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Development of an Enantioselective Route towards the *Lycopodium* Alkaloids: Total Synthesis of Lycopodine

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Abstract

Synthesis of a C_{15}-desmethyl tricycle core of lycopodine has been accomplished. Key steps in the synthetic sequence include organocatalytic, intramolecular Michael addition of a keto sulfone and a tandem 1,3-sulfonyl shift / Mannich cyclization to construct the tricyclic core ring system. Synthetic work towards this natural product family led to the development of *N*-(*p*-dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide – an organocatalyst which facilitiates enantioselective, intramolecular Michael additions. A detailed mechanistic discussion is provided for both the intramolecular Michael addition and the sulfone rearrangement. Finally, the application of these discoveries to the enantioselective total synthesis of alkaloid lycopodine is described.

INTRODUCTION

The *lycopodium* alkaloids have garnered considerable attention over the years due to their wide-ranging biological activity and structural complexity.[1] There are four major sub-classes of *lycopodium* alkaloids shown in Figure 1 – as defined by Gang:[1b] lycopodine (**1**), lycodine (**2**), fawcettimine (**3**) and phlegmarine (**4**). Lycopodine (**1**), was isolated 125 years ago by Bödeker.[2] Over 50 years later, Achmatowicz and Uzieblo assigned the correct molecular formula to lycopodine as well as identified two additional alkaloids present in *Lycopodium clavatum L*. – clavatine and clavatoxine.[3] The final structure and stereochemistry was determined by Ayer and Iverach in 1962.[4] The absolute configuration was later established by Rodgers and Haque.[5] Beneficial medicinal properties such as antipyretic[6] and anticholinesterase activity[7] have been attributed to lycopodine (**1**) and other lycopodium alkaloids. Chinese folk medicine has historically used species of the *lycopodium* (s. l.), (club mosses) for the treatment of muscle bruising, strains and swelling as well as schizophrenia.[1] Recently, additional excitement has been generated by the revelation that these alkaloids have positive effects for learning and memory.[1]

In 2008, our laboratory reported a preliminary account of the enantioselective total synthesis of lycopodine (**1**).[8] Prior to our work, seven racemic total syntheses (two formal racemic syntheses) of **1** had been reported.[9] The Evans laboratory recently reported an elegant total synthesis of a similar alkaloid ring system (clavolonine).[10] Additionally, numerous other total syntheses of structural different *lycopodium* alkaloids have been reported over the past decade by Bosch,[11] Chang,[12] Comins,[13] Dake,[14] Johnston,[15] Liao,[16] Mukai,[17] Overman,[18] Sarpong,[19] Siegel,[20] Toste,[21] Takahashi[22] and Takayama.[23] Herein, we disclose a full account of our work towards the alkaloid lycopodine.

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Supporting Information. Complete experimental procedures are provided, including ^{1}H and ^{13}C spectra, of all new compounds. X-ray crystallographic data for compounds **7a, 25, 37** and **49** are also provided. This material is available free of charge via the Internet at http://pubs.acs.org.

RESULTS AND DISCUSSION

Our synthetic approach to the lycopodine subclass is shown in Scheme 1. Our first major disconnection was an intramolecular Mannich cyclization to form the tricyclic core **5**. Prior work by both Heathcock[9d] and Schumann[9e] has exploited a related cyclization strategy. In Heathcock's work, they noted that the key Mannich cyclization step required extended reaction times in most cases.[9d] We hypothesized that the placement of an α-sulfonyl moiety at C_8 should help to activate the imine to Mannich reaction – thereby speeding up the key cyclization step. The imine **6** should in turn be accessible from an organocatalyzed, intramolecular Michael addition of a keto sulfone moiety **8** which in turn would be available from a cross metathesis with alkene **9**.

Des-methyl Series

Key to this strategy was the successful execution of the intramolecular Michael addition / Mannich reaction sequence. As we were unsure as to the controlling influence of the stereochemistry at C_{15}, we felt it was prudent to first explore a des-methyl keto sulfone series to test the validity of this concept (Scheme 2). One observation that became readily apparent to us was that the nature of R was critical to the stereochemical outcome of the transformation. If a small R group (R_S) was used such as H, one would expect the top pathway A to be favored.[24] In contrast, if a larger R group (R_L) was present, one would expect the diastereoselectivity to switch in the conjugate addition – based on the pioneering work by Stork.[25] Interestingly, the primary stereochemical difference between paths A and B resides in the placement of the ketone in either of the top or right-hand ring. An organocatalyzed protocol would appear to be ideally suited for this transformation; however, we are unaware of any direct examples for accomplishing this type of enantioselective reaction.[26] A somewhat related example by Jørgensen had been reported using β-keto sulfones in a tandem Michael / aldol organocatalyzed process.[27]

We first set out to probe the nature of the diastereoselectivity in the key intramolecular Michael addition reaction racemically (Scheme 3). The sulfone **18** was prepared in a one pot procedure from dibromide **17**. While this transformation could be conducted in two separate steps, the procedural ease and the low cost of starting materials made this one pot approach more advantageous. Initially, we employed a Julia coupling strategy followed by oxidation to access the desired keto sulfone **21**. This approach worked modestly well; however, aldehyde **19** was not commercially available and its volatility during preparation hindered its practicality. Ultimately, we found that the direct sulfone / ester coupling route proved more effective. The choice of base for the sulfone / ester coupling was key to the reaction yield; lithium tetra-methyl piperidine (LiTMP) provided significantly higher yields than LDA or n-BuLi. Our group has previously observed the divergent behavior of different lithium bases in Julia couplings.[28] The cross metathesis (CM) step between **21** and an enone (e.g. methyl vinyl ketone (MVK) or pentenone **22**) is also worthy of additional comment. This transformation is challenging due to the presence of an azide functionality (potential Staudinger reduction by phosphine ligands from the transition metal catalyst) and an internal nucleophile (keto sulfone) for the electrophilic enone formed in the reaction. Consequently, we screened a range of catalysts for this transformation and CM partners. Both 1st and 2nd generation Grubbs catalysts were ineffective. Fortunately, 2nd generation Grubbs-Hoveyda proved useful in this transformation. We also discovered that the nature of the CM partner was also important.[29] Pentenone **22** proved more effective than MVK – generally leading to a 15-20% increase in chemical yield. One possible explanation is that the increased steric hinderance imparted by the β-methyl group on the enone **22** (as compared to MVK) reduced the rate of deleterious side reactions. For the key intramolecular Michael addition of **24**, we initially tested hydride (e.g. NaH, PhH) and alkoxide (e.g. Cs_2CO_3, EtOH) conditions as they had proven effective in prior intramolecular Michael additions with the desired relative

configuration by Stork[25] and Evans.[10] In both cases, we appeared to observe overreaction to provide a product derived from attack of the resultant methyl ketone (after conjugate addition) by an enolate at C_{14}. Even more disheartening, the cyclization occurred with the undesired $C_{7,8}$ *cis* relationship in the initial Michael addition. Fortunately, treatment of the keto sulfone **24** with diisopropylamine [IPA / CH_2Cl_2 (1:1), rt, 76 h, 84%] cleanly induced Michael addition to generate the desired $C_{7,8}$ *trans* diastereomer *rac*-**25** (Table 1, Entry 1). The stereochemical outcome of this transformation was confirmed by X-ray crystallographic analysis. The nature of the enolate geometry is likely key in controlling the stereochemical outcome of the Michael addition.[10,25]

