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Total Syntheses of (±)-Securinine and (±)- Allosecurinine

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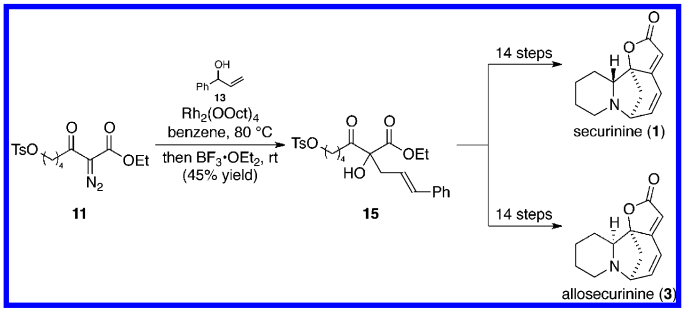
ABSTRACT



Total syntheses of (±)-securinine and (±)-allosecurinine that employ a tandem rhodium carbenoid-initiated Claisen/α-ketol rearrangement sequence as a key step are described.

Securinine (**1**)[1] was first isolated in 1956 from the leaves of the *Securinega suffruticosa* plant and was the first member of the so-called *Securinega* alkaloids[2] to be characterized. In addition to securinine, its enantiomer virosecurinine (**2**)[3] and two diastereomers, allosecurinine (**3**)[1c] and viroallosecurinine (**4**),[4] have also been isolated. Among other notable natural products in this family are the pyrrolizidine congeners of securinine: norsecurinine (**5**)[5] and allonorsecruinine (**6**)[6] (Figure 1).

Because of their interesting compact structures and a variety of biological activities, the *Securinega* alkaloids have received considerable attention from the synthetic community, resulting in several total syntheses.[6,7] Our interest in these molecules stemmed primarily from recent reports of promising anticancer properties.[8] Given the increasing interest in both the securine and norsecurine structural motifs, we set out to develop a unified synthetic approach that would deliver both the pyrrolizidine natural products (e.g., **5** and **6**) as well as their indolizidine homologues (e.g., **1**–**4**) via application of a rhodium-catalyzed O–H insertion/Claisen rearrangement/1,2-allyl migration method, which has been developed in our laboratories.[9] In previous studies, we established a viable route to the pyrrolizidine congeners and herein report the tactics required to deliver (±)-securinine (**1**) and (±)-allosecurinine (**3**).[10]

Retrosynthetically the planned synthesis was seen as delivering both (±)-securinine (**1**) and (±)-allosecurinine (**3**) via the late-state introduction of the butenolide onto hydroxy ketone **7**, a substrate that was expected to derive from oxidative ring closure of **8**. Cyclohexene **8** would arise from a ring-closing metathesis of diene **9**, the allylation and intramolecular reductive amination product of keto-ester **10**. At this stage, the α-hydroxy-β-keto-ester motif common to the products of our rhodium catalyzed O–H insertion/Claisen rearrangement/1,2-allyl migration sequence is apparent, and thus **10**, is seen as arising from

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(1) (a) Murav'eva, V. I.; Ban'kovskii, A. I. *Dokl. Akad. Nauk SSSR* **1956**, *110*, 998–1000. (b) Saito, S.; Kotera, K.; Sugimoto, N.; Horii, Z.; Tamura, Y. *Chem. Ind.* **1962**, 1652. (c) Satoda, I.; Murayama, M.; Tsuji, J.; Yoshii, E. *Tetrahedron Lett.* **1962**, *3*, 1199–1206. (d) Saito, S.; Kotera, K.; Shigematsu, N.; Ide, A.; Sugimoto, N.; Horii, Z.; Hanaoka, M.; Yamawaki, Y.; Tamura, Y. *Tetrahedron* **1963**, *19*, 2085–2099.

(2) (a) Snieckus, V. The Securinega Alkaloids. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. 14, pp 425–506. (b) Weinreb, S. M. *Nat. Prod. Rep.* **2009**, *26*, 758–775.

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(6) Alibés, R.; Ballbé, M.; Busqué, F.; March, P. D.; Elias, L.; Figueredo, M.; Font, J. *Org. Lett.* **2004**, *6*, 1813–1816.

