Protecting Group-Free Total Synthesis of (-)-Lannotinidine B

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J. Am. Chem. Soc. ASAP

Ideal synthesis

“Prepared from readily available, inexpensive starting materials in one simple, safe, environmentally acceptable and resource-effective operation that proceeds quickly and in quantitative yield”

Wender, P. A. Introduction: frontiers in organic synthesis. *Chem. Rev*. 96, 1-2 (1996)

“ Step economy, atom economy, and redox economy”

Protecting-group-free (PGF) synthesis as an opportunity for invention

“ The major challenges (in chemistry) are the construction of molecules without using protecting group chemistry and the ability to put molecules together in fast and efficient ways”

--- R. H. Grubbs

A catalytic lifetime. *Chem. Sci.* 4, C69 (2007)

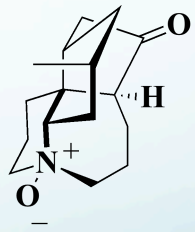
Protecting group:

- **Appends at least two steps to the synthetic sequence, decreasing the step economy, leading to a loss of material.**
- **Atoms corresponding to the blocking group are not found in the final product, which is an unfavorable result in atom economy.**
- **Materials that corresponds to the PG must be separated from the product and discarded, increasing the overall waste production.**

Lycopodium alkaloids

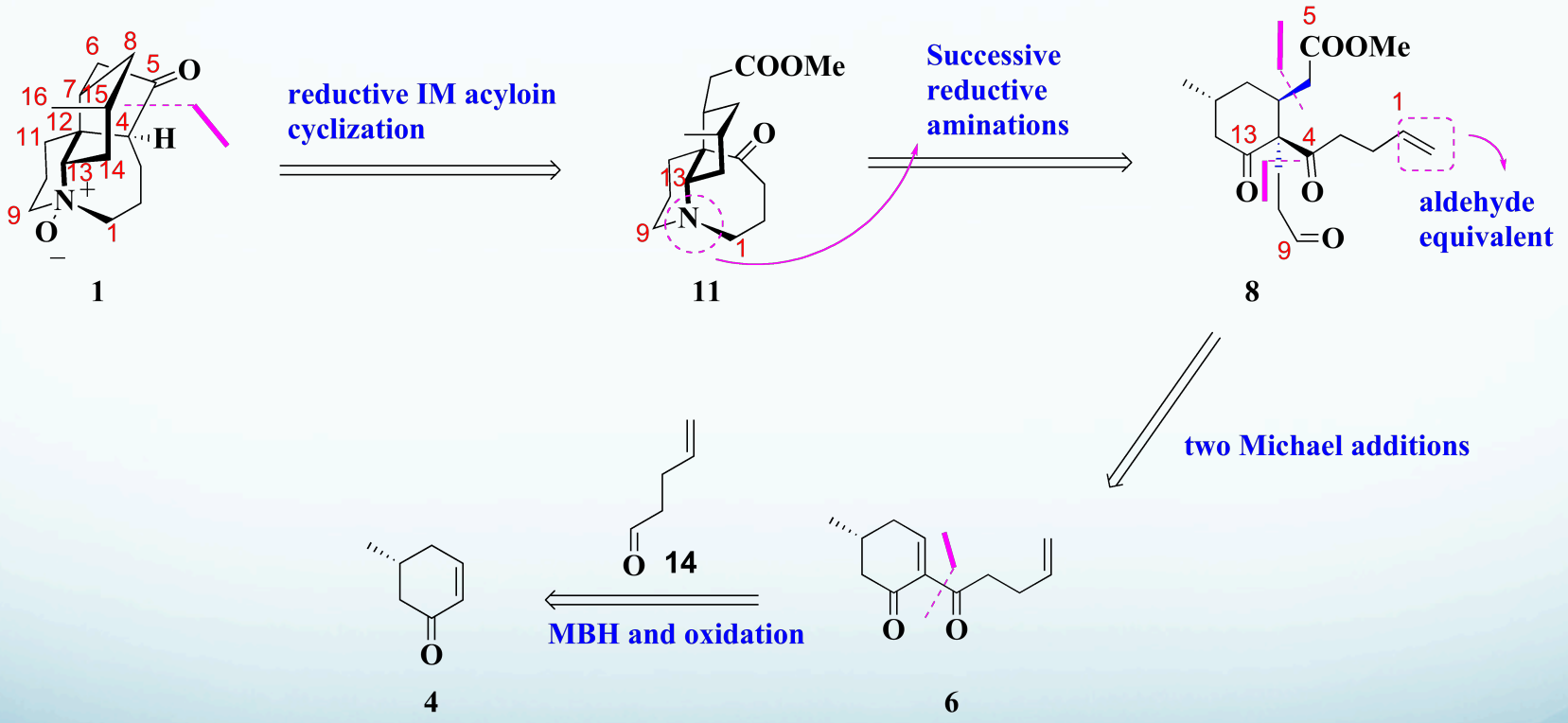
- **Are unique heterocyclic alkaloids having $C_{11}N$, $C_{15}N_2$, $C_{16}N$, $C_{16}N_2$, $C_{22}N_2$, and $C_{27}N_3$ types from genus *Lycopodium*.**
- **~ 201 *Lycopodium* alkaloids have been identified from 54 species of Lycopodium.**
- **Lannotinidine B was isolated in 2005.**
  - **a tetracyclic $C_{16}N$-type alkaloid.**
  - **Consists of an tetracyclic carbon-nitrogen skeleton including five stereogenic centers and a N-oxide functionality.**
  - **Effectively improve mRNA expression of neurotropic growth factor (NGF) in 1321N1 human astrocytoma cells.**

