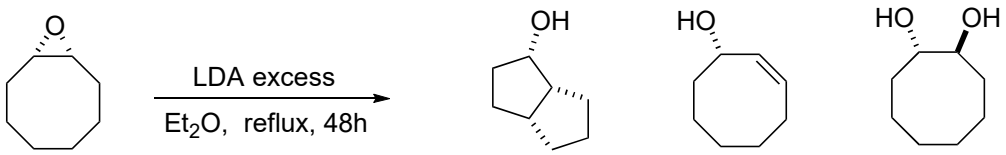
Exercise 1 : *Proximity Effect*

1-A) Considering the deuterium labeling experiment (*vide infra*), please provide a plausible mechanism accounting for the formation of bicyclic alcohol **A**.
1-B) Upon treatment under identical conditions, *trans*-cyclooctene oxide is converted into a mixture of cycloheptanecarboxaldehyde **7** and ***exo*-A.** Provide a mechanism for the formation of **7**.

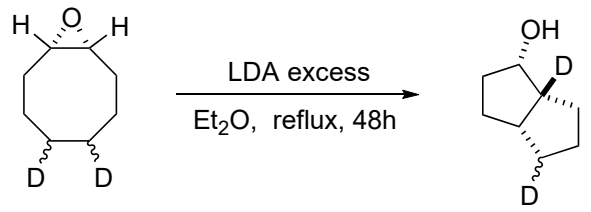


+ 5% recovered **SM**

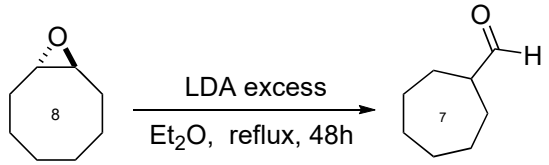
***endo*-A** 69% **B** 16% **C** 2%

A. C. Cope, *JACS* **1958** 2849

Labeling experiment



trans-cyclooctene oxide

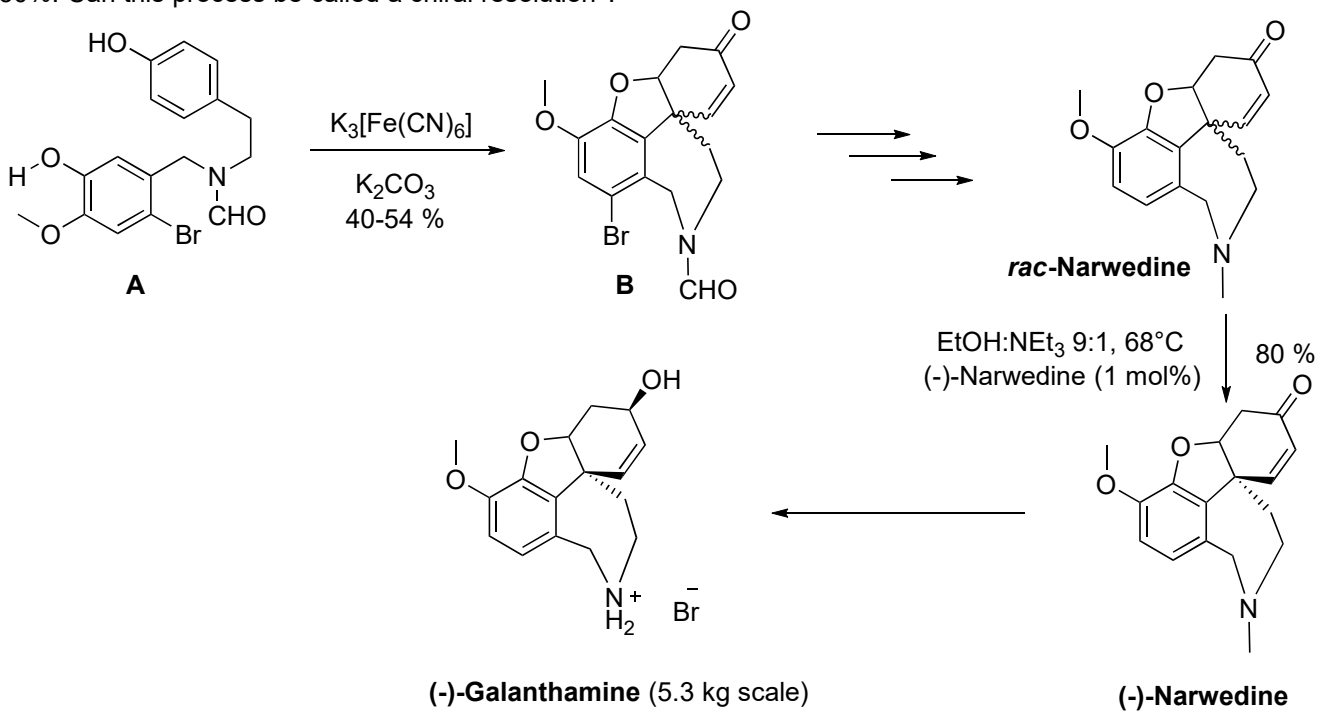


D 32%

Exercise 2 : *Synthesis of (-)-Galanthamine*

Galanthamine is a natural product isolated from snowdrop *Galanthus Caucasicus* (Bulgaria, Turkey, Caucasus mountains). Its use in traditional medecine likely dates back to antiquity. Researchers even suggested that Homer's "Moly" refered to *Galanthus* (Moly is a magical herb mentionned in Homer's Odyssey). It is currently used as a medicine for the treatment of cognitive decline associated with Alzheimer's disease. The first total synthesis of Galanthamine was reported by Sir. D. H. R. Barton (*JCS*, **1962**, 806). In the 1990's, requirements of kg-quantities of material for clinical trials urged the development of a scaleable route. Building-up on Barton's strategy, a process-chemistry group reported the following synthesis (*OPRD*, **1999**, 425).

2-A) Provide a mechanism for the transformation **A** -> **B**.
2-B) *rac*-Narwedine is converted in (-)-Narwedine in 80% yield by crystallisation. Please explain why yield exceeds 50%. Can this process be called a chiral resolution ?



A

B

***rac*-Narwedine**

(-)-Galanthamine (5.3 kg scale)

(-)-Narwedine

Exercice 3 : *Shenvi's Total Synthesis of (-)-Bilobalide* Nature (2019) doi:10.1038/s41586-019-1690-5

3-A) Determine the structure of all missing intermediates (**D, F, I, J** & **L)**. Provide a mechanism for the transformation of **D** -> **E** and **K** -> **L**.
3-B) Compounds **D** and **F** are unstable under basic conditions. Why ?
3-C) During the final step, identify competing positions for oxidation. In addition to the regioselectivity issue, what side reaction could be observed upon treatment of **M** with KHMDS ?