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Convergent synthesis: A strategy to synthesize compounds of biological interest

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Abstract

Convergent synthesis in chemistry is an method of synthesis which mainly works with the aim of improving efficiency of multi step organic synthesis. It mainly helps in assymmetric synthesis, synthesis of natural products and synthesis of heterocyclic compunds of biological interest.In this review we attempt to bring the attention towards this method with its recent applications in synthetic organic chemistry and its future perspectives in relation to current pharmaceutical industries mainly working in relation to synthesis of biologically active nucleus.

Key words: Convergent synthesis, Organic synthesis, Total synthesis, Glycopeptide.
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Introduction

In chemistry a convergent synthesis is a strategy that aims to improve the efficiency of multi-step chemical synthesis, most often in organic synthesis. In linear synthesis the overall yield quickly drops with each reaction step:

$$A \rightarrow B \rightarrow C \rightarrow D$$
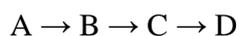
Suppose the yield is 50% for each reaction, the overall yield of D is only 12.5% from A. In a convergent synthesis

$$A \rightarrow B \ (50\%)$$
$$C \rightarrow D \ (50\%)$$
$$B + D \rightarrow E \ (25\%)$$

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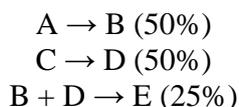
the overall yield of E (25%) looks much better. Convergent synthesis is applied in the synthesis of complex molecules and involve fragment coupling and independent synthesis.

Examples

Convergent synthesis is encountered in dendrimer synthesis [1] where branches (with the number of generations preset) are connected to the central core Proteins of up to 300 amino acids are produced by a convergent approach using chemical ligation.An example of its use in total synthesis is the final step (photochemical [2+2]cycloaddition) towards the compound Biyouyanagin A [2].
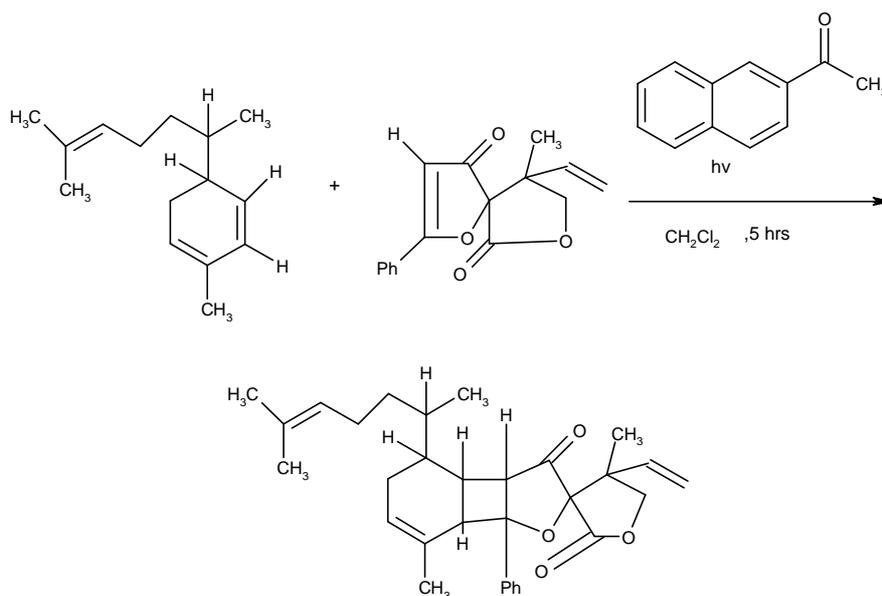
Chemical ligation

Chemical ligation is a set of techniques used for creating long peptide or protein chains. It is the second step of a convergent approach. First smaller peptides containing 30-50 amino acids are prepared by conventional chemical peptide synthesis.[3,4] They are then completely deprotected. Chemical ligation is the technique of coupling these peptides by chemoselective reaction to give a unique reaction product, usually in aqueous solution. With several coupling steps, proteins of up to 200-300 amino acids can be produced.

Methods of chemical ligation

Native chemical ligation has overcome the limitations of the classical synthetic organic chemistry approach to the total synthesis of proteins, and enables the routine total or semi-synthesis of protein molecules.Subsequently, native chemical ligation was developed. [5,6] In native chemical ligation, an unprotected peptide-thioester reacts with a Cys-peptide to give a ligation product with a native amide ('peptide') bond at the ligation site. In this method, the initial thioester-linked ligation product intermediate rearranges to form an amide bond.Native chemical ligation relies on the presence of a cysteine residue at the ligation site.

