

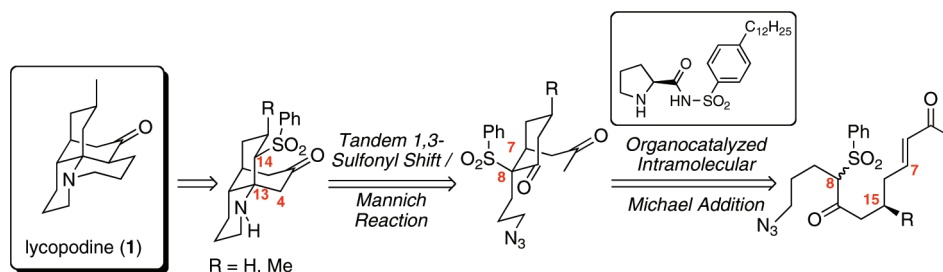
Development of an Enantioselective Route toward the *Lycopodium* Alkaloids: Total Synthesis of Lycopodine

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Synthesis of a C₁₅-desmethyl tricyclic 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 toward this natural product family led to the development of *N*-(*p*-dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide, an organocatalyst which facilitates 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 because of their wide-ranging biological activity and structural complexity.¹ There are four major subclasses 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 antipyretic⁶ and

anticholinesterase activity⁷ 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

(1) (a) Kobayashi, J.; Morita, H. *Alkaloids* **2005**, *61*, 1–57. (b) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752–772.

(2) Bödeker, K. *Justus Liebigs Ann. Chem.* **1881**, *208*, 363–367.

(3) Achmatowicz, O.; Uzieblo, W. *Rocz. Chem.* **1938**, *18*, 88–95.

(4) Ayer, W. A.; Iverach, G. G. *Tetrahedron Lett.* **1962**, *3*, 87–92.

(5) (a) Rogers, D.; Quick, A.; Hague, M. *Acta Crystallogr.* **1974**, *B30*, 552–553. Hague, M.; Rogers, D. *J. Chem. Soc., Perkin Trans. 2* **1975**, 93–98.

(6) Nikonorow, M. *Acta Polon. Pharm.* **1939**, *3*, 23–56.

(7) Ortega, M. G.; Agnese, A. M.; Cabrera, J. L. *Phytomedicine* **2004**, *11*, 539–543.

(8) For a preliminary account, see: Yang, H.; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc.* **2008**, *130*, 9238–9239.

(9) (a) Stork, G.; Kretschmer, R. A.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1968**, *90*, 1647–1648. (b) Ayer, W. A.; Bowman, W. R.; Joseph, T. C.; Smith, P. J. *J. Am. Chem. Soc.* **1968**, *90*, 1648–1650. (c) Kim, S.; Bando, Y.; Hori, Z. *Tetrahedron Lett.* **1978**, 2293–2294. (d) Heathcock, C. H.; Kleinman, E. F.; Binkly, E. S. *J. Am. Chem. Soc.* **1982**, *104*, 1054–1068. (e) Schumann, D.; Mueller, H. J.; Naumann, A. *Lebigs Ann. Chem.* **1982**, 1700–5. (f) Kraus, G. A.; Hon, Y. S. *Heterocycles* **1987**, *25*, 377–386. (g) Grieco, P. A.; Dai, Y. *J. Am. Chem. Soc.* **1998**, *120*, 5128–5129. (h) For formal syntheses of lycopodine, see: Padwa, A.; Brodney, M. A.; Marino, J. P., Jr.; Sheehan, S. M. *J. Org. Chem.* **1997**, *62*, 78–87. (i) Mori, M.; Hori, K.; Akashi, M.; Hori, M.; Sato, Y.; Nishida, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 637–638. (j) For synthetic efforts towards lycopodine, see: Colvin, E. W.; Martin, J.; Parker, W.; Raphael, R. A.; Shroot, B.; Doyle, M. *J. Chem. Soc., Perkin Trans. 1* **1972**, 860–870. (k) Wenkert, E.; Broka, C. A. *J. Chem. Soc., Chem. Commun.* **1984**, 714–715.

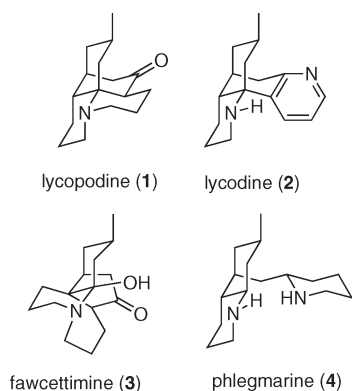


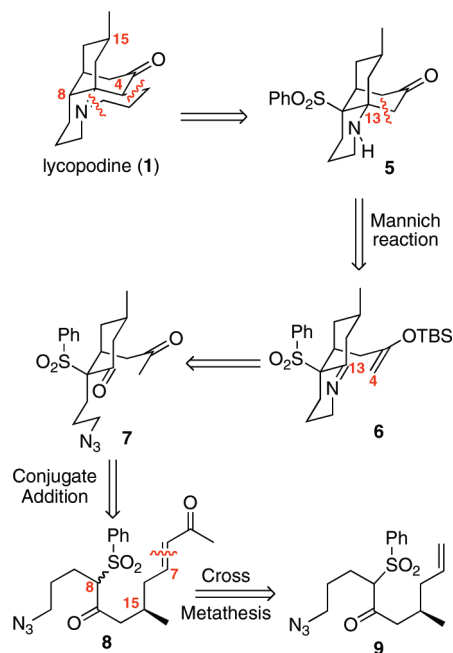
FIGURE 1. Four major subclasses of the *Lycopodium* alkaloids.

racemic syntheses) of **1** had been reported.⁹ The Evans laboratory recently reported an elegant total synthesis of a similar alkaloid ring system (clavonoline).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 toward the alkaloid lycopodine.

