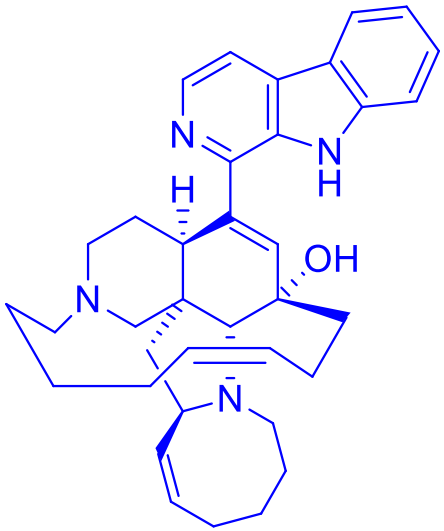
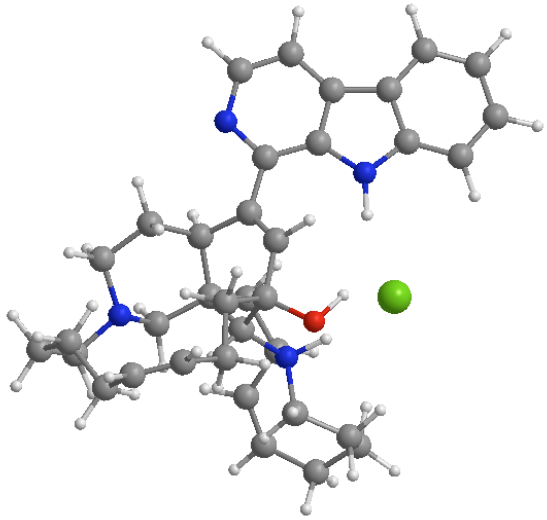
Total Synthesis of Manzamine A and Related Alkoloids

Pavol Jakubec, Alison Hawkins, Wolfgang Felzmannc and Darren J. Dixon

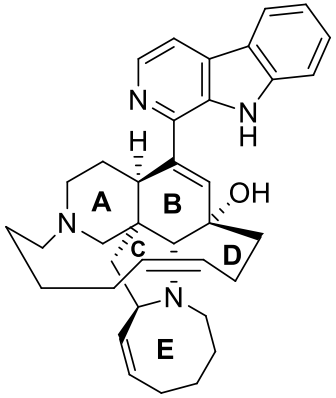
***J. Am. Chem. Soc.*, 2012, *134* (42), 17482–17485**



