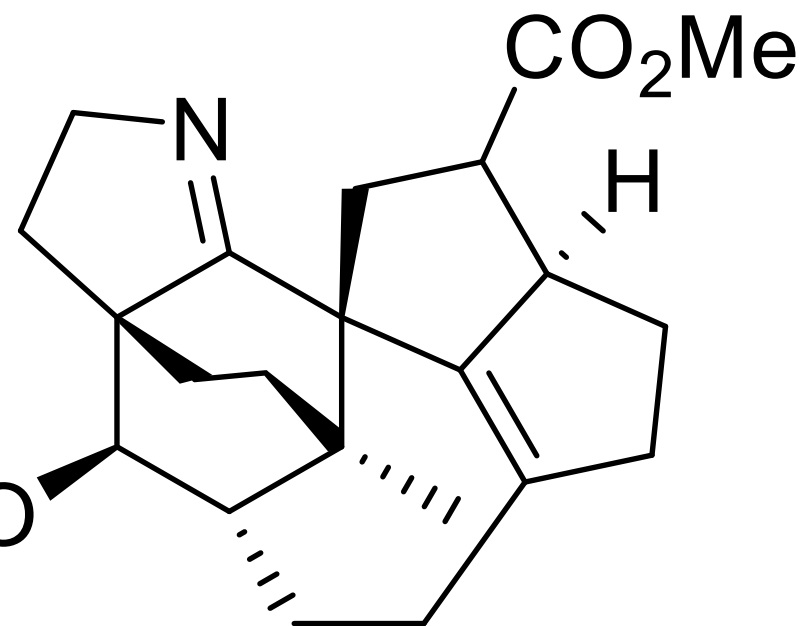


# Total Synthesis of (-)-Calyciphylline N

CEM 852: 02/10/2018

Presented by: Emmanuel Wesonga Maloba



# Total Synthesis of (–)-Calyciphylline N, a Member of Daphniphyllum Alkaloids

Daphniphyllum Alkaloids are traditionally used in the treatment of asthma, rheumatism, and snakebites.

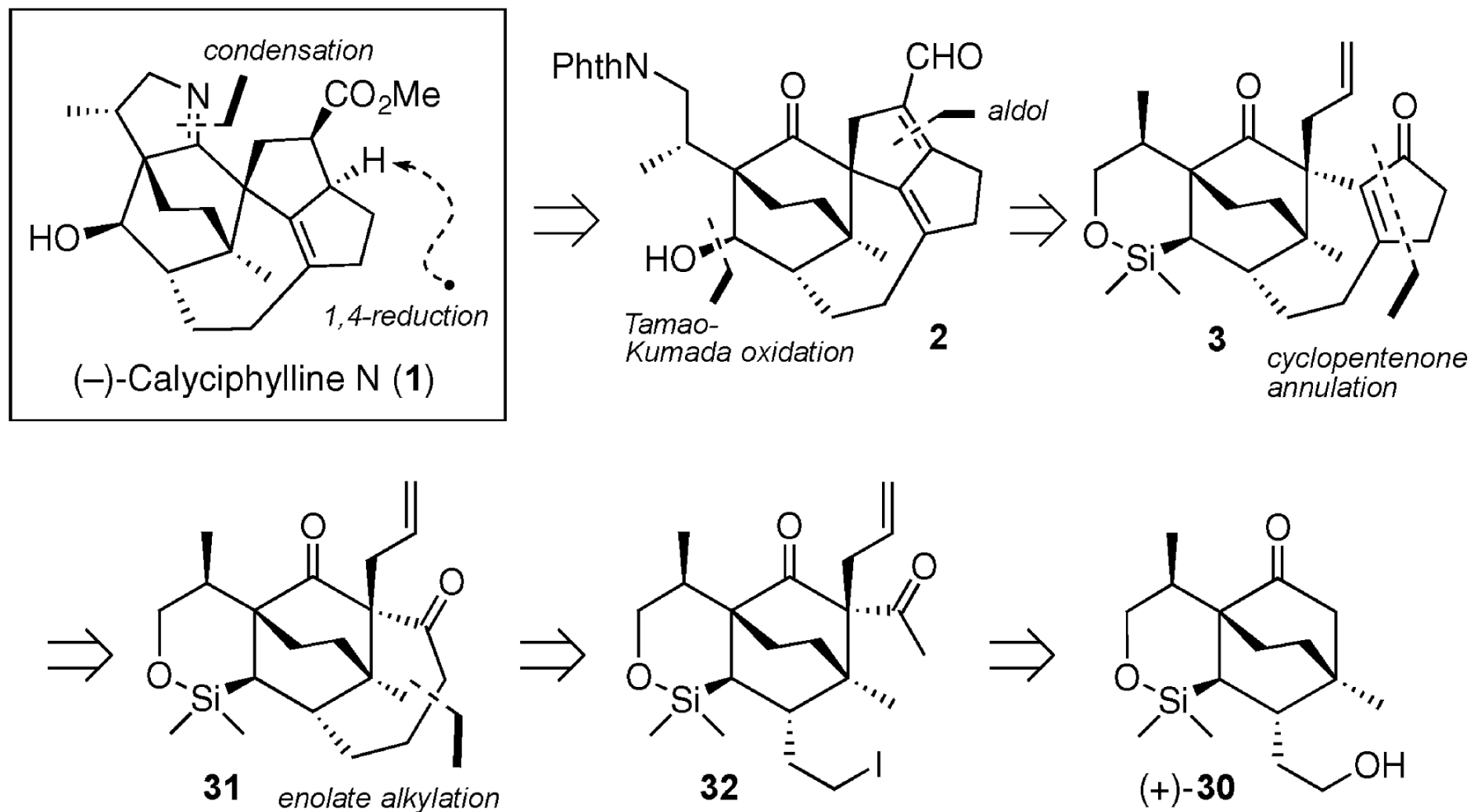
Due to their complex structures, Daphniphyllum Alkaloids have attracted various synthetic strategies.

Presented here is the first total synthesis of (–)-Calyciphylline N reported by Artem Shvartsbart and Amos B. Smith, III.