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Expressed protein ligation

By exploiting naturally occurring inteins it is possible to prepare a recombinant polypeptide C-terminal thioester. This enables the use of large recombinant protein-derived thioesters in native chemical ligation. The recombinant thioester can be ligated to a synthetic peptide bearing an N-terminal cysteine. Native chemical ligation of this kind using recombinant C-terminal thioesters is known as expressed protein ligation. Recombinant expression can also be used to give a Cys-polypeptide for use in native chemical ligation.[7,8]

Staudinger ligation [9]

The Staudinger ligation, first reported in 2000, in principle enables the ligation of peptide segments independent of the terminal amino acids.
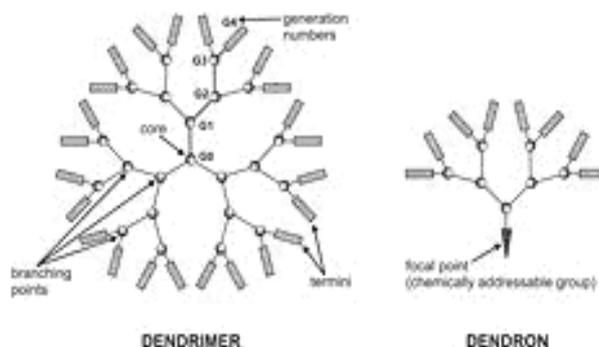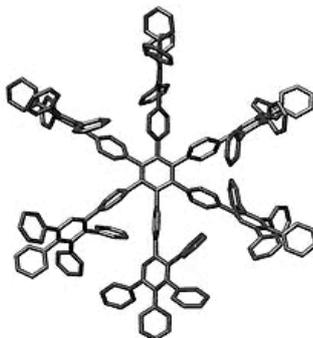
Dendrimer

Figure 1. Dendrimer and Dendron

Crystal structure of a first-generation polyphenyleneBecause of the absence of molar mass distribution, high-molar-mass dendrimers and dendrons are macromolecules but not polymers.The first dendrimers were synthesised divergently by Vögtle in 1978 [10], by Denkewalter and coworkers at Allied Corporation as polylysine dendrimers in 1981[11], by Donald Tomalia at Dow Chemical in 1983 [12] and in 1985 [13], and by Newkome in 1985 [14]. In 1990 a convergent synthesis was introduced by Fréchet [15]. Dendrimers then experienced an explosion of scientific interest because of their unique molecular architecture (Fig 1). This resulted in more than 5,000 scientific papers and patents published by the end of 2005.

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Properties and applications of dendrimers

The properties of dendrimers are dominated by the functional groups on the molecular surface, however, there are examples of dendrimers with internal functionality.[16,17,18] Recently it has been shown that redox-active nanoparticles can be synthesized,despite their isolation, some of the redox molecules (COOH in this case) remained uncoupled, and thus still reactive. If this property can be applied, dendrimers can be used for drug delivery systems (DDS) that can give medication to the affected part inside a patient's body directly.

Photonic excited molecules

It has been discovered that azobenzene is photoisomerized by very weak infrared rays when covered by a dendrimer [19]. Through the discovery of a function that catches light and conveys this energy using excitation of the molecule, attempts have recently been made to synthesize dendrimers that insert porphyrin, absorb light, and photosynthesize artificially.

