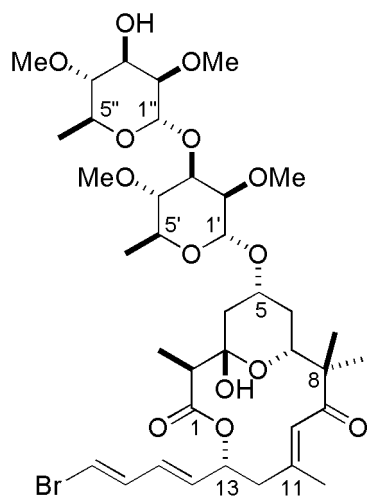
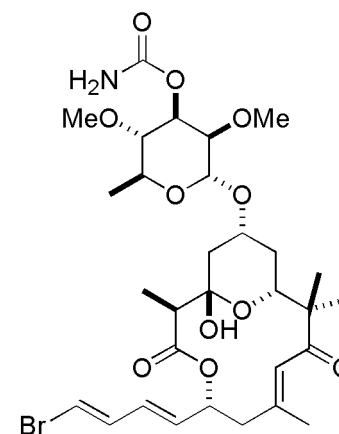


# Stereocontrolled Total Synthesis of (-)- Aurisides A and B

Paterson, I.; Florence, G.J. Heimann, A.C.; MacKay, A.C. *Angew. Chem. Int. Ed.* **2005**, *44*, 1130.

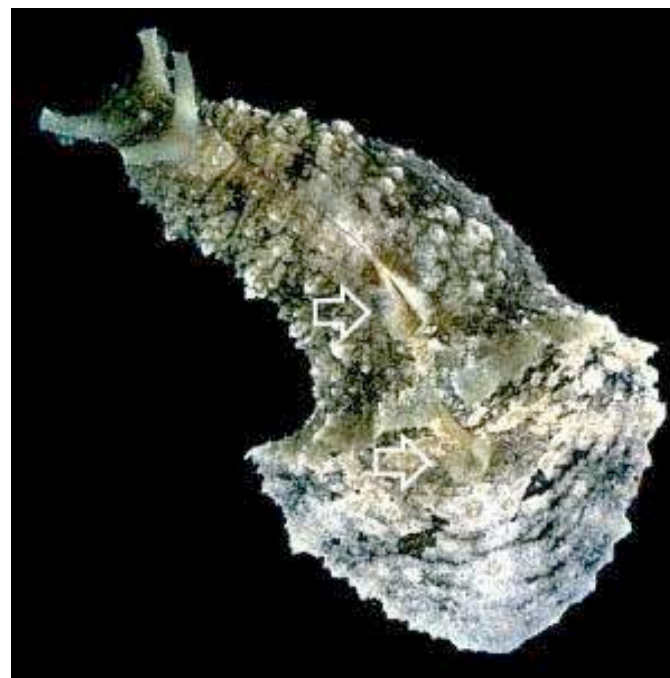


Danielle Jacobs  
Crimmins Group Meeting  
3/2/05



# Aurisides A & B

- Isolated in 1996 from the Japanese sea hare (slug – ewwww!!!) *Dolabella auricularia* by Yamada and coworkers
- Merely 0.8 mg isolated from 278 kg of organism
- Similar in structure to the callipeltoside skeleton
- Show cytotoxicity against HeLa S<sub>3</sub> cervical cancer cells (auriside A IC<sub>50</sub> = 0.17 μg/mL, auriside B IC<sub>50</sub> = 1.2 μg/mL)
- Significant features:
  - 14-membered glycosylated macrolide
  - 6-membered hemiacetal ring
  - *E*- trisubstituted enone
  - *E,E* bromodiene side chain
  - Differing oligosaccharide moieties

