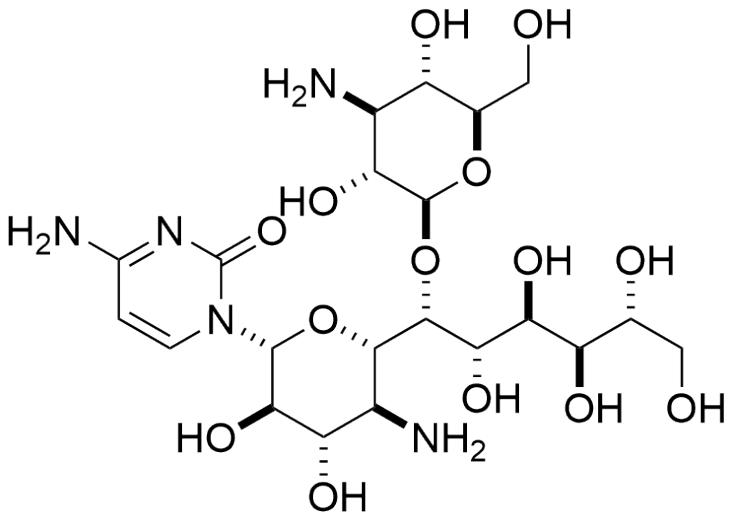
ASAP REPORT

Convergent Total Synthesis of Hikizimycin Enabled by Intermolecular Radical Addition to Aldehyde



Hikizimycin

Haruka Fujino, Takumi Fukuda, Masanori Nagatomo, and Masayuki Inoue

J. Am. Chem. Soc. **2020**, Just Accepted Manuscript.

Reporter: Jie Li

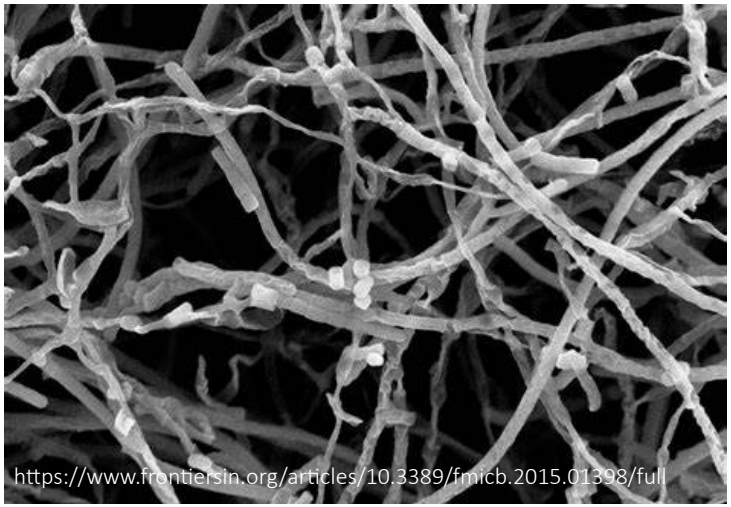
Supervisors: *Prof.* Tao Ye, *Dr.* Yi-an Guo

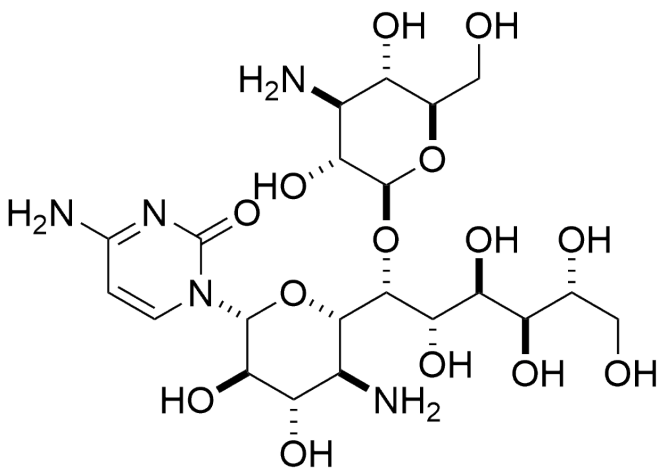
2020.07.27

Outline

- Background
- Retrosynthetic Analysis
- Synthetic Route
- Summary
- Acknowledgement

Background





Hikizimycin

Isolation:

from the fermentation broth of Streptomyces A-5, an organism obtained from a soil sample collected at the Hikizi riverside in Kanagawa, Japan in 1971.

Structure features:

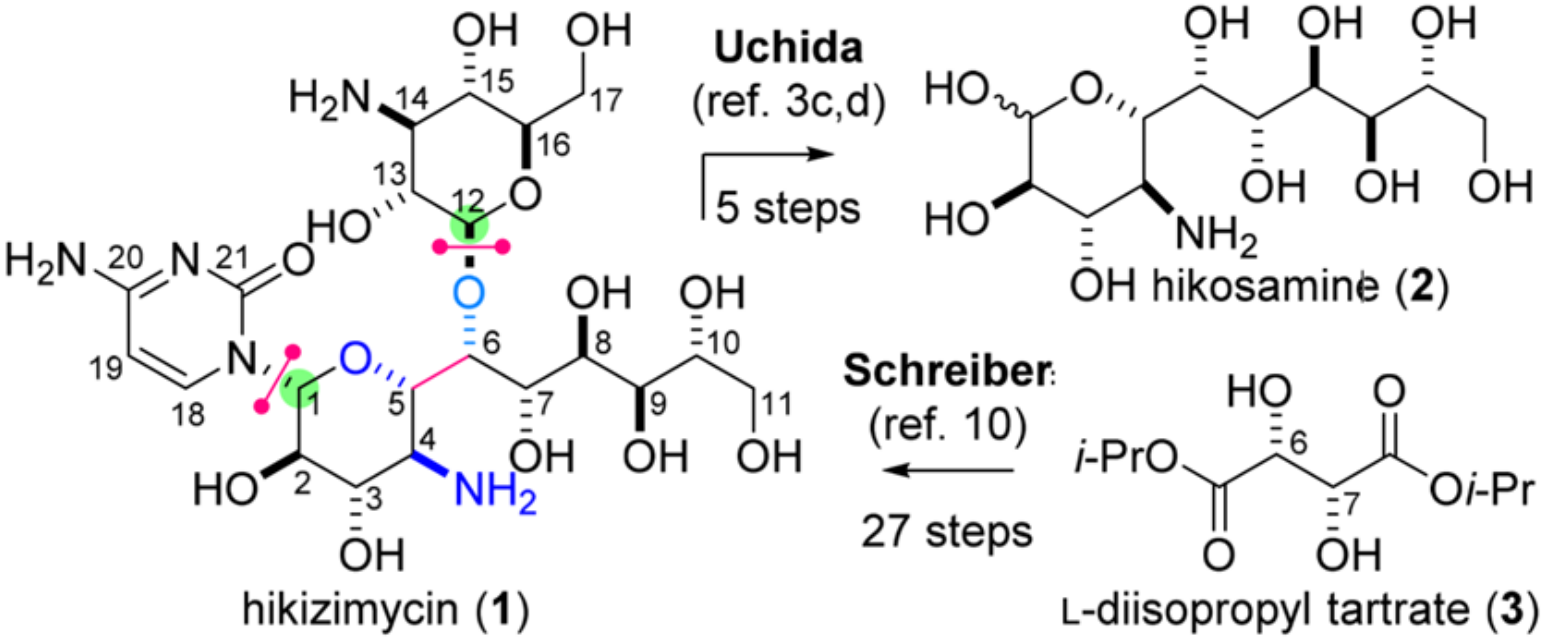
- a cytosine base, a 3-amino-3-deoxyglucose sugar (kanosamine),
- a complex long-chain 4-amino-4-deoxyundecose sugar with 1 amino and 10 hydroxy groups

Biological Activity:

- inhibits protein synthesis by preventing peptide forming reactions
- a powerful anthelmintic agent
- an antibiotic agent

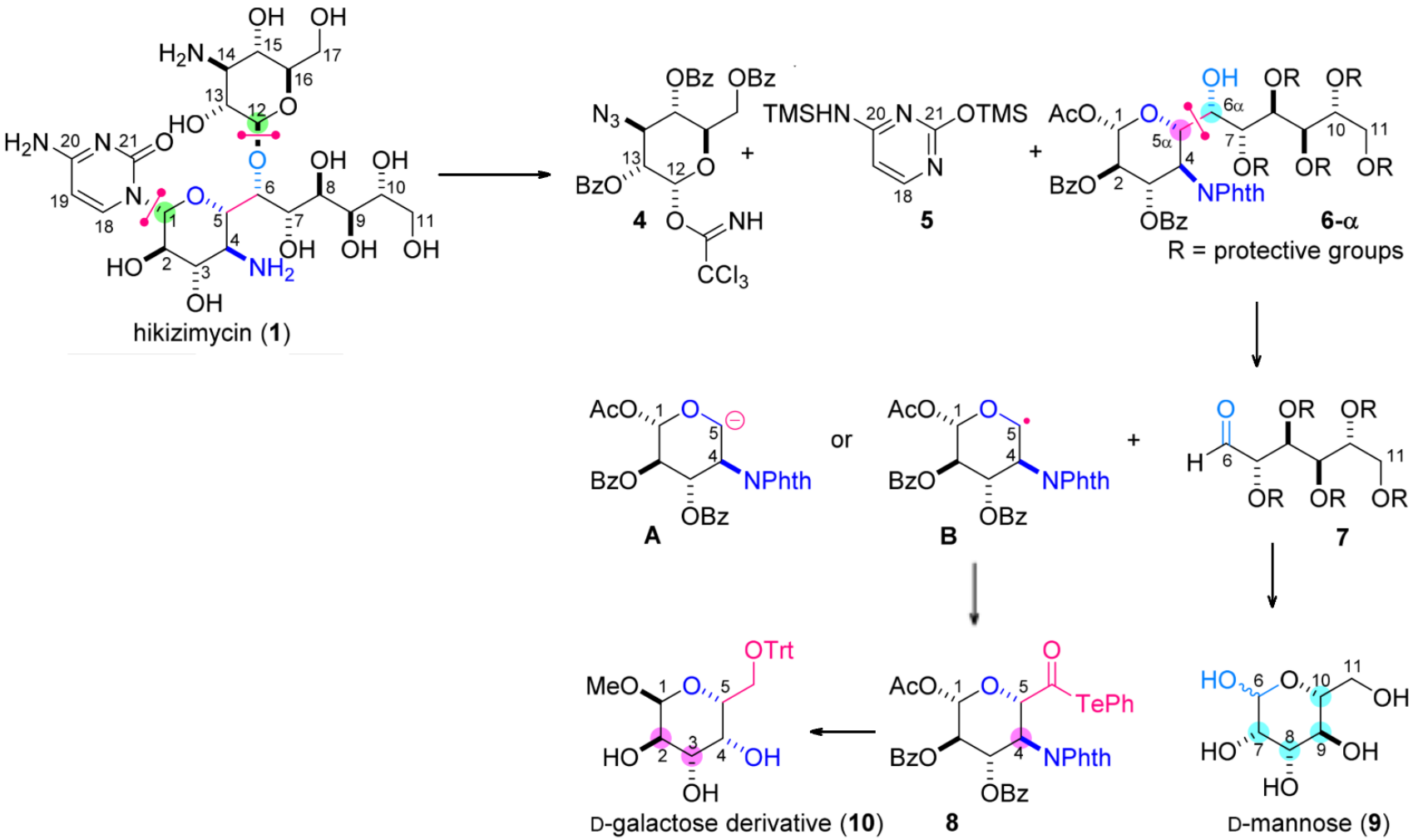
Uchida, K.; Ichikawa, T.; Shimauchi, Y.; Ishikura, T.; Ozaki, A. Hikizimycin, a New Antibiotic. *J. Antibiot.* **1971**, *24*, 259-262.

Background

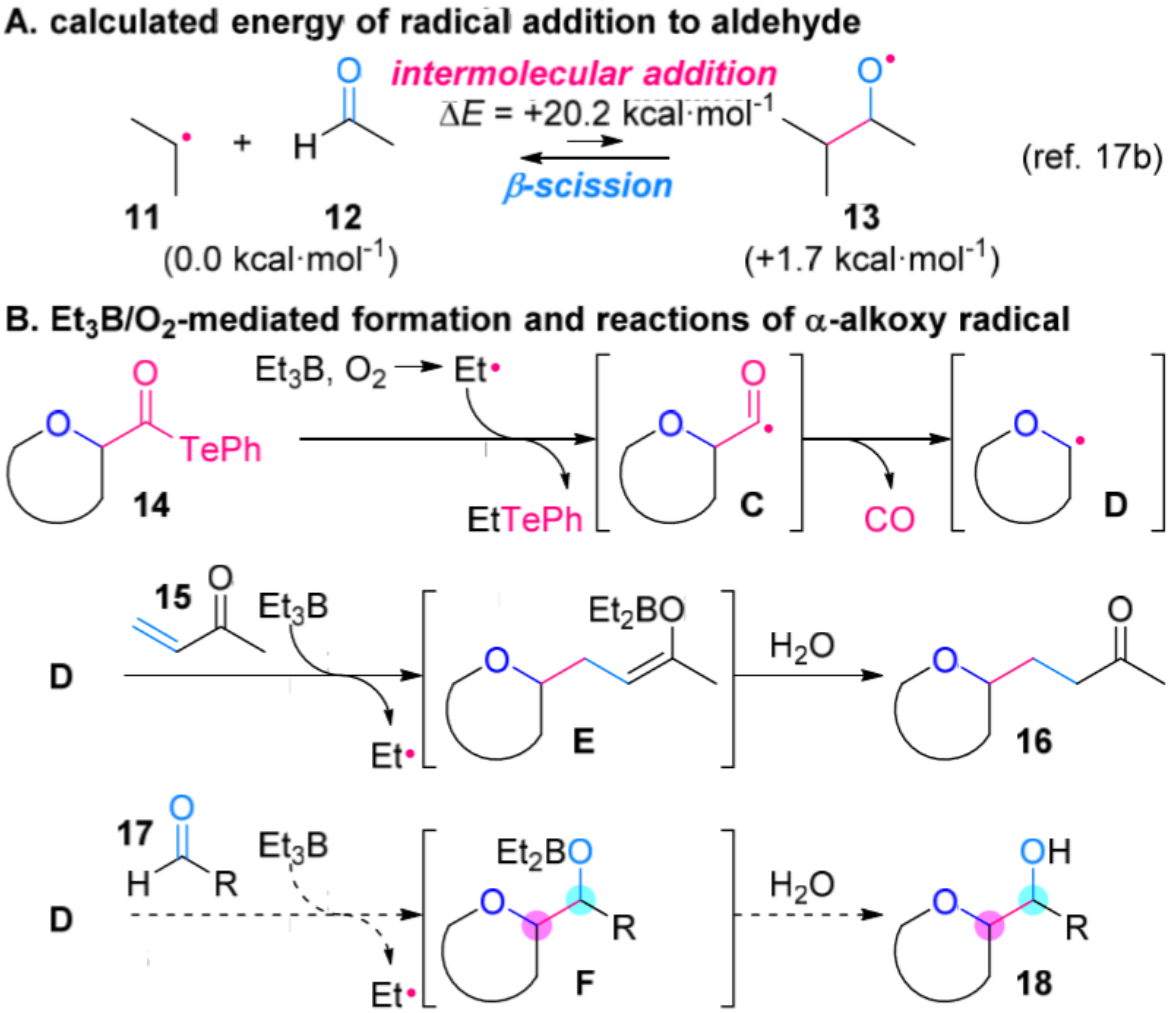


(3c) Das, B. C.; Defaye, J.; Uchida, K. *Carbohydr. Res.* **1972**, *22*, 293-299.
(3d) Uchida, K.; Das, B. C. *Biochimie* **1973**, *55*, 635-636.
(10) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 9657-9659.

