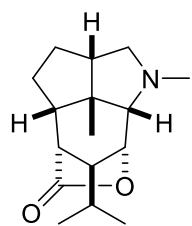


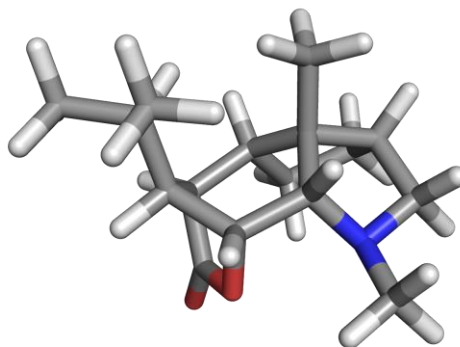
Problem Session (9)

2018/03/03 MASANORI NAGATOMO

Please propose your synthetic route to (-)-dendrobine from a commercially available compound.



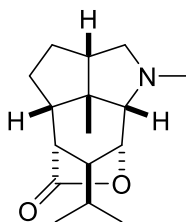
(-)-dendrobine



Problem Session (9)- Answer

2018/03/03 MASANORI NAGATOMO

Synthetic Plan of (-)-Dendrobine

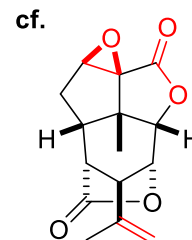


(-)-dendrobine



Dendrobium nobile Lindl.

http://storage.googleapis.com/powop-assets/kew_profiles/PPCONT_010298_fullsize.jpg



picrotoxinin

Isolation: Sesquiterpene alkaloid isolated from the ornamental orchid (Dendrobium nobile Lindl.)

Suzuki, H.; Keimatsu, I.; Ito, K. *Pharm. Soc. Jpn.* **1932**, 52, 1049.; idem **1934**, 54, 802.

Chen, K. K.; Chen, A. L.; *J. Biol. Chem.* **1935**, 111, 653. Chen, K. K.; Chen, A. L.; *J. Pharmacol.* **1935**, 55, 319.

Inubushi, Y. et al. *Tetrahedron* **1964**, 20, 2007. Inubushi, Y. et al. *Tetrahedron Lett.* **1965**, 6, 1519.

Bioactivities: Antipyretic, hypertensive, and convulsant activity

Structural features: Caged tetracyclic pyrrolidine alkaloid having seven contiguous stereocenters

A very similar structure to the powerful convulsant picrotoxinin

Asymmetric total syntheses

Sha, C.-K. et al. *J. Am. Chem. Soc.* **1997**, 119, 4130. [19 steps]

Cassayre, J.; Zard, S. Z. *J. Am. Chem. Soc.* **1999**, 121, 6072. [17 steps]

Carreira, E. M. et al. *Angew. Chem. Int. Ed.* **2012**, 51, 3436. [18 steps]

See detail; 160114_PS_Hiroki_Fujisawa.

Asymmetric formal syntheses

Trost, B. M. et al. *J. Am. Chem. Soc.* **1991**, 113, 670. (Roush) [26 steps]

Mori, M. et al. *J. Org. Chem.* **1994**, 59, 5633. (Kende) [21 steps]

Corey, E. J. et al. *J. Am. Chem. Soc.* **2004**, 126, 13708. (Kende) [12 steps]

Chen, D. Y.-K. et al. *Angew. Chem. Int. Ed.* **2017**, 56, 12250. (Kende) [13 steps]

See detail; 171007_PS_Koichi_Hagiwara.

Racemic total syntheses

Yamada, K. et al. *J. Am. Chem. Soc.* **1972**, 94, 8278. [24 steps]

Inubushi, Y. et al. *J. Chem. Soc. Chem. Commun.* **1972**, 1252. [20 steps]

Kende, A. S. et al. *J. Am. Chem. Soc.* **1974**, 96, 4332. [12 steps]

Roush, W. R. *J. Am. Chem. Soc.* **1978**, 100, 3599. [24 steps]

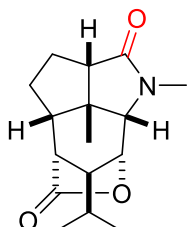
Livinghouse, T. et al. *J. Am. Chem. Soc.* **1992**, 114, 4089. [10 steps]

Racemic formal syntheses

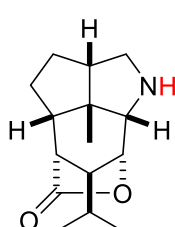
Martin, S. F. et al. *J. Org. Chem.* **1991**, 56, 642. (Inubushi) [14 steps]

Padwa, A. et al. *Org. Lett.* **2000**, 2, 3233. (Kende) [19 steps]

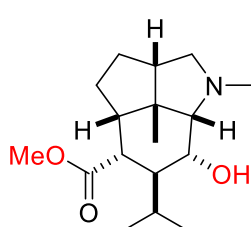
Congeners: Many related compounds have been isolated to date.



