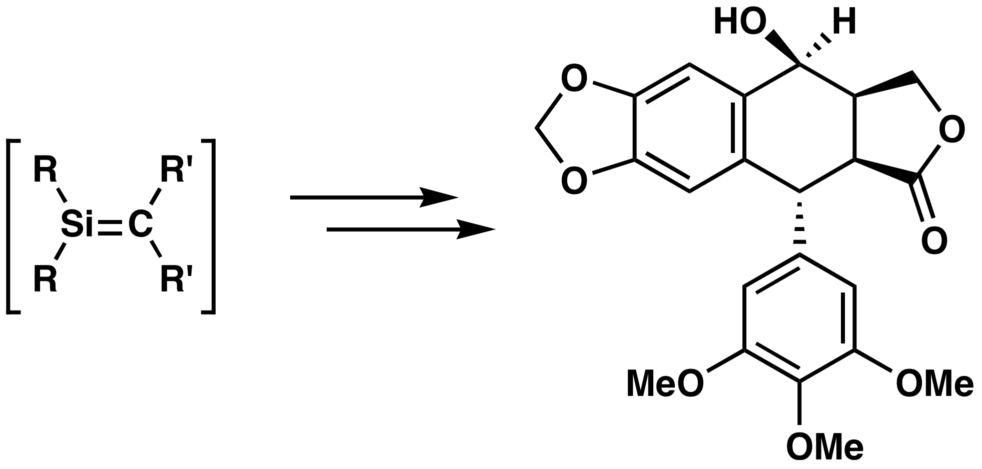
Silenes in organic synthesis: a concise synthesis of (±)-*epi*-picropodophyllin

