Chapter

Methods of Alkaloids Synthesis

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Abstract

The investigation of plants used in traditional medicine in the early nineteenth century found alkaloids have developed into a group of natural products with exceptional structural and taxonomic diversity, as well as important chemical, biological, and medicinal importance. Since the early twentieth century, only a few routes have been thoroughly explored, and researchers have struggled to grasp their biogenesis and biosynthesis. Even for many pharmaceutically important alkaloids, there is still much to learn about how alkaloids are generated in nature, despite recent enzymatic efforts that have significantly advanced our understanding of this process. Certain aspects of empirically determined or speculated mechanistic routes of alkaloids creation are explored, with an emphasis on clinically relevant alkaloids.

Keywords: alkaloids, synthesis, plants, therapeutic, natural products, traditional medicines

1. Introduction

Alkaloids are organic compounds that are naturally occurring and are primarily found in plant sources, such as marine algae, and rarely in animals (e.g., in the toxic secretions of fire ants, ladybugs and toads). They are predominantly located in berries, bark, fruits, roots, and leaves of plants that produce seeds. Alkaloids often have a heterocyclic ring with at least one nitrogen atom [1].

Since their discovery and early isolation in the nineteenth century, alkaloids have attracted the attention of chemists' imaginations, creative energies, and very souls. They are still actively sought after because of their astounding and seemingly unlimited structural variety, the challenges their synthesis poses to even the most skilled and knowledgeable organic chemists, the range of biological reactions they supply, and the profusion of innovation and acrobatics in the routes of biosynthetic creation. In the past 200 years, no other group of natural compounds has stimulated both chemists and biologists [2]. The "principium somniferum" that Serturner isolated from opium and published in the Journal für Pharmazie in 1805 was most likely the first semi-purified alkaloid. However, it was because to the work of French scientists Pelletier and Caventou that alkaloids truly came of age. Following their successful separation of emetine in 1817, they isolated brucine, quinine, and strychnine between 1819 and 1821. Piperine, atropine, caffeine, solanine, chelidonine, coniine, nicotine, aconitine, and colchicine were all identified before 1833 as a result of other chemists

taking on the challenge of researching the components of physiologically relevant plants [3]. By the time Berzelius' Lehrbuch der Chemie was published in 1837, the Swedish chemist had identified thirteen "Pflanzenbasen." Coke was discovered in 1860, and spartine in 1851. Thirteen "Pflanzenbasen" had already been recognised by Berzelius by the time his Lehrbuch der Chemie was published in 1837. However, it has remained difficult to define what an alkaloid is, thus no attempt will be made here to close the apparent gap. Despite not being polypeptides, proteins, or nucleic acids, they do contain nitrogen [4, 5]. A common reason why most alkaloids are optically active is that they contain tertiary nitrogen in their structural makeup. This leads to varied physical, chemical, and pharmacological properties in the various isomeric forms. For example, (+)-tubocurarine, which was isolated from *Chondrodendron tomentosum* (Bisset, 1992), has muscle-relaxant activity, whereas its leavo isomer has less activity [2].

It has given a very helpful overview of alkaloids and their role in biology and medicine [6]. Higher plants, particularly those with medical purposes or a reputation for being exceedingly deadly, provided the first isolates of alkaloids. In the late twentieth century, "alkaloids" were isolated from a wide variety of terrestrial and marine sources, including frogs, arthropods, mammals, insects, sponges, fish, fungus, and bacteria, as well as, of course, *Homo sapiens*, as the natural world was being chemically explored. The number of known alkaloids from higher plants alone has increased to at least 22,000, meaning that the sum from all sources is currently likely to be more than 30,000 [7]. Alkaloid isolations from the beginning were done before stereochemical concepts and the three-dimensional character of compounds were formed, before there was an understanding of the intricacy of molecular structure. The development of methods for figuring out the precise structures of these alkaloids—first via chemical analysis, then spectroscopy—posed one of the main difficulties over the following 160 years [8, 9]. In 1882, the structure of the first known alkaloid, xanthine, was discovered. The initial synthesis of alkaloids was published by Ladenburg, (+)-coniine, in 1886. Chemical deterioration under difficult circumstances was frequently engaged in structure determination. The result is, the core heterocyclic nucleus was occasionally the only one to survive, and this provided the foundation for the new field of organic chemistry known as heterocyclic nuclei. For instance, isolating quinoline from quinine by distilling it with KOH and indigo provided indole [10, 11]. Many of the alkaloids were extremely complicated structurally and stereochemically, making it difficult to determine their structure or synthesise them. Notwithstanding the fact that the indole alkaloid strychnine was discovered in 1818, it was not completely understood until 1947, and its synthesis was initially described by Woodward in a 1954 publication. On the other hand, Robinson successfully synthesised the crucial tropane nucleus in 1917 following what turned out to be biogenetic lines. However, it took a long time before this philosophical idea inspired the biogenetically-patterned synthesis of a wide variety of alkaloids [12, 13]. Synthesis and biogenesis advanced hand in hand in this setting, strengthened at key points by biosynthetic experiments, beginning with radioactive isotopes and afterwards the use of stable isotopes. Following these discoveries, an effort was made to identify, describe, and determine the genes and enzymes in charge of producing alkaloids inside the organism and within its cellular structure. However, testing is still far behind the ideas of spontaneous creation [14]. As a result, it is quite evident that "biogenesis" refers to theoretical ideas about the method of development of a natural product, whereas "biosynthesis" refers to the experimental confirmation of such pathway (feeding experiments with precursors, enzyme isolations and

characterizations, etc.) [15]. For all but a few classes of alkaloid, experimentation has not yet surpassed theory, as will be shown in this chapter. As more and more alkaloid structures were revealed, it became necessary to divide "alkaloids" into different subgroups and analyse each of these groups separately. The "The Alkaloids, Chemistry and Pharmacology" series of publications, edited by R.H.F. Manske, was first released in 1950 and is still in print today. Alkaloids were categorised on the basis of their structural makeup, and groups of alkaloids were given names based on the heterocyclic nucleus of their parent compound, such as tropanes, indole alkaloids, isoquinoline alkaloids, benzylisoquinoline alkaloids, acridine alkaloids, steroidal alkaloids, etc. [16]. As it turned out, these categories also often—though not always—reflected a shared biosynthetic origin. For instance, the amino acid tryptophan, which has an indole nucleus, would provide an indole alkaloid. These alkaloid group names often still reflect a fundamental structural component as well as a shared biosynthetic source [17]. However, it is not suitable to designate them as "piperidine" or "quinoline" alkaloids because a large number of heterocyclic nuclei, such as the piperidine and quinoline nuclei, are known to have numerous biosynthetic origins. On the other hand, higher plants contain alkaloids at a rate of 14.2%, as indicated by plant genera. The 83 higher plant orders identified by Cronquist were examined by Cordell, Quinn, and Farnsworth and found to be the case (1730 of 7231). Though none have been isolated as of yet, alkaloids have been discovered in over 35 higher plant groupings. In addition, the alkaloids of 153 plant groups have never been examined [18]. Over 1870 alkaloid skeletal were recognised at that time, and over 21,120 alkaloids had their structural makeup established. These are the twenty most important: Apocynaceae, Asteraceae, Berberidaceae, Boraginaceae, Buxaceae, Celastraceae, Fabaceae, Lauraceae, Liliaceae, Loganiaceae, Menispermaceae, Papaveraceae, Piperaceae, Poaceae, Ranunculaceae, Rubiaceae, Rutaceae, and Solanace. There was a great deal of conjecture about the formation of alkaloids and the interactions between alkaloid groups before there was any actual evidence that alkaloids were derived from amino acids. Organic chemists took the lead when biosynthetic experimentation started in the early 1950s following the introduction of radio-labelled precursors, with groups led by Birch, Barton, Battersby, Arigoni, Scott, Spencer, and Leete who clarified many crucial fundamental alkaloid biosynthetic pathway elements [19]. When it became apparent, roughly 20 years ago, that research at the cellular and then enzyme levels was required, and from there to the cloning and expression of systems that could generate alkaloids ex situ, the groups of Zenk, Stöckigt, Kutchan, Robins, Yamada, and Verpoorte took the lead. The study of alkaloid biosynthesis from a regulatory and metabolic engineering approach has now entered a new phase. Leaders in this circumstance have included Kutchan, Facchini, and Yamada. Up until recently, Richard Herbert's heroic efforts allowed The Royal Society of Chemistry to publish Natural Products Reports, a review magazine that provided excellent coverage of this area of natural product chemistry and biology. Three significant reactions serve as the foundation for the biosynthesis of alkaloids: the Pictet-Spengler condensation, the Mannich reaction of a Schiff base with a nucleophile, and the phenolic coupling reaction. Before going over some of the amazing pathways that lead to the diversity of alkaloids, it is important to review these three reactions [20]. Alkaloids have long been thought to be crucial for humans, despite the fact that they are secondary metabolites, which might imply that they are useless. In very little quantities, alkaloids exhibited potent biological influences on human and animal species. Alkaloids are found in food and drink used by humans every day, as well as in several stimulant medications (**Figure 1**) [21].

