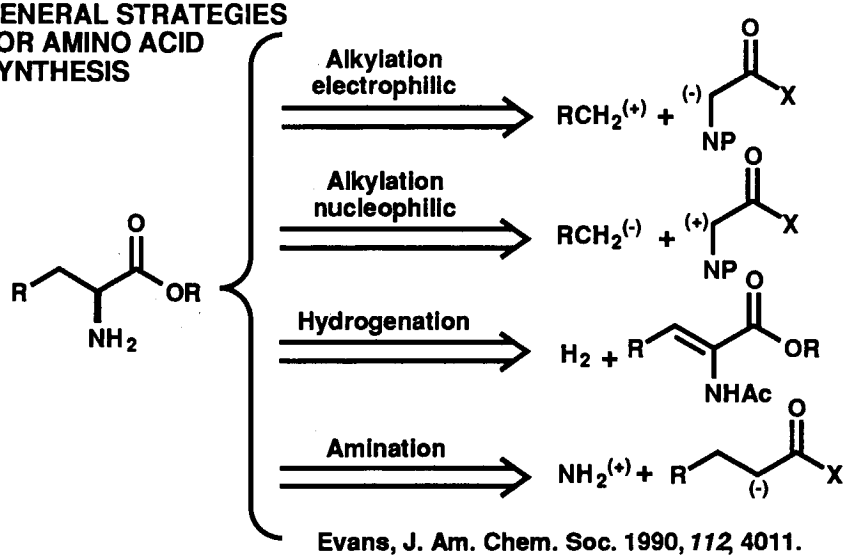
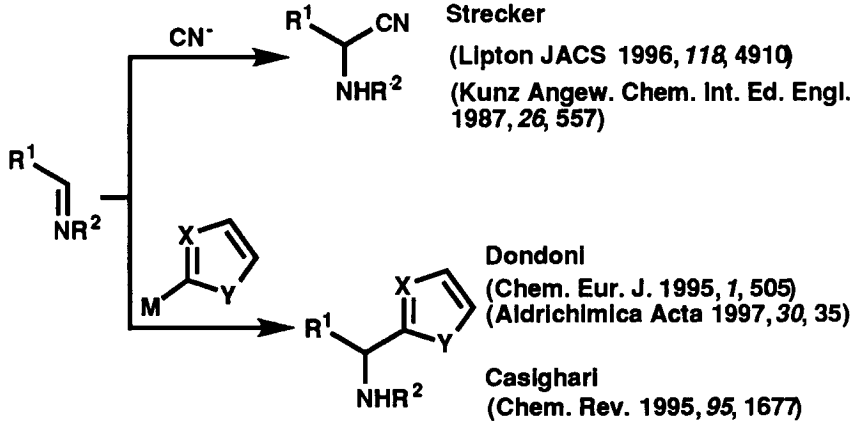
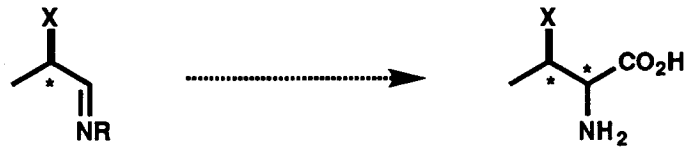
GENERAL STRATEGIES FOR AMINO ACID SYNTHESIS



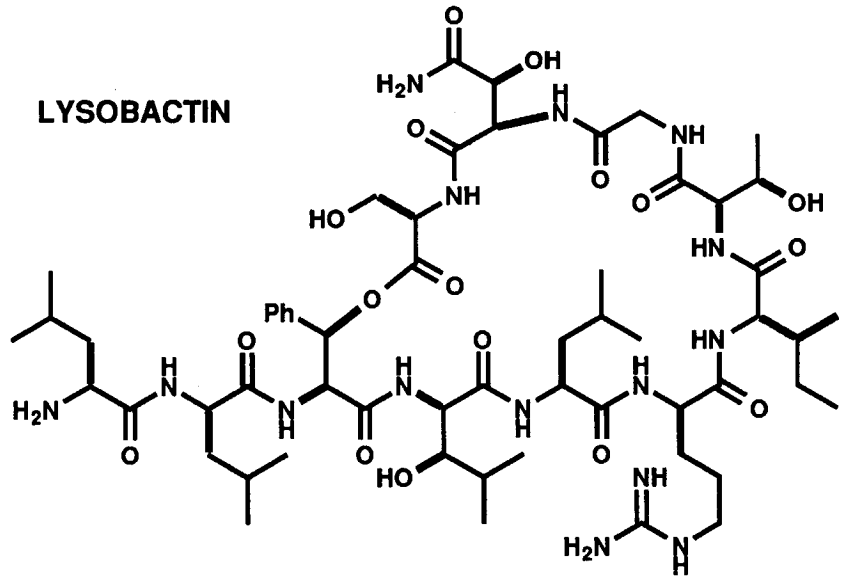
Evans, J. Am. Chem. Soc. 1990, *112*, 4011.

