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Letter

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Synthesis of the Tetracyclic Skeleton of the *Lycopodium* Alkaloid Lycopladine H via a Pivotal Double Hydroformylation/Intramolecular Reductive Amination Sequence

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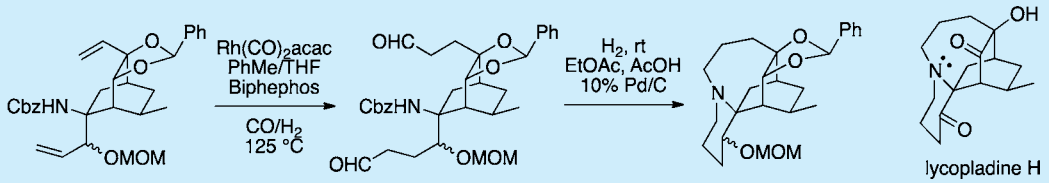
Supporting Information



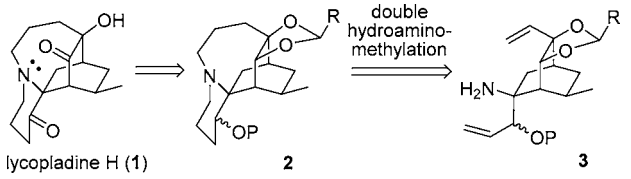
ABSTRACT: A synthesis of the complete tetracyclic framework of the structurally unique *Lycopodium* alkaloid lycopladine H has been accomplished using a strategy involving a double alkene hydroformylation/intramolecular reductive amination to form the azocane and spiro-piperidine moieties of the natural product.

The *Lycopodium* alkaloids are a large family of plant metabolites represented by a remarkably diverse array of structural motifs.[1] In 2009, Kobayashi and co-workers described the isolation of a new type of alkaloid within this class, lycopladine H (**1**), from the club moss *Lycopodium complanatum*.[2,3] This tetracyclic metabolite incorporates several novel architectural features including an azocane (azacyclooctane) and a 3-piperidone spiro-fused onto a bicyclo[2.2.2]-octane skeleton. In some preliminary studies, we have reported methodology for the formation of the bicyclo[2.2.2]octane core of the alkaloid using an approach based upon a Diels–Alder cycloaddition of an *o*-quinone ketal with nitroethylene.[4a,c,5] We have also explored methodology for annulating the azocane moiety of **1** onto a preformed bicyclo[2.2.2]octane scaffold utilizing an intramolecular version of a hydroaminomethylation reaction.[4b,c,6]

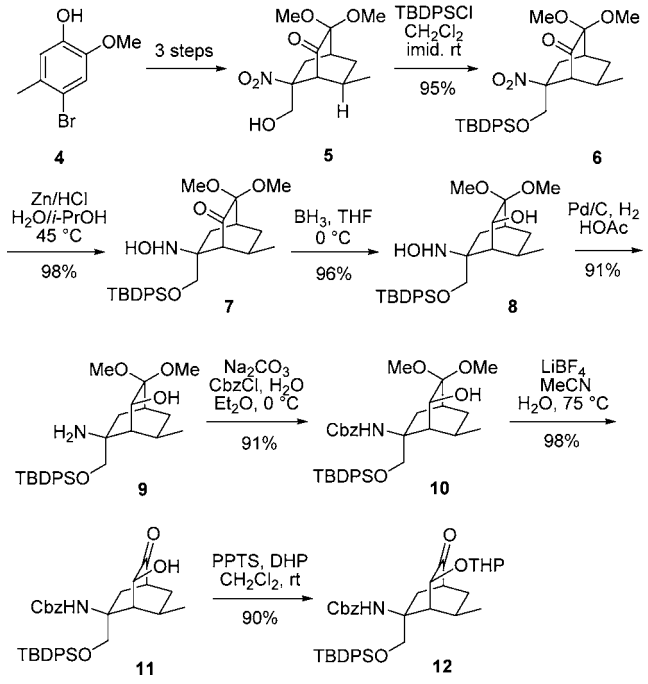
In this letter we now describe the synthesis of the complete skeleton of lycopladine H via a route which utilizes what was learned during these initial model studies.[7] Thus, the original plan was to form a tetracycle such as **2** via a double intramolecular hydroaminomethylation of a divinyl amine **3**, thereby constructing the azocane and spiro-piperidine rings of the natural product directly in a single operation (Scheme 1).[6]

