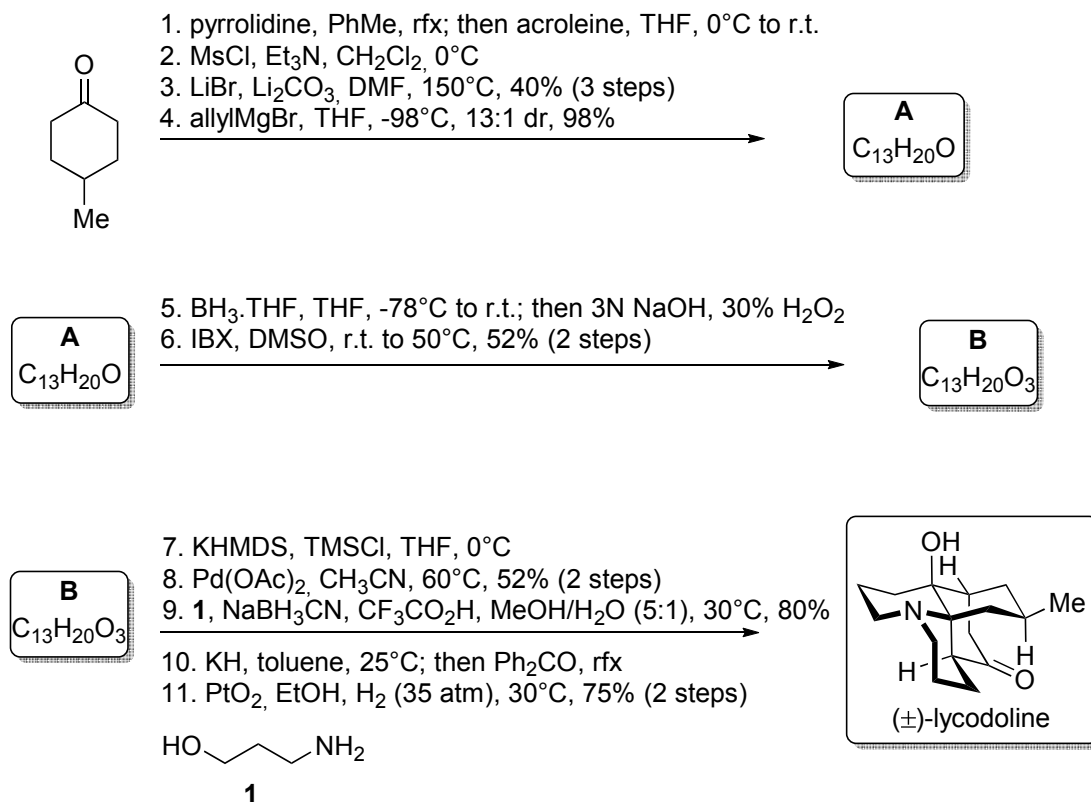


## Problem session (2)

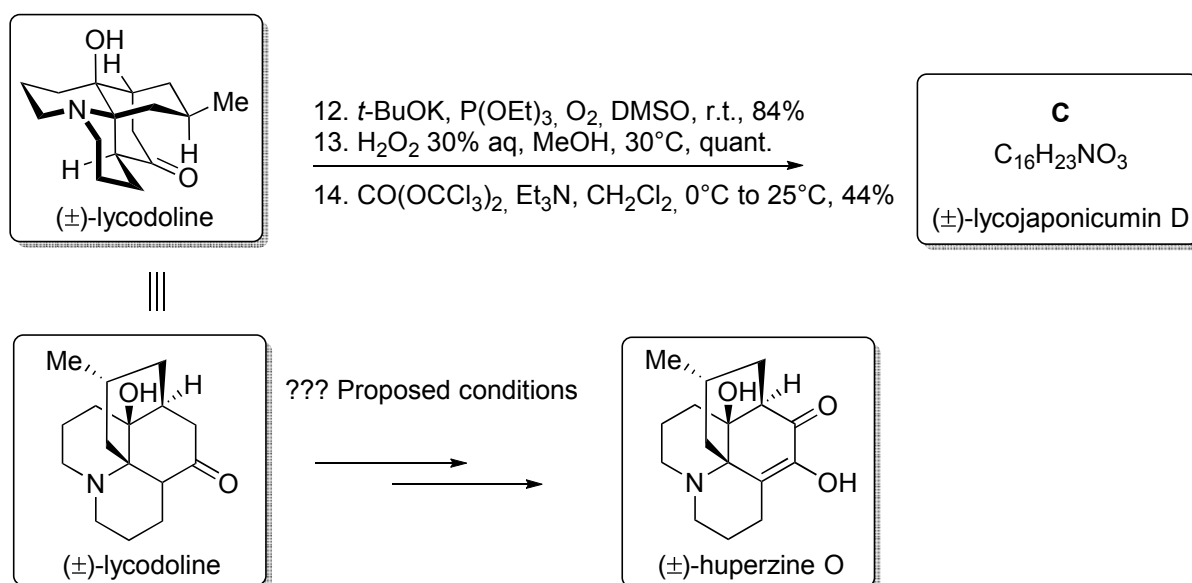
Benjamin Ovadia  
2017.05.13

Please provide structure of compounds **A**, **B**, **C** and give the mechanism of each steps