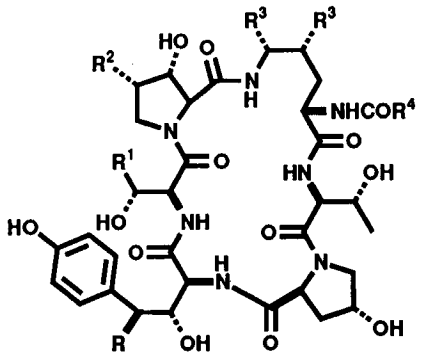




X: OR', NR'$_2$

LYSOBACTIN





Lypopeptide L-688,786

R^4= $-(CH_2)_8$

$R = R^3 = OH$

$R^1 = CH_2CONH_2$ $R^2 = H$

Echinocandins

R^4= $-(CH_2)_6$

B

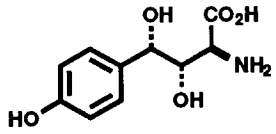
$R = OH$ $R^3 = OH$
$R^1 = R^2 = Me$

C

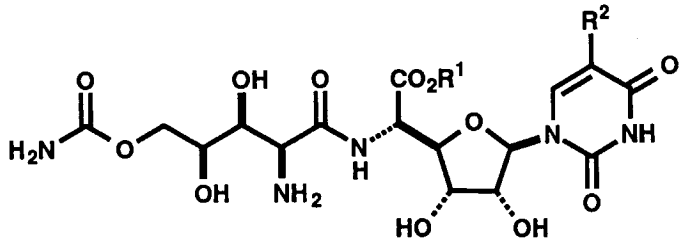
$R = H$, $R^3 = OH$
$R^1 = R^2 = Me$

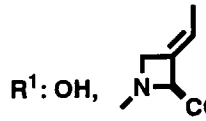
D

$R = R^3 = H$
$R^1 = R^2 = Me$



POLYOXINS

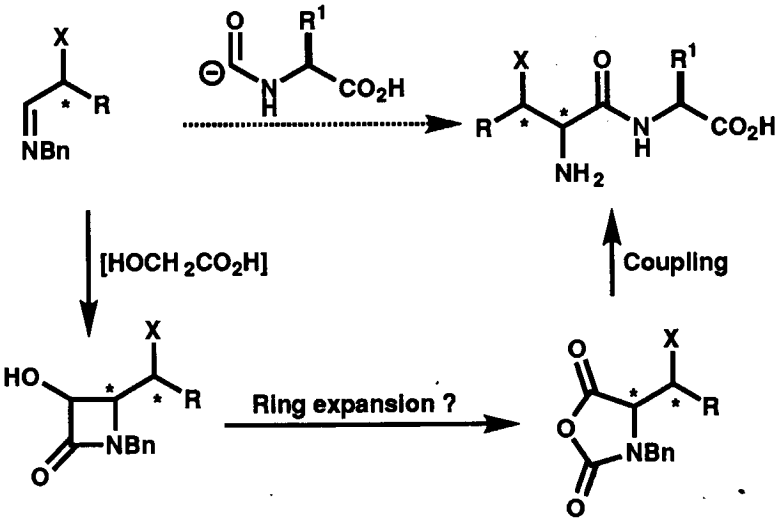


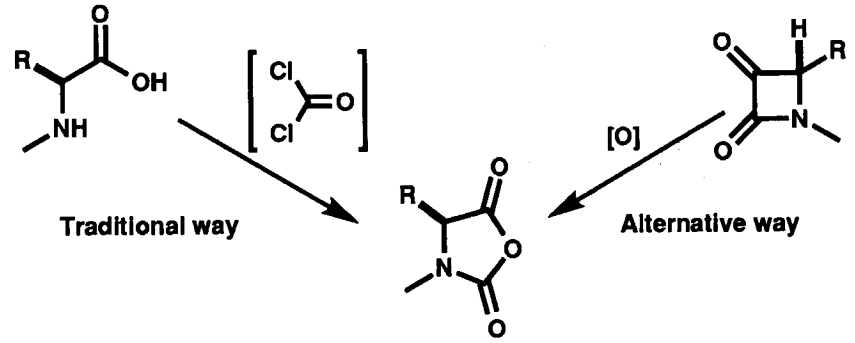


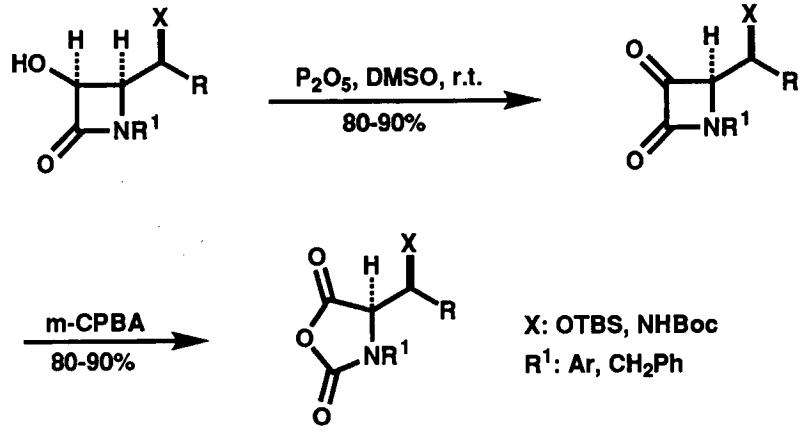
R^1: OH,

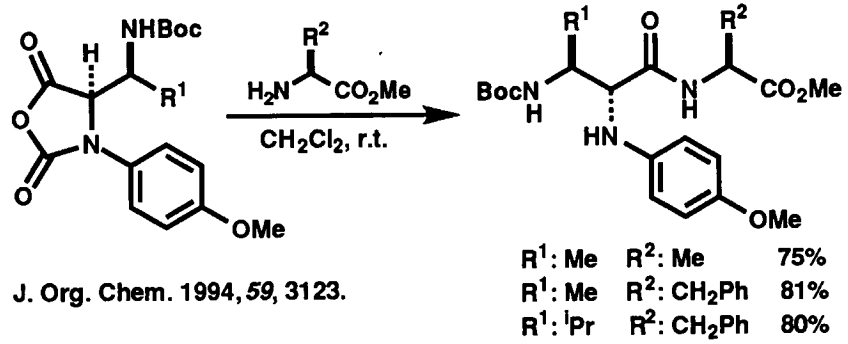
R^2: CO_2H, CH_2OH, CH_3, H

SYNTHETIC PLAN

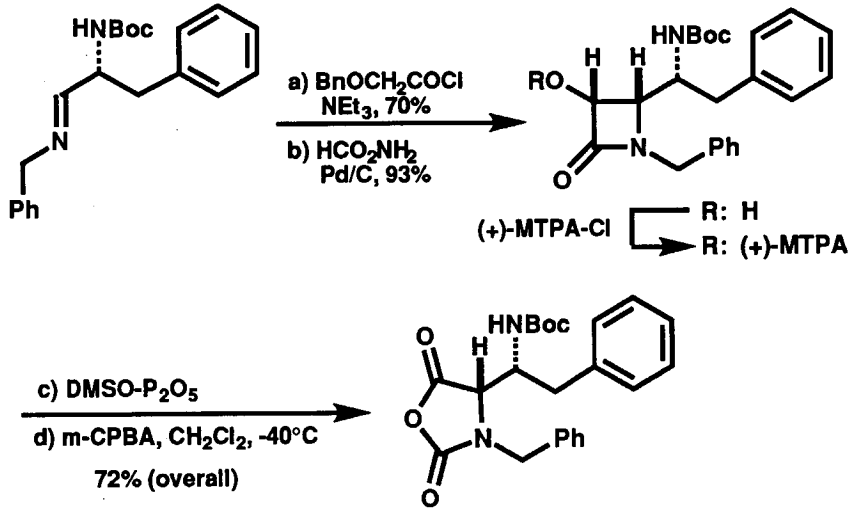


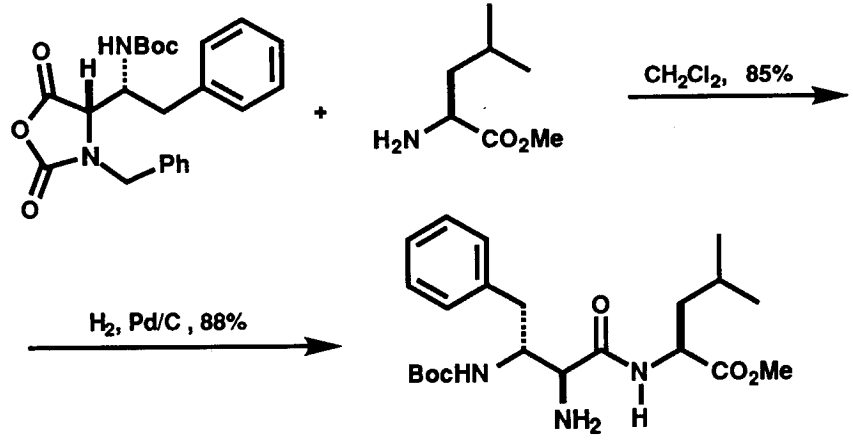




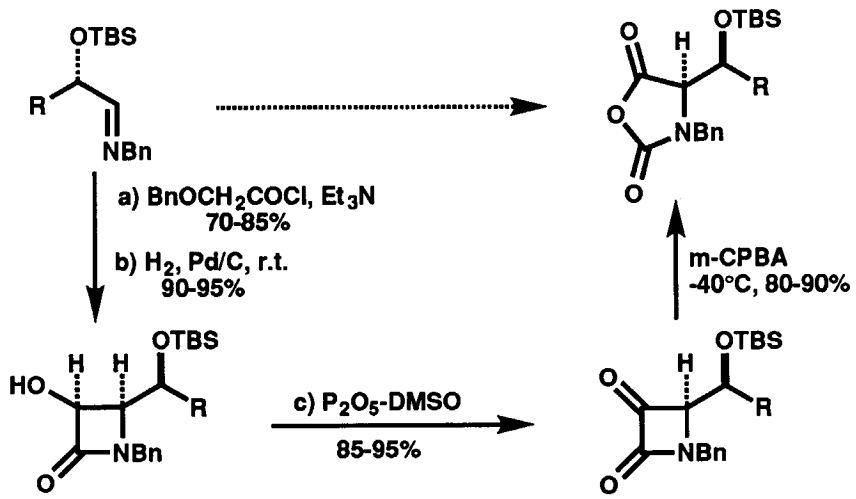


J. Org. Chem. 1994, *59*, 3123.

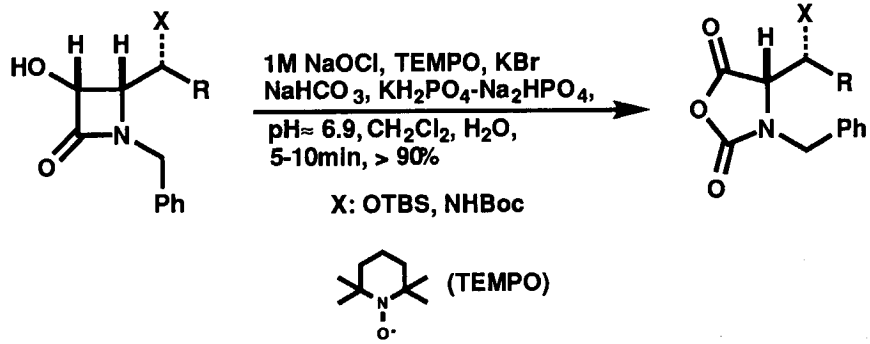




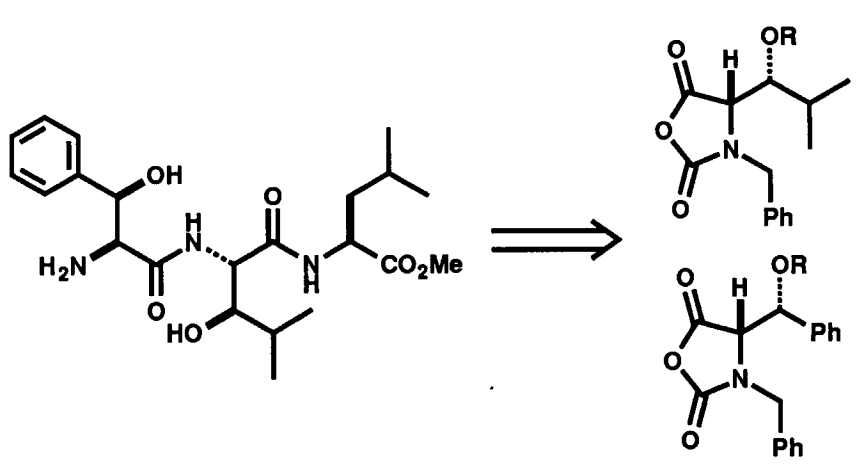
Tetrahedron Lett. 1994, *35*, 2725.