Lycopodium

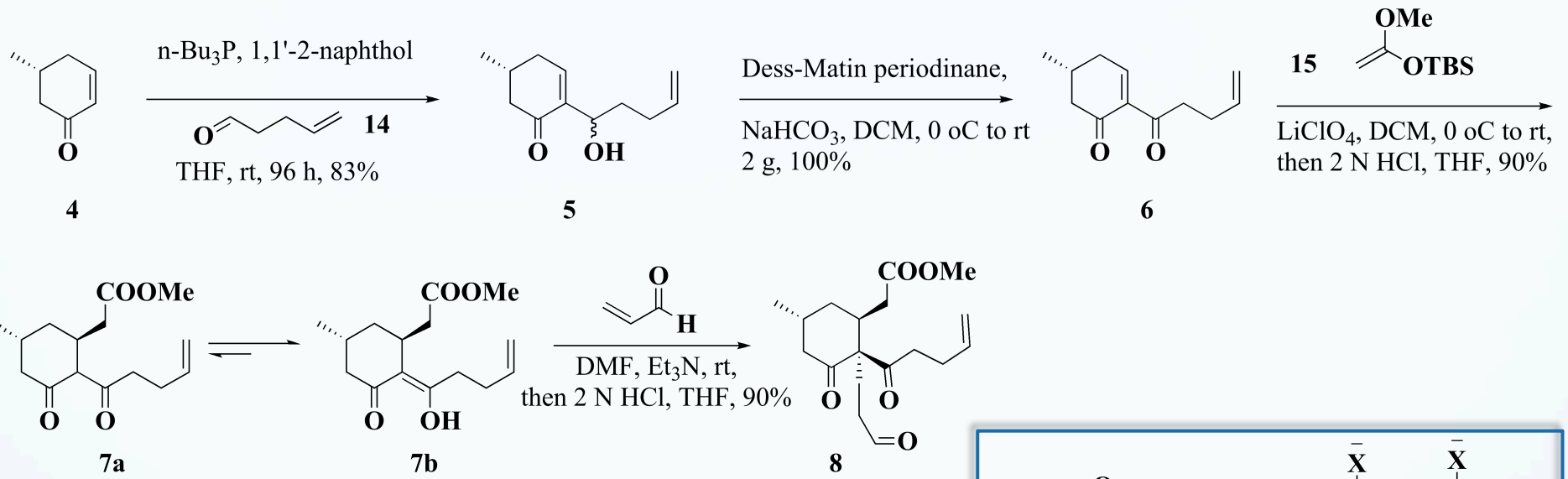


(-)-Lannotinidine B

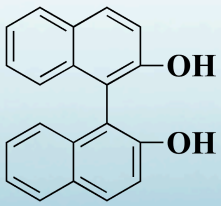
Retrosynthetic analysis of (-)-lannotinidine B