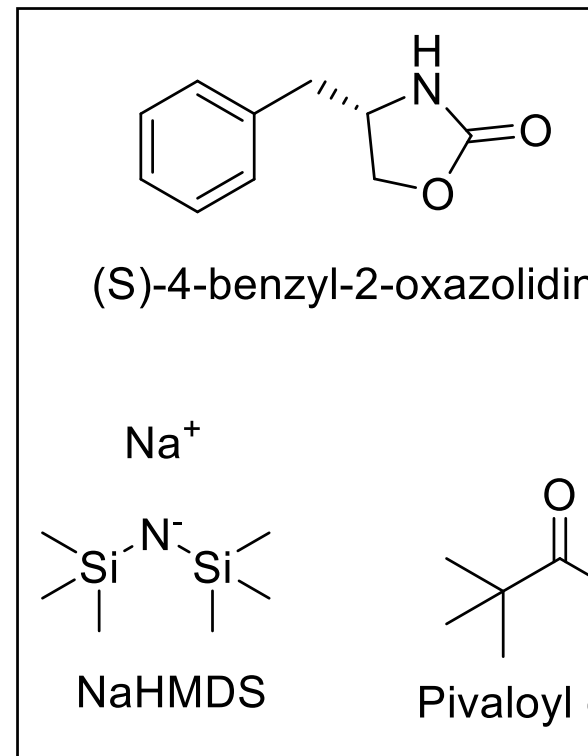
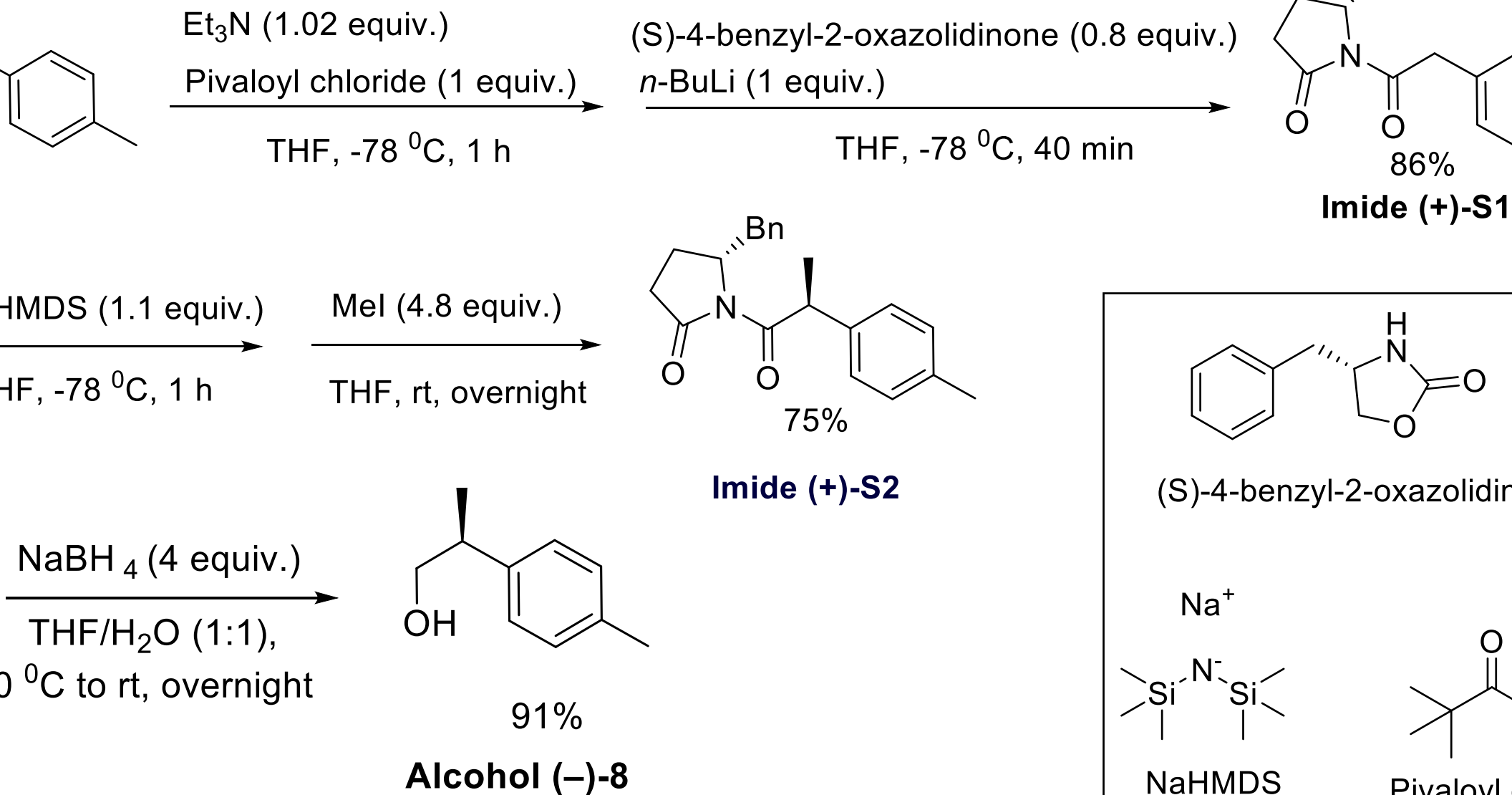
(–)-Calyciphylline N was isolated from the leaves and stems of *Daphniphyllum calycinum* by Kobayashi.

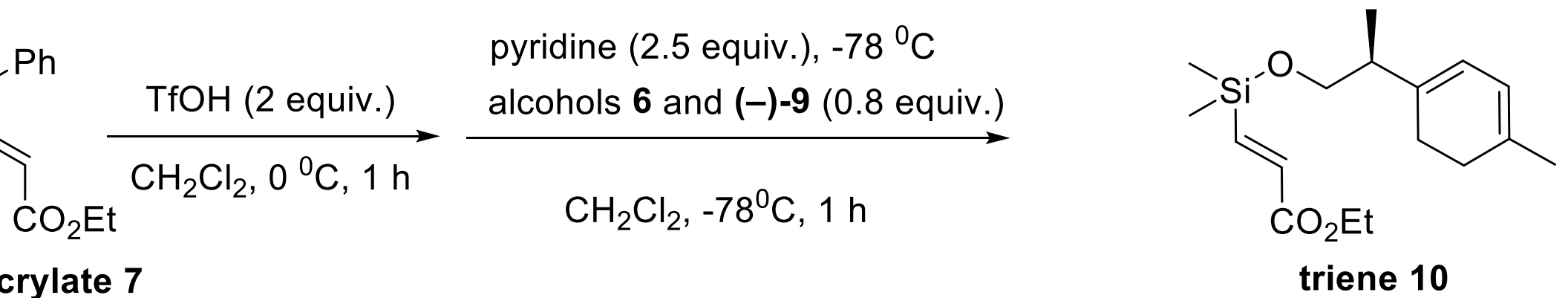
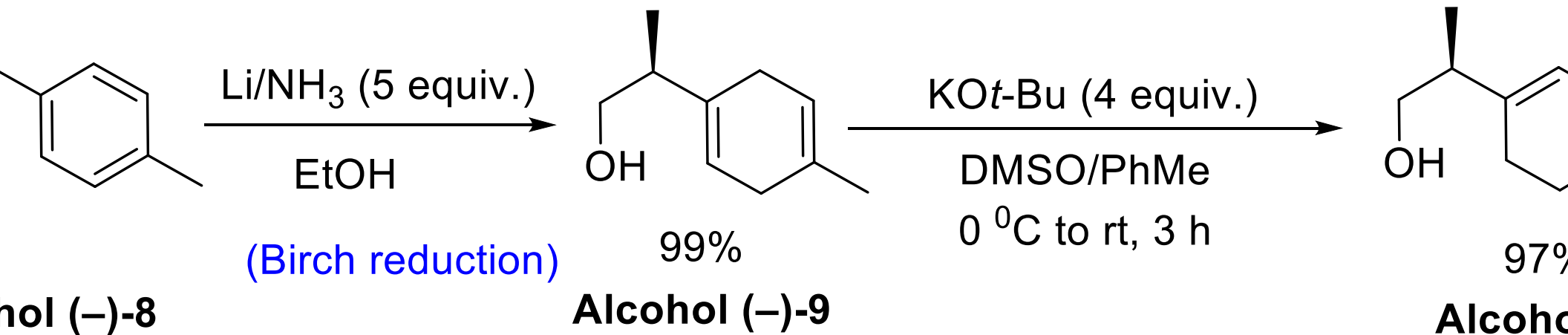
Yahata, H.; Kubota, T.; Kobayashi, J. *J. Nat. Prod.* **2008**, *72*, 148.

