Pyrrolizidine Alkaloids Pyrrolams A-D: Survey on Synthetic Efforts, Biological Activities, and Studies on their Stability

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Abstract

Pyrrolam A, is a microbial metabolite structurally related to plant alkaloids of the necine type, and was isolated from the bacterial strain of \textit{Streptomyces olivaceus} along with its related alkaloids pyrrolams B–D. (S)- and (R)-pyrrolam A has stimulated much attention from synthetic chemists in recent years, with 10 syntheses reported to date. The reported routes widely utilized the advantage of pre-existing chiral proline as starting material with pyrrolidine nucleus as source of one of the two rings on which the second ring have been constructed. This review delineates the isolation of deceptively simple pyrrolizidine alkaloid, pyrrolam A, its biological studies, laboratory syntheses as well as computational studies for the stability of double bond in strained bicyclic skeleton. In addition, the synthesis of pyrrolams B-C and their relation with pyrrolam A has been also discussed.

Keywords

Bicyclic compound; metabolites; natural product; pyrrolams; pyrrolizidine alkaloids
Introduction:

The chemicals from nature are ubiquitous part within medicine. It has been witnessed for several decades that the natural products, especially alkaloids have been the rich source of agent’s value in medicine and is highly effective source of the drug design. The alkaloids, an ocean of diverse chemicals and biomolecules is one of the important class of natural products which have been distributed extensively in plant kingdoms. Moreover, alkaloids figure as a very prominent class of defense compound amongst the plant secondary metabolites. A typical member of alkaloid so-called ‘izidine alkaloids’ is popular amongst synthetic and medicinal chemists, not only because of their diverse biological activities, but also because they endow with challenging targets for testing new synthetic protocols. The fashionable structural features of the izidine alkaloids (pyrrolizidine, indolizidine, quinolizidine) with two rings skeleton is an important structural fact for their biological properties (Figure 1). Furthermore, these alkaloids are also responsible for the disturbance of DNA/RNA and related enzymes. In particular, the pyrrolizidine alkaloids are known to form covalent adduct with DNA bases and also inhibits the ribosomal protein biosynthesis. Although, many alkaloids are famous for their strong toxicity towards animals and humans, they still play pivotal role in immune systems of plants and animals, and proved as successfully used drugs throughout historical treatment of many diseases. As consequences, the pyrrolizidine alkaloids have been extensively reviewed for their evolution of biosynthesis, to explore biological significance and also their synthetic survey over the past several decades. The unique class of pyrrolizidine ring systems with 1,2-unsaturated-1-methylpyrrolizidine functionalized by hydroxyl or ester moieties, where in the nitrogenous alcohol part are known as necines have received considerable interests as several of them shows interesting physiological and pharmacological behavior (e.g. retronecine, supinidine, heliotridine, indicine-N-oxide etc.) (Figure 1). Additionally, the pyrrolizidine alkaloids (PAs) have been extensively studied for their potent glycosidase inhibitory activity, which makes them good candidates as new drugs paradigm for the treatment of many diseases such as cancer, viral infections, diabetes, and so-forth.

![Skeleton of izidine alkaloids and various PAs containing necine bases](image)

**Figure 1:** Skeleton of izidine alkaloids and various PAs containing necine bases
Not surprisingly, a vast body of research has been conducted regarding the syntheses of these alkaloids. The simplest representative example of these class of alkaloids is pyrrolam A. Pyrrolam A has been synthesized on several occasions by different research groups.

**Isolations and biological activity:**

The genus streptomyces has been shown to produce number of secondary metabolites possessing promising biological profile. In 1990, the screening of culture broth of bacterial strain *Streptomyces olivaceus* resulted in identification of four structurally related compounds of pyrrolizidones, namely, pyrrolams A-D (Figure 2). Since then, pyrrolam A has been a subject of fascinations particularly amongst synthetic chemists. The provocative structure of 1 consisting of bicyclic skeleton with a double bond embodied in the conjugation with carbonyl group in lactam ring makes this molecule unique amongst the pyrrolam family. In addition, the presence of double bond of necine base is an imperative factor to the hepatotoxic, mutagenic and carcinogenic nature of various PAs.

