CHAPTER III

Carbohydrate-pyrrolidine based organocatalyst
for enantioselective Michael addition of
 carbonyls to nitroolefins
INTRODUCTION

Chemical reactions are transformations of one set of chemical substances to another and substances which accelerate the rate of the reaction are called catalyst. Organocatalysis is acceleration of chemical reactions with a substoichiometric amount of an organic compound which does not contain a metal atom.

Enantioselective construction of an organic compound in an environmentally benign and economically viable process is still a challenging task for an organic chemist. Traditionally, enantiomerically enriched molecules were prepared by using classical resolution method; one drawback of the resolution techniques is that the desired enantiomer can be isolated only in 50% yield maximum. An Enantioselective synthesis using auxiliary requires stoichiometric amounts of chiral substances which has to be removed after the establishment of the stereogenic centers. Enzymes catalyse organic reactions with high selectivity, however, in this process only one enantiomer of the product can be obtained directly. Recently catalytic organometallic chiral transformations are being extensively studied which led to preparation of several important organic compounds on industrial scale. Use of simple organic molecules to induce chirality in organic reactions has caught the attention of scientific community and has led to emergence of a new concept called asymmetric organocatalysis. Metal-free organic catalysts are generally nontoxic, inexpensive, readily available and stable. These properties allow most reactions to be performed in presence of water and in air which increases the reproducibility and operational simplicity. As these organocatalysts are obtained either directly from nature or by some simple chemical transformations of chiral organic molecules, both the congeners of the catalyst are accessible and offer wide substrate scope, which are complementary to well established chemical and biochemical transformations. Nitrogen containing natural products such as alkaloids and amino acids were among the first organic catalysts to be tested, for eg., Strychnine and brucine were used for kinetic resolution of secondary alcohols and esterification of meso dicarboxylic acids, albeit with low ee-values.¹

The first successful application of organocatalyst was obtained by Hajos-Parrish in 1970 when they used L-proline 1 to catalyse asymmetric Robinson type annulation of an achiral triketone to form steroid precursor (93% ee).² The importance of the organocatalystic approach was realized only in 2000, when Barbas et al., reported the first intermolecular cross-aldol reaction between aldehydes as acceptors and ketones as donors using L-proline 1 as catalyst.³
During the same time, MacMillan reported asymmetric Diels-Alder reaction catalysed by a chiral imidazolidinone $2$. These two publications are largely responsible for the development of organocatalytic reactions, which led to newer reactions and concepts in organic synthesis.\textsuperscript{5,6,7,8}

### Scheme 1

Last few years have seen an exponential growth in the synthesis and application of various asymmetric organocatalysis, especially in the area of proline derivatives or pyrrolidine based catalysts. These derivatives have been shown to exhibit catalytic activities in a diverse range of organic transformations.

### General organo catalytic mechanism

Organocatalyst can be considered as metal-free enzymes. The principles and mechanism of enzyme catalysis can be applied to the organocatalytic reactions. Most of the organocatalyst can be broadly classified as Lewis acids, Lewis bases, Bronsted acids and Bronsted bases. The mechanism of organocatalytic reactions can be classified under two categories.
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1. **Covalent catalysis**

   In this process a covalent adduct forms between the substrate and the catalyst. The catalysis of aldol reactions by formation of donor enamine/iminium ion is an example where a “covalent-active” intermediate is formed. This mechanism is similar to the catalytic mechanism of class-I aldolases.

2. **Non-covalent catalysis**

   The reaction proceeds through a formation neutral host-guest complexation, or acid-base associations between catalyst and substrate. Many enzymes effect reactions by bringing together reactants at an active site without forming any covalent bonds.

   Organometallic catalysts achieve catalytic activity due to Lewis acid functionality through a metal center, whereas, most of the currently used organocatalysts have more than one active center. A vast majority of these catalysts are bifunctional, having commonly a Bronsted acid and Lewis base center. Such catalysts are able to activate both the donor and acceptor respectively and these results not only in a considerable acceleration in reaction rate but also in increased selectivity due to a highly organized transition state. An important class of Lewis base catalysis is asymmetric enamine catalysis. In enamine catalysis, the catalyst reacts with aldehyde/ketone to form an enamine species with a higher HOMO energy compared to the respective carbonyl compound. The enamine acts as a nucleophile and reacts with electrophilic species while forming an iminium ion species. Hydrolysis of this intermediate gives the product and catalyst, thus allowing the catalytic cycle to be completed. (Figure 1). Examples of the organocatalyst reactions that proceed through an active enamine species include aldol, Mannich, Michael and $\alpha$-functionalisation of carbonyl compounds.\(^9\)

![Figure 1](image-url)
MICHAEL ADDITIONS (Conjugate addition)

Michael addition reaction involves addition of nucleophiles (Michael donor) to unsaturated systems in conjugation with an activating group (Michael acceptor) to form a new C-C bond. The asymmetric conjugate addition to form a new bond is widely used in organic synthesis.\(^\text{10}\) Due to the simplicity of the asymmetric organocatalytic approach, Michael addition of various donors and acceptors has been studied in the presence of organocatalysts. Common Michael donors are ketones, aldehydes, \(\alpha\)-heterosubstituted ketones, cyclic ketones, \(\alpha,\alpha\)-disubstituted aldehydes and dioxanone, while Michael acceptors include unsaturated carbonyl compounds,\(^\text{11}\) alkyldiene malonates\(^\text{12}\) and vinyl sulfones (Scheme 3).\(^\text{13}\)
Scheme 3

