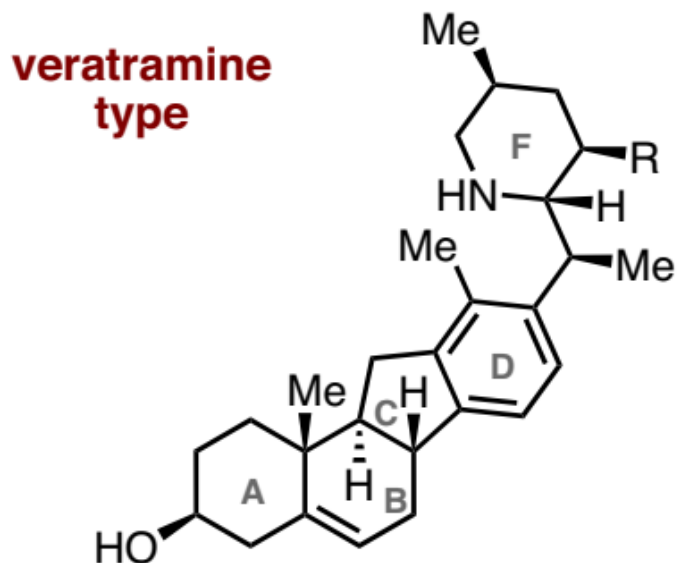


# Divergent and gram-scale syntheses of (–)-veratramine and (–)-cyclopamine

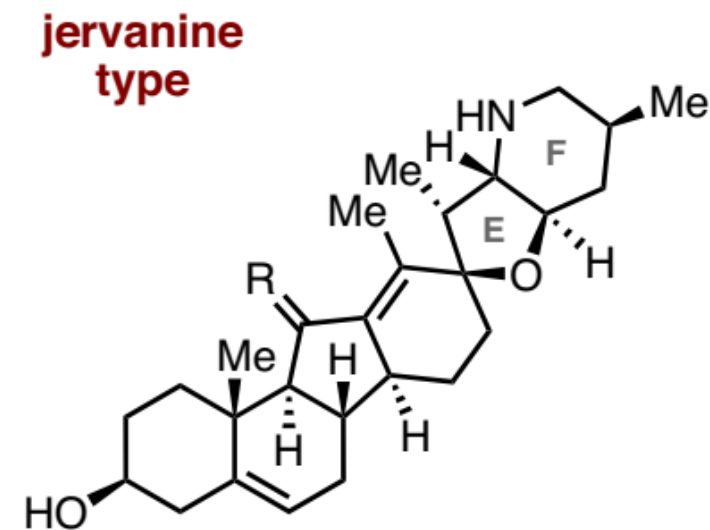
Received: 4 April 2024

