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Strategies for the Synthesis of *Stemona* Alkaloids

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Dedicated to Professor Josep Font on the occasion of his 70th birthday

Keywords: *Stemona* alkaloids / Natural products / Synthesis design / Synthetic methods / Alkaloids

The extracts of several plants of the *Stemonaceae* family have long been used in Asian countries against different diseases and for their antiparasitic properties. Significant constituents of these extracts are a series of structurally related secondary metabolites named *Stemona* alkaloids. All the *Stemona* alkaloids are polycyclic and contain multiple stereocenters. Most of them present a central pyrrolo[1,2-*a*]-azepine system and the majority also incorporate at least one α-methyl-γ-butyrolactone substructure. Their challenging molecular architectures have motivated the development of new strategies for the construction of their skeletons, but only a small number of total syntheses have been published and they are still limited to quite a small number of targets. This microreview briefly examines most of the synthetic approaches to these alkaloids, according to the strategies devised to assemble their intricate structures, stressing the main similarities and differences encountered in the work developed by different laboratories, as well as the variations introduced along the synthetic route when pursuing different alkaloids through a common strategy.

1. Introduction

The deep knowledge of plant curative properties acquired by traditional folk medicine has motivated the scientific community towards the isolation and characterization of their bioactive components and the development of new drugs. The extracts of several plants of the *Stemonaceae* family (*Stemona*, *Croomia*, and *Stichoneuron* genera) have long been used in China, Japan, and other Asian countries for the treatment of respiratory disorders, as antihelmintics, and also as domestic insecticides.[1] Significant constituents of these extracts are a series of structurally related alkaloids that may be responsible for their medicinal and antiparasitic properties, although studies on the specific biological activities of individual members of

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Ramon Alibés studied Chemistry at the Universitat Autònoma de Barcelona (UAB), Spain, where he earned his B.Sc. degree in 1988 and his Ph.D. degree in 1993 working with Prof. Josep Font on the synthesis of (+)-grandisol. He was a postdoctoral scientist at the University of Alberta, Canada, in the laboratories of Prof. David R. Bundle working on the synthesis of tethered trisaccharides. Back at the Universitat Autònoma de Barcelona, he was appointed Associate Professor in 1998. His scientific interests focus on stereoselective organic synthesis, development of antiviral and antitumor agents, and photochemical cycloaddition reactions.

Marta Figueredo was trained in Chemistry at the Universitat Autònoma de Barcelona (UAB), Spain, where she obtained her B.Sc. degree in 1978 and her Ph.D. in 1983, working with Prof. Pelayo Camps on the synthesis of polyquinanes, and then collaborated as a post-doctoral fellow in the laboratory of Prof. Marcial Moreno-Mañas on the development of new photoaffinity probes. Following a period as a NATO-SERC post-doctoral fellow in the group of Prof. Michael Jung at the University of California Los Angeles, working on the stereoselective synthesis of biologically active compounds, she returned to the UAB and joined the group directed by Prof. Josep Font. In 1988, she achieved a position of Associated Professor of Organic Chemistry at the UAB and in 2006 she was promoted to Full Professor. Her research interest is focused on the stereoselective synthesis of molecules with potential or recognized biological activity.

this alkaloid family are quite limited.[2–11] Around one hundred *Stemona* alkaloids are currently known, but in the literature there is a continuous flow of new reports describing the isolation of previously unknown members of the family. The structures of thirty of them have been elucidated by X-ray analyses,[12–35] whereas those of the remainder were determined from their spectroscopic data and/or by chemical correlation.[36–76]

All the *Stemona* alkaloids are polycyclic and most of them possess a central pyrrolo[1,2-*a*]azepine system as a characteristic structural feature, although a few contain a pyrido[1,2-*a*]azepine core instead. The majority also incorporate at least one α-methyl-γ-butyrolactone substructure, which can be linked to the azabicyclic core variously in a spiro or a fused manner or as a substituent. Considering their structural diversity, Pilli and co-workers have recently classified the *Stemona* alkaloids into eight groups.[1] The common structural motif within each group, along with its most representative member, are shown in Figure 1. The stenine, stemoamide, tuberostemospironine, stemonamine, parvistemoline, and stemofoline groups each have the characteristic pyrrolo[1,2-*a*]azepine nucleus, whereas the stemocurtisine group possesses the less usual pyrido[1,2-*a*]azepine core, and a further, miscellaneous group includes those alkaloids either lacking any of these azabicyclic systems or featuring a hidden pyrrolo[1,2-*a*]azepine moiety. From their biosynthetic connections, Greger has suggested an alternative classification into three skeletal types, which are distinguished by the carbon chains attached to C-9 of the azabicyclic core.[2]

The challenging molecular architectures of the *Stemona* alkaloids have motivated the development of new strategies for the construction of their skeletons.[77–92] However, only a small number of total syntheses have been published and they are still limited to quite a small number of targets.[93–109] This microreview briefly examines most of the synthetic approaches to these alkaloids, according to the strategies devised to assemble their intricate structures. The major difficulties encountered in developing the synthetic plans, including the proper installation of their multiple stereocenters, are addressed. It is not intended to summarize comprehensively or to discuss in detail all the syntheses that have appeared in the literature, but to stress the main similarities and differences encountered in the work developed by different laboratories, as well as the variations introduced along synthetic routes in pursuit of different alkaloids through common strategies. The discussion is exclusively focused on the alkaloids belonging to the stemoamide, tuberostemospironine, and stenine groups.

In most of the published syntheses of *Stemona* alkaloids the central azabicyclodecane nucleus is formed by *exo-tet* or *exo-trig* cyclization of a suitably substituted pyrrolidine or azepine, although several authors make use of ring-closing metathesis chemistry or intramolecular cycloaddition processes. A detailed examination of the reported works reveals a certain parallelism between the approaches developed by different groups. The early syntheses launched different types of strategies, which were later on refined to improve efficiency and/or selectivity, but still relied on the same retrosynthetic principles. The discussion that follows has been organized from the perspective of the synthetic design analogies, rather than consideration of other aspects, such as the specific target or their chronological order of appearance in the literature.

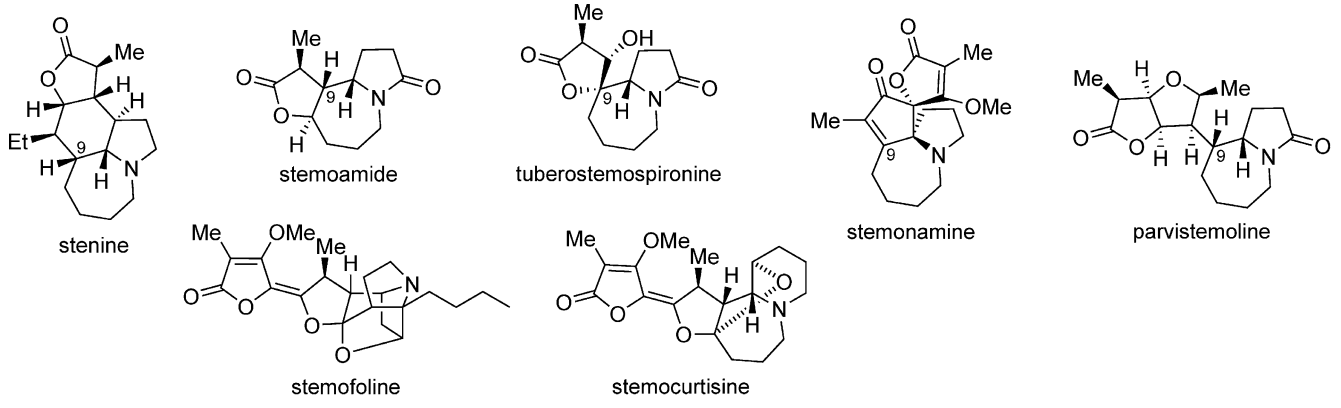


Figure 1. Representative members and characteristic structural feature of the *Stemona* alkaloid groups according to Pilli's classification.[1]

2. Synthetic Strategies in the Stemoamide and Tuberostemospironine Groups

Figure 2 shows the alkaloids in these two groups for which there are published syntheses. Stemoamide is the structurally simplest *Stemona* alkaloid and it is therefore not surprising that the number of reported total syntheses of this member of the family far exceeds those of the rest. The alkaloids of the stemoamide group each feature an α-methylbutyrolactone unit (ring A) fused to the central azabicyclic core, whereas in the tuberostemospironine-type alkaloids the analogous "western" lactone fragment is linked to the nuclear bicycle in a spiro fashion. Nevertheless, through appropriate tactic modifications, it is possible to develop common strategies to access some alkaloids of both these groups.

