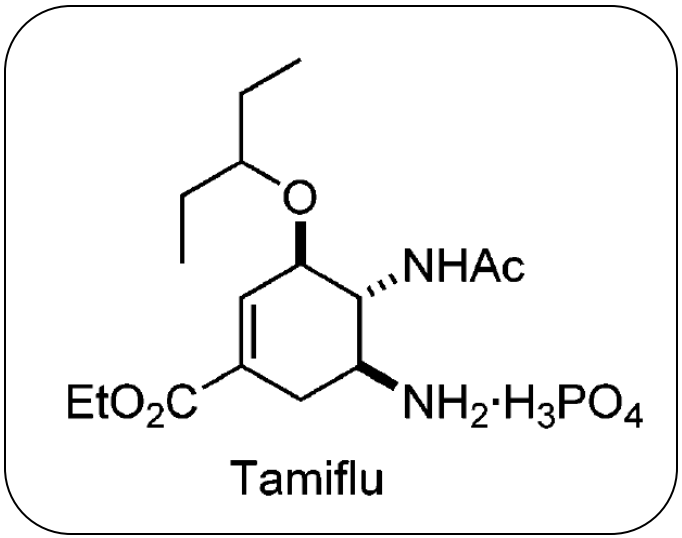
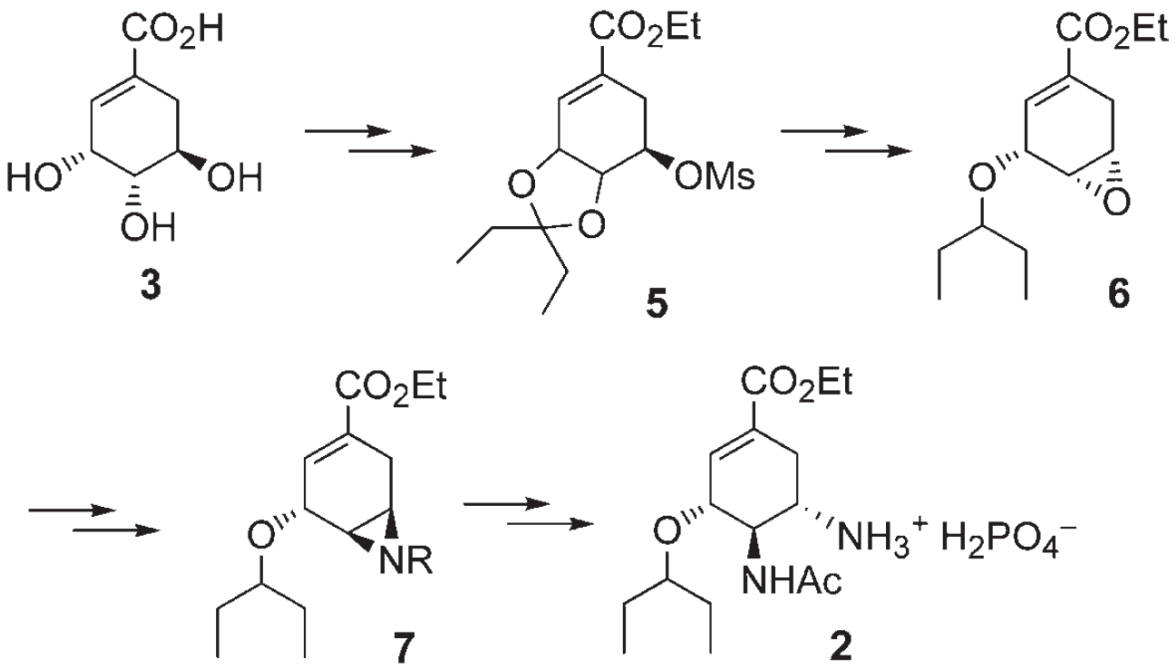
A Practical Synthesis of (-)-Oseltamivir



Tamiflu

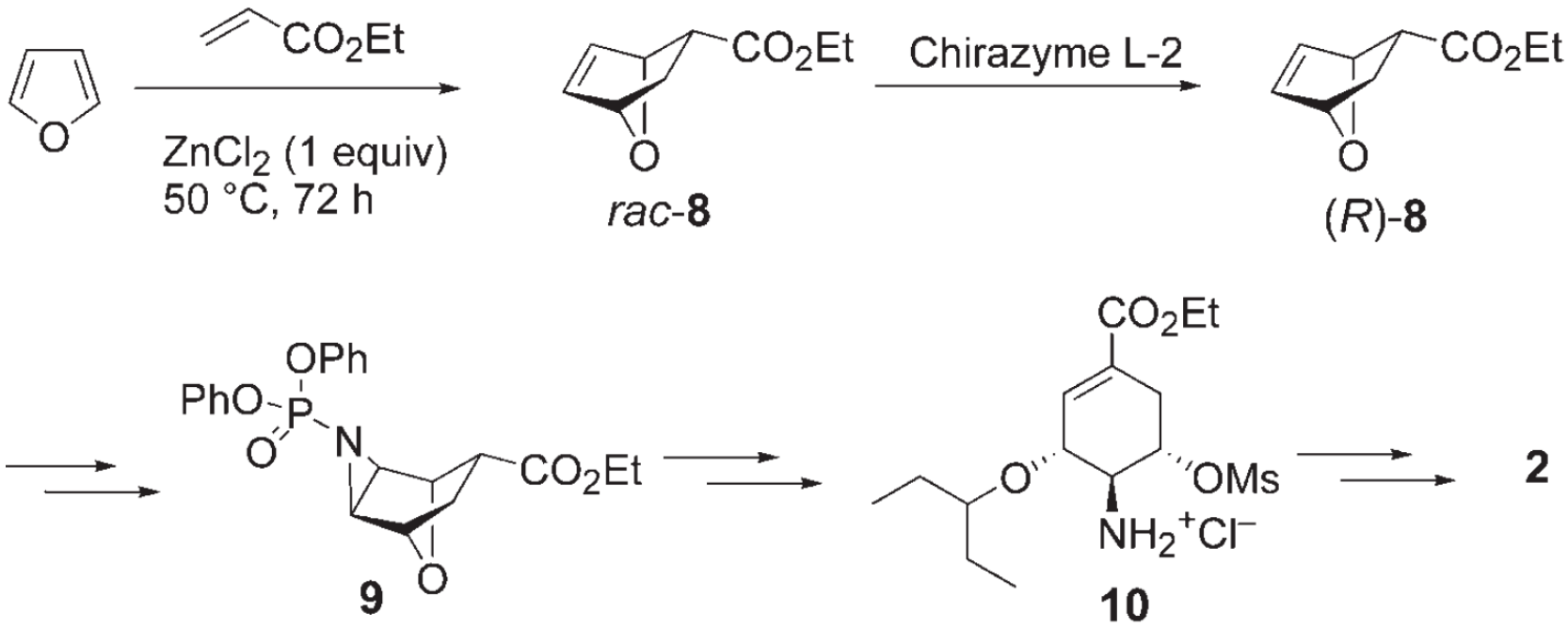
Nobuhiro Satoh, Takahiro Akiba, Satoshi Yokoshima, Tohru Fukuyama
Angew. Chem. Int. Ed. **2007**, 46, 5734