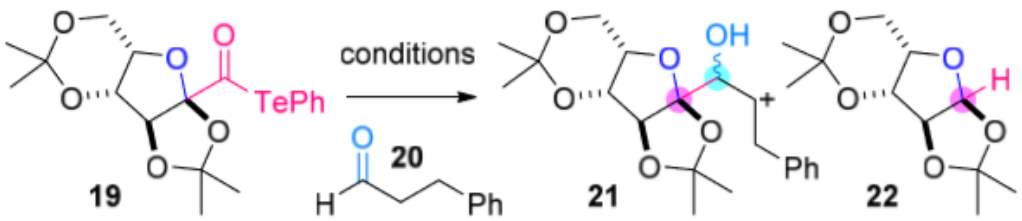
Retrosynthetic Analysis



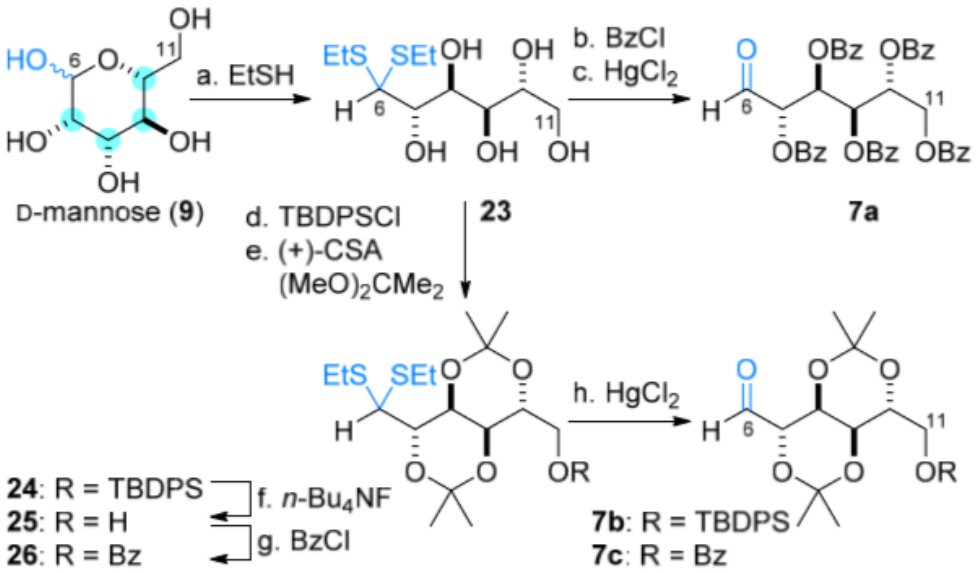
Retrosynthetic Analysis



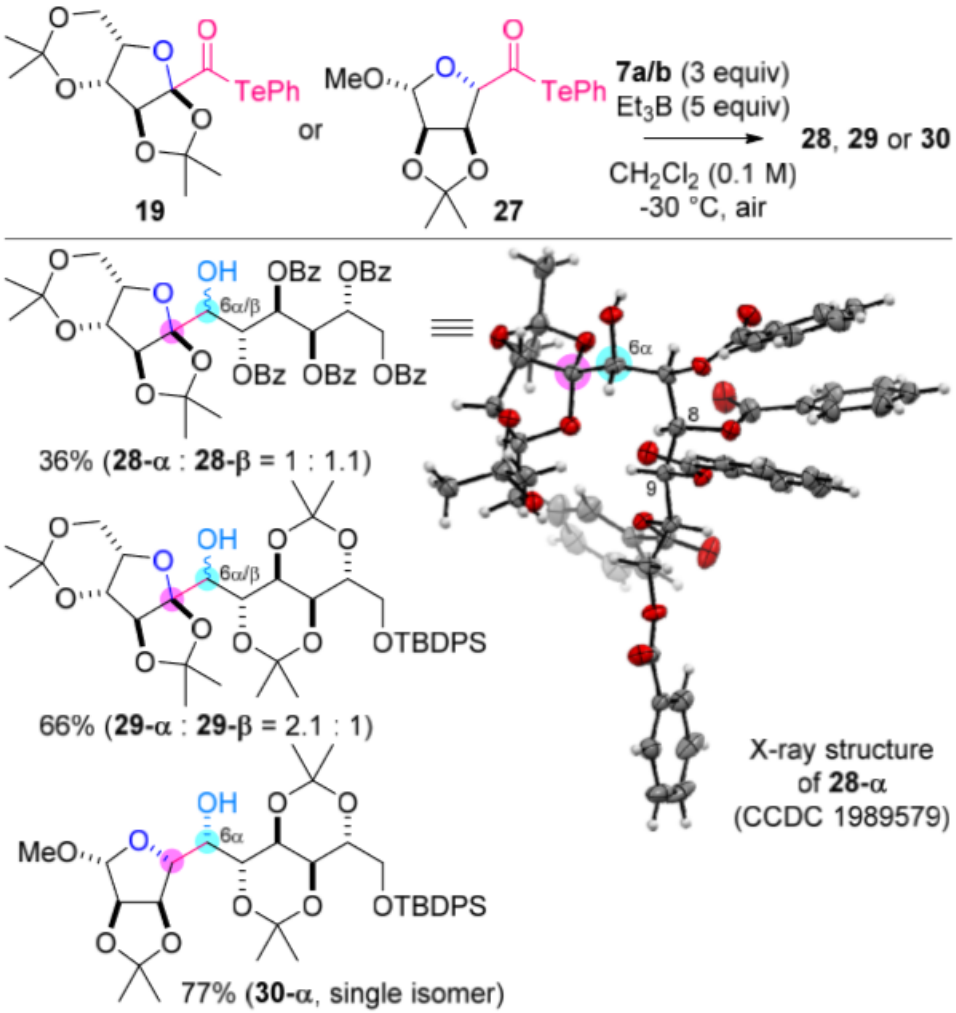
Retrosynthetic Analysis

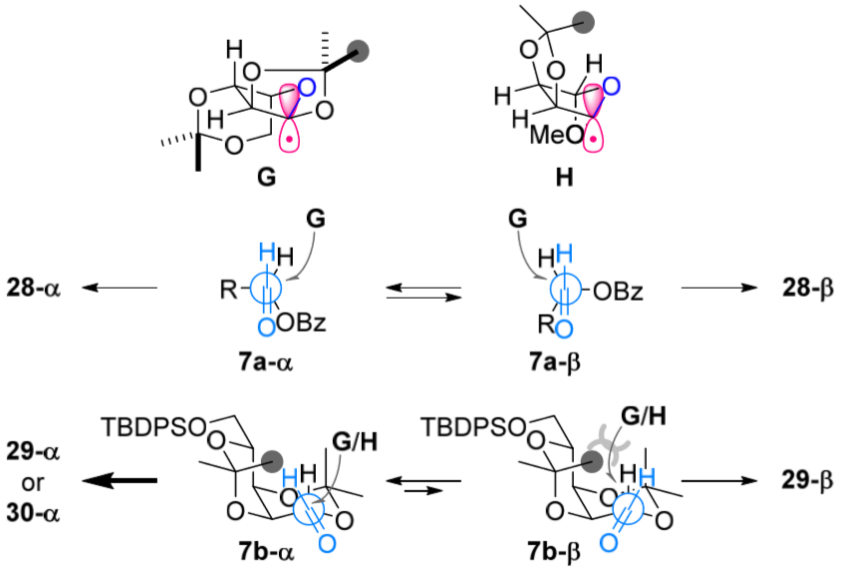


entry	initiator	solvent	yields(%)[b]	
			21	**22**
1	Me_3Al	THF	4	10
2	Me_2Zn	CH_2Cl_2	2	3
3	Et_3B	CH_2Cl_2	28[c]	39
4[d]	Et_3B	CH_2Cl_2	40[c,e]	47

