

# Protecting-Group-Free Total Synthesis of (-)-Rhazinilam and (-)-Rhazinicine using a Gold-Catalyzed Cascade Cyclization

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Checker: Xian-Feng Cai

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**Tokuyama. H. *et al.***  
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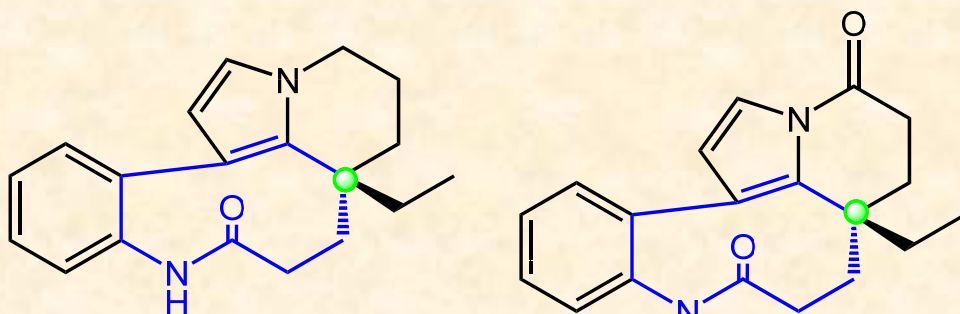
Tohoku University

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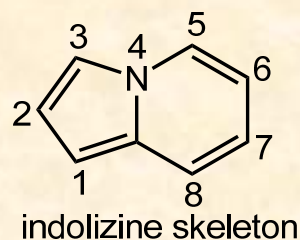
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# Introduction



(-)-Rhazinilam (1)

(-)-Rhazinicine (2)