First generation approach to Tamiflu: current manufacturing process



Angew. Chem. Int. Ed. **2006**, 45, 7330

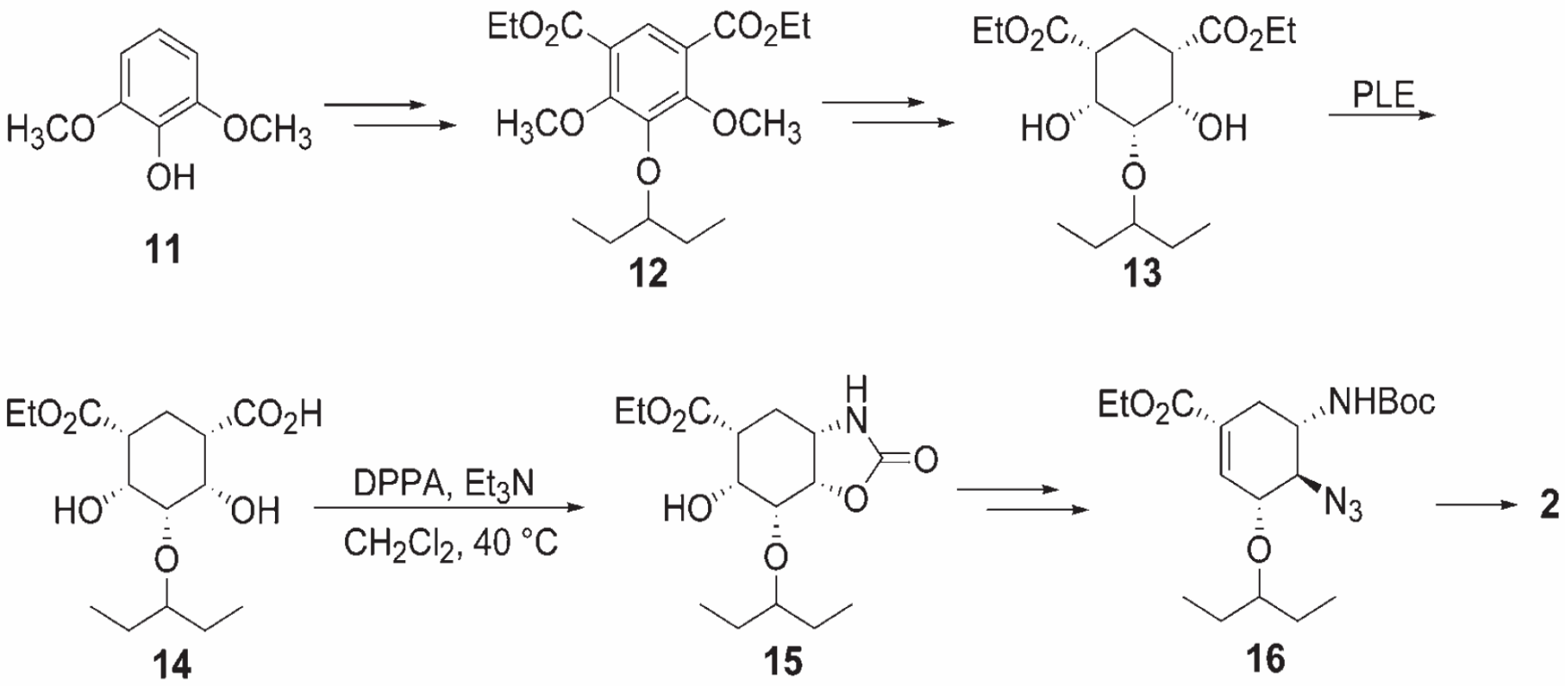
Second generation approach



Angew. Chem. Int. Ed. **2006**, 45, 7330

Several steps required high dilution.
The yield of enzymatic resolution step is 20%

