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A divergent and concise total synthesis of (−)-lycoposerramine R and (+)-lycopladine A†

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A concise, asymmetric and divergent synthesis of lycoposerramine R and lycopladine A is presented. The synthesis features the palladium-catalyzed cycloalkenylation of a silyl enol ether for assembling the 5/6-hydrindane system and generating a quaternary carbon center in one step.

Club mosses, such as *Lycopodium complanatum* and *Lycopodium carinatum*, are a rich source of structurally complex and biologically active alkaloids (Fig. 1).[1–3] Lycoposerramine-R (**1**), isolated by Takayama and co-workers in 2009, was characterized to have a previously unknown skeleton consisting of a fused tetracyclic ring system with four chiral centers, a pyridone ring, and *cis*-fused hydrindane.[4] Its simplified pyridine congener lycopladine A (**2**) was isolated from *L. complanatum* in 2006 and showed modest cytotoxicity against murine lymphoma cells.[5] During the past decade, owing to their compact structures as well as their biological activities, these alkaloids have aroused the interest of a large number of research groups, whose studies have culminated in the completion of several elegant total syntheses of some lycopodium alkaloids and some new synthetic methodologies for assembling their core structures.[6] To date, 4 total syntheses have been reported for lycoposerramine R (**1**)[6h–k] and 7 for lycopladine A (**2**), respectively.[6l–r]

In this communication, we report a facile, alternative entry to these alkaloids that involves some novel chemistry involving the palladium-catalyzed cycloalkenylation of a silyl enol ether,[7] a reaction that we believe will have general utility. As shown in the retrosynthetic analysis (Scheme 1), we reasoned that both lycoposerramine R (**1**) and lycopladine A (**2**) might be constructed from the common intermediate **RS-1** through several different transformations. Intermediate **RS-1** in turn might be accessed from silyl enol ether **RS-2** *via* a sequence of palladium-catalyzed cycloalkenylation of silyl enol ether followed by SeO_2/TBHP oxidation. Silyl enol ether **RS-2** might be obtained from the stereoselective conjugate addition of a Grignard reagent **RS-4** prepared from commercial 4-bromo-1-butene[8] to an α,β-unsaturated carbonyl compound **RS-3**, followed by trapping the enolate with TMSCl, while **RS-3** could be derived from the readily accessible phenylsulfide **1**[9] *via* the introduction of a C3 unit.

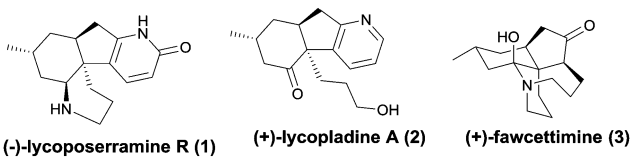
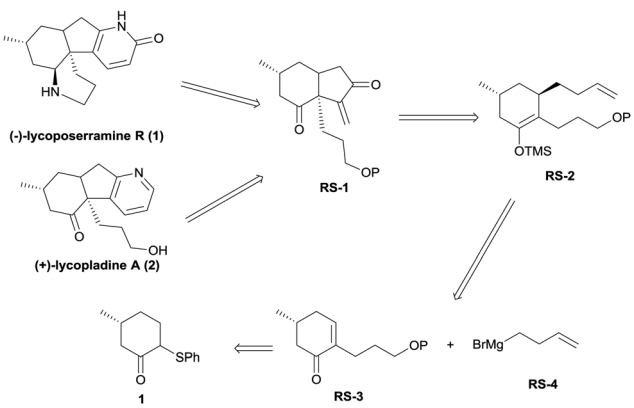


Fig. 1 The structures of lycoposerramine R, lycopladine A, and fawcettimine.



Scheme 1 Retrosynthetic analysis of (−)-lycoposerramine R (**1**) and (+)-lycopladine A (**2**).