### Problem 1



### Problem 2

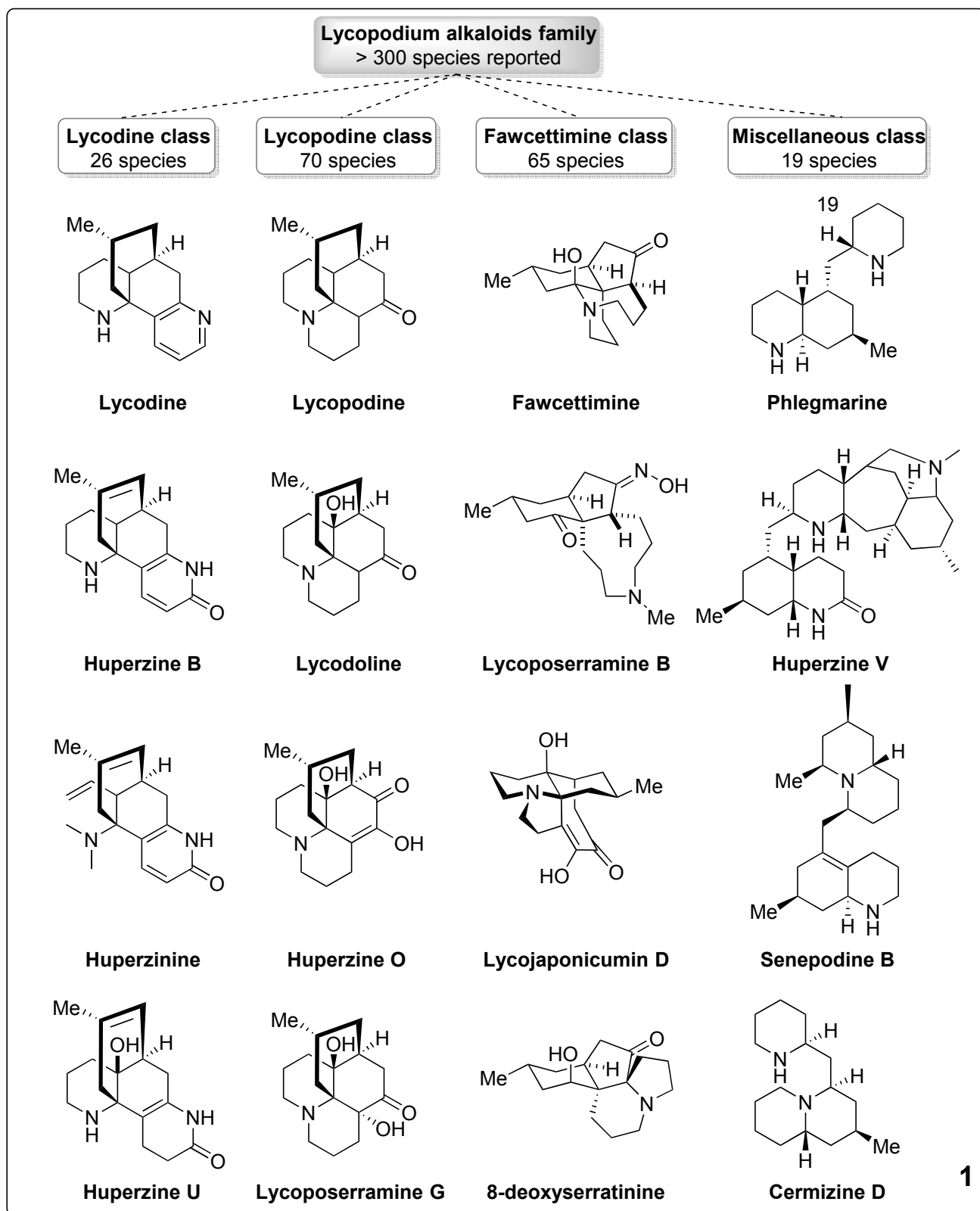


Topic : Total synthesis of Lycodoline-type *Lycopodium* alkaloids

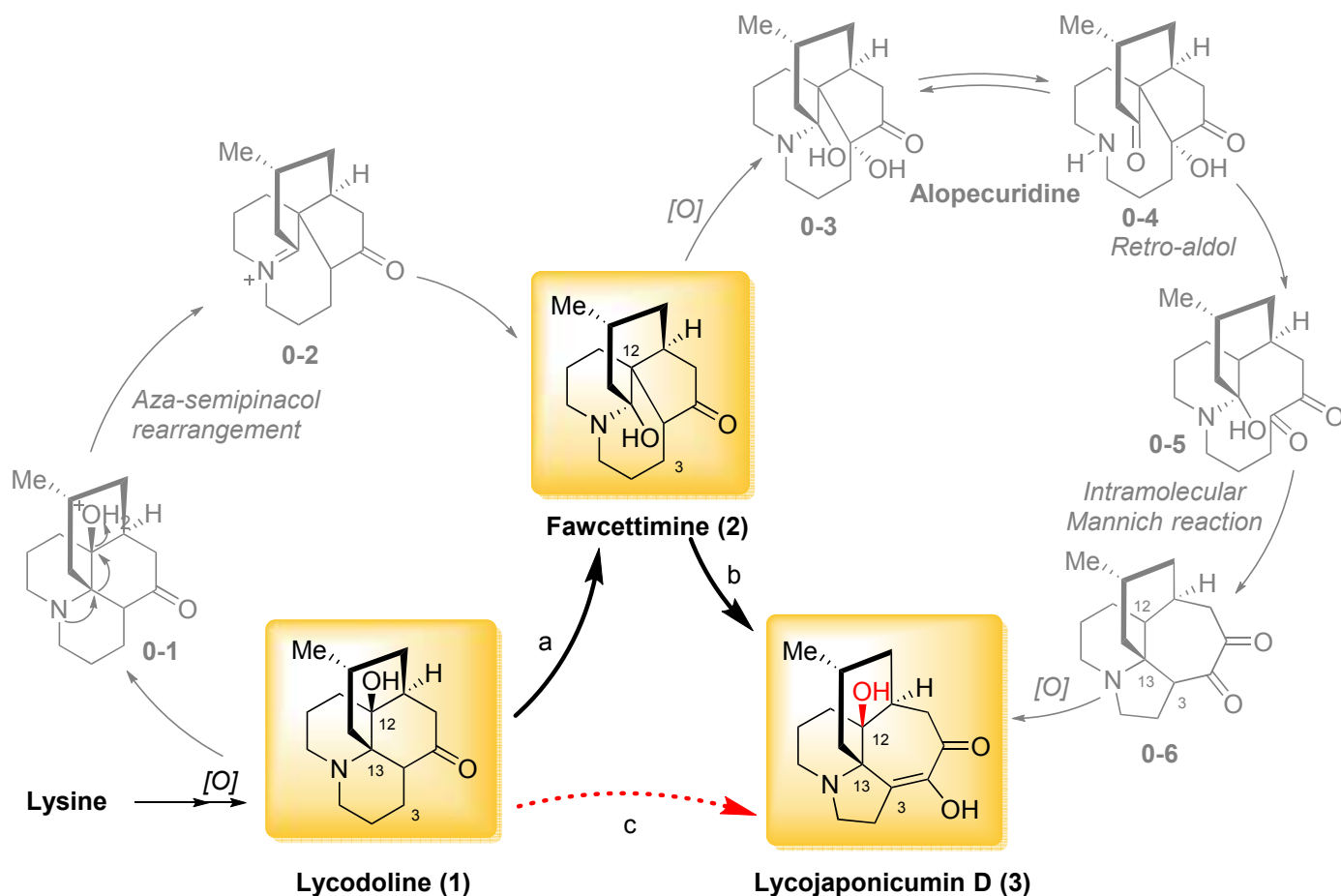
0. Introduction (Sarpong *et al. Chem. Eur. J.* 2014, 20, 42)

0.1. *Lycopodium* alkaloids

- Class of structurally complex alkaloids containing nearly 300 natural products isolated from up to 500 species in the *Lycopodium* genus of club mosses plant
- Investigated for the treatment of various diseases as neurodegenerative disease Alzheimer and Parkinson or as anti-HIV, anti cancer, etc...
- All *Lycopodium* alkaloids are biosynthetically derived from lysine and they have been divided into four class based on structural features



**0.2. Biosynthetic pathway** (Yu *et al. Org. Lett.* 2012, 14, 5688 ; Inubushi *et al. Tetrahedron Lett.* 1966, 7, 1551)



**0.3. Introduction to lycojaponicumine D**

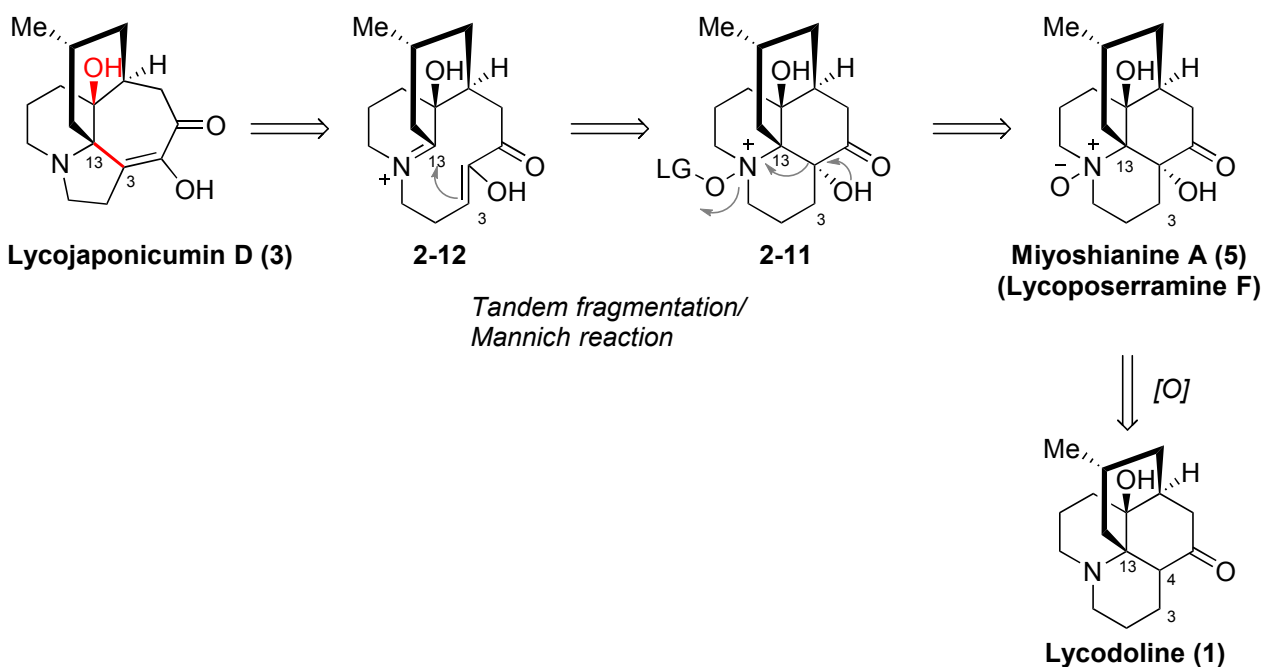
**Isolation** : isolated in 2012 from *Lycopodium Japonicum* by Yu (Yu *et al. Org. Lett.* 2012, 14, 5688 )

