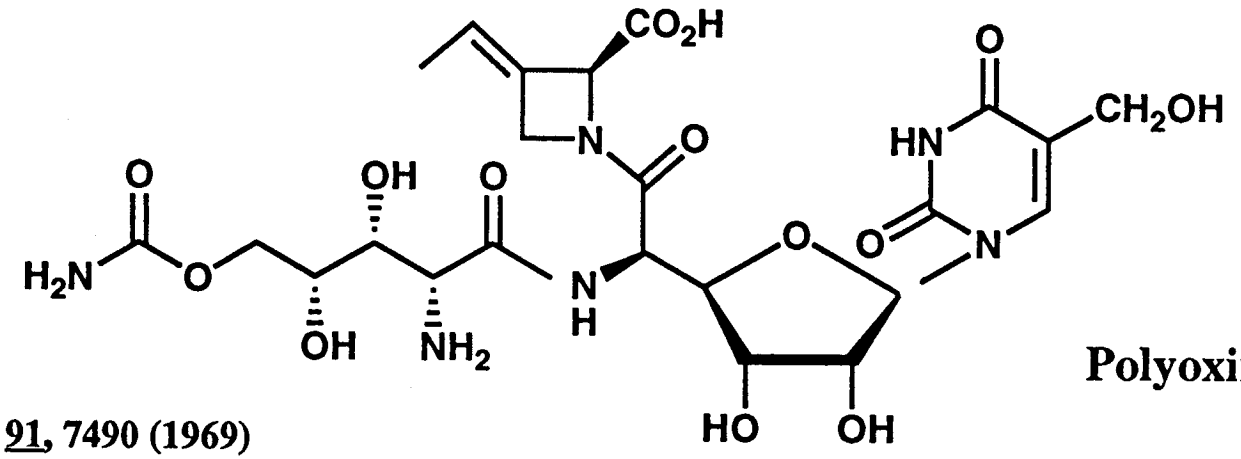
TOTAL SYNTHESIS OF (+)-POLYOXIMIC ACID

Department of Chemistry, University of Montreal

DEGRADATION OF POLYOXIN A



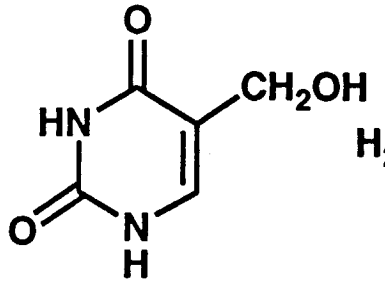
Polyoxin A

K. Isono, et al
J. Am. Chem. Soc. 91, 7490 (1969)

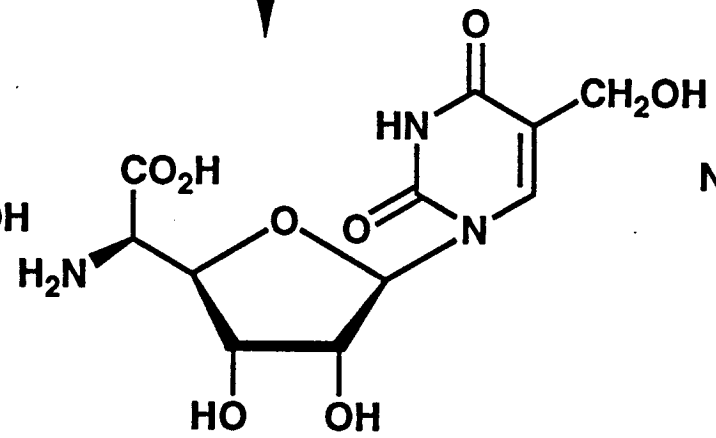
0.5 N NaOH
65°C, 4 h

or

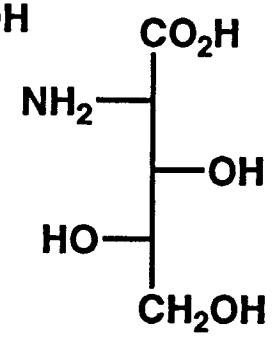
3 N HCl
reflux, 1 h



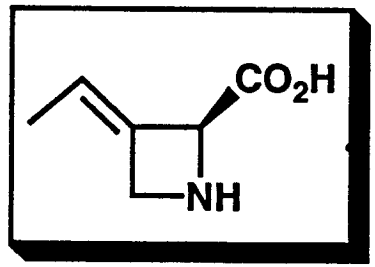
5-Hydroxymethyluracil



Polyoxin C

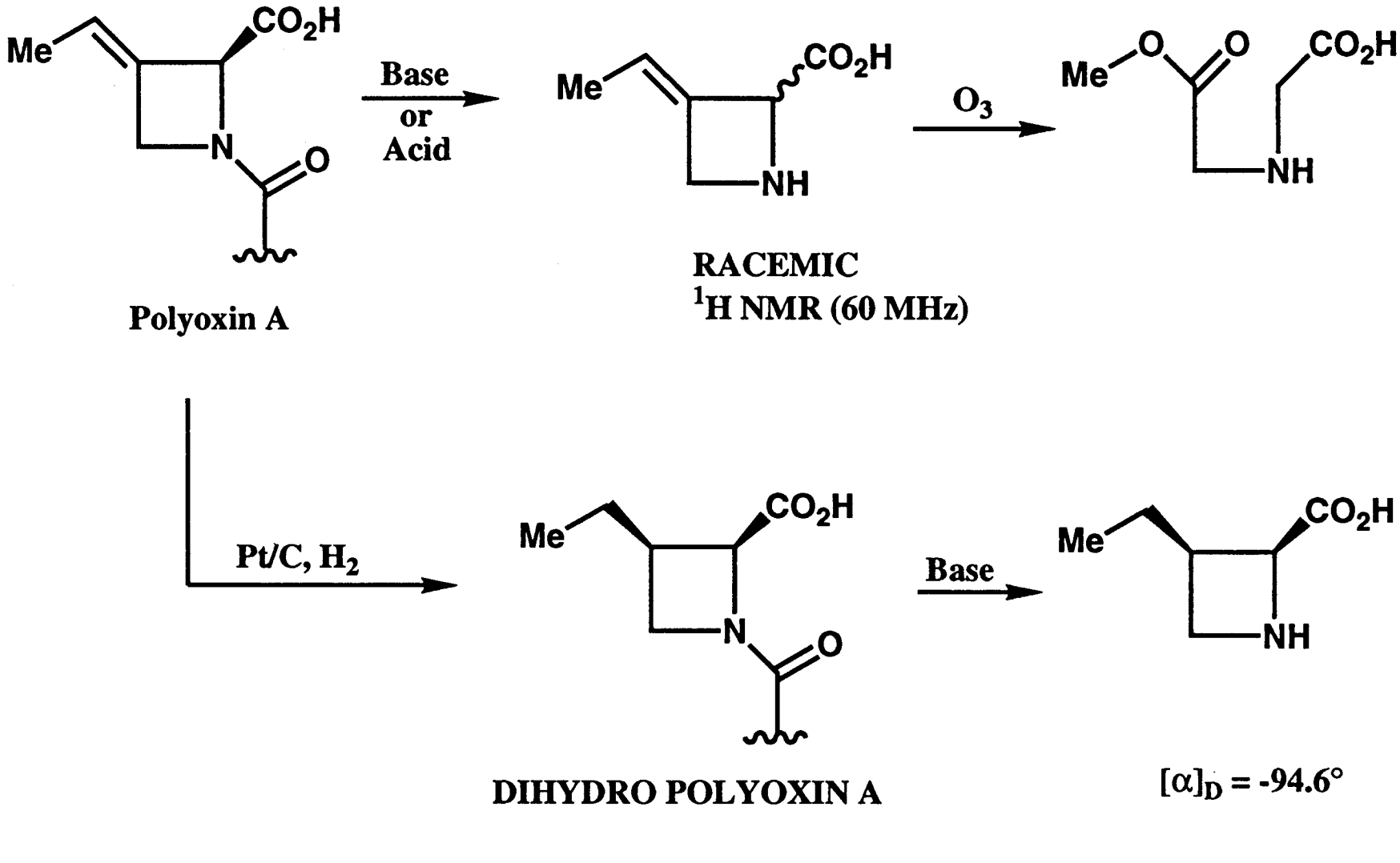


Polyoxamic Acid



Polyoximic Acid

STRUCTURE AND STEREOCHEMICAL ASSIGNMENT



Polyoxin A

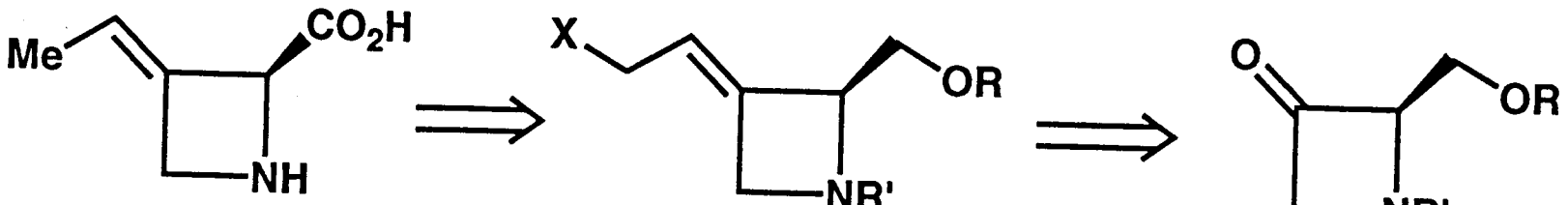
RACEMIC
^{1}H NMR (60 MHz)

