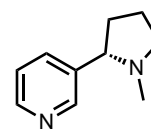


(1) Enamorado, M.; Ondachi, P.; Comins, D. *Org. Lett.* **2010**, *12*, 4513-4515

(S)-Macrostomine is an alkaloid isolated from *Papaver macrostomum*, a poppy variety. It shows activity as a modulator of the cardiovascular system as well as spasmolytic activity superior to a structurally related, approved drug, papaverine.

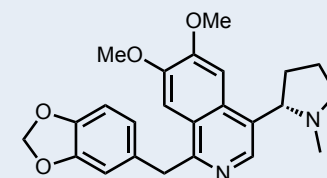
At the core of (S)-Macrostomine's structure is the skeleton of (S)-Nicotine, another neurologically active alkaloid (produced by tobacco, a plant you are more likely to find growing in Dr. Comins' stomping ground of North Carolina).

Exploiting this similarity allowed the Comins group to execute an efficient semisynthesis.



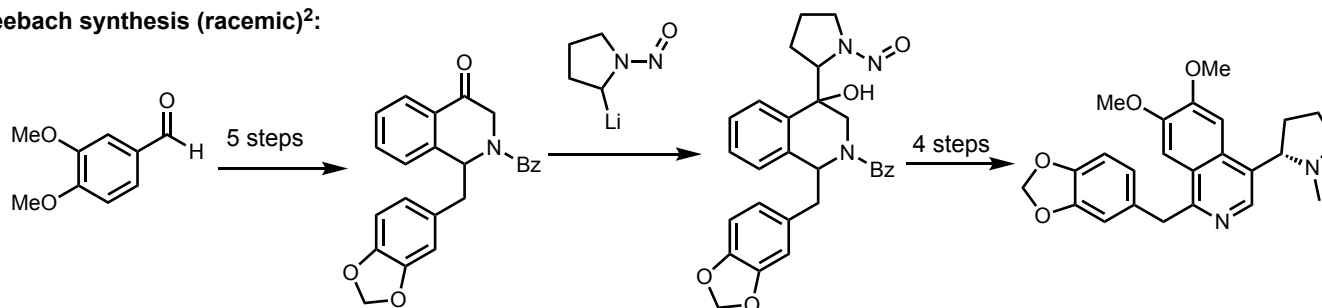
(S)-Nicotine

5 steps



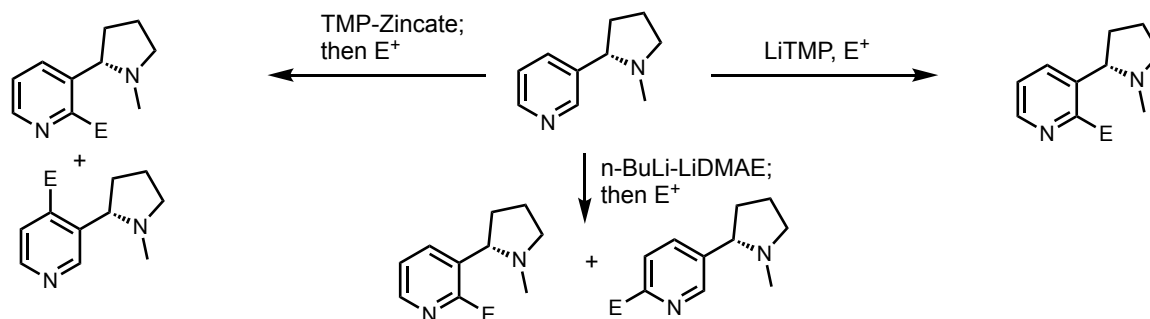
(S)-Macrostomine

### Seebach synthesis (racemic)<sup>2</sup>:



Two racemic syntheses from Wiegrobe and Sharma are published, as well as an enantioselective route from Wiegrobe