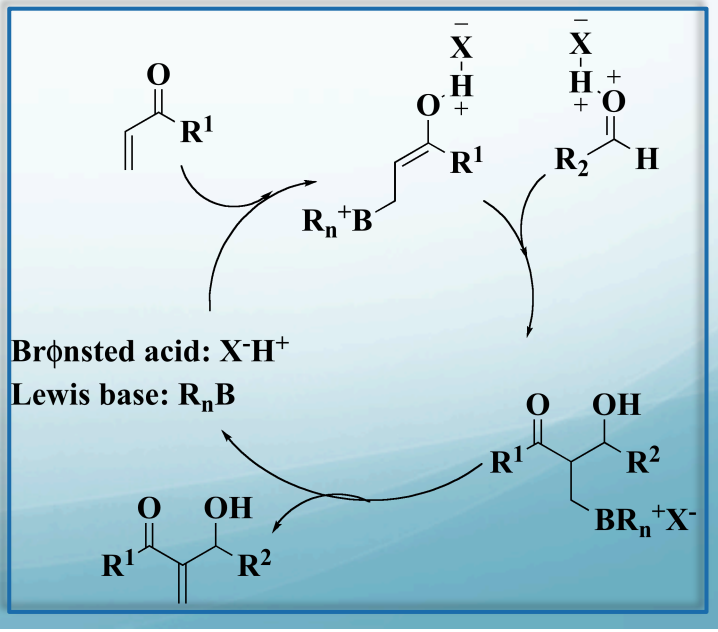
Synthesis of Enantiopure Cyclohexane Precursor 8



Baylis-Hillman reaction under Ikegama conditions:

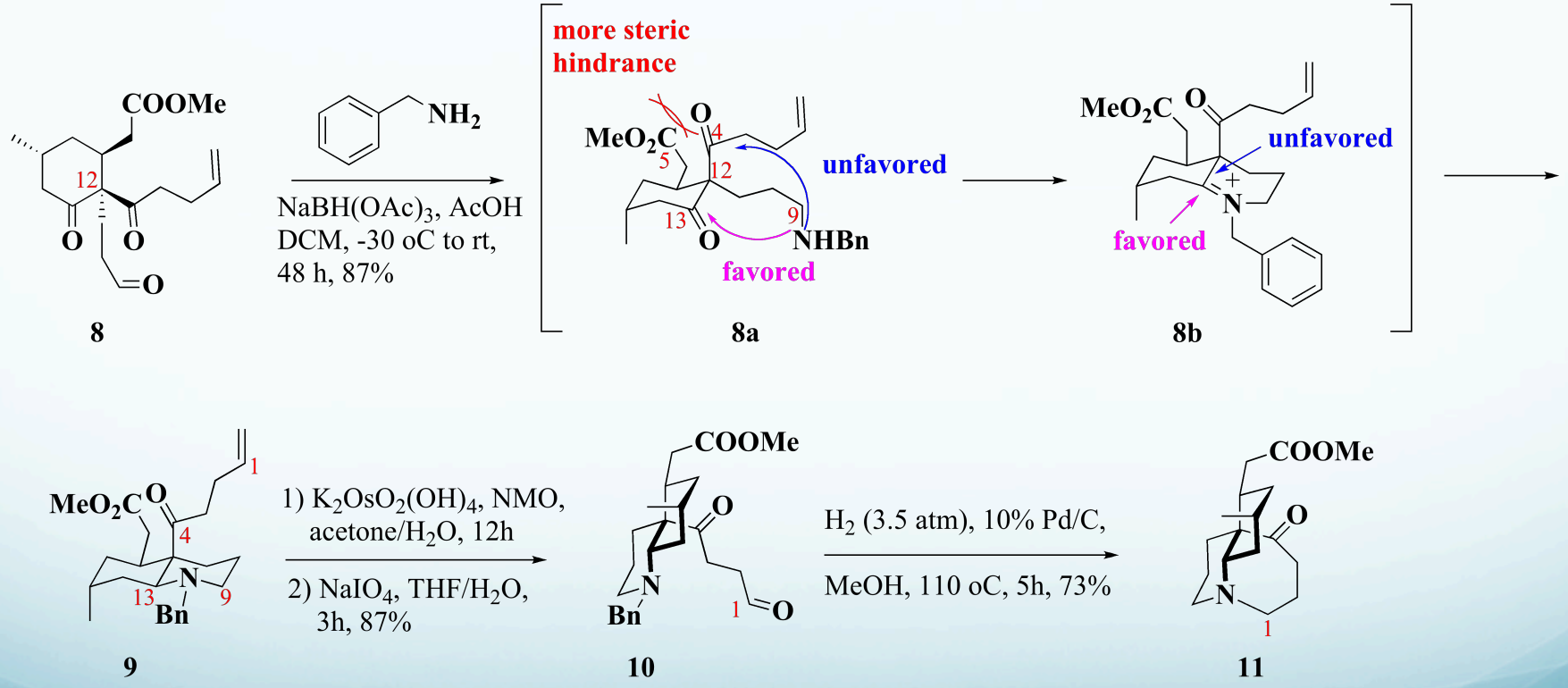


1,1'-2-naphthol



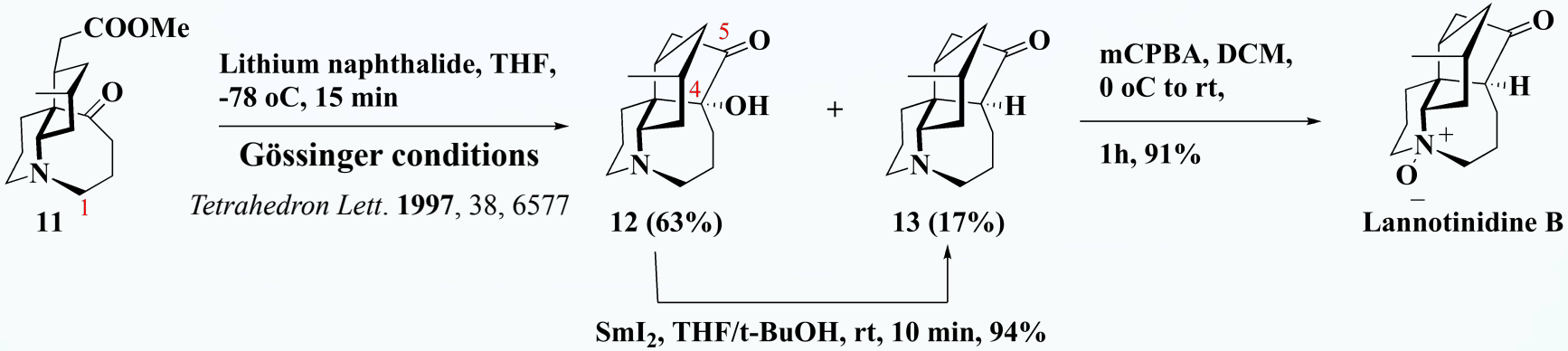
Tetrahedron Letters 41 (**2000**) 2165-2169

