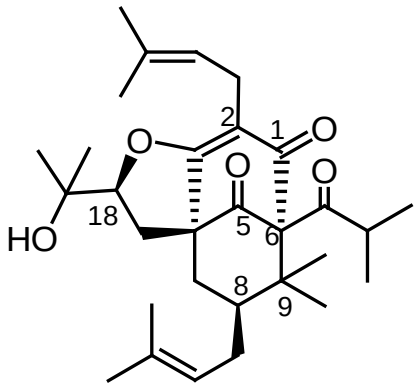
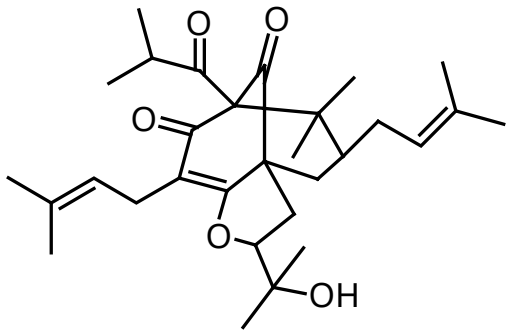
Approaches Towards and Synthesis of Garsubellin A





Jeff Kallemeyn

2/28/06

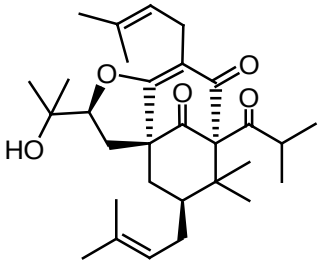
Isolation and Assignment

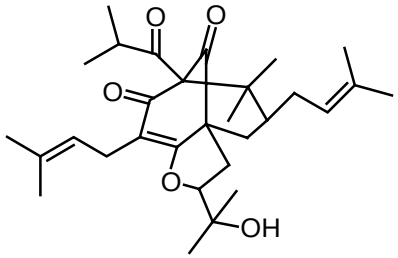
Isolated in 1997 by Fukuyama (Tokushima, Japan) from the wood of Garcinia subelliptica

http://www.tawey.com/product.php?mode=show&cid=6&pid=36

http://biotech.tipo.gov.tw/plantjpg/1/Garcinia%20subelliptica-1.jpg

Obtained 80.5 mg from the CH_2Cl_2 soluble portion (2.6g)





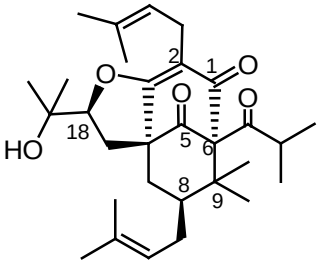
$C_{30}H_{44}O_5$
$[\alpha]_D^{20} = -21.3^o$

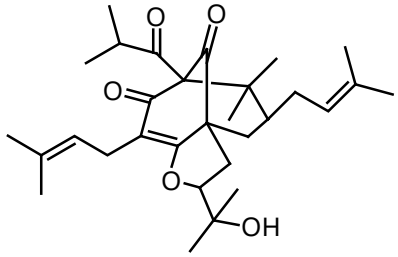
Increases ChAT activity by 154% (Alzheimer's)

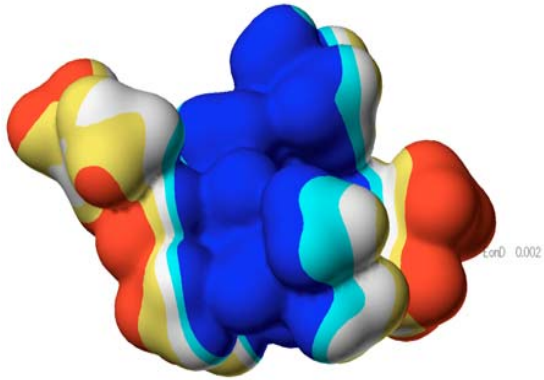
Highly substituted and oxygenated central [3.3.1] nonanone core

Fukuyama et al. Chem. Pharm. Bull. **1997**, *45*, 947-949.

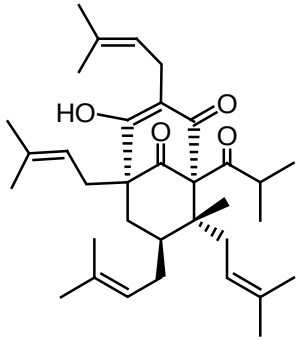
Isolation and Assignment



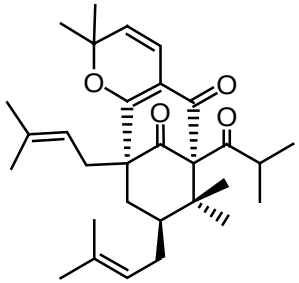




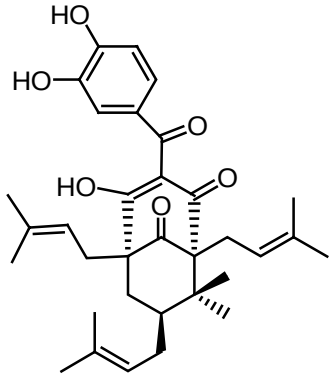
Structure and relative stereochemistry assigned by NMR studies.
Absolute configuration not known. 2 total syntheses, Shibasaki (2005) Danishefsky (2006). Both racemic.
Some freedom as to which antipode is drawn. Drawn in this presentation as shown above.
Can analogy be drawn to other molecules of similar structure?



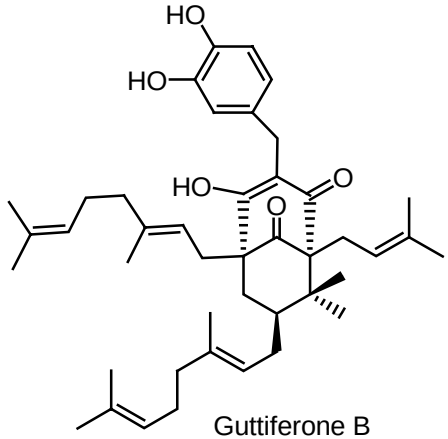
Hyperforin



Paupaforin A



Aristophenone A



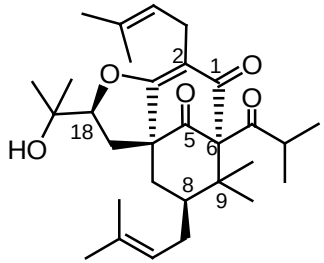
Guttiferone B

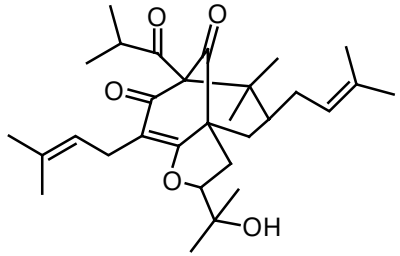
Hyperforin: Anti-depressant found in St. John's Wort

X-ray of p-Bromo benzoate in 1983 showed absolute configuration

Acta. Chem. Scand. A. **1983**, 263.

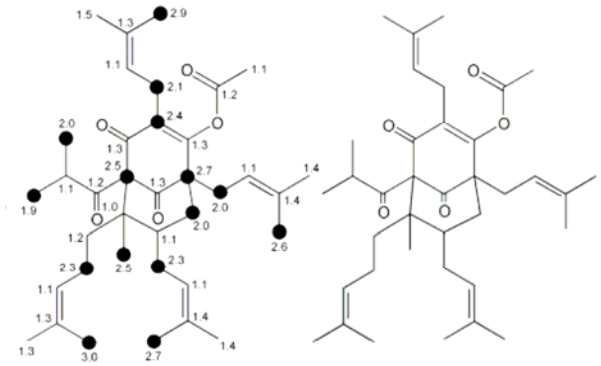
Retrosynthetic Analysis: Construction of the Core





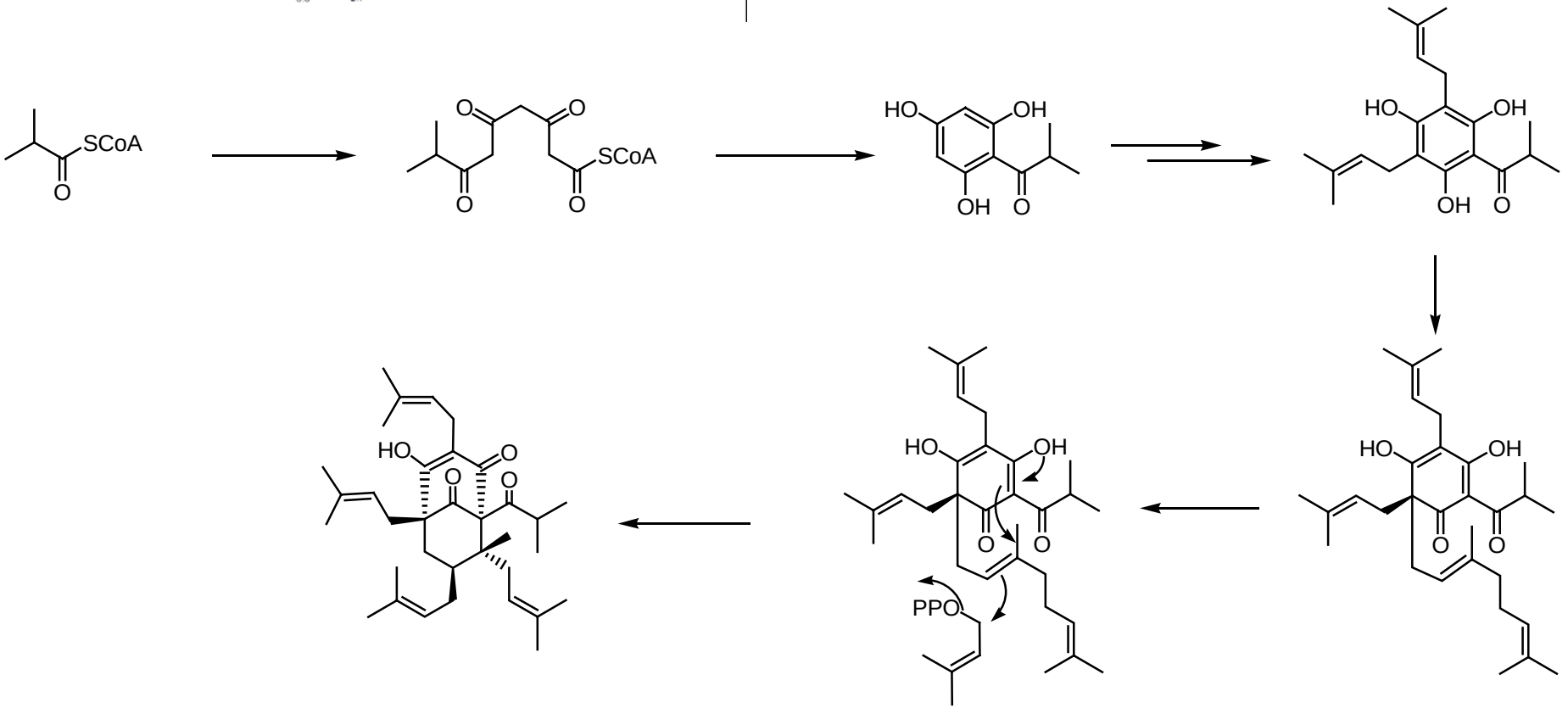
Briefly, brainstorm a disconnection which may be used to construct the [3.3.1] nonanone

Biosynthesis of Hyperforin: Analogous to Garsubellin A?