As nitroalkenes are highly electronegative, they act as good Michael acceptors. Moreover, the nitro group can act as a masked functionality, which can be further transformed after the reaction. The Nef reaction, nucleophilic displacement, reduction to an amino group, Meyer reaction and conversion into a nitrile oxide are some examples of the possible transformations that nitro groups can undergo. Further chiral \( \gamma \)-nitro carbonyl compounds, products of the asymmetric Michael reaction between nitroolefins and carbonyl compounds serve as versatile building blocks for the synthesis of complex organic structures (Scheme 4).

Proline was the first compound used as an organocatalyst for asymmetric conjugate reactions. Barbas and List individually reported the first asymmetric intermolecular Michael-type addition between nitrostyrene and unmodified ketones using proline as catalyst. The desired \( \gamma \)-nitro carbonyl compound was obtained in good yields (85–97\%) and diastereoselectivity but with very low enantioselectivities.

Scheme 4

Later, Enders et al., showed that addition of small amount of methanol rather than DMSO was helpful in increasing the stereoselectivities (65:1 dr and 76\% ee), and proposed an acyclic synclinal transition state based on Seebach’s model, to explain the observed syn-diastereoselectivity and absolute configuration (Figure 2).
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Figure 2

Since then, numerous pyrrolidine based organocatalysts have been successfully employed in asymmetric Michael addition of carbonyl compounds onto nitroalkenes promoting the reaction via an enamine pathway, with diverse range of stereoselectivities.

![Figure 2](image)

Figure 3

Our own interest in organocatalyst field in the identification of new catalysts for aldol, Michael and new domino reactions, to build novel scaffolds, prompted us to explore a new catalyst.

![Figure 3](image)

Figure 4

![Figure 4](image)
Carbohydrates as catalyst

Carbohydrates are some of the very abundant organic compounds in nature. They are found in all living organism and plays biologically important roles. Carbohydrates are highly oxygenated compounds and have a set of chemical and structural features. Due to their low cost and ease of poly-functionalization, they can be easily tuned for the steric, electronic and solubility requirements needed for a reaction. These features made us to consider the possibility of using carbohydrates for stereoselective organic transformations. Moreover, they are cheap and available in a variety of diastereomeric, chiral and conformational isomers. In 1996, Shi et al., reported the first use of fructose derived ketone 15, as a highly effective catalyst for the asymmetric epoxidation of olefins. 29

Scheme 5

Our literature survey revealed carbohydrate containing bifunctional organocatalysts and most of them are derived from pyranose form of the carbohydrates.

Figure 5

100
PRESENT WORK

Present work describes the development and evaluation of a new class of carbohydrate-pyrrolidine based organocatalysts and their application in asymmetric Michael addition of carbonyl compounds to nitro olefins. There are several bifunctional organocatalysts derived from D-glucopyranose, D-glucosamine etc., however, furanose form of the carbohydrate in organocatalyst is rather unexplored. With these observations, we envisaged to synthesize new catalysts 22 and 23 in which a basic pyrrolidine moiety is appended to β-amino acid and β-hydroxy acid which are derived from D-glucose.

![Figure 6](image)

Retrosynthetic analysis

Retrosynthetic analysis of catalyst 22 and 23 is shown in scheme 6. The carbohydrate-pyrrolidine catalysts 22 could be easily obtained by coupling of pyrrolidine amine 28 with β-azido-acid 35. The catalyst 24 can be obtained by coupling of pyrrolidine amine 28 with benzyl protected β-hydroxy-acid 38. Pyrrolidine amine 28 could be obtained from L-proline 1 and the β-acids from the β-D-glucose.

![Scheme 6](image)
Synthesis

The synthesis of organocatalyst commenced from \(L\)-proline. \(L\)-Proline 1 was protected as its carbamate 24 using Cbz-Cl and KOH in 94% yield. Reduction of the acid functionality using borane dimethylsulfide in anhydrous THF afforded the alcohol 25 in 86% yield. The product was confirmed by its \(^1\)H NMR spectrum and ESI-MS showed a peak at 258.0 [M+Na]\(^+\). Compound 25 was tosylated using tosyl chloride and NEt\(_3\) in CH\(_2\)Cl\(_2\). \(^1\)H NMR spectrum of compound 26 showed peaks at \(\delta\) 2.43 as singlet for the aromatic methyl group and in the downfield region for aromatic hydrogens of the tosyl group. Tosyl compound 26 was converted into azide 27 using Na\(_3\) in DMF. The IR spectrum of 29 showed the azide stretching frequency at 2104 cm\(^{-1}\) and absence of peaks for tosyl functionality in \(^1\)H NMR spectrum also confirmed the product. The azide group was chemoselectively reduced to its corresponding amine 28 using Pd-BaSO\(_4\) (poisoned with lead) in methanol under hydrogen atmosphere in quantitative yield. The compound was confirmed by its ESI-MS \(m/z\) 235.0 [M+Na]\(^+\). \(^1\)H NMR spectrum showed group of peaks between \(\delta\) 4.0-3.2 for five hydrogens attached to nitrogen and the specific rotation of compound 28 was in good accordance with the literature data (Scheme 7).