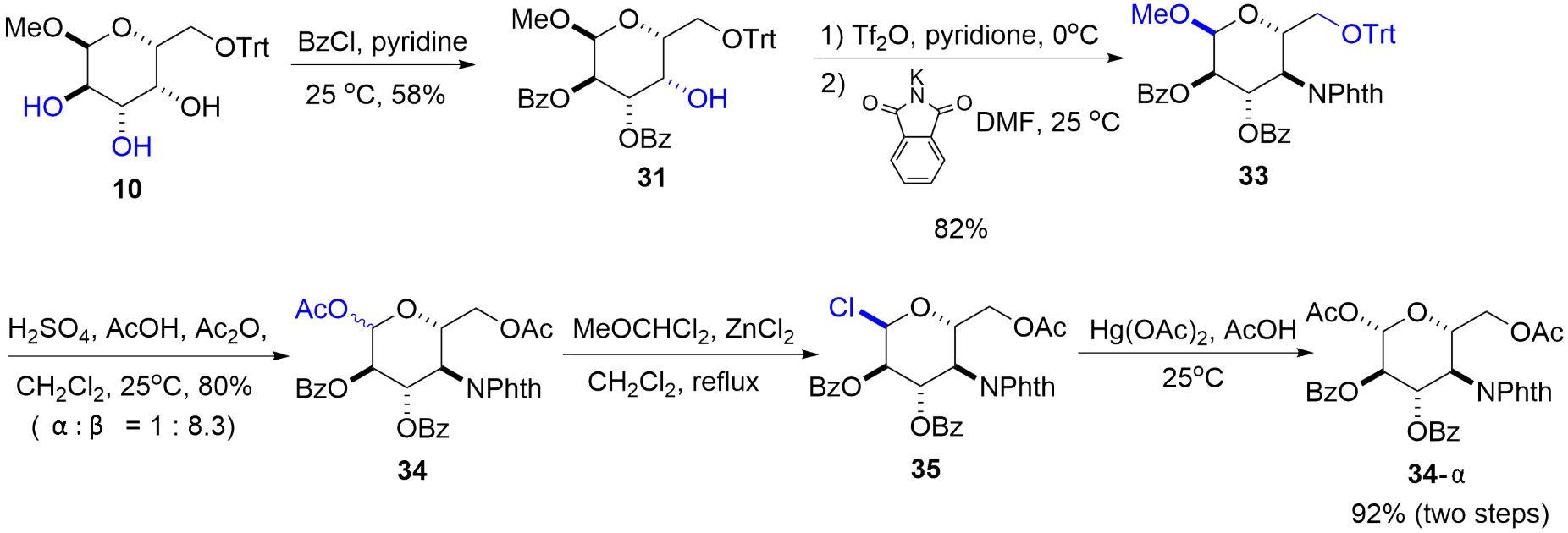


Retrosynthetic Analysis

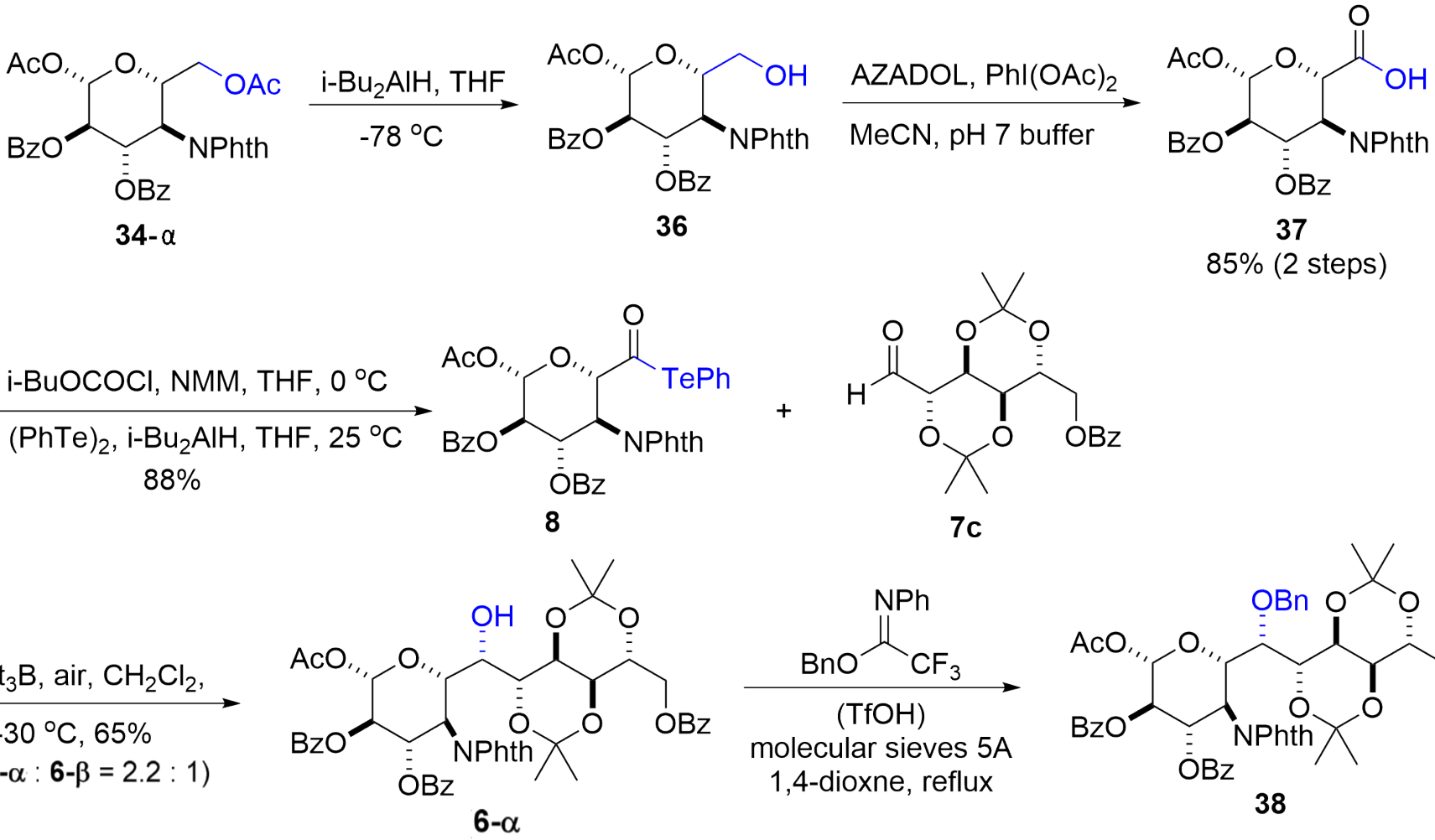




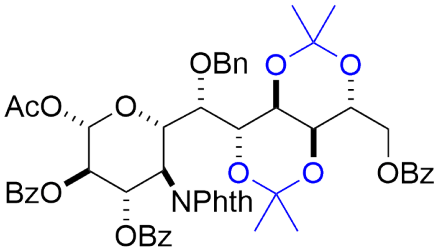
Synthetic Route



Synthetic Route



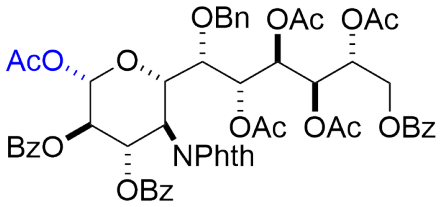
Synthetic Route



38

1) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, MeCN, 25°C

2) Ac_2O, pyridine, 50 °C



39

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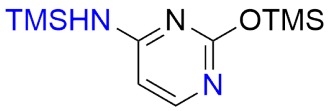
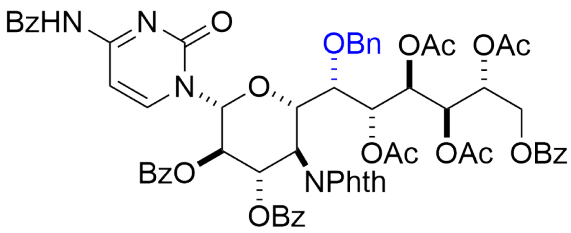


5

1) **5,** TMSOTf, $PhNO_2$, 130 °C

2) i-PrOH, 25 °C;

3) BzCl, pyridine, 25 °C

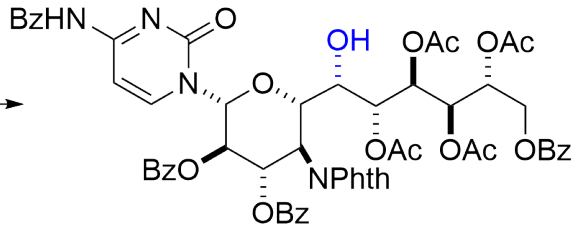


40

(19%, 6 steps)

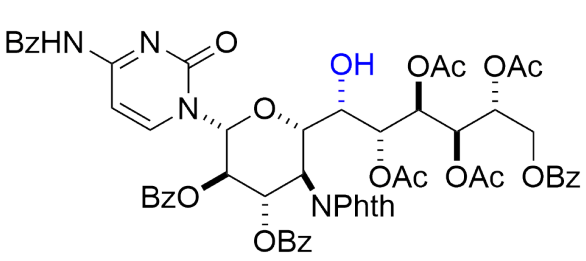
DDQ, CH_2Cl_2

60 °C



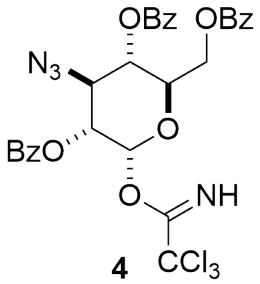
41

Synthetic Route



41

+

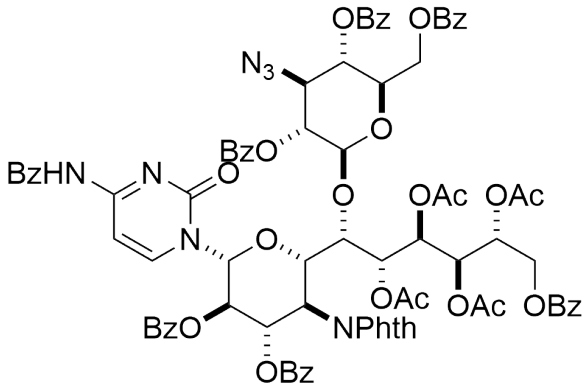


4

TMSOTf, CH_2Cl_2

0°C

(**42** : 12-*epi*-**42** = 1.8 : 1)

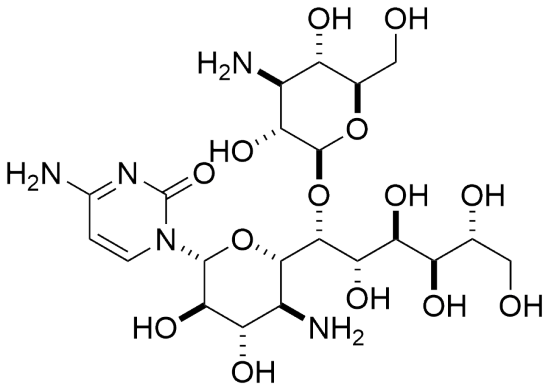


42 (19%, 2 steps)

n-$BuNH_2$, MeOH, reflux; H_2

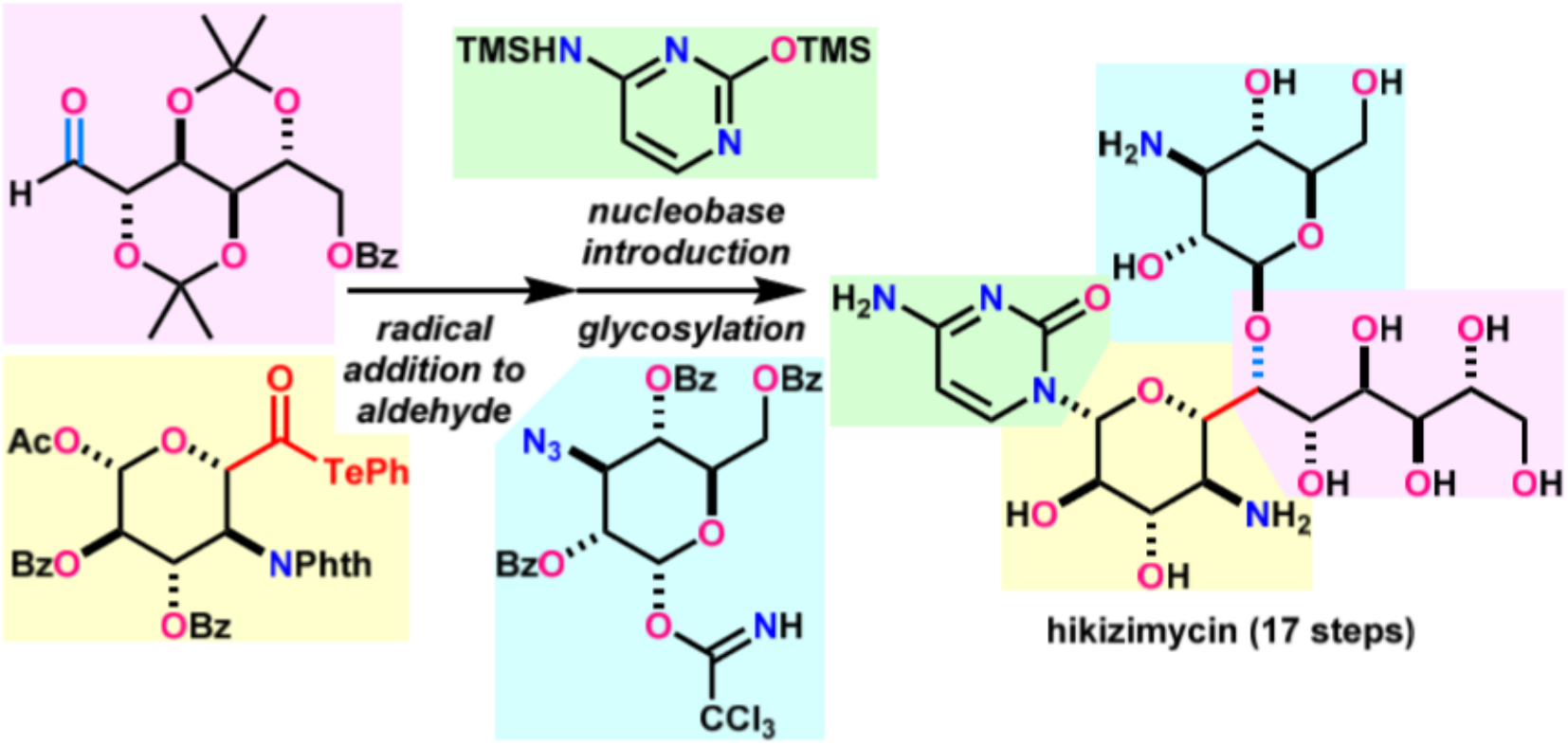
Lindlar catalyst

H_2O, 25 °C, 50%.



Hikizimycin

Summary


TMSHN
N
OTMS
N
nucleobase introduction
radical addition to aldehyde
glycosylation
AcO
TePh
BzO
NPhth
OBz
OBz
OBz
N3
BzO
NH
CCl3
H2N
N
O
OH
OH
H2N
HO
O
O
OH
OH
N
O
OH
OH
OH
HO
NH2
OH
hikizimycin (17 steps)

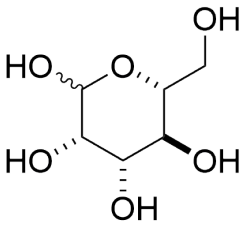
Acknowledgement

- *Prof.* Tao Ye, *Dr.* Yian Guo;
- All my labmates in F211;
- All professors and faculties in SCBB

Thank you

for your kind attention

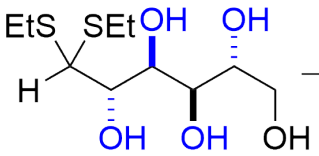
Synthetic Route



D-mannose (**9**)

EtSH, 0.5M HCl in MeOH

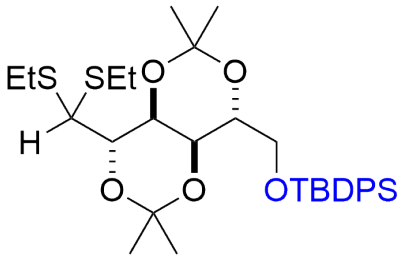
25 °C



23

1) TBDPSCl, Et3N, molecular sieves 4A, N,N-dimethyl4-aminopyridine, THF, 50 °C, 79% (2 steps)

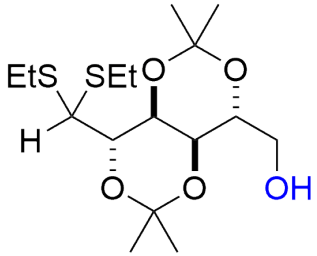
2) (+)-CSA $(MeO)_2CMe_2$ 25 °C, 70%;



24

$n\text{-}Bu_4NF$, THF

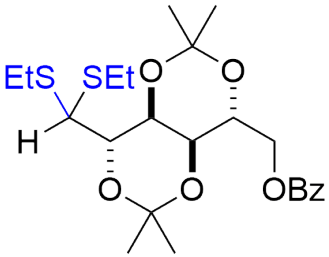
50 °C



25

BzCl, pyridine

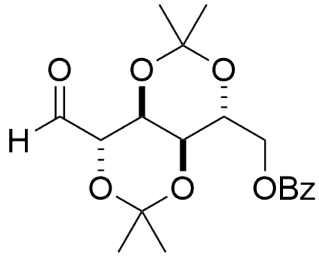
50 °C



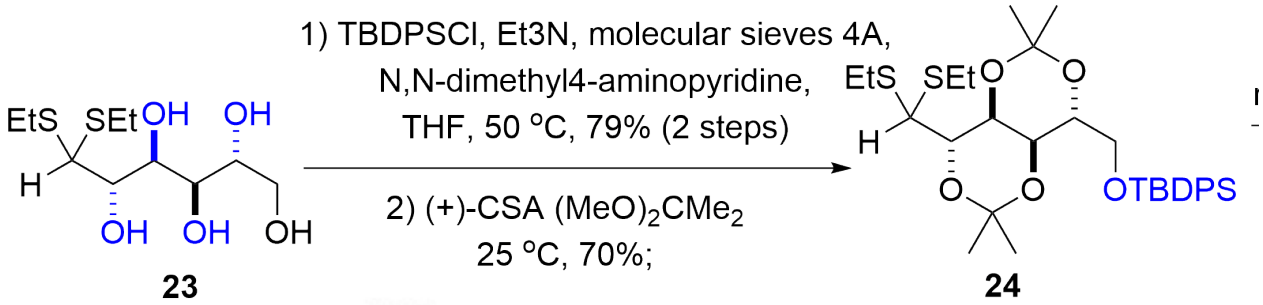
26 (100%, 2 setps)

