

Concise Total Synthesis of
(±)-Lycopladiene A

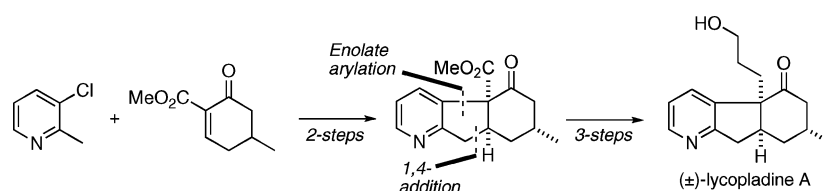
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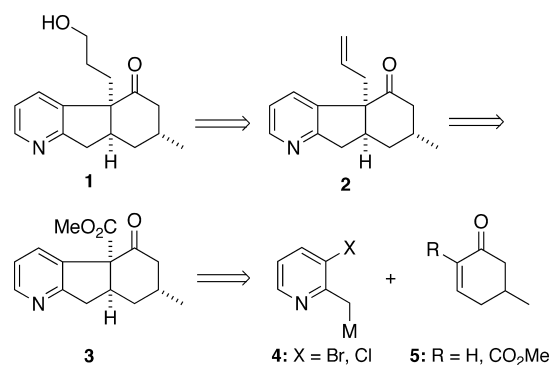
ABSTRACT



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

Lycopladiene 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 C₁₆N-type framework consisting of a pyridyl-fused hydrindanone core, and it shows selective but modest cytotoxicity toward murine lymphoma L1210 cells (IC₅₀ = 7 μg/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**

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

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

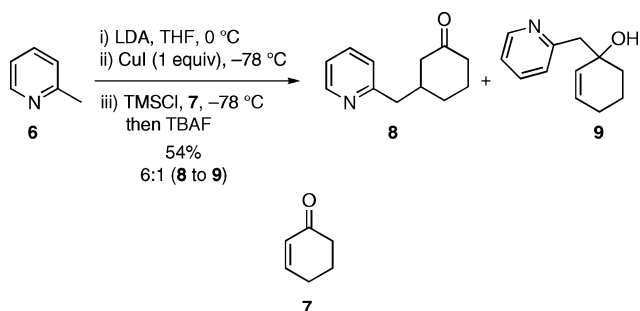
(1) Ishiuchi, K.; Kubota, T.; Morita, H.; Kobayashi, J. *Tetrahedron Lett.* **2006**, 47, 3287–3289.

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

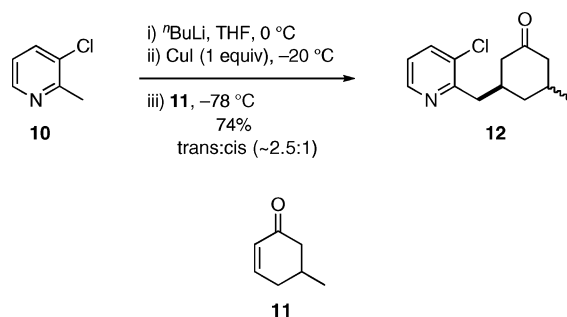
Although there are a few isolated reports of 1,4-additions of metalated picoline derivatives to cyclic and acyclic enones,⁴ this is not a well-known transformation, and 1,2-addition may be a significant side reaction,^{4b,e,5} especially with allylic and benzylic cuprates.⁶ Indeed, in preliminary experiments 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 (Et₂O).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 $-78\text{ }^{\circ}\text{C}$ 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 lycoplamine A, we turned our attention to preparing the organocopper reagent derived from commercially available **10**. Accordingly, deprotonation of **10** with ⁿBuLi in THF at $0\text{ }^{\circ}\text{C}$ proceeded without detectable metal–halogen exchange, and transmetalation with CuI at $-20\text{ }^{\circ}\text{C}$ generated an organocopper intermediate that was allowed to react with racemic 5-methylcyclohex-2-en-1-one (**11**) to provide an inseparable epimeric mixture ($\sim 2.5:1$) of **12** together with small amounts of a mixture of 1,2-adducts (Scheme 3). In this case, addition

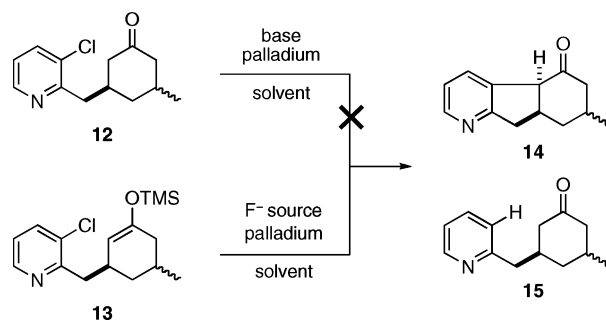
Scheme 3. Conjugate Addition of Pyridyl Anions: Initial Studies



