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GLIMPSE OF RECENTLY DEVELOPED NATURAL PRODUCTS AND THEIR CHEMICAL SYNTHESIS

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Abstract: Natural products have been used in traditional medicine for cure of many diseases. Many of the traditional drugs isolated from organisms include known anti-cancer drug taxol and antibiotics such as penicillin and streptomycin. There are large number of natural products synthesized by large array of microorganisms. However, in most of the cases the amounts of these compounds are low. Organic synthesis is aimed at total synthesis of such natural products. Such synthesis would help in large scale production and utilisation for treatment of diseases. The present review aims to analyse several newly synthesized natural products and various methods for synthesis. .

Index Terms— Natural products, drug discovery, chiral products, enantioselective, spirolactones, pyrroles.

I. INTRODUCTION

For a very long time, natural products have been of great interest and importance in many areas. For combating many of the diseases, natural products have been found to be one of the upcoming future. Although the pharmaceutical industry has made a lot of efforts to develop new drugs to treat several of the diseases that have evolved, the overall success rate has been small. This is primarily due to changing existing drugs to improve their ability to function better. Nevertheless, there were no new drugs found. Drug discovery is a very important area that requires exhaustive scanning of the natural compound library to classify effective molecules. There have been medicinal plants for a very long time. Ayurvedic treatment methods in India have widely extended the use of medicinal plant extracts. There are about 75,000 plant species growing on earth. Nevertheless, for medicinal purposes only a small fraction of these were used. Only 1 percent of this small fraction was thoroughly characterized and optimized for synthesis. Natural products therefore have an enormous impact on the development of medicines. There are several natural products found and used in medication. Numerous biological active natural compounds are alkaloids in which camptothecin and vinblastine shows anticancer activity. Penicillin isolated from Penicillium is a significant agent that works against bacteria Gram+ve. The Taxol anticancer product was derived from the Yew tree bark. Also aspirin and salicin have been discovered from plant genera Salix and Populus. Therefore, the need to classify novel drugs from different medicinal plants is growing. [1-3].

The discovery of drug from the natural products involves number of steps which includes identification of the plants, preparation of extracts, identification of active constituent, its structural elucidation followed by its activity testing and preclinical analysis. Organic synthesis plays a crucial role in this process. Once active constituent has been discovered methods for synthesizing the component becomes vital part of the whole process. The total synthesis of the molecule and process optimisation thus plays a significant role in organic synthesis of the compound. The synthesis of urea played a distinct role in establishing the synthesis of natural products. This was followed by synthesis of aspirin and quinine which helped in establishing the pharmaceutical industry. Several of the Nobel Prize have been awarded to various synthetic reactions that have resulted in establishment of physiologically active molecules in pharmaceutical industry [4].

In the large-scale production of many of the natural products, synthetic biology has gained significant prominence. Many of the processed natural products are relatively small. The development of microbial or plant systems to increase efficiency also helps to produce excellent isolation yields. It is difficult to synthesize some of the natural products. In such instances, genetic engineering of the actual organism is essential in order to produce higher quantities of desired product. Metabolic technology for the manufacture of the desired product requires combining different parameters. One such example was polyketide synthesis, which was successfully modulated by metabolic engineering methods. A large number of molecules that are useful for the petrochemical industry have been successfully synthesized by altering the structures of different polyketides that have been synthesized. Most natural products have a complex structure and are not synthesized easily. There is a distinct barrier to the use of homologous species for synthesis. Since the discovery of the synthesis of heterologous protein, many of the complex natural products have been easily synthesized and appropriately modified. The discovery of new drug products is largely based on the use of genomic data. Total genome mapping with the concept of different proteins being collected and their related research through in silico methods offers more insight into the newest possible drug candidates. A constant genomic research accompanied by bioinformatic methods is therefore also an essential feature in discovering new natural products that can be used for drug discovery [5-6].

II. COMPREHENSIVE DISCUSSION ON NATURAL PRODUCTS

Natural products have a large diversity in their structures. Due to their complex structures with varied functional units it is generally difficult for synthesis and modification. However, with advancement in synthesis of innumerable organic compounds, successful methods have been evaluated that could help in overcoming this problem. Natural products which have been studied till now have greater number of sp^3 hybridized carbons in the configuration. In addition to this, many of the synthesized natural products contains carbon, hydrogen and oxygen and very limited molecules which incorporates nitrogen in them because of Nitrogen fixing ability of microbes is very poor thus making a common consensus across various natural products. In the same way most of the natural products do not have halogen atom in them.

The optical activity and associated chirality play an important role in determining the activity of molecule. Morphine is one such molecule which is complex with 5 chiral carbons. Synthesized derivatives from morphine are much simpler and non-chiral which include drugs like fentanyl. Modification of natural products thus plays an important role. The modification involves retaining the biological activity, increasing the solubility and pharmacokinetic behaviour and in improving the stability of the molecule [7-10].

Tetrameric acid (TA) containing natural products are widely present in many of the organisms but O-methylated TA are rarely seen in the organisms. . The TA structure is derived from amino acids with a chiral carbon in the 5^{th} position. Looking at many areas, core region of TA contain Polycephalin B, macrolide antibiotics, Dolastatine, Aspergillin and azaspirofuarn on which total synthesis has been done. However, due to the complexity of structures the asymmetric methods for synthesis have gained significant importance very late. For the synthesis of acylated TA at C-3 Lacey-Dieckmann procedure has been followed. However, such established methods have not been successful with synthesis of complex TA compounds with varying chiral centres [11].