**Biological activity** : slightly active against lipopolysaccharide (LPS)-induced pro-inflammatory factors in BV2 macrophages

**Synthetic study** : No total synthesis reported

**Structural feature** : Unprecedented 5/7/6/6-tetracyclic skeleton formed by an unusual C3-C13 linkage (first example)

**Retrosynthetic analysis** :



### 0.4. Introduction to lycodoline

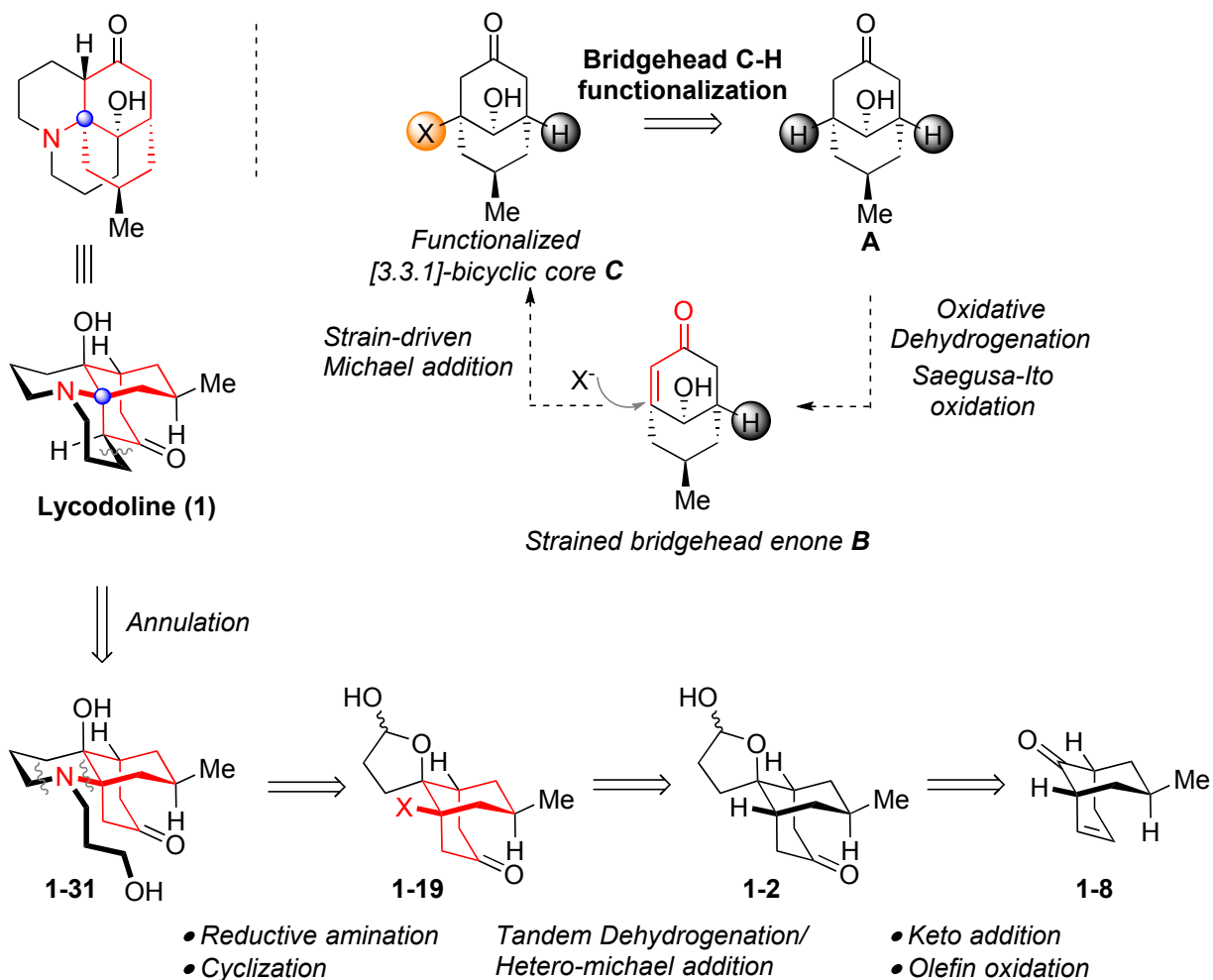
**Isolation** : isolated in 1943 from *Lycopodium. Annotinum Linn.* by Manske and Marion (Manske, R.H, Marion, L. *Can. J. Res.* **1943**, *B21*, 92) and its structure was elucidated by Aver and Iverach in 1961 (Ayer, W.A., Iverach, G.G. *Tetrahedron Lett.* **1962**, *3*, 87)

**Synthetic study** : first total synthesis achieved in 1980 by Heathcock (Heathcock *et al. J. Am. Chem. Soc.* **1982**, *104*, 1054). Formal synthesis reported by Kim in 1981 (Kim *et al. heterocycles* **1981**, *16*, 1515)