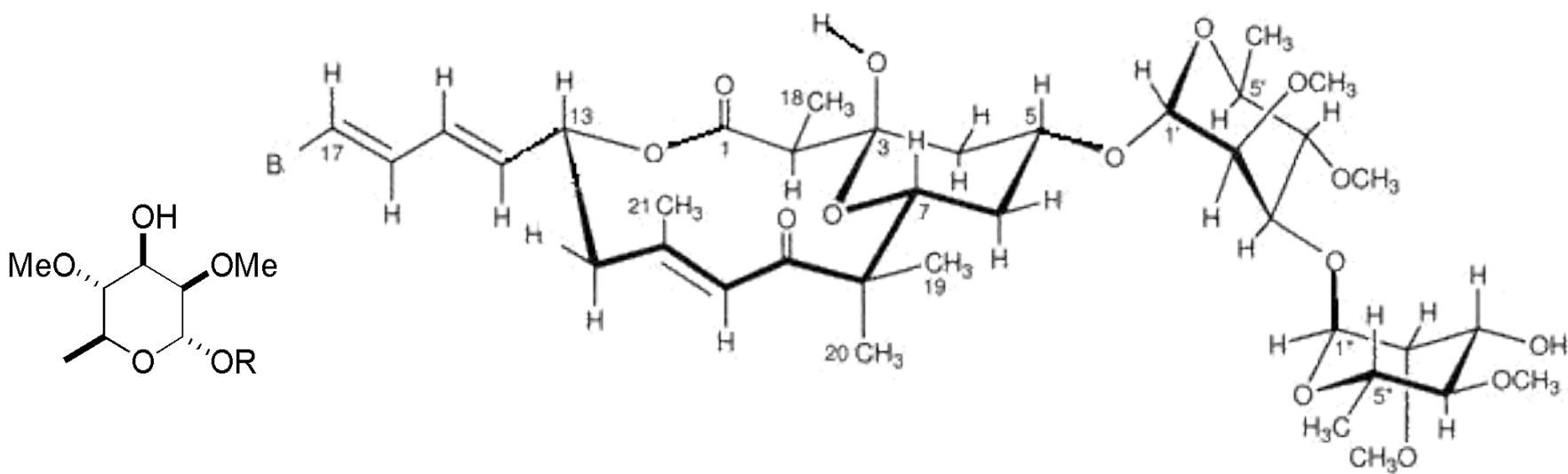


Sone, H.; Kigoshi, H.; Yamada, K. *J. Org. Chem.* **1996**, *61*, 8956.

Romero-Ortega, M.; Colby, D.A.; Olivo, H.F. *Tetrahedron Lett.* **2002**, *43*, 6439

