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Toward a Unified Approach for the Lycopodines: Synthesis of 10-Hydroxylycopodine, Deacetylpaniculine, and Paniculine

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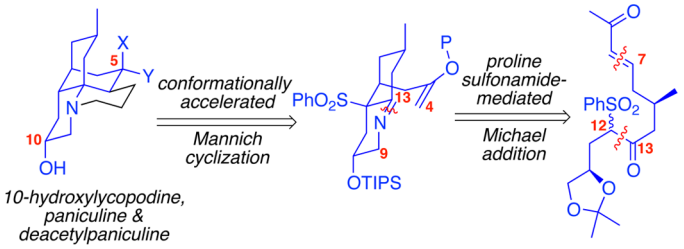
ABSTRACT



The enantioselective syntheses of 10-hydroxylycopodine, deacetylpaniculine, and paniculine have been accomplished through use of a common intermediate. Key steps in the synthetic sequence toward these *lycopodium* alkaloids include formation of the tricyclic core via a conformationally accelerated, intramolecular Mannich cyclization and an organocatalyzed, intramolecular Michael addition to form the C_7-C_{12} linkage.

The *lycopodium* alkaloids represent a sizable collection of natural products with wide-ranging and significant biological activity, consisting of over 200 known compounds from four subfamilies (the lycopodines, lycodines, fawcettimines, and phlegmarines).[1] The lycopodine and lycodine subfamilies have attracted considerable attention from numerous laboratories[2] including our own.[3] Interestingly, despite these efforts, there are wide sections of the *lycopodium* alkaloids that remain unexplored (e.g., compounds **2**–**5** in Figure 1). Herein, we disclose the first total syntheses of three members of the lycopodine subfamily: 10-hydroxylycopodine (**2**),[4] deacetylpaniculine (**3**),[5] and paniculine (**4**).[5] These natural products **2**–**4** were isolated from a Chilean club moss *lycopodium confertum*.[4] In addition, compounds **3** and **4** were also isolated from *lycopodium paniculatum*.[4,5]

Our unified approach to the synthesis of natural products **2**–**4** is shown in Scheme 1. We planned to employ a common intermediate strategy using tricycle **7** which should be accessible from sulfone **6**. Sulfone **6** in turn could be constructed via a combination sulfone migration

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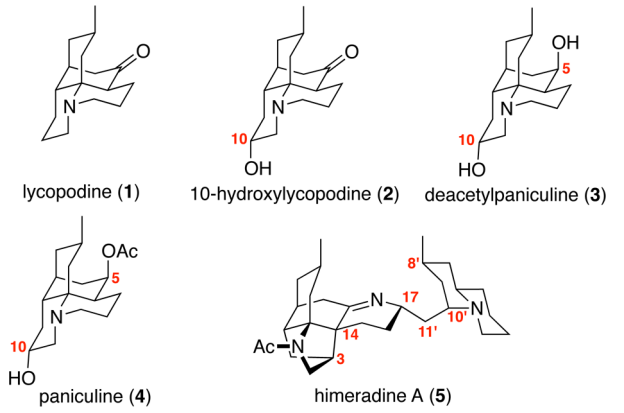
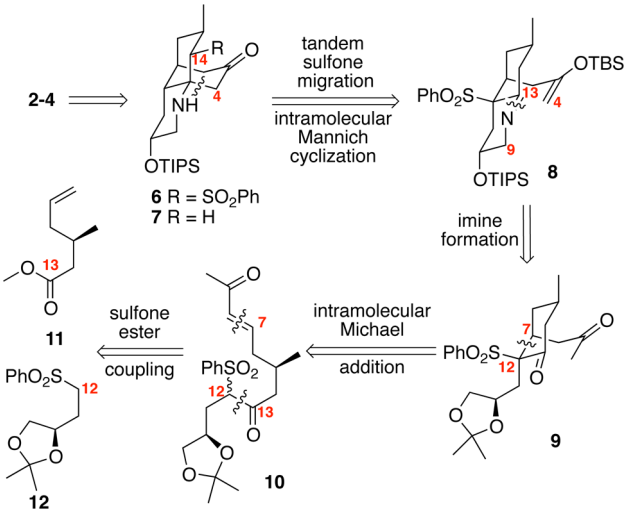


Figure 1. Lycopodine-type *Lycopodium* alkaloids.

