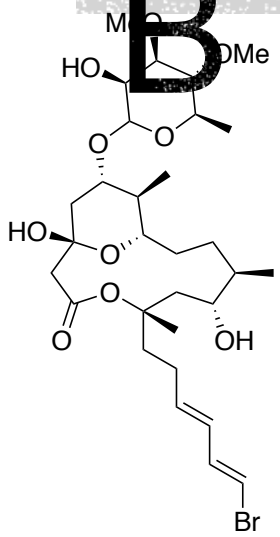
TOTAL SYNTHESIS OF (—)-LYNGBYALOSIDE B

H. Fuwa, Y. Okuaki, N. Yamagata, M. Dadaki, Tohoku University



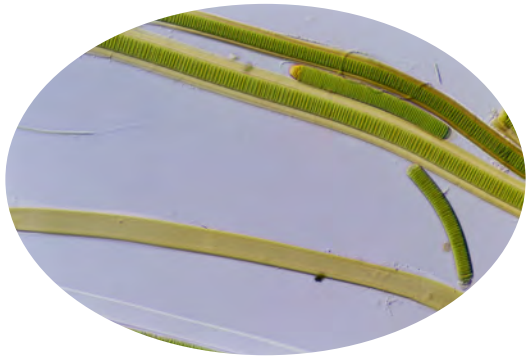
Presented by Zhilin Hou

CEM 852

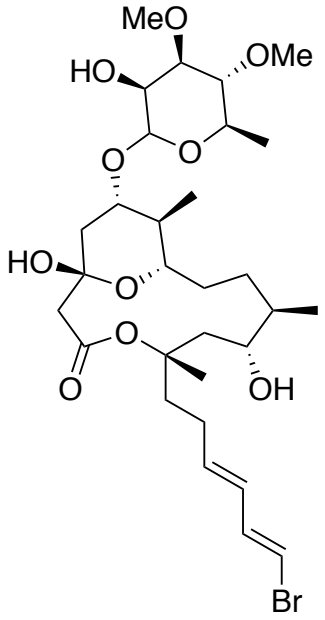
2018.4.14

Angew. Chem. Int. Ed. **2015**, *54*, 868

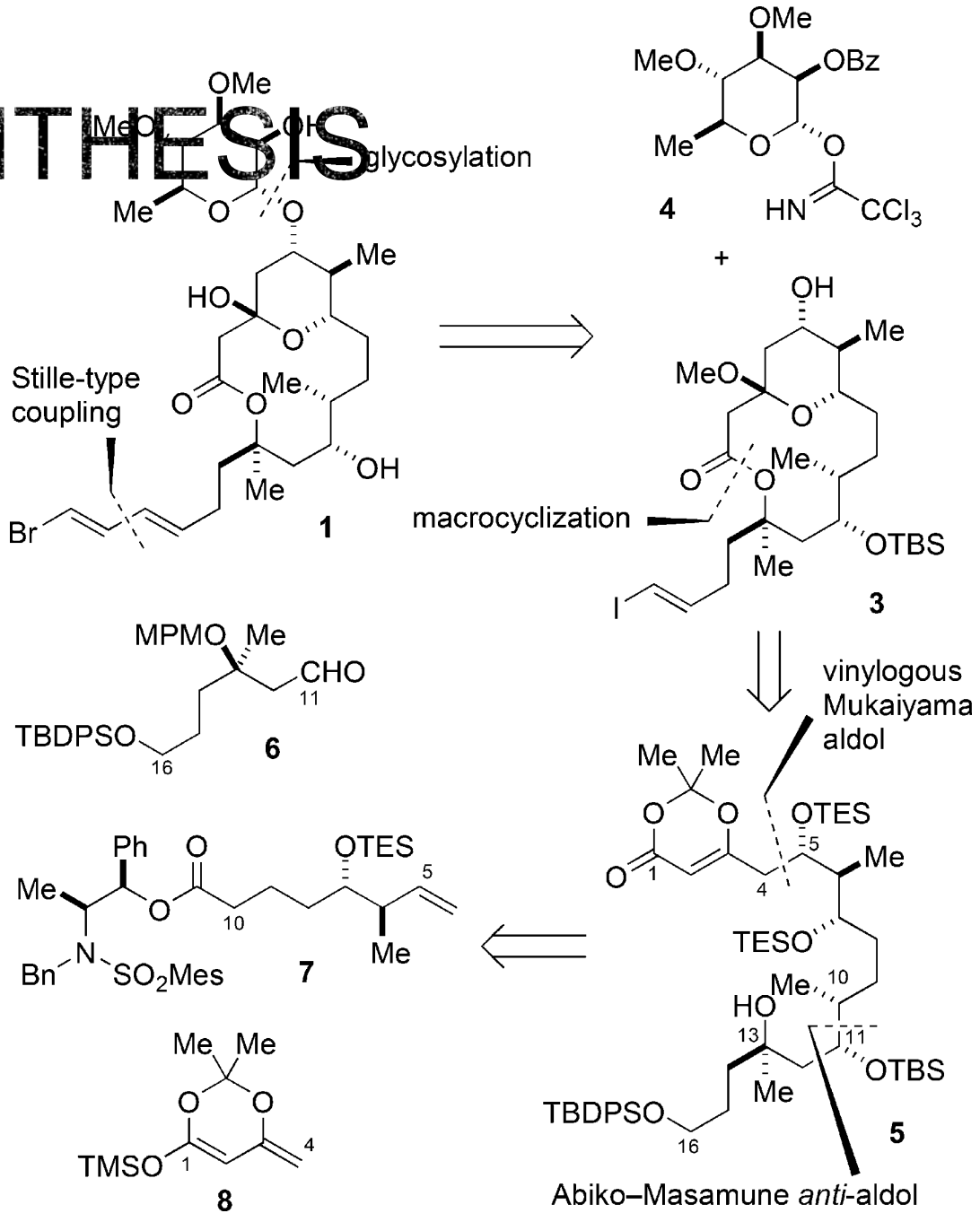
BACKGROUND