### Comins (S)-Nicotine metallation methodology<sup>3</sup>:

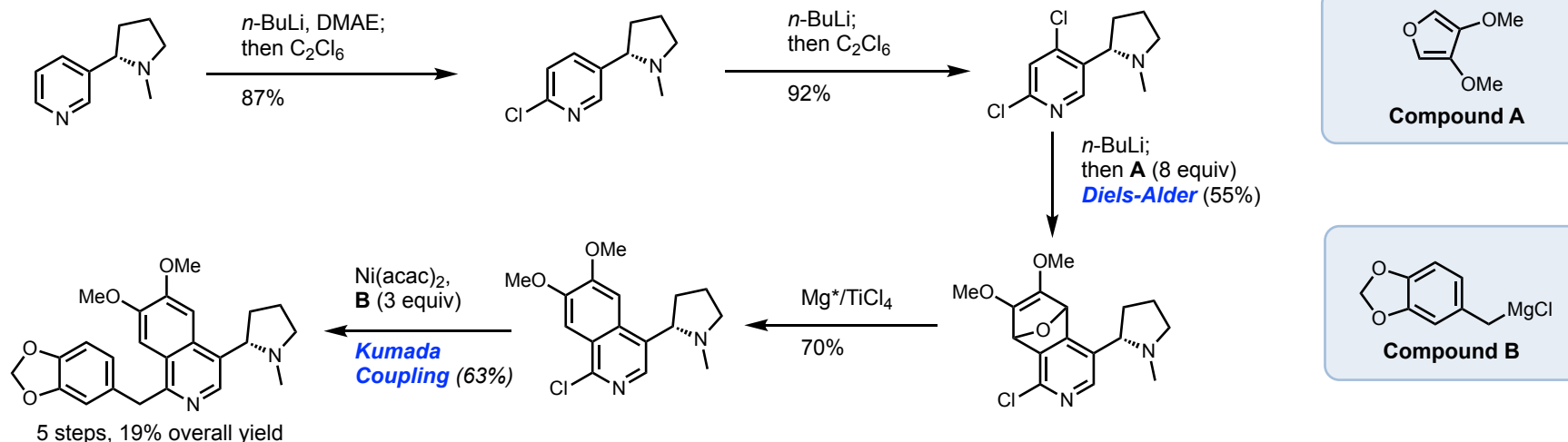
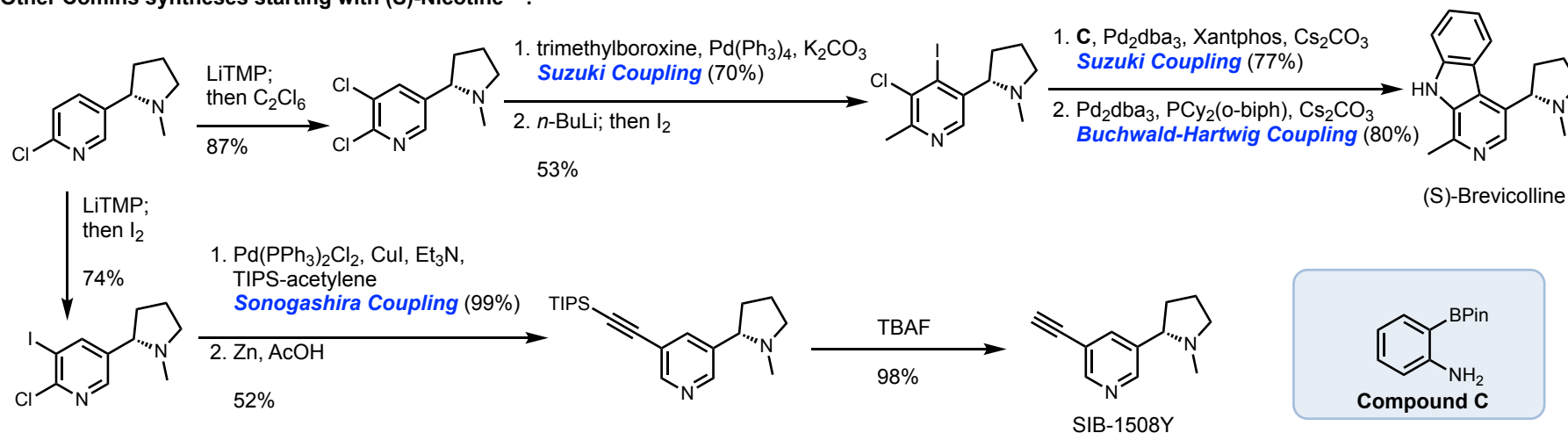


(2) Wykypiel, W.; Seebach, D. *Tetrahedron Lett.* **1980**, *21*, 1927-1930

(3) Fevrier, F.; Smith, E.; Comins, D. *Org. Lett.* **2005**, *7*, 5457-5460



**Daniel L. Comins** is Professor Emeritus at North Carolina State University. His group's research has focused on the diverse chemistries of nitrogenous heterocycles such as N-acyl pyridiniums and (S)-Nicotine. Dr. Comins is the namesake developer of "Comins' Reagent", a popular tool for transferring the triflyl group to enolates.

Comins<sup>1</sup>:Other Comins syntheses starting with (S)-Nicotine<sup>4,5</sup>:(4) Wagner, F.; Comins, D. *Org. Lett.*, **2006**, 8, 3549–3552(5) Wagner, F.; Comins, D. *J. Org. Chem.* **2006**, 71, 8673–8675