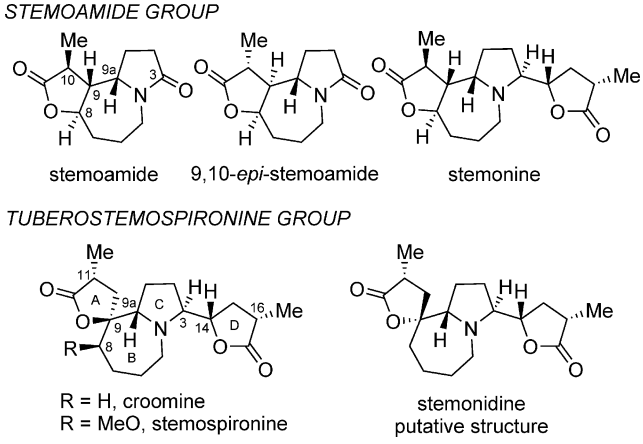
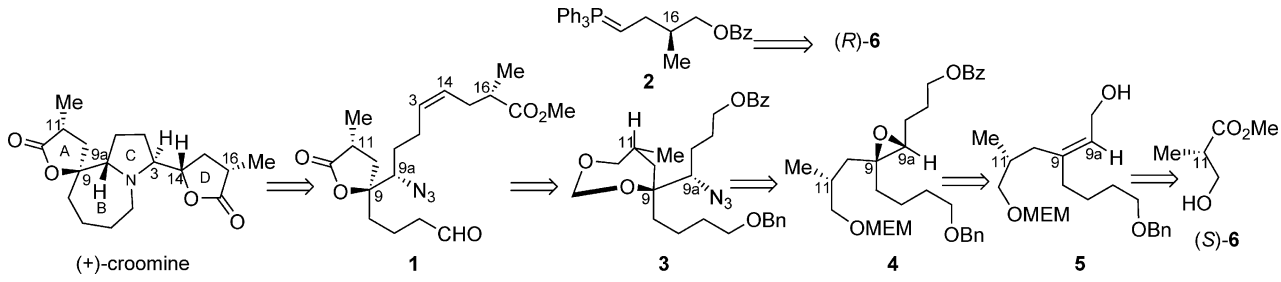


Figure 2. Synthesized alkaloids of the stemoamide and tuberostemospironine groups.

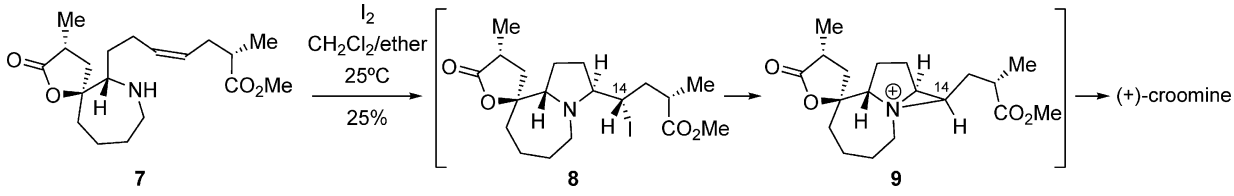
2.1. Azepine Formation by Staudinger–Aza-Wittig Reaction: Williams' Strategy

In 1989, Williams and co-workers published the first total synthesis of a *Stemona* alkaloid.[93a] In their pioneering work, these authors succeeded in completing the preparation of (+)-croomine, through an impressive 24-step linear sequence starting from methyl (2*S*)-3-(hydroxymethyl)propionate [(*S*)-**6**], according to the plan depicted in Scheme 1. Their strategy involves the preliminary construction of a branched carbon chain, followed by consecutive ring closures to generate each heterocycle. The configurations of the stereogenic centers at C-11 and C-16 were controlled by use of precursors derived from (*S*)- and (*R*)-**6** to elaborate the corresponding fragments of the "west"- and "east"-side lactones, respectively, whereas the relative configurations at C-9 and C-9a were established by means of a highly diastereoselective Sharpless epoxidation (>80% *de*) of the intermediate allylic alcohol **5**. The azide group in **3** was used as a surrogate for the amino functionality that was resistant to the several oxidation processes performed throughout the sequence. The central perhydroazepine ring B was formed by means of a Staudinger–aza-Wittig reaction performed on the azidoaldehyde **1**, followed by in situ reduction of the cyclic imine in 90% overall yield.

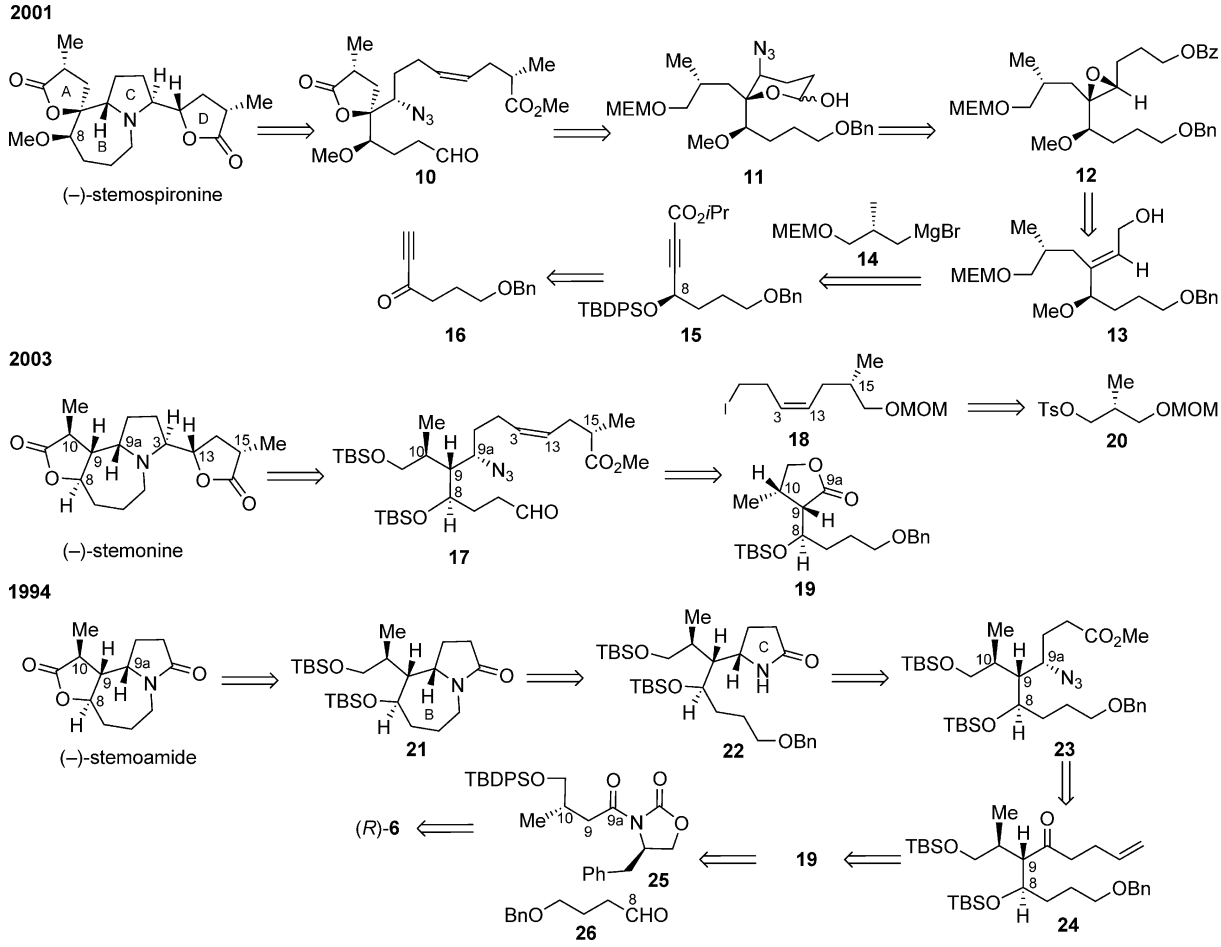
The required formation of the pyrrolidino-butyrolactone unit (rings C and D) was accomplished in a single step (Scheme 2). Treatment of the secondary amine **7** with iodine afforded direct conversion to (+)-croomine, through a double cyclization process involving initial formation of the iodoamination product **8**, followed by anchimeric assistance by the vicinal tertiary amine and subsequent intramolecular capture of the intermediate aziridinium salt **9** by the ester. The overall process resulted in net retention of configuration at C-14.



Scheme 1. Williams' strategy for the synthesis of (+)-croomine.



Scheme 2. Iodine-induced double cyclization for completion of the synthesis of (+)-croomine.



Scheme 3. Williams' strategy for the synthesis of *Stemona* alkaloids.

