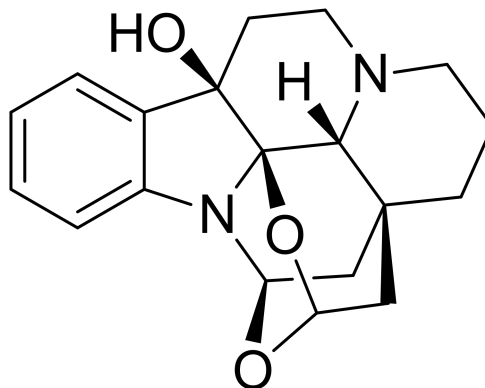


Enantioselective Total Synthesis of (–)-Terengganensine A
Piemontesi, C.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 6556–6560.

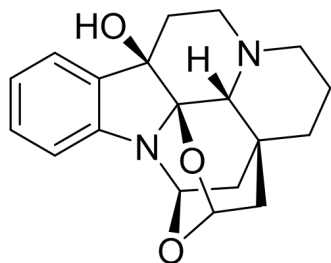


Zachary X. Giustra

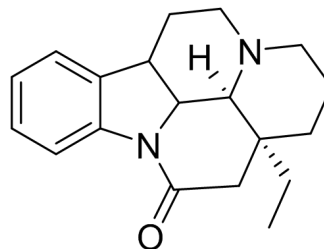
Liu Group

July 1, 2016

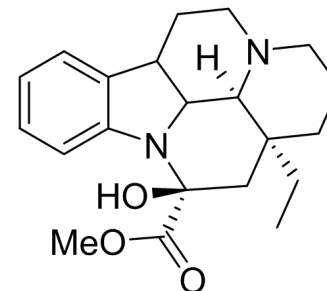
Previous Isolation and Biological Activity



(-)-terengganensine (**1**)



