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A Divergent and Concise Total Synthesis of (-)-Lycoposerramine R and (+)-Lycopladine A

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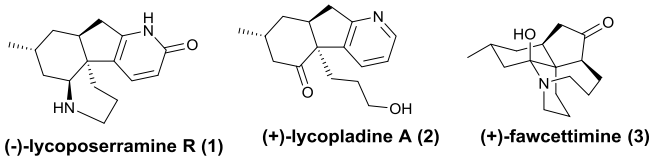
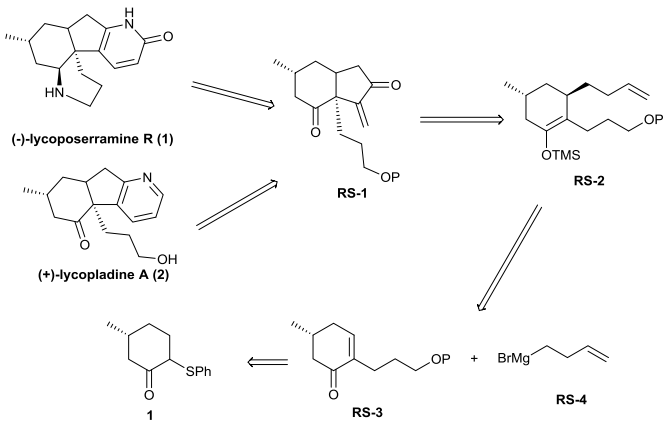
A concise, asymmetric and divergent synthesis of lycoposerramine R and lycopladine A is presented. The synthesis features a palladium-catalyzed cycloalkenylation of a silyl enol ether for assembling the 5/6-hydrindane system and generating a quaternary carbon center in one step.

Club mosses, such as *Lycopodium complanatum* and *Lycopodium carinatum*, are a rich source of structurally complex and biologically active alkaloids (**Figure 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 the 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]

Figure 1 The structures of lycoposerramine R, lycopladine A, and fawcettimine



In this paper, we report a facile, alternative entry to these alkaloids that involves some novel chemistry involving a 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 lycopossserramine 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 a palladium-catalyzed cycloalkenylation of silyl enol ether followed by a SeO_2/TBHP oxidation. Silyl enol ether **RS-2** might be obtained from a 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.



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 =

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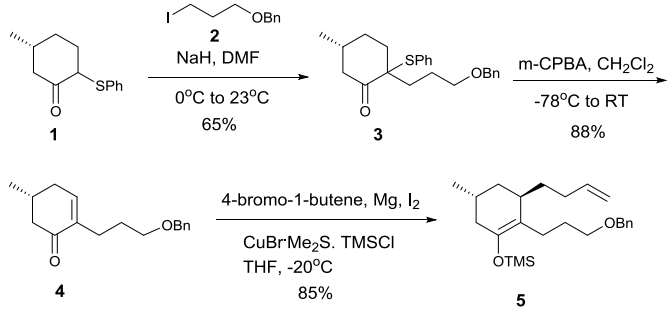
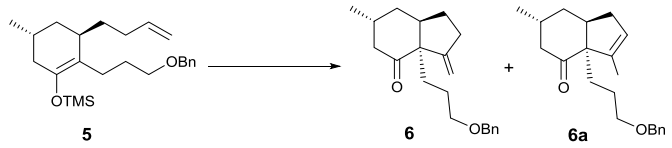
2.6:1) in 65% yield, oxidation of which with *m*-CPBA at -78°C followed by warming to room temperature afforded enone **4**[6q]. After the copper(I)-mediated conjugate addition of the Grignard reagent freshly prepared from 4-bromo-1-butene to enone **4** to generate an enolate, TMSCl was added at -20 °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% yileds, respectively. After many unfruitful attempts, it was found that when treated with 10 mol% of palladium acetate in dry DMSO