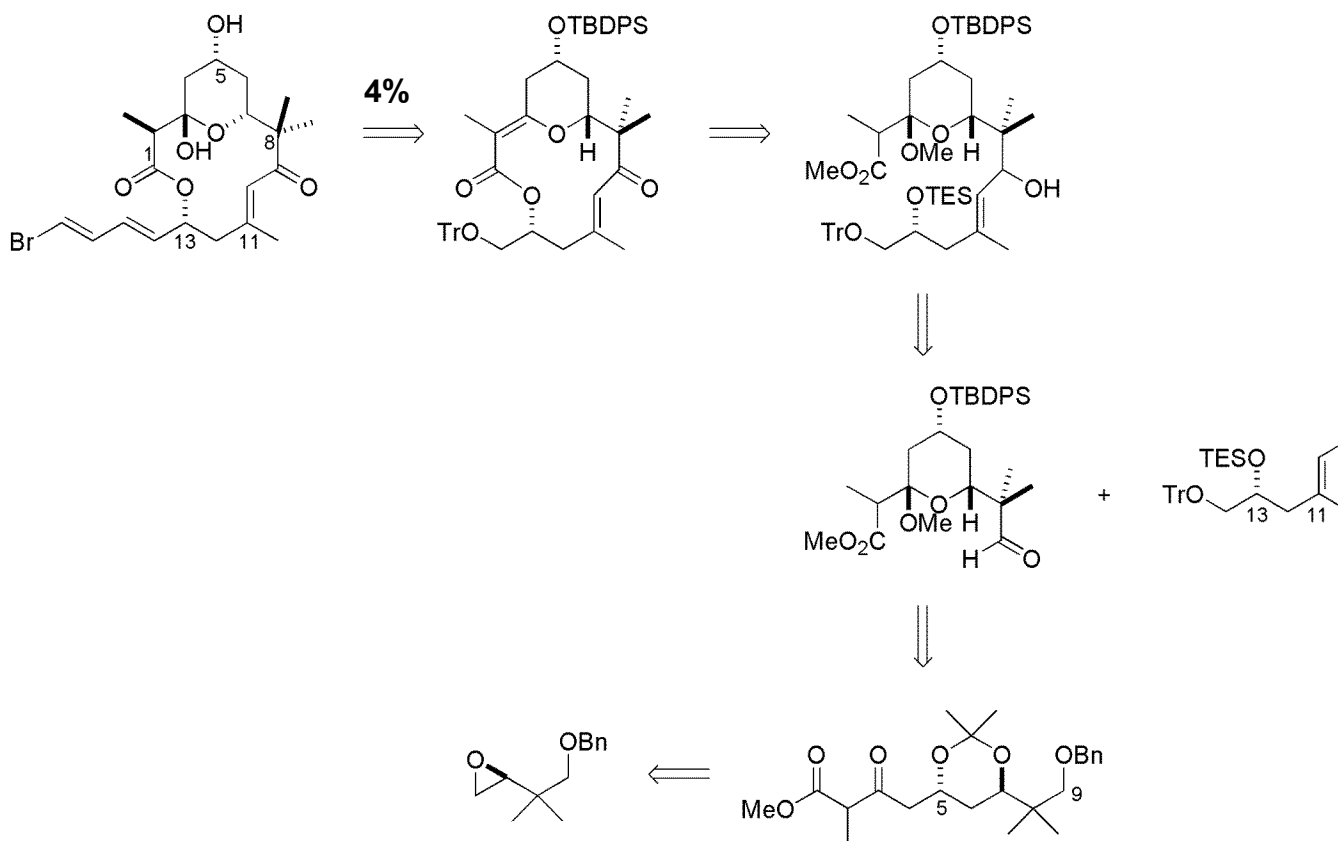
# Structural Elucidation of the Aursides

- Molecular formula ( $C_{37}H_{57}BrO_{14}$ ) via HRFABMS
- IR,  $^1H$ ,  $^{13}C$  NMR, 2D NMR (COSY, NOESY)
- Degradation and derivatization experiments



