CHAPTER -VI

Synthesis and Evaluation of (2s,3s)-3-(Acetyloxy)- 5–OXO-2-[(4-Vinylanilino)Carbonyl] Tetrahydro-3-Furan Carboxylic Acid-Based Polymeric Chiral Stationary Phase

VI.01. Introduction

Liquid chromatographic resolution of enantiomers on chiral stationary phases (CSPs) is one of the most convenient and accurate methods for the determination of optical purity. With increasing evidence of problems related to stereoselectivity in drug action, enantioselective analysis by chromatographic methods is one of the important areas of interest to contemporary separation scientists. Most of the pharmaceutical and pharmacological studies of stereoselectivity of chiral drugs before the mid eighties involved pre-column derivatization of the enantiomers with chiral reagents, forming diastereomers. The diastereomers were subsequently separated in the normal or reverse phase chromatography.

Chiral chromatography has become a necessary tool-not only for the analytical determination of enantiomeric purity, but also for the isolation of pure enantiomers. The differences which make compounds chiral can produce critically different pharmacological effects in biological systems. As a result, demand for stereoselective separation techniques and analytical assays to evaluate the enantiomeric purity of chiral compounds has increased.165

Analytical methods which have been used for the separation of chiral compounds includes High Performance Liquid Chromatography (HPLC),166 Gas Chromatography (GC)167, thin layer chromatography (TLC),168 and recently capillary electrophoresis.169
VI.02. Chiral Stationary Phase (CSP)

Great efforts have been devoted for the development of better methodology for enantioselective chromatography during the past decade and have resulted in the formation of a large number of chiral stationary phases. Chiral agents were derivatized and immobilized on the surface of the support (silica gel mostly) and served as the *in situ* chiral discriminators during the chromatographic process. The preference of chiral stationary phases lies in the inherent advantages of any chromatographic separation such as, the speed of the analysis, the possibility to analyze or purify the enantiomers in complex mixtures, the reproducibility of the analysis and its flexibility. Moreover, analytical chromatographic systems can be adapted to preparative separations in which pure enantiomers can be collected.

In addition to their distinct practical applicability, chiral stationary phases can uniquely contribute to studies of the nature of molecular recognition. Since the differential retention of enantiomers in the chromatographic system employing chiral stationary phases, can be attributed only to chiral discrimination by the chiral sites, these interactions can be identified and explored.

High performance Liquid Chromatography (HPLC) is a chemistry based tool for quantifying and analyzing mixtures of chemical compounds. The chiral-stationary-phase (CSP) method for the liquid chromatographic resolution of enantiomers has gained general acceptance owing to its ease of operation and preparative-scale applications. However, among a number of CSPs developed to date, those with a general scope of application are few. More than 100 chiral stationary phases have been commercialized. Among them, polymeric chiral stationary phases, except the protein based CSPs, are suitable for preparative separations due to their high sample loading capacity. Applications of synthetic polymeric CSPs, including vinyl polymers, polyamides, and polyurethanes, on separation of enantiomers have been increasing recently because of their high stability and loadability.

VI.03. Classification of Chiral Stationary Phases

Based on the structure of the chiral selector, CSPs are divided in to the following classes:

- Polymeric CSP
- Macrocyclic CSP
- \( \pi-\pi \) association CSP
- Ligand exchange CSP and
- Hybrid chiral stationary phases
- Chiral affinity by proteins (serum albumin, a1-acid glycoprotein, ovomucoid and chymotrypsin).
- Host-guest interactions inside chiral cavities (cyclodextrins, crown ethers and imprinted polymers).

In general, polymeric CSPs, with the exception of ones based on proteins, are highly suitable for preparative separation due to their high loading capacity on the support and the fact that a single bonded or adsorbed polymer molecule can interact with several analyte molecules simultaneously along its length. The polymeric chiral selectors can again be classified in two types according to their origins. One class uses natural polymers such as polysaccharide and proteins or their derivative as chiral selectors; another class uses purely synthetic polymers as chiral selectors (Figure VI.01).

