Literature Report

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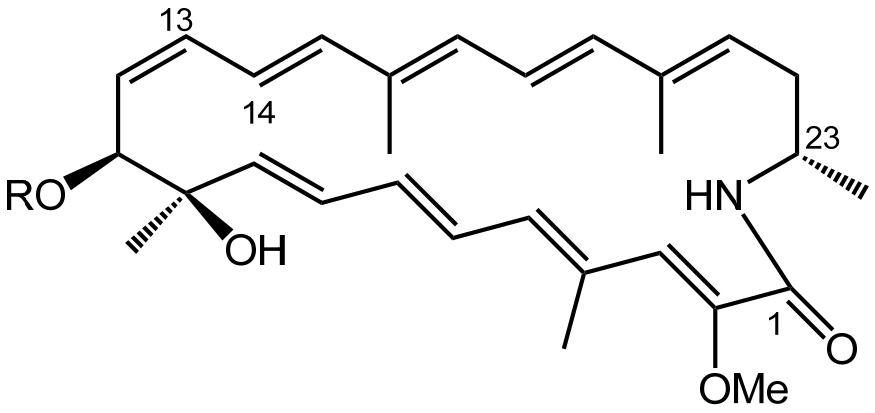
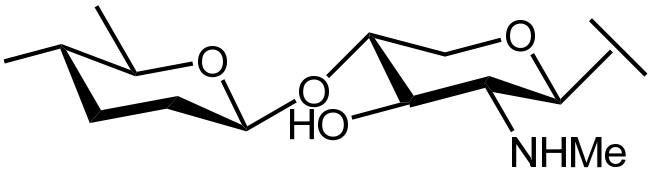
Total Synthesis of Incednam, the Aglycon of Incednine

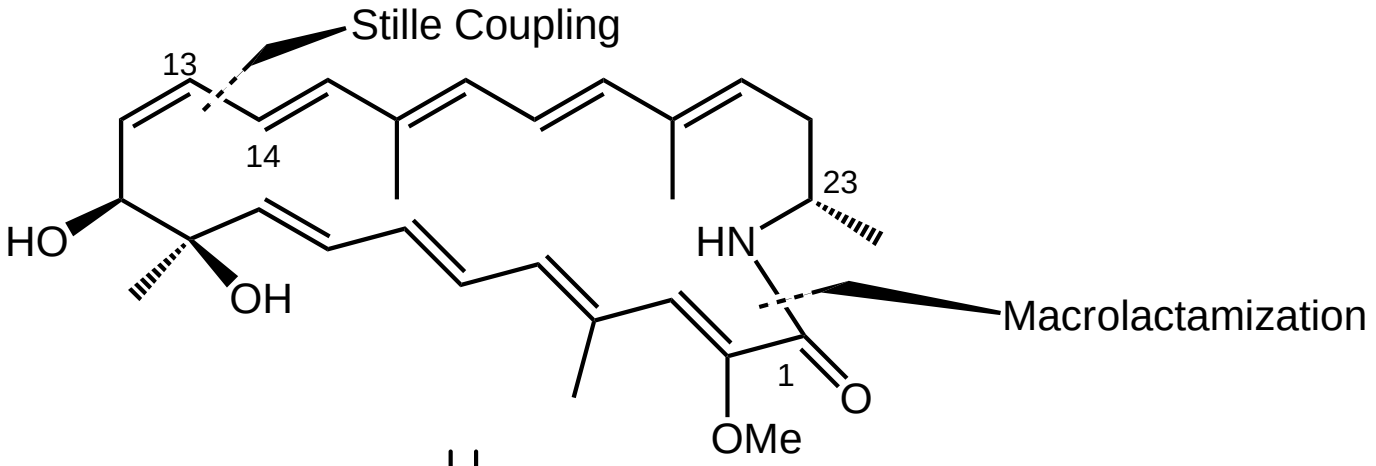
Toshima, K. * *et al*
Org. *Lett*. **2010**, *12*, 5068-5071.