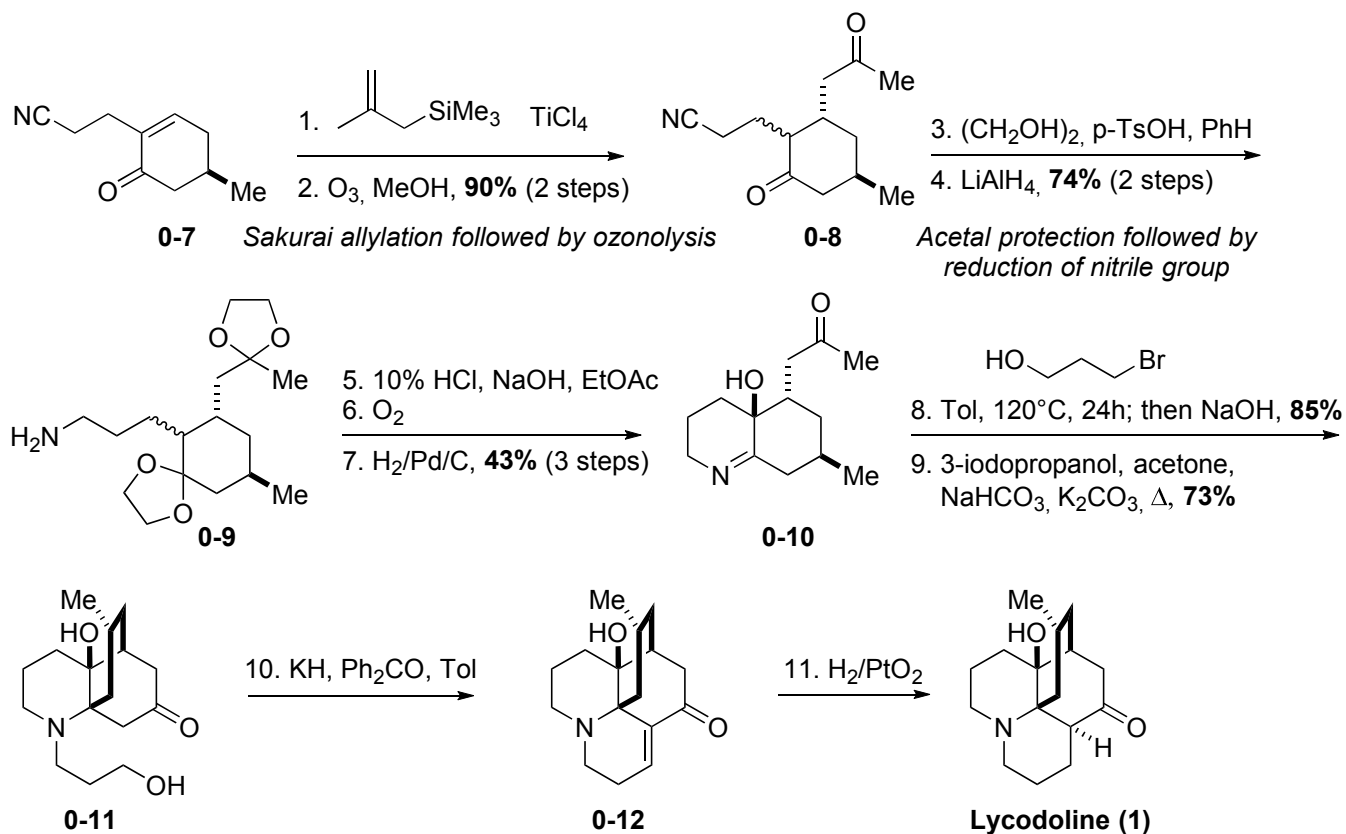
**Structural feature** : 6/6/6-tetracyclic skeleton bearing a functionalized bicyclo[3.3.1]nonane ring system

**Retrosynthetic analysis** :

- Bridgehead C-H heteroatom functionalization

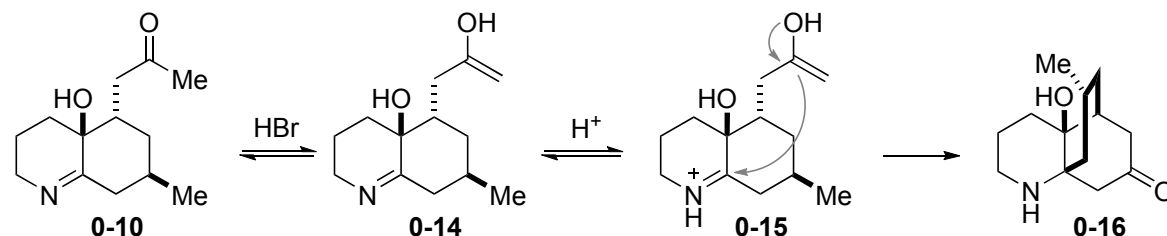


#### 0.4.1. Previous total synthesis of (±)-lycodoline : Heathcock approach



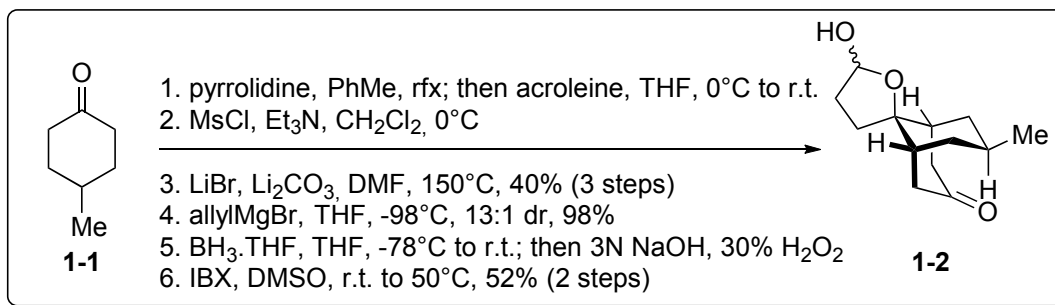
#### Intramolecular Mannich cyclization :

Slow delivery of HBr produced by base-catalyzed polymerization of the bromo alcohol, favorize the enolization to occur without protonation of the imine moiety. Then, when the resulting enol acquires a proton on nitrogen, cyclization occur rapidly.



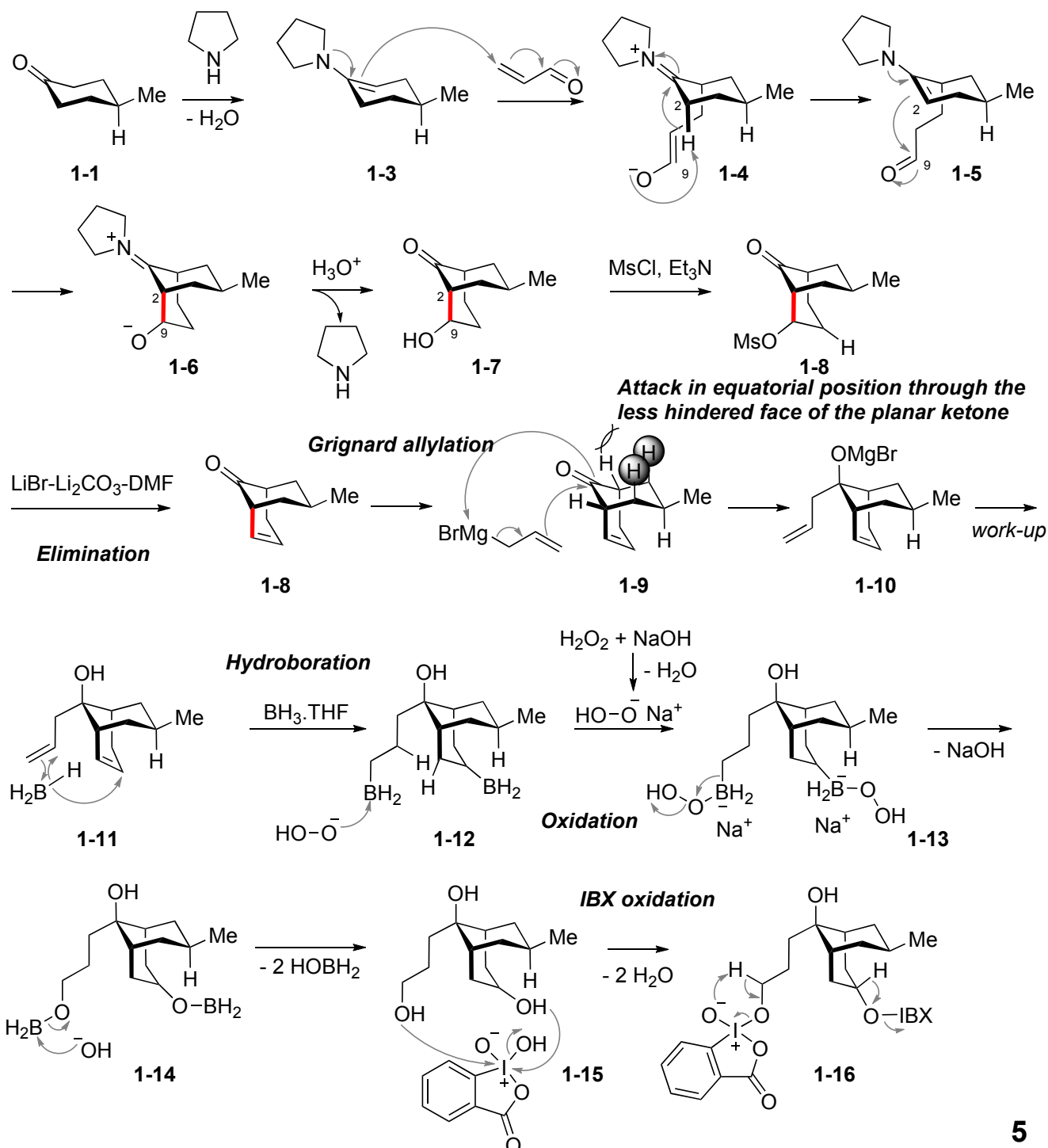
# 1. Total synthesis of (±)-Lycodoline 1