With a working route to a diastereoselective, intramolecular Michael addition, we moved on to the enantioselective variant of this transformation (Table 1). We hypothesized that optimum levels of enantioselectivity would be best obtained in non-polar, chlorinated solvents. We initially screened proline (**26**) but observed no reaction in $CHCl_3$ (Entry a). Sluggish reaction could be observed in more polar media (e.g. DMSO), but the level of enantioselectivity was minimal (<20 % ee). It should be noted that extensive attempts to use chiral HPLC to achieve chromatographic separation of the enantiomers of **25** in order to obtain the level of enantioselectivity from these reactions proved unsuccessful. Fortunately, chiral shift reagent $Eu(hfc)_3$ was able to provide meaningful separation for analysis by NMR.[30] With a valid method for ascertaining the ee of the reaction, we next screened the tetrazole catalyst **27**[31] which has also shown enhanced activity compared to proline (**24**) – particularly in $CHCl_3$. Interestingly, we again observed no reaction after 3 d at room temperature (Entry b). Ley and coworkers have recently shown that the addition of a stoichiometric secondary amine base can affect the rate and enantioselectivity.[32] We were gratified to find that addition of piperidine (Entry c) facilitated the desired transformation with a reasonable rate (16 h) – albeit with a modest enantioselectivity (33% ee). It is important to note that the background reaction (piperidine, $CHCl_3$, rt) gave no product formation – even after prolonged exposure to the reaction conditions. Use of $ClCH_2CH_2Cl$ as solvent led to a decrease in reaction rate but an increase in enantiomeric excess (Entry d). It turned out that the choice of $CHCl_3$ was quite fortuitous as 1% EtOH is typically added commercially as a stabilizing agent for this solvent. This additive turned out to be critical in our hands – use of 1% EtOH in $ClCH_2CH_2Cl$ gave a dramatic increase in rate and enantioselectivity (Entry e). We next explored the use of proline sulfonamides as potential organocatalysts. While these ligands have shown promise in certain organocatalyzed reactions,[33] they have proven problematic in facilitating Michael addition processes.[33c] We were gratified to find that these catalysts performed well in our hands – providing improved enantiomeric excess (e.e.) at room temperature (Entries f-h). While these sulfonamides **28**-**30** proved more soluble than the analogous tetrazole **27**, solubility at lower temperatures continued to be problematic. Other catalysts such as those developed by Jorgensen[27] and MacMillian[34] proved ineffective. We also screened diphenylprolinol[35] in this transformation without success. Ultimately, we found that the previously unknown sulfonamide derivative **31** gave greatly improved solubility properties and continued high levels of enantiomeric excess (entries i and j). This sulfonamide **31** is readily accessible from the commercially available *para*-dodecylsulfonylchloride (**32**)[36,37] and Cbz-protected proline **34** in 3 steps (Scheme 4). We have prepared over 100 millimoles of this catalyst **31** through this procedure. Our laboratory has gone on to show that this catalyst is effective at facilitating a range of transformations in high enantioselectivity.[38] Cooling the reaction to -20°C with 10 mol% catalyst loading gave the optimum results (Table 1, Entry j). The absolute configuration of keto sulfone **25** was conclusively established via X-ray crystallographic analysis.[39] Resubmission of the highly enantioenriched product **25** (88% ee) to conditions which provided reduced enantioselectivity (e.g. 10 mol % **31**, rt, 16 h) did not result in any erosion in enantioselectivity. This experiment indicates that the reaction is likely not

operating under reversible conditions. Please note that the product **25** from this reaction is enantiomeric to the natural series of lycopodine.

Application of this technology to the tricyclic core of lycopodine is shown in Scheme 5. Use of the enantiomeric catalyst *ent*-**31** gave comparable results (71% yield, 88% ee). A single recrystallization provided material *ent*-**25** that was enantiomerically pure (>95% ee, 60-65% yield). This series was required for the synthesis of the correct enantiomer of lycopodine. Subsequent Staudinger reduction with *in situ* imine generation followed by silyl enol ether formation provided the cyclization precursor **36**. Treatment of enol ether **36** with $Zn(OTf)_2$ cleanly generated a cyclization product which was ultimately established to be the rearranged tricyclic product **37** via X-ray crystallographic analysis (Figure 3).[40] Interestingly, none of the expected tricycle **37a** was observed under the reaction conditions. Product **37** is the result of a net 1,3-rearrangement of the sulfone moiety from the expected C_8 position to the C_{14} position. Padwa and several other researchers have reported limited examples of 1,3-rearrangements of allylic sulfones;[41] however, we believe this is the first example of an α-sulfonyl imine undergoing such a shift. A detailed discussion of a possible mechanistic explanation for this transformation is provided later in this manuscript.

We also briefly explored the scope of our novel organocatalyzed, intramolecular Michael reaction (Table 2). It is important to emphasize that this type of intramolecular, keto sulfone Michael addition has not been previously reported using organocatalysis prior to our work (Entry a). We were pleased to observe good tolerance of different moieties on the keto sulfone side arm. The level of diastereoselectivity in each case was excellent (20:1 dr). Additionally, reasonable enantioselectivities were observed (81-88% ee). Finally, the cyclization could be extended to the analogous 5-membered series (Entry e) with good success (58% yield, 84% ee).[42]

Application to Total Synthesis of Lycopodine

With the basis for the tricycle formation established, we sought to apply this approach to the total synthesis of lycopodine. Synthesis of the C_{15} methyl series is outlined in Scheme 6. The sulfone component **18** was dilithiated with LiTMP and the known ester **42**[43] was added to the solution to generate after workup the keto sulfone **44** in good yield (74%) as an inconsequential mixture of diastereomers at C_8. Cross metathesis using 2nd generation Grubbs-Hoveyda provided the desired enone **8**.[44]

We next set out to explore the key intramolecular keto sulfone Michael addition (Scheme 8). Initial inspection of the stereochemistry required in this cyclization would indicate that at least two substituents must be placed axial in a chair transition state. This observation leads to two possible chair transition states **45** and **46**, which would generate the desired stereochemistry. The immediate products from these two pathways would be interconvertable chair conformations of each other. We were concerned that a third chair transition state **47**, which places the maximum number of substituents in the equatorial position might prove to be the preferred reaction pathway. One possible destabilizing force in this third transition state would be disruptive 1,2-diequatorial steric interactions. While 1,2-diequitorial substitution on cyclohexanes is normally viewed as the thermodynamically more stable conformation, large substituents in both those positions can complicate the preferences.[45] An alternative explanation would invoke a stabilizing hydrogen bonding interaction between the methyl ketone and an enol derived from the keto sufone in transition state **45**. A similar stabilizing interaction does not appear to be accessible in alternative pathways **46** and **47**.

