Journal club 2015. 12. 10. Hiroki Hanayama

# Total Synthesis of Gelsemoxonine through a Spirocyclopropane Isoxazolidine Ring Contraction

Stefan Diethelm and Erick M. Carreira, *J. Am. Chem. Soc.* **2015**, *137*, 6084–6096.

## 1. Introduction

### 1.1. Saturated small heterocycles

- Saturated small heterocycles (mainly 4-membered ring) are important building blocks of drugs for drug discovery.
  Crucial physicochemical properties of drugs such as solubility, lipophilicity and metabolic stability can be controlled by introduction of saturated small heterocycles (Figure 1)[1].
  **"How to make a saturated small heterocycles"** is important in drug discovery chemistry.

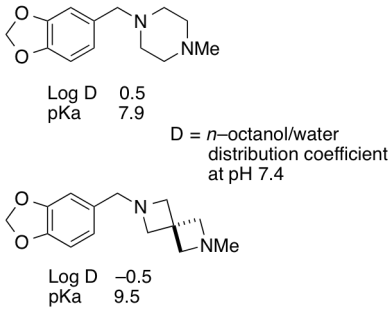
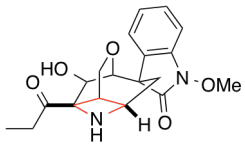



***Figure 1.*** One example of the change in physicochemical properties by introduction of a small heterocycle.

### 1.2. Gelsemoxonine

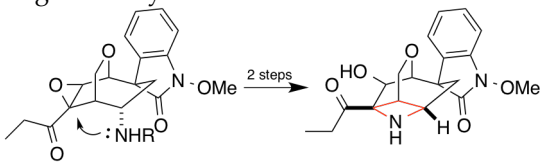
- Gelsemoxonine **1** has a polycyclic framework, which contains azetidine structure (Figure 2).
- In previous work, Fukuyama group has synthesized Gelsemoxonine in 26 steps and 2.2% yield. The azetidine structure was constructed at the last step of the total synthesis[2] (Scheme 1).
- In this work, the azetidine structure was constructed in the early stage by using ring contraction reaction from spirocyclopropane isoxazolidines to β-lactams (Scheme 2)[3].
  This strategy enables us to expand the alternatives for ring contraction in syntheses of drugs and natural products.



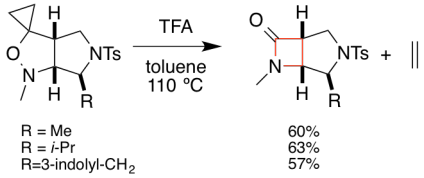
**1**

***Figure 2.*** The structure of Gelsemoxonine.

***Scheme 1.*** The procedure to make azetidine ring in Fukuyama's work.




***Scheme 2.*** Ring contraction reactions from spirocyclopropane isoxazolidines to β-lactams.

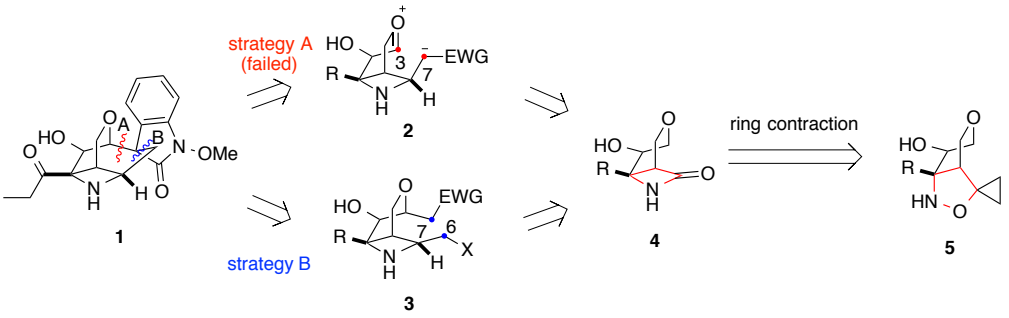



## 2. Results and discussion

### 2.1. Synthetic strategy

- Two synthetic strategies to synthesize Gelsemoxonine are shown in Scheme 3.
- Retrosynthetic cleavage of the C(3)-C(7) bond gives intermediate **2**.
- Retrosynthetic cleavage of the C(6)-C(7) bond leads to intermediate **3**.