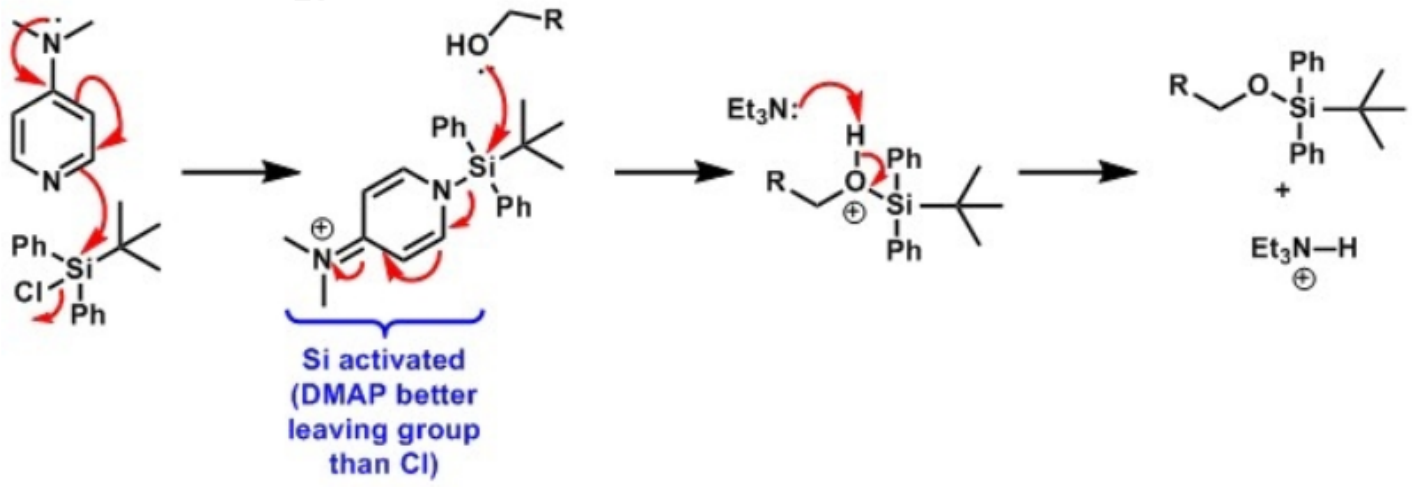
$HgCl_2$, HgO, CH_2Cl_2

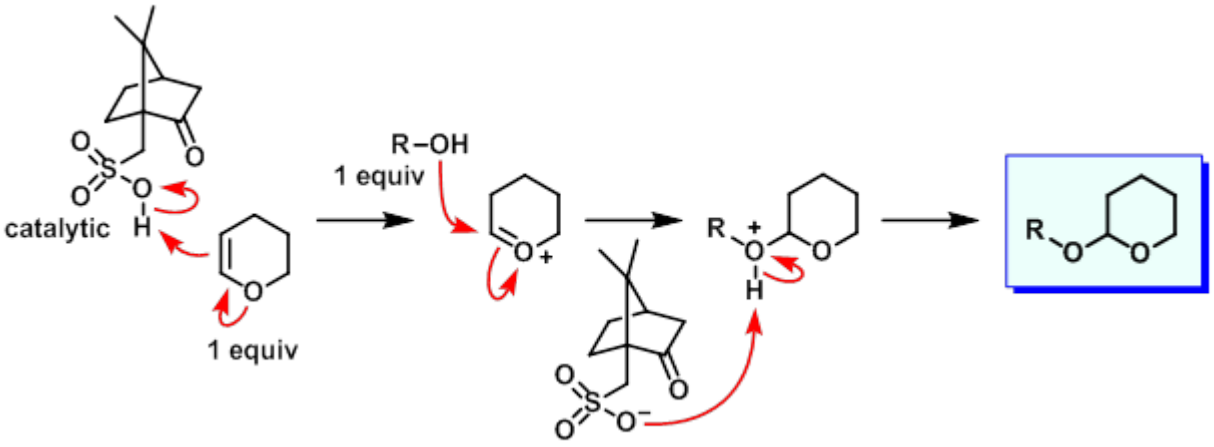
MeCN, H_2O, 25 °C, 97%



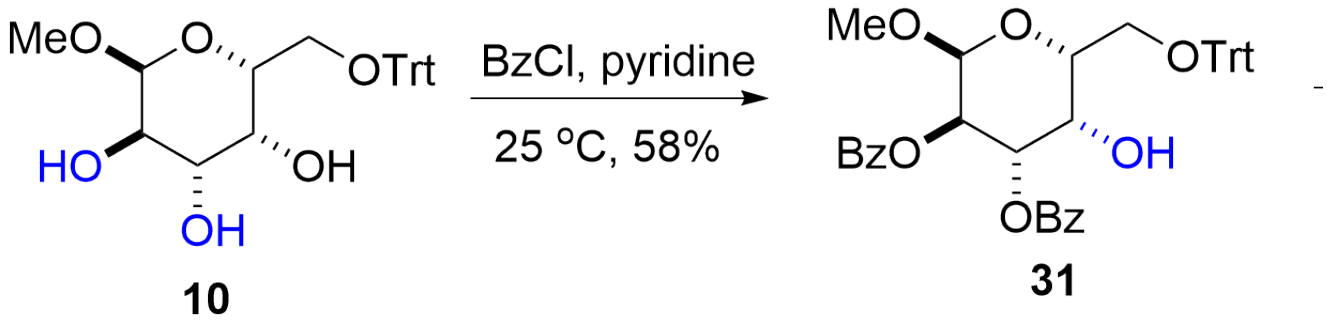
7c


1) TBDPSCl, Et3N, molecular sieves 4A,
N,N-dimethyl4-aminopyridine,
THF, 50 °C, 79% (2 steps)
2) (+)-CSA (MeO)2CMe2
25 °C, 70%;
EtS
SEt
OH
OH
H
OH
OH
OH
23
EtS
SEt
O
O
H
O
O
OTBDPS
24

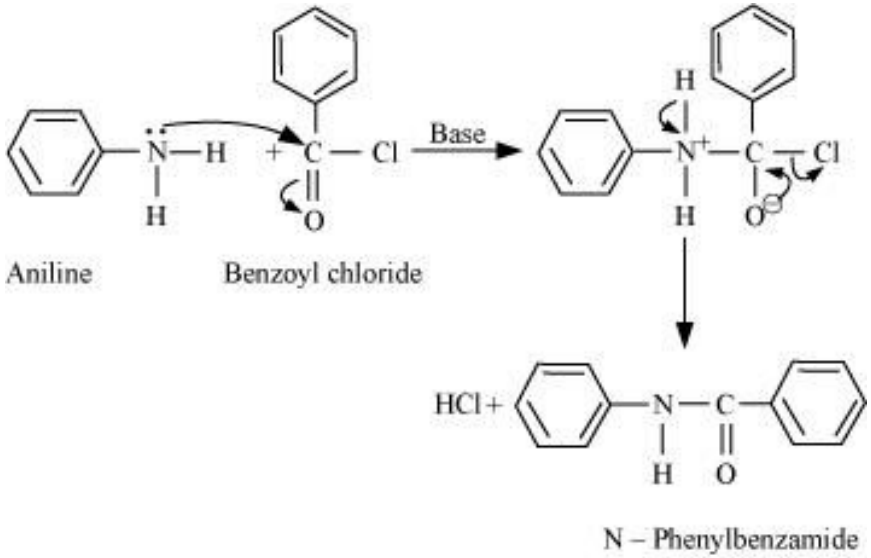

HO
R
Ph
Si
Ph
N
Ph
Si
Cl
Ph
Si activated
(DMAP better
leaving group
than Cl)
Et3N:
H
R
O
Ph
Si
Ph
R
O
Ph
Si
Ph
+
Et3N–H