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 C₈ should help to activate the imine to Mannich reaction,

SCHEME 1. Retrosynthetic Strategy for Lycopodine



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 C₁₅, 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 on the basis of 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 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

(10) Evans, D. A.; Scheerer, J. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 6038–42.

(11) Amat, M.; Grier, R.; Fabregat, R.; Bosch, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1233–1236.

(12) Sha, C.-K.; Lee, F.-K.; Chang, C.-J. *J. Am. Chem. Soc.* **1999**, *121*, 9875–9876.

(13) (a) Comins, D. L.; Libby, A. H.; Al-awar, R. S.; Foti, C. J. *J. Org. Chem.* **1999**, *64*, 2184–2185. (b) Comins, D. L.; Brooks, C. A.; Al-awar, R. S.; Goehring, R. R. *Org. Lett.* **1999**, *1*, 229–231.

(14) Linghu, X.; Kennedy-Smith, J.-J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7671–7673.

(15) Chandra, A.; Pigza, J. A.; Han, J.-S.; Mutnick, D.; Johnston, J. N. *J. Am. Chem. Soc.* **2009**, *131*, 3470–3471.

(16) Yen, C.-F.; Liao, C.-C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4090–4093.

(17) Kozaka, T.; Miyakoshi, N.; Mukai, C. *J. Org. Chem.* **2007**, *72*, 10147–10154.

(18) Nilsson, B. L.; Overman, L. E.; Read de Alaniz, J.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 11297–11299.

(19) (a) Bisai, A.; West, S. P.; Sarpong, R. *J. Am. Chem. Soc.* **2008**, *130*, 7222–7223. (b) West, S. P.; Bisai, A.; Lim, A. D.; Narayan, R. R.; Sarpong, R. *J. Am. Chem. Soc.* **2009**, *131*, 11187–11194. (c) Fischer, D. F.; Sarpong, R. *J. Am. Chem. Soc.* **2010**, *132*, 5926–5927.

(20) Yuan, C.; Chang, C.-T.; Axelrod, A.; Siegel, D. *J. Am. Chem. Soc.* **2010**, *132*, 5924–5925.

(21) Kozak, J. A.; Dake, G. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 4221–4223.

(22) Ishizaki, M.; Niimi, Y.; Hoshino, O.; Hara, H.; Takahashi, T. *Tetrahedron* **2005**, *61*, 4053–4065.

(23) (a) Katakawa, K.; Kitajima, M.; Aimi, N.; Seki, H.; Yamaguchi, K.; Furihata, K.; Harayama, T.; Takayama, H. *J. Org. Chem.* **2005**, *70*, 658–663. (b) Shigeyama, T.; Katakawa, K.; Kogure, N.; Kitajima, M.; Takayama, H. *Org. Lett.* **2007**, *9*, 4069–4072. (c) Nishikawa, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 1987–1990.

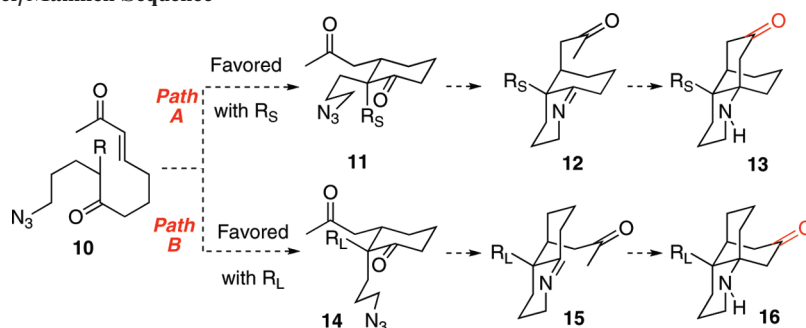
(24) For an example, see: Grossman, R. B.; Pendharkar, D. S.; Patrick, B. O. *J. Org. Chem.* **1999**, *64*, 7178–7183.

(25) Stork, G.; Winkler, J. D.; Saccomano, N. A. *Tetrahedron Lett.* **1983**, *24*, 465–468.

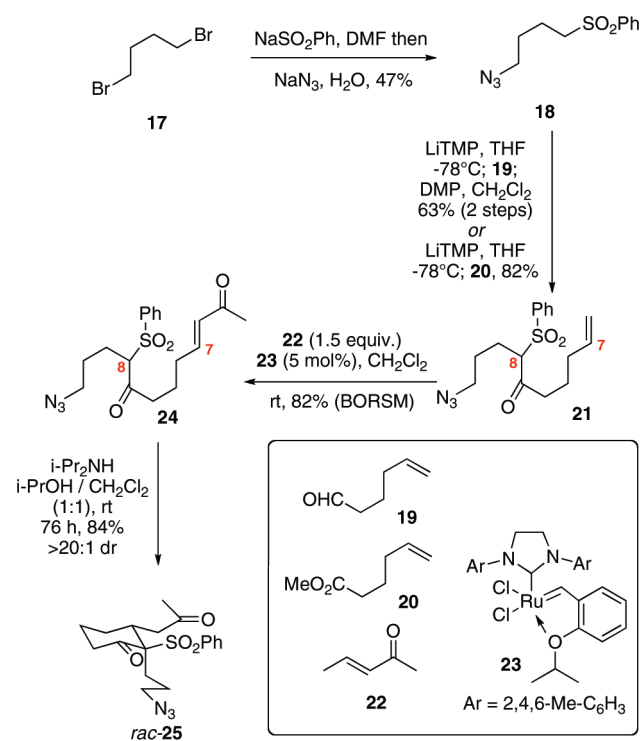
(26) For a recent review of organocatalysis on sulfone substrates, see: Alba, A.-N. R.; Companyó, X.; Rios, R. *Chem. Soc. Rev.* **2010**, *39*, 2018–2033.

