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# Concise Total Synthesis of (±)-Lycopladine A

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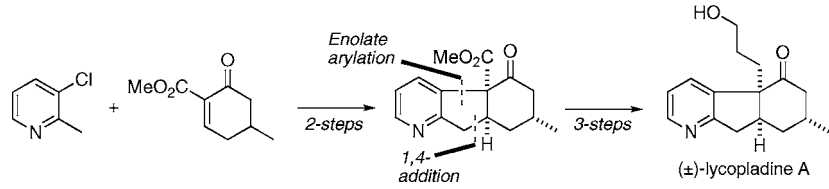
## ABSTRACT

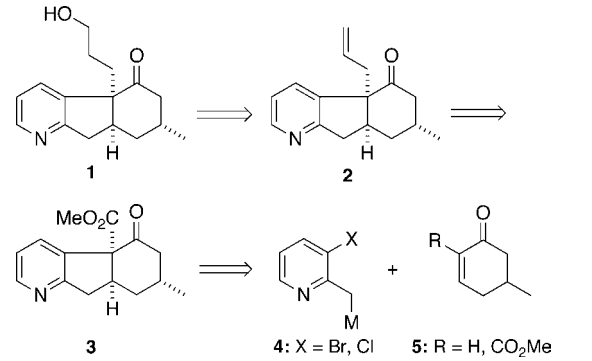



**A concise total synthesis of the *Lycopodium* alkaloid lycopladine A (1) is described that features sequential conjugate addition and enolate arylation reactions to construct the tricyclic core in two steps.**

Lycopladine A (**1**) is a member of the *Lycopodium* alkaloid family that was isolated from the club moss *Lycopodium complanatum* in 2006 by Kobayashi and co-workers.[1] It possesses an unprecedented $C_{16}N$-type framework consisting of a pyridyl-fused hydrindanone core, and it shows selective but modest cytotoxicity toward murine lymphoma L1210 cells ($IC_{50} = 7\ \mu g/mL$).[1] Despite its unusual structure and interesting biological activity, there has been only a single account of the total synthesis of **1** that was reported by Toste and co-workers in 2006 and featured a gold(I)-catalyzed cyclization of a silyl enol ether onto an alkyne to construct the key quaternary center.[2] We now report a facile, alternative entry to this alkaloid that involves some novel chemistry involving the 1,4-addition of a pyridylmethyl carbanion to a cyclic enone, a reaction that we believe has general utility.

In our retrosynthetic analysis, we reasoned that the selective hydroboration/oxidation of **2** would provide the natural product **1** (Scheme 1). Intermediate **2** would then in turn be accessed from tricycle **3** via a sequence comprising of a transesterification using allyl alcohol followed by a palladium-catalyzed decarboxylative allylation. Tricycle **3** could be obtained from a diastereoselective conjugate addition of an organometallic derivative of a commercially available 3-halo-2-methylpyridine **4** (X = Br, Cl) to an α,β-unsaturated carbonyl compound **5**, followed by an intramolecular enolate arylation. In fact, our interest in this approach was stimulated in part by related investigations of enantioselective 1,4-additions.[3]

**Scheme 1.** Retrosynthetic Analysis of (±)-Lycopladine A (**1**)




(1) Ishiuchi, K.; Kubota, T.; Morita, H.; Kobayashi, J. *Tetrahedron Lett.* **2006**, *47*, 3287–3289.

(2) Staben, S. T.; Kennedy-Smith, J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5991–5994.

(3) Smith, A. J.; Abbott, L. K.; Martin, S. F. *Org. Lett.* **2009**, *11*, 4200–4203.

