Studies Toward the Total Synthesis of Daphnicyclidin A

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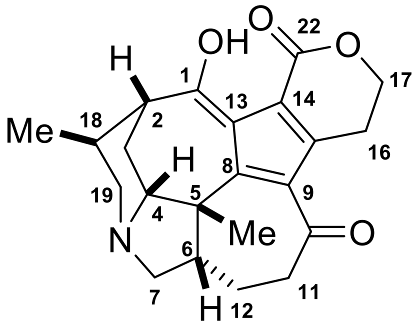
Indiana University

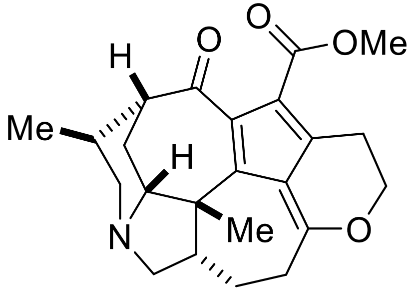
September 17, 2019

Introduction: Structure and Isolation

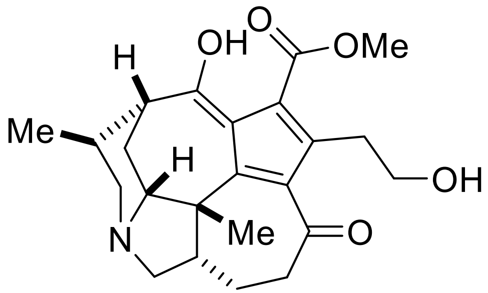
- Novel Polycyclic Alkaloids
- Fused Hexa- and Pentacyclic Rings
- Fully Substituted Cyclopentadienes
- Potent Antitumor Activity
- Treatment of Inflammation and Arthritis in Traditional Chinese Medicines



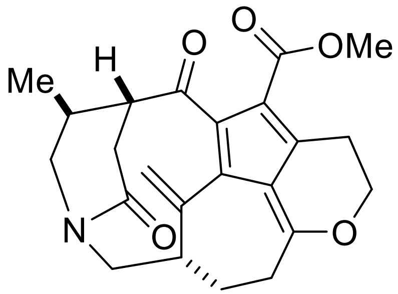
Daphnicyclidin A
L1210 IC_{50} 0.8 μg/mL
KB IC_{50} 6.0 μg/mL



Daphnicyclidin D
L1210 IC_{50} 1.7 μg/mL
KB IC_{50} 4.6 μg/mL



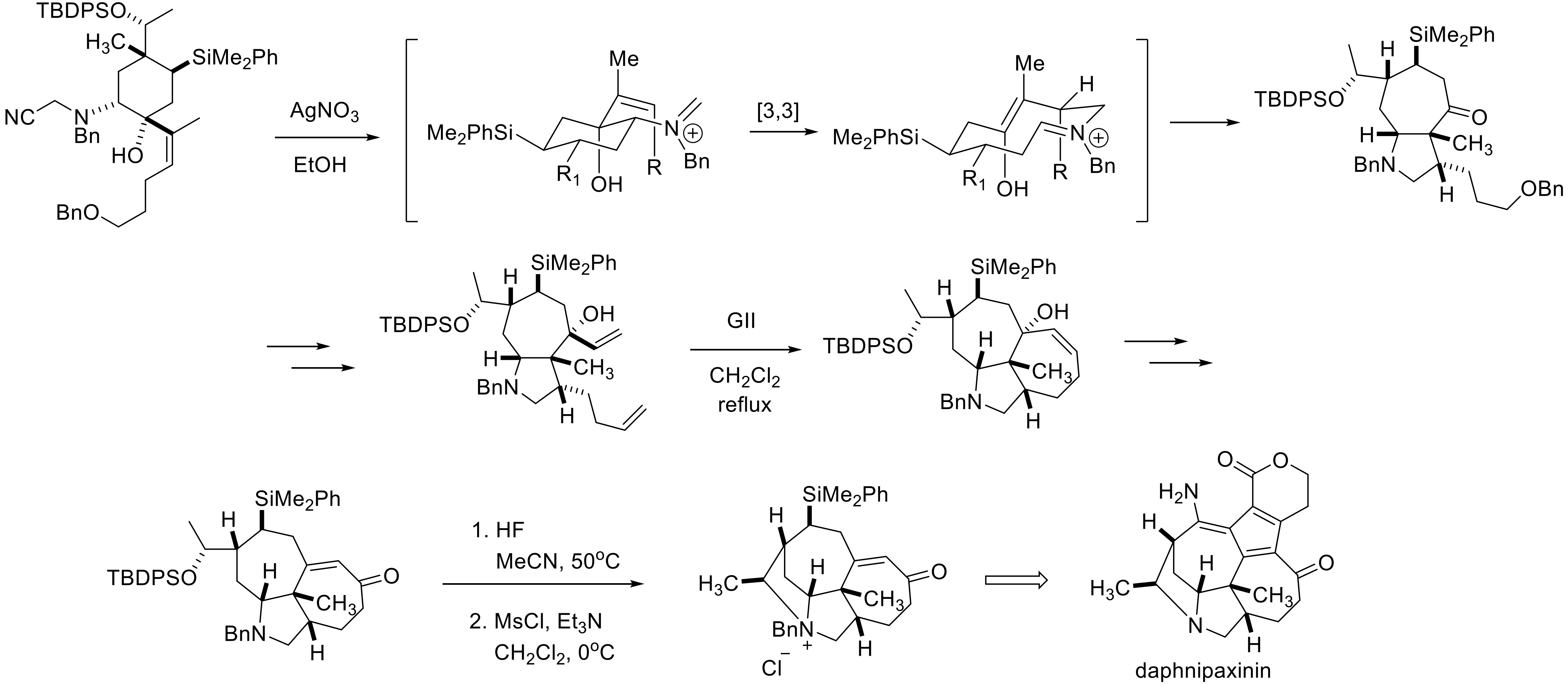
Daphnicyclidin H
L1210 IC_{50} 0.5 μg/mL
KB IC_{50} 0.9 μg/mL



Daphnicyclidin J
L1210 IC_{50} 1.9 μg/mL
KB IC_{50} 2.5 μg/mL

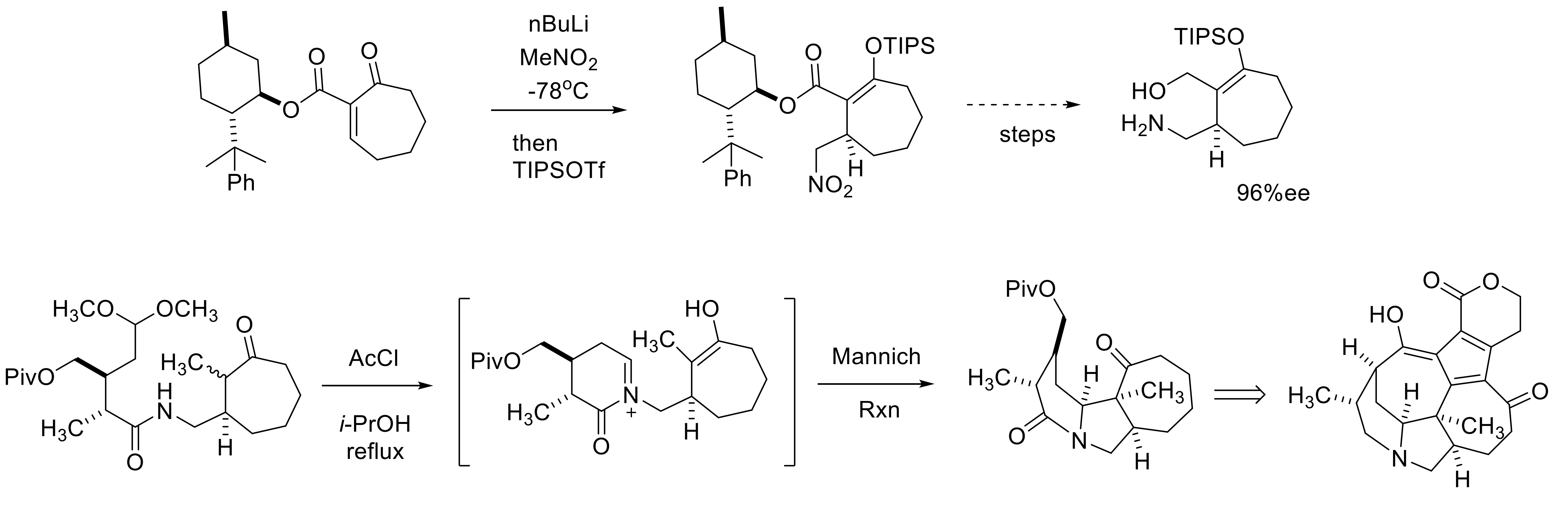
Isolation: Kobayashi, *et al. J. Am. Chem. Soc.* **2001**, *123*, 11402-11408.
For a review: Hanessian *et al. Chem. Rev.* **2017**, *117*, 4104-4146.

Studies Toward Daphnipaxinin



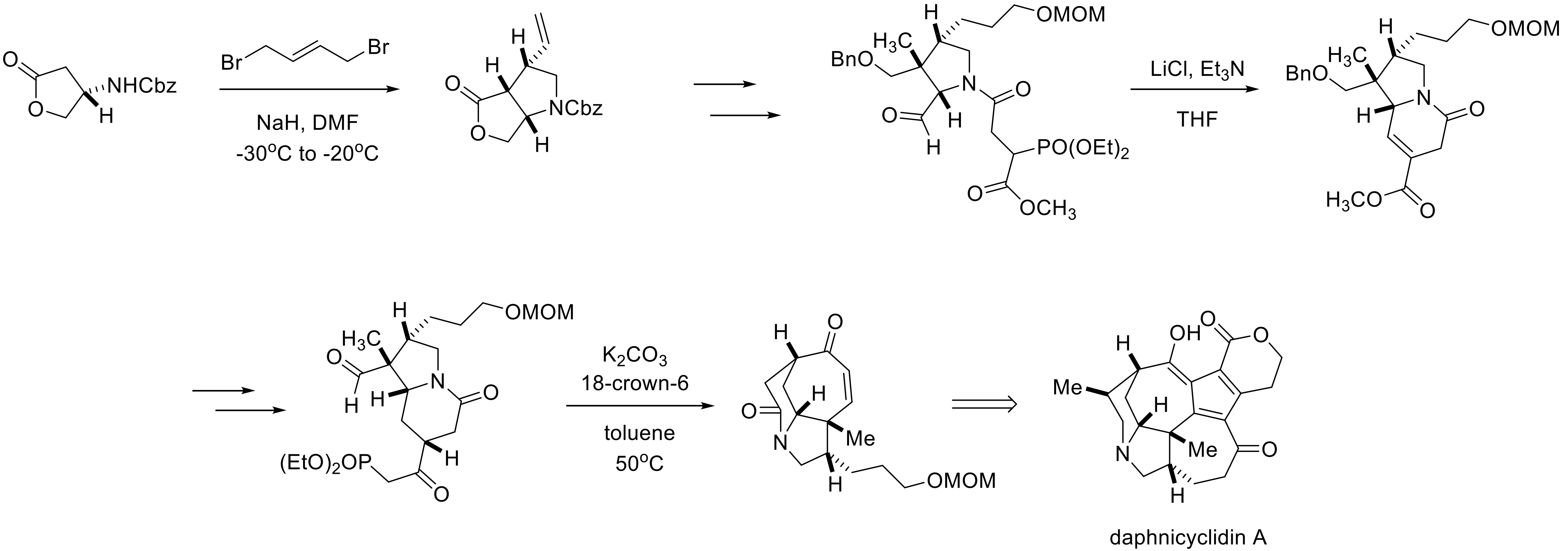
Overman, *et al. Org. Lett.* **2009**, *11*, 5658-5661.

Studies Toward Daphnicyclidin A



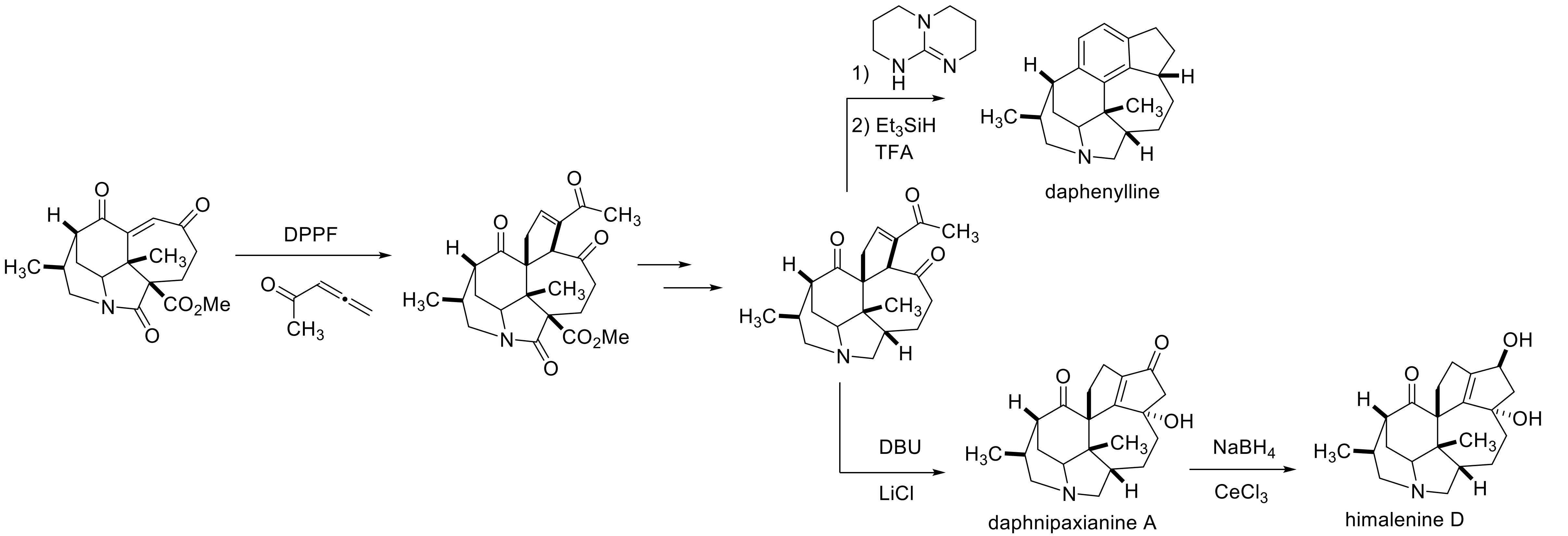
Iwabuchi, *et al. Org. Lett.* **2009**, *11*, 1833-1836.