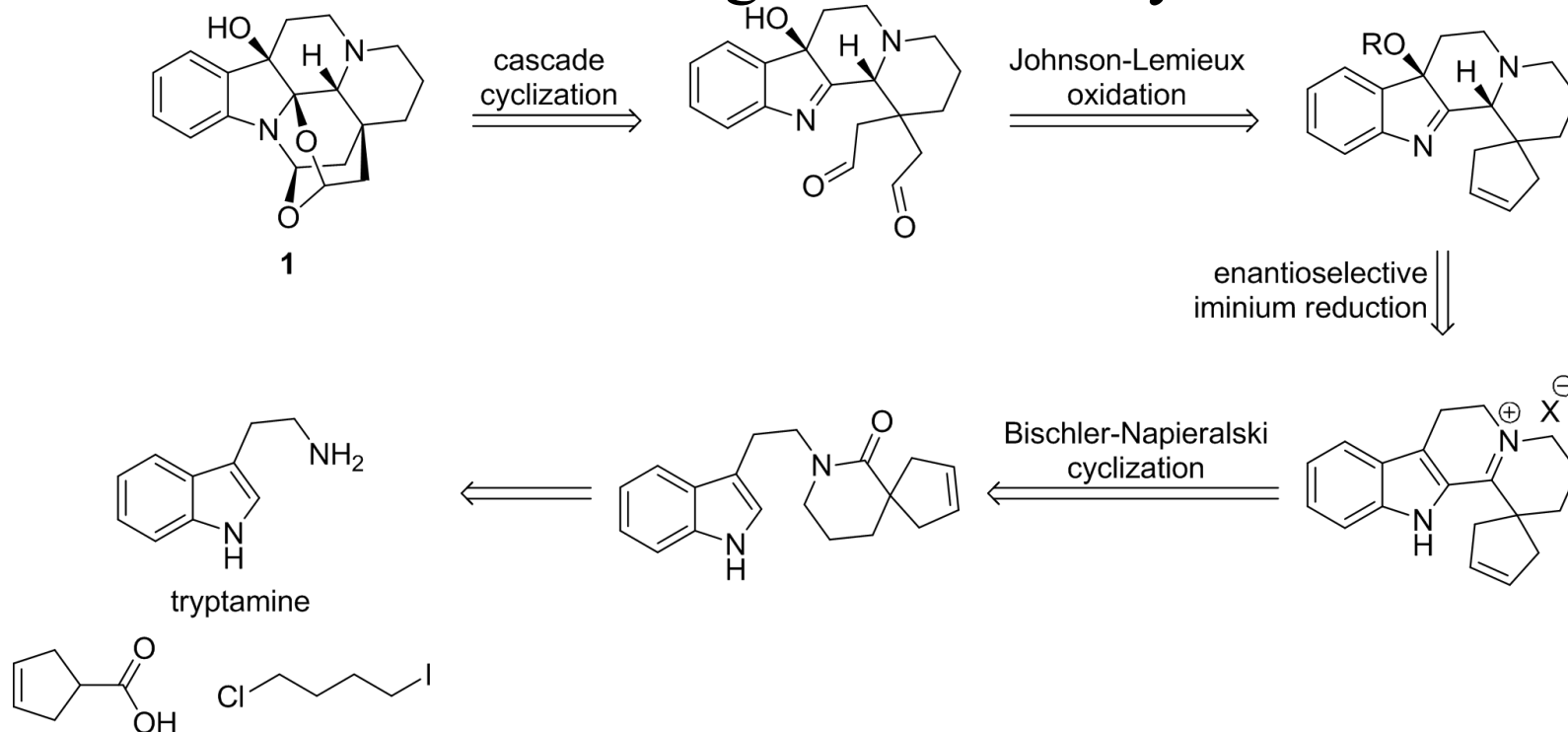
(-)-eburnamonine



(+)-vincamine

- Originally isolated from the bark of *Kopsia terengganensis*.
- Other members of the eburnane alkaloid family have been shown to affect the central nervous system.
- (-)-Eburnamonine works against cerebrovascular disorders; (+)-vincamine is sold as a peripheral vasodilator (Oxybral SR).

