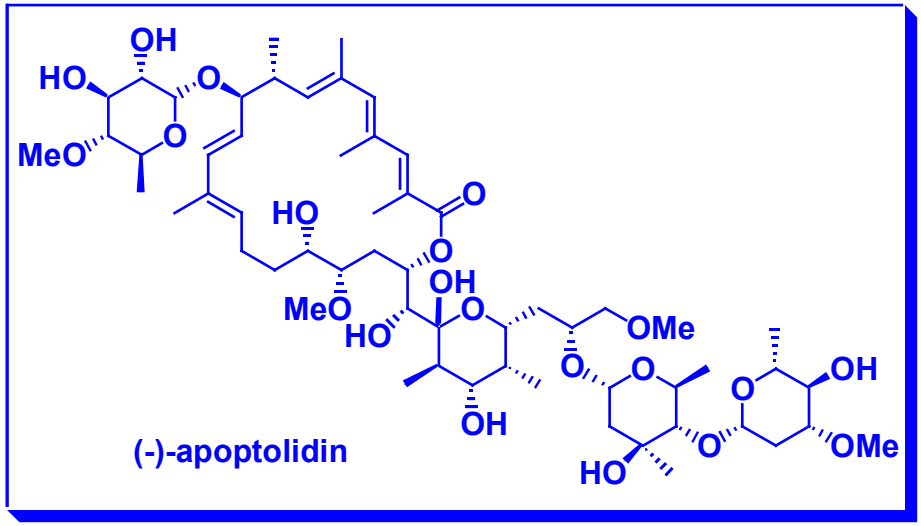
Studies on the Total Synthesis of (-)-Apoptolidin

Xiaorong Liu

University of Rochester

November 2004

(-)-Apoptolidin



(-)-apoptolidin

. Isolated from cultures of *Nocardiopsis* sp. in 1997 and characterized in 1998.

. A 20-membered macrocyclic lactone glycoside.

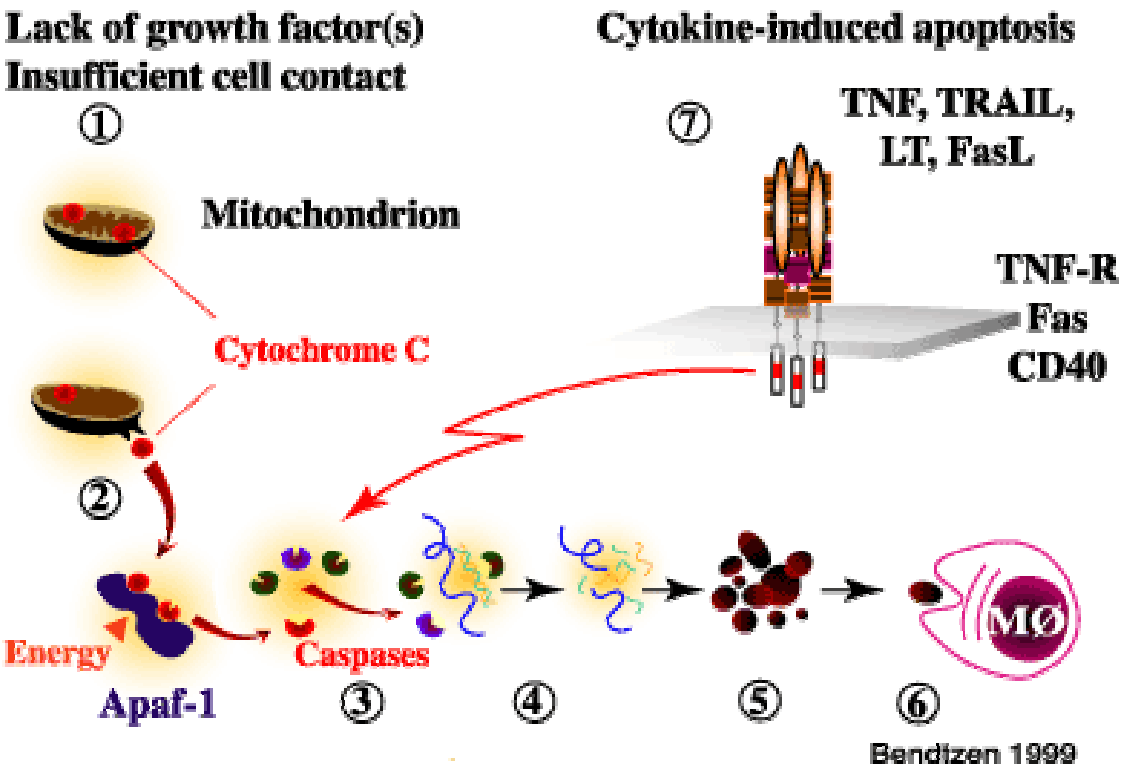
. Specifically induces cell death via apoptosis in rat glia cells transformed by the E1A and E1A/E1B 19K oncogenes while having no cytotoxic effect on the untransformed cell lines

Hayakawa, Y.; et al. *J. Antibiot.* **1997**, *50*, 628.

Hayakawa, Y.; et al. *J. Am. Chem. Soc.* **1998**, *120*, 3524.

How Does Apoptolidin Work?

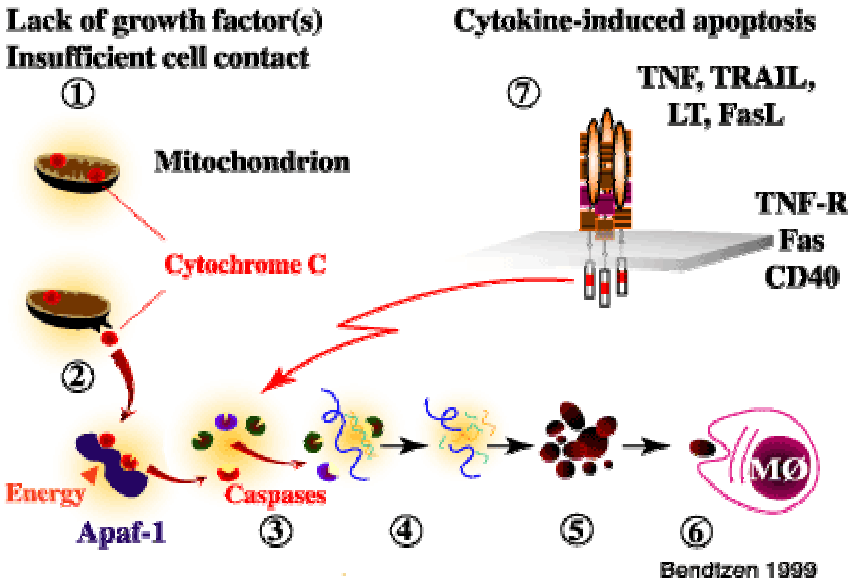
Apoptosis



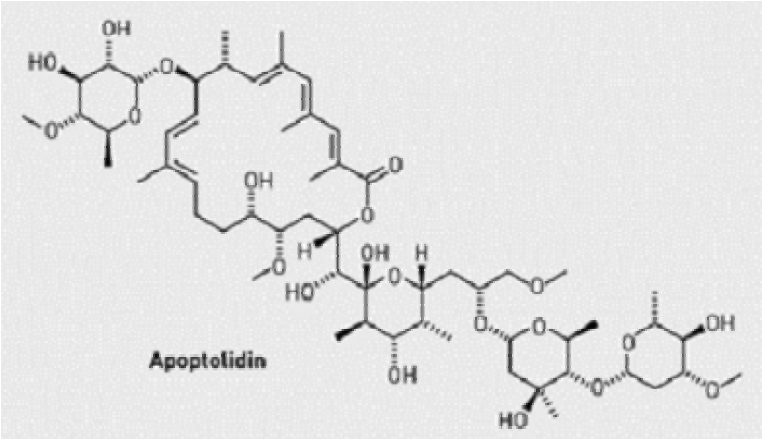
Bovin, L. F.; Bendtzen, K. *Ugeskr Laeger* **1999**, *161*, 5778;

How Does Apoptolidin Work?

Apoptosis



Apoptolidin



Cellular Target: Mitochondrial F_0F_1 ATPase

Structure/Activity Relationship: The aglycone bestows biological activity

while the carbohydrate side chains facilitate cellular transport of the molecule to its mitochondrial target.

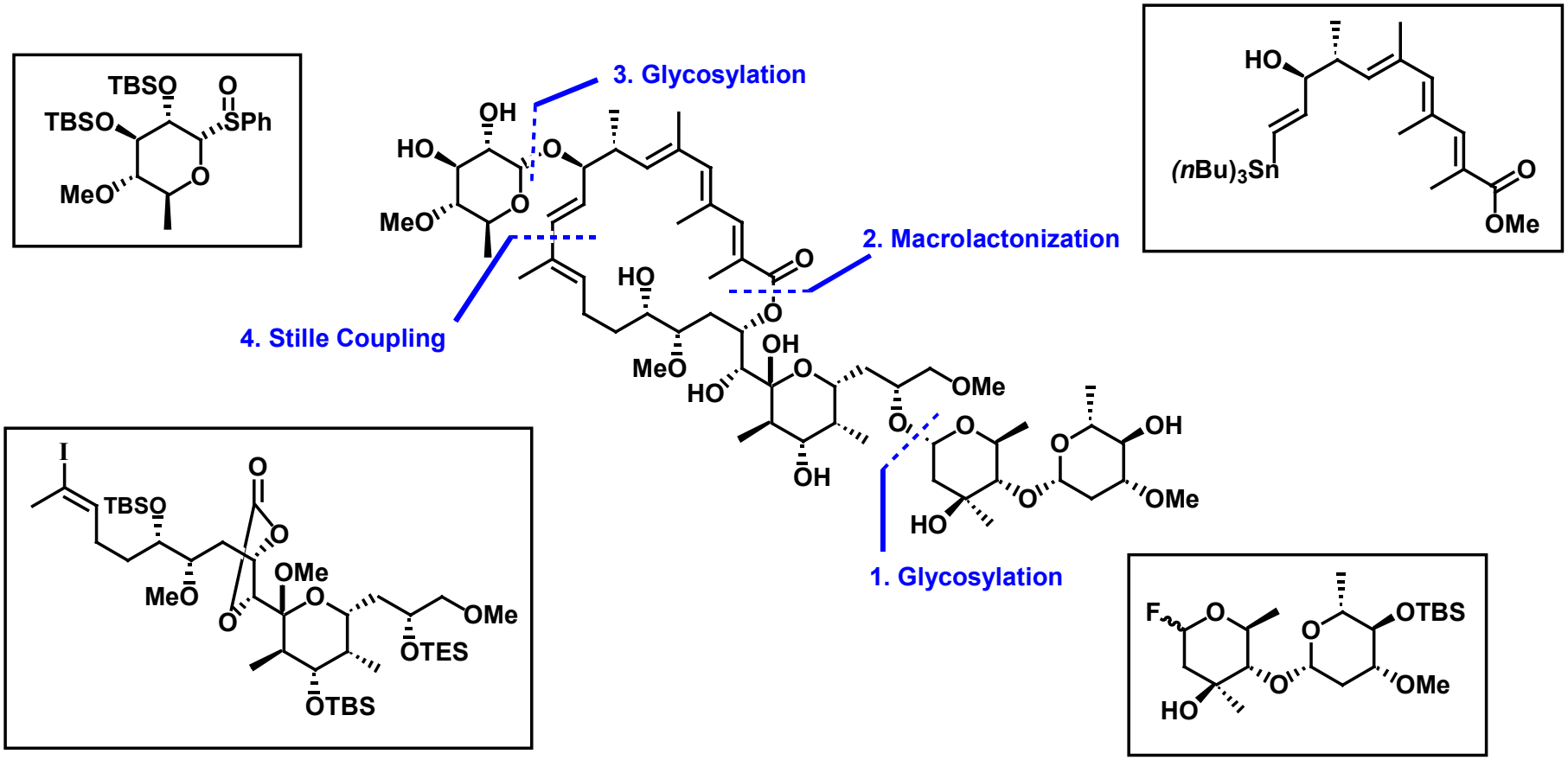
(a) Bovin, L. F.; Bendtzen, K. *Ugeskr Laeger* **1999**, *161*, 5778; (b) Khosla, C.; et al. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 14766; (c) Khosla, C.; et al. *Chemistry & Biology* **2001**, *8*, 71; (d) Khosla, C.; et al. *Org. Lett.* **2001**, *3*, 57.; (e) Wender, P. A.; et al. *Org. Lett.* **2002**, *4*, 3819; (f) Wender, P. A.; et al. *Org. Lett.* **2003**, *5*, 229; (g) Nicolaou, K. C ; et al. *J. Am. Chem. Soc.* **2003**, *125*, 15443

Previous Total Synthesis

- **K . C. Nicolaou**

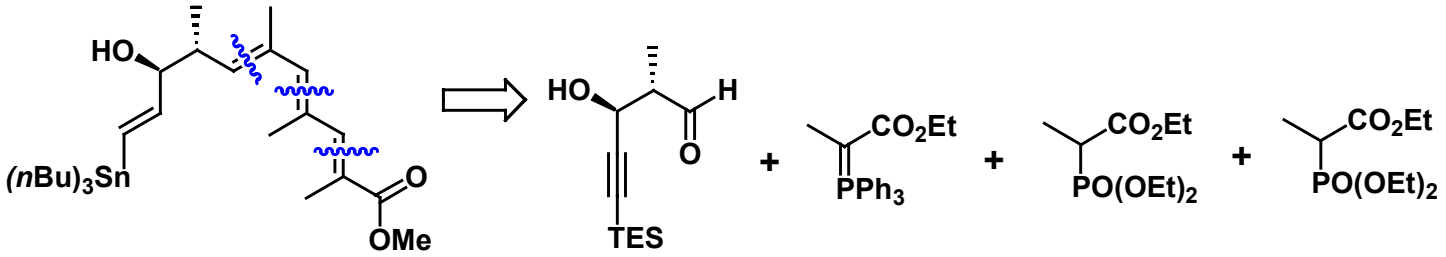
Total Synthesis of (-)-apoptolidin (2001)

Total Synthesis of analogue (2003)

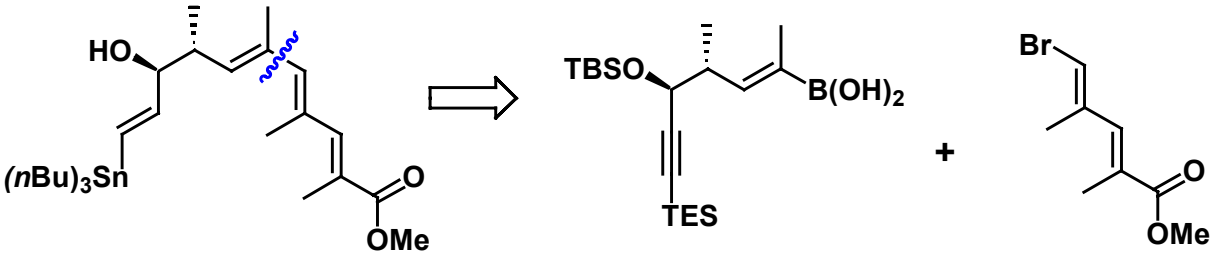


(a) Nicolaou, K. C.; et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 3854; (b) Nicolaou, K. C.; et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 3849; (c) Nicolaou, K. C.; et al. *J. Am. Chem. Soc.* **2003**, *125*, 15433; (d) Nicolaou, K. C.; et al. *J. Am. Chem. Soc.* **2003**, *125*, 15443.