Synthesis

Up to date, there are only a few companies that sell dendrimers; Polymer Factory [20] commercializes biocompatible bis-MPA dendrimers and Dendritech is the only kilogram-scale producers of PAMAM dendrimers.The original Newkome dendrimer or arborol (1985) started by nucleophilic substitution of 1-bromopentane by *triethyl sodiomethanetricarboxylate* in dimethylformamide and benzene. The ester groups were then reduced by lithium aluminium hydride to a triol in a deprotection step. Activation of the chain ends was achieved by converting the alcohol groups to tosylate groups with tosyl chloride and pyridine. The tosyl group then served as leaving groups in another reaction with the tricarboxylate, forming generation two.
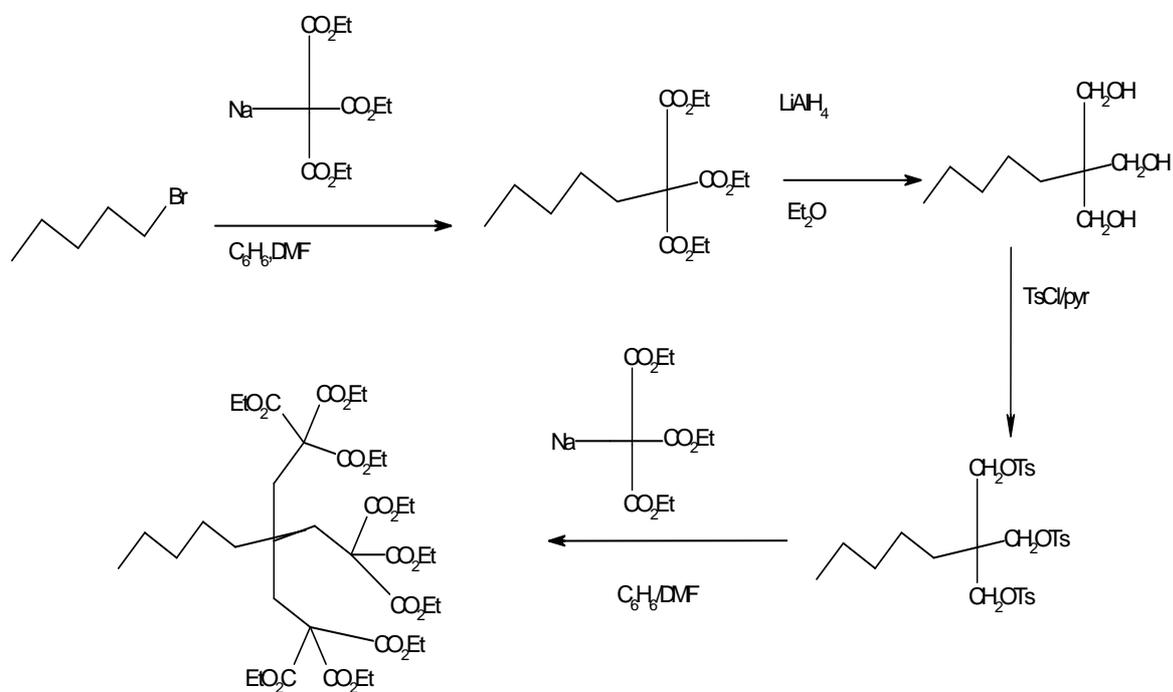
This sequence can be repeated many times.

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Click chemistry

Dendrimers have been prepared via click chemistry employing Diels-Alder reactions [21], thiol-ene reactions [22] and azide-alkyne reactions [23]. An example is the synthesis of certain polyphenylene dendrimers.
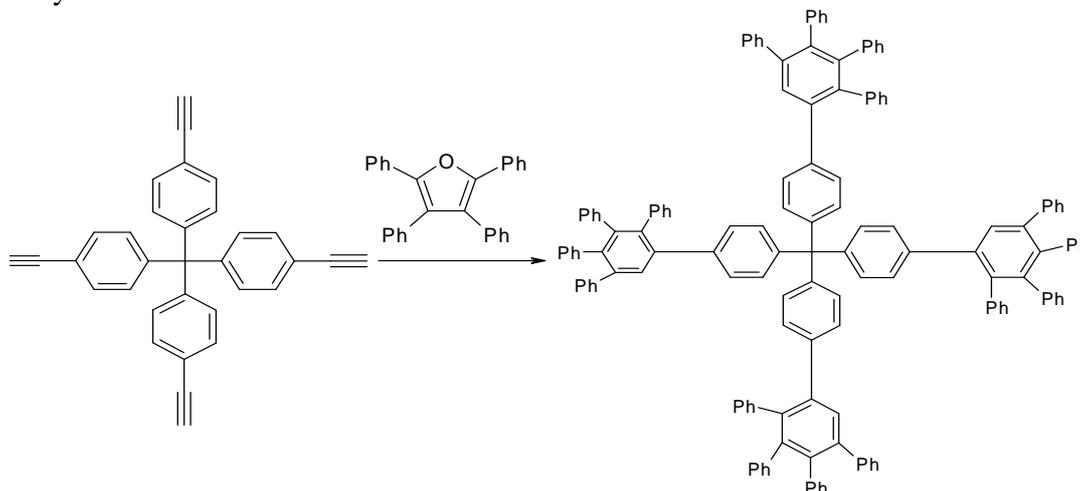
Glycal
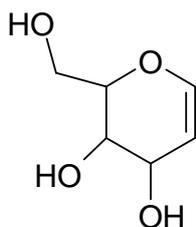
Glucal, the glycal formed from glucose. Glycal is a name for cyclic enol ether derivatives of sugars having a double bond between carbon atoms 1 and 2 of the ring. The term "glycal" should not be used for an unsaturated sugar that has a double bond in any position other than between carbon atoms 1 and 2.[24]