![Figure 2: Pyrrolams A-D and Dimer of pyrrolam](image)

The details of fermentation studies are already mentioned by Grote et al. during their isolation protocol wherein, the pyrrolam producing organism *Streptomyces olivaceus* ssp. *omniyanesis* was isolated from the soil sample obtained from Leshan (PR China). The ornithine amino acid is an important precursor of pyrrolidine nucleus, which is also found in pyrrolizidine alkaloids. Thus, in fermentation process, the strain (Tü 3082) was cultivated using soyabean meal, mannitol (2% each) and ornithin (20 mmol/L). The cultural broth after filtration was passed through resin XAD-16 and subsequent purification on silica gel column led to the isolations of novel pyrrolizidone derivatives, pyrrolams A-D. One attractive observation regarding the dimerization of pure pyrrolam A (on standing in open vessel) to give dimer resulted in the issues related to stabilities of these compounds under various conditions. Furthermore, another interesting fact of these findings would lead to pose question, whether pyrrolam A is a precursor of its other related molecules like pyrrolams B-D and vice-versa. The seriousness of these queries was realized by R. T. Watson group after 14 years since the initial isolation and came out with the reasonable solution using synthetic as well as computational methods. The detail analysis of energies of pyrrolams and their synthetic endeavor is discussed in last section of this review.
Speaking about biological significance in particular, pyrrolam A shows herbicidal activity against wheat and rice seedlings and also causing damage to the fertilized eggs at low concentration.\textsuperscript{11} Later, Jizba \textit{et al.}\textsuperscript{14} found that, both, pyrrolam A \textbf{1} and pyrrolam C \textbf{3} proved to be rather unstable by a non-enzymatic process, which results in transformation of pyrrolam A to pyrrolam C and mixture being approximately 1:2 ratio. As consequences, the acquisition of biological profile of pure \textbf{1} and \textbf{2} separately was difficult and hence it is also not justifiable to conclude that the observed insecticidal effect resulted from the action of both components of the mixtures, or only one of them. But corresponding to the biological profile suggested by Grote \textit{et al.}, who did not observe insecticidal activity of \textbf{1} and \textbf{2} could be the active agent. In spite of this fact the two derivatives of pyrrolam could be considered as active metabolites contributing, together with macrotetrolides\textsuperscript{15} and nonactic acids to the complex insecticidal activity exhibited by \textit{S. globisporus} 0234 and \textit{S. griseus} LKS-1. The significant biological activity of pyrrolam A together with its structural relationship with necine nucleus sparks the attention of chemists in order to develop new methodologies to deliver the compound in large scale, which could facilitate the detail SAR studies of this class of alkaloids.

\textbf{Synthetic approaches:}

The interesting biological activity of the pyrrolams, together with its biogenetically close relationship to necines core (although pyrrolam has bacterial origin and the PA’s are isolated from plants or, in some cases, insects), triggered an immediate attempt to synthesize the molecule. Five years after its initial isolation, the first synthesis was completed by Procter and co-workers in 1994 and then subsequently many syntheses have appeared in literature. The most common synthetic procedures to both the enantiomers of pyrrolam A involves utilization of proline derivatives or suitable amino acids as substrates of choice, being the chirality of the precursors transferred to the target compound \textbf{1}. The chiral pool approach exploits proline as a starting material, which has an advantage of being cheap and also exists in both the enantiomeric forms. The various synthetic methods for the naturally occurring (\textit{R})-pyrrolam A, and its enantiomer have been reported. They have been classified into two main categories according to the starting material utilized (a) chiral pool methods- proline as starting material, (b) miscellaneous methods.

