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Pyrrolizidine Alkaloids Pyrrolams A–D: A Survey of Synthetic Efforts, Biological Activity, 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 *Streptomyces olivaceus* along with the related alkaloids pyrrolams B–D. The synthesis of (*S*)- and (*R*)-pyrrolam A has attracted the attention of chemists in recent years, with 10 syntheses reported to date. The reported routes utilize the advantages of chiral proline as a starting material, with pyrrolidine nucleus as source of one of the two rings on which the second ring has been constructed. This review discusses the isolation of the deceptively simple pyrrolizidine alkaloid pyrrolam A, its biological studies, synthesis, and computational studies on the stability of the double bond in its strained bicyclic skeleton. In addition, the synthesis of pyrrolams B–C and their relationship to pyrrolam A is also discussed.

Key words: bicyclic compound, metabolites, natural product, pyrrolams, pyrrolizidine alkaloids

Introduction

Chemicals from nature are ubiquitous in medicine. Natural products, especially alkaloids, are a rich source of active agents of value in medicine and they are also a highly effective source of molecules for drug design.[1] The alkaloids, as diverse chemicals and biomolecules, are an important class of natural product that are widespread in the plant kingdom.[2] Moreover, alkaloids are a very prominent class of defense compound amongst secondary plant metabolites.[3] A typical member of the alkaloids, the so-called 'izidine alkaloids', are popular amongst synthetic and medicinal chemists, not only because of their diverse biological activity, but also because they are challenging targets to test new synthetic protocols.[4] The structural features of the 'izidine alkaloids' (pyrrolizidine, indolizidine, quinolizidine), with a bicyclic skeleton, are important 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 adducts with DNA bases and also inhibit ribosomal protein biosynthesis.[5] Although, many alkaloids are known for their toxicity in animals and humans, they still play pivotal role in the immune systems of plants and animals, and have thus been successfully used as drugs in the treatment of many diseases.[6] As a consequence, the biosynthesis,[7] biological significance, and synthetic preparation of the pyrrolizidine alkaloids have been extensively reviewed.[8] The unique class of $\Delta^{1,2}$-unsaturated 1-(hydroxymethyl)pyrrolizidines, known as necines, further functionalized by a hydroxyl or ester moiety have received considerable interest as several of them show interesting physiological and pharmacological behavior (e.g., retronecine, supinidine, heliotridine, indicine *N*-oxide, etc.)[9] (Figure 1). Additionally, pyrrolizidine alkaloids have been extensively studied for their potent glycosidase inhibitory activity, which makes them good candidates as new drug paradigms for the treatment of many diseases, such as cancer, viral infections, diabetes, and so-forth.[10]

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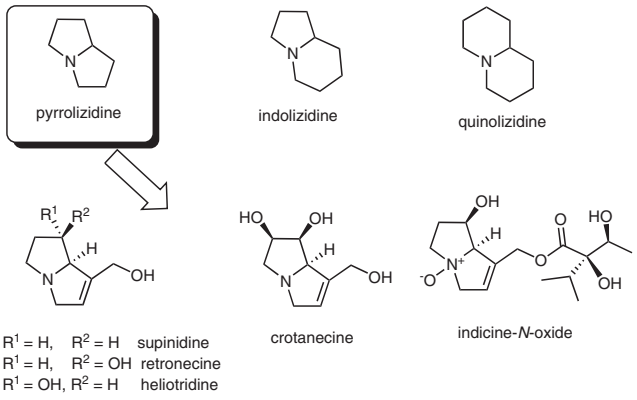


Figure 1 Skeleton of 'izidine alkaloids' and various pyrrolizidine alkaloids containing a necine base

Unsurprisingly, a vast body of research has been conducted regarding the syntheses of these alkaloids. The simplest representative example of this class of alkaloids is pyrrolam A (**1**). Pyrrolam A (**1**) has been synthesized by several research groups.

Isolations and Biological Activity

The genus streptomyces has been shown to produce a number of secondary metabolites possessing a promising biological profile. In 1990, the screening of a culture broth of the bacterial strain *Streptomyces olivaceus* resulted in the identification of four structurally related compounds of pyrrolizidones, namely, pyrrolams A–D (**1**–**4**) (Figure 2).[11] Since then, pyrrolam A (**1**) has been the subject of fascination, particularly amongst synthetic chemists. The provocative structure of **1** consisting of a bicyclic skeleton with a double bond in conjugation with the carbonyl group in the lactam ring, makes this molecule unique amongst the pyrrolam family. In addition, the presence of the double bond in the necine base is an imperative factor in the hepatotoxic, and mutagenic and carcinogenic nature[12] of various pyrrolizidine alkaloids.