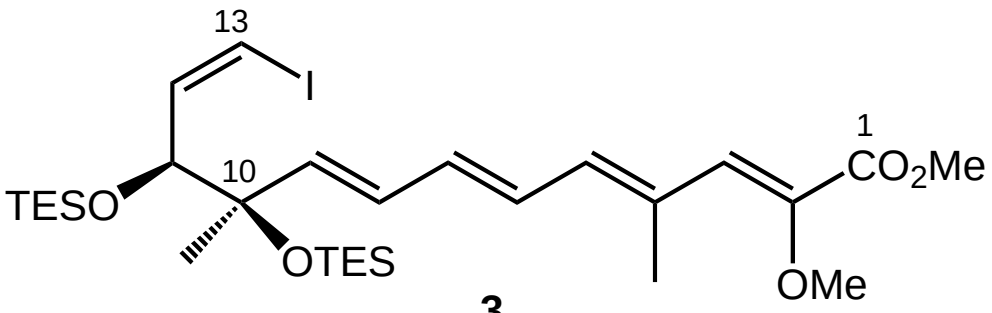


Incednam (**1**): R = H
Incednine (**2**): R = MeHN



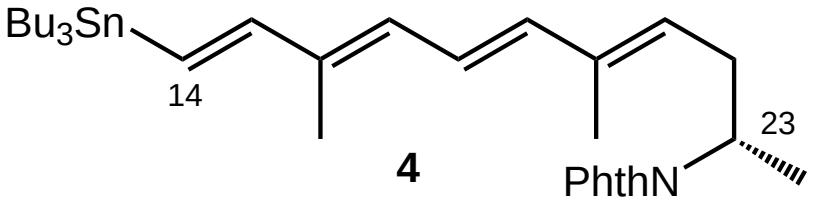
Retrosynthetic analysis





3

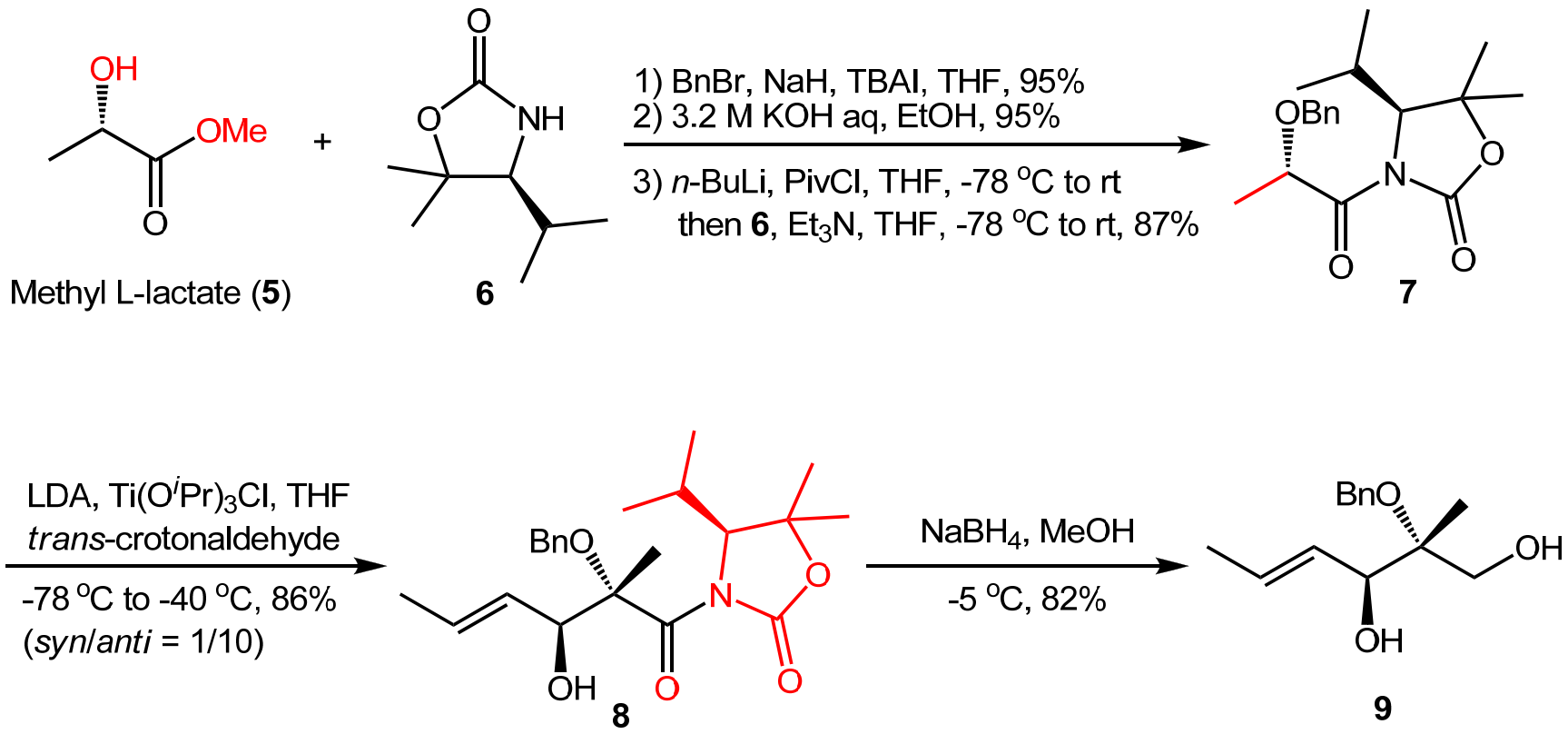
C1 - C13 subunit

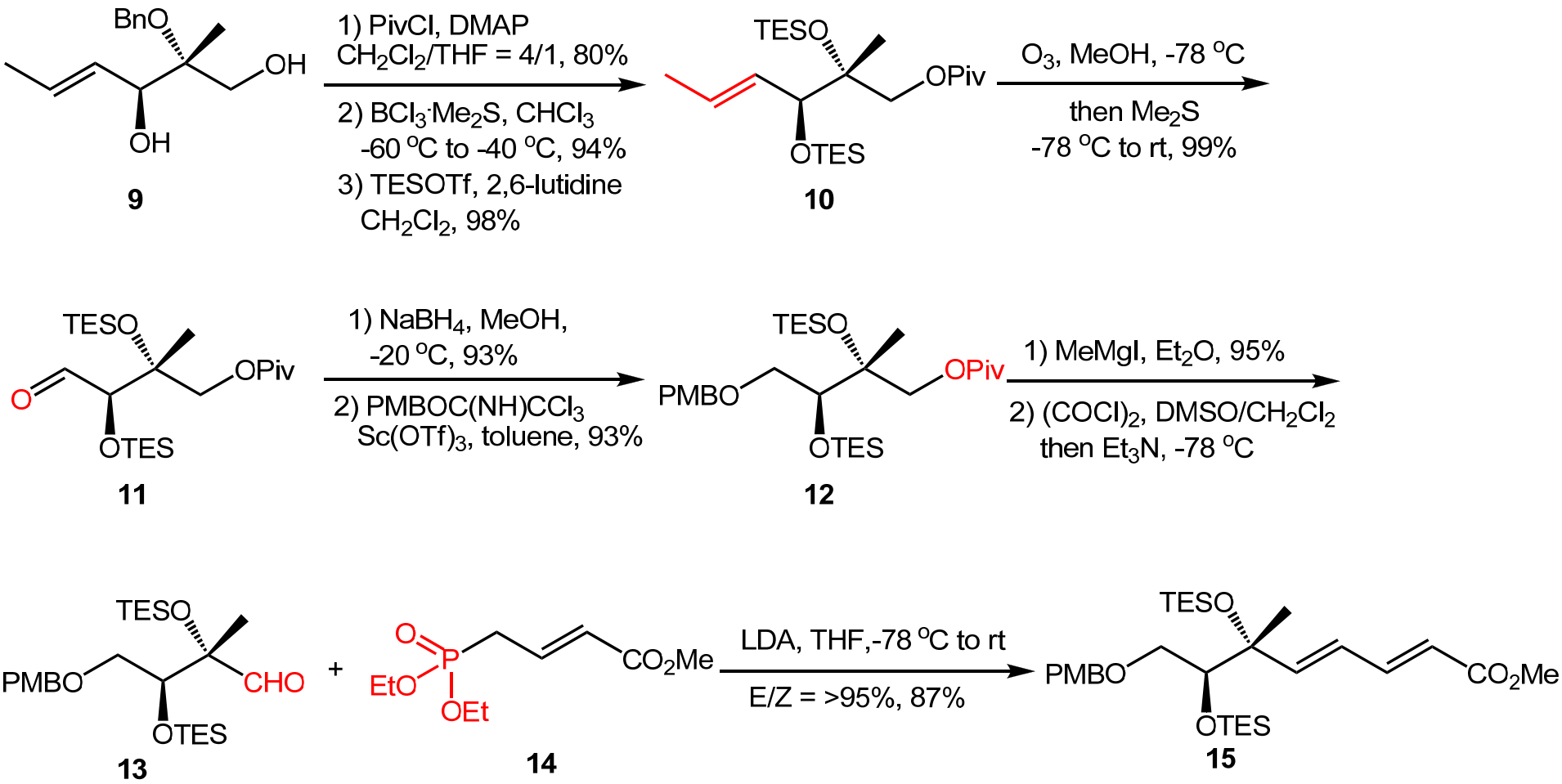


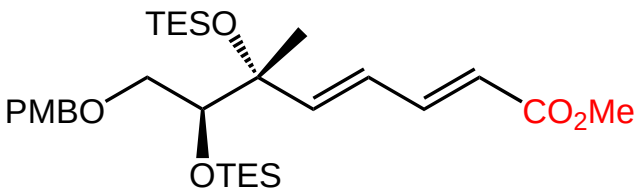
4

C14 - C23 subunit

Synthesis of C1-C13 Subunit **3**



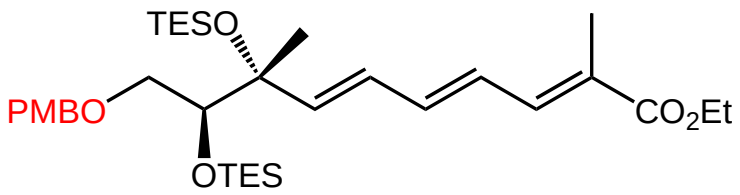

BnO
OH
OH
9
1) PivCl, DMAP
CH2Cl2/THF = 4/1, 80%
2) BCl3·Me2S, CHCl3
-60 °C to -40 °C, 94%
3) TESOTf, 2,6-lutidine
CH2Cl2, 98%
TESO
OPiv
OTES
10
O3, MeOH, -78 °C
then Me2S
-78 °C to rt, 99%
TESO
OPiv
O
OTES
11
1) NaBH4, MeOH,
-20 °C, 93%
2) PMBOC(NH)CCl3
Sc(OTf)3, toluene, 93%
TESO
PMBO
OPiv
OTES
12
1) MeMgI, Et2O, 95%
2) (COCl)2, DMSO/CH2Cl2