Azatriazenes are the common structural motifs seen in many of the natural products including components of amino acids such as pyridines, oxazines, pyrroles and pyridones. They have an essential structural and functional role and hence have been observed as building blocks in the natural synthesized products. The traditional synthesis of azatriazenes involves cycloadditions and sigmatropic rearrangements. However, newer methods for synthesis have gained importance for those molecules which have not been successfully synthesized. These include the electrocyclic transformations which are easy and have significant advantages associated with them [12].

2-formyl pyrroles are found in the large number of natural products. They are utilized in traditional medicine preparations and exhibit a broad range of biological activity which include anti-inflammatory, anti-oxidant and anti-proliferative effects. Most of the synthesis of 2-formyl pyrroles involves the Maillard reaction. This reaction involves condensation of reducing sugars and amines and have been traditionally isolated by proposed non-enzymatic methods and the products are intermediates in condensation reaction. Recently enzymatic methods for synthesis have been proposed [13].

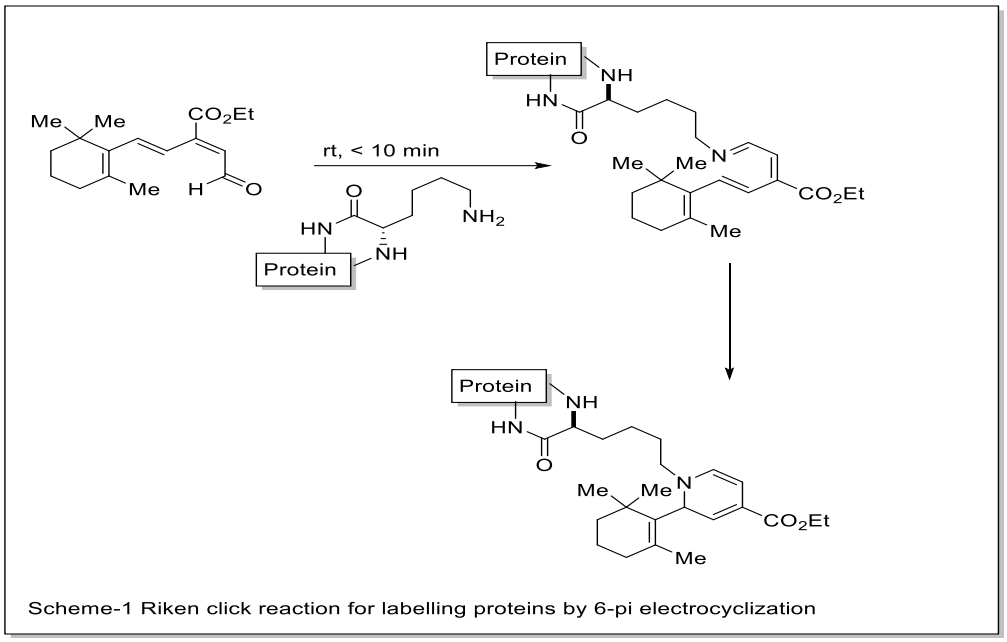
Asymmetric synthesis of chiral centres in compounds have been of intense investigation. Several of the methods has been proposed for synthesis of complex natural compounds. The use of novel ligands as catalysts along with use of transition metals has been very effective in synthesis of many of the natural compounds. Phospha bicyclo noanes and diaminophosphine oxides(DIAPHOX) with chiral carbons have been successfully used as ligands in synthesis of natural products. β- hydroxy amino acids have been synthesized for the first time from β- keto esters utilising the ligands and transition metals such as Ruthenium/Iridium or Nickel [14].

Mycobacterial based tubercular infections are one of the deadliest diseases that is encountered worldwide. They develop drug resistance faster and the cure involves use of multiple combinations of antibiotics. So, the screening for natural products with anti-bacterial activity is the need of the hour. Ramariolide antibiotics a group of novel antibacterial compounds that were isolated from coral mushroom. The total synthesis of these is very tough. However, isolation and purification of these compounds plays an important role at industrial level for the effective treatment of tuberculosis [15].

Spirolactones represent a distinct family of natural products which have diverse structures and are associated with wide range of biological activities. Abyssomycins, Lactonamycins and spiroinducimide are some of the antibacterial compounds that are produced naturally by many microorganisms. Lambertellols are group of spirolactones with potent anti-fungal activity. Plumericin and isoplumericin both exhibit distinct anti parasitic activity. Biyouyanagin A and hyperlactone C exhibit potent anti-viral activity. Many of the hyper lactones exhibit potent cytotoxic activity against various cell lines [16].
Birch reduction is a unique method by which aromatic and non-aromatic compounds have been reduced very effectively. The reduction step is particularly useful in selective modification of specific double bonds in aromatic compounds in a multi-step reaction process. Birch reduction has been used in total synthesis of natural compounds and the novelty has helped in synthesis of many of the natural products. [17]. C-glycosylation is an important modification which imparts distinct activity to many of the natural products. Chemical C-glycosylation has been extensively applied in synthesis of several of the natural products and has been applied in pharmaceutical industry [18].

