Synthesis of (-)-Okilactomycin by a Prins-Type Fragment-Assembly Strategy

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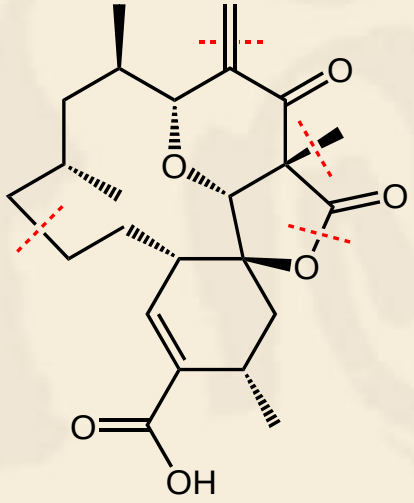
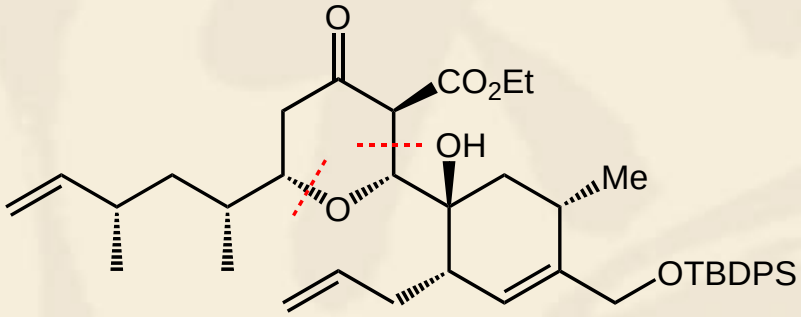
Scheidt, K. A. et al. *Angew. Chem., Int. Ed.* **2011**, *50*, *5892*

Retrosynthetic Strategy



Okilactomycin (**1**)

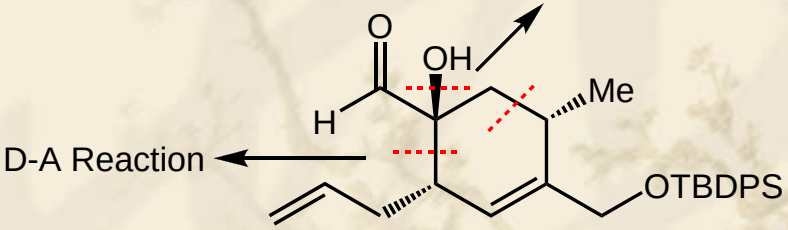
RCM



2

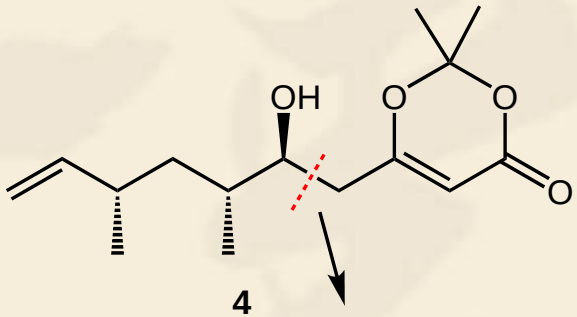
Condensation/Prins
Cyclization Reaction

Rubottom Reaction



D-A Reaction

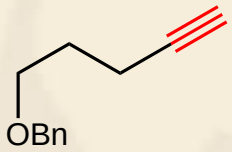
3



4

Aldol Reaction

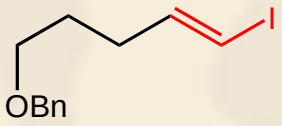
Synthesis of 3



5

$Cp_2Zr(H)Cl$, NIS, THF

84%



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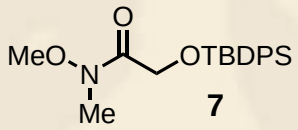
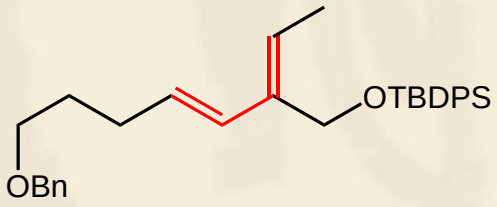


7

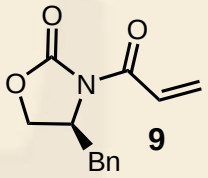
1. *n*-BuLi, THF, -78 ^{o}C (65%)

2. KHMDS, ethyltriphenylphosphonium bromide,THF, -78 to 0 ^{o}C (84%)



8

Et_2AlCl, $AgPF_6$, CH_2Cl_2, -78 ^{o}C
(86%, >20:1 d.r.)



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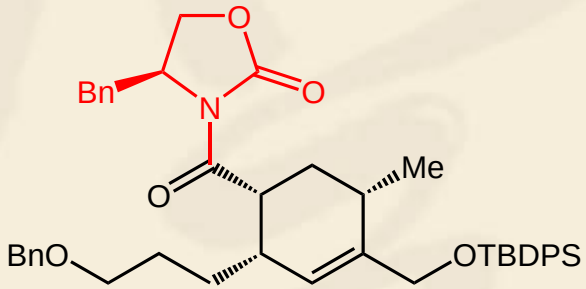
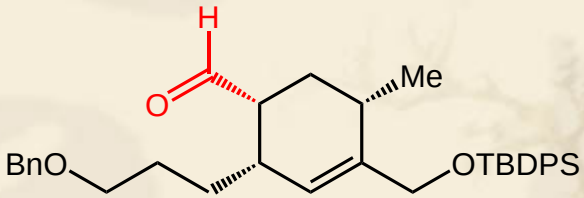


10

1. $LiBH_4$, MeOH, Et_2O, 0 ^{o}C (83%)

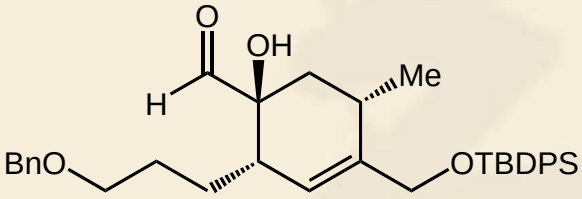
2. Dess-Martin periodinane, CH_2Cl_2, (90%)



11

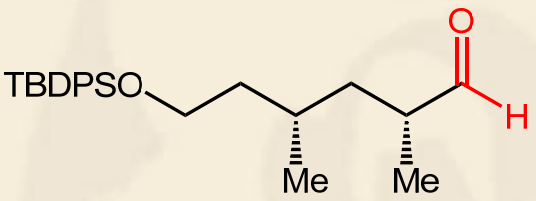
1. TBSOTf, NEt_3, CH_2Cl_2

2. DMDO, CH_2Cl_2, 0 ^{o}C
then H^+ (88%)



3

Synthesis of 4



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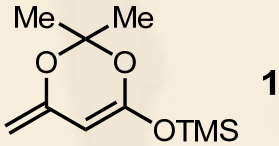
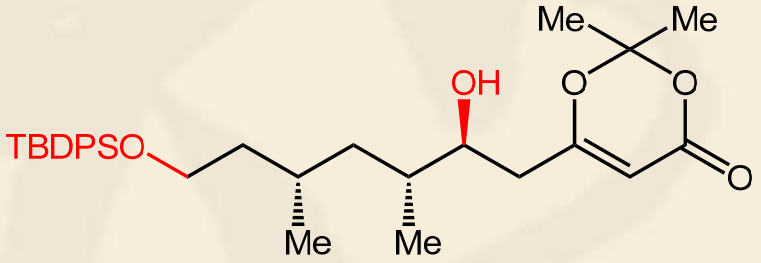


14

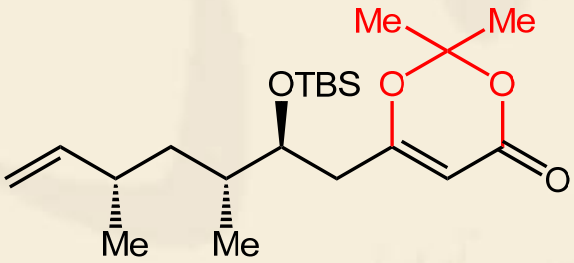
$Cu(OTf)_2$, (*R*)-tol-binap,
TBAT, THF, -50 °C
70%, 10:1 d.r.