then Et3N, -78 °C
TESO
PMBO
CHO
OTES
13
+
O
P
EtO
OEt
CO2Me
14
LDA, THF,-78 °C to rt
E/Z = >95%, 87%
TESO
PMBO
OTES
CO2Me
15



15

1) DIBAL, PhMe, -78 °C
30 min, 95%

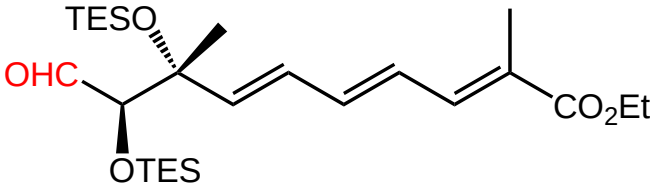
2) MnO_2, PhMe, 40 °C, 5 h
then $Ph_3PC(Me)CO_2Et$
40 °C, 16 h, 95%



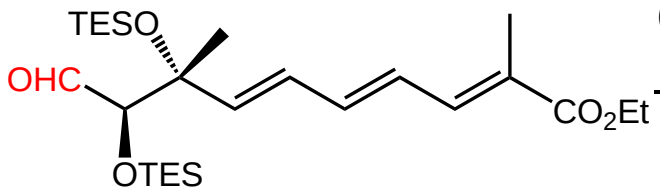
16

1) DDQ, CH_2Cl_2/pH 7.2 phosphate buffer(1/1)
0 °C to rt, 19 h, 72%

2) Dess-Martin periodinane, pyr., CH_2Cl_2
0 °C to rt, 17 h, 92%

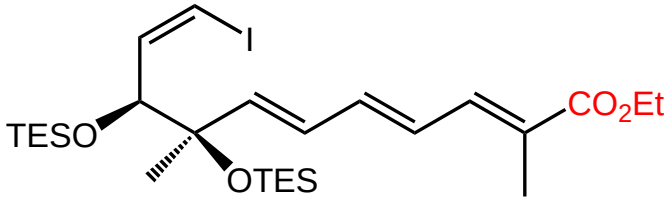


17



17

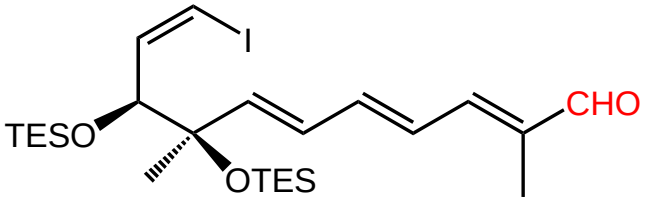
$(Ph_3P^+CH_2I)I^-$, NaHMDS, HMPA
THF, -98 ^oC, 1 h, 67%



18

1) DIBAL, PhMe, -78 ^oC
10 min, 98%

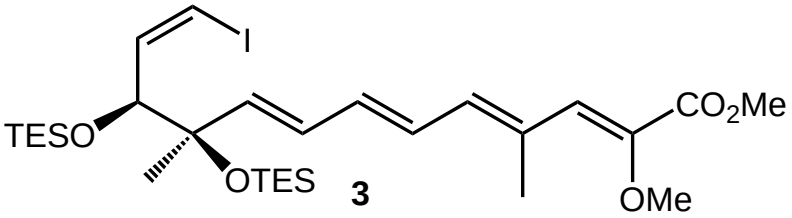
2) MnO_2, CH_2Cl_2, 40 ^oC, 2 h
40 ^oC, 16 h, 77%



