Enantioselective Synthesis of Pactamycin, a Complex Antitumor Antibiotic

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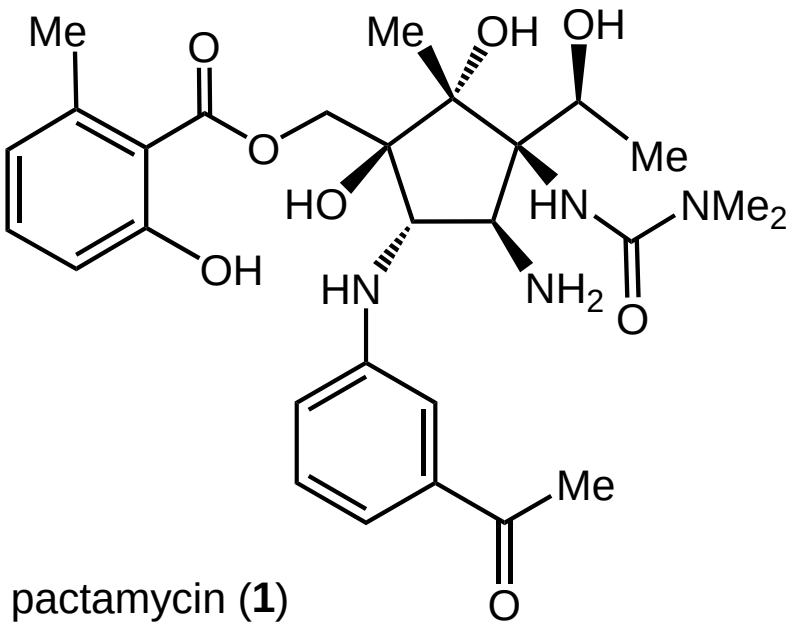
Checker: Ran-Ning Guo

Date: 2013/06/04

Johnson, J. S. et al *Science* **2013**, *340*, 180

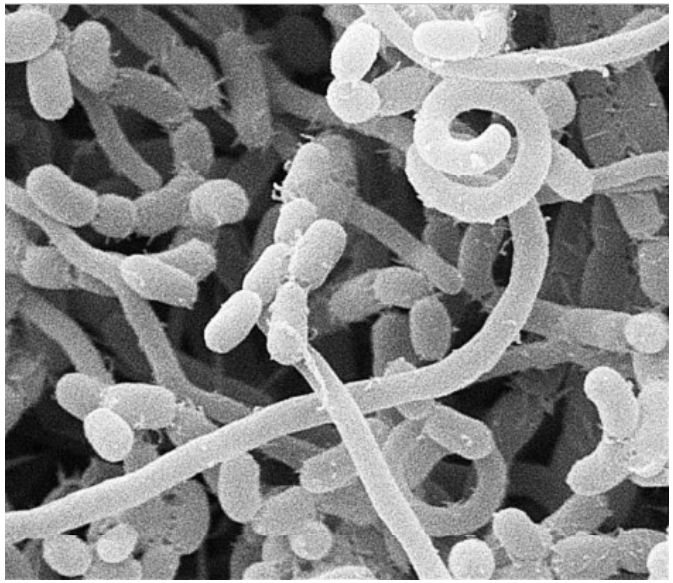
目录

1. 简介



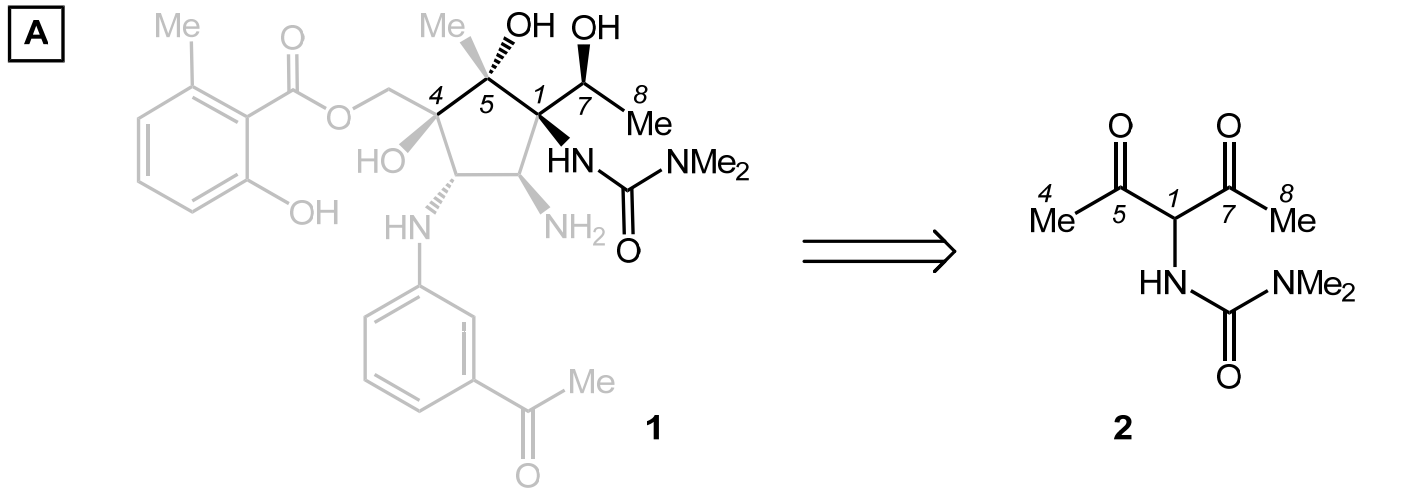
pactamycin (**1**)

