4.1. Chiral Auxiliaries

It is well accepted that most of the drug interactions with biological systems are enantiospecific due to the inherent chiral nature of biological compounds. Therefore, synthesis of chiral compounds has gained enormous importance in modern organic research. Although asymmetric catalysis and bio catalytic methods increasingly allow for the efficient synthesis of many optically pure compounds, chiral auxiliaries retains its importance in asymmetric synthesis.

In recent years considerable attention has been focused on the development of different chiral auxiliaries for the preparation of optically active chiral compounds. Chiral auxiliaries are optically pure or enantiomerically pure compounds which are attached to substrate and influence the course of the reaction [1].

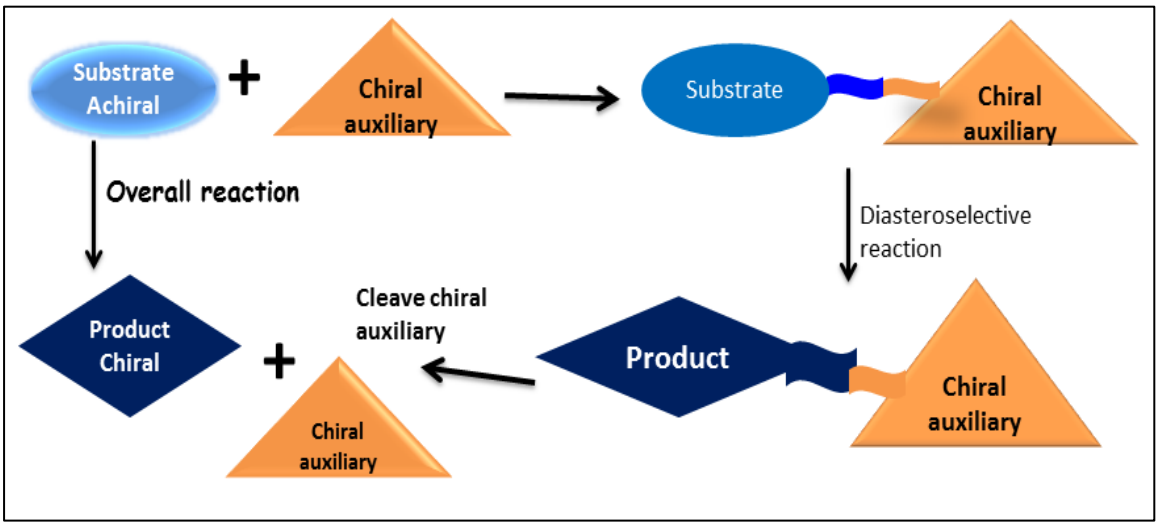
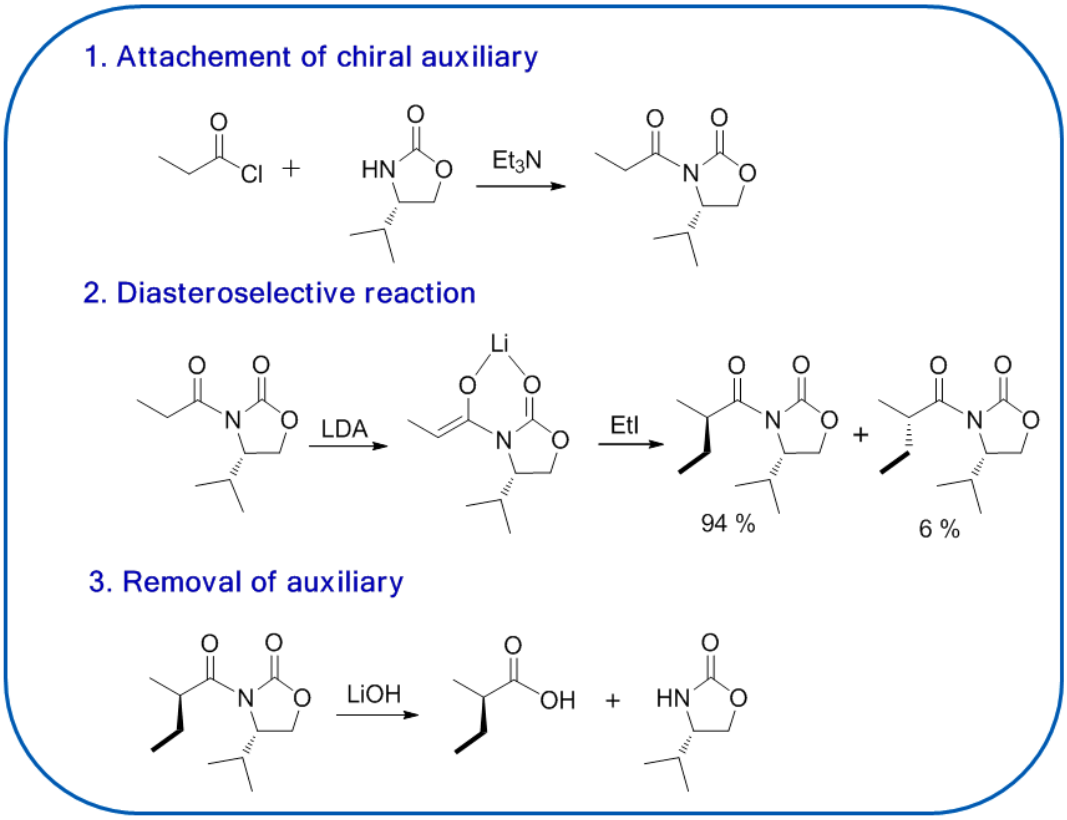


Figure 4.1: Schematic presentation of concept of chiral auxiliary

For many applications, no enantioselective methods exist and chiral auxiliary based synthesis are the only available steroselective approach for synthesis of desired molecules. Most importantly even in cases with imperfect selectivity the use of an attached chiral auxiliary allows the enrichment of diasterosectivity by recrystallization. From last three decades numerous auxiliary controlled reactions were reported, a notable example of Evan's auxiliary, one of the most utilized type of auxiliaries is the class of chiral oxazolidinones [2]. A well-known applications of Evan`s auxiliary is alkylation reaction which is discussed in scheme 4.1.

Scheme 4.1: Alkylation reaction with Valine derived chiral auxiliary

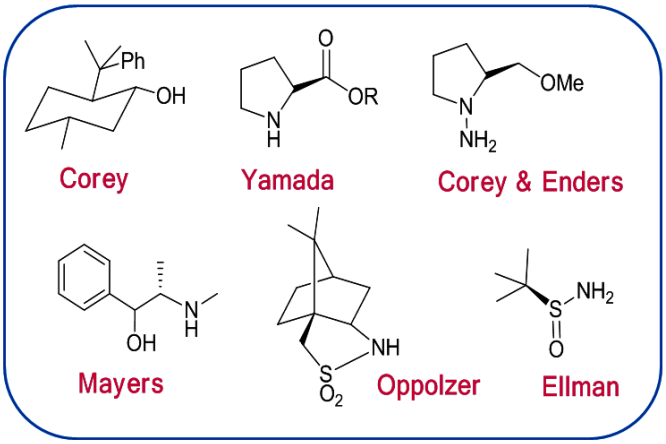


Other notable applications of Evan`s auxiliary is in asymmetric aldol reaction [3] and Diels-Alder reaction [4]. The aldol reaction is extremely valuable in terms of introducing steroselectivity as well as C-C bond formation. Chiral oxazolidinones have been utilized in stereoselective aldol reactions. In case of Aldol reaction, enolization was selective (*Z*-enolates) which was achieved using either lithium or dibutylboryl triflourosulfonate. Subsequently aldol reaction of metal enolates resulted in the products with selective asymmetric induction.

Such type of oxazolidinones are also used in Diel`s-Alder reaction. It was proposed that Lewis acid chelates between the carbonyl groups of the dienophile activates the alkene and locks the conformation so that the bulky isopropyl group blocks one face of the system in the s-*cis* conformation. Diene such as cyclopentadiene undergoes Diels-Alder reaction on the less hindered face.

The use of chiral auxiliaries in the synthesis of enantiomerically pure compounds has found wide applications for a variety of enantioselective reactions. Some other man made chiral auxiliaries which are well known are listed in scheme 4.2.

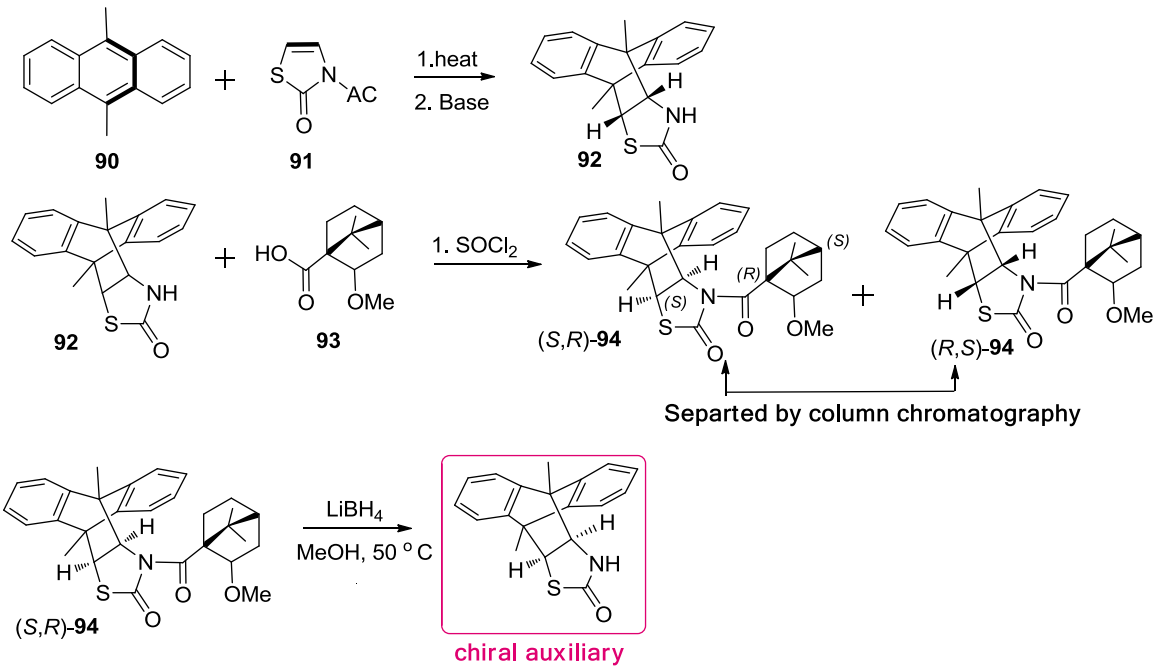
Scheme 4.2: Structure of different chiral auxiliaries



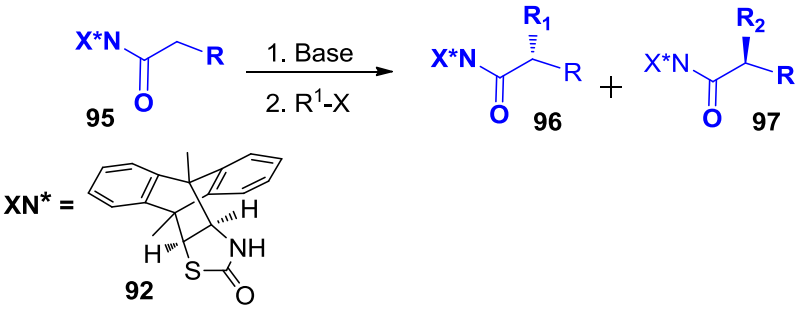
4.2 Roof shape auxiliary

In this context, Kunieda and co-workers used thiazolidinone based (Scheme 4.3) chiral auxiliary for the alkylation reaction [5]. The author described such auxiliary "roofed chiral 2-thiazolidinon" which are sterically congested and conformationally rigid. The required auxiliary was prepared by the [4+2] cycloaddition of 2-thiazolon (**91**) with the cyclic diene dimethylanthracene (**90**), followed by optical resolution with (1*S*,2*R*)-2-methoxy-1-apocamphanecarbonic acid (MAC acid, **93**). The obtained diastereomer **56** was separated with column chromatography.