\textit{(a) Chiral pool methods- proline as starting material:}

The construction of heterocyclic compounds using SmI\textsubscript{2} is well renowned in organic synthesis.\textsuperscript{16} Ayogi \textit{et al.} has disclosed the applicability of samarium iodide mediated cyclization for building bicyclic skeleton in their synthesis of pyrrolam A.\textsuperscript{17}
**Scheme 1:** *Reagents and condition:* (a) i) LiAlH₄, THF, 71%, ii) (Et₂O)₂CO/K₂CO₃, 76%; (b) Lithiumphenylacetylide, 62%; (c) NBS/ PPh₃, 86%; (d) SmI₂, HMPA, 0 °C, 90%; (e) O₃/ Me₂S, 94%; (f) Tf₂O, iPr₂NEt, 50%; (g) Pd(PPh₃)₄/ LiCl, Bu₃SnH, 83%.

Thus, the reduction of D-proline with LAH, followed by cyclization of amino alcohol using diethyl carbonate provided bicyclic oxazolidinone 8, which, when treated with lithium phenyl acetylide, furnished the N-substituted alcohol 9. Conversion of alcohol 9 to bromo compound 10 using NBS/PPh₃ system followed by treatment with SmI₂ provided cyclized pyrrolidone 11. The SmI₂-mediated intramolecular coupling reaction between the haloalkyl and the ynamide group is highlight of this approach. Furthermore, the treatment of 11 with O₃ gave ketoamide 12, which on trifluromethane sulfonylation, provided triflate 13. Reduction of 13 with Bu₃SnH in the presence of Pd (PPh₃)₄ produced (+)-pyrrolam A 1 (Scheme 1).

**Scheme 2:** *Reagents and conditions:* (a) LDA, or LHMDS, THF, -78 °C; (b) NaBH₄, EtOH, rt; 24 h, 69% (2 steps); (c) MsCl, Et₃N, CH₂Cl₂, 0 °C to rt, 5 h, 85%; (d) Et₃N, CHCl₃, reflux, 5 h, 98%.
In 1994, Procter G. R. research team has reported their studies on the application of N-acetyl and N-propionyl anion cyclization reaction in the synthesis of natural pyrrolizidines, wherein, pyrrolam A had been synthesized for the first time in 93.5 % ee.\textsuperscript{18a} Later, in 1996 same group has published identical results towards synthesis of pyrrolam A along with other members of this class of alkaloids.\textsuperscript{18b} The author’s approach was based on cyclization of N-methoxy-N-methyl amide 14 to dione 15 via N-acetyl anion-cyclization reaction. The requisite N-methoxy-N-methyl amide 14 was prepared from N-acetyl prolinate via a mixed anhydride protocol. Reduction of keto functionality of 15 with NaBH\textsubscript{4} furnished alcohol 16, which was subjected to mesylation (MsCl) followed by treatment with triethylamine in refluxing CHCl\textsubscript{3} afforded (S)-pyrrolam A 1 (Scheme 2).

\begin{center}
\textbf{Scheme 3: Reagents and condition:} (a) (Boc)\textsubscript{2}O, CH\textsubscript{2}Cl\textsubscript{2}, rt; (b) triethyl methanetricarboxylate (TEMT), PPh\textsubscript{3}, DEAD 58\% (2 steps); (c) i) TFA, CH\textsubscript{2}Cl\textsubscript{2}, rt, ii) 12N HCl; (d) HMDS, TMSCl, MeCN, reflux, 57\% (2 steps); (e) i) LDA, THF, -78 °C, ii) PhSeCl then H\textsubscript{2}O\textsubscript{2}, 90\% (2 steps).
\end{center}

