



Cite this: *Chem. Commun.*, 2018, 54, 3598

Received 27th February 2018,
Accepted 8th March 2018

DOI: 10.1039/c8cc01626g

rsc.li/chemcomm

A concise, asymmetric and divergent synthesis of lycoposerramine R and lycopladiene 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 lycopladiene 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 lycopladiene 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 lycopladiene 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

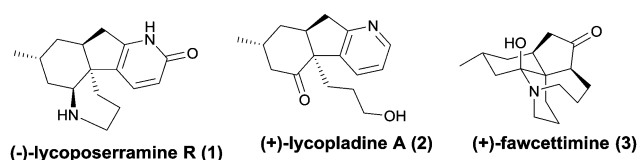
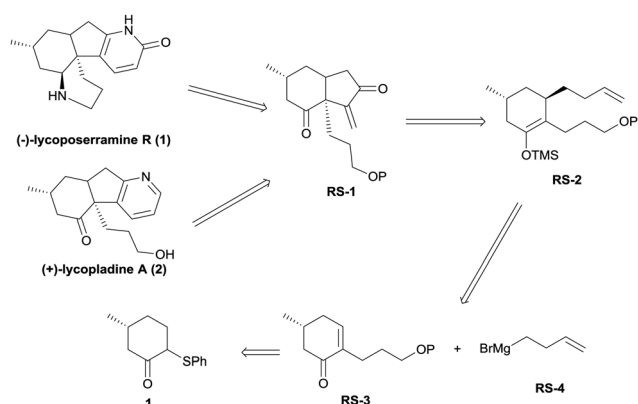


Fig. 1 The structures of lycoposerramine R, lycopladiene A, and fawcettimine.



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

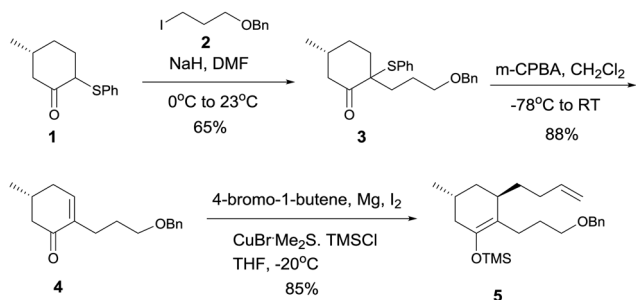
palladium-catalyzed cycloalkenylation of silyl enol ether followed by SeO₂/TBHP oxidation. Silyl enol ether **RS-2** might be obtained from the stereoselective conjugate addition of a Grignard reagent **RS-4** prepared from commercial 4-bromo-1-butene⁸ to an α,β -unsaturated carbonyl compound **RS-3**, 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.

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

^a Guangzhou Institute of Biomedicine and Health, The Chinese Academy of Sciences, 190 Kaiyuan Ave., The Science Park of Guangzhou, Guangdong, 510530, China. E-mail: qiu_fayang@gibh.ac.cn

^b The University of The Chinese Academy of Sciences, Beijing, 100049, China

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8cc01626g

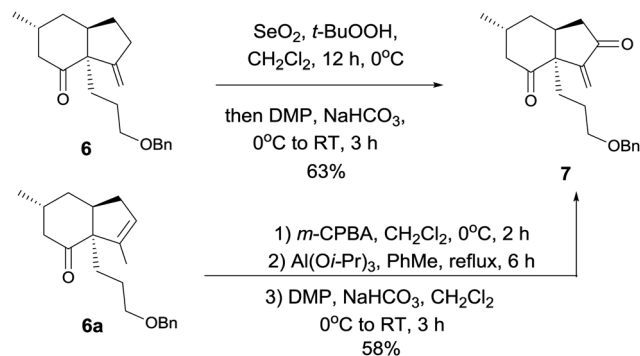


Scheme 2 Synthesis of silyl enol ether 5.