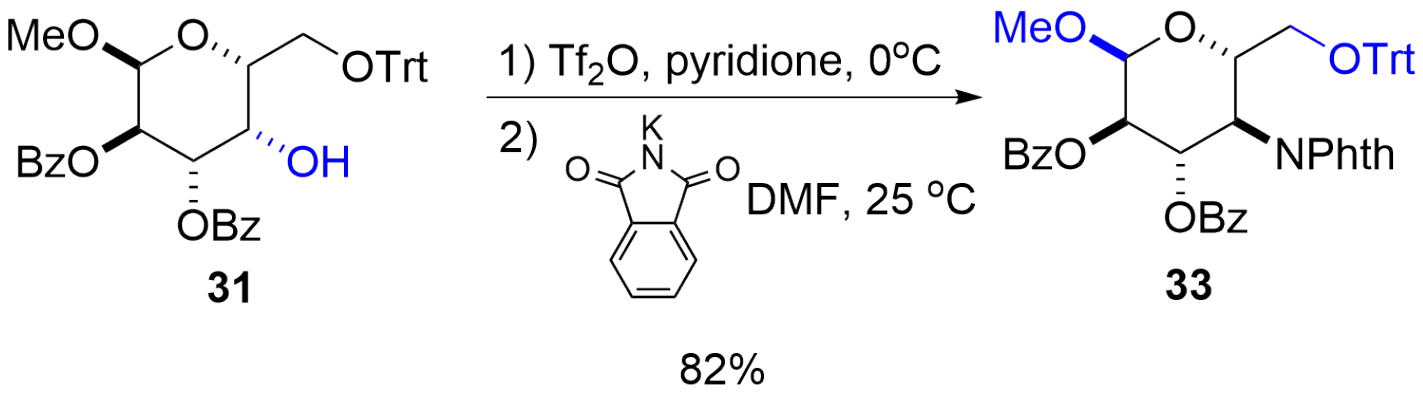

catalytic
O
S
O
O
H
1 equiv
R–OH
1 equiv
R
O
H
O
R
O
O

Bnzolization

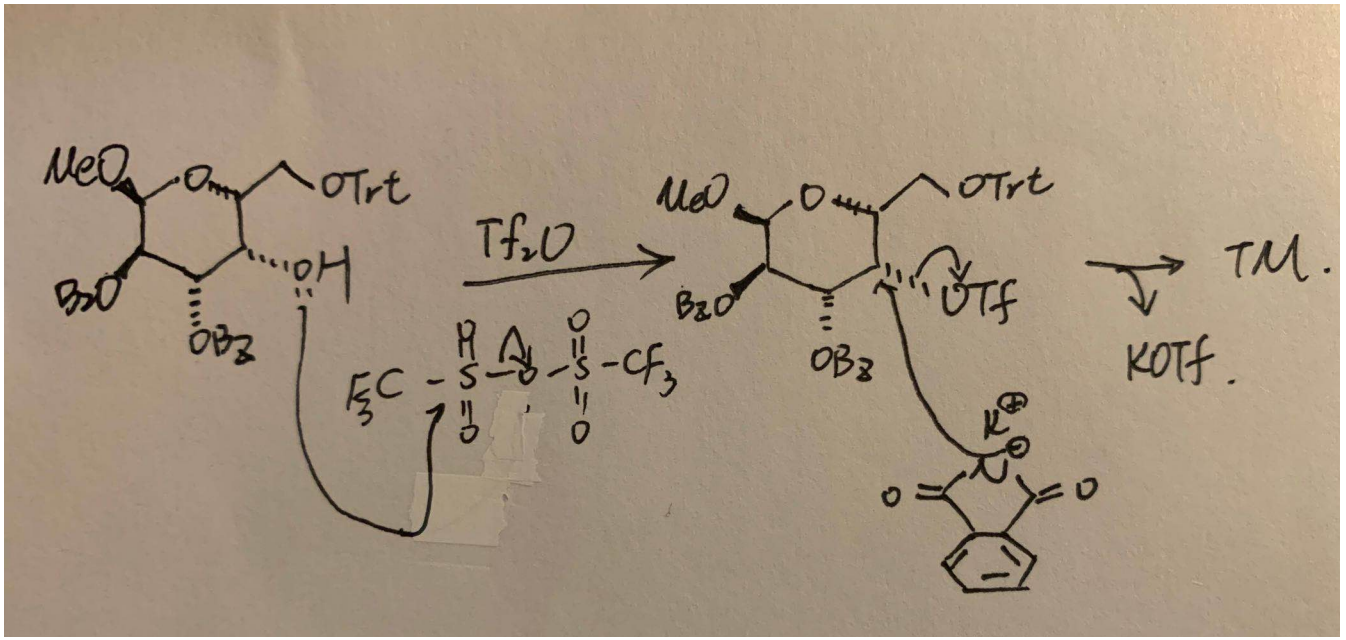


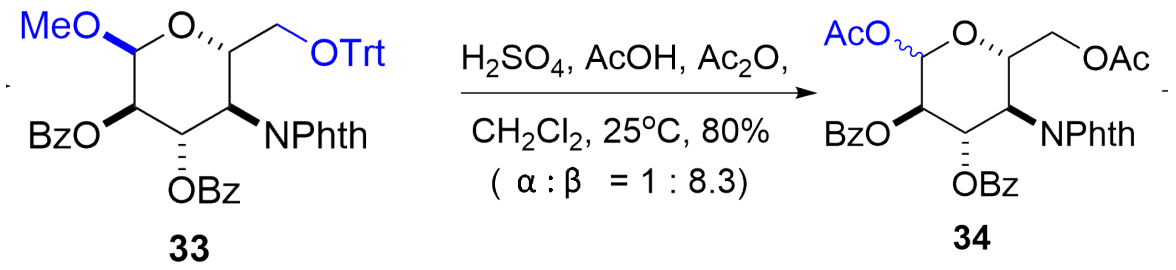
10 **31**



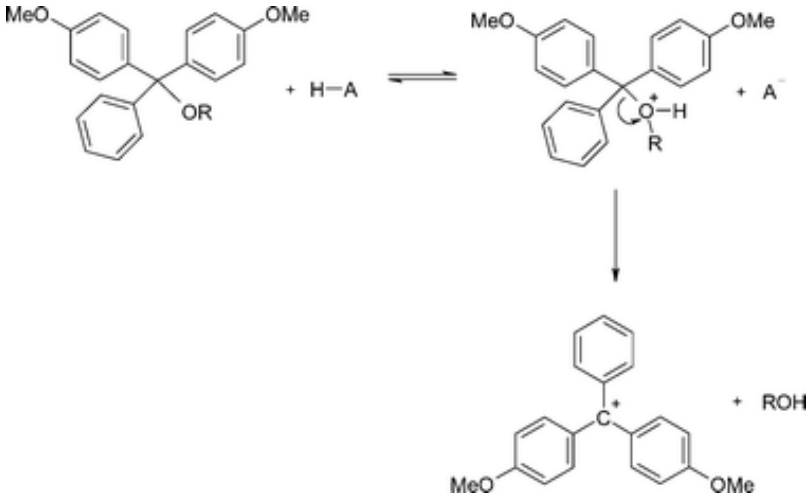


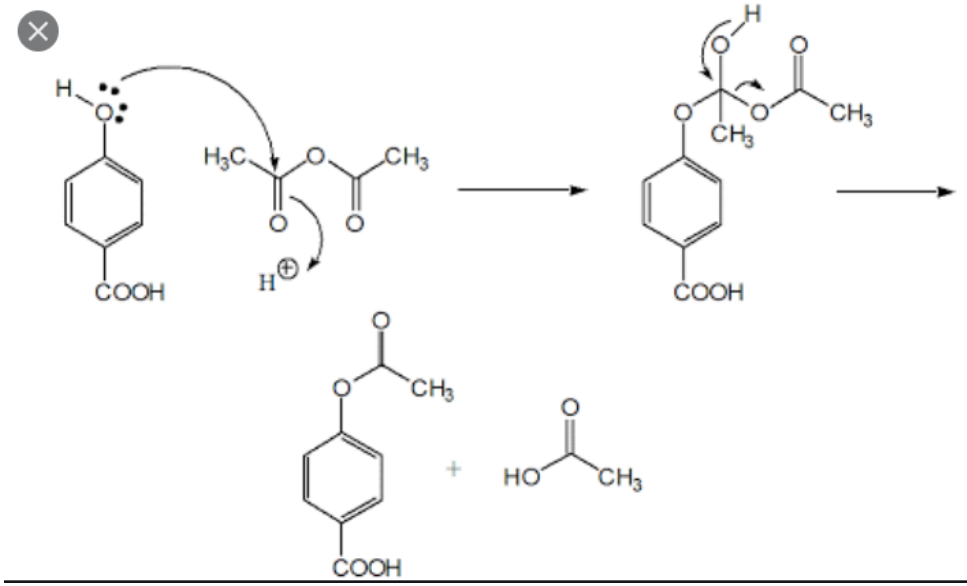
Triflation , NPhth protecting group (SN_2 reaction)

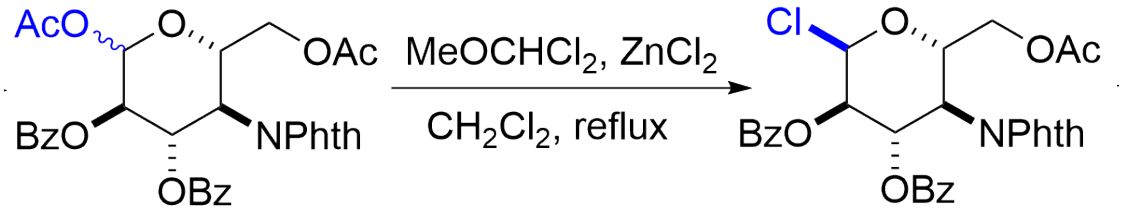




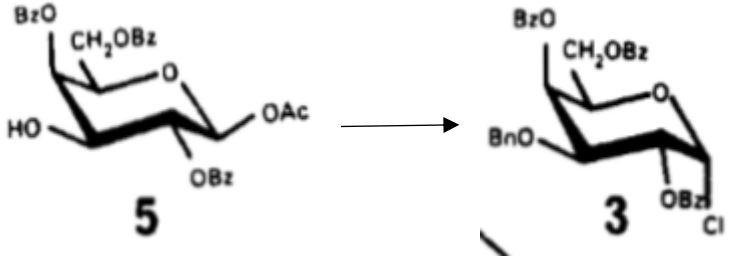
Trt deprotection



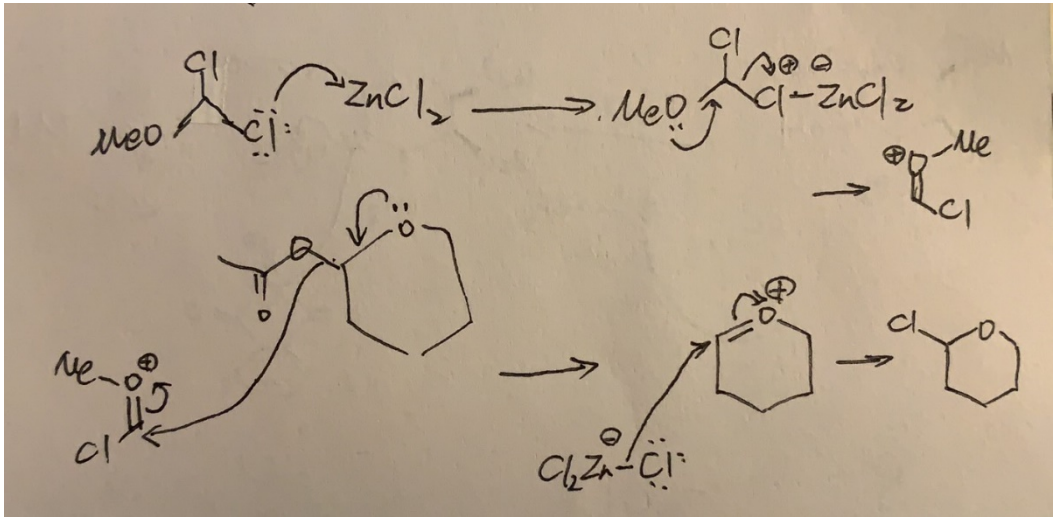




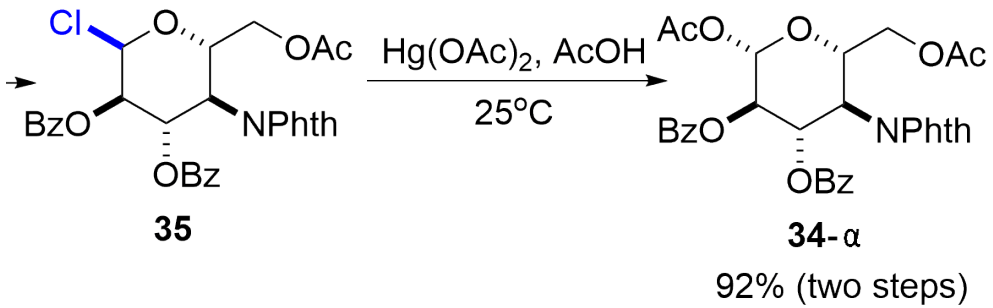
34 **35**



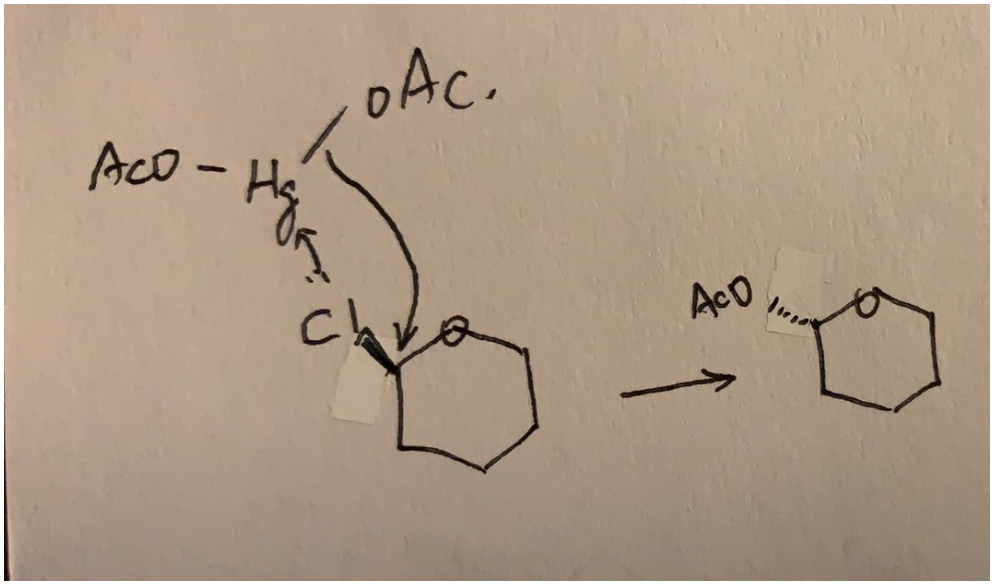
5 **3**

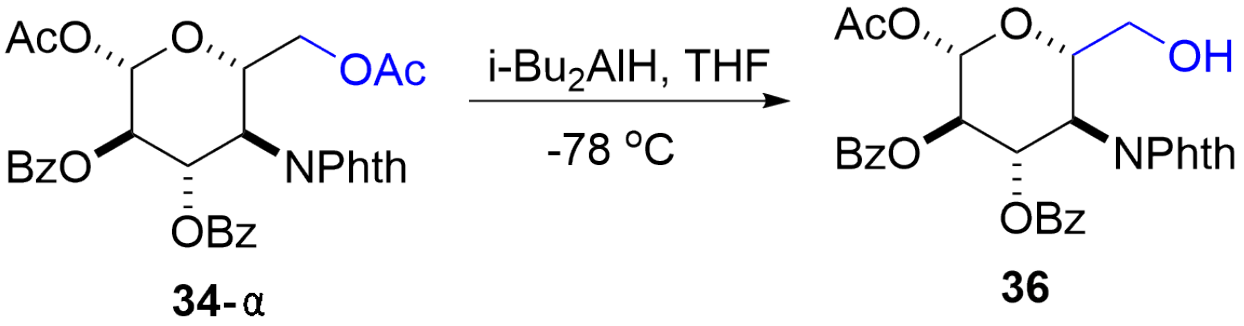


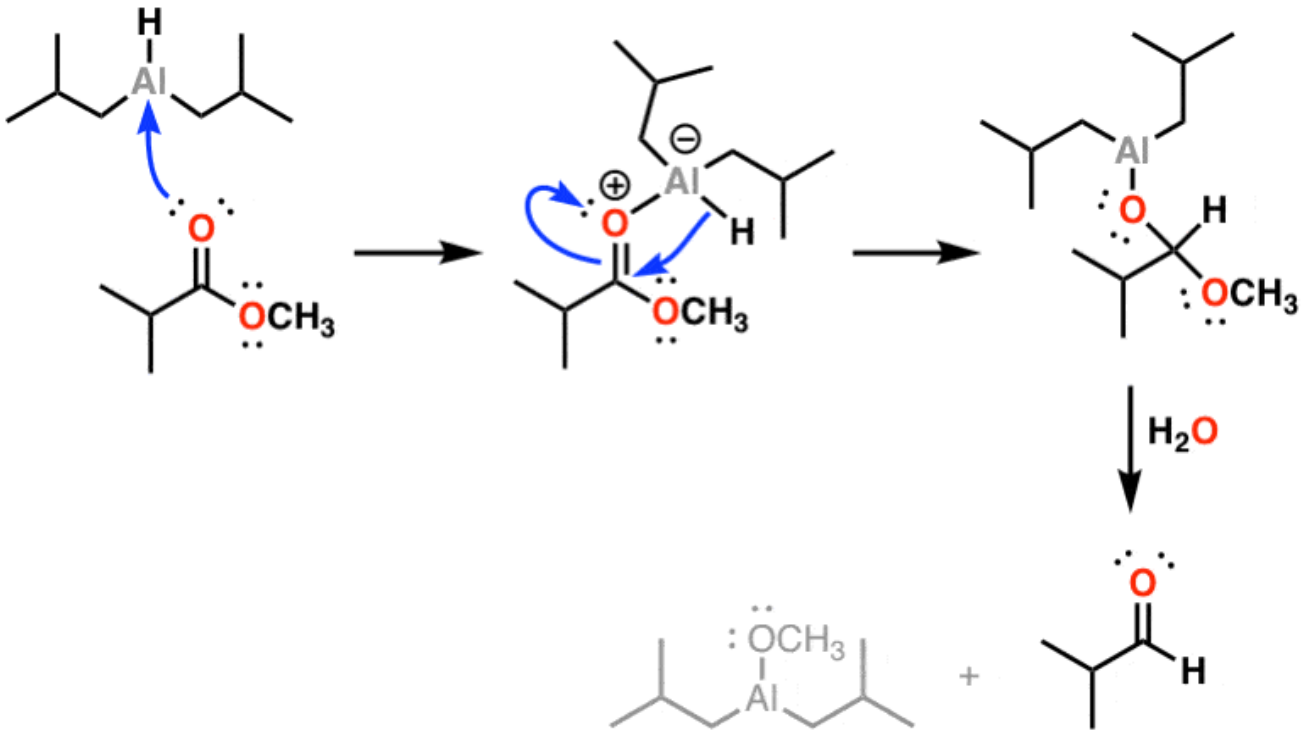
Kovác, P.; Taylor, R. B.; Glaudemans, C. P. J. *J. Org. Chem.* **1985**, 50, 5323-5333.