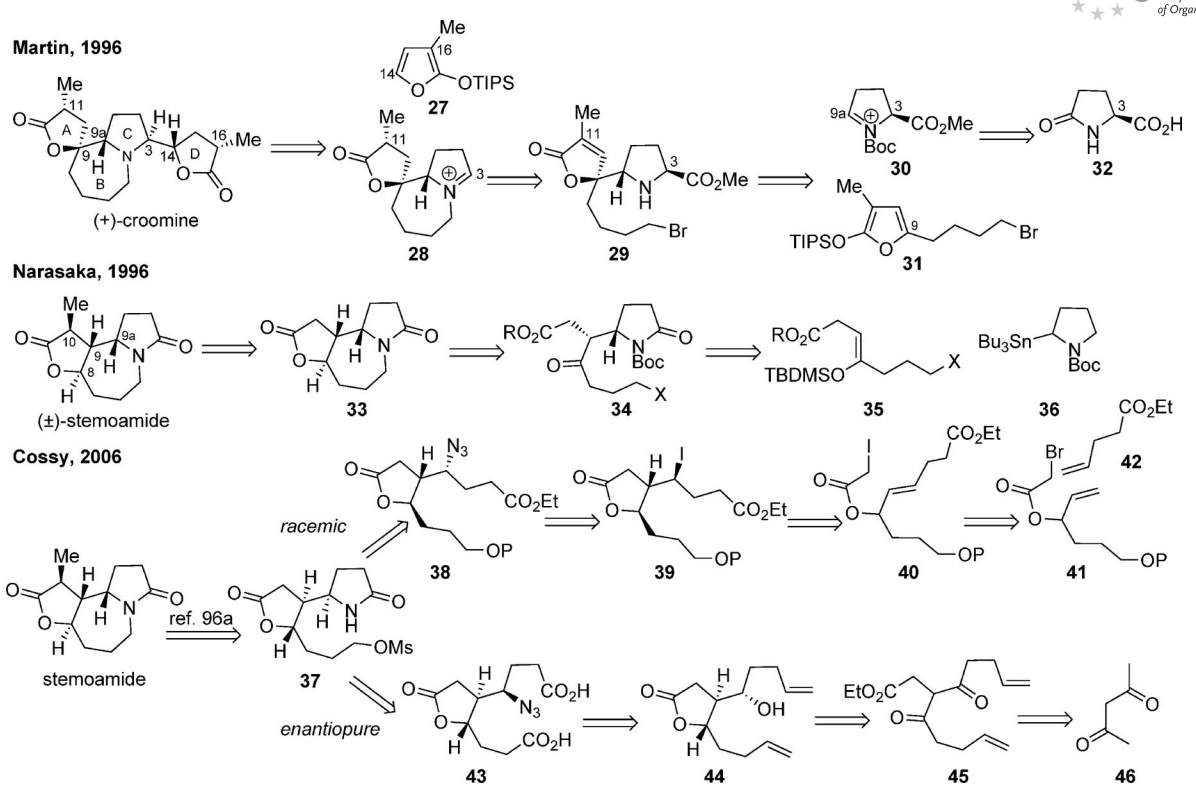
In a similar way, the Staudinger–aza-Wittig reaction and the iodine-induced double cyclization processes were also used later on for the consecutive generation of rings B, C, and D from the crucial intermediates **10** and **17** en route to (–)-stemospironine[94] and (–)-stemonine,[101] respectively, in each case with a moderate improvement in the yield of the final step (Scheme 3). Stemospironine differs from croomine only in the presence of a methoxy group at C-8, which adds an extra stereogenic center. This particular feature was addressed at an early stage of the sequence, through the enantioselective reduction of the acetylenic ketone **16** with (*R*)-Alpine borane (88% *ee*). Curiously, the asymmetric epoxidation of alcohol **13** was considerably less selective (50% *de*) than that of its deoxy analogue **5**.

For the synthesis of (–)-stemonine, the crucial intermediate **17** was constructed in a convergent manner from the optically pure butyrolactone **19** and the homoallylic iodide **18**. Lactone **19** had previously been prepared by the same group and used in their total synthesis of the simpler alkaloid (–)-stemoamide.[97a] In this synthesis, the α-carbonyl stereocenter at C-10 came from (*R*)-**6** and the control of the relative configurations at C-8 and C-9 was accomplished by means of an asymmetric Evans aldol reaction between **25** and **26**, which delivered exclusively the *syn* aldol. The other crucial stereoselective transformation was the reduction of ketone **24** to the corresponding *anti* diol, which, after mesylation and S_N2 displacement, yielded azide **23** with the correct configuration. The consecutive construction of the three rings in this case followed the opposite order. The lactam (ring C) was formed in the first place after reduction of the azide to amine (**23**→**22**), a subsequent 7-*exo*-*tet* cyclization furnished the azepine (ring B), and intramolecular hemiacetalization of the hydroxyaldehyde derived from **21** provided ring A.

2.2. Azepine Formation by 7-*exo*-*tet* Cyclization

Unlike in the syntheses discussed above, in most approaches to these kinds of alkaloids, starting materials already containing a pyrrolidine unit (ring C) have been used. In some cases, the stereogenic centers already present in pyrrolidine-derived chiral pool precursors have served as the asymmetric controllers of the synthetic processes. This is a common trend in most of the strategies discussed below.

The first example in this category is the second successful synthesis of (+)-croomine, published by Martin's group,[93b,93c] in which the appended lactones (rings A and

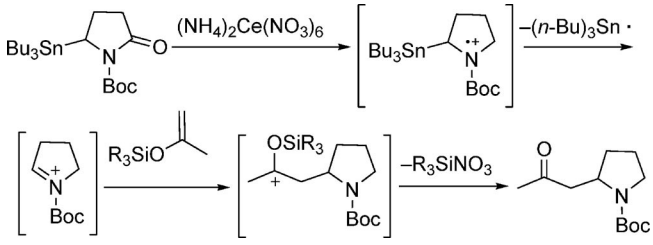


Scheme 4. Strategies forming the azepine (ring B) by 7-*exo-tet* cyclization.

D) were the leitmotiv of the synthetic plan (Scheme 4) and L-pyroglutamic acid (**32**) the origin of chirality. The key transformation in this approach was the vinylogous Mannich reaction between a silyloxyfuran and a cyclic iminium ion to deliver a pyrrolidinebutyrolactone assembly. This transformation, which is applied twice along the synthetic pathway (**30** + **31** and **27** + **28**), produced a very elegant and extremely short synthesis of the alkaloid, although the moderate yields and/or poor stereoselectivities of the vinylogous Mannich processes diminished the efficiency of the synthesis. The α-carbonyl stereogenic centers at C-11 and C-16 were introduced by hydrogenation of α,β-butenolide precursors.

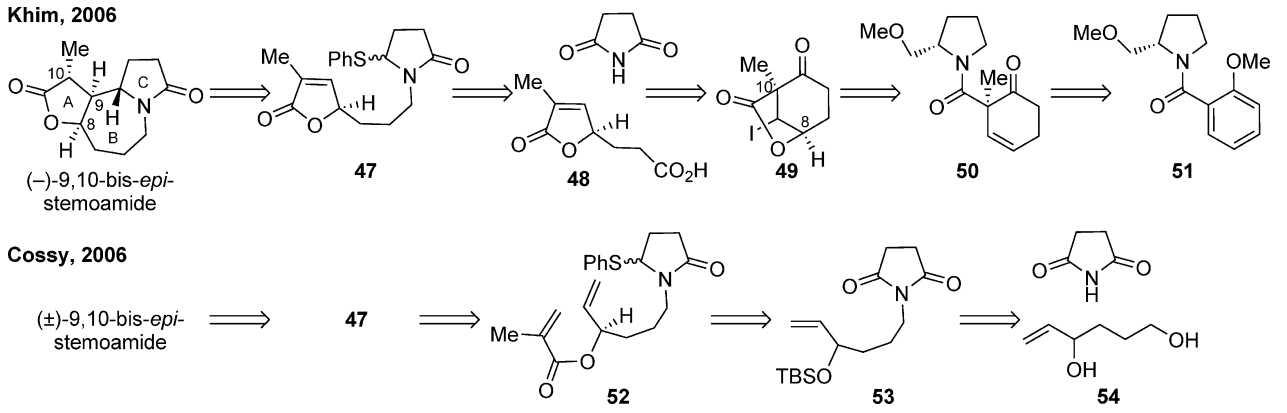
In a contemporary publication by Narasaka and Kohno, a 12-step linear synthesis of (±)-stemoamide using oxidative coupling reactions between silyl enol ethers and stannyl derivatives was accomplished.[96a] The oxidation of the 2-(tributylstannyl)pyrrolidine **36** generated a cation radical, which was cleaved by the elimination of the stannyl radical to afford an acyliminium ion that reacted with the silyl enol ether **35**, in a pathway analogous to that depicted in Scheme 5. A similar reaction was also used to prepare the ketone precursor of the silyl enol ether **35** from a 2-(tributylstannyl)acetate.