Based on the above analysis, the synthetic strategy seemed feasible. Thus, alkylation of enolate of **1** (Scheme 2) with iodide **2**[10] afforded phenylsulfenyl ketone **3** as a diastereomeric mixture (dr = 2.6 : 1) in 65% yield, oxidation of which with *m*-CPBA at −78 °C followed by warming to room temperature afforded enone **4**.[6q] After the copper(I)-mediated conjugate addition of

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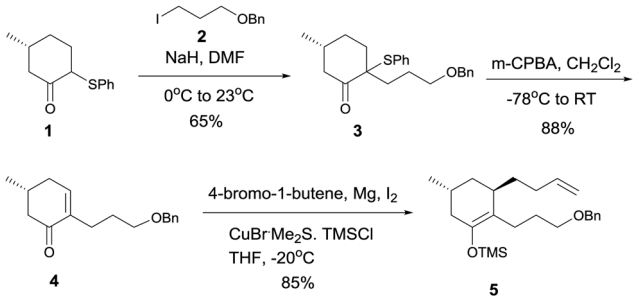
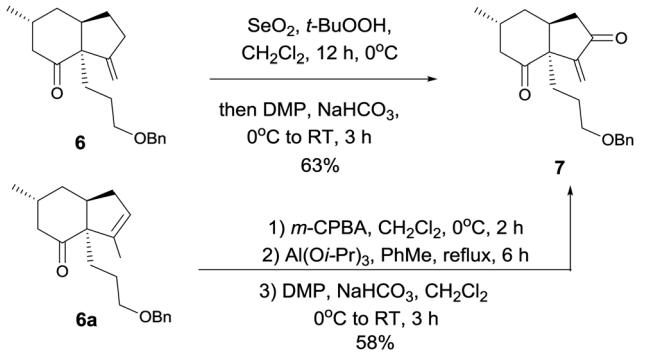


Scheme 2 Synthesis of silyl enol ether **5**.

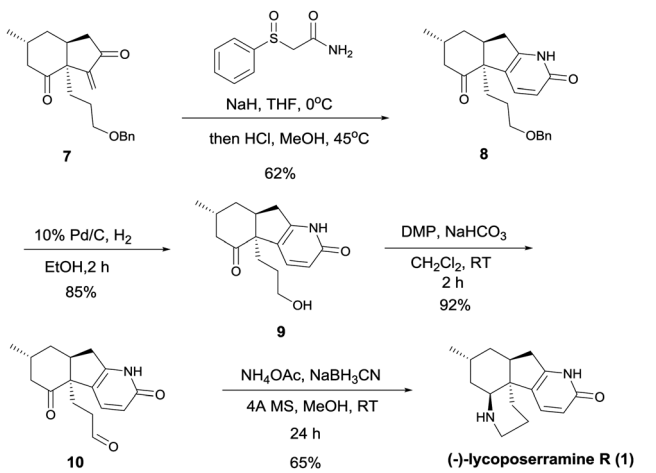


Scheme 3 Synthesis of key intermediate **7**.

the Grignard reagent freshly prepared from 4-bromo-1-butene to enone **4** to generate an enolate, TMSCl was added at −20 °C to yield silyl enol ether **5** in 85% overall yield.

At this stage, we began to investigate the key cycloalkenylation (Table 1). Surprisingly, treatment of the silyl enol ether **5** with stoichiometric amounts of palladium acetate in dry THF yielded *exo*-olefin **6** along with *endo*-olefin **6a** in 35% and 17% yields, respectively. After many unfruitful attempts, it was found that when treated with 10 mol% of palladium acetate in dry DMSO under a balloon pressure of oxygen at 45 °C, silyl enol ether **5** underwent cycloalkenylation and *exo*-olefin **6** was obtained in 48% yield together with *endo*-olefin **6a** in 26% yield. Allylic oxidation of **6** using SeO_2/TBHP, followed by Dess–Martin oxidation yielded the desired key intermediate **7** in 63% yield. Treatment of the *endo*-olefin **6a** with *m*-CPBA, followed by Al(Oi-Pr)$_3$ and oxidation by the Dess–Martin reagent yielded **7** in 58% yield (Scheme 3).