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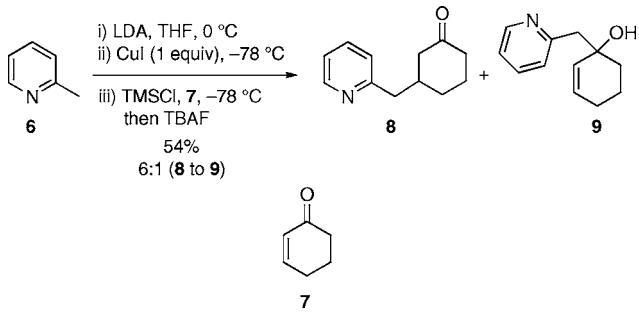
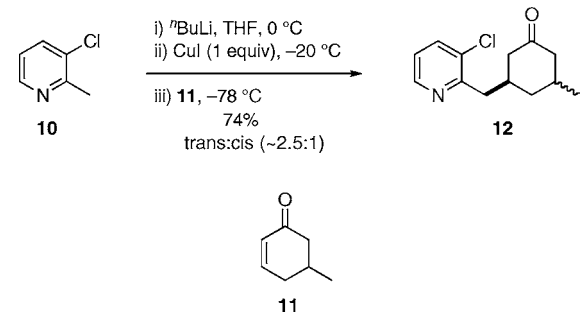
Although there are a few isolated reports of 1,4-additions of metalated picoline derivatives to cyclic and acyclic enones,[4] this is not a well-known transformation, and 1,2-addition may be a significant side reaction,[4b,e,5] especially with allylic and benzylic cuprates.[6] Indeed, in preliminary experiments in which we examined reactions of 1-cyclohex-2-enone (**7**) with organocuprates derived from **6**, 1,2- and 1,4-addition products **8** and **9** were formed in approximately equal amounts. We then examined the corresponding reaction of **7** with the organocopper species generated from **6** using 1 equiv of copper iodide (CuI) and discovered that 1,4-addition dominated giving a mixture (6:1) of **8** and **9**, respectively (Scheme 2). The nature of the copper(I) salt did not appear to matter significantly as comparable yields of the 1,4-adduct were obtained using either CuCN or CuI·0.75DMS. On the other hand, use of tetrahydrofuran (THF) as solvent gave better ratios of the 1,4-adduct than diethyl ether ($Et_2O$).[7] When chlorotrimethylsilane (TMSCl) was not used as an additive,[8] a mixture of **8** to **9** (2:1) was produced. Colder temperatures also seemed to favor 1,4-addition, but cooling below −78 °C did not have a significant effect on the ratio of products.

**Scheme 2.** Conjugate Addition of Pyridyl Anions: Model Study




Having established in a simple model the underlying feasibility of the first stage of our approach to lycopladine A, we turned our attention to preparing the organocopper reagent derived from commercially available **10**. Accordingly, deprotonation of **10** with $^n$BuLi in THF at 0 °C proceeded without detectable metal−halogen exchange, and transmetalation with CuI at −20 °C generated an organocopper intermediate that was allowed to react with racemic 5-methylcyclohex-2-en-1-one (**11**) to provide an inseparable epimeric mixture (∼2.5:1) of **12** together with small amounts of a mixture of 1,2-adducts (Scheme 3). In this case, addition

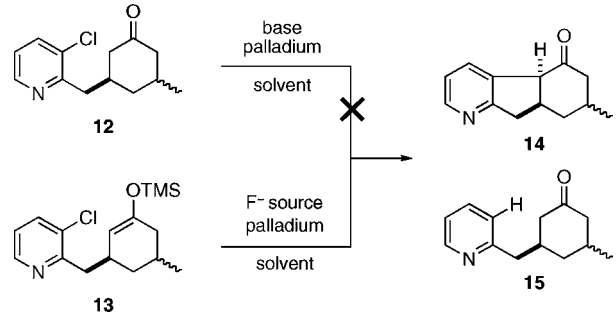
**Scheme 3.** Conjugate Addition of Pyridyl Anions: Initial Studies




of TMSCl had little beneficial affect upon the ratio of 1,4- vs 1,2-addition.

The next step of the synthesis required cyclization of **12** to give the tricyclic core of lycopladine A. However, numerous attempts to effect the palladium-catalyzed cyclization of the enolate of **12** to give **14** were unsuccessful (Scheme 4). On the other hand, we found in preliminary experiments that **13**, which was obtained by trapping the enolate generated from the reaction of **10** with **11** (Scheme 3), afforded an inseparable mixture of **15** and a compound whose spectral characteristics were consistent with those expected for **14**. The low yield of this reaction coupled with the concomitant formation of variable amounts of **15** rendered this approach problematic.

**Scheme 4.** Enolate Arylation: Initial Attempts




Because a number of examples involving arylations of enolates derived from 1,3-dicarbonyl compounds have been reported,[9] we decided to use the unsaturated $\beta$-ketoester **16**[10] as the conjugate addition partner. In the event, reaction of the organocopper reagent derived from **10** with **16** proceeded with a high level of 1,4-selectivity to furnish **17** as a mixture (∼5.5:1 in $CDCl_3$) of enol and keto tautomers (Scheme 5).

