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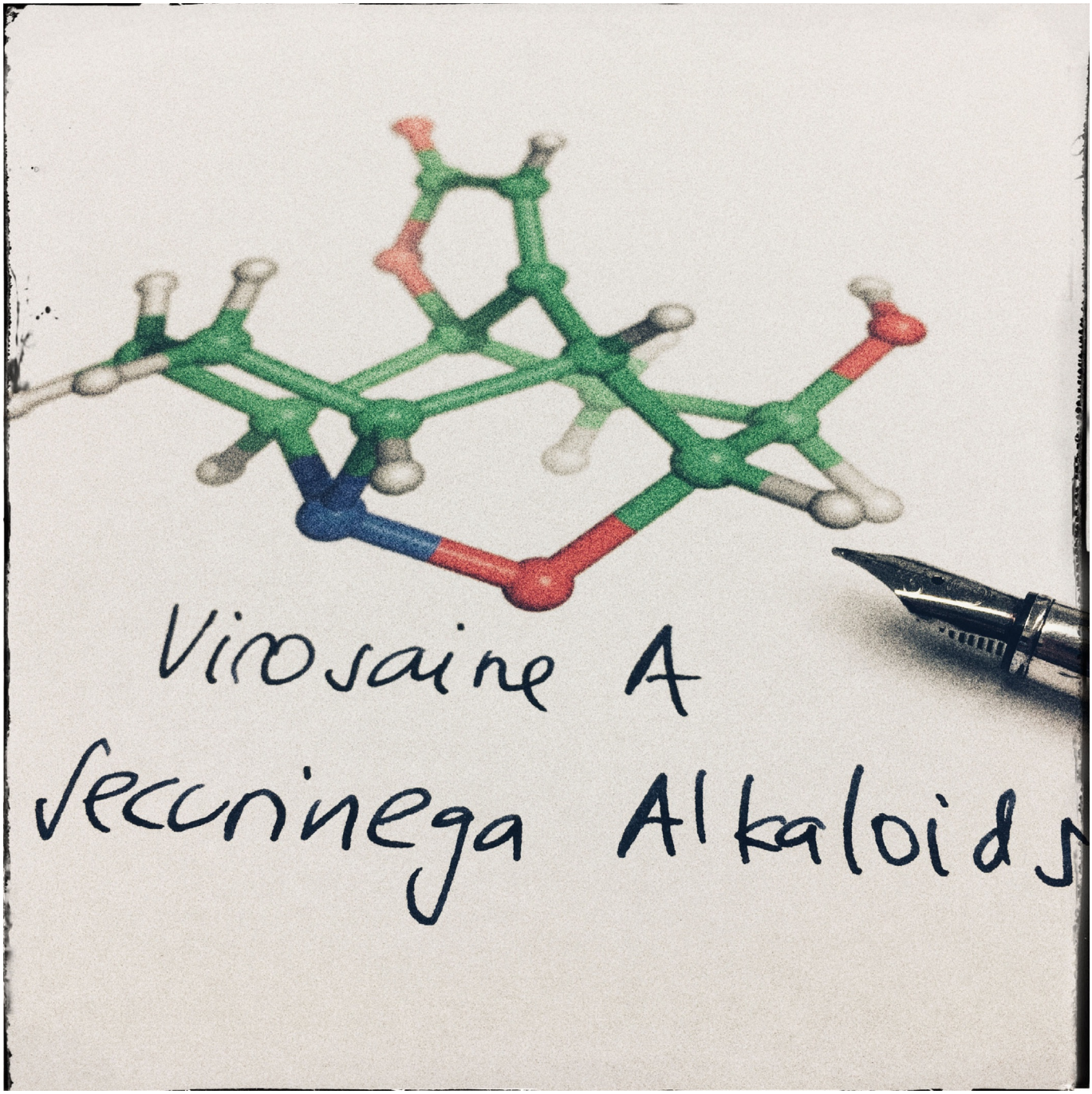
Natural Product Synthesis

SPECIAL ISSUE

Securinega Alkaloids: Complex Structures, Potent Bioactivities, and Efficient Total Syntheses

Robin Wehlauch and Karl Gademann*[a]



Abstract: The *Securinega* alkaloids feature a compact tetracyclic structural framework and can be divided into four subclasses characterized by either a bridged [2.2.2]- or a [3.2.1]-bicyclic core with two homologous series in each subclass. In the last two decades, many innovative strategies to chemically access the *Securinega* alkaloids have been developed. This Focus Review discusses the selected structures and syntheses of representative members of the *Securinega* alkaloids. Ring-closing metathesis has enabled the syntheses of securinine and norsecurinine, and different cycloaddition approaches were key to the syntheses of nirurine and virosaines A and B. Virosine A was accessed through a Vilsmeier–Haack/Mannich reaction cascade. A bio-inspired vinylogous Mannich reaction has enabled the synthesis of allosecurinine and this strategy has been extended by an intramolecular 1,6-addition to obtain bubbialidine and secu'amamine E. A rearrangement process of the latter two alkaloids has furnished allonorsecurinine and allosecurinine, respectively. Finally, an expanded model for the biogenesis of the *Securinega* alkaloid subclasses is discussed.

1. Introduction

Securinega alkaloids have fascinated chemists for decades. This obsession arises from the large structural variety in these alkaloids, their complex architecture, and their potent biological activity, which has even resulted in clinical use. These facts triggered the synthetic efforts of many research groups, culminating in fascinating, efficient and instructive total syntheses of many *Securinega* alkaloids. The goal of this Focus Review is to introduce the reader to the structural complexity of these compounds, and to illustrate recent synthetic approaches towards their preparation. Although this review is by no means comprehensive, it may serve as an introductory overview to the field, and we refer the interested reader to excellent surveys that have been published previously.[1]

The *Securinega* alkaloids comprise a group of more than 60 known natural products found in plants of the Phyllanthaceae family and more precisely in the *Flueggea*, *Margaritaria*, *Phyllanthus* and *Securinega* genera.[1] These plants are commonly found in the subtropical zones of the Americas, Africa and Asia, and are broadly applied as traditional medicines in these regions. For example, the species *Securinega suffruticosa* and *Flueggea virosa*—two rich and well-studied sources of *Securinega* alkaloids—have been applied in Chinese folk medicine to treat a variety of symptoms such as lumbago, indigestion, impotence, rheumatism, infantile paralysis, and eczema.[2] Preparations from *F. virosa* have served as treatments for complications of the liver, kidneys, gall bladder, bladder and genitals as well as bilharzia in Senegalese medicine. In India, this plant has been used against diabetes.[3] *Margaritaria discoidea* has been utilized in Guinean folk medicine to treat malaria, diabetes and diarrhea among others.[4] *Phyllanthus niruri* has been used for the treatment of malaria and other diseases in India and China,[5] and also in Central Africa.[6] In West Africa, it serves as a stomachic.[3,7] Several groups have reported on the isolation of *Securinega* alkaloids from samples of *P. niruri* collected in India[8] and Thailand.[9] However, these alkaloids were not found in samples of the same species collected in Brazil.[10] This result might be explained by the different environmental conditions in which the plants grow. Recently, it was shown that plant growth regulators influence the alkaloid content of *S. suffruticosa* callus cultures, and promotion as well as inhibition of alkaloid production was observed.[11] To date, no report has been published on the isolation of *Securinega* alkaloids from a plant sample collected in the Americas. Interestingly, *Securinega* alkaloids have been obtained from *Zygogynum pauciflorum*,[12] a species of the Winteraceae family found in New Caledonia. Since this family is not related to Phyllanthaceae, the study revealed a rare case of metabolic convergence. The Phyllanthaceae family of plants represents one of several Euphorbiaceae segregates and was classified in 2006.[13] Nevertheless, the *Securinega* alkaloids have often been assigned to the Euphorbiaceae in the recent literature.

In 1956, securinine (**1**) was isolated from *S. suffruticosa* by Murav'eva and Ban'kovskii as the first member of this alkaloid family (Figure 1).[14] Being the most abundant and best-studied *Securinega* alkaloid, it has been the major representative ever since. The tetracyclic structure of **1** was elucidated independently by two research groups in 1962,[15] and the correct absolute configuration was established by chemical degradation studies[16] and an X-ray crystal structure of securinine hydrobro-

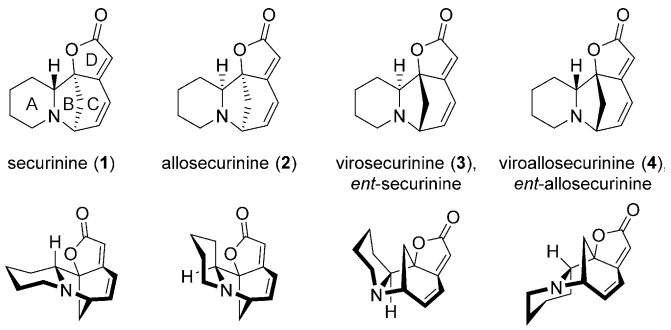


Figure 1. Two- and three-dimensional representations of securinine (**1**) and its stereoisomers.

