Summary of the thesis entitled

Design, Synthesis and Applications of Novel Cyclohexanol Derived Chiral Molecules

To be submitted to

The Maharaja Sayajirao University of Baroda

For the degree of

DOCTOR OF PHILOSOPHY

In

CHEMISTRY

Submitted by

Mr. Aditya N. Khanvilkar

Research Supervisor

Prof. Ashutosh V. Bedekar

Department of Chemistry

Faculty of Science

The Maharaja Sayajirao University of Baroda

Vadodara 390 002

Gujarat (INDIA)

December 2018

Design, Synthesis and Applications of Novel Cyclohexanol Derived Chiral Molecules

Chapter 1: Introduction

Chirality: Definition and its types:

Until half a century ago, it was assumed that the forces of nature were symmetric and that they did not distinguish between right and left, between image and mirror image. The discovery of the violation of parity in 1956 was more than a sensation, for some it was a shock. It implied that the universe displays handedness, or chirality, and that it is fundamentally asymmetric.[1] The idea of chirality has been known in chemistry since chiral chemistry got impetus from pioneering work by Louis Pasteur, a French chemist and biologist, who physically separated the two isomers of sodium ammonium tartrate in 1848 although it would be nearly a hundred years before chemists began using this term. In fact, in the first edition of Eliel's "Stereochemistry of Carbon Compounds" in 1962, the word chiral is not mentioned.[2] The definition of chirality was first given by Lord Kelvin in May 1893, during a conference of the Oxford University Junior Scientific Club:

"*I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself.*[3]"

As Mislow has pointed out, Kelvin's geometric definition of chirality is equivalent to that given many years later by Vladimir Prelog in his 1975 Nobel Prize lecture:

"*An object is chiral if it cannot be brought into congruence with its mirror image by translation or rotation.*"

Asymmetric synthesis: Synthesis of chiral molecule in an achiral environment using achiral starting material results in equimolar mixture of both enantiomers. In order to make single enantiomer, some enantioenriched material must be present in the reaction medium. The synthesis of chiral molecules from symmetrically constituted compounds with the use of optically active materials is regarded as *asymmetric synthesis*. Asymmetric synthesis involves synthesis of chiral molecules using i) Chiral Catalyst and ii) Chiral Auxiliary.

Chiral Catalyst: In the field of asymmetric synthesis, chiral catalysts hold a special appeal due to their ability to produce large quantities of desired enantiomerically pure compounds from simple feedstocks and relatively small quantities of enantio-enriched chiral catalysts. Over the years chiral

catalysis has been categorized into: a) Organo-metallic catalysis, b) Organo-catalysis and c) **Biocatalysis.**

Chiral Auxiliary: Other variants of diastereoselective syntheses include the use of chiral auxiliary molecules (these can be either from chiral pool or synthetic). A chiral auxiliary is a chemical compound or unit that is temporarily incorporated into an organic synthesis in order to control the stereochemical outcome of the synthesis. The chirality present in the auxiliary can bias the stereoselectivity of one or more subsequent reactions.

Importance of optically active molecules in the field of medicine, fragrance and flavours, material science and supramolecular chemistry has already been well established. The supramolecular interactions in biological systems between the chiral receptors and guest substrates are in general more enantiospecific. Crown ethers and other macrocyclic compounds have a unique place in the field of supramolecular chemistry.[2-4] Chiral crown ethers and macrocyclic molecules have been widely employed as CSA for enantiomeric recognition on account of their ability to bind with optically active guest molecules.

Chiral Solvating Agents are optically pure compounds which bind in situ to the substrate comprising of mixture of enantiomers through non covalent, intermolecular forces. CSAs are usually chiral compounds which have ability to participate through non covalent interactions such as hydrogen bonding, π -π interactions, C-*H*- π interactions and charge transfer complexes. Associated complexes of CSA with pair of enantiomers are diastereomers, which is the source of discrimination in NMR spectroscopy.[5]

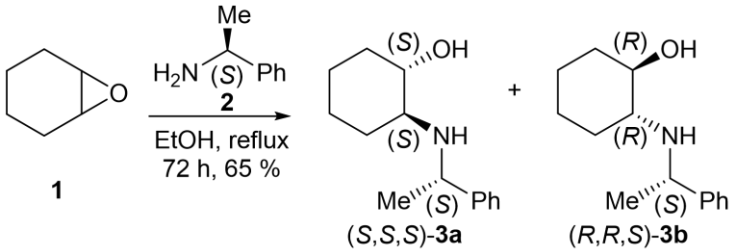
Over the years optical methodologies, especially those based on fluorescence spectroscopic techniques, have drawn substantial interest of researchers, working in molecular recognition, owing to their advantageous features such as simplicity, low cost, high sensitivity and real-time analysis, and diverse signal output modes. Not only do fluorometric methods enable fast in situ determinations of the enantiomeric compositions of chiral analytes but are also reliable and accurate.

Chapter 2: *Synthesis and Application of Chiral Aza-crown ethers and Aza-macrocycles*

Chiral Crown Ethers: The chiral crown ethers have been widely applied as chiral selectors in differentiating the enantiomers of racemic mixture containing a primary amino group. Chiral aza

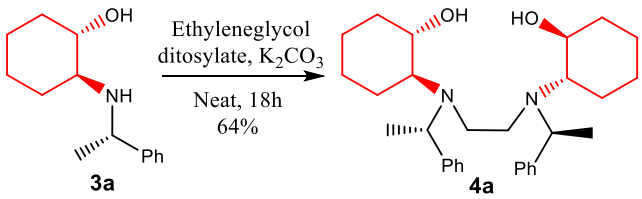
crown ethers have been widely used in enantiomeric recognition of chiral acids. Optically pure crown ethers can be used for the determination of the enantiomeric excess of chiral compounds in NMR spectroscopy. In particular the chiral crown ethers are known to be effective chiral solvating agents. However, these crown ethers are shape and size selective in their molecular recognition. Due to this there is a constant need to synthesize and screen novel chiral crown ethers. In this effort we have synthesized and characterized crown ether and will investigate its utility for the enantioselective discrimination and asymmetric synthesis.