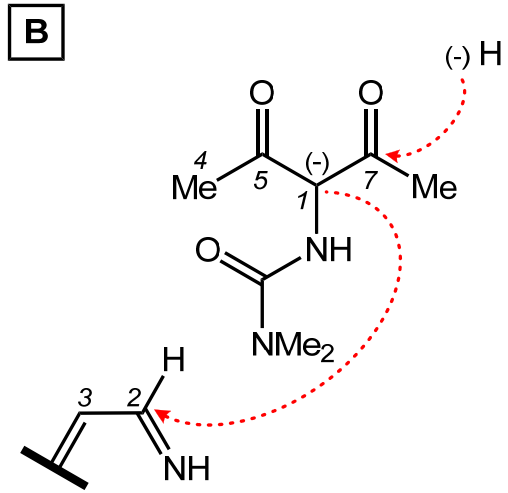
密旋霉素

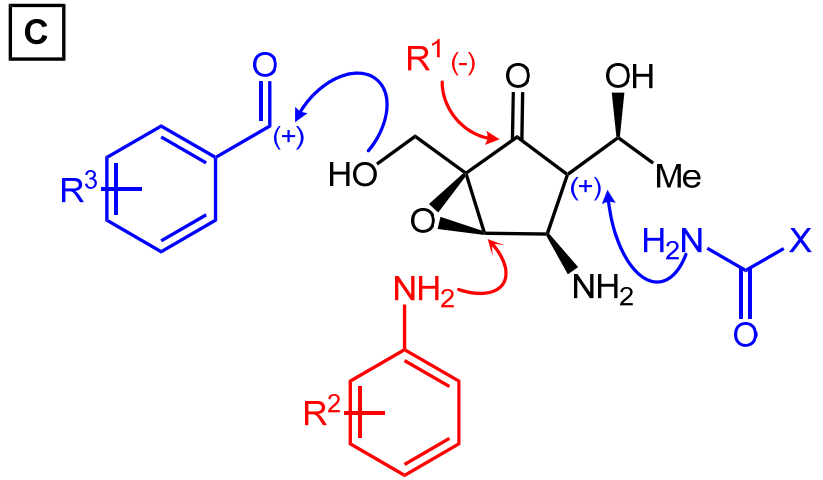


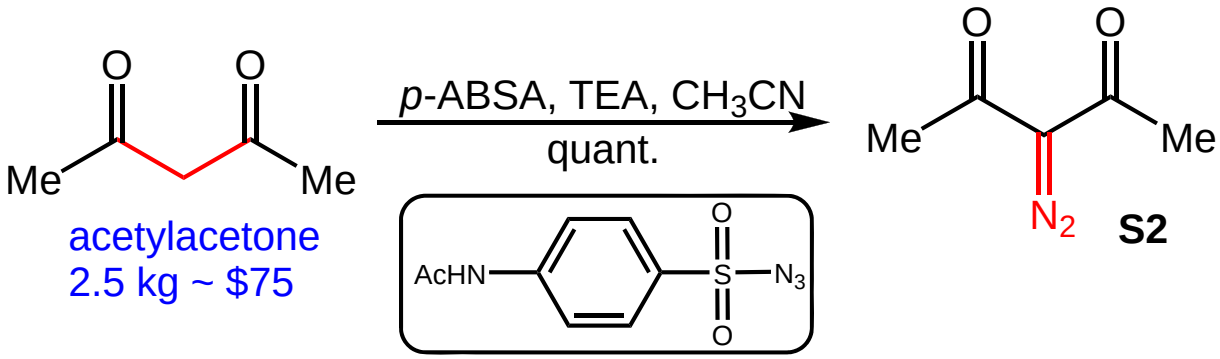
链霉菌

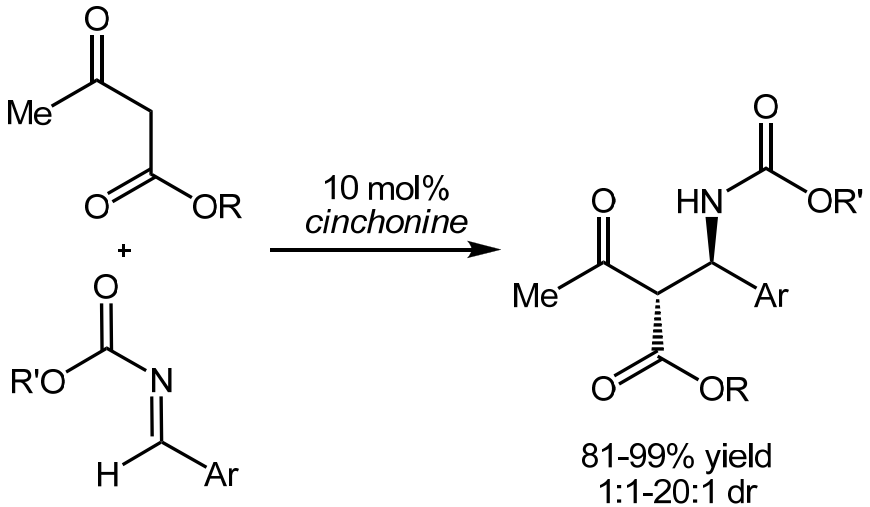
2. Johnson合成方法

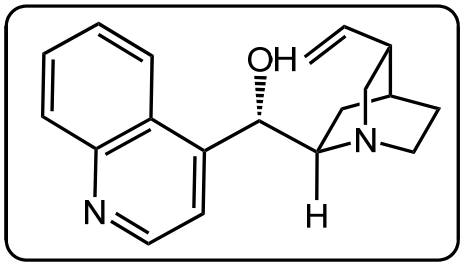