DIHYDRO POLYOXIN A

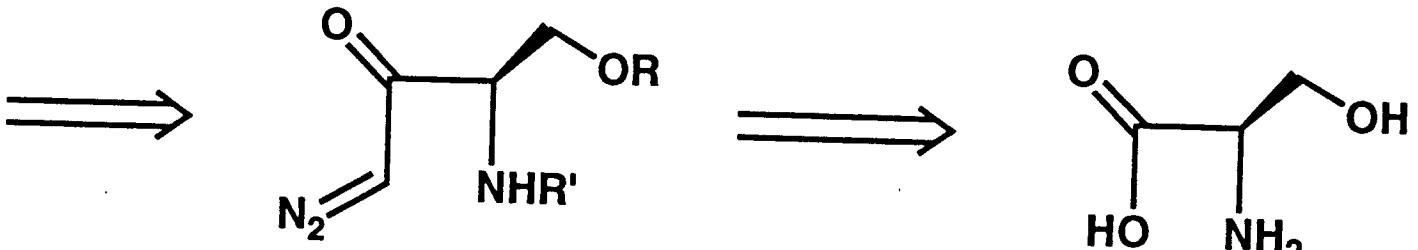
$[\alpha]_D = -94.6°$

K. Isono, et al *J. Am. Chem. Soc.* 91, 7490 (1969)

POLYOXIMIC ACID - DISCONNECTIVE ANALYSIS



Polyoximic acid

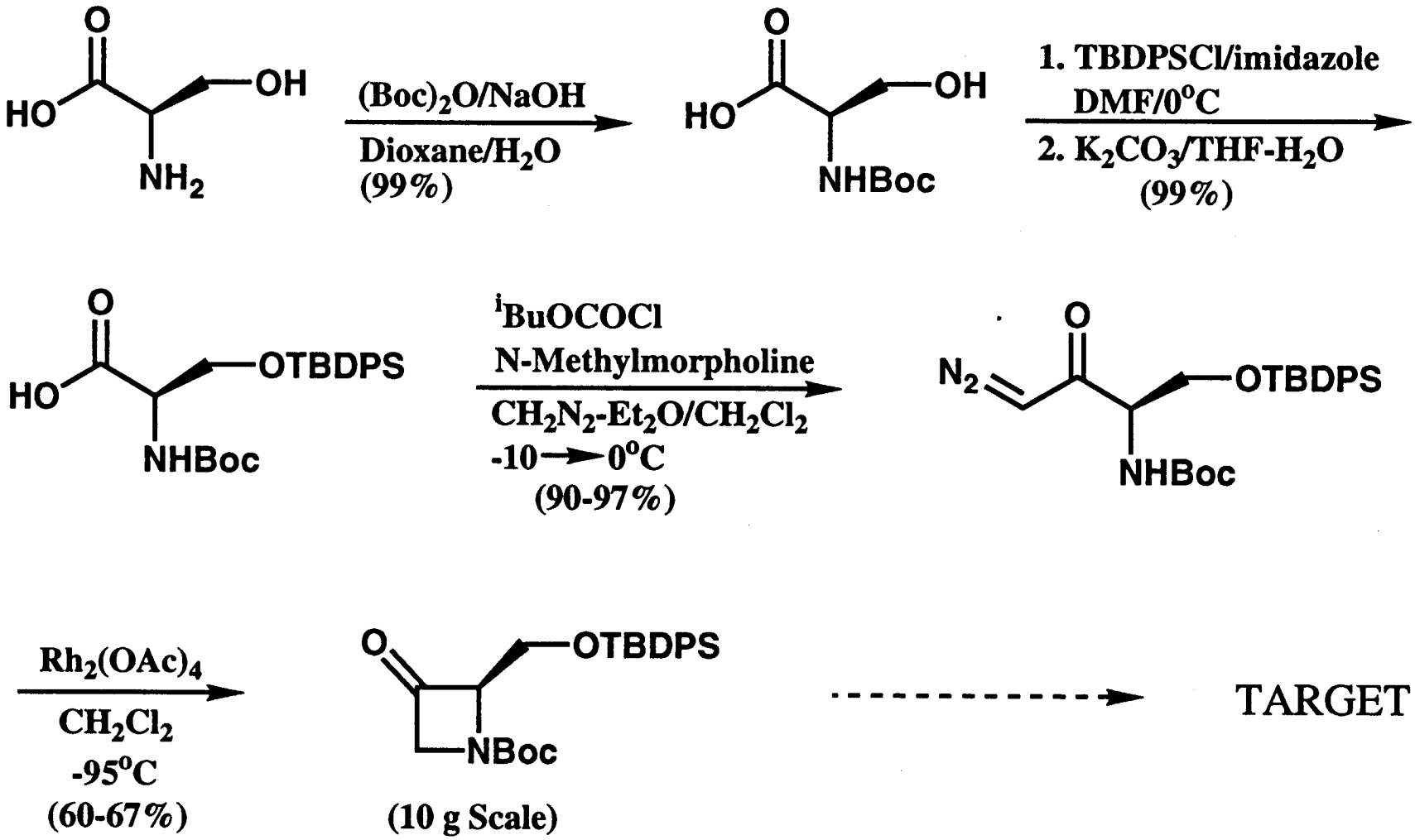


α-Diazoketone

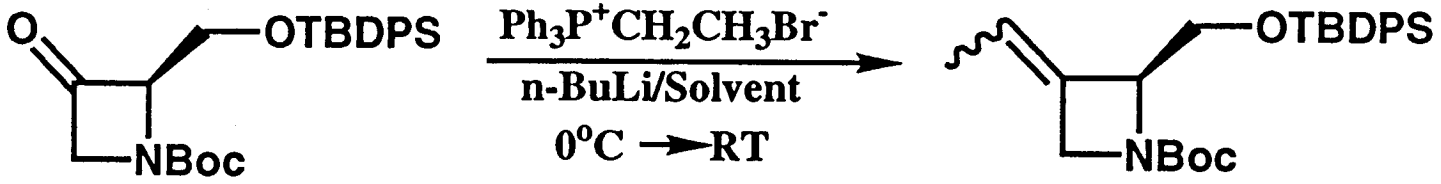
D-Serine

Jian-min Fu

SYNTHESIS OF THE AZETIDINONE PRECURSOR



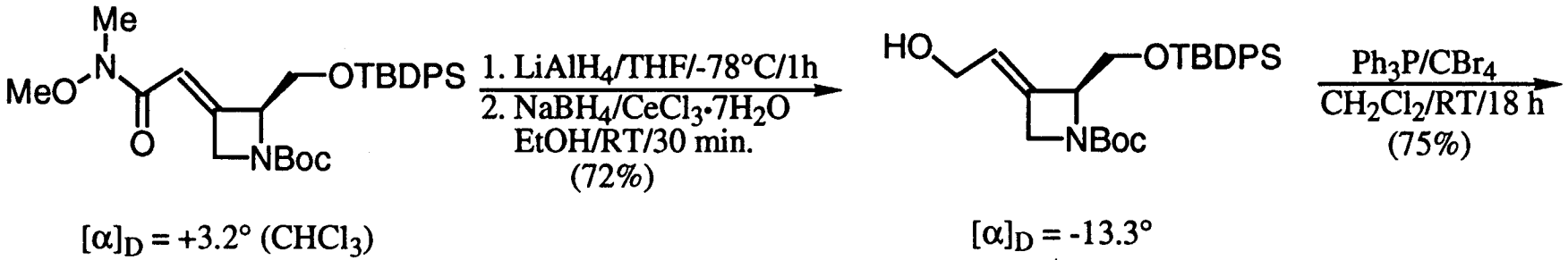
OLEFINATIONS



Solvent	Yield(%)	E:Z
THF	54	33:67
Toluene	50	37:63
HMPA	19	37:63
THF*	24	61:39
THF**	55	37:63

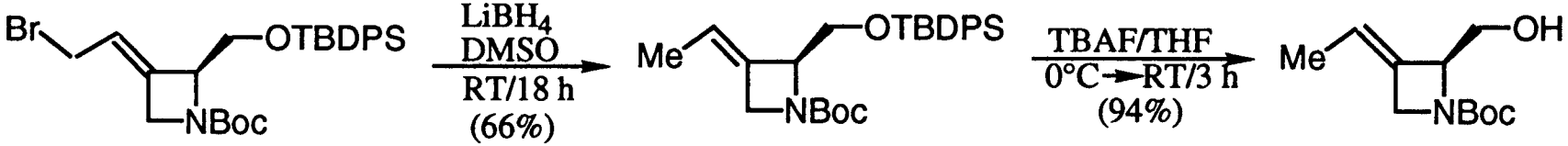
*Wittig-Schlosser conditions:1. 1 eq. n-BuLi; 2. 1 eq. n-BuLi; 3. t-BuOH.
**"Salt free" conditions: NaHMDS/0°C

SYNTHESIS OF (*E*)-POLYOXIMIC ACID



$[\alpha]_D$ = +3.2° ($CHCl_3$)

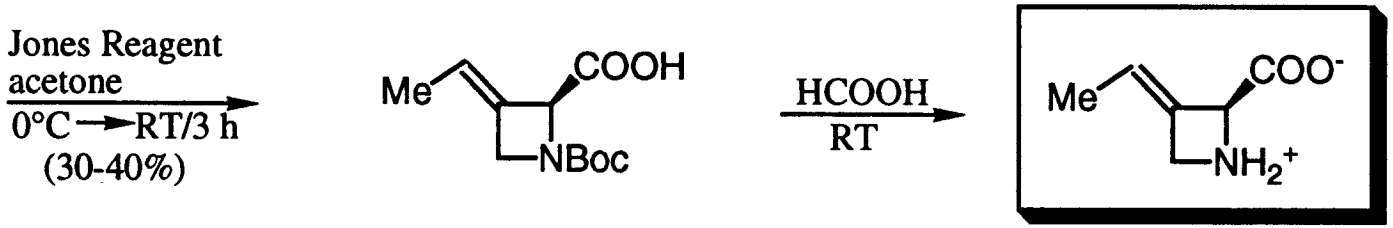
$[\alpha]_D$ = -13.3°



$[\alpha]_D$ = -10.9°

$[\alpha]_D$ = -10.7°

$[\alpha]_D$ = -8.9°

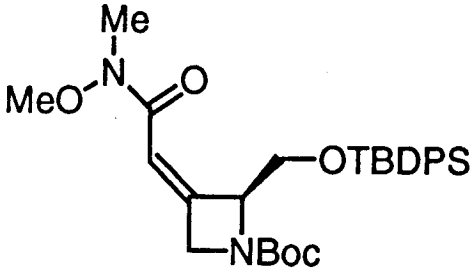


$[\alpha]_D$ = -63.5°
mp 138-140°C

$[\alpha]_D$ = +17.3° (MeOH)

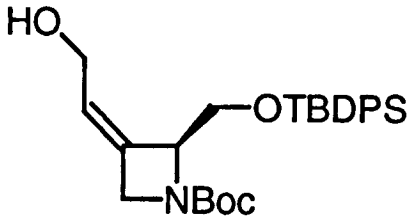
(*E*)-Polyoximic Acid

SYNTHESIS OF (Z)-POLYOXIMIC ACID



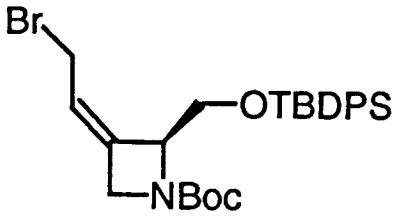
$[\alpha]_D$ = +15.9° ($CHCl_3$)
mp = 119-121°C

1. $LiAlH_4$/THF/-78°C/1h
2. $NaBH_4/CeCl_3 \cdot 7H_2O$
EtOH/RT/30 min.
(75%)



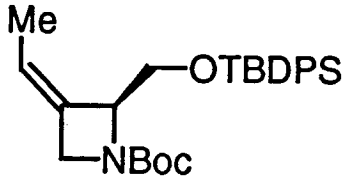
$[\alpha]_D$ = -0.2°

Ph_3P/CBr_4
CH_2Cl_2/RT/18 h
(80%)



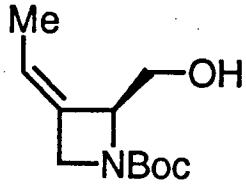
$[\alpha]_D$ = +60.3°

$LiBH_4$
DMSO
RT/18 h
(79%)



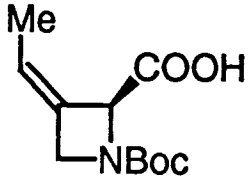
$[\alpha]_D$ = +4.4°

TBAF/THF
0°C → RT/3 h
(97%)



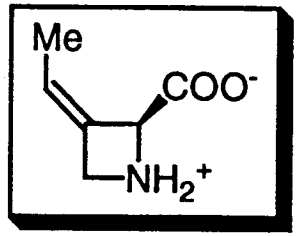
$[\alpha]_D$ = -11.4°

Jones Reagent
acetone
0°C → RT/3 h
(ca. 40%)