Structural Challenges and Retrosynthesis

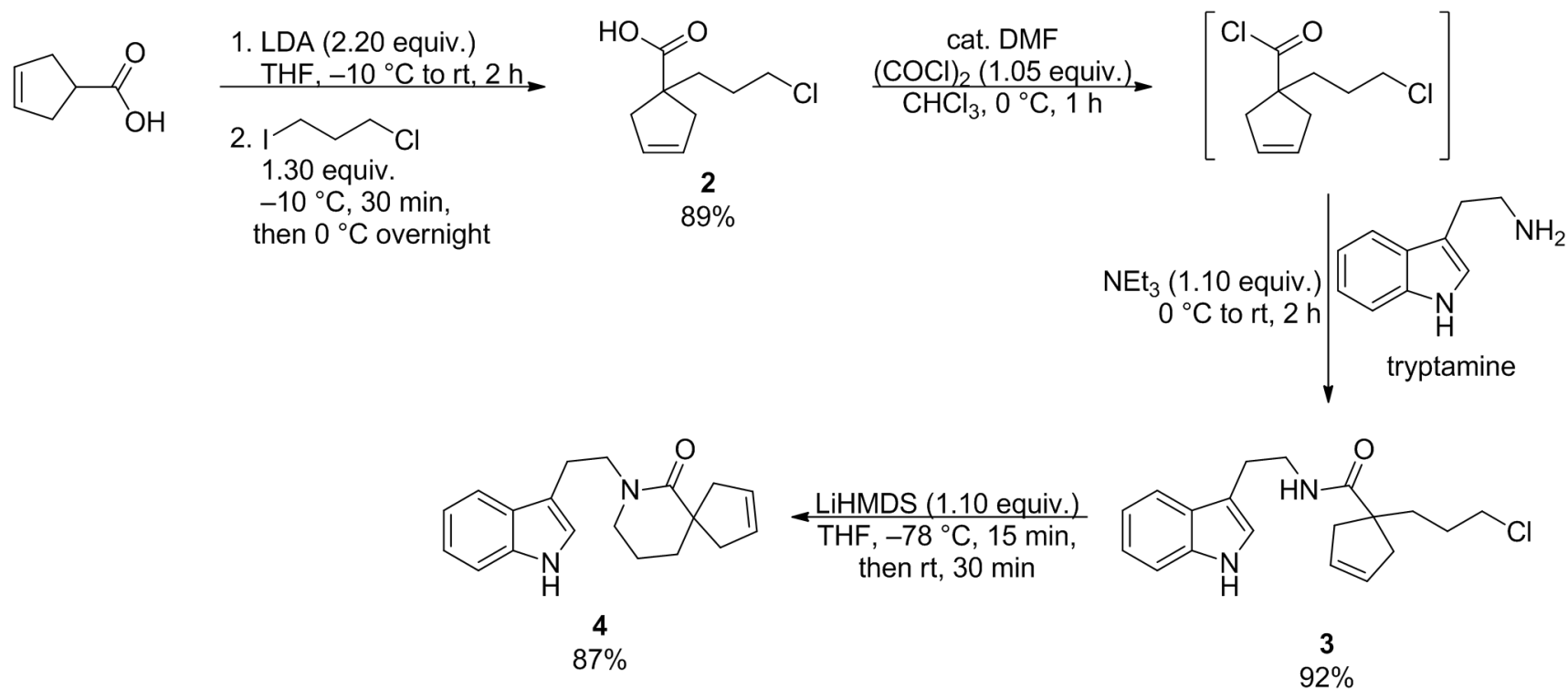


- Heptacyclic compound with a dioxazaadamantane unit as part of a [5.6.6.6]azafenestrane ring system.
- No previous synthesis of terengganensine A reported; retrosynthesis inspired by work of Ho and Chen to synthesize (±)-eburnamine and (±)-eburnamonine.
- Cascade cyclization of di-aldehyde to form dioxazaadamantane unit.
- Enantioselective iminium reduction to set the absolute configuration for all stereocenters.

Piemontesi, C.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 6556–6560.

Ho, T.-L.; Chen, C.-K. *Helv. Chim. Acta* **2005**, *88*, 2764–2770.

Forward Synthesis



LiHMDS = lithium hexamethyldisilazide

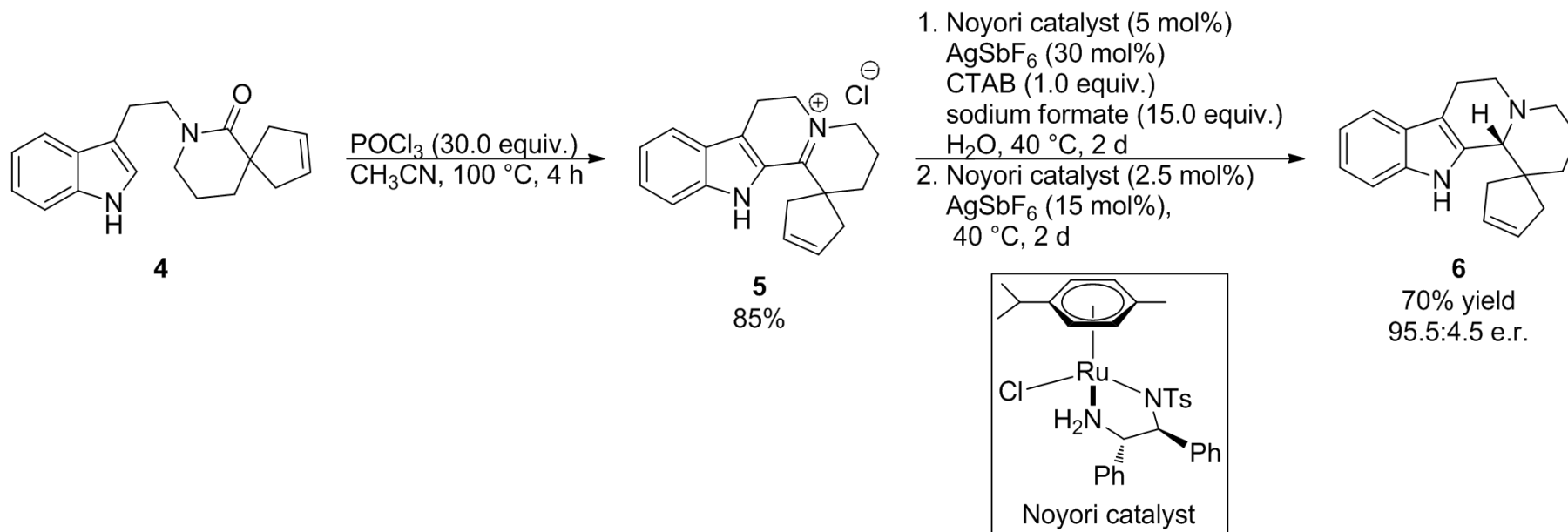
Piemontesi, C.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 6556–6560.

Goto, A. EP 2423189 A1, 2012.

Shibuya, K. L. H. N.; Kawamine, K.; Sato, Y.; Edano, T.; Tanabe, S.; Shirato, S. EP 0807627 A2, 1997.

