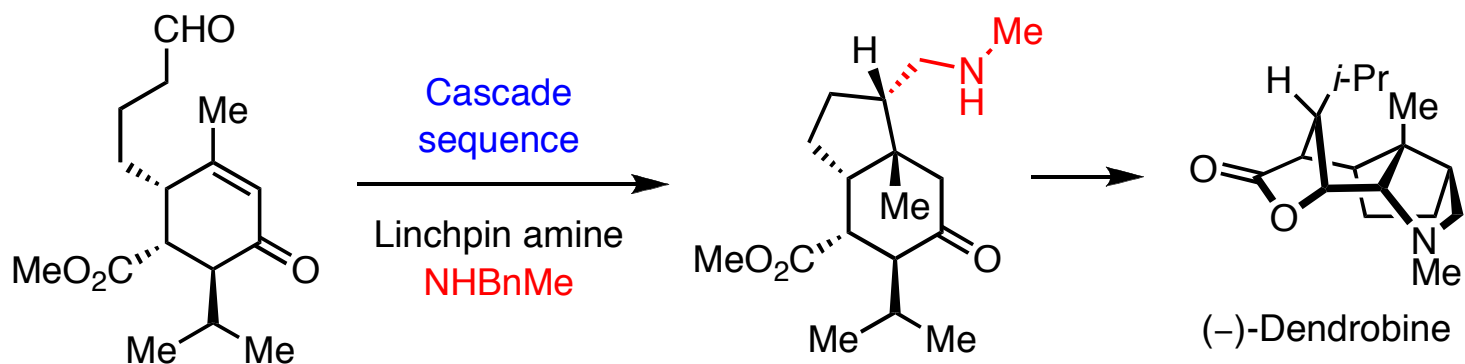


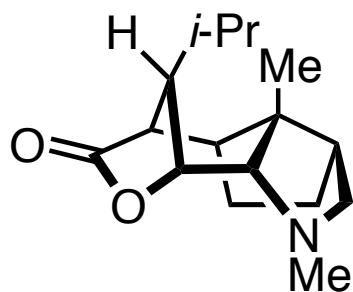
Total Synthesis of (-)-Dendrobine

Kreis, L. M.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 1-5.



Kara George Rosenker
Wipf Group Current Literature
31 March 2011

(-)-Dendrobine: Isolation and Biological Activity



(-)-Dendrobine



- Most abundant sesquiterpene bases isolated from the ornamental orchid “Jinchai Shihu” (*Dendrobium nobile* Lindl.)
- Principle component of the Chinese medicinal tonic “Chin Shih Hu” and exhibits antipyretic, hypertensive, and convulsant activity
- Intriguing structure containing seven contiguous stereocenters
- Has served as a target to examine novel tactics and strategies for chemical synthesis
- 12 syntheses to date

Suzuki, H.; Keimatsu, I.; Ito, K. *Pharm. Soc. Jpn.* **1932**, *52*, 1049-1060.

Suzuki, H.; Keimatsu, I.; Ito, K. *Pharm. Soc. Jpn.* **1934**, *54*, 802-812.

Inubushi, Y.; Sasaki, Y.; Tsuda, Y.; Yasui, B.; Konika, T.; Matsumoto, J.; Katarao, E.; Nakano, J. *Tetrahedron*, **1964**, *20*, 2007-2023.

Inubushi, Y.; Sasaki, Y.; Tsuda, Y.; Nakano, J. *Tetrahedron Lett.* **1965**, *6*, 1519-1523.

Chen, K. K.; Chen, A. L.; *J. Biol. Chem.* **1935**, *111*, 653-658.

Chen, K. K.; Chen, A. L.; *J. Pharmacol.* **1935**, *55*, 319-325.

Dendrobine: Previous Syntheses

▪ Racemic Total Syntheses

- Yamada, K. et al. *JACS*, **1972**, 94, 8278. 24 steps, 0.99% yield
- Inubushi, Y. et al. *J. Chem. Soc. Chem. Commun.* **1972**, 1252. 20 steps, 0.06% yield
- Kende, A. S. et al. *JACS* **1974**, 96, 4332. 15 steps, 1.1% yield
- Roush, W. R. *JACS* **1978**, 100, 3599. 24 steps, 0.66% yield
- Livinghouse, T. et al. *JACS* **1992**, 114, 4089. 10 steps, 6.15% yield

▪ Racemic Formal Syntheses

- Martin, S. F. et al. *JOC* **1991**, 56, 642. (Inubushi) 14 steps, 0.12% yield
- Padwa, A. et al. *Org. Lett.* **2000**, 2, 3233. (Kende) 19 steps, 0.4% yield