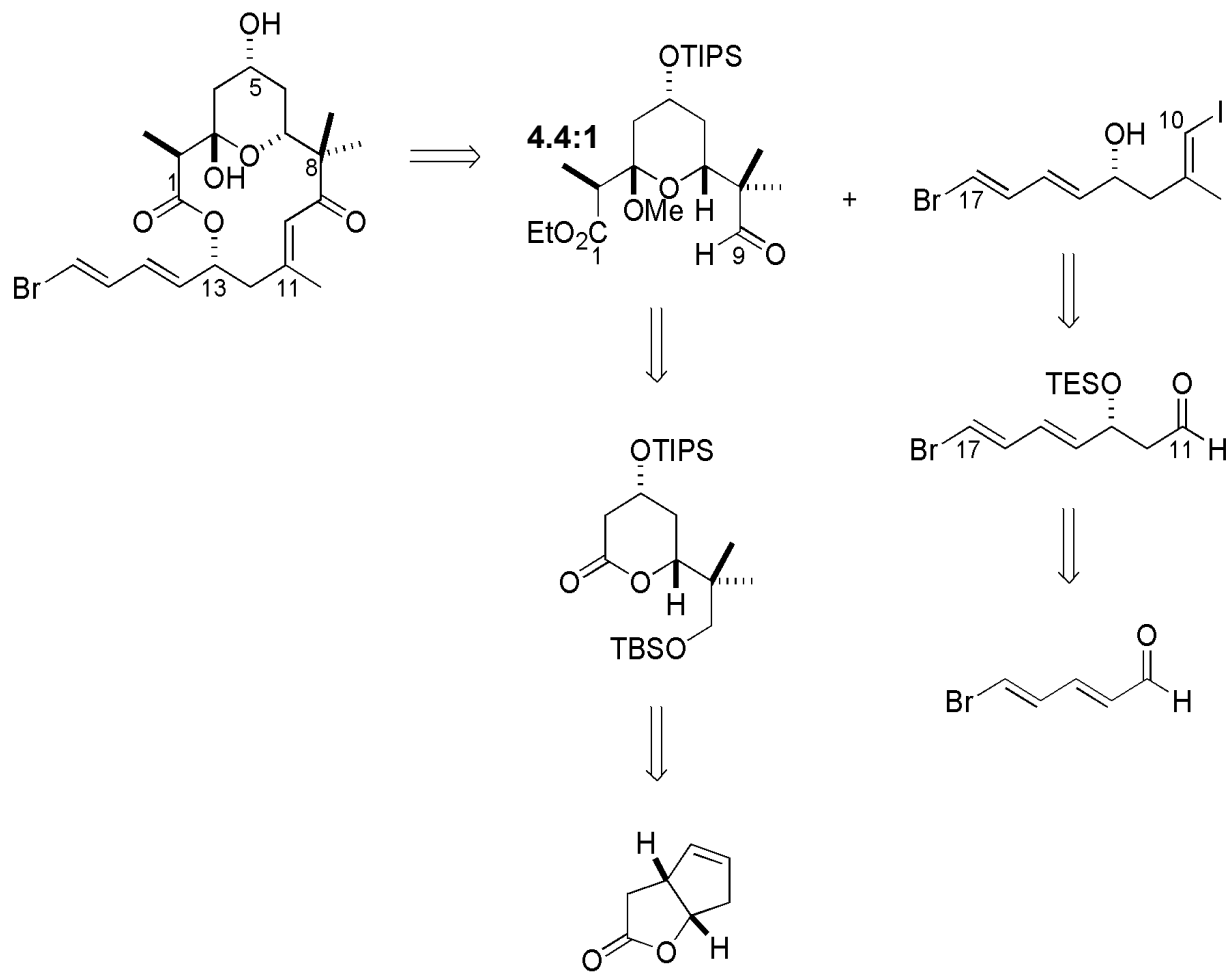
# Previous Syntheses of Aglycon Unit

- Yamada, et. al. *Chem. Lett.* **1998**, 85-86.
- 29 steps from (*R*)-pantolactone