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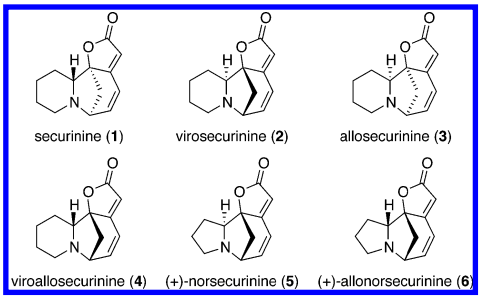
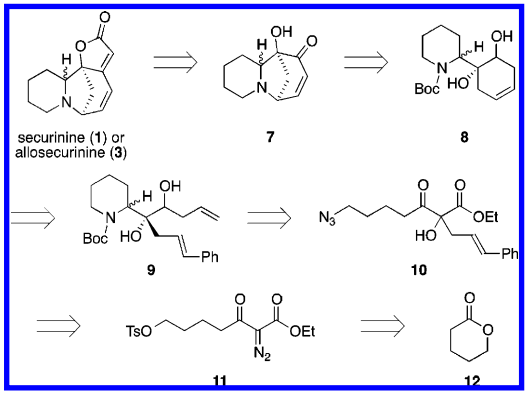


Figure 1. Selected securinega alkaloids.

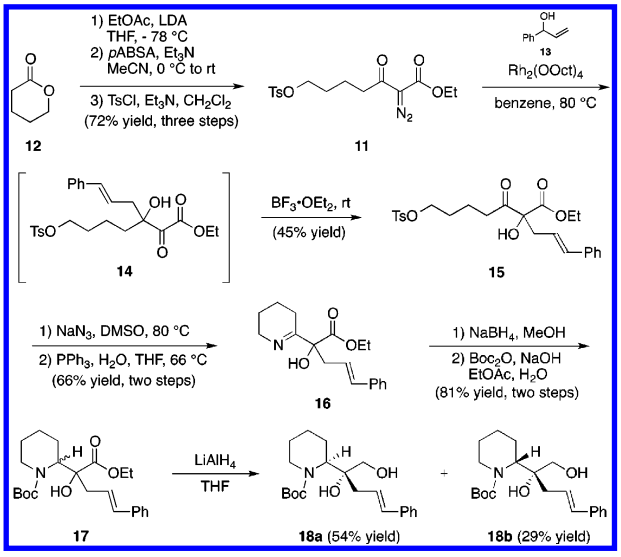
diazoester **11**, which would be prepared in three steps from δ-valerolactone (**12**) (Scheme 1).

Scheme 1. Retrosynthetic Analysis of Securinine (**1**) and Allosecurinine (**3**)



To initiate the synthesis, ethyl acetate was lithiated and added to δ-valerolactone (**12**). The resulting β-keto ester was converted to the diazo compound with *p*ABSA[11] and the primary alcohol activated as the tosylate to give intermediate **11**. At this point, we were ready to investigate the rhodium-catalyzed O−H insertion/Claisen rearrangement/1,2-allyl migration sequence, and while we recognized that utilizing an enantioenriched allylic alcohol would result in an asymmetric synthesis,[10] we opted to explore this reaction with racemic allylic alcohol **13**.[12] To this end, a mixture of diazoester **11** and allylic alcohol **13** was treated with $Rh_2(OOct)_4$, which induced the desired O−H insertion/Claisen rearrangement and furnished intermediate **14**. Subsequent treatment of the reaction mixture with $BF_3 \cdot EtO_2$ promoted a 1,2-allyl migration to furnish **15**. Addition of NaN_3 to the derived tosylate (**15**) followed by azide reduction under Staudinger conditions produced a primary amine, which spontaneously condensed onto the nearby ketone to furnish imine **16** as the only isolable product. Imine **16** was reduced and Boc-protected to give **17**, which when treated with $LiAlH_4$ undergoes ester reduction to furnish diols **18a** and **18b** (Scheme 2). At this point, the two diastereomers were separated and advanced separately.[13]

Scheme 2. Synthesis of Diols **18a** and **18b**



With both diasteromers in hand, we decided to first advance the major isomer, diol **18a**. To this end, **18a** was