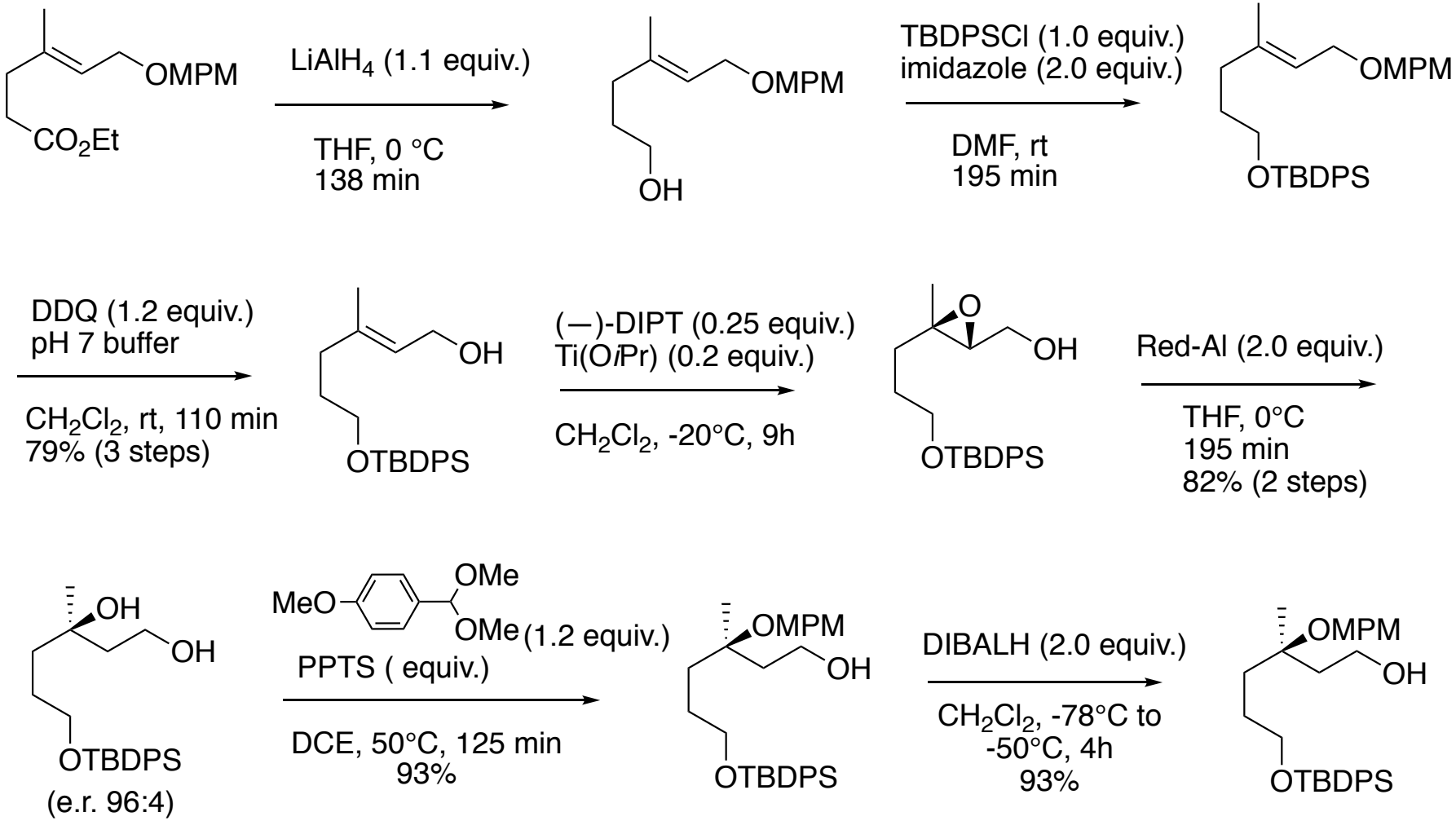


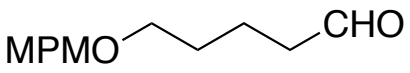
- Marine cyanobacteria are recognized to be a rich source of novel biologically active secondary metabolites.
- (—)-Lyngbyaloside B is a 14-membered macrolide glycoside that was isolated from the marine cyanobacterium *Lyngbya* sp. collected at Palau by the Moore group.