15

1. TBSOTf, 2,6-lutidine, CH_2Cl_2
   0 °C (92%)
2. NH_4F, MeOH, 40 °C (92%)

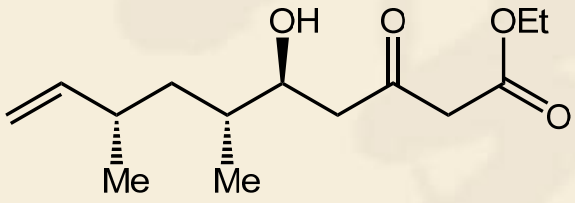
3. *o*-nitrophenyl selenocyanate,
   PBu_3, THF; then H_2O_2
   THF (76%)



16

1. KOEt, CH_2Cl_2 (88%)

2. HF·py, THF (94%)



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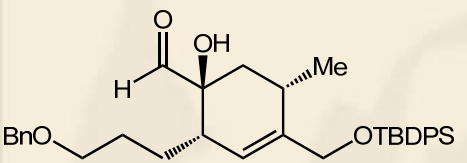

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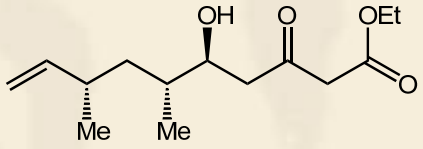
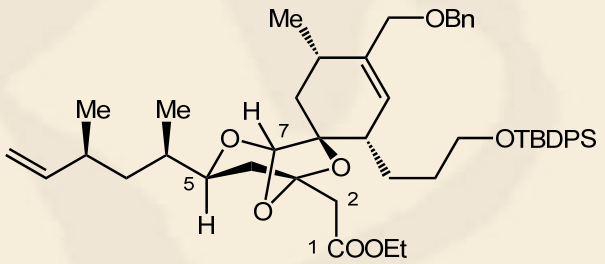


17

TMSOTf, CH_2Cl_2
-78 ºC (35%)



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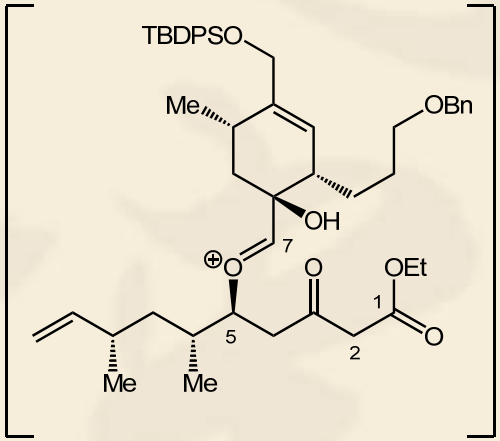
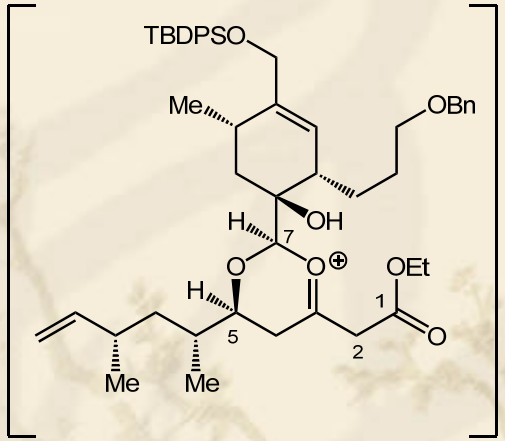
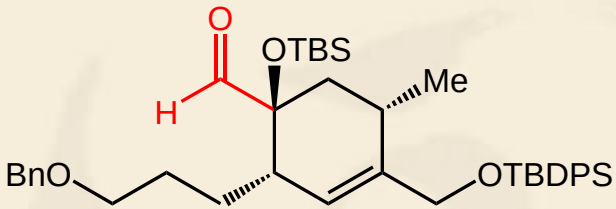
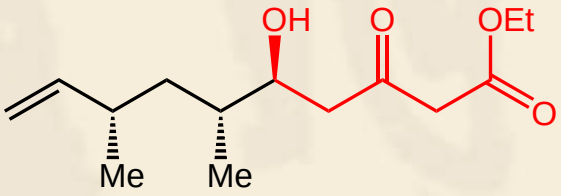






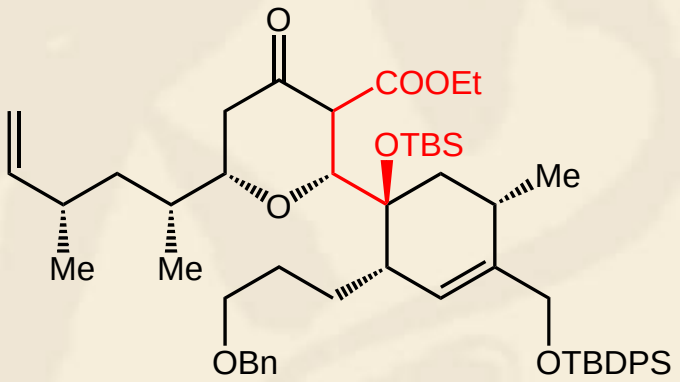
21

+



17

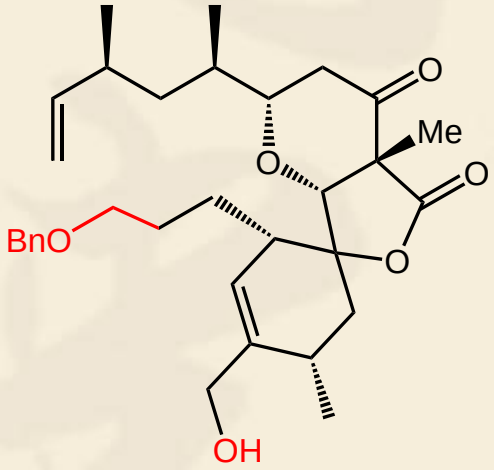
TMSOTf, CH_2Cl_2
-78 °C to -40 °C
60%, 13:1 d.r.



22

1. aq HF, CH_3CN
2. KO*t*-Bu, CH_2Cl_2

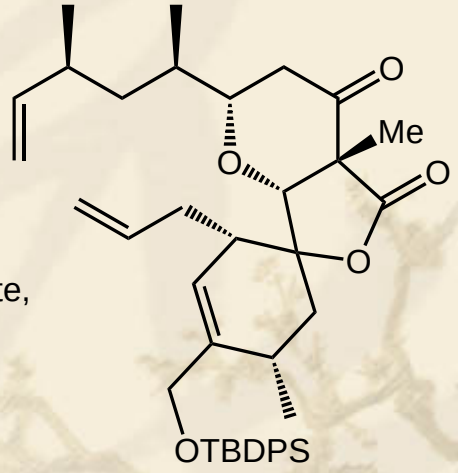
3. K_2CO_3, MeI
CH_3CN, 70 °C
58%



23

1. TBDPSCl, imidazole
CH_2Cl_2 (90%)

2. DDQ, CH_2Cl_2 (61%)
3. *o*-nitrophenyl-selenocyanate,
PBu_3, THF
then H_2O_2, THF (60%)



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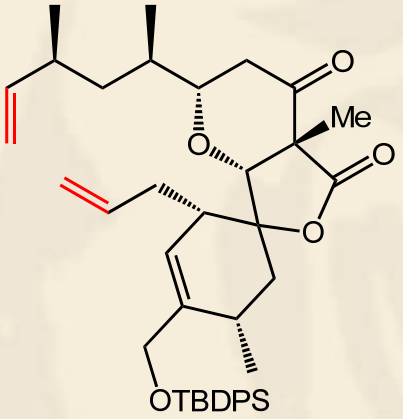
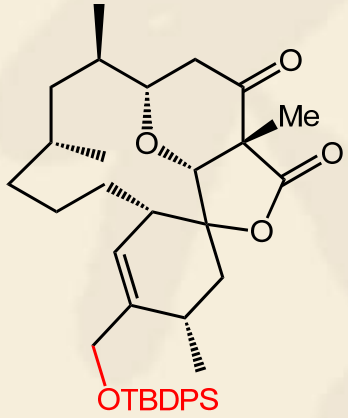