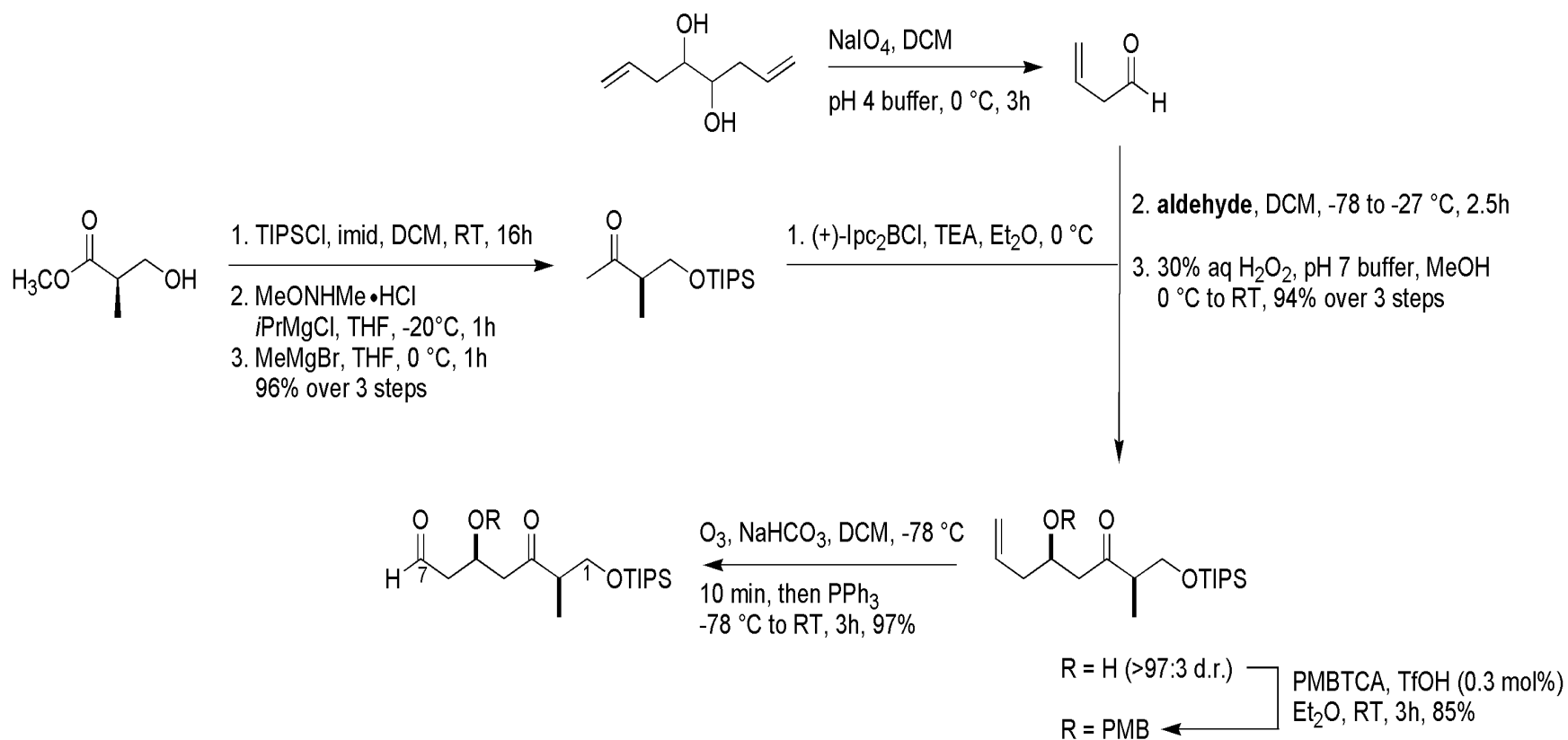
# Previous Syntheses of Aglycon Unit

- Olivo, H.F., et. al.  
*Tetrahedron Lett.* **2002**,  
43, 6439.  
*Tetrahedron.* **2003**, 59,  
6531.
- C1 – C9 fragment 8  
steps from Grieco's  
bicyclic lactone in 40%  
yield
- C10 – C17 fragment 6  
steps from bromodienal  
in 37% yield
- No current attempts at  
total synthesis of  
aglycon unit to date