RETROSYNTHESIS

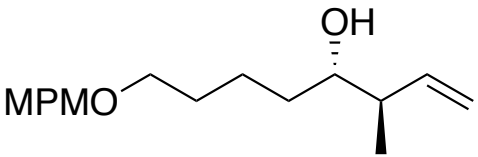



OMPM
CO2Et
LiAlH4 (1.1 equiv.)
THF, 0 °C
138 min
OH
TBDPSCl (1.0 equiv.)
imidazole (2.0 equiv.)
DMF, rt
195 min
OTBDPS
DDQ (1.2 equiv.)
pH 7 buffer
CH2Cl2, rt, 110 min
79% (3 steps)
(—)-DIPT (0.25 equiv.)
Ti(OiPr) (0.2 equiv.)
CH2Cl2, -20°C, 9h
O
Red-Al (2.0 equiv.)
THF, 0°C
195 min
82% (2 steps)
(e.r. 96:4)
MeO
OMe
(1.2 equiv.)
PPTS (equiv.)
DCE, 50°C, 125 min
93%
DIBALH (2.0 equiv.)
CH2Cl2, -78°C to
-50°C, 4h
93%
SO3•py (4.0 equiv.)
Et3N (5.0 equiv.)
DMSO/CH2Cl2 (1:1)
0°C, 22 min
97%
MPMO
TBDPSO
H
(–)-D-DIPT
Na
Al



(+)-Ipc_2BOMe (1.22 equiv.)
trans-2-butene (5.0 equiv.)
nBuLi (1.2 equiv.)
KOtBu (1.2 equiv.)
$BF_3{\cdot}OEt_2$ (1.2 equiv.)

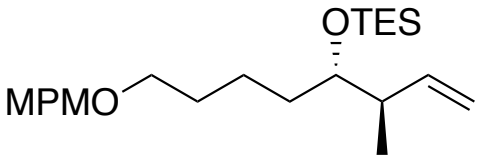
THF, -78°C, then aq NaOH
H_2O_2, rt, 3h
77%



TESCl (1.49 equiv.)
imidazole (3.03 equiv.)

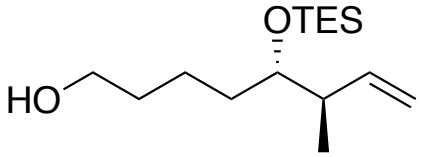
CH_2Cl_2, rt, 2.5h
94%

Brown asymmetric crotylation



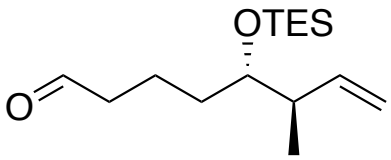
DDQ (1.2 equiv.)
pH 7 buffer

CH_2Cl_2, rt, 40 min
94%



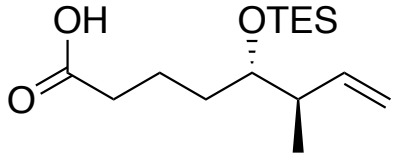
DMP (1.2 equiv.)
$NaHCO_3$ (10.0 equiv.)

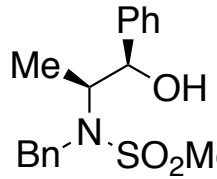
CH_2Cl_2, rt, 45 min



$NaClO_2$ (3.49 equiv.)
NaH_2PO_4 (1.1 equiv.)

$tBuOH/H_2O$/2-methyle-2-butene
(4:2:1), rt, 95 min
89% (2 steps)

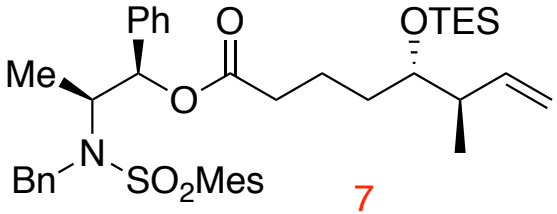




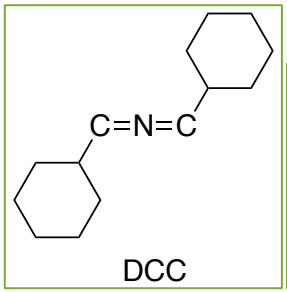
(1.1 equiv.)
DCC (2.0 equiv.)
DMPA (1.2 equiv.)