Scheme 4.3: Synthesis and resolution of auxiliary



Scheme 4.4: Diastereoselective alkylation reaction



The high potential of **92** roof shaped chiral auxiliaries was also demonstrated by diasteromerically controlled alkylation via its enolate. The reactions proceeded with high to excellent diasteroselectivity. Result obtained in diastereoselective reaction are summarised in Table 4.1.

Table 4.1: Diastereoselective alkylation

No.	R	Base	R^1X	Temp (^oC)	Yield(%)	96:97
1	Me	NaHMDS	$PhCH_2Br$	-78	68	53:1
2	Me	NaHMDS	$CH_2=CHCH_2Br$	-78	56	39:1
3	Et	NaHMDS	CH_3I	-78	93	32:1

NaHMDS = Hexamethyldisilazane sodium salt

4.3 Criteria for chiral auxiliary

1. Readily available and easy to synthesise in both the forms
2. Easily attached
3. Induces stereochemistry
4. Chemically inert
5. Easily removed without racemisation

For a number of years, naturally available chiral auxiliaries remained the preferred choice for such studies. However, due to some limitations, such as availability of both isomers, difficulty to access the materials in large quantities in optically pure form and structural limitation, there is a growing need to search for new artificial chiral molecules to scan as auxiliaries for asymmetric synthesis. Several unnatural chiral molecules have been designed and utilized to control stereoselective synthesis involving a number of transformations [6].

The design of molecules suitable for the use as chiral auxiliary requires some specific

structural arrangement. The shape, size and arrangement of functional groups in chiral molecules play a crucial role in the efficiency of their use as auxiliary for asymmetric synthesis. Hence, molecules with unique shape and arrangement of aromatic rings suitable to offer stereocontrol can be examined as auxiliaries. It was previously discussed in chapter 2, that Weber introduced novel class of compounds resembling the shape of a roof and studied in their applications as clathrate hosts with inclusion properties. In our continuing work, in this chapter we utilized roof shape alcohol as chiral auxiliary for the preparation of α halo acids.

4.4 Importance of α halo acids

Optically pure α-substituted halo acids and their number of derivatives are an important class of natural and synthetic compounds. These acids and their derivatives are synthetically useful intermediates that can be converted into range of valuable structural motifs (Figure 4.2). In particular, they are precursors of enantiomerically active 2-amino acids and oxiranes. Many strategies have been investigated for their synthesis including chiral auxiliary based approach [7], asymmetric hydrogenation of acrylates [8], α-alkylation by phase-transfer catalysis [9] etc.

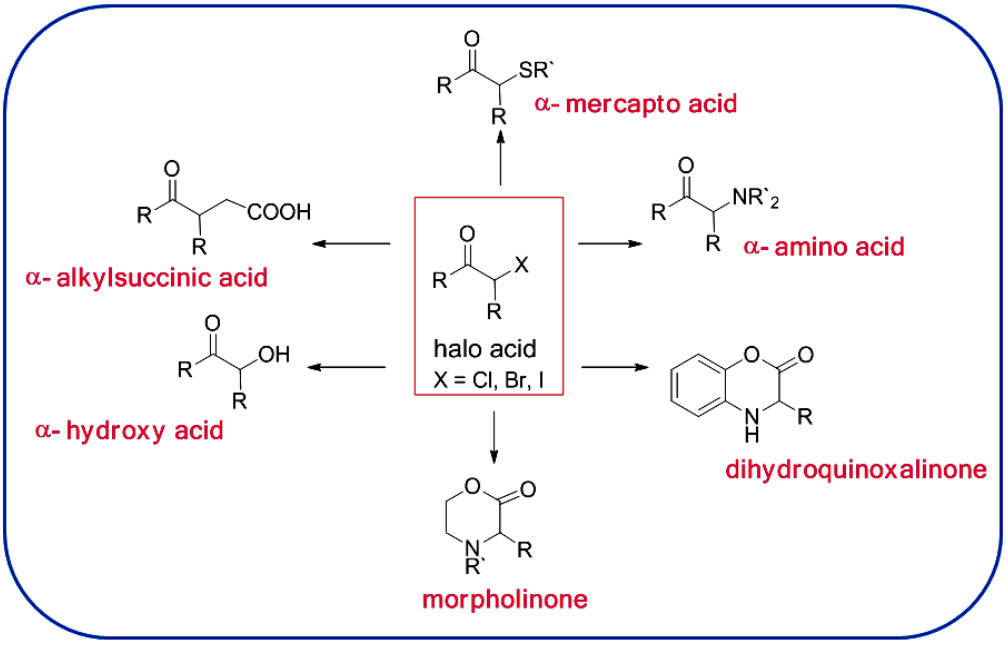


Figure 4.2: Application of α halo acid in synthesis of various compounds

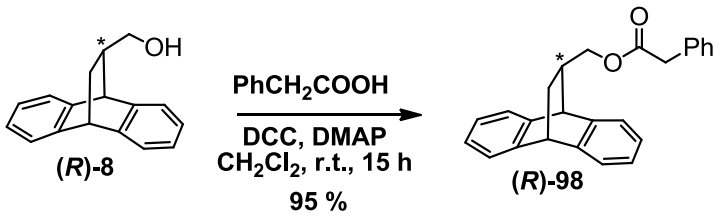
Separation of enantiomers of the easily available α-substituted acids and their straightforward conversion to functionalized derivatives is also an attractive option. This may be achieved by fractional crystallization of its salt with chiral resolving agents [10] or by enzymatic kinetic resolution methods [11]. Both these classical approaches can furnish maximum 50 % yield of the desired isomer. To overcome this limitation Dynamic Kinetic Resolution has been developed where the unreacted isomer of starting material is interconverted to the more reactive one, hence effectively increasing the conversions to quantitative level [12].

In this work we explore the chiral roof shape alcohol **8** as a new auxiliary to access optically enriched α-halo esters, as they can be converted to other derivatives using suitable substitution reactions.

4.5 Esterification reaction

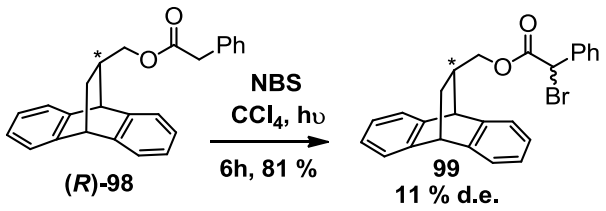
In our initial efforts to synthesize α-halo ester, it was condensed with phenyl acetic acid by the standard ester formation protocol [13] to access **98** in good yield (scheme 4.5).

Scheme 4.5: Esterification of acid with roof shape alcohol (*R*)-**8**



The ester **98** was subjected to α-bromination using NBS, the product **99** was isolated and characterized (Scheme 4.6). However the diastereomer ratio (d.e.) was quite low, as established by HPLC analysis.

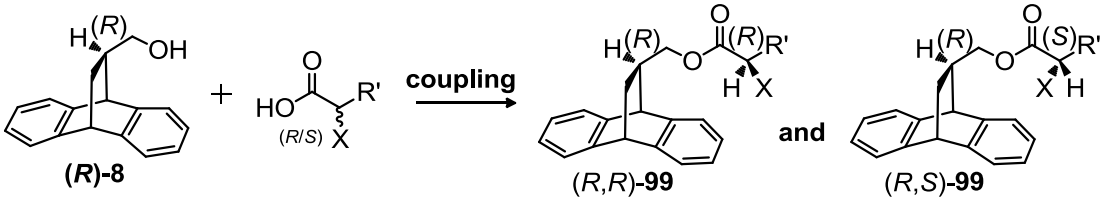
Scheme 4.6: Bromination of roof shape phenyl acetate **98**



Optical enrichment of α-halo ester derivatives of chiral alcohols during nucleophilic substitution reactions has been investigated [14]. In this study we examined the

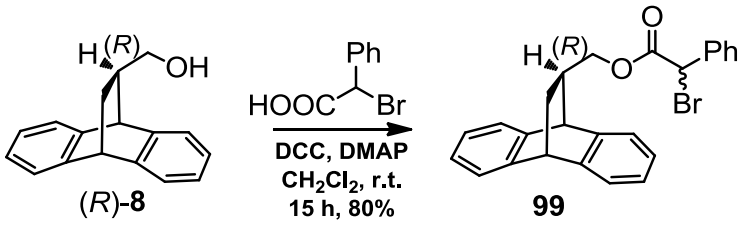
possibility of enrichment of isomers of α-halo ester **99** prepared from α-halo acid and chiral roof shape alcohol **8** (Scheme 4.7). This can take place either during the ester formation step or during the interconversion of isolated sample under appropriate conditions.

Scheme 4.7: Synthesis of diastereo enriched α-halo esters



Accordingly a sample of (*R*)-**8** was subjected to ester formation with (±) α-bromophenylacetic acid (Scheme 4.8). The product has two possible diastereomers, (*R*,*S*)-**99** and (*R*,*R*)-**99**, and their ratio was established by HPLC.

Scheme 4.8: Diastereoselective ester formation with α-bromo acid



The coupling was performed using DCC and DMAP at room temperature in dichloromethane (Table 4.2). The ratio of the two diastereomers, the chiral center on the roof shape alcohol portion was expected to remain unchanged, was established by HPLC analysis. Low d.e. in the absence of DMAP may indicate the possibility of isomerisation by base mediated abstraction of α-hydrogen (Table 4.2, entry 1)

Table 4.2: Diastereoselective coupling of (*R*)-**8** with (±) α-bromo acid.[a]

No	DMAP (mol %)	Reaction time (h)	Yield (%)[b]	Diastereomer ratio[c] (*R*,*S*)-**99**:(*R*,*R*)-**99**	[d.e.]
1	0	15	40	54:46	8
2	20	15	80	76:24	52
3	20	3	60	78:22	56

[a]All reactions run in CH_2Cl_2, addition of DMAP at 0 °C, then at r.t.; [b]Isolated; [c]Determined by HPLC.

In presence of catalytic quantity (20 mol %) of DMAP considerable improvement in the d.e. ratio was observed and longer reaction time only improved yield, without much affecting the selectivity.

4.6 Effect of solvent

Different solvents were also screened to determine the optimum conditions for selectivity and conversion (Table 4.3). Although toluene was found to be slightly better for selectivity the conversion was much better in dichloromethane.

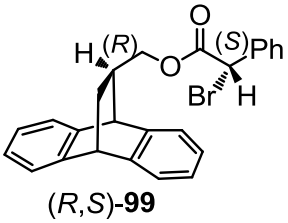
Table 4.3: Effect of solvent on the coupling of (*R*)-**8** with (±) α-bromo acid.[a]

No	Solvent	Yield (%)[b]	Diastereomer ratio[c] (*R*,*S*)-**99**:(*R*,*R*)-**99**	[d.e.]
1	CH_2Cl_2	80	76:24	52
2	THF	54	78:22	56
3	CH_3CN	56	62:38	24
4	Toluene	64	80:20	60

[a]All reactions run with DMAP (20 mol %), addition of DMAP at 0 °C, then at r.t. for 15 h; [b]Isolated; [c]Determined by HPLC.

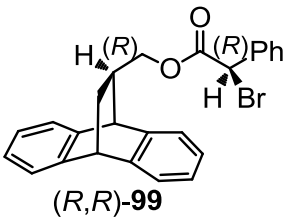
4.7 Separation of Diastereomers

It was significant to observe interesting crystallization pattern for the diastereomer of **99**. The major isomer was crystallized from acetonitrile while the minor one obtained from mixture of ethyl acetate and hexane.