Giovenzana et al. published their studies directed towards the synthesis of (R)-pyrrolam A with the use of Mitsunobu reaction as a key step for the dehydrative alkylation of protected (R)-prolinol with methanetricarboxylate.\textsuperscript{19} Thus, (R)-N-Boc-prolinol 19 was treated with methanetricarboxylate under Mitsunobu condition to give N-Boc triester 20. Further, the two carbon homologated L-proline 21 was obtained \textit{via} Boc-deprotection using trifluoroacetic acid, followed by addition of excess of 12 N HCl. Subsequent cycloamidation was achieved in the presence of HMDS (10 equiv.) and TMSCl (cat.) under refluxing condition. Finally, the installation of the double bond using selenyl chemistry (addition/elimination strategy) provided (R)-pyrrolam A 1 (Scheme 3).
Ring Closing Metathesis (RCM) has played a prominent role in synthetic chemistry of cyclic molecules, such as carbocycles, heterocycles and macrocycles. Hence, several applications of RCM to total synthesis of complex natural products have been extensively reported.\textsuperscript{20} Arisawa et al. used RCM for synthesis of pyrrolam A from diene prepared from proline as a starting material. L-proline was converted to methyl-N-Boc-L-prolinol via a couple of steps.\textsuperscript{21} This was further converted to aldehyde by reduction with DIBAL. Wittig olefination followed by deprotection furnished a pyrrolidinone which, on acylation with unsaturated acid in the presence of diethylphosphorocyanidate gave chiral diene. Chiral diene was subjected to RCM using Grubbs catalyst to give (S)-pyrrolam A. The low yield observed in this approach is attributed to the instability of the product under the reaction conditions used (Scheme 4).

Next approach from our laboratory for pyrrolam demonstrates the utility and applicability of the domino primary alcohol oxidation Wittig reaction (Scheme 5).\textsuperscript{22} L-Proline was converted to N-protected prolinol which was treated with PCC/NaOAc and phosphorane (one-pot) to give α,β-unsaturated ester.
Furthermore, the N-deprotection and double bond reduction, followed by cyclization under basic condition (cat. NaOEt) furnished dihydropyrrolam 28. A one-pot selenium addition/elimination process delivered pyrrolam A 1, but the chromatographic purification of pyrrolam A (removal of unreacted PhSeCl) led to the chemical conversion to its related molecule pyrrolam C. Hence, it has been concluded that, the initially formed pyrrolam A caused isomerization of double bond on silica gel and captured water to give pyrrolam C. Such conversion was addressed first time by Watson R. T et al. This suggests that pyrrolam C may well be an artifact of the isolation process arising from pyrrolam A. To circumvent the problem, the selenyl derivative 29 was purified prior to oxidation (H2O2, NaOH). Finally, oxidative-elimination of selenyl derivative delivered pure pyrrolam A in good yield.

A concise approach towards pyrrolam A was reported by Schobert et al. via domino sequence involving addition-Wittig alkenation reaction with ylide (Ph2PCCO immobilized polystyrene resin) and so benzyl prolinate 30 prepared from D-proline was reacted with the polymer supported cumulated ylide to give the corresponding tetramate.23 A formation of this tetramate was occurred via domino fashion involving the addition of amino group across the C= C bond of cumulated ylide and a subsequent intramolecular Wittig olefination of the acyl ylide. Furthermore, the hydrogenolytic debenzylation furnished dione 32, which on subsequent reduction using NaBH4, followed by mesylation, gave sulfonate. Refluxing of the sulfonate with Et3N afforded (R)-pyrrolam A 1 (Scheme 6).

\[
\begin{align*}
\text{30} & \xrightarrow{a} \text{31} & \xrightarrow{b} \text{32} & \xrightarrow{c} \text{33} & \xrightarrow{d} \text{(-)-1} \\
\end{align*}
\]

**Scheme 6:** Reagents and condition: (a) polystyrene-P(Ph)2=C=C=O, THF, 60 °C, 16 h, 80%; (b) H2, Pd/C, MeOH, 2 h, 99%; (c) i) NaBH4, CH2Cl2-AcOH, 53%, ii) MsCl, Et3N, CH2Cl2, rt, 16 h, 90%; (d) Et3N (7 eqv.), 40 °C, 18 h, 65%.