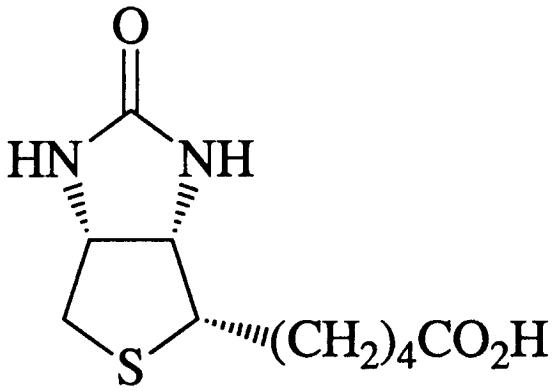
$[\alpha]_D$ = -15.3°

HCOOH
RT

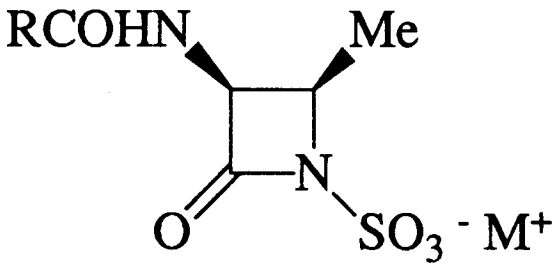


(Z)-Polyoximic Acid

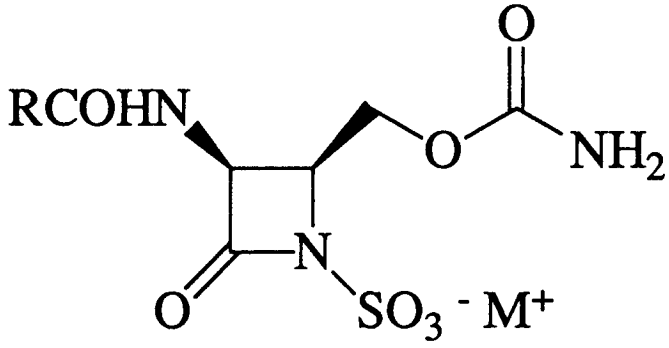
ACCESS TO STEREOCHEMICALLY DEFINED VICINAL DIAMINES



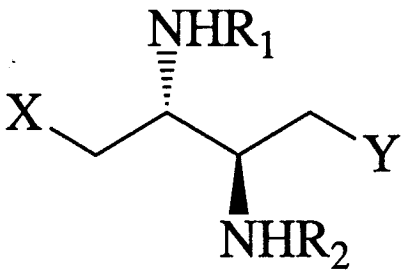
(+)-BIOTIN

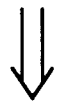


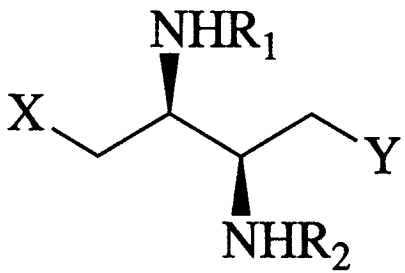
AZTHREONAM

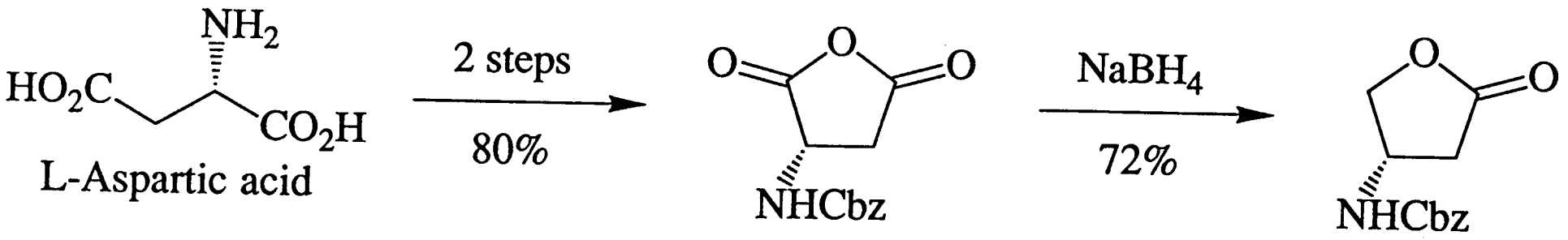


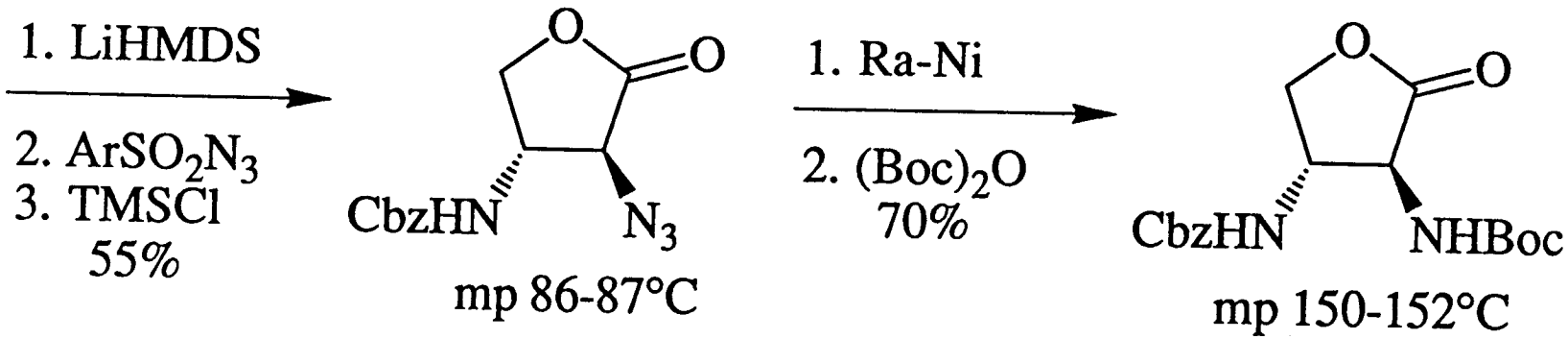
RO-17-2301

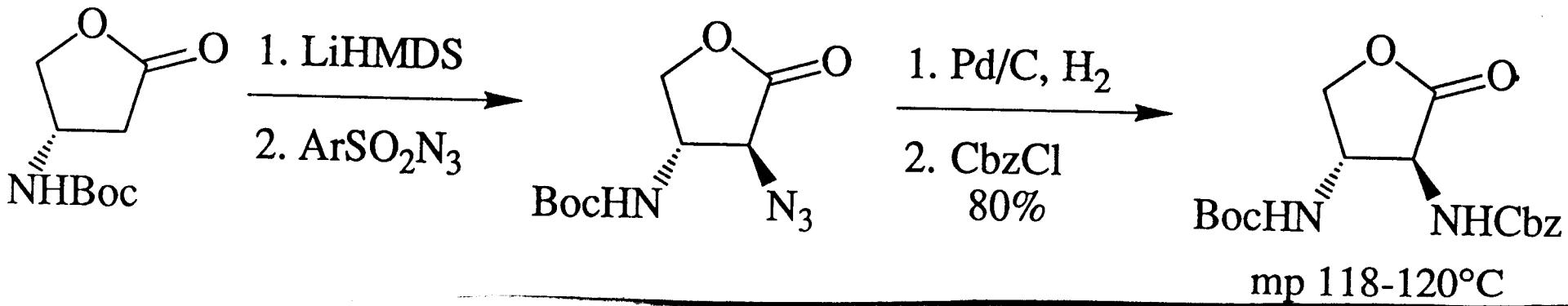




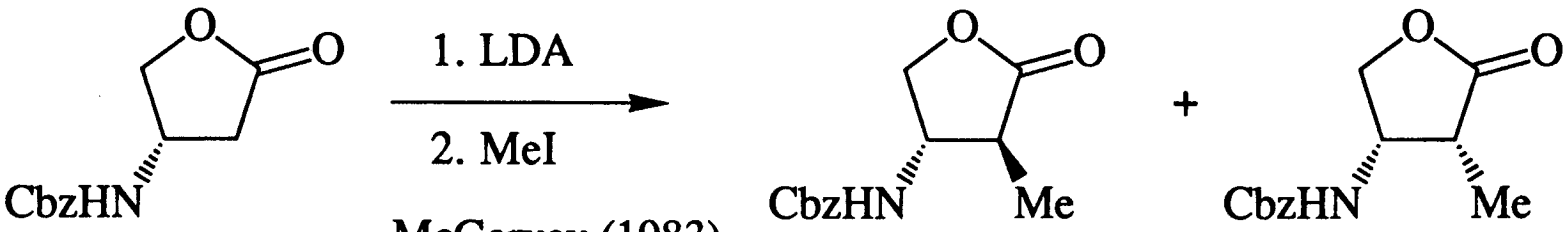


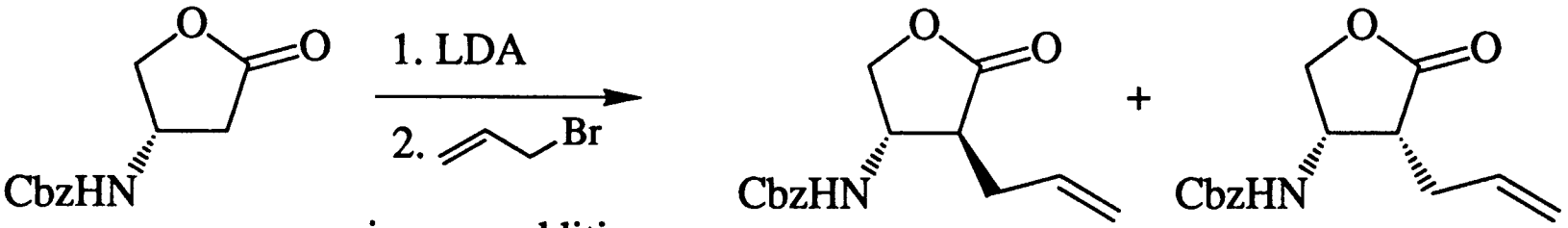

NH2
HO2C
CO2H
L-Aspartic acid
2 steps
80%
O
O
O
NHCbz
NaBH4
72%
O
O
NHCbz

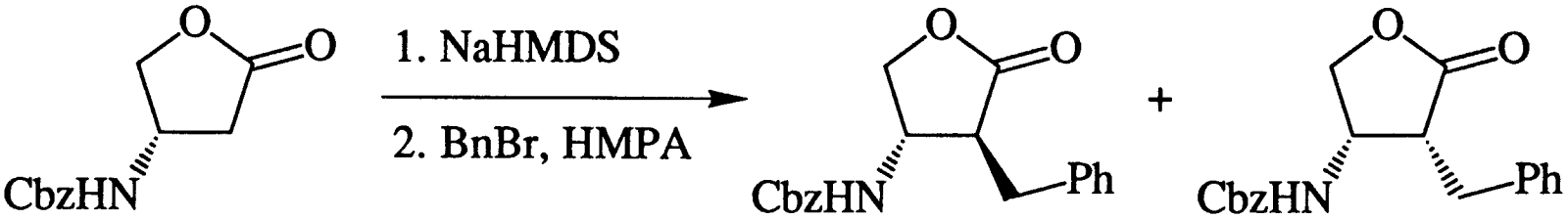

1. LiHMDS
2. ArSO2N3
3. TMSCl
55%
O
O
CbzHN
N3
mp 86-87°C
1. Ra-Ni
2. (Boc)2O
70%
O
O
CbzHN
NHBoc
mp 150-152°C


O
O
NHBoc
1. LiHMDS
2. ArSO2N3
O
O
BocHN
N3
1. Pd/C, H2
2. CbzCl
80%
O
O
BocHN
NHCbz
mp 118-120°C

STEREOSELECTIVE ALKYLATION

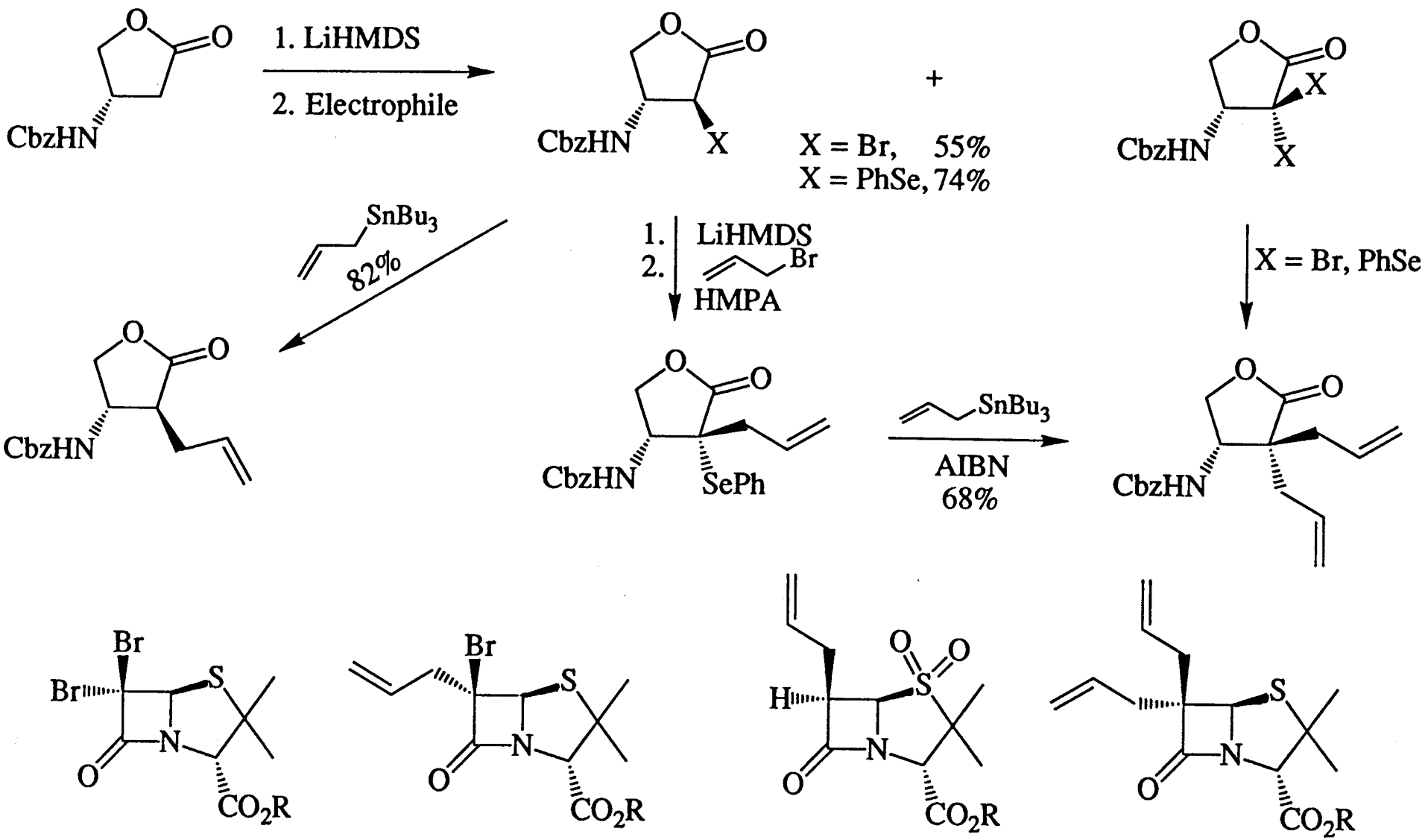






C. Kenny

STEREOSELECTIVE ALLYLATION

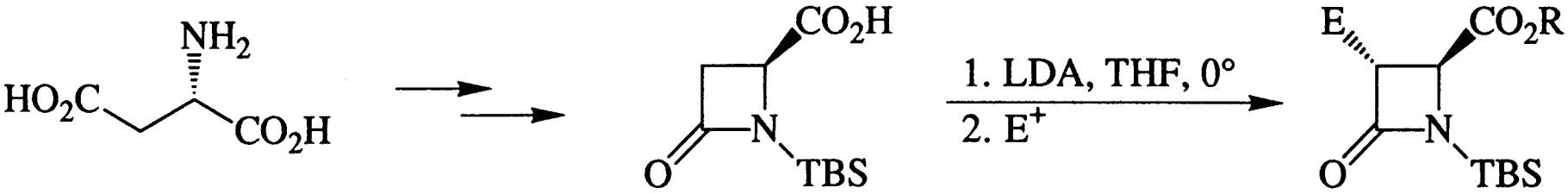


Tetrahedron, 45, 941 (1989)

