Recent progress in the chemistry of the *Stemona* alkaloids

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1 Introduction

This review focuses on the chemistry of the *Stemona* alkaloids, and covers the literature from 1975 to 1998. In this period thirty-five new *Stemona* alkaloids were isolated from Stemonaceae species and had their structures elucidated. More recently, the total syntheses of some of these alkaloids were reported. The biological activity of some representatives has also been evaluated.

The *Stemona* alkaloids represent a class of polycyclic alkaloids with relatively complex structures which emerged from the structural elucidation of its first representative, tuberostemonine (**2**, Fig. 2) in the sixties. The chemical investigation of Stemonaceae species was initially motivated by their use in Chinese and Japanese folk medicine in the treatment of respiratory diseases and as anthelmintics. However, the biological activity of Stemonaceae species could not be associated with any of the *Stemona* alkaloids.[1] The last review of this class of alkaloids covering the structural elucidation of tuberostemonine, stenine, oxotuberostemonine, stemonine, protostemonine, stemofoline and tuberostemonine A was reported by Götz and Strunz in 1975.[1] Additionally, the physical data of eleven representatives of this family possessing unknown structures were included. Since then, the isolation of new *Stemona* alkaloids and the elucidation of some previously unknown structures have been described in the literature.[2–25] The total syntheses of some *Stemona* alkaloids have also been reported.[26–35] More recently, a review with five references concerning the synthetic studies on stenine was reported by Haruna *et al*.[36]

This review focuses on the structural classification, isolation, biological activity and total syntheses of this class of alkaloid. Special attention is paid to both structural classification and synthetic studies.

Ronaldo A. Pilli received his BSc degree in Chemistry from the Universidade Estadual de Campinas (Unicamp), Campinas, SP (Brazil) in 1976 and in 1977 he joined the faculty staff at the same University as a teaching assistant. He carried out his PhD research at the same institution under the supervision of Professor Albert J. Kascheres, working on the reactions of cyclopropenimines with nitrogen ylides (1977–81). In 1982 he joined Professor Clayton H. Heathcock group at the University of California, Berkeley for postdoctoral work on the total synthesis of erythronolide A.

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In 1985 he started his independent research program at Unicamp aimed to develop and apply stereoselective methodologies to the total synthesis of natural products such as pheromones, alkaloids and macrolides. Professor Pilli is the recipient of the 1989 Union Carbide Prize, Brazil as the supervisor of the award winner project and of the 1999 Silver Jubilee Award of the International Foundation for Science, Sweden. He has been a fellow of several national and international scientific organizations and is currently on the Editorial Board of Quimica Nova and Journal of the Brazilian Chemical Society.

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2 Structural classification

The *Stemona* alkaloids are structurally characterized by the presence of the pyrrolo[1,2-*a*]azepine nucleus,[2] also named perhydroazaazulene[3] and 4-azaazulene[4] (**A**, Fig. 1). After the review by Götz and Strunz[1], thirty-five new *Stemona* alkaloids were reported in the literature,[2–25] currently comprising a total of forty-two structures.

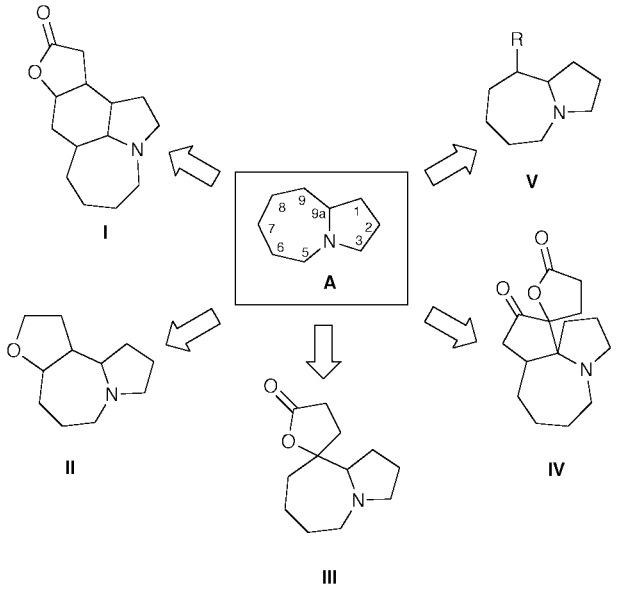


Fig. 1 *Stemona* alkaloid groups.

Xu and coworkers have previously suggested that the *Stemona* alkaloids can be separated into eight structural groups according to the sites of connection between the basic ring and the side chain.[4] However, these authors have only specified the maistemonine,[4] tuberostemonine,[22] croomine[22] and protostemonine[23] groups. We have also classified these alkaloids according to their structural features into five groups (stenine **I**, stemoamide **II**, tuberostemospironine **III**, stemonamine **IV**, tuberostemoamide **V** (Fig. 1)) containing the pyrrolo[1,2-*a*]azepine nucleus characteristic of the majority of the *Stemona* alkaloids and a miscellaneous group lacking this basic nucleus.

The group denominations adopted in this review may differ from those previously suggested by Xu and coworkers[4,22,23] since we decided to consider the name of the structurally simplest alkaloid of each group as the parent name. The name adopted for the basic skeleton in each group was based on the nomenclature of its members described in *Chemical Abstracts*. The numbering system of the structures was based on that described in the literature.[3,4,11,12]

2.1 Stenine group

The stenine group currently comprises seven members: stenine[1] **1**, tuberostemonine[1,3] **2**, tuberostemonine A[1] **3**, tuberostemonol[3] **4**, didehydrotuberostemonine[3] **5**, bisdehydroneotuberostemonine[22,25] **6** and neotuberostemonine[22,25] **7** (Fig. 2), which can be structurally represented by the tetracyclic furo[2,3-*h*]pyrrolo[3,2,1-*jk*][1]benzazepin-10(2*H*)-one nucleus (**I**, Fig. 1). Didehydrotuberostemonine (**5**) has also been named bisdehydrotuberostemonine.[22] Another stenine alkaloid named stemonine LG was reported in the literature[17] but with only partial stereochemical assignment. Later on, Dao and coworkers[37] referring to this alkaloid as tuberostemonine LG, established its structure by X-ray analysis which showed it to be identical to neotuberostemonine (**7**). The absolute configuration of stenine (**1**) was first established through its chemical conversion to derivatives of tuberostemonine (**2**) which had its

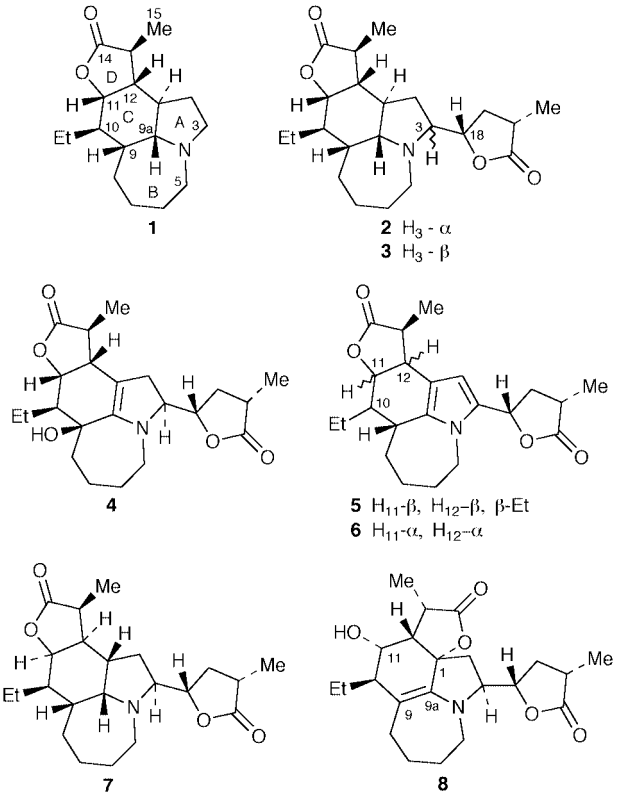


Fig. 2 *Stemona* alkaloids of the stenine group (**1**–**7**) and oxotuberostemonine (**8**).

absolute configuration revealed by X-ray diffraction analysis (heavy-atom method)[1] and later, by its asymmetric synthesis[30,34] (see Section 5.1). The oxidative cleavage of the C-3–C-18 bond in tuberostemonine A (**3**) afforded a lactam identical to the one obtained from tuberostemonine (**2**) thus revealing the absolute configuration depicted for tuberostemonine A (**3**) in Fig. 2.[1] The relative configurations of tuberostemonol (**4**) and neotuberostemonine (**7**) were established by 2D-NMR studies.[3,22] The structure of didehydrotuberostemonine (**5**) was identified by direct comparison of physical and chemical data with those obtained from the oxidation products of tuberostemonine (**2**).[3]

Comparison of the ^{1}H NMR chemical shifts of bisdehydroneotuberostemonine (**6**) and didehydrotuberostemonine (**5**) revealed for **6** the relative configuration represented in Fig. 2, however the stereochemistry at C-10 was not depicted in ref. 22 but the ethyl group at C-10 was represented with β orientation in ref. 25. Except for stenine (**1**), the simplest representative alkaloid of this group, all the other members have an α-methyl-γ-butyrolactone ring attached to C-3 in the pyrrolidine ring A. Stenine (**1**), tuberostemonine (**2**), tuberostemonine A (**3**), tuberostemonol (**4**) and didehydrotuberostemonine (**5**), show *cis* relationships between H-11, H-12 and the methyl group at C-13 in the lactone ring D. Bisdehydroneotuberostemonine (**6**) and neotuberostemonine (**7**) also display the *cis* relationship for these hydrogens which, however, are disposed *trans* to the methyl group at C-13. The absolute configuration at C-13 is the same as the one proposed for the other members of this group. Surprisingly, tuberostemonine A (**3**) is the only *Stemona* alkaloid to display an (*R*)-absolute configuration at C-3 when the α-methyl-γ-butyrolactone ring is attached to this stereogenic center. The *cis* B–C and C–D ring junction is observed for **1**, **2**, **3** and **7** while *trans* stereochemistry for the A–C ring junction is generally adopted, except for neotuberostemonine (**7**). Tuberostemonol (**4**) is the only *Stemona* alkaloid to display a hydroxy group at C-9. Oxotuberostemonine[1] **8** possesses a structure closely related to the stenine group but with the oxygen atom of the lactone ring D reallocated from C-11 to C-1, keeping the same relative configuration. Additionally, oxo-

tuberostemonine (**8**) displays a hydroxy group at C-11 and it is the only *Stemona* alkaloid to display a double bond at C-9–C-9a. Götz[1] pointed out the possibility that oxotuberostemonine (**8**) is an artifact formed by air oxidation of tuberostemonine (**2**) since it has also been obtained from tuberostemonine oxidation with mercuric acetate.