Chemo- and Stereoselective Sequential Reductive Aminations

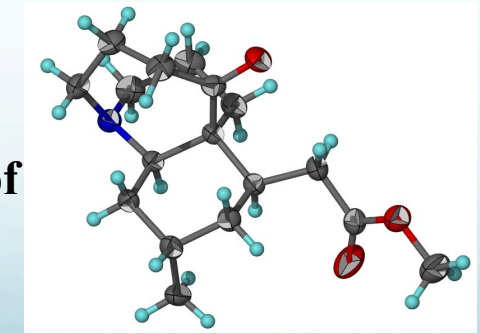


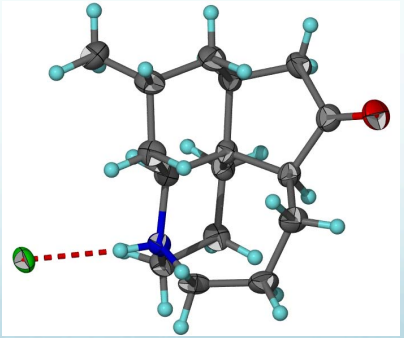
> 99% ee by chiral HPLC analysis

Completion of the Total Synthesis



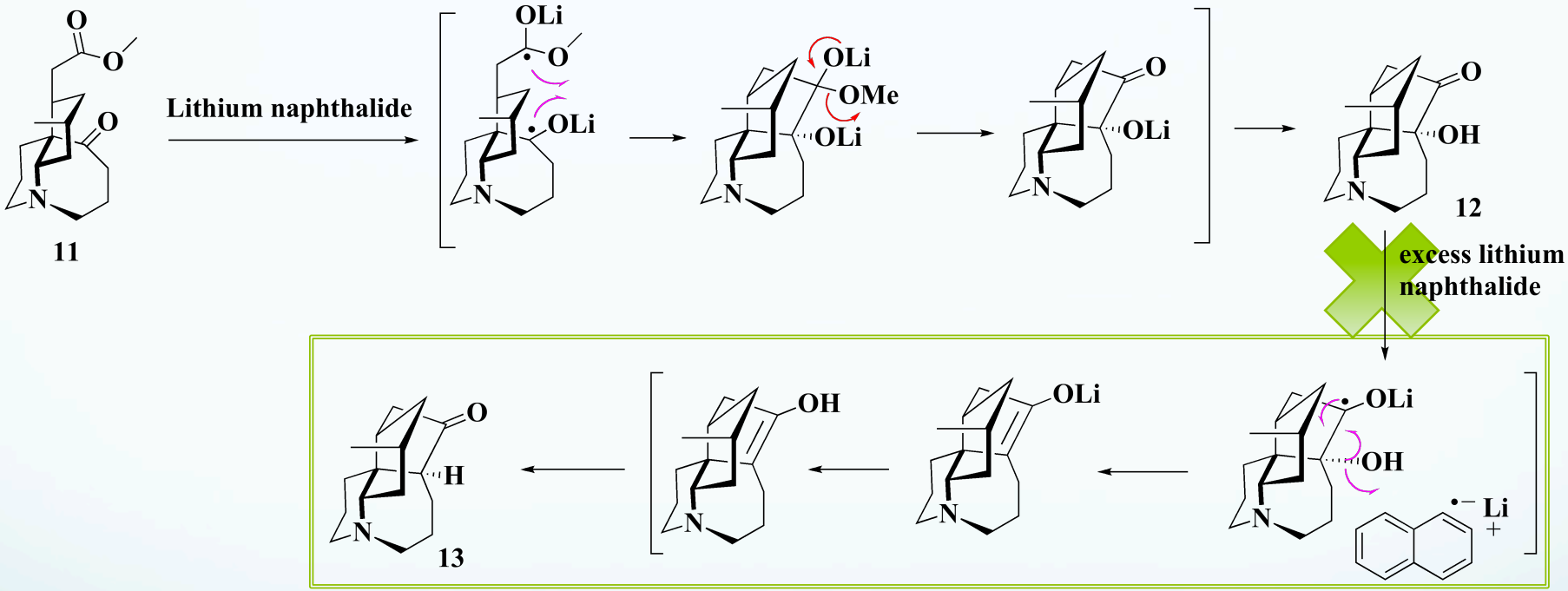
Crystal structure of rac-11





Crystal structure of (-)-13. HCl

What is the mechanism?



- Use of largely excess amount of lithium naphthalide (up to 10.0 equiv) could not completely convert 12 into 13. Instead, several unidentified byproducts were given.
- Ketone 13 was a further reduced product by deoxygenation of the α-hydroxylketone 12

Summary

- First total synthesis of (-)-lannotinidine B in 10 steps, and 23% yield with excellent chemo-and stereoselectivities.
- A successful protecting group-free strategy.
- Step- and redox-economy.