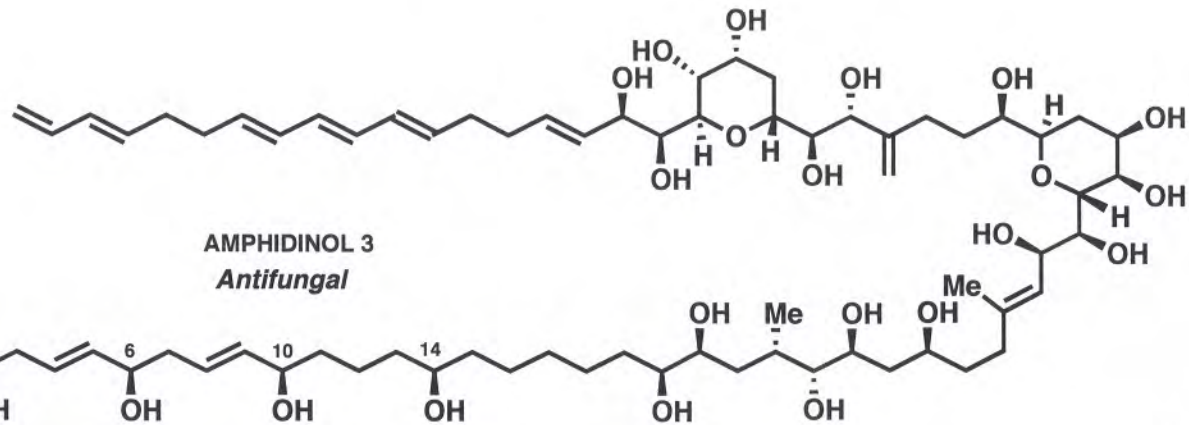
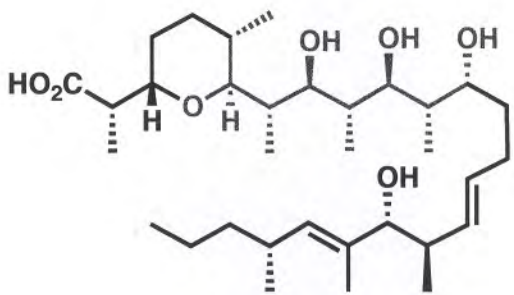
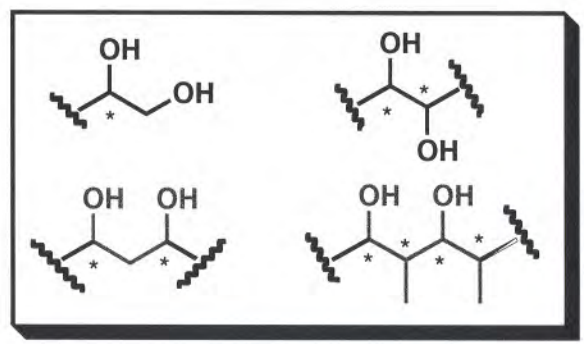
DIOLS, POLYKETIDES AND BIOLOGICALLY ACTIVE COMPOUNDS

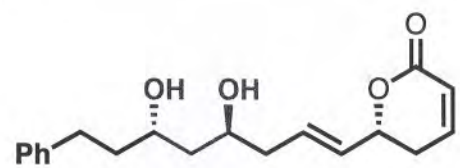


AMPHIDINOL 3
Antifungal

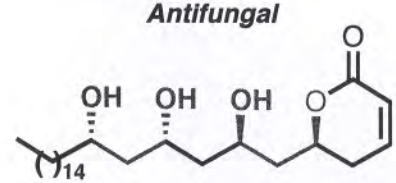


ZINCOPHORIN
Antibacterial

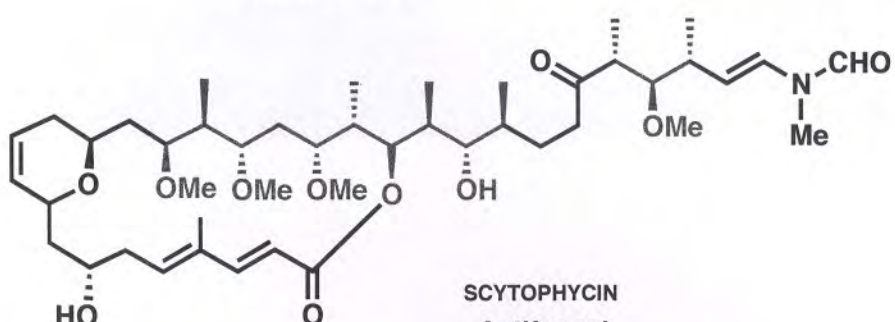




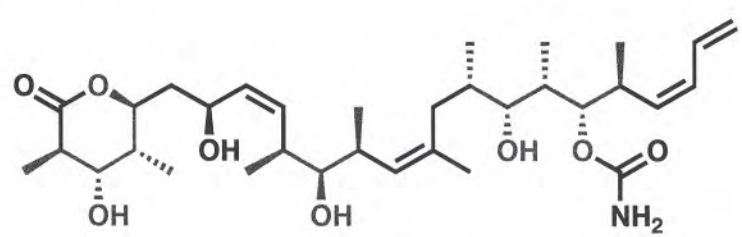
STRICTIFOLIONE
Antifungal



PASSIFLORICINE A
Antifungal

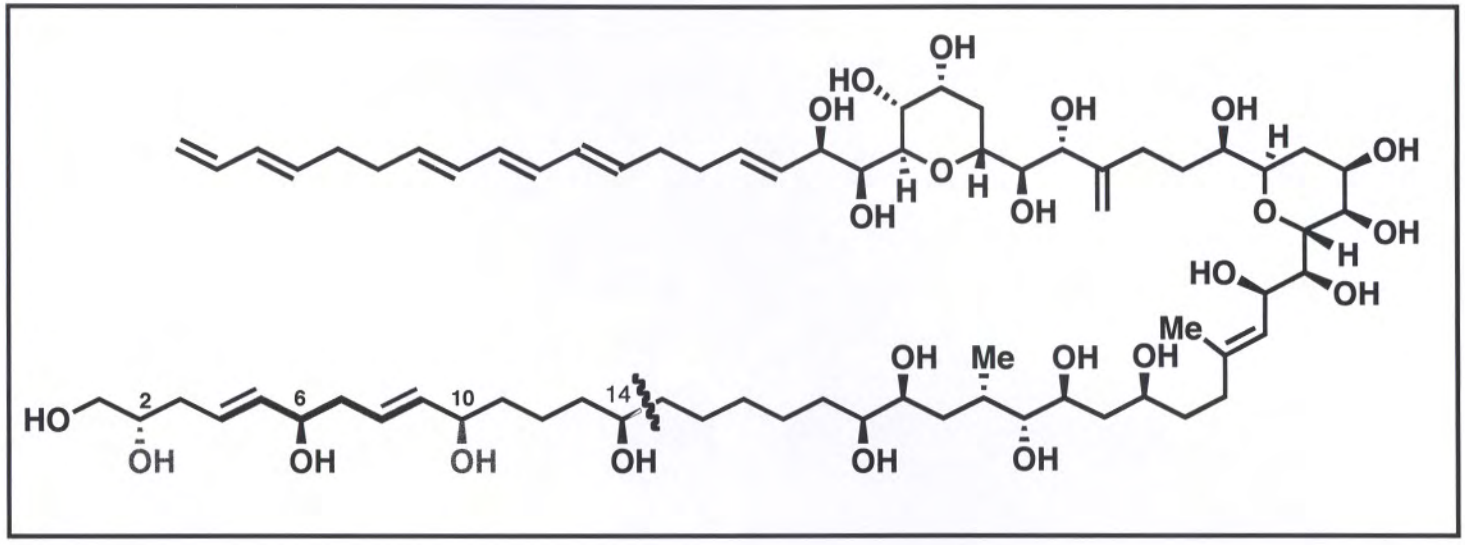


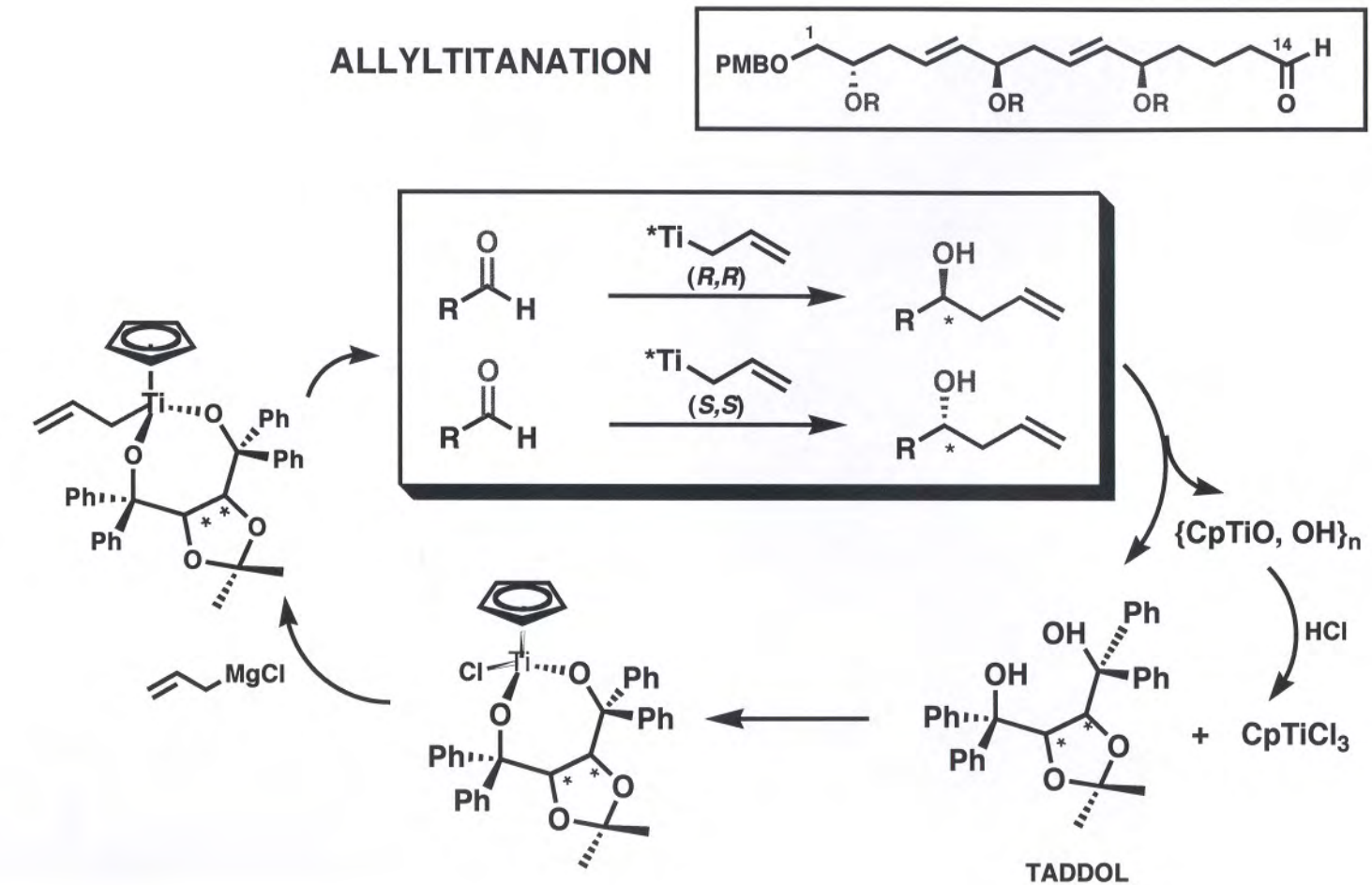
SCYTOPHYCIN
Antifungal,
potential therapeutic value for
the treatment of drug-resistant cancers