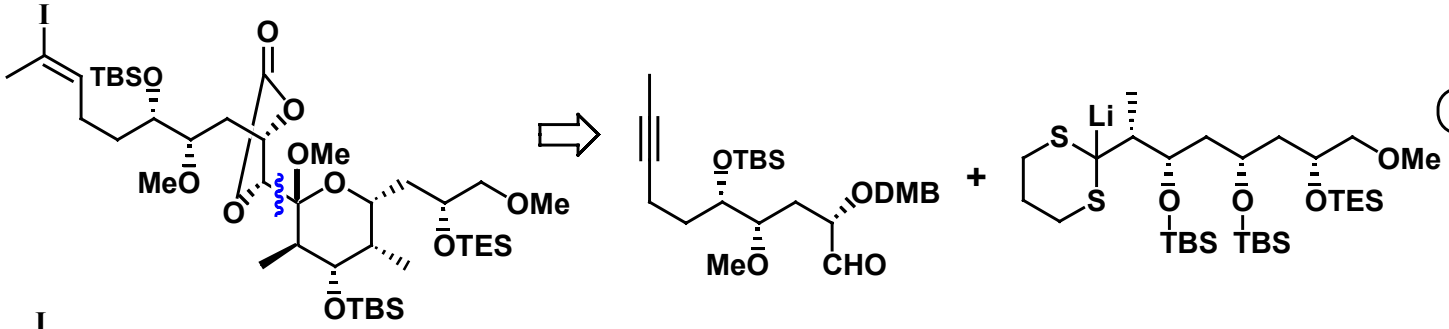
Previous Total Synthesis



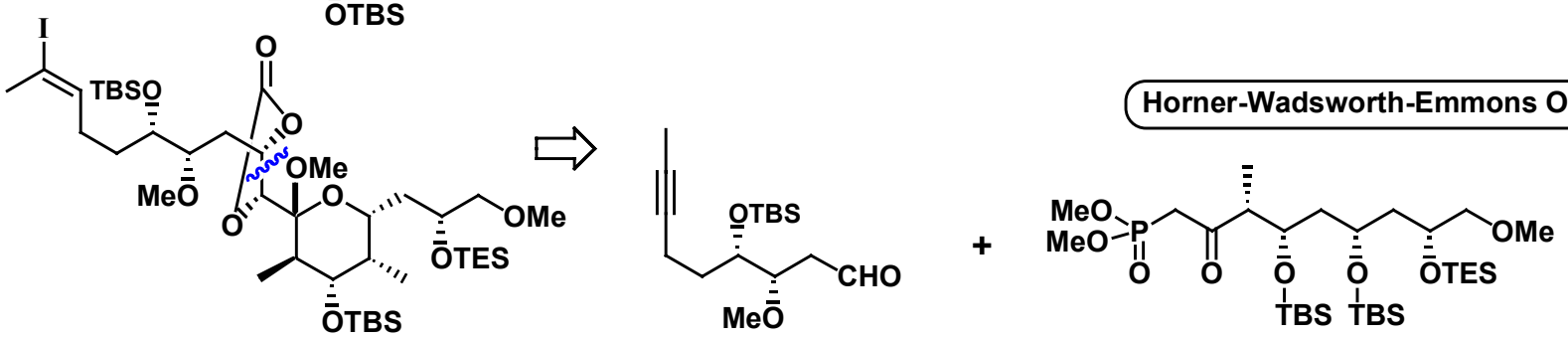
Olefination Approach



Suzuki Coupling Approach



Dithiane Coupling Approach



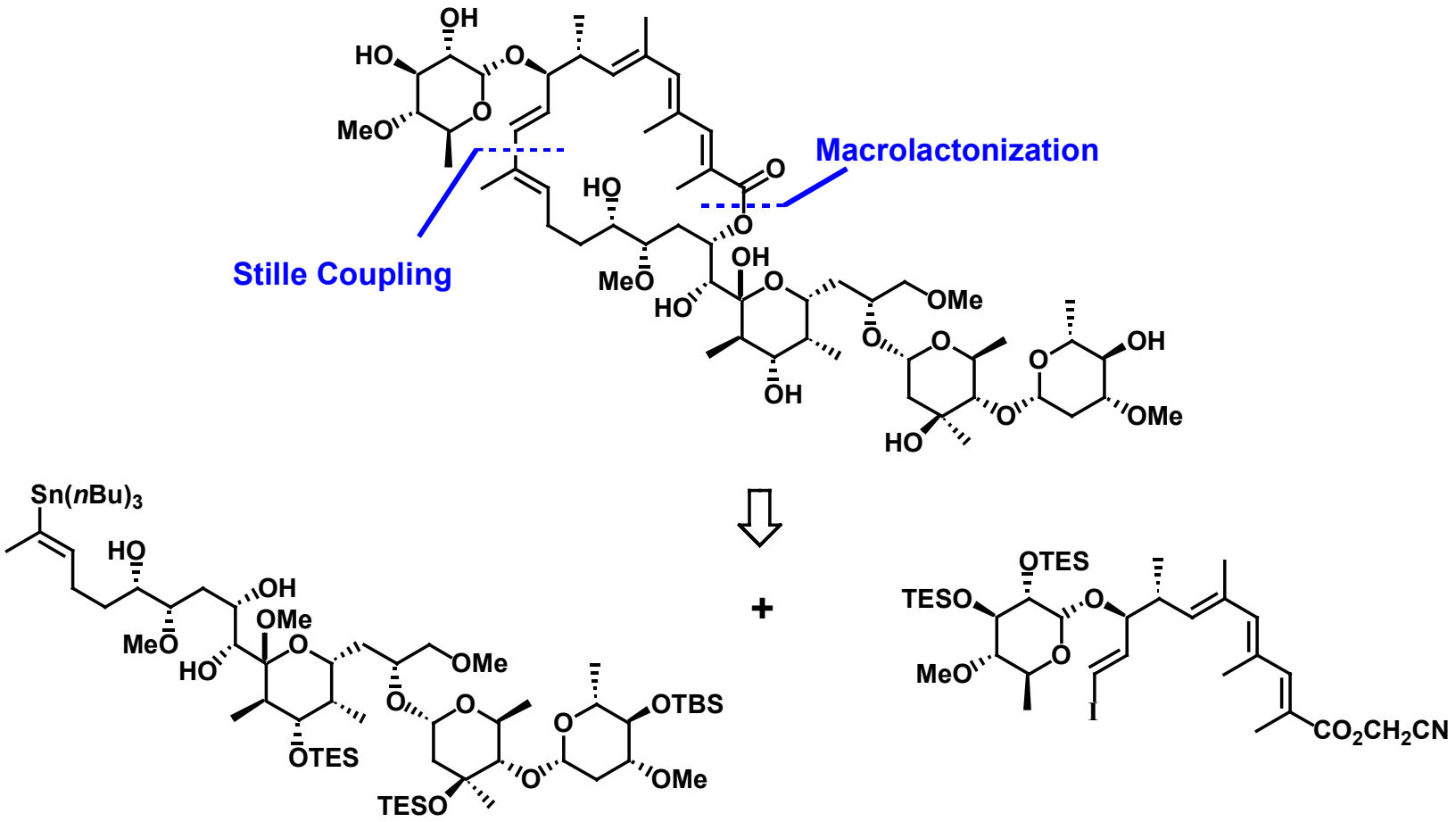
Horner-Wadsworth-Emmons Olefination Approach

(a) Nicolaou, K. C.; et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 3854; (b) Nicolaou, K. C.; et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 3849; (c) Nicolaou, K. C.; et al. *J. Am. Chem. Soc.* **2003**, *125*, 15433; (d) Nicolaou, K. C.; et al. *J. Am. Chem. Soc.* **2003**, *125*, 15443.

Previous Total Synthesis

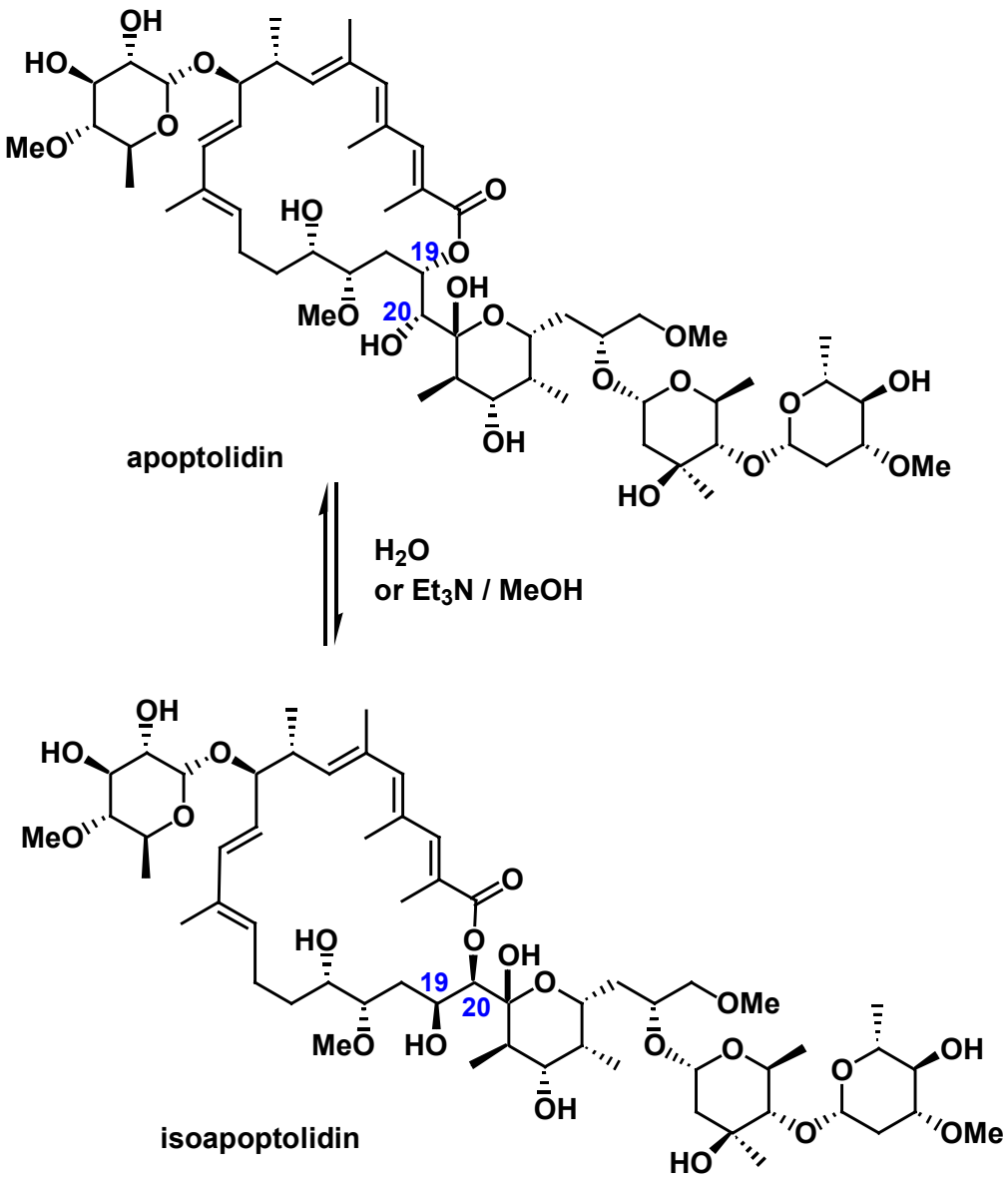
. U. Koert: Total Synthesis of apoptolidinone (2001)

Total Synthesis of (-)-apoptolidin (2004)



(a) Koert, U.; et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 2063; (b) Koert, U.; et al. *Angew. Chem. Int. Ed.* **2004**, *43*, 4597.

Stability

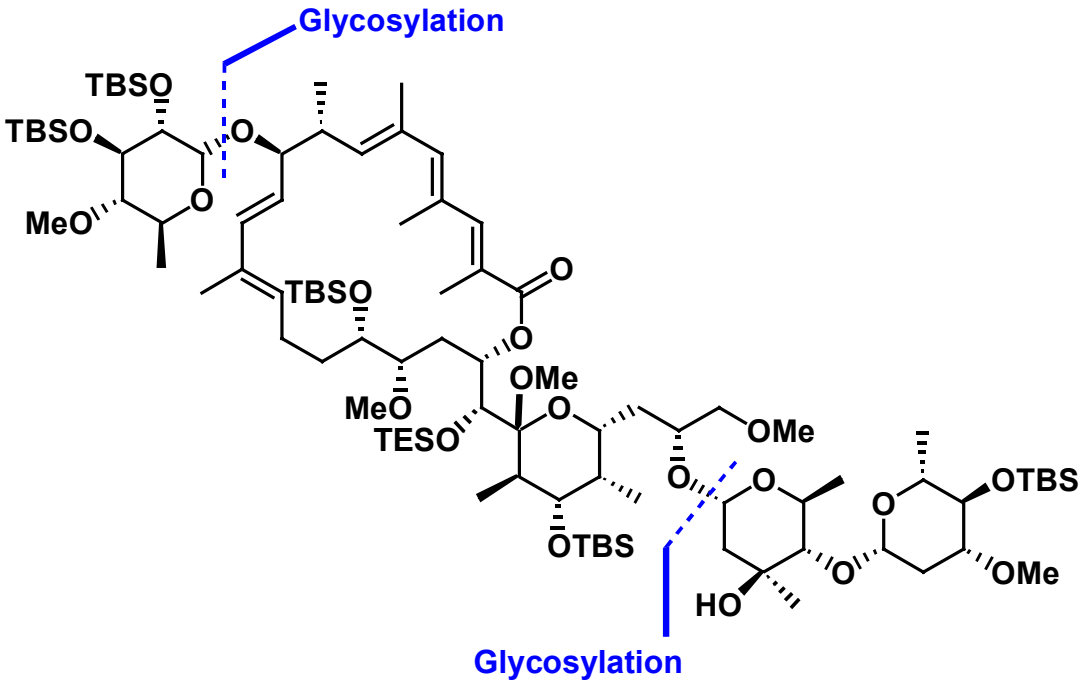


. **Isomerize in aqueous solution or slightly basic methanol to its ring expansion isomer**

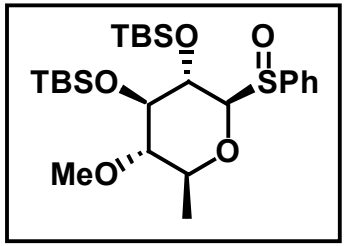
. **Acidic media proved more hospitable to the molecular**

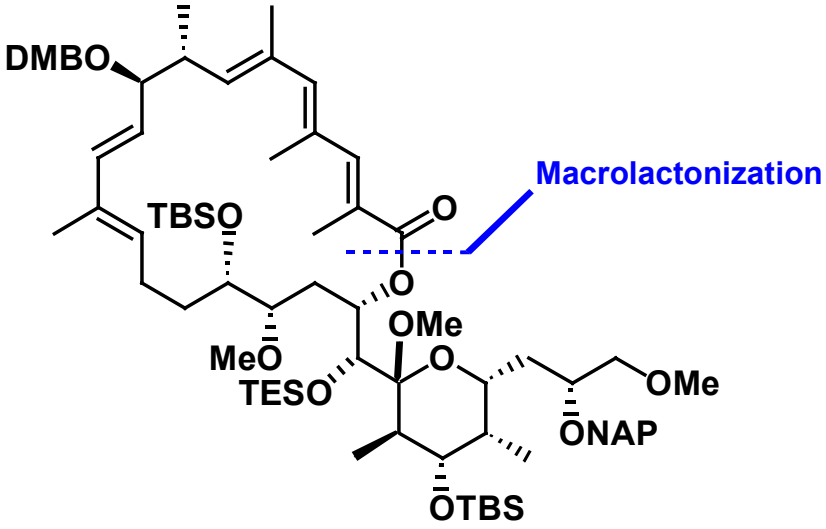
(a) Wender, P. A.; et al. *Org. Lett.* **2002**, *4*, 3819
(b) Wender, P. A.; et al. *Org. Lett.* **2003**, *5*, 229