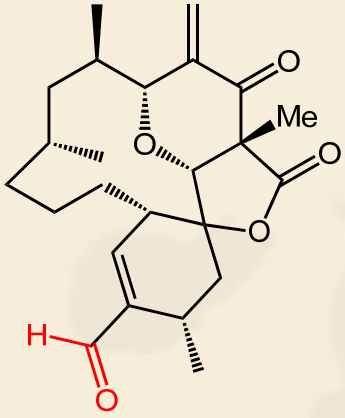
24

1. Grubbs second-generation catalyst, CH_2Cl_2, 40 °C
2. H_2, PtO_2, EtOAc, 65%



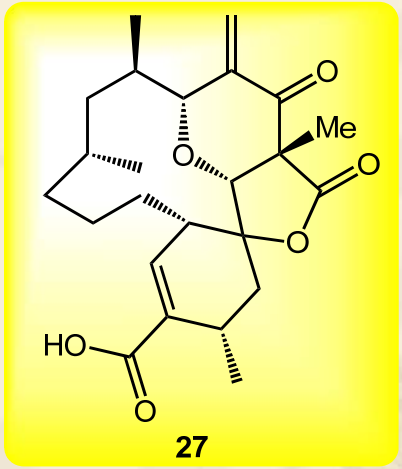
25

1. HF·py, THF (>99%)
2. dimethylmethylideneammonium iodide, LiHMDS, THF (95%)
3. Dess-Martin periodinane CH_2Cl_2 (83%)



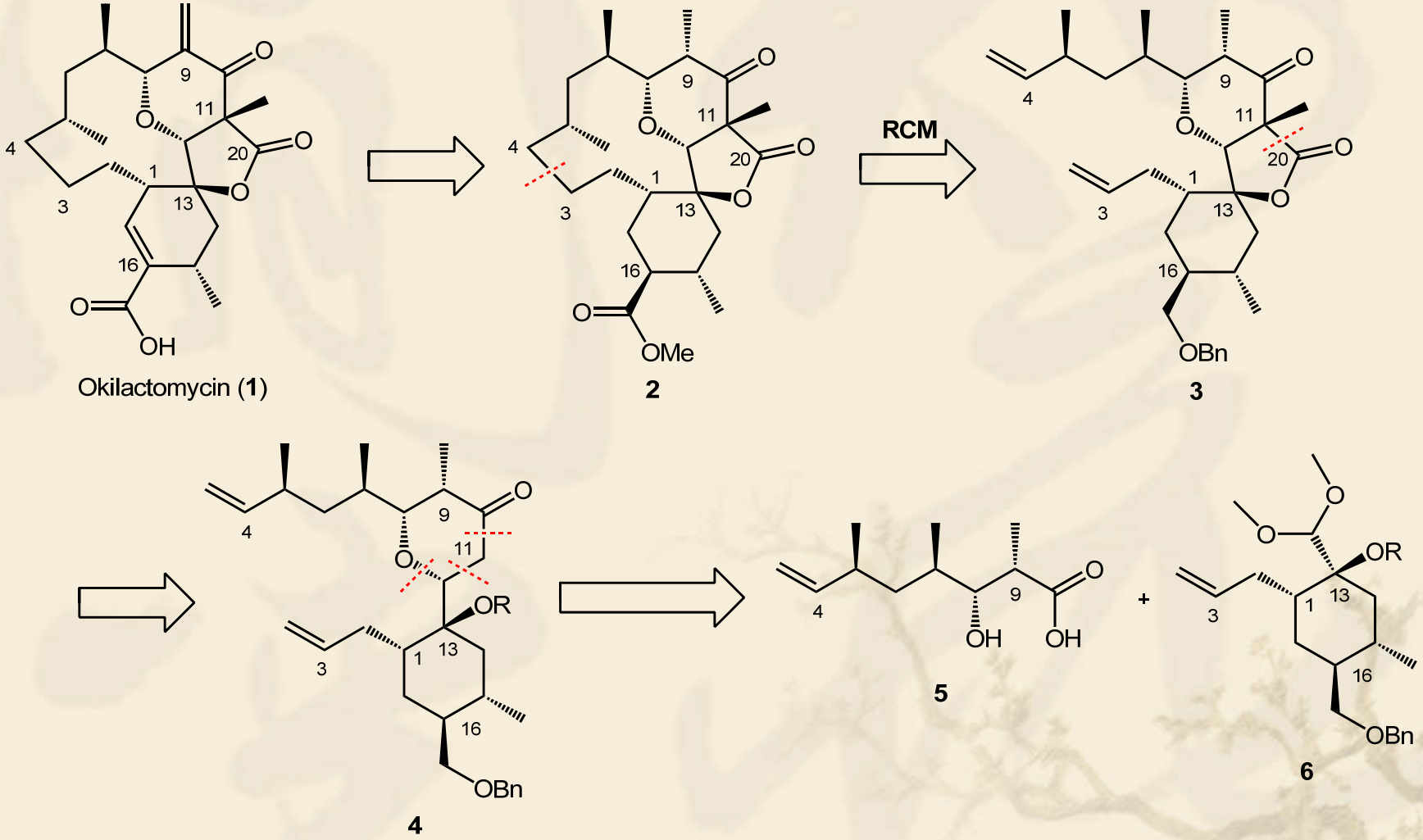
26

1. $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene
t-BuOH/THF/H_2O (4:4:1) (50%)