(a) Cellulose tris(3,5- dimethylphenylcarbamate) and
(b) amylose tris(3,5-dimethylphenylcarbamate).

Figure VI.01: Synthetic polymers as chiral selectors

Chiral stationary phases based on polysaccharide derivatives have been extensively used for analytical and preparative separations of chiral molecules because of their broad enantioselectivities and high sample loading capacities.\(^{179-180}\)

Development of synthetic polymeric CSPs for the effective separation of enantiomers are yet to achieve comparable success. However, research on synthetic polymeric CSPs is also evolving due to combination of attractive features, such as the richness of the chemical structures potentially available, the ease of their chemical
VI.04. Strategies of syntheses of CSPs

Strategically there are minimum four approaches for the preparation of synthetic polymeric CSPs.

First approach involved the co polymerization of chiral monomers with an achiral cross linking agent. Blaschke and his co workers reported the first polymeric CSPs of these type.\textsuperscript{181,182} These CSPs are polymeric beads prepared through the copolymerization of chiral acrylamides or methacrylamide with ethylenediacylate used as the cross linking agent.

A second approach used to prepare chiral polymers uses prochiral monomers via asymmetric catalyzed polymerization.\textsuperscript{183} One handed" helical polymers were prepared by Okamoto and co workers from prochiral monomers such as triphenylmethyl methacrylate (TrMA) and diphenyl-2- pyridylmethyl methacrylate (D\textsubscript{2}PymA) via asymmetric catalyzed anionic polymerization reaction.\textsuperscript{184,185}

The third approach used by Allenmark and coworkers involved the catalyzed copolymerization of chiral monomers with diallyl groups with multifunctional hydrosilane molecules to form network polymeric chiral selectors.\textsuperscript{186-188} These chiral selectors were then bonded to vinyl-functionalized silica gel to form CSPs. Another approach involves the creation of a chiral linear homopolymer attached to the surface of a silica gel support.

Polyacrylamide and polymethacrylamide CSPs with phenylalanine, 1-phenylethyl, 1-cyclohexylethyl \textsuperscript{189}, penicillin\textsuperscript{190} and menthone or menthol \textsuperscript{191} moieties were also reported. The selector-selectant hydrogen-bonding interactions are the important features of amide based CSPs (Figure-VI.02)

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{amide_csp.png}
\caption{The hydrogen- bonding in amide-based CSPs}
\end{figure}
Recently, a new series of synthetic polymeric CSPs based on the derivatives of trans-1,2-diaminocyclohexane, trans-1,2-diphenylethylene diamine, and trans-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid\textsuperscript{192} are also reported (Figure VI.03).

![Diagram](attachment:image.png)

**Figure VI.03:** The 1,2 diaminocyclohexane derived CSPs

*Trans*-1,2-diamino cyclohexane [194] (Commercial name: P-CAP),\textsuperscript{188,189} trans-1,2-diphenylethlyenediamine [195] (Commercial name: P-CAP-DP) and *trans*-9,10-dihydro-9,10-ethanoanthracene-(11S,12S)-11,12-dicarboxylic acid bis-4-vinylphenylamide [196] (DEABV) are examples for synthetic monomers.

Chiral Stationary phases can be prepared either by a surface initiated polymerization or a solution initiated polymerization method. These new polymeric CSPs can separate many chiral molecules in the normal phase mode and the polar organic mode.

In a chiral separation the stationary phase is chosen such that the spatial arrangement of its composite atoms results in the probability or proximity of interaction differing significantly between the two enantiomers to be separated. In practice, this is usually attained by making the stationary phase itself is chiral and, in fact, the first chiral separations in gas chromatography have been achieved by using an enantiomer of amino acid as the stationary phase.
Yasuo Dobashi and Shoji Hara et al. reported that (R,R) N,N’diisopropyl tartramide (DIPTA) functions as a broadly applicable chiral-mobile-phase additive (CMPA) in silica gel chromatography. This CMPA recognizes the molecular chirality of enantiomers through its dual hydrogen bond association and is capable of resolving enantiomers containing α- or β-hydroxy carboxylic acid, α-hydroxy ketone, β-amino alcohol, α-amino acid, α-hydroxy ketoxime, 1,2-diol derivatives, and bi-β-naphthol.

