CHAPTER-I

Organocatalytic asymmetric aldol reaction (OCAAR) in the synthesis of natural products
1.1. INTRODUCTION

The synthesis of potential therapeutics containing molecular complexity has become a challenge for synthetic organic chemists for the treatment of new and existing diseases. Molecules containing chiral centers are better drug candidates compared to racemic ones as unwanted isomer need not be administrated. Synthesis of enantiomerically pure compounds by conventional methods has been a great challenge in the field of organic synthesis. New enantioselective methods were needed to meet this challenge.\textsuperscript{1-8} In asymmetric catalysis a chiral catalyst selectively accelerates a reaction that leads to a single mirror-image isomer (one enantiomer). Along with well known transition metal catalysts and enzymes, in recent years organic catalysts are emerging as a new class of powerful asymmetric catalysts. According to List \textit{et al.} organocatalysis could be considered as a third pillar of asymmetric synthesis (\textbf{Fig. 1}).\textsuperscript{6-8}

![Fig. 1](image_url)

Most of the biological molecules are chiral and are synthesized in living cells by enzymes using asymmetric catalysis. Chemists have used enzymes or even whole cells to synthesize chiral compounds and for a long time, the perfect enantioselectivities often observed in enzymatic reactions, were considered beyond reach for non-biological catalysts. Such biological catalysis is increasingly used on an industrial scale and is particularly favored for hydrolytic reactions. Nature’s aldolases use combinations of acids
and bases, in their active sites, to accomplish direct asymmetric aldolization of unmodified carbonyl compounds. Direct asymmetric aldol reactions catalyzed by metal complexes were reported by Shibasaki et al.\textsuperscript{9} and Trost et al.\textsuperscript{10}

The use of asymmetric metal complexes as catalysts for a wide variety of processes to synthesize chiral molecules has been revolutionized over past 20 years.\textsuperscript{2} Asymmetric hydrogenation has been shown to have tremendous applications in asymmetric synthesis for synthesizing chiral molecules. But such processes are invaluable to the pharmaceutical industry, as they require specific expertise and equipment that are not always available. Possibly they leave toxic traces of heavy metals in the product. Enantioselective catalysis needs to be efficient, facile, reliable and economic if it is to be used widely in pharmaceutical synthesis. Over the past five years, the field of enantioselective organocatalysis has had a significant impact in chemical synthesis.\textsuperscript{6-8} It has developed into a practical synthetic tool since its origination over 30 years ago. Complementary to conventional metal catalysis, it offers a mild, practical and generally simple method of making small, functionalized molecules with high enantiopurity and therefore, has great potential in drug discovery chemistry. Synthesizing enantiopure compounds by resolution methods has their own drawbacks such as wastage of time in synthesizing the racemic compound first and losing half of it. Organocatalysis is an emerging area in asymmetric synthesis.\textsuperscript{11} There are usually fewer toxicity issues associated with organocatalysis due to avoidance of metals, although little is known about the toxicity of many organic catalysts.

**Mechanism of the proline-catalyzed aldol reaction.**

Studies have shown that both the pyrrolidine ring and the carboxylate in L-proline are essential for effective catalysis to occur. An enamine catalysis mechanism was initially proposed (Scheme 1)\textsuperscript{12} involving carbinolamine (I and VI), iminium ion (II and V) and enamine (III) intermediates. The carboxylic acid was proposed to act as a general Brønsted cocatalyst. In the transition state of the carbon-carbon bond formation (IV), protonation of the acceptor carbonyl group occurs by the carboxylic acid, which is anti with respect to the E-enamine double bond. In this context, proline not only acts as an
enamine catalyst but also brings along its own Brønsted acid cocatalyst and therefore can be regarded as a “bifunctional catalyst”.

Scheme 1

Synthetic chemists have used many of the organocatalytic transformations used for the synthesis of natural products.\textsuperscript{13-14} MacMillan’s neologism “organocatalysis” has become the catchword for this field of research at present. We limit this chapter to syntheses which involve the organo catalytic aldol reaction catalyzed by proline and its derivatives.
1.2. APPLICATIONS IN TOTAL SYNTHESIS

Reactions which form carbon-carbon bonds along with the generation of asymmetric carbons are very important in total synthesis of natural products. Aldol reaction is one of the classic examples that offer more disconnection points in retrosynthesis. One of the requirements of modern synthetic methods is receiving chiral products in their enantiomerically or diastereomerically pure. This requirement is not only important for synthetic chemistry but is also an imperative for nature. The aldol reaction fits in easily with nature's chemistry. A great number of enzymatic transformations are based on the aldol addition. This fact has been known for a long time and was best expressed with the following statement by J. W. Cornforth:

“Nature, it seems, is an organic chemist having some predilection for aldol condensation.”