DISCODERMOLIDE
Immunosuppressive
anticancer

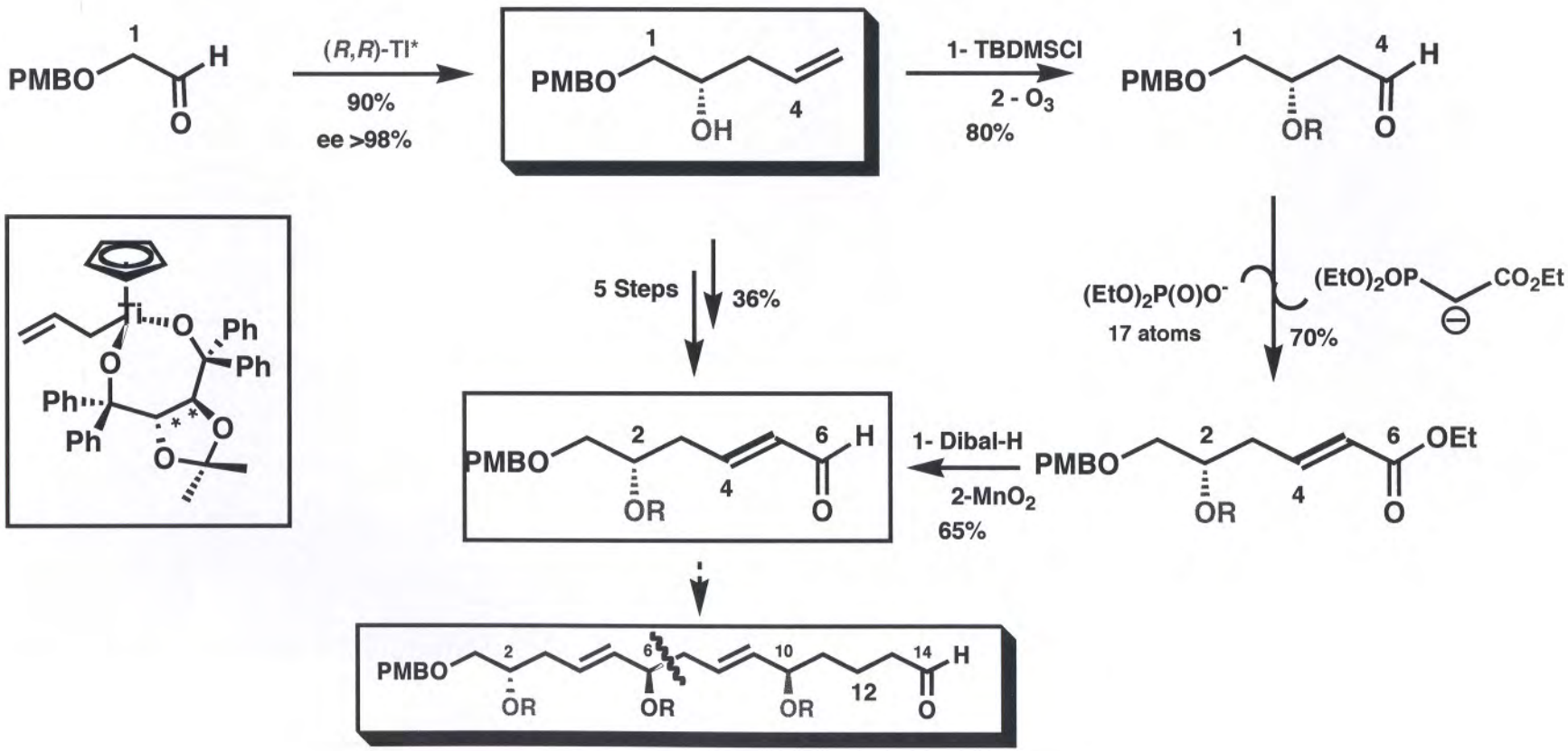
AMPHIDINOL 3



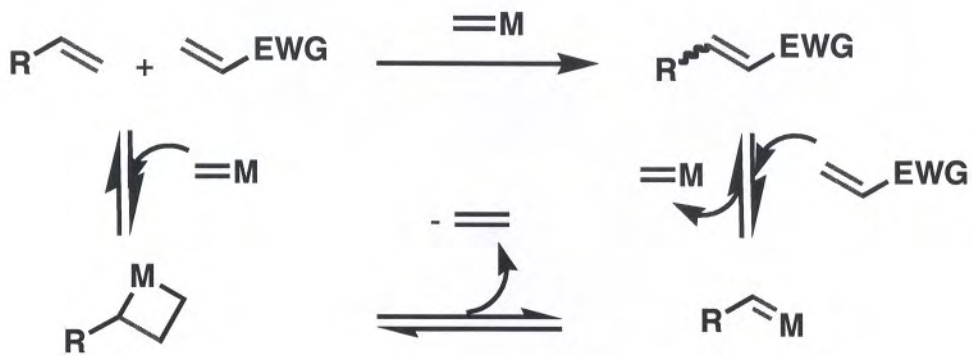


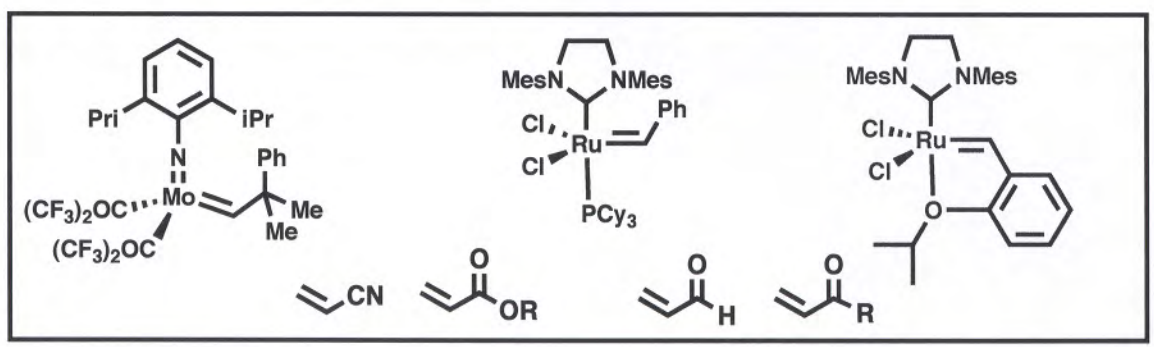
Duthaler, R. O. .... *J. Am. Chem. Soc.* **1992**, *114,* 2321-2336

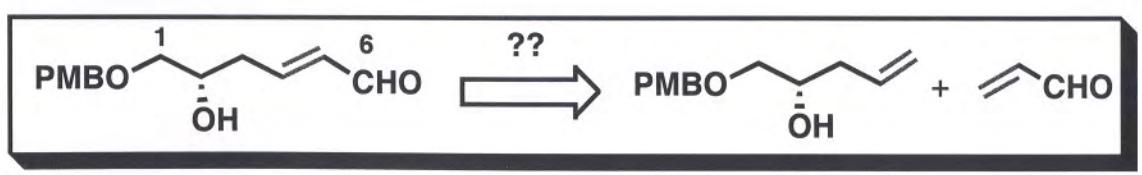
SYNTHESIS OF THE C1-C14 FRAGMENT OF AMPHIDINOL 3