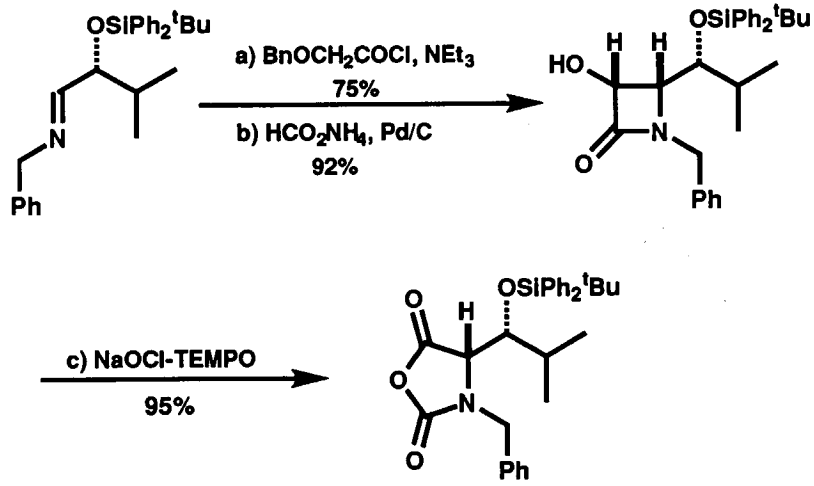


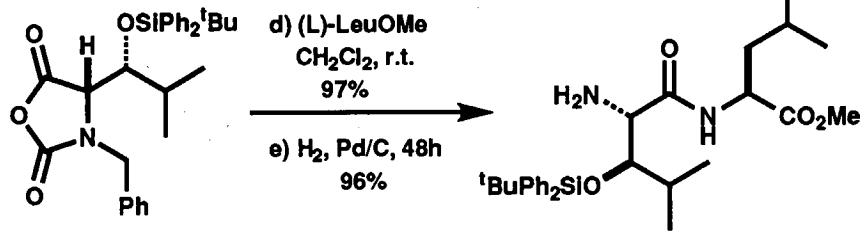
Tetrahedron Lett. 1994, *35*, 2721

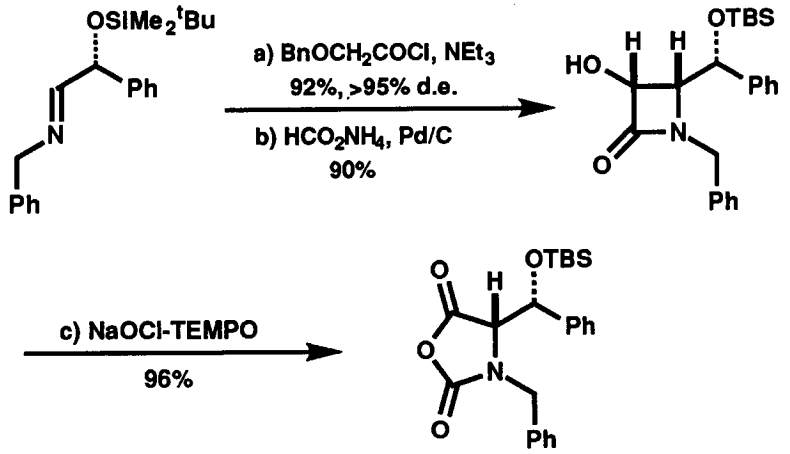


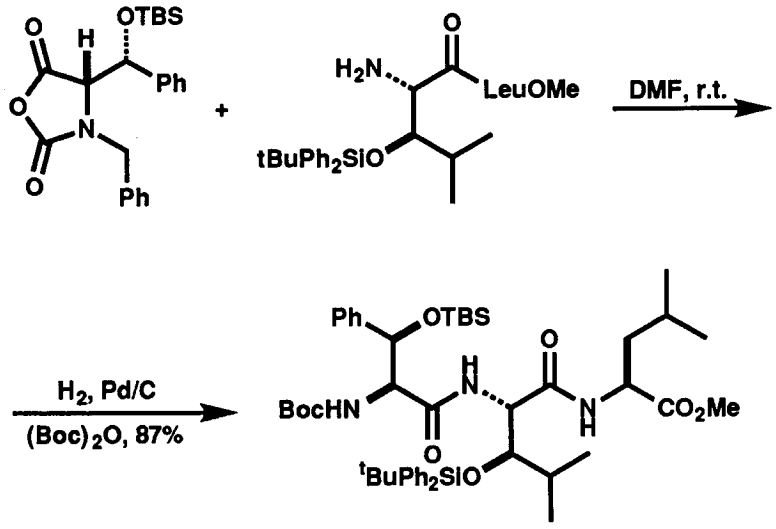
J. Org. Chem. 1996, *61*, 4400

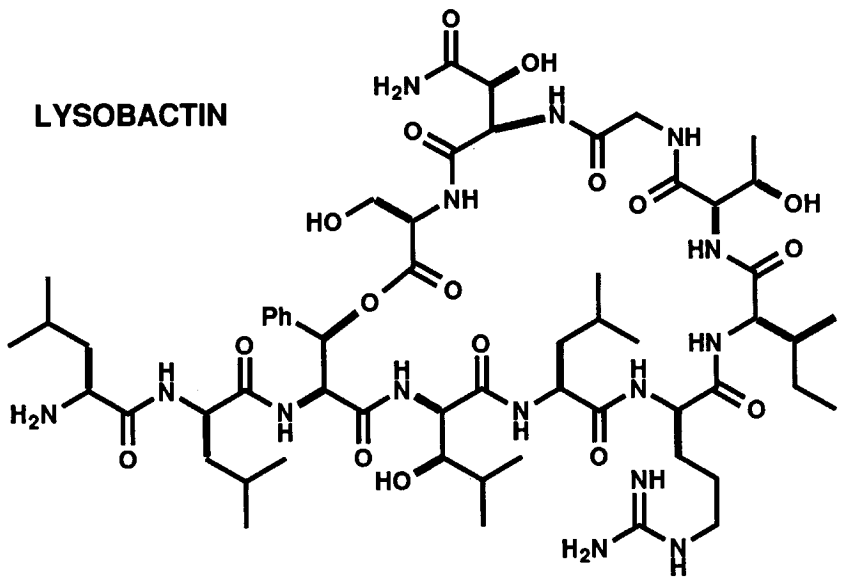


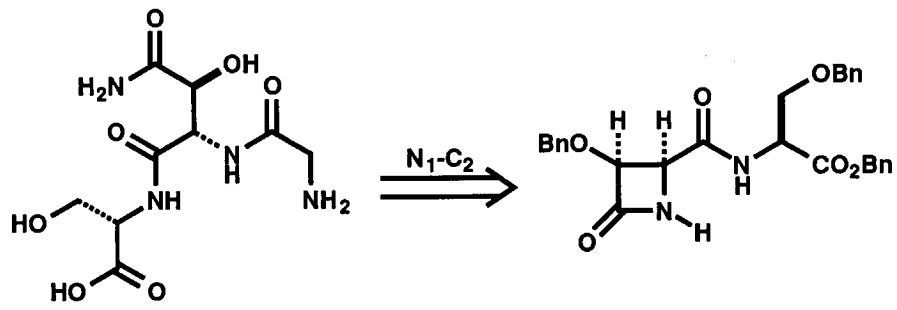


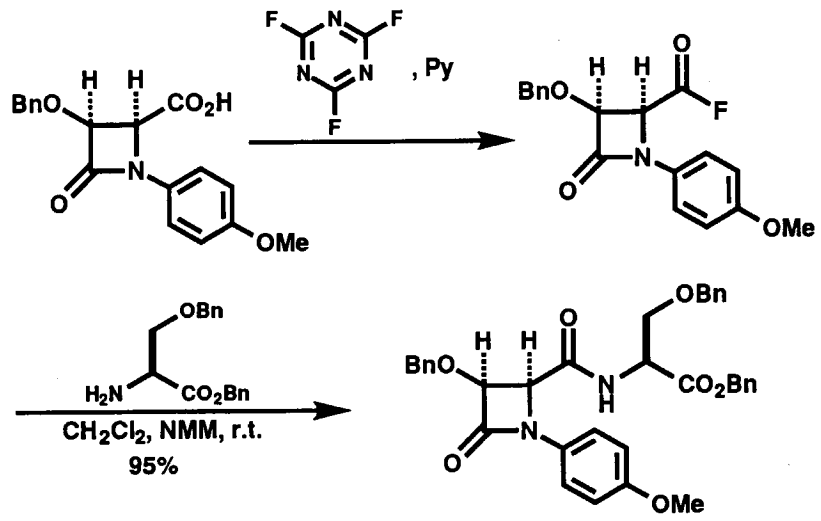

OSiPh2tBu
d) (L)-LeuOMe
CH2Cl2, r.t.
97%
e) H2, Pd/C, 48h
96%
H2N
CO2Me
tBuPh2SiO
Ph

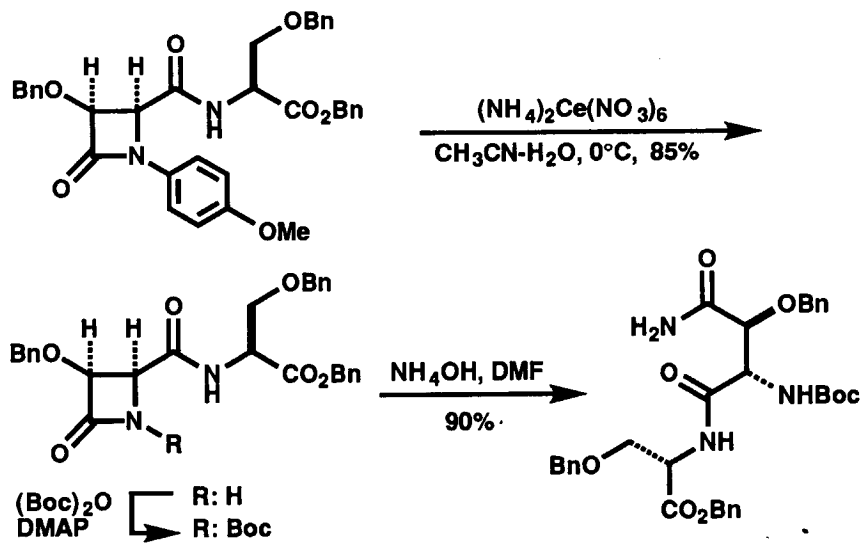

OSiMe2tBu
Ph
a) BnOCH2COCl, NEt3
92%, >95% d.e.
b) HCO2NH4, Pd/C
90%
HO
OTBS
c) NaOCl-TEMPO
96%