III. RECENT DEVELOPMENTS OF SYNTHESIZED NATURAL PRODUCTS

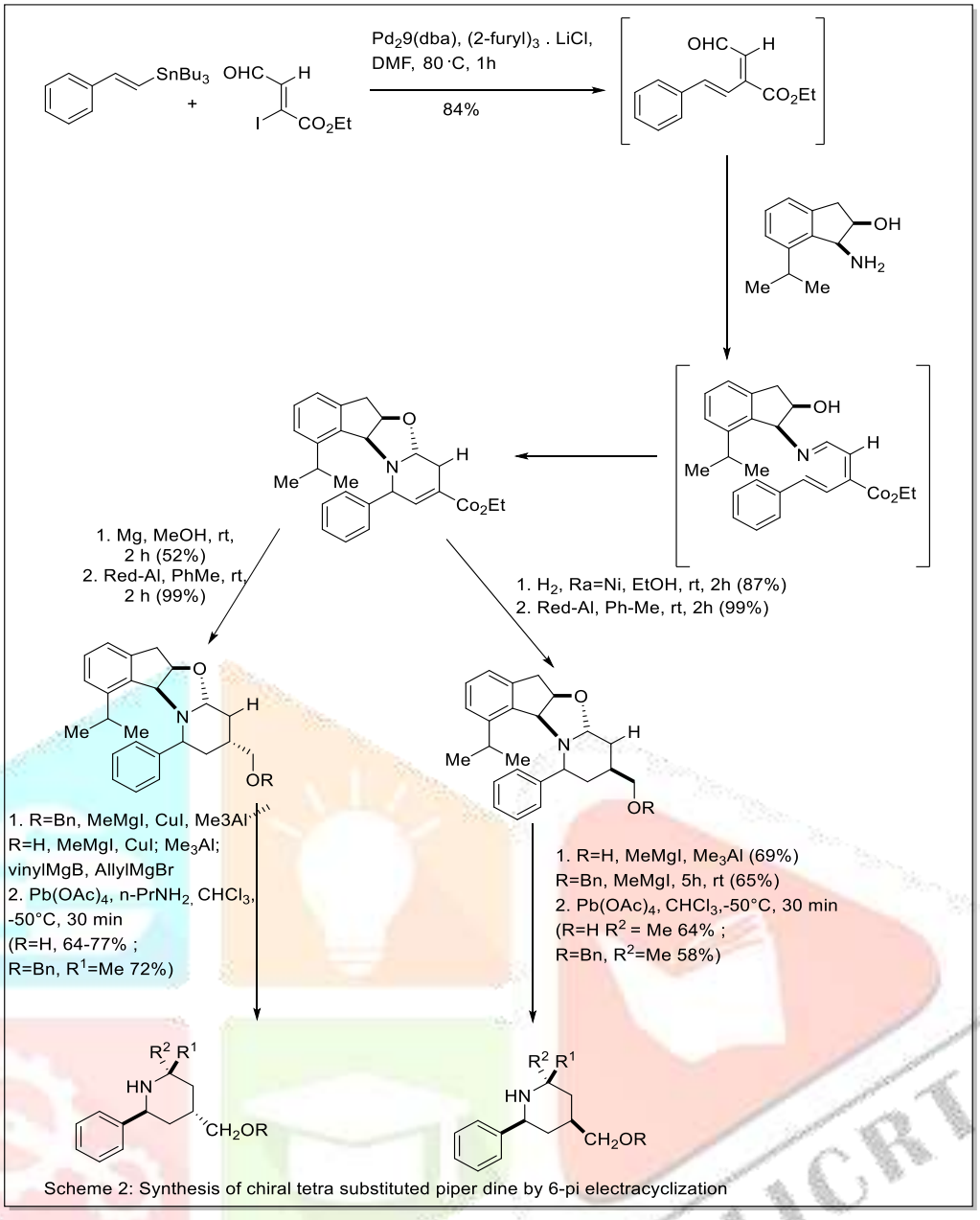
Thetemplateisusedtoformatyourpaperandstylethetext.Allmargins,columnwidths,linespaces,andtextfontsareprescribed; 6Π- azaelectrocyclization reaction has been a new development in synthesis of various azatriazene containing molecules. The method has been used in synthesis of pyridines, pyridones and oxazines from different trienes as starting materials. Naturally the method is utilised for synthesis of cofactor NAD+ in biological systems non-enzymatically. Based on the reaction mechanism synthesis has been proposed for various of the azatriazenes. 6Π- azaelectrocyclization has been successfully used for synthesis of variety of substrates. Substituted pyridines, and piperdines are useful intermediates in organic synthesis which have been successfully synthesized by the electrocyclization method. The labelling of proteins for their *in vivo* imaging and functionality involves conjugating proteins to azatriazene molecules (Scheme 1).