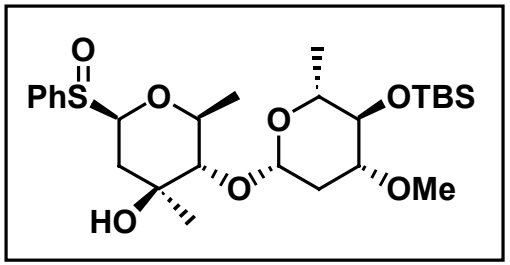
Retrosynthetic Analysis



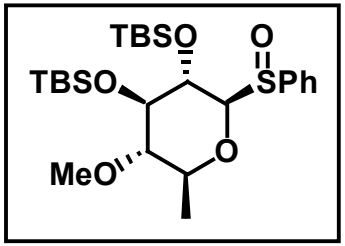
Retrosynthesis and Synthetic Strategy

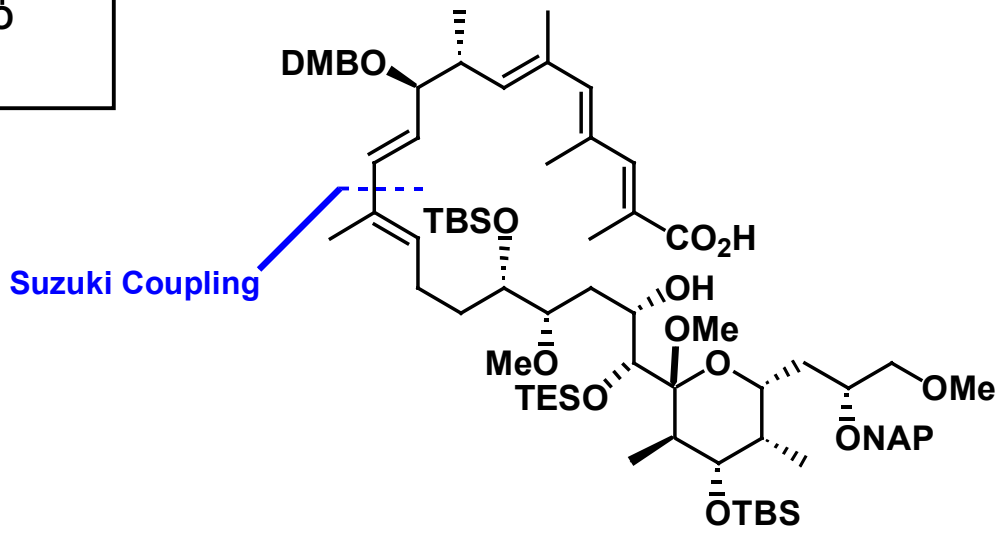


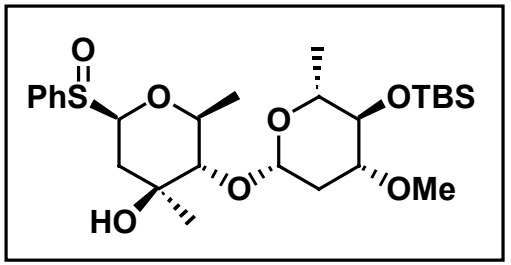




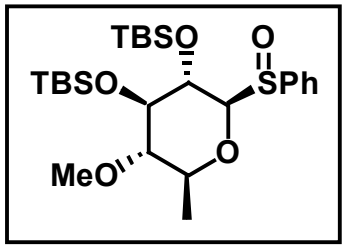
Retrosynthesis and Synthetic Strategy

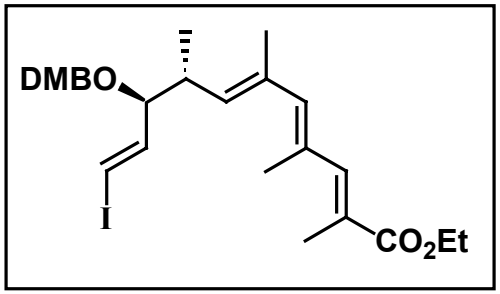


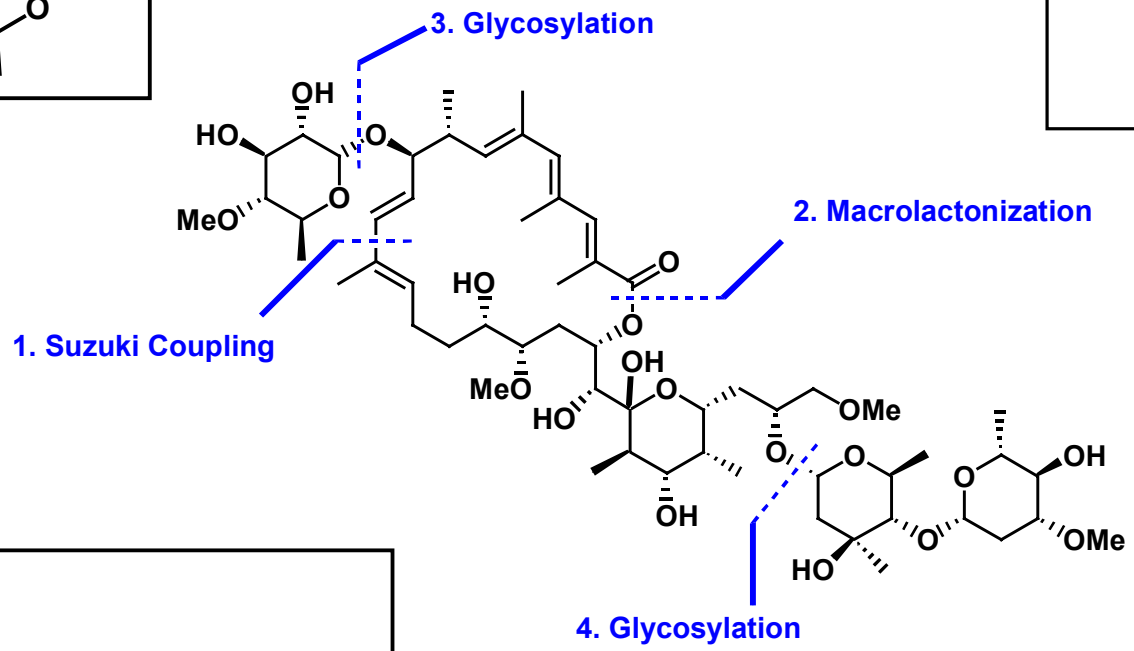


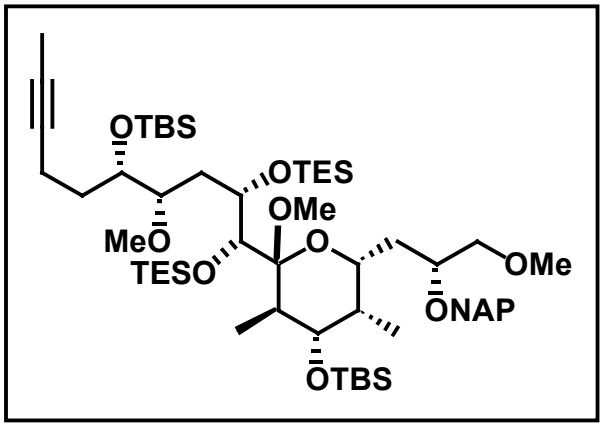


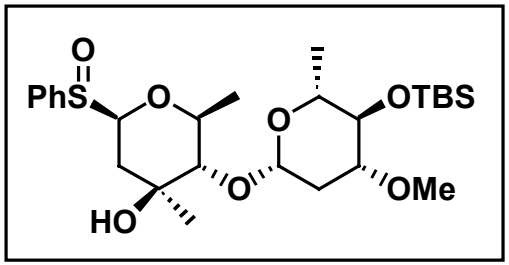
Retrosynthesis and Synthetic Strategy



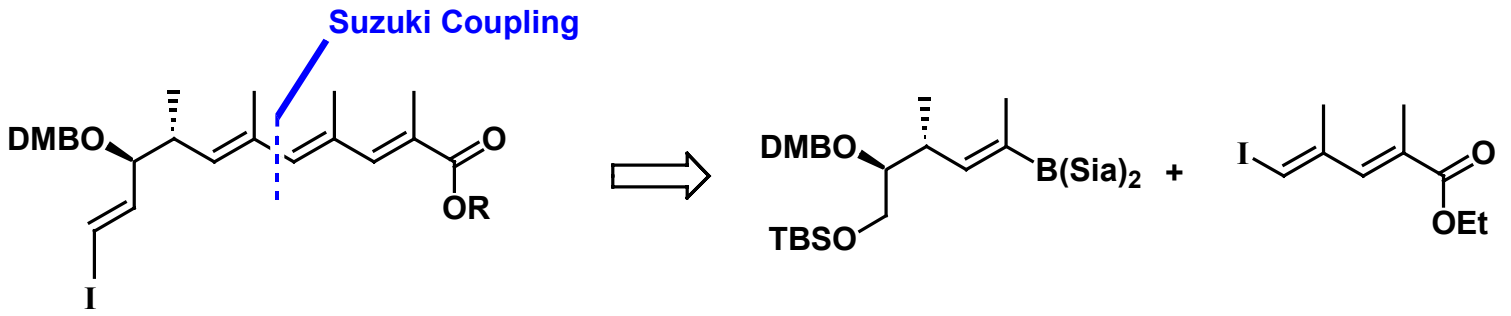




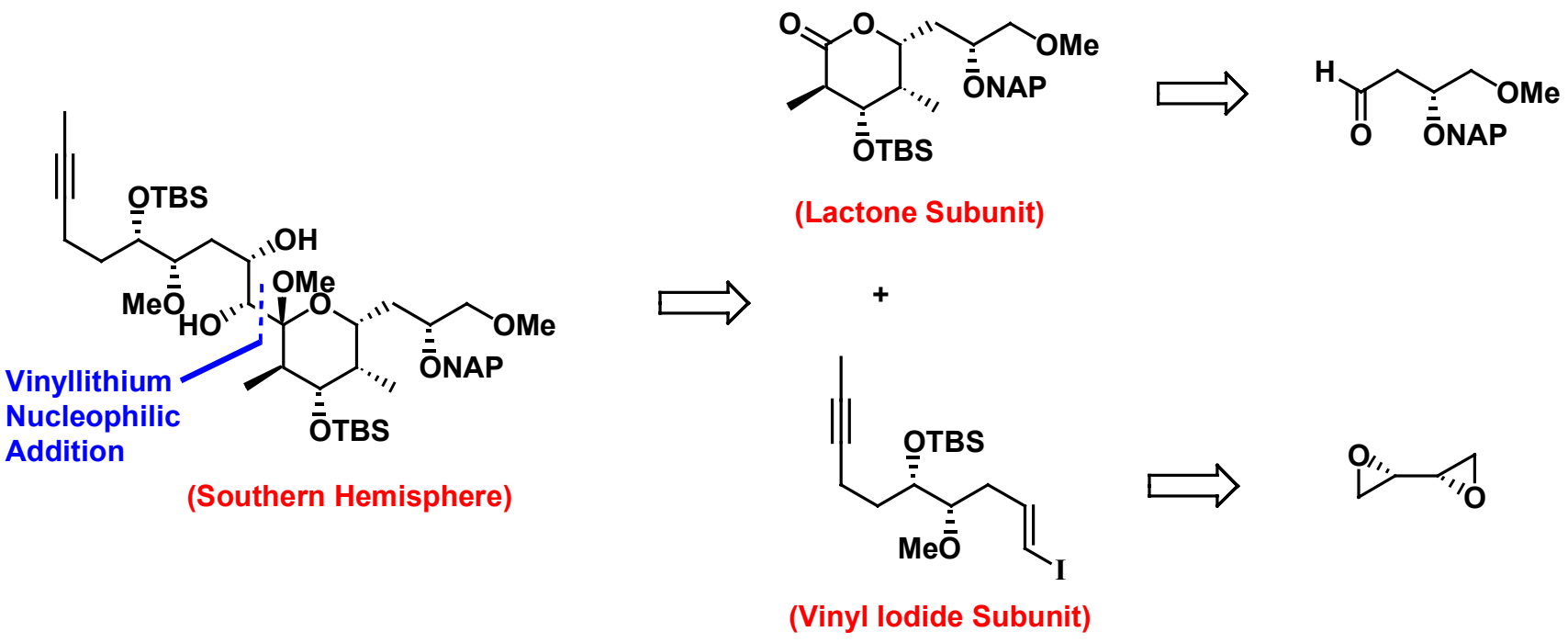




Retrosynthesis and Synthetic Strategy



(Northern Hemisphere)



(Southern Hemisphere)

(Lactone Subunit)

(Vinyl Iodide Subunit)

Contents

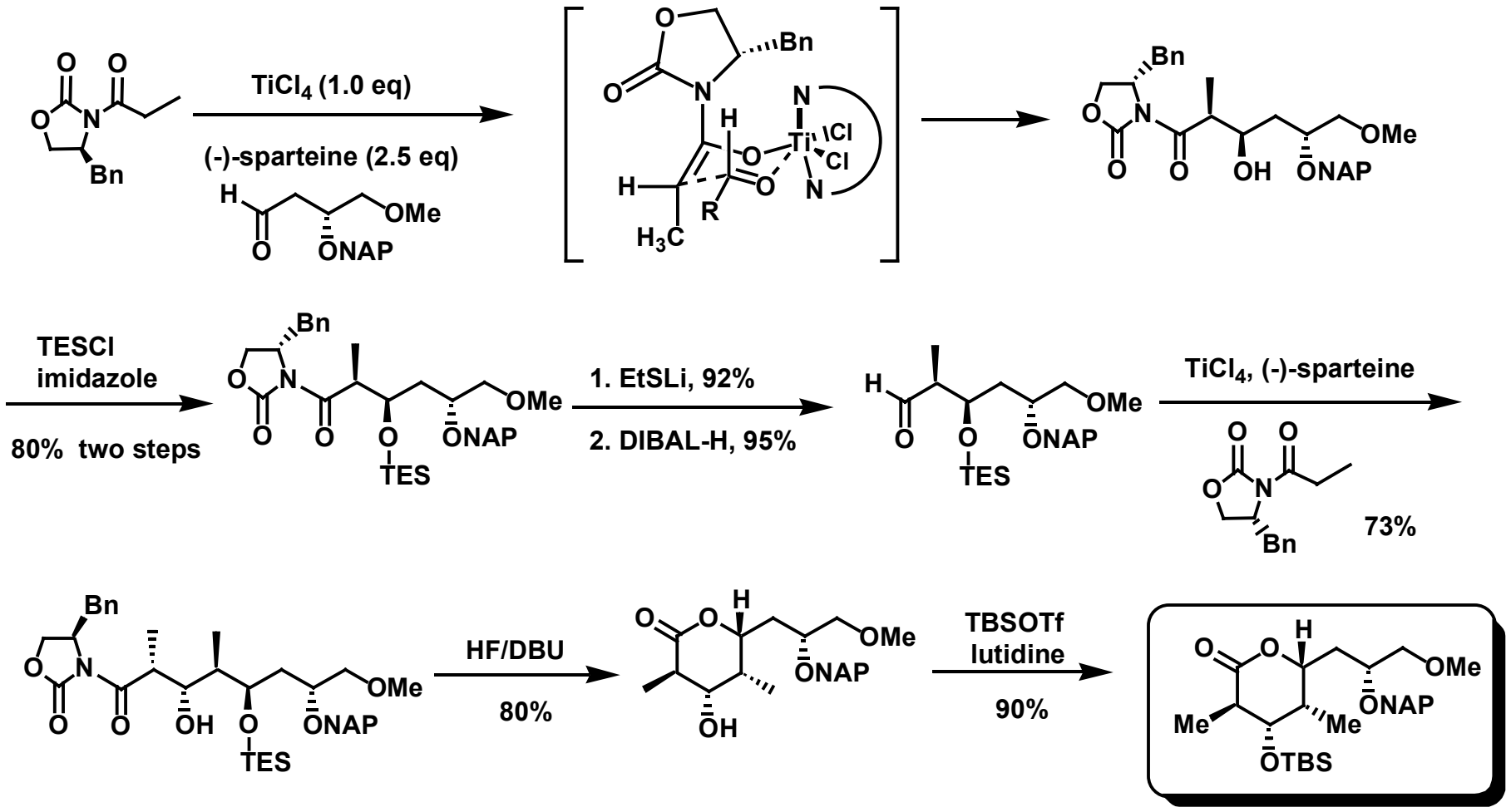
Background

- Construction of lactone subunit
- Construction of northern hemisphere

Results and Discussion

- Two-directional chain extention of a C_2 symmetric four carbon diepoxide as a route to the differentiated *syn*-1,2-diol
- Construction of vinyl iodide subunit
- Construction of southern hemisphere
- Improved synthesis of northern triene pieces
- Exploration of assembly of macrocycle of apoptolidin

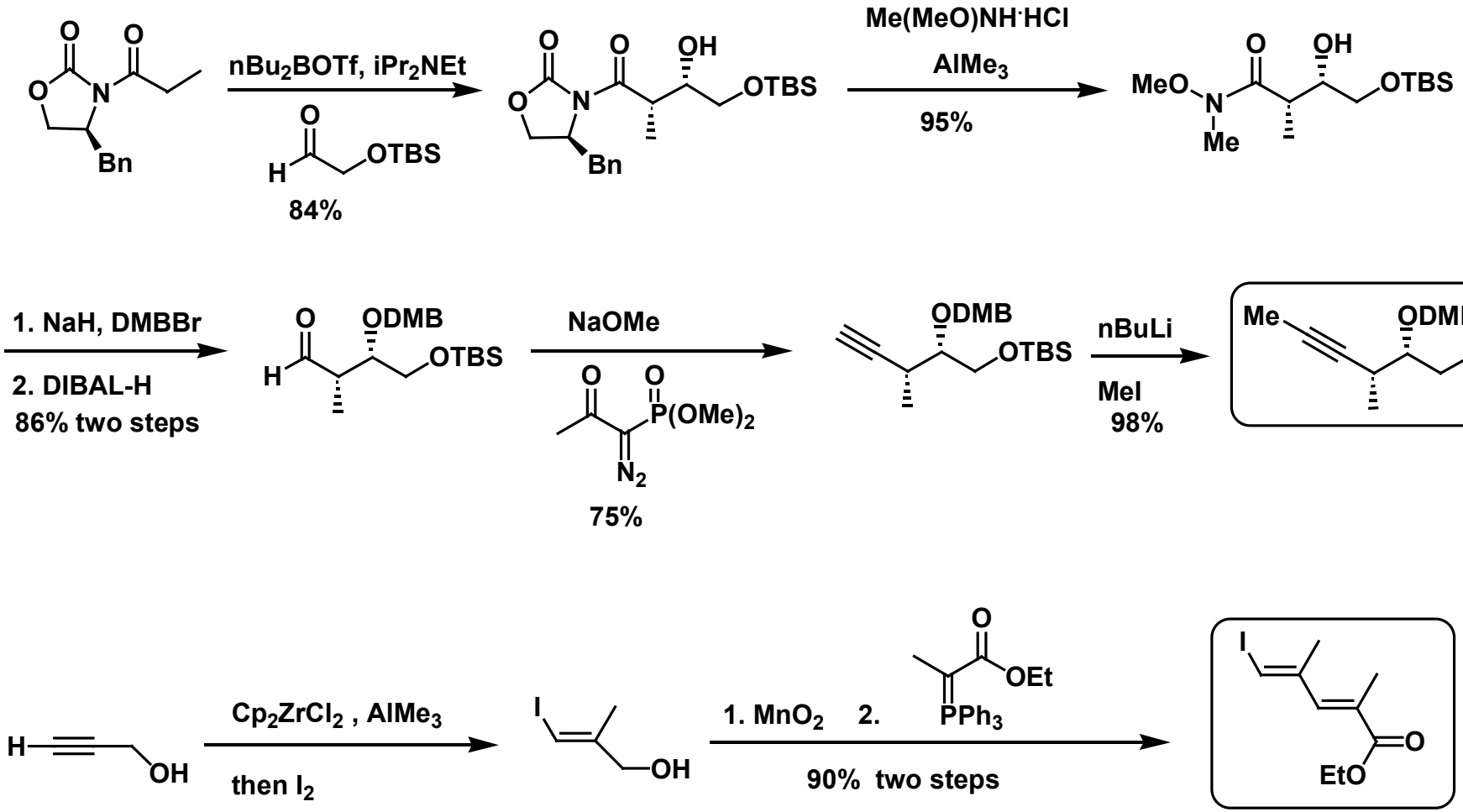
Construction of Lactone Subunit



Lactone Subunit was synthesized through a series of asymmetric aldol reactions

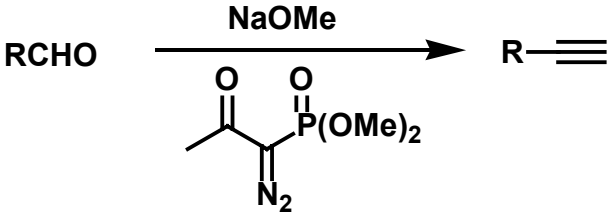
Gabriel Kapur

Construction of Northern Hemisphere



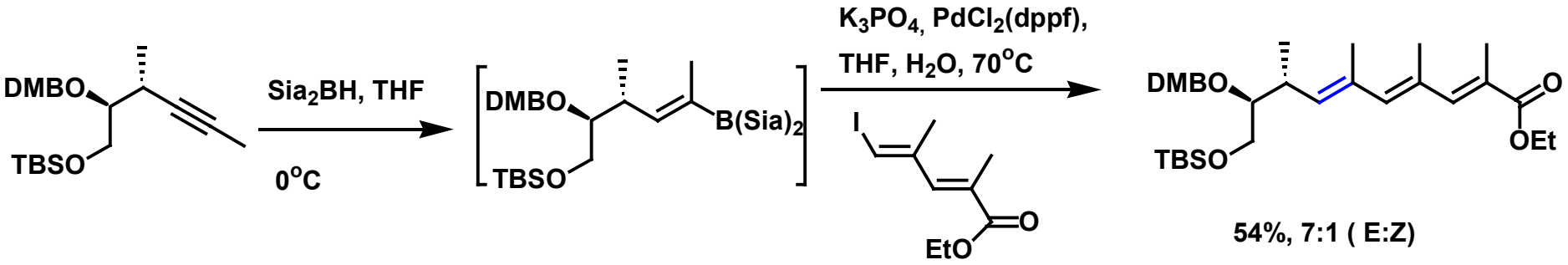
Christina Collison

Problem One

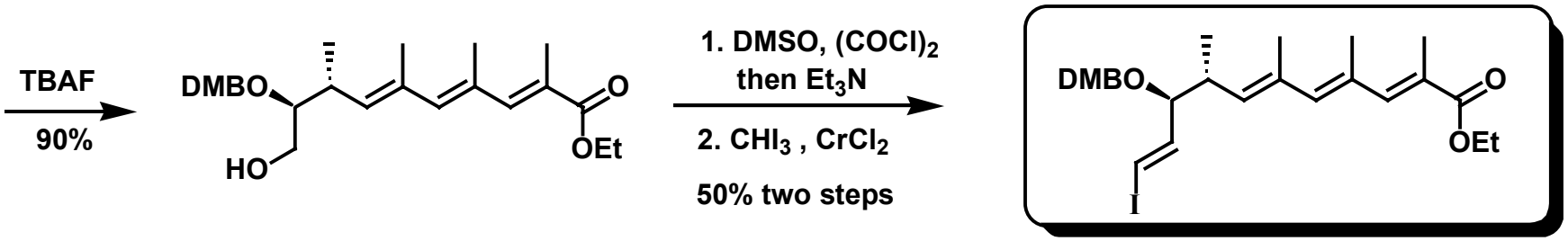


(Ohira-Bestmann reagent)