In the present study diastereomeric mono and diaza crown ethers have been synthesized to study their chiral discriminating ability towards guest molecules. Synthesis of *β*-amino alcohol by ring opening of *meso* cyclohexenoxide using chiral (*S*)-phenylethyl amine resulting in formation of diastereomers **3a** and **3b** in the ratio of 54:46**.**



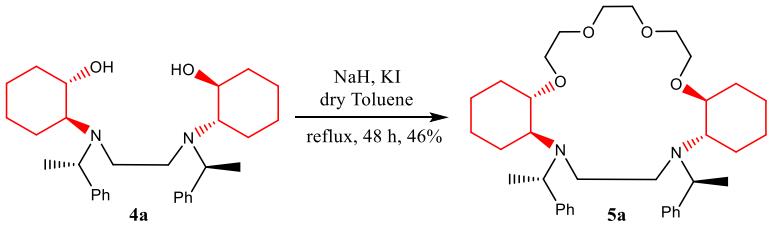
Scheme 1: Synthesis of diastrereomeric amino alcohols (**3**)

The separated diastereomer **3a** was converted to building block diamino diol **4a** for the synthesis of diaza 18-crown-6 derivative by treatment with ethylene glycol ditosylate and base under neat condition.



Scheme 2: Syntheis of diamino diol **4a**

The diamino diols **4a** was treated with triethylene glycol ditosylate in dry toluene in presence of NaH base for 48h resulting in formation of diazacrown ethers **5a**. The reaction was observed to progress upon the addition of KI. The reaction mixture was subjected to column chromatography yielding desired chiral aza crown ethers.



Scheme 3: Syntheis of aza crown ethers **5a.**

Application as CSA:

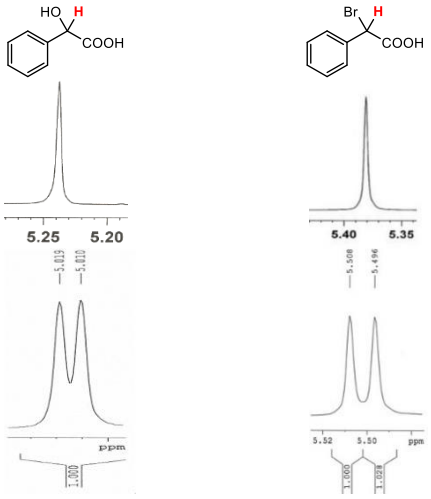
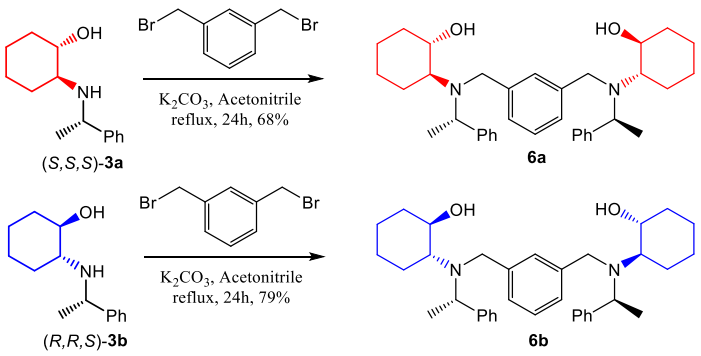


Figure 1: Selected region of ^{1}H NMR Spectra of mandelic acid and a-bromo phenylacetic acid with (**5a**)

The crown ether (**5a**) was used as CSA for racemic Mandelic acid, α-bromophenylacetic acid and α-methoxy acid. Crown ether showed baseline separation with α-bromophenylacetic acid while in case of mandelic acid the separation was low with crown ether (**5a**). This encouraged us to synthesize crown ethers with aromatic ring containing linkers which would facilitate more efficient π-π and C-*H*-π interactions.

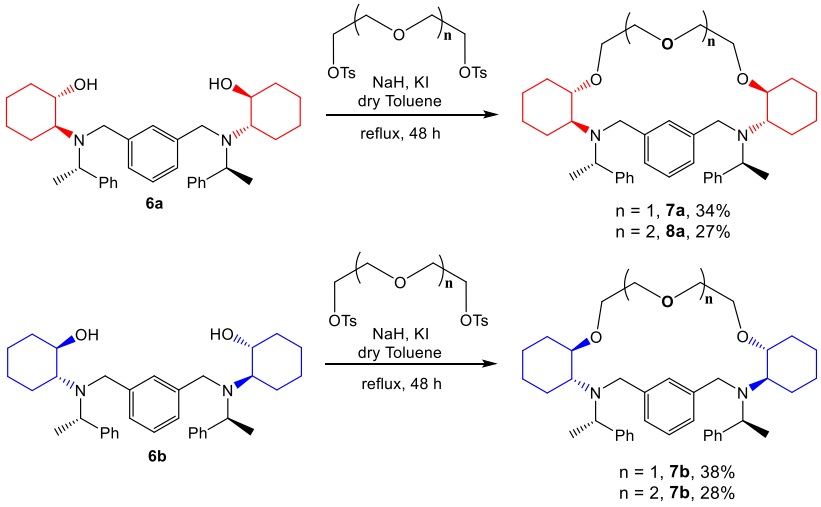
Synthesis of Aza Crown ethers:

The two separated diastereomers (**3a**) were condensed with *m*-xylene dibromide in presence of K_2CO_3 in acetonitrile resulting in formation of diamino diol (**6a**). The other diastereomer of amino alcohol (**3b**) yielded the diastereomeric diol (**6b**) (Scheme 4).



Scheme 4: Synthesis of diamino diol **6a** and **6b**

The synthesized diastereomeric diols were then converted to aza-crown ethers by subsequent cyclization with diethylene glycol ditosylate and triethyleneglycol ditosylate in presence of NaH and KI resulting in formation of aza-crown ethers (**7**) and (**8**) respectively (Scheme 5).