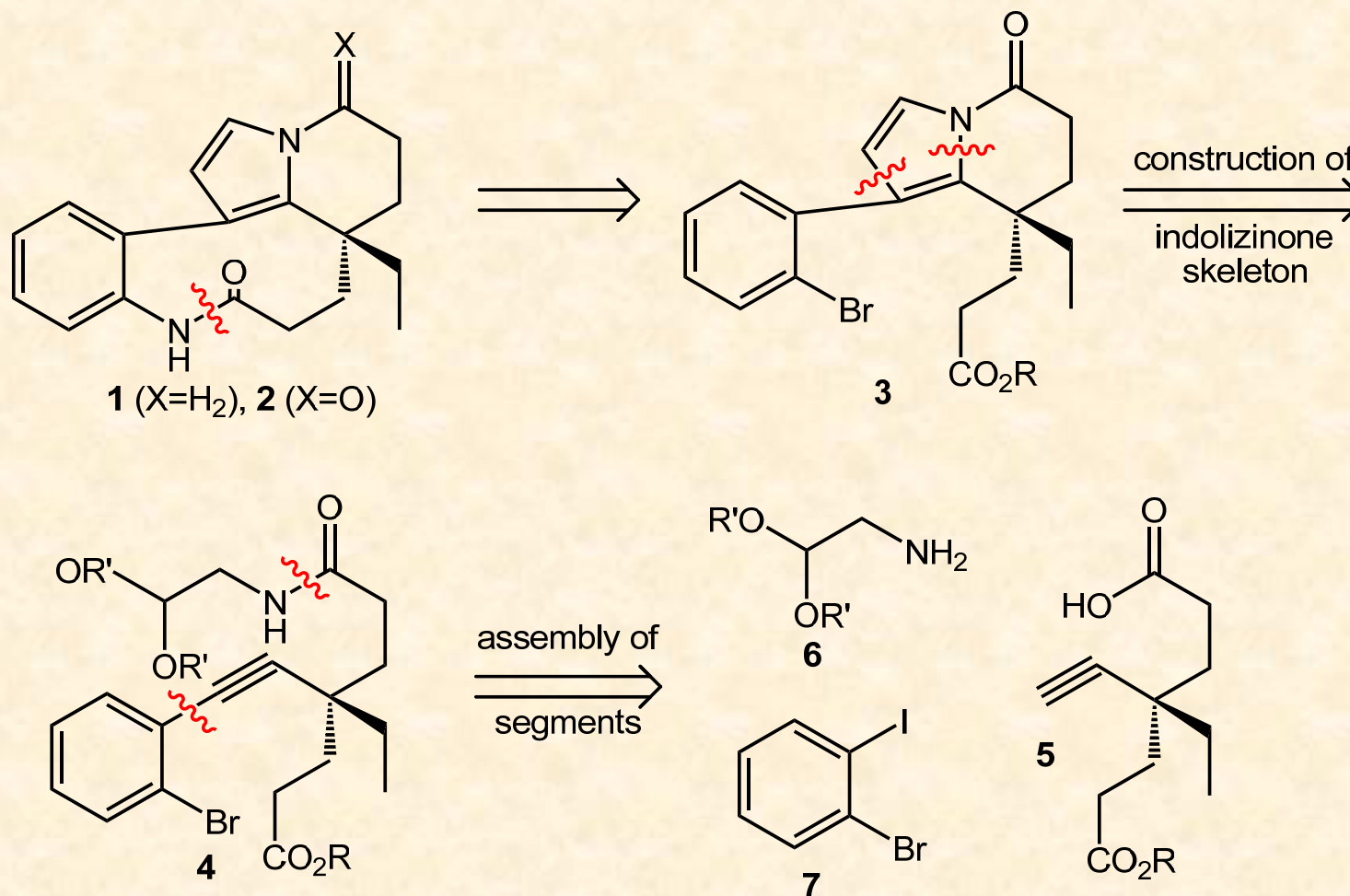


Aspidosperma

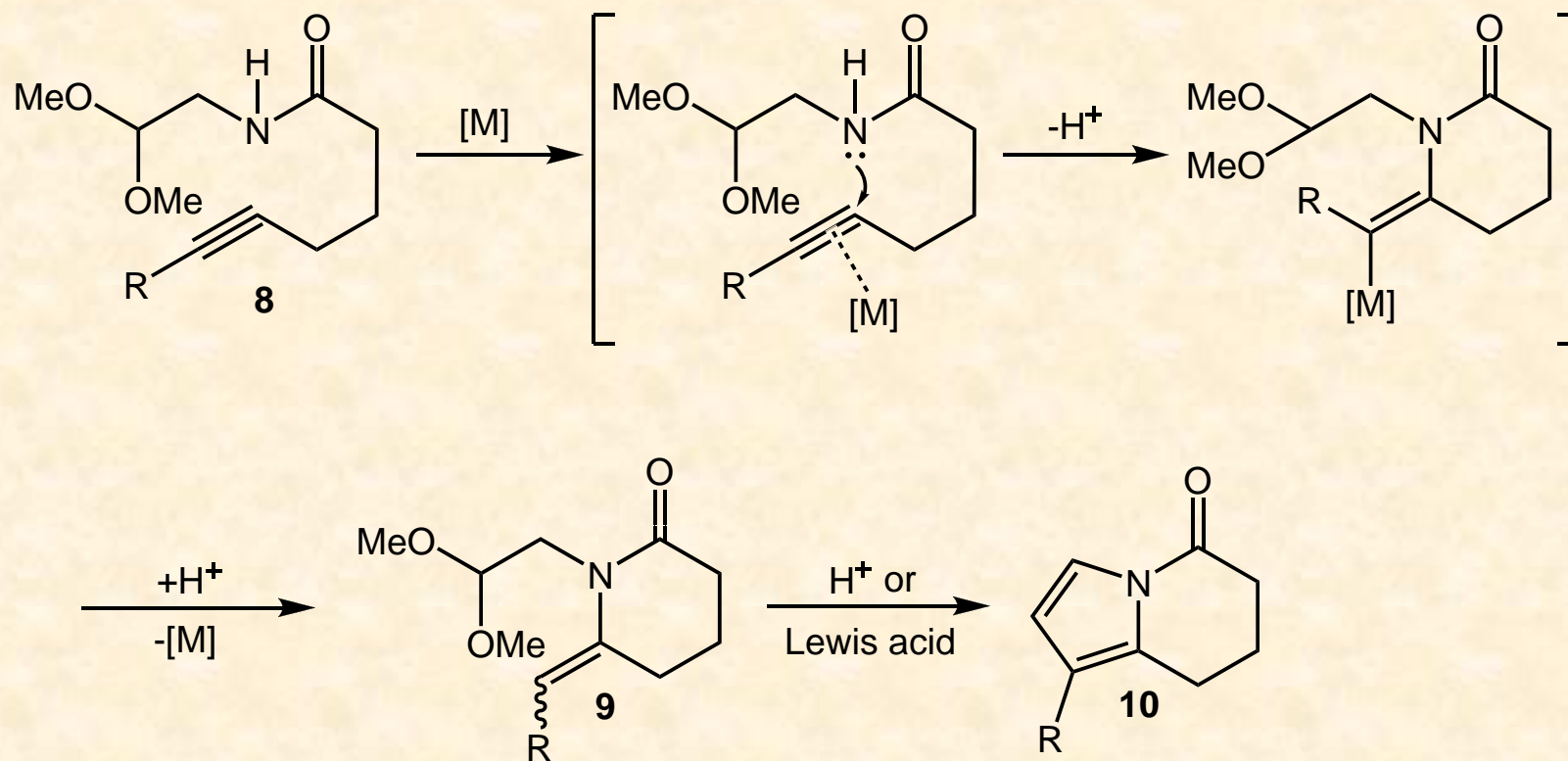
Characters:

- a nine-membered lactam ring fused to its 5,6,7,8-tetrahydroindolizine skeleton and a quaternary carbon center.
- new antitumor agents.