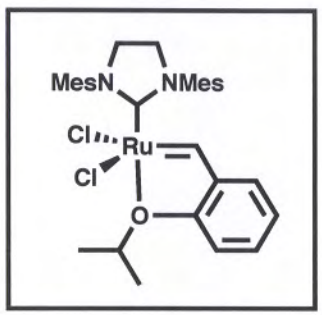


CROSS-METATHESIS REACTION

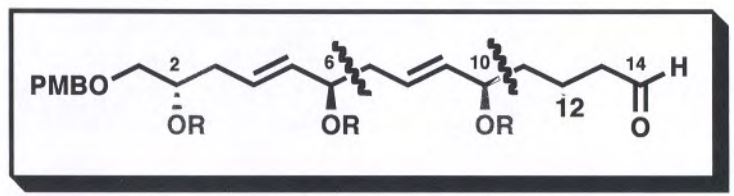


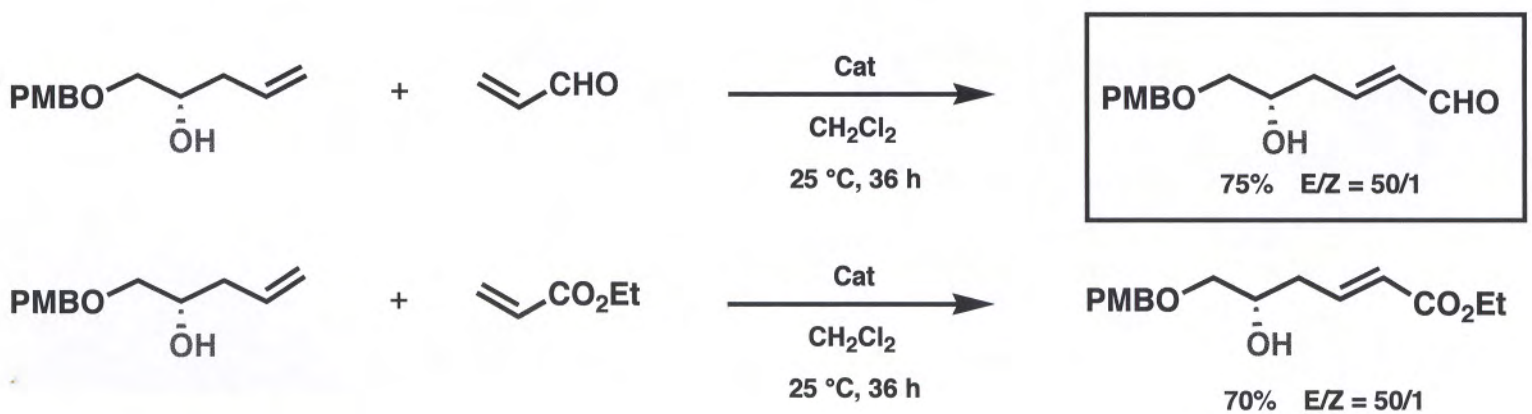




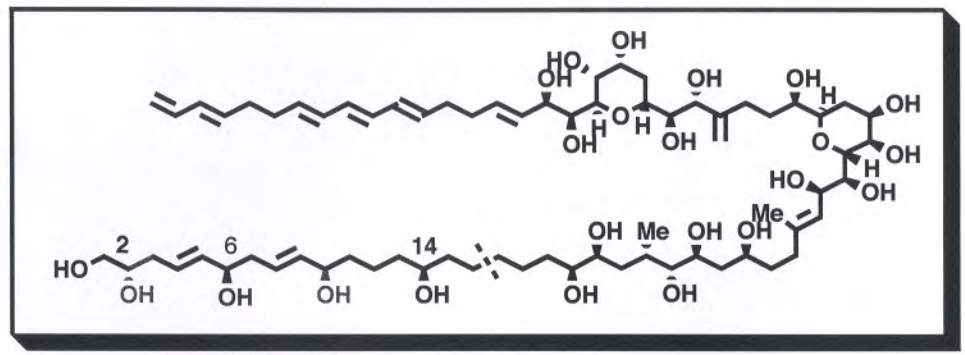


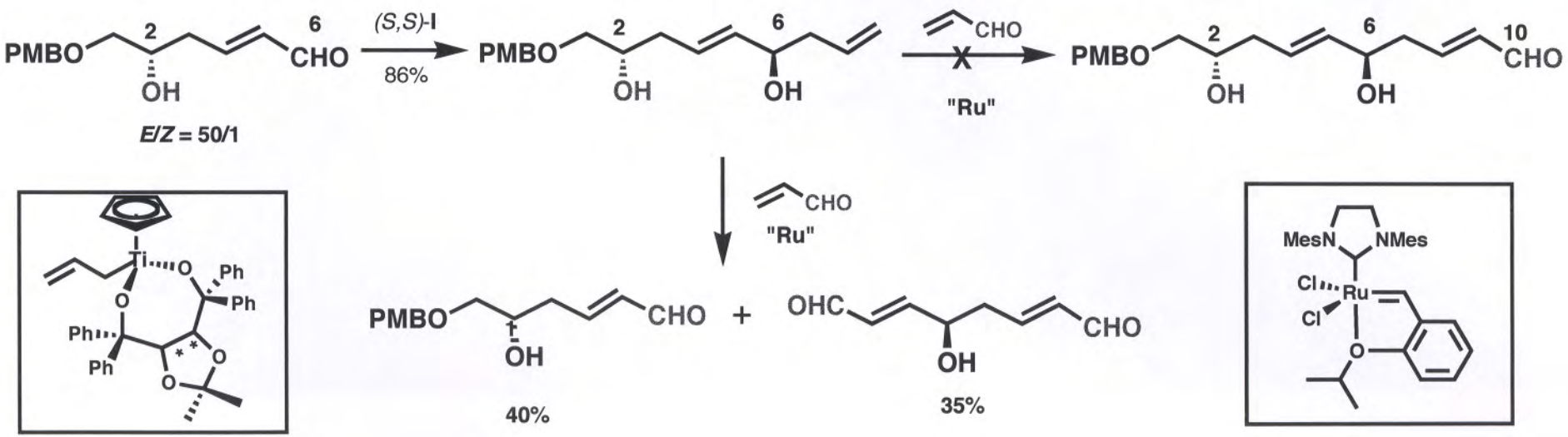
CROSS-METATHESIS REACTION



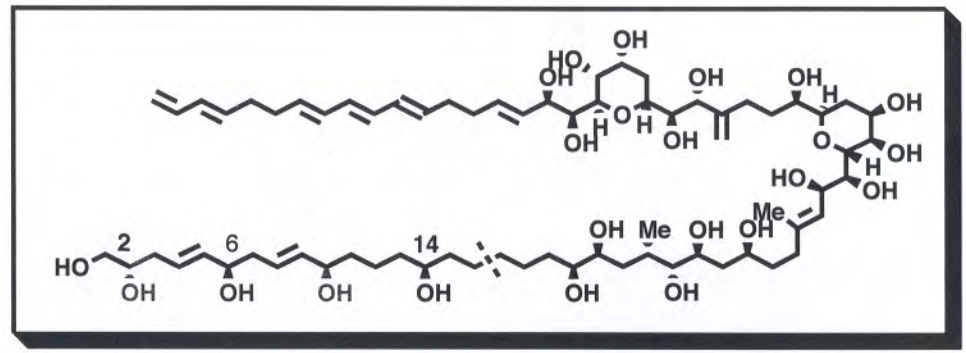


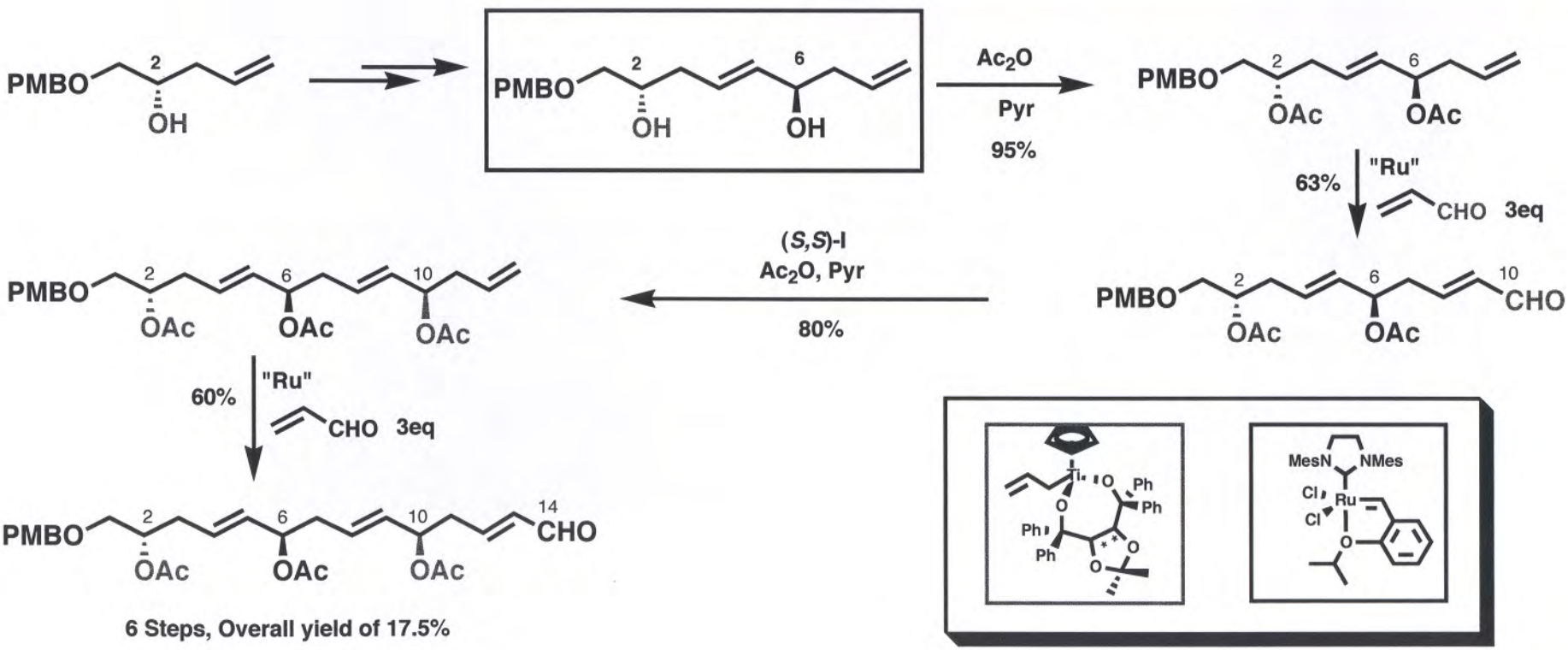
CHEMOSELECTIVITY



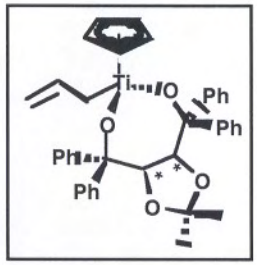


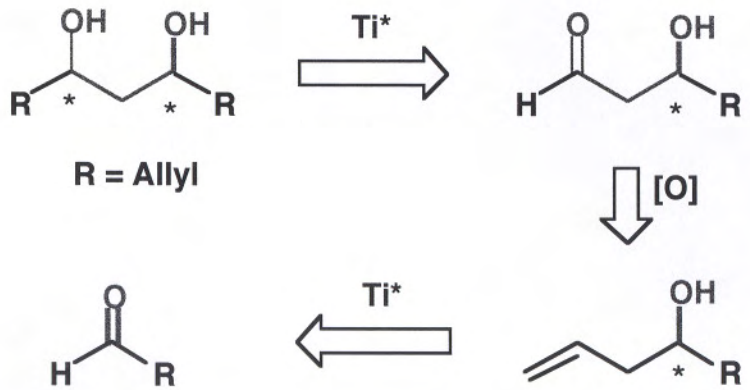
CHEMOSELECTIVITY



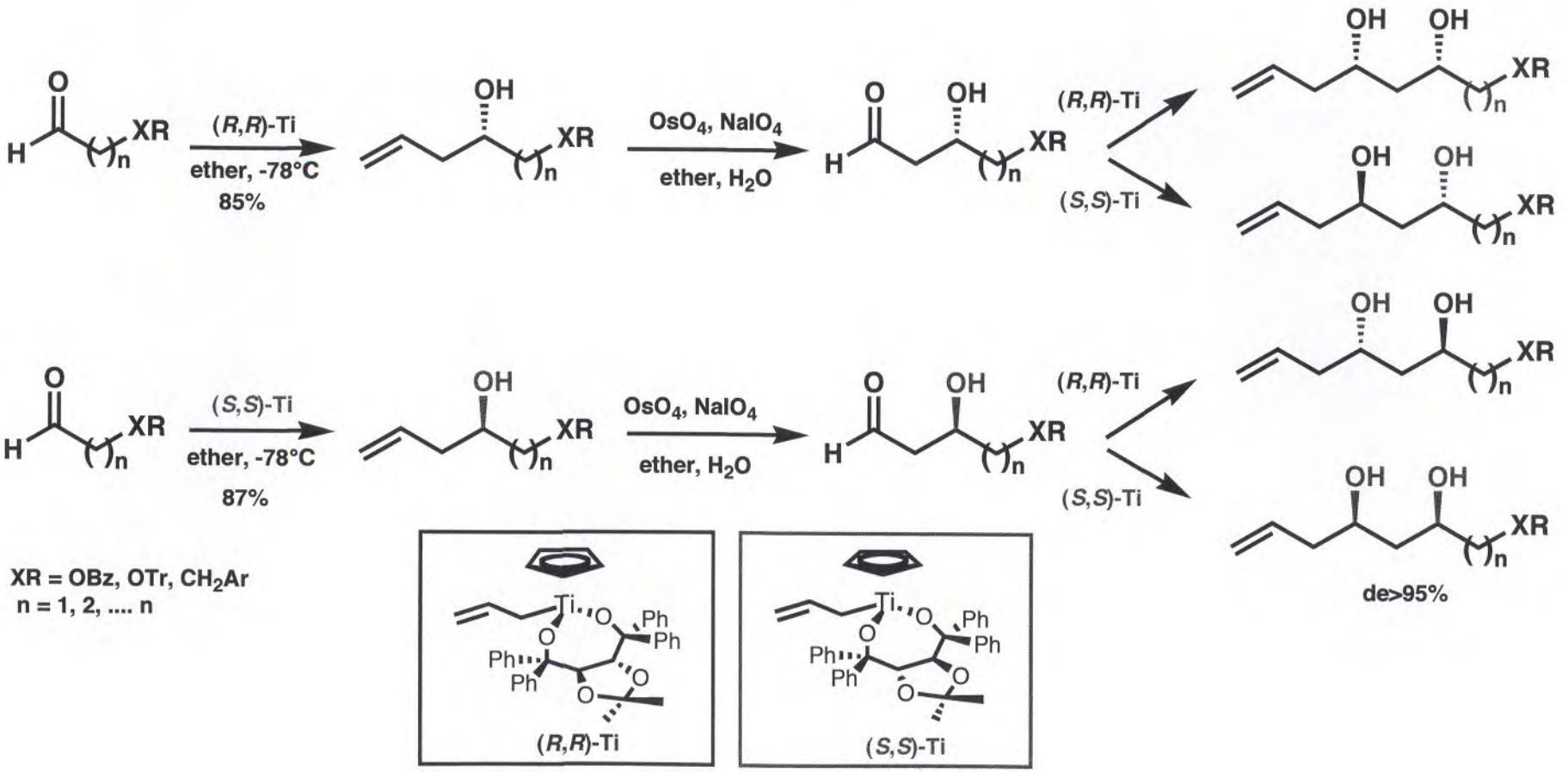


SYNTHESIS OF 1,3-DIOLS

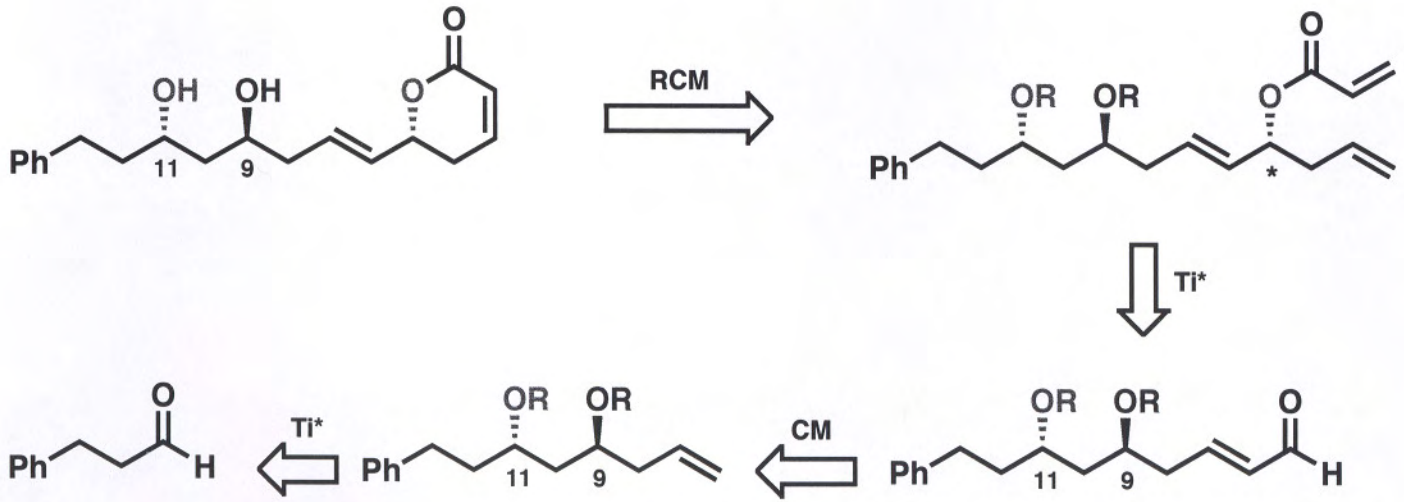




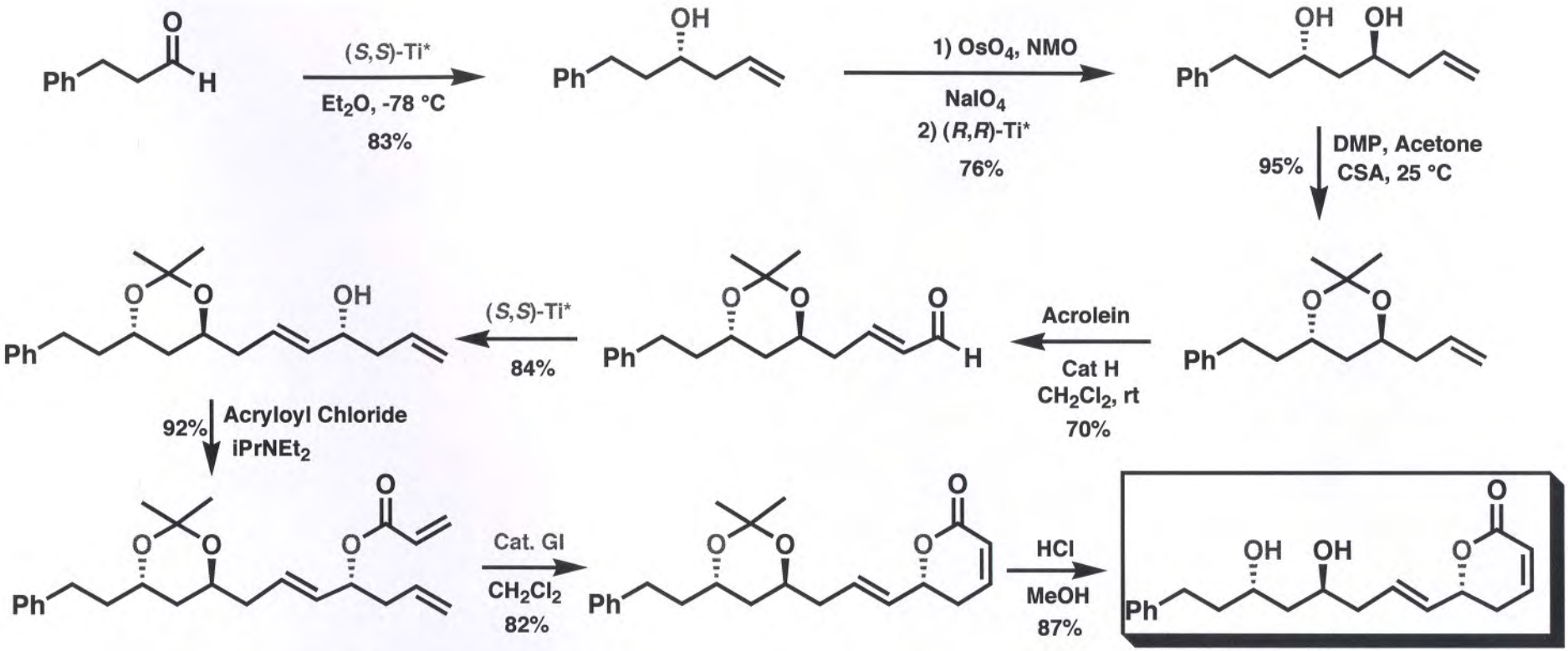
SYNTHESIS OF 1,3-DIOLS



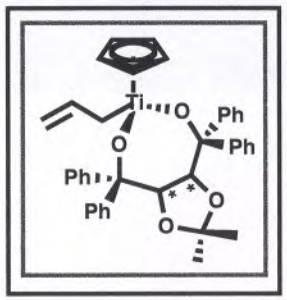
(+)-STRICTIFOLIONE

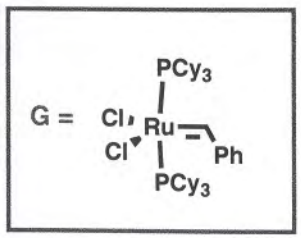