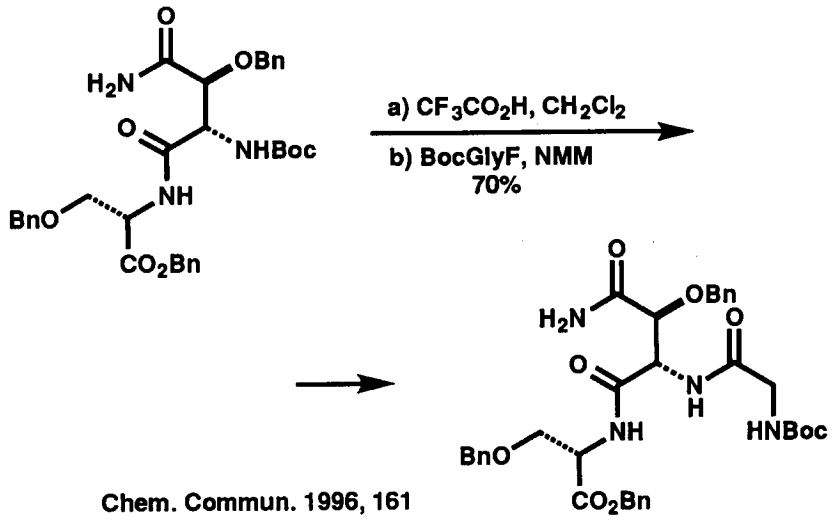

OTBS
Ph
LeuOMe
tBuPh2SiO
DMF, r.t.
H2, Pd/C
(Boc)2O, 87%
BocHN
CO2Me


LYSOBACTIN

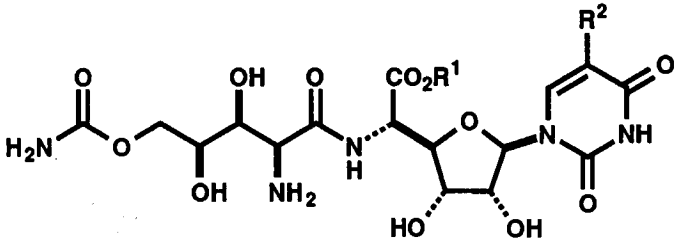

N1-C2

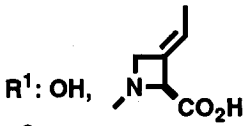

, Py
CH2Cl2, NMM, r.t.
95%


(NH4)2Ce(NO3)6
CH3CN-H2O, 0°C, 85%
NH4OH, DMF
90%
(Boc)2O
DMAP
R: H
R: Boc


a) CF3CO2H, CH2Cl2
b) BocGlyF, NMM
70%
Chem. Commun. 1996, 161

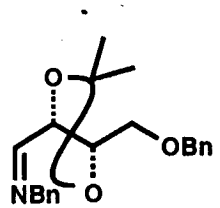
POLYOXINS





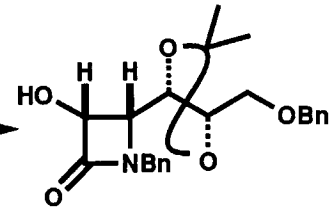
R^1: OH,

R^2: CO_2H, CH_2OH, CH_3, H



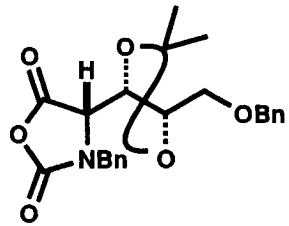
a) $AcOCH_2COCl$, Et_3N
then, LiOH, H_2O_2

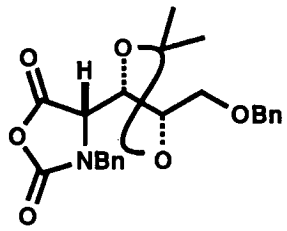
90%



b) NaOCl-TEMPO
1-2 min

~100%





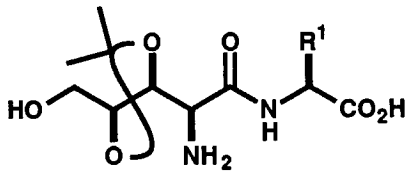
c) H_2N $CH(R^1)$ CO_2Bn

CH_2Cl_2, 90-95%

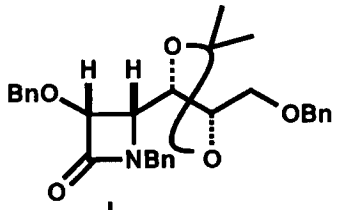
R^1: H, Bn, ^{i}Pr, ^{i}Bu

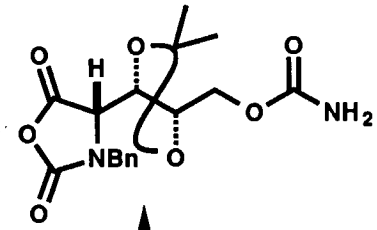
d) H_2, $Pd(OH)_2$

~100%



Chem. Commun. 1997, 691

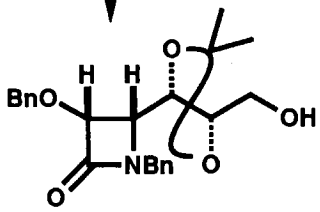




H_2, 10% Pd/C
6 h, 95%

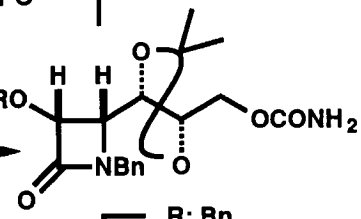
NaOCl, KBr
TEMPO

95%



$ClCO_2PhNO_2$-4,
Py, then NH_4OH

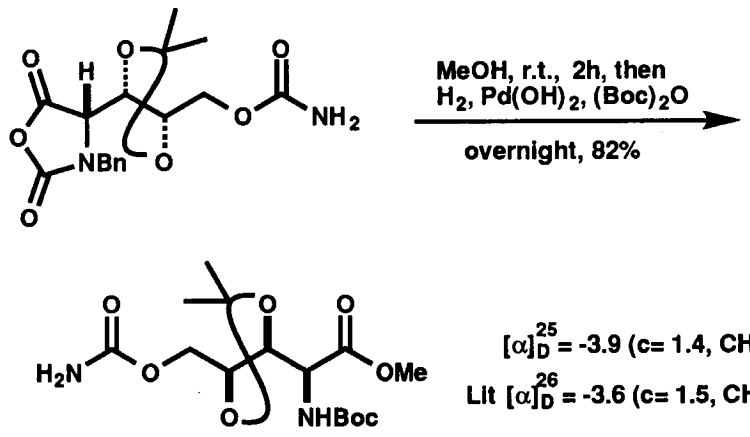
90%

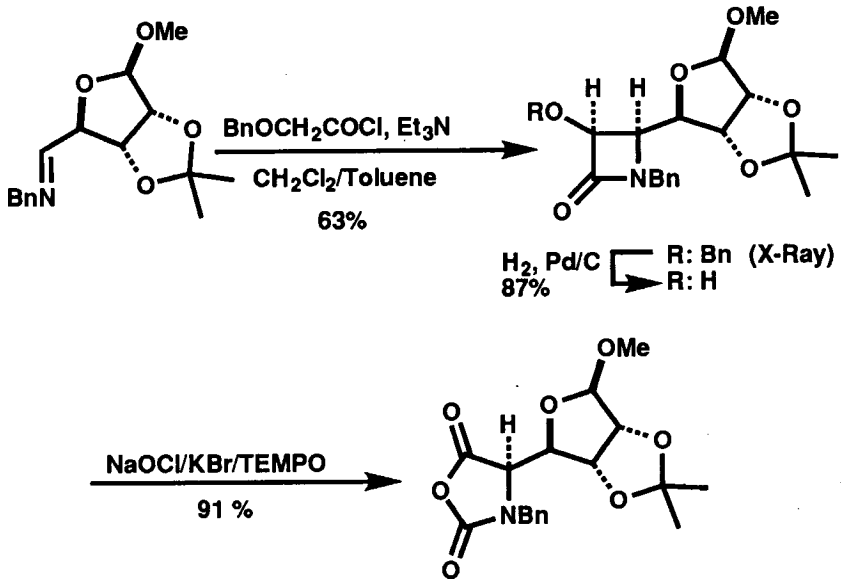


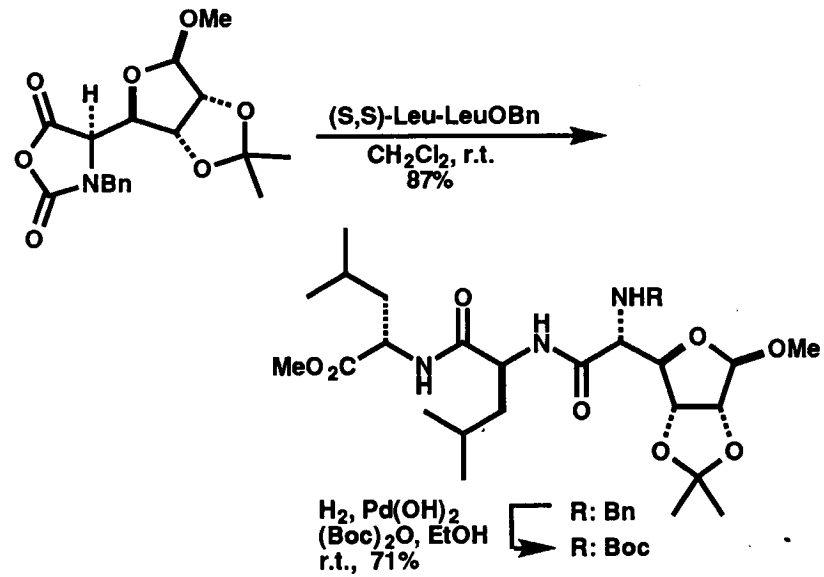
H_2, 10% Pd/C

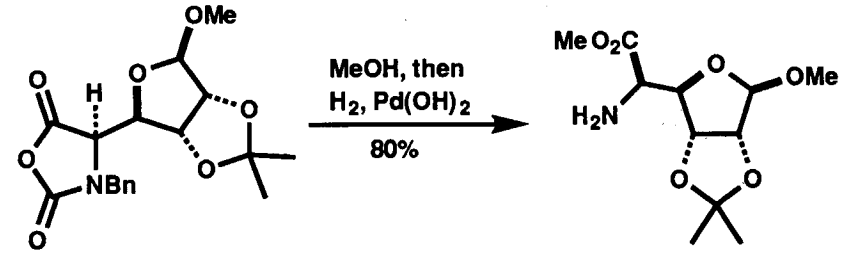
R: Bn

R: H

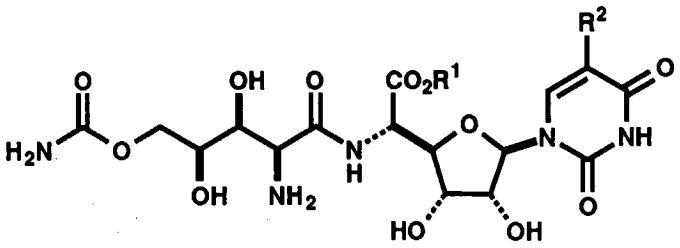

MeOH, r.t., 2h, then
H2, Pd(OH)2, (Boc)2O
overnight, 82%
[α]D25 = -3.9 (c= 1.4, CH2Cl2)
Lit [α]D26 = -3.6 (c= 1.5, CH2Cl2)