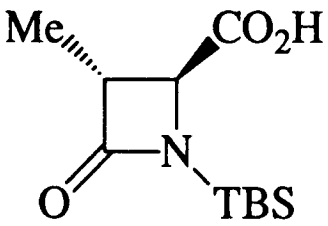
H. Yang

B. Vanasse
M.Alpegiani

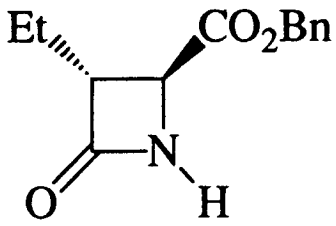
β-ALKYL ASPARTIC ACIDS — THE β-LACTAM ROUTE



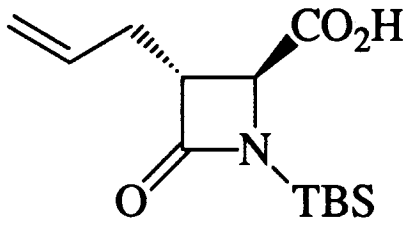
R = H, Bn



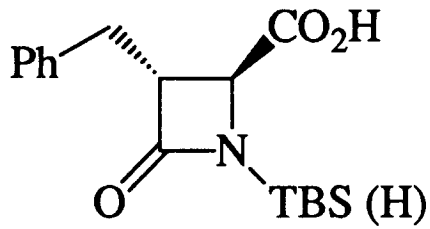
86%



52%
inverse addn.
HMPA

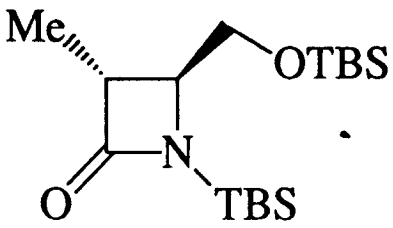


95%

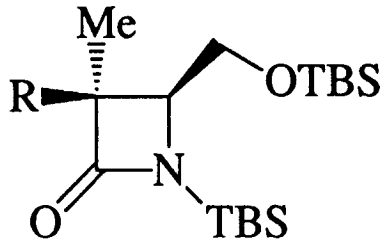


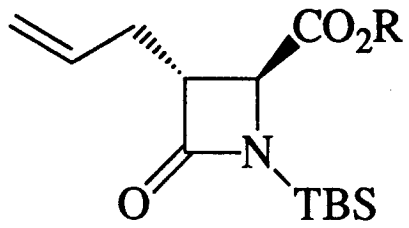
60%

Hanessian, Sumi **Synlett**, 33 (1992)

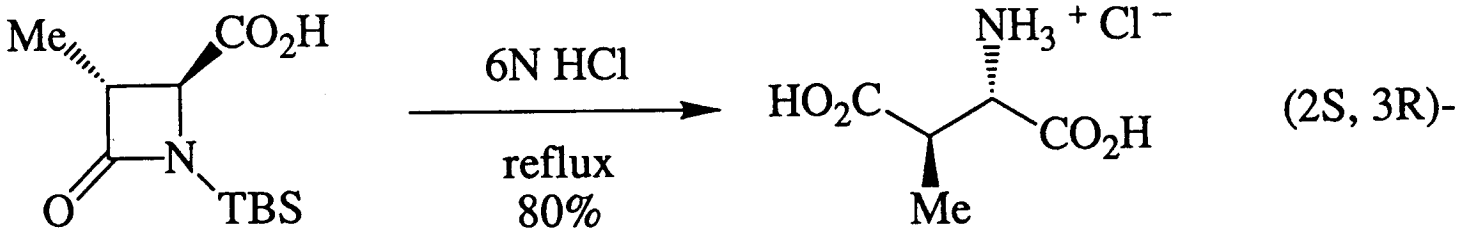


Thomas (1987)





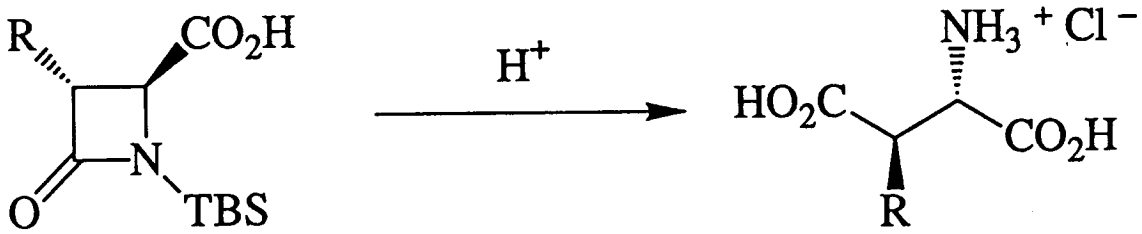
Baldwin (1990)

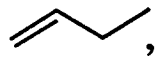


(2S, 3R)-

Reported $[\alpha]_D^{25}$ +35° (c 2.0, 5N HCl)

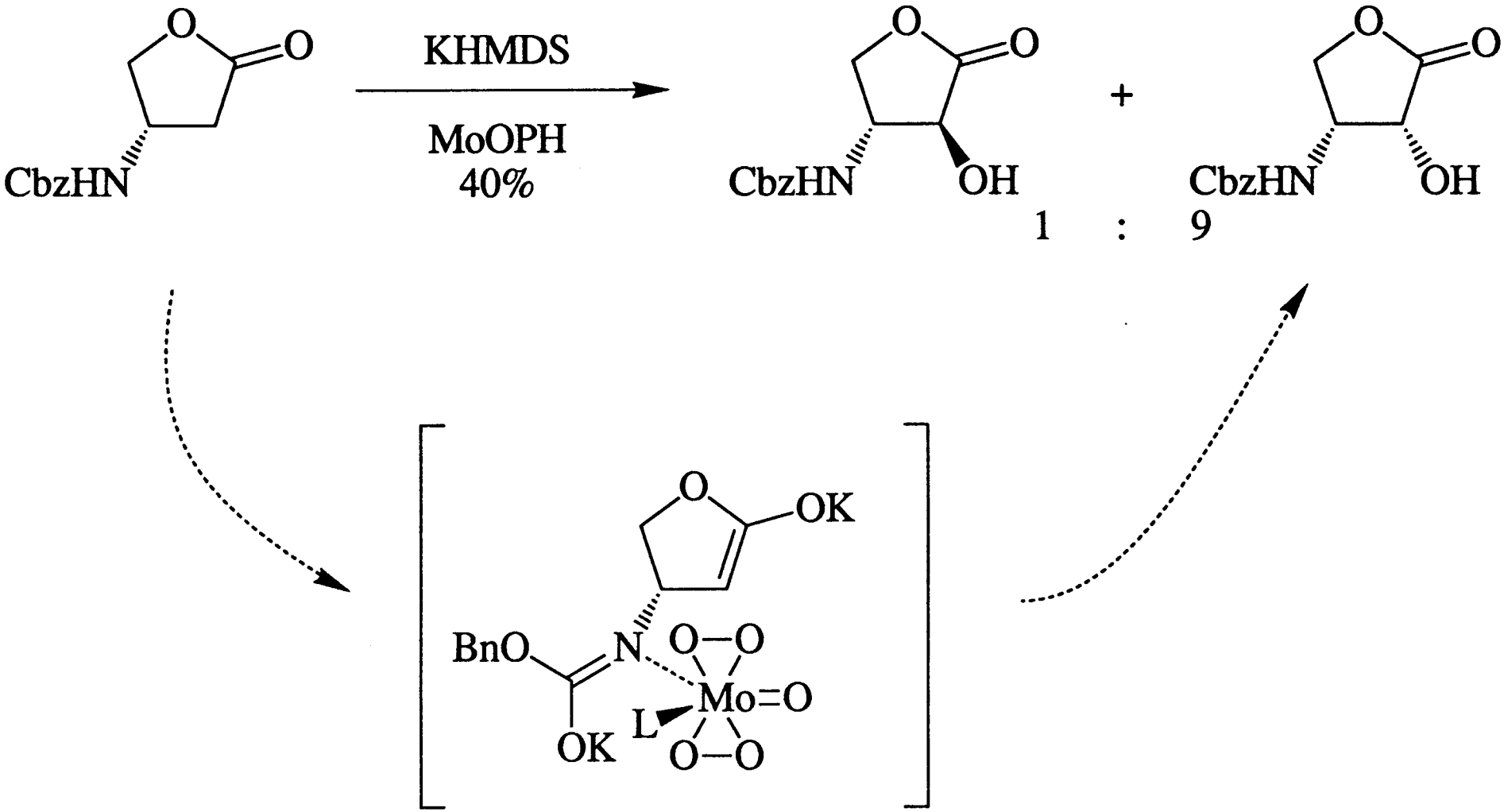
This work $[\alpha]_D^{25}$ +32.9° (c 0.8, 5N HCl)



R = Et,  , Bn

K. Sumi

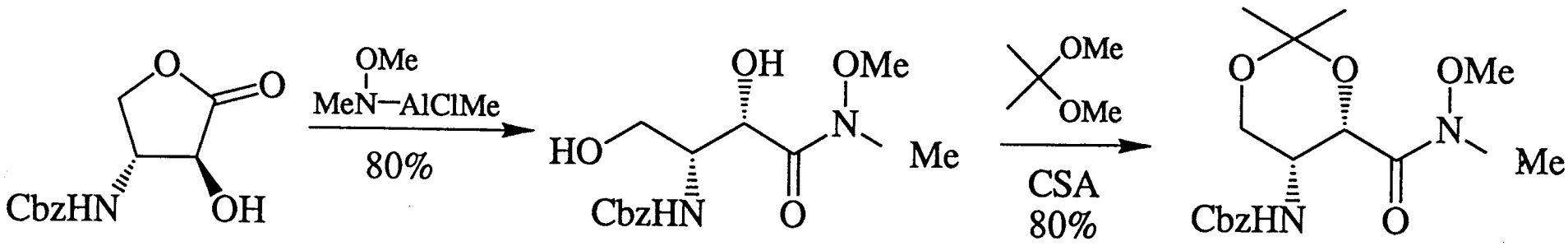
INTERNALLY DIRECTED HYDROXYLATION



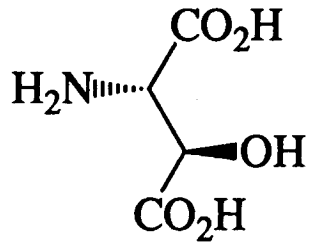
STEREOSELECTIVE ANTI HYDROXYLATION

mp 105-106°C

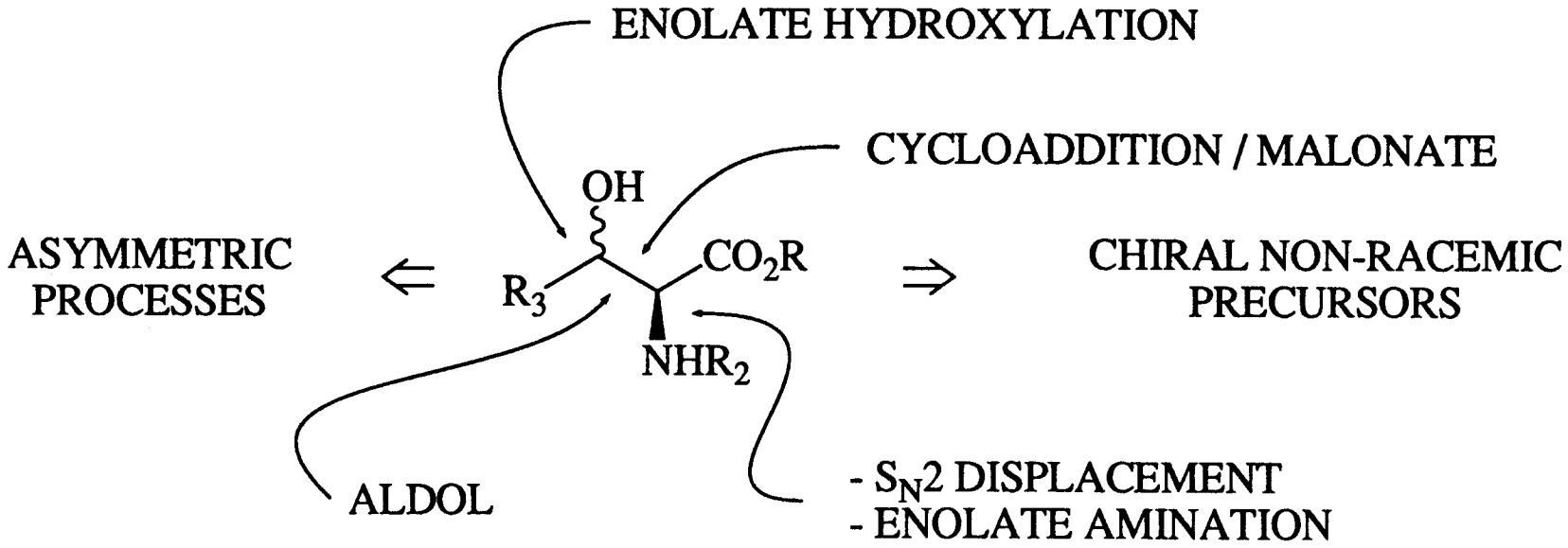
NaHMDS,	56%	14	: 1
KHMDS,	70%	6.5	: 1
LiHMDS,	50%	5	: 1