Synthesis of Glycals

The original Fischer glycal synthesis was the reductive elimination with zinc of a glycosyl halide. This glycosyl halide was formed from a monosaccharide starting material.Some other synthetic routes include:Ring-closing metathesis Reaction of thioglycosides with lithium napthalenide. Mesylation of the anomeric hydroxyl and formation of the anomeric palladium complex, which undergoes beta-elimination [25] A general example of each synthetic route is given below (drawn with first discussed synthesis upper right, moving clockwise).

Reactions and Uses of Glycals

The double bond of a glycal allows many other functional groups to be introduced into a monosaccharide. Glycals have many uses in synthetic carbohydrate chemistry. They are commonly used as glycosylation donors, meaning that they can react with other monosaccharides to form a longer chain of monosaccharides called an oligosaccharide. D-glucal and radiolabelled D-galactal have been used to selectively bind with amino acids in the active sites of several enzymes. These enzyme-glycal complexes allow these amino acids that are

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essential for catalysis to be identified and allow for a better understanding of how these enzymes function. [26]
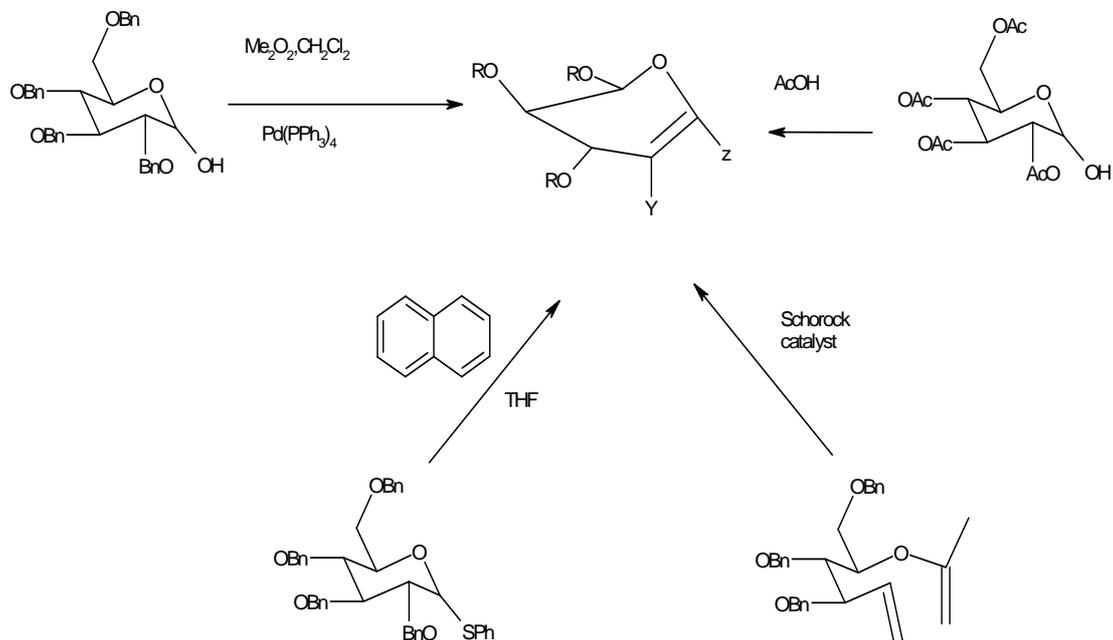
Glycopeptide