Manzamine A



Mustafa Kazancioglu
Current Literature
3 November 2012

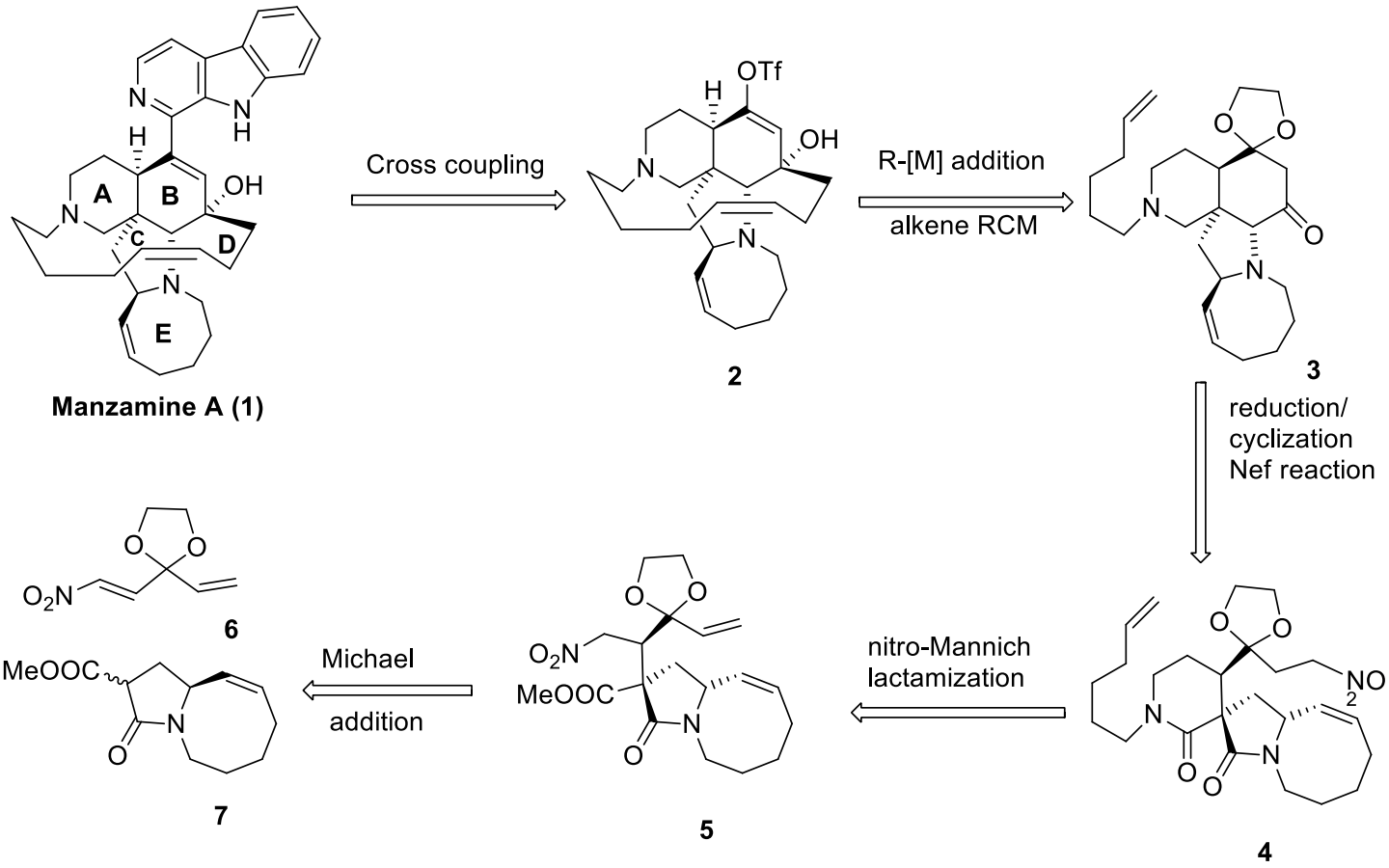


Manzamine A (1)

- Manzamine A is a marine alkaloid first isolated by Hige et al. in 1986 from a sponge in Okinawa Sea.
- It exhibits a range of potent biological properties, ,including insecticidal, anti-bactarial, anti-inflammatory, anti-cancer, and anti-malarial activity.
- Manzamine A has a pentacyclic (ABCDE) core comprising 6-,6-,5-,13-, and 8-membered rings, two *Z*-olefins, two tertiary amines, and five stereocenters including four contiguous and two quaternary centers.
- Manzamine A have three published total synthesis by Winkler, Martin, Fukuyama