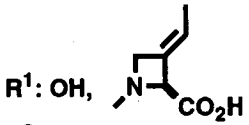

BnOCH2COCl, Et3N
CH2Cl2/Toluene
63%
H2, Pd/C
87%
R: Bn (X-Ray)
R: H
NaOCl/KBr/TEMPO
91 %


(S,S)-Leu-LeuOBn
CH2Cl2, r.t.
87%
H2, Pd(OH)2
(Boc)2O, EtOH
r.t., 71%
R: Bn
R: Boc


MeOH, then
H2, Pd(OH)2
80%

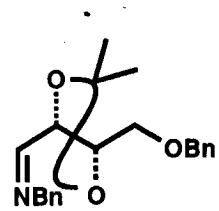
POLYOXINS





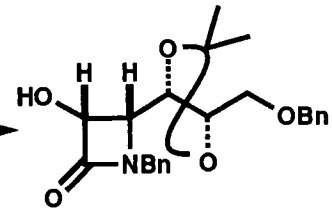
R^1: OH,

R^2: CO_2H, CH_2OH, CH_3, H



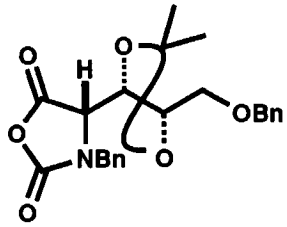
a) $AcOCH_2COCl$, Et_3N
then, LiOH, H_2O_2

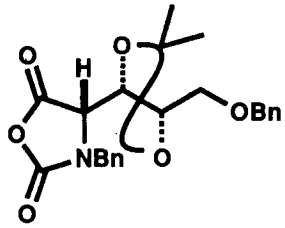
90%



b) NaOCl-TEMPO
1-2 min

~100%





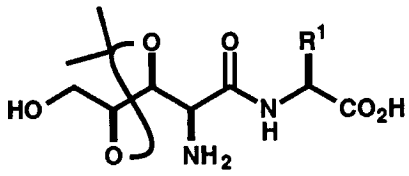
c)

CH_2Cl_2, 90-95%

R^1: H, Bn, ^{i}Pr, ^{i}Bu

d) H_2, $Pd(OH)_2$

~100%



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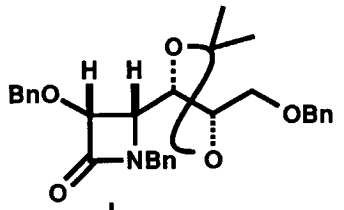
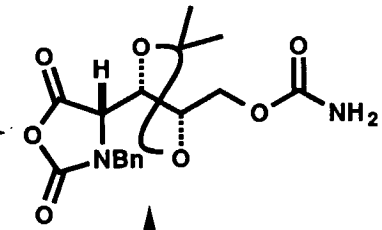
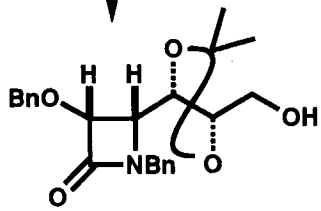