Recently, formal syntheses of (±)- and (+)-stemoamide have been reported by Cossy and co-workers (Scheme 4). As in Williams' approach, the heterocyclic rings were formed on a suitably functionalized acyclic chain and the azido group was used as latent amine functionality, but here



Scheme 5. Oxidative coupling of silyl enol ethers to stannyl derivatives.

the lactone (ring A) was formed before the perhydroazaazulene system (rings B and C). For the synthesis of the racemic alkaloid,[96d] the lactone **39** was derived from the iodoester **40** through a free radical 5-*exo-trig* atom-transfer cyclization. Unfortunately, neither this process, nor the subsequent S_N2 displacement of iodide by azide, was diastereoselective, and although the synthesis was completed in only 12 steps, it ended up with a mixture of diastereomers in a low overall yield. The formal synthesis of the dextrorotatory alkaloid[98] also finished with a mixture of diastereomers (4:1), in which the (+)-stemoamide precursor **37** was the major component. The original feature of this approach was that the asymmetry was introduced in a few steps from pentane-2,4-dione (**46**). The key lactone intermediate **44** was thus derived from dioxo ester **45** by a sequential reductive desymmetrization/lactonization/reduction, with use of Noyori's ruthenium catalyst for the asymmetric induction.



Scheme 6. Strategies using intramolecular radical coupling.

2.3. Azepine Formation through Intramolecular Radical Coupling

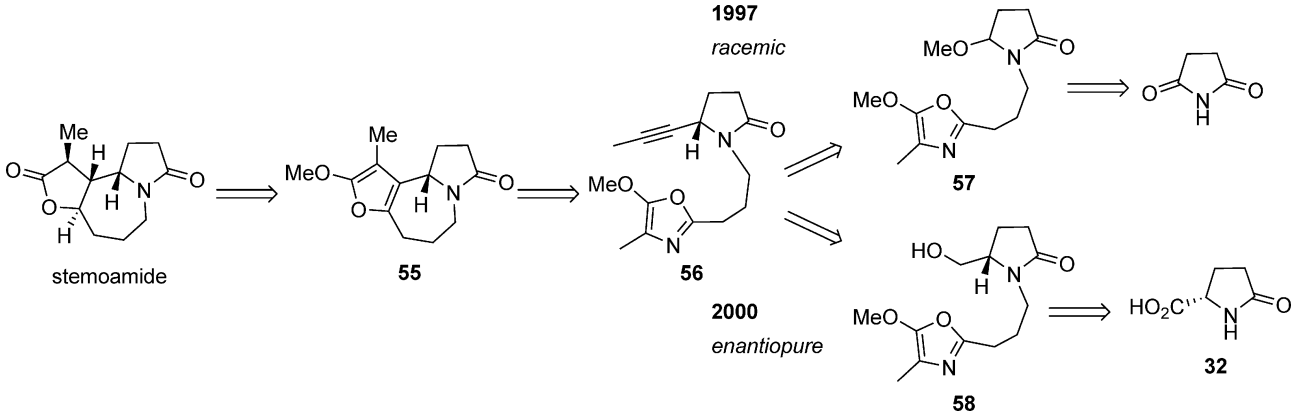
In two recent syntheses of (–)- and (±)-9,10-bis-*epi*-stemoamide, reported by Khim[99] and by Cossy,[100] respectively (Scheme 6), the final steps each consisted of a 7-*exo-trig* radical cyclization leading to the azepine ring B from a phenylthiolactam (**47**) derived from succinimide. In the first case, the lactone moiety **48** was prepared through a sequential asymmetric Birch reduction/methylation of an aromatic substrate bearing a chiral auxiliary (**51**), followed by iodolactonization (**50**→**49**) and lithium hydroxide-promoted fragmentation (**49**→**48**). In the second approach, the α,β-unsaturated lactone **47** was formed from **52** by a RCM process.

2.4. Azepine Formation by [4+2] Cycloaddition: Jacobi's Strategy

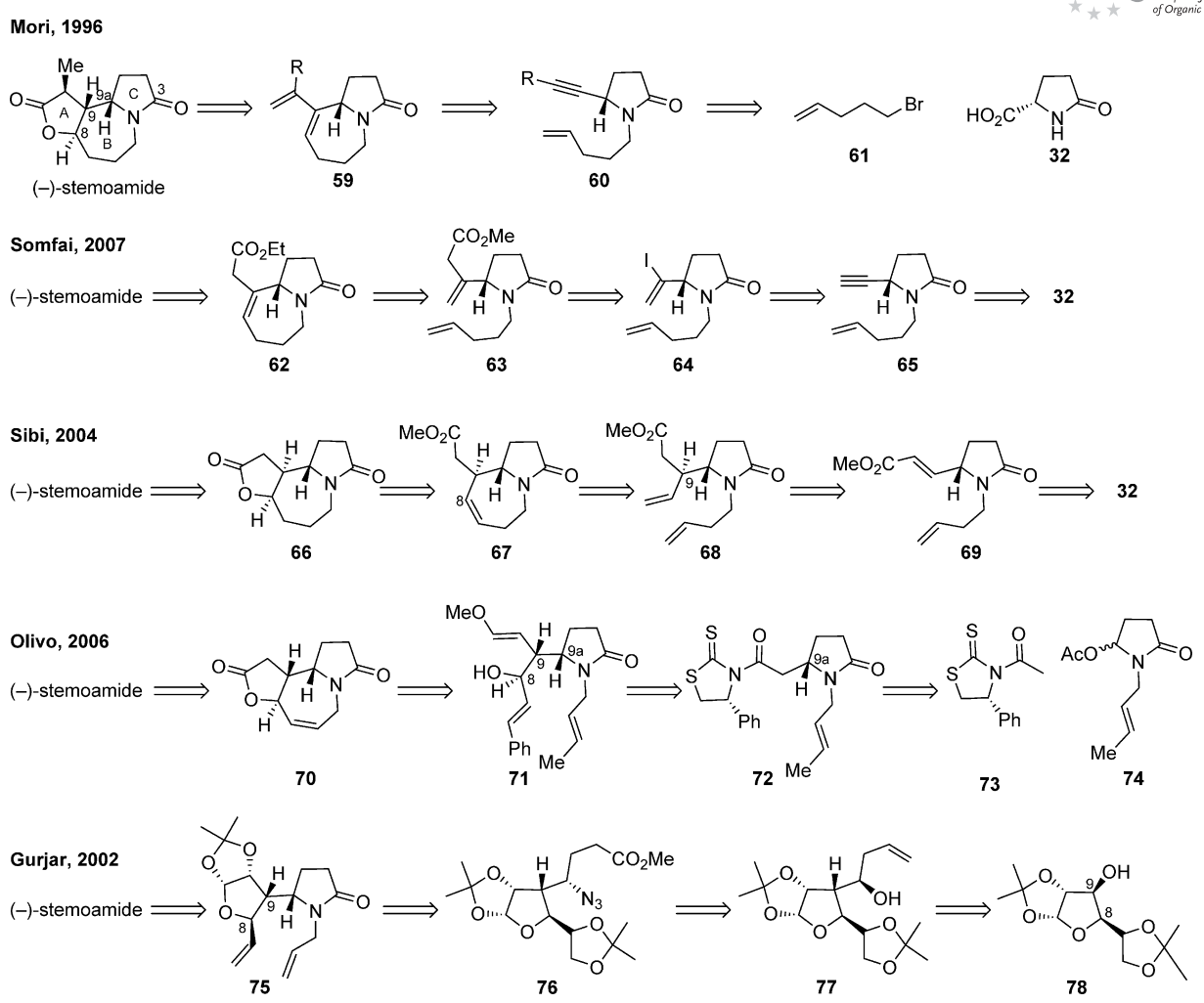
An outstandingly efficient strategy for the synthesis of stemoamide was developed by Jacobi's group (Scheme 7). These authors accomplished the preparation of the racemate in 20% overall yield through a seven-step sequence starting from γ-chlorobutyryl chloride and succinimide.[96b] The key transformation was an intramolecular Diels–Alder/retro-Diels–Alder process (**56**→**55**) that allowed the construction of the entire skeleton in a single step. After a careful analysis of the relative stabilities of the putative epimeric intermediates, the stereogenic centers were introduced in the proper order to ensure excellent stereochemical control. The same strategy was applied to the synthesis of (–)-stemoamide.[97d] Unfortunately, the preparation of the key acetylenic isoxazoline **56** in enantiomerically pure form from L-pyroglutamic acid met with some difficulties that diminished the efficiency of the synthesis.

2.5. Azepine Formation by Ring-Closing Metathesis (RCM)

In several syntheses of (–)-stemoamide, the azepine ring is formed through a RCM process (Scheme 8). The pioneering work in these syntheses was that of Mori and Kinoshita.[97b,97c] In their approach, the key enyne intramolecular metathesis was first performed on the acetylenic precursor **60** with R = Me, but attempts to convert the methyl diene product (**59**, R = Me) into the fused lactone met with failure. Fortunately, although it had been anticipated that for R = CO_2Me the enyne metathesis might be troublesome, due to the instability of the methoxycarbonyldiene group under the reaction conditions, in that particular case the lack of conjugation of the diene, resulting from steric effects, favored the process, which occurred in 87% yield. The



Scheme 7. Jacobi's design for the syntheses of (±)- and (–)-stemoamide.



Scheme 8. Strategies using a RCM process.

lactone was then elaborated from **59** (R = CO_2Me) through a 5-*endo*-*trig* bromolactonization protocol.