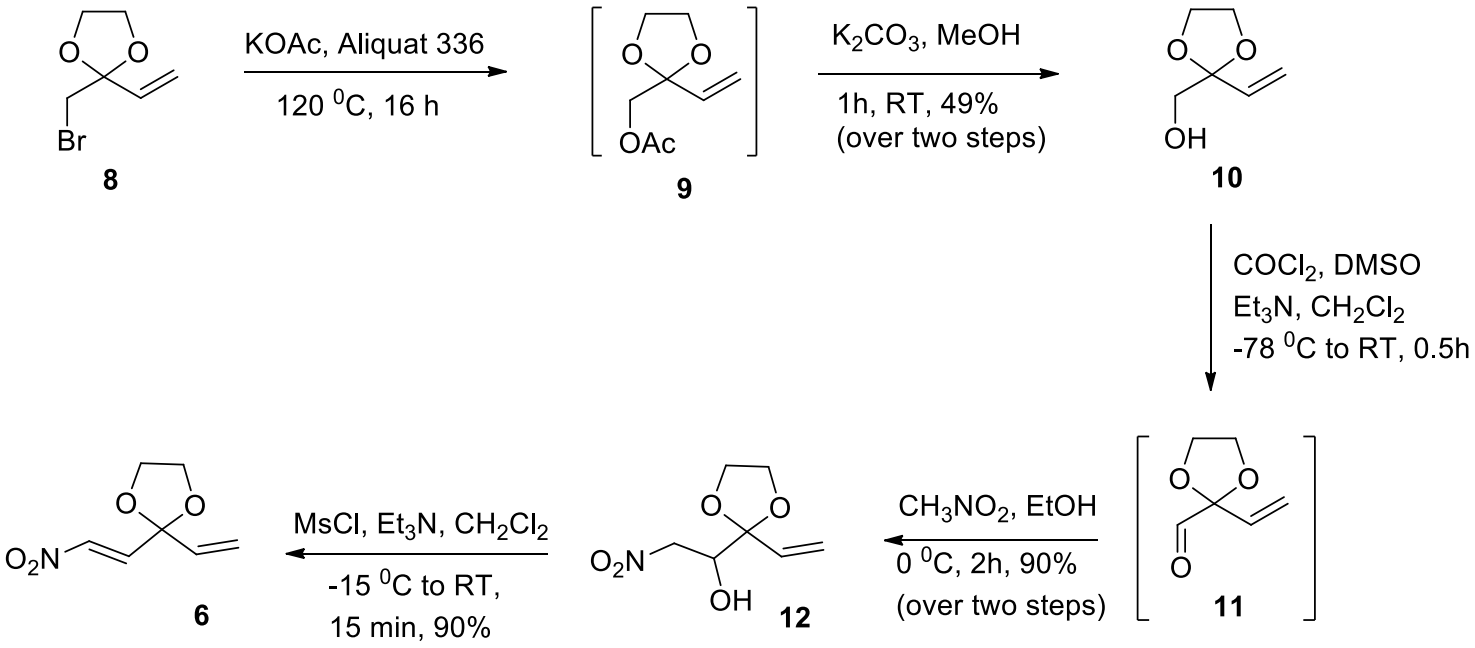
Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, 120, 6425.
Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc*. **1999**, 121, 866.
Toma, T.; Kita, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **2010**, 132, 10233.

Retrosynthetic analysis of manzamine A



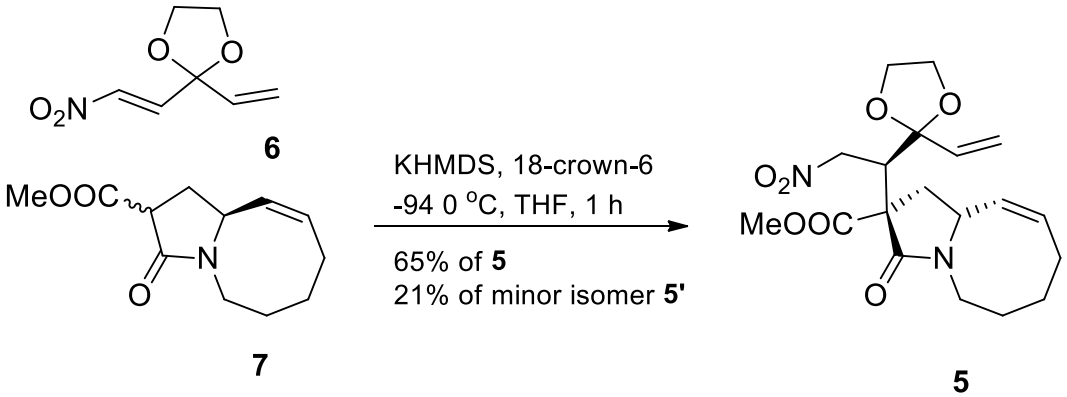
J. Am. Chem. Soc., 2012, *134* (42), 17482–17485