Studies Toward Daphnicyclidin A



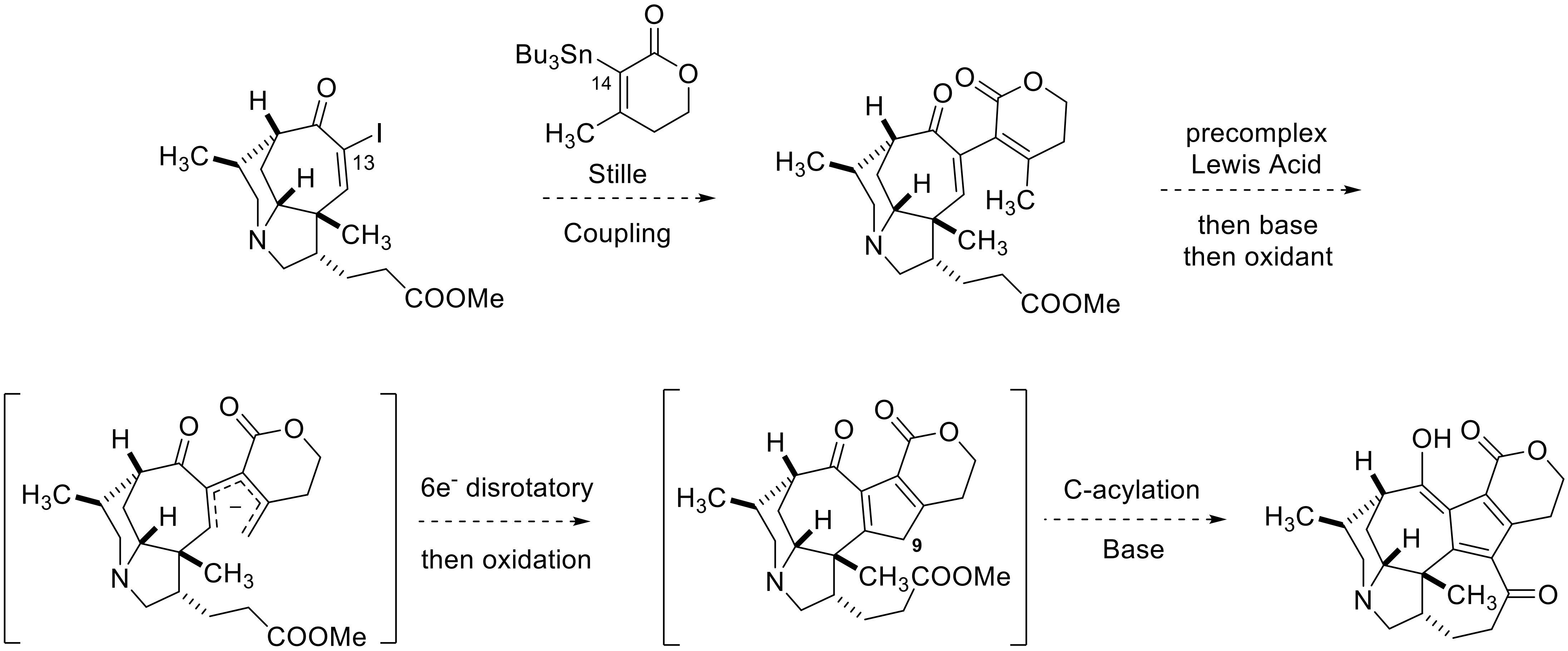
Yang, *et al. Org. Lett.* **2017**, *19*, 1497-1499.

Studies Toward Daphenylline

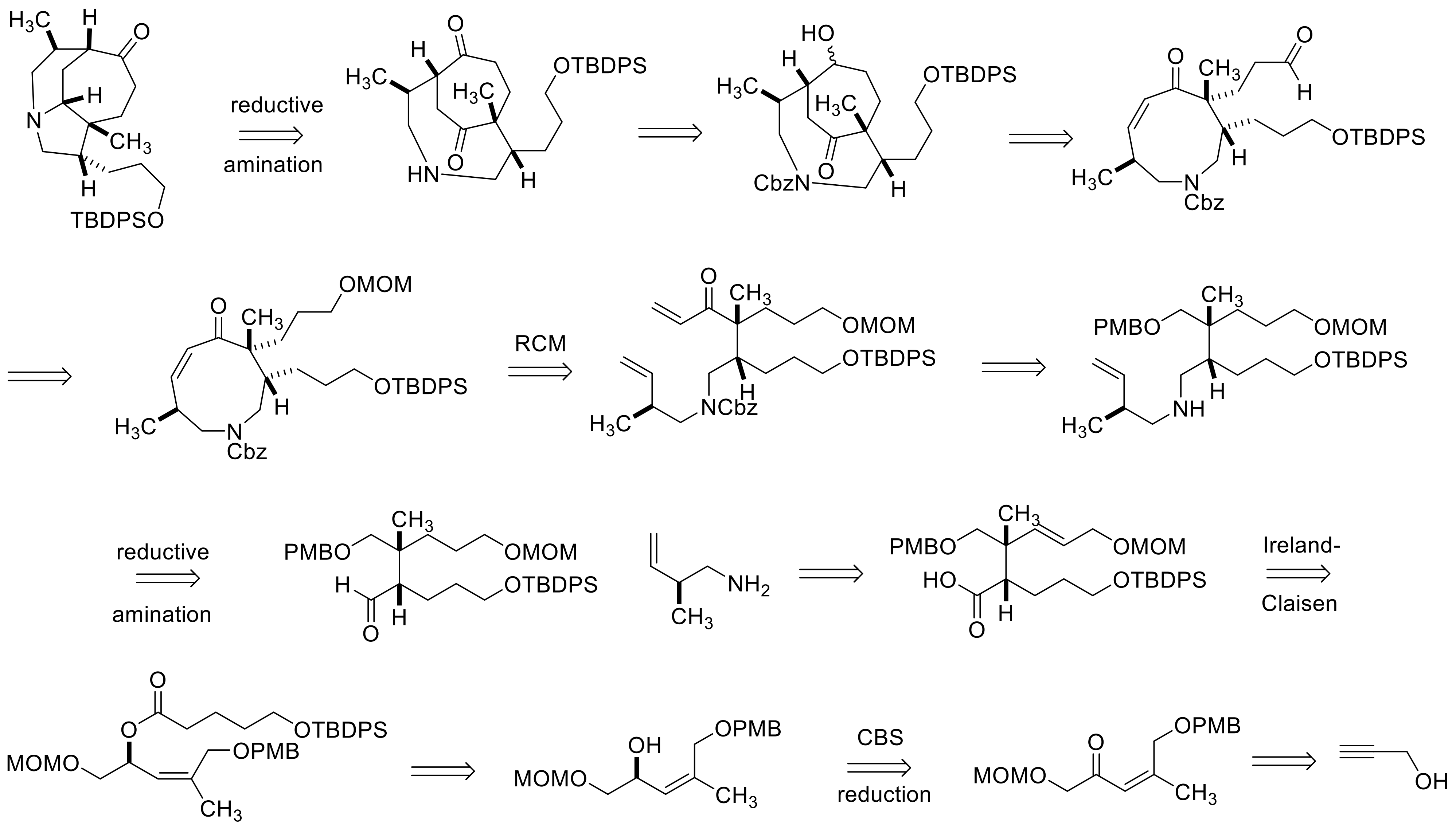


Li, *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 952-956.

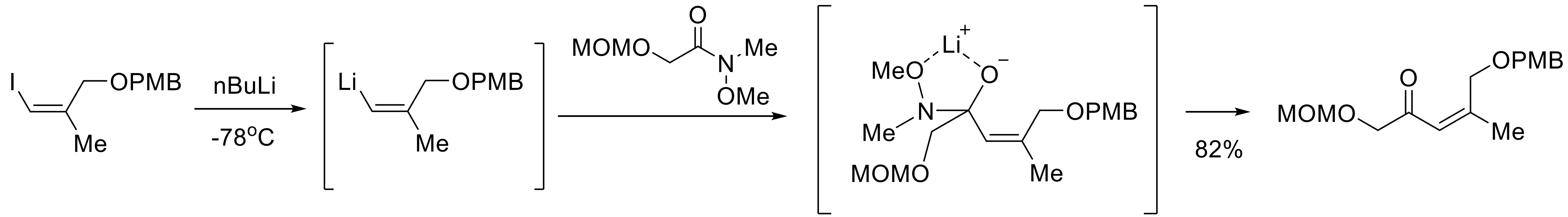
End Game Hypothesis

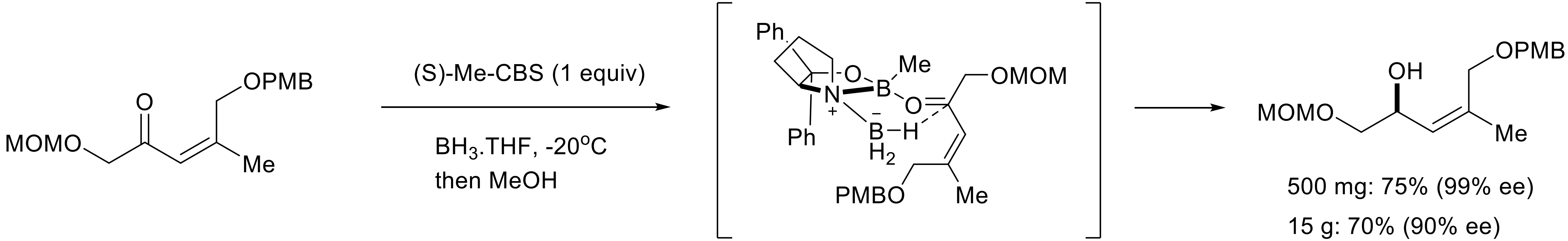


Retrosynthetic Analysis



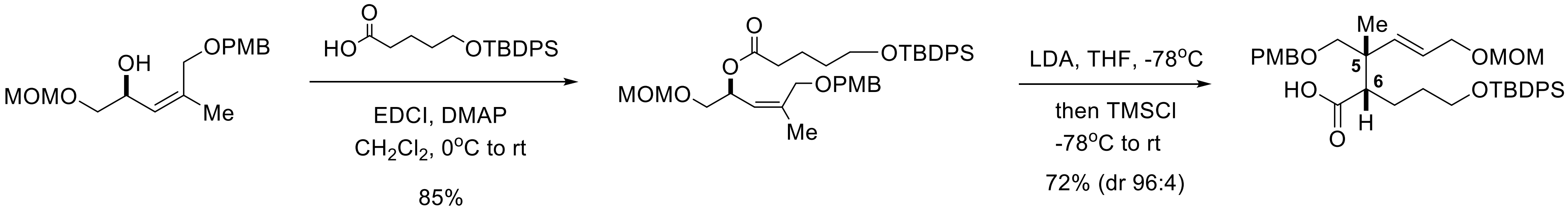
Formation of Enone and CBS Reduction

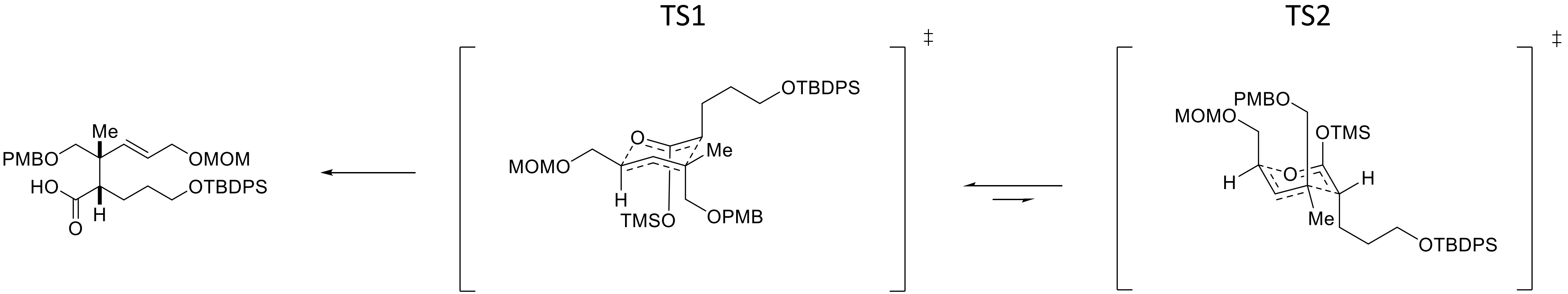




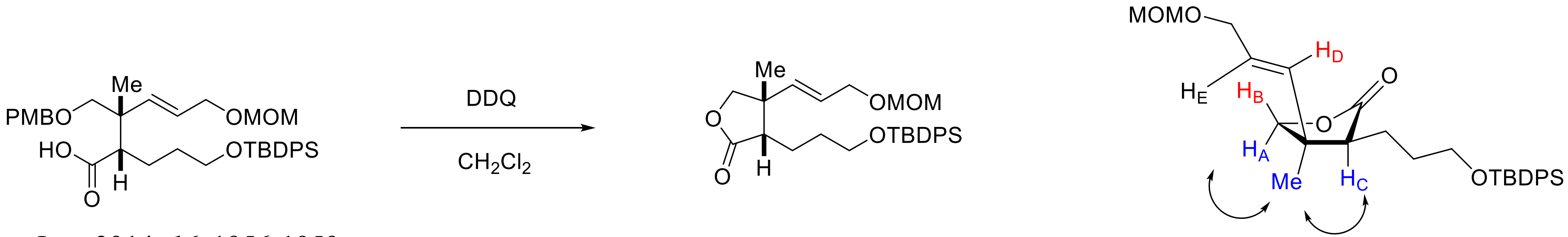
Williams *et al. Org. Lett.* **2014**, *16*, 1956-1959.

