ORGANIC LETTERS

2012
Vol. 14, No. 8
2172–2175

Construction of the Azocane (Azacyclooctane) Moiety of the *Lycopodium* Alkaloid Lycopladine H via an Intramolecular Hydroaminomethylation Strategy

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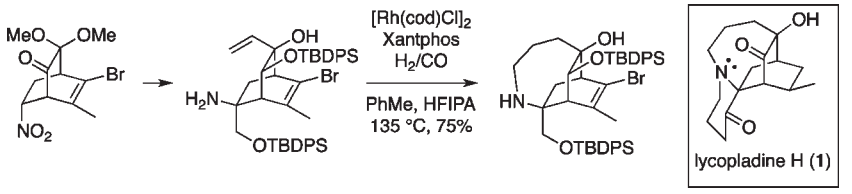
Received March 21, 2012

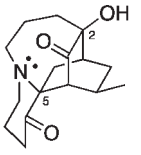
ABSTRACT



An efficient synthetic strategy has been developed for annulation of an azocane ring onto a bicyclo[2.2.2]octane scaffold via an intramolecular hydroaminomethylation protocol to generate an advanced intermediate bearing three of the four rings of the structurally unique *Lycopodium* alkaloid lycopladine H (1).

The *Lycopodium* class of alkaloids has been of scientific interest since the initial isolation of lycopodine from the club moss *Lycopodium complanatum* in 1881.[1] Since then, more than 250 additional *Lycopodium* alkaloids have been isolated, many of which show biological activity.[2] A recently discovered member of the *Lycopodium* alkaloid family is lycopladine H (**1**), which was isolated by Kobayashi et al. from the methanolic extracts of *L. complanatum* in 2009.[3,4]

Lycopladine H exhibits an unprecedented tetracyclic ring system composed of a bicyclo[2.2.2]octane moiety, a spiro-fused 3-piperidone, and a bridging azocane ring. These unique structural features present a significant challenge in any synthetic approach to the alkaloid.



lycopladine H (**1**)

We recently described some preliminary studies on a strategy directed toward a total synthesis of lycopladine H (**1**) based upon a key Diels–Alder cycloaddition of an *o*-quinone ketal with nitroethylene to form the bicyclo-[2.2.2]octane core suitably functionalized for eventual conversion to the alkaloid.[5] In this paper we now report the development of an approach to annulation of the azocane moiety onto a bicyclo[2.2.2]octane scaffold using intramolecular hydroaminomethylation methodology.

Intramolecular hydroaminomethylation of ω-amino alkenes is an attractive method for constructing

(1) Bödeker, K. *Justus Liebigs Ann. Chem.* **1881**, *208*, 363.
(2) Hirasawa, Y.; Kobayashi, J.; Morita, H. *Heterocycles* **2009**, *77*, 679.
(3) Ishiuchi, K.; Kubota, T.; Hayashi, T.; Shibata, S.; Kobayashi, J. *Tetrahedron Lett.* **2009**, *50*, 6534.
(4) Other lycopladines are known but have different skeletons than lycopladine H: (a) Ishiuchi, K.; Kubota, T.; Morita, H.; Kobayashi, J. *Tetrahedron Lett.* **2006**, *47*, 3287. (b) Ishiuchi, K.; Kubota, T.; Hoshino, T.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Bioorg. Med. Chem.* **2006**, *14*, 5995. (c) Kubota, T.; Yahata, H.; Ishiuchi, K.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Heterocycles* **2007**, *74*, 843. (d) Ishiuchi, K.; Kubota, T.; Hayashi, S.; Shibata, T.; Kobayashi, J. *Tetrahedron Lett.* **2009**, *50*, 4221.

(5) Sacher, J. R.; Weinreb, S. M. *Tetrahedron* **2011**, *67*, 10203.