The cyclization of enone **8** is detailed in Scheme 8. In order to probe the exact nature of this cyclization, we first conducted the experiment using a simple (achiral) secondary catalyst –

diispropyl amine. This amine was selected in part due to the steric hinderance imparted by the two iso-propyl moieties attached to the nitrogen. We had previously utilized this system on the desmethyl series **24** (Scheme 3). We were gratified to discover that a single stereoisomer had arisen from these reaction conditions. Through X-ray crystallographic analysis, we were able to determine that the desired stereochemistry **7** from this transformation had been formed.[46] Interestingly, the chair conformation **7a** observed in the crystallographic analysis was the one that placed the sulfone and methyl ketone moieties in the axial position and the C_{15} methyl moiety in the equatorial position. This crystallographic data would appear to indicate that the 1,2-steric interaction between these two substituents is minimized in conformation **7a** as compared to chair conformation **7b**. Furthermore, this data would appear to support transition state **45** as the favored pathway.[47] The amine additive could participate in the transformation through one or more ways: (a) enamine formation with the keto sulfone moiety, (b) deprotonation of the keto sulfone to generate an enolate and / or (c) iminium ion activiation of the methyl ketone. While not depicted in Scheme 8, enamine formation might explain the high level of diastereoselectivity (*syn / anti* between C_7-C_8) through strong *E* selectivity in the enamine – likely due to steric hinderance of the isopropyl groups on nitrogen. Stork showed that enolate geometry is often correlated to *syn / anti* selectivity; although, it is important to note that Stork's cases required aprotic media to obtain good levels of diastereoselectivity.[25] If iminium ion activiation of the methyl ketone occurs, the increased steric bulk of the iminium ion would likely aid in favoring transition state **45**.

The completion of the total synthesis of lycopodine is detailed in in Scheme 9. Staudinger reduction and TBS enol ether formation generated the cyclization precursor **6**. As demonstrated in the desmethyl series, treatment with $Zn(OTf)_2$ in DCE at elevated temperatures in a sealed tube induced the tandem 1,3-sulfone rearrangement and intramolecular Mannich cyclization to yield amine **49**. [48] It should be noted that the C_{15} methyl series does require slightly higher reaction temperatures (96°C) to proceed effectively. Subsequent dessulfurization of tricycle **49** using Na / Hg amalgam provided the intermediate **50**. This amine **50** was converted into lycopodine (**1**) in three chemical transformations.[8] Comparison of the literature values for lycopodine (^{1}H, ^{13}C NMR, $[\alpha]_D$)[9f, 50,51] as well as an authentic sample provided by Professor Heathcock matched nicely with the synthesized material. Due to the basicity of lycopodine's nitrogen, care must be taken to remove any extraneous DCl present in the $CDCl_3$ (e.g. base washing solvent with basic alumina, avoiding exposure to light).

Probe of Mechanism for Tandem Sulfone Rearrangement / Mannich Cyclization

The mechanism for the key Mannich cyclization to form the tricyclic core of lycopodine is worthy of additional discussion. A possible explanation for this transformation is outlined in Scheme 10. After initial complexation of the imine nitrogen, complex **54** likely tautomerizes to metallo-enamine **55**. We believe that it is this intermediate which undergoes a net 1,3-transposition of the sulfonyl moiety to C_{14}. This rearrangement could occur via several possible pathways: (a) / (b) heterolytic cleavage of the C-S bond to a tight ion pair or homolytic cleavage followed by recombination at C_{14} to arise as the axial sulfone **56**, (c) 2,3-sigmatropic rearrangement to the sulfinate ester followed by reorganization to the sulfone **56**[54] or (d) formation of an intermediate 1,1-dioxothietane followed by ring opening. Diastereoselective protonation of the enamine and epimerzation at C_{14} would generate the penultimate intermediate **57** which can undergo intramolecular Mannich cyclization to yield the tricycles **37** or **49**. This net 1,3-shift of the phenyl sulfone moiety may facilitate a more reactive intermediate for the key Mannich cyclization.

In order to probe what possible pathway is facilitating the net 1,3-transposition, we have conducted a series of experiments (Scheme 11). Exclusion of light from the reaction appears

to have no impact on the product formation (Eq. 1). Photolysis of the imino-sulfone **6** at room temperature does not appear to induce the 1,3-shift (Eq. 2). Most interestingly, submission of ketone **58** to the reaction conditions does not appear to lead to the formation of any new compounds (Eq. 3). This experiment seems to imply that the rearrangement is reversible and that the Mannich cyclization drives the reaction to completion. In order to probe a possible crossover process with a sulfonate anion, compound **6** was treated under the standard cyclization but in the presence of $NaSO_2$p-tol. Unfortunately, this experiment only led to complex mixture of products. Ion exchange with $Zn(OTf)_2$ likely generates a catalyst which is less effective at facilitating the transformation. Interestingly, when the reaction was performed under the standard conditions but in the presence of the radical initiator TEMPO, an alternate product was observed (Eq. 5). This product corresponds to the Mannich cyclization product **5** without 1,3-migration of the sulfone moiety. Conversion of **5** to tricycle **50** (Na / Hg, Na_2HPO_4, MeOH, THF, -10°C, 45%) provided additional evidence for the structural assignment. TEMPO appears to initiate a secondary reaction pathway for the cyclization. It should be noted that radical cyclizations involving imines have been documented.[55,56,57] Magnus utilized TEMPO and hypervalent iodine reagents to functionalize the allylic position of silyl enol ethers.[58] Renaud and Studer recently demonstrated the TEMPO-mediated oxidation of catecholboron enolates which is proposed to go through a radical intermediate.[59] As a complement to TEMPO experiment, a radical inhibitor was added to the standard cyclization conditions, but only complex mixture of products was obtained (Eq. 6).

CONCLUSION

The first enantioselective synthesis of lycopodine has been accomplished. Key steps include an organocatalyzed, intramolecular Michael addition of keto sulfone **8** and a tandem 1,3-sulfonyl shift / intramolecular Mannich reaction. Exploration of the mechanism for the tandem sulfonyl shift / Mannich sequence revealed an alternative reaction pathway which generated C_8-sulfonyl product **5**. Additionally, a novel proline-based sulfonamide organocatalyst **31** has been developed. The utility of catalyst **31** at facilitating enantioselective, intramolecular Michael additions has been demonstrated.