# Retrosynthesis

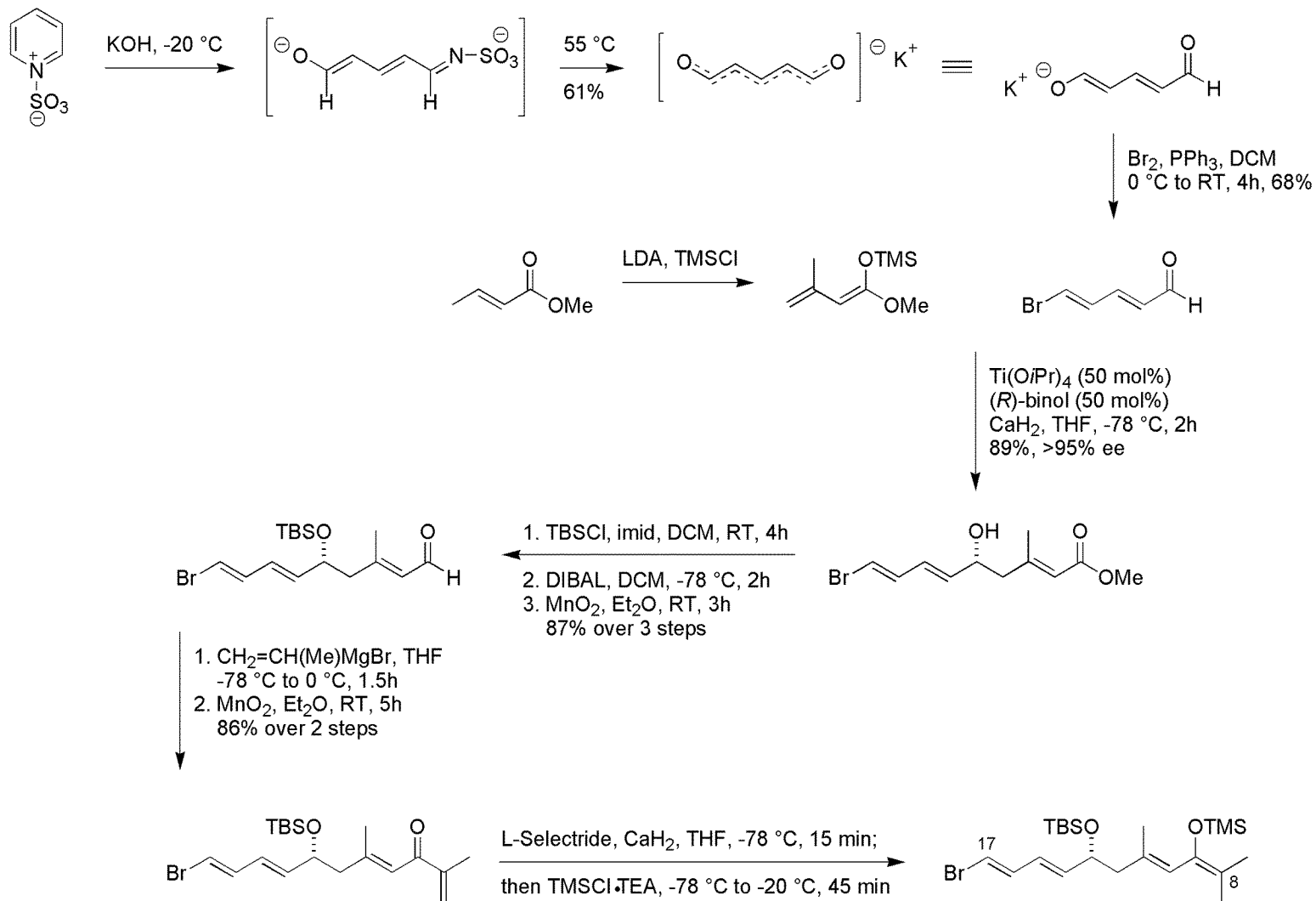
# C1 - C7 Fragment



Crimmins, M.T.; Choy, A.L. *J. Am. Chem. Soc.* **1999**, *121*, 5653.

Paterson, I.; Oballa, R.M. *Tetrahedron Lett.* **1997**, *38*, 8241.

# C8 – C17 Fragment

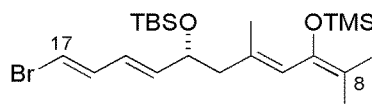
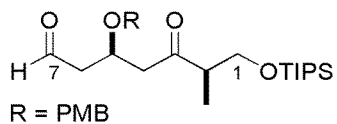


Becher, J. *Synthesis*. **1980**, 589.

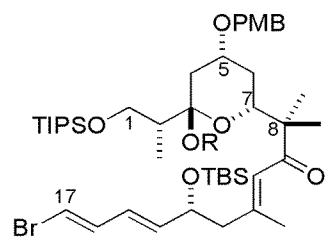
Savard, J.; Bassard, P. *Tetrahedron*. **1984**, 40, 3455.

Saito, S.; Shiozawa, M.; Yamamoto, H. *Angew. Chem. Int. Ed.* **1999**, 38, 1769.

# Completion of the Aglycon Moiety



BF<sub>3</sub>·OEt<sub>2</sub>, CaH<sub>2</sub>, DCM  
-95 °C, 10 min, 66%, 95:5 d.r.