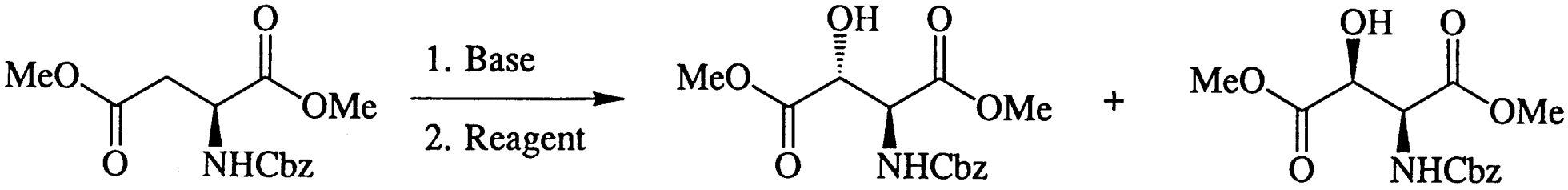
ACYCLIC SYSTEMS – L-ASPARTIC ACID



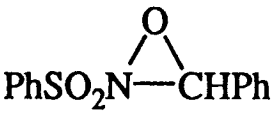
(2S,3R)-β-HYDROXY ASPARTIC ACID

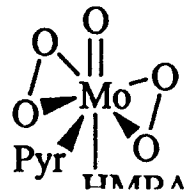


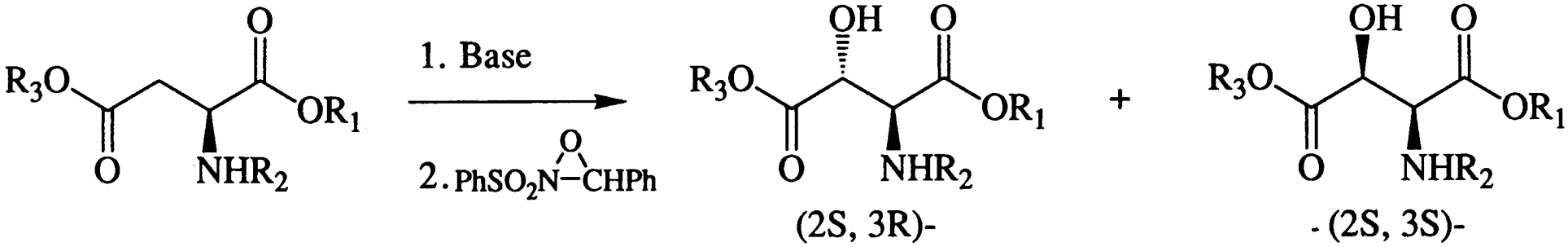
Recent synthesis: R. Wagner et al., Synthesis, 785 (1990)



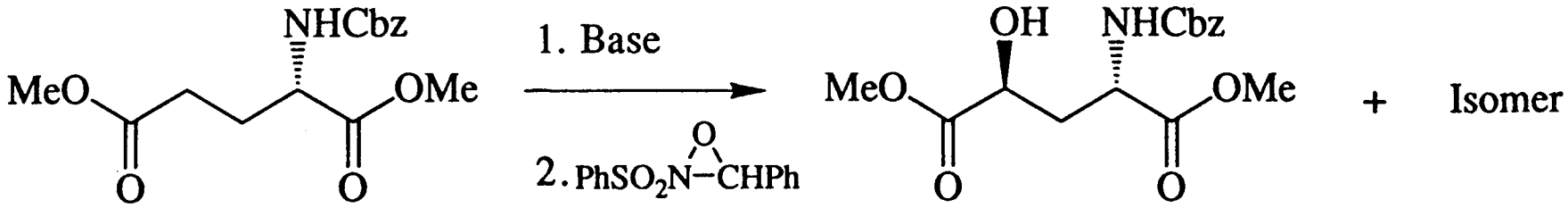
REAGENT	BASE	YIELD	RATIO	
OXAZIRIDINE	NaHMDS	70%	7 : 1	←
	LiHMDS	60%	2.5 : 1	
	KHMDS	70%	1 : 1	
	LDA	60%	1.5 : 1	
MoOPH	KHMDS	50 (60)%	1 : 1	
	LiHMDS	36 (50)%	1 : 2	←

OXAZIRIDINE : 

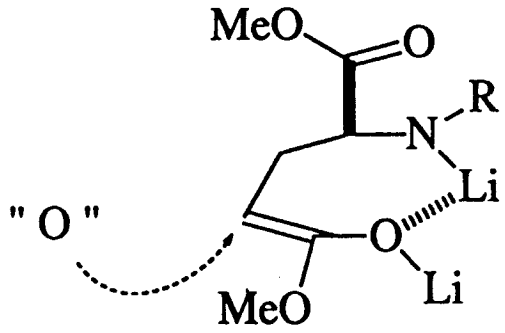
MoOPH : 

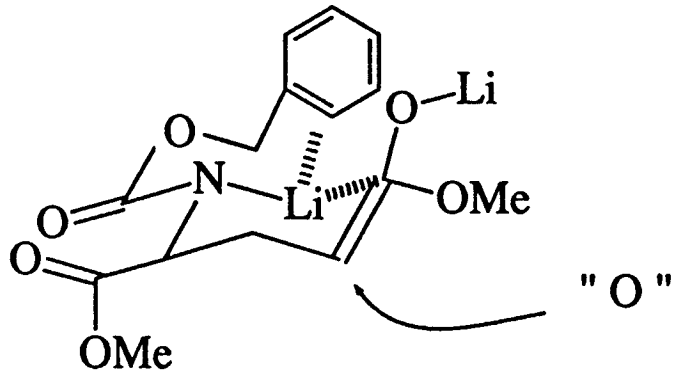


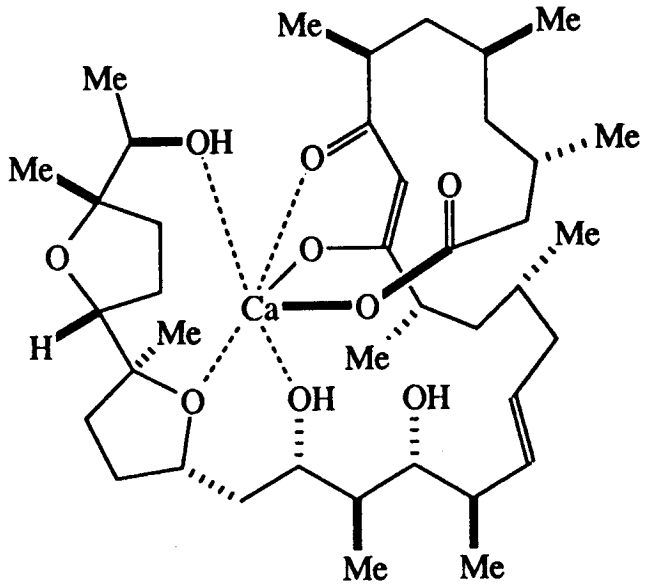
BASE	R1	R2	R3	YIELD	RATIO	
LiHMDS	Me	Cbz	*t*-Bu	40%	10 : 1	←
LiHMDS	*t*-Bu	Cbz	Me	60%	10 : 1	
LiHMDS	*t*-Bu	Cbz	*t*-Bu	70%	10 : 1	
LiHMDS	*t*-Bu	Ts	*t*-Bu	57%	45 : 1	←



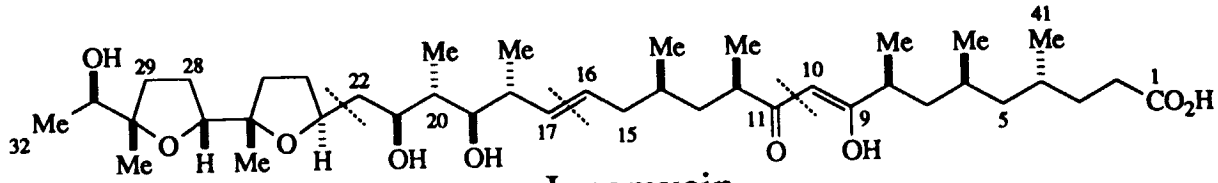
BASE	YIELD	RATIO
LiHMDS	70%	9 : 1
KHMDS	70%	1 : 1
NaHMDS	50%	2.6 : 1



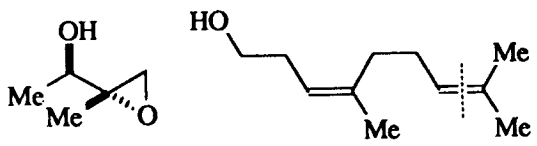




Ionomycin Ca salt



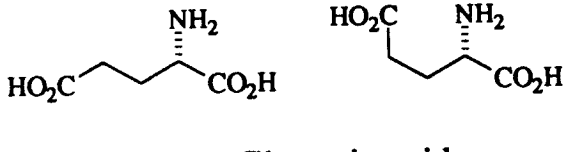
Ionomycin



C_{29}-C_{32}

Geraniol

C_{23}-C_{28}



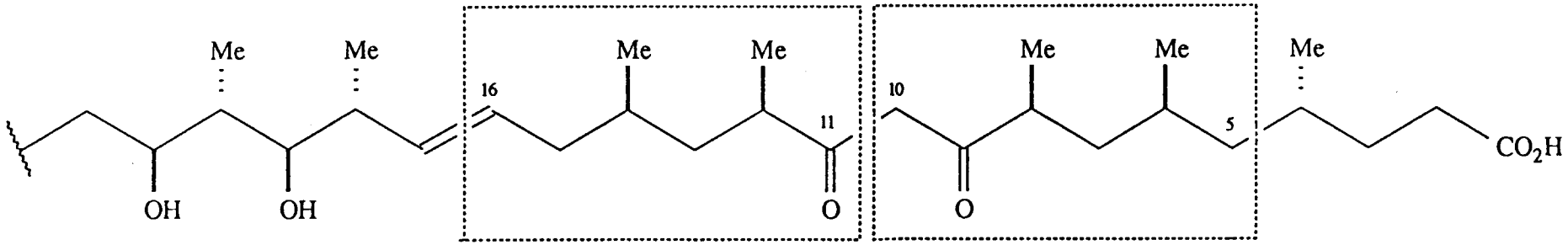
C_5-C_9; C_{11}-C_{15}; C_{17}-C_{20}

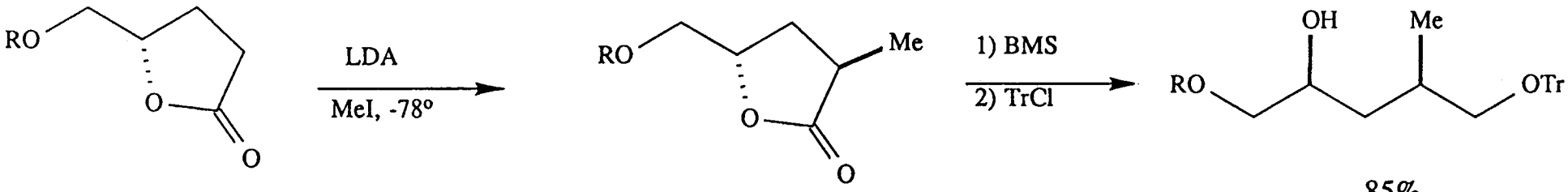
L-Glutamic acid

C_1-C_{41}

Hanessian, Cooke, Dehoff, Sakito **J.A.C.S**, 112, 5276 (1990)