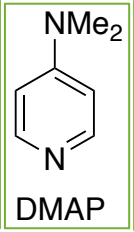
CH_2Cl_2, rt, overnight
68%

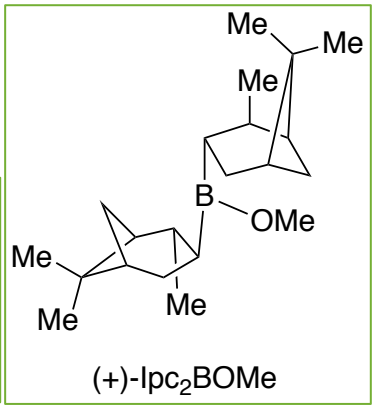
Condensation

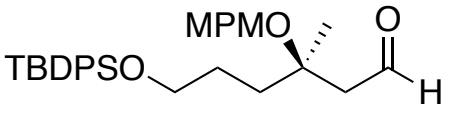


7

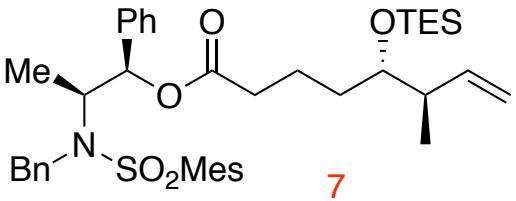








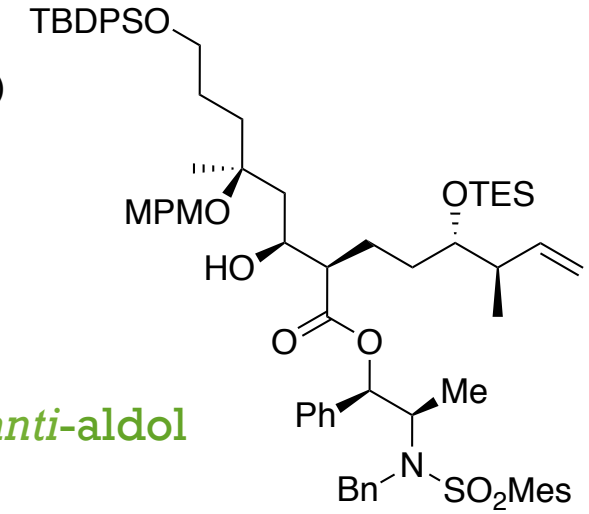
6



7

Cy_2BOTf (2.3 equiv.)
Et_3N (2.5 equiv.)

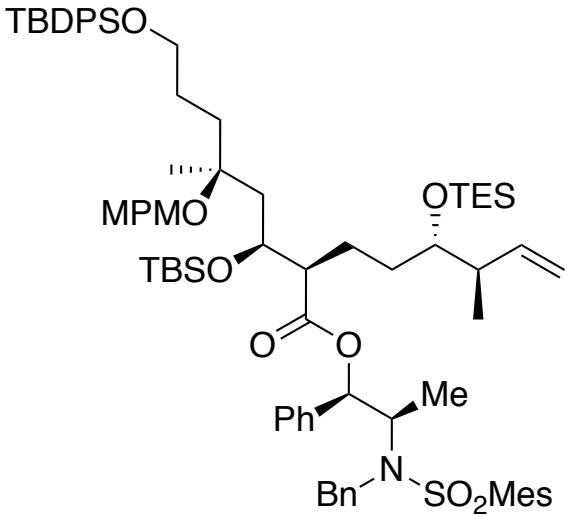
CH_2Cl_2, -78°C,
2h, 87%



TBSCl (6 equiv.)
py (30 equiv.)
$AgNO_3$ (5.88 equiv.)