(*R*,*S*)-**99**

Crystallized from CH_3CN
(Major)



(*R*,*R*)-**99**

Crystallized from EtOAc-hexane
(Minor)

Single crystal X-ray diffraction analysis of pure crystals of both isomers helped us to establish the absolute configuration of newly generated chiral center at the α-carbon of the esters. The major isomer crystallized from acetonitrile clearly indicated the configuration of the α-carbon to be '*S*', while it was '*R*' in the minor isomer (Figure 4.3).

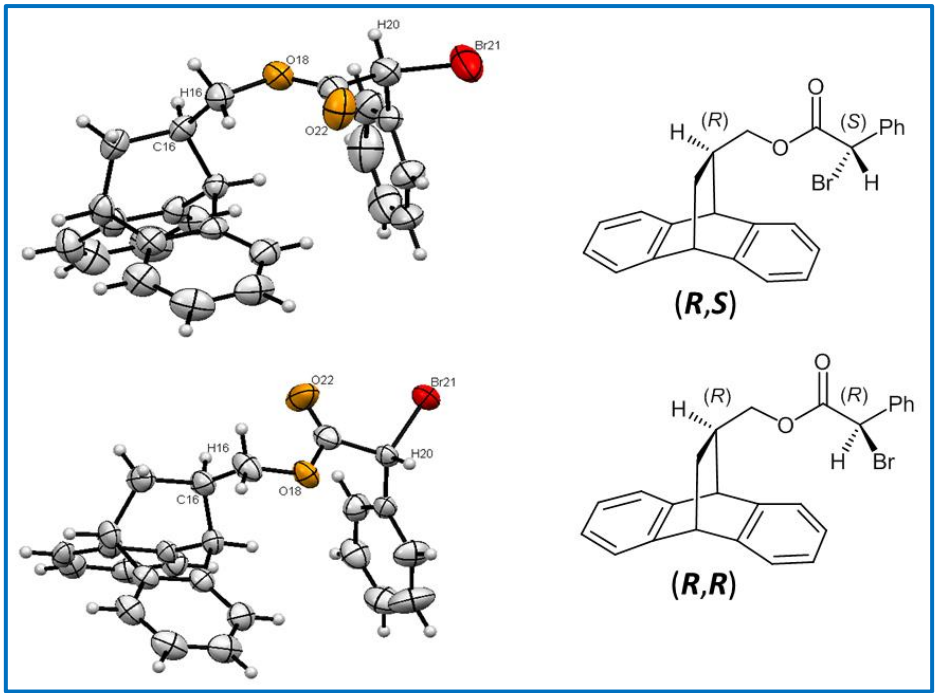


Figure 4.3: ORTEP diagram of (*R*,*S*)-**99** (*R*,*R*)-**99**

4.8 Crystal data of compound (*R*,*S*)-99and (*R*,*R*)-99

The details of the X –ray structure were deposited at the cambridge Crystallographic data Centre for compound **99** and details can be obtained via: www.ccdc.cam.ac.uk/datarequest/cif

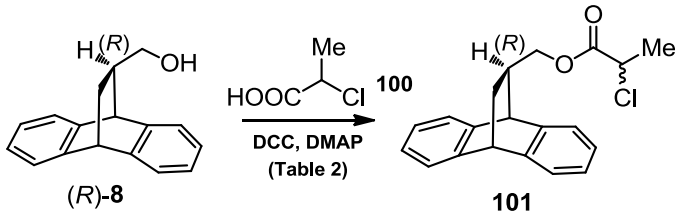
Identification code	**(*RS*)-99**[CCDC 1002050]	**(*RR*)-99** [CCDC 1002040]
Empirical formula	$C_{25}H_{21}BrO_2$	$C_{50}H_{42}Br_2O_4$
Formula weight	433.33	866.66
Temperature/K	293(2)	293(2)
Crystal system	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$P2_1$
Unit cell dimension	a = 9.1608(7) b = 10.3669(5) C = 21.378(2)	a = 10.4843(5) b = 10.8547(5) c = 17.9791(7)
α/°	90.00	90.00
β/°	90.00	90.356(4)
γ/°	90.00	90.00
Volume/Å^3	2030.3(3)	2046.05(16)
Z	4	2
ρ_{calc}mg/mm^3	1.418	1.407
μ/mm^{-1}	2.042	2.026
F(000)	888.0	888.0

2Θ range for data collection	6.24 to 58.06°	6.8 to 57.9°
Index ranges	-6 ≤ h ≤ 12, -14 ≤ k ≤ 7, -20 ≤ l ≤ 26	-12 ≤ h ≤ 14, -14 ≤ k ≤ 12, -23 ≤ l ≤ 24
Reflections collected	6051	13017
Independent reflections	4371[R(int) = 0.0222]	7491[R(int) = 0.0359]
Data/restraints/parameters	4371/0/253	7491/1/505
Goodness-of-fit on F^2	1.031	1.051
Final R indexes [I>=2σ (I)]	R_1 = 0.0716, wR_2 = 0.1607	R_1 = 0.0393, wR_2 = 0.0679
Final R indexes [all data]	R_1 = 0.1098, wR_2 = 0.1865	R_1 = 0.0606, wR_2 = 0.0756
Largest diff. peak/hole / e $Å^{-3}$	1.72/-1.14	0.42/-0.44
Flack parameter	0.02(2)	-0.001(6)

4.9 Coupling with Chloro propionic acid

In the next set of experiment α-chloropropionic acid **100** was condensed with (*R*)-**8** in presence of DCC-DMAP (Scheme 4.9). The product **101** was isolated and the ratio of the diastereomers was established by ^{1}H NMR analysis (Figure 4.4) as the methyl doublet for both appeared at measurable positions which were further confirmed by HPLC analysis.

Scheme 4.9: Diastereoselective ester formation with α-chloro acid



The result of the experiment was almost similar (Table 4.4), however the diastereomer ratio of the product was much higher as compared to **99**.

Table 4.4: Diastereoselective coupling of (*R*)-**8** with (±)-**101**.[a]

No	DMAP (mol %)	Reaction time (h)	Yield (%)[b]	Diastereomer ratio[c] (*R*,*S*)-**101**:(*R*,*R*)-**101**	[d.e.]
1	20	3	76	95:5	90
2	20	15	82	94:6	88
3	50	15	95	93:7	87

[a]All reactions run in CH_2Cl_2, addition of DMAP at 0 °C, then at r.t.; [b]Isolated; [c]Determined by HPLC.

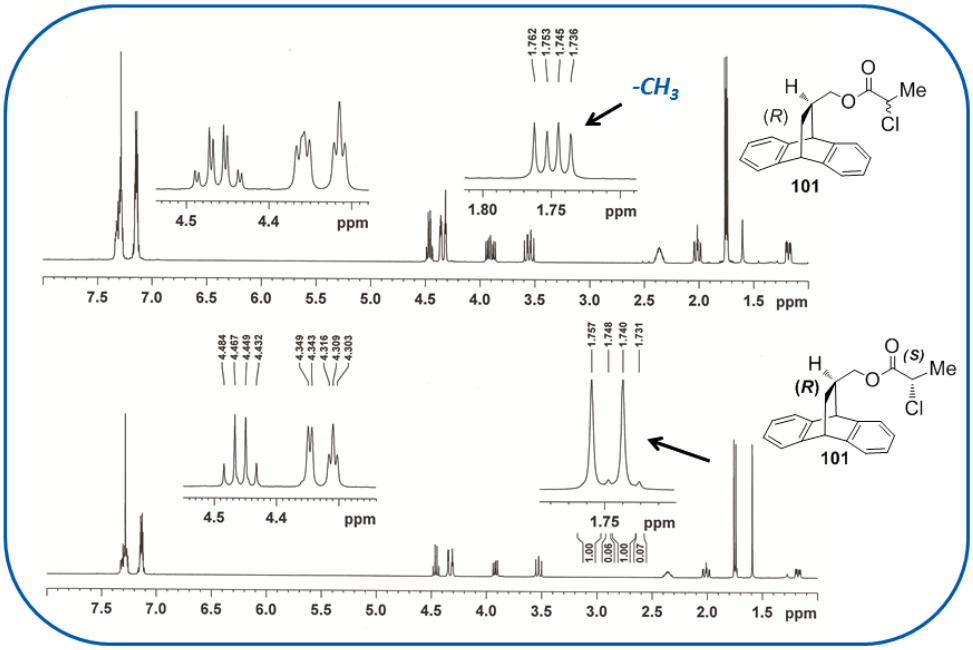


Figure 4.4: ^{1}H NMR spectra (top) racemic (bottom) compound **101**: The peaks of methyl are expanded

4.10 Assignment of absolute configuration

The next phase of our work was to determine the stereochemistry at the newly formed asymmetric center. Since in case of chloro derived ester **101** diastereomeric ratio was already (95:5) hence no further crystallisation was done, its absolute configuration was determined by comparing its retention time with its standard sample that is (*R*,*R*)-**101** which was prepared by coupling of (*R*)- chloro propionic acid **100** with (*R*)-**8** alcohol. In this case **(*S*)** stereochemistry predominated at newly generated chiral center.

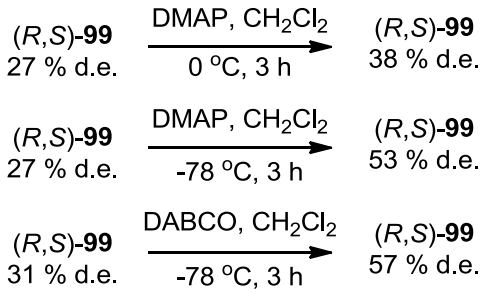
4.11 Enrichment of diastereomeric ratio

These coupling reactions were conducted with equimolar ratio of alcohol (*R*)-**8** and racemic halo acids and the yield and the diastereomer ratios were more than 50%. This reduces the possibility of only one isomer of acid selectively participating in the reaction with chiral alcohol. Hence, the other possibility for enrichment of diastereomer may involve interconversion of isomers of the ester to achieve the equilibrium in favor of stereochemically and thermodynamically stable product.

To test this possibility, sample of **99** with moderate d.e. was subjected to basic condition for some time and quenched. The product was carefully recovered and

analyzed to indicate some enrichment in the ratio (Scheme 4.10). Reaction at room temperature resulted in marginal enrichment, while at low temperature considerable enhancement was found. The organic base DMAP and DABCO showed similar effect in this experiment.

Scheme 4.10: Enrichment of diastereomeric ester (*R*,*S*)-**99**.



When sample of **99** was exposed to base, the acidic α proton was abstracted and the resulting ketene intermediate [15] can have two possible forms A and B (Figure 4.5). Form B may exhibit some steric hindrance between the larger bromine and the bicyclic skeleton, while more stable form A may recapture proton to give (*R*,*S*)-**99** as major product.

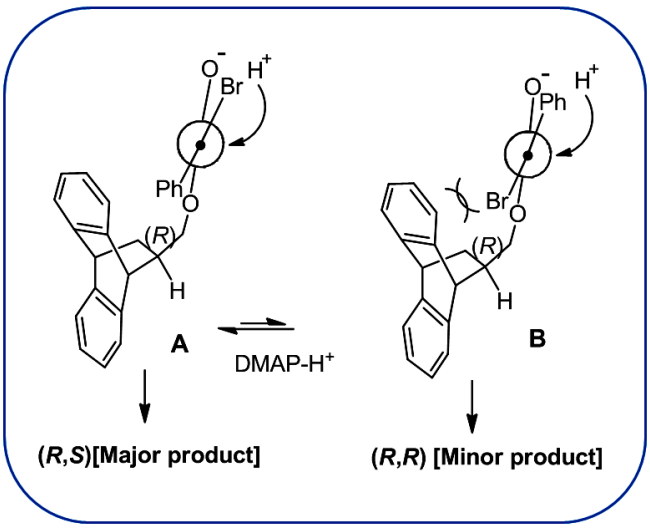


Figure 4.5: Intermediates in the enrichment of diastereomeric ester **99**.