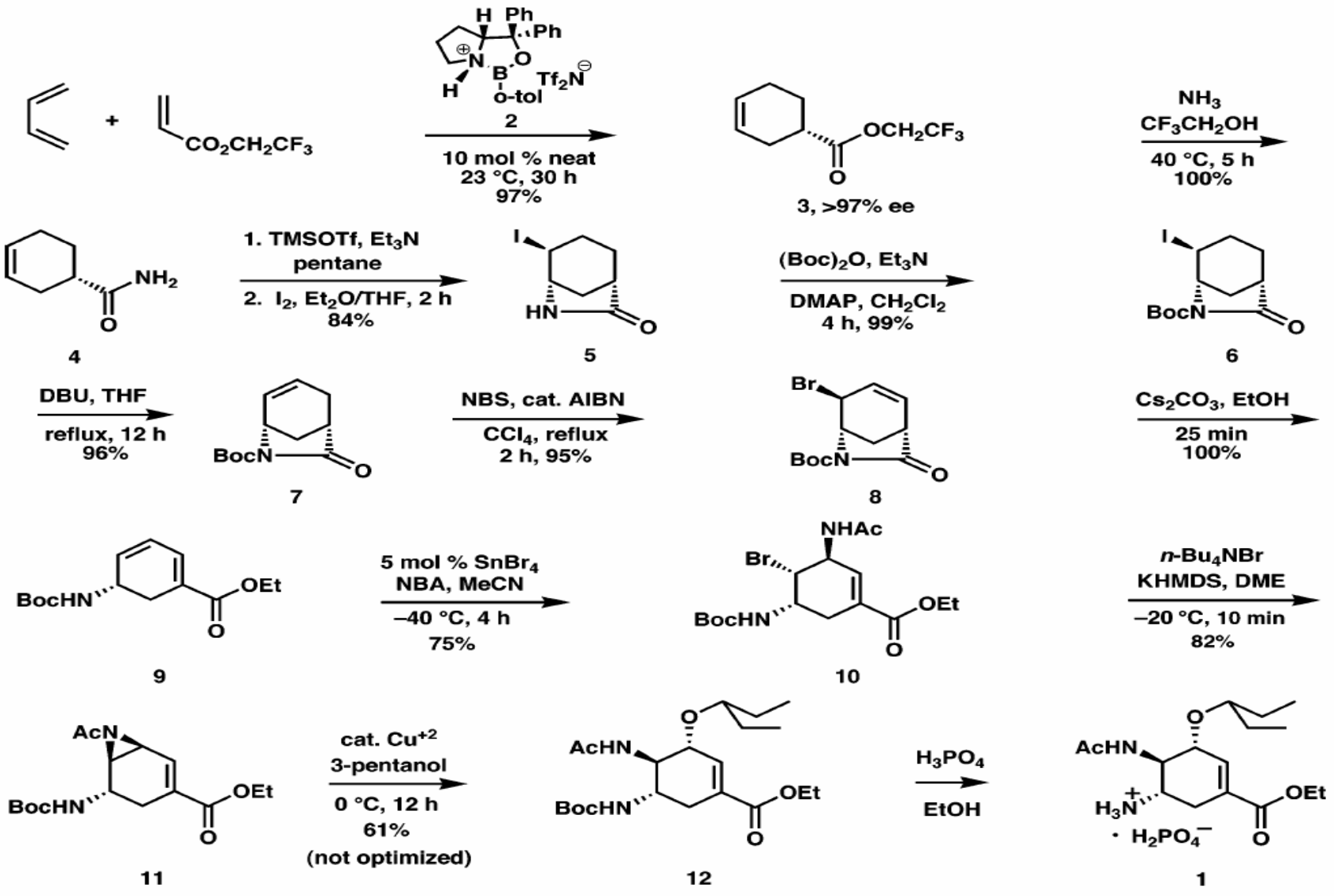
Desymmetrization approach to Oseltamivir



…still uses sodium azide….

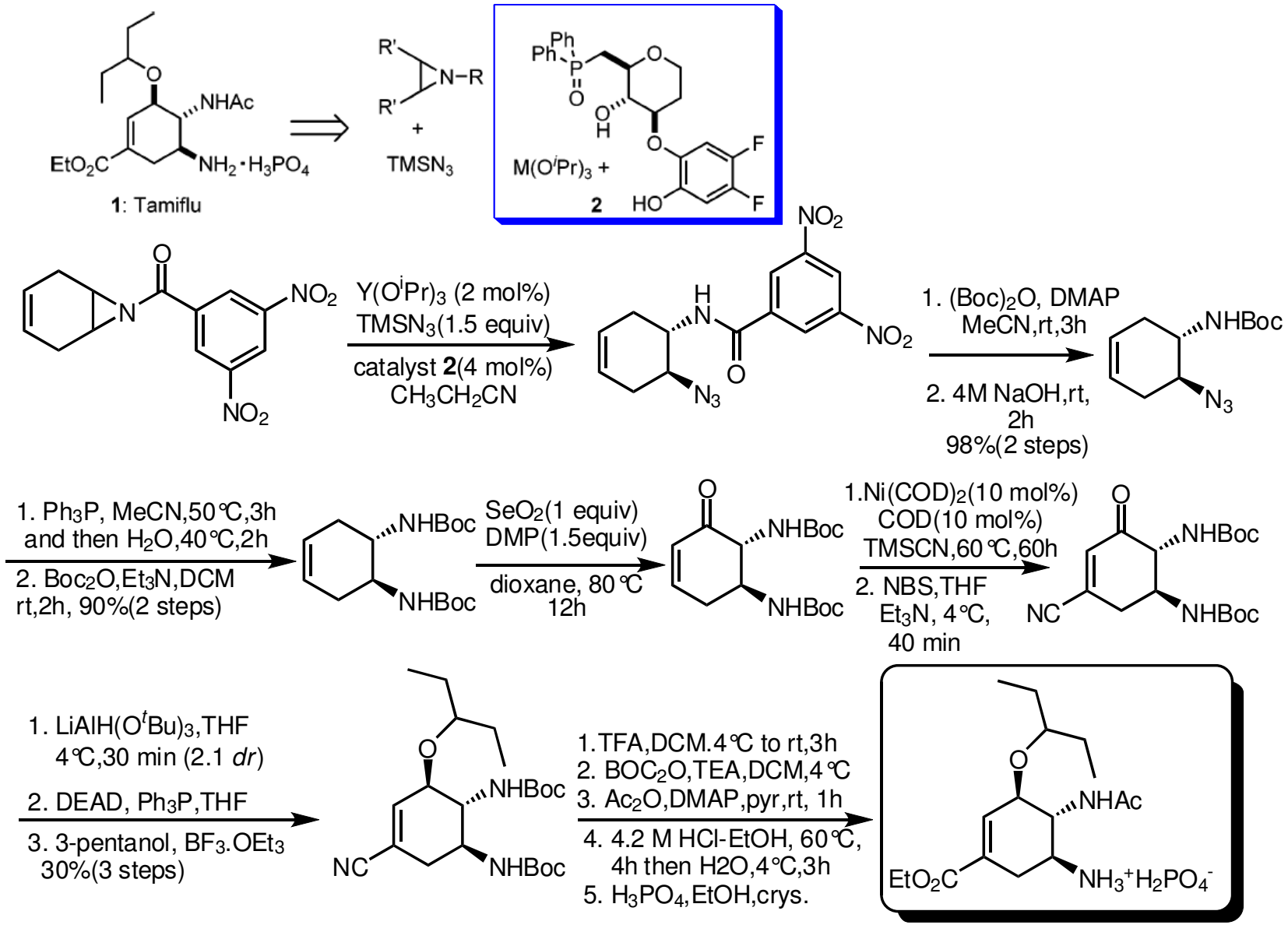
Angew. Chem. Int. Ed. **2006**, 45, 7330