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mide.[17] Total synthesis of the racemic natural product and chiral resolution by recrystallization with (+)-10-camphorsulfonic acid confirmed the structural and stereochemical assignments.[18] Another alkaloid isolated from *S. suffruticosa* showed similarities to **1**[15b] and was identified as the epimer allosecurinine (**2**), in which the A and B rings are fused in an opposite configuration.[19] Surprisingly, the investigation of the alkaloid content of *F. virosa* (synonymous with *S. virosa*) yielded another stereoisomer of **1**, which was found to be its enantiomer virosecurinine (**3**).[20] A systematic study of the two plant species and their metabolites then led to the discovery of the fourth possible stereoisomer viroallosecurinine (**4**), the enantiomer of **2**.[21] The study showed that whereas *S. suffruticosa* contained only **1** and **2**, *S. virosa* contained exclusively their optical antipodes **3** and **4**. However, leaves of the male plant of *S. suffruticosa* var. *amamiensis* contained both **1** and **3** along with **2**.[21] Besides the unusual distribution of stereoisomers, these observations also demonstrate the high diversity of alkaloid constituents in the different plants.

The *Securinega* alkaloids can be divided into four groups based on their core structures (Figure 2). The compounds

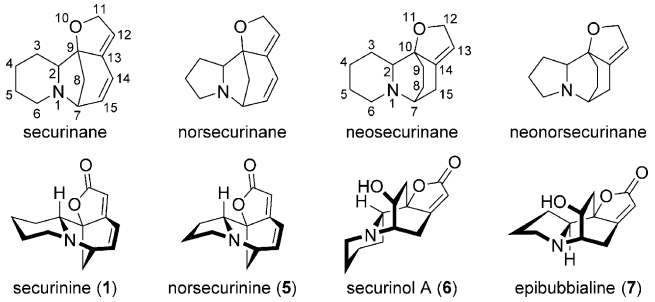

Figure 2. The *Securinega* alkaloid skeletons and representative natural products of each class.

shown in Figure 1 share a securinane-type core, which is characterized by an azabicyclo[3.2.1]octane B/C ring system with fused piperidine (A) and butenolide (D) rings. A homologous series of norsecurinane-type structure contains a pyrrolidine instead of the piperidine A ring; norsecurinine (**5**)[22] represents a member of this class. In contrast to **1**, only two natural stereoisomers of the lower homologue have been isolated, the other being *ent*-norsecurinine.[8b] The numbering for the securinane and norsecurinane skeletons is identical except for the C6 position being omitted for norsecurinane-type alkaloids. Both groups comprise 14,15-dihydro derivatives with most of them bearing 15-hydroxy or 15-methoxy substituents. Also, numerous 4-hydroxy or 4-methoxy derivatives as well as combinations of both (i.e. 4,15-disubstituted 14,15-dihydro compounds) are known. The neosecurinane and neonorsecurinane skeletons are characterized by an azabicyclo[2.2.2]octane core with a fused butenolide and either piperidine or pyrrolidine rings. The neosecurinane-type alkaloid securinol A (**6**) was isolated from *S. suffruticosa* in 1965 by Horii and co-workers.[23] These researchers found that upon treatment with methanesulfonyl chloride and pyridine the compound was dehydrated to **4**. Thus, securinol A (**6**) was assigned a 15-hydroxy-14,15-dihydrosecurinane-type structure. More than 25 years later, Arbain, Sargent and co-workers investigated the alkaloid content of *Margaritaria indica* and revised the structure of **6**.[24] Based on a comparison of NMR spectroscopic data of **6** and other *Securinega* alkaloids, and ultimately on X-ray crystallographic analysis of securinol A hydrobromide, the neosecurinane-type structure shown in Figure 2 was established.

Besides the four groups described so far, several alkaloids have been isolated possessing unprecedented structures, which do not fit the general motifs (Figure 3). Nirurine (**8**) was

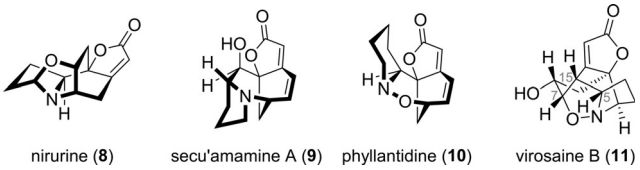

Figure 3. Examples of *Securinega* alkaloids with unusual carbon skeletons.

isolated from *Phyllanthus niruri* in 1986 by Cordell and coworkers, and its structure was elucidated by single-crystal X-ray crystallography.[9] The pentacyclic compound has an additional oxazolidine ring formed by a C5–O–C8 bridge. Secu'amamine A (**9**), which was isolated from *S. suffruticosa* var. *amamiensis* in 2003 by Ohsaki, Kobayashi and co-workers, contains an extended B ring and thus an azabicyclo[3.3.1]nonane core with an additional carbon atom between the C2 and C9 atoms.[25] Its structure was assigned using spectroscopic meth-

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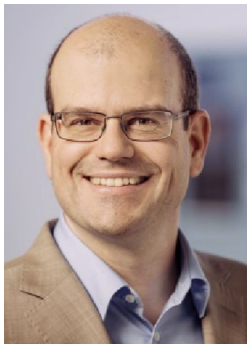
Karl Gademann (1972) currently serves as full professor and head of the Department of Chemistry at the University of Zurich, Switzerland. His previous professional affiliations include the University of Basel, EPFL Lausanne, ETH Zurich, and Harvard University, where he worked with Professors Seebach and Carreira (ETH) and Jacobsen (Harvard). His research interests include the biogenesis and chemical synthesis of natural products, and understanding of their function related to human endeavours.



ods, mainly NMR analysis, and was later confirmed by comparison with material obtained through total synthesis.[26] Also, isolation of the C3–OH epimer secu'amamine H from *F. suffruticosa* (synonymous with *S. suffruticosa*) was reported by Wang, Ye and co-workers in 2014.[27] An extended B ring was also observed for phyllantidine (**10**), which was isolated from *Phyllanthus discoides* in 1965 by Munavalli and Parello.[28] Structural elucidation by Munavalli, Horii and co-workers was based on spectroscopic methods as well as the characterization of chemical degradation products of **10**.[29] This alkaloid features an oxazabicyclo[3.3.1]nonane core with an additional oxygen atom between the N and C7 atoms. Interestingly, this compound can be obtained from **2** by oxidation with hydrogen peroxide. The structure of **10** was also confirmed by comparison with a fully synthetic sample.[30] Arguably the most complex structures among the monomeric *Securinega* alkaloids discovered so far were reported for the pseudoenantiomeric virosaines A and B (**11**), which were isolated from *F. virosa* by Zhang, Ye and co-workers in 2012.[31] The three-dimensional structures of the virosaines are best explained by starting from a neonorsecurinane-type skeleton. The virosaines contain an additional oxygen atom between the N and C7 atoms as well as a bond between the C5 and C15 atoms. Their structures were determined using a combination of NMR spectroscopic, circular dichroism (CD) and X-ray crystallographic analyses, and were both confirmed by comparison with material obtained by total synthesis.[32,33]

A large group within the *Securinega* alkaloids, of which many were only discovered recently, are oligomeric alkaloids. All known oligomers were isolated from *F. virosa* structurally spanning from dimeric to pentameric compounds.[1,34] The dimers discovered so far display a large structural variety with respect to the modes of connectivity of the individual subunits (Figure 4). Although most oligomers contain norsecurinane-type monomers (e.g. **12** and **13**), securinane- and neosecurinane-type subunits have been identified as well (e.g. **14** and **15**). The larger oligomers are structurally less diverse and primarily feature norsecurinane-type monomers connected via C–C bonds between the C12, C14 and C15 atoms (**16**–**19**, Figure 5).