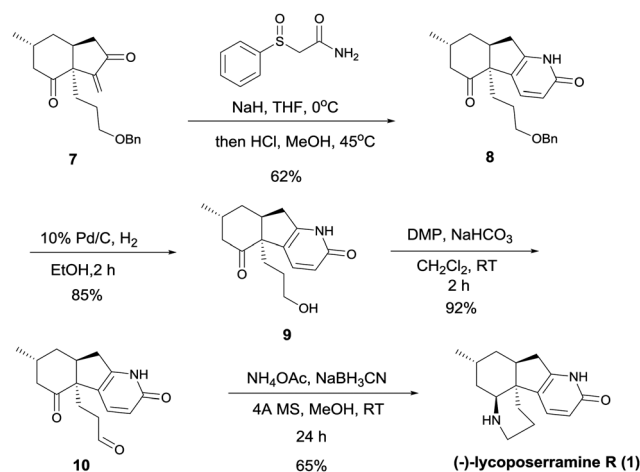
the Grignard reagent freshly prepared from 4-bromo-1-butene to enone 4 to generate an enolate, TMSCl was added at $-20\text{ }^{\circ}\text{C}$ to yield silyl enol ether 5 in 85% overall yield.

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 $45\text{ }^{\circ}\text{C}$, 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 $\text{Al}(\text{O}i\text{-Pr})_3$ and oxidation by the Dess–Martin reagent yielded 7 in 58% yield (Scheme 3).

Addition of 2-(phenylsulfonyl)acetamide¹¹ 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 (–)-lycposerramine R (1) in 65% yield. Synthetic (–)-lycposerramine R (1) was identical in all respects to the natural product.



Scheme 3 Synthesis of key intermediate 7.

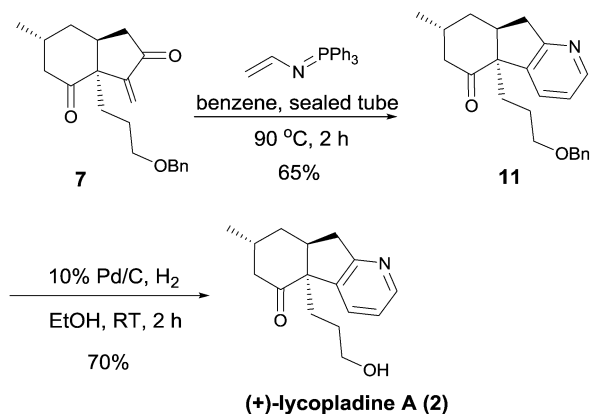


Scheme 4 Total synthesis of (–)-lycposerramine R (1).

With intermediate 7 in hand, the synthesis of (+)-lycpladine A (2) was investigated (Scheme 5). When treated with (*N*-vinylimino)phosphorene¹² in dry benzene at $90\text{ }^{\circ}\text{C}$ in a sealed tube, intermediate 7 underwent cyclization to afford intermediate 11 in 65% yield. Finally, removal of the benzyl group in 11 gave (+)-lycpladine A (2) (70%). The synthetic (+)-lycpladine 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	$\text{PdCl}_2(\text{PPh}_3)_2$ (1.0)	THF	RT	—	0	0
2	$\text{Pd}(\text{CF}_3\text{COOH})_2$ (1.0)	THF	RT	—	Trace	Trace
3	PdCl_2 (1.0)	THF	RT	—	23	10
4	$\text{Pd}(\text{OAc})_2$ (1.0)	THF	RT	—	35	17
5	$\text{Pd}(\text{OAc})_2$ (0.1)	THF	RT	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1.0)	6	2
6	$\text{Pd}(\text{OAc})_2$ (0.1)	THF	RT	Ag_2CO_3 (1.0)	6	2
7	$\text{Pd}(\text{OAc})_2$ (0.1)	THF	RT	Benzoquinone (1.0)	6	2
8	$\text{Pd}(\text{OAc})_2$ (0.1)	DMSO	RT	O_2	33	16
9	$\text{Pd}(\text{OAc})_2$ (0.1)	DMSO	$45\text{ }^{\circ}\text{C}$	O_2	48	26



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

In summary, by using a divergent strategy we have developed a concise, asymmetric total synthesis of both (–)-lycoposerramine-R (1) and (+)-lycopoladine 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.

We are grateful to the National Natural Science Foundation of China for the financial support of this work (Grant #21372221 and #21572228).

Conflicts of interest

There are no conflicts to declare.

Notes and references

- X. Ma and D. R. Gang, *Nat. Prod. Rep.*, 2004, **21**, 752.
- Y. Hirasawa, J. Kobayashi and H. Morita, *Heterocycles*, 2009, **77**, 679.