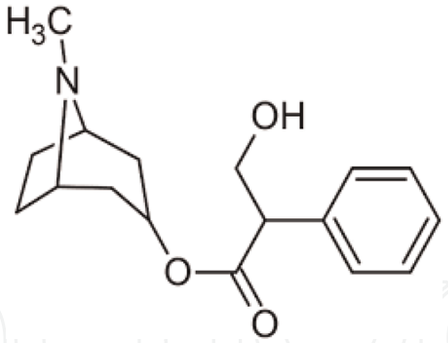

Figure 1.
Structure of atropine.

2. Occurrence

While alkaloids often present in all sections of a plant, they occasionally concentrate solely in one organ, leaving other parts of the plant free of them. For example, The potato plant's edible tubers are free of alkaloids, but its green parts are poisonous because they contain solanine. Alkaloids are not always synthesised in the organ in which they collect; for example, Tobacco's roots are where nicotine is produced before being carried to the leaves, where it is subsequently found. (Harborne and Herbert, 1995). In the epidermis of a human, about 300 alkaloids from over 24 classes have been discovered. The Phyllobates genus of frogs' skin was the source for the lethal neurotoxic alkaloids. Daly, (1993) separated different antibacterial alkaloids from reptile skin. Some isoquinoline and indole alkaloids were includes mammalian morphine but is segregated from them. The human diet includes several alkaloids in both food and beverages. The plants in the human diet in which alkaloids are present are not only coffee seeds, caffeine (**Figure 2**) [22].

3. Medicinal significance

Alkaloids have a variety of medicinal uses. Despite the fact that many of them exhibit local anaesthetic properties, they rarely have therapeutic uses. One of the most

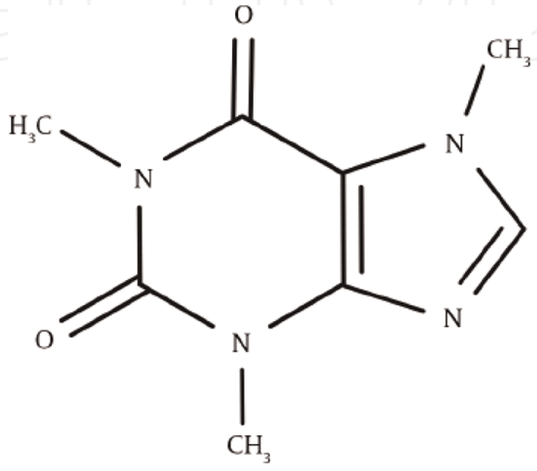

Figure 2.
Structure of caffeine.

well-known alkaloids that has been utilised for medical purposes both historically and currently is morphine. This alkaloid is a strong narcotic that can only be used in small doses to treat pain due to its addictive properties [1].

Medicine has used alkaloids having hallucinogenic, narcotic, or analgesic characteristics, such as morphine, atropine, and quinine. While many alkaloids are abused as illegal substances, such as cocaine, For modern synthesised medications, several alkaloids served as model substances. Some alkaloids, such as strychnine and coniine, are too poisonous for any medicinal use. Additionally, new biologically active chemicals are continually being discovered in the plant. The drug atropine (Mann et al., 1994) relaxes smooth muscles and expands the eyeballs' pupils. Papaverine, a compound isolated from *Papaver somniferum*, has been shown by Pictet and Gums (1909) to have relaxing effects on blood vessel smooth muscle as well as intestinal and bronchial smooth muscle. Strong painkiller morphine is frequently prescribed to individuals with terminal illnesses. Although less strong, codeine performs similar pharmacological processes as morphine. Heroin is a highly addictive synthetic morphine derivative. As a particular analgesic, ergotamine (**Figure 3**) in the form of ergotamine tartrate coupled with caffeine is used to treat migraines [1].

4. Quinolines alkaloid

This particular type of quinolone-nucleus carrying alkaloid is only found in the bark of the Cinchona plant. However, a number of simple heteroaromatic quinolines have also been discovered in a number of marine sources. (2-heptyl-4-hydroxyquinoline from a marine pseudomonad and 4, 8-quinolinediol from cephalopod ink 2-heptyl-4-hydroxyquinoline from a marine pseudomonad). The primary alkaloids in this group include cinchonine, cinchonidine, quinine, and quinidine (**Figure 4**).

4.1 Quinoline alkaloid synthesis

The cross coupling of phenyl magnesium bromide with 2-chloroquinoline product I, which was catalysed by cobalt (II) acetylacetonate in dioxane at 50°C, resulted in the alkaloid in a 74% yield. By heating acetophenone with 2- aminobenzyl alcohol product (II) in dioxane in the presence of the catalyst for oxidation [Ru(DMSO)4]Cl2

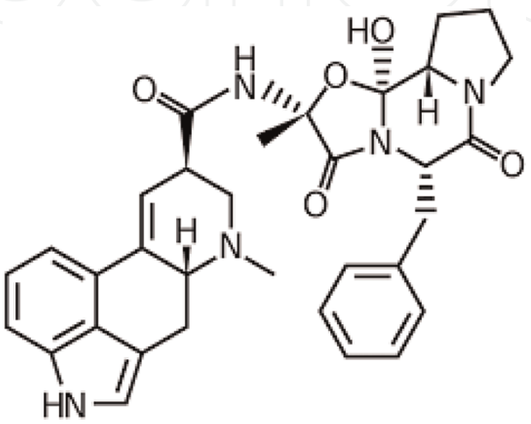

Figure 3.
Structure of ergotamine.

