A Second Approach to the Quaternary Core of the Daphniglaucin A using the Bicyclo[1.1.0]butane Chemistry

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Research Topic Seminar

October 4, 2008

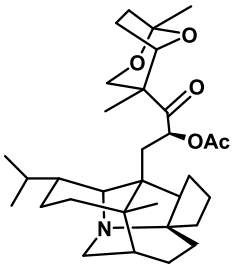
Daphniphyllum Alkaloids

Daphniphyllum alkaloids have highly complex polycyclic structures.

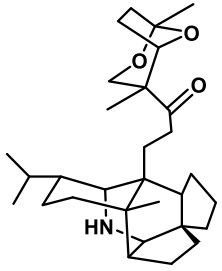
In recent years, more than 60 new *Daphniphyllum* alkaloids were isolated from the oriental tree “Yuzuriha”.

Some of these alkaloids showed cytotoxic activities against several tumor cell lines.

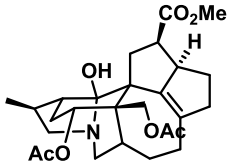
The unusual ring systems have attracted great interest as challenging targets for total synthesis.



Daphniphylline

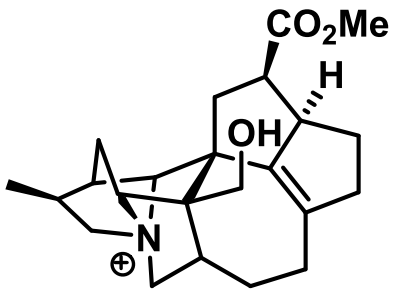


Secodaphniphylline



Yuzurimine

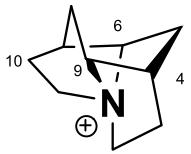
Yuzuriha (*Daphniphyllum macropodum*; Daphniphyllaceae)
dioecious evergreen trees and shrubs native to Japan.
Leaves are used as a pesticide.



Daphniglaucin A

Isolated from the leaves of *Daphniphyllum glaucescens* in 2003.

Unprecedented fused-polycyclic skeleton containing 1-azaniatetracyclo[5.2.2.0.^{1,6}0.^{4,9}]undecane ring.

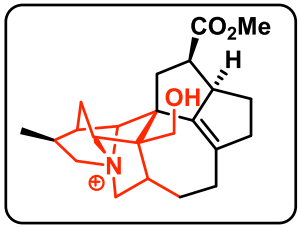


Structure elucidated by MS, 1H and 13C NMR, COSY, HMBC and NOESY

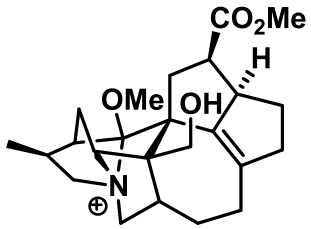
Exhibited cytotoxicity against murine lymphoma L1210 cells (IC_{50} 2.7 μg/mL)
and human epidermoid carcinoma KB cells (IC_{50} 2.0 μg/mL) in vitro.

Kobayashi, J. *et al.*, *Org. Lett.*, **2003**, *5*, 1733.

Related Compounds Isolated from *Daphniphyllum Glaucescens*



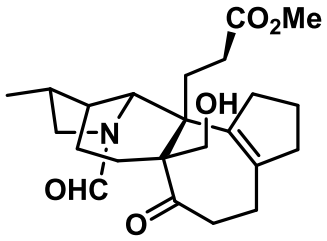
Daphniglaucin A



Daphniglaucin B

cytotoxicity :
murine lymphoma L1210 cells (IC_{50} 3.9 μg/mL)
and human epidermoid carcinoma KB cells
(IC_{50} 10.0 μg/mL).

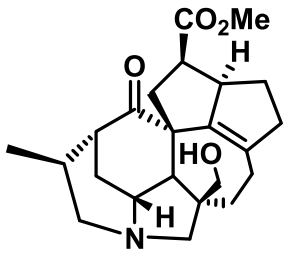
Kobayashi, J. *et al.*, *Org. Lett.*, **2003**, *5*, 1733.



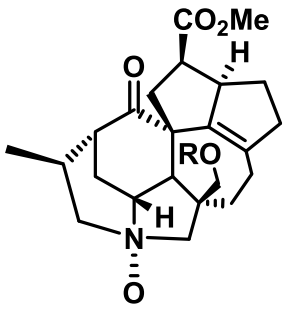
Daphniglaucin C

cytotoxicity murine lymphoma L1210
cells (IC_{50} 0.1 μg/mL)
inhibition the polymerization of tubulin
(IC_{50} 25 μM)

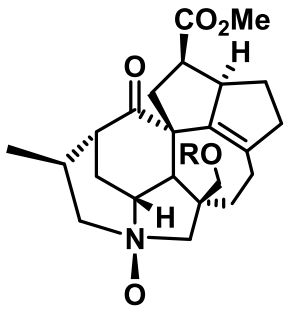
Kobayashi, J. *et al.*, *Tetrahedron Lett.*, **2004**, *45*, 901.



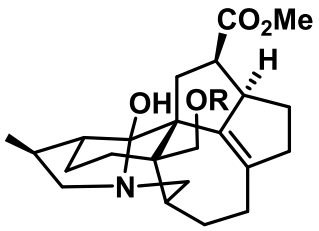
Daphniglaucin D



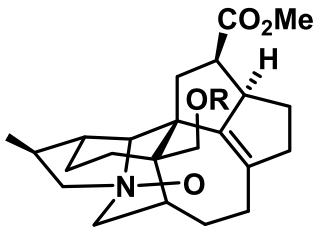
Daphniglaucin E: R=H
Daphniglaucin F: R=Ac