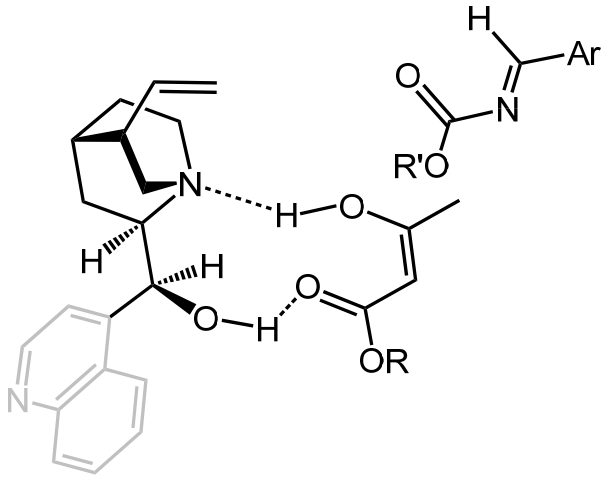




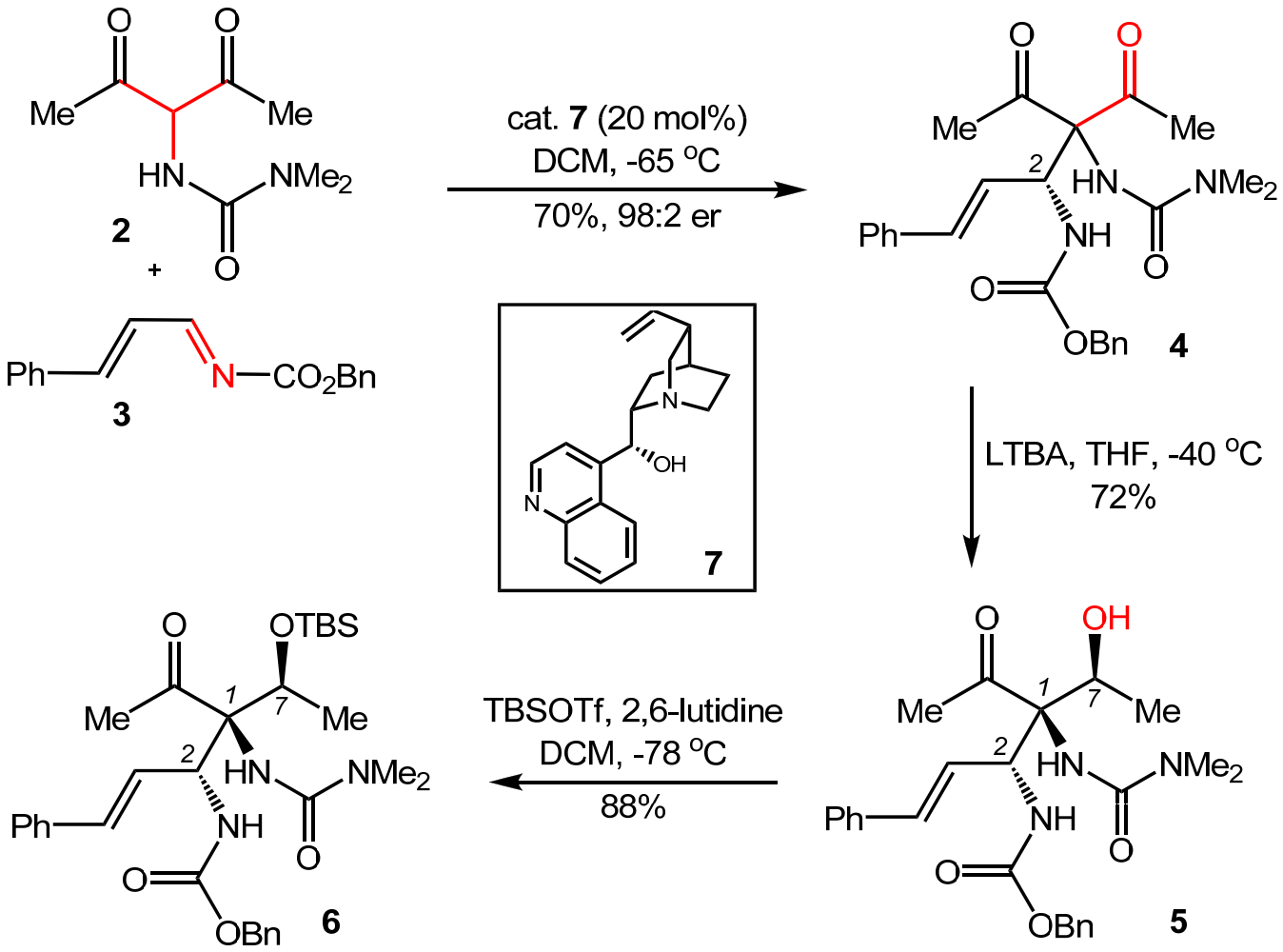

O
O
Me
Me
acetylacetone
2.5 kg ~ $75
p-ABSA, TEA, CH3CN
quant.
AcHN
S
N3
O
O
O
O
Me
Me
N2
S2
Rh2(Oct)4, Me2NCONH2
DCE/PhMe (1:1)
67%
O
O
Me
Me
HN
NMe2
O
2