2.2 Stemoamide group

This group is currently represented by nine alkaloids: stemoamide[3] **9**, stemonine[1,2,23] **10**, neostemonine[23,25]**11**, bisdehydroneostemonine[23,25] **12**, protostemonine[1,16,18,23] **13**, didehydroprotostemonine[18,23,25] **14**, isoprotostemonine[18,23,25] **15**, tuberostemoamide[20,21] **16** and stemoninine[5,7,9] **17** (Fig. 3),

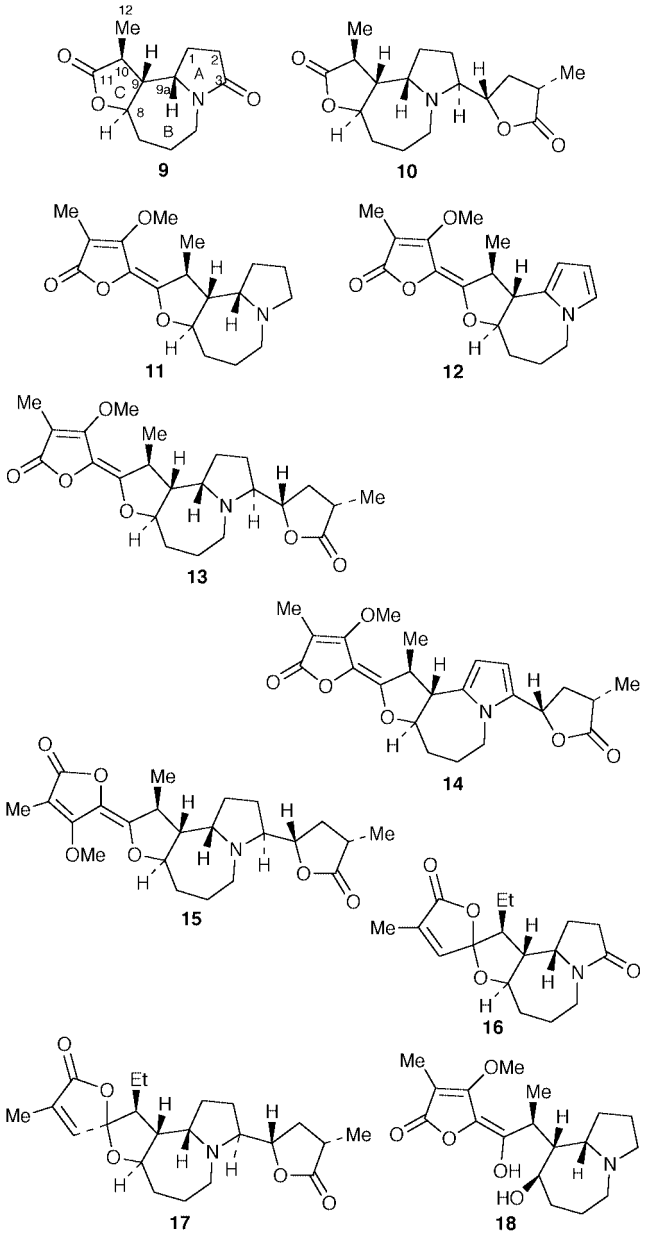


Fig. 3 *Stemona* alkaloids of the stemoamide group and stemodiol (**18**).

which display the tricyclic 2*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepine nucleus (**II**, Fig. 1). Additionally, neostemodiol[18] **18** has been included in the stemoamide group despite lacking ring C since it can be associated to neostemonine (**11**) through dehydration to form ring C. Neostemodiol (**18**) has also been named stemodiol by the same authors.[18] Some members of this group (**10**, **11**, **12**, **13**, **14** and **15**) have been reported as protostemonine-type alkaloids.[23] Before the isolation of **11**, the name neostemonine was applied to **12**,[18] but after that it has been changed to its current name bisdehydroneostemonine.[23] Additionally, **12** has been depicted in ref. 25 with *cis* fused B and C rings. Alkaloid **9** has been mistakenly reported as stemonamide[31] while structures **14** and **16** have also been reported as bisdehydroprotostemonine[23,25] and stemoninoamide,[20,21] respectively. Lin and coworkers reported different optical rotation values ($[\alpha]_D$ +94 (*c* 0.06, MeOH)[20] and $[\alpha]_D$ −94 (*c* 0.06, MeOH)[21]) for **16**. The alkaloid represented by structure **17** was also named stemoninoine[20,21] and stemoninone.[20] Stemoamide (**9**) had its relative configuration obtained by NMR studies and comparison of its ^{1}H NMR chemical shifts and coupling constant values with those of stemoninine (**17**).[3] Later on the absolute configuration of **9** was established through its asymmetric syntheses.[29,33] Stemonine (**10**) had its absolute stereochemistry revealed by X-ray analysis of its hydrobromide hemihydrate by consideration of anomalous dispersion effects.[38] Neostemonine (**11**), bisdehydroneostemonine (**12**) and tuberostemoamide (**16**) are represented by their relative configuration obtained from NMR studies and comparison of their ^{1}H NMR data to those of **13, 14** and **17**, respectively.[20,23] However, the relative configuration at C-11 of **16** has not been specified.[20]

Protostemonine (**13**) and stemoninine (**17**) had their relative stereochemistries revealed from NMR studies[9,18] while didehydroprotostemonine (**14**) had its relative configuration obtained after comparison of its NMR data to those of protostemonine (**13**).[18,23] Additionally, protostemonine (**13**) has been previously converted to its hydrate hydrochloride and than afforded stemonine (**10**) upon K_2CO_3 treatment or vacuum pyrolysis,[1] and oxidation of **13** with Ag_2O afforded **14**.[23] Comparison of the NMR data of isoprotostemonine (**15**) and protostemonine (**13**) revealed for the former alkaloid the relative configuration represented in Fig. 3.[18,23]

The alkaloids **10**, **13**, **14**, **15** and **17** display an α-methyl-γ-butyrolactone ring attached to C-3 in the pyrrolidine ring A. Moreover, the *trans* ring fusion of the B–C rings, the *cis* relationship between the hydrogens at C-9 and C-9a and the (*S*) absolute configuration at C-10 are noteworthy stereochemical features of this group of alkaloids. The *Stemona* alkaloids **11**, **12**, **13**, **14** and **15** have a disubstituted lactone ring attached to ring C at C-11 by a double bond as a distinct characteristic of this group. The *Stemona* alkaloids **16** and **17** display an unsaturated spirolactone ring fused at C-11. Interestingly, these two alkaloids have an ethyl substituent at C-10 instead of the methyl substituent found in the other members of this group. Surprisingly, isoprotostemonine (**15**) has the disubstituted lactone ring disposed with opposite geometry around the exocyclic double bond when compared to the other members of the group. In fact this is the only structural difference between protostemonine (**13**) and isoprotostemonine (**15**).

2.3 Tuberostemospironine group

The tuberostemospironine group of *Stemona* alkaloids is characterized by a 2*H*-spiro[furan-2,9′[9H]pyrrolo[1,2-*a*]azepin]-5-one nucleus which displays a spiro γ-lactone at C-9 of the basic ring (**III**, Fig. 1) and comprises seven members: tuberostemospironine[3] **19**, croomine[6,19] **20**, stemospironine[2] **21**, stemotinine[8] **22**, isostemotinine[8] **23**, stemonidine[1,8] **24** and didehydrocroomine[19] **25** (Fig. 4). The *Stemona* alkaloids **20**, **22**, **23** and **24** have been reported as croomine-type alkaloids.[8,22] The relative configurations of alkaloids tuberostemospironine (**19**), stemotinine (**22**), isostemotinine (**23**) and stemonidine (**24**) were established by NMR studies[3,8] while croomine[6] (**20**) and stemospironine[2] (**21**) had their absolute configurations obtained by X-ray analyses (heavy-atom method). The relative configuration of didehydrocroomine (**25)** was revealed by NMR studies and it was correlated with croomine (**20**) after Ag_2O oxidation.[19] Croomine (**20**), stemospironine (**21**), stemotinine

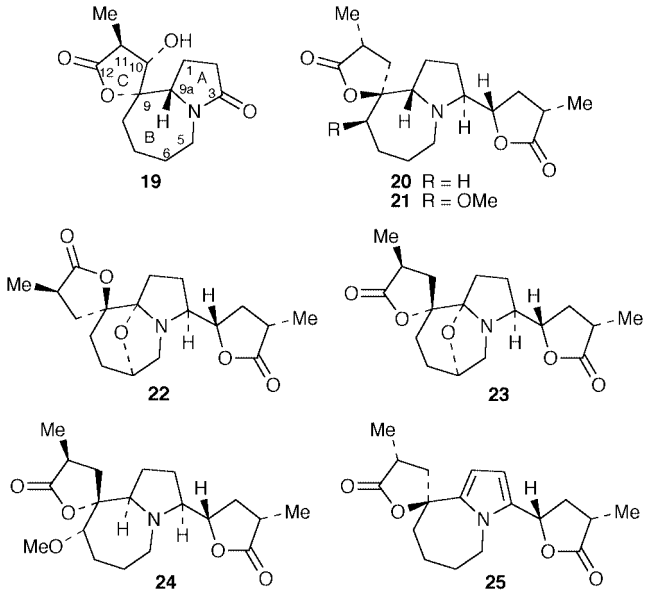


Fig. 4 *Stemona* alkaloids of the tuberostemospironine group.