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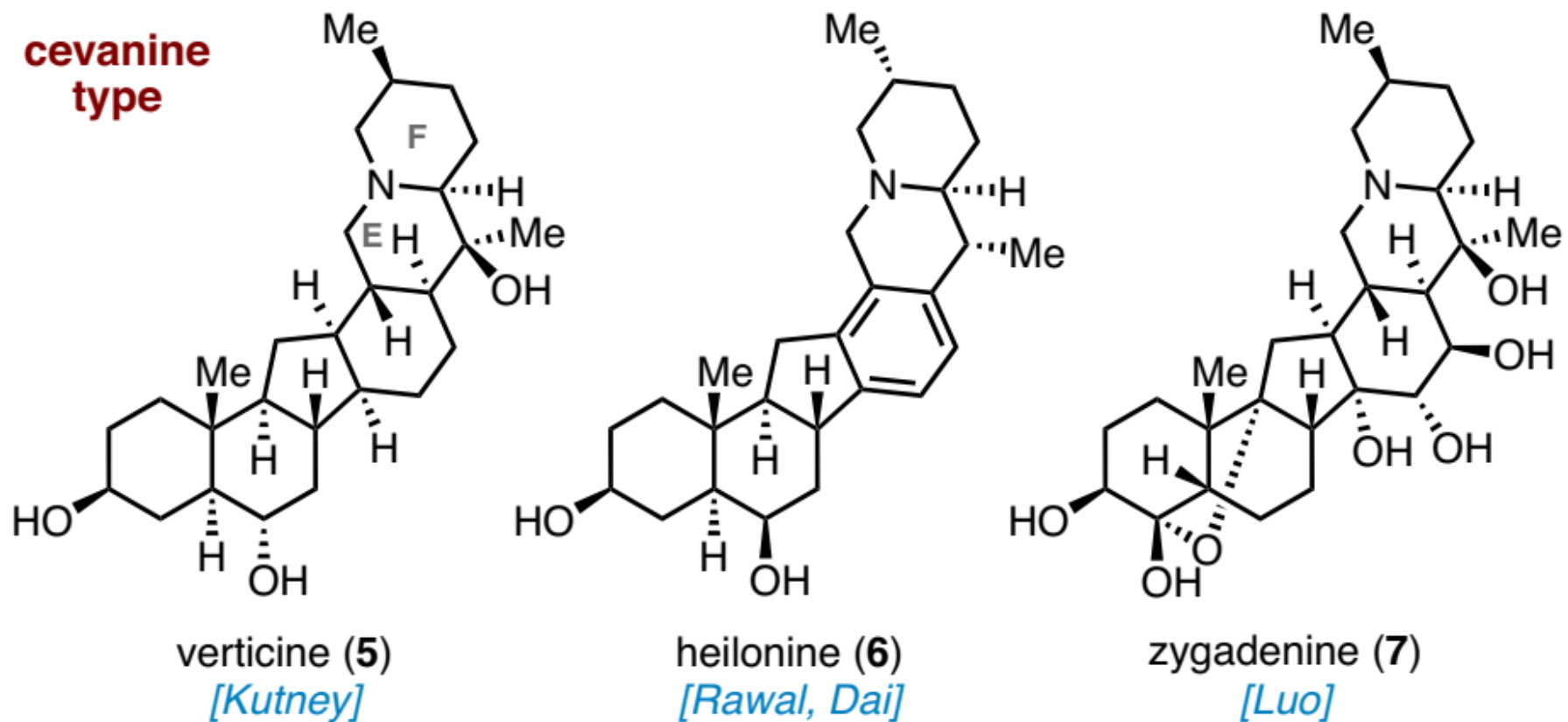


veratramine (**1**, R = OH)  
[Johnson, Gao]  
verarine (**2**, R = H) [Kutney]