Isobe, M.; Fukami, N.; Goto, T. *Chem. Lett.* **1985**, *14*, 71–74.

Forward Synthesis



- Reports of catalytic enantioselective transfer hydrogenations of iminium salts are relatively rare.
- CTAB acts as a cationic surfactant; facilitates the reduction through formation of micelles.

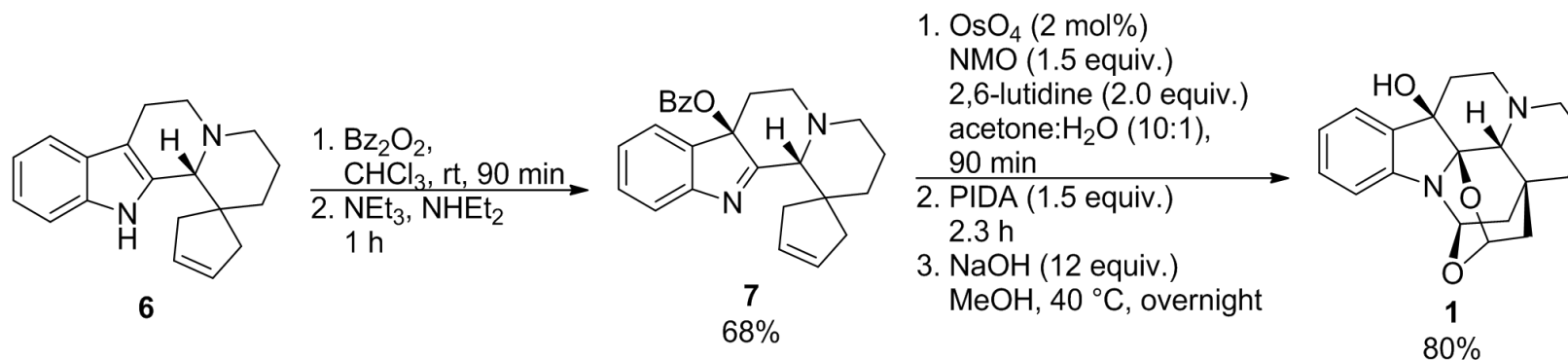
CTAB = cetyltrimethylammonium bromide

Piemontesi, C.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 6556–6560.

Evanno, L.; Ormalo, J.; Pihko, P. M. *Chem. Eur. J.* **2009**, *15*, 12963–12967.

Wang, F.; Liu, H.; Cun, L.; Zhu, J.; Deng, J.; Jian, Y. *J. Org. Chem.* **2005**, *70*, 9424–9429.

Forward Synthesis



- Since the benzoyloxylation can be performed in the dark at room temperature, the authors propose it proceeds through an ionic, rather than radical, mechanism.
- The authors cite Kanaoka *et al.* as the only example of radical C(3) benzoyloxylation of an indole derivative.

PIDA = phenyliodine(III) diacetate

Piemontesi, C.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 6556–6560.