The following compounds have been resolved from their respective enantiomers using DIPTA derived chiral stationary phases (Figure VI-04).
VI.05. Tartaric acid based Chrial selectors

The easy accessibility of tartrates has made them common starting materials for the preparation of both immobilized and dynamic chiral selectors for liquid chromatography. Among other chiral selectors the tartaric acid derived chiral selectors are found to be the most efficient selectors in partition chromatography (Scheme VI.02).

\[
\text{Selector} \quad \begin{array}{c}
\text{OR}_2 \\
\text{C} \\
\text{C} \\
\text{C} \\
\text{C} \\
\text{R}_1
\end{array}
\]

a. \( R_1 = \text{piperidyl}, R_2 = -\text{H}, \quad \alpha^- = 1.00 \)
b. \( R_1 = \text{n-butyl-}O-, R_2 = -\text{H} \quad = 1.04 \)
c. \( R_1 = \text{t-butyl-}O-, R_2 = \text{H} \quad = 1.05 \)
d. \( R_1 = \text{n-octyl-}O-, R_2 = \text{H} \quad = 1.03 \)

\[ \alpha = \text{Stereo-selectivity} \]

Scheme VI.02

Consistent with observation by Prelog et al. the highest selectivity is provided by tartaric acid derivatized with bulky alcohols. Several new chiral stationary phases have been identified and obtained by coupling 2-chrysenyl amine and 1-pyrenylamine to chiral selector groups based on \((R,R)\)-tartaric acid diamide [197–200] (Scheme VI.03)
These new materials were evaluated by HPLC and had been found to exhibit excellent enantioselectivity for various types of compound including aromatic alcohols, binaphthyl derivatives, β-blocking agents and anti-inflammatory agents. Both pyrene and chrysen have been shown to be absorbed strongly on to Porous graphitic carbon (PGC)\textsuperscript{197,198} from appropriate solvent system. Thus it can be used as the anchor components.

Reports are available on the direct separation of enantiomeric alcohols using tartaric acid derivatives as chiral complexing agents in organic stationary or mobile phases.\textsuperscript{199} Among the tartaric acid derivatives reported, only tartrates having hydroxyl groups attached to the asymmetric carbon atoms (C2) and (C3) free, can provide excellent enantioselective retention for ephedrine stereoisomers.

Crown ether-based HPLC chiral stationary phases (CSPs) have been successfully utilized in the resolution of various racemic compounds containing a primary amino group. Especially, CSPs based on chiral crown ethers incorporating chiral binaphthyl unit or tartaric acid unit and based on phenolic pseudo chiral crown ethers have shown high chiral recognition efficiency. Among chiral crown ethers incorporating tartaric acid unit, (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid [201]
(Figure-IV.05), which was first developed by Lehn,\textsuperscript{200} has been widely utilized since early 1990s as a chiral selector for the resolution of racemic primary amino compounds by capillary electrophoresis.\textsuperscript{201}

![Figure VI.05: The tartaric acid derived crown ether](image1)

While treating 201 with aminopropylsilica gel in the presence of a coupling agent EEDQ (2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline) the CSP-7 is formed (Figure- VI-06, Scheme-VI-04)

![CSP-7](image2)  
![CSP-8](image3)

**Figure- VI.06: The crown ether based CSPs**

![Scheme-VI-04](image4)
VI.06. Polysaccharide Derivatives

Polysaccharides such as cellulose and amylose consist of D-glucose units linked by 1-4 glucosidic bonds, forming the natural polymers with a highly ordered helical structure. The three hydroxyls on each glucose unit can be derivatized to form strands around the chiral glucose. The derivatized glucose unit can in principle act as a chiral site discriminating between enantiomers that interact differently with the strands. Resolution can sometimes be achieved with unsupported natural cellulose, but the immobilized version has proven far better. The acetate or bezoate ester, or phenylcarbamate derivatives of glucose [202], have shown better performance. Mobile phases are usually organic, normal phase type solvents, however, aqueous solvents can also be used in many versions of the stationary phase (Figure-VI.07).