Asymmetric versions of this reaction have been most effectively performed using chiral auxiliaries for a long time. Metal catalysis offers many asymmetric methodologies but the application of such routes to total synthesis is often hampered by catalyst accessibility. By contrast, many organocatalysts, such as proline, are readily available in both enantiomeric forms. This saves two synthetic steps (auxiliary attachment and cleavage) and renders the enamine aldol reaction a highly attractive transformation for total synthesis. Exciting progress being made in organocatalytic aldol additions is of particular interest. This highly active topic of research will continue to develop an increasing number of new concepts of configuration-control in future. In the field of catalytic and enantioselective aldol additions the area of organocatalysed aldol addition has shown the highest rates of increase over the last 10 years. Hence organocatalytic methods are being developed at a very rapid pace. Aldol additions and condensations of aldehydes and ketones in the presence of amines have been known for a long time. But the full potential of their synthetic utility, especially with regard to stereoselective and catalytic execution has been discovered systematically over the last 10 years.

1.2.1. Intramolecular aldol reactions

The use of proline in the enantioselective intramolecular aldol reaction (Robinson-type annulation) was a crucial event in the history of organocatalytic processes, with it
being one of the first examples where the potential of enantioselective reactions for the synthesis of natural products, even at large scale was demonstrated.

A synthesis of dione 4 (Hajos-Parrish ketone) using simple amino acid proline as catalyst was independently reported by Hajos and Parrish at Hoffmann La Roche\textsuperscript{21} and Eder, Sauer and Wiechert at Schering\textsuperscript{22} early in 1970’s which was the starting point of organocatalysis. This is a 6-(enolendo)- exo-trig Robinson annulation. Using 30 mol% of proline the intramolecular cyclization of triketone 2 resulted in β- hydroxy diketone 3 which upon dehydration gave enone 4 (H-P ketone). The same sequence was applied for the synthesis of Wieland-Miescher ketone 7 (W-M ketone) starting from triketone 5, (Scheme 2)

Scheme 2

Dione 7 (W-M Ketone) is an important chiral synthon for the synthesis of cortisone 8. H-P and W-M ketones were utilized in the total synthesis of complex molecules such as TAXOL\textsuperscript{®} and cortistatin A, and also of many natural products, especially terpenoids and steroids.\textsuperscript{23} Danishefsky has utilized W-M ketone 7 as a precursor to achieve the total synthesis of TAXOL\textsuperscript{®}.\textsuperscript{23a} Recently, Shair \textit{et al.} accomplished the synthesis of cortistatin A 10 starting from H-P ketone 4 (Fig. 2)\textsuperscript{23g}. 
Synthesis of cocaine:

Cocaine 15 is a tropane alkaloid obtained from the leaves of the coca plant. It is a serotonin norepinephrine–dopamine reuptake inhibitor, which mediates functionality of these neurotransmitters as an exogenous catecholamine transporter ligand. Pearson and Mans utilized the intramolecular enolexo aldolization that was first developed by List et al. in 2003 for the synthesis of cocaine. Desymmetrization of the meso dialdehyde 11 using (S) proline resulted in 12 which can be further transformed into natural cocaine in five steps.

Reagents and conditions: (i) NaOCl; (ii) CH$_3$N$_2$ (76% over two steps); (iii) (PhCO)$_2$O, DMAP, 60%; (iv) TFA; (v) CH$_2$O, NaBH$_3$CN, (74% over two steps).
The products of aldol reaction were unstable, thus a 1:1 mixture of crude aldol products $12_{\text{ax/eq}}$ were immediately converted to the corresponding methyl esters $13_{\text{ax/eq}}$ via oxidation to the acid followed by esterification to provide $\beta$-hydroxy esters. Benzylation of alcohol with benzoic anhydride and DMAP provided separable benzoates, which on Boc deprotection with TFA gave amine 14. Reductive amination of 14 resulted in cocaine 15 (Scheme 3).

**Synthesis of (−)-CP 55940**

(−)-CP 55940 23 is a cannabinoid receptor agonist and was created by Pfizer in 1974 but was never marketed. It is currently used to study the endocannabinoid system. Iwabuchi *et al.* developed desymmetrization of $\sigma$-symmetric 4-substituted cyclohexanones and successfully applied this methodology in the total synthesis of (−)-CP 55940 23 and (+)-juvabione 28. The intramolecular aldolization of keto aldehyde 16 with 25 mol% of the silylated hydroxyproline 17 as catalyst, gave the desired bicyclic product 18 in 68% yield and with 94% ee. The enantiomeric excess was increased up to 99% by recrystallization of the product. Hydroxy group of 18 was protected as MOM ether, followed by dehydrogenation with IBX, resulting in the unsaturated ketone 19.

