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A Formal Synthesis of Swainsonine by Gold-Catalyzed Allene Cyclization

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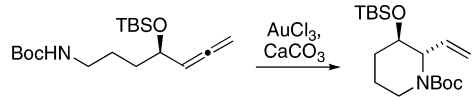
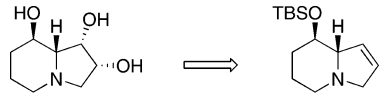
ABSTRACT



A formal synthesis of swainsonine has been achieved using a highly efficient and diastereoselective gold(III)-catalyzed allene cyclization.

Swainsonine **1**, isolated from the fungus *Rhizoctonia leguminicola* and later the Australian plant *Swainsona canesens*, the North American spotted locoweed plant *Astragalous lentiginosus*, and the fungus *Metarhizium anisopline*, is a potent mannosidase inhibitor and has attracted attention due to its potential in the treatment of a range of conditions.

Numerous synthetic studies have been reported.[1] In particular, we were interested in the approach of Pyne,[2] involving the use of dihydroxylation of an unsaturated indolizidine **2** to introduce the *cis*-diol moiety (Figure 1).



1 2

Figure 1. Swainsonine and Pyne's intermediate.

Blechert also employed this step.[3] Carretero employed the corresponding TIPS ether.[4]

For some years, originally inspired by the work of Hegedus,[5] we have been interested in organometallic nucleophilic cyclization reactions of allenes.[6] Such reactions using either a silver(I),[7] a gold(I), or a gold(III) catalyst,[8] when carried out in an *exo*-sense, can yield α-vinyl heterocycles in an overall cycloisomerization process. Combined with ring-closing metathesis, this could produce a short route to Pyne's swainsonine intermediate **2** depending on the diastereoselectivity on cyclization.

The allene precursor for cyclization was synthesized from THF (Scheme 1). Ring opening of THF with sodium iodide in the presence of benzoyl chloride yielded 4-iodobutyl benzoate.[9] Displacement of the iodide with azide, followed by saponification, easily gave 4-azidobutanol **3** on a multigram scale. IBX oxidation gave 4-azidobutanal **4** which underwent efficient addition of (trimethylsilyl)ethynyllithium

(1) For reviews, see: El Nemr, A. *Tetrahedron* **2000**, *56*, 8579. Pyne, S. G. *Curr. Org. Synth.* **2005**, *2*, 39. For some recent syntheses, see: Shi, G.-F.; Li, J.-Q.; Jiang, X.-P.; Cheng, Y. *Tetrahedron* **2008**, *64*, 5005. Guo, H.; O'Doherty, G. A. *Tetrahedron* **2008**, *64*, 304. Déchamps, I.; Pardo, D. G.; Cossy, J. *Tetrahedron* **2007**, *63*, 9082. Martín, R.; Murruzzu, C.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **2005**, *70*, 2325.

(2) Au, C. W. G.; Pyne, S. G. *J. Org. Chem.* **2006**, *71*, 7097. Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774.

(3) Buschmann, N.; Rückert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325.

(4) de Vicente, J.; Arrayás, R. G.; Cañada, J.; Carretero, J. C. *Synlett* **2000**, 53.

(5) Hegedus, L. S.; Inoue, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4917.

(6) Bates, R. W.; Satchareon, V. *Chem. Soc. Rev.* **2002**, 12.

(7) Originally reported by Claesson: Claesson, A.; Sahlberg, C.; Luthman, K. *Acta Chem. Scand. B* **1979**, 309. For additional examples, see ref 6.

(8) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285. For reviews of the use of gold, see: Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. Arcadi, A. *Chem. Rev.* **2009**, *108*, 3266. Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. Arcadi, A.; Di Giuseppe, S. *Curr. Org. Chem.* **2004**, *8*, 795.

(9) Oku, A.; Harada, T.; Kita, K. *Tetrahedron Lett.* **1982**, *23*, 681.

