Chapter I

New strategies for heterocyclic chiral molecules
In 1849, French chemist Louis Pasteur was studying the rotation of polarized light in tartaric acid crystals. He discovered two kinds of crystals one of which rotated the polarized light to the left and the other to the right. The equal mix of the two crystals did not rotate the polarized light.

This is how the existence of chirality in molecules was first demonstrated and further investigation started with the recognition of stereochemistry influencing the properties of molecules. The two kinds of crystals discovered was found to be composed of two non-superimposable mirror image molecules called Enantiomers. The one which rotates the light to left and other right are L and D- Isomers respectively.

The presence of only L or only D isomers is noted as Homochirality. The mixture of L and D isomers in 50/50 ratio is denoted as racemic mixture.

Chirality means 'Handedness' in Greek.
All objects can be classified as chiral or achiral. An excellent example of this is our hands which are mirror images of each other but not superimposable. They are different in a stereo sense. A right hand glove will not fit onto the left hand. Just imagine fitting the right hand to the left arm and try to shake hands with others. It is uncomfortable!

Chirality is a fundamental property of the nature.

**God has created the world chirally!**

While how chirality was introduced onto the Universe, how chiral molecules were created in the world first are still continuing subjects of investigation, this thesis will exemplify how chiral molecules can be synthesized.

Some examples of Chirality: Figures 1 - 3

**Fig 1  Hands**
Fig 2  Sea shells

Fig 3  Snail
In the same way as organs, objects and living creatures are chiral; most of the biomolecules in nature are chiral. Sugars, proteins, amino acids, steroids, DNA which form the integral part of our body are chiral. The DNA structure (Fig 4) itself is chiral and exists as a single enantiomer. The helix is a so-called "right-handed" helix. Like the threads on a screw, helices are chiral, and this form of DNA, called the "B-form" helix is the most commonly seen structure, and it is a super-chiral helix because the nucleic acid bases are chiral.

Fig 4 DNA Structure

The bottom line is that biological molecules are chiral and found as single enantiomers even though they can have hundreds or thousands of chiral centers. This is because biological molecules are built from single
enantiomers of chiral building block molecules (i.e. amino acids). Thus, biology is chiral, and stereochemistry is an extremely important part of biology.

We eat optically active bread & meat, live in houses, wear clothes, and read books made of optically active cellulose. The proteins that make up our muscles, the glycogen in our liver and blood, the enzymes and hormones ... are all optically active. Naturally occurring substances are mostly optically active because the enzymes which catalyze their formation ... are optically active.

The most common type of chiral molecule contains a tetrahedral carbon atom attached to four different groups (Fig 5); the carbon atom is the stereogenic (asymmetric) center of the molecule. Such a molecule can exist as two different compounds that are stereo isomers and have identical chemical properties in an achiral (symmetrical) environment.

**Fig 5  Chiral molecule**
Simple examples of simple chiral molecules

1D chiral molecule (chiral in a line land)

2D chiral molecule (chiral in a flat land)

Optically active compounds are ubiquitous in our everyday life. They are the active constituents of many medicines, vitamins, flavors and fragrances, and the herbicides and pesticides used in crop protection.

An overwhelming majority of naturally occurring medicinal agents and synthetic drugs are chiral molecules.

In contrast, for many years it was common practice to market synthetic chiral drugs as racemates.

However, the situation changed rapidly in the last few decades and a perusal of the top twenty drugs reveals a definite trend towards enantiopure synthetic drugs. The overall pharmacological effect of a drug is influenced by both its pharmacodynamics and pharmacokinetics, and enantioselectivity plays an important role in both phases.

In some cases chiral drugs are administered as racemates since the distomer displays no undesirable side-effects.
For example, Atenolol and Timolol are marketed as racemates as the distomer exhibits no serious side-effects.

In some cases the distomer may exhibit undesirable (toxic) side-effects that are not characteristic of the eutomer. In case of Ethambutol (Fig 6), the (S, S) isomer is an active tuberculostatic whereas the (R, R) enantiomer causes optical neuritis that can result in blindness. The amino acid, Asparagine (Fig 6), the (S) isomer is bitter in taste and the (R) isomer is sweet.

![Fig 6](image)

In some cases both isomers of a chiral drug can have a desirable, but different, therapeutic effect. This is indeed the case with many natural products and also with synthetic drugs. Dextropropoxyphene is an analgesic agent while levopropoxyphene is devoid of analgesic properties but is an effective antitussive (Fig 7).
There are few examples of chiral drugs where both enantiomers contribute, in different ways, to the overall desired effect. This can involve the distomer acting as an antagonist for undesirable side-effects of the eutomer. In case of Indacrinone (Fig.8), the (R)-enantiomer is the active diuretic and also exhibits the undesired side-effect of uric acid retention. The (S)-enantiomer acts as a uricosuric and thus antagonizes the undesired side-effect.

\[ (R) + (S) \] - isouricemic diuretic
Chapter I.2

Introduction to Chiral intermediates

Chiral intermediates are the essential building blocks of the enantiopure drugs. Today most new drugs and those under development consist of a single optically active isomer, and chirality is also becoming an issue for the Pharmaceuticals, agrochemicals, eatables, flavors and other fine chemical industries. Regulatory agencies throughout the world are currently reviewing the importance of chirality with regard to pharmaceuticals and agrochemical products. New guidelines from such agencies have been key drivers for the focus on single enantiomer products in these industries. These scientific and regulatory developments have created the need for a guide for scientists in the pharmaceutical and chemical industries seeking information on chiral molecules, processes, and commercially available chiral chemicals.

It is clear that where one isomer of a chiral compound is 'good' and the other 'bad' or 'ineffective', there is obvious benefit from developing the drug as the single isomer to enhance its safety and tolerability. In addition, this can also speed the progress of the drug through regulatory channels, thereby saving R&D costs. Therefore, the optical compound has a very big market potential, attracting people to carry out the thorough research.
Chiral technologies often originate in academic labs or research-oriented companies. It has been observed that a reaction which is very effective in the laboratory, at small scale, but cannot easily be scaled to a manufacturing plant. The same problem holds for chiral building blocks and intermediates, which often require a complete re-design of the process at significant cost in time and resources.

Two developments have intensified the demand for optically pure substances and the search for the new manufacturing methods during the past decades: New FDA regulations and the 'Racemic switch'. Since 1992, the American Food and Drug administration (FDA) requires clinical trials with racemic mixture and pure enantiomers separately before getting the approval to use the racemic mixture as a drug. Further the 'racemic switch' has become a trend i.e., if a patent on a drug which is marketed in racemic form expires, it is possible to get a new patent for the active enantiomer.

New developments in various technologies for isolating, preparing, and purifying chiral materials have greatly increased the opportunities for utilizing optically pure compounds in commercial applications.

Novel techniques for classical resolution, new methodologies for developing selective enzymes for biocatalysis, advances in the application of microorganisms for chemical production, and continued progress in the area of asymmetric synthesis have all contributed to the growth of this field. The 'Chiral pool' of readily available, relatively inexpensive chiral compounds has been expanding at a rapid rate as more and more products are produced in large quantities at economical prices.
The synthetic methodology to obtain chirally pure materials can be divided into three ways, as follows. (Fig 9)

**Asymmetric synthesis:**

In one form of asymmetric synthesis takes a substrate containing no chiral elements and transforms it via an asymmetric step into a chiral product. This method has an advantage that potentially all the material can be realized as the required isomer directly.

The different approaches of asymmetric synthesis include enantioselective catalysis, chiral auxiliaries, biocatalysis and enantioselective organocatalysis.

**Enantioselective catalysis,** in general, refers to the use of chiral coordination complexes (chiral ligands) as catalysts. Most of these catalysts are effective at low concentrations making them suitable for industrial scale synthesis. The most versatile example of enantioselective synthesis is asymmetric hydrogenation, which is able to reduce a wide variety of functional groups.
Chiral auxiliary is an organic compound which couples to the starting material to form new compound which can then undergo enantioselective reactions via intramolecular induction. The auxiliary is removed at the end, under conditions that will not cause racemization of the product, and then recovered for future use. The chiral auxiliaries must be used in stoichiometric amounts to be effective and require additional synthetic steps.

Biocatalysis makes use of biological compounds, isolated enzymes to living cells, to perform chemical transformations. The advantages of these reagents include high enantiomeric excess, reagent specificity, mild operating conditions and low environmental impact.

Organocatalysis refers to a form of catalysis, where the rate of a chemical reaction is increased by an organic compound consisting of non-metal elements. When the organocatalyst is chiral, enantioselective synthesis can be achieved. These catalysts are often natural compounds and secondary amines. They are inexpensive and environmental friendly as no metals are involved.

Racemate resolution:

The separation of the desired enantiomer from the racemic mixture by different techniques is referred to as Racemate resolution. The different methods for their resolution can be divided into three categories; direct
preferential crystallization, crystallization of diastereoisomeric salts and kinetic resolution.

The racemic mixture occurs in three types: Racemic compounds, Conglomerates and Pseudoracemates.

In case of racemic compound, the racemic crystals consist of a perfectly ordered array of R and S molecules - a crystalline 1:1 addition complex - and the individual crystals contain equal amounts of both enantiomers. This type accounts for about 90% of all racemates.

The conglomerates are a mechanical mixture of crystals of the two enantiomers in equal amounts - individual crystals contain only one enantiomer. This type accounts for about 5-10% of all racemates.

The third type, Pseudoracemates is rarely encountered.

Direct preferential crystallization is based on the physical properties like melting point, solubility of the different enantiomers. Different solvents or mixture of solvents are employed for this crystallization.

Diastereoisomeric salts are formed when a racemic acid or base is combined with optically pure base or acid. Two combination of diastereoisomers are formed one of which is crystallized from solvents based on the difference in solubility of the diastereomers. The pure enantiomer is obtained from the crystallized diastereomerically pure salt by neutralization and isolation.
The recently developed Dutch resolution (Fig 10) using a family of resolving agents seems to be one of the best methods on the basis of yield and enantiopurity. Dutch resolution refers to the use of mixtures of structurally similar resolving agents.

**Fig 10**

**Dutch resolution exemplified**

\[
\begin{align*}
\text{(S)-Mandelic acid} &\quad + \quad \text{Racemic} \\
\text{Substituted Mandelic acids} &\quad \rightarrow \\
\text{(S).(S) salt} &\quad + \quad \text{(S).(R) salt} \\
\text{insoluble} &\quad \rightarrow \quad \text{soluble} \\
\text{precipitated product collected}
\end{align*}
\]
Kinetic resolution is based on the reactivity of the two enantiomers with another chiral entity at different rates. The chiral entity is used in catalytic amounts. The chiral catalyst may be a biocatalyst (enzyme or a microorganism) or a chemo catalyst (chiral acid or base or a chiral metal complex). Kinetic resolution can be defined as a process in which one of the enantiomers of a racemic mixture is more readily transformed than the other one.

**Chirality pool:**

**Chiral pool synthesis** is one of the practical approaches for enantioselective synthesis which does not involve asymmetric induction. Instead a chiral starting material is manipulated through successive reactions to obtain the desired target molecule. This method is attractive for target molecules having similar chirality to relatively inexpensive naturally occurring building blocks such as a sugar or an amino acid.

The easiest method of synthesis of an optically active product is to use an optically active raw material abundantly available from the chirality pool, since many of these inexpensive materials originate from large scale fermentation processes. Examples are Carbohydrates, amino acids, terpenes, alkaloids, etc..

These substances can be transformed into synthetic chiral intermediates by chemical manipulation that may involve complete retention or complete inversion of configuration or chirality transfer. (Fig 11)
A variety of alpha-amino acids are readily available in bulk from fermentation and other processes and they constitute the most important class of compounds within the chirality pool. They have a relatively simple structure, with one or two asymmetric centers, and are amenable to a variety of chemical transformations. For example, L-aspartic acid and L-methionine are available in hundreds of tons.

This part of the thesis involves the chemical transformation of L-Methionine and L-aspartic acid into very important 3-substituted five-membered heterocyclic chiral intermediates. (Fig 12)
Fig 12

\[
\begin{align*}
\text{NH}_2 & \quad \text{NH}_2 & \quad \text{NH}_2 \\
\text{X} & \quad \text{X} & \quad \text{X} \\
\text{X} = \text{O, S, NH, NHCH}_2\text{Ph} & \\
\text{NH-R} & \quad \text{NH-R} & \quad \text{NH-R} \\
\text{X} & \quad \text{X} & \quad \text{X} \\
\text{X} = \text{O, S, NH, NHCH}_2\text{Ph} & \\
\text{R} = \text{Benzoyl, Cbz, Boc, Tosyl} & 
\end{align*}
\]
Chapter I.3

3-Amino tetrahydrofuran
Chapter I.3.a

Introduction

\[
\begin{array}{c|c}
\text{NH}_2 & \text{H}_2\text{N} \\
\text{(R)} & \text{(S)} \\
\end{array}
\]

The importance of chiral materials in pharmaceutical, agrochemical, flavor-fragrance industry has led to a renaissance in synthetic methodologies concentrating on very efficient methods of asymmetric synthesis\(^1\) and resolution methodology\(^2\). The equally important method of converting naturally occurring chiral materials, described earlier as the chiral pool, offers a powerful, simple, and often economic solution for preparing chiral materials if an efficient sequence of converting the chiral pool starting materials into the desired end-product can be designed. While L-amino acids are naturally occurring and available economically, the advent of bio-catalytic technologies based on amino acylase, hydantoinase/carbamoylase and amidases has provided an easy access to D-amino acids\(^3\). As a result, either of the desired optical isomers of a final product can be obtained from either the L- or D- amino acid by simple selection of a suitable precursor amino acid. One important advantage of using chiral pool starting materials is the excellent enantiomeric purity of the final product if any reaction conditions that may lead to racemization in the reaction sequence are carefully avoided.
3-amino tetrahydrofuran forms an important substructure of several pharmacologically active compounds. They seem to confer certain desirable properties on the investigational drug structures. A series of G-protein coupled adenosine receptors mediate cardiac and antilipolytic activities. In particular, selective adenosine A1 receptors have received attention for possible antiarrhythmic activity. For example, 3-(R) - amino tetrahydrofuranyl moiety formed an integrative structural feature of selective, high affinity adenosine A1 receptor agonists⁴.

3-Amino tetrahydrofuranyl moiety also formed part of the structural features of orally bioavailable experimental Calcitonin gene-related peptide (CGRP) receptor antagonists⁵. In spite of such extensive uses⁶ of 3-amino tetrahydrofuran in medicinal chemistry (Fig 13 – 16), methods to obtain its chiral forms are scarce and hard to practice.

Some of the drug candidates and intermediates under studies are shown here.

Drug candidate incorporating (R)-3-amino tetrahydrofuran

Fig 13
Drug candidates incorporating (S)-3-amino tetrahydrofuran (Fig 14 and 15)
Drug candidate incorporating racemic 3-amino tetrahydrofuran

Fig 16
Chapter I.3.b

Literature survey

Optically pure isomer of (R)-3-amino tetrahydrofuran (7) has been obtained through a lengthy sequence starting from L-malic acid. The large number synthetic steps (Scheme 1 & Scheme 2) are a deterrent feature in this methodology described herein below.

L-malic acid (1) is esterified to get L-malic acid dimethyl ester (2) which is reduced using lithium aluminium hydride to obtain (S)-2-hydroxy 1,4 Butanediol (3). Compound (3) is cyclized in toluene medium in reflux conditions in presence of para toluenesulphonic acid to get (S)-3-hydroxy tetrahydrofuran (4).