Scheme 5: Synthesis of crown ether **7** and **8**

Application of crown ethers as CSA

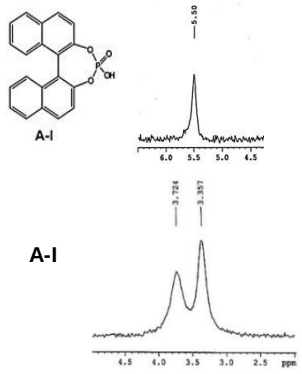
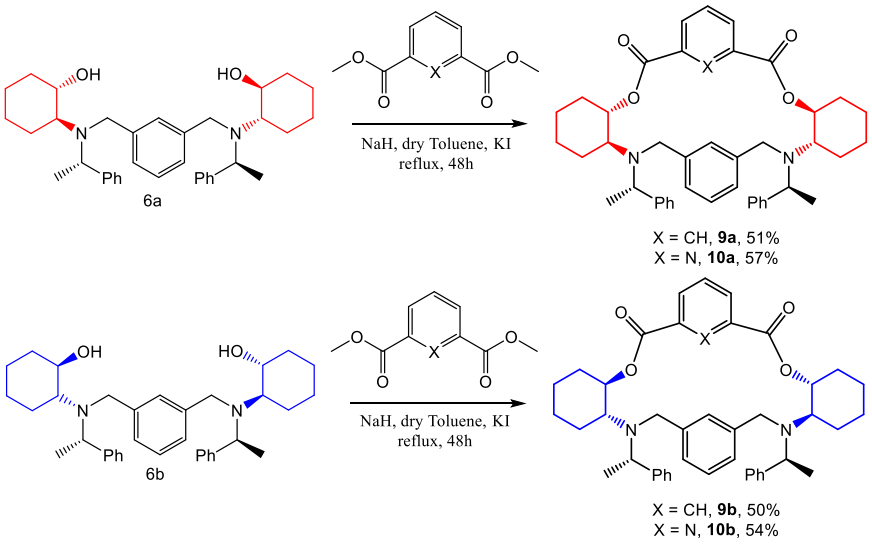


Figure 2: ^{31}P NMR Spectra of binaphthyl phosphoric acid with crown ether (**7a**).

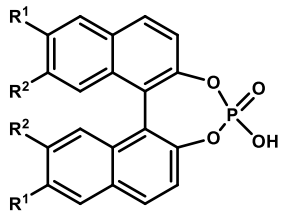
Synthesis of Aza-macrocycle:

In order to increase the rigidity of macrocyclic ring the ethylene glycol unit was replaced with aromatic diester system. The diamino diol (**6**) was subjected to transesterification with dimethyl-isophthalate and pyridine-2,6-dimethyl-carboxylate yielding macrocyclic diesters (**9**) and (**10**) (Scheme 6).



Scheme 6: Synthesis of chiral aza-macrocycles.

Application as CSA for Heteronuclei: Study of Match/ Mismatch effect:



The two derivatives of **10** were screened to study their ability to discriminate the ^{31}P NMR signals of derivatives of **A** by measuring the chemical shift non-equivalence (ΔΔδ) (Table 1). A clear pattern of better discrimination for (*R*,*R*,*S*)-**10b** was observed in all the examples, while the other derivative (*S*,*S*,*S*)-**10a**, with closed cavity was found ineffective.

Table 1: Discrimination of Binaphthyl phosphoric acids **A**[a]

No.	Compound No.	R^1	R^2	ΔΔδ (ppm)	
				(S,S,S)-10a	(R,R,S)-10b
1	A-I	H	H	0.03	0.78
2	A-II	H	OMe	--[b]	0.64
3	A-III	H	O^{i}Pr	--[b]	0.76
4	A-IV	NO_2	H	--[b]	0.81
5	A-V	Br	H	--[b]	0.40

[a]In $CDCl_3$ (20 mM), 162 MHz, ratio of **10**:**A** (2:1); [b]Not resolved.

Fluorescence spectroscopy is employed in molecular recognition by studying the relative quenching of signal. Such chirality dependent quenching of both enantiomers of **A-I** in presence of macrocycles (**10a**) and (**10b**) have been investigated. The recognition ability of macrocycles towards the phosphoric acid was evident from the extent of quenching. The response of quenching the emission of enantiomers of **A-I** with (**10**) follows the Stern-Völmer equation. The fluorescence quenching efficiency can be expressed as a ratio of $K_{sv}^{(R)\ \mathbf{A\text{-}I}}/K_{sv}^{(S)\ \mathbf{A\text{-}I}}$ which was observed to be 1.05. On the other hand quenching of enantiomers of **A-I** with the other macrocycle (**10b**) indicated the ratio $K_{sv}^{(R)\ \mathbf{A\text{-}I}}/K_{sv}^{(S)\ \mathbf{A\text{-}I}}$ to be 1.40 indicating better quenching ability.

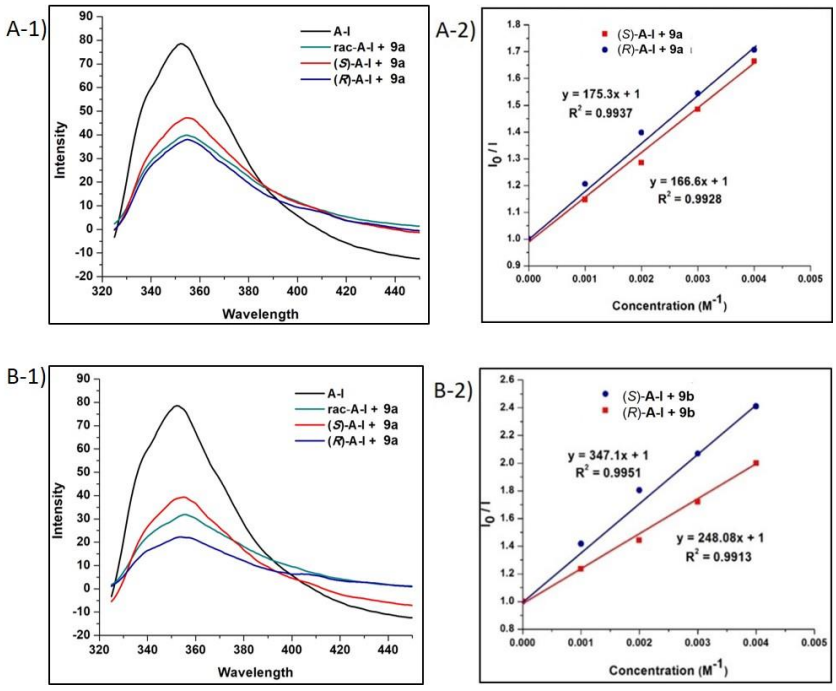
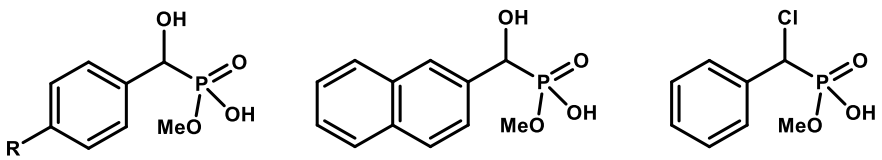