Experimental Section

Sulfonamide 33

To a solution of *p*-dodecylbenzenesulfonyl chloride (**32**) (48.7 g, 150 mmol) in $CHCl_3$ (1.5 L) was NH_4OH (313 mL, 78.9 g, 2.25 mol) at rt. After stirring vigorously for 4 h, the reaction mixture was extracted with $CHCl_3$ (2 × 300 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the product **33** (47.8 g, 147 mmol, 98%). Compound **33** is sold as a mixture of isomers on the $C_{12}H_{25}$ alkyl chain. No attempt was made to separate the isomers in this sequence and the isomeric mixture does not appear to adversely affect the reactivity. ^{1}H NMR (400 MHz, $CDCl_3$) 7.86-7.88 (m, 2H), 7.29-7.35 (m, 2H), 5.03 (s, 2H), 0.78-1.68 (m, 25H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 128.4, 127.8, 126.5, 47.9, 46.1, 40.0, 38.1, 36.7, 31.9, 29.7, 29.5, 29.2, 27.5, 22.7, 14.1.

Cbz sulfonamide 35

To a solution of *Z*-L-proline **34** (36.6 g, 147 mmol) in CH_2Cl_2 (735 mL) was added sulfonamide **33** (47.8 g, 147 mmol), DMAP (3.71 g, 30.4 mmol) and EDCI (28.2 g, 147 mmol) respectively. The reaction mixture was stirred at room temperature for 72 h before being partitioned between EtOAc (500 mL) and aq. HCl (200 mL, 1 N). The organic layer was washed with half-saturated brine (2 × 300 mL). The dried (Na_2SO_4) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10%

EtOAc/CH_2Cl_2, to give **35** (76.1 g, 137 mmol, 93%) as a colorless liquid. Compound **35** is sold as a mixture of isomers on the $C_{12}H_{25}$ alkyl chain. No attempt was made to separate the isomers in this sequence and the isomeric mixture does not appear to adversely affect the reactivity. $[\alpha]_D^{23}$ = +90° (c= 2.2, $CHCl_3$); IR (neat) 3148, 2955, 2925, 2856, 1720, 1677, 1449, 1411, 1355, 1174, 1131, 1088, 826, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 10.4 (br s, 1H), 7.93-7.95 (m, 2H), 7.26-7.40 (m, 7H), 5.23 (s, 2H), 4.31 (br s, 1H), 3.42 (m, 2H), 2.45-2.57 (m, 1H), 0.85-1.87 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 157.2, 135.9, 128.6, 128.4, 128.3, 128.1, 127.5, 68.1, 60.8, 47.2, 46.2, 38.8, 38.1, 36.6, 31.8, 29.6, 29.3, 27.5, 27.2, 26.7, 24.3, 22.7, 14.1; HRMS (EI+) calcd. for $C_{31}H_{45}N_2O_5S$ (M+1), 557.3049 found 557.3067.

Sulfonamide 31

To a solution of Z-L-sulfamide **35** (76.1 g, 137 mmol) in MeOH (685 mL) was added Pd/C (7.60 g, 10 %). The mixture was stirred at rt for under an atmosphere of hydrogen. After 24 h, the reaction was filtered through Celite and silica gel pad, and the filtrate was concentrated *in vacuo* to give white solid. The crude product was recrystalized from MeOH to give the product **35** (43.2 g, 102 mmol, 74%) as a white solid. Compound **31** is sold as a mixture of isomers on the $C_{12}H_{25}$ alkyl chain. No attempt was made to separate the isomers in this sequence and the isomeric mixture does not appear to adversely affect the reactivity. Mp: 184-186°C; $[\alpha]_D^{23}$ = +94° (c= 0.95, $CHCl_3$); IR (neat) 3135, 2955, 2920, 2852, 1626, 1458, 1372, 1308, 1144, 1084, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 8.73 (br s, 1H), 8.06 (br s, 1H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.22-7.26 (m, 2H), 4.33 (t, *J* = 8.0 Hz, 1H), 3.23-3.43 (m, 2H), 2.33-2.40 (m, 1H), 0.82-2.05 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 140.4, 127.8, 127.2, 126.4, 62.8, 47.8, 39.9, 38.2, 36.8, 31.9, 31.8, 30.1, 29.7, 29.6, 29.3, 29.2, 27.6, 27.2, 24.5, 22.7, 14.1; HRMS (EI+) calcd. for $C_{23}H_{39}N_2O_3S$ (M+1), 423.2681 found 423.2701.

Cyclohexanone 25

Racemic Protocol—To a solution of **24** (8.0 mg, 0.0212 mmol) in CH_2Cl_2 / Isopropanol (1:1, 0.2 mL) was added diisopropylamine (2.2 mg, 3.0 μL, 0.0212 mmol) at room temperature. After 76 h, the reaction was loaded directly onto silica gel and was purified by chromatography, eluting with 10-30% EtOAc / hexanes, to give the product cyclohexanone **25** (6.7 mg, 0.0178 mmol, 84%) as a white solid.

Enantioselective Protocol—To a solution of **24** (82.0 mg, 0.217 mmol) in EtOH/DCE (1:99, 1.1 mL) was added *ent*-sulfonamide **31** (9.2 mg, 0.0217 mmol) and piperidine (18.5 mg, 21 μL, 0.217 mmol) at -20°C. After stirring at same temperature for 72 h, the reaction was loaded directly onto silica gel and was purified by chromatography, eluting with 10-30% EtOAc / hexanes, to give the product cyclohexanone **25** (58 mg, 0.154 mmol, 71%, 88% ee) as a white solid. Mp 95-96°C; $[\alpha]_D^{23}$ = +101° (c=0.78, $CHCl_3$); IR (neat) 2925, 2099, 1716, 1699, 1445, 1355, 1303, 1140, 1088, 723, 688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82-7.84 (m, 2H), 7.69-7.72 (m, 1H), 7.56-7.60 (m, 2H), 3.48 (tq, *J* = 10.8, 2.0 Hz, 1H), 3.20-3.40 (m, 3H), 2.89 (dt, *J* = 15.2, 7.2 Hz, 1H), 2.53 (dd, *J* = 17.6, 10.8 Hz, 1H), 2.41 (dt, *J* = 15.2, 7.2 Hz, 1H), 2.26 (s, 3H), 1.85-2.18 (m, 5H), 1.57-1.69 (m, 2H), 1.38-1.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 205.8, 135.9, 134.3, 130.6, 128.8, 78.9, 51.5, 44.6, 39.4, 35.0, 30.5, 27.6, 27.1, 24.5, 21.5; HRMS (FAB+) calcd. for $C_{18}H_{24}N_3O_4S$ (M+H) 378.1488, found 378.1497.