Robert D. C. Pullin, Jonathan D. Sellars, and Patrick G. Steel*

Org. Biomol. Chem., **2007**, 5, 3201-3206



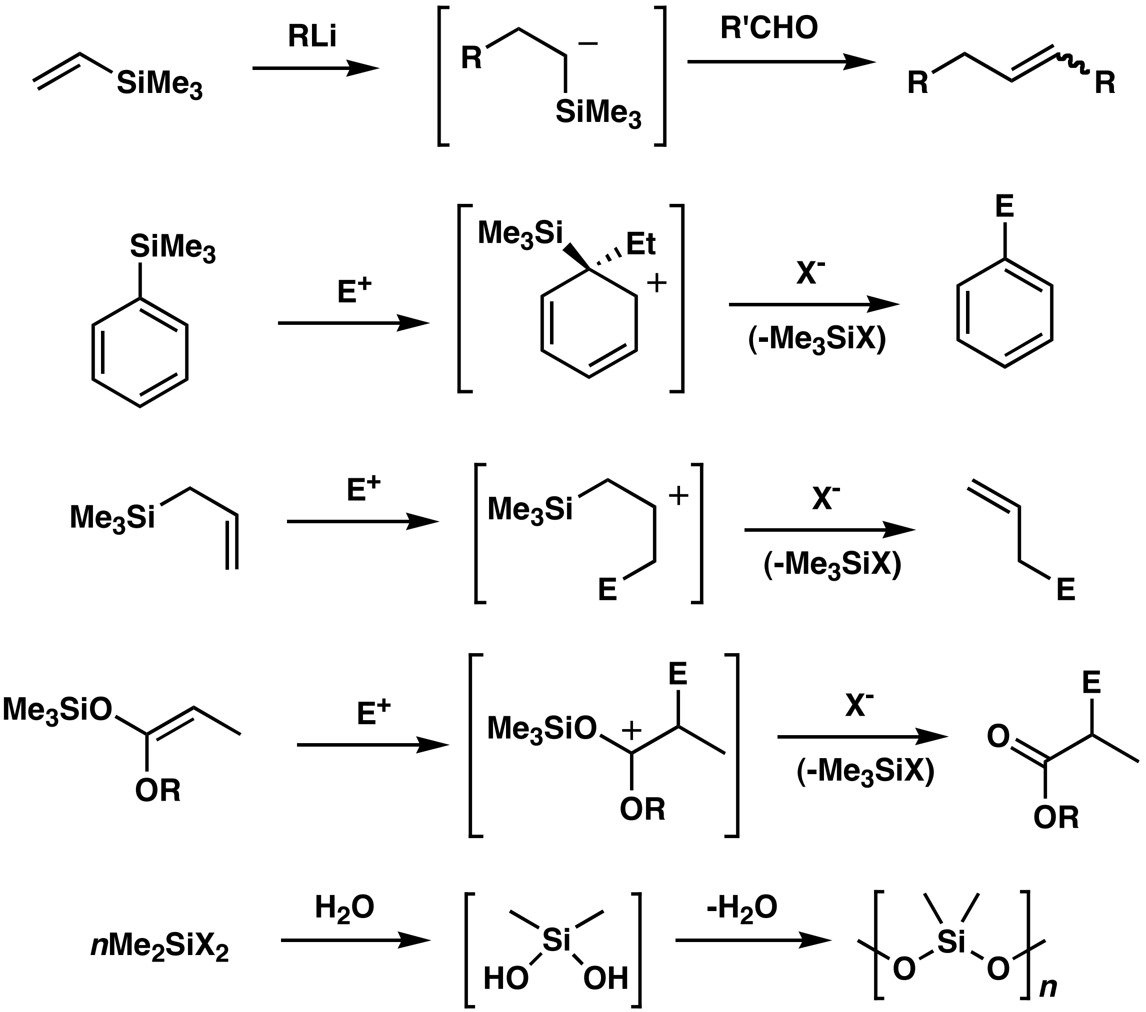
Adam Hoye

Current Literature

Oct. 27th, 2007

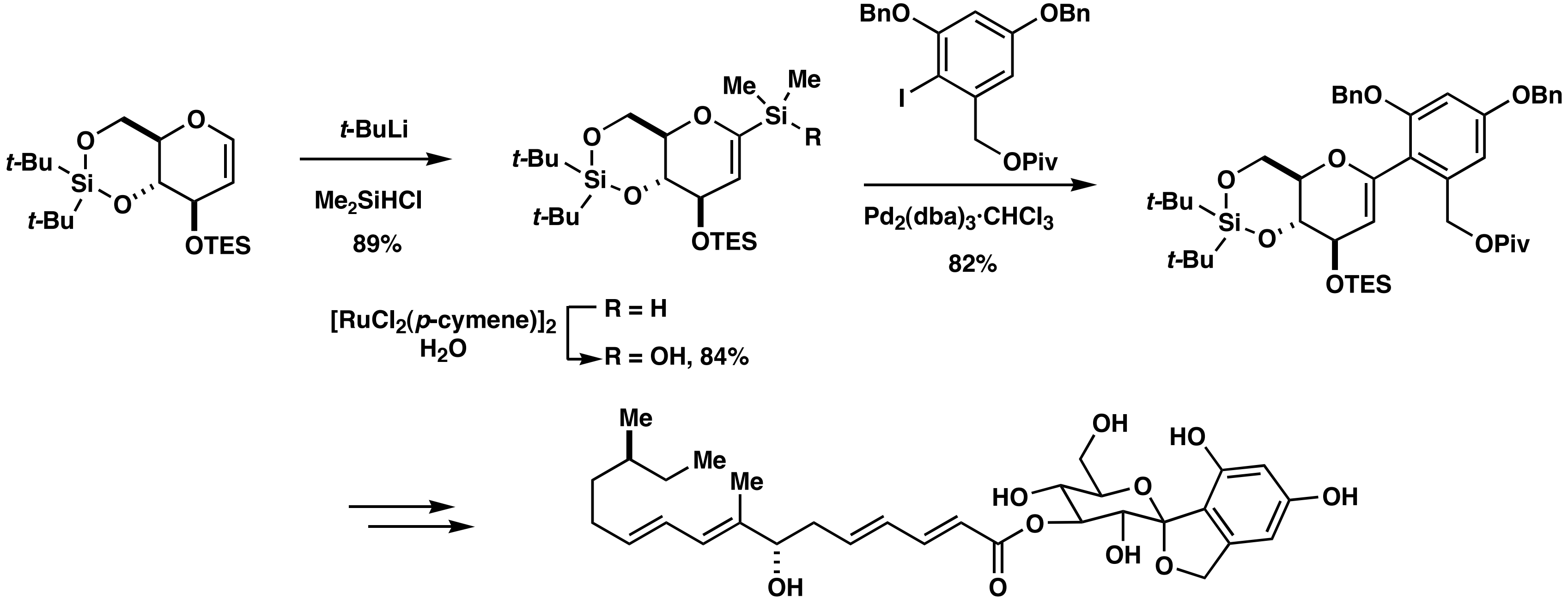
Classic organosilicon chemistry

$$ROH + tBuPh_2SiCl \xrightarrow{\text{imidazole, DMF}} ROSiPh_2tBu$$



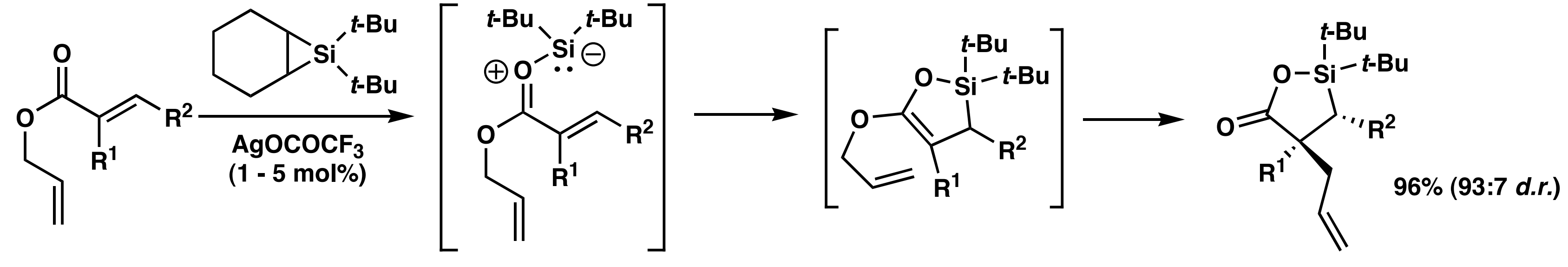
Recent advances in organosilicon chemistry

-Denmark (*J. Am. Chem. Soc.*, **2007**, *129*, 2774)



Papulacandin D

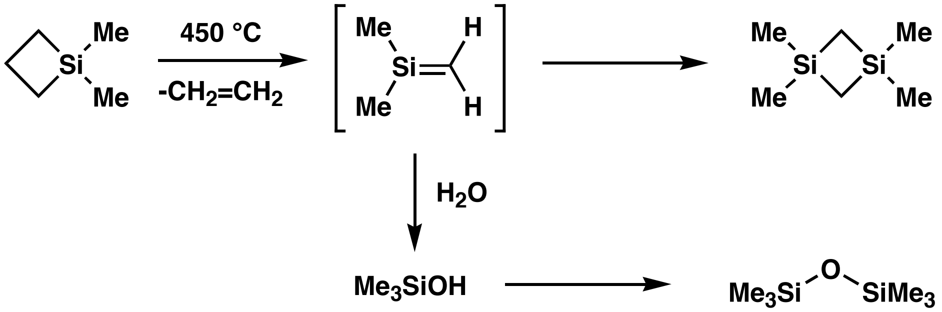
-Woerpel (*J. Am. Chem. Soc.*, **2005**, *127*, 2046)



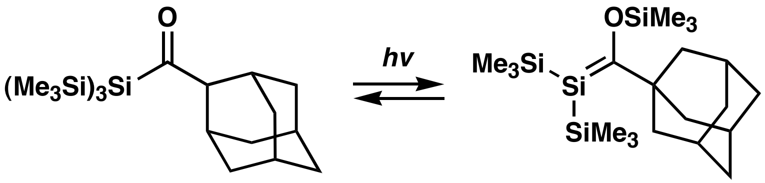
Silenes: a brief history…

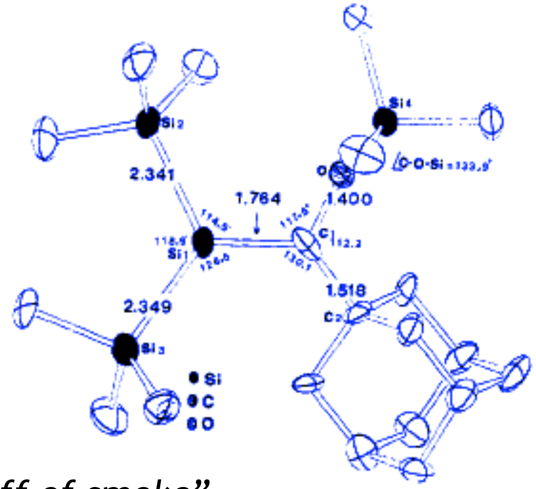
-In 1912 Schlenk and Renning reported silene synthesis by dehydration of a silanol (release of H_2O)
-Kipping showed product was actually a siloxane and concluded multiple bonds to Si were “not a realistic objective”

-1967 Gusel’nikov and Flowers:



-1981 Brook (photolysis of acylsilanes)- steric bulk on the carbon atom key to moderating silene reactivity (stability)



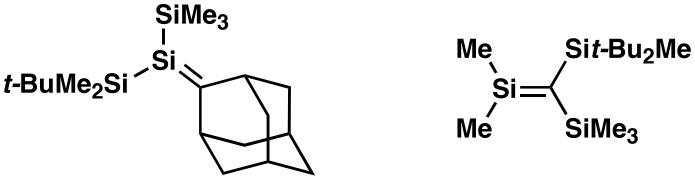


“unchanged after several years although if exposed to air disappears in a puff of smoke”

Ottosson, H.; Steel, P. G. *Chem. Eur. J.* **2006**, *12*, 1576-1585
Brook et al. *J. Am. Chem. Soc.* **1982**, *104*, 5667-5672

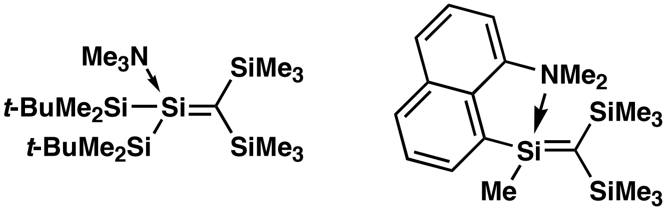
Silenes: a brief history…

-Steric stabilization of silenes

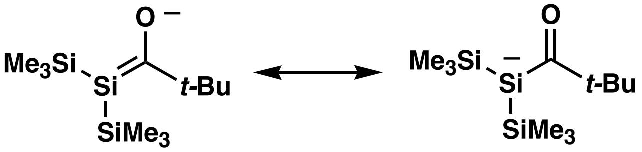


-Electronic stabilization of silenes: reversed Si=C bond polarity (that is $Si^{\delta-}=C^{\delta+}$ instead of $Si^{\delta+}=C^{\delta-}$) leads to lower release of energy upon dimerization; slower rates of addition to silicon

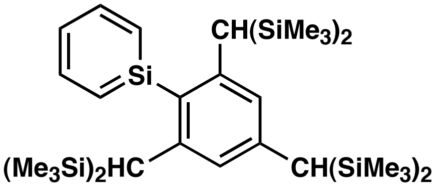
dative stabilization

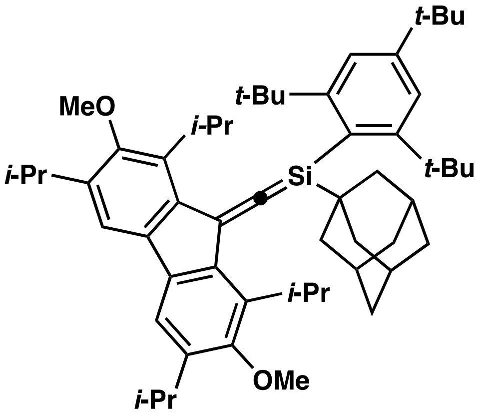


silenolates



-Extension into allenyl and aryl systems:

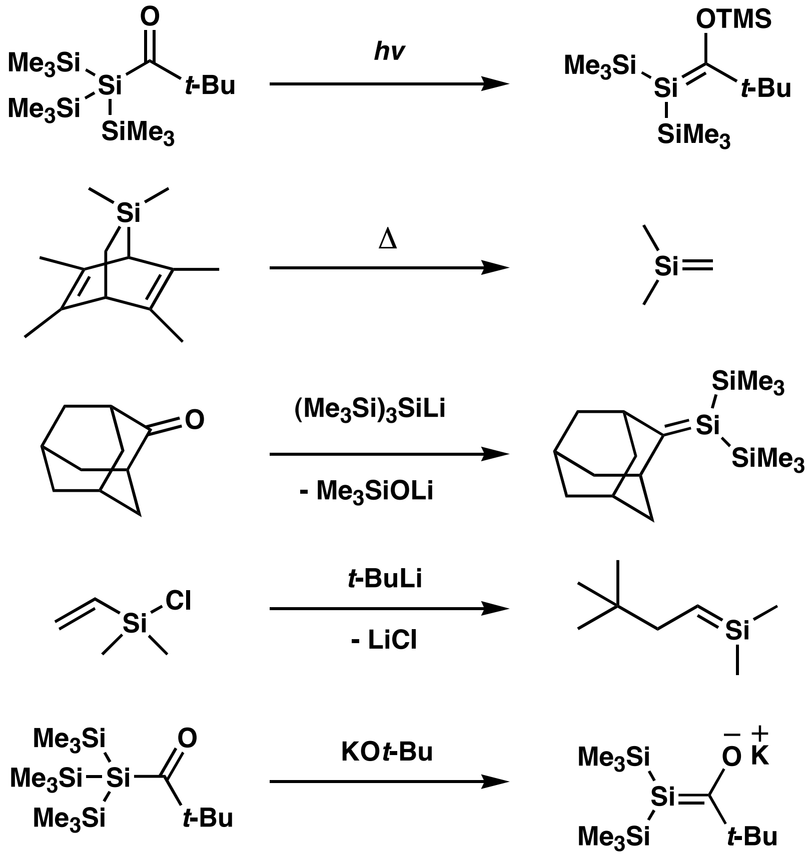




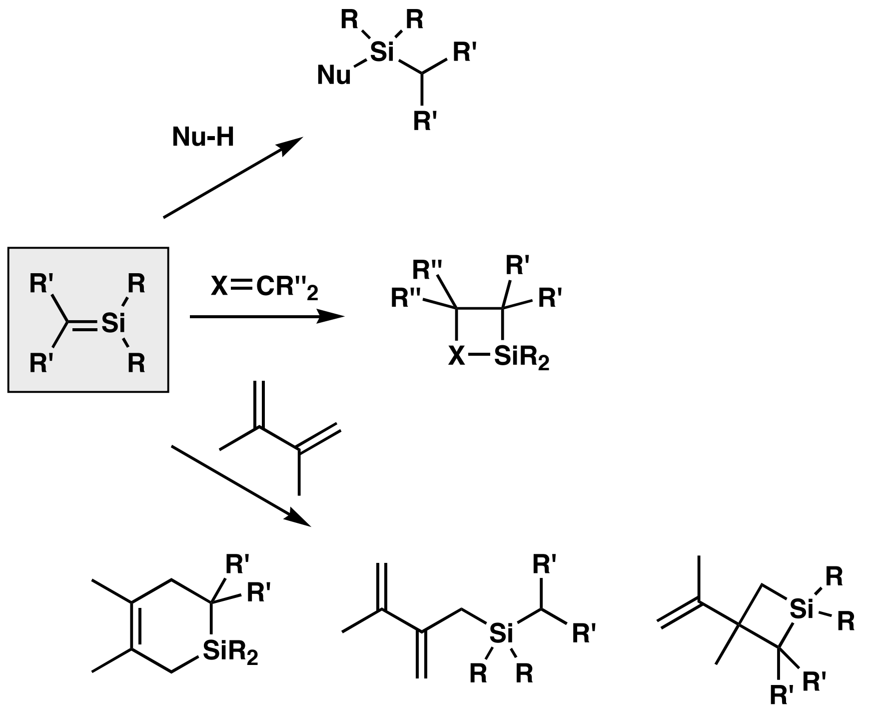
Ottosson, H.; Steel, P. G. *Chem. Eur. J.* **2006**, *12*, 1576-1585