In an effort to establish a more practical and scalable route to pyrrolam A, another synthetic approach involving phosphorus ylide chemistry was simultaneously emerged from our group which demonstrates the practicability of intramolecular Wittig reaction for the construction of bicyclic skeleton of pyrrolam A (Scheme 7).24 Hence, prolinol was converted to (S)-N-(bromoacetyl)prolinol 34 using bromoacetyl bromide. (S)-N-(bromoacetyl)prolinol 34 on oxidation, followed by treatment with PPh3 gave corresponding Wittig salt 36. Deprotection using NaH gave (S)-pyrrolam A 1 *via insitu* formation of phosphorane 37 followed by intramolecular Wittig reaction in one pot.
Scheme 7: Reagents and condition: (a) i) LiAlH$_4$, THF, reflux, 8h; ii) NaOAc, ClCOCH$_2$Br, 0°C, 2 h, 65%; (b) PCC, CH$_2$Cl$_2$, rt, 6 h, 68%; (c) PPh$_3$, benzene, rt, 8 h; (d) NaH, THF, 0°C, 14 h, 41% (2 steps).

The chiral pool approaches have utilized either expensive unnatural D-proline or natural L-proline as source of chirality. Amongst these 7 routes, 3 have utilized ylide chemistry (Wittig olefination, Schemes 5-7) and, the immobilized polystyrene resin approach (Scheme 6) have been found to be superior over scheme 5 and 7 in terms of overall yield and elimination of purification step, but involves expensive chemicals (Scheme 8).

Scheme 8. Construction of pyrrolam skeleton using Wittig approach

b) Miscellaneous method:
An another asymmetric synthesis of (R)-pyrrolam A 1 using cheaply and easily available natural (S)-malic acid was reported by Huang P. Q. et al. which constitute a longest route to this alkaloid till date with reasonable overall yield.$^{25}$
Scheme 9: Reagents and condition: (a) i) AcCl, reflux, 2h, ii) 4-methoxybenzylamine, THF, rt, 18 h, iii) AcCl, EtOH, 50 ºC, 5 h (84%, 3 steps); (b) BnBr, Ag₂O, Et₂O, rt, 94%; (c) BnO(CH₂)₃MgBr, THF, 0 ºC, 90%; (d) Et₃SiH, BF₃OEt₃, CH₂Cl₂, -78 ºC-rt, 64%; (e) H₂; Pd/C, EtOH, rt, 80%, ii) p-TsCl, pyridine, CH₂Cl₂, 0 ºC-rt, 60%; (f) CAN, MeCN:H₂O, 0 ºC, 77%; (g) NaH, THF, -15 ºC-0 ºC, 83%.

(S)-Malic acid 38 was converted to (S)-malimide 39 via one-pot procedure using acetyl chloride, 4-methoxybenzylamine and acetyl chloride, a method previously reported by Louwrier et al.²⁶ Malimide 39 was subjected to O-protection using benzyl bromide to give benzyl ether 40. Reaction of compound 40 with 3-benzyloxy propyl magnesium bromide provided hydroxyl lactam 41, which on reduction with excess of triethylsilane, gave pyrrolidone 42. Selective removal of benzyl group by hydrogenation followed by ditosylation using TsCl, and oxidative N-deprotection using CAN provided ditosylated lactam 44. Finally, base-induced cyclization and elimination of tosyl group using NaH provided (R)-pyrrolam A 1 (Scheme 9).

Scheme 10: Reagents and conditions: (a) Boc₂O, Et₃N, DMAP, THF, 0 ºC, 2 h, 100%; (b) i) (-)-sparteine, sec-BuLi, -78 ºC, ii) CuCN·2LiCl, iii) (Z)-ICH=CHCOOEt, -78 ºC, 83%; (c) i) Me₃SiCl/ MeOH, ii) aq. NaHCO₃, 88%.
The most impressive synthetic route in terms of efficiency is that reported by Watson et al. wherein, authors have utilized α-(N-carbamoyl)alkylcuprate methodology to produce an efficient synthesis of \((R)\)-pyrrolam A (Scheme 10).\(^{13}\) Pyrrolidine 45 on protection gave \(N\)-Boc pyrrolidine, which was converted to stereogenic organolithium reagent by asymmetric deprotonation.\(^{27}\) Organolithium reagent was treated with CuCN•2LiCl to give lithium dialkylcuprate reagent, which gave vinylation product 47 upon quenching with (Z)-3-iodopropenate. The authors anticipated that the deprotection and cyclization should take place in single operation. In practice, the cyclization did take place with low yield of pyrrolam A \(^1\) using trifluoroacetic acid. Furthermore, amongst the different attempted conditions, the use of trimethylsilyl chloride/MeOH (methanolic HCl) was reported as an effective condition for one-pot conversion of (Z)-alkene 47 to \((R)\)-pyrrolam A \(^1\). This asymmetric synthetic route to pyrrolam A \(^1\) constitutes the shortest route to this alkaloid till date.