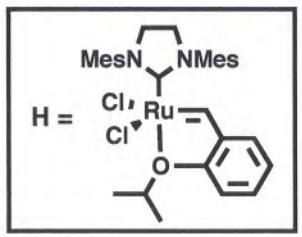
SYNTHESIS OF (+)-STRICTIFOLIONE



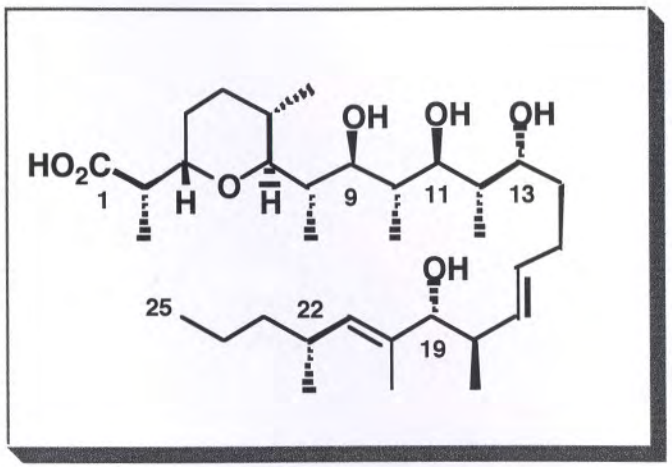
9 Steps, 23% overall yield

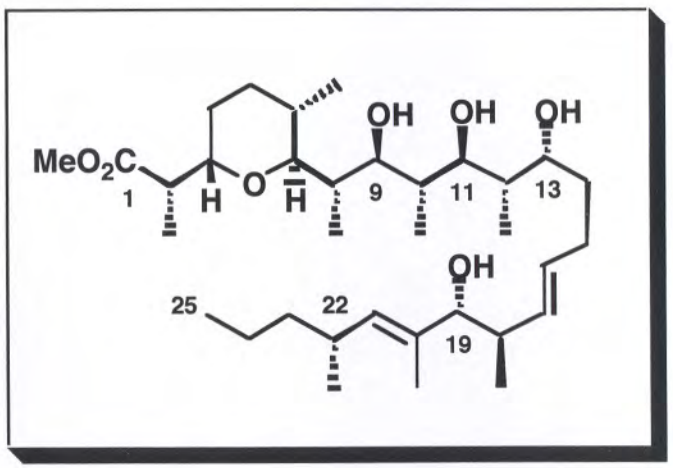






ZINCOPHORIN AND ITS METHYL ESTER





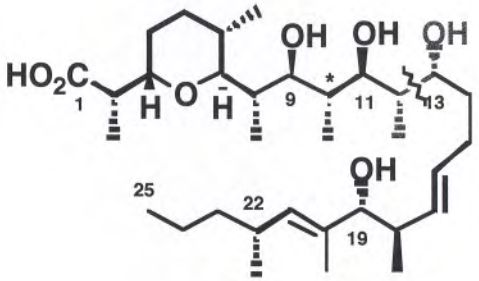
Isolated in 1984 from a strain of *Streptomyces griseus*

High affinity for Zn(II) and Mg(II) cation
Zincophorin and its calcium salt = Strong antibacterial properties against Gram-positive bacteria
The ammonium and sodium salts = anticoccidal activity against *Eimeria tenella* in chicken embryos

Antiviral activity with reduced cell toxicity compare to the free acid

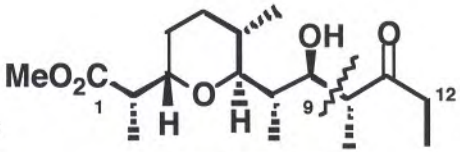
One total synthesis: Danishefsky et al. *J. Am. Chem. Soc.*, 1987, *109*, 1572

