Synthesis of the Indolizidine Core of Virosinine A via a Microwave-Promoted Cascade Cyclization Involving Iminyl Radicals

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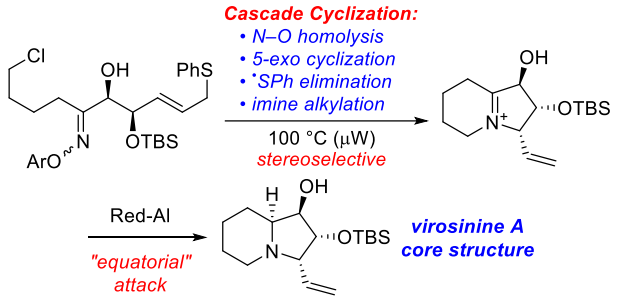
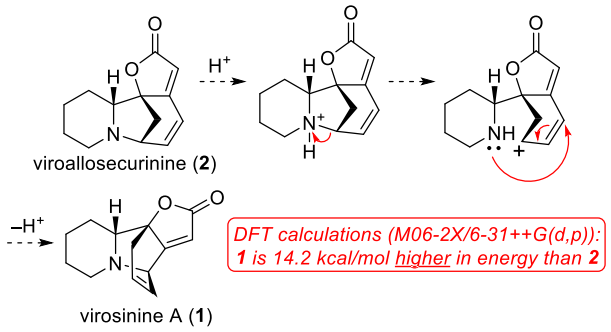
Supporting Information Placeholder



ABSTRACT: The indolizidine core of virosinine A has been synthesized by means of a microwave-promoted cascade reaction featuring 5-*exo*-*trig* iminyl radical cyclization, thiyl radical elimination, and intramolecular imine alkylation. The resulting bicyclic iminium ion underwent stereoselective reduction by Red-Al to deliver the target compound. DFT calculations suggested that both the radical cyclization and thiyl radical elimination steps are reversible at high reaction temperatures.

The *Securinega* alkaloid Virosinine A (**1**, Scheme 1) was isolated by Yue and co-workers in 2015 from the Chinese medicinal plant *Flueggea virosa*.[1] Its novel bridged tetracyclic ring system is related to the skeleton of conventional *Securinega* alkaloids such as viroallosecurinine (**2**, Scheme 1).[2] Indeed, Yue and co-workers speculated that **1** is derived from **2** via the pathway outlined in Scheme 1.[1] Although **1** is higher in energy than **2** according to DFT calculations, the fact that **1** was obtained from the same source as **2** but in much smaller quantities[1,2b] is consistent with this proposal. Preliminary investigations of the bioactivity of **1** revealed modest anti-HIV activity.[1]

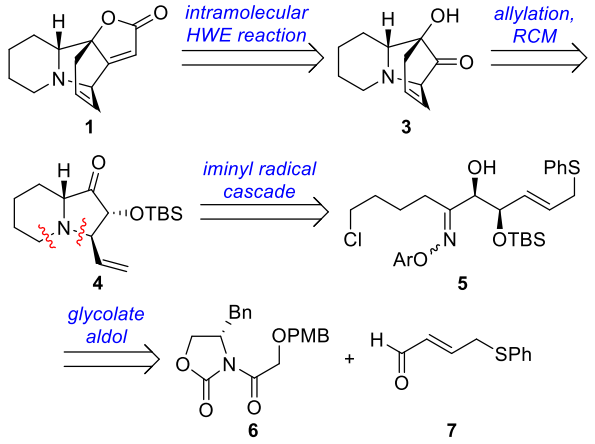
Scheme 1. Virosinine A and Its Proposed Biosynthesis



We were intrigued by the novel structure of **1** and the opportunity to investigate its proposed biosynthesis. Accordingly, we initiated synthetic studies of this *Securinega* alkaloid.[3,4] Herein, we report construction of the indolizidine core of virosinine A. A stereoselective cascade reaction inspired by a microwave-promoted iminyl radical cyclization developed in our lab[5] was central to this effort.