Scheme 1

![Scheme 1 Diagram]

Compound (4) is reacted with para toluenesulphonyl chloride to form the O-tosyl derivative (5) which is further converted to (R)-3-azidotetrahydrofuran (6) using sodium azide in DMF with inversion of configuration. The azide (6) is reduced using Raney-nickel to get (R)-3-aminotetrahydrofuran.
The above method is practically quite difficult to scale up for industrial applications as it involves multisteps with toxic chemicals.

In another method, L-methioninol has been used as starting material. In this approach L-methioninol (8) is converted to its N-tritylderivative (9) in the first step. Methylation of (9) with an excess of methyl iodide producing the corresponding sulphonium salt (10), which in turn has been cyclized upon treatment with sodium hydride in dimethyl formamide to give the cyclic ether (11). Detritylation of (11) on treatment with para toluene sulphonic acid in refluxing methanol affords the corresponding 3-aminotetrahydrofuran as its PTSA salt (Scheme 3).

Use of trityl protecting groups is generally avoided in large scale synthesis as they are expensive and generally need recovery of the tritylcarbinol for economical process.
For example, the useful 3-amino tetrahydrofuran (Molecular weight 87.12) in a para toluene sulphonic acid salt (Molecular weight 259.32) will be only 33.6% whereas in case of hydrochloride salt (Molecular weight 123.58), the useful 3-amino tetrahydrofuran will be 70.45%. This implies that the advantage for the hydrochloride salt would be more than double when compared to the para toluene sulphonic acid salt.

In another approach, a chemo enzymatic method of making 3-(S)-amino tetrahydrofuran from racemic tetrahydrofuran-3-carboxylic acid (13) has been described (Scheme 4). Racemic tetrahydrofuran-3-carboxylic acid reacted with Diphenyl phosphorylazide (DPPA) in a mixture of triethylamine and dioxan at reflux temperature followed by reaction with benzyl alcohol to obtain 3-Benzylxy carbonyl tetrahydrofuran (14). This penultimate material (14) is further subjected to hydrogenation using
palladium/carbon in presence of methanol/hydrochloric acid to get racemic 3-amino tetrahydrofuran (15).

Racemic 3-amino tetrahydrofuran obtained above is resolved by making the amide derivative using (S)-(+) -camphor sulphonyl chloride followed by crystallization in acetone which is further hydrolyzed using conc. hydrochloric acid/acetic acid to get the (S)-3-amino tetrahydrofuran hydrochloride (16) having 90% enantiomeric excess.

This strategy involves handling of azides (for the conversion of –COOH functionality to –NH₂) that will be undesirable from the safety point of view. Further the enantiomeric purity of the isomer isolated is questionable as there is no data for proving the enantiomeric purity.

Scheme 4
Though the separation of the single enantiomer from a racemic mixture is known by methods of derivatisation and crystallization, only a maximum of 50% or lower yield of the desired isomer is possible. Further the efficiency of getting the single enantiomer depends on the effective derivatisation using a chiral auxiliary and selective crystallization.

In a recent strategy, asymmetric hydrogenation of hydrazone derivative of tetrahydrofuran-3-one (17) has been reported\textsuperscript{10} that finally leads to chiral forms of 3-aminotetrahydrofuran. Tetrahydrofuran-3-one (17) is reacted with tert-butyl hydrazine carboxylate (TBHC) to form the tert-butyl hydrazone derivative (18) which is stereoselectively hydrogenated in presence of chiral ligands and Rh (NBD)\textsubscript{2}BF\textsubscript{4} to get tert-butyl hydrazine derivative (19) in 85\% enantiomeric excess which is further crystallized to get 99\% enantiomeric excess. Deprotection using HCl/dioxan and reduction using Raney Ni / H\textsubscript{2} gives the product, (R)-3-amino tetrahydrofuran (21) (Scheme 5). But under optimal conditions the maximum enantiomeric excess values of only 85\% have been reported.

The stereoselective reduction of 18 to 19 is an excellent example for asymmetric synthesis of a chiral hydrazine from a prochiral hydrazone intermediate.
Based on the different approaches explained above, it is clear that there is lot of scope for research to be done on the development of a good synthetic sequence to obtain chirally pure 3-amino tetrahydrofuran as acceptable salts for further use as a potential intermediate in new drug development.

Any amine-based chiral intermediate which could be potential candidate in drug development is better obtained as its hydrochloride salt which will be easier to handle in further reactions. Chirally pure 3-amino tetrahydrofuran which is obtained as para toluene sulphonic acid salt in the above described sequence is very difficult to practice as one has to take large amounts of the compound to incorporate the amino tetrahydrofuran moiety leaving the salt part which has more molar weight than the parent molecule.
Further the 3-amino tetrahydrofuran obtained as its hydrochloride salt on the above sequences (Schemes 1 to 5) does not have the enantiomeric purity more than 90%, which itself is obtained in very poor yields due to repeated crystallizations and consequential loss of material.

3-amino tetrahydrofurans are small chiral heterocyclic molecules which are very difficult to handle as their salts may be highly hygroscopic in nature and even the presence of smaller amount of impurities will affect its crystallization process to obtain pure compounds. So there is a definite need to develop a synthetic method to obtain 3-amino tetrahydrofuran as its hydrochloride salt in chirally pure form so as to incorporate it in a drug sequence easily. Further the method should be easily scalable in pilot scales leading ultimately to industrial scales. The reagents for the synthetic sequence should be simple, cheaper, commercially available and environmental-friendly so that the paucity of chirally pure 3-amino tetrahydrofurans in commercial scale should not be deterrent factor for pharmaceutical industries to develop new drug candidates.

In addition to the above, it is very important to note that the intermediates obtained in different stages should be pure enough for the next stage for cleaner reactions. It would be an advantage to decide the protecting groups for amines and acids in such a way that the intermediates are good solids because solids are always easier to handle, purify by simple washings with solvent or crystallization from suitable solvents. Liquid products or low melting solids are difficult to handle or purify especially in a research for the development of synthetic route to chiral intermediates.
Chapter I.3.c

Novel synthesis of (S)-3-amino tetrahydrofuran from L-aspartic acid

Our present and new approach uses the inherent chirality present in the easily accessible and economical starting materials, L-aspartic acid and L-methionine. L-aspartic acid and L-methionine are converted, in the present work, to (S)-3-amino tetrahydrofuran in a series of simple, easily executable reactions in good yields and complete retention of optical purity.

An identical sequence starting from D-aspartic acid and D-methionine leads to the other enantiomer, namely (R)-3-aminotetrahydrofuran.

L-aspartic acid (22) is converted to its dimethyl ester hydrochloride (23) (Scheme 6) and further the amine group is protected using different protecting groups like Benzoyl, Benzyloxycarbonyl, t-butyloxycarbonyl, Tosyl to get 2-(S)-protected amino aspartic acid dimethyl ester.

2-(S)-protected amino aspartic acid dimethyl ester is easily reduced by metal hydrides such as sodium borohydride to get (S)-2-protected amino 1, 4 butane diol in respectable yields.

Scheme 6
The conversion of L-aspartic acid to its dimethyl ester has been done in methanol in presence of conc. sulphuric acid, or bubbling dry hydrogen chloride gas etc. But the use of acetyl chloride to generate dry hydrochloric acid \textit{in situ} has been found to be the best way of making the esters of amino acids. In this process, acetyl chloride is added to dry methanol at low temperatures generating hydrochloric acid \textit{in situ} and then the amino acid is added. Further the reaction proceeds neatly at mild reflux temperature to completion.

Direct reduction of amino acids has also been reported in different conditions. But the reduction of L-aspartic acid did not work well under these conditions.

L-aspartic acid dimethyl ester hydrochloride (23) obtained earlier is taken for the N-protection with different protecting groups under different reaction conditions. The major requirement of a good protecting group for the amino group should be such that it can be removed easily at the end of the synthetic scheme to obtain the final product, 3-amino tetrahydrofuran as its hydrochloride salt in good purity without the formation of unwanted impurities. Further the protecting group should survive the different stages of reduction, cyclisation that form part of this synthetic scheme. The protecting group should remain intact during reduction step using sodium borohydride under highly basic conditions and also tolerate the highly acidic cyclisation conditions of the diol.

Benzoyl group, benzyloxy carbonyl group, tert. butyloxy carbonyl group, tosyl group have been used for accessing the respective N-protected L-aspartic acid dimethyl esters. (Scheme 7)
Scheme 7

Benzoyl chloride

\[ \text{TEA} \]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

N-benzoyl L-aspartic acid dimethylester

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

N-benzyloxy carbonyl- L-aspartic acid dimethylester

Benzylchloro formate

\[ \text{NaHCO}_3 \]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

N-t-butyloxy carbonyl- L-aspartic acid dimethylester

BOC-anhydride

\[ \text{NaHCO}_3 \]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{H}_3\text{C} & \quad \text{CH}_3 \\
\end{align*}
\]

N-(p-toluenesulphonyl)- L-aspartic acid dimethylester

Tosyl chloride

\[ \text{NaHCO}_3 \]

\[
\begin{align*}
\text{O} & \quad \text{S} \\
\text{N} & \quad \text{O} \\
\text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\end{align*}
\]

N-(p-toluenesulphonyl)- L-aspartic acid dimethylester
Now the next stage is the reduction of the N-protected L-aspartic acid dimethyl ester to its corresponding 1, 4 diol.

Though we can use Lithium aluminium hydride, Diborane for this reduction, sodium borohydride is the best option as it is very safe to handle in industrial scales. Further sodium borohydride has low molecular weight giving the advantage of using lesser quantities for the conversion in molar equivalent calculations.

The reduction of N-protected L-aspartic acid dimethyl ester has been done using sodium borohydride for all the products and reaction goes to completion.
Chapter I.3.c.i - N-Benzoyl protection route

L-aspartic acid dimethyl ester hydrochloride (23) is reacted with benzoyl chloride in presence of triethylamine in methylene dichloride to form N-benzoyl L-aspartic acid dimethylester (24) as nice crystalline product.

N-benzoyl L-aspartic acid dimethylester (24) is reduced using sodium borohydride in THF / ethanol medium at low temperature to reflux temperature to get (S)-2-benzoylamino butane 1, 4 diol (28) (Scheme 8) as solid product.

Scheme 8

![Scheme 8](image)

We discovered that the diol (28) obtained from L-aspartic acid route was partially racemized. But fortunately enantiomeric enrichment upto ~99% enantiomeric excess was possible through crystallization since presumably diol (28) forms a more soluble racemic modification than the enantiomers\textsuperscript{11}. The reported specific rotation values in the literature for 28 reflect the lower optical purity of this substance obtained by earlier workers. Earlier references\textsuperscript{12} report much lower specific rotation values
(reported values < 28°) for this diol 28. Hou et al has reported the diol 28 as a viscous oil\textsuperscript{13} (presumably due to enantiomerically impure nature of the sample) while we are able to obtain the chirally pure diol 28 as a nice solid with mp 90-92° C.

The crude diol (28) isolated by scheme 8 was analyzed for enantiomeric purity by HPLC (Fig 17) and found to contain L- and D-isomers in a ratio of approximately 89.7 / 10.3. The specific optical rotation measured Approx. - 28°.

So we synthesized the racemic form of 28 from DL-aspartic acid and analyzed by HPLC (Fig 19) which is found to consist of two equivalent peaks corresponding to the two enantiomers.

The crude diol (28) is crystallized from a mixture of ethyl acetate and hexane to obtain the enantiomerically pure product, which is analyzed by HPLC (Fig 18) to contain 98.7% pure of the L-isomer. The specific optical rotation measured – 39.7°. But there is an yield loss of around 20%.

The reduction of dimethyl ester (24) is done at reflux temperature of THF/Ethanol medium under highly alkaline conditions due to the presence of sodium borohydride. This alkalinity of the medium and higher temperature may have labilized the chiral proton which may be the reason for the partial racemization of the product (28) in the crude stage.

We tried several experiments for the reduction of ester (24) at various temperatures lower than the reflux temperature. But the reaction did not go to completion. The isolation of the product becomes difficult if the reduction is partial followed by work-up.
The enantiomeric purity of (28) has been firmly established by chiral HPLC data (Fig 17 – 19). The specific rotation value measured for the diol (28) (-39.7°) is much higher than the values reported in the literature for (28) which when assessed with the information of the chiral HPLC and chemical purity of >99% for (28), proves the high enantiomeric purity of 28 obtained by this method.

The next stage is the cyclization of (S)-2-benzoylamino butane 1, 4 diol (28) to obtain (S)-3-benzoylamino tetrahydrofuran (29) (Scheme 9). This cyclization is achieved by refluxing 28 in toluene in presence of catalytic amount of para toluene sulphonic acid removing water azeotropically with the help of Dean-Stark apparatus.
The cyclized product, (S)-3-benzoylamino tetrahydrofuran (29) is a crystalline product with melting point of 106-108°C.

**Scheme 9**

The cyclodehydration of the 1, 4 diols to cyclic tetrahydrofuran moieties has been described in the literature to occur at high temperatures under acid catalysis. For example, 2-hydroxy-1,4 butanediol is cyclized in neat form to 3-hydroxy tetrahydrofuran at nearly 200°C in approximately 2 hours, while it took more than 2 days to complete the same cyclization in a solvent at <120°C. Similarly, the cyclodehydration of 1, 4-butanediol at its boiling point 230°C to THF was catalyzed by supported silicotungstic acid. Diab et al. described the cyclodehydration of diols, especially 1, 4 diols, in the presence of 0.3 equiv. of HMPA at 220°C, with the reaction time ranging from 3 to 10 hours. Another report on the cyclization of 1, 4 butanediol to THF in DMSO was realized at 190°C.

A low temperature cyclization of 1, 4 diols to a THF type structure was also accomplished using dimethyl carbonate in presence of sodium methoxide. The cyclization reaction occurs through the intermediacy of a mixed carbonate that cyclizes faster at lower temperatures.
Excellent yields have been reported by this strategy. For example amberlyn diol has been cyclized quantitatively to ambroxan. (Scheme 10)

Scheme 10

The same group Arico et al have reported the cyclisation of substituted 1, 4 diols to cyclic ethers in excellent yields. For example, 1-methyl butane 1, 4 diol has been cyclized to 2-methyl tetrahydrofuran using dimethyl carbonate with three equivalents of sodium methoxide in acetonitrile medium (Scheme 11).

Scheme 11

We adopted the same strategy of cyclization for the diol (28) to assess the formation of the product (S)-3-benzoylamino tetrahydrofuran (29).
But there was no formation of the product in these conditions (Scheme 11a). This may be due to the presence of the amide group which can affect the formation of the mixed carbonate.

**Scheme 11a**

In contrast to the high temperature and long reaction times employed in the aforementioned examples, we are able to carry out the cyclodehydration of diol (28) to give the cyclized product (29) at the reflux temperature of toluene.

We rationalized that the cyclization is assisted by the amide group through the intermediacy of hydroxyethyl oxazolidine (30) as depicted in the below scheme (Scheme 12).
This speculation is supported by the reported observation\textsuperscript{19} of McGarvey et al. of the formation of tetrahydrofurans through the hydroxyl assisted cyclization of hydroxyethyl oxazolidines. However, the intervening hydroxyethyl oxazolidine is prone to racemization from the increased acidity of the proton. Fortunately, this was not a complicating factor in the present synthesis.