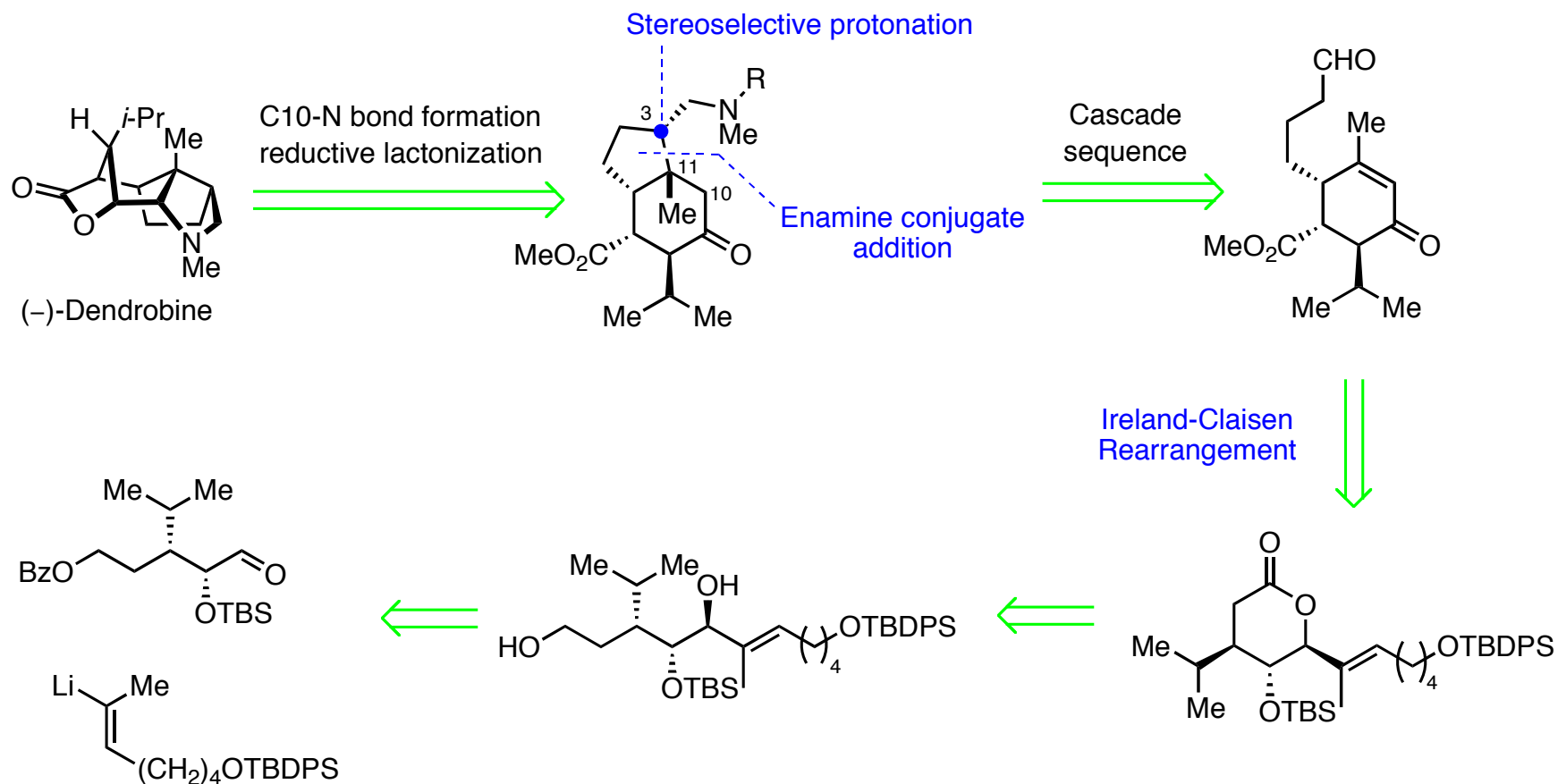
▪ Enantioselective Total Syntheses

- Sha, C.-K. et al. *JACS* **1997**, 119, 4130. 20 steps, 2.0% yield
- Cassayre, S. Z. et al. *JACS* **1999**, 121, 6072. 13 steps, 1.8% yield

▪ Enantioselective Formal Syntheses

- Trost, B. M. et al. *JACS* **1991**, 113, 670. (Roush) 26 steps, 1.98% yield
- Mori, M. et al. *JOC* **1994**, 59, 5633. (Kende) 21 steps, 0.78% yield
- Corey, E. J. et al. *JACS* **2004**, 126, 13708. (Kende) carried out Kende's key Diels-Alder step in an enantioselective fashion

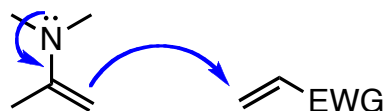
Title Paper: Retrosynthetic Strategy



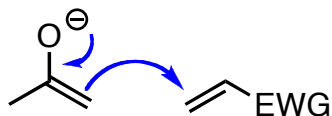
- Strategy is based on a key cascade reaction with an amine functioning as the linchpin
 - Installs both the quaternary C11 center and the stereocenter at C3

Asymmetric Michael Reactions

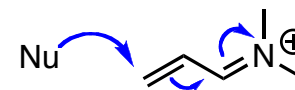
- Catalytic activation:



Enamine

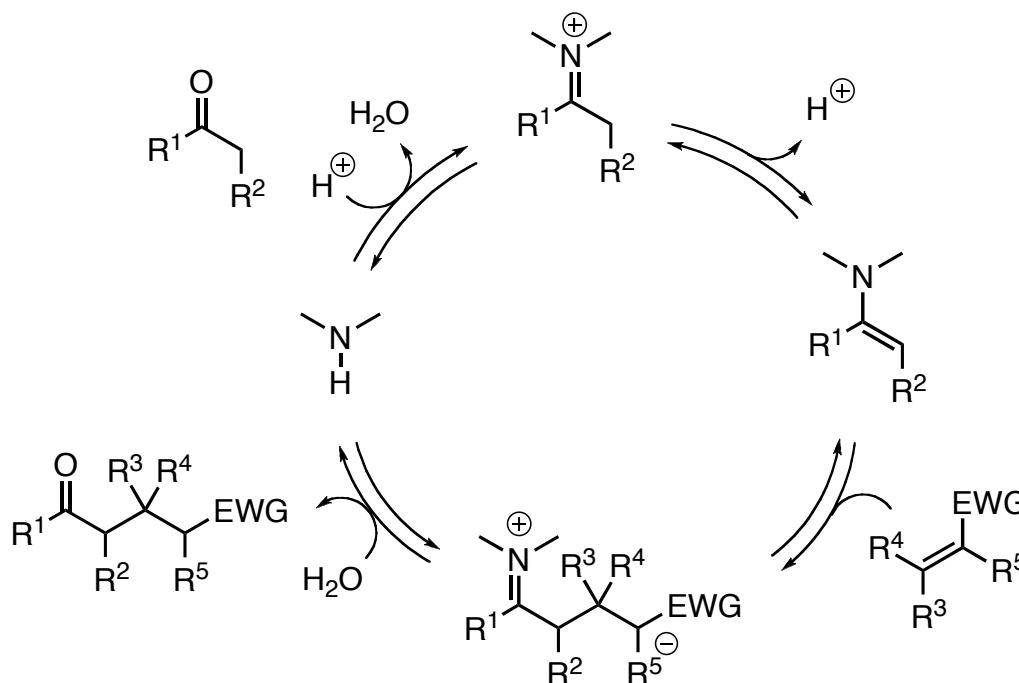


Enolate



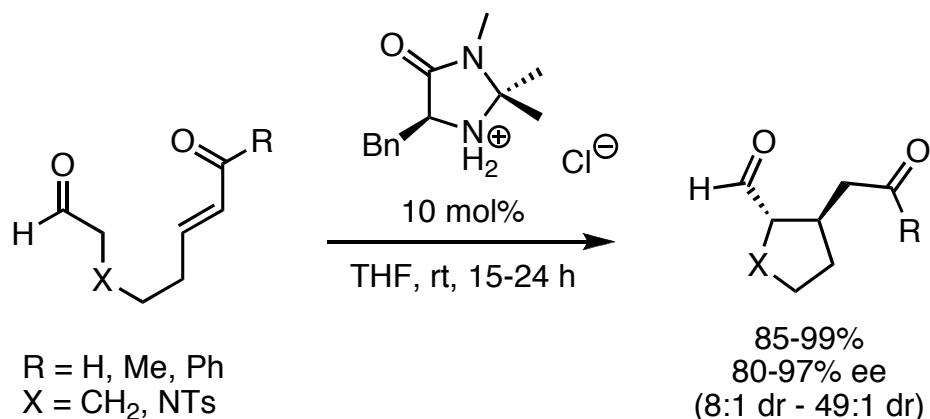
Iminium

- Enamine-Catalyzed Michael Reaction

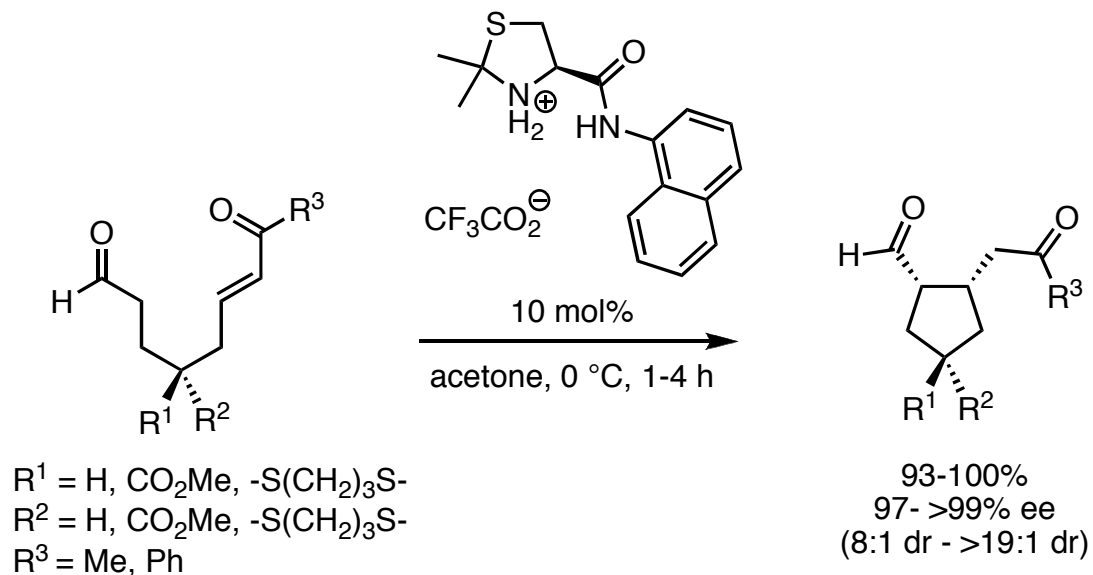


Asymmetric Michael Reactions

- First catalytic asymmetric intramolecular Michael reaction of aldehydes



- Complementary catalytic asymmetric intramolecular Michael reaction of aldehydes

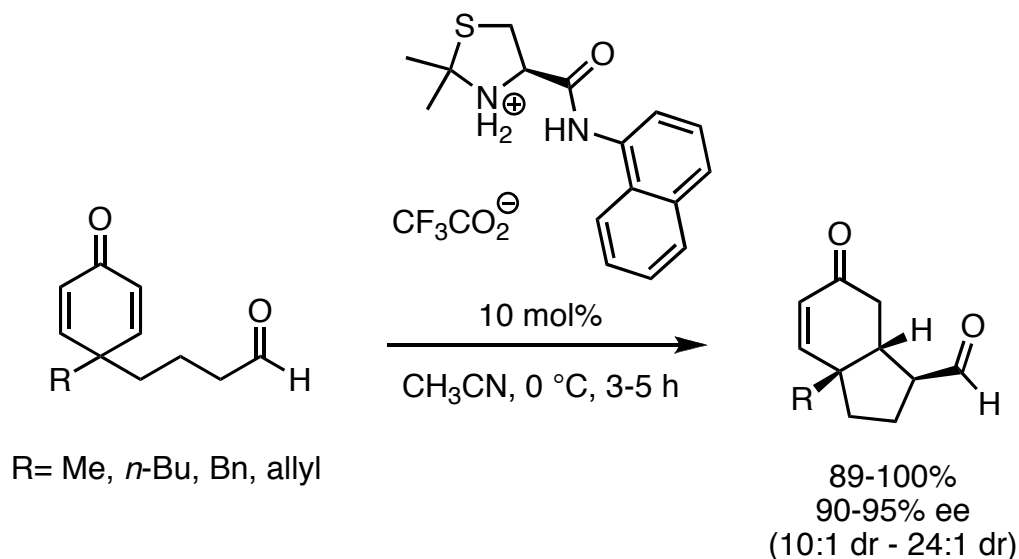


Fonseca, M. T. H.; List, B. *Angew. Chem.* **2004**, *116*, 4048-4050.