![Scheme 7](image)

The carbohydrate fragments were obtained from D-glucose. The \(\beta\)-azido-acid was prepared as shown in scheme 8 following a well documented procedure reported by our group.\(^{36}\) Accordingly, 1,2,5,6 di-O-isopropylidene-\(\alpha\)-D-glucofuranose 29 was prepared from D-glucose by a well documented procedure. The hydroxyl group in 29 was oxidized to ketone with PDC-Ac\(_2\)O and the resultant ketone was reduced with NaBH\(_4\) at 0 °C in methanol to furnish the inverted alcohol 30 in 66% yield (for two steps). Tosylation of alcohol 30 using pyridine, TsCl and cat.DMAP in CH\(_2\)Cl\(_2\) at room temperature provided tosylated product 31 in 94% yield. Tosyl group was replaced with azide using NaN\(_3\) in DMF at 135 °C for 12 h to furnish the azido derivative 32 in 80% yield. The 5,6-O-
isopropylidene unit in compound 32 was successively cleaved with 0.8% H₂SO₄ in methanol at room temperature to liberate diol 33 in 95% yield, which was subjected to oxidative cleavage using NaIO₄ and NaHCO₃ in THF:H₂O (8:2) at room temperature to afford the aldehyde 34. Aldehyde was oxidized using NaClO₂, NaH₂PO₄ and 30% H₂O₂ in acetonitrile and water at room temperature for 12 h to give the acid 35 in 90% yield.

**Scheme 8**

The free hydroxyl group of 1,2,5,6 di-O-isopropylidene-α-D-glucofuranose 29 was protected as its benzyl group using benzyl bromide/sodium hydride and the crude was subjected to deprotection of the acetonide functionality using 0.8% H₂SO₄ in methanol to afford the diol 36 in 84% yield.³⁷ Oxidative cleavage of diol using sodium periodate afforded the aldehyde 37, which on further oxidation using NaClO₂ and NaH₂PO₄ gave the acid 38 in 76% yield.

**Scheme 9**
Amine 28 and acid 35 were coupled using EDC.HCl and HOBr to afford the amide 39 in 81% yield. The compound was characterized by $^1$H NMR study, which showed a broad singlet for the amide proton at 7.51 ppm and its $^{13}$C NMR spectrum showed peaks at 167.4, 144.1 for the carbonyl functional groups. The compound was further confirmed by ESI-MS which showed peak at $m/z$ 446 [M+H]$^+$. Deprotection of –NCbz group and reduction of azide of the compound 39 were carried out under hydrogenation conditions using Pd/C catalyst in methanol for 12 h to afford the compound 22 in 84% yield. $^1$H NMR and $^{13}$C NMR spectrums of the compound showed absence aromatic peaks with the presence of other required resonances. Its ESI-MS showed a peak at $m/z$ 286 [M+H]$^+$ confirming 22 (Scheme 10).

![Scheme 10](image)

Similar reaction sequence was used to synthesize 23. Coupling of the amine 28 and acid 38 using EDC.HCl and HOBr gave the amide 40. The product was confirmed by its $^1$H NMR resonances at 7.38-7.18 as a multiplet corresponding to the ten aromatic protons and ESI-MS, which showed a peak at $m/z$ 511 [M+H]$^+$. Both the -OBn and -NCbz protecting groups were removed by hydrogenation using Pd/C as catalyst in methanol to afford 23. The compound was confirmed by the absence of peaks for aromatic group in the downfield region in $^1$H and $^{13}$C NMR spectra. HRMS provided further evidence, a peak corresponding to $m/z$ 287.1607 [M+H]$^+$ was obtained confirming the molecular formula C$_{13}$H$_{23}$N$_2$O$_5$ (Scheme 11).

![Scheme 11](image)
Evaluation of catalyst

With both the catalysts 22 and 23 in hand, we tested their efficiency in asymmetric Michael addition reaction. As a model reaction, we investigated Michael addition of β-nitrostyrene 24a with cyclohexanone 25. The reactions were conducted in 10 mol% of catalyst in solvent free condition at room temperature. Both catalysts were able to catalyse the reaction however, catalyst 23 bearing hydroxyl functionality provided desired product in good yield (88%) and good stereoselectivity (ee up to 66%, syn:anti 92:8, Table-1, entry-2). After screening the catalysts, we screened THF, CHCl₃, methanol and dioxan as solvents for the same reaction with 20 mol % of the catalyst 23. Increasing the catalyst quantity improved both enantioselectivity and diastereoselectivity of the reaction (ee up to 91%, syn:anti 98:2 Table-1, entry-3). Though the reaction was compatible with various solvents and provided good enantioselectivity, the yields were comparatively less and reaction took longer time for the completion when compared to solvent free condition. On the other hand, the reaction did not proceed in non-polar solvent like hexane and toluene. Usually Michael reactions employing pyrrolidine based catalyst needs small amount of acid catalyst as additive, in our study the reaction under solvent free condition proceeded at a reasonable rate without any additives.
Under these optimized conditions, Michael reaction of various nitroolefin substrates \((24a-24h)\) with cyclohexanone \(25\), cyclopentanone and acetone as Michael acceptors were investigated to check the generality of this procedure. All the \(\beta\)-nitrostyrenes bearing electron donating aryl groups as well as electron withdrawing aryl groups were reacted smoothly with cyclohexanone to give corresponding Michael adducts in good yields with high diastereoselectivity and enantioselectivity.