# Retrosynthetic Pathway (page 13)



# Synthesis

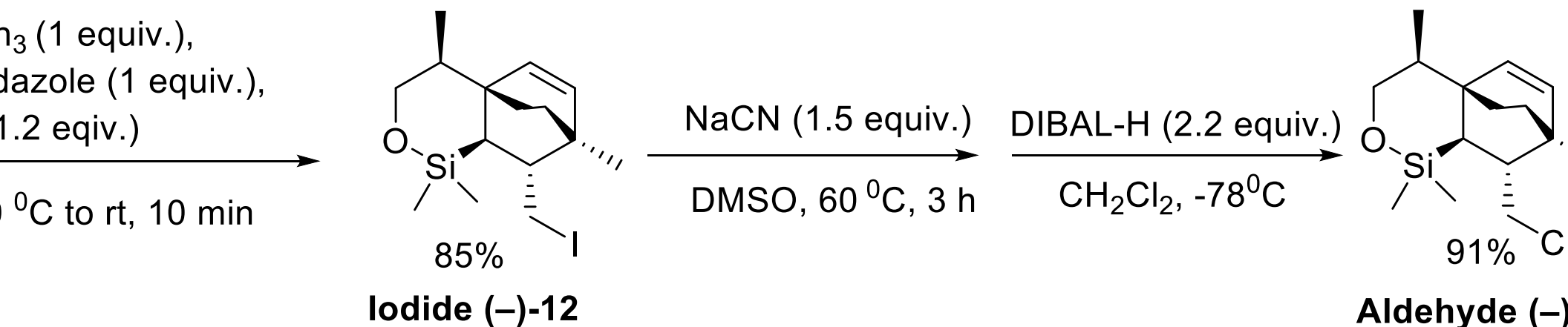
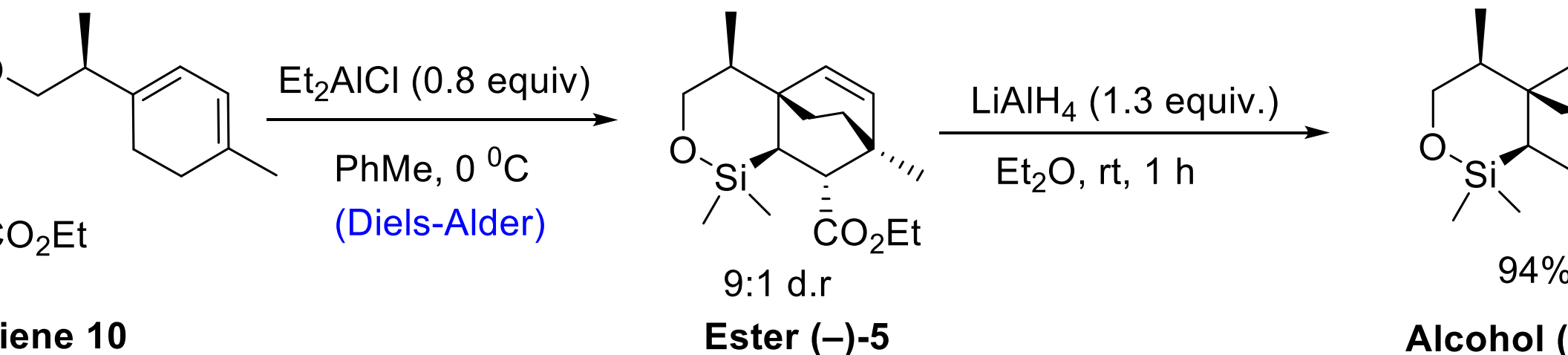