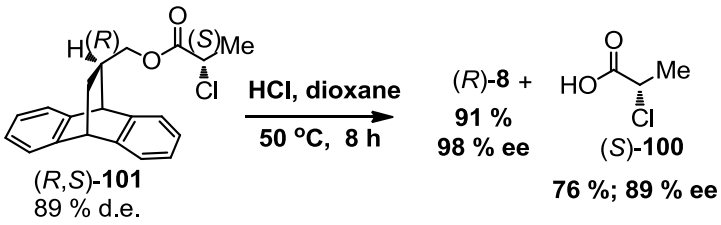
The selectivity was higher for the chloro derivative **101**, probably because the smaller size of methyl compared to the phenyl of **99**, shifts the equilibrium toward the corresponding form A. Such dynamic kinetic resolution for substitution reactions is

reported for α-halo esters attached to chiral axillaries for selective reactions [16] including some different type of roof shape ones [17].

4.12 Hydrolysis

The sample of optically enriched (*R*,*S*)-**101** was subjected to acid catalyzed hydrolysis reaction (Scheme 7) [18]. The recovered alcohol **8** was obtained in optically pure form and the cleaved α-chloropropionic acid **100** was established to be of '*S*' configuration by comparison of its specific rotation.

Scheme 4.11: Hydrolysis of diastereomeric ester of α-chloro acid

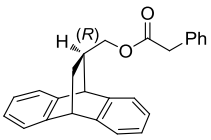


Thus we present the use of new chiral roof shape auxiliary to achieve efficient stereocontrol in base mediated dynamic kinetic resolution of α-halo esters.

Experimental section

(11*R*)-9,10-dihydro-9,10-ethanoanthracen-12-yl)methyl 2-phenylacetate-(*R*)-**98**

In dry two necked round bottom flask alcohol (*R*)-**8** (0.40 g, 1.7 mmol), DCC (0.350 g, 1.7 mmol) and DMAP (0.020 g 0.17 mmol) was added and dissolved in 5 mL of dichloromethane cooled to 0°C. A solution of Phenyl acetic acid (0.23 g, 1.7 mmol) in ~5 mL of DCM was then added drop wise. The reaction mixture was stirred at 0^{o}C for 1 h after which it was allowed to warm to room temperature and stirred for another 14 h. Then whole reaction mixture was passed through celite and washed with dichloromethane and purified by column chromatography over silica gel by eluting with petroleum ether–ethyl acetate. White solid (0.570 g, 95%) M.p = 98-99 °C $[\alpha]_D^{28}$ = 19.1 (*c* = 1, $CHCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08-1.13 (ddd, *J* = 7.6 Hz, 4.8H, 2.8 Hz, 1H), 1.90-1.97(m, 1H), 2.21-2.28 (m, 1H), 3.35-3.40 (dd, *J* = 10.8 Hz, 10 Hz, 1H), 3.67 (s, 2H), 3.82-3.87 (dd, 10.8 Hz, 10 Hz, = 1H), 4.11-4.12 (d, *J* = 2.8 Hz, 1H), 4.25-4.27 (t, *J* = 3.2 Hz, 1H), 7.06-7.13(m, 5H), 7.20-7.38 (m, 3H), 7.40-7.42 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 30.9, 37.4, 41.6, 43.8, 45.5, 67.4, 123.1, 123.4, 123.5, 125.7, 125.8(2C), 126.1, 127.2, 128.7, 129.3, 134.3, 139.8, 143.3, 143.5, 143.6

IR (KBr): υ 767, 979, 1216, 1147, 1457, 1678, 1741, 2942, 3021 cm.$^{-1}$.

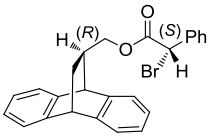
HRMS (TOF): calculated for $C_{25}H_{22}O_2$ $[M+H]^+$ 355.1698, found 355.1681.

Procedure of NBS reaction: In r.b flask, ester **98** (0.30 g, 0.84 mmol), N-bromosuccinmide (0.149 g, 0.84 mmol) and benzoyl peroxide (catalytic amount) in carbon tetrachloride (15 mL) was added and irradiated in 60W tungsten lamp and stirred for 6 h. After that mixture was cooled to room temperature and succinimide produced was removed by filtration. Solvent was removed on rotary evaporator to obtain the crude material which was further purified by column chromatography on silica gel using ethyl acetate and petroleum ether (5:95) as eluent to obtained product as white solid. (0.296 g, 81 %).

Procedure for DCC coupling reaction: Alcohol (*R*)-**8** (0.4 g, 1.7 mmol), DCC (0.350 g, 1.7 mmol) and DMAP (0.041 g 0.34 mmol) was placed in two necked flask under N_2 atmosphere, dissolved in 5 mL of dichloromethane and cooled to 0°C. A

solution of 2-bromo-2-phenyl acetic acid (0.364 g, 1.7 mmol) in 5 mL of dichloromethane was then added drop wise. The reaction mixture was stirred at 0°C for one hour after which it was allowed to stir for another 14 h at room temperature then whole reaction mixture was passed through celite and washed with dichloromethane and purified by column chromatography over silica gel by eluting with petroleum ether–ethyl acetate. White solid (0.58, 80%).

(*S*)-(11*R*)-9,10-dihydro-9,10-ethanoanthracen-12-yl)methyl2-bromo-2-phenylacetate (*R*,*S*)-**99**



M.p = 122 ^{0}C $[\alpha]_D^{28}$ = 83.0 (*c* = 0.25 $CHCl_3$)

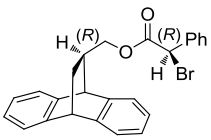
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.09-1.13 (ddd, *J* = 12.4 Hz, 4.8 Hz, 2.4 Hz, 1H), 1.92-1.98 (m, 1H), 2.27-2.35 (m, 1H), 3.46-3.51 (m, 1H), 3.87-3.92 (dd, *J* = 10.8 Hz, 6.0 Hz), 4.17-4.18 (d, *J* = 2.4 Hz, 1H), 4.26-4.27 (t, *J* = 2.4 Hz, 1H), 5.41 (s, 1H), 7.02-7.13 (m, 5H), 7.22-7.26 (m, 3H),7.39-7.47 (m, 3H), 7.60-7.62 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 30.9, 37.3, 43.7, 45.4, 47.2, 68.9, 123.2, 123.5, 123.6, 125.4, 125.7, 125.8, 125.9, 126.2, 128.6, 128.9, 129.4, 135.9, 139.6, 143.1, 143.4, 143.5, 167.9.

IR (KBr): υ 721, 754, 1012, 1138, 1212, 1453, 1744, 2948, 3031, 3060 cm.$^{-1}$

HRMS (TOF-ES+): m/z calculated for $C_{25}H_{21}BrO_2$ $[M+Na]^+$ 455.0623, found 455.0639.

(*R*)-(11R)-9,10-dihydro-9,10-ethanoanthracen-12-yl)methyl2-bromo-2-phenylacetate (*R*,*R*)-**99**

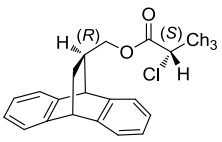


$[\alpha]_D^{28}$ = 41.4 (*c* = 0.25 $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.09-1.14 (ddd, *J* = 12.4 Hz, 4.8 Hz, 2.8 Hz, 1H), 1.92-1.98 (m, 1H), 2.26-2.34 (m, 1H), 3.47-3.52 (m, 1H), 3.89-3.93 (dd, *J* = 10.8Hz, 5.6Hz), 4.16-4.17 (d, *J* = 2.4 Hz, 1H), 4.27-4.28 (t, *J* = 2.4 Hz, 1H), 5.42 (s, 1H), 7.10-7.27 (m, 8H), 7.22-7.26 7.41-7.46 (m, 3H), 7.60-7.63 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 30.9, 37.2, 43.7, 45.4, 47.2, 68.9, 123.2, 123.5, 123.6, 125.4, 125.7, 125.8, 125.9, 126.2, 128.7, 128.9, 129.4, 135.9, 139.6, 143.1, 143.4, 143.5, 167.9.

S-(11*R*)-9,10-dihydro-9,10-ethanoantracene-12-yl)methyl2chloropropanate: (*R*,*S*)-**101**



M.P = 70 ^{o}C $[\alpha]_D^{28}$ = 9.4 (*c* = 1 $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.15-1.20 (ddd, *J* = 12.4 Hz, 4.8 Hz, 2.8 Hz, 1H), 1.73-1.75 (d, *J* = 6.8 Hz, 3H) 1.97-2.04 (m, 1H), 2.34-2.38 (m, 1H), 3.5-3.55 (dd, *J* = 10.8 Hz, 10 Hz, 1H), 3.94-3.89 (dd, *J* = 10.8 Hz, 6.0 Hz,) 4.31-4.30 (t, *J* = 4.8 Hz, 1H), 4.35-4.34 (d, *J* = 10.8 Hz, 1H), 4.43-4.48 (q, *J* = 6.8 Hz, 1H), 7.10-7.16 (m, 4H), 7.25-7.32 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.6, 31.1, 39.9, 43.8, 45.6, 52.7, 68.6, 123.3, 123.5, 123.7, 125.4, 125.8, 125.9, 125.9, 126.3, 139.8, 143.2, 143.5, 169.9.

IR (KBr): υ 752, 1070, 1176, 1273, 1453, 1459, 1677, 1743, 2945, 3021 cm.$^{-1}$

HRMS (TOF ES+): m/z calculated for $C_{20}H_{19}ClO_2$ $[M+Na]^+$ = 349.0971, found 349.0972.

Procedure for Hydrolysis : To a solution of (*R*,*S*)-**101** (1.0 g, 3.1 mmol) in dioxane (5 mL), HCl (0.3 mL, 9.3 mmol, 36%) was added. The reaction mixture was heated for 8h at 50^{o}C. The reaction mixture was quenched by addition of ice water and extracted with ethyl acetate (2X100). The organic layer was dried with sodium sulphate and concentrated and purified by column chromatography.

2-chloropropoinc acid (*S*)-**100**

$[\alpha]_D^{28}$ = -12.5 (neat) lit^{1} $[\alpha]_D^{28}$ = - 13.98 (neat)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.74-1.76 (d, *J* = 6.8 Hz, 3H), 4.44-4.50 (q, *J* = 6.8 Hz, 1H), 8.79 (br signal, 1H).

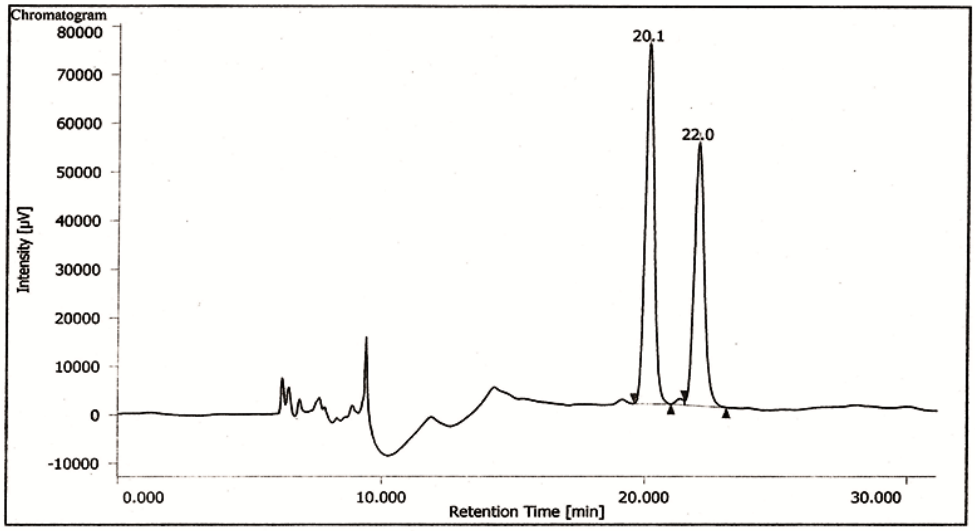
^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 52.1, 176.17.