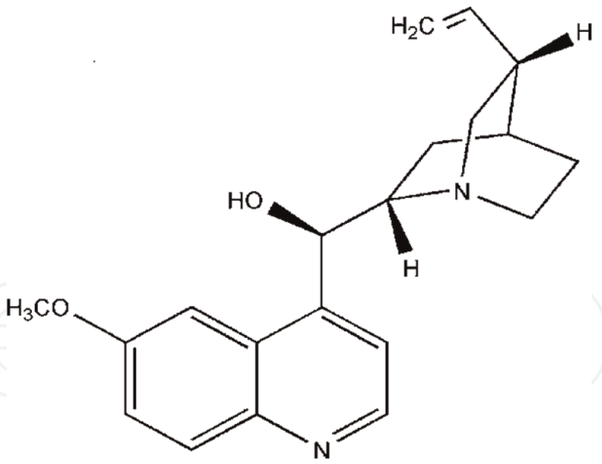

Figure 4.
Structure of quinine.

(2 mol%) and benzophenone as a hydrogen scavenger, the product was produced in 94% yield. In toluene at 100°C, molecular oxygen and hydrotalcite with ruthenium grafts, a multifunctional heterogeneous catalyst, have also been used to achieve this oxidative cyclisation in 89% yield. Reducing the titanium tetrachloride, zinc, and malononitrile-2-nitrochalcone adduct iii in boiling tetrahydrofuran resulted in the production of 2- phenylquinoline in a 78% yield. Finally, ytterbium (III) triflate in dichloromethane was used to achieve the three-component condensation of aniline with benzaldehyde and phenyl vinyl sulphide to yield 2-phenyl-4-phenylthio-1,2,3,4-tetrahydroquinoline 40 at room temperature .32 The alkaloid was subsequently produced in an overall yield of 23% by oxidising product iv with solid-supported periodate and thermolyzing the intermediate sulfoxide. These five adaptable methods were also used to create a variety of synthetic 2-phenylquinoline analogues, so they ought to work just as well when creating additional straightforward 2-arylquinoline alkaloids of related interest is the oxidation of 2-aryl-2,3-dihydroquinolin-4(1H)-ones such as product v with ferric chloride hexahydrate in boiling Methanol is used to produce 2-aryl-4-methoxyquinolines, including the naturally occurring compound 2-phenyl-4-methoxyquinoline vi, which was produced with a 78% yield [23].

4.2 Reagents and conditions in Quinoline alkaloid synthesis

i. PhMgBr (3 equiv.), Co(acac)2 (0.1 equiv.), dioxane, 50°C, 30 min (**Figure 5**);

ii. [Ru(DMSO)4]Cl2 (2 mol%), Ph2CO (1 equiv.), KOH (1 equiv.), dioxane, 80°C;

iii. Ru-grafted hydrotalcite–NEt3 (3 mol% in Ru), O2 (1 atm), PhMe, 100°C, 20 h;

iv. TiCl4 (4 equiv.), Zn (8 equiv.), THF, reflux, 3 h, then 39, rt., 4 h;

v. Yb (OTf)3 (0.05 equiv.), MgSO4, CH2Cl2, rt., 18 h;

vi. IO4 − on Amberlyst, dioxane– H2O, rt., 4 h, then 80°C, 18 h;

vii. $FeCl3{\cdot}6H_2O$ (2.5 equiv.), MeOH, reflux 2.5 h.

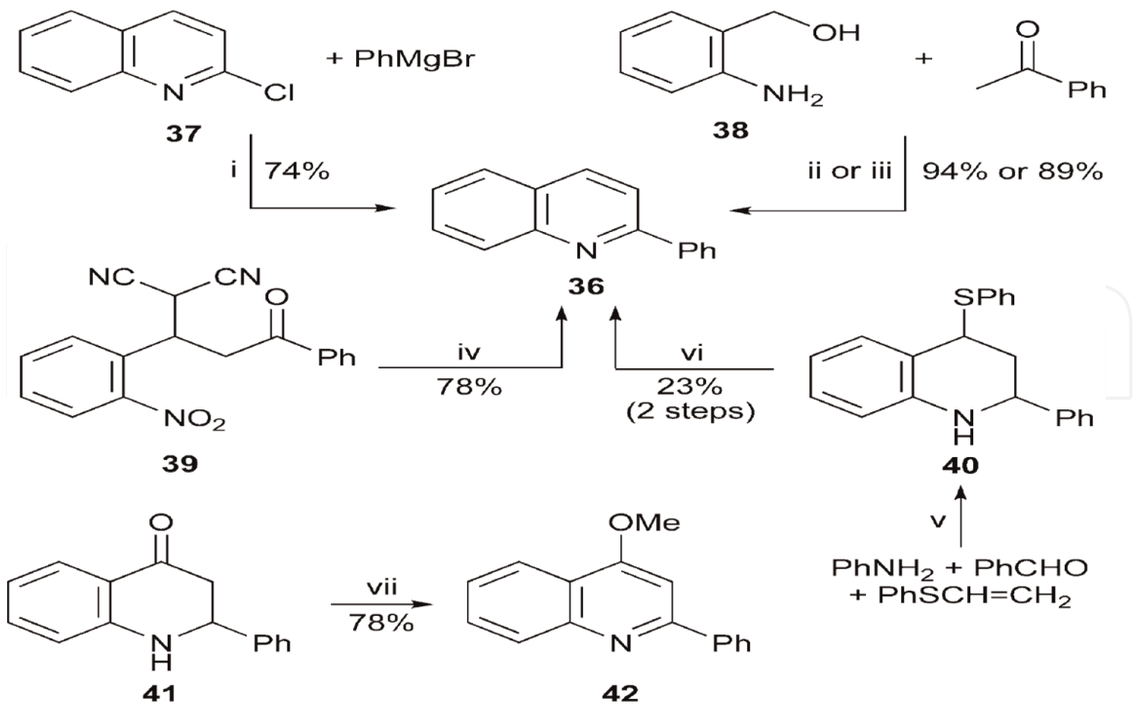

Figure 5.
Quinoline alkaloid synthesis.

5. Isoquinoline alkaloids

There are a few categories of isoquinolinoid marine alkaloids, however the majority of higher plants, isoquinoline alkaloids are present. The fundamental structural element is the isoquinoline nucleus. Numerous therapeutic effects, these particular alkaloids contain substances that have antiviral, antifungal, anticancer, antioxidant, antispasmodic, and enzyme inhibitory properties. Morphine and codeine are the two most significant and extensively studied isoquinoline alkaloids. They originate from tyrosine or phenylalanine.

They are produced using a ketone or an aldehyde and the precursor of dopamine (3, 4-dihydroxytryptamine). These alkaloids are further divided into the following categories: Simple isoquinoline alkaloids, such as salsoline and mimosamycin; benzylisoquinoline alkaloids, such as reticuline and imbricatine; bisbenzylisoquinoline alkaloids, such as fumaricine; manzamine alkaloids, such as manzamine a; pseudobenzylisoquinoline alkaloids, such as polycarpine and ledecorine; and secobisbenzylisoquinoline.

A vast family of naturally occurring substances known as isoquinoline alkaloids exhibits a wide variety of structural variation as well as biological and pharmacological activity. Much work has been done over the past 10 years to develop efficient synthetic methods to obtain these alkaloids in chiral nonracemic form. There have been a variety of approaches used that rely on diastereoselective or enantioselective catalytic processes For a very long time, isoquinoline alkaloids have been important targets for chemical synthesis, both as a source of intellectual challenge and as substances with potential medical value.

