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A bio-inspired cascade and a late-stage directed sp^3 C–H lithiation enables a concise total synthesis of (−)-virosaine A

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ABSTRACT

The asymmetric total synthesis of (−)-virosaine A was achieved in 9% overall yield from commercially/readily available starting materials. Inspired by an intriguing biosynthetic proposal, a novel cascade reaction sequence was developed to efficiently construct the caged polycyclic core of virosaine A. The pivotal cascade precursor was readily available in enantiopure form *via* a robust route that featured an enantioselective one-pot Diels-Alder cycloaddition/organolithium addition. Several contemporary methods of C–H functionalization were applied to the cascade product and yielded a diverse set of novel complex polycycles. Ultimately, a combination of NMR and computational analyses laid the groundwork for a successful directed lithiation strategy to selectively functionalize the caged core and complete the total synthesis of virosaine A.

1. Introduction

The *Securinega* alkaloids are a fascinating class of secondary plant metabolites found within the Euphorbiaceae family.[1] The structural characteristics of these natural products, typified by their bridged tetracyclic scaffolds and an intriguing α,β,γ,δ-unsaturated lactone moiety, have provided a continual source of inspiration for synthetic chemists.[2] Securinine (**1**), the parent member of this family, was isolated more than 60 years ago and has been the most extensively studied *Securinega* alkaloid (Fig. 1). It exhibits an extensive biological activity profile and was for a time marketed as a drug for its stimulant and antiplasmodic effects.[1] Its intriguing profile and structure spurred numerous synthetic efforts which have culminated in a number of elegant total syntheses.[3] As isolation efforts of this natural product class progressed, several highly oxidized and/or rearranged members emerged. Virosaine A (**3**) and B (**4**), isolated in 2012 from the twigs and leaves of *Flueggea virosa* in China, are two such examples that have undergone additional skeletal oxidation and reorganization to yield unprecedented caged polycycles.[4] The virosaines (**3** and **4**) are arguably the most complex monomeric members of this alkaloid family and, interestingly, are pseudoenantiomers, inverted at all stereocenters except C8.[5] They contain several notable structural features that make them particularly challenging synthetic targets. These include the presence of multiple bridged bicycles, six congested stereocenters and, perhaps most intriguingly, an isoxazolidine ring embedded in the pentacyclic framework. The latter is particularly noteworthy, as it is an extremely rare structural motif in natural products and has intriguing biosynthetic origins (*vide infra*).[6] Interestingly, an isoxazolidine moiety is also present in the related *Securinega* alkaloid flueggine A (**5**), uniting the two monomeric fragments from which this dimer is constructed.[7]

The biosynthetic proposals for the virosaines (**3** and **4**) and flueggine A (**5**) all involve a union of cyclic imine **6** with arylpyruvic acid **7** to produce one of three diastereomeric tricyclic intermediates **8a**, **8b**, or **8c** (Scheme 1).[4,7,8] Direct oxidation of **8a** and **8b** is suggested to generate nitrones **9** and **10**, respectively, which are proposed to undergo subsequent intramolecular [3 + 2] cycloaddition to produce virosaine A (**3**) and B (**4**). Of note, synthetic studies suggest that the biosyntheses of **3** and **4** may involve the intermediacy of other *Securinega* alkaloids. Gademann demonstrated that the bubbialidine core could be oxidized/rearranged to access nitrone **9** and Yang and Li showed that nitrone **10** could be accessed from allonorsecurinine in a similar fashion.[9] In the case of flueggine A (**5**), intramolecular dehydration of **8c** generates norsecurinine (**2**), which is then proposed to undergo oxidation/rearrangement to generate nitrone **12**. However, **12** interestingly does not undergo an intramolecular [3 + 2] nitrone

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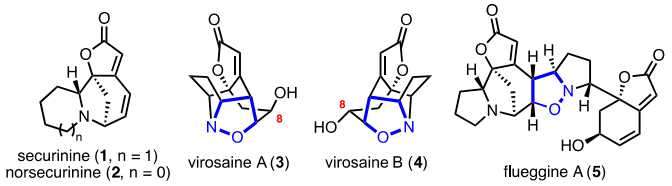
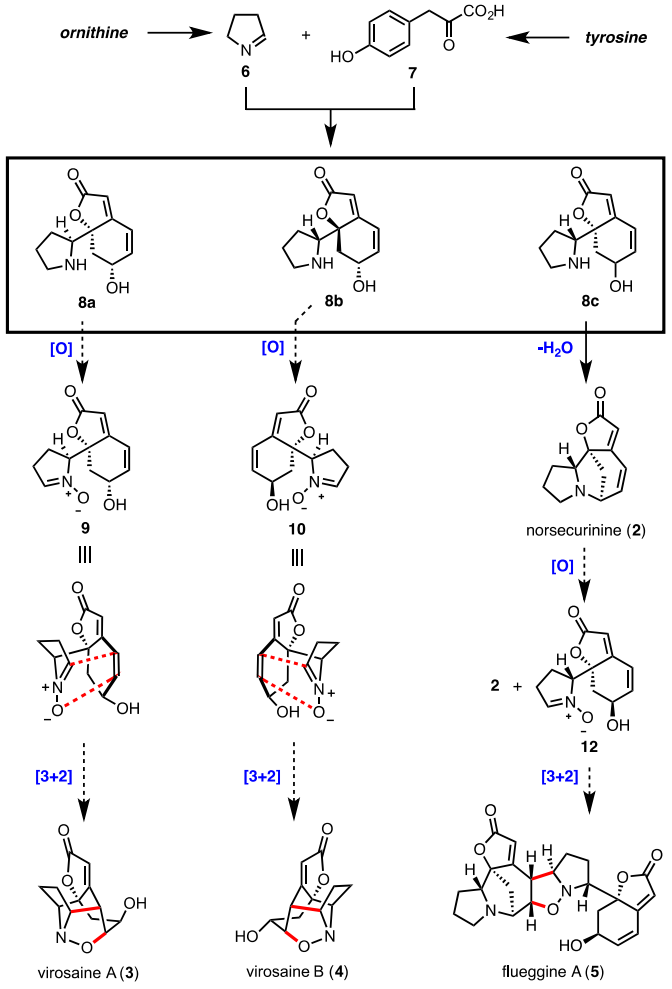