Corey's approach



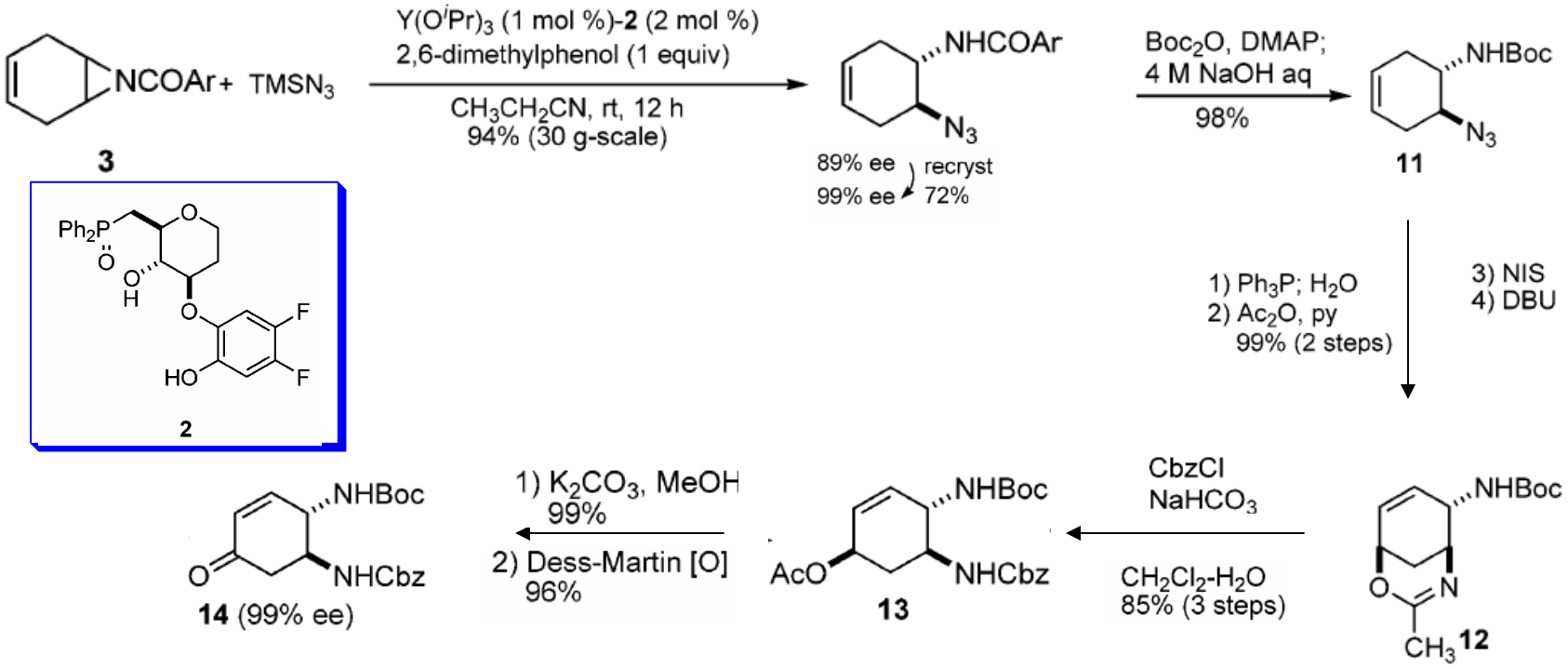
JACS, **2006**, 128, 6310

Shibasaki 1st approach



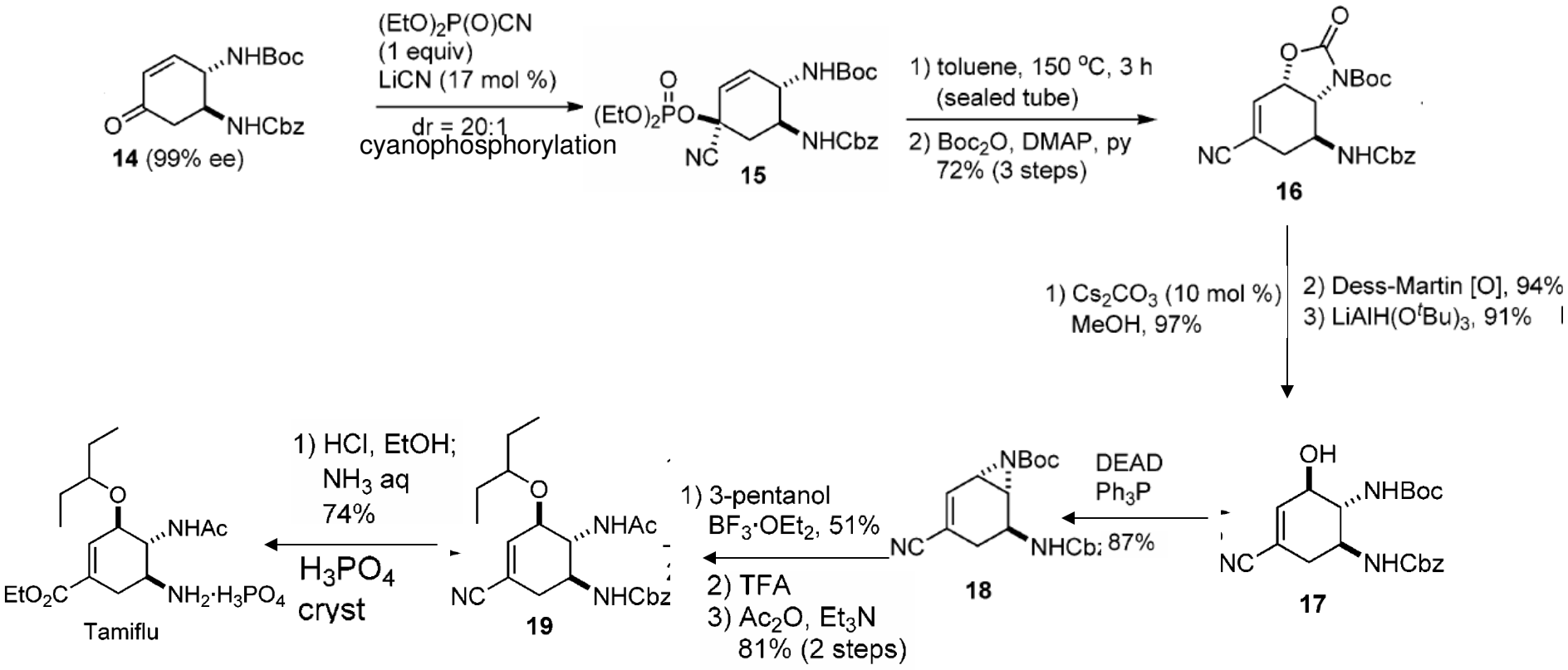