Another plausible variation of the mechanism is given below (Scheme 13).
The chiral purity of the cyclized product, (S)-3-benzoylamino tetrahydrofuran (29) has been proved by HPLC data and specific rotation data. Alternatively the racemic counterpart of the 3-Benzoylamino tetrahydrofuran is made from (DL)-aspartic acid which gives two distinct peaks in HPLC analysis whereas the one, (S)-3-Benzoylamino tetrahydrofuran made from L-aspartic acid gives only one peak proving the enantiomeric purity of the product. This high enantiomeric purity of (29) is because of the fact that the diol used for this cyclisation (scheme 9) has been reported for its highest optical purity (-39.7°) compared to the reported earlier.
The melting point and the specific optical rotation of the enantiomerically pure product have been established.

Finally the hydrolysis of (S)-3-Benzoylamino tetrahydrofuran (29) is accomplished under basic conditions. (S)-3-Benzoylamino tetrahydrofuran (29) is dissolved in ethanol and hydrolyzed using aqueous sodium hydroxide solution at reflux temperatures (Scheme 14). The reaction goes to completion. During work-up, the benzoic acid liberated is isolable and could be recycled, thus contributing to the process and atom economy.

**Scheme 14**

(S)-3-Benzoylamino tetrahydrofuran  
\[ \text{NaOH} \quad \text{Ethanol/Water} \]  
\( \rightarrow \)  
(S)-3-amino tetrahydrofuran hydrochloride

The desired final product, (S)-3-amino tetrahydrofuran is isolated as the hydrochloride salt (16) as shining crystals. The enantiomeric purity of (16) has been established by chiral HPLC (as its benzoyl derivative) as well as by Mosher methods.

The racemic 3-amino tetrahydrofuran (15) and (S)-3-amino tetrahydrofuran 16 are reacted separately with Mosher’s reagent to form the Mosher amides of 3-amino tetrahydrofuran (Scheme 15). The samples are subjected for proton and carbon NMR analysis.
The spectra clearly show separate signals for many of the protons and carbons in the Mosher amide obtained from 15 (mixture of 31 and 32), whereas only one set of signals is detected in the Mosher amide of 16 (31).

Additional evidence of the enantiomeric purity of 16 has been obtained by converting it back into the benzoyl derivative (29) which was analyzed by chiral HPLC. A racemic sample of (29) showed clear baseline separation of the HPLC peaks for the two enantiomers, whereas (29) obtained from the final product (16) gave a single peak reiterating the fact that the hydrochloride salt (16) is chirally pure product.

(S)-3-amino tetrahydrofuran has been synthesized successfully as its hydrochloride salt from L-aspartic acid using benzoyl group as N-protecting group of choice. The product has been analyzed for its enantiomeric purity assessed as high as 99% based on chiral HPLC analysis and NMR analysis by Mosher method.

By the same sequence, D-aspartic acid has been converted to (R)-3-amino tetrahydrofuran as its hydrochloride salt (Scheme 16) which is also a crystalline material as expected.
Further, the racemic product of 3-amino tetrahydrofuran hydrochloride, synthesized from DL-aspartic acid is not a solid product. The product has been obtained as paste form.

The melting point, specific optical rotation, NMR (proton), NMR (carbon) and its chiral purity as its benzoyl derivative by chiral HPLC analysis for the chirally pure (S)-3-amino tetrahydrofuran hydrochloride 16, has not been reported earlier. In this thesis, all the relevant data incorporating the physical, chemical & chiral purity of the product are reported.
Chapter I.3.c.ii - N-Benzylxoy carbonyl protection route

L-aspartic acid dimethylester hydrochloride (23) reacted with benzylchloroformate in methylene dichloride in the presence of triethyl amine at low temperature to RT to give N-benzyloxycarbonyl L-aspartic acid dimethylester (25) in good yield (Scheme 17).

Scheme 17

\[
\begin{align*}
\text{N-Benzylxoy carbonyl L-aspartic acid dimethylester} & \quad \text{Benzylchloroformate} \\
23 & \quad \text{TEA} \\
\text{L-aspartic acid dimethylester hydrochloride} & \quad 25
\end{align*}
\]

N-benzyloxycarbonyl L-aspartic acid dimethylester (25) is reduced using sodium borohydride in THF/ethanol medium at low temperature to reflux temperature to get the diol, (S)-2-benzyloxycarbonyl amino butane 1, 4 diol (38) (Scheme 18)
Tomori et al. have reported\textsuperscript{20} the synthesis of the diol (38) with 100% enantiomeric excess for the crude product. Further they have purified the product by column chromatography to get analytical sample with melting point 45-48°C and rotation of – 32.5°.

We analyzed the sample of the crucial intermediate diol (38) with a melting point of 70-72°C and the specific optical rotation is found to be – 30.922°.

Further the diol (38) is taken for the cyclization in toluene medium in presence of para toluenesulphonic acid at reflux temperature (Scheme 19). The progress of the reaction was not very clean as inferred by the formation of impurities shown by thin layer chromatography. After the absence of the staring material, the crude product was purified by column chromatography to get the product, (S)-3-benzylxoxycarbonylamino tetrahydrofuran (39), in around 40% yield only.
This shows that the benzyloxy carbonyl group is not stable under these reaction conditions.

**Scheme 19**

Then we tried the cyclisation of the intermediate diol (38) using dimethyl carbonate/sodium methoxide in acetonitrile medium as referred\(^\text{18}\) in the benzoyl protection route. But here also the reaction did not go at all.

One more strategy has been adopted for the cyclization by taking the diol (38) in methylene dichloride with two equivalents of triethylamine at the start of the reaction followed by slow addition of one equivalent of methanesulphonyl chloride at ambient temperature anticipating the following reaction through the intermediate (40) (Scheme 20).
Though the thin layer chromatography shows the formation of the product, the reaction was not neat with the formation of considerable dimesyl compound (41) which was very difficult to separate by crystallization. But we could get a poor yield of the cyclized product (39) by column chromatography.
For deprotection, (S)-3-benzyloxycarbonylamino tetrahydrofuran (39) is subjected to hydrogenation in methanol / dil.HCl in presence of palladium/carbon to get the final product, (S)-3-amino tetrahydrofuran hydrochloride (16) in respectable yield (Scheme 21).

The final product (16) accessed from the intermediate (39) is analyzed by proton NMR, carbon NMR, CHN analysis and specific optical rotation data. In all respects, it is matching with the same product obtained from N-benzoylamino product (29).

Comparatively, based on the yield data in the stages of reduction, cyclisation and hydrolysis, the benzoyl protection route (Schemes 8, 9 and 14) is found to be better than the benzyloxy carbonyl protection route.
Chapter I.3.c.iii - N-tert.Butyloxycarbonyl protection route

L-aspartic acid dimethyl ester hydrochloride (23) is reacted with tert.butyl pyrocarbonate (Boc-anhydride) in a mixture of acetone and water in presence of potassium carbonate at ambient temperature to form (S)-N-tert.butyloxycarbonyl L-aspartic acid dimethyl ester (26) (Scheme 22).

Scheme 22

Then the protected diester (26) is taken for reduction in a mixture of THF/ethanol using sodium borohydride at low temperature to reflux temperature to obtain (S)-2-tert-butyloxycarbonylamino butane 1, 4 diol (42) (Scheme 23).
The specific optical rotation of the diol (42) is found to be \(-30.15^\circ\).

The reported specific optical rotation of the diol (42a)\(^{21}\) for the (R)-isomer is \(+30.8\). This clearly indicates the product obtained in the Scheme (23) is optically pure.
When the diol (42) is taken for cyclization in toluene in presence of para toluene sulphonic acid at reflux temperature, it is found that the Boc group is labile in acidic medium; the reaction did not proceed with any trace of the expected product.

We tried for the cyclisation of the diol (42) using dimethyl carbonate / sodium methoxide although this did not work for the benzoyl protected diol (28) and benzyloxy carbonyl protected diol (38). In this case also, no product formation is observed.

Attempt to cyclize (42), dissolved in methylene dichloride in presence of 2 eq. of triethylamine by addition of 1 eq. of methane sulphonyl chloride also ended up with lot of impurities.

In conclusion, we could not get the cyclized product, (S)-2-tert. butyloxy carbonylamino tetrahydrofuran from the diol (42).
Chapter I.3.c.iv - N-tosyl protection route

The diester (23) is taken in a mixture of acetone and water and reacted with para toluene sulphonyl chloride in presence of potassium carbonate at ambient temperature to obtain (S)-N-tosyl L-aspartic acid dimethylester (27) (Scheme 24).

Scheme 24

Then the dimethylester (27) is reduced in a mixture of THF/ethanol using sodium borohydride at low temperature to reflux temperature to obtain (S)-2-tosylamino butane 1, 4 diol (43) (Scheme 25).

Scheme 25
(S)-2-tosylamino butane 1, 4-diol (43) is cyclized in toluene medium at reflux temperature in the presence of para toluene sulphonic acid to obtain the cyclized product, (S)-3-tosylamino tetrahydrofuran (44) (Scheme 26).

Scheme 26

![Scheme 26](image)

The deprotection of Tosyl group has been reported by different methods\(^\text{22}\). The simplest method is using magnesium turnings in methanol medium at room temperature (Scheme 27).

Scheme 27

![Scheme 27](image)
The deprotection did not go for completion even after extended reaction hours and heating. The isolation of the product as its hydrochloride salt has been very difficult and removal of the magnesium salts posed lot of problem. Though, TLC showed the product formation with some starting material (43), the product could not be isolated from the reaction mixture.

The conclusion is that the Tosyl protecting group is not working for the synthesis of 3-amino tetrahydrofuran, especially in the deprotection stage.
Chapter I.3.d

Novel synthesis of (S)-3-amino tetrahydrofuran from L-Methionine

The other naturally occurring amino acid that we have selected from the chiral pool is L-methionine for the conversion to 3-amino tetrahydrofuran. L-methionine is commercially available in tons of quantities and is very economical.

L-methionine (51) is converted to (S)-2-amino-γ-butyrolactone hydrochloride, 54, by a published method \(^\text{23}\) (Scheme 28). L-methionine is reacted with methyl iodide in a mixture of methanol and water to form the L-methionine S-methyl iodide salt (52). The isolated salt (52) is further hydrolyzed using sodium bicarbonate forming L-homoserine (53). Without isolating L-homoserine, it is cyclized \textit{in situ} by acidifying the mixture with dilute hydrochloric acid at higher temperature to form (S)-2-amino γ-butyrolactone hydrochloride (54) as white crystalline material.
The chemical and chiral purity of (S)-2-amino-γ-butyrolactone hydrochloride (54) is crucial since its quality decides the quality of the further stage products. During the preparation of the intermediate (54), there is considerable formation of inorganic salts mixed with (54). So it is imperative that the product (54) is completely devoid of these salts for the subsequent transformations. We obtained the best quality of (54) with good optical rotation and melting point, the highest reported in the literature.
(S)-2-amino-γ-butyrolactone hydrochloride (54) is taken for amine protection using different protecting groups, as earlier, like benzoyl, benzylloxycarbonyl and tert.butyloxy carbonyl under different reaction conditions to get the (S)-2-protected amino-γ-butyrolactone. The conditions adopted for anchoring the protective groups need to be mild to ensure the intact survival of the lactone functionality. The lability of lactone function under alkaline conditions is well known.

**Chapter I.3.d.i - N-Benzoyl protection route**

(S)-2-amino-γ-butyrolactone hydrochloride (53) is reacted with benzoyl chloride in presence of triethylamine in methylene dichloride to (S)-2-benzoylamino-γ-butyrolactone (55) in good yield (Scheme 29).

**Scheme 29**

(S)-2-benzoylamino γ-butyrolactone (55) is reduced using sodium borohydride in ethanol at mild conditions to get (S)-2-benzoylamino butane 1, 4 diol (28) in very good yield and high chiral purity (Scheme 30).
(S)-2-benzoxylamino butane 1, 4 diol (28) obtained by the above route (from L-methionine) is matching with the diol got from L-aspartic acid route based on the proton NMR, carbon NMR, HPLC, melting point and specific optical rotation data. The difference in these two methods is that the enantiomeric purity of the product obtained from L-methionine route is very high even in the crude stage itself which can be directly taken for the next stage. But in the L-aspartic acid route, the crude product has to be crystallized to improve the enantiomeric purity.

(S)-2-benzoxylamino butane 1, 4 diol (28) has been recorded for its highest melting point and specific optical rotation compared with earlier reports.

Thus, the key intermediate (S)-2-benzoxylamino butane 1, 4 diol (28) has been obtained from both L-aspartic acid and L-methionine in different ways. Based on the benevolent reaction conditions, very high yields of the intermediates, quality and yield of the final product, we conclude that L-methionine route is the most desirable one.
Further the (S)-2-benzoylamino butane 1, 4 diol (28) obtained from the protected lactone (55) is taken for cyclisation to get (S)-3-benzoylamino tetrahydrofuran (29) followed by hydrolysis to the final product (S)-3-amino tetrahydrofuran hydrochloride (16) to prove efficiency of this route.

By the same sequence, D-methionine (56) has been converted to (R)-3-amino tetrahydrofuran as its hydrochloride salt (36) (Scheme 31).

Scheme 31

Further, the racemic product of 3-amino tetrahydrofuran hydrochloride, synthesized form DL-methionine is not a good solid product. We could get the product as a paste form only.
Chapter I.3.d.ii - N-benzyloxy carbonyl protection route

(S)-2-amino-γ-butyrolactone hydrochloride (54) is reacted with benzyl chloroformate in acetone in presence of potassium carbonate at room temperature to get (S)-2-benzyloxy carbonylamino γ-butyrolactone (59) (Scheme 32).

Scheme 32

Then (S)-2-benzyloxy carbonylamino γ-butyrolactone (59) obtained above is reduced using sodium borohydride in ethanol at low temperature to room temperature to obtain (S)-2-benzyloxy carbonylamino butane 1, 4 diol (38) (Scheme 33) in good yield and excellent chiral purity.

Scheme 33
(S)-2-benzyloxycarbonylamino butane 1, 4 diol (38) obtained is comparable with the same molecule obtained from L-aspartic acid route (Scheme 18) by proton NMR, carbon NMR, melting point and specific optical rotation data.

The details of cyclization of the diol (38) and further deprotection have been detailed earlier in L-aspartic acid route (Scheme 19 and 21).

**Chapter I.3.d.iii - N-tert.Butyloxy carbonyl protection route**

(S)-2-amino-γ-butyrolactone hydrochloride (54) is reacted with tert.butyl pyrocarbonate in acetone in presence of potassium carbonate at room temperature to get (S)-2-tert-butyloxycarbonylamino γ-butyrolactone (60) (Scheme 34).

**Scheme 34**

(S)-2-tert.butyloxycarbonylamino γ-butyrolactone (60) obtained above is reduced using sodium borohydride in ethanol at low temperature to room temperature to obtain (S)-2-butyloxycarbonylamino butane 1, 4 diol (42) (Scheme 35) in good yield and excellent chiral purity.
(S)-2-tert.butylxycarbonylamino butane 1, 4 diol (42) obtained above is comparable with the same molecule obtained from L-aspartic acid route (Scheme 23) by proton NMR, carbon NMR, melting point and specific optical rotation data.

The reduction of (R)-2-tert.butylxycarbonylamino γ-butyrolactone to (R)-2-tert.butylxycarbonylamino butane 1, 4 diol has been reported\textsuperscript{21}.