We have previously described the synthesis of bicyclic keto alcohol **5** from phenol **4** in four steps (Scheme 2).[4a,c] This route has been modified, and we can now prepare intermediate **5** in only three steps from the phenol in high overall yield (see Supporting Information). A sequence was then developed to convert this intermediate into a hydroaminomethylation substrate similar to **3**. Therefore, the alcohol functionality of

Scheme 1. Retrosynthetic Analysis for Lycopladine H (1)



Scheme 2. Synthesis of Bicyclo[2.2.2]octanone Inermediate 12



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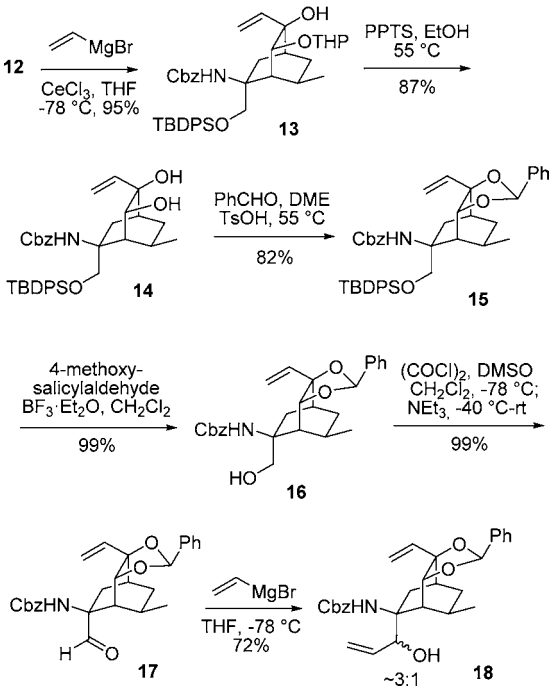
5 was first protected as the TBDPS ether **6**. A large number of methods were then investigated to reduce the nitro group of **6** to the corresponding amine, but inexplicably this transformation could not be effected. It was found, however, that the nitro group could be cleanly reduced to the hydroxylamine **7** using zinc metal/HCl, but further reduction to the amine could not be achieved. The carbonyl group of **7** was reduced stereoselectively with borane[8] to yield alcohol **8**, and at that stage the hydroxylamine functionality could be converted to the amine **9** by catalytic hydrogenation. This amine was protected as the Cbz-derivative **10**, and subsequent lithium fluoroborate-promoted[9] hydrolysis of the ketal led to α-hydroxy ketone **11**. After some experimentation it was found best to protect this compound as the THP ether **12** (1:1 mixture of diastereomers) for further transformations.

We were pleased to find that addition of vinylmagnesium bromide/$CeCl_3$ to ketone **12** was totally stereoselective, affording the desired allylic alcohol isomer **13** in high yield[10] (Scheme 3). Since the THP group proved to be incompatible

Scheme 3. Conversion of Ketone 12 to Divinyl Substrate 18

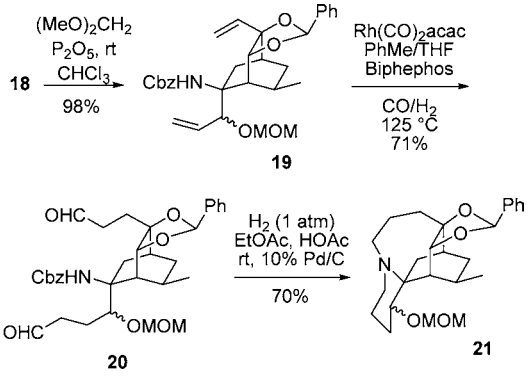


with some subsequent steps, it was removed with PPTS in ethanol to afford diol **14**, which was protected as the benzylidine acetal **15**.[11] This compound is a single stereoisomer whose configuration is assumed to be as shown.

In order to prepare for introduction of the second vinyl moiety, it was necessary to remove the silyl protecting group of intermediate **15**. This transformation proved to be more difficult than anticipated, since the common fluoride sources (i.e., TBAF, HF·pyridine, etc.) were not effective. It was finally discovered, however, that a reported mild method for generating HF using 4-methoxysalicylaldehyde/BF_3·etherate produced the desired alcohol **16** in excellent yield.[12] Swern oxidation of alcohol **16** then afforded aldehyde **17**, and addition of vinylmagnesium bromide yielded allylic alcohol **18** as an ~3:1 mixture of diastereomers that could be separated by chromatography for characterization purposes.