**Scheme 4**

**Reagents and conditions:** (i) MOMCl, DIPEA, CH$_2$Cl$_2$, quantitative; (ii) IBX, DMSO, toluene, 55–75 °C, 80%; (iii) CuBr·SMe$_2$, HMPA, TMSCl, then TBAF, 85%; (iv) 0.1 equiv TsOH, OHCH$_2$CH$_2$OH, xylene, reflux, 80%; (v) TESOTf, 2.6 lutidine, CH$_2$Cl$_2$, 0 °C, H$_2$O (vi) NaBH$_4$, MeOH, 75% (over two steps) (vii) 10% HCl, THF; (viii) LiAlH$_4$, THF; 72% (over two steps); (ix) PrSLi, HMPA, 90%;
A suitable cuprate addition furnished the carbon skeleton of the target compound 21. Retro-aldol reaction with concomitant acetalization of the two carbonyl functions afforded bis-acetal. Deprotection of primary acetal with TESOTf followed by reduction gave compound 22. The ketal was deprotected using 10%HCl and reduction of the resulting ketone afforded alcohol. Finally the cleavage of the methyl ether gave (−)-CP 55940 23 (Scheme 4).

**Synthesis of (+)-juvabione**

(+)-Juvabione, 28 a natural sesquiterpene exhibiting insect juvenile hormone activity has been synthesized from the same chiral synthon 19 obtained from desymmetrization strategy. Other key step involved in the synthesis is Norrish I-type fragmentation. Enone 19 was treated with Me2CuLi to give the 1, 4-adduct. The deprotection of MOM ether with LiBF4 and reprotction with TESCl gave 24, which upon photochemical conditions resulted in aldehyde 25. Isobutyl side chain of juvabione was introduced using Grignard reagent–CeCl3 system to give the secondary alcohol. This upon BOM protection, TBAF-mediated removal of the TES group and MnO2 oxidation, afforded the enone 26.

**Reagents and conditions:** (i) MeLi, Cul, THF, -40 °C, 1.5 h, 98%; (ii) LiBF4, 1,4-dioxane, H2O, 50–70 °C, 7 h, 83%; (iii) TESCl, imidazole, DMF, rt, 12 h, 91%; (iv) hv (300 nm), MeOH, rt, 1.5 h, 66%; (v) i-BuMgBr, CeCl3, THF, 0 °C, 2 h, 81%; (vi) BOMCl, i-Pr2NEt, TBAI, THF, rt, 47 h; (vii) TBAF, THF, rt, overnight; (viii) MnO2, CH2Cl2, rt, 12 h, 92%(over three steps); (ix) (methoxymethyl)triphenylphosphonium chloride, n-BuLi, THF, -30 °C, 2 h; (x) 10% aq. HCl, THF, rt, 2 days, 64% (over two steps); (xi) Dess–Martin periodinane, CH2Cl2, rt, 1 h or cat. 1-Me-AZADO, BAIB, CH2Cl2, rt, 7.5 h, 85%; (xii) NaCN, MnO2, AcOH, MeOH, rt, 24 h, 78%.

**Scheme 5**
A Wittig reaction using (methoxymethyl)triphenylphosphonium chloride and n-BuLi gave the methyl dienol ether, which was immediately treated with aqueous 10% HCl to give the corresponding hydroxy-α, β-unsaturated aldehyde 27. Oxidation of resultant secondary alcohol 27 was carried out with Dess–Martin periodinane to give penultimate ketone, which was subjected to NaCN, MnO₂ and AcOH in MeOH at ambient temperature to give (+) - juvabione 28 (Scheme 5).

**Total Synthesis of (+)-przewalskin B**

Zhang and Tu reported the total synthesis of przewalskin B 34, which was isolated from a chinese medicinal plant Salvia przewalskii, is a novel diterpenoid and exhibits modest anti-HIV-1 activity (EC₅₀ = 30 μg/mL). Iodoallylic phosphate 29 was treated with an organocuprate generated *insitu* from Grignard reagent 30 in the presence of CuCN to give 31. Iodide 31 was lithiated using t-BuLi reacted with DMF to install a formyl group on the A-ring system, gave dioxolane, which was treated with formic acid afforded dialdehyde 32 which precursor of intramolecular aldol reaction. Dialdehyde 32 in presence of 0.1 equivalent of L-prolinamide in NMP resulted in the formation of aldol adduct, which was quickly converted to its MOM ether 33 without purification, to avoid dehydration of the β-hydroxyaldehyde (Scheme 6). Which was further used in the total synthesis of przewalskin B 34.