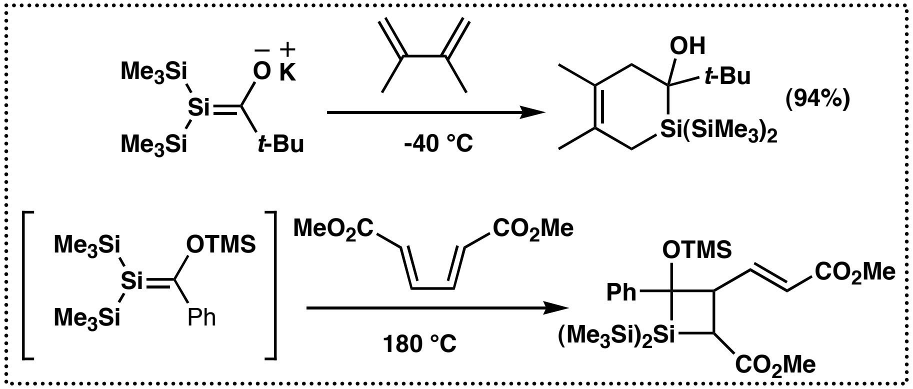
Silenes: preparation and general reactivity

Common methods of preparation:



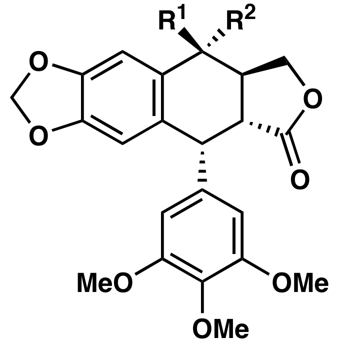
General silene reactivity:





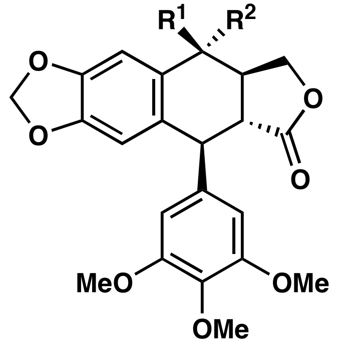
Ottosson, H.; Steel, P. G. *Chem. Eur. J.* **2006**, *12*, 1576-1585

Tetralin lignan lactones



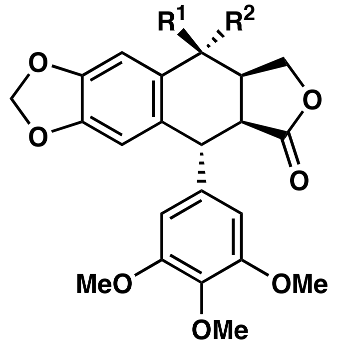
Podophyllotoxin $R^1 = H, R^2 = OH$

Epipodophyllotoxin $R^1 = OH, R^2 = H$



Isopodophyllotoxin $R^1 = H, R^2 = OH$

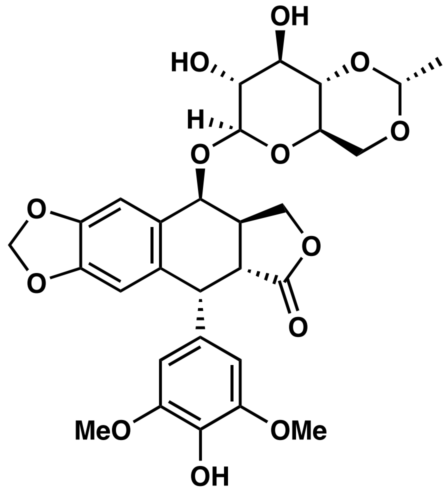
Epiisopodophyllotoxin $R^1 = OH, R^2 = H$



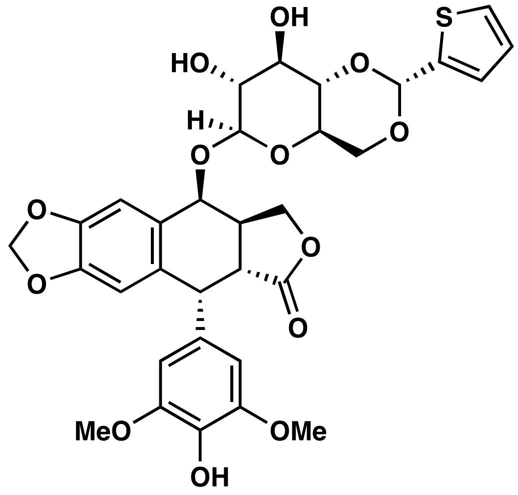
Picropodophyllotoxin $R^1 = H, R^2 = OH$

Epipicropodophyllotoxin $R^1 = OH, R^2 = H$

Podophyllotoxin is a potent antimitotic agent, but highly toxic.

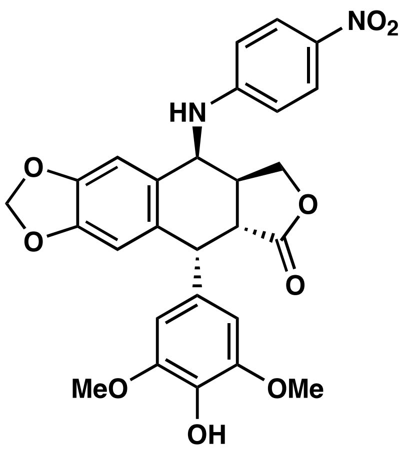


Etoposide



Tenoposide

DNA topoisomerase II inhibitors
(used clinically, but poor solubility and growing drug resistance)