Due to the great structural analogy between the different alkaloids and the plethora of stereoisomers present, the field of *Securinega* alkaloids can be confusing and several discrepancies and errors have found their way into the literature. For example, after the structural revision of securinol A (**6**) in 1991,[24] it became obvious that several other known alkaloids, such as securinol B and C[23,35] or 14,15-dihydroallosecurinine-15β-ol[36] needed or still need to be reinvestigated. Also, the controversial interpretation of analytical data during the structural elucidation of these alkaloids raises questions about the integrity of the results. For example, CD spectroscopy has frequently been used to determine the absolute configuration of previously unknown compounds. The spectra of newly isolated alkaloids were compared to those of known compounds to draw conclusions about the similarities and differences in absolute configuration. But whereas one study attributed the observation of an opposite Cotton effect to an inverted configuration at the A/B ring fusion at C2 of neonorsecurinane-type alkaloids,[37] another study concludes inverted configurations at C7 and C10 in the bridged B/C ring system of neosecurinane-type alkaloids from the same observation.[38] These issues might raise concerns regarding the nature of both constitution and configuration of some alkaloids, in particular for those on which no X-ray crystallographic studies addressing the relative and absolute configurations have been conducted. Moreover, these structural questions call for total synthesis for clarification and verification of structure. These synthetic efforts are discussed in the next section.

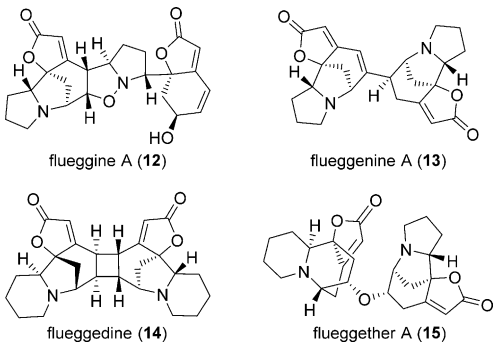


Figure 4. Examples of *Securinega* alkaloid dimers with different connectivity.

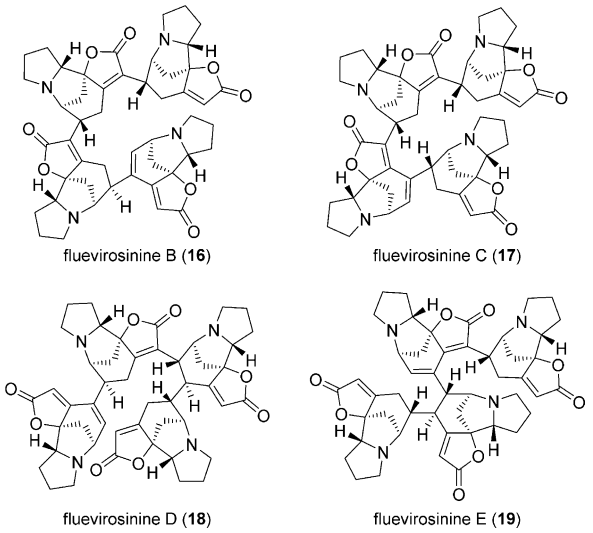


Figure 5. Examples of norsecurinine-based tetrameric *Securinega* alkaloids.

2. Total Synthesis of *Securinega* Alkaloids

Numerous synthetic studies on the *Securinega* alkaloids have been published and more than 20 publications have reported the total synthesis of one or several members of the compound family (Table 1).[39] Most approaches targeted the azabicyclo[3.2.1]octane-based alkaloids, such as securinine (**1**), norsecurinine (**5**), and their stereoisomers. However, other members featuring an azabicyclo[2.2.2]octane core, such as nirurine (**8**),[40] virosine A[41] and bubbialidine,[32] as well as compounds with unusual structures, such as virosaines A[32] and

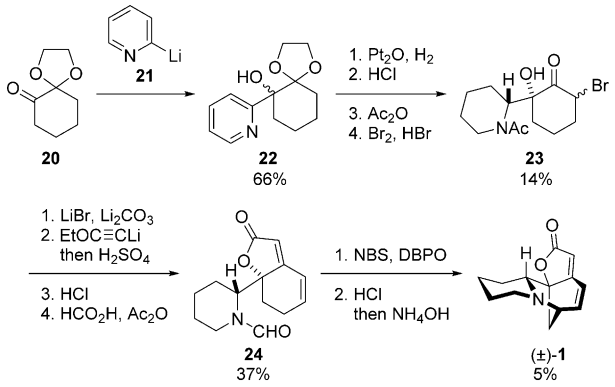
Table 1. Total syntheses of *Securinega* alkaloids published to date in chronological order.

Entry	Authors	Year	*Securinega* alkaloid(s)	Ref.
1	Horii et al.	1967	Securinine (*rac.*)	[18]
2	Heathcock et al.	1987	Norsecurinine (*rac.*)	[43]
3	Jacobi et al.	1991	Norsecurinine, *ent*-norsecurinine	[44]
4	Magnus et al.	1992	Norsecurinine (*rac.*), nirurine (*rac.*)	[40]
5	Weinreb et al.	2000	Norsecruinine, (+)-14,15-dihydronorsecurinine	[59]
6	Honda et al.	2000	Securinine (*rac.*, formal)	[55]
7	Liras et al.	2001	Securinine (*rac.*)	[45]
8	Honda et al.	2004	Viroallosecurinine	[54]
9	Alibes, de March et al.	2004	Securinine, (−)-allonorsecurinine[a]	[51]
10	Honda et al.	2004	Securinine	[53]
11	Figueredo et al.	2005	Norsecurinine	[48]
12	Kerr et al.	2006	(+)-Phyllanthidine	[30]
13	Weinreb et al.	2008	Secu'amamine A	[26]
14	Busqué, de March et al.	2008	Allosecurinine, viroallosecurinine	[57]
15	Kerr et al.	2008	Allosecurinine	[47]
16	Thadani et al.	2009	Securinine	[52]
17	Bayón, Figueredo et al.	2009	Securinine, norsecurinine	[49]
18	Wood et al.	2010	*ent*-Norsecurinine, (+)-allonorsecurinine[a]	[46]
19	Srihari et al.	2012	(−)-Allonorsecurinine[a]	[56]
20	Bélanger et al.	2012	Virosine A	[41]
21	Wood et al.	2012	Securinine (*rac.*), allosecurinine (*rac.*)	[50]
22	Yang, Li et al.	2013	Virosaine B, flueggine A, (+)-allonorsecurinine,[a] norseucrinine	[33]
23	Gademann et al.	2013	Bubbialidine, virosaine A	[32]
24	Yi, Jiang et al.	2014	Norsecurinine, (−)-niruroidine, flueggine A	[42]
25	Zheng et al.	2015	14,15-Dihydrosecurinine, securinine (formal)	[60]
26	Smith et al.	2015	Secu'amamine A	[61]
27	Gademann et al.	2017	Secu'amamine E, bubbialine, allosecurinine, (+)- and (−)-allonorsecurinine[a]	[67]

[a] Allonorsecurinine is a putative natural product that has not yet been isolated from a natural source.

B (**11**)[33] and flueggine A (**12**),[33,42] have also been synthesized. Although a number of innovative strategies have been developed for the construction of the tetracyclic *Securinega* alkaloid core, different motifs have reoccurred over time and certain transformations have proven exceptionally useful.

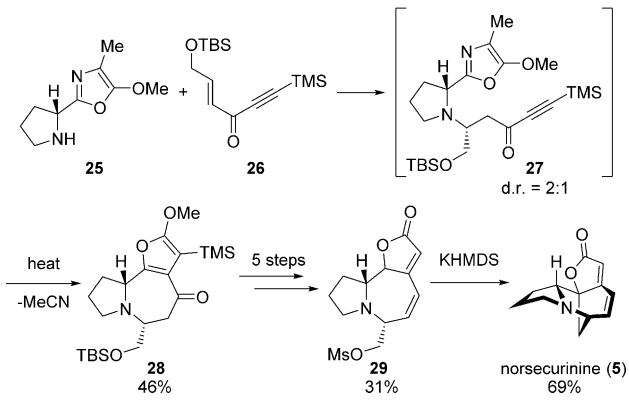
The first total synthesis focused on **1** and was reported by Horii and co-workers in 1967[18] after their structural determination of the compound.[15a,16,17] The synthesis started with ketal **20**, which was reacted with 2-pyridinyllithium (**21**); the two fragments represent the C and A rings of the final natural product, respectively (Scheme 1). The pyridine **22** was reduced by hydrogenation affording diastereoisomers, and the ketal group was cleaved using hydrochloric acid. The amine was protected with acetic anhydride and both diastereoisomers were separated at this stage. By comparison with a degradation



Scheme 1. The first total synthesis of racemic securinine (**1**) reported by Horii et al. in 1967.[1] DBPO: dibenzoyl peroxide.

product of **1**, the major isomer was identified to possess the correct relative configuration, and bromination afforded intermediate **23** in 14% yield. The olefinic double bond in the C ring was introduced by elimination of HBr and the D ring was installed by addition of lithium ethoxyacetylide followed by acidic hydrolysis. The acetyl protecting group on the amine had to be exchanged for a more labile formyl group at this point, affording the tricyclic intermediate **24**. Final formation of the B ring was achieved by applying an allylic bromination–deprotection–nucleophilic substitution sequence to produce racemic (±)-**1**, albeit in low yield. Resolution of the enantiomers afforded pure securinine (**1**) and virosecurinine (**3**).