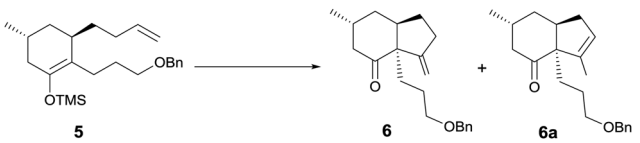
Addition of 2-(phenylsulfonyl)acetamide[11] to intermediate **7** in the presence of sodium hydride, followed by treatment with methanolic hydrogen chloride, resulted in the formation of intermediate **8** in 62% yield (Scheme 4). Removal of the benzyl group by treatment with 10% Pd/C in EtOH under a hydrogen atmosphere gave intermediate **9** (85%). Dess–Martin oxidation of this alcohol yielded ketoaldehyde **10** (92%), which when treated with ammonium acetate in the presence of $NaBH_3CN$ in methanol at room temperature for 24 h afforded (−)-lycoposerramine R (**1**) in 65% yield. Synthetic (−)-lycoposerramine R (**1**) was identical in all respects to the natural product.



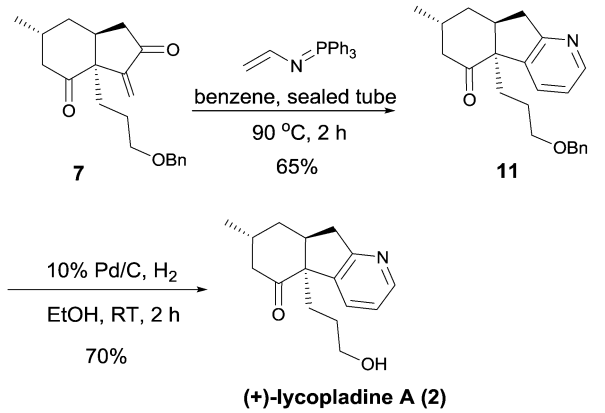
Scheme 4 Total synthesis of (−)-lycoposerramine R (**1**).

With intermediate **7** in hand, the synthesis of (+)-lycopladine A (**2**) was investigated (Scheme 5). When treated with (*N*-vinylimino)phosphorene[12] in dry benzene at 90 °C in a sealed tube, intermediate **7** underwent cyclization to afford intermediate **11** in 65% yield. Finally, removal of the benzyl group in **11** gave (+)-lycopladine A (**2**) (70%). The synthetic (+)-lycopladine A (**2**) showed identical spectroscopic properties in all respects to the natural product.

Table 1 Palladium-catalyzed cycloalkenylation of **5**



Entry	Catalyst (equiv.)	Solvent	Temp.	Additives (equiv.)	**6** (%)	**6a** (%)
1	$PdCl_2(PPh_3)_2$ (1.0)	THF	RT	—	0	0
2	$Pd(CF_2COOH)_2$ (1.0)	THF	RT	—	Trace	Trace
3	$PdCl_2$ (1.0)	THF	RT	—	23	10
4	$Pd(OAc)_2$ (1.0)	THF	RT	—	35	17
5	$Pd(OAc)_2$ (0.1)	THF	RT	$Cu(OAc)_2·H_2O$ (1.0)	6	2
6	$Pd(OAc)_2$ (0.1)	THF	RT	Ag_2CO_3 (1.0)	6	2
7	$Pd(OAc)_2$ (0.1)	THF	RT	Benzoquinone (1.0)	6	2
8	$Pd(OAc)_2$ (0.1)	DMSO	RT	O_2	33	16
9	$Pd(OAc)_2$ (0.1)	DMSO	45 °C	O_2	48	26



Scheme 5 Total synthesis of (+)-lycopladine A (**2**).

In summary, by using a divergent strategy we have developed a concise, asymmetric total synthesis of both (−)-lycoposerramine-R (**1**) and (+)-lycopladine A (**2**) from known phenylsulfide **1** in 9 and 7 steps, respectively. The key features of the current synthesis include a palladium-catalyzed cycloalkenylation of silyl enol ether **5** for assembling the 6,5-fused hydrindane and generating a quaternary carbon center in one step. The application of these synthetic studies to an enantioselective synthesis of the related fawcettimine-type alkaloid **3** will be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

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