As discussed earlier in L-aspartic acid route, the diol (42) did not undergo cyclisation in Toluene/PTSA conditions.
Chapter I.3.e

Experimental procedures

(S)-N-Benzoyl L-aspartic acid dimethyl ester (24)

\[
\begin{align*}
\text{H}_3\text{C}-\text{O} & \quad \text{O} - \text{CH}_3 \\
\text{O} & \quad \text{O} \\
\text{H}_3\text{C}-\text{O} & \quad \text{N} - \text{H} - \text{C}=\text{O} \\
\text{N} & \quad \text{H} - \text{C}=\text{O} \\
\text{O} & \\
\text{O} & \quad \text{C} - \text{H}_3 \\
\text{C} & \quad \text{H}_3
\end{align*}
\]

L-Aspartic acid dimethylester hydrochloride (23) (74g, 0.375 mol) is suspended in methylene dichloride and cooled to 0-10°C. Triethylamine (114ml, 0.82 mol) is added slowly over period of one hour followed by benzoyl chloride (61.7g, 0.439 mol). The reaction mixture is stirred at RT for 3 hours at which time TLC showed the absence of the starting material.

Reaction mixture is quenched in water and MDC layer is separated. It is washed with 5% Sodium bicarbonate solution, then with water and dried over anhydrous sodium sulphate. MDC layer is concentrated completely and diethyl ether was added and stirred for complete precipitation of the product, (S)-N-benzoyl L-aspartic acid dimethyl ester (24). It is filtered and washed with little ether. The product is dried under vacuum.

Yield: 66g (66% of theory)
(S)-2-Benzoylamino butane 1, 4 diol (28)

(S)-N-Benzoyl L-aspartic acid dimethyl ester (24) (25g, 0.094 mol) is dissolved in tetrahydrofuran and ethanol (~260ml each). It is cooled to 10-15°C. Sodium borohydride (11g, 0.29 mol) is added portion wise over a period of one hour and stirred at room temperature for 1 hour. Then it is heated slowly to reflux temperature and maintained for 8-9 hours. TLC showed only traces of the starting material.

The reaction mixture is cooled to 0-10°C and adjusted the pH to 7 using dil.hydrochloric acid and extracted with ethyl acetate three times. The organic extracts were combined and dried over anhydrous sodium sulphate. It is then concentrated to get a white solid product weighing 17g. The crude product (17g) was analyzed for chiral purity by HPLC and found to contain the L and D isomer ratio of 88:10.

The crude product is recrystallized using ethyl acetate / hexane to get chirally pure product analyzed to contain 98.7% pure of L-isomer, (S)-2-benzoylamino butane 1,4 diol (28)

Yield: 13.5g (67% of theory)

Melting point: 90-92°C

\[[\alpha]\]D = -39.67° (c = 0.05, methanol)
(S)-3-Benzoylamino tetrahydrofuran (29)

(S)-3-Benzoylamino tetrahydrofuran (29)

(S)-3-Benzoylamino tetrahydrofuran (29)

(S)-2-Benzoylamino butane 1, 4 diol (28) (35g, 0.167 mol) is taken in a round bottom flask in toluene (350 ml) and para toluene sulphonic acid (3.5g) is added. The reaction is heated to reflux temperature for 10-12 hours. Using Dean-Stark apparatus, water formed during the reaction is removed azeotropically.

After TLC showed the completion of the reaction, the reaction mixture is quenched in water, extracted with ethyl acetate, washed with sodium bicarbonate solution followed by brine. After drying the organic layer over sodium sulphate, it is then concentrated completely and stirred with
hexane. The product, (S)-3-benzoylamino tetrahydrofuran precipitated on chilling. It is filtered and dried under vacuum.

Yield: 20g (63% of theory)

Melting point: 106-108°C

\([\alpha]_D = -29.40^\circ\) (c = 1, methanol)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (PPM) 7.77-7.80 (d, 2H), 7.30-7.55 (m, 3H), 6.65-6.70 (d, 1H), 4.60-4.70 (m, 1H), 3.75-3.98 (m, 4H), 2.26-2.36 (m, 1H), 1.90-1.97 (m, 1H)

\(^{13}\)C NMR (300 MHz, CDCl\(_3\)) \(\delta\) (PPM) 167.61, 134.46, 131.79, 128.75, 127.19, 73.68, 67.19, 51.03, 33.40


APCI MS m/z 192.03 (M+H)⁺

**(S)-3-Amino tetrahydrofuran hydrochloride (16)**

(S)-3-Benzoylamino tetrahydrofuran (29) (20g, 0.105 mol) is dissolved in ethanol (40 ml) and sodium hydroxide solution (25g in 120 ml of water) is added. The reaction mixture is heated to reflux temperature for 9-10 hours. TLC showed absence of starting material.
The reaction mixture is subjected to vacuum distillation to remove most of the ethanol and cooled to room temperature. The mixture is acidified with dil. HCl till acidic pH. Precipitated benzoic acid is filtered off. The aqueous layer is washed with MDC to get rid of any residual benzoic acid and concentrated completely to get the product occluded with salt. Isopropanol is added and stirred for one hour at room temperature. The salt is isolated and is filtered off. The filtrate is concentrated completely to get pasty mass. The pasty mass is stirred with Isopropanol to crystallize out the material, (S)-3-amino tetrahydrofuran hydrochloride (16) as crystalline solid. It is filtered, washed with chilled Isopropanol and dried under vacuum.

Yield: 11g (85% of theory)

Melting point: 165-170°C

\([\alpha]_D = -10.21° \text{ (c = 1, methanol)}\)

\(^1\)H NMR (300 MHz, D\(_2\)O) \(\delta\) (PPM) 3.80-4.11 (m, 5H), 2.37-2.5 (m, 1H), 2.01-2.09 (m, 1H)

\(^13\)C NMR (300 MHz, D\(_2\)O) \(\delta\) (PPM) 70.49, 66.82, 51.21, 30.01


(S)-N-Benzoxycarbonyl L-aspartic acid dimethyl ester (25)
L-Aspartic acid dimethylester hydrochloride (23) (74g, 0.375 mol) is suspended in a mixture of acetone (350 ml) and water (350 ml). To the above mixture, sodium bicarbonate (48g, 0.5625 mol) is added portion wise under stirring. The mixture is stirred for 15 minutes and cooled to 0-5°C.

Now 50% solution of benzylchloroformate in toluene (140g, 0.4125 mol) is added drop wise over period of 45 mts keeping the temperature at 0-5°C. Then the mixture is stirred at ambient temperature for 12 hours for the completion of the reaction. The completion of the reaction is confirmed by TLC.

The reaction mixture is subjected to vacuum distillation to remove acetone diluted with 300ml of water and extracted with MDC. The MDC layer is separated and washed with water twice followed by brine solution. MDC layer is dried over sodium sulphate and concentrated completely. The product is precipitated by stirring the crude product with hexane. The solid product is filtered and dried under vacuum.

Yield: 94g (85% theory)

(S)-2-Benzylxycarbonylamino butane 1, 4 diol (38)
(S)-N-Benzylloxycarbonyl L-aspartic acid dimethyl ester (25) (29.5g, 0.1 mol) is dissolved in tetrahydrofuran and ethanol (~300ml each). It is cooled to 10-15°C. Sodium borohydride (11.5g, 0.3 mol) is added portion wise over a period of one hour and stirred at room temperature for 1 hour. Then it is heated slowly to reflux temperature and maintained for 8-9 hours. TLC showed only traces of the starting material.

The reaction mixture is cooled to 0-10°C and adjusted the pH to 7 using dil. hydrochloric acid and extracted with ethyl acetate three times. The organic extracts were combined and dried over anhydrous sodium sulphate. It is then concentrated to get a thick paste. This crude product is crystallized using a mixture of ethyl acetate and hexane to get as amorphous powder.

Yield: 14.5g (60.6% theory)

Melting point: 70-72°C

\([\alpha]_D = -30.922^\circ \ (c = 0.5, \text{ methanol})\)

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (PPM) 7.30-7.35(m, 5H), 5.50-5.60(d, 1H), 5.05-5.07(s, 2H), 3.50-3.90 (m, 7H), 1.70-1.90 (m, 1H), 1.50-1.70 (m, 1H)

$^{13}$C NMR (300 MHz, CDCl$_3$) $\delta$ (PPM) 157.45, 136.49, 128.79, 128.44, 128.28, 67.21, 65.01, 58.90, 50.43, 34.66

Anal. Calcd for C$_{12}$H$_{17}$NO$_4$ (FW 239.27): C, 60.24; H, 7.16; N, 5.85. Found C, 60.02; H, 7.03; N, 5.86

APCI MS m/z 239.82 (M+H)$^+$

72
(S)-3-Benzylxycarbonylamino tetrahydrofuran (39)

(S)-2-Benzylxycarbonylamino butane 1, 4 diol (38) (24g, 0.1 mol) is taken in a round bottom flask in toluene (250 ml) and para toluene sulphonic acid (2.5g) is added. The reaction is heated to reflux temperature for 10-12 hours. Using Dean-Stark apparatus, water formed during the reaction is removed azeotropically. TLC showed the completion of the reaction with some impurities along with the cyclized product. The reaction mixture is quenched in water, extracted with ethyl acetate, washed with sodium bicarbonate solution followed by brine. After drying the organic layer over sodium sulphate, it is then concentrated completely. The crude product is purified by column chromatography using hexane: ethyl acetate and precipitated by stirring with hexane. The product is filtered and dried under vacuum.

Yield: 9g (40.5% theory)

Melting point: 53-55°C

\[[\alpha]_D = -12.427^\circ \text{ (c = 1, methanol)}\]

$^1$H NMR (300 MHz, CDCl$_3$) δ (PPM) 7.28-7.38 (m, 5H), 5.30-5.40 (d, 1H), 5.07-5.09 (s, 2H), 4.20-4.40 (m, 1H), 3.50-3.90 (m, 4H), 2.03-2.23 (m, 1H), 1.70-1.90 (m, 1H)

$^{13}$C NMR (300 MHz, CDCl$_3$) δ (PPM) 156.17, 136.63, 128.77, 128.41, 128.37, 73.62, 67.00, 52.03, 33.36
Anal. Calcd for C_{12}H_{15}NO_{3} (FW 221.25): C, 65.14; H, 6.83; N, 6.33.
Found C, 65.93; H, 6.33; N, 6.37

APCI MS m/z 221.91 (M+H)⁺

(S)-3-Amino tetrahydrofuran hydrochloride (16)
(from 39)

(S)-3-Benzylxycarbonylamino tetrahydrofuran (39) (22.1g, 0.1 mol) is taken in methanol (200 ml) with palladium/carbon 5% (1.1g). The mixture is charged in an autoclave and hydrogenated at ambient temperature with a hydrogen pressure of 3kg. The pressure is maintained with hydrogen at ambient temperature for 5 hrs. TLC showed the completion of the reaction. The mixture is filtered to remove the insoluble material. Dilute hydrochloric acid (15ml) is added to the filtrate and concentrated completely under vacuum at < 50°C. To the crude product, isopropyl alcohol (50ml) is added and stirred to precipitate the product, (S)-3-amino tetrahydrofuran hydrochloride (16) as crystalline powder. The mixture is cooled for 5 hours at 0-5°C and filtered. The product is washed with chilled isopropyl alcohol and dried under vacuum.

Yield: 9.25g (75% theory)

Melting point: 165-170°C

[α]_D = - 10.15° (c = 1, methanol)
$^{1}$H NMR (300 MHz, D$_2$O) $\delta$ (PPM) 3.80-4.11 (m, 5H), 2.37-2.5 (m, 1H), 2.01-2.09 (m, 1H)

$^{13}$C NMR (300 MHz, D$_2$O) $\delta$ (PPM) 70.49, 66.82, 51.21, 30.01

**(S)-N-tert.Butyloxy carbonyl L-aspartic acid dimethyl ester (26)**

![Chemical Structure](image)

L-Aspartic acid dimethylester hydrochloride (23) (49.4g, 0.25 mol) is suspended in a mixture of acetone (250 ml) and water (250 ml). To the above mixture, sodium bicarbonate (31.5g, 0.375 mol) is added portion wise under stirring. The mixture is stirred for 15 minutes and cooled to 0-5°C.

Now a solution of Boc-anhydride (60g, 0.275 mol) in acetone (50ml) is added drop wise over period of 45 mts keeping the temperature at 0-5°C. Then the mixture is stirred at ambient temperature for 12 hours for the completion of the reaction. The completion of the reaction is confirmed by TLC.

The reaction mixture is subjected to vacuum distillation to remove acetone diluted with 250ml of water and extracted with MDC. The MDC layer is separated and washed with water twice followed by brine solution. MDC layer is dried over sodium sulphate and concentrated completely.
The product is precipitated by stirring the crude product with hexane. The solid product is filtered and dried under vacuum.

Yield: 55.5g (85% theory)

\[
\text{(S)-2-tert.}	ext{Butyloxycarbonylamino butane 1, 4 diol (42)}
\]

(S)-N-tert. Butyloxycarbonyl L-aspartic acid dimethyl ester (26) (26.1g, 0.1 mol) is dissolved in tetrahydrofuran and ethanol (~300ml each). It is cooled to 10-15°C. Sodium borohydride (11.5g, 0.3 mol) is added portion wise over a period of one hour and stirred at room temperature for 1 hour. Then it is heated slowly to reflux temperature and maintained for 8-9 hours. TLC showed only traces of the starting material.

The reaction mixture is cooled to 0-10°C and adjusted the pH to 7 using dil. hydrochloric acid and extracted with ethyl acetate three times. The organic extracts were combined and dried over anhydrous sodium sulphate. It is then concentrated to get a thick paste. This crude product is crystallized using a mixture of ethyl acetate and hexane to get as amorphous powder.

Yield: 12.5g (60% theory)

Melting point: 61-63°C
\[ \alpha_D = -30.15^\circ \ (c = 0.5, \text{ methanol}) \]

$^1$H NMR (300 MHz, DMSO) $\delta$ (PPM) 6.40-6.46 (d, 1H), 4.55-4.60 (t, 1H), 4.35-4.39 (t, 1H), 3.10-3.40 (m, 4H), 1.50-1.70 (m, 1H), 1.35-1.40 (m, 1H), 1.30-1.34 (s, 9H)

$^{13}$C NMR (300 MHz, DMSO) $\delta$ (PPM) 156.13, 78.10, 64.12, 58.68, 50.21, 35.01, 28.92

Anal. Calcd for C$_9$H$_{19}$NO$_4$ (FW 205.25): C, 52.67; H, 9.33; N, 6.82.
Found C, 52.53; H, 9.26; N, 6.82

(S)-2-Benzoylamino $\gamma$-butyrolactone (55)

(S)-2-Amino $\gamma$-butyrolactone hydrochloride (54) (13.7g, 0.1 mol) is taken in chloroform (100ml) and cooled to 0-5°C. Triethylamine (25g, 0.25mol) is added followed by benzoyl chloride (17g, 0.12mol) drop wise over a period of 30 mts. The reaction mixture is stirred at room temperature for 12 hrs. On completion by TLC, water (100ml) is added under stirring. pH is adjusted to 2-3 using dil. HCl. Chloroform layer is separated and washed with water followed by ammonium chloride solution.

Chloroform layer is dried over sodium sulfate and concentrated to get the crude product. The crude product is stirred with hexane: isopropanol (9:1) (100ml) to obtain the product, (S)-2-benzoylamino $\gamma$-butyrolactone as white crystalline solid.

Yield: 19.5g (95% theory)
Melting point: 165-167°C

\[(\alpha)_{D} = -27.8^\circ \text{ (c = 1, ethanol)}\]

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (PPM) 7.77-7.80 (d, J=7.2 2H), 7.35-7.50 (m, 3H), 7.24-7.27 (d, J=7.8, 1H), 4.77-4.87 (m, 1H), 4.44-4.50 (t, J=9.0, 1H), 4.26-4.35 (m, 1H), 2.78-2.87 (m, 1H), 2.23-2.40 (m, 1H)

$^{13}$C NMR (300 MHz, CDCl$_3$) $\delta$ (PPM) 176.22, 167.93, 133.16, 132.25, 128.80, 127.38, 66.47, 49.72, 30.29

Anal. Calcd for C$_{11}$H$_{11}$NO$_3$ (FW 205.21): C, 64.38; H, 5.40; N, 6.83.