- P. Siengalewicz, J. Mulzer and U. Rinner, in *the Alkaloids: Chemistry and Biology*, ed. K. Hans-Joachim, Academic Press, New York, 2013; vol. 72, p 1.
- K. Katakawa, N. Kogure, M. Kitajima and H. Takayama, *Helv. Chim. Acta*, 2009, **92**, 445.
- K. I. Ishiuchi, T. Kubota, H. Morita and J. I. Kobayashi, *Tetrahedron Lett.*, 2006, **47**, 3287.
- For selected recent examples of the total synthesis of lycopodium alkaloids, see: (a) B. K. Hong, H. H. Li, J. B. Wu, J. Zhang and X. G. Lei, *Angew. Chem., Int. Ed.*, 2015, **54**, 1011; (b) P. S. Chauhan, J. R. Sacher and S. M. Weinreb, *Org. Lett.*, 2015, **17**, 806; (c) K. W. Lin, B. Ananthan, S. F. Tseng and T. H. Yan, *Org. Lett.*, 2015, **17**, 3938; (d) C. Bosch, B. Fiser, E. Gomez-Bengoia, B. Bradshaw and J. Bonjoch, *Org. Lett.*, 2015, **17**, 5084; (e) R. A. Samame, C. M. Owens and S. D. Rychnovsky, *Chem. Sci.*, 2016, **7**, 188; (f) B. M. Williams and D. Trauner, *Angew. Chem., Int. Ed.*, 2016, **55**, 2191; (g) Y. Ochi, S. Yokoshima and T. Fukuyama, *Org. Lett.*, 2016, **18**, 1494; (h) V. Bisai and R. Sarpong, *Org. Lett.*, 2010, **12**, 2552; (i) H. Ishida, S. Kimura, N. Kogure, M. Kitajima and H. Takayama, *Tetrahedron*, 2015, **71**, 51; (j) H. Ishida, S. Kimura, N. Kogure, M. Kitajima and H. Takayama, *Org. Biomol. Chem.*, 2015, **13**, 7762; (k) F. W. W. Hartrampf, T. Furukawa and D. Trauner, *Angew. Chem., Int. Ed.*, 2017, **56**, 893; (l) F. W. W. Hartrampf and D. Trauner, *J. Org. Chem.*, 2017, **82**, 8206; (m) L. Meng, *J. Org. Chem.*, 2016, **81**, 7784; (n) K. Hiroya, Y. Suwa, Y. Ichihashi, K. Inamoto and T. Doi, *J. Org. Chem.*, 2011, **76**, 4522; (o) X. J. Liu and S. L. You, *Angew. Chem., Int. Ed.*, 2017, **56**, 1; (p) J. E. DeLorbe, M. D. Lotz and S. F. Martin, *Org. Lett.*, 2010, **12**, 1576; (q) S. T. Staben, J. J. Kennedy-Smith, D. Huang, B. K. Corkey, R. L. LaLonde and F. D. Toste, *Angew. Chem., Int. Ed.*, 2006, **45**, 5991; (r) T. Xu, X. L. Luo and Y. Yang, *Tetrahedron Lett.*, 2013, **54**, 2858.
- (a) M. Toyota, A. Ilangovan, R. Okamoto, T. Masaki, M. Arakawa and M. Ihara, *Org. Lett.*, 2002, **4**, 4293; (b) A. S. Kende, B. Roth, P. J. Sanfilippo and T. J. Blacklock, *J. Am. Chem. Soc.*, 1982, **104**, 5808; (c) A. S. Kende, B. Roth and P. J. Sanfilippo, *J. Am. Chem. Soc.*, 1982, **104**, 1784.
- S. Kumar, P. D. Thornton, T. O. Painter, P. Jain, J. Downard, J. T. Douglas and C. Santini, *J. Org. Chem.*, 2013, **78**, 6529.
- D. Caine, K. Proter and R. A. Cassell, *J. Org. Chem.*, 1984, **49**, 2647.
- B. Guillaume, St. O. Miguel and B. C. Andre, *Org. Lett.*, 2008, **10**, 5497.
- T. Nishimura, A. K. Unni, S. Yokoshima and T. Fukuyama, *J. Am. Chem. Soc.*, 2013, **135**, 3243.
- R. K. Alan, M. Roman, V. S. Christian and F. G. Mikhail, *J. Org. Chem.*, 1994, **59**, 2740.