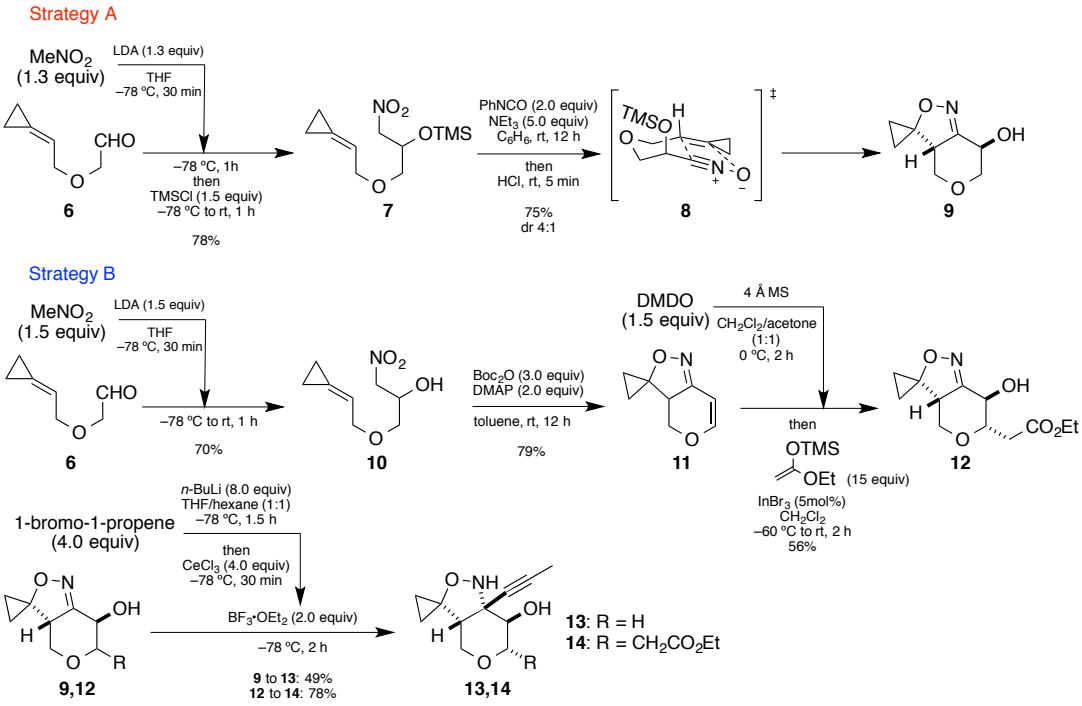
***Scheme 3.*** Two pathways of retrosynthesis of Gelsemoxonine from spirocyclopropane isoxazolidine **5**.




## 2.2. Synthesis of the reaction precursor of the ring contraction

- The ring contraction precursor **13,14** was synthesized from known aldehyde **6** (Scheme 4).

***Scheme 4.*** Synthesis of the ring contraction precursor from known aldehyde **6.**




- Stereoselectivity in the transition state **8** (Figure 3)

  The energy of HOMO of **8b** is lower than that of **8a** because of interaction between C-O bond of trimethylsilyl ether and HOMO of the dipole.

  ⇨ The activation energy of **8b** is higher than **8a**.

  ⇨ Product generates from **8a** preferentially.

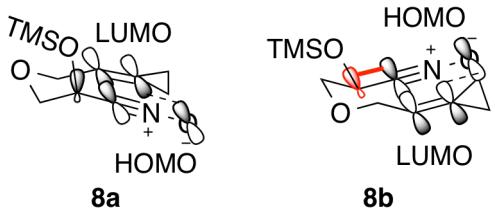



Figure 3. Frontier orbital analysis of **8.**

- Stereoselective addition of nucleophiles to the convex face of isoxazolidine (**9,12** to **13,14**)

- **13** was obtained in good yield when the $CeCl_3$ was added to propen-1-yl lithium. $CeCl_3$ suppressed that the organolithium reagents act as a base (Table 1).

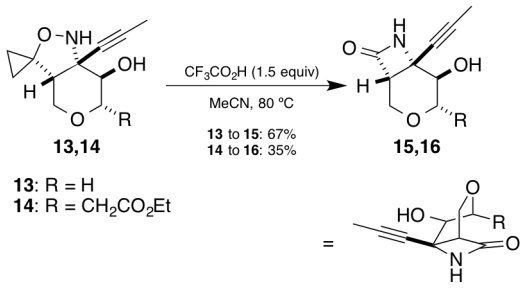
***Table 1.*** The scope of nucleophiles in the reaction **9** to **13**.

| Entry | Nucleophile | Additives | Conditions | Yield |
|---|---|---|---|---|
| 1 | Li— | – | –78 °C, THF | – |
| 2 | Li— | $NEt_3$ or TMEDA | –78 °C, $Et_2O$ | – |
| 3 | Li— | $BF_3$•$OEt_2$ | –78 °C, THF | 22% |
| 4 | $(i\text{-PrO})_3Ti$— | $TiCl_4$ | –78 °C, THF | – |
| 5 | $Cl_2Ce$— | $BF_3$•$OEt_2$ | –78 °C, THF | 68% |

## 2.3. The ring contraction of isoxazolidines 13,14

- Hydroxyl group, alkyne group and ester group were tolerated in the ring contraction reaction (Scheme 5).

