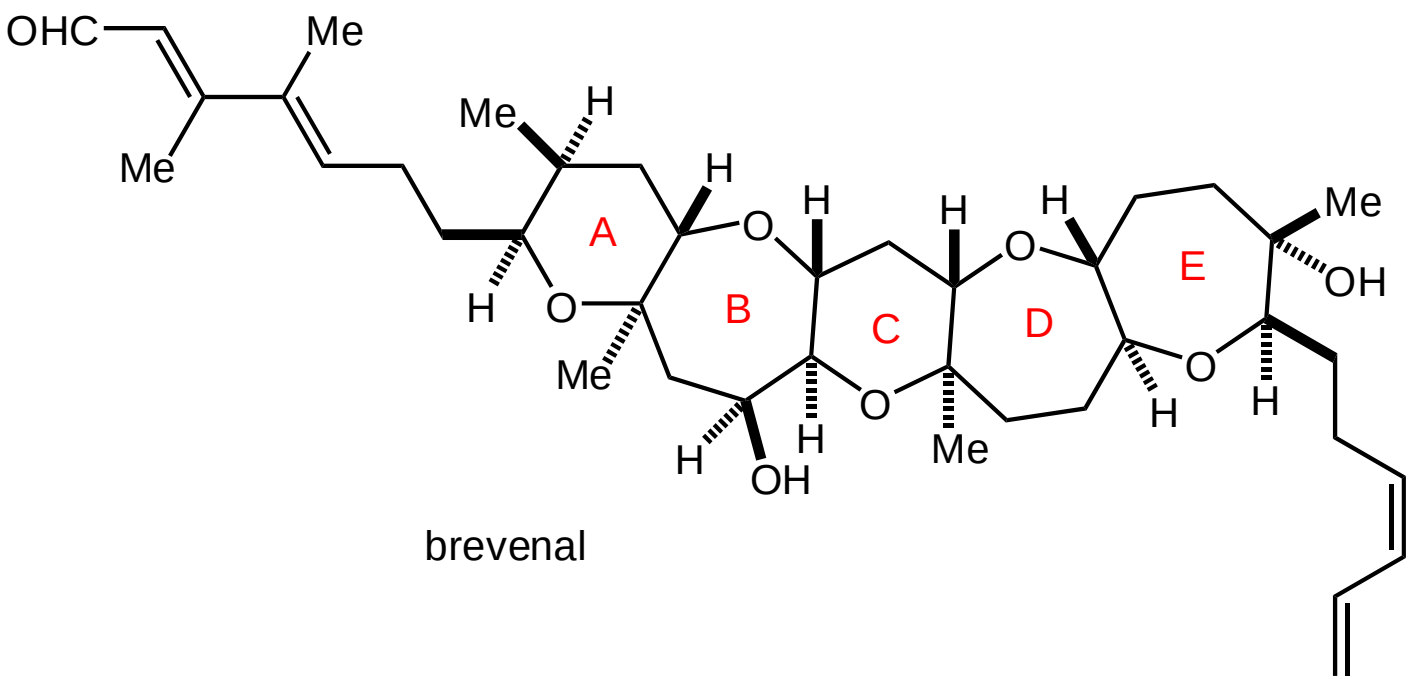
Literature Report 2010-06-01

Mu-Wang Chen
Checker: Ying Duan

A Highly Convergent Approach toward (-)-Brevenal

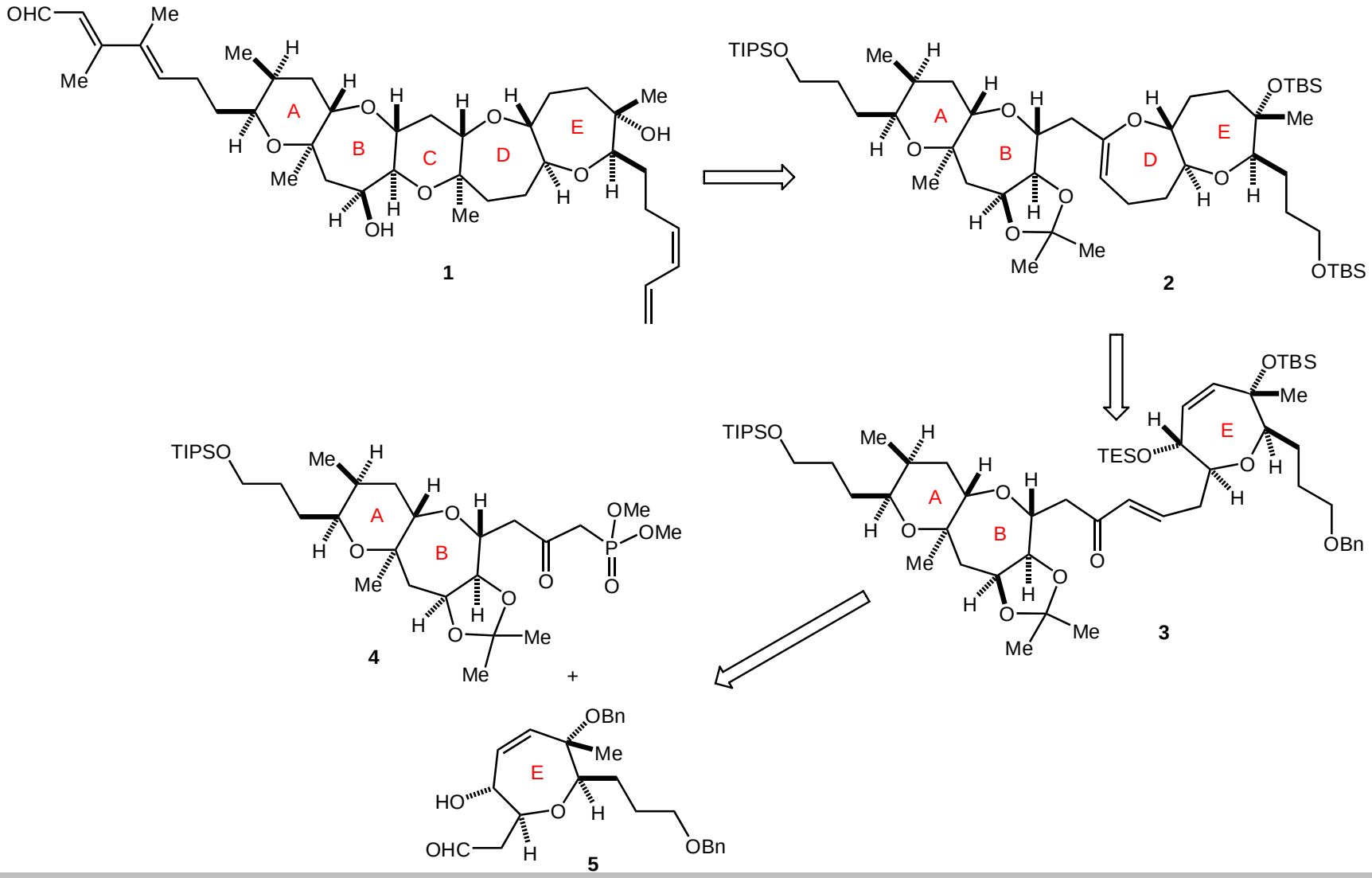
Crimmins, M.* *et al*
Org. Lett. **2010**, *ASAP*