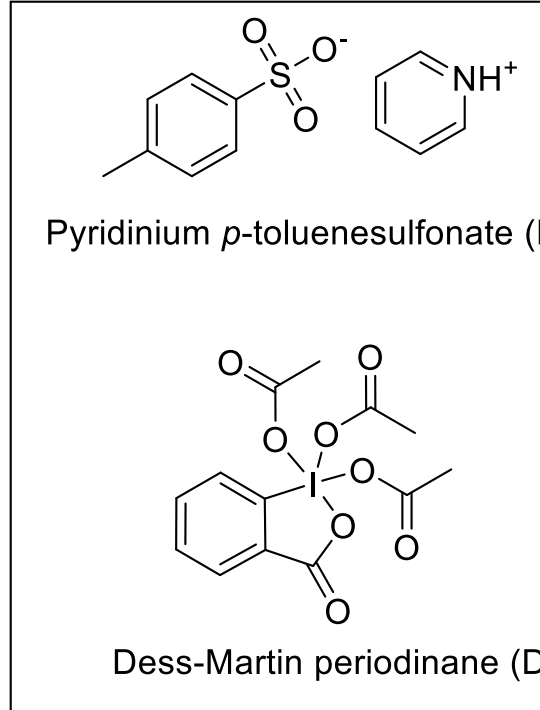
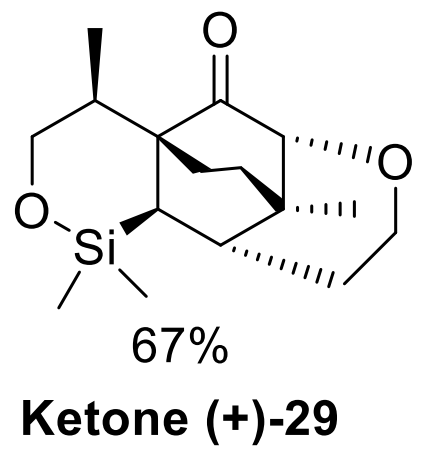
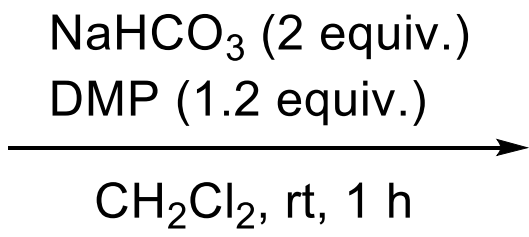
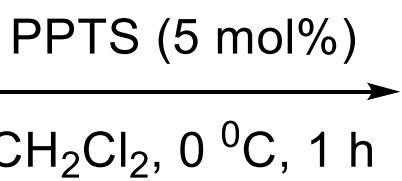
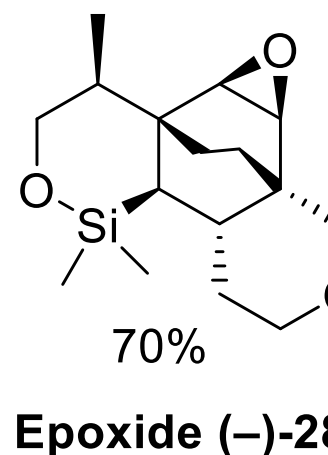
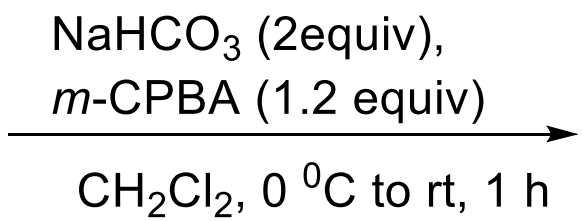
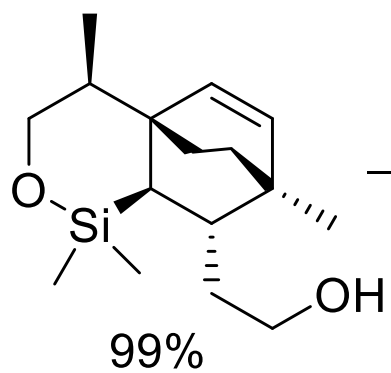
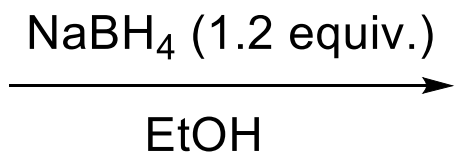
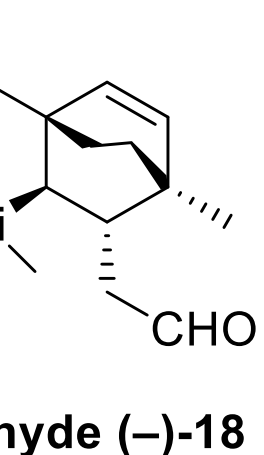
Birch, A. J. *J. Chem. Soc.* **1944**, 430

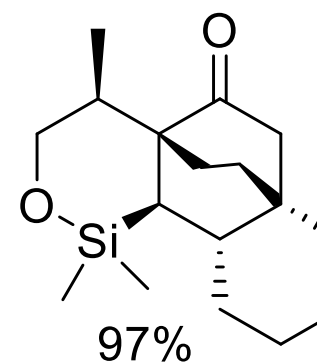
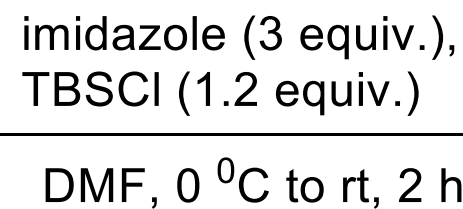
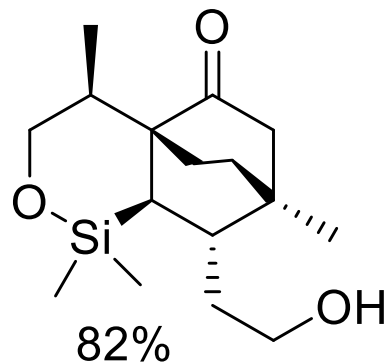
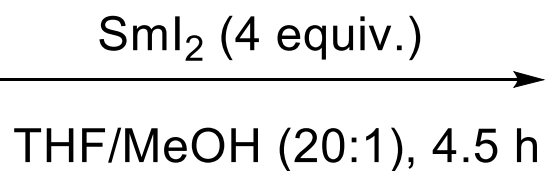
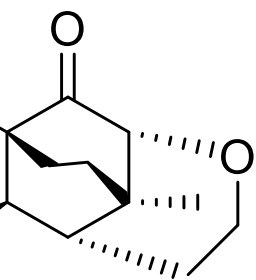
Sieburth, S. M.; Lang, J. *J. Org. Chem.* **1999**, 64, 1780

used for the next step w/o purification



W. R.; Kageyama, M.; Riva, R.; Brown, B. B.; Warmus, J. S.; Moriarty, K. J. *J. Org. Chem.* **1991**, 56, 1024-1028  
 J.; Sustmann, R. *Angew. Chem., Int. Ed.* **1980**, 19, 779  
 K. N.; Strozier, R. W. *J. Am. Chem. Soc.* **1973**, 95, 4094



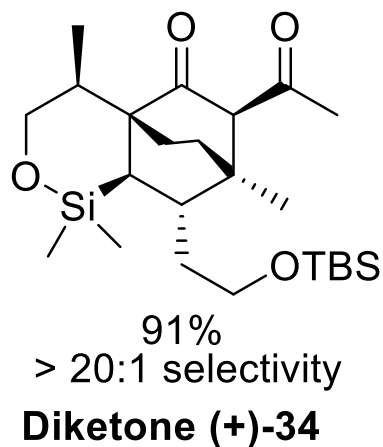
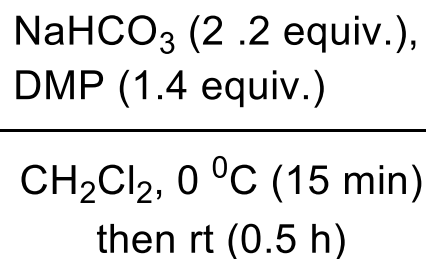
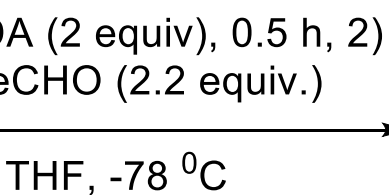