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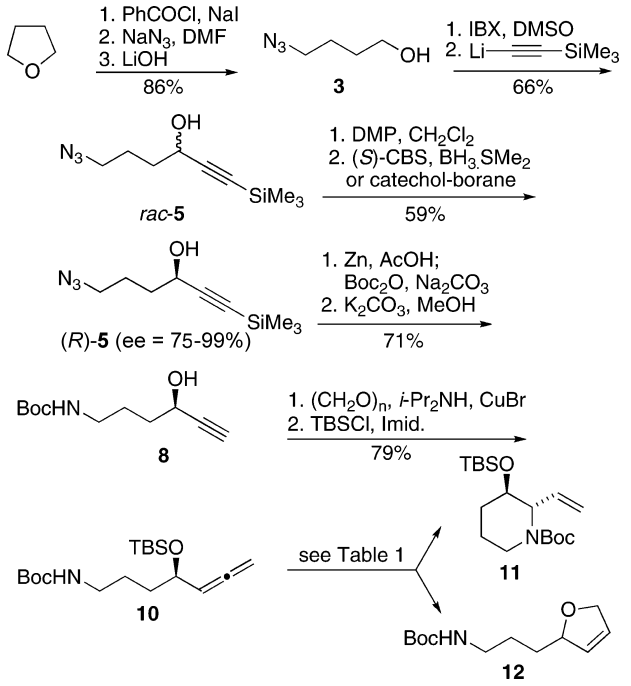
Scheme 1. Allene Synthesis and Cyclization



to give azidoalkyne **5**. This azido alkyne, as expected, proved to be highly unstable, presumably due to intramolecular 1,3-dipolar cycloaddition. This material was either used immediately or stored at −80 °C.

The racemic alkyne *rac*-**5** was converted to its (*R*)-isomer by an oxidation−reduction sequence. The Dess−Martin periodinane was employed for the oxidation to ketone **6** to ensure a rapid conversion. Asymmetric reduction was originally attempted using borane-dimethyl sulfide in the presence of the CBS catalyst.[10] On a small scale, this worked well, delivering (*R*)-**5** in 67% yield and an ee of 99%. On a larger scale, however, the formation of byproduct, including from alkyne hydroboration and possibly attack on the azide, resulted in a low yield. The use of catechol borane gave a more reliable result, delivering the alkyne (*R*)-**5** in a reliable 86% yield, but an ee of only 75%.

At this stage, the azide group was subjected to reduction−protection to give the *t*-Boc derivative **7**. To complete the synthesis of the precursor for cyclization, the trimethylsilyl group was removed, the alkyne **8** was homologated to an allene **9** using the Searles−Crabbé procedure,[11] and the alcohol was protected as its TBS ether **10**.

A number of catalysts and conditions were tested for cyclization. Both silver(I) nitrate[12] and the combination of (triphenylphospine)gold(I) chloride−silver triflate[13] proved ineffective, returning unreacted starting material. The use of gold(III) chloride in dichloromethane resulted in formation of dihydrofuran **12**, isomeric with the desired piperidine **11** (Table 1). A similar result was obtained using acetonitrile as the solvent. We attribute the formation of dihydrofuran **12** to cleavage of the O−Si bond due to traces of hydrogen chloride in the mixture due to adventitious moisture, followed by facile 5-*endo* cyclization. Dihydrofuran formation could be prevented by inclusion of calcium carbonate, leading to formation of piperidine **11** in modest yield. However, an excellent yield of piperidine **11** could only be obtained by inclusion of both calcium carbonate and acetonitrile[14] to solubilize and stabilize the gold(III). Under these conditions, the desired piperidine **11** was obtained as a single diastereoisomer in 99% yield.[15]

Table 1. Allene Cyclization

entry	conditions	product (yield %)
1	$AgNO_3$, aq acetone	NR
2	Ph_3PAuCl, AgOTf, CH_2Cl_2	NR
3	$AuCl_3$, CH_2Cl_2	**12** (ca. 10%[a])
4	$AuCl_3$, CH_3CN	**12** (ca. 10%[a])
5	$AuCl_3$, CH_3CN, $CaCO_3$	**11** (13%[a])
6	$AuCl_3$, CH_2Cl_2, CH_3CN, $CaCO_3$	**11** (99%)

[a] Significant amounts of starting material recovered.