Glycopeptides are peptides that contain carbohydrate moieties (glycans) covalently attached to the side chains of the amino acid residues that constitute the peptide. Over the past few decades it has been recognised that glycans on cell surface (attached to membrane proteins or lipids) and those bound to proteins (glycoproteins) play a critical role in biology. For example these constructs have been showed to play important roles in fertilization, the immune system, brain development, the endocrine system and inflammation [27].
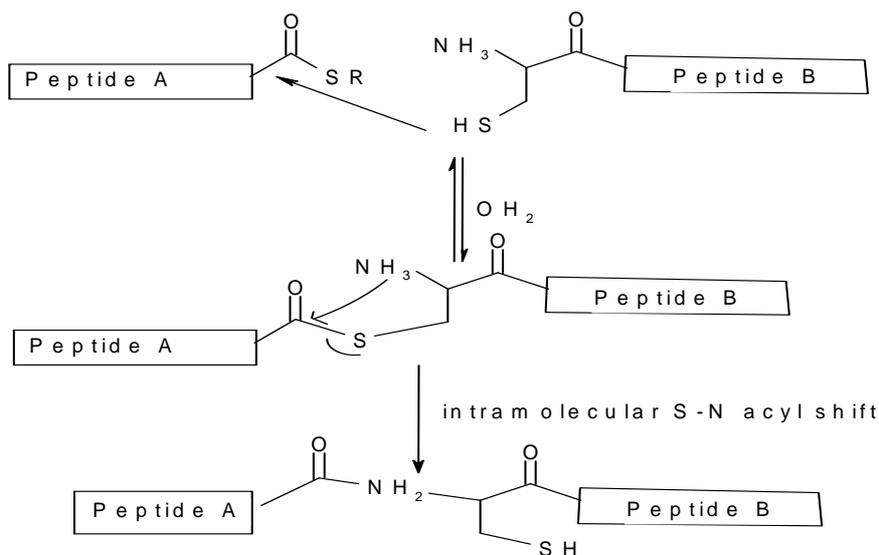
**Scheme: Mechanism of native Chemical Ligation**

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Native Chemical Ligation (NCL)

Native chemical ligation, or NCL, is a convergent synthetic strategy based on the linear coupling of glycopeptide fragments. This technique makes use of the chemoselective reaction between a N-terminal cysteine residue on one peptide fragment with a thio-ester on the C-terminus of the other peptide fragment [28] as illustrated above.

Unlike standard SPPS (which is limited to 50 amino acid residue) NCL allows the construction of large glycopeptides. However the strategy is limited by the fact that it requires a cysteine residue at N-terminus, an amino acid residue that is rare in nature.[28] However this problem has partly been address by the selective desulfurization of the cysteine residue to an alanine.[29]

Linezolid

A member of the oxazolidinone class of drugs, linezolid is active against most Gram-positive bacteria that cause disease, including streptococci, vancomycin-resistant enterococci (VRE), and methicillin-resistant *Staphylococcus aureus* (MRSA).[30] Linezolid is marketed by Pfizer under the trade names Zyvox (in the United States, United Kingdom, Australia, and several other countries), Zyvoxid (in Europe), and Zyvoxam (in Canada and Mexico). Generics are also available in India, such as Linospan (Cipla). As of 2009, it is the only marketed oxazolidinone, although others are in development. As a protein synthesis inhibitor, it stops the growth of bacteria by disrupting their production of proteins. Although many antibiotics work this way, the exact mechanism of action of linezolid appears to be unique to the oxazolidinone class. Linezolid is quite expensive, as a course of treatment can cost up to several thousand U.S. dollars; nonetheless, it appears to be more cost-effective than comparable antibiotics, mostly because of the possibility of switching from intravenous to oral administration as soon as patients are stable enough, without the need for dose adjustments.
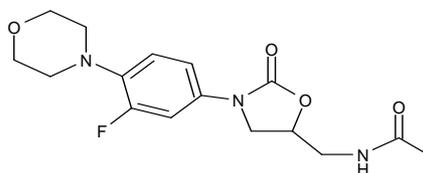

Synthesis

Linezolid is a completely synthetic drug: it does not occur in nature (unlike erythromycin and many other antibiotics) and was not developed by building upon a naturally occurring skeleton (unlike most beta-lactams, which are semisynthetic). Many approaches are available for oxazolidinone synthesis, and several routes for the synthesis of linezolid have been reported in the chemistry literature. [31] Much of the high cost of linezolid has been attributed to the expense of its synthesis. A somewhat more concise and cost-effective route better suited to large-scale production was patented by Upjohn in 1998. Later syntheses have included an "atom-economical" method starting from D-mannitol, developed by Indian pharmaceutical company Dr. Reddy's and reported in 1999, and a route starting from (*S*)-glyceraldehyde acetonide (prepared from vitamin C), developed by a team of researchers from Hunan Normal University in Changsha, Hunan, China. On June 25, 2008, during the 12th Annual Green Chemistry and Engineering Conference in New York, Pfizer reported the development of their "second-