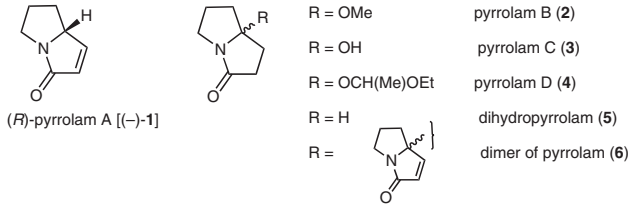


Figure 2 Pyrrolams A–D, dihydropyrrolam, and the dimer of pyrrolam

In the fermentation studies of Grote et al.[11] the pyrrolam producing organism *Streptomyces olivaceus* ssp. *omniyanesis* was isolated from a soil sample obtained from Leshan (P.R. of China). The amino acid ornithine is an important precursor of the pyrrolidine nucleus, which is also found in pyrrolizidine alkaloids. Thus, in the fermentation process, the strain (Tü 3082) was cultivated using soyabean meal, mannitol (2% each), and ornithine (20 mmol/L). The cultured broth, after filtration, was passed through resin XAD-16 and subsequently purified on a silica gel column resulting in the isolation of novel pyrrolizidone derivatives, pyrrolams A–D (**1**–**4**). The observation that pure pyrrolam A, on standing in an open vessel, dimerized to give **6**, gave information related to the stability of these compounds. Furthermore, these findings lead to the question: Is pyrrolam A is a precursor of related molecules like pyrrolams B–D, or vice versa? Later, Snyder and co-workers[13] used synthetic and computational methods to examine this question; detail analysis of the relative energies of pyrrolams and their synthesis is discussed in the final section of this review.

In terms of biological significance, pyrrolam A (**1**) shows herbicidal activity against wheat and rice seedlings and also causes damage to fertilized eggs at low concentration.[11] Jizba et al.[14] found that both pyrrolam A (**1**) and pyrrolam C (**3**) are unstable by a non-enzymatic process, which resulted in the transformation of pyrrolam A (**1**) into pyrrolam C (**3**) in a ratio of ca. 1:2. Consequently the acquisition of the biological profile of pure **1** and **3** 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. Corresponding to the biological profile suggested by Grote et al.,[11] the herbicidical activity of **1** could be also because of **3**. Hence, the two derivatives of pyrrolam could be considered as active metabolites contributing, together with macrotetrolides[15] and nonactic acids, to the complex insecticidal activity exhibited by *S. globisporus* 0234 and *S. griseus* LKS-1. The significant biological activity of pyrrolam A (**1**), together with its structural relationship with the necine nucleus, has engaged the attention of chemists in order to develop new methodologies for its synthesis on a large scale, which could facilitate detailed structure–activity relationship studies of this class of alkaloid.

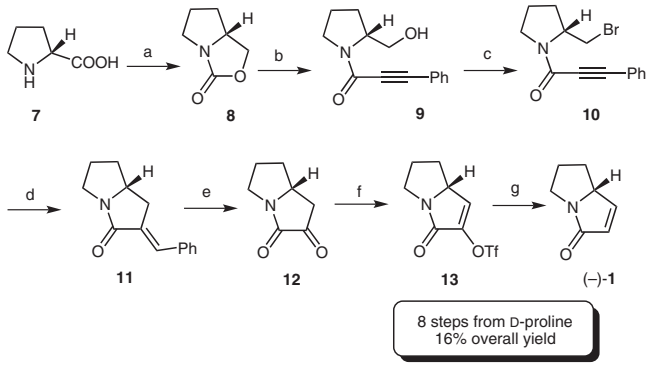
Synthetic Approaches

The interesting biological activity of the pyrrolams, together with their biogenetically close relationship to the necine core (although pyrrolam has bacterial origin and the pyrrolizidine alkaloids 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 Proctor and coworkers in 1995 and subsequently many syntheses have appeared in the literature. The most common synthetic routes to both the enantiomers of pyrrolam A (**1**) involve the utilization of proline derivatives or suitable amino acids as substrates of choice; the chirality of the precursors is transferred to the target compound **1**. The chiral pool approach exploits proline as a starting material, which has the advantages that it is inexpensive and readily available

in both enantiomeric forms. The various synthetic methods for naturally occurring (*R*)-pyrrolam A [(–)-**1**], and its enantiomer (+)-**1** are classified into two main categories according to the starting material utilized: (a) chiral pool methods with proline as the starting material, and (b) miscellaneous methods.