Daphniglaucin G: R=H
Daphniglaucin H: R=Ac



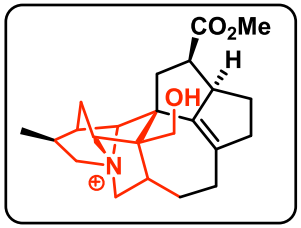
Daphniglaucin J R=Ac



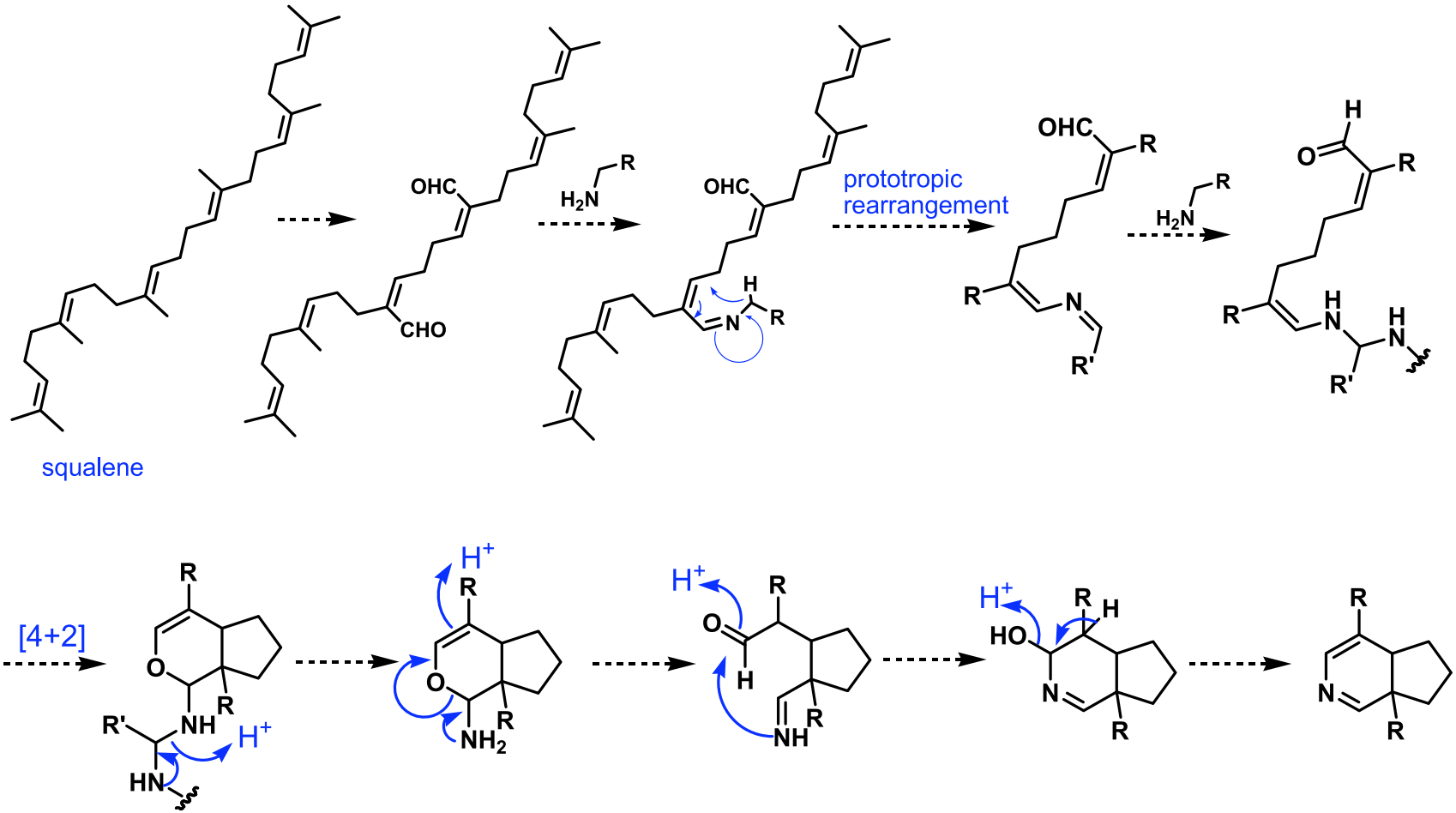
Daphniglaucin K R=Ac

Kobayashi, J. *et al.*, *Tetrahedron*, **2004**, *60*, 6279.

Proposed Biogenetic Pathway for Daphniglaucin A -1

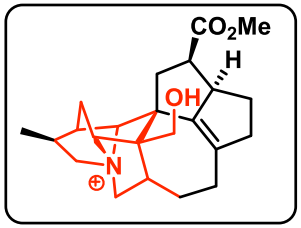


Daphniglaucin A

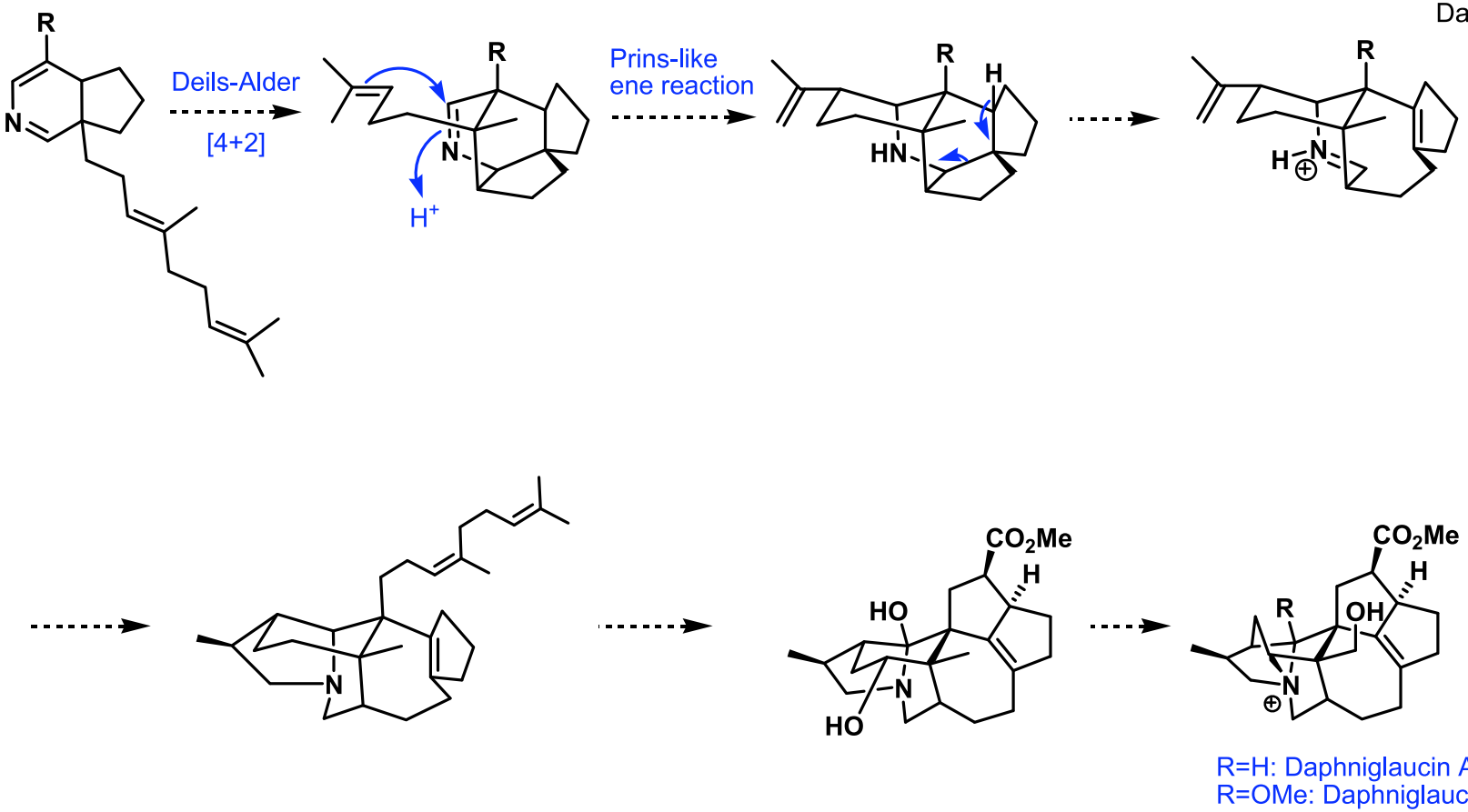


Heathcock, C. H., *et al., J. Am. Chem. Soc.* **1988**, *110*, 8734.
Heathcock, C. H., *et al., Proc. Natl. Acad. Sci. USA.* **1996**, *93*, 14323.