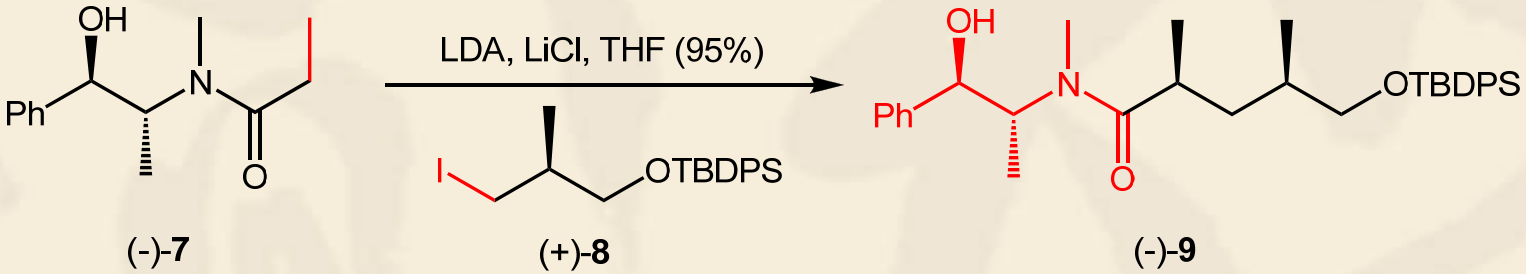
27

Retrosynthetic Strategy

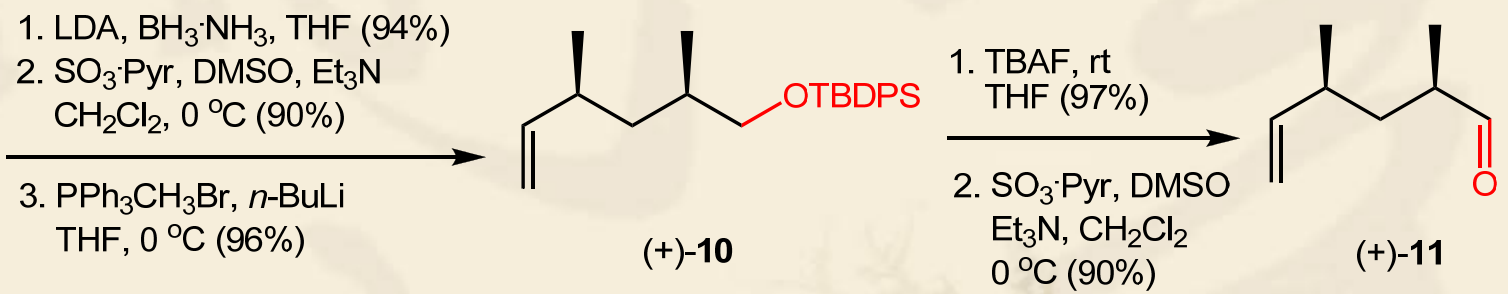


Smith III, A. B. et al. *J. Am. Chem. Soc.* **2007**, *129*, 14872

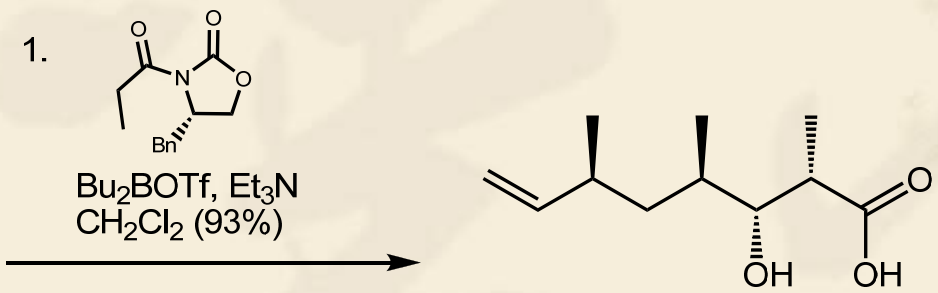
Synthesis of 5



(-)-**7** (+)-**8** (-)-**9**

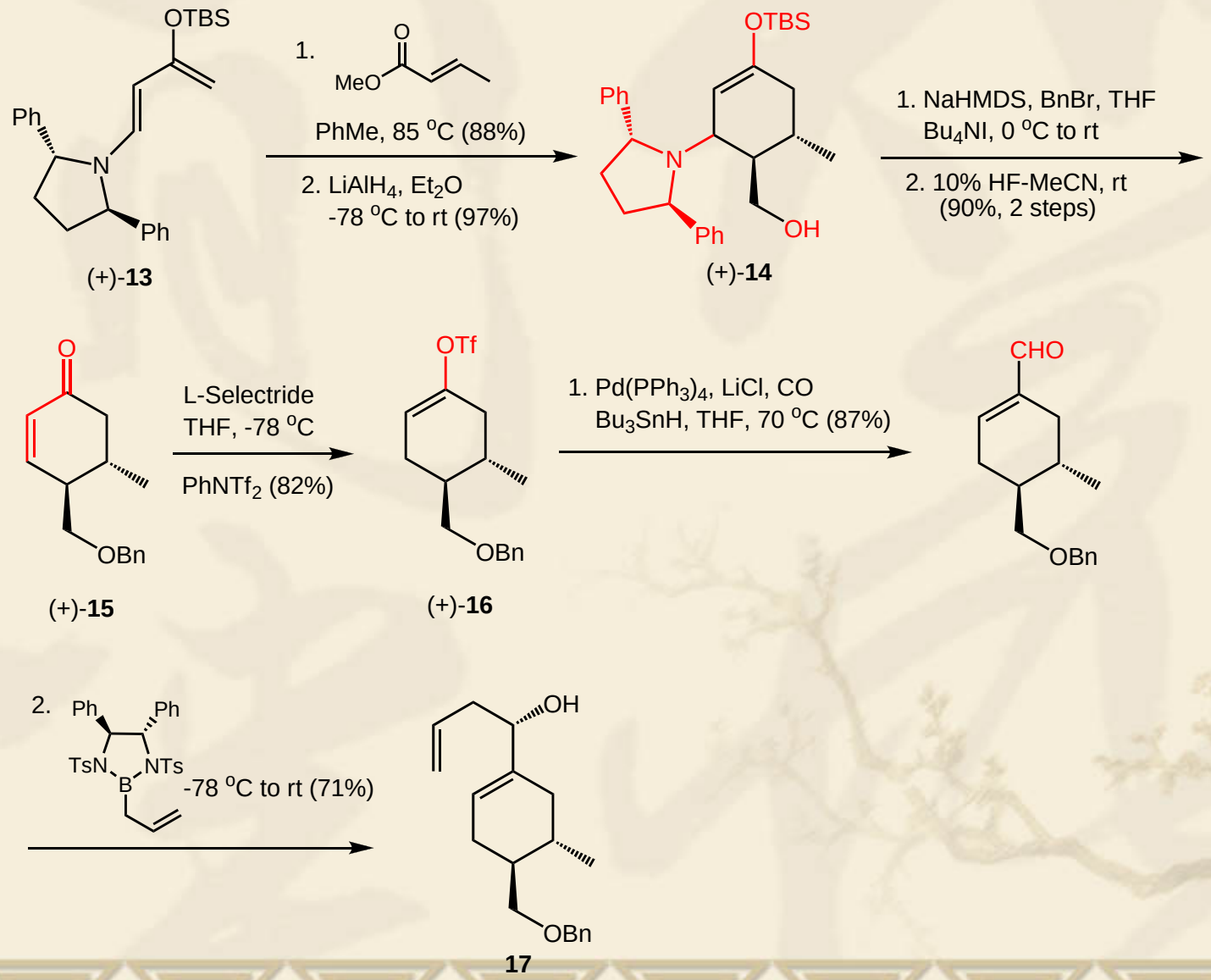


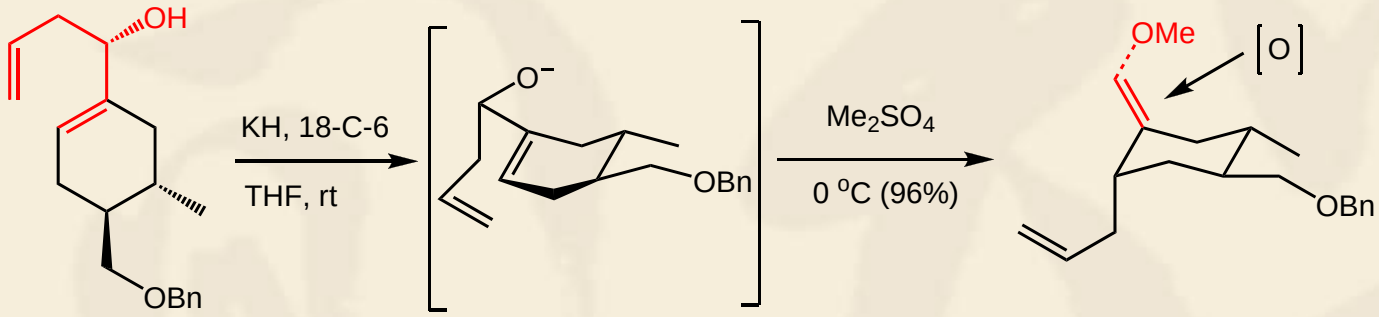
(+)-**10** (+)-**11**



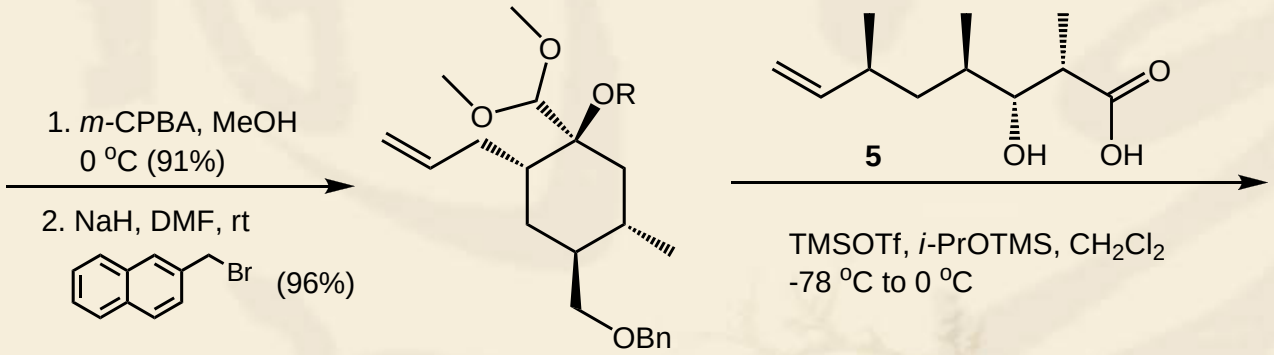
(+)-**5**