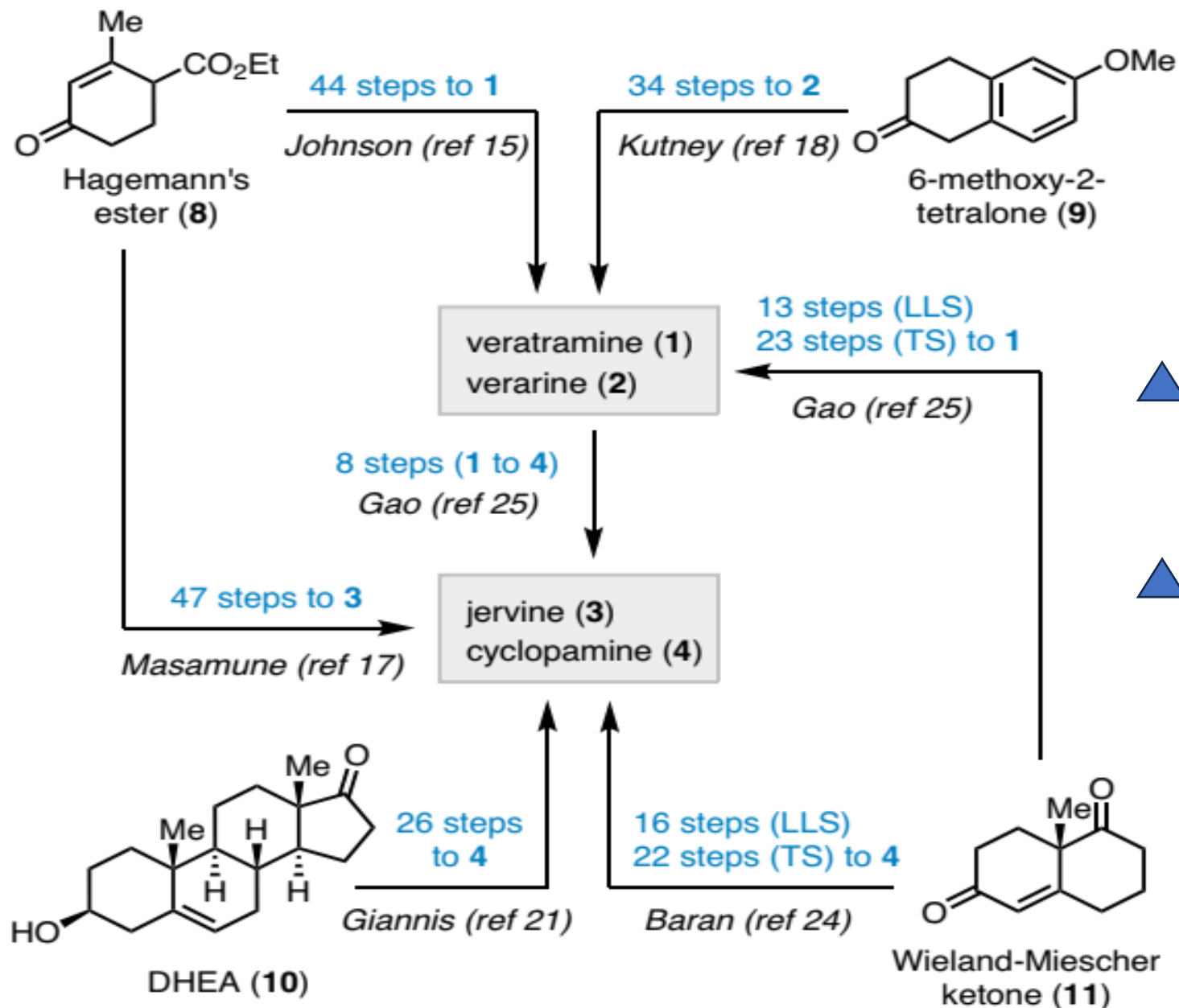


jervine (**3**, R = O) [Masamune]  
cyclopamine (**4**, R = H, H)  
[Giannis, Baran, Gao]