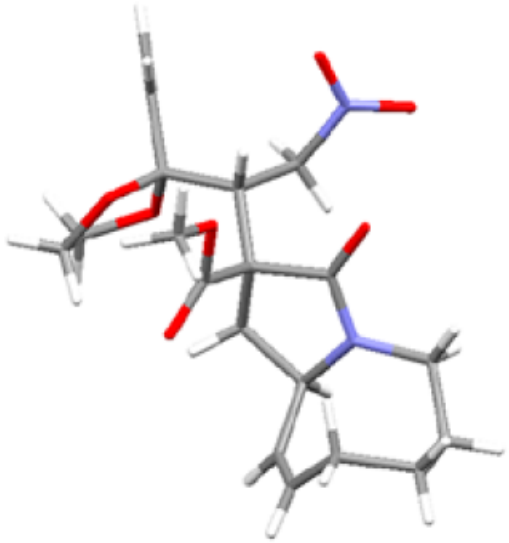
Synthesis of Electrophile 6



J. Am. Chem. Soc., 2012, *134* (42), 17482–17485

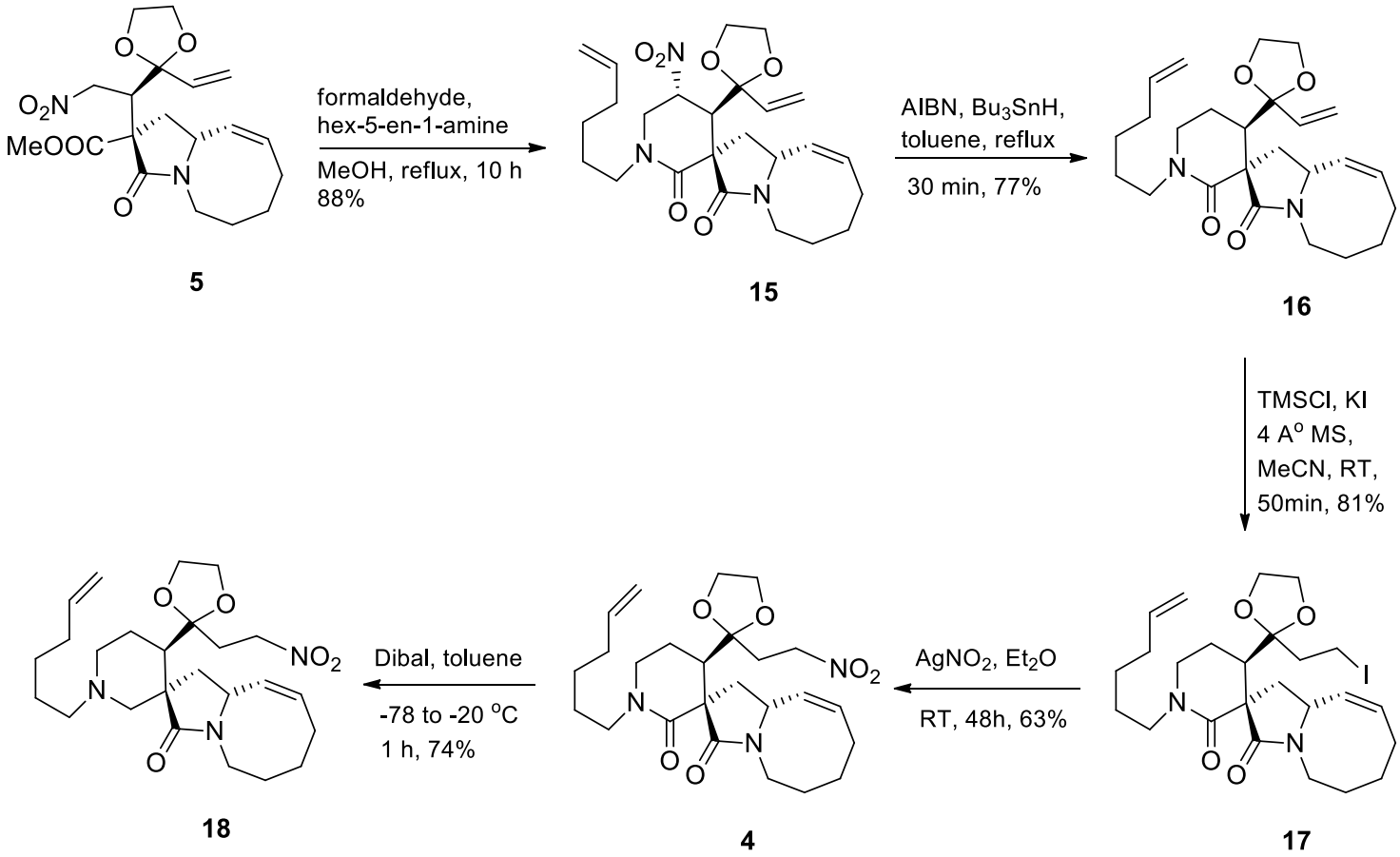
Steroselective Michael Addition of Key Building Blocks