H_2, 10% Pd/C
6 h, 95%

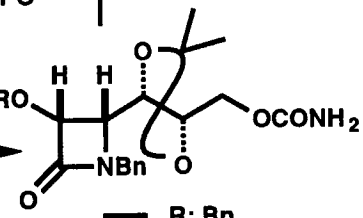
NaOCl, KBr
TEMPO

95%



$ClCO_2PhNO_2$-4,
Py, then NH_4OH

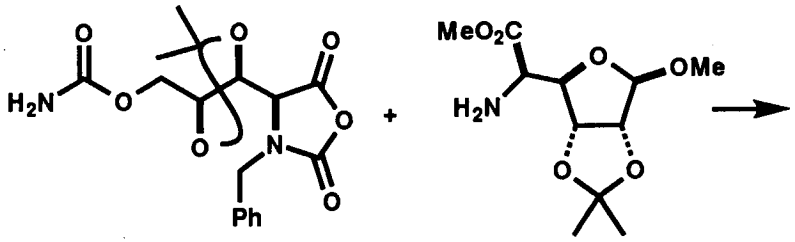
90%

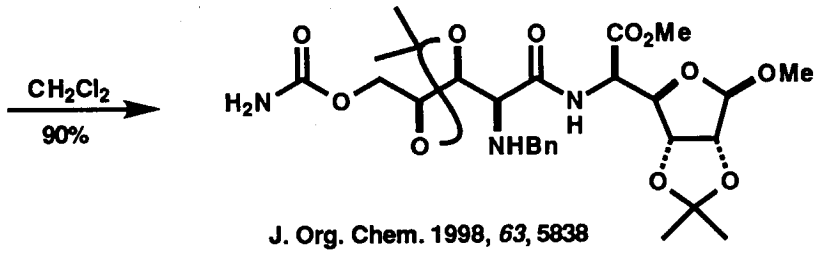


H_2, 10% Pd/C

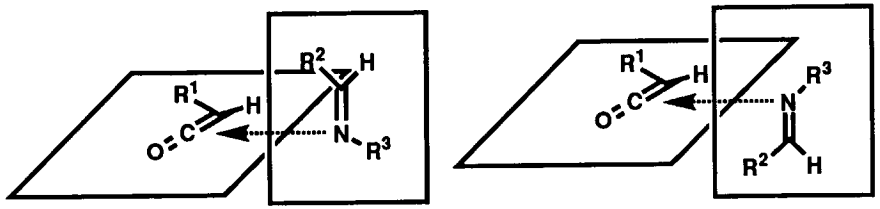
R: Bn

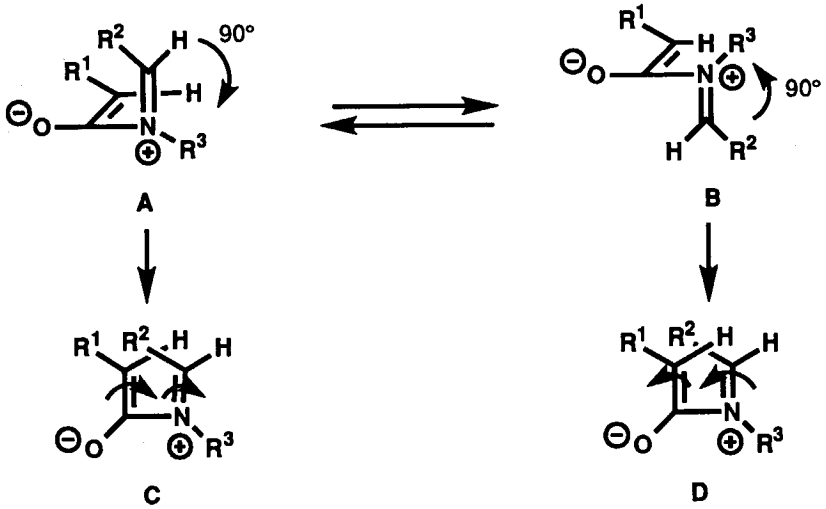
R: H

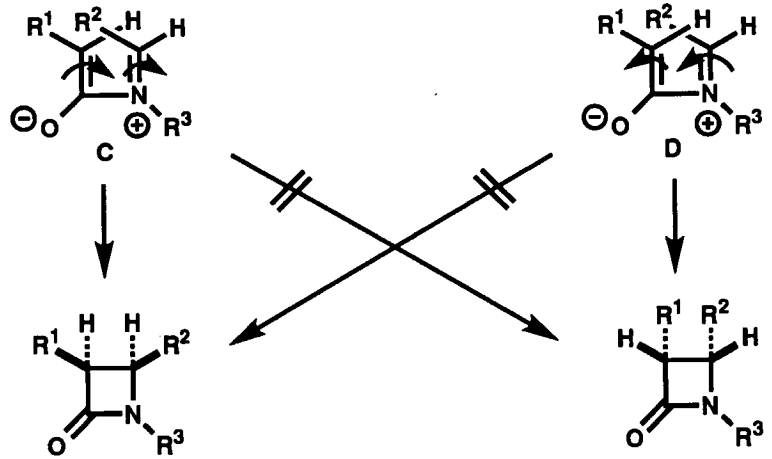


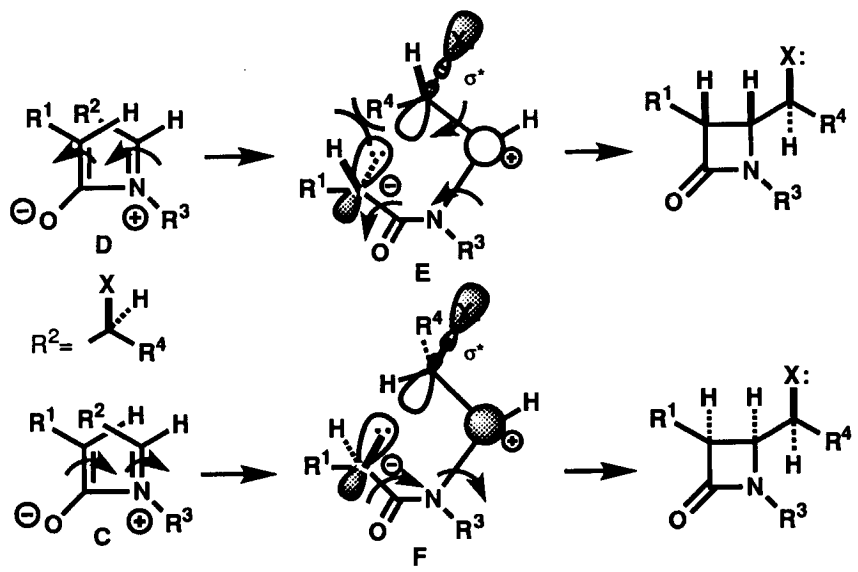


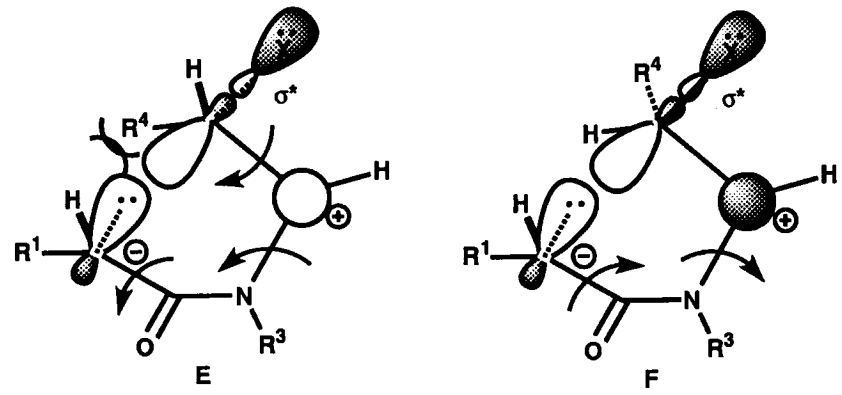
J. Org. Chem. 1998, *63*, 5838









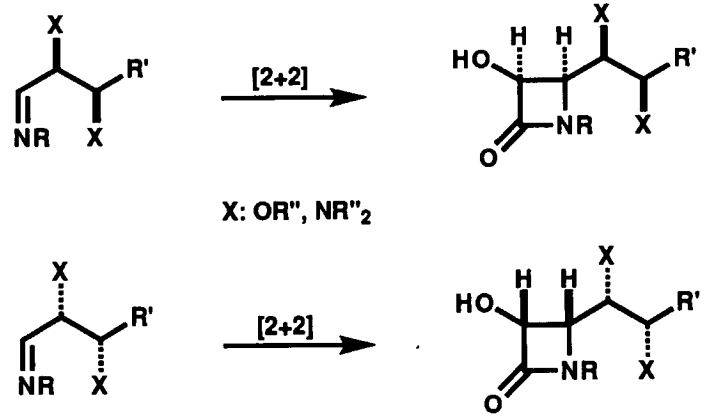


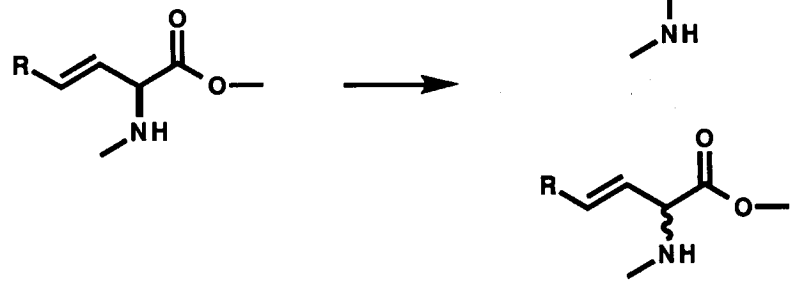
ΔH_f= - 6.6 Kcal/mol

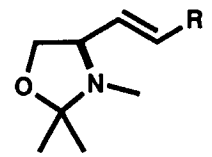
ΔH_f= - 8.0 Kcal/mol

R^1: MeO R^4: Me
R^3: H X: NH_2

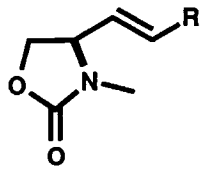
J. Am. Chem. Soc. 1992, *114*, 9360
J. Am. Chem. Soc. 1993, *115*, 995