RETROSYNTHETIC ANALYSIS

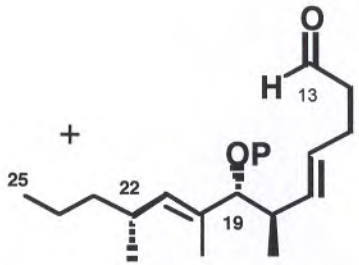


ZINCOPHORIN

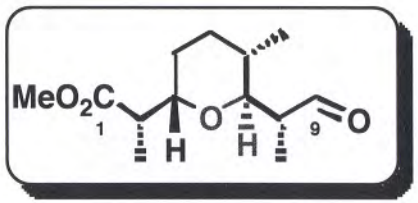
ALDOLISATION



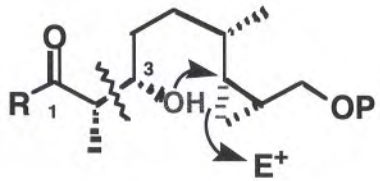
C1-C12 FRAGMENT



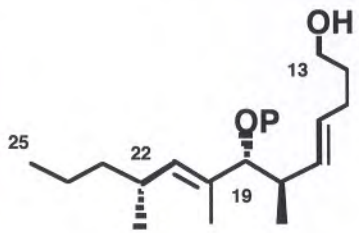
CROTYLMETAL



C1-C9 FRAGMENT

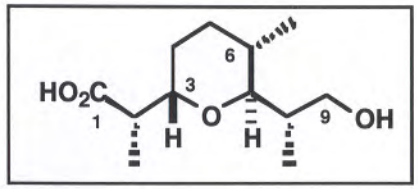


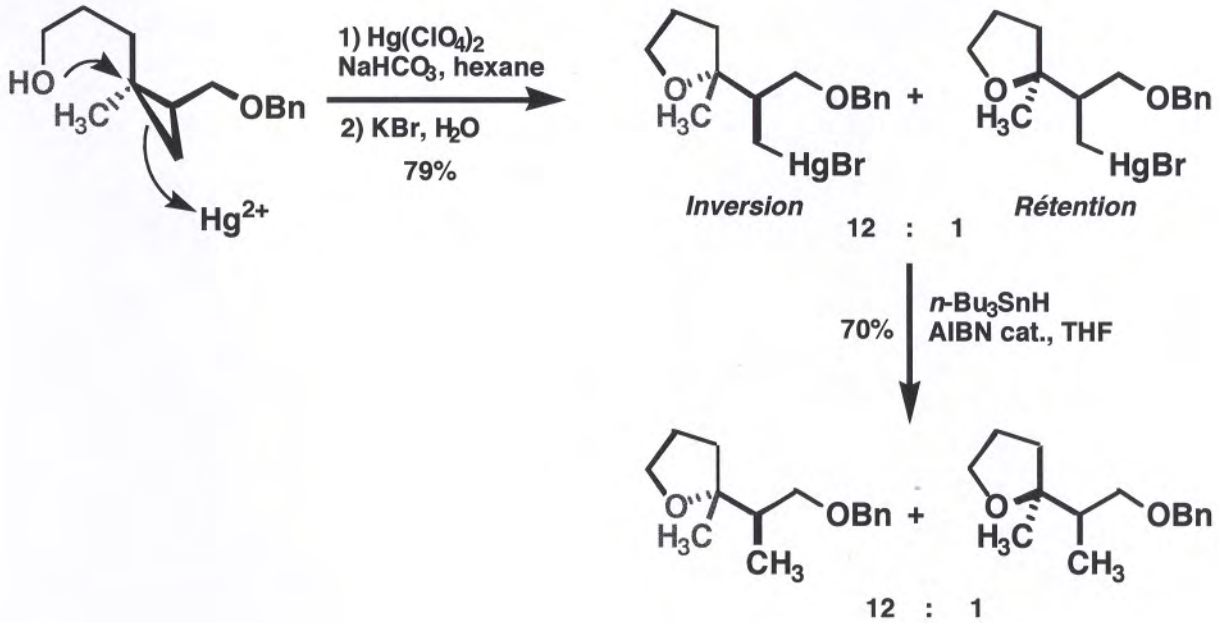
INTRAMOLECULAR ELECTROPHILIC RING OPENING



C13-C25 FRAGMENT

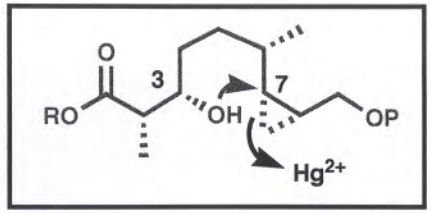
INTRAMOLECULAR OXYMERCURATION OF CYCLOPROPYLCARBINOLS

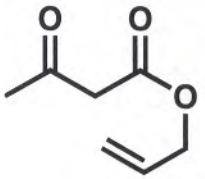




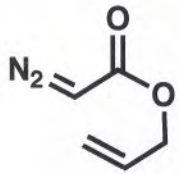
Collum, D. B.; Mohamadi, F.; Hallock, J. S. *J. Am. Chem. Soc.* 1983, *105*, 6882-6889.

SYNTHESIS OF THE CYCLOPROPYLCARBINOL

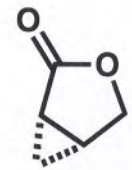




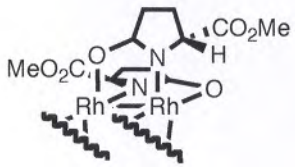
1) TsN_3
Et_3N, MeCN
2) LiOH, H_2O
60%



0.1 % mol
$Rh_2[5(R)\text{-MEPY}]_4$
Slow add of the substrate
CH_2Cl_2, reflux, 30h
90%

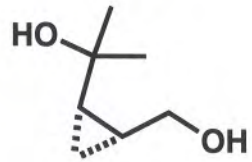


e.e.> 95%

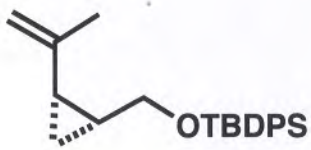


Doyle's Catalyst

MeLi (2 equiv.)
THF, -40°C
91%

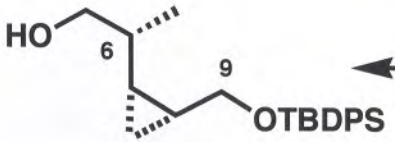


1) TBDPSCl, imidazole
DMF
2) CH_3SO_2Cl, Et_3N
DMAP
CH_2Cl_2
85%



TBDPS = *t*-$BuPh_2Si$-

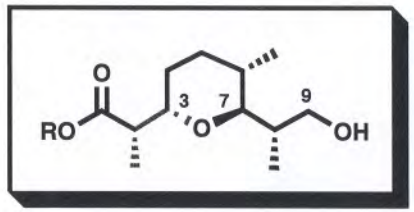
BH_3.THF
H_2O_2, NaOH
91%

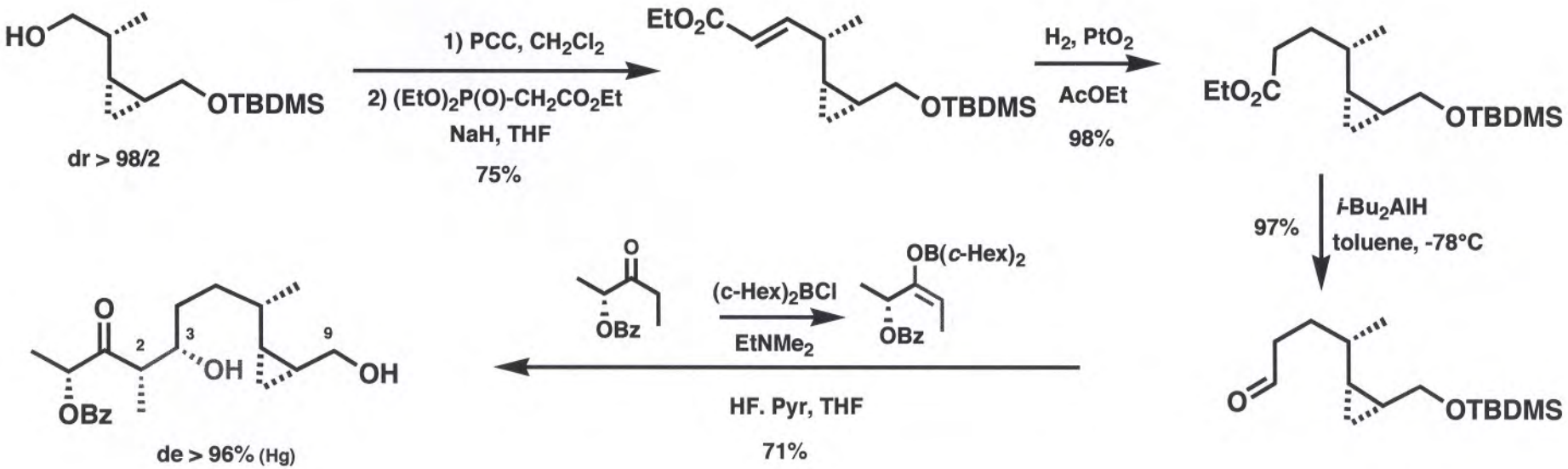


dr > 98/2

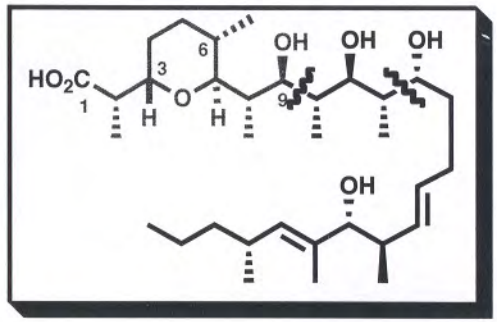
Cossy, J.; Blanchard, N.; Meyer, C. *Eur. J. Org. Chem.* 2001, 339.

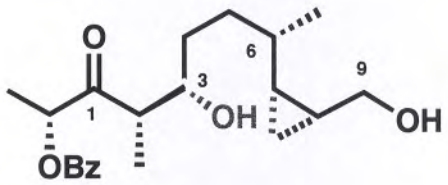
SYNTHESIS OF THE C1-C9 FRAGMENT OF ZINCOPHORIN





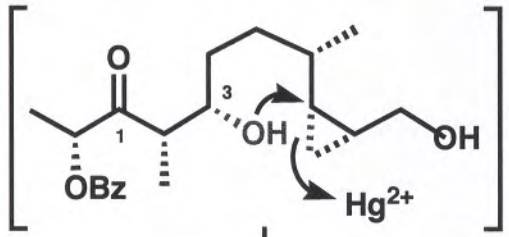
SYNTHESIS OF THE C1-C9 FRAGMENT OF ZINCOPHORIN

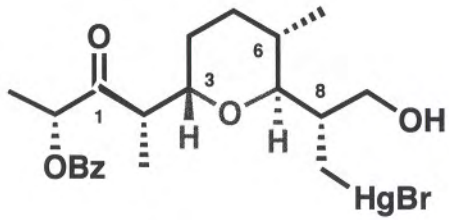




1) $Hg(OCOCF_3)_2$
CH_2Cl_2, t.a.

