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Enantioselective Total Synthesis of Lycopodine

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The *lycopodium* family of alkaloids has garnered considerable attention over the years because of their wide-ranging biological activity and structural complexity.[1] The parent member of this family, lycopodine (**1**), was isolated 125 years ago by Bödeker (Figure 1).[2] Beneficial medicinal properties, such as antipyretic[3] and anticholinesterase activity,[4] have been attributed to lycopodine and other *lycopodium* alkaloids. To date, seven racemic total syntheses and two racemic formal syntheses of **1** have been reported.[5] Herein, we report the first enantioselective total synthesis of **1**. Our retrosynthetic strategy is shown in Figure 1. Key to this strategy is the diastereoselective intramolecular Michael addition of **4** and the Heathcock-inspired[5d] Mannich cyclization to form tricycle **2**.

The synthesis commenced with the known ester **6**,[6] which is readily accessible in two steps from commercially available acyl sultam **5** (Scheme 1). Next, one-pot treatment of commercially available 1,4-dibromobutane (**7**) with $NaSO_2Ph$ in DMF followed by NaN_3 and H_2O generated the sulfone **8** in reasonable yield. Double deprotonation of **8** with lithium tetramethylpiperidide (LiTMP) followed by addition of the chiral ester **6** yielded keto sulfone **9** in 74% yield. It should be noted that use of lithium diisopropylamide or *n*-BuLi resulted in a significant reduction in the yield of this transformation. We have previously observed the superior performance of LiTMP during our synthetic efforts toward the bisspiroketal azaspiracid-1.[7] Next, we turned our attention to the cross metathesis of **9** and 3-penten-2-one (**10**). The presence of the azide moiety as well as an internal nucleophile (the C_8 keto sulfone moiety) and Michael acceptor (the C_5–C_7 enone) within product **4** imparted unique challenges for the cross metathesis. We were gratified to find that use of the highly active second-generation Grubbs–Hoveyda (GH-II) catalyst[8] did generate the desired product **4** in good yield (63%, 88% on the basis of recovered starting material). Also key to this metathesis was the specific choice of the enone **10**.[9] Replacement of **10** with methyl vinyl ketone led to a significant reduction in the efficiency of the transformation.

Our attention then turned to the key intramolecular Michael addition of keto sulfone **4** (Scheme 2). We had initially hypothesized that the C_{15} stereogenic center would disrupt the desired stereochemical outcome at the C_7 and C_8 positions by placing the larger phenyl sulfone and methyl ketone in pseudoequatorial positions in the transition state **11** shown. Consequently, our strategy had intended to explore a suitable organocatalyst for facilitating this reaction while overriding what we perceived to be the favored pathway. Prior to embarking on this investigation, we felt it would be prudent to confirm the inherent stereochemical preference in the system. Treatment of keto sulfone **4** with *i*-Pr_2NH in a mixed-solvent system (4:1 *i*-PrOH/dichloromethane) at room temperature led to clean conversion to a single product that crystallized out of the reaction in 89% yield. Interestingly, X-ray crystallographic analysis

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Supporting Information Available: Complete experimental procedures, including ^1H and ^{13}C spectra, for all of the new compounds, and crystallographic data and CIF files for **3** and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

revealed that the *desired stereochemical outcome* **3** had instead been observed. One possible explanation for this fortuitous diastereoselectivity may be a 1,2-steric interaction between the large substituents at C_7 and C_8 that forces them to adopt a pseudoaxial conformation in the transition state, a feature that would disfavor transition state **11**. Conversion of the methyl ketone **3** into the Mannich cyclization precursor **14** was accomplished in one pot via Staudinger reduction followed by *tert*-butyldimethylsilyl (TBS) enol ether formation.

