utilized as useful synthetic intermediates by using cross-coupling or substitution reactions. Especially when halogen atoms locate on the chiral carbon center, it can be easily converted into various chiral molecules by S_N2 reactions (Scheme 6).



Scheme 6. Derivatization of chiral halogenated molecules by S_N2 reactions.

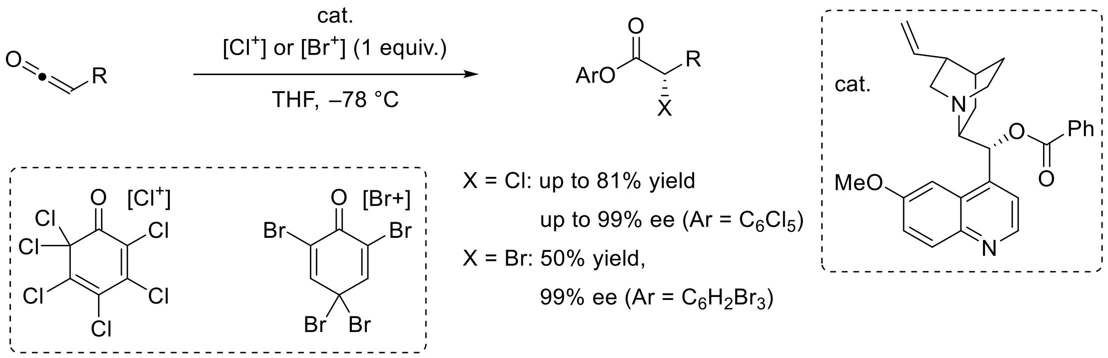
1.3 Synthetic protocols for chiral halogenated compounds

Enantioselective catalytic α-halogenation of carbonyl compounds is a useful protocol to introduce one halogen atom on a stereogenic carbon center. Togni reported highly enantioselective fluorination of β-keto esters by using Ti-TADDOLate as a catalyst (Scheme 7). When this method was applied to chlorination and bromination, the desired product was obtained with low to moderate enantiolsectivity[11]. Later, enantioselectivie halogenation of β-keto esters have been established well by using Lewis acid catalyst[12] and organocatalysts[13].



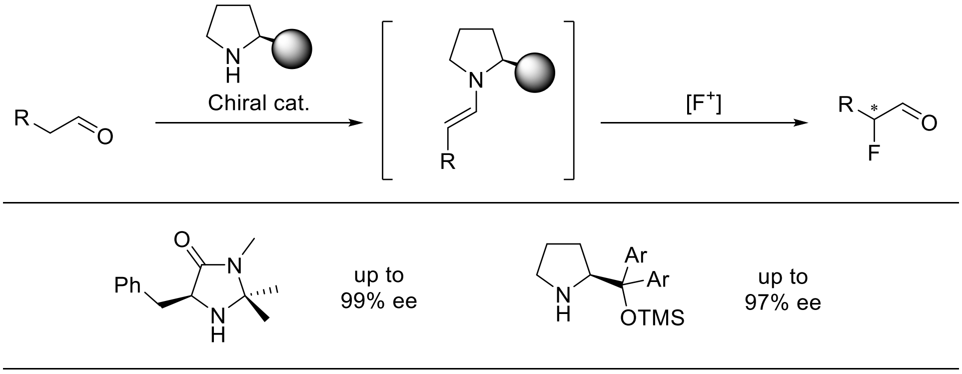
Scheme 7. Asymmetric fluorination of 1,3-dicarbonyl compounds.

In 2001, Lectka reported sequential transformation that provides α-chloro and α-bromoesters with high enantioselectivity (up to 99% ee in both reactions) by halogenation of ketenes in the presenece of catalytic amount of cinchona alkaloid derivative and electrophilic halogenating reagents (Scheme 8)[14].



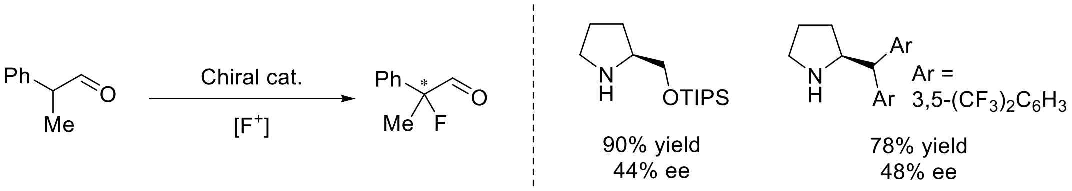
Scheme 8. Enantioselective synthesis of α-haloesters.

Then, MacMillan and Jørgensen independently reported enantioselective chlorinanation of α-alkylaldehydes with chiral secondary amine catalysts[15]. After a while, they applied their methodology into enantioselective fluorination of α-alkylaldehydes with chiral prolinol- or imidazolidinone-derived secondary amine catalysts[16] (Scheme 9). In each cases, these catalysts showed high enantioseletivity (up to 99% ee).



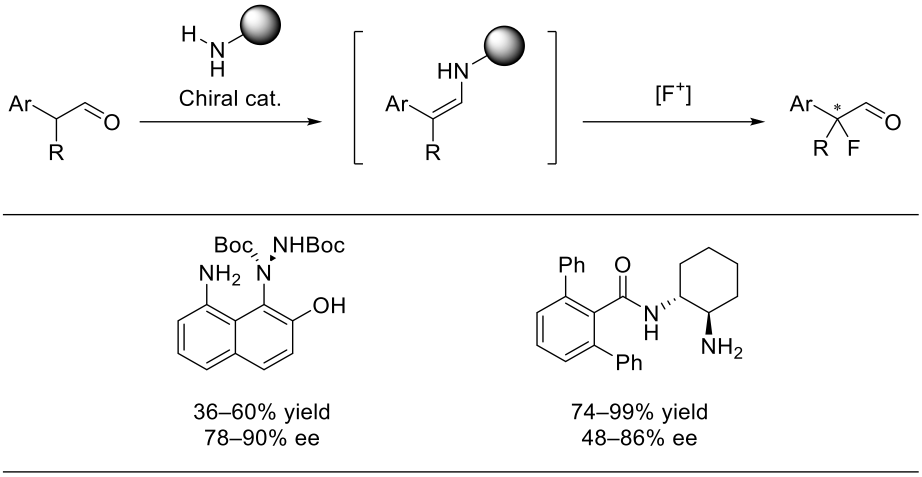
Scheme 9. Enantioselective fluorination of α-alkylaldehydes by using chiral secondary amine catalysts.

On the other hand, few enantioselective halogenation of α,α-dialkylaldehydes have been reported probably because of the difficulty in the design of chiral catalyst to achieve high asymmetric induction and high reactivity. BarBas III and Jørgensen employed several chiral secondary amine catalysts that showed high enantioselectivity in halogenation of α-alkylaldehydes. However, these catalysts showed moderate enantioselectivity in the fluorination of α,α-dialkylaldehyde[16a,c] (Scheme 10).



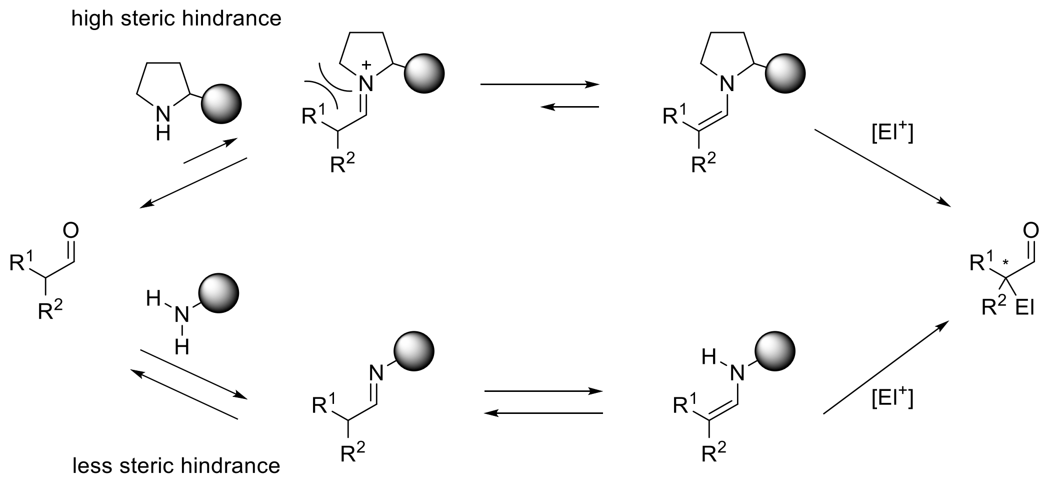
Scheme 10. Fluorination of α,α-dialkylaldehydes by using chiral secondary amine catalysts.

Afterwards, Jørgensen and Jacobsen reported enantioselective fluorination of α,α-dialkylaldehyde with chiral primary amine catalysts[17] (Scheme 11). In these reports, although Jørgensen's catalyst achieved high enantioselectivity (78–90% ee), the desired fluoroaldehyde was afforded in moderate yield (36–60% yield). On the other hand, Jacobsen's catalyst demonstrated higher reactivity than Jørgensen's catalyst (74–99% yield). However, the enantioselectivity of fluoroaldehydes was remained to be high to moderate (48–86% ee). These results might be caused by difficulty in controlling asymmetric induction of chiral primary amine catalysts because reaction center is distant from chiral substituent compared to secondary amine catalysts.



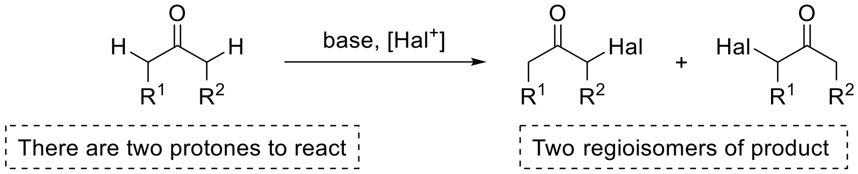
Scheme 11. Enantioselective fluorination of α,α-dialkylaldehydes by chiral primary amine catalysts.

Given these results, our research group started to design and synthesize a new chiral amine catalyst. Generaly speaking, formation of iminium cation intermediate with α,α-dialkylaldehyde is relatively slow with secondary amine catalyst[18] (Scheme 12 above). On the other hand, primary amine catalyst smoothly generate imine intermediate (Scheme 12 below). Thus, sometime primary amine catalyst is favored in functionalization of α,α-dialkylaldehyde.



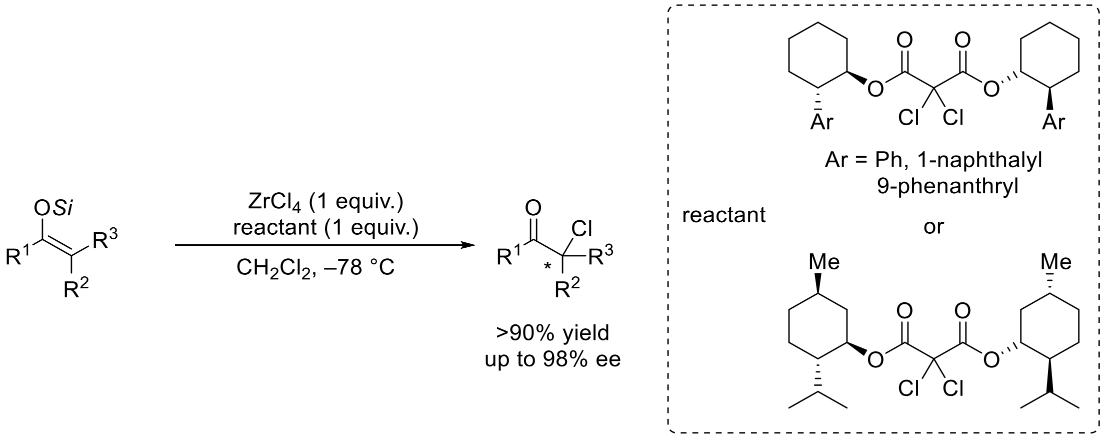
Scheme 12. Difference in the reactivity between primary and secondary amine catalysts.

Furthermore, enantioselective halogenation of asymmetrical ketones is more challenging than other carbonyl compounds. In the case of asymmetrical ketones, it has two reaction centers and catalyst have to selectively react with one reaction center to yield the desired product (Scheme 13).



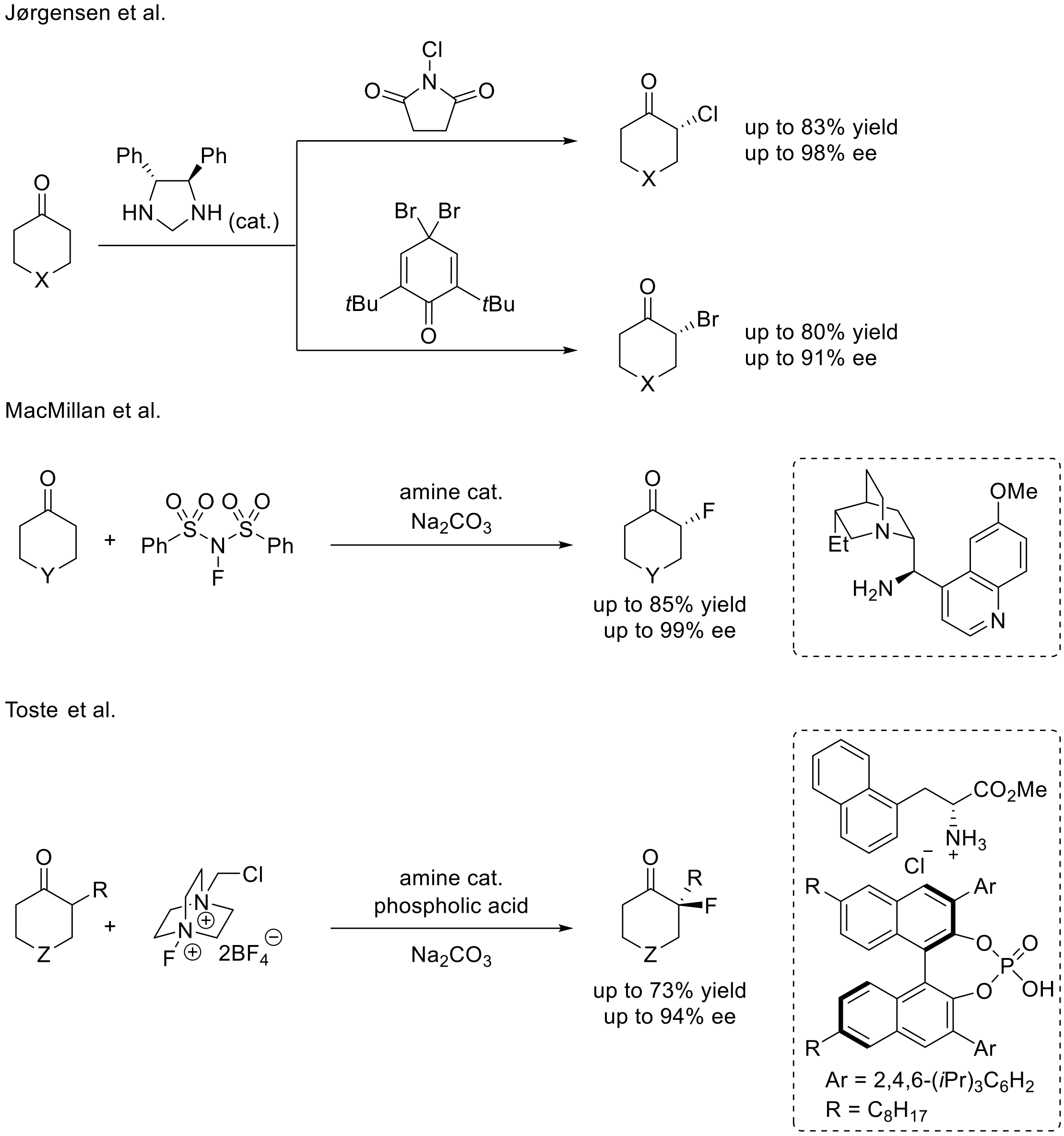
Scheme 13. Halogoneation of asymmetrical ketones.

In 2004, Yamamoto reported the enantioselective chlorination of silyl enolates in the presence of stoichiometric amount of chiral chlorinating reagent. This reaction afforded desired α-chloroketones with high enantioselectivity (Scheme 14)[19].



Scheme 14. Enantioselective chlorination of silyl enolates in the presence of stoichiometric amount of chlorinating reagent.

Catalytic enantioselective halogenations were achieved by Jørgensen, MacMillan and Toste. These reports afforded desired α-halogenated ketones with high enantioselectivity. However, this methodology was only applicable to cyclohexanone derivatives (Scheme 15)[16e,20].



Scheme 15. Enantioselective catalytic halogenation of ketones.

Chapter 2: Purpose of this research

The objectives of this research are highly enantioselective synthesis of chiral tertiary halides and development of subsequent stereospecific derivatization reactions. Stereospecific derivatization reaction uch as S_N2 reaction of resulting chiral tertiary halides will enable quick access to various chiral molecules. The specific target reactions were described bellow.

First, enantioselective fluorination of α-branched aldehydes will be carried out. As mentioned above, conventional method is mostly applicable to asymmetric synthesis of chiral secondary halides by using α-alkylaldehydes except for 1,3-dicarbonyl compounds. Since the relatively efficient examples have been reported with chiral primary amine catalysts, a new chiral primary amine catalyst will be designed and synthesized. The newly developed catalyst will be employed for enantioselective fluorination of α-branched aldehydes to achive high enantioselectivity with high reactivity. Furthermore, the resulting α-fluoroaldehydes will be subjected to stereospecific derivazation into chrial molecules *via* Carbon-Fluorine bond cleavage.

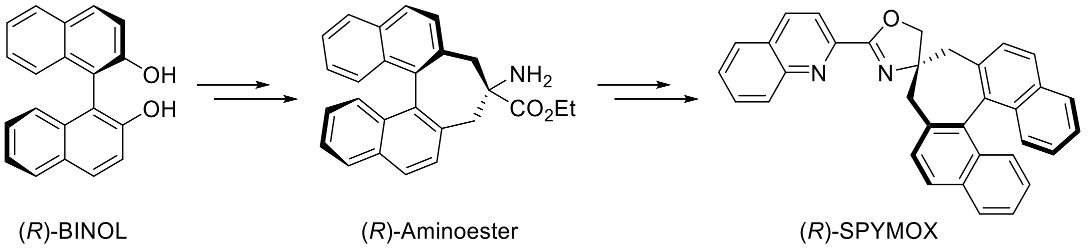
Second, enantioselective synthesis of tertiary α-chloroketones will be achieved by decarboxylative chlorination of β-oxo carboxylic acids. Enantioselective halogenation of ketone is known as more challenging reaction because asymmetrical ketone has two reaction centers. Thus, I focused on the reactivity of β-oxo carboxylic acid which easily react with organocatalyst to cause decarboxylation of carboxyl group. Decarboxylation of the β-oxo carboxylic acid in the presence of chiral amine catalyst and electrophilic halogenating reagent may cause enantioselective halogenation. Based on the design of reaction, decarboxylative chlorintion of β-oxo carboxylic acid will be carried out. Furthermore, resulting tertiary α-chloroketones will be converted into several chiral molecules by S_N2 reaction.

Finally, stereospecific derivatization of 3-chloro-3-fluoropropene which is derived from α-chloro-α-fluoroaldehyde will be carried out to afford chiral fluoroalkene. Enantiolselective synthesis of α-chloro-α-fluoroaldehyde has already been reported previously. Herein, the resulting chiral α-chloro-α-fluoroaldehyde will be transformed into corresponding 3-chloro-3-fluoropropene by olefinaition reaction and subsequent nuclephilic addition to 3-chloro-3-fluoropropene may furnish desired chiral fluoroalkene. In this transformation, the progress of S_N2’ reaction is expected but not S_N2 reaction because of steric hindrance of chiral dihalogenated carbon center.

Chapter 3: Enantioselective fluorination of α-branched aldehydes and subsequent conversion into α-hydroxyacetals[21]

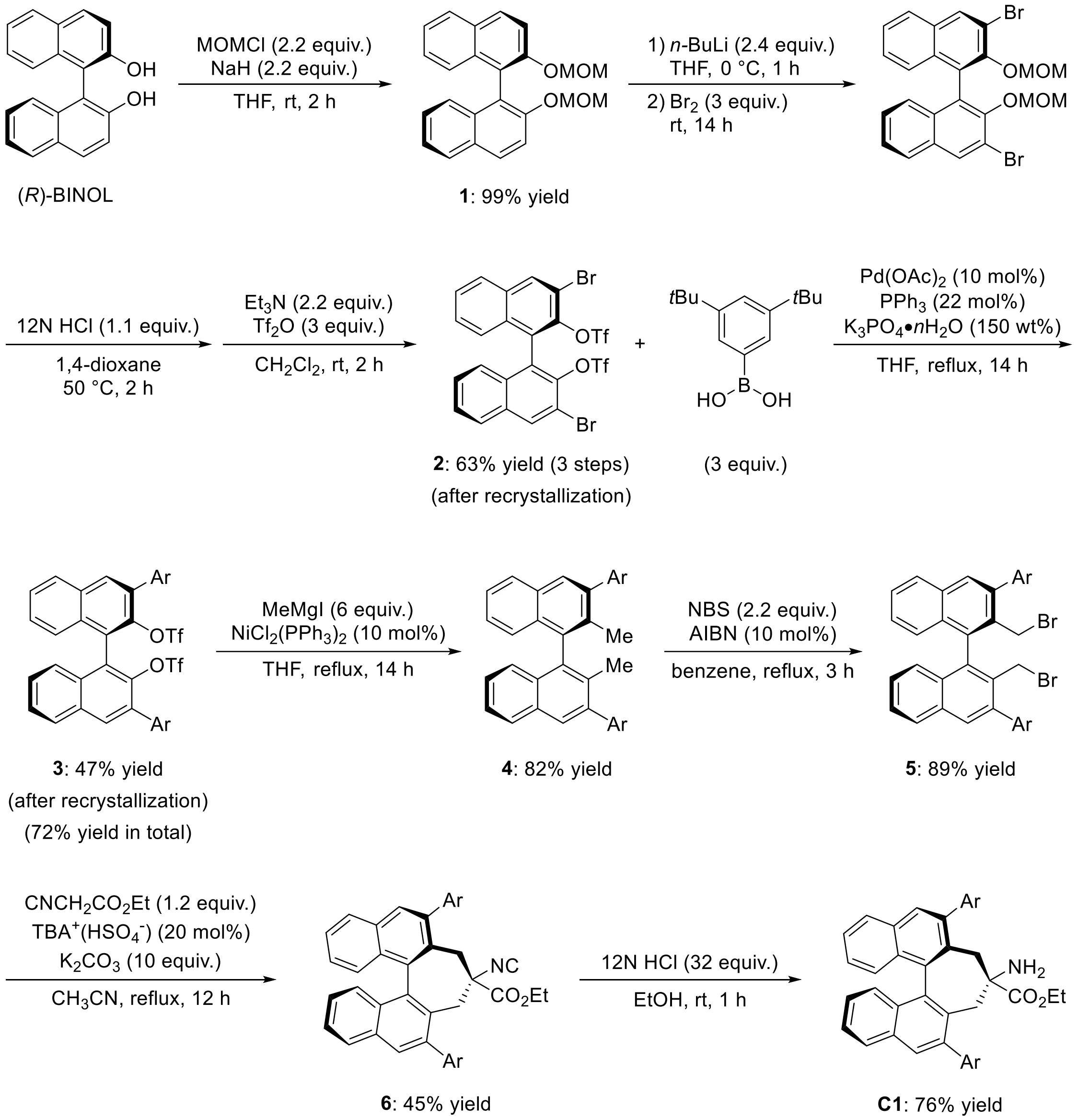
3.1 Design and synthesis of a new chiral primary amine catalyst

First, considering the low reactivity of chiral secondary amine catalysts in halogenation of α,α-dialkylaldehydes, a new chiral primary amine catalyst was designed. Shibatomi and co-workers recently developed a new chiral bisoxazoline ligand called SPYMOX. The combination of SPYMOX and transition metals demonstrated high enantioselectivity in the various transformations such as allylic alkylation and halogenations[22]. SPYMOX was prepared from (*R*)-BINOL *via* (*R*)-aminoester intermediate (Scheme 16). At this time, the (*R*)-aminoester intermediate was expected to work as a chiral amine catalyst because it has primary amine moiety.



Scheme 16. Synthetic route of (*R*)-SPYMOX.

Based on the design of a new chiral primary amine catalyst, the primary amine catalyst was synthesized by following the procedure shown in Scheme 17[23]. First, (*R*)-BINOL was protected by MOM group (**1**) and subsequent *o*-lithiation and bromination afforded corresponding 3,3'-brominated product. MOM group was deprotected in the presence of HCl and the OH group was again protected by triflyl group (**2**). Furthermore, the product was subjected to Suzuki-Miyaura coupling reaction. This reaction afforded relatively pure crude mixture of **3** along with small amount of by-products that require several times of silicagel column chromatography for complete removal. After purification by chromatography, the resulting **3** was completely purified by recrystallization from dichloromethane. Resulting pure **3** was used for Kumada coupling reaction under thoroughly reflux condition in fresh anhydrous TBME to promote complete consumption of **3**. Then, the resulting coupling product **4** was subjected to radical bromination (**5**), cyclization (**6**) and acidolysis to yield the desired chiral primary amine catalyst **C1**. Synthetic methods for other variants have already been reported by Okimi and Abe[24].

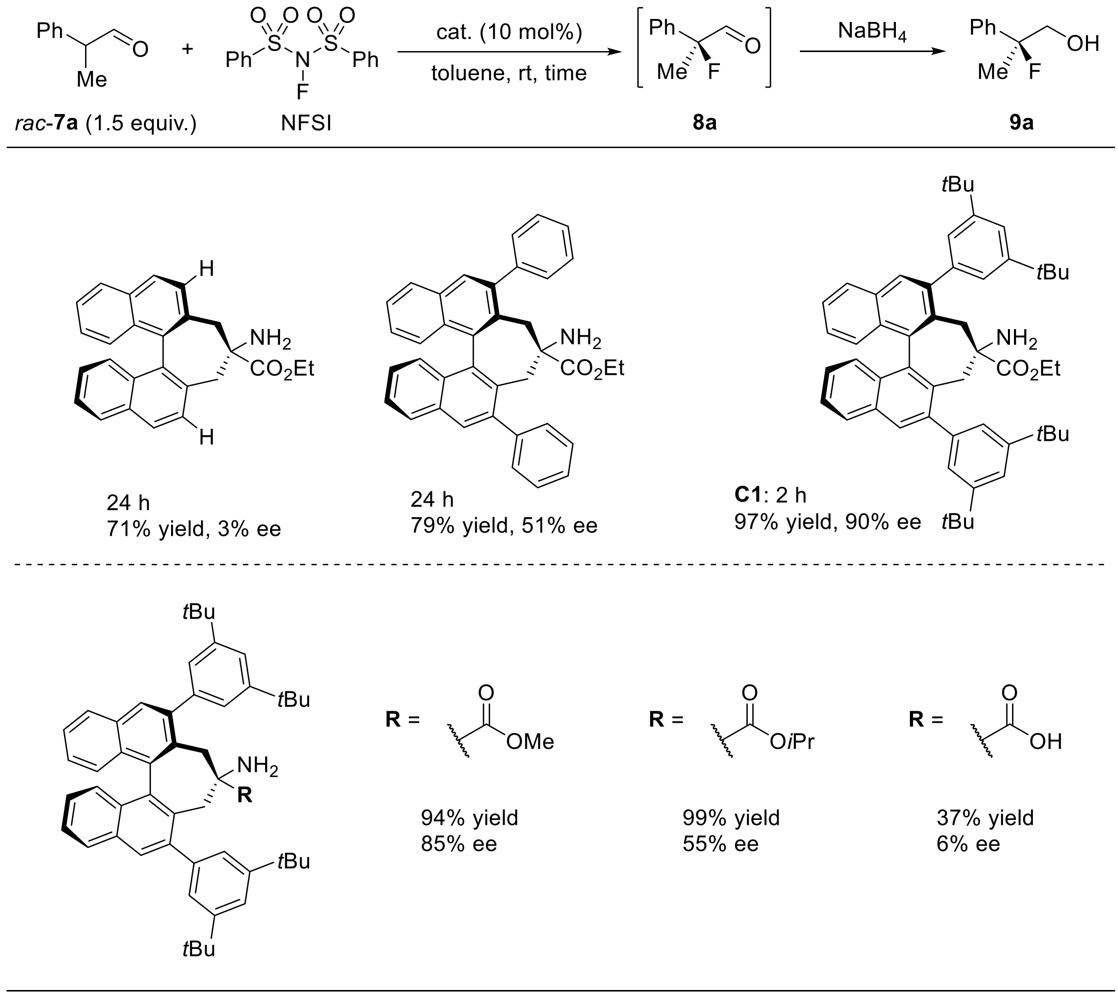


Scheme 17. Synthesis of a new chiral primary amine catalyst **C1**.

3.2 Enantioselective fluorination of α-branched aldehydes

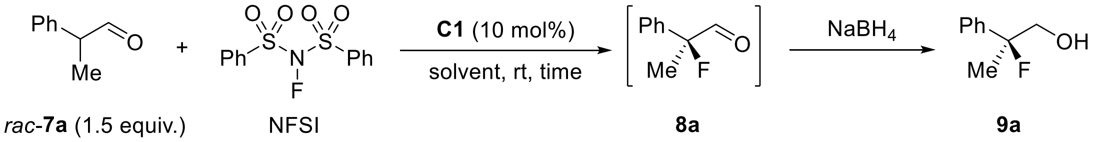
Then, the newly developed chiral primary amine catalysts (10 mol%) were employed for enantioselective fluorination of α-branched aldehyde **7a** by using *N*-fluorobenzenesulfonimide (NFSI) as a fluorine source in toluene (Table 1). Because resulting α-fluoroaldehyde **8a** was unstable to silicagel column chromatography, the yield and enantioselectivity was determined after conversion into fluoroalcohol **9a**. As a result, substituents at 3,3'-position of binaphthyl backbone dramatically improved the enantioselectivity and the best result was obtained with substitution of 3,5-(*t*Bu)C_6H_3 group (**C1**). Alternation of Et ester moiety of **C1** into Me and *i*Pr ester or carboxylic acid diminished enantioselectivity of **9a**. According to these results, **C1** was determined to be the best catalyst.

Table 1. Optimization of chiral primary amine catalyst.



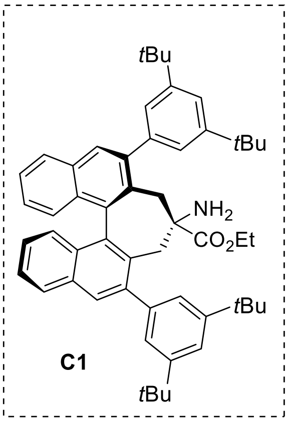
With the best chiral primary amine catalyst in hand, further reaction conditions were investigated (Table 2). First, reaction solvent was changed to CH_2Cl_2, EtOAc, TBME and MeOH (entry 1-5). As a result, except for MeOH which inhibit the formation of enamine intermediate, moderate to high enantiopurity was observed and highest enantioselectivity was obtained in toluene (entry 1). Then, lowered reaction temperature (entry 6) and addition of 10 mol% of 3,5-$(NO_2)_2C_6H_3CO_2H$ (entry 7) slightly improved the enantioselectivity. As a result, entry 7 was the best reaction condition.

Table 2. Optimization of reaction conditions with **C1**.



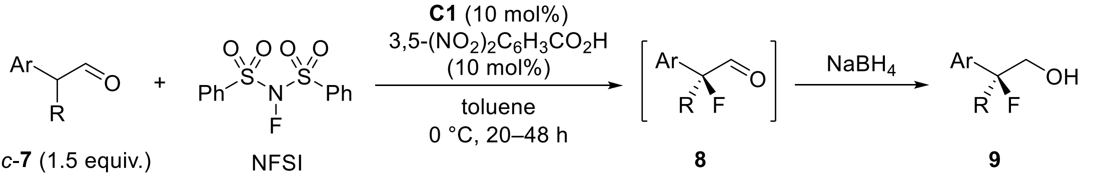
entry	solvent	time (h)	yield (%)	ee (%)
1	toluene	2	97	90
2	CH_2Cl_2	18	86	74
3	EtOAc	4	99	82
4	*t*BuOMe	3	97	86
5	MeOH	48	<10	n.d.
6	toluene	48 (0 °C)	73	93
7	toluene[a]	48 (0 °C)	86	95

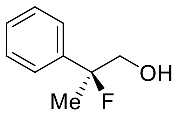
[a] 10 mol% of 3,5-$(NO_2)_2C_6H_3CO_2H$ was added.



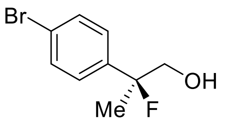
Under the optimized reaction condition, various α-aryl-α-alkyl aldehydes were subjected to enantioselective fluorination (Table 3). When substituent was introduced on the aromatic ring (**9a**–**9g**, **9q**), high enantioselectivity was observed except for para-methoxy, ortho- and meta-bromo substituted substrate. Although generation of desired α-fluoroaldehyde was observed with para-methoxy substituted product **9f** by ^{1}H NMR analysis, the α-fluoroaldehyde decomposed in the presence of $NaBH_4$. The reason why moderate yield and enantioselectivity was observed with ortho- and meta-bromo substituted products **9g**, **9q** is probably due to the high steric hinderance between substrate and amine catalyst. Furthermore, other types of aromatic rings such as naphthalene and biphenyl, and other alkyl group at α-position of carbonyl group was also tolerated in this reaction (**9h**–**9n**). However, the use of α,α-dialkylaldehydes (**9o**–**9p**) and α-monoalkylaldehydes (**9r**–**9s**) dramatically decreased enantioselectivity and/or reactivity.

Table 3. Substrate scope of enantioselective fluorination of α-branched aldehydes.

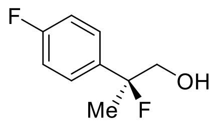




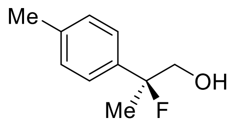
9a: 86% yield
95% ee



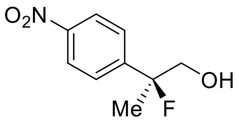
9b: 97% yield
92% ee



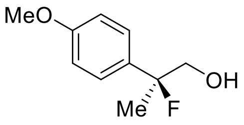
9c: 76% yield
90% ee



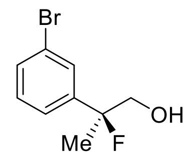
9d: 88% yield
93% ee



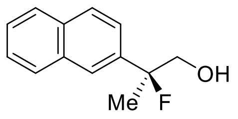
9e: 88% yield
88% ee[a]



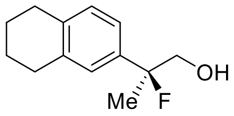
9f: 0% yield



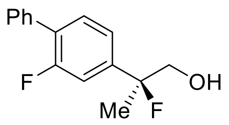
9g: 77% yield
93% ee



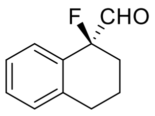
9h: 98% yield
92% ee



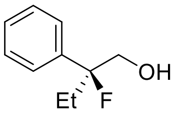
9i: 95% yield
92% ee



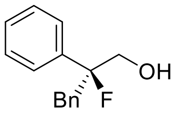
9j: 98% yield
92% ee



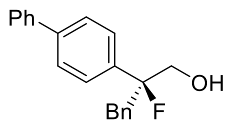
8k: 90% yield
95% ee[a,c]



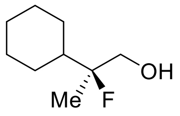
9l: 93% yield, 84% ee[b]



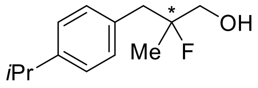
9m: 99% yield
84% ee[b]



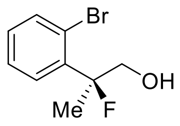
9n: 91% yield
89% ee[b,d]



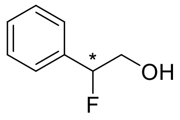
9o: 24% yield
83% ee[e]



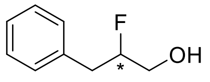
9p: 59% yield
14% ee[b]



9q: 53% yield
74% ee[b]



9r: <10% yield[b,f]



9s: 0%yield[b,g]

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[a] Purified product contained 5% inseparable by-product. [b] At rt for 12-24 h. [c] At rt for 2 h. [d] 20 mol% of catalyst. [e] 30 mol% of catalyst. [f] 2-Phenylacetoaldehyde was used. [g] Hydrocinnamic aldehyde was used.

Plausible transition state of enantioselective fluorination was estimated as follows (Figure 7). Fluorination reaction occurs in the favorable transition-state because another reaction face is well sterically hindered because of substituent at 3,3’ position of binaphtyl backbone. On the other hand, in the disfavorable transition-state, both transition-state has steric repulsion between the catalyst and substrate.

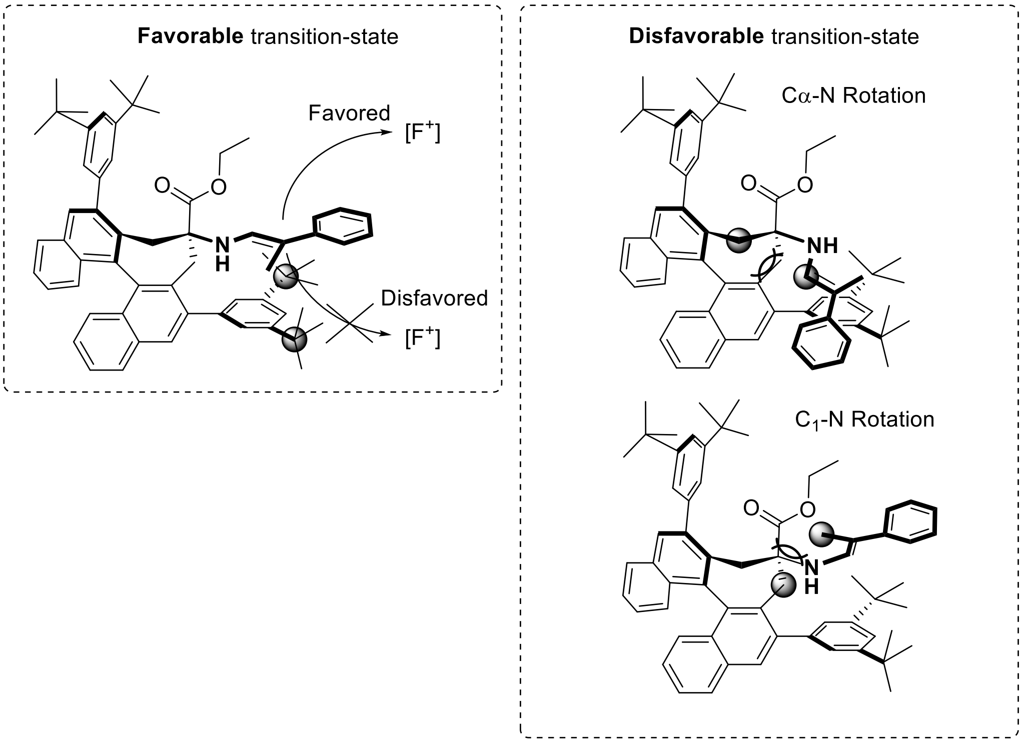
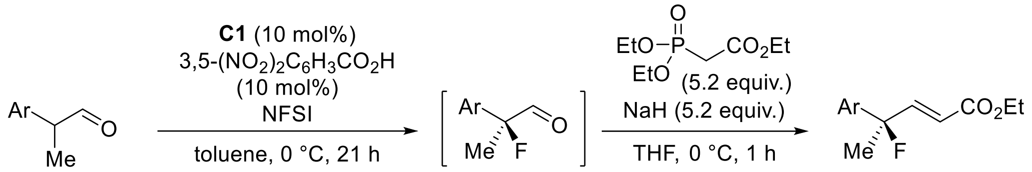


Figure 7. Plausible transition state of enantioselective fluorination.

3.3 Derivatization of α-fluoroaldehydes into fluorinated chiral molecules

Resulting chiral α-fluoroaldehydes were transformed into fluorinated chiral molecules to demonstrate utility of this methodology. First, chiral 3-fluoropropenes (**10b**, **h**) were synthesized by Horner-Wadsworth-Emmons reaction of α-fluoroaldehydes **8b**, **h** (92% ee, Table 4). α-Fluoroaldehydes were synthesized following the same procedure of enantioselective fluorination, and the reaction mixture was added to a solution of HWE reagent to afford 3-fluoropropenes. As a result, the corresponding chiral 3-fluoropropenes **10b**, **h** were obtained in 80% yield (2 steps).

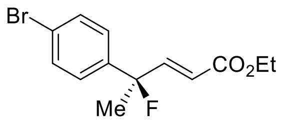
Table 4. Synthesis of chiral 3-fluoropropenes by HWE reaction of α-fluoroaldehydes.



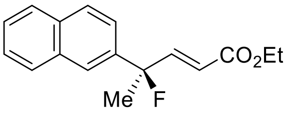
rac-**7b, h**
(1.5 equiv.)

8b, h: 92% ee

10b, h

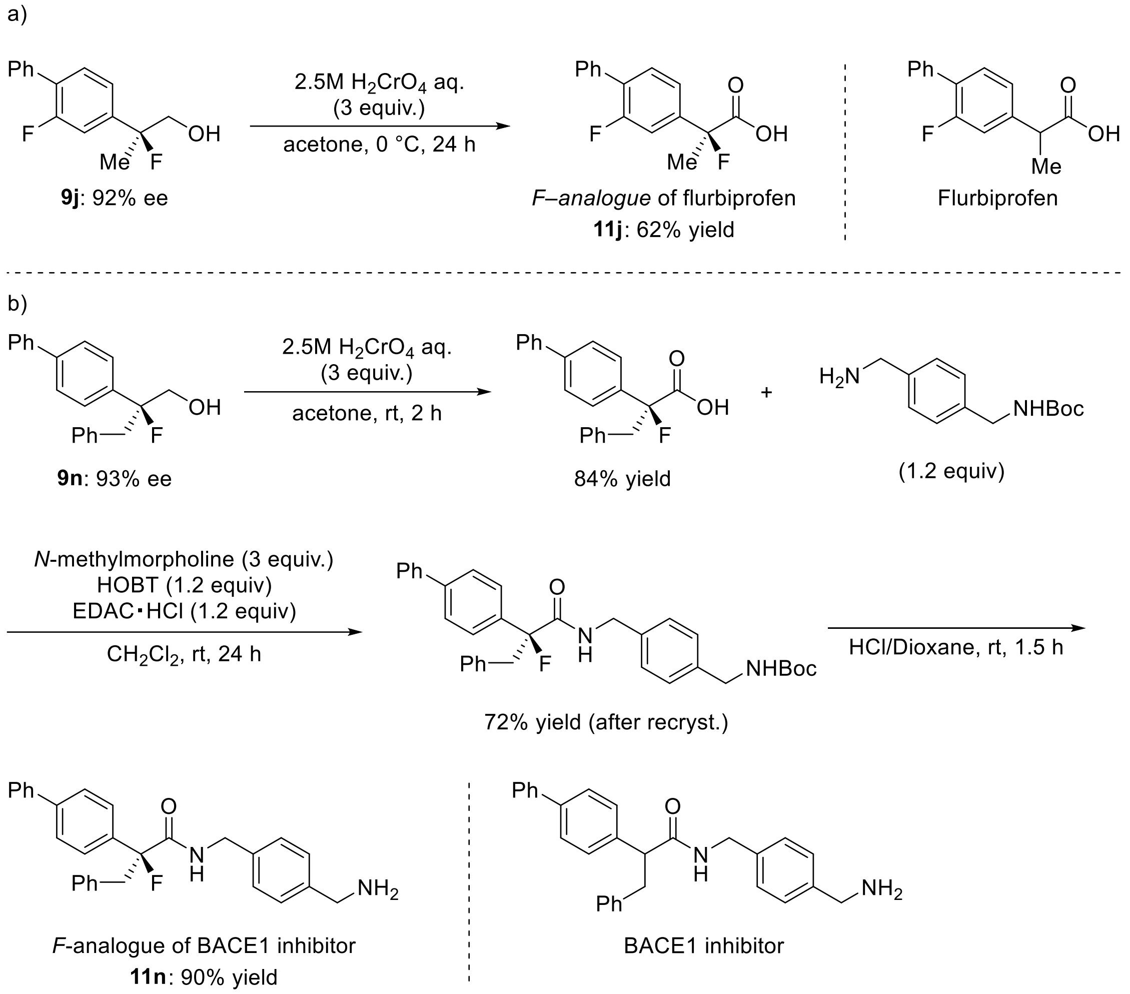


10b: 80% yield (2 steps)



10h: 80% yield (2 steps)

Second, fluorinated analogue of bioactive compounds was synthesized starting from chiral fluoroalcohols. Oxidation of fluoroalcohol (**9j**, 92% ee) afforded corresponding fluorine analogue of Flurbiprofen that is known as anti-inflammatory agent in 62% yield (Scheme 18a). Furthermore, fluoroalcohol (**9n**, 93% ee) was converted into carboxylic acid (84% yield) and subsequent amidation (72% yield) and deprotection (90% yield) yielded fluorine analogue of BACE1 inhibitor that was expected as potent remedy for Alzheimer's disease (Scheme 18b)[25].



Scheme 18. Synthesis of fluorine analogue of bioactive compounds.

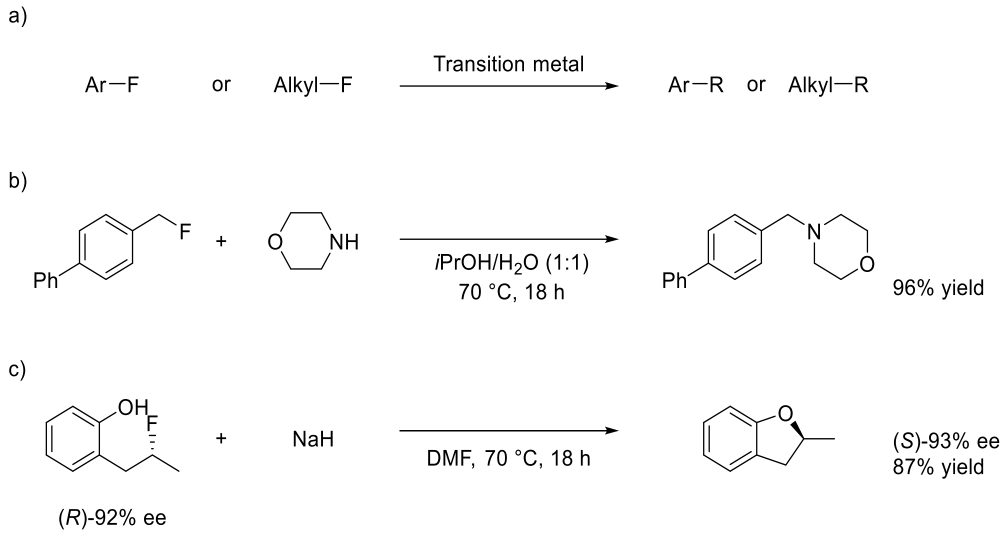
3.4 Stereospecific conversion of α-fluoroaldehydes into α-hydroxyacetals

To demonstrate further utility of resulting chiral α-fluoroaldehydes, stereospecific derivatization of α-fluoroaldehydes *via* C-F bond activation was carried out. Generally speaking, bonding energy of C-F bond is higher than other C-Halogen bonds[26]. This is why, it is difficult to carry out subsequent transformations *via* cleavage of C-F bond (Table 5).

Table 5. Bonding energy of C-Halogen bond.

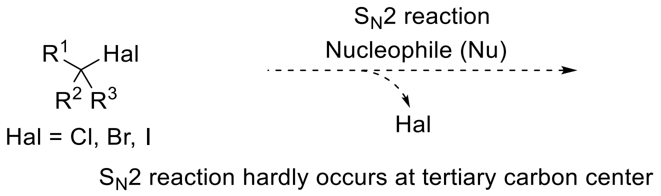
Carbon–Halogen bond	C–F	C–Cl	C–Br	C–I
Bond energy [kJ/mol]	118	81	67	54

However, recently, several successful examples of C-F bond activation have been reported as shown in Scheme 19[27].



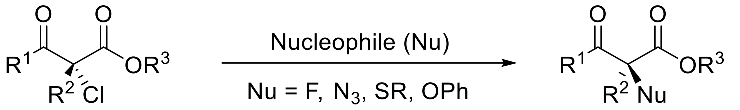
Scheme 19. Successful examples of C-F bond activation.

Furthremore, S_N2 reaction at a tertiary carbon center hardly occurs because of steric hinderance of reaction center (Scheme 20).



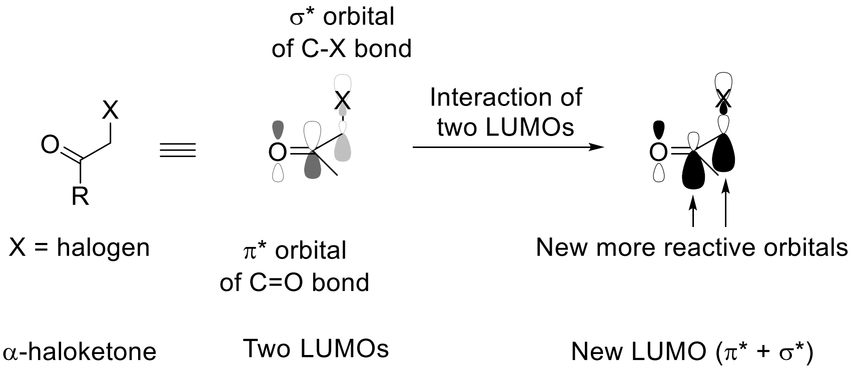
Scheme 20. S_N2 reaction at a tertiary carbon center.

However, recently Shenvi and Toney found the progress of S_N2 reaction under specific reaction conditions even at a tertiary carbon center[28]. Furthermore, the research group of Shibatomi found that smooth progress of S_N2 reaction with various nucleophiles by using α-chloro-β-keto esters and the desired product was obtained without loss of enantiopurity (Scheme 21)[22]. This is probably due to the effect of two strong electron withdrawing carbonyl groups.



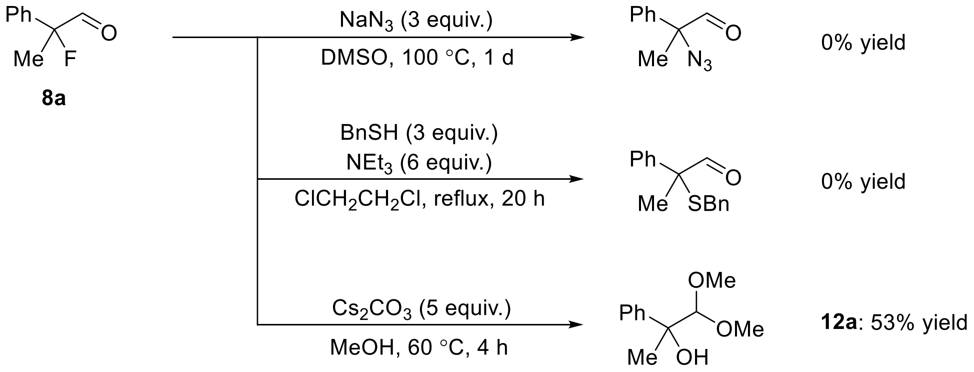
Scheme 21. S_N2 reaction of α-chloro-β-keto esters.

Furthermore, accerelation effect of S_N2 reaction at α-position of carbonyl group can be explained by interaction of molecular orbitals (Scheme 22)[29]. α-Halokeones have two LUMOs (σ* orbital of C-X bond and π* orbital of C=O bond). After the interaction of these two LUMOs, new reactive LUMO (σ* + π* orbital) will be generated and it promotes S_N2 reaction at α-position of carbonyl group because nucleophilic addition to the carbonyl carbon is reversible.



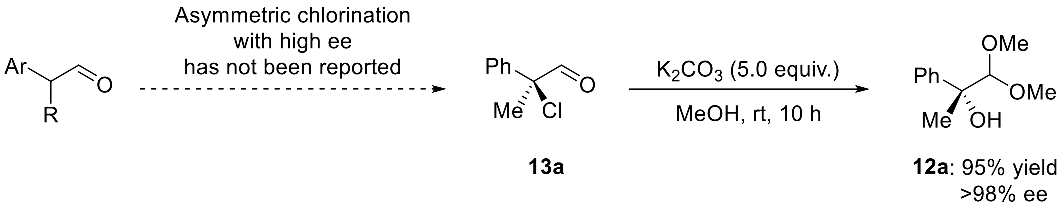
Scheme 22. Molecular orbital of α-Halokeones.

Because of the acceleration effect of carbonyl group, I expected the progress of S_N2 reaction with α-fluoroaldehyde **8a**. First, stereospecific derivatization of resulting α-fluoroaldehyde **8a** was carried out with NaN_3 and alkyl thiolate as nuclephile. However, these nucleophiles did not furnish the desired substituted products (Scheme 23). On the other hand, when α-fluoroaldehyde **8a** was subjected to basic condition in MeOH, α-hydroxyacetal **12a** was isolated in 53% yield.



Scheme 23. Preliminary results of stereospecific derivatization of α-fluoroaldehyde.

The structure of α-hydroxyacetal was confirmed by literature value of ^{1}H NMR. According to the report, Masaki reported the conversion of chiral α-chloroaldehyde **13a** into corresponding α-hydroxyacetal **12a** in 95% yield with high enantiopurity (>98% ee, Scheme 24)[30]. However, there is no practical asymmetric chlorination of α-branched aldehydes has been reported.



Scheme 24. Synthesis of α-hydroxyacetal by using chiral α-chloroaldehyde.

Tertiary alcohol is frequently found in the biologically active compounds and some of them have already been used as a remedy for some disease as shown in Figure 8. However, asymmetric synthesis of tertiary alcohol is still limited and development of convenient synthetic method is required.

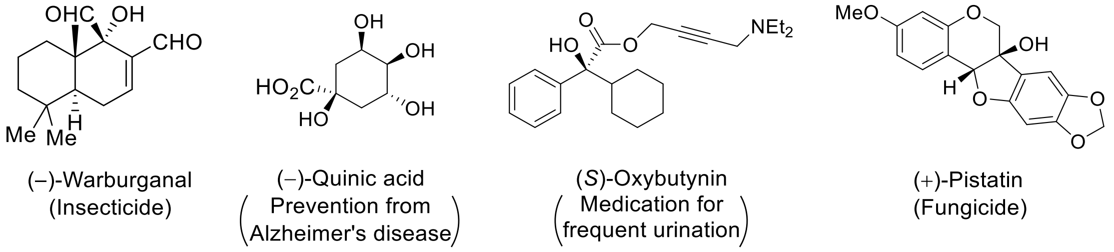
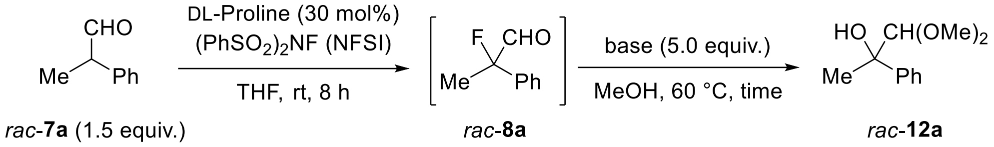


Figure 8. Bioactive compounds containing tertiary alcohol.

Considering these situations, asymmetric synthesis of α-hydroxyacetals was carried out starting from α-fluoroaldehyde **8** that is synthesized by enantioselective fluorination of α-branched aldehydes **7**.

First, racemic α-fluoroaldehyde **8a** was synthesized by fluorination of α-branched aldehyde **7a** in the presence of racemic proline. Then, the resulting α-fluoroaldehyde **8a** was subjected to subsequent derivatization in the presence of various bases as described in Table 6. After the screening of inorganic (entry 1-4) and organic bases (entry 5-7), the use of NaOMe yielded the corresponding product with the best yield (entry 4, 65% yield, 2 steps).

Table 6. Screening of base for the synthesis of α-hydroxyacetal.

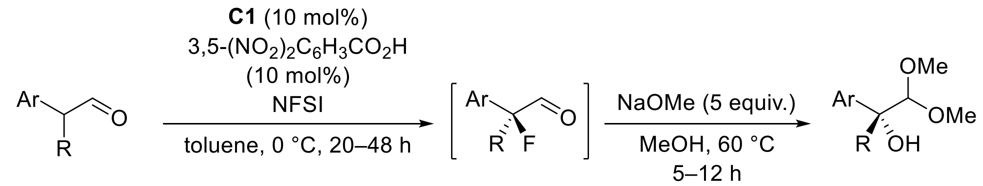


entry	base	time (h)	yield (%)[a]
1[b]	Na_2CO_3	10	3
2	K_2CO_3	10	56
3	Cs_2CO_3	4	42
4	NaOMe	10	65
5	KOH	4	58
6	Et_3N	10	0
7	DBU	10	8

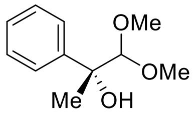
[a] Yield was determined by ^1H NMR of crude mixture using internal standard. 2 Steps yield.
[b] Reaction was carried out using α-fluoroaldehyde. DBU = Diazabicycloundecene

Then, substrate scope was examined under the optimized reaction condition (Table 7). As a result, various type of substrate was tolerated in this reaction and the products were obtained with retained enantiopurity (up to >99 es; es = enantiospecificity) in good to high yield (up to 82% yield, 2 steps). Surprisingly, corresponding para-methoxy substituted product **12f** was obtained in 20% yield with 88% ee. Furthermore, this methodology is applicable to the synthesis of ethyl acetal **12l** and cyclic acetals **12u**,**v**, although racemization occurred in the synthesis of ethyl acetal (88% es). When racemic fluoroalcohol **9a** which is synthesized by reduction of α-fluoroaldehyde **8a** was subjected to standard reaction condition, Me-protected α-hydroxyalcohol **12w** was obtained in 75% yield.

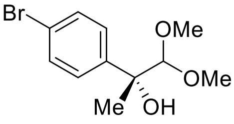
Table 7. Substrate scope of stereospecific derivatization into α-hydroxyacetals.



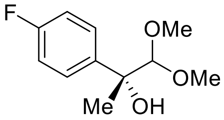
rac-**7** (1.5 equiv.) **8** **12**



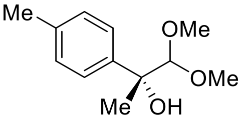
12a: 66% yield
94% ee (99% es)



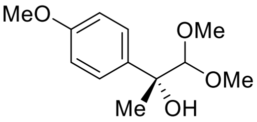
12b: 70% yield
94% ee (>99% es)



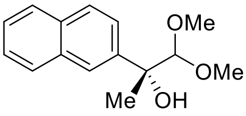
12c: 64% yield
93% ee (>99% es)



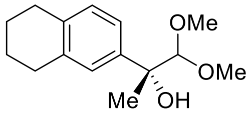
12d: 50% yield
93% ee (>99% es)



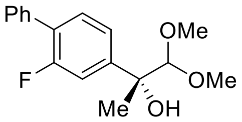
12f: 20% yield
88% ee



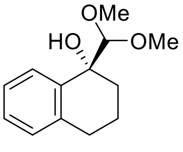
12h: 82% yield
92% ee (>99% es)



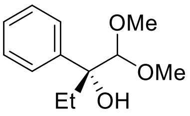
12i: 57% yield
91% ee[a] (99% es)



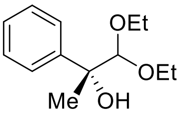
12j: 71% yield
90% ee (98% es)



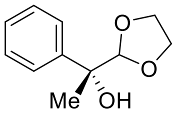
12k: 55% yield
94% ee[a] (99% es)



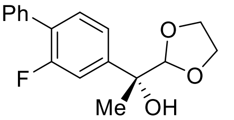
12l: 71% yield
82% ee[a] (98% es)



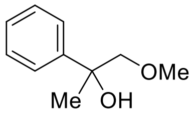
12t: 43% yield
79% ee[a,b] (88% es)



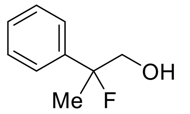
12u: 63% yield
94% ee[c] (99% es)



12v: 76% yield
90% ee[c] (98% es)



12w: 75% yield[d]
(*racemate*)



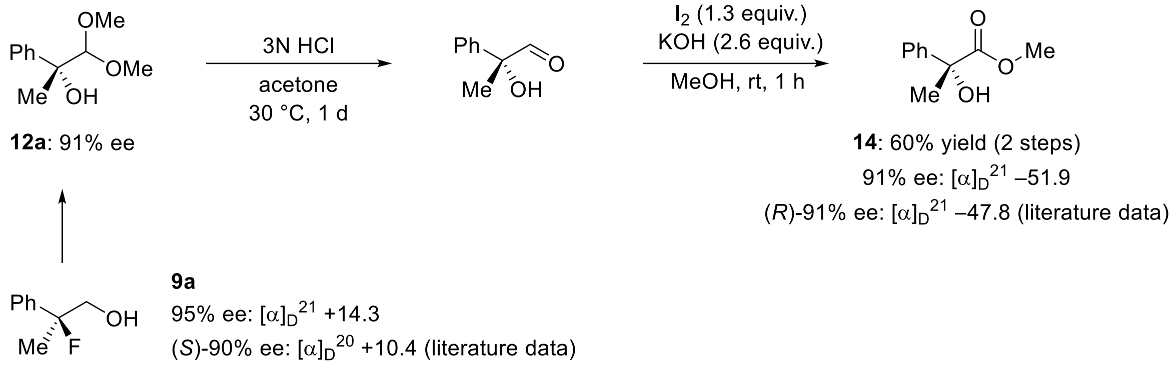
(**9a** (*racemate*):
stirred for 19 h)

---

[a] Fluorination was carried out at room temperature. [b] Reaction was carried out with EtOH under reflux condition. [c] Reaction was carried out using NaH in ethylenglycole instead of MeOH/NaOMe. [d] Fluoroalcohol was subjected to standard reaction condition and stirred for 19 h. Ramemic substrate was used.

3.5 Determination of absolute configuration

Then, resulting α-hydroxyacetal **12a** was transformed into known compound to determine the absolute configuration (Scheme 25). As a result, the $[\alpha]_D$ value of **14** was determined to be –51.9 with 91% ee. On the other hand, $[\alpha]_D$ value of (*R*) form was reported as –47.8 with 91% ee[31]. Thus, absolute configuration of **12a** was determined to be (*R*). The absolute configuration of α-fluoroalcohol **9a** has already been determined to be (*S*) by comparing literature data[12d]. According to these results, inversion of stereochemistry was confirmed, and it was revealed that this reaction proceeded by S_N2 type reaction.



12a: 91% ee

14: 60% yield (2 steps)
91% ee: $[\alpha]_D^{21}$ –51.9
(*R*)-91% ee: $[\alpha]_D^{21}$ –47.8 (literature data)

9a
95% ee: $[\alpha]_D^{21}$ +14.3
(*S*)-90% ee: $[\alpha]_D^{20}$ +10.4 (literature data)

Scheme 25. Determination of stereochemistry by comparing $[\alpha]_D$ value of known compounds.

3.6 Plausible reaction mechanism

Finally, reaction mechanism was estimated. According to the ^1H NMR measurement of **8a** in CD_3OD clearly showed the generation of hemiacetal as a diastereomeric mixture (*dr* = 6 : 4, Figure 9). NMR experiment was carried out as follows. After fluorination of **7a**, $NaHCO_3$ aq. was added to the reaction mixture, and extracted with Et_2O. The organic layer was dried over Na_2CO_3 and concentrated to give the crude mixture of **8a**. The crude product was used for NMR analysis without further purification.

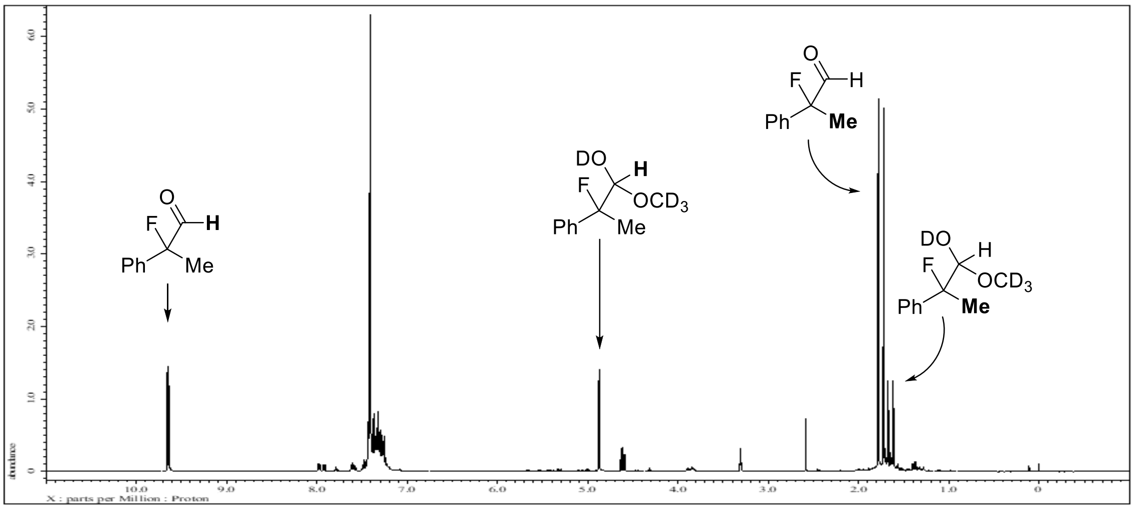
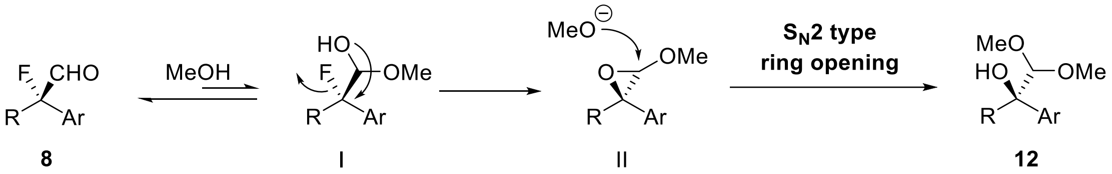


Figure 9. ^{1}H NMR experiment of reaction mixture in CD$_3$OD.

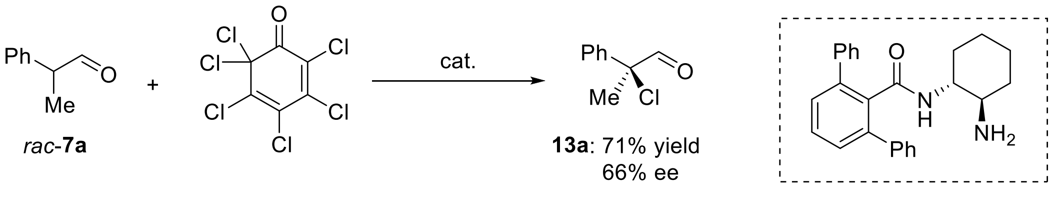
Given these results, plausible reaction mechanism was described as shown in Scheme 26. Generation of hemiacetal (I) have already confirmed by ^{1}H NMR analysis and subsequent intramolecular S$_N$2 reaction afford epoxide (II). Considering the basic condition, S$_N$2 type ring opening yield the corresponding α-hydroxyacetal **12** with inverted stereochemistry.



Scheme 26. Plausible reaction mechanism.

3.7 Asymmetric chlorination of α-branched aldehyde

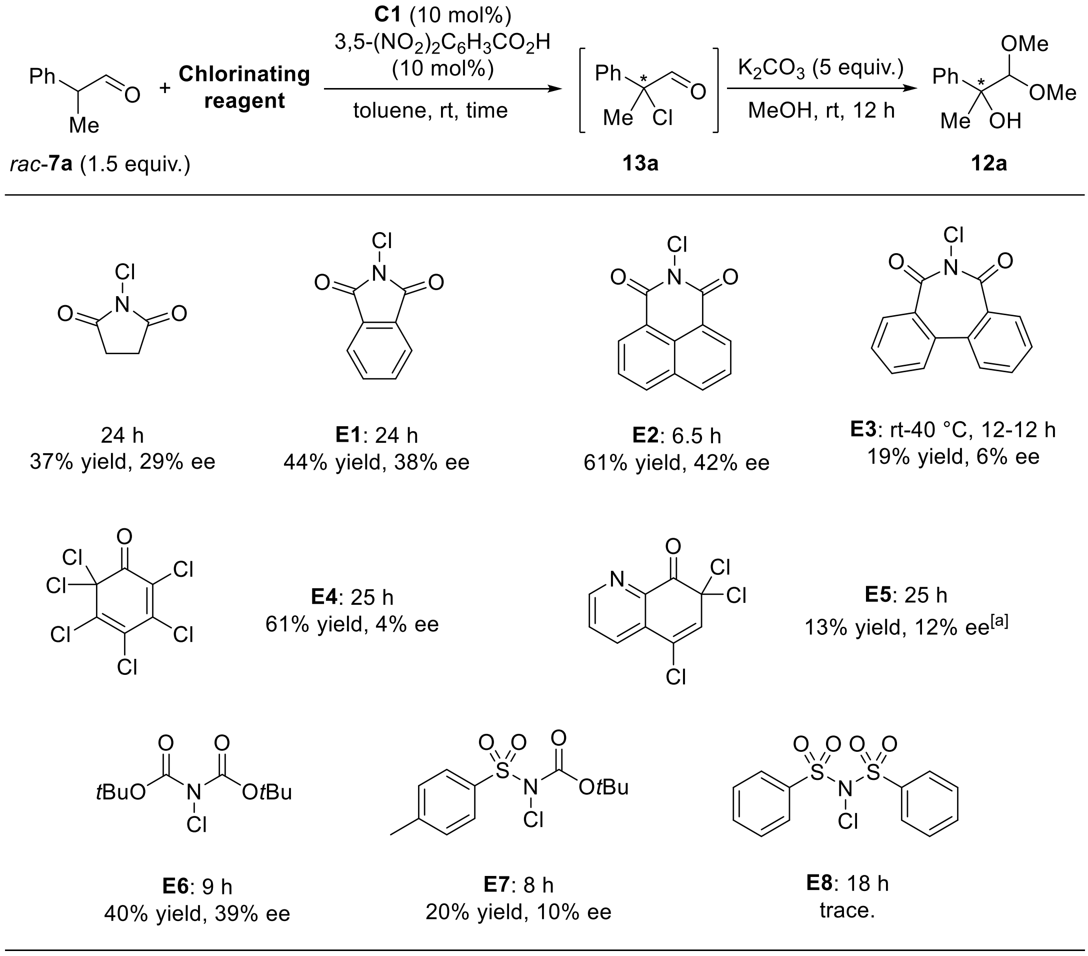
Because of the good leaving ability, resulting tertiary chloride is expected to work as good synthetic intermediate. This is why, the methodology of enantioselective fluorination was applied into enantioselective chlorination of α-branched aldehyde **7**. Catalytic asymmetric chlorination of α-branched aldehyde **7a** was reported by Jacobsen and this reaction yielded desired α-chloroaldehyde **13a** with moderate enantioselectivity (Scheme 27)[17b].



Scheme 27. Catalytic asymmetric synthesis of tertiary chloride.

First, several chlorinating reagents were subjectetd to asymmetric chlorination of α-branched aldehyde **7a** in the presence of chiral primary amine catalyst **C1** (Table 8). Resulting α-chloro aldehyde **13a** was converted into α-hydroxyacetal **12a** and yield and enantioselectivity was determined. NCS affored desired**12a** in 37% yield with 29% ee. Thus, bulkier chlorinating reagents (**E1**–**E3**) was employed for the reaction and highest enantioselectivity was observed with **E2** (42% ee). On the other hand, very low enantioselectivity was observed with other cyclic or acyclic chlorinating reagent (**E4**–**E7**) except for **E8**. According to TLC and NMR, **E8** immediately decomposed in the reaction mixture although **E8** is stable during storage under inert atmosphere.

Table 8. Screening of chlorinating reagent for asymmetric chlorination.



rac-**7a** (1.5 equiv.)

13a

12a

24 h
37% yield, 29% ee

E1: 24 h
44% yield, 38% ee

E2: 6.5 h
61% yield, 42% ee

E3: rt-40 °C, 12-12 h
19% yield, 6% ee

E4: 25 h
61% yield, 4% ee

E5: 25 h
13% yield, 12% ee[a]

E6: 9 h
40% yield, 39% ee

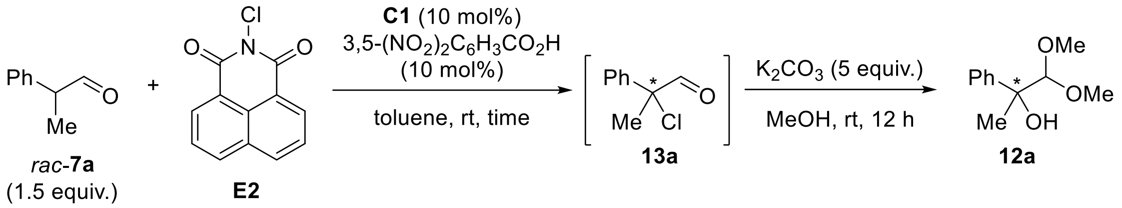
E7: 8 h
20% yield, 10% ee

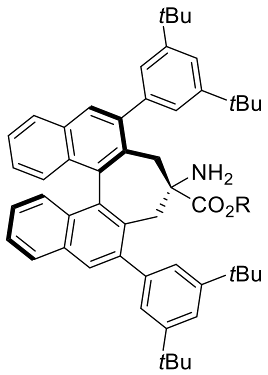
E8: 18 h
trace.

[a] Yield and ee were determined with α-chloroaldehyde.

Then, with the best chlorinating reagent **E2**, several chiral primary amine catalysts were employed for chlorination (Table 9). As a result, **C1** was found to be the best catalyst.

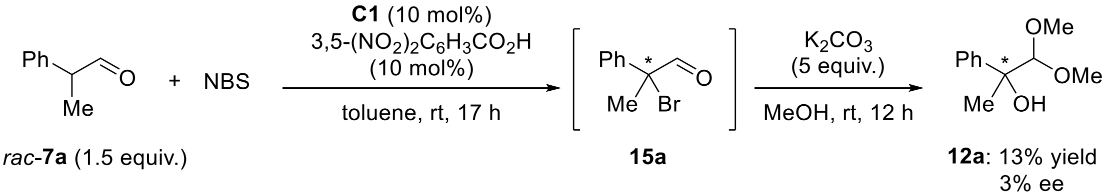
Table 9. Screening of chiral amine catalyst for asymmetric chlorination.





R = Me	R = Et (**C1**)	R = *i*Pr
18 h	6.5 h	25 h
58% yield	61% yield	55% yield
7% ee	41% ee	8% ee

Furthermore, this method was applied into asymmetric bromination. However, this reaction yielded the desired product **15a** with low enantioselectivity (Scheme 28).

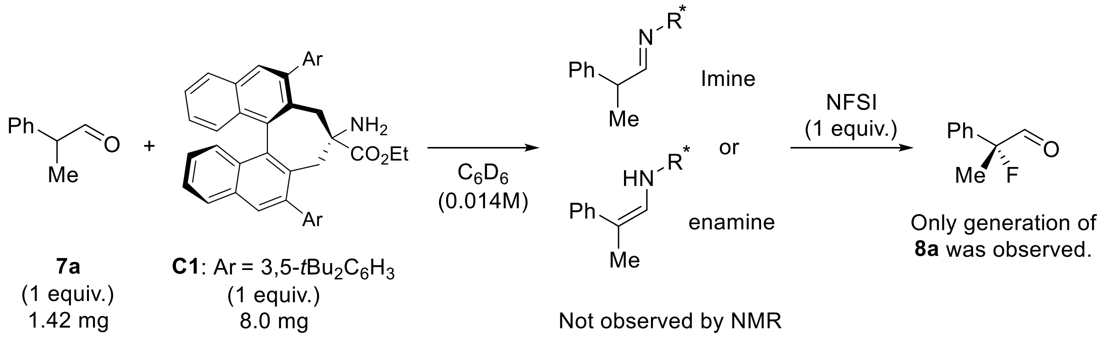


Scheme 28. Asymmetric bromination of α-branched aldehyde.

3.8 NMR experiment of enantioselective fluorination

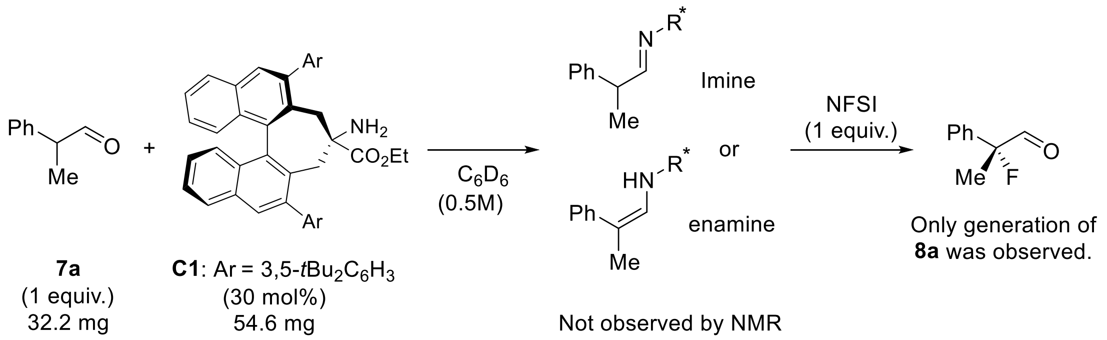
Reaction mixture was monitored by ^{1}H NMR to confirm the generation of imine and enamine intermediate. When the reaction mixture (stoichiometric amount of chiral amine and substrate, Scheme 29a) was monitored in C_6D_6 (0.014 M), generation of only desired α-fluoroaldehyde **8a** was observed. Then NMR experiment was again carried out with catalytic amount of chiral amine under concentrated reaction condition (0.5 M, Scheme 29b), this experiment also detected generation of α-fluoroaldehyde **8a** and conversion of catalyst into unknown product. After the survey, it was found that chiral amine reacted with benzensulfonimide and the product was observed in NMR experiment.

a) NMR experiment with stoichiometric amount of chiral amine



Intermediates weren't observed due to diluted condition?

b) NMR experiment with catalytic amount of chiral amine



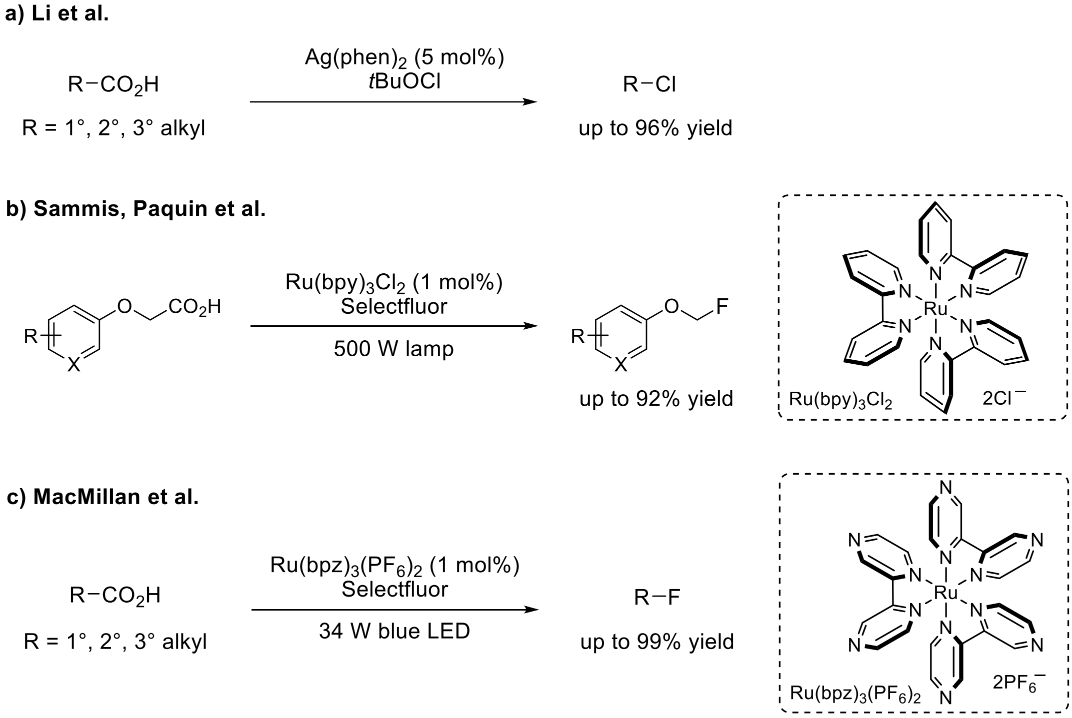
Catalyst was converted into other compound. Peaks shifted downfield.

Scheme 29. NMR experiment of enantioselective fluorination.

Chapter 4: Enantioselective decarboxylative chlorination of β-keto carboxylic acids[32]

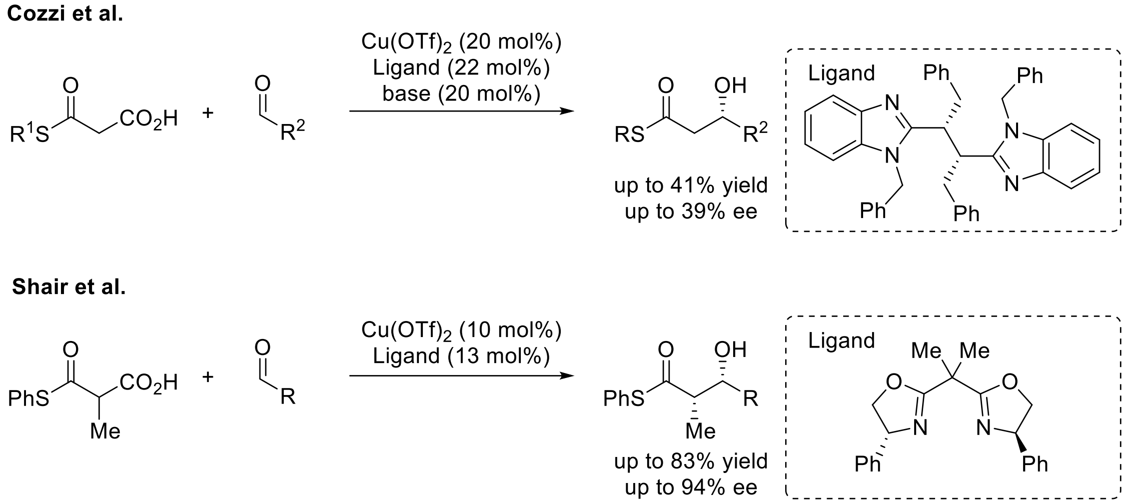
4.1 Design of enantioselective decarboxylative halogenation

Decarboxylative halogenation of carboxylic acid is known as efficient method to synthesize halogenated organic compounds. Original decarboxylative halogenation such as reports by Borodine and Hunsdiecker have used to require stoichiometric amount transition metals[33]. More recently, Li reported decarboxylative halogenation reactions in the presence of silver catalyst (Scheme 30a). Afterwards, Sammis, Paquin and MacMillan reported decarboxylative fluorination of aliphatic carboxylic acids in the presence of photoredox catalyst (Scheme 30b, c)[34]. However, there is no asymmetric decarboxylative halogenation of carboxylic acids has been reported.



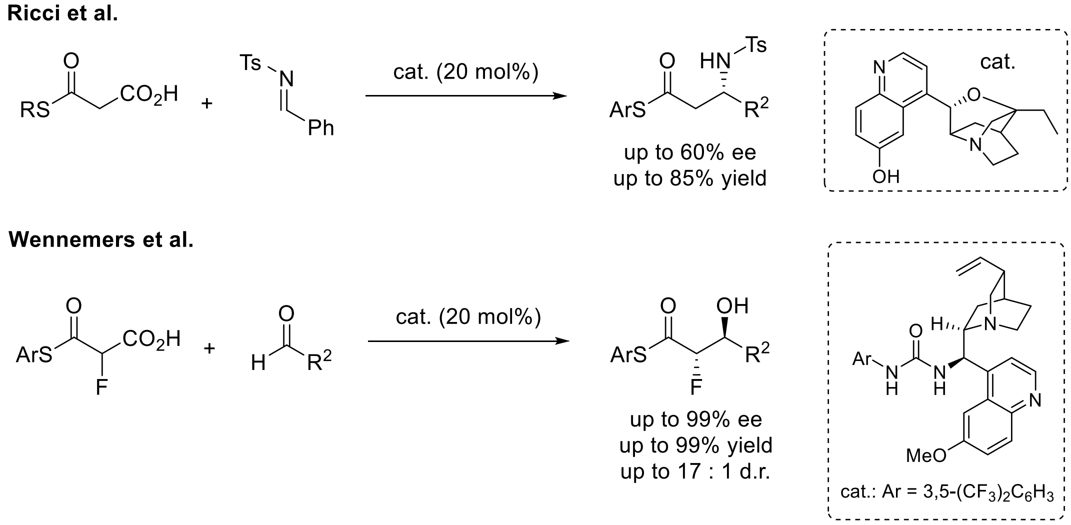
Scheme 30. Decarboxylative halogenation of aliphatic carboxylic acids.

On the other hand, asymmetric decarboxylative C-C bond formation reactions have been reported[35]. Cozzi and Shair reported asymmetric decarboxylative aldol reaction of β-oxo carboxylic acid in the presence of Lewis acid catalysts[36] (Scheme 31).



Scheme 31. Asymmetric decarboxylative C-C bond formation with Lewis acid catalysts.

Asymmetric decarboxylative C-C bond formation reaction have also already achieved in the presence of organocatalysts by Ricci and Wennemers (Scheme 32)[37].



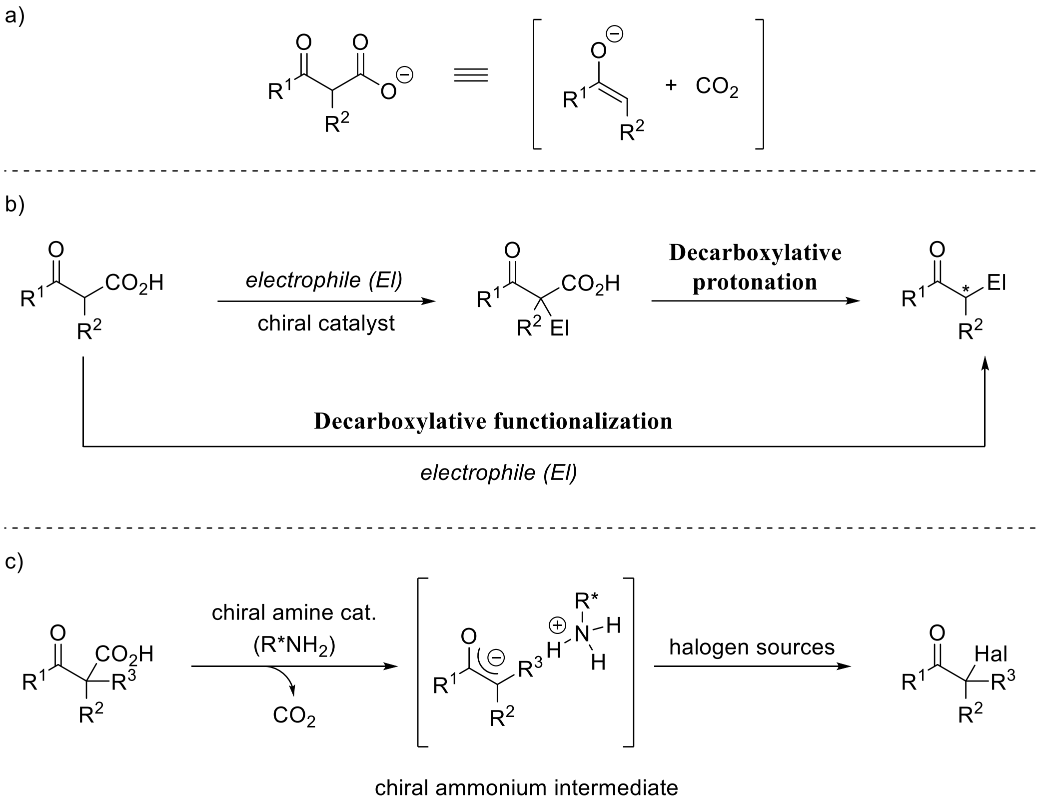
Scheme 32. Asymmetric decarboxylative C-C bond formation with organocatalysts.

According to these results, β-oxo carboxylic acids act as an enolate equivalent after decarboxylation of carboxylic acid moiety (Scheme 33a). Among these reactions, two reaction pathways have been proposed.

Path way 1: Decarboxylative functionalization occurs first and it furnish α-functionalozed β-oxo carboxylic acids, and subsequent decarboxylation affords the desired product (Scheme 33b above).

Path way 2: Functionalization occurs after decarboxylation (Scheme 33b below).

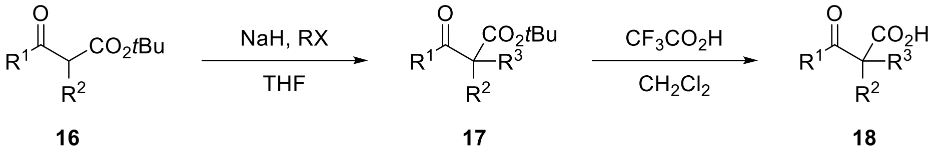
Herein asymmetric decarboxylative halogenation by using β-oxo carboxylic acids and chiral amine catalyst was designed as shown in Scheme 33c. In this reaction, decarboxylation is accererlated by chiral amine and it generate transient chiral ammonium intermediate. Resulting chiral ammonium intermediate will be trapped by electrophilic halogenating reagent to furnish desired α-haloketones.



Scheme 33. Design of asymmetric decarboxylative halogenation.

4.2 Synthesis of substrates

α,α-Dialkyl-β-ketoesters **17** were synthesized by alkylation of α-alkyl-β-ketoesters **16** and β-keto carboxylic acids **18** were prepared by acidolysis of corresponding α,α-dialkyl-β-ketoesters **17** (Scheme 34, See supporting information for the synthesis of α-alkyl-β-ketoesters **16**).

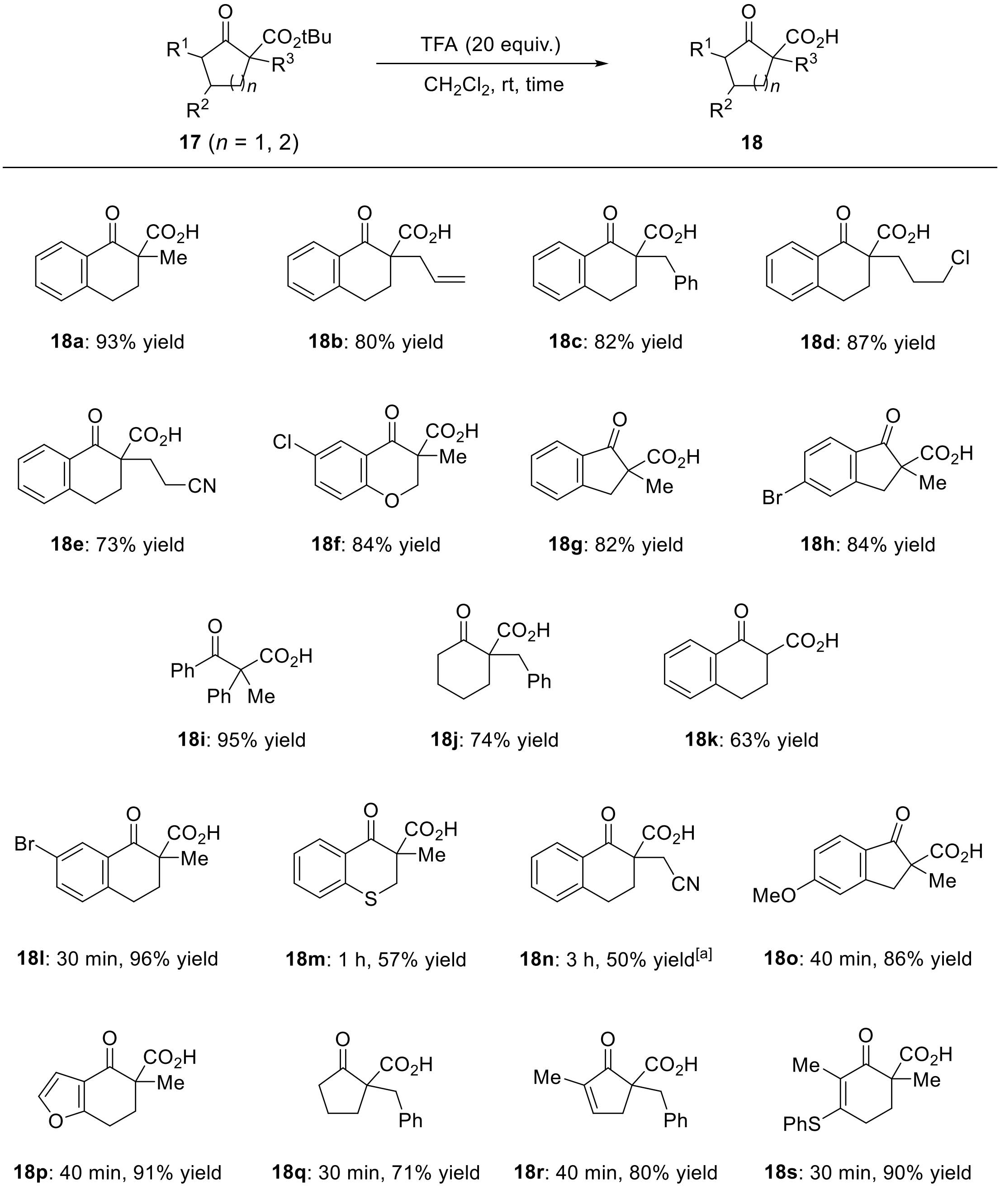


16 **17** **18**

Scheme 34. Synthetic route of β-keto carboxylic acids.

The yield of the β-keto carboxylic acids was described in Table 10. Generally speaking, various β-keto carboxylic acids were synthesized by acidolysis of corresponding α,α-dialkyl-β-ketoesters except for α-cyanomethyl substituted carboxylic acid **18n**. The carboxylic acids were unstable, and it immediately decomposed even during workup.

Table 10. Synthesis of β-keto carboxylic acids.



17 (*n* = 1, 2)

18

18a: 93% yield

18b: 80% yield

18c: 82% yield

18d: 87% yield

18e: 73% yield

18f: 84% yield

18g: 82% yield

18h: 84% yield

18i: 95% yield

18j: 74% yield

18k: 63% yield

18l: 30 min, 96% yield

18m: 1 h, 57% yield

18n: 3 h, 50% yield[a]

18o: 40 min, 86% yield

18p: 40 min, 91% yield

18q: 30 min, 71% yield

18r: 40 min, 80% yield

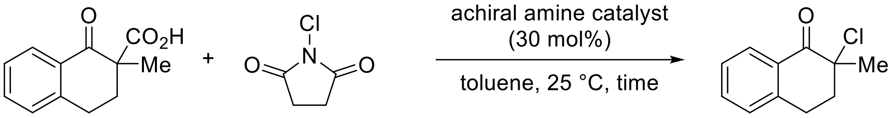
18s: 30 min, 90% yield

[a] Decarboxylative protonation was very fast to isolated the product.

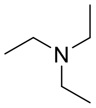
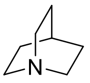
4.3 Enantioselective chlorination of β-keto carboxylic acids

First, decarboxylative chlorination was carried out with achiral amine catalyst to confirm whether the reaction is accelerated or not using tetralone-derived substrate **18a** (Table 11). It was found that this reaction proceeded slowly even in the absence of amine catalyst and the product **19a** was obtained in 34% yield (entry 1). Then, TEA was employed as catalyst and the reaction was slightly accelerated (entry 2). After screening of several amine catalysts, quinuclidine dramatically accelerated the reaction (entry 3, 95% yield).

Table 11. Confirmation of acceleration effect by achiral amine catalyst.

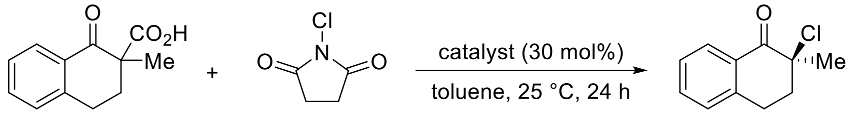


rac-**18a** (3.0 equiv) *rac*-**19a**

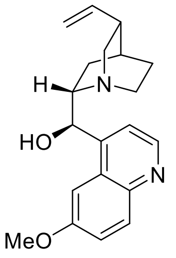
entry	catalyst	time (h)	yield (%)
1	-	24	34
2		24	88
3		1	95

Then, relatively easily available chiral amine catalysts were employed for asymmetric decarboxylative chlorination (Table 12). As a result, although corresponding α-chloroketone **19a** was obtained in good yield, very low enantioselectivity was observed.

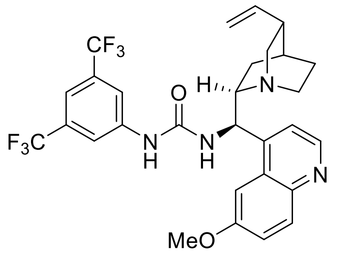
Table 12. Screening of chiral amine catalysts.



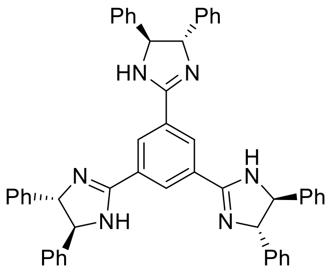
rac-**18a** **19a**



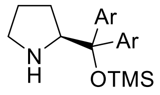
93% yield, 6% ee
(3 h)



28% yield, 0% ee

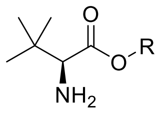


85% yield, 4% ee
(15 °C, 10 mol%)

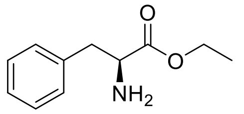


Ar = 3,5-$(CF_3)_2C_6H_3$

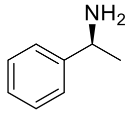
94% yield, 7% ee



R = Et; 86% yield, 1% ee
R = *t*Bu; 93% yield, 0% ee



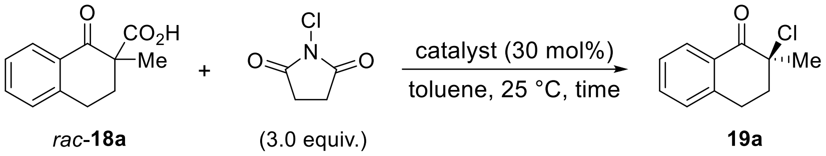
96% yield, 0% ee

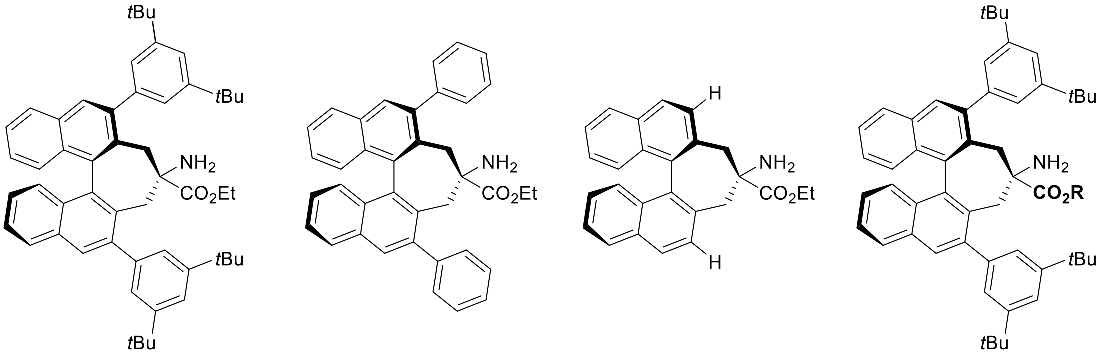


63% yield, 0% ee

Then, our newly developed chiral primary amine catalyst **C1** was used and it demonstrated highest enantioselectivity (99% yield, 97% ee, Table 13). Other variants of catalysts showed diminished enantioselectivity.

Table 13. Screening and optimization of chiral primary amine catalyst.





C1: 99% yield, 97% ee

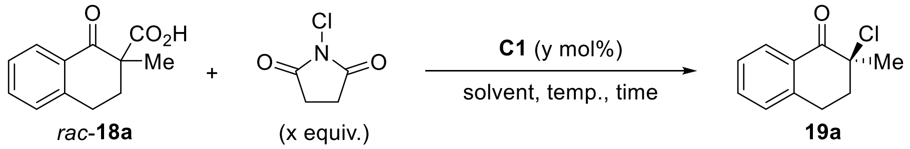
89% yield, 50% ee

71% yield, 8% ee

R = Me; 93% yield, 89% ee
R = *i*Pr; 99% yield, 95% ee

Optimized catalyst in hand, reaction conditions were screened. When the reaction solvent was changed to benzene, CH_2Cl_2, MeCN and THF, the best enantioselectivity was obtained in toluene (Table 14, entry 1-5). Then, reaction temperature was lowered to 15 °C and enantioselectivity was slightly improved to be 96% (entry 7). However, reactivity was diminished at 10 °C (entry 8). Furthermore, when the amount of NCS was decreased to 1.5 equiv., the products was obtained still in high yield and enantioselectivity (entry 9). Finally, catalyst loading was dropped to 5 and 2.5 mol% (entry 10-11), and decreased reactivity and enantioselectivity was observed. As a result, entry 9 was determined to be the optimized condition.

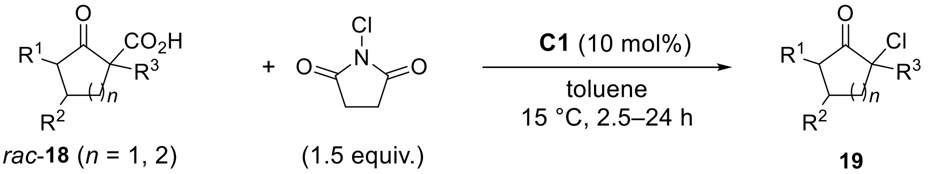
Table 14. Optimization of reaction condition for enantioselective chlorination.

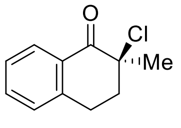


entry	x (equiv.)	y (mol%)	solvent	temp. (°C)	time (h)	yield (%)	ee (%)
1	3	10	toluene	25	24	96	93
2	3	10	benzene	25	24	91	90
3	3	10	CH_2Cl_2	25	24	91	91
4	3	10	CH_3CN	25	24	85	84
5	3	10	THF	25	24	19	66
6	3	10	toluene	25	24	96	93
7	3	10	toluene	15	24	96	96
8	3	10	toluene	10	33	88	96
9	1.5	10	toluene	15	24	94	96
10	1.5	5	toluene	15	48	97	95
11	1.5	2.5	toluene	15	48	79	94

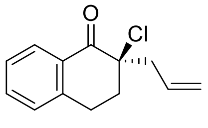
Finally, under the optimized reaction condition, various substrates were subjected to enantioselective decarboxylative chlorination (Table 15). Generally speaking, high enantioselectivity was observed with tetralone-, 4-chlomanone and indanone-derived substrate (**19a**–**19h**) except for Br-substituted tetralone **19l**, 4-thiochlomanone **19m** and methoxy-substituted indanone **19o**. The reason of diminished reactivity and enantioselectivity is probably because of low solubility of carboxylic acids. On the other hand, less bulky aromatic group greatly diminished enantioselectivity (**19p**). Furthermore, simple cyclohexanone or cyclopentanone derivatives were obtained with moderate or low enantioselectivity (**19j**, **19q**–**19s**). Acyclic tetra-substituted substrate was also obtained with moderate enantioselectivity (**19i**) this is due to the difficulty of controlling *E*/*Z* form of enolate intermediate (Scheme 35a). Without methyl group of α-position, the product was obtained with moderate enantioselectivity (**19k**).

Table 15. Substrate scope of enantioselective decarboxylative chlorination.

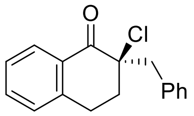




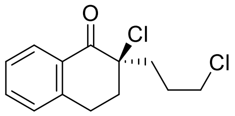
19a: 94% yield
96% ee



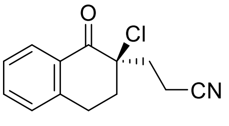
19b: 96% yield
96% ee



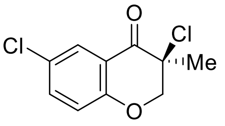
19c: 91% yield
93% ee



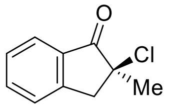
19d: 90% yield
97% ee



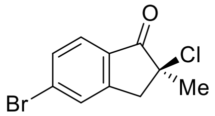
19e: 83% yield
98% ee



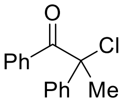
19f: 93% yield
93% ee



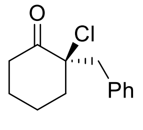
19g: 97% yield
90% ee[a]



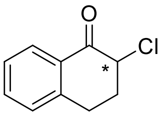
19h: 97% yield
89% ee[b]



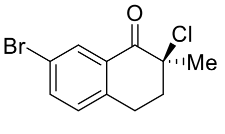
19i: 96% yield
48% ee



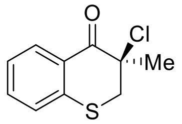
19j: 97% yield
40% ee



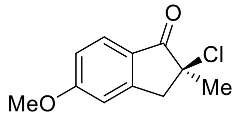
19k: 92% yield
56% ee[c]



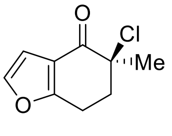
19l: 88% yield, 79% ee[d]
39% yield, 81% ee[e]



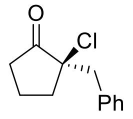
19m: 36% yield
76% ee (2 d)



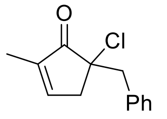
19o: 89% yield
65% ee[f]



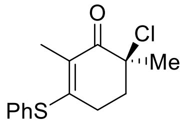
19p: 68% yield
30% ee[g]



19q: 81% yield
11% ee[h]



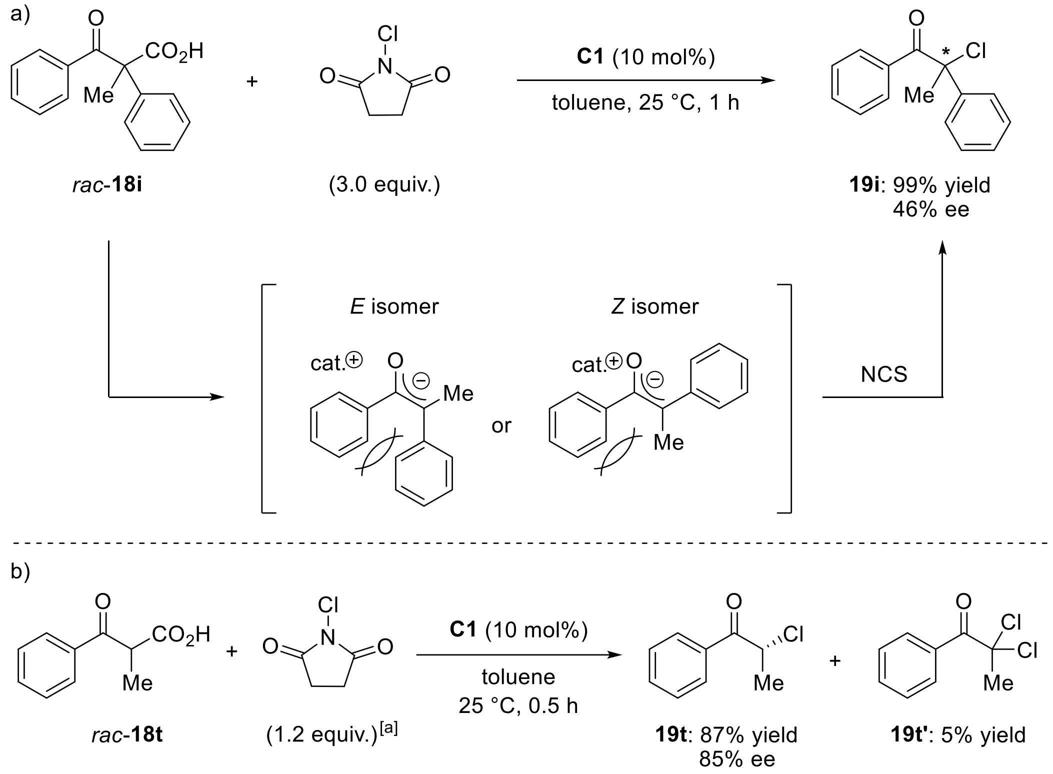
19r: 99% yield
56% ee (8 h)



19s: 63% yield
36% ee[g]

[a] 2 days at –20 °C . [b] 3 days at –30 °C. [c] 1.2 Equiv. of NCS was slowly added over 1 h at 25 °C. [d] 20 vol% CH_2Cl_2 was added to the mixture at 8 h. SA over 24 h. rt for 5 h. [e] 3.0 Equiv. of NCS was used and stirred for 24 h at rt (not full conversion). [f] 3.0 Equiv. of NCS was used and stirred for 3 h at rt. [g] Stirred at rt. [h] 3 Equiv. of NCS was used and stirred for 1.5 h at rt.

The difficulty of controlling *E*/*Z* selectivity can be explained by stability of ammonium enolate intermediate. Both *E*- and *Z*- enolate have steric repulsion between Bz group and Ph or Me group as shown in Scheme 35a. Because of this sterically bulky intermediate, the control of *E*- and *Z*-form was difficult. Because of this phenomenon, Sasaki designed enantiolselective decarboxylative chlorination to afford secondary chloride with high enantioselectivity (Scheme 35b, up to 87% ee) and high yield. In this reaction, NCS was slowly added to the reaction mixture to suppress generation of α,α-dichloketones[38].



[a] A solution of NCS in toluene was slowly added over 1 h.

Scheme 35. Control of *E*/*Z* selectivity of ammonium enolate intermediate for high enantioselectivity.

Plausible transition state of enantioselective chlorination was estimated as follows using tetralone-derived substrate. Chiral ammonium enolate intermediate may react with chlorinating reagent in favorable transition-state (Figure 10). Another reaction face of enolate is well blocked by one of the bulky substituent [3,5-$(t\mathrm{Bu})_2C_6H_3$ group] of the catalyst and it enables enantioselective chlorination. On the other hand, disfavorable transition-state has steric repulsion between catalyst and substrate.

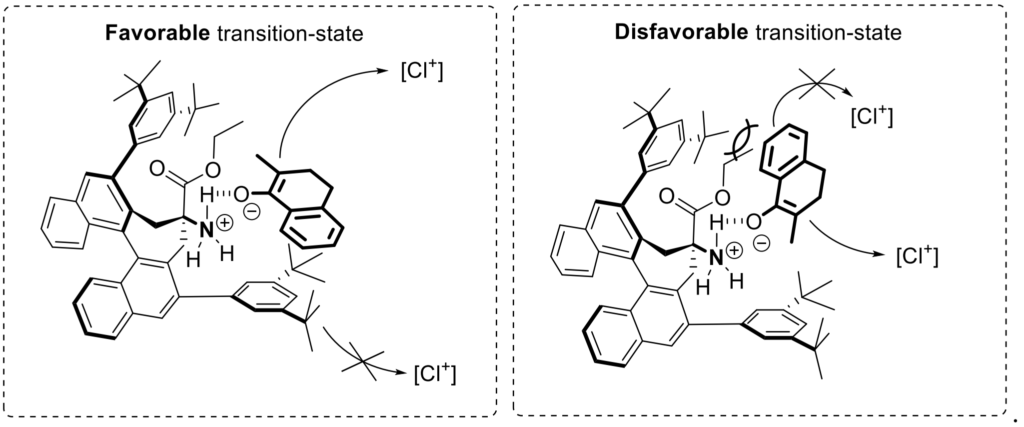
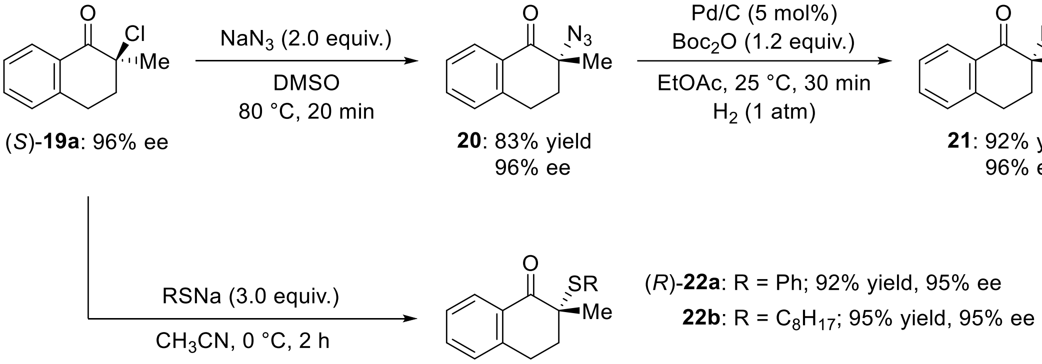


Figure 10. Plausible transition state of enantioselective chlorination.

4.4 $\mathrm{S_N2}$ reaction of chiral tertiary α-chloroketone

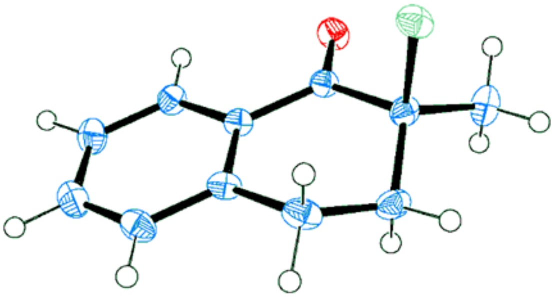
Resulting tertiary α-chloroketone **19a** was subjected to $\mathrm{S_N2}$ reaction to confirm the synthetic utility of this methodology (Scheme 36). When 96% ee of tertiary α-chloroketone **19a** was reacted with NaN_3 and sodium thiolate, the corresponding α-azide ketone **20** and α-sulfenyl ketones **22** were obtained with mostly retained enantiopurity in good yield. Furthermore, α-azide ketone can be converted into corresponding *N*-Boc protected amine **21**.

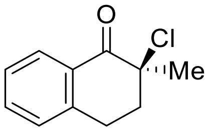


Scheme 36. $\mathrm{S_N2}$ reaction of chiral tertiary α-chloroketone.

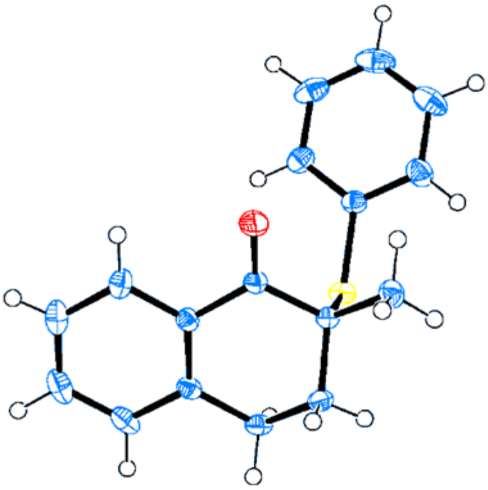
4.5 Determination of absolute configuration by single crystal X-ray analysis

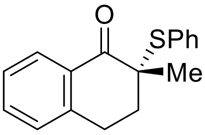
X-ray crystallography analysis of tertiary α-chloroketone **19a** and α-sulfenyl ketone **22a** was carried out to determine the absolute configuration (Figure 11). According to the analysis, configuration of tertiary α-chloroketone (96% ee) was determined to be (*S*). On the other hand, α-thiophenylketone (95% ee) was determined to be (*R*). Thus, inversion of stereochemistry was confirmed, and it suggested this reaction proceeded *via* $\mathrm{S_N2}$ reaction.





(*S*)-**19a**: **96% ee**



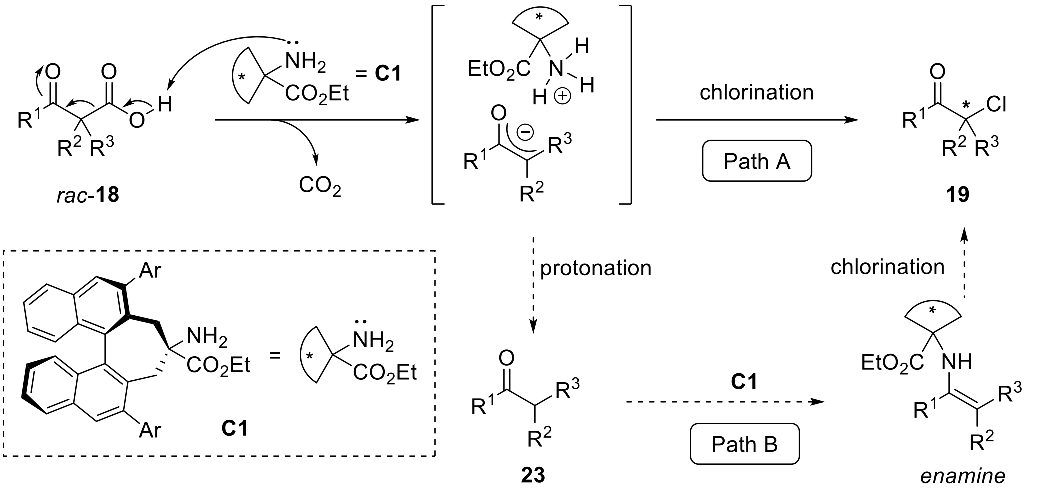


(*R*)-**22a**: **95% ee**

Figure 11. X-ray crystallography of substrate and substituted product.

4.6 Confirmation of reaction pathway

First, this reaction is initiated by the reaction between chiral primary amine catalyst and β-keto carboxylic acid **18**. Then, transient chiral ammonium enolate intermediate will be generated and it is trapped by electrophilic chlorinating reagent to afford desired α-chloroketone **19** (Scheme 37 Path A). On the other hand, there is another reaction pathway to afford the same product by chlorination of enamine which is generated by the reaction with decarboxylated ketone **23** and amine catalyst (Path B).

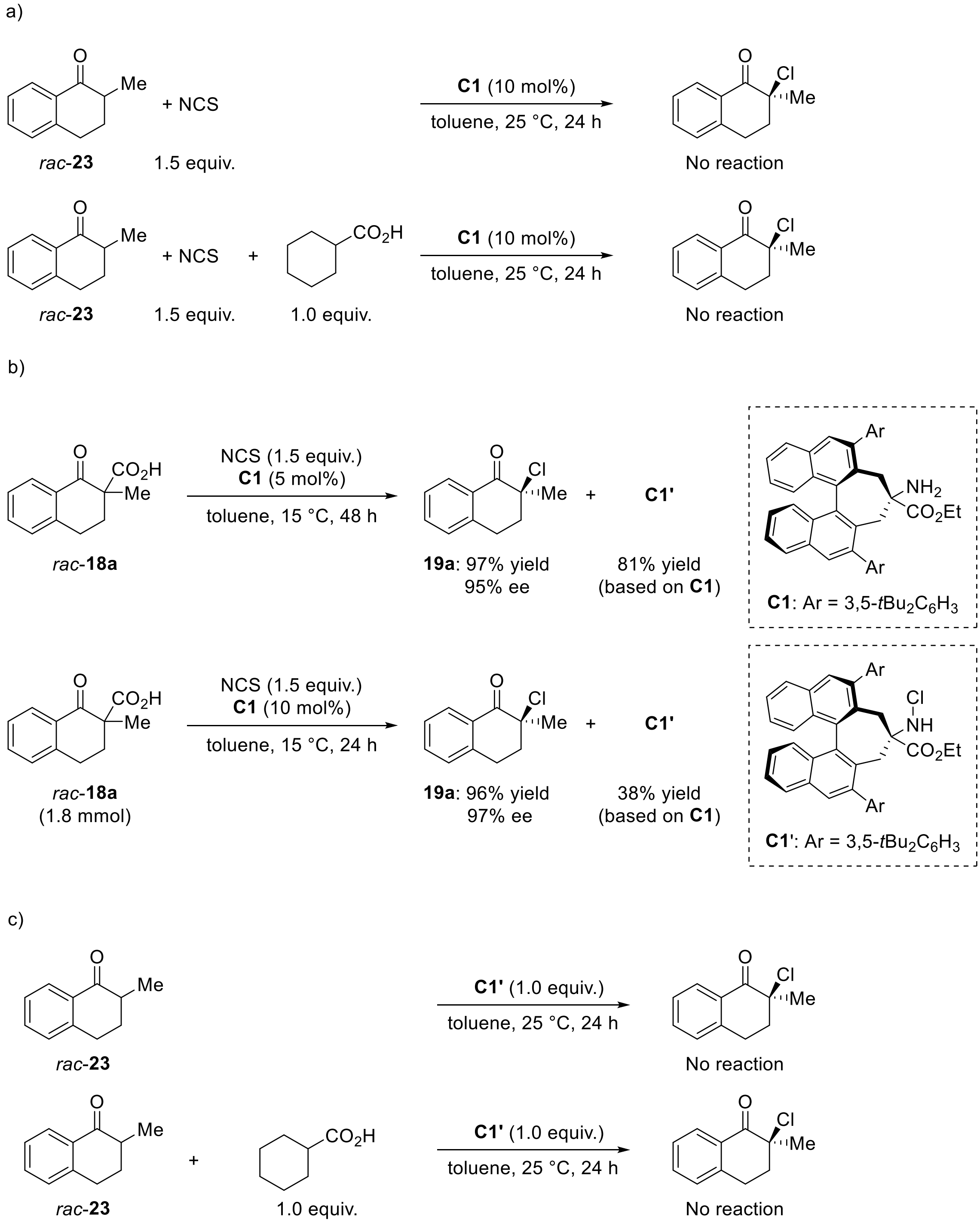


Scheme 37. Plausible reaction mechanism

To discard the possibility of Path B, some control experiments were carried out (Scheme 38). First, decarboxylated ketone was subjected to standard reaction condition with or without cyclohexanecarboxylic acid to confirm the effect of acidify of reaction mixture (Scheme 38a). In each cases, no reaction occurred, and substrate was recovered.

Then, chiral amine catalyst was recovered under optimized reaction condition (Scheme 38b). Some portion of amine catalyst was recovered as chlorinated amine **C1'** (catalyst loading 5 mol%: 81% yield, 10 mol%: 38% yield based on **C1**).

Resulting chlorinated amine **C1'** was used as a chlorine source instead of NCS to confirm whether **C1'** generate enamine with ketone **23**. However, no reaction occurred under these reaction conditions (Scheme 38c). Furth er control experiments were carried out by Kawasaki and Sasaki[38,39].

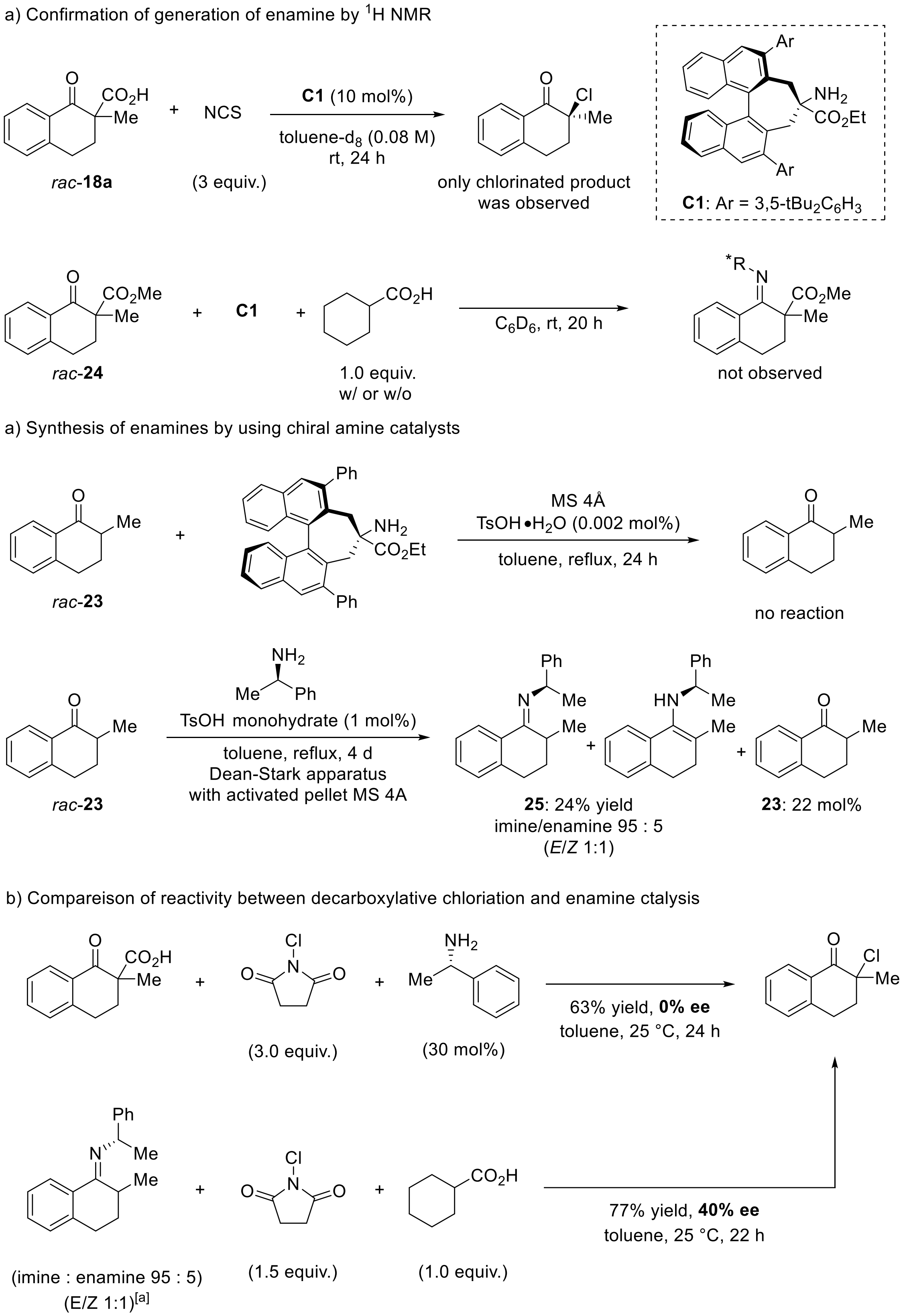


Scheme 38. Control experiments to discard the possibility of chlorination by *in-situ* generated enamine.