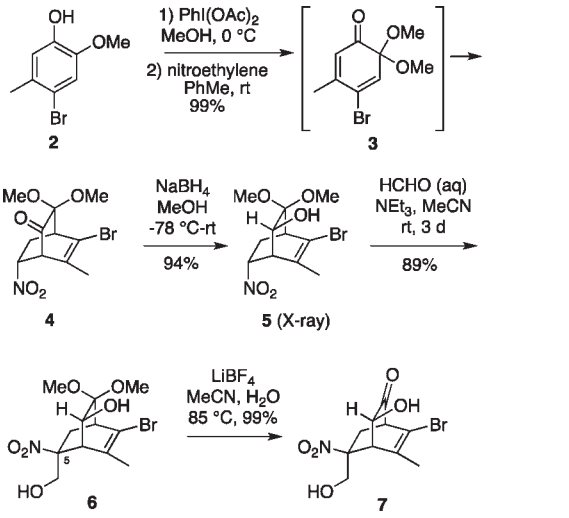
10.1021/ol3007277
Published on Web 04/09/2012

nitrogen-containing heterocycles owing to the often straightforward synthesis of the requisite precursors, as well as the use of inexpensive CO/H_2 (syngas) as a source of an inserted carbon.[6] Thus, transition-metal-catalyzed hydroformylation of the amino alkene, followed by *in situ* reductive amination, has been shown to be an efficient method to form cyclic amines of various ring systems. Although this transformation has primarily been used to produce pyrrolidines, piperidines, and azepines, there are also a few examples in the literature of the synthesis of medium-sized rings.[7] Indeed, one example exists of the formation of an azocane in moderate yield.[8] However, this powerful methodology has not yet been widely applied to complex molecule synthesis.

In order to test the feasibility of this annulation strategy, it was decided to synthesize the necessary precursor from the bicyclo[2.2.2]octane intermediate **4** which we have previously prepared.[5] This compound is readily available from phenol **2** via oxidation to *o*-quinone ketal **3**, followed by a high yielding Diels–Alder reaction with nitroethylene, a process that we had found is both regio- and stereoselective (Scheme 1).[9,10] Reduction of nitro ketone **4** with sodium borohydride proved to be completely stereoselective, affording nitro alcohol **5** in high yield. The structure and stereochemistry of this intermediate were confirmed by X-ray analysis (see Supporting Information). As was observed previously in related systems,[5] Henry reaction of nitro compound **5** with formaldehyde was totally *endo*-stereoselective, affording nitro diol **6** having the correct C-5 stereochemistry for the alkaloid **1**. After some experimentation, it was found that the ketal functionality of **6** could be cleaved to form α-hydroxy ketone **7** using lithium fluoroborate in wet acetonitrile in nearly quantitative yield.[11]

At this point, diol **7** was protected as the *bis*-diphenyl-*tert*-butylsilyl ether **8** (Scheme 2). The next stage of the synthesis was to add a vinyl group to ketone **8**. However, when reacted with vinylmagnesium bromide, ketone **8** rapidly decomposed, even at low temperatures, perhaps due to reaction of the organometallic reagent with the nitro group[12] or by enolization of the ketone. As organocerium reagents are known to be more compatible with enolizable

Scheme 1. Synthesis of α-Hydroxyketone **7**



carbonyl compounds than are Grignard or organolithium reagents,[13] we decided to try this variation for the addition of a vinyl group to ketone **8**. Therefore, the vinyl cerium reagent was preformed by adding vinylmagnesium bromide to anhydrous cerium chloride in THF at −78 °C. Owing to the instability of vinyl cerium reagents at temperatures above −78 °C, ketone **8** was then added slowly to the organometallic suspension at this temperature. These carefully controlled reaction conditions provided the allylic alcohol **9** in excellent yield as a single diastereomer having the required configuration at C-2. The structure and stereochemistry of this intermediate were confirmed by 2D NMR analysis. Finally, the nitro group of **9** was reduced with activated zinc dust[14] and HCl in aqueous isopropanol to produce the desired amino alkene substrate **10** needed for the hydroaminomethylation in excellent yield.

With the requisite amino alkene now in hand, we began to investigate the key intramolecular hydroaminomethylation step with the hope that formation of an eight-membered azocane ring would be facilitated by the conformational rigidity of the bicyclo[2.2.2]octane scaffold. Compound **10** was first subjected to reaction conditions similar to those developed by Beller et al. for intermolecular hydroaminomethylations.[15] Thus, the vinyl amine substrate was treated with $[Rh(cod)Cl]_2$ (with a slightly higher catalyst loading than used by Beller) and Xantphos as the phosphine ligand in a 1:1 mixture of toluene/methanol (with a lower substrate concentration than previously used in order to favor an intramolecular reaction) under a pressurized CO/H_2 atmosphere at 125–135 °C (Table 1, entry 1). Gratifyingly, the desired azocane **13** was isolated from this reaction in 28% yield,

(6) For reviews of hydroaminomethylation, see: (a) Eilbracht, P.; Bärfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329. (b) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (c) Crozet, D.; Urrutigoity, M.; Kalck, P. *ChemCatChem* **2011**, *3*, 1102.