![Figure-VI.07](image-url)

**Figure-VI.07:** The glucose derivative as monomer in CSP

The structure provides the possibilities of π-π interaction of aromatic groups with the aromatic amide at the chiral site with the anchoring effect of hydrogen bonding with the amide groups. The discrimination is affected by the steric fit in the cavity.

Report pertaining to the distribution behavior of ketoprofen enantiomers in methanol, aqueous, and organic solvent mixture containing tartaric esters is available (Figure- VI.08).

![Figure-VI.08](image-url)

**Figure-VI.08:** The ketoprofen enantiomers
Influence of length of alkyl chain of tartaric esters, concentration of \( L \)-tartaric esters, kind of organic solvent on partition ratio and separation factors etc were investigated. The results show that \( L \)-tartaric and \( D \)-tartaric esters have different chiral recognition abilities. \( S \)-ketoprofen is easily extracted by \( L \)-tartaric esters while \( R \)-ketoprofen is easily extracted by \( D \)-tartaric esters. The \( L \)-tartaric esters form more stable diastereomeric complexes with \( S \)-enantiomer than that with \( R \)-enantiomer.

Distribution behavior of mandelic acid enantiomers has been examined in an aqueous-organic solvent of a two-phase system containing \( L \)-tartrate. With the rise of pH, partition coefficient \( (k) \) decreases while the separation factor \( (\alpha) \) increases. With the addition of length of alkyl chain of \( L \)-tartrate, \( k \) and \( \alpha \) decrease. The organic solvent and concentration of phosphate salt also have profound influence on \( k \) and \( \alpha \). A new binary chiral selector system effective for the enantioselective extraction of a series of racemic tropic acid derivatives has been identified.\(^{202}\)

Diester derivatives of tartaric acid are well known as effective chiral selectors. Because these derivatives are symmetric in the C2 axis and two kinds of functional groups, hydroxyl and carbonyl, attached to asymmetric carbons in these derivatives are stereochemically equivalent to those groups attached to other carbons; these structural features are favorable for them to be functioned as chiral selector.

**VI.07. General Performance of CSP**

The performance of a stationary phase is usually evaluated by two criteria: resolution and capacity factor. The resolution is acceptable if the enantiomers are baseline separated; while with small capacity factor, the retention time is short and the mobile phase consumption is low. In addition to the general factors like enantioselectivities, retention factors and resolutions of the racemates, the interactions like hydrogen bond, dipole-dipole and \( \pi-\pi \) interactions are the main factors that determined the grading or efficiency of both natural and synthetic chiral stationary phases. The nature of silica gel often plays an important role in selectivity.
VI.08. Silica: backbone material of liquid chromatographic column packings

Alumina and silica gel are readily available inorganic compounds and are widely utilized as stationary phase in chromatographic separations. The use of alumina or silica gel anchored with appropriate chiral entities as heterogeneous supports and their applications as chiral separators are of vital importance now. Silica-based LC packings have a particle size ranging from 1 to 100 μm. Microscopy is the simple method to determining the particle sizes. Among various particle size analysers, Monodispers latex beads are used as efficient calibrators. However there is optimum particle size with regarded to analysis time, plate number and pressure drops.

It has been shown that the selectivity with a thermally treated silica used in normal-phase LC is greatly dependent on polarity of the mobile phase. The qualities of silica, i.e. high surface area and porosity, facile and versatile preparation, adjustable polarity and good mechanical strength, explain its widespread use in Liquid Chromatographic Stationary phase.\textsuperscript{203}

VI.09. Results and Discussion

On account of the synthesis and application of optically active hydroxyacid like tartaric acid, in the preparation of chiral stationary phase and the subsequent use in liquid chromatographic resolution of enantiomers, attempt have been made to generate \((2S,3S)\)-tetrahydro-3-hydroxy-5-oxo-2,3-furan dicarboxylic acid based chiral stationary phase for the Liquid chromatographic separation of enantiomers.