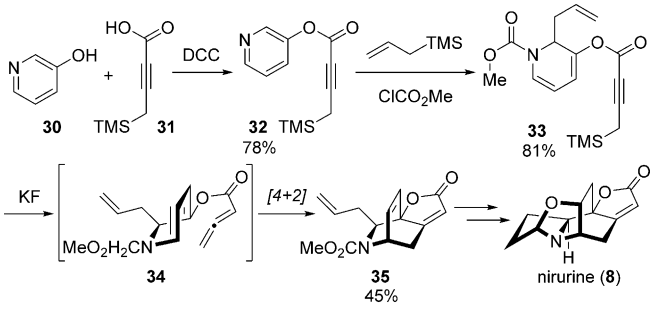
After this seminal work, it took 20 years before the second total synthesis of a *Securinega* alkaloid was published by Heathcock and co-workers in 1987.[43] Starting from proline, representing the A-ring fragment, the B, C and D rings were constructed in that order in 12 linear steps to afford racemic norsecurinine [(±)-**5**] in 2% overall yield. The first enantioselective synthesis of **5** was reported by Jacobi and co-workers in 1991,[44] who also utilized proline as a starting material (Scheme 2). Starting from either L- or D-proline afforded the enantiomerically pure (+)- or (−)-norsecurinine, respectively. In this approach, proline served as the A-ring fragment and was converted to oxazole **25**, which underwent spontaneous Michael addition with enone **26** to generate labile intermedi-



Scheme 2. The first enantiospecific total synthesis of norsecurinine (**5**) reported by Jacobi et al. in 1991.[44]

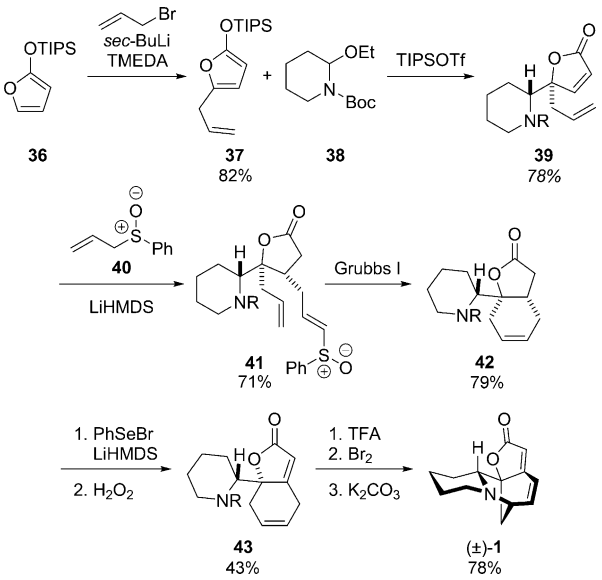
ate **27**. Upon attempted chromatography of intermediate **27**, retro-Michael addition was observed. Tricycle **28** was obtained in 46% yield by heating of the crude substance, which led to a Diels–Alder reaction between the oxazole and acetylene moieties under release of acetonitrile. The minor diastereoisomer could be separated and recycled by retro-Michael addition. Reduction of the keto group followed by dehydration formed the C-ring double bond. The D ring was set up by desilylation and subsequent demethylation. Mesylation of the primary hydroxyl group gave intermediate **29**. Finally, formation of the B ring was achieved by treatment with potassium bis(trimethylsilyl)amide (KHMDS), leading to an intramolecular substitution reaction that afforded the natural product **5** in 69% yield.

One year later, Magnus and co-workers reported the total synthesis of nirurine (**8**), the first synthetic study on a *Securinega* alkaloid containing an azabicyclo[2.2.2]octane core (Scheme 3).[40] This synthesis also relies on a key Diels–Alder reaction to form the tetracyclic core skeleton. 3-Hydroxypyridine (**30**) was coupled with acid **31** to afford ester **32**, which was transformed into diene **33** in one step. Desilylation using potassium fluoride in aqueous acetic acid presumably led to formation of allene **34**. An intramolecular [4+2] cycloaddition produced intermediate **35** in 45% yield, which was further transformed into **8**.



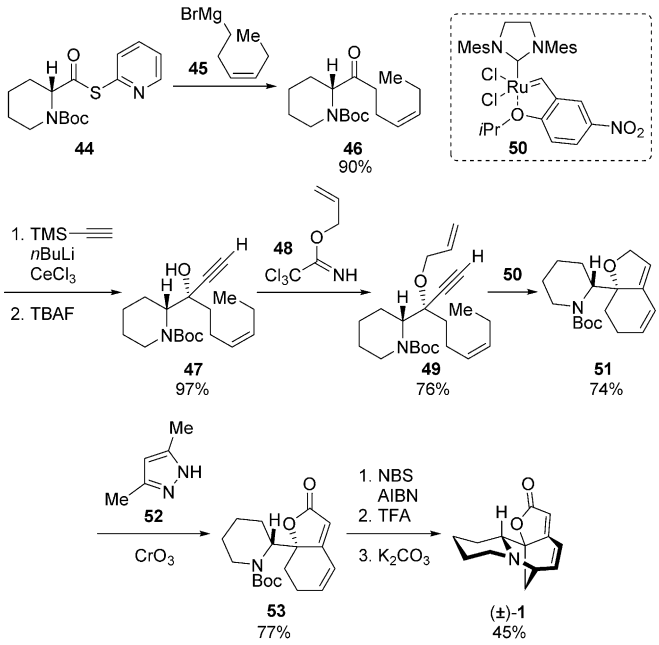
Scheme 3. Key cycloaddition step in the total synthesis of nirurine (**8**) reported by Magnus et al. in 1992.[40]

In the first four decades since their discovery, only four studies on the total synthesis of *Securinega* alkaloids have been published. Since 2000, however, interest in the synthesis of these challenging natural products has increased tremendously and a variety of synthetic strategies have been developed. The total synthesis of (±)-**1** reported by Liras and co-workers in 2001 (Scheme 4)[45] was pioneering in the sense that it established several methodologies that have been frequently utilized in the syntheses published since. Starting from silyloxyfuran **36**, serving as the D-ring precursor, addition to allyl bromide gave allylfuran **37** in good yield. Vinylogous Mannich reaction with an iminium species generated in situ from protected piperidine derivative **38** introduced the A ring into intermediate **39**. Addition of allyl phenyl sulfoxide (**40**) afforded the intermediate **41**, which was cyclized in a ring-closing metathesis (RCM) reaction using Grubbs' first-generation catalyst, providing tricyclic intermediate **42**. The double bond in the D ring was introduced by addition to phenylselenyl bromide and subsequent oxidation–elimination to afford **43**. Final formation of the B ring was achieved by acidic cleavage of the *tert*-butoxycarbonyl (Boc) group followed by sequence of dibromination–nucleophilic substitution–elimination to afford racemic (±)-**1**. This strategy is reminiscent of the allylic bromination–nucleophilic substitution sequence in the synthesis by Horii and co-workers (cf. Scheme 1), but is distinct as it also leads to a net double-bond isomerization. A similar approach has been used by Wood and co-workers in their 2010 total synthesis of (+)-allonorsecurinine.[46]



Scheme 4. The total synthesis of racemic (±)-**1** reported by Liras et al. in 2001.[45]