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 lycoplamine 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

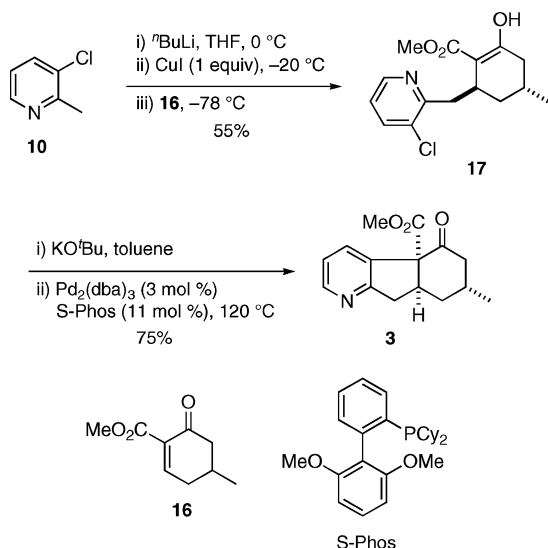


Because a number of examples involving arylations of enolates derived from 1,3-dicarbonyl compounds have been reported,⁹ we decided to use the unsaturated β -ketoester **16**¹⁰ as the conjugate addition partner. In the event, reaction of the organocopper reagent derived from **10** with **16** proceeded with a high level of 1,4-selectivity to furnish **17** as a mixture ($\sim 5.5:1$ in CDCl₃) of enol and keto tautomers (Scheme 5).

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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^tBu) and either Pd(PPh₃)₄ or Pd(P^tBu₃)₂ 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 [Pd₂(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).

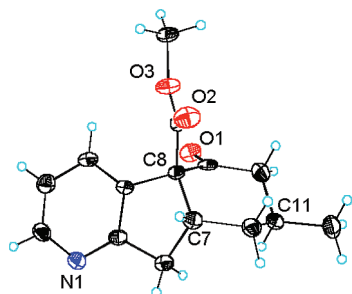


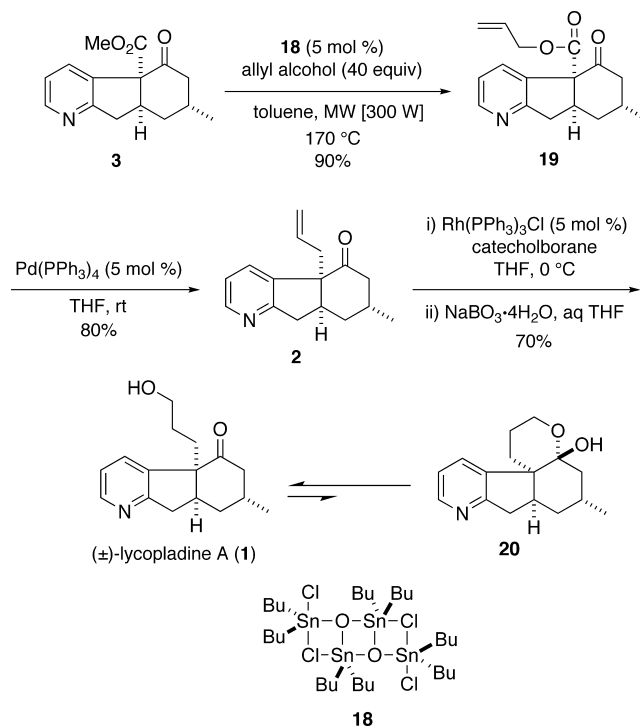
Figure 1. X-ray structure of compound **3**.

It now remained to elaborate the angular methyl ester in **3** into the 3-propanol side chain found in lycopladiene A.

(11) When the tautomeric mixture of **17** was treated with TESCl and Et₃N, a single silyl enol ether was obtained.

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(PPh₃)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, lycopladiene A (**1**) was obtained, albeit in only 12% yield. Alternatively, reaction of **2** with catecholborane in the presence of the Wilkinson

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catalyst $[\text{Rh}(\text{PPh}_3)_3\text{Cl}]^{17}$ afforded an intermediate alkyl boronic ester that was oxidized using aqueous sodium perborate ($\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$) to deliver lycopladiene 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 ($\pm$)-lycopladiene A (**1**) has been completed in 21% overall yield by a process requiring only five steps from the β -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>.

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(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.

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