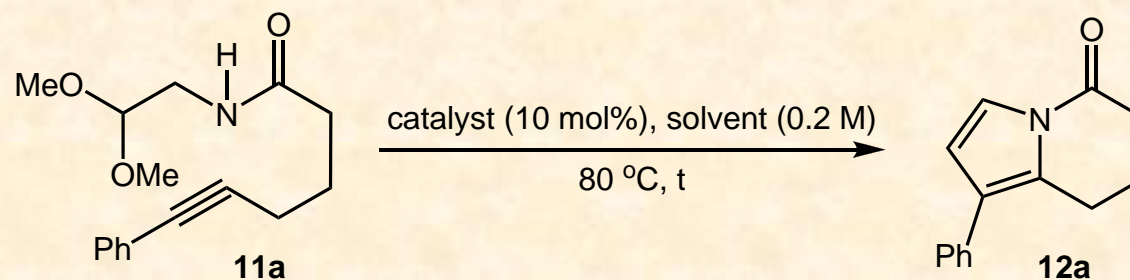
# Retrosynthetic analysis



# Formation of 5-indoliznone



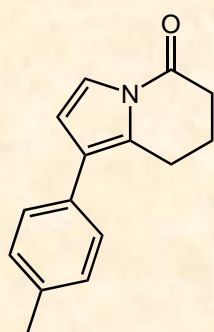
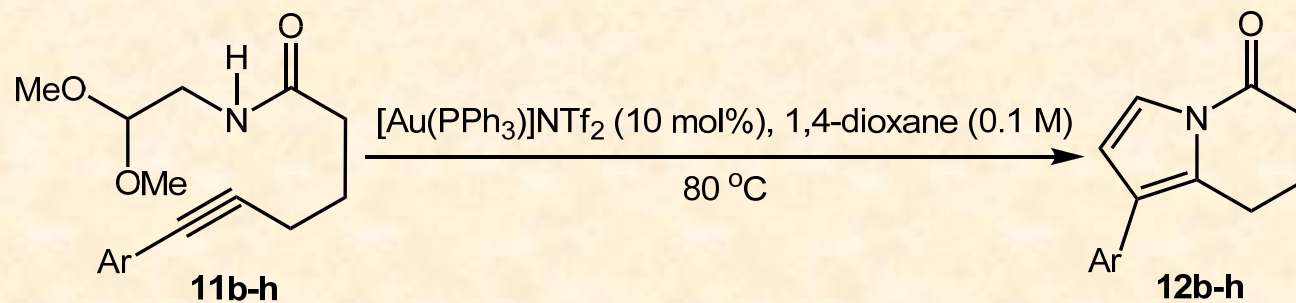
# Gold-Catalyzed Cascade Cyclization



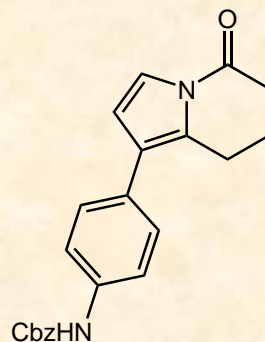
Entry	Catalyst <sup>[a]</sup>	Solvent	t [h]	Yield [%]
1	AuCl	ClCH <sub>2</sub> CH <sub>2</sub> Cl	24	-
2	AuCl <sub>2</sub>	ClCH <sub>2</sub> CH <sub>2</sub> Cl	24	-
3	[Au(PPh <sub>3</sub> )Cl]	ClCH <sub>2</sub> CH <sub>2</sub> Cl	24	-
4	AuCl, AgOTf	ClCH <sub>2</sub> CH <sub>2</sub> Cl	8	-
5	[Au(PPh <sub>3</sub> )Cl], AgOTf	ClCH <sub>2</sub> CH <sub>2</sub> Cl	7	20
6	[Au(PPh <sub>3</sub> )Cl], AgNTf <sub>2</sub>	ClCH <sub>2</sub> CH <sub>2</sub> Cl	2.5	20
7	[Au(PPh <sub>3</sub> )]NTf <sub>2</sub>	ClCH <sub>2</sub> CH <sub>2</sub> Cl	11	50
8	[Au(PPh <sub>3</sub> )]NTf <sub>2</sub>	1,4-dioxane <sup>[b]</sup>	11	69
9	[(Cy-JohnPhos)Au]NTf <sub>2</sub>	1,4-dioxane <sup>[b]</sup>	11	64

[a] CuI or PdCl<sub>2</sub> did not give **12a**. [b] Concentration of **11a** was 0.1 M.