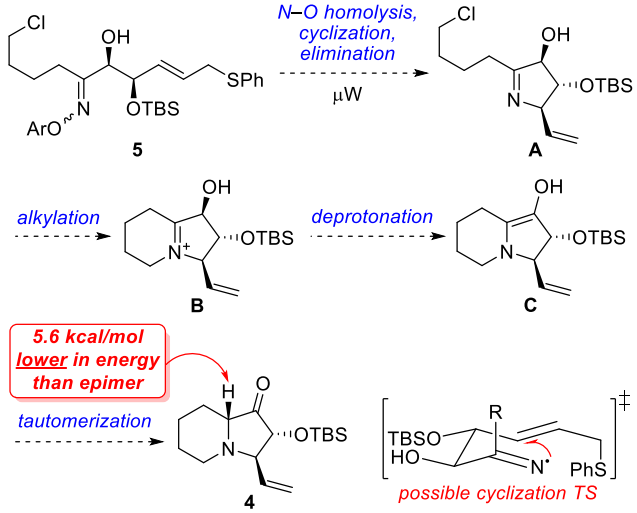
Our retrosynthesis of **1** is outlined in Scheme 2. We envisioned generating virosinine A from tricyclic α-hydroxy ketone **3** via an intramolecular Horner–Wadsworth–Emmons (HWE) reaction.[6] Disconnecting the bridged six-membered ring of **3** using ring-closing metathesis (RCM) and removing the resulting allyl group reveals indolizidinone **4** as a precursor to the tricycle. We planned to construct **4** from acyclic *O*-aryloxime **5** by enlisting a microwave-promoted iminyl radical cascade reaction. An Evans *syn* glycolate aldol reaction between known intermediates **6**[7] and **7**[8] would be employed as the key step to rapidly assemble **5**.

Scheme 2. Retrosynthetic Analysis



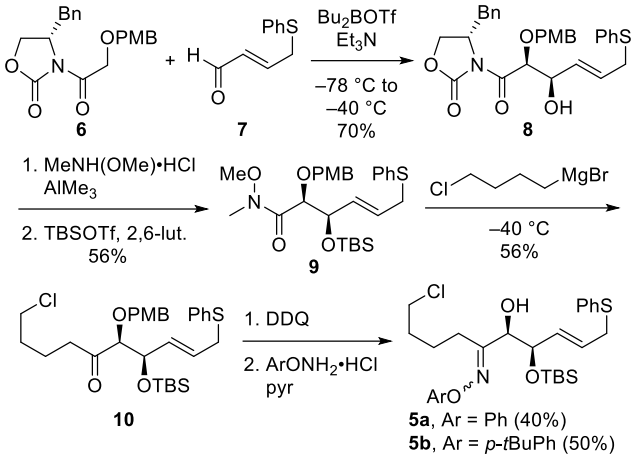
The proposed cascade cyclization is depicted in Scheme 3. Based on our prior work,[5] we reasoned that microwave irradiation of *O*-aryloxime **5** would trigger N–O homolysis, 5-*exo*-*trig* iminyl radical cyclization, and thiyl radical elimination.[9] Cyclization via a chairlike Beckwith–Houk transition state[10] should furnish dihydropyrrole **A** as the major diastereomer. Continued microwave irradiation would then induce intramolecular alkylation and deliver bicyclic iminium ion **B**. Although deprotonation of **B** could afford two regioisomeric enamines, only **C** would undergo essentially irreversible tautomerization reminiscent of an Amadori rearrangement[11] to generate indolizidinone **4**. Models of **4** and its epimer at the bridgehead carbon indicate that **4** is more stable due to its ability to adopt a conformation resembling a *trans*-fused bicyclic system. DFT calculations (Gaussian 09, M06-2X/6-31++G(d,p)) confirm this observation. Thus, we hypothesized that **B**, **C**, and its enamine regioisomer would all converge to **4**.

Scheme 3. Proposed Cascade Cyclization



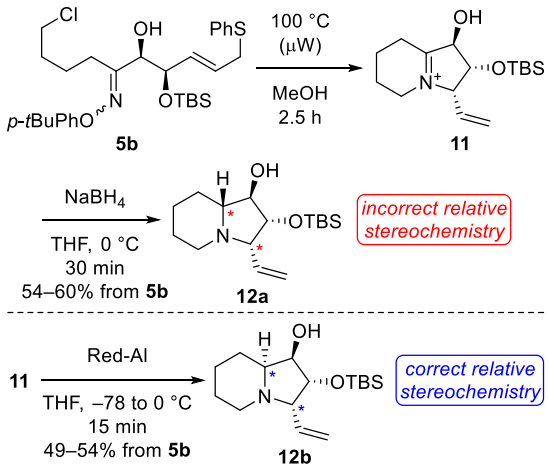
The *syn*-substituted *O*-aryloximes **5a** and **5b** required to attempt the proposed cascade cyclization were assembled as shown in Scheme 4. An Evans aldol reaction between oxazolidinone **6**[7] and aldehyde **7**[8] furnished adduct **8** in good yield as a single detectable diastereomer. Conversion of this intermediate into a Weinreb amide and subsequent TBS protection delivered **9** in acceptable yield over two steps. Addition of 4-chlorobutylmagnesium bromide to **9** afforded ketone **10**.[12] PMB ether cleavage was followed by condensation with either $PhONH_2 \cdot HCl$ or *t*-$BuPhONH_2 \cdot HCl$, generating *O*-aryloximes **5a** and **5b** respectively.