(**22**) and didehydrocroomine (**25**) display at C-9 an opposite stereochemistry to that found in tuberostemospironine (**19**), isostemotinine (**23**) and stemonidine (**24**). Of these seven alkaloids, tuberostemospironine (**19**) is the only one which lacks the α-methyl-γ-butyrolactone ring appended to C-3 of the pyrrolidine ring A. Curiously, stemotinine (**22**) and isostemotinine (**23**) have an oxygen bridge between C-9a and C-6. In fact these two alkaloids are the only *Stemona* alkaloids with such a characteristic and they differ by the absolute configuration at C-9 and C-11.

2.4 Stemonamine group

Previously reported as the maistemonine group,[4] this group is characterized by the tetracyclic 2′*H*,11*H*-spiro[1*H*-cyclopenta-[*b*]pyrrolo[1,2-*a*]azepine-11,2′-furan]-5′,10-dione nucleus with a spirolactone ring at C-12 (**IV**, Fig. 1) which may be found in both absolute configurations. The stemonamine group includes the following *Stemona* alkaloids: stemonamine[4] **26**, isostemonamine[4] **27**, stemonamide[4,25] **28**, isostemonamide[4,25] **29**, maistemonine[4,13,16] **30** and oxymaistemonine[4,13,16] **31** (Fig. 5).

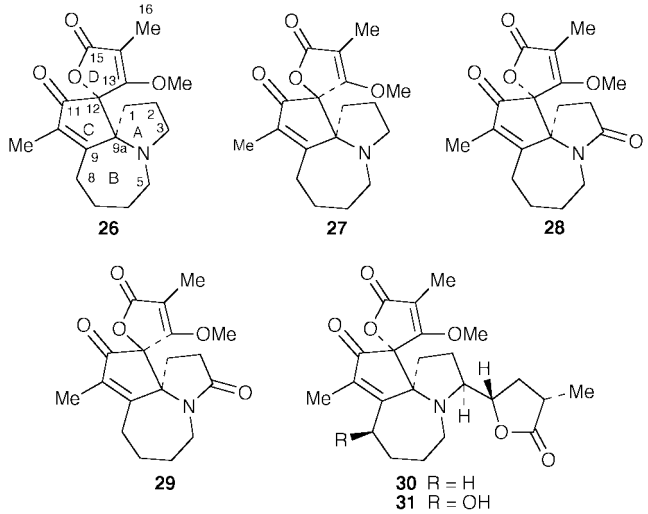


Fig. 5 *Stemona* alkaloids of the stemonamine group.

The alkaloids **30** and **31** were first reported to display (*R*)-absolute configuration at C-9a.[13,16] Later on their correct structures were revealed by conversion of **30** to **28**.[4] The literature[24] also reports the name protostemotinine when referring to structure **30**, despite the difference in the melting points reported for maistemonine[4] (mp 205–207 °C) and protostemotinine[24] (mp 214–246 °C). Curiously, stemonamine (**26**) and isostemonamine (**27**) were identified as racemic alkaloids and stemonamine (**26**) displayed racemic pairs of molecules in the X-ray analysis.[39] Stemonamide (**28**) and isostemonamide (**29**) had their relative configurations established by NMR studies.[4] The relative configuration of oxymaistemonine (**31**) was obtained by comparison of its NMR data with those for maistemonine (**30**).[13] The configuration at C-8 in **31** was confirmed by coupling constant value in combination with the inspection of the Dreiding structural model.[13] Stemonamine (**26**) and stemonamide (**28**) only differ from isostemonamine (**27**) and isostemonamide (**29**), respectively, by the absolute configuration at C-12. All the members of this group show the (*S*)-absolute configuration at C-9a and the α-methyl-γ-butyrolactone ring attached to C-3 is found only in the alkaloids maistemonine (**30**) and oxymaistemonine (**31**).

2.5 Parvistemoline group

The parvistemoline alkaloids are characterized by the lack of the B–C ring fusion and a hexahydro-2,6-dimethyl-5-oxofuro[3,2-*b*]furan-3-yl moiety attached to C-9 in the pyrrolo [1,2-*a*]azepine nucleus (**V**, Fig. 1). This group comprises the alkaloids parvistemoline[11] **32**, parvistemonine[10,15] **33** and didehydroparvistemonine[11] **34** (Fig. 6). Parvistemonine (**33**)

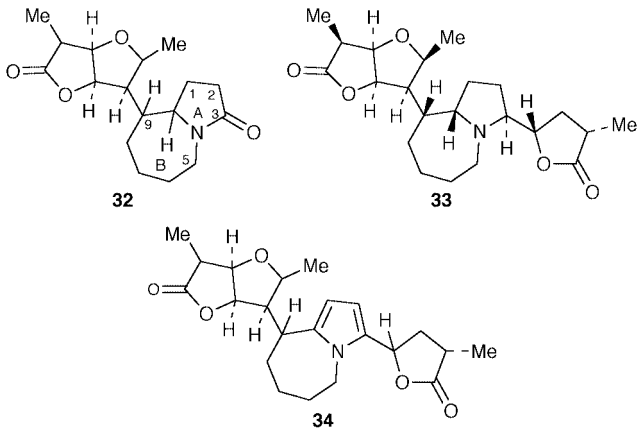


Fig. 6 *Stemona* alkaloids of the parvistemoline group.

and didehydroparvistemonine (**34**) have a γ-lactone ring positioned at C-3. The structures of these alkaloids were established by IR, MS and NMR studies but only parvistemonine (**33**) had its relative configuration unambigously depicted in the literature.[10]

2.6 Miscellaneous group

The miscellaneous group includes eight *Stemona* alkaloids: stemofoline[1,2,12] **35**, oxystemofoline[12] **36**, methoxystemofoline[12] **37**, parvistemoninine[15] **38**, parvistemoninol[15] **39**, tuberostemonone[3,14] **40**, tuberostemoninol[20,21] **41** and parvistemoamide[11,15] **42** (Fig. 7). The relative configurations at C-8, C-9a and C-10 of parvistemoamide (**42**) are not unambiguously depicted in ref. 11 but the same group described in ref. 15 the relative stereochemistry shown in Fig. 7. Stemofoline (**35**) had its absolute configuration established by X-ray analysis of its hydrobromide monohydrate (heavy-atom method)[40] while the alkaloids oxystemofoline[12] (**36**), methoxystemofoline[12] (**37**) and parvistemoamide[11] (**42**) had their relative configurations obtained by 2D-NMR studies. Tuberostemonone[14] (**40**) and tuberostemoninol[20] (**41**) are represented by their relative configuration which were established by X-ray analyses.

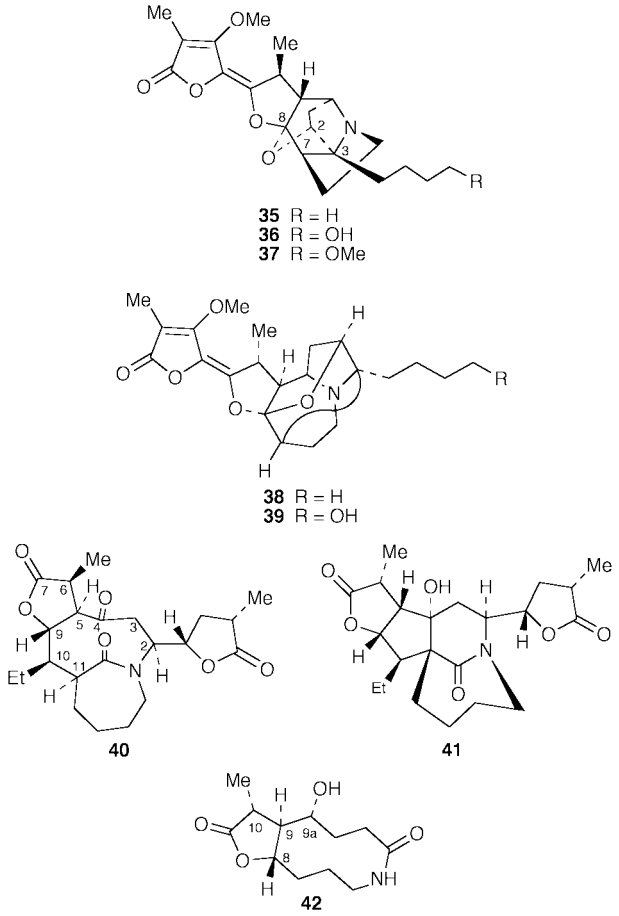


Fig. 7 *Stemona* alkaloids of the miscellaneous group.