# Structures and chemical syntheses of ISAs



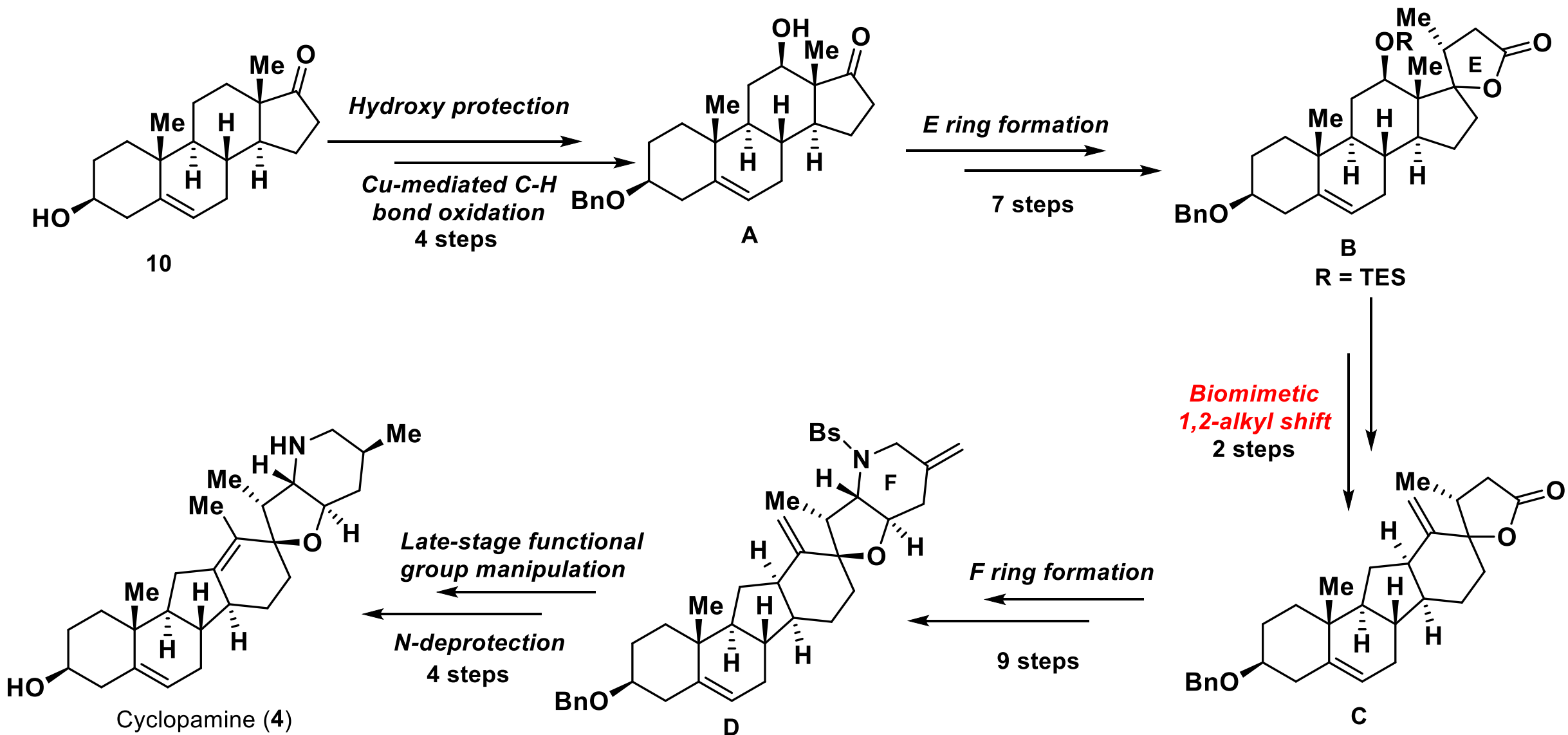
# Summary of the prior syntheses of ISAs and an overview of this work