Ireland-Claisen Rearrangment



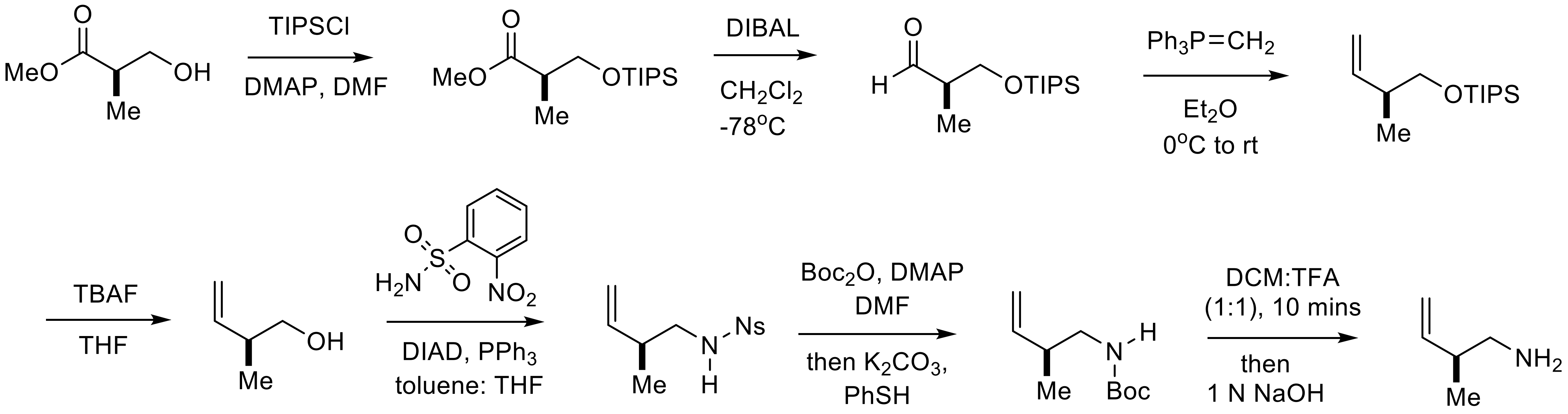


Confirmation of Stereochemistry

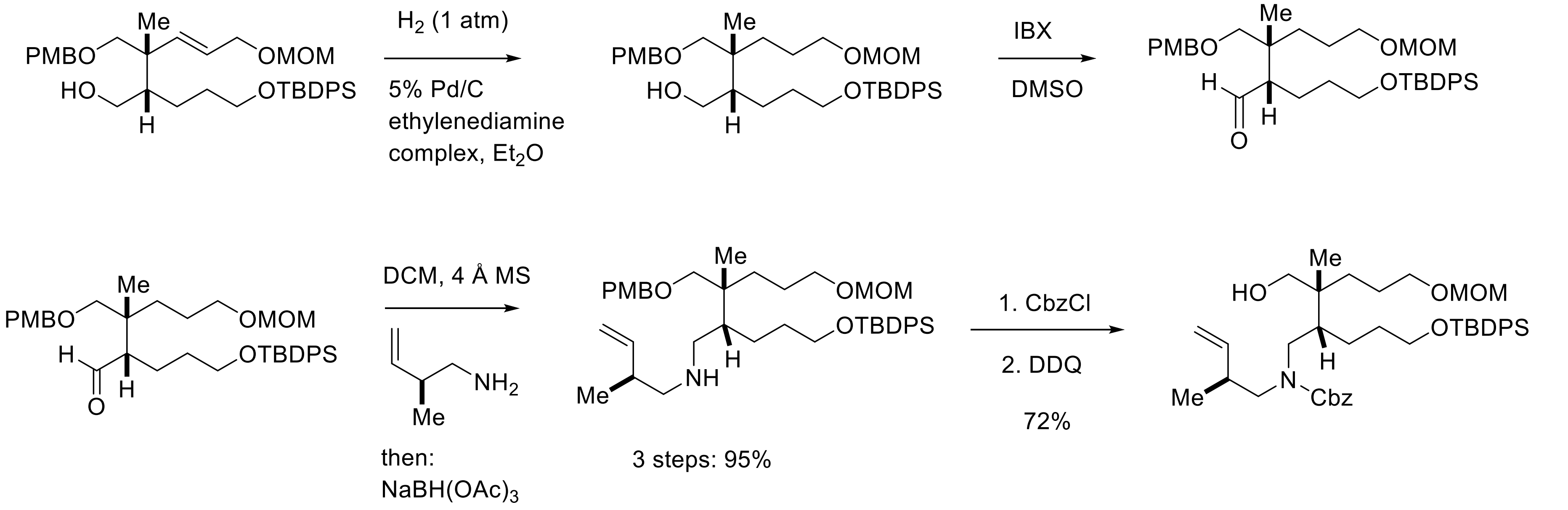


Williams *et al. Org. Lett.* **2014**, *16*, 1956-1959.

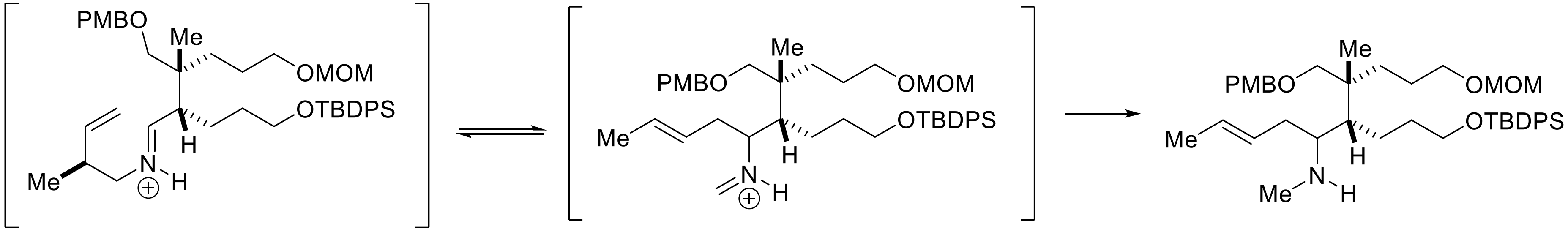
Reductive Amination Partner



Reductive Amination

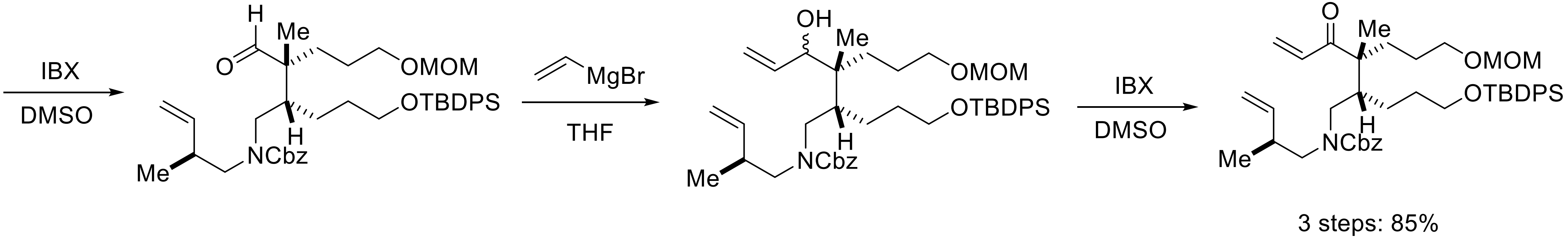


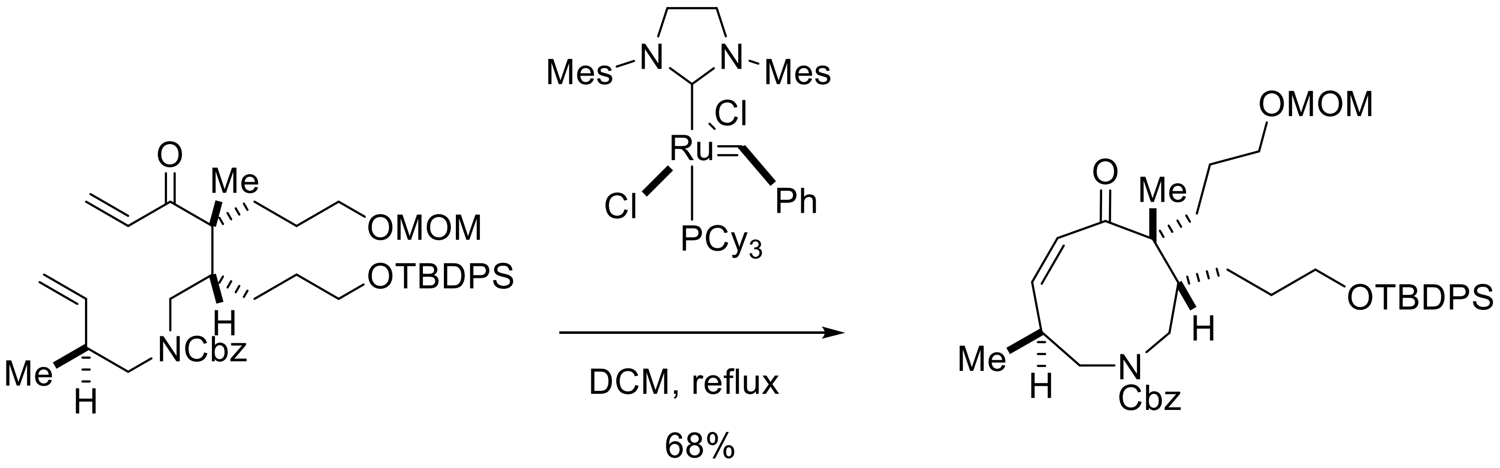
A problem:



Pd/C/ethylenediamine complex: Sajiki *et al*. *J. Org. Chem*. **1998**, *63*, 7990−7992
Abdel-Magid *et a*l. *J. Org. Chem*. **1996**, *61*, 3849-3862.
Williams *et al. Org. Lett*. **2014**, *16*, 1956-1959.

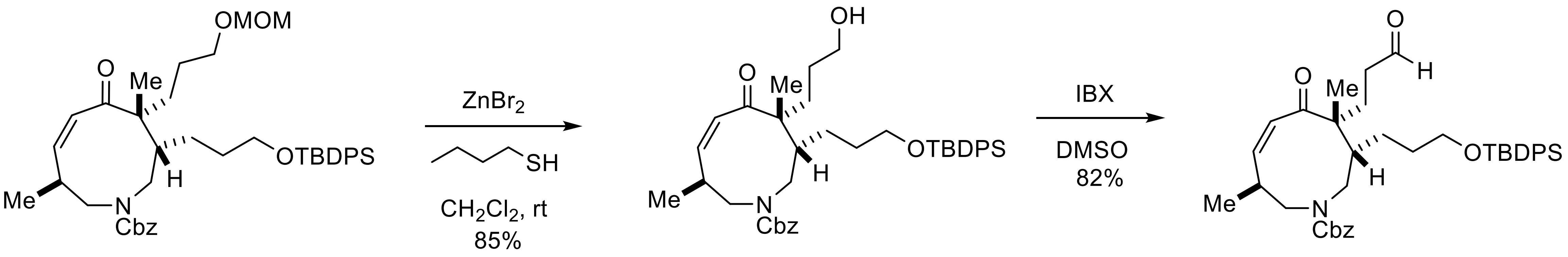
RCM to Form 9-Membered Ring

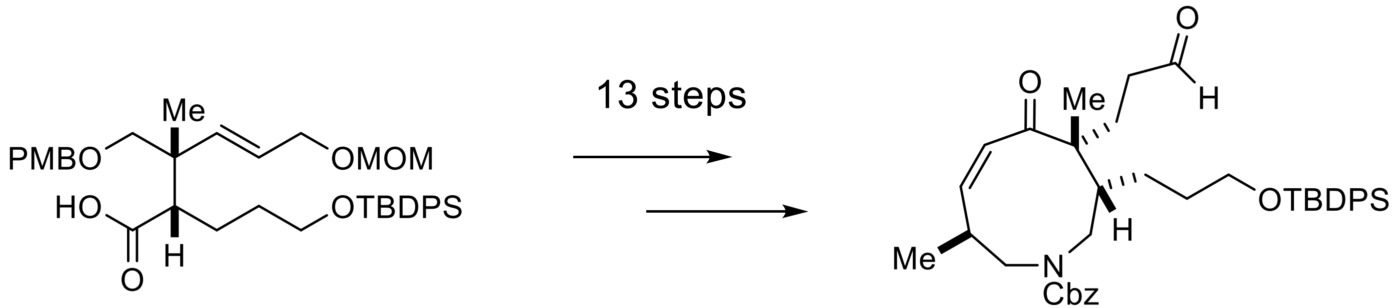




Williams *et al. Org. Lett.* **2014**, *16*, 1956-1959.

Reductive Cyclization Precursor



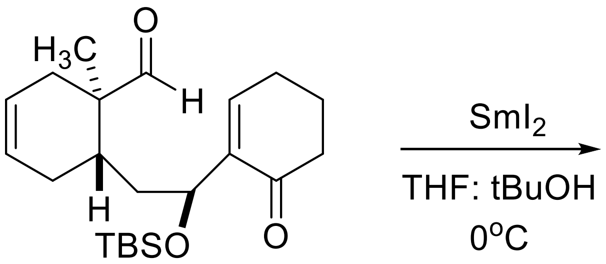


Multi-gram scale; 20% overall yield

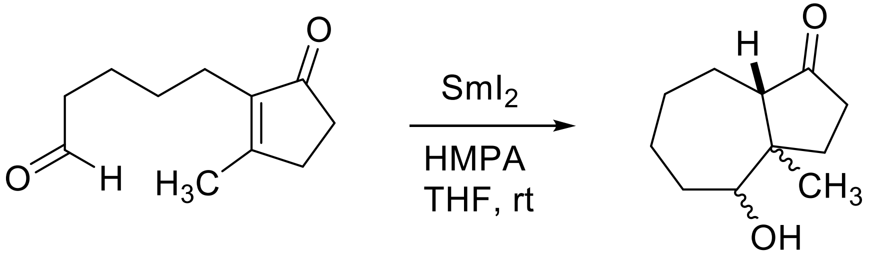
MOM deprotection: Han *et al*. *Tetrahedron* **2010**, *66*, 1673-1677
Williams *et al. Org. Lett*. **2014**, *16*, 1956-1959.