Scheme 4. Synthesis of Cascade Cyclization Substrates



The cascade transformation was then investigated with substrates **5a** and **5b**. Both *O*-aryloximes cyclized when subjected to microwave irradiation, but reactions involving **5b** were cleaner and could be performed at a lower temperature (100 °C vs 120 °C). We tentatively attribute these results to the lower N–O BDE of **5b** compared to that of **5a**.[5b] Excitingly, the radical cyclization, thiyl radical elimination, and intramolecular alkylation proceeded as anticipated. However, the resulting bicyclic iminium ion **11** did not undergo deprotonation to furnish an enamine (Scheme 5). Compound **11** was relatively unstable, so we reduced it immediately with $NaBH_4$. This afforded indolizidine **12a** in good yield as a single detectable diastereomer. Unfortunately, spectroscopic studies (vide infra) revealed that the vinyl-bearing stereocenter did not possess the expected configuration.

Scheme 5. Cascade Cyclization Reaction



The two hydroxyl-bearing stereocenters of indolizidine **12** will be destroyed at later stages of the synthesis, and both enantiomers of *N*-acyl oxazolidinone **6** are readily available. Thus, accessing **1** merely requires installing the correct relative configuration of the two new stereocenters (i.e., bridge-

head carbon and vinyl-bearing carbon) in the cascade cyclization–reduction sequence. Accordingly, we focused on inverting the stereoselectivity of the reduction. Fortunately, sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) furnished the desired indolizidine **12b** as a single detectable diastereomer (Scheme 5). Although the absolute configuration of the two key stereocenters in **12b** is opposite that required to construct **1**, commencing the synthesis with the enantiomer of **6** will rectify this issue.

The relative stereochemistry of **12a** and **12b** was determined by analyzing the coupling between their methine hydrogens, which are labeled as H_a–H_d in Figure 1. Vicinal hydrogens on five-membered rings frequently exhibit larger coupling constants in a *cis* relationship ($J \approx 8$ Hz) than in a *trans* relationship ($J \approx 0$–4 Hz).[13] Thus, the small $J_{a,b}$ value for **12a** indicates the *trans* relationship of H_a and H_b in this compound. In contrast, the large $J_{a,b}$ value for **12b** is diagnostic for a *cis* orientation. The differing H_a–H_b relative stereochemistry in these compounds is manifested in the appearance of the H_b signal in each ^{1}H NMR spectrum (i.e., app t with small J values in **12a** versus dd in **12b**, Figure 1). NOE experiments agreed with our coupling-based structural assignments of **12a** and **12b**, although overlapping peaks in the ^{1}H NMR spectra limited the number of unambiguous correlations that could be observed.

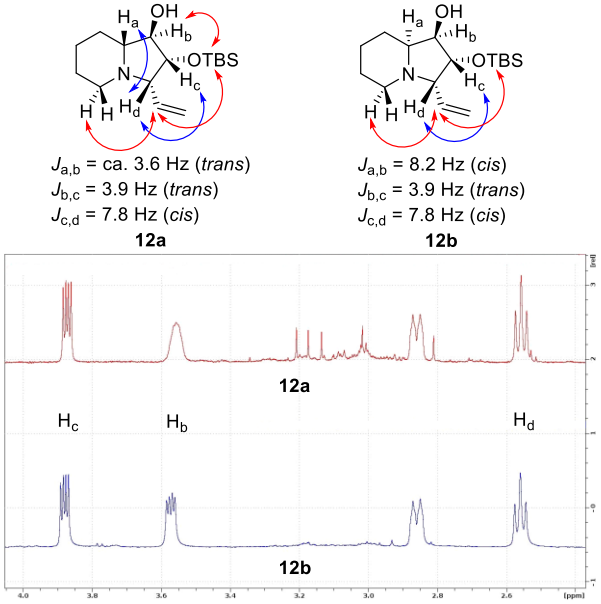


Figure 1. Relative stereochemistry of 12a and 12b. Blue and red arrows represent NOE correlations across the top and bottom faces of the ring systems, respectively.

The differing stereochemical outcomes of reductions of iminium ion **11** with $NaBH_4$ versus Red-Al are consistent with classical studies of reductions of cyclic ketones and iminium ions.[14] $NaBH_4$ is a small reagent that attacks cyclohexanones primarily from the axial direction to minimize torsional strain in the transition state. In contrast, large reagents such as Red-Al substantially increase the steric strain associated with axial attack, thereby favoring equatorial attack instead.[14a,b] Reductions of cyclohexyl iminium ions follow similar trends to cyclic ketone reductions.[14c] Figure 2 depicts the application of these principles to the reductions of **11**. The undesired indolizidine **12a** is obtained from axial-type attack on **11** by $NaBH_4$, whereas the desired indolizidine **12b** is produced via equatorial-type attack on **11** by Red-Al.