Found C, 64.29; H, 5.36; N, 6.83

APCI MS m/z 205.95 (M+H)$^+$

(S)-2-Benzoylamino 1, 4-butanediol (28)
(from 55)

(S)-2-Benzoylamino γ-butyrolactone (55) (65g, 0.317 mol) is taken in ethanol (500 ml) and cooled to 0-5°C. Sodium borohydride (12g, 0.317 mol) is added portion wise over a period of 1 hour while maintaining the temperature at 0-5°C. After complete addition, the reaction mixture is stirred at ambient temperature for 5 hours.

TLC showed the completion of the reaction. Ethanol is then removed completely under vacuum and water (500 ml) is added followed by ethyl acetate (500 ml). While stirring, the pH is adjusted to 2-3 by dilute
hydrochloric acid. Stirring is continued for further 2 hours. The organic layer is separated and washed with water twice followed by ammonium chloride solution. Then organic layer is dried over sodium sulphate and concentrated to give the crude product, which is precipitated by stirring with ether. This mixture is then filtered and dried under vacuum to give the product.

Yield: 62.5g (95% theory)

Melting point: 90-92°C

\([\alpha]_D = -39.15° \text{ (c = 0.05, methanol)}\]

The proton and carbon NMR data has already been disclosed.

(S)-2-Benzylxycarbonylamino \(\gamma\)-butyrolactone (59)

(S)-2-Amino \(\gamma\)-butyrolactone hydrochloride (54) (13.7g, 0.1 mol) is taken in acetone (150 ml) and cooled to 10-15°C. Potassium carbonate (27.6g, 0.2 mol) is added under stirring followed by benzylchloroformate (50% solution in toluene) (37.5g, 0.11 mol) drop wise over a period of 30 minutes. After complete addition, the reaction mixture is stirred at ambient temperature for 12 hrs.
TLC showed the completion of the reaction. The reaction mixture is subjected to vacuum to distill out acetone and quenched to chilled dilute hydrochloric acid (25ml diluted with 125 ml of ice water) under stirring. The product is extracted with MDC (200 ml). The MDC layer is washed with water twice followed by brine solution. Further the MDC layer is dried over sodium sulphate and concentrated completely to get the crude product. The product, (S)-2-benzylxocarbonylamino δ-butyrolactone is precipitated by stirring with hexane for 2 hrs. The mixture is filtered and washed with hexane. The product is dried under vacuum.

Yield: 20g (85% theory)

Melting point: 129-131°C

\[ \alpha_D = -30.734^\circ \text{ (c = 1, methanol)} \]

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (PPM) 7.25-7.35 (m, 5H), 5.50-5.60 (d, 1H), 5.10-5.11 (s, 2H), 4.30-4.50 (t, 2H), 4.10-4.30 (m, 2H), 2.60-2.80 (m, 1H), 2.10-2.30 (m, 1H)

\(^{13}\)C NMR (300 MHz, CDCl\(_3\)) \(\delta\) (PPM) 175.24, 156.35, 136.19, 128.79, 128.52, 128.36, 67.54, 65.94, 50.69, 30.35

Anal. Calcd for C\(_{12}\)H\(_{13}\)NO\(_4\) (FW 235.236): C, 61.27; H, 5.57; N, 5.95. 
  Found  C, 61.15; H, 5.47; N, 5.96

\[(S)-2\text{-Benzyloxy carbonylamino 1, 4-butanediol (38)}\]

(from 59)
(S)-2-Benzylxocarbonylamino γ-butyrolactone (59) (47g, 0.2 mol) is taken in ethanol (500 ml) and cooled to 0-5°C. Sodium borohydride (7.6g, 0.2 mol) is added portion wise over a period of 1 hour while maintaining the temperature at 0-5°C. After complete addition, the reaction mixture is stirred at ambient temperature for 5 hours.

TLC showed the completion of the reaction. Ethanol is then removed completely under vacuum and water (500 ml) is added followed by ethyl acetate (500 ml). While stirring, the pH is adjusted to 2-3 by dilute hydrochloric acid. Stirring is continued for further 2 hours. The organic layer is separated and washed with water twice followed by ammonium chloride solution. Then organic layer is dried over sodium sulphate and concentrated to give the crude product, which is precipitated by stirring with ether. This mixture is then filtered and dried under vacuum to give the product.

Yield: 43g (90% theory)
Melting point: 70-72°C
[α]D = -30.15° (c = 0.05, methanol)

The proton and carbon NMR data has already been disclosed.
(S)-2-Amino \(\gamma\)-butyrolactone hydrochloride (54) (13.7g, 0.1 mol) is taken in acetone (150 ml) and cooled to 10-15°C. Potassium carbonate (27.6g, 0.2 mol) is added under stirring followed by Boc-anhydride (24g, 0.11 mol) drop wise over a period of 30 minutes. After complete addition, the reaction mixture is stirred at ambient temperature for 12 hrs.

TLC showed the completion of the reaction. The reaction mixture is subjected to vacuum to distill out acetone and quenched into chilled dilute hydrochloric acid (25ml diluted with 125 ml of ice water) under stirring. The product is extracted with MDC (200 ml). The MDC layer is washed with water twice followed by brine solution. Further the MDC layer is dried over sodium sulphate and concentrated completely to get the crude product. The product, (S)-2-butyloxycarbonylamino \(\delta\)-butyrolactone is precipitated by stirring with hexane for 2 hrs. The mixture is filtered and washed with hexane. The product is dried under vacuum.

Yield: 16.5g (82% theory)

Melting point: 142-143°C

\([\alpha]_D = -29.42^\circ (c = 1, \text{ methanol})\)

\(^1\text{H} \text{ NMR} (300 \text{ MHz, CDCl}_3) \delta (\text{PPM}) 5.20-5.30 (d, 1H), 4.10-4.50 (m, 3H), 2.60-2.80 (m, 1H), 2.10-2.30 (m, 1H), 1.40-1.42 (s, 9H)

\(^13\text{C} \text{ NMR} (300 \text{ MHz, CDCl}_3) \delta (\text{PPM}) 175.72, 155.72, 80.69, 65.97, 50.34, 30.51, 28.47

Anal. Calcd for C\(_9\)H\(_{15}\)NO\(_4\) (FW 201.22): C, 53.72; H, 7.51; N, 6.96.

Found C, 53.66; H, 7.49; N, 6.96

APCI MS m/z 201.68 (M+H)
(S)-2-Butyloxycarbonylamino 1, 4-butanediol (42)
(from 60)

(S)-2-Butyloxycarbonylamino γ-butyrolactone (60) (20.1g, 0.1 mol) is taken in ethanol (500 ml) and cooled to 0-5°C. Sodium borohydride (3.8g, 0.2 mol) is added portion wise over a period of 1 hour while maintaining the temperature at 0-5°C. After complete addition, the reaction mixture is stirred at ambient temperature for 5 hours.

TLC showed the completion of the reaction. Ethanol is then removed completely under vacuum and water (500 ml) is added followed by ethyl acetate (500 ml). While stirring, the pH is adjusted carefully using dil.hydrochloric acid to 4-5 under good stirring since Boc-group is very labile in highly acidic medium. Stirring is continued for further 2 hours. The organic layer is separated and washed with water twice followed by ammonium chloride solution. Then organic layer is dried over sodium sulphate and concentrated to give the crude product, which is precipitated by stirring with ether. This mixture is then filtered and dried under vacuum to give the product.

Yield: 17g (83% theory)

Melting point: 61-63°C

[α]D = -29.23° (c = 0.05, methanol)

The proton and carbon NMR data had already been disclosed.
Mosher amide of (S)-3-amino tetrahydrofuran (31)

(S)-3-amino tetrahydrofuran hydrochloride (16) (1g, 0.008 mol) is taken in MDC (25ml) and cooled to 10-15°C. Triethylamine (1g, 0.01 mol) is added followed by Mosher’s acid chloride (α-methoxy α-trifluoromethyl phenyl acetyl chloride) (2.2g, 0.0088 mol) drop wise in 10 minutes.

The mixture is stirred at RT for 1 hr. TLC showed the completion of the reaction. The reaction is quenched into 5% sodium bicarbonate solution (20ml). The organic layer is washed with water followed by ammonium chloride solution. Further the MDC layer is concentrated completely to get the crude product (31) which is taken for proton and carbon NMR analysis.

The same procedure is followed for making the Mosher amide of racemic 3-amino tetrahydrofuran and analyzed by proton and carbon NMR.
Chapter I.3.f

Analytical and Spectral data
Std Proton parameters

Automation directory:
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Pulse Sequence: &pul
Solvent: D2O
Ambient temperature
Operator: rajendra
File: RD SAT_83 IN D2O_H1 D20 Jan 14 200801
Mercury-3000B "localhost.localdomain"

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Pulse 45.0 degrees
Acc. time 1.985 sec
Width 4789.0 Hz
8 repetitions
DESSER H1 293.2801 MHz
DATA PROCESSING
FT size 92786
Total time 0 min, 0 sec

Compound 16
NH₂HCl
Compound 16

NH₂HCl
Compound 28

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Compound 28

HO-CH-CH-CH-OH
\[\text{NH-CONH}\]
Benzene ring

Mass spectrum

- RT: 0.24-0.36
- AV: 7
- NL: 3.39E7
- + APCI corona Full ms [50.00-1500.00]
Std Proton parameters

Automation directory:
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Pulse Sequence: s2pul
Solvent: CDC13
Ambient temperature
Operator: reajendra
File: RD_SAT_121_PH_1H_CDC13_H1_CDC13_May_11_2011101

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Width 4796.2 Hz
8 repetitions
OBSERVE H1, 299.8302373 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 25 sec

Compound 29

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2     | 2330.167      | 7.772 | 20.4   | 41    | 1134.340      | 3.783 | 17.7   |
3     | 2325.191      | 7.755 | 9.5    | 42    | 1139.248      | 3.770 | 8.4    |
4     | 2322.849      | 7.747 | 37.0   | 43    | 1127.614      | 3.761 | 9.8    |
5     | 2321.385      | 7.742 | 30.7   | 44    | 1124.686      | 3.751 | 9.7    |
6     | 2320.007      | 7.511 | 6.5    | 45    | 707.247       | 2.359 | 6.6    |
7     | 2316.722      | 7.485 | 4.9    | 46    | 701.093       | 2.328 | 6.5    |
8     | 2244.689      | 7.487 | 20.7   | 47    | 685.992       | 2.334 | 6.4    |
9     | 2242.347      | 7.479 | 6.8    | 48    | 699.050       | 2.331 | 7.0    |
10    | 2238.634      | 7.467 | 11.3   | 49    | 694.074       | 2.315 | 8.4    |
11    | 2237.376      | 7.462 | 10.6   | 50    | 695.610       | 2.310 | 7.2    |
12    | 2235.907      | 7.457 | 9.7    | 51    | 685.877       | 2.288 | 8.0    |
13    | 2228.246      | 7.425 | 20.4   | 52    | 678.559       | 2.263 | 4.1    |
14    | 2225.661      | 7.423 | 29.6   | 53    | 688.982       | 1.944 | 4.1    |
15    | 2219.513      | 7.403 | 20.8   | 54    | 585.762       | 1.954 | 4.4    |
16    | 2219.650      | 7.398 | 30.6   | 55    | 584.592       | 1.950 | 5.1    |
17    | 2212.781      | 7.380 | 6.9    | 56    | 584.005       | 1.948 | 5.3    |
18    | 2211.517      | 7.375 | 14.0   | 57    | 561.371       | 1.939 | 4.8    |
19    | 2209.853      | 7.370 | 9.2    | 58    | 576.029       | 1.931 | 6.6    |
20    | 2193.600      | 7.283 | 7.2    | 59    | 575.516       | 1.919 | 6.5    |
21    | 2000.641      | 6.673 | 5.4    | 60    | 573.487       | 1.913 | 4.0    |
22    | 1984.986      | 6.654 | 5.5    | 61    | 570.832       | 1.904 | 4.2    |
23    | 1412.737      | 4.712 | 5.5    |        |              |      |        |
24    | 1413.102      | 4.703 | 7.7    |        |              |      |        |
25    | 1407.465      | 4.694 | 7.9    |        |              |      |        |
26    | 1404.633      | 4.685 | 7.8    |        |              |      |        |
27    | 1401.906      | 4.676 | 8.0    |        |              |      |        |
28    | 1201.625      | 4.009 | 6.5    |        |              |      |        |
29    | 1153.186      | 3.899 | 11.8   |        |              |      |        |
30    | 1135.575      | 3.954 | 13.8   |        |              |      |        |
31    | 1173.257      | 3.930 | 8.8    |        |              |      |        |
32    | 1173.573      | 3.934 | 12.7   |        |              |      |        |
33    | 1168.011      | 3.856 | 12.4   |        |              |      |        |
34    | 1163.313      | 3.882 | 21.7   |        |              |      |        |
35    | 1158.643      | 3.804 | 20.3   |        |              |      |        |
36    | 1153.081      | 3.846 | 9.4    |        |              |      |        |
37    | 1147.227      | 3.826 | 10.1   |        |              |      |        |
38    | 1144.592      | 3.817 | 10.5   |        |              |      |        |
39    | 1138.737      | 3.798 | 18.4   |        |              |      |        |
Compound 29
Proton NMR Mosher Amide-S-3-AminoTHF- Amide Signal Expanded

Mosher amide with (S)-3-amino tetrahydrofuran (Compound 31)
Proton NMR_Mosher Amide-S-3-AminoTHF- Methoxy Signal Expanded

Acquisition Time (sec): 1.9979  
Comment: Std Proton parameters  
Date: Jul 11 2008  
Date Stamp: Jul 11 2008

File Name: C:\Documents and Settings\kayanam\Desktop\Folder\3-AminoTHF\NMR-MosherAmide-S-3-AminoTHF.dat

Number of Transients: 8  
Original Points Count: 9587  
Points Count: 131072  
Pulse Sequence: s3pu  
Receiver Gain: 36.00  
Temperature (degree C): 30.00

Frequency (MHz): 299.93  
Nucleus: 1H  
Spectrum Offset (Hz): 1802.0001  
Sweep Width (Hz): 4798.46

Mosher amide with (S)-3-amino tetrahydrofuran  
(Compound 31)

Normalized intensity

Vertical/Scale Factor = 1

Chemical Shift (ppm)

Normalized intensity

1.01

4.65  4.70  4.75  4.80  4.85  4.90  4.95  5.00  5.05  5.10

3.00  3.05  3.10  3.15  3.20  3.25  3.30  3.35  3.40  3.45

2.97
Carbon NMR_Mosher Amide-(S)-3-AminoTHF

Mosher amide with (S)-3-amino tetrahydrofuran (Compound 31)
Carbon NMR_Mosher Amide-(S)-3-AminoTHF

Mosher amide with (S)-3-amino tetrahydrofuran
(Compound 31)
Proton NMR_Mosher Amide-Racemic-3-AminoTHF - Methoxy Region Expanded