Spectral Chart

HPLC spectra

HPLC condition:

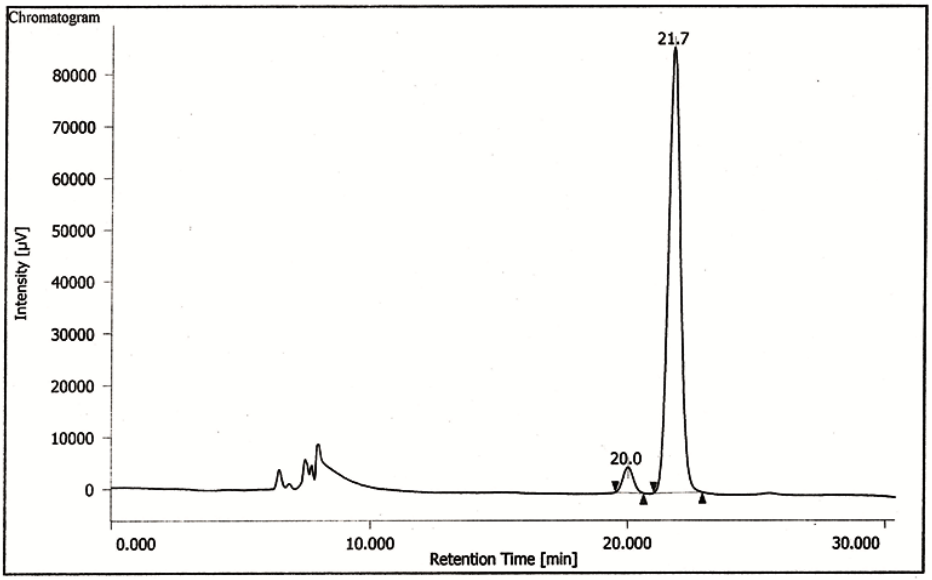
CHIRALPAK IC column
Solvent system 1% *Iso-propanol* in Hexane
Flow = 0.5 mL/min,
UV = 210 nm
Retention time 20.1 min (*R*,*R*), min and 22.0 min (*R*.*S*)



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	20.133	1761639	74080	54.968	16761	2.900	1.128
2	Unknown	1	22.025	1443197	54172	45.032	16494	N/A	1.203

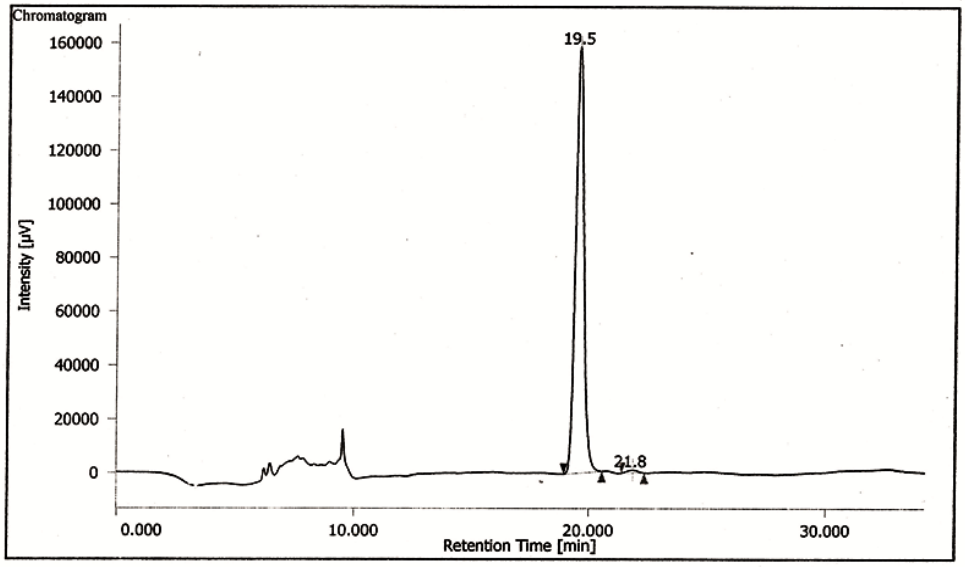
HPLC graph of **99**



Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	20.008	135409	4875	4.667	11511	2.172	1.058
2	Unknown	1	21.733	2766195	85836	95.333	10547	N/A	1.083

HPLC graph of (*R*,*S*)-**99**



Peak Information

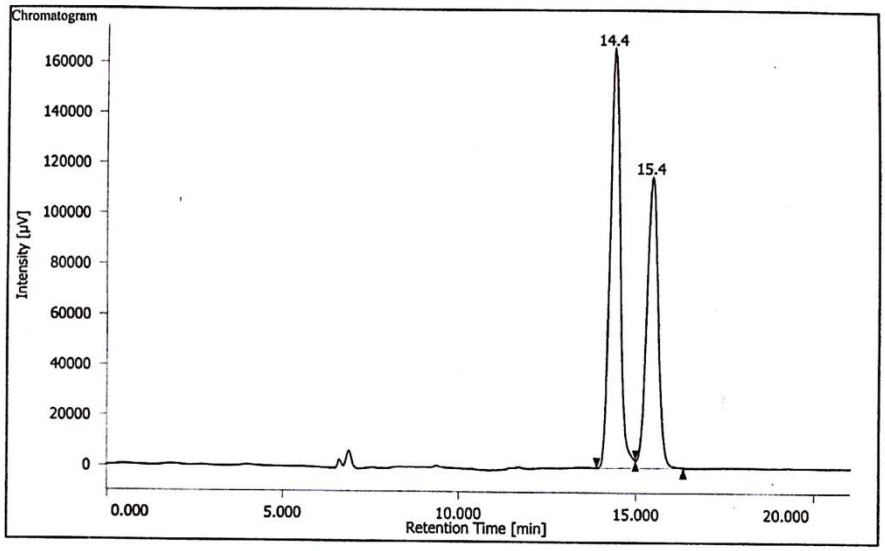
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	19.533	3849653	158561	99.145	15417	3.133	1.193
2	Unknown	1	21.842	33186	1106	0.855	10613	N/A	0.970

HPLC graph of (*R*,*R*)-**99**

HPLC graph of (*R*, *S*)-**101**

HPLC condition: Diacel IC column, 1% *Iso-propanol* in Hexane Flow = 0.5 mL/min, UV = 210 nm Retention time 14.4 min (*R,R*), min and 15.4 min (*R.S*)

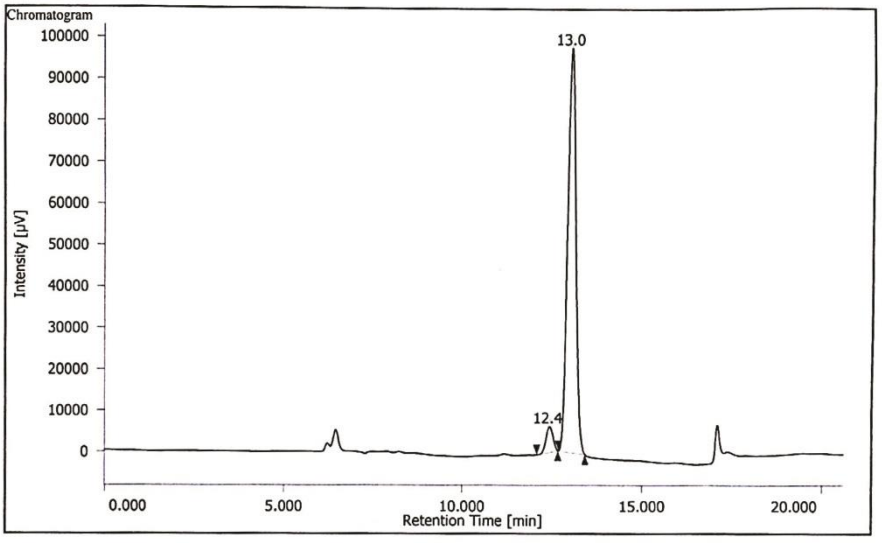
HPLC REPORT



Peak Information

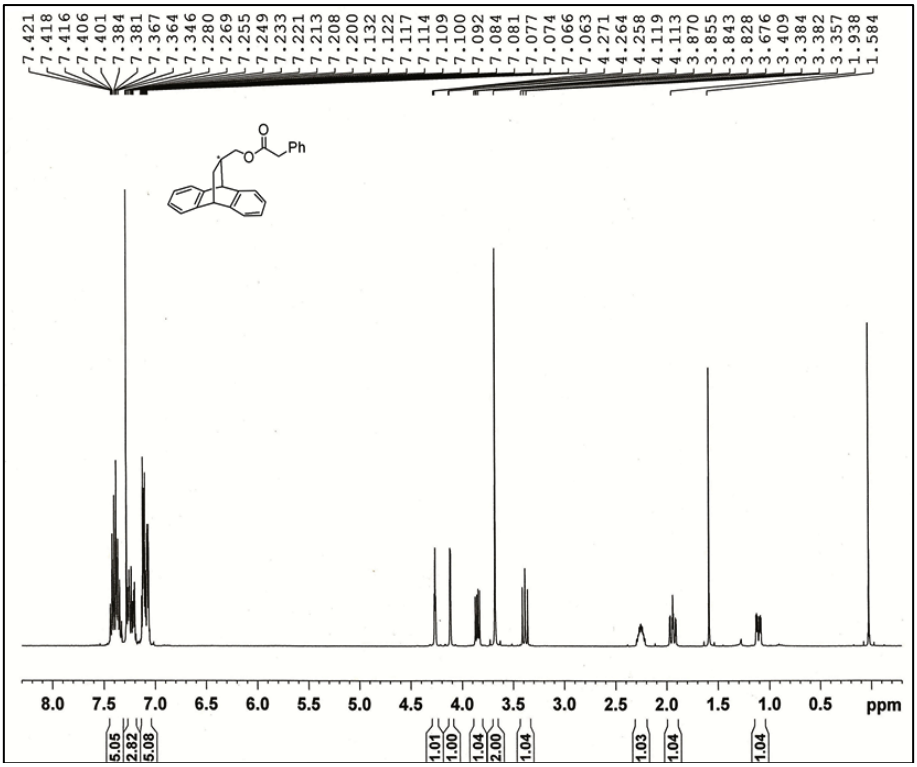
#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	14.375	3284698	166309	56.487	12629	1.948	1.148
2	Unknown	1	15.433	2530285	114929	43.513	11418	N/A	1.030