Proposed Biogenetic Pathway -2



Daphniglaucin A

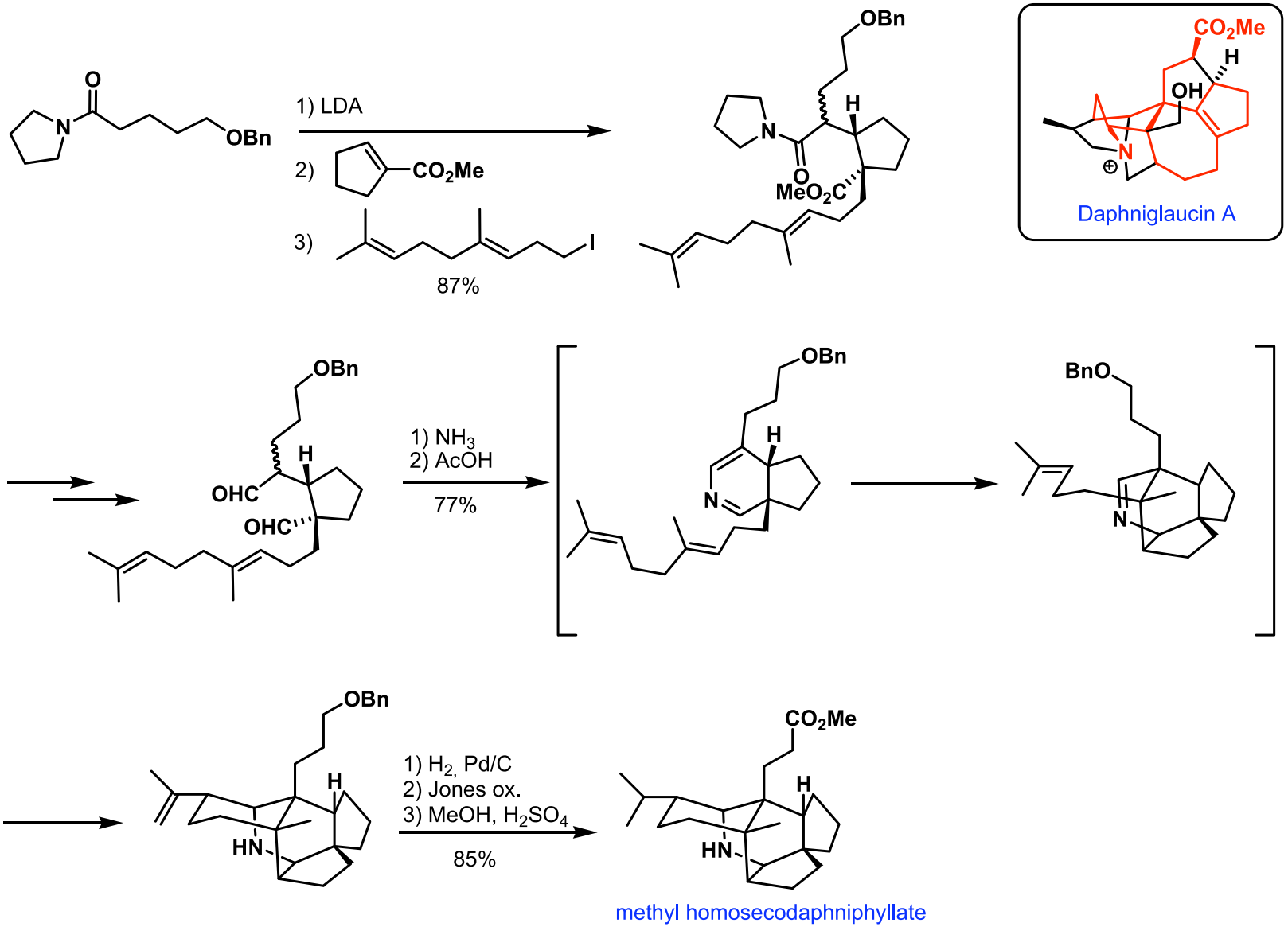


R=H: Daphniglaucin A
R=OMe: Daphniglaucin B

Heathcock, C. H., *Proc. Natl. Acad. Sci. USA.* **1996**, *93*, 14323.

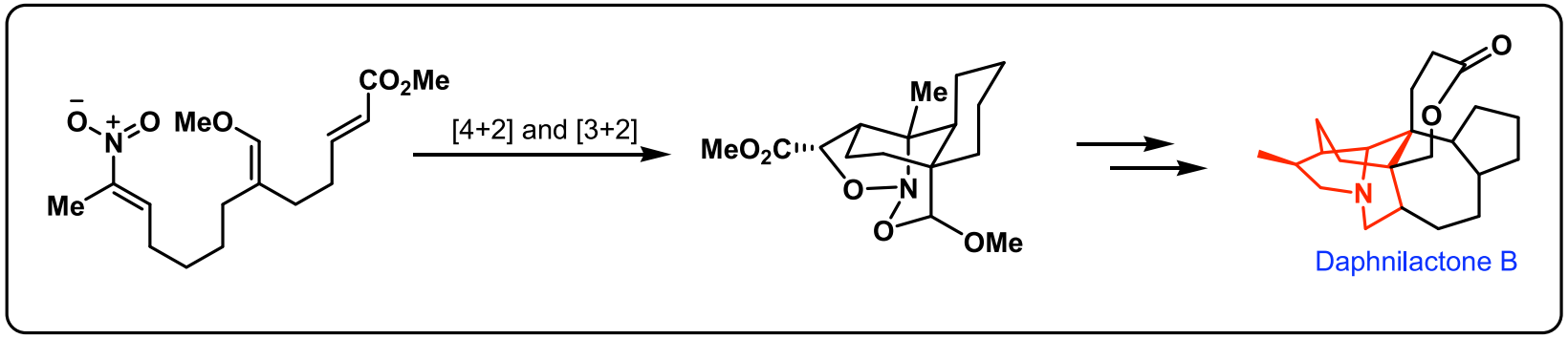
Kobayashi, J. *et al.*, *Org. Lett.*, **2003**, *5*, 1733.