- **File Name**: C:\Documents and Settings\kalvanam\Desktop\Folder\AminoTHF\NMR-MosherAmide-Racemic3-AminoTHF\NMR_MosherAmide-Racemic3-AminoTHF.fld.cat
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- **Nucleus**: 1H
- **Number of Transients**: 8
- **Original Points Count**: 5587
- **Points Count**: 131072
- **Pulse Sequence**: Cosp
- **Receiver Gain**: 32.00
- **Solvent**: CHLOROFORM-d
- **Spectrum Offset (Hz)**: 160279360
- **Sweep Width (Hz)**: 4788.46
- **Temperature (deg C)**: 5.000

**Mosher amide with racemic 3-amino tetrahydrofuran**
Carbon NMR_Mosher Amide-Racemic-3-AminoTHF 0-90 ppm

Vertical Scale Factor = 1

[Graph showing a spectrum with peaks at various chemical shifts]

Mosher amide with racemic 3-amino tetrahydrofuran
Mosher amide with racemic 3-amino tetrahydrofuran
Compound 38

INDEX | FREQUENCY (Hz) | PPM  | HEIGHT
--- | --- | --- | ---
1 | 2198.900 | 7.337 | 9.6
2 | 2192.582 | 7.319 | 150.9
3 | 2162.343 | 7.282 | 8.5
4 | 2177.007 | 7.261 | 9.6
5 | 1678.833 | 5.599 | 11.2
6 | 1670.343 | 5.571 | 11.6
7 | 1517.536 | 5.061 | 48.6
8 | 1151.911 | 3.642 | 6.2
9 | 1147.513 | 3.627 | 6.9
10 | 1105.073 | 3.606 | 9.8
11 | 1030.338 | 3.639 | 24.7
12 | 1002.835 | 3.611 | 23.7
13 | 553.392 | 1.779 | 5.0
14 | 527.600 | 1.760 | 5.9
15 | 524.288 | 1.743 | 5.8
16 | 519.311 | 1.722 | 6.0
17 | 488.867 | 1.630 | 4.7
18 | 484.476 | 1.616 | 5.0
19 | 476.490 | 1.599 | 5.5
20 | 475.492 | 1.568 | 4.9

Pulse Sequence: szpul
Solvent: CDCl3
Ambient temperature
Operator: rajendra
Mercury-300BB "localhost.localdomain"

Relax, delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.898 sec
Width 6795.2 Hz
8 repetitions
OBSERVE HL 299.8302440 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 25 sec
Compound 38

Pulse Sequence: zwpu1
Solvent: CDCl3
Ambient temperature
Operator: rajendra
Mercury-300SB "localhost.localdomain"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 10085.2 Hz
320 repetitions
OBSERVE C13, 75.5929570 MHz
DECOUPLE H1, 298.8917848 MHz
Power 35 dB
continuously ON
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 20 min, 17 sec
Std Carbon experiment
Automation directory:
Sample : RD SAT 100 PH 13C CDC13
Pulse Sequence: s2pul
Solvent: CDC13
Ambient temperature
Operator: rajendra
Mercury-00093 "localhost.localdomain"

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Width 18083.2 Hz
320 repetitions
OBSERVE  C13, 75.3923570 MHz
DECOUPLED H1, 299.8317848 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 6.5 Hz
FT size 85538
Total time 39 min, 38 sec
Compound 39
Compound 42
Compound 42

- Automation directory: ...
- Sample: RD 3AP 262 PH 1H DMSO
- Pulse Sequence: s2pul
- Solvent: DMSO
- Ambient temperature
- Operator: rajendra
- Mercury-3000B "localhost.localdomain"

- Relax. delay 1.000 sec
- Pulse 45.0 degrees
- Acq. time 1.300 sec
- Width 18000.2 Hz
- 320 repetitions
- OBSERVE C13, 75.3927152 MHz
- DECOUPLE H1, 299.8332081 MHz
- Power 35 dB continuously on
- WALTZ-16 modulated
- DATA PROCESSING
- Line broadening 0.5 Hz
- FT size 65536
- Total time 20 min, 17 sec

Graph showing chemical shifts and peaks for Compound 42.
Compound 55

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Sample: RD SAT 110 1H CDC13
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Solvent: CDCl3
Ambient temperature
Operator: rajendra
Mercury-300B "localhost.localdomain"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.998 sec
Width 47340 Hz
8 repetitions

DATA PROCESSING
FT size 32768
Total time 0 min, 25 sec
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Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Operator: rajendra
Mercury-300B "localhost.localdomain"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.000 sec
Width 4756.2 Hz
8 repetitions

DATA PROCESSING
FT size 32768

Total time 0 min, 25 sec
Compound 59

Std Carbon experiment
Automation directory:
Sample: RD 3AP 256 PH 1H CDC13

Pulse Sequence: s2pu1
Solvent: CDCl3
Ambient temperature
Operator: rajendra
Mercury-300BB "localhost.localdomain"

Relax. delay 1.600 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 10043.2 Hz
512 repetitions
OBSERVE C13, 75.3825570 MHz
DECOUPLE H1, 298.8817048 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 20 min, 17 sec
Compound 60

- Pulse Sequence: s2p1
- Solvent: CDCl3
- Ambient temperature
- Operator: rajendra
- Mercury-30038 "localhost.localdomain"

- Relax. delay 1.000 sec
- Pulse 45.0 degrees
- Acq. time 1.300 sec
- Width 10053.2 Hz
- 512 repetitions
- OBSERVE C13, 75.3923570 MHz
- DECOUPLE H1, 239.0317848 MHz
- Power 35 dB
- continuously on
- CW-18 modulated
- DATA PROCESSING
  - Line broadening 0.5 Hz
  - FT size 80536
- Total time 20 min, 17 sec
Chapter I.3.g

References


6. For other recent uses of 3-amino tetrahydrofuran in medicinal chemistry:
   c) WO 2012/126084
d) WO 2012/117062


Chapter I.4

3-Amino pyrrolidine
Optically active 3-amino pyrrolidines are important and versatile intermediates for many chiral pharmaceuticals. For example, 3-amino pyrrolidine is an essential part of the antibacterial agents such as Tosufloxacin\(^1\) (Fig 20), Clinafloxacin\(^2\) (Fig 21) and Ceftobiprole\(^3\) (Fig 22).

Fig 20

Fig 21
Moreover, the skeleton of enantiopure 3-amino pyrrolidine is a component of many promising developmental drug molecules with diverse biological activities, such as antitumor, allergic inflammatory, Ca-sensitive receptor agonist\(^4\) (Fig 23), histamine H3 receptors antagonists and adenosine A\(_{2A}\) receptor agonist\(^5\) (Fig 24) compounds.
This widespread occurrence of 3-amino pyrrolidinyl moiety in biologically active compounds is the reason for researchers’ continued interest in developing innovative routes to obtain enantiopure 3-amino pyrrolidine intermediate with good enantiomeric purity at low cost.

There are two amino groups, one primary and the other secondary, in 3-amino pyrrolidine structure which can generate two mono-substituted products as well as di-substituted products with suitable protecting groups.

To introduce 3-amino pyrrolidine moiety into a drug molecule, protection of one amino group is necessary. It would be always preferred to synthesize the final product as either 1-N-protected 3-amino pyrrolidine or 3-N-protected amino pyrrolidine as its hydrochloride salts as shown below (Fig 25)

![Fig 25](image.jpg)

It is also important that the protecting groups should be easily removable for further reactions without affecting other existing functional groups.
Chapter I.4.b

Literature survey

Optically active 3-amino pyrrolidines have been synthesized by adopting different methodologies by various groups of researchers.

(S) and (R) - 3-amino pyrrolidine have been achieved from the respective optically active 2, 4-diamino butyric acid\(^6\). For example, (S)-2, 4 diamino butyric acid (61) is converted to (S)-3-amino pyrrolidin-2-one (62) using hydrochloric acid in methanol at reflux temperature with a yield of 50%. Further the cyclized amide (62) has been reduced employing Na bis (2-methoxyethoxy) aluminum hydride (Vitride) in Toluene medium resulting in 59% yield of (S)-3-amino pyrrolidine (63) (Scheme 36).

Scheme 36

In another method to obtain optically active 3-amino pyrrolidines, 3-protected amino L-aspartic anhydride has been the starting material\(^7\) (Scheme 37).
3-(benzyloxycarbonylamino) L-aspartic anhydride (64) is reacted with benzylamine followed by in situ cyclisation using PTSA at reflux conditions resulting in 3-(benzyloxycarbonylamino) 1-benzyl pyrrolidin-2, 5-dione (65). Then the protected dione (65) is deprotected in 3-position under hydrogenation conditions in the presence of palladium/carbon to obtain (S)-3-amino 1-benzyl pyrrolidin-2,5-dione (66) which is added to a mixture prepared from sodium borohydride and dimethyl sulphate in THF at room temperature getting (S)-3-amino 1-benzyl pyrrolidine (67). Finally (67) has been subjected to hydrogenation conditions at 60-70°C in presence of palladium/carbon followed by hydrochloric acid treatment giving (S)-3-amino pyrrolidine.dihydrochloride (68).
Recently, Xudone, J. et al has reported the synthesis of (S)-3-amino pyrrolidine dihydrochloride (68) from trans 4-hydroxy L-proline (69) (Scheme 38).

trans 4-Hydroxy L-proline (69) is converted to (R)-3-hydroxy pyrrolidine (70) by decarboxylation reaction in the presence of catalyst, 1-cyclohexene-2-one at high temperatures. Then (70) is reacted with Boc-anhydride in the presence of triethylamine followed by methane sulphonyl chloride in the presence of triethylamine to obtain (R)-3-(methanesulphonyloxy)-1-tert.butyloxycarbonyl pyrrolidine (71). Further, (71) is transformed to (S)-3-azido 1-tert.butyloxycarbonyl pyrrolidine (72) using sodium azide in DMF where an inversion of configuration occurs. Finally (S)-3-amino pyrrolidine dihydrochloride (68) is achieved from the azido product (72) by reacting with triphenylphosphine followed by dil.hydrochloric acid treatment.
Apart from chiral synthesis, the resolution of racemic 3-amino pyrrolidine (73) has also been reported. Racemic 3-amino pyrrolidine (73) is allowed to form salt with molar equivalent of (S)-2-methoxy 2-phenylacetic acid and selectively crystallized the (R)-3-amino pyrrolidine: (S)-2-methoxy 2-phenylacetic acid salt (1:2) (75) with excellent enantiomeric excess (Scheme 39).
In spite of achieving the chiral purity by resolution, this method may not be practical in industrial scales because of poor yields and lack of consistency.

The most impressive and reliable route to obtain optically active protected 3-amino pyrrolidines has been from (S) or (R) 2-protected amino butane 1, 4-diols which has been adopted by various groups\textsuperscript{10, 11, 12}.

Basically, (S) or (R)-2-protected amino butane 1, 4-diols (76) are converted to its dimesyl derivatives (77) which has been cyclized by different amines to obtain 1, 3 protected 3-amino pyrrolidines (78). Then this 1, 3-di-protected 3-amino pyrrolidines are suitably deprotected to obtain 3-protected amino pyrrolidines (79) (Scheme 40).

**Scheme 40**

\[
\begin{align*}
\text{HO} & \quad \text{NH} \quad \text{R} \\
\text{76} & \quad \text{CH}_3\text{SO}_2\text{Cl} \\
\text{TEA} & \quad \text{Am} \text{ine} \\
\text{77} & \quad \text{NH} \quad \text{R} \\
\text{Deprotection} & \quad \text{79} \\
\end{align*}
\]

\[R = \text{Boc or Cbz}\]
\[R^1 = \text{Benzyl, allyl or hydroxyl}\]
2-N-protected amino butane 1, 4-diol has been synthesized from L-aspartic acid and L-methionine in the earlier part of this thesis Chapter I.3.c and d with excellent chiral purity. So the synthetic sequence in the scheme 40 is being adopted for the development.

(S)-2-benzyloxycarbonyl amino butane 1, 4-diol (38) has been synthesized in excellent chiral purity from (S)-2-benzyloxycarbonylamino γ-butyrolactone (59) as explained in scheme 33.

(S)-2-benzyloxycarbonyl amino butane 1, 4-diol (38) is the starting material for the route to achieve optically pure protected (S)-3-amino pyrrolidine and (S)-3-amino pyrrolidine as its salts.
Chapter I.4.c

Synthesis from 2-protected amino butane 1, 4 diol

In this part of the thesis, the synthesis of (S)-3-amino pyrrolidine dihydrochloride, 1-protected 3-amino pyrrolidine dihydrochloride and 3-protected amino pyrrolidine hydrochloride from (S)-2-benzylloxycarbonyl amino butane 1, 4-diol (38) will be discussed.

(S)-2-Benzylloxycarbonylamino butane 1, 4-diol (38) synthesized from (S)-2-benzylloxycarbonylamino δ-butyrolactone (59) has been analyzed for the best optical purity as confirmed by specific optical rotation data. This served as the starting material for the synthesis of (S)-3-amino pyrrolidine dihydrochloride in few steps.

The first step is the dimesylation of (S)-2-benzylloxycarbonylamino butane 1, 4-diol (38) using methanesulphonyl chloride in the presence of triethylamine as the acid scavenger to obtain the product (S)-2-benzylloxycarbonylamino butane 1, 4-methane disuphonate (80) (Scheme 41).
Next (S)-2-benzyloxy carbamylamino butane 1, 4-methane disuphionate (80) is reacted with benzylamine to get the cyclized product, 1-benzyl (S)-3-benzyloxy carbamylamino pyrrolidine (81) (Scheme 42).
Further, 1-benzyl (S)-3-benzyloxy carbonylamino pyrrolidine (81) is subjected to hydrogenation conditions in the presence of palladium/carbon for deprotection followed by dil. hydrochloric acid treatment to achieve (S)-3-amino pyrrolidine dihydrochloride (68) (Scheme 43) as fine crystals which is found to be highly hygroscopic.

(S)-3-amino pyrrolidine dihydrochloride has been well characterized by NMR (proton and carbon), specific optical rotation and melting point data.

**Scheme 43**

![Scheme 43](image)

In another strategy, (S)-benzyloxycarbonylamino butane 1, 4-methane disupphonate (80) is reacted with hydroxylamine hydrochloride instead of benzylamine to access the product, 1-hydroxy (S)-3-benzyloxy carbonylamino pyrrolidine (82) (Scheme 44).
The N-deprotection of 1-hydroxy (S)-3-benzyloxycarbonylamino pyrrolidine (82) is achieved by subjecting to hydrogenation conditions in the presence of Raney Nickel to get the product, (S)-3-benzyloxycarbonylamino pyrrolidine hydrochloride (83) after treatment with dil. hydrochloric acid and work-up (Scheme 45).
The product (S)-3-benzyloxycarbonylamino pyrrolidine hydrochloride (83) has been well characterized by NMR (proton and carbon) analysis, Mass analysis, CHN analysis and specific optical rotation data.

Thus both (S)-3-amino pyrrolidine dihydrochloride (68) and (S)-3-benzyloxycarbonylamino pyrrolidine hydrochloride (83) are successfully synthesized from (S)-3-benzyloxycarbonylamino butane 1, 4-diol (38) in different routes which are very impressive and valuable chiral intermediates for the inclusion onto the investigational drug molecules.
Chapter I.4.d

d. Other new approaches

1st approach

The Iridium metal complex, \([\text{Cp}^* \text{IrCl}_2]_2\) that is di-\(\mu\)-chloro-dichloro bis (\(\eta^5\)-pentamethylcyclopentadienyl) diiridium, has been reported to catalyze cyclization of diols to cyclic amines in a novel way\(^{13}\).

For example, 1, 4-dimethyl 1, 4-diol (84) is cyclized to 1-benzyl 1, 5-dimethyl pyrrolidine (85) when reacted with benzylamine in toluene in the presence of the Iridium complex and sodium bicarbonate at reflux temperature (Scheme 46).