Fig. 1. *Securinega* alkaloids.



Scheme 1. Proposed biosyntheses of the virosaines (**3** and **4**) and flueggine A (**5**).

cycloaddition, presumably due to increased non-bonding interactions incurred in the alternative caged framework that would be formed with this diastereomer.[10] Instead, **12** reacts with norsecurinine (**2**) in an intermolecular sense to produce the dimer flueggine A (**5**). Evidence to support the feasibility of these rare biosynthetic nitrone cycloadditions have mounted in recent years *via* both biomimetic syntheses and computational studies, the latter of which suggest that the energy barriers required for these cycloadditions are low enough such that enzymatic intervention is not required.[11–13]

The synthetically challenging characteristics and unique biosynthetic origin of **3** motivated us to pursue its total synthesis. In particular, at the time we began our studies, the putative [3 + 2] dipolar cycloaddition had not been investigated synthetically. We thus embarked on a bio-inspired approach that would feature the nitrone cycloaddition as an integral step. However, in contrast to the subsequently reported syntheses that generated the nitrone *via* oxidative cleavage of a tertiary amine, our route employed an epoxide opening to generate the nitrone followed in tandem by the dipolar cycloaddition. Moreover, the route was enabled by the selective late-stage manipulation of an unactivated C(sp^3)–H bond in a pentacyclic intermediate, resulting in a short, efficient synthesis. Herein, the evolution and full details of these efforts are reported.[14]

2. Synthetic plan

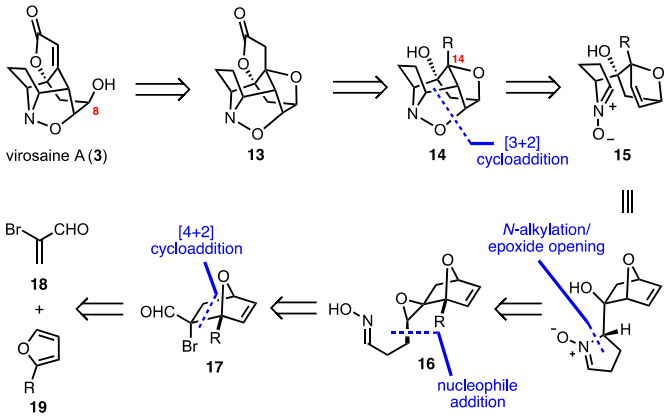
2.1. Retrosynthetic analysis

Retrosynthetically, we identified lactone **13** as precursor of **3** that effectively masks both the butenolide and C8 hydroxyl groups (Scheme 2). Hexacycle **13** could be simplified to pentacycle **14**, with an unspecified R group at C14 that could eventually be elaborated into the butanolide in **13**. Drawing inspiration from the proposed biosynthesis, we traced pentacycle **14** back to the corresponding nitrone **15** *via* a [3 + 2] nitrone cycloaddition. In order to install the requisite nitrone, we planned to open a trisubstituted epoxide with a pendant oxime, leading back to **16**. The advantage of this method is that it would build the nitrone in a stereospecific fashion and would eliminate any concerns of chemo- or regioselectivity compared to oxidative methods of nitrone formation. Furthermore, our goal was to implement this epoxide-opening step in tandem with the subsequent nitrone cycloaddition (**16** → **15** → **14**). The development of such a cascade reaction sequence would enable an efficient entry into the complex polycyclic virosaine core. Finally, we traced the cascade precursor **16** back to aldehyde **17**, the [4 + 2] cycloadduct of 2-bromoacrolein (**18**) and substituted furan **19**.[15]

3. Results and discussion

3.1. Model cascade reaction sequence

Given that the proposed bio-inspired cascade reaction sequence to access the caged pentacycle **14** was a focal point of the synthetic plan, we initially pursued a model study to assess the feasibility of this approach. Cascade reactions involving tandem nitrone formation/[3 + 2] cycloaddition have provided a platform for rapid complexity generation in several total syntheses.[16] However, there is limited literature precedent for cascades that specifically involve an intramolecular epoxide opening/intramolecular nitrone cycloaddition, with only one reported example prior to our work. Specifically, Grigg and coworkers demonstrated that heating an acyclic substrate containing an oxime, epoxide, and olefin resulted in *N*-



Scheme 2. Original retrosynthetic analysis of **3**.