A related approach was recently reported by Somfai and co-workers (Scheme 8).[97h] In their synthesis the RCM process was preceded by a chemoselective iodoboration of the enyne intermediate **65**, followed by sp^2–sp^3 Negishi cross-coupling with a Reformatsky nucleophile (**64**→**63**). Bromolactonization of the β,γ-unsaturated azepine **62** provided the fused lactone. In the synthesis of Sibi and Subramanian,[97f] the RCM diene substrate **68** was prepared by the conjugate addition of vinylmagnesium bromide to an α,β-unsaturated ester (**69**). This reaction provided the incorrect configuration at C-9; it was later on epimerized by a three-step protocol based on Jacobi's work. Conversely, the formation of ring A by 5-*exo*-*trig* iodolactonization of the intermediate γ,δ-azepine **67** delivered the correct configuration at C-8. In all these three syntheses, (–)-pyroglutamic acid (**32**) provided ring C and acted as the source of chirality.

The strategy developed by Olivo's group[97g] made use of a chiral auxiliary and relied on installation of the correct configurations at the three contiguous stereocenters (C-8, C-9, C-9a) before the RCM step was performed (Scheme 8). The diastereoselective addition of a Ti^{IV} enolate of a chiral *N*-acyl thiazolidinethione (**73**) to a cyclic *N*-acyl iminium ion was thus used to prepare the adduct **72** with the necessary configuration at C-9a, and **72** was then employed in an *anti*-aldol reaction with cinnamaldehyde, which provided the required configurations at C-8 and C-9.

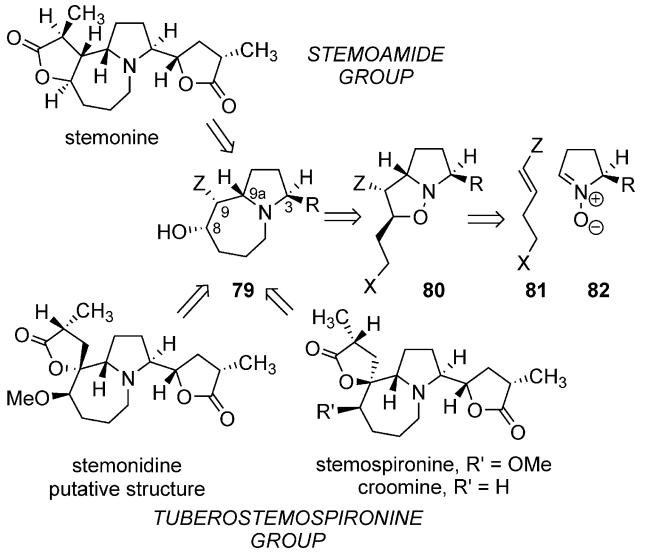
Gurjar and Reddy accomplished a carbohydrate-based synthesis of (–)-stemoamide (Scheme 8).[97e] The starting D-glucose derivative **78** provided the lactone ring and the correct configurations at C-8 and C-9. The essential strategy consisted of a stereocontrolled introduction of a pyrrolidin-2-one derivative at C-9 (C-3 of D-glucose) and formation of the azepine ring by RCM.

2.6. The Cyclic Nitrone Strategy

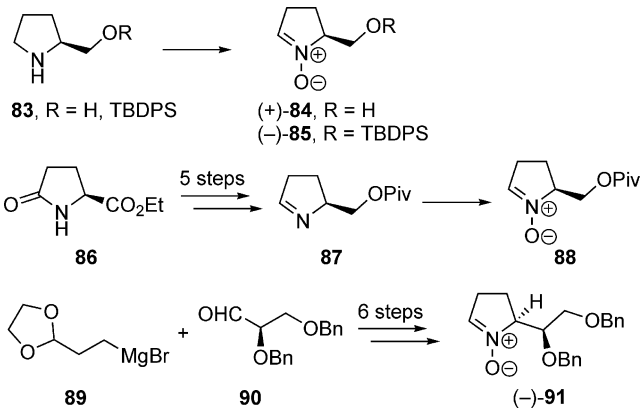
In most of the syntheses discussed above, the azabicyclic core that characterizes most *Stemona* alkaloids is generated from an advanced synthetic intermediate, generally containing multiple stereocenters and specifically assembled for the particular target. We designed a strategy in which the 1-azabicyclo[5.3.0]decane system was generated at an early stage of the sequence and the α-methyl-γ-butyrolactone mo-

tifs and other specific fragments were then incorporated, with the aim of developing a flexible approach, with some intermediates being common precursors for various alkaloids (Scheme 9).[88] A main advantage of this methodology is the high antifacial selectivity accomplished in the 1,3-dipolar cycloadditions between nitrones such as **82** and electron-deficient olefins of type **81**, delivering isoxazolidine adducts **80** with relative *trans* configurations of the stereogenic centers at C-3 and C-9a, as required for the target alkaloids.[110]

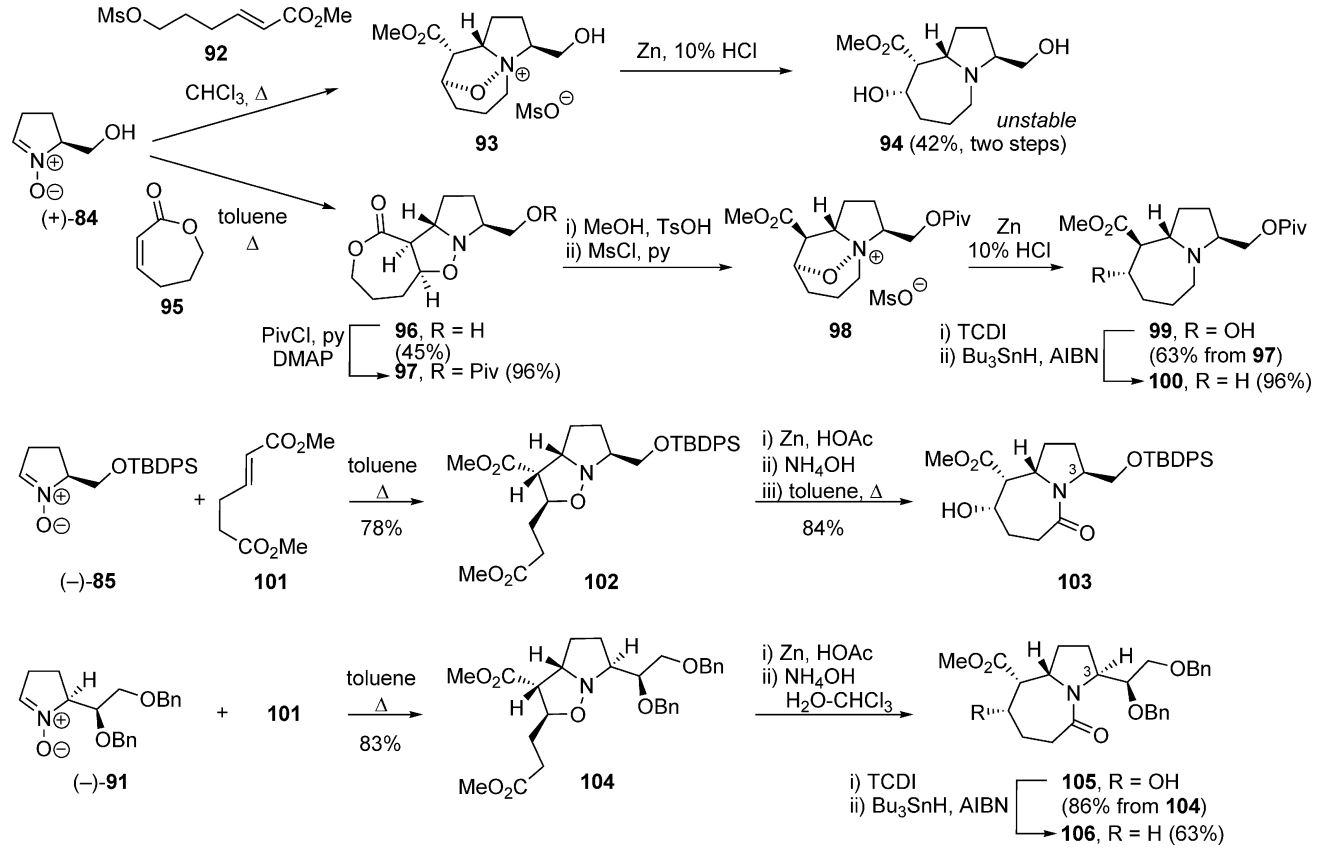
Essential for the success of our approach was the efficient preparation of the initial nitrone in enantiopure form, and so we developed the syntheses of nitrones **84/85**,[95,110a] **88**,[110b] and **91**,[88b,110c] starting from L-prolinol, ethyl L-pyroglutamate, and D-glyceraldehyde, respectively (Scheme 10). Out of these syntheses, the oxidation of the TBDPS derivative of prolinol with oxone is at the moment the most practical one, but nitrone **91** contains an ad-



Scheme 9. The cyclic nitrone strategy for the synthesis of *Stemona* alkaloids.