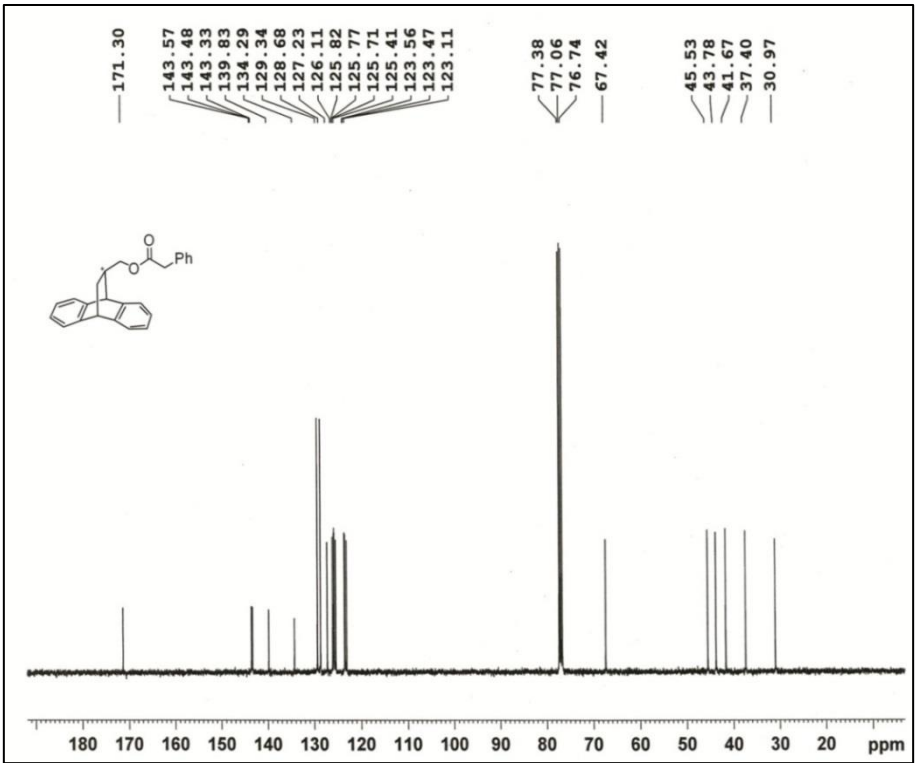
HPLC REPORT



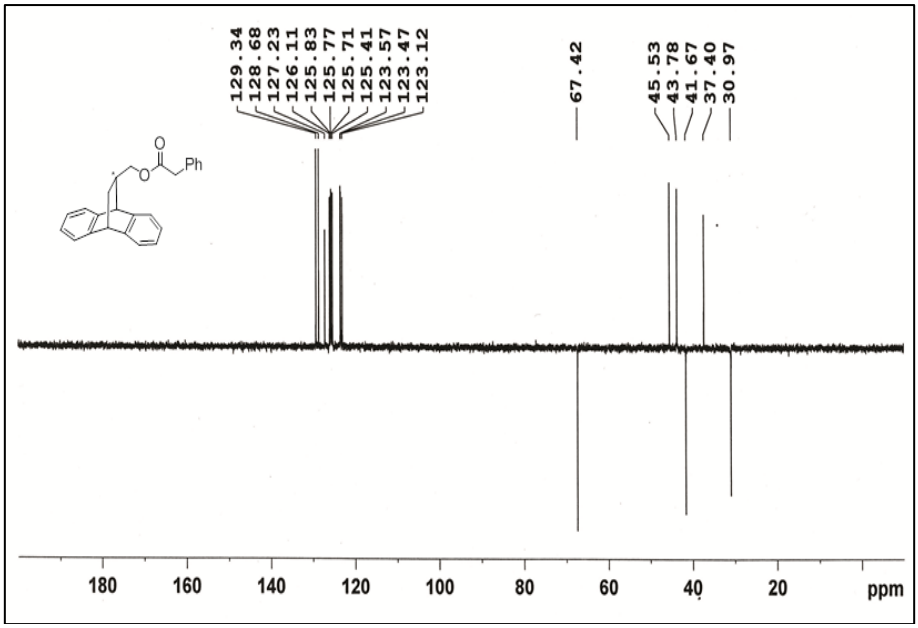
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	12.442	84426	6292	5.218	18381	1.472	0.968
2	Unknown	1	13.017	1533609	97893	94.782	15631	N/A	1.088

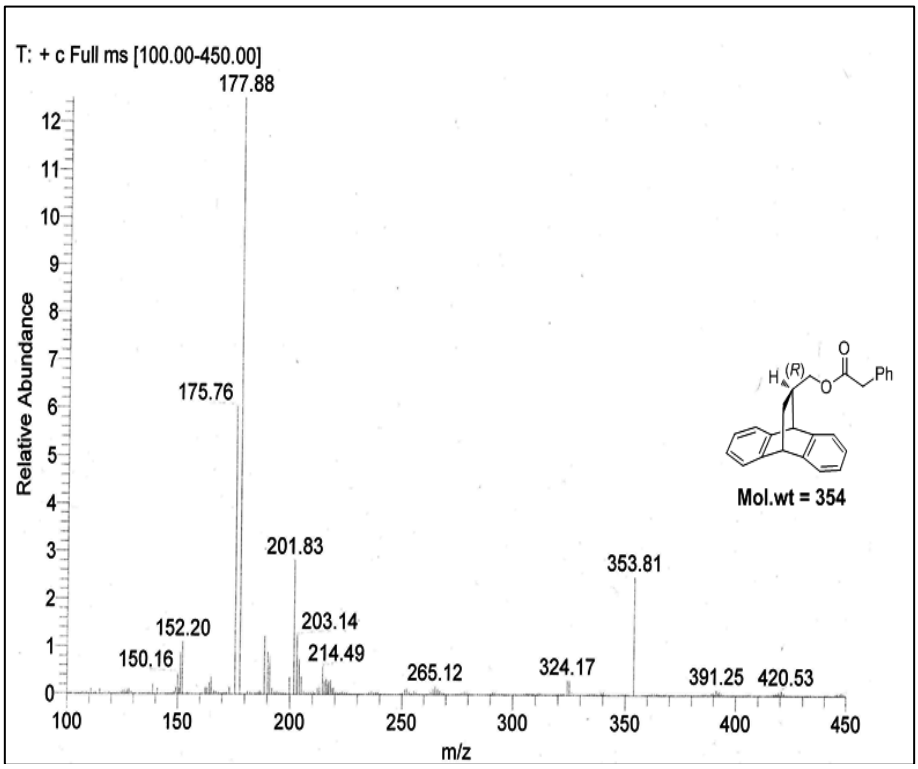




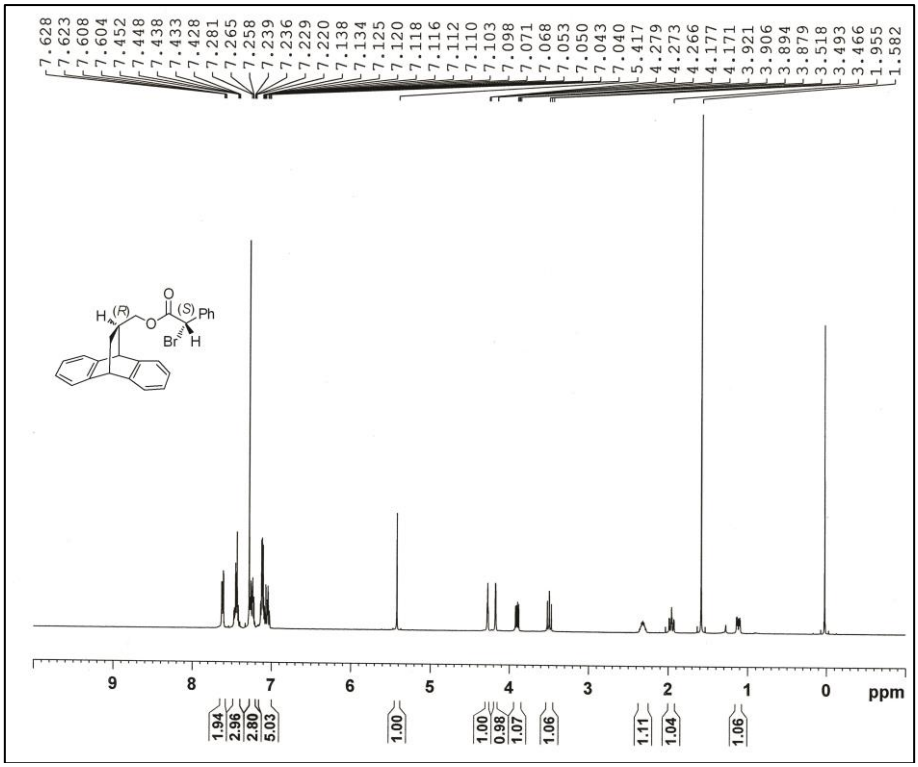
^{1}H NMR & ^{13}C NMR spectra of compound (*R*)-**98** in $CDCl_3$



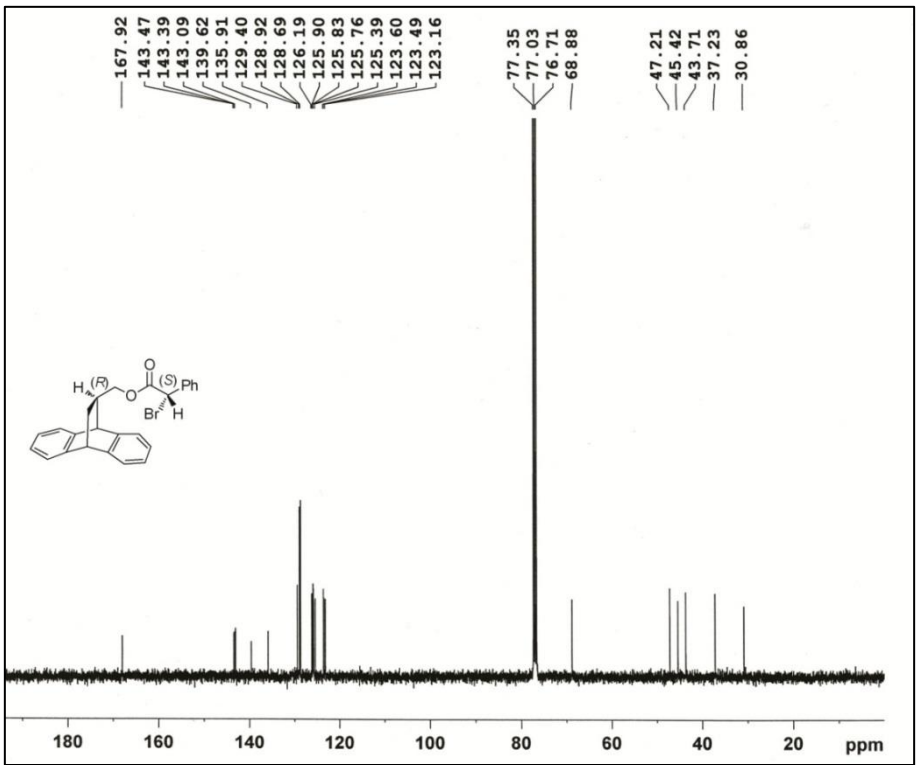
DEPT 135 spectra of compound (*R*)-**98**