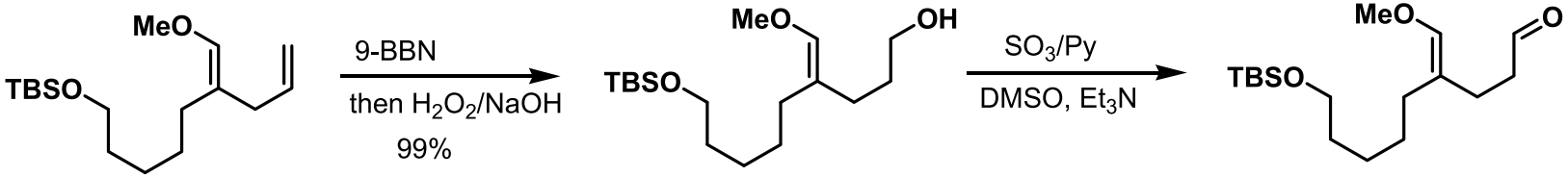
Total Synthesis of Methyl Homosecodaphniphyllate

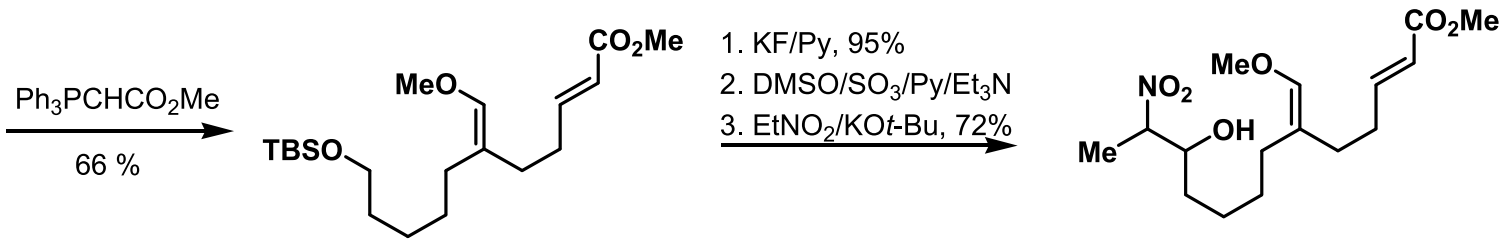


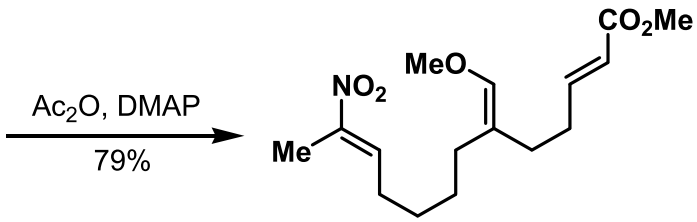
Heathcock, C. H., *et al.*, *J. Am. Chem. Soc.* **1988**, *110*, 8734.

Synthetic Study on Daphnilactone B



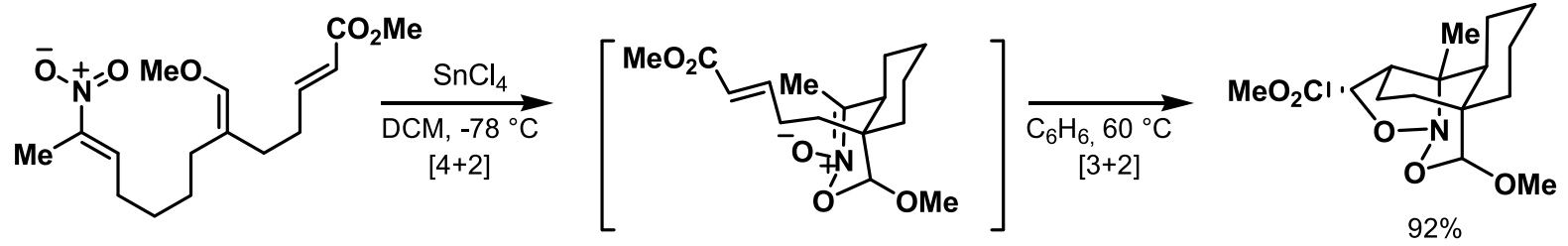


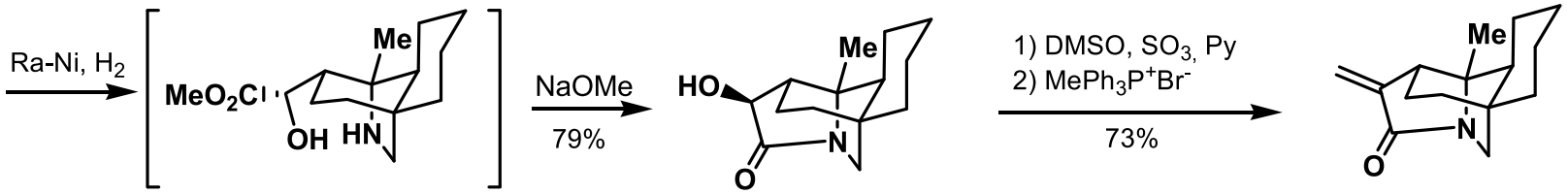


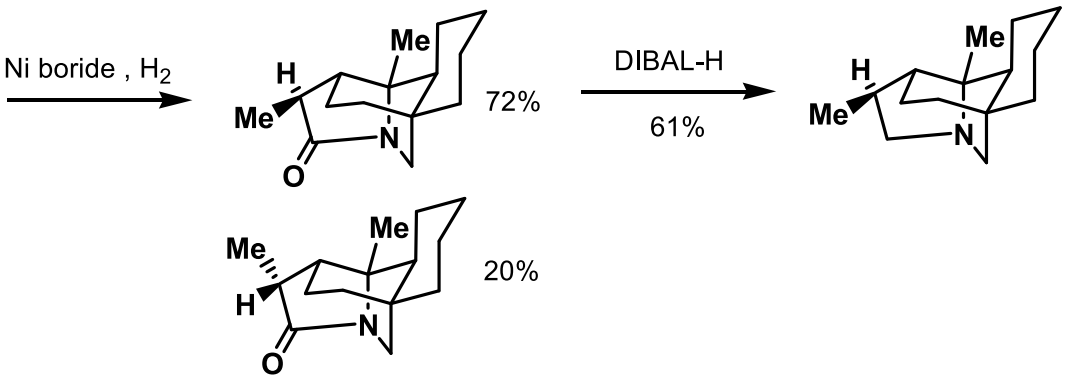


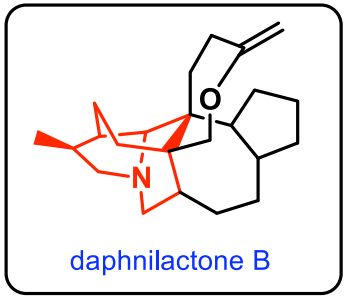
Denmark S. E., *et al.*, *J. Org. Chem.* **2006**, *71*, 593.