Scheme 10. Synthesis of enantiopure nitrones.

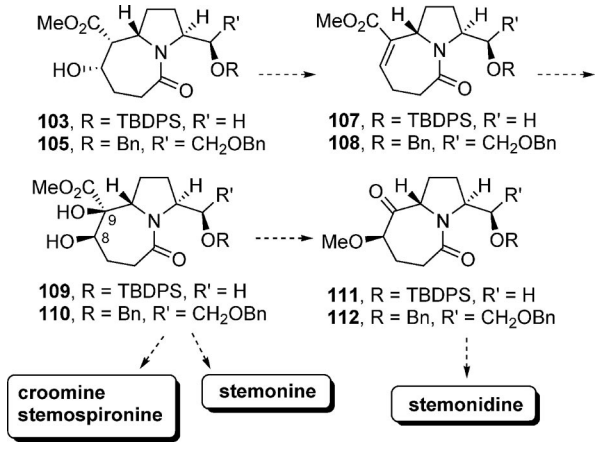


Scheme 11. Formation of azabicyclo intermediates from chiral nitrones.

ditional stereocenter and suitable functionalization for the installation of the alkaloid "east"-side lactone when required.

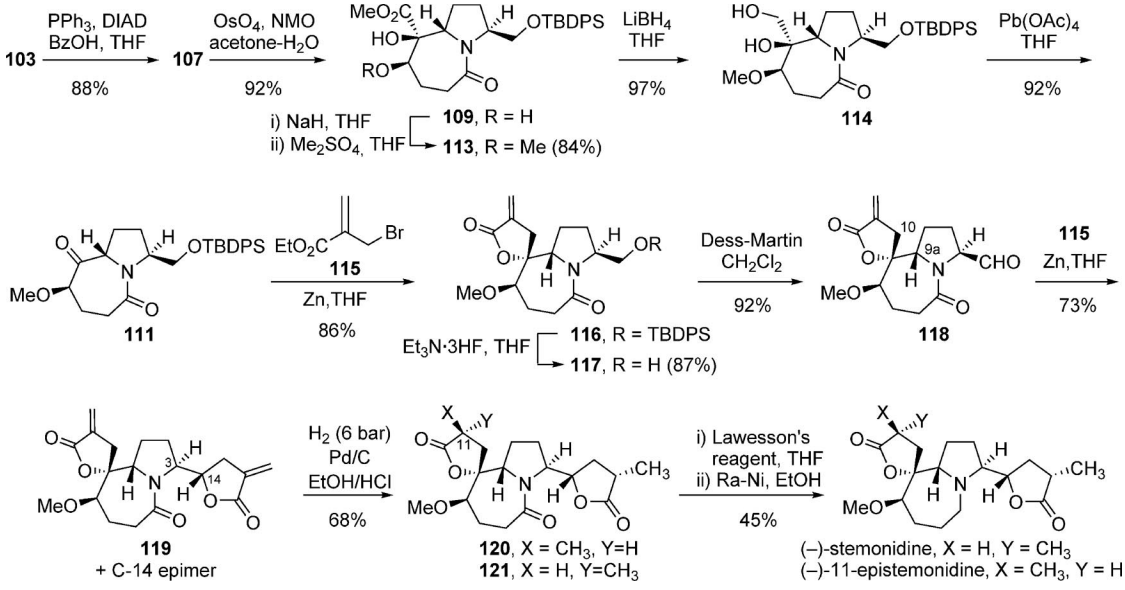
In a first-generation approach, we performed 1,3-dipolar cycloadditions between nitrone (+)-**84** and the C_6 olefins **92** and **95**, which took place with complete antifacial diastereoselectivity through *endo* or *exo* approaches in the transition state, depending on the *trans* or *cis* configuration, respectively, of the dipolarophile (Scheme 11). Reductive cleavage of the N–O bonds of **93** and **98** furnished the corresponding 7-*exo*-*tet* cyclization products **94** and **99**, with the former showing low stability. In a second-generation approach, diester **101** was used as the starting dipolarophile in order to prepare stable azabicyclic intermediates such as **103** and **105**, in which the nitrogen atoms were protected as lactams. In these intermediates, the substituents at C-3 should be further elaborated to construct the "east"-side lactone common to all the targets depicted in Scheme 9 and many other *Stemona* alkaloids. Conversely, the lactones in the "west" region differ from one alkaloid to another and their formation must be specifically devised for each target.

In both the tuberostemospironine and the stemoamide groups, all the alkaloids bearing an oxygen atom at C-8 present the same configuration at this center, opposite to that in compounds **103** and **105** (Scheme 12). Moreover, manipulation of the hydroxy group at C-8 for further synthetic elaboration usually led to elimination products,[88] and a simple conformational analysis of the perhydropyrrolo-azepinone skeleton of these compounds shows that their concave faces are relatively inaccessible. Therefore, dehydration followed by diastereoselective dihydroxylation was devised as a good strategy for further studies (Scheme 12). Intermediate diols such as **109/110** were considered suitable precursors for stemospironine, cromine, and stemonine because they would offer the correct configuration at C-8 and should undergo convenient functionalization to form the spiro- or fused lactones with the appropriate configuration at C-9. Complementarily, spirolactonization of ketones **111/112**, available from **109/110**, should presumably proceed to give the opposite configuration at their spiro stereocenters, as required for stemonidine.



Scheme 12. Synthetic plan from **103/105** to the target alkaloids.

The crucial diol **109** was prepared according to the plan, and from it we completed the synthesis of the structure assigned to natural stemonidine (Scheme 13).[95] Regioselective methylation of diol **109** delivered the corresponding methyl ether, which was converted into ketone **111** by consecutive treatment with $LiBH_4$ and lead tetraacetate. Treatment of **111** with ethyl bromomethylacrylate, **115**, and zinc in THF[111] gave the spiro-α-methylene-γ-lactone **116** with complete facial selectivity. After removal of the protecting silyl group, Dess–Martin oxidation furnished aldehyde **118**. Further treatment of **118** with **115** and zinc produced a roughly 1:1 mixture of bislactone **119** and its C-14 epimer. Hydrogenation of **119** under 6 bar pressure in the presence of Pd/C in EtOH/HCl (2 M) furnished a mixture of C11-



Scheme 13. Synthesis of the putative stemonidine structure.

epimeric azepinones **120** and **121**, which were converted into a mixture of thiolactams. Treatment with Ra-Ni delivered the corresponding azepines. The spectroscopic data for synthetic stemonidine did not match those of the alkaloid isolated from natural sources and it was thus shown that the putative isolated stemonidine was in fact stemospironine.

In a similar way the bicyclic intermediates **110** and **112** were also prepared and their conversion into other target alkaloids is currently being investigated.

3. Synthetic Strategies in the Stenine Group

Figure 3 shows the stenine group alkaloids that have been synthesized. Stenine and neostenine, the simplest representatives of this group, each feature a central cyclohexane unit fused to three other rings and bearing a stereogenic center at every carbon. Tuberostemonine possesses an additional α-methyl-γ-butyrolactone unit attached to the pyrrolidine ring A. The configurations at C-9, C-9a, C-10, and C-13 are identical in all three alkaloids.

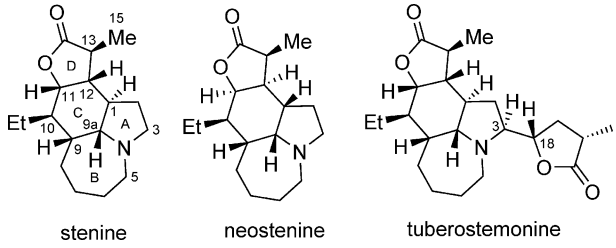


Figure 3. Synthesized stenine group alkaloids.

3.1. Diels–Alder-Based Strategies

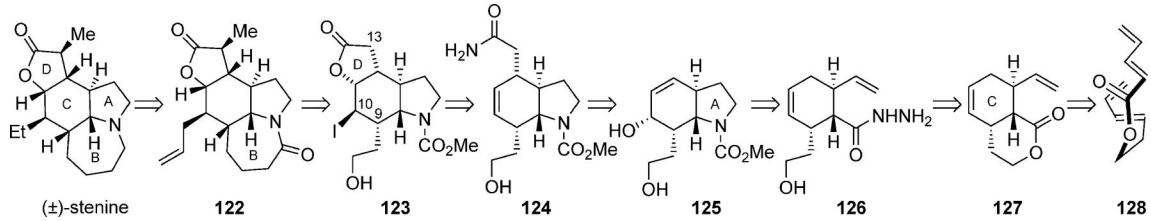
The first total synthesis of racemic stenine, described by Chen and Hart in 1990, was completed through a 25-step linear sequence, starting from the tetraene **128** (Scheme 14).[102a] The strategy involves the stepwise construction of rings C, D, and A, followed by the final formation of ring B.