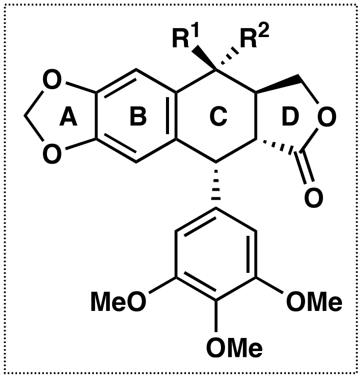
GL-331

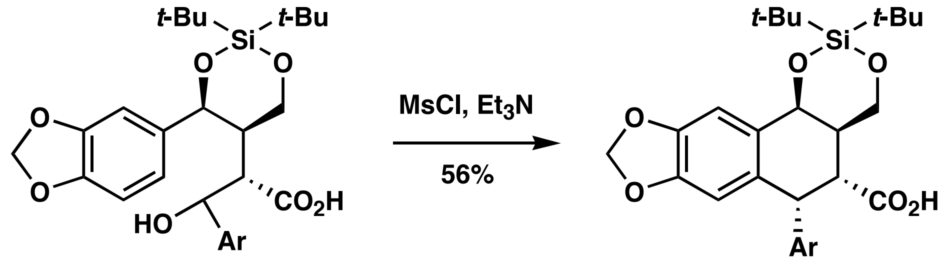
In phase II trials
(more potent, less resisted)

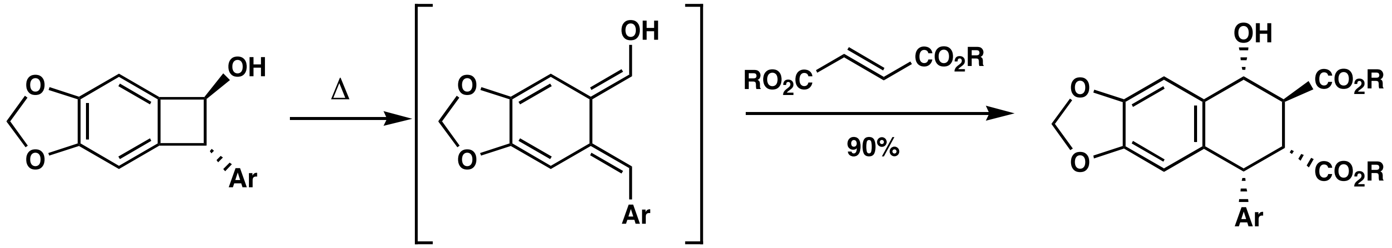
Sellars, J. D.; Steel, P. G., *Eur. J. Org. Chem.*, **2007**, 3815

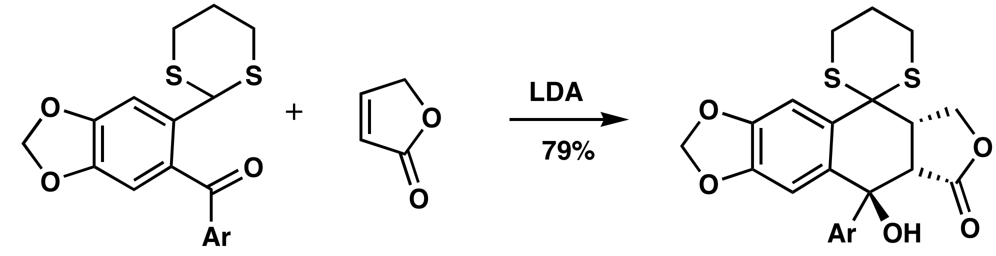
Lignan syntheses

Typical strategies to construct the core:

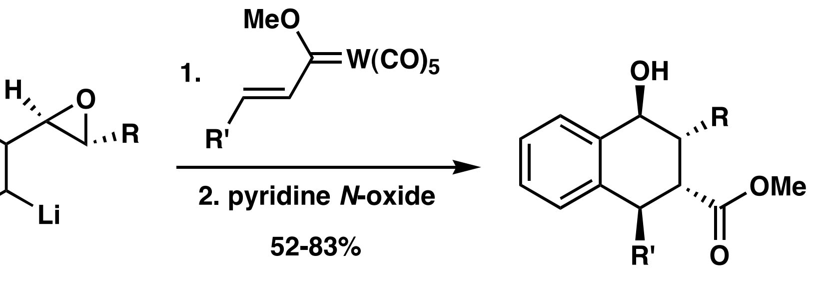




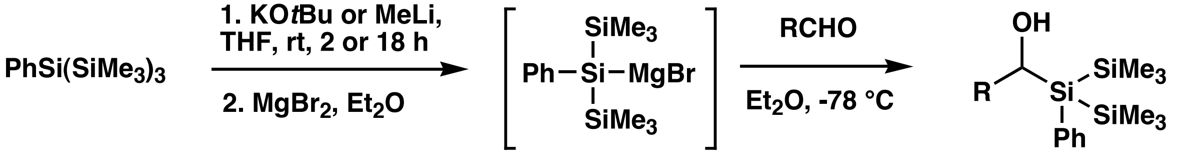




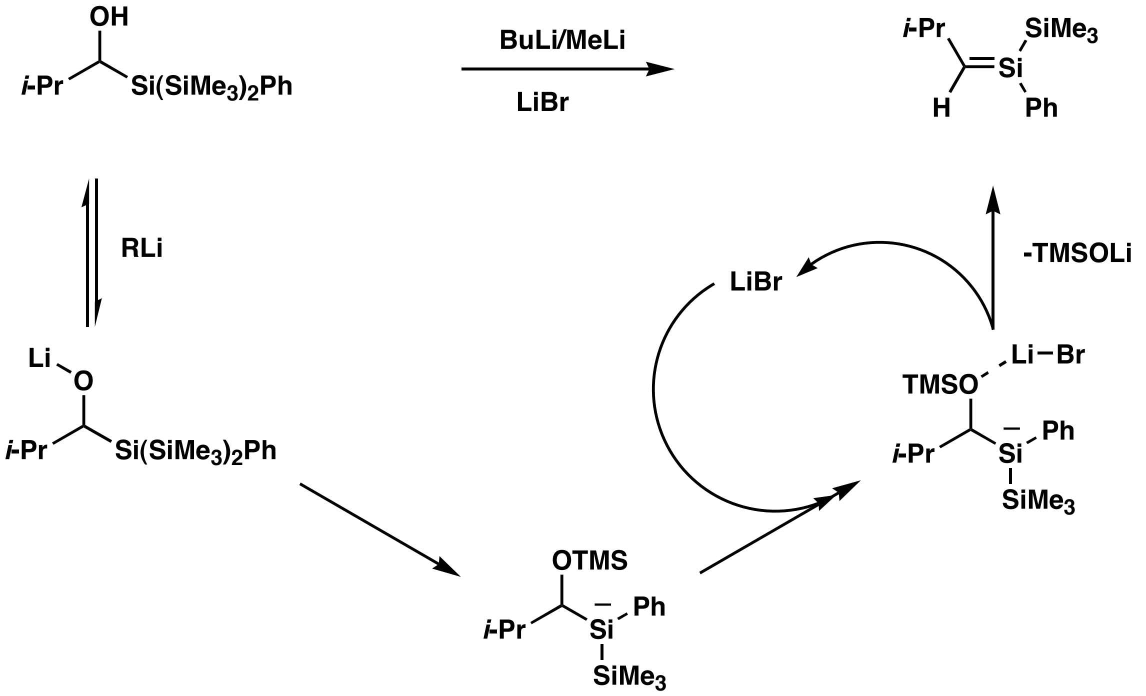
Vanderwalle et al., *Tetrahedron*, **1991**, *47*, 4675
Charlton, J. L., Koh, K., *J. Org. Chem.*, **1992**, *57*, 1514
Harrowven, D. C., *Tetrahedron*, **1993**, *49*, 9039
Florio et al., *Org. Lett.*, **2005**, *7*, 4895