![Scheme 6](image_url)

**Reagents and conditions:**

(i) CuCN, -40 °C- 0 °C, 90%; (ii) t-BuLi, DMF (8.0 equiv), -78 °C, 82% (iii) HCOOH (88% aq), THF, 50 °C, 70%; (iv) L- Prolinamide (10 mol%), NMP, r.t ; v) MOMCl, 1-Pr₂Et, CH₂Cl₂, 0 °C to r.t,(over two steps) 78%.
1.2.2. Intermolecular aldol reactions

In early 2000’s it was found that proline also catalyzes intermolecular aldolizations. Thereafter, the aldol reaction has been extended to other substrate combinations (Aldehyde to aldehyde, aldehyde to ketone, and ketone to ketone). One of the side reaction in the addition of ketone to an aldehyde is self aldolization of the aldehyde or a ketone under enamine catalysis. The later one is uncommon side reaction. If the aldehyde component is non enolizable or α-substituted there is no choice of self aldolization. Usually the reactions using enolizable aldehydes are performed with an excess of ketone or by slow addition of the aldehyde to minimize the self aldol reaction. Few of the important syntheses of natural products which involve intermolecular aldol reactions are discussed below.

1.2.2.1. Aldehyde ketone coupling

**Synthesis of (S)-(−)-3-Butylphthalide**

Chiral 3-substituted phthalides are widely distributed in a large collection of natural products with broad, potent and potentially path-pointing biological activities. 3-Butylphthalide 37, a component in the Chinese folk medicine extracted from celery seed oil, is in phase II clinical trials in China and potentially can be used for the treatment of stroke. Wang et al. devised an unprecedented organocatalytic asymmetric aldol-lactonization reaction of 2-formylbenzoic esters with ketones/aldehydes for convenient construction of the enantio enrich “privileged” scaffold. The aldol reaction was optimized with catalyst L-prolinamide derivative 38 with an acid additive PhCO₂H. Significantly only 2.5 mol % 38 was found to enhance reaction efficiency. Thus aldehyde 35 on treatment with butanone under mentioned conditions and subsequent lactonization with K₂CO₃ gave chiral lactone 36.

![Scheme 7](image_url)

**Reagents and conditions:** (i) Butanone, 38 (2.5 mol%), PhCOOH (2.5mol%), -40 °C; (ii) K₂CO₃, 72%, 96% ee; (iii) HSCH₂CH₂SH, TiCl₄, CHCl₃, r.t, 12h; (iv) Raney-Ni, EtOH, reflux, 4h, 66% (over two steps)
The keto functionality was converted to its thio ketal using ethane dithiol in presence of \( TiCl_4 \). Finally using Raney nickel, desulfurization thioketal provided the target phthalide 37 (Scheme 7).

**Synthesis of (S)-ipsenol**

List et al.\(^{30}\) reported a short synthesis of the bark beetle pheromone (S)-ipsenol 44 which is used in insect traps and needed in kilogram quantities. The key \( \beta \)- hydroxyl ketone 41 was prepared by the addition of acetone to aldehyde 39, the formation of the elimination product 40 reduced the yield of the reaction. However, operationally simple access to enantiomerically enriched intermediate 41 from readily available starting materials acetone and 39 makes this approach highly attractive. Despite the rather modest yields typically obtained under the reaction conditions, can easily be scaled up to generate useful quantities for natural product synthesis. Compound 41 was protected as its TBS ether 42. Under Stille coupling conditions methyl ketone was converted to diene 43. Finally deprotection of the TBS group afforded (S)-ipsenol 44 (Scheme 8).

**Scheme 8**

**Synthesis of D-arabino-phytosphingosine**

Phytosphingosines, one of the major classes of sphingoids, have been isolated from various sources like plants, marine organisms, fungi etc. Sphingoids are long-chain amino-diol and -triol bases that form the backbone and characteristic structural unit of sphingolipids, which are important membrane constituents and play vital roles in cell regulation as well as signal transduction. Enders et al.\(^{31}\) reported a flexible organocatalytic approach to sphingoids synthesis which is demonstrated with efficient asymmetric
synthesis of \( D \)-arabino- (50) and \( L \)-ribo-phytosphingosine (53). Thus under optimized conditions dioxalone 45 was reacted with aldehyde 46 with 30mol% of the proline giving the \textit{anti} product 47 in 60% yield. Selectivity in the reductive amination of 47 was comparatively less. So the hydroxyl group was protected as TBS ether 48 using TBSOTf and 2, 6- lutidine. Then deprotection of TBS with TBAF and acetonide with TFA gave triol 49. Finally the deprotection of benzyl group afforded \( D \)-arabino- phytosphingosine 50. Ketone 48 was reduced with \( L \)-selectiride then mesylated to give 51. A nucleophilic displacement of mesyl with azide gave 52. Azide 52 was reduced to amine with LAH and in the process TBS was also deprotected to give 53 which is a protected form of \( L \)-ribo phytosphingosine (Scheme 9).