Reductive Cyclization Examples

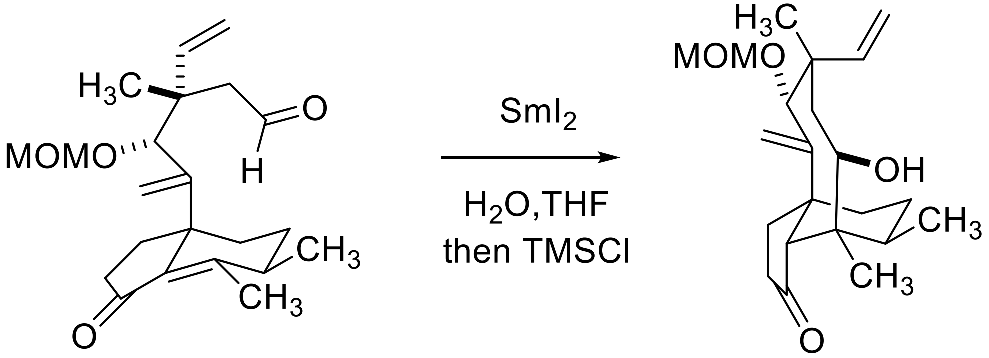
Arimoto



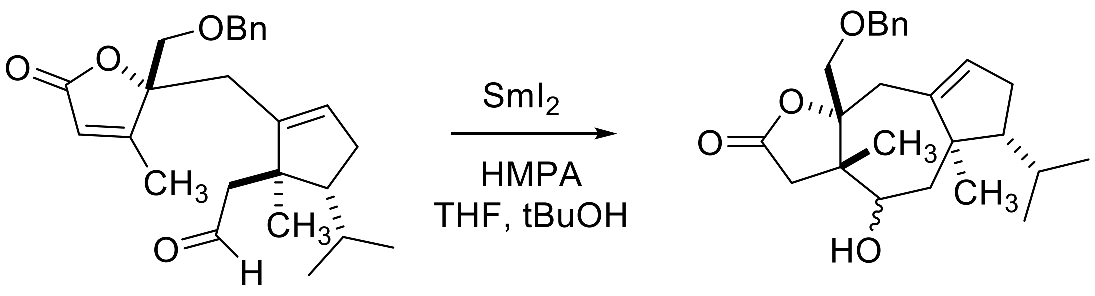
Tori



Reisman

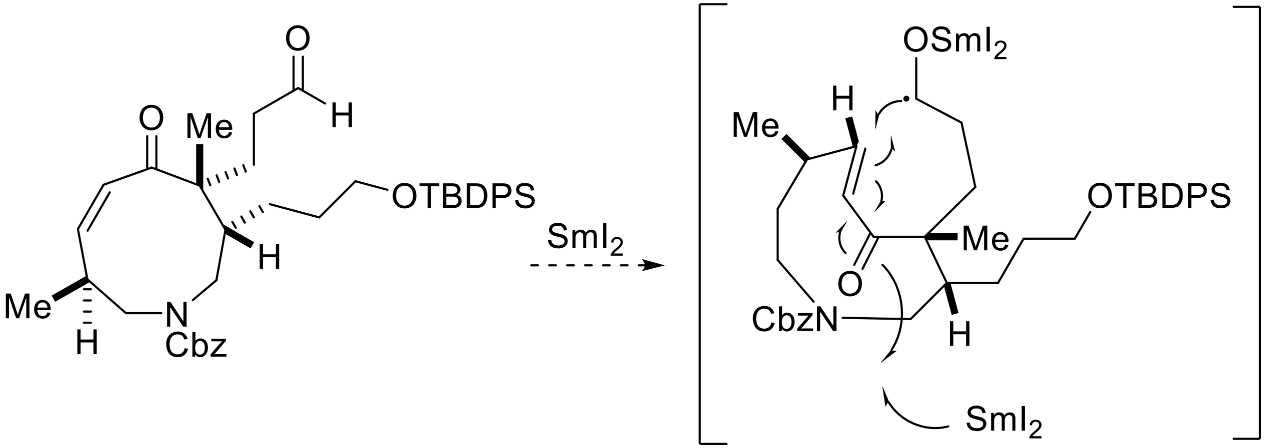


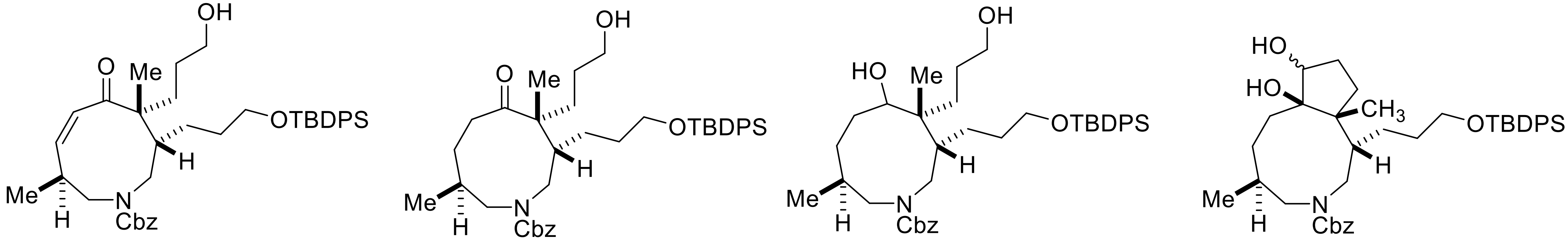
Williams



Arimoto *et al. Org. Biomol. Chem.* **2005**, *3*, 2231-2233
Tori *et al. Tetrahedron* **2008**, *64*, 11096-11104
Reisman *et al. J. Am. Chem. Soc.* **2018**, *140*, 1267-1270
Williams *et al. J. Org. Chem.* **2015**, *80*, 5474-5493

Reductive Cyclization

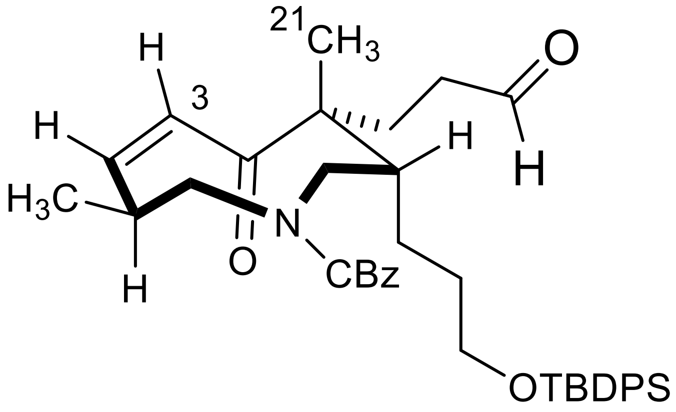


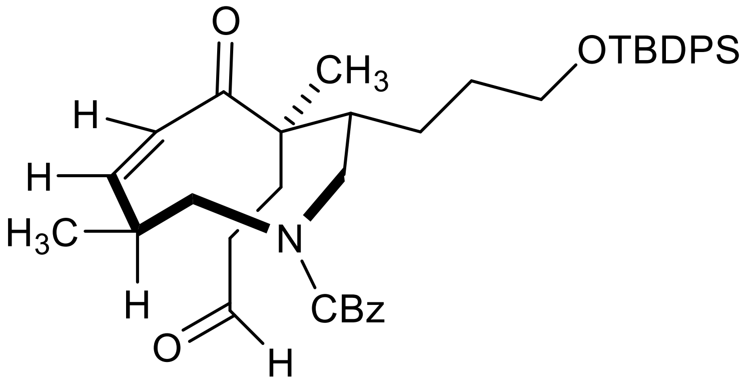


For a review: Nicolaou *et al*. *Angew. Chem. Int. Ed*. **2009**, *48*, 7140-7165

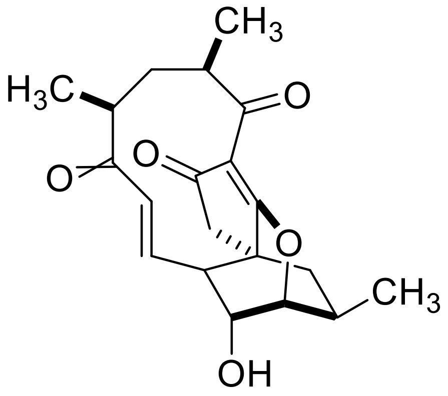
9-Membered Cyclic Enone

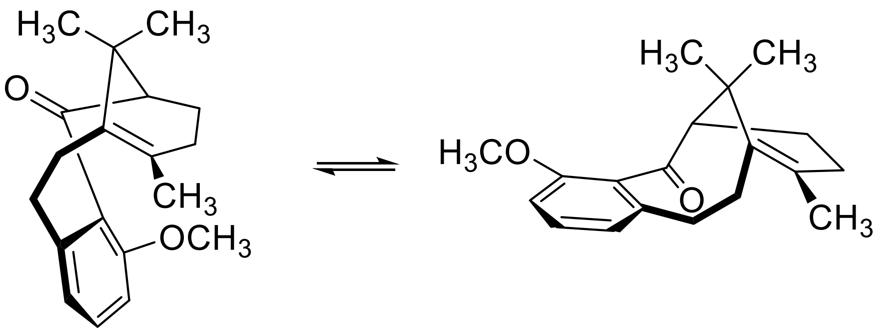
Atropisomers?