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generation" synthesis of linezolid: a convergent, green synthesis starting from (*S*)-epichlorohydrin, with higher yield and a 56% reduction in total waste.[32]

Passerini reaction

The *Passerini reaction* is a chemical reaction involving an isocyanide, an aldehyde (or ketone), and a carboxylic acid to form a α-acyloxy amide.[33]
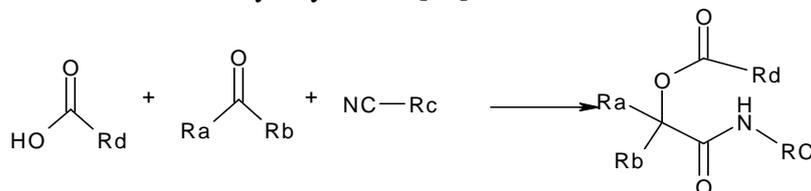

This organic reaction was discovered by Mario Passerini in 1921 in Florence, Italy. It is the first multi-component reaction developed, and currently plays a central role in combinatorial chemistry.

Reaction mechanism

Two different reaction pathways have been hypothesized.

Ionic mechanism

In polar solvents such as methanol or water, the reaction proceeds by protonation of the carbonyl followed by nucleophilic addition of the isocyanide to give the nitrilium ion Addition of a carboxylate gives intermediate. Acyl group transfer and amide tautomerization give the desired ester.
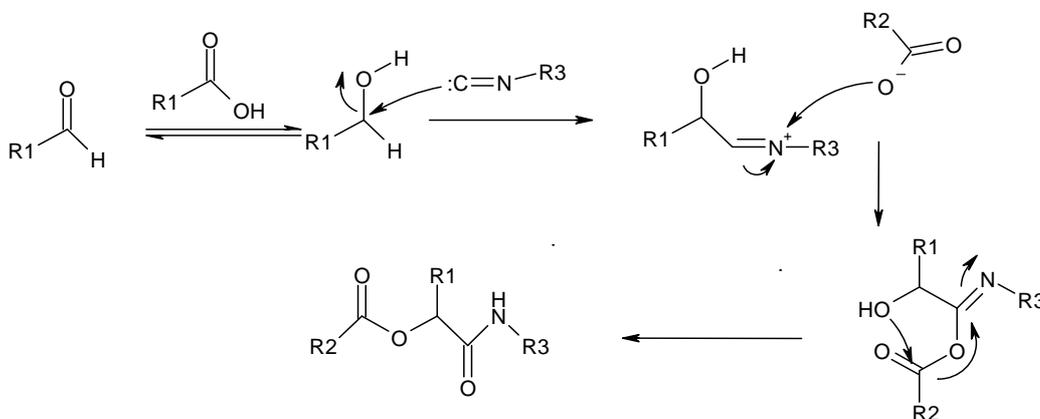

Concerted mechanism

In non-polar solvents and at high concentration a concerted mechanism is likely [34]:

This mechanism involves a trimolecular reaction between the isocyanide (R-NC), the carboxylic acid, and the carbonyl in a sequence of nucleophilic additions. The transition state TS# is depicted as a 5-membered ring with partial covalent or double bonding. The second step of the Passerini reaction is an acyl transfer to the neighboring hydroxyl group. This reaction is a good example of a convergent synthesis.
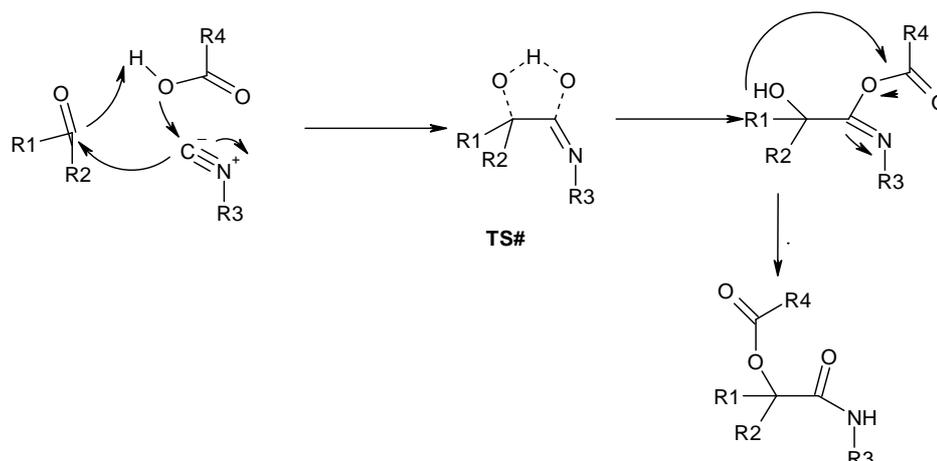
Queuosine