Recently, chiral N-sulfinyl β-arylethylamines have been employed as substrates for the asymmetric synthesis of isoquinoline alkaloids.72,73 The Mexican–Spanish team72 in a short and efficient synthesis of (+)-crispine A (177) applied sulfinamide

193, which was prepared from β-3,4-dimethoxyphenylethylamine and (S)-menthyl p-toluene sulfinate as the starting compounds [1].

5.1 Using chiral Oxazoloisoquinoline 794 and Arylmagnesium bromide as a substrate, (S)-(+)-Cryptostyline II (793) is synthesised

By cyclocondensing 4,5-dimethoxy-2-vinylbenzaldehyde with (R)-phenylglycinol in Asao's method, the main substrate, the oxazoloisoquinoline, was produced in 72% yield as a 93:7 combination of diastereomers and used for the synthesis of (S)-(+)-cryptostyline II (**Figure 5**). Thus, the reaction of 794 with 3, 4-dimethoxyphenylmagnesium bromide produced addition product 797, from which, after the chiral inductor was removed and N-methylation was performed, the target alkaloid 793 was recovered with 96% in 57% overall yield (**Figure 6**).

Amat's group employed it as a substrate for the synthesis of C-1-substituted tetrahydroisoquinoline derivatives (**Figure 6**), including alkaloids, starting with oxazolotetrahydroisoquinolone 795 made from aldehyde ester 796 and (R)-phenylglycinol in 58% yield (**Figure 5**). As a result, the reaction of 795 with the proper Grignard reagents produced addition products 798, which were separated as single isomers in a yield of 49–63%. (**Figure 7**) Removal of the N-chiral auxiliary led to lactam 799, in which reduction of the lactam carbonyl fulfilled the synthesis of five alkaloids: (−)-salsolidine (559), (−)-O,O-dimethylcoclaurine (ent-581), (−)-norcryptostyline II (ent-245), norcryptostyline III (558), and (−)-crispine A (ent-177) [24].

6. Indole Alkaloids

Terpenoid indole alkaloids are present in a large number of plant species from the families Apocynaceae, Loganiaceae, Rubiaceae, and Nyssaceae (TIAs). TIAs are a broad class of structurally varied molecules that include substances with interesting pharmacological properties. The anti-neoplastic drugs vincristine and vinblastine, the anti-hypertensive drugs reserpine and ajmalicine, as well as the anti-arrhythmic drug ajmaline, are only a few of the terpenoid indole alkaloids used in modern medicine. The intermediate strictosidine, which is created by combining the amino acids

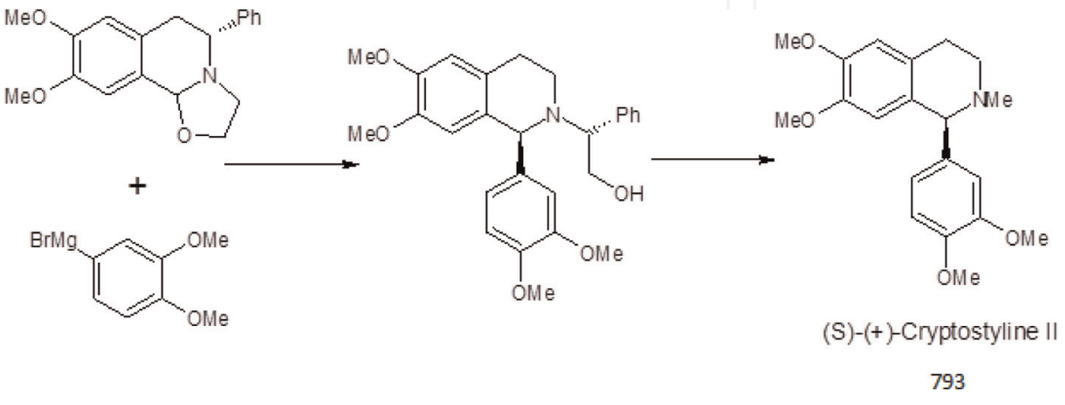

Figure 6.
Synthesis of Cryptostyline II.

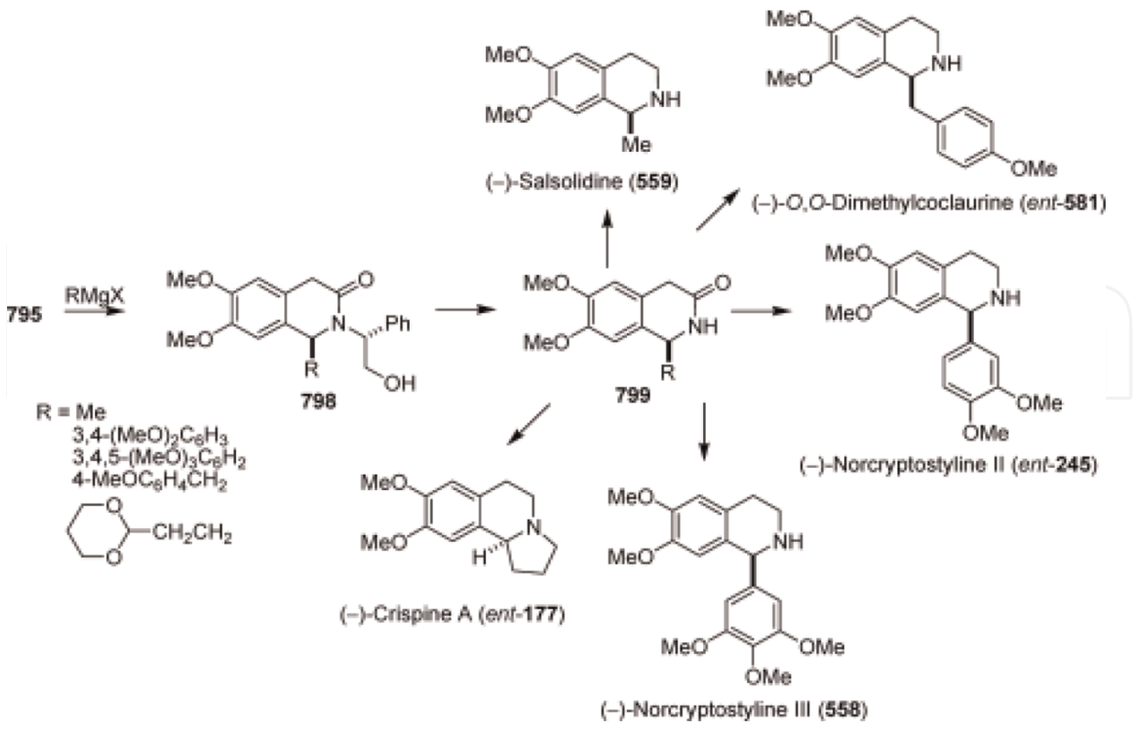

Figure 7.
Synthesis of Norcryptostyline. Grignard reagent reaction of Oxazolotetrahydroisoquinolone 795 with a series of 1-substituted Isoquinoline Alkaloids.

tryptamine and secologanin, which are respectively generated directly from the amino acid tryptophan and indirectly from (10-hydroxy-) geraniol, is essential to the biosynthesis of all terpenoid indole alkaloids [25].

7. Retrosynthetic analysis of arbornamine (monoterpene indole alkaloid)

Arbornamine (1) is a monoterpene indole alkaloid that was discovered in 2016 by Kam and co-unique from a Malayan Kopsia arborea. It has a unique 6/5/6/5/6 "arbornane" skeleton that is different from those of the eburnane and tacaman classes families (**Figure 8**).