Scheme-1 Riken click reaction for labelling proteins by 6-pi electrocyclization

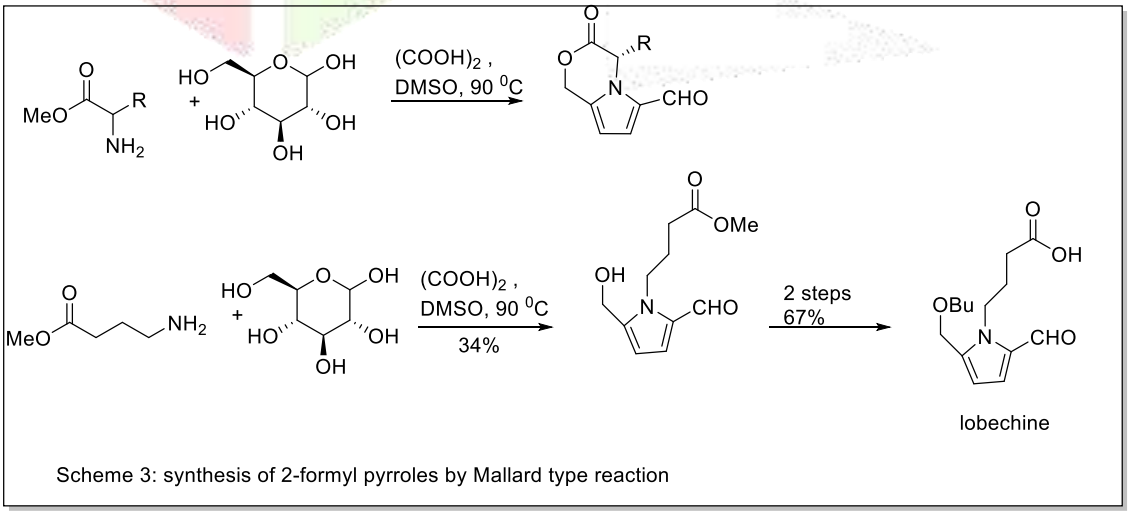
The labelling is usually done by Click reaction which involves electrocyclization. Stereospecific compounds and chiral piperdines have been synthesized by electrocyclization (Scheme 2) and have been valuable in generating many of agonists for Histone H3 and alkaloids [12]

2-formyl pyrrole synthesis though has been done by traditional methods two new methods have been proposed for their synthesis.



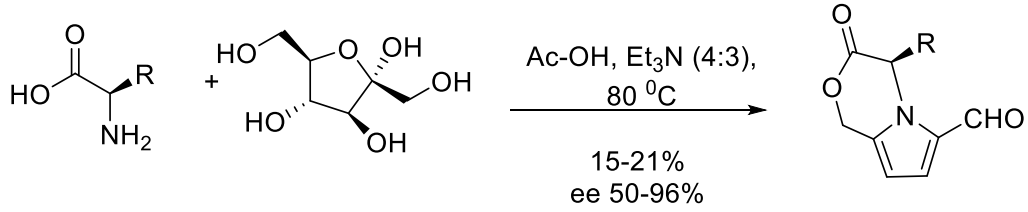
Scheme 2: Synthesis of chiral tetra substituted piper dine by 6-pi electracyclization

The formyl pyrrole was synthesized by treatment of reducing sugar with amines in presence of oxalic acid and DMSO (Scheme 3).



Scheme 3: synthesis of 2-formyl pyrroles by Mallard type reaction

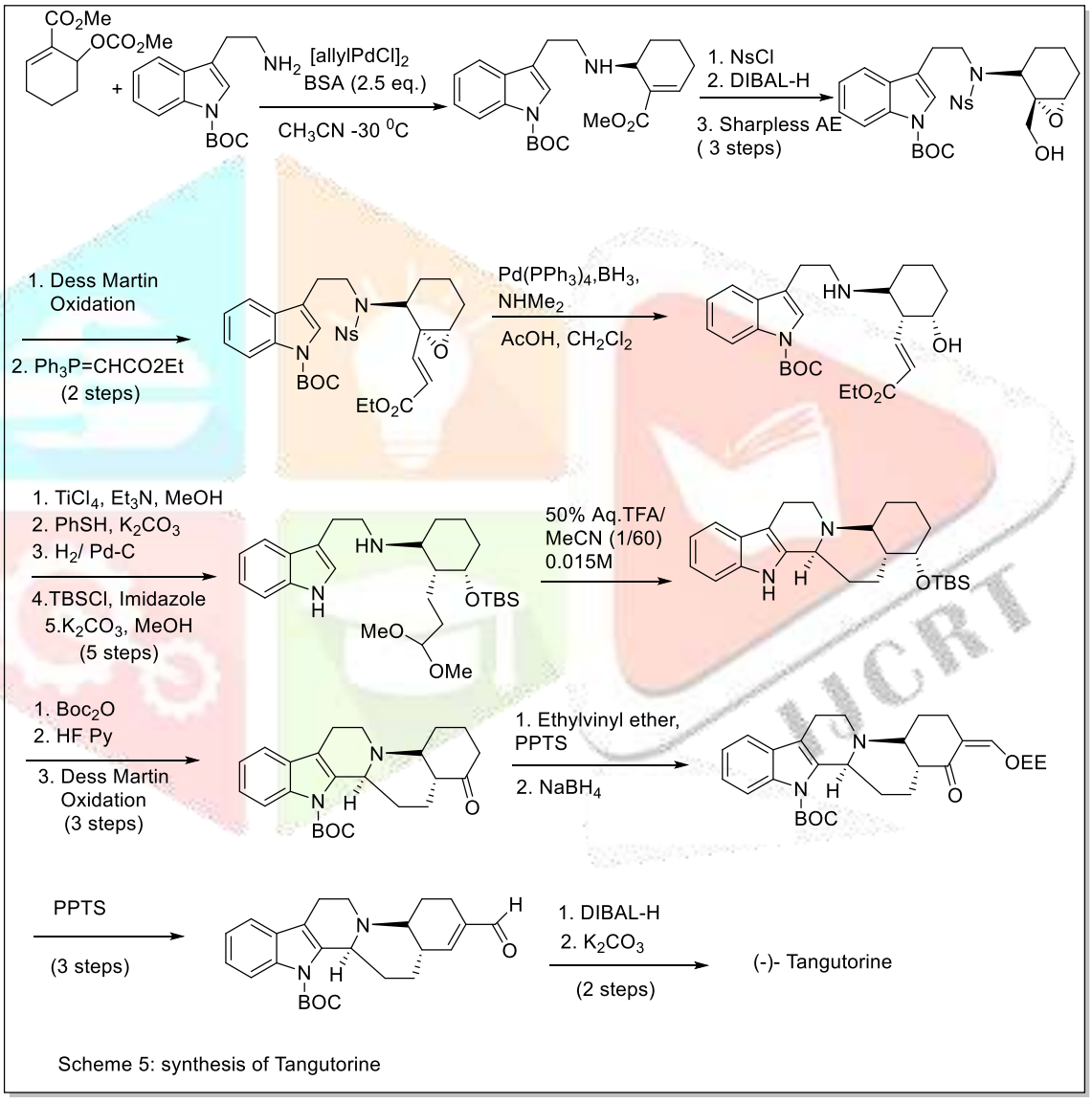
Another new method showed the synthesis of oxazole containing formyl pyrroles from fructose and amino acid utilising acetic acid and triethyl amine (Scheme 4). These two methods have given good yields of pyrroles with desired product and could be used as alternative to Mallard reaction [13].