Queuosine is a modified nucleoside that is present in certain tRNAs in bacteria and eukaryotes. [35] Synthesis of queuosine begins with GTP. In bacteria, two classes of riboswitch are known to regulate genes that are involved in the synthesis or transport of pre-queuosine$_1$, a precursor to queuosine: PreQ1-I riboswitches and PreQ1-II riboswitches.[36]
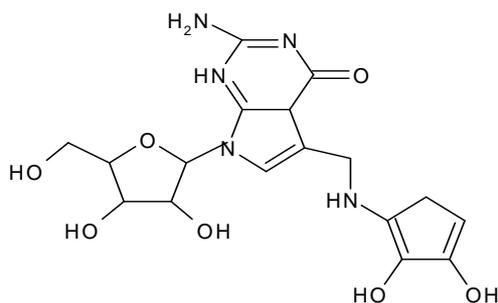

Salvinorin A

Salvinorin A is the main active psychotropic molecule in *Salvia divinorum*, a Mexican plant which has a long history of use as an entheogen by indigenous Mazatec shamans. Salvinorin A is a hallucinogenic compound with dissociative effects.It is structurally distinct from other naturally-occurring hallucinogens (such as N,N-dimethyltryptamine, psilocybin, and mescaline), and from synthetic hallucinogens, (e.g. lysergic acid diethylamide (LSD), 2C-B), because it contains no nitrogen (or tryptamine moiety), hence it is not an alkaloid.Salvinorin A is one of the most potent naturally occurring psychoactive drugs known to date, with an effective dose in humans in the 200–1,000 μg range when smoked. Salvinorin A can produce psychoactive experiences in humans with a typical duration of action being several minutes to an hour or so, depending on the method of ingestion. [37] Salvinorin is a *trans*-neoclerodane diterpenoid. It acts as a kappa opioid receptor agonist and is the first known compound acting on this receptor that is not an alkaloid. Salvinorin A was isolated in 1982 by Alfredo Ortega in Mexico. Its pharmacological mechanism was elucidated in the laboratory of Bryan L. Roth.

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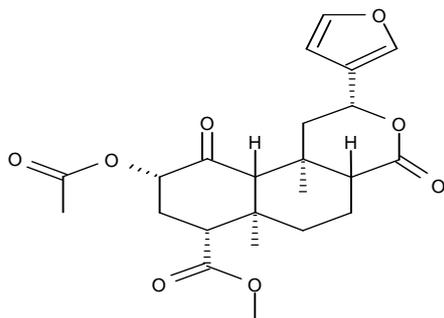
Chemical synthesis

A total asymmetric synthesis of salvinorin A was achieved by Evans and co-workers in 4.5% overall yield over 30 steps, and more recently, a synthesis was published by a Japanese group, requiring 24 steps to yield salvinorin A in 0.15% yield. An approach to the trans-decalin ring system of salvinorin A has been described by Forsyth (et al.) utilizing an intramolecular Diels-Alder reaction/Tsuji allylation strategy. An attempt at the synthesis of salvinorin A has also been published by a group at RMIT University, adopting a convergent synthesis of a functionalized cyclohexanone with a α,β-unsaturated lactone.[38]

Trihexyphenidyl
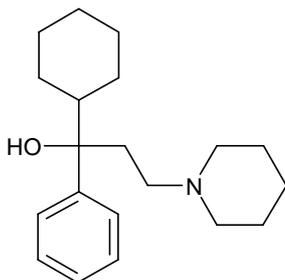
Chemistry

Linear vs Convergent syntheses. Although the convergent synthesis is used on an industry, it is uses hazardous reagents and is not as desirable as the linear procedure for small-scale preparations.[39]

Conclusion

The term convergent synthesis has wide importance in the field of synthetic organic chemistry mainly related to the native chemical ligation. It also deals with the synthesis of proteins and peptides. Certain drugs like Linezolide, Queuosine, Glycals, Trihexyphenidyl etc. can be synthesized on industrial scale with the help of this technique of organic synthesis.

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