JACS, **2006**, 128, 6310

Shibasaki 2nd approach

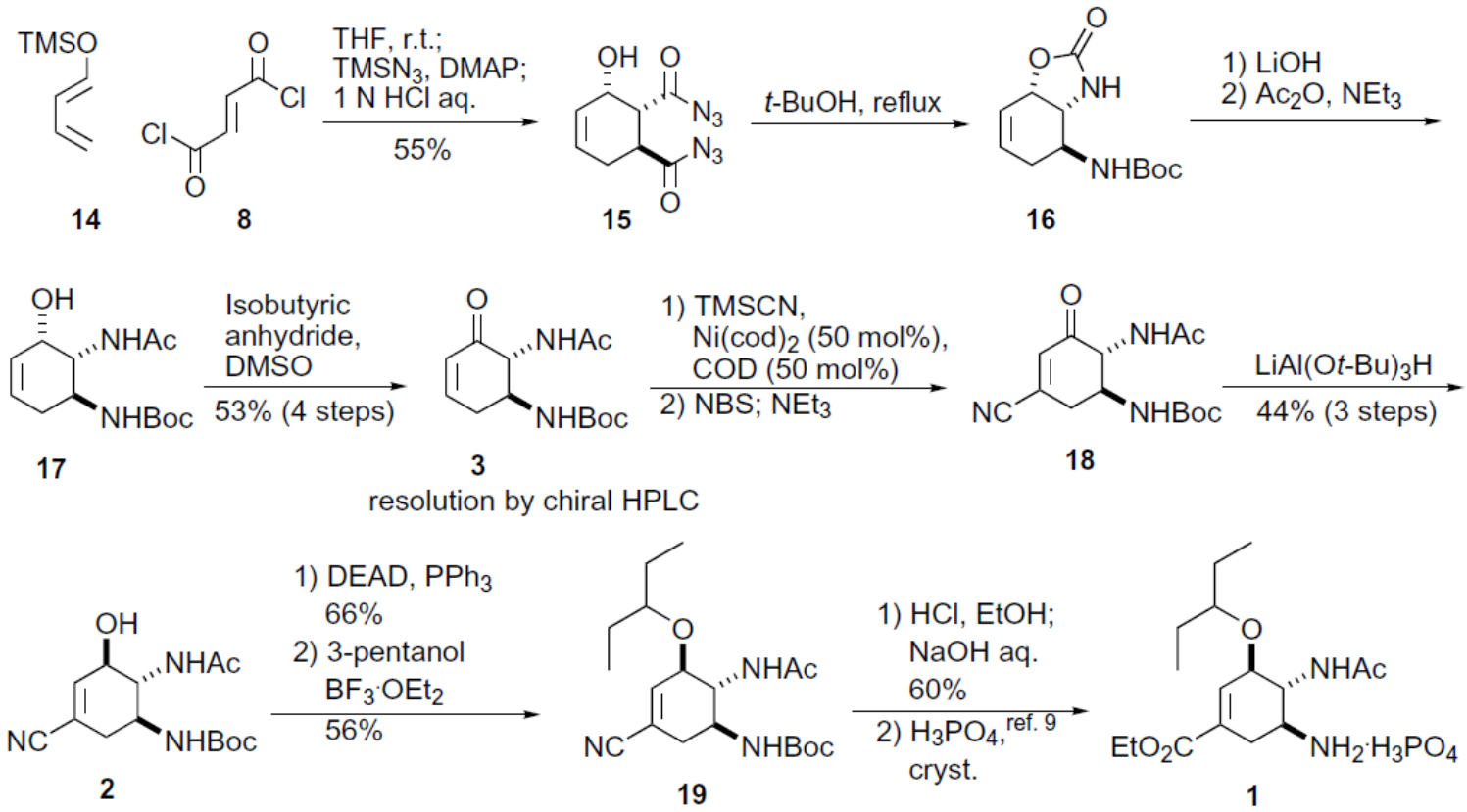


Org. Lett. **2007,** 9, 259

Shibasaki 2nd approach contd..