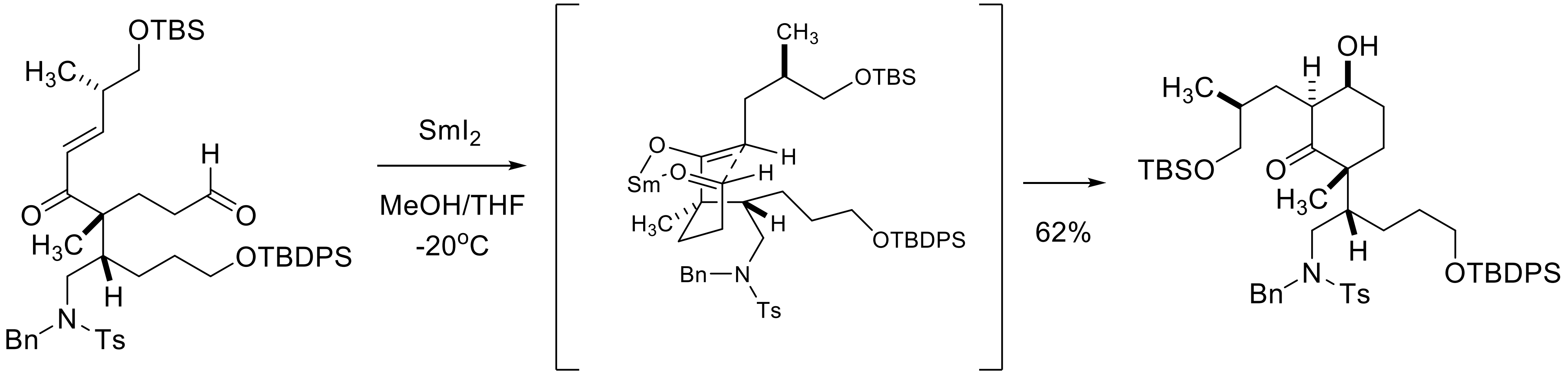
Abyssomicin C

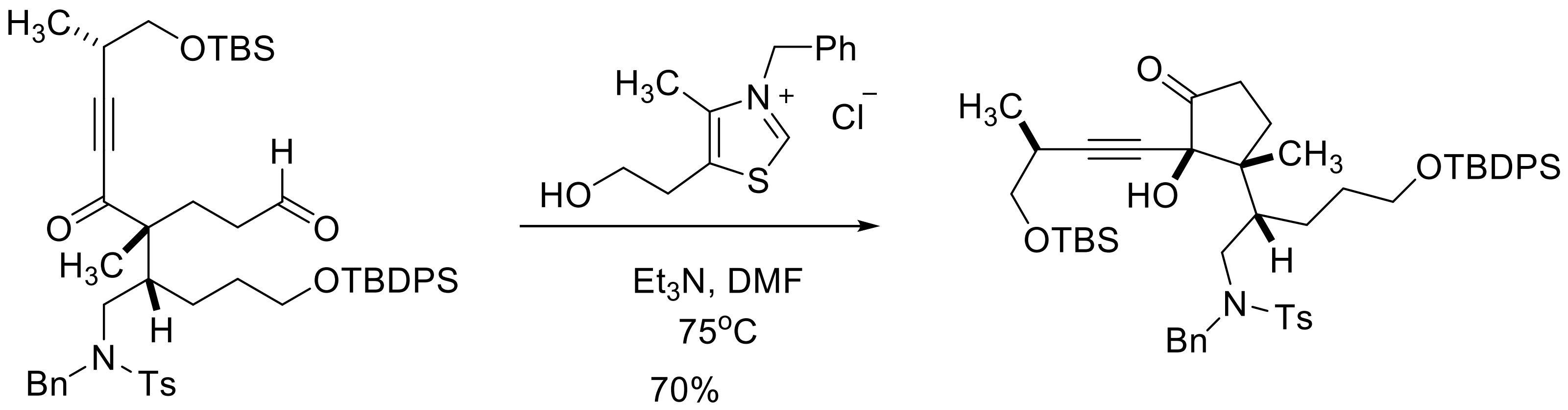




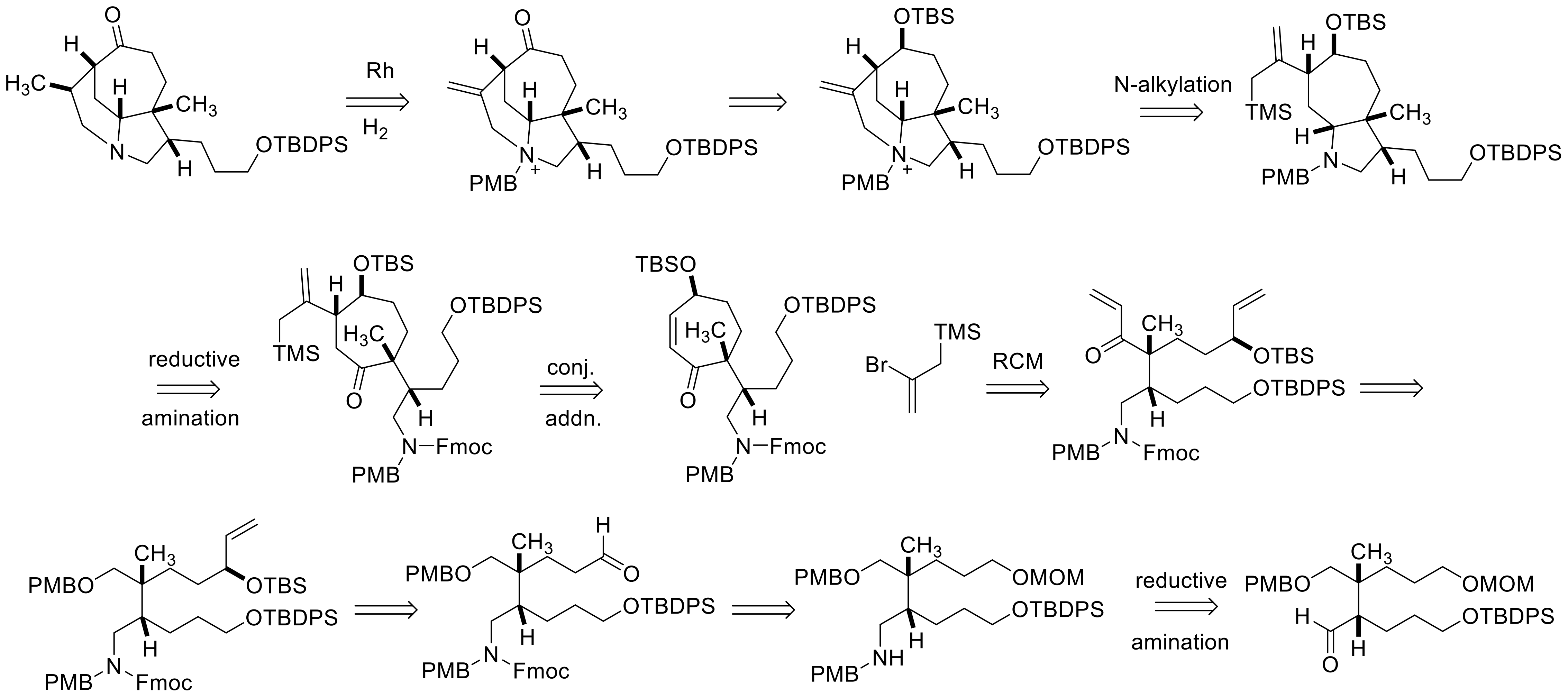
Nicolaou *et al. J. Am. Chem. Soc.* **2007**, *129*, 429-440
Shea *et al. J. Am. Chem. Soc.* **1986**, *108*, 4953-4956