(7) (a) Saito, S.; Yoshikawa, H.; Sato, Y.; Nakai, H.; Sugimoto, N.; Horri, Z.-i.; Hanaoka, M.; Tamura, Y. *Chem. Pharm. Bull.* **1966**, *14*, 313–314. (b) Horii, Z.; Hanaoka, M.; Yamawaki, Y.; Tamura, Y.; Saito, S.; Shigematsu, N.; Kotera, K.; Yoshikawa, H.; Sata, Y.; Nakai, H.; Sugimoto, N. *Tetrahedron* **1967**, *23*, 1165–1174. (c) Horii, Z.-I.; Imanishi, T.; Hanaoka, M.; Iwata, C. *Chem. Pharm. Bull.* **1972**, *20*, 1774–1777. (d) Heathcock, C. H.; von Geldern, T. W. *Heterocycles* **1987**, *25*, 75–78. (e) Jacobi, P. A.; Blum, C. A.; Desimone, R. W.; Udodong, U. E. S. *Tetrahedron Lett.* **1989**, *30*, 7173–7176. (f) Magnus, P.; Rodriguez-Lopez, J.; Mulholland, K.; Matthews, I. *Tetrahedron* **1993**, *49*, 8059–8072. (g) Han, G.; Laporte, M. G.; Folmer, J. J.; Werner, K. M.; Weinreb, S. M. *J. Org. Chem.* **2000**, *14*, 6293–6306. (h) Honda, T.; Namiki, H.; Kudoh, M.; Watanabe, N.; Nagase, H.; Mizutani, H. *Tetrahedron Lett.* **2000**, *41*, 5927–5930. (i) Liras, S.; Davoren, J. E.; Bordner, J. *Org. Lett.* **2001**, *3*, 703–706. (j) Honda, T.; Namiki, H.; Kudoh, M.; Nagase, H.; Mizutani, H. *Heterocycles* **2003**, *59*, 169–187. (k) Honda, T.; Namiki, H.; Kaneda, K.; Mizutani, H. *Org. Lett.* **2004**, *6*, 87–89. (l) Alibés, R. N.; Bayón, P.; de March, P.; Figueredo, M.; Font, J.; García-García, E.; González-Gálvez, D. *Org. Lett.* **2005**, *7*, 5107–5109. (m) Carson, C. A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6560–6563. (n) Bardají, G. G.; Cantó, M.; Alibés, R.; Bayón, P.; Busqué, F.; March, P. D.; Figueredo, M.; Font, J. *J. Org. Chem.* **2008**, *73*, 7657–7662. (o) Leduc, A. B.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 7945–7948. (p) Liu, P.; Hong, S.; Weinreb, S. M. *J. Am. Chem. Soc.* **2008**, *130*, 7562–7563. (q) Dhudshia, B.; Cooper, B. F. T.; Macdonald, C. L. B.; Thadani, A. N. *Chem. Commun.* **2009**, 463–465. (r) González-Gálvez, D.; García-García, E.; Alibés, R.; Bayón, P.; de March, P.; Figueredo, M.; Font, J. *J. Org. Chem.* **2009**, *74*, 6199–6211. (s) Sampath, M.; Lee, P.-Y. B.; Loh, T.-P. *Chem. Sci.* **2011**, *2*, 1988–1991. (t) Bélanger, G.; Dupuis, M.; Larouche-Gauthier, R. *J. Org. Chem.* **2012**, *77*, 3215–3221.

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(9) (a) Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J.; Pflum, D. A.; Petsch, D. T. *J. Am. Chem. Soc.* **1997**, *119*, 9641–9651. (b) Wood, J. L.; Moniz, G. A. *Org. Lett.* **1999**, *1*, 371–374. (c) Wood, J. L.; Moniz, G. A.; Pflum, D. A.; Stoltz, B. M.; Holubec, A. A.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1999**, *2*, 1748–1749.