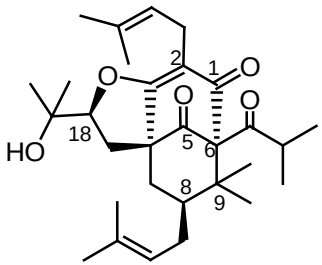
Feeding studies with ^{13}C glucose

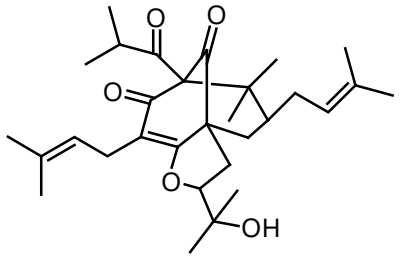
incorporation of 5 isoprenoid groups



Eisenreich et al, *J. Med. Chem.* **2002,** *45,* 4786-4793

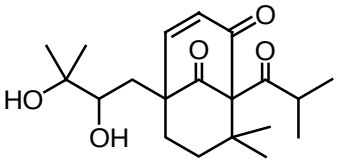
Two Different Approaches to Construct the Core of Garsubellin A

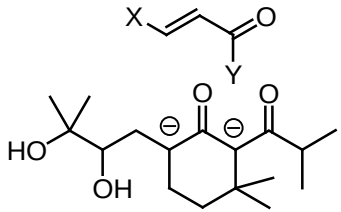


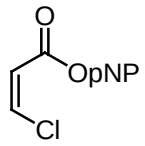


In the synthetic work, 2 major approaches to the core stand out.

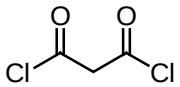
1. Formation of the B ring by annulation



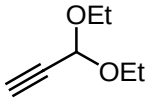




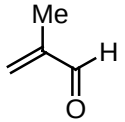
Shibasaki



Stoltz

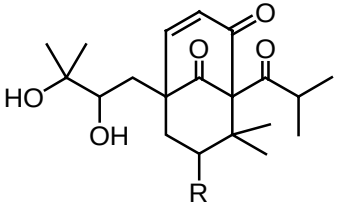


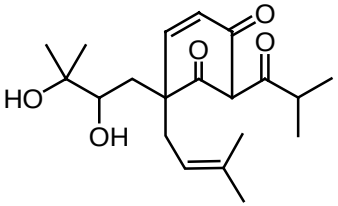
Grossman



Nicalaou

2. Formation of the A ring by electrophilic cyclization





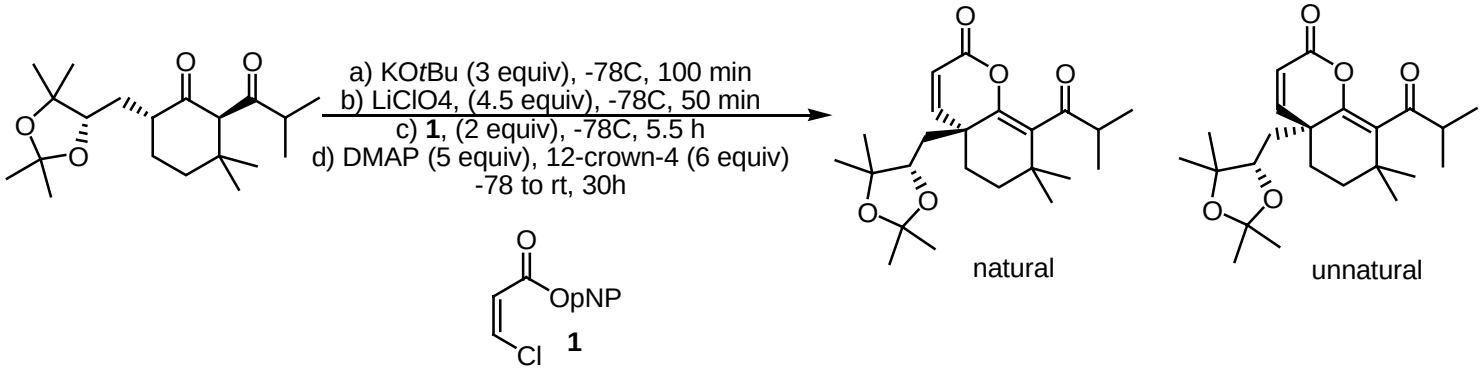
R = PhSe

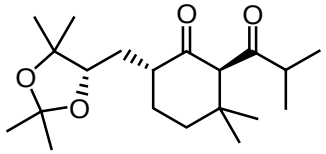
Nicolaou

R = I

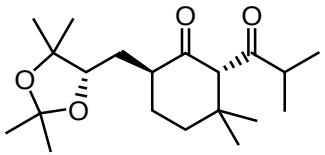
Danishefsky

Shibasaki's Model Study

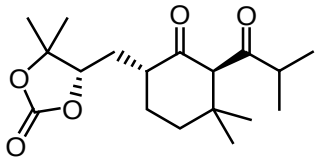




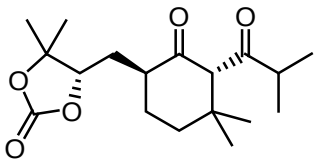
76% yield
1:25 (natural:unnatural)



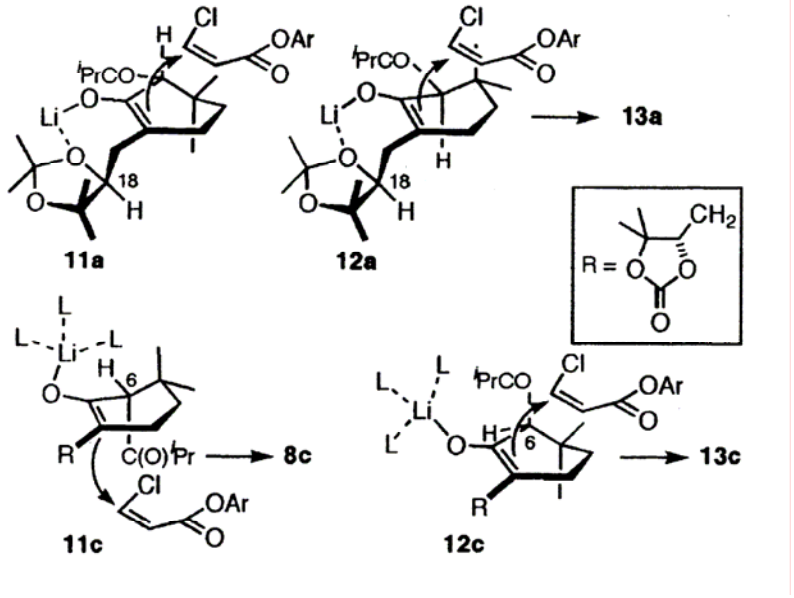
63% yield
1:5 (natural:unnatural)



70% yield
4:1 (natural:unnatural)

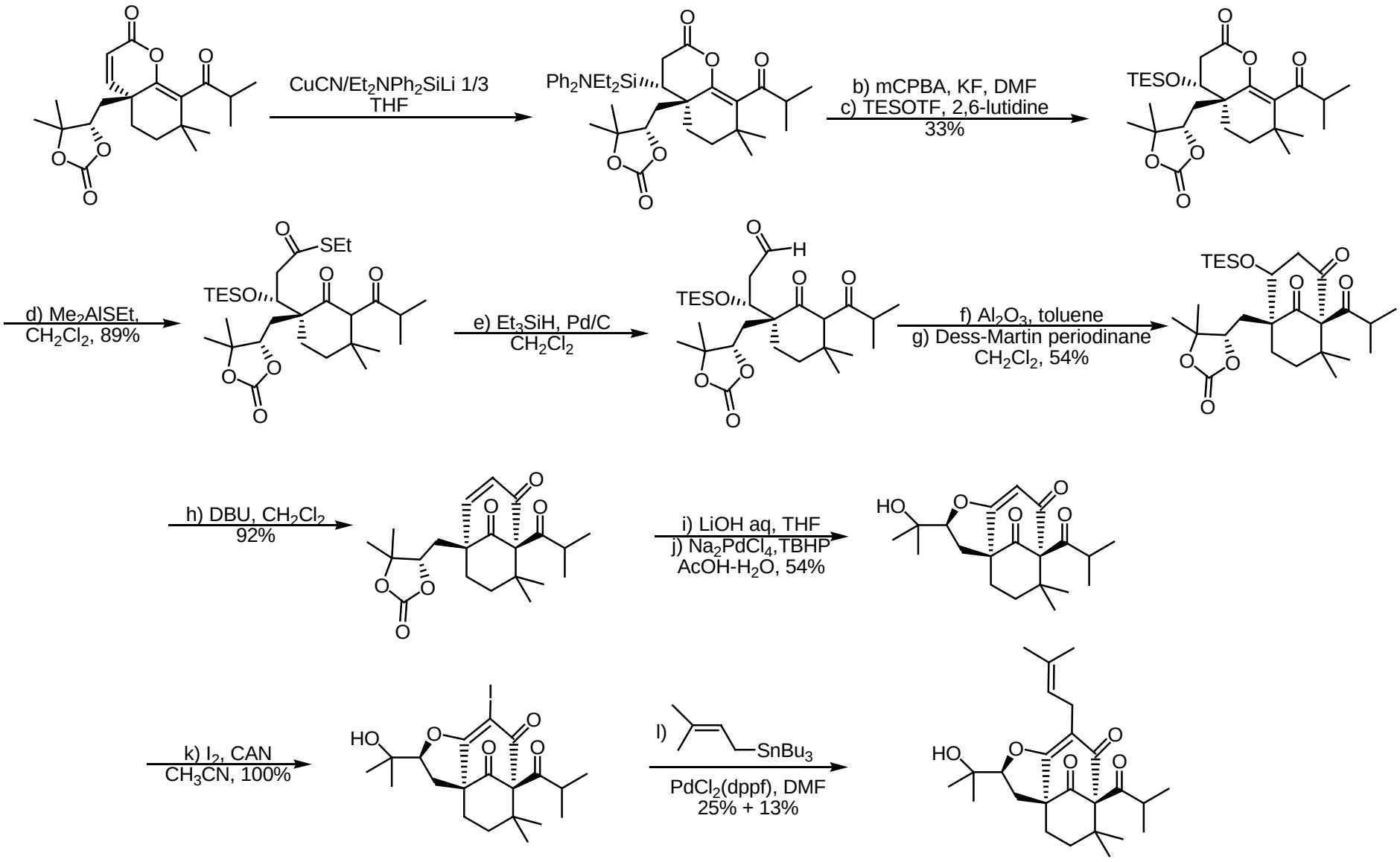


50% yield
1:2.6 (natural:unnatural)



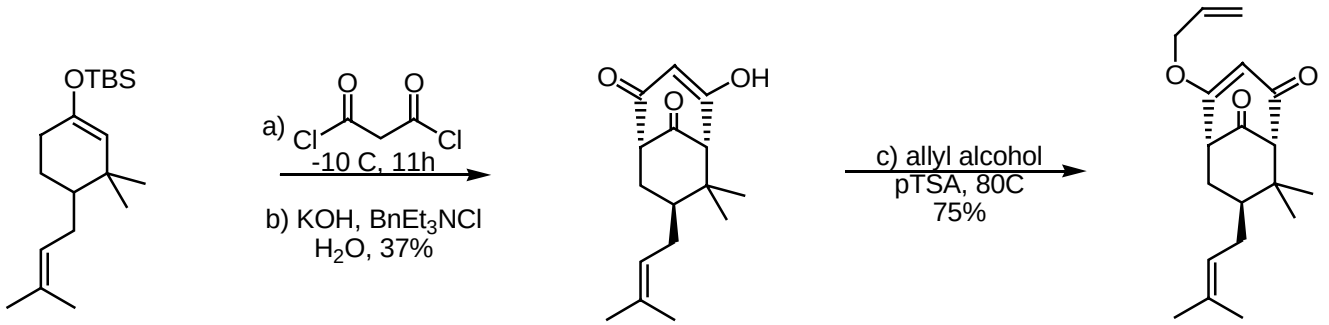
Org.Lett. **2002**, 859.
Tetrahedron Lett, **2002**, 3621.