Other Attempts to Make C1-C2 Bond

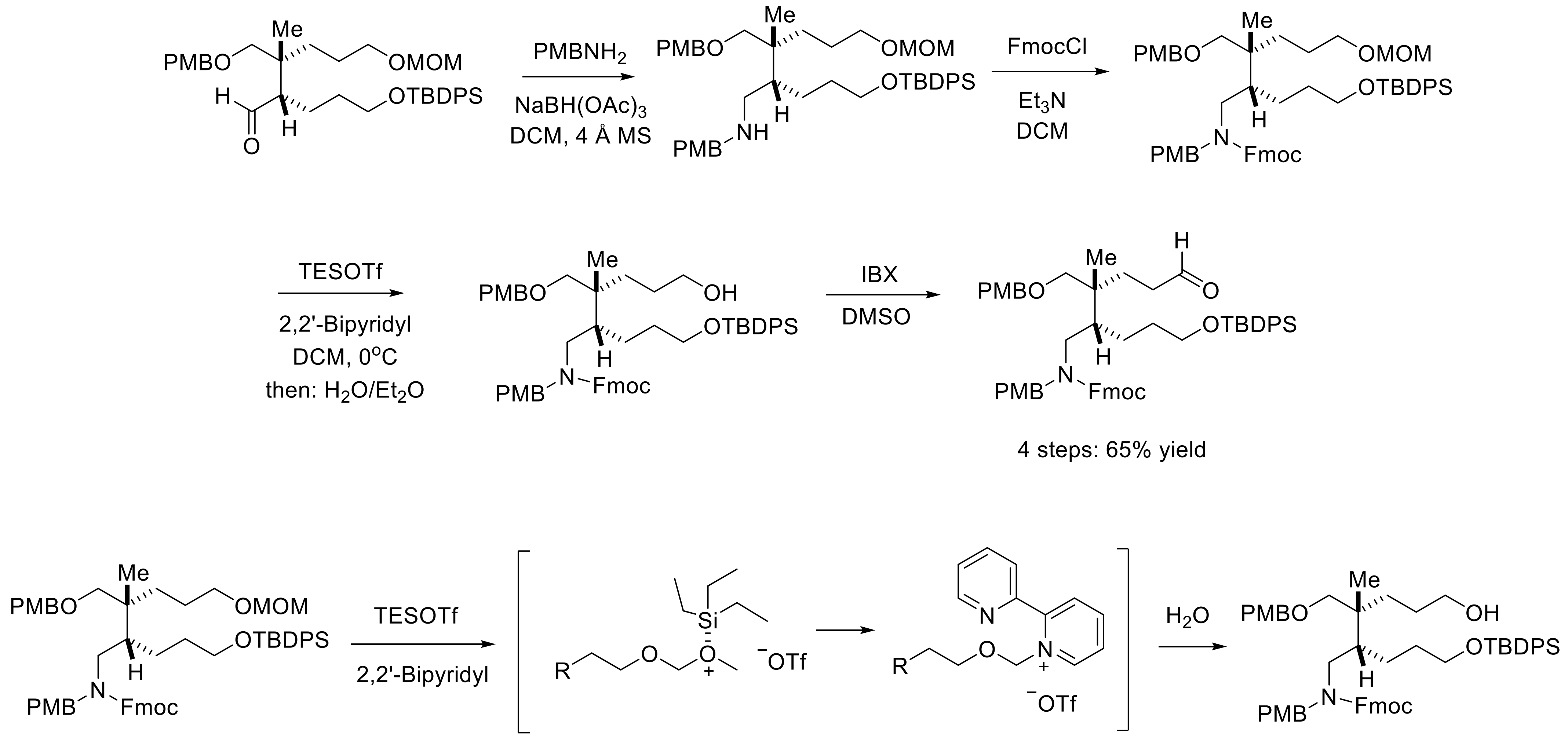




2nd Generation Retrosynthetic Analysis

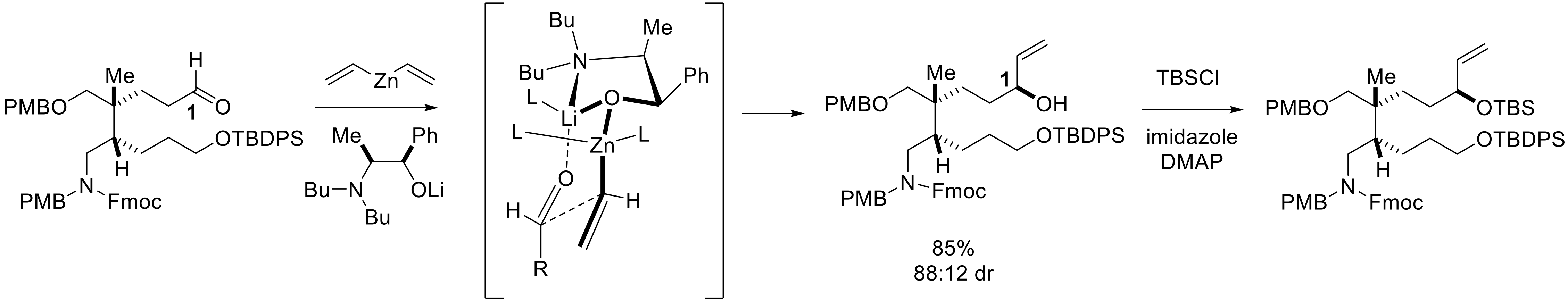


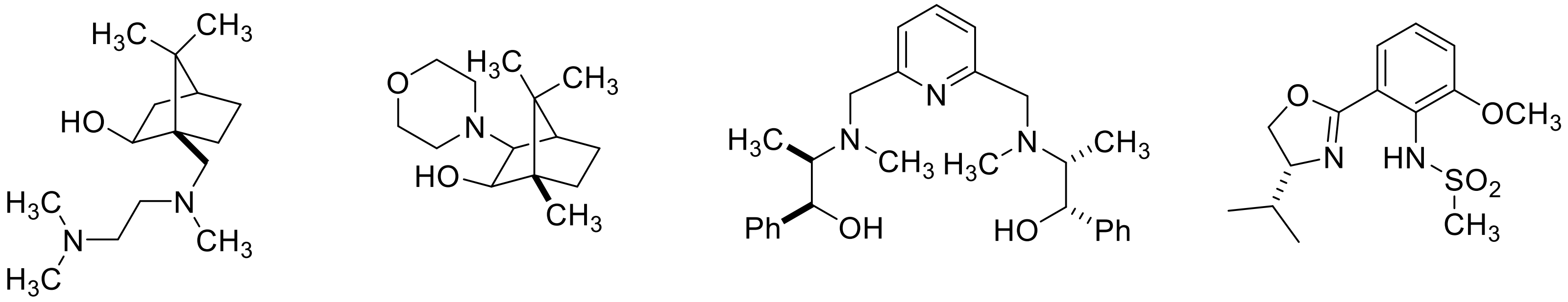
2nd Generation Route



MOM deprotection: Fujioka *et al*. *Tetrahedron* **2011**, *67*, 2949-2960

Asymmetric Vinylation

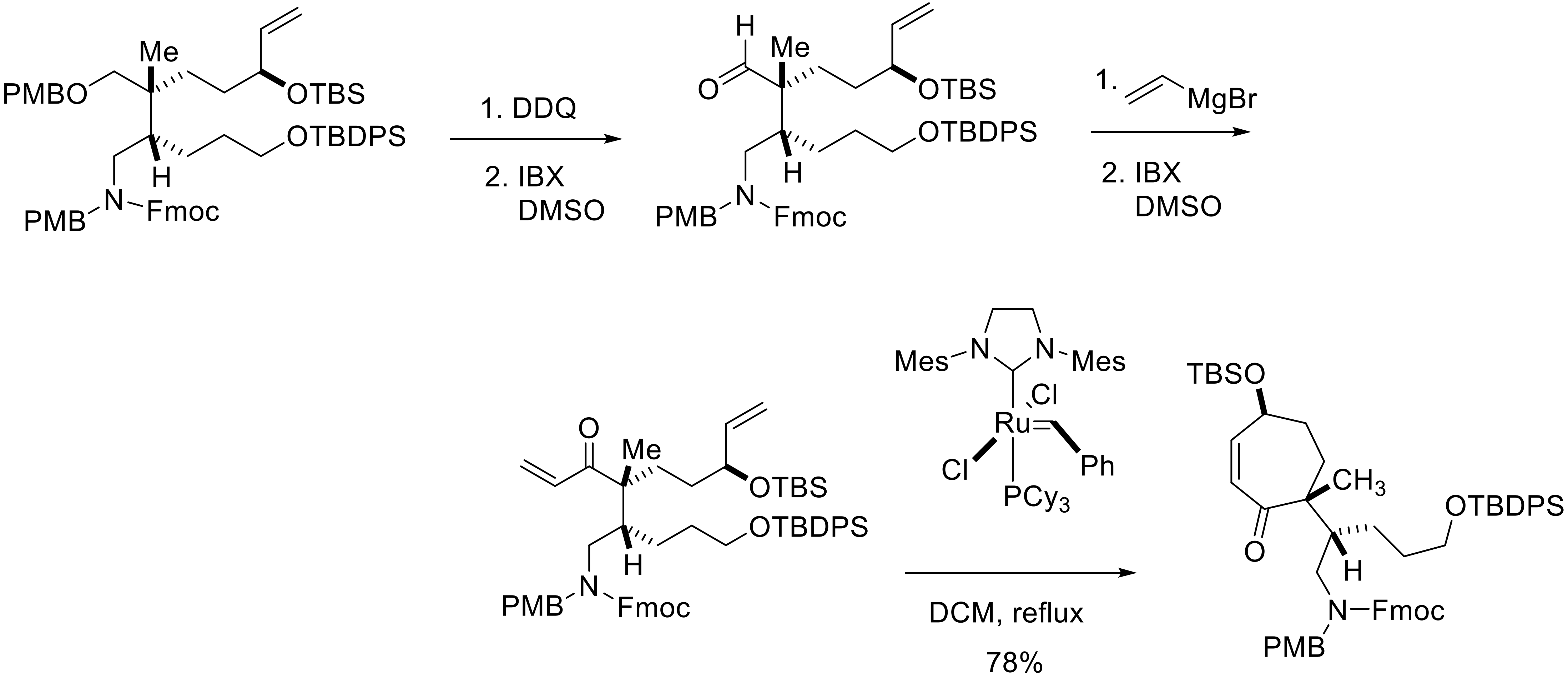




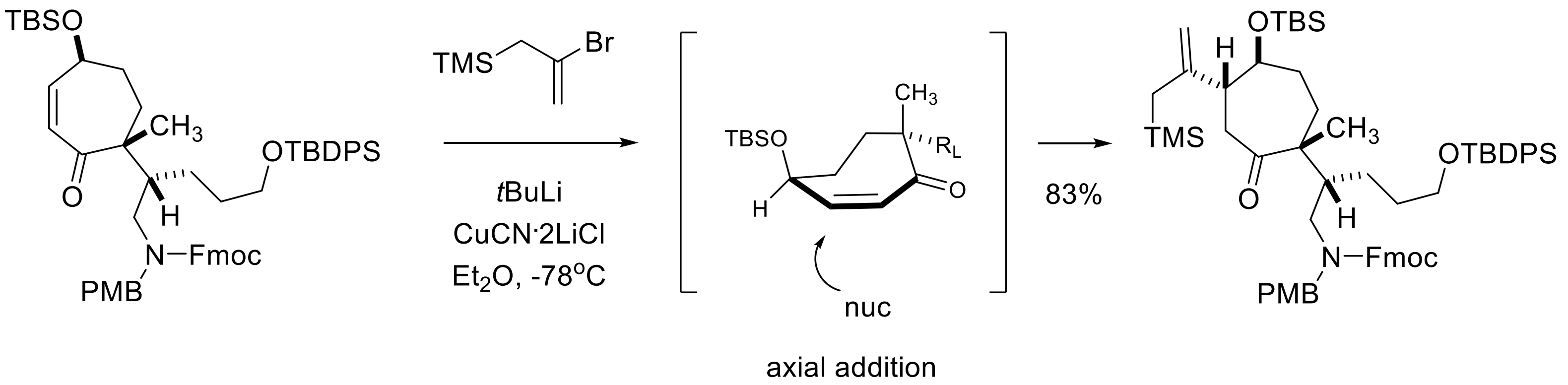
A **B** **C** **D**

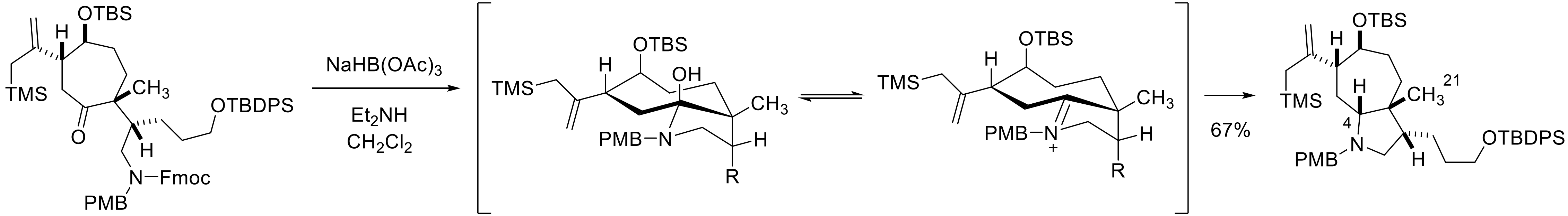
Oppolzer *et al*. *Tet. Lett.* **1991**, *32,* 5777-5800
Myers *et al. Org Lett*. **2007**, *9*, 3523-3525

Closure of the Cycloheptanone via RCM

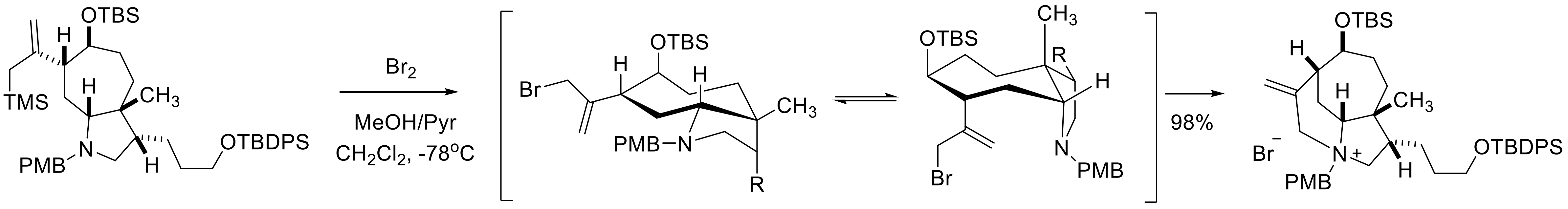


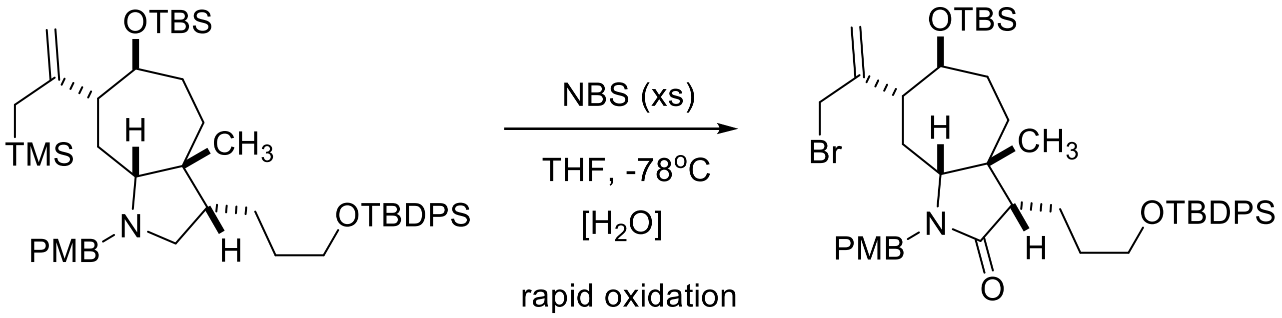
Closure of the C Ring



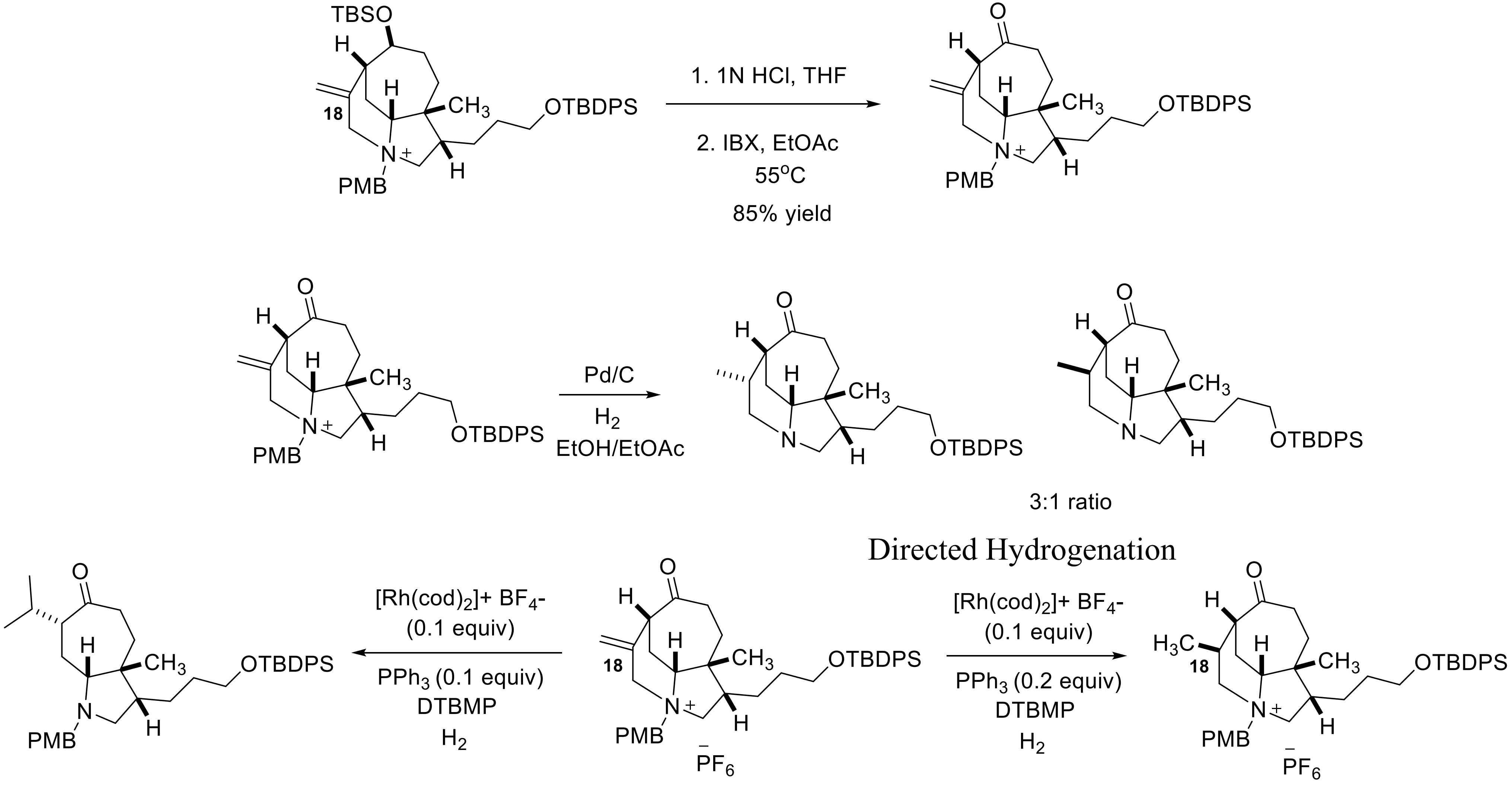


Closure of the B Ring



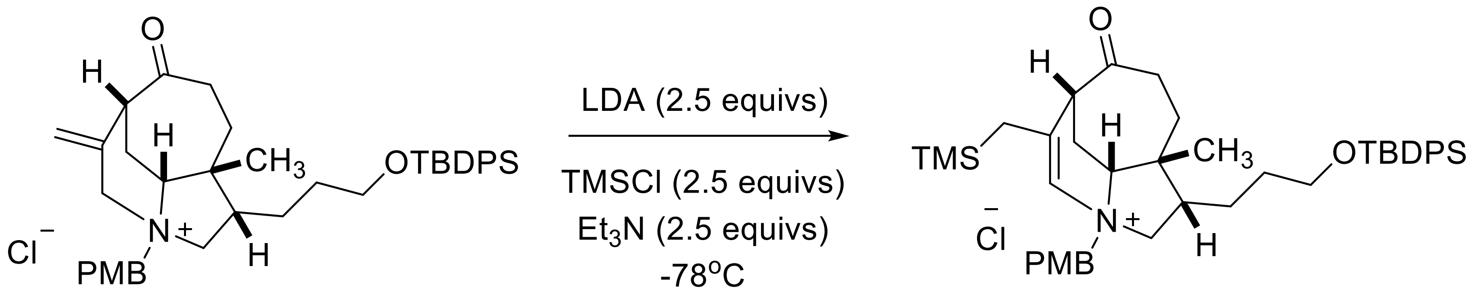


Directed Hydrogenation

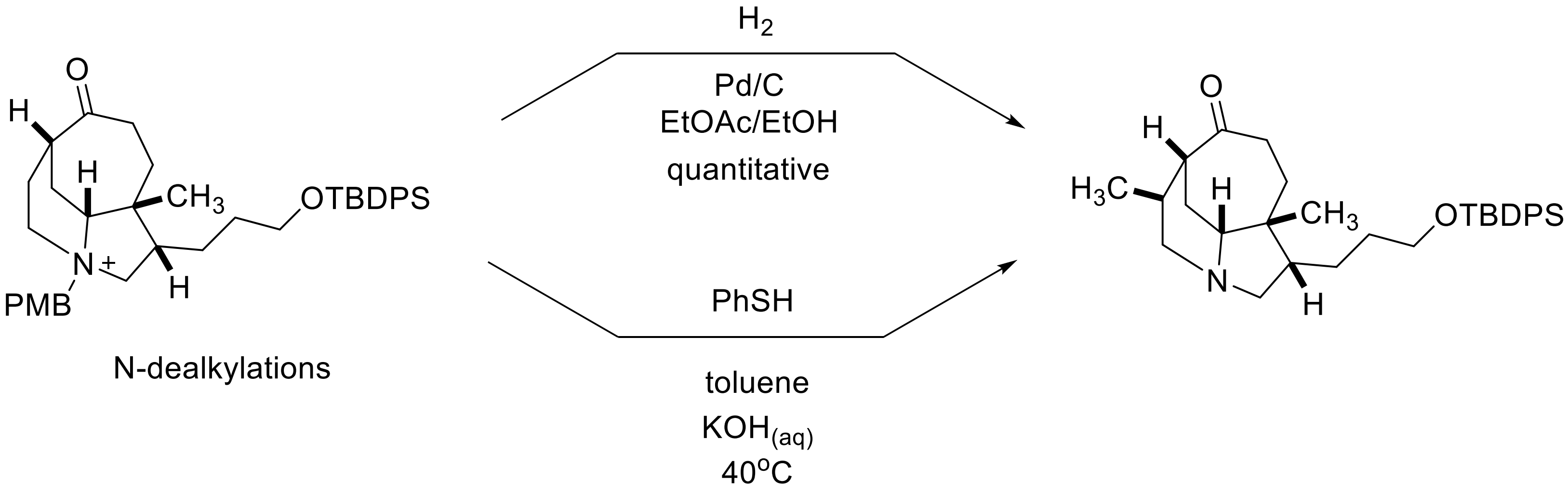


For an amide directed reduction: Li *et al*. *J. Am. Chem. Soc.* **2017**, *139,* 14893-14896.