**(+)-29**

ander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135

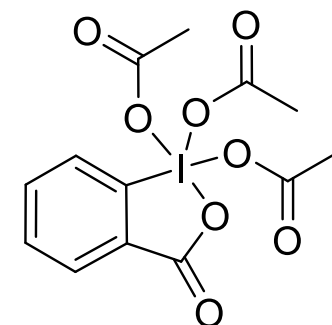
**Alcohol (+)-30**

**Ketone (+)-31**



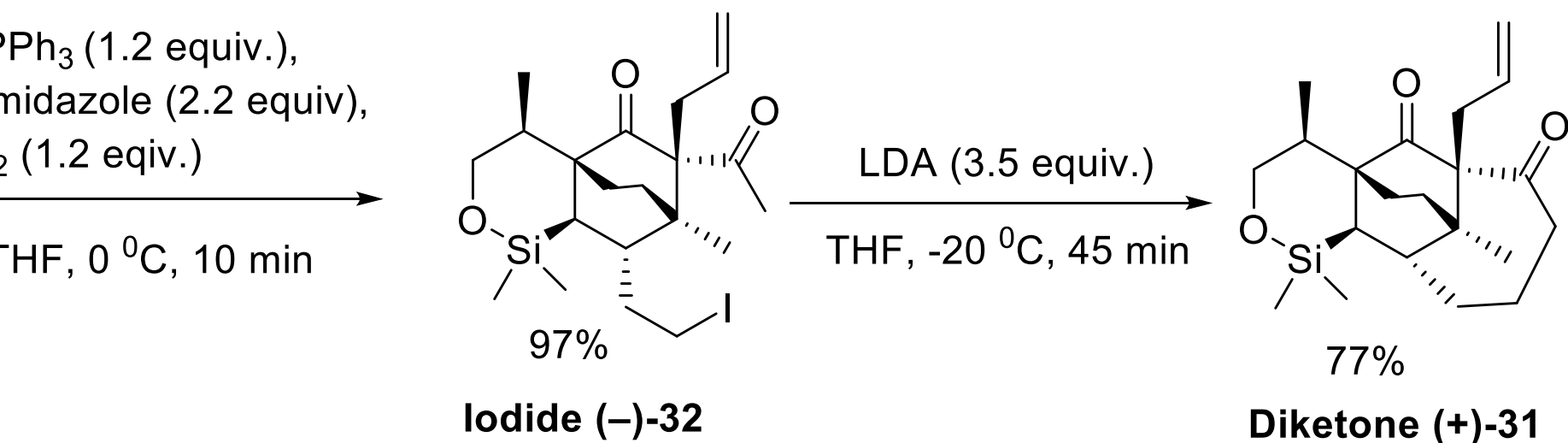
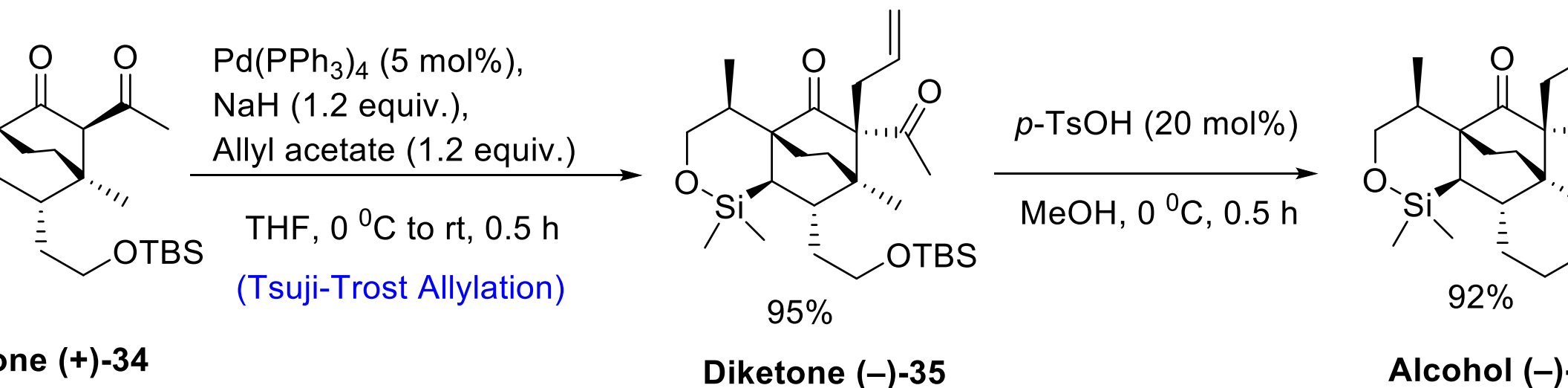
ith, A. B.; Levenberg, P. A. *Synthesis* **1981**, 567

Recall



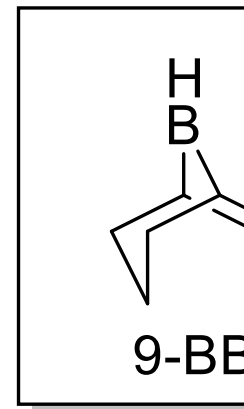
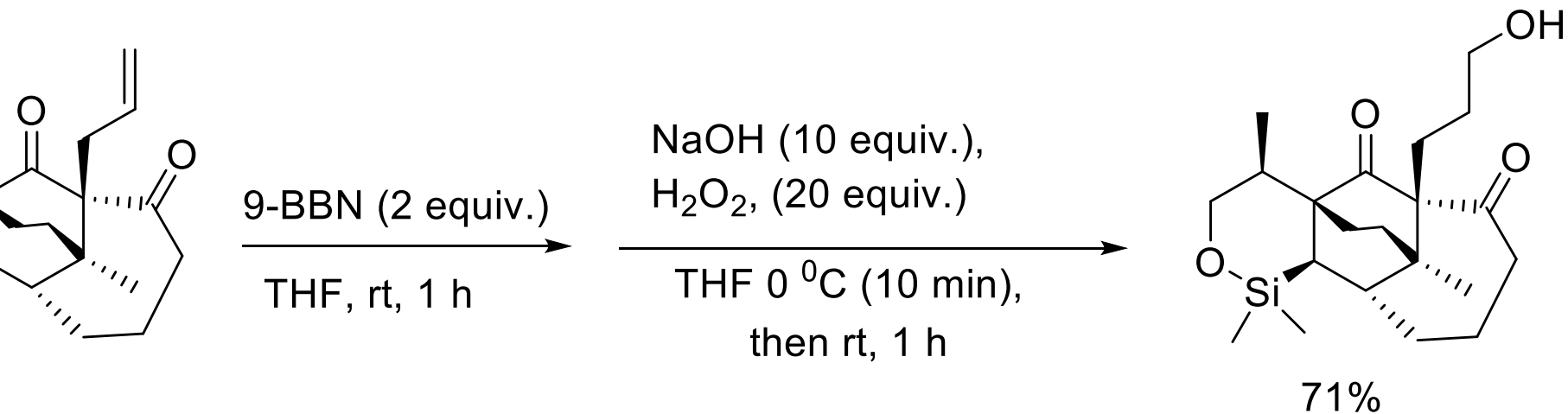
Dess-Martin periodinane



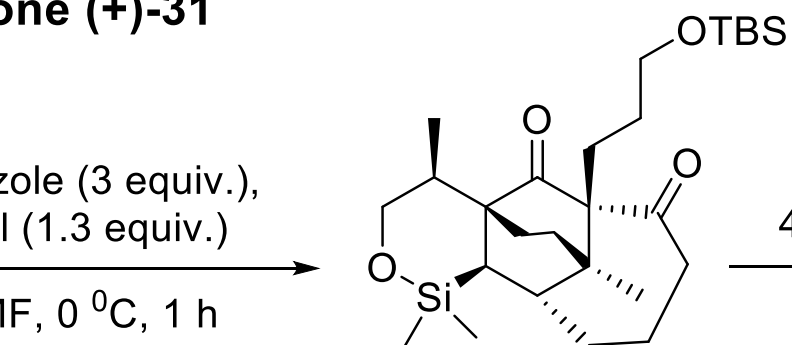


Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292.