Structure of (-)-Brevenal

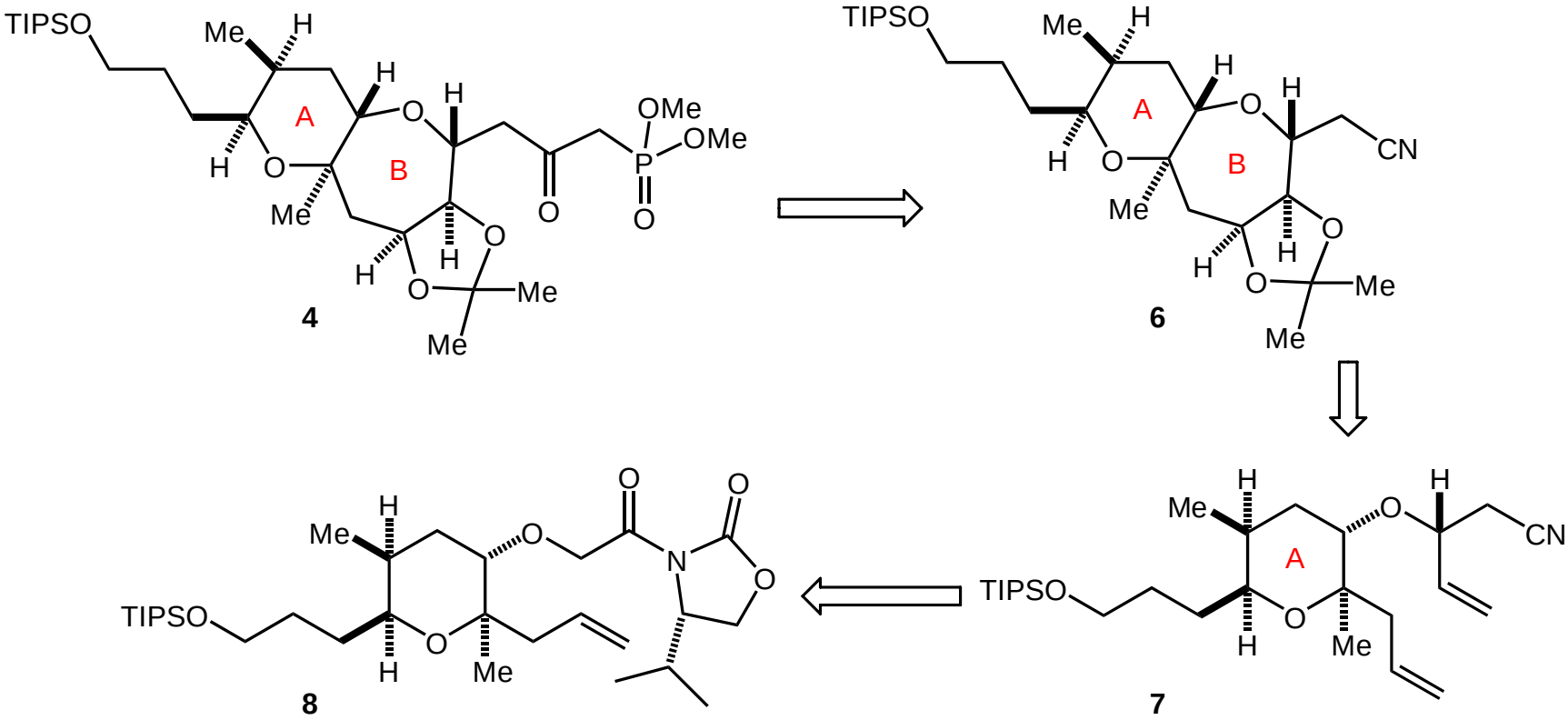


brevenal

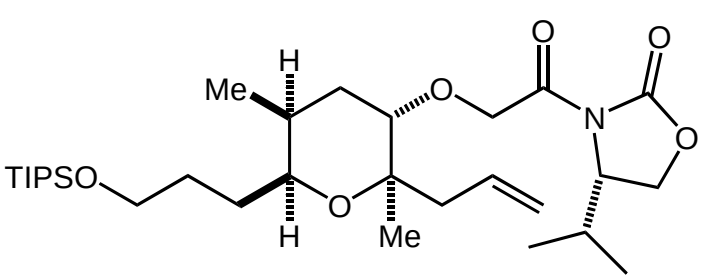
Retrosynthetic analysis



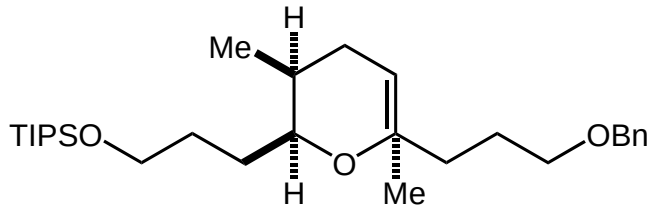
Retrosynthetic Plan for β-Ketophosphonate **4**



Retrosynthetic Plan for β-Ketophosphonate **4**



8



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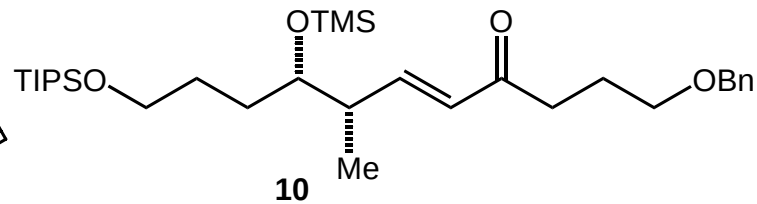

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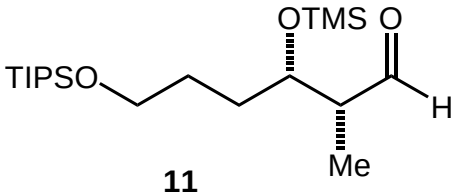

11

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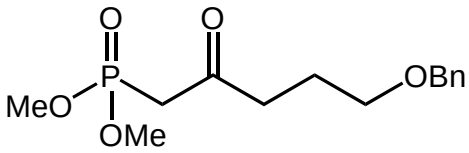

