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Total Synthesis of Lyconadines A-C

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1. Introduction

1.1 The history of Lyconadins

- Lyconadin A, Lyconadin B and Lyconadin C were isolated from *Lycopodium complanatum* and their structural elucidations were identified by Kobayashi et al in 2001, 2006 and 2011, respectively.
- **Structural feature**:
  Pentacyclic skeletons including three six-membered, one five-membered, and one α-pyridone rings are characteristic features.
  ⇒difficulty of total synthesis.
- The first total synthesis of Lyconadin A (27 steps, 2.2% yield) amd Lyconadin B (28 steps, 2.2% yield)[1] were accomplished by Beshore and Smith in 2007, but Lyconadin C has not been totally synthesized still now.

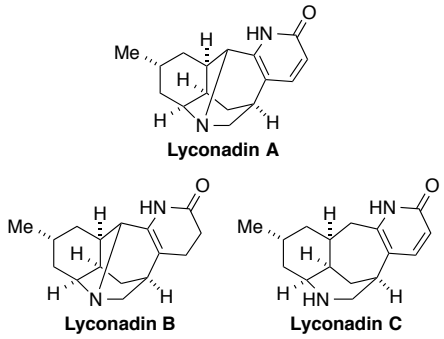
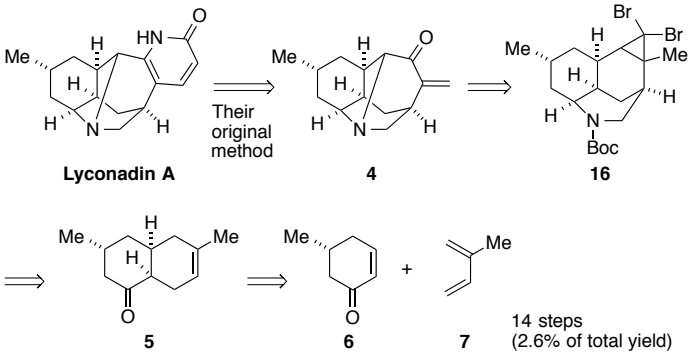


Figure 1. Structure of Lyconadin A-C

1.2 Their previous work

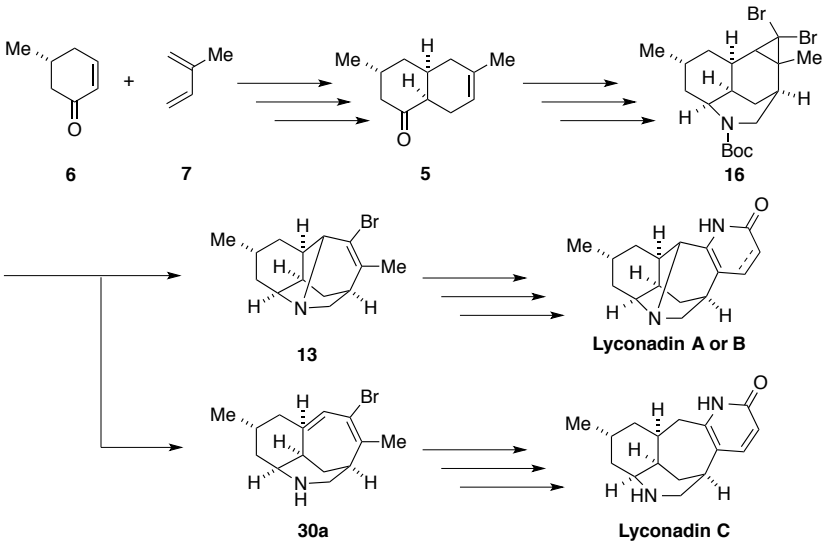
- The authors already reported the total synthesis of Lyconadin A with their unique strategy (from compound **4** to the Lyconadin A). They could synthesize Lyconadin A with much shorter steps and higher yield (14 steps, 12.6% yield) than ever[2].



Scheme 1. Their previous work: retrosynthesis of Lyconadin A

1.3 This work

- In this paper, they applied their unique synthetic strategy to syntheses of Lyconadin B and C, and they achieved total syntheses of Lyconadin B, and C from simple compounds.