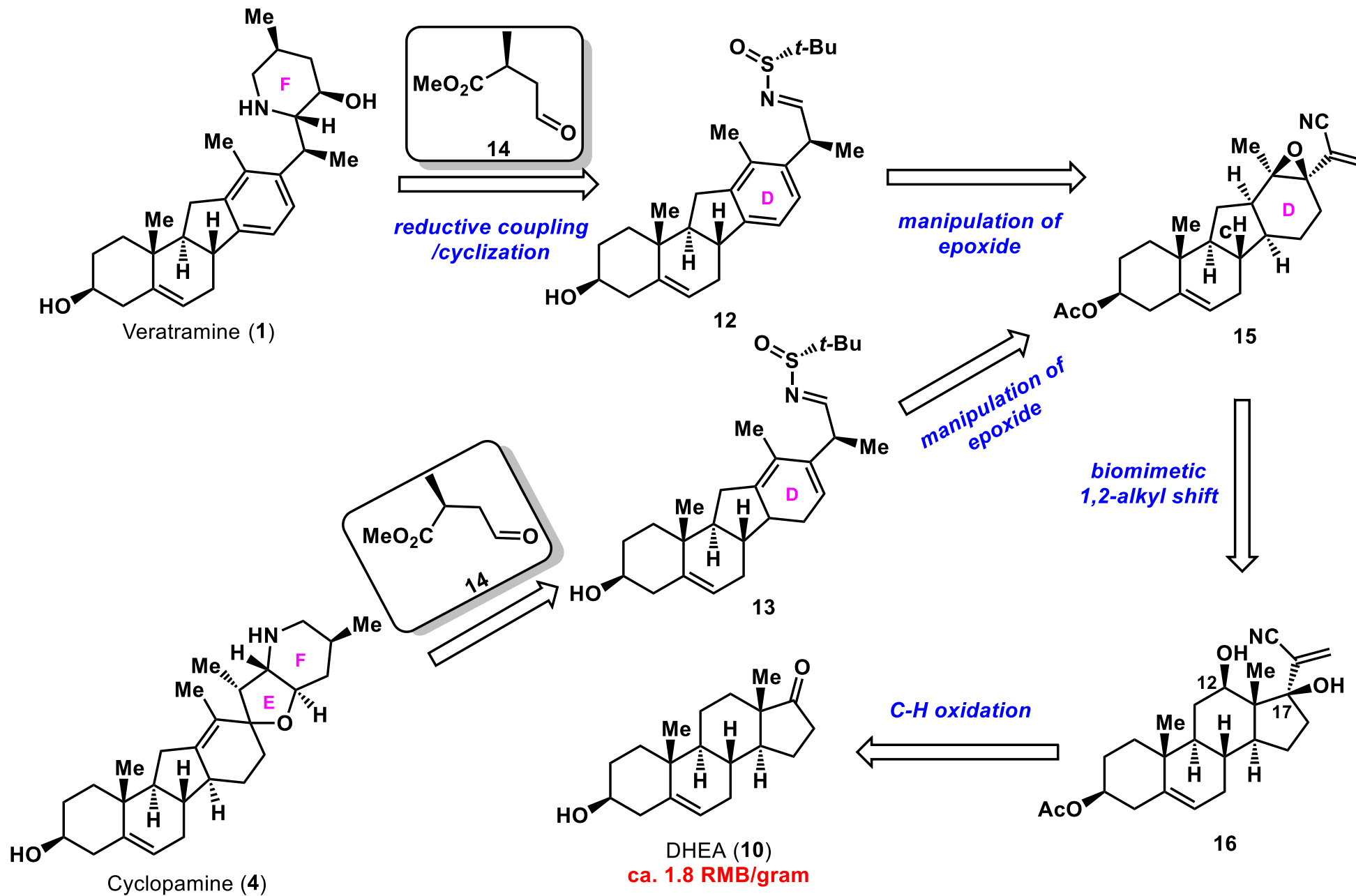
▲ **Prior syntheses:** >22-47 total steps  
mg scale, single target or  
relay synthesis

▲ **This work:** 13 steps (LLS)  
15 total steps  
gram scale, divergent  
approach to 1 and 4