![Scheme 9](image-url)

\textbf{Reagents and conditions:} (i) TBSOTf, 2,6-lutidine, CH\(_2\)Cl\(_2\), -20 °C, 95%, de > 99%; (ii) BnNH\(_2\), NaBH\((\text{OAc})_3\), AcOH,CH\(_2\)Cl\(_2\), 2 °C, 94%, de > 99%; (iii) TBAF, THF, MgSO\(_4\), 50 °C; (iv) TFA, THF, 50 °C, 92% (two steps); (v) H\(_2\), Pd/C, MeOH, 99%; (vi) \( L \)-Selectride, THF, -78 °C, 93%, de > 99%; (vii) MsCl, DMAP, CH\(_2\)Cl\(_2\), -10 to 0 °C, 91%, de > 99%; (viii) NaN\(_3\), 18-crown-6, DMF, 100 °C, 80%, de > 99%; (ix) LAH, THF, 0 °C, 98%, de > 99%.

\textbf{Scheme 9}

\textbf{Synthesis of jaspine B} \(^{32}\)

Enders \textit{et al.} \(^{32}\) used the same sequence of reactions mentioned in Scheme 9 for the synthesis of jaspine B 55 just by changing the catalyst to \((R)\)-proline (Scheme 10). Jaspine B 55 is one of the naturally occurring anhydro phytosphingosine derivatives isolated from marine sponges, \textit{Pachastrissa sp.} and \textit{Jaspis sp.}, exhibited a significant cytotoxicity against P388, A549, HT29, and MEL28 carcinoma cell lines \textit{in vitro}. The
TBS group in compound ent-52 was deprotected using TBAF and the resulted alcohol, which was tosylated to give compound 54. Compound 54 was cyclized using amberlyst underwent deprotection of acetonide. Finally the azide was reduced using Pd/C to give the target jaspine B 55. The same authors has reported the synthesis of α-D-galactosyl ceramide KRN7000 56 in 8 simple steps from the intermediate ent-52. KRN7000 (also called AGL-582 or a-GalCer) displayed the most potent immunostimulatory and antitumor activities.33

Reagents and conditions: (i) TBSOTf, 2,6-lutidine, CH₂Cl₂, -20 °C, 95%, de > 99%; (ii) L-Selectride, THF, -78 °C, 91%, de > 99%; (iii) MsCl, DMAP, CH₂Cl₂, -10 to 0 °C, 15 h, 98%; (iv) NaN₃, 18-crown-6, DMF, 100 °C, 48 h, 79%; (v) TBAF, THF, 0 °C to r.t, 24h, 83%; (vi) TsCl, DMAP, CH₂Cl₂, 0 °C, 4h, 95%; (vii) Amberlyst 15, THF, MeOH, 24h, 76%; (viii) H₂, Pd/C, MeOH, CH₂Cl₂, r.t, 8h, 98%;

Scheme 10

Synthesis of ent-convolutamydine E 34

Hayashi et al.34 reported a short synthesis of ent-convolutamydine E 60 from dibromoisatin derivative 57 (Scheme 11). The asymmetric aldol reaction of dibromoisatin derivative 57 with acetaldehyde using 4-hydroxydiarylprolinol as a catalyst 61, resulted in the aldehyde 58, which was upon reduction with NaBH₄ gave alcohol 59. Finally the TIPS group was deprotected using ammonium fluoride in methanol to give the target compound 60.
Chapter I

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Reagents and conditions: (i) Catalyst 61 (30 mol%), ClCH\(_2\)COOH (60 mol%), 48 h; (ii) NaBH\(_4\), MeOH, 86% (over two steps), 82% ee; (iii) NH\(_4\)F, MeOH, 70 °C, 75%.

Scheme 11

1.2.2.2. Aldehyde aldehyde coupling

C1–C6 fragment of epothilones\(^{35}\)

Avery et al.\(^{35}\) reported the synthesis of C1-C6 fragment 64 of epothilones 65 which is a common intermediate in many total syntheses, using a direct aldol reaction. Acetone was treated with a pivaldehyde-like substance 62, catalyzed with \(D\)-proline, leading to a 2,6-diketoalcohol with better than 99% ee, which on intramolecular ring closure using pyrrolidine gave enone 63. Compound 63 was converted to its TBS ether, followed by oxidation of the silyl protected hydroxycyclohexenone led to the desired keto acid 64 (Scheme 12)

Reagents and conditions: (i) 0.35 equiv. \(D\)-Proline, DMSO–acetone 4:1, rt, 24 h, 75%, 99% ee (ii) 0.1 equiv. pyrrolidine, \(CH_2Cl_2\), rt, 3 h, 76% yield; (iii) TBSCl, imidazole, DMF, rt, 72 h, 81%; (iv) 0.03 equiv. RuCl\(_3\), 5.5 equiv. NaIO\(_4\), CCl\(_4\)–CH\(_2\)CN–H\(_2\)O (1:1:1.6),1 h, 67%.