Previous work in the Steel group

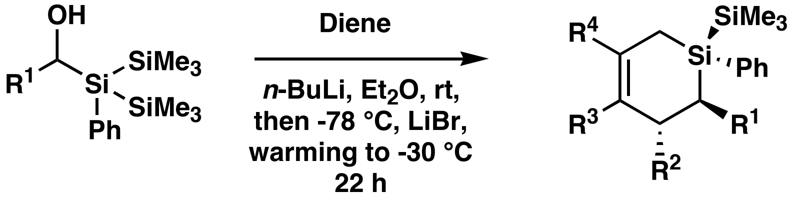


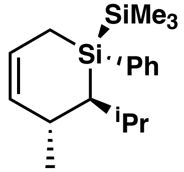
R = *i*-Pr (52%),
C_3H_7 (74%),
Me (49%),
i-Bu (58%),
t- Bu (37%),
c-C_6H_{11} (38%),
Ph (68%)



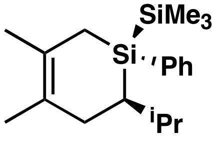
Sanganee, M. J.; Steel, P. G.; Whelligan, D. K., *Org. Biomol. Chem.*, **2004**, *2*, 2393

Previous work in the Steel group

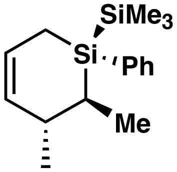




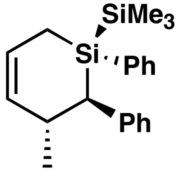
50%
(83:9:8)



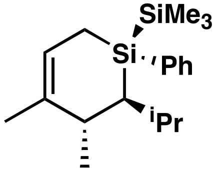
42%
(83:17)



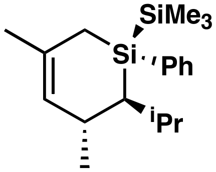
28%
(89:7:4)



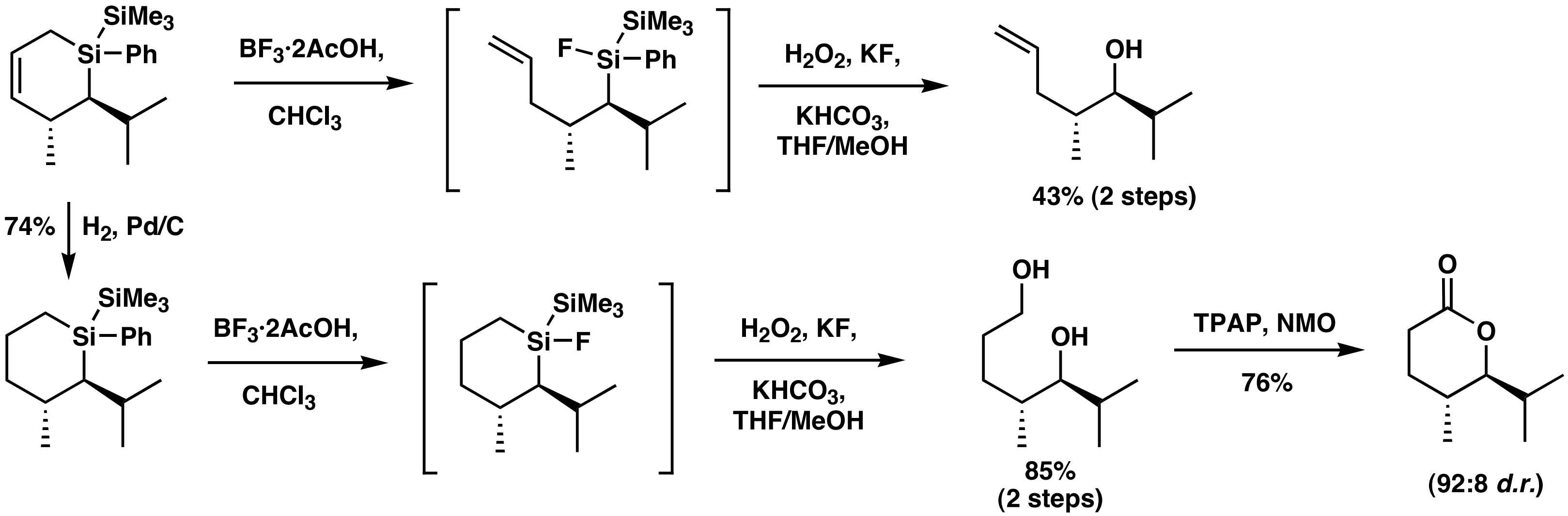
45%
(74:20:6)



38%
(86:9:4:1)