(27) Pulkkinen, J.; Aburel, P. S.; Halland, N.; Jørgensen, K. A. *Adv. Synth. Catal.* **2004**, *346*, 1077–1080.

SCHEME 2. Key Michael/Mannich Sequence



SCHEME 3. Development of Racemic Protocol for Intramolecular, Keto Sulfone Michael Addition



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 tetramethylpiperidine (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

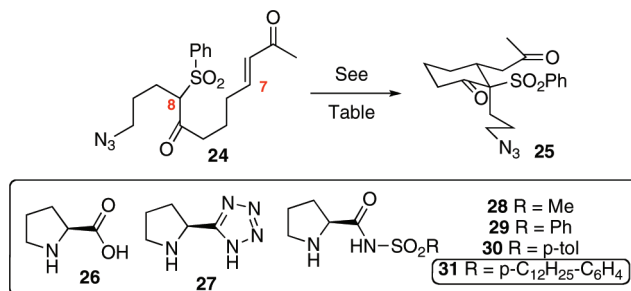
the presence of an azide functionality (potential Staudinger reduction by phosphine ligands from the transition metal catalyst) and an internal nucleophile (keto sulfone) for the electrophilic enone formed in the reaction. Consequently, we screened a range of catalysts for this transformation and CM partners. Both first- and second-generation Grubbs catalysts were ineffective. Fortunately, second-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 hindrance 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., Cs₂CO₃, EtOH) conditions as they had proven effective in prior intramolecular Michael additions with the desired relative configuration by Stork²⁵ 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 C₁₄. 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/CH₂Cl₂ (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 nonpolar, chlorinated solvents. We initially screened proline (**26**) but observed no reaction in CHCl₃ (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

(28) Zhou, X.-T.; Carter, R. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 1787–1790.

(29) Carlson, E. C.; Rathbone, L. K.; Yang, H.; Collett, N. D.; Carter, R. G. *J. Org. Chem.* **2008**, *73*, 5155–5158.

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)	CICH ₂ CH ₂ Cl, rt, 3 d	42% ee (60%)
e	27 (20 mol %)	piperidine (1 equiv), 1% EtOH	CICH ₂ CH ₂ Cl, rt, 16 h	57% ee (72%)
f	28 (20 mol %)	piperidine (1 equiv), 1% EtOH	CICH ₂ CH ₂ Cl, rt, 16 h	64% ee (63%)
g	29 (20 mol %)	piperidine (1 equiv), 1% EtOH	CICH ₂ CH ₂ Cl, rt, 16 h	64% ee (73%)
h	30 (20 mol %)	piperidine (1 equiv), 1% EtOH	CICH ₂ CH ₂ Cl, rt, 16 h	53% ee (75%)
i	31 (20 mol %)	piperidine (1 equiv), 1% EtOH	CICH ₂ CH ₂ Cl, rt, 16 h	59% ee (71%)
j	31 (10 mol %)	Piperidine (1 equiv), 1% EtOH	CICH ₂ CH ₂ Cl (0.2 M), -20 °C, 72 h	88% ee (75%)

^aThe reaction was performed at 0.1 M concentration of substrate unless otherwise noted. ^bThe enantiomeric excess was determined by chiral shift NMR [50% Eu(hfc)₃, C₆D₆]. ^cCommercial CHCl₃ stabilized with 1% EtOH was used without further purification.

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 CHCl₃. Interestingly, we again observed no reaction after 3 d at room temperature (Entry b). Ley and co-workers 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, CHCl₃, rt) gave no product formation, even after prolonged exposure to the reaction conditions. Use of CICH₂CH₂Cl as solvent led to a decrease in reaction rate but an increase in enantiomeric excess (entry d). It turned out that the choice of CHCl₃ 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 CICH₂CH₂Cl 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 (ee) 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 Jørgenson²⁷ and MacMillan³⁴ proved ineffective. We also screened diphenylprolinol³⁵ 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 *p*-dodecylsulfonyl chloride (**32**)^{36,37} and Cbz-protected proline **34** in three steps (Scheme 4). We have prepared over 100 mmol 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

(30) For a recent review of ee determination using NMR methods, see: Seco, J. M.; Quinoa, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17–118.

(31) (a) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558–560. (b) Hartikka, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1831–1834. (c) Torii, H.; Nakadai, N.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983–1986. (d) Knudsen, K. R.; Mitchell, C. E. T.; Ley, S. V. *Chem. Commun.* **2006**, 66–68. (e) For a recent review, see: Longbottom, D. A.; Franckevicius, V.; Kumarn, S.; Oelke, A. J.; Wascholowski, V.; Ley, S. V. *Aldrichim. Acta* **2008**, *41*, 3–11.