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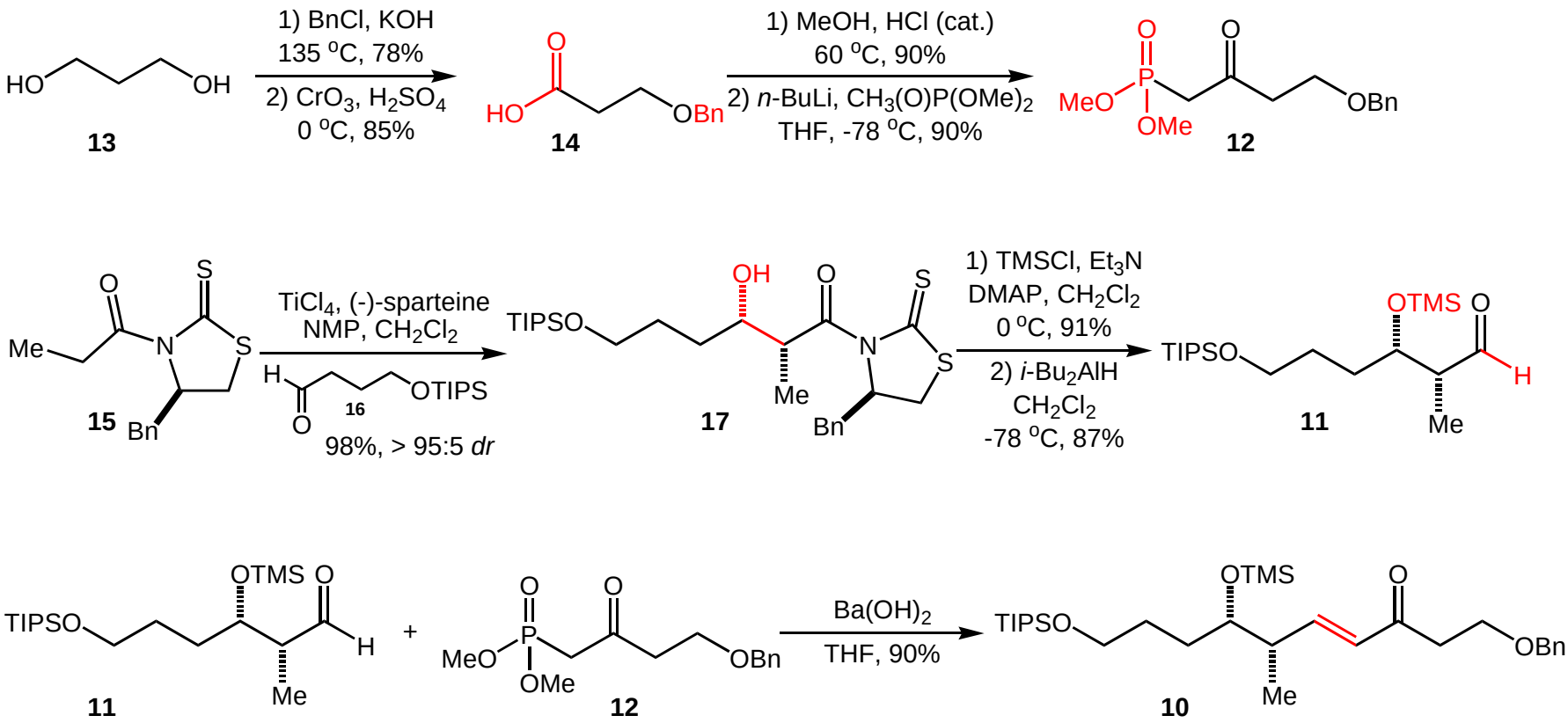
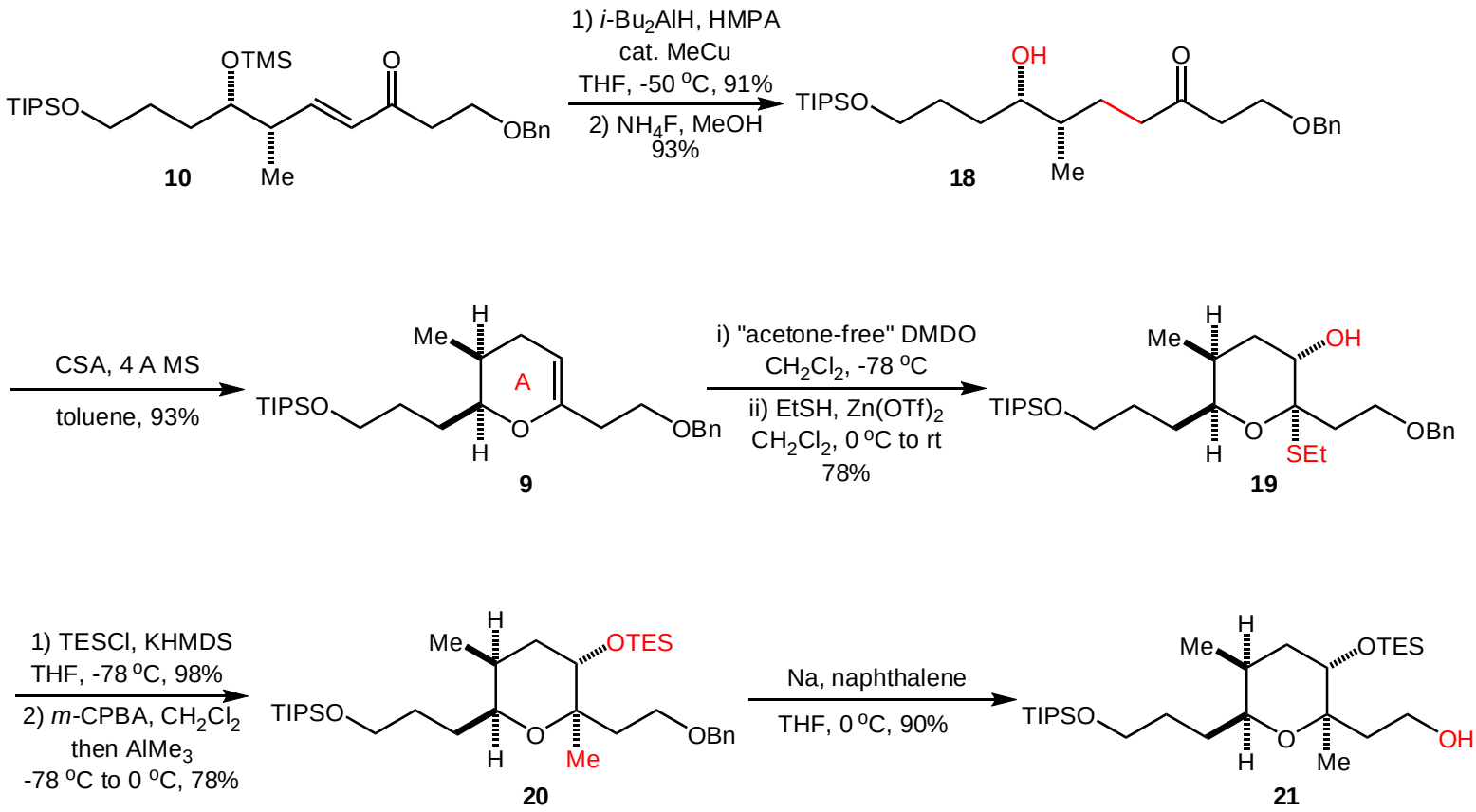
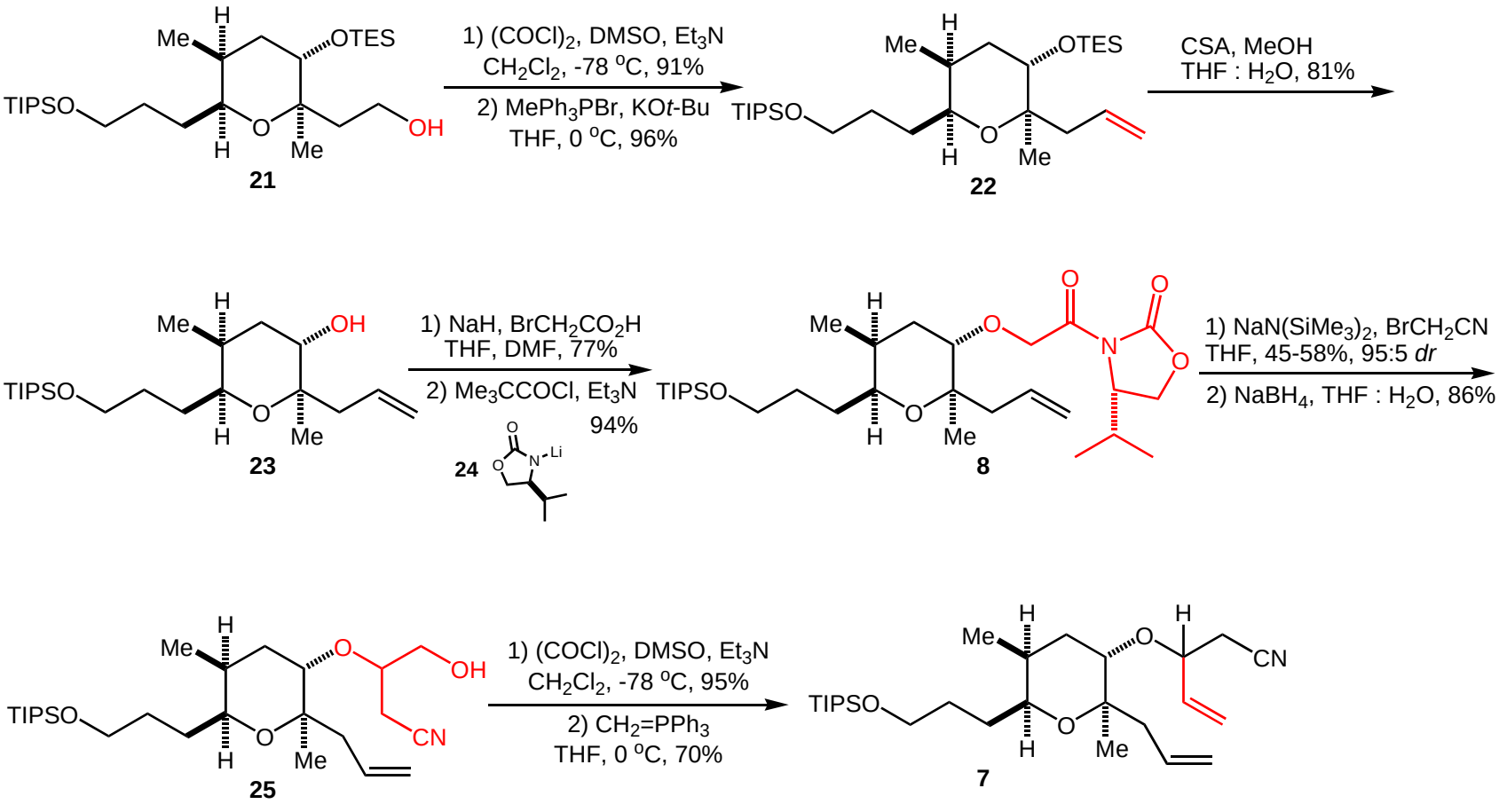
Synthesis of AB-Ring β-Ketophosphonate **4**