The synthesis was initiated with an *endo*-stereoselective intramolecular Diels–Alder (IMDA) reaction that furnished ring C (**128**→**127**). The installation of the nitrogen atom by an aminimide variant of the Curtius rearrangement set the stage for ring A formation by a straightforward sequence. An Eschenmoser–Claisen rearrangement (**125**→**124**) and subsequent iodolactonization delivered the butanolide substructure **123**.

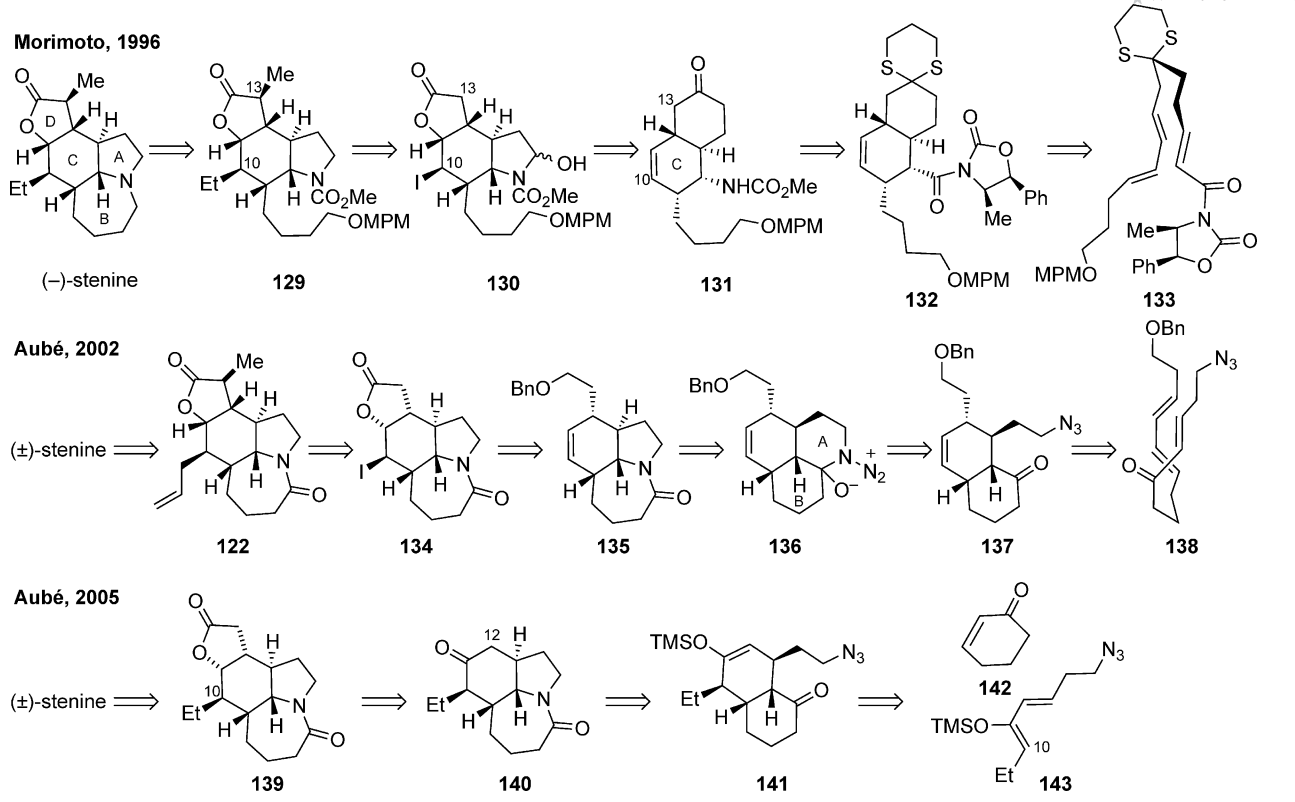
Ring B was then put in place by lactam formation after two-carbon homologation of the side chain at C-9. Finally, Keck radical allylation at C-10, conversion of the allylic residue into the requisite ethyl substituent, methylation at C-13 on the convex side of the tetracyclic system, and adjustment of the oxidation level at ring B led to the target compound. This pioneering synthesis paved the way for the use of other IMDA-based strategies and also established the iodolactonization/Keck allylation sequence for the stereoselective installation of the ethyl group at C-10.

Morimoto and co-workers described a highly stereocontrolled, 25-step synthesis of (–)-stenine (Scheme 15),[103b,103c] in which the key IMDA led to the simultaneous construction of a decalin skeleton and four of the six stereogenic centers of ring C. The Me_2AlCl-catalyzed IMDA reaction of the (*E*,*E*,*E*)-triene **133**, bearing an oxazolidinone chiral auxiliary, proceeded smoothly to produce the corresponding adduct **132** with good facial and complete *endo* selectivity. Sequential manipulation of the cycloadduct and introduction of the nitrogen functionality by a modified Curtius rearrangement (as in Hart's approach) furnished the bicyclic intermediate **131**. Rings A and D were set up by regioselective enolization of **131** under thermodynamically controlled conditions, followed by oxidative cleavage and stereoselective iodolactonization, to afford the tricyclic intermediate **130**. Allylation at C-10 and methylation at C-13 were also accomplished by Hart's procedure. Finally, ring B was constructed by means of a 7-*exo*-*tet* cyclization, after removal of the methoxycarbonyl group.

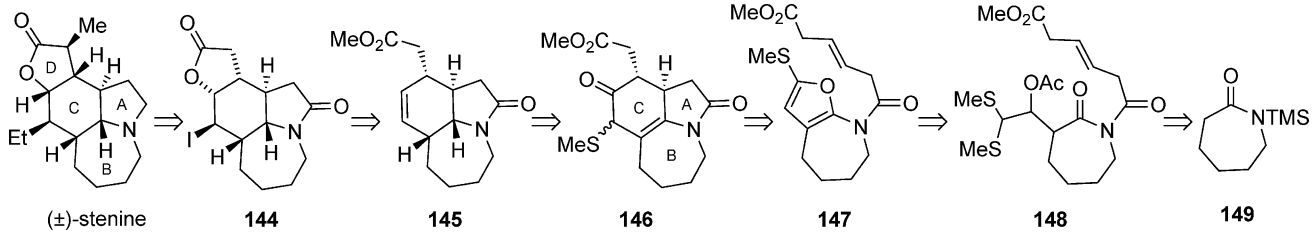
Aubé's group described a formal synthesis of racemic stenine[102d] starting from pentane-1,5-diol in a 21-step sequence, in which rings A, B, and C and four stereocenters of the cyclohexane moiety were formed in a single chemical step, consisting of a domino Diels–Alder/Schmidt reaction, from the acyclic azidodiene precursor **138** (Scheme 15). Treatment of **138** with $MeAlCl_2$ afforded the azepinoindole **135** in 43% yield. The overall transformation consisted of an *endo* IMDA cycloaddition, followed by a ring A-forming/ring B-expansion process (**137**→**136**→**135**). As in the previous syntheses, subsequent iodolactonization (**135**→**134**), stereoselective Keck allylation, and α-lactone methylation provided intermediate **122**, previously transformed into stenine by Hart. In a second-generation approach, Aubé and co-workers improved the efficiency of the synthesis by combining an intermolecular Diels–Alder reaction with a Schmidt rearrangement.[102e] Treatment of the azidosilyloxydiene **143** with cyclohexenone **142** and $SnCl_4$ afforded the azepinoindole **140**, originating from an *exo*-



Scheme 14. Hart's strategy for the synthesis of (±)-stenine.



Scheme 15. Other strategies using Diels–Alder reactions.

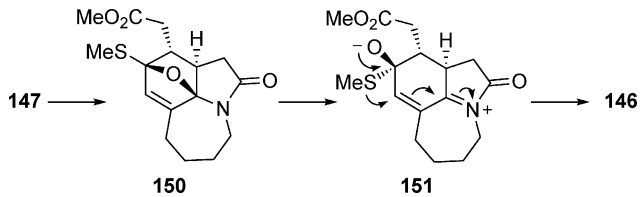


Scheme 16. Padwa's strategy for the synthesis of (±)-stenine.

selective Diels–Alder process, as the major product (45% yield). A remarkable feature of this new approach is that it allows the early incorporation of the C-10 ethyl side chain with the correct relative configuration. From **140**, an axially directed alkylation at C-12 and subsequent reduction installed the butyrolactone moiety, and the synthesis was then completed by well established procedures. Impressively, the total synthesis was accomplished in nine steps from commercially available reagents and in 14% overall yield.