Scheme 12
Synthesis of prelactone B

Prelactone B is a natural product isolated from bafilomycin-producing Streptomyces griseus representing an early metabolite in the biosynthesis of polyketide antibiotics. Pihko et al. reported remarkably short synthesis of prelactone B using organocatalysis. The MacMillan variant of the proline-catalyzed crossed-aldol reaction between isobutyraldehyde and propionaldehyde afforded the aldol product. The crude aldol product was protected as TBS ether in a mixture of Et₂O and CH₂Cl₂. The remaining stereocenter required a Felkin selective aldol reaction between an ester enolate equivalent and aldehyde. Diastereoselective Mukaiyama-type aldol reactions between aldehyde and silylenol ethers in presence of BF₃·Et₂O gave ester. Finally silyl deprotection of with aqueous HF afforded prelactone (Scheme 13).

**Synthesis of carbohydrates using organocatalysis.**

MacMillan et al. used their trademark homo aldol reaction of protected hydroxyl acetaldehyde in the synthesis of carbohydrates monosaccharides. The synthesis involves an aldol coupling of three aldehydes in two chemical steps. The first step is dimerization of α-oxyaldehydes, catalyzed by L-proline, followed by a tandem Mukaiyama aldol addition cyclization step catalyzed by a Lewis acid. Thus the homo aldol reaction of triisopropylsilyloxy acetaldehyde with 10 mol% of natural proline afforded β-hydroxyl aldehyde, which upon a Mukaiyama aldol reaction with TMS enol acetate in presence of different Lewis acids such as MgBr₂·Et₂O, TiCl₄ resulted in...
different monosaccharides. Differentially protected glucose 74, allose 76, and mannose 75 stereoisomers can each be selected, in high yield and stereochemical purity, synthesis of which can be achieved simply by changing the solvent and Lewis acid used (Scheme 14).

Reagents and conditions: (i) MgBr₂, Et₂O, Et₂O, -20-4 °C, 10:1 dr, 95% ee, 79%; (ii) MgBr₂, Et₂O, CH₂Cl₂, -20-4 °C, 19:1 dr, 95% ee, 87%; (iii) TiCl₄, CH₂Cl₂, -78 to -40 °C, 19:1 dr, 95% ee, 97%.

Scheme 14

Synthesis of glycosidic part in littoralisone

Littoralisone 77 isolated in 2001, was demonstrated to be the active agent for increased NGF-induced neurite outgrowth in PC12D cells. McMillan et al. 39 disclosed the first total synthesis, whose retro synthesis shown in Scheme 15. The sugar part was synthesized using their two step aldol strategy. 38 Thus the benzyloxy acetaldehyde 82 treated with D-Proline in DMF gave the aldehyde 83 in 78% yield and 98% ee. The β-hydroxyl aldehyde under Mukaiyama conditions with TMS enoether 86 in presence of MgBr₂ Et₂O resulted the differentially substituted glucose 84 which was protected as
benzyl ether and selective deprotection of anomeric benzyl ether and protected as TMS ether to give 85 which was used further in the total synthesis of the natural product 77.

\[
\begin{align*}
\text{Reagents and conditions: (i) D-Proline, 98%ee, 78%; (ii) 86, MgBr_2, OEt_2 ether, 10:1dr, 65%; (iii) Ag_2O, BnBr, (iv) Pd/Al_2O_3, HCO_2NH_4, (v) TMSCl, NEt_3, 80^\circ C, 62\% (three steps)}
\end{align*}
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**Scheme 15**

**Total synthesis and structural revision of callipeltoside C**\(^{40}\)

Callipeltosides C was isolated by Minale and co-workers in 1996 and 1997 from the lithistid sponge *Callipelta sp.* indigenous to the shallow waters off New Caledonia. These marine macrolides are active against human bronchopulmonary cells NSCLC-N6. McMillan *et al.*\(^{40}\) reported the total synthesis of callipeltoside C in 18 chemical steps.
and 12% overall yield using organocatalytic and organometallic technologies which gave an access to useful quantities of the natural product. The retro synthesis is shown in Scheme 16. The organocatalytic two step sugar synthesis not only helped in the total synthesis but also in the structural revision. Further a cross organocatalytic aldol reaction\textsuperscript{41} was employed in the synthesis of the pyran core of the natural product.

![Scheme 16](Image)

The sugar part of the molecule was synthesized using the McMillan’s two step carbohydrate synthesis. The triisopropylsilyloxyacetaldehyde 72 was treated with 10 mol\% of proline which gave the aldehyde 73 which on Mukaiyama reaction with TES enolether in presence of MgBr\textsubscript{2} Et\textsubscript{2}O led to carbohydrate core 92. An acid catalyzed benzyl protection of the anomeric hydroxy group and concomitant removal of the primary silyloxy protecting group was accomplished prior to selective formation of the corresponding primary phenyl thiocarbonate. Deoxygenation following the Barton–McCombie\textsuperscript{42} protocol and then Dess–Martin oxidation of the secondary alcohol provided the desired tetrahydropyranyl ketone 93. Addition of MeMgBr to 93 in presence of MgBr\textsubscript{2}·OEt\textsubscript{2} produced the desired stereoisomer 94 (Scheme 17).
Reagents and conditions: (i) D-Proline, DMF; (ii) MgBr$_2$·Et$_2$O, CH$_2$Cl$_2$; (iii) AcCl, BnOH, 110 °C; (iv) PhOCSCl, pyridine, CH$_2$Cl$_2$; (v) Bu$_3$SnH, AIBN, toluene, 120 °C; (vi) Dess–Martin periodinane, CH$_2$Cl$_2$, 0 °C; (vii) MgBr$_2$·Et$_2$O, CH$_3$MgBr, CH$_2$Cl$_2$; (viii) H$_2$, Pd/C, EtOAc; Cl$_3$CCN, Cs$_2$CO$_3$, CH$_2$Cl$_2$.