Furthermore, to discard the existence of enamine in the reaction mixture, decarboxylative chlorination of β-keto carboxylic acid **18a** was monitored by ^{1}H NMR in toluene-d6 because carboxylic acid group of **18a** may accelerate the generation of enamine (Scheme 39a). However, only generation of chlorinated product **19a** was observed. When β-keto ester **24** was mixed with amine **C1** with or without cyclohexanecarboxylic acid, no reaction occurred according to ^{1}H NMR analysis.

Thus, enamine was synthesized from tetralone-derived ketone **23** and chiral amine (Scheme 39b). First, our newly developed chiral amine was employed for the reaction, and no reaction occured. This is probably because of bulkiness of the amine. Then, easily available 2-phenethylamine was used and this reaction successfully afforded the mixture of imine and enamine **25** along with ketone **23**. The crude mixture was rapidly purified by flash column chromatography with a pad of silicagel to reduce the amount of ketone **23**. As a result, desired imine and enamine **25** was obtained as a mixture along with 22 mol% of **23**.

Finally, the resulting mixture of enamine **25** was subjected to chlorination reaction and it afforded corresponding tertiary α-chloroketone **19a** with 40% ee in 77% yield (Scheme 39c). On the other hand, decarboxylative chlorination with 2-phenethylamine (catalyst) afforded the product with 0% ee in 63% yield. According to these results, it was found that the possibility of formation of enamine can be discarded in this reaction.



a) Confirmation of generation of enamine by ^1H NMR

a) Synthesis of enamines by using chiral amine catalysts

b) Compareison of reactivity between decarboxylative chloriation and enamine ctalysis

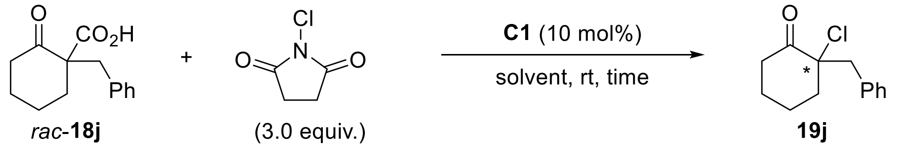
[a] Contains 22 mol% of 2-methyl-1-tetralone.

Scheme 39. Synthesis of enamine and comparison of reaction pathway.

4.7 Further optimization of reaction conditions

Further optimization of reaction conditions was carried out to improve the enantioselectivity of less bulky substrates such as cyclohexanone derivative **18j**. When cyclohexanone derivative was subjected to decarboxylative chlorination in toluene, enantioselectivity was 40% (Table 16, entry 1). Thus, reaction temperature was decreased to –40 °C. Although enantioselectivity was improved to be 48%, reactivity was dramatically decreased (entry 2). Other reaction solvents were examined, and it was found that CH_2Cl_2 showed slightly improved enantioselectivity (45% ee) with moderate reactivity (entry 3-9). Thus, the most balanced result was obtained in toluene at rt (entry 1).

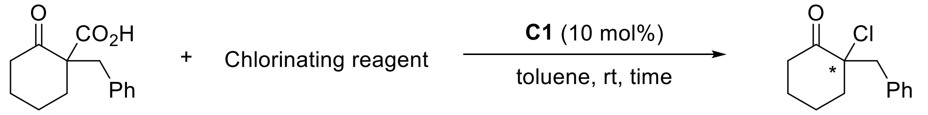
Table 16. Optimization of reaction solvent.



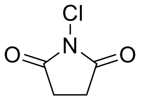
entry	solvent	time (h)	yield (%)	ee (%)
1	toluene	1.5	99	40
2	toluene (–40 °C)	24	22	48
3	CH_2Cl_2	9	79	45
4	MeCN	4	97	26
5	THF	24	20	8
6	TBME	18	96	31
7	MeOH	12	95	0
8	hexane	4	99	33
9	CCl_4	4.5	99	41

Then, several chlorinating reagents were employed for the reaction (Table 17). As a result, NCS was the best chlorinating reagent and lower enantioselectivity was observed with other chlorinating reagents (**E1**, **E2**, **E4–6**, **E9**).

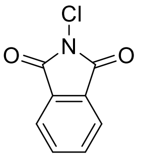
Table 17. Optimization of chlorinating reagent.



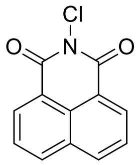
rac-**18j** **19j**



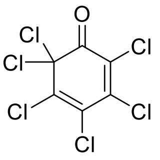
1.5 h
99% yield
40% ee



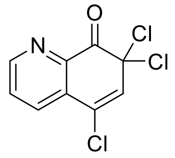
E1:1 h
99% yield
24% ee



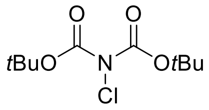
E2: 1.5 h
99% yield
38% ee



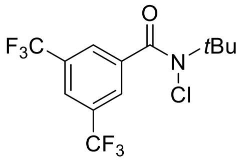
E4: 25 h
57% yield
17% ee



E5: 25 h
35% yield
19% ee



E6: 24 h
68% yield
1% ee

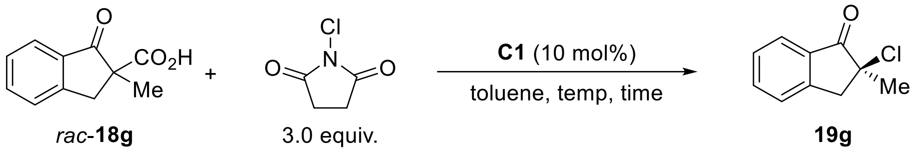


E9: 1 h[a]
86% yield
5% ee

[a] Without light.

Furthermore, effect of reaction temperature was examined by using indanone-derived substrate **18g** (Table 18). When the reaction was carried at –20 °C, the desired product was obtained with 89% ee (entry 3). Thus, the temperature was lowered to be –40 °C and the enantioselectivity was slightly improved with greatly decreased reactivity (entry 4, 91% ee). When the amount of NCS was decreased to 1.5 equivalent and it slightly improved the enantioselectivity (entry 5, 90% ee).

Table 18. Optimization of reaction temperature.



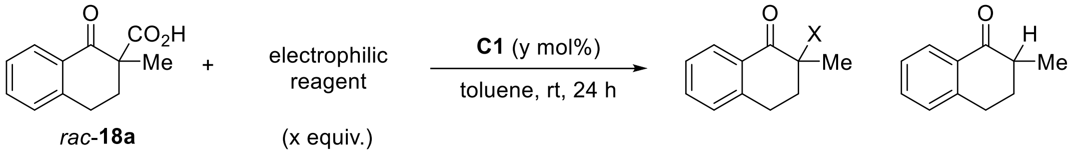
entry	temp (°C)	time (h)	yield (%)	ee (%)
1	25	2	86	84
2	0	6	83	87
3	–20	48	90	89
4	–40	76	23	91
5[a]	–20	48	97	90

[a] 1.5 equiv. of NCS was used for the reaction.

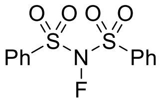
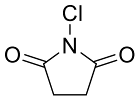
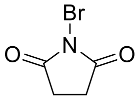
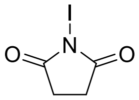
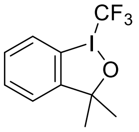
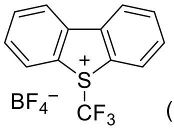
4.8 Enantioselective decarboxylative functionalizations with chiral primary amine catalyst

The methodology of enantioselective decarboxylative chlorination was applied to various types of functionalization in the presence of **C1** (Table 19). First, When, NCS was switched to NFSI, enantioselectivity and the yield of desired fluoroketone were dramatically decreased. This is probably because of acidity of benzenesulfonimide which may deactivate the chiral amine catalyst (Table 19, entry 1, 2). Bromination and iodination also showed very low enantiolselectivity because of relatively small acceleration effect by the amine catalyst (entry 5–8). On the other hand, protonation reaction afforded corresponding ketone **23** with moderate enantioselectivity (entry 9, 64% ee). Furthermore, trifluoromethylation afforded complex crude product and the generation of desired product **19CF$_3$** was not observed (entry 10, 11).

Table 19. Decarboxylative functionalization with chiral amine catalyst **C1**.

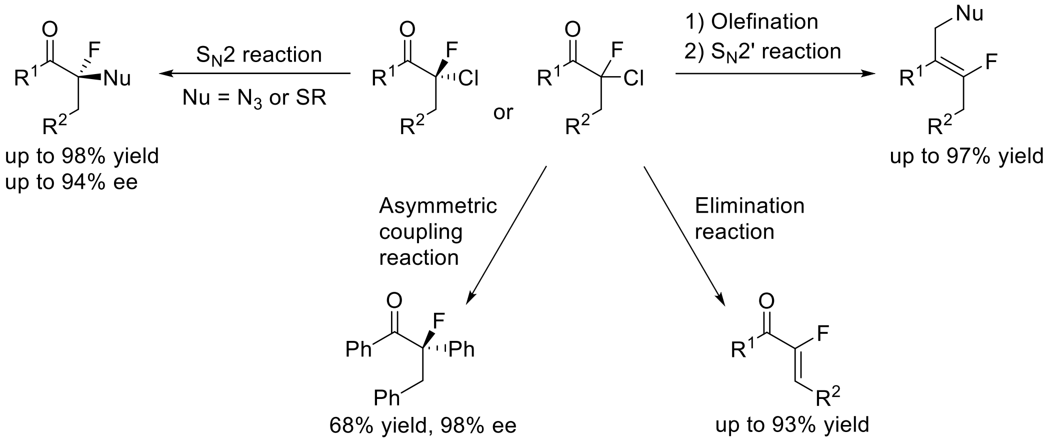


rac-**18a**

entry	reagent (x equiv.)	y (mol%)	temp. (°C)	time (h)	yield (%)	ee (%)
1 (**19F**)	 (1.5 equiv.)	10	15	24	20 (38)	0
2 (**19F**)		0	15	24	22 (21)	-
3 (**19a**)	 (1.5 equiv.)	10	15	24	94	96
4 (**19a**)		0	15	24	34	-
5 (**19Br**)	 (3.0 equiv.)	30	rt	24	57	2
6 (**19Br**)		0	rt	24	47	-
7 (**19I**)	 (1.5 equiv.)	10	15	4	53 (53% conv.)	1
8 (**19I**)		0	15	5	20 (30% conv.)	-
9 (**23**)	none	0	15	24	78	64
10 (**$19CF_3$**)	 (3.0 equiv.)	30	rt	28	complex mixture	
11(**$19CF_3$**)	 (3.0 equiv.)	30	rt	21	complex mixture	

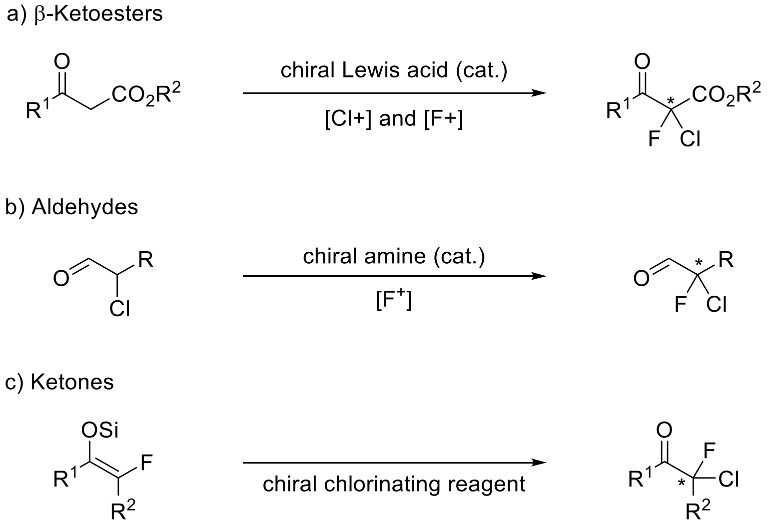
4.9 Asymmetric synthesis of α-chloro-α-fluoroketones

From the view point of synthetic organic chemistry, α-chloro-α-fluorocompounds work as good synthetic intermediate for the synthesis of chiral fluorinated compounds. Shibatomi reported stereospecific derivatization of optically active α-chloro-α-fluoroketones to afford chiral α-heteroatom-α-fluoroketones (Scheme 40). Furthermore, α-chloro-α-fluorocompounds is useful even racemic form. Fu reported asymmetric coupling reaction of racemic α-chloro-α-fluoroketones. Furthermore, when α-chloro-α-fluoroketones was treated with base, elimination rection occurred to afford corresponding fluoroenones. Paquin reported S_N2' reaction of 3-chloro-3-fluoropropenes which is preopared by olefination of α-chloro-α-fluoroketones to yield fluoroalkenes[22a,40].



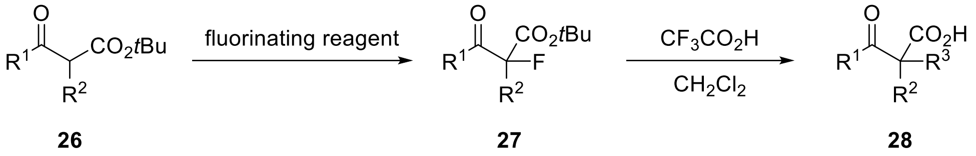
Scheme 40. Synthetic applications of α-chloro-α-fluoro carbonyl compounds.

Although the synthetic method for α-chloro-α-fluoro-β-keto esters[22a,41] (Scheme 41a) and α-chloro-α-fluoroaldehydes[40a,42] (Scheme 41b) have already established well, catalytic enantioselective synthesis of α-chloro-α-fluoroketones has not been achieved yet. To the best of our knowledge, only Yamamoto and Shibatomi achieved enantioselective synthesis of α-chloro-α-fluoroketones in the presence of stoichiometric amount of chiral chlorinating reagent (Scheme 41c)[40a].



Scheme 41. Synthetic method of chiral α-chloro-α-fluoro carbonyl compounds.

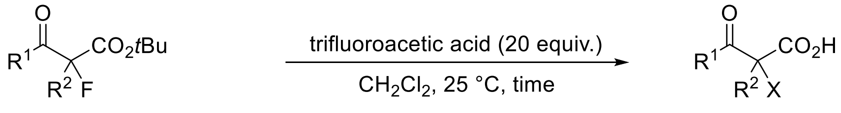
Because of the lack of enantioselective synthetic method for α-chloro-α-fluoro ketones, enantioselective decarboxylative chlorination was applied to the synthesis of α-chloro-α-fluoro ketones. First, α-fluoro-β-keto carboxylic acids **28** was prepared by acidolysis of corresponding α-fluoro-β-keto esters **27** which is prepared by fluorination of β-keto esters **26** (Scheme 42).



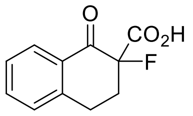
Scheme 42. Synthesis route of α-fluoro-β-keto carboxylic acids.

α-Fluoro-β-keto carboxylic acids were prepared in the presence of trifluoroacetic acid and was obtained in good yield as shown in Table 20. However, due to the instability of p-methoxy substituted carboxylic acid **28k**, the products could not isolated. Furthermore, 8-Br tetralone derivative **28j** contained inseparable by-product and it could not used for subsequent chlorination.

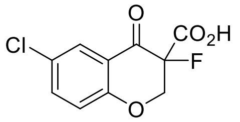
Table 20. Synthesis of α-fluoro-β-keto carboxylic acids.



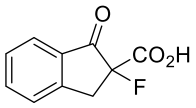
27 → **28**



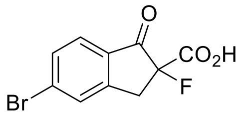
28a: 80 min
72% yield
2% protonated



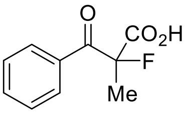
28b: 90 min
86% yield
0% protonated



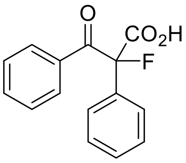
28c: 50 min
62% yield
0% protonated



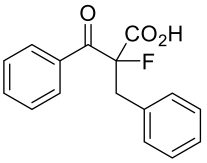
28d: 90 min
80% yield
0% protonated



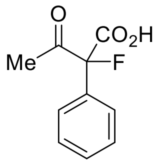
28e: 1 h
92% yield
1% protonated



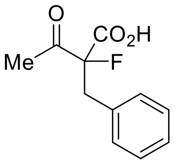
28f: 60 min
62% yield
0% protonated



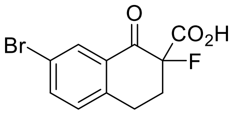
28g: 60 min
85% yield
0% protonated



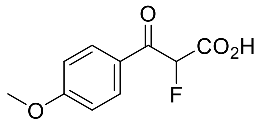
28h: 90 min
71% yield
4% protonated



28i: 90 min
85% yield
0% protonated



28j: 90 min
37% yield
11% bypro

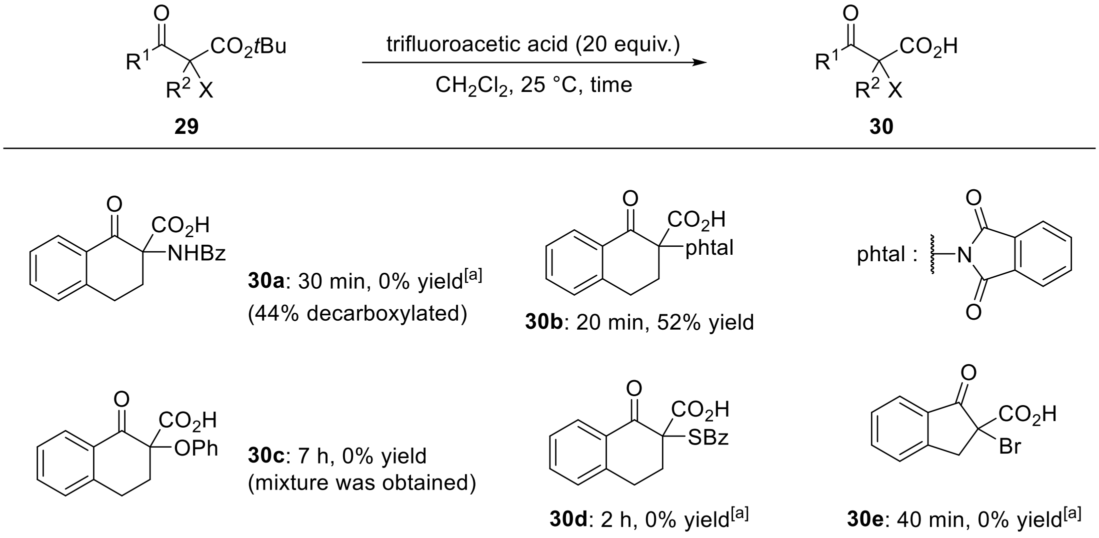


28k: 1 h (0 °C)
0% yield[b]

[a] Decarboxylated during column chromatography. [b] Decarboxylated even during reaction.

Furthermore, this methodology was applied to the synthesis of α-heteroatom substituted chloroketones (Table 21). However, α-heteroatom substituted β-keto carboxylic acids **30** were mostly instable even during the acidolysis and they could not be isolated except for α-phthalimide substituted carboxylic acid **30b**. When the carboxylic acid **30b** was subjected decarboxylative chlorination, no reaction occurred probably because of extremely low solubility of the carboxylic acid.

Table 21. Synthesis of α-heteroatom substituted-α-chloroketones



30a: 30 min, 0% yield[a] (44% decarboxylated)

30b: 20 min, 52% yield

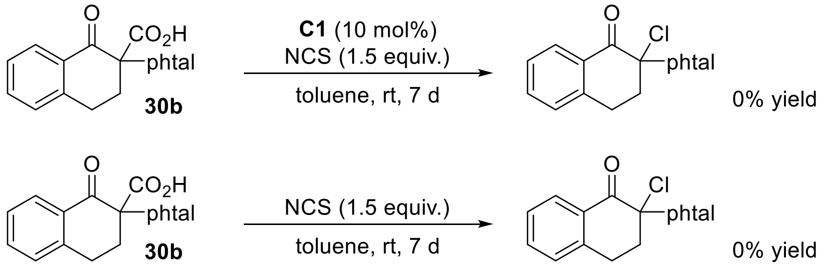
30c: 7 h, 0% yield (mixture was obtained)

30d: 2 h, 0% yield[a]

30e: 40 min, 0% yield[a]

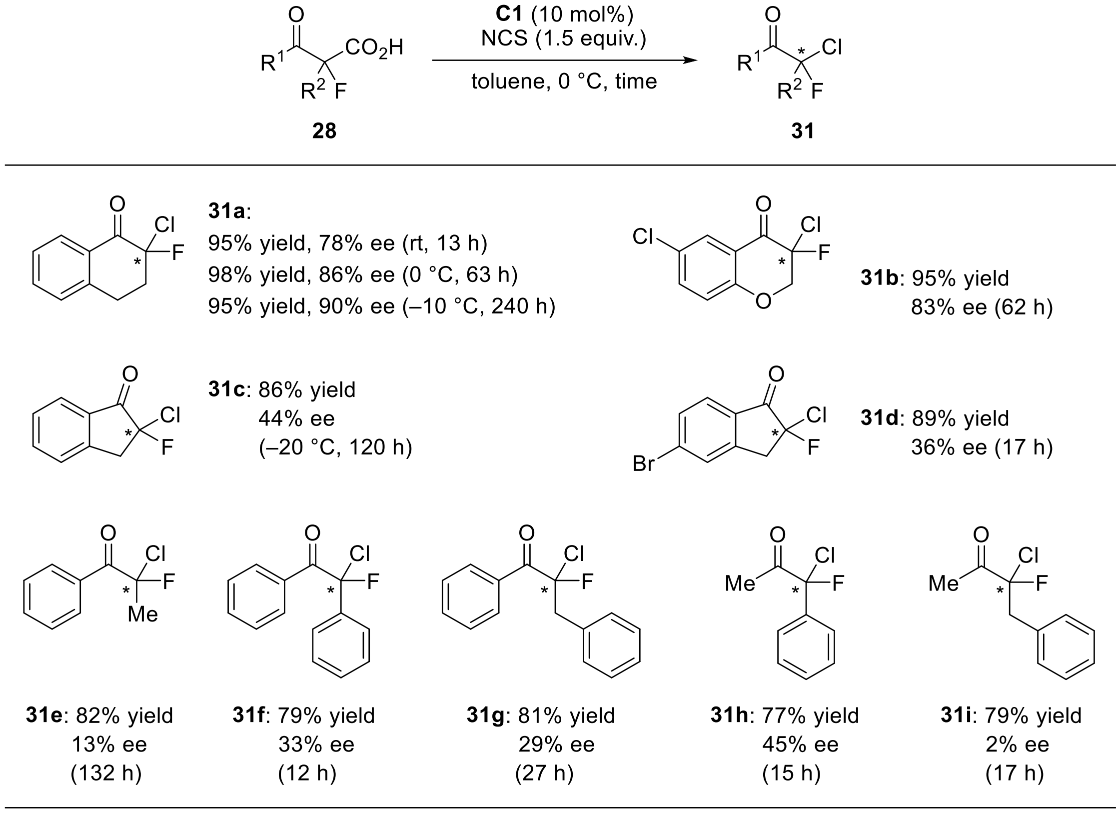
[a] Decarboxylated even during reaction.

Decarboxylative halogenation of β-keto acids **30b**

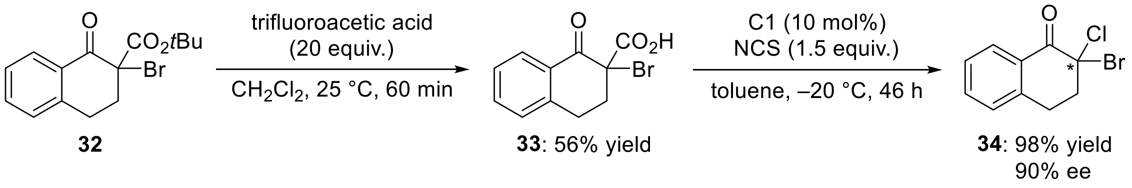


Then, resulting α-fluoro-β-keto carboxylic acids **28** were subjected to decarboxylative chlorination in the presence of chiral primary amine catalyst **C1**. First, tetralone-derived substrate was employed and the desired α-chloro-α-fluoroketones **31a** was obtained in 98% yield with the enantioselecitivity of 78% (Table 22). Thus, reaction temperature was lowered to 0 °C, and the enantioselectivity was improved to be 86% ee. At –10 °C, the ee was furthrer improved to be 90% ee in long reaction time (240 h). Thus, reaction temperature was basically fixed to 0 °C and substrate scope was examined. As a result, although high enantioselectivity was observed with 4-chlomanone derivative **31b**, indanone-derived or acyclic α-chloro-α-fluoroketones were obtained with moderate to low enantioselectivity (**31c**–**i**).

Table 22. Asymmetric decarboxylative chlorination of α-fluoro-β-keto carboxylic acids.



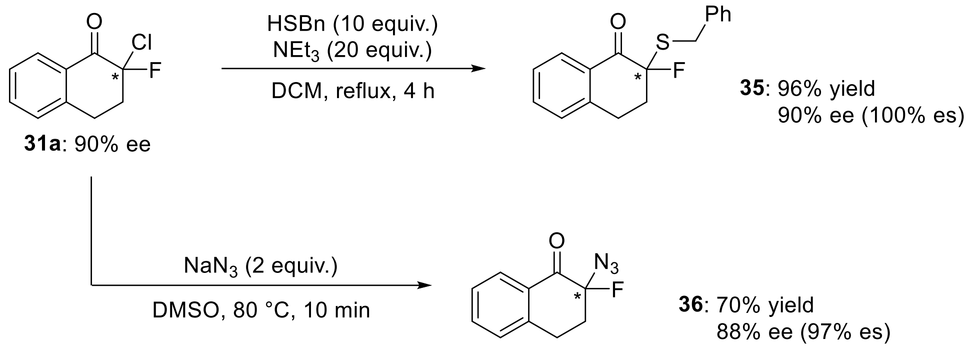
Furthermore, α-bromo-α-chloroketone **34** was synthesized by decarboxylative chlorination of α-bromo-β-keto carboxylic acid **33**. This reaction yielded corresponding tetralone-derived α-bromo-α-chloroketone **34** in 98% yield with 90% ee (Scheme 43).



Scheme 43. Asymmetric synthesis of α-bromo-α-chloroketone.

4.10 S$_N$2 reaction of α-chloro-α-fluoroketone

Finally, S$_N$2 reaction of α-chloro-α-fluoroketone **31a** was carried out. This reaction yielded corresponding α-fluoro-α-surfenyl and α-fluoro-α-azide ketones in good yield with mostly retained enantiopurity (Scheme 44).

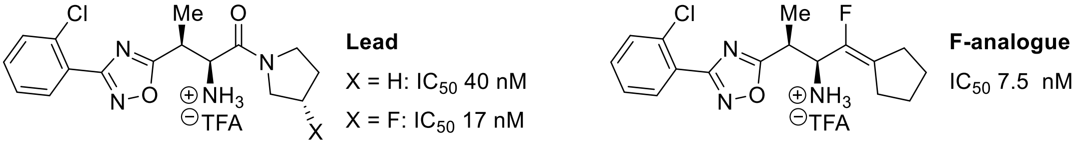


Scheme 44. S_N2 reaction of α-chloro-α-fluoroketone.

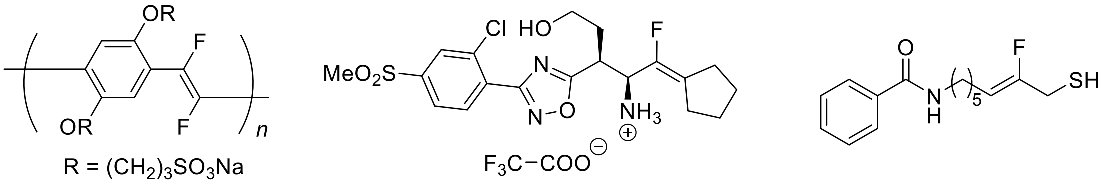
Chapter 5: Enantioselective synthesis of chiral fluoroalkene *via* S$_N$2' reaction

5.1 Importance of fluoroalkenes and design of the reaction

Fluoroalkene is an important substructure especially in medicinally-relevant chemistry because fluoroalkenes sometime act as a bioisostere of peptide. A report says F-analogue of DPP IV inhibitor that is potent remedy for type II diabetes have superior biological acidity compared to its lead compounds (F-analogue IC$_{50}$: 7.5 nM, Lead IC5$_{50}$; 40 and 17 nM, Figure 12). Furthermore, fluoroalkene is expected as potent drugs for some diseases and material of LEC[43].



DPP IV inhibitor (potent remedy for type II diabates)



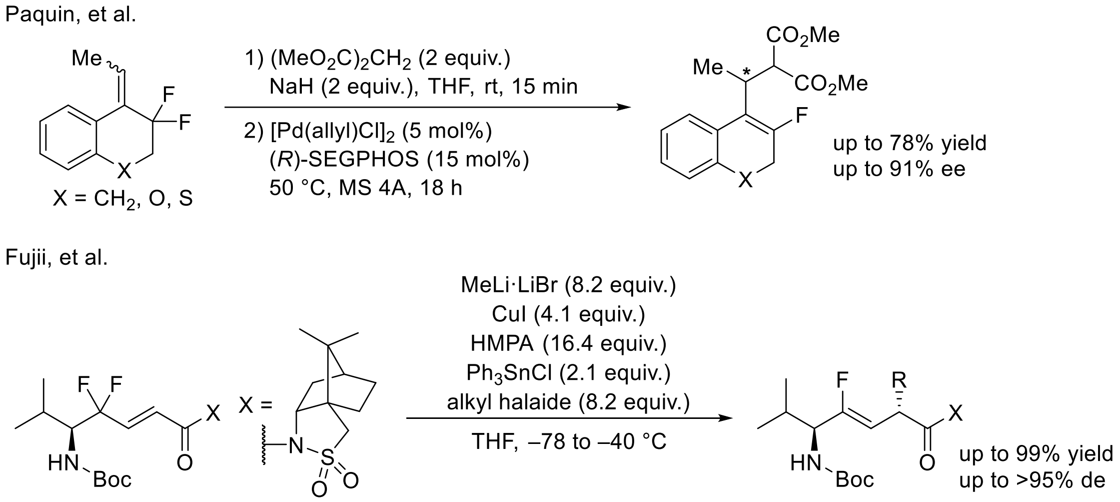
LEC (Candidate molecule)

Drug for frequent urination (Candidate molecule)

Anti-cancer agent (Candidate molecule)

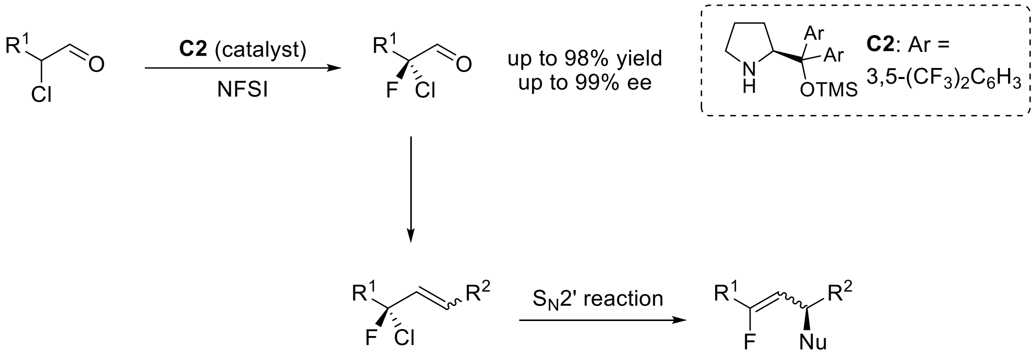
Figure 12. Utilities of fluoroalkenes.

Although the demand in pharmaceutical and material sciences, synthetic method for chiral fluoroalkene have not established yet (Scheme 45)[44]. The research group of Paquin reported S$_N$2' reaction of 3,3-difluoropropenes with sodium malonates as nucleophile. This reaction yielded chiral cyclic fluoroalkenes with high enantioselectivity. However, it was difficult to apply this method into acyclic substrate. On the other hand, Fujii reported the synthesis of acyclic chiral fluoroalkenes by diastereoselective alkylation of metal dienolate that is derived from γ,γ-difluoro-α,β-unsaturated esters.



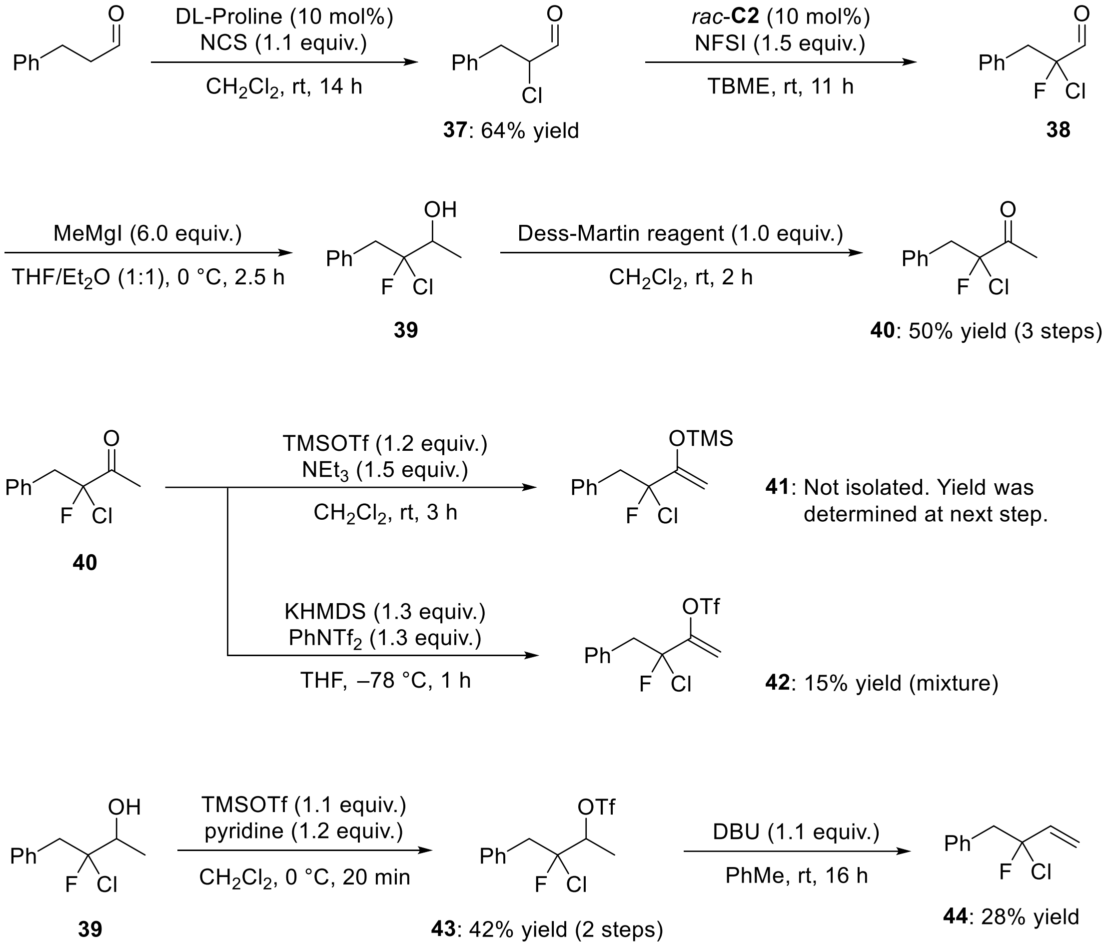
Scheme 45. Synthesis of chiral fluoroalkenes by using 3,3-difluropropenes.

Cosidering the lack of efficient synthetic method for chiral fluoroalkenes, new synthetic strategy for chiral fluoroalkenes was designed as described in Scheme 46. Chiral α-chloro-α-fluoroaldehydes are easily available by fluorination of α-chloroaldehydes in the presence of Hayashi-Jørgensen catalyst **C2** by following literature method. Herein, I designed new synthetic mehod for chiral fluoroalkenes by S_N2' reaction of 3-chloro-3-fluoropropenes which is synthesized by olefination of α-chloro-α-fluoroaldehydes.



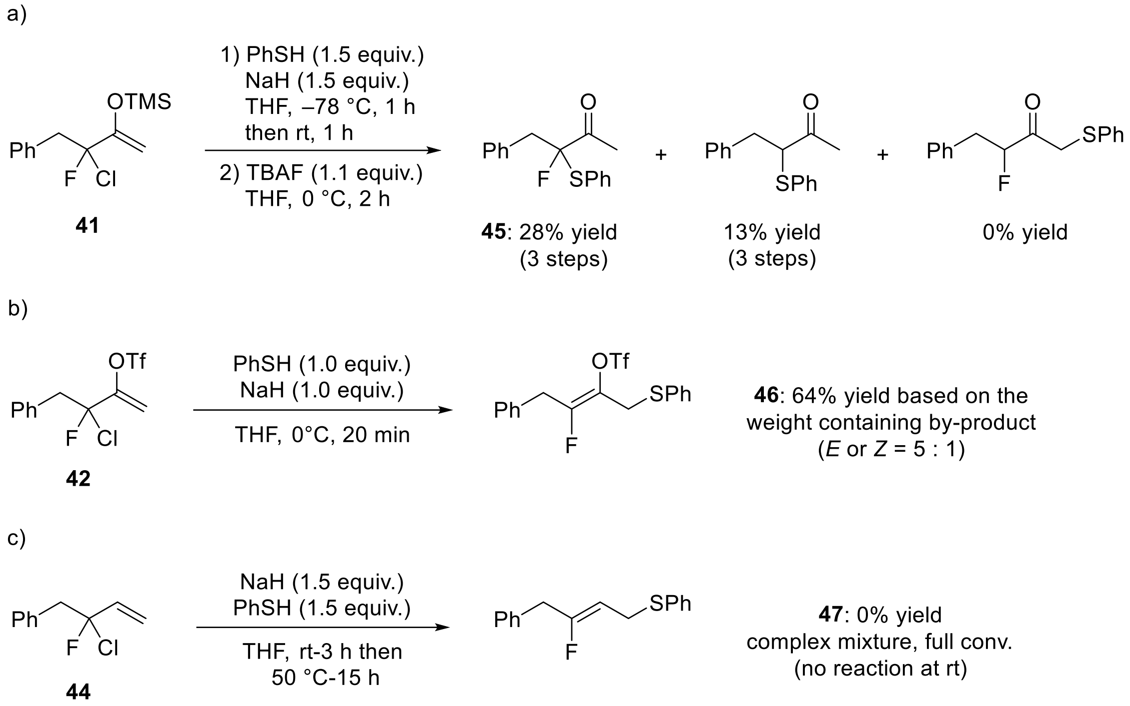
Scheme 46. Design of synthetic method for chiral fluoroalkenes.

Based on the design of the reaction, several 3-chloro-3-fluoropropenes **41**, **42**, **44** were prepared by using racemic α-chloro-α-fluoroaldehyde as shown in Scheme 47. First, α-chloro-α-fluoroaldehyde **38** was converted into corresponding ketone **40** by addition of Grignard reagent (**39**) and subsequent oxidation by Dess-Martin reagent. The resulting ketone **40** was converted to silyl or triflyl enolate **41** and **42**. Furthermore, alcohol **39** was protected by triflyl group and following elimination reaction afforded simple 3-chloro-3-fluoropropene **44**.



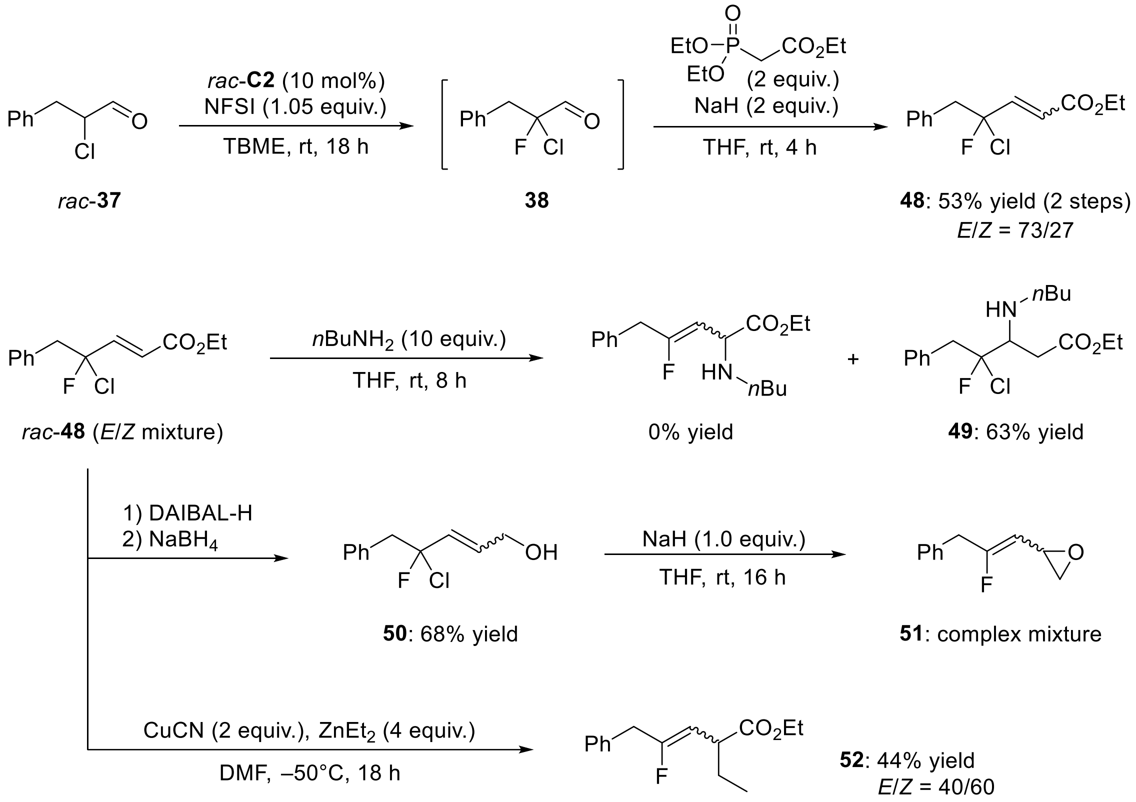
Scheme 47. Synthesis of 3-chloro-3-fluoropropenes **41**, **42**, **44**.

Next, resulting 3-chloro-3-fluoropropenes **41**, **42**, **44** were subjected to $\mathrm{S_N}2$’ reaction (Scheme 48 a–c). However, only desired tetra-substituted fluoroalkene **42** was obtained in 64% yield (Scheme 48b).



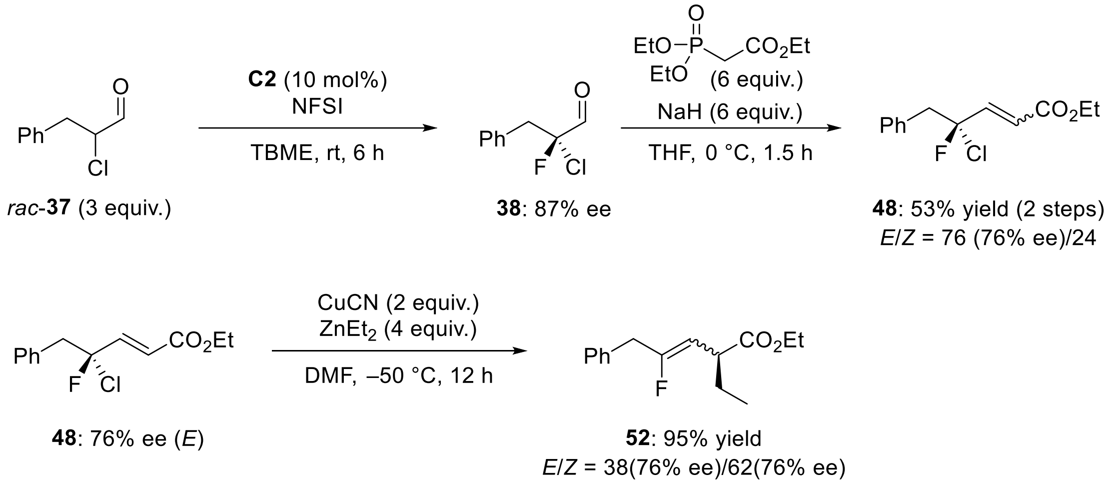
Scheme 48. S_N2’ reaction of 3-chloro-3-fluoropropenes **41**, **42**, **44**.

Then, α-chloro-α-fluoroaldehyde **38** was subjected to Horner-Wadsworth-Emmons reaction to afford corresponding 3-chloro-3-fluoropropene **48** in 53% yield as *E*/*Z* mixture (2 steps, Scheme 49). The resulting 3-chloro-3-fluoropropene **48** was treated with *n*$BuNH_2$ and it furnished only Micheal adduct **49**. Furthermore, ester moiety of the 3-chloro-3-fluoropropene **48** was reduced to alcohol (**50**). When the alcohol **50** was treated with NaH, only complex mixture was obtained (**51**). After further screening of reaction conditions, it was revealed that CuCN and $ZnEt_2$ successfully afforded the corresponding chiral fluoroketone **52** in 44% yield as a mixture of *E*/*Z* isomers (*E*/*Z* =40/60).



Scheme 49. HWE reaction of α-chloro-α-fluoroaldehyde and subsequent S_N2' reactions.

Thus, this reaction was applied to asymmetric synthesis of chiral fluoroalkene to confirm whether this reaction proceed on a stereospecific manner (Scheme 50). Chiral α-chloro-α-fluoroaldehyde **38** was prepared by following literature method by using Hayashi-Jørgensen catalyst **C2** with 87% ee. The resulting α-chloro-α-fluoroaldehyde was converted into 3-chloro-3-fluoropropene **48** in 53% yield. At this step racemization of **48** was observed (76% ee from 87% ee). *E* isomer of 3-chloro-3-fluoropropene **48** was isolable and the enantioselectivity was determined to be 76%. Subsequent S_N2' reaction of **48** yielded corresponding chiral fluoroalkene **52** in 95% yield with retained enantiopurity.

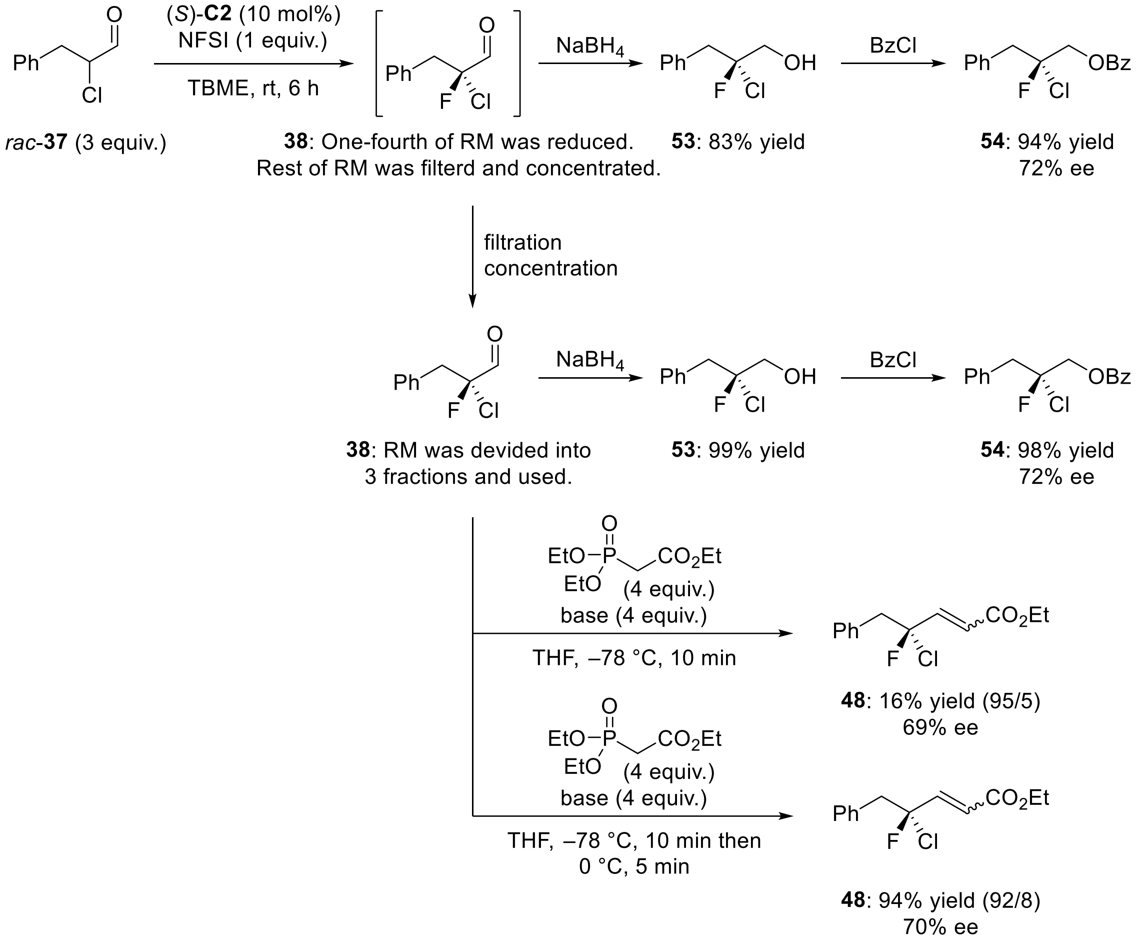


Scheme 50. Asymmetric synthesis of chiral fluoroalkenes.

5.2 Optimization of reaction conditions for HWE reaction

Racemization step in the synthesis of 3-chloro-3-fluoropropene **48** was confirmed as described in Scheme 51. First, the enantiopurity of α-chloro-α-fluoroaldehyde **38** was determined to be 72% after conversion into chlorofluoroalcohol **53** and corresponding benzoate **54**. Then, to omit the possibility of racemization during the workup such as filtration and concentration of α-chloro-α-fluoroaldehyde **38**, after workup, one-third of the crude mixture **38** was reduced to alcohol **53** and ee was determined to be 72%.

Then, rest of crude **38** was used for two HWE reactions. One HWE reaction was quenched at –78 °C and desired propene **48** was obtained in 16% yield with 69% ee (96% es). Another HWE reaction was carried out at –78 °C and quenched at 0 °C. It afforded propene **48** in 94% yield with 70% ee (97% es). As a result, regardless of workup, it was found that racemization occurred at HWE reaction.



rac-**37** (3 equiv.)

38: One-fourth of RM was reduced.
Rest of RM was filterd and concentrated.

53: 83% yield

54: 94% yield
72% ee

38: RM was devided into
3 fractions and used.

53: 99% yield

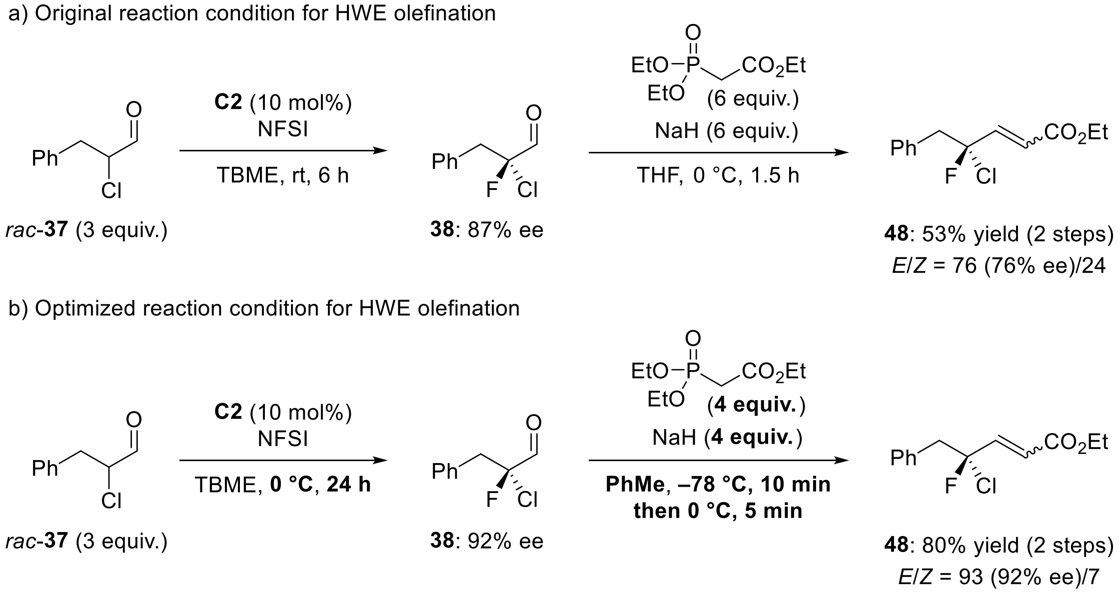
54: 98% yield
72% ee

48: 16% yield (95/5)
69% ee

48: 94% yield (92/8)
70% ee

Scheme 51. Determination of racemization step.

After the screening of reaction conditions for HWE olefination, optimized reaction condition was determined as shown in Scheme 52. Compared to original reaction condition (Scheme 52a), fluorination was carried out at 0 °C and subsequent olefination was carred out at –78 °C in toluene to suppress racemization. Furthermore, due to the stability of oxaphosphetane intermediate at –78 °C, the reaction mixture was warmed to 0 °C and quenched by HCl. As a result, desired 3-chloro-3-fluoropropene **52** was obtained in 70% yield (2 steps) with relatively high diastereoselectivity (*E*/*Z* = 94/6) with mostly retained enantiopurity (99% enantiospecificity).

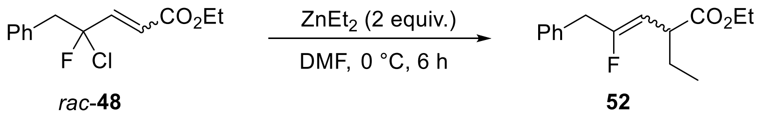


Scheme 52. Optimization of reaction conditions for HWE reaction.

5.3 Asymmetric synthesis of chiral fluoroalkenes

First, to confirm the effect of CuCN, racemic 3-chloro-3-fluoropropene **48** was subjected to S_N2' reaction with $ZnEt_2$ (Table 23, entry 1). This reaction afforded the desired chiral fluoroalkene **52** in 74% yield with 29/71 diastereoselectivity. Then, *E*/*Z* mixture of substrate **48** (*E*/*Z* = 68/32) was employed for the reaction (entry 2), and the yield was decreased to 49%. This is probably because *Z* isomer mainly decomposed during reaction [32-5=27% of excess *Z* isomer, it mostly equal to decreased yield of **52** (74%-49%=25% yield)]. Thus, it was found that *Z* isomer of **48** mainly cause side reactions in the presence of $ZnEt_2$.

Table 23. Effect of diastereoselectivity of substrate.



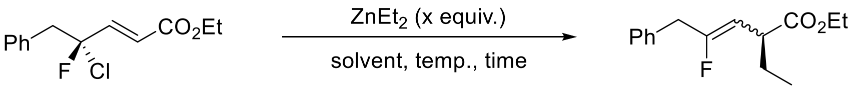
entry	*E*/*Z* (**48**)	conv. (%)[a]	yield (**52**, %)[a]	*E*/*Z* (**52**)
1	95:5	85	74	29:71
2	68:32	92	49	26:74

[a] Determined by ^1H NMR with ethylacetate as an internal standard.

S$_N$2' reaction with ZnEt$_2$ afforded the desired chiral fluoroalkene with higher diastereoselectivity as shown in Scheme 50 and Table 23. Thus, reaction condition was screened with ZnEt$_2$ in several reaction solvents (Table 24). When the reaction was carried out in DMF at 0 °C, desired **52** was obtained with 23/77 of diastereoselectivity and racemization was observed (entry 1). In entry 2, to suppress the racemization, S$_N$2' reaction was carried out at –50 °C and the product was obtained with mostly retained enantiopurity. After stirring for 16 h at –50 °C, the reaction mixture was warmed to 0 °C to confirm the racemization of **52**. As a result, **52** was obtained with decreased enantiopurity (entry 4) and racemization of **52** was confirmed. Furthermore, the used of 4 equiv. of ZnEt$_2$ decreased the yield and *E*/*Z* selectivity of **52** (entry 4).

Then, the reaction solvent was switched to MeCN/DMSO (entry 5) and THF/DMSO (entry 6). Because THF/DMSO showed better *E*/*Z* selectivity, the reaction was carried out at lower temperature (entry 7–9). Unexpectedly, at –50 and –78 °C, generation of opposite enantiomer of *Z* isomer was observed. According to these results, existence of other reaction pathway was confirmed besides of S$_N$2' reaction.

Table 24. S$_N$2' reaction with ZnEt$_2$.

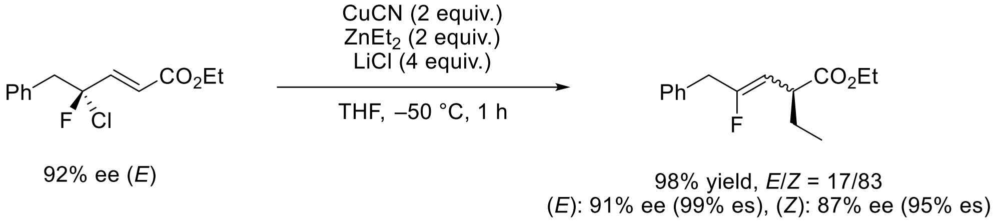


(*E*)-**48** (73% ee) **52**

entry	solvent	x (equiv.)	temp. (°C)	time (h)	yield (conv., %)	*E*/*Z* (**52**)	ee (**52**)
1	DMF	2	0	6	50 (68)[a]	23/77	68/36
2	DMF	2	–50	16	53 (55)[a]	24/76	72/72
3	DMF	2	–50, 0	16, 6	57 (57)[a]	24/76	68/58
4	DMF	4	–50	16	65 (95)[a]	35/65	73/71
5	MeCN/DMSO (9:1)	2	0	3	88 (100)[b]	33/67	72/49
6	THF/DMSO (9:1)	2	0	3	81 (100)[b]	25/75	5/14
7	THF/DMSO (9:1)[c]	2	–50	5	41 (50)[b]	9/91	9/–2
8	THF/DMSO (9:1)[c]	2	–64	5	9 (16)[b]	7/93	18/–22
9	THF/DMSO (9:1)[c]	2	–78	5	no reaction	-	-

[a] Determined by ^{1}H NMR using tetrachloroethane as an internal standard after purification.
[b] Determined by ^{1}H NMR after short silica gel chromatography. [c] DMSO was distilled using CaH$_2$ *in vacuo*.

After the further screening of reaction conditions, S_N2' reaction with CuCN, $ZnEt_2$ and LiCl afforded the desired chiral fluoroalkene with mostly retained enantiopurity (99% es for *E* isomer, 95% es for *Z* isomer) in good *E*/*Z* selectivtity (Scheme 53).



Scheme 53. S_N2' reaction with CuCN, $ZnEt_2$ and LiCl.

Chapter 6: Conclusions

First, enantioselective synthesis of tertiary fluoride was achieved by fluorination of α-branched aldehyde with a newly developed chiral primary amine catalyst. A new chiral primary amine catalyst with binaphthyl backbone was developed and it demonstrated high enantioselectivity in fluorination of α-branched aldehydes (up to 95% ee). Resulting tertiary fluorides were converted into chiral 3-fluoropropenes by following Horner-Wadsworth-Emmons reaction and fluorinated analogue of bioactive compounds such as Flurbiprofen which is known as anti-inflammatory drug. Furthermore, α-fluoroaldehydes were converted into α-hydrxyacetal *via* C-F bond activation on a stereospecitic manner (up to >99% es). After the confirmation of stereochemistry, it was confirmed that this reaction proceeded *via* S_N2 type reaction.

Second, enantioselective synthesis of tertiary chloride was achieved by decarboxylative chlorination of β-keto carboxylic acids in the presence of chiral primary amine catalyst. This reaction afforded various secondary and tertiary α-chloroketones with high enantioselectivity (up to 98% ee). Furthermore, resulting tertiary chloroketone was subjected to S_N2 reactions and this reaction afforded corresponding α-surfenyl or α-azide ketones without loss of enantiopurity (up to >99% es). The absolute configuration of the substrate and the product were determined by X-ray crystallography and it was confirmed that inversion of stereochemistry was surely occurred. Furthermore, this methodology was also applicable to asymmetric synthesis of α-chloro-α-fluoroketones (up to 90% ee) by asymmetric decarboxylative chlorination of α-fluoro-β-keto carboxylic acids. Then, resulting α-chloro-α-fluoroketone was subjected to S_N2 reaction and it yielded the corresponding chiral α-heteroatom-α-fluoroketones with almost retained enantiopurity (up to >99% es).

Finally, asymmetric synthesis of chiral fluoroalkenes was achieved by S_N2' reaction of 3-chloro-3-fluoropropenes. 3-Chloro-3-fluoropropenes which was prepared by Horner-Wadsworth-Emmons reaction of α-chloro-α-fluoroaldehydes was subjected to S_N2' reaction with CuCN, $ZnEt_2$ and LiCl. The reaction yielded the desired chiral fluoroalkene with mostly retained enantiopurity (99% es for *E* isomer, 95% es for *Z* isomer) in good *E*/*Z* selectivtity.

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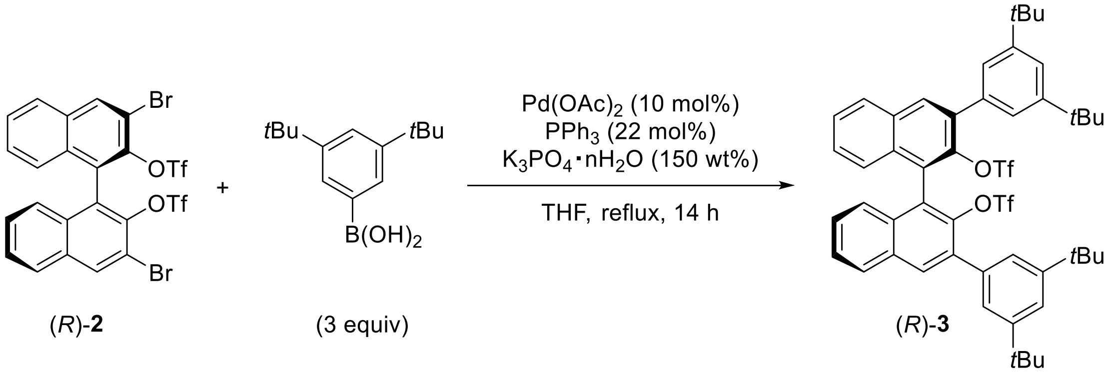
Kazumasa Kitahara

Experimental section

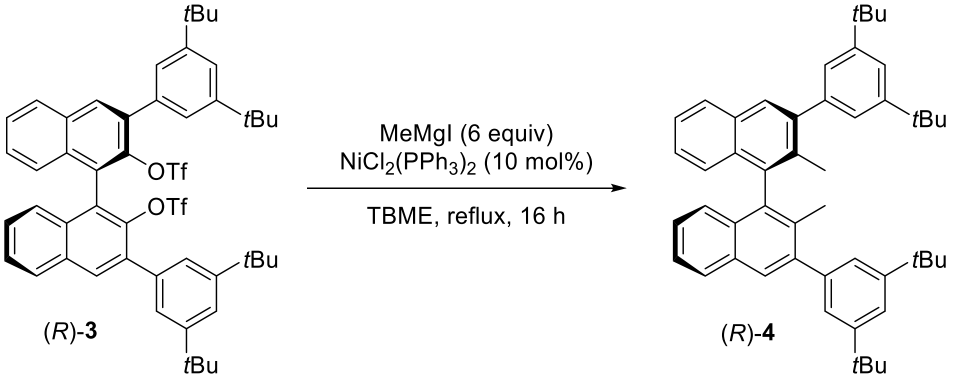
General methods: All non-aqueous reactions were carried out in dried glassware under an argon atmosphere and stirred using magnetic stir-plates. Thin-layer chromatography analyses were performed using pre-coated silica gel plates with a fluorescent indicator (F254) (Merck Millipore, Darmstadt, Germany). Visualization was accomplished by ultraviolet (UV) light (254 nm), potassium permanganate, phosphomolybdic acid, or *p*-anisaldehyde. Flash column chromatography was performed using silica gel 60 (mesh size 40–100) supplied by Kanto Chemical Co., Inc. (Tokyo, Japan). ^{1}H, ^{13}C, and ^{19}F nuclear magnetic resonance (NMR) spectra were recorded on a JNM-ECS400 (400 MHz ^{1}H, 100 MHz ^{13}C, 376 MHz ^{19}F) or a JNM-ECX500 (500 MHz ^{1}H, 126 MHz ^{13}C, 470 MHz ^{19}F) instrument (JEOL Ltd., Tokyo, Japan). Chemical shift values (δ) are reported in ppm (tetramethylsilane δ 0.00 ppm, residual acetone δ 2.05 or residual methanol δ 3.30 ppm for ^{1}H; hexafluorobenzene δ −162.2 ppm for ^{19}F; residual chloroform δ 77.0 ppm, acetone δ 29.8 ppm or methanol δ 49.0 ppm for ^{13}C). All ^{13}C NMR spectra were recorded with ^{1}H-decoupling. Infrared (IR) spectra were recorded on an FT/IR-4600 instrument (JASCO Co., Ltd., Tokyo, Japan). Direct analyses in real time (DART) mass (positive mode) analyses were performed on a JMS-T100TD time-of-flight mass spectrometer (JEOL Ltd.). Melting points were recorded on a YANACO MP-500P micro melting point apparatus (Japan). Optical rotations were measured on a P-1030 digital polarimeter (JASCO Co., Ltd.). Analytical high-performance liquid chromatography (HPLC) was performed on a PU1586 instrument with a MD-2018 plus diode array detector or PU1586 with a UV-1575 UV/Vis detector (JASCO Co., Ltd.) using a chiral column under the conditions described below. The enantiomeric purity of the compounds was determined by HPLC analyses using chiral stationary phase columns.

Materials: Commercial grade reagents and solvents were used without further purification unless otherwise noted. Anhydrous acetonitrile, ethyl acetate, dimethylformamide (DMF), dimethyl sulfoxide (DMSO). *t*-butyl methyl ether (TBME), methanol, ethylene glycol and triethylamine were purchased from Sigma-Aldrich (St. Louis, MO). Anhydrous toluene, dichloromethane, tetrahydrofurane (THF) were purchased from Kanto Chemical Co., Inc. and used after purification by a Glass Contour solvent dispensing system (Pure Process Technology, Nashua, NH). Benzene were purchased from Kanto Chemical Co. Inc. and used without purification. β-Ketocarboxylic acids were synthesized by acidolysis of the corresponding *tert*-butyl β-ketoesters. We confirmed that the optical purity of selected products **9a** and **12a** did not change even after chromatographic purification using silica gel and subsequent solvent evaporation[1].

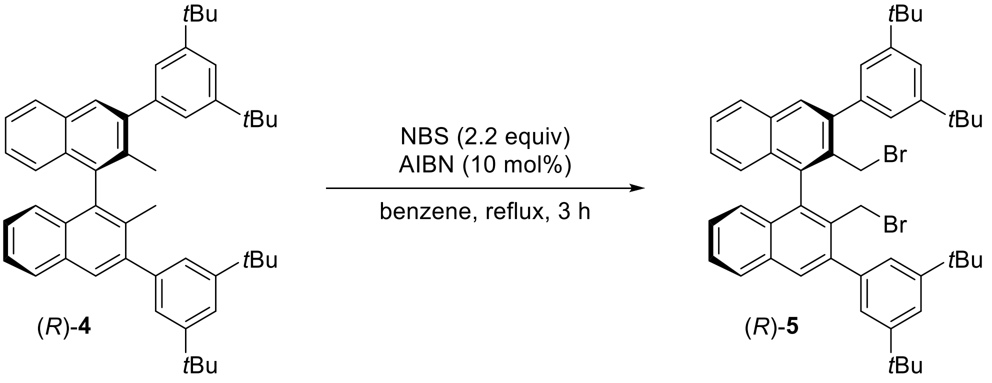
Synthesis and characterization of chiral primary amine catalysts



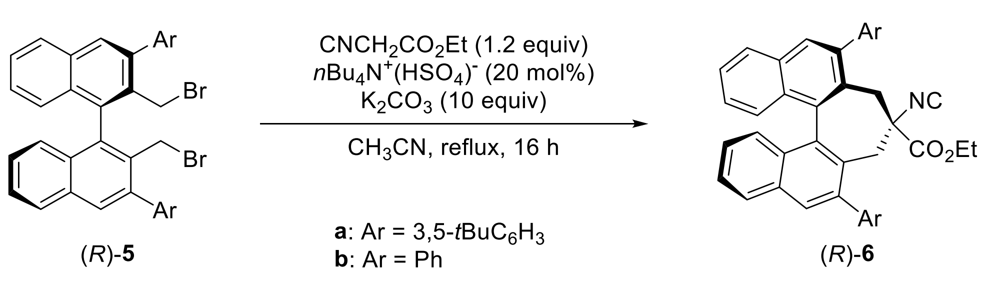
A solution of (*R*)-**2**[2] (3 mmol), 3,5-di-*t*-Bu-phynylboronic acid (9 mmol, 3 equiv.), $Pd(OAc)_2$ (67.4 mg, 0.3 mmol, 10 mol%), PPh_3 (173.1 mg, 0.66 mmol, 22 mol%), and $K_3PO_4{\cdot}nH_2O$ (150 wt%) in dry THF (30 mL) was degassed by bubbling argon through this solution for 30 min. The solution was refluxed for 15 h under argon atmosphere. The resulting mixture was poured into saturated aq. NH_4Cl, and the whole mixture was filtered to remove the catalyst, then extracted with ethyl acetate. The organic extracts were dried over Na_2SO_4 and concentrated. The crude mixture was purified by silica gel column chromatography (hexane:CH_2Cl_2 = 5:1) to give 75% yield of (*R*)-**3** (white solid). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 2H), 7.99 (d, *J* = 7.9 Hz, 2H), 7.58–7.36 (m, 12H), 1.40 (s, 36H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.9, 144.3, 135.5, 135.3, 132.9, 132.5, 132.5, 128.3, 127.6, 127.4, 127.3, 125.5, 124.0, 122.2, 119.2, 116.0, 34.9, 31.3; ^{19}F NMR (376MHz, $CDCl_3$): δ –75.8; $[\alpha]_D^{23}$ –194.3 (c = 6.4, $CHCl_3$); HRMS (DART): Anal. For $C_{50}H_{53}F_6O_6S_2^{+1}$ $[M+H]^+$ Calcd.: 927.3188, Found: 927.3185.



To a solution of (*R*)-**3** (1.46 mmol) and $NiCl_2(PPh_3)_2$ (95.5 mg, 0.146 mmol, 10 mol%) in TBME (14.6 mL) was added 3M ethereal solution of MeMgI (2.92 mL, 8.76 mmol, 6 equiv.) at 0 ºC. The solution was refluxed for 16 h under argon atmosphere. This mixture was poured into ice-cooled 1M HCl, and the whole mixture was filtered to remove the catalyst. The filtrate was poured into saturated aq. $NaHCO_3$, and extracted with dichloromethane. The organic extracts were dried over Na_2SO_4 and concentrated. The crude mixture was purified by silica gel column chromatography (hexane:CH_2Cl_2 = 10:1) to give 91% yield of (*R*)-4 (white solid). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94–7.87 (m, 4H), 7.48–7.45 (m, 2H), 7.41–7.38 (m, 2H), 7.36–7.34 (m, 4H), 7.25–7.18 (m, 4H), 2.03 (s, 6H), 1.40 (s, 36H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.2, 142.4, 141.4, 136.6, 132.9, 132.1, 132.0, 128.2, 127.9, 126.0, 125.8, 125.3, 123.9, 120.7, 35.0, 31.6, 18.4; $[\alpha]_D^{21}$ +51.5 (c = 9.5, $CHCl_3$); HRMS (DART): Anal. For $C_{50}H_{58}{}^{+1}$ $[M+H]^+$ Calcd.: 659.4617, Found: 659.4616.



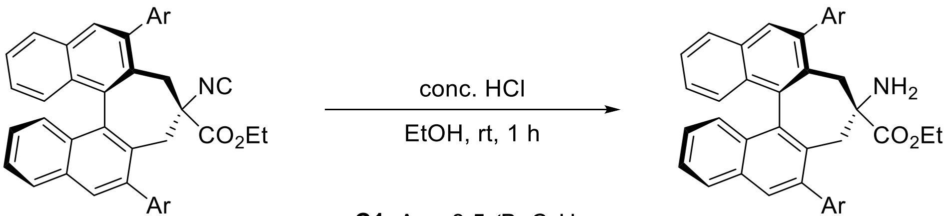
A solution of (*R*)-**4** (3.24 mmol), *N*-bromosuccinimide (NBS) (1.27 g, 7.13 mmol, 2.2 equiv.), and 2,2'-azobis(isobutyronitrile) (AIBN) (53.2 mg, 0.324 mmol, 10 mol%) in benzene (16.2 mL) was refluxed for 3 h. After being cooled to room temperature, the mixture was poured into water and extracted with ethyl acetate. The organic extracts were dried over Na_2SO_4 and concentrated. The crude mixture was purified by silica gel column chromatography (hexane:CH_2Cl_2 = 10:1) to give 97% yield of (*R*)-**5** (white solid). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98–7.88 (m, 4H), 7.50–7.46 (m, 8H), 7.29–7.18 (m, 4H), 4.29 (s, 4H), 1.40 (s, 36H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 142.2, 139.6, 136.5, 133.2, 132.5, 131.8, 130.1, 127.8, 127.4, 127.1, 126.2, 124.0, 121.2, 35.0, 32.7, 31.6; $[\alpha]_D^{22}$ +31.7 (c = 9.4, $CHCl_3$); HRMS (DART): Anal. For $C_{50}H_{57}Br_2{}^{+1}$ $[M+H]^+$ Calcd.: 815.2827, Found: 815.2827.



To a suspension of (*R*)-**5a** or (*R*)-**5b**[2] (5.25 mmol), tetrabutylammonium hydrogen sulfate (356.5 mg, 1.05 mmol, 20 mol%) and K_2CO_3 (7.26 g, 52.5 mmol, 10 equiv.) in CH_3CN (105 mL) was added ethyl isocyanoacetate (688 μL, 6.30 mmol, 1.2 equiv.) at 0 ºC. The solution was refluxed for 16 h under argon atmosphere. The resulting mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel to afford (*R*)-**6**.

(*R*)-**6a**: The crude mixture was purified by silica gel column chromatography (hexane:CH_2Cl_2 = 3:1) to give 48% yield of (*R*)-**6a** (white solid). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98–7.92 (m, 3H), 7.88 (s, 1H), 7.65–7.14 (m, 12H), 4.00 (d, J = 14.0 Hz, 1H), 3.76–3.68 (m, 1H), 3.37–3.27 (m, 2H), 3.06 (d, J = 14.3 Hz, 1H), 2.91 (d, J = 14.0 Hz, 1H), 1.37 (s, 36H), 0.82 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 160.2, 150.5, 142.2, 140.7, 139.8, 139.6, 136.3, 135.6, 133.0, 132.6, 131.1, 131.0, 130.5, 129.8, 129.5, 129.5, 128.2, 127.3, 127.1, 126.1, 126.0, 125.9, 125.8, 124.7, 121.2, 120.9, 70.6, 62.1, 39.0, 34.9, 34.6, 31.5; $[\alpha]_D^{23}$ +13.0 (c = 6.5, $CHCl_3$); HRMS (DART): Anal. For $C_{55}H_{62}N_1O_2^{+1}$ $[M+H]^+$ Calcd.: 768.4781, Found: 768.4781.

(*R*)-**6b**: The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 10 : 1) to give 69% of (*R*)-**6b** (white solid). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.93 (dd, J = 22.9, 8.2 Hz, 2H), 7.82 (s, 1H), 7.51–7.20 (m, 16H), 3.88–3.80 (m, 1H), 3.77 (d, J = 13.7 Hz, 1H), 3.56–3.48 (m, 1H), 3.32 (d, J = 14.3 Hz, 1H), 3.09 (d, J = 14.3 Hz, 1H), 2.84 (d, J = 14.0 Hz, 1H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 159.8, 141.0, 140.6, 139.8, 136.0, 135.5, 131.2, 131.1, 130.6, 130.1, 130.1, 129.6, 129.4, 128.3, 128.2, 128.2, 128.1, 127.2, 127.2, 127.1, 127.0, 126.2, 126.1, 126.1, 126.1, 70.7, 62.6, 38.9, 34.8. 13.4; $[\alpha]_D^{30}$ +3.5 (c = 0.74, $CHCl_3$); HRMS (DART): Anal. For $C_{39}H_{30}N_1O_2^{+1}$ $[M+H]^+$ Calcd.: 544.2277, Found: 544.2280.



(*R*)-**6**

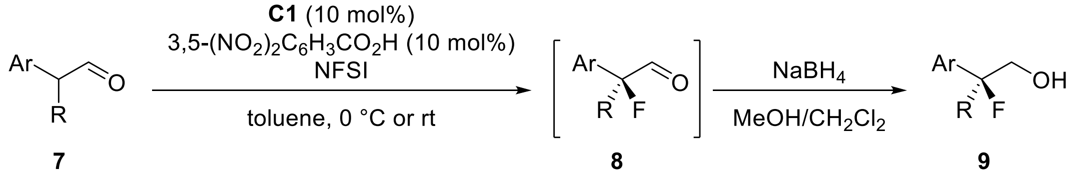
C1: Ar = 3,5-*t*BuC_6H_3
6b': Ar = Ph

To a solution of (*R*)-**6** (2.3 mmol) in ethanol (230 mL) was added conc. HCl (6.1 mL) at 0 ºC. The solution was stirred at room temperature for 1 h under argon atmosphere. The resulting mixture was poured into ice-cooled saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel to afford the products.

(*R*)-**C1**: The crude mixture was purified by silica gel column chromatography (hexane:CH_2Cl_2 = 1:1) to give 86% yield of (*R*)-**C1** (white solid). ^{1}H NMR (400 MHz, C_6D_6): δ 8.02 (s, 2H), 7.76 (dd, *J* = 8.4, 8.0 Hz, 2H), 7.63–7.51 (m, 8H), 7.24–7.18 (m, 2H), 7.01–6.94 (m, 2H), 3.83 (d, *J* = 13.4 Hz, 1H), 3.60–3.54 (m, 1H), 3.49 (d, *J* = 13.7 Hz, 1H), 3.36–3.28 (m, 1H), 3.24 (d, *J* = 13.7 Hz, 1H), 2.69 (d, *J* = 13.4 Hz, 1H), 1.31 (s, 36H), 0.55 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 174.2, 150.5, 143.0, 142.0, 141.6, 141.4, 136.5, 136.1, 134.3, 134.0, 133.2, 132.9, 132.0, 132.0, 129.9, 129.1, 128.6, 126.2, 126.1, 125.9, 125.9, 125.5, 125.4, 120.9, 120.6, 68.8, 60.4, 40.3, 36.6, 35.0, 31.6, 13.7; The enantiopurity was determined by HPLC (hexane : 2-propanol = 300 : 1; 0.5 mL/min; using a CHIRALPAK IB-3 column (0.46 cmφ × 25 cm)): 8.7 min (minor) and 9.4 min (major); $[\alpha]_D^{27}$ –14.1 (c = 1.1, $CHCl_3$); HRMS (DART): Anal. For $C_{54}H_{64}N_1O_2^{+1}$ $[M+H]^+$ Calcd.: 758.4937, Found: 758.4935.

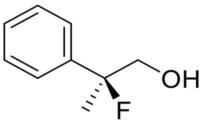
(*R*)-**6b'**: The crude mixture was purified by silica gel column chromatography (hexane:ethyl acetate = 3 : 1) to afford 79% of (*R*)- **6b'** (white solid). ^{1}H NMR (500 MHz, C_6D_6): δ 7.81 (d, *J* = 23.7 Hz, 2H), 7.74 (dd, *J* =16.8, 8.0 Hz, 2H), 7.60 (dd, *J* = 8.4, 3.1 Hz, 2H), 7.39–7.09 (m, 12H), 7.05–6.99 (m, 2H), 3.66–3.60 (m, 1H), 3.46 (d, *J* = 13.8 Hz, 1H), 3.40–3.34 (m, 2H), 3.12 (d, *J* = 13.8 Hz, 1H), 2.51 (d, *J* = 13.4 Hz, 1H), 0.98 (s, 2H), 0.58 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 174.4, 142.5, 142.1, 142.0, 140.7, 136.2, 135.9, 134.0, 133.9, 133.0, 132.9, 132.0, 131.9, 130.7, 130.6, 129.5, 129.3, 128.7, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.1, 126.9, 126.2, 126.2, 126.0, 125.9, 68.8, 60.6, 40.0, 36.6; $[\alpha]_D^{28}$ –16.8 (c = 0.9, $CHCl_3$); HRMS (DART): Anal. For. $C_{38}H_{32}N_1O_2^{+1}$ $[M+H]^+$ Calcd.: 534.2433, Found: 534.2431.

Enantioselective synthesis and characterization of α-fluoroaldehydes



General procedure for fluorination of α-branched aldehydes: All of aldehydes were purified before the reactions by flash column chromatography on silica gel or Kugelrohr distillation. To a solution of catalyst **C1** (20 mg, 0.026 mmol, 10 mol%) in toluene (0.54 mL) was added 3,5-dinitrobenzoic acid (5.5 mg, 0.026 mmol, 10 mol%), aldehydes **7** (0.39 mmol, 1.5 equiv.), and N-fluorobenzenesulfonimide (NFSI) (0.26 mmol, 82 mg, 1 equiv.) at 0 ºC. The reaction mixture was stirred at room temperature or at 0 °C, then poured into MeOH/CH_2Cl_2 (1:4, 1.3 mL) at 0 °C. To this solution, $NaBH_4$ (1.6 mmol, 6 equiv.) was added, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with Et_2O. The organic layer was dried over Na_2SO_4, concentrated, and chromatographed on silica gel to give **9**.

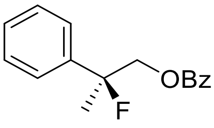
(*S*)-2-Fluoro-2-phenylpropan-1-ol [(*S*)-9a]



The reaction was carried out at 0 °C and stirred for 48 h. The crude mixture was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1) to give 86% yield of (*S*)-**9a** (white solid). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.27 (m, 5H), 3.88–3.69 (m, 2H), 2.50 (s, 1H), 1.69 (d, *J* = 23.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.5 (d, *J* = 21.1 Hz), 128.4, 127.8, 124.4 (d, *J* = 9.6 Hz), 97.8 (d, *J* = 172.5 Hz), 69.5 (d, *J* = 24.9 Hz), 23.1 (d, *J* = 24.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ –157.6 (m); $[\alpha]_D^{22}$ +14.3 (c = 0.87, $CHCl_3$); HRMS (DART): Anal. For $C_9H_{11}F_1O_1^{+1}$ $[M+NH_4]^+$ Calcd.: 172.1138, Found: 172.1135. The enantiopurity was determined after conversion into the corresponding benzoate (*S*)-**9a’**. The absolute configuration of the major enantiomer was determined to be *S* by comparing the specific rotation with that in the literature[3].

General procedure for benzoylation of 9: A flame-dried flask under argon was charged with **9** (0.30 mmol) and CH_2Cl_2 (1.0 mL). Triethylamine (0.60 mmol), benzoyl chloride (0.45 mmol), and 4-dimethylaminopyridine (0.03 mmol) were added to this solution, and the mixture was stirred for 1 h at 0 °C. The mixture was diluted by saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography to afford **9’**.

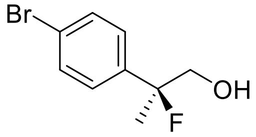
(*S*)-2-Fluoro-2-phenylpropyl benzoate [(*S*)-9a’]



The crude mixture was purified by flash column chromatography on silica gel (hexane:ethylacetate = 20:1) to afford the desired benzoate (*S*)-**9a’** in 85 % yield (white solid, 95% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.58–7.54 (m, 1H), 7.46–7.38 (m, 6H), 7.36–7.32 (m, 1H), 4.63–4.50 (m, 2H), 1.81 (d, *J* = 22.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 141.1 (d, *J* = 22.0 Hz), 133.1, 129.7, 128.4, 128.4, 128.0, 124.5, 124.4, 95.6 (d, *J* = 176.4 Hz), 69.7 (d, *J* = 24.9 Hz), 23.6 (d, *J* = 24.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ –153.8 (m); $[\alpha]_D^{20}$ +12.1 (c = 1.6, $CHCl_3$); HRMS (DART): Anal. For $C_{16}H_{15}F_1O_2^{+1}$ $[M+NH_4]^+$

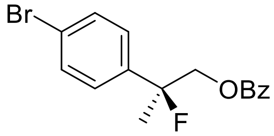
Calcd.: 276.1400, Found: 276.1400. The enantiopurity was determined by HPLC (hexane:2-propanol = 99:1; 0.5 mL/min; using a CHIRALPAK ID column (0.46 cmφ × 25 cm)): 16.7 min (major) and 19.0 min (minor).

2-(4-Bromophenyl)-2-fluoropropan-1-ol (9b)



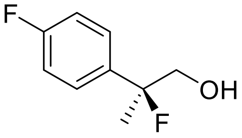
The reaction was stirred for 20 h at 0 °C. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1) to give 98% yield of **9b** (white solid). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.52 (d, *J* = 8.9 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 3.87–3.70 (m, 2H), 1.83 (t, *J* = 6.6 Hz, 1H), 1.68 (d, *J* = 22.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 140.6 (d, *J* = 22.0 Hz), 131.6, 126.3 (d, *J* = 9.6 Hz), 121.9, 97.5 (d, *J* = 172.5 Hz), 69.3 (d, *J* = 24.9 Hz), 23.1 (d, *J* = 24.9 Hz); ^{19}F NMR (376 MHz, CDCl$_3$): δ –157.8 (m); $[\alpha]_D^{20}$ +18.4 (c = 0.31, CHCl$_3$); HRMS (DART): Anal. For $C_9H_{10}Br_1F_1O_1^{+1}$ $[M+NH_4]^+$ Calcd.: 250.0243, Found: 250.0245. The enantiopurity was determined after conversion into the corresponding benzoate **9b’**.

2-(4-Bromophenyl)-2-fluoropropyl benzoate (9b’)



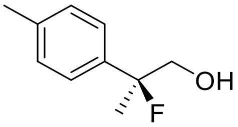
According to the general procedure, **9b** was converted into **9b’**, the crude mixture was purified by flash column chromatography on silica gel (hexane:ethylacetate = 20:1) to afford the desired benzoate **9b’** in 93 % yield (white solid, 92% ee). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.99 (d, *J* = 7.3 Hz, 2H), 7.58–7.51 (m, 3H), 7.45–7.41 (m, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 4.63–4.48 (m, 2H), 1.79 (d, *J* = 22.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 165.9, 140.2 (d, *J* = 22.0 Hz), 133.3, 131.6, 129.7, 129.5, 128.4, 126.3 (d, *J* = 9.6 Hz), 122.2, 95.3 (d, *J* = 176.4 Hz), 69.3 (d, *J* = 25.9 Hz), 23.6 (d, *J* = 24.0 Hz); ^{19}F NMR (376 MHz, CDCl$_3$): δ –153.9 (m); $[\alpha]_D^{29}$ +19.0 (c = 1.6, CHCl$_3$); HRMS (DART): Anal. For $C_{16}H_{14}Br_1F_1O_2^{+1}$ $[M+NH_4]^+$ Calcd.: 354.0505, Found: 354.0503. The enantiopurity was determined by HPLC (hexane:2-propanol = 99:1; 0.5 mL/min; using a CHIRALPAK ID column (0.46 cmφ × 25 cm)): 17.8 min (major) and 21.2 min (minor).

2-Fluoro-2-(4-fluorophenyl)propan-1-ol (9c)



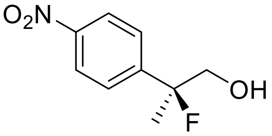
The reaction was carried out at 0 °C and stirred for 48 h. The crude mixture was purified by silica gel column chromatography (hexane:diethyl ether = 2:1–1:1) to give 76% yield of **9c** (white solid; including ca. 3% of an inseparable by-product, 90% ee). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.34–7.32 (m, 2H), 7.08–7.04 (m, 2H), 3.85–3.69 (m, 2H), 1.94 (bs, 1H), 1.68 (d, J = 22.6 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$): δ 162.3 (d, J = 247.1 Hz), 137.3 (dd, J = 22.2, 3.0 Hz), 126.3 (t, J = 8.4 Hz), 115.3 (d, J = 21.6 Hz), 97.6 (d, J = 171.5 Hz), 69.5 (d, J = 26.4 Hz), 23.2 (d, J = 25.2 Hz); ^{19}F NMR (470 MHz, CDCl$_3$): δ –115.2 (s), –156.3 (m); $[\alpha]_D^{23}$ +10.9 (c = 0.80, CHCl$_3$); HRMS (DART): Anal. For $C_9H_{10}F_2O_1^{+1}$ $[M+NH_4]^+$ Calcd.: 190.1044, Found: 190.1044. The enantiopurity was determined by HPLC (hexane:2-propanol = 20:1; 1.0 mL/min; using a CHIRALPAK AD-H column (0.46 cmφ × 25 cm)): 11.5 min (minor) and 12.8 min (major).

2-Fluoro-2-(p-tolyl)propan-1-ol (9d)



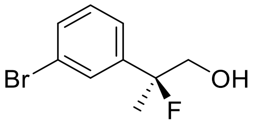
The reaction was carried out at 0 °C and stirred for 48 h. The crude mixture was purified by silica gel column chromatography (hexane:diethyl ether = 2:1–1:1) to give 88% yield of **9d** (white solid, 93% ee). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.25 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 3.86–3.68 (m, 2H), 2.35 (s, 3H), 1.92 (t, J = 6.1 Hz, 1H), 1.68 (d, J = 22.6 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$): δ 138.5 (d, J = 21.6 Hz), 137.6, 129.1, 124.4 (d, J = 8.4 Hz), 97.8 (d, J = 171.5 Hz), 69.6 (d, J = 25.2 Hz), 23.1 (d, J = 24.0 Hz), 21.0; ^{19}F NMR (470 MHz, CDCl$_3$): δ –157.0 (m); $[\alpha]_D^{23}$ +14.4 (c = 1.25, CHCl$_3$); HRMS (DART): Anal. For $C_{10}H_{13}F_1O_1^{+1}$ $[M+H]^+$ Calcd.: 169.1029, Found: 169.1029. The enantiopurity was determined by HPLC (hexane:2-propanol = 20:1; 1.0 mL/min; using a CHIRALPAK AD-H column (0.46 cmφ × 25 cm)): 12.2 min (major) and 14.7 min (minor).

2-Fluoro-2-(4-nitrophenyl)propan-1-ol (9e)



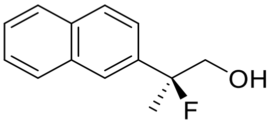
The reaction was stirred for 48 h at 0 °C. The crude mixture was purified by silica gel chromatography (hexane : diethyl ether = 1 : 1–1 : 2) to give 88% yield of **9e** (white solid; including small amount of inseparable by-product, 88% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 3.91–3.80 (m, 2H), 2.16 (s, 1H), 1.72 (d, *J* = 22.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 148.9 (d, *J* = 21.6 Hz), 147.4, 125.6 (d, *J* = 9.6 Hz), 123.6, 97.5 (d, *J* = 173.9 Hz), 69.0 (d, *J* = 25.2 Hz), 23.2 (d, *J* = 24.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ –158.0 (m); $[\alpha]_D^{28}$ +19.0 (c = 1.1, $CHCl_3$); HRMS (DART): Anal. For $C_{19}H_{10}FNO_3^{+1}$ $[M+NH_4]^+$ Calcd.: 217.0988, Found: 217.0989. The enantiopurity was determined by HPLC (hexane : 2-propanol = 9 : 1; 1 mL/min; using a CHIRALCEL OD-H column (0.46 cmφ × 25 cm)): 9.3 min (minor) and 10.4 min (major).

2-(3-Bromophenyl)-2-fluoropropan-1-ol (9g)



The reaction was stirred for 48 h at 0 °C. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1) to give 77% yield of **9g** (colorless oil, 93% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (s, 1H), 7.48–7.41 (m, 1H), 7.32–7.20 (m, 2H), 3.87–3.70 (m, 2H), 1.92 (bs, 1H), 1.67 (d, *J* = 22.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8 (d, *J* = 22.0 Hz), 130.9, 130.0, 127.7 (d, *J* = 10.5 Hz), 123.1 (d, *J* = 8.6 Hz), 122.7, 97.3 (d, *J* = 174.4 Hz), 69.3 (d, *J* = 24.9 Hz), 23.2 (d, *J* = 24.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ –157.8 (m); $[\alpha]_D^{20}$ +12.3 (c = 0.32, $CHCl_3$); HRMS (DART): Anal. For $C_9H_{10}BrFO^{+1}$ $[M+NH_4]^+$ Calcd.: 250.0245, Found: 250.0243. The enantiopurity was determined by HPLC (hexane : 2-propanol = 50 : 1; 1 mL/min; using a CHIRALPAK ID-3 column (0.46 cmφ × 25 cm)): 12.8 min (major) and 27.2 min (minor).

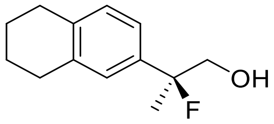
2-Fluoro-2-(naphthalen-2-yl)propan-1-ol (9h)



The reaction was stirred for 21 h at 0 °C. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1) to give 98% yield of **9h** (white solid, 92% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86–7.82 (m, 4H), 7.52–7.47 (m, 2H), 7.42 (d, *J* = 8.8 Hz, 1H), 3.97–3.78 (m, 2H), 2.01 (bs, 1H), 1.77 (d, *J* = 22.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8 (d, *J* = 21.1 Hz), 132.9, 132.7, 128.3, 128.2, 127.6, 126.4, 126.3, 123.5 (d, *J* = 10.5 Hz), 122.4 (d, *J* = 8.6 Hz), 98.0 (d, *J* = 172.5 Hz), 69.4 (d, *J* = 25.9 Hz), 23.2 (d, *J* = 24.9 Hz); ^{19}F NMR (376

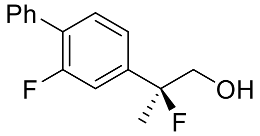
MHz, $CDCl_3$): δ –157.2 (m); $[\alpha]_D^{20}$ +16.4 (c = 1.4, $CHCl_3$); HRMS (DART): Anal. For $C_{13}H_{13}F_1O_1^{+1}$ $[M+NH_4]^+$ Calcd.: 222.1294, Found: 222.1294. The enantiopurity was determined by HPLC (hexane : 2-propanol = 99 : 1; 2 mL/min; using a CHIRALPAK ID column (0.46 cmφ × 25 cm)): 15.2 min (major) and 25.0 min (minor).

2-Fluoro-2-(5,6,7,8-tetrahydronaphthalen-2-yl)propan-1-ol (9i)



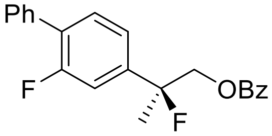
The reaction was stirred for 20 h at 0 °C. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1) to give 95% yield of **5i** (white solid, 92% ee). ^1H NMR (400 MHz, $CDCl_3$): δ 7.10–7.05 (m, 3H), 3.88–3.69 (m, 2H), 2.91–2.76 (m, 4H), 1.82–1.79 (m, 5H), 1.67 (d, *J* = 22.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6 (d, *J* = 21.1 Hz), 137.2, 136.9, 129.2, 125.2 (d, *J* = 9.6 Hz), 121.5 (d, *J* = 8.6 Hz), 97.8 (d, *J* = 171.6 Hz), 69.6 (d, *J* = 24.9 Hz), 29.5, 29.0, 23.3, 23.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ –157.2 (m); $[\alpha]_D^{20}$ +17.3 (c = 0.63, $CHCl_3$); HRMS (DART): Anal. For $C_{13}H_{17}F_1O_1^{+1}$ $[M+NH_4]^+$ Calcd.: 226.1607, Found: 226.1608. The enantiopurity was determined by HPLC (hexane : 2-propanol = 50 : 1; 1 mL/min; using a CHIRALPAK IC-3 column (0.46 cmφ × 25 cm)): 18.1 min (major) and 21.3 min (minor).

2-Fluoro-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propan-1-ol (9j, 92% *ee*)



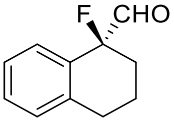
The reaction was stirred for 24 h at 0 °C. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1) to give 98% yield of **9j** (white solid). ^1H NMR (500 MHz, $CDCl_3$): δ 7.56–7.53 (m, 2H), 7.48–7.41 (m, 3H), 7.39–7.36 (m, 1H), 7.22–7.16 (m, 2H), 3.92–3.76 (m, 2H), 1.97–1.94 (m, 1H), 1.72 (d, *J* = 22.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.6 (d, *J* = 248.3 Hz), 143.0 (dd, *J* = 22.8, 7.2 Hz), 135.2, 130.8 (d, *J* = 3.6 Hz), 128.9 (d, *J* = 3.6 Hz), 128.5, 127.8, 120.4 (dd, *J* = 9.6, 3.6 Hz), 112.8 (d, *J* = 10.8 Hz), 112.6 (d, *J* = 9.6 Hz), 97.3 (d, *J* = 172.7 Hz), 69.3 (d, *J* = 25.2 Hz), 23.2 (d, *J* = 25.2 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ –117.7 (m), –157.3 (m); $[\alpha]_D^{21}$ +20.5 (c = 1.1, $CHCl_3$); HRMS (DART): Anal. For $C_{15}H_{14}F_2O_1^{+1}$ $[M+NH_4]^+$ Calcd.: 266.1357, Found: 266.1354. The enantiopurity was determined after conversion into the corresponding benzoate **9j**.

2-Fluoro-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propyl benzoate (9j')



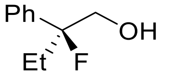
According to the general procedure, **9j** was converted into **9j'**, the crude mixture was purified by flash column chromatography on silica gel (hexane : ethylacetate = 20:1) to afford the desired benzoate **9j'** in 97 % yield (white solid, 92% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.3 Hz, 2H), 7.59–7.54 (m, 3H), 7.50–7.42 (m, 5H), 7.40–7.37 (m, 1H), 7.30–7.26 (m, 2H), 4.66–4.53 (m, 2H), 1.83 (d, *J* = 22.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 159.6 (d, *J* = 248.2 Hz), 142.6 (dd, *J* = 23.0, 7.7 Hz), 135.1, 133.3, 130.8 (d, *J* = 3.8 Hz), 129.7, 129.5, 129.0 (d, *J* = 2.9 Hz), 128.7 (d, *J* = 13.3 Hz), 128.5 (d, *J* = 3.8 Hz), 127.9, 120.5 (dd, *J* = 8.6, 2.9 Hz), 112.9 (d, *J* = 10.5 Hz), 112.7 (d, *J* = 9.6 Hz), 95.1 (d, *J* = 177.3 Hz), 69.4 (d, *J* = 24.9 Hz), 23.6 (d, *J* = 24.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ –117.6 (m), –153.3 (m); $[\alpha]_D^{20}$ +23.8 (c = 0.74, $CHCl_3$); HRMS (DART): Anal. For $C_{22}H_{18}F_2O_2^{+1}$ $[M+NH_4]^+$ Calcd.: 370.1619, Found: 370.1618. The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1; 0.5 mL/min; using a CHIRALPAK IB-3 column (0.46 cmφ × 25 cm)): 18.2 min (minor) and 21.7 min (major).

1-Fluoro-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde (8k)



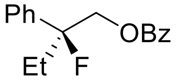
After completion of fluorination (stirred for 2 h at room temperature), the reaction mixture was added saturated aq. $NaHCO_3$ at 0 °C. The mixture was extracted with Et_2O, and the organic later was dried over Na_2SO_4, concentrated and purified by silica gel column chromatography (pantane : diethyl ether = 10 : 0 – 10 : 1) to afford 90% yield of **8k** (colorless oil; including small amount of impurities, 95% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (d, *J* = 6.1 Hz, 1H), 7.34–7.20 (m, 4H), 2.92–2.74 (m, 2H), 2.28–2.09 (m, 2H), 2.05–1.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9 (d, *J* = 38.3 Hz), 138.9 (d, *J* = 3.8 Hz), 130.3 (d, *J* = 21.1 Hz), 129.7 (d, *J* = 3.8 Hz), 129.6, 128.6 (d, *J* = 3.8 Hz), 126.7 (d, *J* = 1.9 Hz), 95.5 (d, *J* = 181.2 Hz), 29.5 (d, *J* = 21.1 Hz), 28.9, 18.5 (d, *J* = 2.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ –142.4 (t, *J* = 23.1 Hz); $[\alpha]_D^{22}$ –18.5 (c = 0.49, $CHCl_3$); HRMS (DART): Anal. For $C_{11}H_{15}F_1N_1O_1^{+1}$ $[M+NH_4]^+$ Calcd.: 196.1138, Found 196.1131; The enantiopurity was determined by GC (100–150 °C, 5 °C/min; using a β-DEX 120 column): 21.5 min (minor) and 21.8 min (major).

2-Fluoro-2-phenylbutan-1-ol (9l)



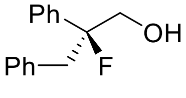
The reaction was stirred for 12 h at room temperature. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1) to give 93% yield of **9l** (colorless oil). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.40–7.29 (m, 5H), 3.90–3.78 (m, 2H), 2.21–2.09 (m, 1H), 1.98–1.80 (m, 2H), 0.81 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 139.7 (d, *J* = 21.1 Hz), 128.3, 127.6, 124.8 (d, *J* = 9.6 Hz), 100.3 (d, *J* = 175.4 Hz), 68.7 (d, *J* = 24.0 Hz), 28.8 (d, *J* = 23.0 Hz), 7.1 (d, *J* = 5.8 Hz); ^{19}F NMR (376 MHz, CDCl$_3$): δ –170.6 (m); $[\alpha]_D^{23}$ +2.90 (c = 1.8, CHCl$_3$); HRMS (DART): Anal. For $C_{10}H_{13}F_1O_1^{+1}$ $[M+NH_4]^+$ Calcd.: 186.1294, Found: 186.1294. The enantiopurity was determined after conversion into the corresponding benzoate **9l'**.

2-Fluoro-2-phenylbutyl benzoate (9l')



According to the general procedure, **9l** was converted into **9l'**. The crude mixture was purified by flash column chromatography on silica gel (hexane : ethylacetate = 20:1) to afford the desired benzoate **9l'** in 92 % yield (white solid, 84% ee). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.97 (d, *J* = 8.2 Hz, 2H), 7.57–7.53 (m, 1H), 7.43–7.37 (m, 6H), 7.35–7.30 (m, 1H), 4.68–4.53 (m, 2H), 2.30–2.18 (m, 1H), 2.11–1.94 (m, 1H), 0.86 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 166.1, 139.4 (d, *J* = 22.0 Hz), 133.1, 129.7, 129.7, 128.4, 127.7, 124.9, 124.8, 98.1 (d, *J* = 179.2 Hz), 69.1 (d, *J* = 24.9 Hz), 29.3 (d, *J* = 24.0 Hz), 7.1 (d, *J* = 4.8Hz); ^{19}F NMR (376 MHz, CDCl$_3$): δ –167.6 (m); $[\alpha]_D^{20}$ +8.90 (c = 0.61, CHCl$_3$); HRMS (DART): Anal. For $C_{17}H_{17}F_1O_2^{+1}$ $[M+NH_4]^+$ Calcd.: 290.1556, Found: 290.1558. The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1; 0.5 mL/min; using a CHIRALCEL OJ-H column (0.46 cmφ × 25 cm)): 22.5 min (minor) and 25.8 min (major).

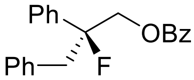
2-Fluoro-2,3-diphenylpropan-1-ol (9m)



The reaction was stirred for 12 h at room temperature. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1) to give 99% yield of **9m** (white solid). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.34–7.16 (m, 8H), 7.01–6.99 (m, 2H), 3.99–3.84 (m, 2H), 3.35 (dd, *J* = 17.7, 14.0 Hz, 1H), 3.22 (dd, *J* = 26.1, 14.2 Hz, 1H), 1.86 (t, *J* = 6.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 139.6 (d, *J* = 21.1 Hz), 134.9 (d, *J* = 3.8 Hz), 130.5, 128.2, 127.9, 127.7, 126.6, 124.9, 124.8, 99.3 (d, *J* = 177.3 Hz), 67.5 (d, *J* = 24.0 Hz), 43.1 (d, *J* = 23.0 Hz); ^{19}F NMR

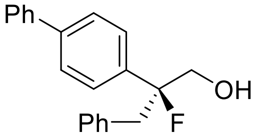
(376 MHz, CDCl$_3$): δ –165.5 (m); [α]$_D^{20}$ −35.1 (c = 1.1, CHCl$_3$); HRMS (DART): Anal. For $C_{15}H_{15}F_1O_1^{+1}$ [M+NH$_4$]$^+$ Calcd.: 248.1451, Found: 248.1453. The enantiopurity was determined after conversion into the corresponding benzoate **9m'.**

2-Fluoro-2,3-diphenylpropyl benzoate (9m')



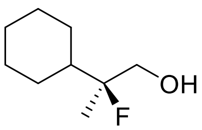
According to the general procedure, **9m** was converted into **9m'**. The crude mixture was purified by flash column chromatography on silica gel (hexane : ethylacetate = 20:1) to afford the desired benzoate **9m'** in 95 % yield (white solid, 84% ee). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.95 (d, *J* = 8.2 Hz, 2H), 7.56–7.52 (m, 1H), 7.42–7.39 (m, 2H), 7.35–7.26 (m, 5H), 7.22–7.16 (m, 3H), 7.06–7.04 (m, 2H), 4.72–4.59 (m, 2H), 3.44 (dd, *J* = 19.7, 14.2 Hz, 1H), 3.33 (dd, *J* = 25.2, 14.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 166.0, 139.4 (d, *J* = 21.1 Hz), 134.5 (d, *J* = 1.9 Hz), 133.1, 130.5, 129.6, 128.4, 128.2, 128.0 127.9, 126.8, 124.9, 124.8, 97.2 (d, *J* = 182.1 Hz), 68.5 (d, *J* = 24.9 Hz), 43.8 (d, *J* = 23.0 Hz); ^{19}F NMR (376 MHz, CDCl$_3$): δ –162.3 (m); [α]$_D^{20}$ −16.5 (c = 1.3, CHCl$_3$); HRMS (DART): Anal. For $C_{22}H_{19}F_1O_2^{+1}$ [M+NH$_4$]$^+$ Calcd.: 352.1713, Found: 352.1714. The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1; 0.7 mL/min; using a CHIRALPAK ID column (0.46 cmφ × 25 cm)): 15.4 min (minor) and 17.5 min (major).

2-([1,1'-Biphenyl]-4-yl)-2-fluoro-3-phenylpropan-1-ol (9n)



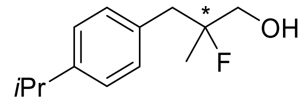
The reaction was stirred for 20 h at 0 °C using 20 mol% of **C1**. The crude mixture was purified by silica gel column chromatography (hexane : dethyl ether = 2:1) to give 91% yield of **9n** (89% ee) with a trace amount of impurity. Subsequent recrystallization from dichloromethane/hexane gave pure product with 93% ee (white solid). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.56–7.50 (m, 4H), 7.42–7.38 (m, 2H), 7.33–7.29 (m, 1H), 7.26 (d, *J* = 10.4 Hz, 2H), 7.17–7.16 (m, 3H), 7.03–7.01 (m, 2H), 3.95–3 .83 (m, 2H), 3.35 (dd, *J* = 18.0, 14.0 Hz, 1H), 3.22 (dd, *J* = 25.8, 14.2 Hz), 2.15 (bs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 140.3 (d, *J* = 4.7 Hz), 138.7 (d, *J* = 21.9 Hz), 134.9 (d, *J* = 2.9 Hz), 130.5, 128.7, 127.9, 127.4, 127.0,. 126.8, 126.6, 125.4, 125.3, 99.2 (d, *J* = 176.4 Hz), 67.3 (d, *J* = 23.8 Hz), 43.0 (d, *J* = 23.9 Hz); ^{19}F NMR (376 MHz, CDCl$_3$): δ –164.9 (m); [α]$_D^{20}$ −51.9 (c = 2.0, CHCl$_3$); HRMS (DART): Anal. For $C_{21}H_{19}F_1O_1$ [M+NH$_4$]$^+$ Calcd.: 324.1764, Found: 324.1761. The enantiopurity was determined by HPLC (hexane : 2-propanol = 30: 1; 1 mL/min; using a CHIRALPAK ID-3 column (0.46 cmφ × 25 cm)): 21.1 min (minor) and 24.6 min (major).

2-Cyclohexyl-2-fluoropropan-1-ol (9o)



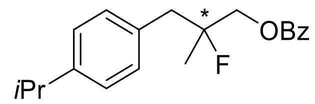
The reaction was carried out at 0 °C and stirred for 48 h with 30 mol% catalyst **C1** in the absence of $3,5\text{-}(NO_2)_2C_6H_3CO_2H$. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1) to give 24% yield of **5o** (colorless oil, mixture of **9o** and 2-cyclohexylpropan-1-ol, 83% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.69 (dd, *J* = 21.4, 12.2 Hz, 1H), 3.57 (dd, *J* = 23.0, 11.8 Hz, 1H), 1.84–1.62 (m, 7H), 1.28–1.20 (m, 1H), 1.24 (d, 3H), 1.18–1.07 (m, 2H), 1.02–0.94 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 99.8 (d, *J* = 167.9 Hz), 66.8 (d, *J* = 24.0 Hz), 42.9 (d, *J* = 21.6 Hz), 27.6 (d, *J* = 7.2 Hz), 26.4–26.3 (3C), 17.6 (d, *J* = 25.2 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ –158.1; HRMS (DART): Anal. For $C_9H_{17}FO_1^{+1}$ $[M+NH_4]^+$ Calcd.: 178.1605, Found: 178.1607. The enantiopurity was determined by GC (100 °C–130 °C, 8 °C/min, then 60 min at 130 °C) using a β-DEX 120 column: 20.0 (major) and 22.4 (minor).

2-Fluoro-3-(4-isopropylphenyl)-2-methylpropan-1-ol (9p)



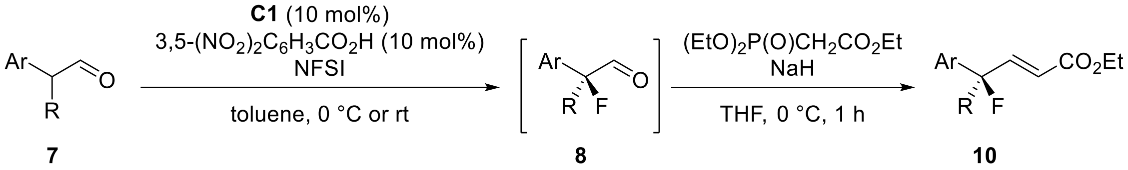
The reaction was stirred for 24 h at room temperature. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1) to give 59% yield of **9p** (colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (s, 4H), 3.58 (dd, *J* = 19.5, 5.5 Hz, 2H), 3.01–2.82 (m, 3H), 1.88 (m, 1H), 1.30–1.23 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 133.2 (d, *J* = 5.8 Hz), 130.3, 126.3, 97.4 (d, *J* = 169.7 Hz), 67.5 (d, *J* = 24.0 Hz), 41.9 (d, *J* = 23.0 Hz), 33.7, 24.0, 20.9 (d, *J* = 24.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ –154.7 (m); HRMS (DART): Anal. For $C_{13}H_{19}F_1O_1^{+1}$ $[M+NH_4]^+$ Calcd.: 210.1420, Found: 210.1419. The enantiopurity was determined after conversion into the corresponding benzoate **9p'**.

2-Fluoro-3-(4-isopropylphenyl)-2-methylpropyl benzoate (9p')



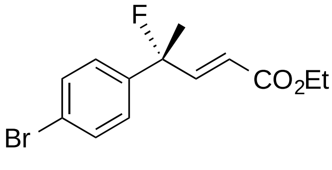
According to the general procedure, **9p** was converted into **9p'**. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 10 : 1) to afford 91% of **9p'** (colorless oil, 14% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.2 Hz, 2H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.16 (s, 4H), 4.35 (dd, *J* = 37.0, 11.9 Hz, 1H), 4.30 (dd, *J* = 37.2, 11.9 Hz,1H), 3.06 (d, *J* = 19.5 Hz, 2H), 2.88 (sept, *J* = 7.0, 1H), 1.41 (d, *J* = 21.5 Hz, 3H), 1.24 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.1, 147.5, 133.2, 132.6 (d, *J* = 4.8 Hz), 130.2, 129.8, 129.7, 128.5, 126.4, 95.0 (d, *J* = 175.1 Hz), 68.1 (d, *J* = 25.2 Hz), 42.8 (d, *J* = 22.8 Hz), 33.7, 24.0, 21.7 (d, *J* = 24.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ –151.6; HRMS (DART): Anal. For $C_{20}H_{24}F_1O_2^{+1}$ [M+H$^+$] Calcd.: 315.1760, Found: 315.1763; The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1; 0.5 mL/min; using a CHIRALCEL OJ-H column (0.46 cmφ × 25 cm)): 26.5 min (minor) and 27.9 min (major).

Synthesis and characterization of chiral 3-fluoropropenes



To a solution of catalyst **C1** (20 mg, 0.026 mmol, 10 mol%) in toluene (0.54 mL) was added 3,5-dinitrobenzoic acid (5.5 mg, 0.026 mmol, 10 mol%), aldehydes **3** (0.39 mmol, 1.5 equiv.), and NFSI (0.26 mmol, 82 mg, 1 equiv.) at 0 ºC. The mixture was stirred for 24 h at 0 °C, then poured into aq. $NaHCO_3$, and extracted by Et_2O. The organic layer was dried over Na_2SO_4 and concentrated under the reduced pressure gave **8** as the crude product. To a solution of $(EtO)_2P(O)CH_2CO_2Et$ (1.35 mmol) in THF (0.7 mL) was added NaH (60%, 1.35 mmol) at 0 °C. After the mixture was stirred for 0.5 h at 0 °C, a solution of **8** in THF (1.0 mL) was added to the mixture, then stirred for another 1 h. The mixture was quenched with saturated aq. NH_4Cl and extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The crude mixture was purified by flash column chromatography on silica gel to afford **10**.

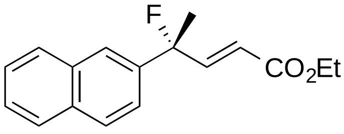
Ethyl (*E*)-4-(4-bromophenyl)-4-fluoropent-2-enoate (10b)



The crude mixture was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 30 : 1) to afford 80% yield of **10b** (colorless oil). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.05 (dd, *J* = 18.7, 15.7 Hz, 1H), 6.09 (d, *J* = 15.7 Hz, 1H), 4.20 (q, *J* = 7.13 Hz, 2H), 1.80 (d, *J* = 21.8 Hz, 3H), 1.29, (t, *J* = 7.3 Hz, 3H); ^{13}C NMR

(125 MHz, $CDCl_3$): δ 166.0, 148.0 (d, *J* = 22.8 Hz), 140.5 (d, *J* = 22.8 Hz), 131.7, 126.4 (d, *J* = 8.4 Hz), 122.3, 119.8 (d, *J* = 10.8 Hz), 94.8 (d, *J* = 176.3 Hz), 60.8, 26.5 (d, *J* = 25.2 Hz), 14.2; ^{19}F NMR (470 MHz, $CDCl_3$): δ –146.2 (m); $[\alpha]_D^{29}$ +17.1 (c = 1.2, $CHCl_3$); HRMS (DART): Anal. For $C_{13}H_{18}Br_1F_1N_1O_2^{+1}$ $[M+NH_4]^+$ Calcd.: 318.0505, Found: 318.0504.

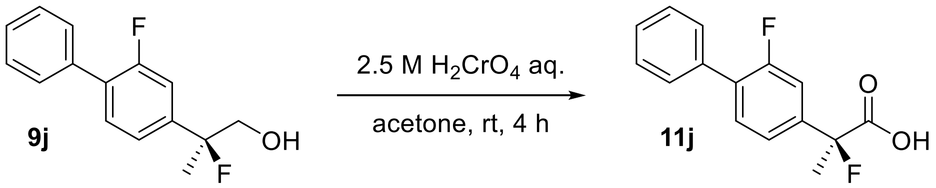
Ethyl (*E*)-4-fluoro-4-(naphthalen-2-yl)pent-2-enoate (10h)



The crude mixture was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 30 : 1) to afford 80% yield of **10h** (white solid). ^1H NMR (500 MHz, $CDCl_3$): δ 7.85–7.81 (m, 4H), 7.51–7.46 (m, 3H), 7.20 (dd, *J* = 18.7, 15.7 Hz, 1H), 6.16 (dd, *J* = 15.6, 0.8 Hz, 1H), 4.20 (q, *J* = 7.3 Hz, 2H), 1.92 (d, *J* = 22.2 Hz, 3H), 1.27 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 148.7 (d, *J* = 24.0 Hz), 138.7 (d, *J* = 22.8 Hz), 132.9 (d, *J* = 10.8 Hz), 128.5, 128.3, 127.6, 126.5, 123.4 (d, *J* = 9.6 Hz), 122.6 (d, *J* = 6.0 Hz), 119.6 (d, *J* = 10.8 Hz), 95.3 (d, *J* = 175.1 Hz), 60.7, 26.5 (d, *J* = 25.2 Hz), 14.1; ^{19}F NMR (470 MHz, $CDCl_3$): δ –145.5 (m); $[\alpha]_D^{29}$ +24.5 (c = 1.1, $CHCl_3$); HRMS (DART): Anal. For $C_{17}H_{21}F_1N_1O^{+1}$ $[M+NH_4]^+$ Calcd.: 290.1556, Found: 290.1554.

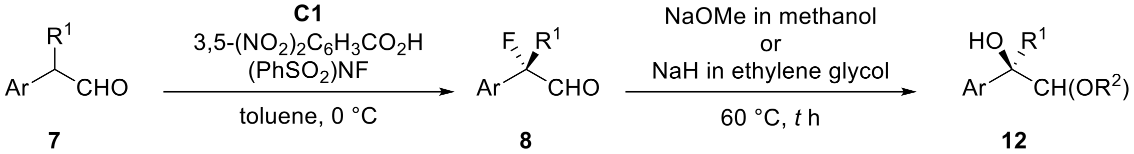
Synthesis and characterization of fluorine analogue of flurbiprofen

2-Fluoro-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanoic acid (9, 92% *ee*)



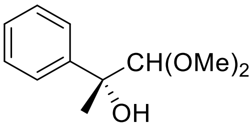
A solution of **9j** (0.106 mmol) in acetone (1.06 mL) was added to 2.5 M aq.H_2CrO_4 (3 mmol, 128 μL) at 0 °C. After the mixture was stirred for 4 h at room temperature, 2-propanol was added to this mixture. The mixture was filtered, extracted by CH_2Cl_2, and the organic layer was washed by 1.2N HCl twice and brine, dried over Na_2SO_4 and concentrated. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1 – 1 : 4) to afford 69% yield of **11j** (white solid; including small amount of impurities). ^1H NMR (500 MHz, CD_3OD): δ 7.54–7.49 (m, 3H), 7.45–7.40 (m, 3H), 7.39–7.34 (m, 2H), 1.93 (d, *J* = 22.2 Hz, 3H); ^{13}C NMR (126 MHz, CD_3OD): δ 173.7 (d, *J* = 27.6 Hz), 160.8 (d, *J* = 247.1 Hz), 142.7 (d, *J* = 7.2 Hz), 142.5 (d, *J* = 7.2 Hz), 136.4, 132.0 (d, *J* = 2.4 Hz), 130.5 (d, *J* = 13.2 Hz), 130.0 (d, *J* = 2.4 Hz), 129.0, 122.1 (d, $J = 3.6$ Hz), 122.0 (d, $J = 3.6$ Hz), 113.9 (d, $J = 9.2$ Hz), 113.7 (d, $J = 9.2$ Hz), 95.1 (d, $J = 184.7$ Hz), 25.0 (d, 24.0 Hz); ^{19}F NMR (470 MHz, CD_3OD): δ –116.1, –147.9 (q, $J = 22.0$ Hz); $[\alpha]_D^{27}$ +28.6 (c = 0.84, $CHCl_3$); HRMS (DART): Anal. For $C_{15}H_{16}F_2N_1O_2^{+1}$ $[M+NH_4]^+$ Calcd.: 280.1149, Found 280.1143.

Synthesis and characterization of α-hydroxyacetals



General procedure: Enantioselective fluorination of **7** was carried out according to the procedure described. After completion of the reaction, MeOH (2.64 mL)/NaOMe (1.32 mmol, 5 equiv.) or ethylene glycol (2.64 mL)/NaH (1.32 mmol, 5 equiv.) were added at 0 °C. The mixture was stirred at room temperature, then diluted by adding sat. $NaHCO_3$ aq., and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography to give α-hydroxylacetals **12**.

(*R*)-1,1-Dimethoxy-2-phenylpropan-2-ol [(*R*)-12a]

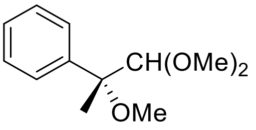


The reaction was stirred for 10 h. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give 66% yield of (*R*)-**12a** (pale yellow oil). ^{1}H NMR (400 MHz, C_6D_6): δ 7.70–7.67 (m, 2H), 7.26–7.22 (m, 2H), 7.14–7.10 (m, 1H), 3.98 (s, 1H), 3.04 (s, 3H), 2.95 (s, 3H), 2.50 (s, 1H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 145.1, 128.0, 127.1, 126.6, 111.1, 76.1, 57.4, 57.3, 23.8; $[\alpha]_D^{25}$ –7.6 (c = 1.00, $CHCl_3$); HRMS (DART): Anal. For $C_{11}H_{20}N_1O_3^{+1}$ $[M+NH_4^+]$ Calcd.: 214.1443, Found: 214.1441; The enantiopurity was determined after conversion into methyl ether (*R*)-**12a'**.

Methylation of 12.

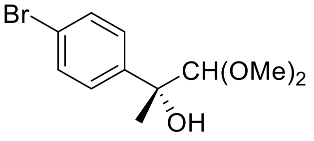
General procedure: To a suspension of NaH (0.408 mmol, 2 equiv.) in DMF (1.0 mL), α-hydroxyacetal **10** (0.204 mmol) was added, and the mixture was stirred at 0 °C for 30 min. MeI (0.408 mmol, 2 equiv.) was added to the mixture, and stirred for 60 min at 0 °C. The reaction was quenched by adding sat. NH_4Cl aq. and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography to afford **12’**.

(*R*)-(1,1,2-Trimethoxypropan-2-yl)benzene [(*R*)-12’]



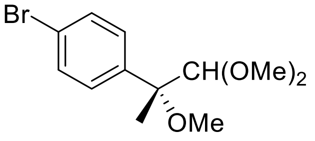
According to the general procedure, reaction was carried out with 0.204 mmol of (*R*)-**12a**. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 15 : 1) to afford 83% yield of (*R*)-**12a’** (colorless oil, 94% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.42 (m, 2H), 7.38–7.34 (m, 2H), 7.30–7.26 (m, 1H), 4.13 (s, 1H), 3.48 (s, 3H), 3.10 (s, 3H), 3.08 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.2, 127.9, 127.5, 127.2, 111.0, 81.7, 58.2, 57.3, 50.2, 15.5; $[\alpha]_D^{23}$ –53.2 (c = 1.00, $CHCl_3$); HRMS (DART): Anal. For $C_{12}H_{22}N_1O_3^{+1}$ [M+NH_4^+] Calcd.: 228.1600, Found: 228.1600; The enantiopurity was determined by HPLC (hexane : 2-propanol = 300 : 1, 1.0 mL/min, 220 nm) using a CHIRALPAK IC-3 column (0.46 cmφ x 25 cm): 10.6 min (major) and 12.9 min (minor).

2-(4-Bromophenyl)-1,1-dimethoxypropan-2-ol (12b)



The reaction was stirred for 12 h. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give 70% yield of **12b** (pale yellow oil). ^{1}H NMR (500 MHz, C_6D_6): δ 7.34 (s, 4H), 3.81 (s, 1H), 2.99 (s, 3H), 2.89 (s, 3H), 2.38 (s, 1H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 144.0, 131.1, 128.5, 121.3, 110.7, 75.7, 57.4, 57.3, 23.7; $[\alpha]_D^{21}$ –3.2 (c = 1.02, $CHCl_3$); HRMS (DART): Anal. For $C_{11}H_{19}Br_1N_1O_3^{+1}$ [M+NH_4^+] Calcd.: 292.0548, Found: 292.0548; The enantiopurity was determined after conversion into **12b’**.

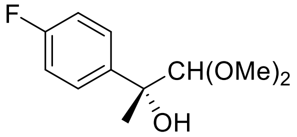
1-Bromo-4-(1,1,2-trimethoxypropan-2-yl)benzene (12b’)



According to the general procedure, reaction was carried out with 0.145 mmol of **12b**. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 15 : 1) to give 76% yield of **12b’** (colorless oil, 92% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49–7.47 (m, 2H), 7.31–7.28 (m, 2H), 4.08 (s, 1H), 3.48 (s, 3H), 3.16 (s, 3H), 3.09 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4, 131.0, 129.4, 121.4, 110.6, 81.6, 58.2, 57.6, 50.2, 15.9; $[\alpha]_D^{23}$ –41.0 (c = 1.01, $CHCl_3$); HRMS (DART): Anal. For $C_{12}H_{21}N_1O_3^{+1}$ [M+NH_4^+] Calcd.: 306.0705, Found: 306.0705; The enantiopurity was determined by HPLC (hexane : 2-propanol = 300 : 1, 1.0

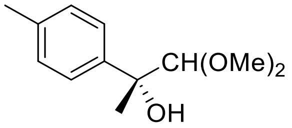
mL/min, 220 nm) using a CHIRALPAK IC-3 column (0.46 cmφ x 25 cm): 7.7 min (major) and 9.0 min (minor).