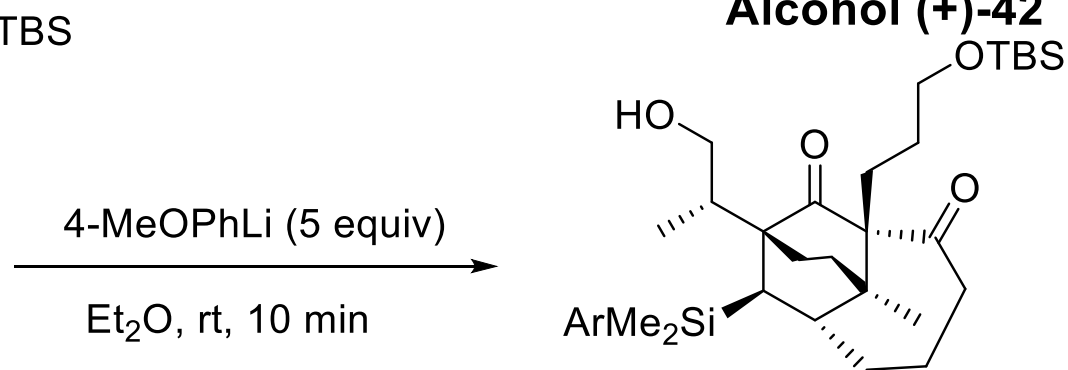
Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, 4387.



one (+)-31

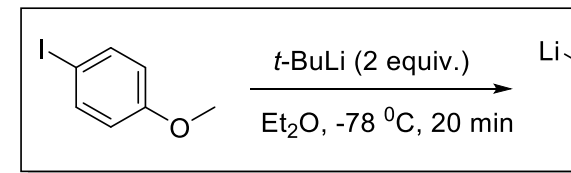


Silyl ether (+)-43

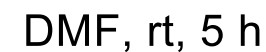
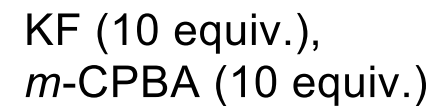
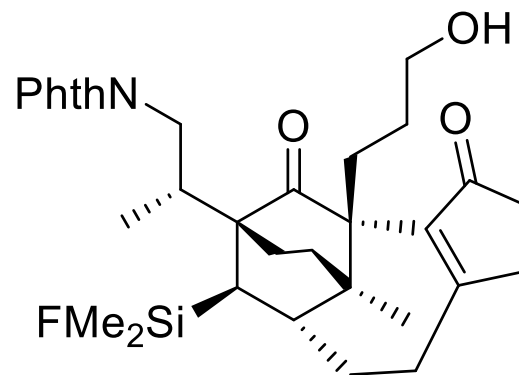
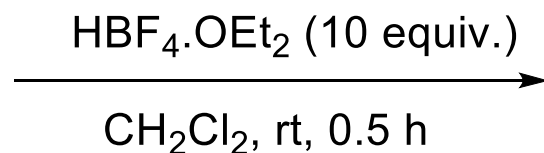
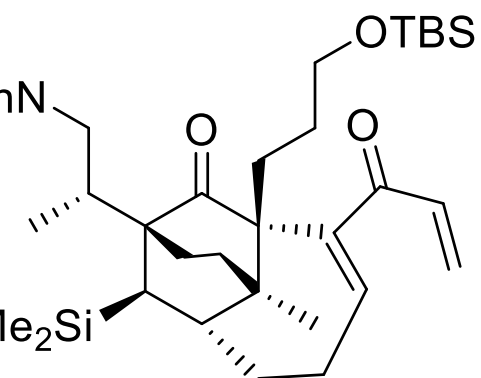


Alcohol (+)-59

own, H. C.; Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* **1974**, *96*, 7765.





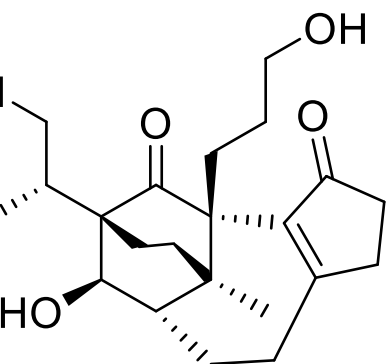


(Fleming-Tamao oxidation)

82%

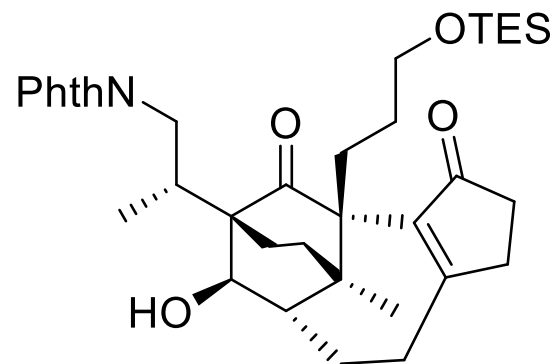
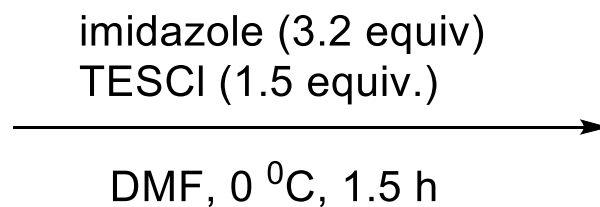
**Enone (+)-62**