Arbornamine's (1) retrosynthesis calls for the worldwide Pentacyclic lactam 4 is reduced and produce the amino moiety and hydro Xymethine group. It was believed that the pentacyclic lactam 4 would result from a reductive Heck cyclization of vinyl iodide 5.4. The tetracyclic-lactam 6 would result from a The tryptamine derivative 75 and the dimethyl ester 8 of 2-ketoglutaric acid undergo Pictet-Spengler cyclization/ intramolecular ammonolysis. The unsaturated tetracyclic-lactam 5 may then created from there. The tryptamine Nb-nitrogen atom has a protecting group called a benzyl group. An undesirable regioisomeric -lactam 9 makes this design strategically important. In the foregoing one-pot reaction, it might have been produced if the free tryptamine had been employed.

We started our synthesis with a key cascade cyclization. According to **Figure 6**, The tetracyclic -lactam 6 was isolated in a yield of 73% by heating benzyl tryptamine 7 with dimethyl ester 8 and 2 equiv. of TFA in refluxing toluene. Using Pearlman's catalyst, −lactam 6 was first hydrogenolyzed under atmospheric pressure to produce vinyl iodide under the circumstances required for the Nb-nitrogen atom's

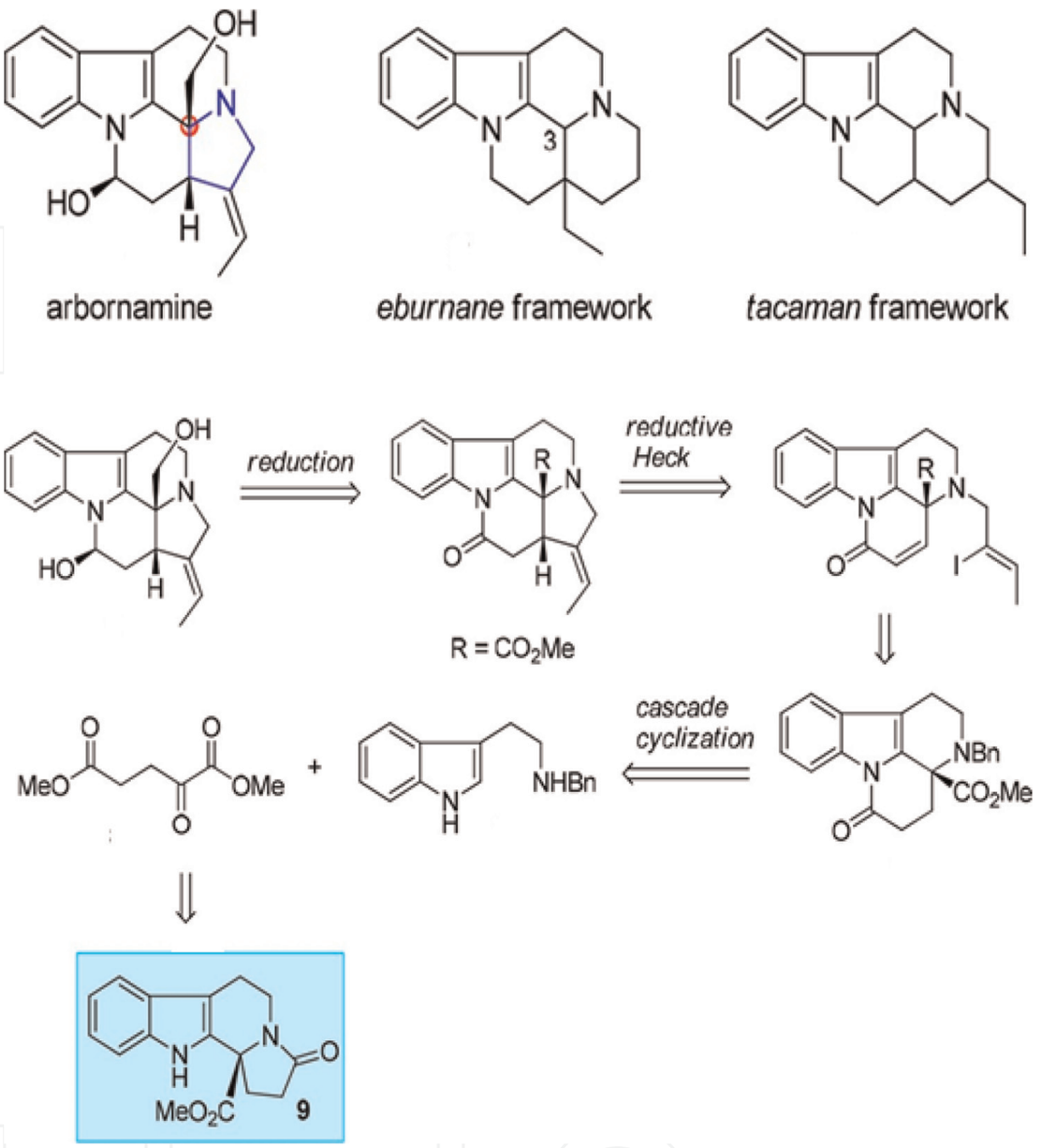

Figure 8.
Synthesis of monoterpene indole alkaloid.

benzyl protective group to be removed and transform it into 11. Thereafter, easily reachable The product was alkylated with (Z)-1- bromo-2-iodobut-2-ene7 to create vinyl iodide 11.

To produce arbornamine, it was globally reduced using lithium aluminium hydride (1). Both the methyl ester and the -lactam have been decreased during this process. The great facial selectivity of -lactam reduction was most likely related to the C-3 methyl ester's top-side shielding action, which allowed the hydride to approach from the bottom side. The synthetic sample's NMR results match those from the literature. As a result, we have created a brief initial method for arbornamine (1), a recently identified monoterpene indole alkaloid, to be completely synthesised. Six steps were all that it took to complete the synthesis, which had a 31% total yield. With the exception of the phase where the N-benzyl protecting group is cleaved, which is used deliberately to prevent the creation of the undesirable product, each step is effective in increasing molecular complexity.

Our synthesis got underway with a critical cascade cyclization. According to above Synthetic pathway, the tetracyclic -lactam 6 was isolated with a yield of 73% the benzyl tryptamine 7 is heated along with the dimethyl ester 8 and two equivalents of TFA in refluxing toluene. At room temperature and pressure, −lactam 6 was first hydrogenolyzed with Pearlman's catalyst to produce vinyl iodide, which was then applied to remove the benzyl protecting group from the Nb-nitrogen atom and transform it into 11. The result was then alkylated with easily available (Z)-1- bromo-2-iodobut-2-ene7 to create vinyl iodide 11. Combining vinyl iodide 11 with a common selenenylation/elimination procedure produced a conjugated tetracyclic -lactam 5. The scene was prepared for the last ring's completion with - lactam 5 in hand. Using a reductive Heck cyclization, Ni(cod)2 was used to mediate the creation of the necessary pentacyclic product 4 in 91% yield. The next product was a pentacyclic -lactam 4. Remaining solvent signals for CDCl3 were detected by 1H NMR (7.26) and 13C NMR (77.0). The following peak multiplicities were noted: Brs for electrospray ionisation (ESI), high resolution mass spectral (HRMS) data were acquired, and There were reported mass-to-charge ratios (m/z). Melting points were determined on a WRX- 5A melting point apparatus [25].