Although the members of this group lack the pyrrolo[1,2-*a*]azepine nucleus, they still keep in their structure some characteristic fragments present in the members of the other groups. The alkaloids **35**–**37** and **38**–**39** are structurally the most complex *Stemona* alkaloids and differ from each other by the nature of the substituent attached to the side chain at C-3. The removal of the C-2–oxygen and C-8–oxygen bonds, the C-3–C-7 bond and the side chain at C-3 in **35**–**37** formally leads to the stemoamide alkaloid neostemonine (**11**) (Fig. 3). Tuberostemonone (**40**) can be associated with the stenine group as a product of their oxidative cleavage of the C-1–C-9a bond. Unlike the members of that group, **40** shows a *trans* relationship between the C-5 and C-9 hydrogens and between the hydrogen at C-11 and the ethyl group at C-10.

As for **40**, tuberostemoninol (**41**) can also be associated with the stenine group by the oxidative cleavage of the C-1–C-9a bond (stenine group numbering) to form a dicarbonylic system, followed by the nucleophilic attack of the enol form of the carbonyl group at C-9 to the carbonyl group at C-1. The structurally simplest *Stemona* alkaloid, parvistemoamide (**42**) may be associated with the members of stemoamide group (Fig. 3) by the nucleophilic attack of the nitrogen atom of **42** to a keto group at C-9a followed by reduction at this carbon.

3 Natural sources

3.1 Stemonaceae family

The family Stemonaceae (order Dioscoreales) is today the only source of the *Stemona* alkaloids. This family is a monocotyledon described by Engler in 1887.[41] Although Dahlgren[41] reported for this family the genera *Stemona*, *Croomia*, *Stichoneuron* and *Pentastemona*, Duyfjes,[42] and later Bouman,[43] found evidence which allowed them to separate the genus *Pentastemona* into a new family, Pentastemonaceae. *Stemona*, earlier named *Roxburghia*, is the most representative genus of the family Stemonaceae, occurring from southern Asia and Malaysia to northern Australia. The literature reports the existence of 25 species for this genus. The genus *Croomia* comprises three species and occurs in Atlantic North America and Japan. The third genus, *Stichoneuron*, is composed of two species distributed in eastern Asia.[41]

3.2 Phytochemical studies

Although the Stemonaceae family comprises more than 30 species, the phytochemical investigation of this family is restricted to only eight of them, most belonging to the genus *Stemona* (Table 1). As far as we know, no phytochemical study has been reported so far for the genus *Stichoneuron*. Ren-sheng Xu and coworkers initiated an extensive investigation of some

Table 1 *Stemona* alkaloids isolated from Stemonaceae species

Stemonaceae species	*Stemona* alkaloid	Reference
S. tuberosa	Stenine **1**	1
	Tuberostemonine **2**	1, 3
	Tuberostemonol **4**	3
	Didehydrotuberostemonine **5**	3
	Bisdehydroneotuberostemonine **6**	22, 25
	Neotuberostemonine **7**	22, 25
	Oxotuberostemonine **8**	1
	Stemoamide **9**	3
	Tuberostemoamide (Stemoninoamide) **16**	20, 21
	Tuberostemospironine **19**	3
	Stemotinine **22**	8
	Isostemotinine **23**	8
	Tuberostemonone **40**	3, 14
	Tuberostemoninol **41**	20, 21
S. japonica	Stemonine **10**	1, 23
	Neostemonine **11**	23, 25
	Bisdehydroneostemonine **12**	18, 23, 25
	Protostemonine **13**	1, 18, 23
	Didehydroprotostemonine **14**	18, 23, 25
	Isoprotostemonine **15**	18, 23, 25
	Stemospironine **21**	2
	Stemonidine **24**	1
	Stemonamine **26**	4
	Isostemonamine **27**	4
	Stemonamide **28**	4, 25
	Isostemonamide **29**	4, 25
	Maistemonine (Protostemotinine) **30**	4, 18
	Neostemodiol (Stemodiol) **18**	18
	Stemofoline **35**	1, 2
S. parviflora	Parvistemoline **32**	11
	Parvistemonine **33**	10, 15
	Didehydroparvistemonine **34**	11
	Stemofoline **35**	12
	Oxystemofoline **36**	12, 15
	Methoxystemofoline **37**	12
	Parvistemoninine **38**	15
	Parvistemoninol **39**	15
	Parvistemoamide **42**	11, 15
S. sessilifolia	Tuberostemonine **2**	1
	Tuberostemonine A **3**	1
	Stemoninine **17**	9
	Protostemotinine (Maistemonine) **30**	24
S. mairei	Protostemonine **13**	16
	Maistemonine (Protostemotinine) **30**	13, 16
	Oxymaistemonine **31**	13, 16
Stemona sp.	Protostemonine **13**	1
	Stemoninine **17**	5, 7
C. japonica	Croomine **20**	19
	Didehydrocroomine **25**	19
C. heterosepala	Croomine **20**	6

Stemona species in the early 80's leading to the isolation and structural elucidation of most of the currently known *Stemona* alkaloids.[25] Most of the phytochemical studies of this family were restricted to the roots although studies of leaves,[2] stems[2] and rhizomes[1,6,24] have also been reported. Due to their complex structures, most of the *Stemona* alkaloids had their structure elucidated by crystallographic analyses.[2,6,14,20,37–40]

4 Biological activities

The popular use of Stemonaceae extracts as insecticides, vermifuges and in the treatment of respiratory diseases in China and Japan is described in the literature.[1,2,23,44] The water extracts obtained from the roots of some Stemonaceae species were widely used in China against human and cattle parasites, agricultural pests and as domestic insecticides.[2] The basic methanolic extracts obtained from fresh leaves of *Stemona japonica* showed strong insecticidal activity against silk worm larvae.[2] The crude extracts of Stemonaceae species have also shown antitubercular and antitussive activities.[44] These biological activities motivated the chemical investigation of Stemonaceae species in order to find their active principles. Tuberostemonine (**2**) (Fig. 2) was the first *Stemona* alkaloid to have its biological activity tested. Although the initial results did not show activity against *Hymenolepis nana* and *Nematospiroides dubius*,[1] its anthelminthic activity was detected when tested against *Angiostrongylus cantonensis*, *Dipylidium caninum* and *Fasciola hepatica* with an effect on the motility of these helminthic worms. These results motivated Shinozaki and Ishida to test the action of this alkaloid on the neuromuscular transmission in crayfish which is considered a model for studying the mechanism of drug action in the mammalian central nervous system. The results obtained in the tests demonstrated that tuberostemonine depressed glutamate-induced responses at similar concentrations to those of established glutamate inhibitors.[44] The insecticidal activity of stemonine (**10**) (Fig. 3), stemospironine (**21**) (Fig. 4) and stemofoline (**35**) (Fig. 7) against the fourth instar *Bombyx mori* (silkworm larvae) is reported in the literature.[2] Alkaloid **35** showed a very potent activity against the larvae, being 10^4 times more toxic than alkaloid **21**. Stemonine (**10**) and stemospironine (**21**) showed similar moderate results. Otherwise, these three alkaloids showed no activity against the fifth instar larvae of cabbage army worm (*Mamestra brassicae*). Neostemonine (**11**) and isoprotostemonine (**15**) (Fig. 3) had their antifeeding activity tested against last-instar larvae of *Spodoptera litura* but with little activity.[23] No antimicrobial or antiviral activities were detected for these two alkaloids.[23] As far as we know no other *Stemona* alkaloid has had its biological activity tested.

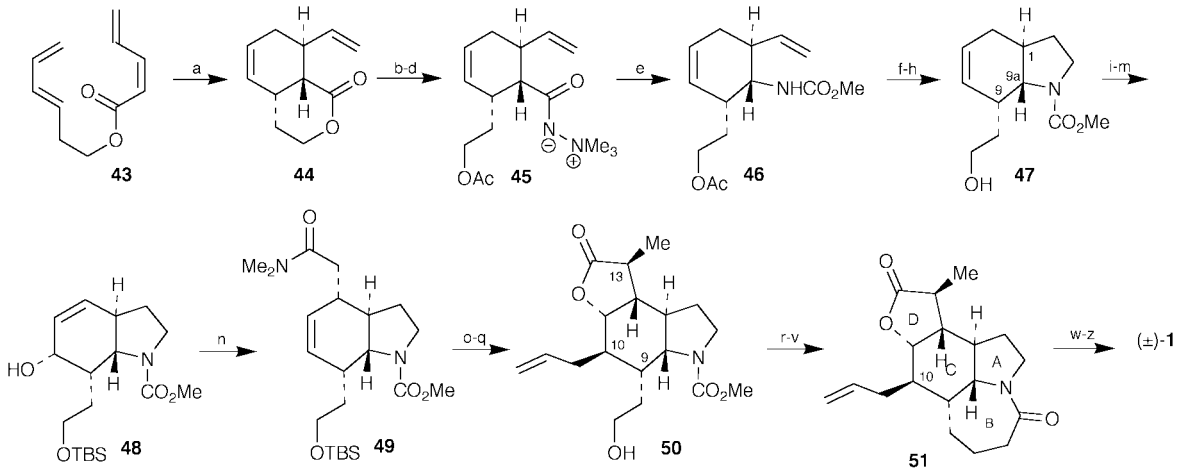
5 Synthetic sources

The complex molecular architecture of the *Stemona* alkaloids has stimulated the synthetic work on this family of natural products. In this section only the approaches which culminated in the total synthesis of a member of this family will be discussed, although several studies have also appeared directed towards the assembly of their major structural motifs.[45–53]