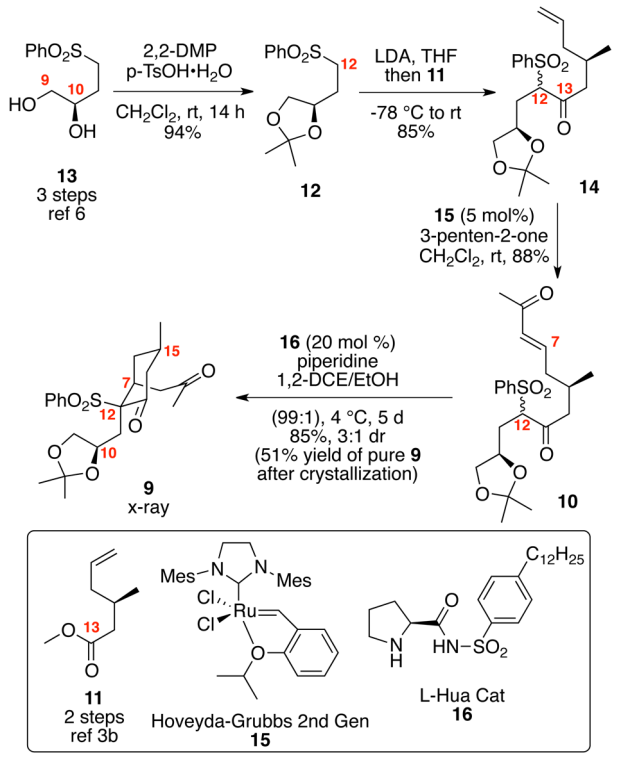
followed by intramolecular Mannich cyclization of imine **8**, a process first developed for our total synthesis of lycopodine (**1**).[3b,c] The imine **8** would be derived from keto sulfone **9**. The key C_7-C_{12} linkage could be accessed via a diastereoselective intramolecular Michael addition. The proposed strategy builds on our prior work in the total synthesis of **1**;[3b,c] however, the presence of the additional stereochemistry and functionality at C_{10} complicates the approach. While natural products **2**–**4** represent the only known *lycopodium* alkaloids containing oxygenation at the C_{10} position, this functionality could provide an important handle for accessing compounds possessing an additional C–C bond at this position (e.g., compound **5**).

We commenced our synthesis of the key cyclohexanone **9** with known diol **13**[6] (Scheme 2). Compound **13** is available in enantioenriched form in three steps from 1-bromo-3-butene via sulfone incorporation, epoxidation, and Jacobsen hydrolytic kinetic resolution.[7] Acetonide formation under standard conditions followed by sulfone ester coupling with ester **11**[3b,c] cleanly provided the coupled material **14**. Next, cross metathesis with 3-penten-2-one and Hoveyda–Grubbs second generation catalyst **15** produced the enone **10**. Intramolecular Michael

Scheme 1. Retrosynthetic Analysis



Scheme 2. Organocatalyzed Intramolecular Michael Reaction



addition of the keto sulfone **10** was smoothly facilitated by the acylsulfonamide catalyst **16** developed in our lab[3c,8] to provide cyclohexanone **9** in 85% yield and modest 3:1 diastereoselectivity (51% isolated yield of pure **9** after crystallization). The stereochemistry of **9** was conclusively established by X-ray crystallographic analysis. Addtion of 1% EtOH was key to this transformation, as its presence