![Scheme 11](https://example.com/scheme.png)

**Scheme 11:** Reagents and conditions: (a) LHMDS, CH\(_2\)Cl\(_2\), -78 °C, 20 min, 70%; b) i) TFA/ MeOH, 0 °C to rt, 2 h, ii) Boc\(_2\)O, Et\(_3\)N, DMAP, THF, 0 °C, 2 h; (c) hv, 375W, benzene, 3 h, 60 % (3 steps); (d) Pd(PPh\(_3\))\(_4\), THF, rt, morpholine, 88%; (e) i) TFA, CH\(_2\)Cl\(_2\), rt, overnight, ii) LAH, THF, 60 °C, 4 h, iii) CH\(_2\)=CHC(O)Cl, K\(_2\)CO\(_3\), EtOAc/ H\(_2\)O, 0 °C, 5 min 60% (3 steps); (f) Grubbs 2\(^{nd}\) generation, toluene, overnight, 68%.

Wang and coworkers have developed diastereoselective nucleophilic addition approach involving lithium enolate of \(\alpha\)-diazoacetoacetate to chiral \(N\)-sulfinyl imine to construct the pyrrolidine skeleton and exploited this methodology for the synthesis of \((R)\)-pyrrolam A (Scheme 11).\(^{28}\) Addition of lithium enolate of \(\alpha\)-diazoacetoacetate to chiral \(N\)-sulfinyl imine 48 afforded \(\delta\)-\(N\)-sulfinylamino \(\alpha\)-diazo \(\beta\)-ketoester 50 with 97% de whose absolute configuration was established by X-ray analysis. \(N\)-sulfinyl group was replaced by \(N\)-Boc group using TFA and Boc-anhydride to give \(N\)-Boc protected diazo compound 51, which on irradiation with high-pressure Hg lamp (\(\lambda\)>300 nm) in a pyrex tube gave (5\(R\))-2-oxo-3-allyloxycarbonyl-5-vinylpyrrolidine 52. Vinylpyrrolidine 52 was formed through a photo-induced Wolff rearrangement.\(^{29}\) The Pd(PPh\(_3\))\(_4\)-catalyzed deallyloxycarbonylation in the presence of morpholine, followed by Boc-deprotection, LAH reduction, acylation and finally RCM reaction gave \((R)\)-pyrrolam A.
The miscellaneous methods (Scheme 9-11), employ very different concepts, starting from utility of natural malic acid for construction of pyrrolidine ring (longest sequence), asymmetric deprotonation using organolithium reagents (concise route) and last approach identified chiral N-sulfinyl imine (chiral auxiliaries) towards construction of pyrrolidine ring.

![Scheme 12](image)

**Scheme 12.** Competing synthetic route via RCM

Furthermore, the problem associated with RCM route in scheme 4 was successfully solved by Wang group (Scheme 11) by changing the diene which leads to increase the yield from 30 to 80 % for ring closing metathesis step (Scheme 12).

**Computational studies for evaluation of relative energies of pyrrolam isomers:**

The different computational methods and molecular mechanics approaches are available in literature to understand the molecular properties or structural stabilities of various conformers of the necine bases in particular retronecine and heliotridine as a typical representative example containing 1,2-unsaturated PAs.30 Watson et al. had first realized the need for the analyses of conformational studies of pyrrolam isomers, wherein the results were analyzed by comparing the data obtained by statistical methods with that of the calculated data obtained from experimental observations. Accordingly, various isomers of pyrrolam were synthesized in order to support the hypothesis of computational studies.13

![Scheme 13](image)