THE C_5 - C_{10} AND C_{11} - C_{16} SUBUNITS - AN EXPEDITIOUS APPROACH



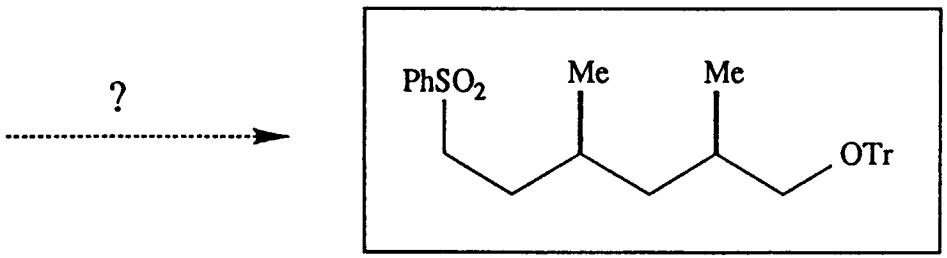


R = t-butyldiphenylsilyl

83%

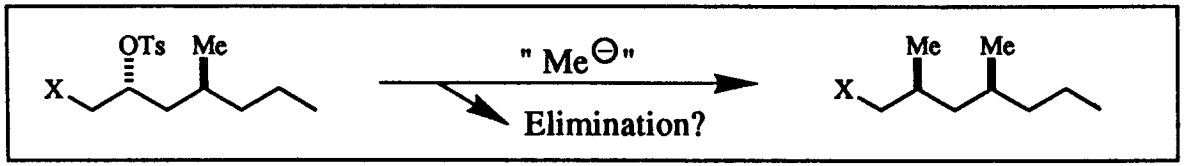
85%

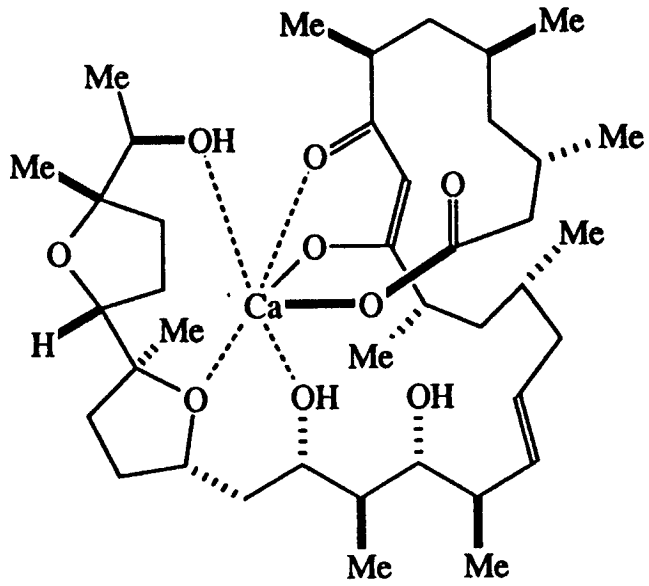
Tetrahedron Lett. **1985**,26, 5623



HOW TO REPLACE A SECONDARY HYDROXYL GROUP BY A METHYL WITH INVERSION?

WOULDN'T IT BE NICE TO C-METHYLATE VIA AN S_N2-TYPE DISPLACEMENT REACTION ?



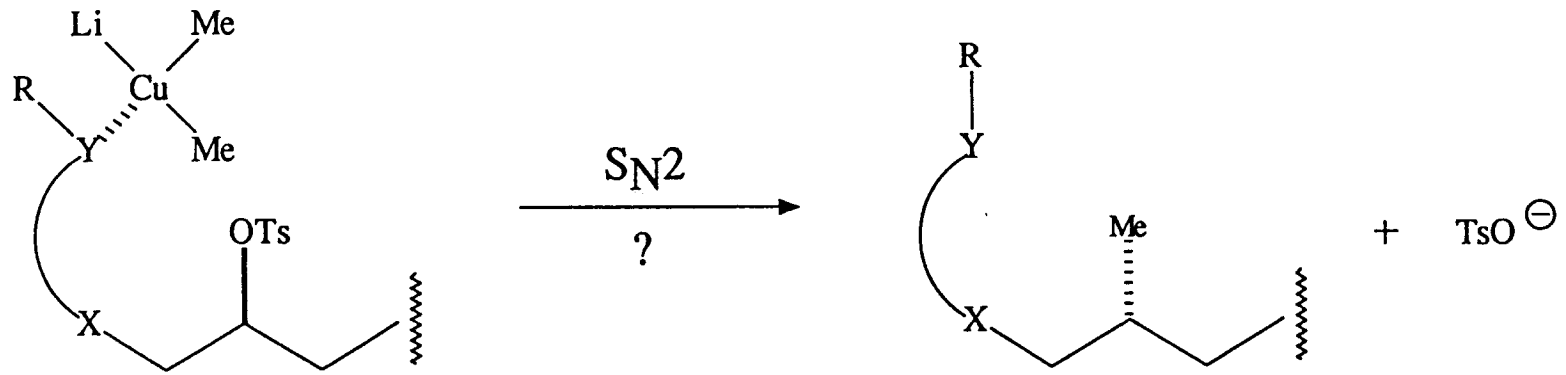


Ionomycin Ca salt

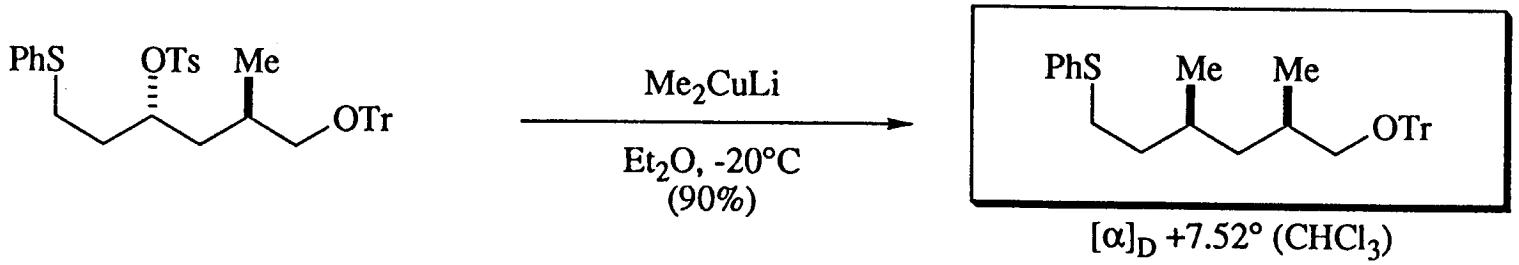
- Evans and Dow, 1985
- Hanessian, Cooke, Dehoff, Sakito, 1989

JACS 112, 5276 (1990)

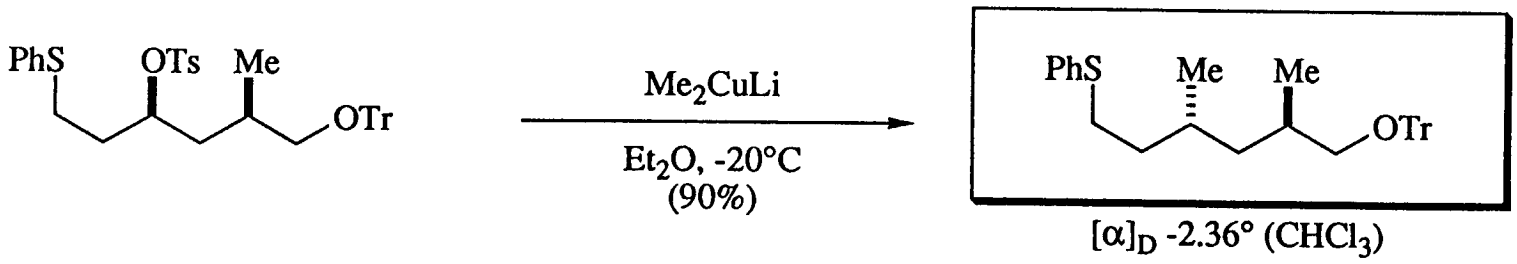
INTERNALLY ASSISTED S_N2 CUPRATE ...



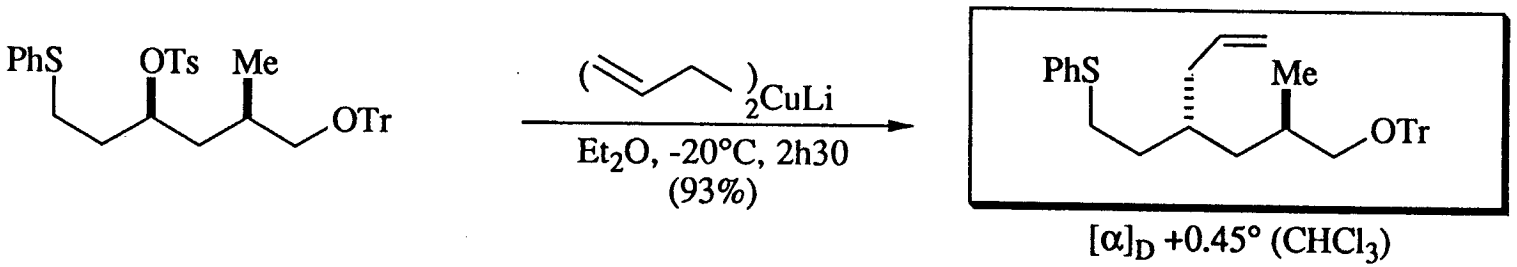
1,3- SUBSTITUTION — DEOXYPROPIONATE SUBUNITS



$[\alpha]_D$ +7.52° ($CHCl_3$)



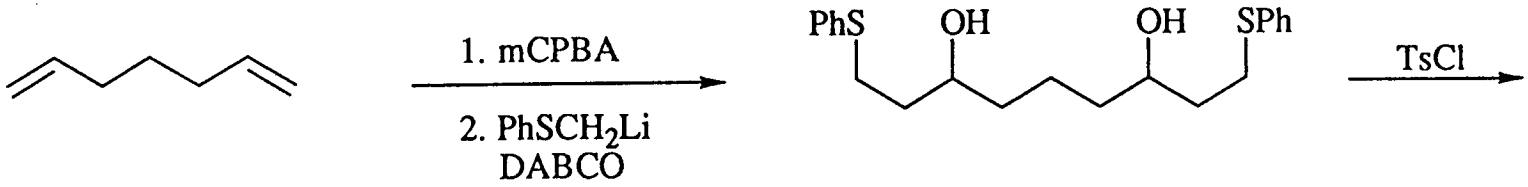
$[\alpha]_D$ -2.36° ($CHCl_3$)

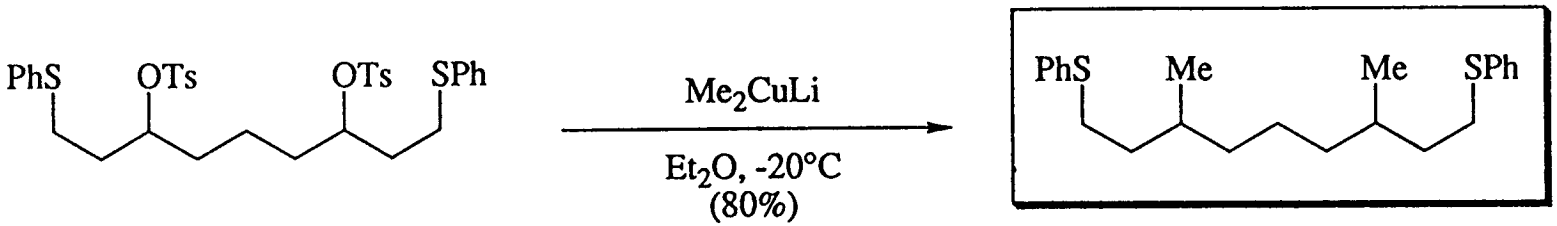


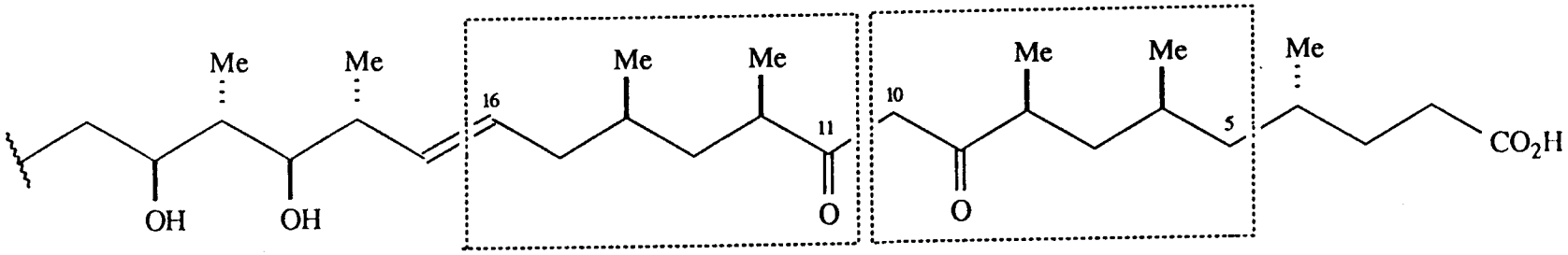
$[\alpha]_D$ +0.45° ($CHCl_3$)