**Silyl fluoride (+)-63**



74%

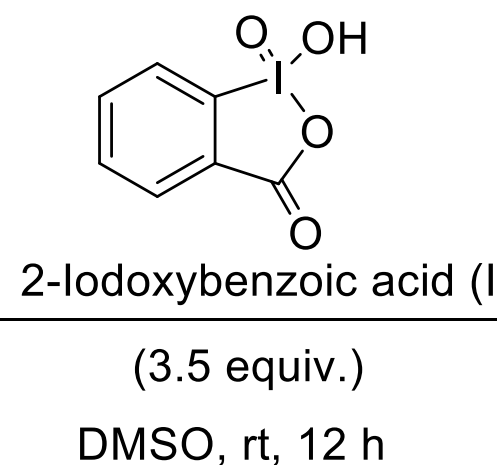
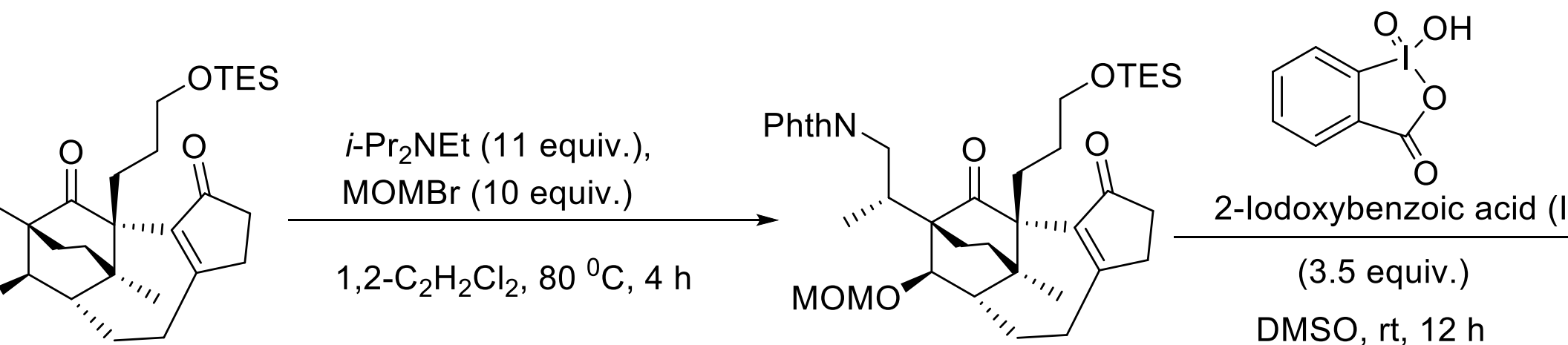
**Diol (+)-58**



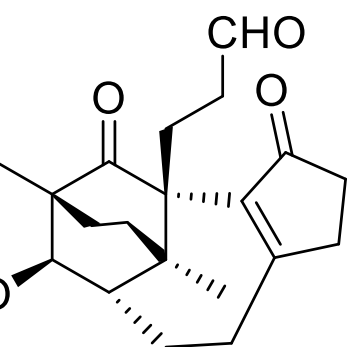
83%

**Alcohol (+)-64**

Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29.

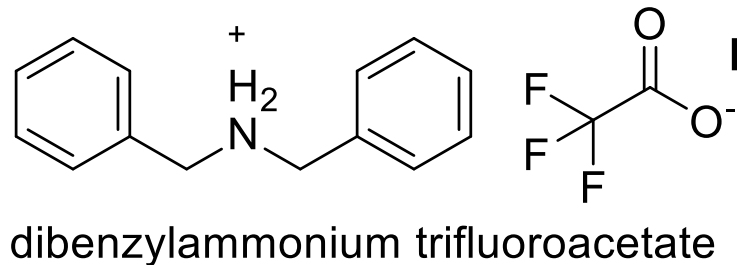


**Alcohol (+)-64**



95%

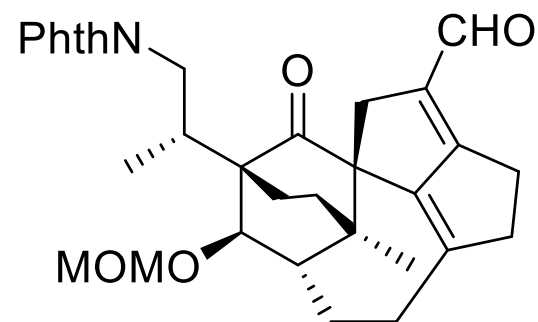
**Aldehyde (+)-66**



$\text{Benzene}$ ,  $50\text{ }^\circ\text{C}$ , 17 h

(Aldol condensation)

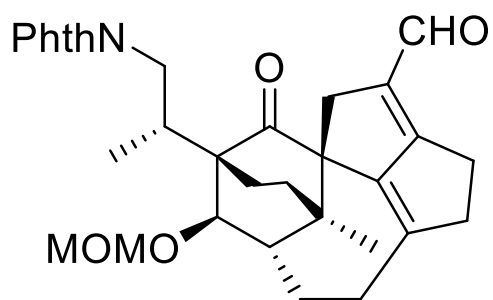
88%  
**Enone (+)-65**



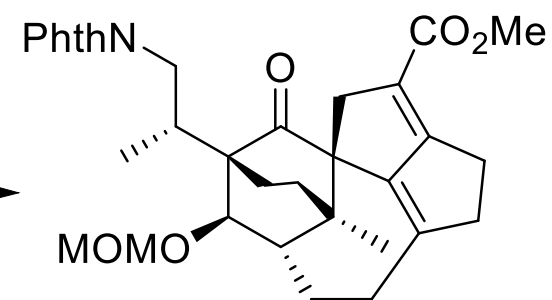
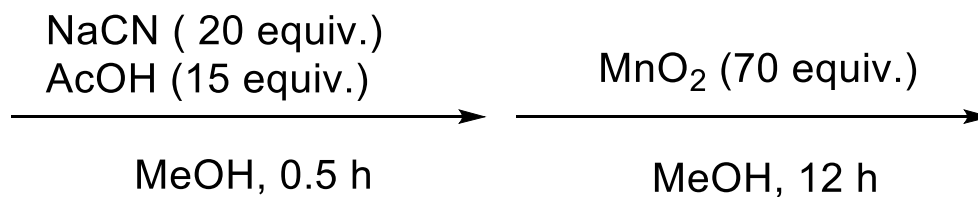
69%