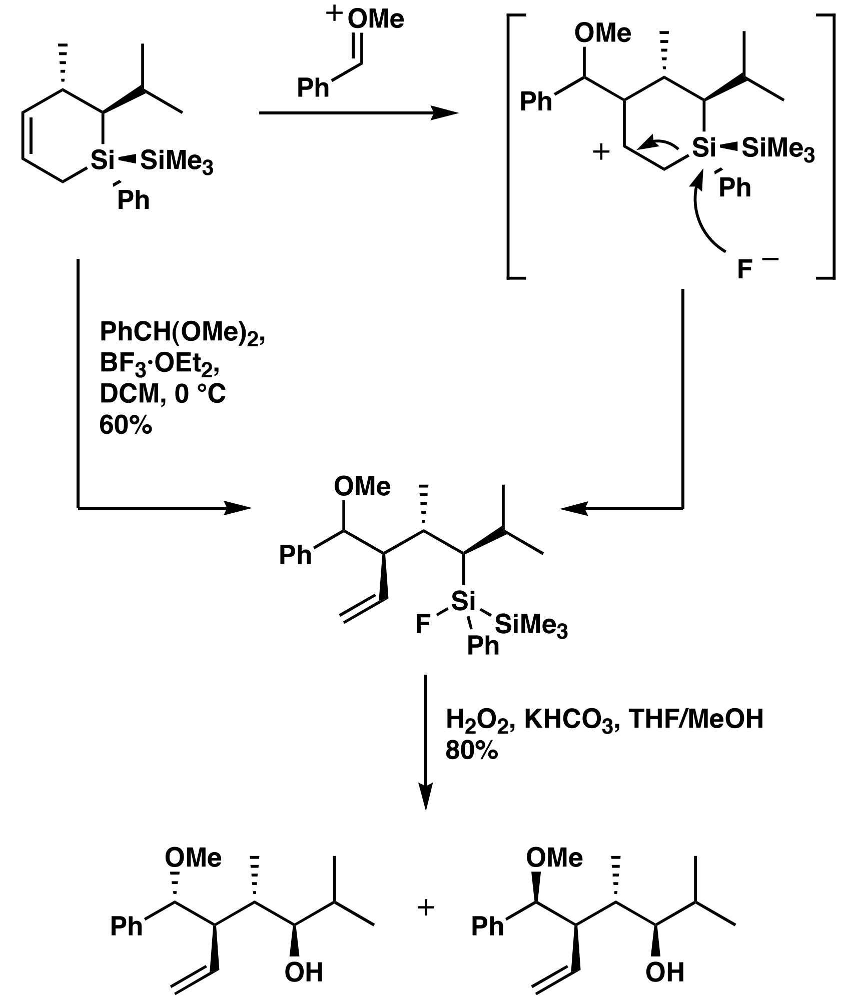


28%
(80:14:4:2)

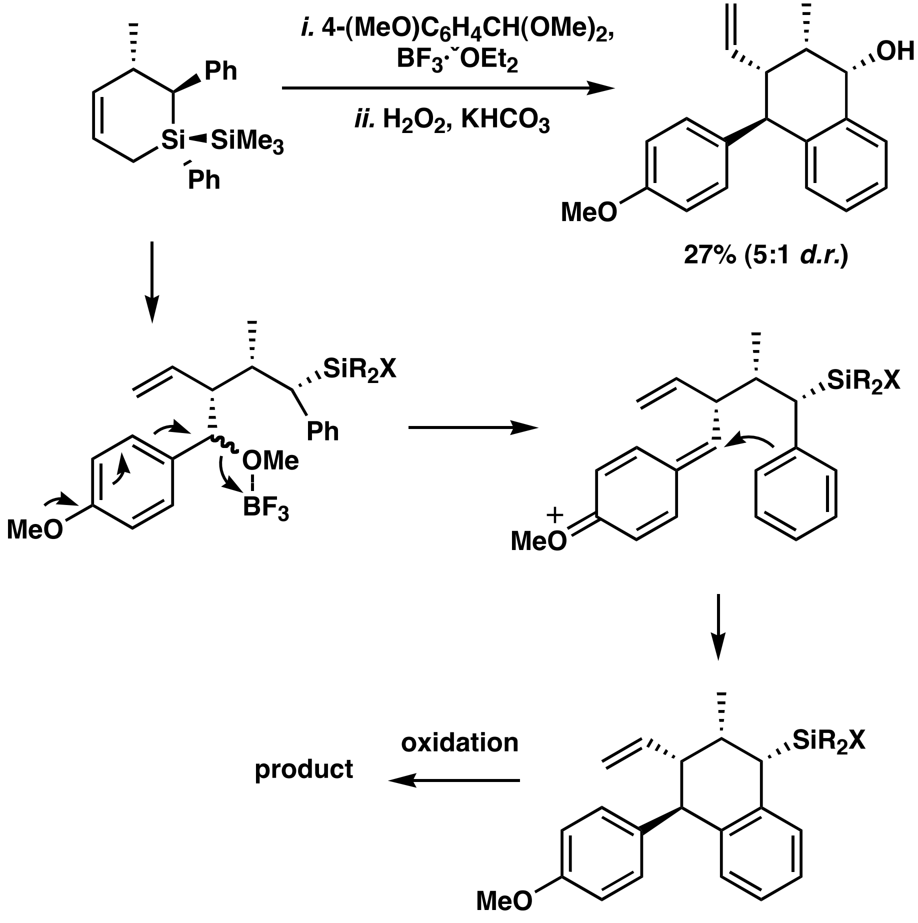


Berry, M. B.; Griffiths, R. J.; Sanganee, M. J.; Steel, P. G.; Whelligan, D. K., *Org. Biomol. Chem.* **2004**, *4*, 2381
Berry, M. B.; Griffiths, R. J.; Sanganee, M. J.; Steel, P. G.; Whelligan, D. K., *Tetrahedron Lett.*, **2003**, *44*, 9135
Sanganee, M. J.; Steel, P. G.; Whelligan, D. K., *Org. Biomol. Chem.*, **2004**, *2*, 2393