(4) (a) Zhuang, Z.-P.; Zhou, W.-S. *Tetrahedron* **1985**, *41*, 3633–3641. (b) Kraus, G. A.; Vines, D. R.; Malpert, J. H. *Tetrahedron* **1995**, *51*, 1337–1344. (c) Celanire, S.; Salliot-Maire, I.; Ribereau, P.; Godard, A.; Queguiner, G. *Tetrahedron* **1999**, *55*, 9269–9282. (d) Bennasar, M.-L.; Roca, R.; Monerris, M. *J. Org. Chem.* **2004**, *69*, 752–756. (e) Pirnot, M. T.; Taber, D. F. Thesis, The University of Delaware, Spring 2009.

(5) Sanchez-Sancho, F.; Herradon, B. *Heterocycles* **2003**, *60*, 1843–1854.

(6) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1990**, *112*, 4404–4410.

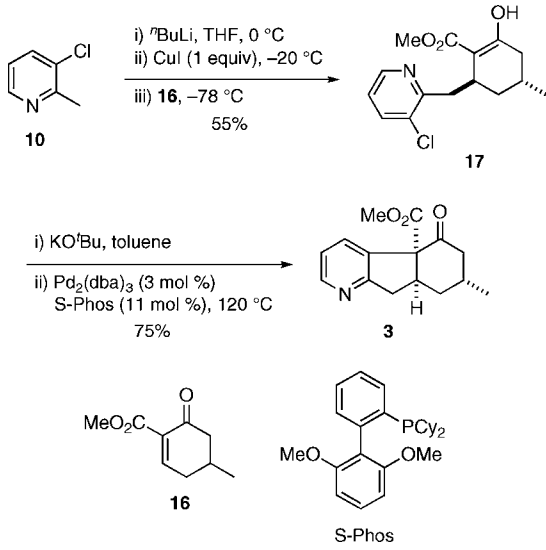
(7) House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1978**, *43*, 2443–2454.

(8) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019–6022.

(9) For a review of Pd-catalyzed α-arylations of carbonyl compounds, see: Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245.

(10) Heuschmann, M. *Chem. Ber.* **1988**, *121*, 39–49.

**Scheme 5.** Conjugate Addition and Enolate Arylation




The diastereoselectivity of this 1,4-addition was judged to be >20:1 as the epimer was not detected by NMR spectroscopy.[11]

Initial attempts to effect the cyclization of **17** using potassium *tert*-butoxide (KO$^t$Bu) and either Pd(PPh$_3$)$_4$ or Pd(P$^t$Bu$_3$)$_2$[12] as the catalyst were unsuccessful. However, when 2-(2′,6′-dimethoxybiphenyl)dicyclohexylphosphine (S-Phos), an electron-rich ligand developed by Buchwald,[13] was used together with tris(dibenzylideneacetone)dipalladium [Pd$_2$(dba)$_3$], the potassium enolate of **17** underwent facile cyclization to deliver the requisite tricycle **3** as a single diastereomer. Although S-Phos had originally been reported to be effective in promoting Suzuki−Miyaura couplings, it has also been successfully employed in other enolate arylations.[14] The relative stereochemistry of **3** was confirmed unequivocally by single-crystal X-ray diffraction (Figure 1).

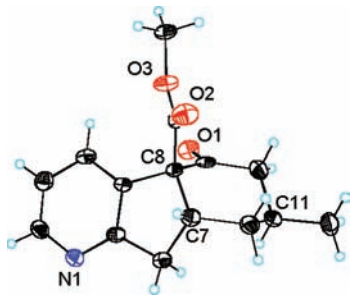
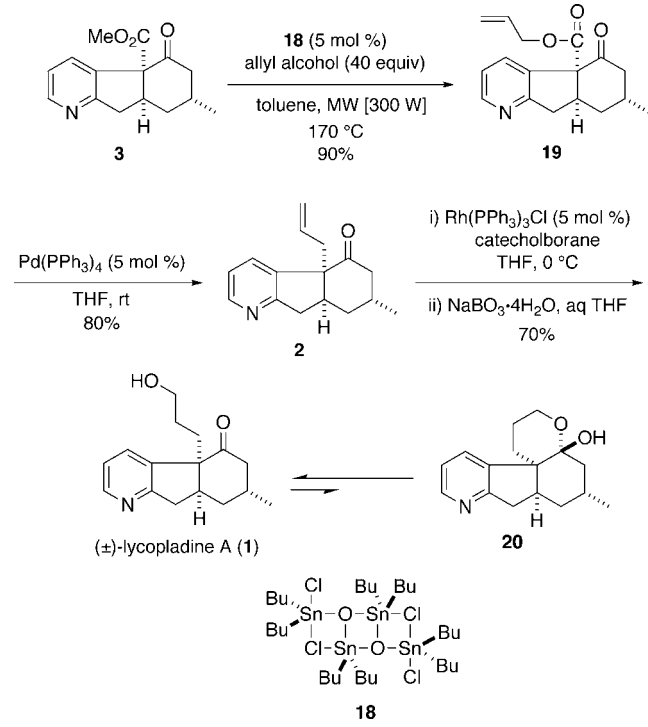