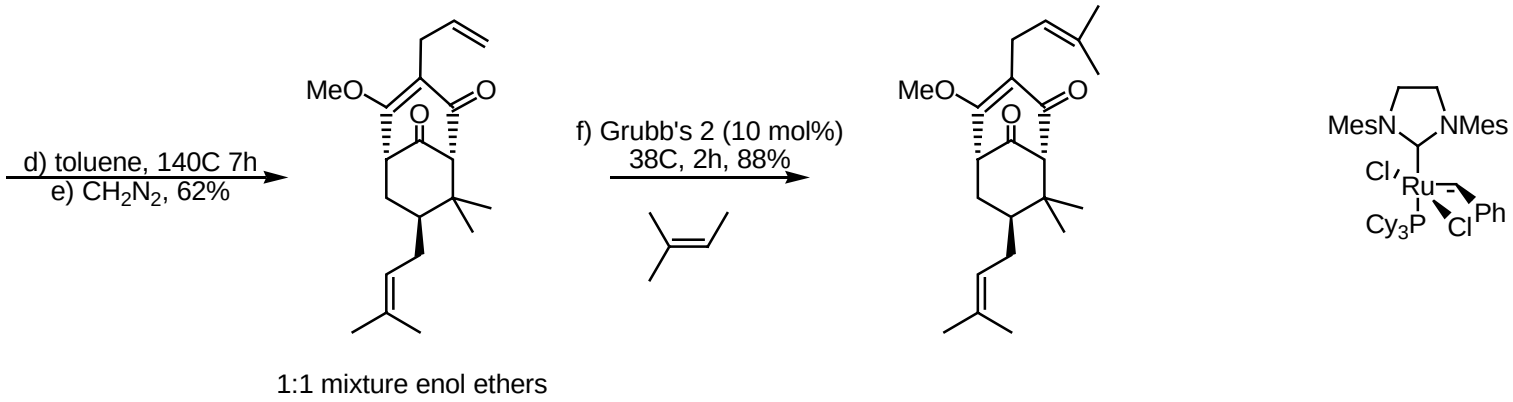
Shibasaki's Model Study



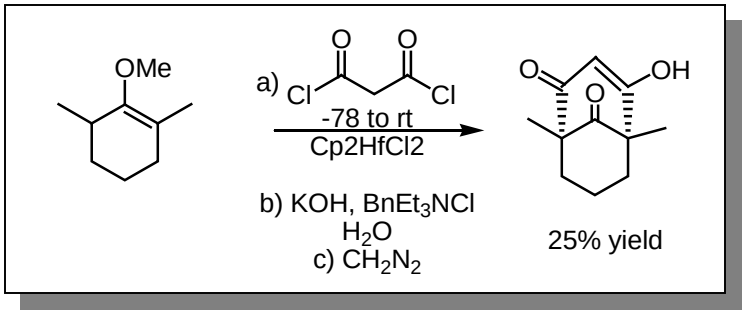
Org.Lett. **2002**, 859.
Tetrahedron Lett, **2002**, 3621.

Other Annulation Approaches: Stoltz



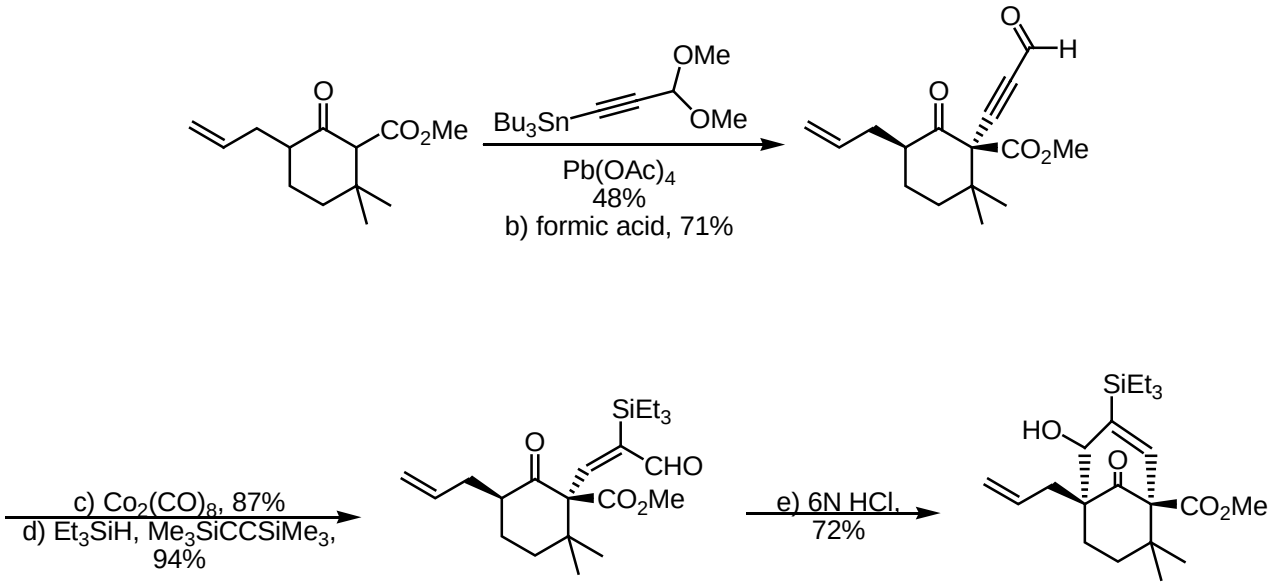


1:1 mixture enol ethers



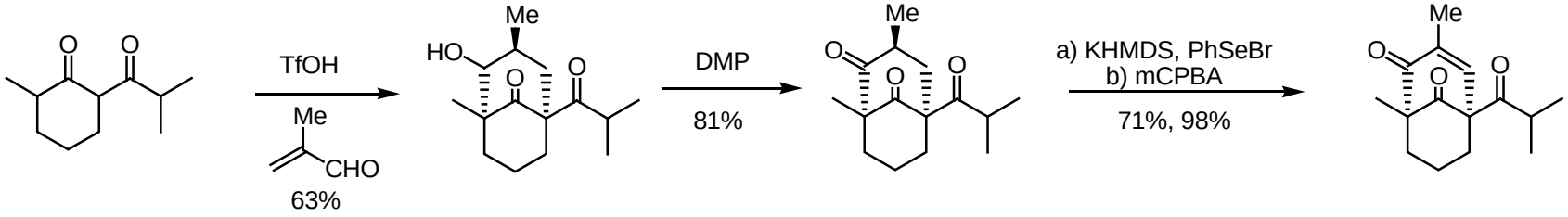
Org.Lett. **2002**, 1943.

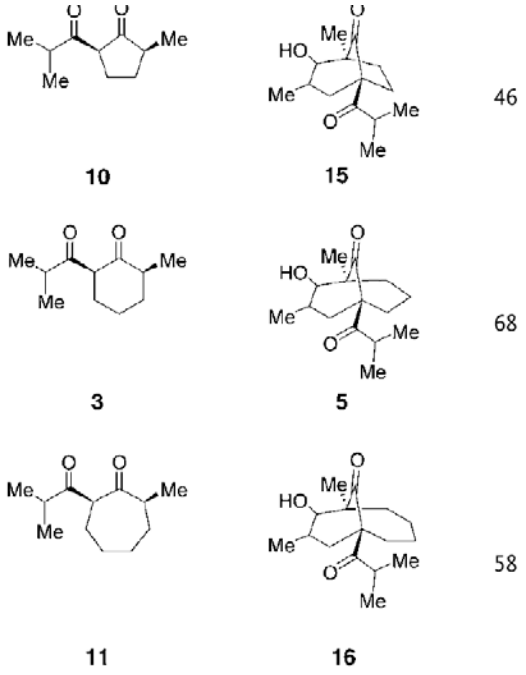
Other Annulation Approaches: Grossman

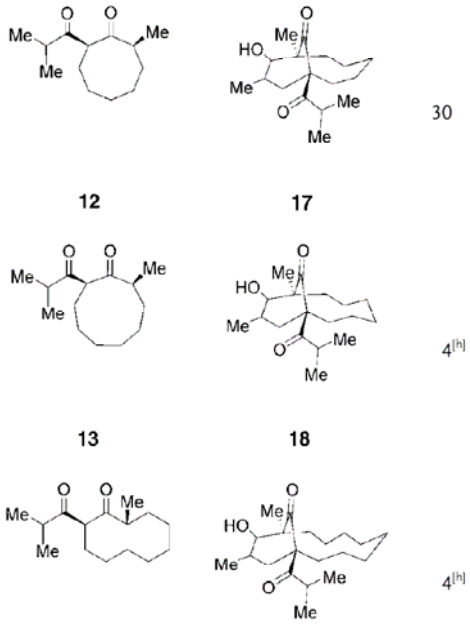


Org.Lett. **2003**, 4619.

Other Annulation Approaches: Nicolaou

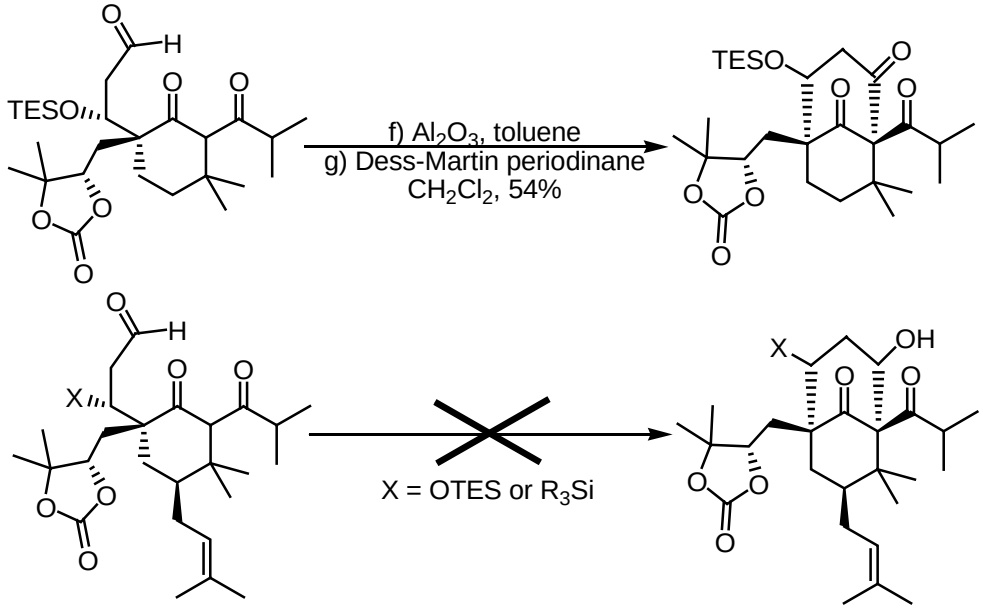






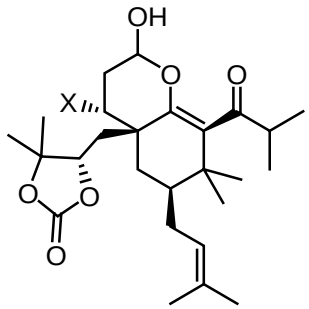
Angew. Chem. Int. Ed. **2005**, 3895

Shibasaki: Back to the Drawing Board



"the desired cyclization did not proceed, possibly due to the destabilization of the reactive conformation for this cyclization by the prenyl group."