Synthetic Study on Daphnilactone B



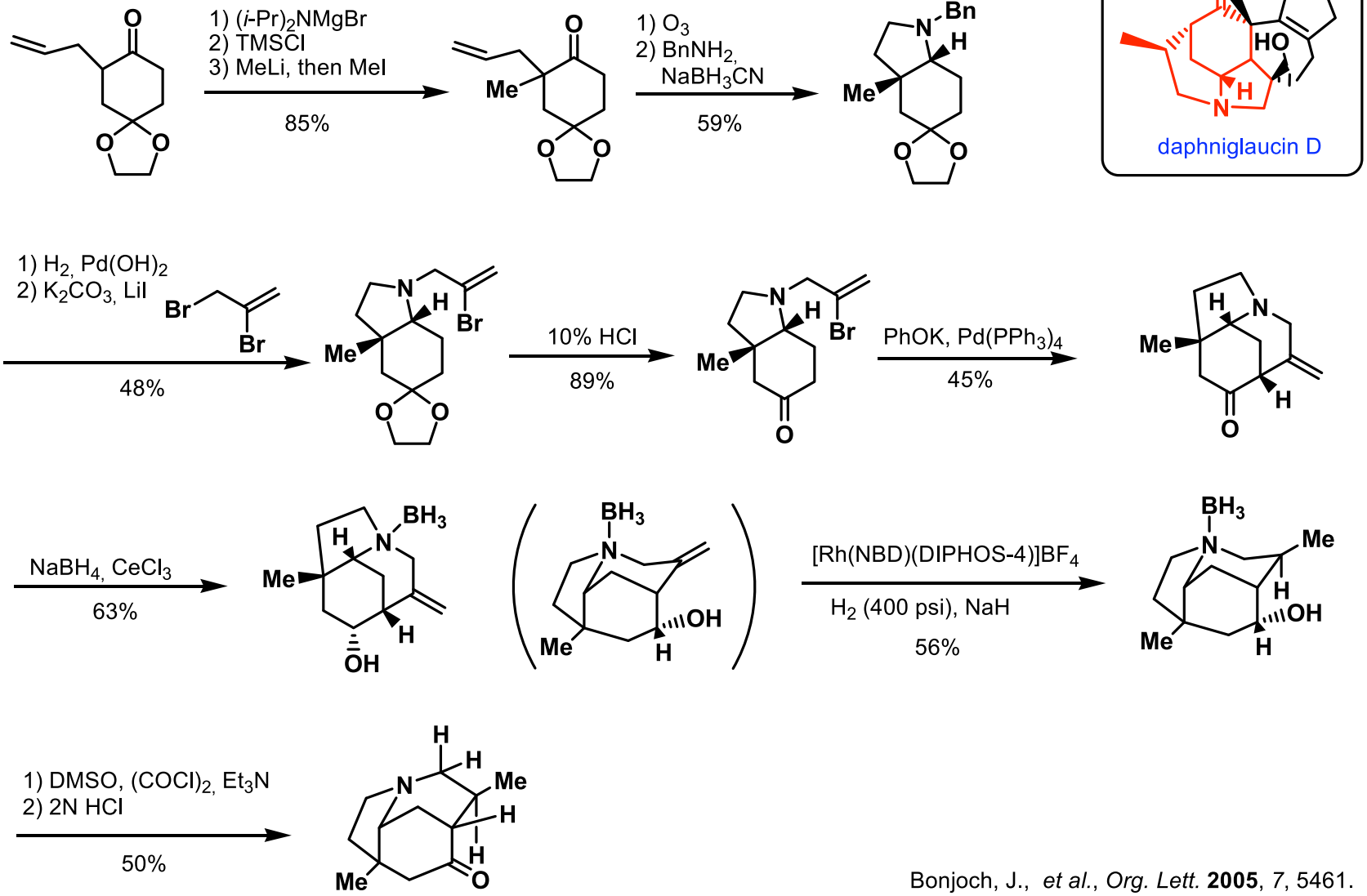






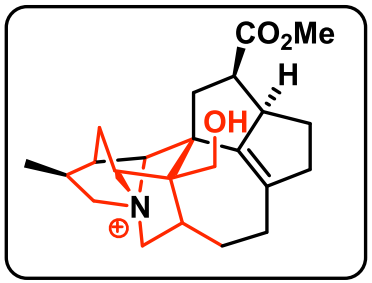
Denmark S. E., *et al.*, *J. Org. Chem.* **2006**, *71*, 593.

Synthetic Study on Daphniglaucin D

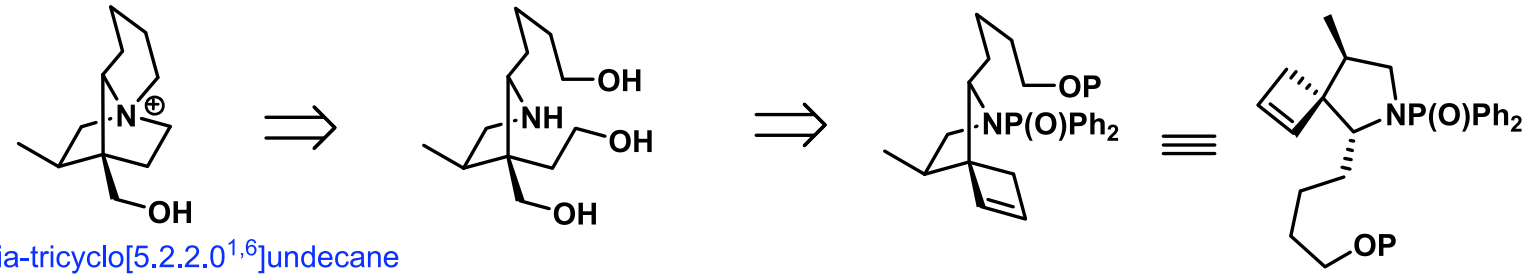


Bonjoch, J., *et al.*, *Org. Lett.* **2005**, *7*, 5461.

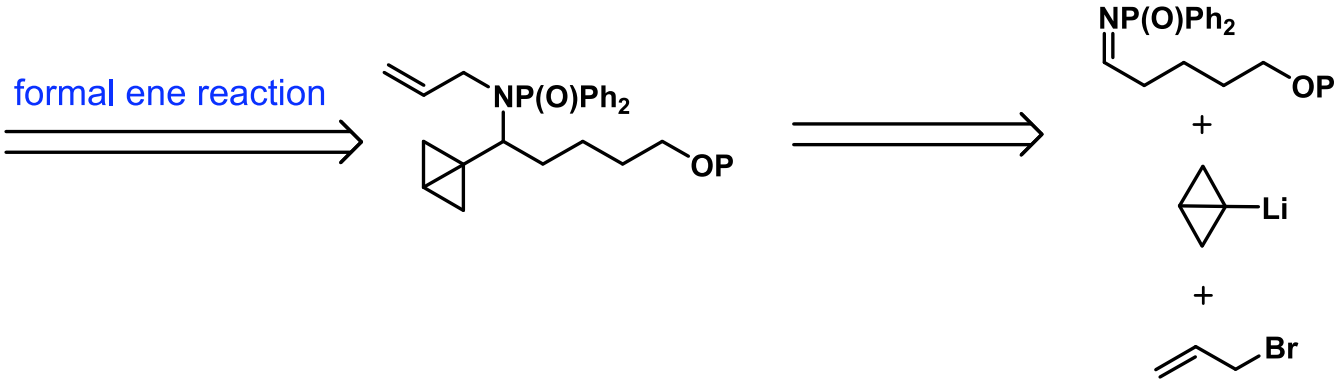
Masafumi's Work : Synthetic Strategy as a Model Study