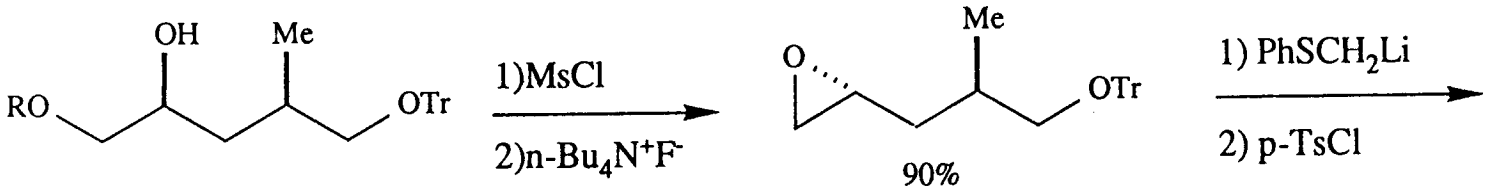
JOC 54, 5831 (1989)

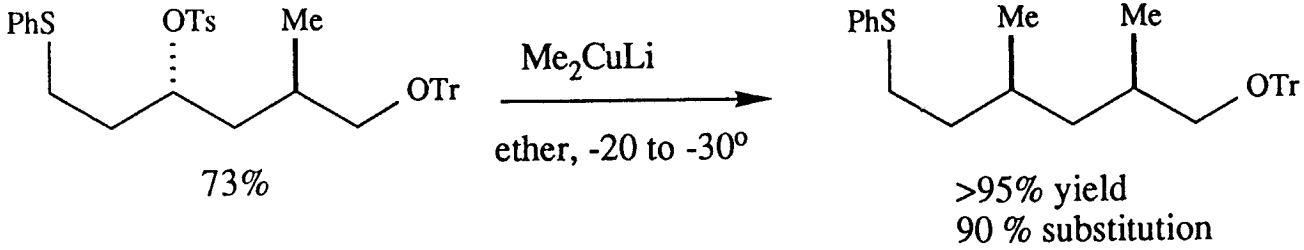
1,5- SUBSTITUTION — ISOPRENOID SUBUNITS

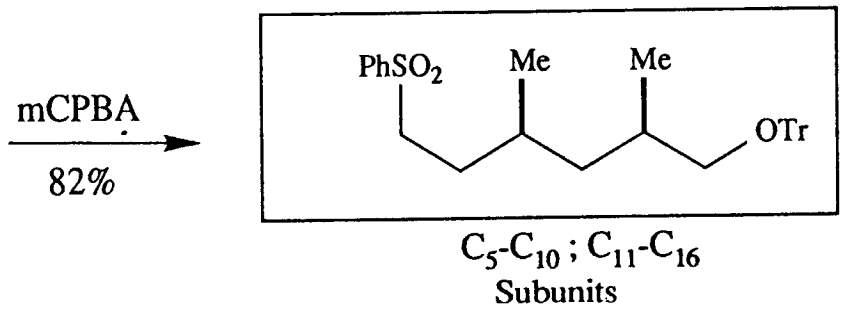





Me
Me
Me
Me
Me
Me
16
11
10
5
OH
OH
O
O
CO2H

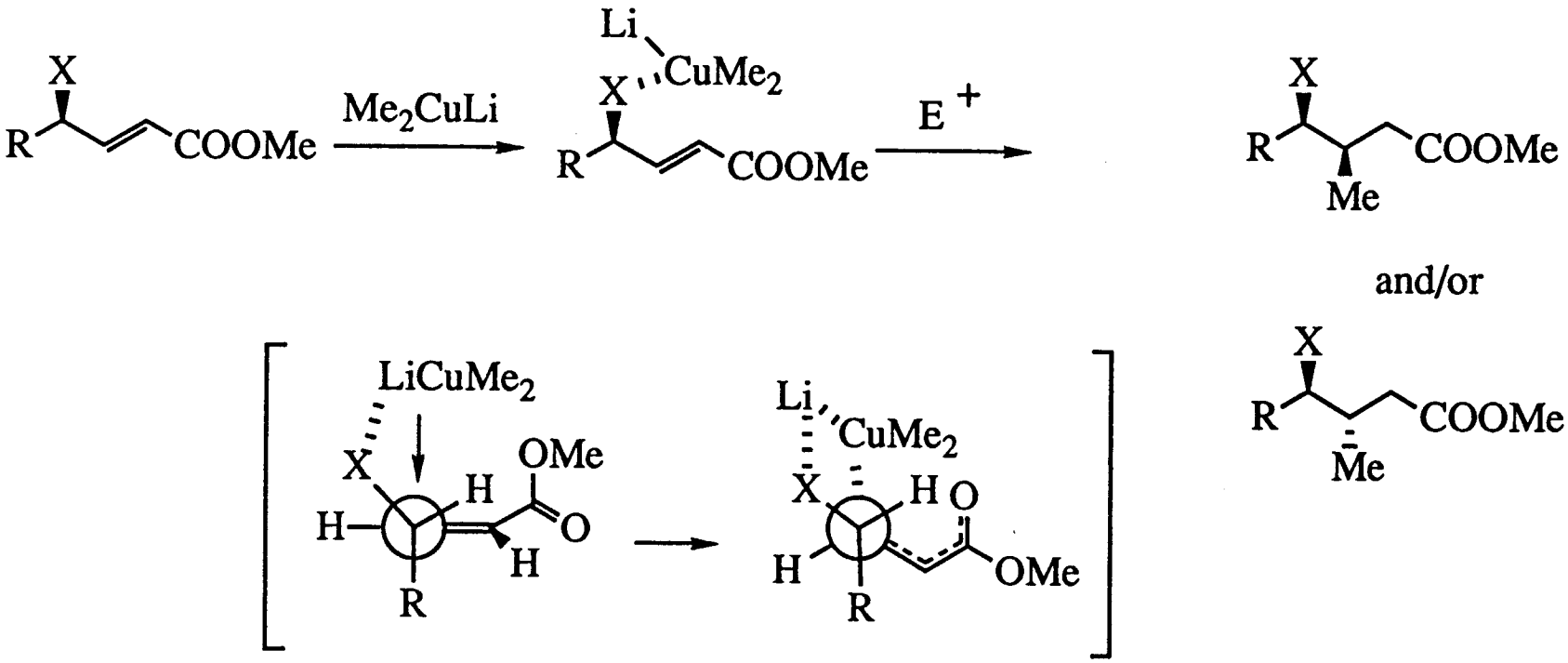

OH
Me
RO
OTr
1)MsCl
2)n-Bu4N+F-
Me
O
OTr
90%
1) PhSCH2Li
2) p-TsCl


PhS
OTs
Me
OTr
73%
Me2CuLi
ether, -20 to -30°
PhS
Me
Me
OTr
>95% yield
90 % substitution


mCPBA
82%
PhSO2
Me
Me
OTr
C5-C10 ; C11-C16
Subunits

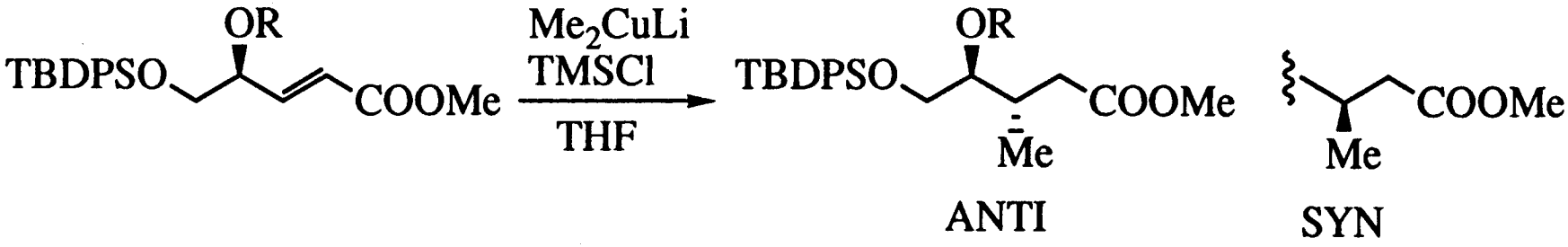
B. DeHoff

CONJUGATE ADDITION *VIA* INTERNAL ASSISTANCE ?

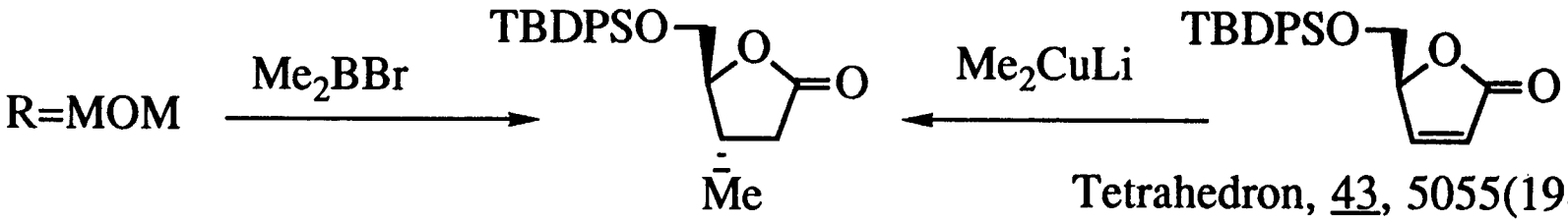


R=alkyl, alkoxy
X=O, N (Protected)

THE γ-ALKOXY EFFECT



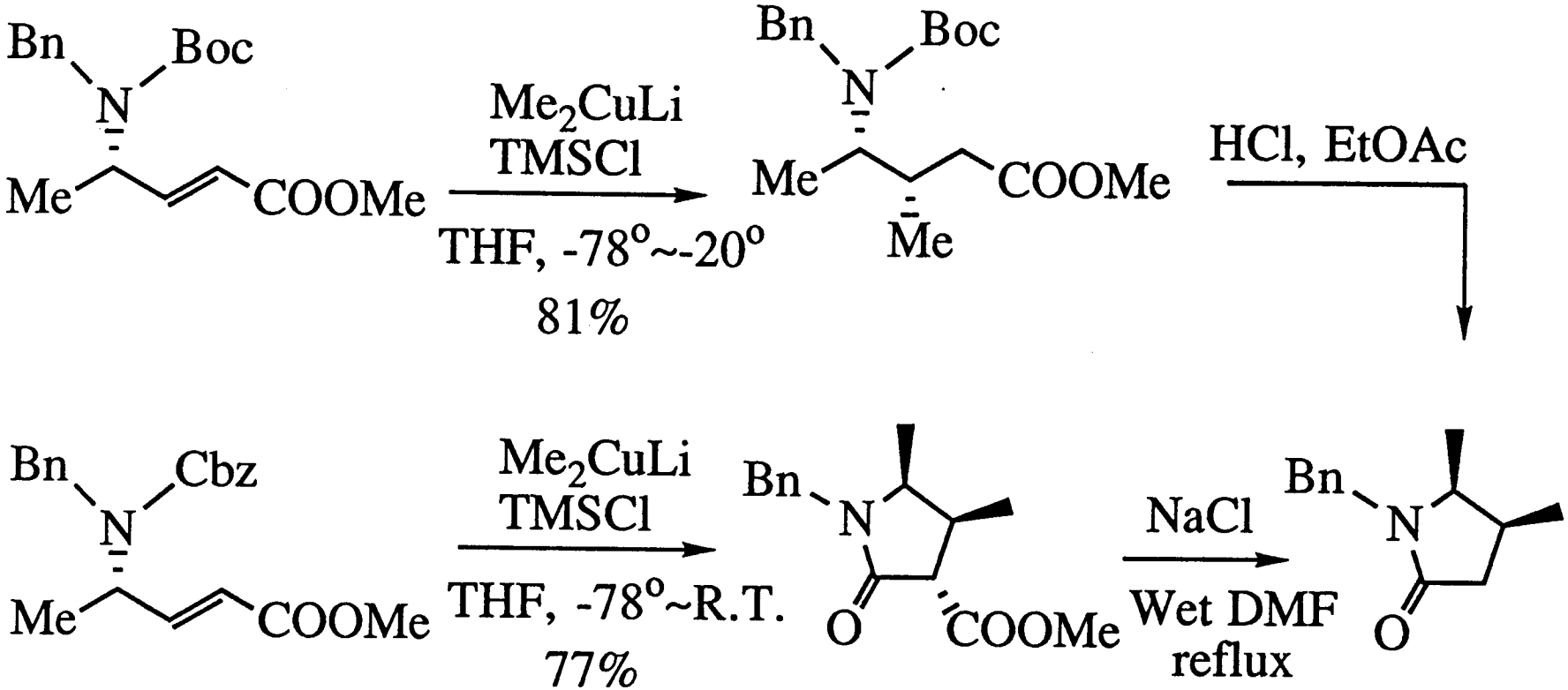
1, R=BOM	87%	14	:	1
2, R=MOM	87%	11	:	1
3, R=MTM	78%	9.8	:	1
4, R=Me	88%	9.9	:	1



