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Total Synthesis of the *Securinega* Alkaloid (−)-Secu'amamine A

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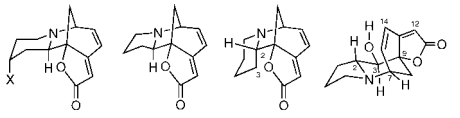
The *Securinega* alkaloids are a family of approximately 25 tetracyclic compounds produced by several species of *Securinega* and *Phyllanthus* plants.[1] The most abundant *Securinega* alkaloid is securinine (**1**), isolated from the leaves of *Securinega suffruticosa*. Allosecurinine (**4**), which is the C2 epimer of **1**, is also a common alkaloid of this group. Some additional congeneric alkaloids are (−)-norsecurinine (**3**) and phyllanthine (**2**). These alkaloids have a wide range of biological activities.[1b] For example, securinine is a GABA receptor antagonist,[2a] an antimalarial,[2b] and has antibacterial activity.[2c] Some *Securinega* alkaloids have been sporadically used in the clinic for diseases such as poliomyelitis, ALS, and chronic aplastic anemia.[1b]



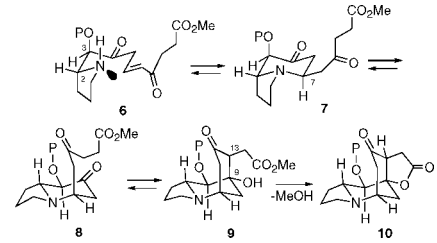
1 securinine X = H
2 phyllanthine X = OMe
3 norsecurinine
4 allosecurinine
5 (-)-secu'amamine A

In 2003, Ohsaki and co-workers isolated (−)-secu'amamine A (**5**), a *Securinega* alkaloid having a new structural framework, from the leaves and twigs of *Securinega suffruticosa* var. *amamiensis*.[3] The constitution and relative stereochemistry of this compound were determined primarily by NMR spectral analysis to be as depicted in **5**. The absolute configuration of the alkaloid was established using the OMe-mandelate NMR method. Although the stereochemistry of the indolizidine moiety was not initially addressed, we have determined that the *trans*-fused invertomer shown in **5** is thermodynamically preferred (vide infra). Therefore, this metabolite has an intriguing tetracyclic bridged ring system containing four stereogenic centers, which differs in structure from all the other *Securinega* alkaloids. Recently, Magnus and Padilla have proposed that secu'amamine A is derived biogenetically from allosecurinine (**4**) via oxidation at C3 followed by a rearrangement.[4] In this communication, we describe the first total synthesis of (−)-secu'amamine A (**5**).

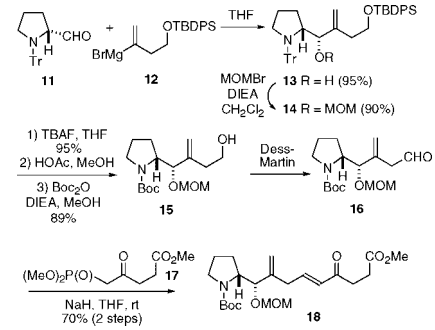
Our initial concept was to effect a multistep cascade cyclization sequence of the pyrrolidino enedione substrate **6** to afford the tetracyclic lactone **10** that possesses the complete secu'amamine A skeleton (Scheme 1). The first step of this transformation is conjugate addition of the amino group of **6** to the α,β-unsaturated ketone moiety to afford intermediate indolizidine **7**. Compound **7** would then undergo a ring flip and nitrogen inversion to conformer **8**. Subsequent ketone enolization, followed by intramolecular aldol condensation, would lead to keto hydroxy ester **9**. Finally, this compound would cyclize to tetracyclic γ-lactone **10**. We speculated that all of the steps from amino enone **6** to hydroxy ketone **9** would be reversible under basic protic conditions, and that the final lactonization to form tetracycle **10** might drive the overall process and produce the desired stereochemistry at the four requisite centers (C2, C3, C7, C9).

The synthesis commenced with *N*-tritylpyrrolidine aldehyde **11**, which was prepared enantiomerically pure from D-proline.[5] On the

Scheme 1



Scheme 2



basis of the work of Chemla et al.,[5] aldehyde **11** was combined with known vinyl Grignard reagent **12**[6] via a Felkin−Ahn addition to produce amino alcohol **13** as a single stereoisomer having the desired C2,3 configuration (Scheme 2). This alcohol was then protected as the MOM ether **14**. The silyl group of **14** was removed with fluoride, and the labile *N*-trityl group was replaced with a more stable Boc substituent to generate carbamate alcohol **15**. Dess−Martin oxidation of the primary alcohol functionality of **15** led to aldehyde **16**, which without purification reacted with the anion derived from known levulinate phosphonate **17**[7] to yield (*E*)-enone **18**. Although a number of attempts were made to oxidatively cleave the *exo*-methylene group of **18** to produce the *N*-Boc-protected precursor to the enedione cyclization substrate **6**, this transformation could not be effected. Therefore, we elected to explore a modified strategy using **18**.