R= CH_3, $CH(CH_3)_2$,$CH(CH_3)CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH_2C_6H_5$ or $CH_2C_6H_4OH$

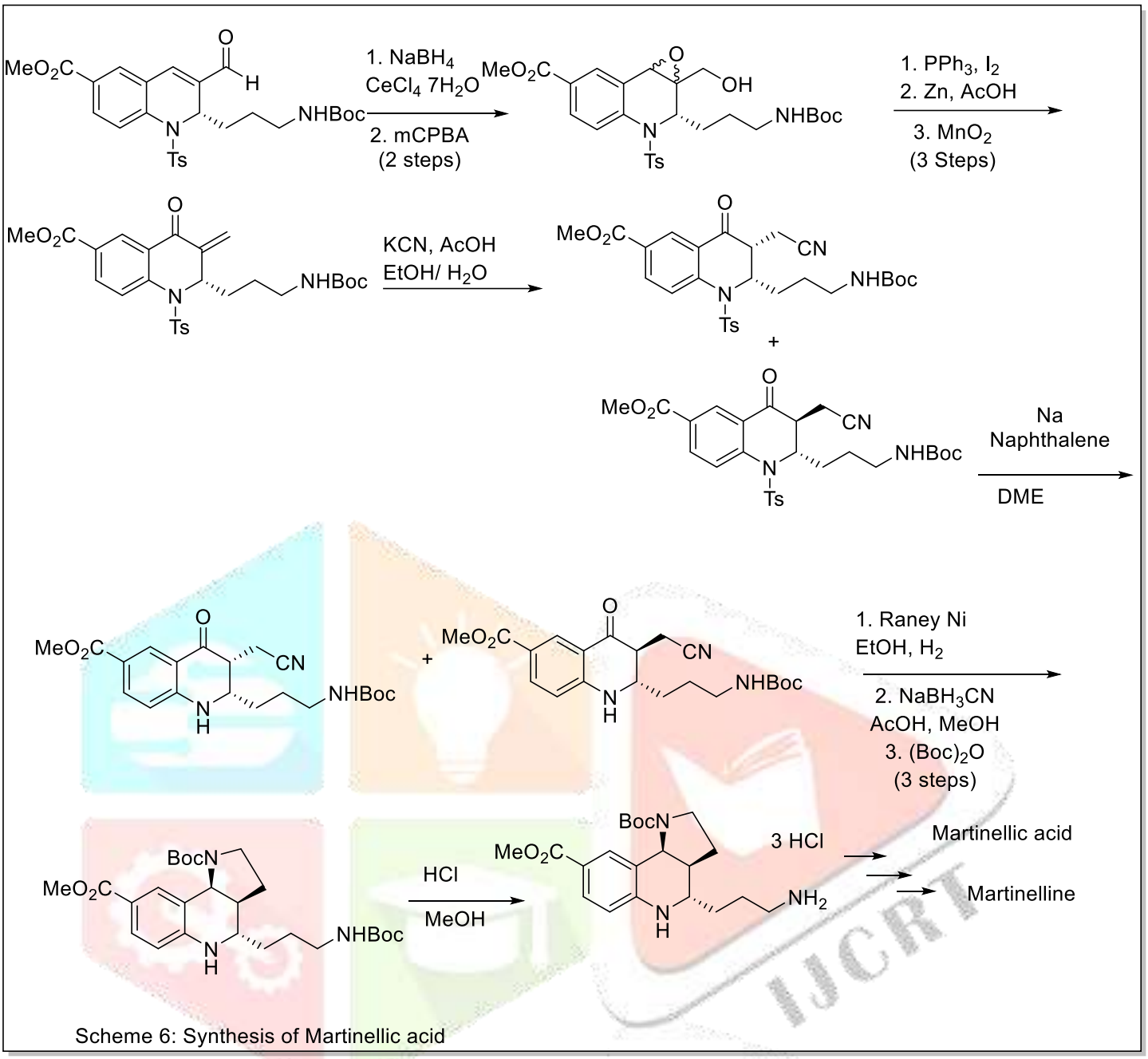
Scheme 4: Mallard type reaction for synthesis of pyrroles

Asymmetric alkylation and related methods for total synthesis of natural products have been tried by newer methods. Tangutorine is a known anti-cancer compound against colon cancer. Enantiomeric synthesis of these compound was achieved by using DIAPHOX catalyst-based system in presence of Palladium. The asymmetric amination results in final product that is around 88% yield (Scheme 5).