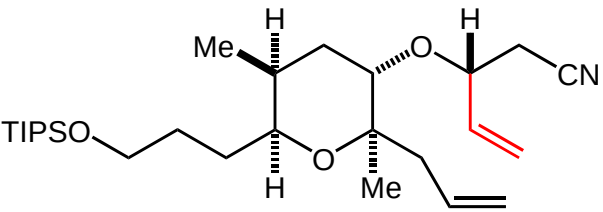
Synthesis of AB-Ring β-Ketophosphonate **4**



Synthesis of AB-Ring β-Ketophosphonate **4**

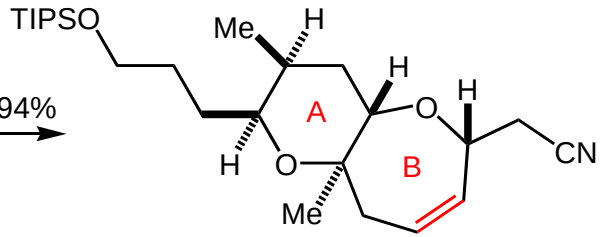


Synthesis of AB-Ring β-Ketophosphonate **4**



7

Grubbs' 2nd Gen. 94%



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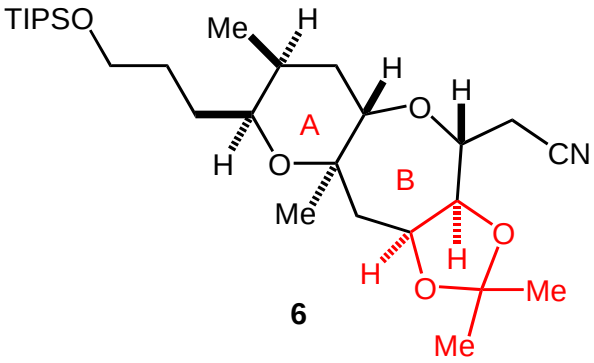
1) OsO_4, NMO, THF, 94%