**General reaction procedure for carbohydrate-Based Pyrrolidine 25 as organocatalyst for asymmetric Michael Addition of ketones to nitrostyrenes**

Catalyst \(23\) (20 mol\%) was added to a mixture of cyclohexanone \(25\) (10 mmol) at room temperature and stirred for 10 min, then nitroolefin \(24a-24h\) (1 mmol) was added and mixture stirred at the same temperature. After completion of reaction (monitored by TLC) the reaction mixture was directly loaded on a silica-gel (60-120 mesh) column and purified to give the corresponding Michael adducts \(26a-26j\). Relative configurations of the Michael products were determined by comparison of \(^1\)H NMR spectra of the products with the known compounds. Absolute configuration of the major isomer was established by

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**Table 1: Screening of catalyst and solvent\(^a\)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>mol %</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)(^b)</th>
<th>dr (syn/anti)(^c)</th>
<th>ee (syn)(^d)</th>
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<td>85</td>
<td>90:10</td>
<td>18</td>
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<td>36</td>
<td>88</td>
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<td>3</td>
<td>23</td>
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<td>26</td>
<td>94</td>
<td>98:2</td>
<td>91</td>
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<td>4</td>
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<td>THF</td>
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<td>85</td>
<td>92:8</td>
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<td>5</td>
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<td>20</td>
<td>CHCl(_3)</td>
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<td>72</td>
<td>95:5</td>
<td>92</td>
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<td>6</td>
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<td>20</td>
<td>Methanol</td>
<td>56</td>
<td>78</td>
<td>93:7</td>
<td>88</td>
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<tr>
<td>7</td>
<td>23</td>
<td>20</td>
<td>Dioxan</td>
<td>52</td>
<td>82</td>
<td>85:15</td>
<td>90</td>
</tr>
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</table>

\(^a\) All reactions were performed with nitrostyrene (1 mmol), cyclohexanone (10 mmol), solvent (0.5 mL) at room temperature

\(^b\) Isolated yields; \(^c\) Determined by \(^1\)H NMR of the crude product or HPLC

\(^d\) Determined by chiral HPLC of the syn product.
comparison to literature value of optical rotation. Enantiomeric excess was determined by chiral HPLC.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitro olefin</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)$^a$</th>
<th>dr (syn/anti)$^b$</th>
<th>ee (syn)$^c$</th>
</tr>
</thead>
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<td>60</td>
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In summary, we have developed a new type of carbohydrate-pyrrolidine-based organocatalyst for asymmetric Michael reaction of ketones to $\beta$-nitrostyrenes under solvent-free condition without any additives. Michael adducts were formed in high yields and diastereoselectivity with good to moderate enantioselectivities.

$^a$Isolated yields.  
$^b$Determined by $^1$H NMR and HPLC analysis.  
$^c$Determined by chiral HPLC using chiral pak-IA, IC
EXPERIMENTAL PROCEDURE

(S)-1-(Benzylxocarbonyl)pyrrolidine-2-carboxylic acid (24)

\[ \text{Cbz} \quad \text{COOH} \]

\[ \text{L-Proline 1 (10.0 g, 86.9 mmol) was dissolved in 60 mL of 2N KOH solution and cooled to 0 °C. To this solution Cbz-Cl (13.0 mL, 91.2 mmol) and 30 mL of 4N KOH solution were simultaneously added slowly for a period of 30 min. Reaction was stirred for 3 h at room temperature. Ethyl acetate (200 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was neutralized with 1N HCl to pH 6-7 and diluted with ethyl acetate (100 mL). Layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 75 mL). The organic layers were combined, washed with water, dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under vacuum to afford 24 (20.4 g, 94%) as a white solid.} \]

\[ \text{H NMR (300 MHz, CDCl}_3\text{): 7.4-7.22 (m, 5H), 5.20-5.09 (m, 2H), 3.68-3.41 (m, 1H), 2.35-1.83 (m, 4H).} \]

\[ \text{C NMR (75 MHz, CDCl}_3\text{): 178.08, 176.3, 136.2, 128.4, 128.3, 128.0, 127.8, 127.6, 67.4, 67.1, 59.3, 58.6, 46.8, 46.6, 30.8, 29.3, 24.2, 23.4.} \]

(S)-Benzyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (25)

\[ \text{Cbz} \quad \text{OH} \]

\[ \text{To a stirred solution Cbz-L-proline 24 (8.0 g, 32.0 mmol) in anhydrous THF at 0 °C under nitrogen atmosphere, borane dimethylsulphide complex (6.0 mL, 64.0 mmol) was added. The reaction mixture was stirred for 12 h at room temperature. The reaction mixture was cooled to 0 °C and water (20 mL) was added slowly. The mixture was diluted with ethyl acetate and organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 x 30 mL). The combined organic phase were washed water and dried over Na\(_2\)SO\(_4\) and concentrated to give alcohol 25 (6.4 g, 86%) as a colourless oil.} \]
\begin{itemize}
\item \textbf{H NMR (300 MHz, CDCl\textsubscript{3})}: 7.36-7.26 (m, 5 H), 5.18-5.06 (m, 2 H), 4.04-3.92 (m, 1 H), 3.68-3.49 (m, 3 H), 3.44-3.34 (m, 1 H), 2.10-1.98 (m, 1 H), 1.96-1.74 (m, 2 H), 1.63 (septet, \( J = 6.1 \) Hz, 1 H).