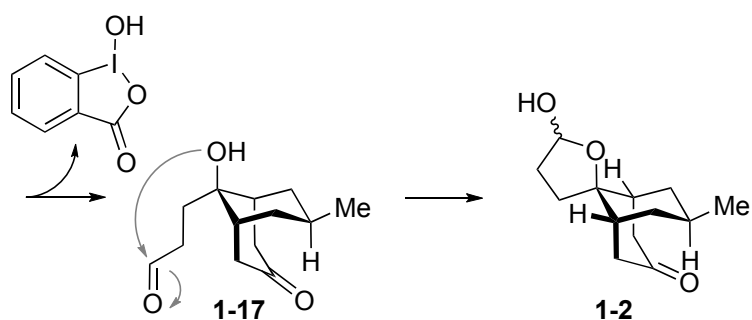
## 1.1. Preparation of precursor 1-2



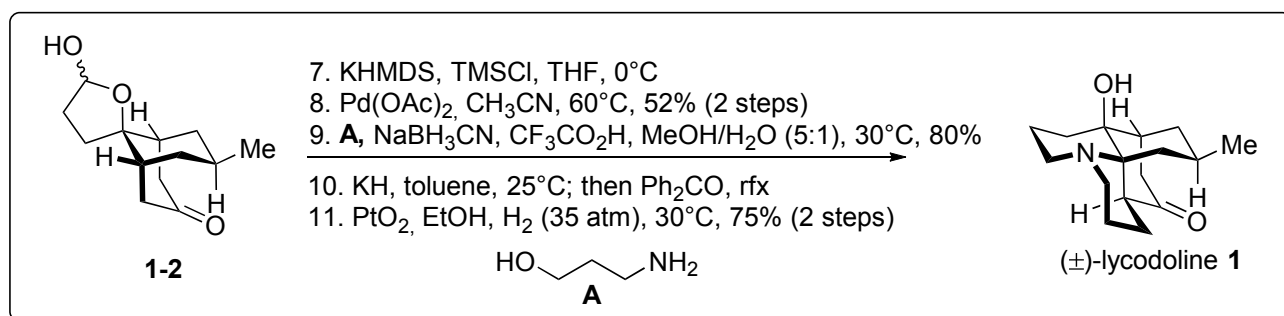
### 1.1.1. Stork-Landesman two carbon ring expansion :

Boucher, R.J., Campbell, A.C., Campbell, M.M., Rae, D. *Tetrahedron* **1990**, *46*, 6839

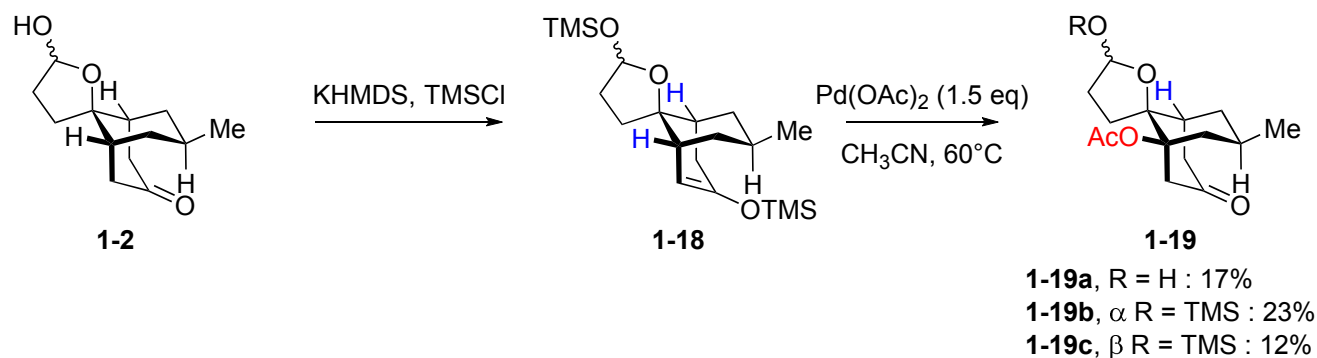




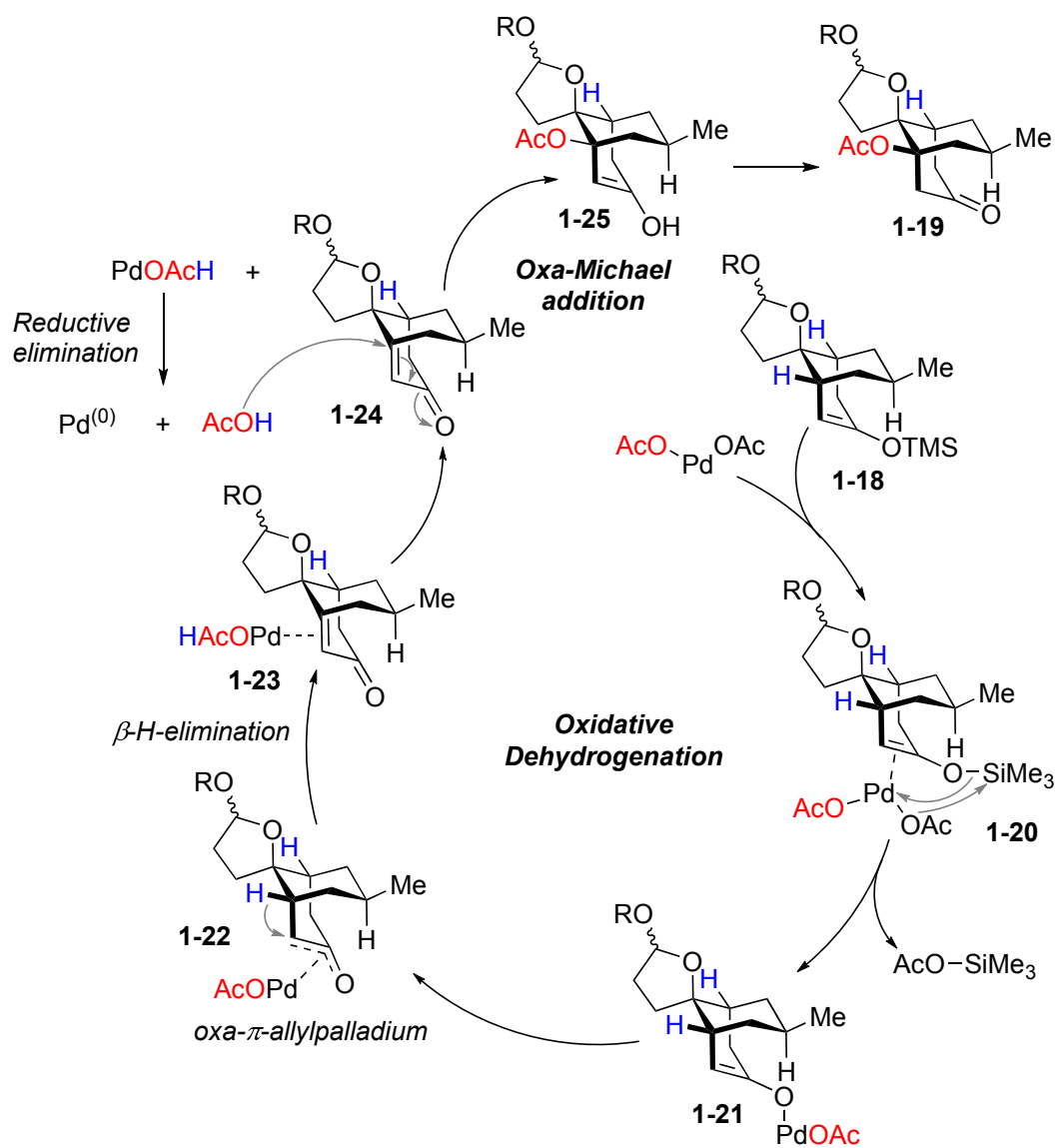
## 1.2. Completion of the synthesis of (±)-lycodoline **1**