Scheme 5: synthesis of Tangutorine

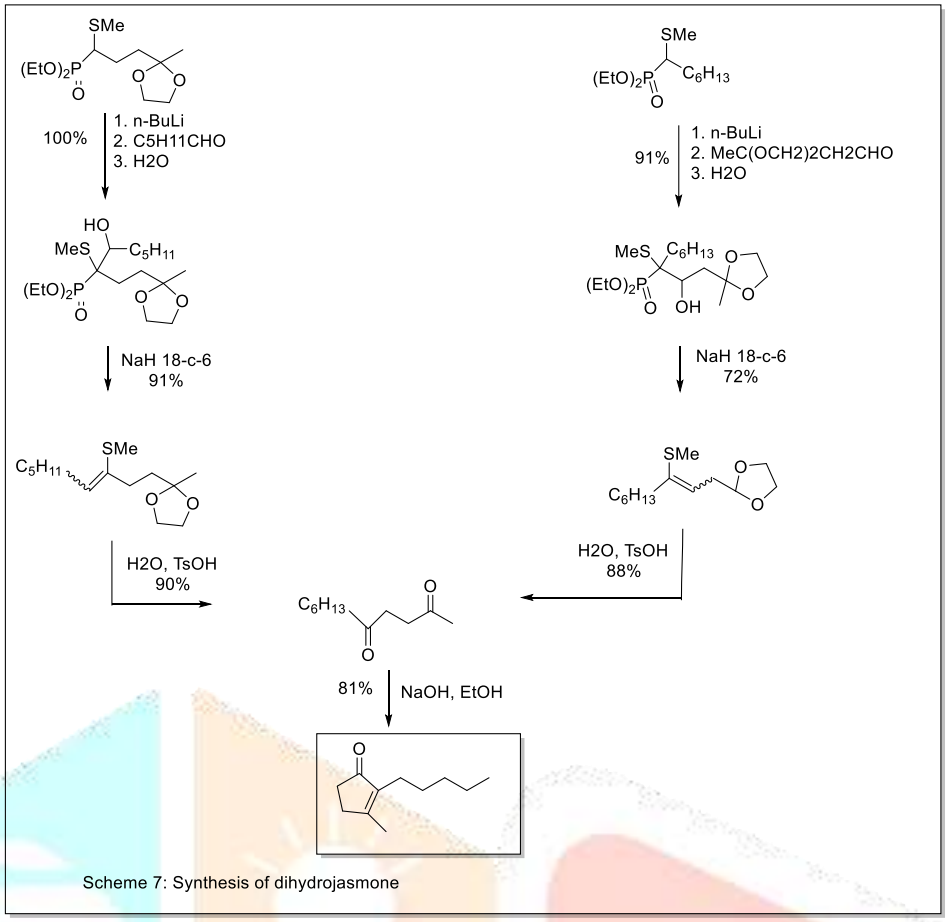
Martinellic acid was synthesized by Michael aldol reaction. It is a tandem reaction which was asymmetric in nature (Scheme 6).



Scheme 6: Synthesis of Martinellic acid

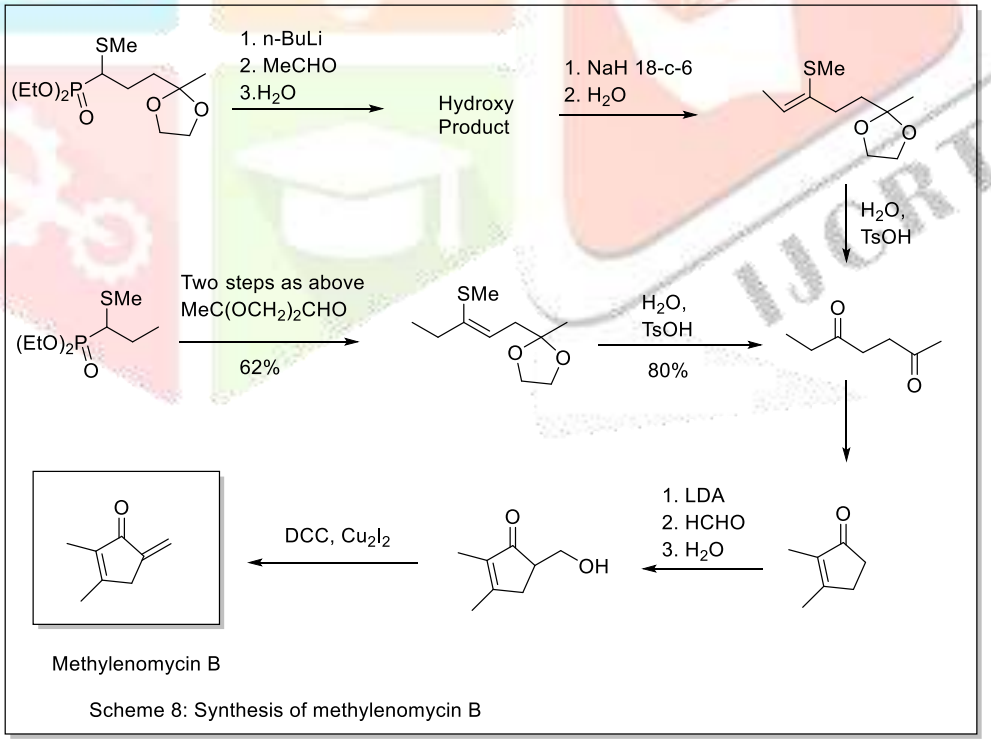
Unnatural amino acids have been synthesized by newer methods which include the utilisation of asymmetric hydrogenation. α- amino beta keto esters were subjected to asymmetric hydrogenation in presence of Iridium which resulted in generation of unnatural amino acids in good yields [15].