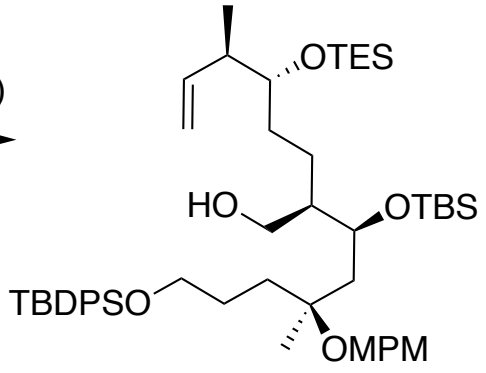
DMF, 0°C
8h, 91%

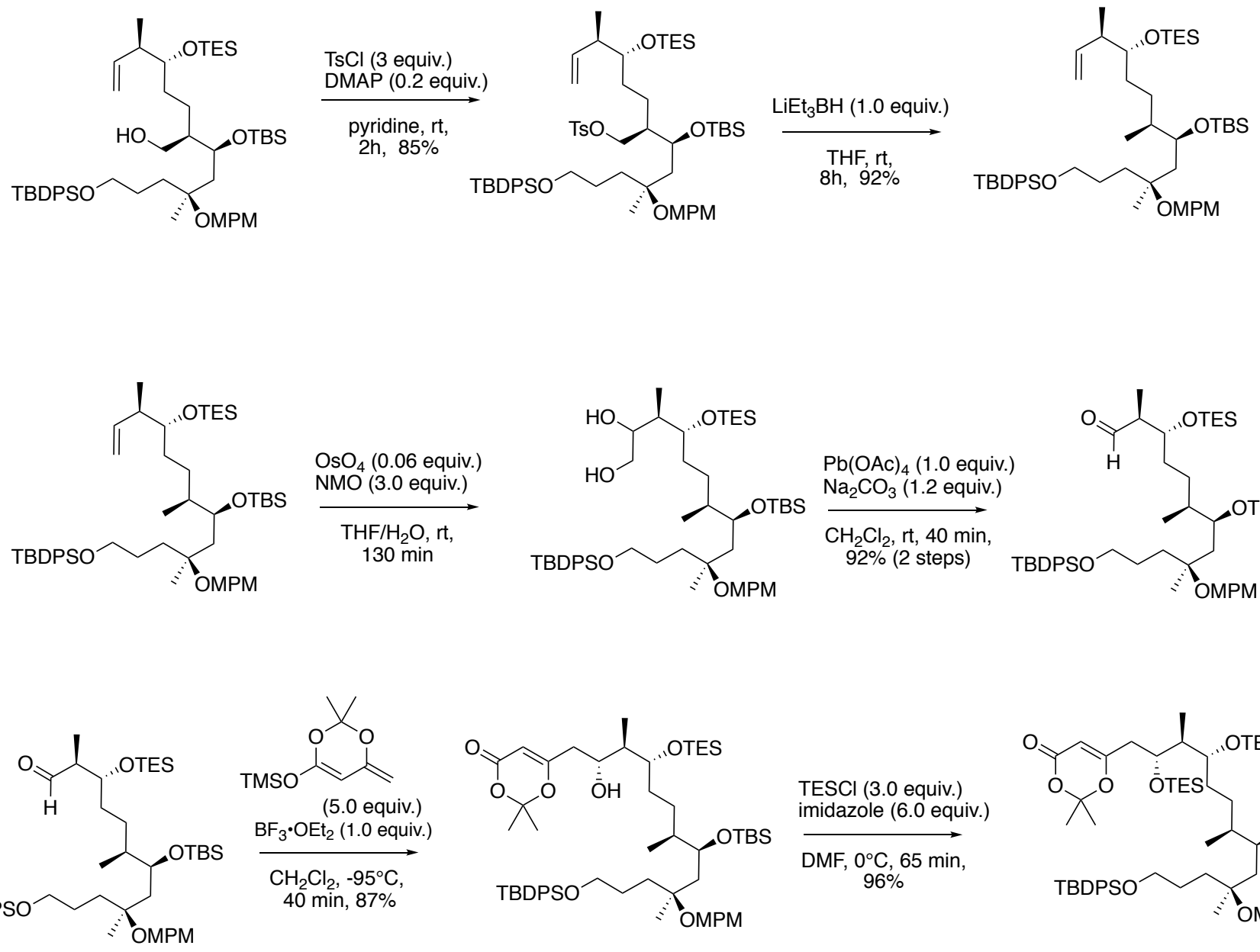
Abiko–Masamune *anti*-aldol Reaction



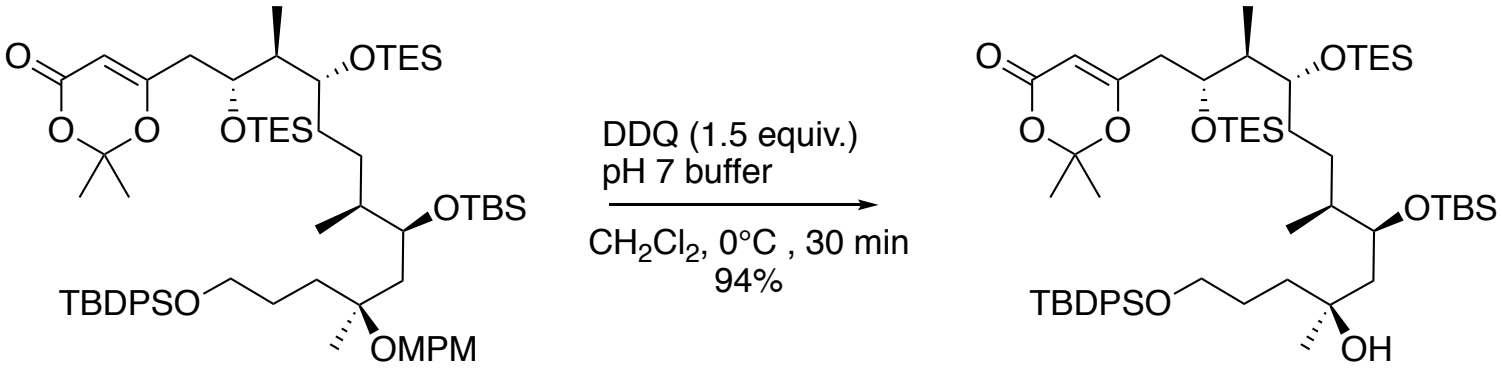
DIBALH(3 equiv.)