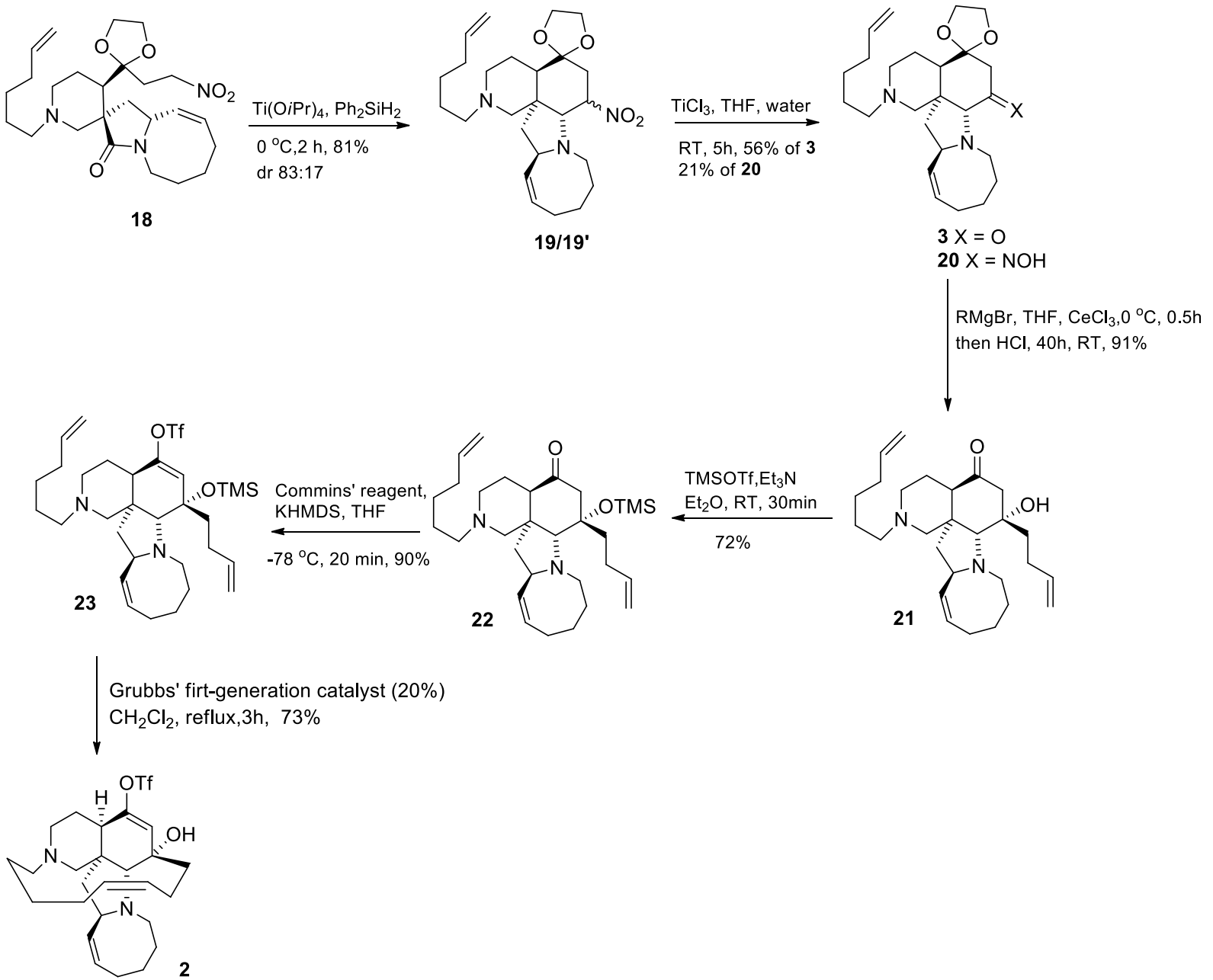


J. Am. Chem. Soc., 2012, *134* (42), 17482–17485

Synthesis of Pentacyclic Core of Manzamine Alkoloids

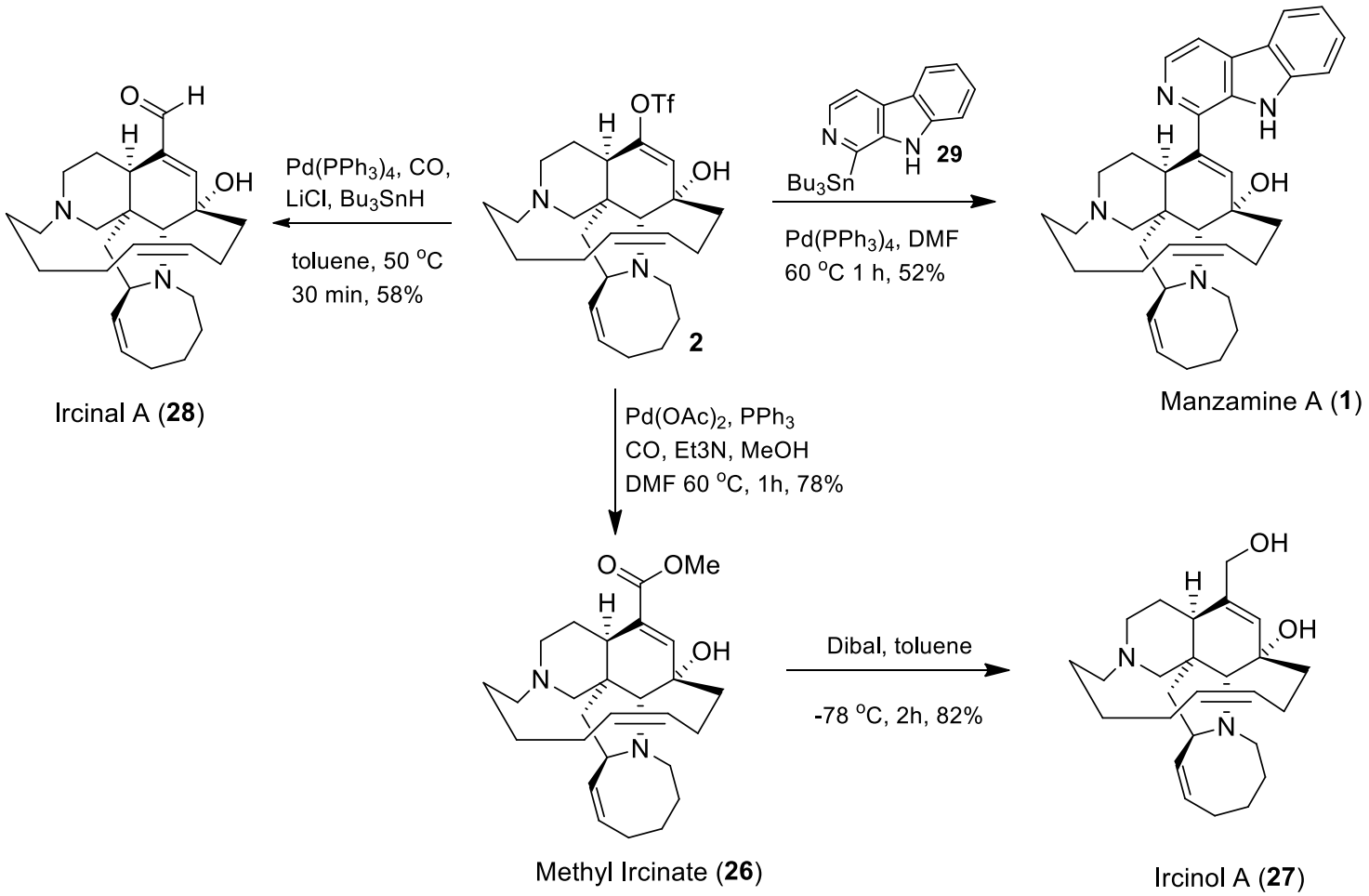


J. Am. Chem. Soc., 2012, *134* (42), 17482–17485



J. Am. Chem. Soc., 2012, *134* (42), 17482–17485

Completion of the Total Syntheses of Manzamine A, Ircinol A, and Ircinal A



J. Am. Chem. Soc., 2012, *134* (42), 17482–17485

CONCLUSION:

- Developed a short and stereoselective synthesis (18-step longest linear sequence) of manzamine A
- By the adoption of a cross-coupling strategy to attach the β-carboline, important for its biological activity, to key late-stage intermediate enol triflate **2**.
- This approach allowed to synthesize ircinal A (**28**) and methyl ircinate (**26**) via alternative coupling reactions and is ideally suited for future manzamine A analogue synthesis.