8. Tropane alkaloid

In general, but not always, the roots are where tropane alkaloid production takes place. Translocation then takes place through the aerial sections' xylem, where limited further metabolism may occur. For instance, many Datura species only convert hyoscyamine to hyoscine in the roots, so some synthesis may possibly take place in the aerial parts. For instance, despite the fact that A. Concentrations of mydriatic alkaloids are present in belladonna scions grown on foreign stocks and detached leaves of *A. belladonna* were discovered to have an increase in alkaloid content after 5 days, which was associated with a decrease in protein nitrogen (171).

From grafting studies, which typically used stocks and scions from plants of various solanaceous genera containing distinct alkaloids, such as Datura and Nicotine, it was possible to infer the root origins and subsequent migrations of alkaloids in a number of species (**Figure 9**).

8.1 Biosynthetic pathway of tropane alkaloid

Arginase is aAR. Ornithine decarboxylase, abbreviated ODC. Putrescine N-methyltransferase, or PMT. N-methylputrescine oxidase, or MPO. Tropineforming Reductase, abbreviated TRI. littorine mutase, CYP80F1. The hydroxylase of hyoscyamine 6 (H6H). Transferase for aromatic amino acids, AT4. Phenylpyruvic acid reductase, or PPAR.

8.2 Tropate ester biosynthesis

The (S)-tropic acid 7 ester moiety is a structural component of the alkaloids hyoscyamine 1 and scopolamine 2. Since even before the year 2000, there has been active discussion about the The biosynthesis of tropic acid 7, and the matter is still unresolved, at least in the finer points. We need to go back and look at Robinson's work from the years 1927 and 1955, when he first brought the topic of tropic acid biosynthesis to light and then went into greater detail about it in his book on the

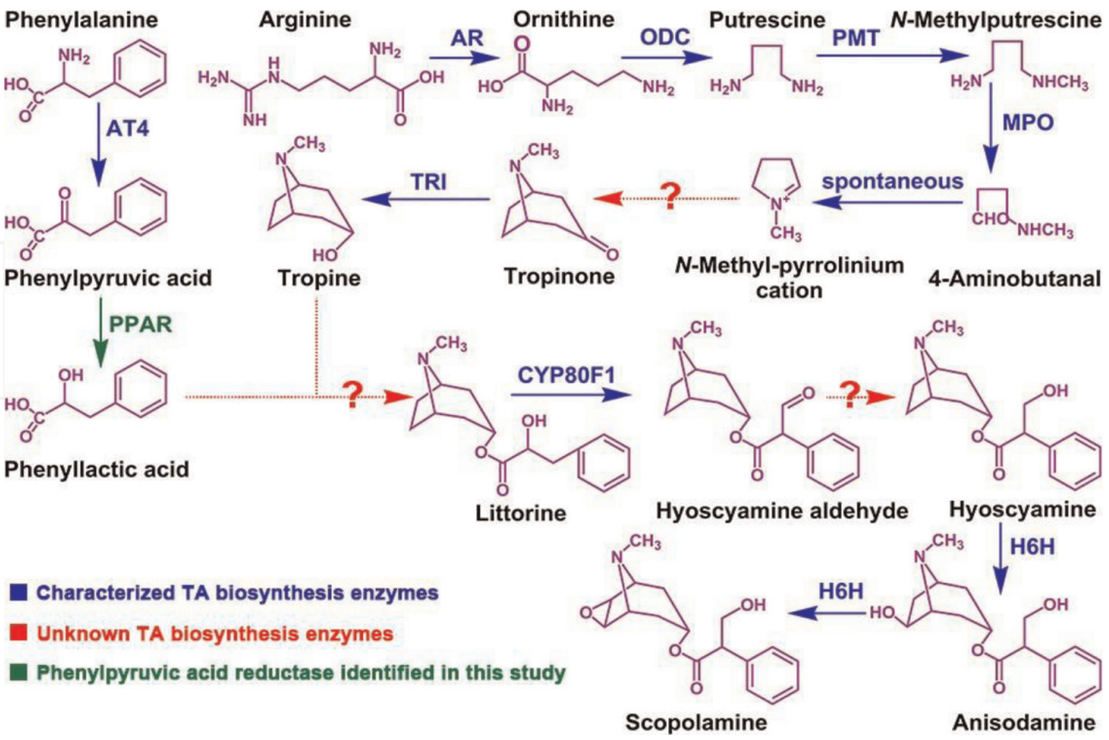

Figure 9.
Tropane alkaloid synthesis. Tropane Alkaloids' proposed biosynthetic pathway in the Solanaceae.

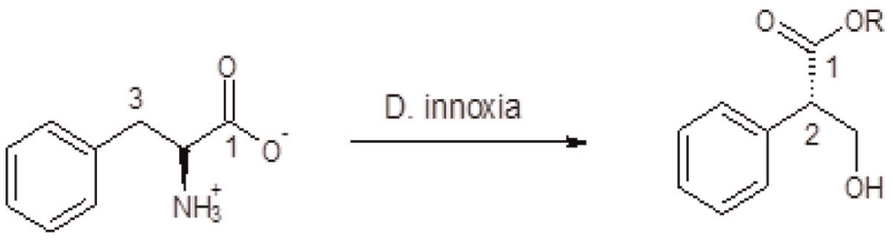

Figure 10.
Ester alkaloid synthesis.

structural relationships of natural products. The fact that tropic acid 7 has a branching carbon skeleton and must originate either from the isomerization of a phenylpropionoid moiety or through a unique synthesis was acknowledged. After feeding (1, 3-C_2) phenylalanine to Datura innoxia, Leete was able to conclusively demonstrate that it derived by isomerization. As indicated in the following scheme, the resulting hyoscyamine 1C now has the isotopes close to one another in positions C-1 and C-2 of the alkaloid (**Figure 10**) [26].

9. Xanthine alkaloids

Purine alkaloids, commonly referred to as xanthine alkaloids, consist of methylxanthines and methyluric acids and their structures are based on the xanthine and uric acid skeletons. Coffee (Coffea arabica), tea (*Camellia sinensis*), mate (*Ilex paraguariensis*), cocoa (*Theobroma cacao*), and guarana (*Paullinia cupana*), which are used to make popular non-alcoholic beverages, all contain caffeine