ESI-MS: \( m/\text{z} \) 258.0 [M+Na]\textsuperscript{+}.

\([\alpha]_D^{27}\): -39.5 (c 1.0, CHCl\textsubscript{3})
\end{itemize}

(S)-Benzyl 2-(tosyloxymethyl)pyrrolidine-1-carboxylate (26)

(S)-Benzyl-2-(hydroxymethyl)pyrrolidine-1-carboxylate 25 (6.0 g, 24.1 mmol) was dissolved in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (40 mL) and NEt\textsubscript{3} (10.0 mL, 72.3 mmol) was added. The solution was cooled to 0 °C and tosyl chloride (5.5 g, 28.9 mmol) was added in three portions and the reaction was stirred at room temperature for 6 h. The reaction mixture was cooled to 0 °C and 1N HCl solution was added till pH 4 to neutralize excess NEt\textsubscript{3}. The organic layer was separated and the aqueous phase was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 25 mL). The combined organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. The crude product was purified by silicagel (hexane:ethyl acetate-8:2) column chromatography to give tosylated compound 26 (7.7 g, 84%).

\begin{itemize}
\item \textbf{H NMR (300 MHz, CDCl\textsubscript{3})}: 7.7 (dd, \( J = 24.1 \), 7.5 Hz, 2 H), 7.36-7.23 (m, 7 H), 5.13-4.92 (m, 2 H), 4.22-3.84 (m, 3 H), 3.38 (t, \( J = 6.0 \) Hz, 2 H), 2.43 (s, 3 H), 2.10-1.77 (m, 4 H).

\([\alpha]_D^{27}\): -39.5 (c 1.2, CHCl\textsubscript{3})
\end{itemize}

(S)-Benzyl-2-(hydroxymethyl)pyrrolidine-1-carboxylate (27)

To a stirred solution compound 26 (7.5 g, 19.2 mmol) in DMF (50 mL) were added NaN\textsubscript{3} (3.7 g, 57.8 mmol), TBAI (0.35 g, 0.96 mmol) and heated to 80 °C. The reaction was
stirred for 8 h and then brought to room temperature. The reaction mass was filtered and filtrate was diluted with diethyl ether (100 mL) and water (30 mL). The organic phase was separated and washed with water (3 x 20 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (hexane:ethyl acetate-9:1) to afford the azide 27 (4.3 g, 86.0%).

IR (KBr) : \( v_{\text{max}} \) 2104, 1380, 1217, 1074, 1014 cm$^{-1}$

$^1$H NMR (300 MHz, CDCl$_3$) : 7.37-7.27 (m, 5H), 5.18-5.05 (m, 2H), 4.03-3.90 (m, 1H), 3.61 (dd, \( J = 12.2 \), 6.4 Hz, 1H), 3.52-3.26 (m, 3H), 2.06-1.81 (m, 4H).

ESI-MS : $m/z$ 283.0 [M+Na]$^+$

$(S)$-Benzyl 2-(aminomethyl)pyrrolidine-1-carboxylate (28)

Pd-CaCO$_3$ poisoned with lead (0.5 g) was added to a solution of 27 (2.5 g, 9.6 mmol) in methanol (20 mL) and stirred under hydrogen atmosphere at room temperature for 4 h. After the completion of reaction (by TLC), the mixture was filtered through a pad of celite. Concentration of the filtrate afforded the amine 28 (2.14, 95.0%). The amine was pure enough and used as such for further transformations.

$^1$H NMR (300 MHz, CDCl$_3$) : 7.45-7.25 (m, 5H), 5.20-5.03 (m, 2H), 3.90-3.75 (br.s, 1H), 3.55-3.31 (m, 2H), 2.96-2.60 (m, 2H), 2.09-1.72 (m, 4H).

ESI-MS : $m/z$ 235.0 [M+Na]$^+$

$[\alpha]_D^{25}$ : -42.2 ($c$ 0.85, CHCl$_3$)

$(S)$-Benzyl 2-(((3aR,5S,6R,6aR)-6-azido-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole-5-carboxamido)methyl)pyrrolidine-1-carboxylate (39)
To a stirred solution of acid 35 (0.49 g, 2.13 mmol) in CH₂Cl₂ (10 mL) was added EDC.HCl (0.5 g, 2.6 mmol) and HOBT (0.35 g, 2.6 mmol) at 0 °C and resultant mixture stirred for 15 min. A solution of amine 28 (0.5 g, 2.13 mmol) in CH₂Cl₂ was added and stirred at room temperature for 8 h. The reaction was diluted with water and the aqueous layer was separated. The organic layer was washed with water (2 x 25 mL), dried over Na₂SO₄ and concentrated under vacuum. The crude product was purified by silica gel column chromatography (hexane:ethyl acetate - 1:1) to give the amide 39 (0.77 g, 81%).