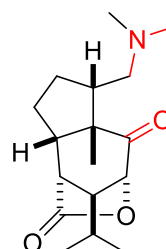
mubironine A



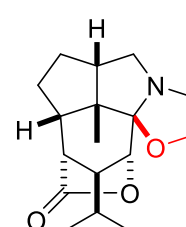
mubironine B



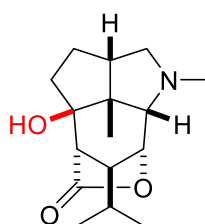
mubironine C



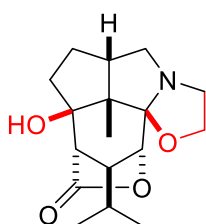
nobilonine



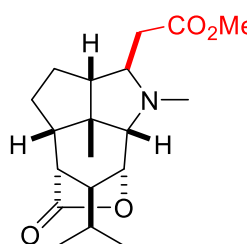
dendroxine



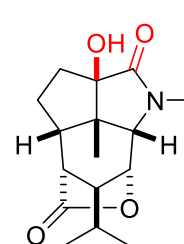
dendramine



6-hydroxydendroxine

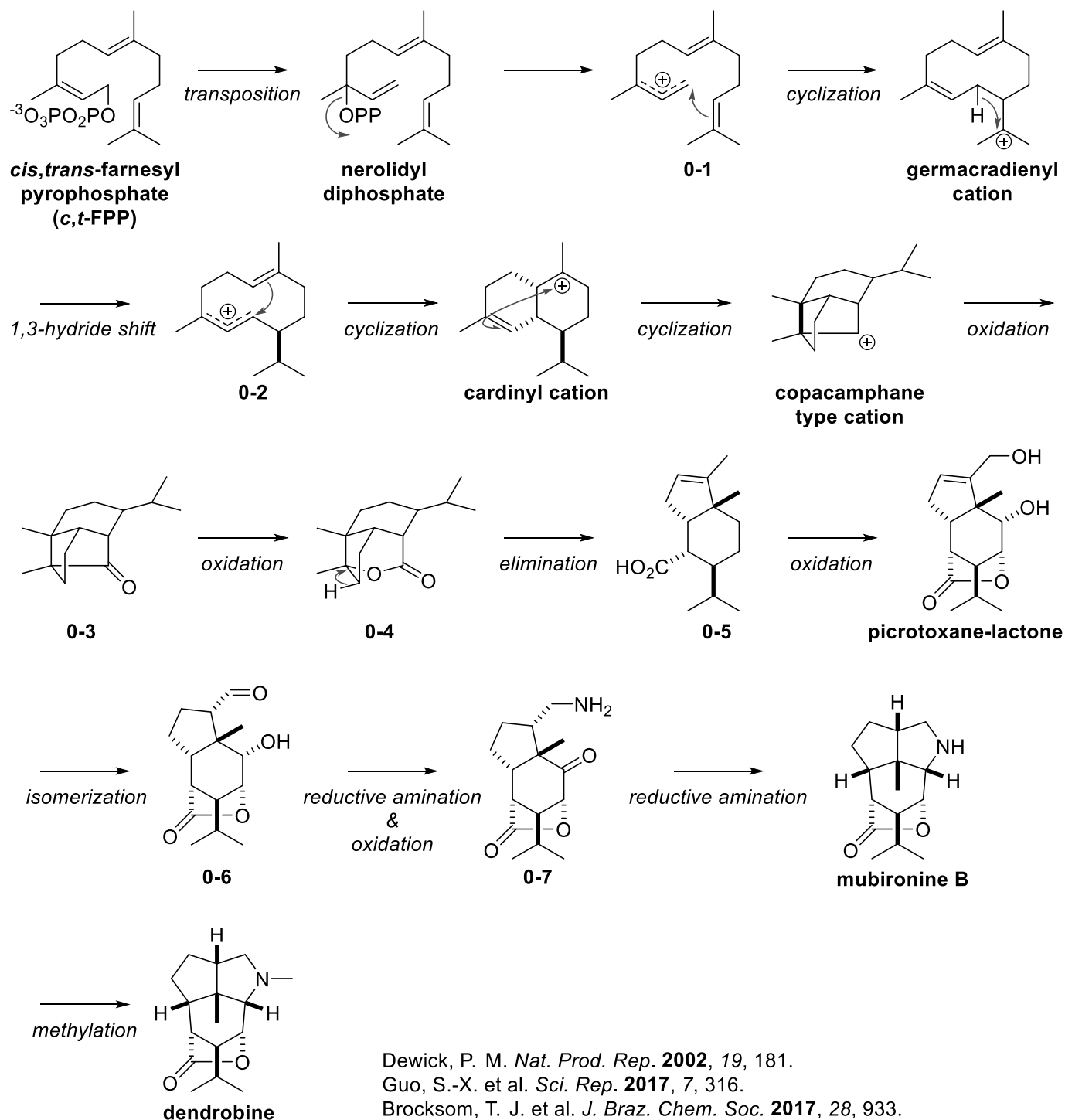


dendrine