5.1 Stenine group

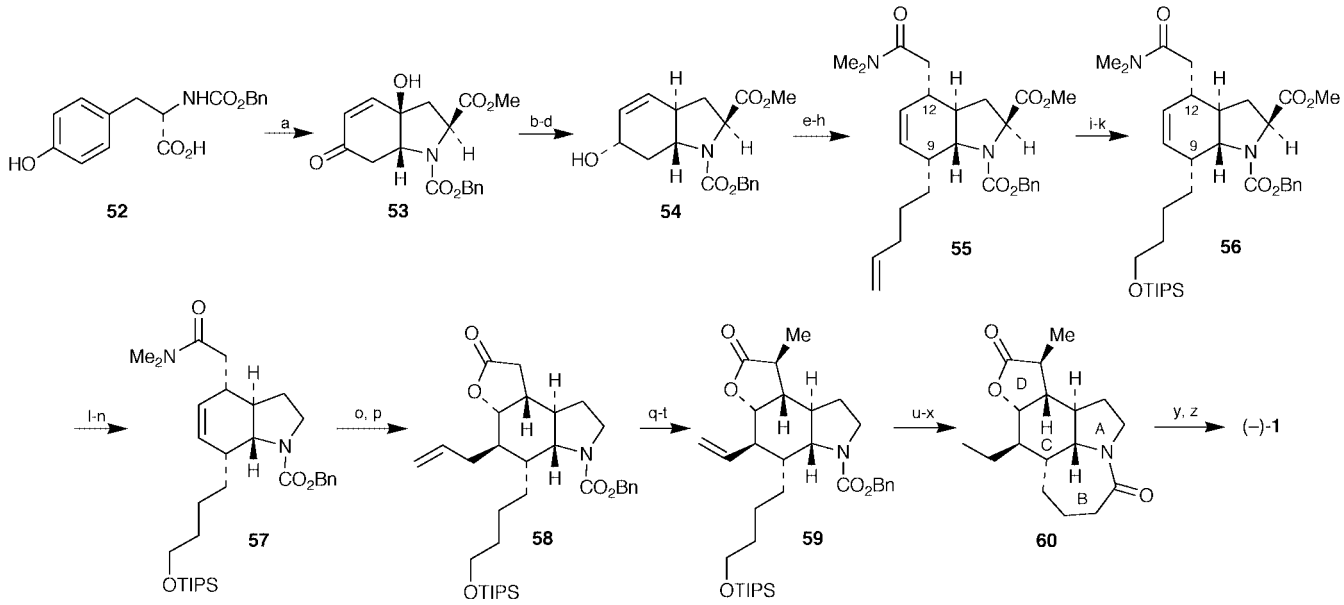
Stenine (**1**) is the only representative of this group of *Stemona* alkaloids which has so far yielded to total synthesis. Chen and Hart first described the total synthesis of racemic stenine (**1**) in 1990.[27,28] The construction of the advanced intermediate **50** containing the ACD substructure was initiated with an intramolecular Diels–Alder reaction (**43** → **44**, Scheme 1) followed by a Curtius rearrangement (**45** → **46**) which set the stage for ring A formation (Scheme 1). Claisen–Eschenmoser rearrangement (**48** → **49**) and iodolactonization completed the assembly of tricyclic intermediate **50**. Ring B was finally put in place after homologation of the side chain at C-9 and intramolecular lactam formation (**50** → **51**). The first total synthesis of racemic stenine (**1**) was completed in 25 steps from **43** and 7.2% overall yield after the conversion of the allylic residue at C-10 to the requisite ethyl substituent and the adjustment of the oxidation level at ring B.

Wipf and coworkers[30] have reported the first asymmetric synthesis of (−)-stenine (**1**) based on an efficient preparation of a hydroindolenone intermediate through the oxidation of *N*-benzyloxycarbonyltyrosine with hypervalent iodine, followed by the reduction of the corresponding π-allylpalladium intermediate (**52** → **54**, Scheme 2). The stereogenic center at C-9 was established through enolate alkylation and the acetamido side chain at C-12 by a Claisen–Eschenmoser rearrangement (**54** → **55**). Selective cleavage of the terminal olefin was accomplished with Sharpless asymmetric dihydroxylation fol-

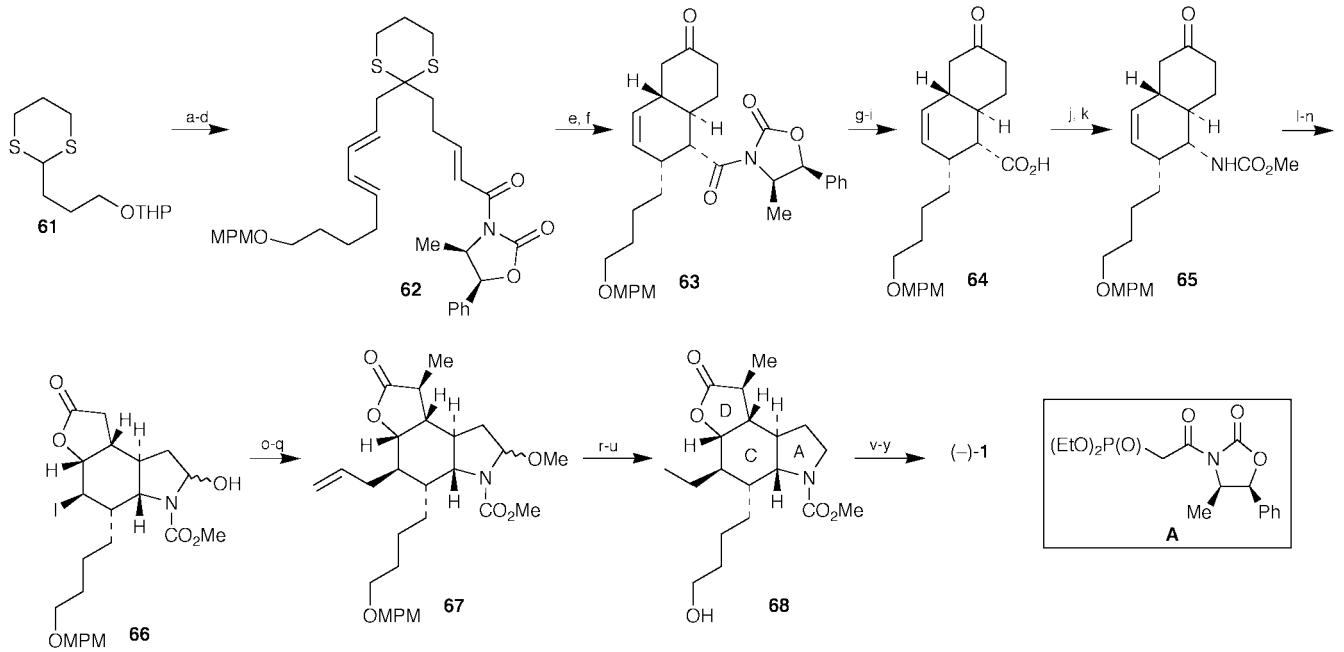


Scheme 1 *Reagents*: (a) Et_2AlCl, $CHCl_3$, 80 °C (67%); (b) H_2NNH_2, H_2O, MeOH, reflux (87%); (c) MeI, K_2CO_3, MeOH, reflux (100%); (d) AcCl, 0 °C → rt (100%); (e) mesitylene, reflux; then, MeOH, reflux (94%); (f) 9-BBN, THF, 0 °C → rt; then $NaBO_3{\cdot}4H_2O$, H_2O, rt (95%); (g) MsCl, Et_3N, CH_2Cl_2, 0 °C → rt (100%); (h) MeLi, THF, −78 °C → rt (83%); (i) Jones' reagent, acetone, 0 °C (83%); (j) I_2, THF–Et_2O, aq. $NaHCO_3$, 0 °C → rt (95%); (k) DBU, toluene, reflux (98%); (l) 2-methylpropan-2-ol, MeOH, $NaBH_4$, 50 °C (100%); (m) TBSCl, Et_3N, CH_2Cl_2, DMAP, rt (97%); (n) $MeC(OMe)_2NMe_2$, xylenes, reflux (93%); (o) I_2 THF, H_2O, rt (75%); (p) $CH_2CHCH_2SnBu_3$, AIBN, C_6H_6, reflux (83%); (q) LDA, MeI, THF, HMPA, −78 °C (87%); (r) DMSO, $(COCl)_2$, CH_2Cl_2; −78 °C then Et_3N (99%); (s) $Ph_3P{=}CHCO_2Et$, $CHCl_3$, reflux (91%); (t) Red-Al, CuBr, THF, butan-2-ol, −78 °C → −20 °C (85%); (u) Me_3SiI, $CHCl_3$, rt (94%); (v) mesitylene, reflux (91%); (w) OsO_4 (cat.), $NaIO_4$ THF, H_2O, rt (84%); (x) $HSCH_2CH_2SH$, SiO_2–$SOCl_2$, CH_2Cl_2, rt (100%); (y) (p-$MeOC_6H_4PS_2)_2$, CH_2Cl_2, rt (100%); (z) W-2 Raney-Ni, EtOH, reflux (80%).

lowed by sodium periodate cleavage of the corresponding diol. Reductive decarboxylation (**56** → **57**) set the stage for iodolactonization, followed by a stereoselective radical allylation (**57** → **58**) and enolate alkylation, a sequence of events which resembles the approach by Chen and Hart.[27,28] The azepine ring B was formed through intramolecular nitrogen