Synthesis of 6

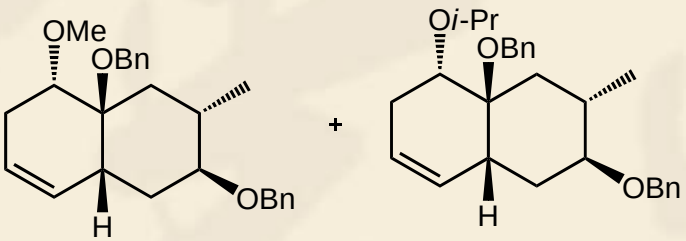




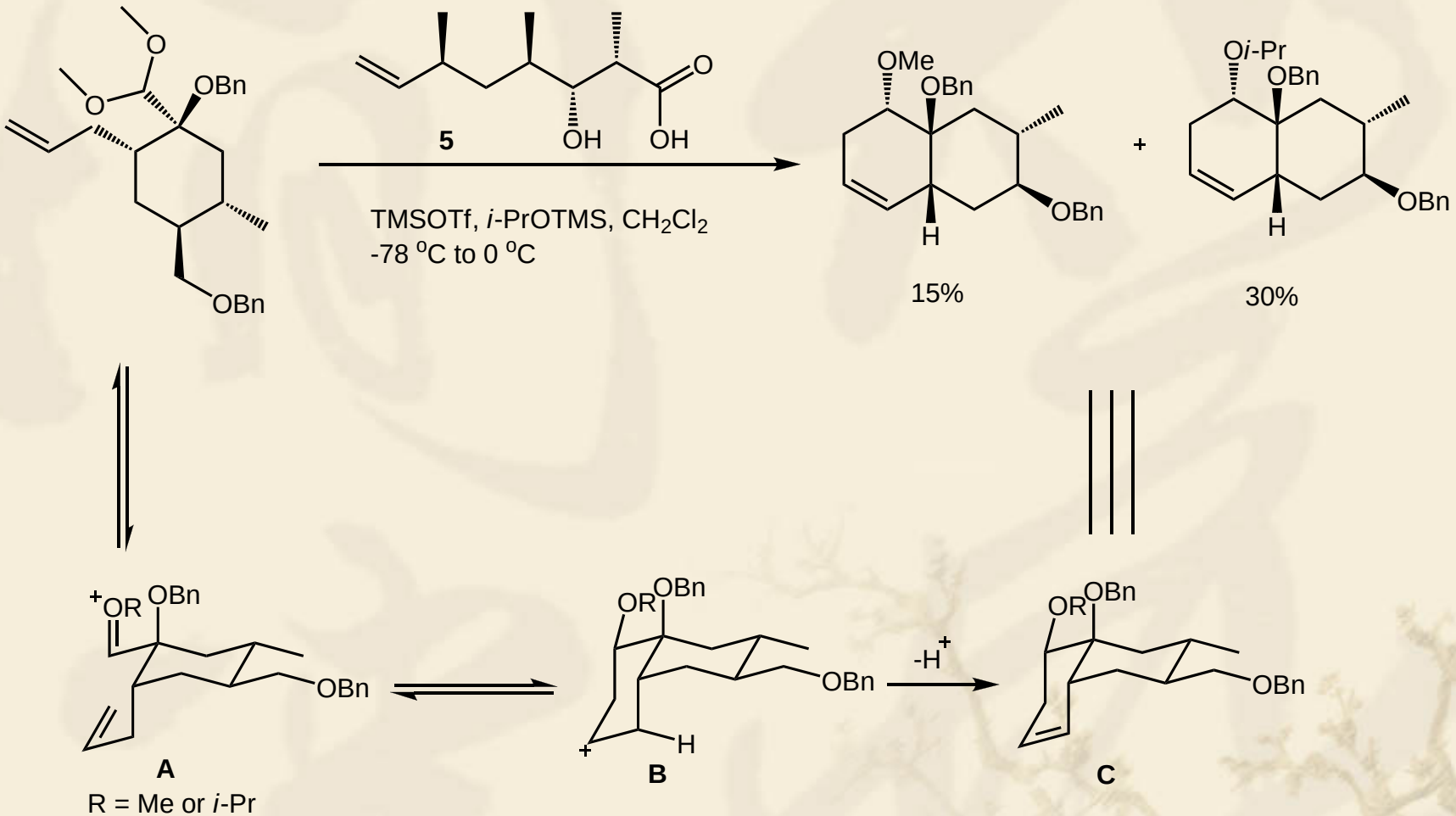
17 **18**

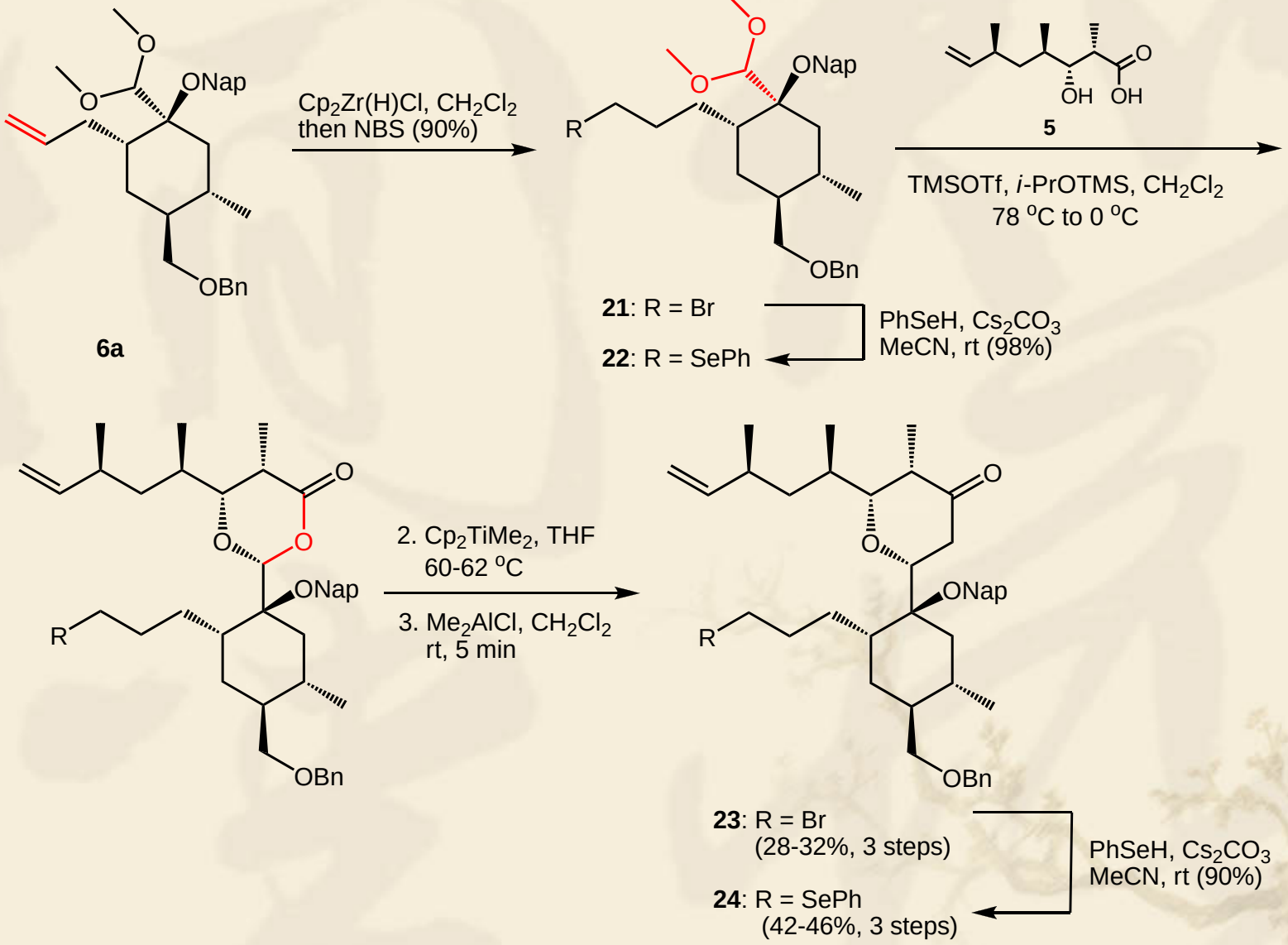


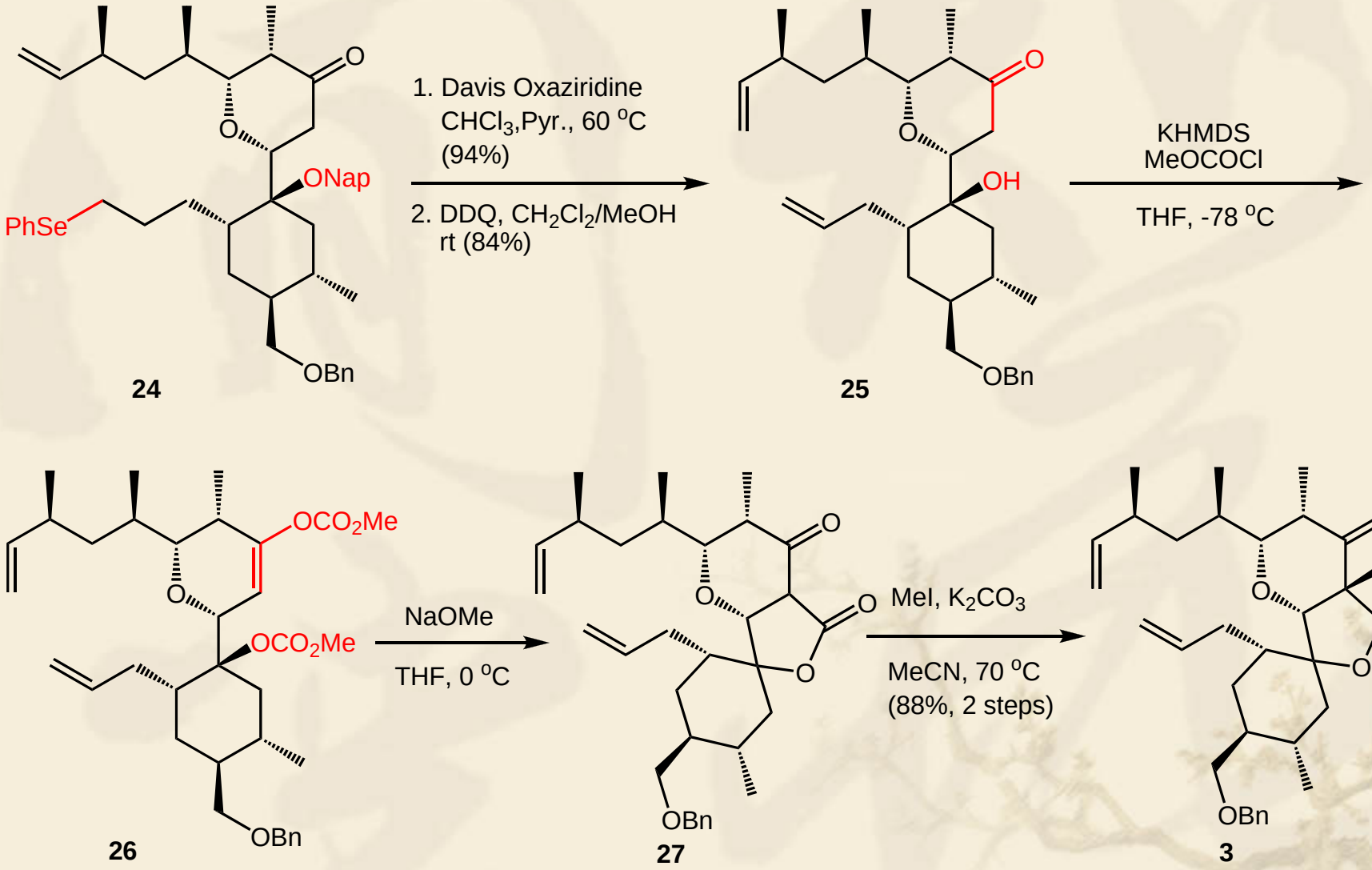
6a: R = Nap
6b: R = Bn

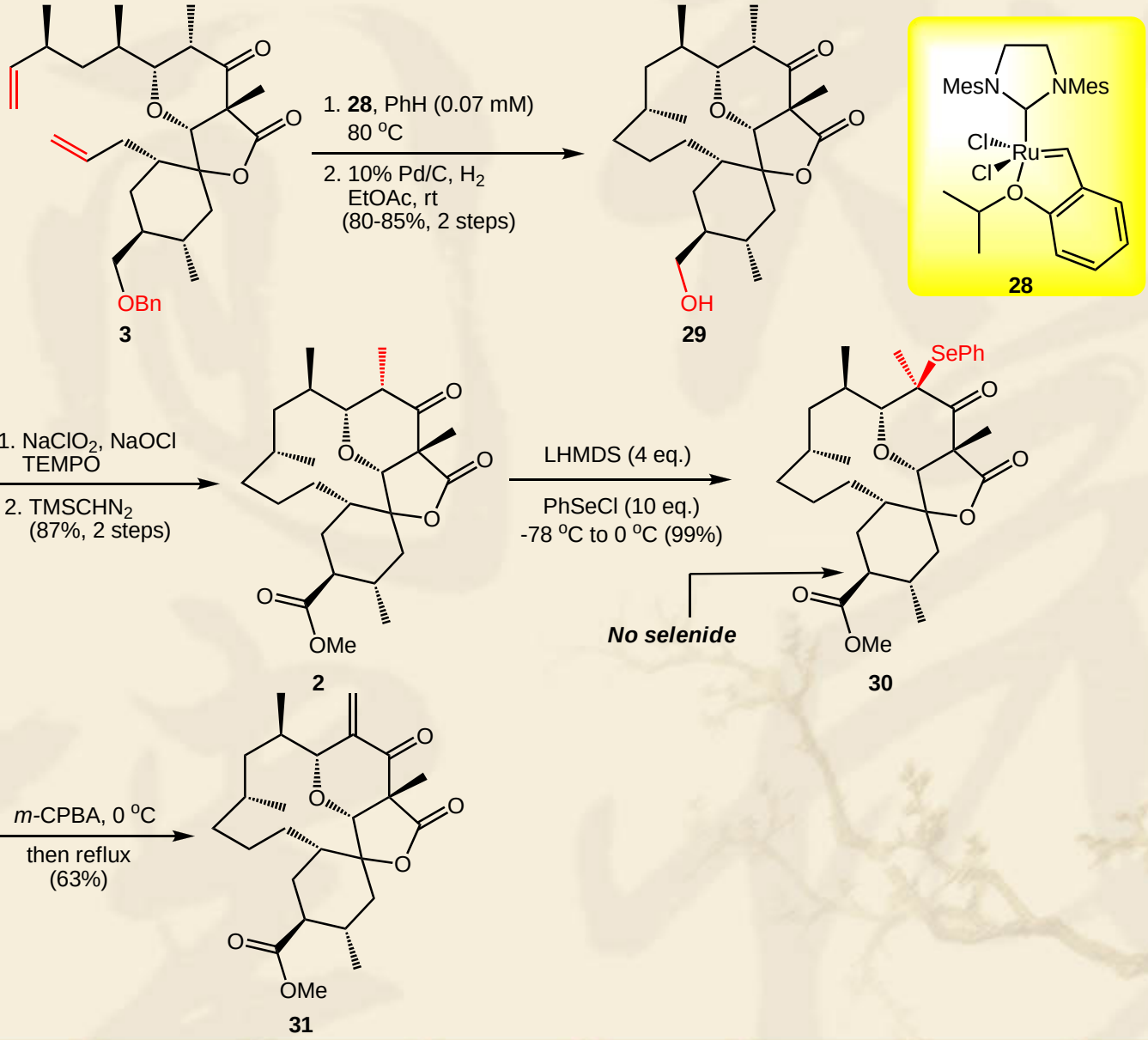


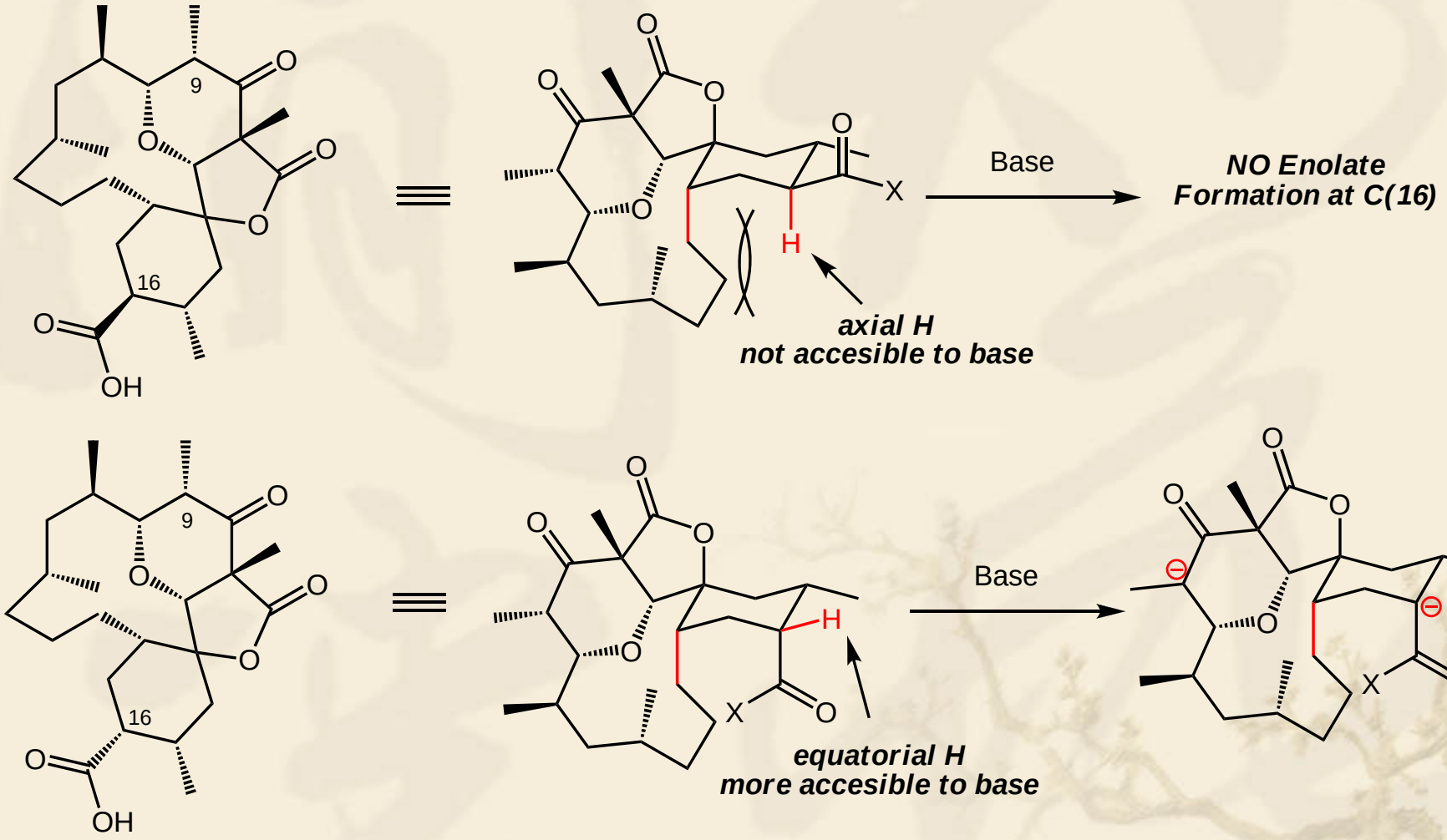
15% 30%

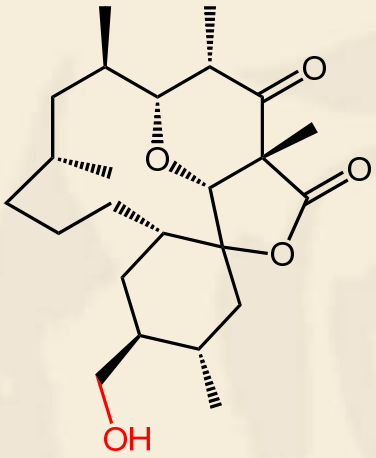

O
O
OBn
OBn
5
OH
OH
O
TMSOTf, i-PrOTMS, CH2Cl2
-78 °C to 0 °C
OMe
OBn