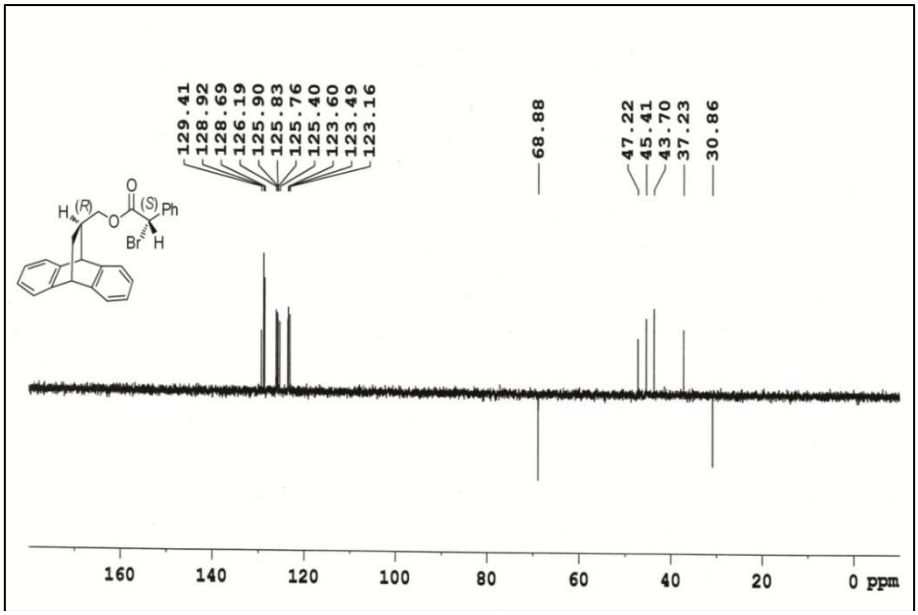
Mass spectra of compound (*R*)-**98**



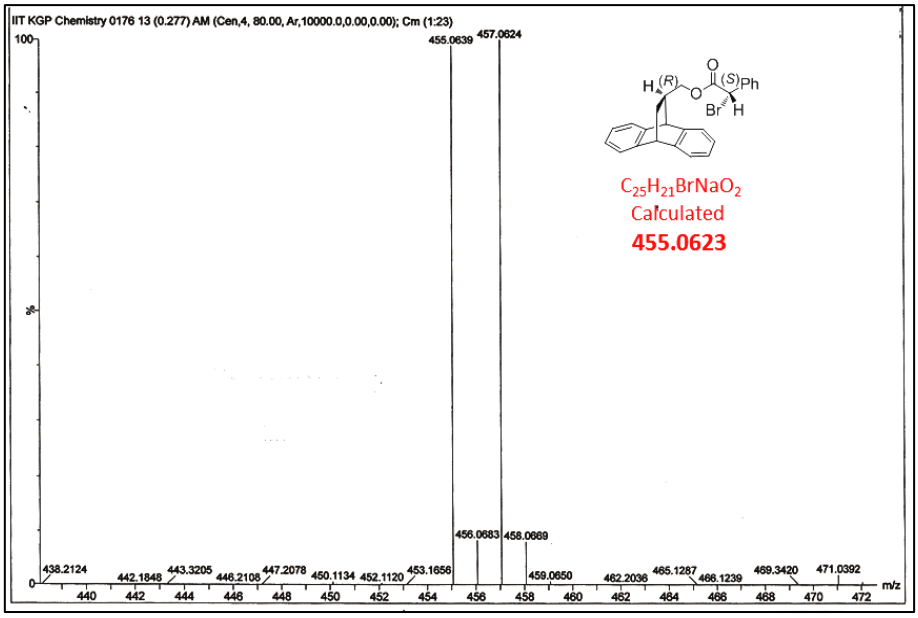
^{1}H NMR spectra of compound (*R,S*)-**99** in $CDCl_3$



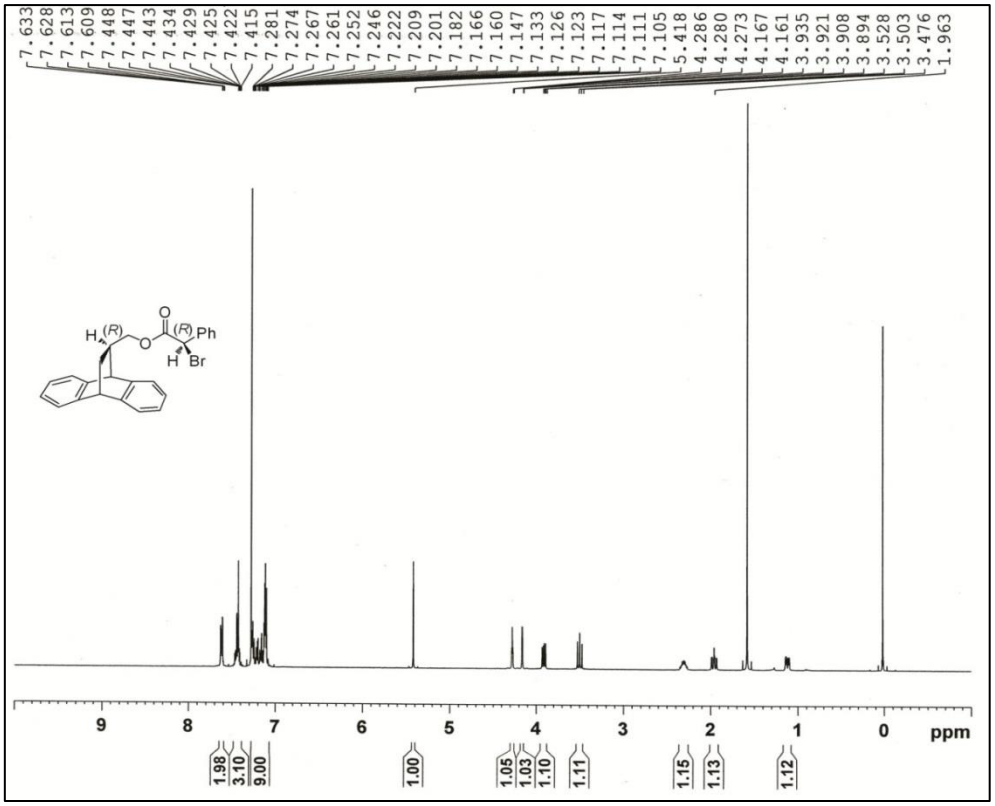
^{13}C NMR spectra of compound (*R,S*)-**99** in $CDCl_3$



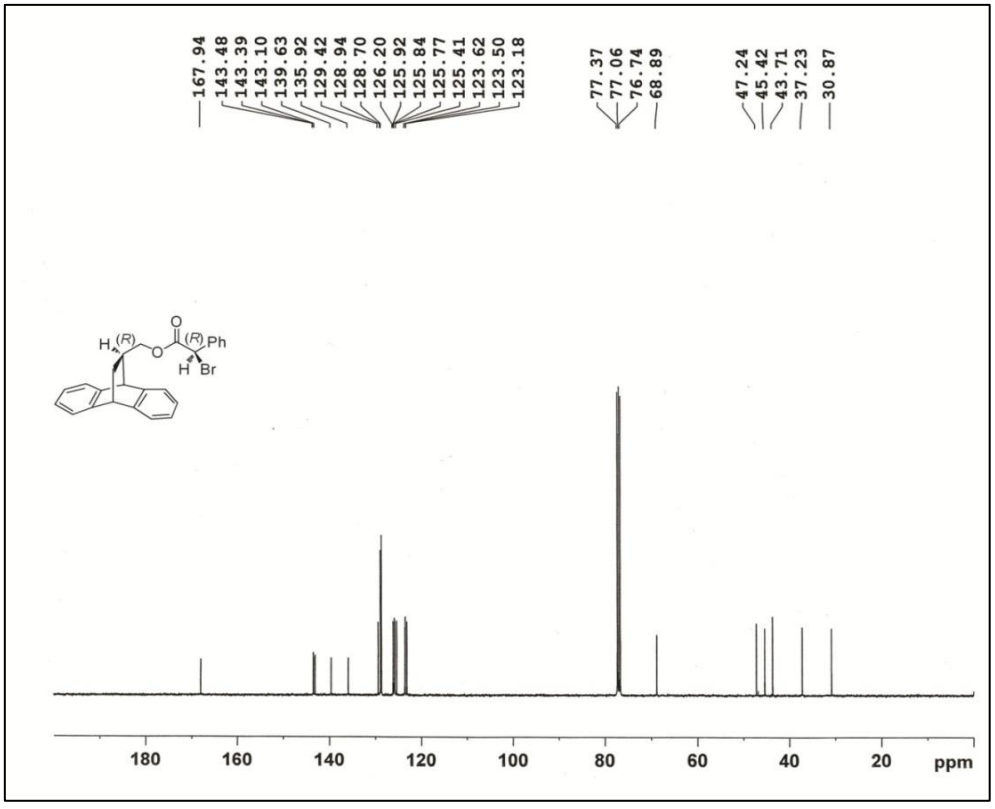
DEPT 135 spectra of compound (*R,S*)-**99** in $CDCl_3$



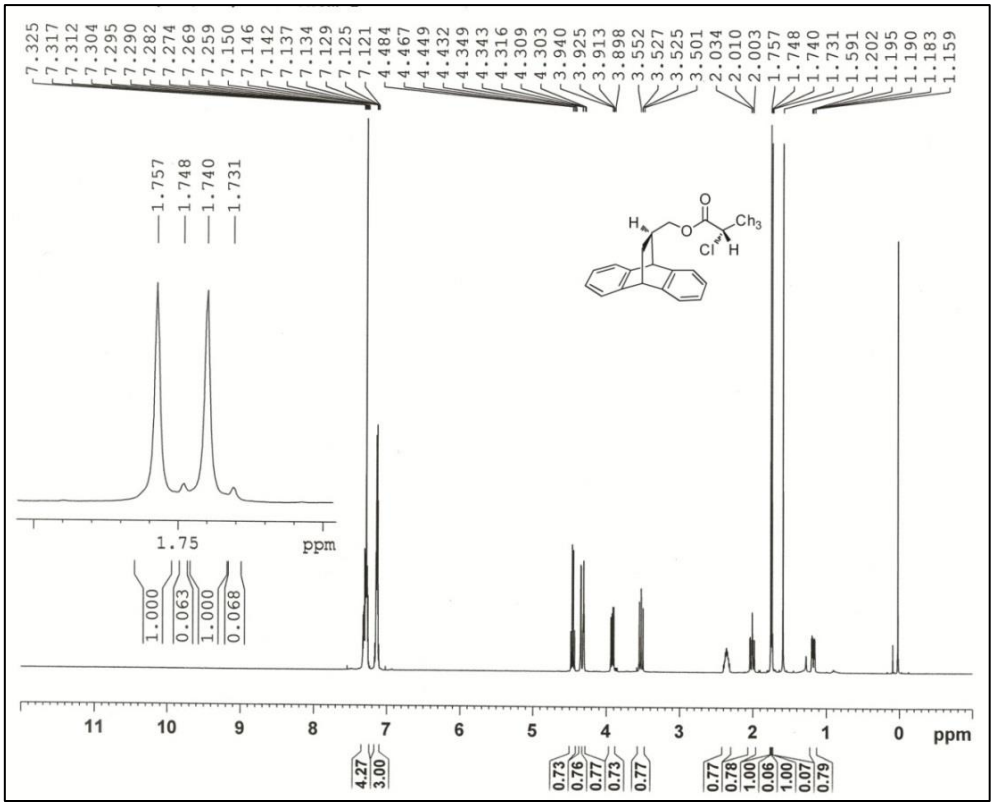
HRMS spectra of compound (*R,S*)-**99** [M+Na]