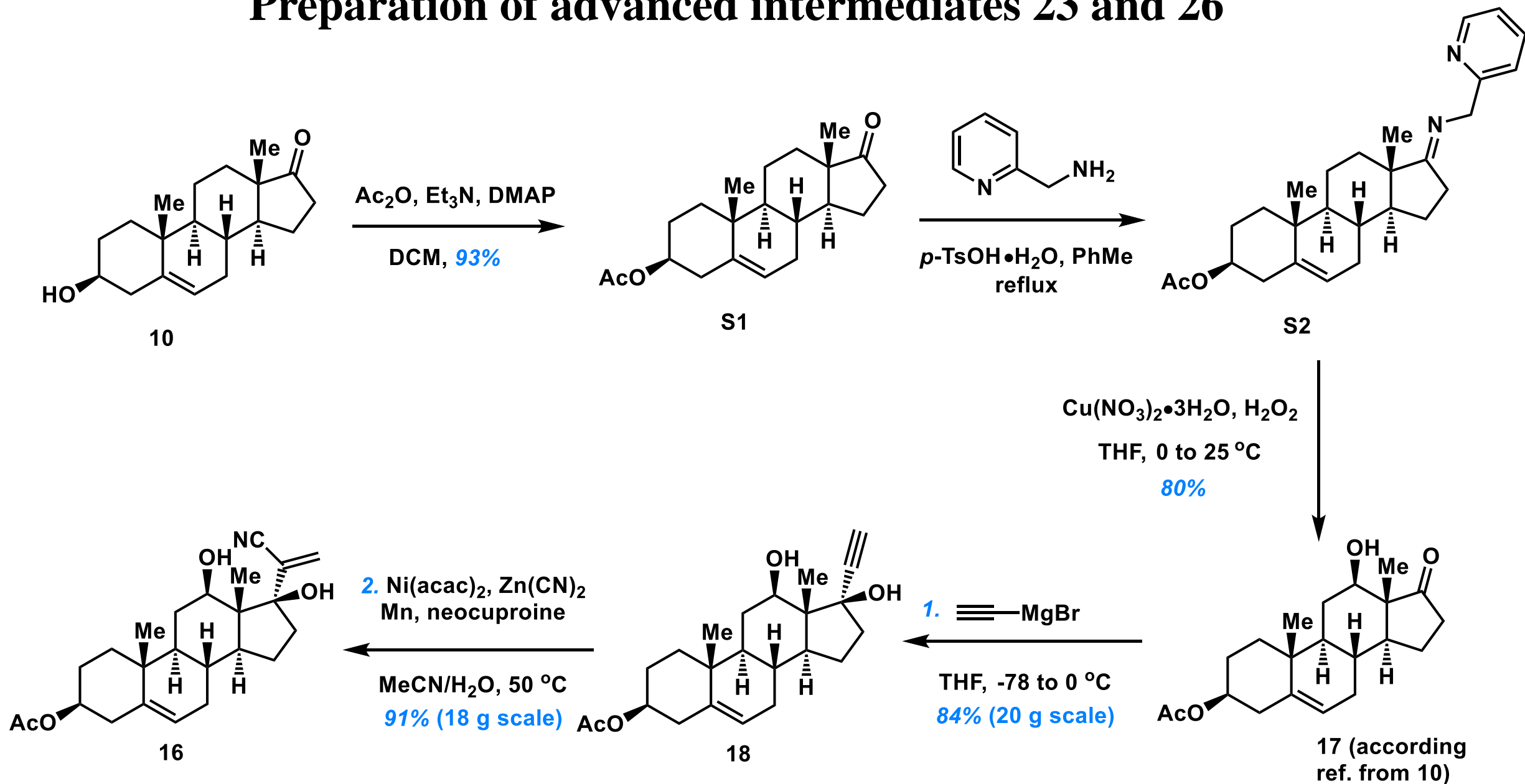
# The prior syntheses of Cyclopamine (4) by Gianni's group