Cache calculations: Very little difference between the systems.
Minor changes to bond lengths and dihedral angles in "transition structures"

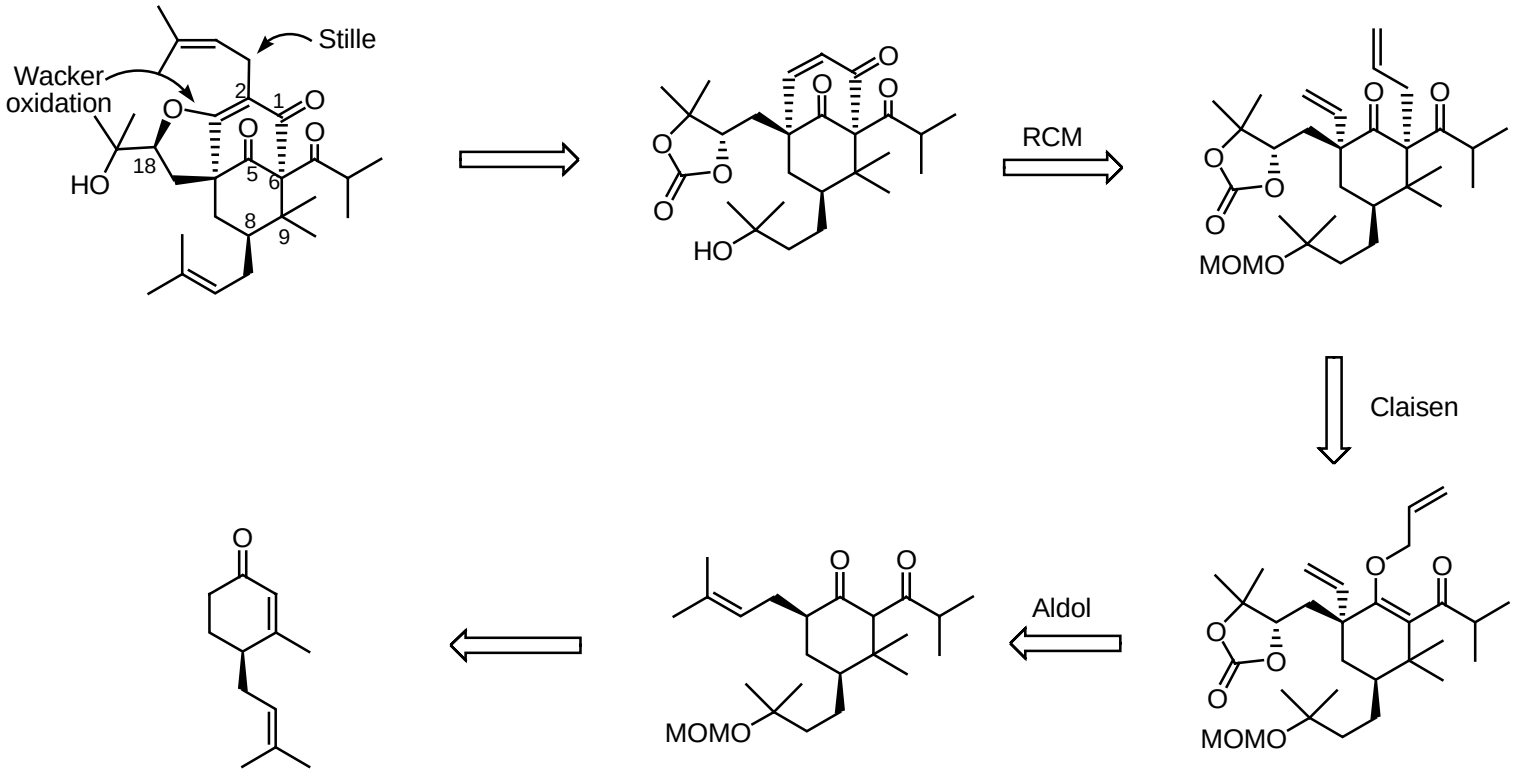


One possible problem may be formation of acetal
(pure speculation on my part)

J. Am. Chem. Soc.. **2005**, 14200.

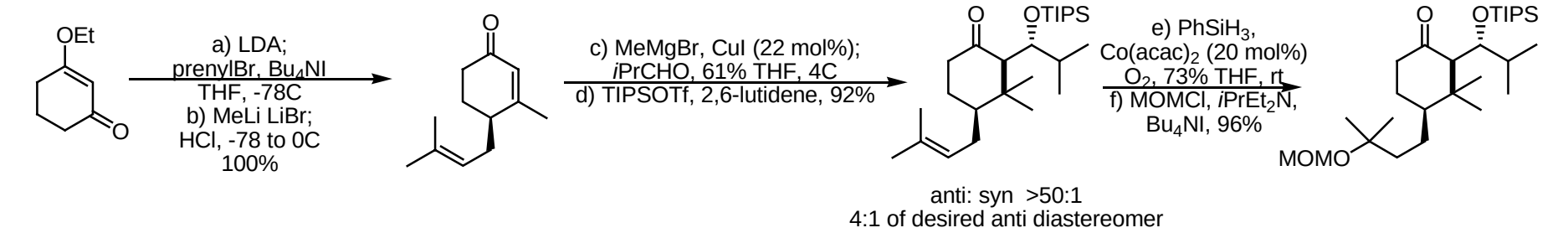
Shibasaki: Back to the Drawing Board

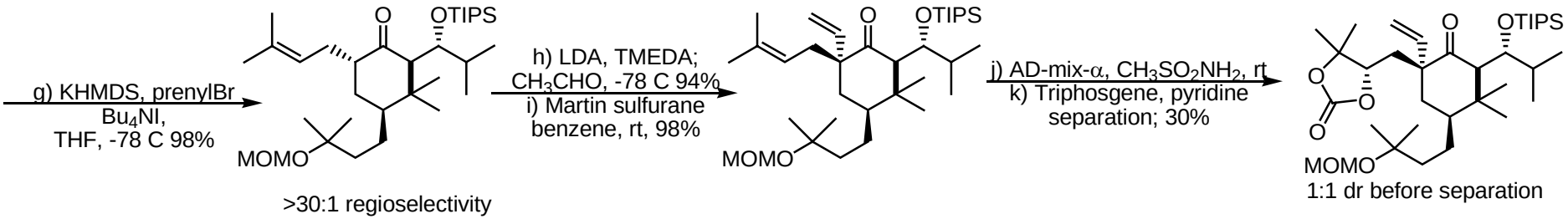
What did he learn from the model study?