Chiral Pool Methods: Proline as a Starting Material

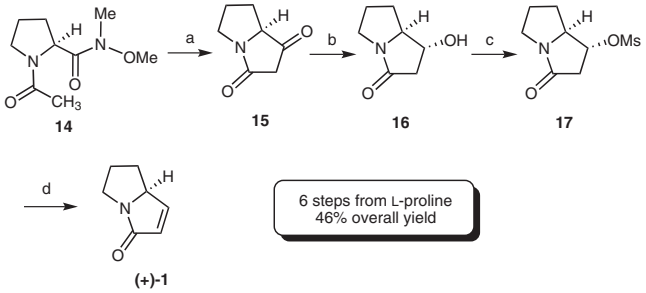
The construction of heterocyclic compounds using samarium diiodide is well known in organic synthesis.[16] Aoyagi et al. utilized a samarium diiodide mediated cyclization for the construction of the bicyclic skeleton in their synthesis of (*R*)-pyrrolam A [(–)-**1**] (Scheme 1).[17]



Scheme 1 *Reagents and conditions:* (a) 1. $LiAlH_4$, THF, 71%, 2. $(Et_2O)_2CO$, K_2CO_3, 76%; (b) lithium phenylacetylide, 62%; (c) NBS, Ph_3P, 86%; (d) SmI_2, HMPA, 0 °C, 90%; (e) O_3, Me_2S, 94%; (f) Tf_2O, *i*-Pr_2NEt, 50%; (g) $Pd(PPh_3)_4$, LiCl, Bu_3SnH, 83%.

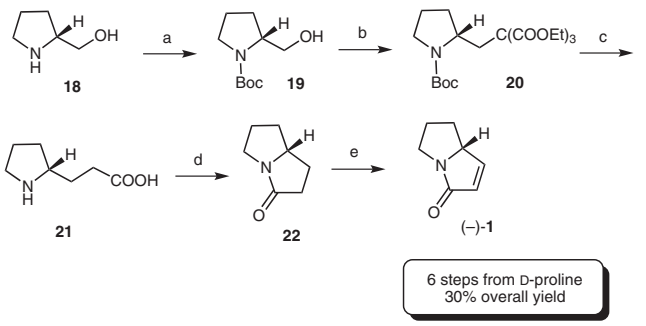
Thus, the reduction of D-proline (**7**) with lithium aluminum hydride followed by cyclization of the amino alcohol using diethyl carbonate provided bicyclic oxazolidinone **8**, which, when treated with lithium phenylacetylide, furnished the N-substituted alcohol **9**. Conversion of alcohol **9** into bromo compound **10** using the *N*-bromosuccinimide/triphenylphosphine system followed by treatment with samarium diiodide provided cyclized pyrrolidone **11**. The samarium diiodide mediated intramolecular coupling reaction between the haloalkyl and the ynamide group is the highlight of this approach. Furthermore, the treatment of **11** with ozone gave ketoamide **12**, which on trifluoromethylsulfonylation, provided triflate **13**. Reduction of **13** with tributyltin hydride in the presence of $Pd(PPh_3)_4$ produced (*R*)-pyrrolam A [(–)-**1**].

In 1995, Proctor and co-workers reported their studies on the application of *N*-acetyl and *N*-propionyl anion cyclization reactions in the synthesis of natural pyrrolizidines, whereby, (*S*)-pyrrolam A [(+)-**1**] was synthesized for the first time with 93.5% ee (Scheme 2).[18a] Later, in 1996 they published identical results towards the synthesis of pyrrolam A along with other members of this class of alkaloids.[18b] Their approach was based on the cyclization of *N*-methoxy-*N*-methylamide **14** to dione **15** via an *N*-acetyl anion cyclization reaction. The requisite *N*-methoxy-*N*-methylamide **14** was prepared from *N*-acetylprolinate via a mixed anhydride protocol. Reduction of the keto functionality of **15** with sodium borohydride furnished the alcohol **16**, which was subjected to mesylation followed by treatment with triethylamine in refluxing chloroform to afford (*S*)-pyrrolam A [(+)-**1**].



Scheme 2 *Reagents and conditions:* (a) LDA or LHMDS, THF, –78 °C; (b) $NaBH_4$, EtOH, r.t.; 24 h, 69% (2 steps); (c) MsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 5 h, 85%; (d) Et_3N, $CHCl_3$, reflux, 5 h, 98%.

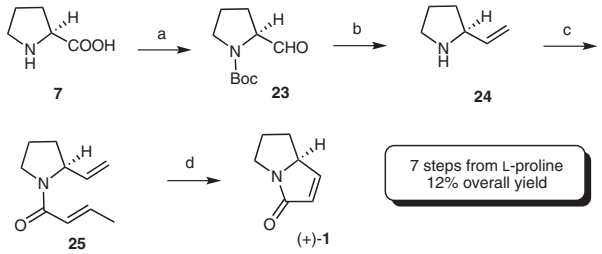
Giovenzana et al. published their studies directed towards the synthesis of (*R*)-pyrrolam A [(–)-**1**] with the use of the Mitsunobu reaction as a key step for the dehydrative alkylation of protected (*R*)-prolinol with triethyl methanetricarboxylate (Scheme 3).[19] Thus, (*R*)-*N*-Boc-prolinol **19** was treated with triethyl methanetricarboxylate under Mitsunobu conditions to give *N*-Boc triester **20**. The two-carbon homologated L-proline **21** was obtained using trifluoroacetic acid, followed by addition of excess of 12 M hydrochloric acid. Subsequent cycloamidation was achieved in the presence of HMDS (10 equiv) and TMSCl (cat.) in refluxing acetonitrile. Finally, the installation of the double bond using selenenyl chemistry (addition/elimination strategy) provided (*R*)-pyrrolam A [(–)-**1**].