Determination of the enantiomeric excess—Product **25** (3 mg) in C_6D_6 (0.55 ml) with 40 mol% (+) $Eu(hfc)_3$ (3.8 mg) at 400 MHz. ^1H NMR difference of α-methylene protons (doublet at 3.31 ppm) on C_6 for two enantiomers is 18.8 Hz. The enantiomeric excess can be obtained based on the calculation of ratio for two sets of doublets.

Cyclohexanone 39b

To a solution of **38b** (25 mg, 0.0812 mmol) in EtOH/DCE (1:99, 0.4 mL) was added sulfonamide **31** (3.4 mg, 0.00812 mmol) and piperidine (6.9 mg, 8 μL, 0.0812 mmol) at -20°C. After stirring at same temperature for 72 h, the reaction was loaded directly onto silica gel and was purified by chromatography, eluting with 10-30% EtOAc / hexanes, to give the product **39b** (20 mg, 0.0649 mmol, 80%, 82% ee) as colorless oil. $[\alpha]_D^{23}$ = +63.3° (c=1.3, $CHCl_3$); IR (neat) 2949, 2884, 1713, 1446, 1375, 1310, 1364, 1141, 1108, 1075, 972, 754, 721, 629 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.84-7.86 (m, 2H), 7.00-7.09 (m, 3H), 3.84-3.90 (m, 1H), 3.15 (dt, *J* = 14.4, 9.6 Hz, 1H), 2.87 (dd, *J* = 17.2, 3.2 Hz, 1H), 2.18-2.32 (m, 2H), 1.34-1.87 (m, 6H), 2.15 (s, 3H), 0.94-1.02 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 205.1, 204.2, 136.4, 133.5, 130.4, 128.4, 75.9, 44.7, 38.2, 34.8, 29.4, 26.0, 20.9, 15.2; HRMS (EI+) calcd. for $C_{16}H_{20}O_4S$ (M+) 308.1082, found 308.1078.

Cyclohexanone 39c

: To a solution of **38c** (35 mg, 0.077 mmol) in EtOH/DCE (1:99, 0.39 mL) was added sulfonamide **31** (3.3 mg, 0.0077 mmol) and piperidine (6.6 mg, 7.7 μL, 0.077 mmol) at -20°C. After stirring at same temperature for 5 days, the reaction was loaded directly onto silica gel and was purified by chromatography, eluting with 10-20% EtOAc / hexanes, to give the product **39c** (26.6 mg, 0.0588 mmol, 76%, 83% ee) as colorless oil. $[\alpha]_D^{23}$ = +35° (c=0.8, $CHCl_3$); IR (neat) 2922, 2851, 1718, 1364, 1299, 1255, 1075, 836, 716, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.2 Hz, 2H), 7.67 (t, *J* = 7.2 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 3.74 (t, *J* = 6.4 Hz, 1H), 3.46 (d, *J* = 17.6 Hz, 1H), 3.37 (t, *J* = 7.6 Hz, 1H), 2.45-2.72 (m, 4H), 2.18-2.32 (m, 5H), 1.74-1.96 (m, 3H), 1.40-1.50 (m, 1H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 205.4, 136.3, 134.0, 131.0, 128.6, 78.5, 59.3, 45.3, 39.6, 35.3, 32.9, 30.5, 29.7, 27.7, 25.9, 21.9, 18.3, -5.51; HRMS (ES+) calcd. for $C_{23}H_{36}O_5NaSSi$ (M+Na) 475.1950, found 475.1959.

Cyclohexanone 39d

To a solution of **38d** (32 mg, 0.0833 mmol) in EtOH/DCE (1:99, 0.4 mL) was added sulfonamide **31** (3.5 mg, 8.33 μmol) and piperidine (7.1 mg, 8.2 μL, 0.0833 mmol) at -20°C. After stirring at same temperature for 72 h, the reaction was loaded directly onto silica gel and was purified by chromatography, eluting with 10-30% EtOAc / hexanes, to give the product **39d** (28.6 mg, 0.0745 mmol, 89%, 81%ee) as colorless oil. $[\alpha]_D^{23}$ = +44.4° (c=1.1, $CHCl_3$); IR (neat) 2922, 1718, 1696, 1304, 1141, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57-7.84 (m, 5H), 7.14-7.29 (m, 5H), 3.63-3.77 (m, 3H), 3.20 (d, *J* = 13.6 Hz, 1H), 2.72 (dt, *J* = 15.6, 8.8 Hz, 1H), 2.58-2.65 (m, 1H), 2.18-2.26 (m, 4H), 1.72-1.81 (m, 1H), 1.53-1.61 (m, 1H), 1.41-1.49 (m, 1H), 0.56-0.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 206.2, 135.5, 135.2, 134.2, 131.2, 130.5, 128.68, 128.65, 127.5, 79.9, 45.6, 39.1, 35.7, 33.2, 30.3, 26.5, 19.3; HRMS (ES+) calcd. for $C_{22}H_{24}O_4SNa$ (M+) 407.1293, found 407.1288.

Cyclopentanone 39e

To a solution of **38e** (40 mg, 0.137 mmol) in EtOH/DCE (1:99, 0.68 mL) was added sulfonamide **31** (5.7 mg, 0.0137 mmol) and piperidine (11.6 mg, 13 μL, 0.137 mmol) at -20°C. After stirring at same temperature for 6 days, the reaction was loaded directly onto silica gel and was purified by chromatography, eluting with 10-30% EtOAc / hexanes, to give the product **39e** (23.2 mg, 0.0792 mmol, 58%, 84% ee) as colorless oil: $[\alpha]_D^{23}$ = -22° (c=0.3, $CHCl_3$); IR (neat) 2960, 2916, 2845, 1745, 1713, 1446, 1299, 1146, 1130, 1086, 759, 721, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57-7.86 (m, 5H), 3.49-3.56 (m, 1H), 3.08 (dd, *J* = 17.2, 2.0 Hz, 1H), 2.30-2.49 (m, 4H), 2.22 (s, 3H), 1.24-1.45 (m, 4H); ^{13}C NMR (100 MHz, CCl_3) δ 210.1, 206.0, 135.3, 134.3, 130.8, 128.8, 72.5, 44.9, 38.6, 36.3, 30.3, 25.6, 14.1; HRMS (ES+) calcd. for $C_{15}H_{18}O_4NaS$ (M+Na) 317.0824, found 317.0834.