(32) Mitchell, C. E. T.; Brenner, S. E.; García-Fortanet, J.; Ley, S. V. *Org. Biomol. Chem.* **2006**, *4*, 2039–2049.

(33) (a) Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141–1146. (b) Dahlin, N.; Boegevig, A.; Adolffson, H. *Adv. Synth. Catal.* **2004**, *346*, 1101–1105. (c) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84–96. (d) Sundén, H.; Dahlin, N.; Ibrahim, I.; Adolffson, H.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 3385–3389. (e) Bellis, E.; Vasiatou, K.; Kokotos, G. *Synthesis* **2005**, 2407–13. (f) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417–4420. (g) Silva, F.; Sawicki, M.; Gouverneur, V. *Org. Lett.* **2006**, *8*, 5417–19. (h) Vogt, H.; Baumann, T.; Nieger, M.; Braese, S. *Eur. J. Org. Chem.* **2006**, *2006*, 5315–5338. (i) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958–961. (j) Aratake, S.; Itoh, T.; Okano, T.; Nagae, N.; Sumiya, T.; Shoji, M.; Hayashi, Y. *Chem.—Eur. J.* **2007**, *13*, 10246–10256. (k) Huang, J.; Zhang, X.; Armstrong, D. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 9073–9077. (l) Wang, X.-J.; Zhao, Y.; Liu, J.-T. *Org. Lett.* **2007**, *9*, 1343–1345. (m) Zu, L.; Xie, H.; Wang, J.; Wang, W. *Org. Lett.* **2008**, *10*, 1211–1214.

(34) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. M. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051–15053.

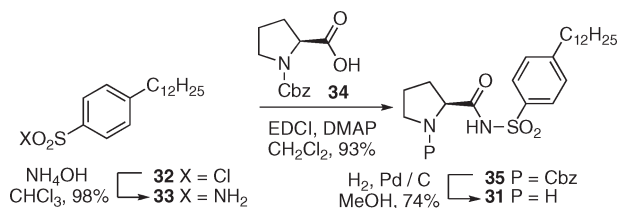
(35) Kobahashi, S.; Ogawa, C.; Kawamura, M.; Sugiura, M. *Synlett* **2001**, 983–985.

(36) Wako Chemicals catalog no. 040-19872.

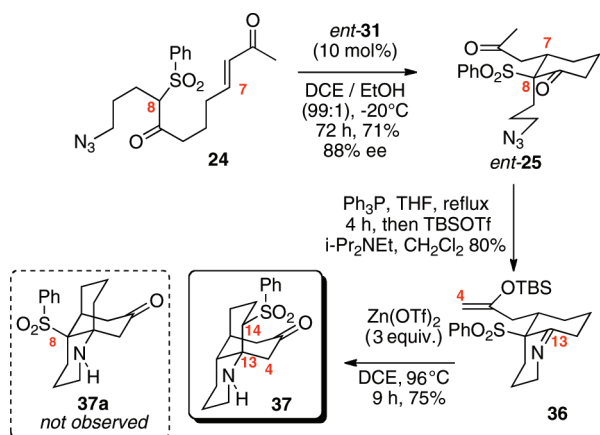
(37) Compound **32** is sold as a mixture of isomers on the C₁₂H₂₅ alkyl chain. No attempt was made to separate the isomers in this sequence, and the isomeric mixture does not appear to adversely affect the reactivity.

(38) (a) Yang, H.; Carter, R. G. *Org. Lett.* **2008**, *10*, 4649–4652. (b) Yang, H.; Carter, R. G. *J. Org. Chem.* **2009**, *74*, 2246–2249. (c) Yang, H.; Carter, R. G. *J. Org. Chem.* **2009**, *74*, 5151–5156. (d) Yang, H.; Carter, R. G. *Tetrahedron* **2010**, *66*, 4854–4859. (e) Yang, H.; Carter, R. G. *Org. Lett.* **2010**, *12*, 3108–3111.

SCHEME 4. Synthesis of Novel Sulfonamide 31



SCHEME 5. Enantioselective Synthesis of the Lycopodine Tricyclic Core 37



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 % of **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. 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 $\text{Zn}(\text{OTf})_2$ cleanly generated a cyclization product which was ultimately established to be the rearranged tricyclic product **37** via X-ray crystallographic analysis (Supporting Information).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

(39) This crystal structure was determined using the *ent*-**31** catalyst derived from D-proline. CCDC-663,290 (*ent*-**25**) 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.

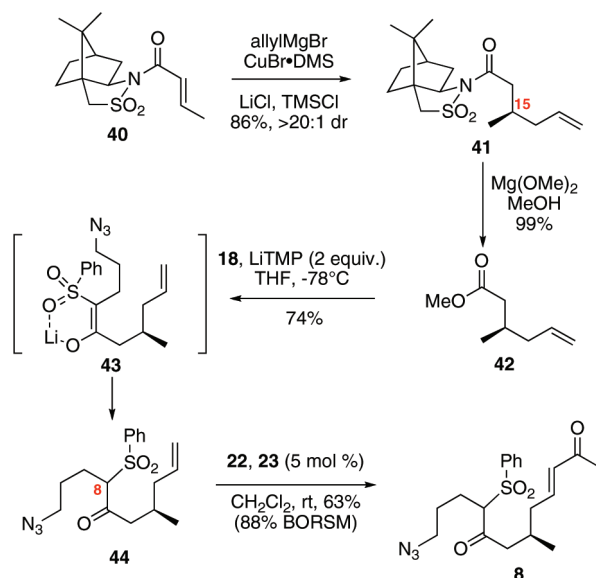
(40) CCDC-663,289 (**37**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