We next turned to the key Mannich cyclization step (Scheme 3). To this end, treatment of silyl enol ether **14** with $Zn(OTf)_2$(96 °C, $ClCH_2CH_2Cl$, 16 h) generated a new compound. One might have expected product **2** to be formed; however, X-ray crystallographic analysis established that the rearranged tricycle **19** had been constructed. Product **19** was the result of a net 1,3-rearrangement of the sulfone moiety from the expected C_8 position to the C_{14} position. While a limited number of examples of 1,3-rearrangements of allylic sulfones have appeared in the literature,[10] we believe this result is the first example of an R-sulfonyl imine undergoing such a shift. This rearrangement likely occurs via initial complexation of the imine nitrogen followed by imine/enamine interconversion to form intermediate **16**. Next, the 1,3-transposition of the sulfonyl moiety might occur via either heterolytic cleavage of the C–S bond to a tight ion pair[11] or homolytic cleavage followed by recombination at C_{14} to produce the axial sulfone **17**. An alternate mechanism would invoke a 2,3-sigmatropic rearrangement to the sulfinate ester followed by reorganization to the sulfone **18**.[12,13] Subsequent conversion to the $C_{13,14}$ enamine followed by reprotonation would generate the penultimate intermediate **18**. Final Mannich cyclization would yield the tricycle **19**. Presumably, this net 1,3-shift of the phenyl sulfone moiety generates a more reactive intermediate for the key Mannich cyclization. Completion of a formal synthesis of lycopodine was accomplished by desulfurization using Na/Hg amalgam in good yield to give the known tricycle **20**.[5e] Attempts to follow Schumann's outlined route for alkylation of **20** with 3-bromopropan-1-ol gave disappointing results.[5e] Fortunately, alkylation with the 3-iodo variant proved effective (68% yield over 2 steps). The final cyclization was performed using a slight modification of Heathcock's original conditions [*t*-BuOK (6 equiv), Ph_2CO (18 equiv), PhH, 110 °C, sealed tube, 50 min].[5d] These improved conditions suppressed a retro-Michael pathway that competitively produced the tricycle **20**. Finally, reduction using Stryker's reagent[14] yielded **1**, which matched the reported spectral data.[5f,15] Importantly, comparison of the optical rotation {$[\alpha]_D = -23.2°$ (*c* = 0.22, 100% EtOH)} with the literature value[16] {$[\alpha]_D = -24.5°$ (*c* = 1.10, 100% EtOH)} allowed us to confirm the assigned absolute configuration of **1**.

In conclusion, we have completed the first enantioselective total synthesis of lycopodine. This approach should open the door to accessing other *lycopodium* alkaloids. Further synthetic studies will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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9. We purchased **10** (70% pure) from Aldrich Flavors and Fragrances (Aldrich cat. no. W341703, 25 g, $92). The impurity (mesityl oxide) did not affect the performance of the cross metathesis. Alternate sources of **10** were significantly higher in cost and less pure.

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11. The heterolytic cleavage would appear unlikely given the tethered nucleophile in the form of the silyl enol ether.

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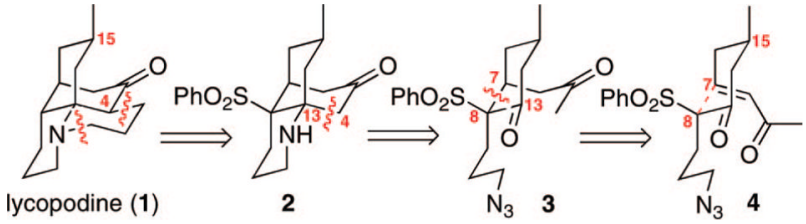
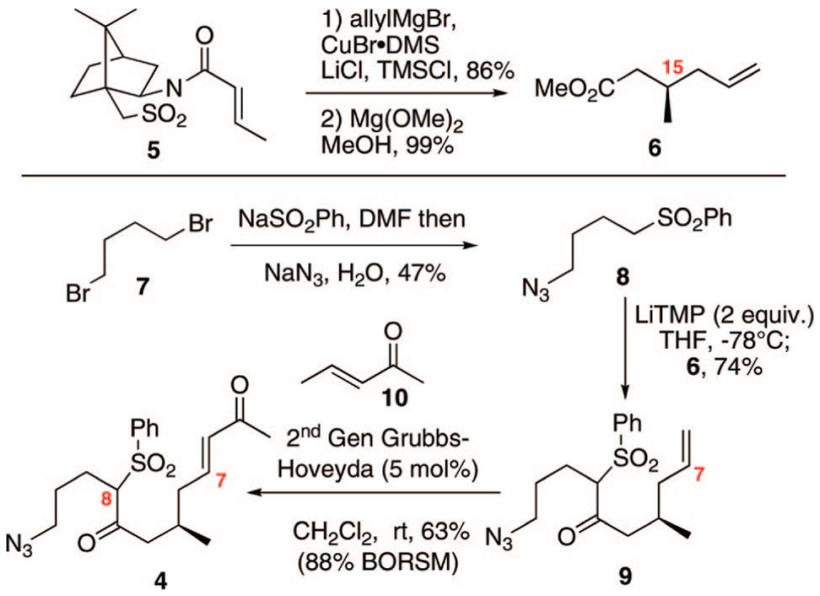
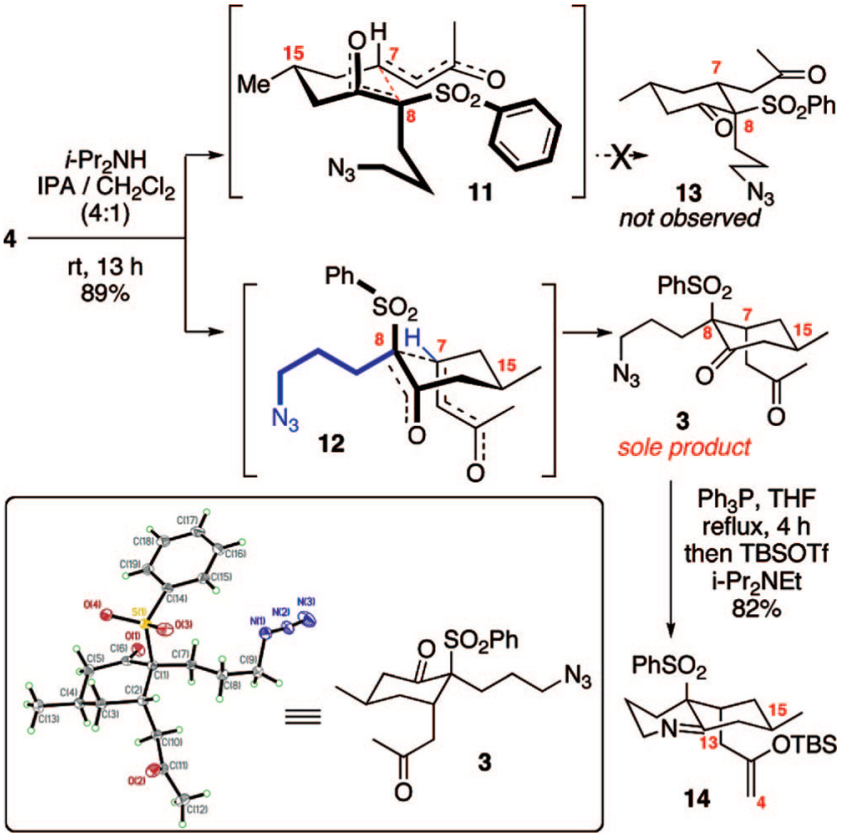