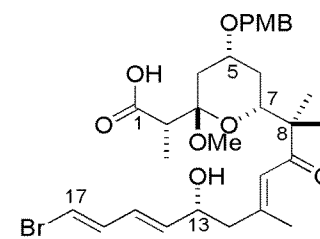


PPTS (20 mol%)  
CH(OMe)<sub>3</sub>, MeOH, RT  
4h, 94%

R = H  
R = Me

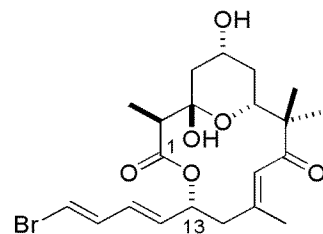
1. TASF, H<sub>2</sub>O, DMF, 0 to 15 °C, 5h, 72%

2. a. TEMPO, Ph(OAc)<sub>2</sub>, MeCN  
pH 7 buffer, 6h  
b. NaClO<sub>2</sub>, NaH<sub>2</sub>PO<sub>4</sub>, H<sub>2</sub>O  
2-methyl-2-butene, RT, 30 min, 60%



1. 2,4,6 TCBC, TEA, PHCH<sub>3</sub>  
RT, 30 min

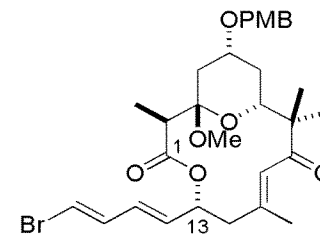
2. DMAP, RT, 4h  
86% over 2 steps



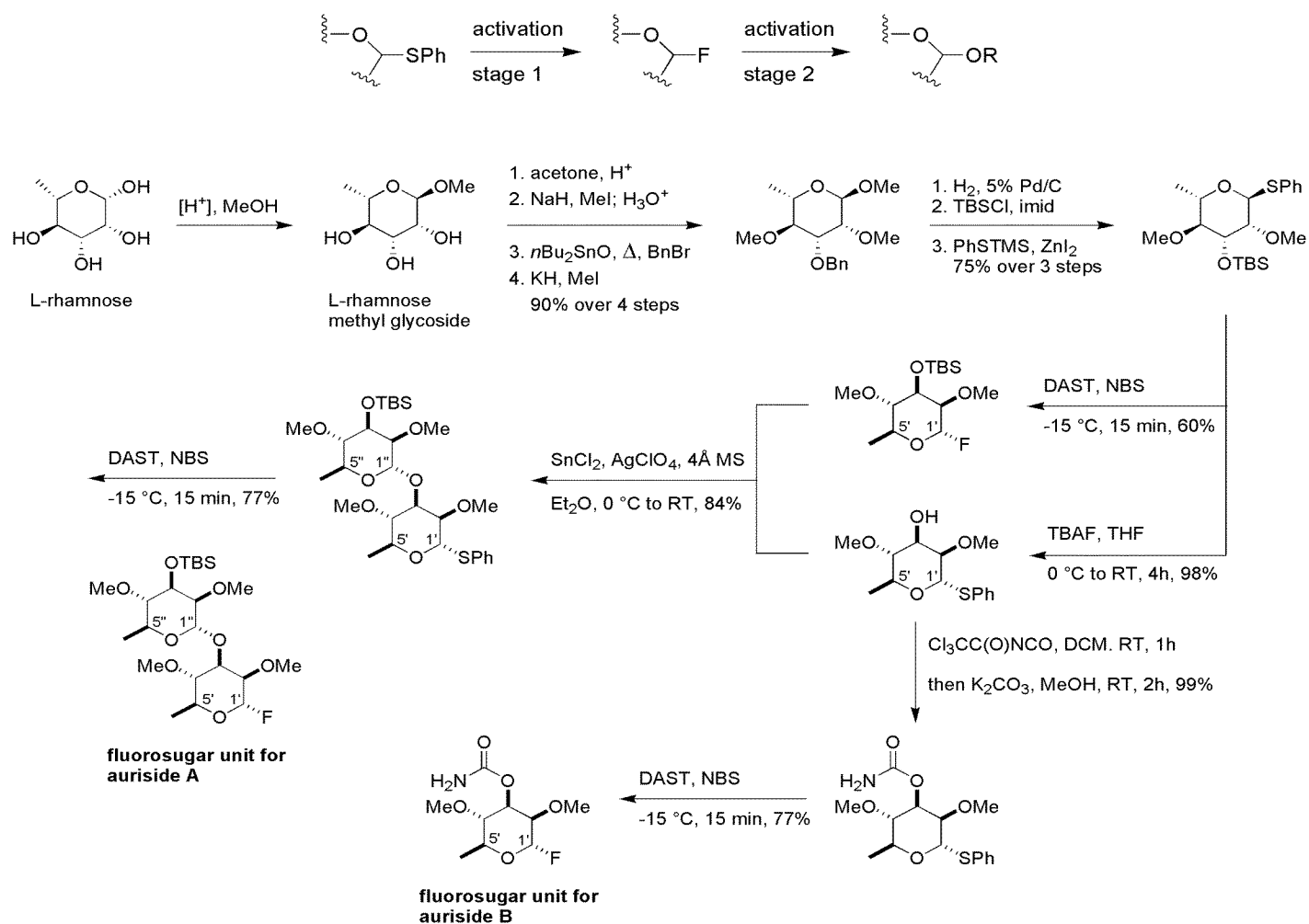
auriside aglycon

1. DDQ, DCM, pH 7 buffer, RT, 30 min

2. *p*TsOH H<sub>2</sub>O, THF, H<sub>2</sub>O, RT, 16h  
74% over 2 steps

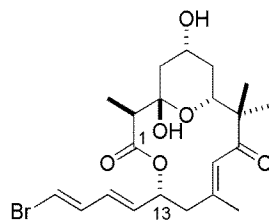


# Oligosaccharide Synthesis

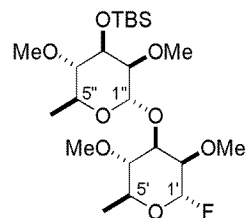