19

$(MeO)_2P(O)CH(OMe)CO_2Me$
KHMDS, 18-crown-6 ether

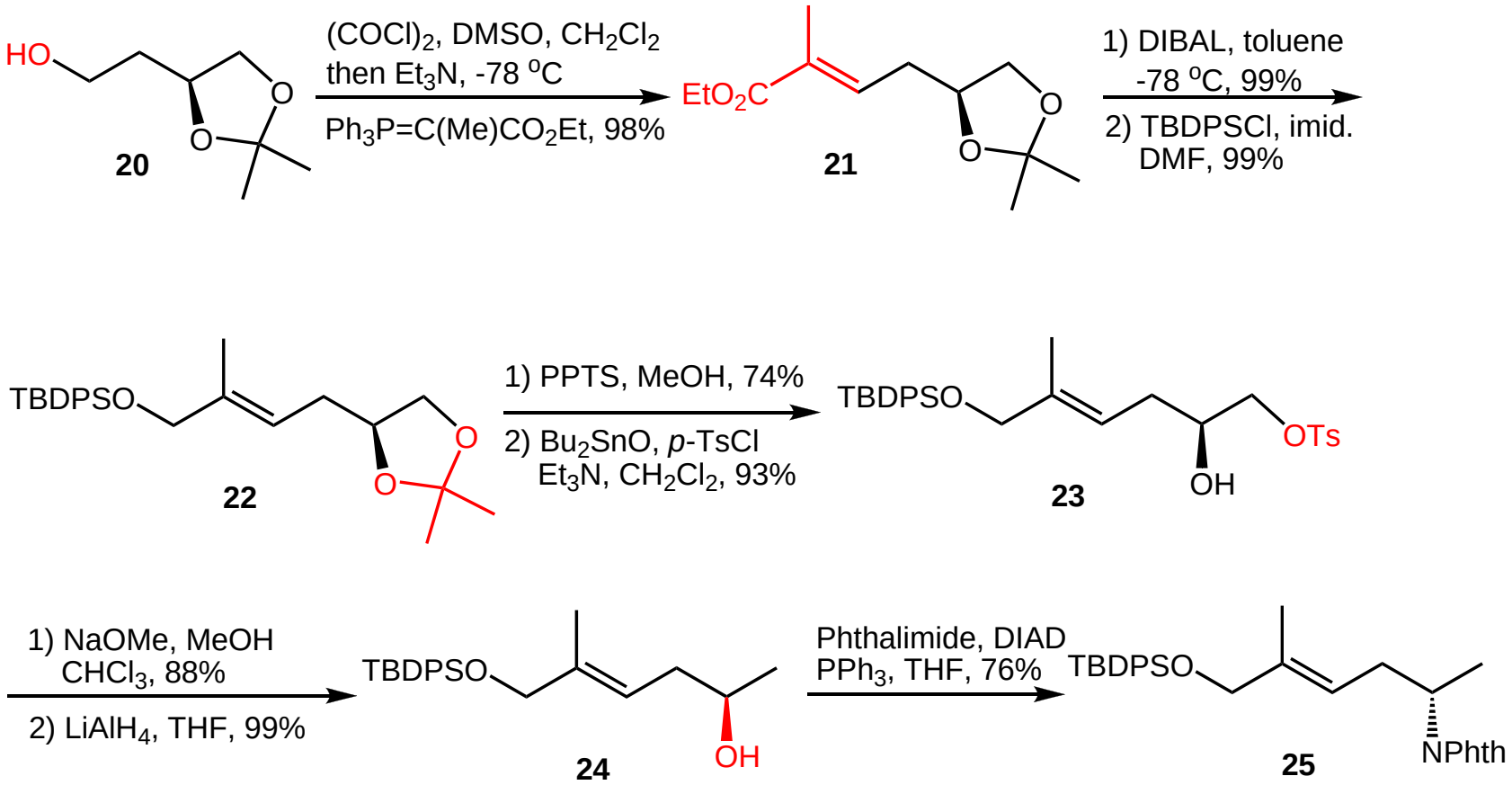
THF, 0 ^oC to rt, 1 h, 82%

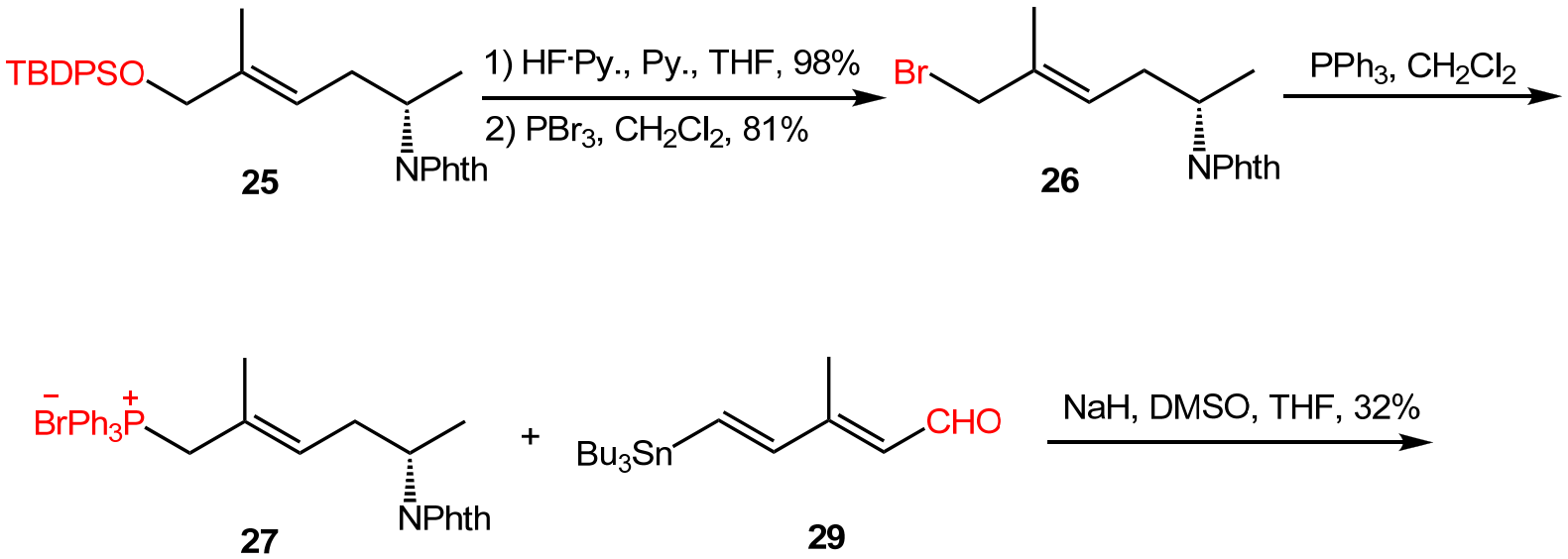


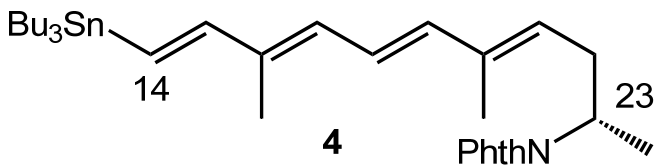