H
OBn
15%
+
Oi-Pr
OBn
H
OBn
30%
+OR
OBn
OBn
A
R = Me or i-Pr
OR
OBn
OBn
H
B
-H+
OR
OBn
OBn
C


ONap
OBn
6a
Cp2Zr(H)Cl, CH2Cl2
then NBS (90%)
R
21: R = Br
22: R = SePh
PhSeH, Cs2CO3
MeCN, rt (98%)
OH
OH
5
TMSOTf, i-PrOTMS, CH2Cl2
78 °C to 0 °C
2. Cp2TiMe2, THF
60-62 °C
3. Me2AlCl, CH2Cl2
rt, 5 min
23: R = Br
(28-32%, 3 steps)
24: R = SePh
(42-46%, 3 steps)
PhSeH, Cs2CO3
MeCN, rt (90%)


1. Davis Oxaziridine
CHCl3,Pyr., 60 °C
(94%)
2. DDQ, CH2Cl2/MeOH
rt (84%)
KHMDS
MeOCOCl
THF, -78 °C
NaOMe
THF, 0 °C
MeI, K2CO3
MeCN, 70 °C
(88%, 2 steps)
ONap
PhSe
OBn
OH
OCO2Me
24
25
26
27
3


OBn
3
1. 28, PhH (0.07 mM)
80 °C
2. 10% Pd/C, H2
EtOAc, rt
(80-85%, 2 steps)
OH
29
MesN
NMes
Cl
Ru
Cl
O
28
1. NaClO2, NaOCl
TEMPO
2. TMSCHN2
(87%, 2 steps)
OMe
2
LHMDS (4 eq.)
PhSeCl (10 eq.)
-78 °C to 0 °C (99%)
SePh
No selenide
OMe
30
m-CPBA, 0 °C
then reflux
(63%)
OMe
31