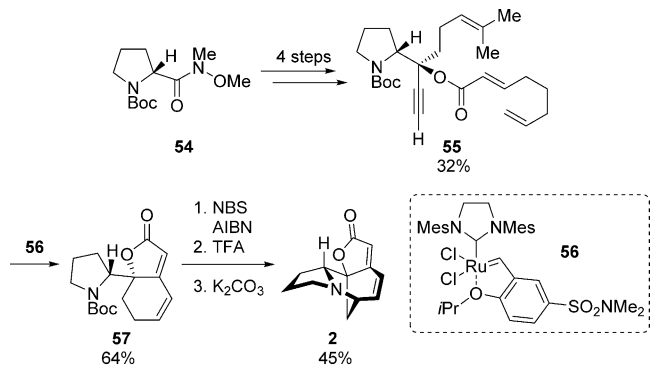
The synthesis by Liras and co-workers exemplified the utility of RCM in the construction of the tetracyclic *Securinega* alkaloid frameworks and several other groups have used this transformation in their syntheses. Whereas several approaches have adopted RCM for the formation of the C ring, as described above,[30,40,47–50] there are also examples of D-ring formations accomplished by this technique.[51,52] An impressive one-step C/D ring formation approach by tandem RCM in the first stereoselective total synthesis of **1** has been reported by Honda and co-workers in 2004 (Scheme 5).[53] Starting from known (*R*)-pipecolic-acid-derived thioester **44**, unsaturated side chains were introduced sequentially by addition of (*Z*)-3-hexenylmagnesium bromide (**45**) to the thioester followed by addition of ethynyltrimethylsilane to the ketone and desilylation to give enyne **47** in excellent yield. Alkylation of the hydroxyl function using allyl trichloroacetimidate (**48**) to afford dienyne **49** set the stage for the key tandem RCM reaction using the ruthenium catalyst **50** to construct the C/D ring system (intermediate **51**) in one step and in high yield. Attempts to use an acrylate ester instead of allyl ether **49** in this transformation were unsuccessful, and thus allylic oxidation with chromium trioxide and 3,5-dimethylpyrazole (**52**) was applied to form the butenolide **53**. Final B-ring formation was accomplished using the bromination–deprotection–substitution sequence originally developed by Horii and co-workers. A similar strategy has been ap-



Scheme 5. Diastereoselective total synthesis of securinine (**1**) reported by Honda et al. in 2004.[53]

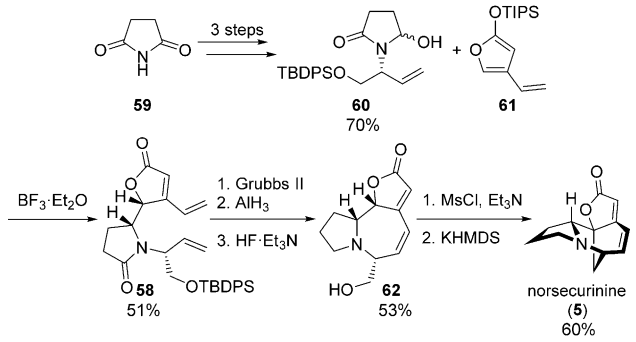
plied in the total synthesis of viroallosecurinine (**4**), which was reported in a follow-up publication by Honda and co-workers in 2004.[54]

This tandem RCM strategy was later picked up by Yang, Li and co-workers in their total syntheses of virosaine B (**11**) and flueggine A (**12**) published in 2013,[33] which proceeded via norsecurinine (**5**) and (+)-allonorsecurinine as intermediates. In that report, commercially available Weinreb amide **54** was converted into intermediate **55** in an alkylation sequence similar to the one described above (Scheme 6). The use of relay RCM with catalyst **56** facilitated tandem enyne metathesis on the α,β-unsaturated ester **55**, allowing for the direct formation of the butenolide moiety, obviating an additional oxidation step. Again, B-ring formation of tricyclic intermediate **57** was accomplished using the sequence of Horii and co-workers to afford norsecurinine (**5**) in this case. Interestingly, this sequence became increasingly popular and many groups have reported on its use in recent years.[42,51,55,56]



Scheme 6. Tandem ring-closing metathesis in the synthesis of norsecurinine (**5**) reported by Yang and Li et al. in 2013.[33]

Application of the vinylogous Mannich reaction to connect the A- and D-ring fragments, which was pioneered by Liras and co-workers (Scheme 4), was also implemented by other research groups. In the total synthesis of norsecurinine (**5**) reported by Figueredo and co-workers in 2005 (Scheme 7),[48] this transformation was used to prepare RCM precursor **58**. Succinimide **59** was converted into hydroxylactam **60** in three

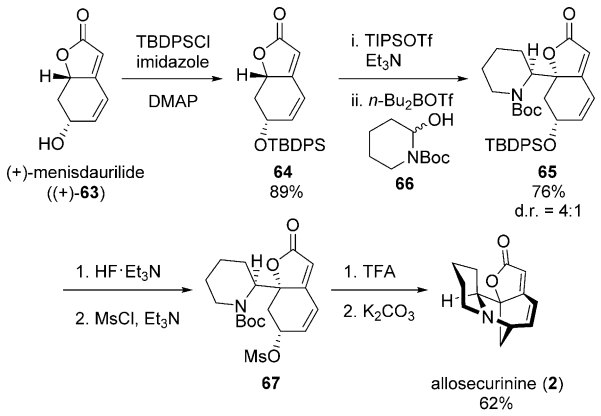


Scheme 7. Total synthesis of norsecurinine (**5**) reported by Figueredo et al. in 2005.[48]

steps. Exposure of **60** to boron trifluoride etherate led to formation of the corresponding *N*-acyliminium ion, which was captured with silyloxyfuran **61** to form product **58**. Cyclization by RCM, followed by reduction of the lactam and desilylation gave known intermediate **62**. Use of the mesylation–nucleophilic substitution sequence developed by Jacobi and co-workers (cf. Scheme 2) yielded norsecurinine (**5**). This approach has also been applied in the total synthesis of securinine (**1**) reported by the same group in 2009.[49]

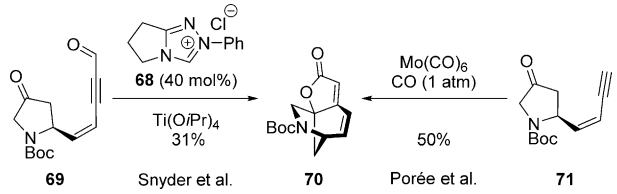
The same group reported another strategy involving a key vinylogous Mannich reaction in 2008.[57] Their synthesis commenced from the natural product (+)-menisdaurilide [(+)-**63**], the synthesis of which they had reported previously,[58] and a possible biogenetic relevance of the key transformation was suggested. After protection of (+)-**63**, a one-pot procedure involving formation of a silyloxyfuran from butenolide **64** followed by vinylogous Mannich reaction with an *N*-acyliminium ion afforded intermediate **65** (Scheme 8). The *N*-acyliminium ion was generated in situ from lactamol **66** by Lewis acid activation using dibutylboron triflate. Only two chromatographically separable diastereoisomers were formed in this transformation in a ratio of 4:1 with the major isomer **67** possessing the desired absolute configuration. The synthesis was completed by desilylation followed by mesylation to create a leaving group. Acidic cleavage of the Boc group and subsequent intramolecular substitution furnished allosecurinine (**2**). The same synthetic route was applied using (−)-menisdaurilide [(−)-**63**] to provide viroallosecurinine (**4**).

As well as the frequently reoccurring synthetic motifs described so far, other interesting methods have enriched the diversity of *Securinega* alkaloid total synthesis. For example, the studies on butenolide D-ring formation by Horner–Wadsworth–Emmons reaction or a related one-pot procedure applying the Bestmann ylide during the total syntheses of norsecuri-



Scheme 8. Total synthesis of allosecurinine (**2**) starting from the natural product (+)-menisdaurilide [(+)-**63**] reported by Busqué and de March et al. in 2008.[57]

nine (**5**), (+)-14,15-dihydronorsecurinine and phyllanthine by Weinreb and co-workers,[59] have been adopted for the recent total synthesis of 14,15-dihydrosecurinine by Zheng and co-workers.[60] Also, the sequence of intramolecular aza-Michael addition–aldol addition–lactonization developed by Weinreb and co-workers for the construction of secu'amamine A from a linear precursor should be mentioned at this point.[26] Smith and co-workers synthesized this alkaloid using anion relay chemistry.[61] Another unique approach toward the bridged B/C/D ring system of **1** was recently reported by Snyder and co-workers (Scheme 9).[62] By an intramolecular *N*-heterocyclic-carbene-catalyzed [3+2] cycloaddition using catalyst precursor **68** in the presence of titanium isopropoxide, the ynal and keto functions of compound **69** were cyclized in a single step to yield the protected *Securinega* alkaloid core **70** in 31%. Inspired by this work, Porée and co-workers developed a [2+2+1] cycloaddition approach featuring a hetero-Pauson–Khand reaction.[63] Thus, the precursor **71** carries a terminal alkyne and the missing C_1 unit is introduced by metal-bound carbon monoxide. Although the product **70** was obtained in only 50% yield, this transformation seems highly valuable for the development of further strategies toward synthesis of the *Securinega* alkaloid family.