Keto sulfone 44

To a stirred solution of **18** (2.52 g, 10.55 mmol) in THF (120 mL) at –78°C was added lithium 2,2,6,6-tetramethylpiperidine[60] (21.1 mL, 21.1 mmol, 1.0 M in THF) dropwise. After 5 min, a solution of **42** (3.00 g, 21.1 mmol) in pre-cooled THF (5 mL) was added via cannula to the sulfone solution. After stirring at -78 to -20°C for 90 min, the reaction was removed from the cooling bath, quenched with sat. aq. NH_4Cl (40 mL) and extracted with diethyl ether (3 × 50 mL). The dried (Na_2SO_4) extract was concentrated *in vacuo* and purified chromatography over silica gel, eluting with 5-20% EtOAc / hexanes, to give **44** (2.72 g, 7.79 mmol, 74%) as a colorless oil: IR: (neat) 2959, 2929, 2873, 2095, 1712, 1449, 1320, 1153, 1084, 912, 748, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, two diastereomers) δ 7.80-7.82 (m, 2H), 7.71-7.75 (m, 1H), 7.59-7.61 (m, 2H), 5.73-5.79 (m, 1H), 5.03-5.08 (m, 2H), 4.11-4.16 (m, 1H), 3.26-3.30 (m, 2H), 2.93 (dd, *J* = 18.4, 5.2 Hz, 1H), 2.62-2.80 (m, 1H), 2.48 (dd, *J* = 18.4, 7.2 Hz, 1H), 1.87-2.15 (m, 5H), 1.46-1.80 (m, 2H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 201.4, 136.34, 136.25, 136.20, 136.1, 134.5, 129.45, 129.43, 129.2, 116.9, 74.7, 74.4, 51.8, 51.6, 50.8, 40.9, 40.6, 28.3, 28.0, 26.3, 24.7, 24.6, 19.60, 19.57; HRMS (ES+) calcd. for $C_{17}H_{23}N_3O_3NaS$ (M+Na) 372.1358, found 372.1333.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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40. CCDC- 663,289 (**37**) contains the supplementary crystallographic data for this paper.. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via. www.ccdc.cam.ac.uk/data_request/cif
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47. Attempts to switch the diastereoselectivity of this reaction through the use of sulfonamide catalyst **31** conditions led to a formation the same diastereomer 7; however, use of enantiomeric sulfamide catalyst *ent*-**31** gave what we have tentatively assigned as the alternate *trans*-disatereomer 48 in modest diastereosectivity (1.5:1 dr).
48. The CIF containing the supplementary crystallographic data for compound **49** has been previously reported.. These data can be obtained free of charge from the American Chemical Society via. http://pubs.acs.org/doi/suppl/10.1021/ja803613w/suppl_file/ja803613w-file007.cif
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60. Preparation of LiTMP: To a solution of 2,2,6,6-tetramethylpiperidine (283 mg, 340 μL, 2.0 mmol) in THF (0.86 mL) was added *n*-BuLi (0.8 mL, 2.0 mmol, 2.5 M in hexanes). The reaction was warmed to -10°C and stirred for 30 min prior to use.

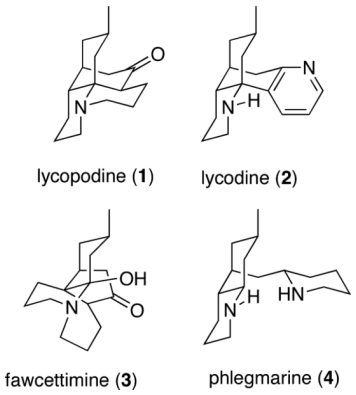
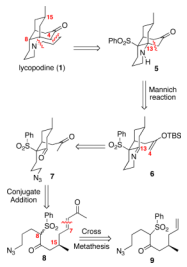
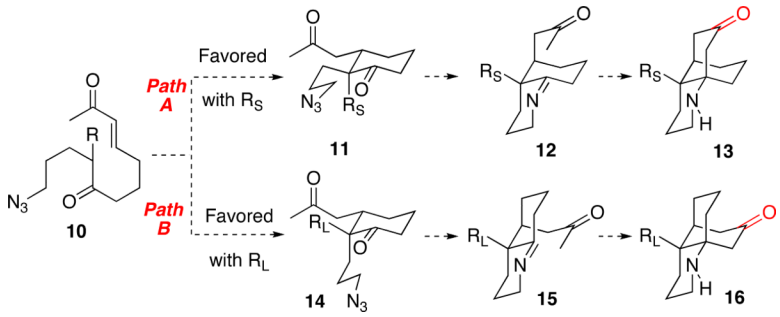


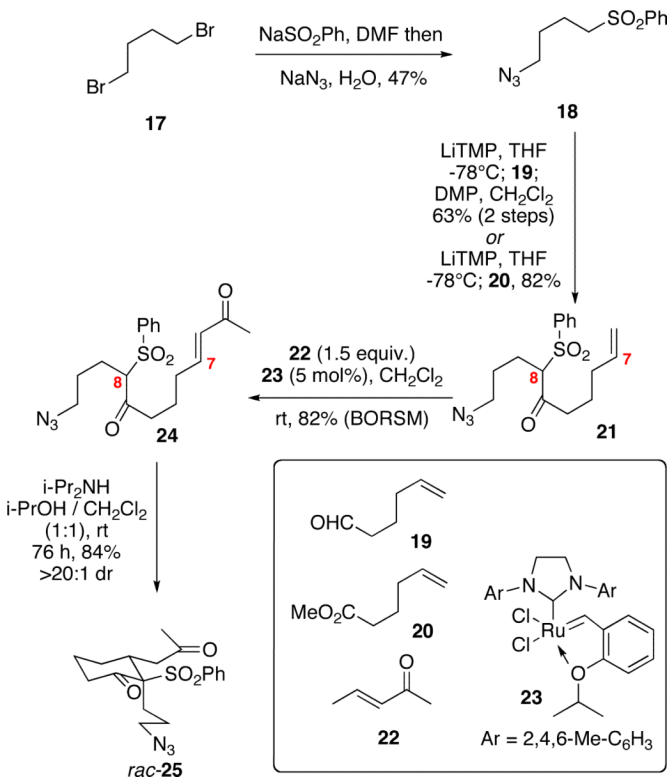
Figure 1.
Four Major Subclasses of the *Lycopodium* alkaloids.



Scheme 1.
Retrosynthetic Strategy for Lycopodine.

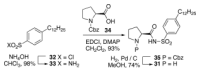


Scheme 2.
Key Michael / Mannich Sequence.

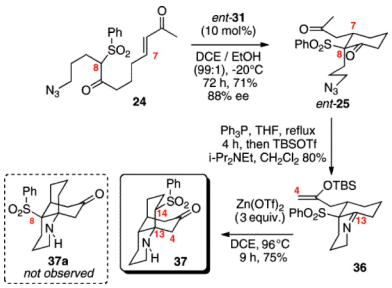


Scheme 3.