VI.09 (i). Synthesis of \((2S,3S)\)-3-(Acetyloxy)-5-oxo-2-[4-Vinyl anilino carbonyl] tetrahydro-3-furan carboxylic acid (AVTFCA) – the monomer

Towards this direction \((2S,3S)\)-3-(Acetyloxy)-5-oxo-2-[4-Vinyl anilino carbonyl] tetrahydro-3-furan carboxylic acid (AVTFCA)[\textsuperscript{205}], the monomer component of the CSP, has been synthesized by the reaction between (6-aS)-2,4,6-trioxotetrahydrofuro[3,4-b]furan-3(4H)-yl-acetylate\textsuperscript{[203]} and 4-Vinylaniline [\textsuperscript{204}](Scheme-VI.05).
The formation of the monomer namely \((2S,3S)-3\) -(Acetyloxy)-5-oxo-2-[ 4-Vinyl anilino carbonyl] tetrahydro-3- furan carboxylic acid [205] has been ascertained by 1H NMR, 13C NMR and mass spectral data (Figure- VI.09a-c).

**VI.09(ii). Synthesis of Poly-AVTFC CSP [206]**

On subsequent polymerization of this monomer 205 with Silica gel functionalized with dichloride of 4,4’-azo-bis-cyanovaleric acid yield the new CSP (Poly-AVTFC), 206. This new CSP has been effectively used as chiral stationary phase in Liquid Chromatography for the enantiomeric resolution of \(\alpha\)- methyl benzylamine (Schemes-VI.06 & VI.07).
VI.09 (iii). Performance of new CSP

The efficiency and performance of the new Chiral stationary phase (Poly-AVFCA) derived from molecule 1 and 4-vinyl aniline, has been carried with only a few racemic mixtures initially. Among them the CSP separation of α-methyl benzyl amine showed comparatively good separation chromatogram (Figure-VI.10) and the CSP separation on several other compounds are in progress. The formation of the monomer, (2S,3S)-3-(Acetyloxy)-5-oxo-2-[4-Vinyl anilino carbonyl] tetrahydro-3-furan carboxylic acid has been ascertained by 1H,13C NMR and mass spectral data (Fig.VI.9 a-c).

\[ ^1\text{H} \text{NMR (CDCl}_3\text{)} \]

Figure-VI.09 a
Figure VI.10: The chromatogram obtained for Poly-AVTCA [206] in the Chiral separation of racemic α-methyl benzylamine

Mode: Polar organic mode

Solvent – Heptane –ethylacetate (50: 50, V/v)
VI.09 (iv). **Analytical data**

The following parameters can be assigned from the chromatogram (Table-VI.01).

<table>
<thead>
<tr>
<th>Table-VI.01</th>
<th>Analytical data for the liquid chromatographic separation of racemic α- methyl benzylamine using Poly–AVTFCA chiral stationary phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Start</td>
<td>2.8 Min.</td>
</tr>
<tr>
<td>Peak end</td>
<td>3.6 Min.</td>
</tr>
<tr>
<td>Capacity factor (K)</td>
<td>- 0.714</td>
</tr>
<tr>
<td>Peak width (Base)</td>
<td>0.8</td>
</tr>
<tr>
<td>Peak height of 1st enantiomer</td>
<td>11.5 m AU</td>
</tr>
<tr>
<td>Peak height of 2nd enantiomer</td>
<td>10.0 m AU</td>
</tr>
</tbody>
</table>

VI.09(v). **Column performance of poly- AVTFCA CSP**

The mobile phase mode where the new CSP investigated was the Polar organic mode. The major solvent components used for organic phase separation was heptane–ethylacetate (50:50 (V/V). The following recemic mixtures of compounds [181-190] were investigated (Table. VI.02).