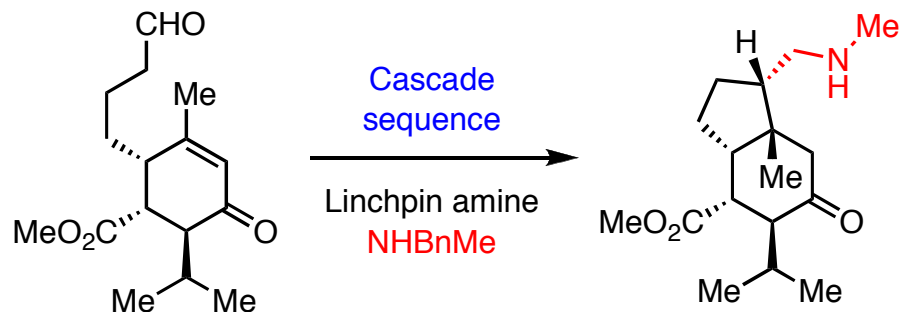
Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028-16029.

Asymmetric Michael Reactions

- Complementary catalytic asymmetric intramolecular Michael reaction of aldehydes

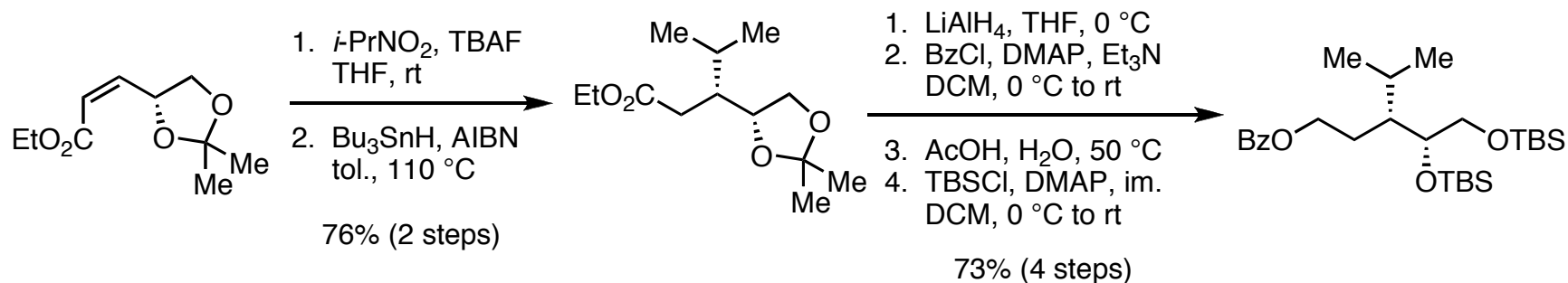


- No examples of a Michael reaction involving β -substituted enones to generate quaternary centers



Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028-16029.

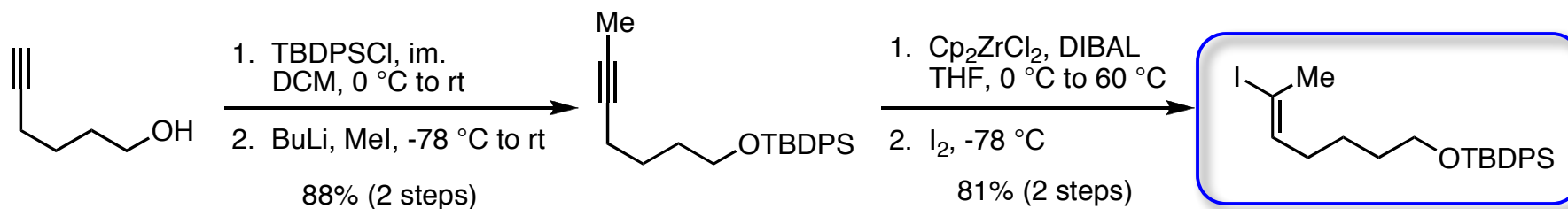
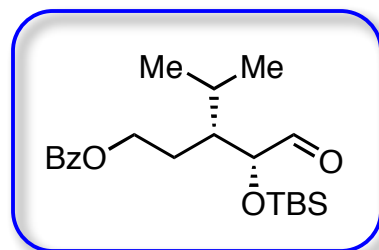
Fragment Synthesis