2-(4-Fluorophenyl)-1,1-dimethoxypropan-2-ol (12c)



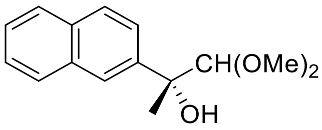
The reaction was stirred for 10 h. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1–2 : 1) to give 64% yield of **12c** (colorless oil, 93% ee). ^{1}H NMR (500 MHz, C_6D_6): δ 7.50–7.46 (m, 2H), 6.90–6.86 (m, 2H), 3.85 (s, 1H), 3.03 (s, 3H), 2.91 (s, 3H), 2.42 (s, 1H), 1.52 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.4 (d, *J* = 244.7 Hz), 140.6, 128.4 (d, *J* = 7.2 Hz), 114.6 (d, *J* = 21.6 Hz), 111.0, 75.7, 57.5, 57.3, 23.7; ^{19}F NMR (470 MHz, $CDCl_3$): δ –115.8; $[\alpha]_D^{25}$ –7.6 (c = 0.33, $CHCl_3$); HRMS (DART): Anal. For $C_{11}H_{15}FO_3^{+1}$ $[M+NH_4]^+$ Calcd.: 232.1347, Found: 232.1349. The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1; 1.0 mL/min; using a CHIRALPAK IA-3 column (0.46 cmφ × 25 cm)): 12.2 min (minor) and 14.2 min (major).

1,1-Dimethoxy-2-(p-tolyl)propan-2-ol (12d)



The reaction was stirred for 10 h. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1–2 : 1) to give 50% yield of **12d** (colorless oil, 93% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.08 (*J* = 8.0 Hz, 2H), 4.01 (s, 1H), 3.06 (s, 3H), 2.98 (s, 3H), 2.50 (s, 1H), 2.14 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 142.2, 136.3, 128.7, 126.6, 111.2, 75.9, 57.4, 57.2, 23.8, 21.0; $[\alpha]_D^{25}$ –8.5 (c = 0.90, $CHCl_3$); HRMS (DART): Anal. For $C_{12}H_{18}O_3^{+1}$ $[M+NH_4]^+$ Calcd.: 228.1597, Found: 228.1600. The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1; 1.0 mL/min; using a CHIRALPAK IA-3 column (0.46 cmφ × 25 cm)): 17.0 min (minor) and 19.8 min (major).

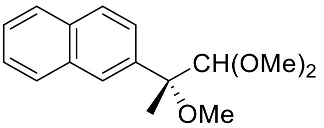
1,1-Dimethoxy-2-(naphthalen-2-yl)propan-2-ol (12h)



The reaction was stirred for 12 h. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give 82% yield of **12h** (pale yellow oil). ^{1}H

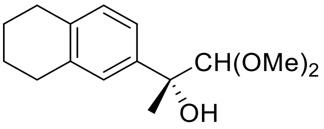
NMR (400 MHz, C_6D_6): δ 8.25 (s, 1H), 7.81–7.65 (m, 4H), 7.28–7.25 (m, 2H), 4.08 (s, 1H), 3.06 (s, 3H), 2.94 (s, 3H), 2.64 (s, 1H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 142.6, 133.7, 133.1, 128.6, 127.8, 127.6, 126.1, 125.9, 125.4, 125.2, 111.0, 76.2, 57.4, 57.2, 23.9; [□]$_D^{23}$ –1.0 (c = 1.00, $CHCl_3$); HRMS (DART): Anal. For $C_{15}H_{22}N_1O_3^{+1}$ [$M+NH_4^+$] Calcd.: 264.1600, Found: 264.1603; The enantiopurity was determined after conversion into **12h’**.

2-(1,1,2-Trimethoxypropan-2-yl)naphthalene (12h’)



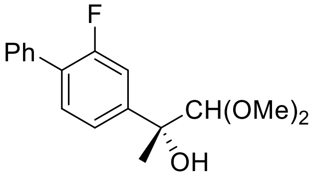
According to the general procedure, reaction was carried out with 0.162 mmol of **12h**. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 10 : 1) to give 84% yield of **12h’** (white solid, 92% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88–7.86 (m, 4H), 7.62–7.59 (m, 1H), 7.50–7.46 (m, 2H), 4.25 (s, 1H), 3.52 (s, 3H), 3.13 (s, 3H), 3.07 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 133.0, 132.6, 128.2, 127.44, 127.40, 126.8, 125.9, 125.8, 125.5, 110.9, 81.9, 58.2, 57.5, 50.3, 15.7; [α]$_D^{23}$ –55.2 (c = 1.00, $CHCl_3$); HRMS (DART): Anal. For $C_{16}H_{24}N_1O_3^{+1}$ [$M+NH_4^+$] Calcd.: 278.1756, Found: 278.1757; The enantiopurity was determined by HPLC (hexane : 2-propanol = 300 : 1, 1.0 mL/min, 254 nm) using a CHIRALPAK IC-3 column (0.46 cmφ x 25 cm): 14.1 min (major) and 17.6 min (minor).

1,1-Dimethoxy-2-(5,6,7,8-tetrahydronaphthalen-2-yl)propan-2-ol (12i)



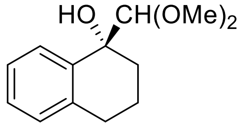
The reaction was stirred for 12 h. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1–2 : 1) to give 57% yield of **12i** (colorless oil, 91% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.46 (dd, J = 7.8, 1.7 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 4.09 (s, 1H), 3.10 (s, 3H), 3.03 (s, 3H), 2.68–2.66 (m, 2H), 2.61–2.59 (m, 2H), 2.58 (s, 1H), 1.68 (s, 3H), 1.60–1.54 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 142.3, 136.3, 135.5, 128.8, 127.1, 123.9, 111.1, 76.0, 57.3, 57.2, 26.9, 26.3, 24.0, 23.7, 23.6; [α]$_D^{25}$ –4.2 (c = 0.98, $CHCl_3$); HRMS (DART): Anal. For $C_{15}H_{22}O_3^{+1}$ [$M+H]^+$ Calcd.: 251.1650, Found: 251.1647. The enantiopurity was determined by HPLC (hexane : 2-propanol = 50 : 1; 1.0 mL/min; using a CHIRALPAK IC-3 column (0.46 cmφ × 25 cm)): 25.3 min (minor) and 32.7 min (major).

2-(2-Fluoro-[1,1'-biphenyl]-4-yl)-1,1-dimethoxypropan-2-ol (12j)



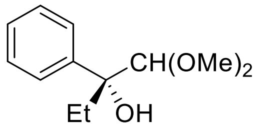
The reaction was stirred for 10 h. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1–2 : 1) to give 71% yield of **12j** (colorless oil, 90% ee). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.61 (dd, *J* = 12.6, 1.9 Hz, 1H), 7.55–7.52 (m, 2H), 7.44 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.30 (t, *J* = 8.4 Hz, 1H), 7.21–7.18 (m, 2H), 7.12–7.09 (m, 1H), 3.95 (s, 1H), 3.06 (s, 3H), 2.98 (s, 3H), 2.54 (s, 1H), 1.56 (s, 3H); ^{13}C NMR (126 MHz, CDCl$_3$): δ 160.0 (d, *J* = 245.9 Hz), 147.0 (d, *J* = 7.2 Hz), 136.2, 130.3 (d, *J* = 3.6 Hz), 129.4 (d, *J* = 2.4 Hz), 128.7, 128.3, 127.9, 122.6 (d, *J* = 3.6 Hz), 114.7 (d, *J* = 25.2 Hz), 110.7, 75.8, 57.5, 57.4, 23.9; ^{19}F NMR (470 MHz, CDCl$_3$): δ –117.8 (*J* = 14.7 Hz); $[\alpha]_D^{24}$ –3.5 (c = 1.65, CHCl$_3$); HRMS (DART): Anal. For $C_{17}H_{19}FO_3^{+1}$ $[M+NH_4]^+$ Calcd.: 308.1664, Found: 308.1662. The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1; 1.0 mL/min; using a CHIRALPAK IA-3 column (0.46 cmφ × 25 cm)): 16.7 min (major) and 18.0 min (minor).

1-(Dimethoxymethyl)-1,2,3,4-tetrahydronaphthalen-1-ol (12k)



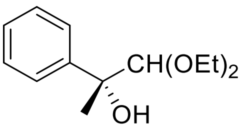
The reaction was carried out with 10 equiv. of NaOMe and stirred for 8 h at room temperature. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give 55% yield of **12k** (pale yellow oil, 94% ee). ^{1}H NMR (400 MHz, C$_6$D$_6$): δ 7.70–7.68 (m, 1H), 7.16–7.13 (m, 1H), 7.10–7.06 (m, 1H), 6.97–6.95 (m, 1H), 4.30 (s, 1H), 3.19 (s, 3H), 2.91 (s, 3H), 2.60–2.56 (m, 2H), 2.46–2.37 (m, 2H), 1.94–1.85 (m, 2H), 1.78–1.69 (m, 1H); ^{13}C NMR (100 MHz, C$_6$D$_6$): δ 139.1, 138.9, 129.0, 127.9, 127.3, 126.0, 73.8, 57.6, 57.4, 32.5, 30.4, 19.8; $[\alpha]_D^{21}$ –3.7 (c = 1.00, CHCl$_3$); HRMS (DART): Anal. For $C_{13}H_{22}N_1O_3^{+1}$ $[M+NH_4^+]$ Calcd.: 240.1600, Found: 240.1597; The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1, 1.0 mL/min, 220 nm) using a CHIRALPAK IE-3 column (0.46 cmφ x 25 cm): 41.1 min (major) and 36.6 min (minor).

1,1-Dimethoxy-2-phenylbutan-2-ol (12l)



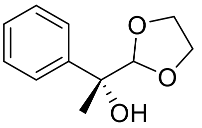
The reaction was stirred for 24 h under reflux condition. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 6 : 1) to give 71% yield of **12l** (colorless oil). ^{1}H NMR (400 MHz, C_6D_6): δ 7.67–7.65 (m, 2H), 7.27–7.23 (m, 2H), 7.14–7.10 (m, 1H), 4.02 (s, 1H), 3.00 (s, 6H), 2.41 (s, 1H), 2.09–1.97 (m, 2H), 0.869 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, C_6D_6): δ 142.9, 128.0, 127.0, 126.8, 110.9, 78.7, 57.20, 57.15, 28.9, 7.4; $[\alpha]_D^{21}$ +12.2 (c = 0.99, $CHCl_3$); HRMS (DART): Anal. For $C_{12}H_{22}N_1O_3^{+1}$ $[M+NH_4^+]$ Calcd.: 228.1600, Found: 228.1590. The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1, 1.0 mL/min, 220 nm) using a CHIRALPAK IC-3 column (0.46 cmφ x 25 cm): major isomer 12.3 min and minor isomer 11.4 min.

1,1-Diethoxy-2-phenylpropan-2-ol (12t)



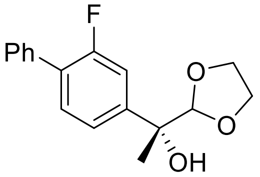
Fluorination was carried out at room temperature and stirred for 1.5 h. The reaction was stirred for 17 h in ethanol under reflux condition. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 15 : 1–10 : 1) to give 43% yield of **12t** (yellow oil, including ca. 10% of an inseparable by-product, 79% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75–7.72 (m, 2H), 7.26–7.23 (m, 2H), 7.15–7.11 (m, 1H), 4.19 (s, 1H), 3.47 (qd, *J* = 9.4, 7.1 Hz, 1H), 3.36 (qd, *J* = 9.2, 6.9 Hz, 1H), 3.13 (qd, *J* = 9.4, 7.1 Hz, 1H), 2.95 (qd, *J* = 9.2, 6.9 Hz, 1H), 2.68 (s, 1H), 1.68 (s, 3H), 0.94 (t, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 5.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 145.2, 127.9, 127.0, 126.7, 108.7, 75.9, 65.7, 65.4, 23.6, 15.4, 15.3; $[\alpha]_D^{25}$ –9.9 (c = 1.20, $CHCl_3$); HRMS (DART): Anal. For $C_{13}H_{20}O_3^{+1}$ $[M+NH_4]^+$ Calcd.: 242.1759, Found: 242.1756. The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1; 1.0 mL/min; using a CHIRALPAK IA-3 column (0.46 cmφ × 25 cm)): 6.5 min (minor) and 7.1 min (major).

1-(1,3-Dioxolan-2-yl)-1-phenylethan-1-ol (12u)



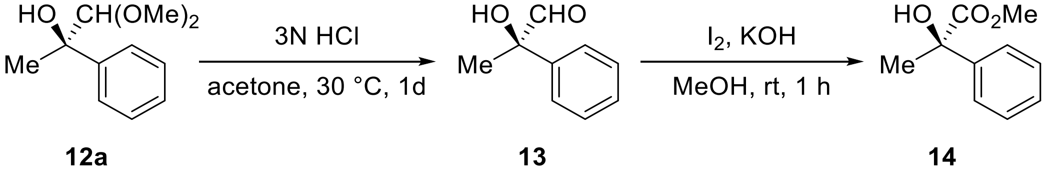
According to the typical procedure, reaction was carried out using ethyleneglycole and NaH instead of MeOH and NaOMe and stirred for 5 h. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give 63% yield of **12u** (colorless oil, 94% ee). ^{1}H NMR (400 MHz, C_6D_6): δ 7.64–7.62 (m, 2H), 7.24–7.20 (m, 2H), 7.13–7.08 (m, 1H), 4.90 (s, 1H), 3.30–3.18 (m, 4H), 2.49 (bs, 1H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 144.5, 128.1, 127.1, 126.3, 107.9, 75.0, 65.6, 65.3, 24.7; $[\alpha]_D^{19}$ –3.4 (c = 1.00, $CHCl_3$); HRMS (DART): Anal. For $C_{11}H_{18}N_1O_3^{+1}$ [M+NH_4^+] Calcd.: 212.1287, Found: 212.1284; The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1, 1.0 mL/min, 220 nm) using a CHIRALPAK IB-3 column (0.46 cmφ x 25 cm): 20.3 min (major) and 22.3 min (minor).

1-(1,3-Dioxolan-2-yl)-1-(2-fluoro-[1,1'-biphenyl]-4-yl)ethan-1-ol (12v)



The reaction was stirred for 10 h. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1–1 : 1) to give 76% yield of **12v** (colorless oil, 90% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55–7.51 (m, 3H), 7.37 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.21–7.17 (m, 2H), 7.12–7.09 (m, 1H), 4.82 (s, 1H), 3.32–3.18 (m, 4H), 2.32 (s, 1H), 1.49 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.1 (d, *J* = 245.9 Hz), 146.4 (d, *J* = 8.4 Hz), 136.2, 130.4 (d, *J* = 3.6 Hz), 129.4 (d, *J* = 2.4 Hz), 128.7, 128.3, 127.8, 122.3 (d, *J* = 3.6 Hz), 114.5 (d, *J* = 25.2 Hz), 107.5, 74.7, 65.6, 65.4, 24.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ –117.7 (*J* = 22.0 Hz); $[\alpha]_D^{24}$ –4.8 (c = 1.97, $CHCl_3$); HRMS (DART): Anal. For $C_{17}H_{17}FO_3^{+1}$ $[M+H]^+$ Calcd.: 289.1242, Found: 289.1249. The enantiopurity was determined by HPLC (hexane : 2-propanol = 50 : 1; 1.0 mL/min; using a CHIRALPAK IA-3 column (0.46 cmφ × 25 cm)): 28.1 min (minor) and 31.6 min (major).

Synthesis and characterization of α-hydroxyester



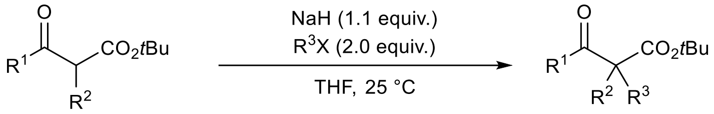
Methyl (*R*)-2-hydroxy-2-phenylpropanoate [(*R*)-13]

The reaction was carried out according to the reported procedure[4]. To a solution of α-hydroxyacetal (*R*)-**12a** (0.335 mmol, 91% ee) in acetone (4.8 mL) was added 3N HCl (2.1 mL) at 0 °C. The mixture was stirred for 1 d at 30 °C. After being quenched with K_2CO_3 aq., acetone was removed under reduced pressure. The mixture was extracted with ethyl acetate, and the organic layer was dried over Na_2SO_4, and concentrated. The residue was dissolved in MeOH (11.2 mL) and cooled to 0 °C. To this solution were added KOH (0.872 mmol, 2.6 equiv.) and I_2 (0.436

mmol, 1.3 equiv.) successively. The mixture was stirred for 1h and quenched by adding 1.2N HCl. Sat. $Na_2S_2O_3$ aq. was added until the mixture turned colorless. MeOH was removed under reduced pressure and the mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified silica gel column chromatography (hexane : MTBE = 9 : 1–2 : 1) to give 60% yield of (*R*)-**14** (colorless oil, 91% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56–7.54 (m, 2H), 7.38–7.34 (m, 2H), 7.31–7.28 (m, 1H), 3.78 (s, 3H), 3.75 (s, 1H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 142.6, 128.3, 127.8, 125.1, 75.7, 53.2, 26.6; $[\alpha]_D^{21}$ –51.9 (c = 0.98, $CHCl_3$); HRMS (DART): Anal. For $C_{10}H_{16}N_1O_3^{+1}$ $[M+NH_4^+]$ Calcd.: 198.1130, Found: 198.1130; The enantiopurity was determined by HPLC (hexane : 2-propanol = 50 : 1, 1.0 mL/min) using a CHIRALPAK AD-3 column (0.46 cmφ x 25 cm): major isomer 10.2 min and minor isomer 8.9 min. The absolute configuration of the major enantiomer was determined to be *R* by comparing the specific rotation with that in the literature[5].

Synthesis and characterization of β-ketoesters

β-Ketoesters **17** were synthesised by either **General procedure** described below, except for **17i**.

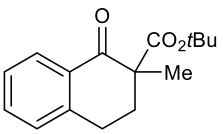


16 **17**

(X = Br or I, *t*Bu = *tert*-butyl group)

General procedure: To a stirred suspension of NaH (60% in oil, washed with hexane, 1.1 equiv.) in THF (20 mL) was added a solution of β-ketoester in THF at 0 °C, and the mixture was stirred at 0 °C for 1 h. Then, alkyl halide (2.0 equiv.) was added, and the reaction mixture was stirred at 25 °C. The reaction mixture was quenched by adding saturated NH_4Cl aqueous solution at 0 °C, and then extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and then purified by flash column chromatography on silica gel to give alkylated β-ketoester **17**.

***Tert*-butyl 2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (17a)**

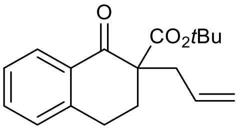


The title compound was prepared following **General procedure**, using NaH (185 mg, 7.70 mmol), *tert*-butyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (1.73 g, 7.00 mmol), and iodomethane (1.99 g, 14.0 mmol) in THF (25 mL), and the reaction mixture was stirred for 1 h.

The combined organic layer was dried over anhydrous $MgSO_4$. The crude product was purified by flash column chromatography (hexane : ethyl acetate = 10 : 1) to provide the title compound as a colourless oil (1.71 g, 94% yield).

TLC (hexane : ethyl acetate = 9 : 1): R_f = 0.43; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.9 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 1H), 7.29 (t, *J* = 7. 6 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 3.10–3.02 (m, 1H), 2.94–2.88 (m, 1H), 2.56–2.51 (m, 1H), 2.05–1.96 (m, 1H), 1.45 (s, 3H), 1.34 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 196.2, 171.9, 142.7, 132.9, 132.0, 128.4, 127.5, 126.4, 81.5, 54.1, 34.0, 27.5, 25.9, 20.3; **IR** (neat): 2973, 2934, 1729, 1690, 1603, 1458, 1371, 1310, 1256, 1230, 1158, 1116, 740 cm^{-1}; **HRMS** (DART): $[M+H]^+$calcd. for $C_{16}H_{21}O_3$, 261.1491; found, 261.1492.

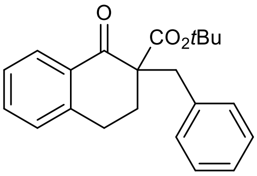
***Tert*-butyl 2-allyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (17b)**



The title compound was prepared following **General procedure**, using NaH (59.0 mg, 2.48 mmol), *tert*-butyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (555 mg, 2.25 mmol), and allyl bromide (327 mg, 2.70 mmol) in THF (8 mL), and the reaction mixture was stirred for 24 h. The combined organic layer was dried over anhydrous $MgSO_4$. The crude product was purified by flash column chromatography (hexane : ethyl acetate = 20 : 1) to provide the title compound as a colourless oil (523 mg, 81% yield).

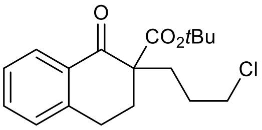
TLC (hexane : ethyl acetate = 4 : 1): R_f = 0.50; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.03 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.44 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 5.87 (ddt, *J* = 17.2, 9.9, 7.3 Hz, 1H), 5.16–5.11 (m, 1H), 5.10–5.07 (m, 1H), 3.09 (ddd, *J* = 16.4, 10.7, 4.6 Hz, 1H), 2.91 (dt, *J* = 17.6, 4.6 Hz, 1H), 2.67 (d, *J* = 7.3 Hz, 2H), 2.45 (dt, *J* = 13.8, 4.6 Hz, 1H), 2.11 (ddd, *J* = 13.9, 10.8, 5.0 Hz, 1H), 1.34 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 195.3, 170.6, 142.7, 133.6, 133.0, 132.4, 128.5, 127.6, 126.5, 118.4, 81.8, 57.5, 38.5, 30.7, 27.6, 25.8; **IR** (neat): 3075, 2977, 2931, 1729, 1694, 1599, 1454, 1367, 1249, 1154, 926, 740 cm^{-1}; **HRMS** (DART): $[M+H]^+$calcd. for $C_{18}H_{23}O_3$, 287.1647; found, 287.1649.

***Tert*-butyl 2-benzyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (17c)**[6]



The title compound was prepared following **General procedure**, using NaH (53.0 mg, 2.22 mmol), *tert*-butyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (496 mg, 2.01 mmol), and benzyl bromide (689 mg, 4.03 mmol) in THF (7.1 mL), and the reaction mixture was stirred for 13 h. The combined organic layer was dried over anhydrous $MgSO_4$. The crude product was purified by flash column chromatography (hexane : ethyl acetate = 10 : 1 to 5 : 1) to provide the title compound as a colourless oil (568 mg, 84% yield).

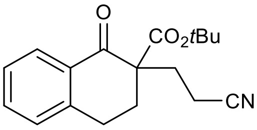
***Tert*-butyl 2-(3-chloropropyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (17d)**



The title compound was prepared following **General procedure**, using NaH (43.8 mg, 1.83 mmol), *tert*-butyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (300 mg, 1.22 mmol), and 1-chloro-3-iodopropane (374 mg, 1.83 mmol) in THF (4.3 mL), and the reaction mixture was stirred for 30 h. The reaction mixture was extracted with diethyl ether. The crude product was purified by flash column chromatography (hexane : diethyl ether = 95 : 5 to 80 : 20) to provide the title compound as a colourless oil (72.8 mg, 19% yield).

TLC (hexane : ethyl acetate = 4 : 1): $R_f = 0.47$; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.01 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.46 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 3.61–3.54 (m, 2H), 3.09 (ddd, *J* = 16.9, 11.1, 4.8 Hz, 1H), 2.92 (dt, *J* = 17.6, 4.6 Hz, 1H), 2.50 (dt, *J* = 13.8, 4.6 Hz, 1H), 2.13–1.95 (m, 4H), 1.89–1.78 (m, 1H), 1.34 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 195.8, 170.9, 142.6, 133.1, 132.5, 128.5, 127.7, 126.6, 82.2, 57.4, 45.2, 31.6, 31.3, 28.1, 27.7, 26.0; **IR** (neat): 2973, 2934, 1729, 1690, 1599, 1454, 1371, 1253, 1230, 1154, 910, 842, 740 cm^{-1}; **HRMS** (DART): $[M + H]^+$ calcd. for $C_{18}H_{24}Cl_1O_3$, 323.1414; found, 323.1414.

***Tert*-butyl 2-(2-cyanoethyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (17e)**

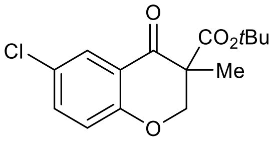


The title compound was prepared following **General procedure**, using NaH (74.4 mg, 3.10 mmol), *tert*-butyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (382 mg, 1.55 mmol), and 3-bromopropionitrile (415 mg, 3.10 mmol) in THF (5.5 mL), and the reaction mixture was stirred for 6 days. The reaction mixture was extracted with diethyl ether. The crude product was purified by flash column chromatography (hexane : ethyl acetate = 4 : 1) to provide the title compound as a colourless oil (282 mg, 61% yield).

TLC (hexane : ethyl acetate = 4 : 1): $R_f = 0.30$; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.99 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.48 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 3.08

(ddd, *J* = 17.1, 11.4, 4.8 Hz, 1H), 2.95 (dt, *J* = 17.6, 4.6 Hz, 1H), 2.75 (ddd, *J* = 13.8, 10.5, 5.7 Hz, 1H), 2.51–2.43 (m, 2H), 2.23 (dddd, *J* = 26.0, 14.1, 10.2, 5.7 Hz, 2H), 2.11 (ddd, *J* = 13.5, 11.0, 5.0 Hz, 1H), 1.33 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 195.0, 169.9, 142.1, 133.4, 132.0, 128.5, 127.4, 126.7, 119.5, 82.9, 56.6, 31.8, 30.1, 27.5, 25.7, 13.1; **IR** (neat): 3066, 2977, 2921, 2861, 2248, 1730, 1686, 1606, 1451, 1376, 1253, 1148, 1095, 905, 846, 742 cm^{-1}; **HRMS** (DART): $[M+H]^+$calcd. for $C_{18}H_{22}N_1O_3$, 300.1600; found, 300.1601.

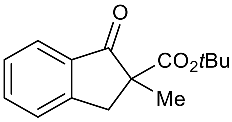
***Tert*-butyl 6-chloro-3-methyl-4-oxochromane-3-carboxylate (17f)**



The title compound was prepared following **General procedure**, using NaH (12.6 mg, 0.527 mmol), *tert*-butyl 6-chloro-4-oxochromane-3-carboxylate (135 mg, 0.479 mmol), and iodomethane (81.5 mg, 0.574 mmol) in THF (1.0 mL), and the reaction mixture was stirred for 21 h. The reaction mixture was extracted with diethyl ether. The crude product was purified by flash column chromatography (hexane : ethyl acetate = 20 : 1) to provide the title compound as a white solid (116 mg, 82% yield).

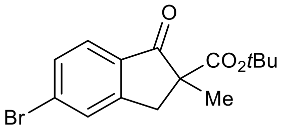
mp: 83 °C; **TLC** (hexane : ethyl acetate = 9 : 1): $R_f = 0.50$; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.87 (d, *J* = 2.7 Hz, 1H), 7.41 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.94 (d, *J* = 9.2 Hz, 1H), 4.74 (d, *J* = 11.5 Hz, 1H), 4.15 (d, *J* = 11.5 Hz, 1H), 1.39 (s, 3H), 1.35 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 189.6, 169.4, 159.4, 135.4, 127.0, 126.7, 121.2, 119.2, 82.9, 74.1, 53.6, 27.6, 15.3; **IR** (neat): 2981, 2935, 1731, 1704, 1607, 1476, 1422, 1372, 1283, 1249, 1133, 1029, 836, 821, 682, 643 cm^{-1}; **HRMS** (DART): $[M+H]^+$calcd. for $C_{15}H_{18}Cl_1O_4^{+1}$, 297.0894; found, 297.0894.

***Tert*-butyl 2-methyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (17g)**[7]



The title compound was prepared following **General procedure**, using NaH (114 mg, 4.74 mmol), *tert*-butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1.00 g, 4.31 mmol), and iodomethane (1.22 g, 8.61 mmol) in THF (15 mL), and the reaction mixture was stirred for 1 h. The combined organic layer was dried over anhydrous $MgSO_4$. The crude product was purified by flash column chromatography (hexane : ethyl acetate = 20 : 1 to 5 : 1) to provide the title compound as a white solid (937 mg, 88% yield).

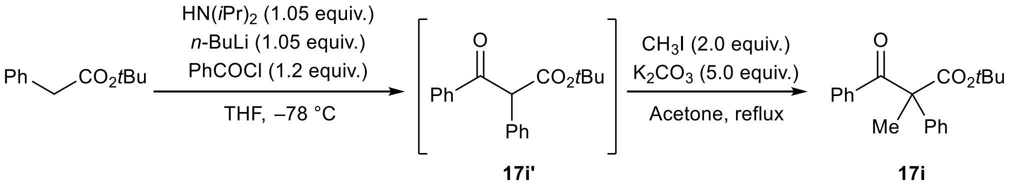
Tert-butyl 5-bromo-2-methyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (17h)



The title compound was prepared following **General procedure**, using NaH (89.0 mg, 3.70 mmol), *tert*-butyl 5-bromo-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (960 mg, 3.09 mmol), and iodomethane (569 mg, 4.01 mmol) in THF (11 mL), and the reaction mixture was stirred for 13 h. The combined organic layer was dried over anhydrous $MgSO_4$. The crude product was purified by flash column chromatography (hexane : ethyl acetate = 20 : 1 to 5 : 1) to provide the title compound as a white solid (660 mg, 66% yield).

mp: 52 °C; **TLC** (hexane : ethyl acetate = 9 : 1): $R_f = 0.40$; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.65–7.63 (m, 2H), 7.55–7.53 (m, 1H), 3.62 (d, J = 17.6 Hz, 1H), 2.94 (d, J = 17.6 Hz, 1H), 1.46 (s, 3H), 1.38 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 202.7, 170.7, 154.2, 133.9, 131.4, 130.5, 129.7, 126.0, 81.9, 56.9, 39.8, 27.8, 20.6; **IR** (neat): 2980, 2934, 1736, 1721, 1599, 1371, 1264, 1203, 1150, 975, 846 cm^{-1}; HRMS (DART): $[M+NH_4]^+$calcd. for $C_{15}H_{21}Br_1N_1O_3$, 342.0705; found, 342.0705.

Tert-butyl 2-methyl-3-oxo-2,3-diphenylpropanoate (17i)



To a stirred solution of diisopropyl amine (1.18 g, 11.1 mmol) in THF (38 mL) was added a solution of *n*-butyl lithium in 1.6 M hexane (6.9 mL, 11.1 mmol) at −78 °C. The solution was stirred at −78 °C for 1 h. Then, a solution of *tert*-butyl 2-phenylacetate (2.03 g, 10.6 mmol) in THF (15 mL) was added dropwise. After stirring for 30 min, benzoyl chloride (1.78 g, 12.7 mmol) was added, and the reaction mixture was stirred at −78 °C for 1 h. The reaction mixture was quenched by adding saturated NH_4Cl aqueous solution at 0 °C, and then extracted with diethyl ether. The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and then purified by column chromatography on silica gel (hexane : ethyl acetate = 30 : 1 to 10 : 1) to give *tert*-butyl 3-oxo-2,3-diphenylpropanoate **17i'** (2.12 g, 68% yield).

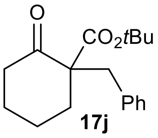
TLC (hexane : ethyl acetate = 10 : 1): $R_f = 0.39$; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.97 (d, J = 7.6 Hz, 2H), 7.53 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.40–7.34 (m, 4H), 7.30 (t, J = 7.3 Hz, 1H), 5.50 (s, 1H), 1.42 (s, 9H).

To a stirred solution of **17i** (1.53 g, 5.16 mmol) in acetone (52 mL) was added iodomethane (1.47

g, 10.3 mmol) and K_2CO_3 (3.57 g, 25.8 mmol). The reaction mixture was stirred under reflux conditions for 12 h. The reaction mixture was cooled to 25 °C and then filtered. The filtrate was concentrated and dissolved in diethyl ether. Then, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated, and then purified by flash column chromatography on silica gel (hexane : diethyl ether = 20 : 1 to 10 : 1) to give the title compound as a colourless oil (1.32 g, 82% yield).

TLC (hexane : ethyl acetate = 10 : 1): $R_f = 0.43$; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.71 (d, $J = 7.3$ Hz, 2H), 7.48 (d, $J = 7.3$ Hz, 2H), 7.42 (t, $J = 7.3$ Hz, 1H), 7.33–7.24 (m, 5H), 1.86 (s, 3H), 1.25 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 197.2, 171.2, 140.3, 136.2, 132.2, 129.4, 128.3, 128.0, 127.6, 127.1, 82.1. 62.6, 27.5, 26.1; **IR** (neat): 2978, 2935, 1735, 1692, 1449, 1372, 1264, 1164, 1133, 1094, 967, 693 cm^{-1}; **HRMS** (DART): $[M+H]^+$calcd. for $C_{20}H_{23}O_3$, 311.1647; found, 311.1645.

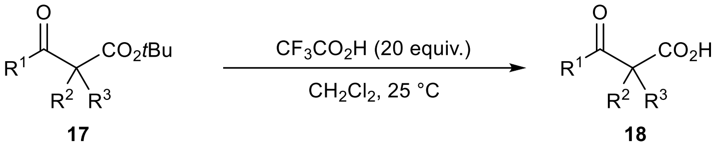
Tert-butyl 1-benzyl-2-oxocyclohexane-1-carboxylate (17j)[7]



17j

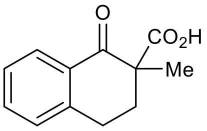
The title compound was prepared following **General procedure**, using NaH (19.0 mg, 0.792 mmol), *tert*-butyl 2-oxocyclohexane-1-carboxylate (151 mg, 0.762 mmol), and benzyl bromide (156 mg, 0.910 mmol) in THF (2.7 mL), and the reaction mixture was stirred for 7 h. The reaction mixture was extracted with diethyl ether. The crude product was purified by flash column chromatography (hexane : ethyl acetate = 10 : 1) to provide the title compound as a colourless oil (147 mg, 67% yield).

Synthesis and characterization of β-ketoacids



General procedure: To a stirred solution of β-ketoester **17** in dichloromethane was added trifluoroacetic acid (20 equiv.) at 0 °C, and the reaction mixture was stirred at 25 °C. The mixture was concentrated, and then purified by flash column chromatography on silica gel to give β-ketocarboxylic acid **18**.

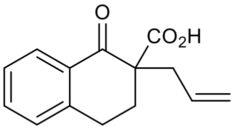
2-Methyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (18a)[8]



The title compound was prepared following **General procedure**, using **17a** (437 mg, 1.68 mmol) and trifluoroacetic acid (3.83 g, 33.6 mmol) in dichloromethane (8.4 mL), and the reaction mixture was stirred for 30 min. The crude product was purified by flash column chromatography (hexane : diethyl ether = 4 : 1 to 1 : 10) to provide the title compound as a white solid (318 mg, 93% yield) including 2% of a decarboxylated product.

TLC (dichloromethane : methanol = 9 : 1): R_f = 0.41; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.06 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.49 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 3.09 (ddd, *J* = 17.4, 8.6, 4.6 Hz, 1H), 3.00–2.94 (m, 1H), 2.57 (ddd, *J* = 13.7, 6.8, 5.0 Hz, 1H), 2.14 (ddd, *J* = 13.4, 8.8, 4.6 Hz, 1H), 1.53 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 196.5, 178.5, 143.3, 133.9, 131.1, 128.8, 128.2, 126.9, 53.2, 33.2, 25.7, 20.6; **HRMS** (DART): $[M+H]^+$calcd. for $C_{12}H_{13}O_3$, 205.0865; found, 205.0867.

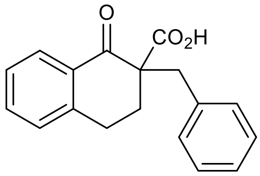
2-Allyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (18b)



The title compound was prepared following **General procedure**, using **17b** (523 mg, 1.83 mmol) and trifluoroacetic acid (4.17 g, 36.5 mmol) in dichloromethane (9.0 mL), and the reaction mixture was stirred for 30 min. The crude product was purified by flash column chromatography (hexane : diethyl ehter = 4 : 1 to 1 : 1) to provide the title compound as a colourless oil (336 mg, 80% yield) including 4% of a decarboxylated product. Carboxylic acid was crystallized at −20 °C, filtered, and washed with hexane.

TLC (dichloromethane : methanol = 9 : 1): R_f = 0.45; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.09 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.54 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 5.79 (ddt, *J* = 17.2, 10.0, 7.2 Hz, 1H), 5.17–5.12 (m, 2H), 3.05 (t, *J* = 6.1 Hz, 2H), 2.70 (d, *J* = 7.6 Hz, 2H), 2.48–2.36 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 195.9, 176.6, 143.4, 134.0, 132.5, 131.2, 128.8, 128.2, 126.9, 119.5, 56.7, 38.4, 29.7, 25.3; **HRMS** (DART): $[M+H]^+$calcd. for $C_{14}H_{15}O_3$, 231.1021; found, 231.1020.

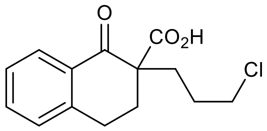
2-Benzyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (18c)



The title compound was prepared following **General procedure**, using **17c** (189 mg, 0.562 mmol) and trifluoroacetic acid (1.28 g, 11.2 mmol) in dichloromethane (2.8 mL), and the reaction mixture was stirred for 40 min. The crude product was purified by flash column chromatography (hexane : diethyl ether = 4 : 1 to 1 : 1) to provide the title compound as a colourless oil (129 mg, 82% yield) including 9% of a decarboxylated product.

TLC (dichloromethane : methanol = 9 : 1): $R_f = 0.34$; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.10 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.54 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.27–7.21 (m, 5H), 7.11 (d, *J* = 7.3 Hz, 1H), 3.36 (d, *J* = 13.8 Hz, 1H), 3.26 (d, *J* = 13.8 Hz, 1H), 3.15–3.05 (m, 2H), 2.45–2.31 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 195.8, 176.6, 143.5, 135.7, 134.2, 131.7, 130.6, 128.9, 128.4, 128.3, 127.1, 127.0, 58.1, 40.2, 29.9, 25.7; **HRMS** (DART): $[M+NH_4]^+$ calcd. for $C_{18}H_{20}N_1O_3$, 298.1443; found, 298.1445.

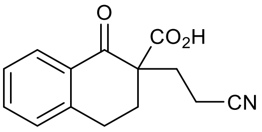
2-(3-Chloropropyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (18d)



The title compound was prepared following **General procedure**, using **17d** (160 mg, 0.497 mmol) and trifluoroacetic acid (1.13 g, 9.94 mmol) in dichloromethane (2.5 mL), and the reaction mixture was stirred for 20 min. The crude product was purified by flash column chromatography (hexane : diethyl ether = 4 : 1 to 1 : 2) to provide the title compound as a white solid (115 mg, 87% yield) including 3% of a decarboxylated product.

TLC (dichloromethane : methanol = 9 : 1): $R_f = 0.45$; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.62 (bs, 1H), 8.05 (d, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 3.59–3.50 (m, 2H), 3.11–2.98 (m, 2H), 2.55–2.50 (m, 1H), 2.30–2.24 (m, 1H), 2.08–2.05 (m, 2H), 1.98–1.81 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 196.4, 176.5, 143.2, 134.2, 131.1, 128.8, 128.3, 127.0, 56.3, 44.8, 31.3, 29.9, 27.8, 25.4; **HRMS** (DART): $[M+H]^+$calcd. for $C_{14}H_{16}Cl_1O_3$, 267.0788; found, 267.0787.

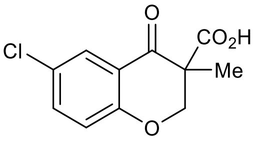
2-(2-Cyanoethyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (18e)



The title compound was prepared following **General procedure**, using **17e** (165 mg, 0.551 mmol) and trifluoroacetic acid (1.25 g, 11.0 mmol) in dichloromethane (2.8 mL), and the reaction mixture was stirred for 1.5 h. The crude product was purified by flash column chromatography (hexane : diethyl ether = 4 : 1 to 1 : 5) to provide the title compound as a pale yellow oil (98.6 mg, 73% yield) including 9% of a decarboxylated product.

TLC (dichloromethane : methanol = 9 : 1): $R_f = 0.16$; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.06 (dd, *J* = 7.8, 2.5 Hz, 1H), 7.56–7.53 (m, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 6.9 Hz, 1H), 3.17–3.00 (m, 2H), 2.68–2.55 (m, 3H), 2.36–2.24 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 194.9, 174.5, 142.7, 134.1, 131.4, 128.8, 128.1, 127.0, 119.3, 56.1, 31.3, 29.9, 25.6, 13.3; **HRMS** (DART): $[M+NH_4]^+$calcd. for $C_{14}H_{17}N_2O_3$, 261.1239; found, 261.1236.

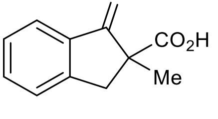
6-Chloro-3-methyl-4-oxochromane-3-carboxylic acid (18f)



The title compound was prepared following **General procedure**, using **17f** (116 mg, 0.391 mmol) and trifluoroacetic acid (891 mg, 7.81 mmol) in dichloromethane (2.0 mL), and the reaction mixture was stirred for 2 h. The crude product was purified by flash column chromatography (hexane : diethyl ether = 4 : 1 to 1 : 5) to provide the title compound as a white solid (75.9 mg, 84% yield).

TLC (dichloromethane : methanol = 9 : 1): $R_f = 0.20$; **^{1}H NMR** (500 MHz, Acetone-d_6): δ 7.78 (d, *J* = 2.7 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.06 (d, *J* = 9.2 Hz, 1H), 4.82 (d, *J* = 11.9 Hz, 1H), 4.41 (d, *J* = 11.9 Hz, 1H), 1.41 (s, 3H); **^{13}C NMR** (126 MHz, Acetone-d_6): δ 190.0, 171.9, 160.8, 136.3, 127.3, 127.0, 122.2, 120.8, 74.8, 53.6, 15.8; **HRMS** (DART): $[M+H]^+$calcd. for $C_{11}H_{10}Cl_1O_4$, 241.0268; found, 241.0270.

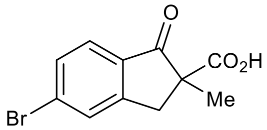
2-Methyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylic acid (18g)



The title compound was prepared following **General procedure**, using **17g** (190 mg, 0.771 mmol) and trifluoroacetic acid (1.76 g, 15.4 mmol) in dichloromethane (3.9 mL), and the reaction mixture was stirred for 30 min. The crude product was purified by flash column chromatography (hexane : diethyl ether = 4 : 1 to 1 : 2) to provide the title compound as a white solid (120 mg, 82% yield) including 9% of a decarboxylated product

TLC (dichloromethane : methanol = 9 : 1): R_f = 0.41; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.0 Hz, 1H), 7.64 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.49–7.47 (m, 1H), 7.41 (dt, *J* = 7.6, 0.8 Hz, 1H), 3.77 (d, *J* = 17.2 Hz, 1H), 3.03 (d, *J* = 17.2 Hz, 1H), 1.52 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 203.5, 177.3, 152.7, 135.8, 134.4, 128.1, 126.6, 125.2, 56.1, 40.0, 21.4; **HRMS** (DART): $[M+NH_4]^+$calcd. for $C_{11}H_{14}N_1O_3$, 208.0974; found, 208.0973.

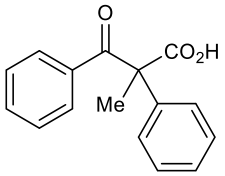
5-Bromo-2-methyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylic acid (18h)



The title compound was prepared following **General procedure**, using **17h** (149 mg, 0.458 mmol) and trifluoroacetic acid (1.04 g, 9.16 mmol) in dichloromethane (2.3 mL), and the reaction mixture was stirred for 30 min. The crude product was purified by flash column chromatography (hexane : diethyl ether = 4 : 1 to 1: 1) to provide the title compound as a white solid (103 mg, 84% yield) including 7% of a decarboxylated product.

TLC (dichloromethane : methanol = 9 : 1): R_f = 0.36; **^{1}H NMR** (500 MHz, Acetone-d_6): δ 7.82 (t, *J* = 1.2 Hz, 1H), 7.64 (d, *J* = 0.8 Hz, 2H), 3.73 (dd, *J* = 17.6, 0.8 Hz, 1H), 3.11 (dd, *J* = 17.8, 0.8 Hz, 1H), 1.45 (s, 3H); **^{13}C NMR** (126 MHz, Acetone-d_6): δ 202.9, 172.8, 155.9, 134.8, 132.1, 130.8, 130.7, 126.5, 56.6, 40.2, 20.7; **HRMS** (DART): $[M+NH_4]^+$calcd. for $C_{11}H_{13}Br_1N_1O_3$, 286.0079; found, 286.0077.

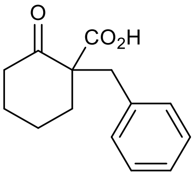
2-Methyl-3-oxo-2,3-diphenylpropanoic acid (18i)



The title compound was prepared following **General procedure**, using **17i** (85.8 mg, 0.276 mmol) and trifluoroacetic acid (630 mg, 5.53 mmol) in dichloromethane (1.4 mL), and the reaction mixture was stirred for 30 min. The crude product was purified by flash column chromatography (hexane : diethyl ether = 4 : 1 to 1 : 1) to provide the title compound as a white solid (66.9 mg, 95% yield) including 1% of a decarboxylated product.

TLC (dichloromethane : methanol = 5 : 1): R_f = 0.40; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.63–7.62 (m, 2H), 7.44–7.40 (m, 3H), 7.35–7.24 (m, 5H), 1.97 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 197.8, 177.6, 138.5, 134.9, 132.7, 129.8, 128.6, 128.2, 127.8, 127.6, 62.7, 24.1; **HRMS** (DART): $[M+H]^+$calcd. for $C_{16}H_{15}O_3$, 255.1021; found, 255.1023.

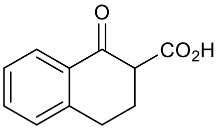
1-Benzyl-2-oxocyclohexane-1-carboxylic acid (18j)



The title compound was prepared following **General procedure**, using **17j** (750 mg, 2.60 mmol) and trifluoroacetic acid (5.93 g, 52.0 mmol) in dichloromethane (13 mL), and the reaction mixture was stirred for 20 min. The crude product was purified by flash column chromatography (hexane : diethyl ether = 4 : 1 to 1 : 1) to provide the title compound as a white solid (444 mg, 74% yield) including 2% of a decarboxylated product.

TLC (dichloromethane : methanol = 9 : 1): R_f = 0.60; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.28–7.23 (m, 3H), 7.14 (dd, *J* = 7.3, 1.2 Hz, 2 H), 3.34 (d, *J* = 14.1 Hz, 1H), 3.06 (d, *J* = 13.8 Hz, 1H), 2.61–2.48 (m, 2H), 2.31–2.27 (m, 1H), 2.02–1.96 (m, 1H), 1.85–1.68 (m, 4H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 207.6, 176.9, 135.9, 130.2, 128.1, 126.9, 61.8, 41.0, 40.3, 35.3, 27.3, 22.2; **HRMS** (DART): $[M+H]^+$calcd. for $C_{14}H_{17}O_3$, 233.1178; found, 233.1177.

1-Oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (18s)

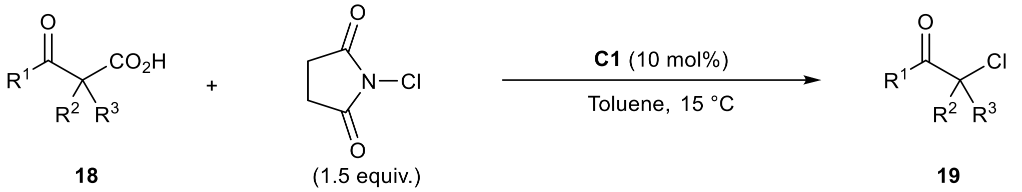


The title compound was prepared following **General procedure**, using **17s** (266 mg, 1.08 mmol) and trifluoroacetic acid (2.46 g, 21.6 mmol) in dichloromethane (5.4 mL), and the reaction mixture was stirred for 40 min. The crude product was purified by flash column chromatography (hexane : diethyl ether = 4 : 1 to 1 : 1) to provide the title compound as a white solid (134 mg, 63% yield) including 2% of a decarboxylated product.

TLC (dichloromethane : methanol = 9 : 1): R_f = 0.30; **^{1}H NMR** (500 MHz, $CDCl_3$): [keto form]: δ 8.11 (d, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 3.54 (dd, *J* = 11.9, 4.6 Hz, 1H), 3.14–3.03 (m, 2H), 2.69–2.65 (m, 1H), 2.41–2.33 (m, 1H); [enol form]: δ 12.19 (s, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 2.85 (t, *J* = 7.8 Hz, 2H), 2.63 (t, *J* = 7.8 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): [keto and enol form]: δ 194.4, 177.2, 174.5, 167.4, 144.1, 140.0, 134.5, 131.3, 131.1, 129.6, 128.9, 127.9, 127.5, 127.0, 126.6, 124.7, 96.1, 53.1, 27.8, 27.6, 26.0, 20.5; **HRMS** (DART): [M+H]$^+$calcd. for $C_{11}H_{11}O_3$, 191.0708; found, 191.0708.

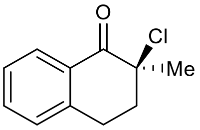
Enantioselective synthesis and characterization of α-chloroketones

Enantioselective decarboxylative chlorination of **1** was performed by General procedure described below. When the reactions were performed, some starting compounds **1** contained 1–9% of decarboxylated by-product as an impurity, as noted in the description of the synthesis of each compound, because some of **1** decomposed slowly while standing at ambient temperature.



To a stirred solution of amine catalyst **C1** (10 mol%) and *N*-chlorosuccinimide (1.5 equiv.) in toluene was added α,α-dialkyl-β-ketocarboxylic acid **18**. Then, the reaction mixture was stirred in the dark. The mixture was purified by flash column chromatography on silica gel to give α-chloroketone **19**.

(*S*)-2-Chloro-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (19a)[9]



The title compound was prepared following **General procedure**, using **C1** (18.6 mg, 0.0245 mmol), *N*-chlorosuccinimide (49.1 mg, 0.368 mmol), and **18a** (50.1 mg, 0.245 mmol) in toluene (1.2 mL), and the reaction mixture was stirred for 24 h. The crude product was purified by flash column chromatography (hexane : dichloromethane = 2 : 1 to 1 : 2) to provide the title compound as a white solid (44.9 mg, 94% yield, 96% ee).

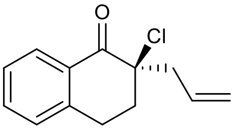
mp: 32 °C; **TLC** (hexane : dichloromethane = 2 : 1): $R_f = 0.34$; $[\alpha]_D^{25} = +51.6$ (*c* 1.4, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.11 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.51 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 3.39 (ddd, *J* = 17.2, 11.3, 4.8 Hz, 1H), 2.89 (ddd, *J* = 17.2, 4.4, 3.4 Hz, 1H), 2.50 (ddd, *J* = 14.5, 4.6, 3.1 Hz, 1H), 2.34 (ddd, *J* = 14.5, 11.3, 4.8 Hz, 1H), 1.83 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 191.5, 143.2, 133.9, 129.9, 129.1, 128.8, 127.1, 67.7, 38.6, 26.8, 26.1; **IR** (neat): 2932, 1695, 1601, 1458, 1307, 1234, 1074, 905, 804, 740, 606, 481 cm^{-1}; **HRMS** (DART): [M+H]$^+$calcd. for $C_{11}H_{12}Cl_1O_1$, 195.0577; found, 195.0575.

The enantiomeric purity of the title compound was determined by HPLC analyses (DAICEL

CHIRALCEL OD-H (0.46 cmφ × 25 cm), hexane : 2-propanol = 500 : 1, flow rate = 1.0 mL/min, retention time; 8.9 min (major) and 10.0 min (minor)).

The absolute configuration of **19a** was determined to be *S* by X-ray crystallographic analysis (see Supplementary Table 3).

2-Allyl-2-chloro-3,4-dihydronaphthalen-1(2*H*)-one (19b)[10]

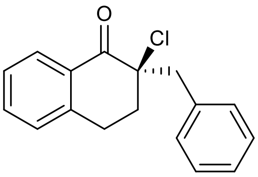


The title compound was prepared following **General procedure**, using **C1** (9.3 mg, 0.012 mmol), *N*-chlorosuccinimide (24.6 mg, 0.184 mmol), and **18b** (28.3 mg, 0.123 mmol) in toluene (0.62 mL), and the reaction mixture was stirred for 18 h. The crude product was purified by flash column chromatography (hexane : dichloromethane = 4 : 1 to 1 : 2) to provide the title compound as a colourless oil (26.1 mg, 96% yield, 96% ee).

TLC (hexane : ethyl acetate = 9 : 1): $R_f = 0.45$; $[\alpha]_D^{24} = +50.5$ (*c* 0.7, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.51 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 6.9 Hz, 1H), 5.88 (ddt, *J* = 16.8, 10.4, 7.2 Hz, 1H), 5.23–5.21 (m, 1H), 5.19 (t, *J* = 1.2 Hz, 1H), 3.34 (ddd, *J* = 18.1, 11.1, 5.0 Hz, 1H), 2.98 (ddt, *J* = 14.1, 6.9, 1.2 Hz, 1H), 2.93–2.86 (m, 2H), 2.43 (ddd, *J* = 14.5, 4.6, 3.4 Hz, 1H), 2.32 (ddd, *J* = 14.8, 11.0, 4.7 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 190.9, 143.2, 134.0, 132.4, 130.1, 129.1, 128.8, 127.1, 120.0, 69.9, 43.0, 35.2, 25.9; **IR** (neat): 3075, 2953, 2935, 1690, 1599, 1454, 1429, 1287, 1241, 1225, 922, 745 cm^{-1}; **HRMS** (DART): $[M+NH_4]^+$calcd. for $C_{13}H_{17}Cl_1N_1O_1$, 238.0999; found, 238.0999.

The enantiomeric purity of the title compound was determined by HPLC analyses (DAICEL CHIRALCEL OD-H (0.46 cmφ × 25 cm), hexane : 2-propanol = 500 : 1, flow rate = 1.0 mL/min, retention time; 8.7 min (major) and 10.5 min (minor)).

2-Benzyl-2-chloro-3,4-dihydronaphthalen-1(2*H*)-one (19c)

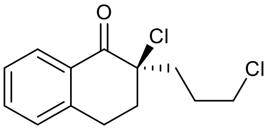


The title compound was prepared following **General procedure**, using **C1** (7.8 mg, 0.010 mmol), and *N*-chlorosuccinimide (20.6 mg, 0.155 mmol), and **18c** (28.8 mg, 0.103 mmol) in toluene (1.0 mL), and the reaction mixture was stirred for 6 h. The crude product was purified by flash column chromatography (hexane : dichloromethane = 2 : 1 to 1 : 2) to provide the title compound as a as a colourless oil (25.2 mg, 91% yield, 93% ee).

TLC (hexane : ethyl acetate = 9 : 1): $R_f = 0.48$; $[\alpha]_D^{27} = -22.7$ (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.15 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.49 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.31–7.23 (m, 5H), 7.21 (d, *J* = 7.9 Hz, 1H), 3.60 (d, *J* = 13.7 Hz, 1H), 3.47 (d, *J* = 14.0 Hz, 1H), 3.30 (ddd, *J* = 16.6, 11.3, 4.9 Hz, 1H), 2.83 (dt, *J* = 17.1, 3.7 Hz, 1H), 2.31 (ddd, *J* = 14.7, 4.9, 3.1 Hz, 1H), 2.23 (ddd, *J* = 14.7, 11.3, 4.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 190.6, 143.0, 135.5, 133.8, 131.2, 130.0, 129.0, 128.6, 128.1, 127.0, 127.0, 70.4, 44.1, 34.7, 25.6; **IR** (neat): 3063, 3031, 2933, 1690, 1603, 1495, 1453, 1436, 1295, 1238, 739, 703, 584, 534 cm^{-1}; **HRMS** (DART): $[M+NH_4]^+$calcd. for $C_{17}H_{19}Cl_1N_1O_1$, 288.1155; found, 288.1153.

The enantiomeric purity of the title compound was determined by HPLC analyses (DAICEL CHIRALCEL OD-H (0.46 cmφ × 25 cm), hexane : 2-propanol = 500 : 1, flow rate = 1.0 mL/min, retention time; 13.5 min (major) and 17.9 min (minor)).

2-Chloro-2-(3-chloropropyl)-3,4-dihydronaphthalen-1(2*H*)-one (19d)

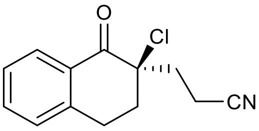


The title compound was prepared following **General procedure**, using **C1** (8.4 mg, 0.011 mmol), *N*-chlorosuccinimide (22.2 mg, 0.166 mmol), and **18d** (29.6 mg, 0.111 mmol) in toluene (0.56 mL), and the reaction mixture was stirred for 8 h. The crude product was purified by flash column chromatography (hexane : dichloromethane = 2 : 1 to 1 : 1) to provide the title compound as a colourless oil (25.6 mg, 90% yield, 97% ee).

TLC (hexane : ethyl acetate = 9 : 1): $R_f = 0.38$; $[\alpha]_D^{28} = +29.4$ (*c* 1.2, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.11 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.52 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 3.67–3.58 (m, 2H), 3.36 (ddd, *J* = 16.3, 10.7, 4.6 Hz, 1H), 2.94 (dt, *J* = 17.2, 4.2 Hz, 1H), 2.49 (ddd, *J* = 14.5, 4.6, 3.8 Hz, 1H), 2.41–2.30 (m, 2H), 2.22 (ddd, *J* = 14.0, 11.7, 4.2 Hz, 1H), 2.13–2.04 (m, 1H), 1.97–1.89 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 190.9, 142.7, 133.9, 129.9, 129.0, 128.7, 127.1, 70.6, 44.8, 35.9, 35.4, 27.6, 25.8; **IR** (neat): 2957, 2931, 2851, 1690, 1604, 1459, 1294, 1238, 918, 819, 743 cm^{-1}; **HRMS** (DART): $[M+H]^+$calcd. for $C_{13}H_{15}Cl_2O_1$, 257.0500; found, 257.0503.

The enantiomeric purity of the title compound was determined by HPLC analyses (DAICEL CHIRALPAK IB-3 (0.46 cmφ × 25 cm), hexane : 2-propanol = 100 : 1, flow rate = 1.0 mL/min, retention time; 8.3 min (major) and 8.8 min (minor)).

3-(2-Chloro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)propanenitrile (19e)

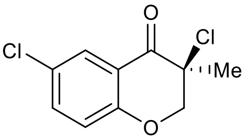


The title compound was prepared following **General procedure**, using **C1** (7.7 mg, 0.010 mmol), *N*-chlorosuccinimide (20.4 mg, 0.153 mmol), and **18e** (25.1 mg, 0.102 mmol) in toluene (1.0 mL), and the reaction mixture was stirred for 6 h. The crude product was purified by flash column chromatography (hexane : dichloromethane = 1 : 1) to provide the title compound as a white solid (19.6 mg, 83% yield, 98% ee).

mp: 57–58 °C; **TLC** (hexane : ethyl acetate = 9 : 1): $R_f = 0.09$; $[\alpha]_D^{30} = +44.9$ (*c* 1.0, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.07 (d, J = 7.6 Hz, 1H), 7.54 (dt, J = 7.5, 1.2 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 3.39 (ddd, J = 16.4, 11.1, 4.6 Hz, 1H), 2.96 (dt, J = 17.6, 3.8 Hz, 1H), 2.83–2.76 (m, 1H), 2.71–2.63 (m, 2H), 2.51 (dt, J = 14.3, 3.9 Hz, 1H), 2.39–2.30 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 190.4, 142.4, 134.3, 129.5, 128.9, 128.7, 127.2, 119.3, 68.9, 35.7, 34.3, 25.5, 13.0; **IR** (neat): 2954, 2928, 2250, 1688, 1603, 1457, 1431, 1304, 1238, 818, 745 cm^{-1}; **HRMS** (DART): $[M+H]^+$calcd. for $C_{13}H_{13}Cl_1N_1O_1$, 234.0686; found, 234.0684.

The enantiomeric purity of the title compound was determined by HPLC analyses (DAICEL CHIRALCEL OD-H (0.46 cmφ × 25 cm), hexane : 2-propanol = 20 : 1, flow rate = 1.0 mL/min, retention time; 29.3min (major) and 24.0 min (minor)).

3,6-Dichloro-3-methylchroman-4-one (19f)

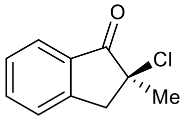


The title compound was prepared following **General procedure**, using **C1** (9.0 mg, 0.012 mmol), *N*-chlorosuccinimide (23.9 mg, 0.179 mmol), and **18f** (28.6 mg, 0.119 mmol) in toluene (0.60 mL), and the reaction mixture was stirred for 16 h. The crude product was purified by flash column chromatography (hexane : ethyl acetate = 20 : 1) to provide the title compound as a white solid (25.5 mg, 93% yield, 93% ee).

mp: 59 °C; **TLC** (hexane : ethyl acetate = 9 : 1): $R_f = 0.39$; $[\alpha]_D^{28} = +29.5$ (*c* 1.3, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.90 (d, J = 2.7 Hz, 1H), 7.47 (dd, J = 8.8, 2.7 Hz, 1H), 7.00 (d, J = 9.2 Hz, 1H), 4.53 (d, J = 12.6 Hz, 1H), 4.34 (d, J = 12.6 Hz, 1H), 1.75 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 185.5, 159.0, 136.3, 127.8, 127.6, 119.6, 119.0, 75.6, 63.0, 21.0; **IR** (neat): 3387, 3072, 2984, 2927, 2855, 1709, 1604, 1477, 1421, 1287, 1268, 1158, 1116, 1039, 822, 697, 615, 519 cm^{-1}; **HRMS** (DART): $[M+H]^+$calcd. for $C_{10}H_9Cl_2O_2$, 230.9980; found, 230.9978.

The enantiomeric purity of the title compound was determined by HPLC analyses (DAICEL CHIRALCEL OD-H (0.46 cmφ × 25 cm), hexane : 2-propanol = 500 : 1, flow rate = 1.0 mL/min, retention time; 11.0 min (major) and 14.4 min (minor)).

2-Chloro-2-methyl-2,3-dihydro-1*H*-inden-1-one (19g)[9]

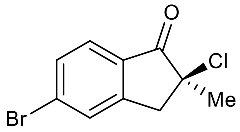


The title compound was prepared following **General procedure**, using **C1** (8.6 mg, 0.011 mmol), *N*-chlorosuccinimide (22.7 mg, 0.170 mmol), and **18g** (19.0 mg, 0.113 mmol) in toluene (0.57 mL), and the reaction mixture was stirred at –20 °C for 48 h. The crude product was purified by flash column chromatography (hexane : dichloromethane = 2 : 1) to provide the title compound as a white solid (17.6 mg, 97% yield, 90% ee).

mp: 75–76 °C; **TLC** (hexane : ethyl acetate = 9 : 1): $R_f = 0.36$; $[\alpha]_D^{25} = -27.1$ (*c* 1.0, CHCl$_3$); **^{1}H NMR** (500 MHz, CDCl$_3$): δ 7.84 (d, *J* = 7.3 Hz, 1H), 7.67 (dt, *J* = 14.9, 1.2 Hz, 1H), 7.45–7.43 (m, 2H), 3.65 (d, *J* = 18.0 Hz, 1H), 3.46 (d, *J* = 18.0 Hz, 1H), 1.80 (s, 3H); **^{13}C NMR** (126 MHz, CDCl$_3$): δ 200.5, 149.7, 136.1, 133.0, 128.4, 126.5, 125.7, 66.8, 45.6, 26.3; **IR** (neat): 2980, 2930, 1724, 1603, 1465, 1331, 1286, 1218, 1055, 977, 797, 749, 624, 529 cm^{-1}; **HRMS** (DART): $[M+NH_4]^+$calcd. for $C_{10}H_{13}Cl_1N_1O_1$, 198.0686; found, 198.0684.

The enantiomeric purity of the title compound was determined by HPLC analyses (DAICEL CHIRALCEL OD-H (0.46 cmφ × 25 cm), hexane : 2-propanol = 500 : 1, flow rate = 1.0 mL/min, retention time; 10.7 min (major) and 12.4 min (minor)).

5-Bromo-2-chloro-2-methyl-2,3-dihydro-1*H*-inden-1-one (19h)

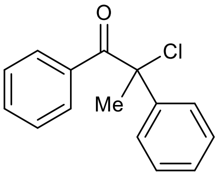


The title compound was prepared following **General procedure**, using **C1** (8.6 mg, 0.011 mmol), *N*-chlorosuccinimide (22.7 mg, 0.170 mmol), and **18h** (30.4 mg, 0.113 mmol) in toluene (0.57 mL), and the reaction mixture was stirred at –30 °C for 72 h. The crude product was purified by flash column chromatography (hexane : dichloromethane = 2 : 1) to provide the title compound as a white solid (28.4 mg, 97% yield, 89% ee).

mp: 50–51 °C; **TLC** (hexane : ethyl acetate = 9 : 1): $R_f = 0.43$; $[\alpha]_D^{28} = -55.9$ (*c* 1.2, CHCl$_3$); **^{1}H NMR** (500 MHz, CDCl$_3$): δ 7.71 (d, *J* = 8.4 Hz, 1H), 7.62 (s, 1H), 7.60–7.58 (m, 1H), 3.63 (d, *J* = 18.0 Hz, 1H), 3.43 (d, *J* = 18.0 Hz, 1H), 1.80 (s, 3H); **^{13}C NMR** (126 MHz, CDCl$_3$): δ 199.2, 151.1, 132.0, 132.0, 131.4, 129.7, 126.8, 66.4, 45.0, 26.0; **IR** (neat): 2969, 2927, 2859, 1732, 1595, 1427, 1322, 1264, 1215, 1056, 975, 865, 830, 654 cm^{-1}; **HRMS** (DART): $[M+NH_4]^+$calcd. for $C_{10}H_{12}Br_1Cl_1N_1O_1$, 275.9791; found, 275.9790.

The enantiomeric purity of the title compound was determined by HPLC analyses (DAICEL CHIRALCEL OD-H (0.46 cmφ × 25 cm), hexane : 2-propanol = 500 : 1, flow rate = 1.0 mL/min, retention time; 14.1 min (major) and 15.6 min (minor)).

2-Chloro-1,2-diphenylpropan-1-one (19i)[11]

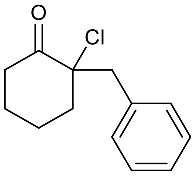


The title compound was prepared following **General procedure**, using **C1** (8.1 mg, 0.011 mmol), *N*-chlorosuccinimide (21.4 mg, 0.160 mmol), and **18i** (27.2 mg, 0.107 mmol) in toluene (0.54 mL), and the reaction mixture was stirred for 2.5 h. The crude product was purified by flash column chromatography (hexane : diethyl ether = 99 : 1 to 90 : 10) to provide the title compound as a white solid (25.1 mg, 96% yield, 48% ee).

mp: 41–42 °C; **TLC** (hexane : dichloromethane = 2 : 1): $R_f = 0.44$; $[\alpha]_D^{28} = -120.6$ (*c* 0.73, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) : δ 7.76–7.74 (m, 2H), 7.51–7.48 (m, 2H), 7.42–7.35 (m, 3H), 7.33–7.29 (m, 1H), 7.27–7.24 (m, 2H), 2.04 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 194.3, 141.6, 133.6, 132.6, 130.8, 128.9, 128.1, 127.8, 125.3, 73.6, 33.2; **IR** (neat): 3063, 3026, 2996, 2931, 1687, 1596, 1492, 1446, 1373, 1249, 1184, 1055, 958, 838, 761, 701, 599 cm^{-1}; **HRMS** (DART): $[M+NH_4]^+$calcd. for $C_{15}H_{17}Cl_1N_1O_1$, 262.0999; found, 262.0999.

The enantiomeric purity of the title compound was determined by HPLC analyses (DAICEL CHIRALPAK IB-3 (0.46 cmφ × 25 cm), hexane : 2-propanol = 500 : 1, flow rate = 0.5 mL/min, retention time; 11.4 min (major) and 12.4 min (minor)).

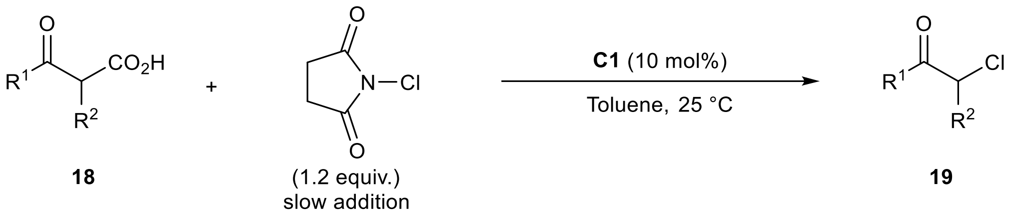
2-Benzyl-2-chlorocyclohexan-1-one (19j)



The title compound was prepared following **General procedure**, using **C1** (9.3 mg, 0.012 mmol), *N*-chlorosuccinimide (24.6 mg, 0.185 mmol), and **18j** (28.5 mg, 0.123 mmol) in toluene (0.62 mL), and the reaction mixture was stirred at 25 °C for 1.5 h. The crude product was purified by flash column chromatography (hexane : ethyl acetate = 20 : 1) to provide the title compound as a colourless oil (26.6 mg, 97% yield, 40% ee).

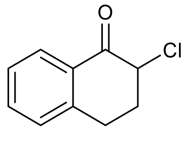
TLC (hexane : ethyl acetate = 9 : 1): $R_f = 0.38$; $[\alpha]_D^{30} = -53.8$ (c 0.50, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.31–7.23 (m, 5H), 3.31 (d, *J* = 14.5 Hz, 1H), 3.23 (d, *J* = 14.5 Hz, 1H), 3.07 (dt, *J* = 14.0, 6.1 Hz, 1H), 2.41–2.36 (m, 1H), 2.08 (dq, *J* = 14.7, 3.1 Hz, 1H), 2.05–1.91 (m, 2H), 1.81 (ddd, *J* = 14.7, 12.0, 3.8 Hz, 1H), 1.71–1.54 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 204.7, 135.6, 131.3, 127.9, 126.9, 73.1, 43.7, 39.3, 37.3, 26.5, 20.8; **IR** (neat): 3030, 2942, 2863, 1721, 1494, 1451, 1434, 1124, 1082, 735, 699, 602 cm^{-1}; **HRMS** (DART): $[M+H]^+$ calcd. for $C_{13}H_{16}Cl_1O_1$, 223.0890; found, 223.0890.

The enantiomeric purity of the title compound was determined by HPLC analyses (DAICEL CHIRALPAK IC-3 (0.46 cmφ × 25 cm), hexane : 2-propanol = 500 : 1, flow rate = 1.0 mL/min, retention time; 19.0 min (major) and 20.7 min (minor)).



To a stirred solution of amine catalyst **C1** (10 mol%), *N*-chlorosuccinimide (0.1 equiv.) and α-alkyl-β-ketocarboxylic acid **18** in toluene was added slowly a solution of *N*-chlorosuccinimide (1.1 equiv.) in toluene over 1 h using a syringe pump in the dark. Then, the reaction mixture was stirred at 25 °C for another 2 h. The mixture was purified by flash column chromatography on silica gel to give α-chloroketone **19**.

2-Chloro-3,4-dihydronaphthalen-1(2*H*)-one (19s)[12]



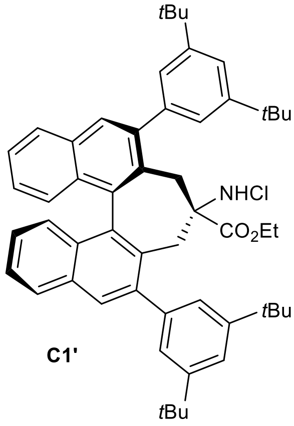
The title compound was prepared following **Method B**, using **C1** (12.6 mg, 0.0166 mmol), *N*-chlorosuccinimide (2.2 + 24.4 mg, 0.017 + 0.182 mmol), and **18s** (31.6 mg, 0.166 mmol) in toluene (0.83 + 2.5 mL). After the completion of adding *N*-chlorosuccinimide, the reaction mixture was stirred for another 2 h. The crude product was purified by flash column chromatography (hexane : dichloromethane = 2 : 1) to provide the title compound as a white solid (27.6 mg, 92% yield, 56% ee).

mp: 42 °C; **TLC** (hexane : ethyl acetate = 9 : 1): $R_f = 0.34$; $[\alpha]_D^{29} = -1.5$ (c 0.41, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.0 Hz, 1H), 7.53 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 4.64 (dd, *J* = 7.6, 3.8 Hz, 1H), 3.29 (ddd, *J* = 16.8, 8.0, 4.6 Hz, 1H), 3.00 (ddd, *J* = 17.2, 6.9, 4.6 Hz, 1H), 2.59 (dddd, *J* = 16.8, 6.9, 4.6, 3.8 Hz, 1H), 2.46

(dddd, *J* = 17.2, 8.0, 7.6, 4.6 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 190.8, 143.1, 134.1, 130.4, 128.7, 128.5, 127.1, 59.8, 32.4, 26.3; **IR** (neat): 3067, 2942, 1691, 1599, 1451, 1435, 1307, 1218, 895, 800, 740, 621, 523 cm^{-1}; **HRMS** (DART): $[M+H]^+$calcd. for $C_{10}H_{10}Cl_1O_1$, 181.0420; found, 181.0418.

The enantiomeric purity of the title compound was determined by HPLC analyses (DAICEL CHIRALCEL OD-H (0.46 cmφ × 25 cm), hexane : 2-propanol = 500 : 1, flow rate = 0.9 mL/min, retention time; 22.9 min (major) and 20.8 min (minor)).

Control experimental procedure for determination of the side product.



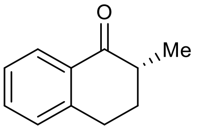
C1'

Enantioselective decarboxylative chlorination of **18a** (104.6 mg, 0.512 mmol) was performed by **General procedure** with 10 mol% **C1** (0.0512 mmol). After the reaction completed, 24% yield of **C1** (9.4 mg) was recovered by flash column chromatography (hexane : dichloromethane = 3 : 2 to 1 : 4), along with a mixture of **19a** and **C1'**. Then, the mixture was purified again by flash column chromatography (hexane : dichloromethane = 4 : 1 to 1 : 1) to give **C1'** as a white solid (27.6 mg, 68% yield based on **C1**).

mp: 168–169 °C; **TLC** (hexane : dichloromethane = 2 : 1): $R_f = 0.50$; $[\alpha]_D^{13} = +58.5$ (*c* 3.10, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 36.7 Hz, 2H), 7.74 (dd, *J* = 19.1, 8.0 Hz, 2H), 7.58 (dd, *J* = 22.4, 8.6 Hz, 2H), 7.55 (d, *J* = 27.5 Hz, 2H), 7.44 (bs, 4H), 7.21 (quint., *J* = 6.5 Hz, 2H), 6.97 (q, *J* = 7.6 Hz, 2H), 4.09 (s, 1H), 3.93 (d, *J* = 14.5 Hz, 1H), 3.84 (d, *J* = 13.0 Hz, 1H), 3.82–3.76 (m, 1H), 3.36–3.29 (m, 2H), 2.63 (d, *J* = 13.0 Hz, 1H), 1.48 (s, 9H), 1.30 (s, 27H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.1, 151.1–150.3, 143.6, 141.5, 141.4, 141.1, 137.0, 135.9, 133.8, 133.3, 133.2, 131.9, 131.8, 131.7, 130.2, 129.4, 128.6, 128.6, 128.3, 127.6, 126.4, 126.3, 126.1, 126.0, 125.2, 121.1, 120.6, 79.1, 61.0, 35.8, 35.0, 31.6, 30.9, 13.8; **IR** (neat): 2966, 2900, 2866, 1746, 1592, 1476, 1445, 1395, 1364, 1272, 1249, 1175, 1052, 882, 747, 716 cm^{-1}; **HRMS** (DART): $[M+H]^+$calcd. for for $C_{54}H_{63}Cl_1N_1O_2$, 792.4547; found, 792.4549.

Enantioselective synthesis and characterization of decarboxylated product

(*R*)-2-Methyl-3,4-dihydronaphthalen-1(2*H*)-one (23)[13]



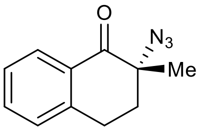
To a stirred solution of amine catalyst **C1** (24.2 mg, 0.0319 mmol) in toluene (1.6 mL) was added **18a** (65.1 mg, 0.319 mmol). Then, the reaction mixture was stirred at 15 °C for 24 h in the dark. The crude product was purified by flash column chromatography (hexane : ethyl acetate = 20 : 1 to 4 : 1) to provide the title compound as a colourless oil (48.3 mg, 78% yield, 64% ee).

The enantiomeric purity of the title compound was determined by HPLC analyses (DAICEL CHIRALCEL OD-H (0.46 cmφ × 25 cm), hexane : 2-propanol = 100 : 1, flow rate = 0.5 mL/min, retention time; 12.3 min (major) and 13.6 min (minor)).

The absolute configuration of the major enantiomer of **23** was determined to be *R* by comparing the retention times on chiral HPLC with those in the literature.[13]

Stereospecific synthesis and characterization of substituted products by S_N2 reactions

2-Azido-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (20)[14]

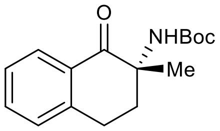


To a stirred solution of **19a** (122.7 mg, 0.630 mmol, 96% ee) in DMSO (2.5 mL) was added NaN_3 (81.9 mg, 1.26 mmol), and the reaction mixture was stirred at 80 °C for 20 min. Diethyl ether and water were added to the mixture, and the mixture was washed with water. The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and then purified by flash column chromatography on silica gel (hexane : ethyl acetate = 10 : 1) to give **20** as a colourless (106.7 mg, 84% yield, 96% ee).

TLC (hexane : dichloromethane = 2 : 1): $R_f = 0.32$; $[\alpha]_D^{27} = +255.1$ (*c* 1.0, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.09 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.52 (dt, *J* = 7.5, 1.4 Hz, 1H), 7.35 (dt, *J* = 7.3, 0.8 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 3.13 (ddd, *J* = 17.2, 8.0, 5.0 Hz, 1H), 2.91 (ddd, *J* = 17.1, 7.1, 4.9 Hz, 1H), 2.21 (ddd, *J* = 13.8, 7.3, 4.6 Hz, 1H), 2.09 (ddd, *J* = 13.7, 7.9, 4.9 Hz, 1H), 1.58 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 194.7, 143.4, 134.2, 130.4, 128.8, 128.7, 127.2, 64.6, 35.0, 25.7, 20.4; **IR** (neat): 2977, 2934, 2107, 1688, 1600, 1458, 1430, 1378, 1308, 1228, 895, 800, 743, 700 cm^{-1}; **HRMS** (DART): $[M+NH_4]^+$calcd. for $C_{11}H_{15}N_4O_1$, 219.1246; found, 219.1244.

The enantiomeric purity of the title compound was determined by HPLC analyses (DAICEL CHIRALPAK IC-3 (0.46 cmφ × 25 cm), hexane : 2-propanol = 500 : 1, flow rate = 1.0 mL/min, retention time; 35.7 min (major) and 39.2 min (minor)).

Tert-butyl (2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)carbamate (21)

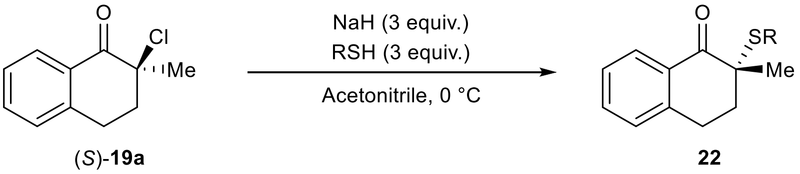


To a stirred suspension of Pd/C (Palladium assay 10%, 2.9 mg, 0.027 mmol) in ethyl acetate (6.1 mL) was added a solution of **7** (110.3 mg, 0.548 mmol, 96% ee) and di-*tert*-butyl dicarbonate (143.6 mg, 0.658 mmol) in ethyl acetate (12.2 mL) under a hydrogen atmosphere. Then, the reaction mixture was stirred at 25 °C for 15 min. The mixture was filtered, and the filtrate was concentrated, and then purified by flash column chromatography on silica gel (hexane : ethyl acetate = 9 : 1) to give **21** as a white solid (139.4 mg, 92% yield, 96% ee).

mp: 95–96 °C; **TLC** (hexane : ethyl acetate = 9 : 1): R_f = 0.24; $[\alpha]_D^{30}$ = –41.3 (*c* 0.61, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.05 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.49 (dt, *J* = 7.5, 1.3 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 5.84 (bs, 1H), 3.09 (ddd, *J* = 17.8, 12.8, 5.0 Hz, 1H), 2.96 (ddd, *J* = 17.7, 5.3, 2.3 Hz, 1H), 2.84 (bs, 1H), 2.36 (dt, *J* = 13.2, 5.4 Hz, 1H), 1.51 (s, 3H), 1.45 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 197.9, 154.6, 142.8, 133.7, 130.3, 128.7, 128.4, 126.7, 79.3, 58.6, 33.1, 28.4, 26.2, 20.4; **IR** (neat): 3410, 2977, 2931, 1717, 1692, 1606, 1491, 1453, 1313, 1170, 1066, 975, 740 cm^{-1}; **HRMS** (DART): $[M+H]^+$calcd. for $C_{16}H_{22}N_1O_3$, 276.1600; found, 276.1602.

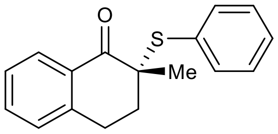
The enantiomeric purity of the title compound was determined by HPLC analyses (DAICEL CHIRALCEL OJ-H (0.46 cmφ × 25 cm), hexane : 2-propanol = 20 : 1, flow rate = 1.0 mL/min, retention time; 6.7 min (major) and 8.9 min (minor)).

S$_N$2 Reaction of α-chloroketones 19a with alkyl thiolate



General procedure: To a stirred suspension of NaH (60% in oil, washed with hexane, 3.0 equiv.) in acetonitrile was added thiols (3.0 equiv.) at 0 °C, and the mixture was stirred at 0 °C for 1 h. Then, a solution of **19a** (96% ee) in acetonitrile was added, and the reaction mixture was attired at 0 °C. The reaction mixture was quenched by adding saturated NH_4Cl aqueous solution at 0 °C, and then extracted with diethyl ether. The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and then purified by flash column chromatography on silica gel to give sulfenyl ketone **22**.

(*R*)-2-Methyl-2-(phenylthio)-3,4-dihydronaphthalen-1(2*H*)-one (22a)[15]



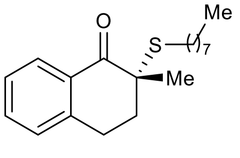
The title compound was synthesised according to **General procedure**, using NaH (36.5 mg, 1.52 mmol), benzenethiol (169.0 mg, 1.52 mmol), and **19a** (98.9 mg, 0.508 mmol, 96% ee) in acetonitrile (4.0 mL). The crude product was purified by flash column chromatography (hexane : dichloromethane = 2 : 1 to 1 : 2) to provide the title compound as a pale yellow oil (133.9 mg, 93% yield, 95% ee).

mp: 102 °C; **TLC** (hexane : dichloromethane = 2 : 1): $R_f = 0.15$; $[\alpha]_D^{30} = +144.6$ (*c* 1.0, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.10 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.48 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.39–7.28 (m, 6H), 7.24 (d, *J* = 7.6 Hz, 1H), 3.51–3.41 (m, 1H), 2.88 (dt, *J* = 17.2, 3.8 Hz, 1H), 2.40–2.33 (m, 2H), 1.44 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 193.3, 142.4, 137.4, 133.0, 131.3, 129.5, 129.4, 128.6, 128.6, 128.3, 126.8, 54.8, 36.1, 25.7, 24.0; **IR** (neat): 3060, 2925, 1678, 1603, 1473, 1454, 1440, 1300, 1230, 963, 903, 747, 690 cm^{-1}; **HRMS** (DART): $[M+H]^+$ calcd. for $C_{17}H_{17}O_1S_1$, 269.1000; found, 269.1004.

The enantiomeric purity of the title compound was determined by HPLC analyses (DAICEL CHIRALPAK AD-H (0.46 cmφ × 25 cm), hexane : 2-propanol = 100 : 1, flow rate = 0.8 mL/min, retention time; 13.1 min (major) and 15.0 min (minor)).

The absolute configuration of the major enantiomer of **22a** was determined to be *R* by X-ray crystallographic analyses (See Supplementary Table 4).

2-Methyl-2-(octylthio)-3,4-dihydronaphthalen-1(2*H*)-one (22b)



The title compound was synthesised according to **General procedure**, using NaH (37.0 mg, 1.54 mmol), 1-octanethiol (225.3 mg, 1.54 mmol), and **19a** (99.6 mg, 0.512 mmol, 96% ee) in acetonitrile (5.1 mL), and the reaction mixture was stirred for 20 min. The crude product was purified by flash column chromatography (hexane : dichloromethane = 2 : 1) to provide the title compound as a colourless oil (149.7 mg, 96% yield, 95% ee).

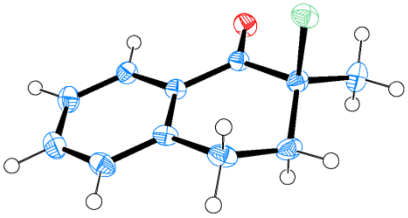
TLC (hexane : dichloromethane = 2 : 1): $R_f = 0.28$; $[\alpha]_D^{20} = +22.9$ (*c* 1.2, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.11 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.44 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 7.3 Hz, 1H), 3.34 (ddd, *J* = 17.3, 12.7, 5.2 Hz, 1H), 2.77 (qd, *J* = 17.2, 2.3 Hz, 1H), 2.58 (dt, *J* = 11.9, 7.5 Hz, 1H), 2.38–2.28 (m, 2H), 2.23 (qd, *J* = 13.8, 2.3 Hz, 1H), 1.58 (s, 3H), 1.47–1.41 (m, 2H), 1.31–1.21 (m, 10H), 0.86 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 192.8, 142.5, 132.8, 130.7, 128.4, 128.3, 126.6, 50.4, 36.5, 31.7, 29.1, 29.1, 29.0, 27.4, 25.6, 23.8, 22.6, 14.0; **IR** (neat): 2958, 2924, 2854, 1677, 1604, 1453, 1376, 1299, 1229, 963, 905, 743 cm^{-1}; **HRMS** (DART): $[M+H]^+$calcd. for $C_{19}H_{29}O_1S_1$, 305.1939; found, 305.1941. The enantiomeric purity of the title compound was determined by HPLC analyses (DAICEL CHIRALCEL OD-H (0.46 cmφ × 25 cm), hexane : 2-propanol = 500 : 1, flow rate = 1.0 mL/min, retention time; 8.5 min (major) and 6.9 min (minor)).

Recrystallization of 19a and 22a

Single crystals of **19a** or **22a** for the X-ray crystallographic analysis prepared by the following procedure. **19a** (96% ee) or **22a** (95% ee) was dissolved in a minimum amount of diethyl ether, and five times the amount of hexane was added. Then, **19a** or **22a** was recrystallized at −20 °C for 1 or 2 days. The obtained crystal was used for the X-ray crystallographic analyses to determine absolute configuration.

X-ray crystallographic analysis of 19a and 22a

Crystal data and structure refinement for **19a**

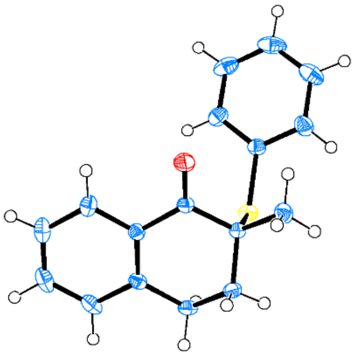


Deposition number	CCDC 1516051	
Empirical formula	C11 H11 Cl O	
Formula weight	194.65	
Temperature	120(2) K	
Wavelength	0.71069 Å	
Crystal system	Orthorhombic	
Space group	$P\ 2_12_12_1$	
Unit cell dimensions	a = 6.2460(10) Å	α= 90°.
	b = 9.5642(16) Å	β= 90°.
	c = 16.163(3) Å	γ = 90°.
Volume	965.6(3) Å^3	
Z	4	
Density (calculated)	1.339 Mg/m^3	
Absorption coefficient	0.350 mm^{-1}	
F(000)	408	
Crystal size	0.50 x 0.30 x 0.30 mm^3	
Theta range for data collection	2.47 to 33.98°.	
Index ranges	-9<=h<=6, -14<=k<=12, -24<=l<=25	

Reflections collected	11097
Independent reflections	3649 [R(int) = 0.0246]
Completeness to theta = 33.98°	97.6 %
Max. and min. transmission	0.9024 and 0.8446
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3649 / 0 / 162
Goodness-of-fit on F^2	1.070
Final R indices [I>2sigma(I)]	R1 = 0.0281, wR2 = 0.0747
R indices (all data)	R1 = 0.0297, wR2 = 0.0765
Absolute structure parameter	0.05(4)
Largest diff. peak and hole	0.281 and -0.246 e.Å^{-3}
Hydrogen treatment	refine all parameters

Crystal data and structure refinement for **22a**

Deposition number	CCDC 1516052	
Empirical formula	C17 H16 O S	
Formula weight	268.36	
Temperature	120(2) K	
Wavelength	0.71069 Å	
Crystal system	Monoclinic	
Space group	P 2_1	
Unit cell dimensions	a = 8.1745(7) Å	α = 90°.
	b = 12.6892(7) Å	β= 96.208(3)°.
	c = 13.4055(9) Å	γ = 90°.
Volume	1382.37(17) Å^3	
Z	4	
Density (calculated)	1.289 Mg/m^3	
Absorption coefficient	0.223 mm^{-1}	
F(000)	568	
Crystal size	0.30 x 0.30 x 0.20 mm^3	
Theta range for data collection	1.53 to 34.00°.	
Index ranges	-10<=h<=12, -19<=k<=19, -21<=l<=21	

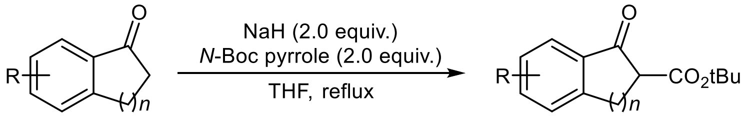


Reflections collected	33516
Independent reflections	10847 [R(int) = 0.0256]
Completeness to theta = 33.98°	99.0 %
Max. and min. transmission	0.9568 and 0.9362
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10847 / 1 / 471
Goodness-of-fit on F^2	1.045
Final R indices [I>2sigma(I)]	R1 = 0.0347, wR2 = 0.0830
R indices (all data)	R1 = 0.0383, wR2 = 0.0861
Absolute structure parameter	0.01(3)
Largest diff. peak and hole	0.327 and -0.204 e.$Å^{-3}$
Hydrogen treatment	refine all parameters

Synthesis and characterization of α-alkyl-β-keto esters

β-keto esters **26** were prepared by following procedure below. **26b**[16] and **26i**[17] was prepared by following literature method and ^{1}H NMR spectra were in good agreement with those reported in the literatures.

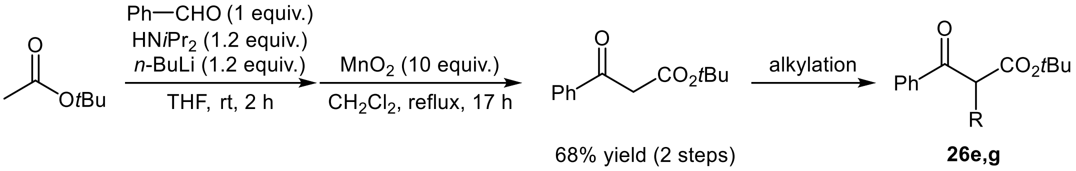
Synthesis of 26a[18], 26c[19], 26d[20]



26a,b,d

To a stirred suspension of NaH (60% in oil, washed with hexane, 2.0 equiv.) in THF (20 mL) was added a solution of ketone (1 equiv.) in THF at room temperature and the mixture was stirred for 1 h under reflux condition. Then, *N*-Boc pyrrole (2.0 equiv.) was added to the mixture at room temperature and the reaction mixture was monitored by Thin-Layer chromatography and after full consumption of starting material, the reaction mixture was quenched by adding 1.2N HCl at 0 °C, and then extracted with diethylether, dried over anhydrous Na_2SO_4, concentrated, and then purified by flash column chromatography on silica gel to give alkylated α-alkyl-β-ketoester **25**.

Synthesis of 26e, 26g

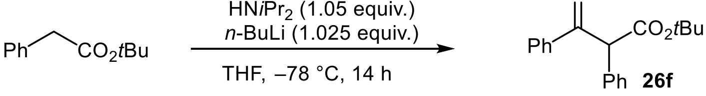


To a stirred solution of diisopropyl amine (1.2 equiv., 24 mmol) in THF (25 mL) was added a solution of *n*-butyl lithium in 1.6 M hexane (1.2 equiv., 24 mmol) at 0 °C. The solution was stirred at 0 °C for 15 min. Then, *t*-butyl acetate (1 equiv., 20 mmol) was added dropwise at −78 °C. After stirring for 30 min, benzaldehyde (1 equiv., 20 mmol) was added, and the reaction mixture was stirred at ambient temperature for 2 h. The reaction mixture was quenched by adding saturated NH_4Cl aqueous solution at 0 °C, and then extracted with dichloromethane, dried over anhydrous $N_{a2}SO_4$, concentrated. The resulting crude mixture was directly subjected to oxidation without further purification. The crude mixture was dissolved with dichloromethane (24 mL) and manganese (IV) oxide (10 equiv., 200 mmol) was added. The reaction mixture was stirred under reflux condition for 17 h, then cooled to 0 °C, filtered by Celite. The filtrate was concentrated, and then purified by flash column chromatography on silica gel to give β-ketoester.

26e[21]: The β-ketoester (1 equiv., 6.81 mmol) was dissolved with acetone (16 mL). The solution was added K_2CO_3 (1.1 equiv., 7.49 mmol), MeI (1.45 equiv., 9.87 mmol) and stirred at 40 °C for 23 h. The reaction mixture was filtered by Celite and diluted by dichloromethane, washed by 1.2N HCl, dried over Na_2SO_4, concentrated. The crude mixture was purified by flash column chromatography on silica gel (hexane/diethylether 19:1 to 87:13) to give **26e** (1110 mg, 70% yield).

26g[22]: To a stirred suspension of NaH (60% in oil, washed with hexane, 1.2 equiv., 8.17 mmol) in THF 29 mL) was added a solution of the β-ketoester (1 equiv., 6.81 mmol) in THF (5 mL) at 0 °C, and the mixture was stirred at 0 °C for 1 h. Then, benzylbromide (1.5 equiv., 10.2 mmol) was added, and the reaction mixture was stirred at room temperature for 19 h. The reaction mixture was quenched by adding saturated NH_4Cl aqueous solution at 0 °C, and then extracted with dichloromethane, dried over anhydrous Na_2SO_4, concentrated, and then purified by flash column chromatography on silica gel (hexane/diethylether 10:1) to give **26g** (967 mg, 46% yield).

Synthesis of 26f



To a stirred solution of diisopropyl amine (1.05 equiv., 5.23 mmol) in THF (20 mL) was added a solution of *n*-butyl lithium in 1.6 M hexane (1.05 equiv. 5.23 mmol) at −78 °C. The solution was stirred at −78 °C for 1 h. Then, a solution of *t*-butyl 2-phenylacetate (1 equiv., 4.98 mmol) in THF (5 mL) was added dropwise. After stirring for 30 min, benzoyl chloride (1.2 equiv., 5.98 mmol) was added, and the reaction mixture was stirred at −78 °C for 1 h. The reaction mixture was quenched by adding saturated NH_4Cl aqueous solution at 0 °C, and then extracted with dichloromethane, dried over anhydrous Na_2SO_4, concentrated, and then purified by column chromatography on silica gel (hexane /EtOAc = 30 : 1 to 4 : 1) and the resulting solid was washed by cold hexane to give **25f**.

Yield: 815 mg (55% yield); white solid; R_f = 0.33 (hexane/EtOAc 4:1), mp: 81.2 °C.

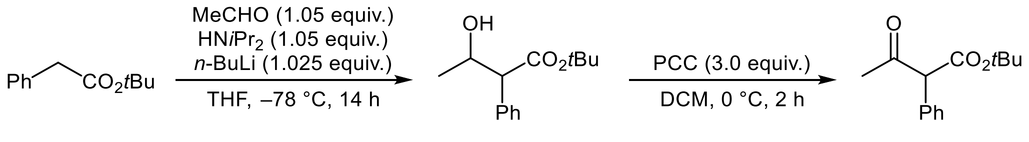
IR (NaCl): 3063, 3030, 2978, 1741, 1682, 1449, 1393, 1369, 1264, 1218, 1144, 747, 698, 402 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.97–7.96 (m, 2 H, H_{Ar}), 7.51 (t, J = 7.3 Hz, 1 H, H_{Ar}), 7.43–7.39 (m, 4 H, H_{Ar}), 7.35 (t, J = 7.3 Hz, 2 H, H_{Ar}), 7.29 (t, J = 7.3 Hz, 1 H, H_{Ar}), 5.51 (s, 1 H, CH), 1.42 (s, 9 H, C_3H_9).

^{13}C NMR ($CDCl_3$, 126 MHz): δ =193.6 (CO), 167.8 (COO), 135.9 (C_{Ar}), 133.3 (C_{Ar}), 133.2 (C_{Ar}), 129.5 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.6 (C_{Ar}), 127.9 (C_{Ar}), 82.2 (CH), 61.4 ($\textit{C}C_3H_9$), 27.8 (C_3H_9).

HRMS (DART): m/z $[M + H]^+$ calcd for $C_{19}H_{21}O_3$: 297.1491; found: 297.1490.

Synthesis of 26h



55: 80% yield (7:3 d.r.)

26h

To a stirred solution of diisopropyl amine (1.05 equiv., 5.94 mmol) in THF (14 mL) was added a solution of *n*-butyl lithium in 1.6 M hexane (1.05 equiv., 5.80 mmol) at −78 °C. The solution was stirred at −78 °C for 1 h. Then, a solution of *t*-butyl 2-phenylacetate (1 equiv., 5.66 mmol) in THF (5 mL) was added dropwise. After stirring for 1 h, acetoaldehyde (1.05 equiv., 5.94 mmol) was added, and the reaction mixture was stirred at −78 °C for 14 h. The reaction mixture was quenched by adding 1.2N HCl at 0 °C, extracted with dichloromethane, dried over anhydrous Na_2SO_4, concentrated, and then purified by column chromatography on silica gel (hexane/EtOAc = 7 : 1 to 4 : 1) to give **55** as diastereomixture.

***Tert*-butyl 3-hydroxy-2-phenylbutanoate 55**

Yield: 1075 mg (80%); colorless oil; R_f = 0.3 (major), 0.23 (minor), (hexane/EtOAc 7:1).

IR (NaCl): 3438, 3030, 2976, 2934, 1705, 1600, 1492, 1455, 1393, 1369, 1248, 1142, 948, 754, 700, 595, 515 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): (major) δ = 7.36–7.32 (m, 5 H, H_{Ar}), 4.32–4.27 (m, 1 H, C*H*OH), 3.40 (d, *J* = 7.3 Hz, 1 H, PhC*H*), 1.40 (s, 9 H, C_3H_9), 1.19 (d, *J* = 6.1 Hz, 3 H, CH_3). (minor) δ = 7.32–7.23 (m, 5 H, H_{Ar}), 4.27–4.22 (m, 1 H, C*H*OH), 3.39 (d, *J* = 9.2 Hz, 1 H, PhC*H*), 1.39 (s, 9 H, C_3H_9), 1.02 (d, *J* = 6.5 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 126 MHz): (major) δ = 172.3 (COO), 135.6 (C_{Ar}), 128.9 (C_{Ar}), 128.4 (C_{Ar}), 127.4 (C_{Ar}), 81.2 (Ph*C*), 68.5 (*C*C_3H_9), 59.7 (CHOH), 27.8 (C_3H_9), 20.4 (CH_3). (minor) δ = 172.9 (COO), 136.8 (C_{Ar}), 128.5 (C_{Ar}), 128.1 (C_{Ar}), 127.2 (C_{Ar}), 81.3 (Ph*C*), 69.6 (*C*C_3H_9), 60.8 (CHOH), 27.8 (C_3H_9), 20.3 (CH_3).

HRMS (DART): m/z $[M + H]^+$ calcd for $C_{14}H_{21}O_3$: 237.1491; found: 237.1490.

Resulting **55** was subjected to oxidation reaction with pyridinium chlorochromate. MS 4A (9.05 g) was added to a flask and the flask was flame dried *in vacuo*. The flask was added dichloromethane (73 mL) and a solution of **55** (1 equiv., 4.13 mmol) in dichloromethane (10 mL). The suspension was added pyridinium chlorochromate (3 equiv., 12.4 mmol) at 0 °C. After stirring for 2 h at 0 °C , the reaction mixture was diluted diethylether (80 mL) and filtered by Celite, and then purified by column chromatography on silica gel (hexane : EtOAc = 6 : 1) to give **26h**.

***Tert*-butyl 3-oxo-2-phenylbutanoate 26h**

Yield: 364 mg (38% yield); white solid; R_f = 0.70–0.36 (hexane/EtOAc 4:1), mp: 48.5 °C.

IR (NaCl): 3003, 2979, 2933, 1713, 1496, 1455, 1369, 1355, 1249, 1137, 856, 751, 699 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.36–7.28 (m, 5 H, H_{Ar}), 4.62 (s, 1 H, CH), 2.14 (s, 3 H, CH_3), 1.46 (s, 9 H, C_3H_9).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 201.6 (CO), 167.4 (COO), 132.8 (C_{Ar}), 129.1 (C_{Ar}), 128.5 (C_{Ar}), 127.8 (C_{Ar}), 81.8 (CH), 66.3 (*C*C_3H_9), 28.5 (CH_3), 27.6 (C_3H_9).

HRMS (DART): m/z $[M + H]^+$ calcd for $C_{14}H_{19}O_3$: 235.1334; found: 235.1334.

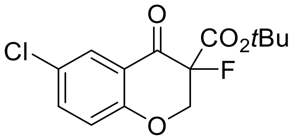
Synthesis and characterization of α-alkyl-β-fluoro-β-ketoesters

α-Alkyl-α-fluoro-β-ketoesters **27** were prepared by following **General procedure A** (**27a**–**27e**, **27g**, **27i**) or **General procedure B** (**27f**, **27h**). ^{1}H NMR spectra of α-alkyl-α-fluoro-β-ketoesters **27a**[24], **27c**[24], **27d**[25], **27e**[26], **27g**[27], **27i**[2b] and α-fluoro-β-keto carboxylic acids **28a**,[23] **28g**[23], **28i**[23] were in good agreement with those reported in the literatures.

General procedure A: α-Alkyl-β-ketoester (1.32 mmol) was added to a stirred suspension of NaH (60% in oil, washed with hexane, 1.1 equiv., 1.45 mmol) in THF (6.7 mL) at 0 °C, and the mixture was stirred at 0 °C for 30 min and then at ambient temperature for 30 min. Subsequently, *N*-fluorobenzenesulfonimide (NFSI) (1.1 equiv., 1.45 mmol) was added, and the reaction mixture was stirred at 0 °C for 45 min. The reaction mixture was quenched by adding saturated NH_4Cl aqueous solution at 0 °C, and then extracted with dichloromethane, dried over anhydrous Na_2SO_4, concentrated, and then purified by flash column chromatography on silica gel (hexane/EtOAc 7:1) to yield α-alkyl-α-fluoro-β-ketoesters.

General procedure B: α-Alkyl-β-ketoester (2 mmol) was added to a suspension of NaH (60% in oil, washed with hexane and dried *in vacuo*, 2.2 equiv., 2.2 mmol) in THF (10 mL for **27f**, 6 mL for **27h**) at 0 °C. The mixture was stirred at ambient temperature for 20 min. Subsequently, the mixture was diluted with DMF (10 mL), and Selectfluor (1.1 equiv., 2.2 mmol) was added at 0 °C. The reaction mixture was stirred for 14 h. After addition of H_2O, the organic layer was extracted using Et_2O, dried over anhydrous $NaSO_4$, concentrated, and then purified by flash column chromatography on silica gel (hexane/EtOAc 10:1) to yield α-alkyl-α-fluoro-β-ketoesters.

***Tert*-butyl 6-chloro-3-fluoro-4-oxochromane-3-carboxylate (27b)**



Prepared by following **General procedure A**. Yield: 329 mg (83%); white solid; R_f = 0.45 (hexane/ethyl acetate 4:1); mp: 86.0 °C.

IR (NaCl): 2982, 2935, 1762, 1704, 1606, 1475, 1422, 1288, 1156, 1117, 1099, 832, 640 cm^{-1}.

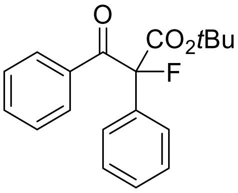
^1H NMR ($CDCl_3$, 500 MHz): δ = 7.90 (d, J = 2.7 Hz, 1 H, H_{Ar}), 7.51 (dd, J = 8.8, 2.7 Hz, 1 H, H_{Ar}), 7.01 (d, J = 8.8 Hz, 1 H, H_{Ar}), 4.76 (dd, J = 21.8, 12.6 Hz, 1 H, C*H*H'), 4.61 (dd, J = 12.6, 9.5 Hz, 1 H, CH*H'*), 1.47 (s, 9 H, C_3H_9).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 182.5 (d, J = 20.4 Hz, CO), 163.6 (d, J = 24.0 Hz, COO), 159.3 (C_{Ar}), 136.9 (C_{Ar}), 128.0 (C_{Ar}), 127.0 (C_{Ar}), 120.2 (C_{Ar}), 119.7 (C_{Ar}), 88.5 (d, J = 197.9 Hz, CF), 85.3 (CH_2), 70.4 (d, J = 26.4 Hz, *C*C_3H_9), 27.8 (C_3H_9).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –173.7 (d, J = 22.0 Hz).

HRMS (DART): m/z $[M + NH_4]^+$ calcd for $C_{14}H_{18}O_4FClN$: 318.0908; found: 318.0906.

***Tert*-butyl 2-fluoro-3-oxo-2,3-diphenylpropanoate (27f)**



Prepared by following **General procedure B**. Yield: 346 mg (55%); colorless oil; R$_f$ = 0.36 (hexane/ethyl acetate 10:1).

IR (NaCl): 3064, 2980, 2935, 1749, 1696, 1597, 1449, 1371, 1261, 1153, 1071, 751, 698, 614, 410 cm^{-1}.

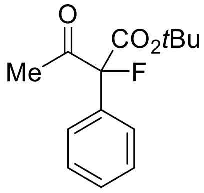
^{1}H NMR (CDCl$_3$, 500 MHz): δ = 7.98 (d, *J* = 8.0 Hz, 2 H, H$_{Ar}$), 7.59–7.57 (m, 2 H, H$_{Ar}$), 7.49–7.46 (t, *J* = 7.4 Hz, 1 H, H$_{Ar}$), 7.40–7.33 (m, 5 H, H$_{Ar}$), 1.42 (s, 9 H, C$_3$H$_9$).

^{13}C NMR (CDCl$_3$, 126 MHz): δ = 191.0 (d, *J* = 26.4 Hz, CO), 165.0 (d, *J* = 26.4 Hz, COO), 133.7 (C$_{Ar}$), 133.5 (C$_{Ar}$), 129.6 (d, *J* = 22.8 Hz, C$_{Ar}$), 128.9 (C$_{Ar}$), 128.2 (C$_{Ar}$), 128.0 (C$_{Ar}$), 125.5 (d, *J* = 8.4 Hz, C$_{Ar}$), 98.4 (d, *J* = 199.1 Hz, CF), 84.2 (*C*C$_3$H$_9$), 27.4 (C$_3$H$_9$).

^{19}F NMR (CDCl$_3$, 470 MHz): δ = –156.3 (s).

HRMS (DART): m/z [M + NH$_4$]$^+$ calcd for C$_{19}$H$_{23}$O$_3$FN: 332.01662; found: 332.1663.

***Tert*-butyl 2-fluoro-3-oxo-2-phenylbutanoate (27h)**



Prepared by following **General procedure B**. Yield: 415 mg (82%); colorless oil; R$_f$ = 0.41 (hexane/ethyl acetate 10:1).

IR (NaCl): 2981, 2935, 1728, 1450, 1371, 1356, 1277, 1155, 1069, 838, 756, 697, 566 cm^{-1}.

^{1}H NMR (CDCl$_3$, 500 MHz): δ = 7.55–7.53 (m, 2 H, H$_{Ar}$), 7.43–7.39 (m, 3 H, H$_{Ar}$), 2.29 (d, *J* = 5.0 Hz, 3 H, CH$_3$), 1.50 (s, 9 H, C$_3$H$_9$).

^{13}C NMR (CDCl$_3$, 126 MHz): δ = 200.1 (d, *J* = 29.0 Hz, CO), 164.2 (d, *J* = 25.2 Hz, COO), 132.7 (d, *J* = 21.6 Hz, C$_{Ar}$), 128.9 (C$_{Ar}$), 128.1 (C$_{Ar}$), 125.3 (d, *J* = 9.6 Hz, C$_{Ar}$), 98.6 (d, *J* = 199.1 Hz, CF), 84.1 (*C*C$_3$H$_9$), 27.5 (C$_3$H$_9$), 25.2 (CH$_3$).

^{19}F NMR (CDCl$_3$, 470 MHz): δ = –161.9 (s).

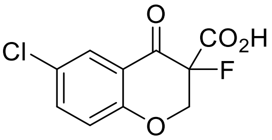
HRMS (DART): m/z [M + NH$_4$]$^+$ calcd for C$_{14}$H$_{21}$O$_3$FN: 270.1506; found: 270.1507.

Synthesis and characterization of α-fluoro-β-ketoacids 28

α-Fluoro-β-keto carboxylic acids **28** were synthesized by acidolysis of the corresponding α-fluoro-β-ketoesters **27**.

Typical procedure: Trifluoroacetic acid (20 equiv., 21.1 mmol) was added to a stirred solution of α-alkyl-α-fluoro-β-ketoester **27b** (1.05 mmol) in CH$_2$Cl$_2$ (5.3 mL) at 0 °C, and the reaction mixture was stirred at ambient temperature for 90 min. The mixture was concentrated, and then purified by flash column chromatography on silica gel (hexane/Et_2O 4:1 to 1:2) to yield α-fluoro-β-keto carboxylic acids **28b**.

6-Chloro-3-fluoro-4-oxochromane-3-carboxylic acid (28b)



Yield: 222 mg (86%); white solid; R_f = 0.09 (CH_2Cl_2/MeOH 9:1).

IR (NaCl): 3626, 3414, 1714, 1667, 1473, 1267, 1212, 1109, 900, 818, 637 cm^{-1}.

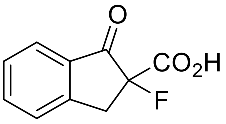
^{1}H NMR (CD_3OD, 500 MHz): δ = 7.79 (d, *J* = 2.7 Hz, 1 H, H_{Ar}), 7.55 (dd, *J* = 8.8, 2.3 Hz, 1 H, H_{Ar}), 7.06 (d, *J* = 8.8 Hz, 1 H, H_{Ar}), 4.86–4.73 (m, 2 H, CH_2).

^{13}C NMR (CD_3OD, 126 MHz): δ = 183.7 (d, *J* = 20.4 Hz, CO), 167.5 (d, *J* = 25.2 Hz, COO), 161.0 (C_{Ar}), 138.0 (C_{Ar}), 128.8 (C_{Ar}), 127.5 (C_{Ar}), 121.2 (C_{Ar}), 121.1 (C_{Ar}), 90.3 (d, *J* = 195.5 Hz, CF), 71.6 (d, *J* = 26.4 Hz, CH_2).

^{19}F NMR (CD_3OD, 470 MHz): δ = –182.5 (s).

HRMS (DART): m/z $[M + NH_4]^+$ calcd for $C_{10}H_{10}ClFO_4N$: 262.0282; found: 262.0285.

2-Fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylic acid (28c)



1.25 mmol of **27c** was used and the product was purified by (hexane/Et_2O 4:1 to 1:5); Yield: 151 mg (62%); pale purple solid; R_f = 0.14 (CH_2Cl_2/MeOH 5:1).

IR (NaCl): 3462, 2961, 2917, 2848, 1721, 1605, 1268, 1200, 923, 660 cm^{-1}.

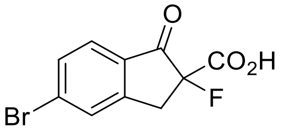
^{1}H NMR (CD_3OD, 500 MHz): δ = 7.78–7.72 (m, 2 H, H_{Ar}), 7.58 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.48 (t, *J* = 7.6 Hz, 1 H, H_{Ar}), 3.80 (dd, *J* = 17.6, 10.7 Hz, 1 H, C*H*H’) 3.41 (dd, *J* = 23.3, 17.6 Hz, 1 H, CH*H’*).

^{13}C NMR (CD_3OD, 126 MHz): δ = 197.7 (d, *J* = 18.0 Hz, CO), 170.3 (d, *J* = 28.8 Hz, COO), 152.9 (d, *J* = 4.8 Hz, C_{Ar}), 138.0 (C_{Ar}), 134.6 (C_{Ar}), 129.7 (C_{Ar}), 128.0 (C_{Ar}), 126.0 (C_{Ar}), 95.8 (d, *J* = 197.9 Hz, CF), 39.2 (d, *J* = 25.2 Hz, CH_2).

^{19}F NMR (CD_3OD, 470 MHz): δ = –172.4 (d, *J* = 14.7 Hz).

HRMS (DART): m/z $[M + NH_4]^+$ calcd for $C_{10}H_{11}FO_3N$: 212.0723; found: 212.0721.

5-Bromo-2-fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylic acid (28d)



0.693 mmol of **27d** was used and the product was purified by (hexane/Et$_2$O 4:1 to 1:5); Yield: 152 mg (80%); white solid; R$_f$ = 0.35 (CH$_2$Cl$_2$/MeOH 5:1).

IR (NaCl): 3486, 2361, 2340, 1725, 1593, 1267, 1210, 1057, 923, 668, 491 cm^{-1}.

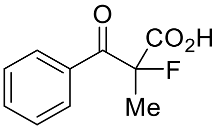
^{1}H NMR (CD$_3$OD, 500 MHz): δ = 7.82 (s, 1 H, H$_{Ar}$), 7.68–7.65 (m, 2 H, H$_{Ar}$), 3.80 (dd, *J* = 18.0, 9.9 Hz, 1 H, C*H*H'), 3.42 (dd, *J* = 23.3, 18.0 Hz, 1 H, CH*H'*).

^{13}C NMR (CD$_3$OD, 126 MHz): δ = 196.5 (d, *J* = 19.2 Hz, CO), 169.8 (d, *J* = 28.8 Hz, COO), 154.4 (d, *J* = 4.8 Hz, C$_{Ar}$), 133.6 (C$_{Ar}$), 133.3 (C$_{Ar}$), 133.1 (C$_{Ar}$), 131.3 (C$_{Ar}$), 127.3 (C$_{Ar}$), 95.7 (d, *J* = 199.1 Hz, CF), 38.9 (d, *J* = 24.0 Hz, CH$_2$).

^{19}F NMR (CD$_3$OD, 470 MHz): δ = –173.8 (d, *J* = 22.0 Hz).

HRMS (DART): m/z [M + NH$_4$]$^+$ calcd for C$_{10}$H$_{10}$FBrO$_3$N: 289.9828; found: 289.9828.

2-Fluoro-2-methyl-3-oxo-3-phenylpropanoic acid (28e)



1.19 mmol of **27e** was used and the product was purified by (hexane/Et$_2$O 4:1 to 1:2); Yield: 214 mg (92%), including 1% of decarboxylated product; colorless oil; R$_f$ = 0.20 (CH$_2$Cl$_2$/MeOH 5:1).

IR (NaCl): 3513, 3072, 1697, 1597, 1449, 1271, 1132, 981, 698, 657, 535, 431, 423 cm^{-1}.

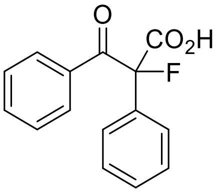
^{1}H NMR (CDCl$_3$, 500 MHz): δ = 11.2 (s, 1 H, COOH), 8.06–8.04 (m, 2 H, H$_{Ar}$), 7.60–7.56 (m, 1 H, H$_{Ar}$), 7.46–7.42 (m, 2 H, H$_{Ar}$), 1.90 (d, *J* = 22.5 Hz, 3 H, CH$_3$).

^{13}C NMR (CDCl$_3$, 126 MHz): δ = 191.6 (d, *J* = 24.0 Hz, CO), 173.4 (d, *J* = 25.2 Hz, COO), 134.2 (C$_{Ar}$), 132.9 (d, *J* = 3.6 Hz, C$_{Ar}$), 129.8 (d, *J* = 4.8 Hz, C$_{Ar}$), 128.7 (C$_{Ar}$), 96.9 (d, *J* = 197.9Hz, CF), 21.1 (d, *J* = 22.8 Hz, CH$_3$).

^{19}F NMR (CDCl$_3$, 470 MHz): δ = –153.0 (q, *J* = 22.0 Hz).

HRMS (DART): m/z [M + NH$_4$]$^+$ calcd for C$_{10}$H$_{13}$O$_3$FN: 214.0880; found: 214.0881.

2-Fluoro-3-oxo-2,3-diphenylpropanoic acid (28f)



1.10 mmol of **27f** was used and the product was purified by (hexane/Et_2O 4:1 to 1:4); Yield: 175 mg (62%); white solid; R_f = 0.1 (CH_2Cl_2/MeOH 9:1).

IR (NaCl): 3020, 2830, 1731, 1684, 1446, 1278, 1228, 1069, 887, 696, 676, 563 cm^{-1}.

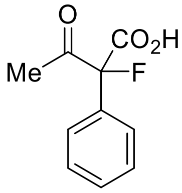
^1H NMR (CD_3OD, 500 MHz): δ = 7.93 (d, *J* = 7.6 Hz, 2 H, H_{Ar}), 7.56–7.52 (m, 3 H, H_{Ar}), 7.41–7.39 (m, 5 H, H_{Ar}).

^{13}C NMR (CD_3OD, 126 MHz): δ = 192.8 (d, *J* = 26.4 Hz, CO), 169.4 (d, *J* = 26.4 Hz, COO), 135.5 (d, *J* = 21.6 Hz, C_{Ar}), 135.0 (C_{Ar}), 134.9 (d, *J* = 3.6 Hz, C_{Ar}), 130.9 (d, *J* = 4.8 Hz, C_{Ar}), 130.2 (C_{Ar}), 129.6 (C_{Ar}), 129.4 (C_{Ar}), 126.8 (d, *J* = 8.4 Hz, C_{Ar}), 100.1 (d, *J* = 197.9 Hz, CF).

^{19}F NMR (CD_3OD, 470 MHz): δ = –162.7 (d, *J* = 22.0 Hz).

HRMS (DART): m/z $[M + NH_4]^+$ calcd for $C_{15}H_{15}O_3FN$: 276.1036; found: 276.1035.

2-Fluoro-3-oxo-2-phenylbutanoic acid (28h)



1.20 mmol of **27h** was used and the product was purified by (hexane/Et_2O 4:1 to 1:2); Yield: 167 mg (71%), including 4% of protonated product; colorless oil; R_f = 0.36 (CH_2Cl_2/MeOH 5:1).

IR (NaCl): 3504, 3064, 1735, 1686, 1596, 1449, 1259, 1212, 1186, 1070, 696, 663 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 10.67 (s, 1 H, COOH), 7.57–7.55 (m, 2 H, H_{Ar}), 7.42–7.40 (m, 3 H, H_{Ar}), 2.32 (d, *J* = 5.0 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 200.3 (d, *J* = 28.8 Hz, CO), 169.9 (d, *J* = 26.4 Hz, COO), 131.7 (d, *J* = 21.6 Hz, C_{Ar}), 129.7 (C_{Ar}), 128.6 (C_{Ar}), 125.1 (d, *J* = 9.6 Hz, C_{Ar}), 98.2 (d, *J* = 200.3 Hz, CF), 25.3 (CH_3).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –163.9 (s).

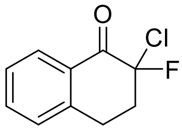
HRMS (DART): m/z $[M + NH_4]^+$ calcd for $C_{10}H_{13}O_3FN$: 214.0880; found: 214.0880.

Asymmetric synthesis and characterization of α-chloro-α-fluoroketones

Enantioselective decarboxylative chlorination of **28** was performed by following **Typical procedure** described below. A few starting compounds **28** contained 1–4% of decarboxylated product before use.

Typical procedure: α-Fluoro-β-keto carboxylic acid **28b** (0.303 mmol) was added to a stirred solution of **C1** (10 mol%, 0.0303 mmol) and *N*-chlorosuccinimide (1.5 equiv., 0.455 mmol) in toluene (1.5 mL). The reaction mixture was stirred at 0 °C for 62 h. Then, the reaction mixture was directly subjected to flash column chromatography on silica gel (hexane/CH_2Cl_2 2:1 then hexane/EtOAc 20:1) to give α-chloro-α-fluoroketone **31b**.

2-Chloro-2-fluoro-3,4-dihydronaphthalen-1(2H)-one (31a)



0.146 mmol of **28a** was used and the reaction was carried out at –20 °C for 10 d, and the product was purified by (hexane/Et_2O 10:1 to 5:1); Yield: 27.6 mg (95%, 90% ee); white solid; R_f = 0.36 (hexane/CH_2Cl_2 2:1); mp: 75.4 °C; $[\alpha]_D^{27.8}$ +74.96 (*c* 1.49, $CHCl_3$).

HPLC: DAICEL CHIRALCEL OB–H (0.46 cmφ × 25 cm); hexane/*i*-PrOH (9:1), flow rate = 1.0 ml/min, λ = 254 nm; t_R = 9.5 min (major), t_R = 11.3 min (minor).

IR (NaCl): 2922, 2852, 1709, 1603, 1455, 1306, 1227, 1136, 1038, 932, 829, 731, 654 cm^{-1}.

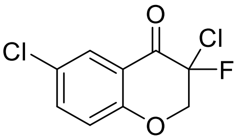
^1H NMR ($CDCl_3$, 500 MHz): δ = 8.13 (dd, *J* = 8.0, 1.2 Hz, 1 H, H_{Ar}), 7.58 (dt, *J* = 7.6, 1.2 Hz, 1 H, H_{Ar}), 7.40 (t, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.30 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 3.35 (ddd, *J* = 17.0, 12.0, 4.2 Hz, 1 H, PhC*H*H'), 3.12 (quintd, *J* = 17.2, 2.3 Hz, 1 H, PhCH*H'*), 2.84–2.78 (m, 1 H, C*H*H'), 2.74–2.67 (m, 1 H, CH*H'*).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 185.3 (d, *J* = 21.6 Hz, CO), 142.0 (C_{Ar}), 134.8 (C_{Ar}), 129.1 (C_{Ar}), 128.8 (C_{Ar}), 128.8 (C_{Ar}), 127.5 (C_{Ar}), 105.2 (d, *J* = 256.7 Hz, CF), 37.2 (d, *J* = 20.4 Hz, Ph*C*H_2), 26.9 (d, *J* = 7.2 Hz, CH_2).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –116.8 (s).

HRMS (DART): m/z $[M + NH_4]^+$ calcd for $C_{10}H_{12}ClFON$: 216.0591; found: 216.0590.

3,6-Dichloro-3-fluorochroman-4-one (31b)



0.303 mmol of **28b** was used and the product was purified by (hexane/CH_2Cl_2 2:1 then hexane/EtOAc 20:1); Yield: 67.7 mg (95%, 83% ee); white solid; R_f = 0.27 (hexane/CH_2Cl_2 2:1); mp: 71.9 °C; $[\alpha]_D^{27.7}$ +71.38 (*c* 1.28, $CHCl_3$).

HPLC: DAICEL CHIRALCEL OJ–H (0.46 cmφ × 25 cm); hexane/*i*-PrOH (500:1), flow rate = 1.0 ml/min, λ = 254 nm; t_R = 24.9 min (minor), t_R = 42.8 min (major).

IR (NaCl): 3082, 2921, 2860, 1713, 1604, 1476, 1424, 1280, 1213, 1114, 1051, 654, 443, 426 cm^{-1}.

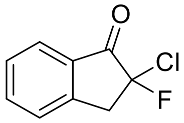
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.94 (d, *J* = 2.3 Hz, 1 H, H_{Ar}), 7.55 (ddd, *J* = 9.0, 2.7, 1.0 Hz, 1 H, H_{Ar}), 7.05 (d, *J* = 8.8 Hz, 1 H, H_{Ar}), 4.70–4.63 (m, 2 H, CH_2).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 179.5 (d, *J* = 21.6 Hz, CO), 158.6 (C_{Ar}), 137.4 (C_{Ar}), 128.8 (C_{Ar}), 127.7 (C_{Ar}), 119.9 (C_{Ar}), 118.5 (C_{Ar}), 99.9 (d, *J* = 256.7 Hz, CF), 72.8 (d, *J* = 31.2 Hz, CH_2).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –136.0 (s).

HRMS (DART): m/z $[M + NH_4]^+$ calcd for $C_9H_9Cl_2FO_2N$: 251.9994; found: 251.9997.

2-Chloro-2-fluoro-2,3-dihydro-1H-inden-1-one (31c)



0.266 mmol of **28c** was used and the reaction was performed at –20 °C for 5 d. The product was purified using (hexane/CH_2Cl_2 5:1 to 1:1); Yield: 42.3 mg (86%, 44% ee); white solid; R_f = 0.24 (hexane/CH_2Cl_2 2:1); mp: 53.5 °C; $[\alpha]_D^{27.7}$ +11.30 (*c* 1.06, $CHCl_3$).

HPLC: DAICEL CHIRALCEL OB–H (0.46 cmφ × 25 cm); hexane/*i*-PrOH (9:1), flow rate = 1.0 ml/min, λ = 254 nm; t_R = 19.6 min (minor), t_R = 9.9 min (major).