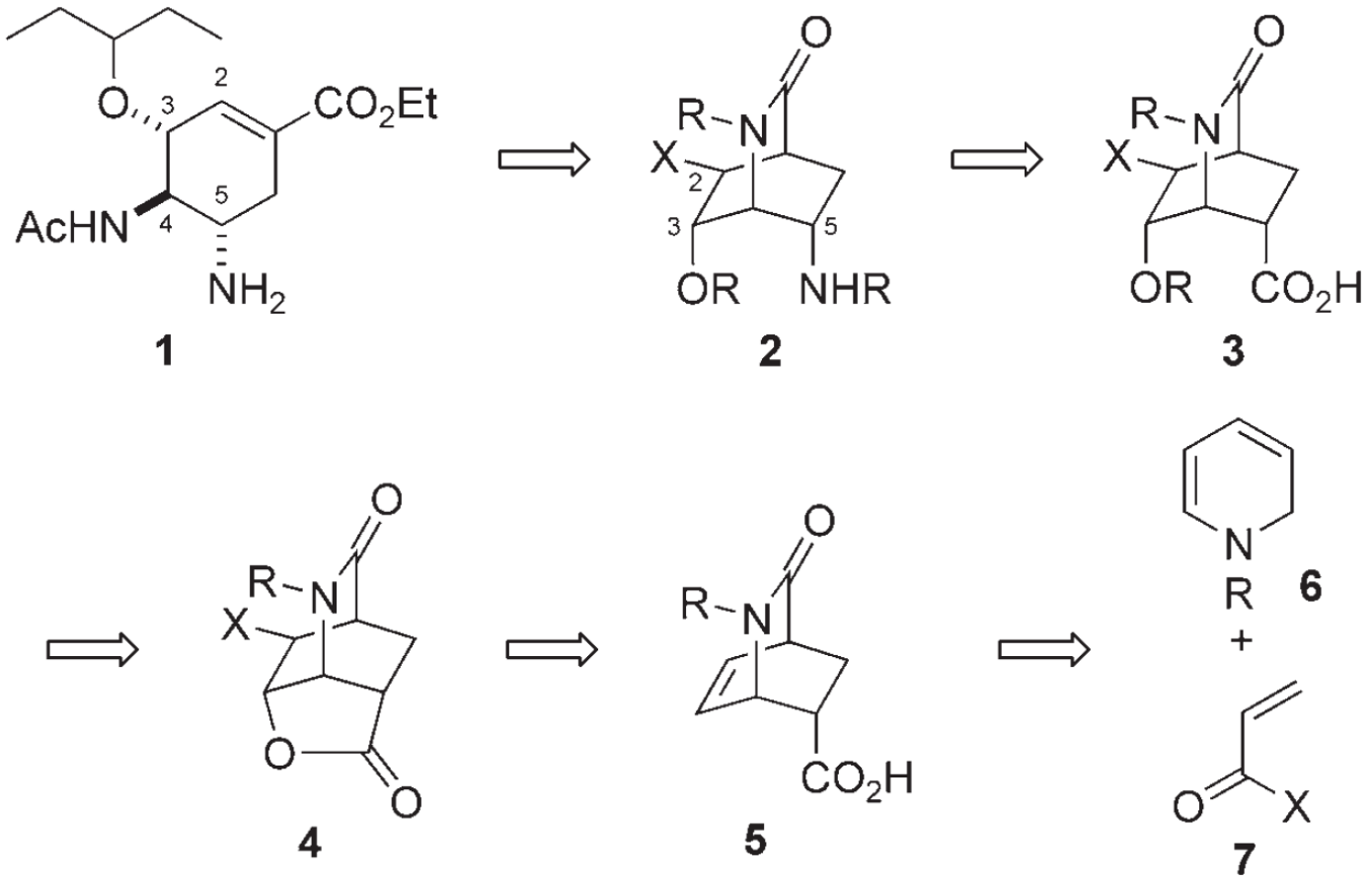


Shibasaki 3rd approach

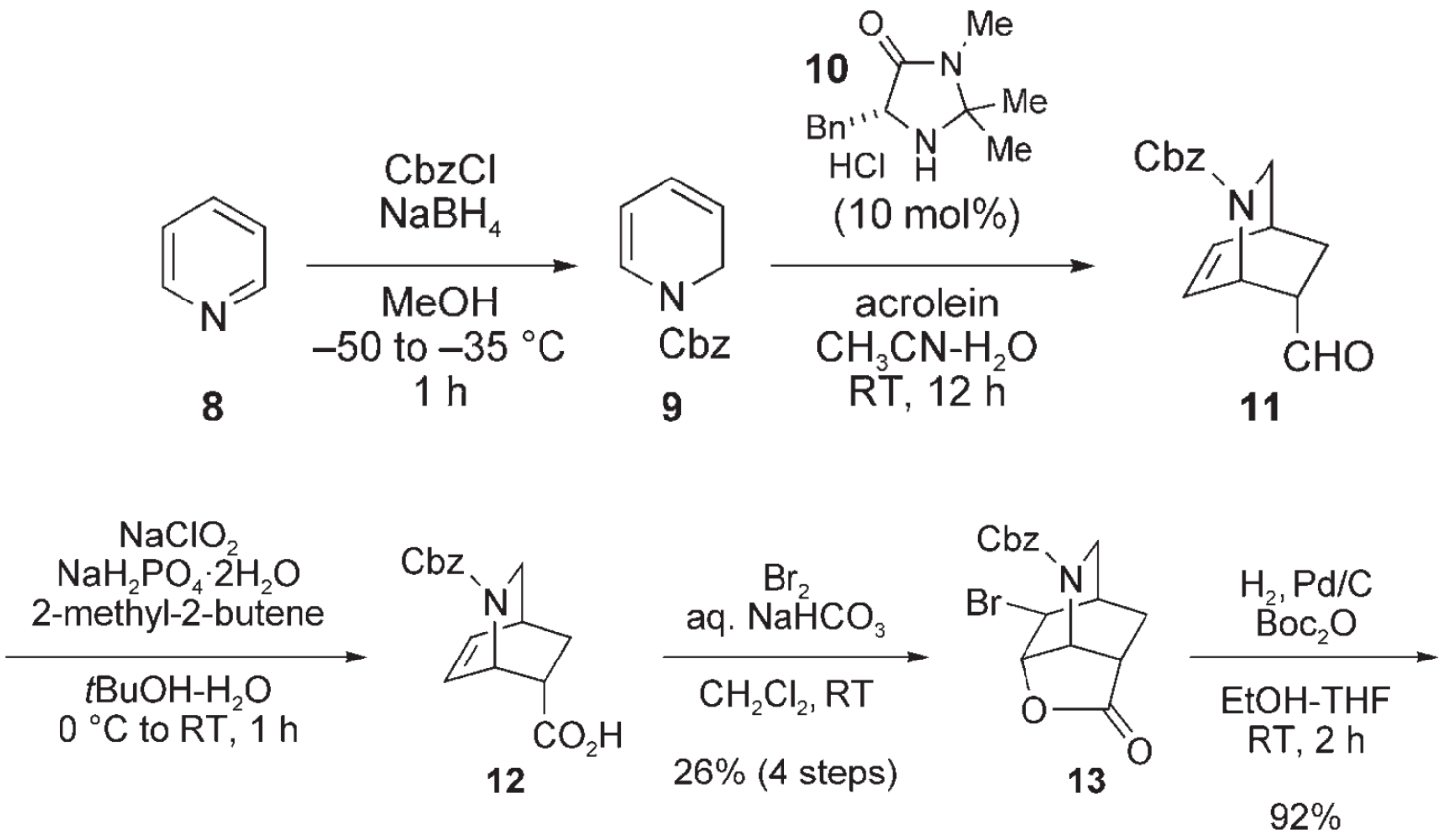