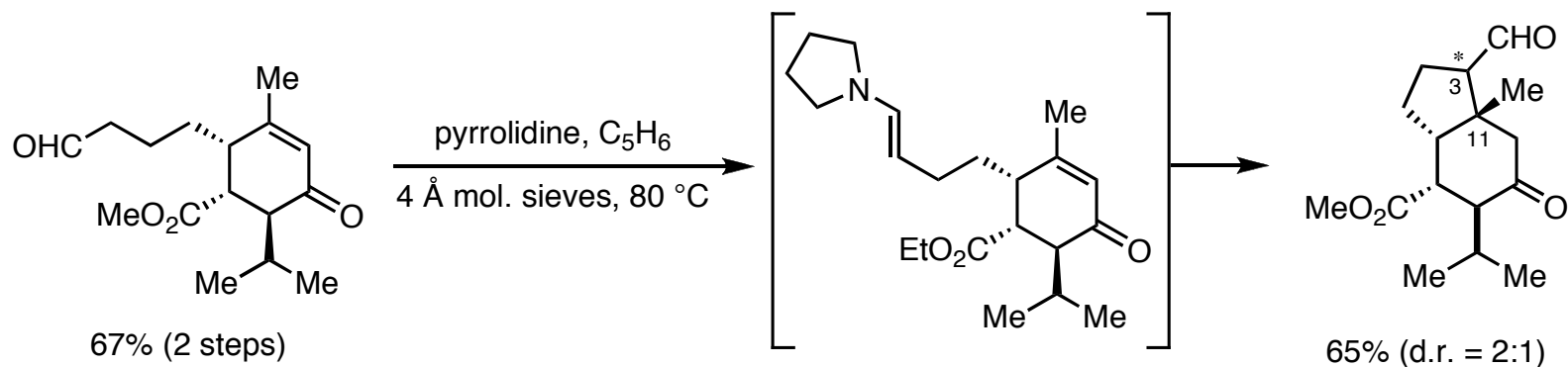
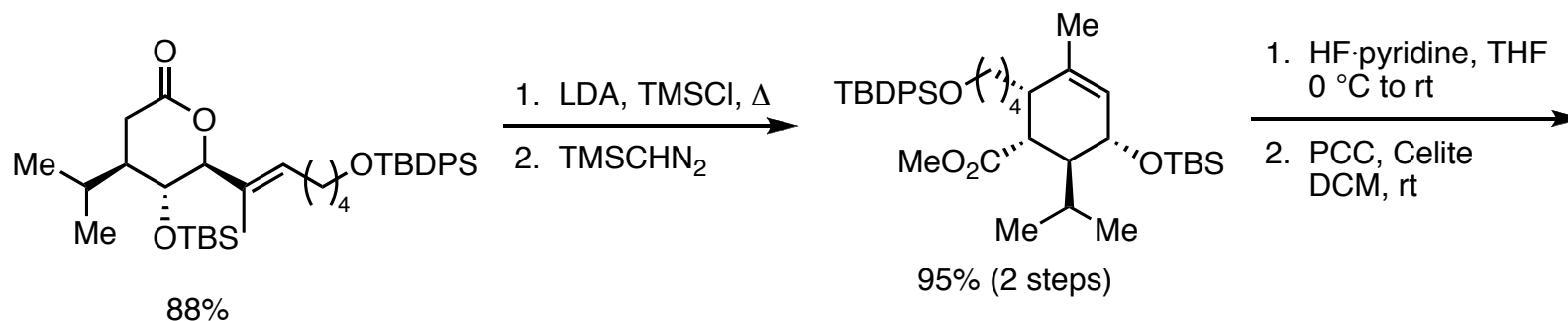
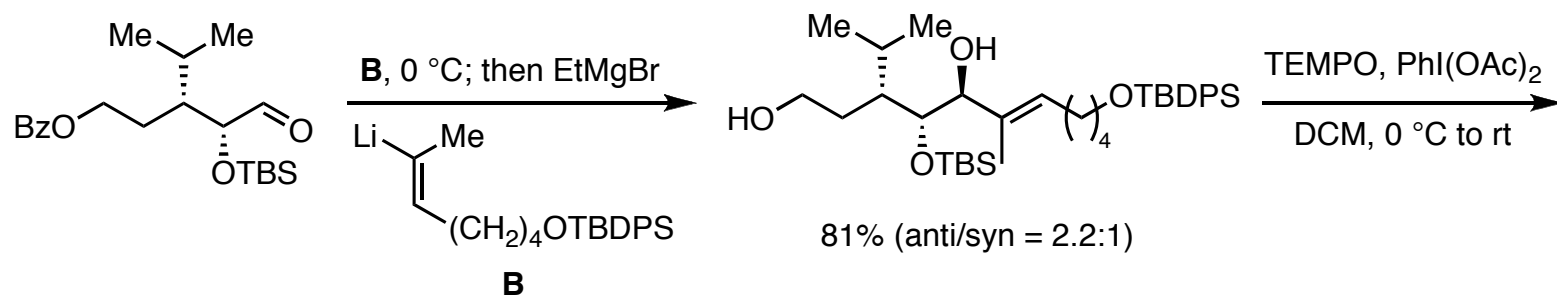
5. $\text{HF}\cdot\text{pyridine}$, THF
0 °C to rt

6. $(\text{COCl})_2$, DMSO, Et_3N
-78 °C to rt

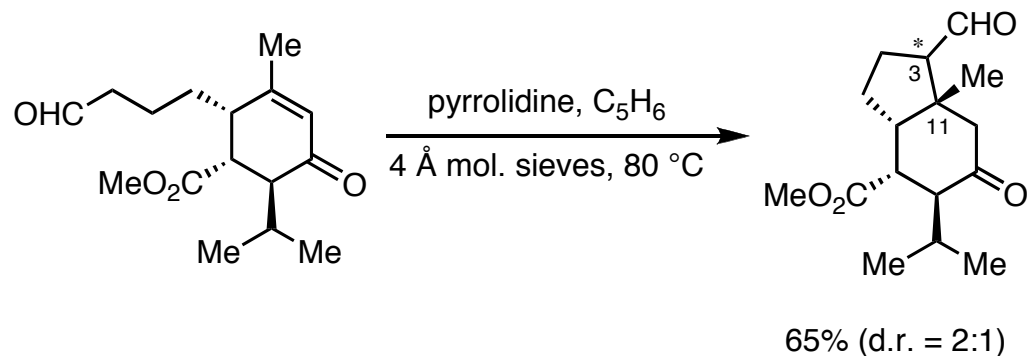
82% (2 steps)