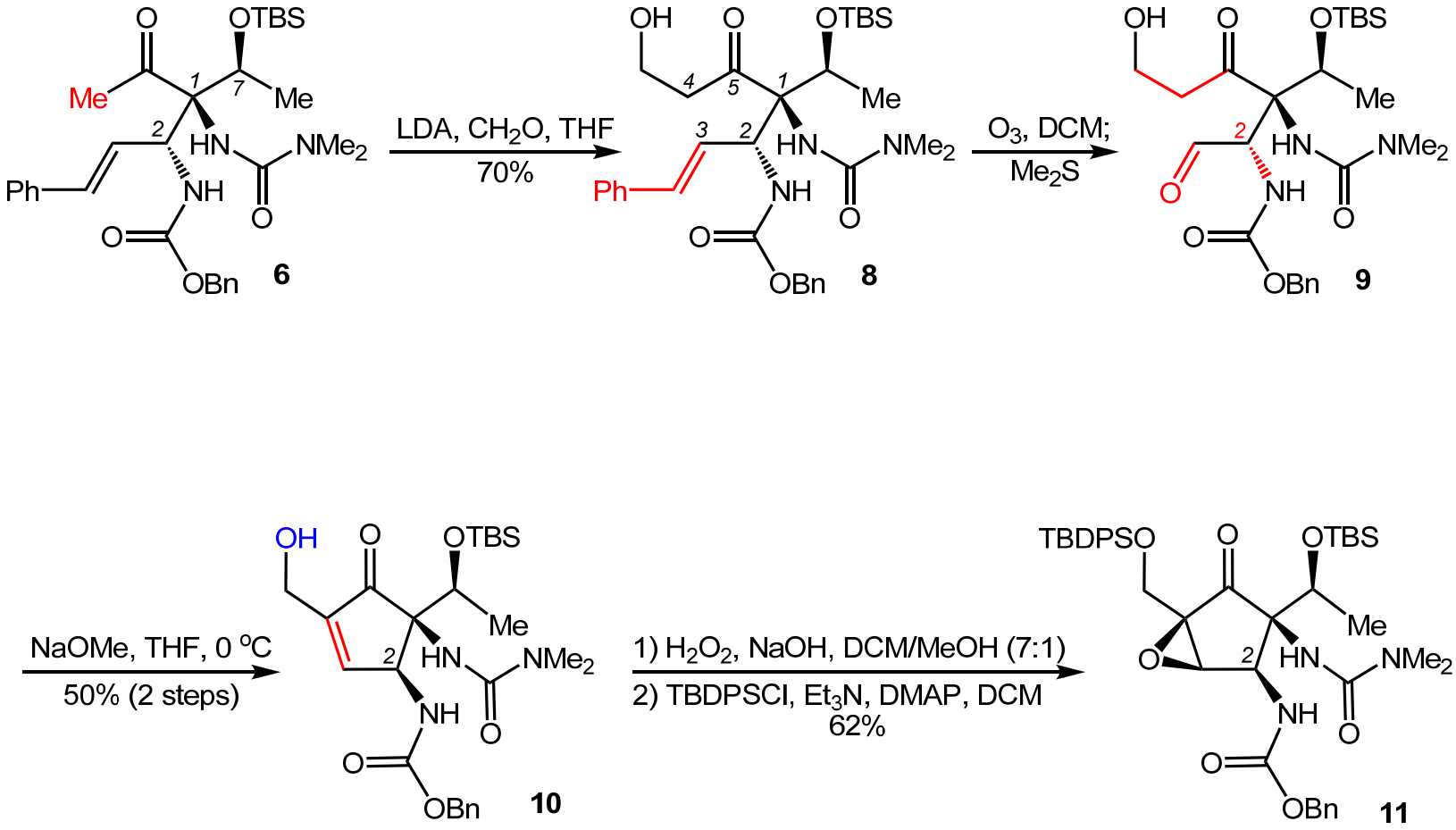


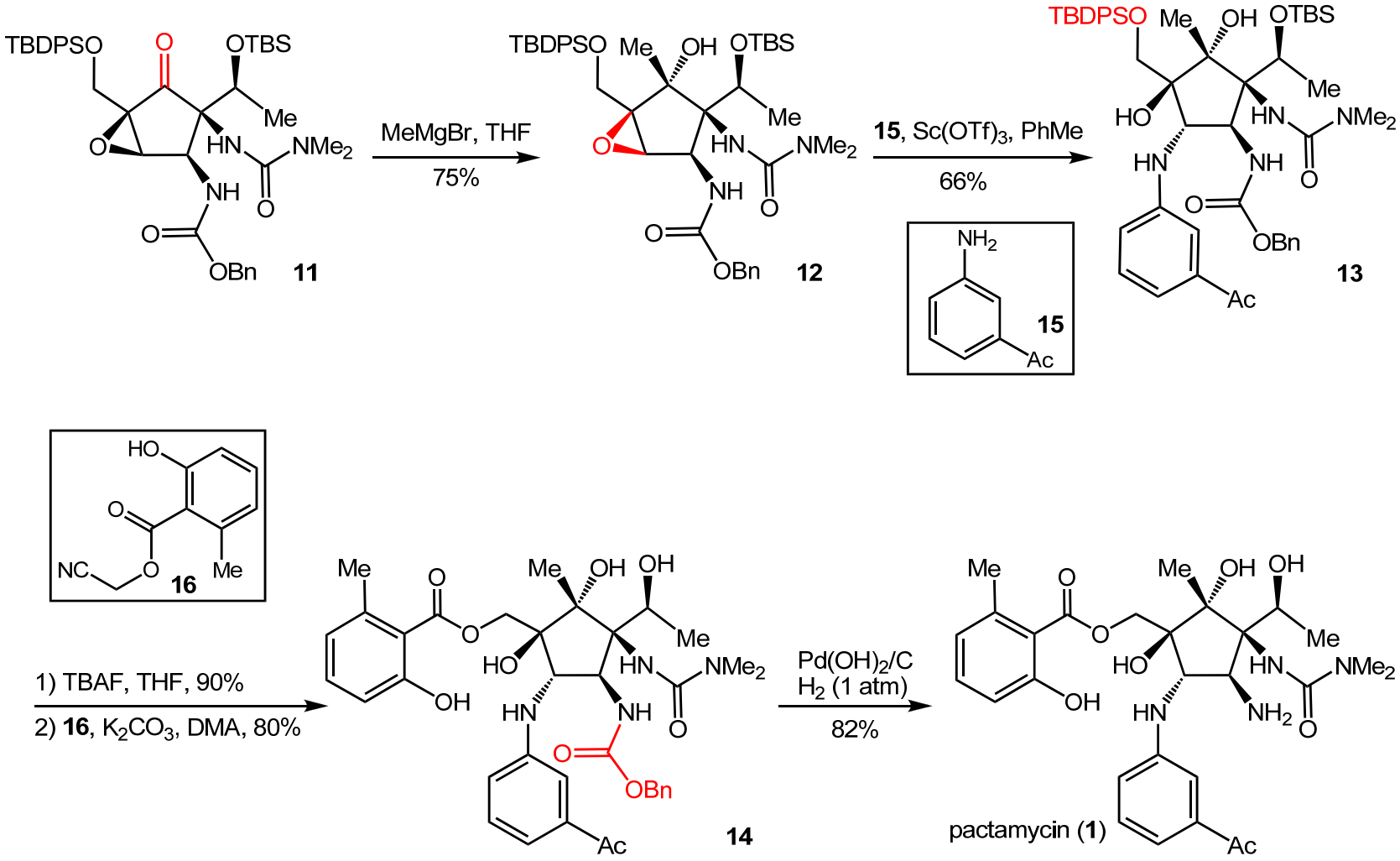




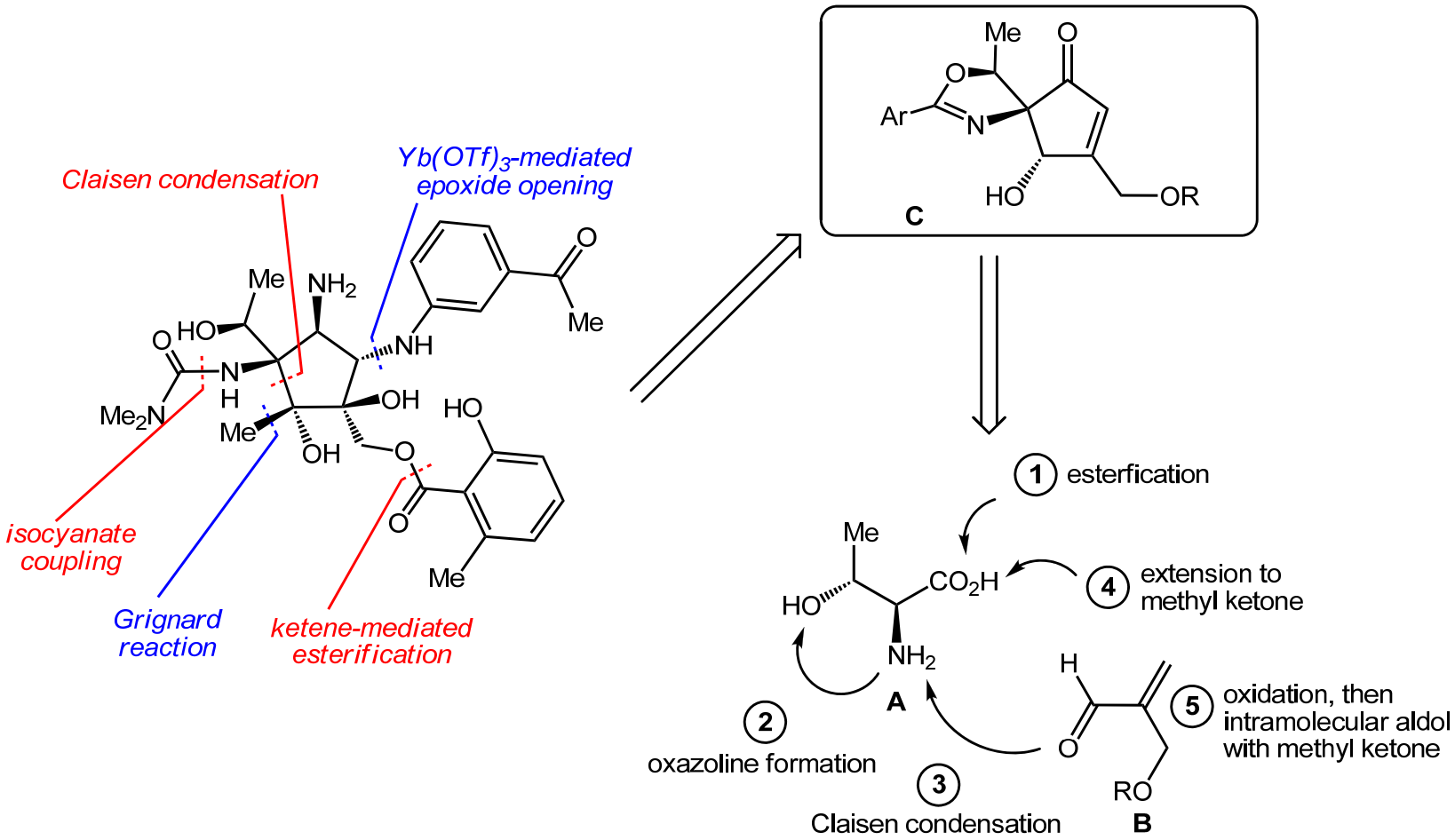
Schaus, S. E. et al *J. Am. Chem. Soc.* **2005**, *127*, 11256
Org. Lett. **2006**, *8*, 2003


Me
O
O
Me
HN
NMe2
O
2
+
Ph
N
CO2Bn
3
cat. 7 (20 mol%)
DCM, -65 °C
70%, 98:2 er
N
OH
N
7
Me
O
O
Me
2
HN
NMe2
Ph
NH
O
O
OBn
4
LTBA, THF, -40 °C
72%
Me
O
OH
1
7
Me
2
HN
NMe2
Ph
NH
O
O
OBn
5
TBSOTf, 2,6-lutidine
DCM, -78 °C
88%
Me
O
OTBS
1
7
Me
2
HN
NMe2
Ph
NH
O
O
OBn
6