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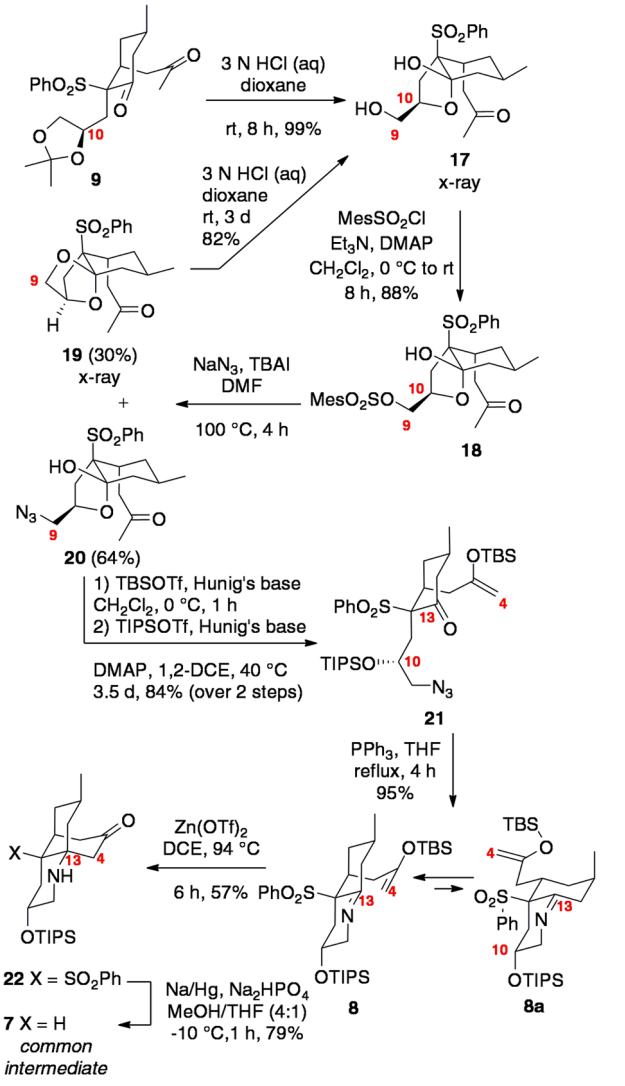
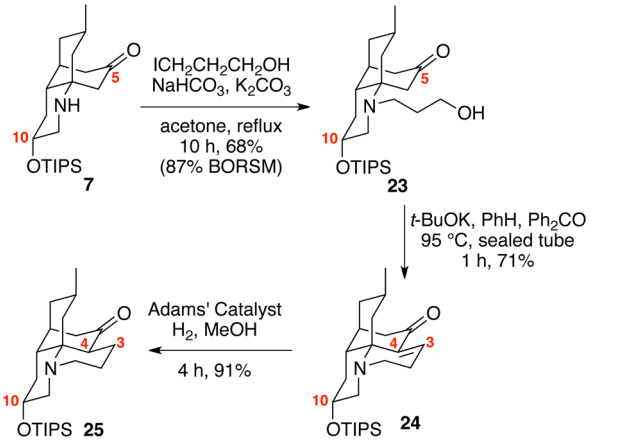
Scheme 3. Synthesis of the Common Intermediate



Scheme 4. Synthesis of the Tetracycle



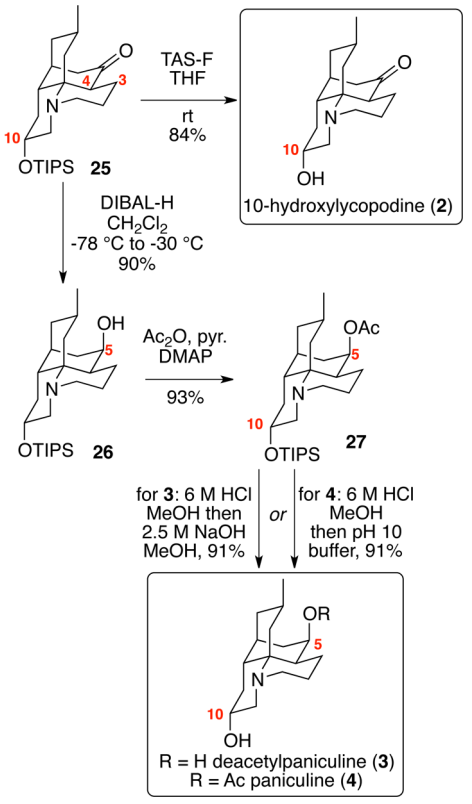
led to a noticeable acceleration in reaction rate. It should also be noted that, in the absence of catalyst **16** or the use of an alternate base, the conversion and diastereoselectivity were significantly reduced. In fact, use of our *i*-Pr_2NH, IPA/CH_2Cl_2 conditions (which worked smoothly in lycopodine synthesis[3b,c]) resulted in $<50\%$ conversion and low diastereoselectivity (1.5:1 dr). This divergence in reactivity is related to the presence of the additional functionality at C_{10} which likely counteracts the directing influence of the C_{15} methyl moiety.

With the functionalized cyclohexanone in hand, we turned our attention to the synthesis of the key common intermediate (Scheme 3). Acetonide deprotection was facilitated using aqueous HCl in dioxane to give the hemiketal **17**. Sulfonate activation at C_9 followed by azide displacement provided compound **20** along with the ketal **19**. We attribute the formation of **19** to the close conformational proximity of the C_{13} alcohol and the C_9 mesitylate. In fact, both mesitylate **18** and the azide **20** were prone to forming the ketal **19** upon prolonged storage. Compound **19** could easily be recycled by treatment with aqueous acid to reveal the hemiketal **17**. The hemiketal **20** was sequentially silylated with TBSOTf followed by TIPSOTf to reveal the ketone **21**. Aza-Wittig reaction provided the cyclization precursor **8**. Treatment with $Zn(OTf)_2$ provided the unexpected tricycle **22** in 57% yield. While compound **22** was a productive intermediate in the synthetic sequence, we had anticipated that the rearranged sulfone **6** would be the major product.[3b,c] We attribute this divergence in the expected and observed reactivity to the presence of the C_{10} stereocenter. This additional stereochemistry likely increases the conformational preference for conformer **8** over comformer **8a** (as compared to the C_{10} deoxy series) for placement of both the C_{12} sulfone and the C_7 side arm in the pseudoaxial positions. This conformationally accelerated intramolecular Mannich cyclization proceeded significantly faster than the C_{10} deoxy series, leading to preferential Mannich cyclization prior to sulfone rearrangement.[3b,c] The location of the sulfone moiety is inconsequential, as desulfurization using sodium/mercury amalgam provided the key common intermediate **7**.