Figure 3: Quenching study: A-1) Fluorescence spectra of **A-I** (10^{-5} M, $CHCl_3$); (±)-**A-I**, (*S*)-**A-I** and (*R*)-**A-I** in presence of **10a** (λ_{ex} = 305 nm); A-2) Stern-Völmer plots of (*S*)-**A-I** and (*R*)-**A-I** with **10a**; B-1) Fluorescence spectra of A-I (10^{-5} M, $CHCl_3$); (±)-**A-I**, (*S*)-**A-I** and (*R*)-**A-I** in presence of **10b** (λ_{ex} = 305 nm); B-2) Stern-Völmer plots of (*S*)-**A-I** and (*R*)-**A-I** with **10b**



B **B-IV** **C**

Table 2 Discrimination of monomethyl esters of substituted hydroxyl-phosphonic acids **B** and **C**[a]

No.	Compound No.	R^1	ΔΔδ (ppm)	
			(S,S,S)-10a	(R,R,S)-10b
1	B-I	H	0.17	--[b]
2	B-II	Me	0.19	--[b]
3	B-III	Cl	0.16	--[b]
4	B-IV	--	0.17	--[b]
5	C	--	--[b]	--[b]

[a]In CD_3OD (5%) in $CDCl_3$ (20 mM), 162 MHz, ratio of **B** and **C**:**10** (2:1); [b]Not resolved.

Table 3 Discrimination of monomethyl esters of substituted amino-phosphonic acids **D**[a]

No.	Compound No.	R^1	ΔΔδ (ppm)	
			(S,S,S)-10a	(R,R,S)-10b
1	D-I	H	0.40	--[b]
2	D-II	Me	0.42	--[b]
3	D-III	Cl	0.45	0.10
4	D-IV	OMe	0.43	--[b]
5	D-V	NO_2	0.40	0.12
6	D-VI	--	0.37	--[b]

[a]In CD_3OD (5%) in $CDCl_3$ (20 mM), 162 MHz, ratio of **D**:**10** (2:1); [b]Not resolved.

The aza crown ethers were screened as CSA for enantiomeric recognition of α-functional carboxylic acids. The detailed investigation of crown ethers as CSA along with mechanistic study of binding with guest molecules is currently under progress. Furthermore, two diastereomeric N,O-macrocycles were synthesized and evaluated as CSA for effective discrimination by ^{31}P NMR signals and fluorescence quenching of several organo phorphoric and phosphonic acid derivatives.

Chapter 3: *Synthesis, Resolution and Application of Cyclohexanol based Chiral Auxiliary*

Cyclohexanol as Chiral Auxiliary:

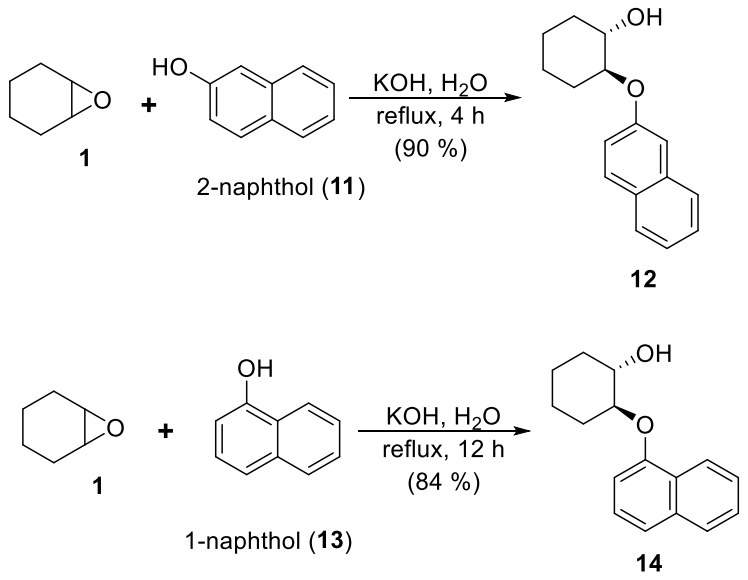
A chiral auxiliary is a chemical compound or unit that is temporarily incorporated into an organic synthesis in order to control the stereochemical outcome of the synthesis. The chirality present in the auxiliary can bias the stereoselectivity of one or more subsequent reactions. The auxiliary can be cleaved from the substrate and is typically recovered for future use.

Application of cyclohexanol based chiral auxiliaries is well known in asymmetric transformation. 8-Phenylmenthol and 2-phenylcyclohexanol have been widely used as auxiliaries in asymmetric

reactions. In the present study cyclohexanol based chiral auxiliary has been synthesized and resoloved by enzymatic resolution.

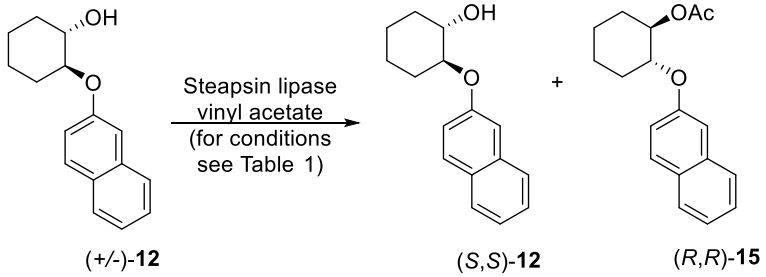
Synthesis of Chiral Auxiliary:

(±)-*trans*-2-Aryloxy cyclohexanols (**12** and **14**) have been prepared by using cyclohexene oxide (1 eq) and corresponding naphthol (3 eq) in the presence of potassium hydroxide (3 eq) in water.