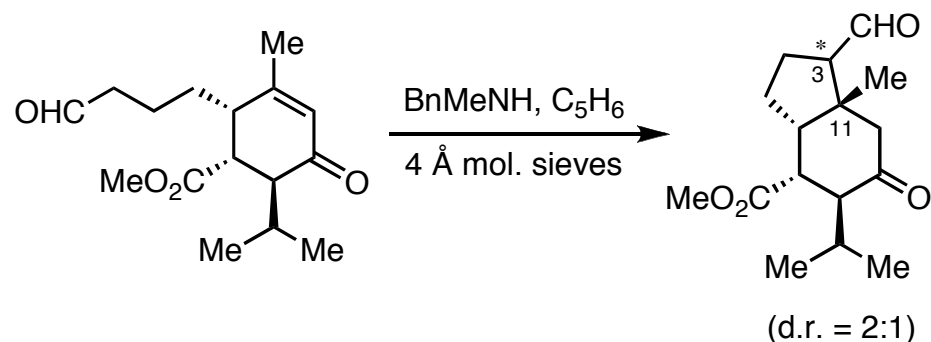
Synthesis of Key Intermediate



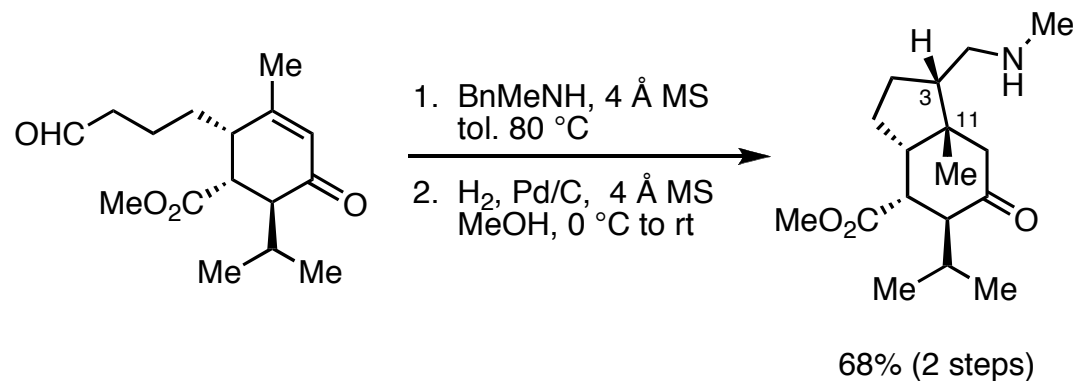
Intramolecular Enamine Michael Addition: Cyclization Studies



Preliminary cyclization studies revealed good stereocontrol at C11, and no stereocontrol at C3



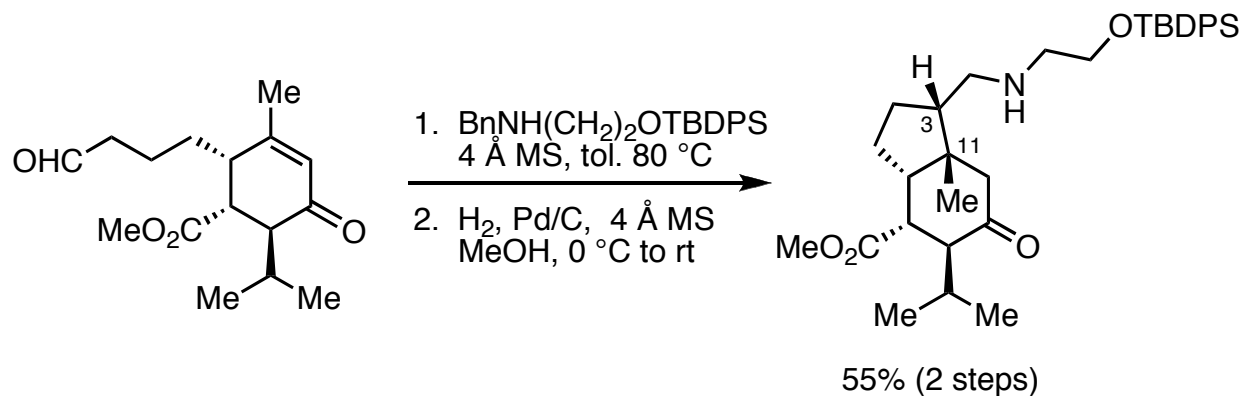
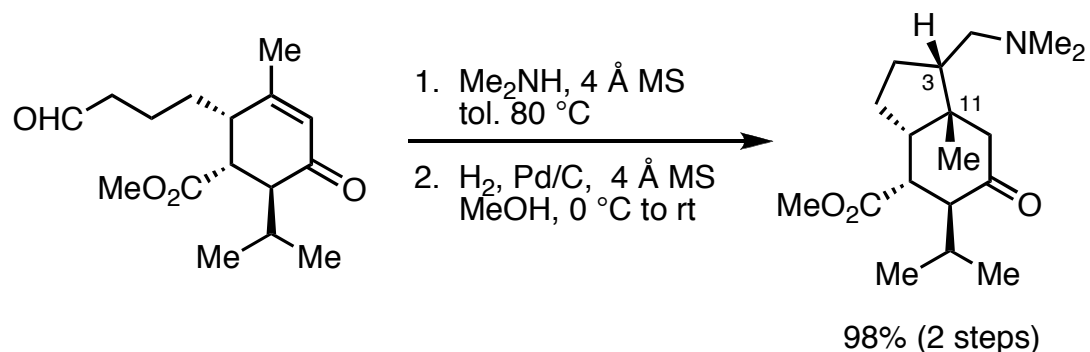
Cyclization with *N*-methylbenzylamine gave same d.r. (2:1)