The mixture of alcohols **18** was next protected as the MOM ether **19** (Scheme 4).[13] Although it was possible to convert the

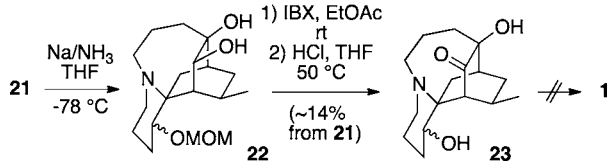
Scheme 4. Double Hydroformylation/Intramolecular Reductive Amination of Carbamate Bis-alkene 19



Cbz-carbamate **19** to the corresponding amine, it was found that effecting a one-pot double intramolecular hydroaminomethylation of this substrate, as was our initial plan (cf. Scheme 1), did not work satisfactorily.[14] It therefore became necessary to modify the strategy, and it was discovered that simply reversing the last two steps easily solved the problem. Thus, carbamate bis-alkene **19** was first hydroformylated to produce dialdehyde **20**.[15] Subsequent exposure of this dialdehyde to hydrogenation conditions using 10% Pd/C catalyst in a mixture of ethyl acetate/acetic acid resulted in removal of the Cbz group, followed by an *in situ* double reductive amination to afford the desired tetracycle **21**.

With advanced tetracyclic intermediate **21** in hand, a number of attempts were made to convert this compound into the natural product (Scheme 5). For example, it was possible to

Scheme 5. Attempts to Convert Tetracycle 21 to Lycopladine H (1)



remove the benzylidine group of **21** to produce diol **22** via a dissolving metal reduction. Oxidation of this intermediate with IBX then led to the desired α-hydroxy ketone, which upon MOM removal gave amino diol **23** (yields unoptimized). However, all attempts to oxidize **23** to the alkaloid failed using a variety of oxidants such as IBX, Jones reagent, PCC, TPAP, etc., in most cases leading only to decomposition.[16]

In conclusion, synthesis of the framework of the structurally unique *Lycopodium* alkaloid lycopladine H (**1**) has been achieved in 19 steps from phenol **4** using a strategy involving a novel double alkene hydroformylation/intramolecular reductive amination to form the azocane and spiro-piperidine moieties of the natural product in the form of advanced tetracyclic intermediate **21**. Disappointingly, we have been unable to convert this compound into the natural product.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures for preparation of new compounds including spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(2) Ishiuchi, K.; Kubota, T.; Hayashi, T.; Shibata, S.; Kobayashi, J. *Tetrahedron Lett.* **2009**, *50*, 6534.

(3) Other alkaloids have been named "lycopladines," but all have skeletons very different from **1**: (a) Ishiuchi, K.; Kubota, T.; Morita, M.; 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.

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(6) For reviews of hydroaminomethylation reactions, 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) Prior to the isolation of lycopladine H (**1**), a similar tetracyclic skeleton was constructed via a multistep process: Evans, D. A.; Scheerer, J. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 6038.

(8) Other reducing reagents such as $NaBH_4$, $LiAlH_4$, Dibal-H, or SmI_2 led to either decomposition or no reaction.[4d]

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

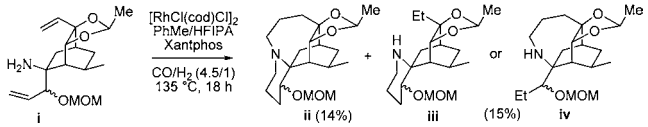
(10) Direct addition of the same vinyl Grignard/$CeCl_3$ reagent to α-hydroxy ketone **11** gave a mixture of epimeric adducts.

(11) Other diol protection was also examined, including an ethylidine acetal, which proved difficult to remove, and a cyclic carbonate, which was found to be too labile for our purposes.[4d]

(12) Mabic, S.; Lepoittevin, J.-P. *Synlett* **1994**, 851.

(13) Fuji, K.; Nakano, S.; Fujita, E. *Synthesis* **1975**, 276.

(14) For example, attempted intramolecular hydroaminomethylation of related ethylidine acetal-protected substrate **i** using reaction conditions that we previously reported[4b] led to only a poor yield of the desired tetracycle **ii** along with a small amount of a second, partially reduced compound which was either **iii** or **iv**. All attempts to improve the yield of **ii** by modifying the experimental conditions failed.[4d]



(15) Related double hydroformylation processes have been reported in simpler systems: (a) Ojima, I.; Iula, D. M.; Tzamarioudaki, M. *Tetrahedron Lett.* **1998**, *39*, 4599. (b) Airiau, E.; Spangenberg, T.; Girard, N.; Breit, B.; Mann, A. *Org. Lett.* **2010**, *12*, 528.

(16) Due to the small amounts of material available and difficulties in purification, the compounds in Scheme 5 were not fully characterized.

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