^1H NMR (300 MHz, CDCl₃): 7.51 (br. s, 1H), 7.41-7.28 (m, 5H), 6.05-5.92 (m, 1H), 5.28-5.08 (m, 2H), 4.79-4.68 (m, 1H), 4.65-4.53 (m, 1H), 4.38 (d, J = 3.2 Hz, 1H), 4.07-3.93 (m, 1H), 3.70-3.25 (m, 4H), 2.08-1.60 (m, 4H), 1.49 (s, 3H), 1.33 (s, 3H).

^13C NMR (75 MHz, CDCl₃): 167.4, 144.1, 136.6, 129.6, 128.4, 127.9, 115.8, 114.2, 105.2, 83.1, 79.6, 66.4, 67.0, 66.8, 57.4, 55.3, 46.8, 43.0, 29.1, 26.7, 26.3, 23.8.

ESI-MS: m/z 446 [M+H]^+

[^25]D: -42.8 (c 0.25, CHCl₃)

Pd/C (0.20 g) was added to a solution of amide 39 (0.70 g, 1.5 mmol) in methanol and the resulting suspension was stirred under H₂ atmosphere for 12 h. The reaction mass was filtered through a pad of celite and washed with ethyl acetate. The filtrate was concentrated under reduced pressure to afford 22 (0.54 g, 84 %)

^1H NMR (300 MHz, CDCl₃): 7.54 (s, 1H) 5.96 (d, J = 3.4 Hz, 1H), 4.64 (d, J = 3.4 Hz, 1H), 4.36 (d, J = 3.4 Hz, 1H), 3.74 (d, J = 3.4 Hz, 1H), 3.60-3.35 (m, 5H), 3.23-2.91 (m, 3H), 1.98-1.66 (m, 3H), 1.51-1.38 (m, 4H), 1.30 (s, 3H).

^13C NMR (75 MHz, CDCl₃): 169.9, 112.0, 105.0, 85.6, 81.2, 58.8, 51.2, 44.8, 40.5, 27.9, 26.7, 26.1, 23.8.
ESI-MS : m/z 286 [M+H]^+
[α]_D^{25} : -33.2 (c 1.4, CHCl_3)

(3aR,5S,6R,6aR)-6-(benzyloxy)-2,2-dimethyl-N-((S)-pyrrolidin-2-ylmethyl)
tetrahydrofuro[2,3-d][1,3]dioxole-5-carboxamide (40)

To a stirred solution of acid 38 (0.49 g, 2.13 mmol) in CH_2Cl_2 (10 mL) were added EDC.HCl (0.5 g, 2.6 mmol) and HOBt (0.35 g, 2.6 mmol) at 0 °C and stirred for 15 min. A solution of amine 28 (0.63 g, 2.13 mmol) in CH_2Cl_2 was added and stirred at room temperature for 10 h. Water (25 mL) was added to the reaction mixture and stirred. The layers were separated and the organic layer was washed with water (2 x 25 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by silicagel column chromatography (hexane:ethyl acetate-1:1) to give the amide 40 (0.84 g, 77%).

^1^H NMR (300 MHz, CDCl_3) : 7.38-7.18 (m, 10H), 6.01 (d, J = 2.6 Hz, 1H), 5.23-5.0 (m, 2H), 4.76-4.67 (m, 1H), 4.61-4.51 (m, 3H), 4.35-4.28 (m, 1H), 3.93-3.81 (m, 1H), 3.55-3.24 (m, 4H), 1.93-1.61 (m, 4H), 1.44 (s, 3H), 1.28 (s, 3H).

^1^3^C NMR (75 MHz, CDCl_3) : 167.4, 154.9, 136.7, 136.1, 127.9, 127.7, 127.3, 127.2, 127.0, 118.8, 104.9, 81.6, 80.5, 72.2, 66.2, 56.9, 46.2, 41.5, 28.1, 26.4, 25.7, 23.1

ESI-MS : m/z 511 [M+H]^+
[α]_D^{25} : -31.6 (c 0.196, CHCl_3)

(3aR,5S,6R,6aR)-6-hydroxy-2,2-dimethyl-N-((S)-pyrrolidin-2-ylmethyl) tetrahydrofuro[2,3-d][1,3]dioxole-5-carboxamide (23)
To a stirred solution of amide 40 (0.80 g, 1.57 mmol) in methanol Pd/C (0.20 g) was added and the resulting suspension was stirred under H₂ atmosphere for 15 h. The reaction mass was filtered through a pad of celite and washed with ethyl acetate. The filtrate was concentrated under reduced pressure to afford 23 (0.37 g, 83%)

\[
{\text{H NMR (300 MHz, CDCl}_3{)}}: 7.38-7.18 \text{ (m, 10H)}, 6.01 \text{ (d, } J = \text{ 2.6 Hz, 1H)}, 5.23-5.0 \text{ (m, 2H), 4.76-4.67 \text{ (m, 1H), 4.61-4.51 \text{ (m, 3H), 3.93-3.81 \text{ (m, 3H), 3.55-3.24 \text{ (m, 4H), 1.93-1.61 \text{ (m, 4H), 1.44 \text{ (s, 3H), 1.28 \text{ (s, 3H)}}}}}}
\]

\[
{\text{C NMR (75 MHz, CDCl}_3{)}}: 169.5, 112.4, 105.9, 84.6, 82.0, 75.4, 57.6, 45.5, 41.6, 28.2, 26.9, 26.3, 24.5
\]