Scheme 3 *Reagents and conditions:* (a) Boc_2O, CH_2Cl_2, r.t.; (b) triethyl methanetricarboxylate, Ph_3P, DEAD, 58% (2 steps); (c) 1. TFA, CH_2Cl_2, r.t., 2. 12 M HCl; (d) HMDS, TMSCl, MeCN, reflux, 57% (2 steps); (e) 1. LDA, THF, –78 °C, 2. PhSeCl then H_2O_2, 90% (one-pot, 2 steps).

Ring-closing metathesis has played a prominent role in the synthetic chemistry of cyclic molecules, such as carbocycles, heterocycles, and macrocycles. Hence, the application of ring-closing metathesis to the total synthesis of complex natural products has been extensively reported.[20] Arisawa et al. used ring-closing metathesis for the synthesis of pyrrolam A from a diene prepared from pro-

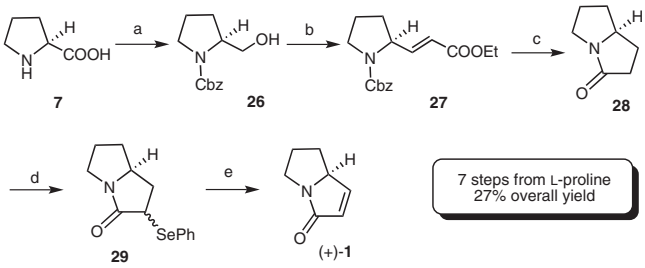
line as a starting material (Scheme 4). L-Proline (**7**) was converted into methyl *N*-Boc-L-prolinate in two steps.[21] This was further converted into aldehyde **23** by reduction with DIBAL-H. Wittig olefination of **23** followed by deprotection furnished a pyrrolidine **24** that was acylated with an unsaturated acid in the presence of diethyl phosphorocyanidate to give chiral diene **25**. This chiral diene **25** was subjected to ring-closing metathesis using Grubbs' catalyst to give (*S*)-pyrrolam A [(+)-**1**]. The low yield observed in this approach is attributed to the instability of the product under the reaction conditions used.



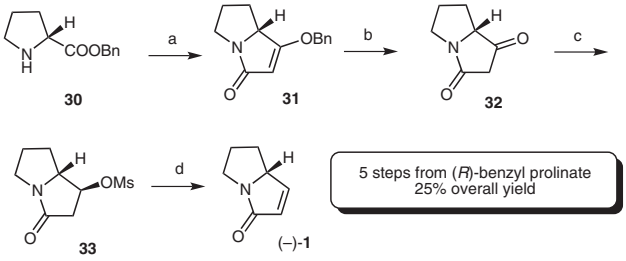
Scheme 4 *Reagents and conditions:* (a) 1. NaOH, Boc_2O, 79%, 2. K_2CO_3, MeI, DMF, 93%, 3. DIBAL-H, toluene, –78 °C, 91%; (b) 1. $KN(TMS)_2$, $Ph_3P^+CH_3\ Br^-$, THF, 73%, 2. 10% HCl, MeOH; (c) $MeCH{=}CHCO_2H$, $(EtO)_2P(O)CN$, Et_3N, 82% (2 steps); (d) Grubbs' catalyst, 30%.

Our approach to (*S*)-pyrrolam A [(+)-**1**] demonstrates the utility and applicability of the domino primary alcohol oxidation–Wittig reaction (Scheme 5).[22] L-Proline (**7**) was converted into N-protected prolinol **26** which was treated with PCC/NaOAc and phosphorane (one pot) to give α,β-unsaturated ester **27**. N-Deprotection of **27** and double bond reduction, followed by cyclization under basic condition (cat. NaOEt) furnished dihydropyrrolam **28**. A one-pot selenium addition/elimination process delivered (*S*)-pyrrolam A [(+)-**1**], but the chromatographic purification of (*S*)-pyrrolam A [(+)-**1**] (removal of unreacted PhSeCl) led to its conversion into the related pyrrolam C (**3**). Hence, it was concluded that the double bond of the initially formed pyrrolam A (**1**) underwent isomerization on silica gel followed by addition of water to give pyrrolam C (**3**); this conversion was first examined Snyder and coworkers.[13] This suggests that pyrrolam C (**3**) may well be an artifact of the isolation process arising from pyrrolam A (**1**). To circumvent the problem, the selenenyl derivative **29** was purified prior to oxidation (H_2O_2, NaOH). Finally, oxidative elimination of selenenyl derivative delivered pure (*S*)-pyrrolam A [(+)-**1**] in good yield.