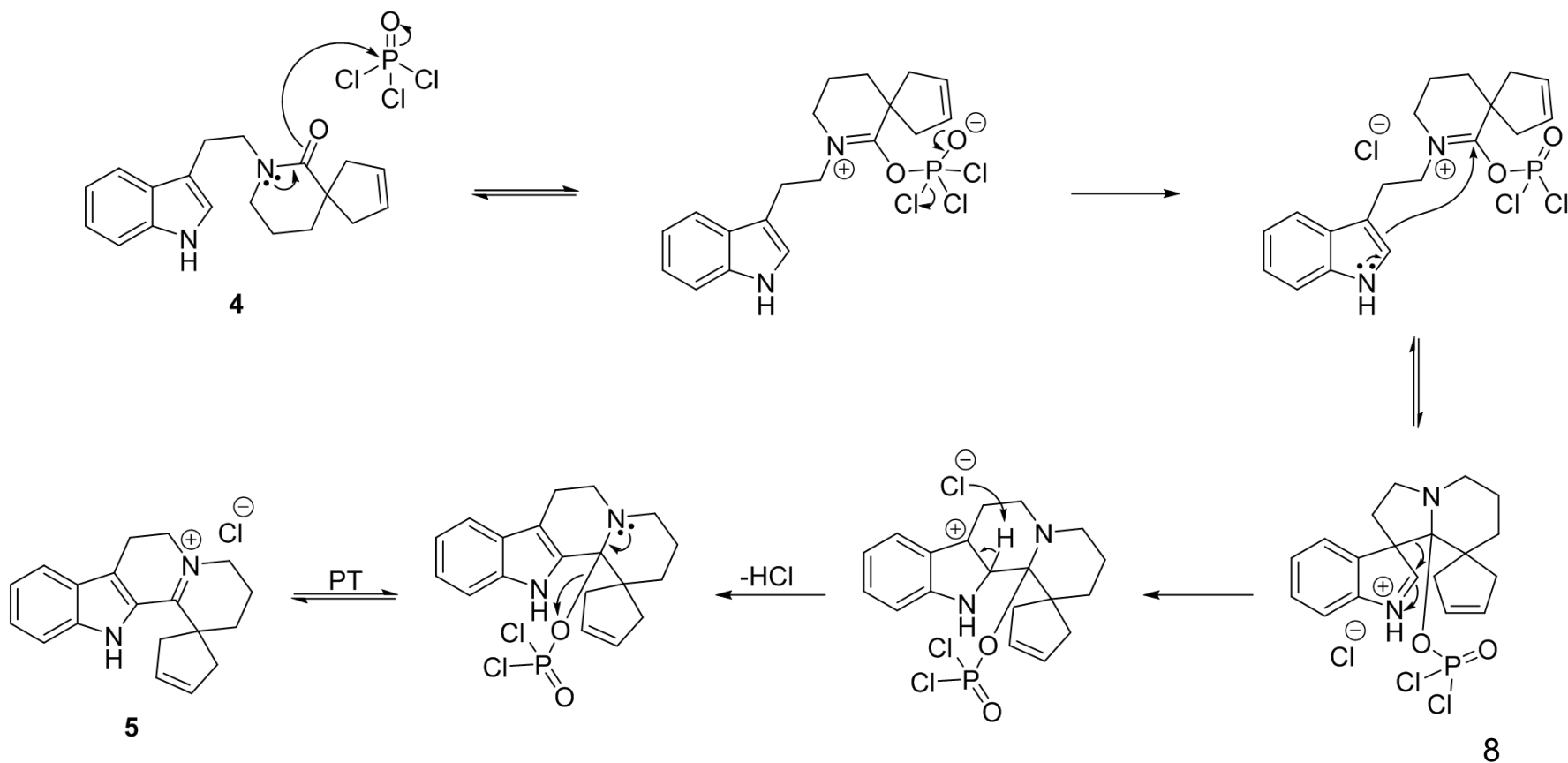
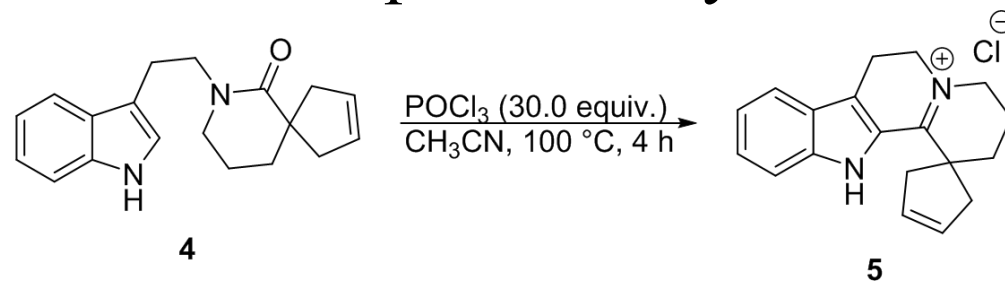
Güller, R.; Borschberg, H.-J. *Helv. Chim. Acta* **1993**, *76*, 1847–1862.

Kanaoka, Y.; Aiura, M.; Hariya, S. *J. Org. Chem.* **1971**, *36*, 458–460.