(7) Bergmann, D. J.; Campi, E. M.; Jackson, W. R.; Patti, A. F.; Saylik, D. *Aust. J. Chem.* **2000**, *53*, 835.

(8) Kranemann, C. L.; Kitsos-Rzychon, B. E.; Eilbracht, P. *Tetrahedron* **1999**, *55*, 4721.

(9) For reviews of *o*-quinone ketals, see: (a) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383. (b) Pouysegu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235.

(10) See also: (a) Liao, C. C.; Wei, C.-P. *Tetrahedron Lett.* **1989**, *30*, 2255. (b) Lai, C.-H.; Shen, Y.-L.; Liao, C.-C. *Synlett* **1997**, 1351. (c) Liu, W.-C.; Liao, C.-C. *Synlett* **1998**, 912. (d) Lai, C.-H.; Shen, Y.-L.; Wang, M.-N.; Rao, N. S. K.; Liao, C.-C. *J. Org. Chem.* **2002**, *67*, 6493. (e) Chang, C.-P.; Chen, C.-H.; Chuang, G. J.; Liao, C.-C. *Tetrahedron Lett.* **2009**, *50*, 3414.

(11) Lipshutz, B. H.; Harvey, D. F. *Synth. Commun.* **1982**, *12*, 267.

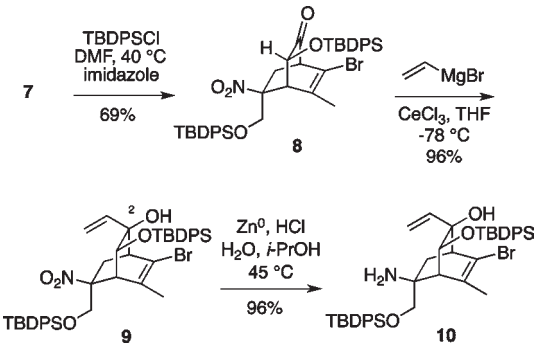
(12) Yost, Y.; Gutmann, H. R.; Muscoplat, C. C. *J. Chem. Soc. C* **1971**, 2119.

(13) For a review of organocerium reagents, see: Liu, H.-J.; Shia, K.-S.; Shang, X.; Zhu, B.-Y. *Tetrahedron* **1999**, *55*, 3803.

(14) Ferraz, H. M. C.; Longo, L. S. *J. Org. Chem.* **2007**, *72*, 2945.

(15) Ahmed, M.; Seayad, A. M.; Jackstell, R.; Beller, M. *J. Am. Chem. Soc.* **2003**, *125*, 10311.

Scheme 2. Synthesis of Hydroaminomethylation Precursor **10**



along with 41% of the corresponding *N*,*O*-acetal **14** (Scheme 3).

We believe that an initial hydroformylation of alkene **10** occurs to provide amino aldehyde **11**, which undergoes *in situ* intramolecular cyclodehydration to form eight-membered ring imine **12** (and/or the corresponding enamine). Rhodium-catalyzed hydrogenation of the imine/enamine then furnishes the desired azocane **13**, while nucleophilic addition of methanol to the imine produces *N*,*O*-acetal **14** (R = Me). Interestingly, this *N*,*O*-acetal is a single stereoisomer, but we have not determined its configuration. Although the addition of methanol to the imine in principle should be reversible, the *N*,*O*-acetal appears to be relatively stable under the reaction conditions. However, isolation of *N*,*O*-acetal **14** by chromatography, followed by reduction with sodium cyanoborohydride under acidic conditions, furnished the azocane **13** in 67% total yield.