Construction of Northern Hemisphere



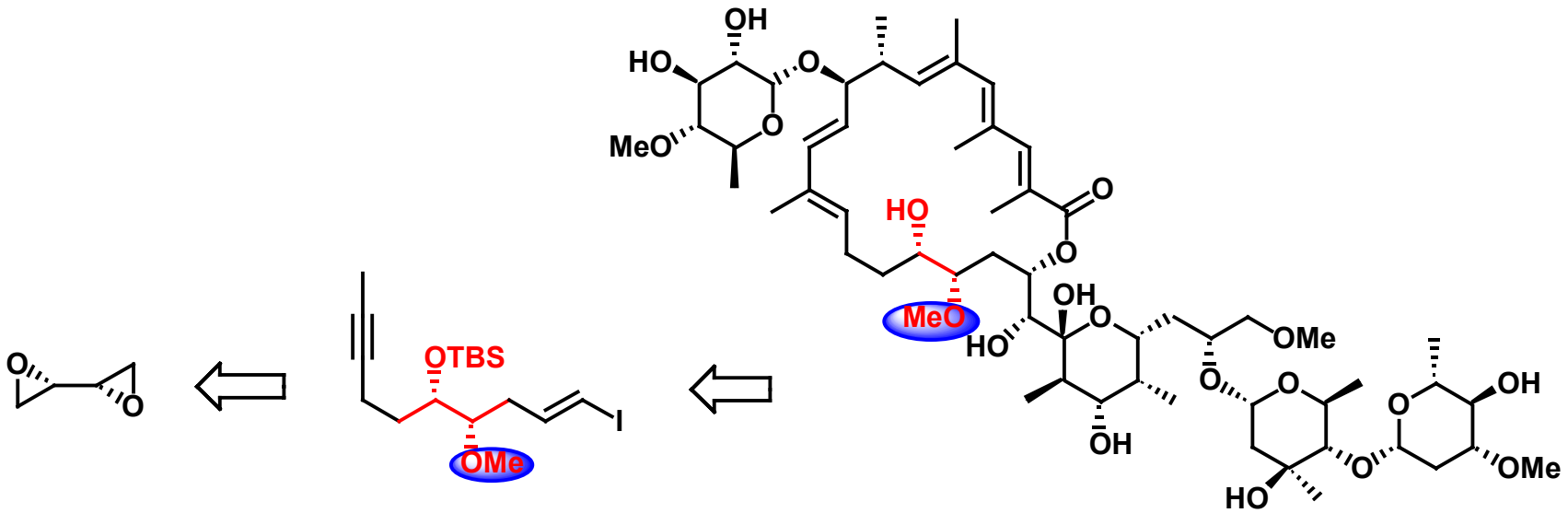
dppf =bis(diphenylphosphino) ferrocene

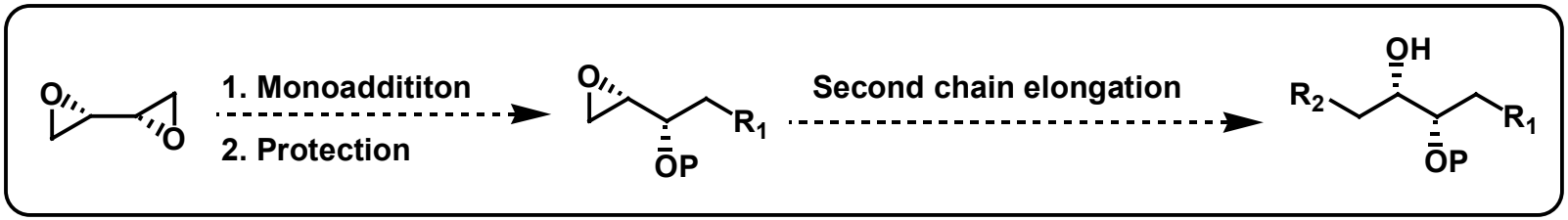


Northern triene unit was constructed by a Suzuki coupling reaction in a convergent fashion

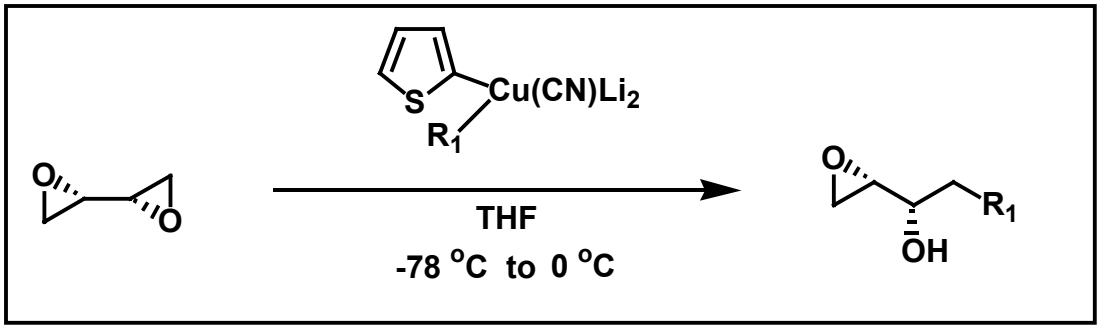
Christina Collison

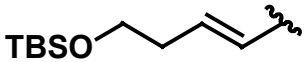
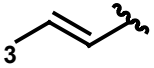
Construction of Vinyl Iodide Subunit





Two-directional Chain Extention

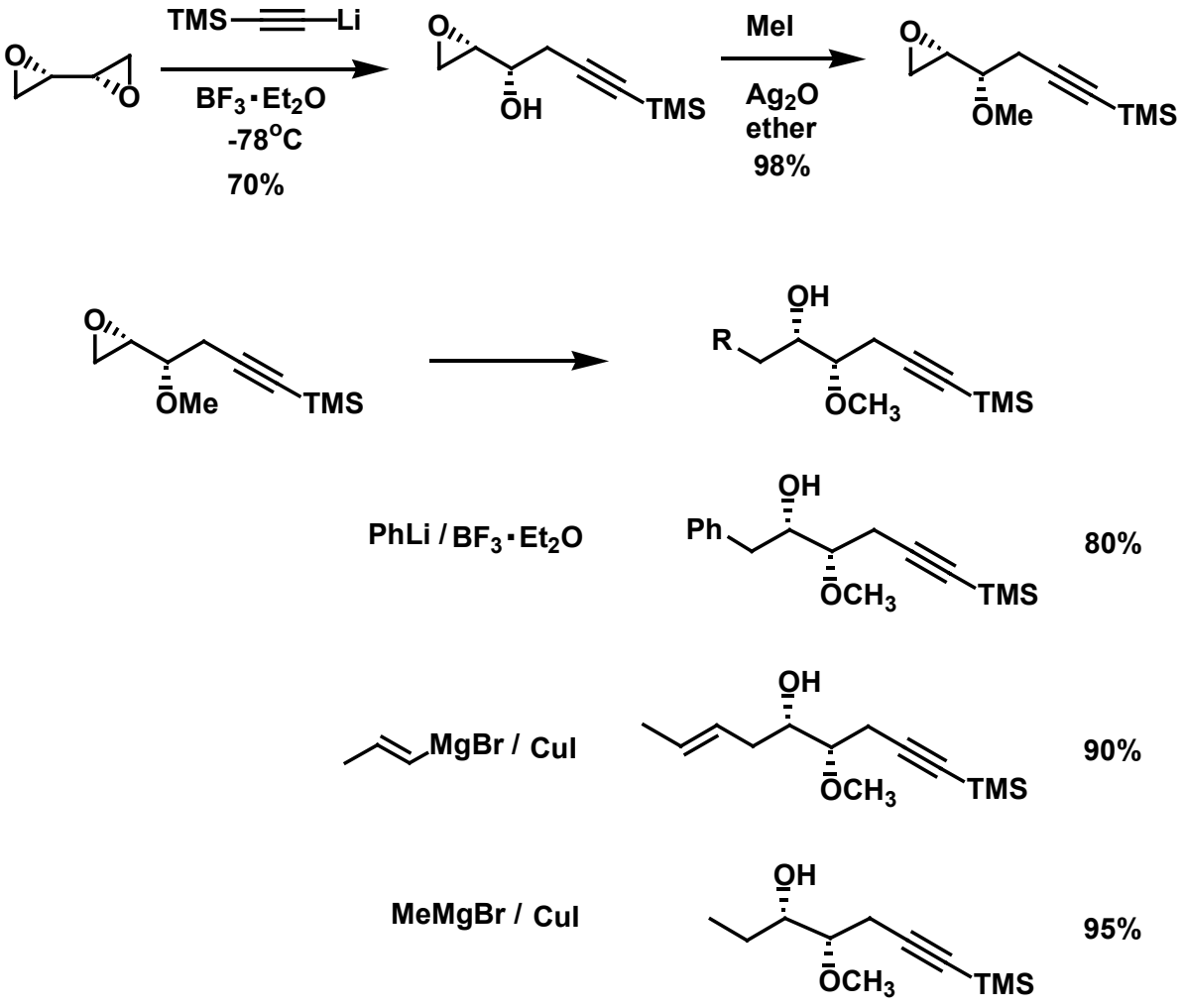


R_1	Yield (%)
TBSO 	85
C_6H_{13} 	70
*n*Bu	79
CH_3	82

The mixed 2-thienyl higher order cyanocuprates bearing both alkenyl and alkyl groups afford exclusively the monoadducts

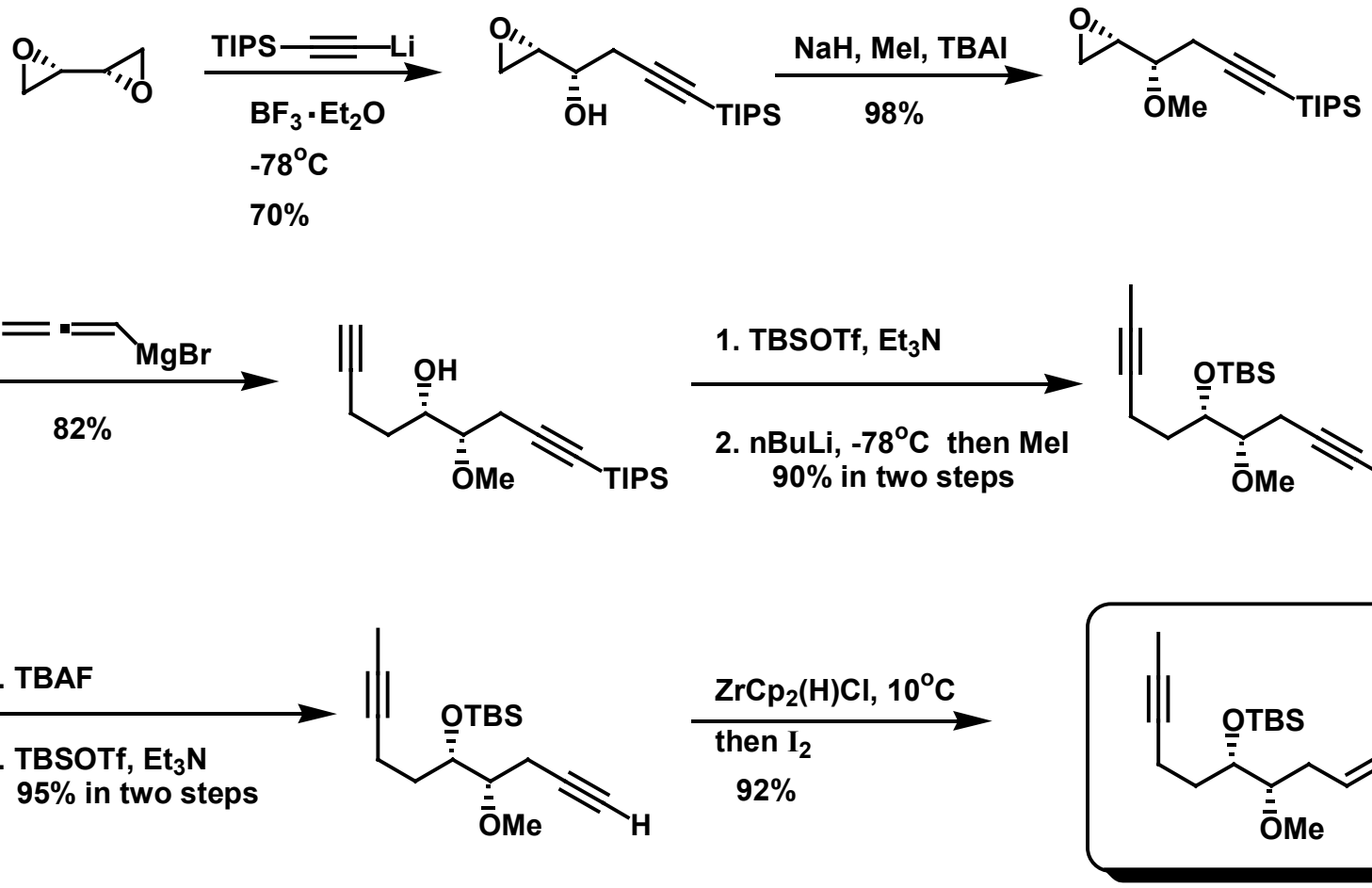
Robert K. Boeckman Jr, Xiaorong Liu, *Synthesis* **2002**, *14*, 2138-2142

Two-directional Chain Extention



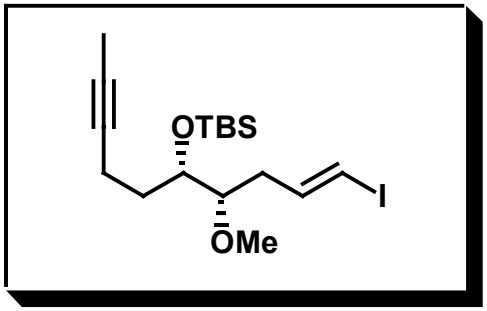
Robert K. Boeckman Jr, Xiaorong Liu, *Synthesis* **2002**, *14*, 2138-2142

Construction of Vinyl Iodide Subunit

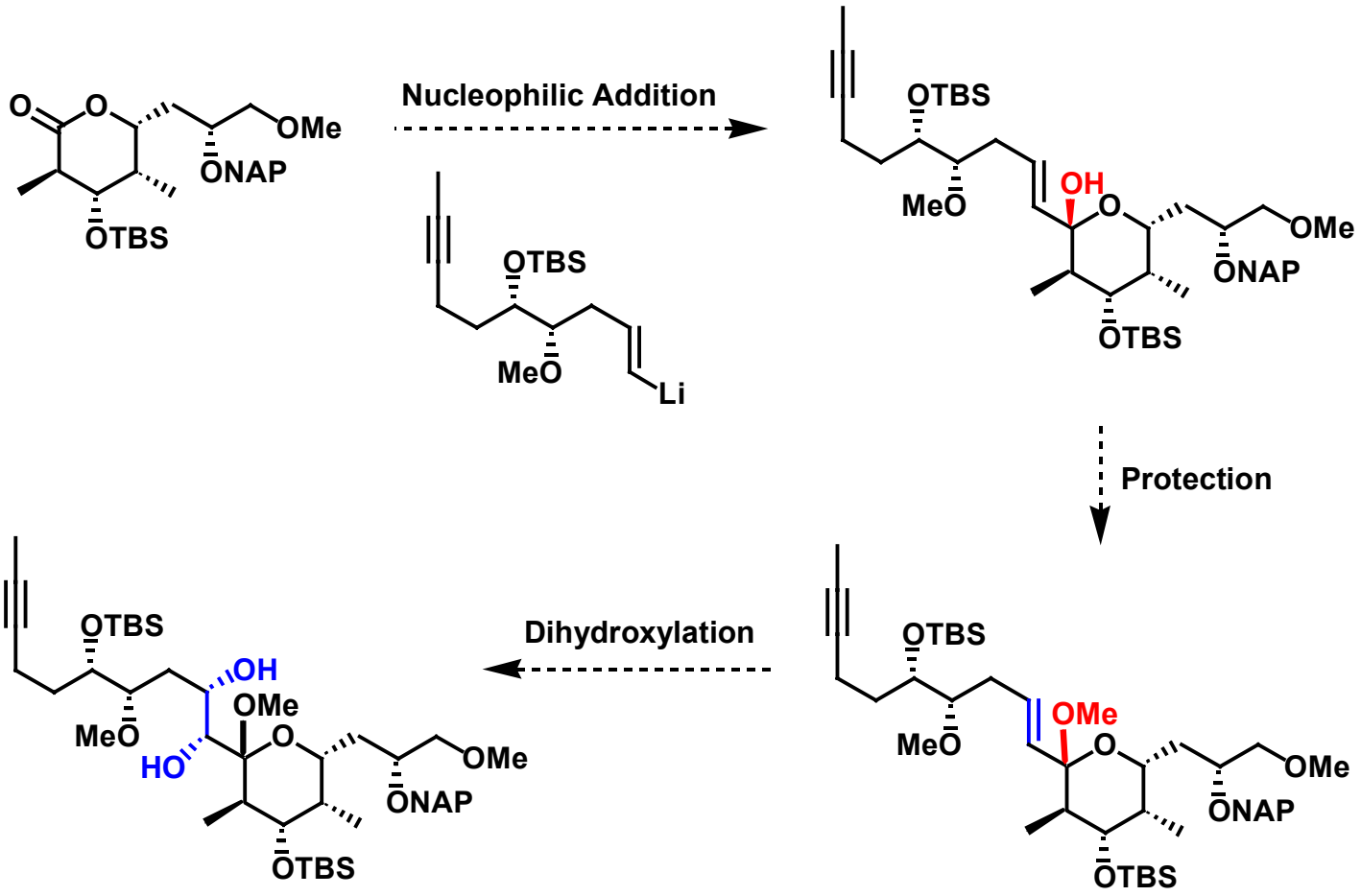


Vinyl iodide subunit was synthesized featuring a two-directional elongation strategy