A concise approach towards (*R*)-pyrrolam A [(–)-**1**] was reported by Schobert et al. via a domino sequence involving an addition–Wittig alkenation reaction with the ylide $Ph_2P{=}C{=}C{=}O$ immobilized on polystyrene resin (Scheme 6). Benzyl prolinate (**30**), prepared from D-proline, was reacted with the polymer-supported phosphacumulene ylide to give the corresponding tetramate **31**.[23] The formation of tetramate **31** occurred in a domino fashion involving the addition of the amino group across the C=C bond of the phosphacumulene ylide and subsequent intramolecular Wittig olefination of the acyl ylide. Furthermore, the hydrogenolytic debenzylation of **31** furnished dione **32**, which on subsequent reduction using sodium borohydride, followed by mesylation, gave sulfonate **33**. Refluxing the sulfonate **33** with triethylamine afforded (*R*)-pyrrolam A [(–)-**1**].



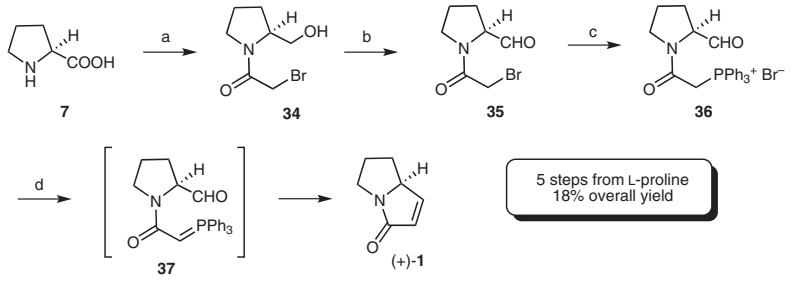
Scheme 5 *Reagents and conditions:* (a) 1. $LiAlH_4$, THF, reflux, 8 h; 2. $ClCO_2Bn$; (b) PCC/NaOAc, CH_2Cl_2, $Ph_3P{=}CHCO_2Et$, 7 h, r.t., 76%; (c) 1. H_2, 10% Pd/C, EtOH, 12 h; 2. NaOEt (cat.), EtOH, heat, 6 h, 67% (2 steps); (d) LDA, THF, PhSeCl, –78 °C; (e) H_2O_2, NaOH, THF, 0 °C, 30 min, 61% (2 steps).



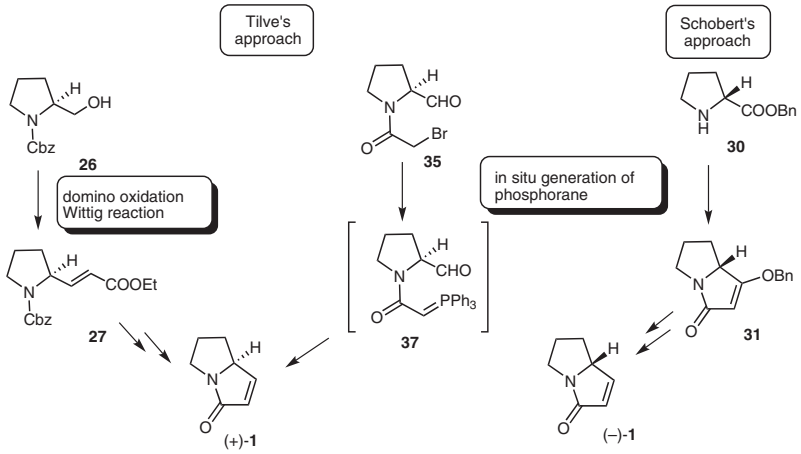
Scheme 6 *Reagents and conditions:* (a) polystyrene-$P(Ph)_2{=}C{=}C{=}O$, THF, 60 °C, 16 h, 80%; (b) H_2, Pd/C, MeOH, 2 h, 99%; (c) 1. $NaBH_4$, CH_2Cl_2–AcOH, 53%, 2. MsCl, Et_3N, CH_2Cl_2, r.t., 16 h, 90%; (d) Et_3N (7 equiv), 40 °C, 18 h, 65%.

In an effort to establish a more practical and scalable route to pyrrolam A, another synthetic approach involving phosphorus ylide chemistry simultaneously emerged from our group, which demonstrates the practicability of intramolecular Wittig reaction for the construction of the bicyclic skeleton of (*S*)-pyrrolam A [(+)-**1**] (Scheme 7).[24] Prolinol was converted into (*S*)-*N*-(bromoacetyl)prolinol (**34**) using bromoacetyl bromide. Oxidation of (*S*)-*N*-(bromoacetyl)prolinol (**34**) followed by treatment with triphenylphosphine gave the corresponding Wittig salt **36**. Deprotonation using sodium hydride gave (*S*)-pyrrolam A [(+)-**1**] via in situ formation of phosphorane **37** followed by intramolecular Wittig reaction in one pot.