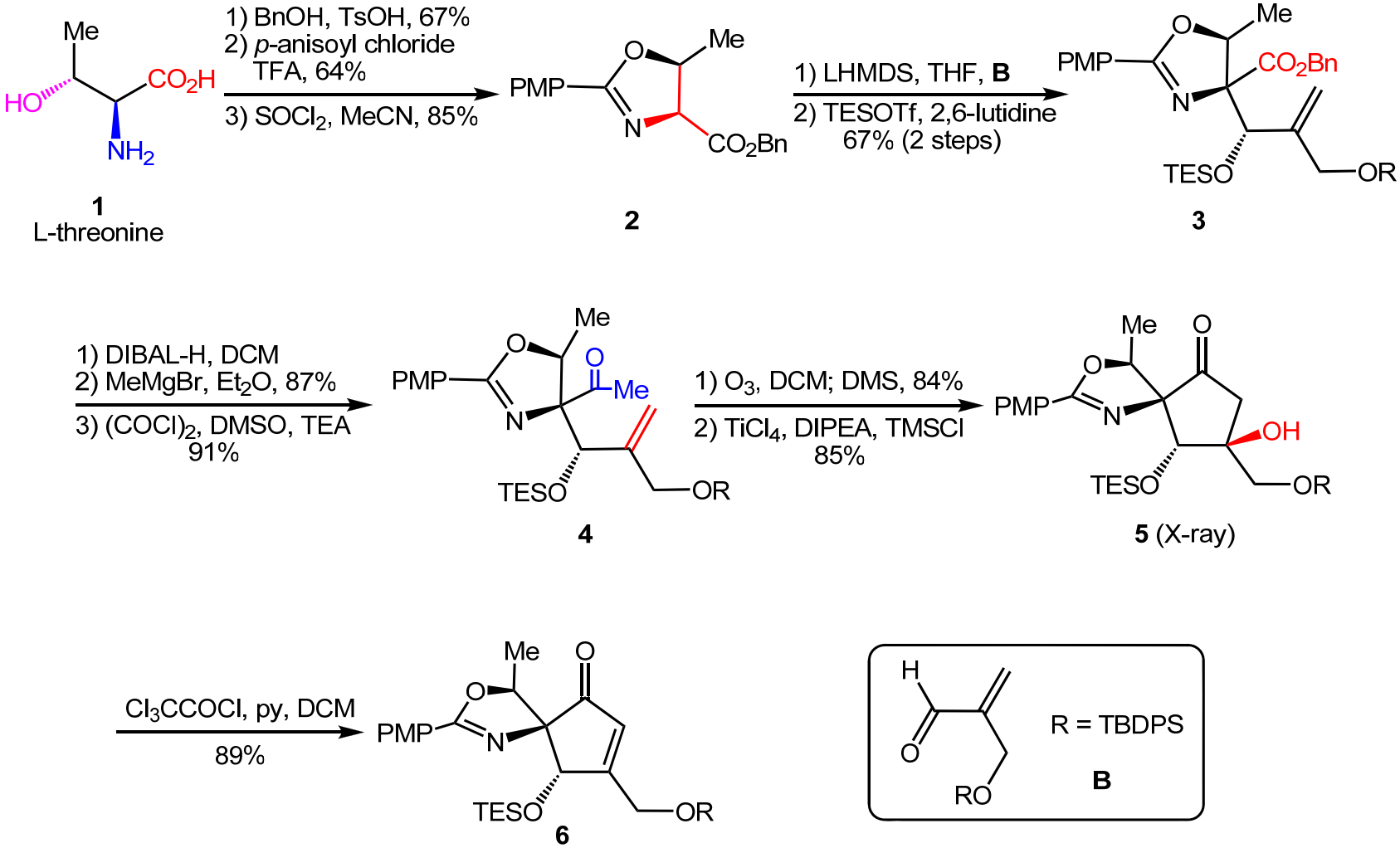

O
OTBS
Me
1
7
Me
2
HN
NMe2
Ph
NH
O
O
OBn
6
LDA, CH2O, THF
70%
OH
O
OTBS
4
5
1
Me
3
2
HN
NMe2
Ph
NH
O
O
OBn
8
O3, DCM;
Me2S
OH
O
OTBS
Me
2
HN
NMe2
O
NH
O
O
OBn
9
NaOMe, THF, 0 °C
50% (2 steps)
OH
O
OTBS
Me
2
HN
NMe2
NH
O
O
OBn
10
1) H2O2, NaOH, DCM/MeOH (7:1)
2) TBDPSCl, Et3N, DMAP, DCM
62%
TBDPSO
O
OTBS
Me
O
2
HN
NMe2
NH
O
O
OBn
11


TBDPSO
OTBS
Me
HN
NMe2
NH
OBn
11
MeMgBr, THF
75%
12
15, Sc(OTf)3, PhMe
66%
NH2
15
Ac
13
HO
16
NC
1) TBAF, THF, 90%
2) 16, K2CO3, DMA, 80%
14
Pd(OH)2/C
H2 (1 atm)
82%
pactamycin (1)