Tet. Lett. **2007**,48, 1403

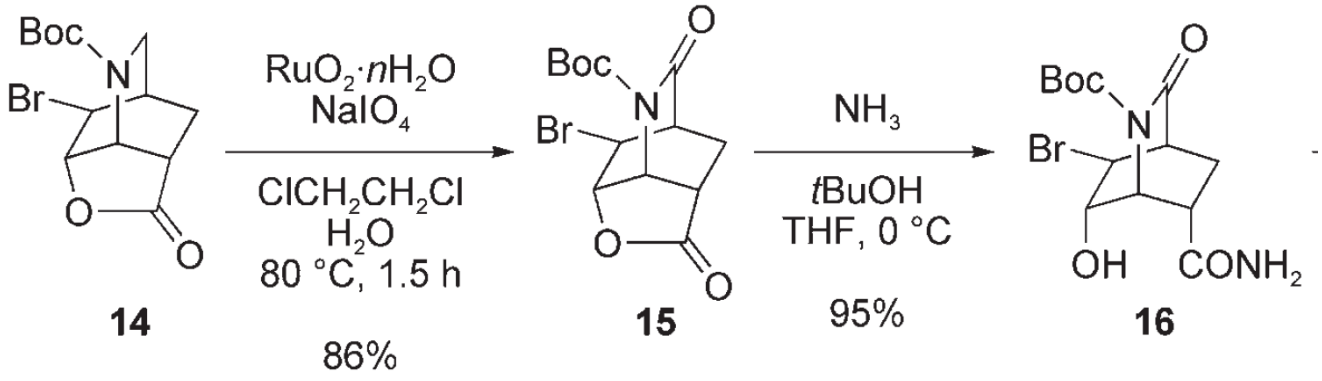
Fukuyama's approach: Retro-synthetic analysis