### 1.2.1 Bridgehead C-H heteroatom functionalization : Tandem oxidative dehydrogenation (Saegusa-Ito oxidation)/Oxa-Michael addition

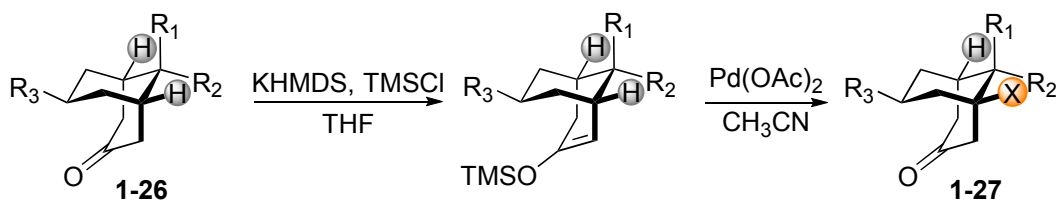


**Mechanism of the Saegusa-Ito oxidation/oxa-Michael addition :**

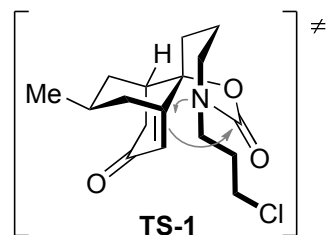




## Scope of the tandem oxidative dehydrogenation/hetero-Michael addition



Entry	Substrates	Products	Yield (%)
1	<p><b>1-26a</b> R = H</p>	<p><b>1-27a</b> R = H R = TMS</p>	52
2	<p><b>1-26b</b>, X = O</p> <p><b>1-26c</b>, X = CH<sub>2</sub></p>	<p><b>1-27b</b>, X = O</p> <p><b>1-27c</b>, X = CH<sub>2</sub></p>	35 39
3	<p><b>1-26d</b></p>	<p><b>1-27d</b></p>	46
4	<p><b>1-26e</b></p>	<p><b>1-27e</b></p>	22
5	<p><b>1-26f</b></p>	<p><b>1-27f</b></p>	46
7	<p><b>1-26g</b></p>	<p><b>1-27g</b></p>	13
8	<p><b>1-26h</b></p>	<p><b>1-27h</b></p>	59



### Strained energy for bridgehead enones

House *et al.* *J. Org. Chem.* 1983, 48, 1643



[3.2.1]

32.3 kcal/mol



[3.3.1]

21.3 kcal/mol



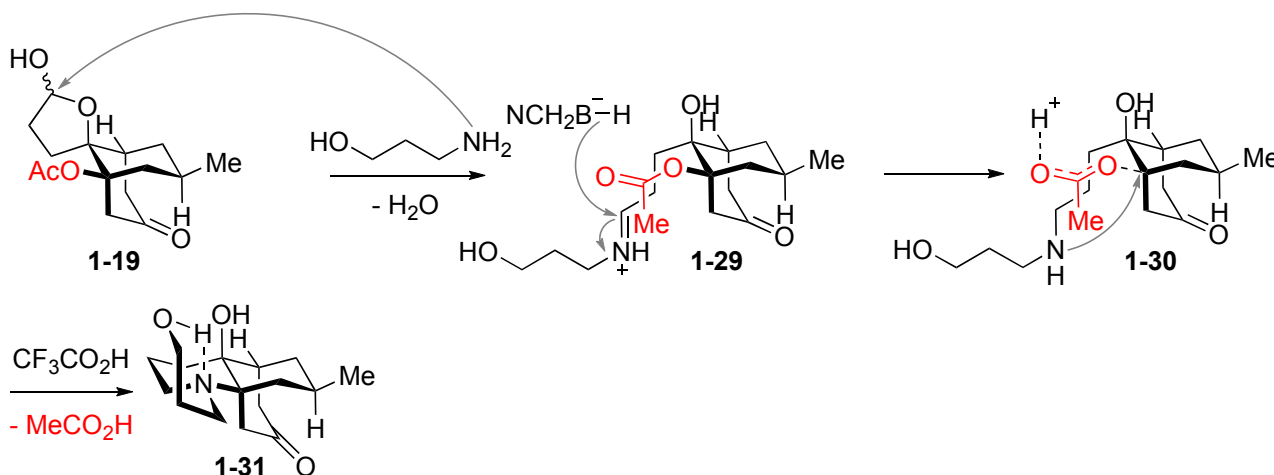
[4.3.1]

17.7 kcal/mol

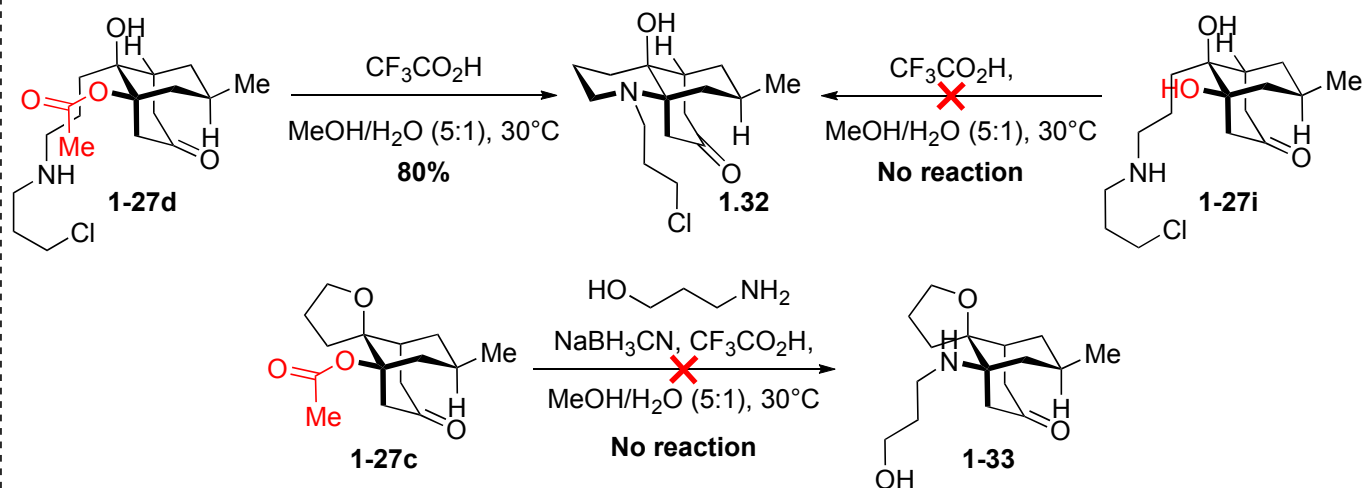
### Discussion

- When possible, intramolecular addition occurs predominantly
- Some extent of bridgehead strain is crucial for the subsequent hetero-Michael addition