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



Scheme 7 *Reagents and conditions:* (a) 1. $LiAlH_4$, THF, reflux, 8 h; 2. NaOAc, $ClCOCH_2Br$, 0 °C, 2 h, 65%; (b) PCC, CH_2Cl_2, r.t., 6 h, 68%; (c) Ph_3P, benzene, r.t., 8 h; (d) NaH, THF, 0 °C, 14 h, 41% (2 steps).



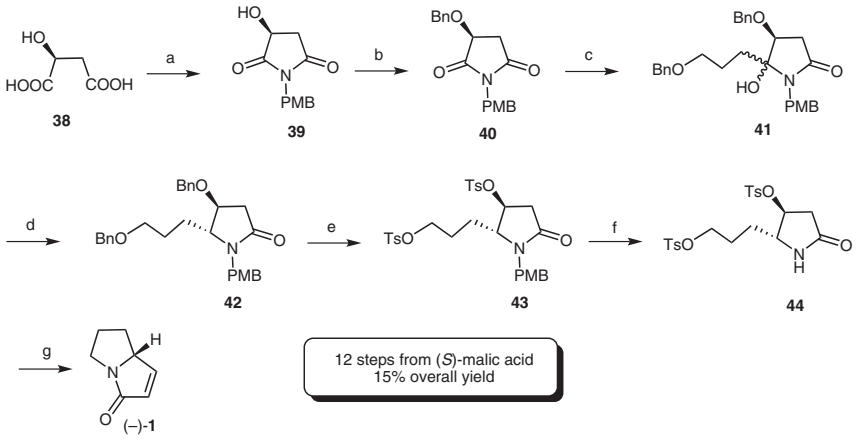
Scheme 8 Construction of pyrrolam skeleton using the Wittig approach

Miscellaneous Methods

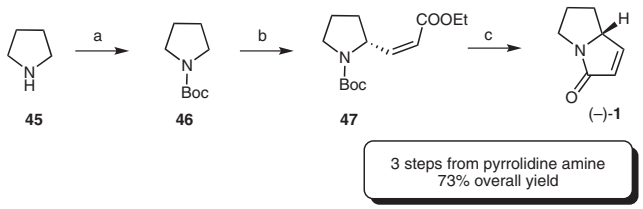
Another asymmetric synthesis of (*R*)-pyrrolam A [(–)-**1**] using inexpensive and easily available natural (*S*)-malic acid, reported by Huang et al., was the longest route to this alkaloid to date, with a reasonable overall yield.[25]

(*S*)-Malic acid (**38**) was converted into (*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)propylmagnesium bromide regioselectively provided hydroxylactam **41**, which on reduction with excess triethylsilane gave pyrrolidone **42**. Selective removal of the 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 the tosyl group using sodium hydride provided (*R*)-pyrrolam A [(–)-**1**] (Scheme 9).

The most impressive synthetic route in terms of efficiency is that reported by Snyder and co-workers wherein, the authors utilized α-(*N*-carbamoyl)alkylcuprate methodology to produce an efficient synthesis of (*R*)-pyrrolam A [(–)-**1**] (Scheme 10).[13] Protection of pyrrolidine **45** gave *N*-Boc-pyrrolidine **46**, which was converted into a stereogenic organolithium reagent by asymmetric deprotonation.[27] This organolithium reagent was treated with CuCN·2 LiCl to give a lithium dialkylcuprate reagent that was vinylated upon quenching with ethyl (*Z*)-3-iodopropenate to give **47**. The authors anticipated that deprotection and cyclization would take place in single operation, however, in practice the cyclization using trifluoroacetic acid gave a low yield of (*R*)-pyrrolam A [(–)-**1**]. Various conditions were examined; chlorotrimethylsilane in methanol (methanolic HCl) was found to be effective for the one-pot conversion of (*Z*)-alkene **47** into (*R*)-pyrrolam A [(–)-**1**]. This asymmetric synthetic route to (*R*)-pyrrolam A [(–)-**1**] constitutes the shortest route to this alkaloid to date.



Scheme 9 *Reagents and conditions:* (a) 1. AcCl, reflux, 2 h, 2. 4-methoxybenzylamine, THF, r.t., 18 h, 3. AcCl, EtOH, 50 °C, 5 h, 84% (3 steps); (b) BnBr, Ag_2O, Et_2O, r.t., 94%; (c) $BnO(CH_2)_3MgBr$, THF, 0 °C, 90%; (d) Et_3SiH, $BF_3{\cdot}OEt_3$, CH_2Cl_2, –78 °C to r.t., 64%; (e) 1. H_2, Pd/C, EtOH, r.t., 80%, 2. TsCl, pyridine, CH_2Cl_2, 0 °C to r.t., 60%; (f) CAN, MeCN–H_2O, 0 °C, 77%; (g) NaH, THF, –15 °C to 0 °C, 83%.

