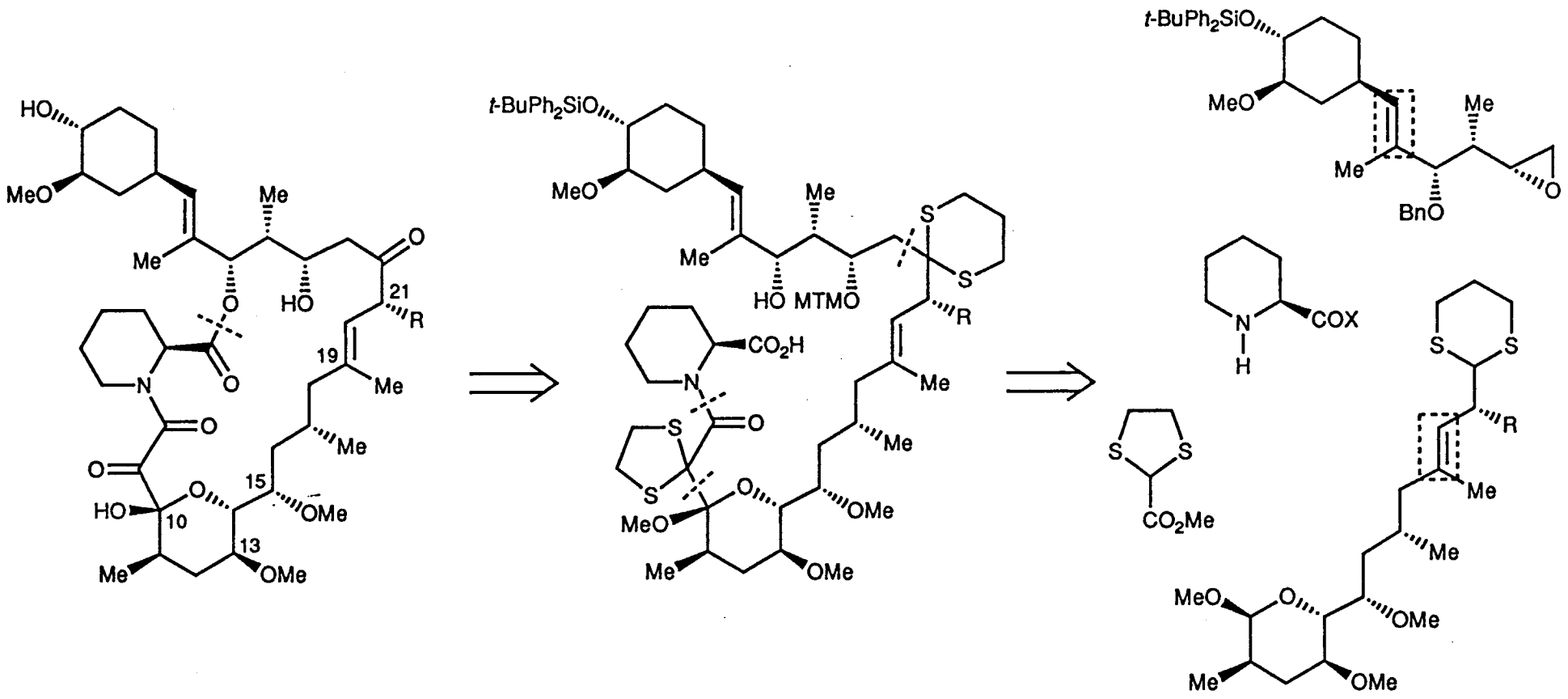
UNIFIED RETROSYNTHETIC ANALYSIS OF FK506, FR900520, AND FR900523



Synthetic Goal: Unified Synthetic Strategy for the Effector Domain of all three Compounds: **FK506, FR900520, and FR900523.**

- 2 Trisubstituted Olefins – Via Stereoselective σ-Bond Formation not π-Bond Formation.
- Union of Large Building Blocks.
- 14 Chiral Centers.
- Utilization of Hydroxyl Directed Reduction.
- 23 Membered Ring Macrolactone/lactam.