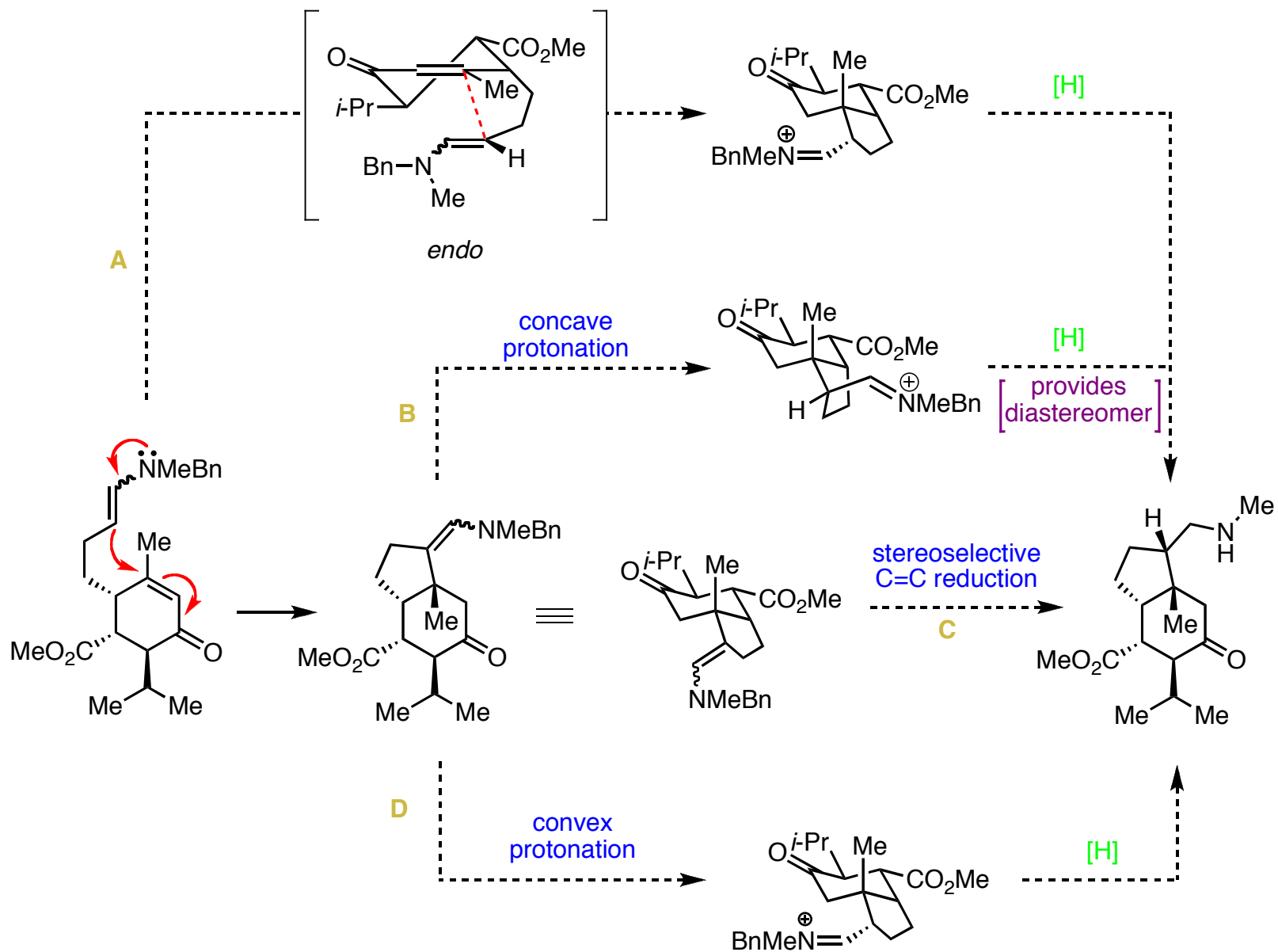
Cyclization and subsequent reduction provided a d.r. > 10:1 and allows for introduction of the desired pendant amine

Intramolecular Enamine Michael Addition: Cyclization Studies

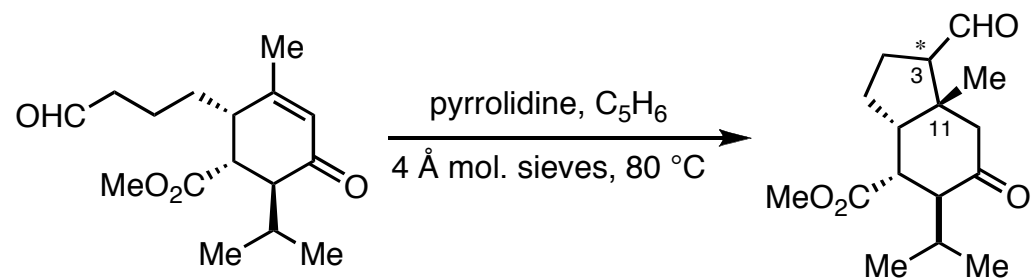
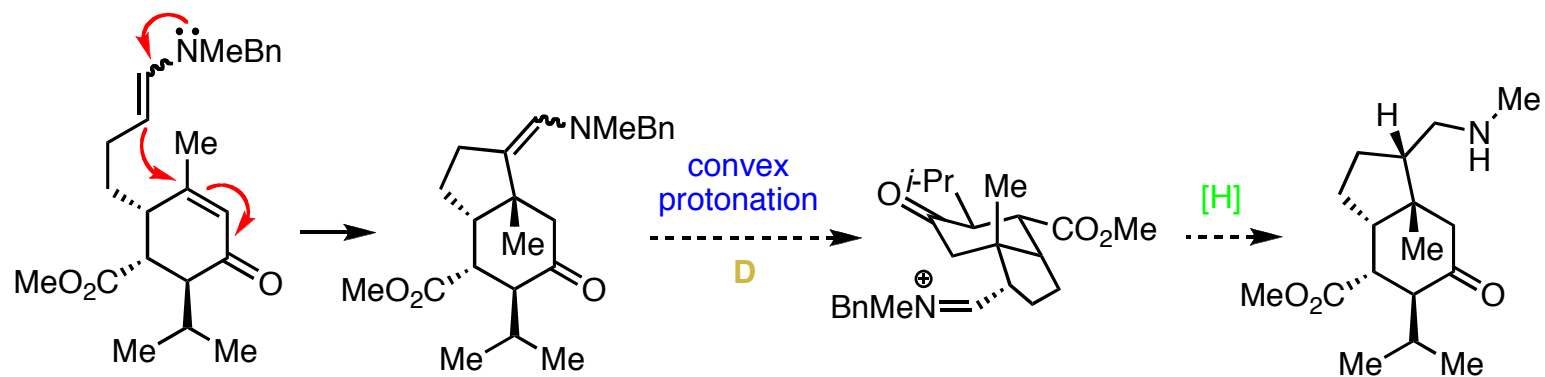
- The cyclization cascade can also be applied to other amines