Kinetic Deprotonation

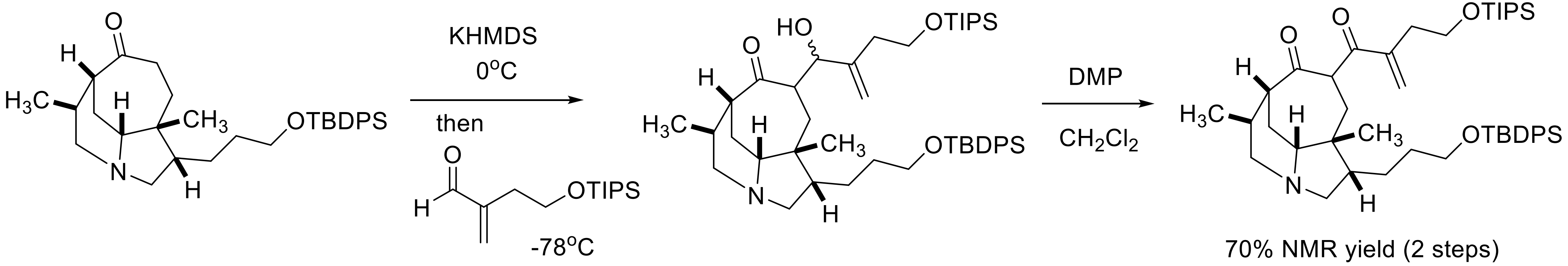


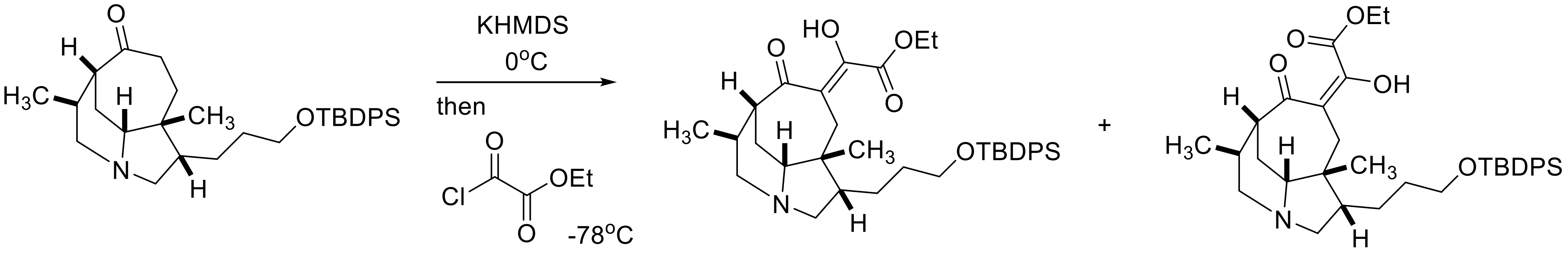
Kinetic Deprotonation
[< 20% MeOD Incorporation]



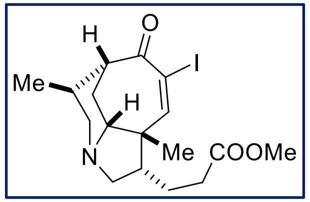
N-dealkylations

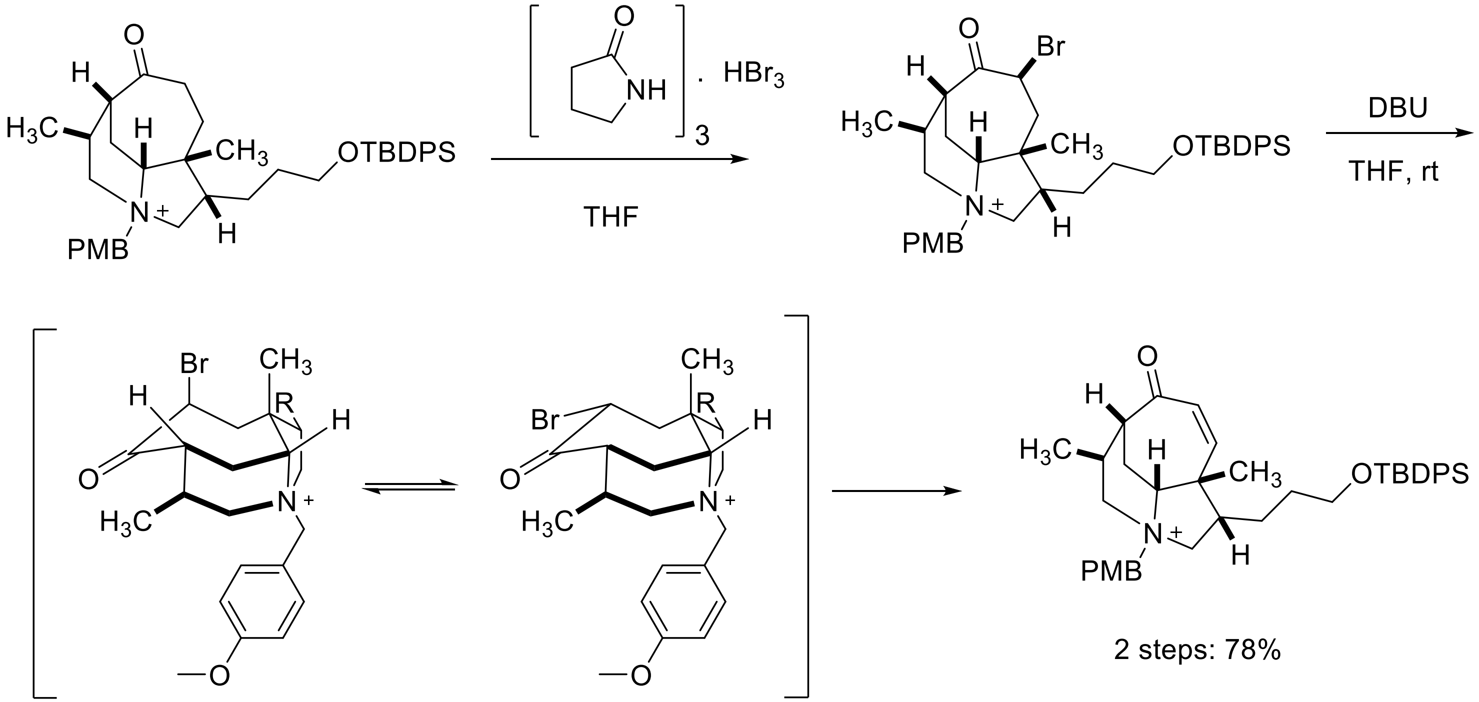
Aldol Additions

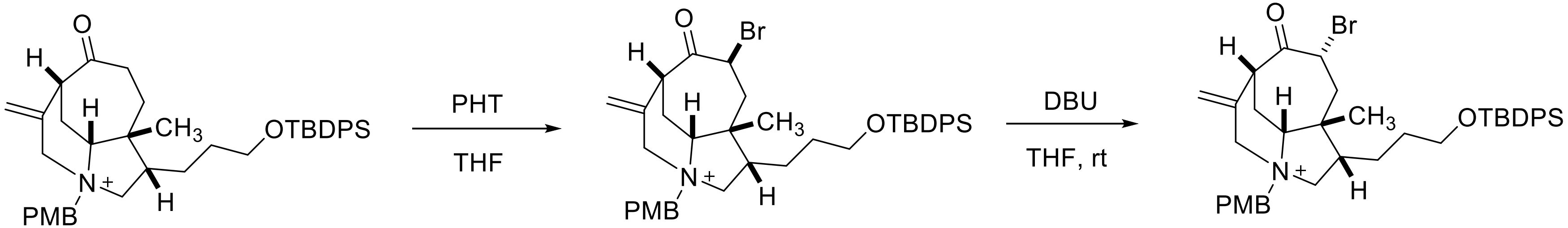




Facile Elimination to Form Enone

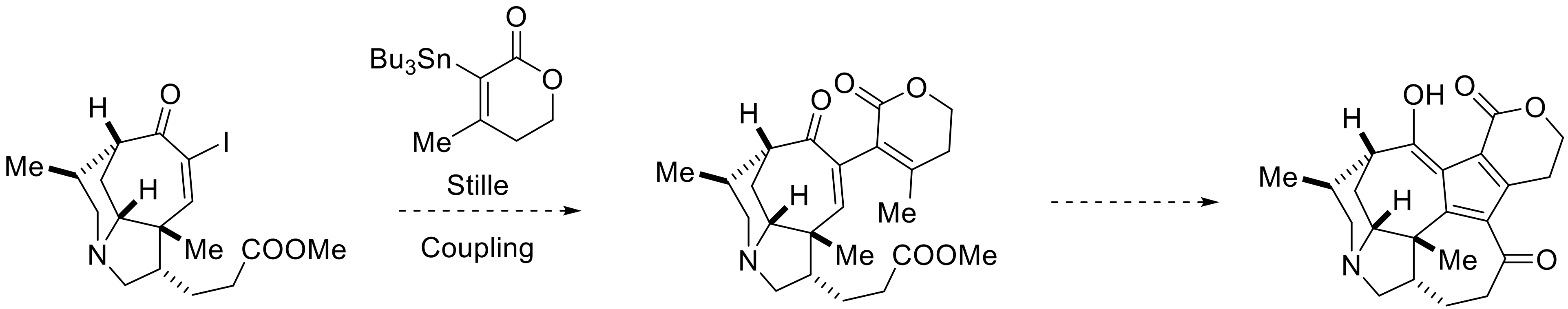




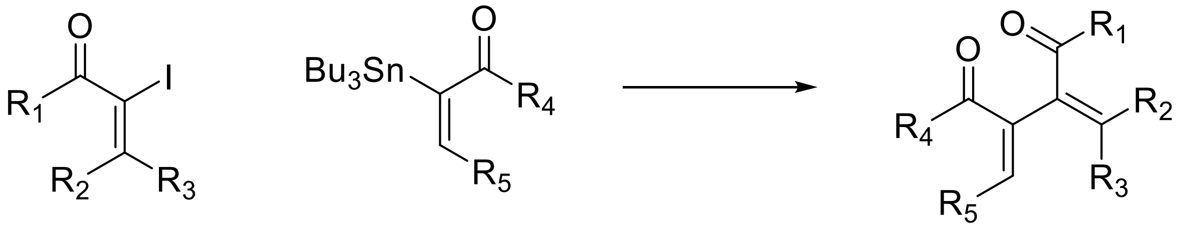


PHT: Wolfe *et al. Can. J. Chem.* **1969**, *47*, 706-709

Synthesis Hypothesis



"Ligandless" Palladium Reactions for Synthesis of a-Linked Bis-Enone Systems

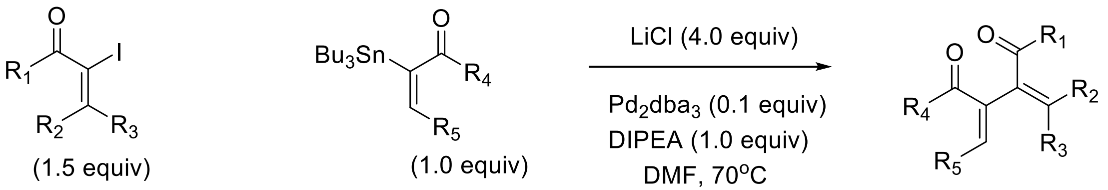


Selected Optimization Studies:

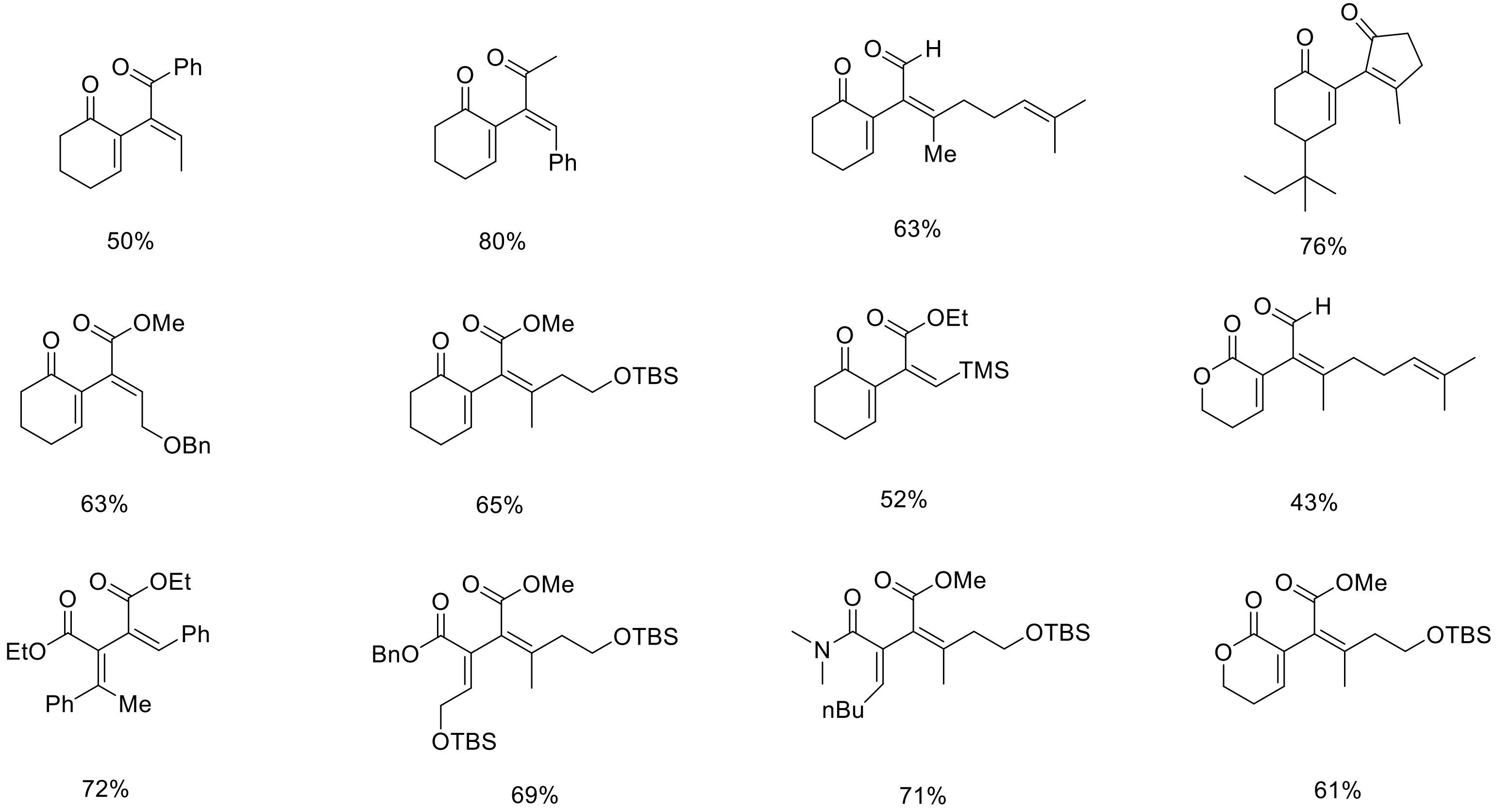
	Conditions			
Entry	**Catalyst (0.1 equiv)**	**Additive**	**Ligand**	**Yield**
1	$Pd(PPh_3)_4$	CuCl (5 equiv), LiCl (6 equiv)	none	0%
2	$Pd(PPh_3)_2Cl_2$	CuI	none	0%
3	Pd_2dba_3	LiCl (4.0 equiv)	Tri(2-furyl)phosphine (0.8 equiv)	0%
4	Pd_2dba_3	CuI	$AsPh_3$	10%
5	Pd_2dba_3	LiCl (4.0 equiv), CuI (0.8 equiv)	none	38%
6	Pd_2dba_3	LiCl (4.0 equiv), TBAI (2.0 equiv)	none	55%
7	Pd_2dba_3	LiCl (4.0 equiv)	DIPEA (1.0-3.0 equiv)	70%

Obora, *et al*. *Chem. Comm.* **2011**, *47,* 5750-5752.
Obora, *et al. J. Organomet. Chem*. **2013**, 258-262, 745-746.