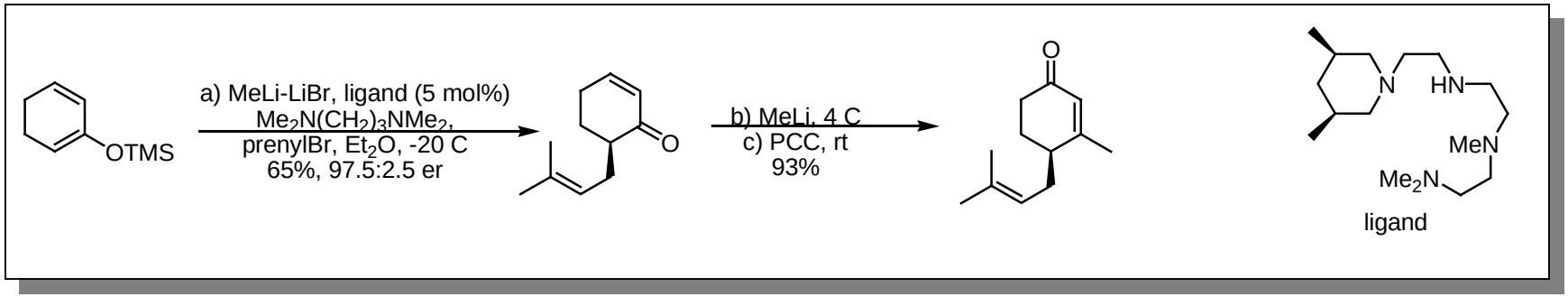


J. Am. Chem. Soc.. **2005**, 14200.

Shibasaki: First Total Synthesis of Garsubellin A

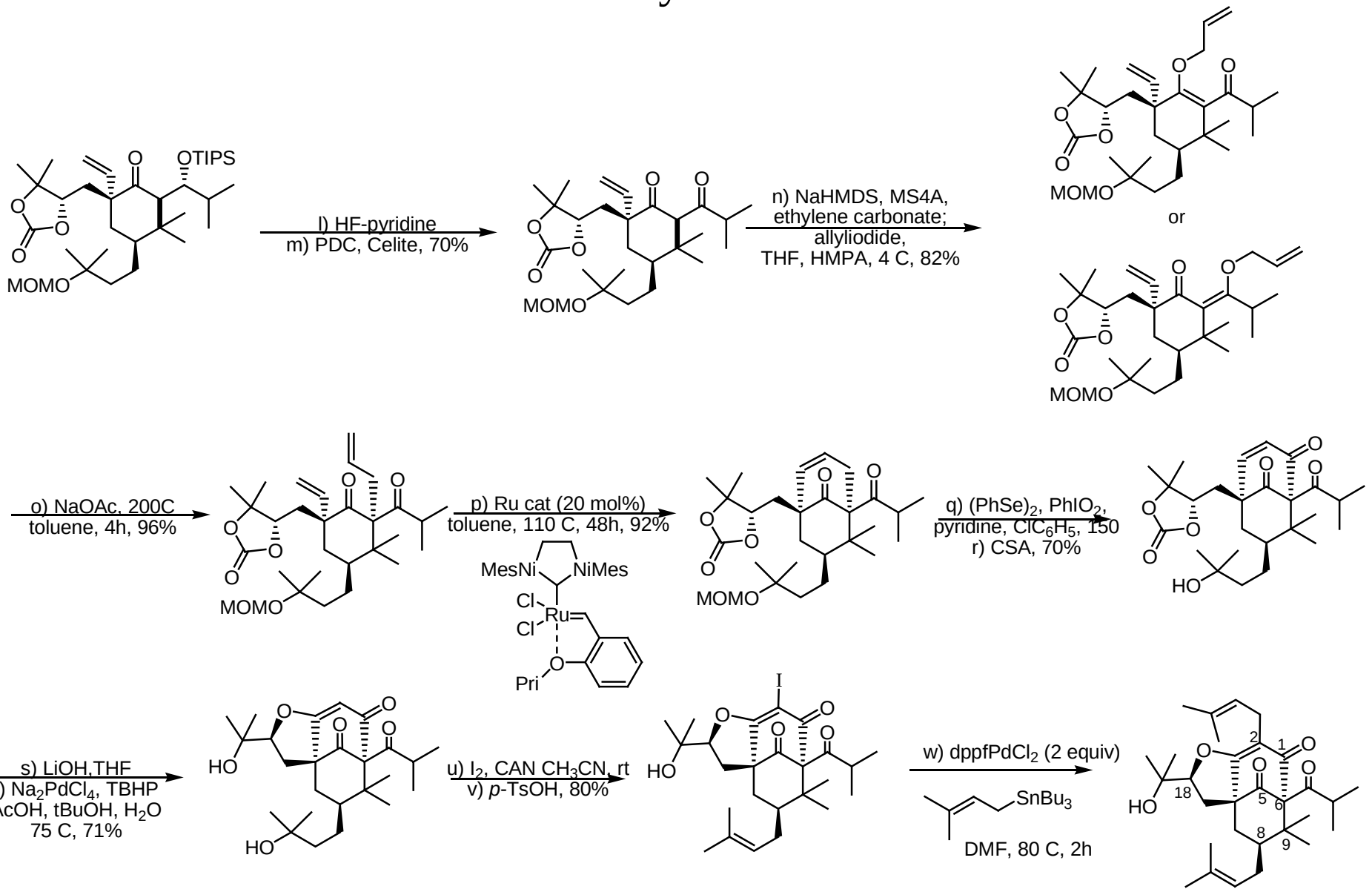






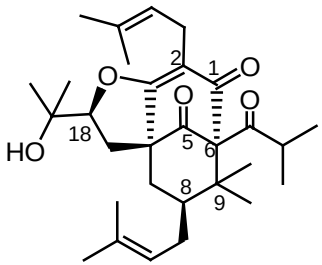
J. Am. Chem. Soc.. **2005**, 14200.

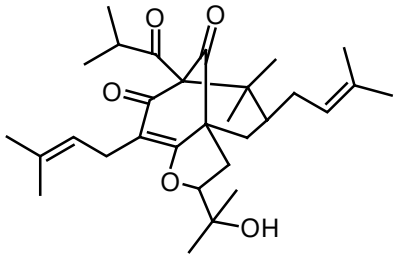
Shibasaki: First Total Synthesis of Garsubellin A



J. Am. Chem. Soc.. **2005**, 14200.

Two Different Approaches to Construct the Core of Garsubellin A





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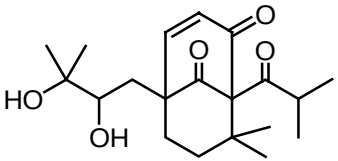
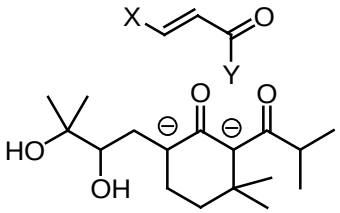
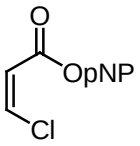
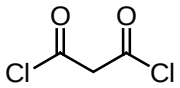


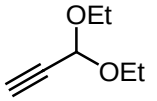




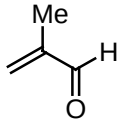
Shibasaki



Stoltz

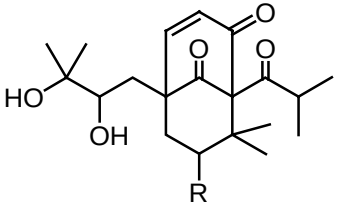


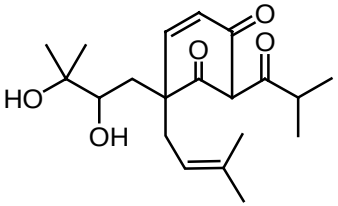
Grossman



Nicalaou

2. Formation of the A ring by electrophilic cyclization





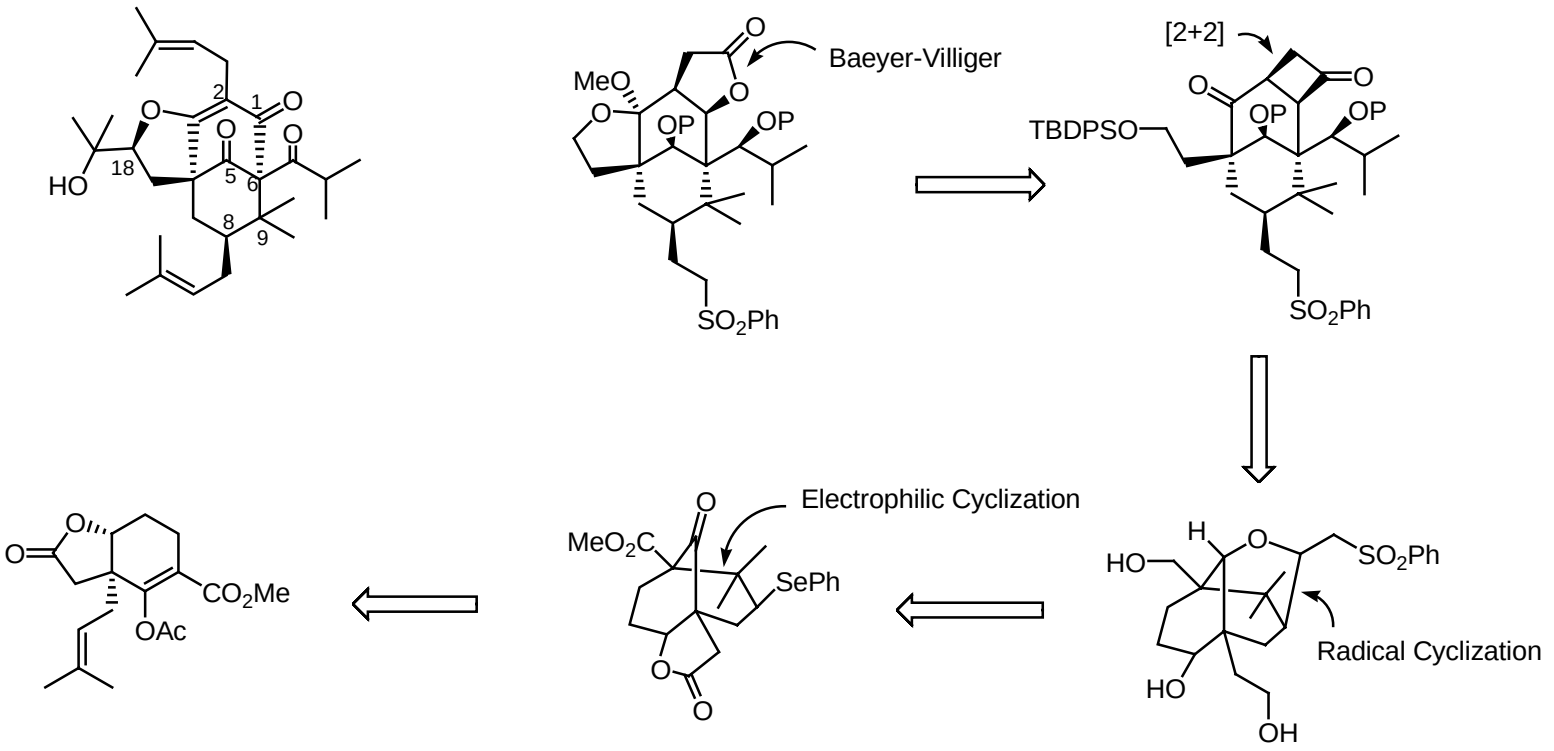
R = PhSe

Nicolaou

R = I

Danishefsky

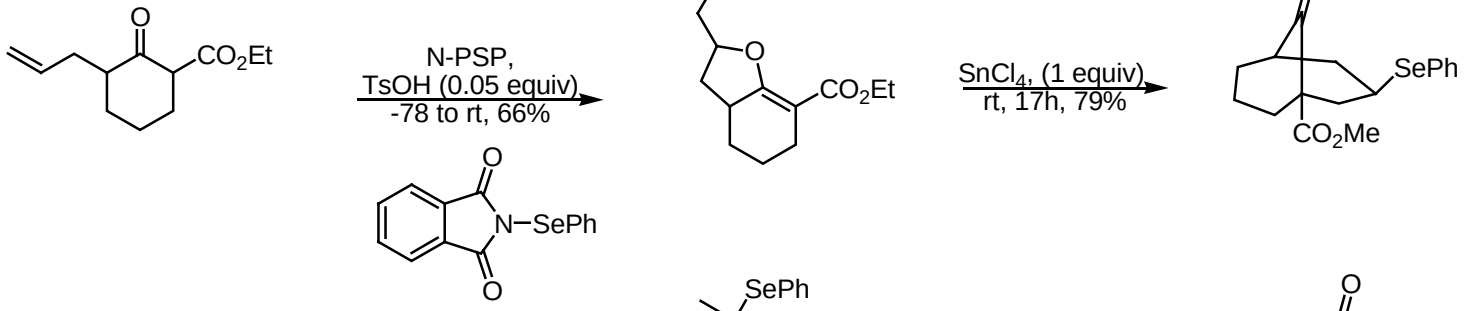
Nicolaou's Model Retrosynthesis



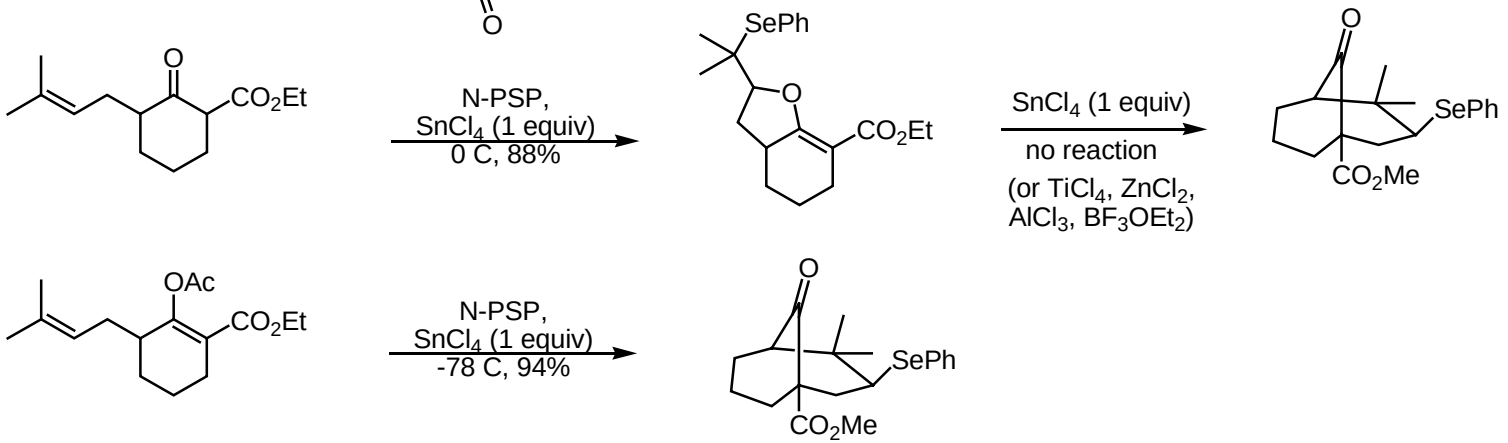
J. Am. Chem. Soc.. **1999**, 4724.