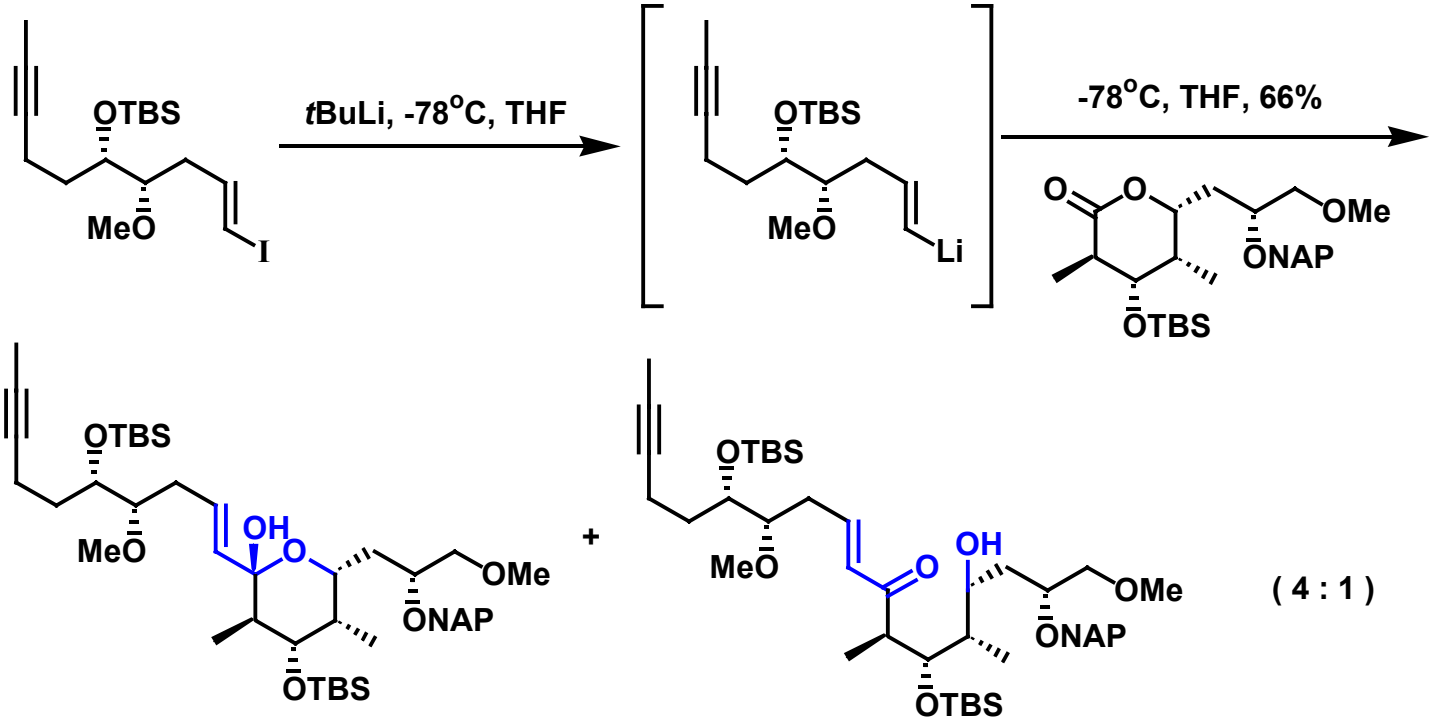
Problem Two



Construction of Southern Hemisphere

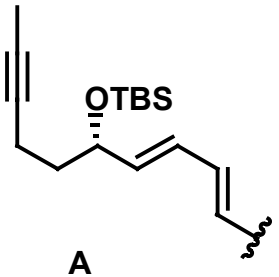


Construction of Southern Hemisphere --- Nucleophilic Addition

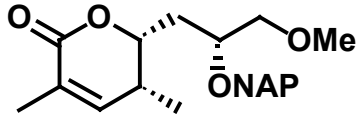


--- 1.5 eq *t*BuLi was used instead of 2.0 eq in order to avoid the formation of A.

--- -78°C as the reaction temperature was crucial

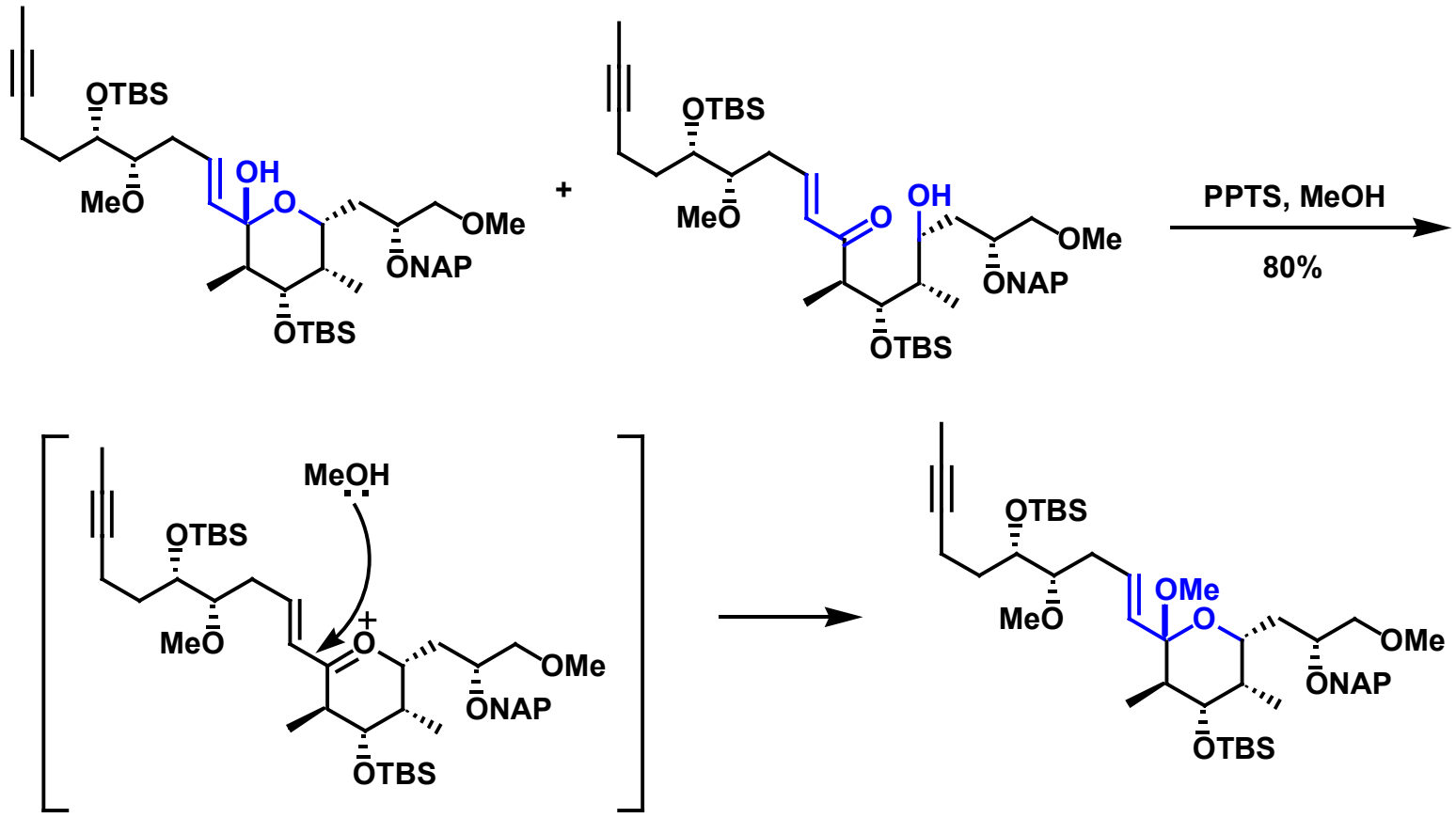


A



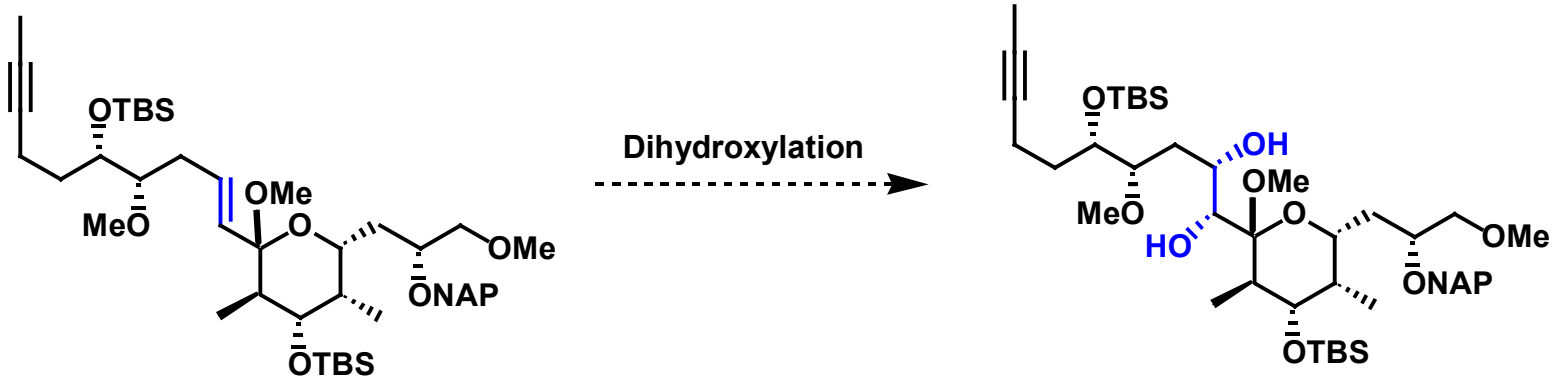
B

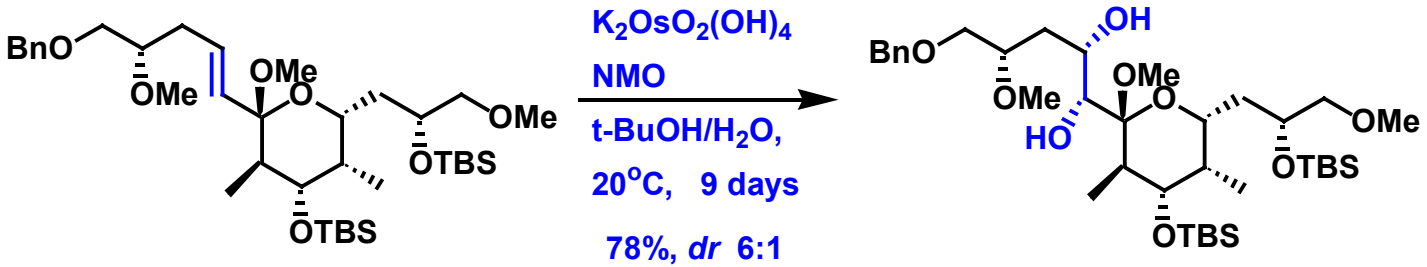
Construction of Southern Hemisphere --- Protection



The anomeric methoxy group was introduced exclusively on the desired axial position

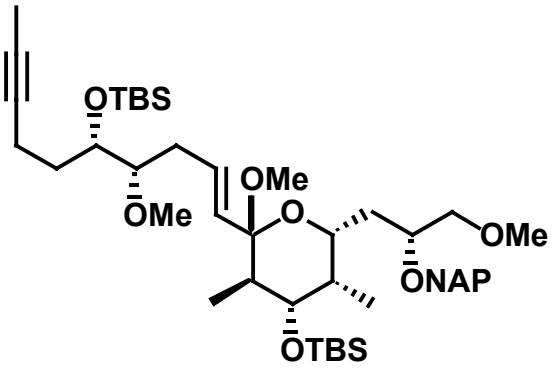
Construction of Southern Hemisphere --- Dihydroxylation





Schuppan, J.; Wehlan, H.; Keiper, S.; Koert, U. *Angew. Chem., Int. Ed.* 2001, 40, 2063

Construction of Southern Hemisphere --- Dihydroxylation



10% $K_2OsO_2(OH)_4$ 3eq. NMO
t-BuOH/H_2O, rt

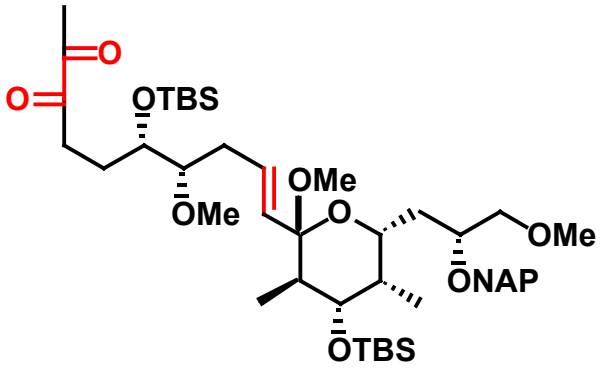
5 hr

A + B + S.M.

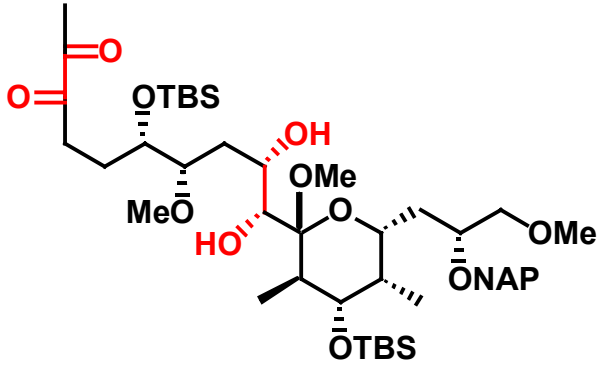
10% $K_2OsO_2(OH)_4$, 3eq. NMO
t-BuOH/H_2O, rt