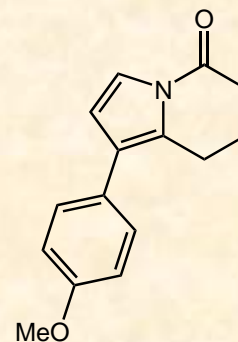
# Substrate scope



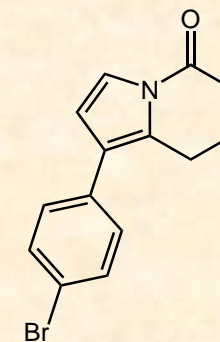
**12b** 59%



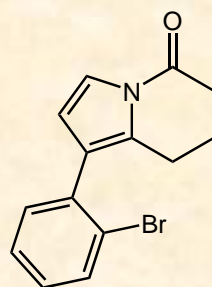
**12c** 67%



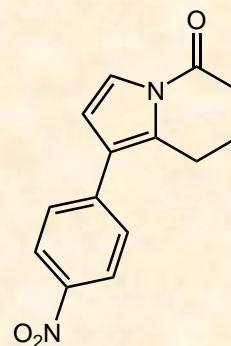
**12d** 23%



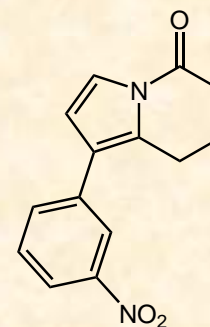
**12e** 59%



**12f** 60%

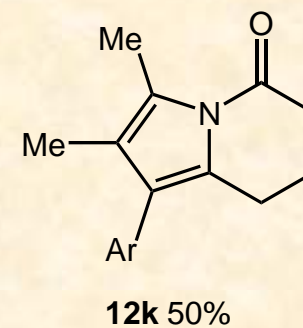
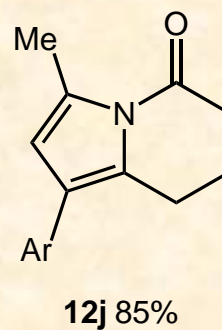
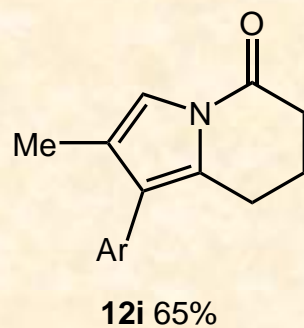
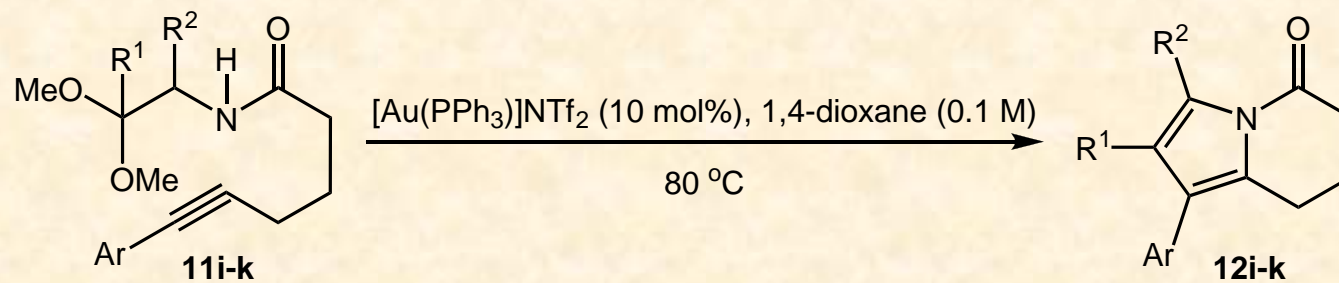


**12g** 92%



**12h** 79%

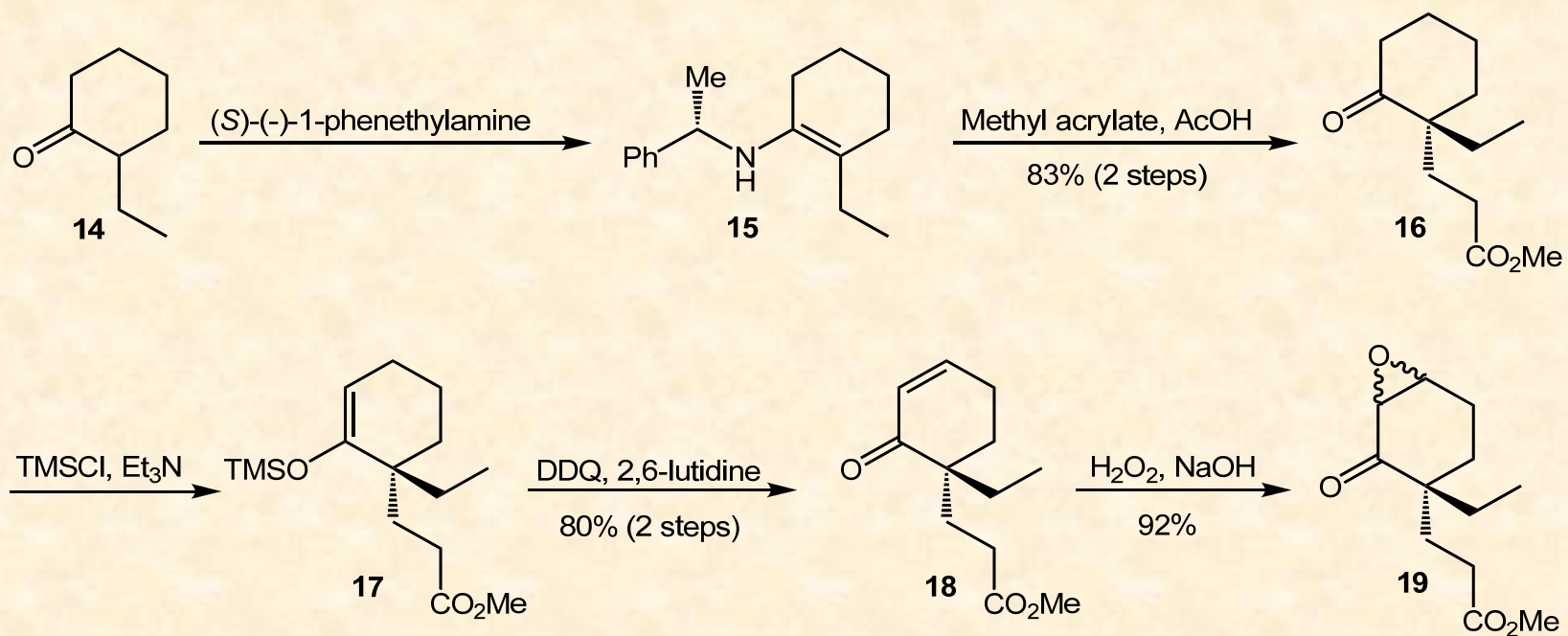
# Construction of multisubstituted indolizinones