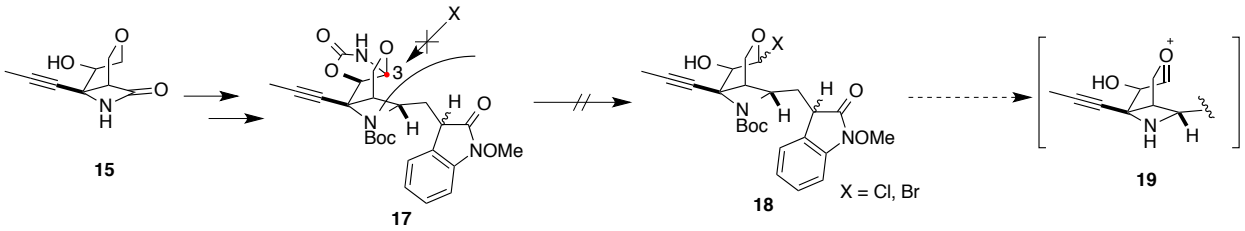
***Scheme 5.*** Ring contraction to construct the azetidine structure from **13,14**.




## 2.4. Strategy A ended in failure.

- Strategy A did not work, because cyclization did not take place due to steric hindrance on C(3) (Scheme 6).

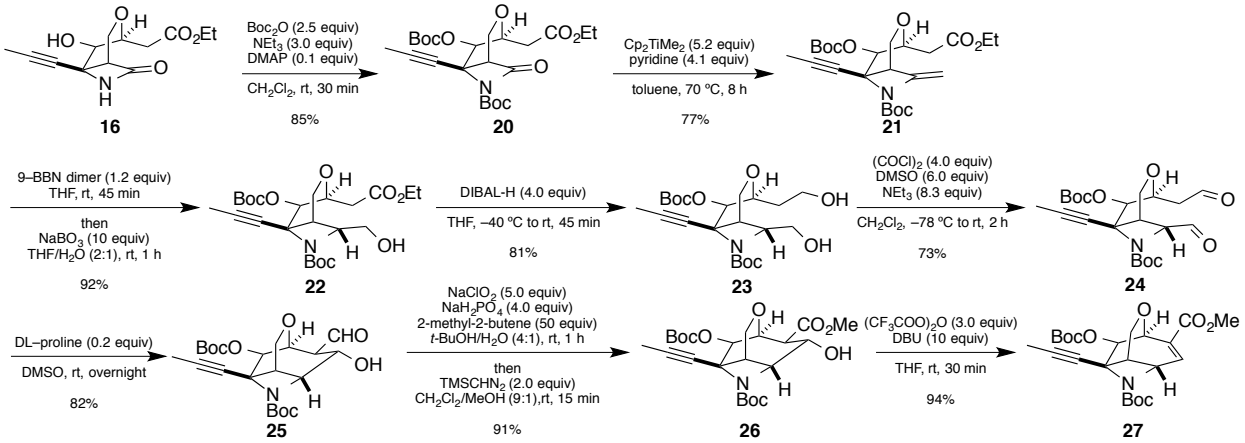
***Scheme 6.*** Unsuccessful steps in strategy A.