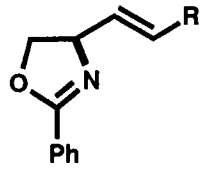




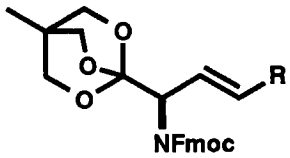
P.L. Beaulleau
JOC 1991, *56*, 4196



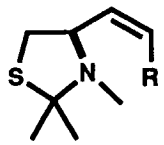
M.P. Sibi
TL 1990, *31*, 7407



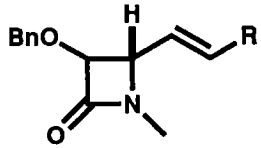
D.R. Dalton
JOC 1997, *62*, 372

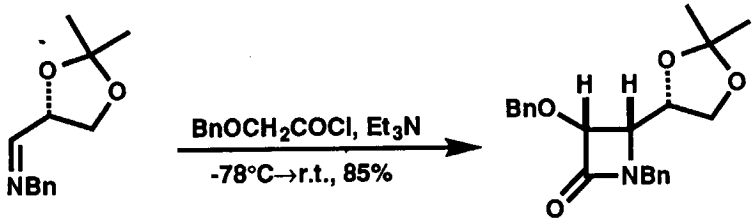


G.A. Lajoie
JACS 1993, *115*, 5021

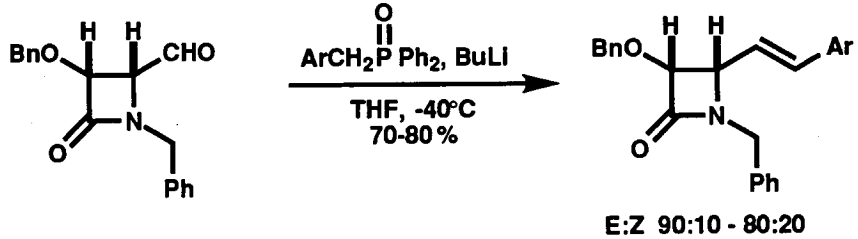


R.O. Duthaler
AG 1991, *103*, 729

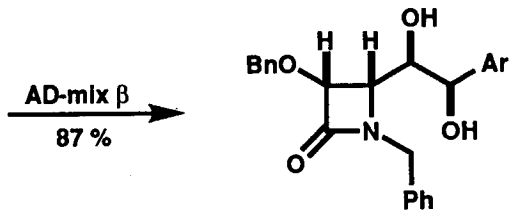




Bose et al. JOC 1988, *53*, 4227

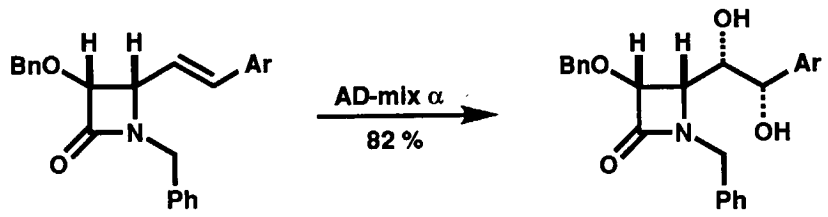


E:Z 90:10 - 80:20

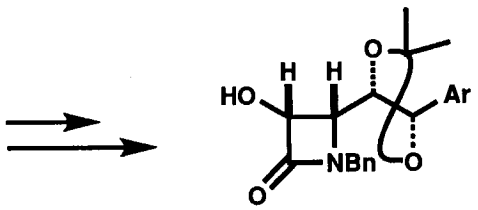


d.r. ≥ 99 : 1

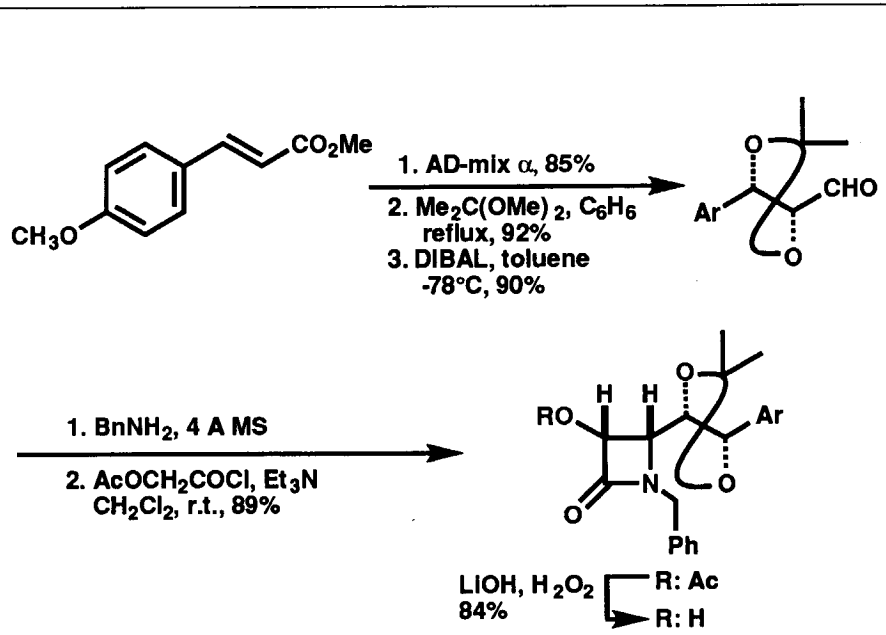
Ar: C_6H_5, 4-MeC_6H_4
4-MeOC_6H_4

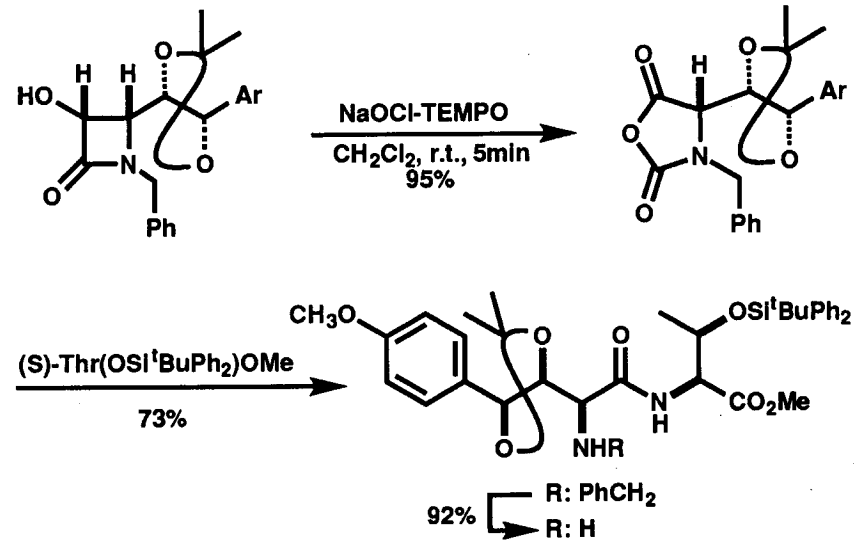


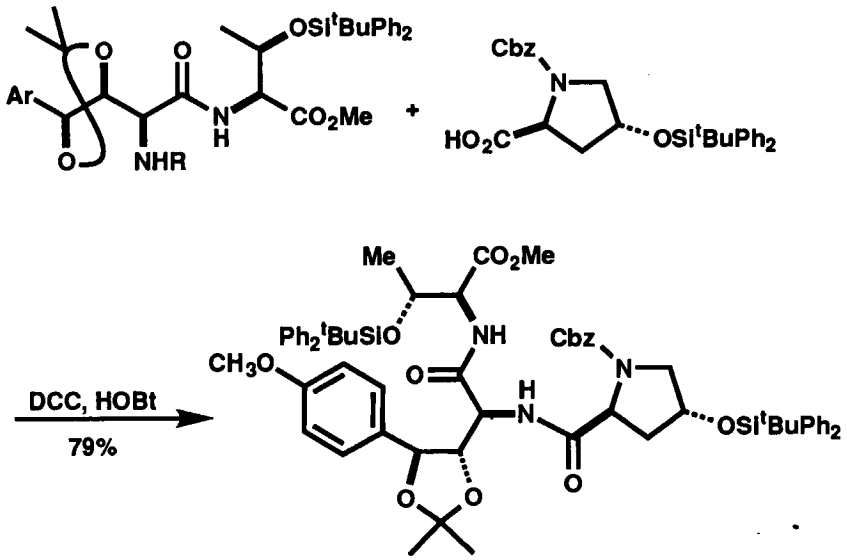
dr 89 : 11

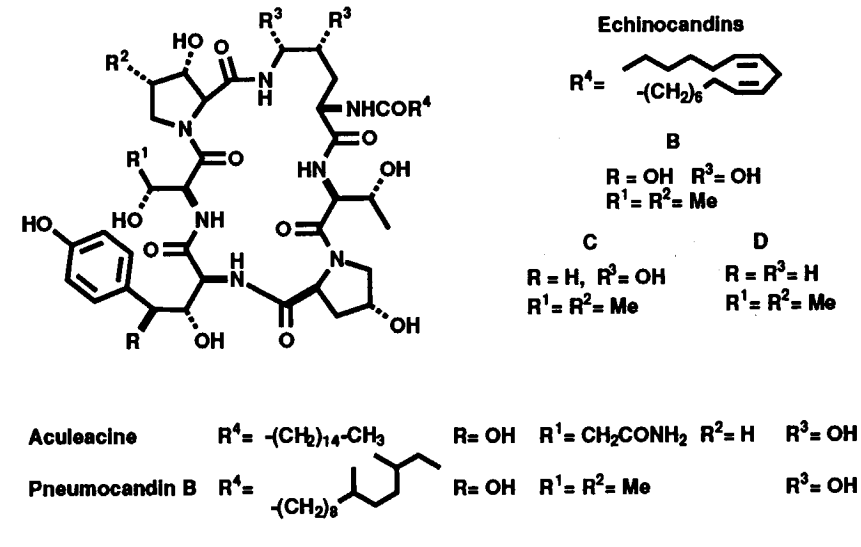


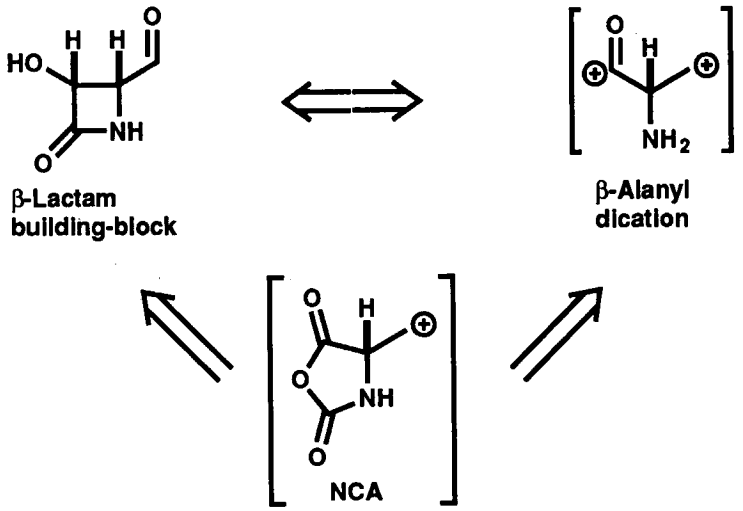
Ar: 4-MeOC_6H_4

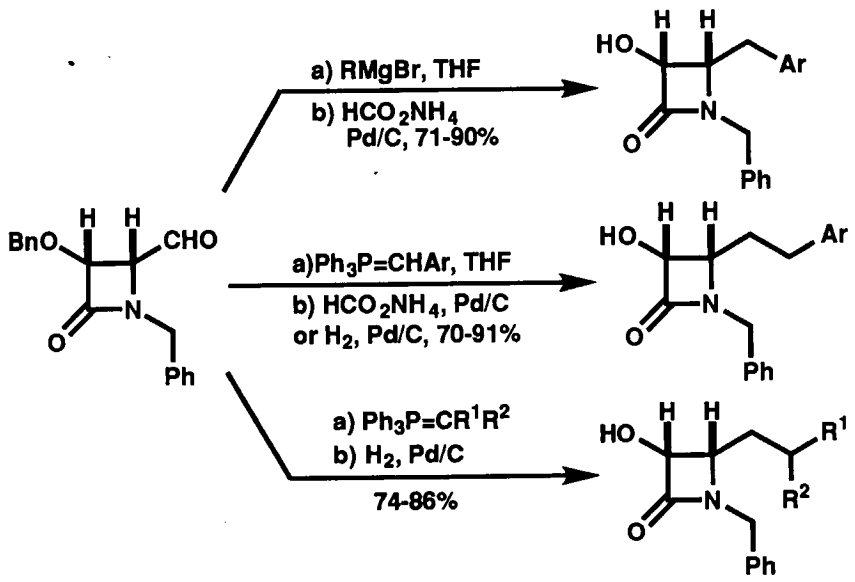

CO2Me
CH3O
1. AD-mix α, 85%
2. Me2C(OMe)2, C6H6
reflux, 92%
3. DIBAL, toluene
-78°C, 90%
CHO
Ar
1. BnNH2, 4 A MS
2. AcOCH2COCl, Et3N
CH2Cl2, r.t., 89%
RO
H
H
O
N
Ph
LiOH, H2O2
84%
R: Ac
R: H

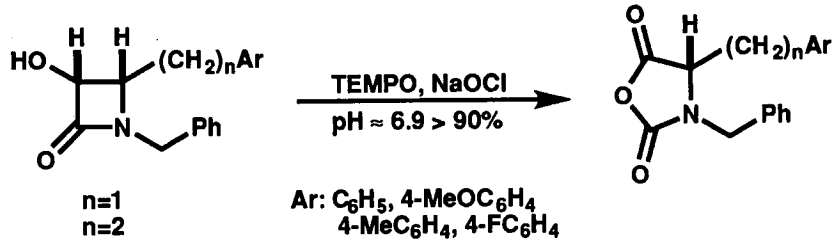

HO
H
H
Ar
O
N
Ph
NaOCl-TEMPO
CH2Cl2, r.t., 5min
95%
(S)-Thr(OSi tBuPh2)OMe
73%
CH3O
OSi tBuPh2
CO2Me
NHR
92%
R: PhCH2
R: H