IR (NaCl): 3065, 2963, 2868, 1740, 1611, 1469, 1306, 1217, 1103, 1000, 919, 734, 658, 416 cm^{-1}.

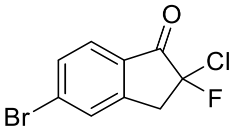
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.88 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.75 (dt, *J* = 7.6, 1.2 Hz, 1 H, H_{Ar}), 7.52–7.47 (m, 2 H, H_{Ar}), 3.90–3.80 (m, 2 H, CH_2).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 191.6 (d, *J* = 22.8 Hz, CO), 146.9 (d, *J* = 7.8 Hz, C_{Ar}), 137.3 (C_{Ar}), 131.0 (C_{Ar}), 129.0 (C_{Ar}), 126.5 (C_{Ar}), 126.1 (C_{Ar}), 105.9 (d, *J* = 261.5 Hz, CF), 43.8 (d, *J* = 24.0 Hz, CH_2).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –121.0 (s).

HRMS (DART): m/z $[M + NH_4]^+$ calcd for $C_9H_{10}ClFON$: 202.0435; found: 202.0434.

5-Bromo-2-chloro-2-fluoro-2,3-dihydro-1H-inden-1-one (31d)



0.300 mmol of **28d** was used and the product was purified by hexane/CH_2Cl_2 2:1 then hexane/EtOAc 30:1); Yield: 70.2 mg (89%, 36% ee); white solid; R_f = 0.27 (hexane/EtOAc 30:1); mp: 116.5 °C; $[\alpha]_D^{27.6}$ –13.08 (*c* 1.06, $CHCl_3$).

HPLC: DAICEL CHIRALCEL OB–H (0.46 cmφ × 25 cm); hexane/*i*-PrOH (9:1), flow rate = 1.0 ml/min, λ = 254 nm; t_R = 16.4 min (minor), t_R = 23.8 min (major).

IR (NaCl): 3078, 3061, 2929, 1735, 1594, 1571, 1423, 1293, 1212, 1186, 1111, 1056, 999, 919, 845, 748, 667, 596 cm^{-1}.

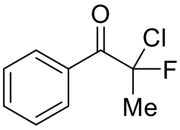
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.75 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 7.66–7.64 (m, 2 H, H_{Ar}), 3.87–3.79 (m, 2 H, CH_2).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 190.5 (d, *J* = 22.8 Hz, CO), 148.3 (d, *J* = 4.8 Hz, C_{Ar}), 132.9 (C_{Ar}), 132.7 (C_{Ar}), 129.8 (C_{Ar}), 129.8 (C_{Ar}), 127.2 (C_{Ar}), 105.4 (d, *J* = 262.7 Hz, CF), 43.4 (d, *J* = 24.0 Hz, CH_2).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –120.6 (d, *J* = 14.7 Hz).

HRMS (DART): m/z $[M + NH_4]^+$ calcd for $C_9H_9ClBrFON$: 279.9540; found: 279.9543.

2-Chloro-2-fluoro-1-phenylpropan-1-one (31e)



0.335 mmol of **28e** and 3.4 mL of toluene was used, and the product was purified by (pentane/CH_2Cl_2 100:0 to 25:1); Yield: 51.2 mg (82%, 13% ee); colorless oil; R_f = 0.43 (hexane/CH_2Cl_2 2:1); $[\alpha]^D$ have not collected because of low enantioselectivity.

HPLC: DAICEL CHIRALCEL OJ–H (0.46 cmφ × 25 cm); hexane/*i*-PrOH (1000:1), flow rate = 0.5 ml/min, λ = 254 nm; t_R = 15.2 min (minor), t_R = 14.5 min (major).

IR (NaCl): 3064, 3001, 2943, 1699, 1599, 1449, 1380, 1282, 1151, 1081, 984, 893, 807, 705, 653, 541 cm^{-1}.

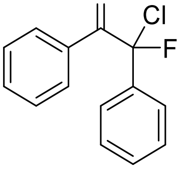
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.18 (m, 2 H, H_{Ar}), 7.60 (t, *J* = 7.5 Hz, 1 H, H_{Ar}), 7.47 (t, *J* = 7.8 Hz, 2 H, H_{Ar}) 2.17 (d, *J* = 20.3 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 189.2 (d, *J* = 23.0 Hz, CO), 134.0 (C_{Ar}), 131.3 (d, *J* = 3.6 Hz, C_{Ar}), 130.6 (d, *J* = 6.0 Hz, C_{Ar}), 128.4 (C_{Ar}), 108.4 (d, *J* = 256.7 Hz, CF), 27.3 (d, *J* = 22.8 Hz, CH_3).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –106.7 (q, *J* = 22.0 Hz).

HRMS (DART): m/z $[M + H]^+$ calcd for C_9H_9ClFO: 187.0326; found: 187.0324.

2-Chloro-2-fluoro-1,2-diphenylethan-1-one (31f)



0.306 mmol of **28f** was used and the product was purified by hexane/CH_2Cl_2 2:1 then hexane/Et_2O 30:1); Yield: 59.8 mg (79%, 33% ee); colorless oil; R_f = 0.42 (hexane/CH_2Cl_2 2:1); $[\alpha]_D^{27.7}$ +7.99 (*c* 1.43, $CHCl_3$).

HPLC: DAICEL CHIRALPAK IA–3 (0.46 cmφ × 25 cm); hexane/*i*-PrOH (150:1), flow rate = 1.0 ml/min, λ = 254 nm; t_R = 6.4 min (minor), t_R = 5.9 min (major).

IR (NaCl): 3063, 1703, 1596, 1448, 1238, 1216, 1090, 1017, 877, 817, 744, 694, 631 cm^{-1}.

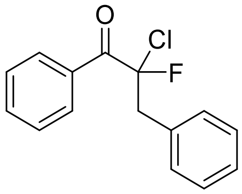
^1H NMR ($CDCl_3$, 500 MHz): δ = 7.99–7.97 (m, 2 H, H_{Ar}), 7.66–7.62 (m, 2 H, H_{Ar}), 7.56–7.53 (m, 1 H, H_{Ar}), 7.45–7.38 (m, 2 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 188.7 (d, *J* = 28.8 Hz, CO), 136.4 (d, *J* = 22.8 Hz, C_{Ar}), 133.8 (C_{Ar}), 132.0 (d, *J* = 2.4 Hz, C_{Ar}), 130.6 (d, *J* = 4.8 Hz, C_{Ar}), 130.3 (C_{Ar}), 128.7 (C_{Ar}), 128.4 (C_{Ar}), 125.8 (d, *J* = 7.2 Hz, C_{Ar}), 109.8 (d, *J* = 255.5 Hz, CF).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –107.1 (s).

HRMS (DART): m/z $[M + NH_4]^+$ calcd for $C_{14}H_{14}ClFON$: 266.0748; found: 266.0749.

2-Chloro-2-fluoro-1,3-diphenylpropan-1-one (31g)



0.354 mmol of **28g** and 3.6 mL of toluene were used, and the product was purified by hexane/EtOAc 100:0 to 95:5); Yield: 75.8 mg (81%, 29% ee); white solid; R_f = 0.45 (hexane/CH_2Cl_2 2:1); mp: 49.7 °C; $[\alpha]_D^{27.5}$ +15.01 (*c* 0.99, $CHCl_3$).

HPLC: DAICEL CHIRALCEL OD–H (0.46 cmφ × 25 cm); hexane/*i*-PrOH (500:1), flow rate = 0.5 ml/min, λ = 254 nm; t_R = 17.2 min (minor), t_R = 19.5 min (major).

IR (NaCl): 3064, 3033, 2923, 2851, 1697, 1597, 1448, 1264, 1133, 892, 698, 593 cm^{-1}.

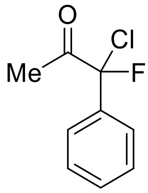
^1H NMR ($CDCl_3$, 500 MHz): δ = 8.06–8.03 (m, 2 H, H_{Ar}), 7.57–7.53 (m, 1 H, H_{Ar}), 7.43–7.40 (m, 2 H, H_{Ar}), 7.33–7.26 (m, 5 H, H_{Ar}), 3.83 (dd, *J* = 22.6, 14.5 Hz, 1 H, C*H*H’), 3.67 (dd, *J* = 22.2, 14.5 Hz, 1 H, CH*H’*).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 190.0 (d, *J* = 30.0 Hz, CO), 133.8 (C_{Ar}), 132.6 (C_{Ar}), 132.1 (d, *J* = 3.6 Hz, C_{Ar}), 131.2 (C_{Ar}), 130.3 (d, *J* = 4.8 Hz, C_{Ar}), 128.4 (C_{Ar}), 128.2 (C_{Ar}), 127.6 (C_{Ar}), 108.9 (d, *J* = 262.7 Hz, CF), 45.1 (d, *J* = 20.4 Hz, CH_2).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –115.4 (t, *J* = 22.0 Hz).

HRMS (DART): m/z $[M + H]^+$ calcd for $C_{15}H_{13}ClFO$: 263.0639; found: 263.0641.

1-Chloro-1-fluoro-1-phenylpropan-2-one (31h)



0.335 mmol of **28h** and 3.4 mL of toluene were used, and the product was purified by pentane/CH_2Cl_2 9:1 to 7:3); Yield: 48.1 mg (77%, 45% ee); colorless oil; R_f = 0.45 (hexane/CH_2Cl_2 2:1); $[\alpha]_D^{27.5}$ +285.02 (*c* 1.02, $CHCl_3$)

HPLC: DAICEL CHIRALPAK IA–3 (0.46 cmφ × 25 cm); hexane/*i*-PrOH (500:1), flow rate = 1.0 ml/min, λ = 254 nm; t_R = 5.9 min (minor), t_R = 6.3 min (major).

IR (NaCl): 3063, 1702, 1596, 1448, 1238, 1216, 817, 744, 694, 631 cm^{-1}.

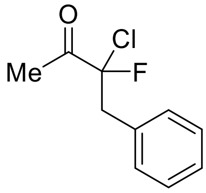
^1H NMR ($CDCl_3$, 500 MHz): δ = 7.61–7.57 (m, 2 H, H_{Ar}), 7.46–7.43 (m, 3 H, H_{Ar}), 2.35 (d, *J* = 3.4 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 196.8 (d, *J* = 31.2 Hz, CO), 134.8 (d, *J* = 22.8 Hz, C_{Ar}), 130.4 (C_{Ar}), 128.6 (C_{Ar}), 125.9 (d, *J* = 7.2 Hz, C_{Ar}), 108.7 (d, *J* = 255.5 Hz, CF), 23.7 (CH_3).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –115.8 (s).

HRMS (DART): m/z $[M + H]^+$ calcd for C_9H_9ClFO: 187.0326; found: 187.0327.

3-Chloro-3-fluoro-4-phenylbutan-2-one (31i)



0.306 mmol of **28i** and 3 mL of toluene were used, and the product was purified by hexane/Et_2O 10:1 to 5:1 then hexane/EtOAc 100:0 to 92:8); Yield: 48.3 mg (79%, 2% ee); colorless oil; R_f = 0.15 (hexane only); $[\alpha]^D$ have not collected because of low enantioselectivity.

HPLC: DAICEL CHIRALCEL OJ–H (0.46 cmφ × 25 cm); hexane/*i*-PrOH (1000:1), flow rate = 1.0 ml/min, λ = 254 nm; t_R = 17.2 min (minor), t_R = 38.8 min (major).

IR (NaCl): 3089, 3064, 3033, 2933, 1698, 1597, 1449, 1265, 1134, 941, 892, 749, 698, 663, 593 cm^{-1}.

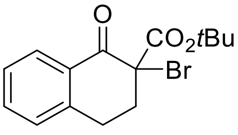
^1H NMR ($CDCl_3$, 500 MHz): δ = 7.33–7.28 (m, 3 H, H_{Ar}), 7.26–7.24 (m, 2 H, H_{Ar}), 3.59 (dd, *J* = 24.9, 14.5 Hz, 1 H, C*H*H'), 3.50 (dd, *J* = 19.7, 14.7 Hz, 1 H, CH*H'*), 2.24 (d, *J* = 3.8 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 199.0 (d, *J* = 32.4 Hz, CO), 132.3 (C_{Ar}), 130.8 (C_{Ar}), 128.4

(C_{Ar}), 127.7 (C_{Ar}), 109.3 (d, *J* = 259.1 Hz, CF), 44.1 (d, *J* = 20.4 Hz, CH_2), 24.0 (CH_3).
^{19}F NMR ($CDCl_3$, 470 MHz): δ = –119.2 (t, *J* = 22.0 Hz).
HRMS (DART): m/z $[M + NH_4]^+$ calcd for $C_{10}H_{14}ClFON$: 218.0748; found: 218.0747.

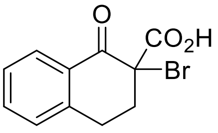
Asymmetric synthesis and characterization of α-bromo-α-chloroketone

***Tert*-butyl 2-bromo-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (32)**



α-Alkyl-β-ketoester (3.65 mmol) was added to a stirred suspension of NaH (60% in oil, washed with hexane, 1.4 equiv., 5.11 mmol) in THF (20 mL) at 0 °C, and the mixture was stirred at 0 °C for 30 min. Subsequently, *N*-bromosuccinimide (1.4 equiv., 5.11 mmol) was added in one portion, and the reaction mixture was stirred at ambient temperature for 30 min. The reaction mixture was quenched by adding saturated NH_4Cl aqueous solution at 0 °C, and then extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, concentrated, and then purified via flash column chromatography on silica gel (hexane/EtOAc 10:1 to 7:1) to yield α-alkyl-α-bromo-β-ketoester **32**.
Yield: 1090 mg (92%); white solid; R_f = 0.27 (hexane/ethyl acetate 20:1); mp: 44.3 °C.
IR (NaCl): 2978, 2933, 1751, 1725, 1686, 1455, 1369, 1295, 1254, 1153, 735, 403 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.09 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.53 (t, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.36 (t, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.27 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 3.20 (ddd, *J* = 17.2, 9.0, 4.8 Hz, 1 H, PhC*H*H'), 3.03 (dt, *J* = 17.2, 5.2 Hz, 1 H, PhCH*H'*), 2.95 (ddd, *J* = 14.1, 9.2, 5.2 Hz, 1 H, C*H*H'), 2.56 (dt, *J* = 14.1, 5.4 Hz, 1 H, CH*H'*)1.47 (s, 9 H, C_3H_9).
^{13}C NMR ($CDCl_3$, 126 MHz): δ = 187.8 (CO), 166.0 (COO), 142.2 (C_{Ar}), 134.1 (C_{Ar}), 129.7 (C_{Ar}), 128.8(C_{Ar}), 128.7 (C_{Ar}), 127.1 (C_{Ar}), 84.1 (CBr), 66.5 (*C*C_3H_9), 35.8 (Ph*C*H_2), 27.6(C_3H_9), 26.9 (CH_2).
HRMS (DART): m/z $[M + NH_4]^+$ calcd for $C_{15}H_{21}O_3BrN$: 342.0705; found: 32.0704.

2-Bromo-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (33)



Trifluoroacetic acid (20 equiv., 18.4 mmol) was added to a stirred solution of α-alkyl-α-bromo-β-ketoester **32** (0.919 mmol) in CH_2Cl_2 (4.6 mL) at 0 °C, and the mixture was stirred at ambient temperature for 60 min. The reaction mixture was concentrated, and then purified by flash column chromatography on silica gel (hexane/Et_2O 4:1 to 1:2) to give α-bromo-β-keto carboxylic acid **33**.
Yield: 183 mg (74%), including 2% of protonated product; white solid; R_f = 0.34 (CH_2Cl_2/MeOH

5:1).

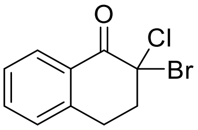
IR (NaCl): 3509, 2938, 1729, 1682, 1597, 1455, 1428, 1297, 1225, 910, 787, 734 cm^{-1}.

^{1}H NMR (CD_3OD, 500 MHz): δ = 8.00 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 7.55 (t, *J* = 6.9 Hz, 1 H, H_{Ar}), 7.35 (t, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.32 (d, *J* = 6.9 Hz, 1 H, H_{Ar}), 3.19–3.13 (m, 1 H, PhC*H*H'), 3.06–3.03 (m, 1 H, PhCH*H'*), 2.93–2.88 (m, 1 H, C*H*H'), 2.57–2.53 (m, 1 H, CH*H'*).

^{13}C NMR (CD_3OD, 126 MHz): δ = 189.6 (CO), 170.2 (COO), 144.2 (C_{Ar}), 135.6 (C_{Ar}), 130.7 (C_{Ar}), 130.1 (C_{Ar}), 129.4 (C_{Ar}), 128.2 (C_{Ar}), 67.0 (CBr), 37.2 (Ph*C*H_2), 27.7 (CH_2).

HRMS (DART): m/z [M + H]$^+$ calcd for $C_{11}H_{10}BrO_3$: 268.9813; found: 268.9810.

2-Bromo-2-chloro-3,4-dihydronaphthalen-1(2H)-one (34)



Amine catalyst **C1** (10 mol%, 0.0296 mmol) and *N*-chlorosuccinimide (1.5 equiv., 0.444 mmol) were added to a stirred solution of α-bromo-β-ketocarboxylic acid **33** (0.296 mmol) in toluene (1.5 mL) at –20 °C, and the mixture was stirred for 46 h. The reaction mixture was directly subjected to flash column chromatography on silica gel (hexane/CH_2Cl_2 1:1) to give α-bromo-α-chloroketone **34**.

Yield: 75.4 mg (98%, 90% ee); brown solid; R_f = 0.63 (hexane/CH_2Cl_2 1:1); mp: 67.6 °C; $[\alpha]_D^{27.6}$ –21.45 (*c* 1.07, $CHCl_3$).

HPLC: DAICEL CHIRALPAK IA–3 (0.46 cmφ × 25 cm); hexane/*i*-PrOH (150:1), flow rate = 1.0 ml/min, λ = 254 nm; t_R = 10.0 min (minor), t_R = 10.8 min (major).

IR (NaCl): 3067, 2956, 2938, 1703, 1599, 1454, 1292, 1220, 886, 807, 742, 628, 577, 464 cm^{-1}.

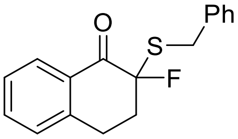
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.16 (dd, *J* = 8.0, 1.2 Hz, 1 H, H_{Ar}), 7.56 (dt, *J* = 7.5, 1.2 Hz, 1 H, H_{Ar}), 7.39 (t, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.28 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 3.25 (ddd, *J* = 17.3, 10.0, 4.2 Hz, 1 H, PhC*H*H'), 3.09 (dt, *J* = 17.2, 4.6 Hz, 1 H, PhCH*H'*), 3.03 (dt, *J* = 14.5, 4.6 Hz, 1 H, C*H*H'), 2.85 (ddd, *J* = 19.1, 9.9, 4.6 Hz, 1 H, CH*H'*).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 184.1 (CO), 141.9 (C_{Ar}), 134.5 (C_{Ar}), 129.8 (C_{Ar}), 128.6 (C_{Ar}), 127.8 (C_{Ar}), 127.5 (C_{Ar}), 77.7 (CBr), 44.2 (Ph*C*H_2), 28.5 (CH_2).

HRMS (DART): m/z [M + NH_4]$^+$ calcd for $C_{10}H_{12}ClBrON$: 275.9791; found: 275.9793.

Stereospecific synthesis and characterization of chiral fluoroketones by S_N2 reactions

2-(Benzylthio)-2-fluoro-3,4-dihydronaphthalen-1(2H)-one (35)[28]



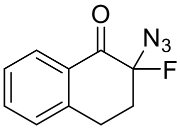
α-chloro-α-fluoroketone **31a** (0.294 mmol) was added CH2Cl2 (1.2 mL) and BnSH (5 equiv., 1.47 mmol) and NEt_3 (10 equiv., 2.94 mmol). The reaction mixture was refluxed for 2 h. Then, the reaction mixture was cooled to ambient temperature and BnSH (5 equiv., 1.47 mmol) and NEt_3 (10 equiv., 2.94 mmol) was added. Again, the reaction mixture was refluxed for 2 h. The reaction mixture was directly purified by column chlomatography on silica gel (hexane/Et_2O 20:1 to 5:1) to give the α-fluoro-α-sulfenylketone **35** as a colorless oil (96% yield, 90% ee).

HPLC: DAICEL CHIRALPAK IC (0.46 cmφ × 25 cm); hexane/*i*-PrOH (100:1), flow rate = 1.0 ml/min, λ = 254 nm; t_R = 17.7 min (minor), t_R = 21.8 min (major).

$[\alpha]_D^{25.6}$ –25.87 (*c* 1.09, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.12 (d, *J* = 8.0, 0.76 Hz, 1 H), 7.53 (dt, *J* = 7.5, 1.2 Hz, 1 H), 7.37 (t, *J* = 7.6 Hz, 1 H), 7.26–7.20 (m, 5 H), 4.06 (dd, *J* = 12.4, 1.2 Hz, 1 H), 3.78 (dd, *J* = 12.6, 1.2 Hz, 1 H), 2.23 (ddd, *J* = 17.5, 12.9, 4.6 Hz, 1 H), 3.05–3.00 (m, 1 H), 2.73–2.59 (m, 2 H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.5 (d, *J* = 22.8 Hz), 141.5, 136.0, 134.0, 130.0, 129.1, 128.5, 128.4, 127.2, 127.1, 100.8 (d, *J* = 235.1 Hz), 34.6 (d, *J* = 20.4 Hz), 32.2, 27.5 (d, *J* = 7.2 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz): δ –137.4 (s).

2-Azido-2-fluoro-3,4-dihydronaphthalen-1(2H)-one (36) [28]



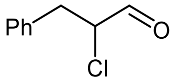
α-chloro-α-fluoroketone **31a** (0.306 mmol) was added DMSO (1.2 mL) and NaN3 (2 equiv., 0.612 mmol). The mixture was stirred at 80 °C for 30 min. The reaction mixture was cooled to ambient temperature, H_2O was added, extracted with Et_2O, deried over Na_2SO_4, concentrated. The resulting crude product was purified by rapid column chlomatography on silica gel (hexane/CH_2Cl_2 1:1) to give the α-azide-α-fluoroketone **36** as a colorless oil including small amount of impurity (67% yield, 88% ee).

HPLC: DAICEL CHIRALCEL OB-H (0.46 cmφ × 25 cm); hexane/*i*-PrOH (50:1), flow rate = 1.0 ml/min, λ = 254 nm; t_R = 9.1 min (minor), t_R = 12.5 min (major).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.13 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.58 (dt, *J* = 7.5, 1.2 Hz, 1 H), 7.40 (t, *J* = 7.6 Hz, 1 H), 7.28 (d, *J* = 7.6 Hz, 1 H), 3.14–3.02 (m, 2H), 2.48–2.41 (m ,1H), 2.38–2.29 (m, 1 H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 186.8 (d, *J* = 27.6 Hz), 143.2, 134.9, 129.5, 128.9, 128.8, 127.4, 100.6 (d, *J* = 225.5 Hz), 33.0 (d, *J* = 21.6 Hz), 25.5 (d, *J* = 6.0 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz): δ –128.4 (s).

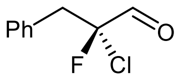
Preparation of α-chloroaldehyde and α-chloro-α-fluoroaldehyde

2-Chloro-3-phenylpropanal (37)



3-Phyenyl propionaldehyde (23.2 mmol) was added CH_2Cl_2 (23 mL) and the solution was cooled to 0 °C. To a solution was added racemic proline (20 mol%, 2.32 mmol), NCS (1.5 equiv., 34.8 mmol) and stirred at 0 °C for 2 h. Full consumption of starting material was confirmed by TLC and it was concentrated and filtered by hexane. The crude mixture was subjected to flash column chromatography on silica gel (hexane/ethyl acetate 10:1 to 5:1), evaporated. Then, white precipitate was filtered off with hexane and desired product was obtained in 93% yield as a colorless oil including impurity (less than 20% according to ^{1}H NMR by using internal standard).

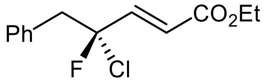
(*R*)-2-Chloro-2-fluoro-3-phenylpropanal (38)



The flask was flamed dried *in vacuo* in advance. Resulting α-chloroaldehyde **37** (3 equiv., 6 mmol, The purity of **37** was exactly calculated for the sake of reproducability) was charged to the flask and added TBME (6.6 mL) and the solution was cooled to 0 °C. To a solution was added diarylprolinol derived catalyt **C2** (10 mol%, 0.2 mmol), NFSI (2 mmol) and stirred for 24 h at 0 °C. Full consumption of NFSI was confirmed by TLC, diluted with hexane (12 mL), filterd off with hexane 12 mL), the residue was washed with hexane (12 mL) and hexane/Et_2O (8/4 mL) and concetrated. The crude product was used for HWE reaction without further purification.

HWE reaction of α-chloro-α-fluoroaldehyde

Ethyl (*R*, *E*)-4-chloro-4-fluoro-5-phenylpent-2-enoate (48)



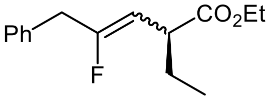
The flask was charged with NaH (4 equiv., 7.2 mmol, 60%), washed with hexane, and dried *in vacuo*. To the flask was added toluene (9 mL), $(EtO)_2P(O)CH_2CO_2Et$ (4 equiv., 7.2 mmol) at 0 °C. The suspension was stirred for 1 h at rt, it was cooled to –78 °C and added a solution of α-chloro-α-fluoroaldehyde **38** (1.8 mmol) in toluene (9 mL) *via* cannula (Both HWE reagent and α-chloro-α-fluoroaldehyde were well cooled to –78 °C in advance). After the addition of α-chloro-α-fluoroaldehyde, the mixture was stirred for another 10 min at –78 °C, warmed to 0 °C and stirred for 5 min, quenched by addition of 1.2N HCl, extracted by CH_2Cl_2, dried over Na_2SO_4, concentrated. The crude mixture was subjected to column chromatography on silica gel (hexane/Et_2O 13:1) to afford the desired product **48** in 80% yield as a mixture of *E* and *Z* isomers

(*E*/*Z* = 93/7) as a colorless oil. The mixture was again purified by column chromatography on silica gel (hexane/Et_2O 13:1) to afford pure *E* isomer. *E* isomer was obtained as a colorless oil and the ee was determined to be 92%.

HPLC: DAICEL CHIRALPAK IF-3 (0.46 cmφ × 25 cm); hexane/*i*-PrOH (1000:1), flow rate = 0.5 ml/min, λ = 220 nm; t_R = 73.2 min (minor), t_R = 67.4 min (major).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.31 (m, 3 H), 7.26–7.24 (m, 2 H), 6.94 (dd, *J* = 18.8, 15.6 Hz, 1 H), 6.10 (d, *J* = 15.6 Hz, 1 H), 4.27–4.15 (m, 2H), 3.57–3.40 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3 H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.83 (d, *J* = 3.8 Hz), 143.0 (d, *J* = 21.1 Hz), 132.4 (d, *J* = 1.9 Hz), 130.6, 128.2, 127.6, 121.9 (d, *J* = 8.6 Hz), 109.5 (d, *J* = 249.2 Hz), 60.8, 48.9 (d, *J* = 23.0 Hz), 13.9.
^{19}F NMR ($CDCl_3$, 376 MHz): δ –110.6 (q, *J* = 17.3 Hz).
HRMS (DART): m/z $[M + NH_4]^+$ calcd for $C_{13}H_{18}ClFNO_2$: 274.1010; found: 274.1010.

Synthesis of chiral fluoroalkene by S_N2' reaction
Ethyl 2-ethyl-4-fluoro-5-phenylpent-3-enoate (52)



The flask was flamed dried *in vacuo* in advance. The flask was charged CuCN (2 equiv., 0.332mmol), THF (7.3 mL), and LiCl (4 equiv., 0.664 mmol), The suspension was cooled to –78 °C, the mixture was added Et_2Zn (2 equiv., 0.332 mmol, 1M in hexane) and stirred for 10 min at 0 °C. Again the solution was cooled to –50 °C, added a solution of 3-chloro-3-fluoropropene **48** (92% ee, 0.166 mmol) in THF (1 mL), and stirred for 1 h at –50 °C. The reaction mixture was added 28% NH_3/NH_4Cl aq. (pH 10 buffer), warmed to rt, extracted by Et_2O, dried over $MgSO_4$, concentrated. The crude mixture was purified by flash column chromatography on silica gel (hexane/Et_2O 10:1). The desired product (colorless oil) was afforded in 98% yield as a mixture of *E* and *Z* isomers (*E*/*Z* = 13/87, 91/87% ee).

HPLC: DAICEL CHIRALPAK ID-3 (0.46 cmφ × 25 cm) and ID (0.46 cmφ × 25 cm) were directly connected with an adaptor and used for the analysis; hexane/*i*-PrOH (1000:1), flow rate = 0.5 ml/min, λ = 220 nm; (*E*): t_R = 70.5 min (minor), t_R = 76.1 min (major); (*Z*): t_R = 66.1 min (minor), t_R = 61.5 min (major).

^{1}H NMR: δ 7.33–7.30 (m, 2H, *E* and *Z*), 7.26–7.23 (m, 3H, *E* and *Z*), 5.20 (dd, *J* = 20.2, 10.5 Hz, 1H, *E*), 4.74 (dd, *J* = 35.7, 9.8 Hz, 1H, *Z*), 4.19–4.08 (m, 2H, *E* and *Z*), 3.64–3.57 (m, 2H, *E*), 3.5 (d, *J* = 17.4 Hz, 2H, *Z*), 3.42–3.63 (m, 1H, *Z*), 3.09–3.02 (m, 1H, *E*), 1.88–1.72 (m, 1H, *E* and *Z*), 1.62–1.48 (m, 1H, *E* and *Z*), 1.26–1.23 (m, 3H, *E* and *Z*), 0.94–0.88 (m, 3H, *E* and *Z*).

^{13}C NMR ($CDCl_3$, 100 MHz, *EZ* miture): δ 174.0 (d, *J* = 1.9 Hz, *Z*), 173.7 (d, *J* = 1.9 Hz, *E*), 159.7 (d, *J* = 252.1 Hz, *E*), 159.4 (d, *J* = 257.8 Hz, *Z*), 136.1 (Z), 136.0 (*E*), 128.7 (*E* and *Z*), 128.5 (*E* and *Z*), 126.8 (*E* and *Z*), 106.0 (d, *J* = 24.9 Hz, *E*), 105.0 (d, *J* = 13.4 Hz, *Z*), 60.7 (*E*), 60.5 (*Z*), 44.7 (d, *J* = 8.6 Hz, *E*), 42.4 (d, *J* = 3.8 Hz, *Z*), 38.5 (d, *J* = 27.8 Hz, *Z*), 34.6 (d, *J* = 28.8 Hz, *E*), 26.2 (*E*), 26.1 (*Z*), 14.2 (*E* and *Z*), 11.5 (*E*), 11.5 (*Z*).

^{19}F NMR ($CDCl_3$, 376 MHz): δ –99.4 (q, *J* = 23.1 Hz, *E*), –106.1 (quint, *J* = 17.3 Hz, *Z*).

HRMS (DART): m/z $[M + NH_4]^+$ calcd for $C_{15}H_{23}FNO_2$: 268.1713; found: 268.1714.

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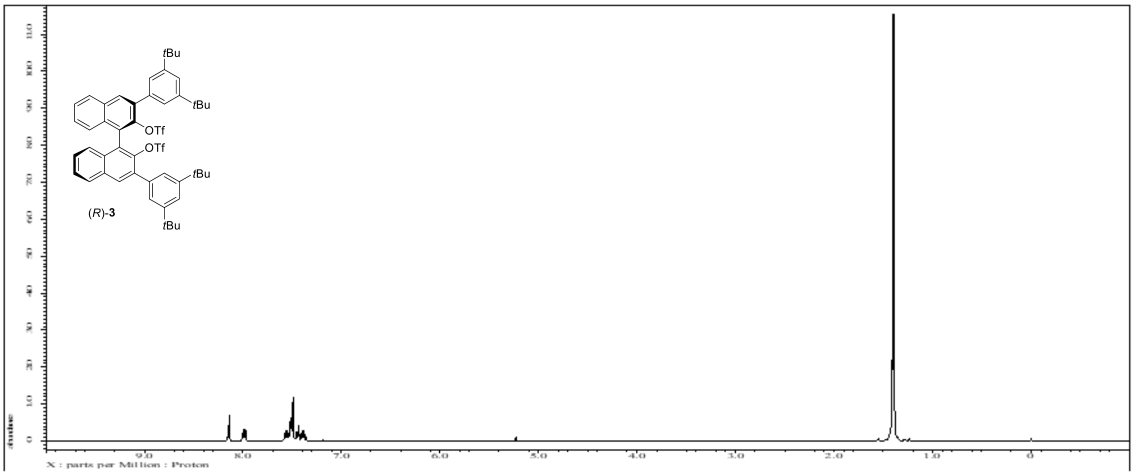
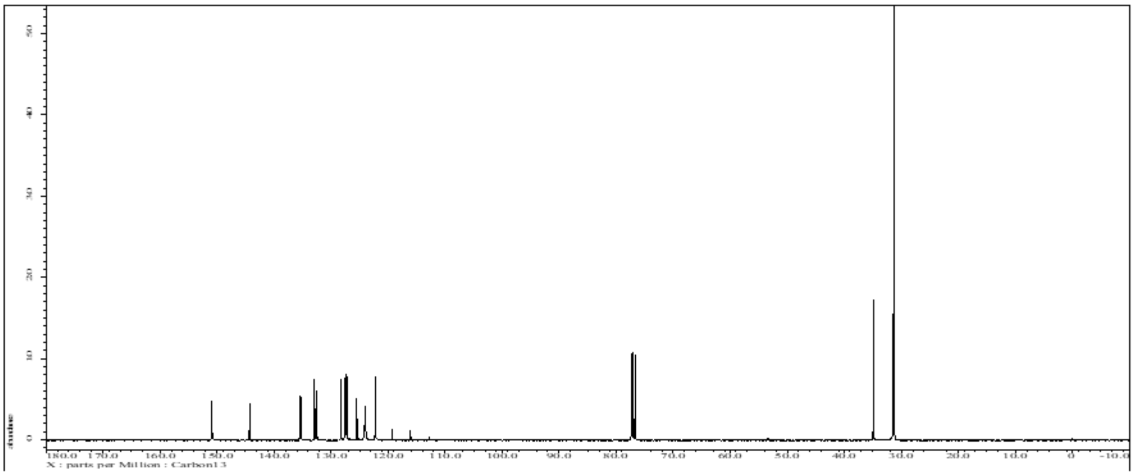
Copy of NMR spectra and HPLC traces

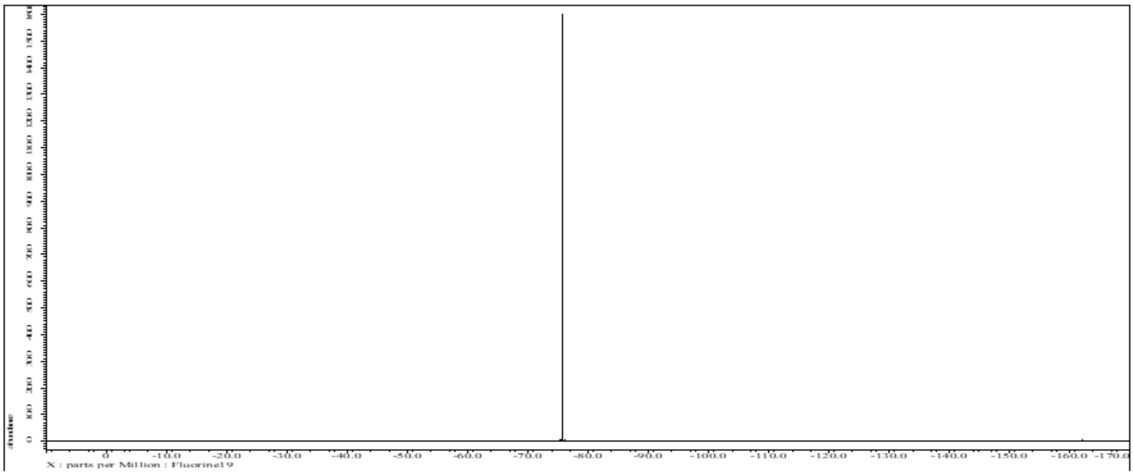
^{1}H NMR spectrum [(*R*)-**3**]



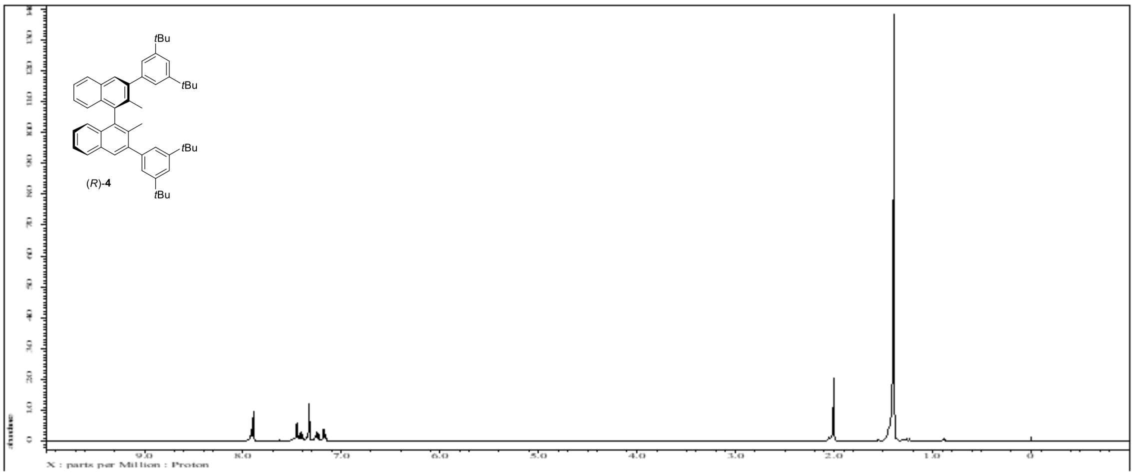
^{13}C NMR spectrum [(*R*)-**3**]



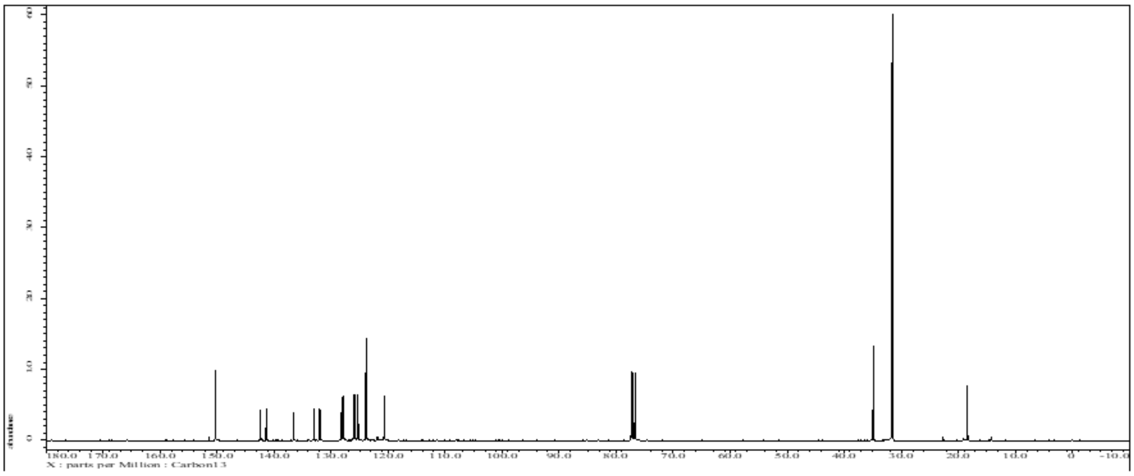
^{19}F NMR spectrum [(*R*)-**3**]



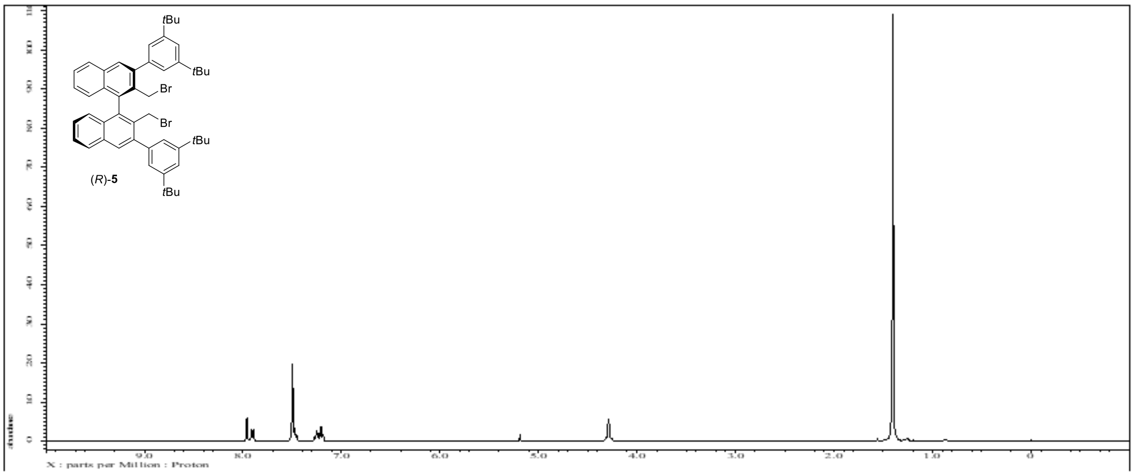
^{1}H NMR spectrum [(*R*)-**4**]



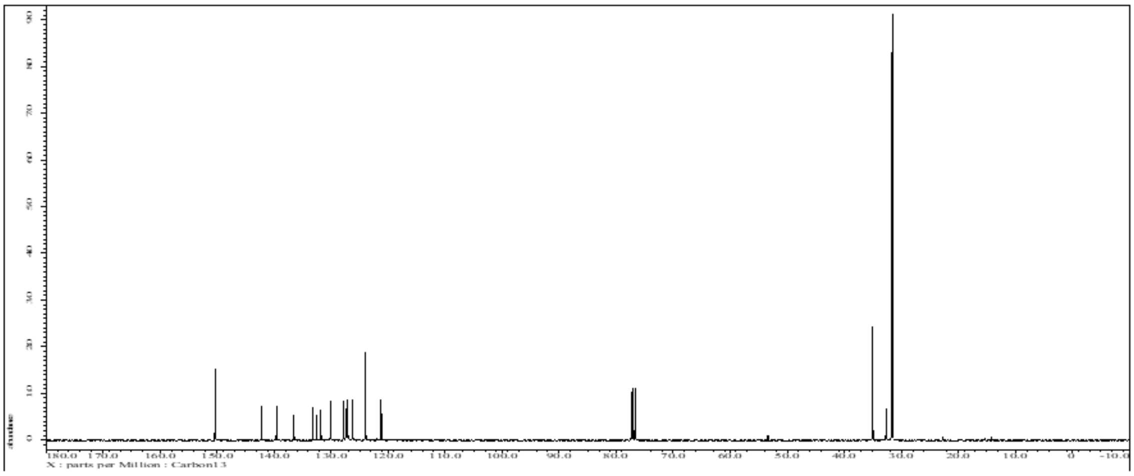
^{13}C NMR spectrum [(*R*)-**4**]



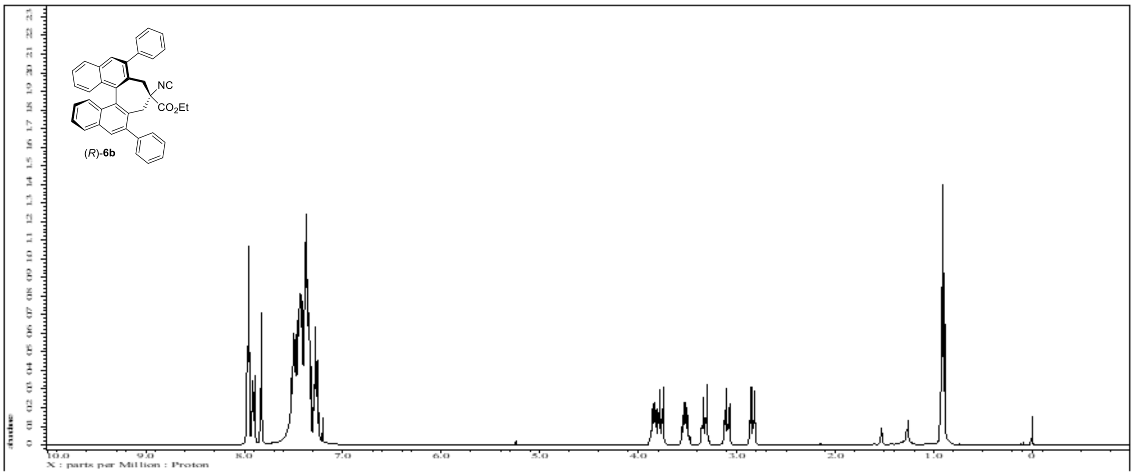
^{1}H NMR spectrum [(*R*)-**5**]



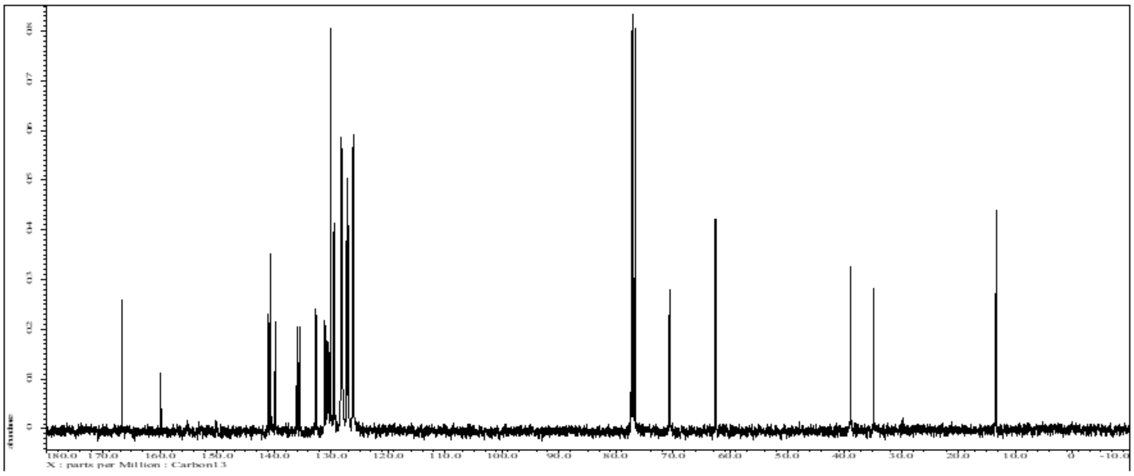
^{13}C NMR spectrum [(*R*)-**5**]



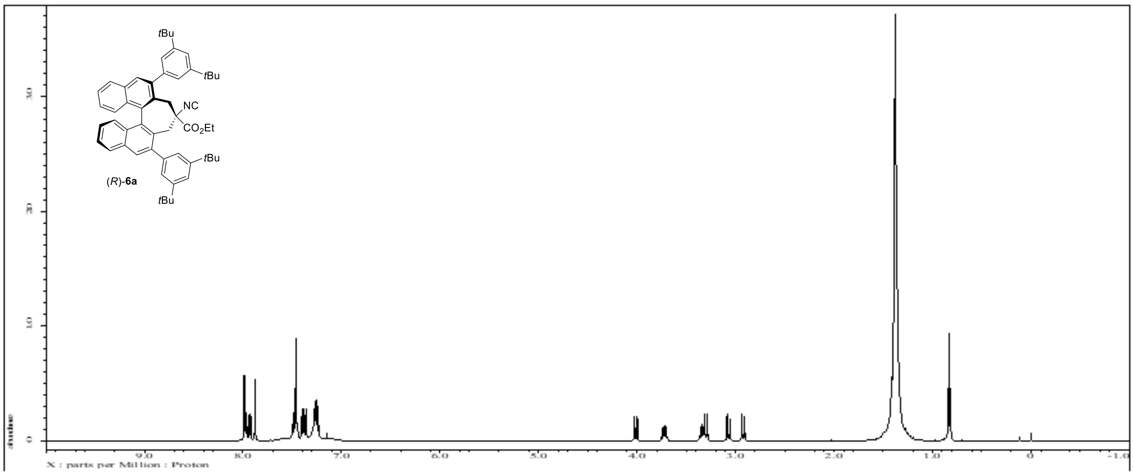
^{1}H NMR spectrum [(*R*)-**6b**]



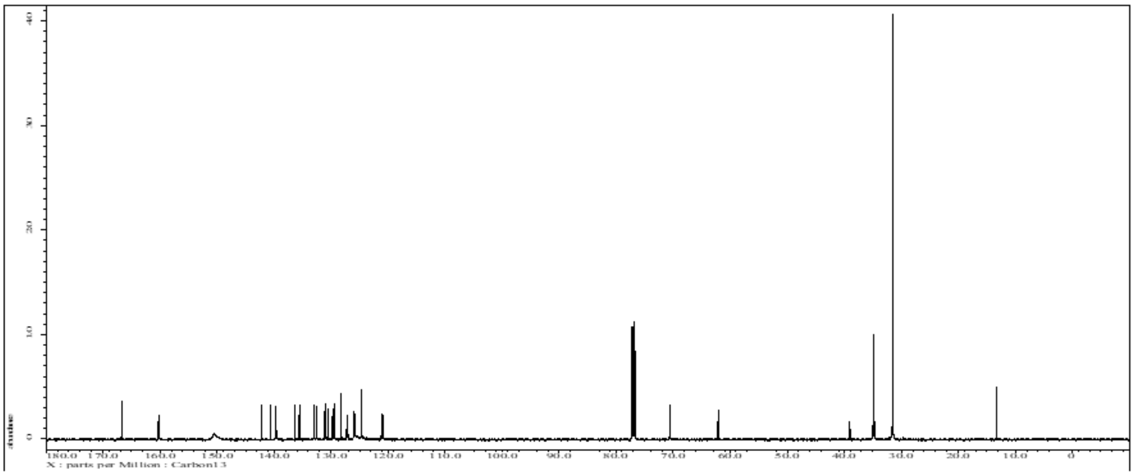
^{13}C NMR spectrum [(*R*)- **6b**]



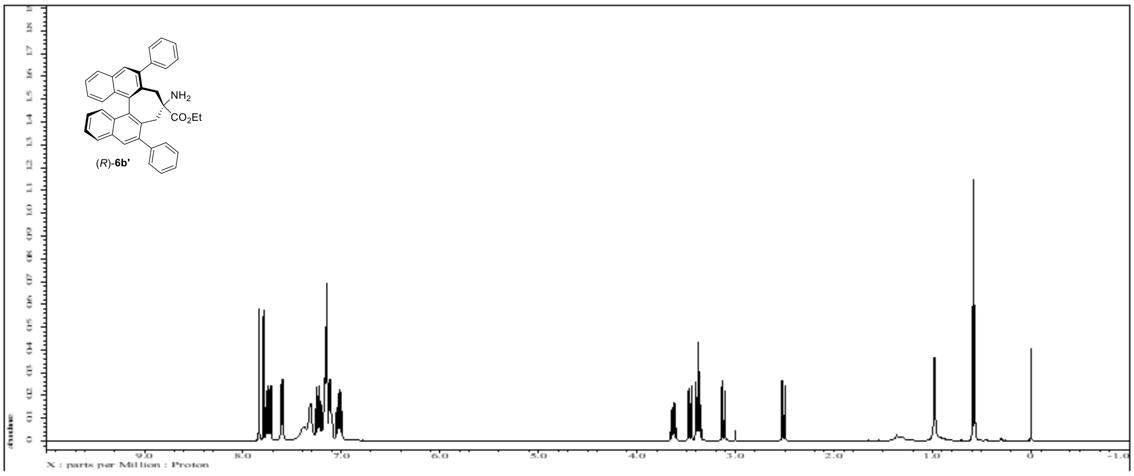
^{1}H NMR spectrum [(*R*)-**6a**]



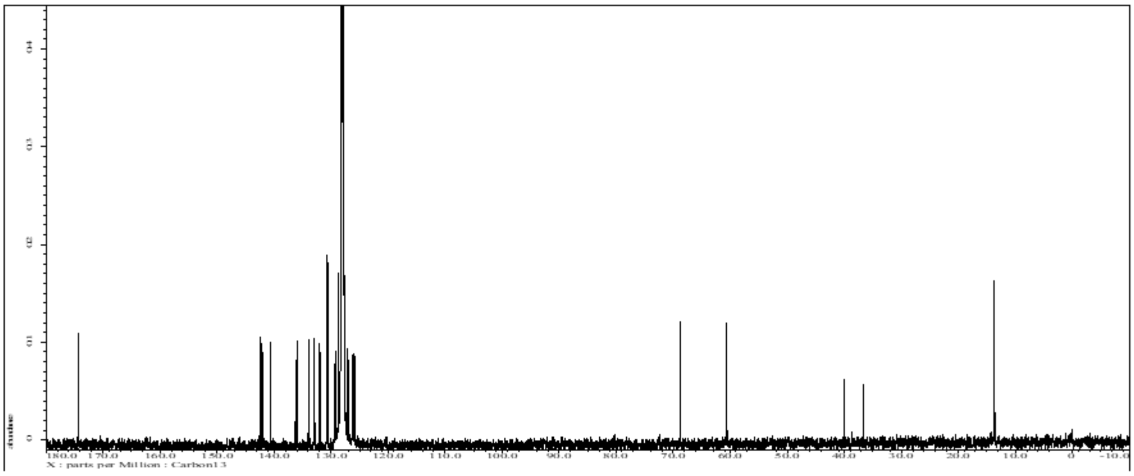
^{13}C NMR spectrum [(*R*)-**6a**]



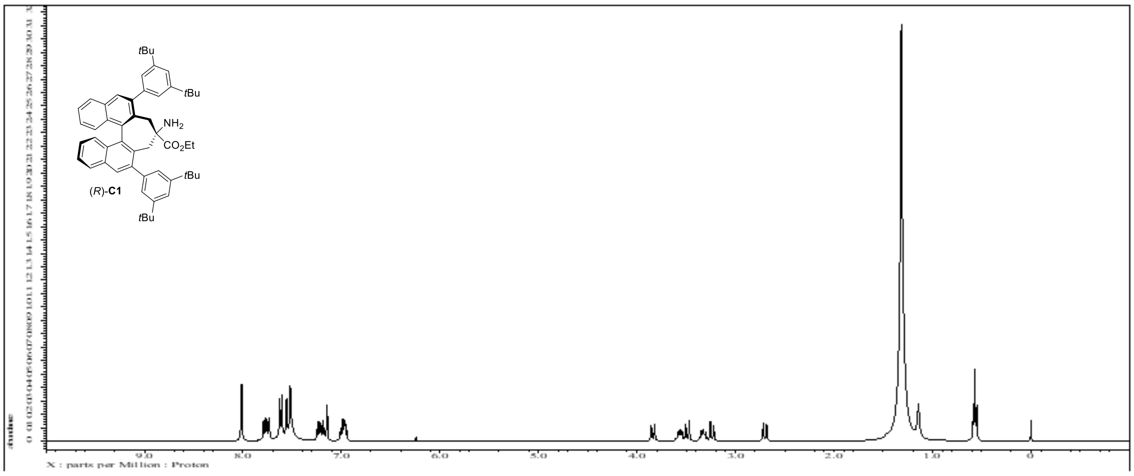
^{1}H NMR spectrum [(*R*)-**6b’**]



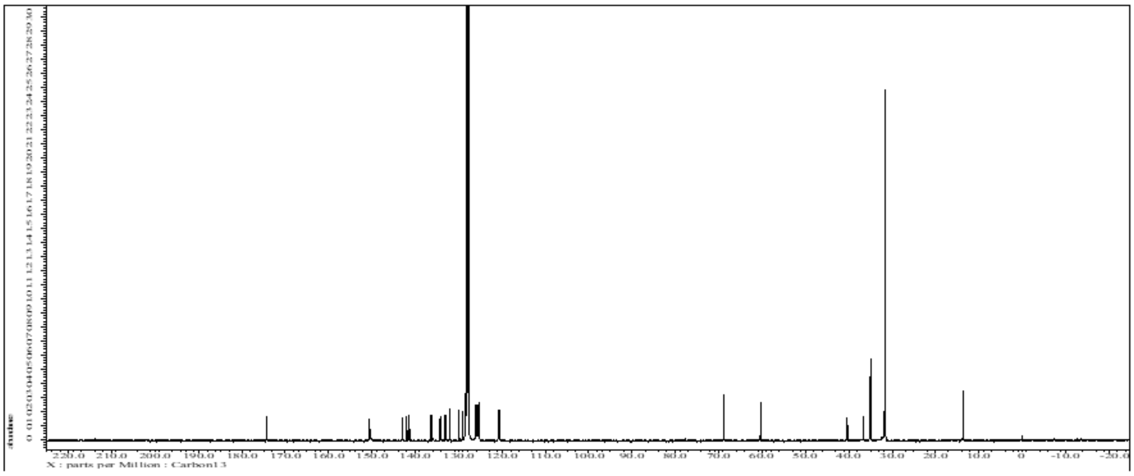
^{13}C NMR spectrum [(*R*)-**6b’**]



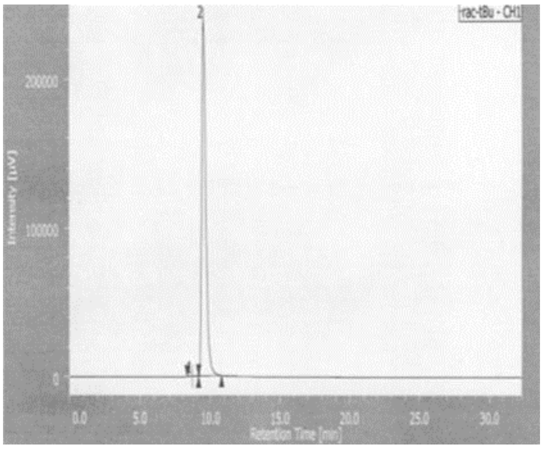
^{1}H NMR spectrum [(*R*)-**C1**]



^{13}C NMR spectrum [(*R*)-**C1**]

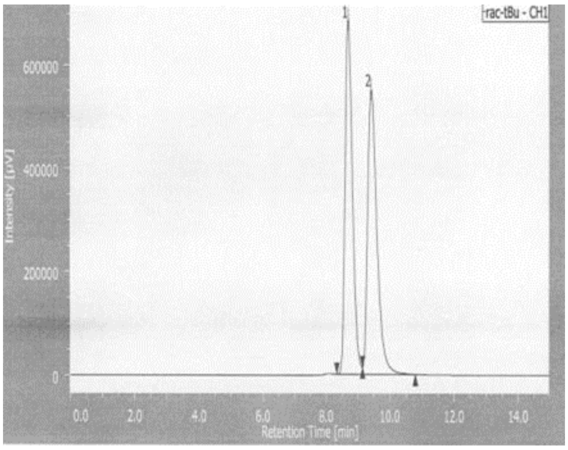


HPLC *optically active* [(*R*)-**C1**]



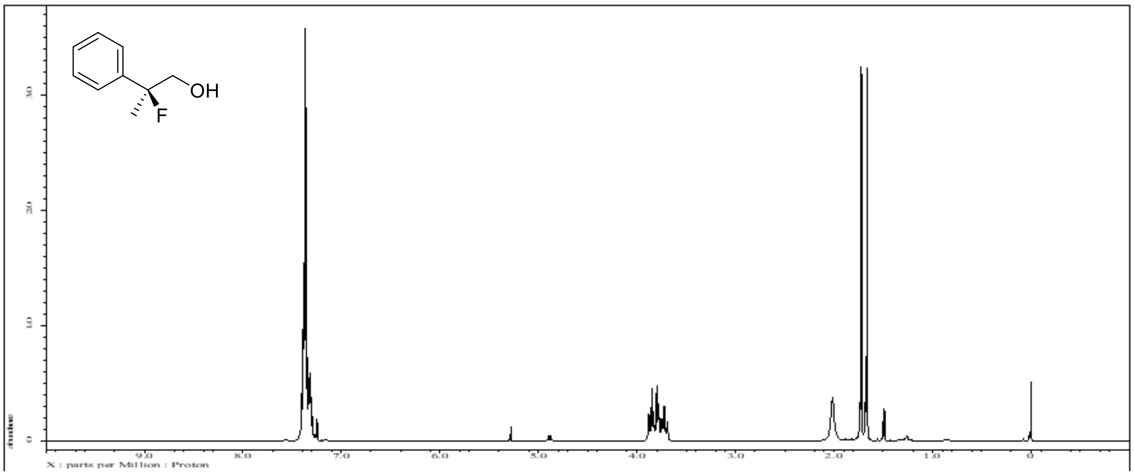
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	8.692	956	96	0.019	0.040	N/A	14571	1.962	0.722	
2	Unknown	1	9.483	4909183	239404	99.981	99.960	N/A	5297	N/A	1.556	

HPLC *racemic* (**C1)**

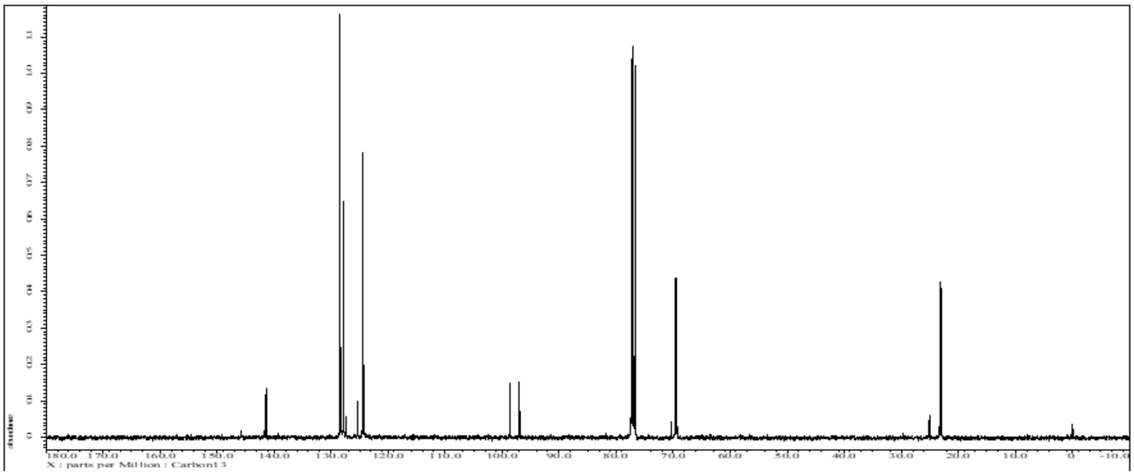


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	8.692	11063983	686069	49.752	55.556	N/A	6779	1.546	1.334	
2	Unknown	1	9.417	11174501	548839	50.248	44.444	N/A	5291	N/A	1.542	

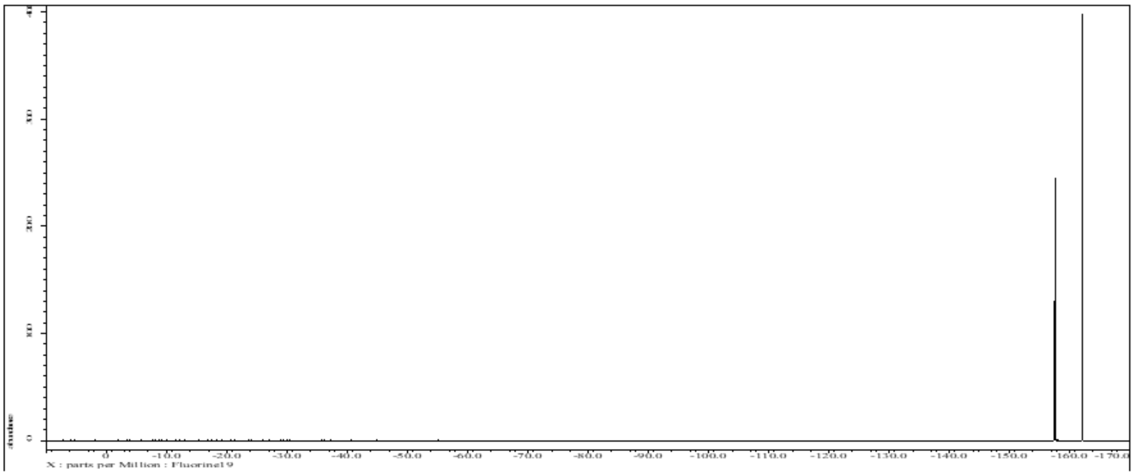
^{1}H NMR spectrum [(*S*)-**9a**]



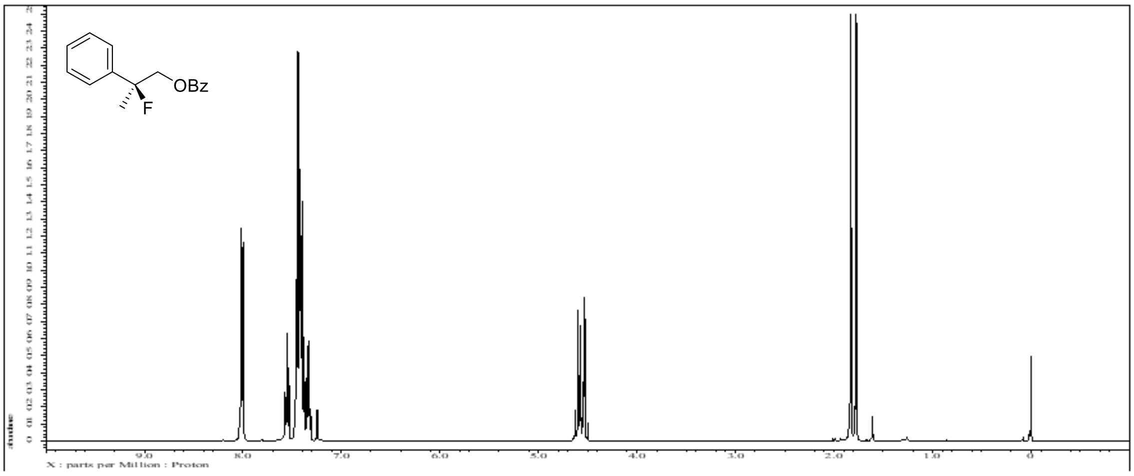
^{13}C NMR spectrum [(*S*)-**9a**]



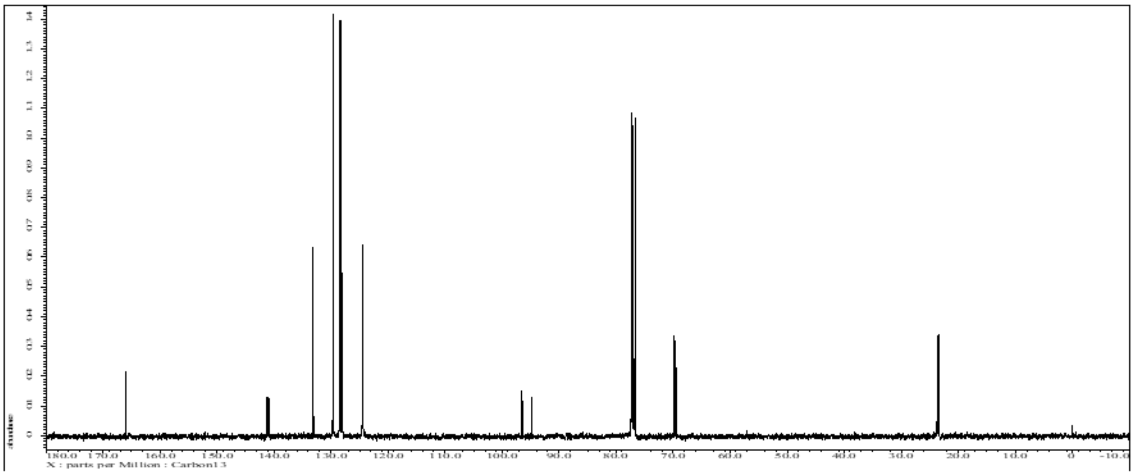
^{19}F NMR spectrum [(*S*)-**9a**]



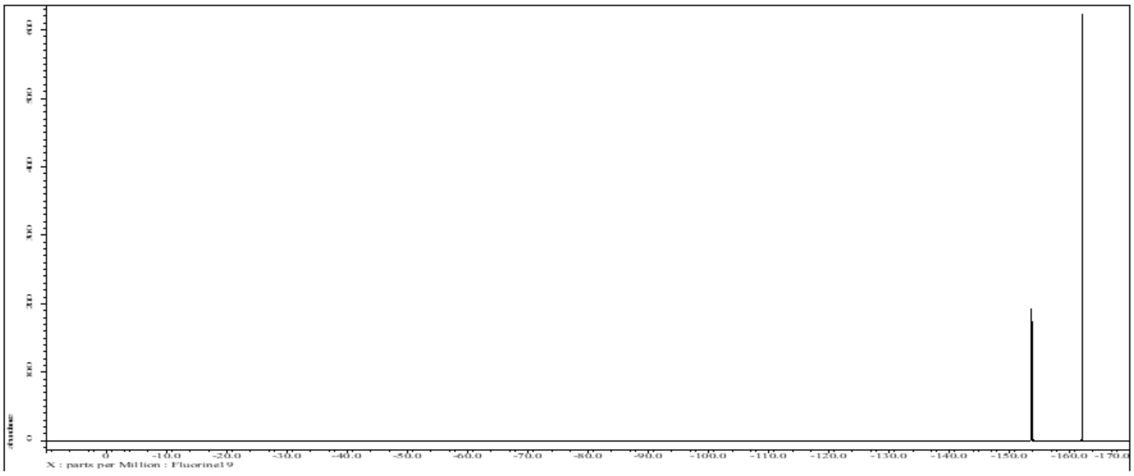
^{1}H NMR spectrum [(*S*)-**9a’**]



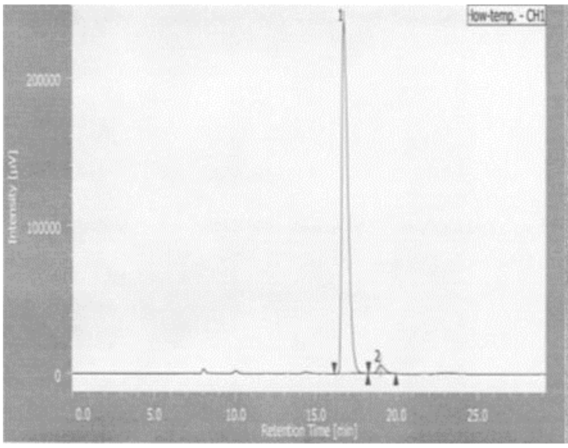
^{13}C NMR spectrum [(*S*)-**9a’**]



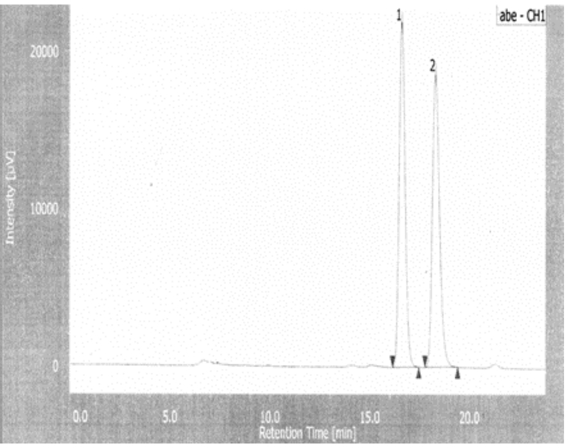
^{19}F NMR spectrum [(*S*)-**9a'**]



HPLC *optically active* [(*S*)-**9a'**]



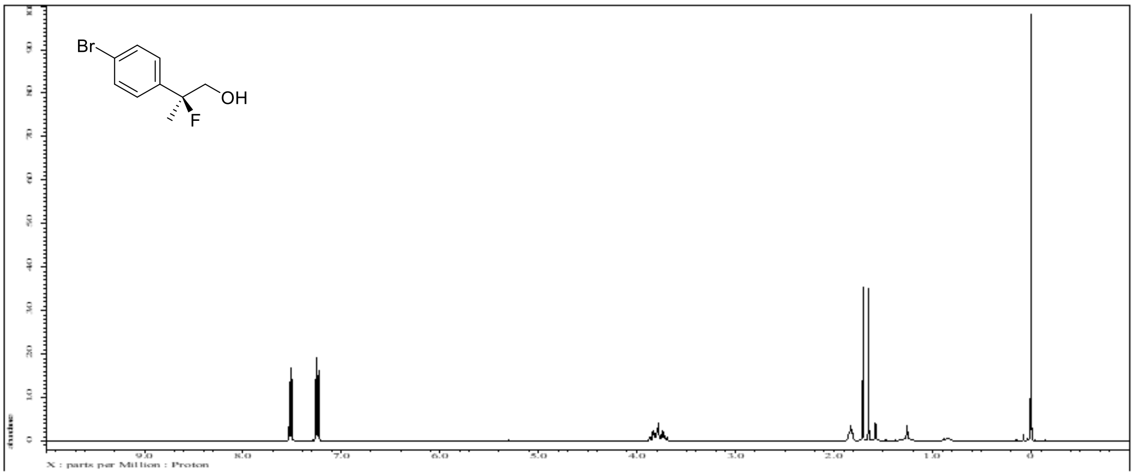
HPLC *racemic* [(*S*)-**9a'**]



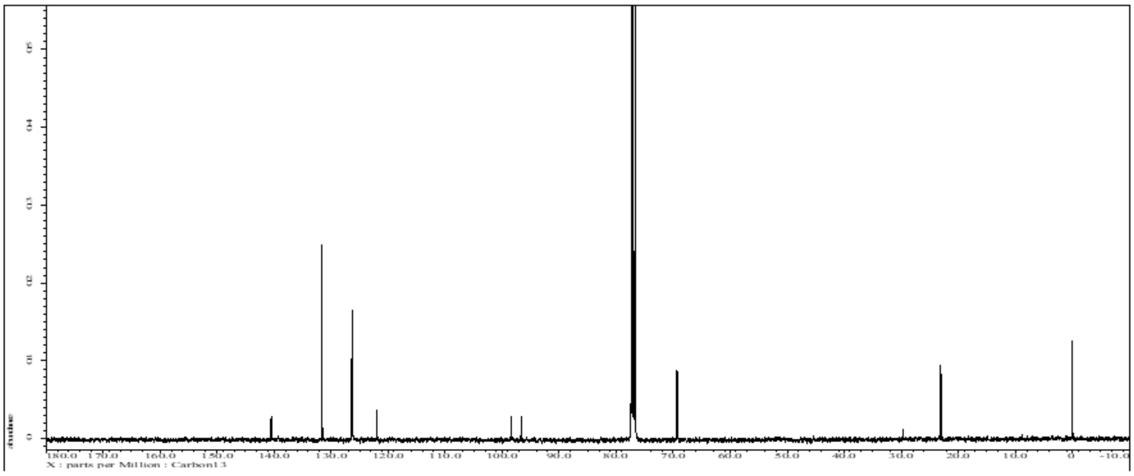
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	16.725	6385238	237257	97.416	97.657	N/A	9007	3.113	1.969	
2	Unknown	1	19.017	169374	5692	2.584	2.343	N/A	9729	N/A	1.454	

#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	16.592	462277	21958	49.826	54.137	N/A	14441	2.807	1.191	
2	Unknown	1	18.275	465498	18602	50.174	45.863	N/A	12639	N/A	1.311	

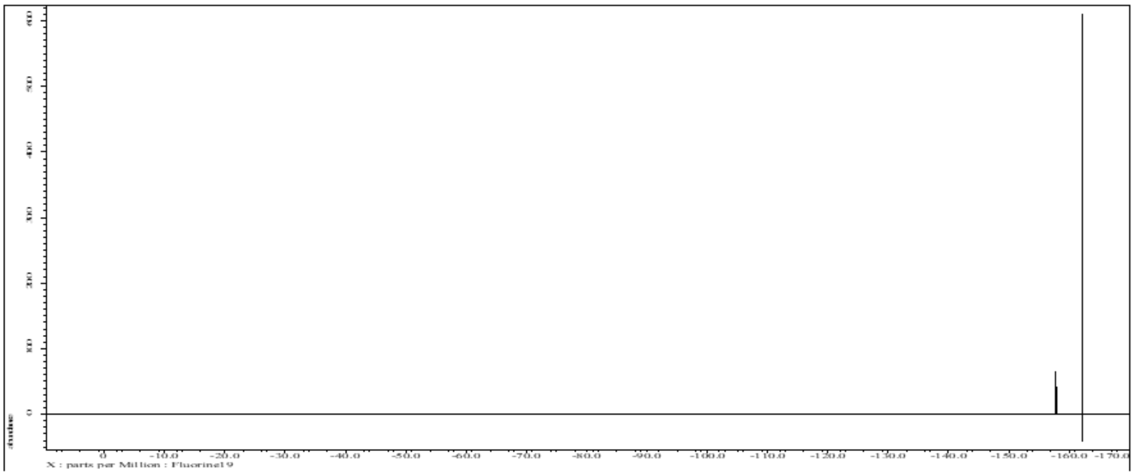
^{1}H NMR spectrum (**9b**)



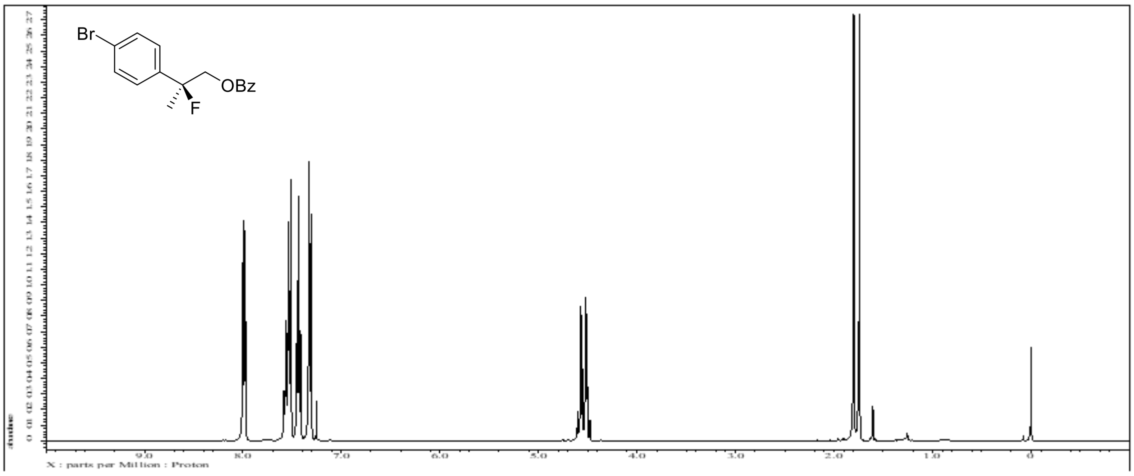
^{13}C NMR spectrum (**9b**)



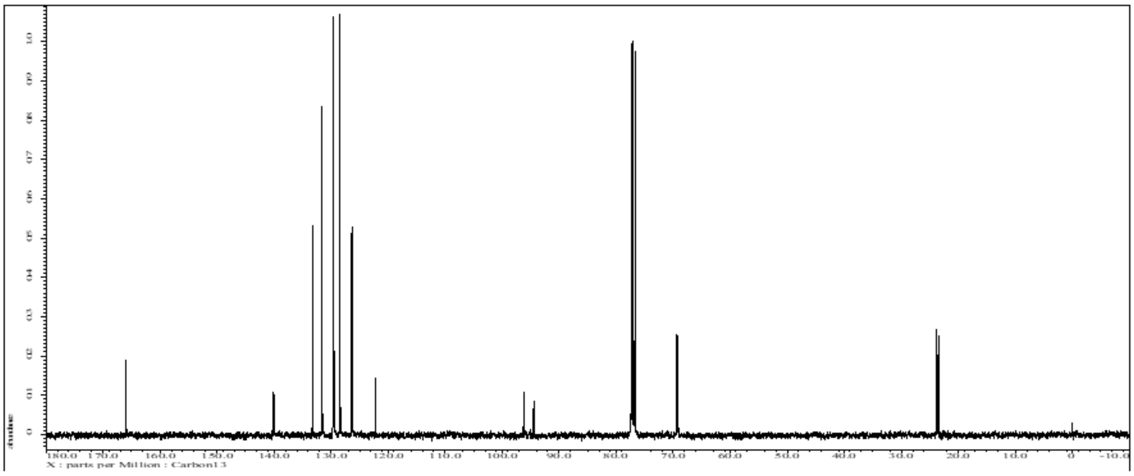
^{19}F NMR spectrum (**9b**)



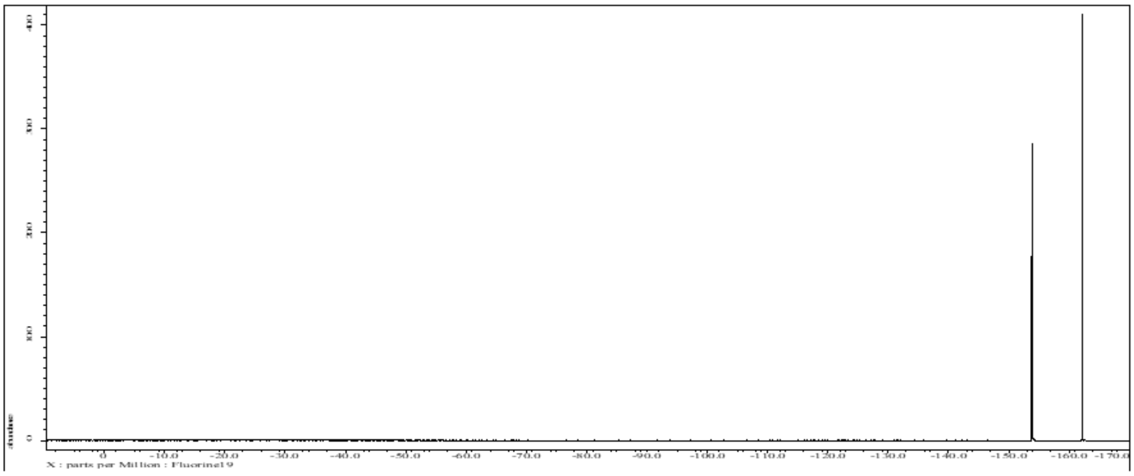
^{1}H NMR spectrum (**9b’**)



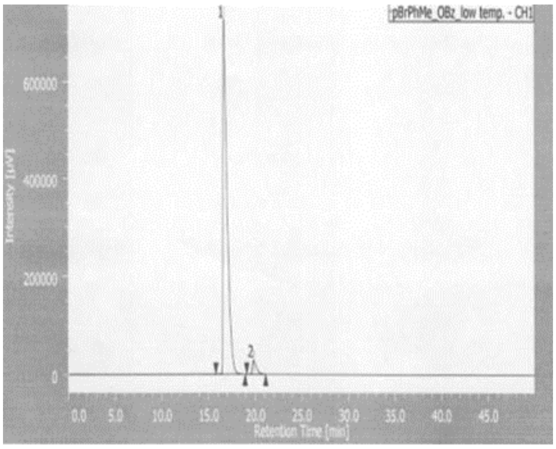
^{13}C NMR spectrum (**9b’**)

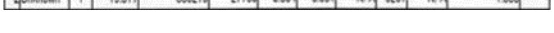


^{19}F NMR spectrum (**9b’**)



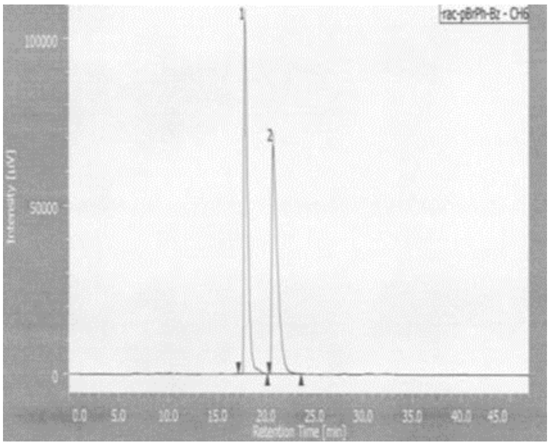
HPLC *optically active* (**9b’**)





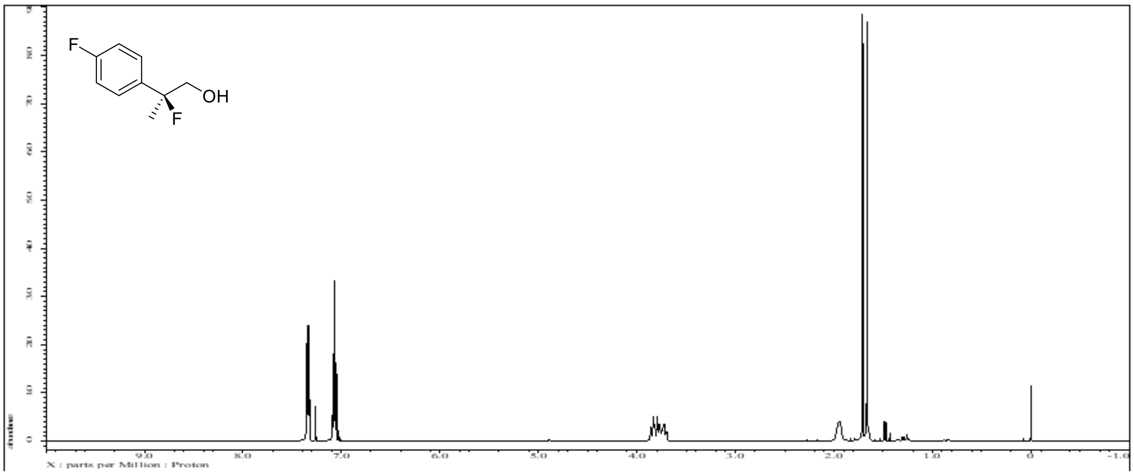
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	16.642	22204070	726475	96.166	96.319	N/A	7557	4.006	3.359	
2	Unknown	1	19.817	885275	27760	3.834	3.681	N/A	9267	N/A	1.888	

HPLC *racemic* (**9b’**)

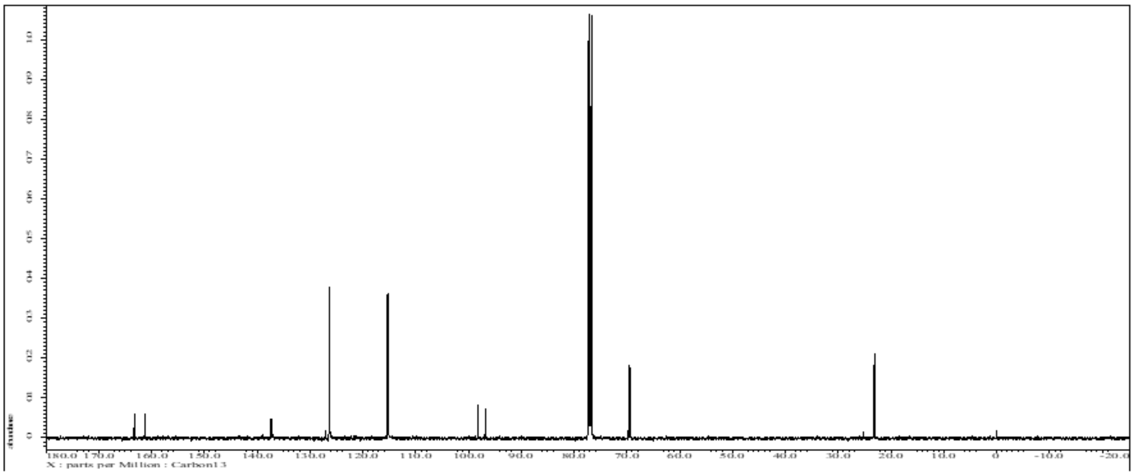


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	6	17.840	2780841	104997	50.783	60.688	N/A	11834	3.520	2.469	
2	Unknown	6	20.725	2695071	68015	49.217	39.312	N/A	7044	N/A	3.316	

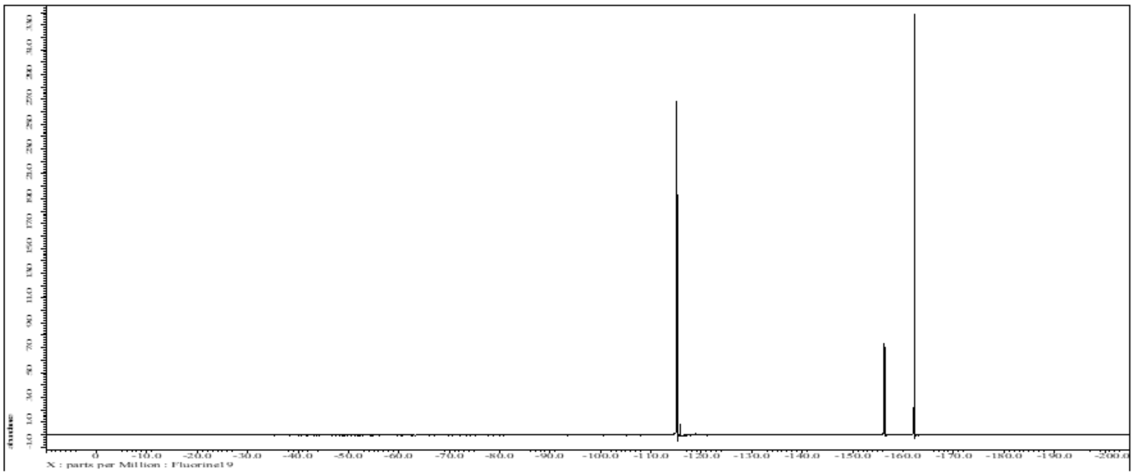
^{1}H NMR spectrum (**9c**)



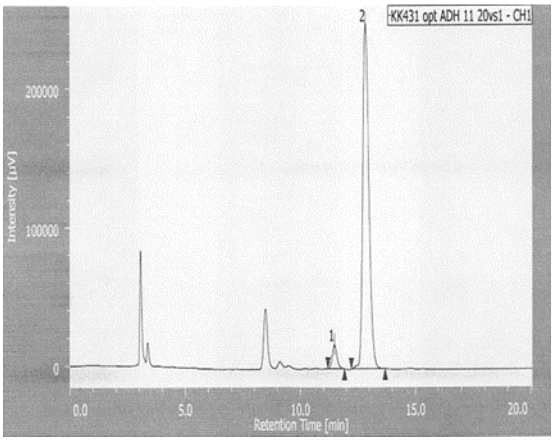
^{13}C NMR spectrum (**9c**)



^{19}F NMR spectrum (**9c**)

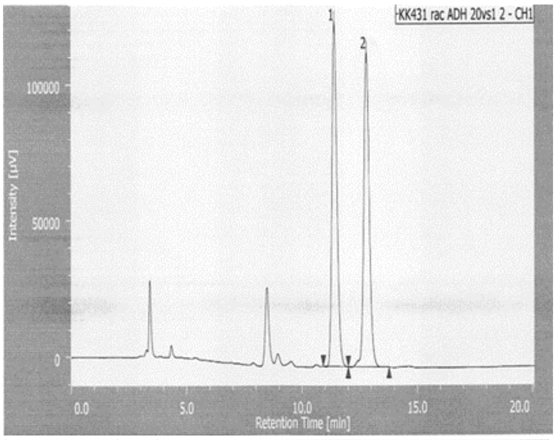


HPLC *optically active* (**9c**)



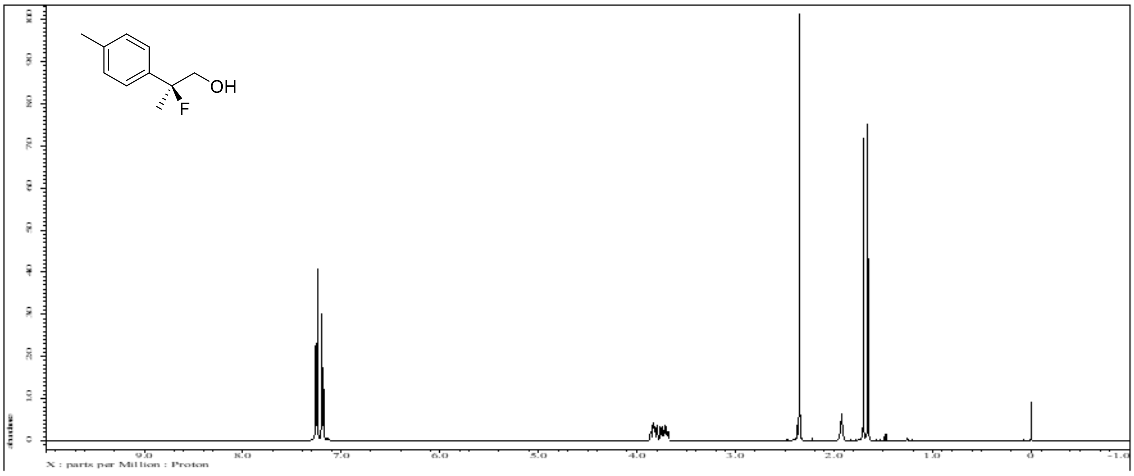
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	11.483	247386	17520	4.963	6.566	N/A	16088	3.128	1.204	
2	Unknown	1	12.825	4737414	249323	95.037	93.434	N/A	10610	N/A	1.323	

HPLC *racemic* (**9c**)

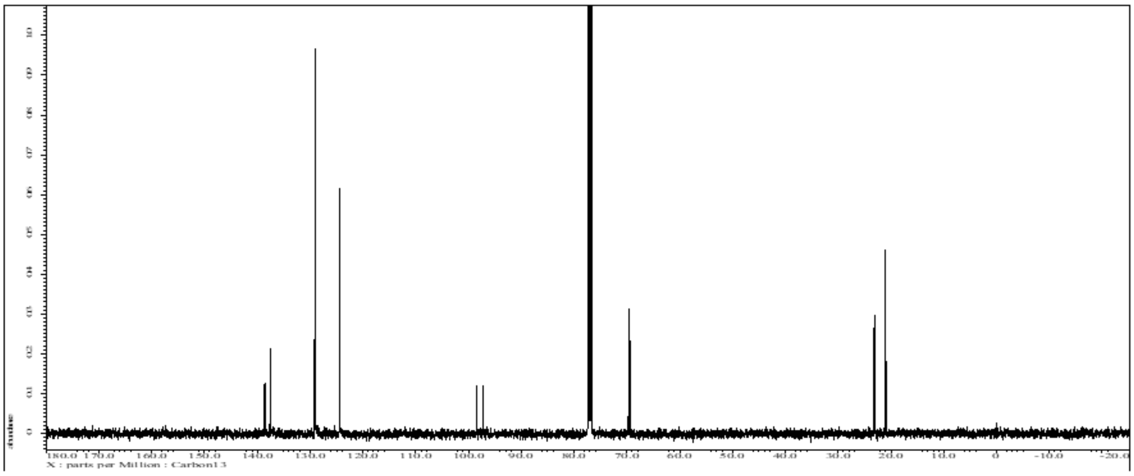


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	11.400	1899933	126352	49.276	52.263	N/A	13536	3.380	1.253	
2	Unknown	1	12.792	1955731	115410	50.724	47.737	N/A	13914	N/A	1.199	

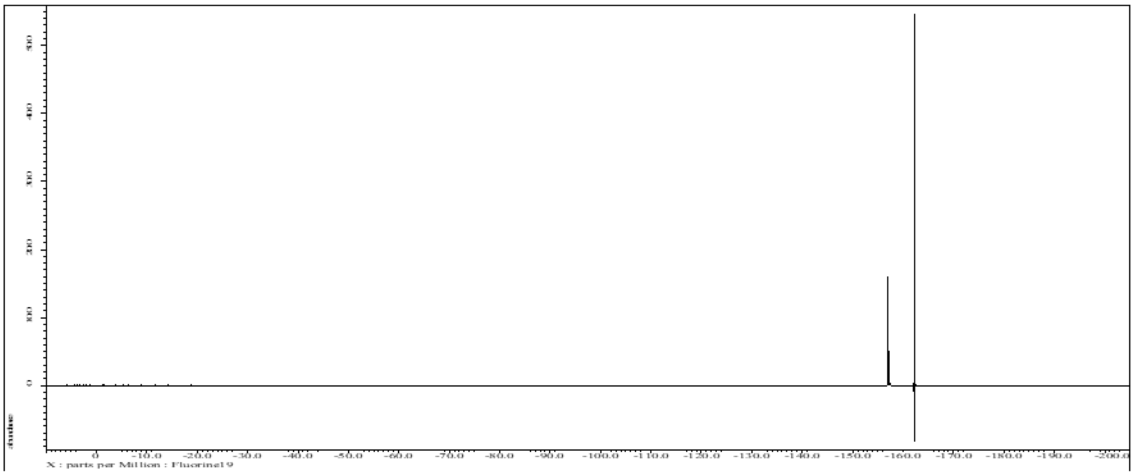
^{1}H NMR spectrum (**9d**)



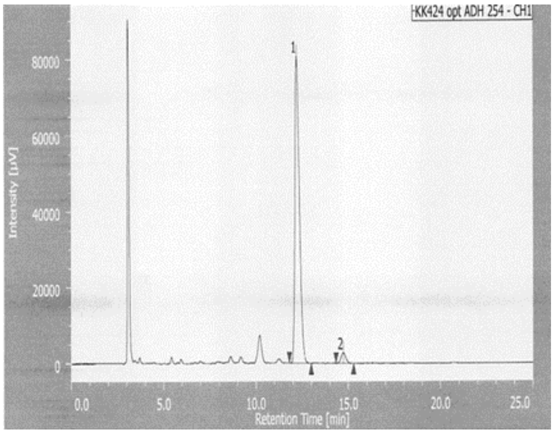
^{13}C NMR spectrum (**9d**)



^{19}F NMR spectrum (**9d**)

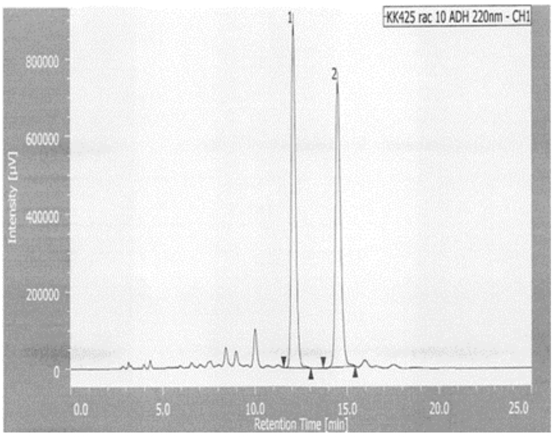


HPLC *optically active* (**9d**)



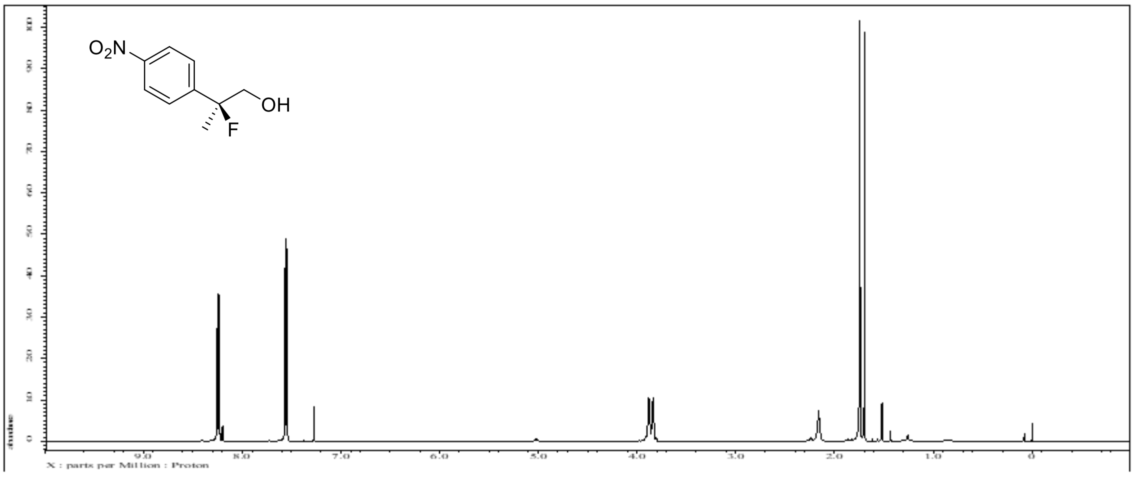
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	12.200	1374930	80619	96.523	96.646	N/A	12031	5.559	1.508	
2	Unknown	1	14.725	49526	2798	3.477	3.354	N/A	15983	N/A	1.056	

HPLC *racemic* (**9d**)

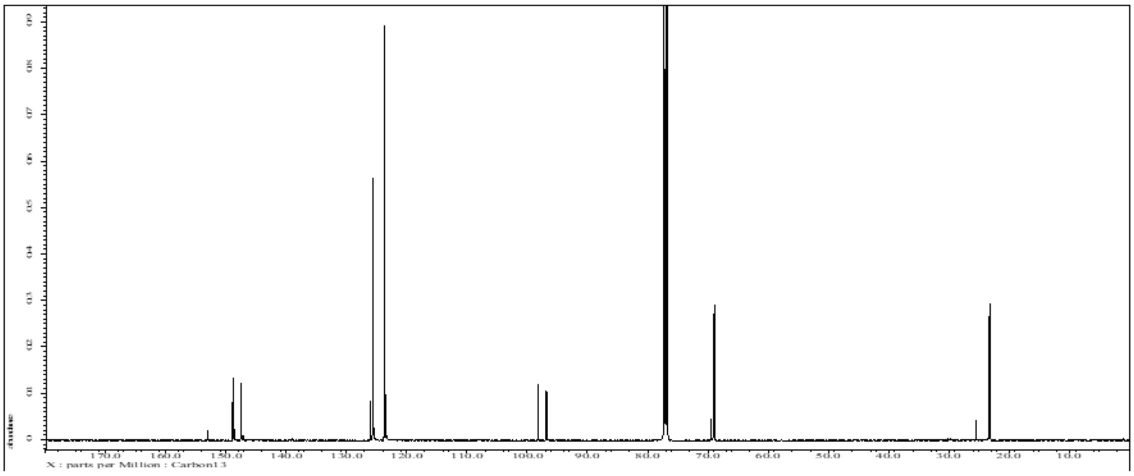


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	12.075	14588707	884459	50.288	54.687	N/A	12825	5.207	1.274	
2	Unknown	1	14.492	14421532	732855	49.712	45.313	N/A	13214	N/A	1.288	

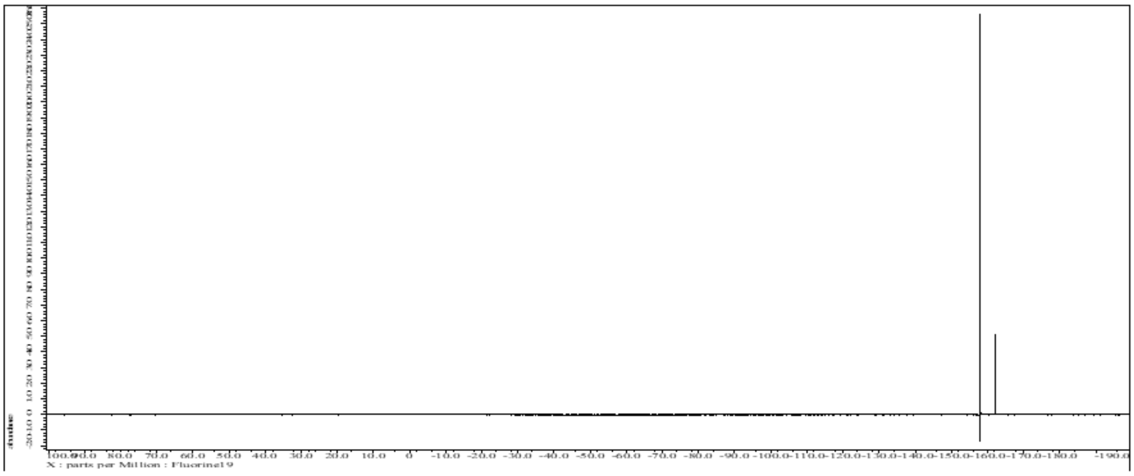
^{1}H NMR spectrum (**9e**)



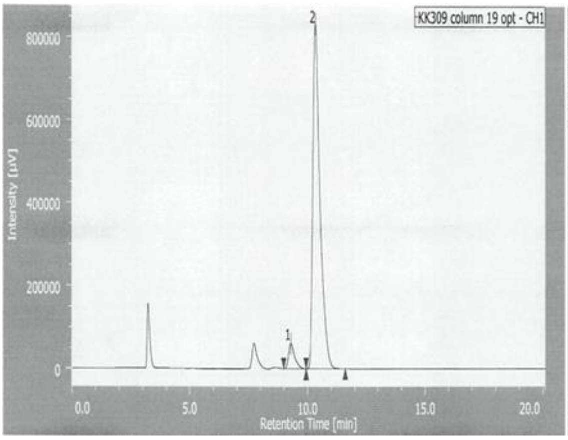
^{13}C NMR spectrum (**9e**)



^{19}F NMR spectrum (**9e**)

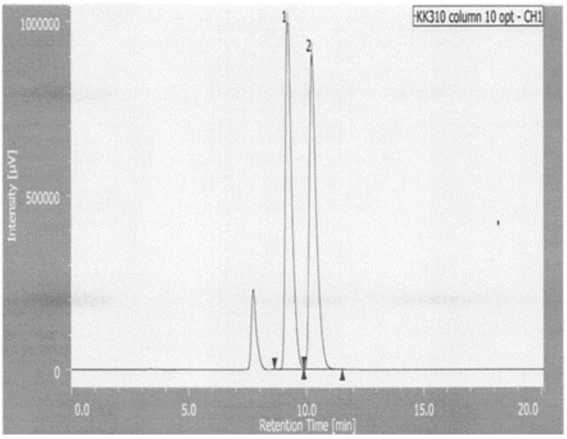


HPLC *optically active* (**9e**)



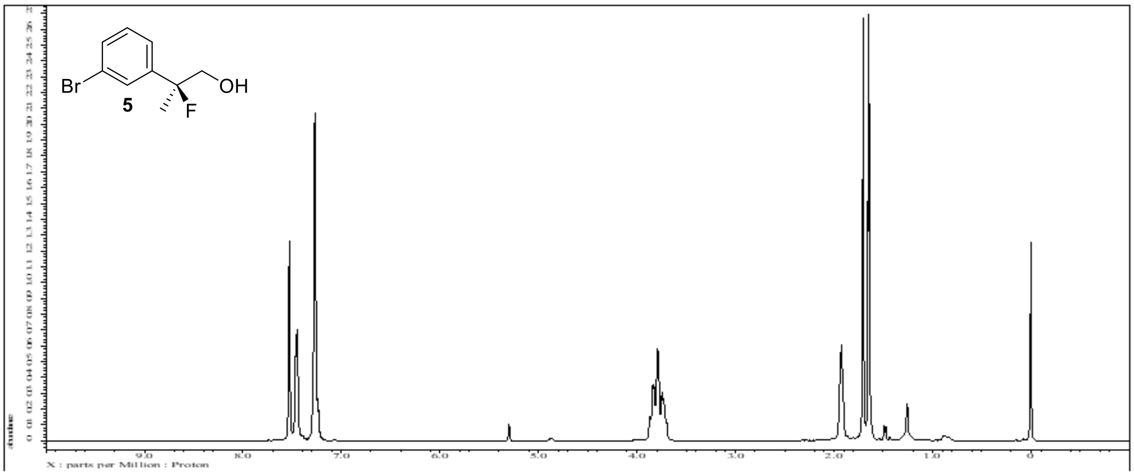
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	9.292	1097510	61941	5.888	6.924	N/A	7241	2.222	1.573	
2	Unknown	1	10.350	17543077	832612	94.112	93.076	N/A	6382	N/A	1.657	

HPLC *racemic* (**9e**)

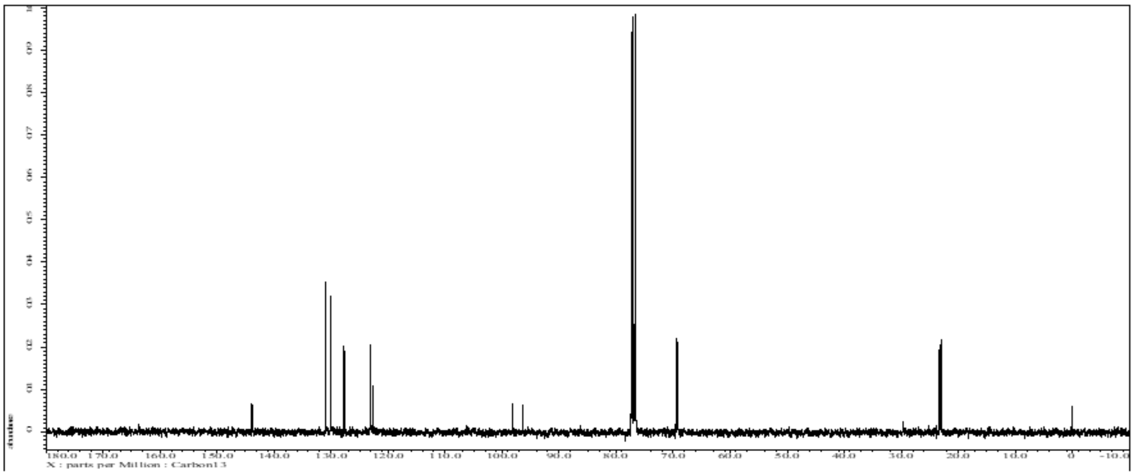


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	9.200	19448024	994777	50.734	52.332	N/A	5712	2.075	1.709	
2	Unknown	1	10.242	18885666	906120	49.266	47.668	N/A	6210	N/A	1.660	

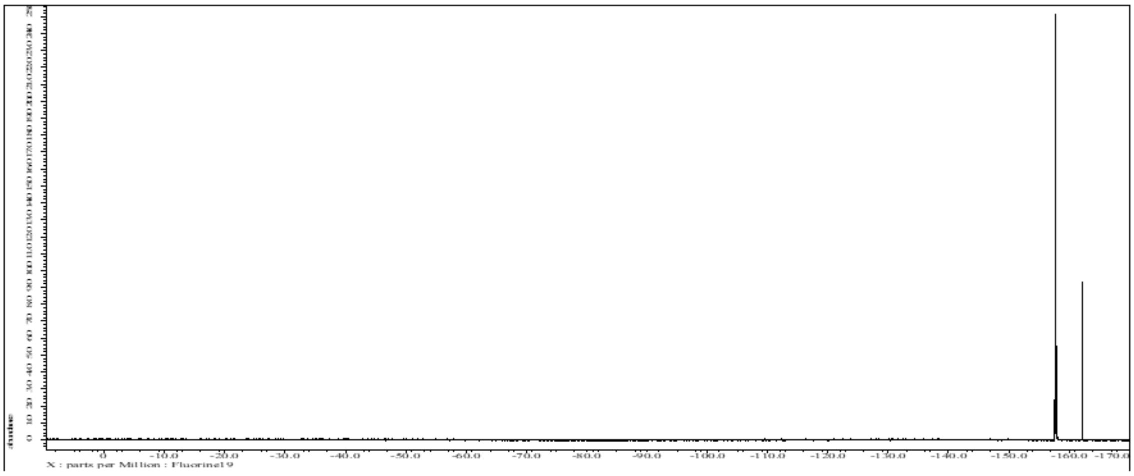
^{1}H NMR spectrum (**9g**)



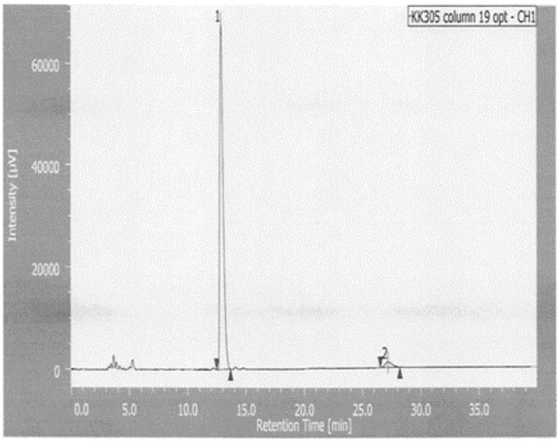
^{13}C NMR spectrum (**9g**)



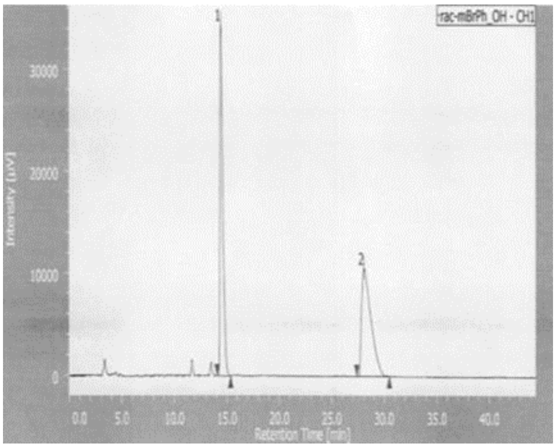
^{19}F NMR spectrum (**9g**)



HPLC *optically active* (**9g**)



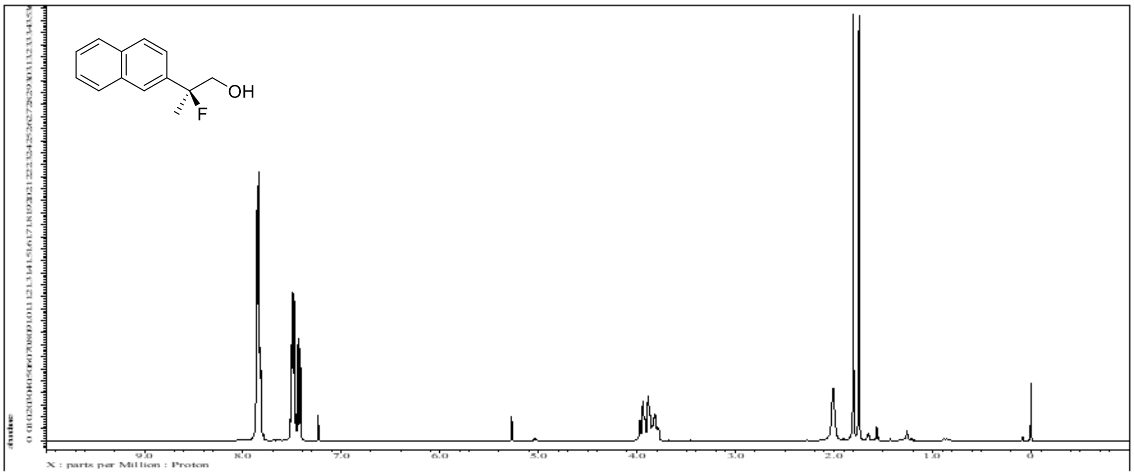
HPLC *racemic* (**9g**)



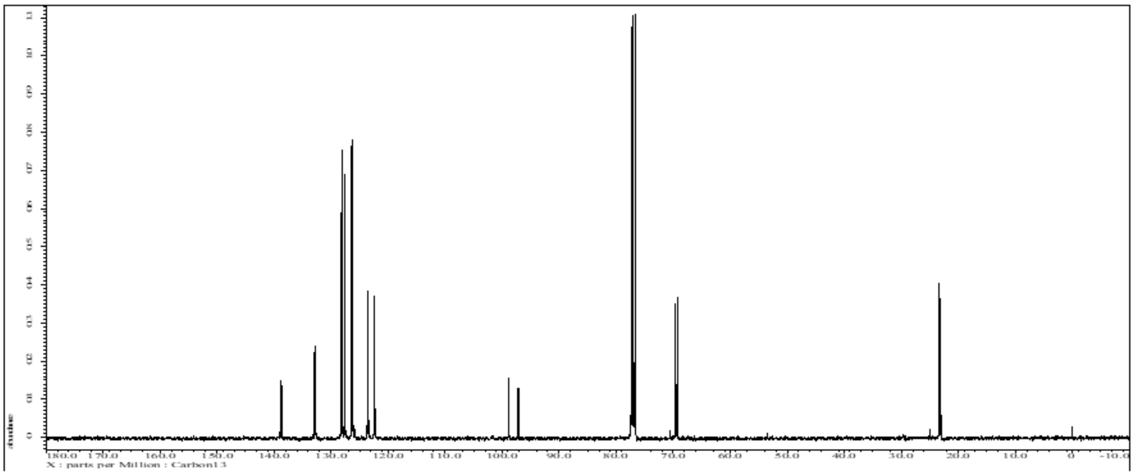
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	12.842	1384953	67909	96.705	98.407	N/A	9345	17.224	2.019	
2	Unknown	1	27.183	47195	1099	3.295	1.593	N/A	9123	N/A	1.369	

#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	14.408	677931	34626	50.762	76.566	N/A	13134	12.710	2.124	
2	Unknown	1	28.058	657569	10598	49.238	23.434	N/A	4623	N/A	2.369	

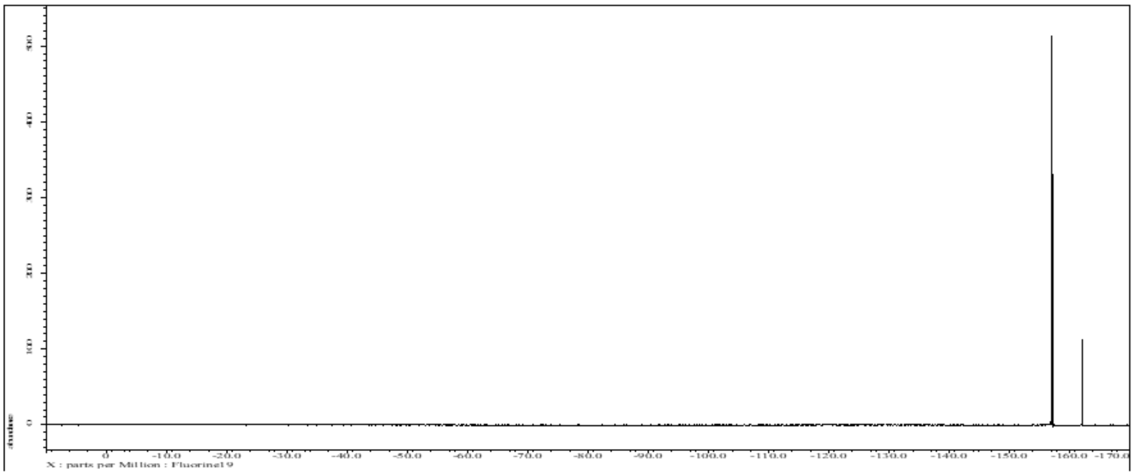
^{1}H NMR spectrum (**9h**)



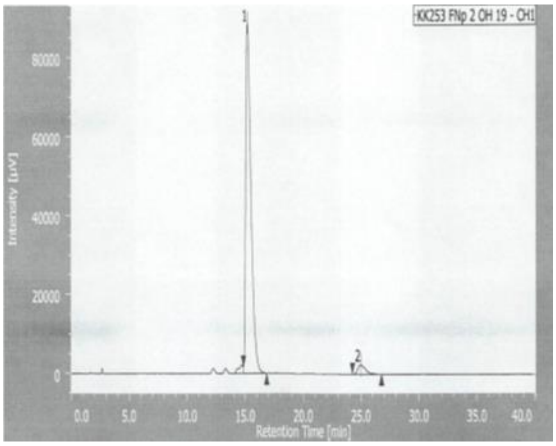
^{13}C NMR spectrum (**9h**)



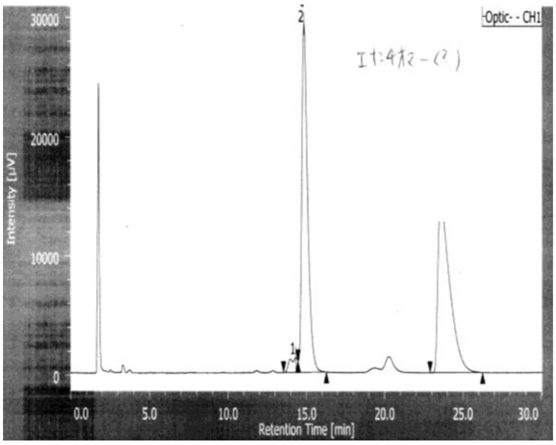
^{19}F NMR spectrum (**9h**)



HPLC *optically active* (**9h**)



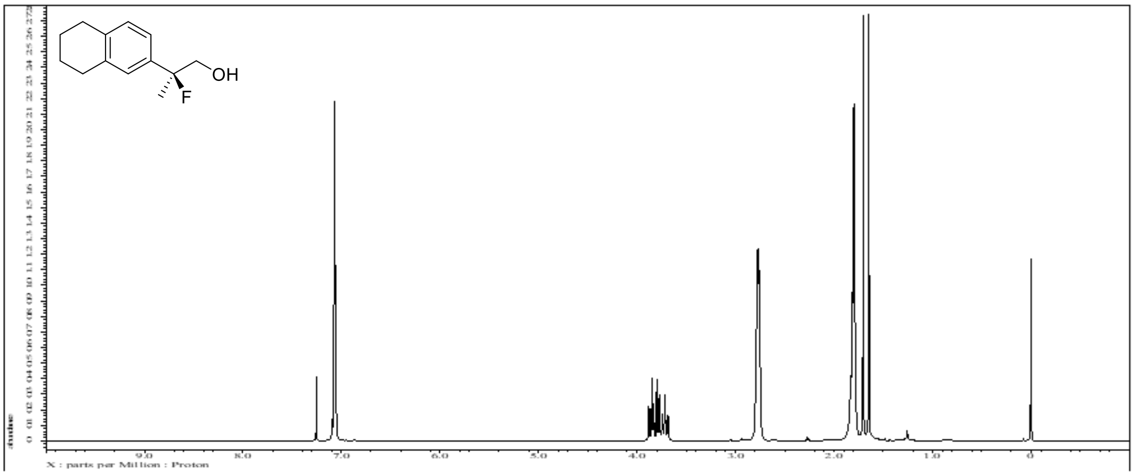
HPLC *racemic* (**9h**)



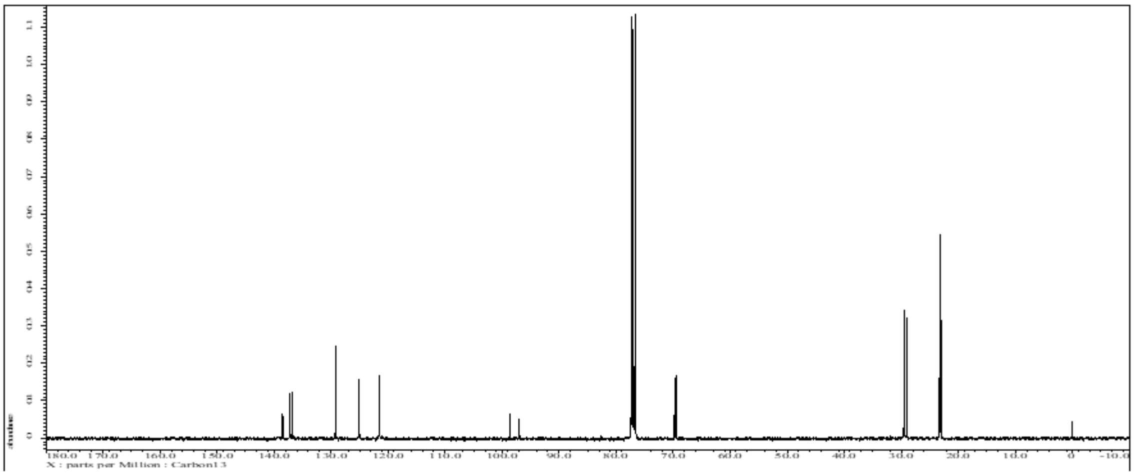
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	15.200	2802883	88711	96.194	97.434	N/A	5520	9.561	1.990	
2	Unknown	1	24.958	110884	2337	3.806	2.566	N/A	6605	N/A	1.630	

#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	14.325	42104	1225	2.695	2.742	N/A	N/A	N/A	N/A	
2	Unknown	1	14.858	768959	29227	49.221	65.410	N/A	7952	8.666	1.519	
3	Unknown	1	23.608	751197	14230	48.084	31.848	N/A	4834	N/A	2.434	

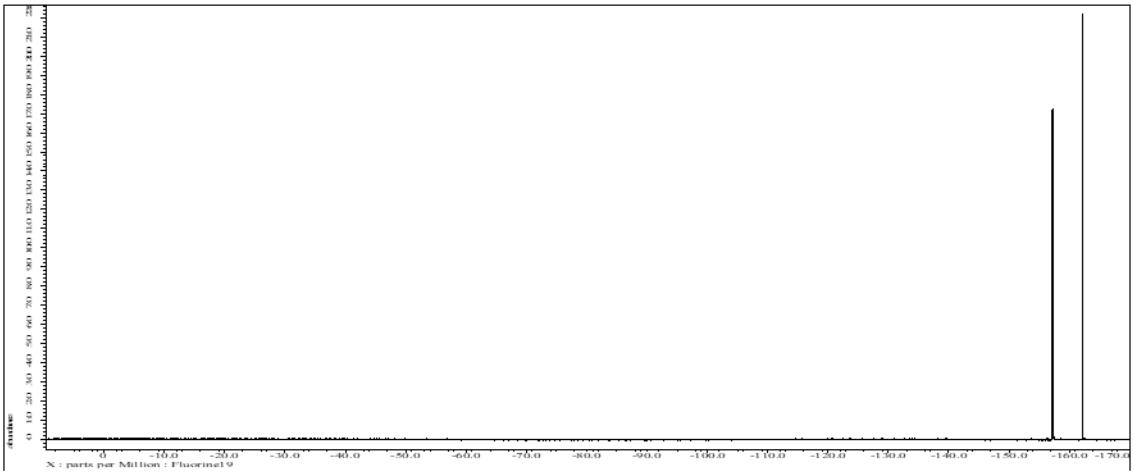
^{1}H NMR spectrum (**9i**)