Scheme 17

A proline-catalyzed double diastereo-differentiating aldol reaction between propionaldehyde and the Roche ester-derived aldehyde 95 gave aldehyde 96. Felkin-selective chelation-controlled addition of propargyl zinc to aldehyde 96 afforded alkynyl diol 97. Semmelhack reaction was utilized to build the central heterocyclic ring of callipeltoside C by a palladium-catalyzed alkoxy carbonylation.

Reagents and conditions: (i) L-Proline (10 mol%), DMSO, +4 °C; (ii) HCCCH$_2$Br, Zn, THF; (iii) 5% [PdCl$_2$(CH$_3$CN)$_2$], $p$-benzoquinone, CO, MeOH, 0 °C; (iv) TBSCI, imidazole, DMF; (v) DDQ, CH$_2$Cl$_2$; (vi) SO$_3$·pyridine, Et$_3$N, CH$_2$Cl$_2$, DMSO

Scheme 18

Using the conditions developed by Marshall and co-workers exposure of alkynyl alcohol 97 to Pd[II] catalyst in presence of CO and MeOH did indeed furnish the highly functionalized tetrahydropyran 98. Protection of the remaining secondary hydroxy group as a tert-butylidimethylsilyl ether followed by cleavage of the PMB protecting group and
then Parikh–Doering oxidation provided the key tetrahydropyran coupling fragment 88 which was further used in the synthesis of aglycon part of callipeltoside 99 (Scheme 18).

The usefulness of the antipodes 94 ant ent-94 was demonstrated in the final coupling reaction. The coupling of the hexose 94 and the aglycone 99 was accomplished according to the glycosylation procedure of Tietze et al. Silyl deprotection of the resulting material using tris(dimethylamino)-sulfonium difluorotrimethylsilicate (TASF) provided a compound having the reported structure of callipeltoside C 87. Spectroscopic data for the macrolide 87 did not match the characterization data reported for the natural isolate. The other antipode of the sugar part ent-94 coupled to the macrocyclic core 99 followed by silyl deprotection gave the target callipeltoside C 100. 100 was identical to callipeltoside C with respect to the spectroscopic data obtained for the natural isolate (Scheme 19).

![Chemical Structure]

**Scheme 19**

Reagents and conditions: (i) TMSOTf, CH₂Cl₂; (ii) TASF, 58% for 87; 63% for 100 (over two steps)
Cordova’s complete aminoacid catalyzed carbohydrate synthesis

Cordova et al.\textsuperscript{45} reported the direct amino acid catalyzed asymmetric \textit{denovo} synthesis of hexoses with excellent chemo-, diastereo-, and enantioselectivity. Here the two aldol steps were controlled by aminoacid proline. Employment of a two-step direct catalytic synthetic protocol furnished either \textit{L-} or \textit{D-}sugars in most cases with >99\%ee. The examples shown in \textbf{Scheme 20} are the products of sugars catalyzed by \textit{L-}proline in the first step and \textit{D-}proline in the second aldol reaction. The ability of amino acids to mediate asymmetric formation of natural sugars may support a catalytic prebiotic homochirality pathway in which chiral amino acids transferred their stereochemical information to carbohydrates.

![Chemical Structure](image)

\textbf{Scheme 20}

Cordova et al.\textsuperscript{46} examined amino acids for asymmetric neogenesis of natural aldoses in organic solvents as well as under prebiotic conditions. The amino acid catalyzed, highly enantioselective \textit{de novo} syntheses of deoxy and polyketide sugars from simple aldehydes was reported (\textbf{Scheme 21}). The catalytic efficiency as well as the enantiomeric excess of the sugar derivative from amino acids tested was found to decrease in the following order: proline > hydroxyproline > alanine > valine and phenylalanine.

![Chemical Structure](image)

\textbf{Scheme 21}
It is important to underline that the yields of hexoses produced by amino acid catalysis were comparable or higher than most conventional multistep sugar synthesis.