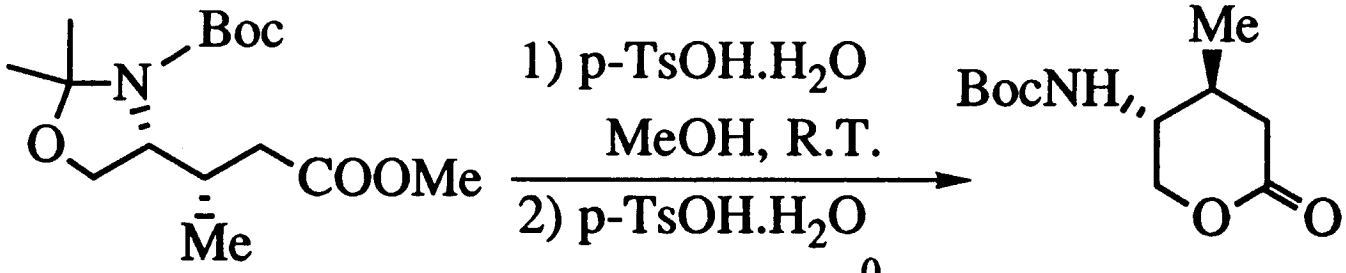
Tetrahedron, 43, 5055(1987)

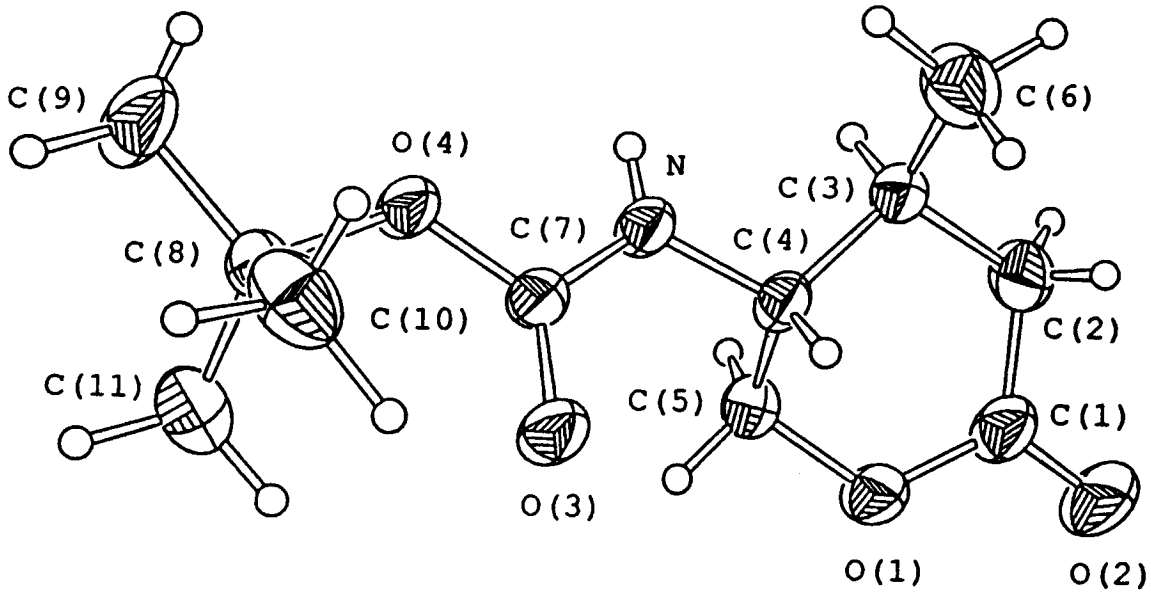
Hanessian, Sumi **Synthesis**, 1083 (1991)

K. SUMI


Bn
Boc
N
Me
COOMe
Me2CuLi
TMSCl
THF, -78°~-20°
81%
Me
COOMe
HCl, EtOAc
Bn
Cbz
N
Me
COOMe
Me2CuLi
TMSCl
THF, -78°~R.T.
77%
Bn
N
O
COOMe
NaCl
Wet DMF
reflux
Bn
N
O
via
O
Bn
N
OBn
Me
OMe
Me
OTMS

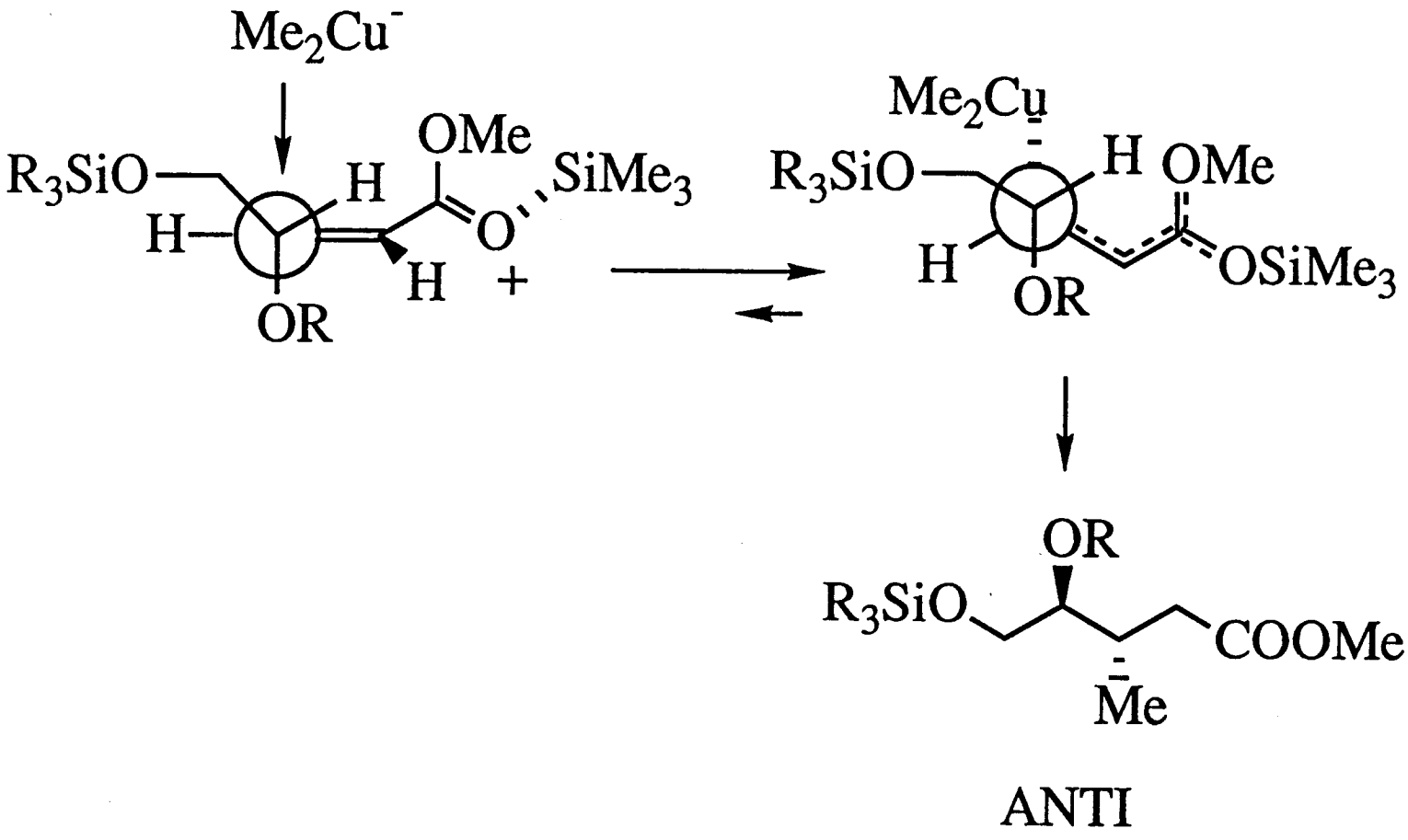
K. SUMI


Boc
N
O
COOMe
Me
1) p-TsOH.H2O
MeOH, R.T.
2) p-TsOH.H2O
Toluene, 80°
Me
BocNH
O
O


C(9)
O(4)
N
C(3)
C(6)
C(8)
C(7)
C(4)
C(10)
C(2)
C(11)
C(5)
C(1)
O(3)
O(1)
O(2)

K. SUMI

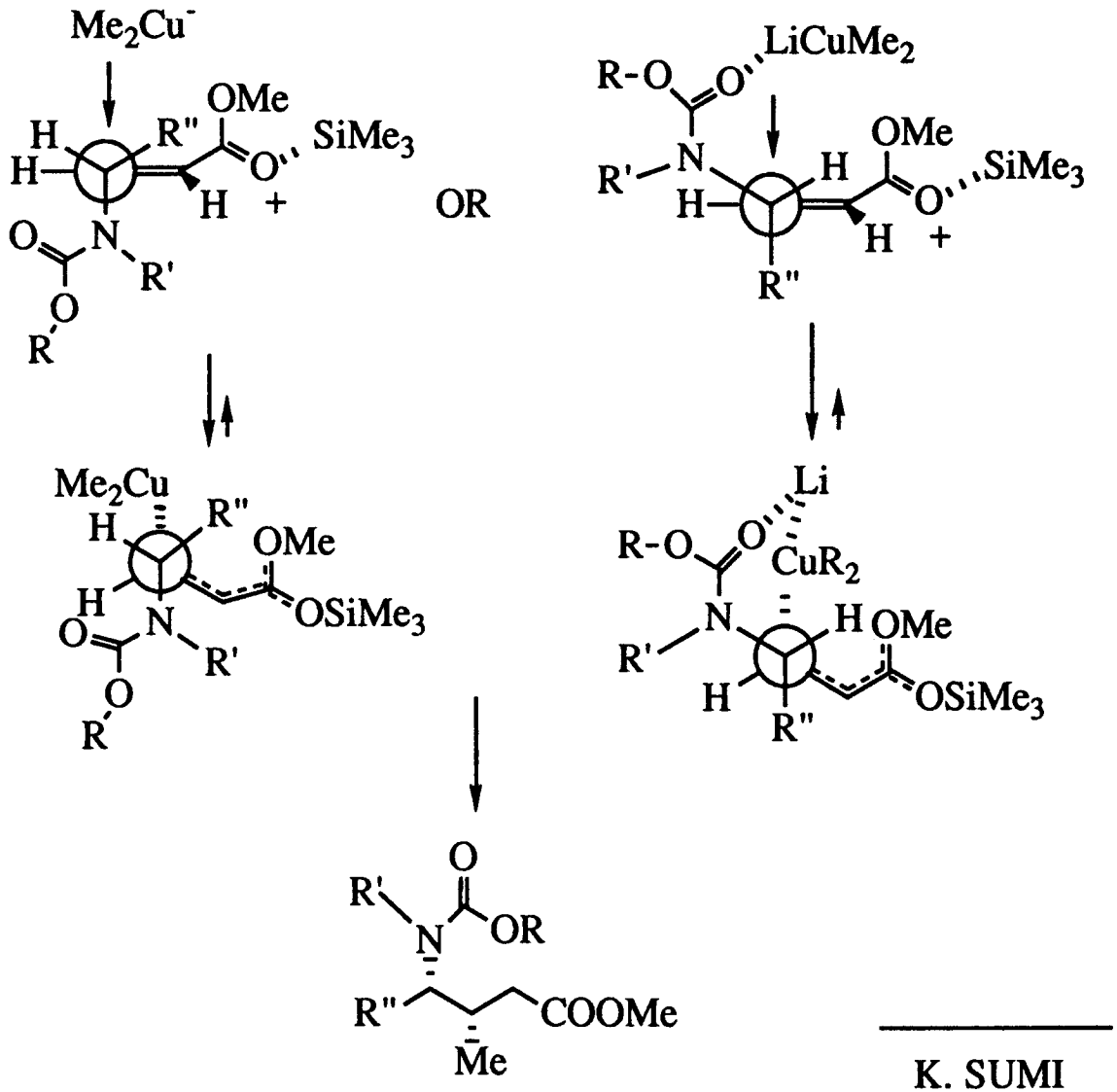
NON-CHELATED ATTACK IN ALKOXY SERIES



ANTI

K. SUMI

CHELATED OR NON-CHELATED ATTACK IN NITROGEN SERIES



K. SUMI