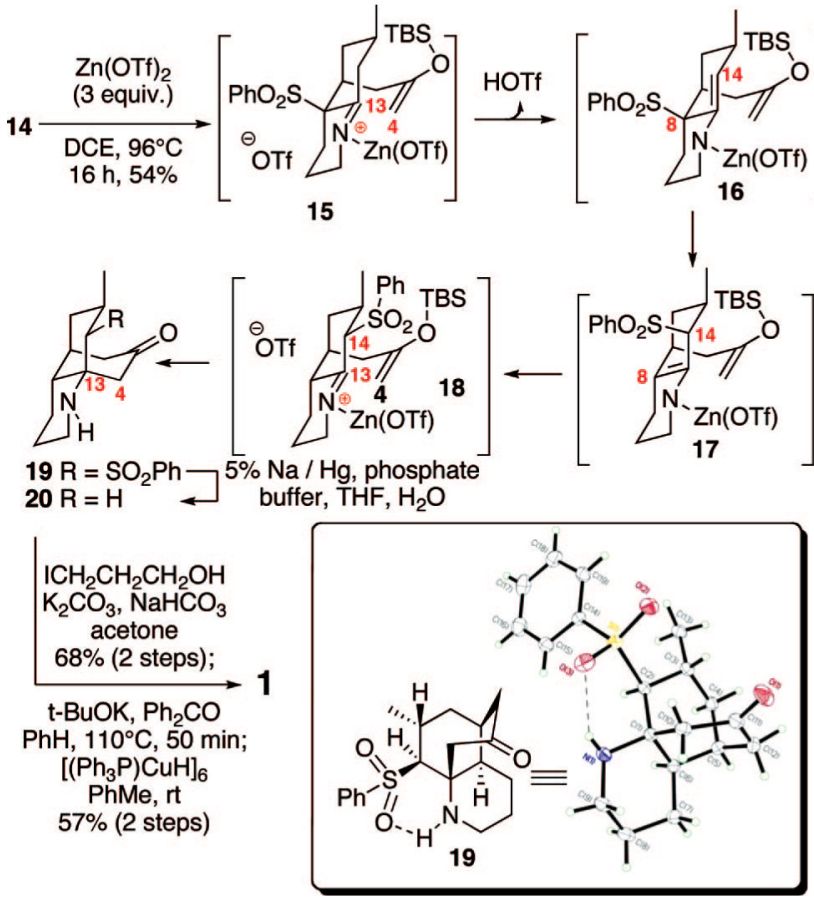
Figure 1.
Retrosynthetic strategy for lycopodine.



Scheme 1.
Synthesis of the Keto Sulfone Subunit



Scheme 2.
Diastereoselective Intramolecular Michael Addition and ORTEP Representation of Keto Sulfone **3**



Scheme 3.
Total Synthesis of Lycopodine