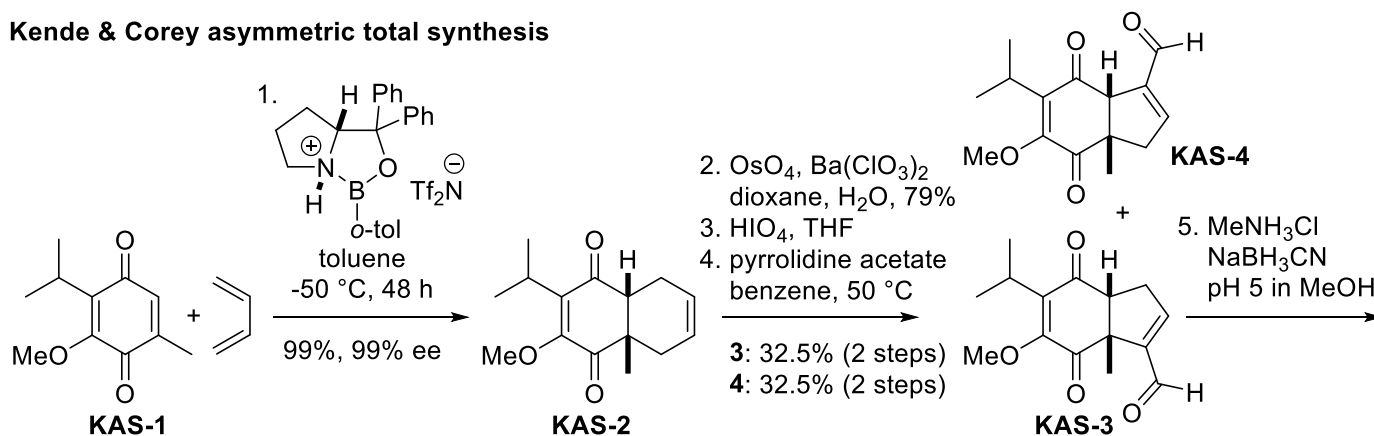


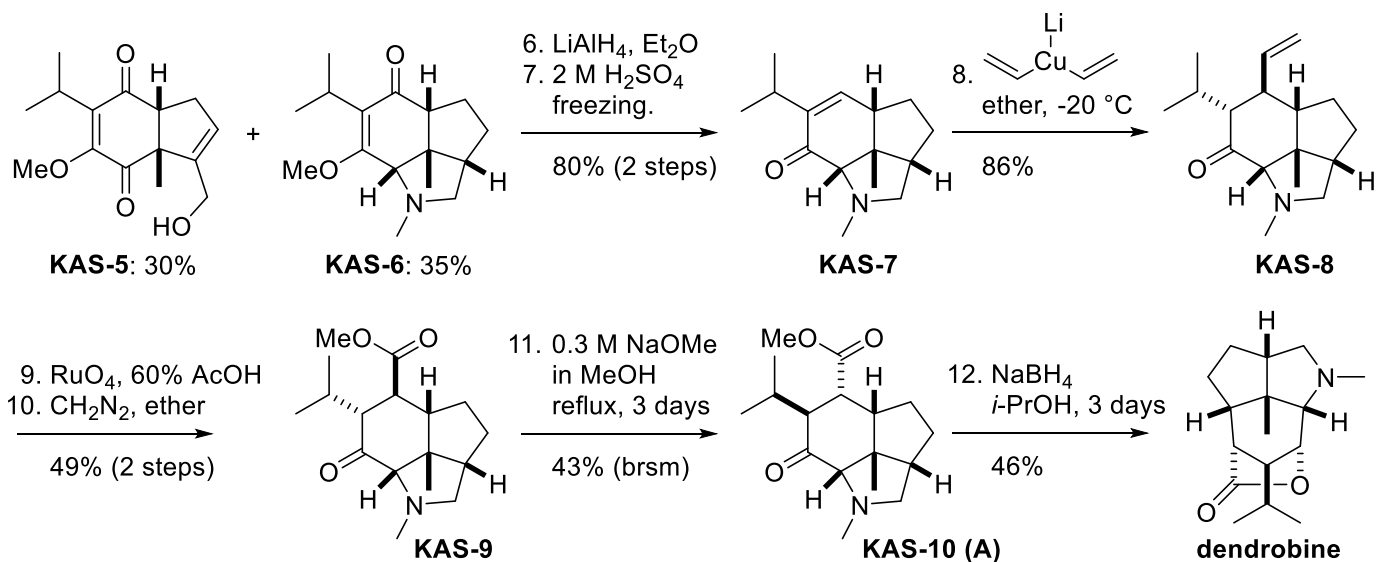
3-hydroxy-2-oxodendrobine

Postulated dendrobine biosynthetic pathway

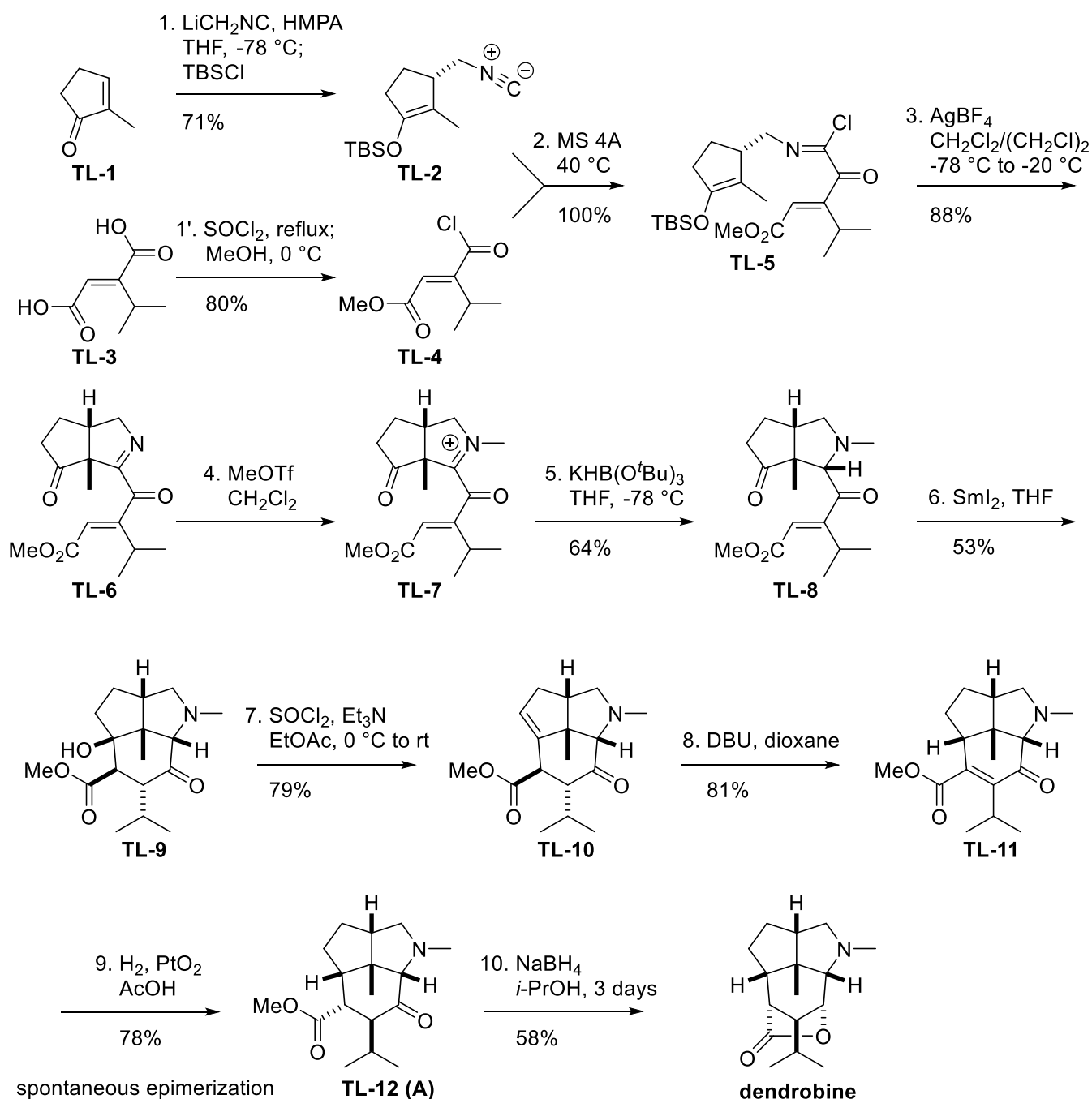


Kende & Corey asymmetric total synthesis