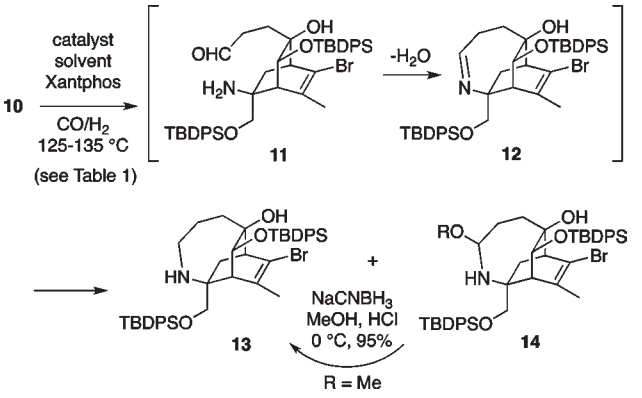
Although the two-step hydroformylation/sodium cyanoborohydride reduction sequence was serviceable, we sought to streamline this hydroaminomethylation reaction (Table 1). In comparison to the modified Beller conditions used initially (entry 1), the use of the aprotic solvents toluene or THF under the same conditions in the absence of an alcohol (entries 2 and 3) led to an increase in the isolated yield of the azocane **13**. However, neither single-solvent system produced a yield of the azocane **13** that approached the 67% yield benchmark from the aforementioned two-step process. Although it is not completely clear why the total yield of cyclization products is reduced here relative to the reaction run in toluene/methanol, Beller has noted that in intermolecular hydroaminomethylations using a secondary amine, hydrogenation of the intermediate enamine is slow in aprotic solvents.[16]

We therefore posited that use of the protic solvent trifluoroethanol (TFE) rather than methanol might improve the selectivity and yield for formation of the azocane **13** through both steric and electronic effects. The electron-withdrawing CF_3 group makes the alcohol a poor nucleophile and would allow for a more facile reversal of *N*,*O*-acetal formation due to the enhanced leaving-group ability

(16) See also: Wawrzyniak, J. A. F. P.; Roff, G. J.; Buhl, M.; Clarke, M. L. *Catal. Sci. Technol.* **2011**, *1*, 431.

(17) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

Scheme 3. Intramolecular Hydroaminomethylation of Vinyl Amine **10**



of TFE (pK_a = 12.5[17]). We expected that the increased steric bulk of TFE relative to methanol would further disfavor *N*,*O*-acetal formation. Additionally, we hoped that the increased acidity of TFE might even accelerate the hydrogenation of the imine/enamine by shifting the equilibrium toward the protonated iminium ion species, which should be more reactive toward hydrogenation.

Indeed, when TFE was employed as a cosolvent (entry 4), azocane **13** was formed in 59% isolated yield, with only 8% of *N*,*O*-acetal **14** (R = trifluoroethyl) observed in the ^{1}H NMR spectrum of the crude mixture. Use of hexafluoroisopropanol (HFIPA), an even less nucleophilic and more sterically encumbered protic solvent (entry 5, pK_a = 9.3[17]), furnished azocane **13** in 75% yield, with none of the corresponding *N*,*O*-acetal observed. When the purportedly more active catalyst $[Rh(cod)_2]BF_4$ (entry 6) was used in conjunction with HFIPA, the result was nearly identical to that observed with the more stable and less expensive $[Rh(cod)Cl]_2$ catalyst.

Table 1. Optimization of the Intramolecular Hydroaminomethylation of Vinyl Amine **10**

entry	catalyst[a]	solvent	azocane **13** (%)	*N*,*O*-acetal **14** (%)
1	$[Rh(cod)Cl]_2$	PhMe/MeOH	28	46
2	″	PhMe	46	–
3	″	THF	58	–
4	″	PhMe/TFE	59	8
5	″	PhMe/HFIPA	75	0
6	$[Rh(cod)_2]BF_4$	PhMe/HFIPA	71	0

[a] Catalyst loading: 1 mol % $[Rh(cod)Cl]_2$; 2 mol % $[Rh(cod)_2]BF_4$.

In conclusion, we have successfully tested a strategy for annulation of an azocane ring onto a preformed bicyclo[2.2.2]octane core utilizing an intramolecular hydroaminomethylation reaction. The substrate for this transformation, vinyl amine **10**, can be prepared stereoselectively in six steps in high overall yield from readily available Diels–Alder adduct **4**. The key intramolecular

hydroaminomethylation to produce an eight-membered azocane ring proceeds in good yield, probably due to the conformational rigidity imparted by the bicyclo-[2.2.2]octane nucleus. The application of hexafluoroisopropanol as a cosolvent in this type of reaction may also prove to be a useful general protocol in hydroaminomethylations. We are presently applying what we have learned from the research outlined here and in our previous work[5] to complete a total synthesis of lycopladine H (**1**).[18]

(18) The skeleton of this alkaloid was actually constructed prior to its isolation: Evans, D. A.; Scheerer, J. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 6038.

Acknowledgment. We are grateful to the National Science Foundation (CHE-1105653) for financial support of this research. We also wish to thank Dr. H. Yennawar (Penn State Small Molecule X-ray Cystallographic Facility) for the X-ray structure determination.

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

The authors declare no competing financial interest.