Sakurai reactions with cyclic allyl silanes

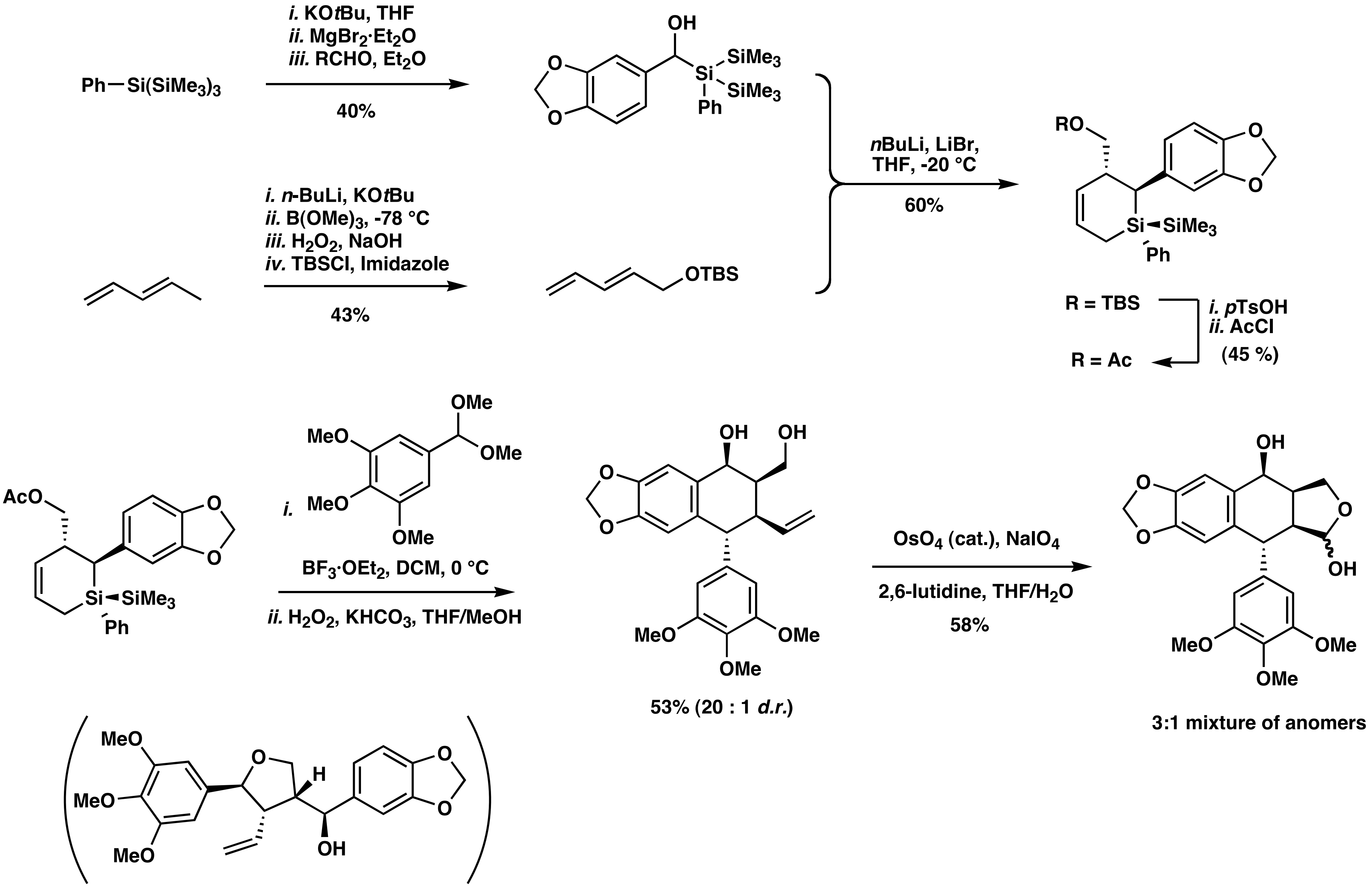


With electron-rich aromatics:



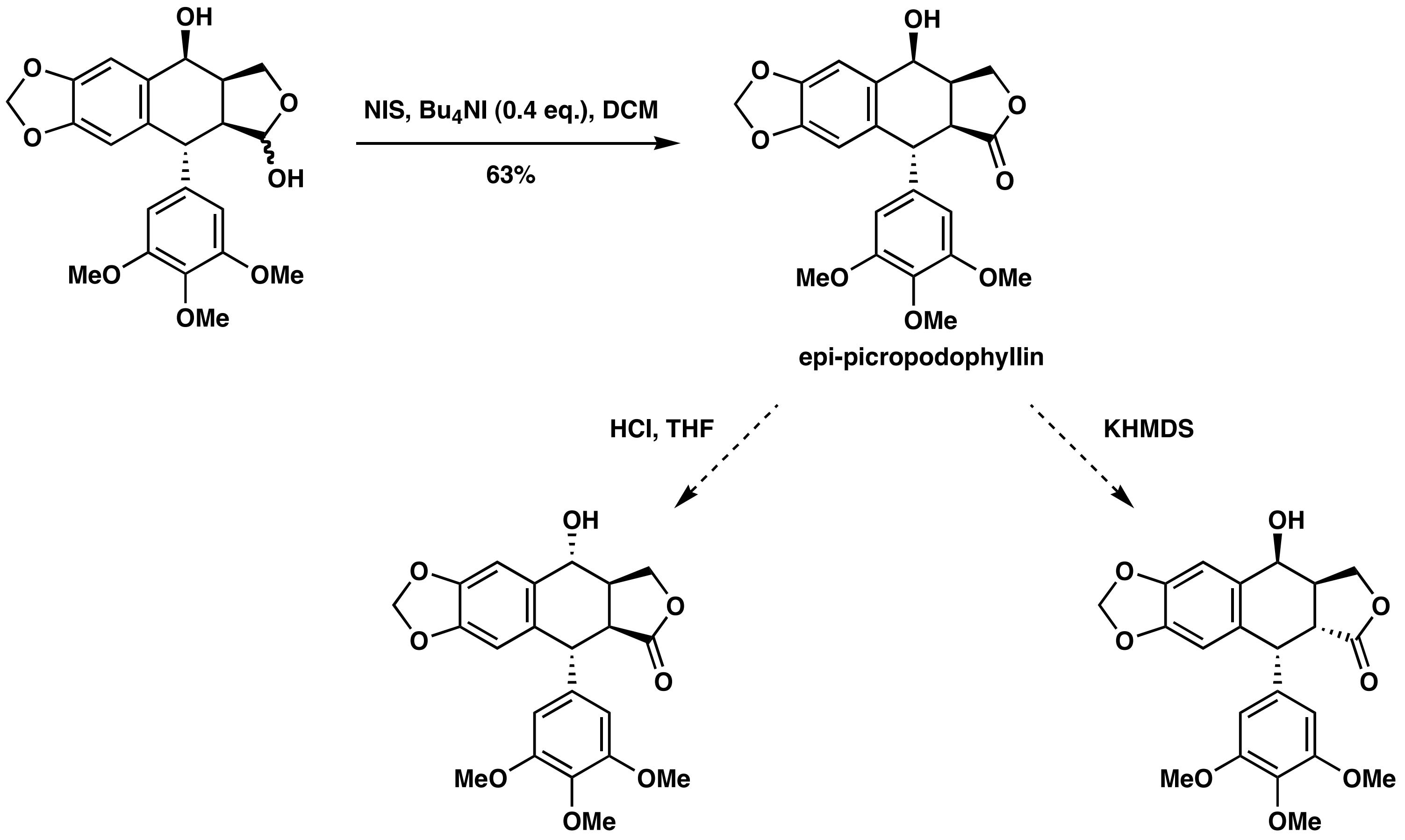
Sellars, J. D.; Steel, P. G.; Turner, M., *Chem. Commun.*, **2006**, 2385
Steel et al. *Org. Biomol. Chem.*, **2007**, *5*, 2841

Current paper



formed if unprotected alcohol used

Current paper



Conclusions

-Access to tetralin lignan lactone family using silene cycloaddition/cyclic allylsilane Sakurai reactions

-Highly modular synthesis; facilitates future analogue development

-Truly "concise" synthesis (9 steps, 2.2% overall yield)