2) PPTS, CH_2Cl_2
2-methoxypropene, 77%

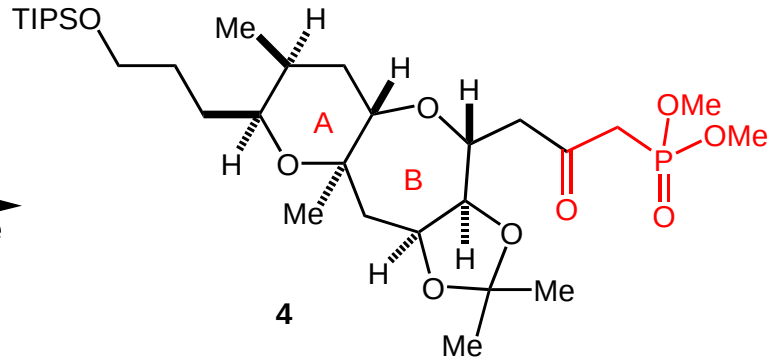


6

1) $(i\text{-Bu})_2AlH, CH_2Cl_2$, 80%

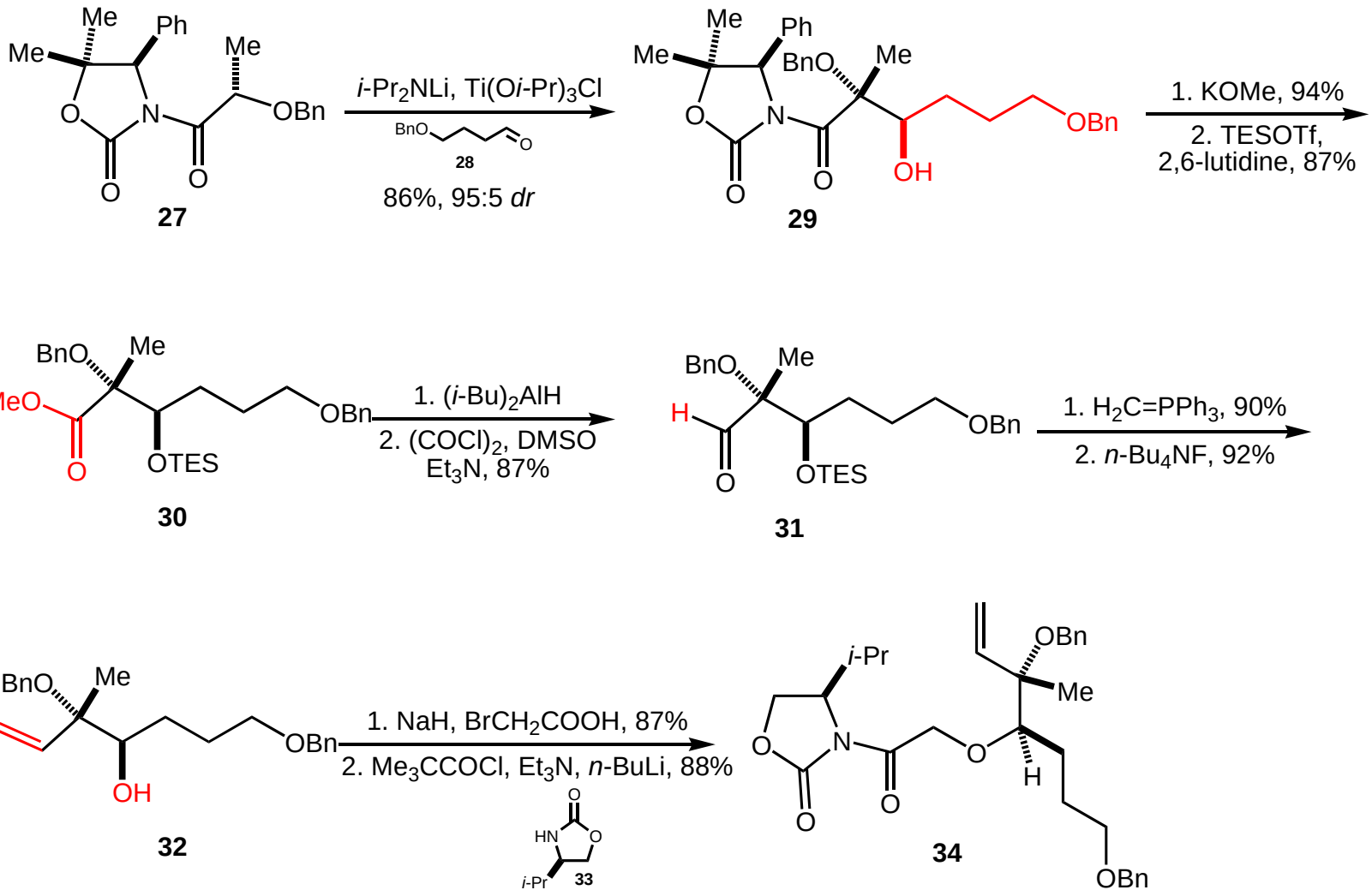
2) *n*-BuLi, $CH_3(O)P(OMe)_2$
THF, -78 ^oC, 90%

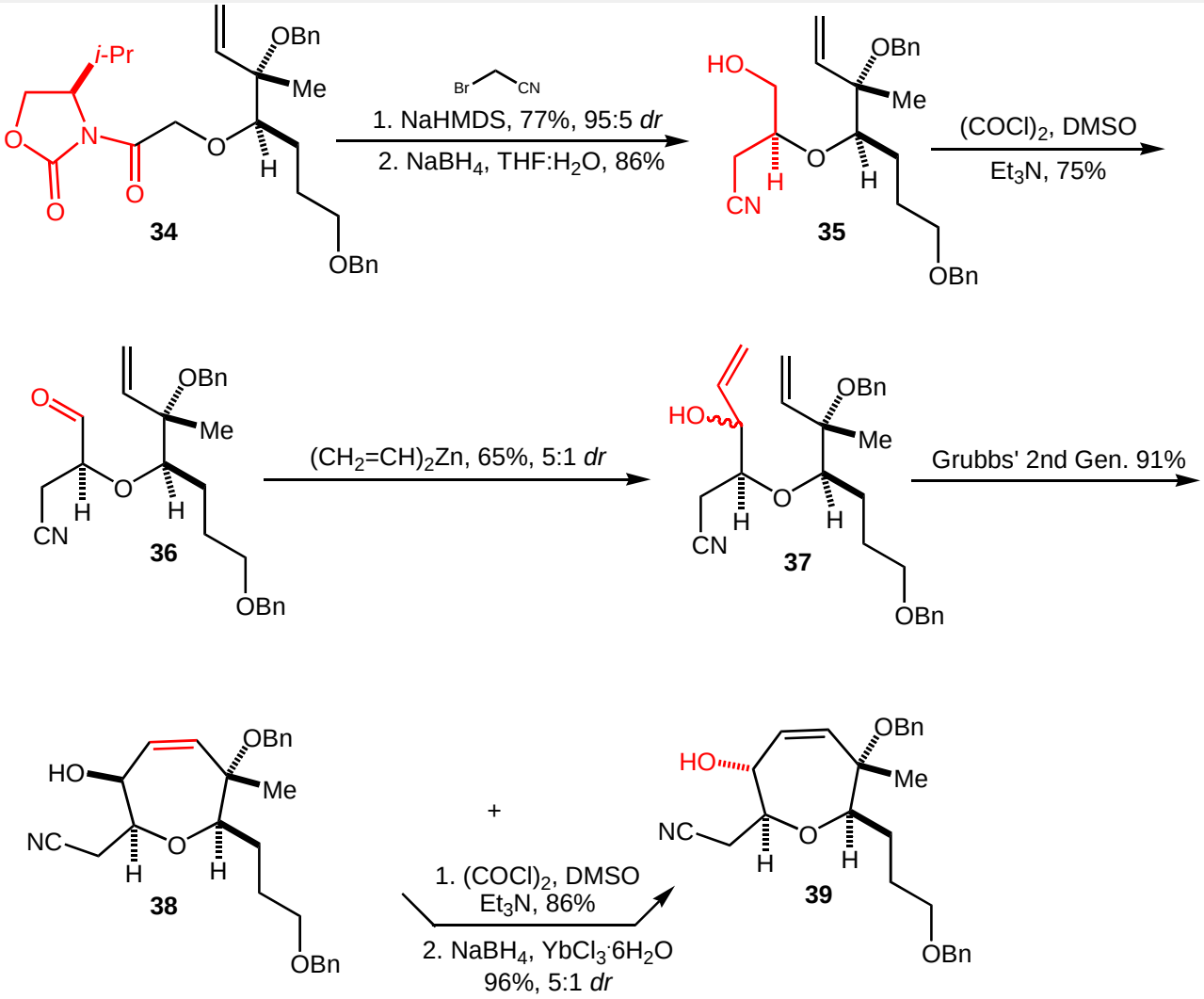
3) Dess-Martin periodinane
CH_2Cl_2, 90%