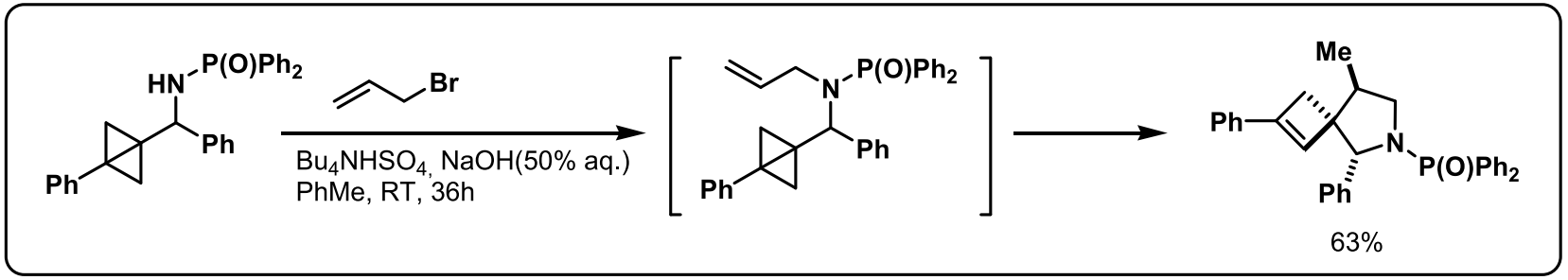
Daphniglaucin A

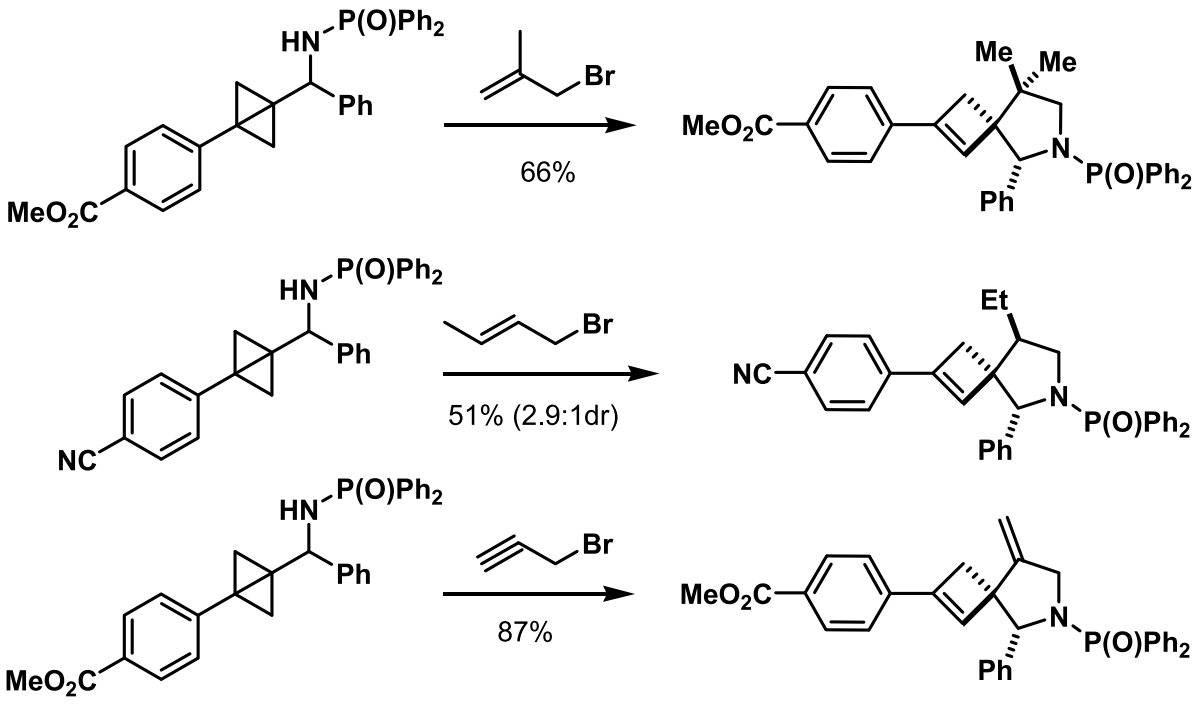


1-Azonia-tricyclo[5.2.2.0^{1,6}]undecane



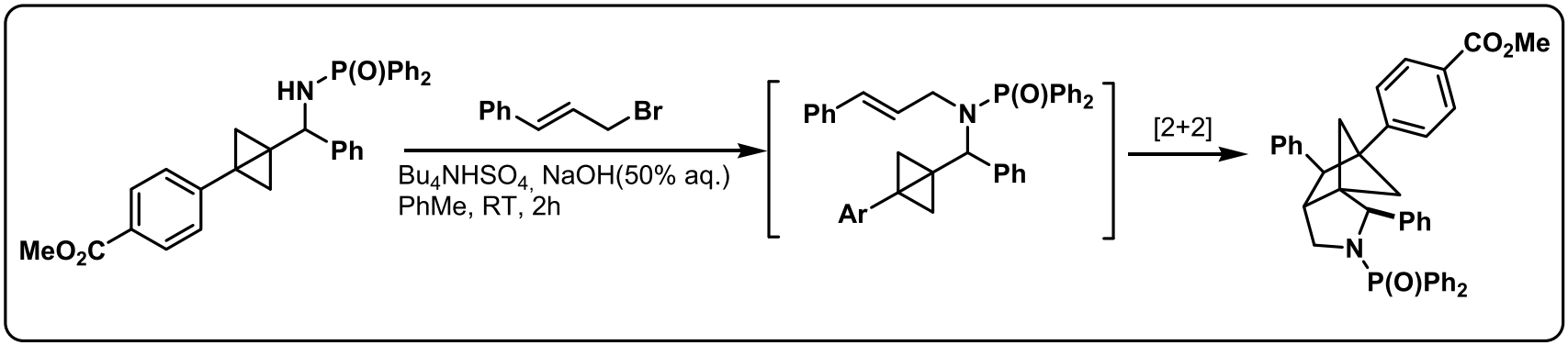
Pericyclic Cascade Reaction of (Bicyclo[1.1.0]Butylmethyl)Amine

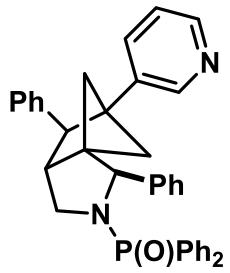




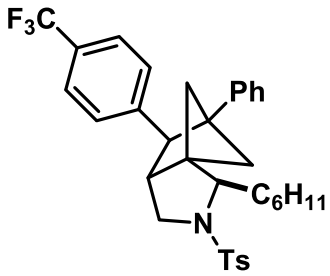
Wipf, P. and Walczak, M. A. A., *Angew Chem. Int. Ed.* **2006**, *45*, 4172.