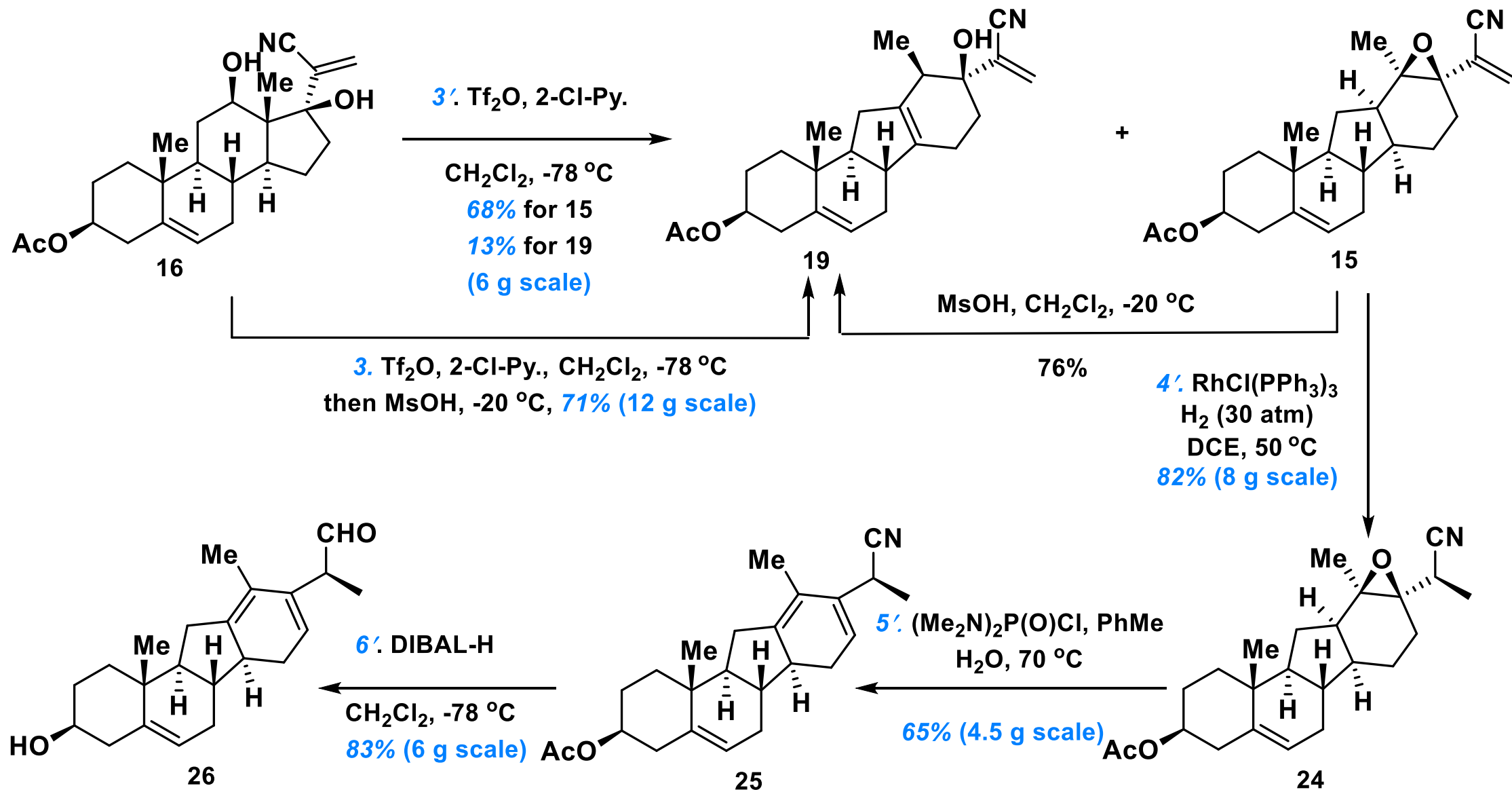
# Retrosynthetic analysis of Veratramine (1) and Cyclopamine (4)



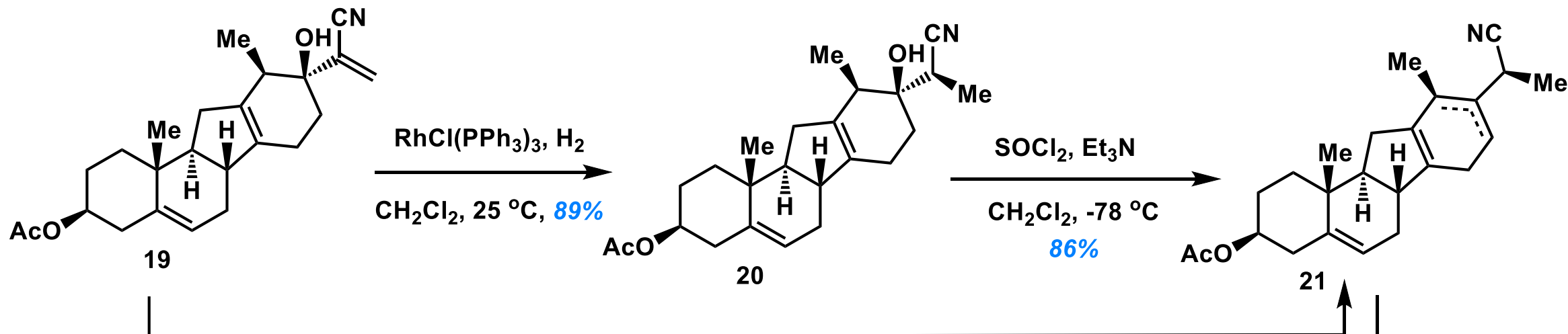
# Preparation of advanced intermediates 23 and 26