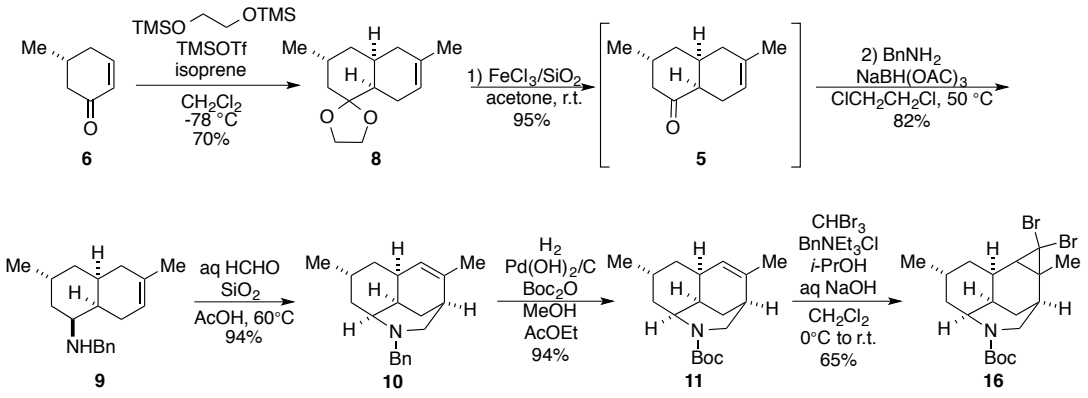
Scheme 2. Synthetic route of Lyconadins

- In this paper, they also developed a strategy to synthesize 13 and 30a from the same compound 16 (Scheme 2).

2. Results and discussion

2.1 Synthesis of the compound 16, the precursor of Lyconadin A–C.

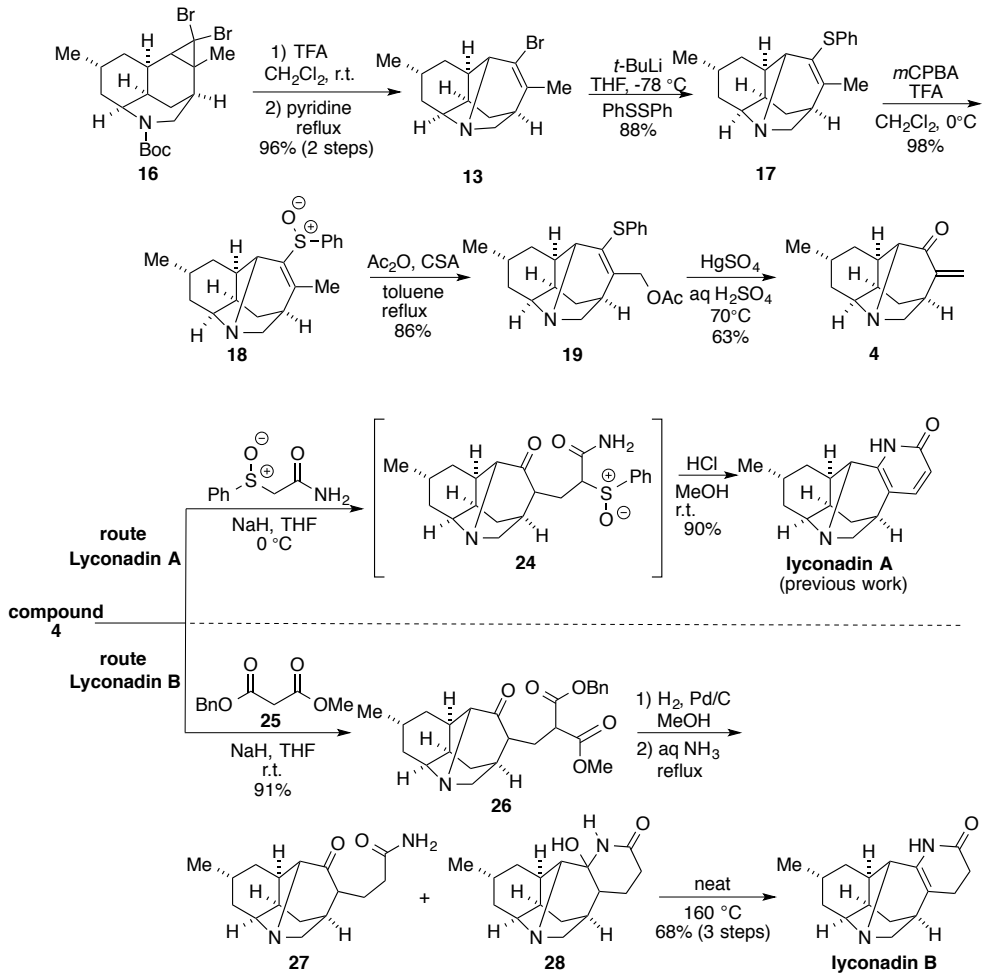
- They started the total synthesis of 16 from the known unsaturated ketone **6,** because compound **16** can be converted to Lyconadin A–C in a few steps.
- The key reaction in Scheme 3 is cyclization reaction (aza-Prins reaction) from compound **9** to compound **10**. ⇒ Because this ring is difficult to be formed.