**Synthesis of trichostatin A**

Trichostatin A 111 is a potent and specific HDAC inhibitor, which has been extensively used as a valuable biological tool for studying the functions of the enzyme and as a lead compound for developing new anti-cancer agents. Wang et al. reported a practical, enantioselective organocatalytic route to the preparation of the trichostatin A in 9 steps. Thus L-proline-catalyzed cross-aldol reaction between p-nitrobenzaldehyde 105 and propionaldehyde afforded the desired aldol adduct 106. The crude aldehyde 106 was transformed into α, β-unsaturated ester 107 by a Wittig reaction with Ph₃P=CH(CH₃)₂COOMe. An oxidation / reduction sequence using DIBAL-H followed by MnO₂ oxidation gave aldehyde 108. The aldehyde 108 underwent a Horner–Emmons reaction with triethyl phosphonoacetate to produce conjugated ester 109 which was selectively reduced to the amine by Lindlar catalyst-promoted hydrogenation.

**Scheme 22**

Reductive amination by treatment with HCHO and NaBH(OAc)₃ in THF furnished the dimethylamine 110, which was subsequently exposed to NH₂OH/MeOH
solution to provide the hydroxamic acid. Finally the benzylic hydroxy group of 110 was selectively oxidized by DDQ in dioxane without affecting the hydroxamic acid group to give the target trichostatin A 111 (Scheme 22).

Organocatalytic aldol approach to F ring of spongistatin 148

The spongistatins (altohyrtin A 117 and althohyrtin C 118) have been found to be extraordinarily effective against a variety of chemoresistant tumor types, which comprise the NCI panel of 60 human cancer cell lines. Smith et al.48 reported the total synthesis of spongistatin in which they have employed organocatalytic anti-aldol reaction in the synthesis of F ring.

Reagents and conditions: (i) 10 mol% L-proline, DMF, 4 °C; (ii) PPh₃=CHCO₂Me, C₆H₆, 94% (over two steps), (iii) AD-mix β, MeSO₂NH₂, t-BuOH·H₂O; (iv) PPTS, Tol, r.t., 94% (over two steps); v) BnBr, Ag₂O, CaSO₄, DCE, 40-60 °C, 78%; vi) (Z)-CH₂CH₂CH=CHCH₂Br 119, Mg, Et₂O; vii) Et₃SiH, BF₃·Et₂O, 89%, (over two steps); viii) SO₃·Py, DMSO, 4-PrEt₂N, 94%

Scheme 23
The cross aldol reaction of TBDPS aldehyde 112 with propanal in presence of proline gave the aldol adduct which was directly subjected a Horner–Wadsworth–Emmons reaction with methyl (triphenylphosphoranylidene)acetate to provide ester 113. Sharpless asymmetric dihydroxylation, followed by lactonization then led to lactone 114. Bis-benzylation was then followed by addition of the Grignard derived from bromide 119, reduction of the resultant lactol with Et$_3$SiH/BF$_3$Et$_2$O, the latter occurring with concomitant removal of the O-TBDPS protecting group, and Parikh–Doering oxidation to furnish aldehyde 116 (Scheme 23). The aldehyde 116 further used in the synthesis of spongistatin1.

1.2.2.3. Ketone–Ketone Coupling

Synthesis of convolutamydine A$^{49-51}$

Convolutamydines A–E were isolated from the Floridian marine bryozoan Amathia convolute. Convolutamydines A and B shows a potent inhibitory activity towards the differentiation of HL-60 human promyelocytic leukemia cells at 0.1 and 12.5 mg/mL, respectively. These indole alkaloids possess a 4, 6-dibromo-3-hydroxyoxindole core carrying different side chains at the C3 quaternary center. Convolutamydine A 121 has been independently synthesized by five different research groups using organocatalytic asymmetric aldol reactions, out of which three groups used proline based chiral amines catalysts 122-124 and dibromoisatin as starting material (Scheme 24-26). Tomasini’s approach$^{49}$:

![Scheme 24](image-url)
Xiao’s approach\(^{50}\)

\[
\begin{align*}
\text{Catalyst 123 (20 mol\%)} & \quad \text{Acetone, HOAc (40 mol\%)} \\
& \quad \text{(-15 $^\circ$C, 39h)} \\
\end{align*}
\]

\[
\begin{align*}
\text{120} & \quad \rightarrow & \quad \text{121} \\
\end{align*}
\]

\[(S)-\text{Convolutamidine}
\]

45% after R.C

87% ee after R.C

\text{ent-121}

\text{Scheme 25}

Nakamura’s approach\(^{51}\)

\[
\begin{align*}
\text{Catalyst 124 (5 mol\%)} & \quad \text{Acetone H}_2\text{O (10 equiv)} \\
& \quad \text{(-15 $^\circ$C, 9h)} \\
\end{align*}
\]

\[
\begin{align*}
\text{120} & \quad \rightarrow & \quad \text{121} \\
\end{align*}
\]

\[(R)-\text{Convolutamidine A}
\]

99% after R.C

95% ee 121

\text{Scheme 26}
1.3. REFERENCES