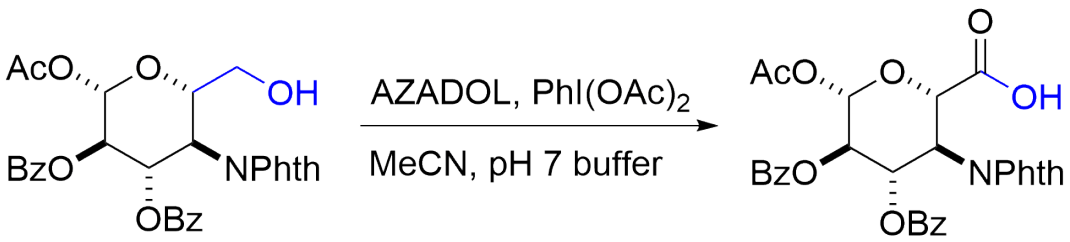

Cl
O
OAc
BzO
NPhth
OBz
35
Hg(OAc)2, AcOH
25°C
AcO
O
OAc
BzO
NPhth
OBz
34-α
92% (two steps)

SN_2

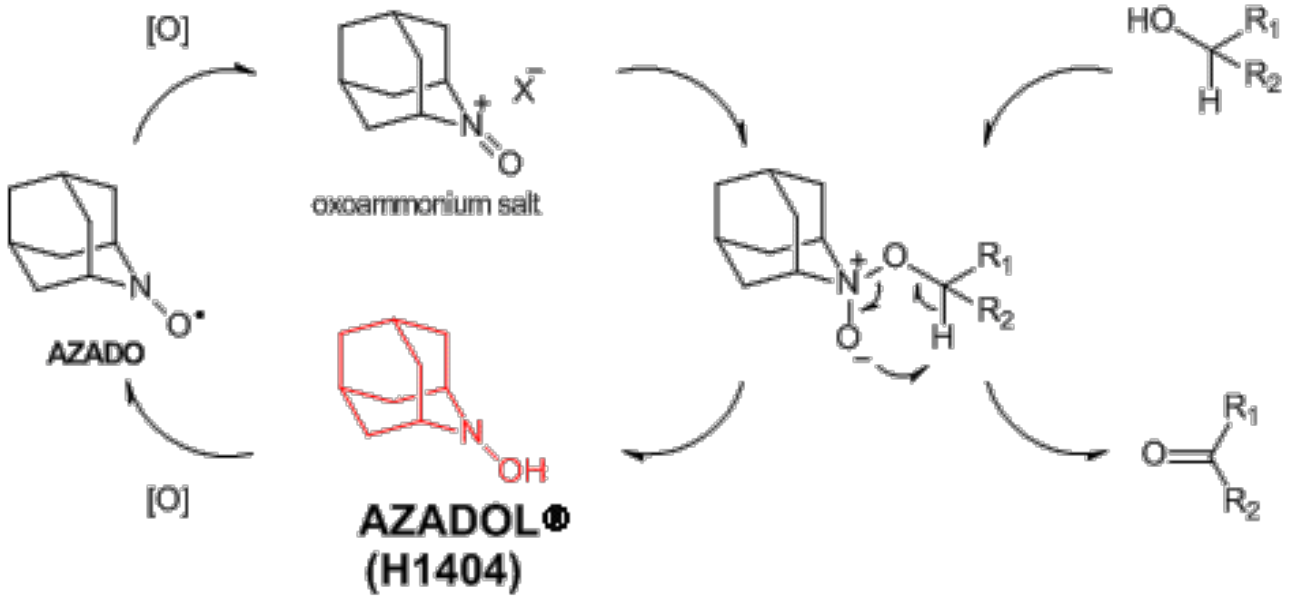

OAc
AcO – Hg
Cl
AcO
O

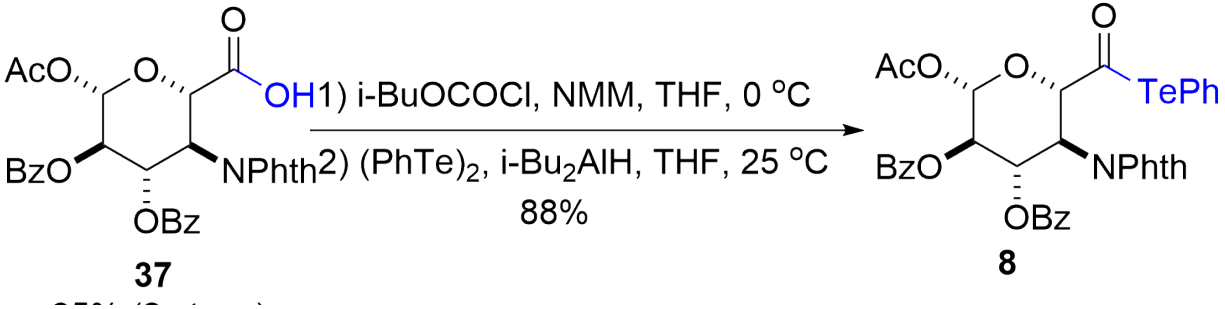

AcO
O
OAc
BzO
NPhth
OBz
34-α
i-Bu2AlH, THF
-78 °C
AcO
O
OH
BzO
NPhth
OBz
36

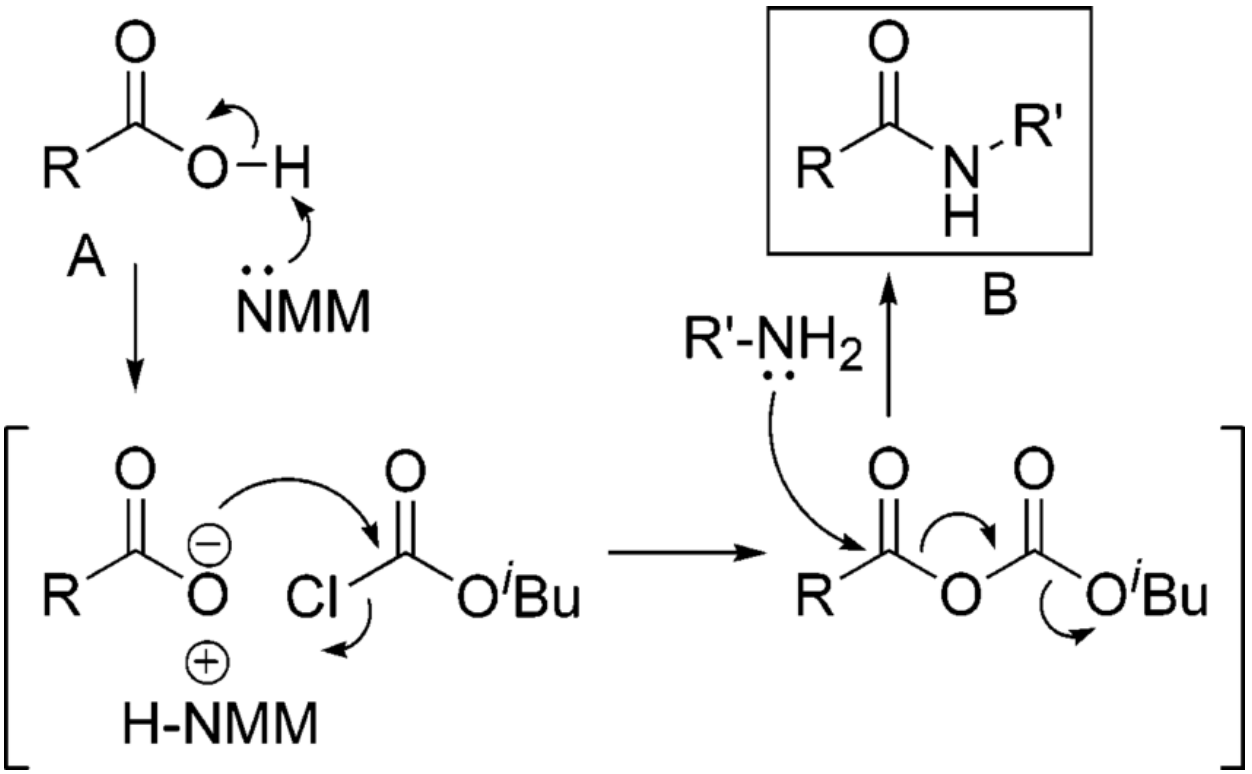

H
Al
O
OCH3
Al
O
H
OCH3
Al
O
H
OCH3
H2O
O
H
: OCH3
Al
+

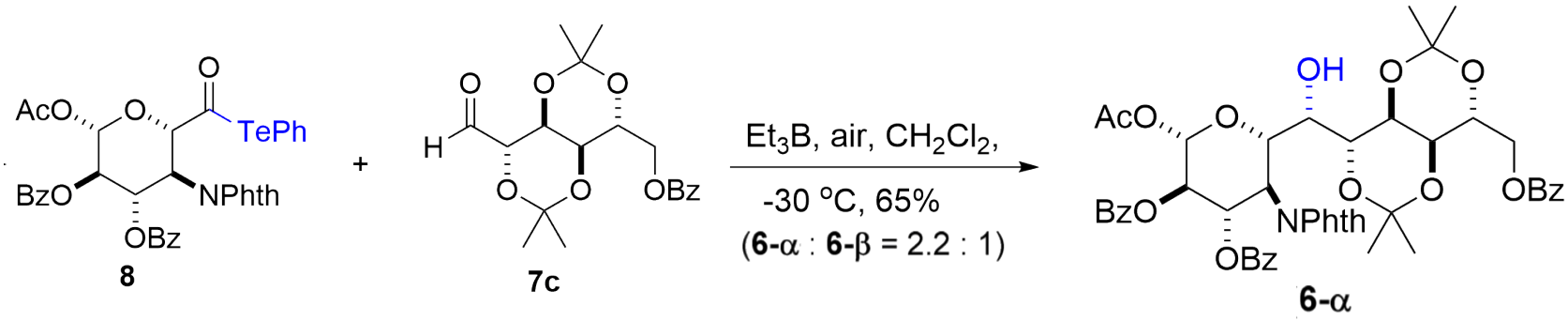

AcO
O
OH
BzO
NPhth
OBz
AZADOL, PhI(OAc)2
MeCN, pH 7 buffer
O
AcO
O
OH
BzO
NPhth
OBz

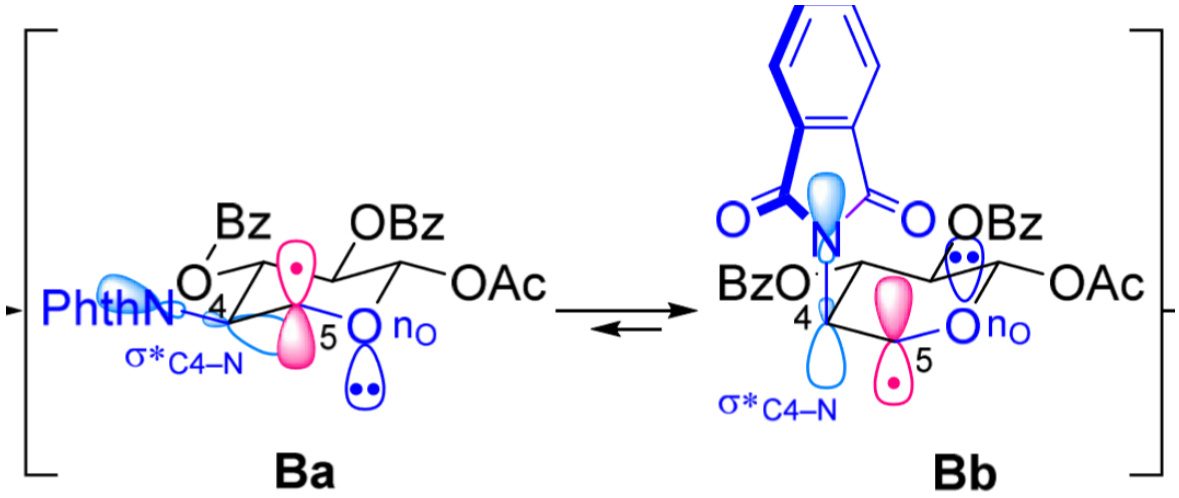
36 **37**


[O]
X⁻
N
O
oxoammonium salt
HO
R1
R2
H
N
O•
AZADO
N
O
R1
R2
H
O⁻
N
OH
[O]
AZADOL®
(H1404)
R1
O
R2