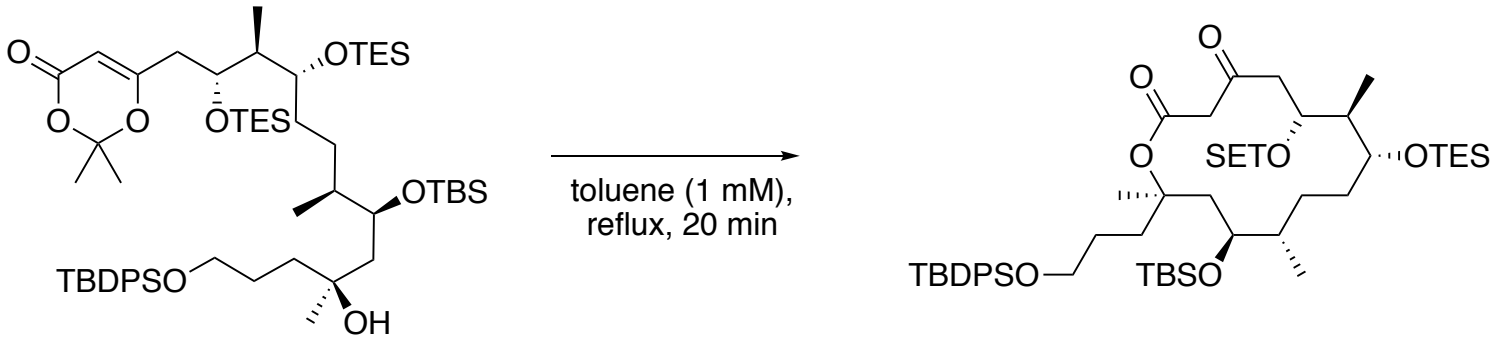
CH_2Cl_2, -78°C,
70 min, 79%

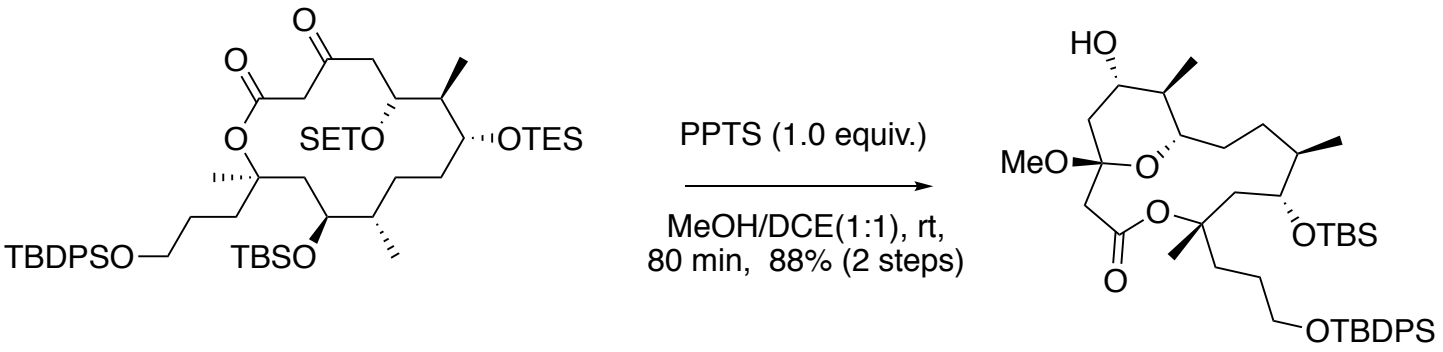


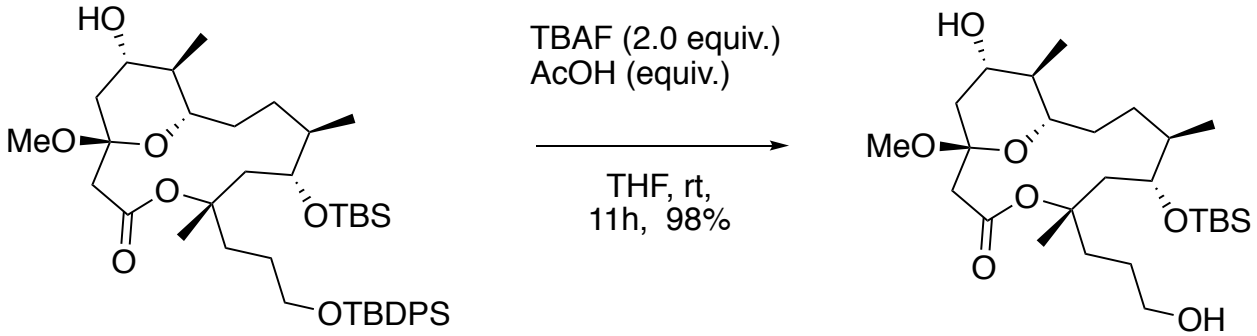


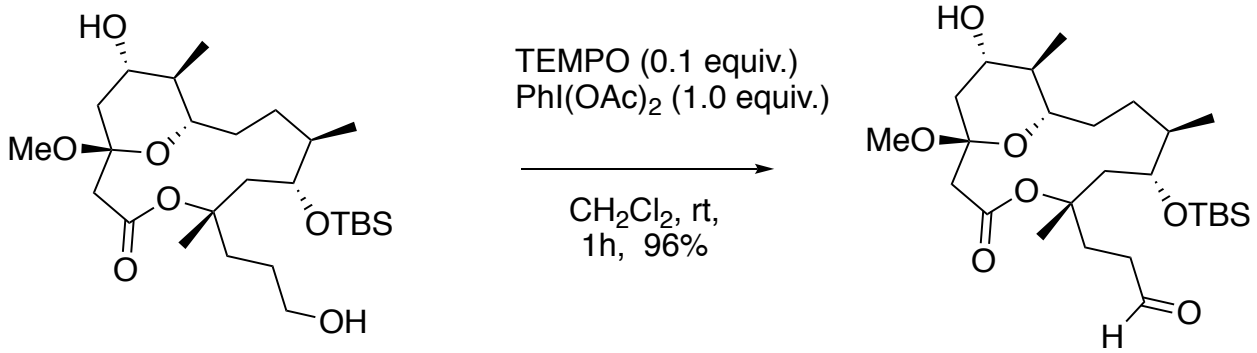
Mukaiyama aldol Reaction

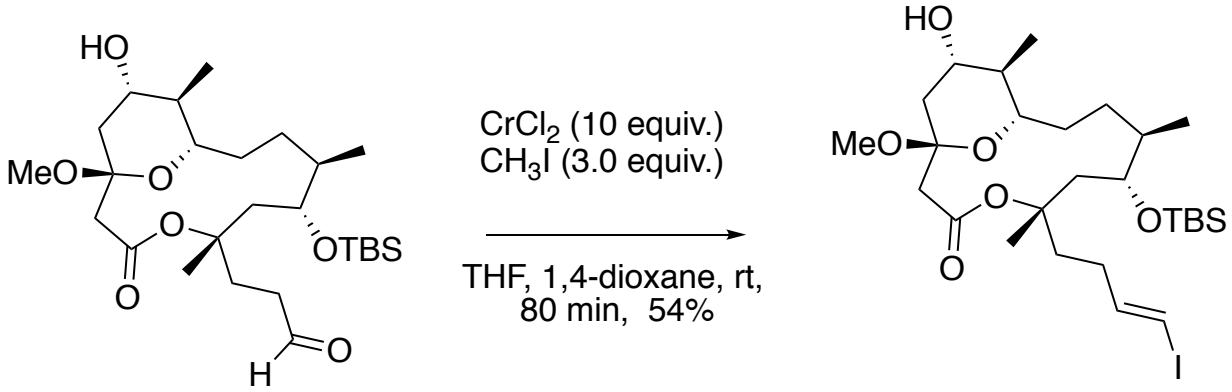

O
O
O
OTES
OTES
OTBS
TBDPSO
OMPM
DDQ (1.5 equiv.)