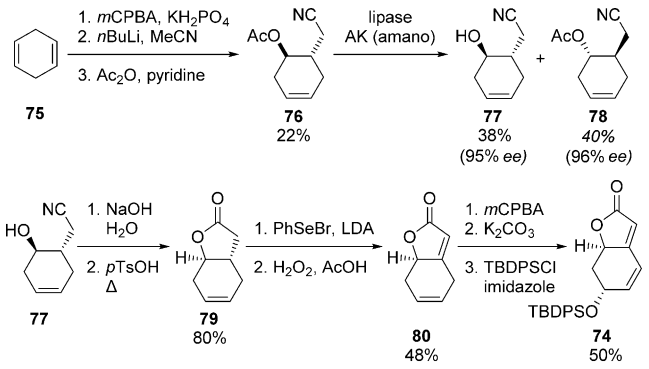


Scheme 9. Recent approach to the tricyclic core of *Securinega* alkaloids using *N*-heterocyclic carbene catalysis by Snyder et al.[62] and an extension of the methodology using a hetero-Pauson–Khand reaction by Porée et al.[63]

3. The Total Syntheses of Bubbialidine and Virosaine A

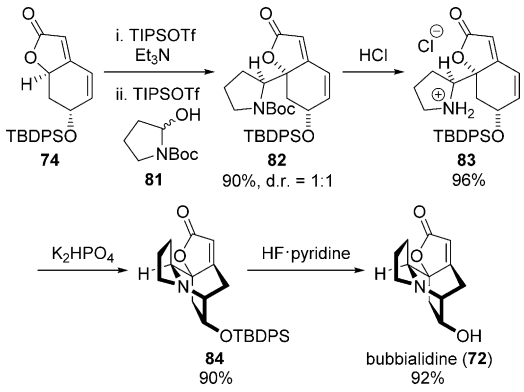
In 2013, our research group published the first enantioselective total syntheses of the neosecurinane-type alkaloid bubbialidine (**72**) and the unusual birdcage-shaped virosaine A (**73**),[32] which were both accessed by the synthetic route outlined as follows. A key intermediate of the synthesis is the butenolide **74**, which represents the C and D rings in the final natural product and is the *tert*-butyldiphenylsilyl (TBDPS)-protected form of the natural product (+)-aquilegiolide. The route to compound **74** was based on related synthetic studies reported in the literature.[57,64] Initially the synthesis was designed to yield **73**, which had been isolated from *F. virosa* in 2012 by Wang, Zhang, Ye and co-workers.[31] Alkaloid **72** was obtained by deprotection of an intermediate en route.

The synthesis commenced with mono-epoxidation of commercially available 1,4-cyclohexadiene (**75**) with *meta*-chloroperbenzoic acid (*m*CPBA), followed by epoxide opening using cyanomethyllithium (Scheme 10). The resulting secondary alcohol was acetylated with acetic anhydride giving the racemic acetate **76** in 22% yield. Kinetic resolution by an enzyme was applied in the synthesis and alcohol **77** was obtained in 95% enantiomeric excess. Basic hydrolysis of the nitrile function and subsequent acid-catalyzed lactone formation gave compound **79** in 80% yield.[64a] The D-ring double bond was introduced by an α-selenation–oxidative elimination sequence to afford the butenolide **80** in a moderate yield of 48%. Diastereoselective introduction of the hydroxyl group and concomitant isomerization of the C–C double bond into conjugation with the butenolide moiety was achieved through epoxidation using *m*CPBA followed by regioselective epoxide opening using potassium carbonate. Protection with TBDPSCl afforded the intermediate **74** in 50% yield.



Scheme 10. Synthesis of the key bicyclic intermediate **74**.

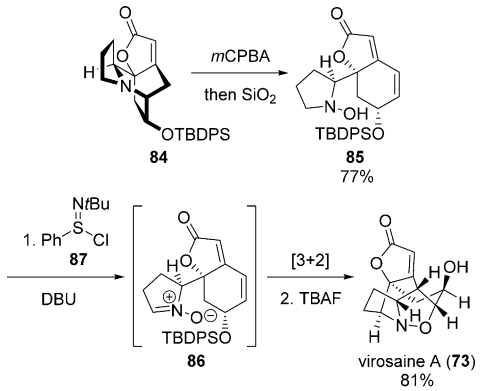
The A-ring pyrrolidine fragment was introduced by a vinylogous Mannich reaction, applying the one-pot procedure developed by Busqué, de March and co-workers (Scheme 11).[57] The reaction afforded an excellent yield of 90% and only two out of four possible diastereoisomers were formed and could be separated chromatographically giving compound **82**. Although the original publication reported a diastereoisomeric ratio of



Scheme 11. Construction of the bridged tetracyclic framework and synthesis of bubbialidine (**72**).

4:1 in favor of the desired isomer using a homologous six-membered lactamol, the present transformation proceeded without diastereoselectivity. The Boc group was removed by acidic treatment affording the corresponding hydrochloride salt **83**. Under extremely mild conditions using dipotassium hydrogen phosphate as a base, intramolecular vinylogous aza-Michael addition occurred, producing the bridged tetracycle **84** in a good yield of 86% over the two steps. Desilylation of this intermediate using Olah's reagent led to the natural product bubbialidine (**72**) in 92% yield.

For the second natural product, intermediate **84** was oxidized to the corresponding *N*-oxide using *m*CPBA (Scheme 12). Cope elimination was observed upon exposure to silica, opening the B ring to give hydroxylamine **85**. Oxidation to the nitrene **86** with *N*-*tert*-butylbenzenesulfinimidoyl chloride (**87**) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) proceeded regioselectively and a spontaneous intramolecular 1,3-dipolar cycloaddition furnished the unusual alkaloid framework. Final desilylation using tetrabutylammonium fluoride (TBAF) produced the natural product virosaine A (**73**) in 81% yield. In an independent effort, Yang, Li and co-workers have prepared the pseudoenantiomeric virosaine B (**11**) from (+)-allonorsecurinine using a similar sequence of oxidation–1,3-dipolar cycloaddition.[33] (+)-Allonorsecurinine, by contrast, was accessed by the tandem RCM strategy outlined in Scheme 6.



Scheme 12. Final steps in the total synthesis of virosaine A (**73**).

4. Secu′amamine E and its Enantiomer Virosine A

In continuation of the synthetic program on *Securinega* alkaloids within our research group, we turned our focus to the neosecurinane-type alkaloid secu′amamine E (**88**, Figure 6), which

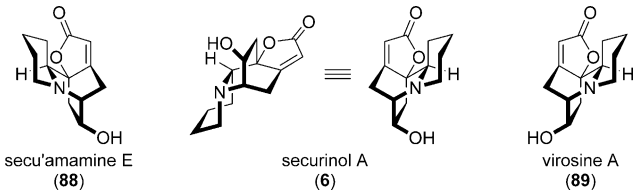
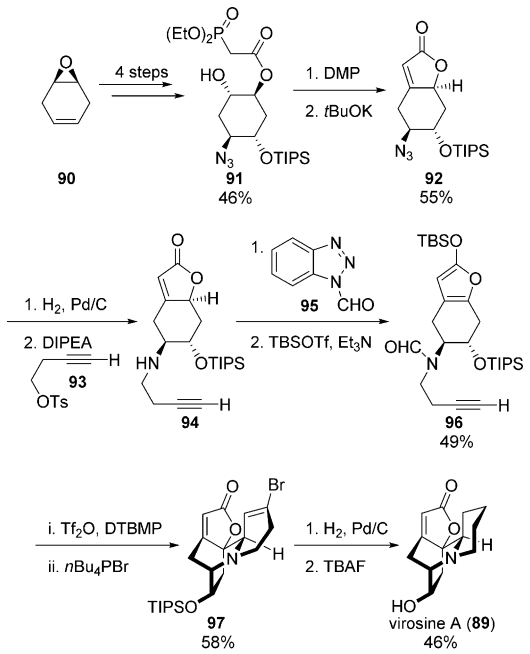


Figure 6. Structures of different neosecurinane-type alkaloids.

was isolated alongside secu′amamines F and G from *Securinega suffruticosa* var. *amamiensis* by Ohsaki and co-workers in 2009.[65] Their structures were elucidated by spectroscopic means (mainly NMR spectroscopy) and the absolute configuration of their B/C ring systems was determined to be opposite to securinol A (**6**) by a comparison of the respective CD spectra showing an opposite Cotton effect. Thus, **88** constitutes the higher homologue of bubbialidine (**72**) and represented an attractive target for total synthesis, as it should be obtainable using a similar synthetic strategy. No detailed investigation concerning the bioactivity of secu′amamine E (**88**) has been reported. The paper describing its isolation states in a short comment at the end of the publication that no cytotoxicity on P388 leukemia cells was observed.[65]

Another neosecurinane-type alkaloid isolated from *F. virosa* by Ye and co-workers in 2008 is virosine A (**89**), the optical antipode of **88**.[38] Its structure and absolute configuration were determined using the techniques described above and no investigations concerning the bioactivity of this alkaloid have been reported. The structure of **89** was confirmed by total synthesis of the natural product by Bélanger and co-workers in 2012.[41] Due to the enantiomeric relationship between **89** and **88**, which has not been noted in the literature, the key features of the synthesis by Bélanger and co-workers are presented here.