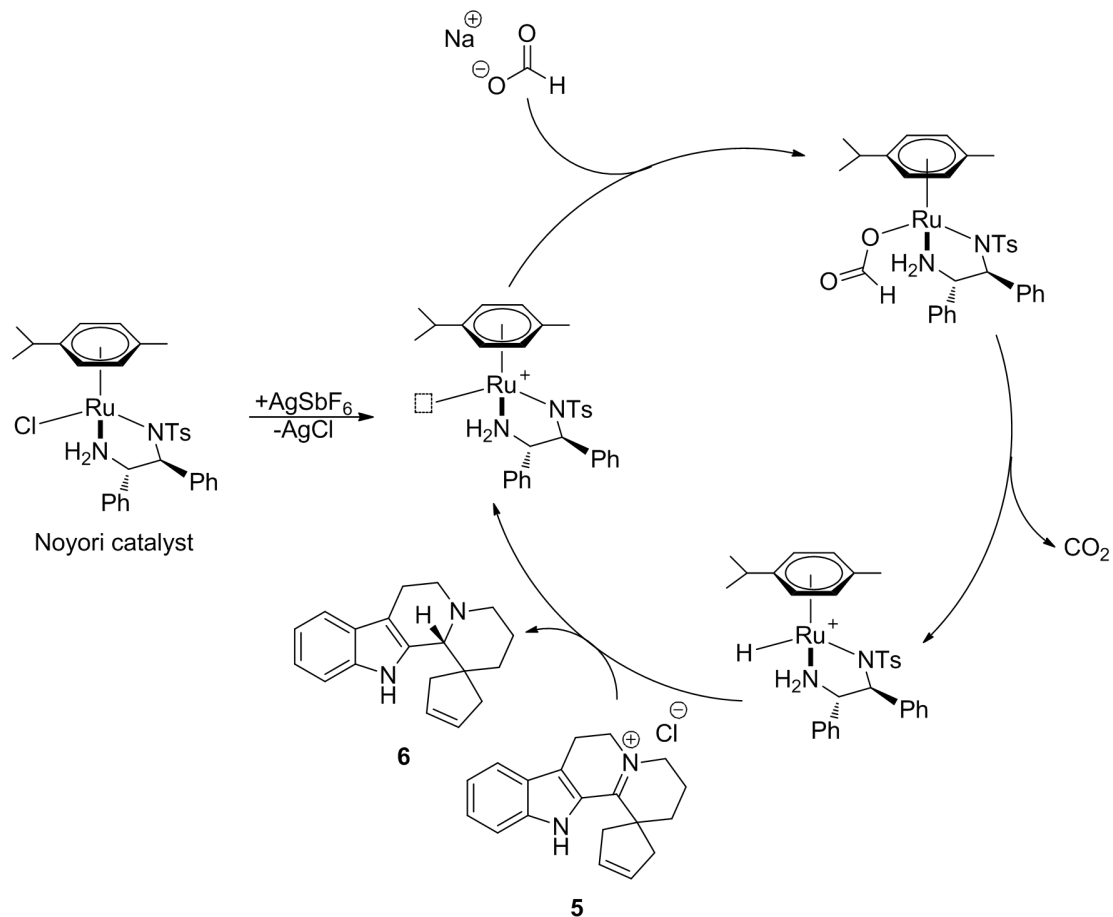
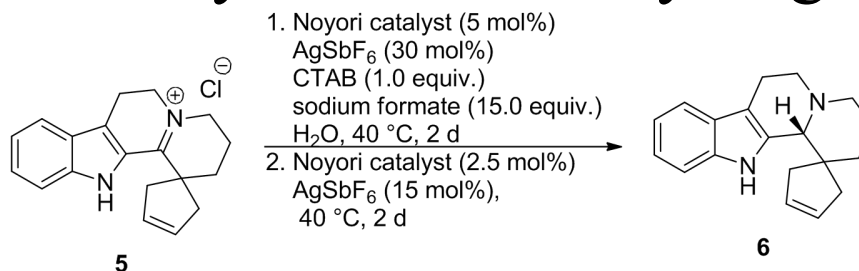
Summary

- Asymmetric synthesis of (–)-terrengganensine A in 23% overall yield; 7 steps longest linear sequence from 3-cyclopentene carboxylic acid.
- Minimal protecting group usage and functional group interconversion contribute to the efficiency of the synthesis.
- Absolute stereochemistry set by rare Noyori-type enantioselective transfer hydrogenation of an iminium salt.
- Dioxoazaadamantane unit constructed in a single cascade cyclization following Johnson-Lemieux oxidation of the cyclopentene ring.

Mechanisms: Bischler-Napieralski Cyclization



Mechanisms: Noyori Catalytic Transfer Hydrogenation



SbF₆⁻ counteranions omitted from catalytic cycle for clarity.

Mechanisms: Johnson-Lemieux Oxidation/Cascade Cyclization