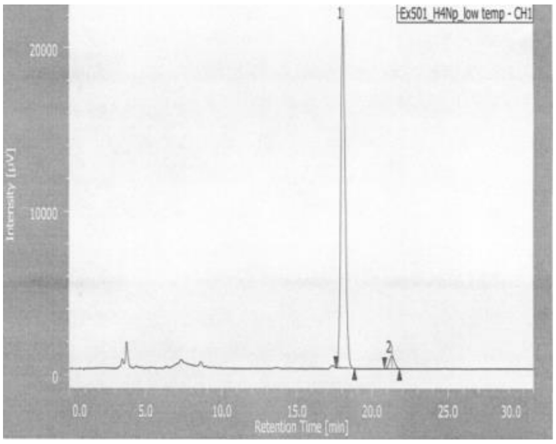
^{13}C NMR spectrum (**9i**)



^{19}F NMR spectrum (**9i**)

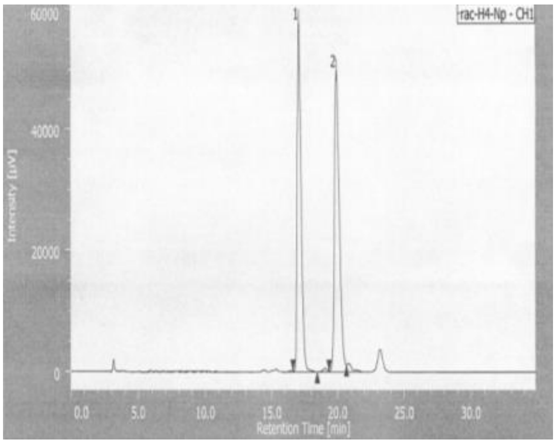


HPLC *optically active* (**9i**)



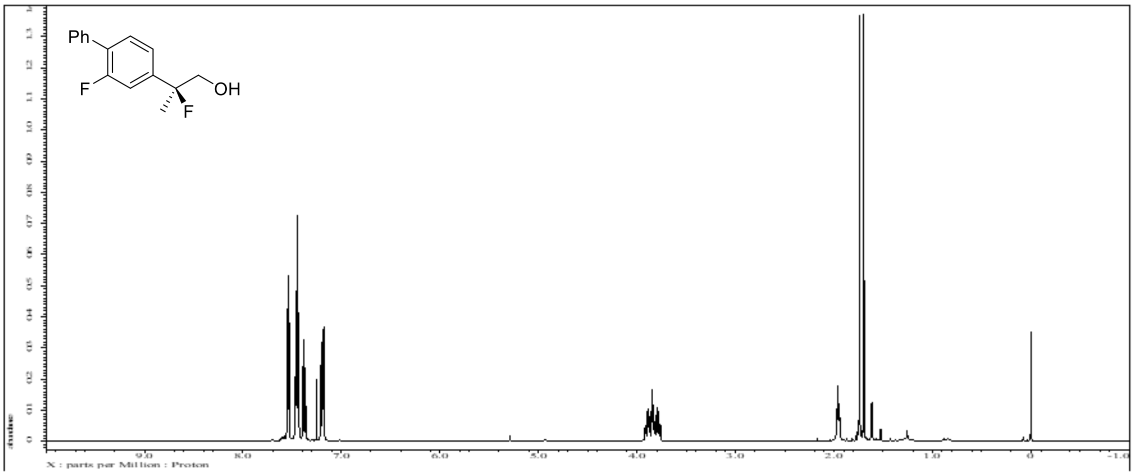
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	18.058	427388	21238	95.893	96.481	N/A	18855	5.643	1.223	
2	Unknown	1	21.317	18307	775	4.107	3.519	N/A	18208	N/A	1.043	

HPLC *racemic* (**9i**)

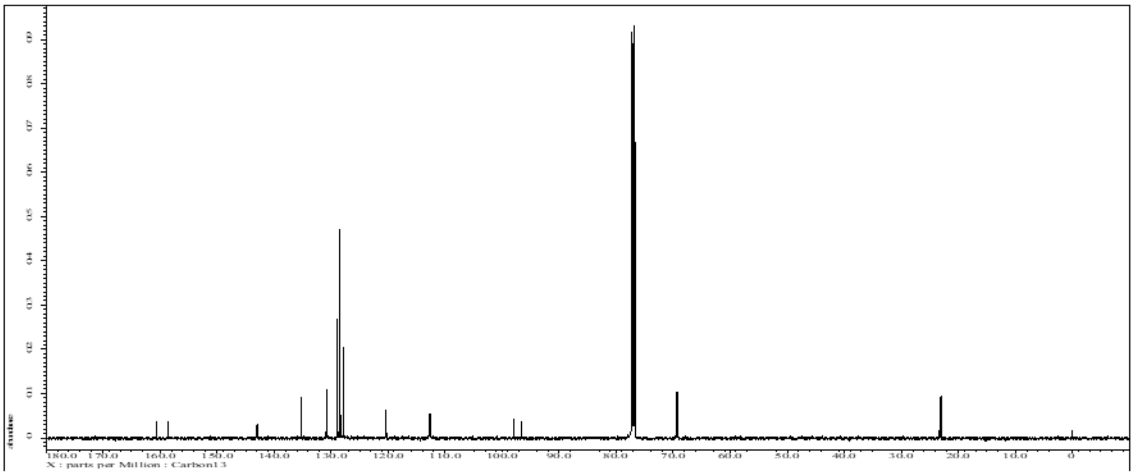


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	17.050	1195402	57928	48.324	53.755	N/A	16506	4.776	1.532	
2	Unknown	1	19.892	1278300	49836	51.676	46.245	N/A	14432	N/A	1.497	

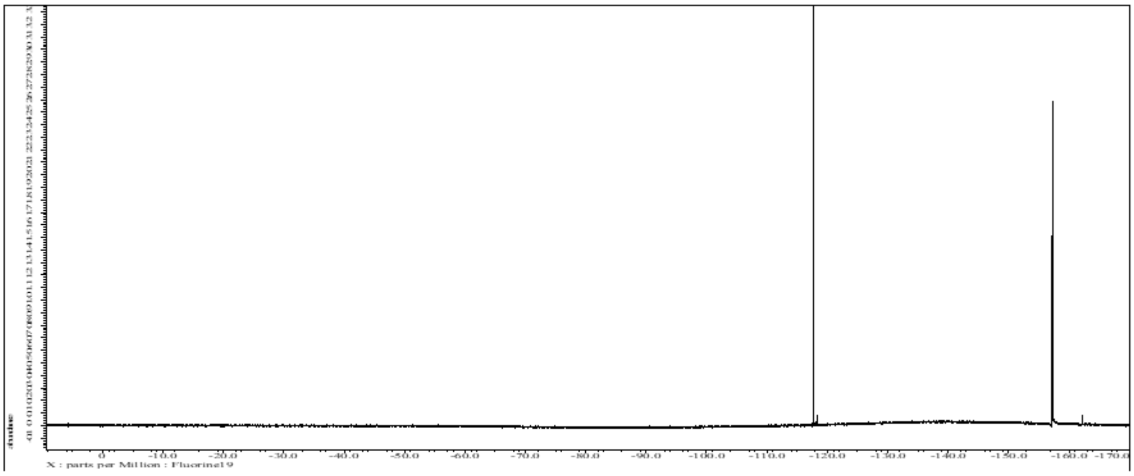
^{1}H NMR spectrum (**9j**)



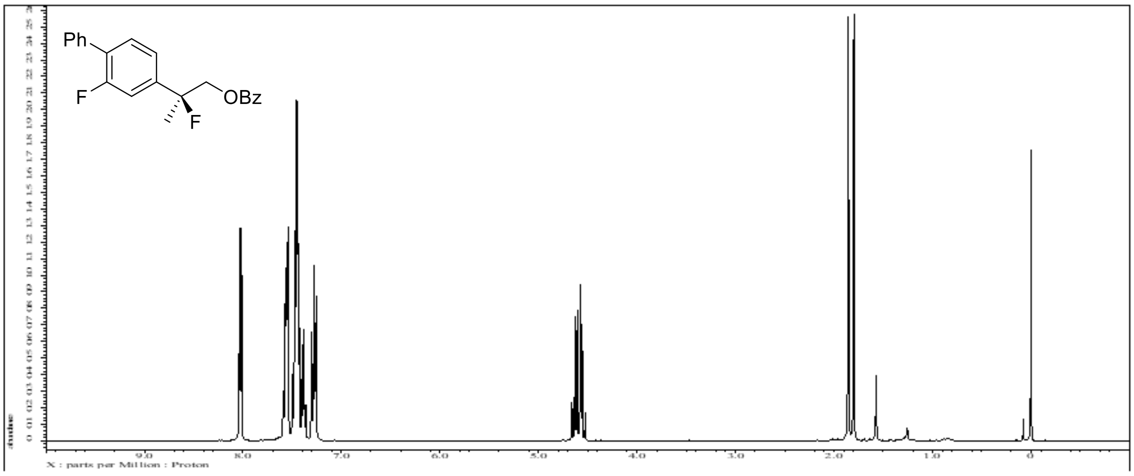
^{13}C NMR spectrum (**9j**)



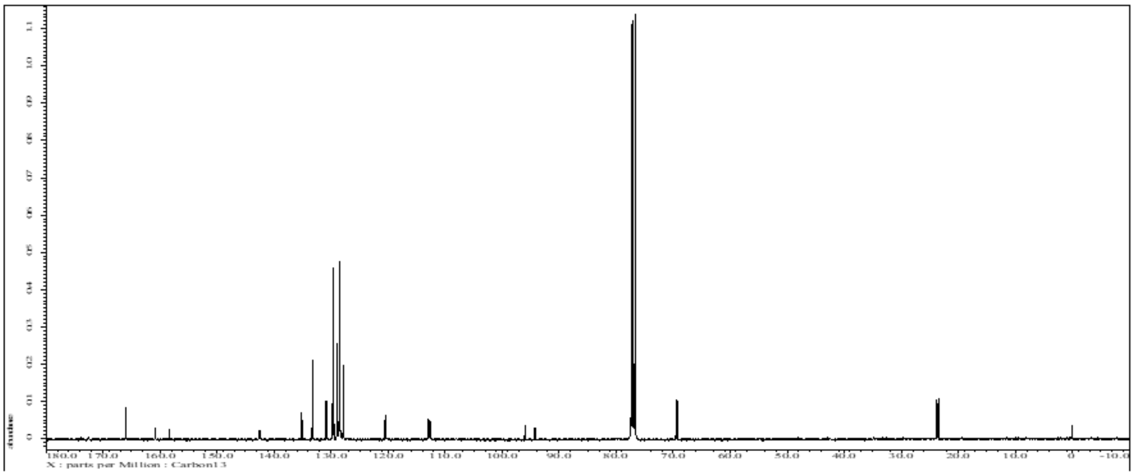
^{19}F NMR spectrum (**9j**)



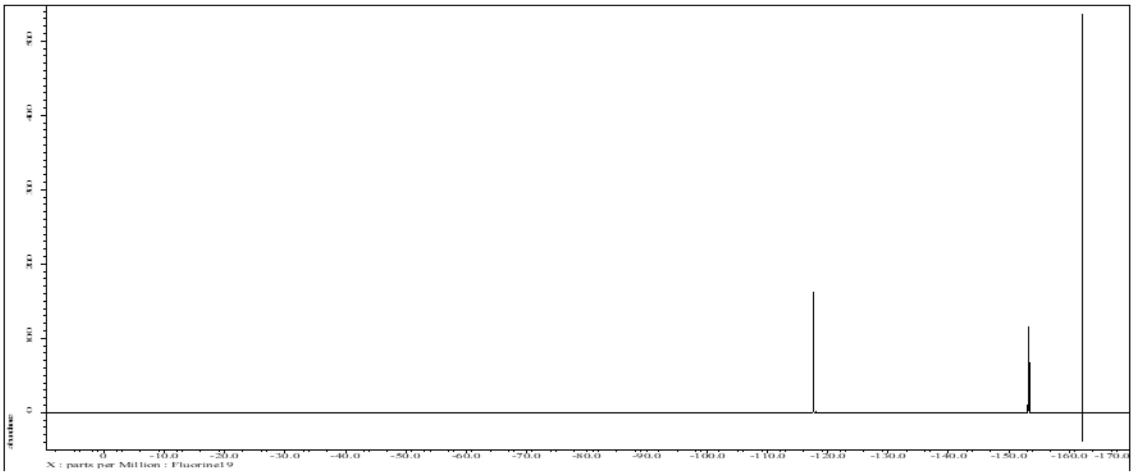
^{1}H NMR spectrum (**9j’**)



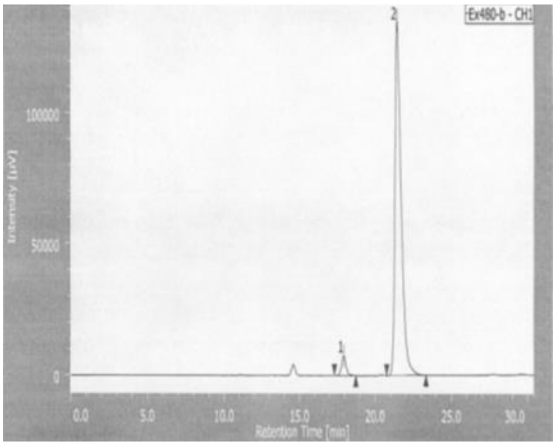
^{13}C NMR spectrum (**9j’**)



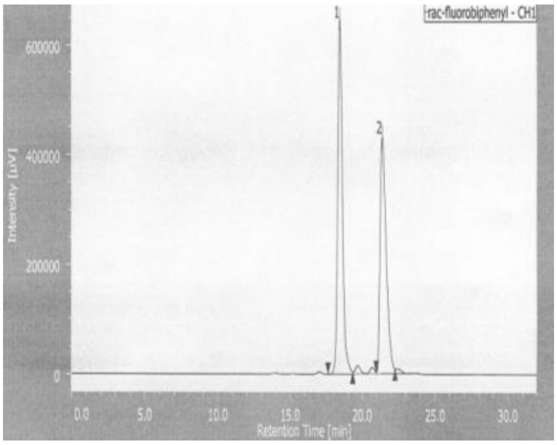
^{19}F NMR spectrum (**9j’**)



HPLC *optically active* (**9j’**) HPLC *racemic* (**9j’**)

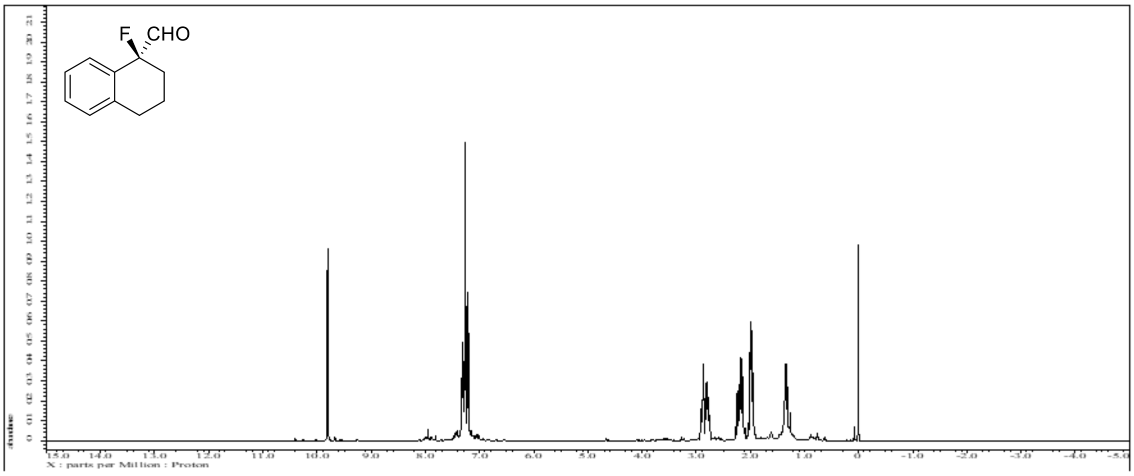


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	17.933	152379	7482	3.868	5.246	N/A	19574	5.791	1.107	
2	Unknown	1	21.417	3786899	135144	96.132	94.754	N/A	15259	N/A	1.803	

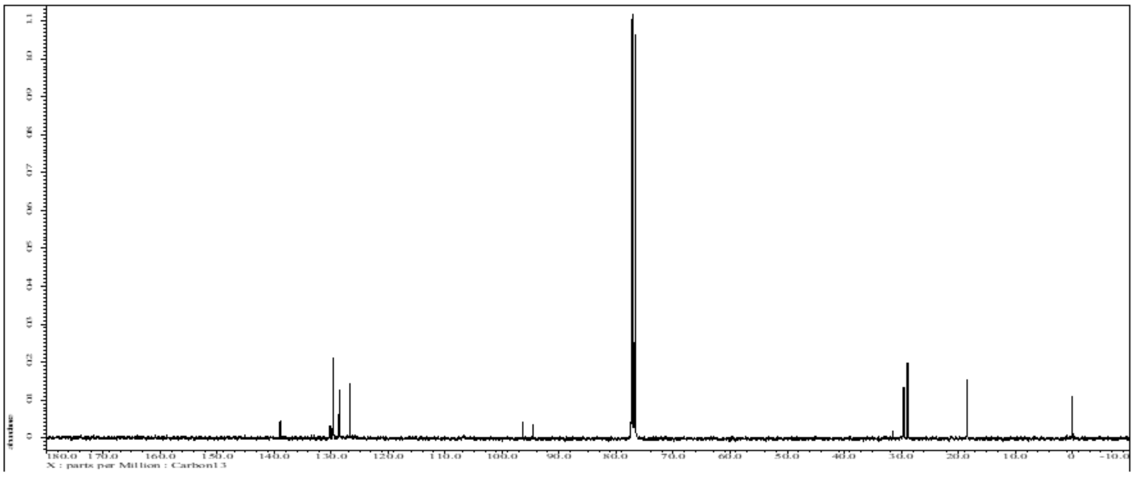


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	18.433	14558269	645557	54.094	59.990	N/A	16710	4.464	1.310	
2	Unknown	1	21.358	12354566	430553	45.906	40.010	N/A	13197	N/A	1.722	

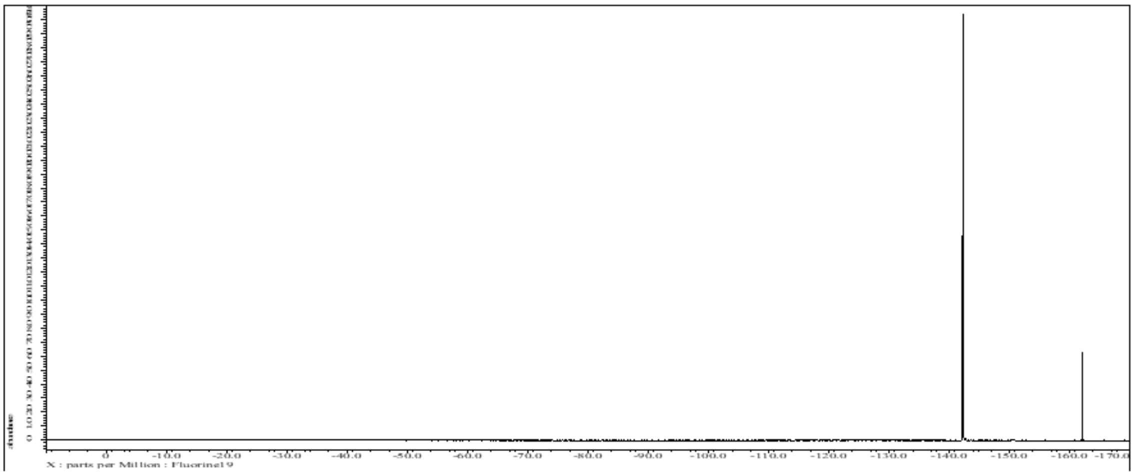
^{1}H NMR spectrum (**8k**)



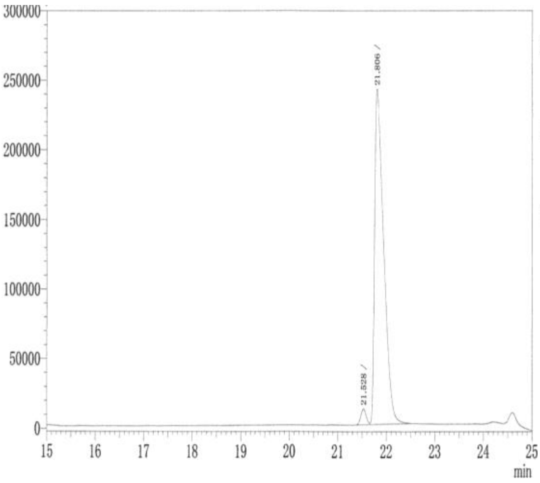
^{13}C NMR spectrum (**8k**)



^{19}F NMR spectrum (**8k**)

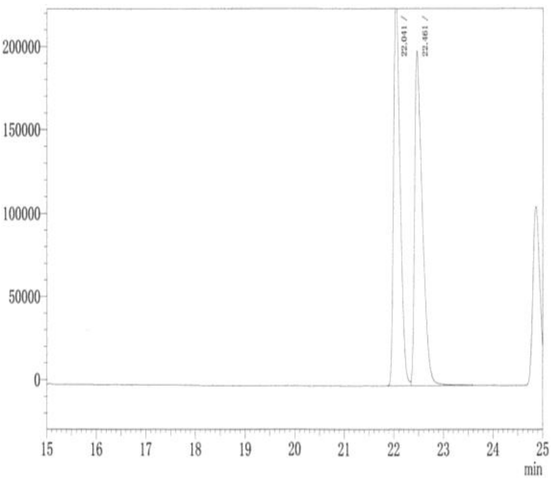


GC *optically active* (**8k**)



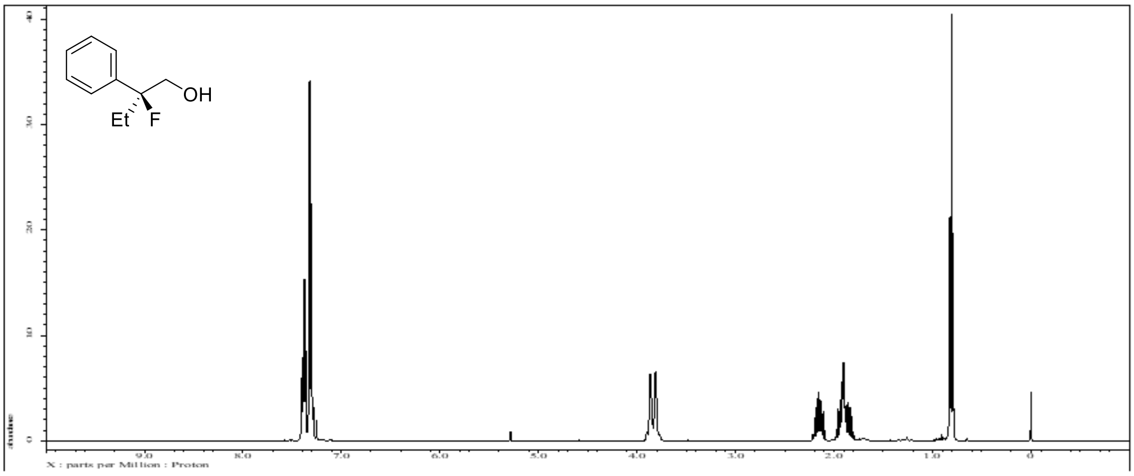
ピーク番号	保持時間	面積	高さ	濃度
1	21.528	84671	11221	2.604
2	21.806	3166809	240423	97.396

GC *racemic* (**8k**)

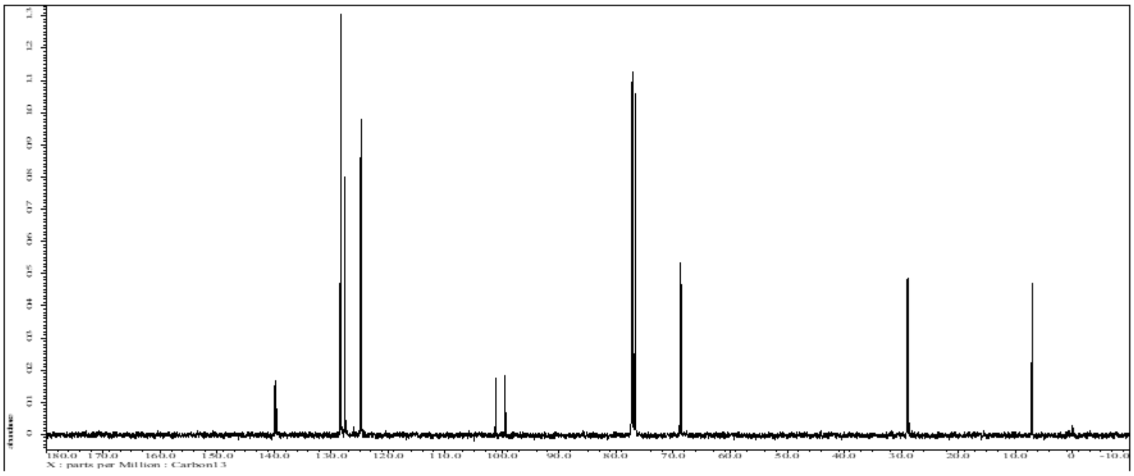


ピーク番号	保持時間	面積	高さ	濃度
1	22.041	2136055	237537	35.901
2	22.461	2162570	200602	36.346

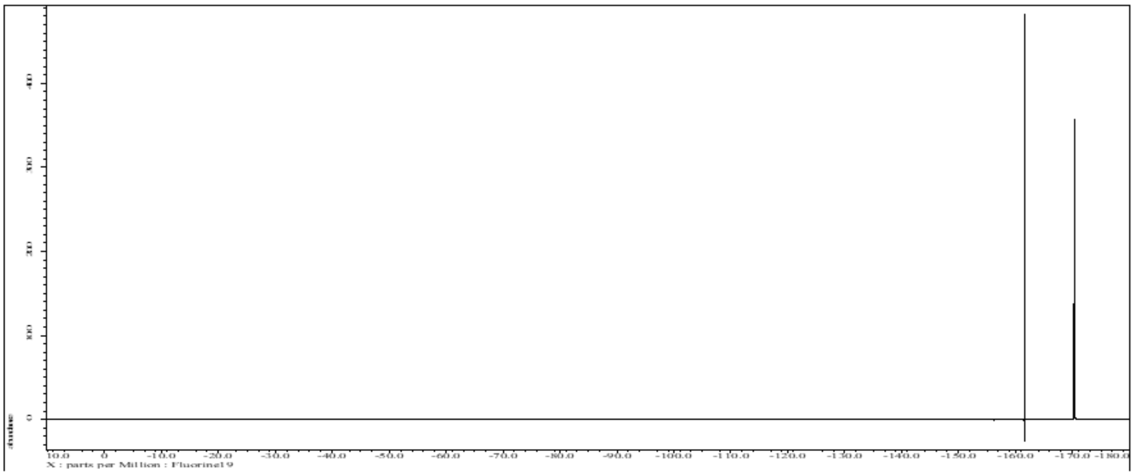
^{1}H NMR spectrum (**9l**)



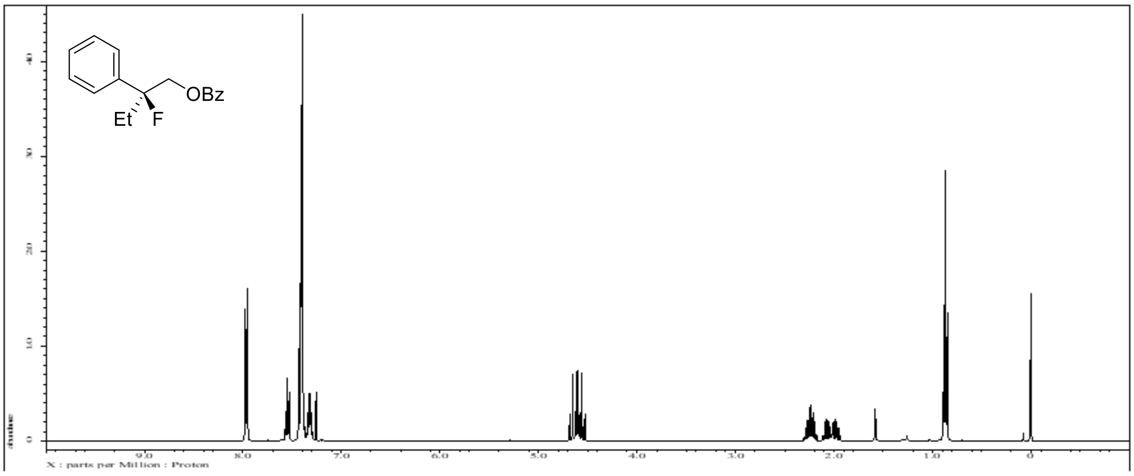
^{13}C NMR spectrum (**9l**)



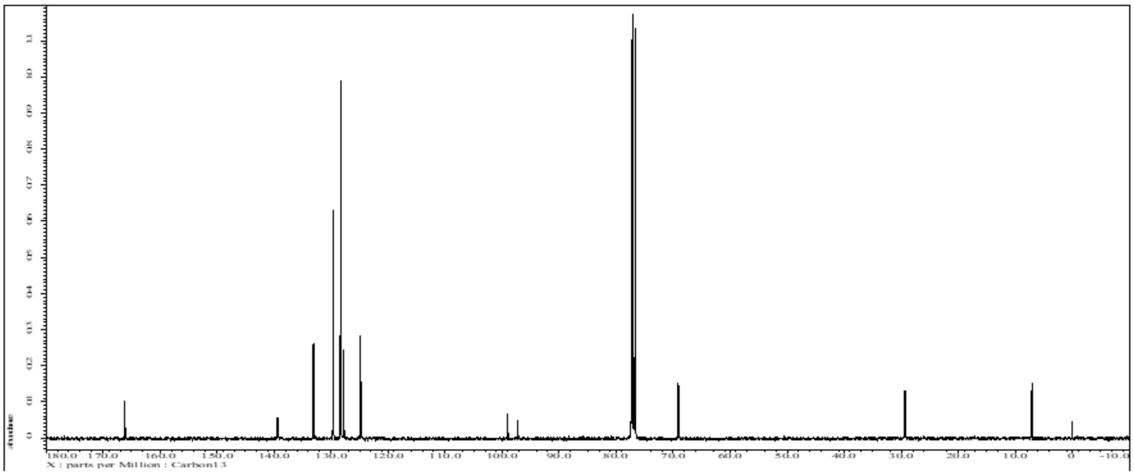
^{19}F NMR spectrum (**9l**)



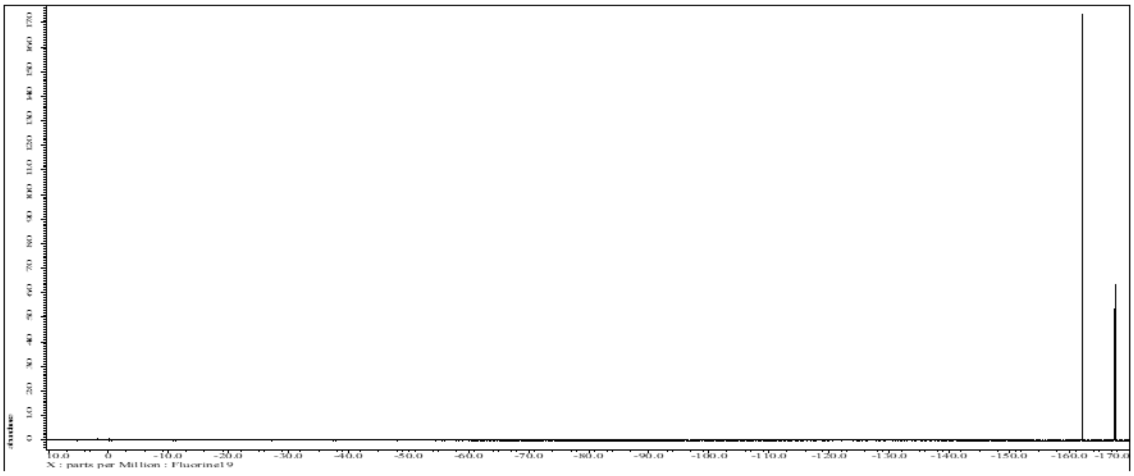
^{1}H NMR spectrum (**9l'**)



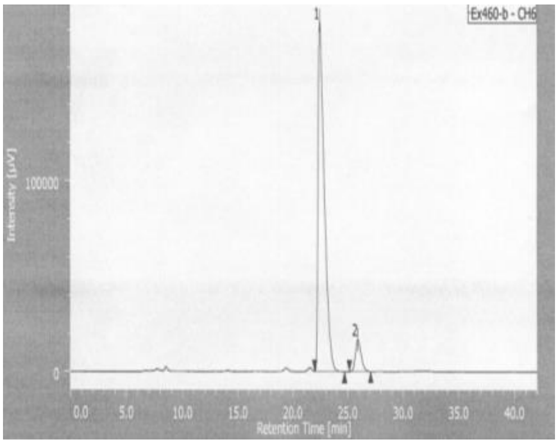
^{13}C NMR spectrum (**9l’**)

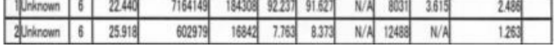


^{19}F NMR spectrum (**9l’**)



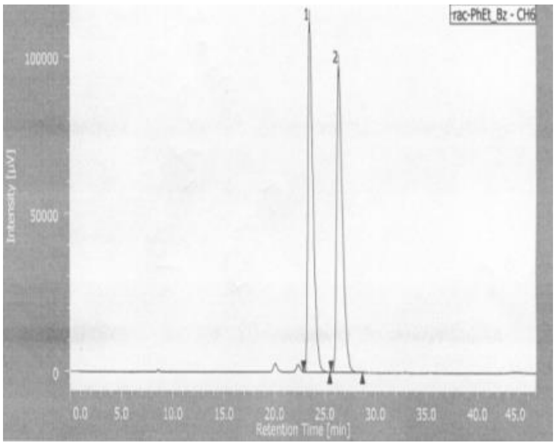
HPLC *optically active* (**9l’**)

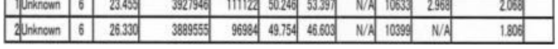




#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	6	22.440	7164149	184308	92.237	91.627	N/A	8031	3.615	2.486	
2	Unknown	6	25.918	602979	16842	7.763	8.373	N/A	12488	N/A	1.263	

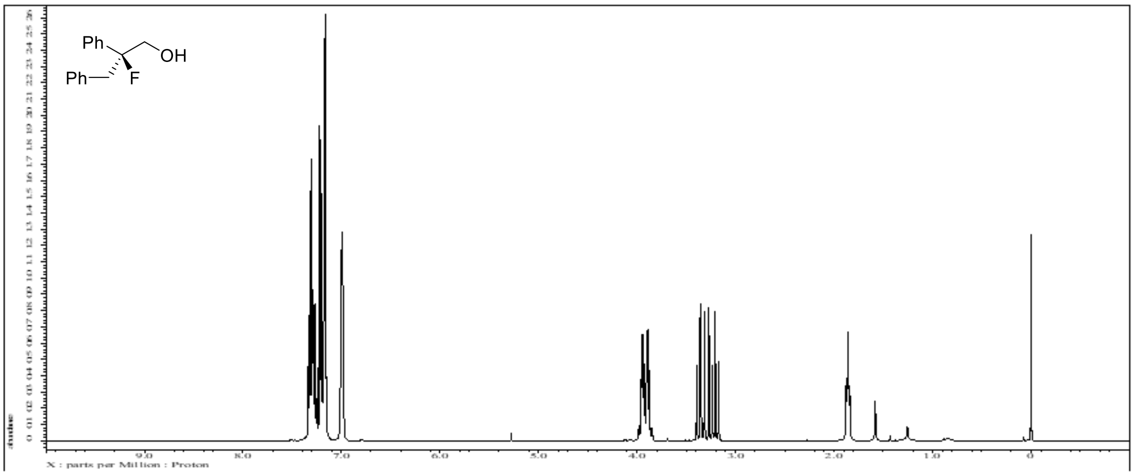
HPLC *racemic* (**9l’**)



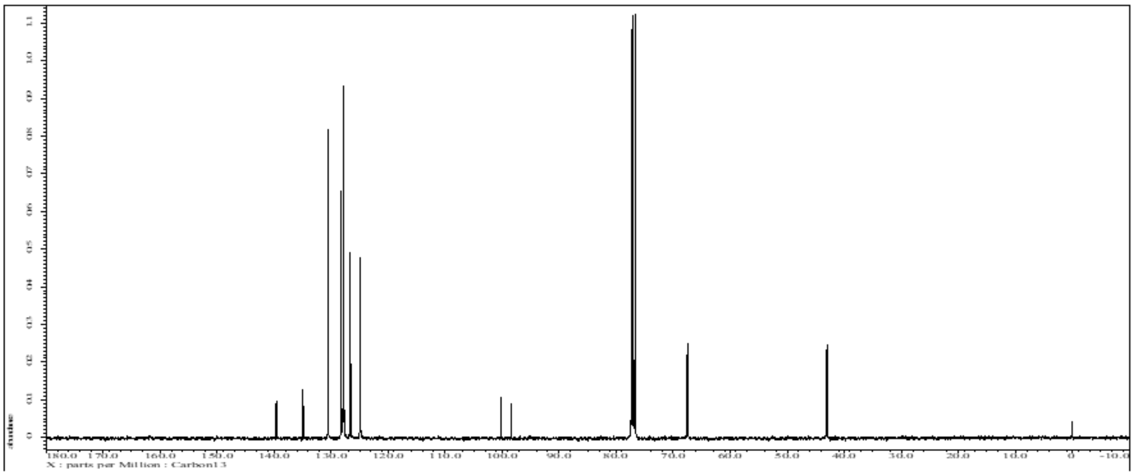


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	6	23.455	3927946	111122	50.246	53.397	N/A	10633	2.968	2.068	
2	Unknown	6	26.330	3889555	96984	49.754	46.603	N/A	10399	N/A	1.806	

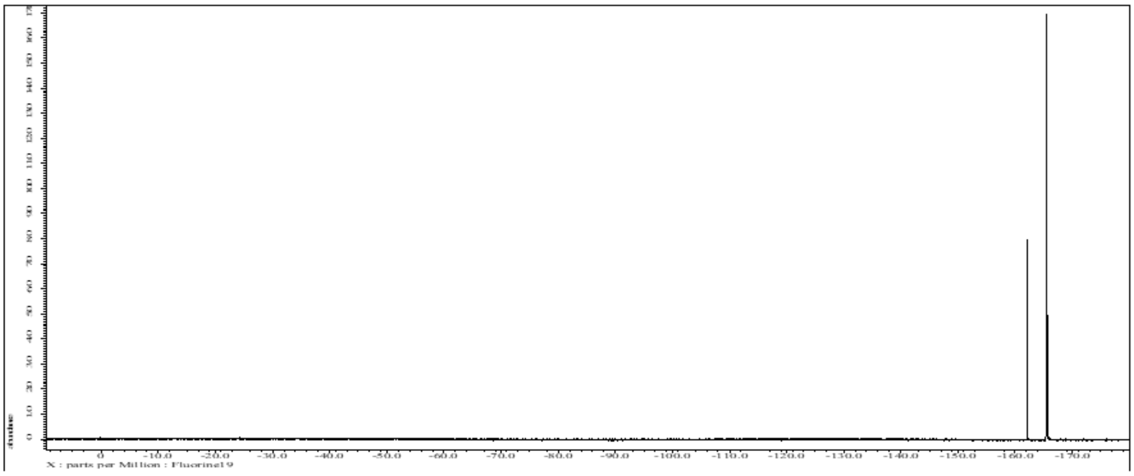
^{1}H NMR spectrum (**9m**)



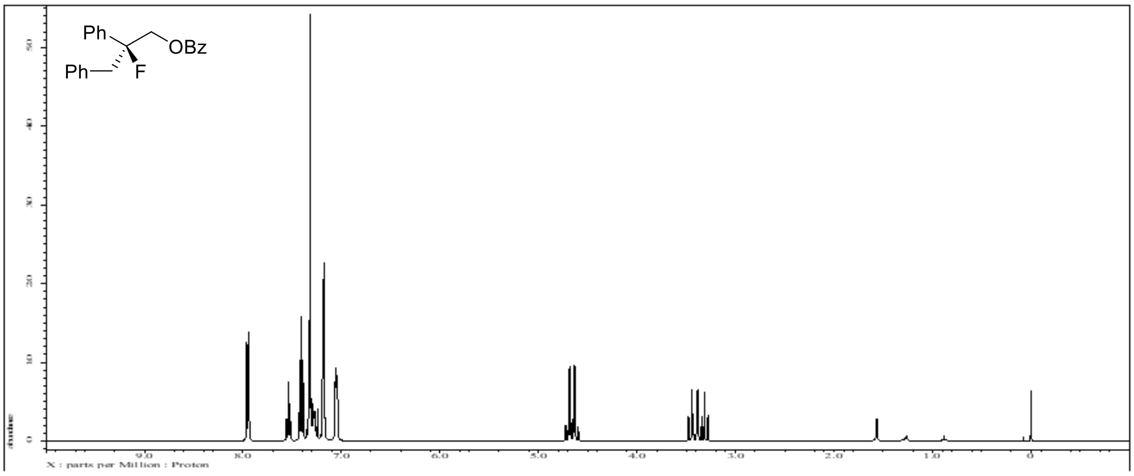
^{13}C NMR spectrum (**9m**)



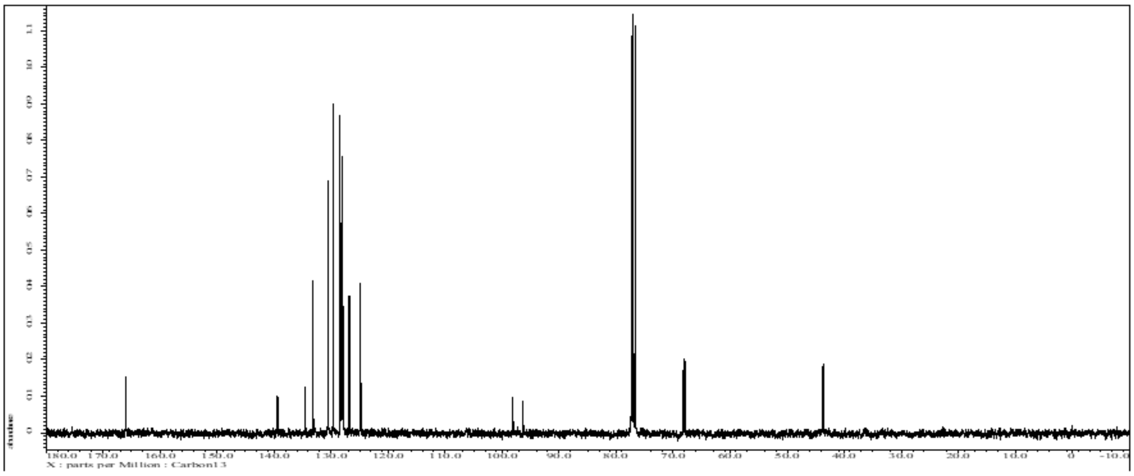
^{19}F NMR spectrum (**9m**)



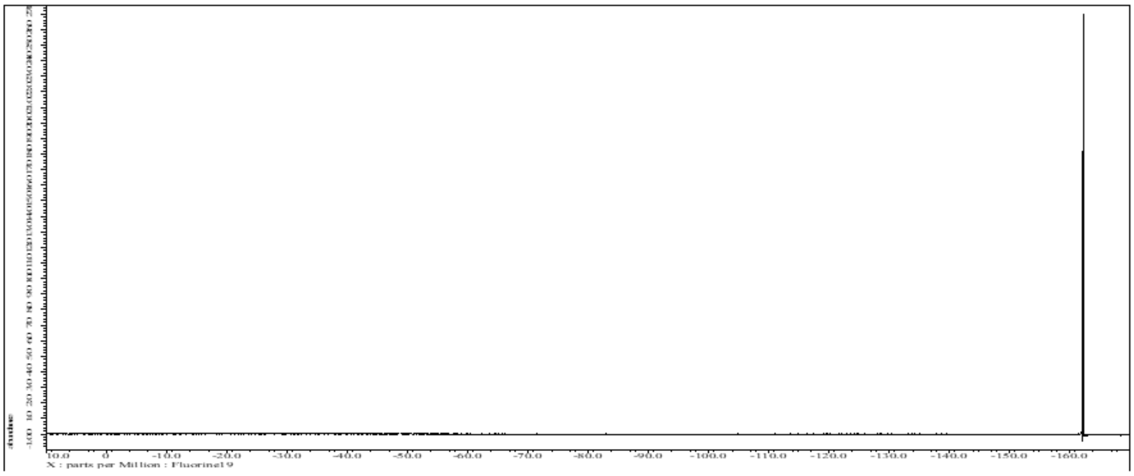
^{1}H NMR spectrum (**9m’**)



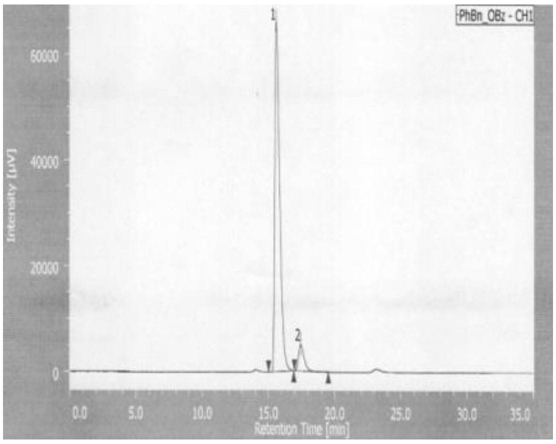
^{13}C NMR spectrum (**9m’**)



^{19}F NMR spectrum (**9m’**)

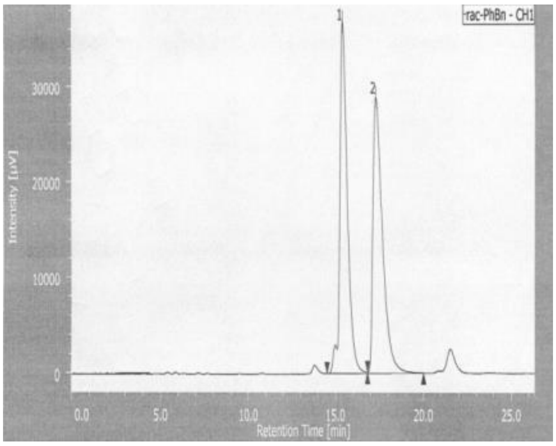


HPLC *optically active* (**9m’**)



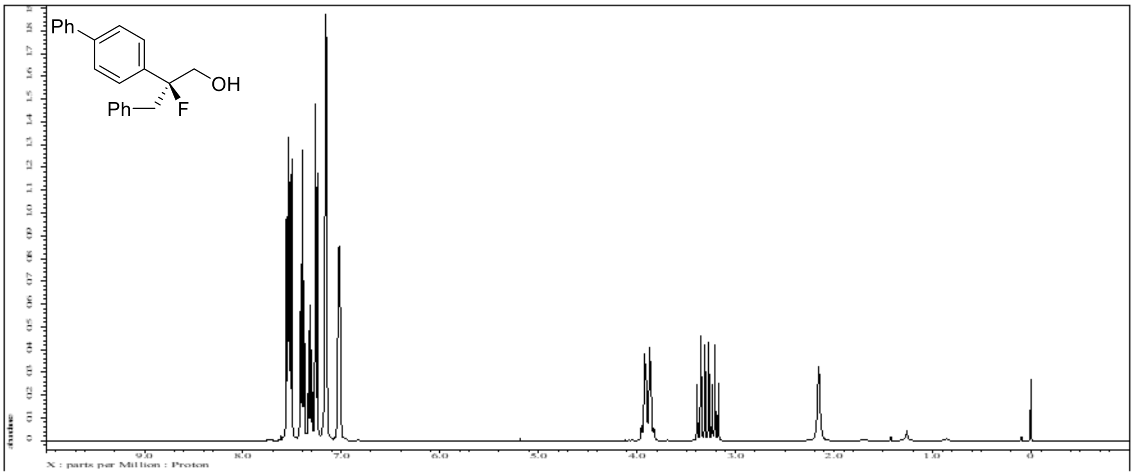
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	15.592	1706169	66289	92.007	92.947	N/A	8819	2.594	1.958	
2	Unknown	1	17.433	148211	5030	7.993	7.053	N/A	8432	N/A	1.473	

HPLC *racemic* (**9m’**)

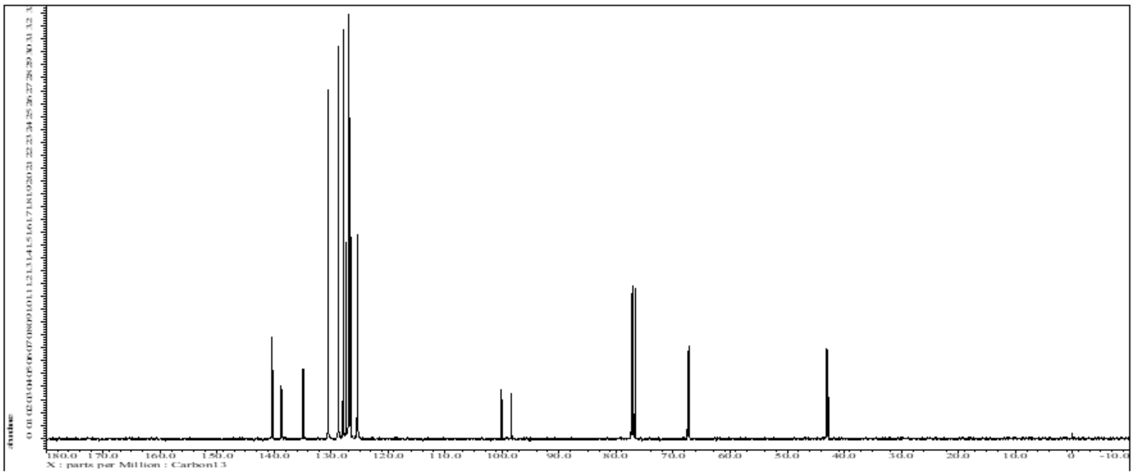


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	15.392	1104539	36778	50.382	56.052	N/A	7174	2.286	1.221	
2	Unknown	1	17.300	1087773	28836	49.618	43.948	N/A	5339	N/A	2.161	

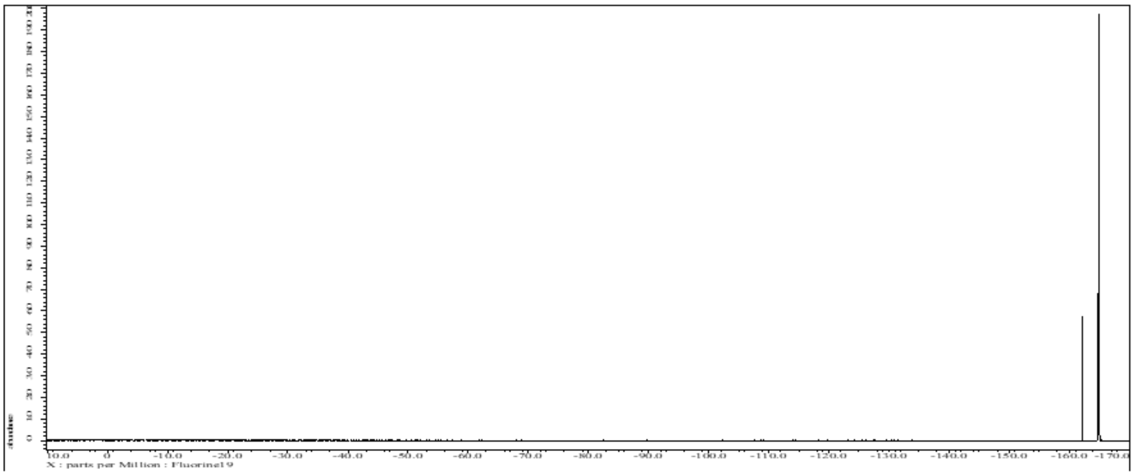
^{1}H NMR spectrum (**9n**)



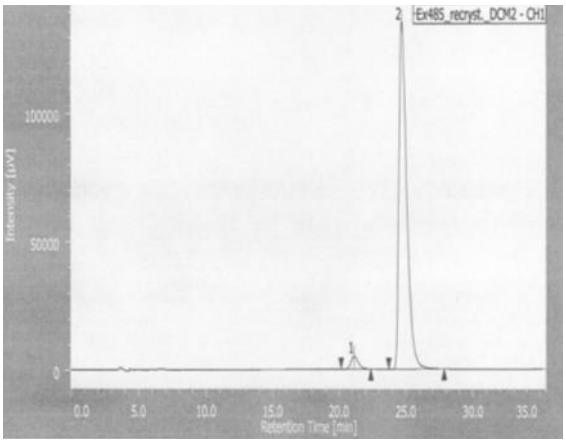
^{13}C NMR spectrum (**9n**)



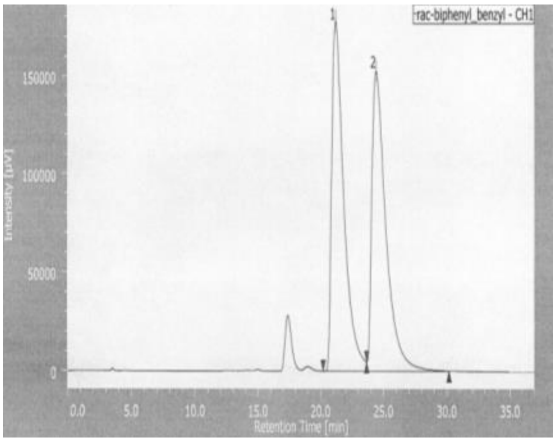
^{19}F NMR spectrum (**9n**)



HPLC *optically active* (**9n**)



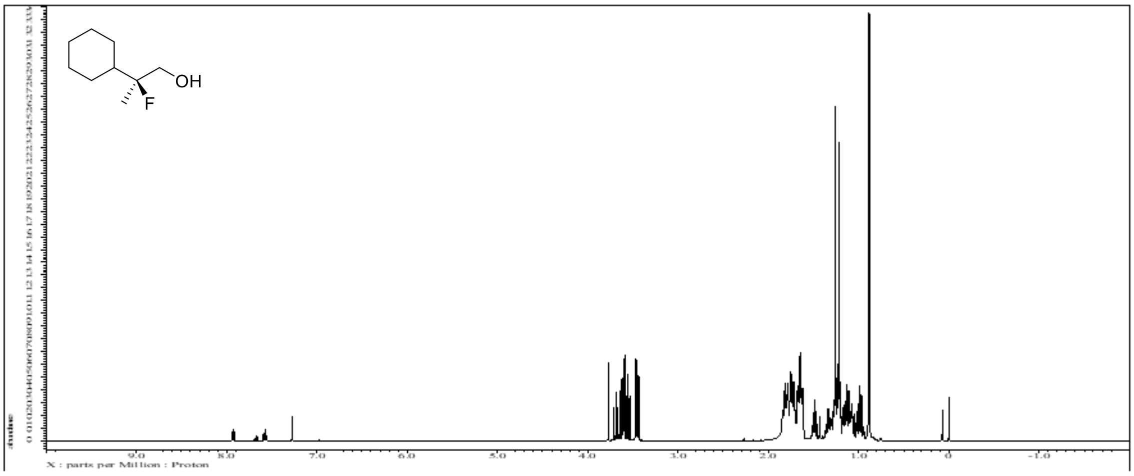
HPLC *racemic* (**9n**)



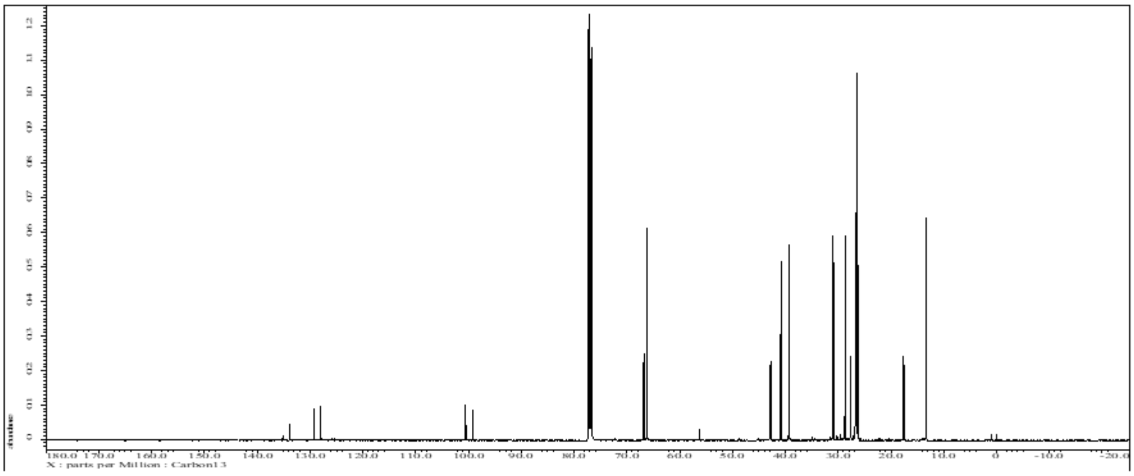
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	21.142	189586	4956	3.358	3.531	N/A	7276	3.527	1.330	
2	Unknown	1	24.692	5456613	135403	96.642	96.469	N/A	9250	N/A	1.725	

#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	21.192	11963810	177645	50.698	53.809	N/A	2560	1.822	2.228	
2	Unknown	1	24.417	11634478	152493	49.302	46.191	N/A	2717	N/A	2.247	

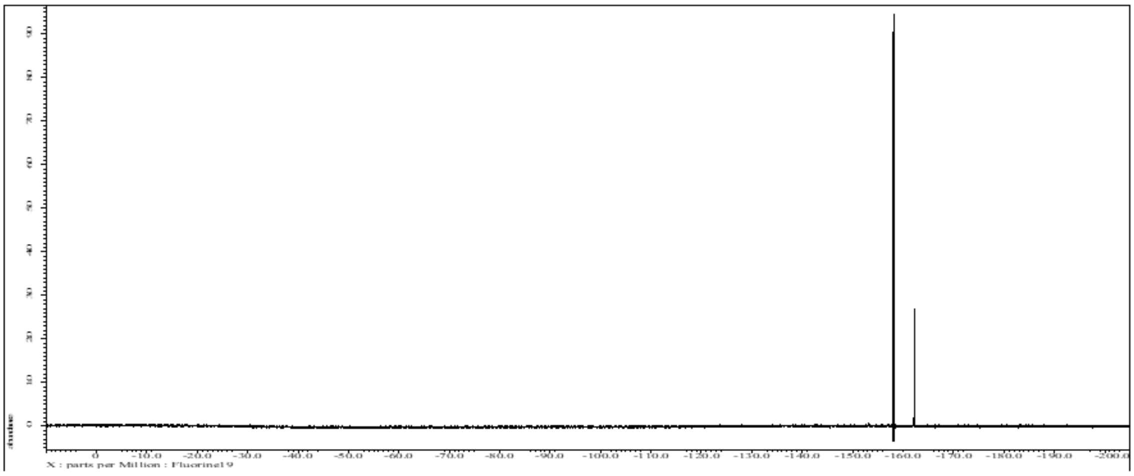
^{1}H NMR spectrum (**9o**)



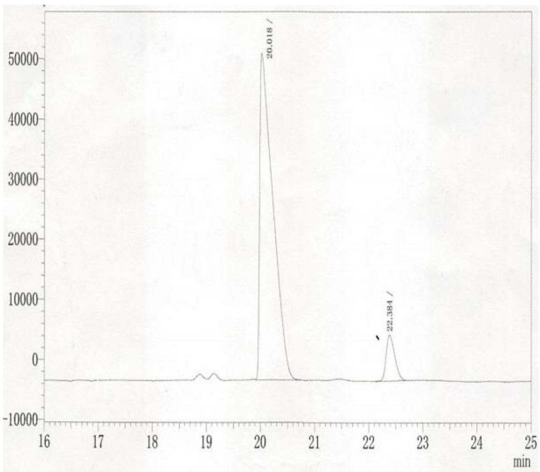
^{13}C NMR spectrum (**9o**)



^{19}F NMR spectrum (**9o**)

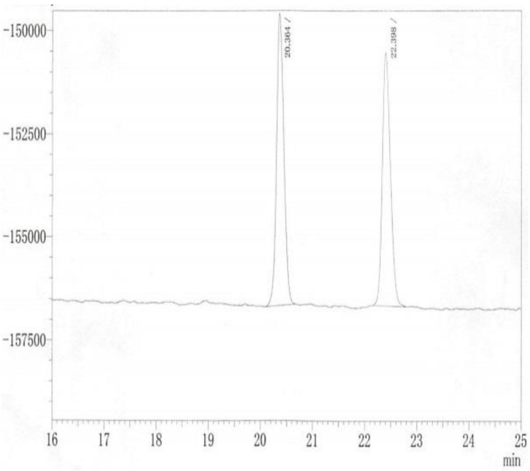


GC *optically active* (**9o**)



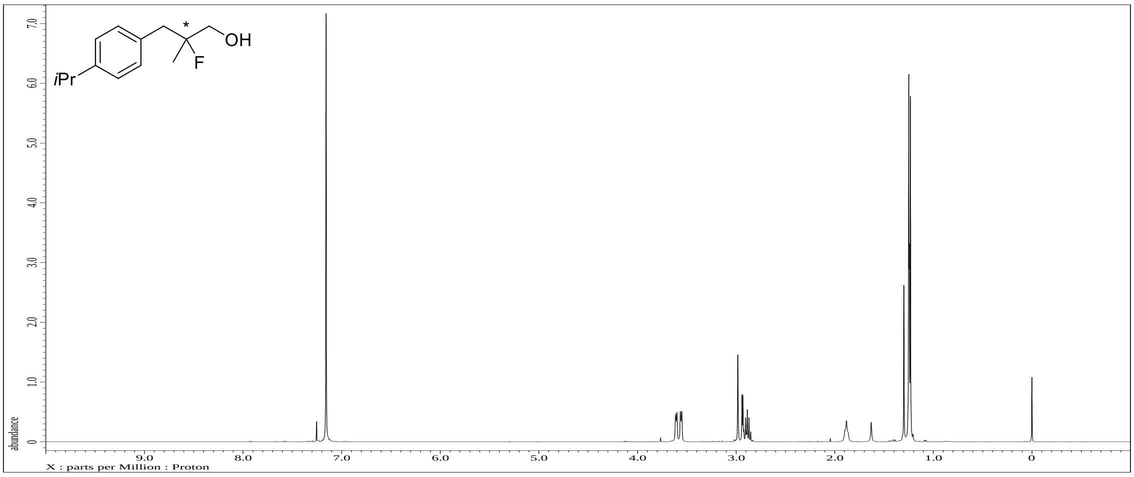
ﾋﾟｰｸ番号	保持時間	面積	高さ	濃度
1	20.018	913096	54304	91.525
2	22.384	84547	7682	8.475

GC *racemic* (**9o**)

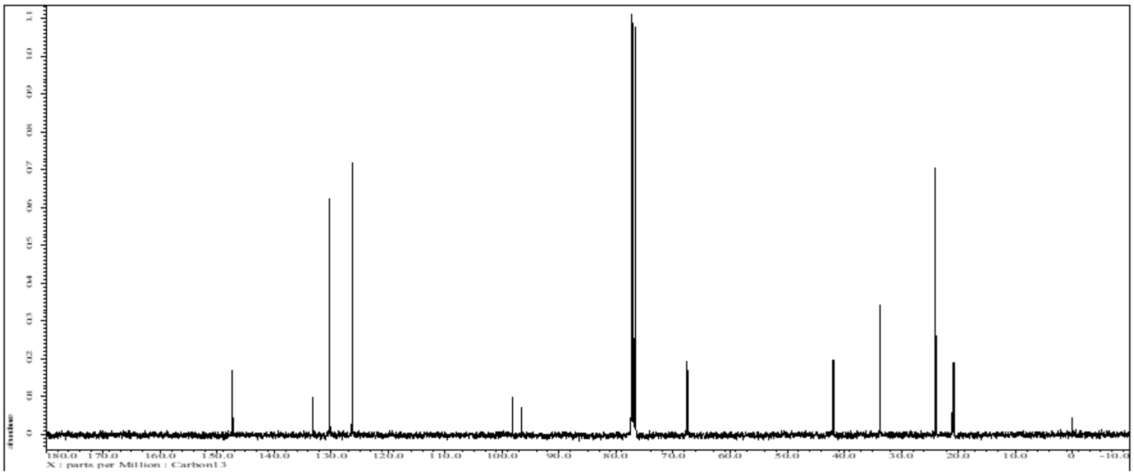


ﾋﾟｰｸ番号	保持時間	面積	高さ	濃度
1	20.364	68701	7063	50.844
2	22.398	66419	6135	49.156

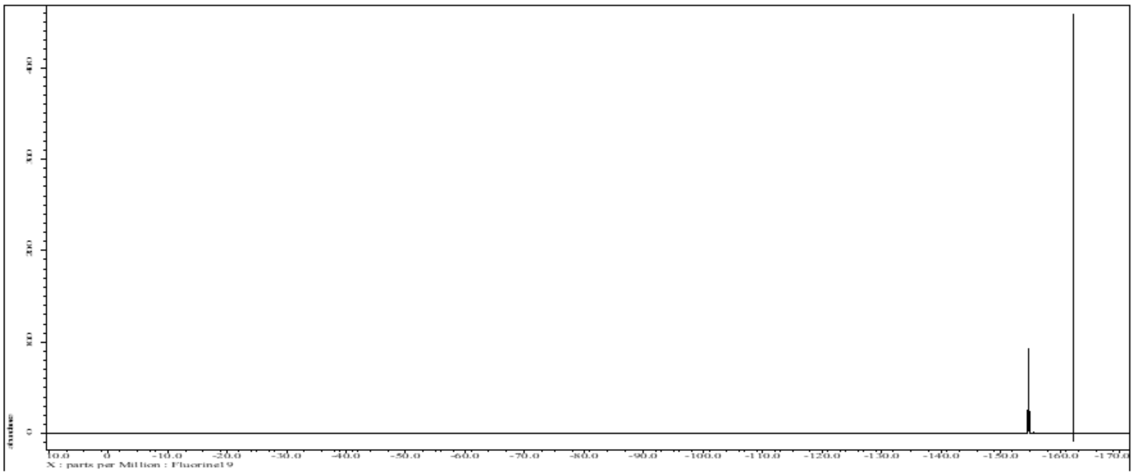
^{1}H NMR spectrum (**9p**)



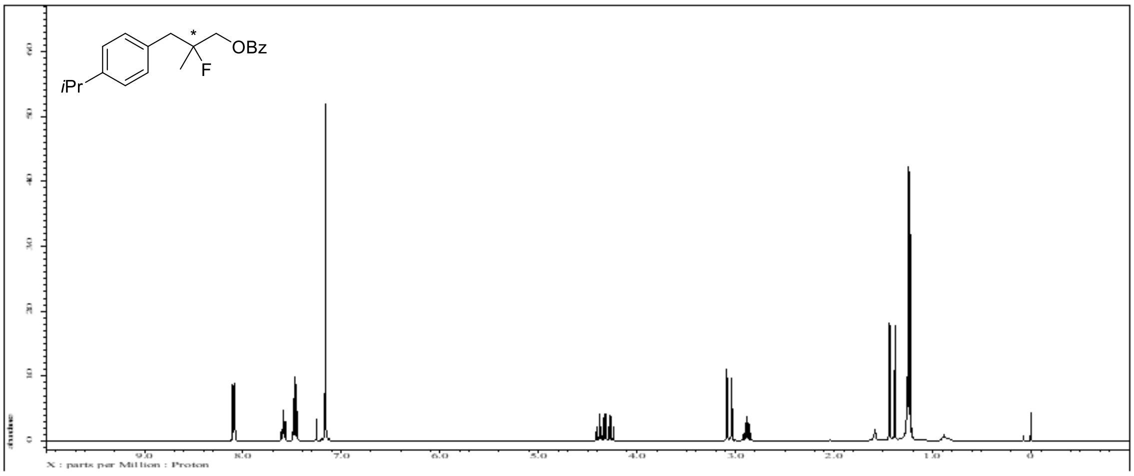
^{13}C NMR spectrum (**9p**)



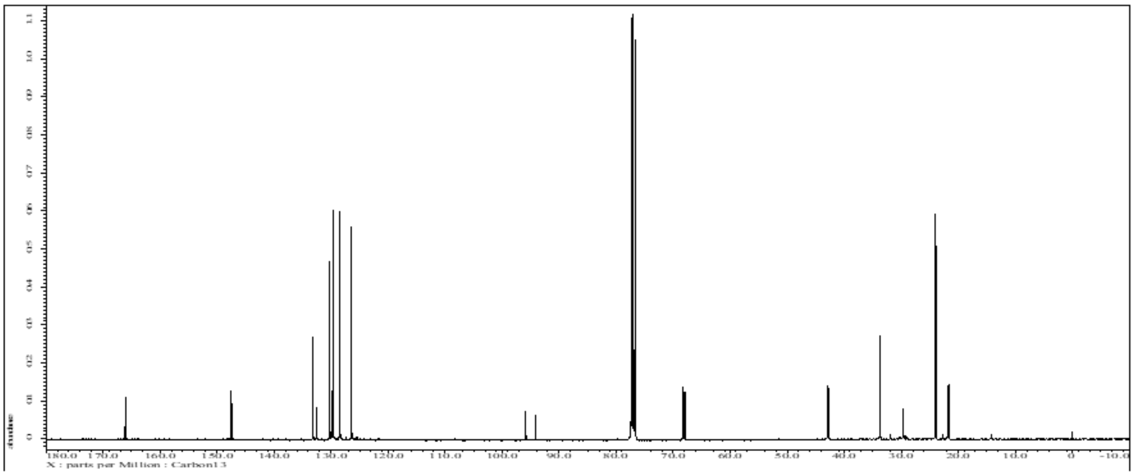
^{19}F NMR spectrum (**9p**)



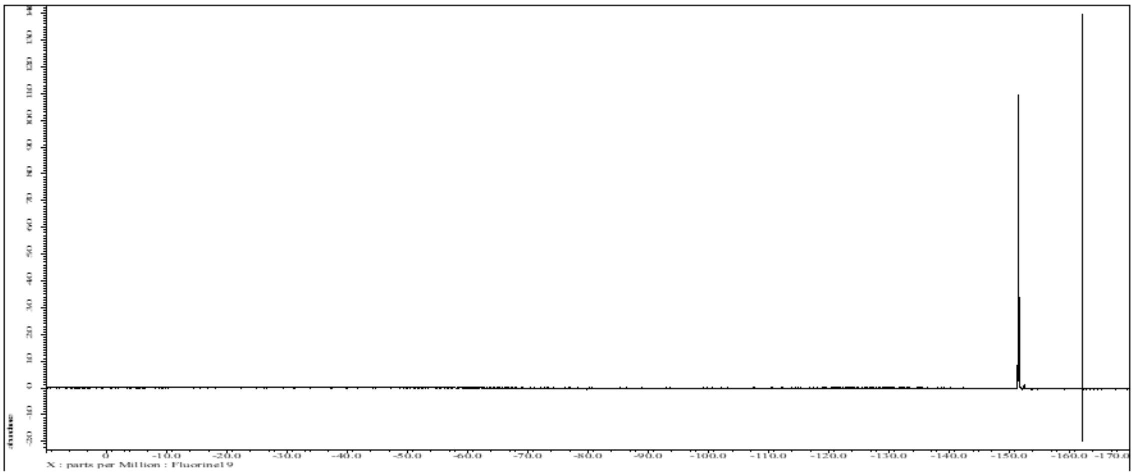
^{1}H NMR spectrum (**9p’**)



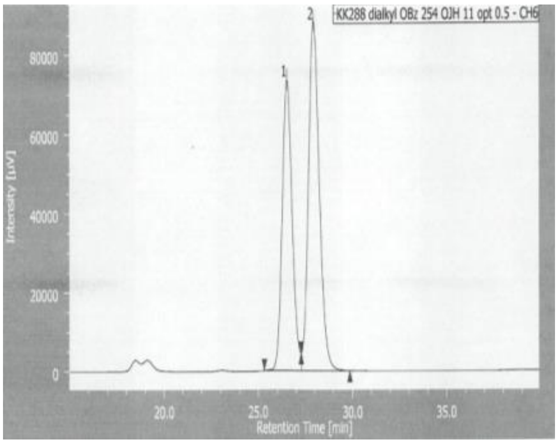
^{13}C NMR spectrum (**9p’**)



^{19}F NMR spectrum (**9p’**)

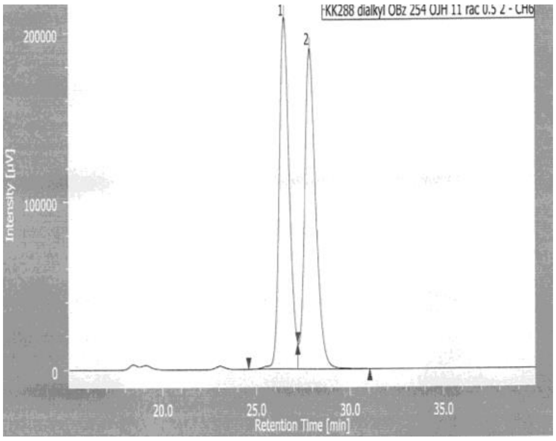


HPLC *optically active* (**9p’**)



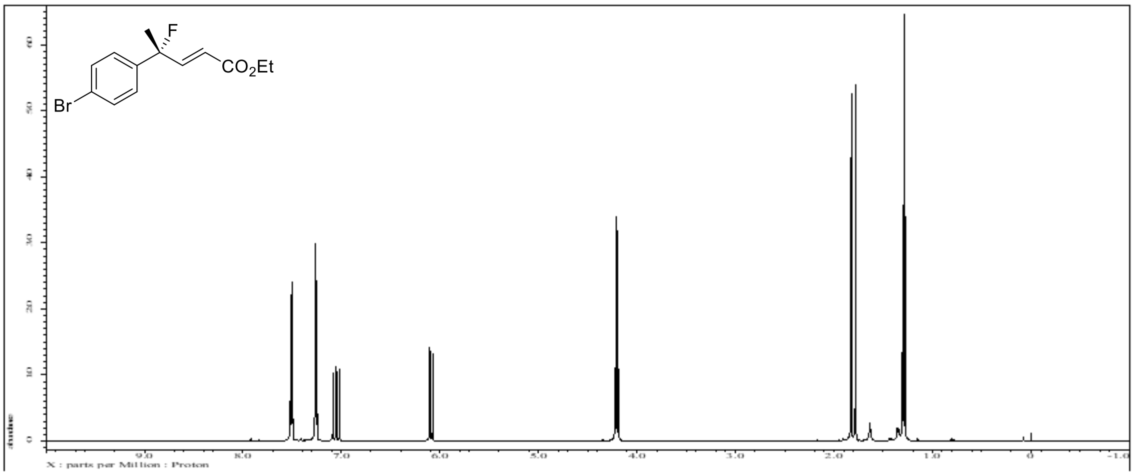
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	6	26.515	2690899	73434	43.149	45.386	N/A	12340	1.435	N/A	
2	Unknown	6	27.937	3545454	88366	56.851	54.614	N/A	11722	N/A	N/A	

HPLC *racemic* (**9p’**)

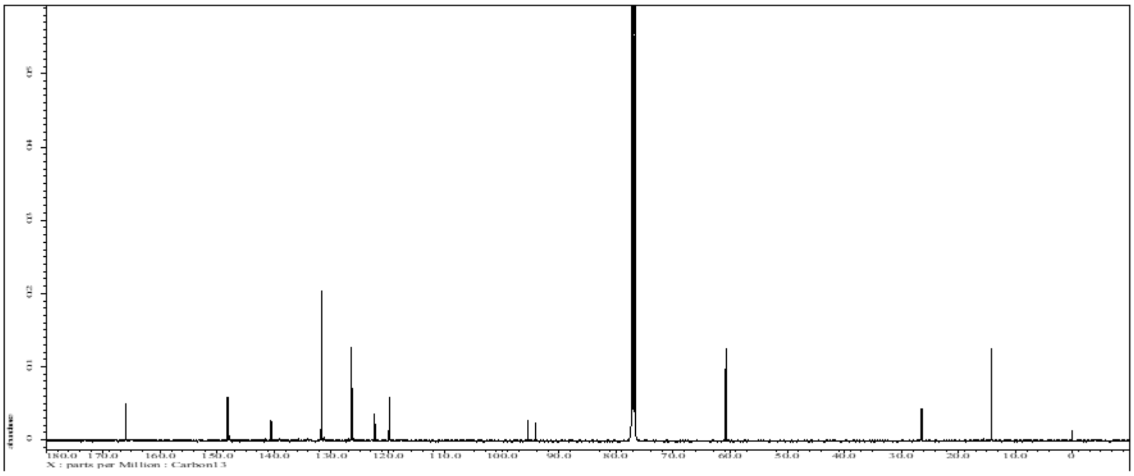


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	6	26.487	7724341	208617	49.548	52.320	N/A	12089	1.367	N/A	
2	Unknown	6	27.862	7865422	190115	50.452	47.680	N/A	11202	N/A	N/A	

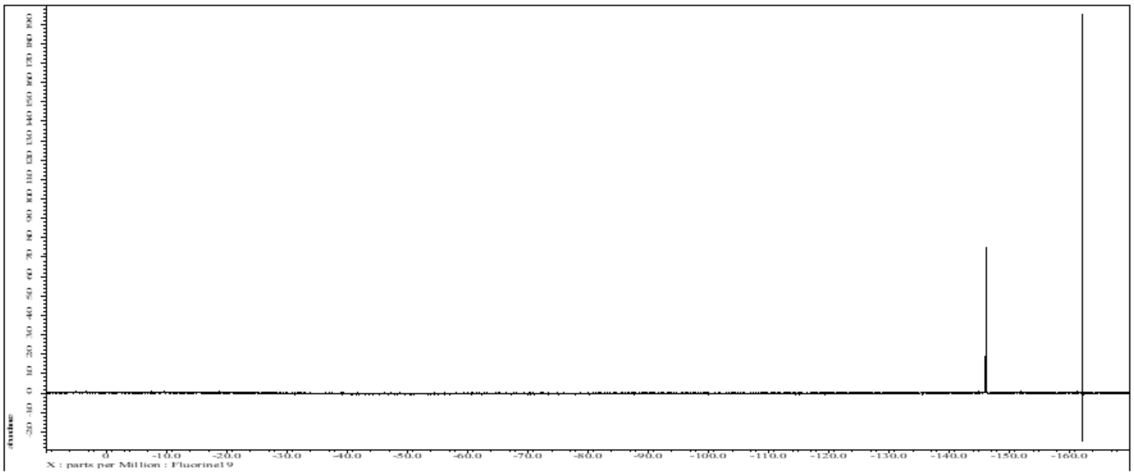
^{1}H NMR spectrum (**10b**)



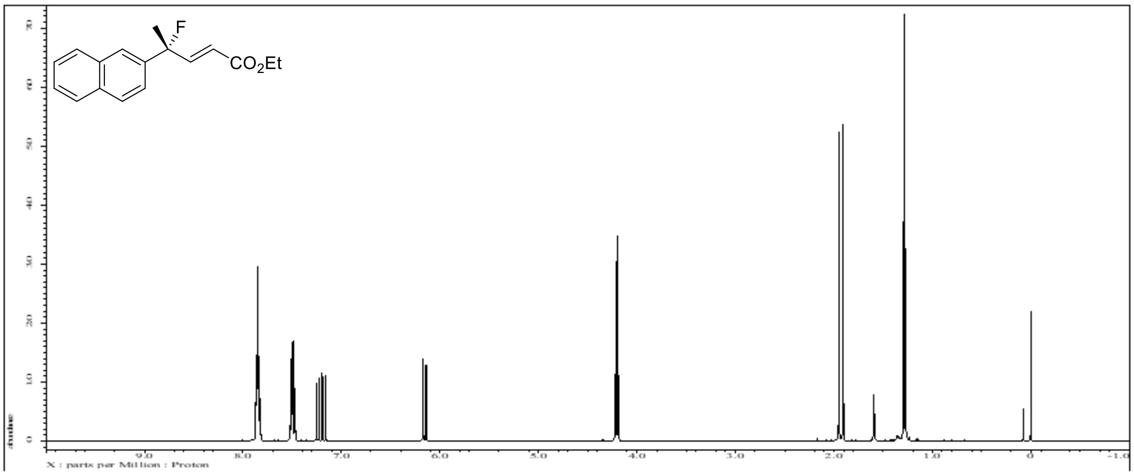
^{13}C NMR spectrum (**10b**)



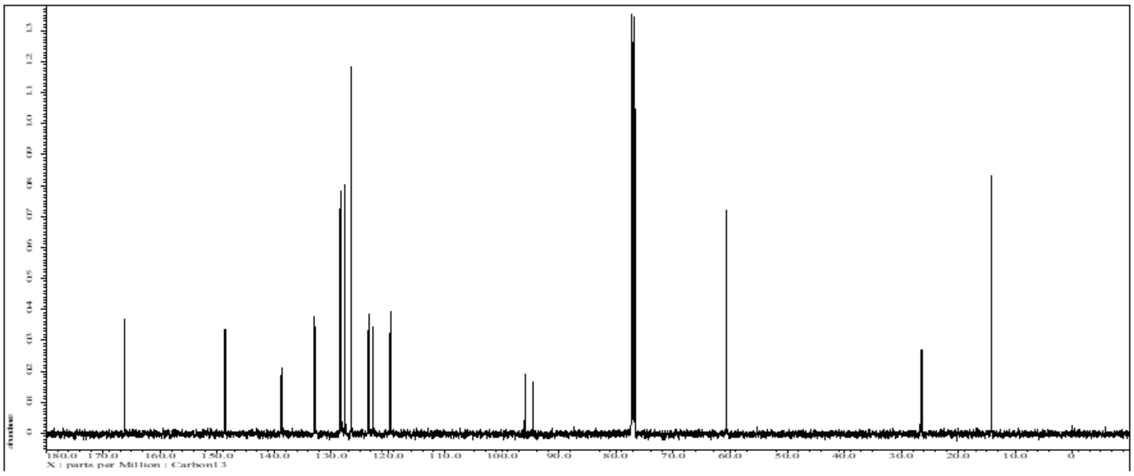
^{19}F NMR spectrum (**10b**)



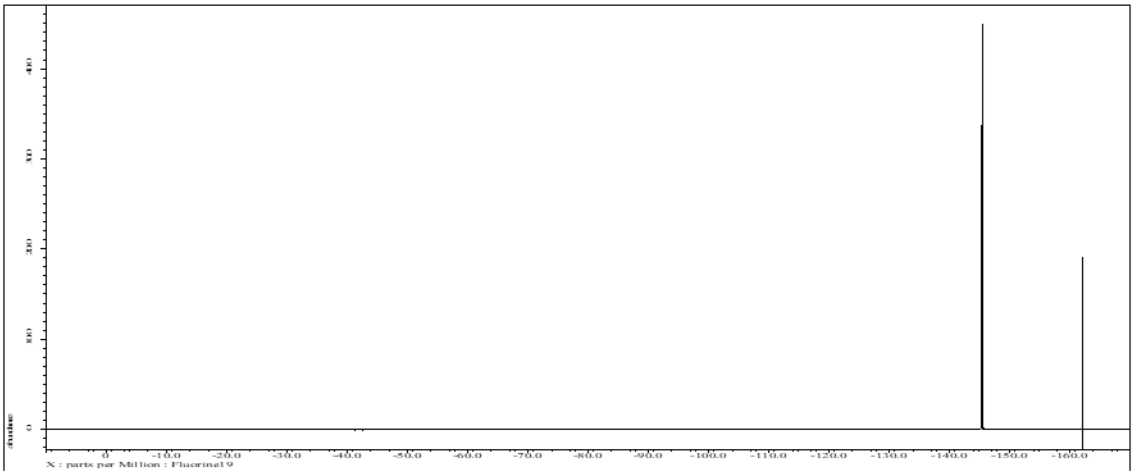
^{1}H NMR spectrum (**10h**)



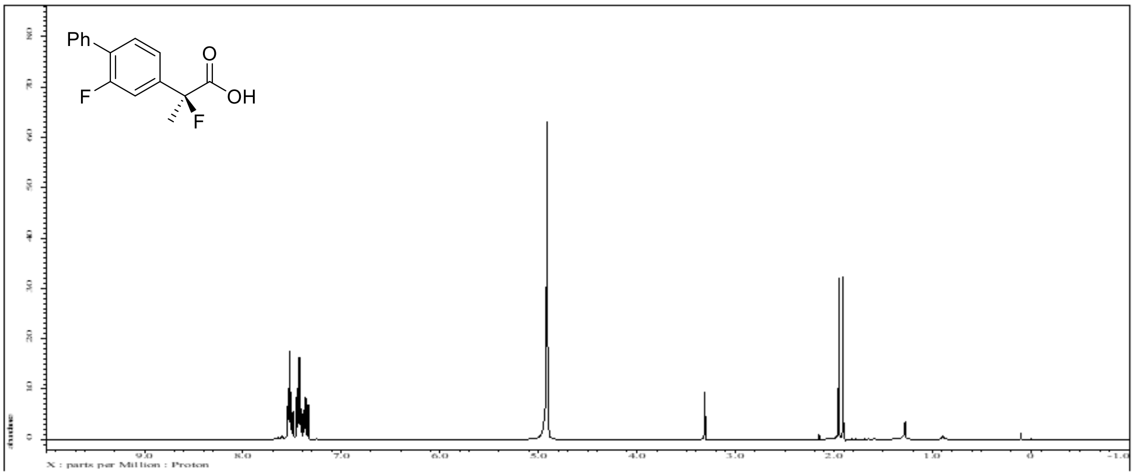
^{13}C NMR spectrum (**10h**)



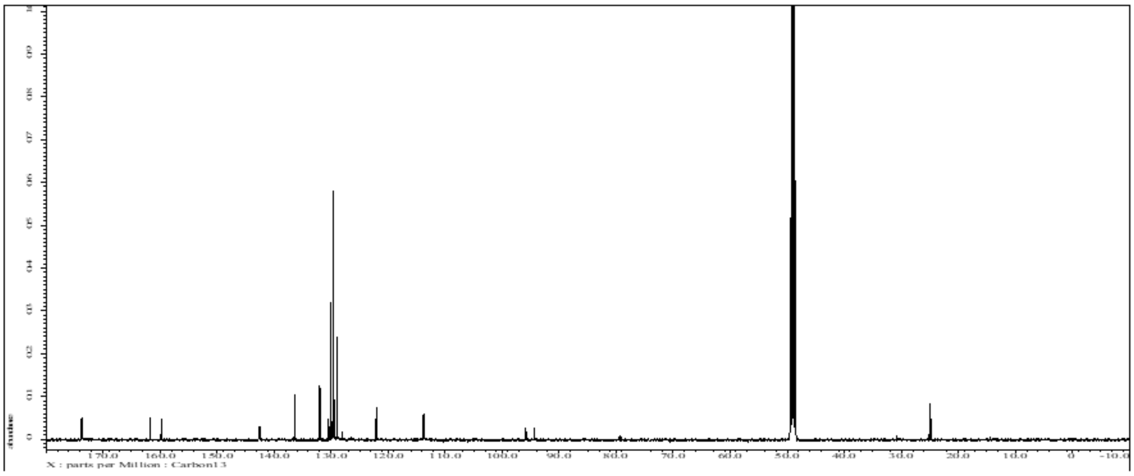
^{19}F NMR spectrum (**10h**)



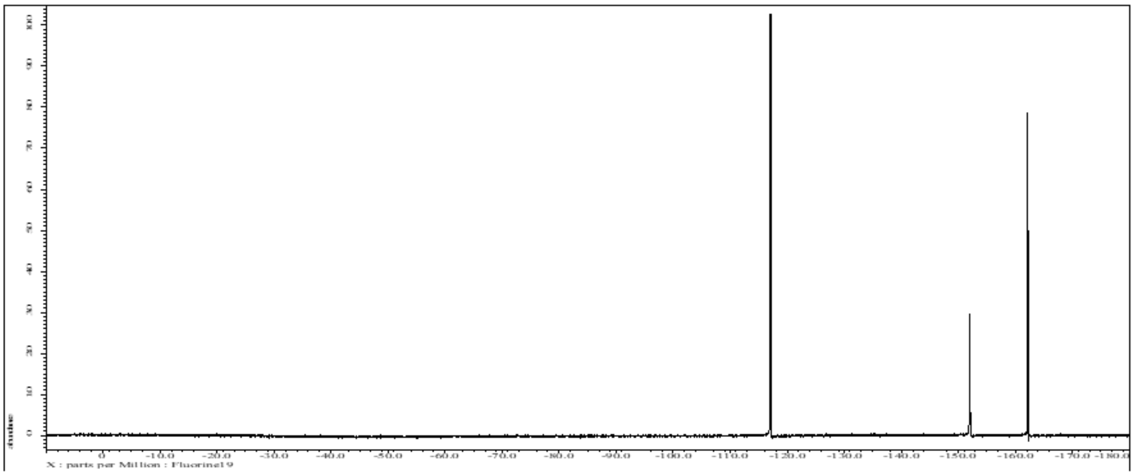
^{1}H NMR spectrum (**11j**)



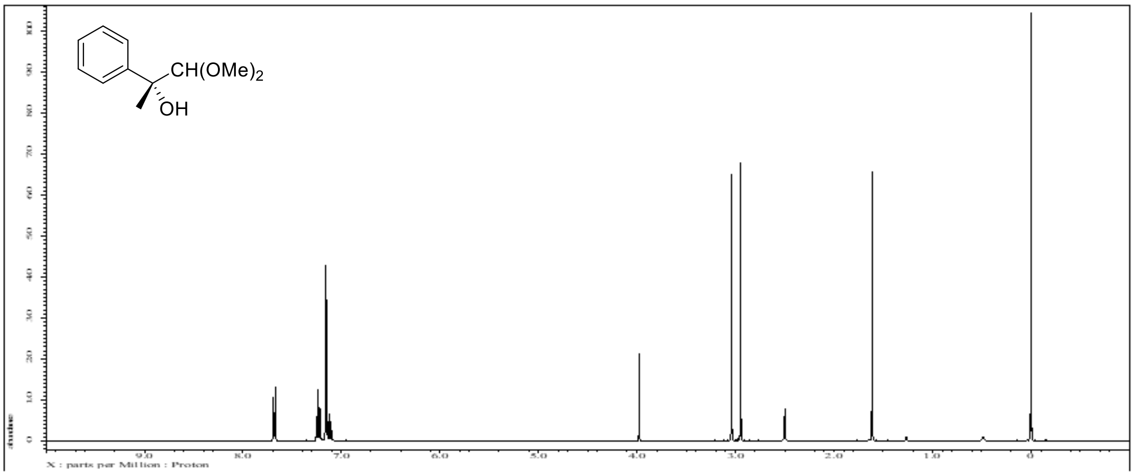
^{13}C NMR spectrum (**11j**)



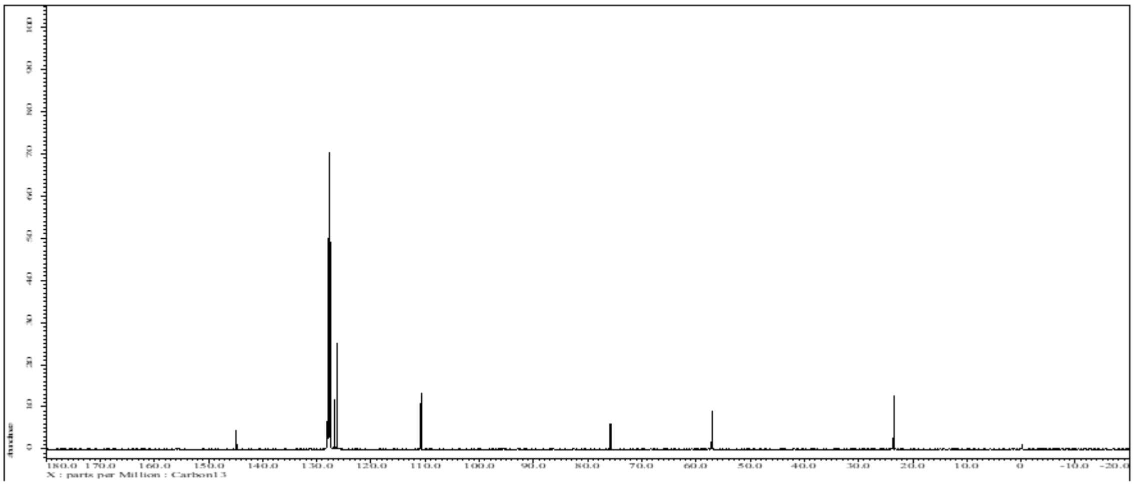
^{19}F NMR spectrum (**11j**)



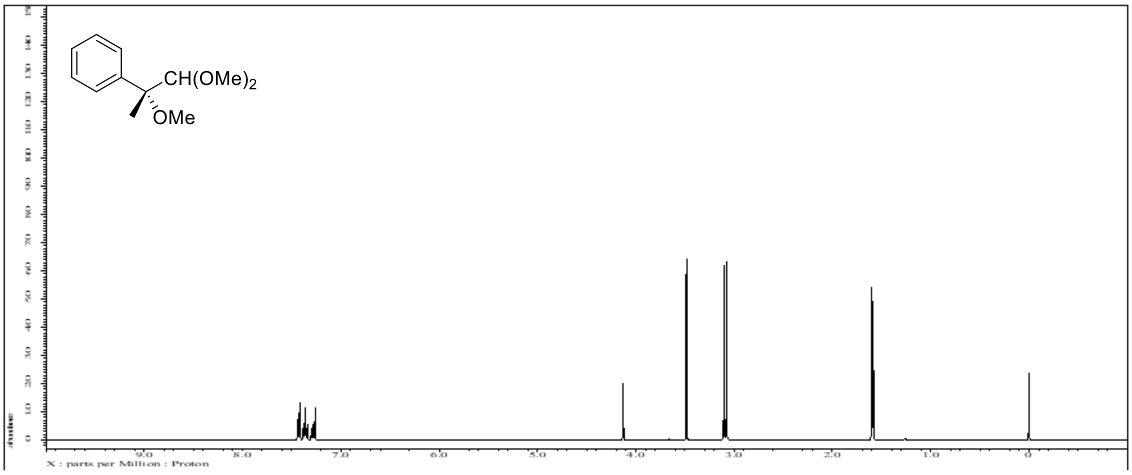
^{1}H NMR spectrum [(*R*)-**12a**]



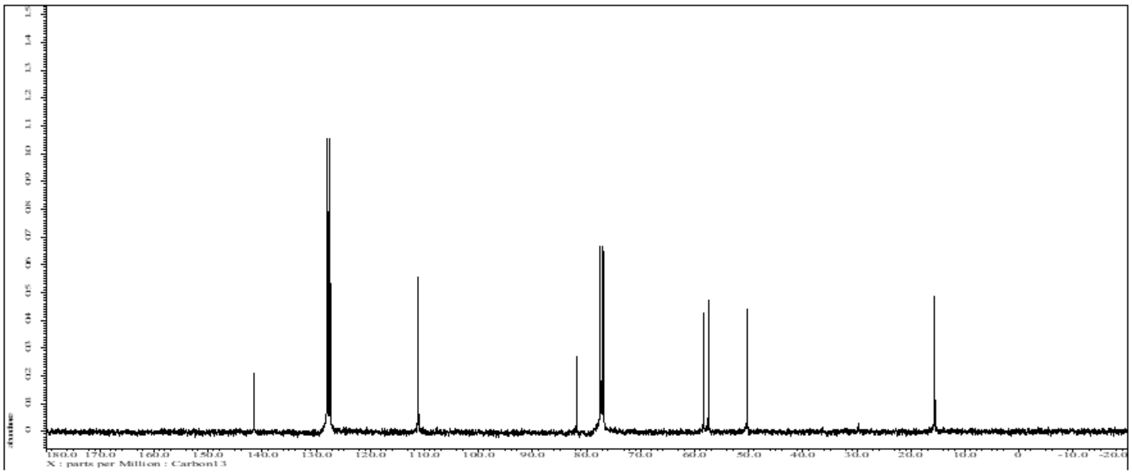
^{13}C NMR spectrum [(*R*)-**12a**]



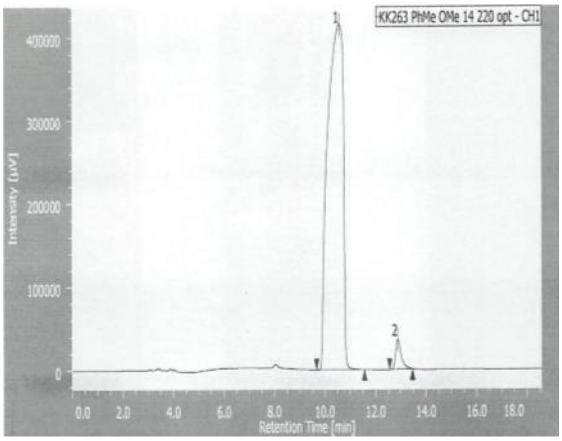
^{1}H NMR spectrum [(*R*)-**12a'**]



^{13}C NMR spectrum [(*R*)-**12a'**]

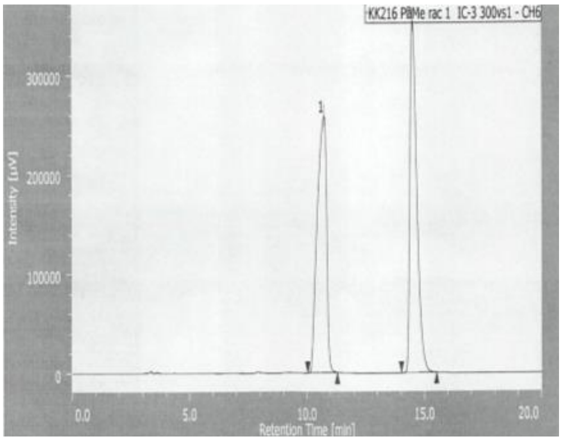


HPLC *optically active* [(*R*)-**12a'**]



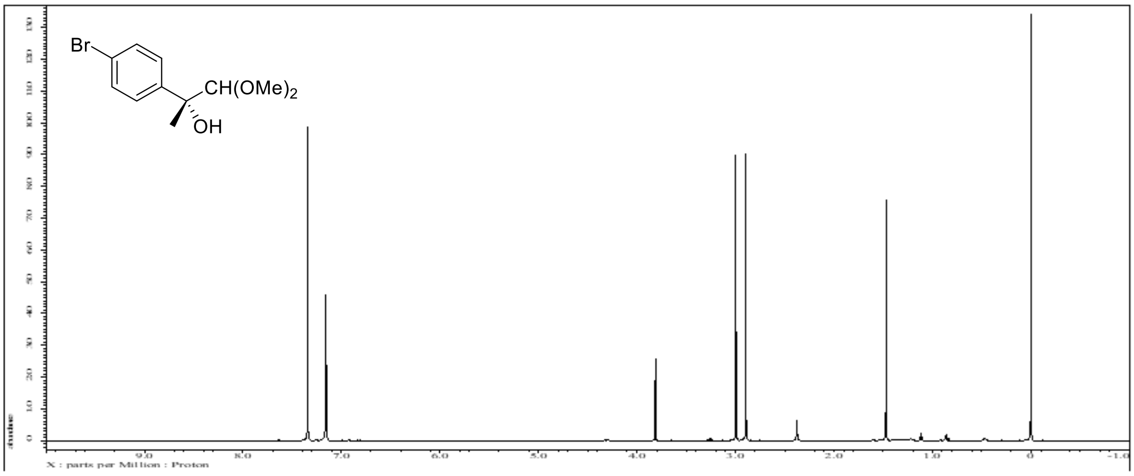
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	10.575	17602370	414230	96.971	92.058	N/A	1067	2.768	0.687	
2	Unknown	1	12.883	549750	35738	3.029	7.942	N/A	18672	N/A	1.659	

HPLC *racemic* (**12a'**)

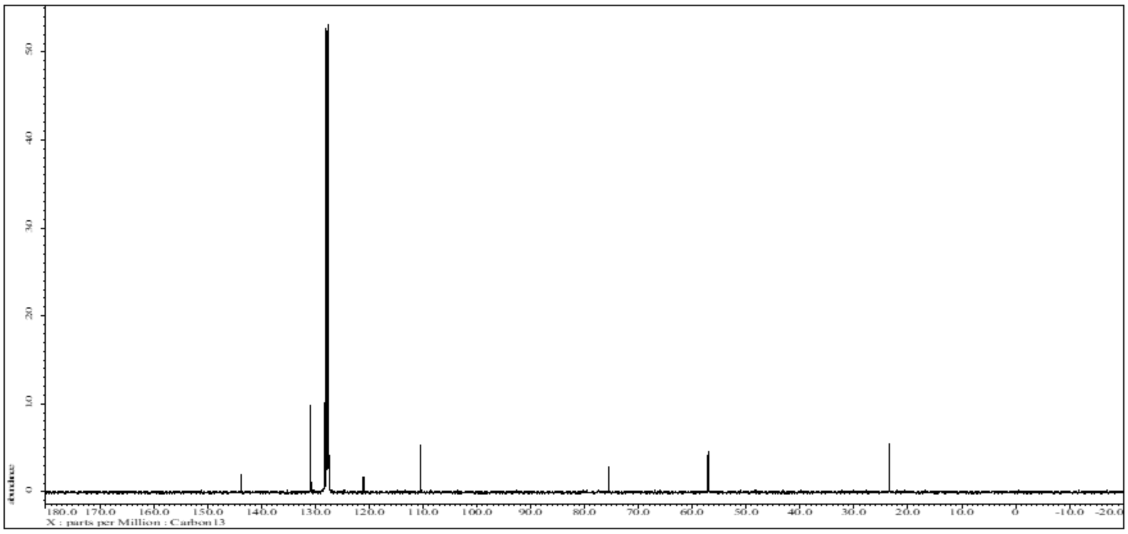


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	6	10.738	7071403	258609	49.363	42.172	N/A	3004	5.761	0.724	
2	Unknown	6	14.507	7253857	354614	50.637	57.828	N/A	12077	N/A	1.625	

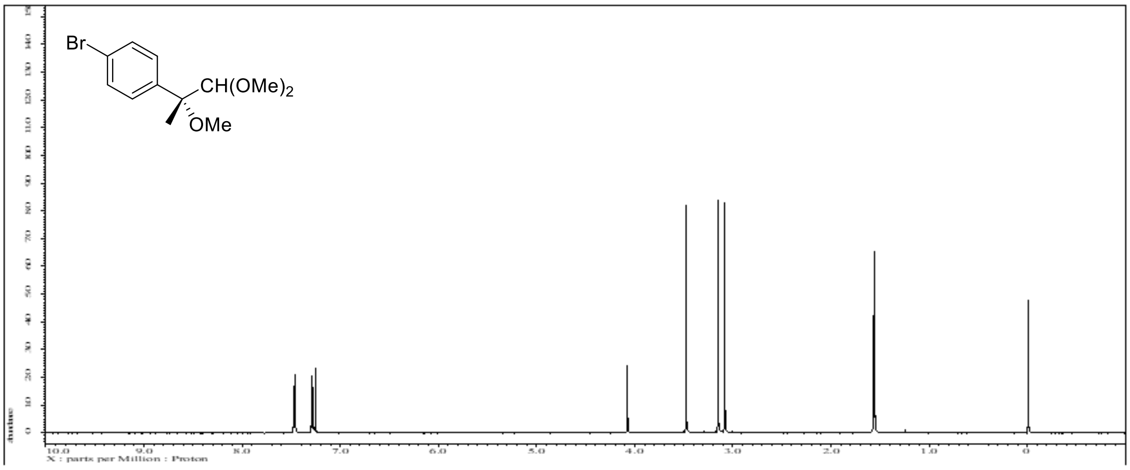
^{1}H NMR spectrum (**12b**)



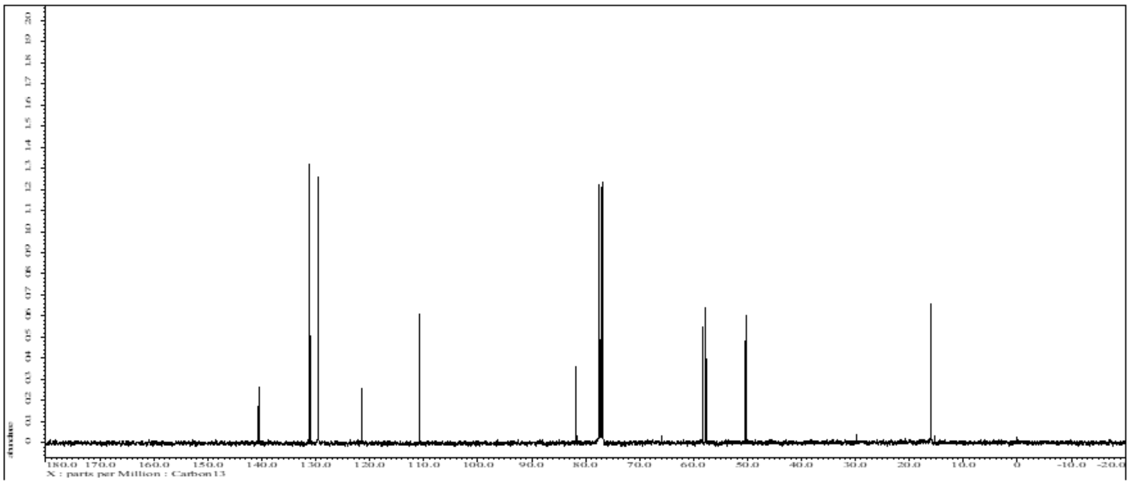
^{13}C NMR spectrum (**12b**)



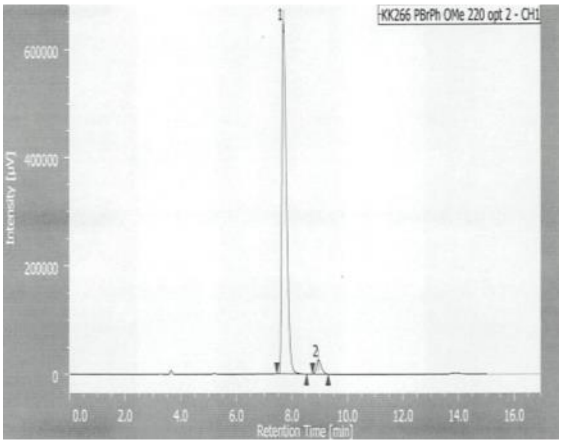
^{1}H NMR spectrum (**12b’**)



^{13}C NMR spectrum (**12b’**)

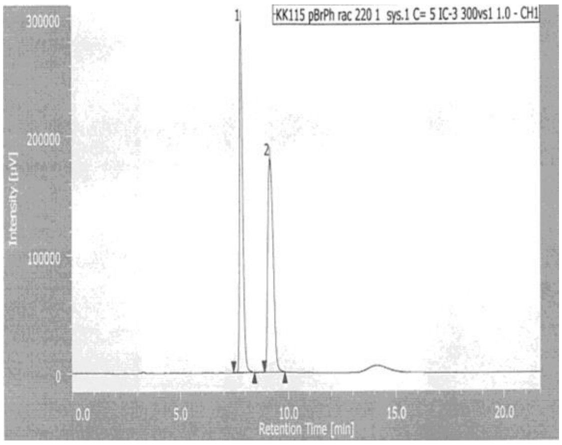


HPLC *optically active* (**12b’**)



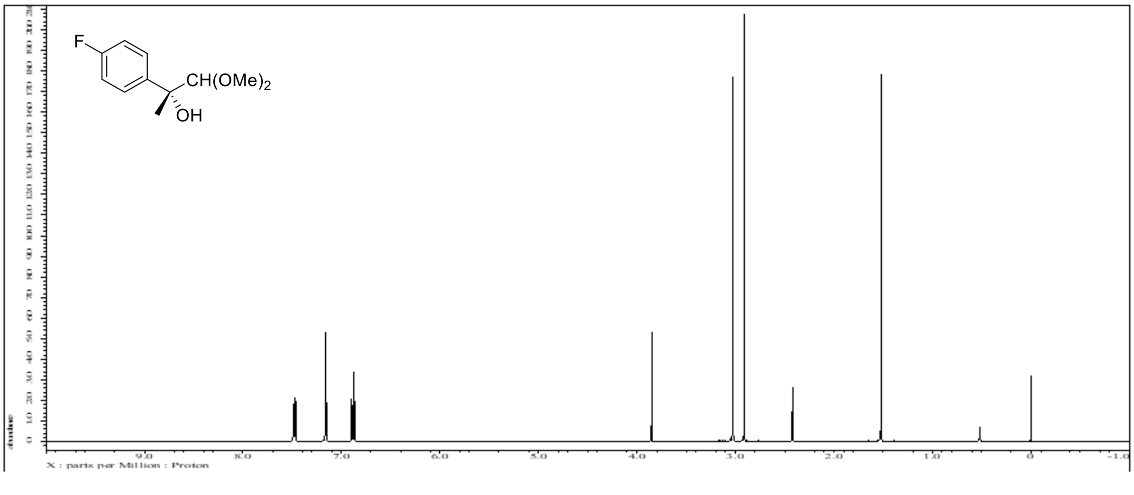
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	7.692	7339801	649186	95.921	96.127	N/A	10820	4.182	1.765	
2	Unknown	1	8.958	312154	26156	4.079	3.873	N/A	13219	N/A	1.319	

HPLC *racemic* (**12b’**)

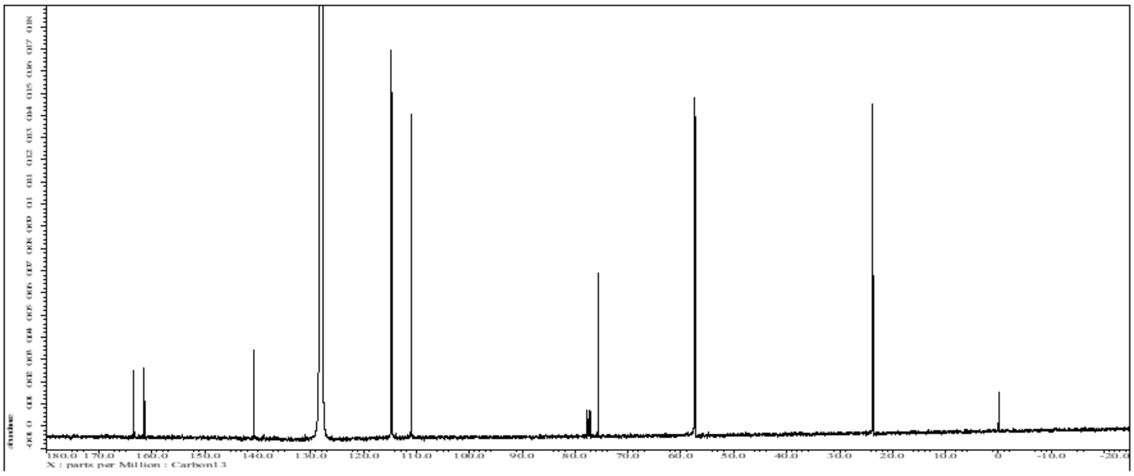


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	7.808	3006776	295724	49.078	62.222	N/A	14180	3.639	1.483	
2	Unknown	1	9.158	3119805	179551	50.922	37.778	N/A	5785	N/A	1.386	

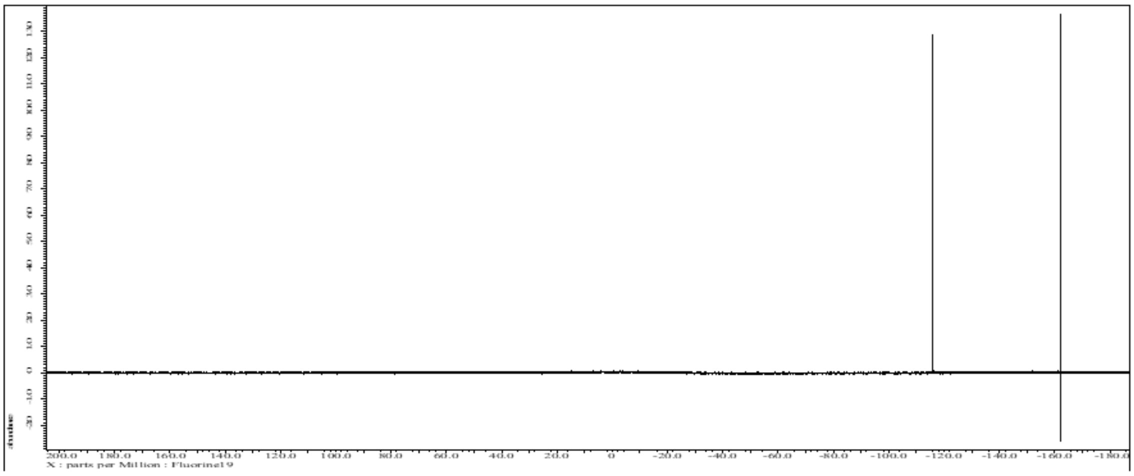
^{1}H NMR spectrum (**12c**)



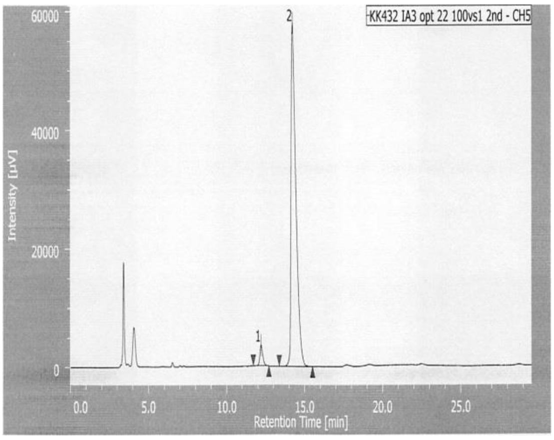
^{13}C NMR spectrum (**12c**)

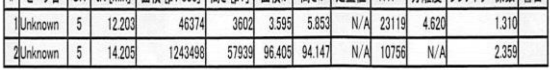


^{19}F NMR spectrum (**12c**)



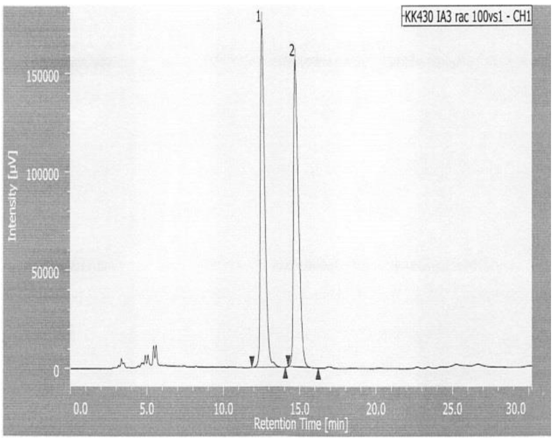
HPLC *optically active* (**12c**)

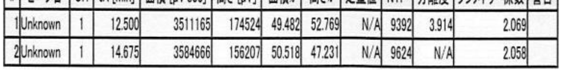




#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	5	12.203	46374	3602	3.595	5.853	N/A	23119	4.620	1.310	
2	Unknown	5	14.205	1243498	57939	96.405	94.147	N/A	10756	N/A	2.359	

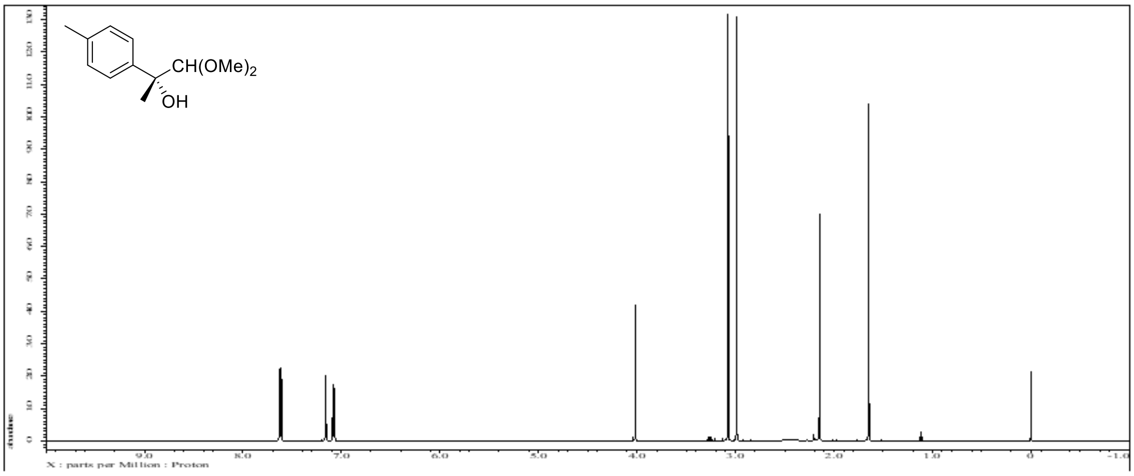
HPLC *racemic* (**12c**)



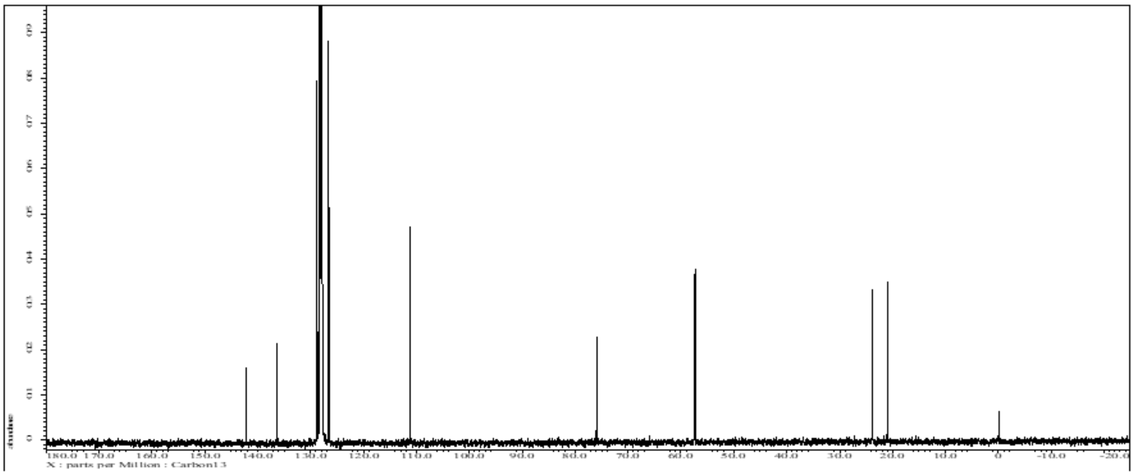


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	12.500	3511165	174524	49.482	52.769	N/A	9392	3.914	2.069	
2	Unknown	1	14.675	3584666	156207	50.518	47.231	N/A	9624	N/A	2.058	

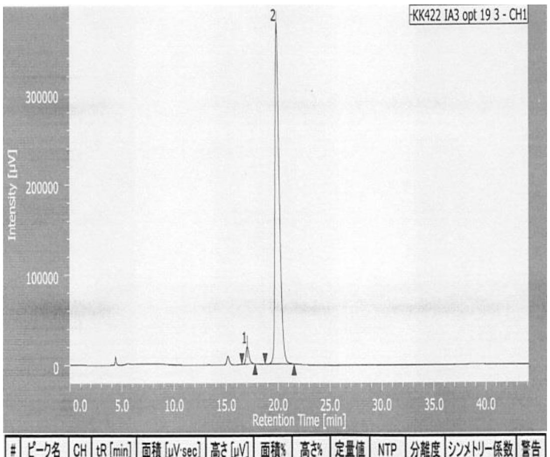
^{1}H NMR spectrum (**12d**)



^{13}C NMR spectrum (**12d**)

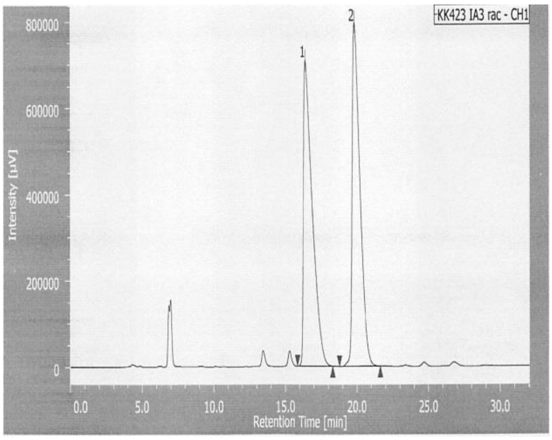


HPLC *optically active* (**12d**)



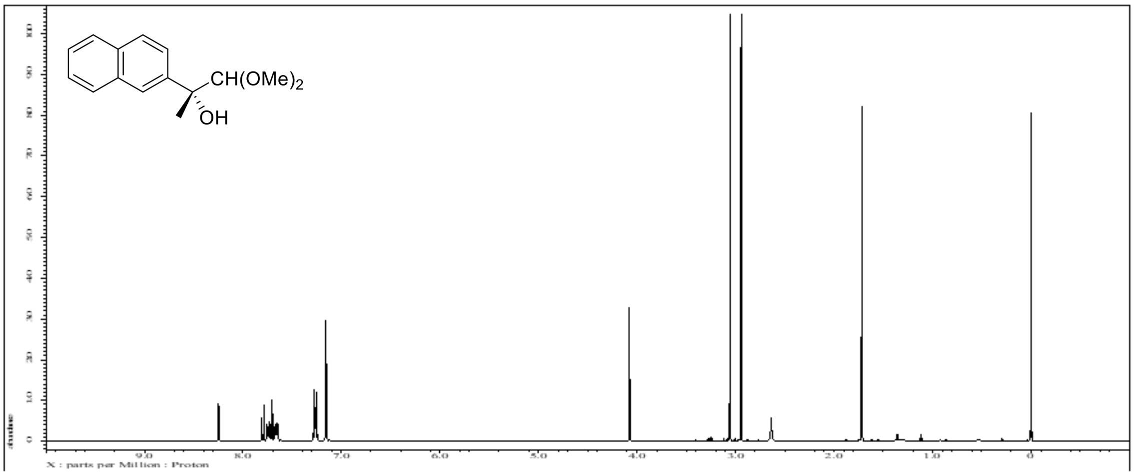
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	17.042	405117	19556	3.595	4.914	N/A	17085	4.482	1.355	
2	Unknown	1	19.842	10863568	378437	96.405	95.086	N/A	11784	N/A	1.855	

HPLC *racemic* (**12d**)

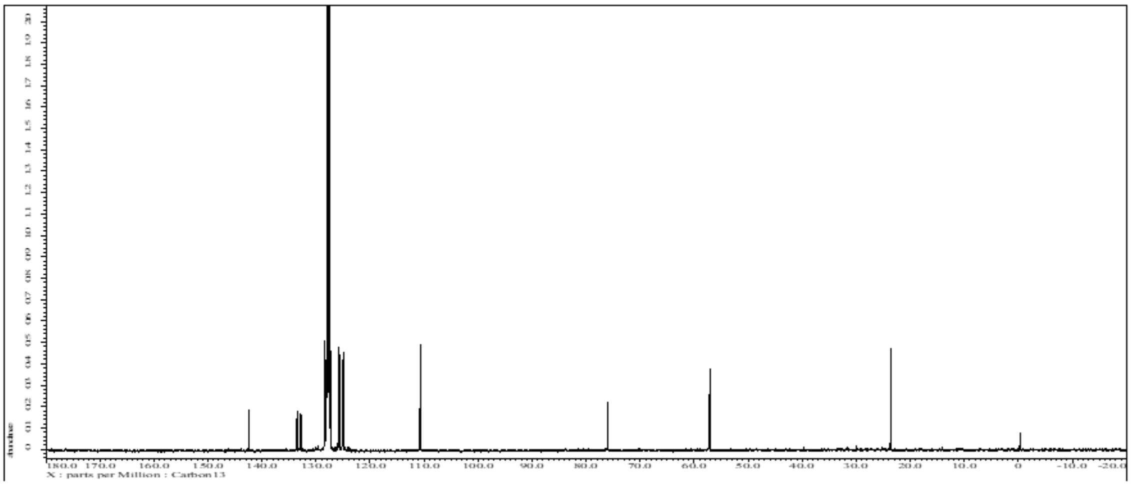


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	16.400	30215188	707099	50.168	47.058	N/A	3480	3.258	2.989	
2	Unknown	1	19.808	30013068	795500	49.832	52.942	N/A	6465	N/A	2.244	

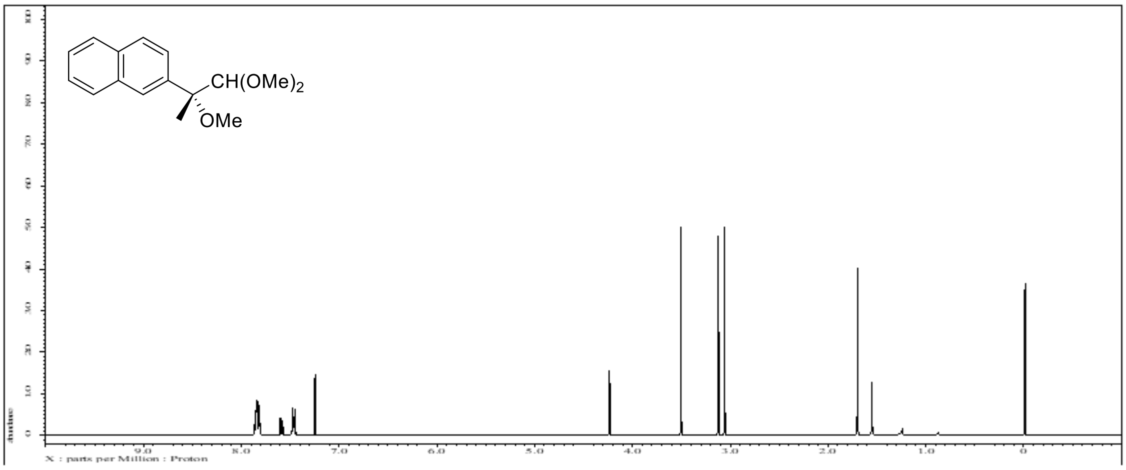
^{1}H NMR spectrum (**12h**)