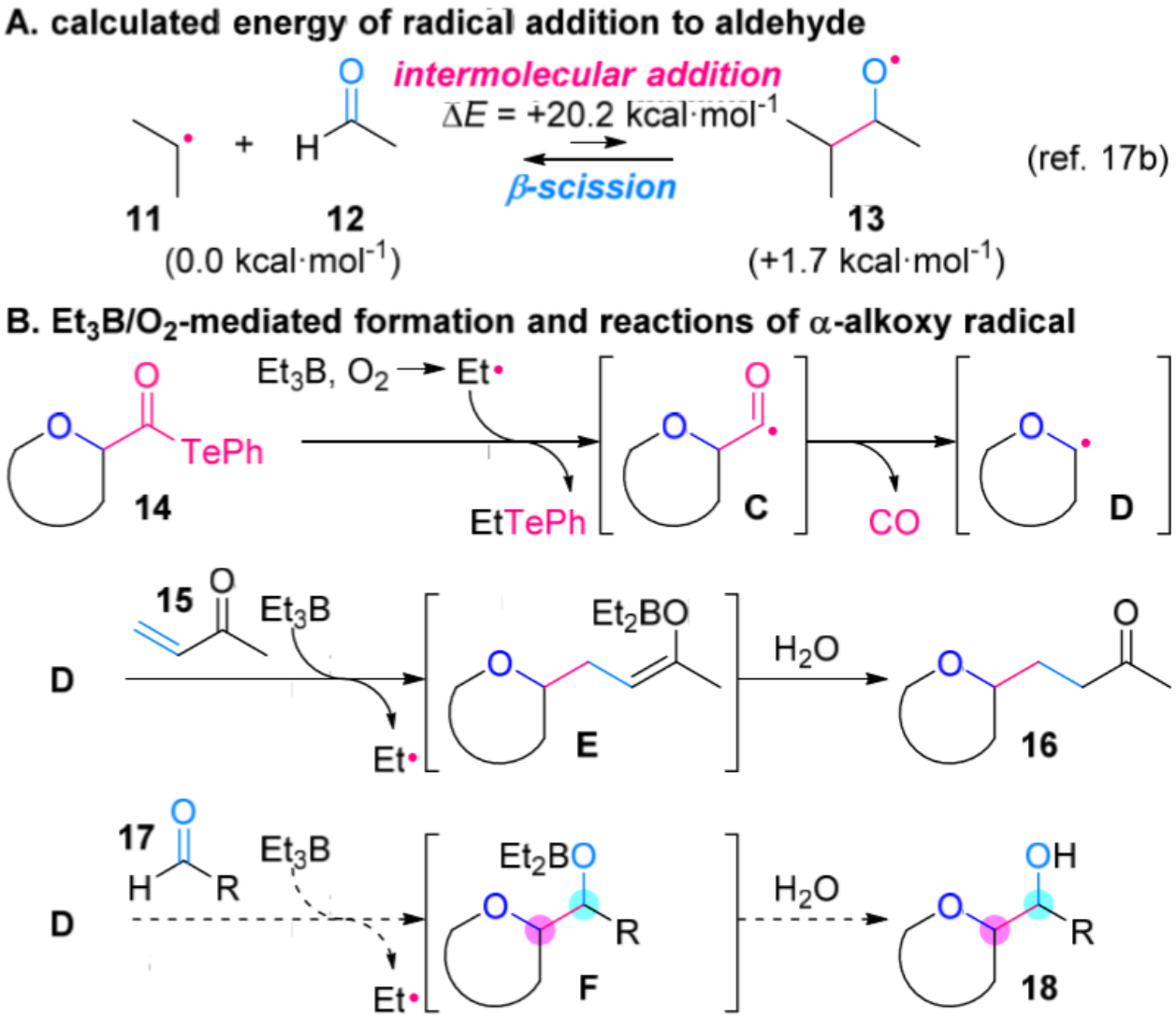

AcO
O
OH
BzO
NPhth
OBz
37
1) i-BuOCOCl, NMM, THF, 0 °C
2) (PhTe)2, i-Bu2AlH, THF, 25 °C
88%
TePh
8


A
NMM
B
R'-NH2
H-NMM
Cl
O^iBu

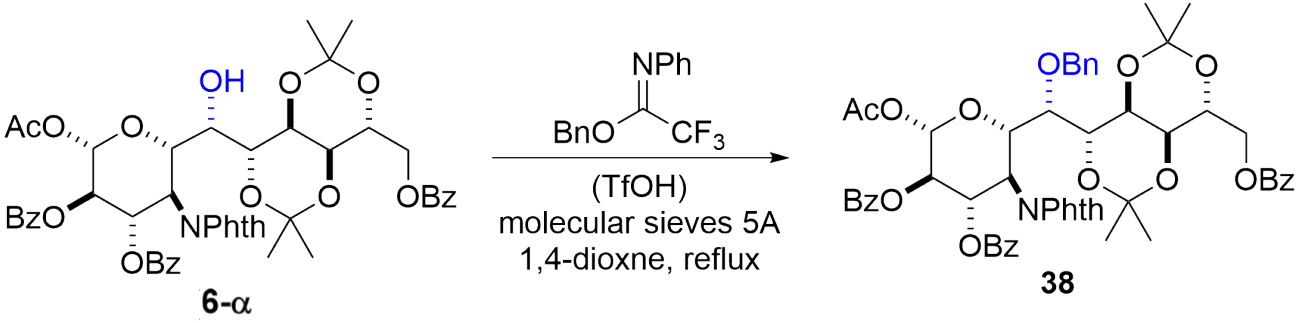

AcO
BzO
OBz
NPhth
TePh
8
+
H
OBz
7c
Et3B, air, CH2Cl2,
-30 °C, 65%
(6-α : 6-β = 2.2 : 1)
OH
AcO
BzO
OBz
NPhth
OBz
6-α

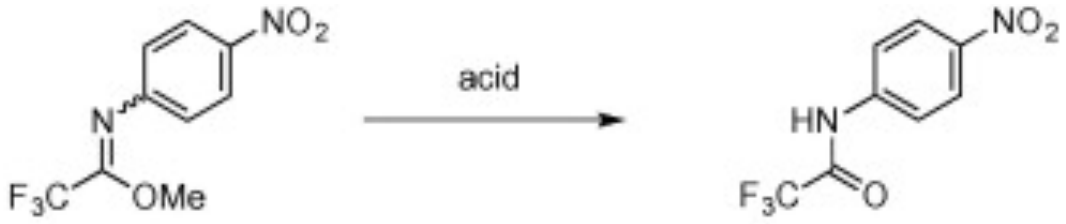

Bz
OBz
OAc
PhthN
σ*C4–N
nO
Ba
OBz
OAc
BzO
σ*C4–N
nO
Bb

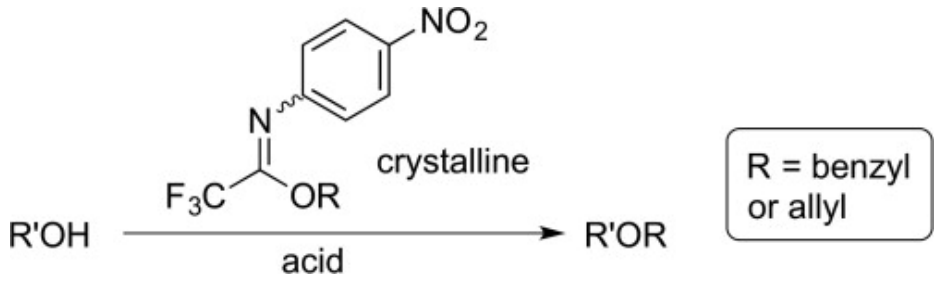
Retrosynthetic Analysis

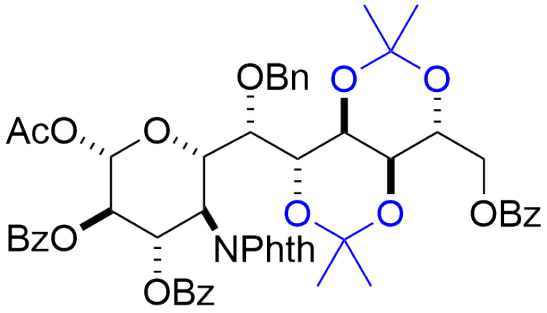


Wilsey, S.; Dowd, P.; Houk, K. N. *J. Org. Chem.* **1999**, *64*, 8801-8811.


OH
AcO
BzO
OBz
NPhth
OBz
6-α
NPh
BnO
CF3
(TfOH)
molecular sieves 5A
1,4-dioxne, reflux
OBn
AcO
BzO
OBz
NPhth
OBz
38


NO2
N
F3C
OMe
acid
NO2
HN
F3C
O

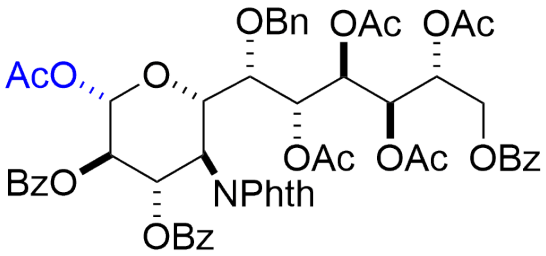

NO2
N
F3C
OR
crystalline
R'OH
acid
R'OR
R = benzyl
or allyl



38

1) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$
MeCN, 25°C

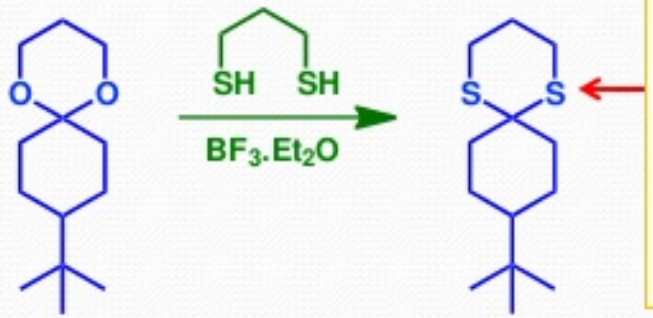
2) Ac_2O, pyridine, 50 °C

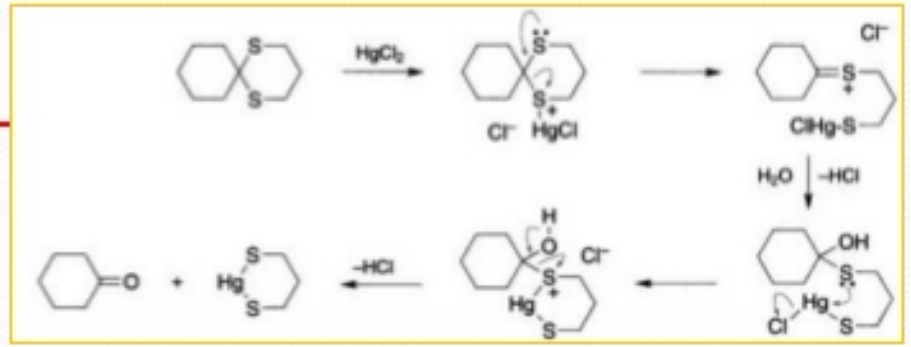


39

Formation: $HS(CH_2)_nSH$, $BF_3.Et_2O$, DCM, 25°C

1,3-dioxolanes and 1,3-dioxanes can be readily converted into 1,3-dithiolanes and 1,3-dithianes