**Scheme 13:** Pyrrolam A 1 exist in two conformations, 1 and 1’
The possible double bond migration in pyrrolam ring is shown in scheme 13 (picture 1 and 1’ are taken from ref. 13). The MP2 model evaluation of the pyrrolam isomer energy surface as well as analysis of experimental observation under different reaction conditions concluded that the stability order is most likely $56 > 55 > 1$ with $\Delta G^{298}$ energy spread of 0.0, 0.6, and 1.4 kcal/mol (i.e. 12: 4: 1) respectively. Furthermore, compound 1 exists as a folded structure in two conformations, which are depicted in Scheme 13. The chair like form is more stable than the boat form of compound 1 by 1.1 kcal/ mol. Additionally, isomer 55 is nearly flat but sustains a slightly envelope shape in the saturated five-membered ring, whereas compound 56 is completely planar. Experiment to study the rearrangement of 1 to 55 was also carried out by Watson et al. Subsequent experiment with pyrrolam 1 (i.e. 55:1 = 15:85 ratio) and its isomer 55 (i.e. 55:1 = 99:1) led to almost identical 75:25 and 80:20 mixture of 55:1 respectively, when either sample was subjected to alumina column chromatography (EtOAc as eluent). Overall experiment leads to a conclusion that the 75:25 to 80:20 values represents the mixture at thermodynamic equilibrium under the particular reaction conditions.

**Pyrrolams B-D are artifacts: Pyrrolam captures Nucleophile**

The small strained cyclic molecule with conjugated functionality leads to the instability of pyrrolam A (Scheme 14). Hence, construction of small bicyclic skeleton is always challenging for the synthetic chemist. Studies towards the stability of the isomers of pyrrolam under various reaction conditions were demonstrated by Watson et al. Furthermore, the mystery of interconversion of pyrrolam isomers was successfully solved using synthetic as well as computational chemistry in combination.

![Scheme 14: Interconversion of isomers of pyrrolam](image)

Nucleophilic capture during preparation of 1 and 55 involves iminium cation such species is an obvious intermediate to both the oxygenated substances of pyrrolam and its dimer (pyrrolams B-D). To test this hypothesis compound 55 (isomer of pyrrolam) was treated with MeOH, H$_2$O or EtOAc under acidic conditions to get a complex mixture of products. Furthermore, treatment of 55 dissolved in EtOAc with wet silica gel cleanly gave pyrrolam C 3 in high yield, which in turn was converted to pyrrolam B 2 by treatment with methanol and dry silica gel.
Scheme 15: Formation of Pyrrolam C and Pyrrolam B

Although, pyrrolam D has not been synthesized till date, the formation of pyrrolam B, pyrrolam C, as well as dimer-pyrrolam from pyrrolam A suggest that pyrrolam D could be form in similar manner. These experiment by Watson and co-workers clearly suggest that the pyrrolams B-D are artifacts of the isolation procedure, rather than the metabolites from organism.

Conclusion:

Last three decades have witnessed a large increase in the number of publications on the chemistry and biology of pyrrolizidine alkaloids, where azabicyclo skeleton is an essential component of the target molecules in spite of their relatively small structures. The present review gives explicit information about the importance of deceptively simple pyrrolizidine skeleton of pyrrolam A, their natural occurrence, biological activities as well as structural stabilities and also synthetic methodologies. In the majority of the procedures discussed herein, the pyrrolizidine skeleton was forged on to the pre-existing pyrrolidine nucleus, particularly L- or D-proline. The first synthesis via intramolecular lactam formation, samarium diiodide promoted cyclization, utilization of olefin metathesis, Dieckmann condensation, utilization of (-)-sparteine for chiral induction during deprotonation, domino strategies using inter- and intramolecular Wittig reaction, utilization of chiral N-sulfinyl imine together with RCM are the various synthetic endeavors used for construction of pyrrolam A. Without doubt these synthetic issues represent remarkable contributions when targets of biological interest are involved. The advancement of new methodologies towards the construction of small pyrrolizidine library could be useful for the rapid identification of new biological leads. It shall be certainly of help to make further progress and develop new strategies for functionalized pyrrolizidine core including pyrrolams, based on this literature report.

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