<table>
<thead>
<tr>
<th>Table. VI.02</th>
<th>Racemic mixtures of compounds where the new CSP has been employed.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>citrulline, 207</td>
</tr>
<tr>
<td></td>
<td>2-Amino-5 (carbamoylamino) pentanoic acid</td>
</tr>
<tr>
<td></td>
<td>N-ethyl-3-hydroxy-2-phenyl-N-(pyridine-4-ylmethyl)propanamide [Tropicamide]</td>
</tr>
<tr>
<td></td>
<td>4,4’ diamino-2,2’-biphenyl disulphonic acid</td>
</tr>
<tr>
<td></td>
<td>(2,5-Dioxo-4-imidazolidyl) urea (Allantoin)</td>
</tr>
</tbody>
</table>
Among them only α-methyl benzyl amine[214], gave significant chiral separation chromatogram (Fig. VI.10).

### VI.10. Conclusion

A new silica gel based Chiral Stationary Phase, Poly-AVTFCA, has been developed from (2S, 3S)-tetrahydro-3-hydroxy-5-oxo-2,3-furan dicarboxylic acid for liquid chromatographic separation of enantiomers. The anhydride namely (6-aS)-2,4,6-trioxo tetrahydrofuro[3,4-b] furan-3(4H)-yl-acetylate obtained from the acid was condensed with 4- Vinyl aniline to get the monomer, (2S,3S)-3 -( Acetyloxy)-5-oxo-2-[ 4-Vinyl anilino carbonyl ] tetrahydro-3- furan carboxylic acid, in good yield. This monomer on subsequent polymerization reaction with Silica gel functionalized with dichloride of 4,4’-azo-bis-cyanovaleric acid to yield the subject Chiral Stationary Phase. Attempts have been made for the Liquid chromatographic
separation of various racemic compounds and it is found that racemic α-methyl benzyl amine was resolved in heptane - ethyl acetate solvent system.

Figure- VI. 11. CSP column packing and packed column used for analysis.

VI.11. General Experimental details

Spherical silica gel (partial diameter: 5 μm, pore size: 200 Å, surface area: 213 m2/g) functionalized with dichloride of 4, 4'-azo-bis-cyanovaleric acid was obtained from Advanced Separation Technologies ( Whippany, NJ, USA). Cyclobond I 2000 RSP column was also obtained from Advanced Separation Technologies. 4-vinylaniline, triethylamine, anhydrous chloroform, anhydrous toluene, acetone, thionyl chloride, and trifluoroacetic acid (TFA) were purchased from Aldrich (Milwaukee, WI, USA). HPLC-grade methylene chloride, methanol, ethanol, acetonitrile, 2-propanol, and n-heptane were purchased from Fisher (Fairlawn, NJ, USA.)

Equipment

Chromatographic separations were carried out using a HP 1050 HPLC system with an autosampler, a UV VWD detector, and computer-controlled Chem-station data processing software (Agilent Technologies, Palo Alto, CA, USA). The mobile phases were degassed under helium for 7 min. UV detection was carried out at 254 nm for all analytes. All separations were carried out at room temperature (~23 °C) and the flow rate of the mobile phase for all separations was 1.0 mL min⁻¹.

VI.11(i). Preparation of (3aS,6aS)-3a-hydroxy dihydrofuro[3,4-b] furen 2,4,6 (3H) trione

A suspension of garcinia acid [1] 1 gram (5 mmol) in acetyl chloride (4 ml) was refluxed two hours till all acids dissolves. The solution is allowed to cool undisturbed
and is finally chilled in ice bath. The garcinia acid anhydride formed is separated as white crystals. The crystals are washed thrice with dry hexane and concentrated in vacuum.

Yield : 0.980 gm

\[ \alpha \]_D^25 : -146.28 °(c 0.108, CH₂Cl₂)

M.P : 116-120 °C

VI.11(ii). Preparation of (2S,3S)-3-(Acetyloxy)-5-oxo-2-[4-Vinyl anilino carbonyltetrahydro-3- furan carboxylic acid (AVTFCA)]

A suspension of the title acid 1 (1gm, 5mmol.) in acetyl chloride (4ml) was refluxed for 2hrs. The resulting mixture was concentrated in vacuum to give a white solid, which was dissolved in dry THF (5ml). 4-vinyl aniline (0.59 g, 5mmol) was added, the mixture was stirred at room temp for 4h and thoroughly concentrated in vacuum. Further acetyl chloride (5ml) was added and the mixture was refluxed for 18h. After concentration in vacuum, recrystallisation (EtOH) afforded 205 as white crystals.