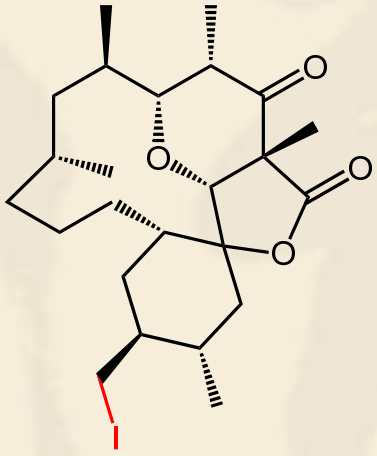

9
16
OH
Base
NO Enolate
Formation at C(16)
axial H
not accesible to base
equatorial H
more accesible to base



29

I_2, PPh_3, Imid

THF (90%)

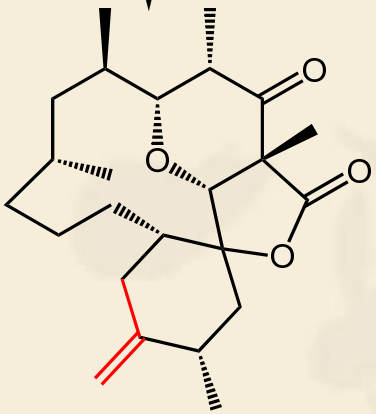


32

1. $PhSeH$, Cs_2CO_3 (80%)

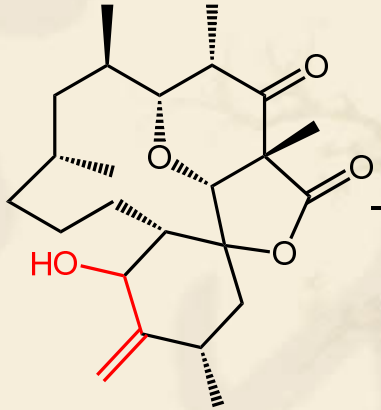
2. Davis oxazirdine Pyr., $CHCl_3$, 60 °C (70%)

ArSeCN, Bu_3P, Pyr.
H_2O_2, 45 °C (90%)

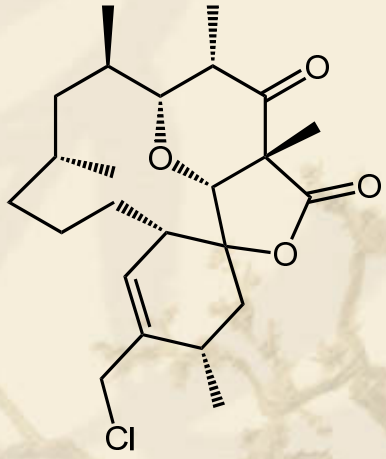


33

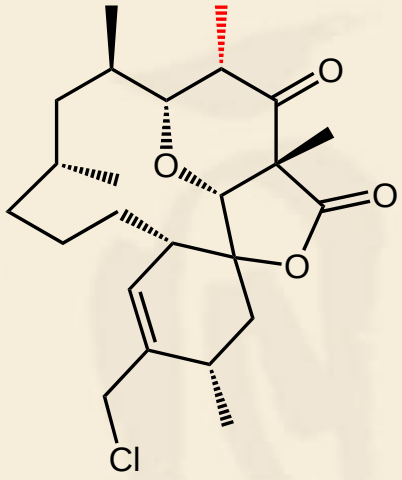
1. SeO_2, *t*-BuO_2H
CH_2Cl_2, 10 °C
(62%)



2. $SOCl_2$, Et_2O
0 °C (74%)



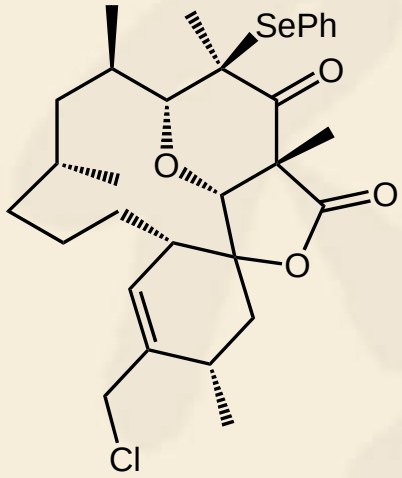
34



34

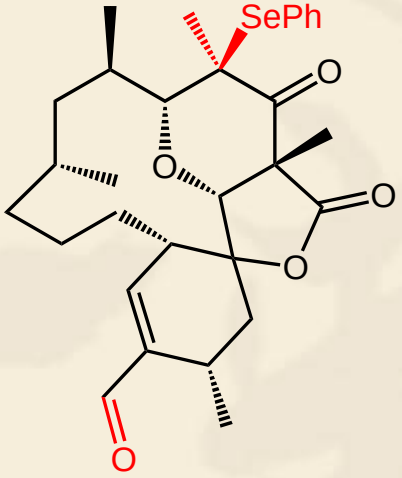
1. NaHMDS
   PhSeCl

THF, -78 °C
(83%)



2. Me_3NO, DMSO

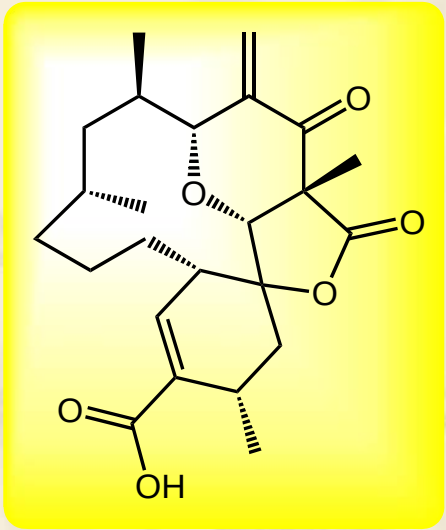
rt (65%)



35

1. $NaIO_4$, rt, $THF:H_2O$ (4:1)
   (90%)

2. $NaClO_2$, NaH_2PO_4
   2-methyl-2-butene
   $THF:t\text{-}BuOH:H_2O$
   (3:3:1), rt (80%)



(-)-Okilactomycin (**1**)

Okilactomycin (**1a**) is a structurally interesting antitumor antibiotic that was isolated from Streptomyces griseoflavus in 1987. In vitro studies have demonstrated that **1a** exhibits significant antitumor and antiproliferative activity against both lymphoid leukemia L1210 cells and P388 leukemia cells with IC_{50} values of 216 nm and 89 nm, respectively. A closely related compound, chrolactomycin (**1b**), differs only in structure by the replacement of a methyl group with a methoxy moiety at the pyranone/lactone ring fusion and displays promising telomerase inhibition. In addition to their potent biological activity, these compounds posses a compact and intriguing architecture. The tricyclic core is characterized by a unique 6,5-fused tetrahydropyranone γ–lactone bicycle with a spiro fusion to a highly substituted cyclohexene. Despite the biological activity and structural complexity, there have been only limited reports on the synthesis of okilactomycin (**1a**) over the last two decades, namely from the laboratories of Takeda, Paquette, and Smith. These synthetic efforts culminated in a total synthesis of unnatural enantiomer (-)-**1a** and determination of the absolute configuration of the natural product by Smith et al. in 2007. There are no syntheses of chrolactomycin reported to date. We disclose herein a convergent synthesis of (-)-**1a** utilizing a Prins-type Maitland–Japp cyclization strategy of two advanced fragments.

In summary, the total synthesis of (-)-okilactomycin (**1a**) has been achieved in 1.0% overall yield over 26 steps as the longest linear sequence. Stereoselective alkylation and Diels–Alder routes facilitated quick access to the δ-hydroxy β-ketoester and α-silyloxy aldehyde fragments, respectively. A Lewis acid promoted Maitland–Japp reaction established the full carbon core with a high degree of diastereoselectivity for the 2,6-*cis*-tetrahydropyrans core. This Prins-type transformation is one of the most advanced to date in terms of size and functionality of the reactants and further defines the potential of this approach for late-state unions of complex intermediates. The installation of the exocyclic olefin at the end of the synthesis and convergent nature of this route makes this synthesis amenable to the production of analogues and structure-activity relationship studies. The synthesis of these related compounds, which are intended for biological investigations, based on our complex fragment assembly Prins/Maitland–Japp route described here are ongoing in our laboratory.

Thank You