**Figure 1.** X-ray structure of compound **3**.

It now remained to elaborate the angular methyl ester in **3** into the 3-propanol side chain found in lycopladine A. Toward this end, we envisioned that the allyl ester **19** would serve as a useful intermediate. However, initial efforts to effect the acid-catalyzed transesterification of **3** with allyl alcohol returned only starting material, whereas use of basic conditions led to ring cleavage by a retro-Dieckmann reaction. We eventually discovered that **3** could be smoothly transformed into **19** in 90% yield by heating with an excess of allyl alcohol in the presence of the Otera catalyst **18** under microwave conditions (Scheme 6).[15] Central to the success of this reaction was the rigorous exclusion of water in order to prevent the formation of the ketone via sequential hydrolysis of the ester and decarboxylation.

**Scheme 6.** Completion of the Synthesis of **1**




Subsequent exposure of **19** to catalytic amounts of Pd(PPh$_3$)$_4$ led to a facile decarboxylation−allylation reaction to give **2** in 80% yield.[16] When **2** was treated with 9-borabicyclo[3.3.1]nonane (9-BBN-H) followed by oxidation of the intermediate organoborane, lycopladine A (**1**) was obtained, albeit in only 12% yield. Alternatively, reaction of **2** with catecholborane in the presence of the Wilkinson

(11) When the tautomeric mixture of **17** was treated with TESCl and Et$_3$N, a single silyl enol ether was obtained.

(12) (a) Iwama, T.; Rawal, V. H. *Org. Lett.* **2006**, *8*, 5725–5728. (b) Su, W.; Raders, S.; Verkade, J. G.; Liao, X.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2006**, *45*, 5852–5855.

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(14) Chobanian, H. R.; Liu, P.; Chioda, M. D.; Guo, Y.; Lin, L. S. *Tetrahedron Lett.* **2007**, *48*, 1213–1216.

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(16) (a) Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199–3202. (b) Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381–6384.

catalyst $[Rh(PPh_3)_3Cl]$[17] afforded an intermediate alkyl boronic ester that was oxidized using aqueous sodium perborate ($NaBO_3 \cdot 4H_2O$) to deliver lycopladine A in 70% yield. The spectral data ($^1H$ and $^{13}C$ NMR) of synthetic **1** were consistent with those previously reported.[1,2,18] Additionally, we observed minor amounts of what appears to be the isomeric lactol **20**, the proportion of which varies with solvent.

In summary, a concise total synthesis of (±)-lycopladine A (**1**) has been completed in 21% overall yield by a process requiring only five steps from the $\beta$-ketoester **16**. The synthesis features a novel sequence of conjugate addition and enolate arylation to form the tricyclic core in only two steps. Because **16** can be prepared in enantiomerically pure form,[19] this approach is also amenable to an enantioselective synthesis of **1**.

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**Supporting Information Available:** Experimental procedures, spectral data, copies of $^1H$ NMR and $^{13}C$ NMR for **1**−**3**, **8**, **9**, **12**, **13**, **17**, **19**, and **21**, and comparison of spectral data for synthetic and naturally occurring **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100273P

(17) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671–6679.

(18) In $CD_3OD$ the lactol **20** comprises about 8% of the total mixture, whereas in $C_6D_6$ the amount of **20** increases to about 20%. When a mixture of **1** and **20** was treated with TBSCl/imidazole, a single silyl ether **21** was obtained in 95% yield.

(19) Gruseck, U.; Heuschmann, M. *Tetrahedron Lett.* **1987**, *28*, 2681–2684.