ORGANIC LETTERS

2012
Vol. 14, No. 17
4531–4533

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

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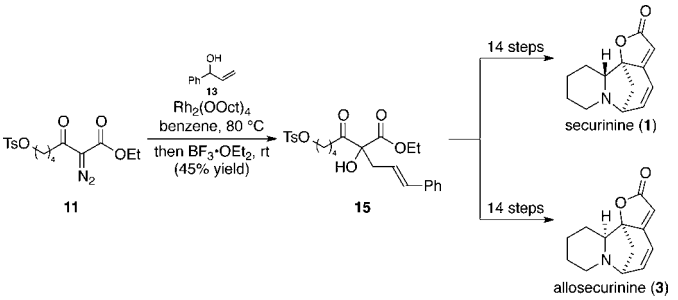
Received July 19, 2012

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.

(3) Nakano, T.; Yang, T. H.; Terao, S. *Chem. Ind.* **1962**, 1651–1652.

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(5) Joshi, B. S.; Gawad, D. H.; Pelletier, S. W.; Kartha, G.; Bhandary, K. *J. Nat. Prod.* **1986**, *49*, 614–620.

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

10.1021/ol3020072
Published on Web 08/22/2012

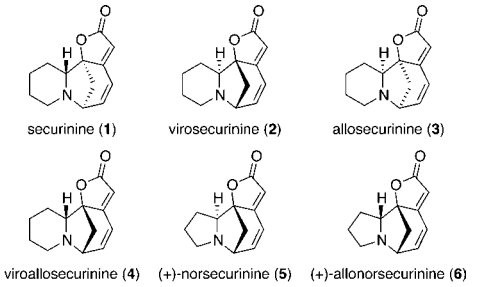
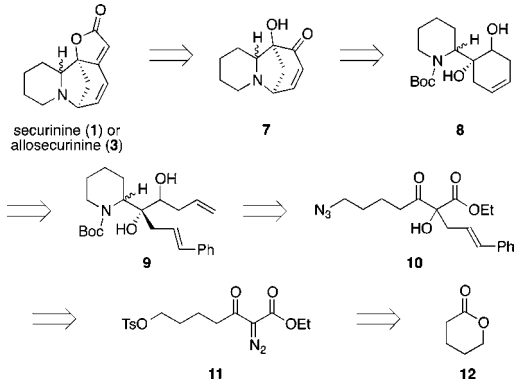


Figure 1. Selected securinega alkaloids.

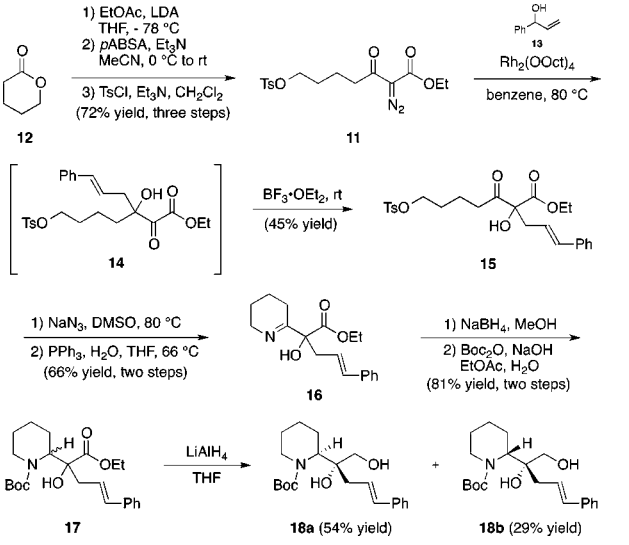
diazoester **11**, which would be prepared in three steps from δ-valerolactone (**12**) (Scheme 1).

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

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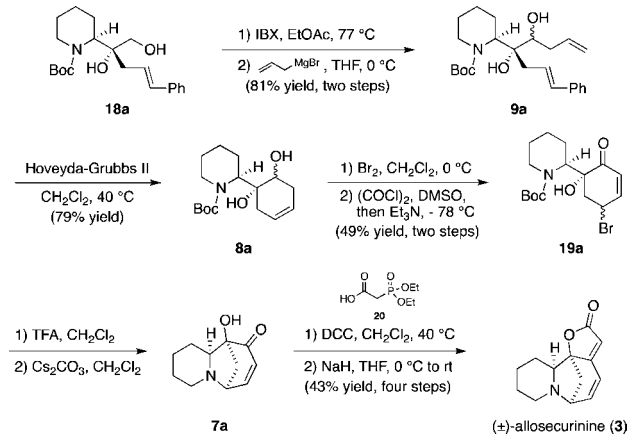
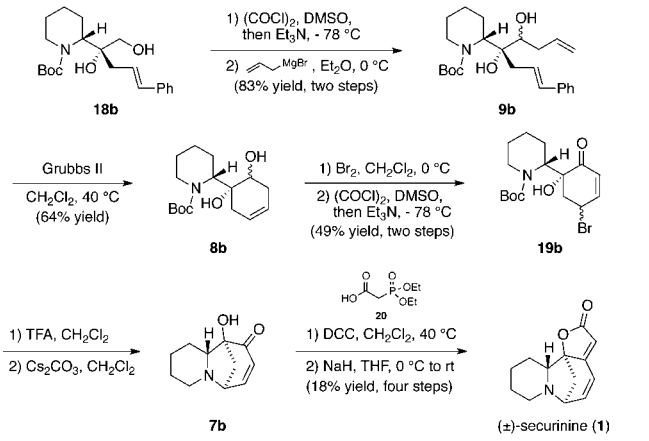
(12) For the synthesis of racemic allylic alcohol **13**, see the Supporting Information in: Nowrouzi, F.; Janetzko, J.; Batey, R. A. *Org. Lett.* **2010**, *12*, 5490–5493.

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.

Acknowledgment. H.C. thanks the National Science Council, ROC (Taiwan), and J.F.B. thanks the Swiss National Science Foundation (SNF) and the Novartis Jubilee Foundation for financial support. J.L.W. thanks Amgen and the NSF (CHE-1058292) for financial support. Dr. Chris Rithner, Don Heyse, and Don Dick of the CSU central instrumentation facility are acknowledged for their assistance with spectroscopic analyses.

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.

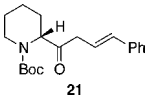
(13) The relative stereochemistry of diols **18a** and **18b** was not determined at the time of synthesis and instead was assigned after proceeding to natural products **1** and **3** separately and comparing those to literature data.

(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**.



The authors declare no competing financial interest.