Yield = 1.2 g

H NMR(CDCl₃) : \( \delta \) 7.381-7.259 (m, 4H); 6.631-6.573(m, 1H); 5.696-5.192(d, 1H J = 17.4 Hz), 5.229-5.192(d, 1H, J = 11.1 Hz); 5.119(s,1H),3.680-3.619 (d, 1H J = 18.3 Hz.), 3.018-2.956 (d,1H J=18.6 Hz), 2.116(s, 3H).

\( \alpha \) : 7.442-7.291 ( m,4H), 6.634-6.576 (m,1H), 5.699-5.64 0(d, 1H,J = 17.7H), 5.229 – 5.192 (d,1H,J = 11.1 Hz), 5.12 (s,1H), 3.694-3.632(d,1H J = 18.6 Hz) 2.14 (s,3H).

C NMR(CDCl₃) : \( \delta \) 172.087, 170.309, 168.311, 163.320, 135.934, 135.589, 135.073, 126.894, 121.053, 113.982, 82.829, 82.083, 38.281, 21.101 ppm

Mass spectrum : m/z 332 (M+) (100), 664 (2 M+) (Dimer) (81),
VI.11(iii). **Preparation of Poly-AVTFCA CSP** [206]

The procedure used to prepare **Poly-AVTFCA CSP** is shown in Scheme-VI.06. The silica gel functionalized with dichloride of 4,4'-azo-bis-cyanovaleric acid was obtained from Advanced Separation Technologies. To 50 mL of a heated anhydrous, degassed chloroform solution of AVTFCA (0.7 g), silica gel functionalized with dichloride of 4,4'-azo-bis-cyanovaleric acid (1.60 g) was added under an argon atmosphere. The suspension was stirred at 50-60 °C for 4-5 h and heated to reflux for 1 h. The CSP was collected by filtration, and then washed with 100 mL of methanol, acetone, and chloroform respectively to remove the unreacted monomer. The CSP was dried under vacuum at 50 °C overnight to obtain in the pure form. The CSP was packed into a 250 mm × 4.6 mm (i.d.) stainless steel column.

VI.12. **Attempted synthesis employing (2S,3S) and 2S,3R)-Tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acids**

VI.12(i). **Asymmetric Diels–Alder reactions of Dimethyl (2S,3S) and (2S,3R) -3-(acryloxy)-5-oxotetrahydro-2,3 furandicarboxylate [4a]**

Development of methods for the asymmetric induction is of current interest. The use of chiral auxiliaries to this end has some notable solution to specific problems, but the need to invest separate reaction steps in the incorporation and subsequent jettisoning of the auxiliaries is a generally inherent limitation.

The usefulness of Diels–Alder reaction in synthetic organic chemistry arises from its versatility and remarkable stereo selectivity. There has been a great deal of interest among chemists to develop new chiral auxiliaries to accomplish synthetic transformations with a high degree of asymmetric induction. Efficient asymmetric syntheses of large number of natural products are available in literature using tartaric acid as precursor. However very little information is available with that of (-) Hydroxycitric acid.

With this view, rational designing of acid lactone based dienophile auxiliaries would be preferred and the extent of asymmetric induction may be estimated (Scheme-VI.08).
VI.12(ii). Synthesis of Optically active pyrrolizidine alkaloid [5a].

Pyrrolizidines are a group of alkaloids that exhibit remarkably diverse type of biological activity. The azabicyclo[3.3.0] octane ring systems have been reported to act as antitumor, hypotensive, local anesthetic, antispasmodic, anti inflammatory or hepatotoxic agents. The method developed by Richard Chamberlin and John Y.L Chung have been used for the synthesis of 5a (Scheme-VI.09) The product cannot be isolated.