Cascade Sequence: Mechanistic Proposals

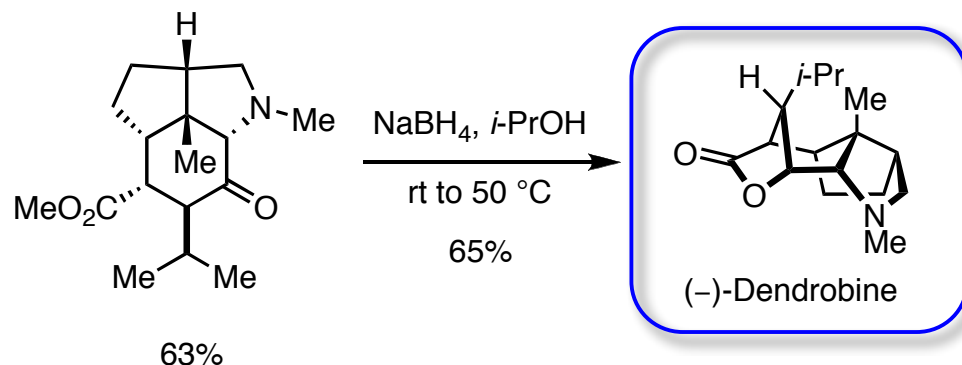
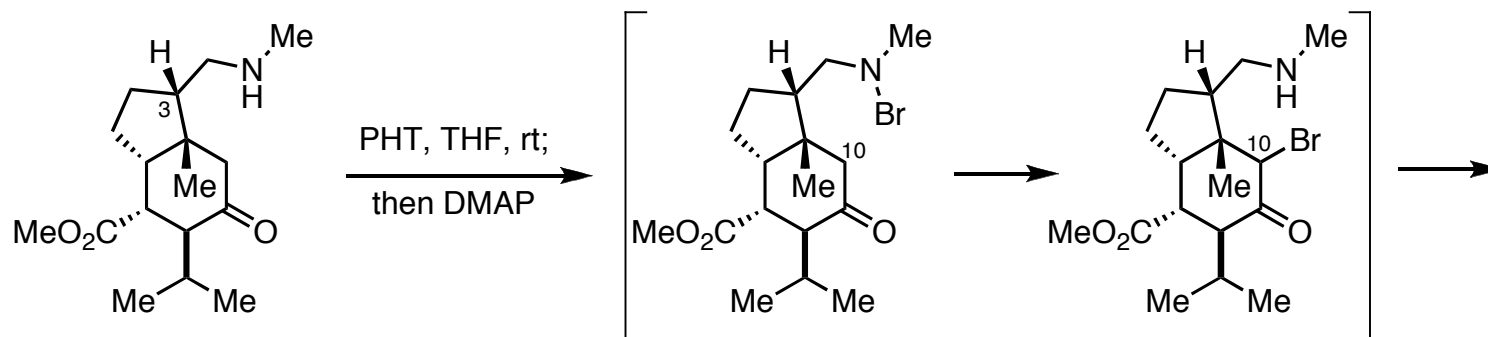


Cascade Sequence: Pathway D Favored

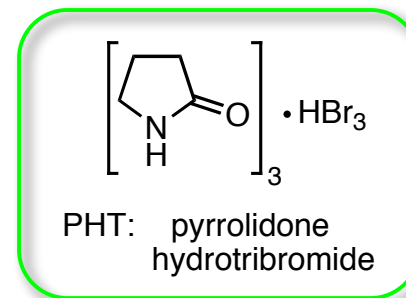


65% (d.r. 2:1)
(d.r. 5:1)

Completion of (-)-Dendrobine



- 18 linear steps, 4.0% overall yield



Awang, D. V. C.; Wolfe, S. *Canadian J. Chem.* **1969**, *47*, 706-709.
McKenzie, T. C. *J. Org. Chem.* **1974**, *39*, 629-631.

Conclusions

- Asymmetric total synthesis of (–)-dendrobine was achieved in 18 linear steps, 4.0% overall yield
- Key features of the synthesis include:
 - Efficient construction of the central cyclohexane core by an Ireland-Claisen rearrangement
 - A conjugate enamine addition/hydrogenation sequence to install the quaternary center as well as the pendant methyl amino group
 - Regioselective ketone bromination followed by pyrrolidine formation
- The first report of an enamine conjugate addition to a β -disubstituted enone to generate a quaternary stereocenter