pH 7 buffer
CH2Cl2, 0°C , 30 min
94%
O
O
O
OTES
OTES
OTBS
TBDPSO
OH


O
O
O
OTES
OTES
OTBS
TBDPSO
OH
toluene (1 mM),
reflux, 20 min
O
O
O
SETO
OTES
TBDPSO
TBSO

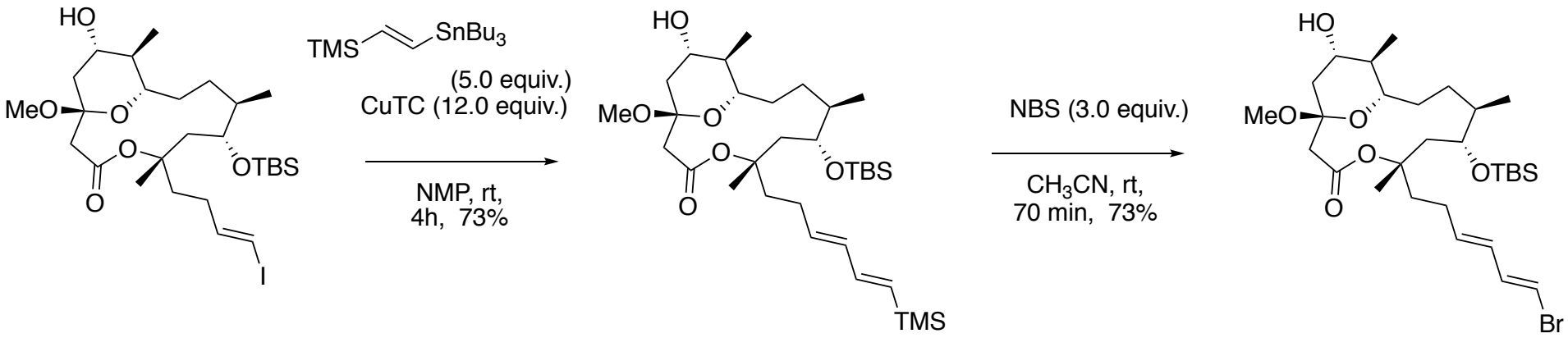

O
O
O
SETO
OTES
TBDPSO
TBSO
PPTS (1.0 equiv.)
MeOH/DCE(1:1), rt,
80 min, 88% (2 steps)
HO
MeO
O
O
O
OTBS
OTBDPS