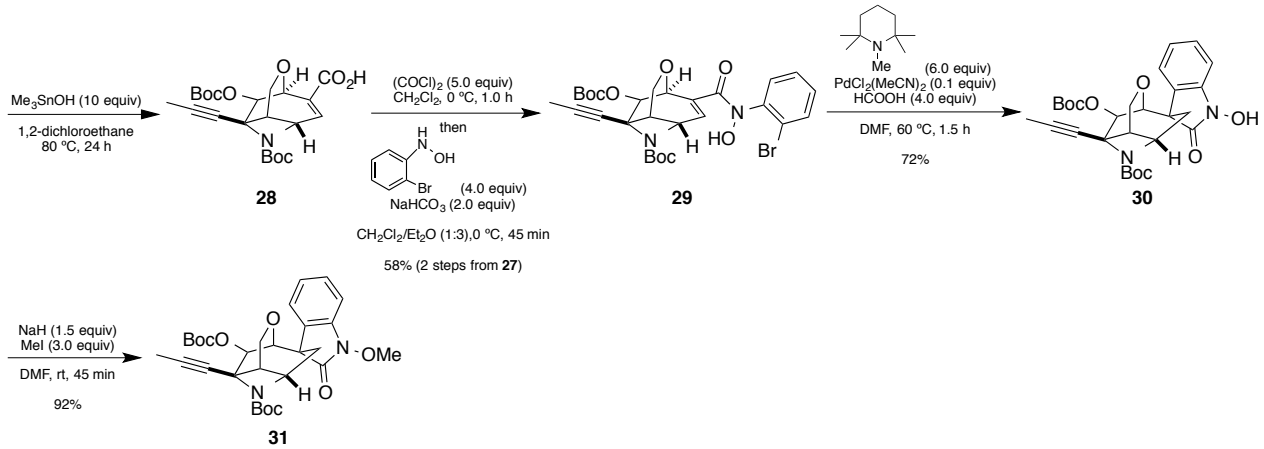



## 2.5. Synthesis of Gelsemoxonine from 16 (Strategy B)

- The structure of Gelsemoxonine was constructed with aldol reaction (**24** to **25**) and reductive Heck cyclization (**29** to **30**) (Scheme 7).

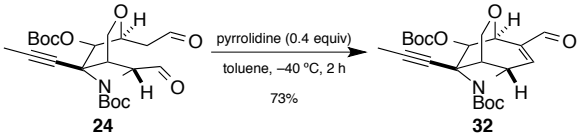
***Scheme 7.*** Synthesis of the polycyclic structure of Gelsemoxonine from **16**.





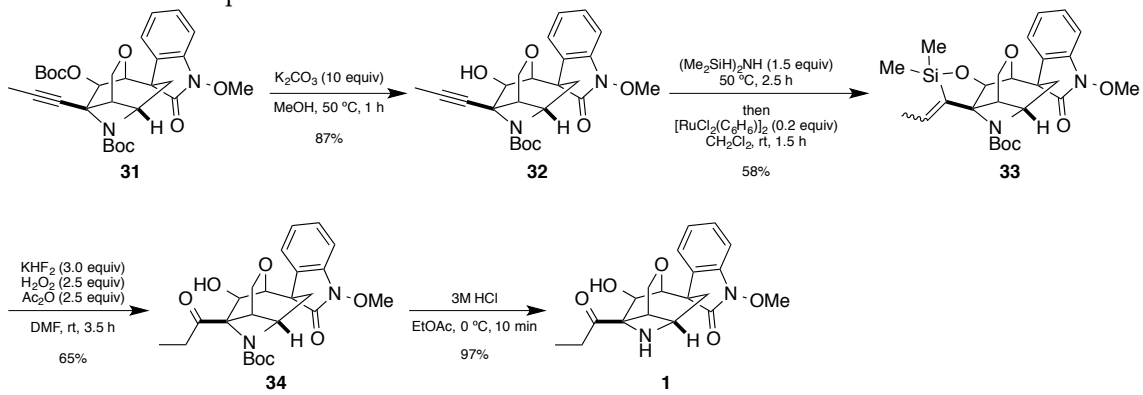

- In **23** to **24**, other product was obtained with pyrrolidine (Scheme 8).

***Scheme 8***. The condition of another aldol reaction from **24**.




- The synthesis of Gelsemoxonine was completed by regioselective hydration via directed hydrosilylation (Scheme 9).

***Scheme 9.*** The completion of Gelsemoxonine from **33**.




## 3. Conclusion

- Gelsemoxonine was synthesized in 22 steps and 0.3% yield from **6**.
- The construction of the azetidine core was succeeded by using the ring contraction reaction of spirocyclopropane isoxazolidines and extended the scope of tolerance of funcrtional groups in the reaction.
- Polycyclic structure was successfully synthesized after the introduction of the azetidine structure.

## 4. References

1. Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Muller, K.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2010,** *49,* 3524–3527.

2. Shimokawa, J.; Harada, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2011,** *133,* 17634–17637.

3. Cordero, F. M.; Pisaneschi, F.; Goti, A.; Ollivier, J.; Salaun, J.; Brandi, A. *J. Am. Chem. Soc.* **2000,** *122,* 8075–8076.