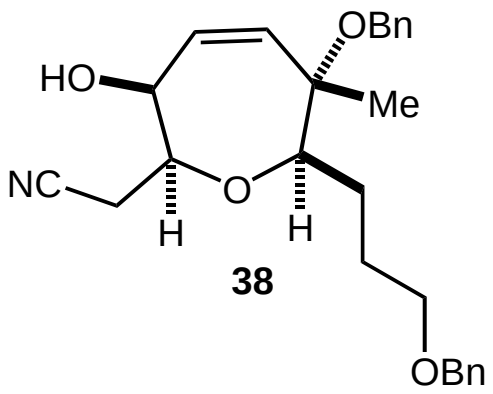


4

Synthesis of Aldehyde **5**




i-Pr
OBn
Me
O
N
O
O
O
H
OBn
34
Br
CN
1. NaHMDS, 77%, 95:5 dr
2. NaBH4, THF:H2O, 86%
HO
OBn
Me
O
H
CN
H
35
OBn
(COCl)2, DMSO
Et3N, 75%
O
OBn
Me
H
CN
O
H
36
OBn
(CH2=CH)2Zn, 65%, 5:1 dr
HO
OBn
Me
H
CN
O
H
37
OBn
Grubbs' 2nd Gen. 91%
HO
OBn
Me
NC
O
H
H
38
OBn
+
1. (COCl)2, DMSO
Et3N, 86%
2. NaBH4, YbCl3·6H2O
96%, 5:1 dr
HO
OBn
Me
NC
O
H
H
39
OBn



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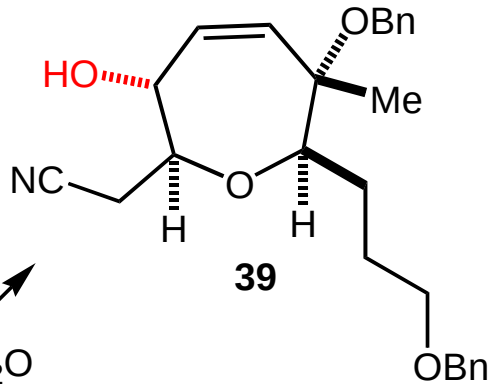
1. $(COCl)_2$, DMSO
Et_3N, 86%

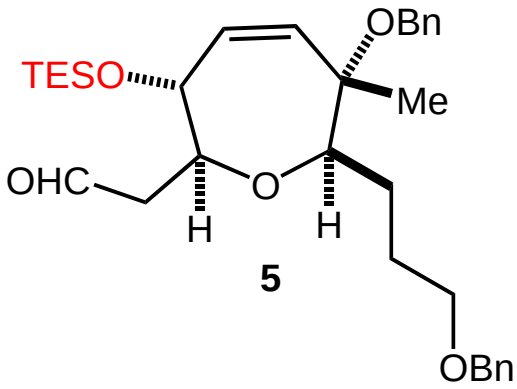
2. $NaBH_4$, $YbCl_3{\cdot}6H_2O$
96%, 5:1 *dr*