Pericyclic Cascade Reaction of (Bicyclo[1.1.0]Butylmethyl)Amine

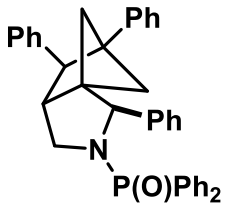




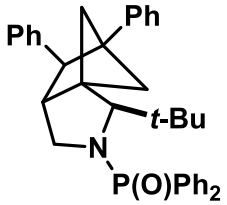
32%



68%



59%

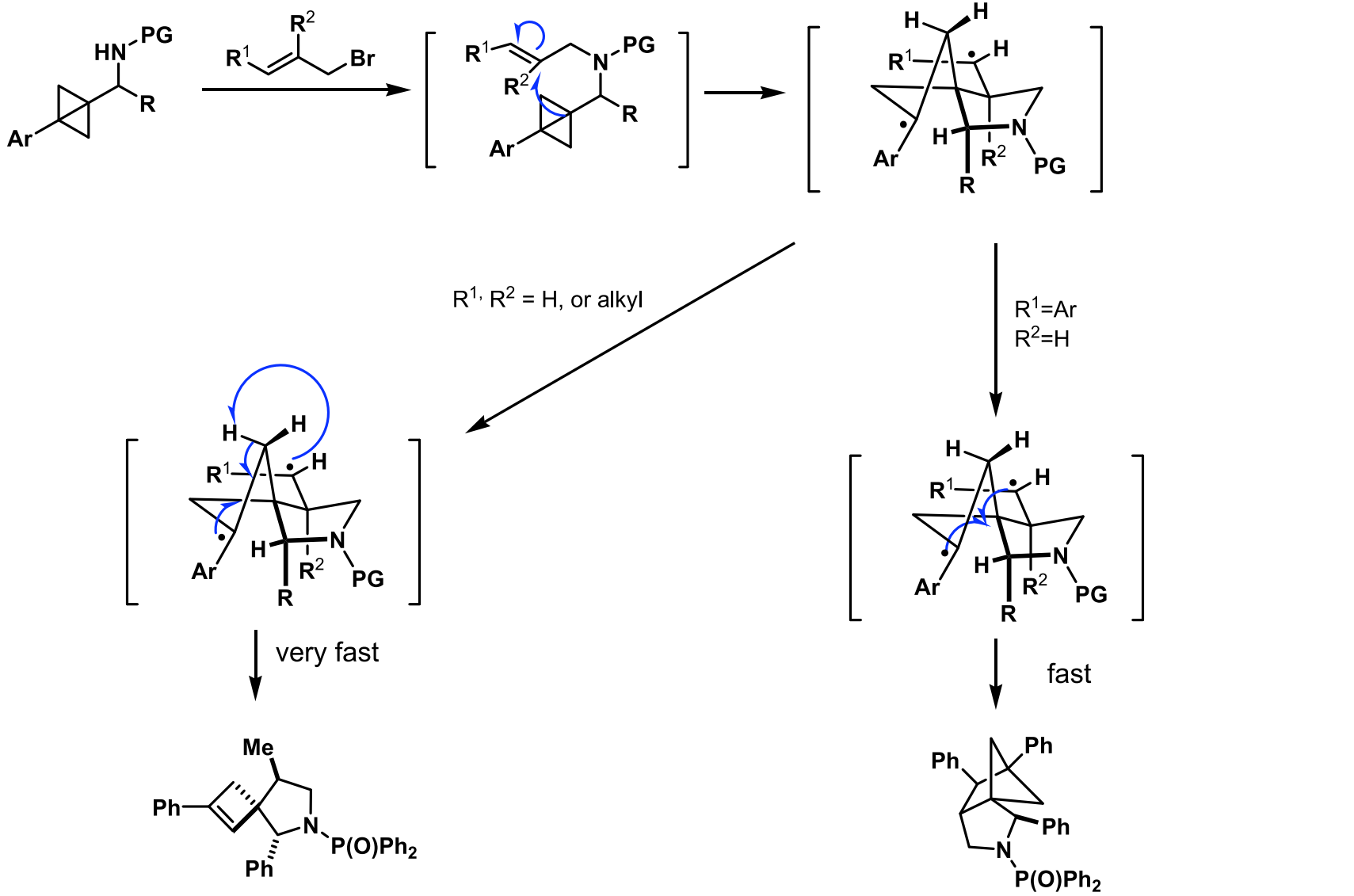


54%

First example of the synthesis of 3-azatricyclo[5.1.1.$0^{1,5}$] nonanes .

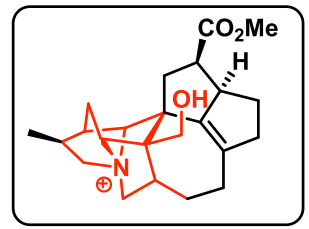
Wipf, P. and Walczak, M. A. A., *Angew Chem. Int. Ed.* **2006**, *45*, 4172.