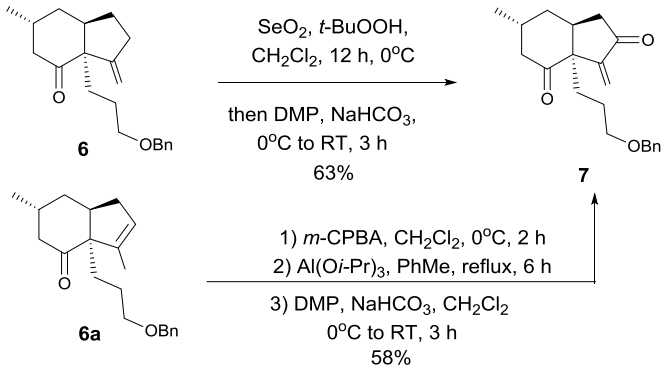
Scheme 2. Synthesis of silyl enol ether 5.

Table 1. Palladium-Catalyzed Cycloalkenylation of 5.



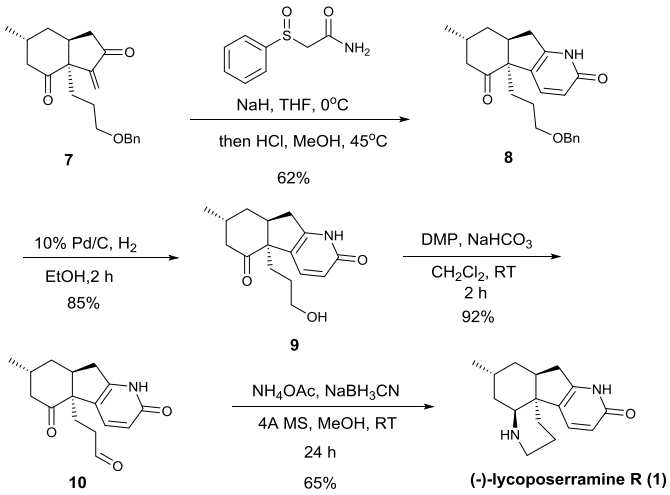
Entry	Catalyst (equiv)	Solvent	Temp	Additives (equiv)	6 (%)	6a (%)
1	$PdCl_2(PPh_3)_2$ (1.0)	THF	RT	-	0	0
2	$Pd(CF_2COOH)_2$ (1.0)	THF	RT	-	trace	trace
3	$PdCl_2$ (1.0)	THF	RT	-	23	10
4	$Pd(OAc)_2$ (1.0)	THF	RT	-	35	17
5	$Pd(OAc)_2$ (0.1)	THF	RT	$Cu(OAc)_2·H_2O$ (1.0)	6	2
6	$Pd(OAc)_2$ (0.1)	THF	RT	Ag_2CO_3 (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

under a balloon pressure of oxygen at 45°C, silyl enol ether **5** underwent the 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 $Al(Oi\text{-}Pr)_3$ and oxidation by Dess-Martin reagent yielded **7** in 58% yield (**Scheme 3**).



Scheme 3. Synthesis of key intermediate 7.

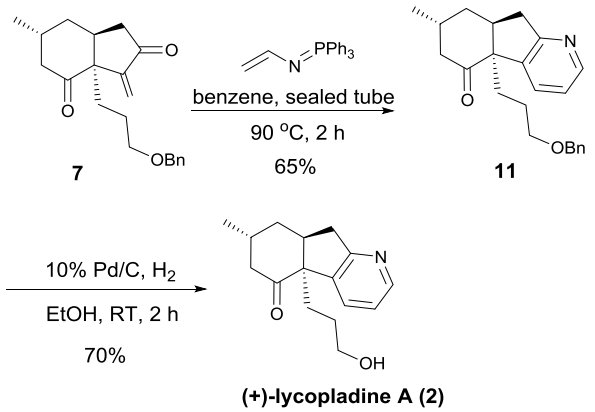
Addition of 2-(phenylsufinyl)acetamide[11] to intermediate **7** in the presence of sodium hydride, followed by treatment with methanolic hydrogen chloride, resulted in the formation of intermediate **8** in 62% yield (**Scheme 4**). Removal of the benzyl group by treatment with 10% Pd/C in EtOH under 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.



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.

Acknowledgements

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