To construct the five-membered ring, it was necessary at this stage to achieve selective deprotection of the nitrogen. Attempts to do this by the method of Cavelier and Enjalbal proved fruitless,[16] but to our surprise, simple treatment of **11** with trifluoroacetic acid in anhydrous dichloromethane yielded the desired piperidine **13** with the silyl ether intact. We attribute this to the absence of any nucleophile in the reaction mixture capable of nucleophilic attack on the silicon atom.

Allylation of the nitrogen atom under standard conditions (allyl bromide, sodium hydroxide) gave only a modest yield (28%) of the desired diene **15**. On the other hand, a sequence of allyl carbamate (alloc) formation,[17] followed by palladium(0)-catalyzed "alloc contraction"[18] proved to be highly satisfactory, delivering diene **15** in 83% yield from the piperidine. The formal synthesis was completed by ring-closing metathesis using Grubbs second-generation catalyst in the presence of 1 equiv of tosic acid, followed by a basic workup (NaOH), to give indolizidine **2** in good yield (Scheme 2). The synthetic material[19]

(10) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986. Corey, E. J.; Magriotis, P. A.; Helal, C. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938. Ledeboer, M. W.; Parker, K. A. *J. Org. Chem.* **1996**, *61*, 3214.

(11) Searles, S.; Li, Y.; Nassim, B.; Lopes, M.-T. R.; Tran, P. T.; Crabbé, P. *J. Chem. Soc., Perkin I* **1984**, 747.

(12) Claesson, A.; Sahlberg, C.; Luthman, K. *Acta Chem. Scand. B* **1979**, 309.

(13) Hyland, C. J. T.; Hegedus, L. S. *J. Org. Chem.* **2006**, *71*, 8658. Gold(I) complexes with other ligands have also been employed: Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066. Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 2887. Kinder, R. E.; Zhang, Z.; Widenhoefer, R. A. *Org. Lett.* **2008**, *10*, 3157.

(14) Krause, N.; Morita, N. *Org. Lett.* **2004**, *6*, 4121.

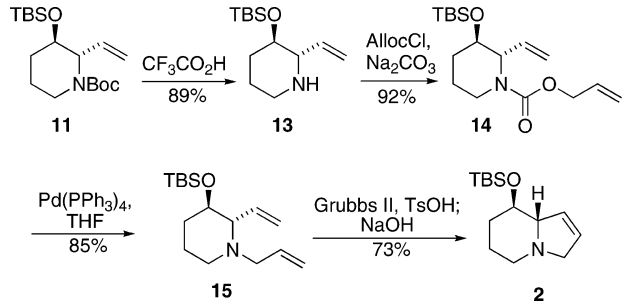
(15) The corresponding alloc protected material also underwent cyclization with excellent diastereoselectivity, but in low yield.

(16) Cavelier, F.; Enjalbal, C. *Tetrahedron Lett.* **1996**, *37*, 5131.

(17) The allyl carbamate derivative did not undergo ring-closing metathesis with either the Grubbs I or II catalysts.

(18) For examples, see: Torque, C.; Sueur, B.; Cabou, J.; Bricout, H.; Hapiot, F.; Monflier, E. *Tetrahedron* **2005**, *61*, 4811. Gomez-Martinez, P.; Dessolin, M.; Guibé, F.; Albericio, F. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 2871.

Scheme 2. Completion of the Formal Synthesis



was spectroscopically identical to that reported by Pyne[2] and by Blechert.[3]

In conclusion, a formal synthesis of swainsonine has been achieved employing a highly stereoselective, gold-catalyzed allene cyclization which uses a simple catalyst system.

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Supporting Information Available: Complete experimental procedures and spectroscopic data for compounds **2**−**15**, 4-iodobutyl benzoate, and 4-azidobutyl benzoate. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) For material prepared via the catechol borane reduction, $\alpha_D^{23} = -59.6$, $c = 1$, CH_2Cl_2 (ref 2, −72, $c = 0.65$, benzene), is consistent with an ee of ca. 75%.