2) KBr, H_2O

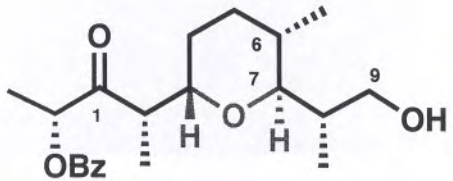




n-Bu_3SnH, AIBN cat.

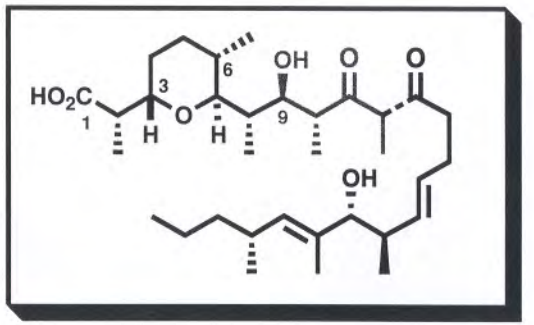
THF, toluene

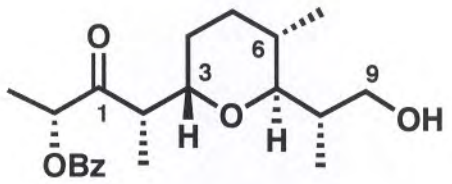
85%



dr = 93/7

SYNTHESIS OF THE C1-C9 FRAGMENT OF ZINCOPHORIN

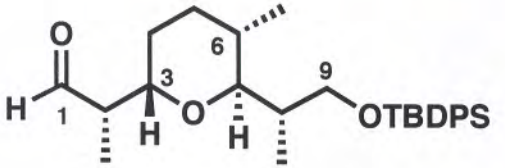




1) TBDPSCl
imidazole/DMF

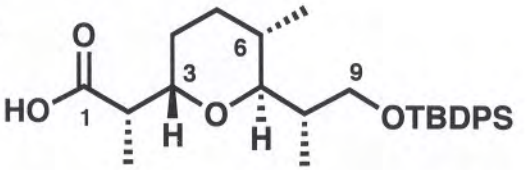
2) $LiBH_4$, THF

3) $NaIO_4$ / MeOH



90% (4 steps)

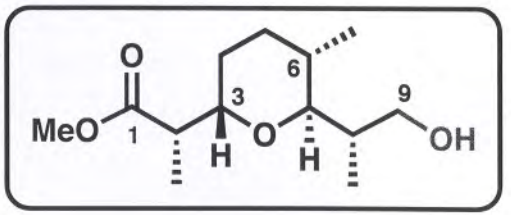
$NaClO_2$, NaH_2PO_4
2-Me-2-butene
H_2O, *t*-BuOH



1) $TMSCHN_2$
MeOH, Benzene

2) HF Pyridine
THF

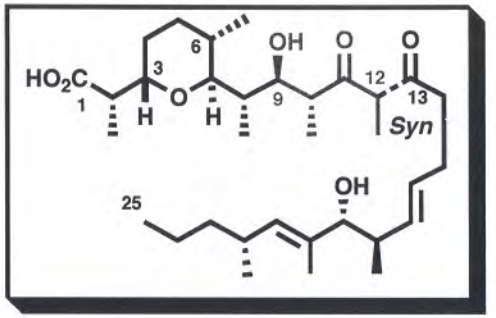
69%

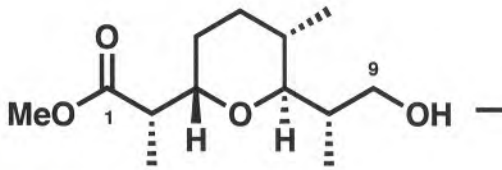


C1-C12

Cossy, J.; Blanchard, N.; Defosseux, M.; Meyer, C. *Angew. Chem. Int. Ed. Engl.* 2002, *41*, 2144

SYNTHESIS OF THE C1-C12 FRAGMENT OF ZINCOPHORIN

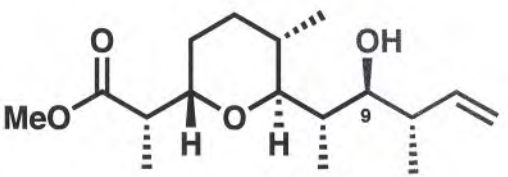


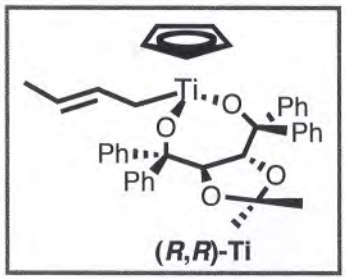


1) Dess-Martin
Pyridine, CH_2Cl_2

2) 

63 % (diastereomer-*anti,anti*)

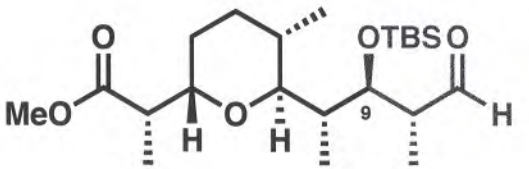




(*R,R*)-Ti

1) TBSOTf, 2,6-lutidine
CH_2Cl_2, -78 °C

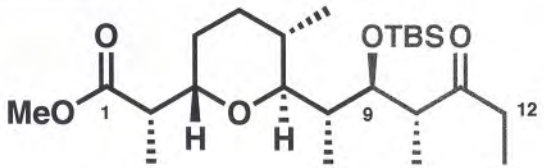
2) OsO_4 cat., NMO, acétone/H_2O
puis $NaIO_4$, THF/H_2O



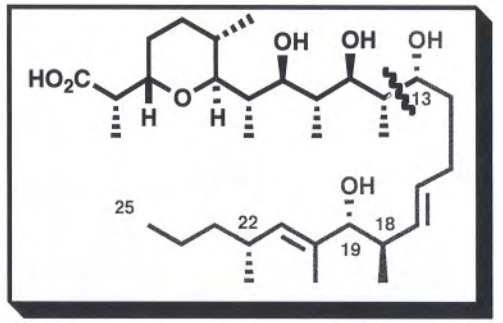
1) Et_2CuLi (excess)
Et_2O, -78 °C

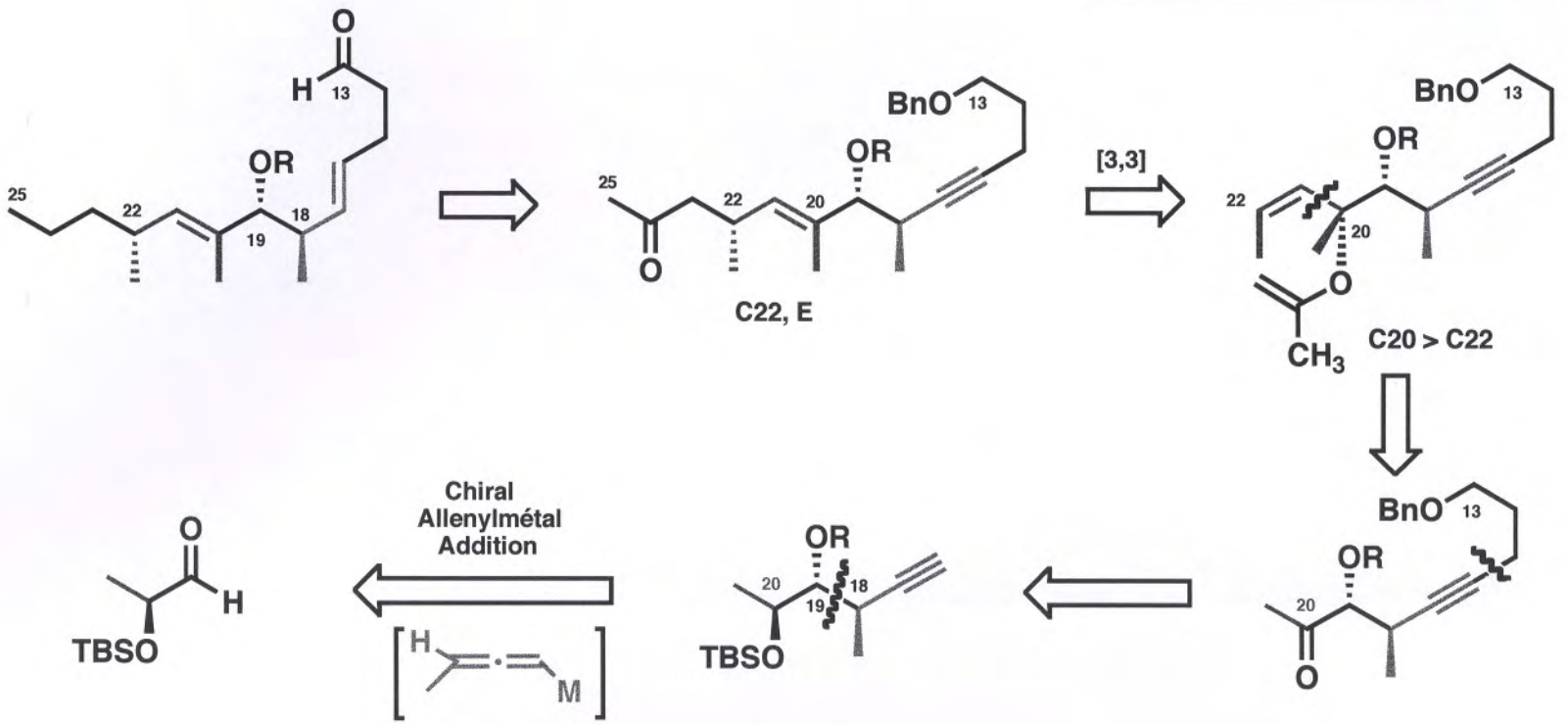
2) Dess-Martin
Pyridine, CH_2Cl_2

60% (4 steps)