**Aldehyde (+)-67**

Y. K.; Huang, J. H.; Shen, X.; Hu, Q.; Tang, C. J.; Li, L. *Org. Lett.* **2002**, 4, 2141.



**Aldehyde (+)-67**



82%

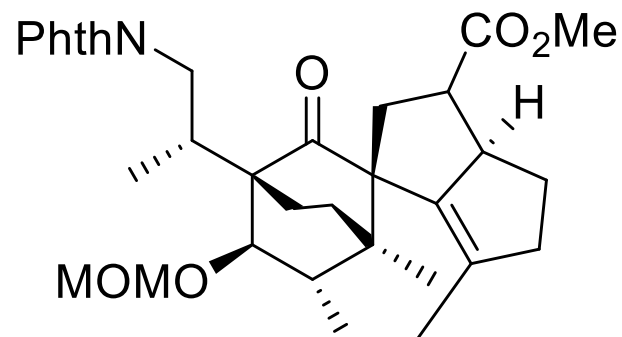
**Ester (+)-68**

**Pfaltz-modified Crabtree catalyst)**

**(cod)(Py)(PCy)<sub>3</sub>]IrBARf (1 equiv.)**

**H<sub>2</sub> (900 psi)**

**1,2-dichloroethane, 19 h**



84%, 4:1 d.r

**Ester (-)-69**

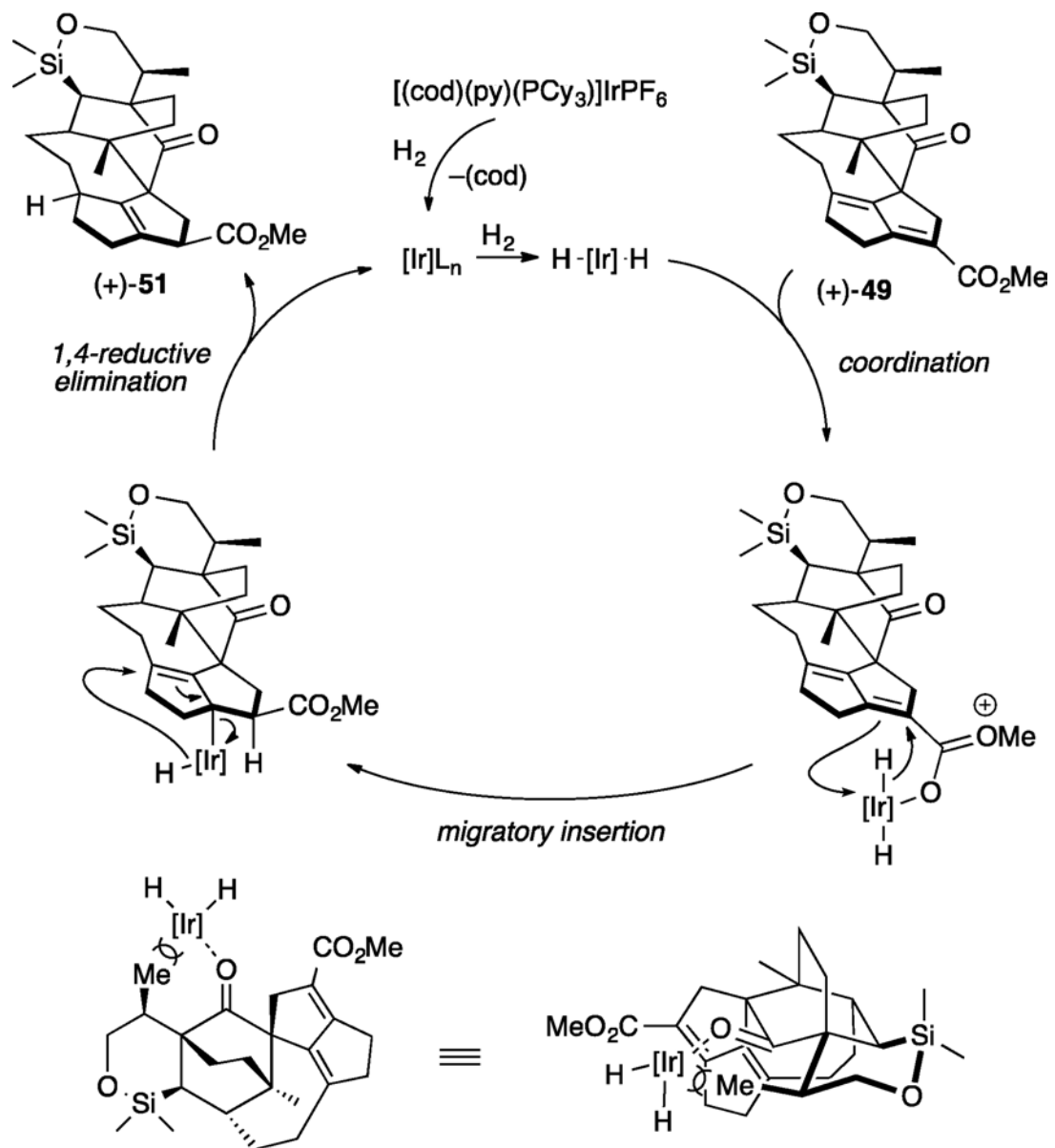
**Wuestenberg, B.; Pfaltz, A. *Adv. Synth. Catal.* **2008**, *350*, 174**

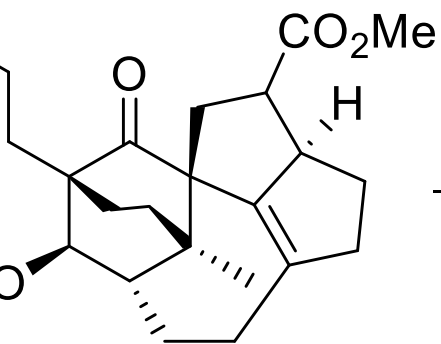
**Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655**

**Brown, J. M. *Angew. Chem., Int. Ed.* **1987**, *26*, 190**

**AN STATE  
R S I T Y**

Artem Shvartsbart and Amos B. Smith, III, *J. Am. Chem. Soc.* **2015**, *137*, 3510–3519



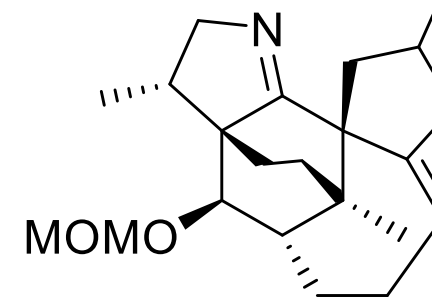


$\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$  (50 equiv.)

EtOH, rt, 12 h

aq.  $\text{NH}_4\text{Cl}$

EtOH, 70  $^\circ\text{C}$ , 18 h



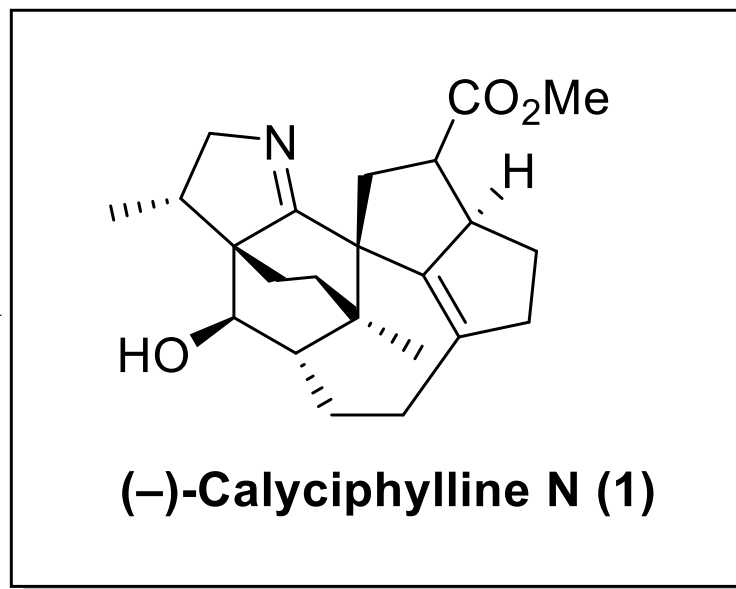
73%

Imine (-)

Ester (-)-69

$\text{Ph}_2\text{BBr}$  (5 equiv.)  
added at -40  $^\circ\text{C}$ )

$\text{CH}_2\text{Cl}_2$ , rt, 0.5 h



(-)-Calyciphylline N (1)

79%

on, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, 49, 3912.

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RSITY

Artem Shvartsbart and Amos B. Smith, III, *J. Am. Chem. Soc.* **2015**, 137, 3510–3519



**THANK YOU!!!**