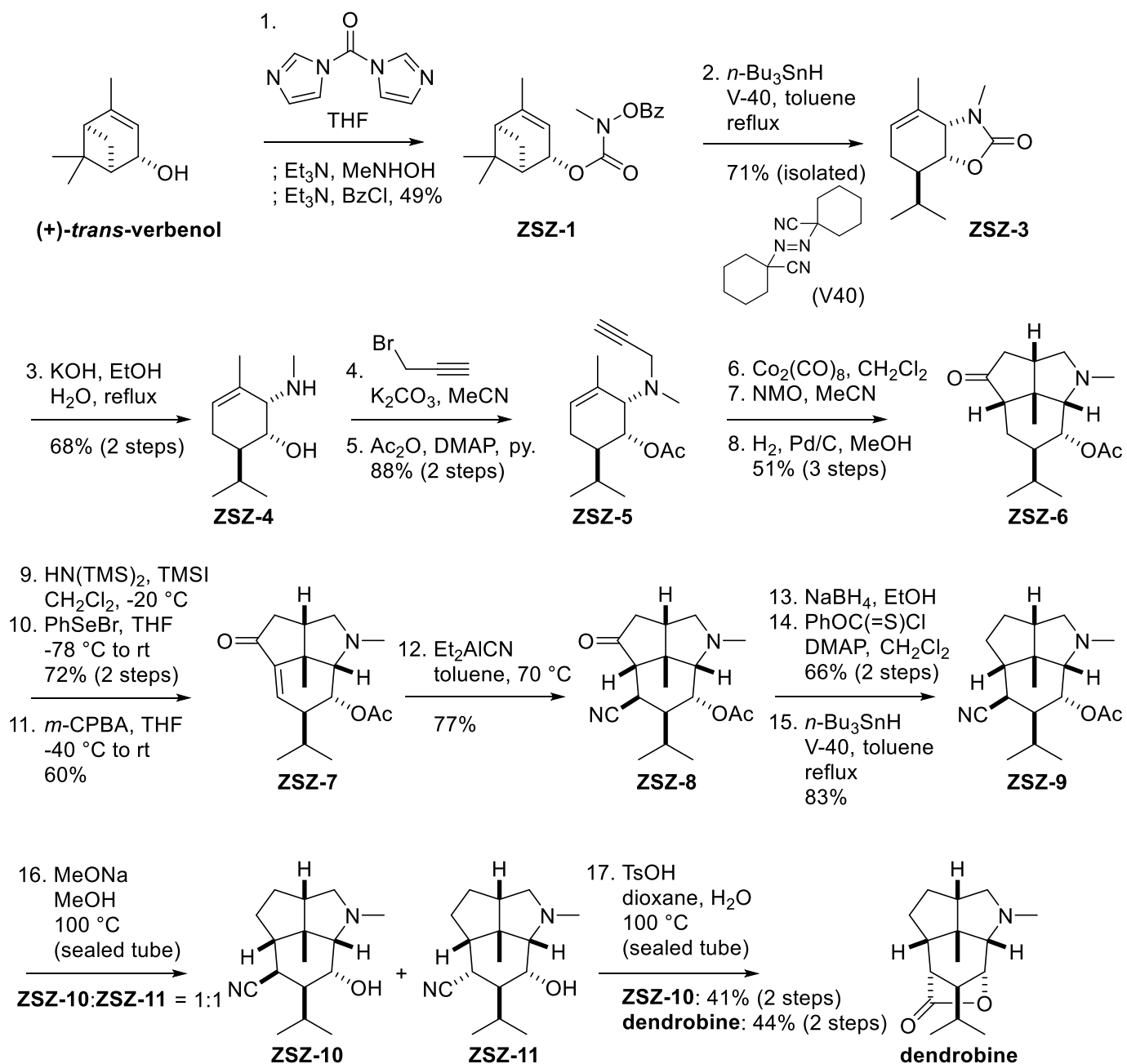




Livinghouse racemic total synthesis



Cassayre & Zard asymmetric total synthesis



Our original synthetic plans of (-)-dendrobine are not depicted.