ESI-MS: \(m/z 287 \text{ [M+H]+}}

HRMS: Calcd for C₁₃H₂₃N₂O₅[M+H]+: 287.1606 found: 287.1607

\(\lbrack \alpha\rbrack_{D}^{25}: -33.2 \text{ (c 1.1, CHCl}_3{)}}

**Examples**

(S)-2-((R)-2-Nitro-1-phenylethyl)cyclohexanone (26a)

![Chemical Structure](attachment:image.png)

\[
\text{Mp}: 131-133 \degree C
\]

\[
{\text{H NMR (400 MHz, CDCl}_3{)}}: \delta 7.34-7.14 \text{ (m, 3H), 7.18-7.14 \text{ (m, 2H), 4.93 \text{ (dd, } J = \text{ 12.8, 4.9 Hz, 1H), 4.43 \text{ (dd, } J = \text{ 11.8, 9.8 Hz, 1H), 3.76 \text{ (dt, 1H, } J = \text{ 9.8, 4.9 Hz), 2.72-2.65 \text{ (m, 1H), 2.51-2.44 \text{ (m, 1H), 2.42-2.34 \text{ (m, 1H), 2.13-2.01 \text{ (m, 1H), 1.83-1.50 \text{ (m, 4H), 1.38-1.18 \text{ (m, 1H)}}}}}}}}
\]

ESI-MS: \(m/z 270 \text{ [M+Na]+}}

\(\lbrack \alpha\rbrack_{D}^{25}: -22.5 \text{ (c 0.4, CHCl}_3{)}}

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Chapter III

HPLC: chiral pak-IA column, 210 nm, hexane/isopropanol = 9:1, 1 mL/min, Rt = 18.5 (minor), 22.08 (major), 91% ee, syn/anti = 98/2.

\[(S)-2-((R)-2-Nitro-1-(3-nitrophenyl)ethyl)cyclohexanone (26b)\]

\[
\text{ESI-MS} \quad : 315 [M+Na]^+ \\
[\alpha]^{25}_D \quad : -19.4 (c 0.5, CHCl_3)
\]

HPLC: chiral pak-IC column, 210 nm, hexane/isopropanol = 9:1, 1 mL/min, Rt = 19.7 (minor), 21.7 (major), 89% ee, syn/anti = 96/4.

\[(S)-2-((R)-1-(4-Chlorophenyl)-2-nitroethyl)cyclohexanone (26c)\]

\[
\text{ESI-MS} \quad : 304 [M+Na]^+ \\
[\alpha]^{25}_D \quad : -21.2 (c 0.82, CHCl_3)
\]

HPLC: CPAK-IC column 210 nm, hexane/isopropanol = 9:1, 1 mL/min, Rt = 7.15 (minor), 8.59 (major), 87% ee, syn/anti = 99:1
(S)-2-((R)-1-(5-Chloro-2-nitrophenyl)-2-nitroethyl)cyclohexanone (26d)

\[ \text{1H NMR (300 MHz, CDCl}_3 \text{): } 8.21-8.14 (m, 1H), 8.09 (dd, } J = 8.7, 2.9 \text{ Hz, 1H}), 7.60 (dd, } J = 8.7, 3.6 \text{ Hz, 1H}), 4.96-4.88 (m, 2H), 4.45-4.29 (m, 2H), 2.97-2.78 (m, 2H), 2.58-2.27 (m, 2H), 2.25 - 2.07 (m, 1H), 1.92-1.58 (m, 4H), 1.53-1.34 (m, 1H).
\]

ESI-MS: 349 [M+Na]\^+;

\[ [\alpha]_{D}^{25} = -5.2 \text{ (c 0.6, CHCl}_3 \text{)} \]

HPLC: CPAK-IC column 210 nm, hexane/isopropanol = 8:2, 1 mL/min, Rt = 14.8 (minor), 15.9 (major), 68 % ee, syn/anti = 93:7

(S)-2-((R)-1-(4-Methoxyphenyl)-2-nitroethyl)cyclohexanone (26e)

\[ \text{1H NMR (300 MHz, CDCl}_3 \text{): } \delta \ 7.08 \text{ (d, } J = 9.0 \text{ Hz, 2H}), 7.00 \text{ (d, } J = 9.0 \text{ Hz, 2H), 4.83 (dd, } J = 12.1, 4.5 \text{ Hz, 1H}), 4.57 \text{ (dd, } J = 12.0, 9.8 \text{ Hz, 1H}), 3.77 \text{ (s, 3H), 3.65 (dt, } J = 14.3, 9.8, 4.5 \text{ Hz, 1H), 2.69-2.58 (m, 1H), 2.51 -2.30 (m, 2H), 2.12-2.02 (m, 1H), 1.83-1.49 (m, 4H), 1.32-1.15 (m, 1H) }
\]

ESI-MS: m/z 300 [M+Na]\^+;

\[ [\alpha]_{D}^{25} = -19.7 \text{ (c 0.5, CHCl}_3 \text{)} \]

HPLC: CPAK-IC column 210 nm, hexane/isopropanol = 9:1, 1 mL/min, Rt = 10.5 (minor), 12.48 (major), 79% ee, syn/anti = 93:7
(S)-2-((R)-1-(2,5-Dimethoxyphenyl)-2-nitroethyl) cyclo-hexanone (26f)

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 6.77-6.67 (m, 2H), 6.61 (d, $J = 3.0$ Hz, 1H), 4.77 (d, $J = 2.2$ Hz, 1H), 4.75 (s, 1H), 3.90-3.83 (m, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 2.97-2.86 (m, 1H), 2.50-2.30 (m, 2H), 2.12-2.03 (m, 1H), 1.84-1.52 (m, 4H), 1.28-1.19 (m, 1H).