Scheme 7: Synthesis of Chiral Auxiliaries **12-14**

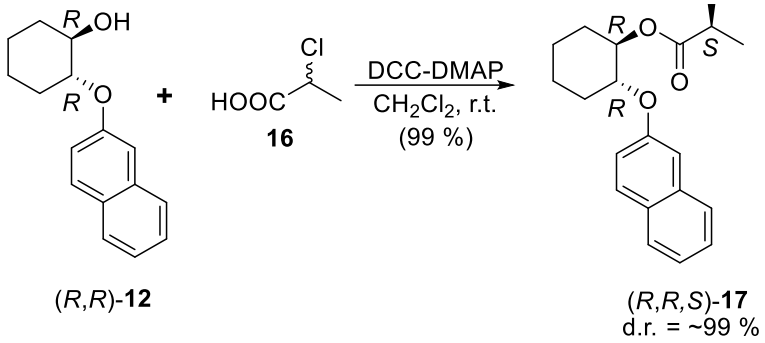
Enzymatic Resolution: (±)-*trans*-2-(2-naphthyloxy)cyclohexanols **12** has been subjected to enzymatic resolution in presence of Steapsin lipase and vinyl acetate as acyl donor (Scheme 8).



Scheme 8: Enzymatic resolution of alcohol **12**

The cyclohexanol derivatives **12** and **14** have been synthesized and resolved using previously used conditions. The resolved alcohols were then converted to esters by reaction with (*R*)-*O*-acetyl-mandelic acid for determination of absolute configuration. The Single crystal X-Ray analysis of crystals of chiral esters showed that *R,R*-isomer of alcohol undergoes enzymatic acylation while *S,S*-isomer remains unreacted.

Application of trans-2-aryloxy cyclohexan-1-ol as Chiral Auxiliary: Deracemization of 2-chloropropanoic acid



(*R*,*R*)-**12**

(*R*,*R*,*S*)-**17**
d.r. = ~99 %

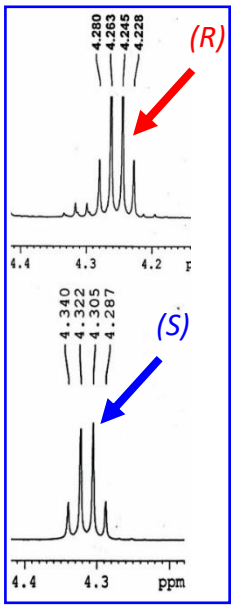


Table 4: Base study in deracemization of 2-chloropropanoic acid

Entry	Base	Time (hours)	Diastereomeric Ratio (dr)
1	DMAP	12	>99
2	DABCO	12	>99
3	Triethyl amine	12	98
4	K_2CO_3	12	97

Effect of temperature on diastereoselectivity

Table 5: Effect of temperature on diastereomeric ratio

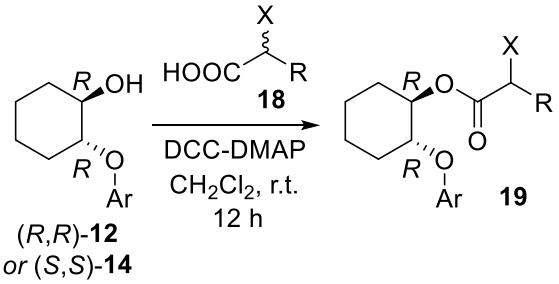
No	Initial Composition (*R*:*S*)	Time (hours)	Temperature	Product %dr (*αS*)
1	50:50	12	Rt	>99
2	50:50	12	Reflux	>99
3	50:50	12	0 ^oC	>99
4	67:33	12	Rt	72
5	67:33	12	reflux	72
6	67:33	12	0 ^oC	50

Effect of time on diastereomeric ratio:

The reaction of chiral alcohol **12** and 2-chloro propanoic acid was monitored at different times. The diastereomeric ratio of product **17** showed gradual increase with increase in time. When the

reaction was stopped after 6 h the product showed *dr* of 69% whereas after 48 h it showed increase in *dr* up to 84%.

Table 6: Effect of substituents on diastereoselectivity



Entry	Chiral auxiliary	R in α-halo acid (**16**/**18**)	X in α-halo acid (**16**/**18**)	Yield (%)	% d.e.[b] [**19**]
1	(*S*,*S*)-**14**	Me	Cl	98	68 [(*S*,*S*,*S*)- **19a**] [b,c]
2	(*R*,*R*)-**12**	Me	Cl	99	>99 [(*R*,*R*,*S*)-**17**] [b]
3	(*R*,*R*)- **12**	Me	Br	98	66 [(*R*,*R*,*S*)- **19b**] [b]
4	(*R*,*R*)- **12**	Et	Cl	97	50 [**19c**][b,d]
5	(*R*,*R*)- **12**	Et	Br	98	40 [**19d**][b,d]
6	(*R*,*R*)- **12**	i-Pr	Cl	98	42 [**19e**][b,c,d]
7	(*R*,*R*)- **12**	i-Pr	Br	96	46 [**19f**][c,d]
8	(*R*,*R*)- **12**	Bn	Cl	94	43 [**19g**][b,d]
9	(*R*,*R*)- **12**	Bn	Br	92	38 [**19h**] [b,d]
10	(*S*,*S*)-**14**	Ph	Br	95	8 [**19i**] [b,d]
11	(*R*,*R*)- **12**	Ph	Br	98	65 [(*R*,*R*,*R*)- **19j**][b]
12	(*R*,*R*)- **12**	Ph	Cl	94	34 [**19k**][b,d]

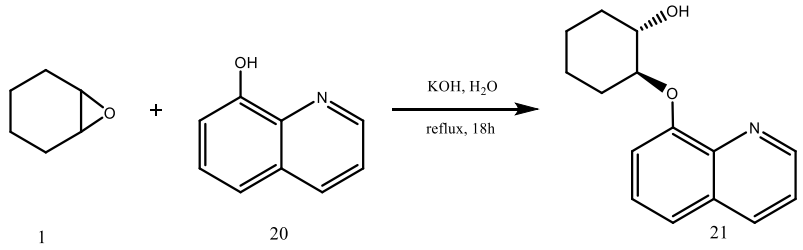
In summary, practical synthesis and resolution of *trans*-2-aryloxy cyclohexan-1-ols **12** and **14** have been carried out. The enzymatic resolution of *trans*-2-aryloxy cyclohexan-1-ols yield both the enantiomers in optically pure form. The naphthyloxy cyclohexanol derivatives have been further screened as chiral auxiliary for deracemization of *rac*-α-chloropropanoic acid. The results indicate diastereoselective ester formation in presence of DCC and DMAP. The diastereomeric ratio of the product has been established from the ^{1}H NMR signal for the α -C*H*- proton and by HPLC. The auxiliary **12** has been employed for deracemization of *a*-halo acids with varying alkyl groups and diastereomeric enrichment has been observed. The detailed mechanistic study and theoretical calculations for diastereoselective esterification are currently under progress.