Cleavage: $Hg(ClO)_4$, MeOH, $CHCl_3$, 25 °C

NBS, acetone, 0 °C

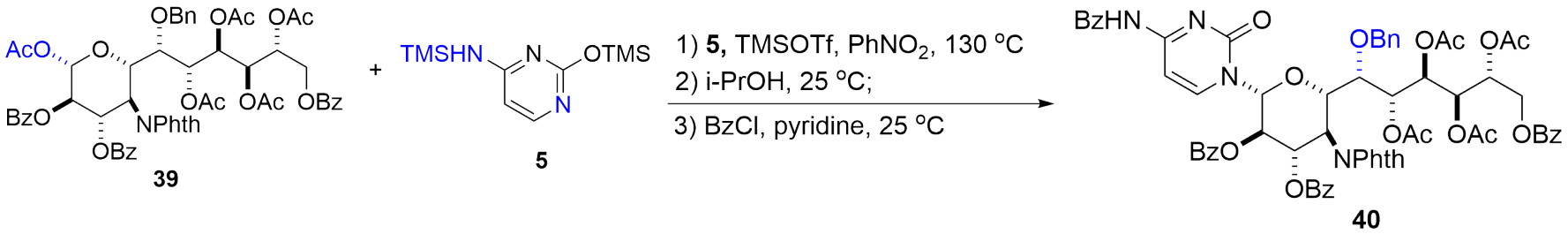
I_2, DMSO

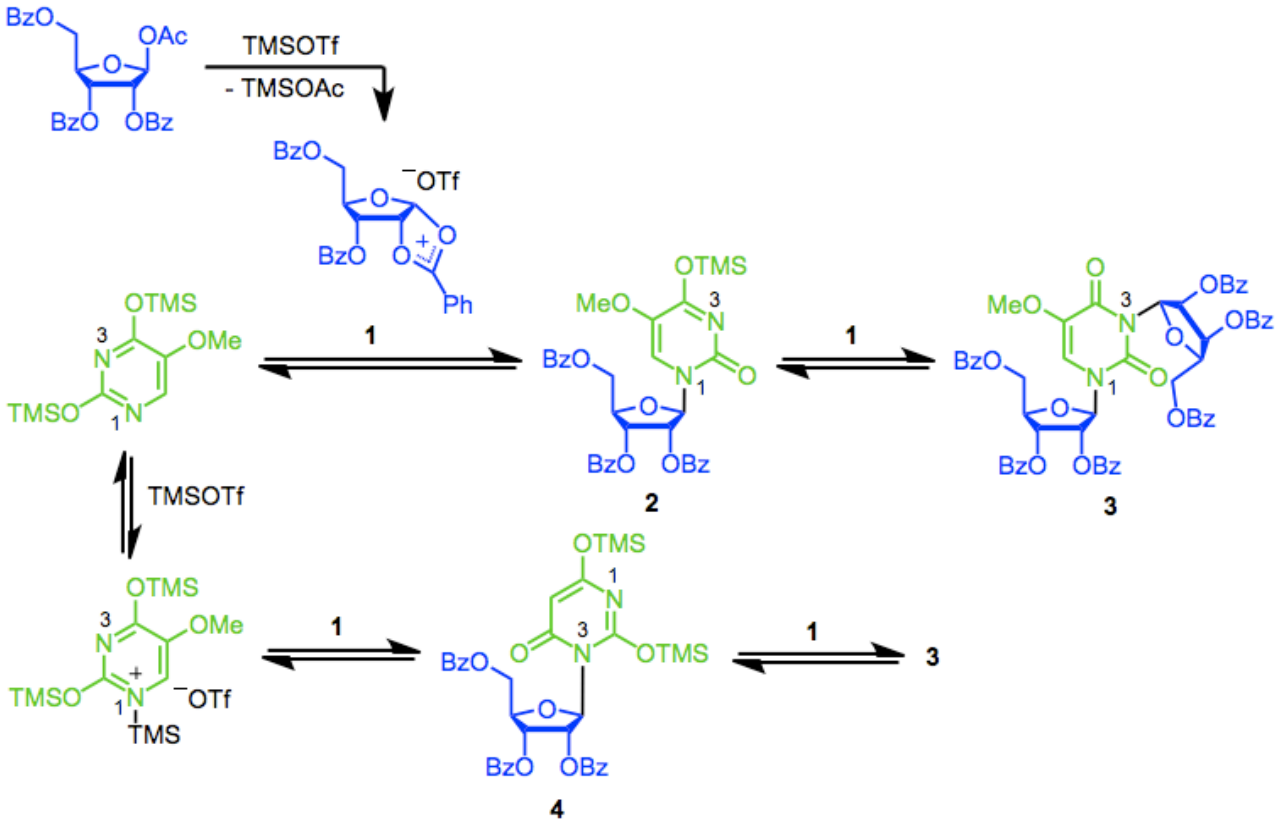
CAN, aq. CH_3CN

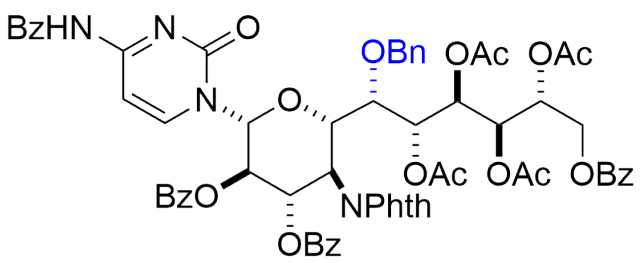
m-CPBA, Ac_2O

DDQ, aq. CH_3CN

Raney Ni

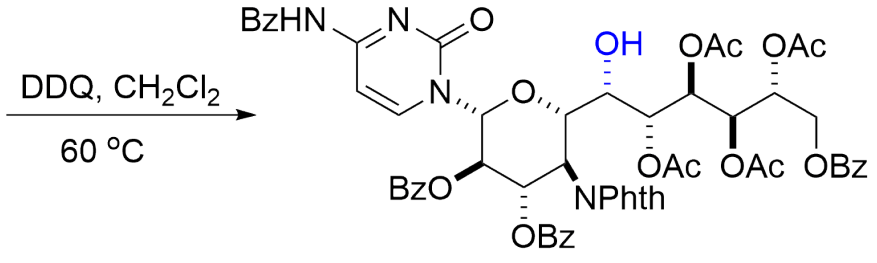

AcO
OBn
OAc
OAc
BzO
NPhth
OAc
OAc
OBz
OBz
39
+
TMSHN
N
OTMS
N
5
1) 5, TMSOTf, PhNO2, 130 °C
2) i-PrOH, 25 °C;
3) BzCl, pyridine, 25 °C
BzHN
N
O
N
O
OBn
OAc
OAc
BzO
NPhth
OAc
OAc
OBz
OBz
40


BzO
OAc
BzO
OBz
TMSOTf
- TMSOAc
BzO
OTf
O
O
BzO
O
+
Ph
1
OTMS
3
N
OMe
TMSO
N
1
MeO
OTMS
3
N
BzO
N
1
O
BzO
OBz
2
1
MeO
O
3
N
OBz
OBz
BzO
N
1
O
O
OBz
BzO
OBz
3
TMSOTf
OTMS
3
N
OMe
TMSO
+
N
1
OTf
TMS
1
OTMS
1
N
3
O
N
OTMS
BzO
O
BzO
OBz
4
1
1
3

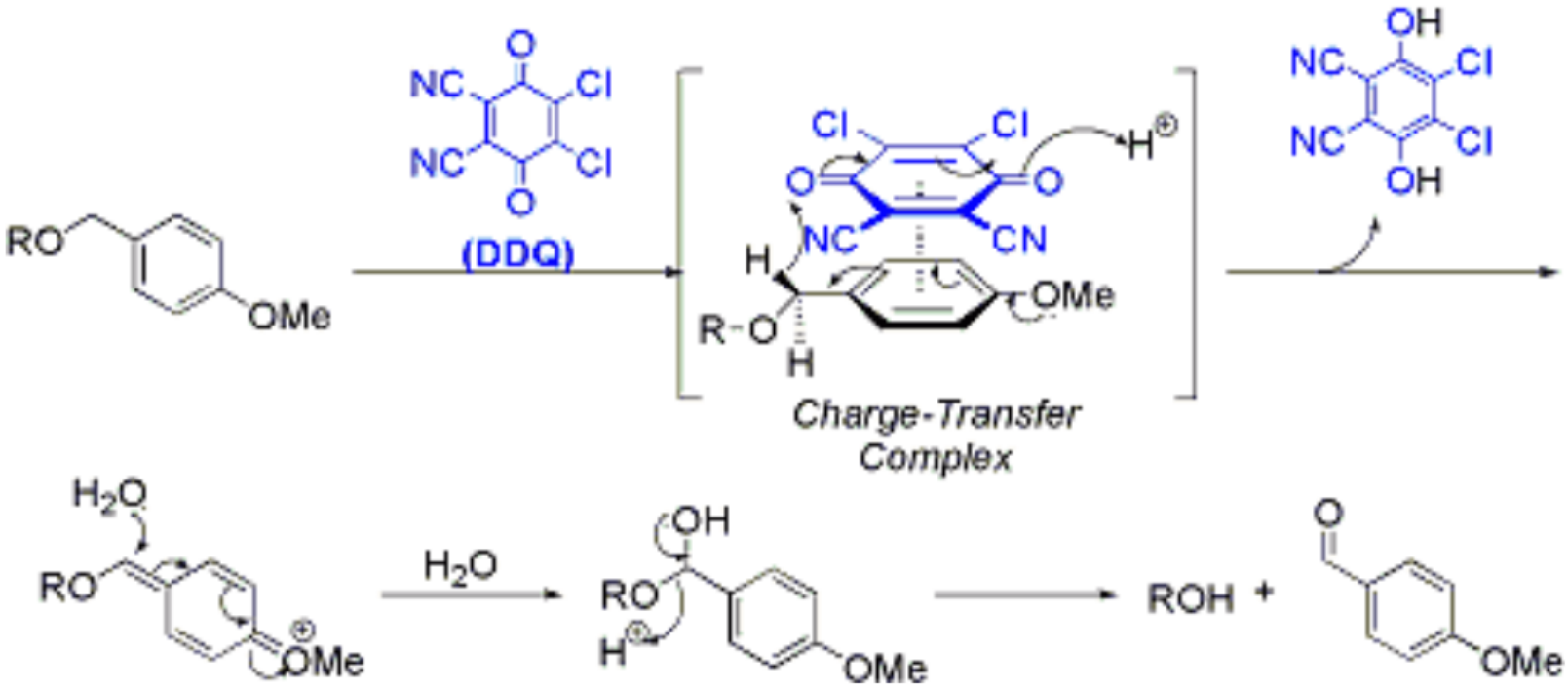


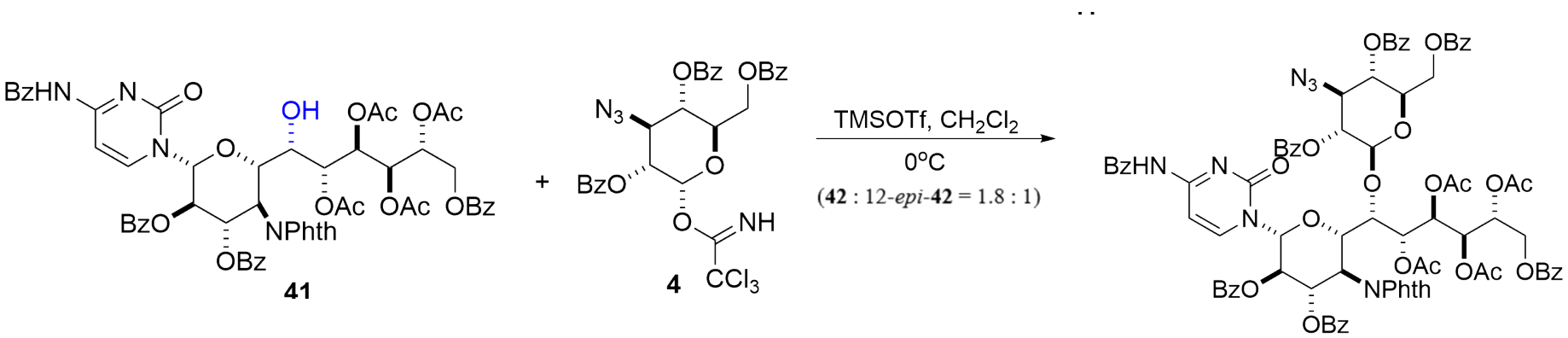
40

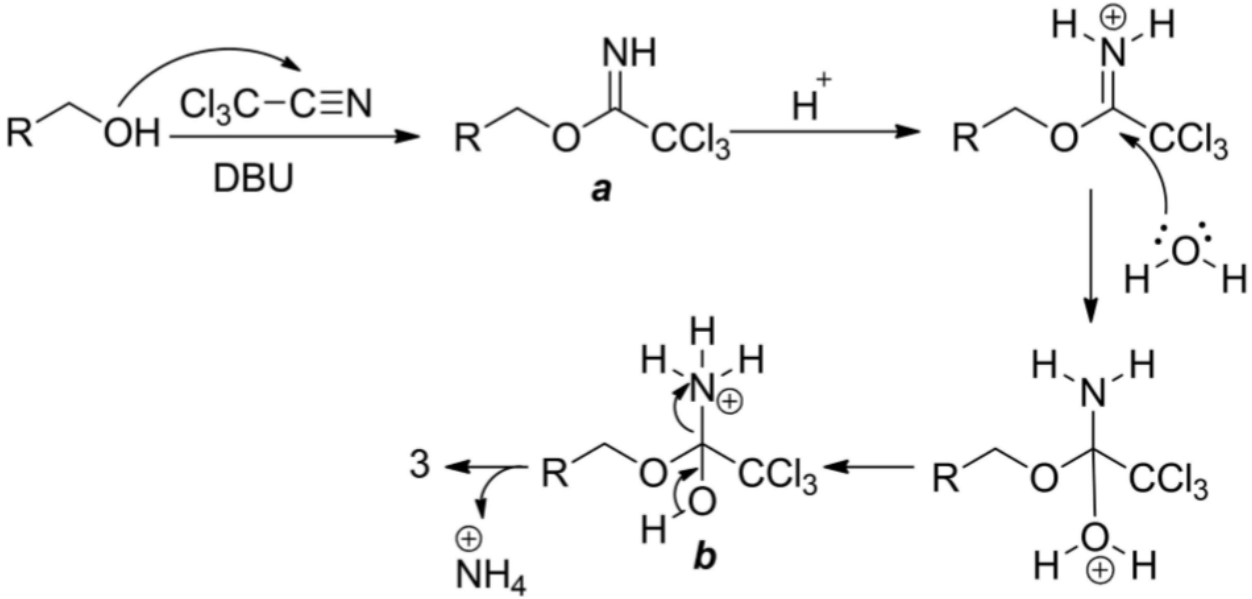
(19%, 6 steps)



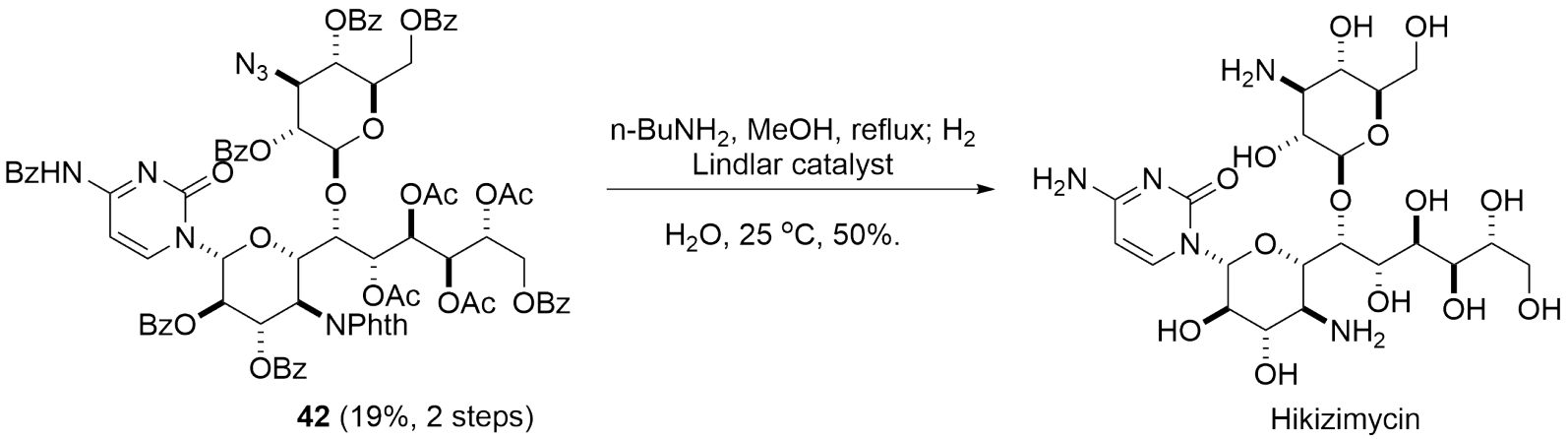
41







- Soumya Poshala, Sanjeeva Thunga, Sivaparwathi Golla, Vanaparthi Satheesh, and HariPrasad Kokatla. *ChemistrySelect* **2019,** 4, 10466–10470



42 (19%, 2 steps)

Hikizimycin

- Lindlar catalyst [(5% Pd-$CaCO_3$, $Pb(OAc)_2$, quinoline), 500 wt%]