- Dolle, R.E.; Nicolaou, K.C. *J. Am. Chem. Soc.* **1985**, *107*, 1691.  
 Nicolaou, K.C.; Mitchell, H.J. *Angew. Chem. Int. Ed.* **2001**, *40*, 1576.  
 Binkley, R.W.; Goewey, G.S.; Johnston, J.C. *J. Org. Chem.* **1984**, *49*, 992.  
 Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, 481.  
 Nicolaou, et. al. *J. Am. Chem. Soc.* **1984**, *106*, 4189

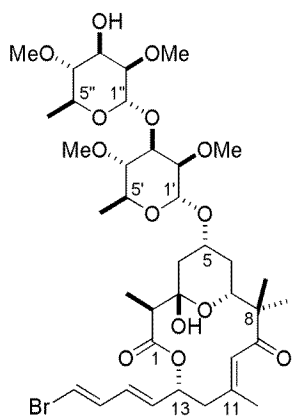
# Completion of Total Synthesis



1.  $\text{SnCl}_2$ ,  $\text{AgClO}_4$ , 4Å MS  
 $\text{Et}_2\text{O}$ , 0 °C to RT, 16h

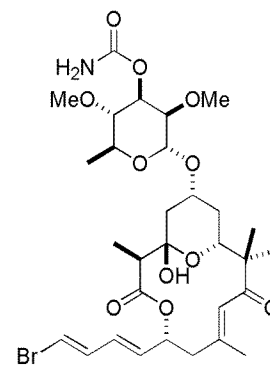
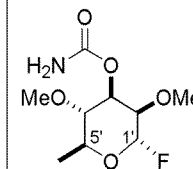


2. HF-py, THF, 0 °C to RT  
16h, 37% over 2 steps



auriside A

$\text{SnCl}_2$ ,  $\text{AgClO}_4$ , 4Å MS  
 $\text{Et}_2\text{O}$ , 0 °C to RT, 8h, 74%



auriside B

auriside A: 18 steps (1.7% overall)  
auriside B: 17 steps (3.5% overall)