In 2002, Padwa and Ginn described a synthesis of racemic stenine starting from *N*-trimethylsilyl ε-caprolactam (**149**) in a 17-step sequence including a remarkable Diels–Alder/ring opening/1,2-methylthio shift cascade to attach rings A and C onto a precursor azepinone (ring B) in a single operation (Scheme 16).[102c]

Methylsulfenylation of one of the sulfur atoms of **148** with dimethyl(methylthio)sulfonium tetrafluoroborate induces a thionium-promoted cyclization, and the resulting dihydrofuran readily loses acetic acid to furnish furan **147**. IMDA cycloaddition followed by nitrogen-assisted ring opening (Scheme 17) generates a zwitterionic intermediate (**151**) that, after a 1,2-methylthio shift, provides the tricyclic lactam **146**. Subsequent reduction reactions set the desired A/C *trans* and B/C *cis* ring fusions. Then, formation of the butyrolactone ring through iodolactonization of **145** precedes a stereoselective Keck allylation by Hart's protocol.



Scheme 17. Diels–Alder/ring opening/1,2-methylthio shift cascade.

3.2. Wipf's Strategy

The first enantioselective total synthesis of (–)-stenine was described by Wipf and co-workers in 1995 and involved a 26-step linear sequence starting from L-tyrosine,[103a] which was converted into the key enantio- and diastereomerically pure indolone **155** in a single step (Scheme 18). One of the crucial transformations in this synthesis is the formation of the spirocycle **156**, generated by the phenolic oxidation of **157** by hypervalent iodine. The *cis*-fused indolone is converted into the *trans*-fused stenine core upon reduction of a π-allylpalladium complex (**155**→**154**). An Eschenmoser–Claisen rearrangement set the stage for butyrolactone formation by iodolactonization in **152**. Subsequent Keck allylation and functional group manipulations provided the target alkaloid.

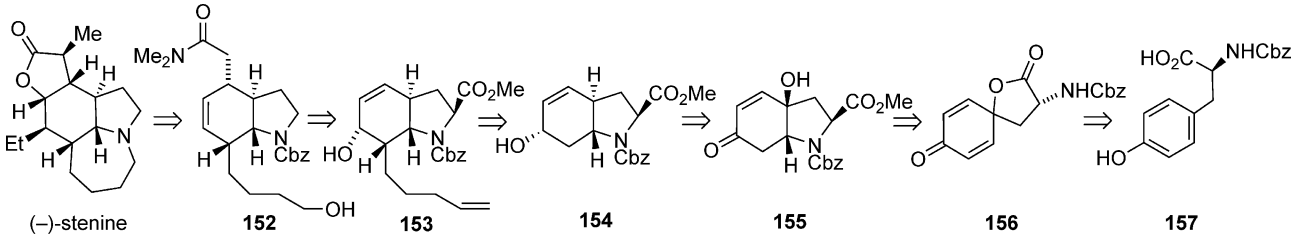
In a subsequent work, these authors used the same *trans*-hexahydroindole **154** as a key intermediate in the enantioselective synthesis of (–)-tuberostemonine through a 24-step linear sequence (Scheme 19).[104a,104b] Highlights of the sequence from **154** to the target alkaloid are azepine formation by RCM of **162**, followed by regioselective hydrogenation, and the stereoselective attachment of the "east"-side γ-butyrolactone at C-3 by treatment of a Weinreb amide derivative of **161** with the lithiated asymmetric orthoester **160**. The final transformations to afford tuberostemonine were an Eschenmoser–Claisen rearrangement (**159**→**158**), selenolactonization, Keck allylation, and selective α-methylation of the fused lactone.

3.3. Booker-Milburn's Strategy

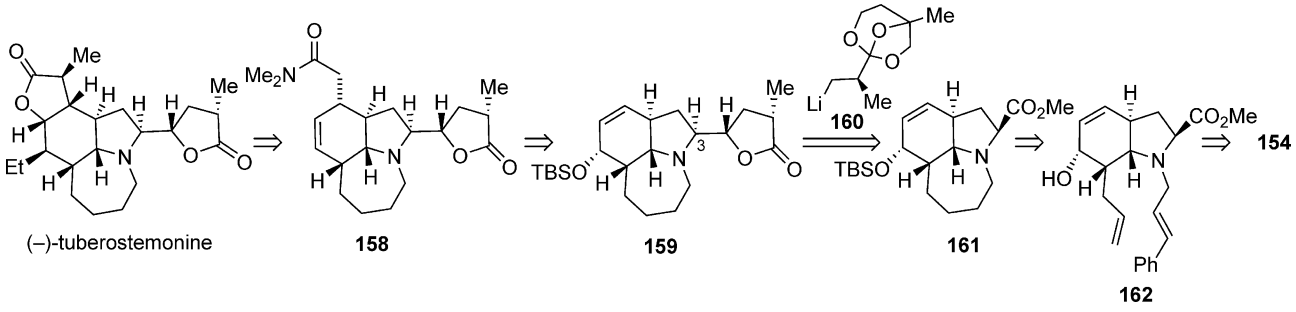
In 2008, Booker-Milburn reported an outstanding total synthesis of (±)-neostenine[105a] through a 14-step linear sequence starting from furan **167** and involving, as a key transformation, a [5+2] maleimide photocycloaddition on intermediate **164** to assemble the fused pyrrolo[1,2-*a*]azepine core (Scheme 20). The synthesis makes use of an acid-catalyzed bislactonization of the bridged dihydrofuran diacid **167** to furnish the C_2-symmetric intermediate **166**. The ethyl group is next introduced by *anti*-selective organocopper-mediated S_N2' ring opening of **166**. The conjugated dichloro-keto-amide functionality in the advanced tetracycle **163** is reduced/deoxygenated and the lactone ring D stereoselectively methylated to deliver neostenine.

3.4. The Cyclic Nitrone Strategy for the Synthesis of Stenine

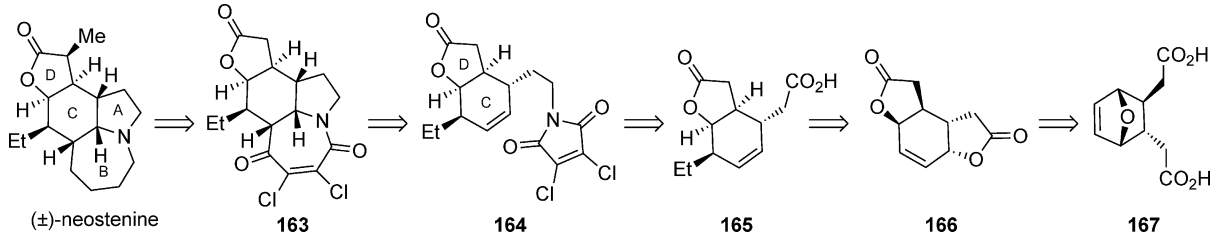
To extent the scope of the cyclic nitrone approach to the group of alkaloids related to stenine, we evaluated the se-



Scheme 18. Wipf's strategy for the synthesis of (–)-stenine.

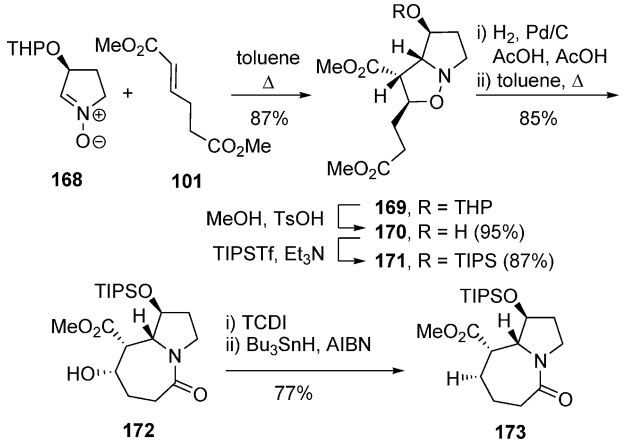


Scheme 19. Wipf's strategy for the synthesis of (–)-tuberostemonine.



Scheme 20. Booker-Milburn's strategy for the synthesis of (±)-neostenine.

quence depicted in Scheme 21. The starting nitrone **168** can be prepared from (*S*)-malic acid on a multi-gram scale.[112] Because of the stereogenic center at the THP protecting group, this nitrone is obtained as a mixture of two epimers. Consequently, although its cycloaddition to diester **101** in toluene at reflux occurred with complete stereoselectivity (*endo*-*anti*), a mixture of two isoxazolidines **169** with identical relative configurations at the newly formed stereogenic centers was isolated. To allow analytical simplicity in the subsequent steps, the THP group was removed and silyl ether protection was installed instead. Catalytic hydrogenation and subsequent heating in toluene at reflux furnished lactam **172**, which was converted into the corresponding deoxygenation product **173**. The conversion of **173** into (–)-stenine is currently being investigated.



Scheme 21. Preparation of intermediates for the synthesis of stenine.

Conclusions

A number of syntheses of various *Stemona* alkaloids, some of which are elegant illustrations of novel synthetic strategies, have been described. Many of the successful approaches to alkaloids of the stemoamide, tuberostemospironine, and stenine groups present some strategic and/or tactic analogies in their planning and execution. However, in view of the large amount of *Stemona* alkaloids isolated from natural sources to date, their structural diversity, and their biological potential, there is still large scope for further synthetic investigation in the field.

Acknowledgments

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