Scheme 46

Many substituted 1, 4-, 1, 5-, 1, 6-diols have been cyclized to the respective cyclic amines in good yields\(^{14}\).
In the same lines, (S)-2-benzyloxycarbonylamino butane 1, 4-diol (38) is reacted with benzylamine in toluene in the presence of sodium bicarbonate and the Iridium complex at reflux temperatures (Scheme 47).

But there is no formation of the expected product, 1-benzyl 3-(benzyloxycarbonylamino) pyrrolidine (81) as indicated by thin layer chromatography. The reaction did not proceed even after extended hours at reflux temperatures.

The reason may be the presence of the amide group which can affect the catalytic activity of the Iridium complex.
**IIInd approach**

The next approach is from (S)-2-benzyloxycarbonylamino γ-butyrolactone (59) through the formation of pyrrolidone ring as detailed in Scheme (48).

(S)-2-benzyloxycarbonylamino γ-butyrolactone (59) is reacted with benzylamine in dichloromethane solvent at reflux temperature to give (S)-2-benzyloxycarbonylamino 4-hydroxy butyric acid benzylamide (86). Further reaction with thionyl chloride gave the chloro compound, (S)-2-benzyloxycarbonylamino 4-chloro butyric acid benzylamide (87).

The next step is the cyclization reaction of the chloro compound (87) using potassium tert.butoxide in THF medium to access the product, 1-benzy (S)-3-benzyloxycarbonylamino pyrrolidin-2-one (88).

Finally the cyclized amide product (88) is reduced using Vitride® (Sodium bis (2-methoxyethoxy) aluminium hydride) solution (65% wt in toluene) to obtain the key intermediate, 1-benzy (S)-3-benzyloxycarbonylamino pyrrolidine (81) (Scheme 48).

The final step of reduction is not a neat reaction and yield is poor. The crude product is subjected to column chromatography to get the pure product. This product matches with the same product synthesized from (S)-2-benzyloxycarbonylamino butane 1, 4-methane disuphonate (80) as in Scheme (42).
Scheme 48

Benzylamine
Dichloromethane

Thionyl chloride
Dichloromethane

Methanol
aq. NaOH solution

NaBH₄
Dimethylsulphate
In another variation, (S)-2-benzyloxycarbonylamino \( \gamma \)-butyrolactone (59) is reacted with a mixture of thionylchloride/methanol to obtain the product, (S)-2-benzyloxycarbonylamino 4-chloro butyric acid methylester (89) in very good yield and purity.

This ester (89) is treated with benzylamine in toluene at reflux temperature to give the cyclized product, 1-benzyl 3-benzyloxycarbonylamino pyrrolidin-2-one (88) as indicated by thin layer chromatography. But the reaction is not complete with considerable impurities. So the crude product is purified by column chromatography.

As previously done in the Scheme 48, further reduction of (88) employing Vitride® (Sodium bis (2-methoxyethoxy) aluminium hydride) solution (65% wt in toluene) gave the important intermediate 1-benzyl 3-benzyloxycarbonylamino pyrrolidine (81) (Scheme 49).
Scheme 49

1. Thionyl chloride in Methanol
2. Benzylamine in Toluene/reflux
3. Sodium borohydride with Dimethylsulphate
Chapter I.4.e

Experimental procedures

(S)-2-Benzylxycarbonylamino butane 1, 4 methane disuphonate (80)

(S)-2-Benzylxycarbonylamino 1, 4 butane diol (38) (10g, 0.042 mol) is dissolved in chloroform (100ml) and triethylamine (13g, 0.126 mol) is added under stirring. The solution is cooled to -5 to -10°C and methanesulphonyl chloride (10.5g, 0.09 mol) is added drop wise at -5 to -10°C over a period of 30 mts.

The reaction mixture is maintained at that temperature for 3 hrs for the completion of the reaction. TLC shows the absence of the starting material. The mixture is quenched into ice cold dilute hydrochloric acid and stirred well. The chloroform layer is washed with water twice followed by brine solution. Further the organic layer is dried over sodium sulfate and concentrated to get the crude product. The crude product is stirred with methanol (100ml) to precipitate the product, (S)-2-benzylxycarbonylamino butane 1, 4 methane disuphonate as white solid.
The precipitated product is filtered and washed with little methanol and dried under vacuum.

Yield: 13.25g (80% theory)

\[ \text{1H NMR (300 MHz, CDCl}_3\text{) } \delta \text{ (PPM) 7.30-7.40(m, 5H), 5.20-5.30(d, 1H), 5.05-5.20(s, 2H), 4.20-4.30(m, 4H), 4.05-4.20(m, 1H), 2.95-3.00(2s, 6H), 1.90-2.10(m, 2H)} \]

\[ \text{13C NMR (300 MHz, CDCl}_3\text{) } \delta \text{ (PPM) 156.11, 136.31, 128.86, 128.60, 128.41, 70.80, 67.38, 66.30, 47.59, 37.59, 37.49, 30.94} \]

Anal. Calcd for C_{14}H_{21}NO_{8}S_{2} (FW 395.45): C, 42.52; H, 5.35; N, 3.52; S, 16.22 Found: C, 42.98; H, 5.08; N, 3.63; S, 16.29

APCI MS m/z 395.83 (M+H)$^+$

**1-Benzyl (S)-3-benzyloxycarbonylamino pyrrolidine (81)**

\[
\begin{align*}
\text{(S)-2-Benzylxoxycarbonylamino butane 1, 4 methane disuphonate (80)}
\text{ (13g, 0.033 mol) is dissolved in chloroform (75ml) and benzylamine (17.5g, 0.165 mol) is added drop wise at room temperature over a period of 15 mts. Then the reaction mixture is slowly heated to 50-55°C and}
\end{align*}
\]
maintained for 3 hrs. TLC showed the completion of the cyclisation reaction.

The reaction mixture is quenched in water (100ml) and stirred well. The organic layer is separated and washed with ammonium chloride solution.

Further the organic layer is dried over sodium sulfate and concentrated completely to get the crude product as a pasty mass. The crude product is stirred with water (100ml) and decanted and this process is repeated thrice to get the product, 1-Benzyl (S)-3-benzoxycarbonylamino pyrrolidine (81) as an off-white solid. The wet product is dried and recrystallized using ethyl acetate / hexane.

Yield: 7.1g (70% theory)

Melting point: 62-64°C

$^1$H NMR (300 MHz, CDCl$_3$) δ (PPM) 7.20-7.30(m, 10H), 5.25-5.35(d, 1H), 5.05-5.15(s, 2H), 4.10-4.30(m, 1H), 3.50-3.60(s, 2H), 2.70-2.85(m, 1H), 2.50-2.60(d, 2H), 2.10-2.30(m, 2H), 1.50-1.70(m, 1H)

$^{13}$C NMR (300 MHz, CDCl$_3$) δ (PPM) 156.05, 138.90, 136.82, 129.04, 128.78, 128.54, 128.41, 128.35, 127.32, 66.82, 61.00, 60.28, 52.77, 50.61, 32.82

Anal. Calcd for C$_{19}$H$_{22}$N$_2$O$_2$ (FW 310.39): C, 73.52; H, 7.14; N, 9.03; Found: C, 73.41; H, 7.11; N, 9.09;

APCI MS m/z 311.10 (M+H)
1-Benzyl (S)-3-benzyloxycarbonylamino pyrrolidine (81) (7g, 0.0225 mol) is taken in methanol (100ml) with acetic acid (5ml) and palladium/carbon (10%) (700mg). The mixture is subjected to hydrogenation in an autoclave with hydrogen pressure of 5kg and maintained at 50-55°C temperature for 10 hrs. The reaction is complete as shown by thin layer chromatography.

The mixture is filtered to remove the palladium/carbon and to the filtrate is added dil. hydrochloric acid (7.5ml). The filtrate is concentrated completely and isopropyl alcohol (25ml) is added to precipitate the product, (S)-3-amino pyrrolidine dihydrochloride as fine crystals. Further the product in isopropyl alcohol is chilled for 5 hrs and filtered. The product is washed with little isopropyl alcohol and dried under vacuum at 60°C.

Yield: 2.15g (60% theory)

\[ ^1H \text{ NMR (300 MHz, D}_2\text{O)} \delta \text{ (PPM) 4.10-4.30(m, 1H), 3.80-3.90(m, 1H), 3.40-3.70(m, 3H), 2.50-2.70(m, 1H), 2.10-2.30(m, 1H) } \]

\[ ^{13}\text{C NMR (300 MHz, D}_2\text{O)} \delta \text{ (PPM) 48.75, 47.72, 44.68, 28.59 } \]
1-Hydroxy (S)-3-benzyloxy carbonylamino pyrrolidine (82)

(S)-2-Benzylxocarbonylamino butane 1, 4 methane disphonate (80) (10g, 0.09 mol) is taken in DMSO (50ml) and triethylamine (45g, 0.45 mol). To the above mixture, hydroxylamine hydrochloride (25g, 0.36 mol) is added at room temperature under stirring. The mixture is heated to 50-55°C and maintained for 15 hrs. TLC showed the completion of the reaction.

The reaction mixture is quenched into dil. hydrochloric acid and the product is extracted by ethyl acetate (100ml). The ethyl acetate layer is separated and washed with water twice followed by brine solution. The organic layer is dried over sodium sulfate and concentrated to get the product, 1-hydroxy (S)-3-benzyloxy carbonylamino pyrrolidine (82) as pale yellow oil.

The above crude product is taken for the next stage without any purification.

Yield: 4.2g (crude product)

APCI MS m/z 237.07 (M+H)⁺
(S)-3-Benzoxycarbonylamino pyrrolidine hydrochloride (83)

1-Hydroxy (S)-3-benzyloxycarbonylamino pyrrolidine (82) (4.2g crude product, 0.018 mol) is dissolved in methanol (50ml) and charged in an autoclave. Raney nickel (1g) is added and the mixture is subjected to hydrogen pressure of 4kg for a period of 5 hrs. The TLC showed the absence of the starting material.

The mixture is filtered to remove the catalyst and dil.hydrochloric acid (5ml) is added to the filtrate. Then the filtrate is concentrated completely and product is precipitated after stirring with isopropyl alcohol (25ml). The product suspended in isopropyl alcohol is chilled for 2 hrs and filtered to get the product, (S)-3-benzyloxycarbonylamino pyrrolidine hydrochloride (83) as crystalline product. The product is dried under vacuum.

Yield: 3.5g (75% theory)

Melting point: 132-134°C

$^1$H NMR (300 MHz, D$_2$O) $\delta$ (PPM) 7.40-7.50(m, 5H), 5.10-5.20(s, 2H), 4.25-4.40(m, 1H), 3.30-3.60(m, 3H), 3.20-3.30(dd, 1H), 2.25-2.40(m, 1H), 1.95-2.10(m, 1H)

$^{13}$C NMR (300 MHz, D$_2$O) $\delta$ (PPM) 160.62, 139.10, 131.66, 131.31, 130.59, 69.91, 52.79, 47.10, 32.51
Anal. Calcd for C\textsubscript{12}H\textsubscript{17}ClN\textsubscript{2}O\textsubscript{2} (FW 256.73): C, 56.14; H, 6.67; N, 10.91; Found: C, 56.06; H, 7.03; N, 10.82; APCI MS m/z 221.03 (M+H)\textsuperscript{+}

(S)-2-Benzyloxycarbonylamino 4-hydroxy butyric acid benzylamide (86)

(S)-2-Benzyloxycarbonylamino γ-butyrolactone (59) (15g, 0.064 mol) is dissolved in dichloromethane (100ml) and benzylamine (10g, 0.093 mol) is added under stirring. The solution is slowly heated to mild reflux temperature and maintained for 5 hrs. TLC is checked which showed the completion of the reaction.

The reaction mixture is quenched into dil. hydrochloric acid (1N, 100ml) and stirred well. The organic layer is separated and washed with water twice followed by brine solution. Further the organic layer is concentrated completely and the product, (S)-2-benzyloxycarbonylamino 4-hydroxy butyric acid benzylamide (86) is precipitated after stirring with hexane (100ml). The precipitated mixture is filtered and washed with hexane and dried under vacuum.
Yield: 20g (91.5% theory)

$^1$H NMR (300 MHz, DMSO) $\delta$ (PPM) 8.35-8.45(t, 1H), 7.40-7.48(d, 1H), 7.10-7.40(m, 10H), 5.00-5.05(s, 2H), 4.50-4.60(t, 1H), 4.00-4.20(m, 3H), 1.60-1.90(m, 2H)

$^{13}$C NMR (300 MHz, DMSO) $\delta$ (PPM) 172.83, 156.67, 140.16, 137.69, 129.03, 128.90, 128.48, 128.42, 127.67, 127.36, 66.09, 58.22, 52.89, 42.68, 35.58

Anal. Calcd for C$_{19}$H$_{22}$N$_2$O$_4$ (FW 342.39): C, 66.65; H, 6.48; N, 8.18; Found: C, 66.04; H, 6.42; N, 8.17;

APCI MS m/z 342.93 (M+H) $^+$

(S)-2-Benzylcarbonylamino 4-chloro butyric acid benzylamide (87)

(S)-2-Benzylcarbonylamino 4-hydroxy butyric acid benzylamide (86) (20g, 0.058 mol) is dissolved in dichloromethane (100ml) and thionyl chloride (10.5g, 0.087 mol) is added drop wise over a period of 30 mts. The reaction mixture is slowly heated to reflux and maintained for 4 hrs. TLC has showed the completion of the reaction. The reaction is cooled to ambient temperature and quenched into ice cold water (100ml).
The organic layer is separated and washed with sodium bicarbonate solution (5%) (100ml) followed by water and brine solution. The dichloromethane layer is dried over sodium sulphate and concentrated completely to get the crude solid product. The crude product is stirred with hexane (100ml) for 1 hr and filtered to obtain the product, (S)-2-benzyloxycarbonylamino 4-chloro butyric acid benzylamide (87) as off-white powder.

Yield: 17.75g (85% theory)

\(^1\)H NMR (300 MHz, DMSO) \(\delta\) (PPM) 8.50-8.60(t, 1H), 7.55-7.65(d, 1H), 7.10-7.40(m, 10H), 5.00-5.05(s, 2H), 4.15-4.30(m, 3H), 3.60-3.70(m, 2H), 1.95-2.20(m, 2H)

\(^13\)C NMR (300 MHz, DMSO) \(\delta\) (PPM) 171.91, 156.76, 140.01, 137.58, 129.03, 128.93, 128.53, 128.45, 127.72, 127.42, 66.27, 53.11, 42.81, 42.46, 35.25

Anal. Calcd for C\(_{19}\)H\(_{21}\)ClN\(_2\)O\(_3\) (FW 360.83): C, 63.24; H, 5.87; N, 7.76; Found: C, 62.94; H, 5.81; N, 7.87;

APCI MS m/z 360.81(M+H) +

**1-Benzyl (S)-3-benzyloxycarbonylamino pyrrolidin-2-one (88)**

\[\text{O} \quad \text{O} \quad \text{N} \]

![Chemical Structure](image)
The chloro compound (87) (17g, 0.047 mol) is dissolved in dry THF (150ml) and cooled to 0-5°C under stirring. Potassium tert.butoxide (6.5g, 0.059 mol) is added at that temperature portion wise over a period of 30 minutes.

After the addition, the reaction mixture is stirred at its own temperature for 5 hours. The thin layer chromatography showed the completion of the cyclisation reaction. The mixture is quenched into cold ammonium chloride solution (300 ml) under stirring and the product is extracted with ethyl acetate (200 ml). The ethyl acetate layer is washed with water twice followed by brine. The organic layer is dried over sodium sulphate and concentrated to get the crude product.