48 hr

B

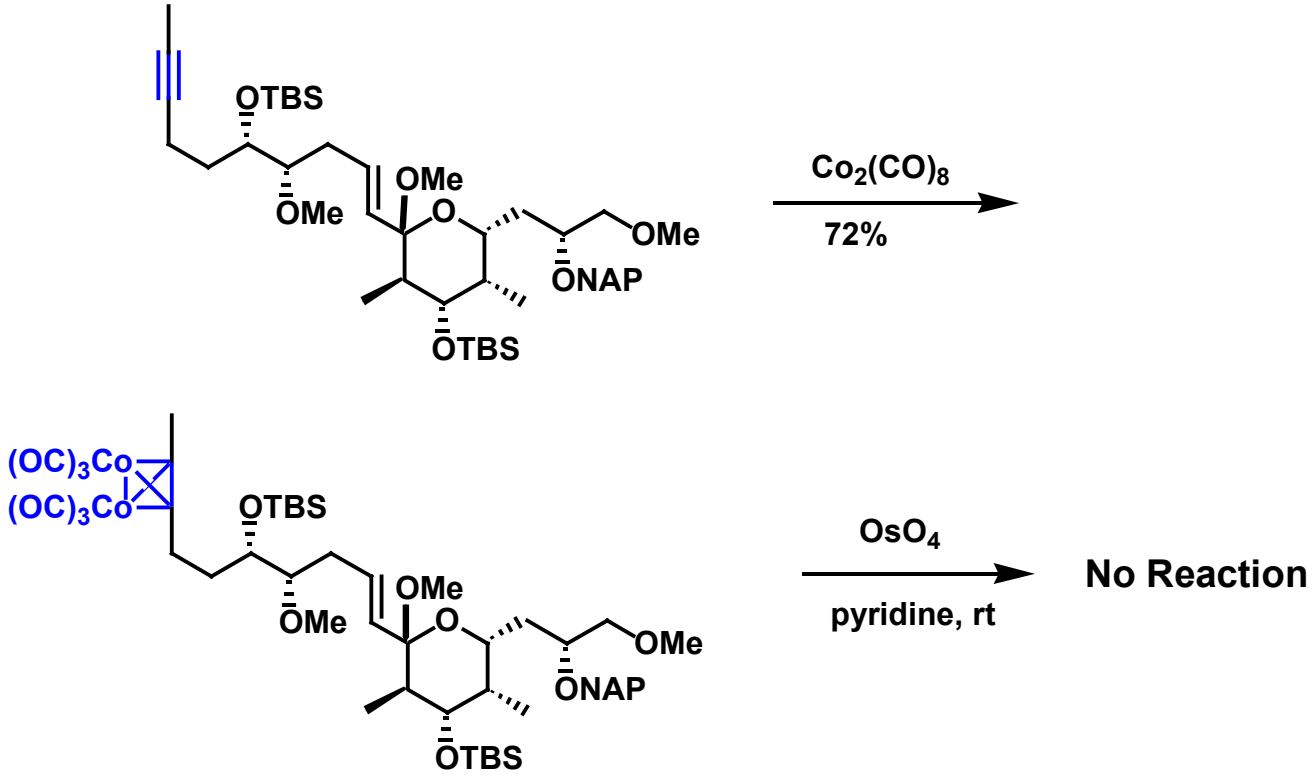


A



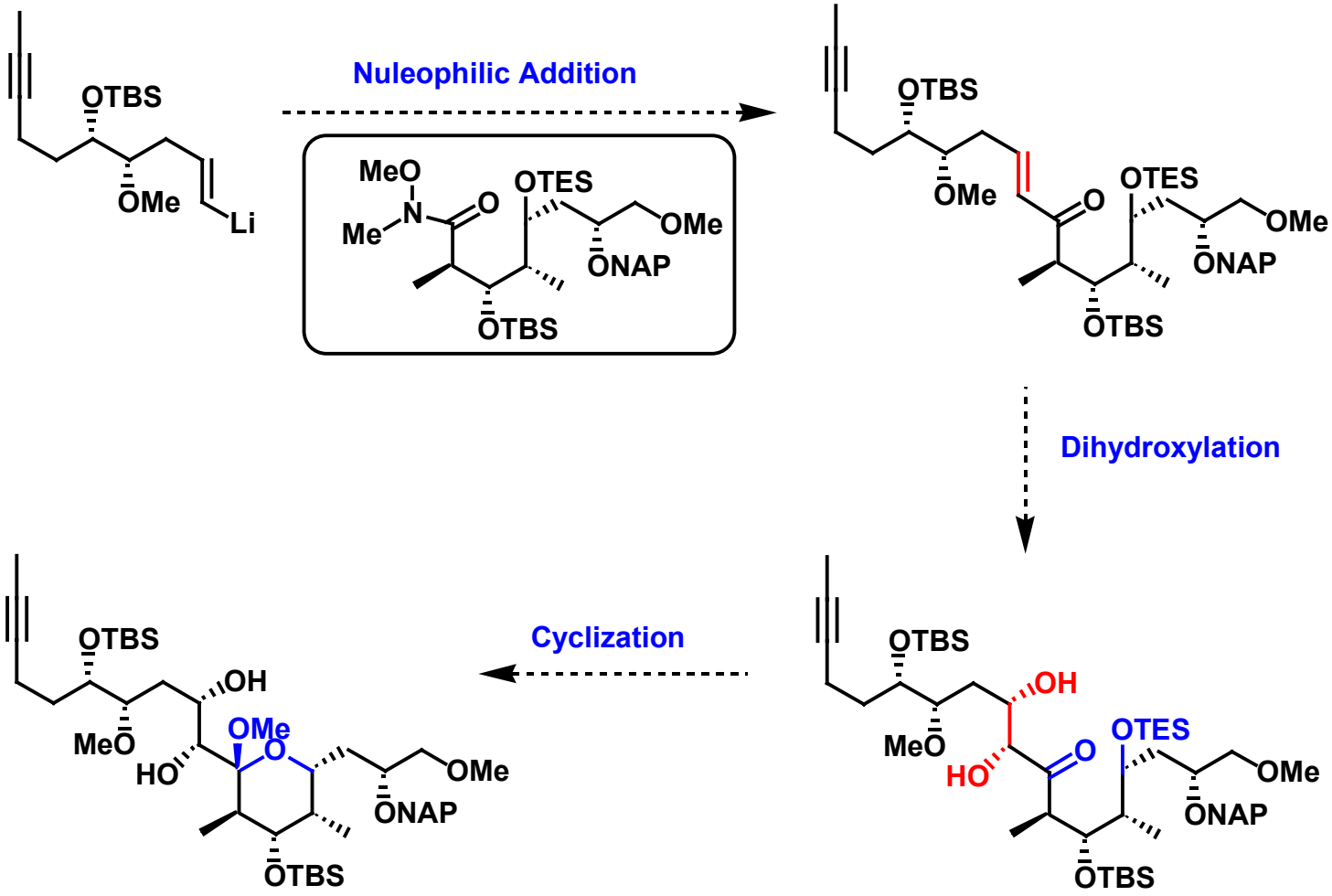
B

Construction of Southern Hemisphere --- Dihydroxylation

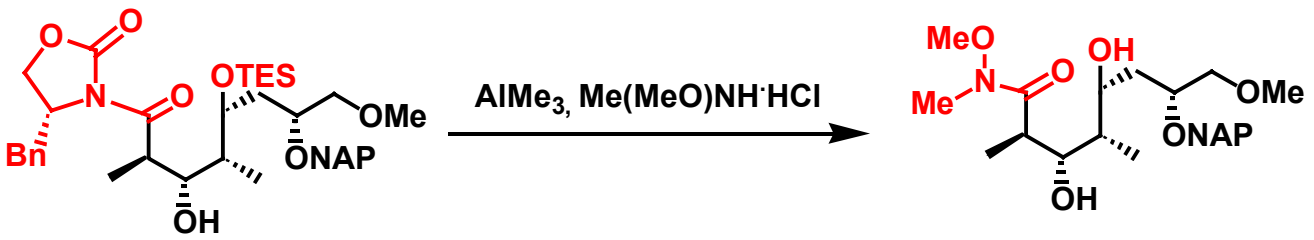


The olefin moiety was not reactive enough for the dihydroxylation reaction

Construction of Southern Hemisphere: Second Generation Approach

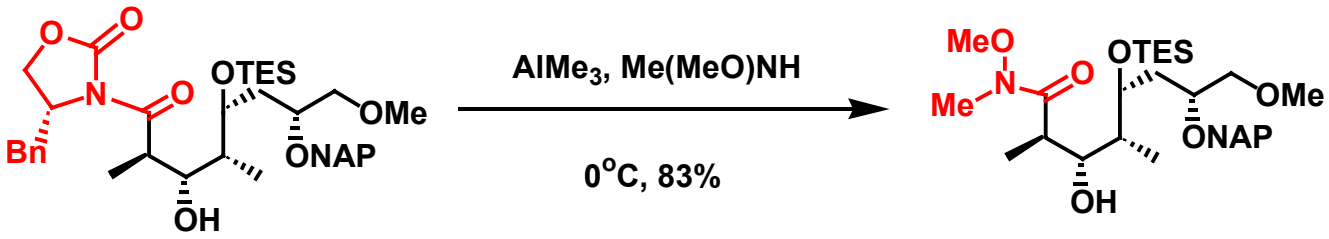


Construction of Weinreb Amide



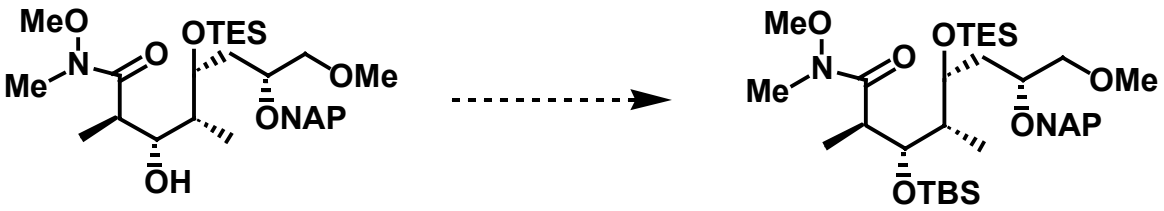
$AlMe_3$, Me(MeO)N·HCl ⟶ Me(MeO)NAlMeCl

$AlMe_3$, Me(MeO)NH ⟶ $Me(MeO)NAlMe_2$



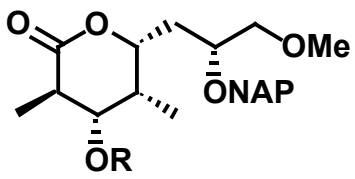
The less Lewis acidic amidation reagent was the key for the transformation

Construction of Weinreb Amide



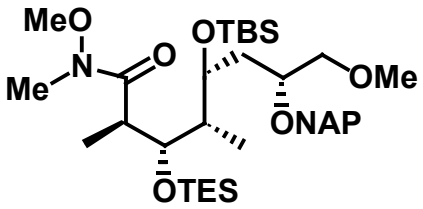
Condition	S.M.	Prod.	A	B
TBSOTf, lutidine, -78°C	100%			
TBSOTf, lutidine, -40°C	50%	20%	10%	20%
TBSOTf, lutidine, 0°C		40%	20%	40%
TBSCl, Imid. DMAP, rt	100%			
TBSCl, Et_3N, DMAP, rt	100%			

A



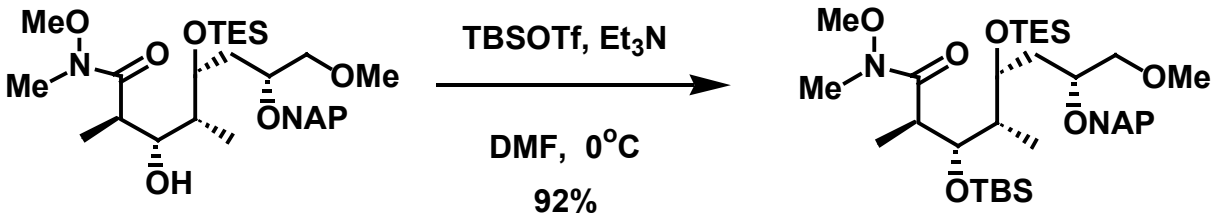
R = TBS or TES

B



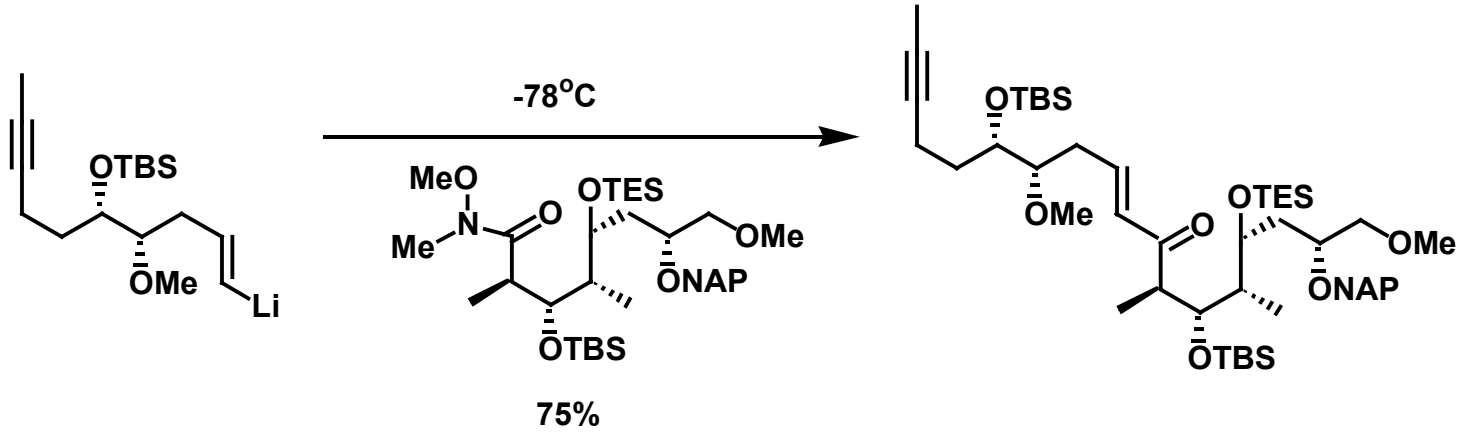
The initial efforts to protect the alcohol as TBS ether suffered 1,3-silyl transfer

Construction of Weinreb Amide

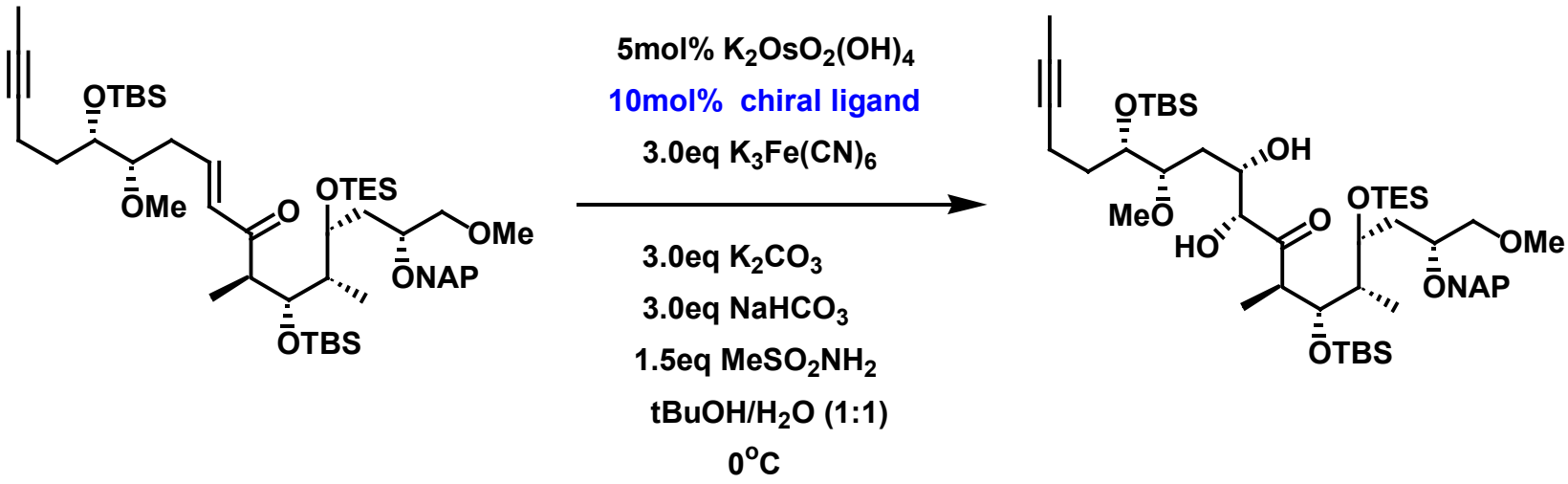


Using a stronger base, Et_3N, successfully suppressed the 1,3-silyl transfer

Construction of Southern Hemisphere -- Nucleophilic Addition



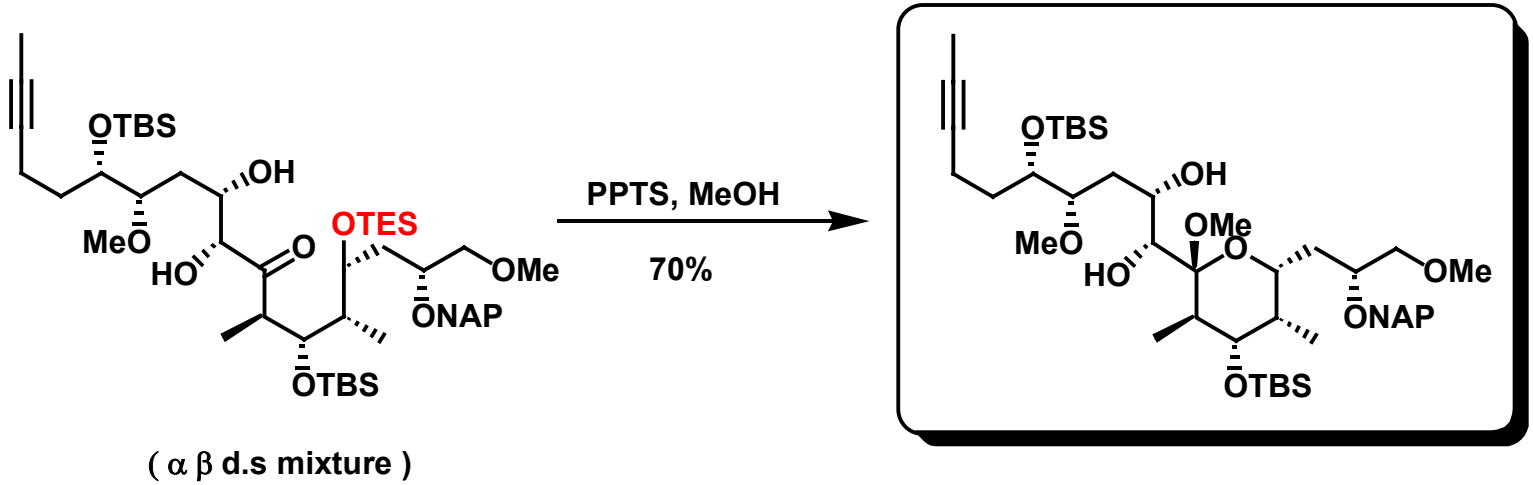
Construction of Southern Hemisphere --- Dihydroxylation



Chiral Ligand	dr (α : β)
$(DHQ)_2AQN$	7.0 : 1 (yield=85%)
$(DHQ)_2PHAL$	1.3 : 1
none	1 : 1.2
$(DHQD)_2PHAL$	1 : 1.5
$(DHQ)_2PYR$	4.0 : 1

DHQ = dihydroquinine
AQN = anthraquinone
PHAL = phthalazine
PYR = phenylpyrimidine
DHQD = dihydroquinidine

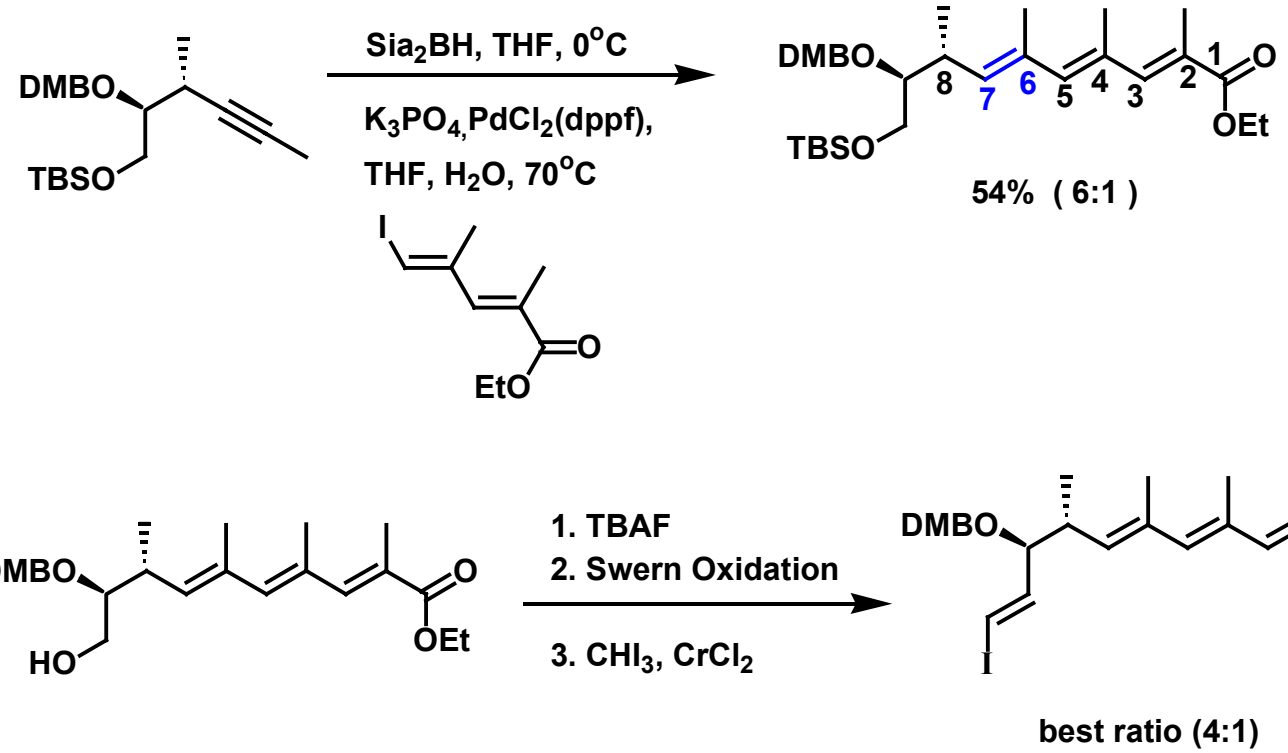
Construction of Southern Hemisphere --- Cyclization