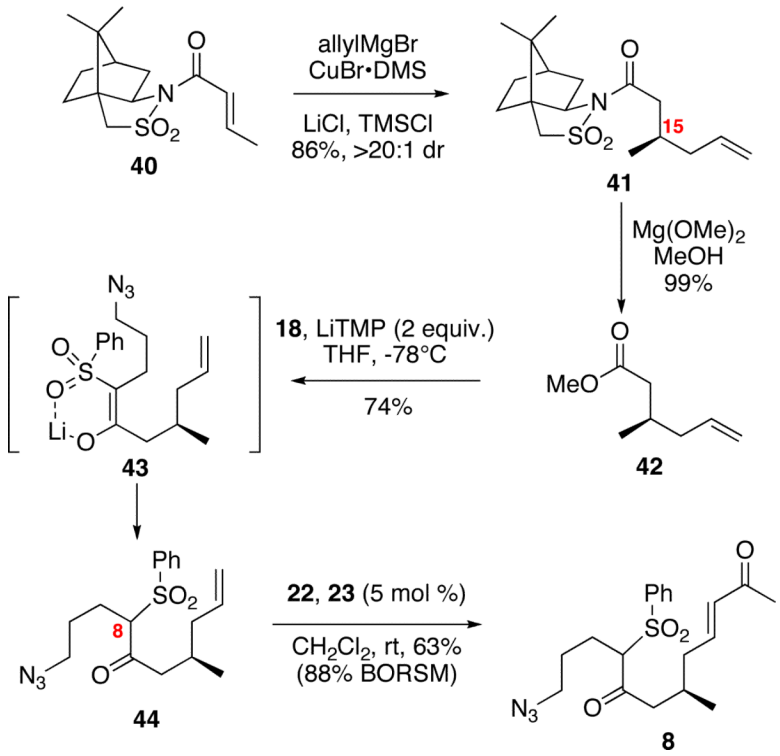
Development of Racemic Protocol for Intramolecular, Keto Sulfone Michael Addition.



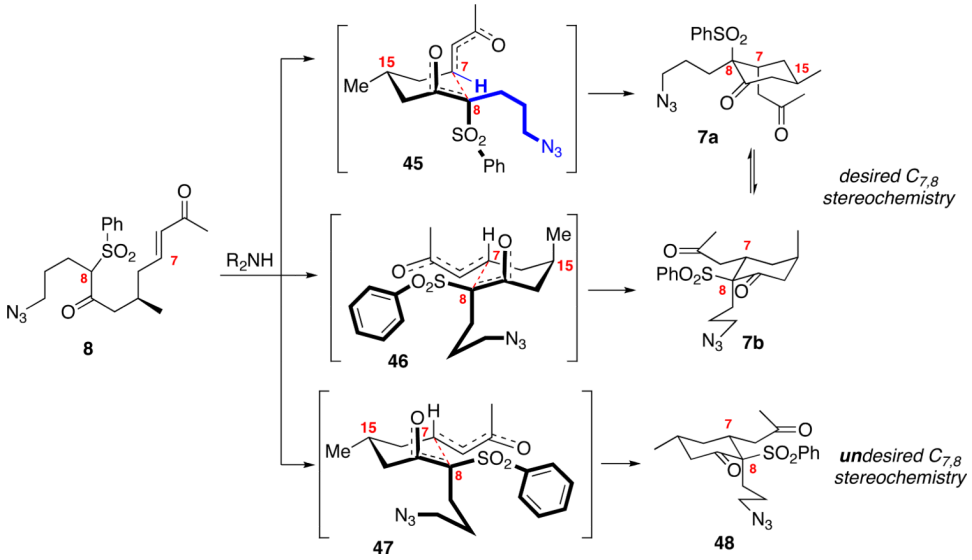
Scheme 4.
Synthesis of Novel Sulfonamide **31**.



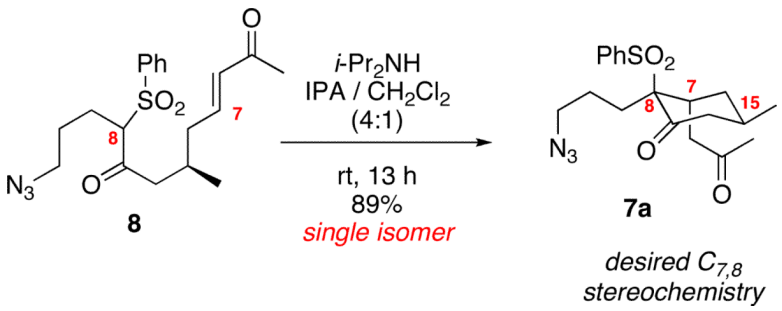
Scheme 5.
Enantioselective Synthesis of the Lycopodine Tricyclic Core **37**.



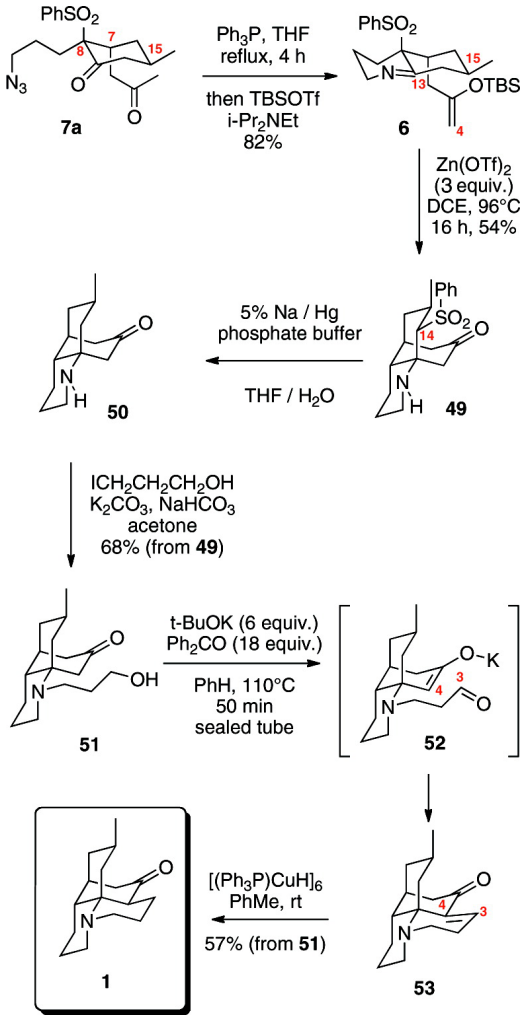
Scheme 6.
Synthesis of the Key Enone Intermediate.