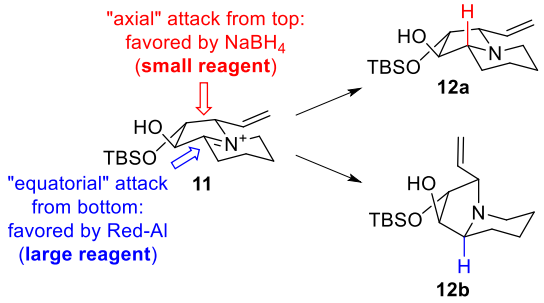
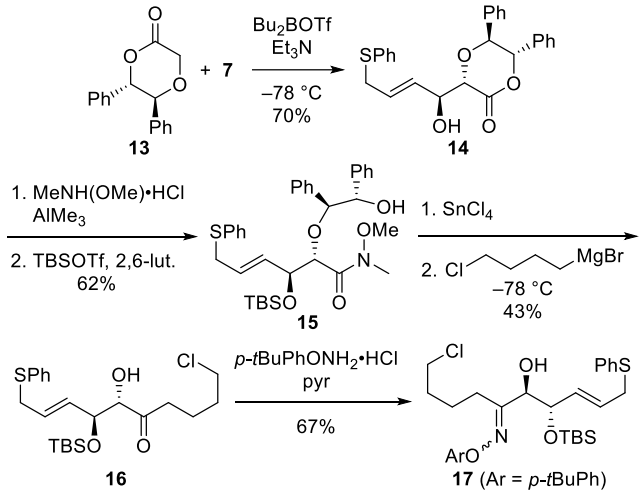


Figure 2. Rationale for stereoselective reductions of 11.

The formation of iminium **11** with the adjacent OTBS and vinyl groups in a *cis* arrangement indicated that the iminyl radical cyclization step did not proceed through the chairlike Beckwith–Houk transition state shown in Scheme 3. In an effort to determine the impact of substrate stereochemistry on the outcome of the radical cyclization, we synthesized *anti*-substituted *O*-aryloxime **17** (Scheme 6). The key step in this endeavor was an *anti* glycolate aldol reaction of aldehyde **7** with oxapyrone **13**.[15] The resulting adduct **14** was then transformed into TBS-protected Weinreb amide **15**. $SnCl_4$-mediated cleavage of the chiral auxiliary was best accomplished prior to Grignard addition, as inverting the order of these reactions led to lower yields. Condensation of the resulting ketone **16** with *t*-BuPhONH$_2$·HCl furnished *O*-aryloxime **17**. Attempts to obtain **17** via inversion of *syn O*-aryloxime **5b** or its ketone precursor were plagued by silyl migration.

Scheme 6. Synthesis of *anti O*-Aryloxime 17



Unfortunately, microwave irradiation of **17** afforded a complex mixture of compounds. While the mass of the desired product was detected in this mixture, we were unable to isolate its individual components. ^{1}H NMR spectra of the mixture suggested the presence of multiple related compounds. Thus, we tentatively conclude that the radical cyclization of **17** was less selective than that of its diastereomer **5b**. It appears that the stereochemistry of the substrate strongly influences the outcome of the iminyl radical cascade cyclization.

We performed DFT calculations in an attempt to uncover the factors responsible for the unexpected stereoselectivity of

the radical cyclization. We suspected that the high reaction temperature could render the cyclization step reversible. In fact, DFT calculations suggested that both the 5-*exo* radical cyclization and the subsequent thiyl radical elimination are reversible at elevated temperatures.[16] We then surmised that the irreversible imine alkylation might be under Curtin–Hammett control and therefore functioning as the stereochemistry-determining step. Unfortunately, the calculations were inconclusive regarding this point. Our previous efforts to rationalize the stereoselectivity of 5-*exo*-*trig* iminyl radical cyclizations using DFT calculations were also plagued by problems.[5b] The origin of these difficulties remains uncertain. Nonetheless, it is possible that the stereoselectivity of the cascade cyclization might be governed by a combination of kinetic and thermodynamic factors. A complicated mechanistic scenario of this type would presumably be difficult to study computationally.

In conclusion, we have developed a cascade cyclization that provides access to the indolizidine core of virosinine A. The process is initiated by microwave-promoted N–O homolysis of an *O*-aryloxime, and it features a 5-*exo*-*trig* iminyl radical cyclization followed by thiyl radical elimination and intramolecular imine alkylation. Stereoselective reduction of the resulting bicyclic iminium ion by Red-Al furnishes the indolizidine. DFT calculations indicated that the irreversible alkylation step is preceded by radical cyclization and thiyl radical elimination steps that are reversible under the high-temperature reaction conditions. The transformation of indolizidine **12b** into virosinine A is in progress.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectral data, summary of computational studies of the cascade reaction, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. (PDF)

Computed molecule Cartesian coordinates (XYZ)

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Notes

The authors declare no competing financial interest.

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