Phosphonate based reagents have been used in synthesis of 1,2 and 1,4 dicarbonyl compounds. Number of derivatives of phosphonate compounds have been used for synthesis of several natural products. Dihydrojasomone is an important component in several of the plants which imparts fragrance and also is involved in defence mechanism. Complete synthesis of dihydrojasmone was achieved using alpha phosphoryl sulphide. The use of lithium salts in reaction was very helpful in generation of stable intermediates which could be converted to dihydrojasmone with good yields (Scheme 7).



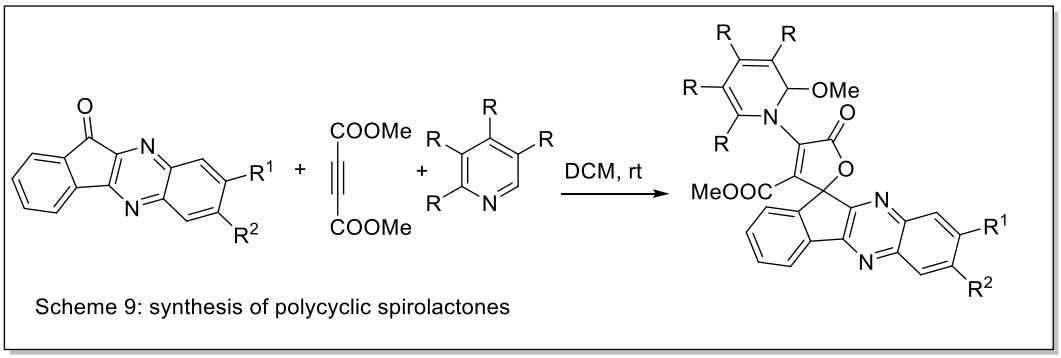
Scheme 7: Synthesis of dihydrojasmone

Biologically active antibiotic compounds such as methylenomycin have been successfully synthesized using these phosphonate reagents (Scheme 8) [3 &19]



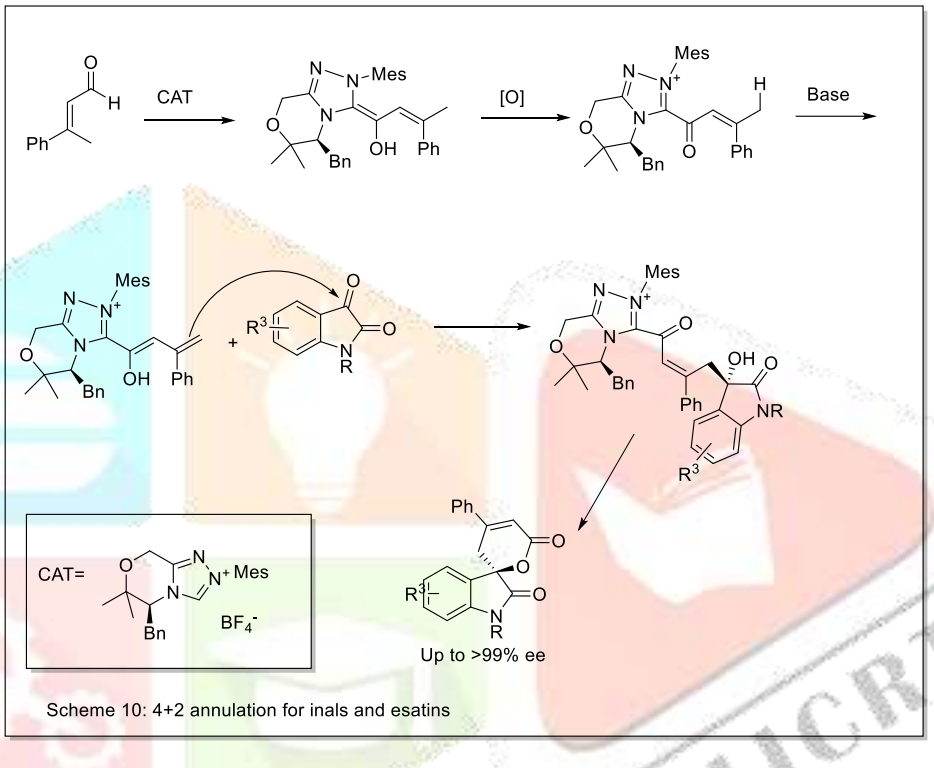
Scheme 8: Synthesis of methylenomycin B

Spirolactones have been seen in large number of naturally occurring bioactive compounds such as anti-bacterial, anti-fungal, anti-parasitic and anti-viral compounds respectively. Spirolactones have been synthesized by many successful modified methods which have given good yields. (Scheme 9).