The synthesis started from *meso*-epoxide **90**, which was elaborated into intermediate **91** in 46% overall yield by chromium-catalyzed desymmetrization using azidotrimethylsilane, then hydroxyl-directed epoxidation followed by silyl protection and subsequent epoxide opening with diethylphosphonoacetic acid (Scheme 13). The hydroxyl function was oxidized using Dess–Martin periodinane (DMP) and treatment with potassium *tert*-butoxide triggered an intramolecular Horner–Wadsworth–Emmons reaction to afford butenolide **92**, which represented the C/D ring system of the final natural product. The azide group was then reduced and the resulting amine was alkylated and formylated sequentially using 3-butynyl tosylate (**93**) and *N*-formylbenzotriazole (**95**), respectively. Silylation of the butenolide moiety afforded silyloxyfuran **96** in 49% yield from azide **92**. The key transformation of the synthesis was a Vilsmei-

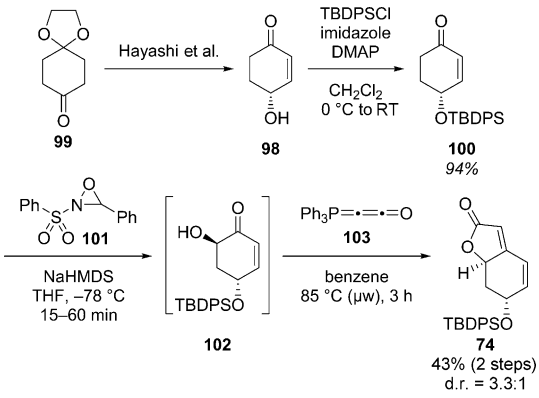


Scheme 13. Enantioselective total synthesis of virosine A (**89**) reported by Bélanger et al. in 2012.[41]

er–Haack/Mannich cyclization cascade leading to the bridged tetracyclic core structure, a method that had been reported by the same group in 2008.[66] Activation of the formyl group using triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) led to a Vilsmeier–Haack reaction with the silyloxyfuran moiety. The resulting iminium species then reacted with the terminal alkyne function in a Mannich reaction upon addition of tetrabutylphosphonium bromide giving tetracycle **97** in 58% yield. Cleavage of the bromide, reduction of the A ring by hydrogenation, and final desilylation of the hydroxyl group provided virosine A (**89**) in 46% yield. In summary, the natural product **89** was obtained by a sequence of 13 linear steps in 3.4% overall yield from *meso*-epoxide **90**.

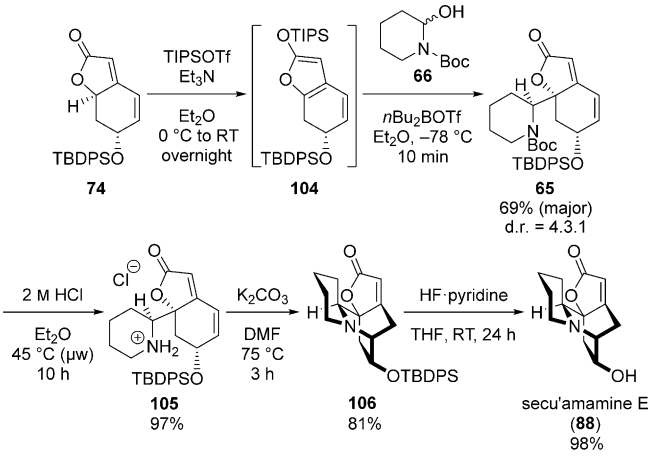
5. The First Total Synthesis of Secu′amamine E

Our synthesis of secu′amamine E (**88**)[67] started with the preparation of the chiral hydroxyenone **98**, and an efficient route to this compound starting from mono-ketal **99** was developed by Hayashi and co-workers for the total synthesis of (+)-panepophenanthrin.[68] Alcohol **98** was then protected as the silyl ether **100**, (Scheme 14) and a mixture of **100** and oxaziridine **101** was treated with NaHMDS to obtain the desired α-hydroxy ketone **102** as a single diastereoisomer. If crude compound **102** was heated in presence of the Bestmann ylide (**103**),[69] a 43% yield of the key intermediate **74** was obtained in a diastereoisomeric ratio of 3.3:1. This attractive strategy had been applied by Weinreb and co-workers for the late-stage D-ring formation in their synthesis of (+)-14,15-dihydronorsecurinine.[59] Compared to our original synthesis of butenolide **74** (cf. Scheme 10), the overall yield could be improved by a factor of 10.



Scheme 14. Synthesis of key intermediate **74**.

Due to the structural similarity between secu′amamine E (**88**) and bubbialidine (**72**), we planned to adopt the remaining steps from our total synthesis of the latter alkaloid. By using the methodology described by Busqué, de March and co-workers,[57] butenolide **74** was converted into silyloxyfuran **104** (Scheme 15). Because the stereogenic center of the butenolide



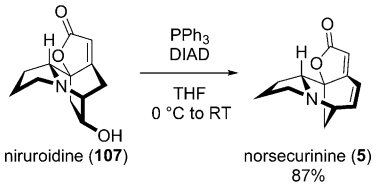
Scheme 15. Synthesis of secu′amamine E (**88**).

moiety is lost during this step, the starting material could be utilized as a diastereoisomeric mixture. Addition of dibutylboron triflate to a mixture of silyloxyfuran **104** and lactamol **66** triggered the formation of an *N*-acyliminium ion, followed by Mannich addition affording a mixture of two diastereoisomers in a ratio of 4.3:1, and the major isomer **65** was isolated in 69% yield. The Boc group was removed using an ethereal hydrogen chloride solution and hydrochloride **105** was then subjected to an intramolecular vinylogous aza-Michael addition to close the bridging B ring and form the azabicyclo[2.2.2]octane core **106** of the natural product in 81% yield. Final desilylation produced **88** in an excellent yield of 98%. Thus, the total synthesis of **88** was achieved in 12 synthetic steps from commercially available ketal **99** in an overall yield of 8.5%. We investigated the ecotoxicity of **88** in an assay against *Thamnocephalus platyurus* (beaver-tail fairy shrimp).[67] No toxic effects were

observed with concentrations up to 100 μM, confirming the findings by Ohsaki and co-workers.[65]

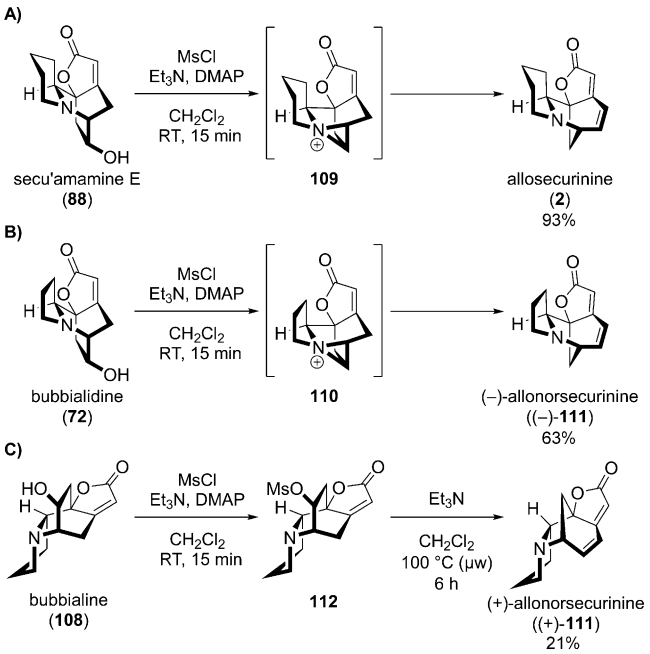
6. Rearrangements of Neo(nor)securinane- to (Nor)securinane-type Alkaloids