The synthesis of the tetracyclic core for the *lycopodium* alkaloids is shown in Scheme 4. *N*-Alkylation using 3- iodopropanol provided the primary alcohol **23**. The reaction time for this alkylation appeared to be critical, as less than 10 h provided more recovered starting material and longer reaction times led to overalkylation. The tandem Oppenauer oxidation/intramolecular aldol condensation produced the desired enone **24** in 71% yield. The use of freshly prepared potassium *tert*-butoxide and freshly distilled benzene were necessary to achieve a reproducibly high yield in this transformation. A small amount of the retro-Michael product **7** (17%) was also isolated in this reaction. Hydrogenation using Adams' catalyst in methanol cleanly yielded the desired product **25**.[2u,w]

With the tetracycle in hand, we shifted our attention to the completion of the total syntheses of 10-hydroxylycopodine (**2**), deacetylpaniculine (**3**), and paniculine (**4**) (Scheme 5). TAS-F removal of the TIPS protecting group cleanly provided 10-hydroxylycopodine (**2**). DIBAL-H reduction of ketone **25** cleanly proceeded to provide the

Scheme 5. Total Syntheses of 10-Hydroxylycopodine, Deacetylpaniculine, and Paniculine



axial alcohol as a single stereoisomer.[9] Acylation using Ac_2O and pyridine in the presence of DMAP yielded the C_5 acetate. Cleavage of the C_{10} TIPS ether was best accomplished using aqueous HCl to produce the des-silyl product as its HCl salt. Treatment with pH 10 buffer provided paniculine (**4**), and treatment with aqueous sodium hydroxide yielded deacetylpaniculine (**3**).

One important aspect of this work is the clarification of the structural assignments and spectral data for this subfamily of natural products. For example, optical rotation data for these natural products were not provided in the isolation papers.[4,5] Our synthetic material provides a reference for future isolation chemists to confirm the absolute configuration by comparison to our reported synthetic data. We hypothesize that the absolute stereochemistry should be assigned based on analogy to other *lycopodium* alkaloids (e.g., **1**) for which we have confirmed synthetically.[3b,c] For **2**, the isolation paper only provided limited spectroscopic data for comparison.[4] From what data were provided, our synthesized material was in good agreement with the natural product. To garner additional confirmation of the original structural assignment of 10-hydroxylycopodine (**2**), we sought to link **2** with other *lycopodium* alkaloids isolated from the same plant. Synthesis of related members of this family (**3** and **4**) showed excellent agreement between the synthesized material and the literature data.[5] For **3**, the isolation paper[5e] provided a tabular listing of the spectral data which shows both H_{1eq} and H_{14eq} as doublets of doublets at 2.61 ppm; however, careful analysis of actual ^1H NMR spectra provided by the isolation chemists revealed that these data were tabulated incorrectly in the isolation paper.

The first total syntheses of three related members of the lycopodine subfamily have been accomplished. Key aspects to this work include the development of an acylsulfonamide-mediated intramolecular Michael reaction to incorporate the C_7 and C_{12} stereocenters, a conformationally accelerated intramolecular Mannich cyclization to construct the tricyclic core, and development of a common intermediate **7** that should provide access to additional members of this family of alkaloids.

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Supporting Information Available. Complete experimental procedures are provided, including ^1H and ^{13}C spectra of all new compounds. X-ray crystallographic data (CIF) for **9**, **17** and **19** are also provided. This material is available free of charge via the Internet at http://pubs.acs.org.

(9) It was imperative that this reaction be quenched with saturated aqueous Rochelle's salt for an extended period to fully break up the aluminium complex. We attribute this reactivity to the presence of the neighbouring basic nitrogen. In support of this hypothesis, this product **26** readily forms the DCl salt upon standing in $CDCl_3$.

The authors declare no competing financial interest.