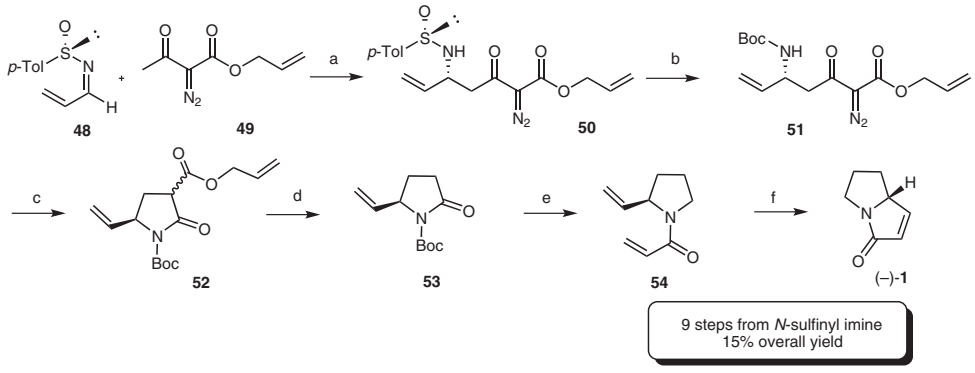


Scheme 10 *Reagents and conditions:* (a) Boc_2O, Et_3N, DMAP, THF, 0 °C, 2 h, 100%; (b) 1. (–)-sparteine, *s*-BuLi, –78 °C, 2. CuCN·2 LiCl, 3. (*Z*)-ICH=$CHCO_2Et$, –78 °C, 83%; (c) 1. Me_3SiCl, MeOH, 2. aq $NaHCO_3$, 88%.

Wang and co-workers developed an approach involving the diastereoselective nucleophilic addition of the lithium enolate of an α-diazoacetoacetate to a chiral *N*-sulfinyl imine to construct the pyrrolidine skeleton and exploited this methodology for the synthesis of (*R*)-pyrrolam A [(–)-**1**] (Scheme 11).[28] Addition of the lithium enolate of an α-diazoacetoacetate **49** to chiral *N*-sulfinyl imine **48** afforded δ-(*N*-sulfinylamino)-α-diazo-β-keto ester **50** with 97% de; the absolute configuration of **50** was established by X-ray crystal structure analysis. The *N*-sulfinyl group in **50** was replaced using trifluoroacetic acid and then Boc_2O to give *N*-Boc-protected diazo compound **51**, which on irradiation with a high-pressure mercury lamp (λ >300 nm) in a Pyrex tube gave (5*R*)-3-(allyloxycarbonyl)-2-oxo-5-vinylpyrrolidine (**52**). Vinylpyrrolidine **52** was formed through a photoinduced Wolff rearrangement.[29] The $Pd(PPh_3)_4$-catalyzed deallyloxydecarbonylation in the presence of morpholine, followed by Boc deprotection, lithium aluminum hydride reduction, acylation, and finally ring-closing metathesis reaction gave (*R*)-pyrrolam A [(–)-**1**].

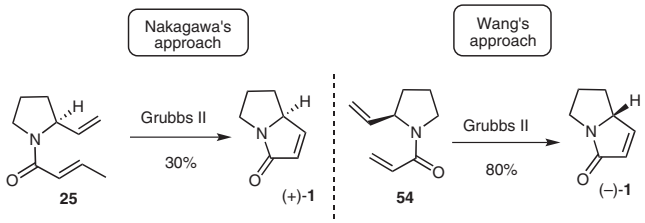
The miscellaneous methods (Schemes 9–11), employ very different concepts, starting from natural malic acid for construction of pyrrolidine ring (longest sequence), asymmetric deprotonation using organolithium reagents (concise route), and the final approach used chiral *N*-sulfinyl imines (chiral auxiliaries) towards the construction of the pyrrolidine ring.

Furthermore, the problem associated with ring-closing metathesis route in Scheme 4 was successfully solved by Wang group (Scheme 11) by changing the diene, which



Scheme 11 *Reagents and conditions:* (a) LHMDS, CH_2Cl_2, –78 °C, 20 min, 70%; (b) 1. TFA–MeOH, 0 °C to r.t., 2 h, 2. Boc_2O, Et_3N, DMAP, THF, 0 °C, 2 h; (c) *hν*, 375 W, benzene, 3 h, 60% (3 steps); (d) $Pd(PPh_3)_4$, THF, r.t., morpholine, 88%; (e) 1. TFA, CH_2Cl_2, r.t., overnight, 2. $LiAlH_4$, THF, 60 °C, 4 h, 3. CH_2=CHC(O)Cl, K_2CO_3, EtOAc–H_2O, 0 °C, 5 min, 60% (3 steps); (f) Grubbs II catalyst, toluene, overnight, 68%.

resulted in an increase in the yield from 30% to 80% in the ring-closing metathesis step (Scheme 12).