3. Hanessian合成方法



Hanessian, S. et al *Angew. Chem. Int. Ed.* **2011**, *50*, 3497



1
L-threonine

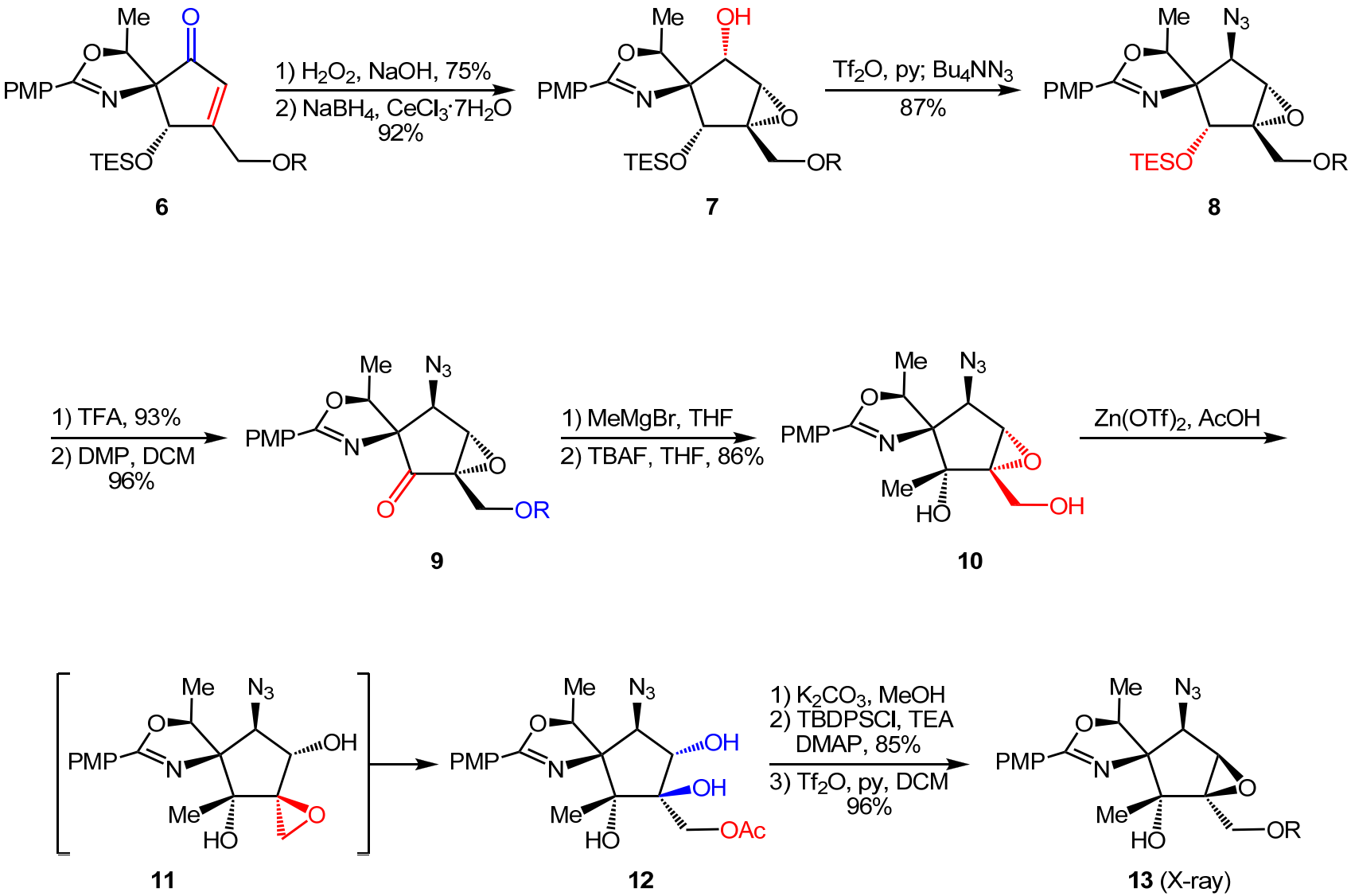
2

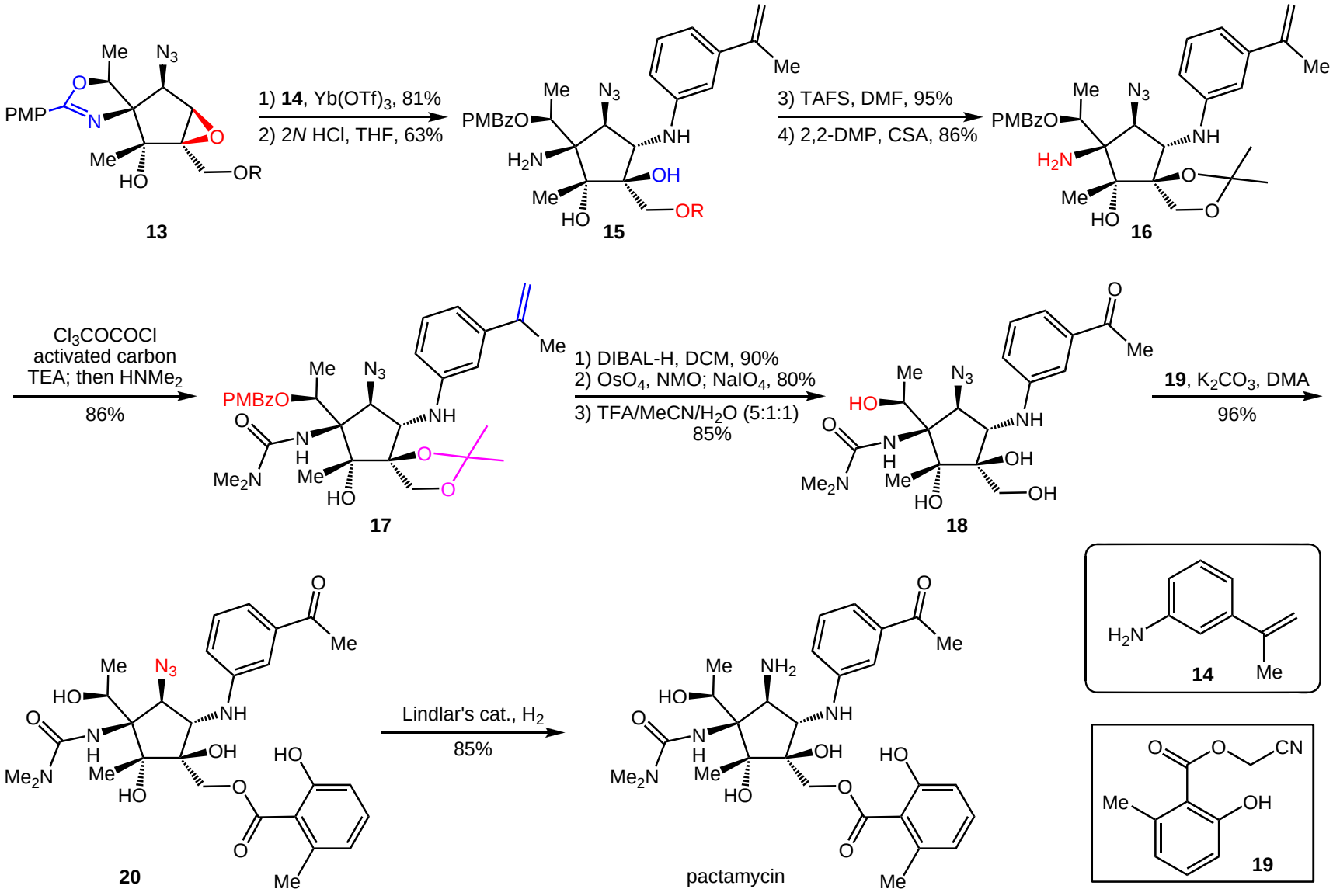
3

4

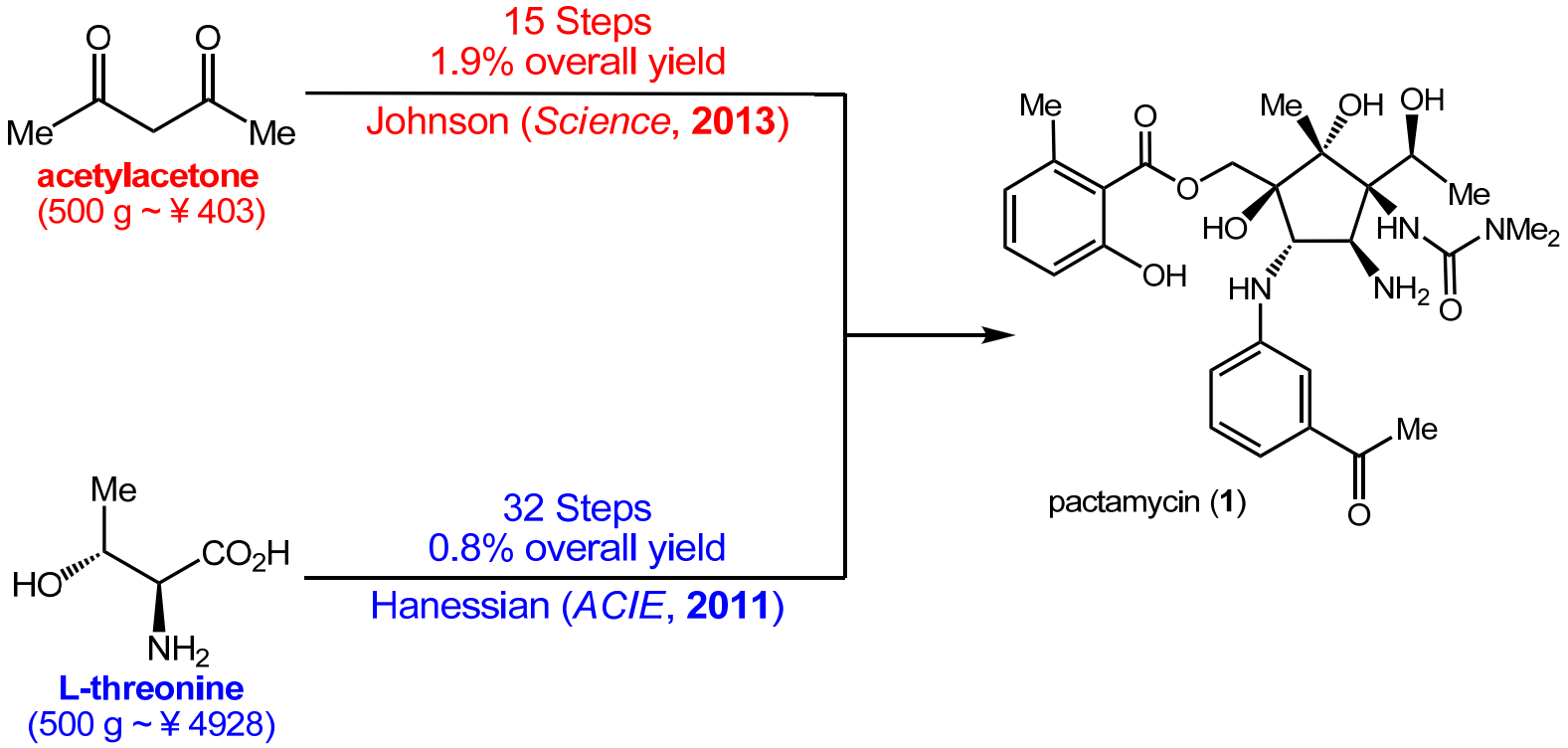
5 (X-ray)

6


Me
O
PMP
N
O
TESO
OR
6
1) H_2O_2, NaOH, 75%
2) $NaBH_4$, $CeCl_3 \cdot 7H_2O$
92%
Me
OH
PMP
N
O
TESO
OR
7
Tf_2O, py; Bu_4NN_3
87%
Me
N_3
PMP
N
O
TESO
OR
8
1) TFA, 93%
2) DMP, DCM
96%
Me
N_3
PMP
N
O
O
OR
9
1) MeMgBr, THF
2) TBAF, THF, 86%
Me
N_3
PMP
N
O
Me
HO
OH
10
$Zn(OTf)_2$, AcOH
Me
N_3
PMP
N
O
Me
HO
OH
11
Me
N_3
PMP
N
O
Me
HO
OH
OH
OAc
12
1) K_2CO_3, MeOH
2) TBDPSCl, TEA
DMAP, 85%
3) Tf_2O, py, DCM
96%
Me
N_3
PMP
N
O
Me
HO
O
OR
13 (X-ray)


1) 14, Yb(OTf)3, 81%
2) 2N HCl, THF, 63%
3) TAFS, DMF, 95%
4) 2,2-DMP, CSA, 86%
Cl3COCOCl
activated carbon
TEA; then HNMe2
86%
1) DIBAL-H, DCM, 90%
2) OsO4, NMO; NaIO4, 80%
3) TFA/MeCN/H2O (5:1:1)
85%
19, K2CO3, DMA
96%
Lindlar's cat., H2
85%
13
15
16
17
18
20
pactamycin
14
19

4. 总结与讨论


15 Steps
1.9% overall yield
Johnson (*Science*, **2013**)
acetylacetone
(500 g ~ ¥ 403)
32 Steps
0.8% overall yield
Hanessian (*ACIE*, **2011**)
L-threonine
(500 g ~ ¥ 4928)
pactamycin (**1**)

Complex organic molecules produced by bacteria have been used to treat numerous disease types for nearly a century. However, many naturally derived compounds that exhibit interesting bioactivities are practically inaccessible via synthetic organic chemistry. A natural product's structural complexity can create an insurmountable impediment to the preparation of analogs that might exhibit improved characteristics. An ongoing challenge in the field of synthetic chemistry is the development of methods that close the gap between the efficiency of biosynthetic machinery and laboratory synthesis. Because of the inherent flexibility of the latter, success in this endeavor could provide access to useful structural variants that might otherwise be inaccessible.

Carboxybenzyl deprotection occurred rapidly under hydrogenolysis conditions with the use of Pearlman's catalyst in 82% yield. This deprotection completed the synthesis of pactamycin in 15 steps and 1.9% overall yield. The route is flexible and should be amenable to the preparation of congeners since the introduction of highly functionalized side chains in unprotected form (urea, salicylate, *meta*-acetyl aniline) has been demonstrated.