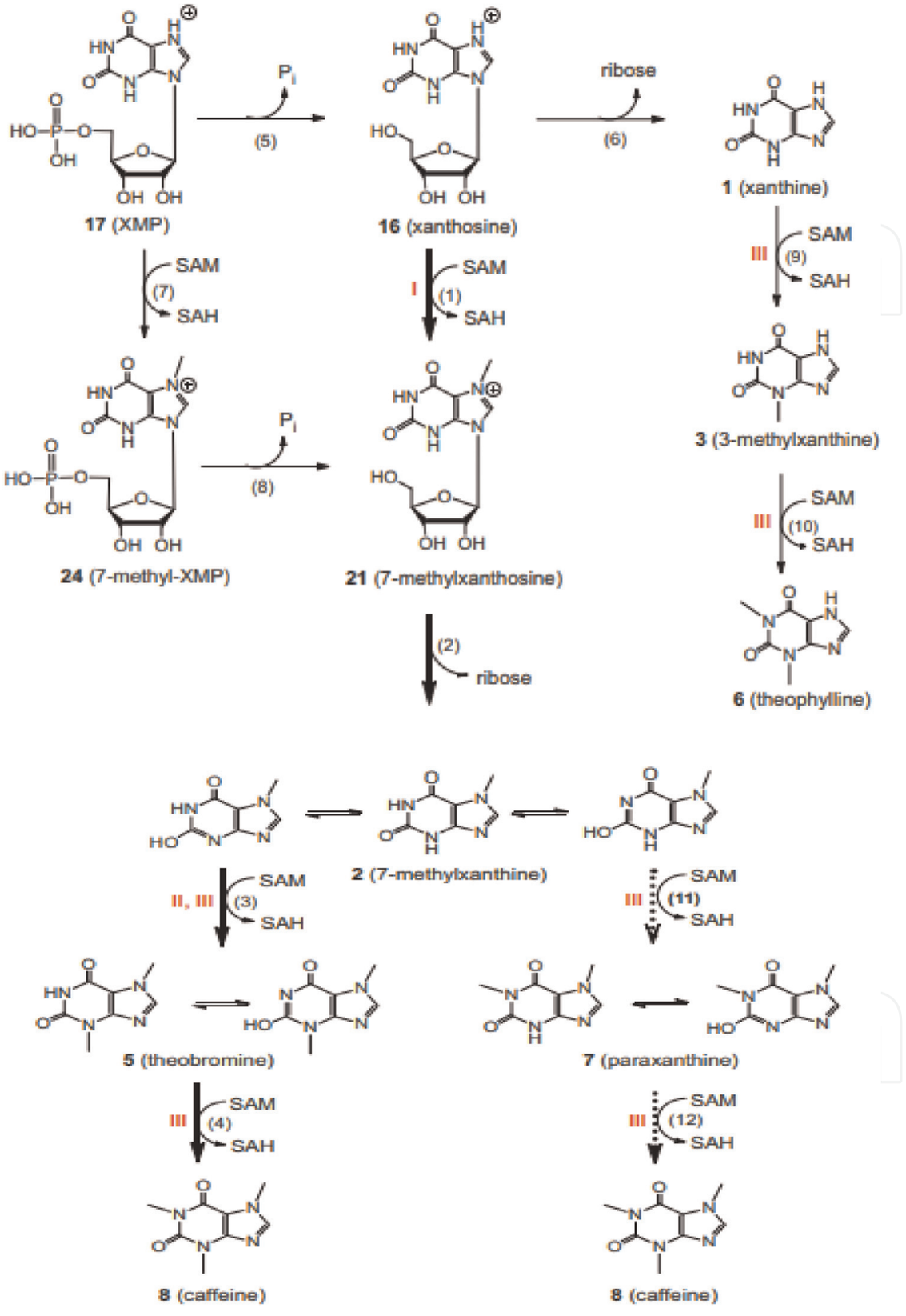

Figure 11.
Synthesis of caffeine.

(1, 3, 7-trimethylxanthine) and theobromine (3,7-dimethylxanthine). The isolation Caffeine of from coffee seeds was first reported independently in 1820 by the German researchers, Runge and von Giese. Caffeine was found as "thein" in tea

leaves by Oudry in 1827. Daniell discovered it in kola nuts (*Cola acuminata*) in 1865, while Stenhouse discovered it in mate' in 1843. Woskresensky identified theobromine in cacao seeds in 1842. Salomon discovered paraxanthine (1,7-dimethylxanthine) from human urine in 1883, but Chou and Waller did not find it in coffee seeds until 1980. Fischer and Ach published the complete chemical synthesis of Caffeine in 1895. Studies on caffeine biosynthesis were initiated in the 1960s, while highly purified caffeine synthase was isolated by Kato et al. (**Figure 11**) [27].

Solid arrows represent the four steps that make up the main pathway (steps1–4). Three different N-methyltransferases are shown as I, II, and III: caffeine synthase, theobromine synthase, and 7-methylxanthosine synthase. N-methylnucleosidase is responsible for catalysing the second step, which converts 7-methylxanthosine to 7-methylxanthine. I, III. Due to the broad substrate specificities of caffeine synthase, minor routes, denoted by dotted arrows, may take place (III). The production of 7-methylxanthosine from XMP via 7-methyl-XMP (steps 7–8) was suggested by Schulthess et al. [109], but no recombinant N-methyltransferases have been found to catalyse these conversions [27].

10. Pyrrole-imidazole alkaloids

As an example, consider the pyrrole-imidazole alkaloids (**Figure 1A**). Sponge natural products classified as pyrrole-imidazole alkaloids have approximately 150 congeners and are a broad and highly intricate class. Because of their chemical complexity, pyrrole-imidazole alkaloids have undergone a number of structural revisions, provided title compounds for organic synthesis, and maintained pharmaceutical interest due to their attractive bioactivity profiles. The enantioselective dimerization of three important monomeric building blocks, oroidin (1), hymenidin (2), and clathrodin (3), is suggested by retrosynthetic pathways for pyrrole-imidazole alkaloids. In fact, in vitro biomimetic research, these monomeric building blocks were dimerized utilising enzymes isolated from sponges that contained pyrrole-imidazole alkaloids. But there have not been many insights into the biosynthesis of 1–3 themselves; the only information we presently have came from observing the incorporation of radiolabeled amino acid precursors into 1 product (**Figure 12**) [28].

11. Synthesis of pyrrole-imidazole alkaloids is proposed

Retrobiosynthetic plan explaining how product 1 is produced from the building blocks of amino acids. 8 and 9 are hypothesised to be directly connected with pyrrole carboxylic acids in the chemical structures of pyrrole-imidazole alkaloids (B-E) EICs and MS^2 spectra mirror plots comparing the *Stylissa* metabolome's 7–9 and 11 identified metabolites to synthetic standards. We have highlighted important MS^2 ions (**Figure 13**).

Barbaleucamides A–B are shown in the metabolome BPC, which has superimposed EICs showing their existence. (B) EICs, produced within 1 ppm error tolerance for 7–12 across *Stylissa, Axinella, Agelas*, and *Dysidea* polar metabolomics LC/MS datasets. With the exception of EIC 7, which has the high abundance structural annotations of fragment ions, all EIC y-axes are similar as indicated. Each structural annotation's