Scheme 2 *Reagents*: (a) $PhI(OAc)_2$, MeOH, $NaHCO_3$, 23 °C (54%); (b) Bz_2O, CH_2Cl_2, pyridine, DMAP, reflux (90%); (c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, THF, rt (99%); (d) $Pd_2(dba)_3{\cdot}CHCl_3$, THF, nBu_3P, HCO_2H, Et_3N, 60 °C (68%); (e) TPAP (cat.), NMO, CH_2Cl_2, MS 4 Å, 0 °C → rt (90%); (f) KHMDS, toluene, −80 °C; then, $CH_2CH(CH_2)_3OTf$, THF, −60 °C (51%); (g) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, THF, MeOH, 40 °C (91%); (h) $MeC(OMe)_2NMe_2$, xylenes, reflux (85%); (i) AD-mix-β, *tert*-BuOH, H_2O, 5 °C; then, *tert*-BuOH, H_2O, $NaIO_4$, rt (82%); (j) $NaBH_4$, THF, MeOH (93%); (k) TIPSCl, imidazole, 4-DMAP (cat.), CH_2Cl_2, rt (100%); (l) LiOH, THF, MeOH, H_2O, 40 °C (90%); (m) $PhOP(O)Cl_2$, C_6H_5SeH, Et_3N, THF, 0 °C → 22 °C; (n) nBu_3SnH, AIBN (cat.), xylenes, 130 °C (79%, 2 steps); (o) I_2, THF, pH 5.5, 21 °C (85%); (p) $CH_2CHCH_2SnBu_3$, AIBN (cat.), 80 °C (90%); (q) LDA, THF, HMPA, MeI, −78 °C (87%); (r) OsO_4 (cat.), $NaIO_4$, THF, H_2O, *tert*-BuOH, 0 °C → 21 °C; (s) $NaBH_4$, THF, MeOH, −40 °C (63%, 2 steps); (t) *o*-$(NO_2)PhSeCN$, nBu_3P, THF, 0 °C; then, H_2O_2, THF, 21 °C (87%); (u) HF, CH_3CN, 0 °C; (v) Dess–Martin periodinane, CH_2Cl_2, 21 °C; then, THF, 2-methylbut-2-ene, $NaClO_2$, aq. Na_2HPO_4, 0 °C; (w) H_2, $Pd(OH)_2$/C, MeOH, 21 °C; (x) $C_6F_5P(O)Ph_2$, CH_2Cl_2, 21 °C (71%, 4 steps); (y) $(p\text{-}MeOC_6H_4PS_2)_2$, CH_2Cl_2, 21 °C (93%); (z) Raney-Ni, EtOH, 21 °C (78%).



Scheme 3 *Reagents*: (a) nBuLi, THF, −25 °C; then, (*E*,*E*)-$MPMO(CH_2)_4CH{=}CH{-}CH{=}CH{-}CH_2Cl$, HMPA, −78 °C → rt; (b) pTsOH, H_2O, MeOH, THF, rt (68%, 2 steps); (c) pyr·SO_3, DMSO, Et_3N, CH_2Cl_2, 0 °C → rt (85%); (d) **A**, Et_3N, LiCl, THF, 0 °C → rt (90%); (e) Me_2AlCl, CH_2Cl_2, −20 °C (85%); (f) $AgNO_3$, *N*-chlorosuccinimide, CH_3CN–H_2O, 0 °C (80%); (g) LiSEt, THF, 0 °C (91%); (h) Et_3SiH, 10% Pd/C, acetone, 0 °C → rt (100%); (i) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, *tert*-BuOH, H_2O, 0 °C → rt (100%); (j) $(PhO)_2P(O)N_3$, DMF, Et_3N, 60 °C; (k) MeOH, CuCl (cat.), rt (82%, 2 steps); (l) TMSCl, NaI, CH_3CN, Et_3N, 50 °C; (m) MCPBA, hexane, CH_2Cl_2, −15 °C → rt; (n) H_5IO_6, THF, H_2O, rt; then, I_2, $NaHCO_3$, rt (50%, 3 steps); (o) CSA, $CH(OMe)_3$, MeOH, CH_2Cl_2, rt (90%); (p) $CH_2{=}CHCH_2SnBu_3$, AIBN (cat.), toluene, 80 °C (80%); (q) LDA, THF, HMPA, −78 °C; then, MeI, −78 °C (73%); (r) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_3CN, 0 °C (82%); (s) OsO_4 (cat.), $NaIO_4$, THF, H_2O, rt (75%); (t) $HSCH_2CH_2SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −15 °C (81%); (u) W2-Raney-Ni, EtOH, reflux (85%); (v) MsCl, Et_3N, CH_2Cl_2, 0 °C (88%); (w) NaI, acetone, reflux (98%); (x) TMSI, CH_2Cl_2, rt; (y) CH_3CN, reflux (70%, 2 steps).

acylation and the total synthesis was completed by the reduction of lactam **60** to afford (−)-**1** in 26 steps from Cbz-tyrosine (**52**) and *ca*. 1.0% yield.

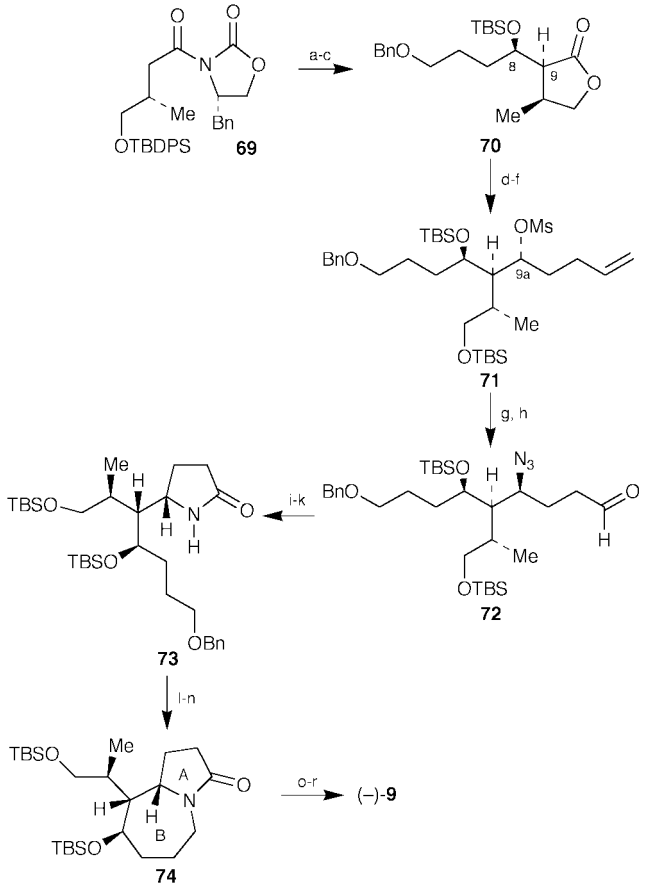
An asymmetric intramolecular Diels–Alder reaction was employed by Morimoto and coworkers[34] to construct the bicyclic ketone **63** with four stereogenic centers correctly assembled for the synthesis of (−)-**1** and which was later on converted to the tricyclic key intermediate **66** containing the ACD rings after a modified Curtius rearrangement (**64** → **65**, Scheme 3), iodolactonization (**65** → **66**), radical allylation and methylation at C-11 (**66** → **67**). The synthesis of (−)-**1** was completed in 24 steps from dithiane **61** and *ca*. 2% overall yield after construction of ring B through an intramolecular nitrogen alkylation (**68** → **1**).

5.2 Stemoamide group

The tricyclic alkaloid stemoamide (**9**) is a typical representative of this group of *Stemona* alkaloids and it has been synthesized several times over the last few years, including some very efficient approaches. Williams and coworkers[29] succeeded in preparing (−)-stemoamide (**9**) starting from commercially available methyl (*R*)-3-hydroxy-2-methylpropionate which was homologated and coupled with (*S*)-4-benzyloxazolidin-2-one to afford chiral imide **69** (7 steps and 85% overall yield). An asymmetric boron aldol reaction with 4-benzyloxybutanal installed the stereogenic centers at C-8 and C-9 (**70**, Scheme 4). The correct stereochemistry at C-9a was established after chain elongation, reduction with lithium triethylborohydride (exclusively from the carbonyl *si* face), mesylation (**70** → **71**) and methanesulfonate displacement with sodium azide which proceeded with inversion of configuration (**71** → **72**). At this point all the carbons and the stereogenic centers of (−)-stemoamide (**9**) were in place and the remaining steps were dedicated to the formation of rings A, B and C and functional group interconversions (Scheme 4). The first total synthesis of (−)-stemoamide was then completed in 25 steps from (*R*)-methyl-3-hydroxy-2-methylpropionate and 5.6% overall yield.

Kohno and Narasaka[31] devised a short synthesis of (±)-stemoamide (**9**), mistakenly designated as (±)-stemonamide by these authors, by applying the oxidative coupling reaction of 2-tributylstannyl-*N*-Boc-pyrrolidine with silyl enol ethers. The key intermediate **77** was produced in 65% yield as a mixture of stereoisomers which led to a separable mixture of diastereoisomers (**78a**:**78b** = 4:1) upon hydrogenation of the acetylenic bond. The formation of **77** is rationalized through the addition of silyl enol ether **76** (*E*:*Z* = 1:1) to an intermediate *N*-acyliminium ion derived from *N*-Boc-2-tributylstannylpyrrolidine (Scheme 5). The stereogenic center at C-8 was established after $NaBH_4$ reduction of **78a** which afforded γ-lactone **79** in 59% yield. The alcohol with the wrong stereochemistry at C-8 was also obtained in 25% yield and it was converted to **79** through a 3-step sequence. In the final steps of the synthesis, ring B was formed by intramolecular nitrogen alkylation and the correct stereochemistry at C-10 was established by stereoselective methylation of the lithium enolate of the γ-lactone. This concise approach required 12 steps from 5-benzyloxypent-3-yn-2-one and provided (±)-stemoamide (**9**) in *ca*. 2% overall yield.