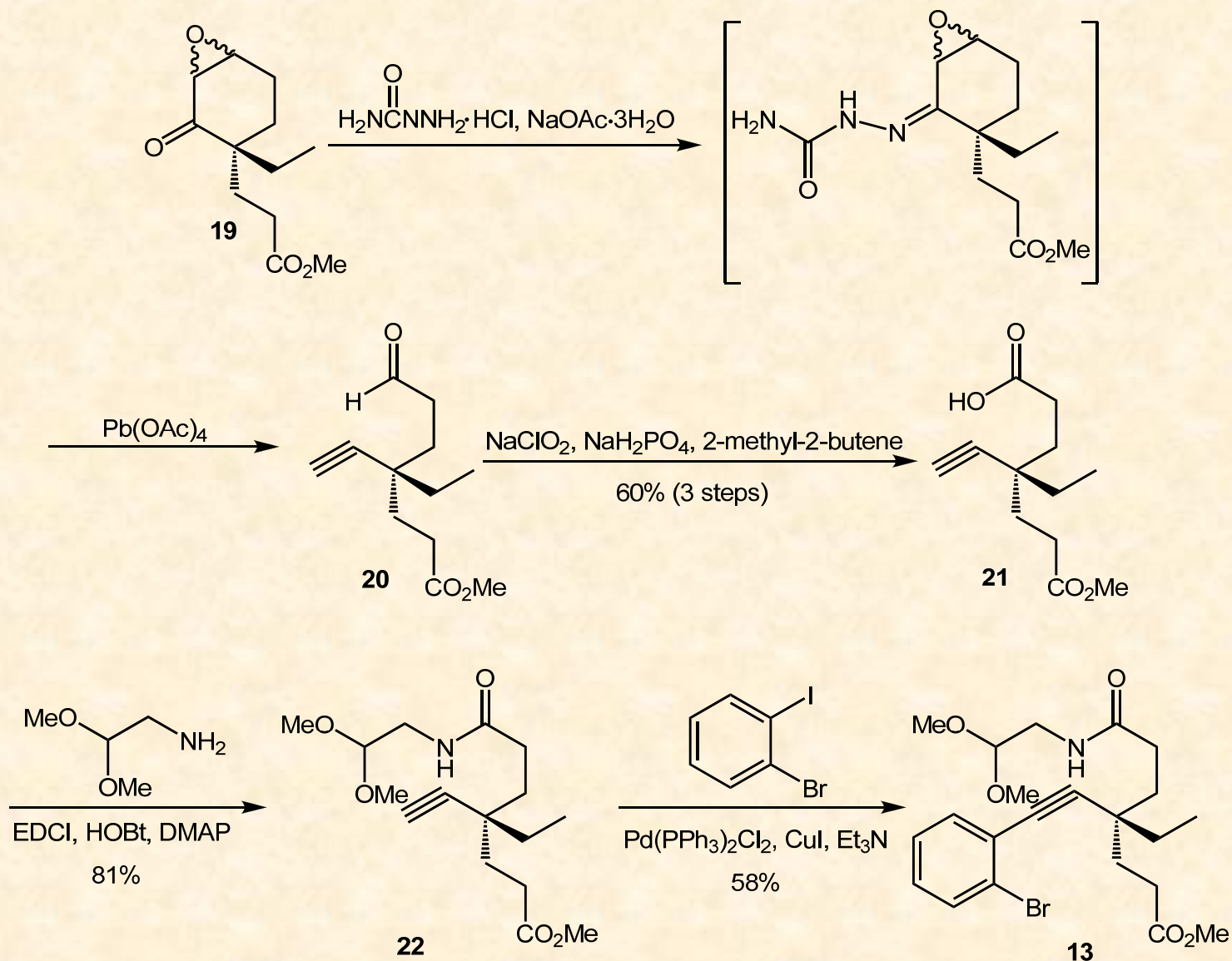
Ar = 4-nitrophenyl

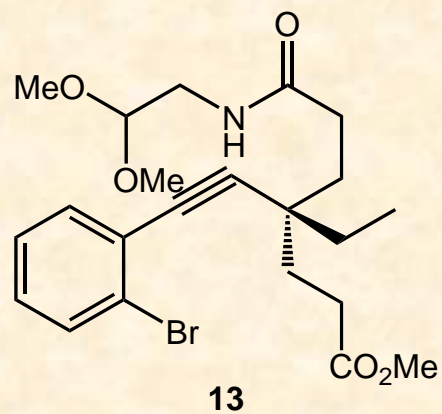


# Synthesis of (-)-Rhazinilam and (-)-Rhazinicine

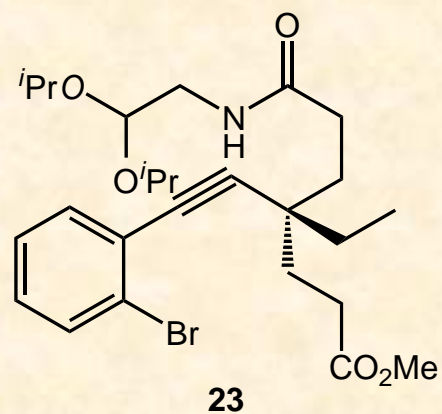