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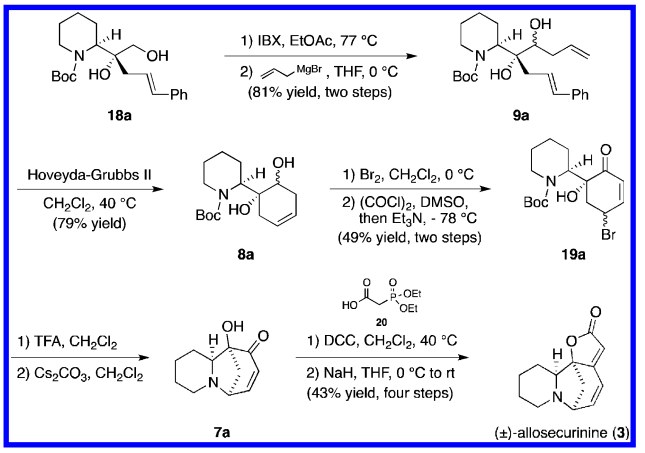
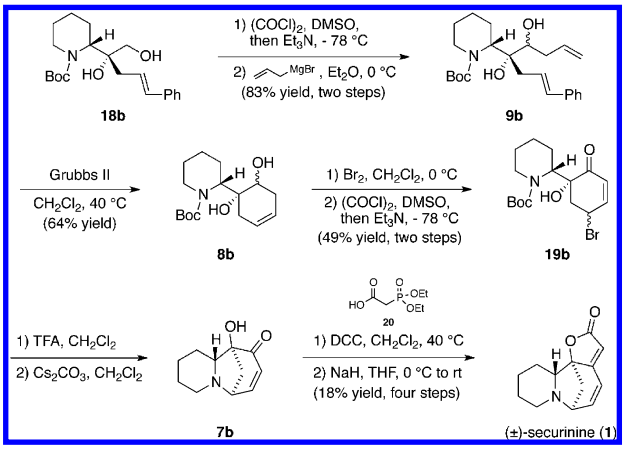
(11) Davies, H. M. L.; Cantrell, W. R. J.; Romines, K. R.; Baum, J. S. *Org. Synth.* **1992**, *70*, 93–97.

(12) For the synthesis of racemic allylic alcohol **13**, see the Supporting Information in: Nowrouzi, F.; Janetzko, J.; Batey, R. A. *Org. Lett.* **2010**, *12*, 5490–5493.

Scheme 3. Synthesis of (±)-Allosecurinine (**3**)



Scheme 4. Synthesis of (±)-Securinine (**1**)



converted to the corresponding aldehyde by treatment with IBX[14] and then exposed to allyl Grignard to provide **9a**. Diene **9a** was treated with the Hoveyda–Grubbs II catalyst,[15] which efficiently induced ring-closing metathesis and furnishes cyclohexene **8a**. Treatment of **8a** with bromine gave a dibromide, which when treated under Swern conditions provided enone **19a**. The Boc protecting group was removed, and the resulting amine was treated with Cs_2CO_3 to give indolizidine **7a**.[16] Completion of the synthesis was realized by first coupling acid **20** to tertiary alcohol **7a** followed by an intramolecular Horner–Wadsworth–Emmons olefination to give (±)-allosecurinine (**3**) (Scheme 3).

Turning next to (±)-securinine (**1**), we attempted to apply the same reaction sequence to diol **18b**; however, oxidation of the primary alcohol of diol **18b** under the conditions we utilized for diol **18a** (i.e., IBX) resulted in a product mixture that contained a considerable amount of an inseparable byproduct.[17] In an effort to circumvent this deleterious event, we turned to the Swern conditions, which cleanly delivered the desired aldehyde. As before, treatment with allyl Grignard provided the corresponding secondary alcohol (**9b**), which upon ring-closing metathesis furnished cyclohexene **8b**. Bromination followed by oxidation to the enone (**19b**) proceeded in a fashion similar to the diastereomeric system. Boc-deprotection and base-mediated ring closure then gave indolizidine **7b** which, upon acylation with acid **20**, underwent Horner–Wadsworth–Emmons olefination to give (±)-securinine (**1**) (Scheme 4).

In summary, we have completed the total syntheses of (±)-securinine and (±)-allosecurinine via a route that employs a highly efficient rhodium-catalyzed O–H insertion/Claisen rearrangement/1,2-allyl migration domino process. Efforts to employ this chemistry to facilitate the emerging biological investigations into this class of compounds are underway.

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Supporting Information Available. Experimental details and copies of ^1H and ^{13}C NMR for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

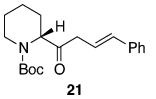
(13) The relative stereochemistry of diols **18a** and **18b** was not determined at the time of synthesis and instead was assigned after proceeding to natural products **1** and **3** separately and comparing those to literature data.

(14) For the employed IBX protocol, see: More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001–3003.

(15) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

(16) The relative stereochemistry of bromides **19a** and **19b** was not determined; however, as demonstrated by both Honda[7k] and Figueredo,[7n] this stereochemistry is inconsequential as both diastereomers can be advanced to the desired product.

(17) Although not characterized in a pure state, we believe the undesired material to be oxidative cleavage product **21**.



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The authors declare no competing financial interest.