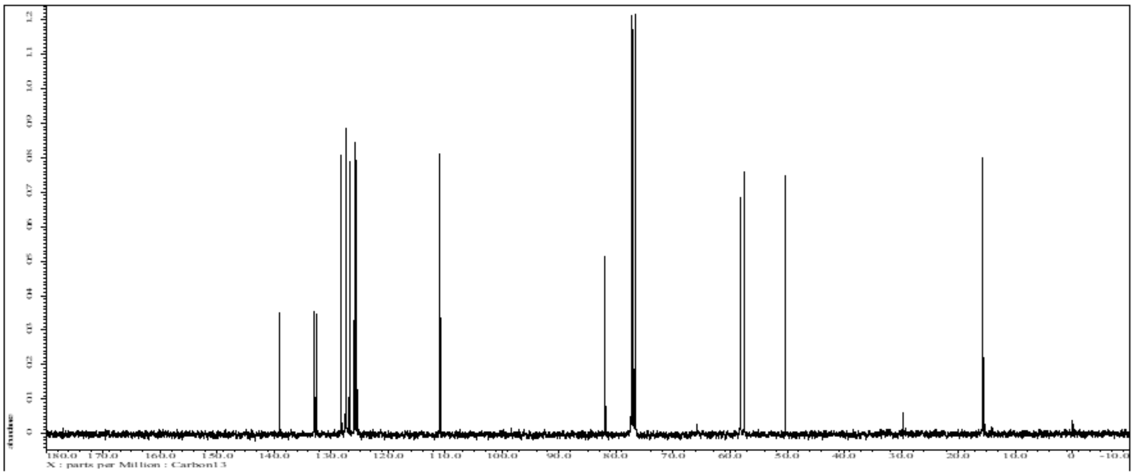
^{13}C NMR spectrum (**12h**)



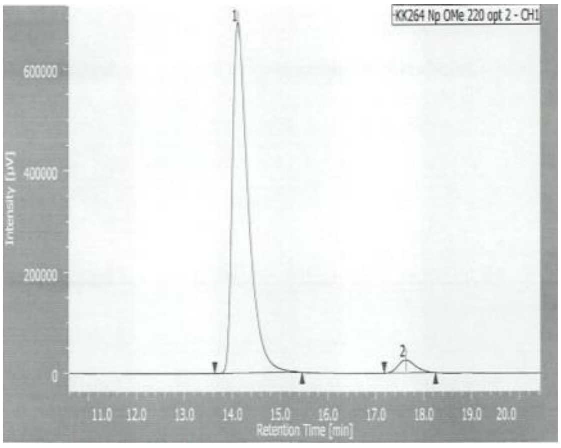
^{1}H NMR spectrum (**12h’**)



^{13}C NMR spectrum (**12h’**)

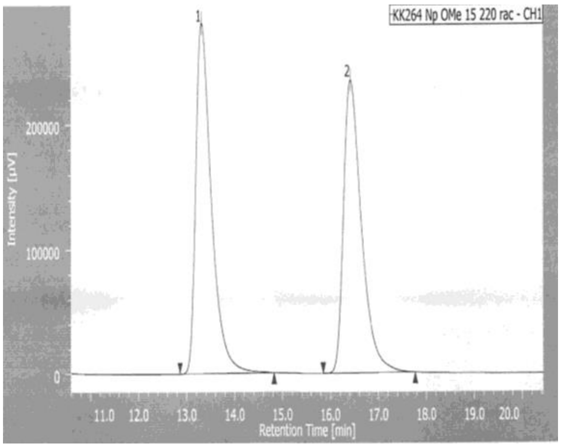


HPLC *optically active* (**12h’**)



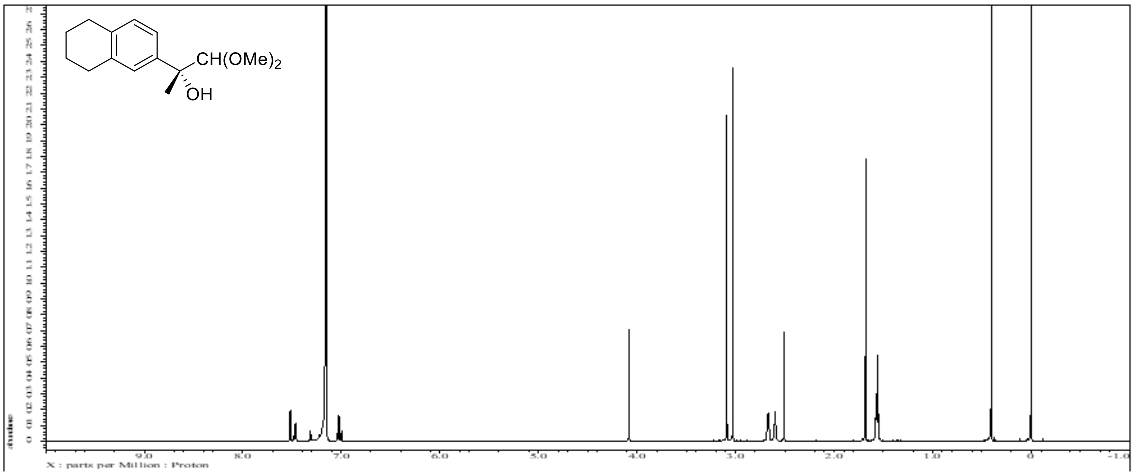
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	14.117	16020688	690588	96.158	96.456	N/A	9303	5.628	1.814	
2	Unknown	1	17.625	640099	25376	3.842	3.544	N/A	11254	N/A	1.244	

HPLC *racemic* (**12h’**)

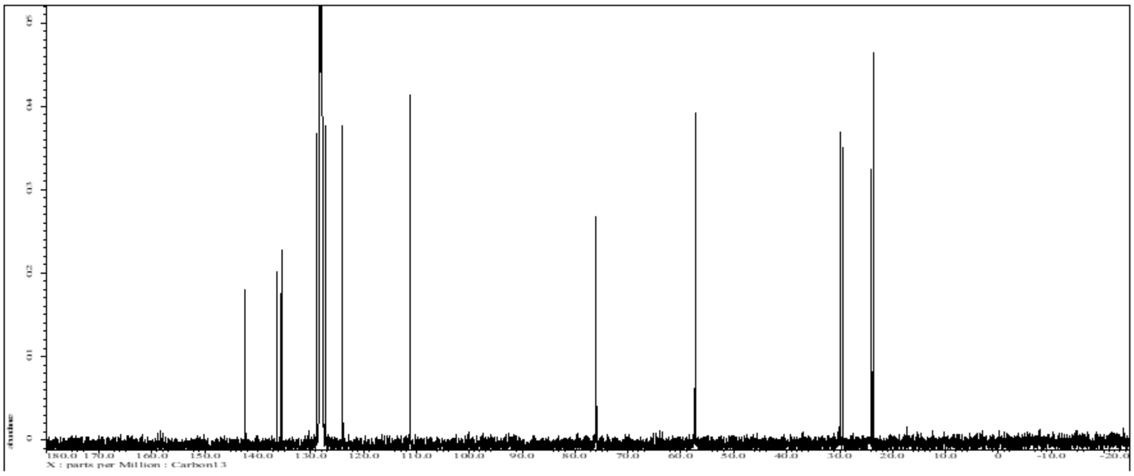


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	13.317	6388197	282002	50.932	54.511	N/A	8945	5.086	1.653	
2	Unknown	1	16.417	6154392	235333	49.068	45.489	N/A	9929	N/A	1.576	

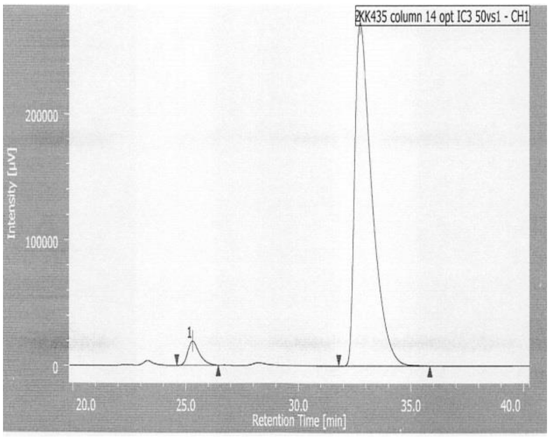
^{1}H NMR spectrum (**12i**)



^{13}C NMR spectrum (**12i**)

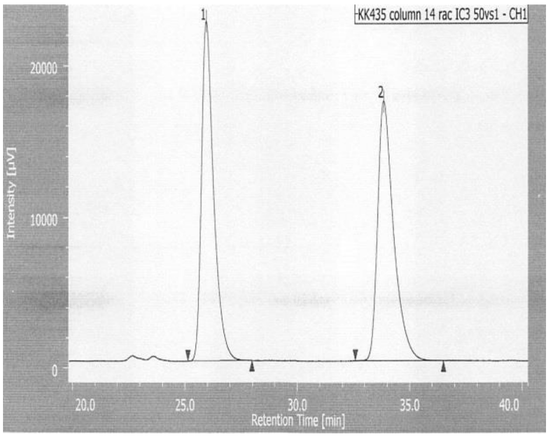


HPLC *optically active* (**12i**)



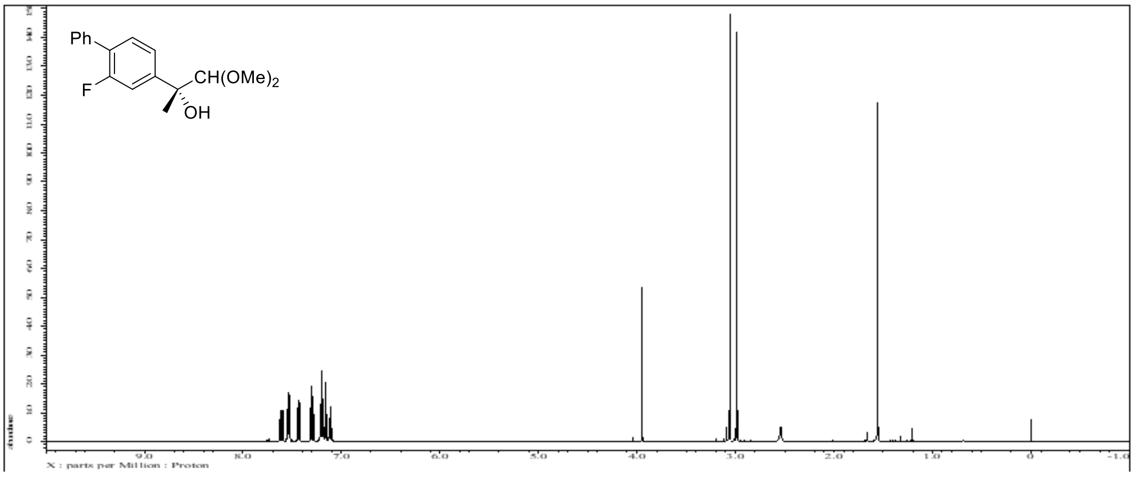
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	25.300	677122	19488	4.436	6.670	N/A	13377	6.650	1.413	
2	Unknown	1	32.733	14587405	272699	95.564	93.330	N/A	9180	N/A	2.030	

HPLC *racemic* (**12i**)

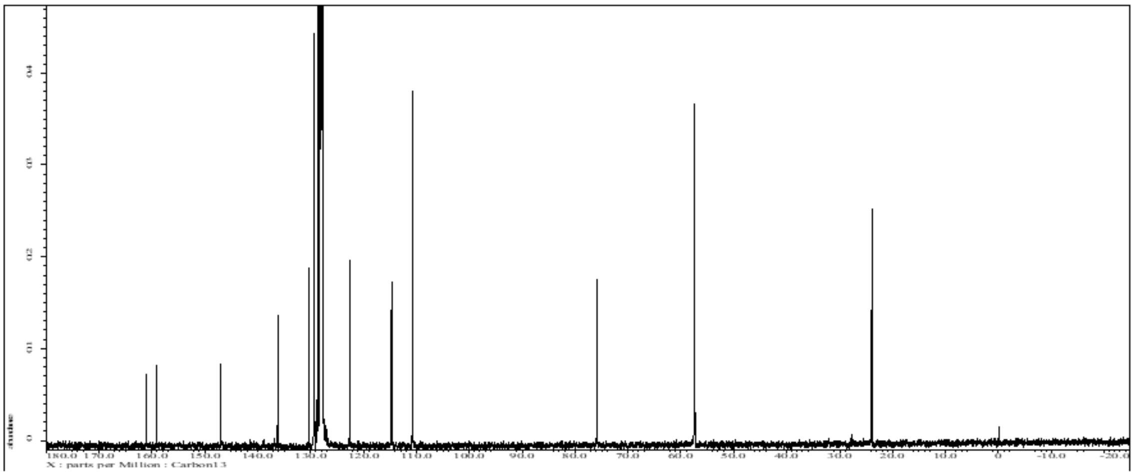


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	25.950	841184	22451	49.936	56.666	N/A	12332	7.328	1.493	
2	Unknown	1	33.850	843352	17168	50.064	43.334	N/A	12175	N/A	1.535	

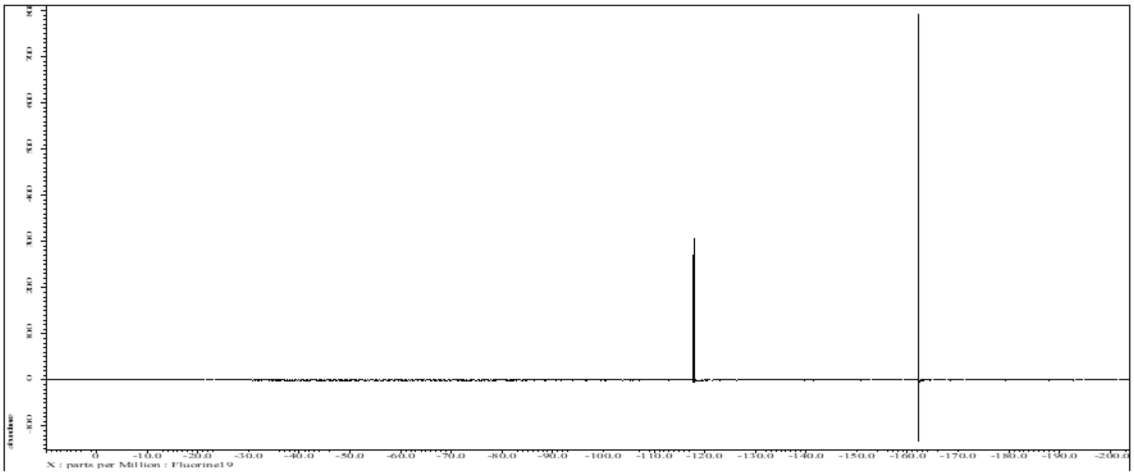
^{1}H NMR spectrum (**12j**)



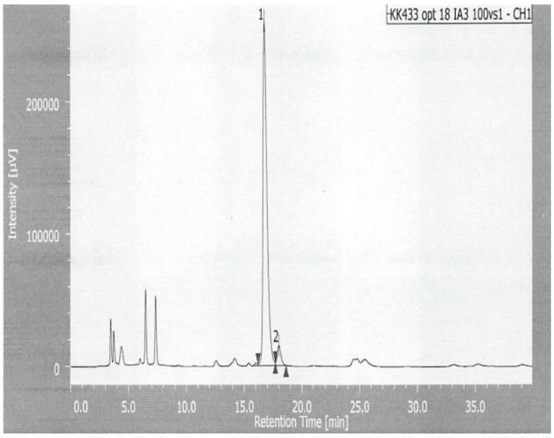
^{13}C NMR spectrum (**12j**)



^{19}F NMR spectrum (**12j**)

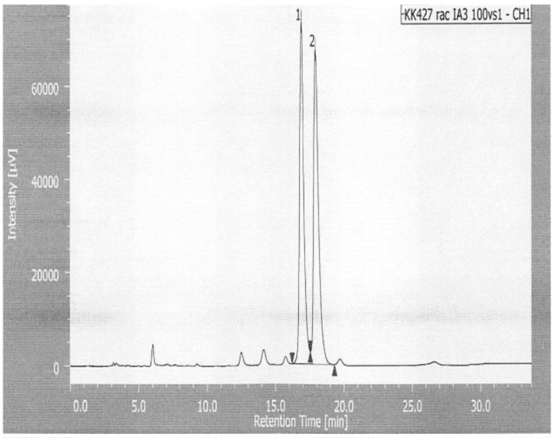


HPLC *optically active* (**12j**)



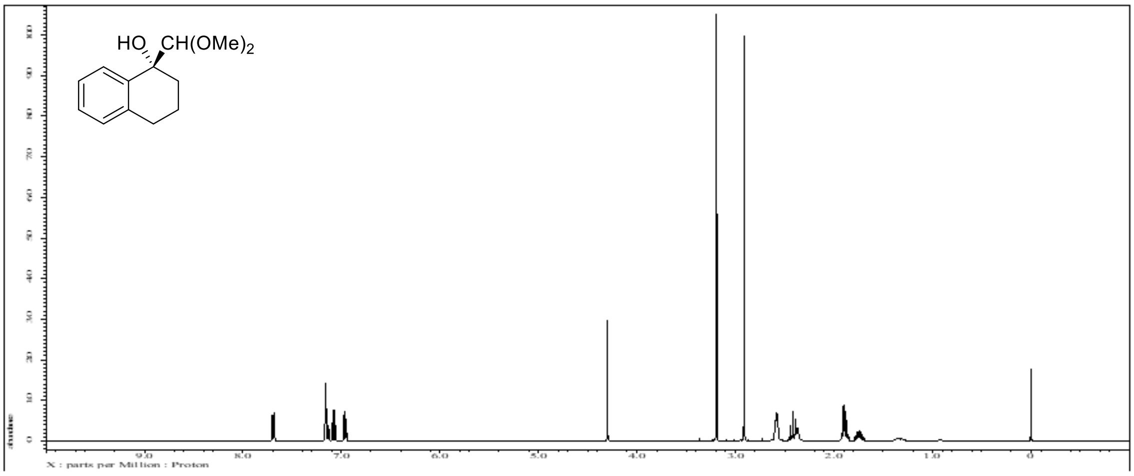
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	16.733	6223020	259333	95.006	94.518	N/A	12400	2.190	1.870	
2	Unknown	1	17.992	327125	15040	4.994	5.482	N/A	17053	N/A	N/A	

HPLC *racemic* (**12j**)

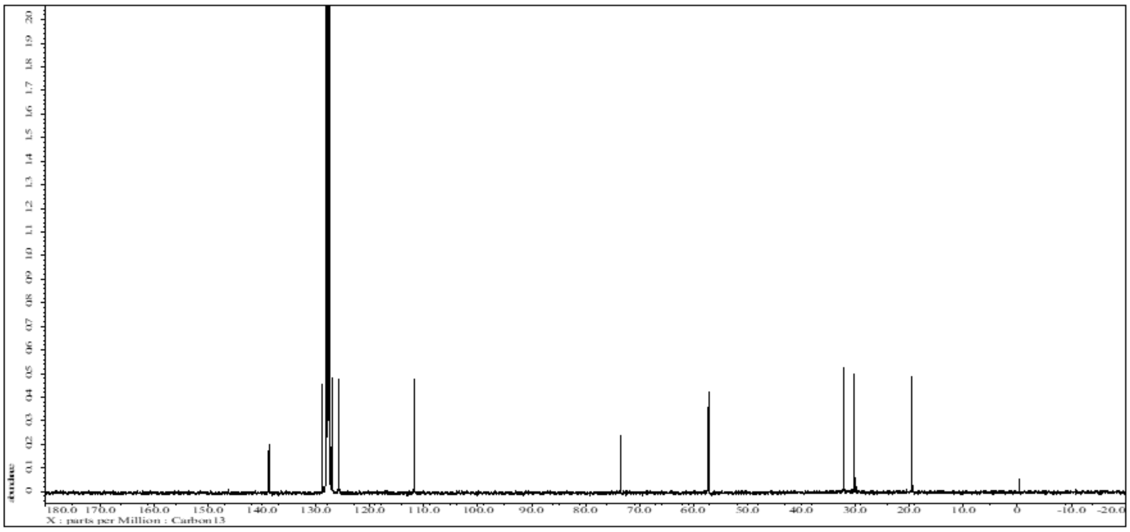


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	16.875	1639611	73291	49.896	52.123	N/A	14780	1.783	1.551	
2	Unknown	1	17.908	1646449	67321	50.104	47.877	N/A	13933	N/A	1.648	

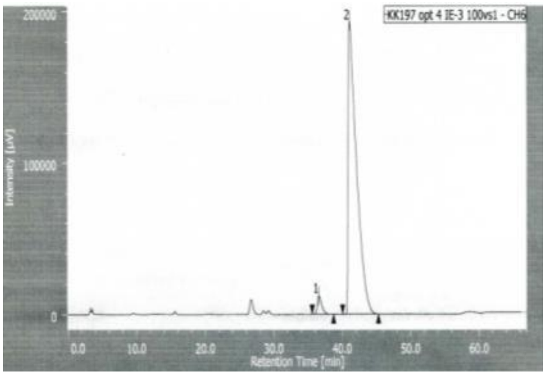
^{1}H NMR spectrum (**12k**)



^{13}C NMR spectrum (**12k**)

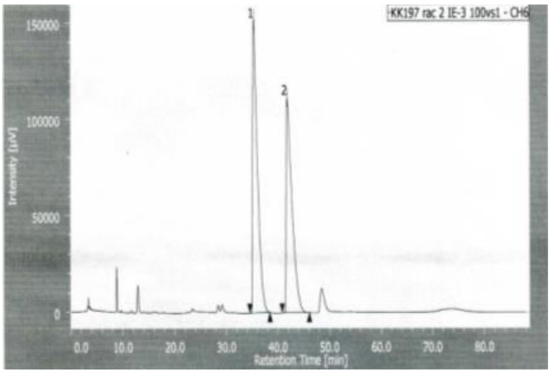


HPLC *optically active* (**12k**)



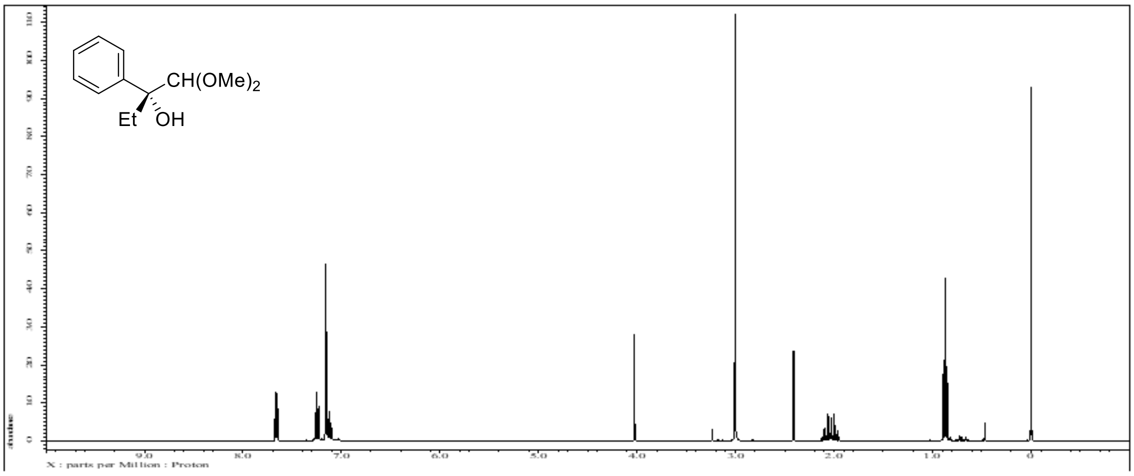
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	6	36.592	540064	12126	3.187	5.891	N/A	16736	2.747	1.613	
2	Unknown	6	41.132	16407744	193723	96.813	94.109	N/A	5683	N/A	3.755	

HPLC *racemic* (**12k**)

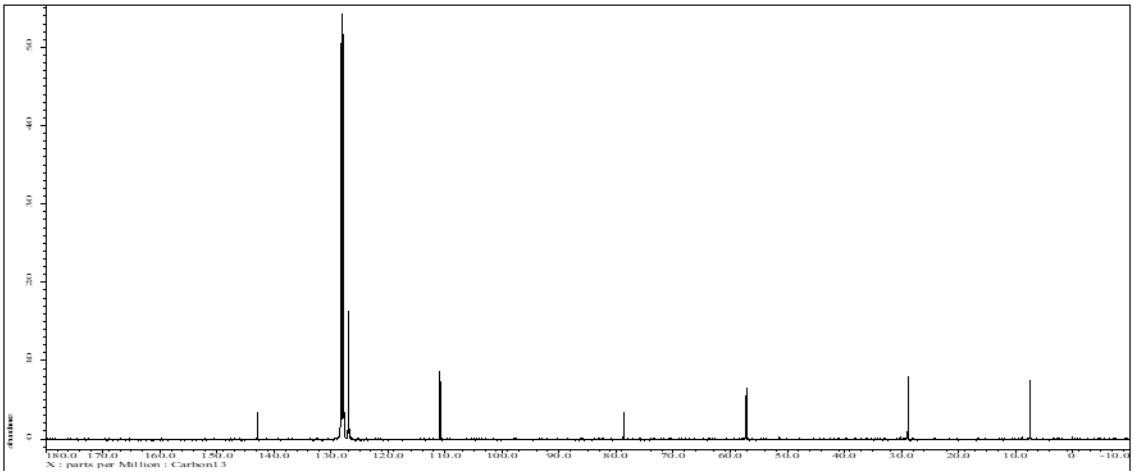


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	6	35.338	9623164	152485	52.220	57.728	N/A	7675	3.594	3.097	
2	Unknown	6	41.845	8804952	111657	47.780	42.272	N/A	6884	N/A	3.347	

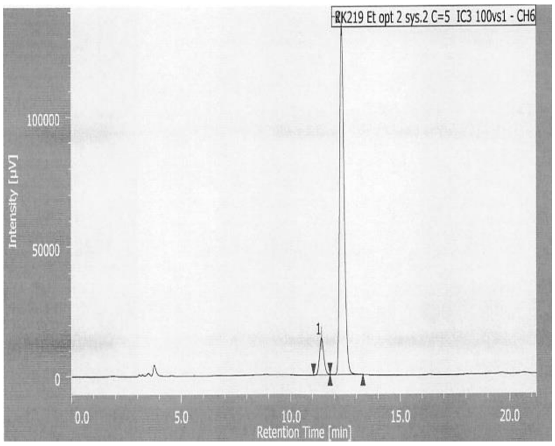
^{1}H NMR spectrum (**12l**)



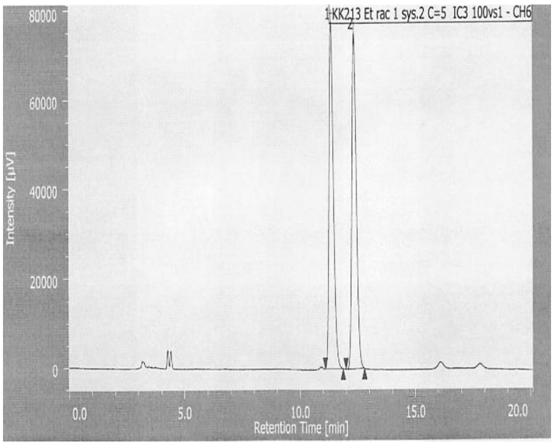
^{13}C NMR spectrum (**12l**)



HPLC *optically active* (**12l**)



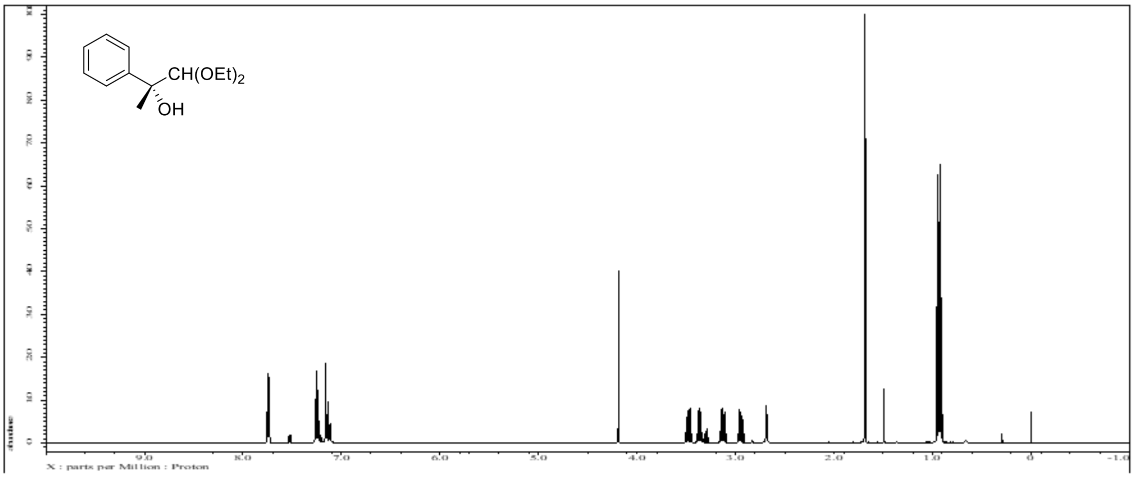
HPLC *racemic* (**12l**)



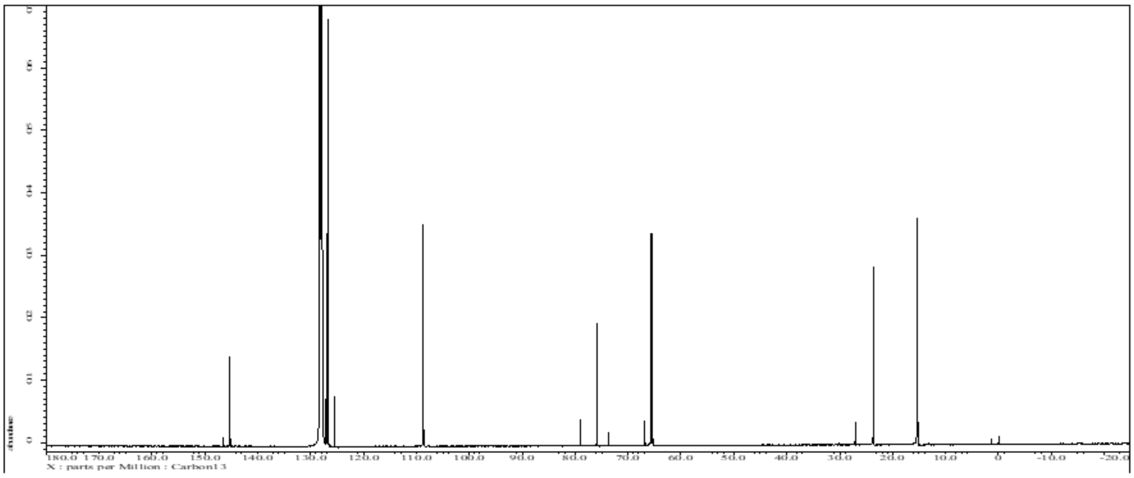
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	6	11.405	191326	14358	9.116	9.630	N/A	17519	2.615	1.190	
2	Unknown	6	12.335	1907501	134732	90.884	90.370	N/A	17920	N/A	1.261	

#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	6	11.355	1026054	77875	50.285	50.857	N/A	17660	2.865	1.295	
2	Unknown	6	12.348	1014421	75251	49.715	49.143	N/A	19529	N/A	1.193	

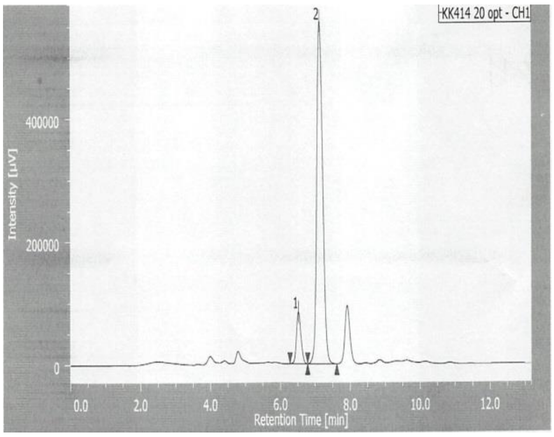
^{1}H NMR spectrum (**12t**)



^{13}C NMR spectrum (**12t**)

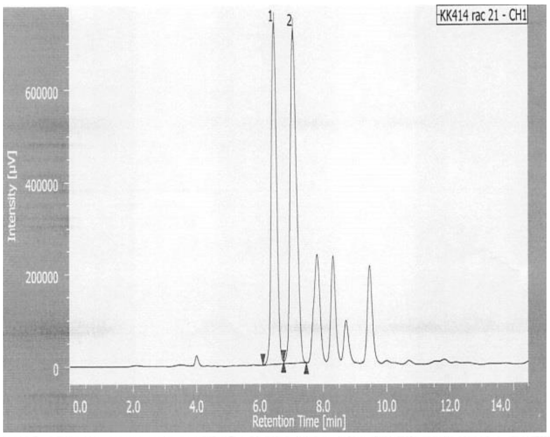


HPLC *optically active* (**12t**)



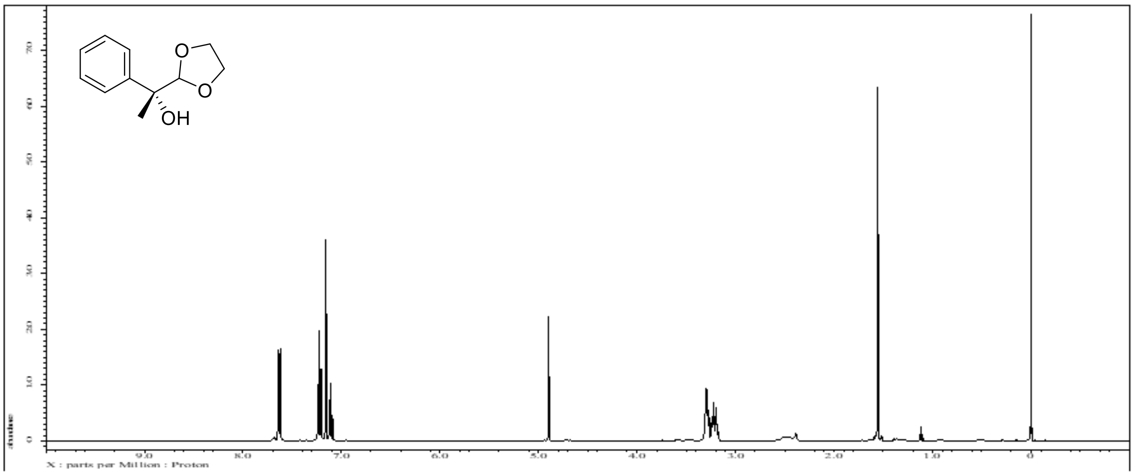
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	6.517	752349	84592	10.304	13.174	N/A	12574	2.238	1.156	
2	Unknown	1	7.125	6549056	557517	89.696	86.826	N/A	8305	N/A	1.174	

HPLC *racemic* (**12t**)

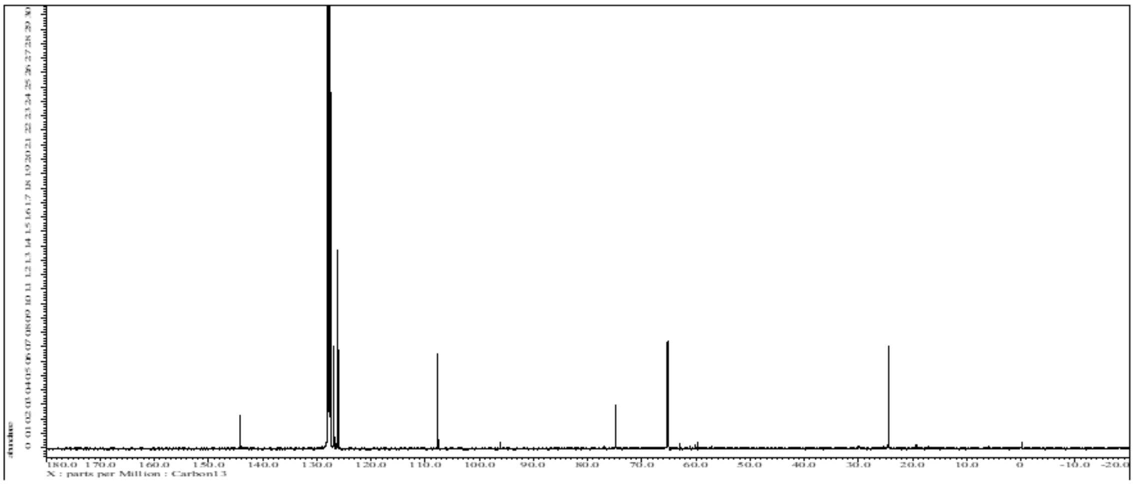


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	6.442	8685911	739751	46.223	50.540	N/A	6637	1.719	1.130	
2	Unknown	1	7.033	10105591	723936	53.777	49.460	N/A	5665	N/A	1.356	

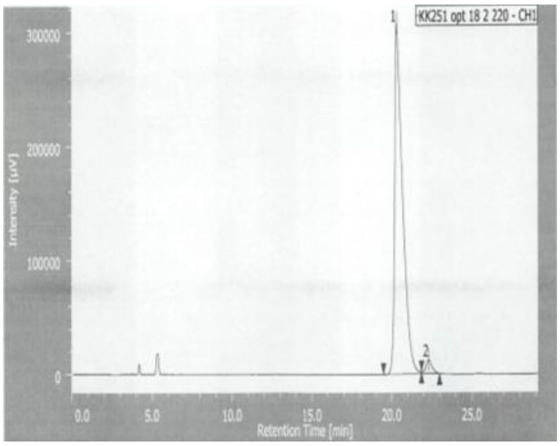
^{1}H NMR spectrum (**12u**)



^{13}C NMR spectrum (**12u**)

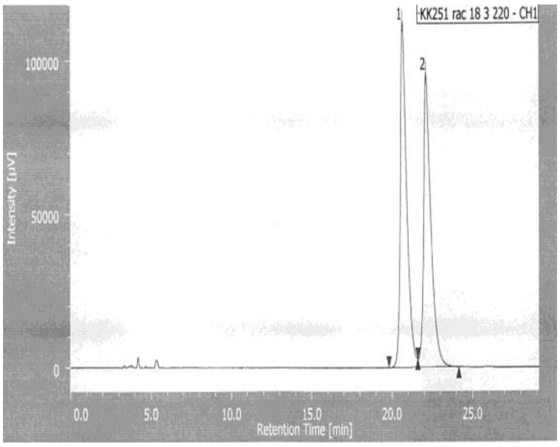


HPLC *optically active* (**12u**)



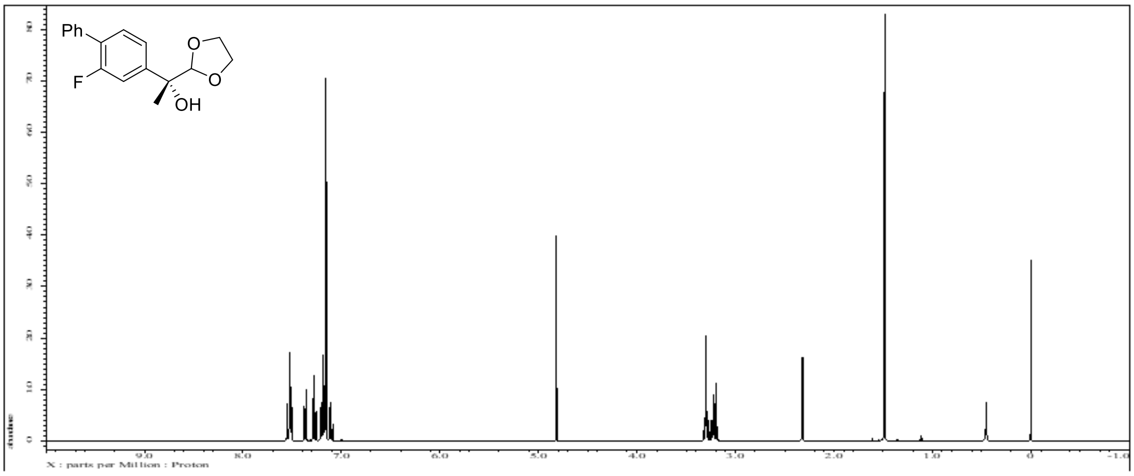
#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	20.308	10567621	307717	96.905	96.151	N/A	9006	2.605	2.121	
2	Unknown	1	22.300	337564	12318	3.095	3.849	N/A	17352	N/A	N/A	

HPLC *racemic* (**12u**)

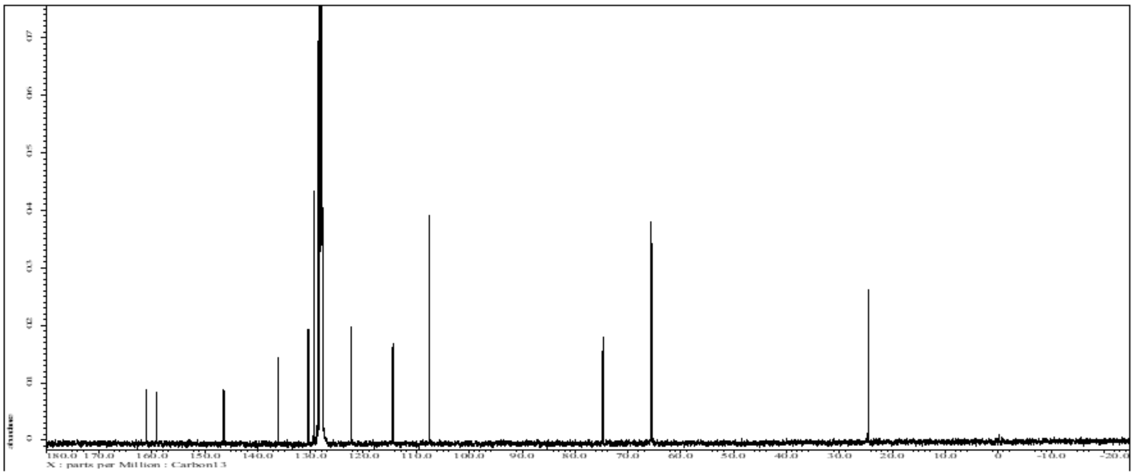


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	20.642	3128643	112697	50.834	54.073	N/A	14938	2.049	1.683	
2	Unknown	1	22.100	3025978	95721	49.166	45.927	N/A	13818	N/A	1.717	

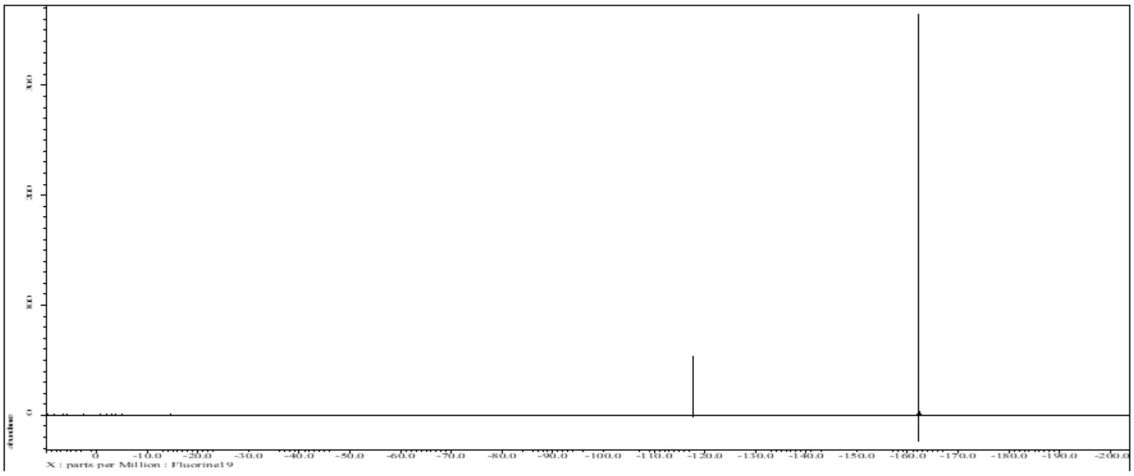
^{1}H NMR spectrum (**12v**)



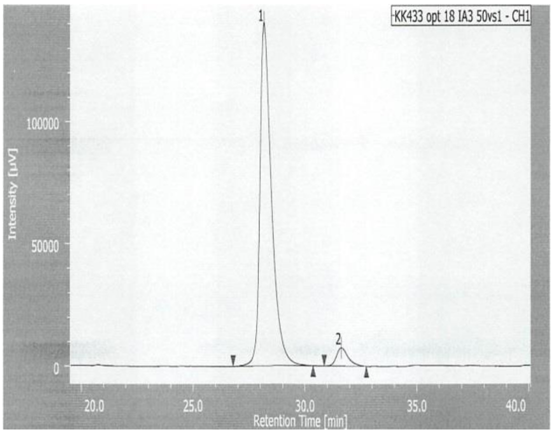
^{13}C NMR spectrum (**12v**)



^{19}F NMR spectrum (**12v**)

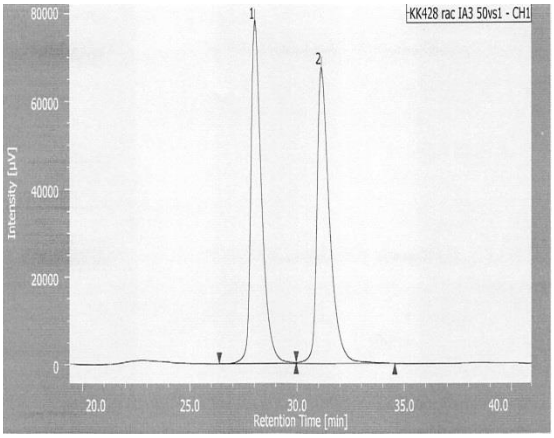


HPLC *optically active* (**12v**)



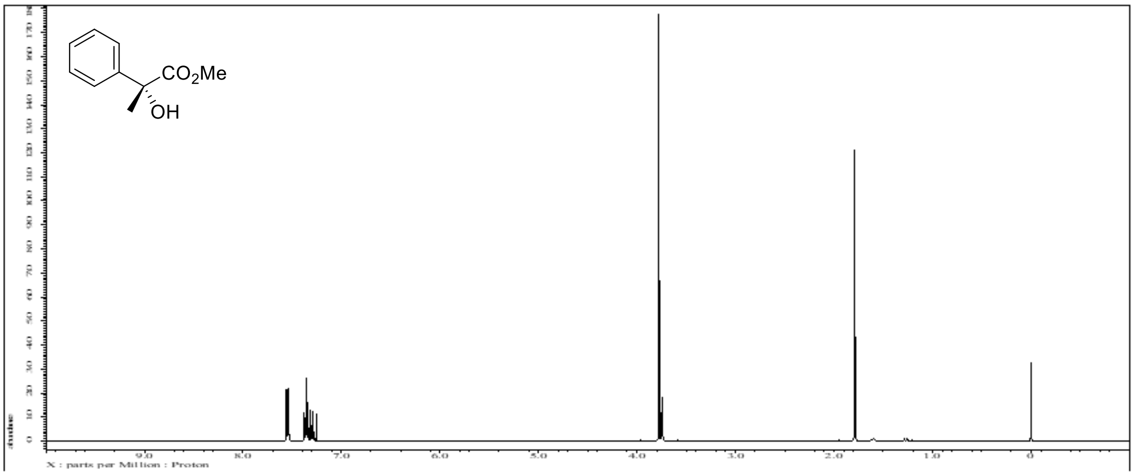
#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	28.158	5033274	140355	94.881	94.839	N/A	16300	3.919	1.617	
2	Unknown	1	31.617	271559	7638	5.119	5.161	N/A	20318	N/A	1.369	

HPLC *racemic* (**12v**)

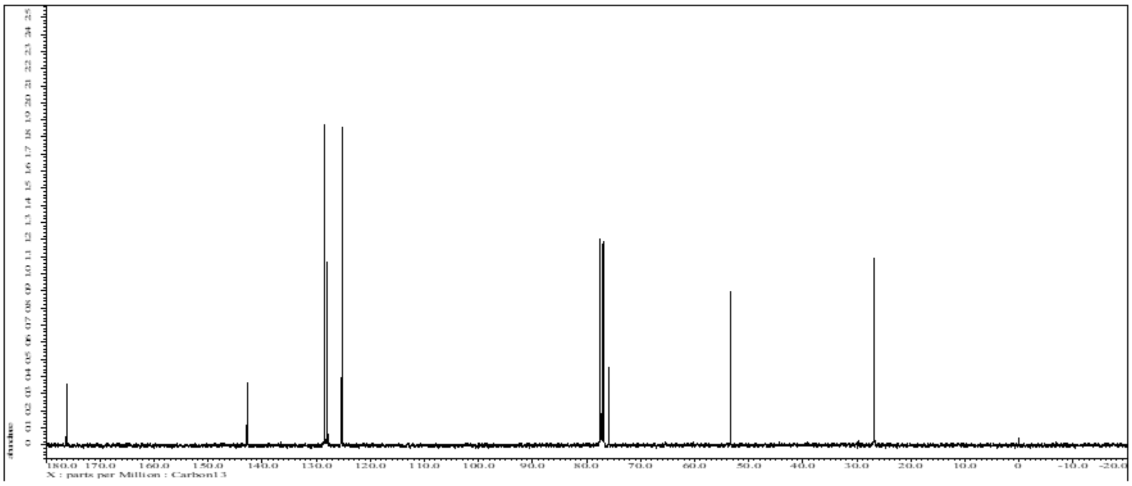


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	28.033	2711315	78195	49.695	53.693	N/A	17375	3.368	1.563	
2	Unknown	1	31.133	2744590	67439	50.305	46.307	N/A	15670	N/A	1.676	

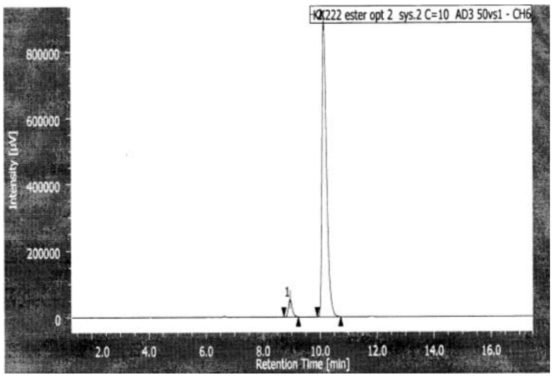
^{1}H NMR spectrum [(*R*)-**14**]



^{13}C NMR spectrum [(*R*)-**14**]

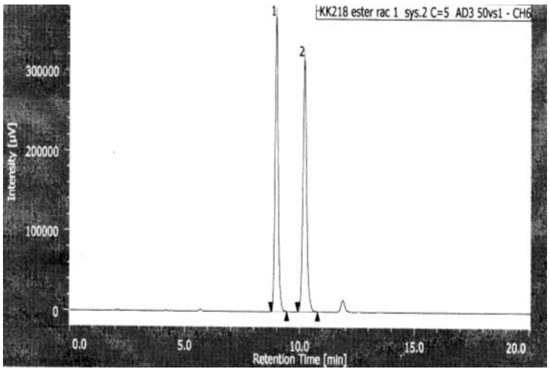


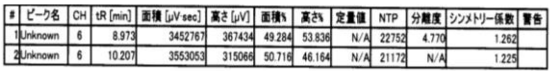
HPLC *optically active* [(*R*)-**14**]



#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	6	8.947	482599	52932	4.615	5.620	N/A	23567	4.651	1.212	
2	Unknown	6	10.150	9974732	888842	95.385	94.380	N/A	20187	N/A	1.385	

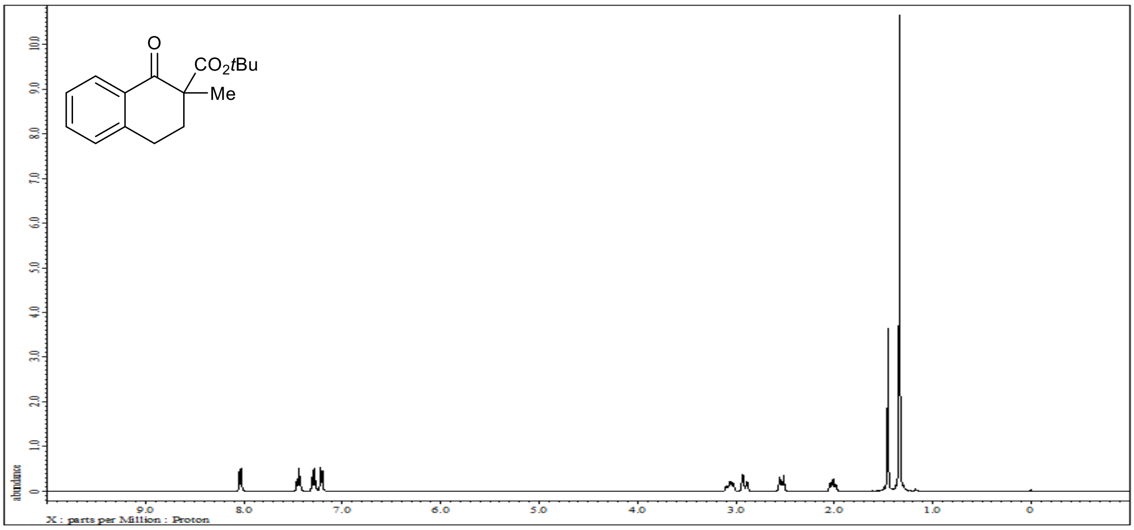
HPLC *racemic* (**14**)



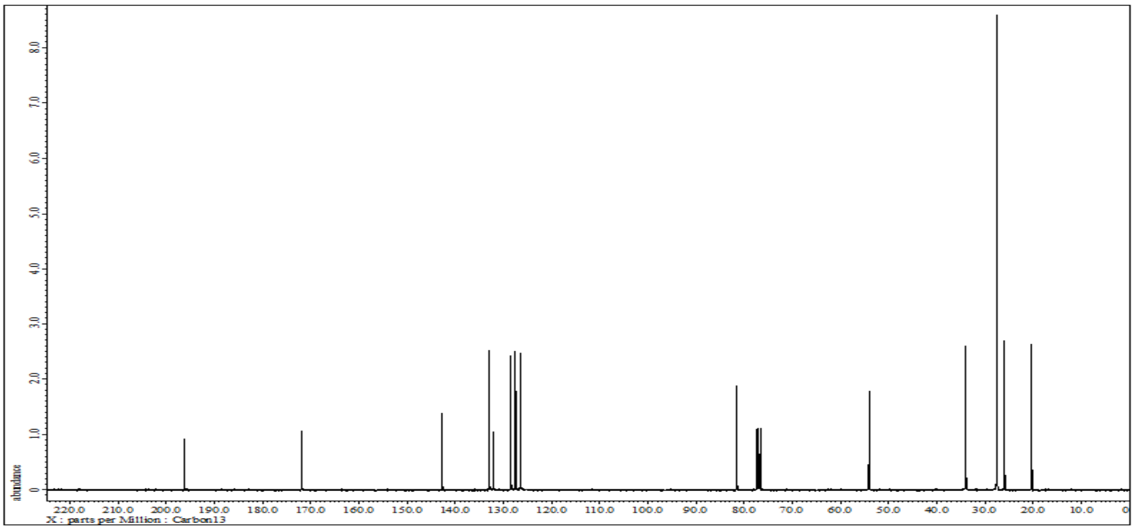


#	ピーク名	CH	tR [min]	面積 [µV·sec]	高さ [µV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	6	8.973	3452767	367434	49.284	53.836	N/A	22752	4.770	1.262	
2	Unknown	6	10.207	3553053	315066	50.716	46.164	N/A	21172	N/A	1.225	

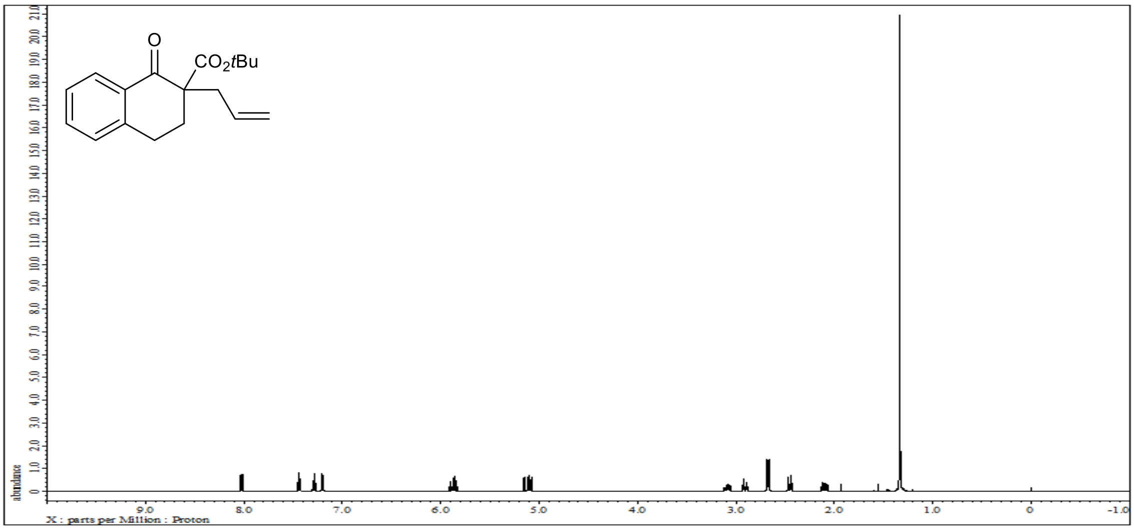
^{1}H NMR spectrum (**17a**)



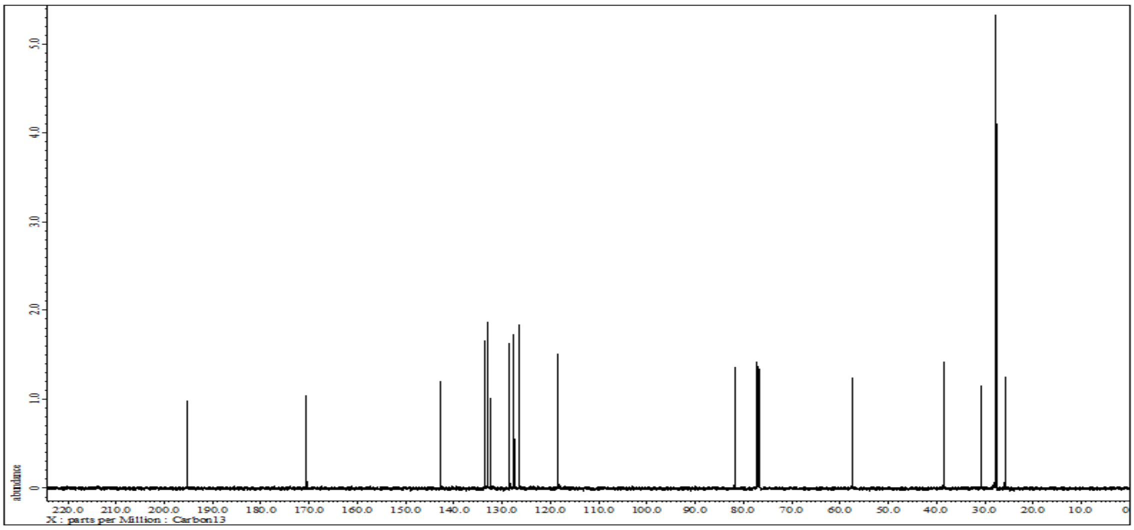
^{13}C NMR spectrum (**17a**)



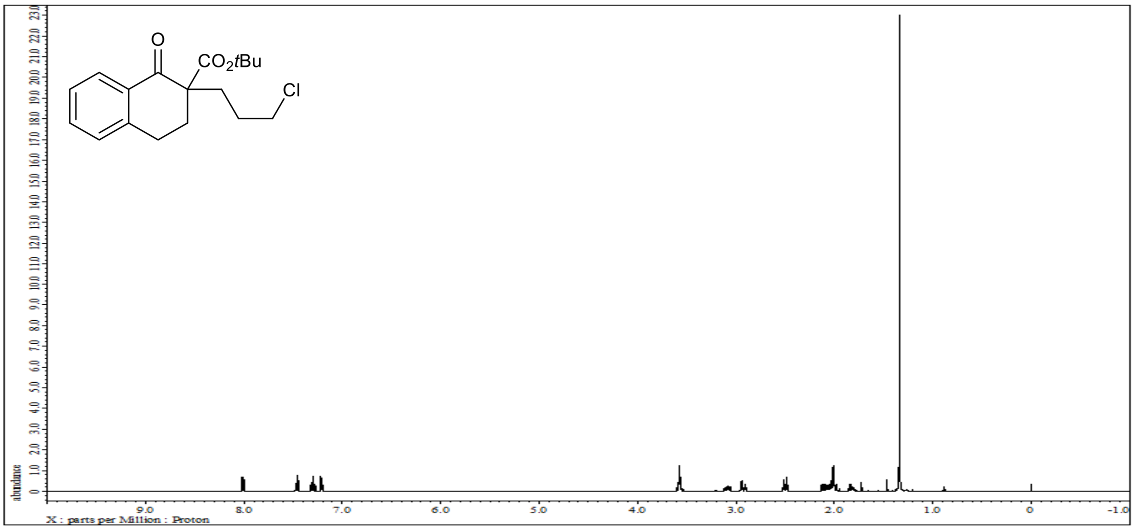
^{1}H NMR spectrum (**17b**)



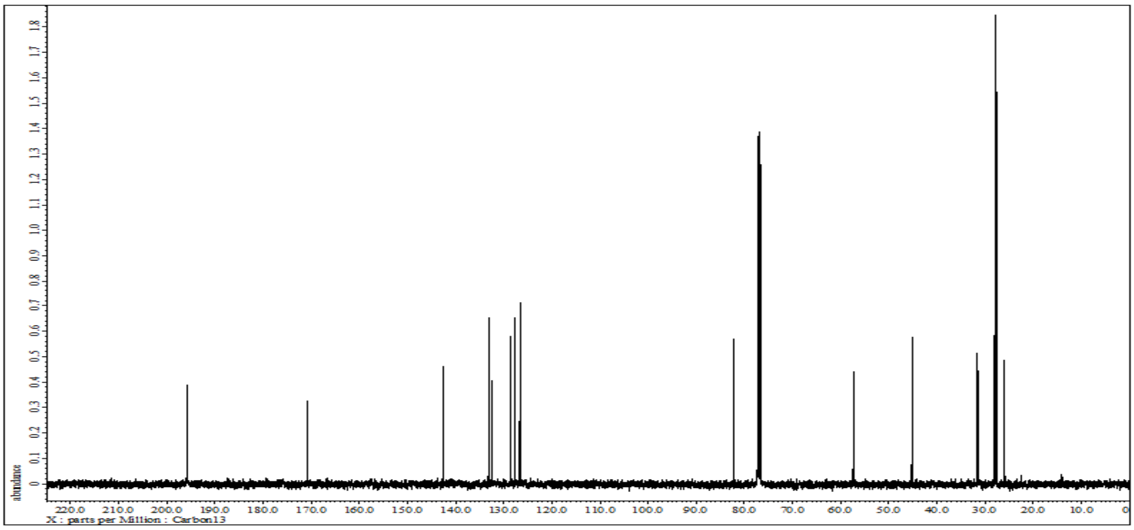
^{13}H NMR spectrum (**17b**)



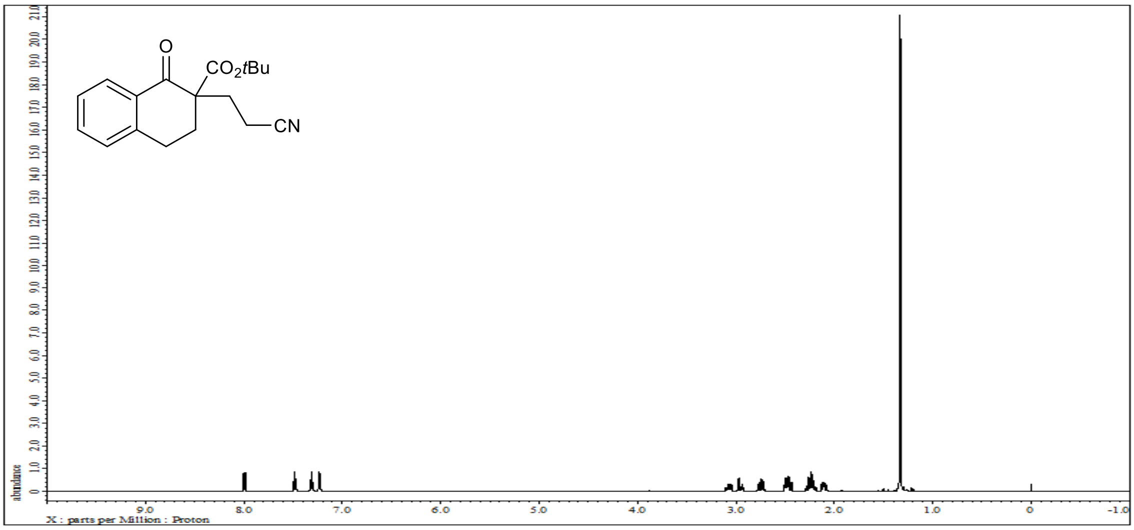
^{1}H NMR spectrum (**17d**)



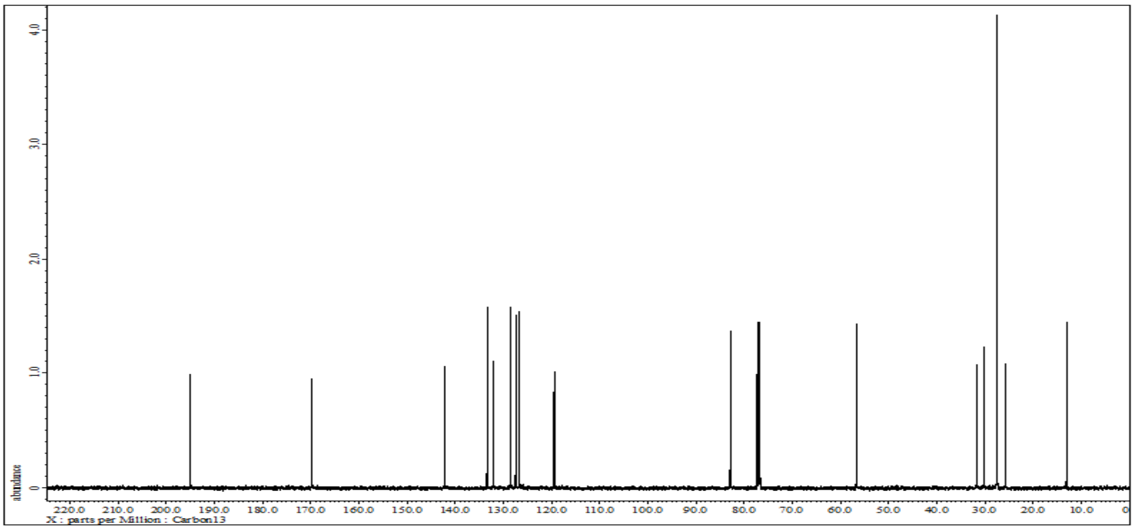
^{13}C NMR spectrum (**17d**)



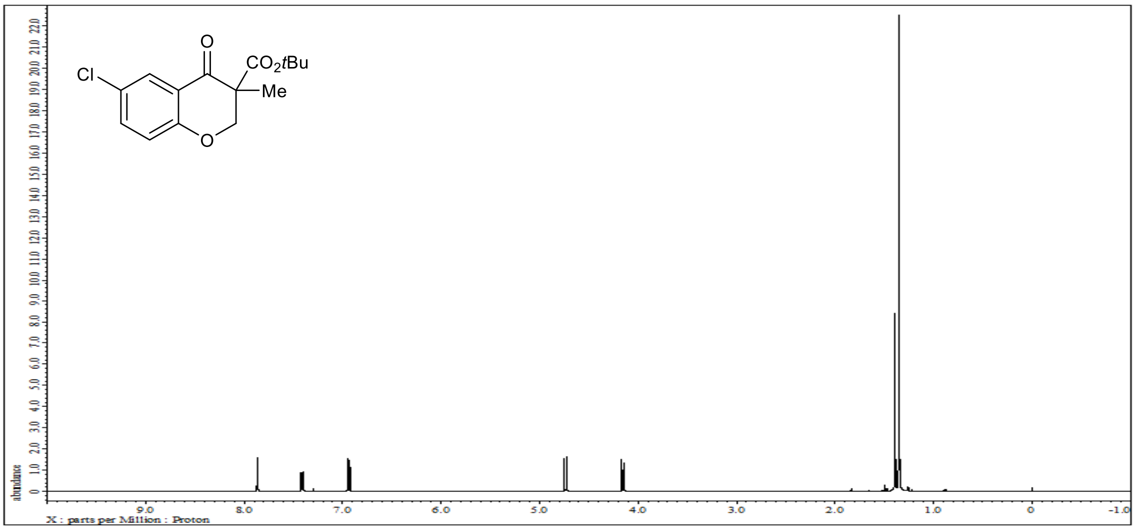
^{1}H NMR spectrum (**17e**)



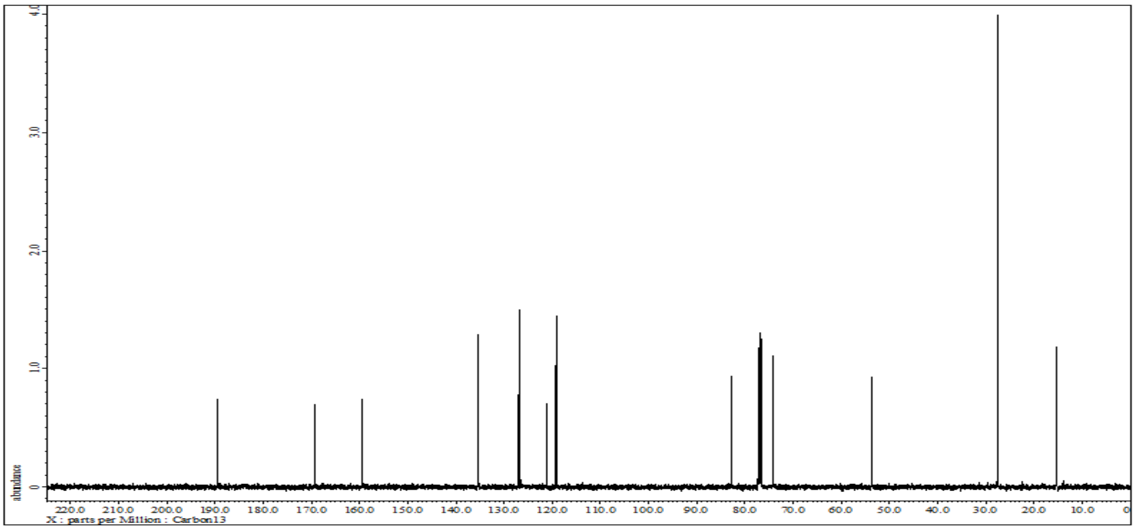
^{13}C NMR spectrum (**17e**)



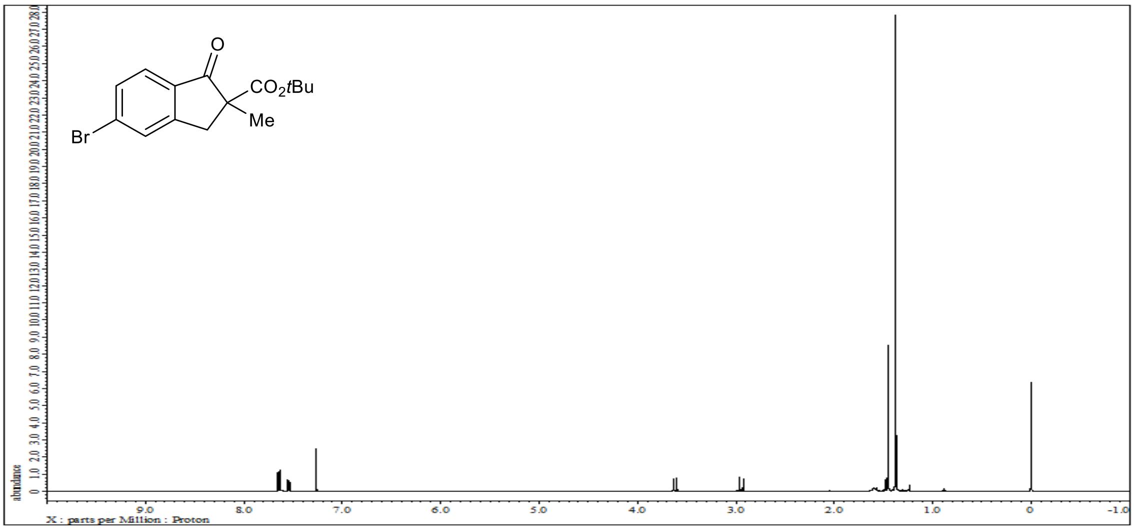
^{1}H NMR spectrum (**17f**)



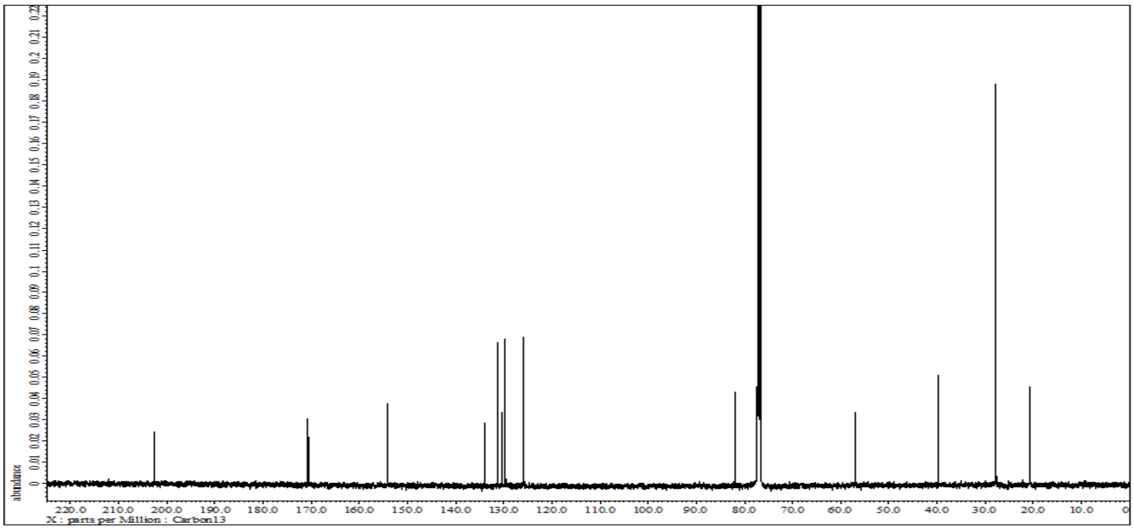
^{13}HC NMR spectrum (**17f**)



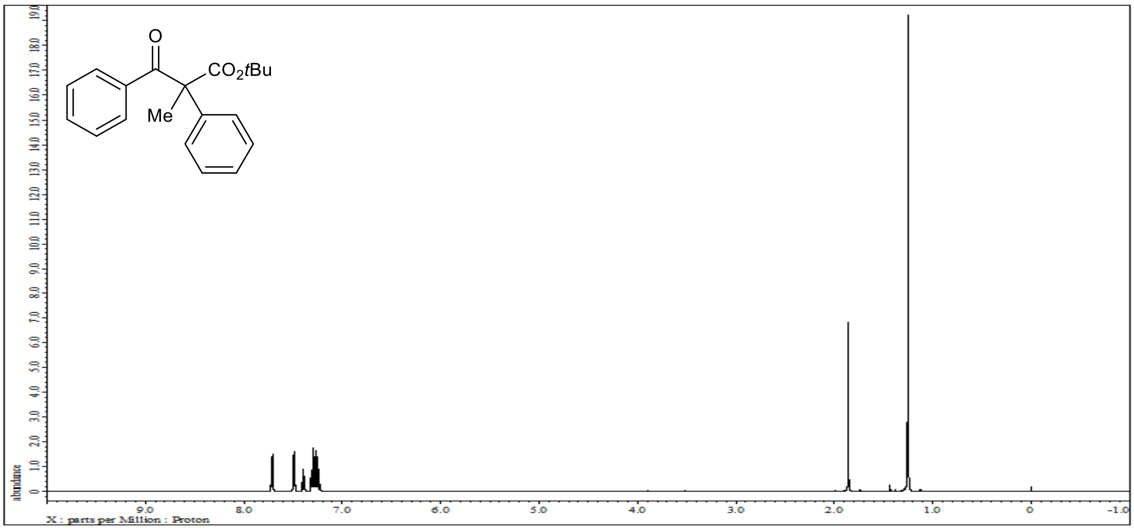
^{1}H NMR spectrum (**17h**)



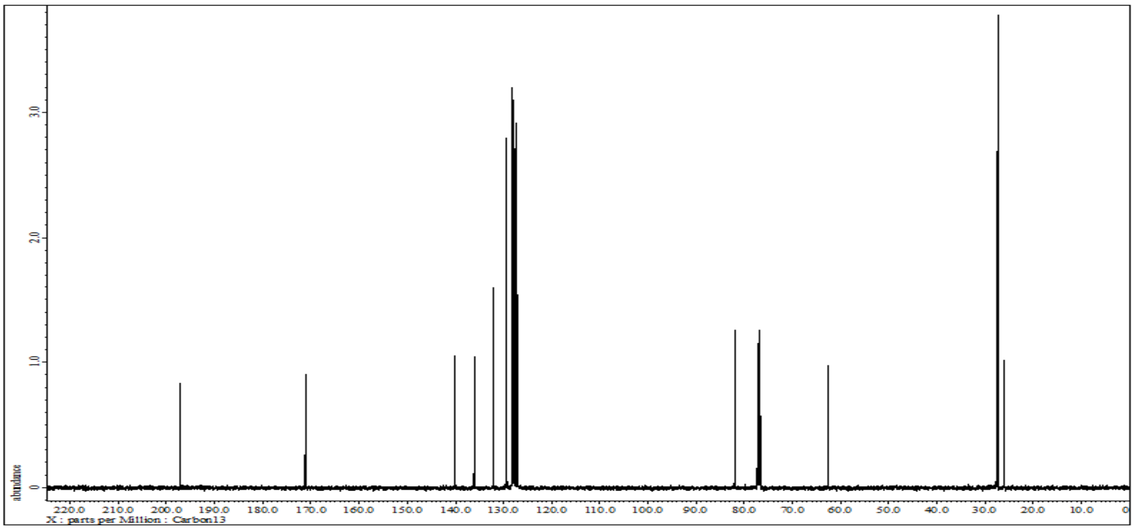
^{13}C NMR spectrum (**17h**)



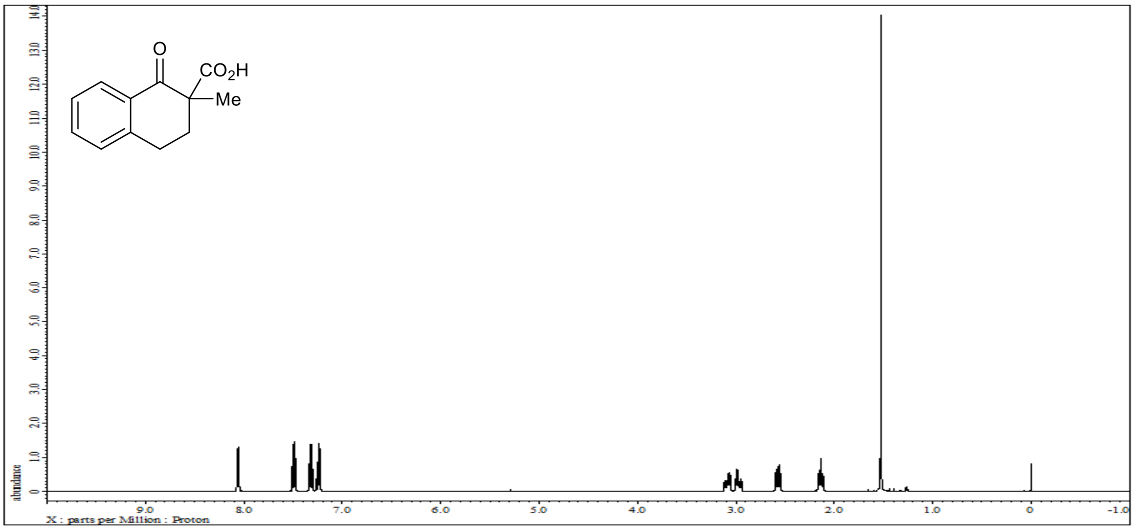
^{1}H NMR spectrum (**17i**)



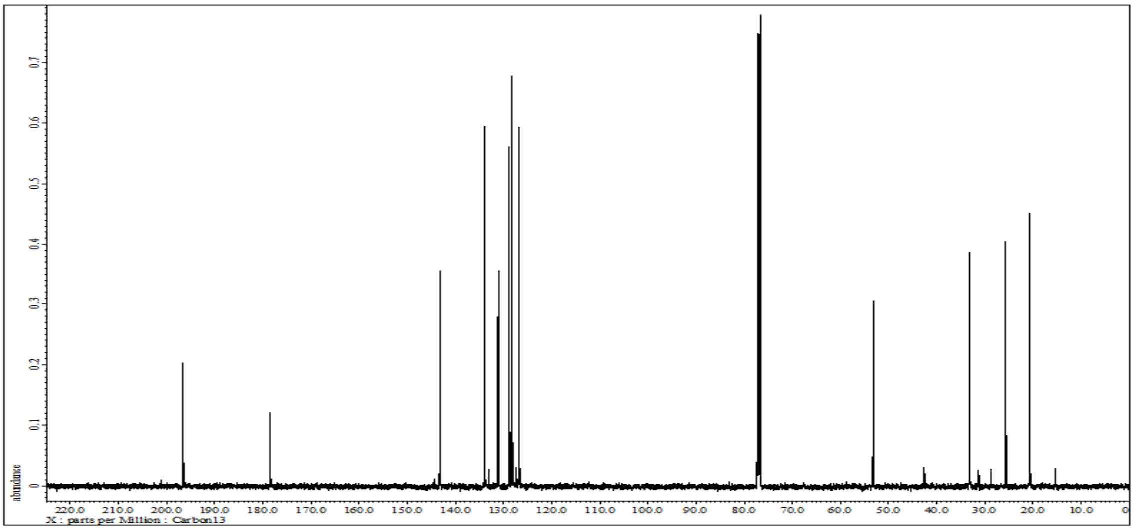
^{13}C NMR spectrum (**17i**)



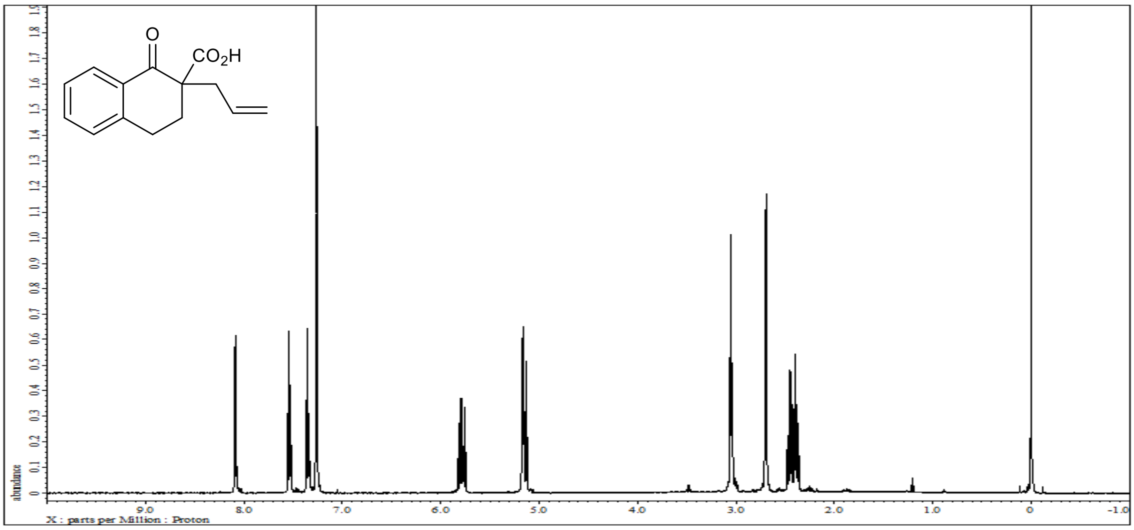
^{1}H NMR spectrum (**18a**)



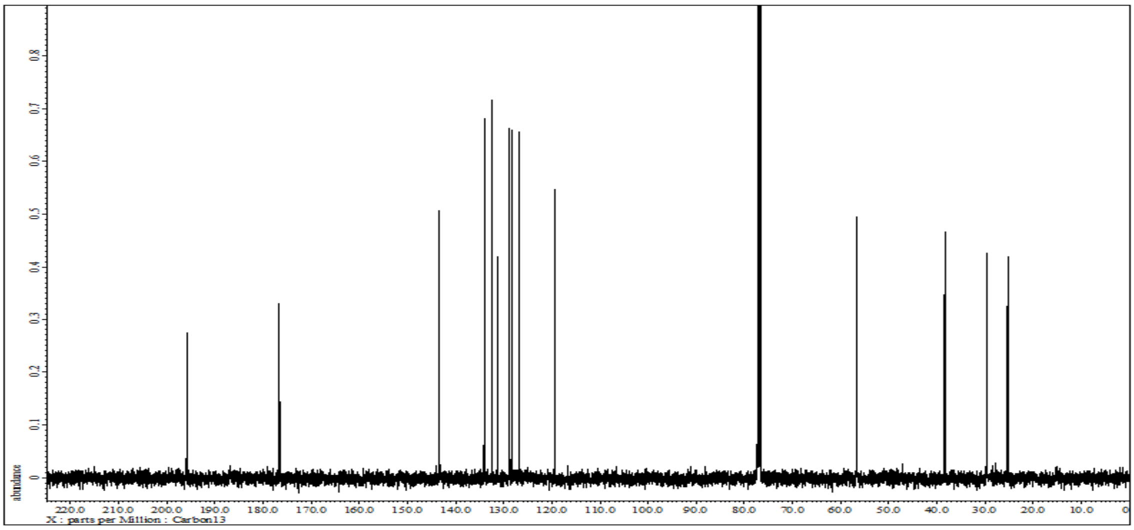
^{13}C NMR spectrum (**18a**)



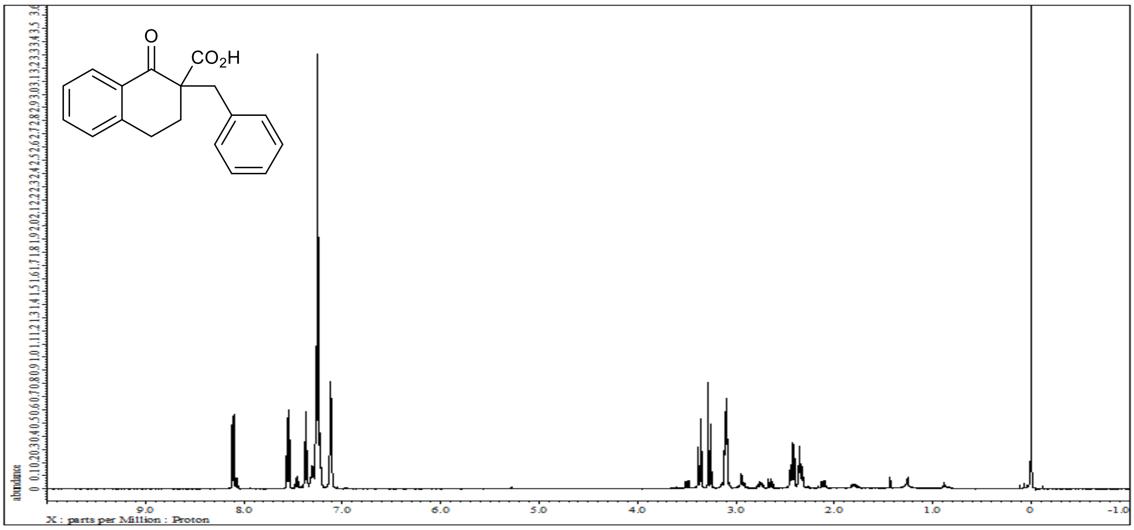
^{1}H NMR spectrum (**18b**)



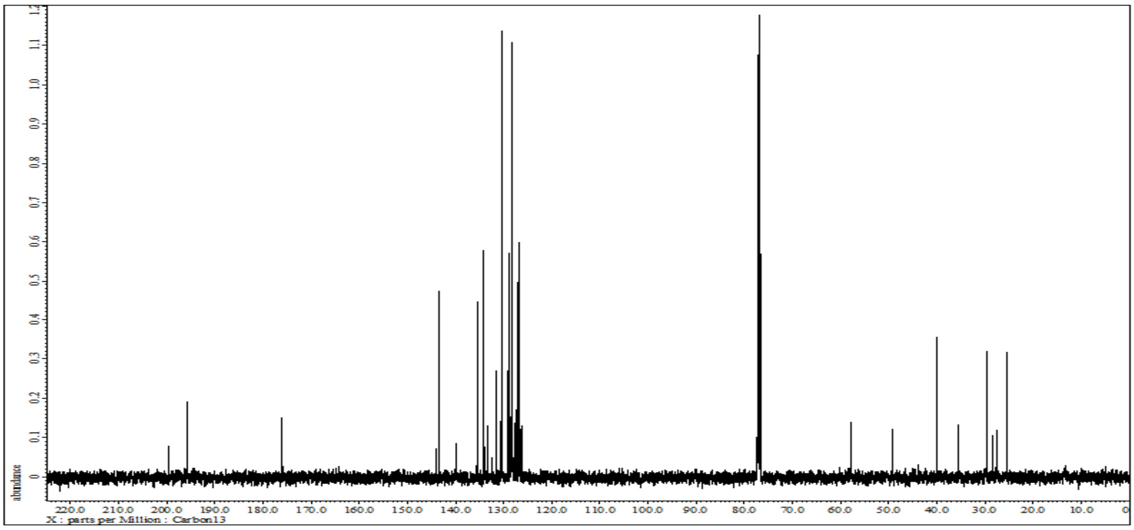
^{13}C NMR spectrum (**18b**)



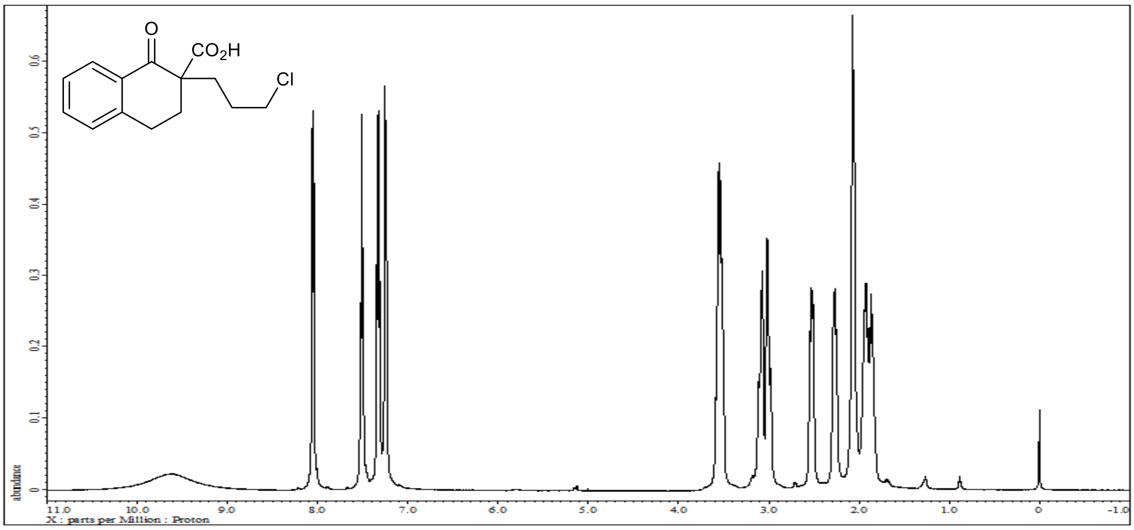
^{1}H NMR spectrum (**18c**)



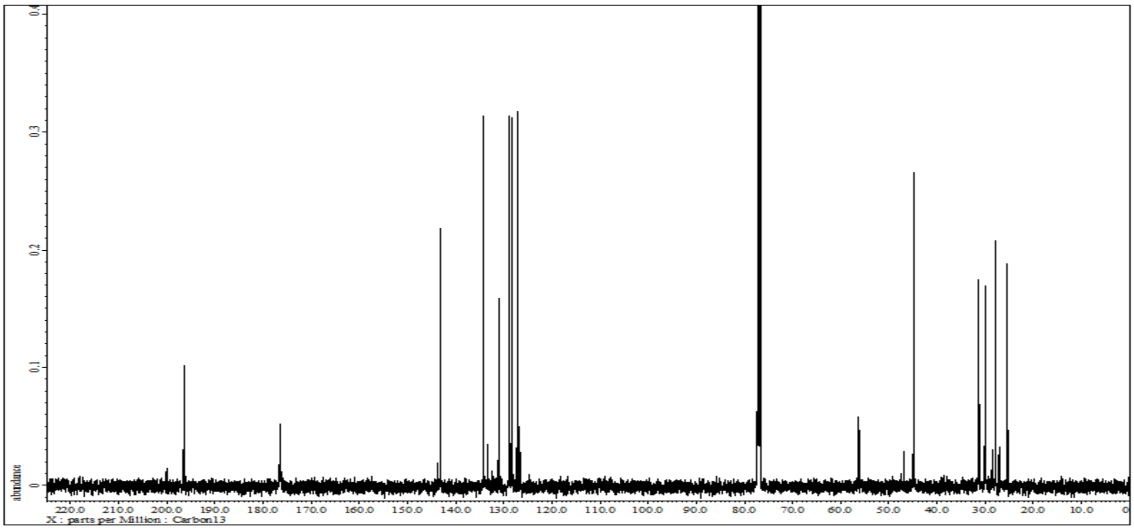
^{13}C NMR spectrum (**18c**)



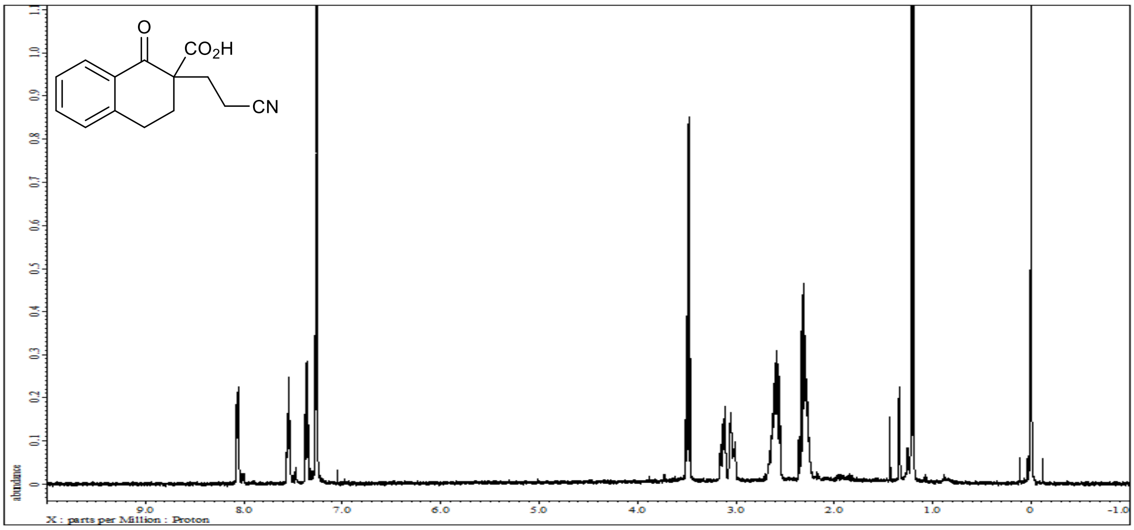
^{1}H NMR spectrum (**18d**)



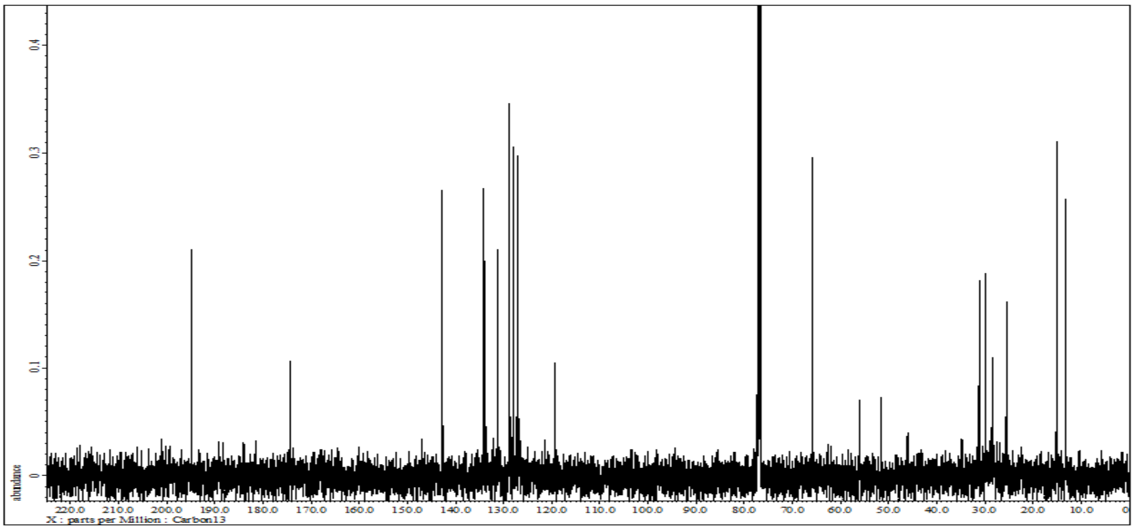
^{13}C NMR spectrum (**18d**)



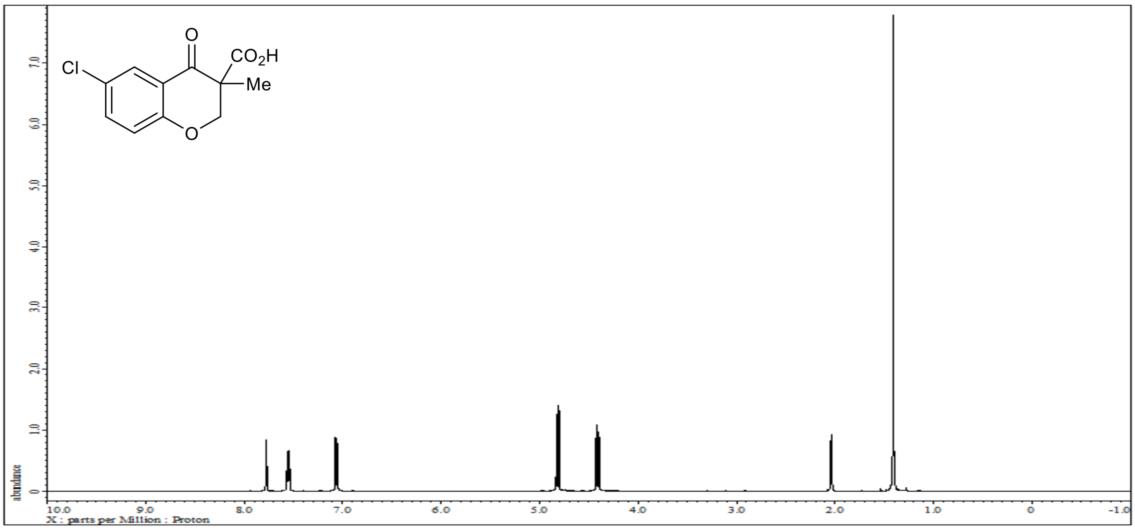
^{1}H NMR spectrum (**18e**)



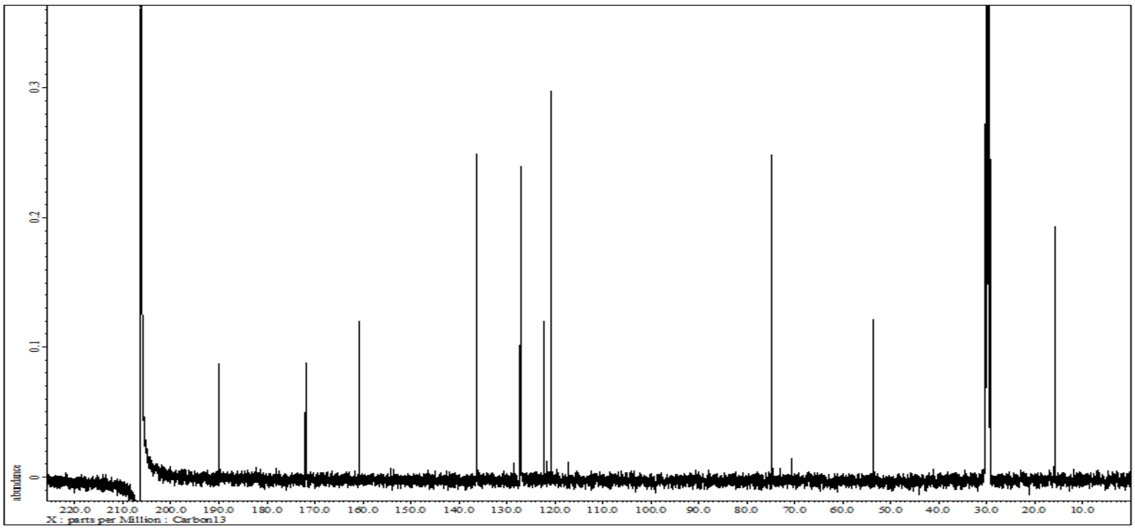
^{13}C NMR spectrum (**18e**)



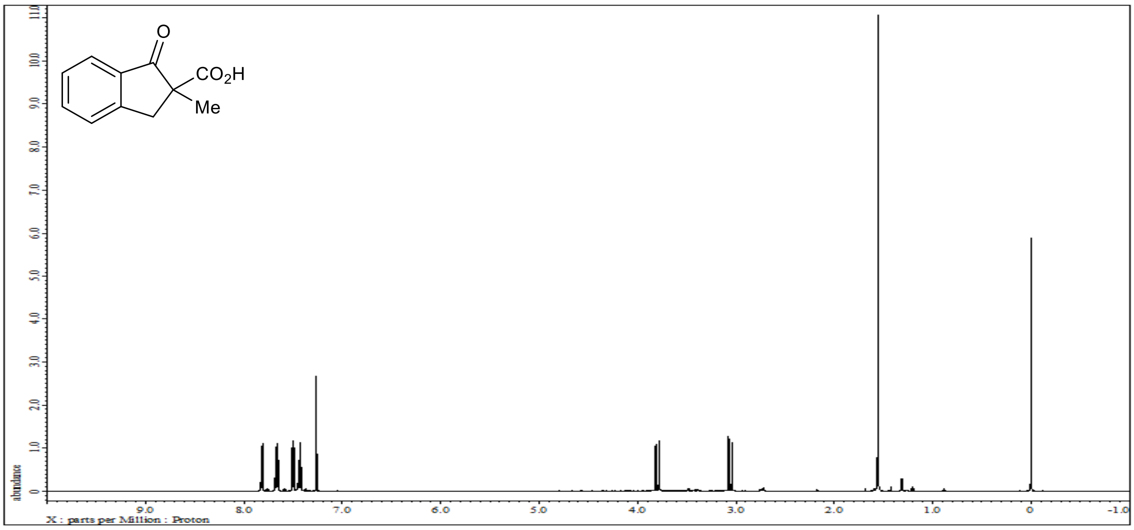
^{1}H NMR spectrum (**18f**)



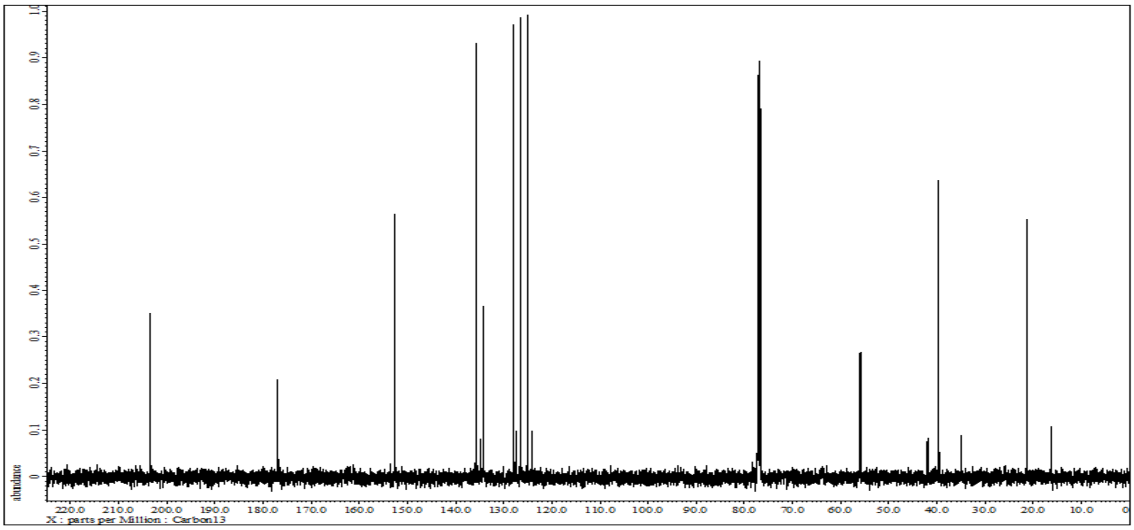
^{13}C NMR spectrum (**18f**)



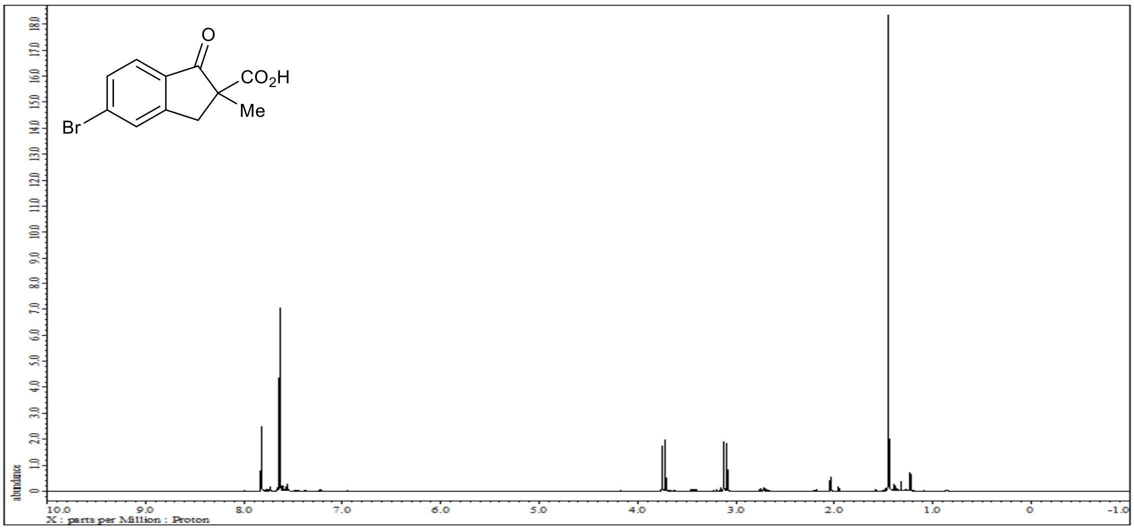
^{1}H NMR spectrum (**18g**)



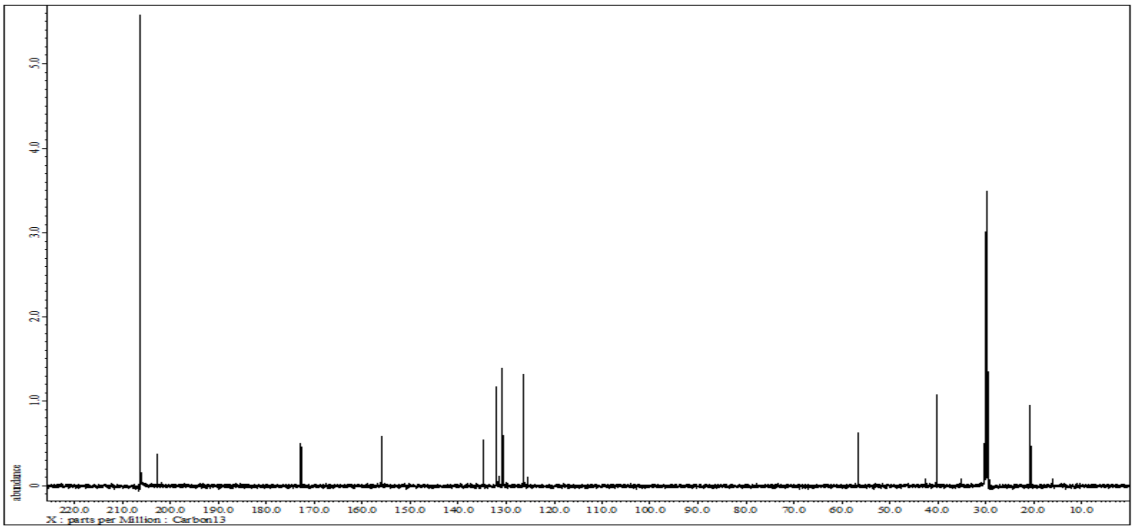
^{13}C NMR spectrum (**18g**)



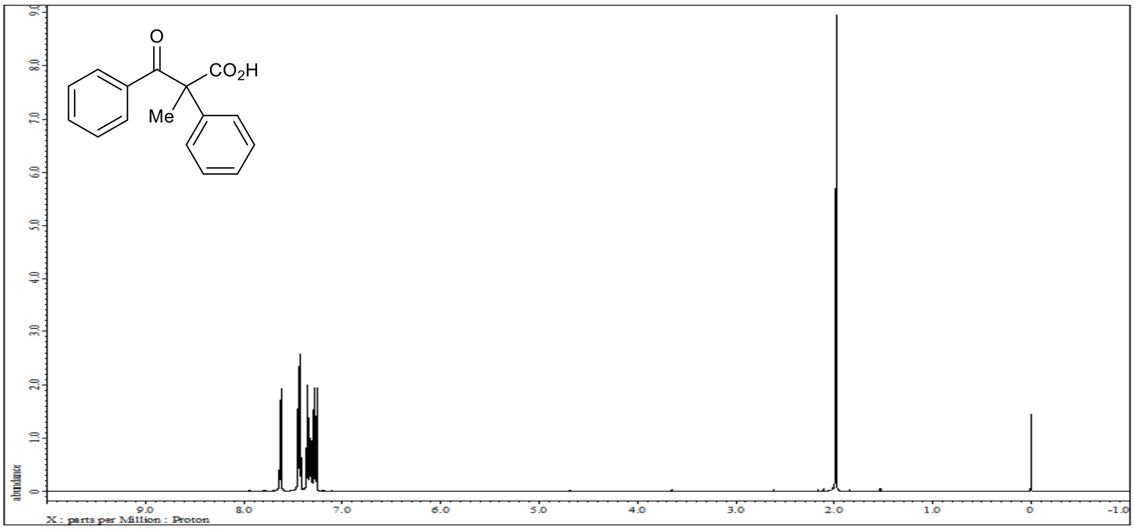
^{1}H NMR spectrum (**18h**)



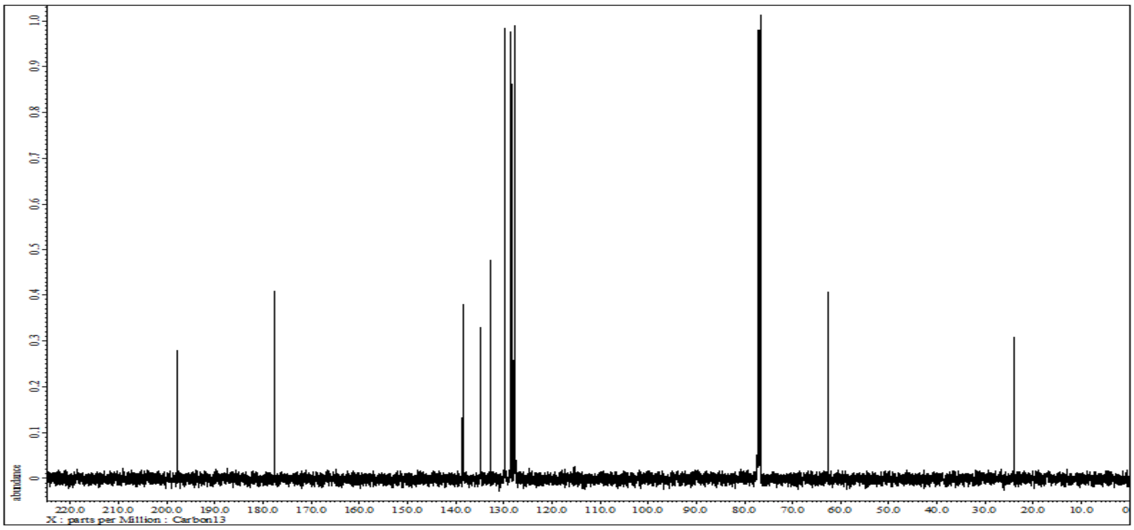
^{13}C NMR spectrum (**18h**)



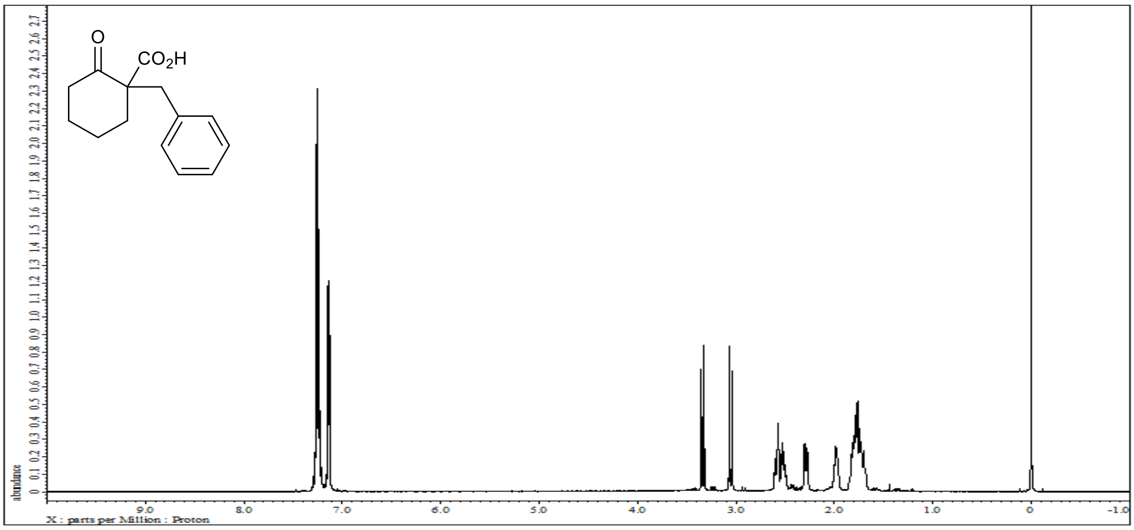
^{1}H NMR spectrum (**18i**)



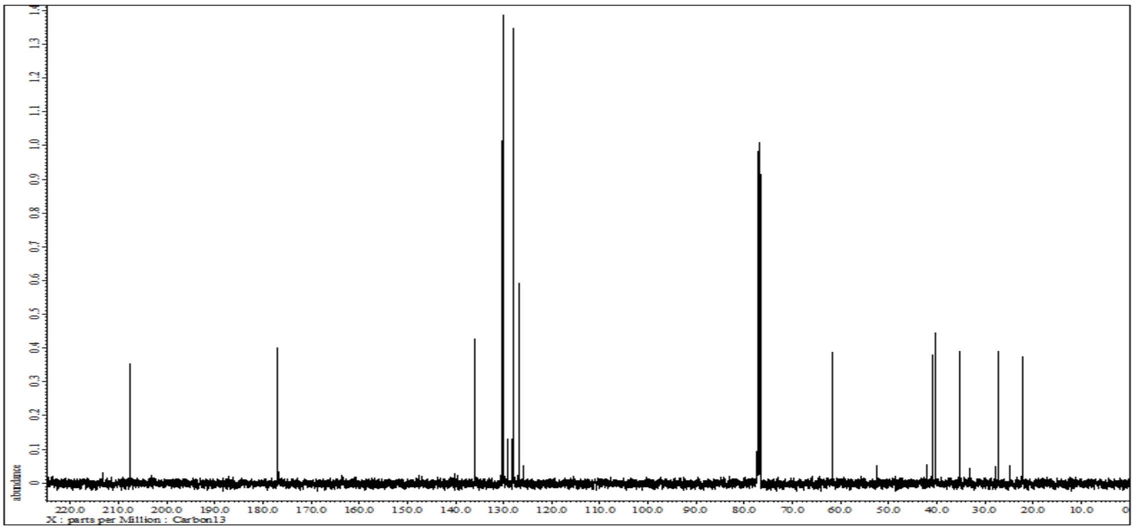
^{13}C NMR spectrum (**18i**)



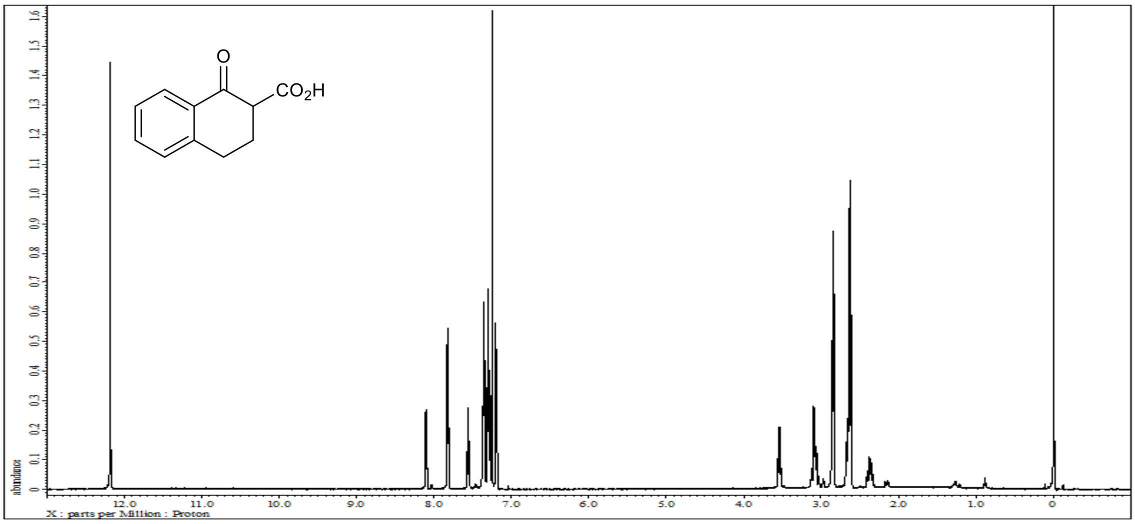
^{1}H NMR spectrum (**18j**)



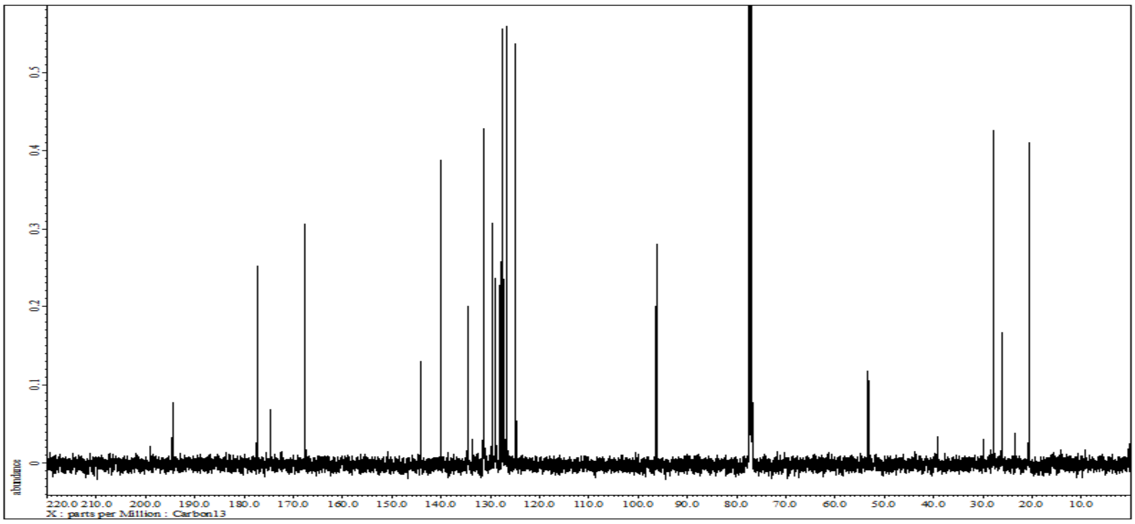
^{13}C NMR spectrum (**18j**)



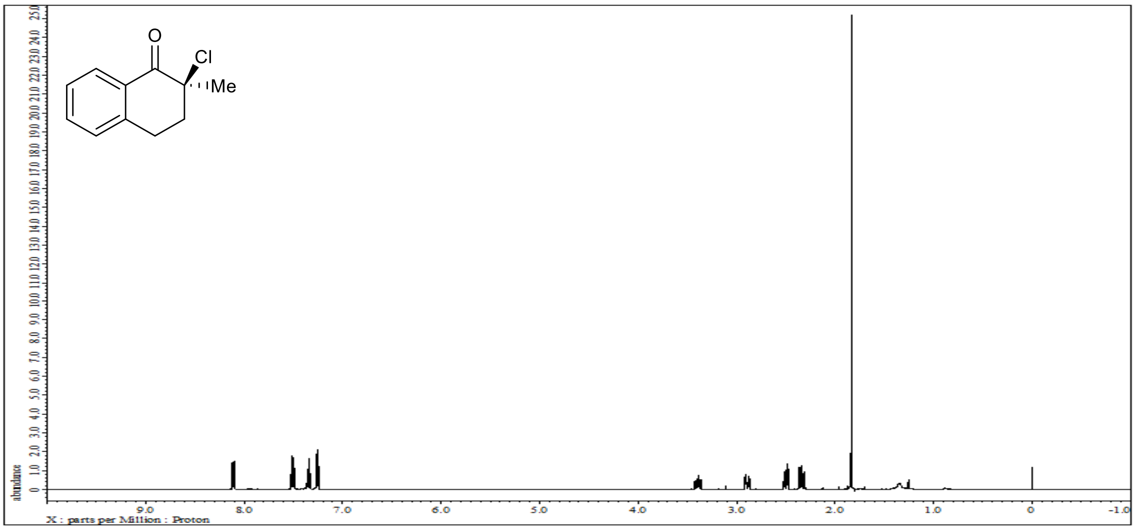
^{1}H NMR spectrum (**18s**)



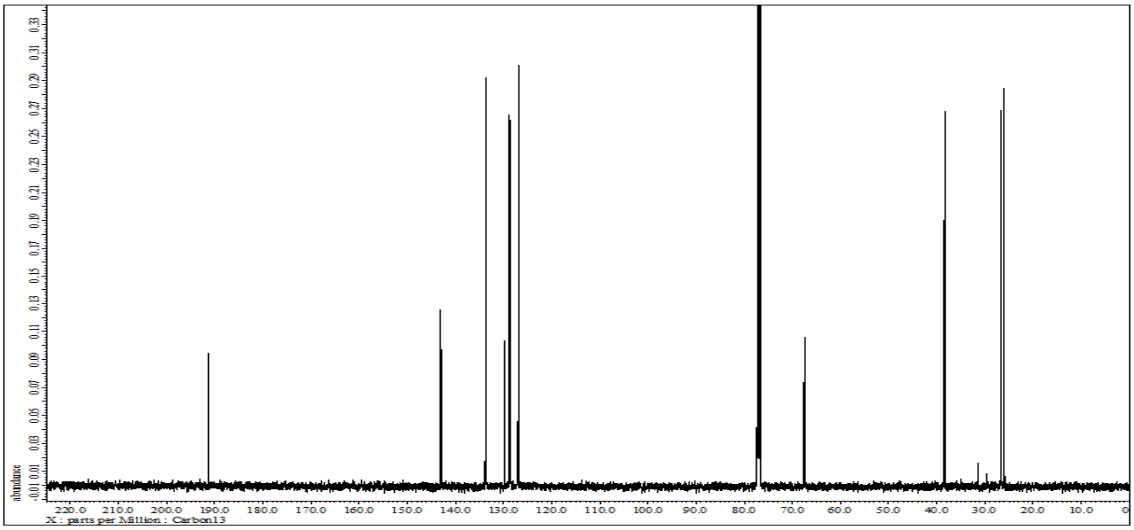
^{13}C NMR spectrum (**18s**)



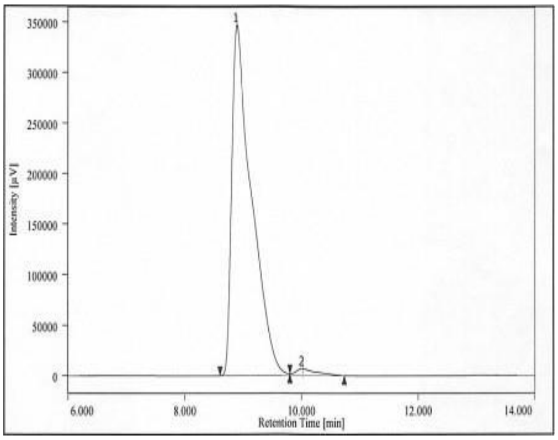
^{1}H NMR spectrum (**19a**)



^{13}C NMR spectrum (**19a**)

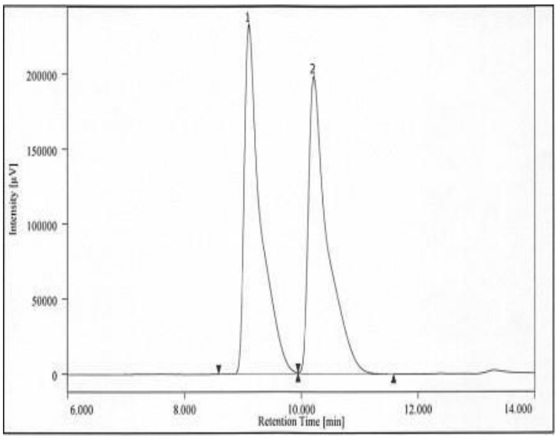


HPLC optically active (**19a**)