ESI-MS : $m/z$ 330 [M+Na]$^+$

$[\alpha]^{25}_D$ : -20.5 (c 0.6, CHCl$_3$)

HPLC : CPAK-IC column 210 nm, hexane/isopropanol = 9:1, 1 mL/min, Rt = 18.2 (minor), 19.5 (minor), 79% ee, syn/anti =94:6

(S)-2-((R)-1-(Furan-3-yl)-2-nitroethyl)cyclohexanone (26g)

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 7.36 (s, 1H), 7.28 (s, 1H), 6.24 (s, 1H), 4.74 (dd, $J = 13.0$, 6.0 Hz, 1H), 4.56 (dd, $J = 12.0$ 9.0 Hz, 1H), 3.78 (dt, $J = 8.0$ 5.0 Hz, 1H), 2.63-2.55 (m, 1H), 2.47-2.41 (m, 1H, 2.12-2.04 (m, 1H), 1.99-1.92 (m, 1H), 1.88-1.81 (m, 1H), 1.69-1.58 (m, 2H), 1.35-1.25 (m, 1H).

ESI-MS : $m/z$ 260 [M+Na]$^+$

$[\alpha]^{25}_D$ : -12.5 (c 0.5, CHCl$_3$)

HPLC : CPAK-IC column 210 nm, hexane/isopropanol = 80:20, 1 mL/min, Rt = 21.02 (minor), 26.8 (minor), 93% ee, syn/anti = 97:3
(S)-2-((R)-2-Nitro-1-(thiophen-3-yl)ethyl)cyclohexanone (26h)

\[
\text{\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) : } 7.35-7.31 (m, 1H), 6.28 (dd, J = 3.2, 1.8 Hz, 1H), 6.19-6.15 (m, 1H), 4.78 (dd, J = 12.4, 4.9 Hz, 1H), 4.66 (dd, J = 12.4, 9.2 Hz, 1H), 3.96 (dt, J = 9.06, 4.9 Hz, 1H), 2.81-2.68 (m, 1H), 2.51-2.28 (m, 2H), 2.17-2.0 (m, 1H), 1.91-1.55 (m, 4H), 1.35-1.20 (m, 1H).
\]

ESI-MS : m/z 296 [M+Na]\textsuperscript{+}

\([\alpha]\textsubscript{D}^{25} : -21.1 (c = 0.5, CHCl\textsubscript{3})\]

HPLC: chiral pak-IC column, 210 nm, hexane/isopropanol = 90:10, 1 mL/min, Rt = 8.2 (major), 9.9 (minor), 85% ee, syn/anti = 97/3.

(S)-2-((R)-2-Nitro-1-phenylethyl)cyclopentanone (26i)

\[
\text{\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) : } 7.35-7.27 (m, 3H), 7.19-7.14 (m, 2H), 5.33 (d, J = 12.8, 5.3 Hz, 1H), 4.71 (dd, J = 12.8, 9.8 Hz, 1H), 3.69 (dt, J = 9.8, 5.2 Hz, 1H), 2.44-2.29 (m, 2H), 2.20-2.06 (m, 1H), 1.98-1.82 (m, 2H), 1.78-1.65 (m 1H), 1.55-1.41 (m, 1H).
\]

ESI-MS : m/z 256 [M+Na]\textsuperscript{+}

\([\alpha]\textsubscript{D}^{25} : -25.8 (c = 0.52, CHCl\textsubscript{3})\]

HPLC: chiral pak-IC column, 210 nm, hexane/isopropanol = 9:1, 1 mL/min, Rt = 16.87 (minor), 21.42 (major), 79% ee, syn/anti = 93:7
(R)-5-Nitro-4-phenylpentan-2-one (26j)

\[
\begin{align*}
\text{1H NMR (300 MHz, CDCl}_3\text{)} & : 7.38-7.19 (m, 5H), 4.70 (dd, J = 12.1, 6.7 Hz, 1H), 4.60 (dd, J = 12.1, 7.5 Hz, 1H), 4.01 (dd, J = 12.7, 7.5 Hz), 2.92 (d, J = 6.7 Hz, 2H), 2.12 (s, 3H). \\
\text{ESI-MS} & : m/z 208 [M+H]^+ \\
\text{[α]}_{D}^{25} & : -1.8 (c = 0.6, CHCl}_3\text{)} \\
\text{HPLC: CPAK-IC column, 268 nm, hexane/isopropanol = 9:1, 1 mL/min, Rt = 16.8 (minor), 21.4 (major), 57% ee.}
\end{align*}
\]