TABLE 2. Exploration of Scope for Enantioselective, Organocatalyzed Intramolecular Michael Addition

entry	<i>n</i>	R (reaction time)	% ee ^a (% yield, dr)
a	2	$\text{CH}_2\text{CH}_2\text{CH}_2\text{N}_3$ (72 h)	88% ee (75%, 20:1 dr)
b	2	Me (5 d)	83% ee (80%, 20:1 dr)
c	2	$\text{CH}_2\text{CH}_2\text{OTBS}$ (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)

^aThe enantiomeric excess was determined by chiral shift NMR [50% $\text{Eu}(\text{hfc})_3$, C_6D_6].

SCHEME 6. Synthesis of the Key Enone Intermediate

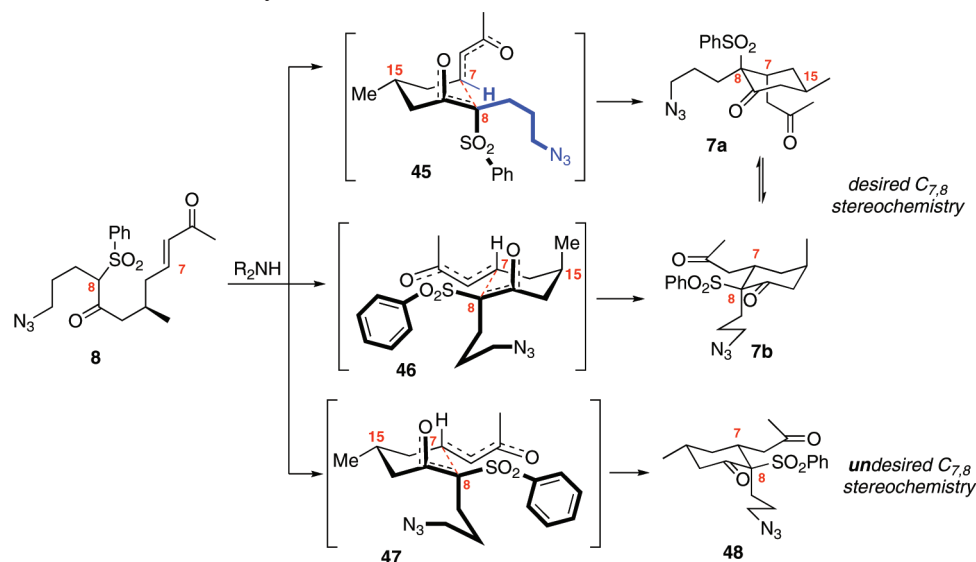


limited examples of 1,3-rearrangements of allylic sulfones;⁴¹ however, we believe this is the first example of an α -sulfonyl imine undergoing such a shift. A detailed discussion of a possible mechanistic explanation for this transformation is provided later in this manuscript.

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

(41) (a) Padwa, A.; Bullock, W. H.; Dyszlewski, A. D. *Tetrahedron Lett.* **1987**, 28, 3193–3196. (b) Ogura, K.; Iihama, T.; Kiuchi, S.; Kajiki, T.; Koshikawa, O.; Takahashi, K.; Iida, H. *J. Org. Chem.* **1986**, 51, 700–705. (c) Lin, P.; Whitman, G. H. *J. Chem. Soc., Chem. Commun.* **1983**, 1102–1103. (d) Baechler, R. D.; Bentley, P.; Deuring, L.; Fisk, S. *Tetrahedron Lett.* **1982**, 23, 2269–2272. (e) For palladium-catalyzed methods, see: Jagusch, T.; Gais, H.-J.; Bondarev, O. *J. Org. Chem.* **2004**, 69, 2731–2736. and references cited therein.

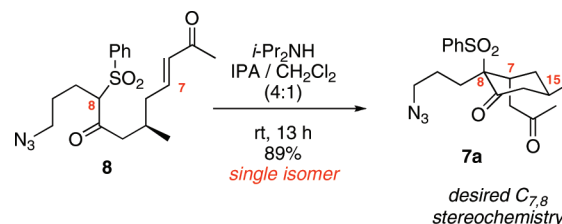
SCHEME 7. Possible Mechanistic Pathway for Diastereoselective Michael Addition



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 C₁₅ 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 C₈. Cross-metathesis using second-generation Grubbs–Hoveyda provided the desired enone **8**.⁴⁴

We next set out to explore the key intramolecular keto sulfone Michael addition (Scheme 7). 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 interconvertible 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-diequatorial 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 sulfone in

SCHEME 8. Diastereoselective Michael Addition of **8**

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, diisopropylamine. This amine was selected in part due to the steric hindrance imparted by the two isopropyl 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 C₁₅ 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

(42) Absolute and relative configuration of product **39e** were assigned based on analogy to the 6-membered series.

(43) (a) Boulet, S. L.; Paquette, L. A. *Synthesis* **2002**, 895–900. (b) Lipshutz, B. H.; Hackmann, C. *J. Org. Chem.* **1994**, *59*, 7437–7444.