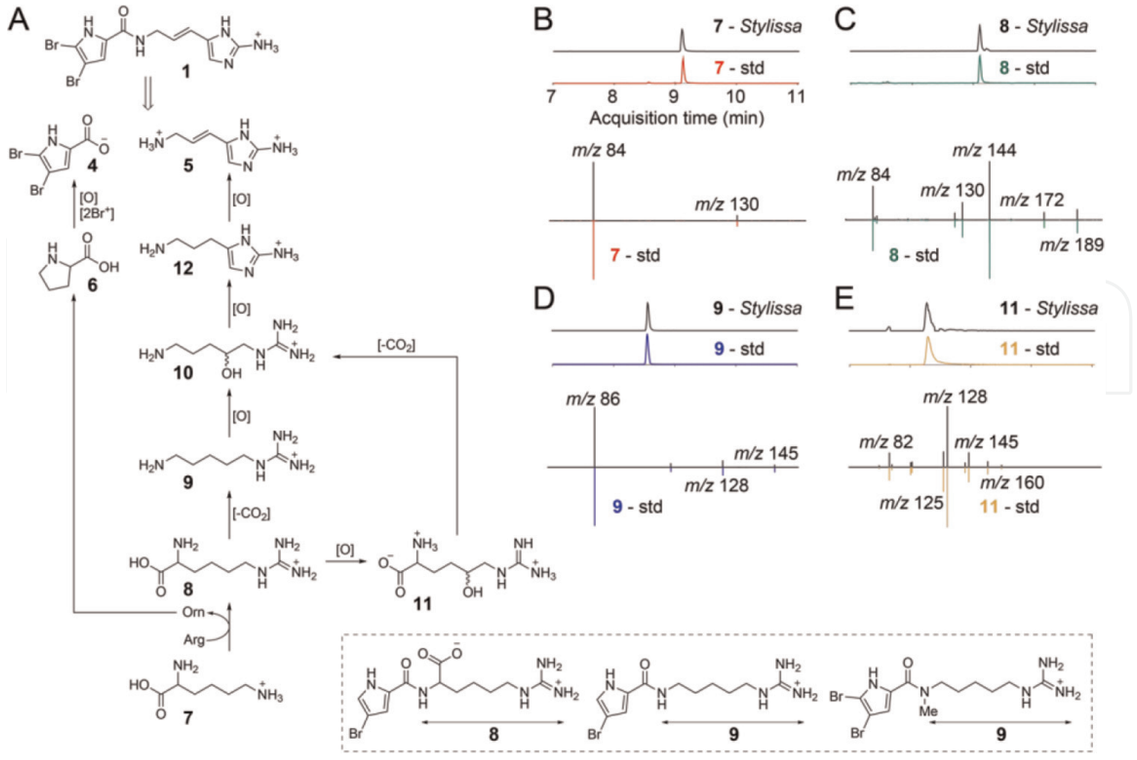

Figure 12.
Pyrrole imidazole alkaloid synthesis.

related ppm mistake is listed. The MS^2 spectra displayed here were obtained using an orbitrap mass spectrometer and extremely precise Fourier transform mass spectrometric fragmentation.

12. Piperidine alkaloids

This class of alkaloids' primary ring system is the piperidine nucleus. Monocycle molecules with the C5N nucleus are the primary defining feature of true piperidine alkaloids. The odour of piperidine alkaloids is one of their shared characteristics. They lead to long-term neurotoxicity. The majority of them come from plants. Even though the piperidine alkaloid is made from lysine, some piperidine alkaloids, like the straightforward pyrrolidine alkaloids, are also made from acetoacetate. Lobeline is a major alkaloid in this group [22].

13. Imidazole alkaloid

The imidazole ring structure of this form of alkaloid is what makes it unique. Since the imidazole ring was already formed during the precursor step, these alkaloids constitute an exception to the structure-transformation process. This type of structurally diverse alkaloids occurs in a variety of situations, particularly in marine and microbial alkaloids. They have a significant potential for therapeutic use and demonstrate a wide spectrum of biological activities [29].

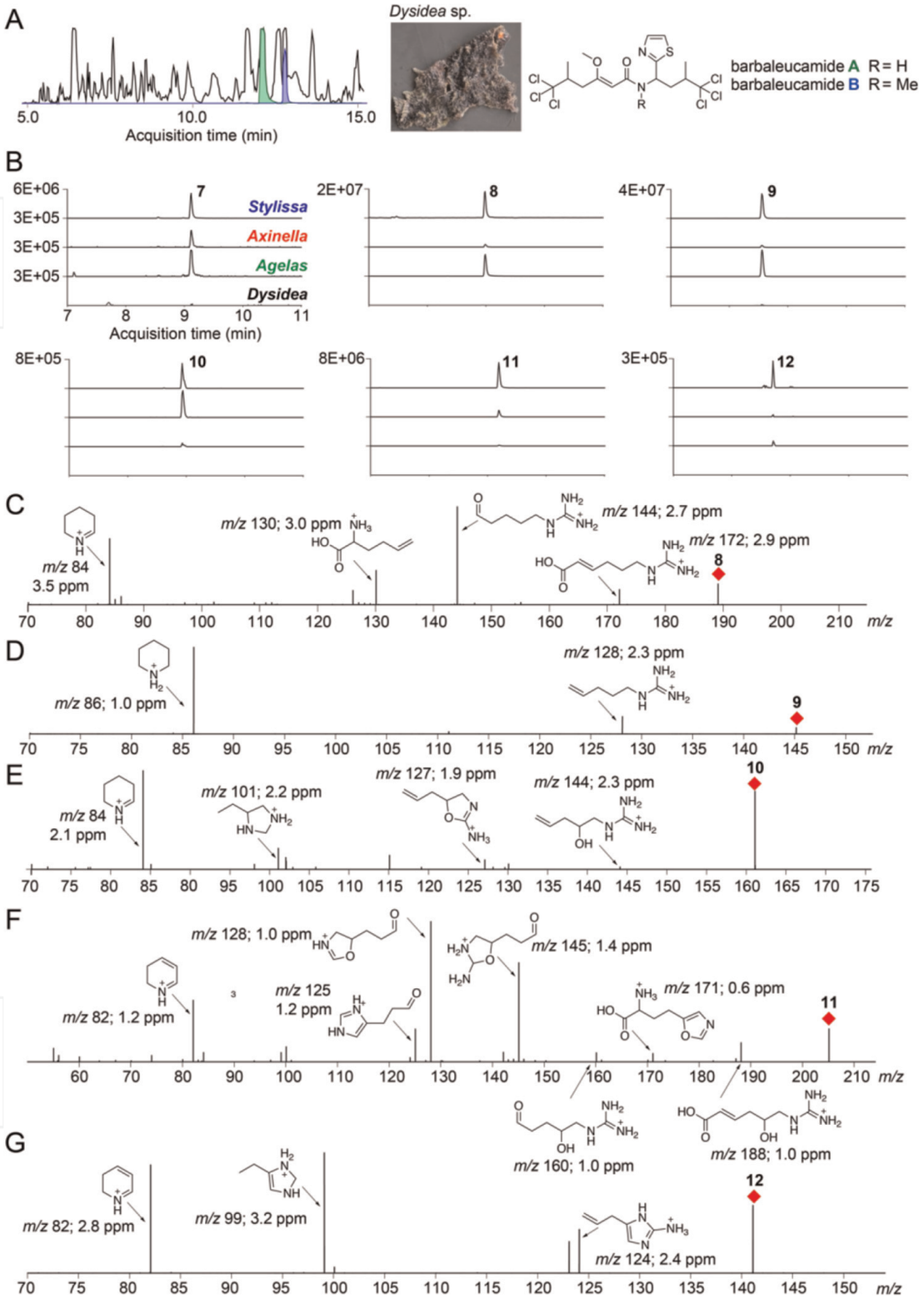

Figure 13.
List of pyrrole-imidazole alkaloid biosynthesis intermediates that have been rationalised. A Dysidea species.

14. Pyrrolizidine alkaloids

The pyrrolizidine nucleus is the defining characteristic of this class of alkaloids. Plants from the Fabaceae and Asteraceae families contain them. The bulk of

pyrrolizidine alkaloids are present in plants as N-oxides, but when they are separated, they lose their functionality. A lot of research has been done on alkaloids because of their potentially harmful side effects, particularly liver damage. The animals that consume these alkaloids become antifeedants when they enter the food chain [30].

Acknowledgements

All authors are thankful to management and principal of Dadasaheb Balpande College of diploma in Pharmacy, Nagpur.

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