Chapter 4: *Synthesis, Resolution and Application of Cyclohexanol derivatives in Enantiomeric Recognition:*

In this part we report preparation of a simple chiral molecule, 2-(quinolin-8-yloxy)cyclohexan-1-ol, which has three distinct binding sites along with the aromatic quinoline moiety for effective supramolecular interactions as well as being capable of exhibiting good fluorescence response.

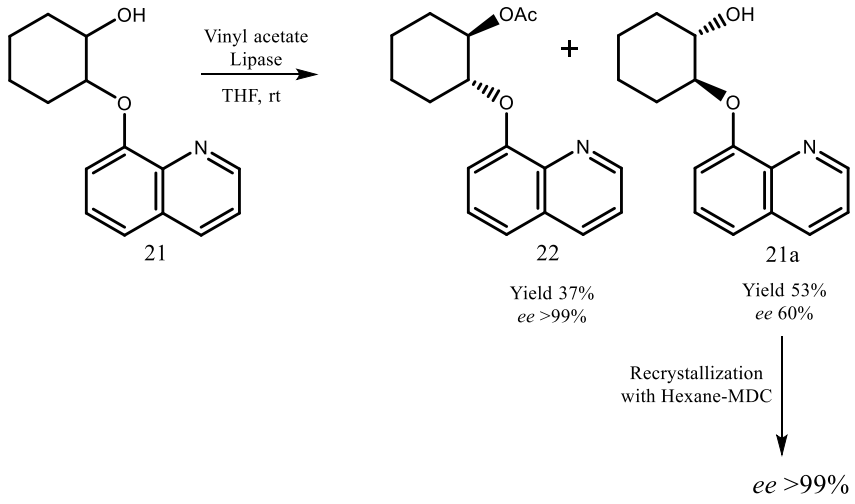
Synthesis of Quinolin-8-yl-cyclohexanol:

(±)-*trans*-2-(quinolin-8yloxy)cyclohexanol (**21**) has been prepared by using cyclohexene oxide (1 eq) and 8-hydroxyl quinoline (1 eq) in the presence of potassium hydroxide (1 eq) in water. The quinolinyl alcohol was further crystallized and subjected to enzymatic resolution.



Scheme 9: Synthesis of quinolin-8yloxy cyclohexanol

(±)-*trans*-2-(quinolin8-yloxy)cyclohexanol (**21**) has been subjected to enzymatic resolution in presence of Steapsin lipase and vinyl acetate as acyl donor. The unreacted alcohol with *ee* 60% was further recrystallized resulting in enhanced *ee* of >99%.



Scheme 10: Enzymatic resolution of quinolin-8yloxy cyclohexanol

Application of Quinolinyl cyclohexanol as CSA

Having optimized the synthesis and established absolute configuration of (*R*,*R*)-**21**, we tested our hypothesis to screen it as chiral solvating agent for evaluating enantiodiscrimination of signals of optically active acid analytes Type-A-F by NMR spectroscopy.

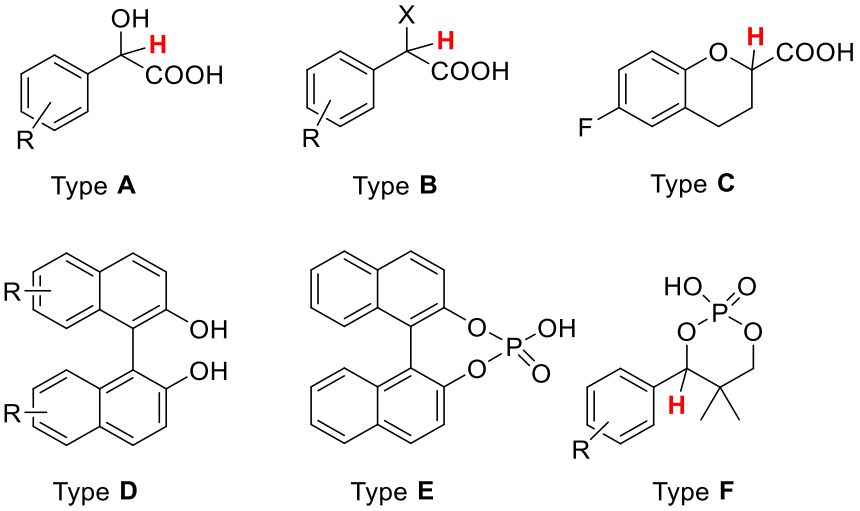


Figure 4: List of substrates screened by NMR

To understand the interactions between the (*R*,*R*)-**21** and the isomers of mandelic acid, attempt to grow the crystal of its salt with both isomers of **A-I** was made. A suitable quality crystal of (*R*,*R*)-**21** and (*R*)-**A-I** could be obtained from acetonitrile, while the other pair resulted in amorphous salt. The single crystal X-ray analysis of (*R*,*R*)-**21**•(*R*)-**A-I** confirmed the three point supramolecular interactions.

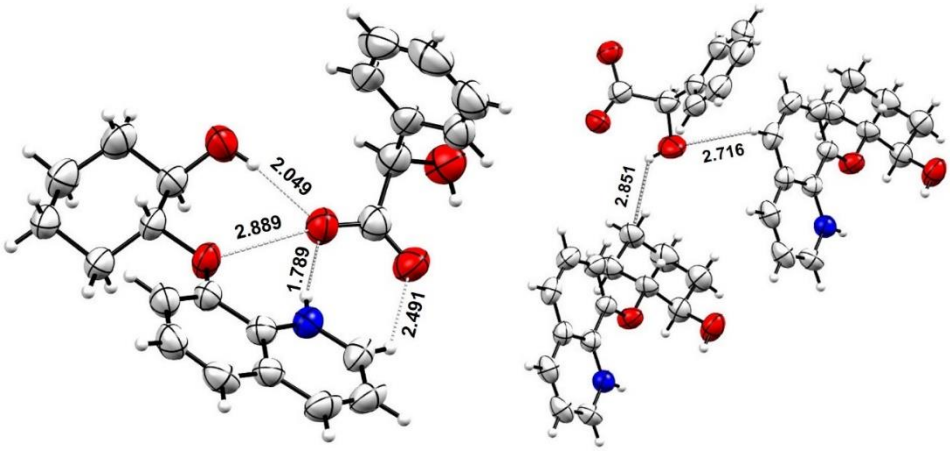
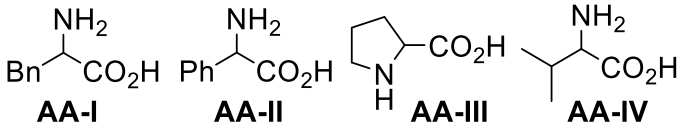