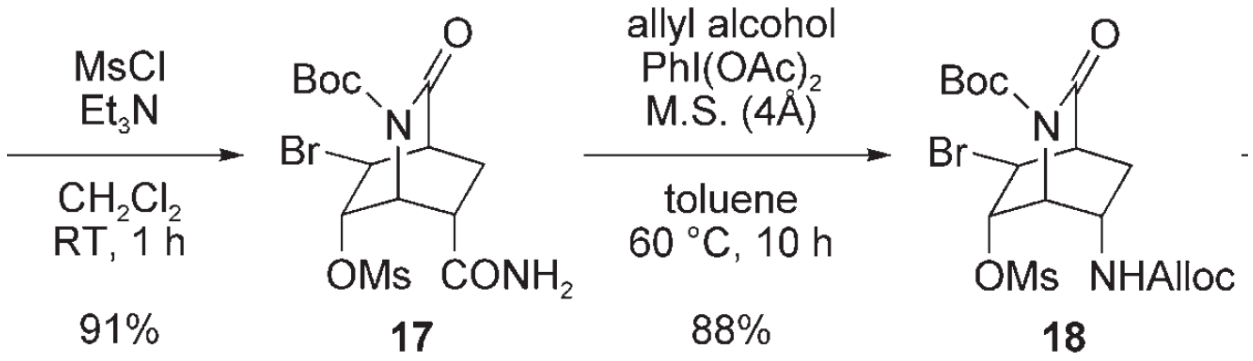


Synthesis

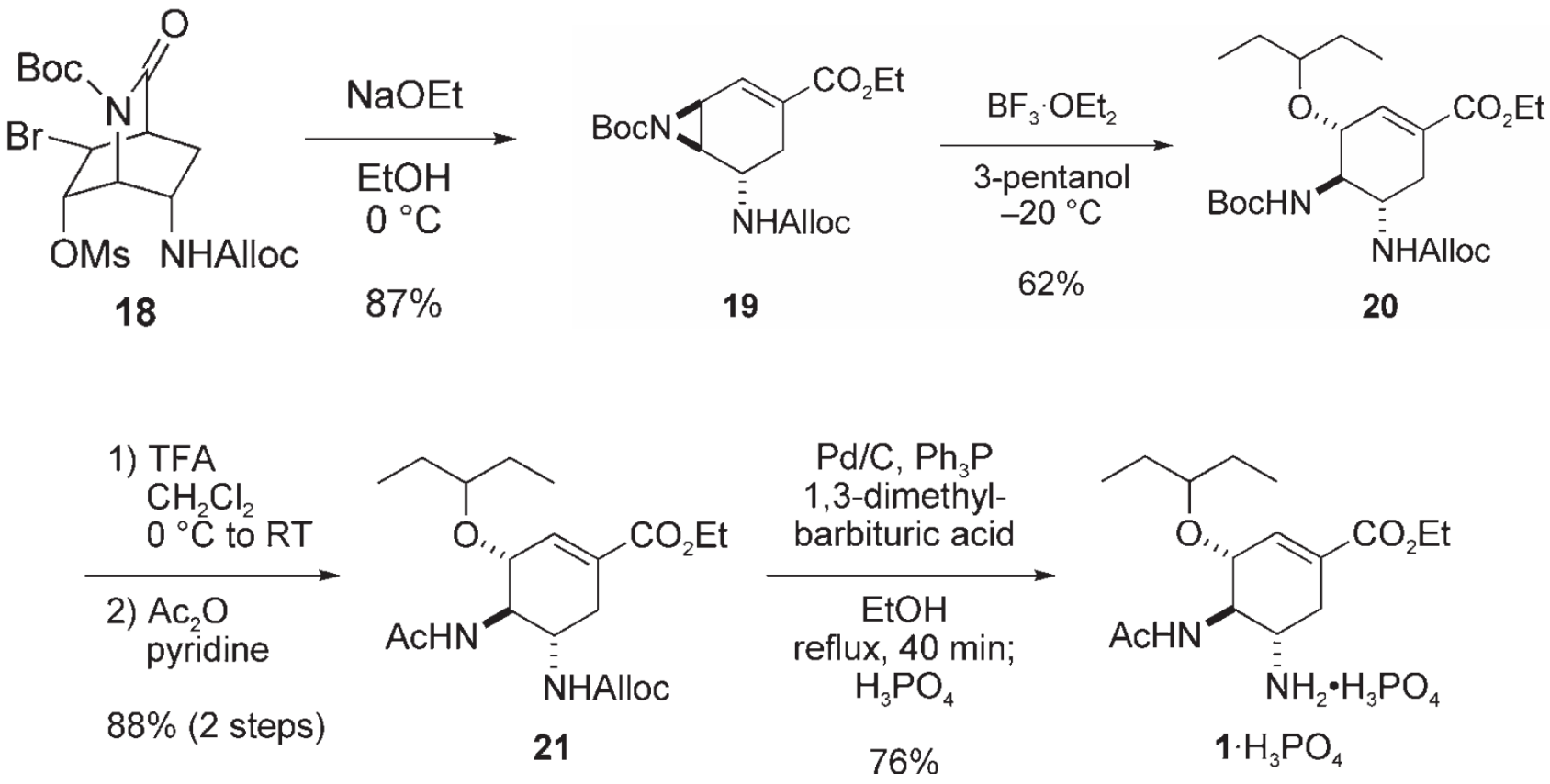

CbzCl
NaBH4
MeOH
–50 to –35 °C
1 h
8
9
Cbz
10
Me
Me
Me
Bn
HCl
(10 mol%)
acrolein
CH3CN-H2O
RT, 12 h
11
CHO
NaClO2
NaH2PO4·2H2O
2-methyl-2-butene
tBuOH-H2O
0 °C to RT, 1 h
12
CO2H
Br2
aq. NaHCO3
CH2Cl2, RT
26% (4 steps)
13
Br
H2, Pd/C
Boc2O
EtOH-THF
RT, 2 h
92%

Synthesis contd..





Synthesis contd..



Conclusion

- They employed inexpensive and commonly used reagents.
- Overall yield of lactone 13 from benzyl chloroformate was low, but the intermediate can be obtained as crystals on large scale.
- Other reactions proceed in high yield
- This synthesis begins with a readily available starting material as compare to shikimic acid.
- This route has great potential to synthesize tamiflu derivatives.