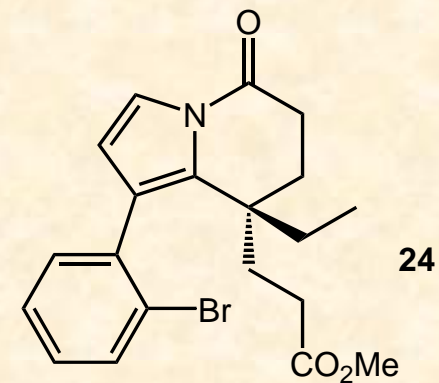


# Synthesis of (-)-Rhazinilam and (-)-Rhazinicine

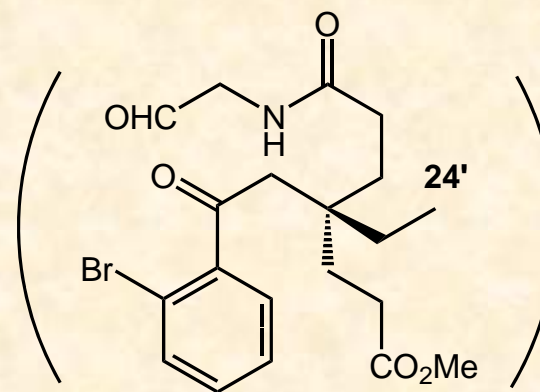


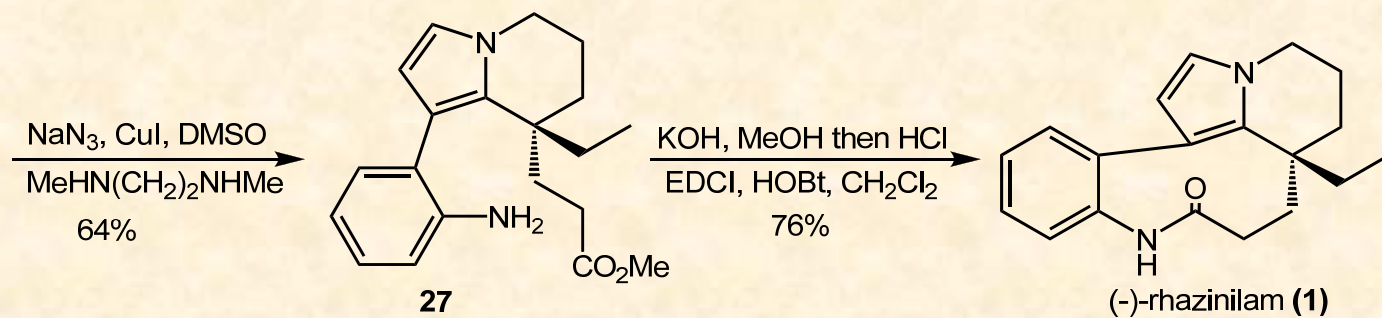
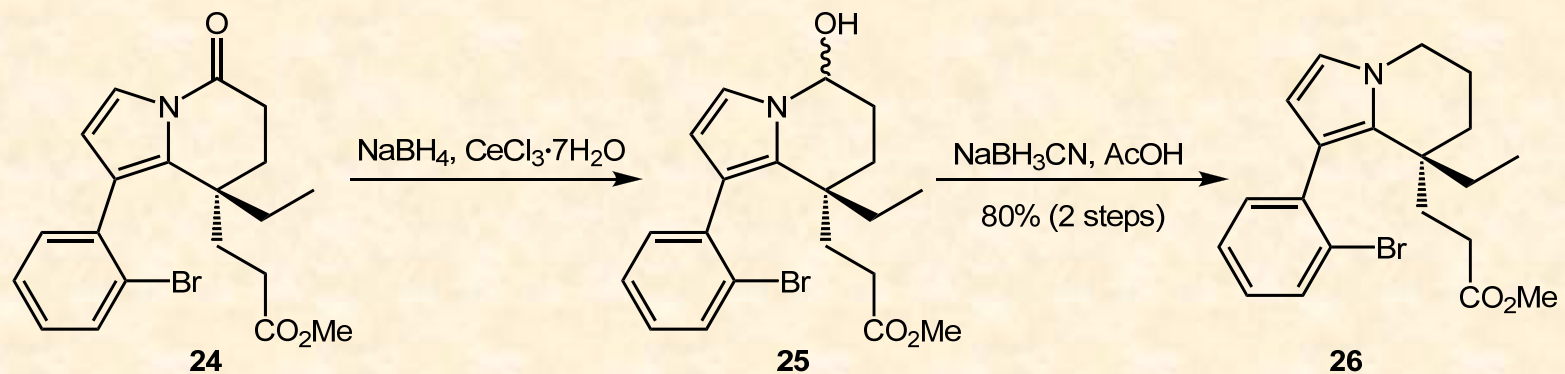