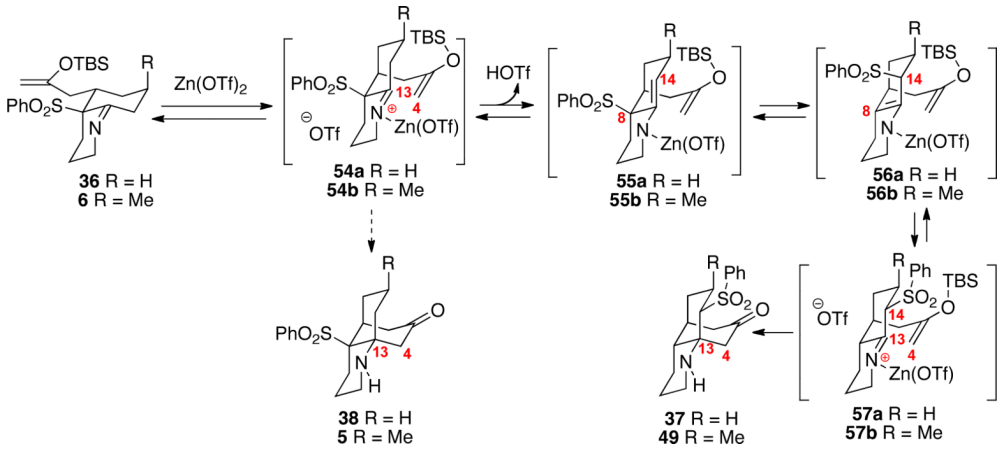
Scheme 7.
Possible Mechanistic Pathway for Diastereoselective Michael Addition.



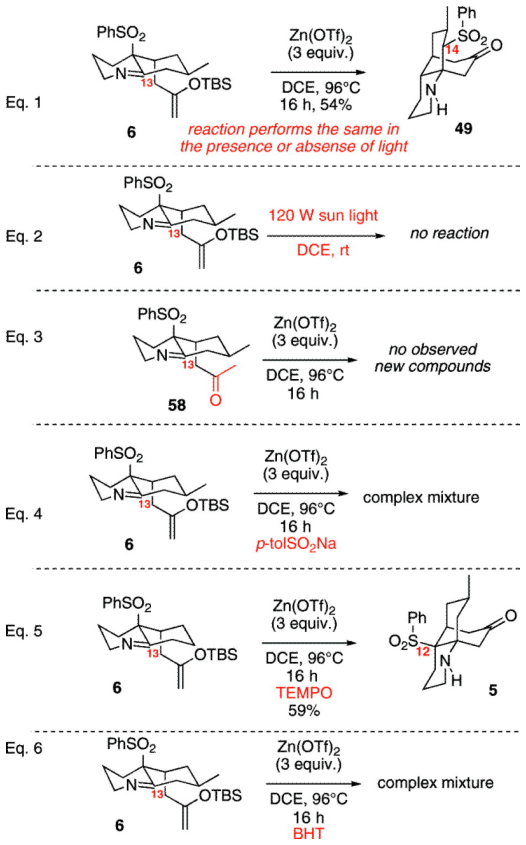
Scheme 8.
Diastereoselective Michael Addition of **8**.



Scheme 9.
Enantioselective Total Synthesis of Lycopodine.



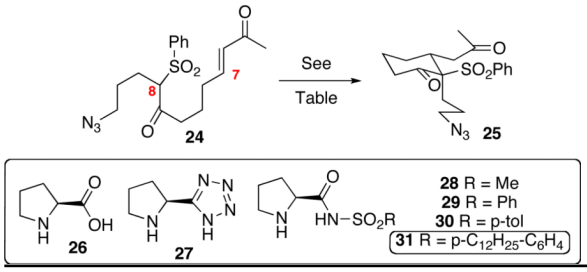
Scheme 10.
Possible Mechanistic Pathway for Tricycle Formation.



Scheme 11.
Probing the Mechanistic Pathway for Sulfone Rearrangement / Mannich Cyclization.

Table 1

Optimization of Conditions for Enantioselective, Organocatalyzed Intramolecular Michael Addition.



Entry	Catalyst	Additive	Conditions[a]	% ee[b] (% yield)
a	**26** (20 mol%)	-	$CHCl_3$[c], rt, 3 d	No reaction
b	**27** (20 mol%)	-	$CHCl_3$[c], rt, 3 d	No reaction
c	**27** (20 mol%)	Piperidine (1 equiv.)	$CHCl_3$[c], rt, 16 h	33% ee (82%)
d	**27** (20 mol%)	Piperidine (1 equiv.)	$ClCH_2CH_2Cl$, rt, 3 d	42% ee (60%)
e	**27** (20 mol%)	Piperidine (1 equiv.), 1% EtOH	$ClCH_2CH_2Cl$, rt, 16 h	57% ee (72%)
f	**28** (20 mol%)	Piperidine (1 equiv.), 1% EtOH	$ClCH_2CH_2Cl$, rt, 16 h	64% ee (63%)
g	**29** (20 mol%)	Piperidine (1 equiv.), 1% EtOH	$ClCH_2CH_2Cl$, rt, 16 h	64% ee (73%)
h	**30** (20 mol%)	Piperidine (1 equiv.), 1% EtOH	$ClCH_2CH_2Cl$, rt, 16 h	53% ee (75%)
i	**31** (20 mol%)	Piperidine (1 equiv.), 1% EtOH	$ClCH_2CH_2Cl$, rt, 16 h	59% ee (71%)
j	***31*** (10 mol%)	*Piperidine (1 equiv.), 1% EtOH*	*$ClCH_2CH_2Cl$ (0.2 M) -20°C, 72 h*	*88% ee (75%)*

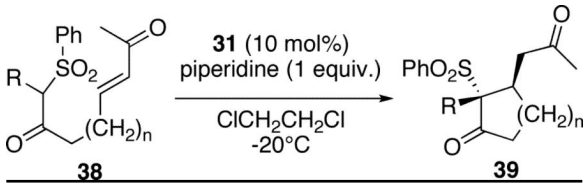
[a] The reaction was performed at 0.1 M concentration of substrate unless otherwise noted.

[b] The enantiomeric excess was determined by chiral shift NMR [50% $Eu(hfc)_3$, C_6D_6].

[c] Commercial $CHCl_3$ stabilized with 1% EtOH was used without further purification.

Table 2

Exploration of Scope for Enantioselective, Organocatalyzed Intramolecular Michael Addition.



Entry	n	R (reaction time)	% ee[a] (% yield, dr)
a	2	$CH_2CH_2CH_2N_3$ (72 h)	88% ee (75%, 20:1 dr)
b	2	Me (5 d)	83% ee (80%, 20:1 dr)
c	2	CH_2CH_2OTBS (72 h)	83% ee (76%, 20:1 dr)
d	2	CH_2Ph (72 h)	81% ee (89%, 20:1 dr)
e	1	Me (6 d)	84% ee (58%, 20:1 dr)

[a]The enantiomeric excess was determined by chiral shift NMR [50% $Eu(hfc)_3$, C_6D_6].