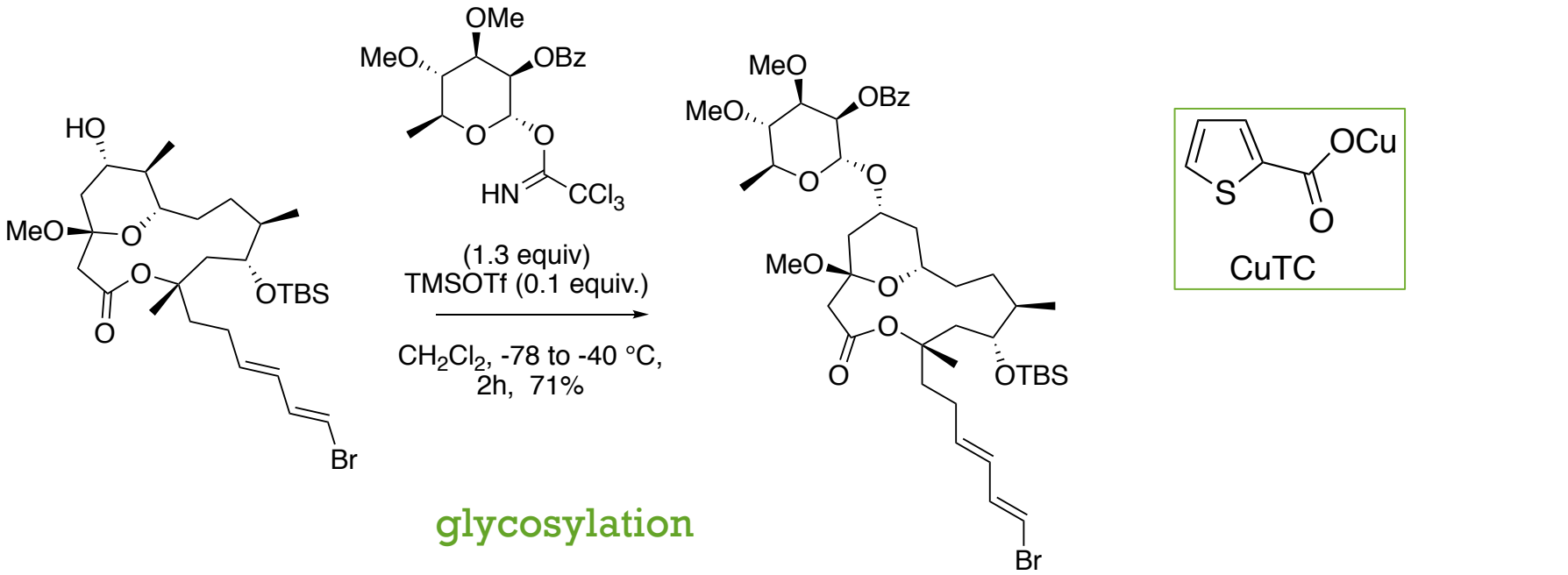




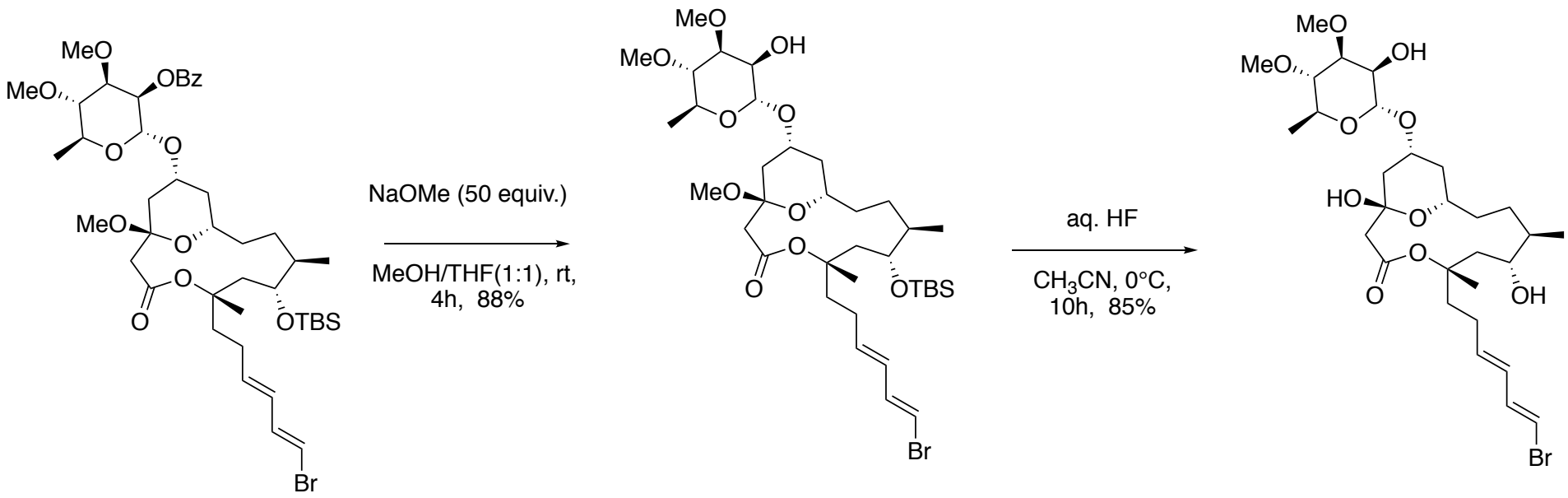


Takai olefination





glycosylation


MeO
MeO
OBz
O
O
MeO
O
O
O
OTBS
Br
NaOMe (50 equiv.)
MeOH/THF(1:1), rt,
4h, 88%
MeO
MeO
OH
O
O
MeO
O
O
O
OTBS
Br
aq. HF
CH3CN, 0°C,
10h, 85%
MeO
MeO
OH
O
O
HO
O
O
O
OH
Br

Thank you for your attention!