Figure 5: ORTEP diagram of the compound (*R*,*R*,)-**21**-(*R*)-MA (50% probability factor for thermal ellipsoids) CCDC-1853113

Application as Fluorescent sensor:

Fluorescence recognition of **AA-I** to **AA-IV** with (*R*,*R*)-**21** in EtOH showed significant enhancement indicating selectivity towards one enantiomer. The fluorescence spectra of (*R*,*R*)-**21** in presence of **AA-I** resulted in marked enhancement at short wavelength emission with *L*-isomer, while insignificant change was seen with the other isomer.



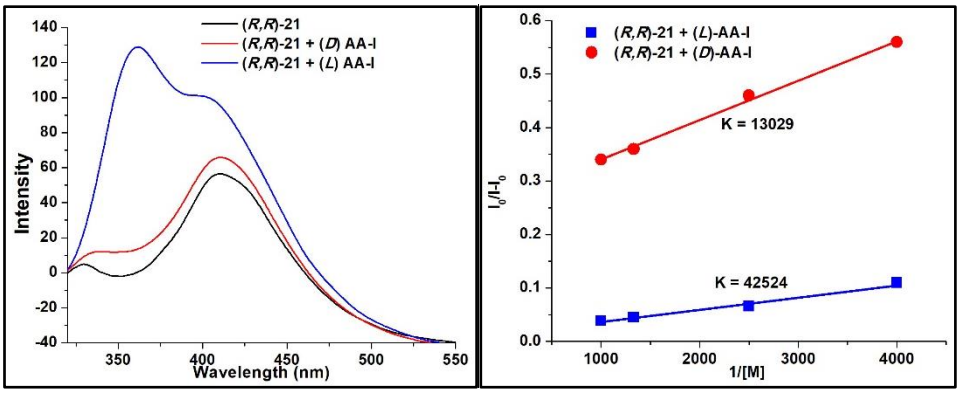
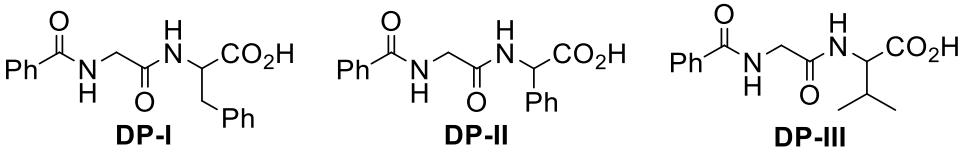


Figure 6: Fluorescence spectra of (*R*,*R*)-**21** (1.0 X10^{-5} M in EtOH) in the presence of *D*- and *L*-phenyl alanine (AA-**I**) (1.0 X 10^{-3} M in EtOH) (bottom left) (λ_{ex} 300 nm) (left); Benesi-Hildebrand plot of (*R*,*R*)-**21** (1.0 X10^{-5} M in EtOH) in the presence of *D*- and *L*-phenyl alanine (AA-I) right.

With the aim to further explore the possibility of using (*R*,*R*)-**21** for determining fluorescence response with isomers of peptides and its subsequent use as marker with other biomolecules, we investigated few dipeptides as analytes for this study (**DP-I** to **DP-III**).



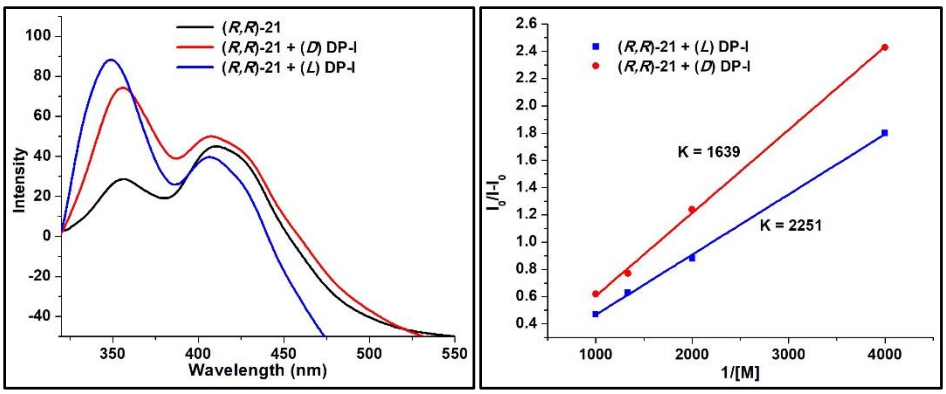
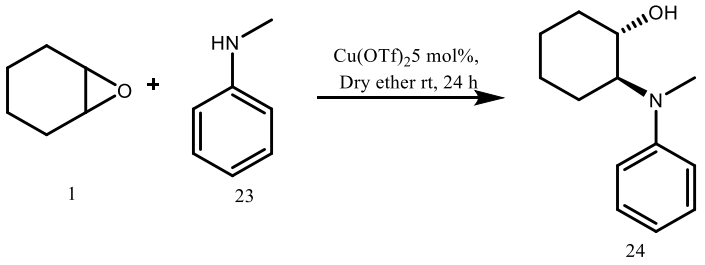


Figure 7: Dipeptides investigated as analytes for the fluorescence response with of (*R*,*R*)-**21** (top). Fluorescence spectra of (*R*,*R*)-**21** (5.0 X10^{-6} M in EtOH) in the presence of *D*- and *L*-**DP-I** (1.0 X 10^{-3} M in EtOH) [λ_{ex} 300 nm] (bottom left). Benesi-Hildebrand plot of (*R*,*R*)-**17** (5.0 X10^{-6} M in EtOH) in the presence of *D*- and *L* **DP-I** (bottom right)

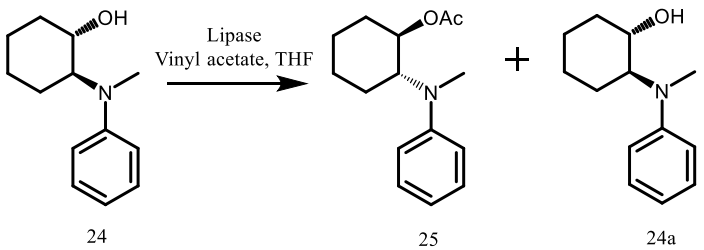
Synthesis and resolution of aminoalcohol:

Amino alcohol **24** was synthesized by ring opening of meso cyclohexenoxide (1eq) with N-methyl aniline (1eq) in presence of $Cu(OTf)_2$ in dry ether. The amino alcohol **24** was then subjected to enzymatic resolution in presence of lipase and vinyl acetate as acyl donor in THF.