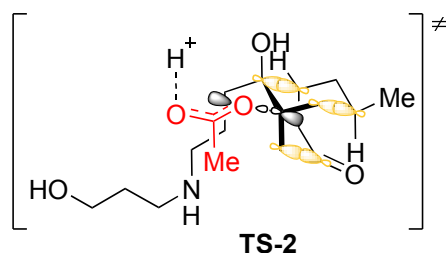
### 1.2.2. Reductive amination/Bridgehead aminolysis :



### Discussion about the bridgehead aminolysis : control experiments

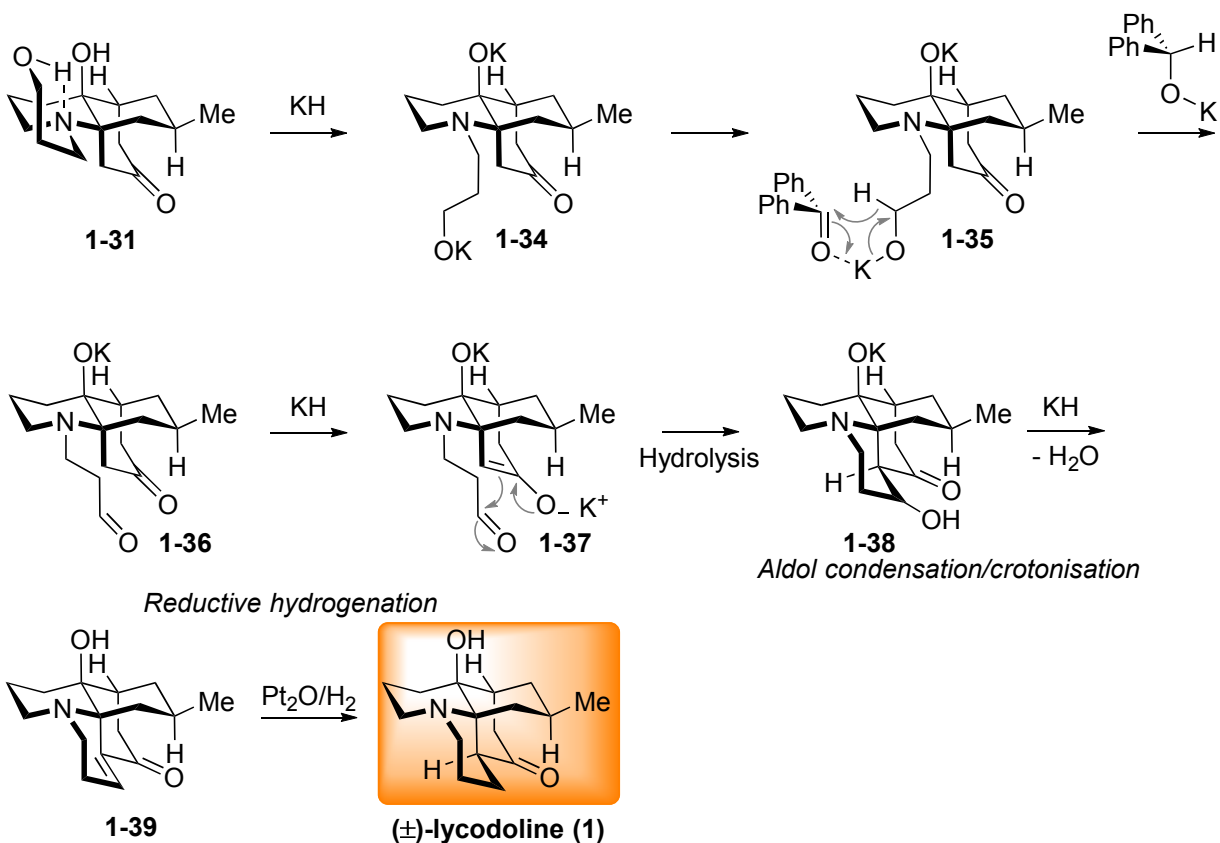


- Inert reactivity of **1-27c** ruled out the intermolecular pathway
- Inert reactivity of **1-27i** shows the importance of the bridgehead acetate
- Leaving ability of bridgehead acetate partially accelerated by the favorable hyperconjugative effect in the [3.3.1] bicyclic system

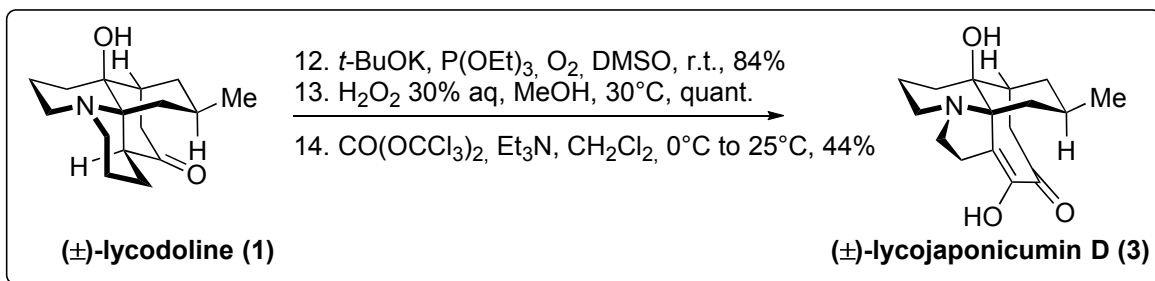


### 1.2.3. Modified Oppenauer oxidation : Heathcock's conditions

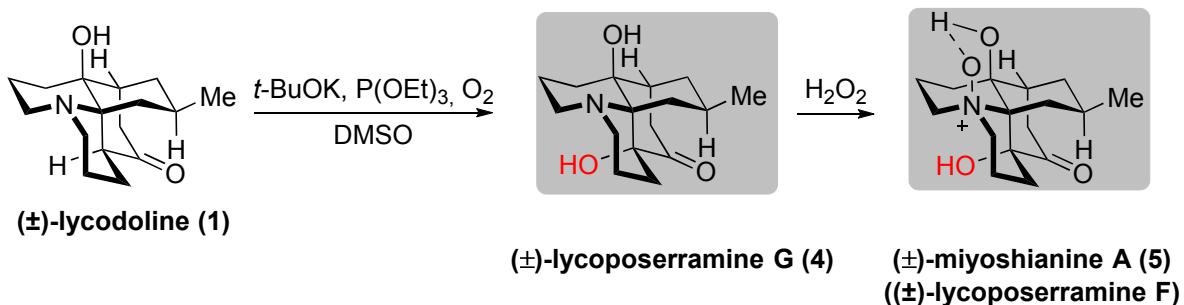
Heathcock *et al.* *J. Am. Chem. Soc.* **1982**, *104*, 1054



## 2. Bio-inspired synthesis of (±)-lycojaponicum D :



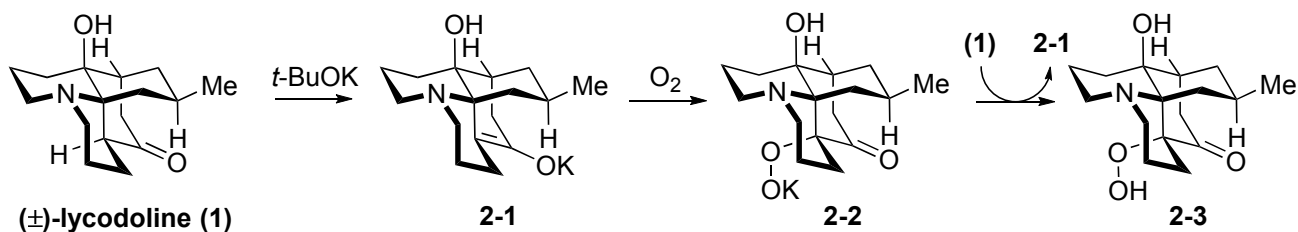
### 2.1. C-H hydroxylation of ketone with oxygene/*N*-oxide formation