A concise and efficient approach to (−)-stemoamide (**9**) based on an intramolecular enyne metathesis was developed by Kinoshita and Mori.[33] Starting from lactam **81**, prepared from (−)-pyroglutamic acid, the acetylene **82** was obtained in 5 steps and 50% overall yield (Scheme 6). The construction of ring B was efficiently accomplished by enyne metathesis (87% yield) using catalytic amount of Grubb's catalyst (**82** → **83**, Scheme 6). Reduction to the saturated ester, followed by bromolactonization of the mixture of epimeric carboxylic acids, afforded unsaturated lactone **85** (31% yield) and the corresponding bromolactone **84** (21% yield) which could be converted to **85** (50% yield) by treatment with Et_3N. The correct stereochemistry at C-10 was established by reduction of **85** with $NaBH_4$ in the presence of $NiCl_2$•$6H_2O$ in methanol to give (−)-stemoamide (**9**), in 14 steps from (−)-pyroglutamic acid and 9% overall yield.

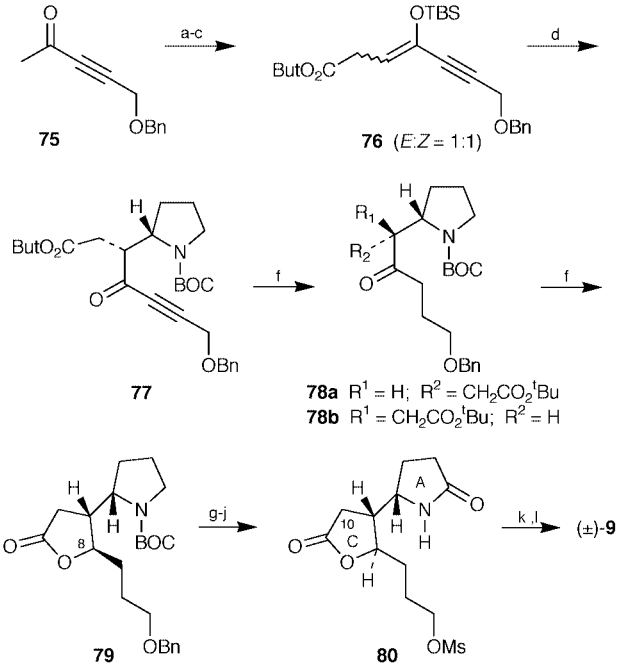


Scheme 4 *Reagents*: (a) n-Bu_2BOTf, CH_2Cl_2, Et_3N, −78 °C → 0 °C; then, 4-benzyloxybutanal, −78 °C → 0 °C (88%); (b) aq. HF, CH_3CN, rt; sat. aq. $NaHCO_3$, K_2CO_3 (82%); (c) TBDMSOTf, collidine, CH_2Cl_2, −78 °C → rt (97%); (d) 4-iodobut-1-ene, *tert*-BuLi, Et_2O, −100 °C; then, TBDMSOTf, collidine, −78 °C → rt (78%); (e) $LiEt_3BH$, THF, −78 °C → rt (91%); (f) MsCl, pyridine, rt (96%); (g) NaN_3, HMPA, rt; (h) O_3, CH_2Cl_2, MeOH, −78 °C; then, Me_2S, −78 °C → rt (49%, 2 steps); (i) $NaClO_2$, NaH_2PO_4•H_2O, CH_3CN, *tert*-BuOH, H_2O, 2-methylbut-2-ene, 0 °C; (j) CH_2N_2, Et_2O, 0 °C (96%, 2 steps); (k) PPh_3, THF, H_2O, reflux (87%); (l) H_2, 10% Pd/C, EtOH; (m) MsCl, pyridine, rt; (n) NaH, THF, rt (71%, 3 steps); (o) HF·Et_3N, CH_3CN, rt (63%); (p) Dess–Martin periodinane, pyridine, CH_2Cl_2, rt; (q) TBAF, THF, rt (94%, 2 steps); (r) PDC, CH_2Cl_2, reflux (80%).

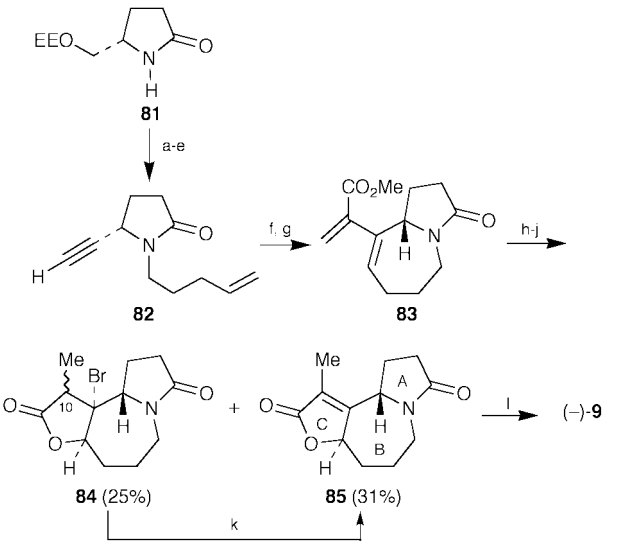
By far the most concise and efficient approach to (±)-stemoamide (**9**) was developed by Jacobi and Lee[35] and featured an intramolecular Diels–Alder–retro Diels–Alder cycloaddition between the 2-methoxyoxazole and acetylenic moieties in **89** followed by hydrolysis to set the correct relative configuration at C-8 and C-9a (**89** → **90**, Scheme 7). The stereochemistry at C-9 and C-10 was established after nickel boride reduction of the unsaturated butyrolactone ring and epimerization at C-10 to afford (±)-stemoamide (**9**) in 73% yield, together with its epimer at C-9 and C-10. Overall the total synthesis of (±)-stemoamide (**9**) was achieved in 7 steps from 4-chlorobutyryl chloride (**86**) and 20% overall yield.

5.3 Tuberostemospironine group

(+)-Croomine (**20**), a prototypical example of the tuberostemospironine group, was the first S*temona* alkaloid to yield to total synthesis. In 1989, Williams and coworkers[26] disclosed its total synthesis featuring an intermolecular Staudinger reaction followed by an iodoamination step to construct the

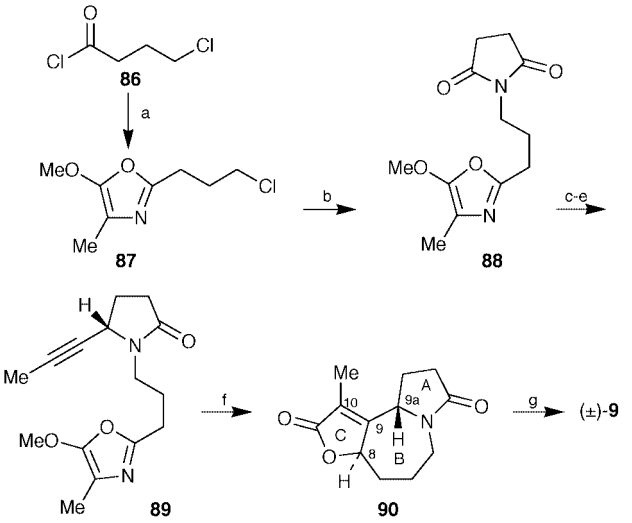


Scheme 5 *Reagents*: (a) TBSCl, Et_3N, NaI, CH_3CN, 50 °C (92%); (b) *tert*-butyl-2-(tributylstannyl)acetate, TBACN, EtCN, K_2CO_3, MS 4 Å, 0 °C (85%); (c) TBSCl, Et_3N, NaI, CH_3CN, 50 °C (60%); (d) 1-(*tert*-butoxycarbonyl)-2-(tributylstannyl)pyrrolidine, CAN, MS 4 Å, EtCN, −45 °C (65%); (e) H_2, 10% Pd/C, MeOH, rt (90%, **78a** : **78b** = 4:1); (f) $NaBH_4$, THF, MeOH, rt (59%); (g) 10% Pd/C, MeOH, HCO_2H, rt (89%); (h) MsCl, Et_3N, CH_2Cl_2, rt (96%); (i) RuO_2 (cat.), $NaIO_4$, AcOEt, H_2O, rt (60%); (j) 1 M HCl–AcOEt, rt (89%); (k) NaH, THF, rt (62%); (l) LDA, THF, −78 °C; then, MeI, −78 °C → rt (59%).



Scheme 6 *Reagents*: (a) NaH, DMF, 5-bromopent-1-ene (89%); (b) TsOH, MeOH (91%); (c) $(COCl)_2$, DMSO, Et_3N; (d) CBr_4, Ph_3P (87%, 2 steps); (e) n-BuLi, THF, −98 °C (72%); (f) LDA, HMPA, THF, $ClCO_2Me$, −98 °C (68%); (g) $Cl_2Ru[P(C_6H_{11})_3]_2CHPh$, CH_2Cl_2, rt (87%); (h) $NaBH_4$, MeOH (85%); (i) NaOH, MeOH, H_2O; (j) $CuBr_2$ on Al_2O_3 (**84**, 25% and **85**, 31%); (k) Et_3N, rt (50%); (l) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, MeOH (76%).

pyrrolo[1,2-*a*]azepine nucleus and the γ-butyrolactone ring attached at C-3 (Scheme 8). As in the total synthesis of (−)-stemoamide by the same group,[29] Williams and coworkers started with methyl (*S*)-2-methyl-3-hydroxypropionate which was converted to acetylene **91** after 4 steps and 72% overall yield. Sharpless asymmetric epoxidation of (*E*)-trisubstituted allylic alcohol **93** and a two-carbon homologation of the corresponding aldehyde provided epoxide **94** which set the stage for the regioselective epoxide opening with lithium azide (**94** → **95**, Scheme 8). Chain homologation (**95** → **96**) and γ-lactone formation (**96** → **97**) was followed by ring B formation



Scheme 7 *Reagents*: (a) $CH_3CH(NH_2)CO_2Me$, C_5H_5N; then, P_2O_5 (80%); (b) succinimide (97%); (c) $NaBH_4$; (d) MeOH, H^+ (72%, 2 steps); (e) $CH_3C{\equiv}CSnBu_3$, $BF_3{\cdot}OEt_2$ (92%); (f) diethylbenzene, reflux (50–55%); (g) $NaBH_4$, $NiCl_2$, MeOH, −30 °C (73%).

through an intramolecular Staudinger reaction (**97** → **98**). Rings A and D were formed in a single step by iodoamination of bicyclic intermediate **98**, an impressive transformation which also set the correct stereochemistry at C-3 and C-14, and yielded (+)-croomine (**20**) in 25% yield from **98** which was recovered in 50–60% yield. The first total synthesis of (+)-croomine (**20**) was carried out in 26 steps and about 0.5% overall yield from methyl (*S*)-2-methyl-3-hydroxypropionate.