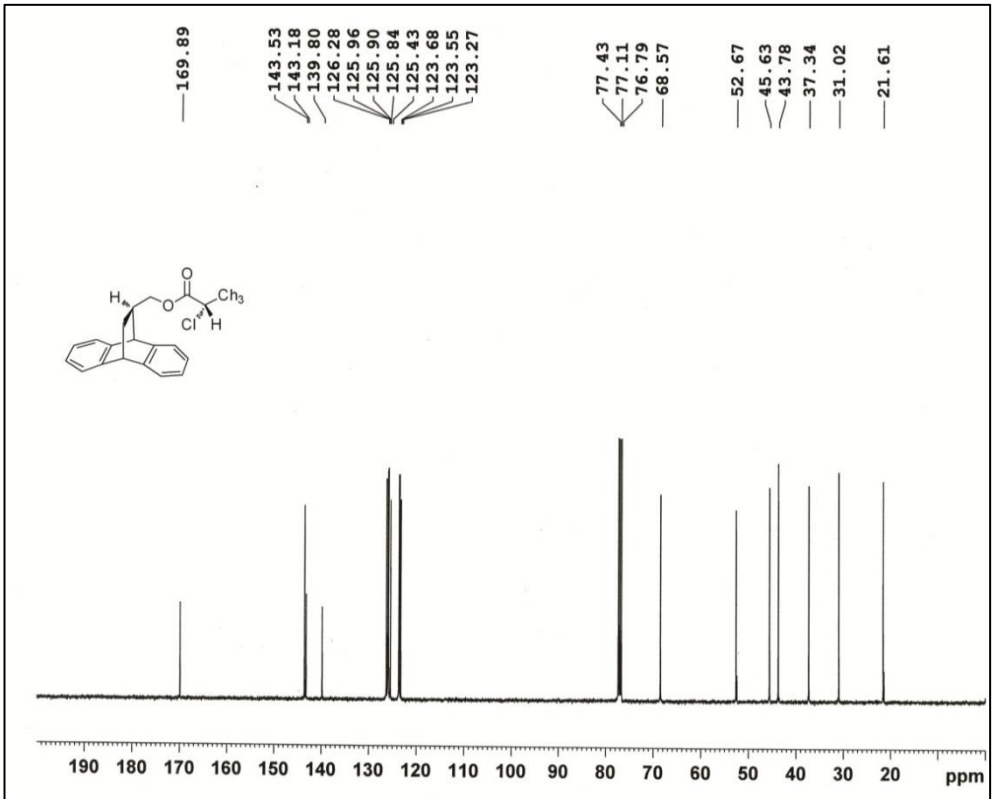
^{1}H NMR spectra of compound (*R*,*R*)-**99** in $CDCl_3$



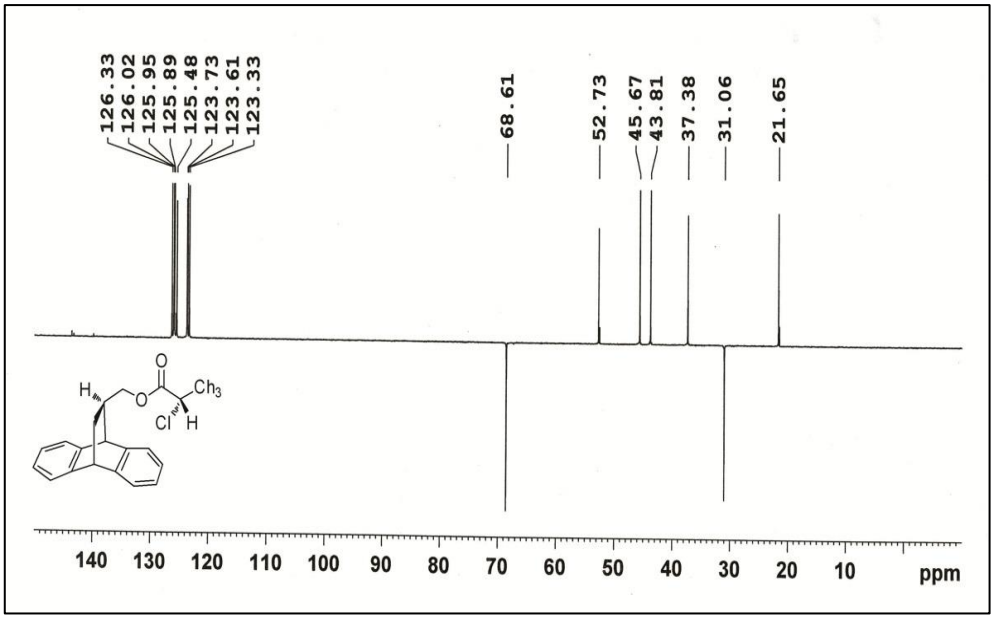
^{13}C NMR spectra of compound (*R*,*R*)-**99** in $CDCl_3$



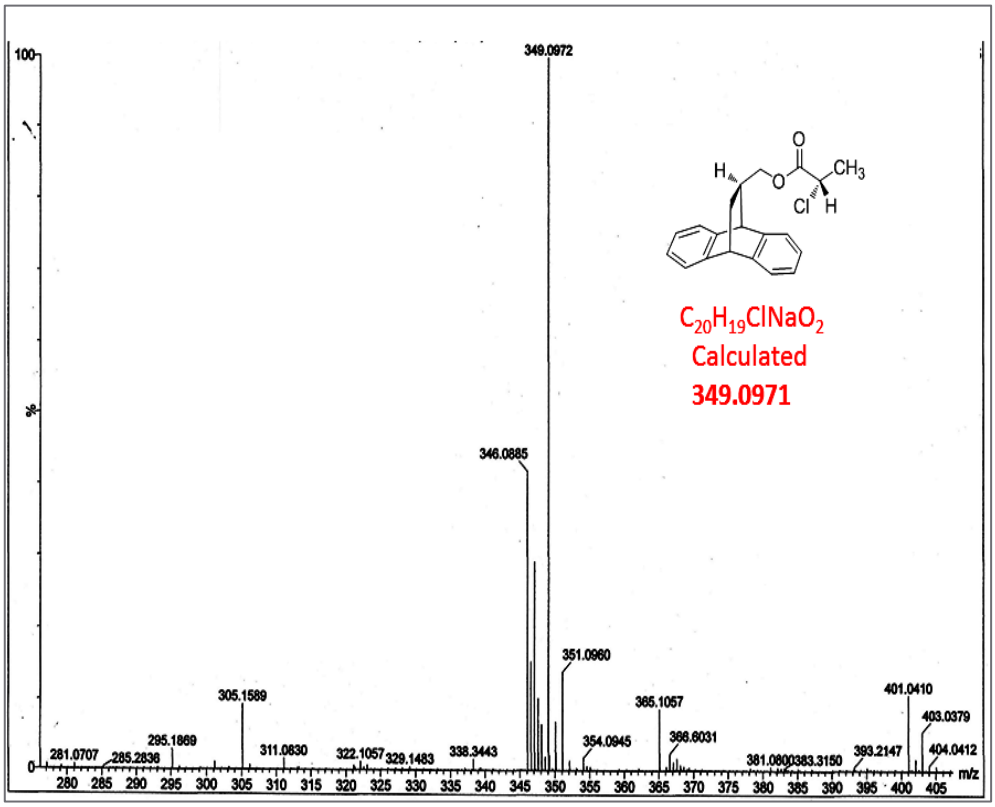
^{1}H NMR spectra of compound (*R*,*S*)-**101** in $CDCl_3$



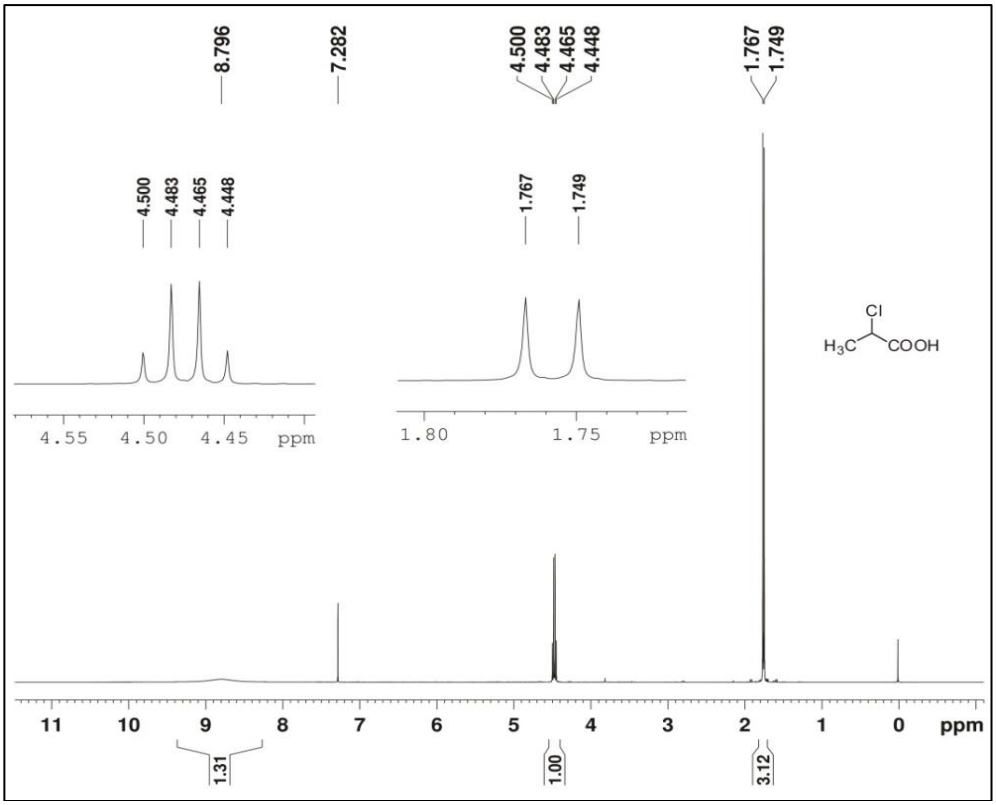
^{13}C NMR spectra of compound (*R*,*S*)-**101** in $CDCl_3$

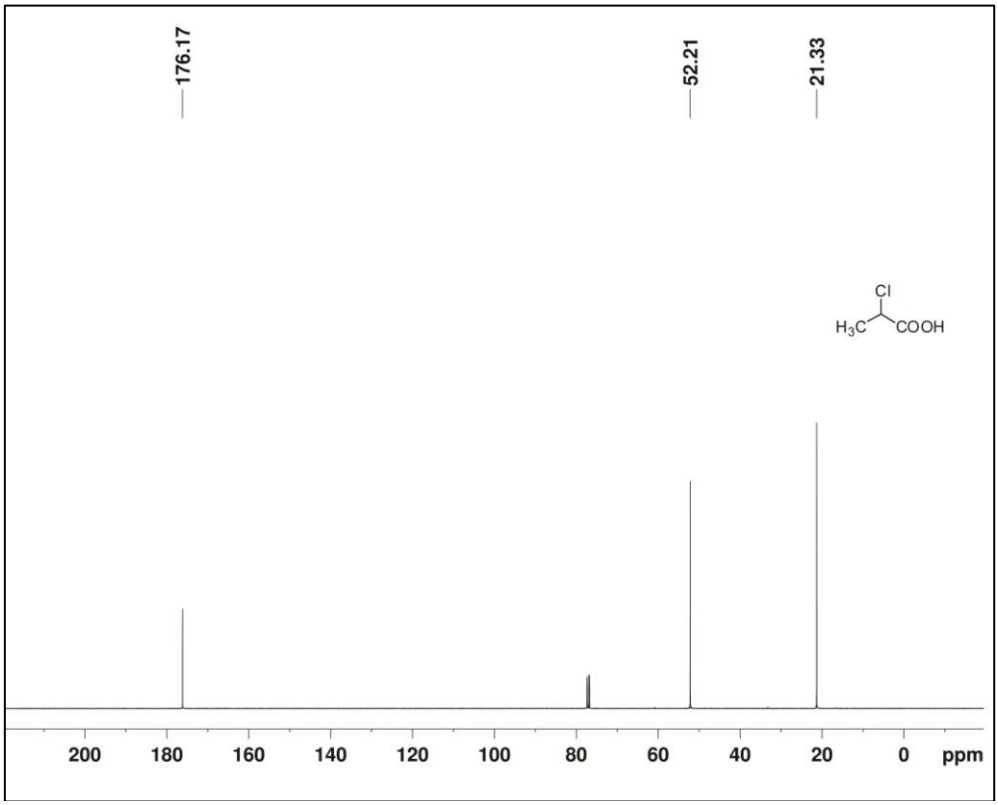


DEPT-135 spectra of compound (*R*,*S*)-**101** in $CDCl_3$



HRMS of compound (*R*,*S*)-**101** $[M+Na]^+$





^{1}H NMR & ^{13}C NMR spectra of compound **100** in $CDCl_3$

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