3

C1 - C13 subunit

Synthesis of C14-C23 Subunit **4**

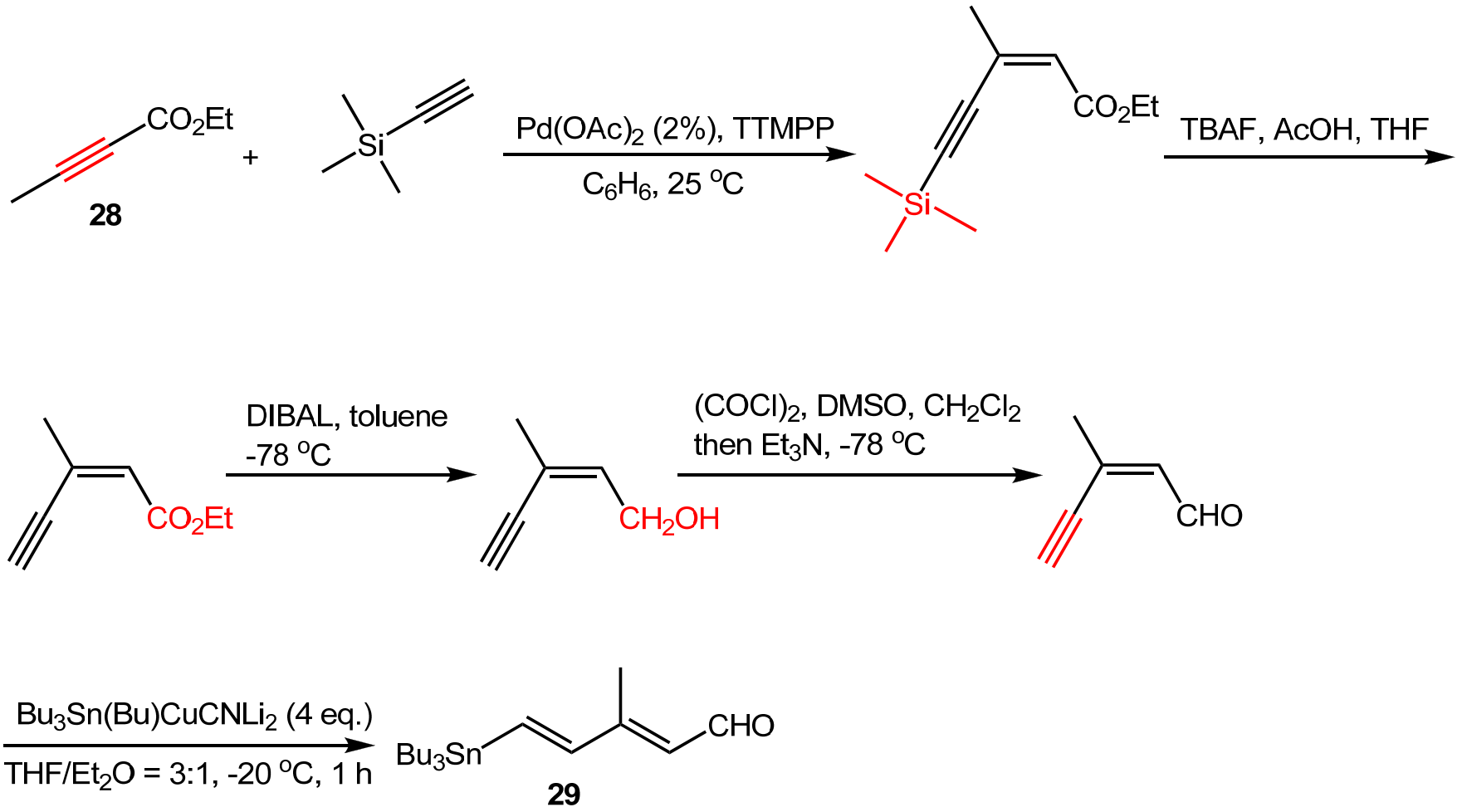




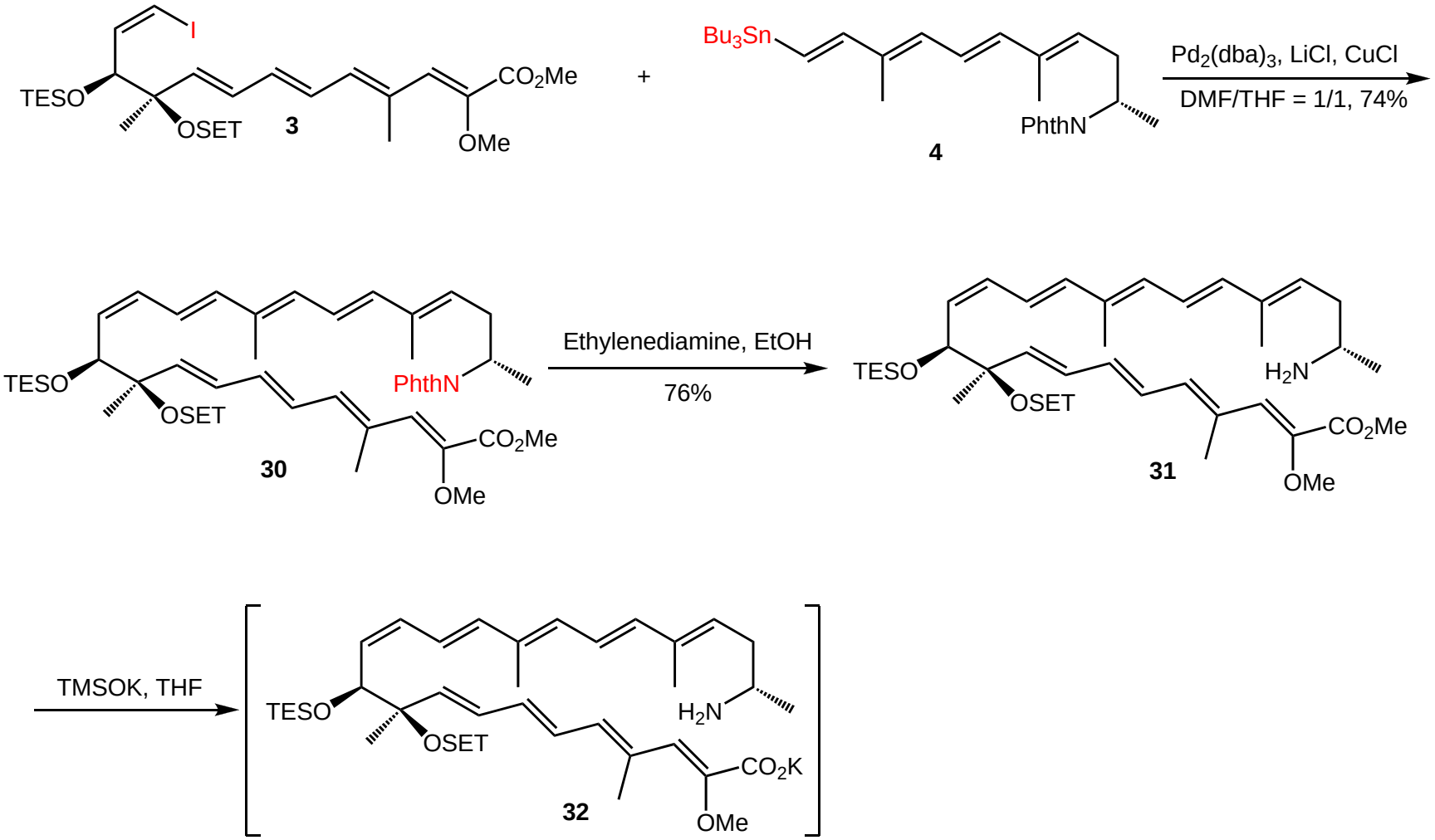


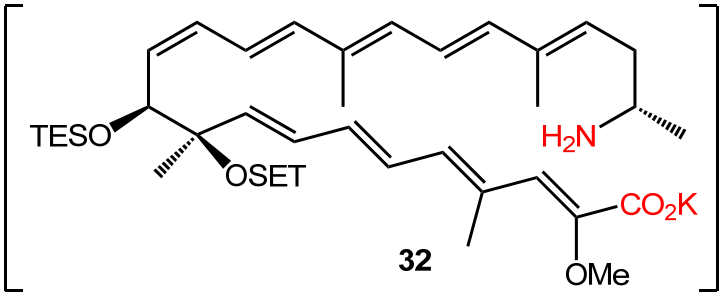