A shorter and more efficient route to (+)-croomine (**20**) was devised by Martin and Barr[32] who employed the vinylogous Mannich addition of 2-silyloxyfuran **100** to a chiral *N*-acyliminium ion derived from (*S*)-pyroglutamic acid to connect rings A and C and to set the correct stereochemistries at C-9 and C-9a (**100** → **101**, Scheme 9). The stereochemistry at C-11 was set after hydrogenation of the double bond in ring C (**101** → **102**), probably directed by the basic nitrogen of the pyrrolidine ring and ring B was put in place through an intramolecular nitrogen alkylation (**102** → **103**). The thermally unstable acid chloride from intermediate **103** gave rise to the corresponding iminium ion which was trapped with 2-triisopropylsilyloxy-3-methylfuran. This second vinylogous Mannich transformation (**103** → **104**) afforded a 47% combined yield of the desired isomer **104** and its C-14 epimer (2 : 1 ratio). The desired adduct **104** was submitted to a stereoselective hydrogenation to afford (+)-croomine (**20**) in 9 steps and approximately 5% overall yield from 3-methylfuran-2(5*H*)-one.

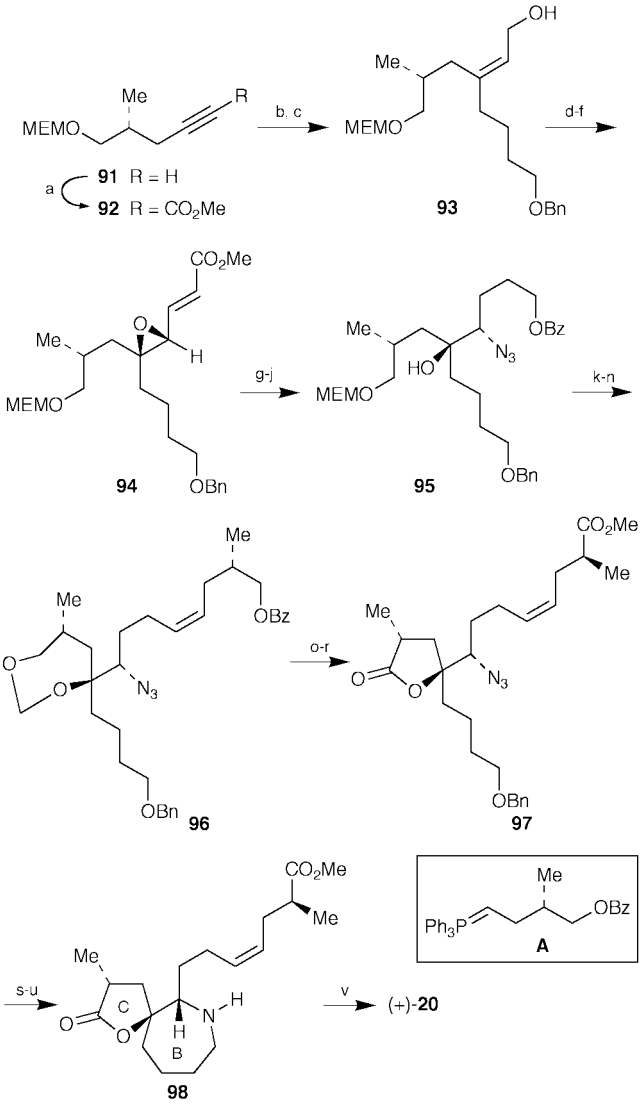
6 Conclusion

Since the publication of the last review on the chemistry of the *Stemona* alkaloids in 1975 the body of information about this family of alkaloids has grown steadily.

From a few representatives with defined structure (stenine (**1**), tuberostemonine (**2**), tuberostemonine A (**3**), oxotuberostemonine (**8**), stemonine (**10**), protostemonine (**13**) and stemofoline (**35**)) known at that time, 35 new representatives were isolated and had their structures elucidated.

Croomine (**20**), stemospironine (**21**), stemonamine (**26**), isostemonamine (**27**), tuberostemonone (**39**) and tuberostemoninol (**40**) had their structures established by X-ray analyses which also provided the absolute configuration for croomine (**20**) and stemospironine (**21**). Interestingly, stemonamine (**26**) and isostemonamine (**27**) were isolated in racemic form.

For the other alkaloids of this family isolated in the period covered in this review, structural evidence was provided mainly by NMR studies.



Scheme 8 *Reagents*: (a) nBuLi, THF, −78 °C → 0 °C; then, $ClCO_2Me$, −78 °C, (63%); (b) $BnO(CH_2)_4MgBr$, DMS, CuBr, TMEDA, Et_2O, −78 °C (95%); (c) DIBAL-H, CH_2Cl_2, −78 °C (98%); (d) $Ti(O^iPr)_4$ (cat.), D-DIPT (cat.), *tert*-BuOOH, MS 4 Å, CH_2Cl_2, −50 °C (83%); (e) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C → 0 °C; (f) $Ph_3P{=}CHCO_2Me$, 0 °C → rt (89%, 2 steps); (g) $LiBH_4$, Et_2O, MeOH, 0 °C (81%); (h) 5% Rh/Al_2O_3, H_2, THF (62%); (i) BzCl, Et_3N, CH_2Cl_2, 0 °C → rt (97%); (j) LiN_3, DMPU, 110 °C (94%); (k) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C (81%); (l) LiOH, THF, aq. MeOH (97%); (m) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C → 0 °C (91%); (n) **A**, THF, −10 °C (70–81%); (o) aq. HBF_4, MeOH (72%); (p) LiOH, THF, MeOH, H_2O, 22 °C (86%); (q) Jones' reagent, THF, 0 °C; (r) CH_2N_2, Et_2O (78%, 2 steps); (s) BCl_3, CH_2Cl_2, −78 °C → 0 °C; then, MeOH, −78 °C (77%); (t) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C → 0 °C (92%); (u) Ph_3P, THF, 22 °C; then, $NaBH_4$, MeOH (90%); (v) I_2, CH_2Cl_2, Et_2O, 22 °C (25%).

Noteworthy are the total syntheses of stenine (**1**), stemoamide (**9**) and croomine (**20**) carried out by several groups which definitively established the absolute configuration of these three alkaloids. Considering that the Stemonaceae family comprises more than 30 species and currently phytochemical investigation is restricted to only 8 of them, the isolation of other *Stemona* alkaloids can be expected in the future as well as continuing progress towards the total syntheses of other representatives.

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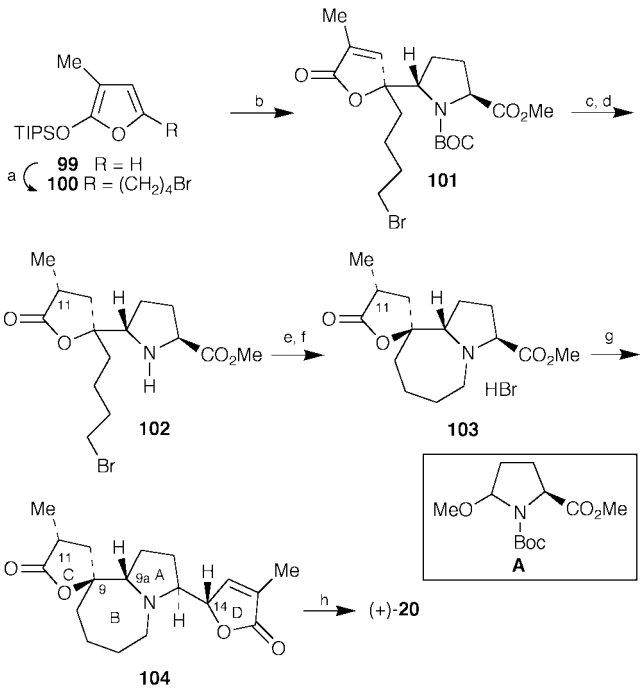

Scheme 9 *Reagents*: (a) s-BuLi, TMEDA, THF, 0 °C; then, $BrCH_2(CH_2)_2CH_2Br$ (83%); (b) **A**, 5% TIPSOTf, CH_2Cl_2, 0 °C (32%); (c) CF_3CO_2H, CH_2Cl_2, rt; (d) 3% Rh/C, H_2, EtOAc, EtOH (> 96%, 2 steps); (e) *N*-methylmorpholine, DMF, reflux; (f) 3 M aq. HBr, 60 °C (74%, 2 steps); (g) $POCl_3$, DMF, rt; then, **99** (*ca*. 32%); (h) 10% Pd/C, H_2, 10% HCl–EtOAc (85%).

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