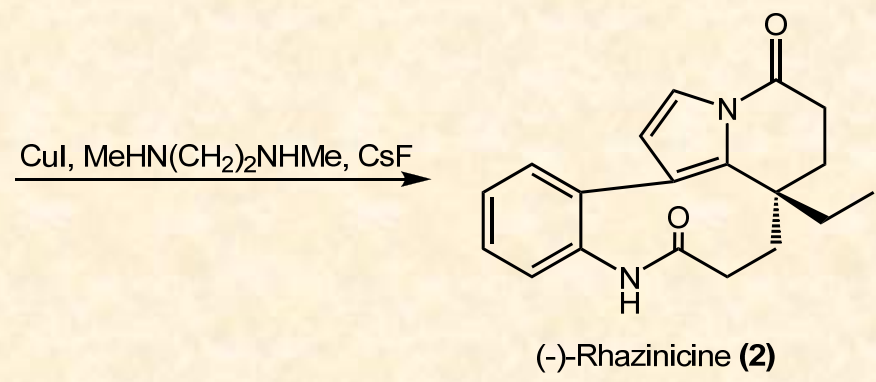
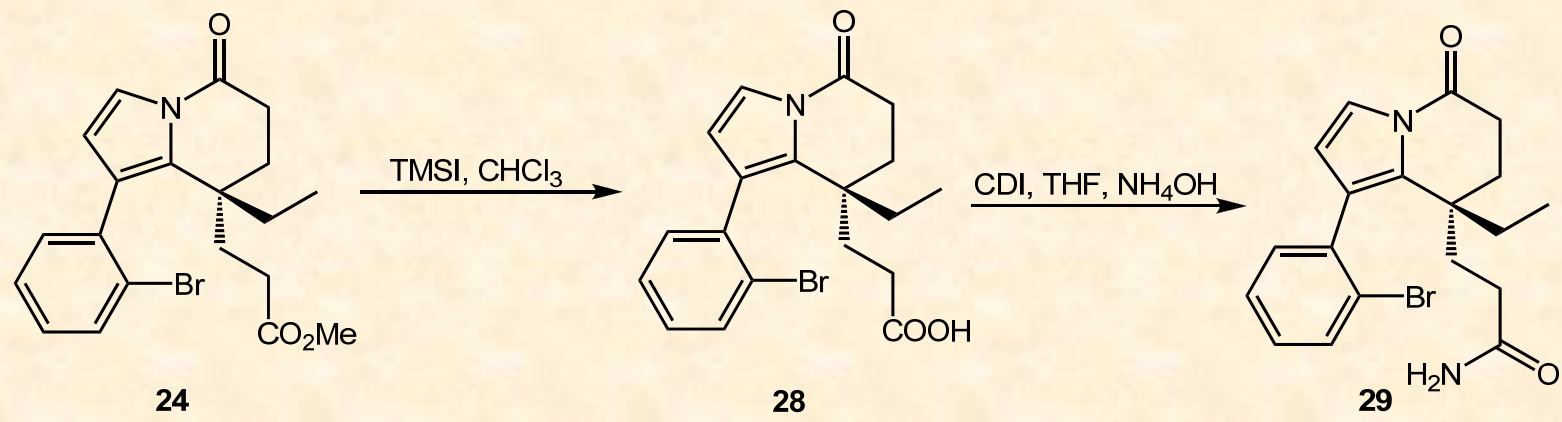
$[\text{Au}(\text{PPh}_3)]\text{NTf}_2$   
1,4-dioxane, 80 °C  
**28%**