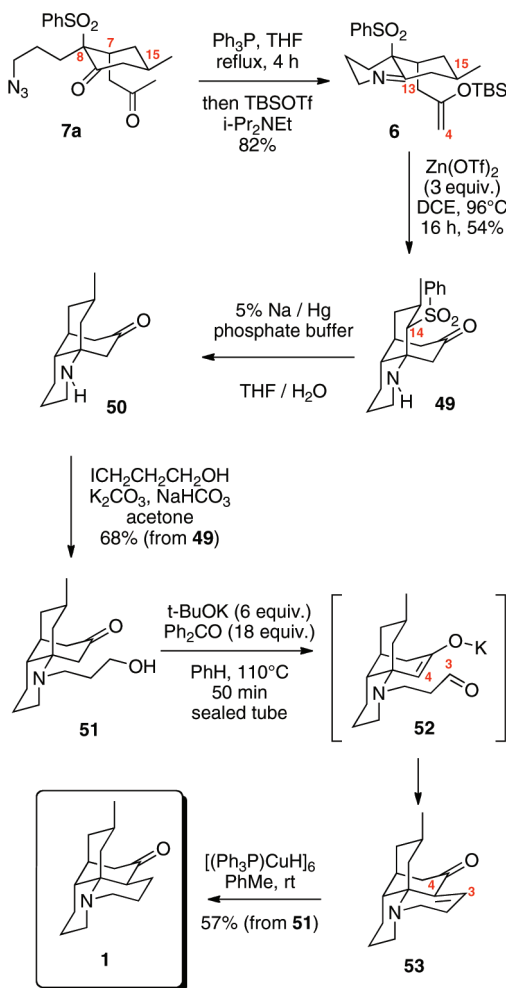
(44) It should be noted that the C₁₅ methyl series appears to perform slightly better in the CM than the desmethyl series. We are unsure as to the exact explanation for that difference.

(45) (a) Golan, O.; Goren, Z.; Biali, S. E. *J. Am. Chem. Soc.* **1990**, *112*, 9300–9307. (b) Weiser, J.; Golan, O.; Fitjer, L.; Biali, S. E. *J. Org. Chem.* **1996**, *61*, 8277–8284.

(46) The CIF containing the supplementary crystallographic data for compound **7** 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-file006.cif.

(47) Attempts to switch the diastereoselectivity of this reaction through the use of sulfonamide catalyst **31** conditions led to a formation of the same diastereomer **7**; however, use of enantiomeric sulfamide catalyst *ent*-**31** gave what we have tentatively assigned as the alternate *trans*-diastereomer **48** in modest diastereoselectivity (1.5:1 dr).

SCHEME 9. Enantioselective Total Synthesis of Lycopodine



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 activation of the methyl ketone. While not depicted in Scheme 8, enamine formation might explain the high level of diastereoselectivity (*syn/anti* between C₇–C₈) through strong *E* selectivity in the enamine, likely due to steric hindrance 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 activation 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 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 C₁₅ methyl series does require slightly higher reaction temperatures (96 °C) to proceed effectively. Subsequent desulfurization 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 (¹H, ¹³C NMR, [α]_D)^{9f,49,50} as well as an authentic sample provided by Heathcock matched nicely with the synthesized material. Because of the basicity of lycopodine's nitrogen, care must be taken to remove any extraneous DCl present in the CDCl₃ (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 C₁₄. 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 C₁₄ to arise as the axial sulfone **56**, (c) 2,3-sigmatropic rearrangement to the sulfinate ester followed by reorganization to the sulfone **56**⁵¹ or (d) formation of an intermediate 1,1-dioxothietane followed by ring-opening. Diastereoselective protonation of the enamine and epimerization at C₁₄ 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 NaSO₂-*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**

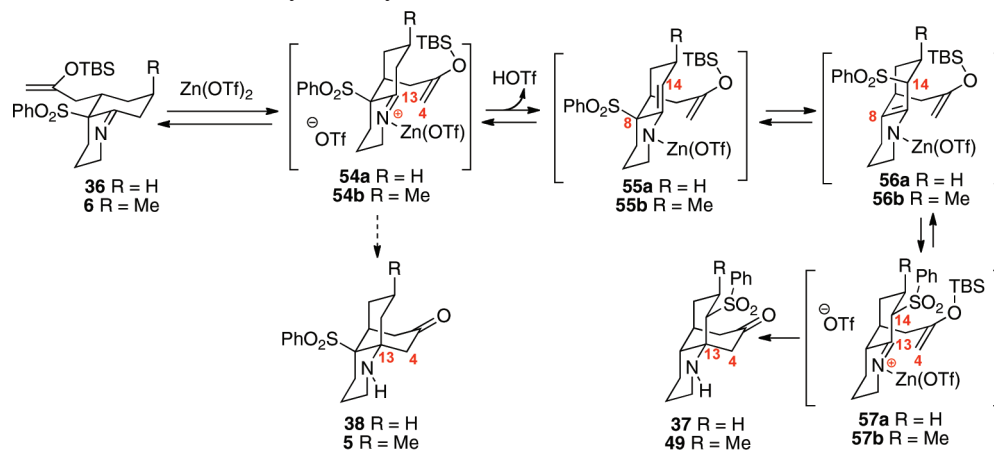
(49) Nakashima, T. T.; Singer, P. P.; Browne, L. M.; Ayer, W. A. *Can. J. Chem.* **1975**, *53*, 1936–1942.