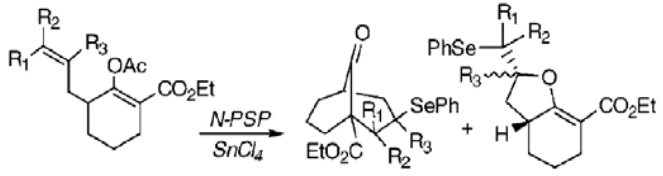
Selenium Cyclization

Ley's studies



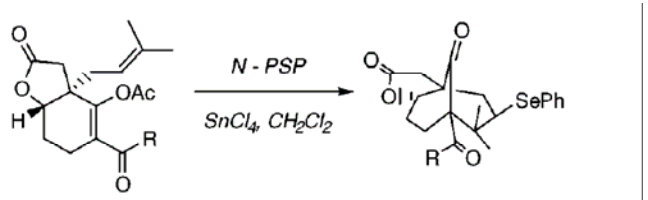
Nicolaou's studies





substrate	R_1	R_2	R_3	*C*-Cyclized (%) [b]	*O*-Cyclized (%) [b]
25	H	H	H	0	91 [c]
26	H	Me	H	45	41 [c]
12	Me	Me	H	94	0
27	H	H	Me	0	64 [c]
28	H	Me	Me	0	89
29	Me	Me	Me	0	86

[a] Reaction conditions: 1.1 equiv of *N*-PSP, 1.0 equiv of $SnCl_4$, CH_2Cl_2, −23 °C, 15 min. [b] Isolated yield after purification unless otherwise noted. [c] Yield as a mixture of stereoisomers.

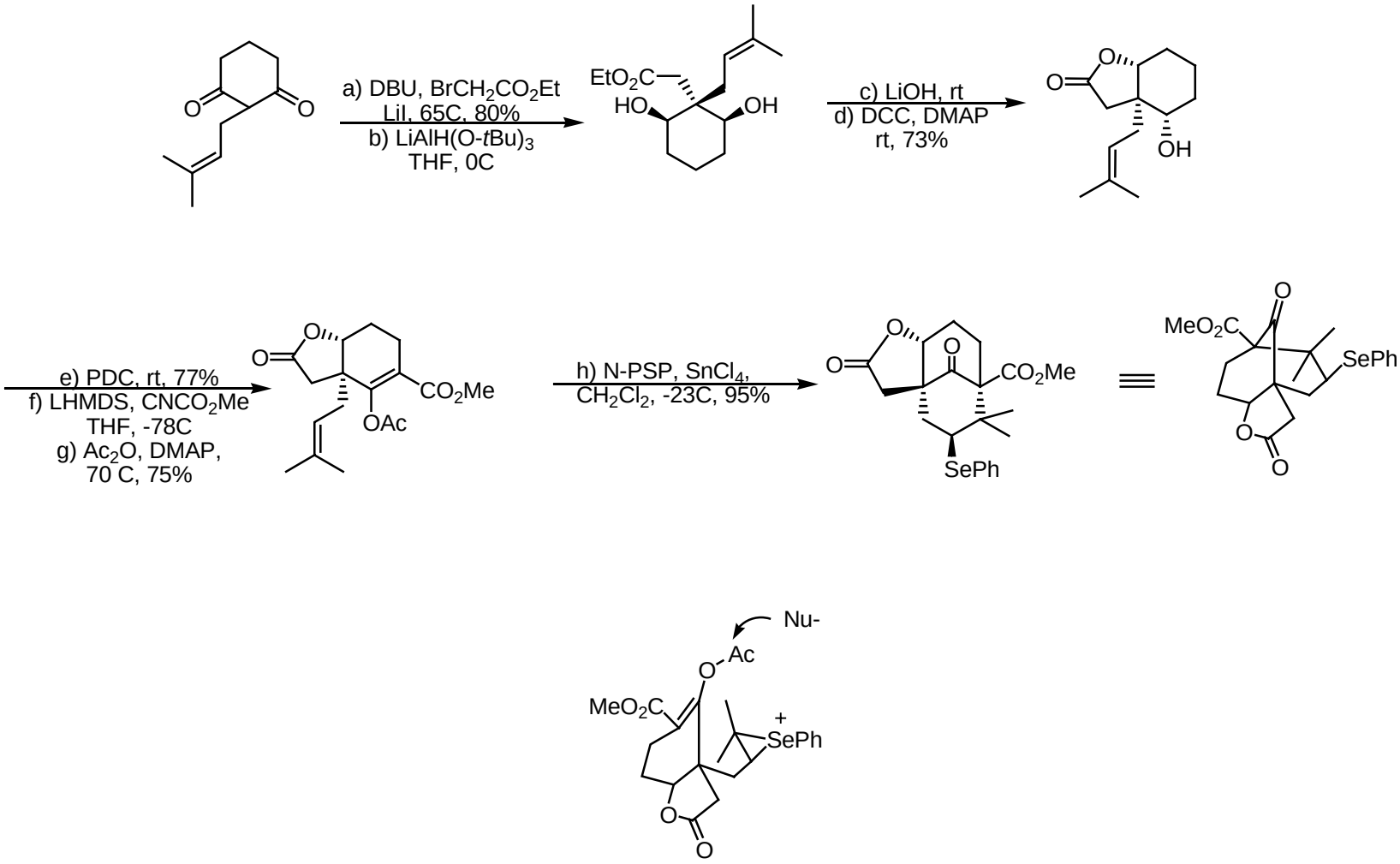


substrate	R	temp(°C)	time(min)	yield(%) [a]
14	OMe	-23	5	95
15	Me	-23	5	93
16	*i*-Pr	-10	15	80 [b]
17	Ph	-23	10	85
18	$CH{=}CMe_2$	-23	15	62

[a] Isolated yield after purification unless otherwise noted. [b] Yield at 40% conversion by ^1H NMR of crude reaction mixture.

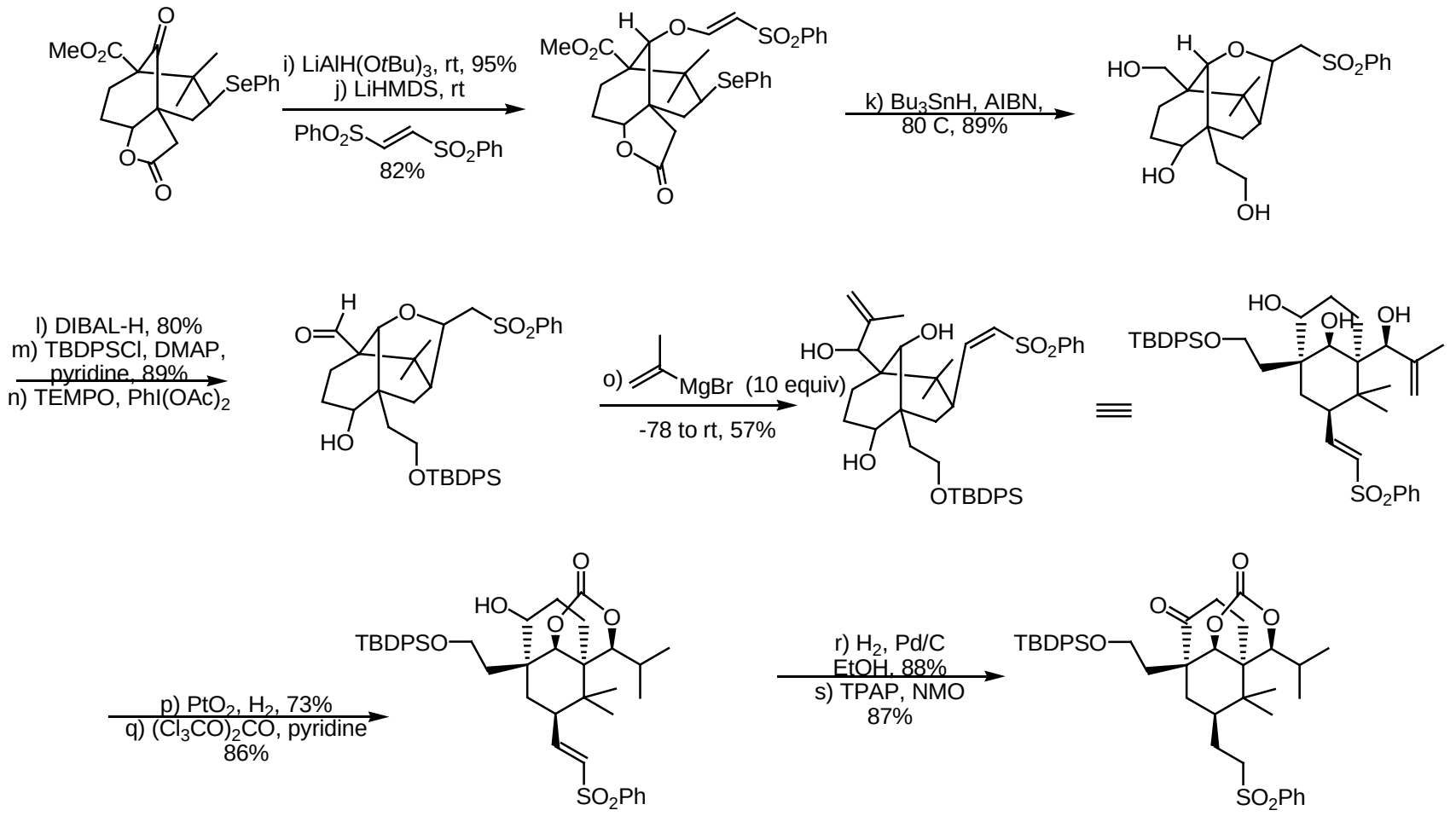
J. C. S.Chem. Comm. **1980**, 1028 and 1173.
Org. Lett. **1999**, 807.