Mechanistic Hypothesis

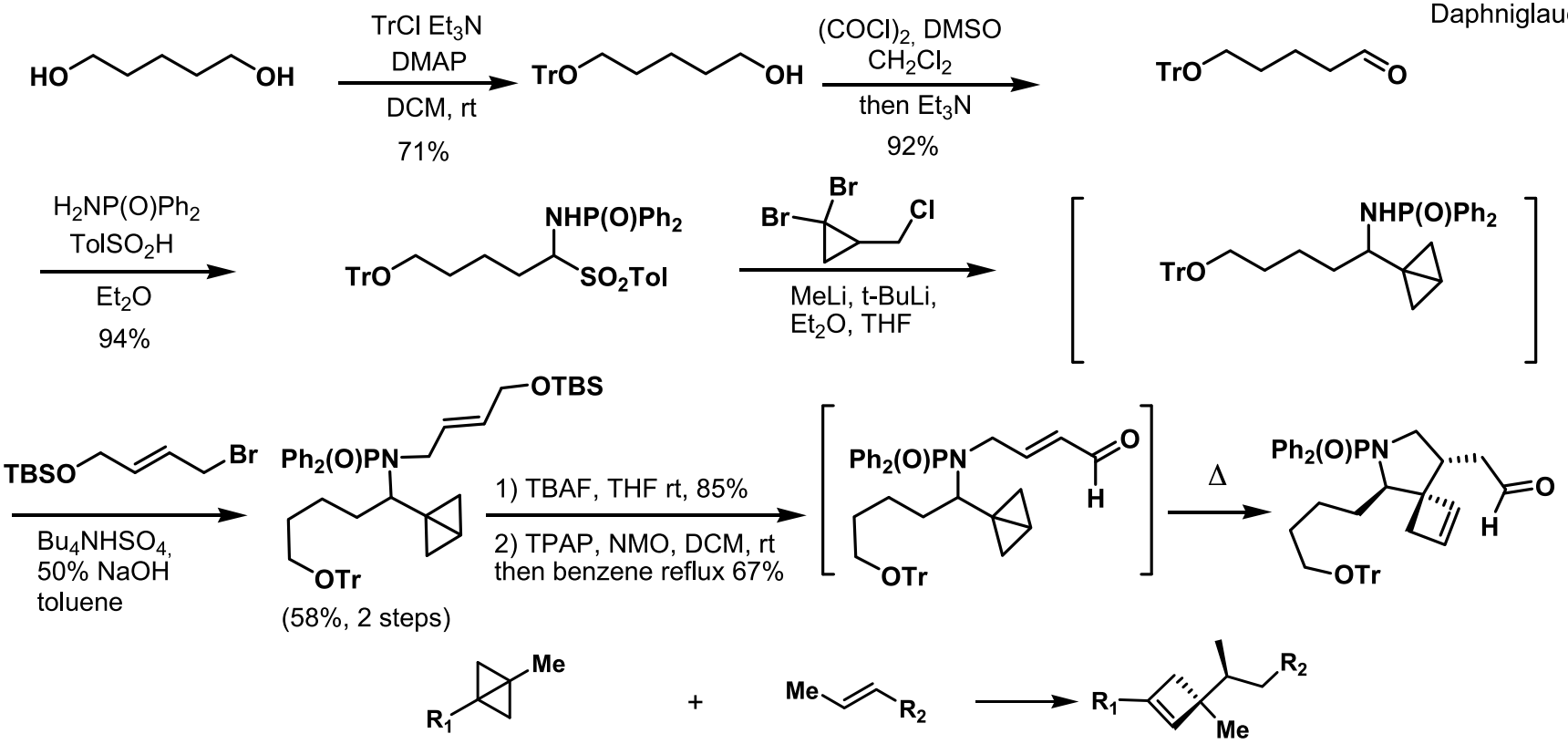


Wipf, P. and Walczak, M. A. A., *Angew Chem. Int. Ed.* **2006**, *45*, 4172.

Masafumi's work: First Approach to the Daphniglaucin Core

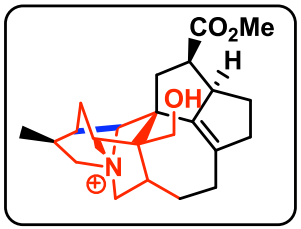


Daphniglaucin A

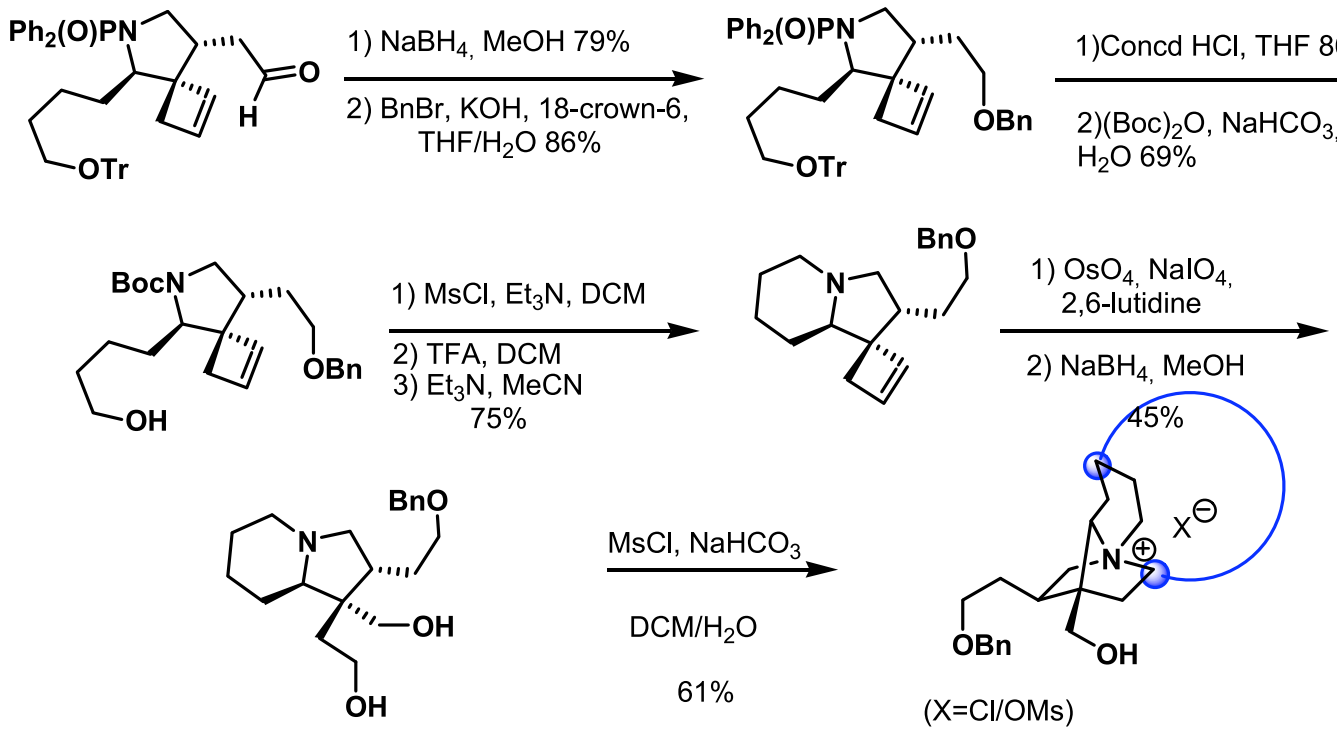


Entry	R_1	HOMO of bicyclobutane (eV)	R_2	LUMO of alkene (eV)	ΔE (LUMO-HOMO) (eV)
1	Ph	-7.95	H	5.25	13.20
2	H	-9.37	H	5.25	14.62
3	CHO	-9.73	H	5.25	14.98
4	H	-9.37	CHO	2.95	12.32
5	H	-9.37	$COOCH_3$	3.38	12.75

Masafumi's Work: Synthesis of The Quaternary Ammonium Core



Daphniglaucin A



18 steps:

2.4% overall yield

Ueda, M.; Walczak, M. A. A.; Wipf, P. *Tetrahedron Letters* **2008**, *49*, 5986

Highlights:

-successful application of the formal ene reaction with bicyclobutane

-first synthesis of the quaternary core of the Daphniglaucin A

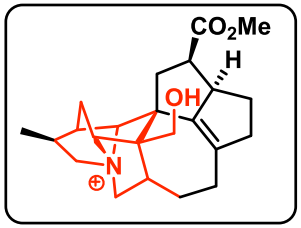
Problems:

-high number of steps

-Not the real structure of the core of the Daphniglaucin A

-improvement in the ene reaction could be done.

Acknowledgment



Daphniglaucin A

- Prof. Peter Wipf
- Maciej Walczak
- Dr. Rob Lettan
- Dr. Masafumi Ueda
- Wipf group members