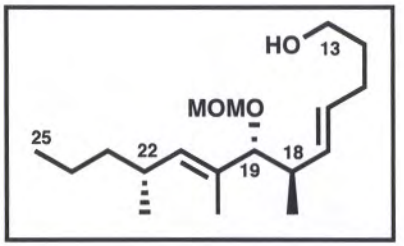


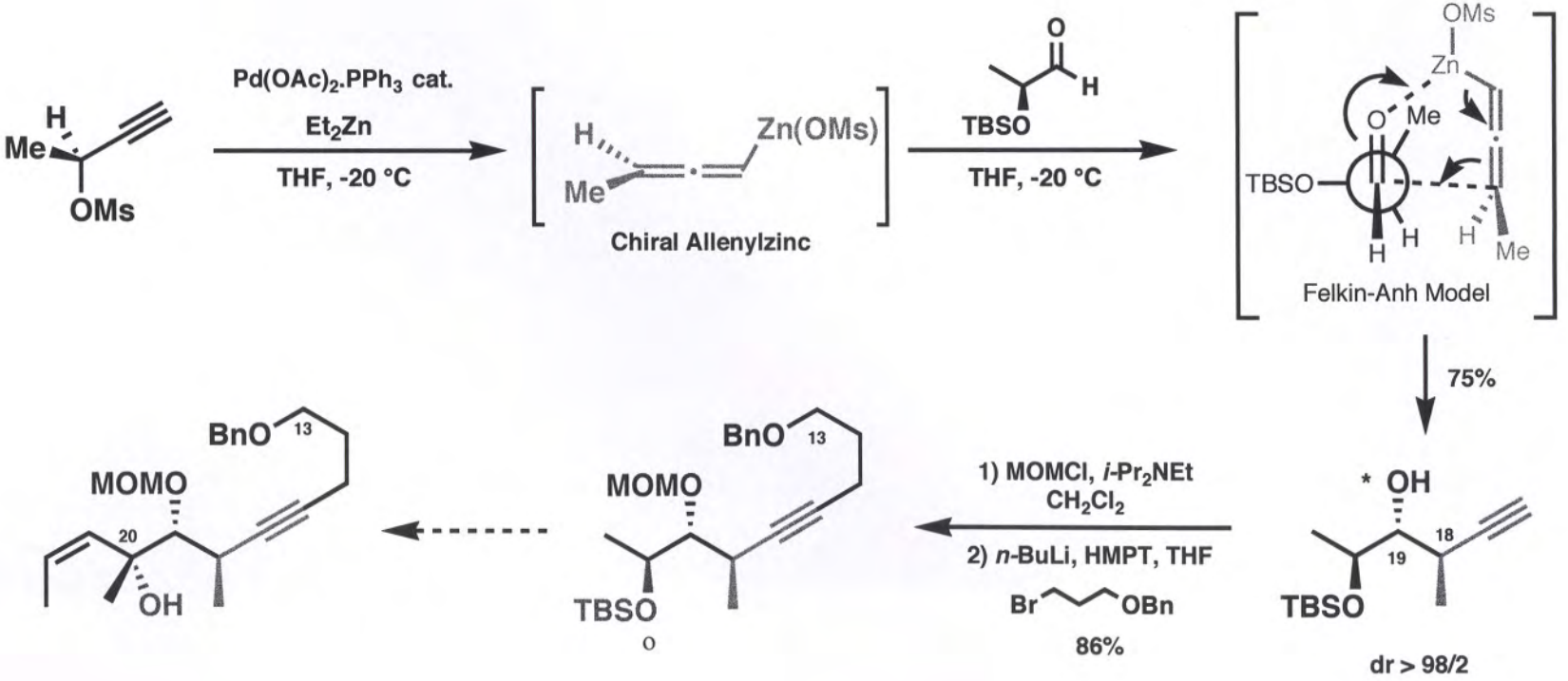
RETROSYNTHESIS OF THE C13-C25 FRAGMENT



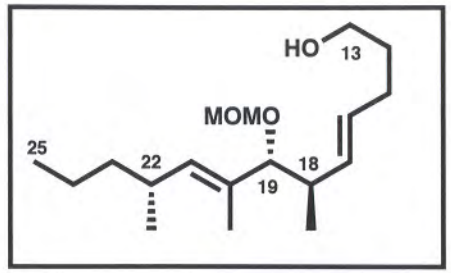


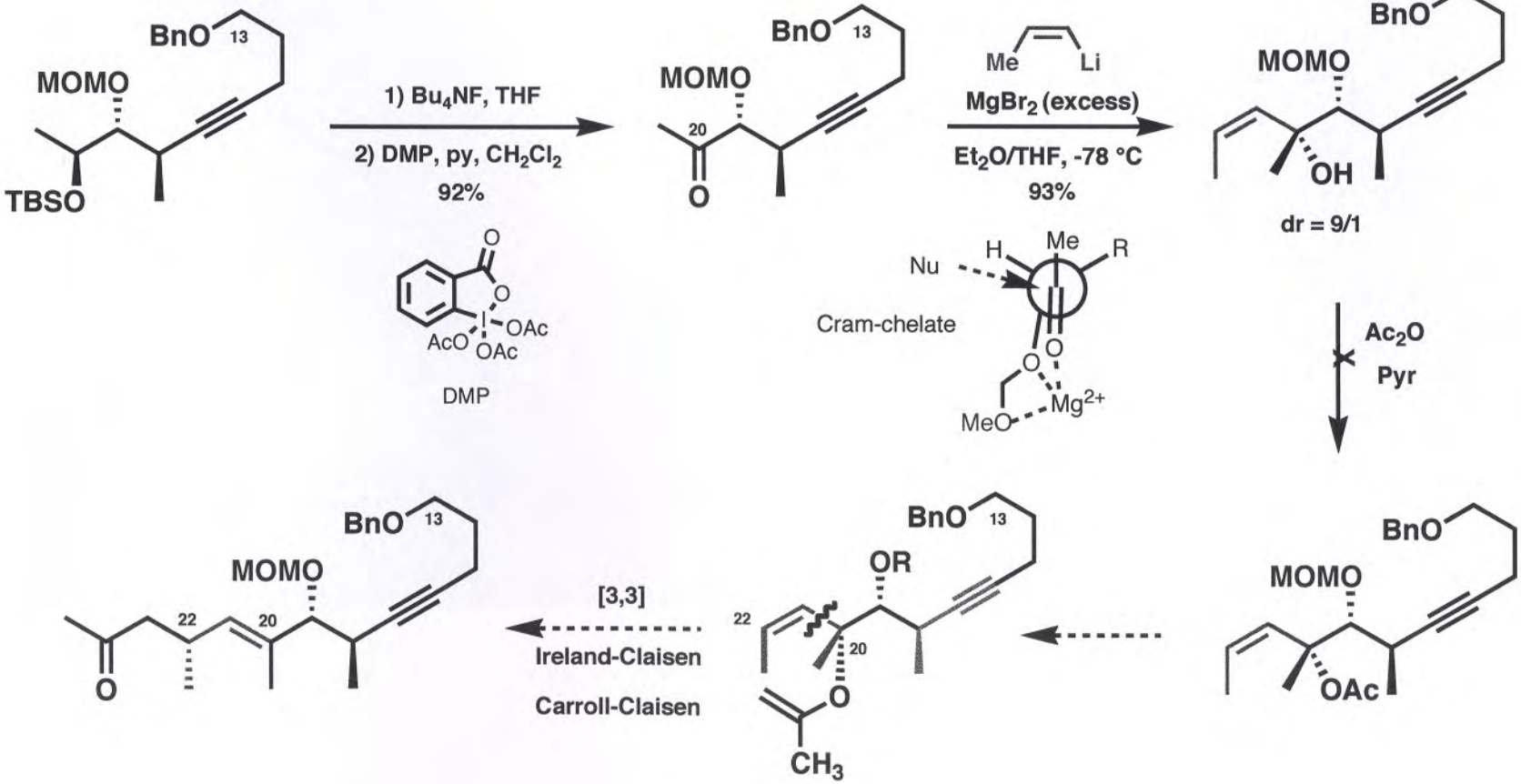
SYNTHESIS OF THE C13-C25 FRAGMENT OF ZINCOPHORIN



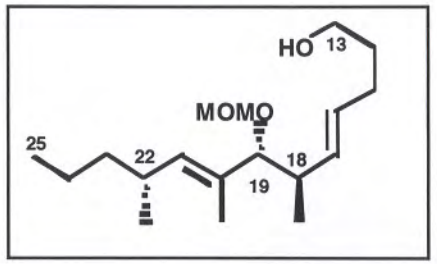


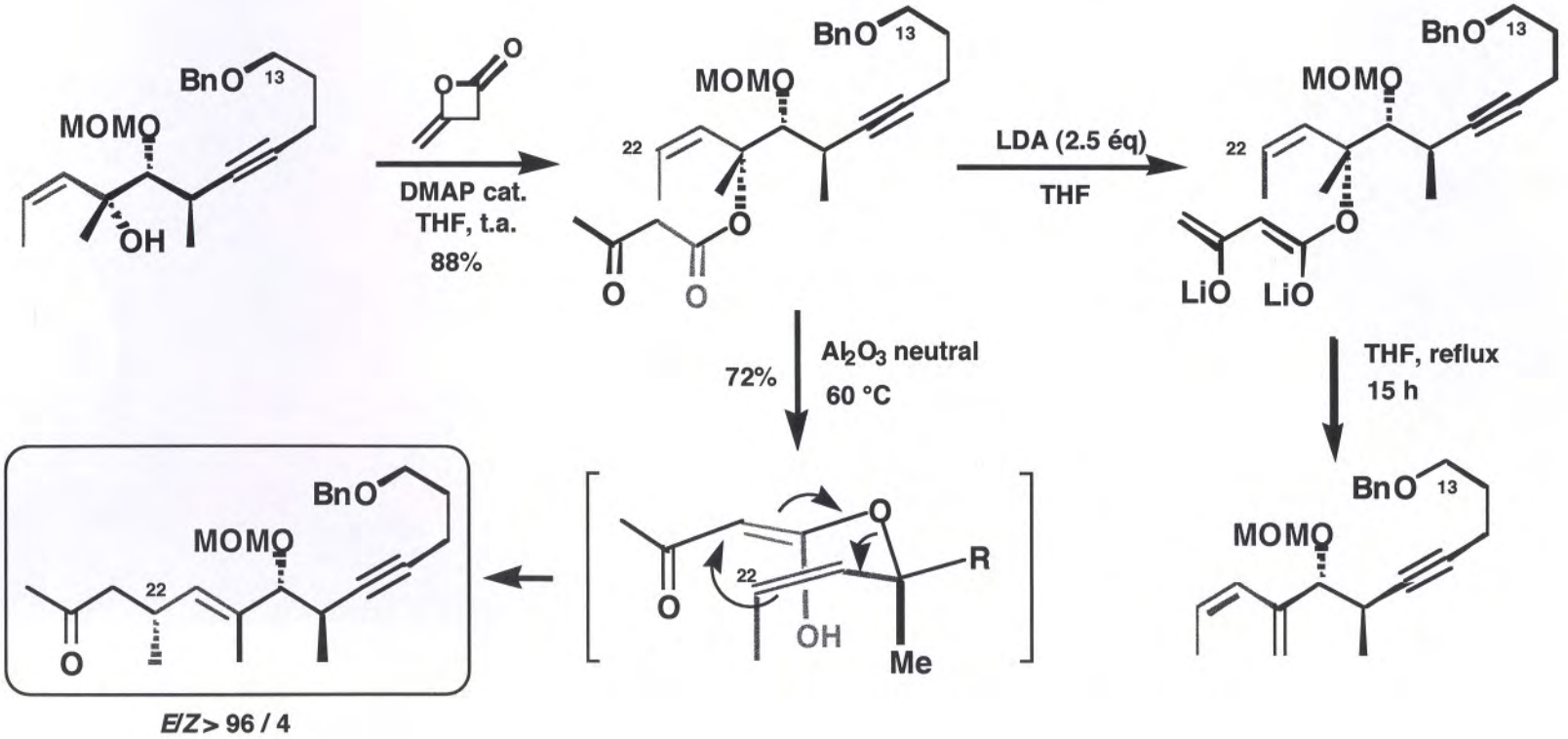
SYNTHESIS OF THE C13-C25 FRAGMENT OF ZINCOPHORIN