The crude product is stirred with hexane (100 ml) to precipitate the pure product, 1-benzyl 3-benzyloxycarbonylamino pyrrolidin-2-one (88) as off-white solid. The precipitated product is filtered and washed with little hexane. The product is dried under vacuum.

Yield: 11.5g (75% theory)

$^1$H NMR (300 MHz, CDCl$_3$) δ (PPM) 7.15-7.40(m, 10H), 5.50-5.60(d, 1H), 5.05-5.15(s, 2H), 4.40-4.50(s, 2H), 4.20-4.35(m, 1H), 3.10-3.25(m, 2H), 2.50-2.70(m, 1H), 1.75-1.95(m, 1H)

$^{13}$C NMR (300 MHz, CDCl$_3$) δ (PPM) 172.05, 156.62, 136.50, 135.97, 129.05, 128.76, 128.38, 128.35, 128.32, 128.07, 67.17, 53.08, 47.40, 43.63, 28.09

Anal. Calcd for C$_{19}$H$_{20}$N$_2$O$_3$ (FW 324.37): C, 70.35; H, 6.21; N, 8.64;
Found: C, 70.16; H, 6.10; N, 8.66;

APCI MS m/z 325.01(M+H)$^+$
1-Benzyl (S)-3-benzyl oxycarbonylamino pyrrolidine (81) (from 88)

\[
\begin{align*}
\text{O} & \quad \text{NH} \\
\text{O} & \quad \text{N}
\end{align*}
\]

1-benzyl 3-benzyl oxycarbonylamino pyrrolidin-2-one (88) (10g, 0.031 mol) is dissolved in a mixture of toluene (70ml) and THF (30ml) and cooled to 10-15°C under stirring. Vitride® (Sodium bis (2-methoxyethoxy) aluminium hydride) solution (65% wt in toluene) (13.5g, 0.043 mol) is added drop wise at 10-15°C over a period of 1 hour.

After complete addition of vitride solution, the reaction mixture is stirred at ambient temperature for 12 hrs. The TLC showed the completion of the reduction reaction forming the product (81).

The reaction mixture is quenched into cold 5% sodium hydroxide solution (100ml) and the toluene layer is separated. The toluene layer is washed with water twice followed by brine solution. Further the toluene layer is concentrated completely to get the crude product as a thick pasty mass. The crude product is purified by column chromatography to get the product, 1-benzyl (S)-3-benzyl oxycarbonylamino pyrrolidine (81) as solid after stirring with hexane.

Yield: 5g (52% theory) (This product analytically matches with the same product synthesized from (80))
Methanol (150 ml) is taken and cooled to 0-5°C. Thionyl chloride (30.5g, 0.256 mol) is added drop wise over a period of 1 hour under good stirring. After complete addition, the solution is stirred for 30 minutes at 0-5°C.

Now, (S)-2-Benzoyloxycarbonylamino γ-butyrolactone (59) (15g, 0.064 mol) is added to the above solution and the mixture is stirred at ambient temperature for 12 hours. TLC showed the completion of the reaction. The mixture is concentrated to remove methanol under vacuum and quenched into cold dilute hydrochloric acid. The product is extracted using ethyl acetate (300 ml).

The ethyl acetate layer is separated and washed with water twice followed by brine solution. Further the organic layer is dried over sodium sulfate and concentrated to get the crude product as thick paste which precipitated as solid product after stirring with hexane (200 ml).

The product, (S)-2-Benzoyloxycarbonylamino 4-chloro butyric acid methylester (89) is dried under vacuum after filtration and washing with little hexane.
Yield: 17.5g (95% theory)

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \delta (PPM) 7.30-7.40(m, 5H), 5.25-5.40(d, 1H), } \\
\[ 5.10-5.20(s, 2H), 4.45-4.60(m, 1H), 3.70-3.80(s, 3H), 3.55-3.61(t, 2H), } \\
\[ 2.25-2.45(m, 1H), 2.05-2.25(m, 1H) \]

\[ ^13C \text{ NMR (300 MHz, CDCl}_3 \delta (PPM) 172.36, 156.15, 136.24, 128.81, } \\
\[ 128.53, 128.40, 67.45, 52.97, 52.02, 40.66, 35.51 \]

Anal. Calcd for C\textsubscript{13}H\textsubscript{16}ClNO\textsubscript{4} (FW 285.72): C, 54.65; H, 5.64; N, 4.90;  
Found: C, 54.60; H, 5.57; N, 4.91;

1-Benzyl (S)-3-benzyloxycarbonylamino pyrrolidine-2-one (88)  
(from 89)

(S)-2-Benzyloxycarbonylamino 4-chloro butyric acid methylester (89) (15g, 0.0525 mol) is dissolved in toluene (100ml) and benzylamine (7g, 0.066 mol) is added under stirring at room temperature. The mixture is slowly heated to reflux temperature in 2 hours and maintained at reflux temperature for 6 hrs.

Thin layer chromatography showed the completion of the reaction with the formation of the product with some impurities. The contents are cooled to RT and quenched into dilute hydrochloric acid under good
stirring. The organic layer is separated and washed with water twice followed by brine solution. Further the organic layer is concentrated completely to get the crude product as a paste.

The pasty product is crystallized from ethyl acetate: hexane (1:1, 50ml) to get the product, 1-benzyl 3-benzyloxycarbonylamino pyrrolidin-2-one (88) as off-white solid product.

Yield: 9.5g (56% theory)

This product matches analytically with the same product synthesized from (S)-2-benzyloxycarbonylamino 4-chloro butyric acid benzylamide (87).
Chapter I.4.f

**Analytical and Spectral data**
Std Proton parameters
Automation directory:
Sample: RD3AP 263 1H D2O
Pulse Sequence: zpul
Solvent: D2O
Ambient temperature
Operator: rajendra
File: RD3AP_263 1H D2O_H1 D2O_Aug 31 2010 01
Mercury-300M  localhost.localdomain"

Relax. delay 1.300 sec  
Pulse 45.0 degrees
Acq. time 1.008 sec
Width 4785.2 Hz
8 repetitions
OBSERVE: H1, 293.850.141 MHz
DATA PROCESSING
FT size 50706
Total time 9 min, 25 sec

Compound 68

NH2

N

.2HCl

INDEX | FREQUENCY | PPM | HEIGHT
1     | 1458.666 | 4.865 | 45.8
2     | 1264.321 | 4.217 | 7.3
3     | 1258.173 | 4.196 | 11.6
4     | 1250.552 | 4.171 | 8.6
5     | 1244.415 | 4.159 | 3.5
6     | 1160.460 | 3.879 | 8.7
7     | 1152.486 | 3.844 | 8.5
8     | 1147.521 | 3.821 | 11.6
9     | 1139.583 | 3.800 | 8.8
10    | 1097.755 | 3.661 | 3.2
11    | 1080.651 | 3.635 | 5.2
12    | 1055.732 | 3.621 | 8.3
13    | 1043.769 | 3.614 | 8.0
14    | 1078.141 | 3.599 | 11.8
15    | 1071.468 | 3.575 | 8.0
16    | 1061.458 | 3.540 | 7.7
17    | 1051.210 | 3.509 | 19.3
18    | 1045.855 | 3.486 | 19.3
19    | 1041.842 | 3.475 | 13.6
20    | 1038.057 | 3.462 | 12.4
21    | 1032.182 | 3.449 | 11.7
22    | 785.932 | 2.621 | 5.9
23    | 778.967 | 2.598 | 8.3
24    | 771.341 | 2.575 | 9.8
25    | 764.623 | 2.559 | 7.5
26    | 757.366 | 2.526 | 3.3
27    | 601.466 | 2.279 | 2.4
28    | 673.875 | 2.248 | 7.2
29    | 666.849 | 2.224 | 8.6
30    | 659.824 | 2.201 | 8.5
31    | 652.790 | 2.177 | 5.9
32    | 645.772 | 2.154 | 2.9
33    | 0.000   | 0.000 | 3.6
Compound 68

NH₂

H

.2HCl

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 10085.2 Hz
128 repetitions
OBSERVE C13, 75.3925500 MHz
DECOUPLE H1, 289.035554 MHz
Power 25 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 33 min, 39 sec
Compound 80

INDEX | FREQUENCY | PPM | HEIGHT
--- | --- | --- | ---
1 | 2297.511 | 7.363 | 16.8
2 | 2203.999 | 7.351 | 106.0
3 | 2183.157 | 7.315 | 4.9
4 | 2178.531 | 7.366 | 11.5
5 | 1974.912 | 5.253 | 5.0
6 | 1966.423 | 5.224 | 5.4
7 | 1941.833 | 5.142 | 2.8
8 | 1928.959 | 5.099 | 26.6
9 | 1939.741 | 4.925 | 4.1
10 | 1294.472 | 4.317 | 8.8
11 | 1268.818 | 4.259 | 10.8
12 | 1263.641 | 4.281 | 21.4
13 | 1264.936 | 4.272 | 16.9
14 | 1276.920 | 4.256 | 12.5
15 | 1270.468 | 4.237 | 5.0
16 | 1265.442 | 4.221 | 4.3
17 | 1245.586 | 4.154 | 2.6
18 | 1241.195 | 4.190 | 3.0
19 | 1236.304 | 4.125 | 4.0
20 | 1231.827 | 4.106 | 4.8
21 | 1226.921 | 4.096 | 3.6
22 | 895.475 | 2.987 | 72.9
23 | 605.320 | 2.986 | 55.4
24 | 616.489 | 2.056 | 3.2
25 | 616.937 | 2.038 | 5.5
26 | 608.880 | 2.031 | 5.9
27 | 605.618 | 2.013 | 8.0
28 | 590.349 | 1.899 | 5.6
29 | 593.958 | 1.881 | 4.3
30 | 585.335 | 1.962 | 2.5
31 | 515.219 | 1.718 | 11.4
32 | ~0.000 | ~0.000 | 6.2
Compound 80

Std Carbon experiment
Automation directory:
Sample: RD 3AP 220 PH 13C CDCl3

Pulse Sequence: e2pu1
Solvent: CDCl3
Ambient temperature
Operator: rajendra
Mercury-300BB "localhost.localdomain"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.380 sec
Width 18003.2 Hz
512 repetitions
OBSERVE C13, 75.802657 MHz
DECOUPLE HH; 298.817848 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 6.5 Hz
FT size 65536
Total time 20 min, 17 sec

Graph showing the NMR spectrum of Compound 80 with peaks at various ppm values.
Compound 80

A diagram showing a molecule with labeled mass-to-charge ratios (m/z) ranging from 50.00 to 1500.00, with notable peaks at 210.03, 300.00, 418.77, 485.81, and 535.81.
Compound 81

Std Proton parameters
Automation directory:
Sample: RD 3AP 277 PH 1H CDC13
Pulse Sequences: t2pul
Solvent: CDC13
Ambient temperature
Operator: rajendra
Mercury-900B8 "localhost.localdomain"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.550 sec
Width 4796.2 Hz
9 repetitions
OBSERVE 121.2593202522 MHz
DATA PROCESSING
FT size 32768
Total time 6 min, 26 sec
Compound 81

Chemical structure and mass spectrum data:
- Mass to Charge (m/z) values: 311.10, 177.14, 209.17, 267.05, 338.46, 350.82, 385.38, 434.16, 447.11, 487.27, 533.36, 549.31, 577.27
- RT: 0.03-0.22
- AV: 8
- NL: 1.04E5
- APCI corona Full ms [50.00-2000.00]
Std Proton parameters
Automation directory:
Sample: RA GAP 127 PM 1H DMSO
Pulse Sequences: s equival
Solvent: DMSO
Ambient temperature
Operator: rajendra
Mercury-3000B "localhost.localdomain"

Relax. delay 1.006 sec
Pulse 45.0 degrees
Acq. time 1.858 sec
Width 4296.2 Hz
3 repetitions
OBSERVE H1, 293.6210609 MHz
DATA PROCESSING
FT size 32758
Total time 0 min, 20 sec
Compound 86

Std Carbon experiment
Automation directory:
Sample: RD SAP 127 PH 12C DMSO
Pulse Sequence: e2pul
Solvent: DMSO
Ambient temperature
Operator: rajendra
Mercury-3005B "localhost.localdomain"

Relax, delay 1.900 sec
Pulse 45.0 degrees
Acq. time 1.390 sec
Width 10088.2 Hz
1000 repetitions
OBSERVE CI, 75.3827151 MHz
DECOUPLE H1, 298.932091 MHz
Power 30 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 29 min, 39 sec
Compound 86
Compound 87

Std Proton parameters
Automation directory:
Sample: RD 38P 150 1H DMSO
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
Operator: reijenda
Mercury-300HG "localhost.localdomain"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.150 sec
Width 4756.2 Hz
8 repetitions
OBSERVE H1 299.8310996 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 25 sec

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Compound 87

Std Carbon experiment
Automation directory:
Sample: RD SAP 120 PH 13C DMSO
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
Operator: rajendra
Mercury-300B "localhost.localdomain"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acc. time 1.300 sec
Width 10083.2 Hz
256 repetitions
OBSERVE Cl3, 75.2827152 MHz
DECUPLE H1, 298.8553041 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 85736
Total time 39 min, 39 sec
Compound 87
Compound 88

Std Proton parameters
Automation directory:
Sample: BD 3AP 184 PM 1H CDC19
Pulse Sequence: s2pul
Solvent: CDC19
Ambient temperature
Operator: rajendra
Mercury-300BB "localhost.localdomain"

Relax. delay 1.000 sec
Pulse 45.8 degrees
Acq. time 1,356 sec
Width 0.786.2 Hz
8 repetitions
RESOLVE, N1, 239.302452 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 25 sec

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Compound 88

Std Carbon experiment

Automation directory:
Sample : RD SAP 164 PH 13H CDCl3

Pulse Sequence: s2pol
Solvent: CDCl3
Ambient temperature
Operator: rajendra
Mercury-300B "localhost.localdomain"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 10083.2 Hz
760 repetitions

OBSERVE C13, 75.3929570 MHz
DECOUPLE H1, 299.9317848 MHz
Power 35 dB
continuously on
WALTZ-18 modulated

DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 58 min, 38 sec

175

200 180 160 140 120 100 80 60 40 20 ppm
Compound 88

m/z: 98.00, 119.96, 181.22, 246.12, 281.15, 325.01, 380.93, 415.09, 448.00, 497.11, 569.59, 514.81

Intensity
Compound 89

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Compound 89

\[
\text{O} \quad \begin{array}{c}
\text{Cl} \\
\text{O} \\
\text{CH}_3
\end{array}
\]

172.354
155.158
138.248

126.361
126.401

77.718
57.877
41.877
38.977
33.513
40.667
52.970
52.010

Total time 38 min, 39 sec

 relaxation delay 1.000 sec
Pulse 90.0 degrees
Acq. time 1.000 sec
Width 10003.2 Hz
640 repetitions

Observe C13, 75.493570 MHz
Decouple H2, 299.631780848 MHz
Power 36 dB
continuously on

WALTZ-16 modulated

DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536

Sample: RD AEC 255 PM 13C CDE13

Operator: rajendra

Mercury-3600S "localhost.localdomain"
Chapter I.4.g

References

1. Merck Index, 14 ed., No. 9555, 2006
2. Merck Index, 14 ed., No. 2355, 2006
   ii) Rong, L.; Sichuan Huagong (2012), 15(2), 13
12. Muller, M.; Soukup, M. US 7064199