39

1. TESOTf, 2,6-lutidine, 99%

2. $(i\text{-Bu})_2AlH$, 99%



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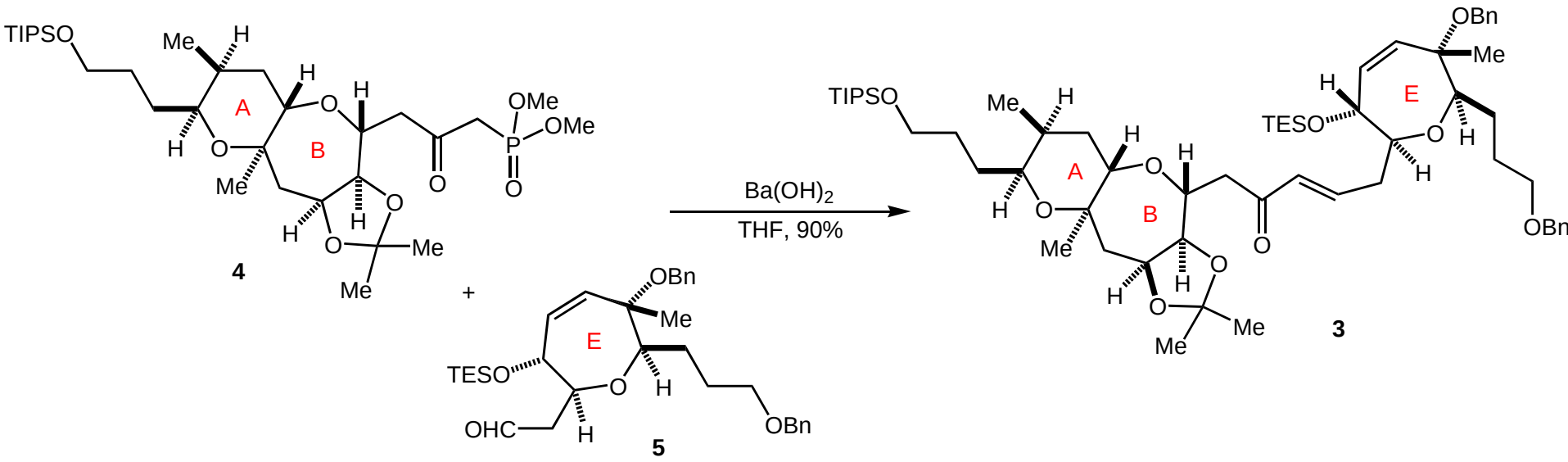
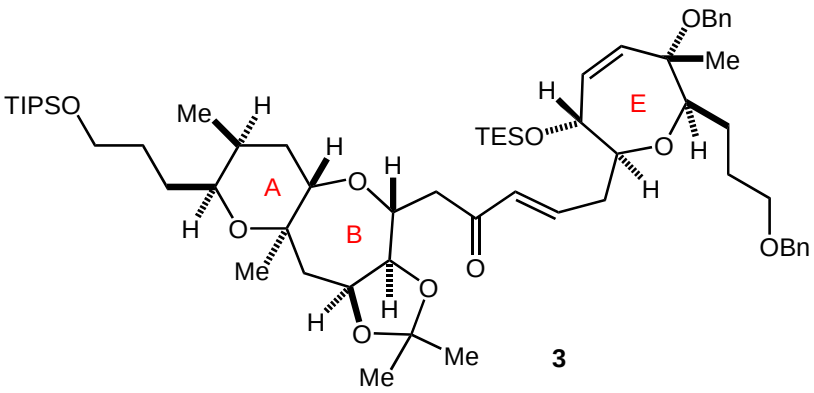
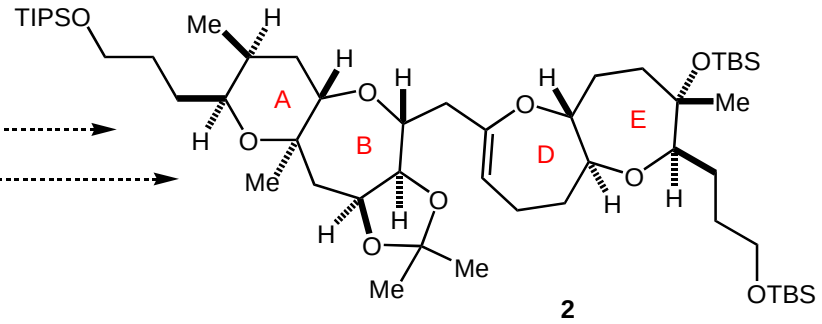
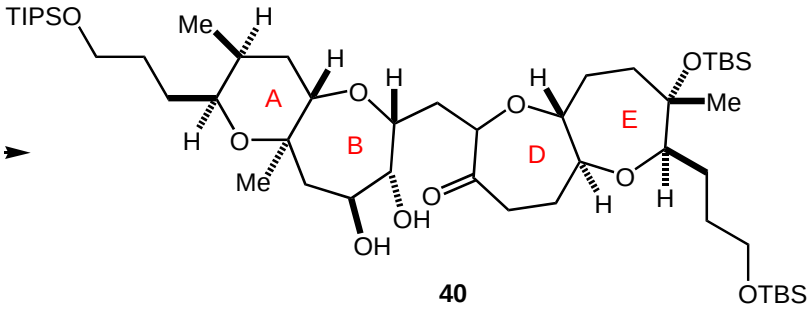
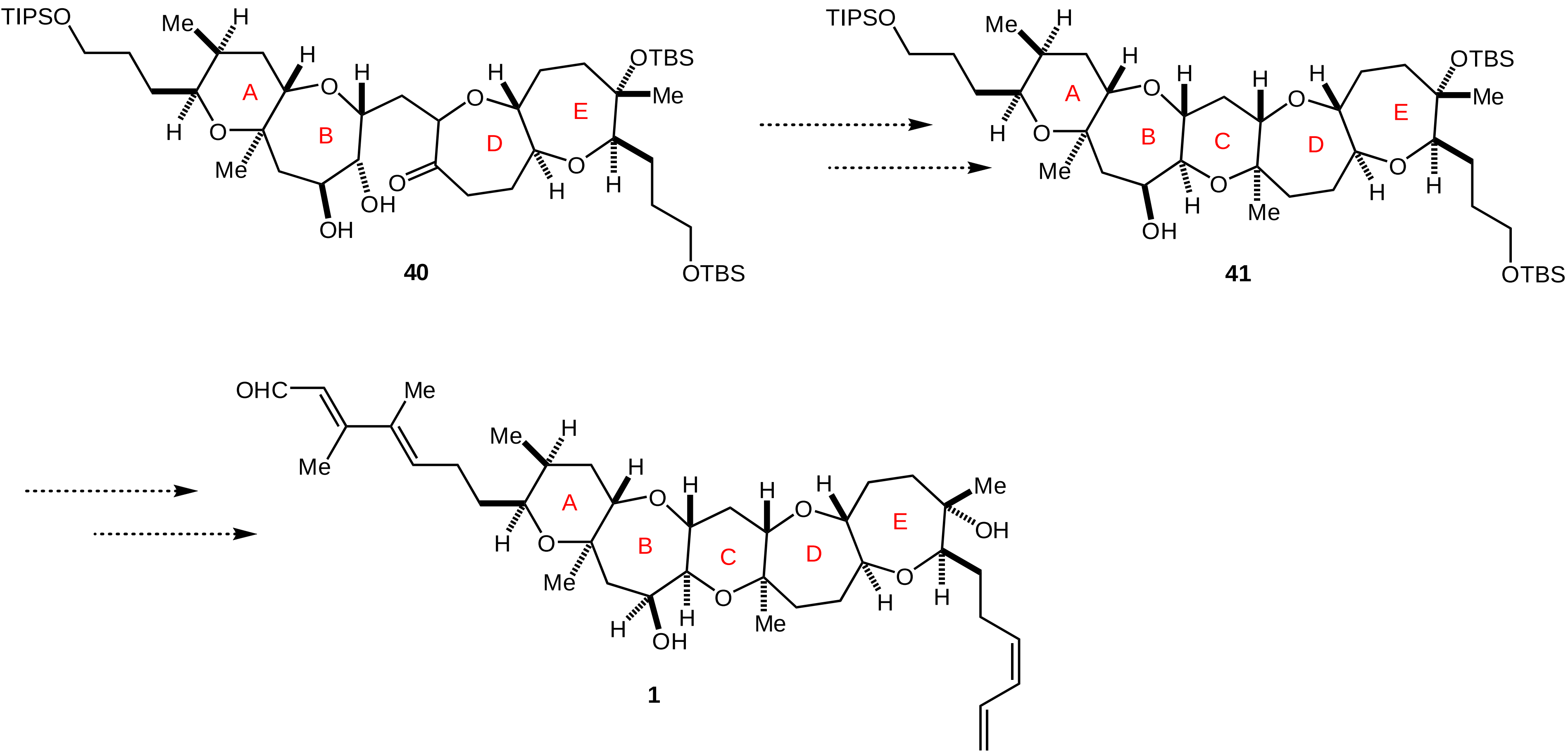

TIPSO
Me
H
A
B
H
O
H
OMe
OMe
P
O
O
Me
H
O
H
O
Me
Me
4
+
OBn
Me
E
TESO
O
H
OHC
H
OBn
5
Ba(OH)2
THF, 90%
TIPSO
Me
H
A
B
H
O
H
O
Me
H
O
H
O
Me
Me
3
OBn
Me
H
E
TESO
O
H
H
OBn