C14 - C23 subunit

Synthesis of the **29**



Total Synthesis of the Incednam (1)

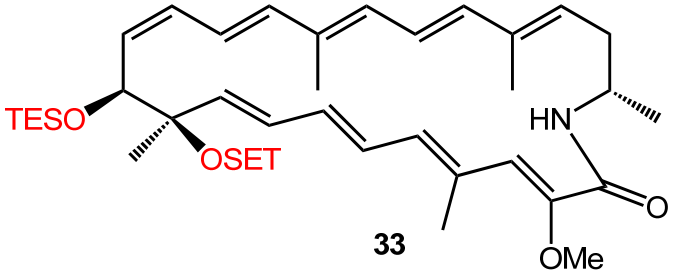




32

DMT-MM, Et_3N, MeOH

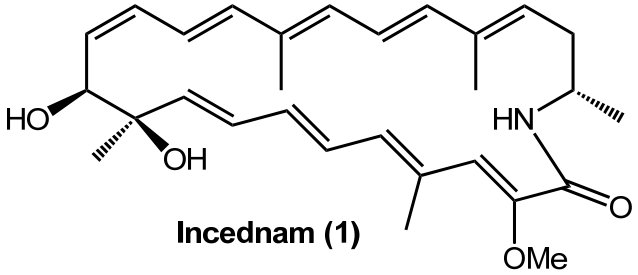
27% (2 steps)