Scheme 3. Synthesis of compound **16** from compound **6**

2.2 The synthesis of Lyconadin A and B from compound 16

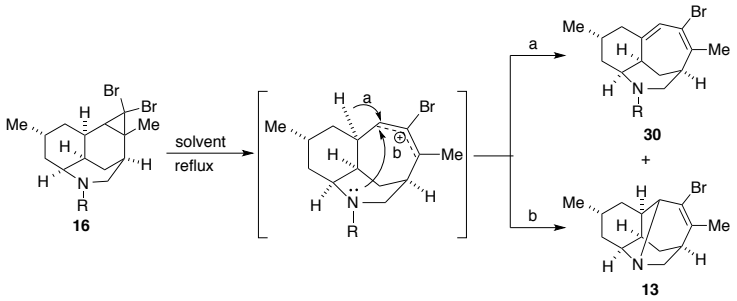
- The authors could synthesize Lyconadin A in 14 steps with 12.6% yield. (previous work)
- They could also synthesize Lyconadin B (16 steps, 8.7% yield) from the compound **6**.
- The key step in Scheme 4 is electrocyclic ring opening reaction from compound **16** to compound **13**



Scheme 4. Synthesis of Lyconadin A and B from compound **16**

2.3 Separate-synthesis of compound 13 or 30a from 16

- To synthesize Lyconadin C, they had to develop new electrocyclic ring opening reaction strategy which do not synthesize C–N bond. (Compound 30 in Table 1).
- They optimized the reaction conditions from compound **16**, to obtain compound **30** with high yield.

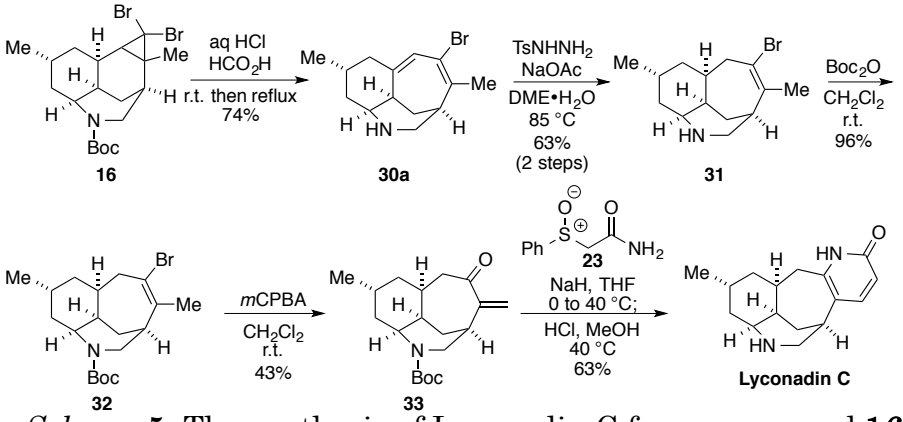


entry	R	solvent	yield (%) 30	13
1	Boc	pyridine	20	46
2	Ts	AcOH	43	51
3	*p*-Ns	AcOH	51	42
4	*o*-Ns	AcOH	89	trace
5	HCl	AcOH	62	20
6	**HCl**	**HCO_2H**	**74**	**n.d.**

Table 1. Scope of the reaction from compound **16** to **30**

2.4 The synthesis of Lyconadin C from 6

- The authors could synthesize Lyconadin C (14 steps, 12.6% yield) from the compound **6** with their original strategy shown in Table 1.



Scheme 5. The synthesis of Lyconadin C from compound **16**

3. Conclusion

- They accomplished total syntheses of Lyconadin A and Lyconadin B with much shorter steps and higher yields (14 steps, 12.6% yield and 16 steps, 8.7% yield, respectively) than previous ones (27 steps, 2.2% yield amd 28 steps, 2.2% yield), and the first total synthesis of Lyconadin C (12 steps, 5.1% yield).
- The authors developed their previous synthetic strategy of Lyconadin A, and applied it to syntheses of Lyconadin B and C.

4. References

(1) Beshore, D. C.; Smith, A. B., *J. Am. Chem. Soc.* **2008**, *130,* 13778.

(2) (a) Nishimura, T.; Unni, A. K., Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 418.

(b) Koshiba, T.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2009**, *11*, 5354.