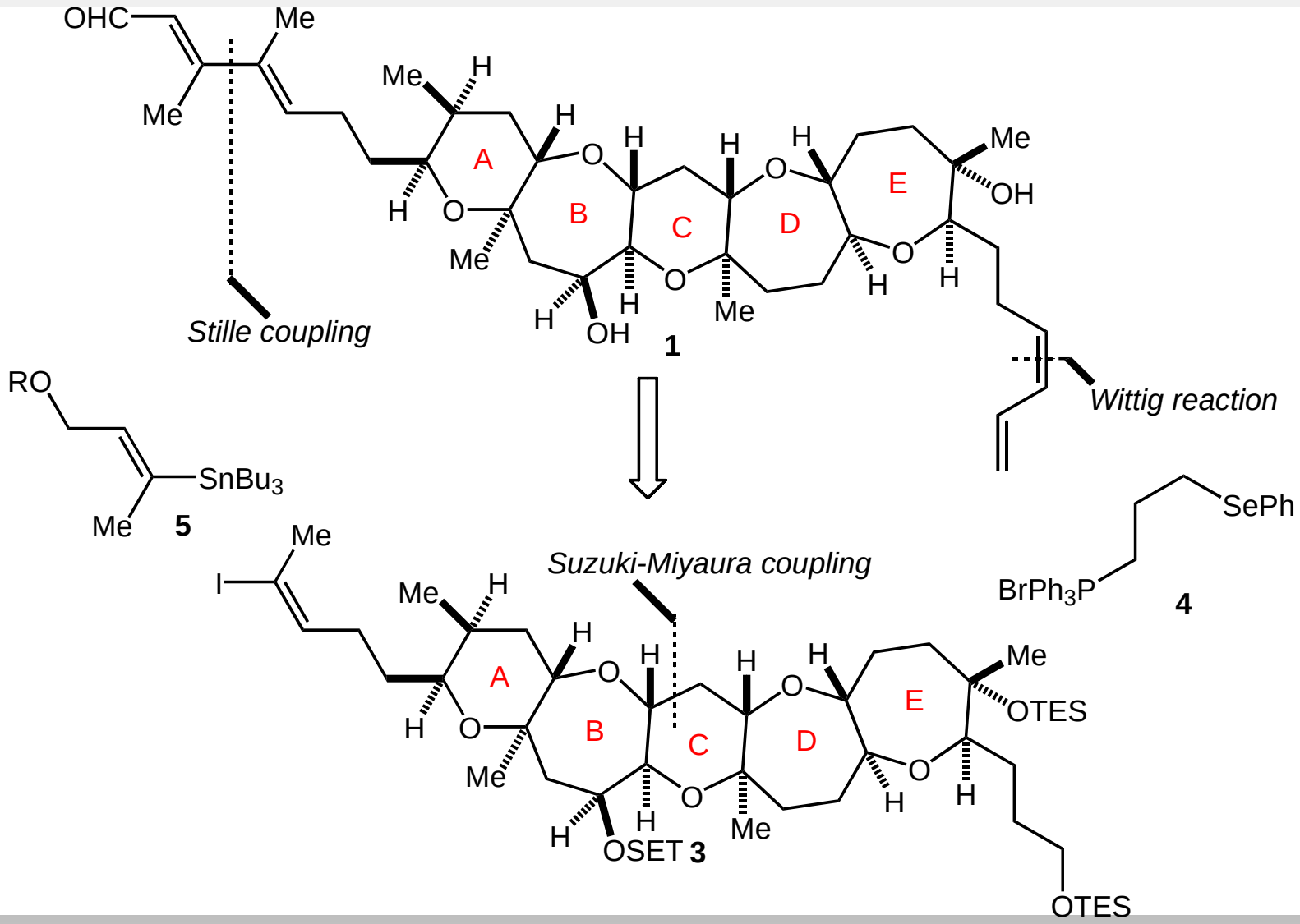
Envision Synthesis of **1**



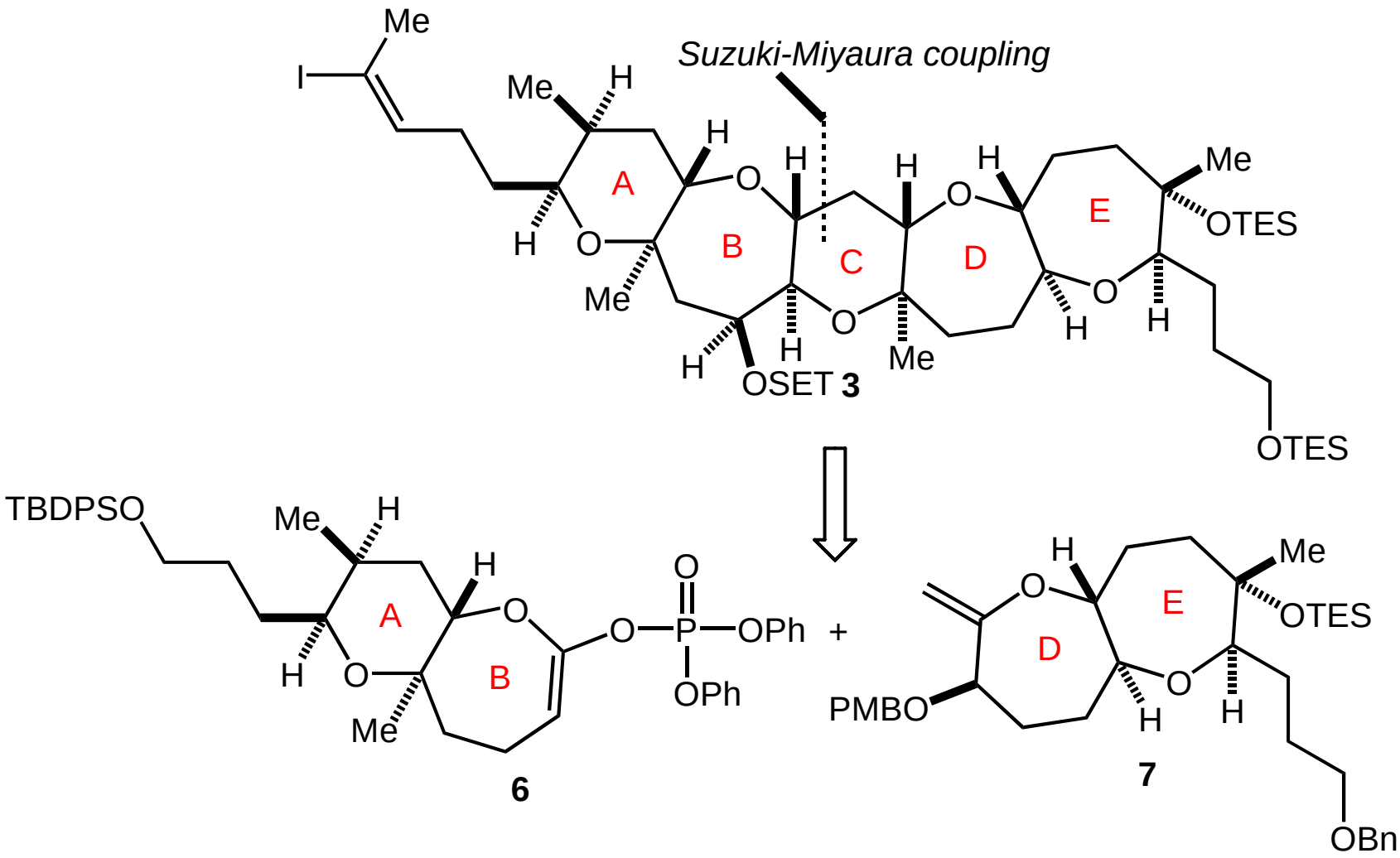





TIPSO
Me
H
A
B
C
D
E
O
OH
OTBS
40
41
1
OHC



Sasaki, M. *et al J. Am. Chem. Soc.* **2006**, *128*, 16989.



Sasaki, M. *et al J. Am. Chem. Soc.* **2006**, *128*, 16989.

Marine polycyclic ether natural products have received much attention over the years due to their unique and highly complex molecular architecture, in addition to their diverse and potent biological activities. A number of bioactive polyether natural products have been isolated from the marine dinoflagellate *Karenia brevis*, the organism responsible for toxic red tides along Florida's Gulf Coast. The most wellknown compounds isolated from *K. brevis* are a family of neurotoxins called the brevetoxins. The brevetoxins are responsible for massive kills of fish and marine animals and can also adversely affect humans; inhaled brevetoxins cause respiratory irritation and breathing difficulties in sensitive populations. At high concentrations, ingested brevetoxins lead to a collection of symptoms commonly referred to as neurotoxic shellfish poisoning (NSP).

In summary, a highly convergent approach toward the total synthesis of brevenal has been reported. Two key cyclic ether fragments have been constructed utilizing our asymmetric glycolate alkylation/ring-closing metathesis approach. Fragment coupling has been carried out in excellent yield, and efforts to complete the carbon framework and elaborate the side chains are ongoing. .