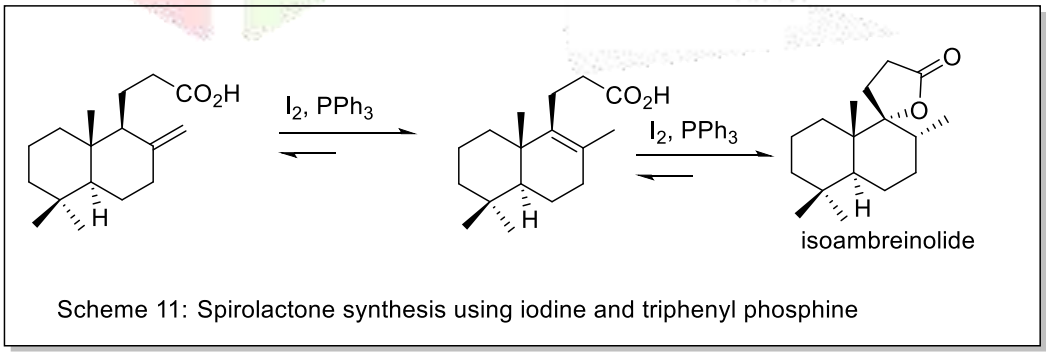
Scheme 9: synthesis of polycyclic spirolactones

Spiro delta lactones with distinct chiral centres were synthesized by hetero Diels Alder reaction between dienes and isatins. Polycyclic spiro lactones were synthesized by disasteroselective [3+2] addition reaction. The reaction was catalysed by rhodium. The reaction proposed could generate total synthesis of naturally occurring products. A modified reaction included the use of [4+2] annulation of enals and isatins.(Scheme10).



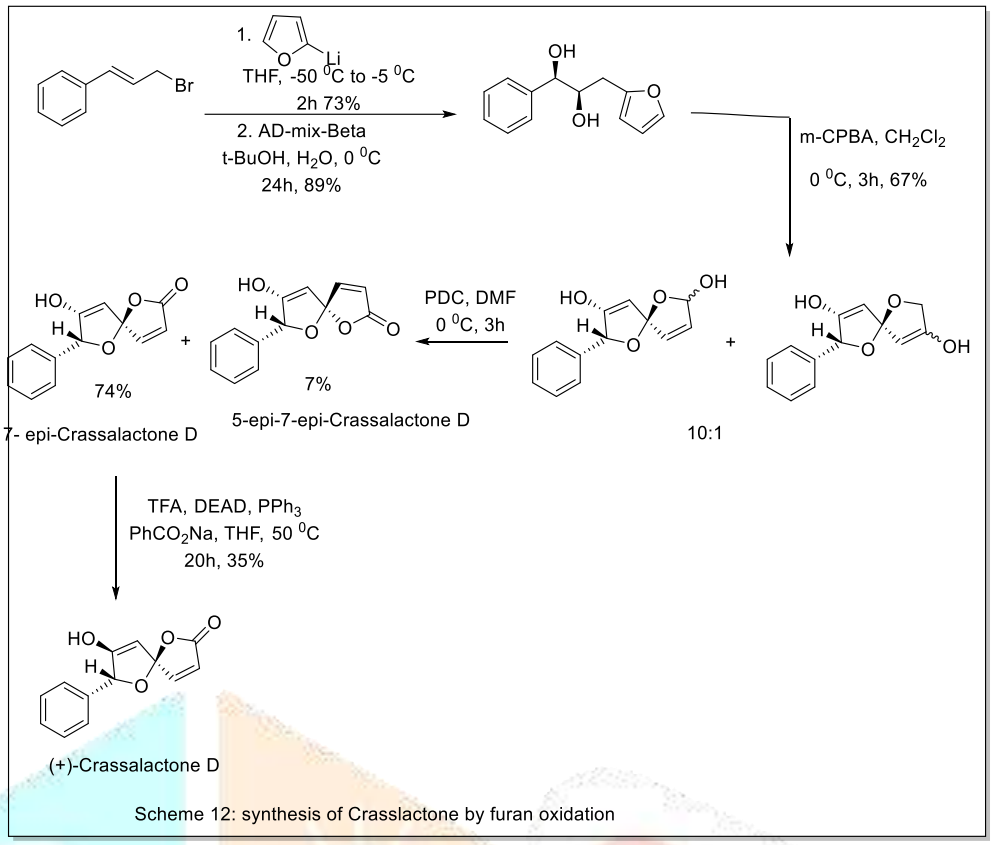
Scheme 10: 4+2 annulation for inals and esatins

The reaction resulted in generation of spiro delta lactones in high yields. Similarly, iodine and triphenylphosphine based catalysis of spirolactone synthesis has also been proposed (Scheme 11) [4 &16].



Scheme 11: Spirolactone synthesis using iodine and triphenyl phosphine

Oxaspirolactones are another distinct group of naturally occurring products with wide range of biological activity. They have been synthesized by oxidative spirocyclization, retro aldol rearrangement, transistion metal catalysed cycloaddition, epoxidation of lactones and acid or base mediated rearrangement of oxaspirolactones (Scheme 12) [2 & 20]



Scheme 12: synthesis of Crasslactone by furan oxidation

VII. Conclusion

Various plants and microbes produce a huge number of natural products which have distinct biological activity. However, over production of such components for medicinal usage requires genome engineering of plants and microbes. With the advancement in few genetic methods, it has been successful achieved the production of many of the natural compounds by various organisms. Total synthesis of natural compounds has been always challenging because of the complex structures and the associated chirality. The synthesis of these compounds has been effectively attained by variety of methods. Seeing to decades ago, recent synthetic methods such as asymmetric hydrogenation, use of transition metal catalyst and the development of new reagents such as phosphonic acid and DIAPHOX based systems have been extensively helpful in synthesizing a lot more of natural products. Thus, the present methods have helped in enhanced production of complex natural products which have extensive scope in the treatment of many of the diseases.

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