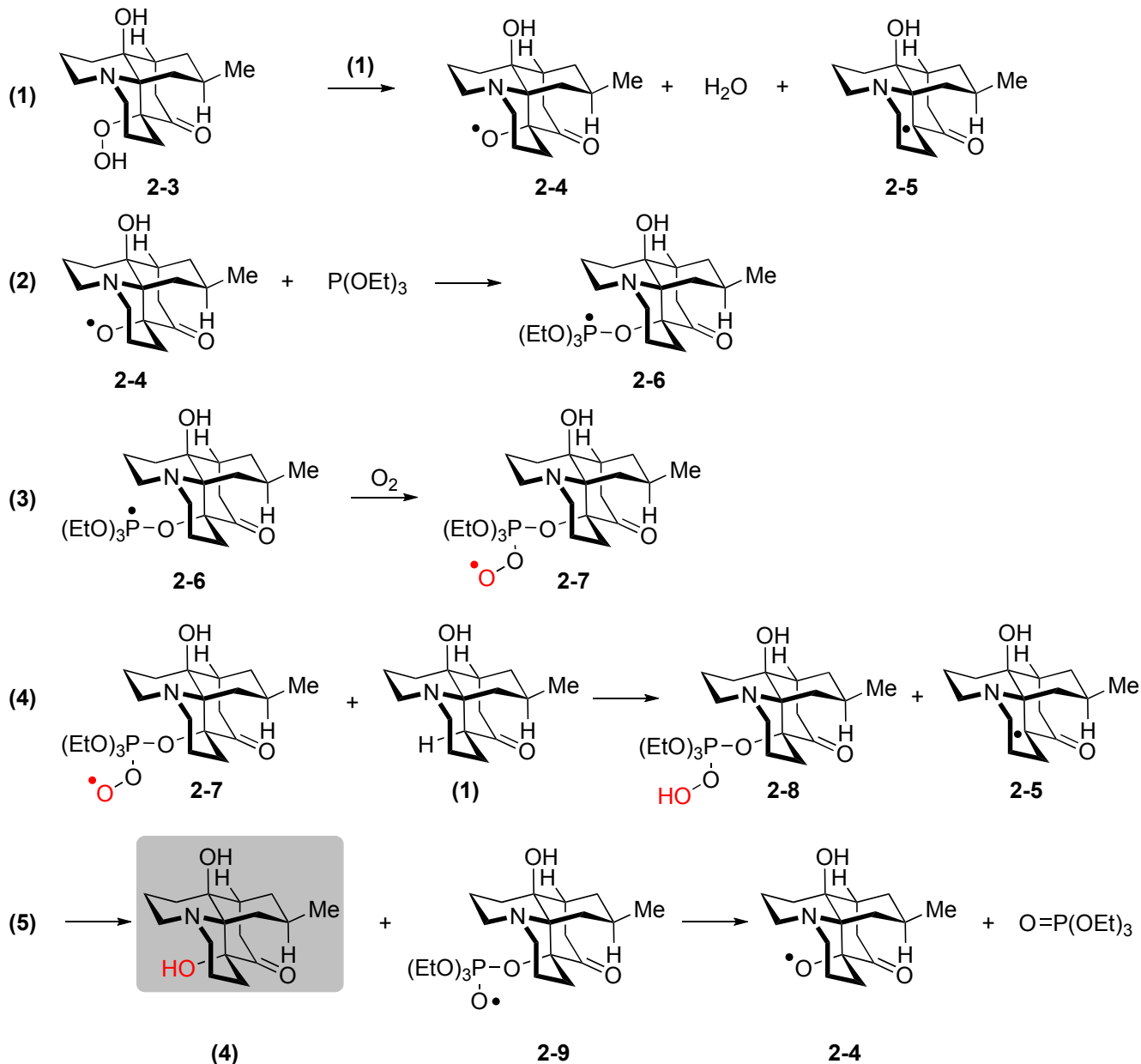
## Mechanism of the $\alpha$ -hydroxylation of ketone

Jiao *et al.* *Angew. Chem. Int. Ed.* **2014**, *53*, 548  
 Barton *et al.* *J. Chem. Soc.* **1962**, 1578.

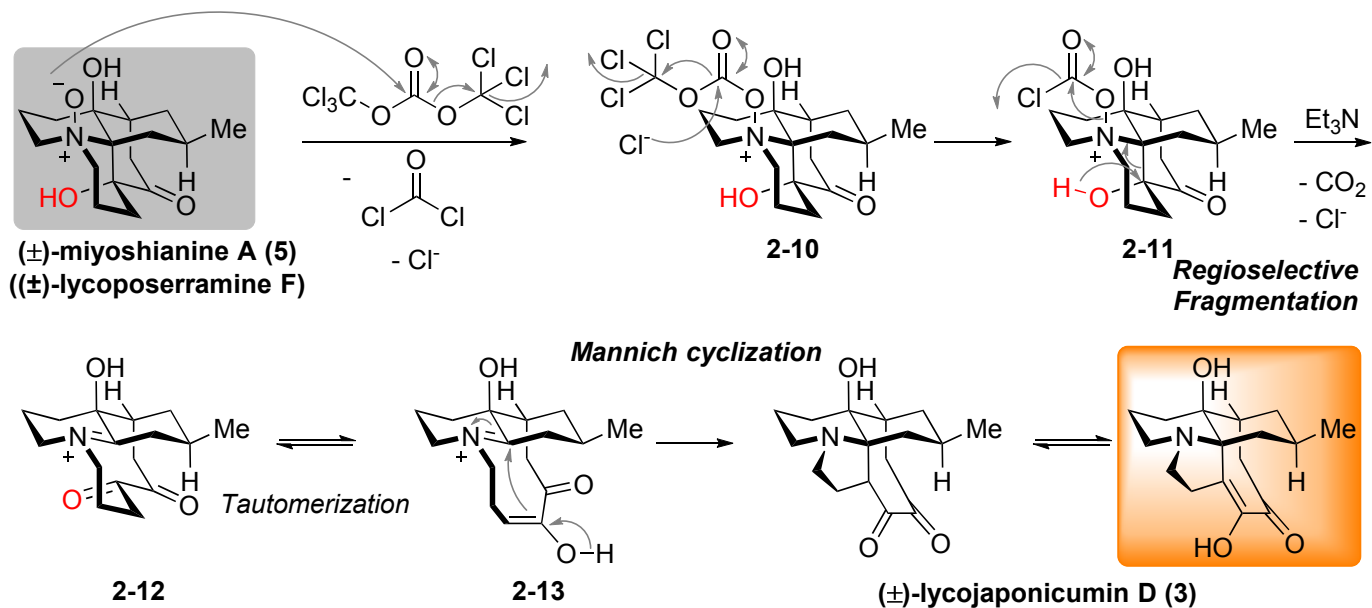
### (1). Formation of hydroperoxide 2-3



### (2). Reduction of hydroperoxide by $\text{P}(\text{OEt})_3$



## 2.2. Tandem fragmentation/Mannich cyclization



## 3. Bio-inspired synthesis of lycodoline-type Lycopodium alkaloids