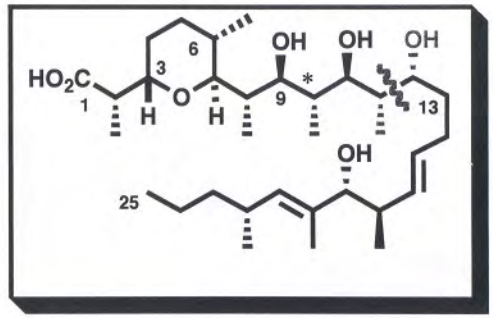


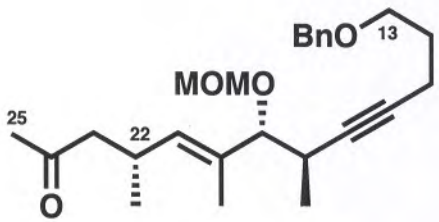
SYNTHESIS OF THE C13-C25 FRAGMENT OF ZINCOPHORIN





SYNTHESIS OF THE C13-C25 FRAGMENT OF ZINCOPHORIN





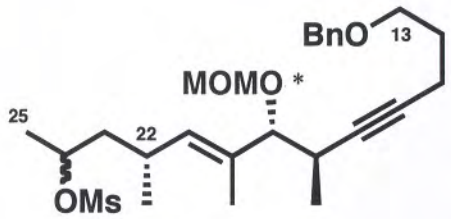
1) DIBAL-H

Et_2O, -78°C

2) $MeSO_2Cl$

i-Pr_2NEt, CH_2Cl_2, 0 °C

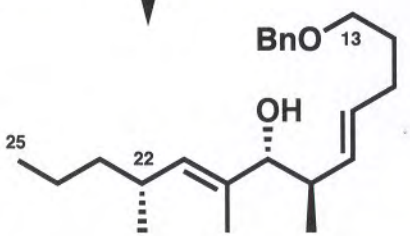
92%



88%

1) p-TSA, MeOH (2)

2) $LiAlH_4$, THF, reflux



1) TBSOTf, 2,6-lutidine

2) Li (excess)

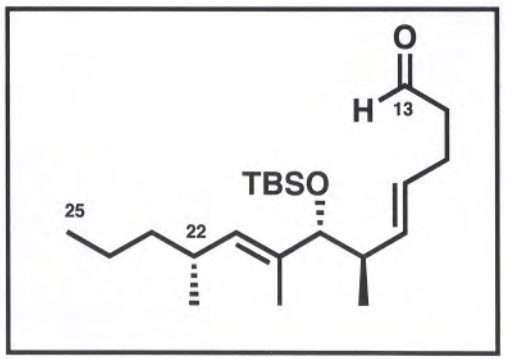
THF/*t*-BuOH

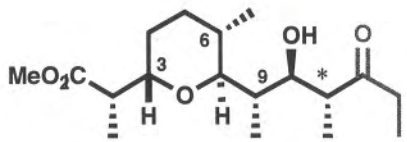
NH_3 liq., -33°C

3) Dess-Martin

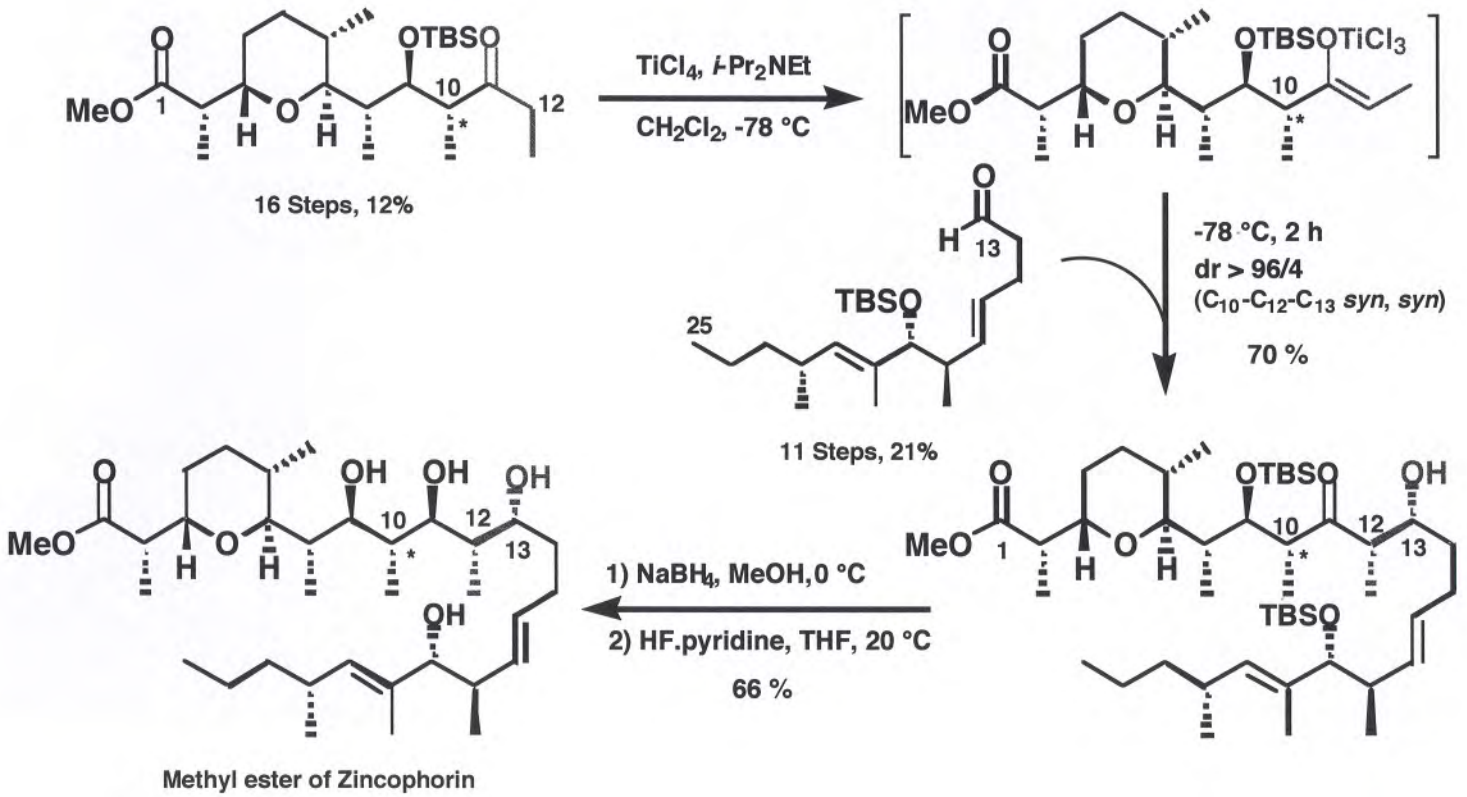
Pyridine, CH_2Cl_2

65%

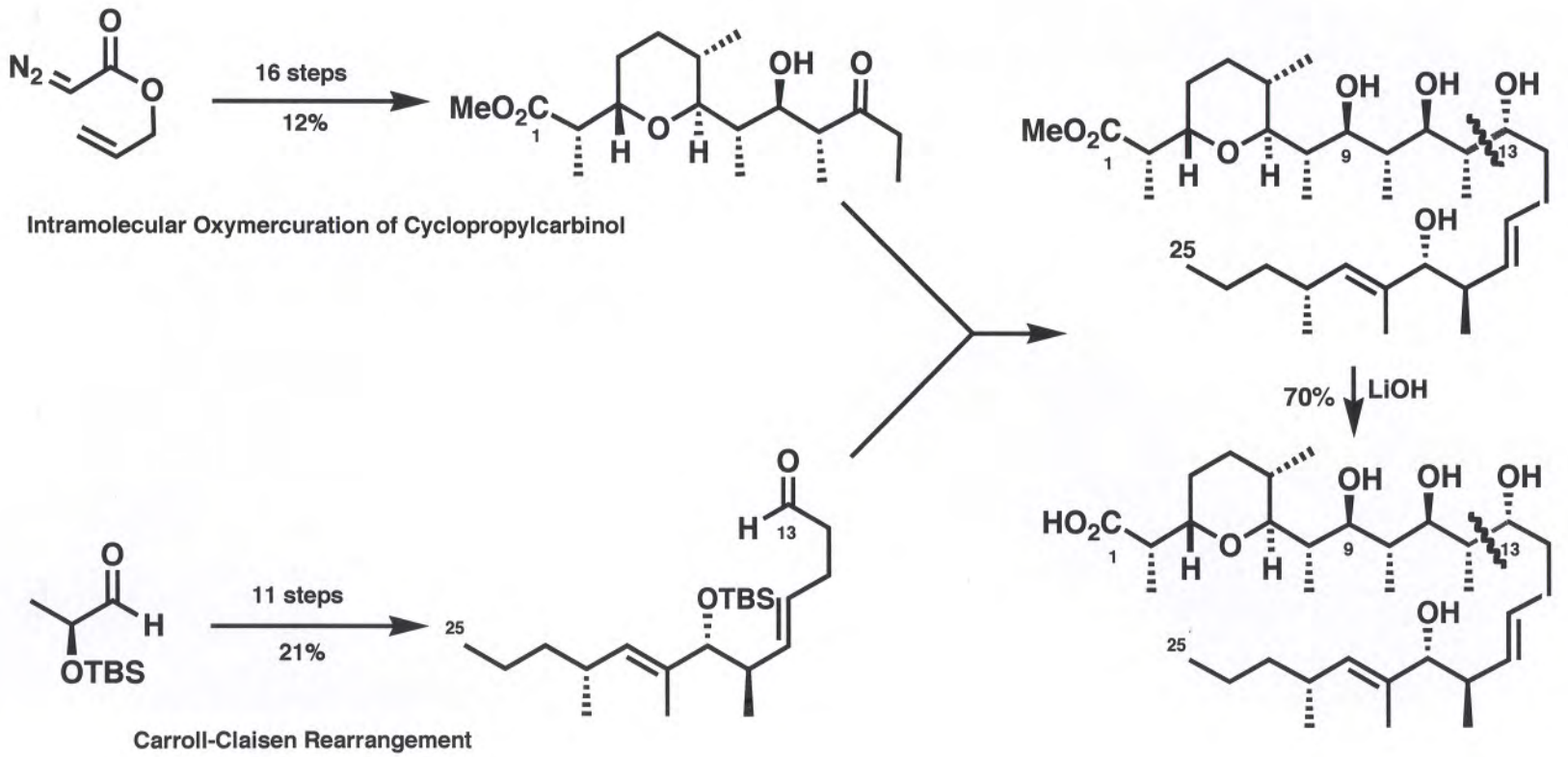




SYNTHESIS OF THE METHYL ESTER OF ZINCOPHORIN



SYNTHESIS OF ZINCOPHORIN



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ACKNOWLEDGMENTS

S. BOUZBOUZ
C. MEYER
M. DEFOSSEUX
N. BLANCHARD

SPECIAL THANKS

R. DUTHALER
A. HOVEYDA

FINANCIAL SUPPORT
Fr $ Fr $ Fr $ Fr $ Fr $ Fr $ Fr

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RHODIA
PPG-SIPSY
LABORATOIRE LAFON
AVENTIS
ELI-LILLY (USA)