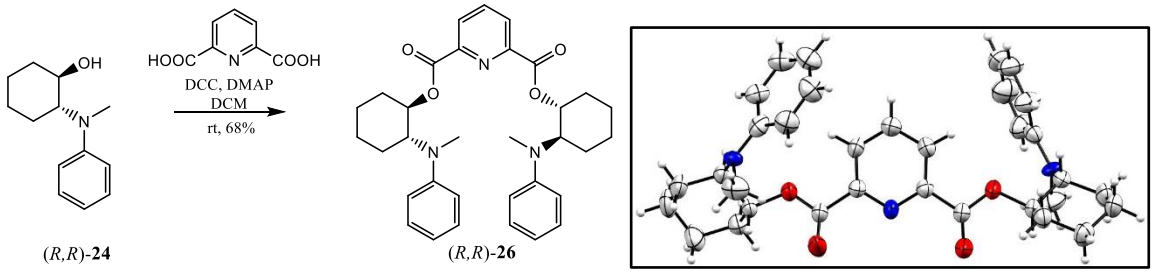
Scheme 11: Synthesis of amino alcohol

Enzymatic resolution of amino alcohol:



Scheme 12: Resolution of amino alcohol (**24**)

Synthesis of amino esters:



Scheme 13: Synthesis of amino ester (**26**)

This amino ester (**26**) has been screened as CSA for mandelic acid and binaphthyl phosphoric acid derivatives. The preliminary results of CSA experiments indicate low to moderate degree of separation of signals.

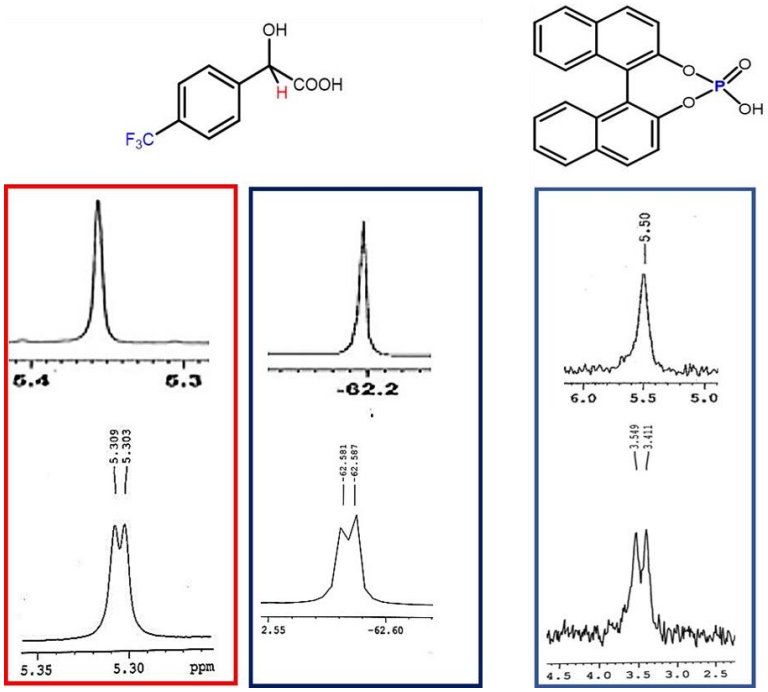


Figure 8: ^{1}H and ^{19}F NMR spectra of **A-II** with (*R*,*R*)-**26** (left); ^{31}P NMR spectra of **E** with (*R*,*R*,)-**26** (right).

2-(quinolin-8-yloxy)cyclohexan-1-ol (**21**) has been successfully screened as chiral solvating agent by NMR spectroscopy for series of acid analytes ranging from α-substituted acids, binol derivatives and cyclic phosphoric acid analgues. Furthermore, the utility of 2-(quinolin-8-yloxy)cyclohexan-1-ol (**21**) as a chiral fluorescent sensor has been explored establishing the role of (*R*,*R*)-**21** as chiral sensor for the recognition of amino acid derivatives and dipeptide derivatives. The chiral amino alcohol derivative was converted to amino ester (**26**) derivatives and screened

for enantiomeric discrimination of acid derivatives. The CSA experiments indicate lesser separation of signal due to presence of aryl group attached to amine nitrogen making it less efficient for molecular recognition studies.

References:

1. Kelvin, W. T. *Baltimore lectures on molecular dynamics and the wave theory of light*. CJ Clay and Sons, **1904**.
2. Pedersen, C. J.; *J. Am. Chem. Soc.* **1967**, *89*, 7017
3. Girodeau, J. M., Lehn, J., Sauvage, J. P.; *Angew. Chem. Int. Ed.*, **1975**, *14*, 764.
4. Peacock, S., Walba, D., Gaeta, F., Helgeson, R., Cram, D. J.; *J. Am. Chem. Soc*. **1980**, *102*, 2043.
5. Bradshaw J., Guynn, J., Wood, S., Krakowiak, K., Izzat, R., McDaniel. C., Wilson, B., Dalley, K. Lindh, G.; *J. Org. Chem.* **1992,** *57*, 5383
6. Quinn, T., Atwood, P., Tanski, J., Moore, T., Andersen, J.; *J. Org. Chem.*, **2011**, *76*, 10020.
7. Schiffers, I., Rantanen, T., Schmidt, F., Bergmans, W., Zani, L., Bolm, C.; *J. Org. Chem.*, **2006**, *71*, 2320.
8. Corey, E. J., Ensley, H. E.*; J. Am. Chem. Soc***., 1975**, *97*, 6908.
9. Whitesell, J., Chen, H., Lawrence, R; *J. Org. Chem.*, **1985**, *50*, 4663.