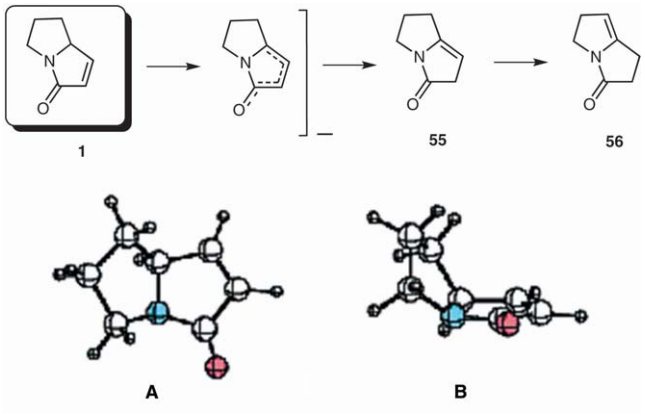


Scheme 12 Competing synthetic route via ring-closing metathesis

Computational Studies to Evaluate the Relative Energies of Pyrrolam Isomers

There are different computational methods and molecular mechanics approaches available in the literature to understand the molecular properties or structural stabilities of various conformers of necine bases, in particular retronecine and heliotridine as typical representative examples of 1,2-unsaturated pyrrolizidine alkaloids.[30] Snyder and co-workers 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]

The possible double bond migration in pyrrolam ring is shown in Scheme 13 (**A** and **B** are taken from ref. 13). The MP2 model evaluation of the pyrrolam isomer energy surface as well as the analysis of experimental observations under different reaction conditions concluded that the stability order is most likely **56** > **55** > **1** with a ΔG^{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 chairlike 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. Experiments to study the rearrangement of **1** to **55** were also carried out. Subsequent experiments 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 mixtures of **55**/**1** respectively, when either sample was subjected to alumina column chromatography (EtOAc as eluent). Overall the experiments lead to the conclusion that the 75:25 to 80:20 values represents the mixture at thermodynamic equilibrium under the particular reaction conditions.

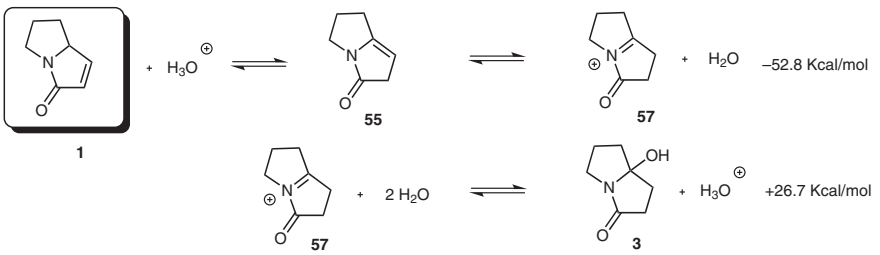


Scheme 13 Pyrrolam A (**1**) exists in two conformations, **A** and **B**[13] (structures **A** and **B** are reprinted with permission from *J. Org. Chem.* **2004**, *69*, 6105; copyright 2004, American Chemical Society)

Pyrrolams B–D Are Artifacts: Pyrrolam Captures Nucleophile

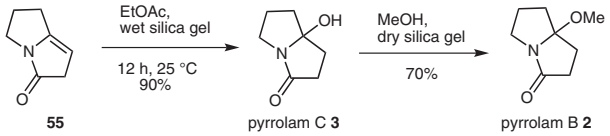
The small strained cyclic molecular structure with conjugated functionality of pyrrolam A leads to its instability (Scheme 14). The construction of small bicyclic skeletons is always challenging for the synthetic chemist. Studies towards the stability of the isomers of pyrrolam under various reaction conditions were demonstrated by Snyder and co-workers.[13] Furthermore, the mystery of the interconversion of pyrrolam isomers was successfully solved using synthetic as well as computational chemistry in combination.

Nucleophilic capture during the preparation of **1** and **55** involves an iminium cation species, which is an intermediate to both the oxygenated substances of pyrrolam and its dimer (pyrrolams B–D). To test this hypothesis, compound **55** (an isomer of pyrrolam) was treated with methanol, water or ethyl acetate under acidic conditions to give a complex mixture of products. Furthermore, treatment of **55** dissolved in ethyl acetate with wet silica gel cleanly



Scheme 14 Interconversion of isomers of pyrrolam

gave pyrrolam C (**3**) in high yield, which in turn was converted into pyrrolam B (**2**) by treatment with methanol and dry silica gel (Scheme 15).



Scheme 15 Formation of pyrrolam C (**3**) and pyrrolam B (**2**)

Although, pyrrolam D has not been synthesized to date, the formation of pyrrolam B (**2**), pyrrolam C (**3**), as well as dimer-pyrrolam **6** from pyrrolam A (**1**) suggest that pyrrolam D could be formed in a similar manner. These experiments by Snyder and co-workers clearly suggest that the pyrrolams B–D are artifacts of the isolation procedure, rather than metabolites from the 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, its natural occurrence, biological activity, structural stability, and synthetic methodologies. In the majority of the procedures discussed herein, the pyrrolizidine skeleton was formed onto 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 ring-closing metathesis 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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