$[\text{Au}(\text{PPh}_3)]\text{NTf}_2$   
 $\text{KHSO}_4$   
 $i\text{PrOH}/1,4\text{-dioxane}$   
MWI, 80 °C  
1 min x 40 times  
**65%**

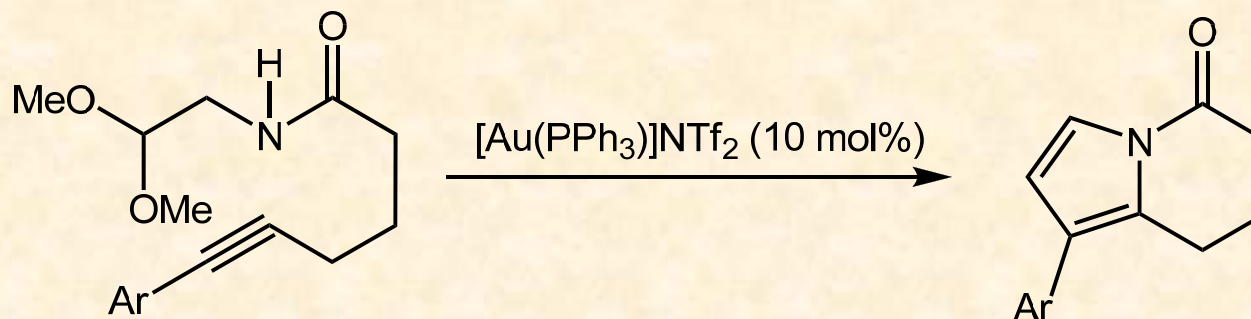




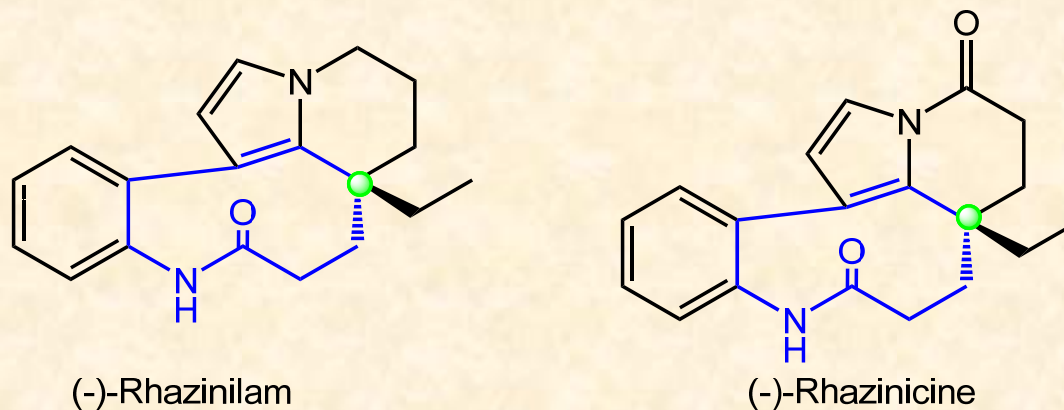


# Summary

1. Develop a gold-catalyzed cascade double cyclizations



2. Using this method to complete the total synthesis of (-)-Rhazinilam and (-)-Rhazinicine



The first total synthesis

(-)-Rhazinilam (**1**), isolated from various Apocynaceae species, originally from *Rhazya stricta* Decaisne, is a member of the Aspidosperma class of alkaloids. This compound interferes with tubulin polymerization and dynamics. Because of its significant biological effects, (-)-rhazinilam (**1**) and its congeners such as (-)-rhazinicine have been recognized as lead compounds for new antitumor agents. In addition to its interesting biological activity, its unique structure, with a nine-membered lactam ring fused to its 5,6,7,8-tetrahydroindolizine skeleton and a quaternary carbon center, has received considerable attention as a synthetic target and provided an attractive platform for demonstrating the utility of novel synthetic methodologies and tactics. We describe herein a total synthesis of (-)-rhazinilam (**1**) and the first total synthesis of (-)-rhazinicine (**2**) using a facile construction of the highly substituted indolizininone by a newly developed gold-catalyzed cascade cyclization reaction.

In summary, we have achieved a total synthesis (-)-rhazinilam (**1**) and the first asymmetric total synthesis of (-)-rhazinicine (**2**) by using the efficient construction of the per-substituted indolizinone core through a gold-catalyzed cascade reaction of linear substrates. The mild reaction conditions for the construction of the indolizinone core and the nine-membered lactam ring allowed us to achieve these protecting-group-free total syntheses. We have also demonstrated the scope and generality of this cascade reaction for synthesis of highly substituted indolizinones. Further applications of this gold-catalyzed cascade reaction for the construction of other heterocyclic skeletons are currently under investigation, and will be reported in due course.