# Preparation of advanced intermediates 23 and 26

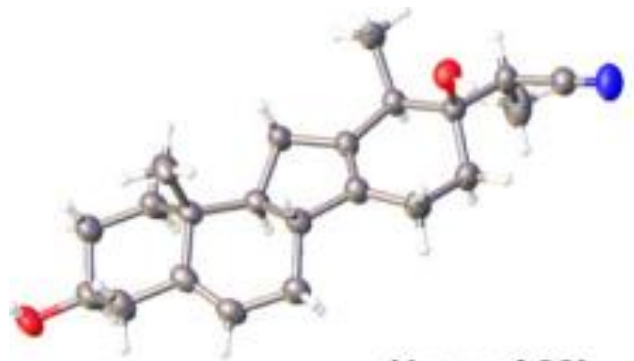


# Preparation of advanced intermediates 23 and 26



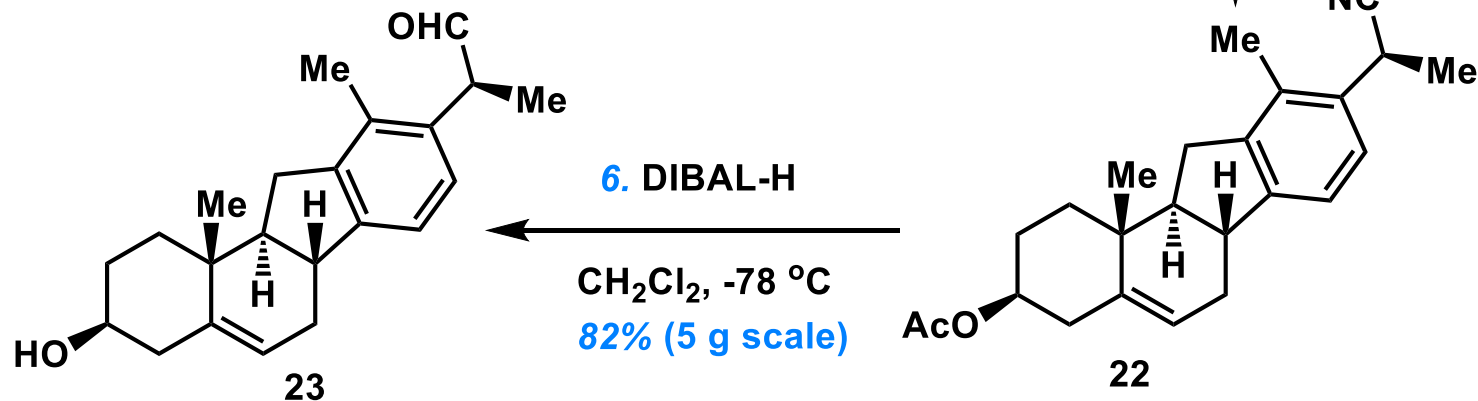
4.  $\text{RhCl}(\text{PPh}_3)_3$ ,  $\text{H}_2$ ,  $\text{CH}_2\text{Cl}_2$ , then  $\text{SOCl}_2$ ,  $\text{Et}_3\text{N}$ ,  $-78^\circ\text{C}$   
81% (10 g scale)

5. CAN, MeCN/THF  
0 to  $25^\circ\text{C}$   
80% (6 g scale)



X-ray of 20'  
[CCDC 2321472]

20': without Ac group in 20



6. DIBAL-H

$\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$   
82% (5 g scale)



# Total synthesis of (-)-Veratramine (1) and (-)-Cyclopamine (4)