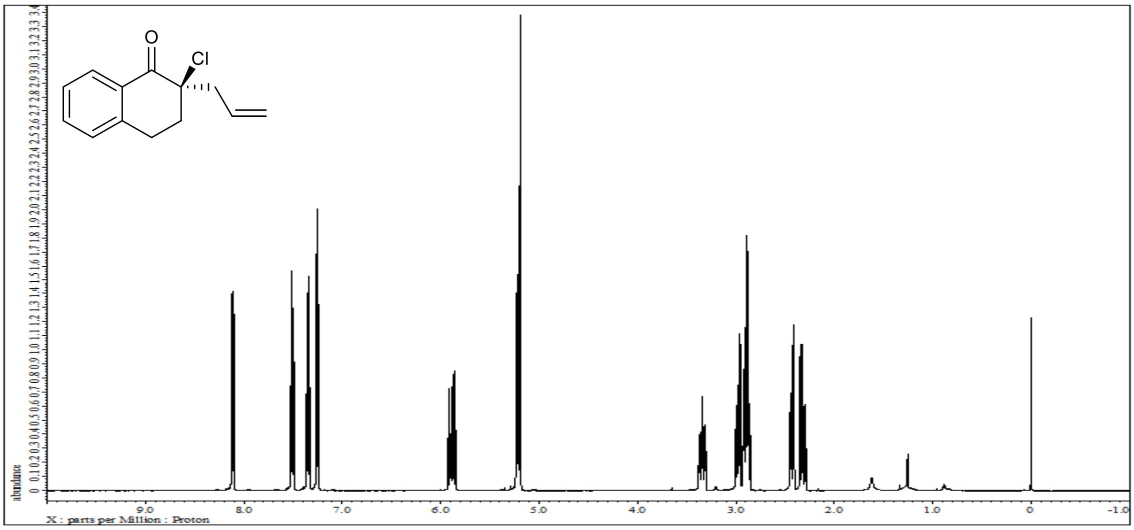
Peak	Retention Time [min]	Area [%]
1	8.9	98.001
2	10.0	1.999

HPLC racemic (**19a**)

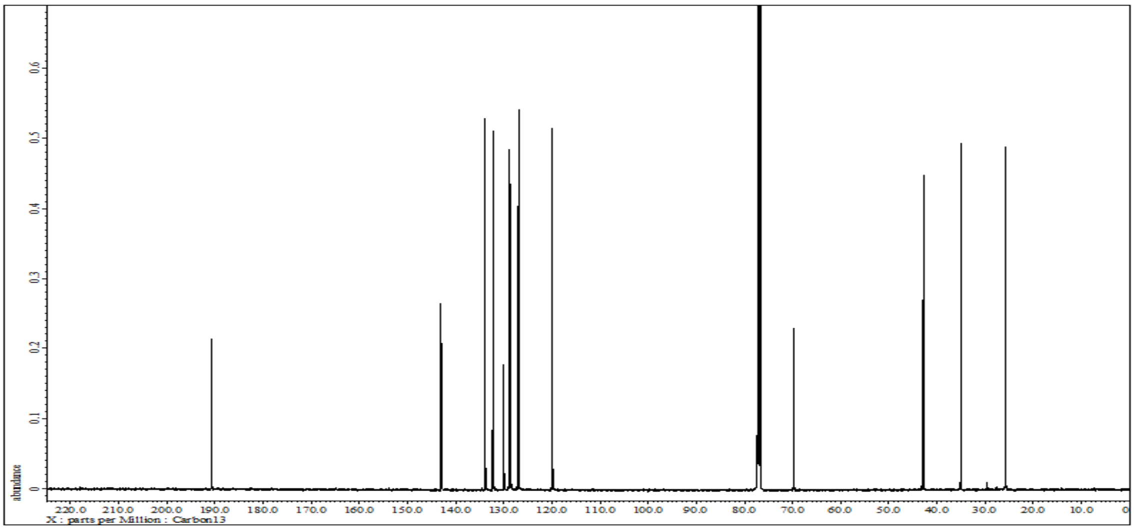


Peak	Retention Time [min]	Area [%]
1	9.1	50.214
2	10.2	49.786

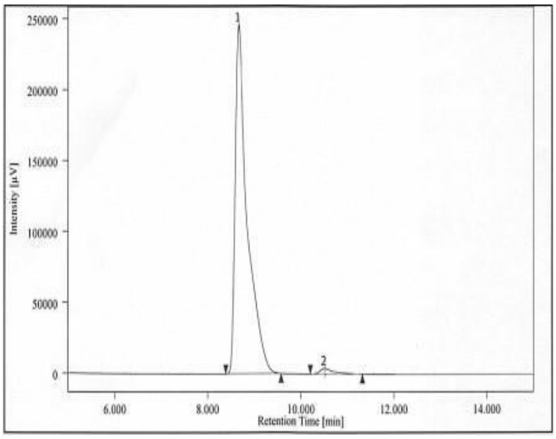
^{1}H NMR spectrum (**19b**)



^{13}C NMR spectrum (**19b**)

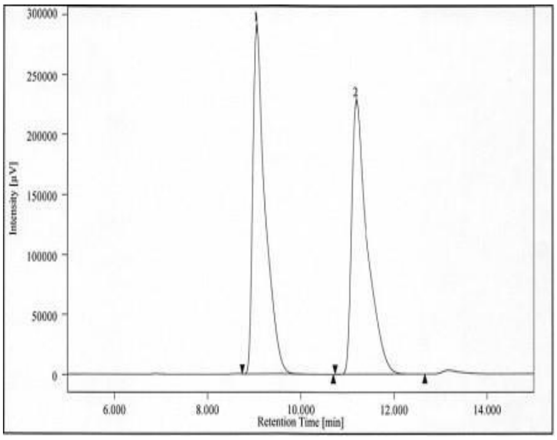


HPLC optically active (**19b**)



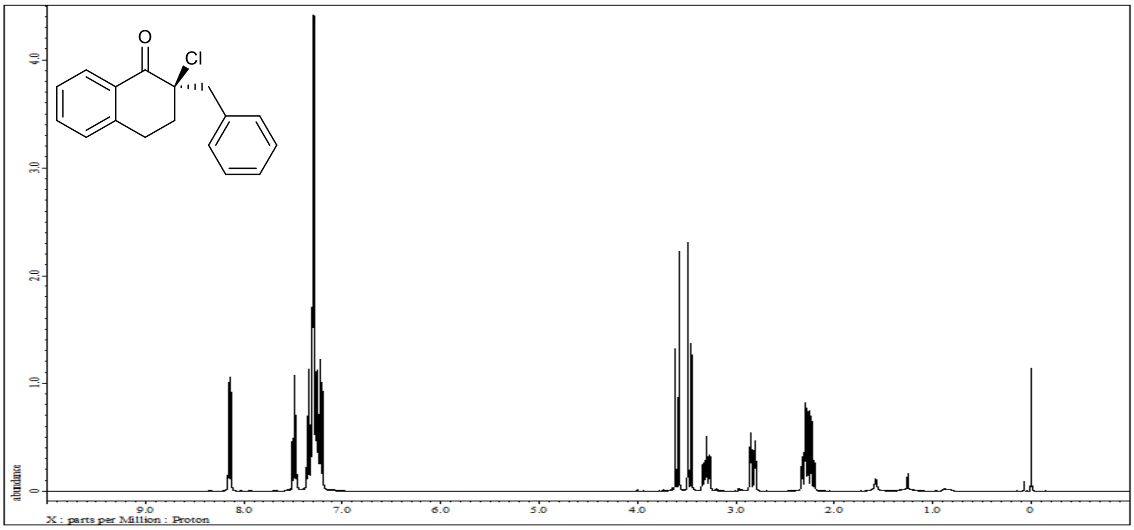
Peak	Retention Time [min]	Area [%]
1	8.7	98.122
2	10.5	1.878

HPLC racemic (**19b**)

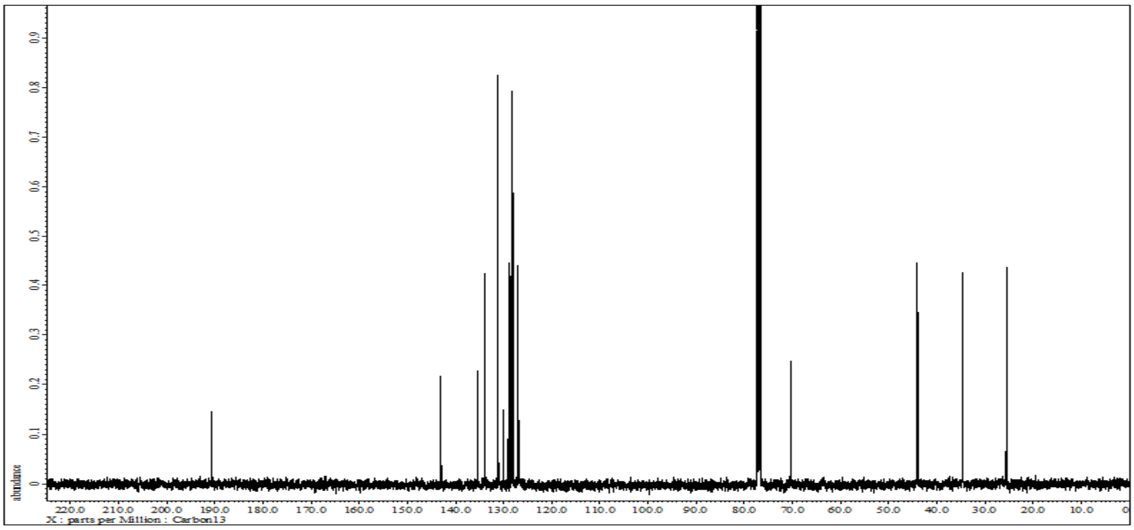


Peak	Retention Time [min]	Area [%]
1	9.1	49.934
2	11.2	50.066

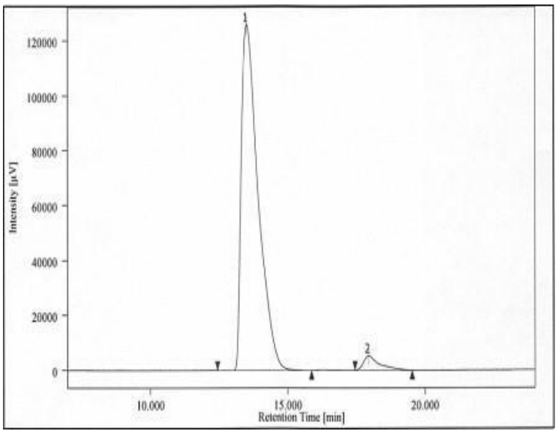
^{13}HC NMR spectrum (**19c**)



^{13}HC NMR spectrum (**19c**)

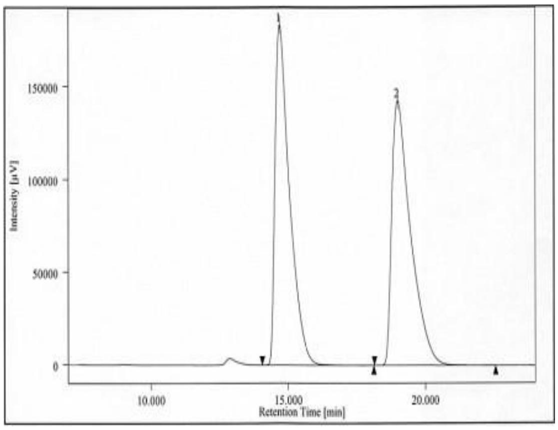


HPLC optically active (**19c**)



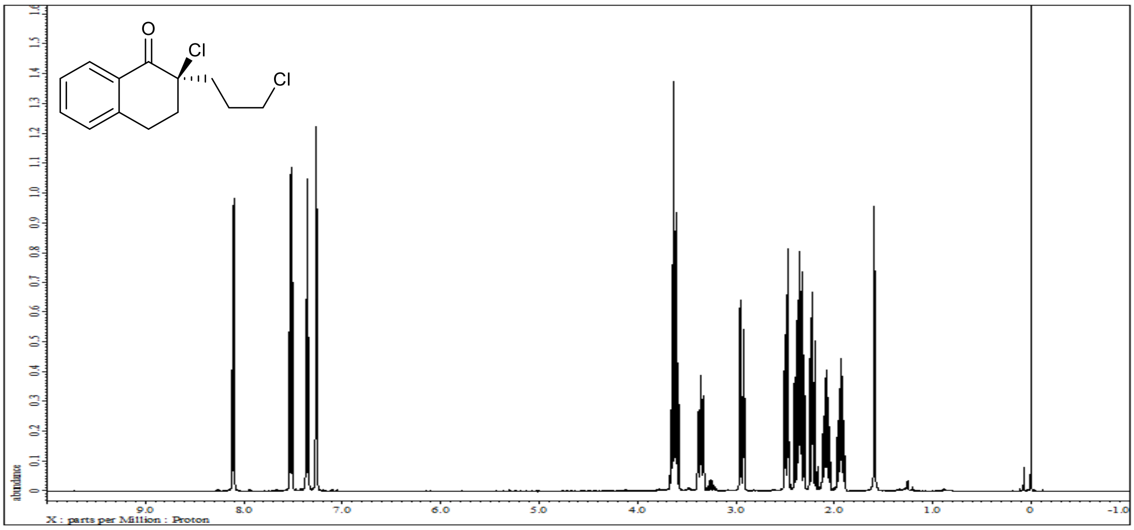
Peak	Retention Time [min]	Area [%]
1	13.5	96.295
2	17.9	3.705

HPLC racemic (**19c**)

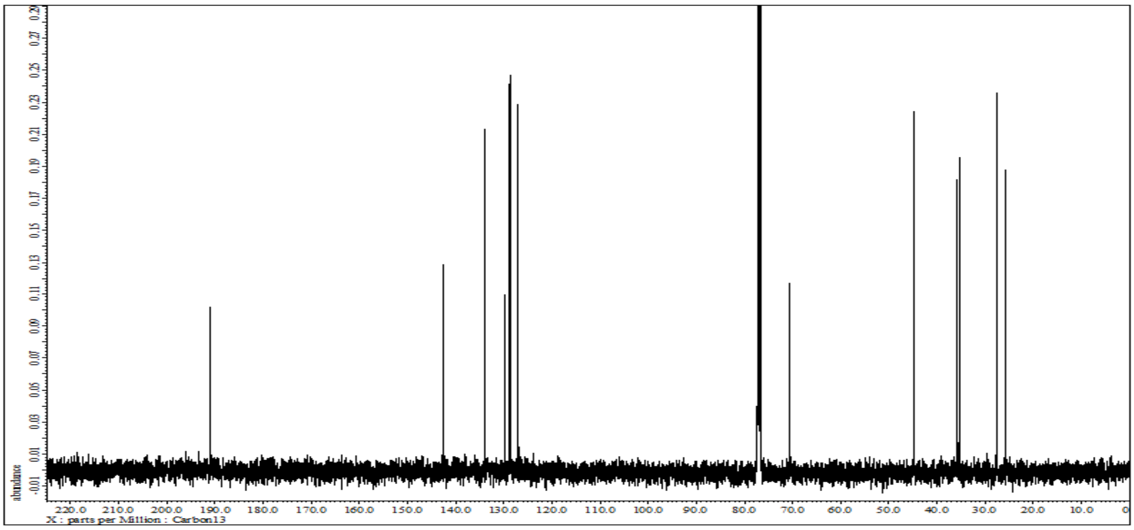


Peak	Retention Time [min]	Area [%]
1	14.7	49.998
2	19.0	50.002

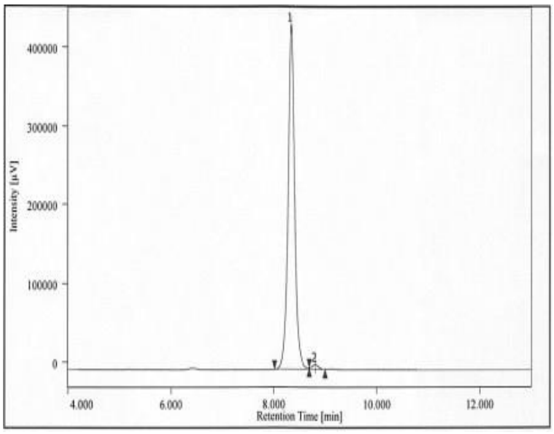
^{1}H NMR spectrum (**19d**)

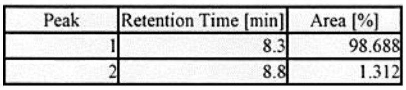


^{13}C NMR spectrum (**19d**)



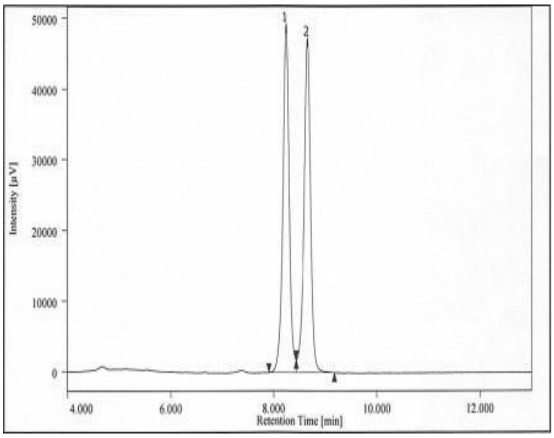
HPLC optically active (**19d**)

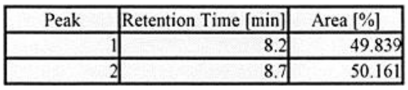




Peak	Retention Time [min]	Area [%]
1	8.3	98.688
2	8.8	1.312

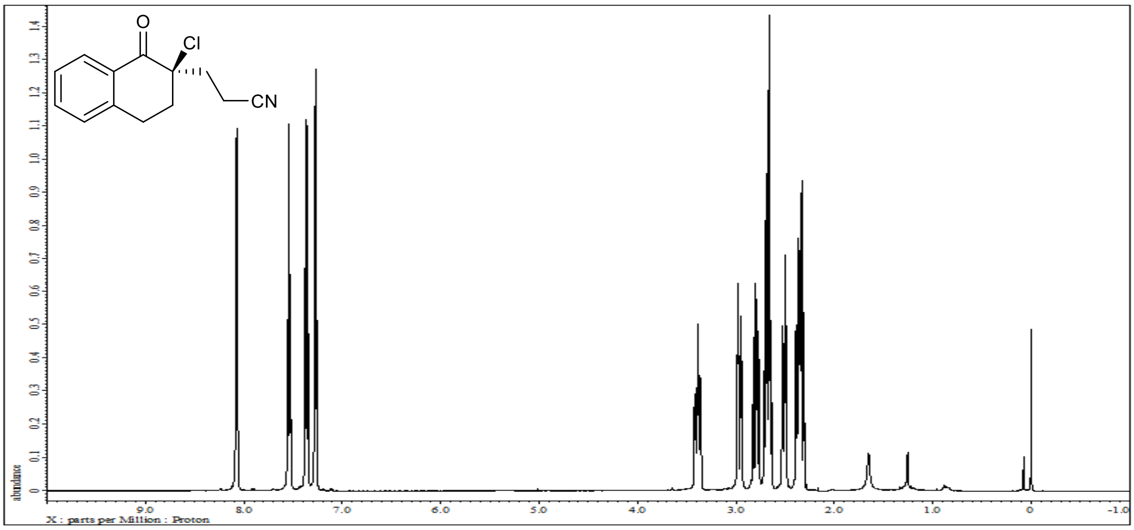
HPLC racemic (**19d**)



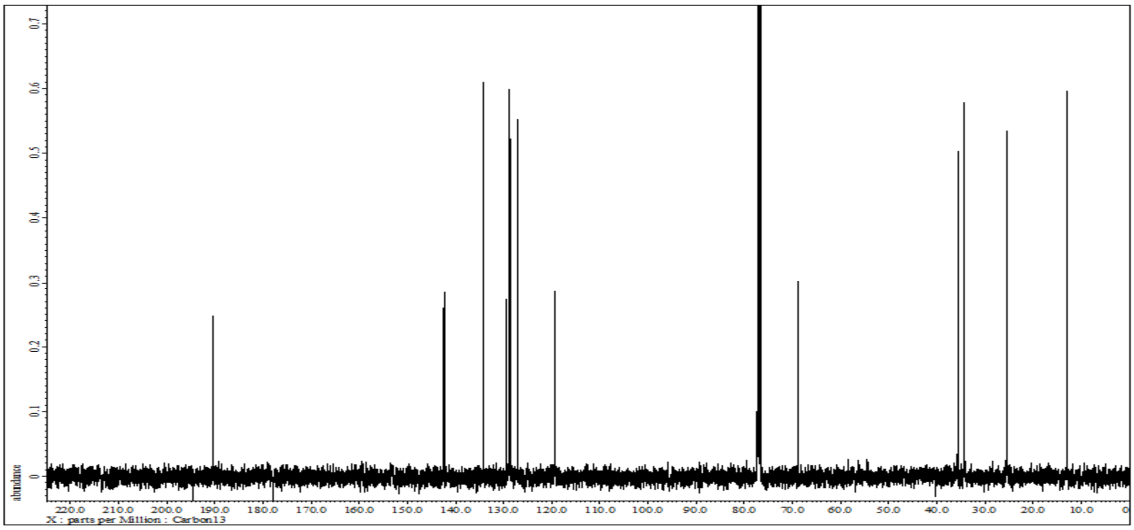


Peak	Retention Time [min]	Area [%]
1	8.2	49.839
2	8.7	50.161

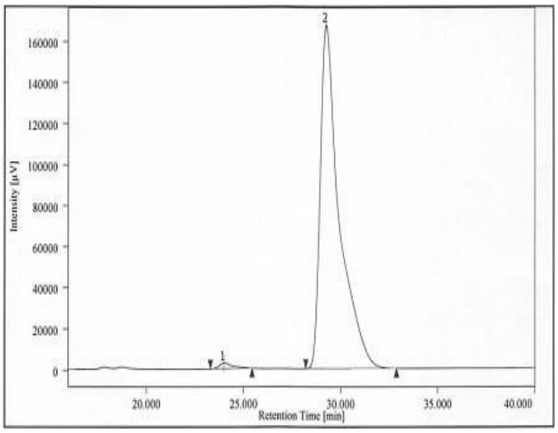
^{1}H NMR spectrum (**19e**)



^{13}C NMR spectrum (**19e**)

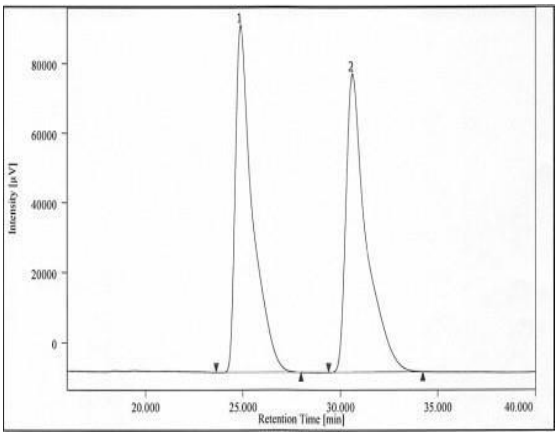


HPLC optically active (**19e**)



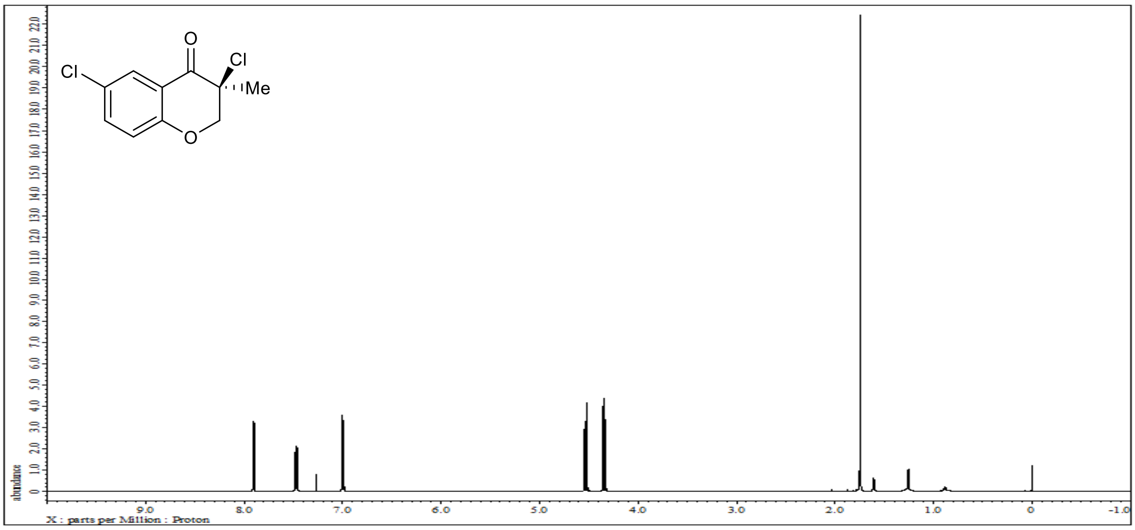
Peak	Retention Time [min]	Area [%]
1	24.0	1.179
2	29.3	98.821

HPLC racemic (**19e**)

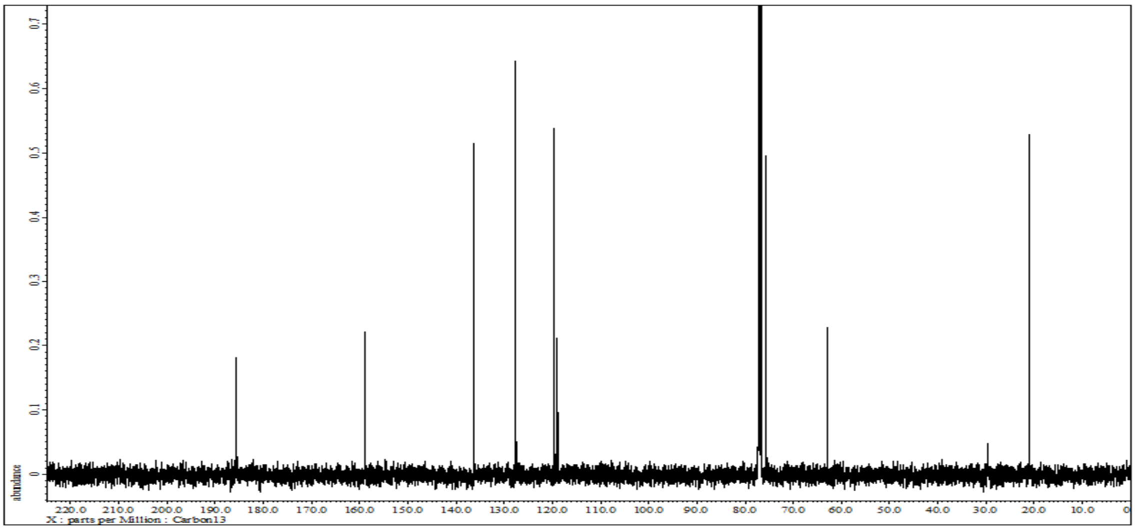


Peak	Retention Time [min]	Area [%]
1	24.9	49.892
2	30.6	50.108

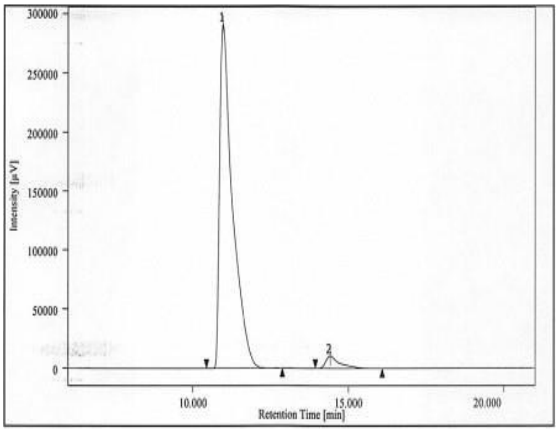
^{1}H NMR spectrum (**19f**)



^{13}C NMR spectrum (**19f**)

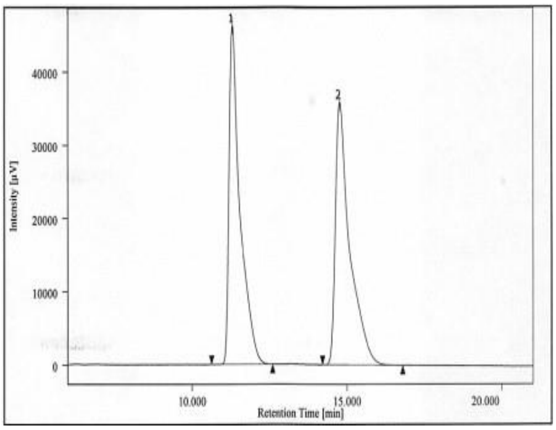


HPLC optically active (**19f**)



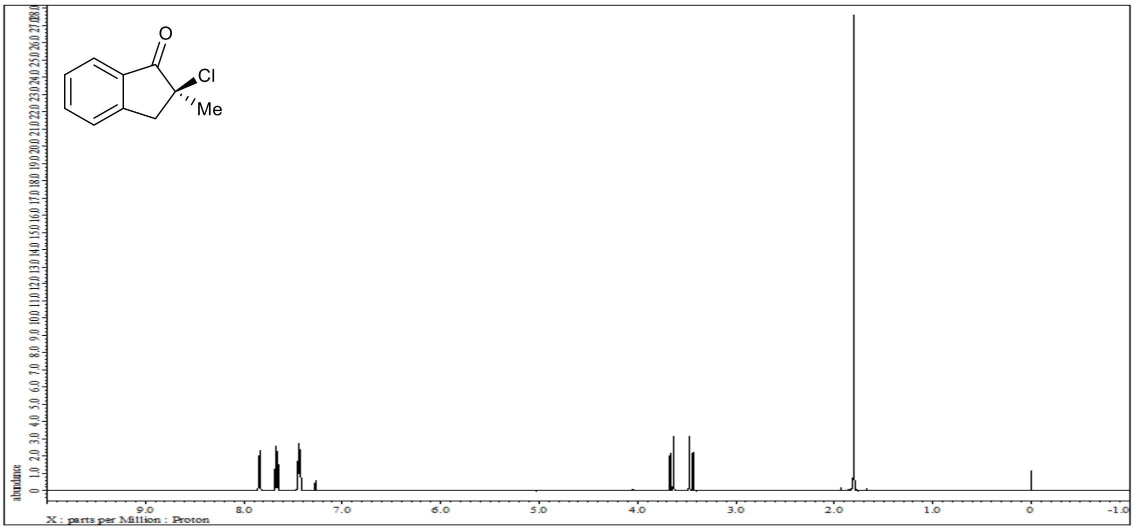
Peak	Retention Time [min]	Area [%]
1	11.0	96.249
2	14.4	3.751

HPLC racemic (**19f**)

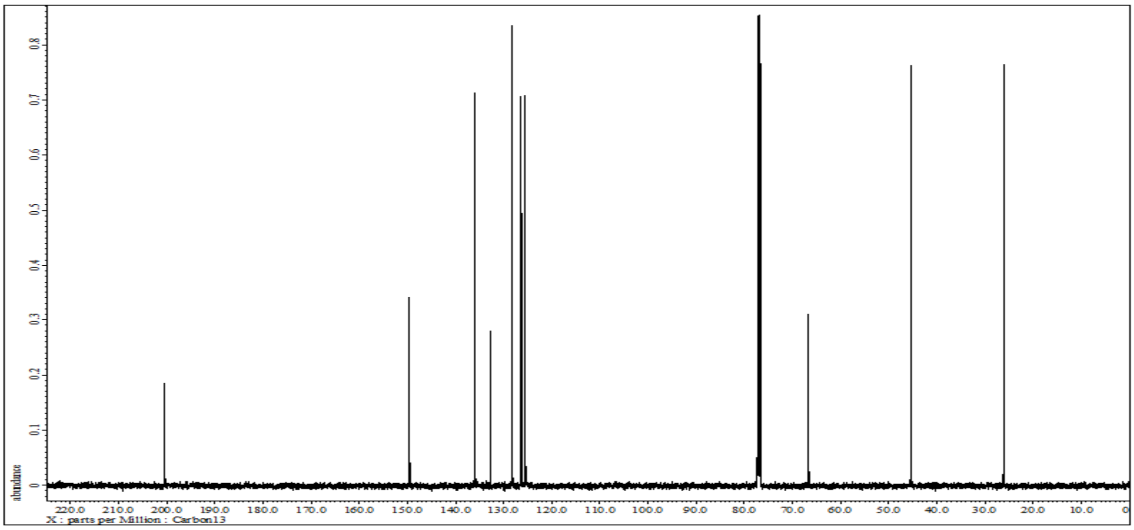


Peak	Retention Time [min]	Area [%]
1	11.3	49.965
2	14.8	50.035

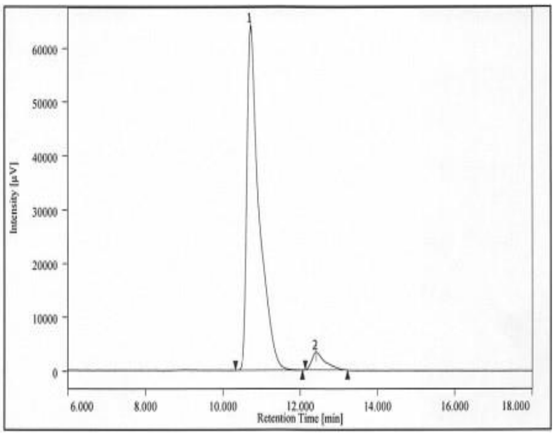
^{13}HC NMR spectrum (**19g**)



^{13}HC NMR spectrum (**19g**)

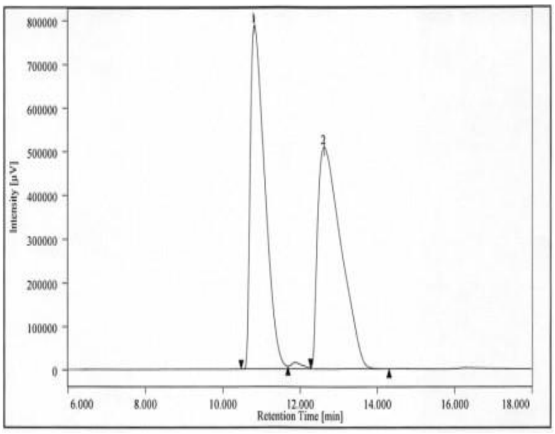


HPLC optically active (**19g**)



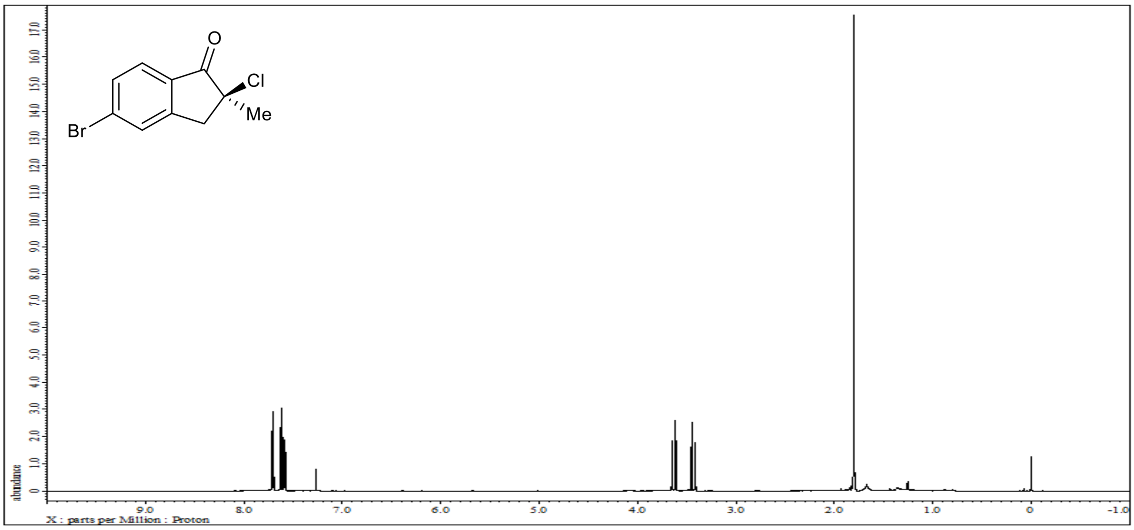
Peak	Retention Time [min]	Area [%]
1	10.7	94.823
2	12.4	5.177

HPLC racemic (**19g**)

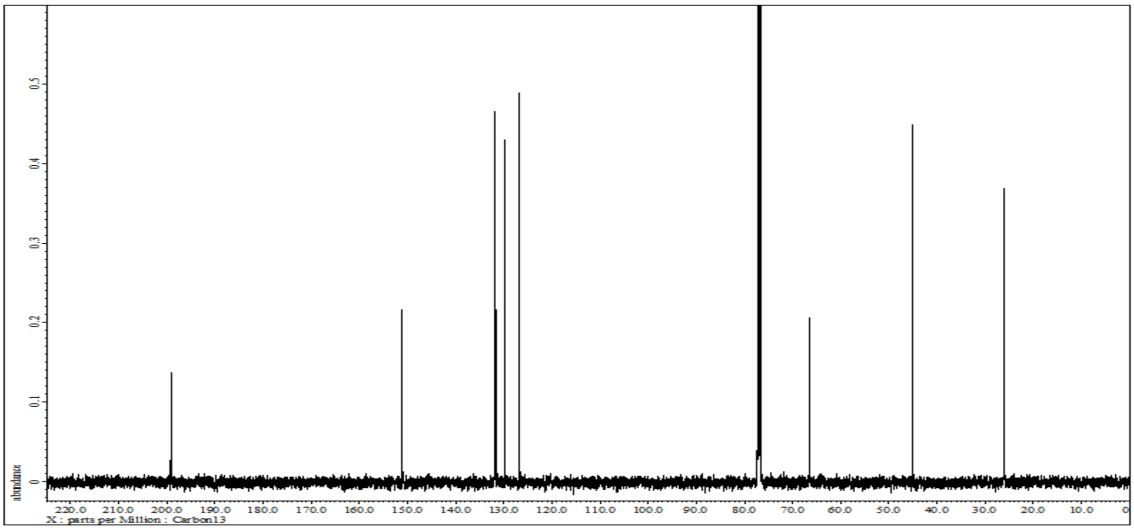


Peak	Retention Time [min]	Area [%]
1	10.8	48.964
2	12.6	51.036

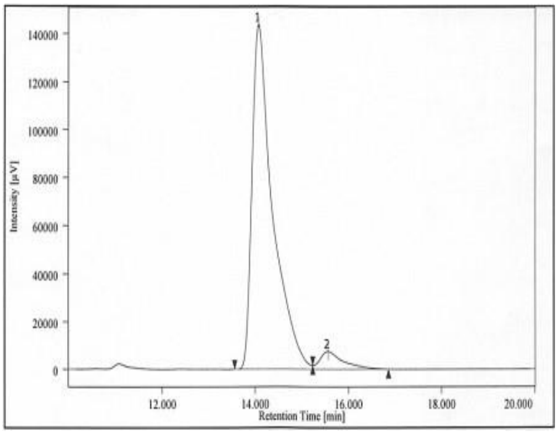
^{13}HC NMR spectrum (**19h**)



^{13}HC NMR spectrum (**19h**)

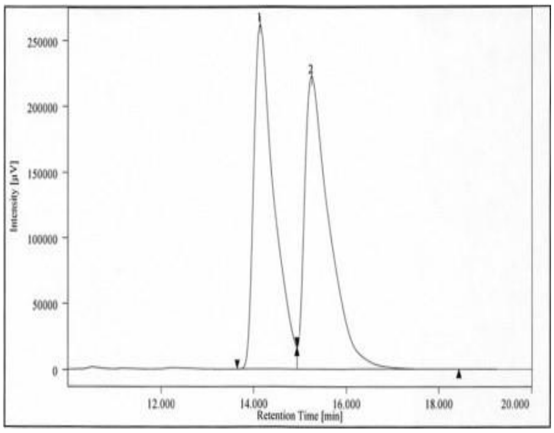


HPLC optically active (**19h**)



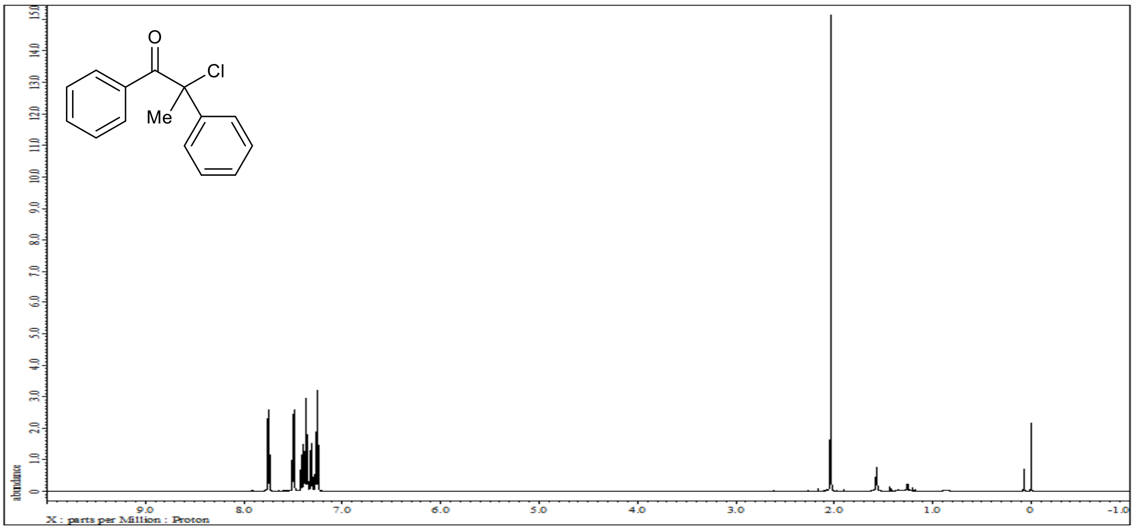
Peak	Retention Time [min]	Area [%]
1	14.1	94.527
2	15.6	5.473

HPLC racemic (**19h**)

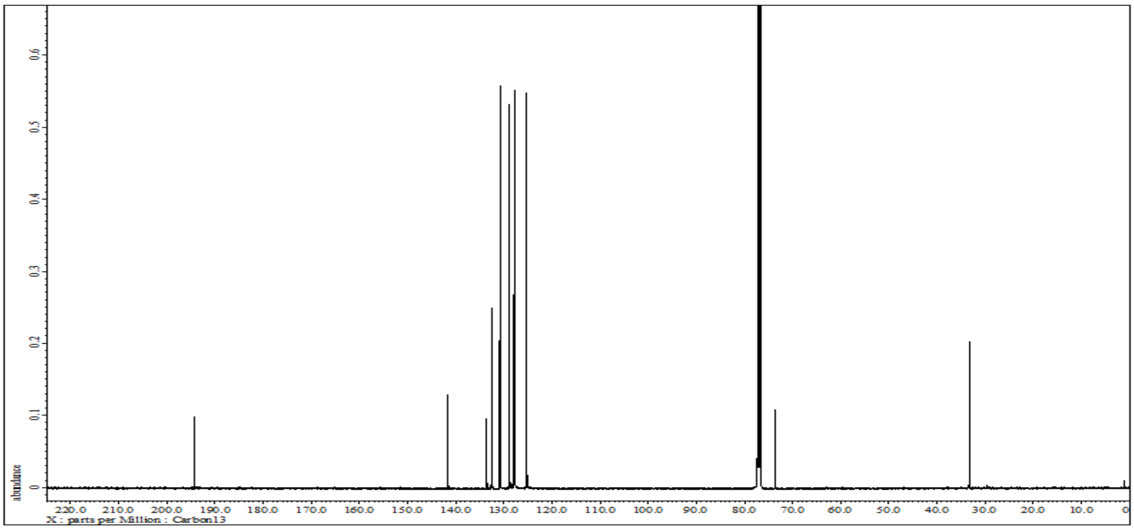


Peak	Retention Time [min]	Area [%]
1	14.1	48.816
2	15.3	51.184

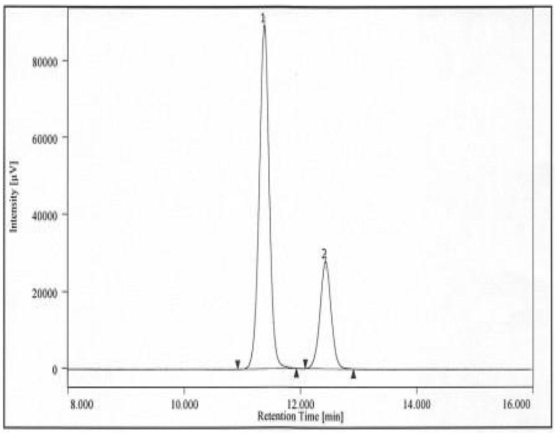
^{13}HC NMR spectrum (**19i**)



^{13}HC NMR spectrum (**19i**)

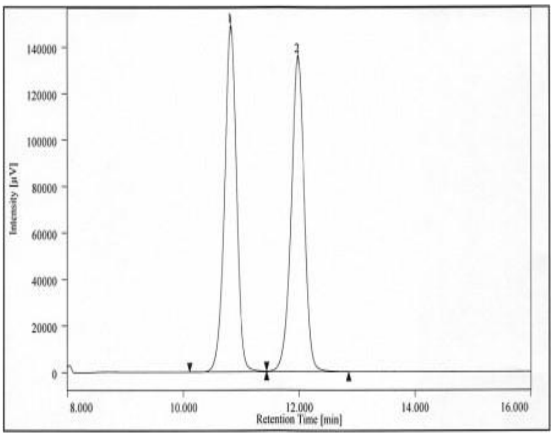


HPLC optically active (**19i**)



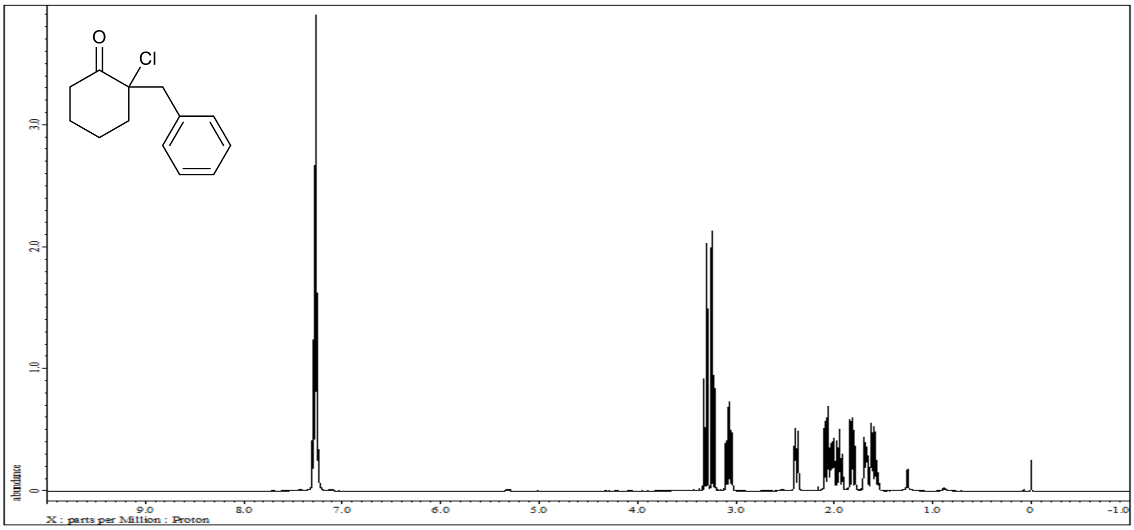
Peak	Retention Time [min]	Area [%]
1	11.4	74.189
2	12.4	25.811

HPLC racemic (**19i**)

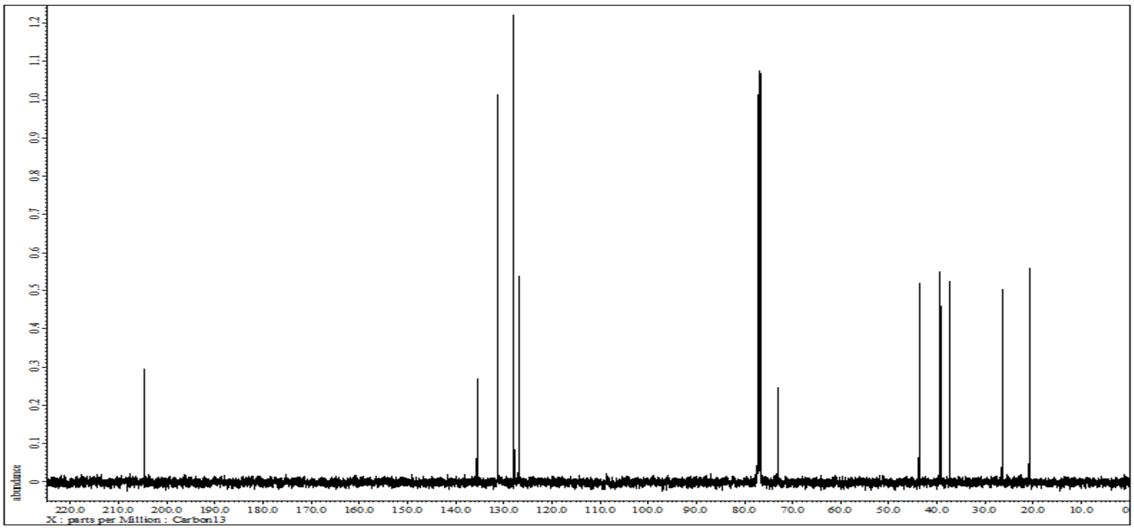


Peak	Retention Time [min]	Area [%]
1	10.8	50.015
2	12.0	49.985

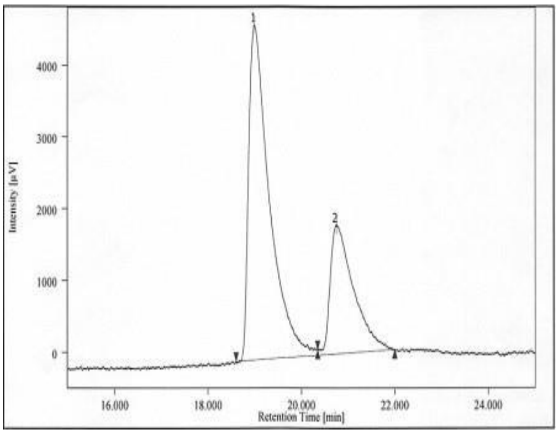
^{1}H NMR spectrum (**19j**)



^{13}C NMR spectrum (**19j**)

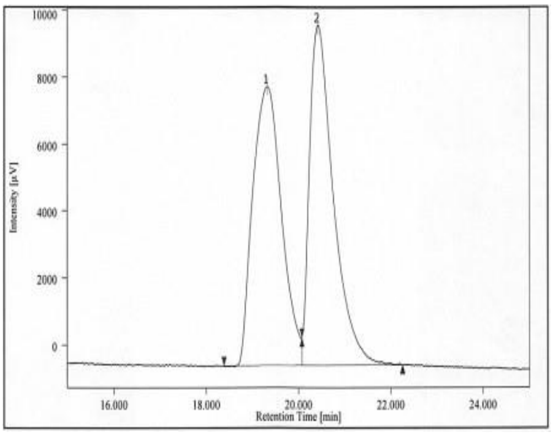


HPLC optically active (**19j**)



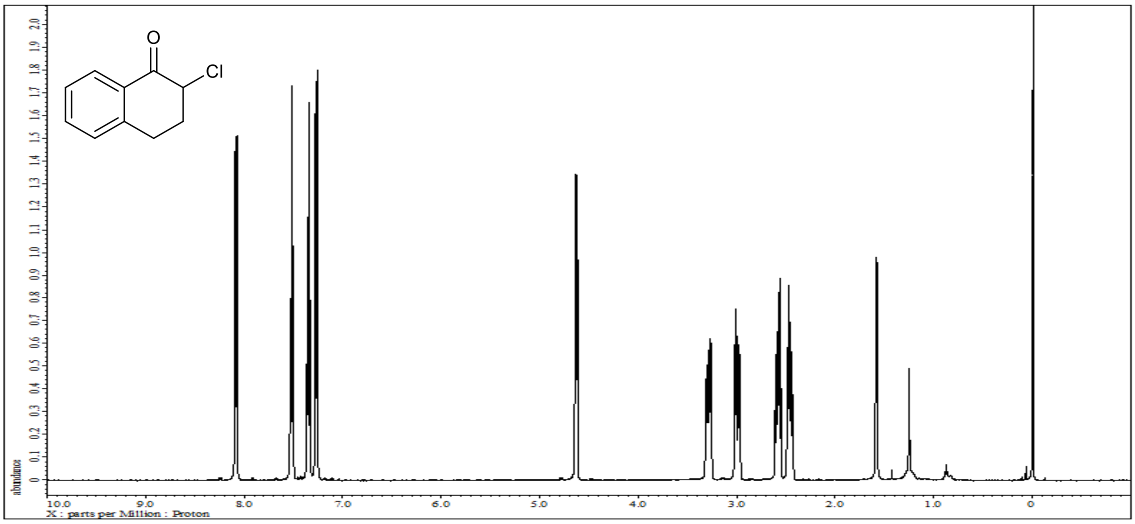
Peak	Retention Time [min]	Area [%]
1	19.0	69.793
2	20.7	30.207

HPLC racemic (**19j**)

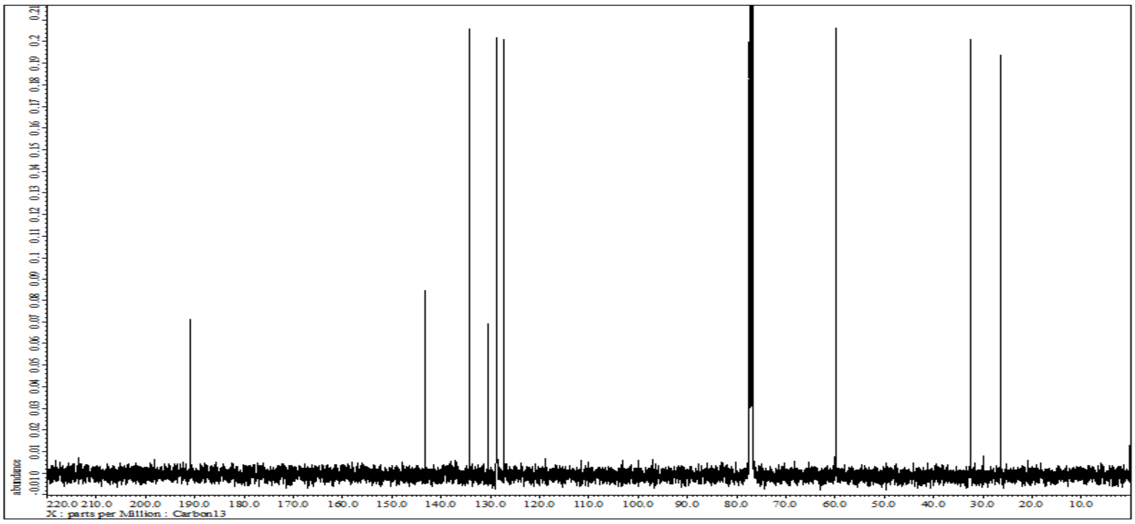


Peak	Retention Time [min]	Area [%]
1	19.3	49.575
2	20.4	50.425

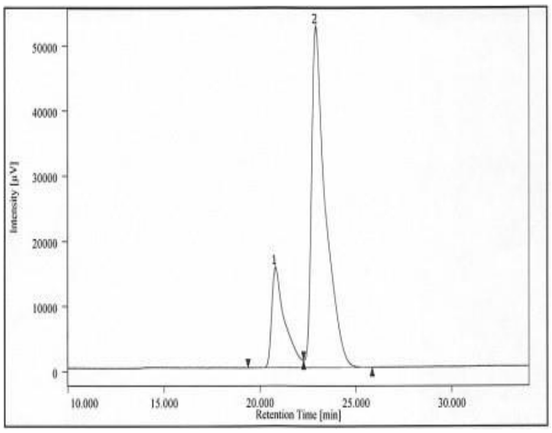
^{1}H NMR spectrum (**19s**)



^{13}C NMR spectrum (**19s**)

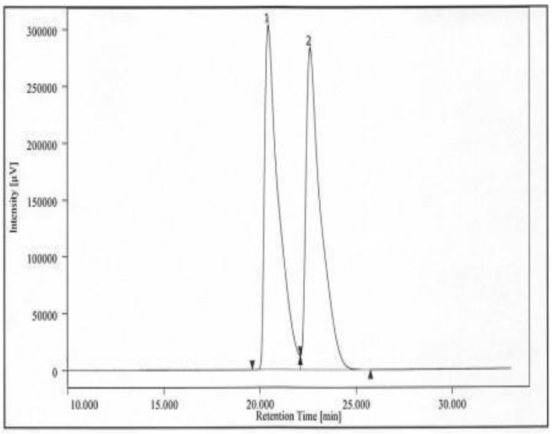


HPLC optically active (**19s**)



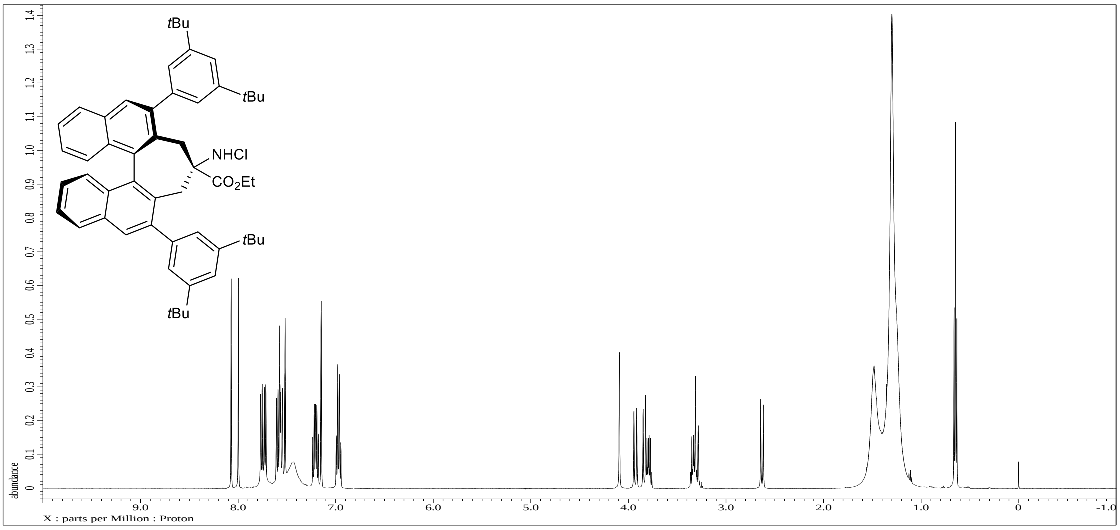
Peak	Retention Time [min]	Area [%]
1	20.8	21.666
2	22.9	78.334

HPLC racemic (**19s**)

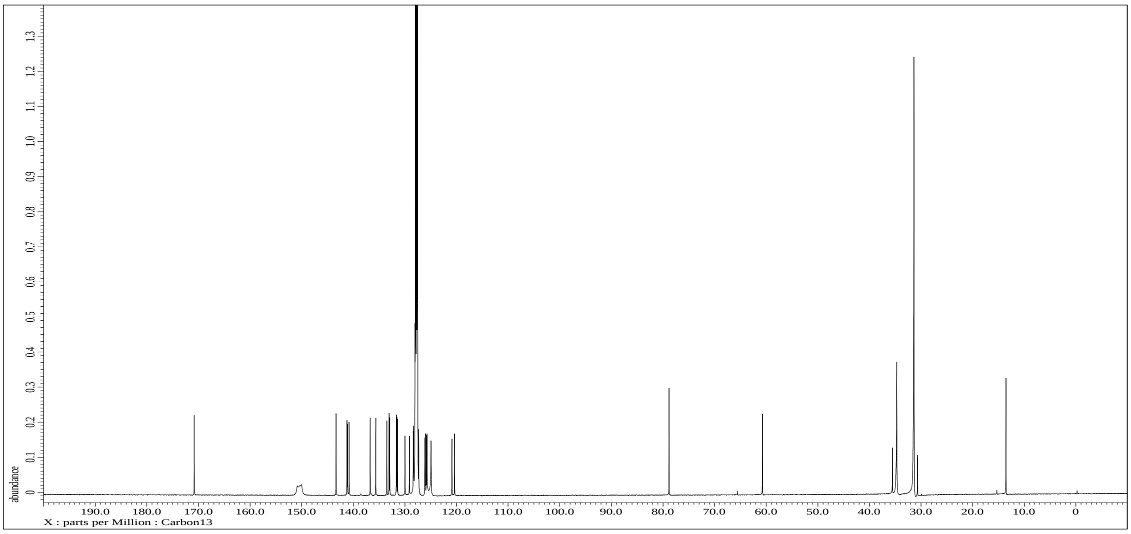


Peak	Retention Time [min]	Area [%]
1	20.4	50.059
2	22.6	49.941

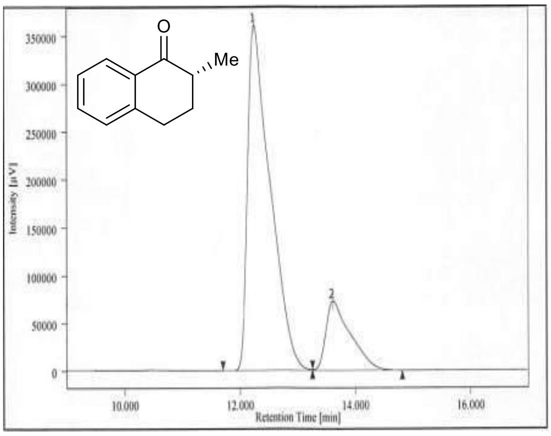
^{1}H NMR spectrum (**C1'**)



^{13}C NMR spectrum (**C1'**)

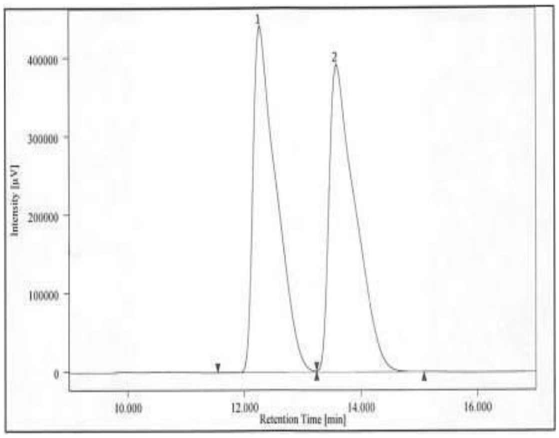


HPLC optically active (**23**)



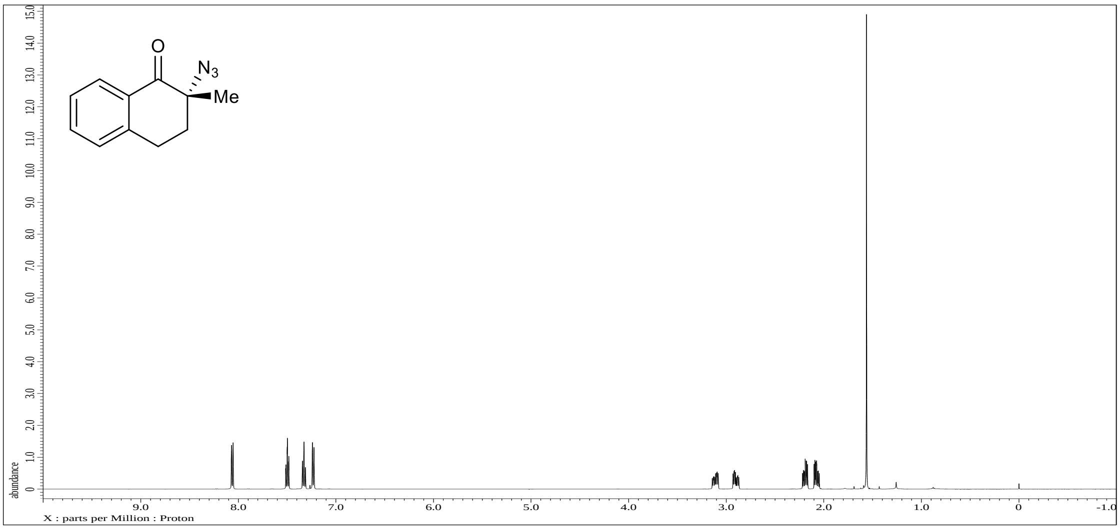
Peak	Retention Time [min]	Area [%]
1	12.3	82.130
2	13.6	17.870

HPLC racemic (**23**)

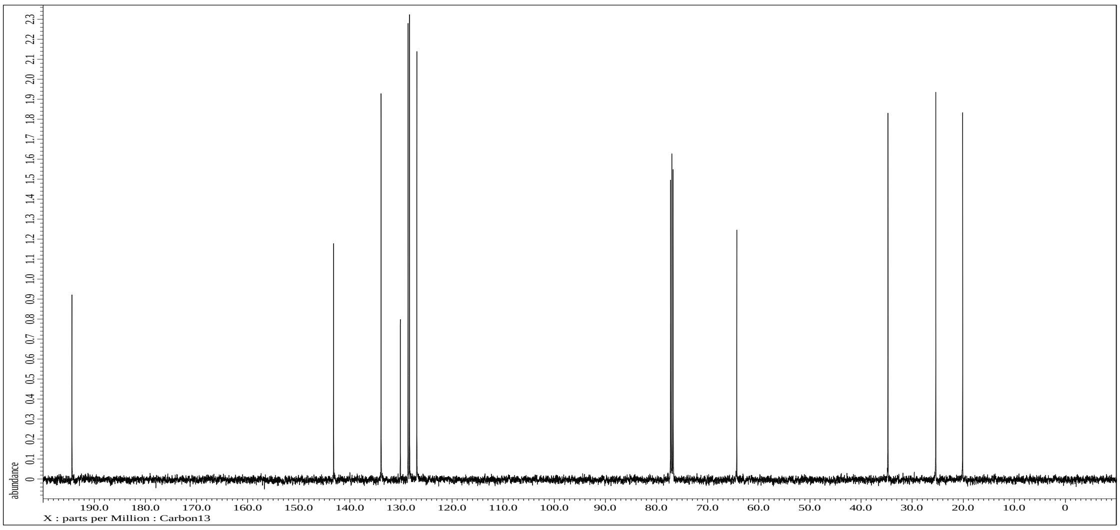


Peak	Retention Time [min]	Area [%]
1	12.3	49.888
2	13.6	50.112

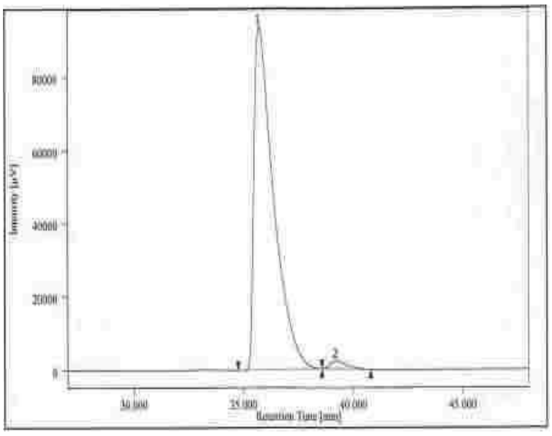
^{1}H NMR spectrum (**20**)



^{13}C NMR spectrum (**20**)

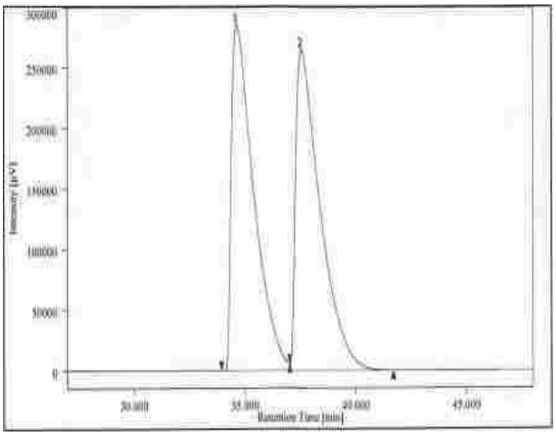


HPLC optically active (**20**)



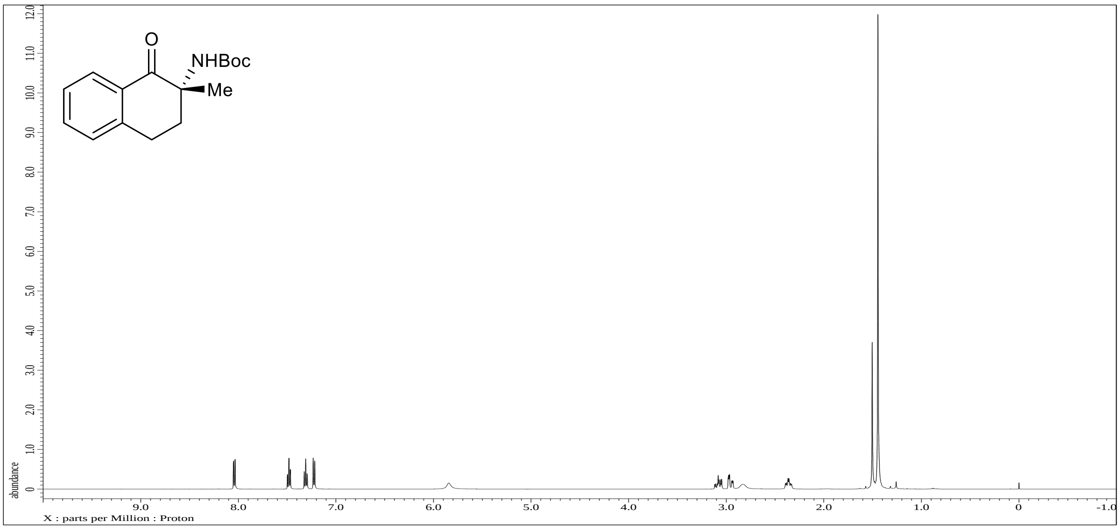
Peak	Retention Time [min]	Area [%]
1	35.7	98.028
2	39.2	1.972

HPLC racemic (**20**)

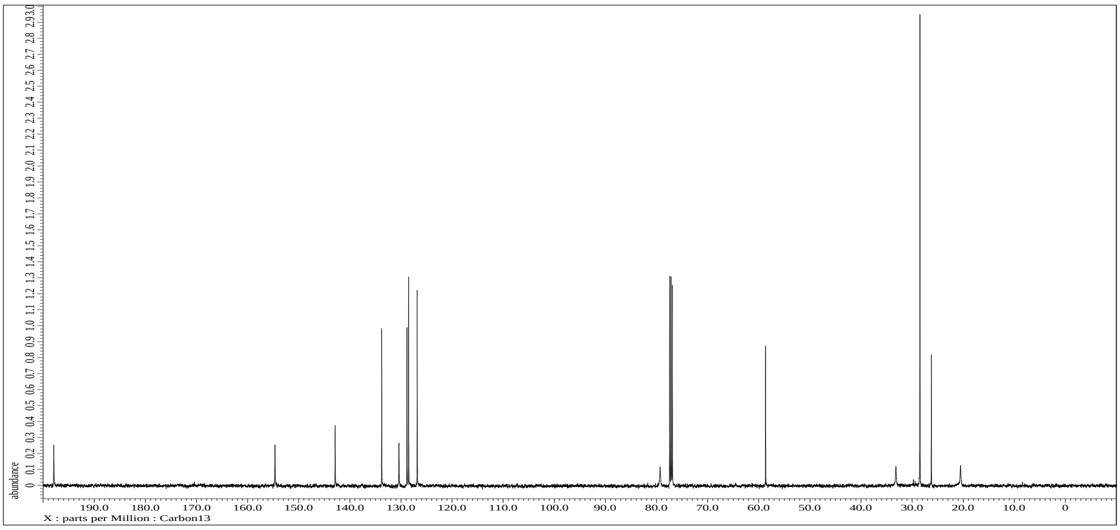


Peak	Retention Time [min]	Area [%]
1	34.6	49.740
2	37.5	50.260

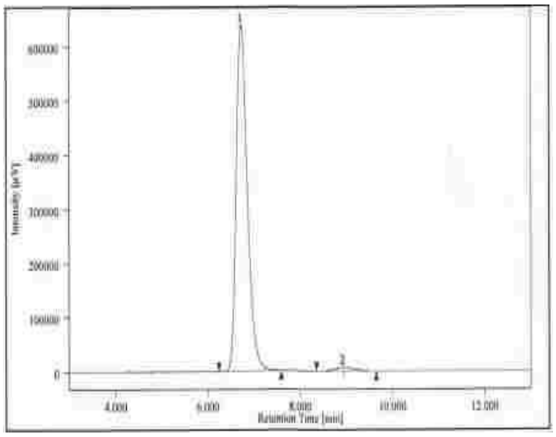
^{13}HC NMR spectrum (**21**)



^{13}HC NMR spectrum (**21**)

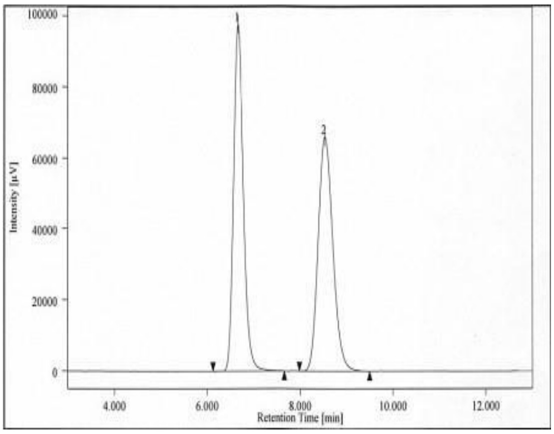


HPLC optically active (**21**)



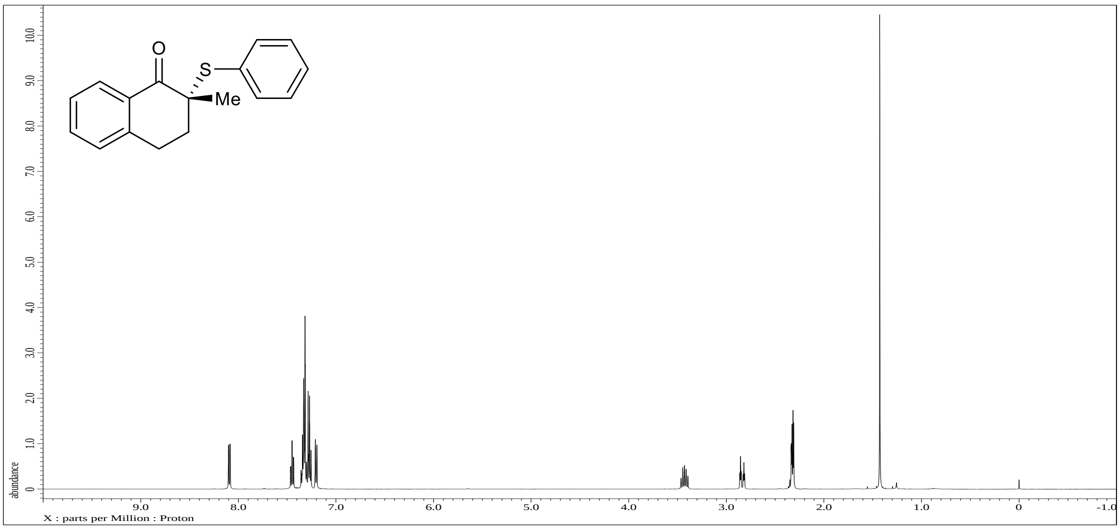
Peak	Retention Time [min]	Area [%]
1	6.7	98.195
2	8.9	1.805

HPLC racemic (**21**)

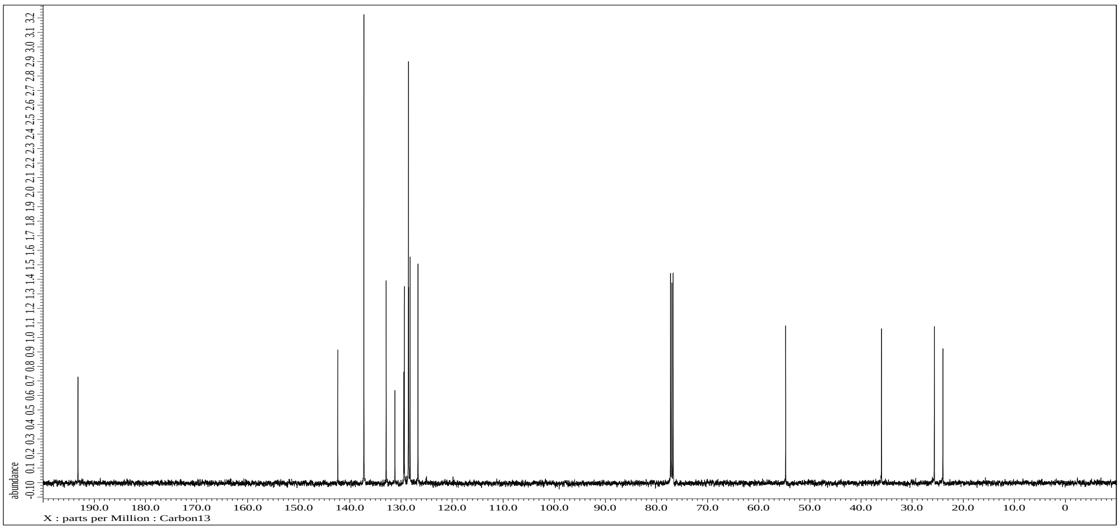


Peak	Retention Time [min]	Area [%]
1	6.7	50.089
2	8.5	49.911

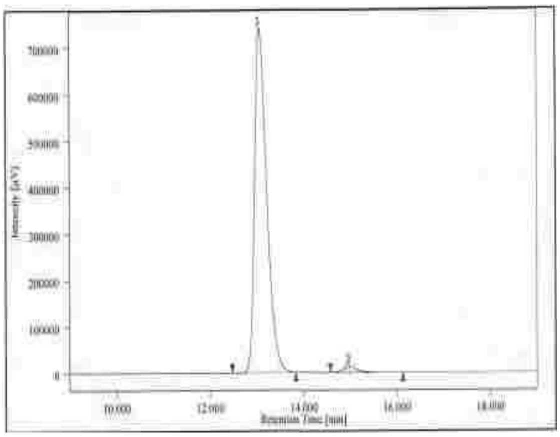
^{1}H NMR spectrum (**22a**)



^{13}C NMR spectrum (**22a**)

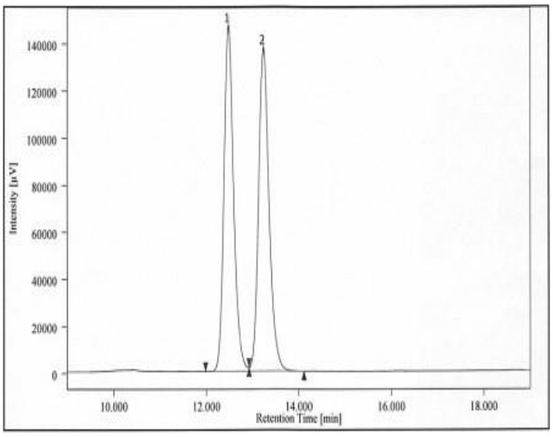


HPLC optically active (**22a**)



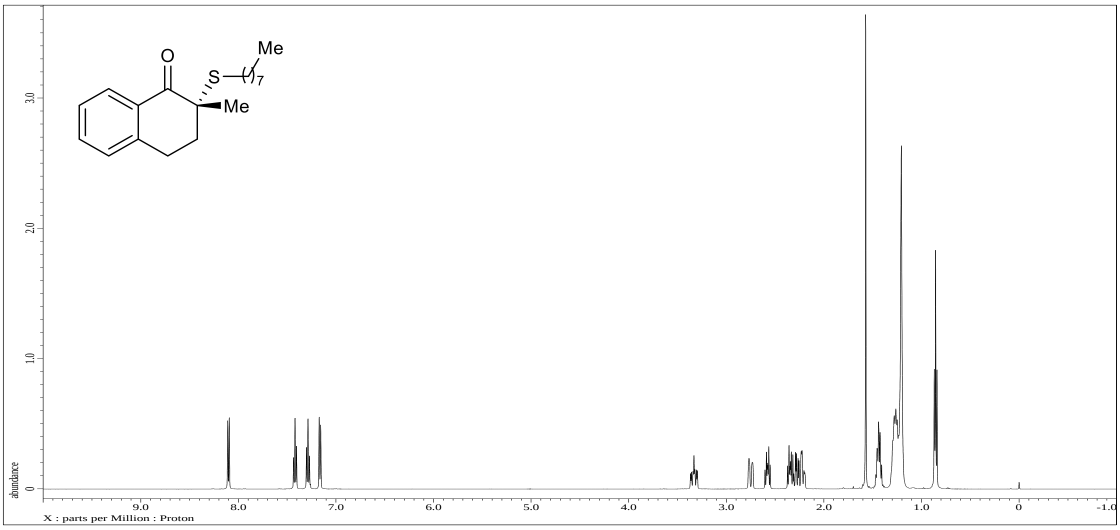
Peak	Retention Time [min]	Area [%]
1	13.1	98.170
2	15.0	1.830

HPLC racemic (**22a**)

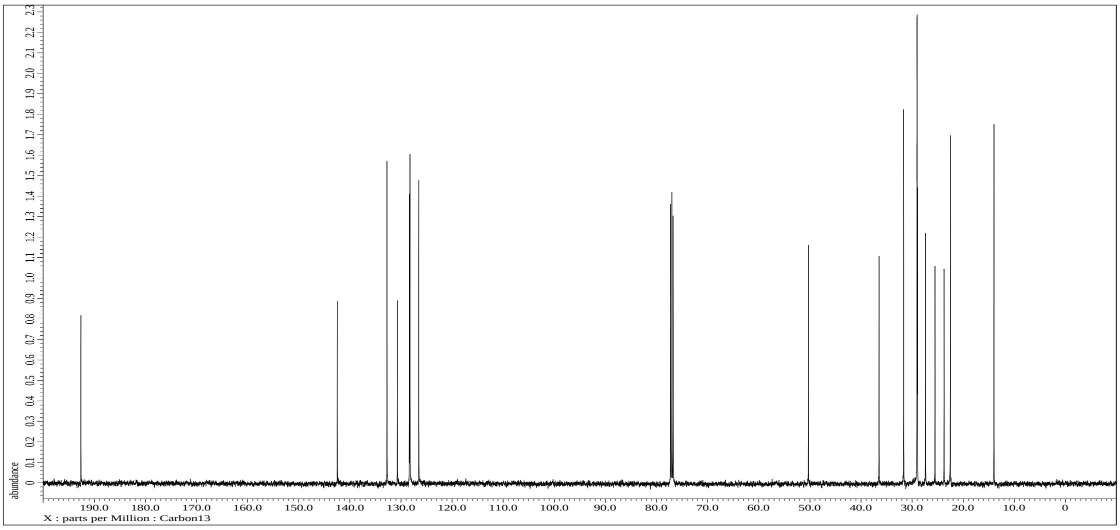


Peak	Retention Time [min]	Area [%]
1	12.5	49.924
2	13.2	50.076

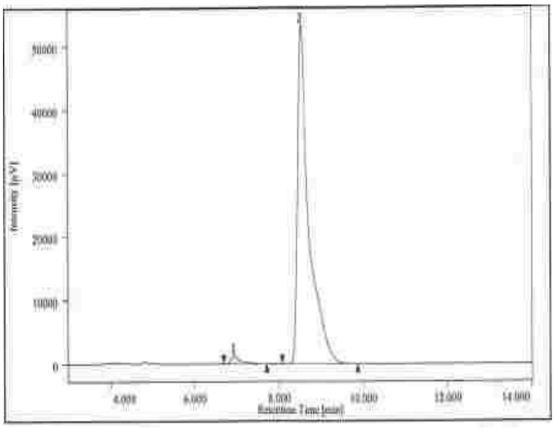
^{13}HC NMR spectrum (**22b**)



^{13}HC NMR spectrum (**22b**)

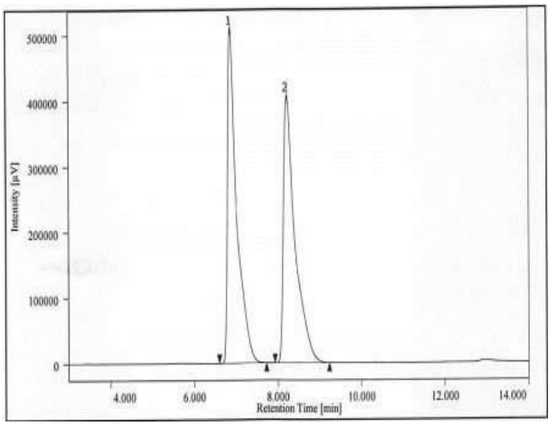


HPLC optically active (**22b**)



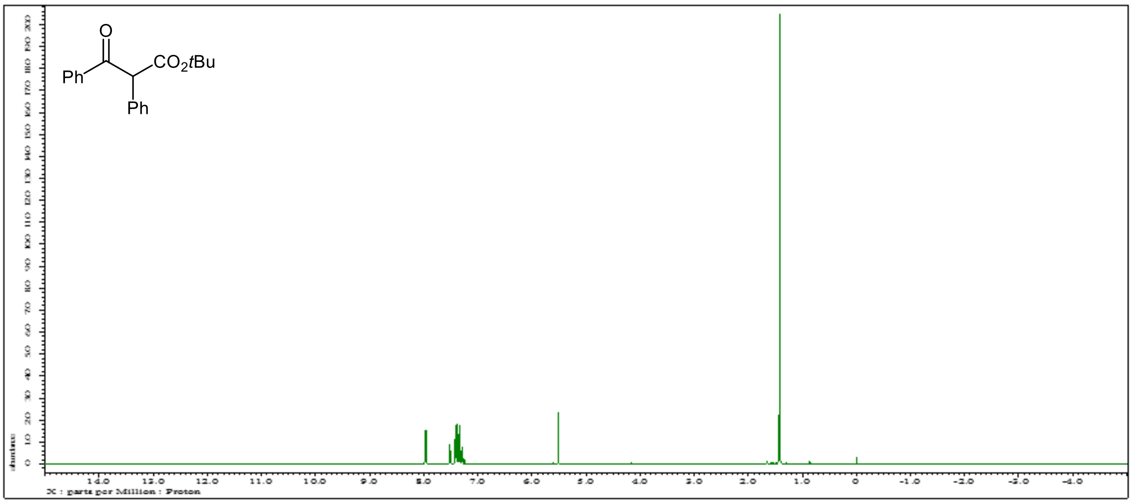
Peak	Retention Time [min]	Area [%]
1	6.9	1.866
2	8.5	98.134

HPLC racemic (**22b**)

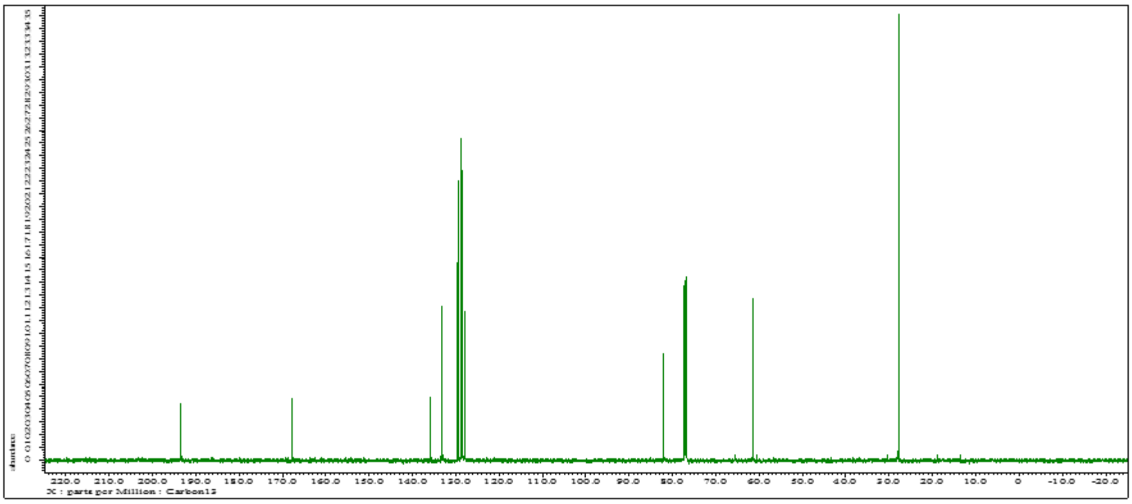


Peak	Retention Time [min]	Area [%]
1	6.9	49.904
2	8.2	50.096

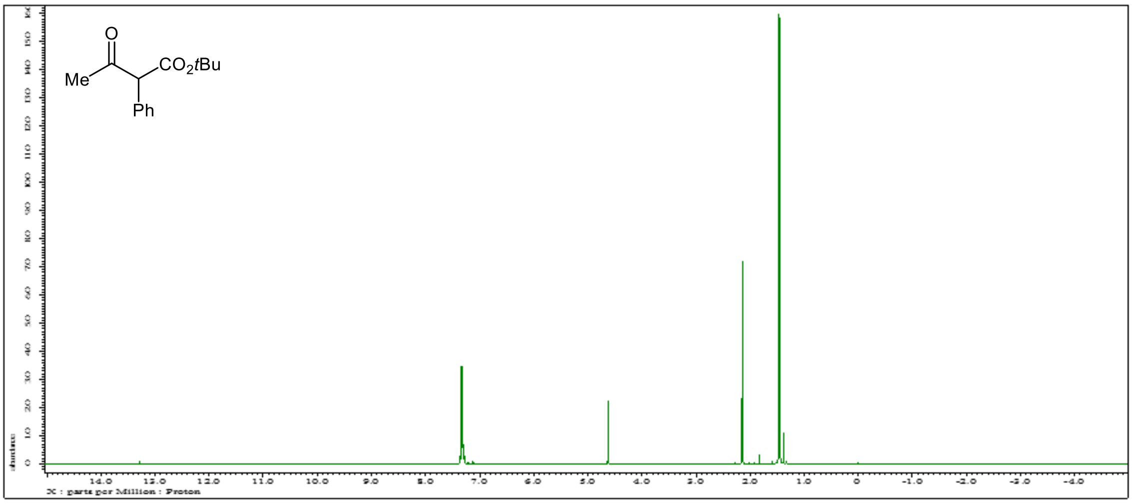
^{1}H NMR spectrum (**26f**)



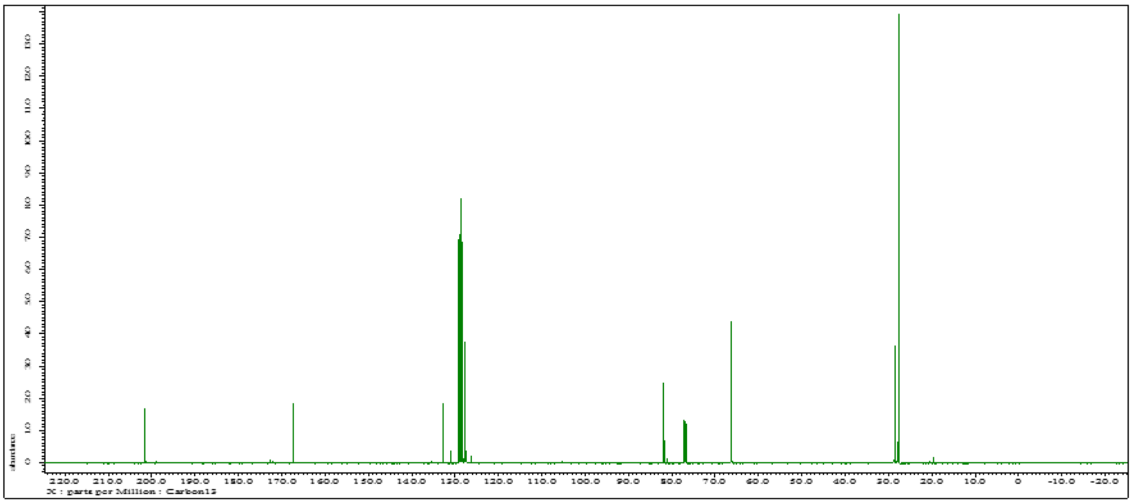
^{13}C NMR spectrum (**26f**)



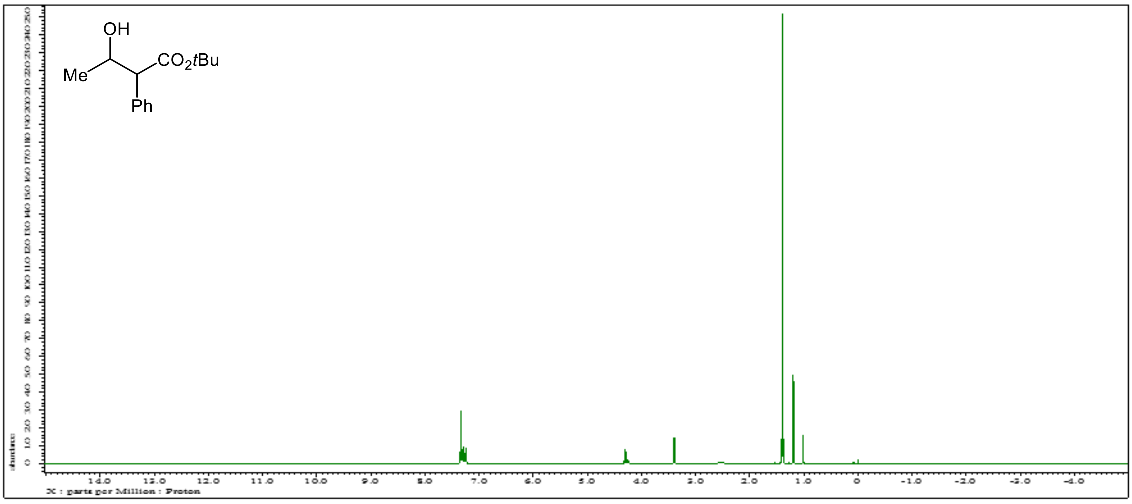
^{1}H NMR spectrum (**26h**)



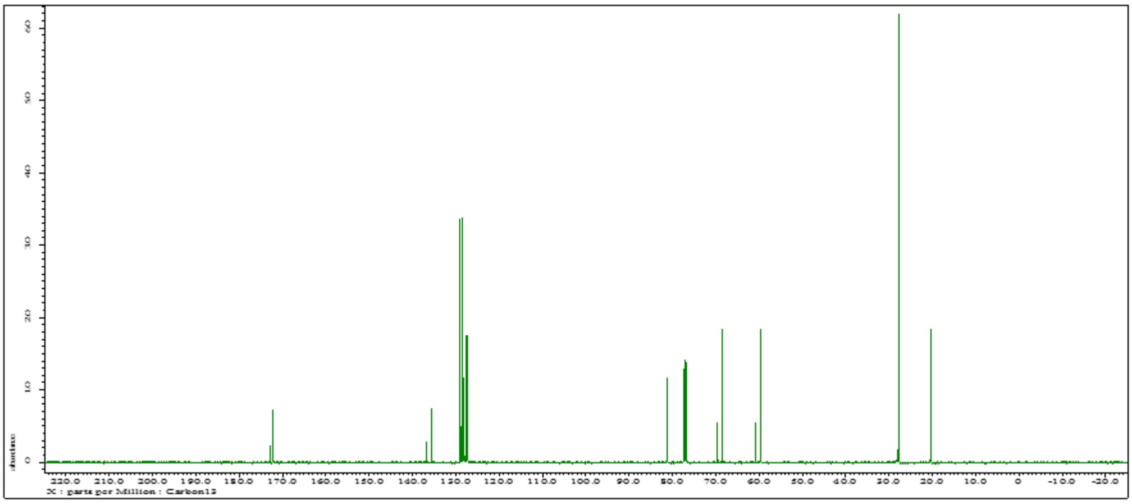
^{13}C NMR spectrum (**26h**)



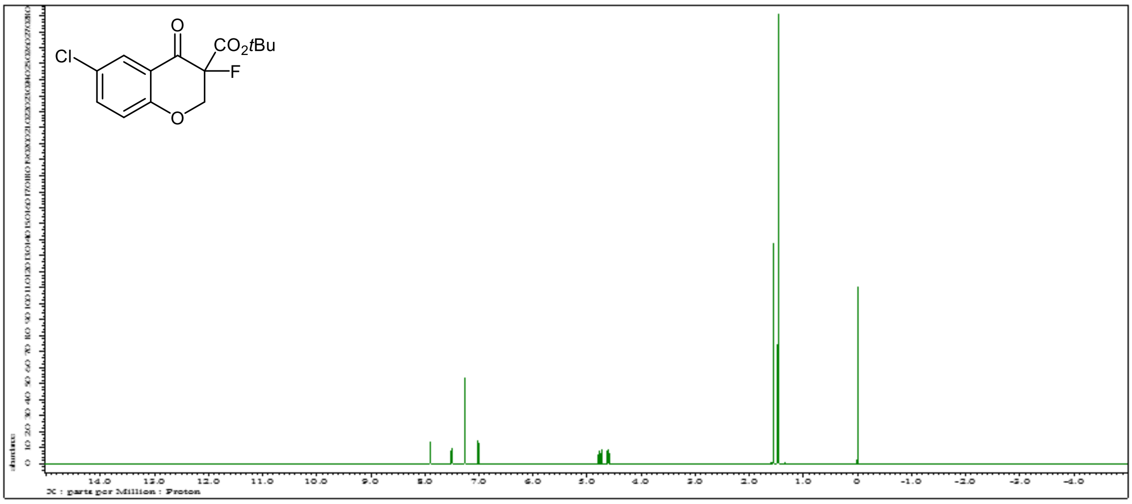
^{1}H NMR spectrum (**55**)



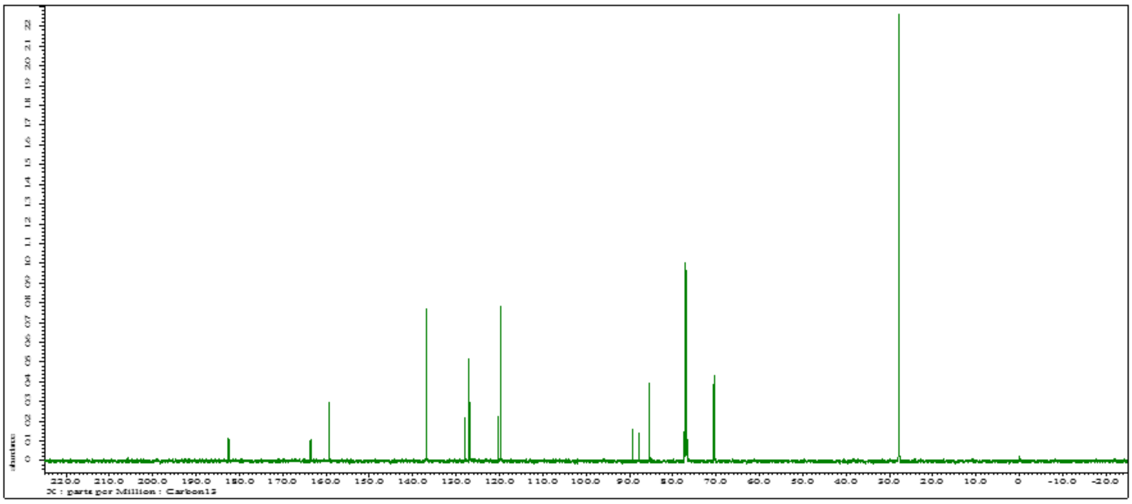
^{13}C NMR spectrum (**55**)



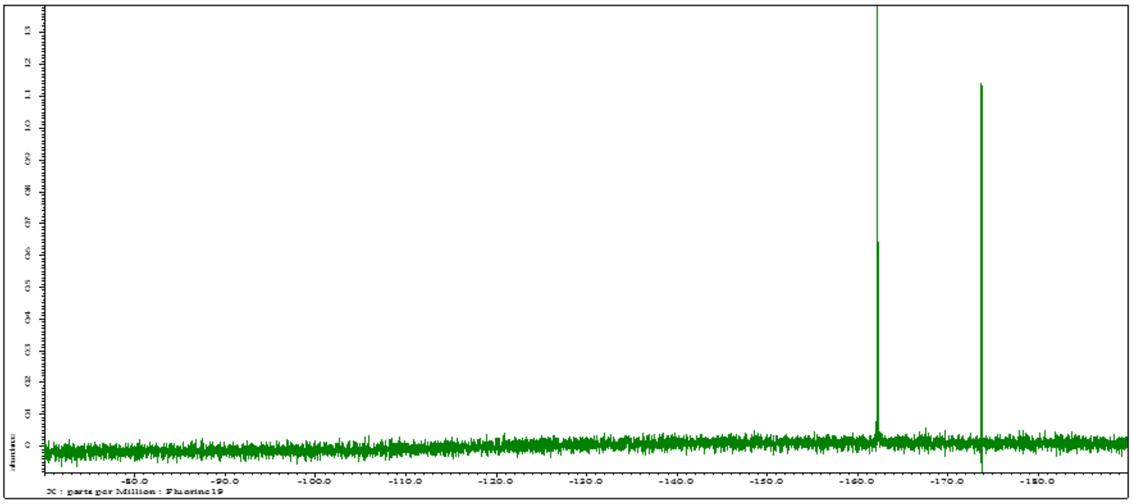
^{1}H NMR spectrum (**27b**)



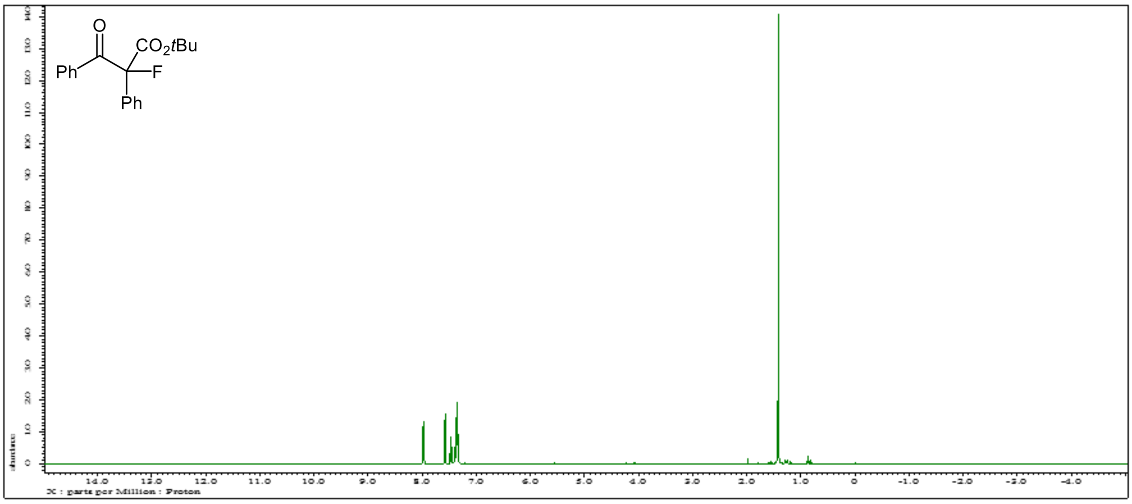
^{13}C NMR spectrum (**27b**)



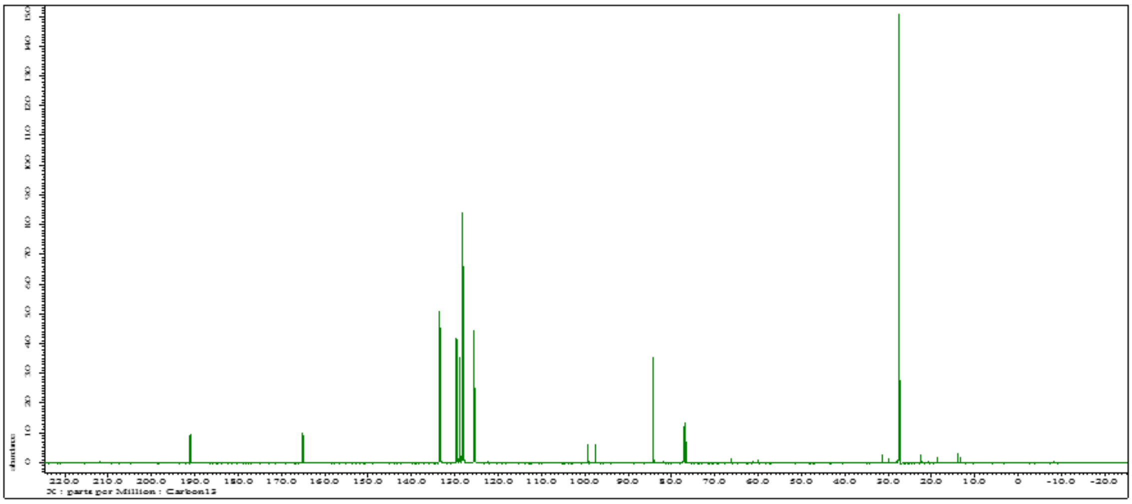
^{19}F NMR spectrum (**27b**)



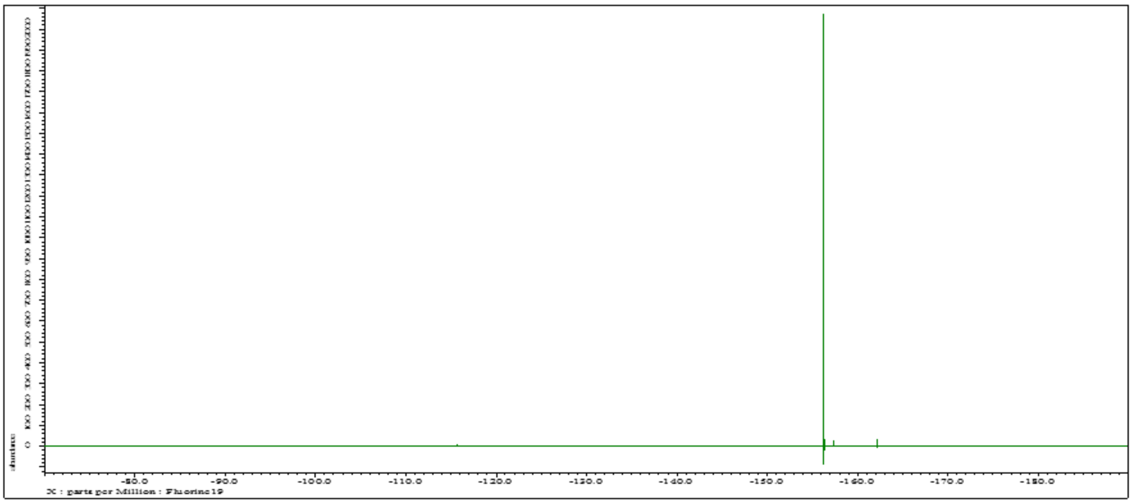
^{1}H NMR spectrum (**27f**)



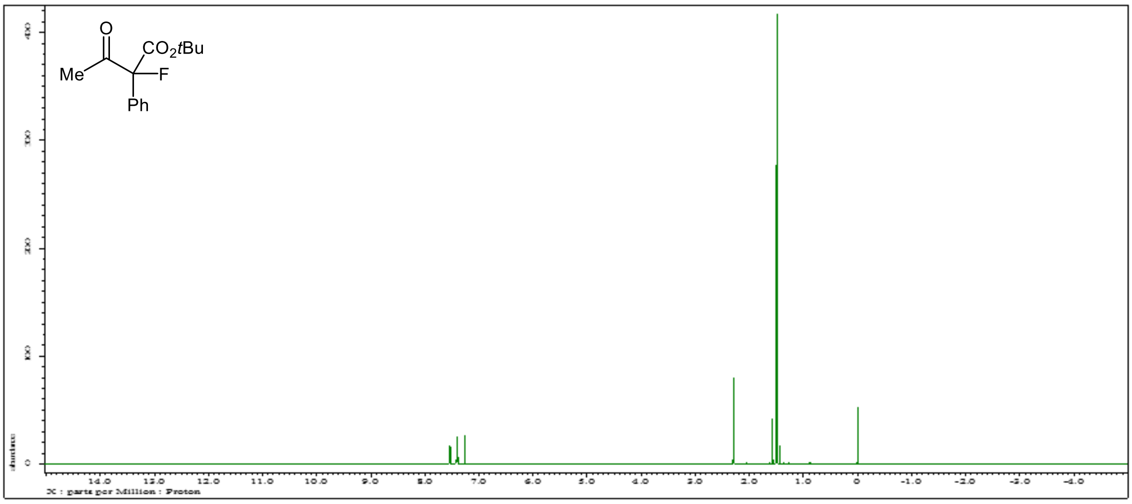
^{13}C NMR spectrum (**27f**)



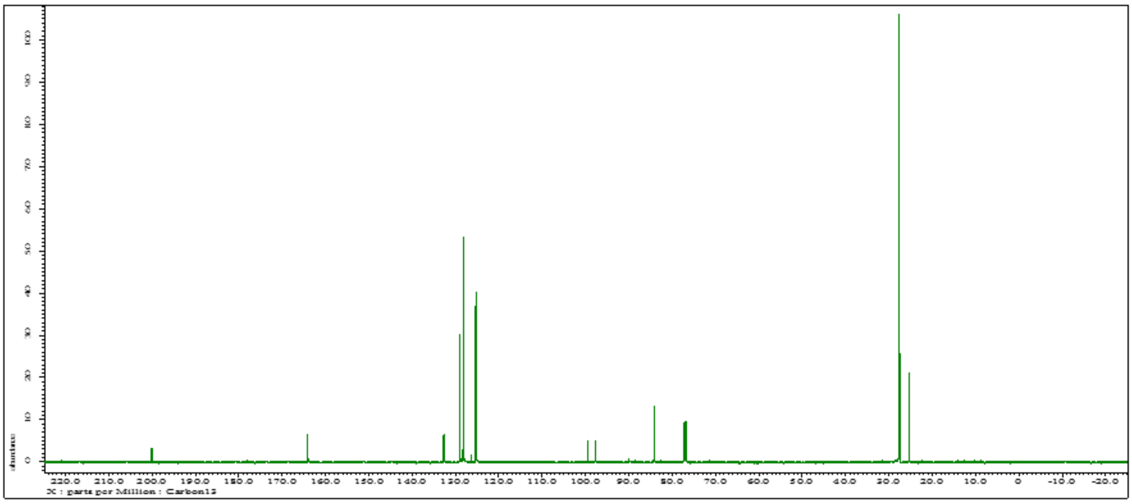
^{19}F NMR spectrum (**27f**)



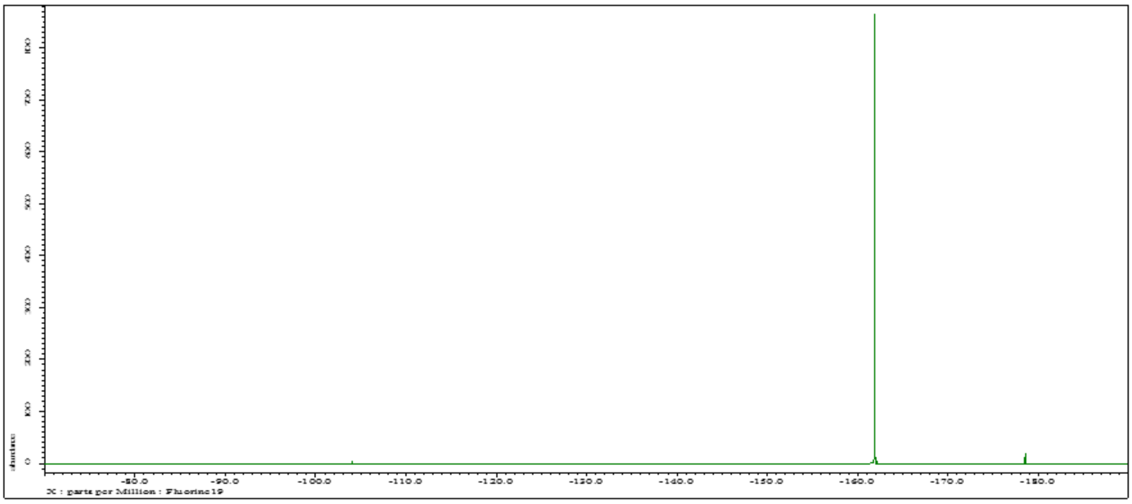
^{1}H NMR spectrum (**27h**)



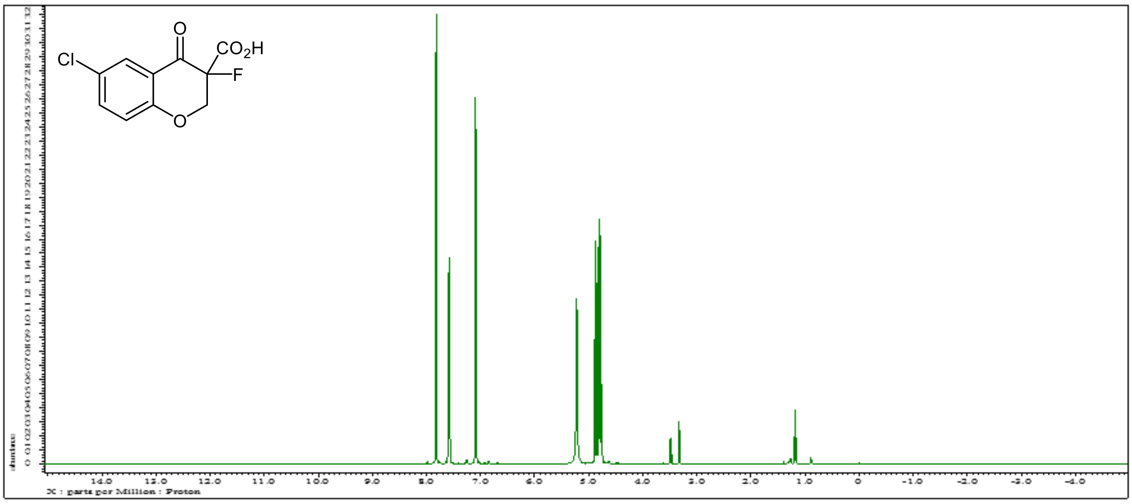
^{13}C NMR spectrum (**27h**)



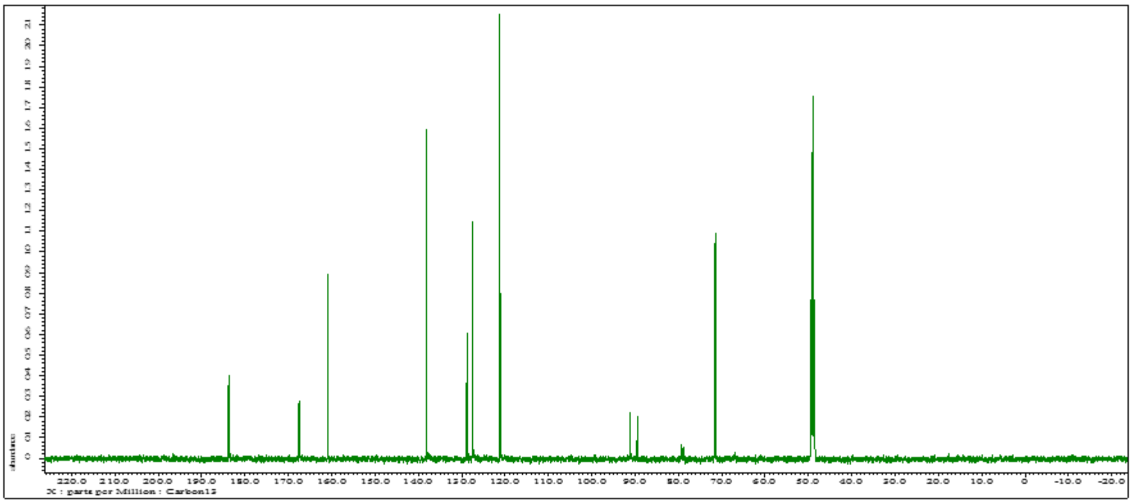
^{19}F NMR spectrum (**27h**)



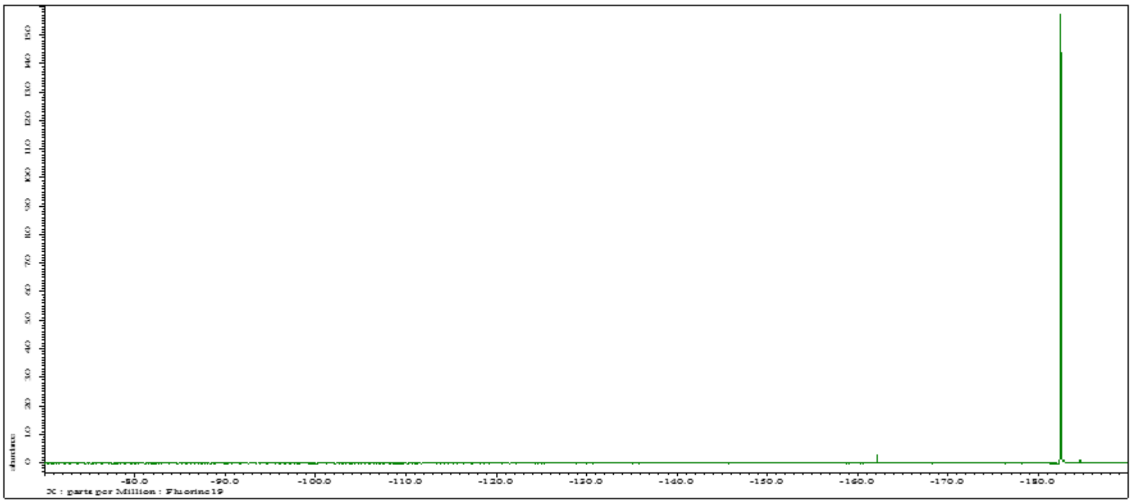
^{1}H NMR spectrum (**28b**)



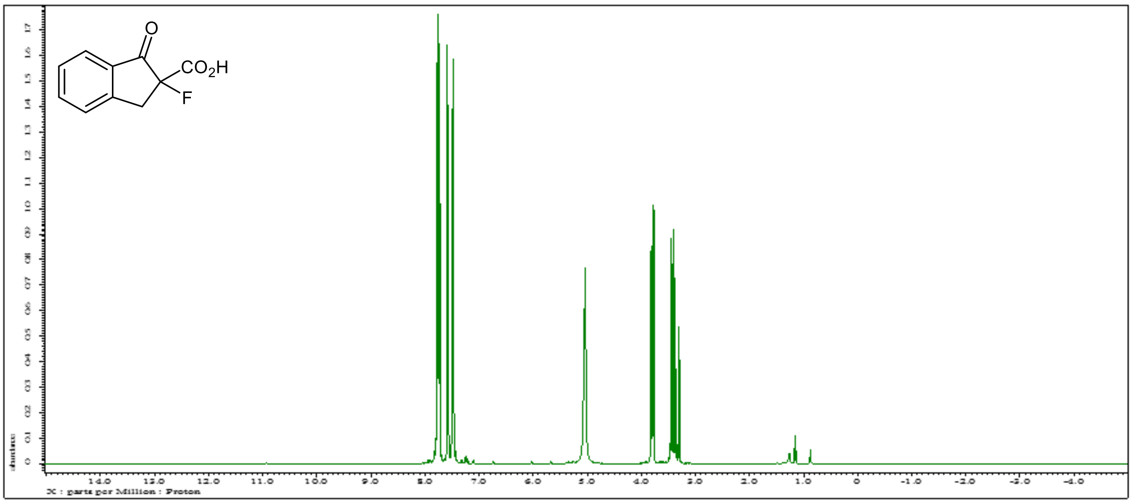
^{13}C NMR spectrum (**28b**)



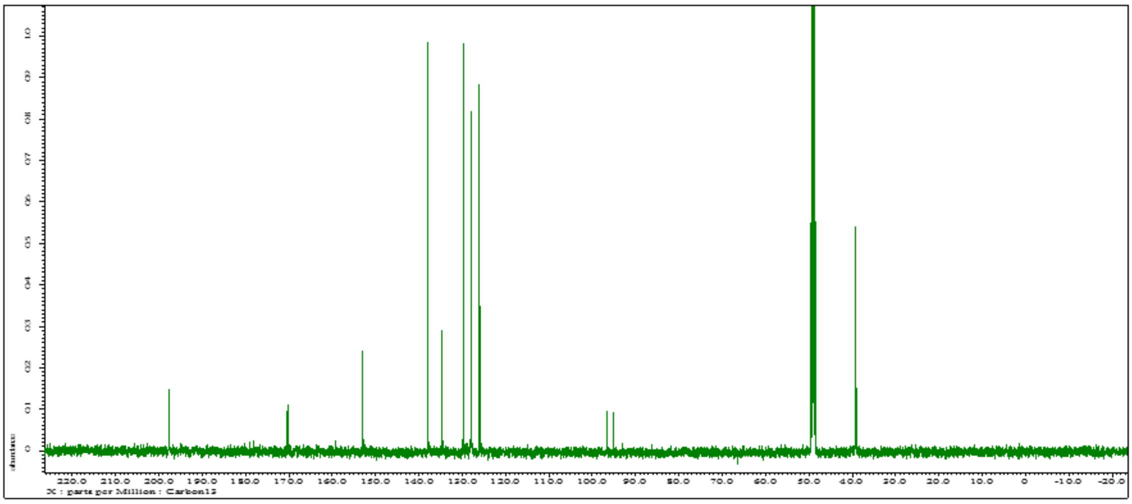
^{19}F NMR spectrum (**28b**)



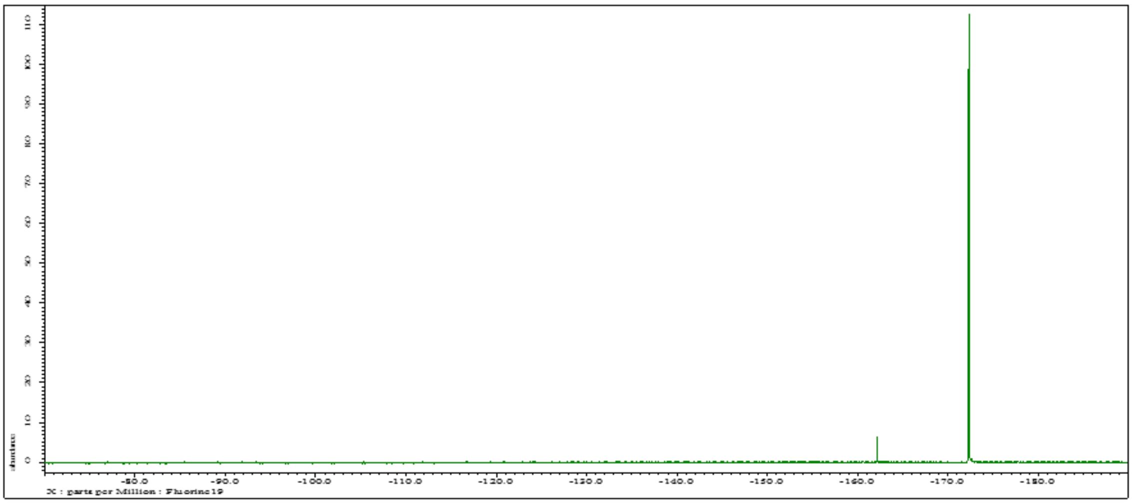
^{1}H NMR spectrum (**28c**)



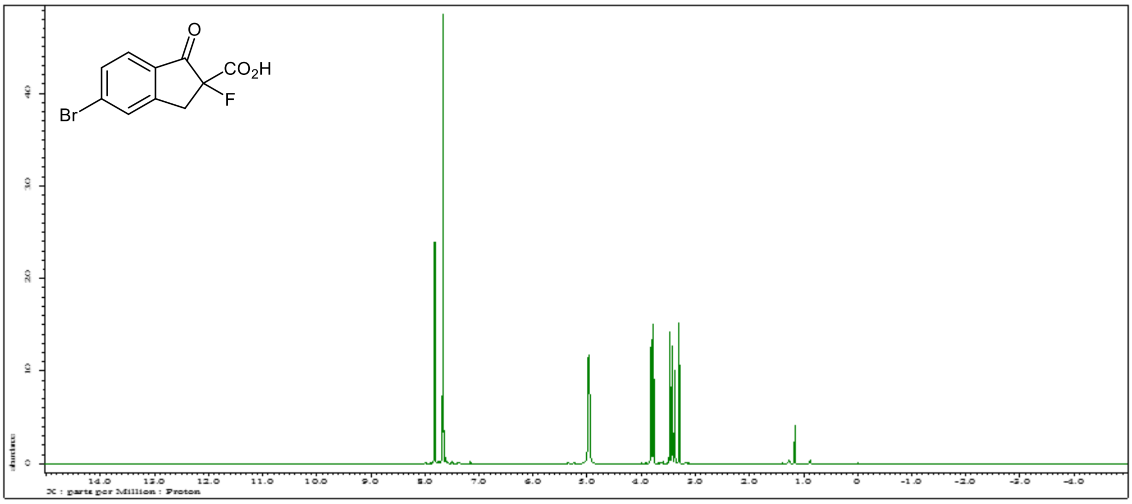
^{13}C NMR spectrum (**28c**)



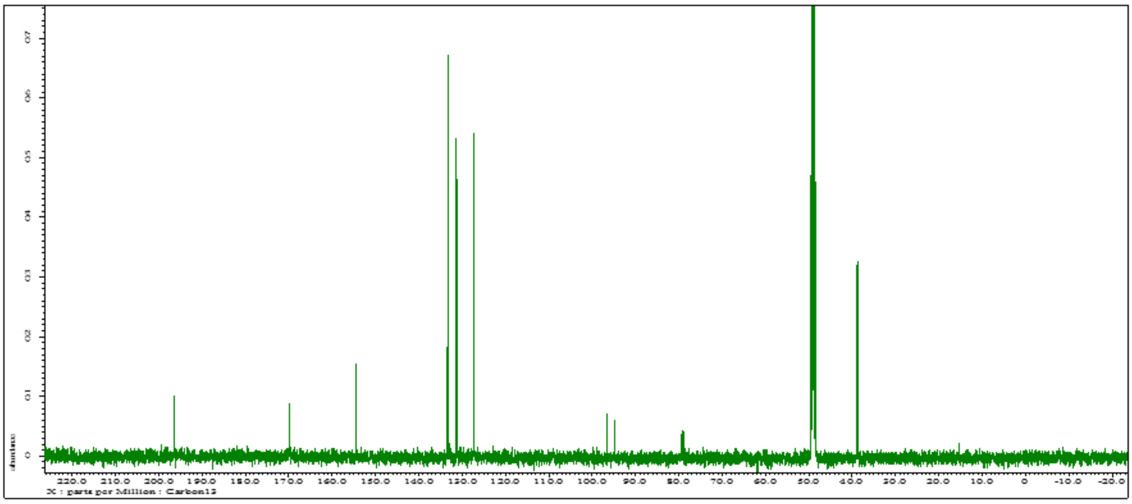
^{19}F NMR spectrum (**28c**)