(50) Douglas, B.; Lewis, D. G.; Marion, L. *Can. J. Chem.* **1953**, *31*, 272–276.

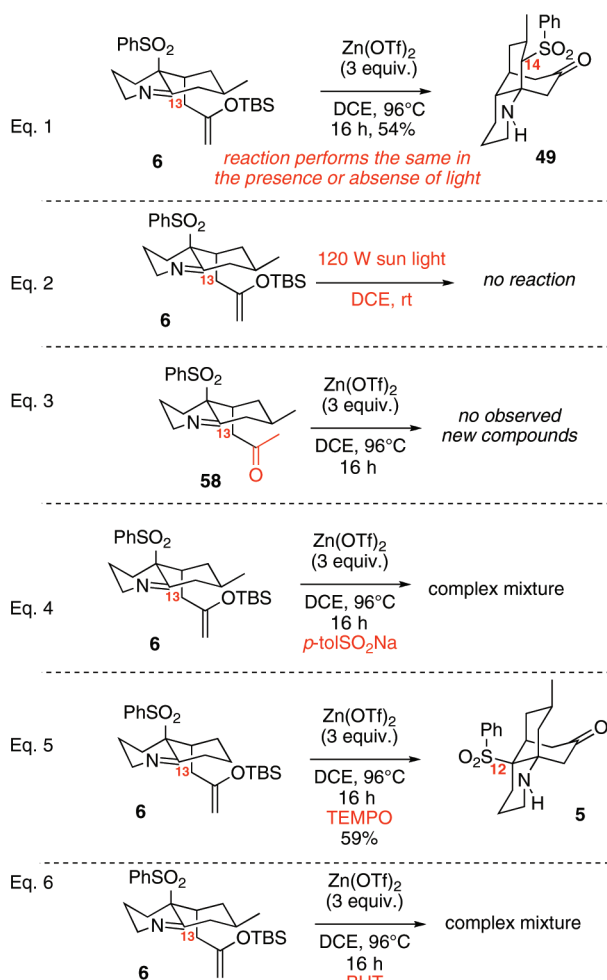
(51) One example of such a [2,3]-sigmatropic rearrangement has been reported: (a) Hatanaka, N.; Ozaki, O.; Matsumoto, M. *Tetrahedron Lett.* **1986**, *27*, 3169–3172. See also: (b) Knight, D. J.; Whitman, G. H.; Williams, J. G. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2149–2152. (c) Ball, D. B.; Hernandez, L. S. 232nd ACS National Meeting, San Francisco **2006**, CHED-329.

(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.

SCHEME 10. Possible Mechanistic Pathway for Tricycle Formation



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



to tricycle **50** (Na/Hg, Na₂HPO₄, 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.^{52–54} Magnus utilized TEMPO and hypervalent iodine reagents to functionalize the allylic position of silyl enol ethers.⁵⁵ Renaud and Studer recently demonstrated the TEMPO-mediated oxidation of catecholboron enolates which is proposed to go through a radical intermediate.⁵⁶ As a complement to the standard cyclization conditions, a radical inhibitor was added to the standard cyclization conditions, but only complex mixture of products was obtained (eq 6).⁵⁷

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 C₈-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 CHCl₃ (1.5 L) was NH₄OH (313 mL, 78.9 g, 2.25 mol) at rt. After being stirred vigorously for 4 h, the reaction mixture was extracted with CHCl₃ (2 × 300 mL).

(53) (a) Johnston, J. N.; Plotkin, M. A.; Viswanathan, R.; Prabhakaran, E. N. *Org. Lett.* **2001**, *3*, 1009–1011. (b) Prabhakaran, E. N.; Nugent, B. M.; Williams, A. L.; Nailor, K. E.; Johnston, J. N. *Org. Lett.* **2002**, *4*, 4197–4200. (c) Viswanathan, R.; Prabhakaran, E. N.; Plotkin, M. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 163–EOA. (d) Nugent, B. M.; Williams, A. L.; Prabhakaran, E. N.; Johnston, J. N. *Tetrahedron* **2003**, *59*, 8877–8888. (e) Srinivasan, J. M.; Burks, H. E.; Smith, C. R.; Viswanathan, R.; Johnston, J. N. *Synthesis* **2005**, 330–333.

(54) Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *J. Org. Chem.* **2006**, *71*, 2099–2106.

(55) (a) Magnus, P.; Roe, M. B.; Hulme, C. *J. Chem. Soc., Chem. Commun.* **1995**, 263–265. (b) Magnus, P.; Lacour, J.; Evans, P. A.; Roe, M. B.; Hulme, C. *J. Am. Chem. Soc.* **1996**, *118*, 3406–3418.

(56) Pouliot, M.; Renaud, P.; Schenk, K.; Studer, A.; Vogler, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 6037–6040.

(57) **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.

(52) For a recent review, see: Pastori, N.; Gambarotti, C.; Punta, C. *Mini-Rev. Org. Chem.* **2009**, *6*, 184–195.

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 32 is sold as a mixture of isomers on the $\text{C}_{12}\text{H}_{25}$ 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.* $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.86–7.88 (m, 2H), 7.29–7.35 (m, 2H), 5.03 (s, 2H), 0.78–1.68 (m, 25H); $^{13}\text{C NMR}$ (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.