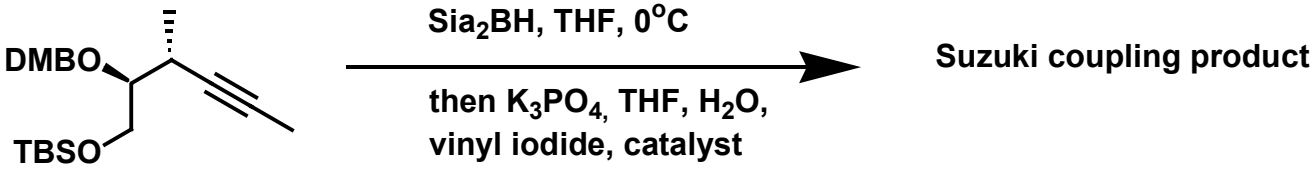
(α β d.s mixture)

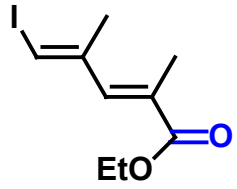
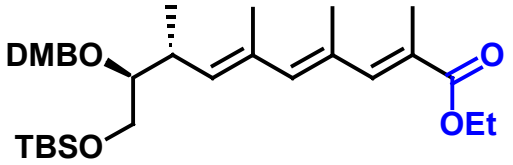
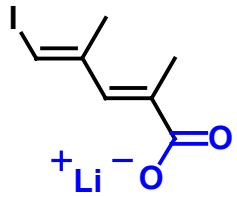
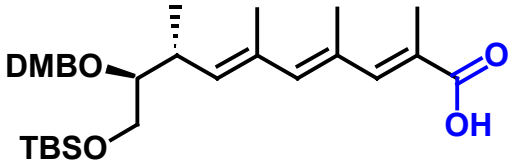
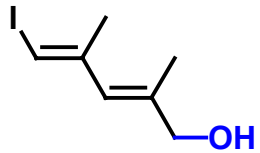
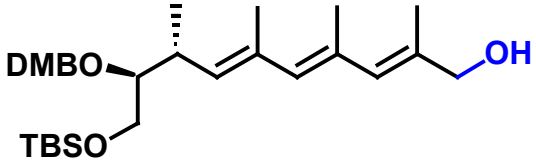
The enantiomerically pure southern hemisphere of the macrocycle was synthesized

Improved Syntheses of Northern Triene Pieces

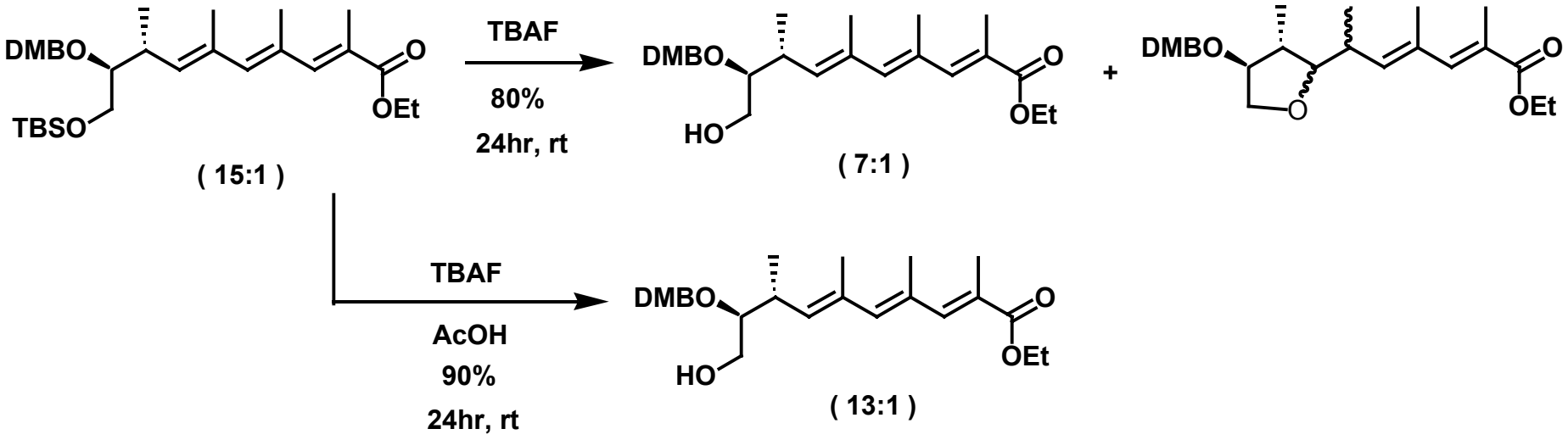


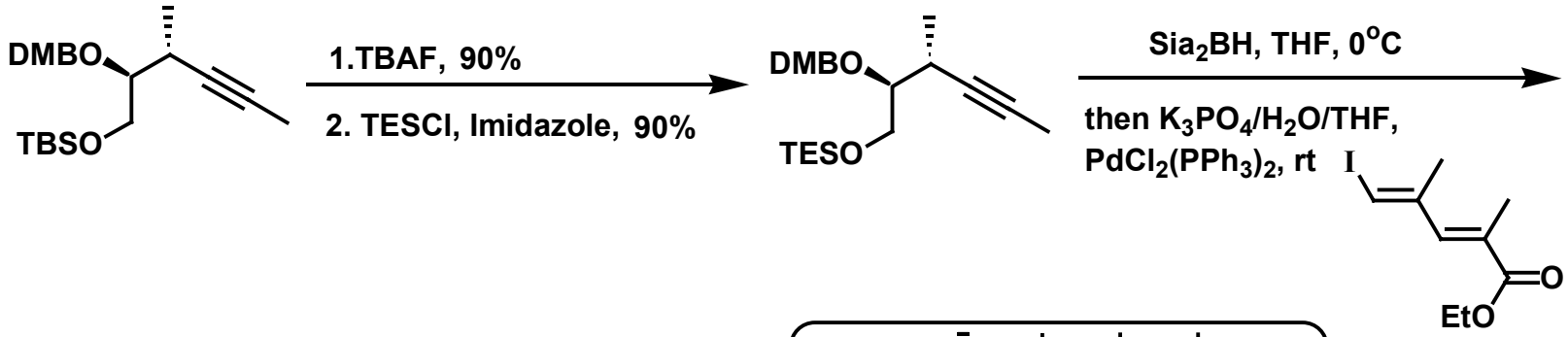
Improved Syntheses of Northern Triene Pieces

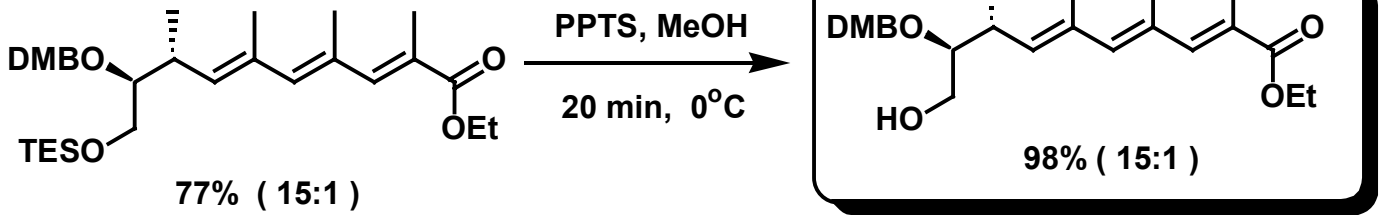


Vinyl Iodide	Catalyst /Temp.	E:Z (yield)	Product
	$PdCl_2(dppf)$ / 50°C $PdCl_2(PPh_3)_2$ / 50°C $PdCl_2(PPh_3)_2$ / 22°C	6:1 (70%) 10:1 (66%) 15:1 (70%)	
	$PdCl_2(dppf)$ / 50°C	30:1 (45%)	
	$PdCl_2(dppf)$ / 50°C	30:1 (65%)	

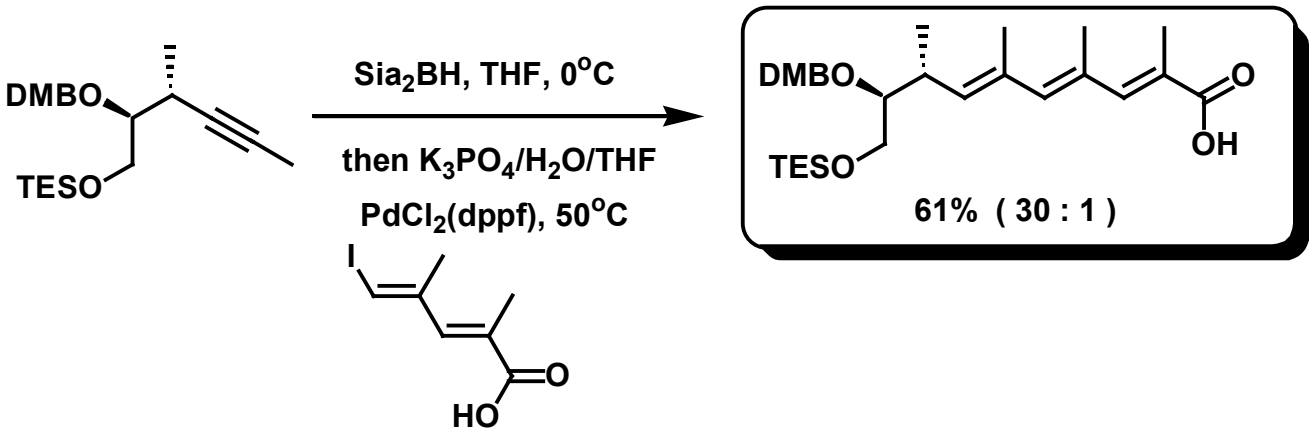
Improved Syntheses of Northern Triene Pieces



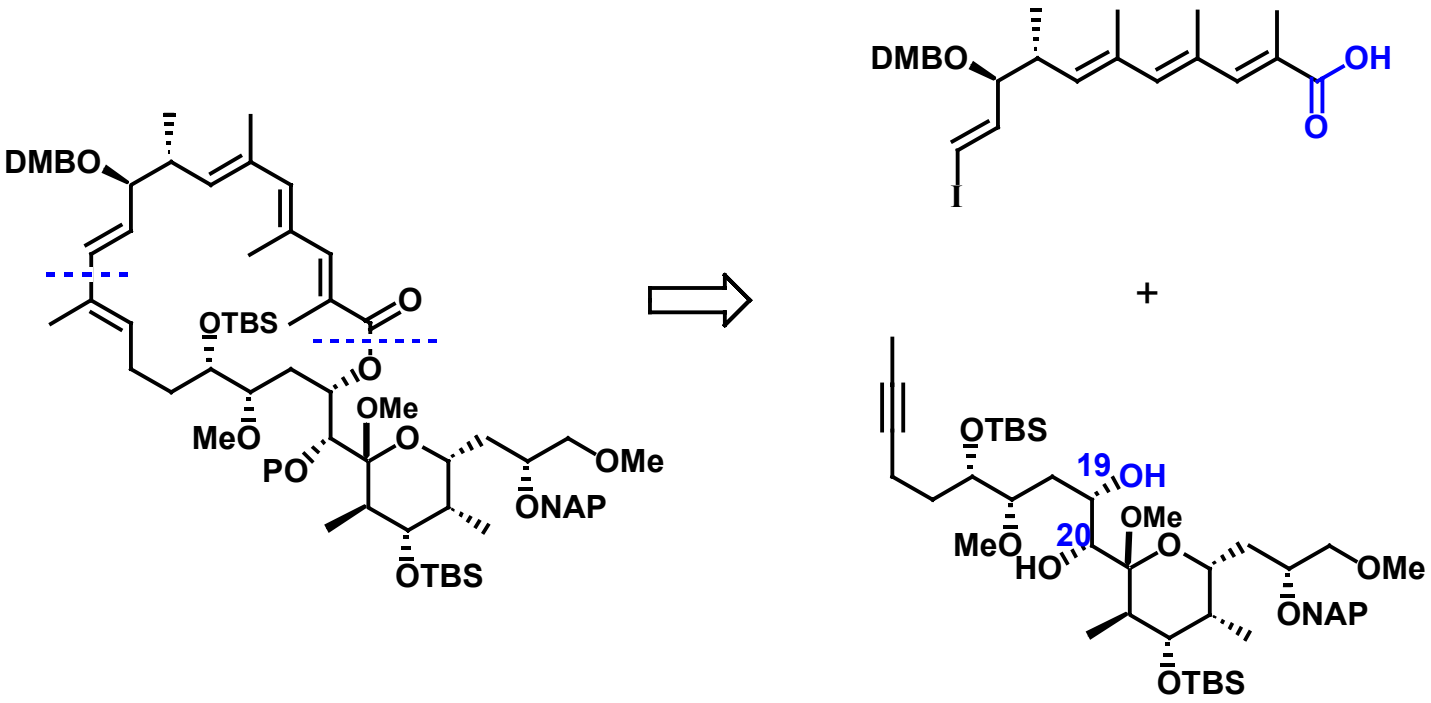




Improved Syntheses of Northern Triene Pieces



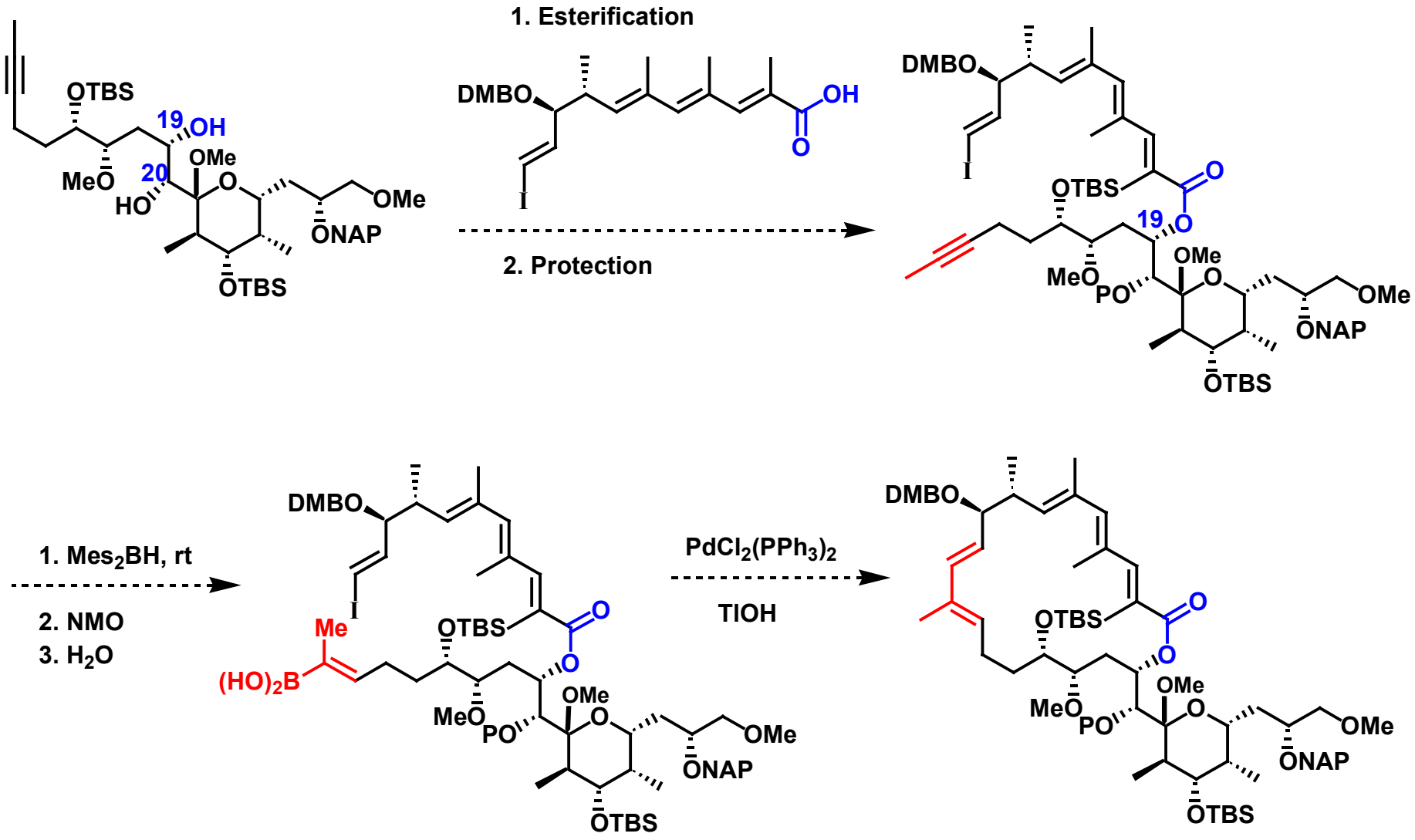
Assembly of Macrocycle



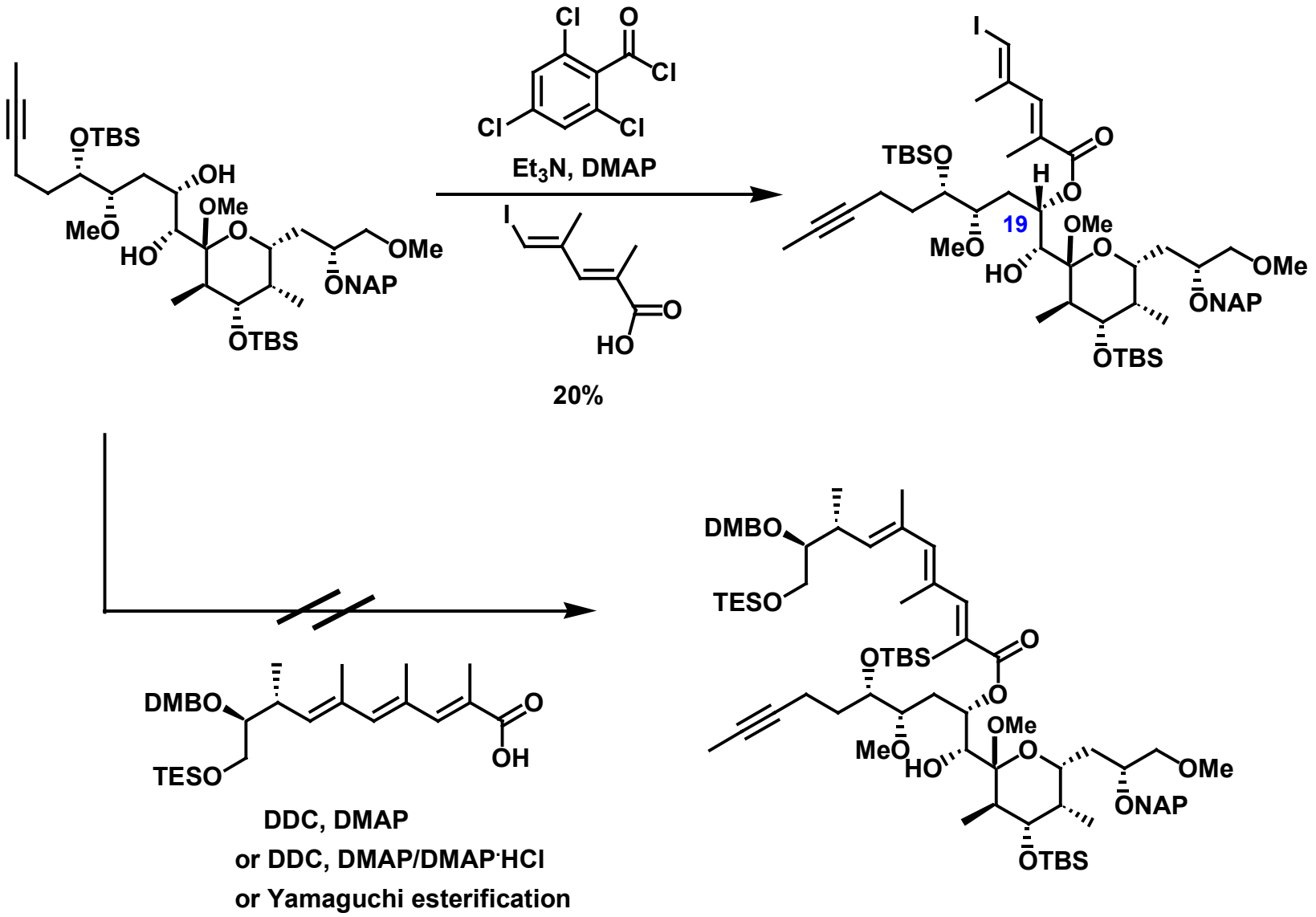
Two options to assemble the macrocycle:

1. **Suzuki coupling followed by macrocyclization**
2. **Esterification followed by intramolecular Suzuki coupling**

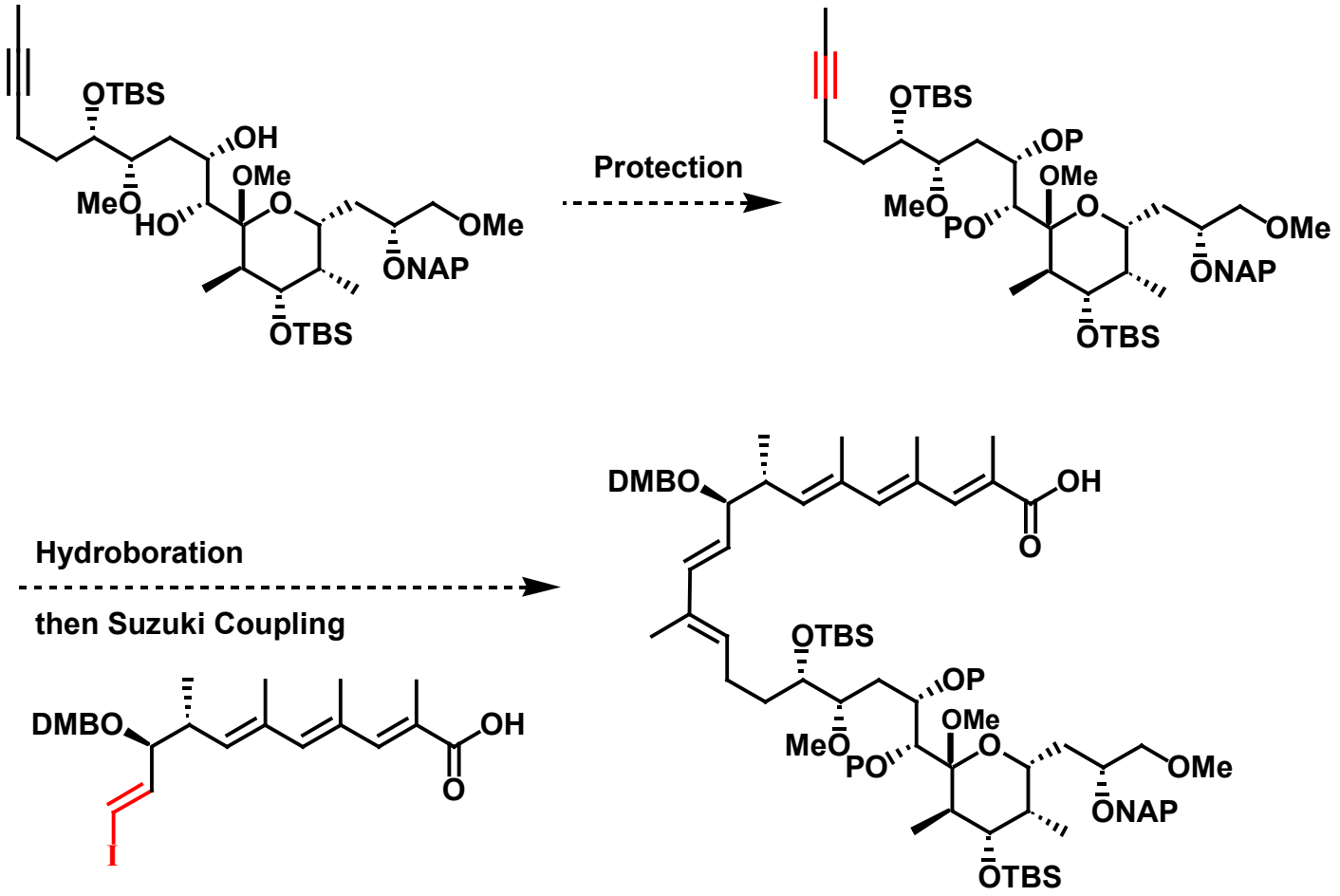
Assembly of Macrocycle -- Esterification and Suzuki Coupling



Assembly of Macrocycle ---- Esterification



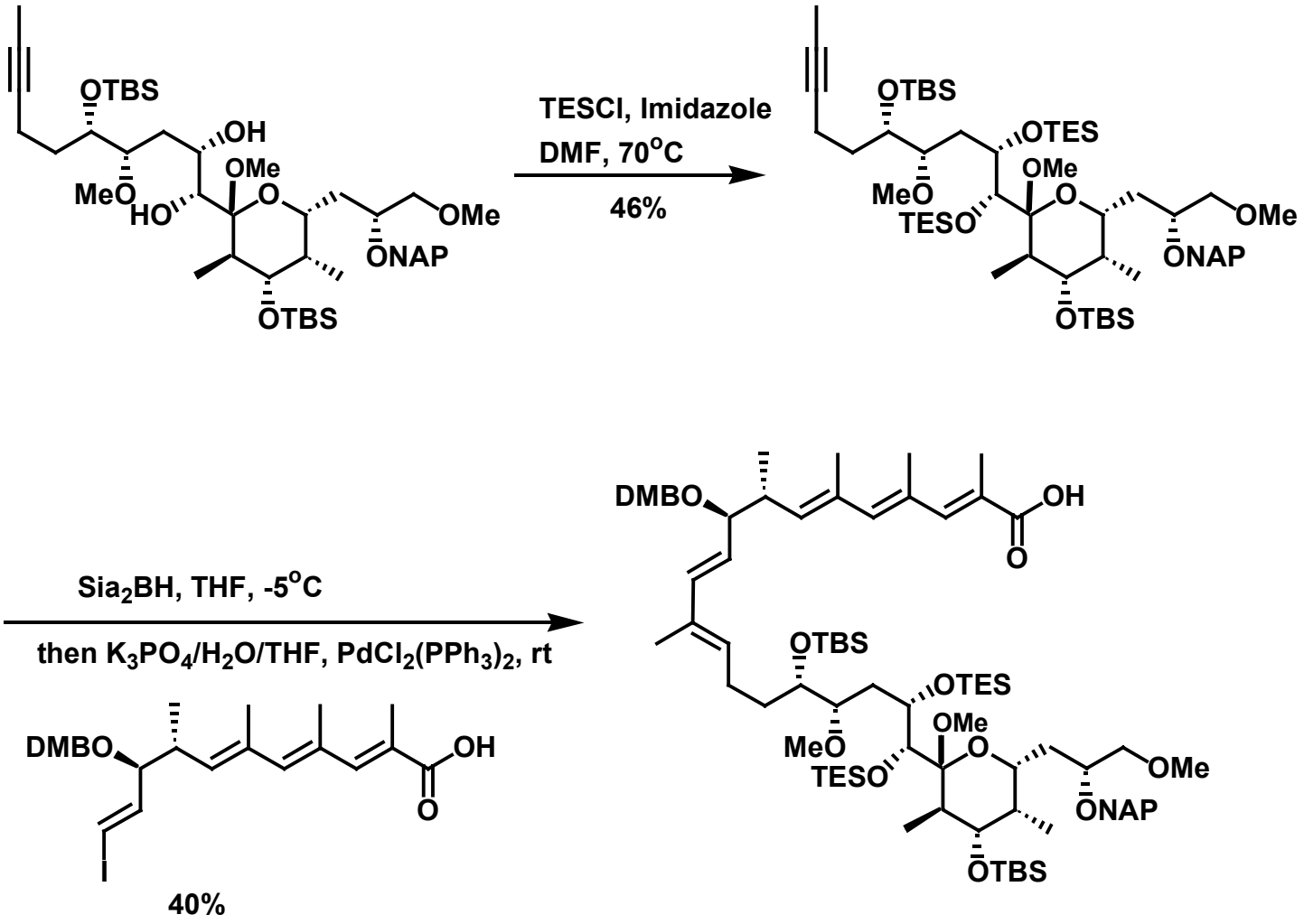
Assembly of Macrocycle -- Suzuki Coupling and Macrolactonization



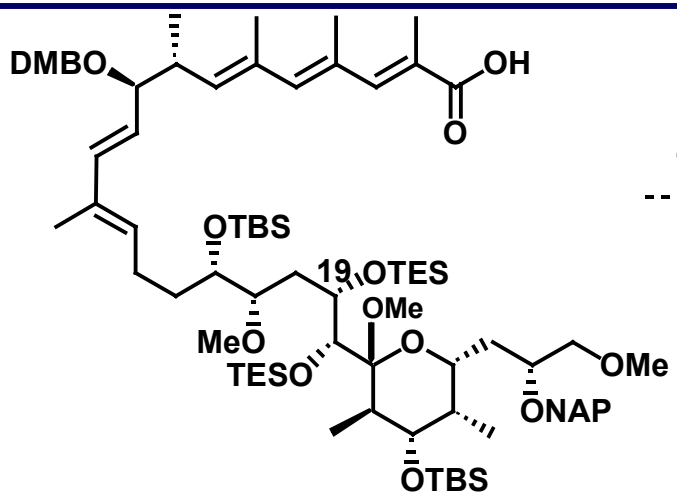
1. Deprotection
2. Macrolactonization

Macrocycle of Apoptolidin

Assembly of Macrocycle --- Suzuki Coupling

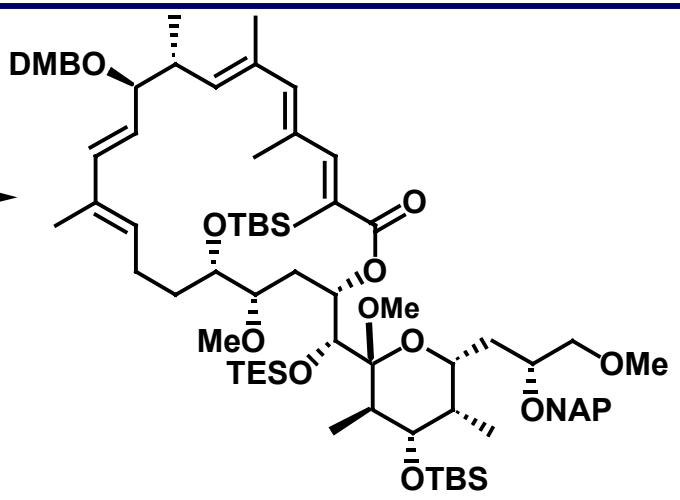


Future Study

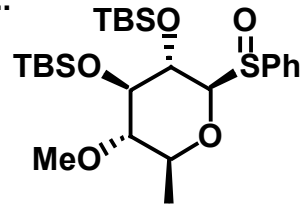


1. PPTS/MeOH, 0°C

2. Yamaguchi Macrolactonization

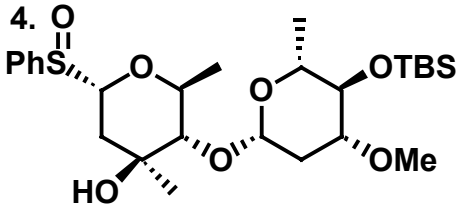


1. DDQ
2.



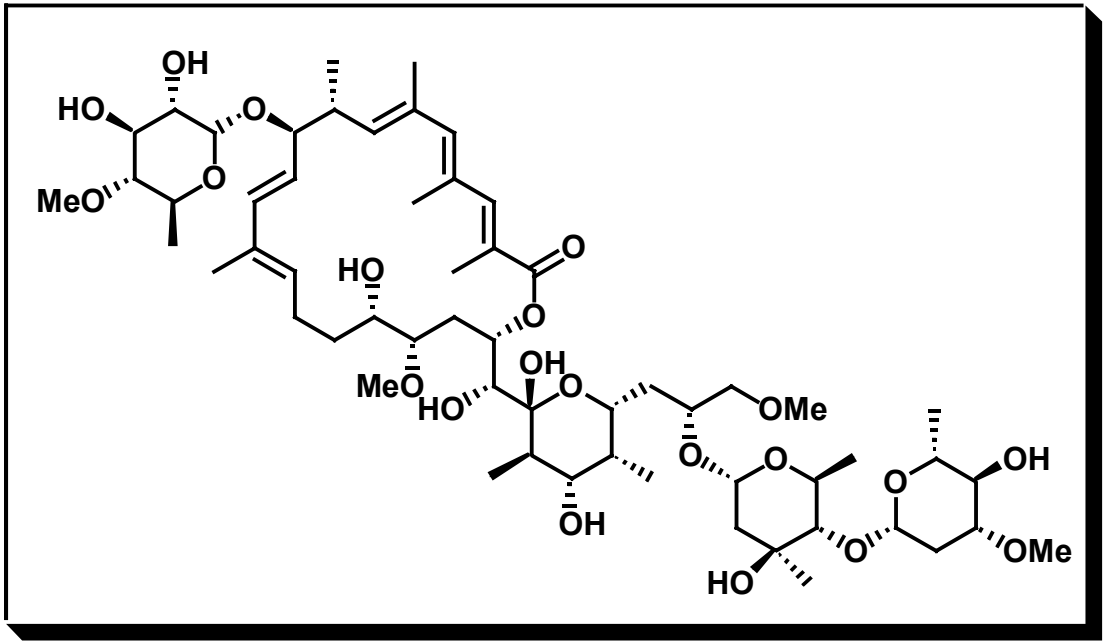
Tf_2O, DTBMP

3. DDQ
4.



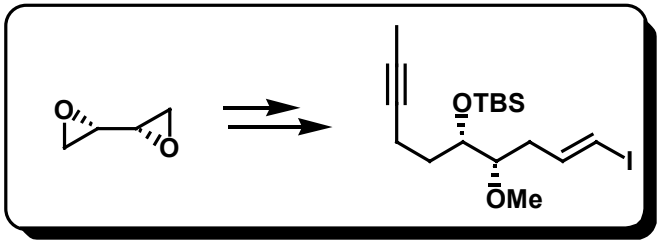
Tf_2O, DTBMP

5. Universal Deprotection

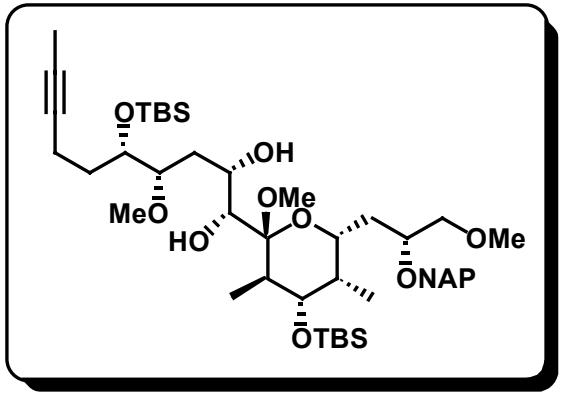


Conclusions

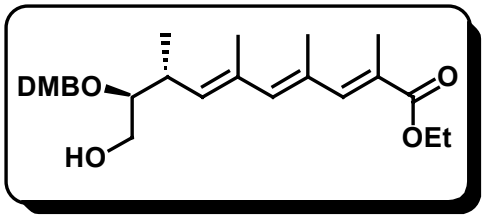
1. A methodology as the route to the differentiated *syn*-1,2-diol has been developed. By employing this methodology, vinyl iodide subunit of apoptolidin has been developed.



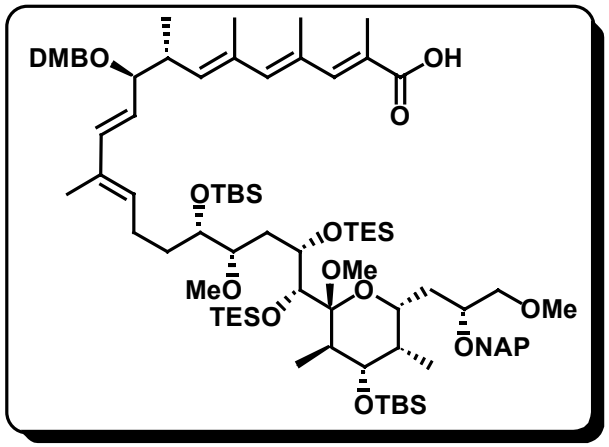
2. The enantiomerically pure and suitably functionalized southern hemisphere of apoptolidin has been achieved.



3. The improved syntheses of the triene pieces for the northern hemisphere of apoptolidin have been developed.



4. The exploration study demonstrated that the northern and southern hemispheres of apoptolidin were assembled smoothly by a mild Suzuki coupling reaction.



Acknowledgments

Prof. Robert K. Boeckman, Jr.

Apoptolidin Team Members

Gabriel Kapur
Christina Collison
Venkat Srinivasan

Sherman-Clarke Fellowship

Elon Huntington Hooker Fellowship

Department of Chemistry

University of Rochester

Thank you!!