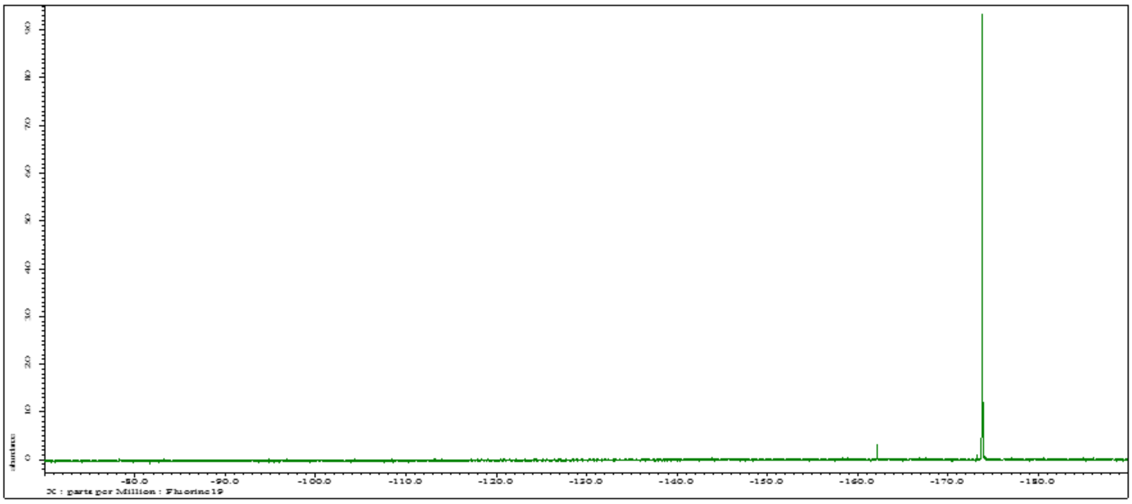
^{1}H NMR spectrum (**28d**)



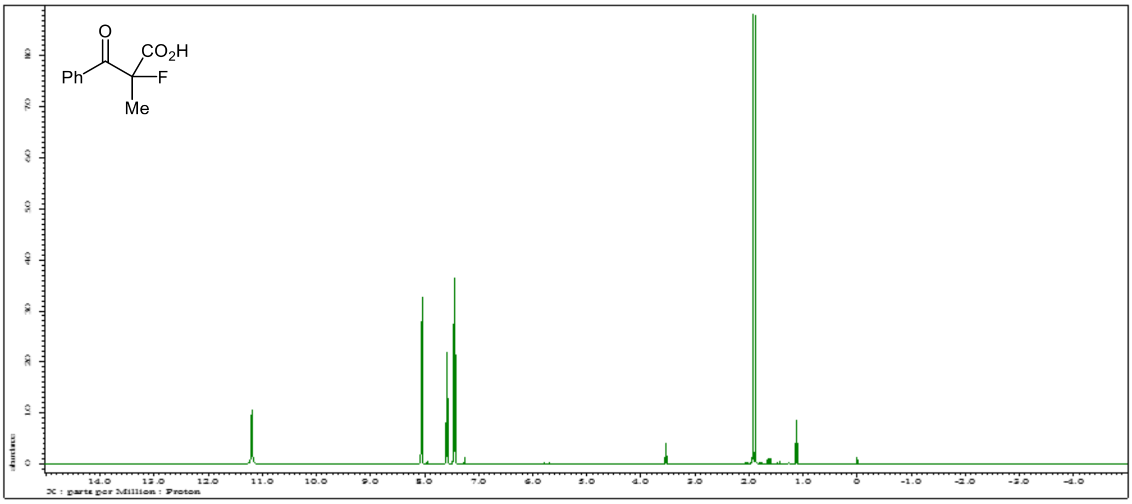
^{13}C NMR spectrum (**28d**)



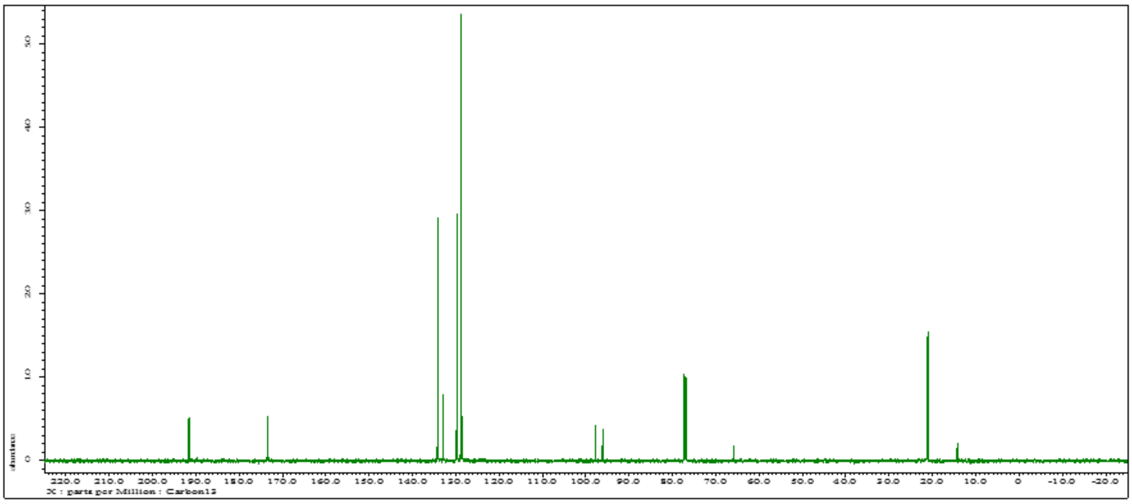
^{19}F NMR spectrum (**28d**)



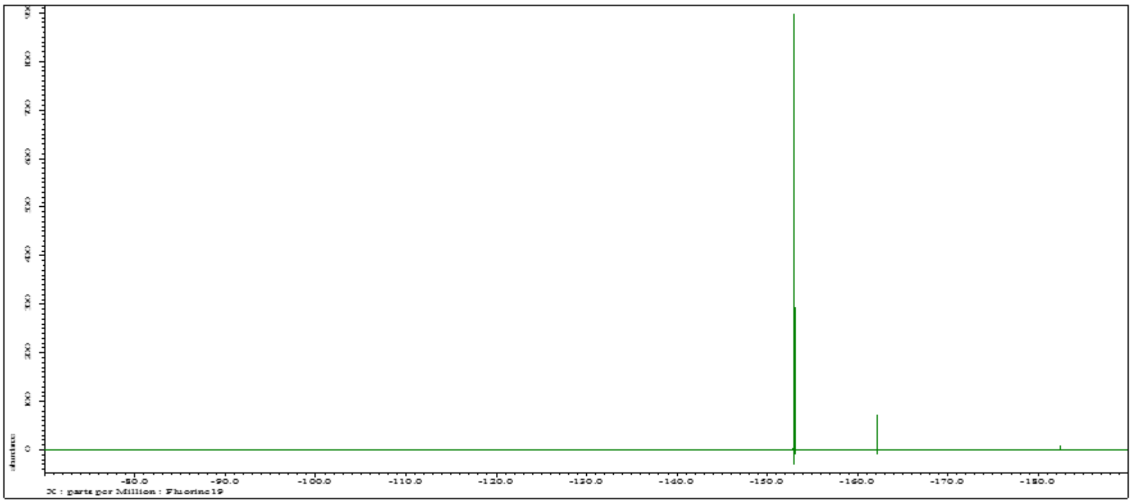
^{1}H NMR spectrum (**28e**)



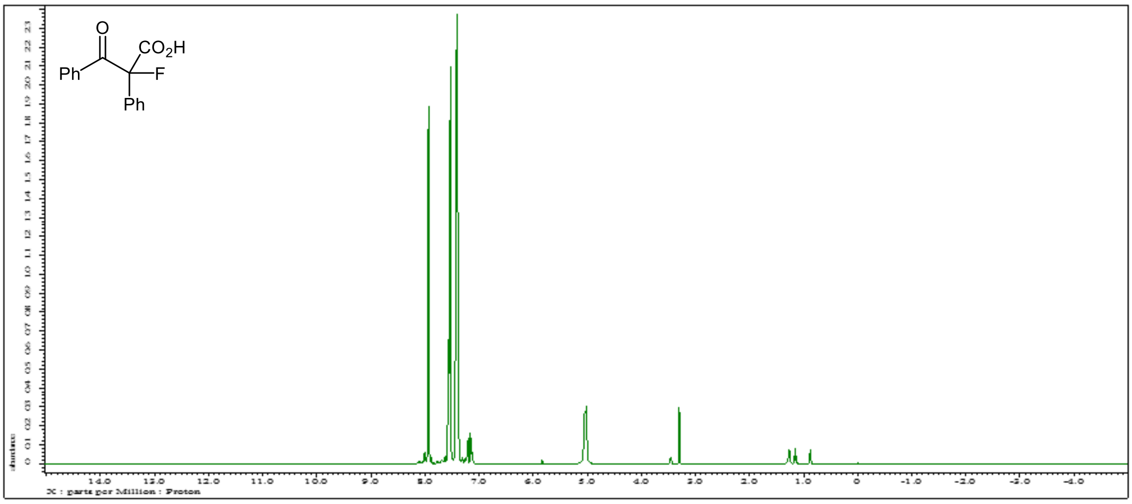
^{13}C NMR spectrum (**28e**)



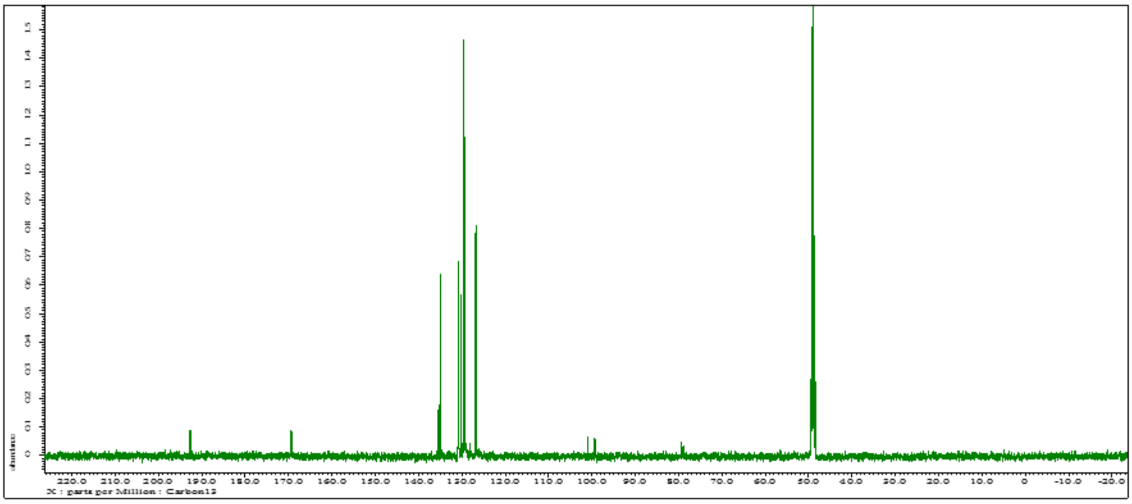
^{19}F NMR spectrum (**28e**)



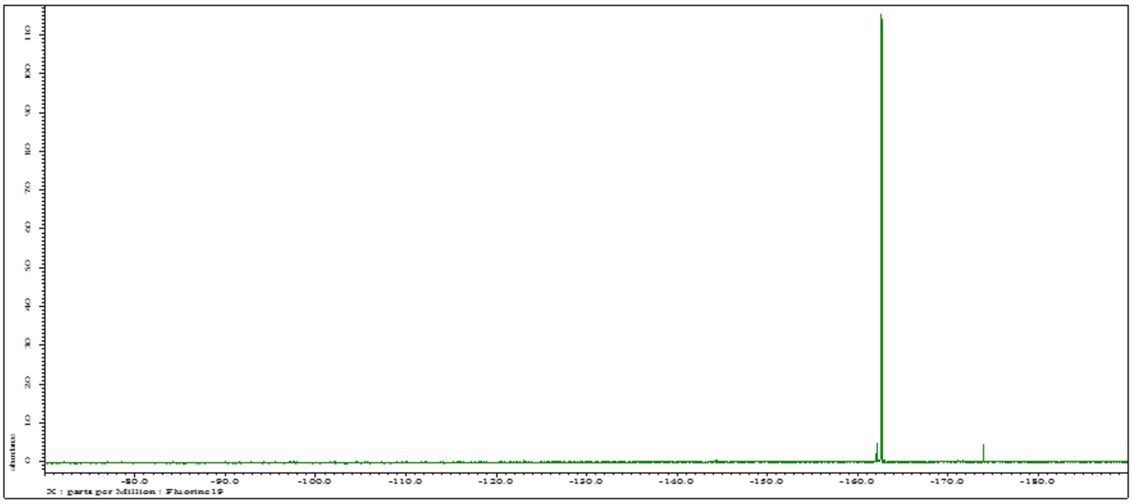
^{1}H NMR spectrum (**28f**)



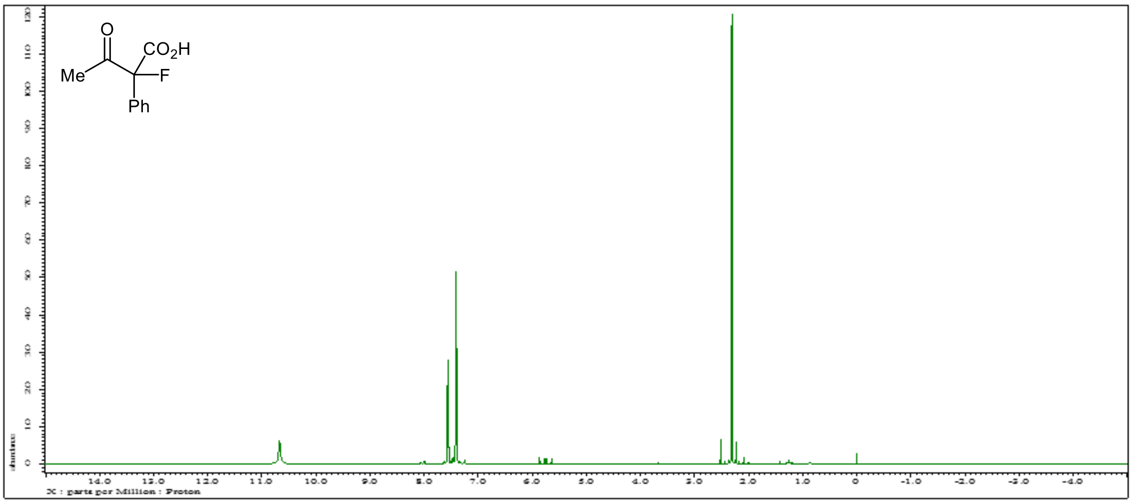
^{13}C NMR spectrum (**28f**)



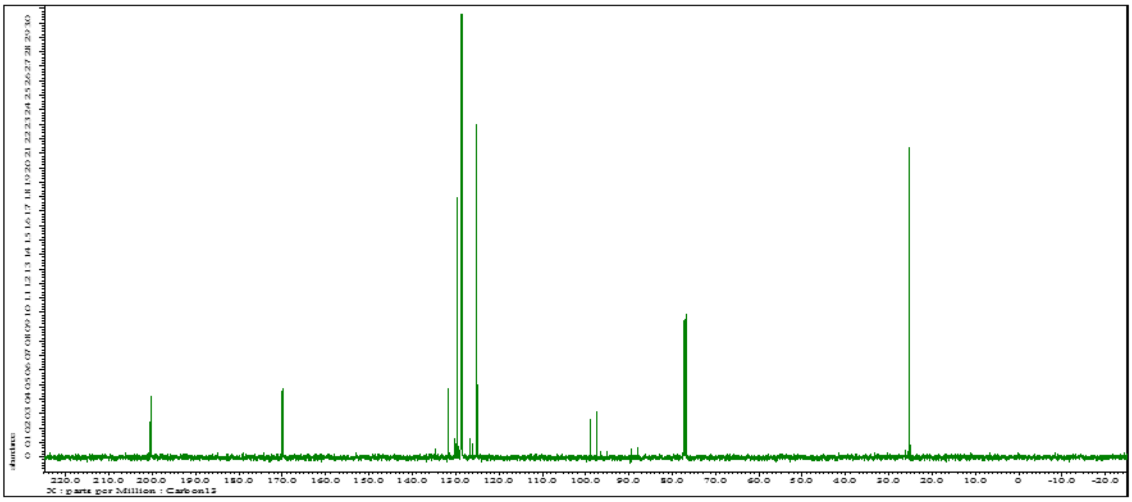
^{19}F NMR spectrum (**28f**)



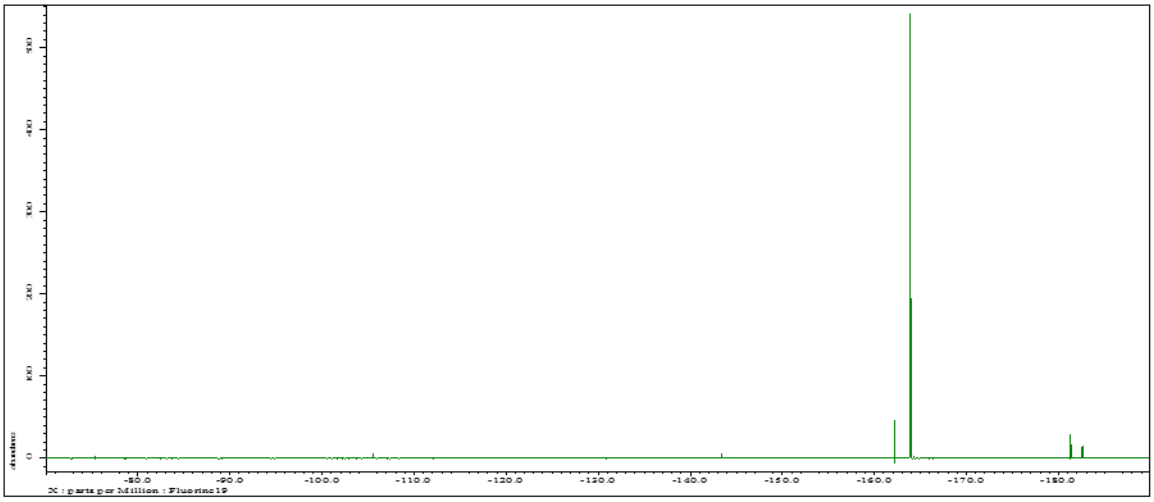
^{1}H NMR spectrum (**28h**)



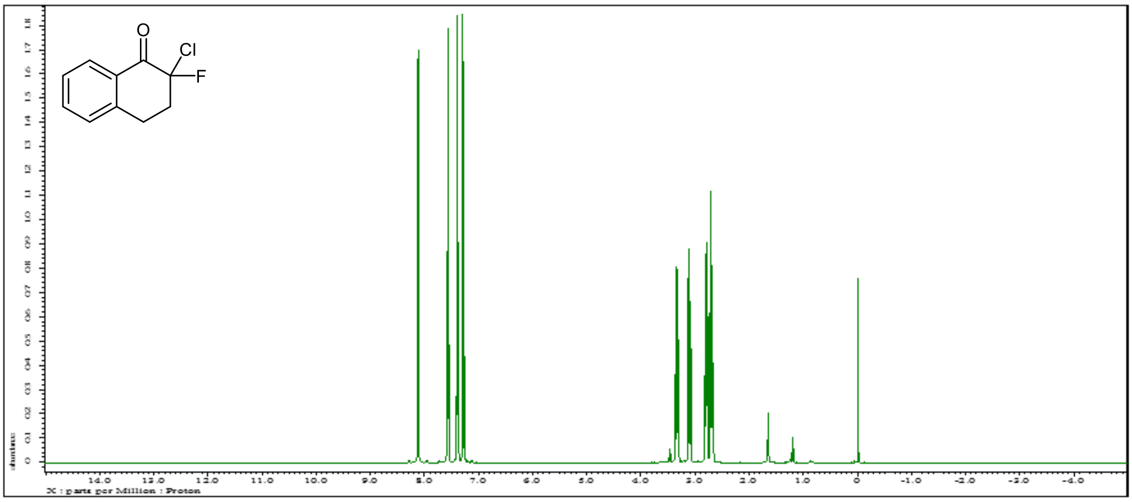
^{13}C NMR spectrum (**28h**)



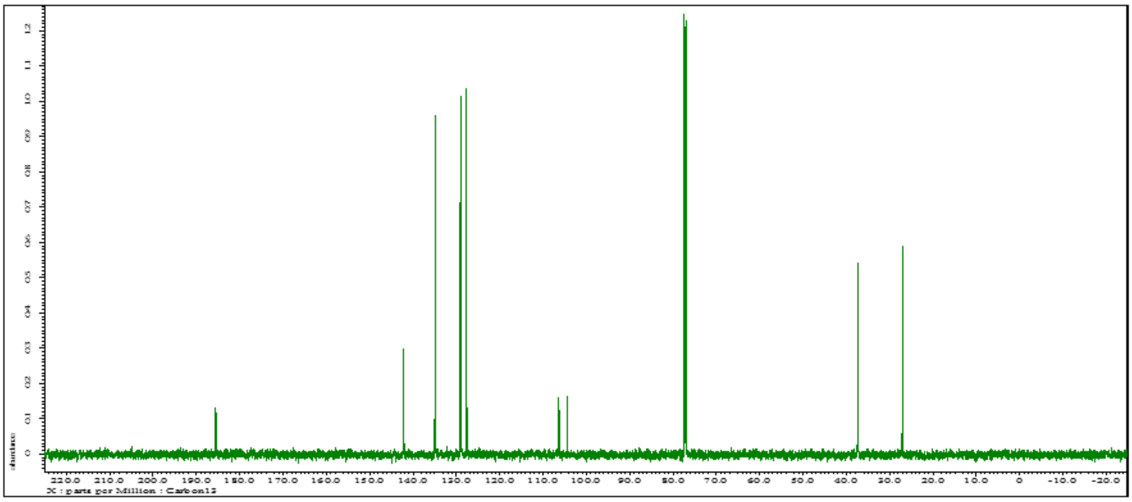
^{19}F NMR spectrum (**28h**)



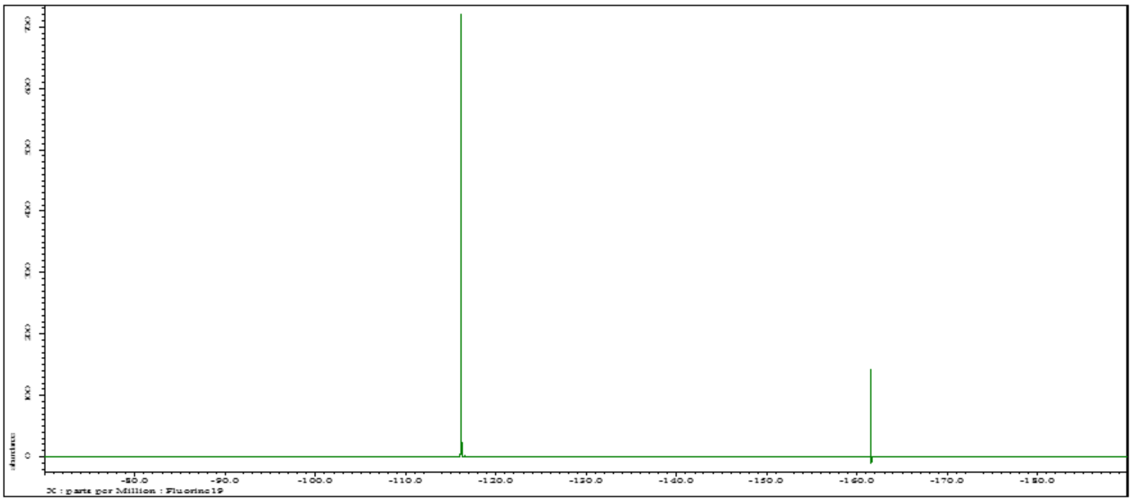
^{1}H NMR spectrum (**31a**)



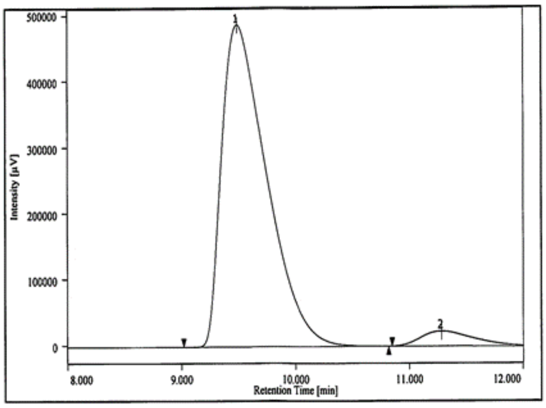
^{13}C NMR spectrum (**31a**)



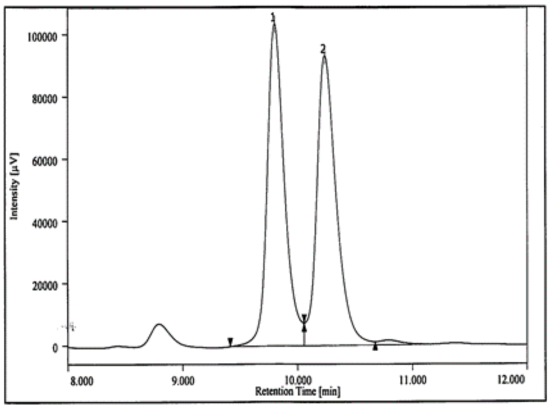
^{19}F NMR spectrum (**31a**)

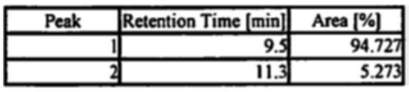


HPLC optically active (**31a**)

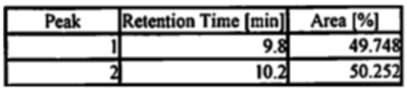


HPLC racemic (**31a**)



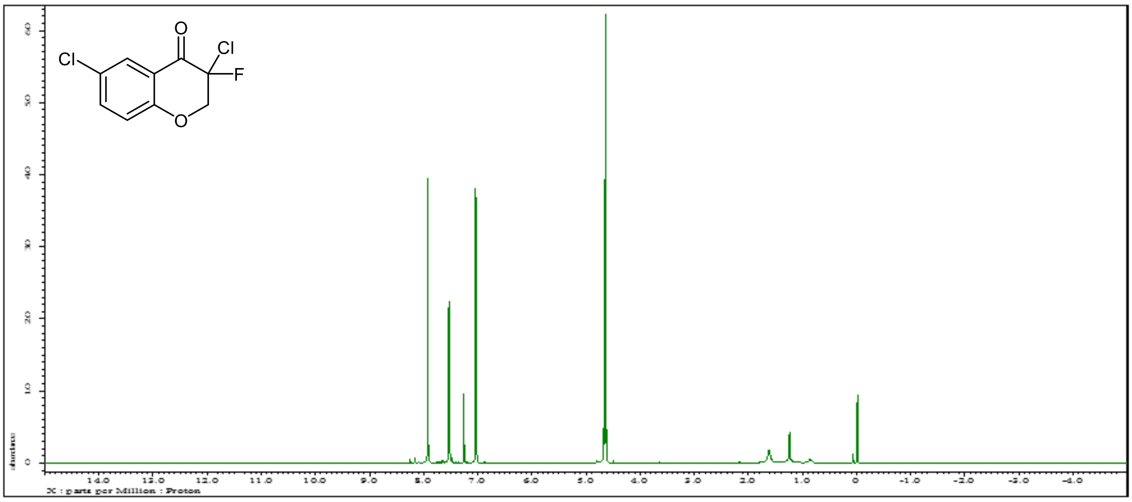


Peak	Retention Time [min]	Area [%]
1	9.5	94.727
2	11.3	5.273

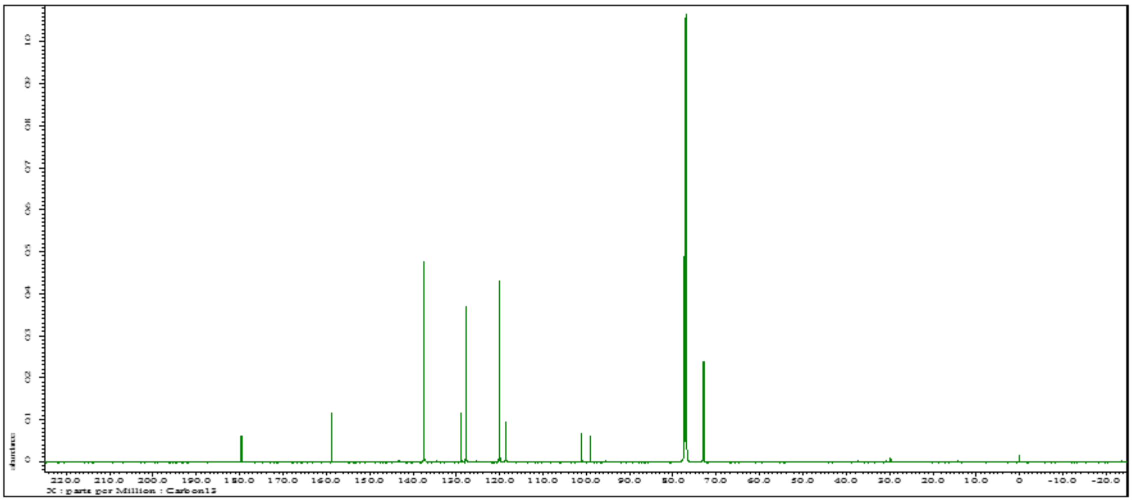


Peak	Retention Time [min]	Area [%]
1	9.8	49.748
2	10.2	50.252

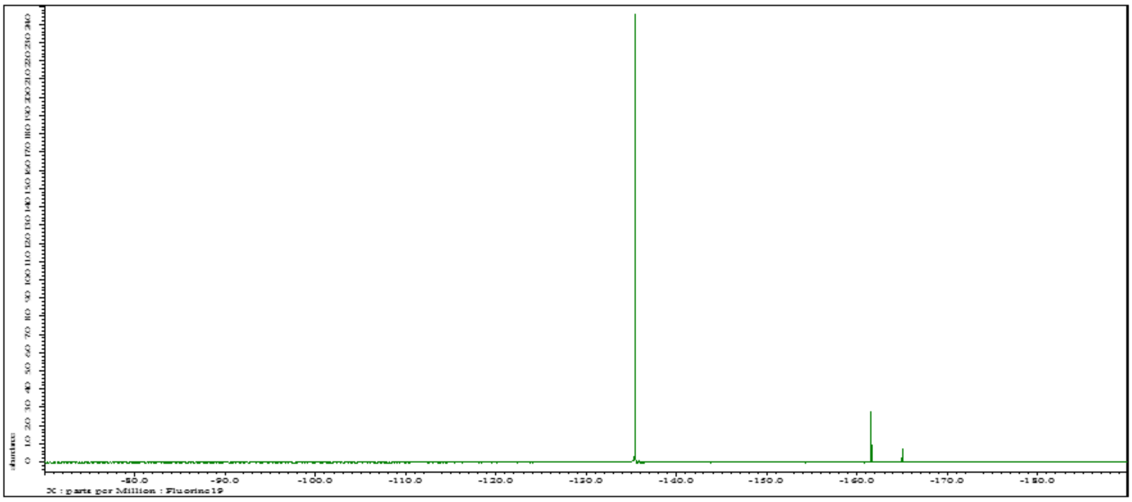
^{1}H NMR spectrum (**31b**)



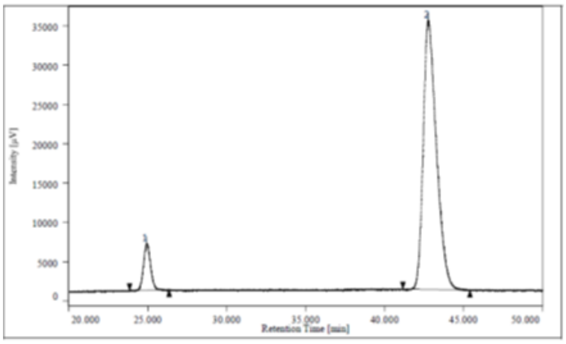
^{13}C NMR spectrum (**31b**)

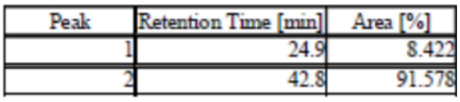


^{19}F NMR spectrum (**31b**)



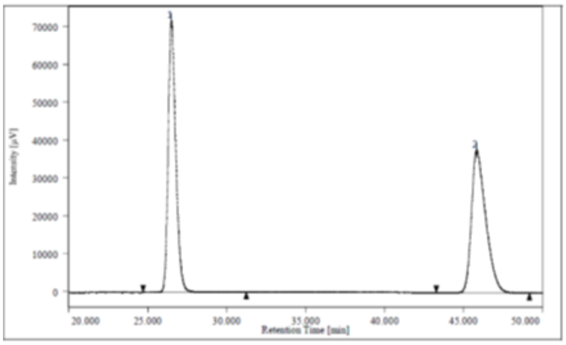
HPLC optically active (**31b**)

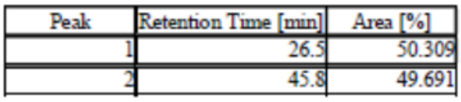




Peak	Retention Time [min]	Area [%]
1	24.9	8.422
2	42.8	91.578

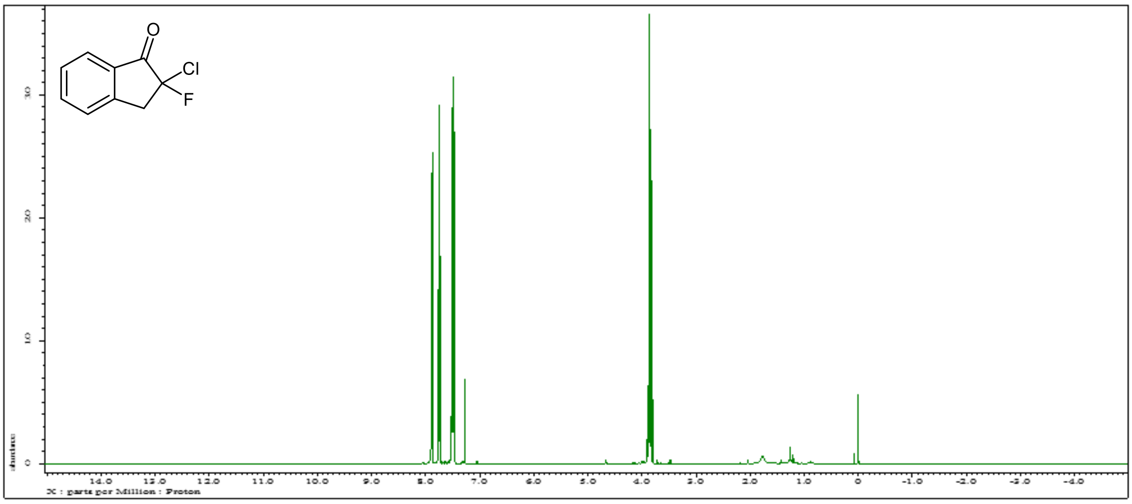
HPLC racemic (**31b**)



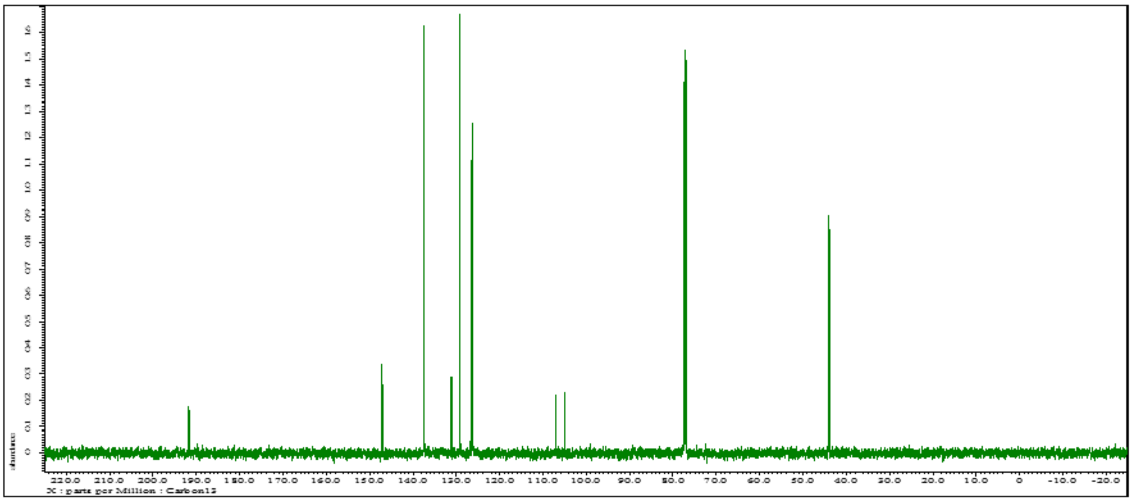


Peak	Retention Time [min]	Area [%]
1	26.5	50.309
2	45.8	49.691

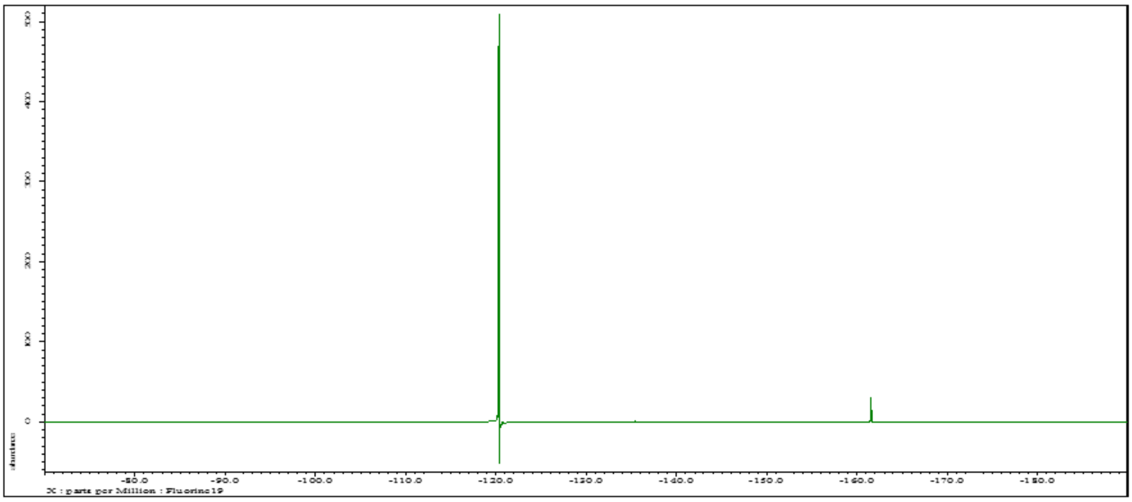
^{1}H NMR spectrum (**31c**)



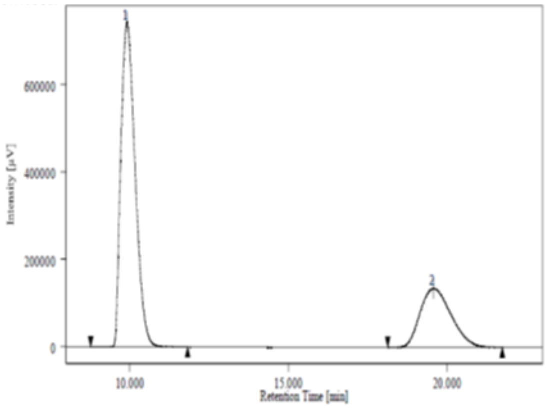
^{13}C NMR spectrum (**31c**)



^{19}F NMR spectrum (**31c**)

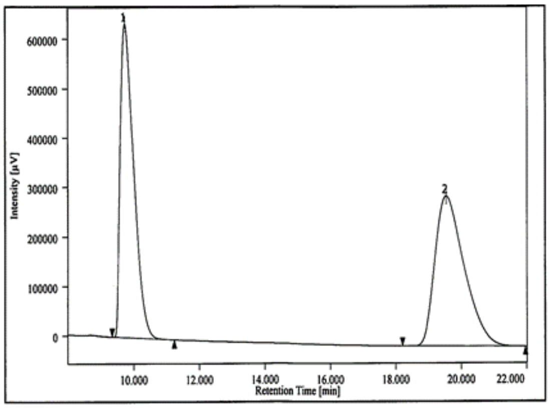


HPLC optically active (**31c**)



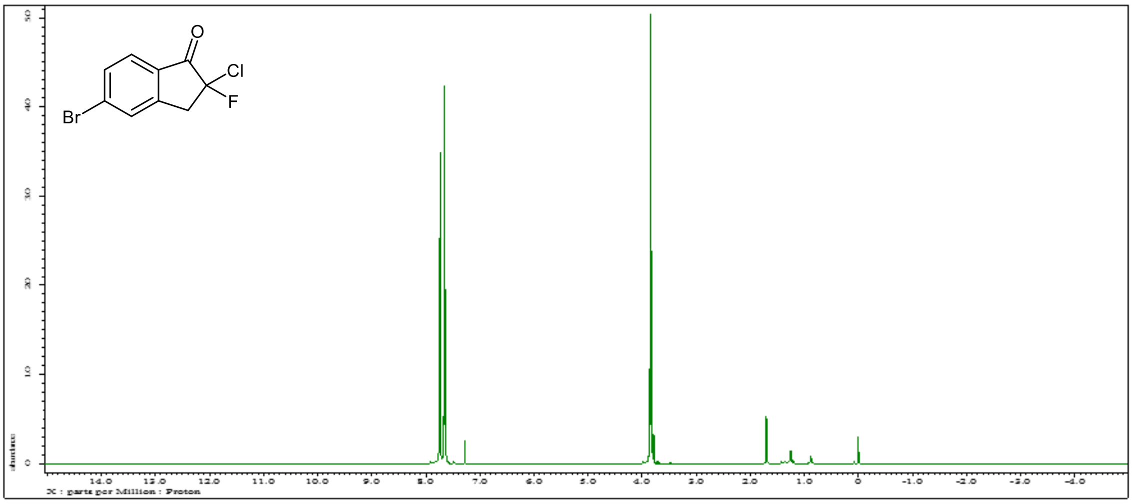
Peak	Retention Time [min]	Area [%]
1	9.908	71.771
2	19.567	28.229

HPLC racemic (**31c**)

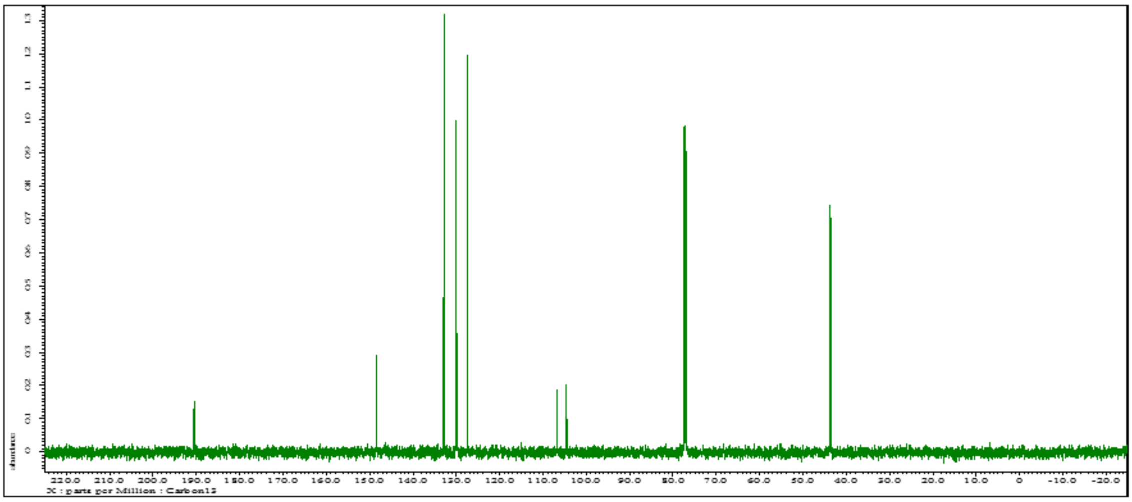


Peak	Retention Time [min]	Area [%]
1	9.7	48.936
2	19.5	51.064

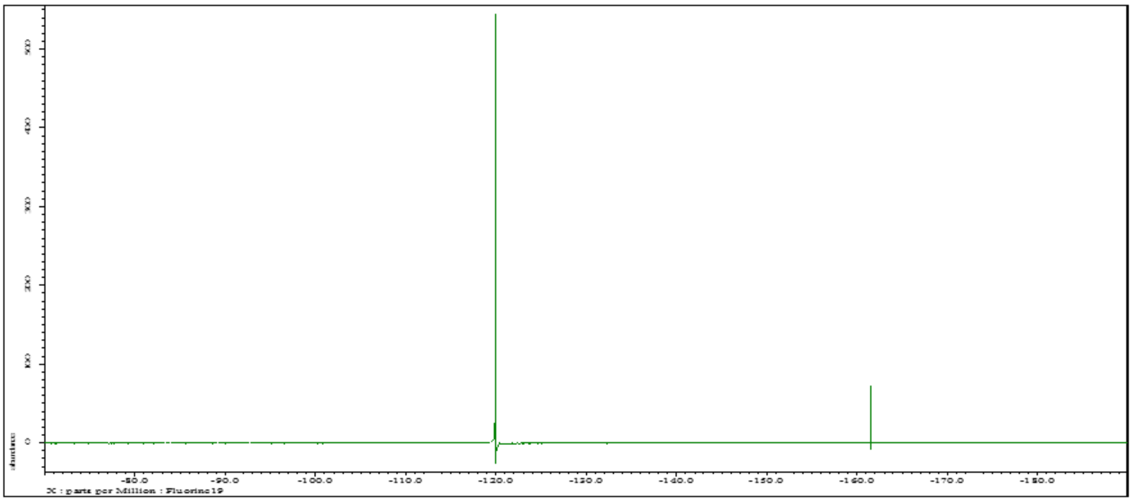
^{1}H NMR spectrum (**31d**)



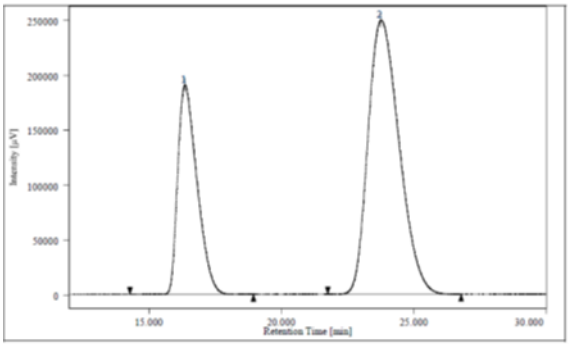
^{13}C NMR spectrum (**31d**)



^{19}F NMR spectrum (**31d**)

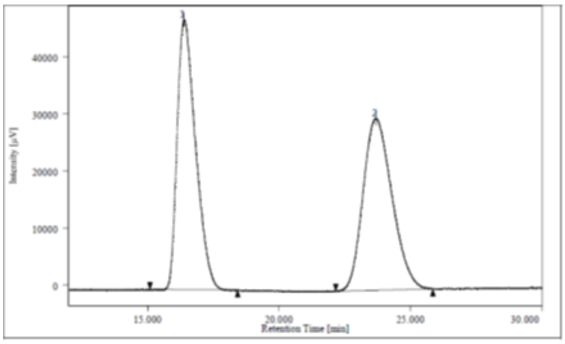


HPLC optically active (**31d**)



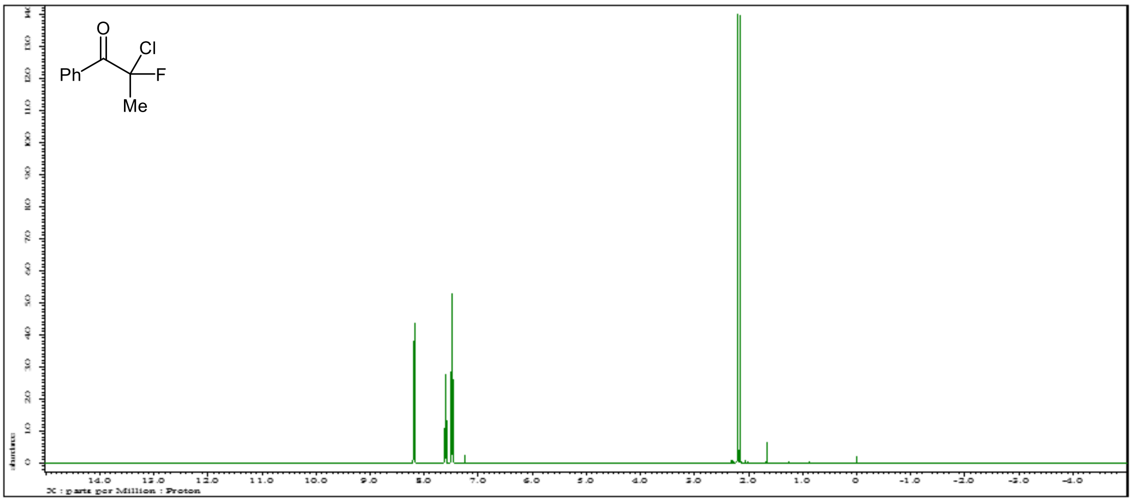
Peak	Retention Time [min]	Area [%]
1	16.4	32.084
2	23.8	67.916

HPLC racemic (**31d**)

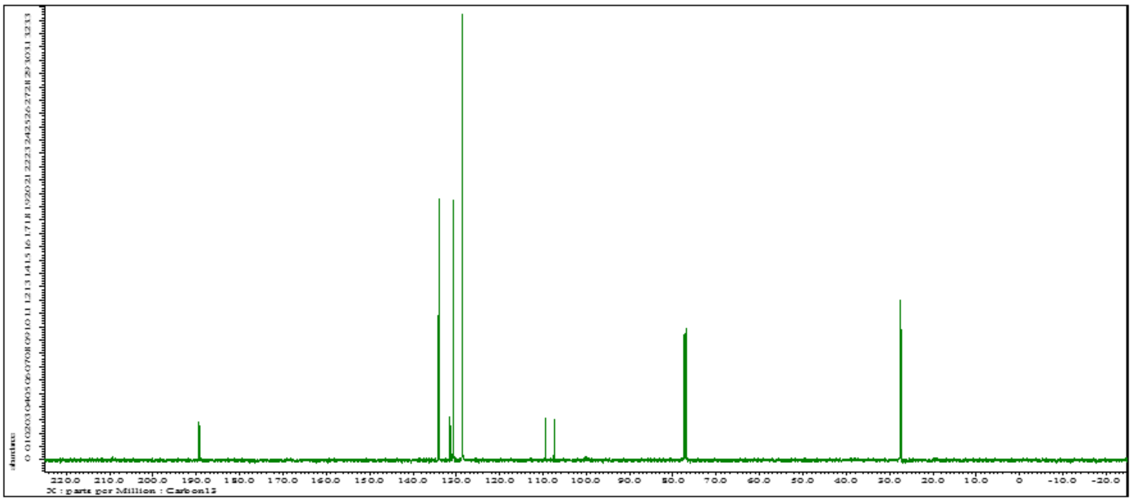


Peak	Retention Time [min]	Area [%]
1	16.4	49.921
2	23.7	50.079

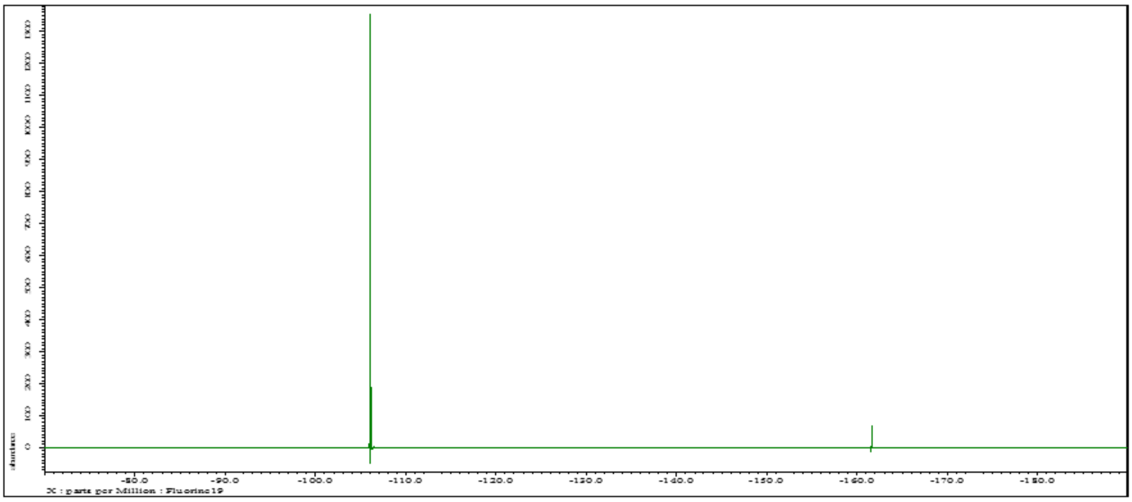
^{1}H NMR spectrum (**31e**)



^{13}C NMR spectrum (**31e**)

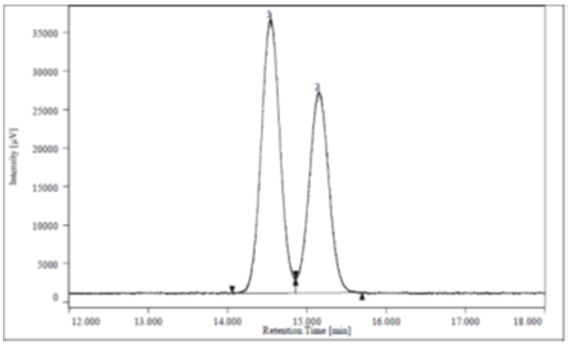


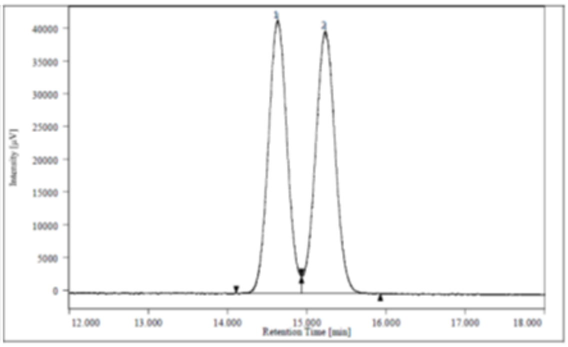
^{19}F NMR spectrum (**31e**)

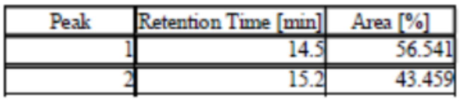


HPLC optically active (**31e**)

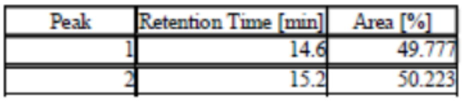
HPLC racemic (**31e**)





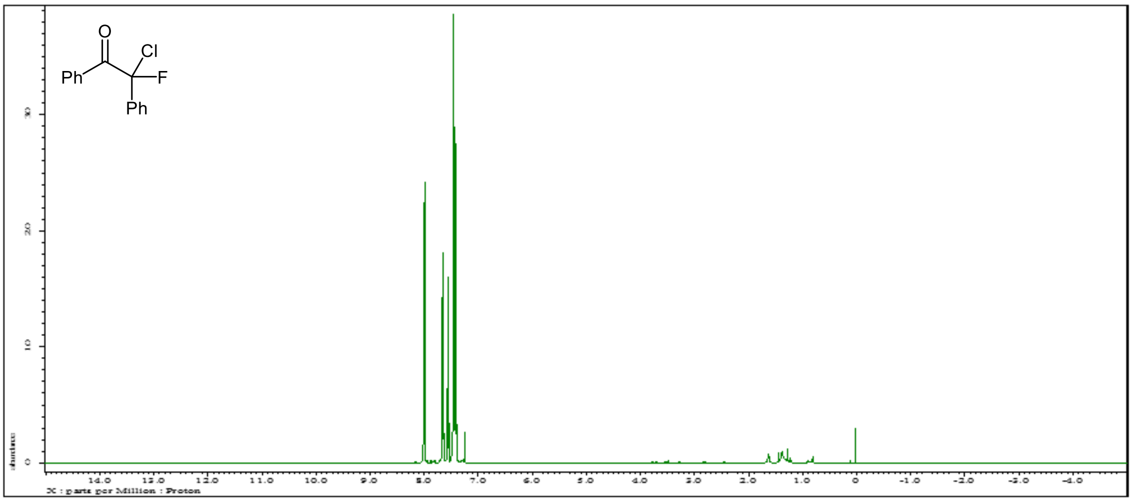


Peak	Retention Time [min]	Area [%]
1	14.5	56.541
2	15.2	43.459

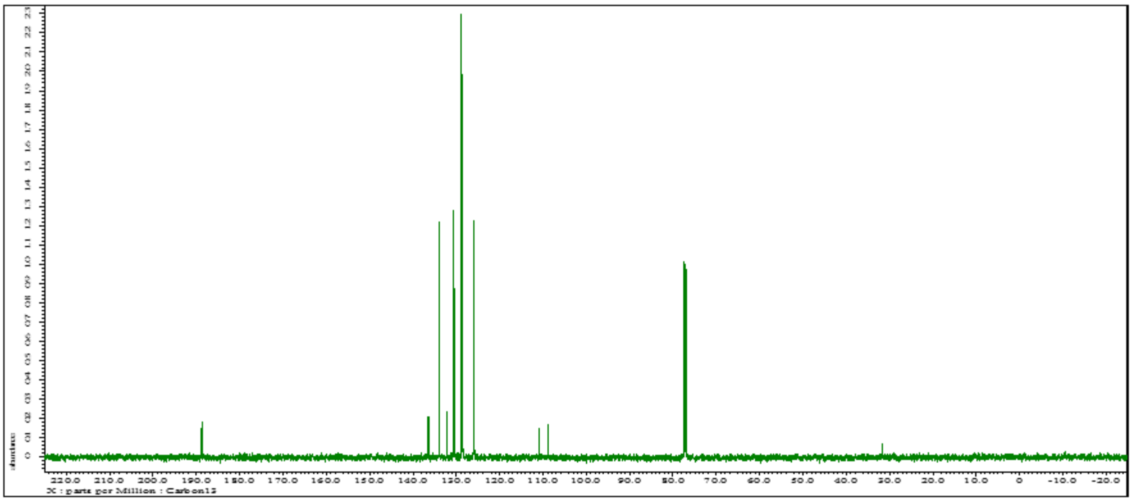


Peak	Retention Time [min]	Area [%]
1	14.6	49.777
2	15.2	50.223

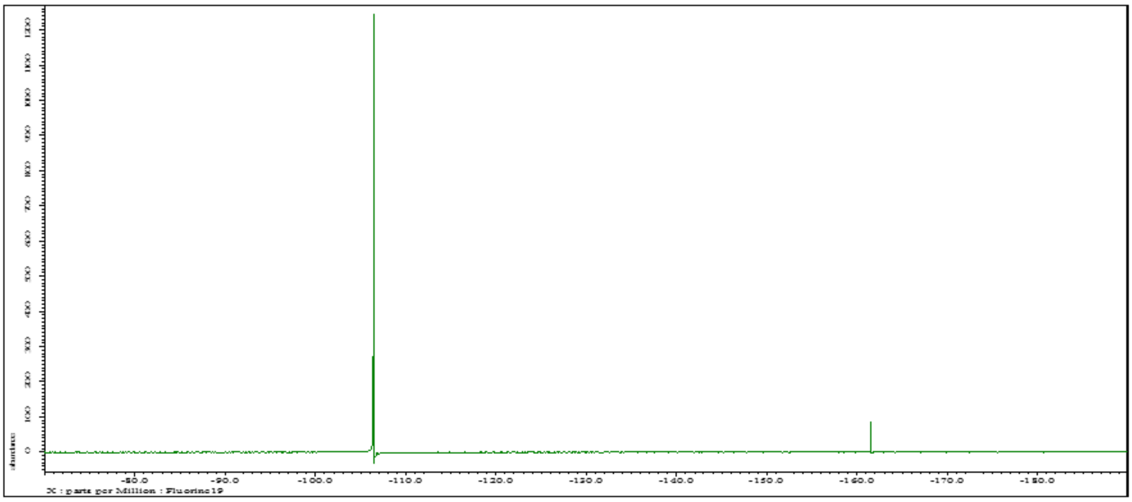
^{1}H NMR spectrum (**31f**)



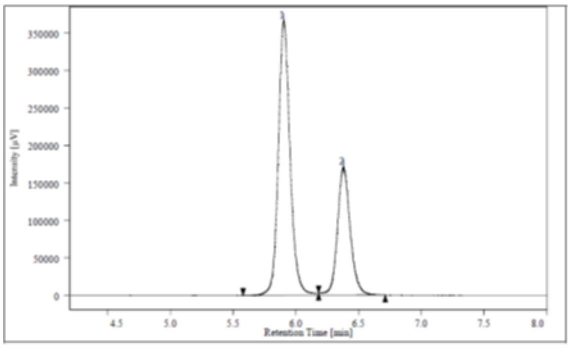
^{13}C NMR spectrum (**31f**)

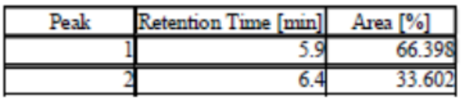


^{19}F NMR spectrum (**31f**)



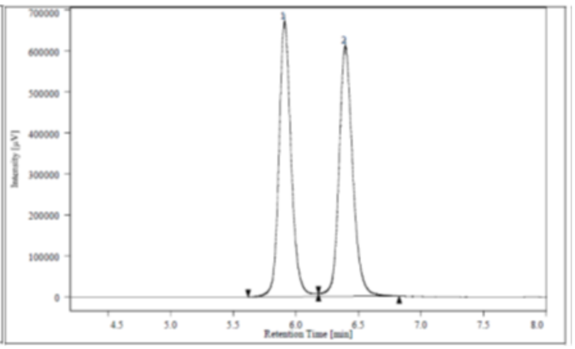
HPLC optically active (**31f**)

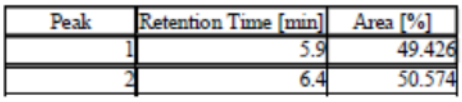




Peak	Retention Time [min]	Area [%]
1	5.9	66.398
2	6.4	33.602

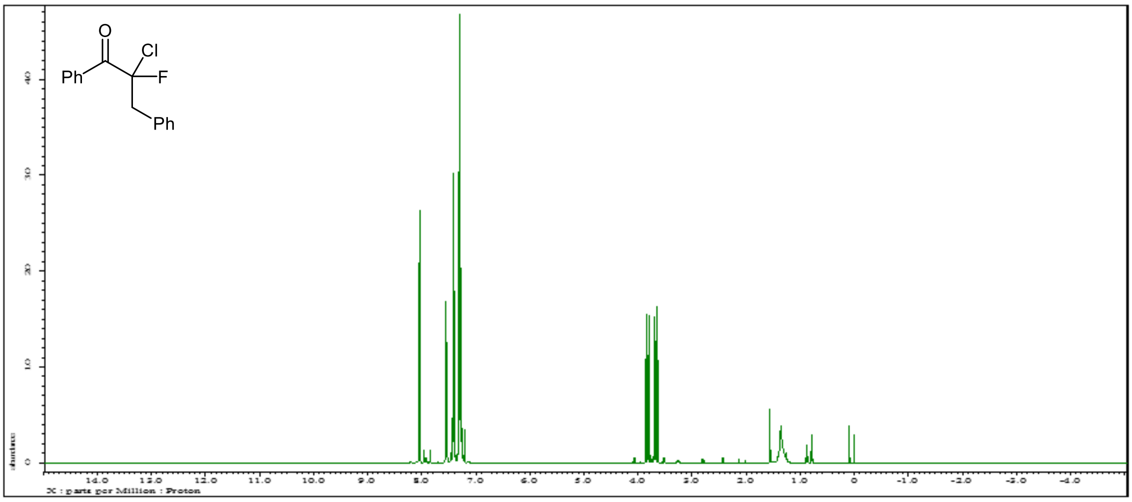
HPLC racemic (**31f**)



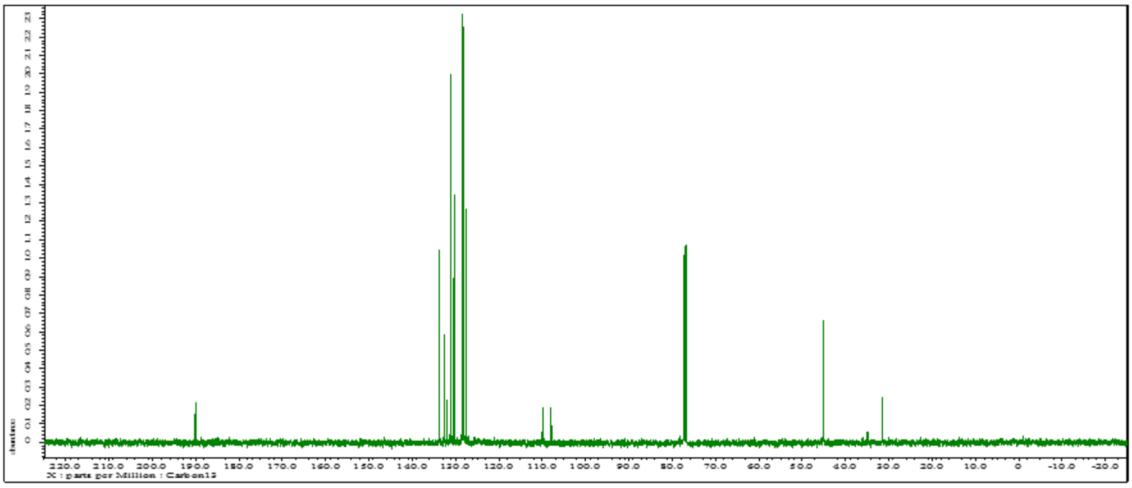


Peak	Retention Time [min]	Area [%]
1	5.9	49.426
2	6.4	50.574

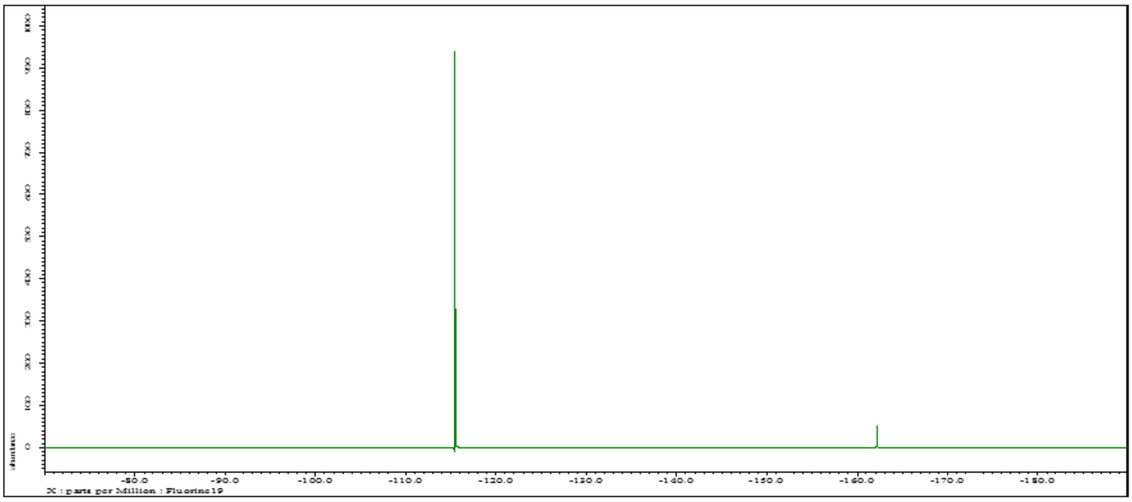
^{1}H NMR spectrum (**31g**)



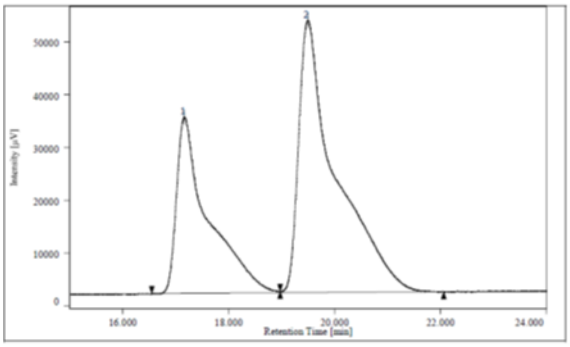
^{13}C NMR spectrum (**31g**)



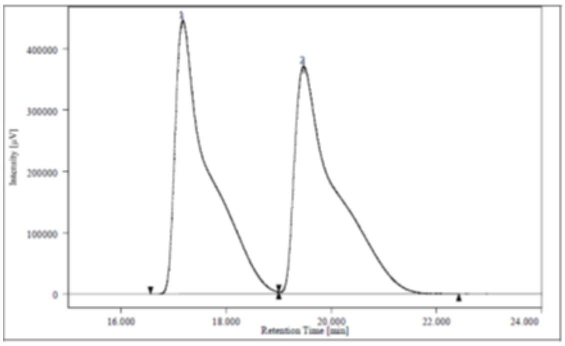
^{19}F NMR spectrum (**31g**)



HPLC optically active (**31g**)



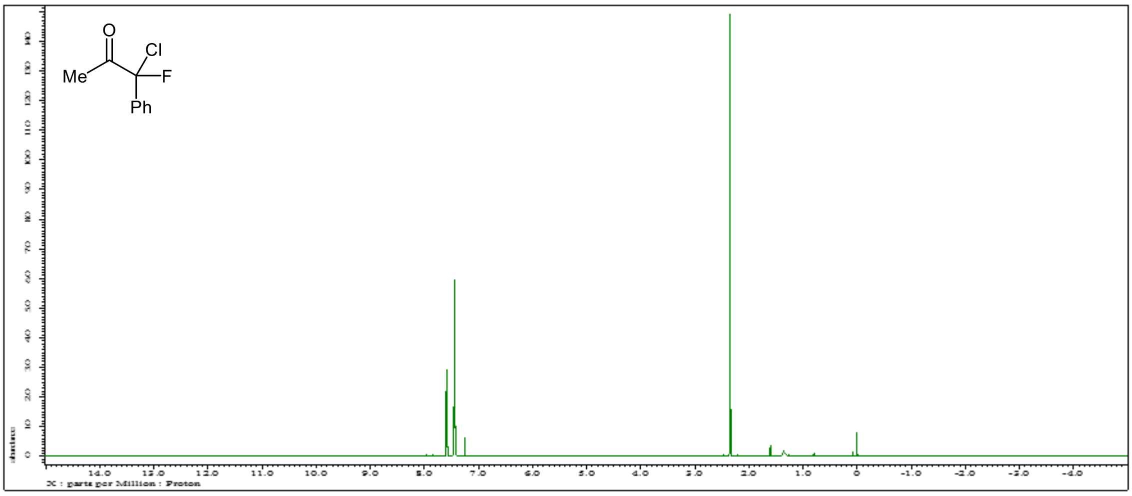
HPLC racemic (**31g**)



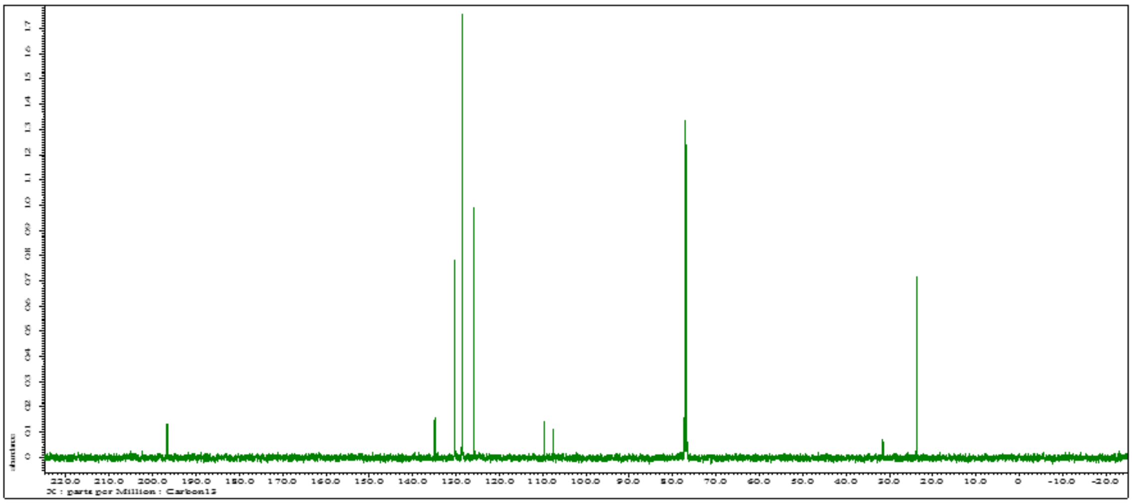
Peak	Retention Time [min]	Area [%]
1	17.2	35.484
2	19.5	64.516

Peak	Retention Time [min]	Area [%]
1	17.2	49.842
2	19.5	50.158

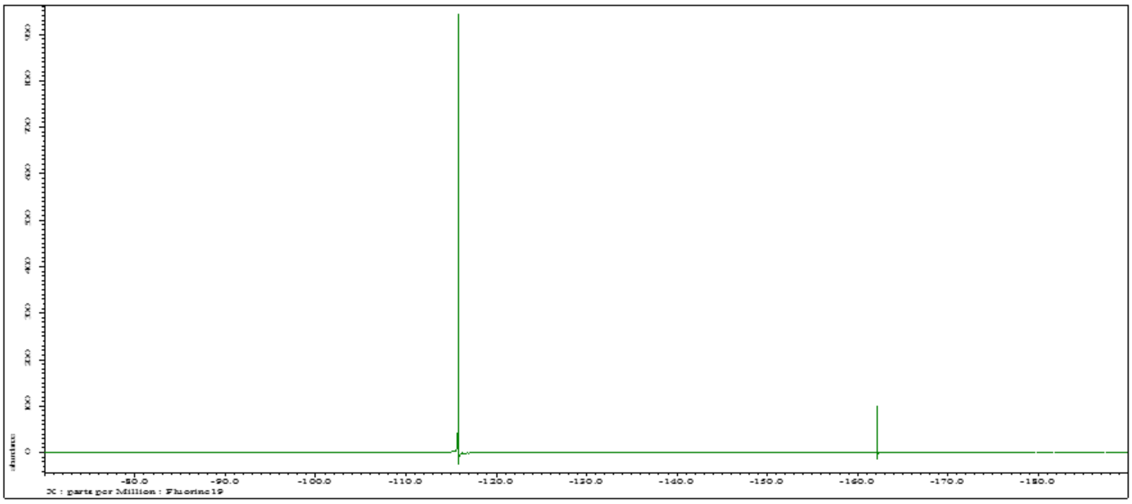
^{1}H NMR spectrum (**31h**)



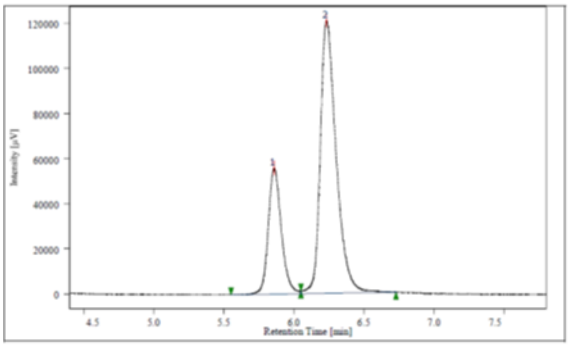
^{13}C NMR spectrum (**31h**)



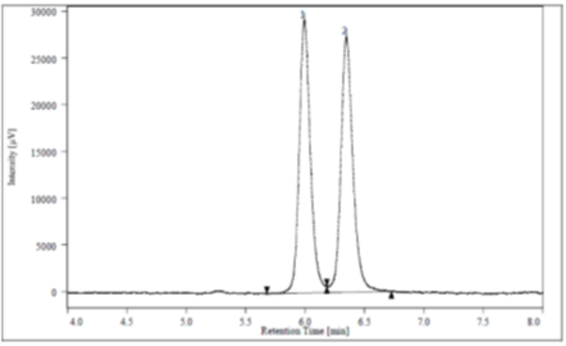
^{19}F NMR spectrum (**31h**)

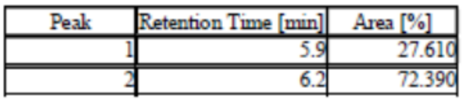


HPLC optically active (**31h**)

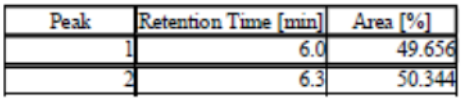


HPLC racemic (**31h**)



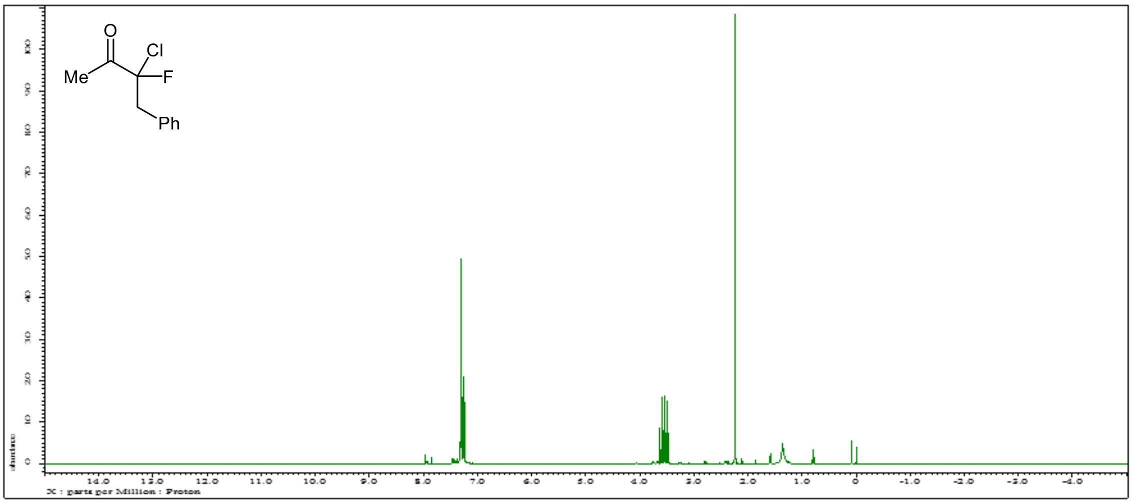


Peak	Retention Time [min]	Area [%]
1	5.9	27.610
2	6.2	72.390

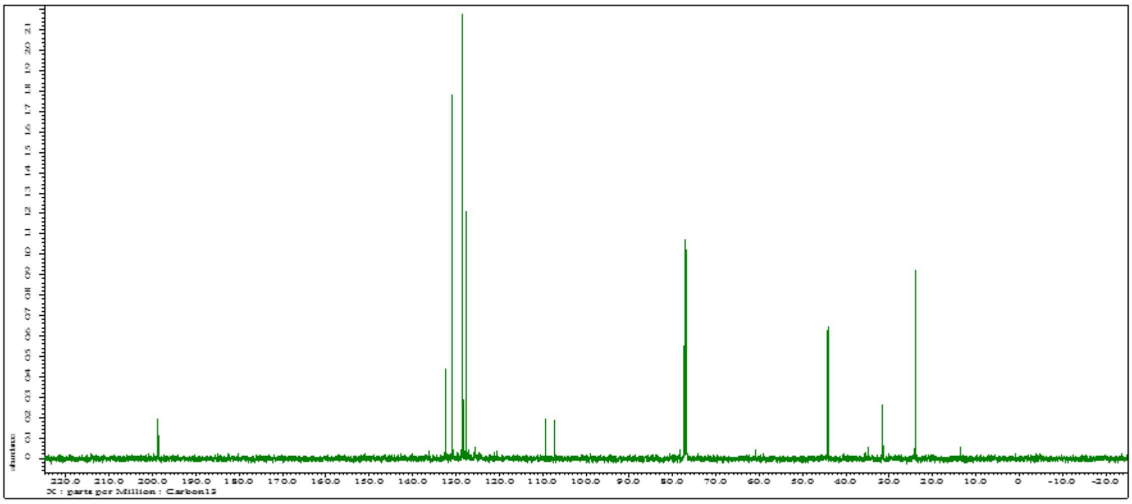


Peak	Retention Time [min]	Area [%]
1	6.0	49.656
2	6.3	50.344

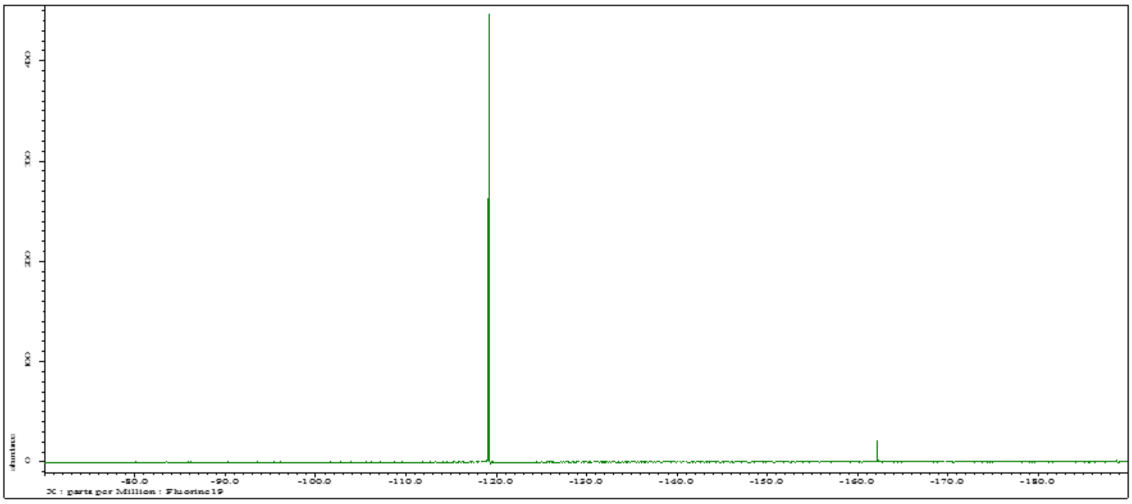
^{1}H NMR spectrum (**31i**)



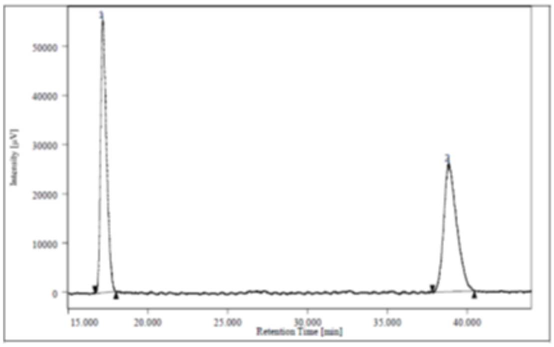
^{13}C NMR spectrum (**31i**)



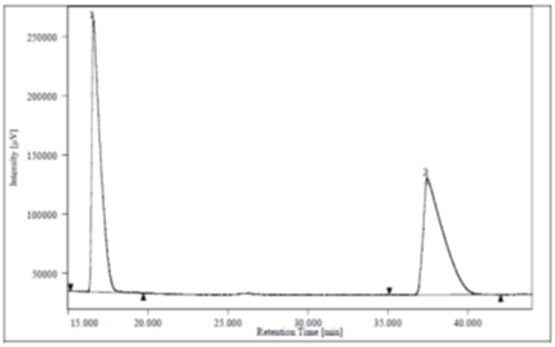
^{19}F NMR spectrum (**31i**)



HPLC optically active (**31i**)



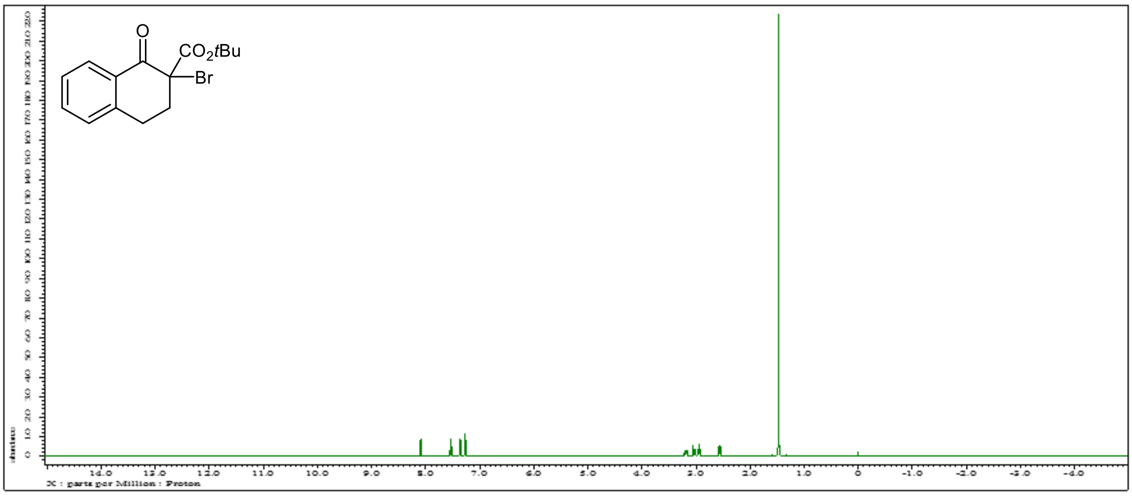
HPLC racemic (**31i**)



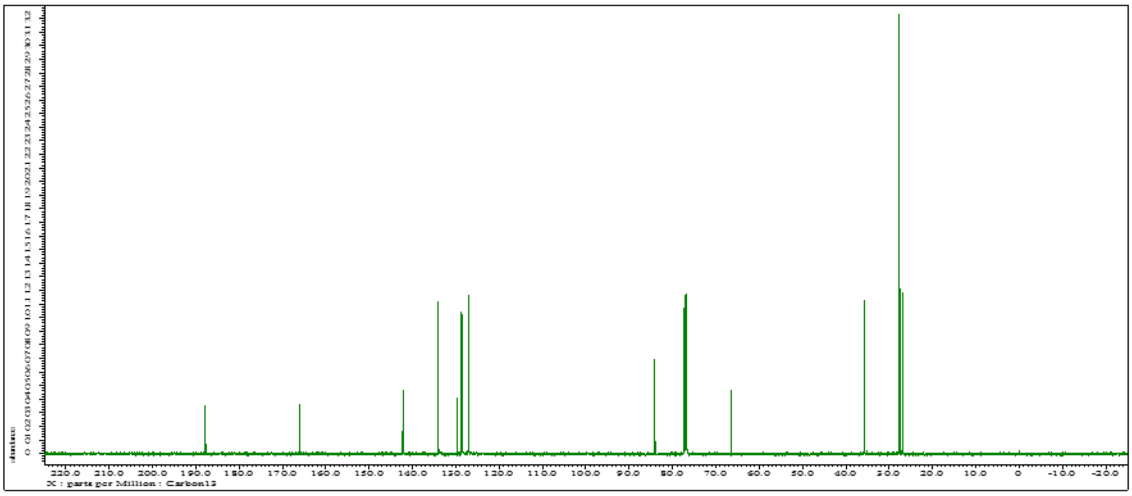
Peak	Retention Time [min]	Area [%]
1	17.2	49.206
2	38.8	50.794

Peak	Retention Time [min]	Area [%]
1	16.6	49.831
2	37.4	50.169

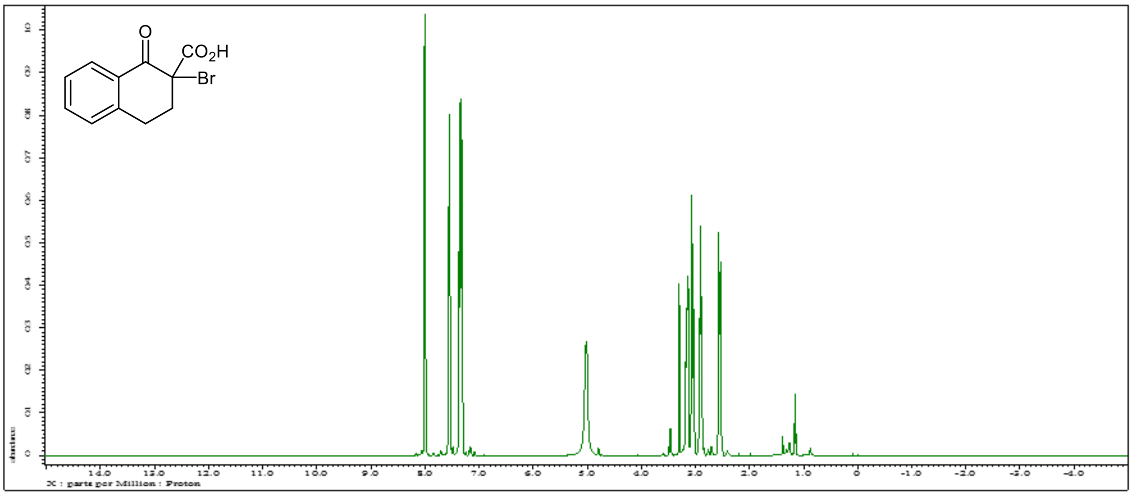
^{1}H NMR spectrum (**32**)



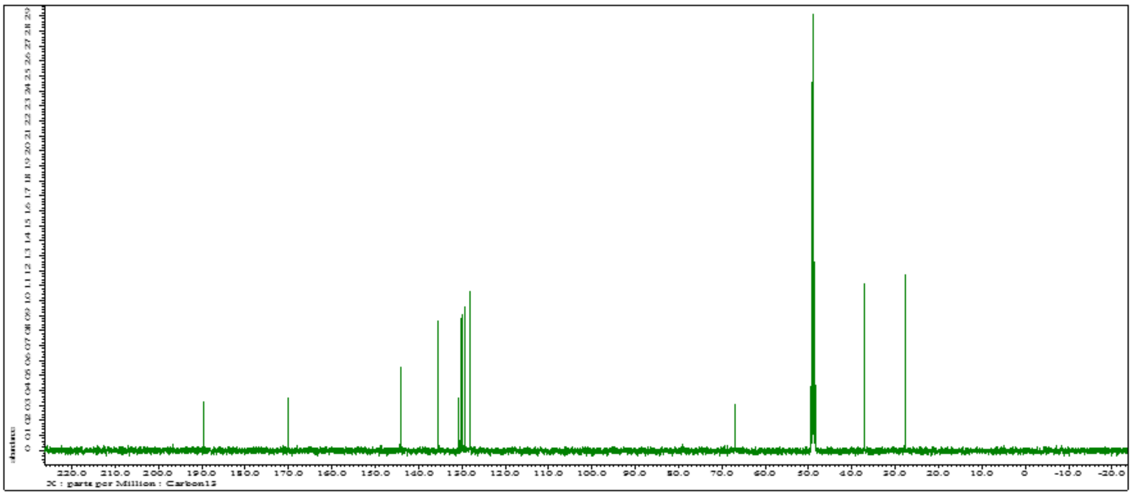
^{13}C NMR spectrum (**32**)



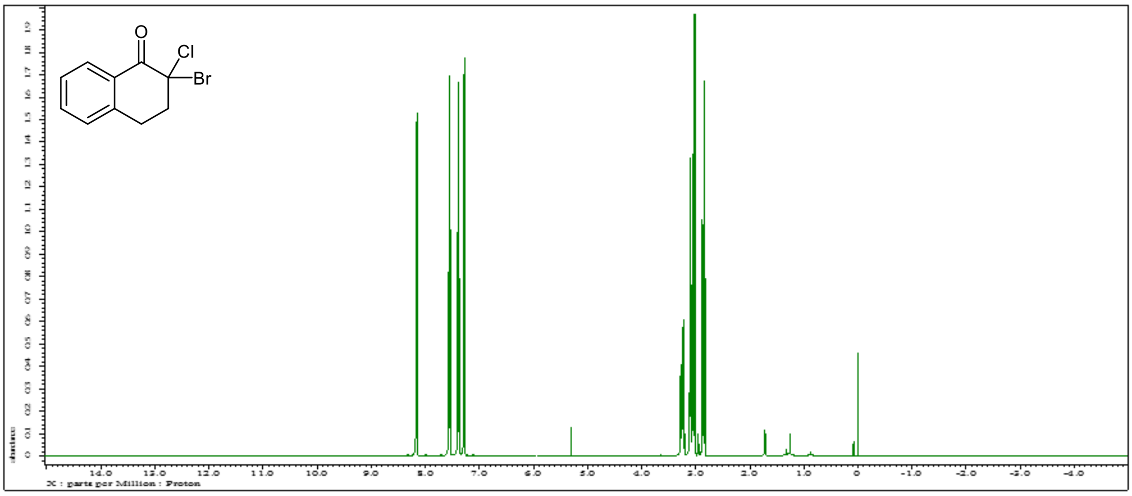
^{1}H NMR spectrum (**33**)



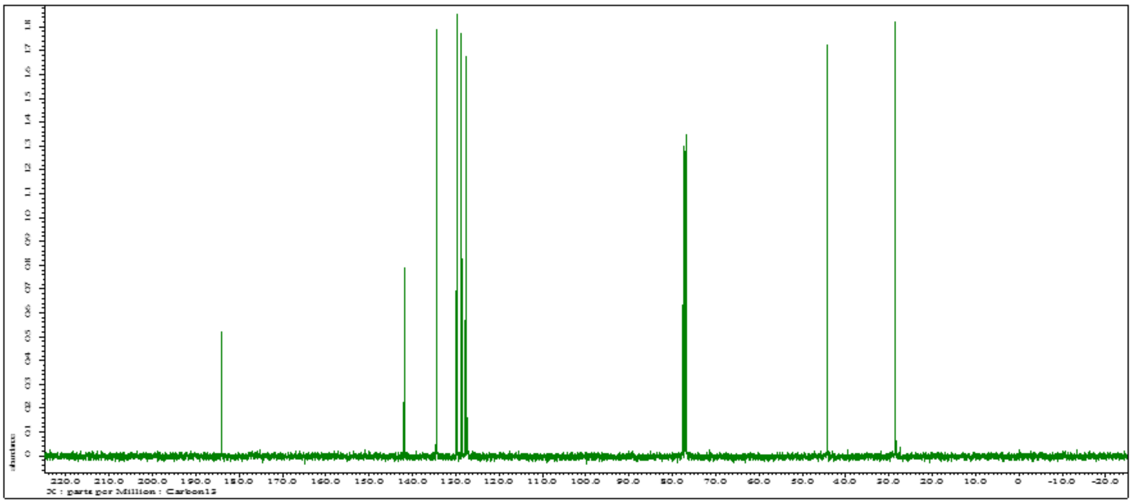
^{13}C NMR spectrum (**33**)



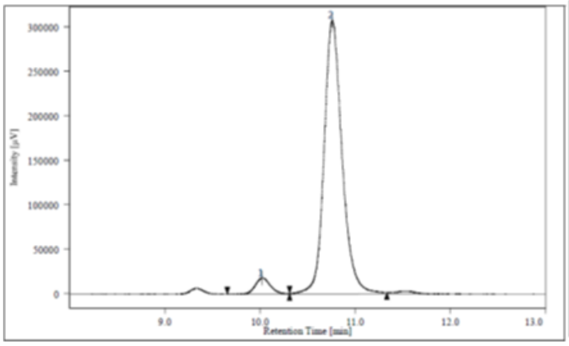
^{1}H NMR spectrum (**34**)



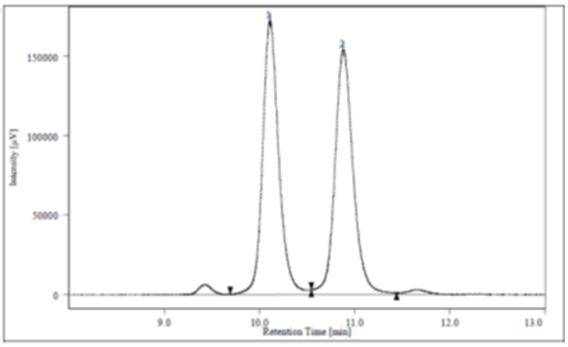
^{13}C NMR spectrum (**34**)

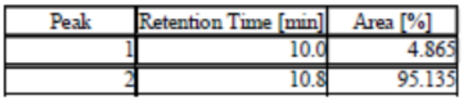


HPLC optically active (**34**)

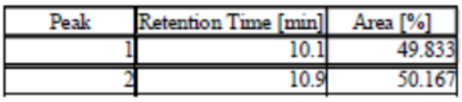


HPLC racemic (**34**)



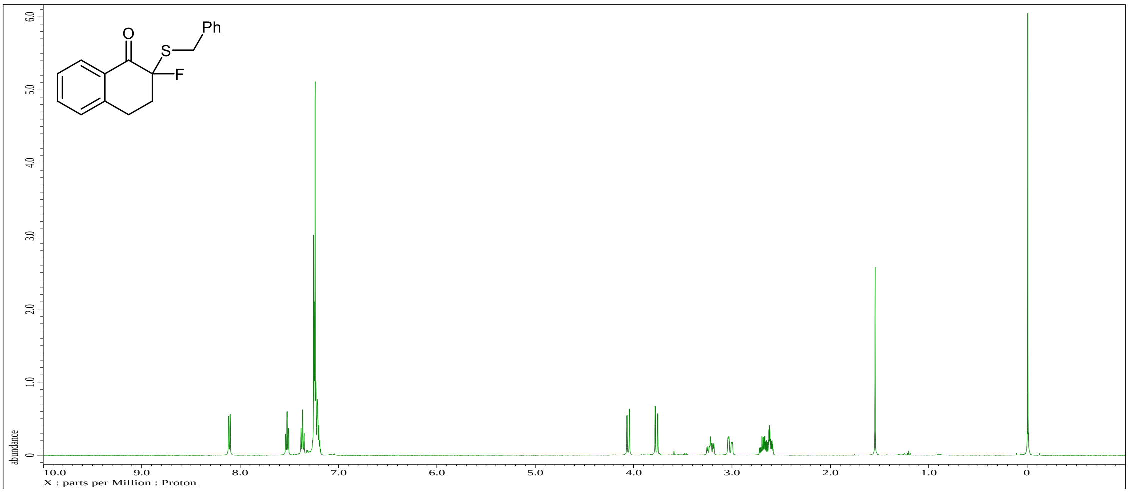


Peak	Retention Time [min]	Area [%]
1	10.0	4.865
2	10.8	95.135

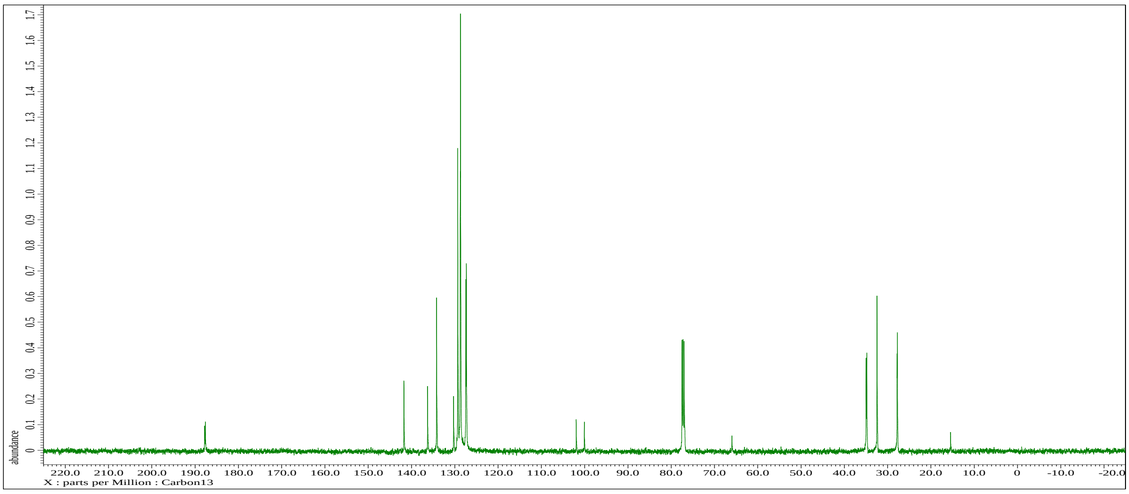


Peak	Retention Time [min]	Area [%]
1	10.1	49.833
2	10.9	50.167

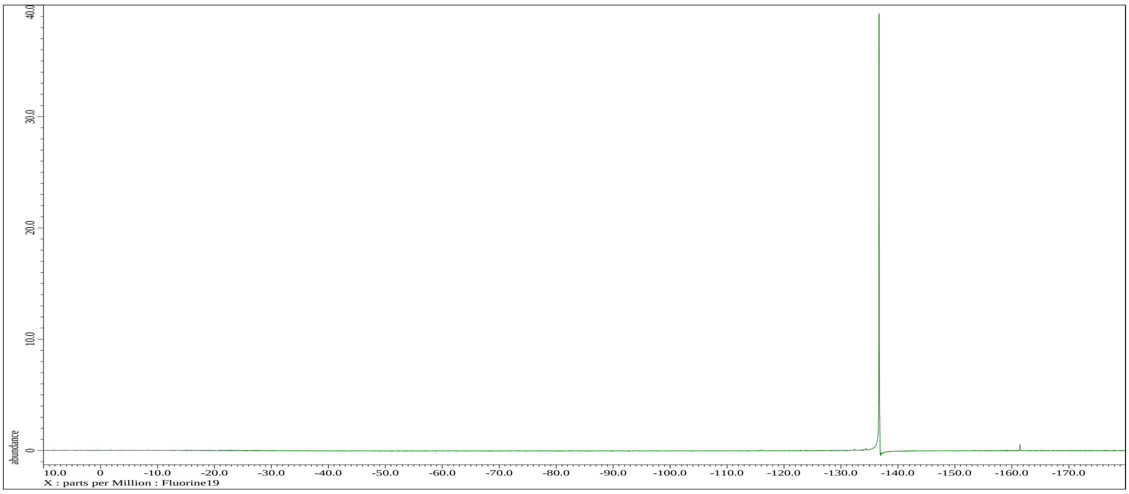
^{1}H NMR spectrum (**35**)



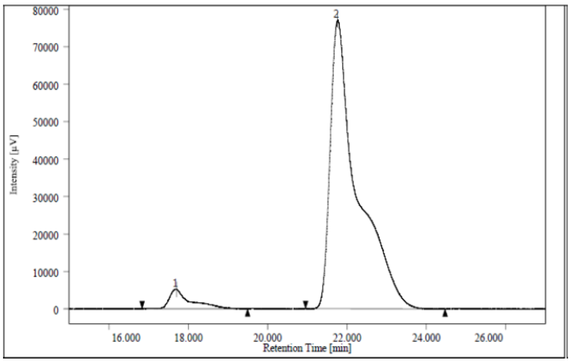
^{13}C NMR spectrum (**35**)



^{19}F NMR spectrum (**35**)

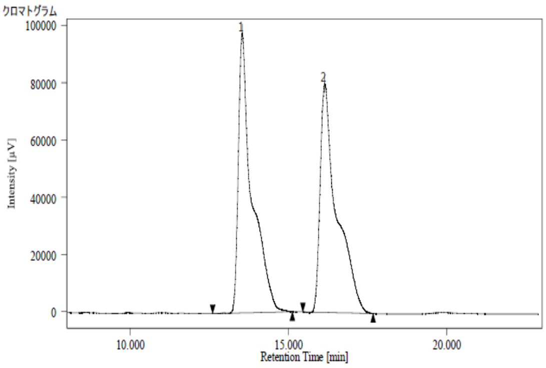


HPLC optically active (**35**)



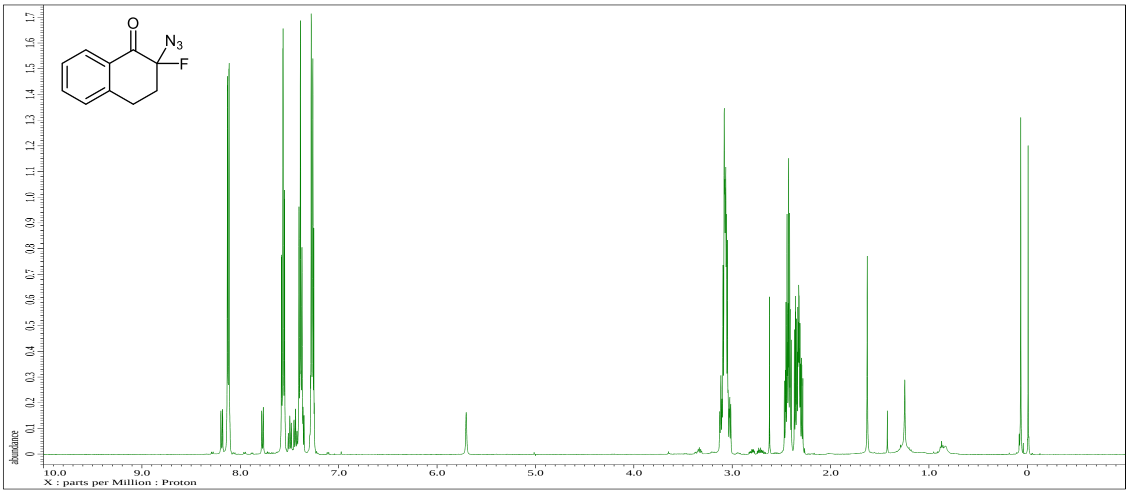
Peak	Retention Time [min]	Area [%]
1	17.7	5.042
2	21.8	94.958

HPLC racemic (**35**)

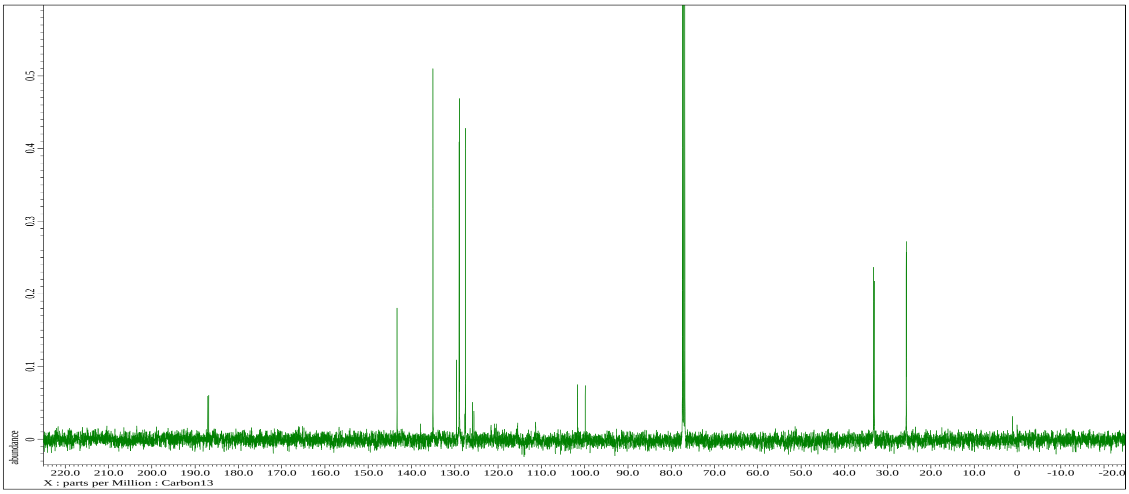


Peak	Retention Time [min]	Area
Unknown	13.533	49.904
Unknown	16.142	50.096

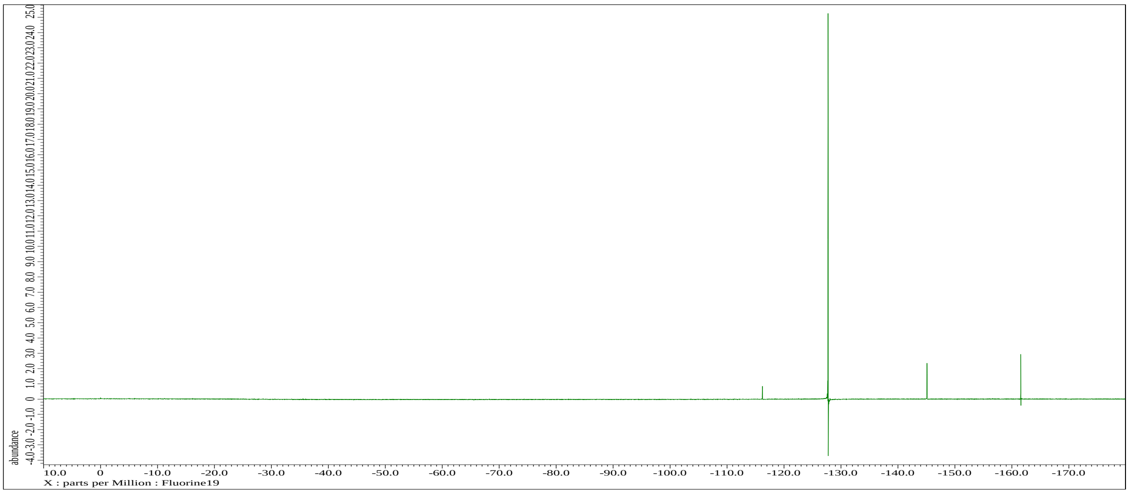
^{1}H NMR spectrum (**36**)



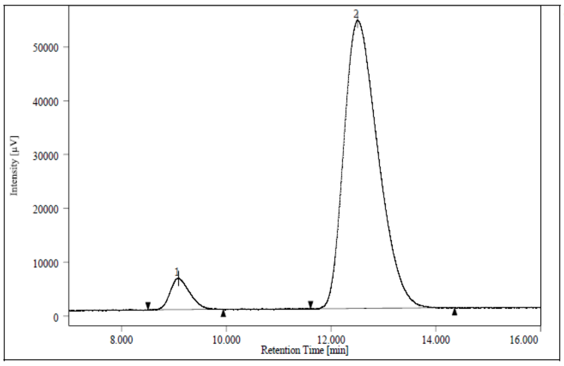
^{13}C NMR spectrum (**36**)

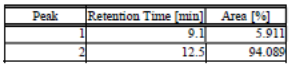


^{19}F NMR spectrum (**36**



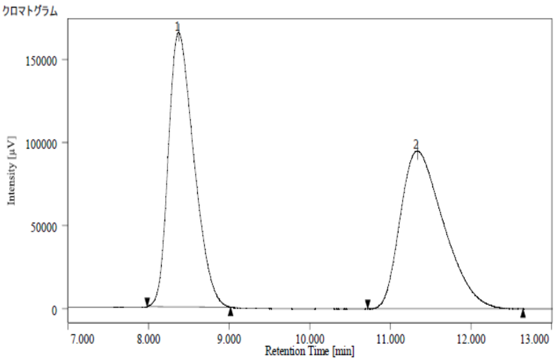
HPLC optically active (**36**)

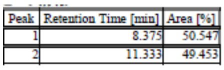




Peak	Retention Time [min]	Area [%]
1	9.1	5.911
2	12.5	94.089

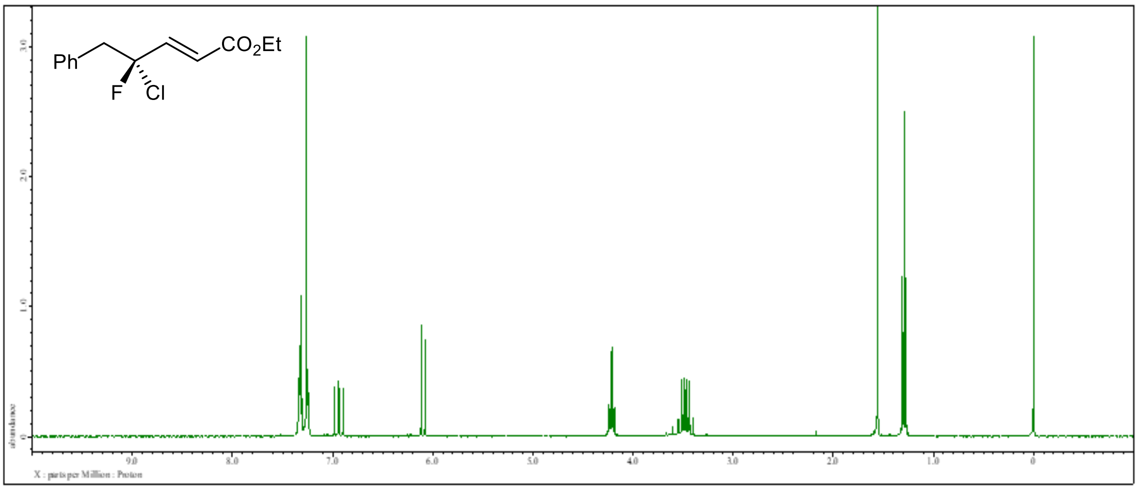
HPLC racemic (**36**)



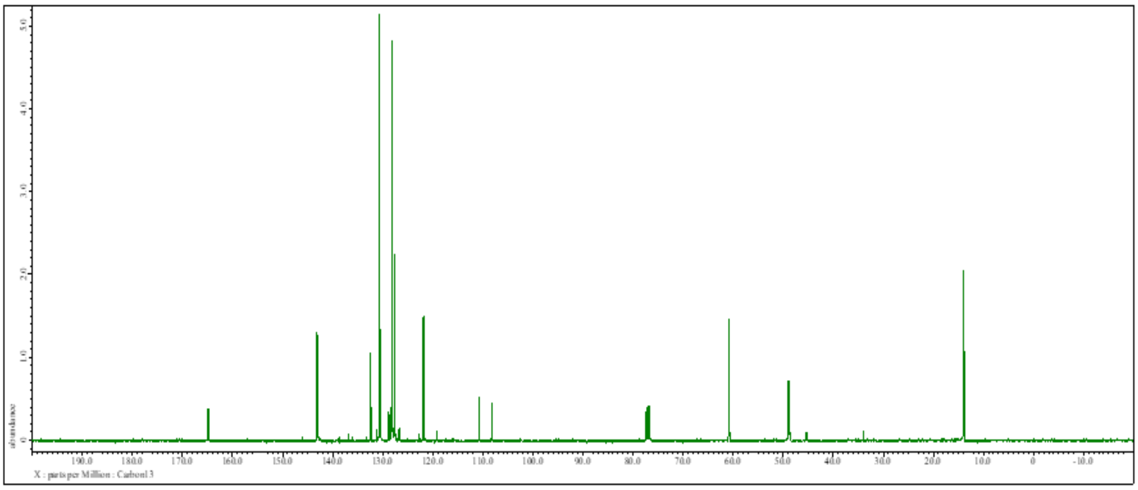


Peak	Retention Time [min]	Area [%]
1	8.375	50.547
2	11.333	49.453

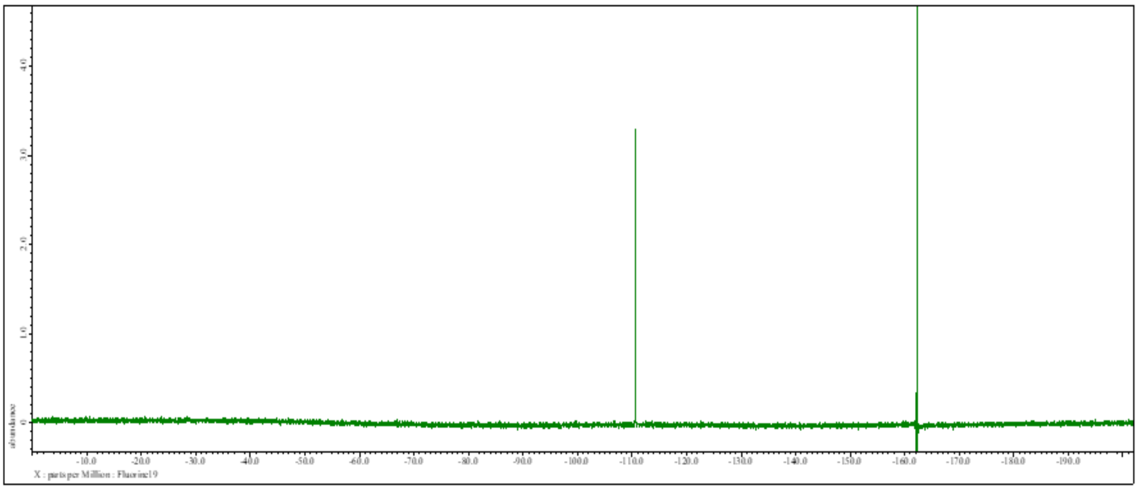
^{1}H NMR spectrum (**48**)



^{13}C NMR spectrum (**48**)

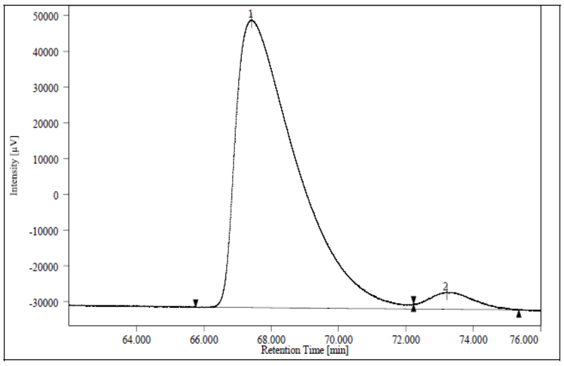


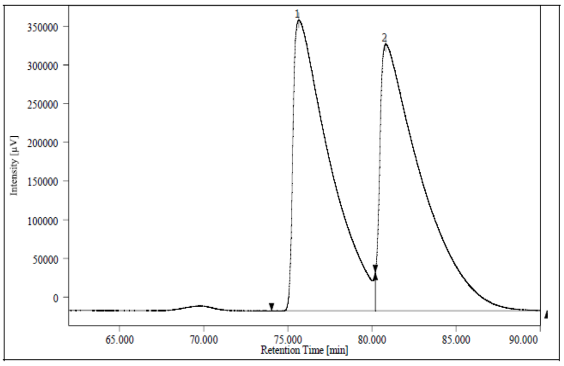
^{19}F NMR spectrum (**48**)

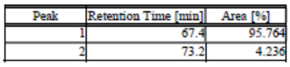


HPLC optically active (**48**)

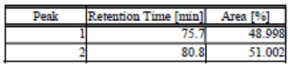
HPLC racemic (**48**)





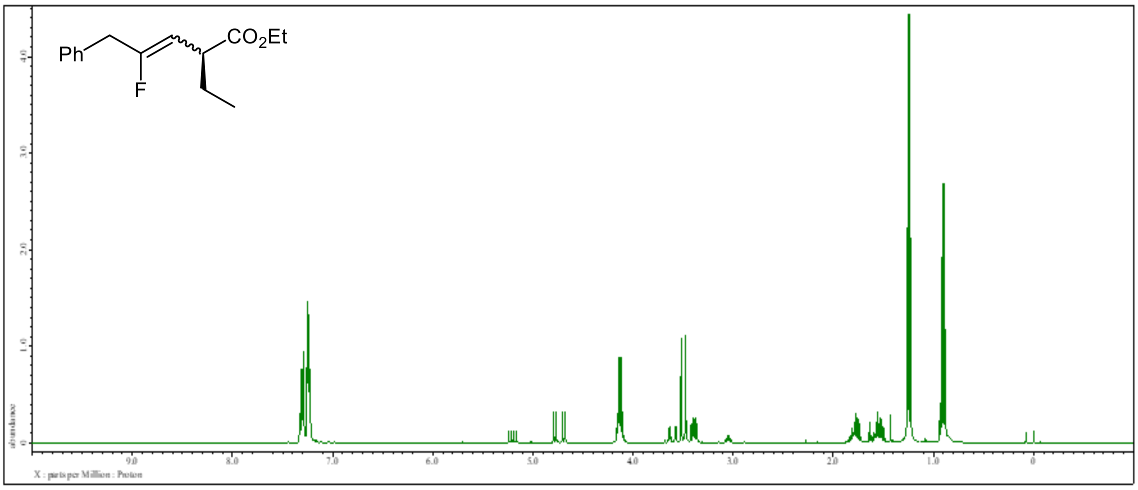


Peak	Retention Time [min]	Area [%]
1	67.4	95.764
2	73.2	4.236

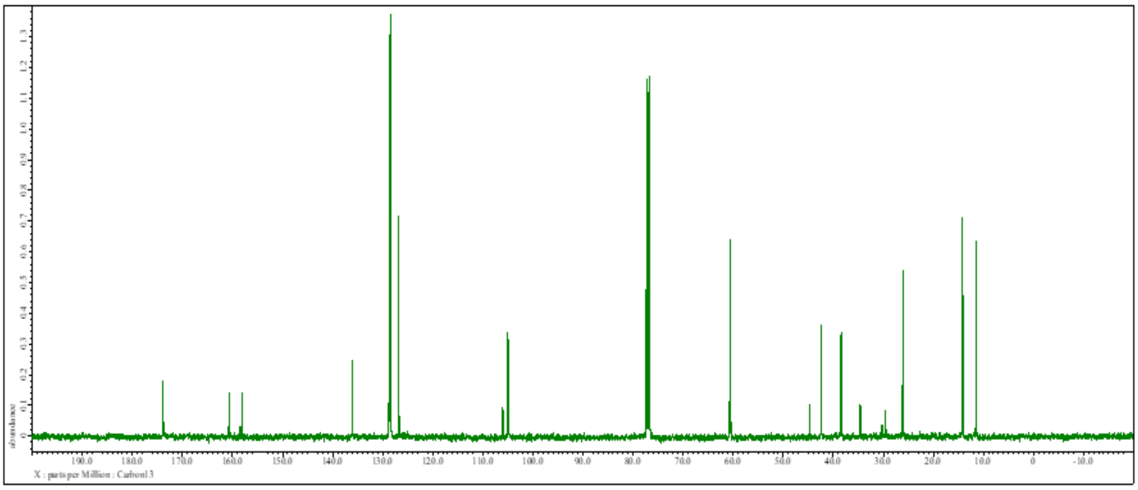


Peak	Retention Time [min]	Area [%]
1	75.7	48.998
2	80.8	51.002

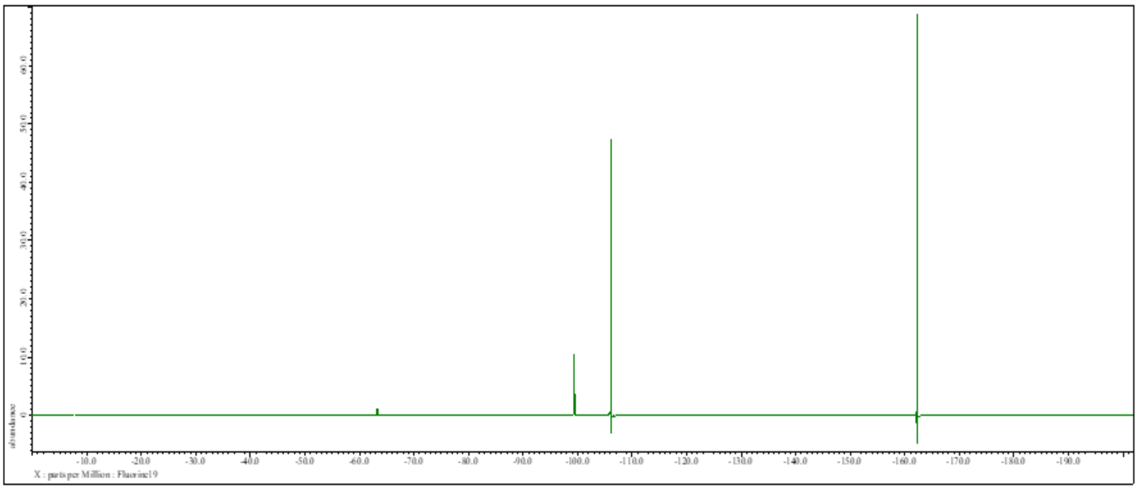
^{1}H NMR spectrum (**52**)



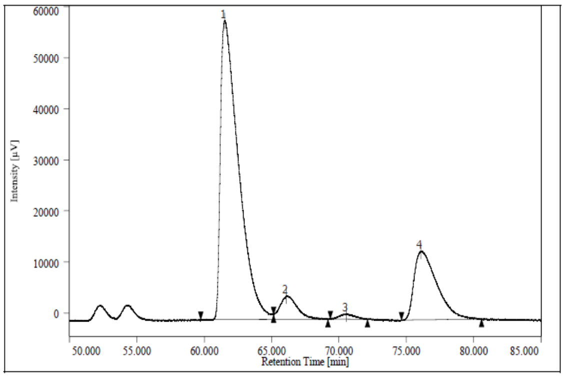
^{13}C NMR spectrum (**52**)



^{19}F NMR spectrum (**52**)

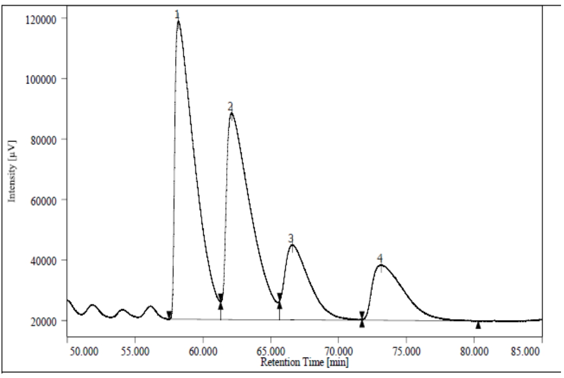


HPLC optically active (**52**)



Peak	Retention Time [min]	Area [%]
1	61.5	72.483
2	66.1	5.536
3	70.5	1.019
4	76.1	20.962

HPLC racemic (**52**)



Peak	Retention Time [min]	Area [%]
1	58.2	40.645
2	62.1	34.537
3	66.6	12.741
4	73.1	12.077