Nicolaou: Synthesis of the Core



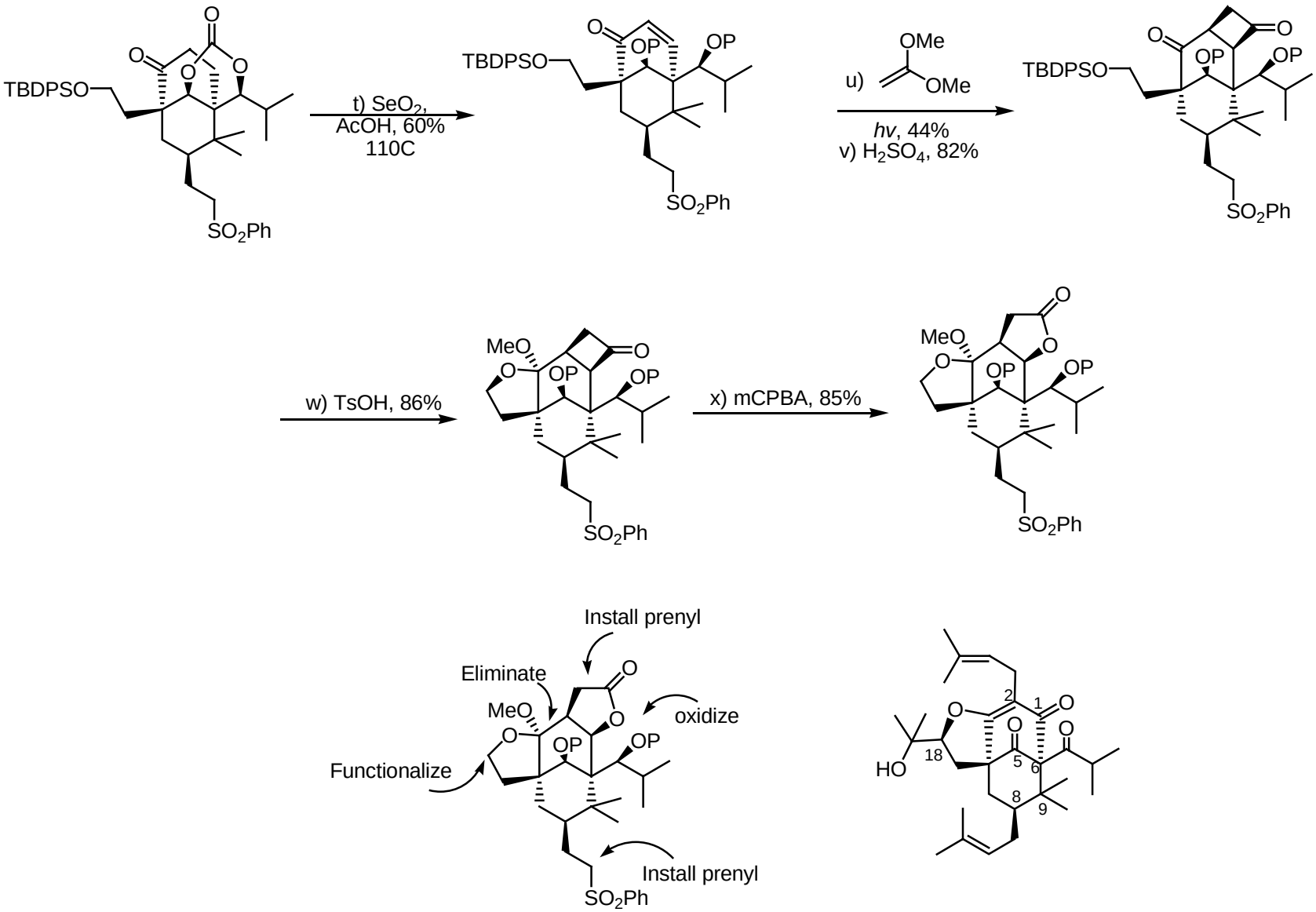
J. Am. Chem. Soc.. **1999**, 4724.

Nicolaou: Elaboration of the Core



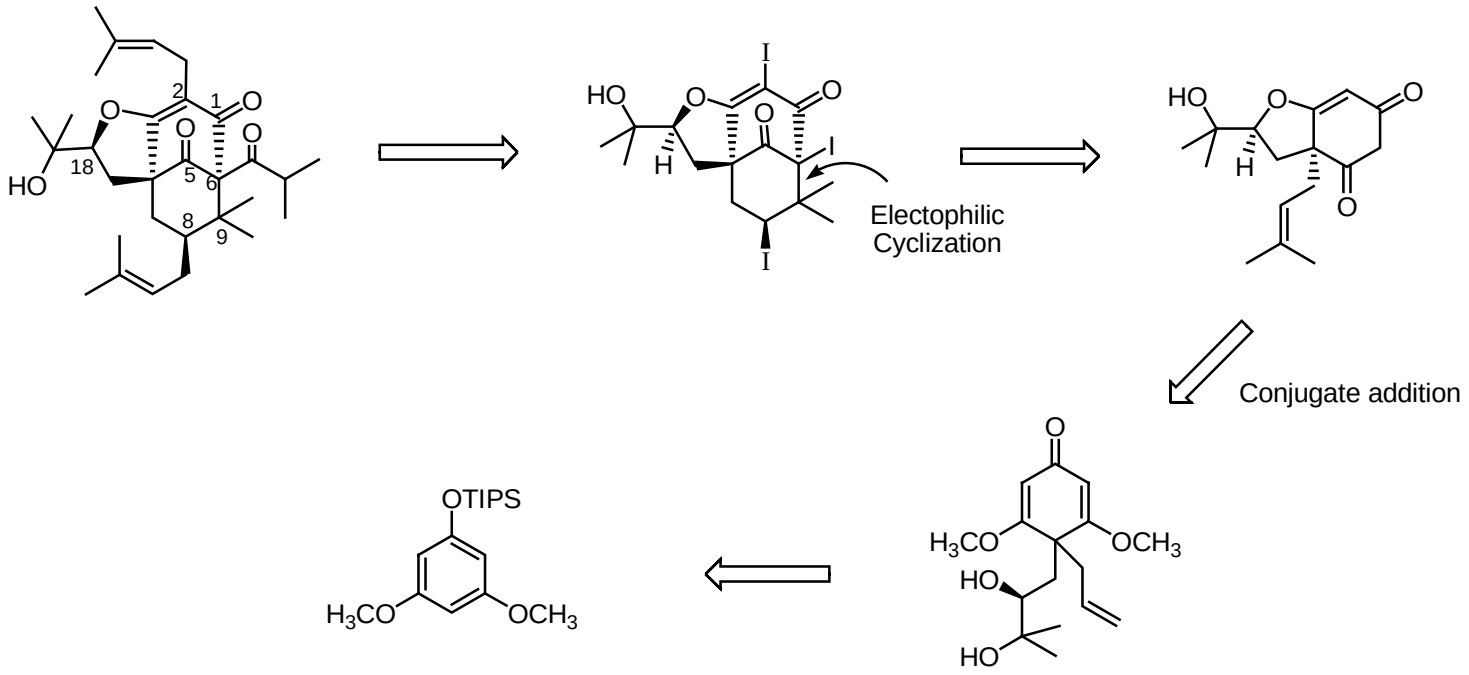
J. Am. Chem. Soc.. **1999**, 4724.

Nicolaou: Final Steps



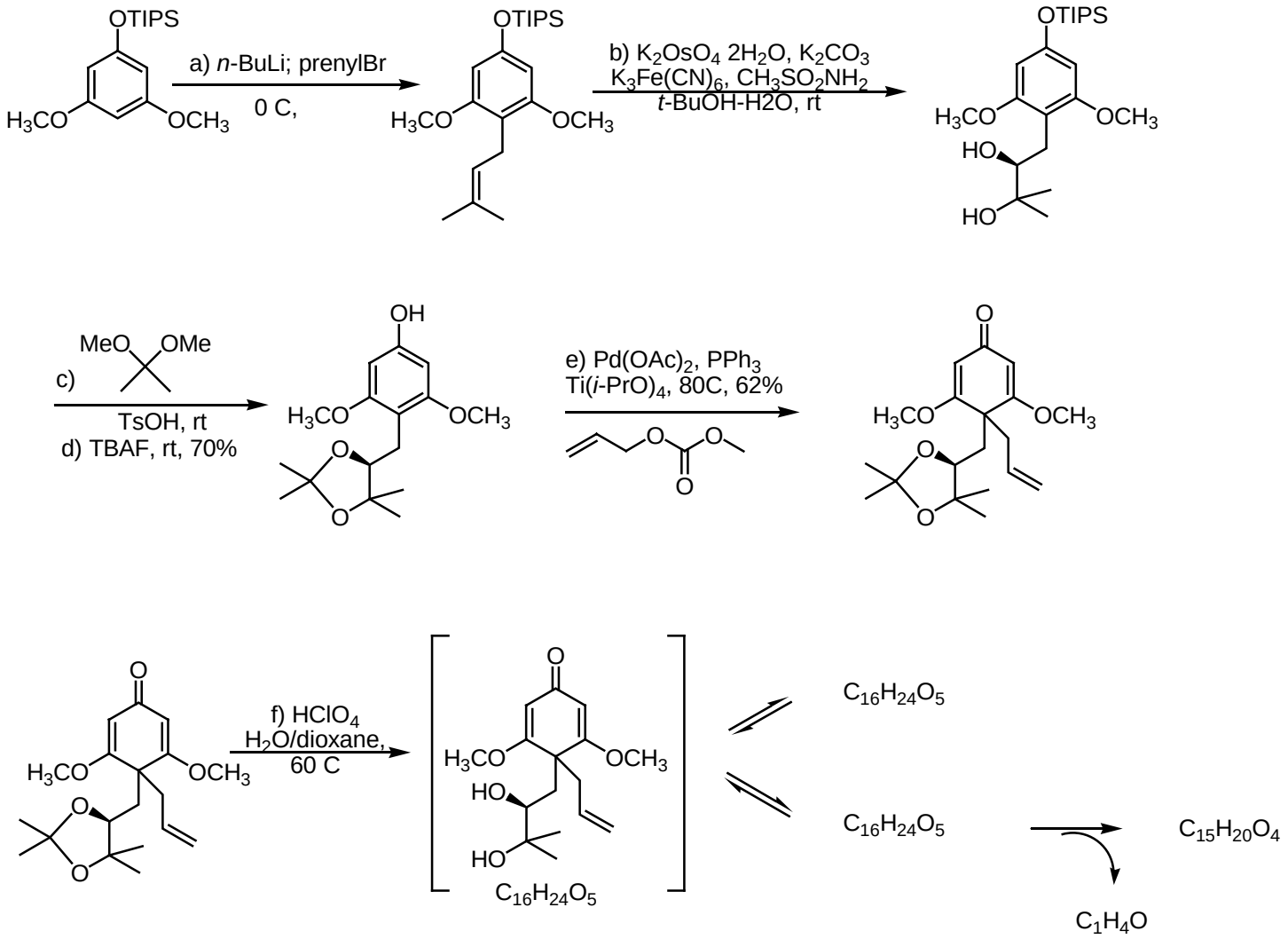
J. Am. Chem. Soc.. **1999**, 4724.

Danishefsky: Retrosynthesis



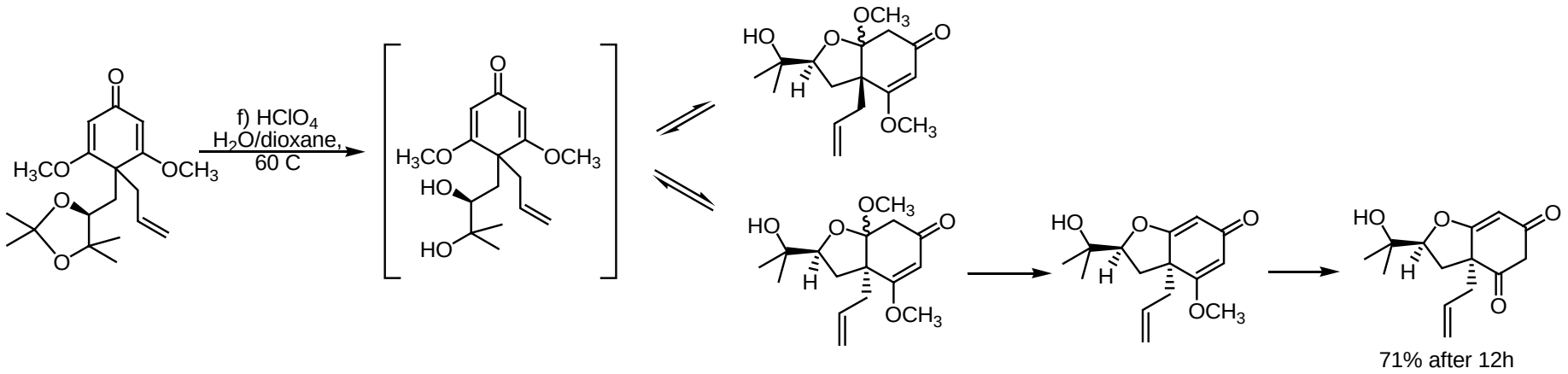
J. Am. Chem. Soc. **2006**, 1048.