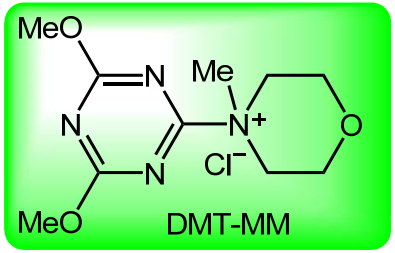
33

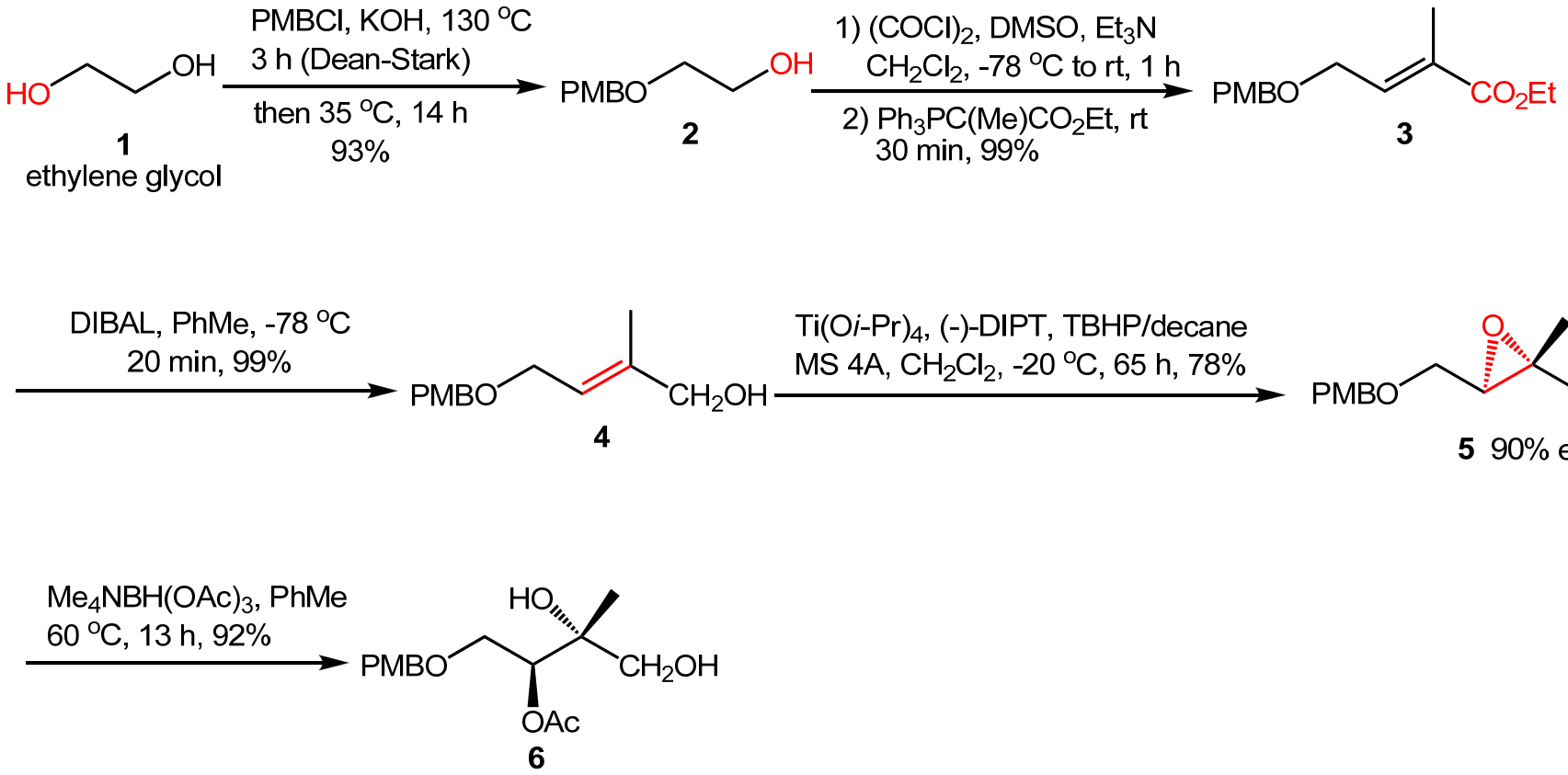
TBAF, AcOH, THF

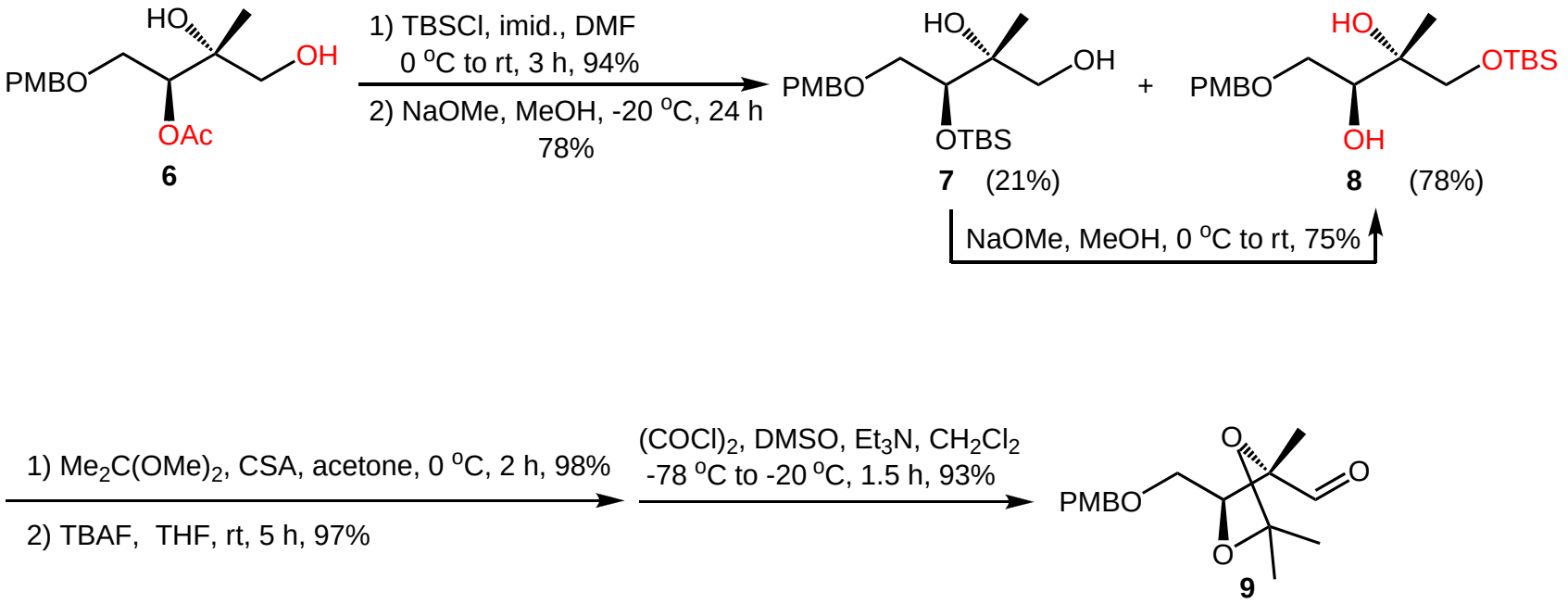
87%

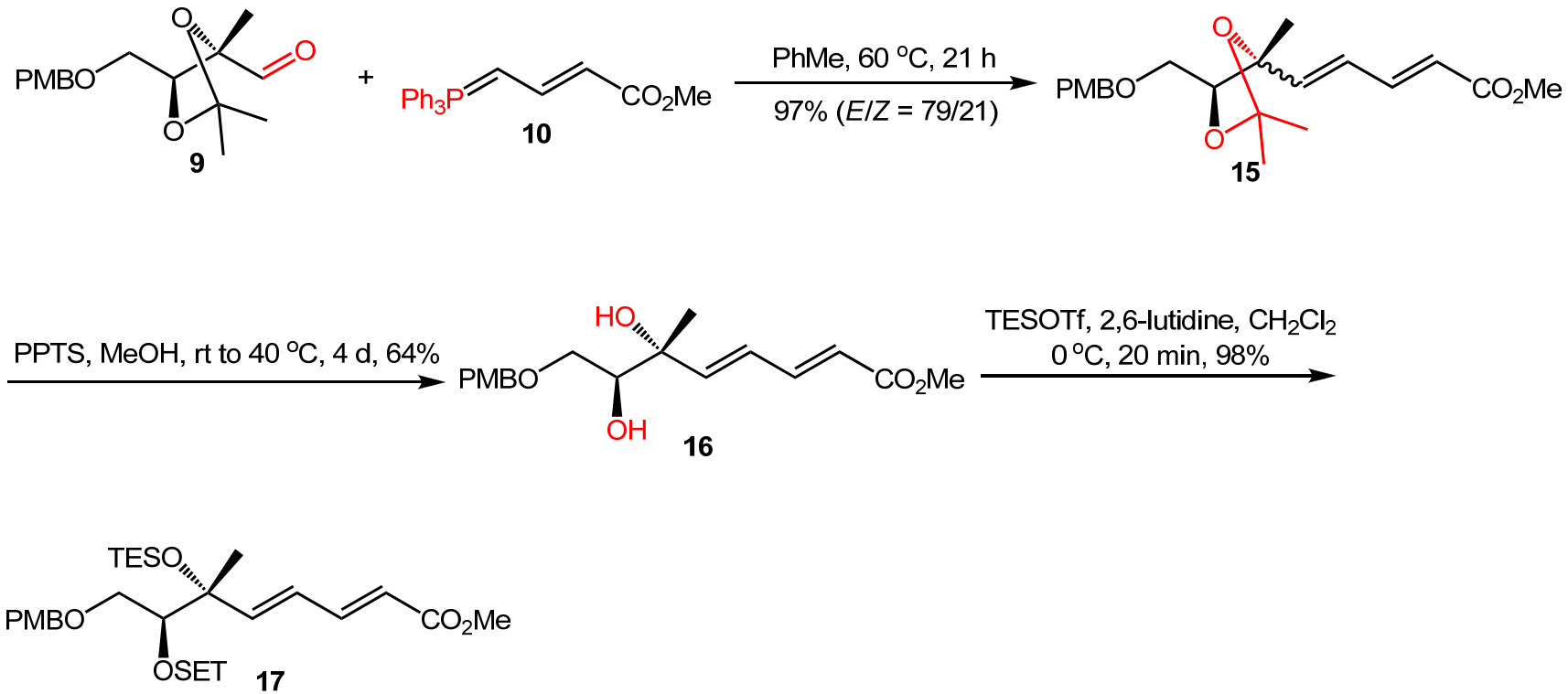


Incednam (1)




PMBCl, KOH, 130 °C
3 h (Dean-Stark)
then 35 °C, 14 h
93%
1
ethylene glycol
2
1) (COCl)2, DMSO, Et3N
CH2Cl2, -78 °C to rt, 1 h
2) Ph3PC(Me)CO2Et, rt
30 min, 99%
3
DIBAL, PhMe, -78 °C
20 min, 99%
4
Ti(Oi-Pr)4, (-)-DIPT, TBHP/decane
MS 4A, CH2Cl2, -20 °C, 65 h, 78%
5 90% ee
Me4NBH(OAc)3, PhMe
60 °C, 13 h, 92%
6


HO
PMBO
OH
OAc
6
1) TBSCl, imid., DMF
0 °C to rt, 3 h, 94%
2) NaOMe, MeOH, -20 °C, 24 h
78%
HO
PMBO
OH
OTBS
7 (21%)
+
HO
PMBO
OTBS
OH
8 (78%)
NaOMe, MeOH, 0 °C to rt, 75%
1) Me2C(OMe)2, CSA, acetone, 0 °C, 2 h, 98%
2) TBAF, THF, rt, 5 h, 97%
(COCl)2, DMSO, Et3N, CH2Cl2
-78 °C to -20 °C, 1.5 h, 93%
O
O
PMBO
O
9


PMBO
O
O
O
9
+
Ph3P
CO2Me
10
PhMe, 60 °C, 21 h
97% (E/Z = 79/21)
PMBO
O
O
CO2Me
15
PPTS, MeOH, rt to 40 °C, 4 d, 64%
HO
PMBO
OH
CO2Me
16
TESOTf, 2,6-lutidine, CH2Cl2
0 °C, 20 min, 98%
TESO
PMBO
OSET
CO2Me
17

Incednam (**1**) is the aglycon of the 24-membered macrolactam glycoside antibiotic incednine (**2**), which was isolated from *Streptomyses* sp. in 2008. It was demonstrated that **2** exhibits significant inhibitory activity against the antiapoptotic oncoproteins Bcl-2 and Bcl-xL, with a mode of action distinctly different from those of other compounds that inhibit the binding capacity of Bcl-xL to the pro-apoptotic protein Bax. In addition, it is known that these proteins are overexpressed in many cancer cells, resulting in the expansion of a transformed population and the advancement of the multidrug-resistant stage. Although **1** was also isolated from *Streptomyses* sp., its semisynthesis from **2** has not been realized, in part, because of the inherent chemical instabilities mentioned above. Furthermore, the stereochemical configuration at C23 was postulated on the basis of computational modeling studies, thus the configuration has not been conclusively defined. Because of its important biologicalactivity and novel molecular architecture, **1** and **2** were considered to be prime targets for chemical synthesis. Herein we report the first total synthesis of **1** leading to the unambiguous stereochemical assignment of the configuration at C23.

In conclusion, we have developed a convergent synthetic route to incednam (**1**), which is the aglycon of the 24- membered macrolactam glycoside antibiotic incednine (**2**). Furthermore, this synthesis serves to unambiguously define the stereochemical configuration at C23 in **1**. Additional studies with respect to the total synthesis of incednine (**2**) from **1** are currently underway in our laboratory.