OSi tBuPh2
Ar
CO2Me
NHR
Cbz
HO2C
DCC, HOBt
79%
Me
Ph2 tBuSiO
CH3O
NH
OSi tBuPh2

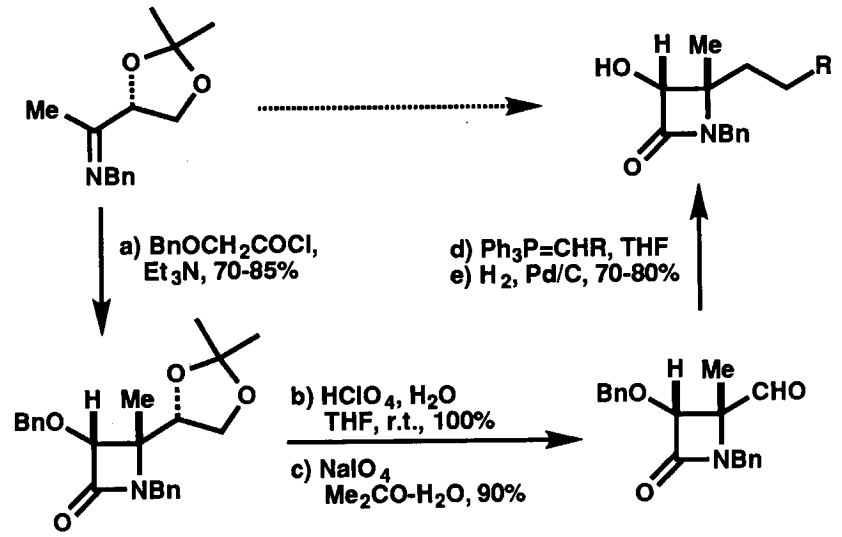

Echinocandins
R4=
-(CH2)6
B
R = OH R3= OH
R1= R2= Me
C
R = H, R3= OH
R1= R2= Me
D
R = R3= H
R1= R2= Me
NHCOR4
Aculeacine R4= -(CH2)14-CH3 R= OH R1= CH2CONH2 R2= H R3= OH
Pneumocandin B R4= -(CH2)8 R= OH R1= R2= Me R3= OH

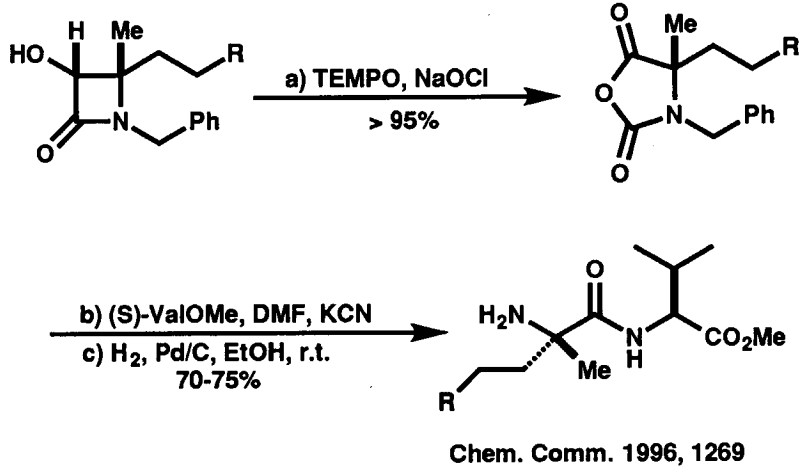




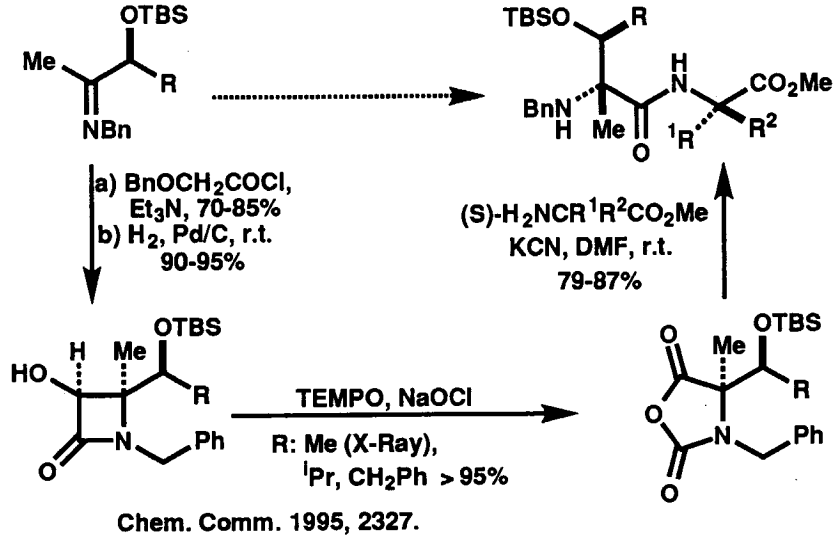


Chem. Commun. 1994, 1505.

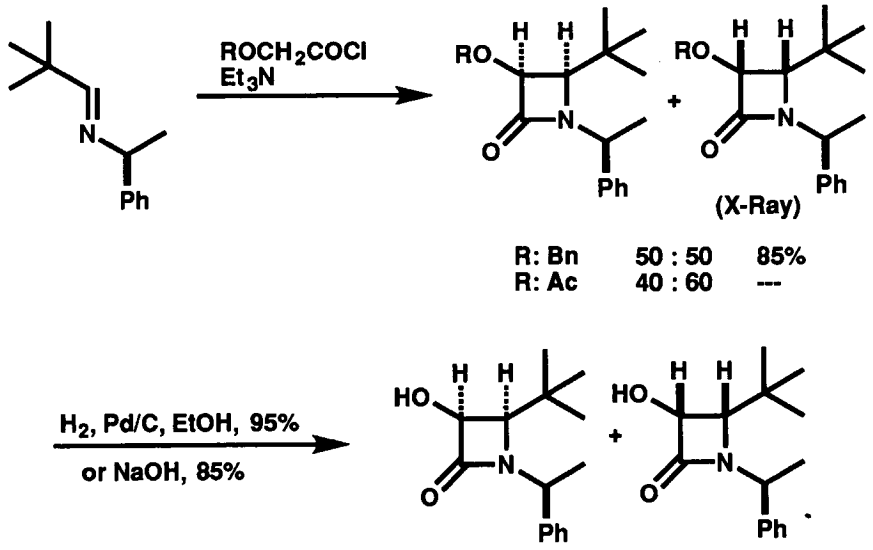


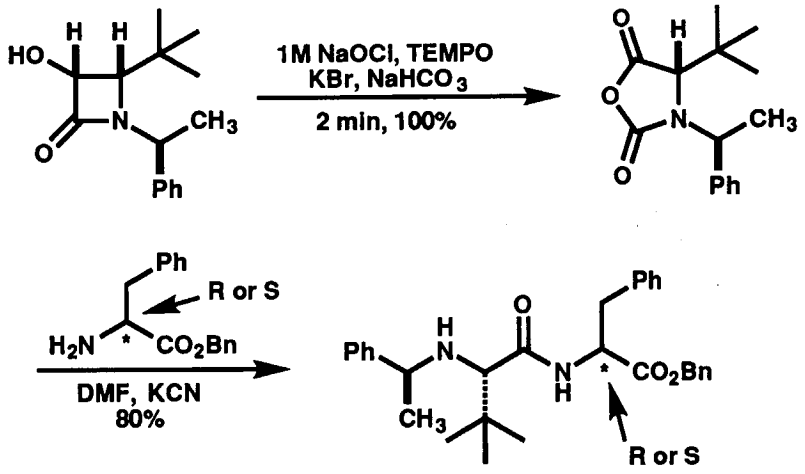


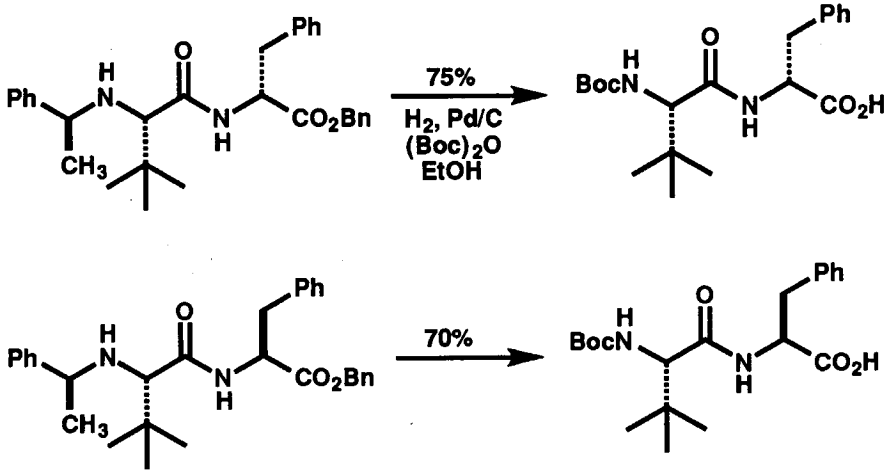
Chem. Comm. 1996, 1269



Chem. Comm. 1995, 2327.







Tetrahedron Lett. 1997, *38*, 3093

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C. Cuevas	α,β-Diamino acid-NCAs	A. Landa	Echinocandins
J. I. Miranda	α-amino-β-hydroxy-NCAs	E. Maneiro	Aryl- and homoaryl alanine-NCAs
B. Odriozola	Lysobactin t-Leucine-NCAs	R. Urchegui	α-Branched-NCAs
A. Esnal	Polyoxins	A. Linden	X-Ray

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- UNIVERSITY OF THE BASQUE COUNTRY