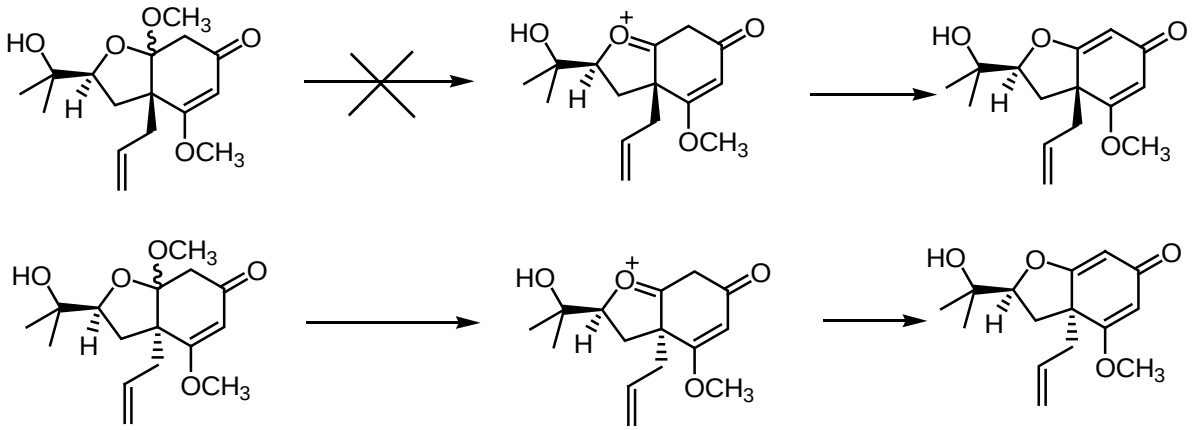
Danishefsky's Total Synthesis



J. Am. Chem. Soc. **2006**, 1048.

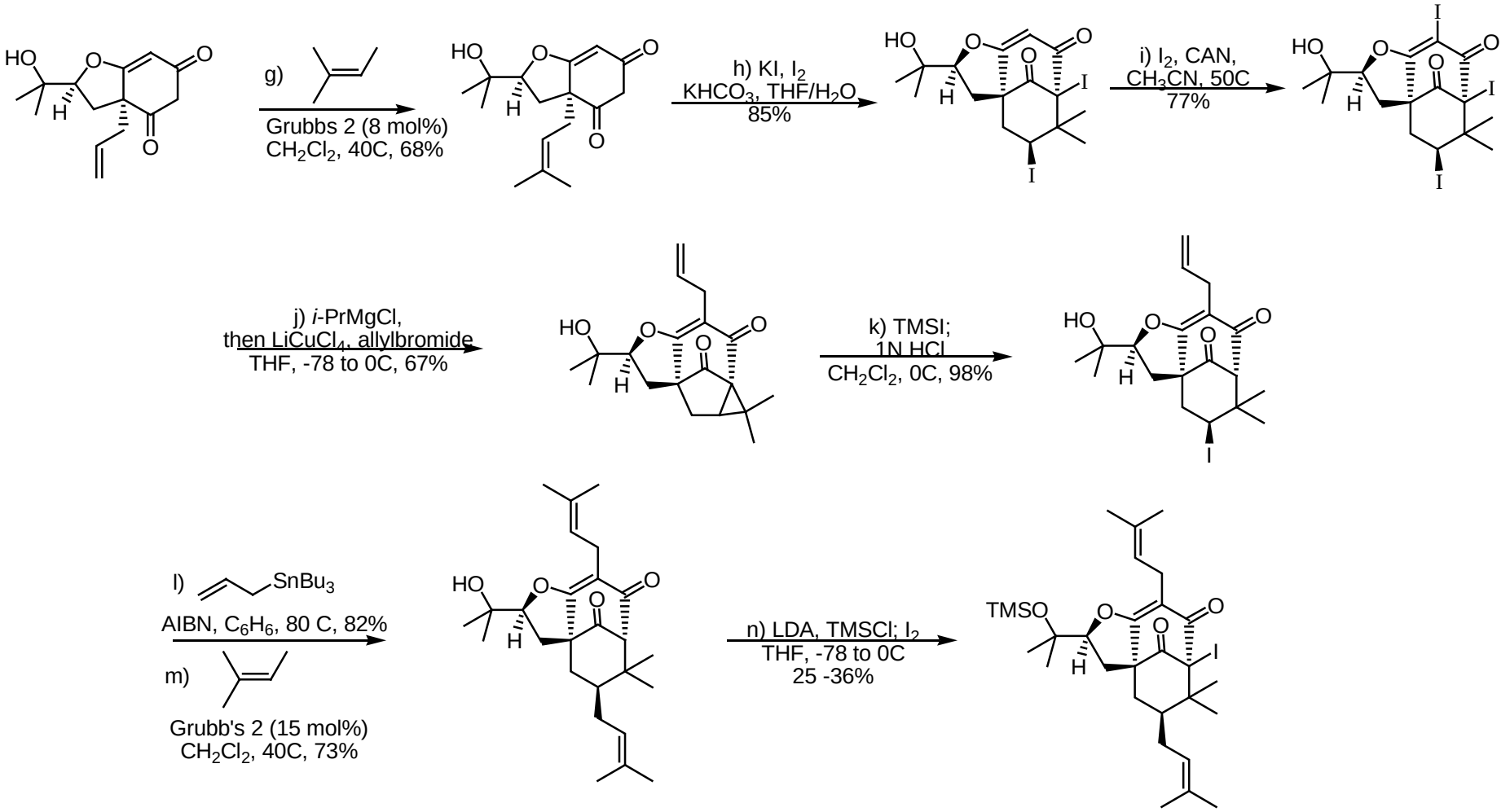
Danishefsky: Stereocontrol





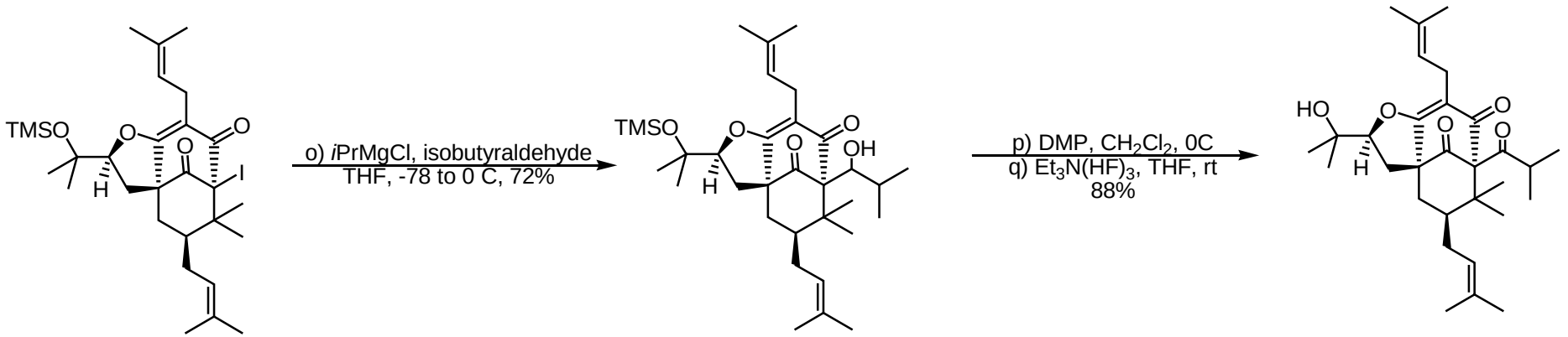
J. Am. Chem. Soc. **2006**, 1048.

Danishefsky: Constructing the Core

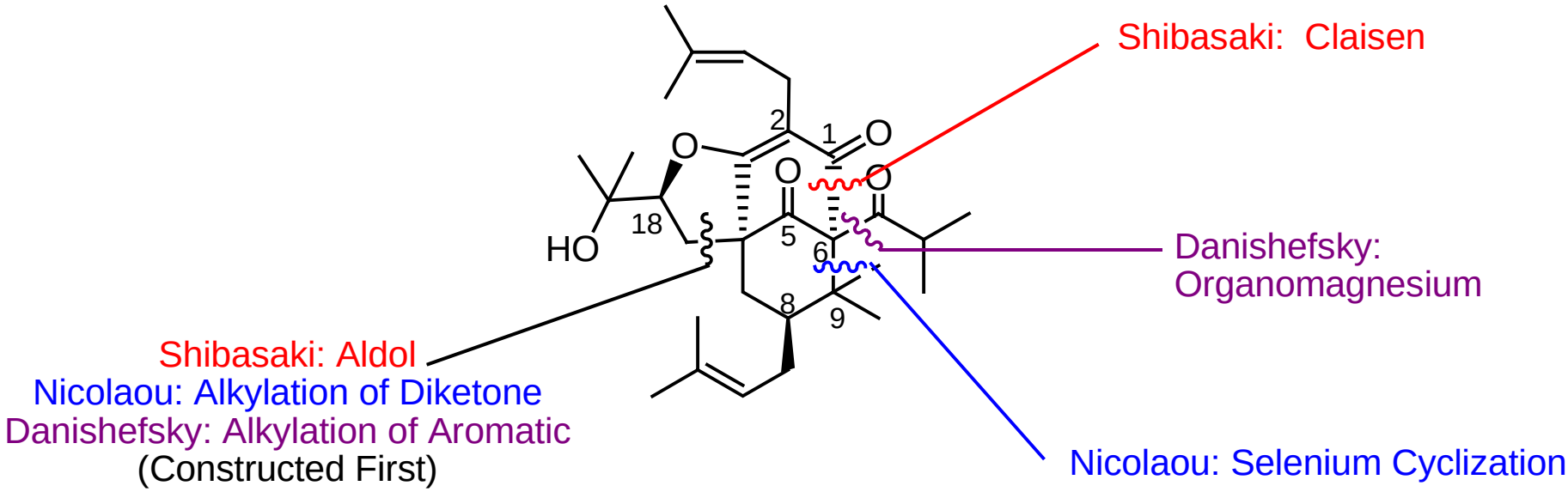


J. Am. Chem. Soc. **2006**, 1048.

Danishefsky: Last Steps



J. Am. Chem. Soc. **2006**, 1048.



RMC, Wacker oxidative cyclization. Substrate control by C(8)

[2+2]; requires desymterization of meso-compound for lactone formation

Iodocyclization, diasteroselective C-ring closure; Substrate control by AD at C(18)

-Several unique approaches to the construction of the hindered, functionalized core

-Examples of overcoming the delicate balance between reactivity and non-reactivity due to hindrance (and subsequent modification of approach to complete the synthesis).

-Due to the pharmaceutical interest, many synthetic routes may be needed for the selective construction of analogs.

-The recent total syntheses (Shibasaki: Aug 12, 2005; Danishefsky: Oct 31, 2005) show interest is alive and well in this class of molecules.