Stille Cross Coupling Results

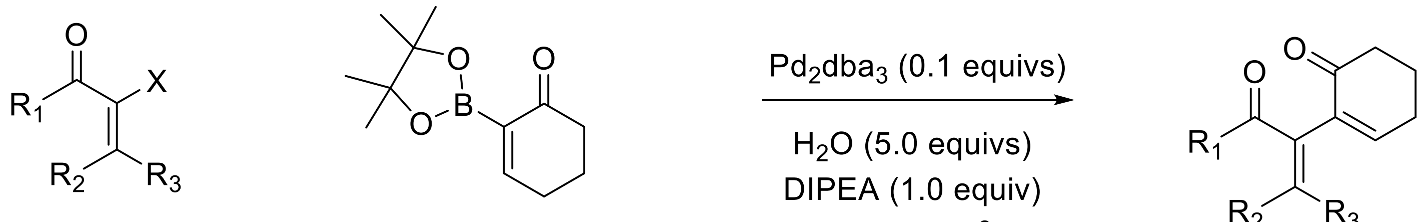


Examples:



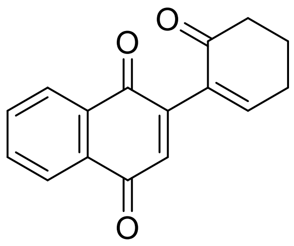
Williams, *et al. Org. Lett.* **2017**, *19*, 1730-1733.

Suzuki-Miyaura Cross Coupling Results

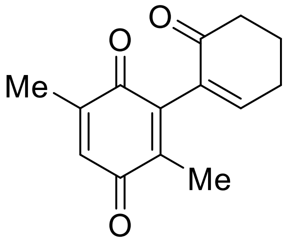


(X = OTf or I)

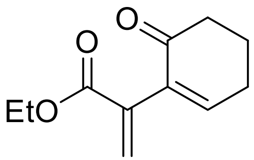
Examples:



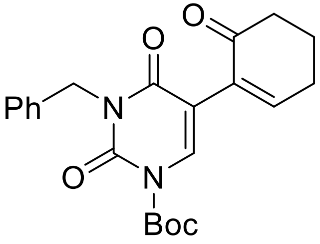
77%



80%



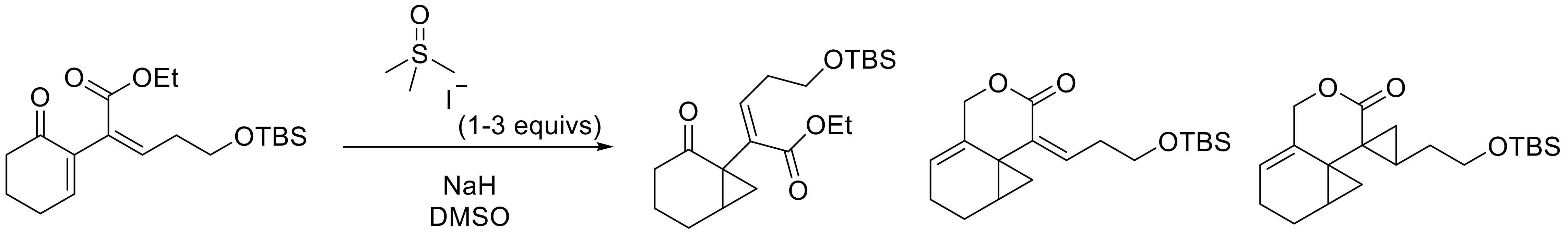
75%

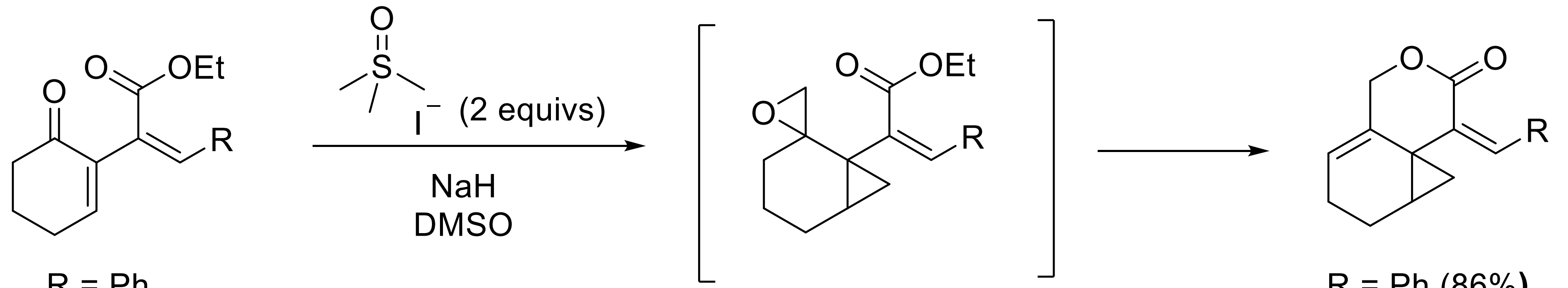


69%

Williams, *et al.* *Org. Lett.* **2017**, *19*, 1730-1733.

Corey – Chaykovsky Reaction

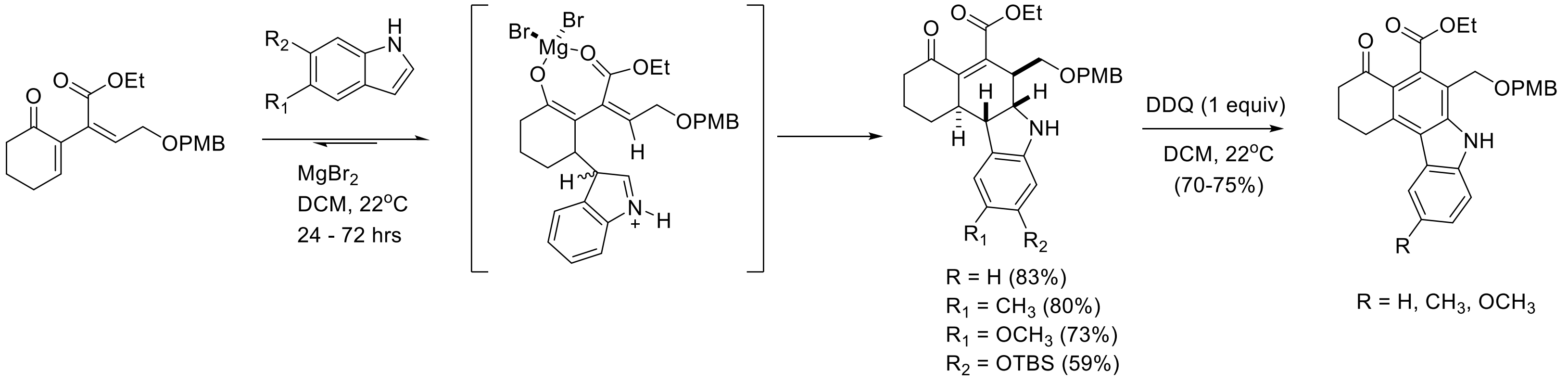


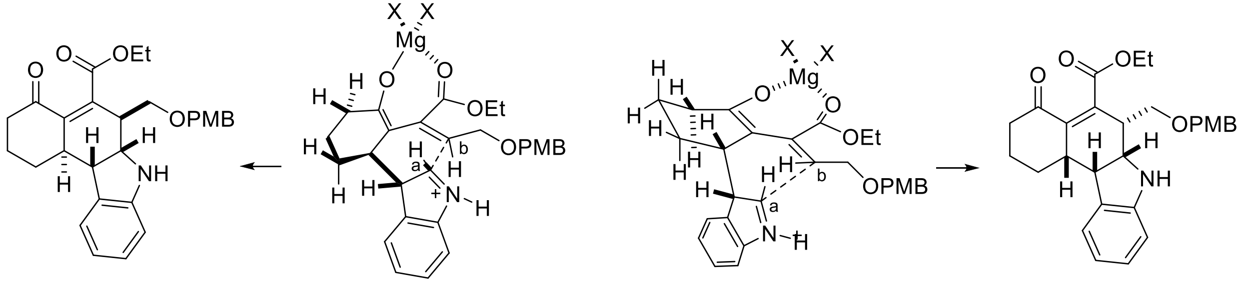


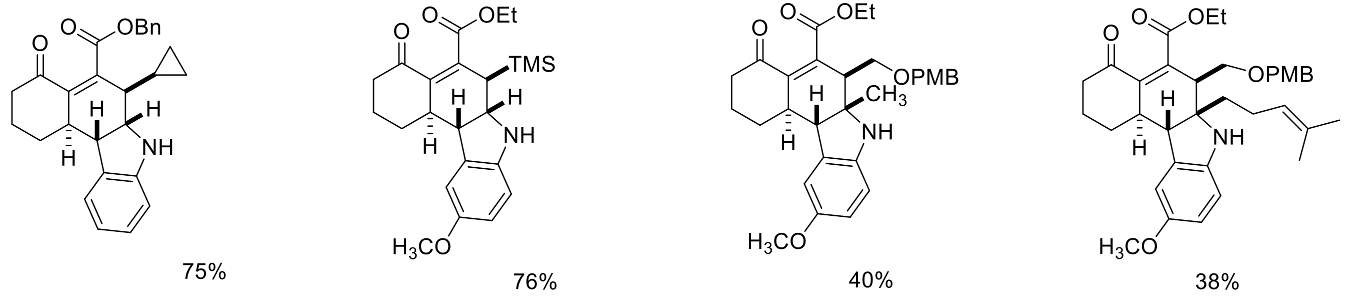
R = Ph
R = TMS

R = Ph (86%)
R = TMS (87%)

Stereocontrolled Synthesis of Tetrahydrocarbazoles

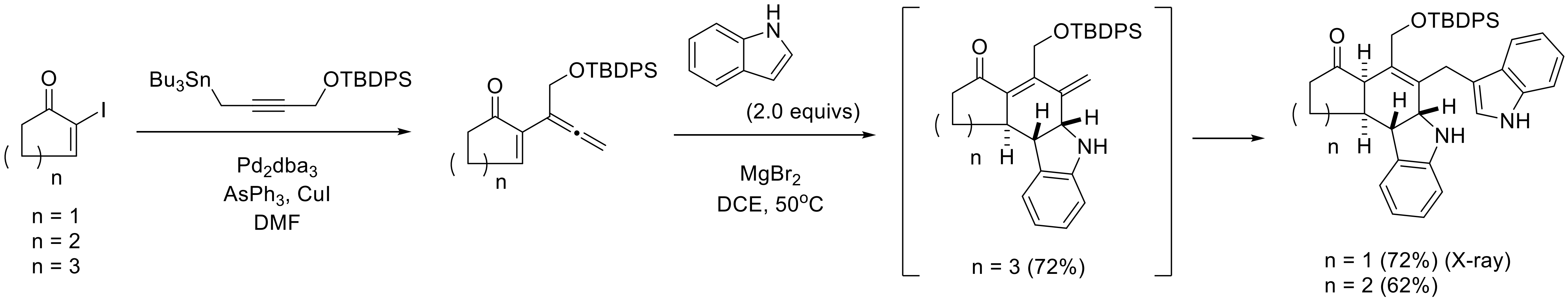


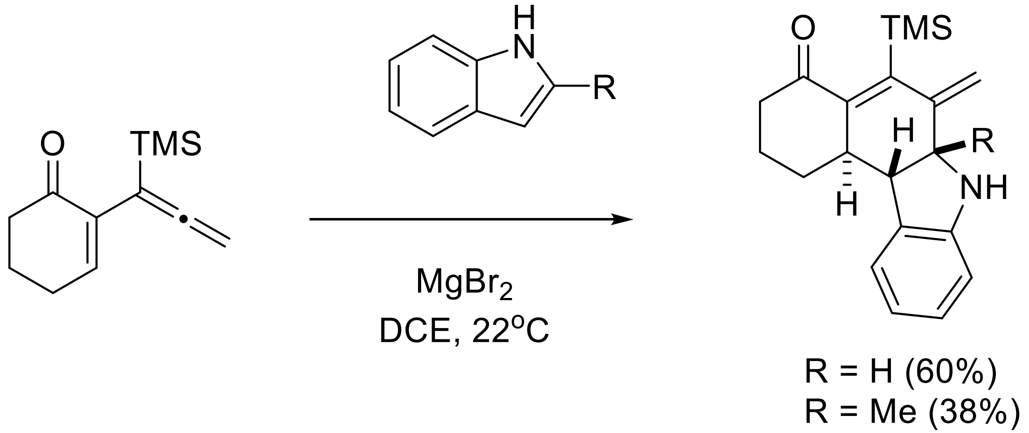




Williams, *et al. Org. Lett.* **2017**, *19*, 5098-5101.

Sequential Conjugate Additions Yield Bis-Indoles





Williams, *et al. Org. Lett.* **2017**, *19*, 5098-5101.