The transformation of an azabicyclo[2.2.2]octane core into an azabicyclo[3.2.1]octane core observed by Magnus and co-workers during the total synthesis of nirurine (**8**) might be of great significance for the biosynthesis of the *Securinega* alkaloids.[40] Although Horii and co-workers also reported similar transformations for securinol A (**6**),[23] B and C,[35] the correct structures involved had not been established at the time. Follow-up work corrected the misassignment and validated the underlying transformations.[24] As a consequence, these observations have not been considered during the development of the general biosynthetic pathway formulated in the 1970s.[70] The observations by Magnus and co-workers did not receive much attention in the literature. The only similar transformation reported to date is the rearrangement of niruroidine (**107**) to norsecurinine (**5**, Scheme 16).[42] However, a closer look at the reported substrates reveals that **107** represents the (−)-enantiomer of the racemic synthetic intermediate reported by Magnus and co-workers.[40]



Scheme 16. Rearrangement reported by Ye and Jiang et al. in 2014.[42]

With synthetic access to secu'amamine E (**88**), we decided to investigate the generality of the dehydrative rearrangement of neo(nor)securinane-type to (nor)securinane-type alkaloids (Scheme 17). Synthetic bubbialidine (**72**) was obtained through the previously published route[32] and bubbialine (**108**) was prepared from the second diastereoisomer of intermediate **82**. Thus, three different alkaloids were tested. If **88** was treated with methanesulfonyl chloride in the presence of 4-dimethylaminopyridine (DMAP) and triethylamine, rapid conversion of the substrate was observed and allosecurinine (**2**) was obtained in a yield of 93% (Scheme 17 A). Although reactions were typically run for 10–15 min, complete consumption of the alkaloid **88** within the first minute was observed by thin-layer chromatography (TLC). Similar results were obtained with the homologous **72** (Scheme 17 B). A fast spot-to-spot transformation proceeded and (−)-allonorsecurinine [(−)-**111**] was isolated, albeit in a lower yield of 63%. If **108** was treated under the same conditions, again, fast spot-to-spot transformation was observed (Scheme 17 C). However, bubbialine mesylate (**112**) was isolated in almost quantitative yield. Only under forcing conditions (100 °C, microwave irradiation, 6 h) was rearrangement of this intermediate observed to afford (+)-**111** in a low yield of 21% and only in moderate purity.

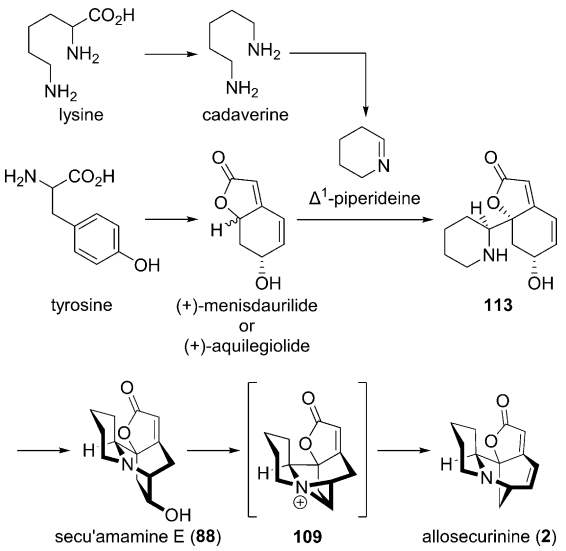


Scheme 17. Dehydrative rearrangement of *Securinega* alkaloids.

The results of these experiments are consistent with the proposed mechanism of the rearrangement process. The configuration at C2 appears to have no influence on the transformation when compared to the results of Magnus and co-workers.[40] For the lower yield of (−)-**111** compared to **2**, two reasons were considered. On the one hand, a loss of material during purification by flash chromatography cannot be excluded. On the other hand, norsecurinine (**5**) is known to be a reactive compound and the large variety of known norsecurinine-based oligomers is a result and testament thereof. Whereas decomposition of the synthesized **2** upon storage at 4 °C was observed within several days to a few weeks, the decomposition of both allonorsecurinine enantiomers, (+)-**111** and (−)-**111**, appeared to be faster. Also, the clean transformation observed by TLC analysis of the reaction mixture did not indicate undesired side reactions. The stability of the mesylate intermediate **112** obtained from **108** can be explained by the *syn-periplanar* configuration of the amine and ester groups. Whereas the *anti-periplanar* configuration of the other two alkaloids allows for an intramolecular S_N2 reaction leading to aziridinium intermediates **109** or **110**, this is not possible with mesylate **112**. The lone pair of the nucleophilic amine group cannot donate electron density into the σ* orbital of the C–O bond and thus the mesylate needs to be extruded in an S_N1 mechanism. The high temperatures required for the S_N1 reaction probably led to undesired side reactions as well as decomposition of (+)-**111**. Hence, a low yield of impure product (+)-**111** was obtained.

7. A Refined Hypothesis for the Biogenesis of *Securinega* Alkaloids

The results presented above support the hypothesis that a dehydrative rearrangement of neo(nor)securinane-type alkaloids with an azabicyclo[2.2.2]octane core to (nor)securinane-type alkaloids featuring an azabicyclo[3.2.1]octane core is involved in the biogenesis of *Securinega* alkaloids. Based on these findings, together with reports on earlier biogenetic steps described in the literature, experimental support for a refined model for the biogenesis of these alkaloids is presented: a linear biosynthetic pathway for these compounds (Scheme 18). In the 1970s, plant



Scheme 18. Linear biogenetic hypothesis for allosecurinine (**2**).

feeding experiments using radioactively labeled compounds showed that *Securinega* alkaloids are derived from tyrosine and lysine catabolites.[70] Furthermore, the asymmetric incorporation of lysine retaining the ε-nitrogen atom via cadaverine and Δ^1-piperideine intermediates was demonstrated.[70f] According to the hypothesis of Busqué, de March and co-workers, tyrosine would be metabolized into the C/D-ring fragment, which, in the case of allosecurinine (**2**), is represented by (+)-menisdaurilide [(+)-**63**] or (+)-aquilegiolide. The lysine-derived A-ring fragment would be introduced in a net vinylogous Mannich reaction to give intermediate **113**. The amino group would then attack the unsaturated lactone moiety in an intramolecular 1,6-addition to furnish the neosecurinane-type secu'amamine E (**88**). Dehydrative rearrangement of alkaloid **88** through the aziridinium ion **109** would afford the securinane-type **2**. Thus, we hypothesize that the neo(nor)securinane alkaloids possessing a [2.2.2]-bicyclic core are the direct biosynthetic precursors of the (nor)securinane alkaloids that feature a [3.2.1] core. However, this hypothesis raises new questions about the family of *Securinega* alkaloids, some of which might be addressed through further phytochemical investigations of the plants producing these compounds. Because the rearrangement favorably proceeds with alkaloids featuring an *anti-periplanar* configuration of the amine and hydroxyl groups, the fate of the *syn*-configured congeners remains unclear. These alkaloids were not reported to accumulate in plants, and isomerization at the C15 position to invert the orientation of the hydroxyl function might occur in nature. A linear biogenesis implies a connection between certain alkaloid members and should allow for a prediction of which compounds occur in the same plant. For example, every plant that contains **88** should also contain **2** due to the hypothetical biogenetic relationship outlined herein. Accordingly, every plant that contains bubbialidine (**72**) should also contain (−)-allonorsecurinine [(−)-**111**]. So far, neither enantiomer of **111** has been isolated from a natural source. Therefore, isolation of either compound would corroborate the linear biogenetic hypothesis outlined herein. Furthermore, a general detailed mapping of the occurrence of the different alkaloids and their relative amounts would help in understanding their interrelationships.

8. Conclusion

The *Securinega* alkaloids represent a fascinating family of plant natural products with bridged tetracyclic structures exhibiting interesting bioactivities. Although the compounds are generally small and compact, the myriad known stereoisomers and representatives featuring unique variations of the common backbone generates a diverse group of alkaloids. After being overlooked for more than 20 years, the synthetic community has rediscovered the *Securinega* alkaloids as challenging targets for total synthesis and, especially during the last two decades, numerous remarkable strategies have been developed to access these substances chemically. Several studies have contributed to the formulation of a biosynthetic pathway and future phytochemical investigations might provide additional insights into the origins and the chemistry of these natural products.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkaloids · natural products · rearrangement · structure · total synthesis

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