Chz-sulfonamide 35. To a solution of (*Z*)-L-proline **34** (36.6 g, 147 mmol) in CH_2Cl_2 (735 mL) were 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 a mixture of isomers on the $\text{C}_{12}\text{H}_{25}$ 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:* $[\alpha]_{\text{D}}^{23} = +90$ ($c = 2.2$, CHCl_3); IR (neat) 3148, 2955, 2925, 2856, 1720, 1677, 1449, 1411, 1355, 1174, 1131, 1088, 826, 692 cm^{-1} ; $^1\text{H NMR}$ (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); $^{13}\text{C NMR}$ (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 $\text{C}_{31}\text{H}_{45}\text{N}_2\text{O}_5\text{S}$ ($M + 1$) 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 a white solid. The crude product was recrystallized from MeOH to give the product **35** (43.2 g, 102 mmol, 74%) as a white solid. *Compound 31 is a mixture of isomers on the $\text{C}_{12}\text{H}_{25}$ 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; $[\alpha]_{\text{D}}^{23} = +94$ ($c = 0.95$, CHCl_3); IR (neat) 3135, 2955, 2920, 2852, 1626, 1458, 1372, 1308, 1144, 1084, 843 cm^{-1} ; $^1\text{H NMR}$ (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); $^{13}\text{C NMR}$ (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 $\text{C}_{23}\text{H}_{39}\text{N}_2\text{O}_3\text{S}$ ($M + 1$) 423.2681, found 423.2701.

Cyclohexanone 25. Racemic Protocol. To a solution of **24** (8.0 mg, 0.0212 mmol) in $\text{CH}_2\text{Cl}_2/2$ -propanol (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) were added *ent*-sulfonamide **31** (9.2 mg, 0.0217 mmol) and piperidine (18.5 mg, 21 μL , 0.217 mmol) at -20 °C. After being stirred at the 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; $[\alpha]_{\text{D}}^{23} = +101$ ($c = 0.78$, CHCl_3); IR (neat) 2925, 2099, 1716, 1699, 1445, 1355, 1303, 1140, 1088, 723, 688 cm^{-1} ; $^1\text{H NMR}$ (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); $^{13}\text{C NMR}$ (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 $\text{C}_{18}\text{H}_{24}\text{N}_3\text{O}_4\text{S}$ ($M + \text{H}$) 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. The $^1\text{H NMR}$ 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 on the basis of 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) were added sulfonamide **31** (3.4 mg, 0.0812 mmol) and piperidine (6.9 mg, 8 μL , 0.0812 mmol) at -20 °C. After being stirred at the 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: $[\alpha]_{\text{D}}^{23} = +63.3$ ($c = 1.3$, CHCl_3); IR (neat) 2949, 2884, 1713, 1446, 1375, 1310, 1364, 1141, 1108, 1075, 972, 754, 721, 629 cm^{-1} ; $^1\text{H NMR}$ (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); $^{13}\text{C NMR}$ (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 $\text{C}_{16}\text{H}_{20}\text{O}_4\text{S}$ (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) were added sulfonamide **31** (3.3 mg, 0.077 mmol) and piperidine (6.6 mg, 7.7 μL , 0.077 mmol) at -20 °C. After being stirred at the 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 a colorless oil: $[\alpha]_{\text{D}}^{23} = +35$ ($c = 0.8$, CHCl_3); IR (neat) 2922, 2851, 1718, 1364, 1299, 1255, 1075, 836, 716, 689 cm^{-1} ; $^1\text{H NMR}$ (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); $^{13}\text{C NMR}$ (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 $\text{C}_{23}\text{H}_{36}\text{O}_5\text{NaSSi}$ ($M + \text{Na}$) 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) were added sulfonamide **31** (3.5 mg, 8.33 μmol) and piperidine (7.1 mg, 8.2 μL , 0.0833 mmol) at -20 °C. After being stirred at the same temperature for 72 h, the reaction mixture 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: $[\alpha]_{\text{D}}^{23} = +44.4$ ($c = 1.1$, CHCl_3); IR (neat) 2922, 1718, 1696, 1304, 1141, 689 cm^{-1} ; $^1\text{H NMR}$ (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); $^{13}\text{C NMR}$ (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 $\text{C}_{22}\text{H}_{24}\text{O}_4\text{SNa}$ (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) were added sulfonamide **31**

(5.7 mg, 0.0137 mmol) and piperidine (11.6 mg, 13 μ L, 0.137 mmol) at $-20\text{ }^{\circ}\text{C}$. After being stirred at same temperature for 6 days, the reaction mixture 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 a colorless oil: $[\alpha]_{\text{D}}^{23} = -22$ ($c = 0.3$, 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, CDCl_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 $\text{C}_{15}\text{H}_{18}\text{O}_4\text{NaS}$ ($\text{M} + \text{Na}$) 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 $-78\text{ }^{\circ}\text{C}$ was added lithium 2,2,6,6-tetramethylpiperidine⁵⁴ (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 precooled THF (5 mL) was added via cannula to the sulfone solution. After being stirred at -78 to $-20\text{ }^{\circ}\text{C}$ for 90 min, the reaction mixture was removed from the cooling bath, quenched with satd 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 by 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 $\text{C}_{17}\text{H}_{23}\text{N}_3\text{O}_3\text{NaS}$ ($\text{M} + \text{Na}$) 372.1358, found 372.1333.

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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 compounds **7a**, **25**, **37**, and **49** are also provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.