After some experimentation, it was discovered that exposure of carbamate **18** to TFA in methylene chloride to remove the Boc group, followed by careful neutralization of the amine salt at low temperature using Hunig's base, led to a mixture of indolizidines **23** and **24**, with the desired latter stereoisomer being formed as the major product with 5:1 selectivity in good combined yield (Scheme 3). The configuration and conformation of these compounds were determined to be as shown by 2D NMR NOE analysis. Although the cyclization products cannot be interconverted by exposure to various bases in solution, it was found that, when the major isomer **24** is adsorbed onto dry basic alumina and allowed to remain at room temperature overnight, it is transformed completely to the minor isomer **23**. It seems reasonable that **24** arises from cyclization

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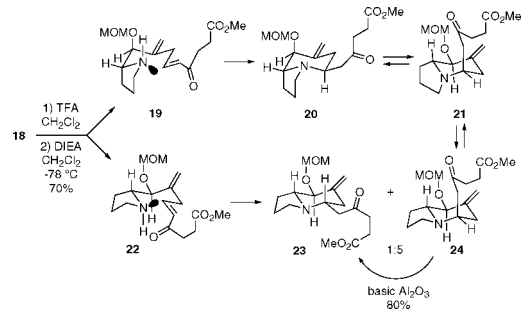
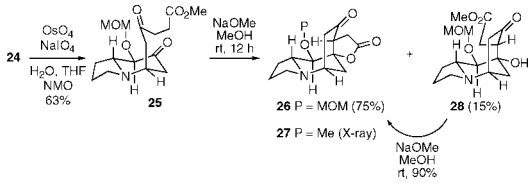
Scheme 3



Scheme 4



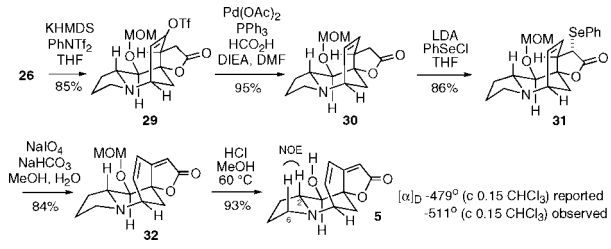
of the free amine derived from carbamate **18** via conformation **19**, leading initially to the intermediate *cis*-indolizidine **20**. This compound can undergo conformational isomerization to **21**, followed by nitrogen lone pair inversion, to produce **24**.

The isomeric cyclization product **23** could form directly via amino enone conformation **22**. Our rationale for the conjugate addition to occur primarily via conformer **19** to afford **24** as the major kinetic product is based upon the known conformational preferences of acyclic allylic ethers.[8] Thus, work by Gung and others has shown that the allylic hydrogen in such systems prefers to be eclipsed (in plane) with the double bond as is the case in conformation **19**. An in plane C−O bond, as in the alternative conformer **22**, is generally disfavored.

To continue the synthesis, the major *exo*-methylene indolizidine **24** was first oxidatively cleaved to ketone **25** (Scheme 4). We were pleased to find that exposure of this compound to sodium methoxide in methanol at room temperature afforded the desired tetracyclic lactone **26** in 75% yield along with a small amount of a polar compound which we believe is epimeric hydroxy ester **28**. Support for this assignment is that treatment of **28** with NaOMe/MeOH produces lactone **26** in high yield. The structure of γ-lactone **26** was confirmed by an X-ray crystal structure analysis of the methyl-protected analogue **27**, prepared via the same route used for the MOM compound. Interesting features of the structure include a *trans*-fused indolizidine and a boat cyclohexanone ring.

Completion of the synthesis involved first selectively converting ketone **26** to the enol triflate **29**,[9] followed by palladium-mediated reduction to alkene **30** (Scheme 5).[10] The γ-lactone moiety of **30** could be stereoselectively selenated to produce **31**, which upon periodate oxidation underwent *syn*-elimination to give diene lactone **32**.[11] Finally, removal of the MOM protecting group with MeOH/HCl yielded (−)-secu'amamine A (**5**) having proton and carbon NMR spectra identical to those of authentic material.[3,12] Moreover, the observed optical rotation of synthetic **5** was in good accord with that of the natural alkaloid, thereby confirming the original assignment of absolute configuration. In addition, we have found

Scheme 5



that, if the ^{1}H NMR spectrum of **5** is run in deuteriobenzene, peaks due to the protons at C2,6 are sufficiently dispersed to allow NOE analysis, which clearly demonstrated that the indolizidine is *trans*-fused. We have also been able to obtain an X-ray crystal structure of synthetic **5** which supports these conclusions.

In summary, we have devised a convergent enantioselective total synthesis of the novel *Securinega* alkaloid secu'amamine A (**5**). The synthesis requires 15 steps starting from D-proline-derived aldehyde **11** and proceeds in approximately 9% overall yield. Key steps include a stereoselective conjugate addition of amino enedione **19** to afford indolizidine **24** as the major product and cyclization of diketoester **25** to produce tetracyclic γ-lactone **26**.

Acknowledgment. Dedicated to Professor Deukjoon Kim on the occasion of his 60th birthday. We are grateful to the National Science Foundation (CHE-0404792) for support of this research. We also thank Dr. Hemant Yennawar (Penn State Small Molecule X-Ray Crystallographic Facility) for the crystal structure determinations.

Supporting Information Available: Experimental procedures for preparation of new compounds and copies of NMR spectra, as well as X-ray data for compounds **5** and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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