A Mechanistic Presentation of the Total Synthesis of Galanthamine by Yu Feng and Zhi-Xiang Yu

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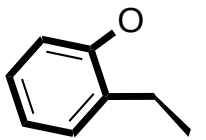
Introduction

INTRODUCTION: Galanthamine is an alkaloid part of a broader family of galanthamine and morphine-like alkaloids. These alkaloids are isolated from bulbous flowering plants; galanthamine in particular is isolated from the bulb of the Amaryllidaceae family. Galanthamine has demonstrated activity as a reversible and competitive acetylcholine esterase inhibitor. Researchers have used galanthamine in the early treatment of Alzheimer's disease.

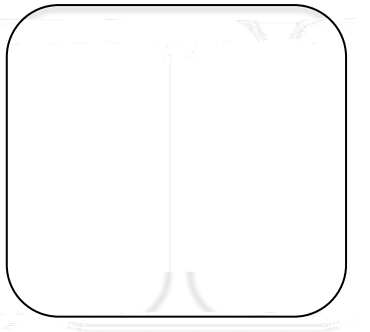


SYNTHETIC CONSIDERATIONS: The morphine and galanthamine-like alkaloids all feature a tetracyclic structure with an azepane ring (highlighted in **Figure 1)** and an all-carbon quaternary, stereogenic center. Galanthamine has already been synthesized by several groups using a number of strategies, nearly all of which approach the problem by tethering the two six-membered rings through the amine and then fusing them through the central furan ring at a late state of the synthesis. The authors of this total synthesis took a different approach whereby they construct the azepane skeleton in a single Rh(I)-catalyzed [(3 + 2) + 1] cycloaddition step. The authors synthesize galanthamine in 15 steps.

Figure 1!

Retrosynthetic Analysis

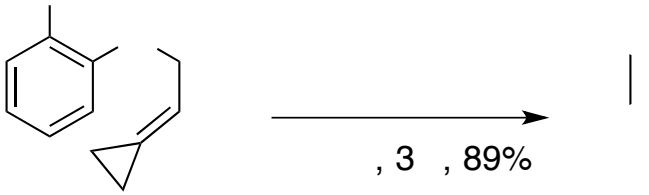
Forward Synthesis



Scheme 2. Formal Synthesis of (+/–)-Galanthamine and (+/–)-Lycoramine!

Mitsunobu Reaction

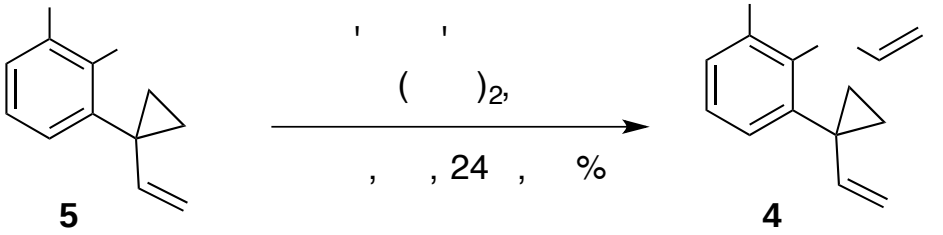
Claisen Rearrangement



Scheme 2c. Claisen Rearrangement!

Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

Vinylation with O’Shea’s Reagent



Scheme 2d. Vinylation with O’Shea’s Reagent!

McKinley, N. F.; O’Shea, D. F. *J. Org. Chem.* **2004**, 69, 5087.
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

Key Step: [(3 + 2) + 1] Cycloaddition

Scheme 2f. Ketal Protection

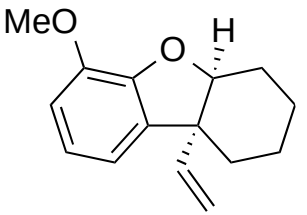
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

Forward Synthesis Continued

[redacted]

Scheme 3. Formal Synthesis of (+/–)-

Hydroboration, Oxidation



Scheme 3a. Hydroboration, Oxidation!

Brown, H. C. *Tetrahedron* **1961**, *12*, 117.
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

Pyridinium

Amidation via Acyl Bromide

Scheme 3c. Amidation via Acyl bromide!

Markó, I. E.; Mekhalfia, A. *Tet. Lett.* **1990**, *31*, 7237.
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

Pictet-Spengler Reaction

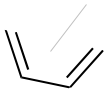
12 **2**

[redacted]

Scheme 3d. Pictet-Spengler Reaction!

Pictet, A.; Spengler, T. *Berichte der deutschen chemischen Gesellschaft* **1911**, *44*, 2030.
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

Final Steps to Galanthamine



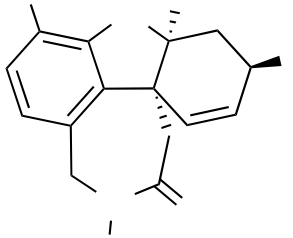
12 (2)

Scheme 4. Formal Synthesis of (+/–)-Galanthamine and (+/–)-Lycoramine!

Chen, J.-Q.; Xie, J.-H.; Bao, D.-H.; Liu, S.; Zhou, Q.-L. *Org. Lett.* **2012**, 14, 2714.
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

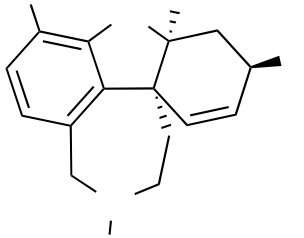
Saegusa-Ito Oxidation

Amide Reduction



15

$Zn(OAc)_2$



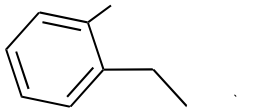
galanthamine (1a)

$[\ X_2Zn\text{---}H\text{---}Si(OEt)_3\ ]$

Scheme 4b. Amide Reduction!

Das, S. et al. *J. Am. Chem. Soc.* **2010**, 132, 1770.
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

Final Step to Lycoramine



Scheme 5. Formal Synthesis of (+/–)-Galanthamine and (+/–)-Lycoramine!

Ishizaki, M.; Ozaki, K.; Kanematsu, A.; Isoda, T.; Hoshino, O. J. *Org. Chem.* **1993**, 58, 3877.
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.