Current Research Programs

Natural Products and Bio-Organic Chemistry

⟹ (1) Total Synthesis of Architectually Complex, Biologically Active Compounds

(2) Non-Peptide Peptidomimetics

(a) Renin and AIDS Protease Inhibitors

- Ralph Hirschmann

(b) β-Turn Mimetics

- Ralph Hirschmann

(3) Development of Catalytic Antibodies

- Ralph Hirschmann

(4) Taste Receptor Charaterization (Monell Chemical Senses Center)

- Joseph Brand and Bruce Bryant

Physical Organic Chemistry

(1) Synthesis of Theoretically Interesting Unnatural Products (Möbius Antiaromatic Systems

(2) Synthesis and Chatacterization of Novel Materials

(a) Buckminsterfullerenes and Related Derivatives (e.g., $C_{60}F_{52}$, $C_{60}O$)

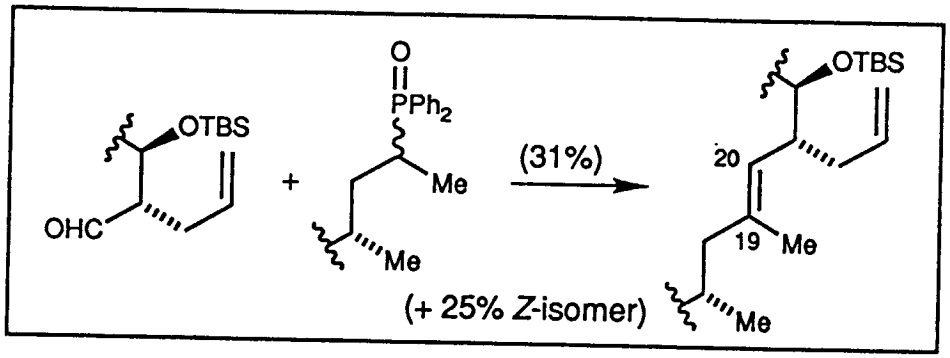
- Jack Fischer and Paul Heiney

(b) Polar and Discotic Liquid Crystals

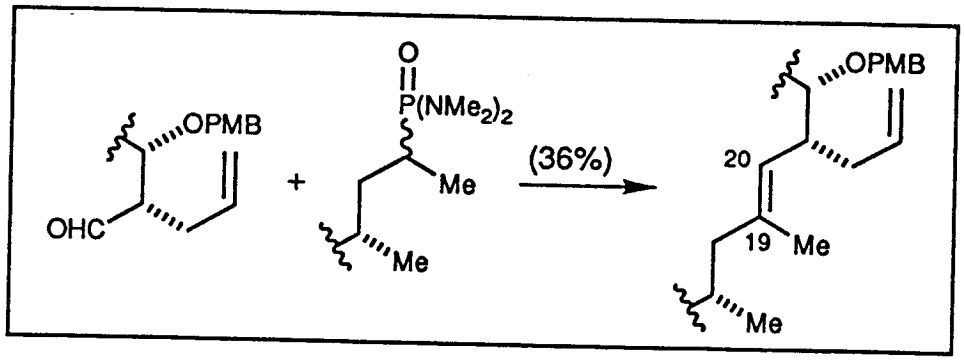
- Paul Heiney

PREVIOUS SOLUTIONS TO THE INTRODUCTION OF THE C(19,20) TRISUBSTITUTED OLEFIN IN FK506

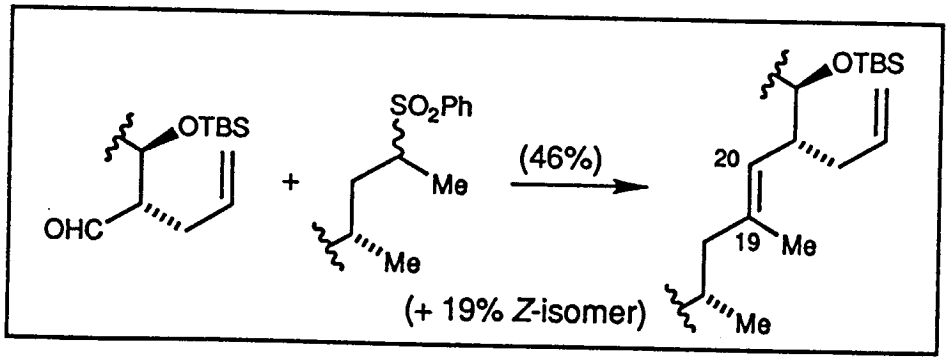
Merck Total Synthesis:



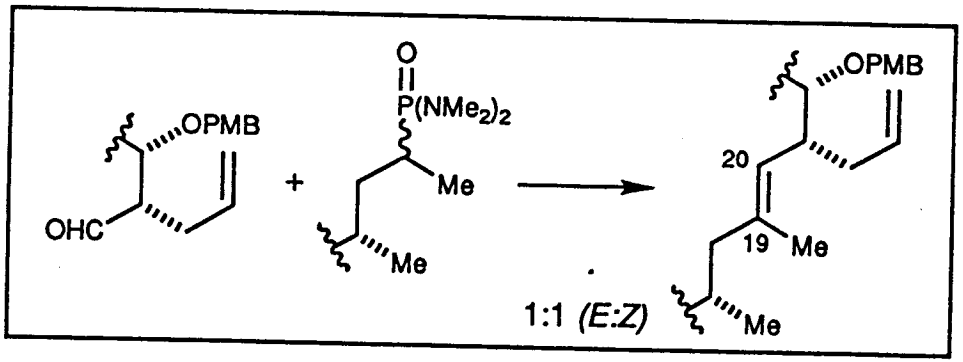
Schreiber Total Synthesis:



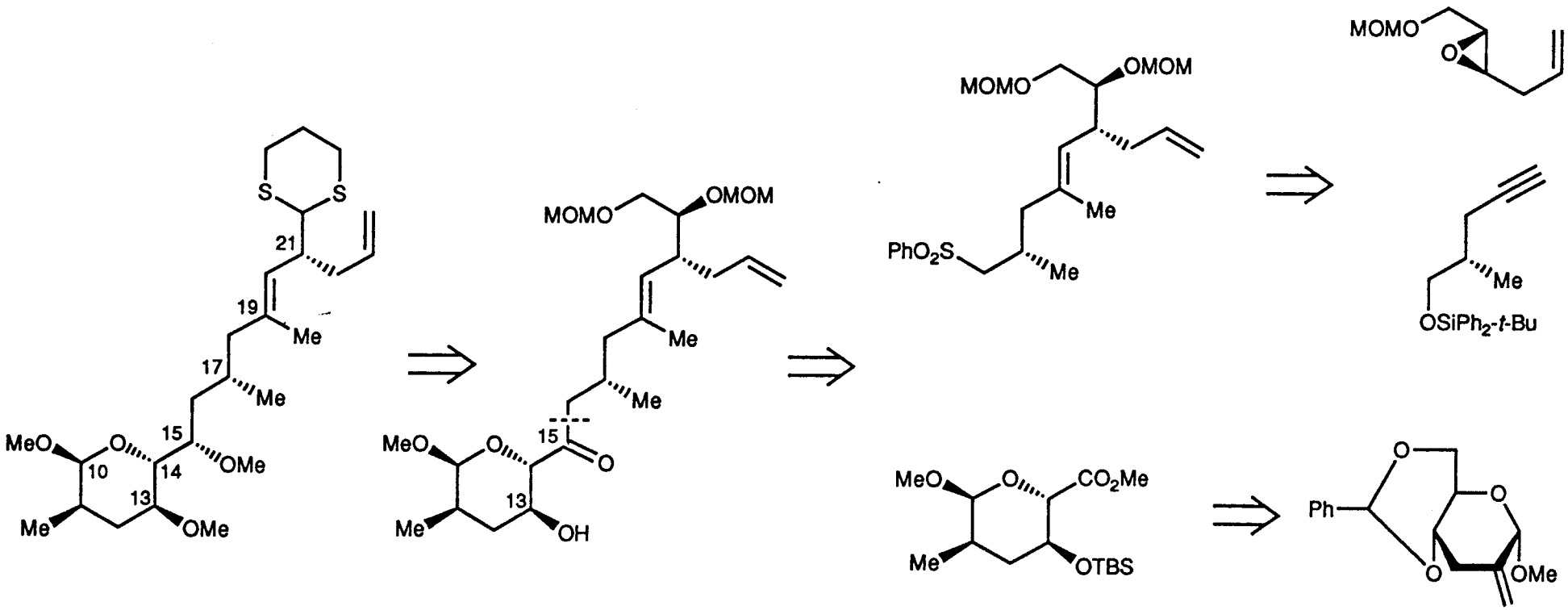
Danishefsky Formal Synthesis:

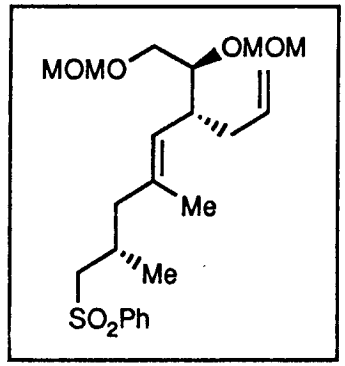


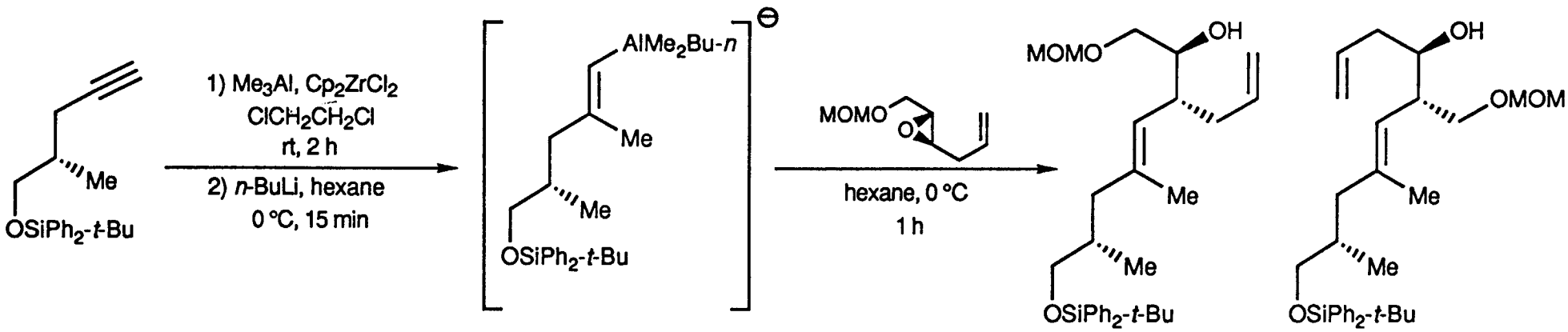
Sih Formal Synthesis:



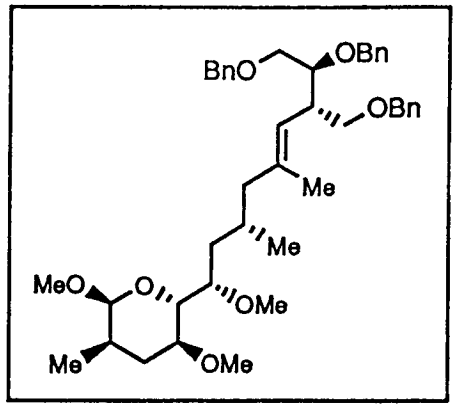
RETROSYNTHETIC ANALYSIS OF THE EASTERN HEMISPHERE OF FK506

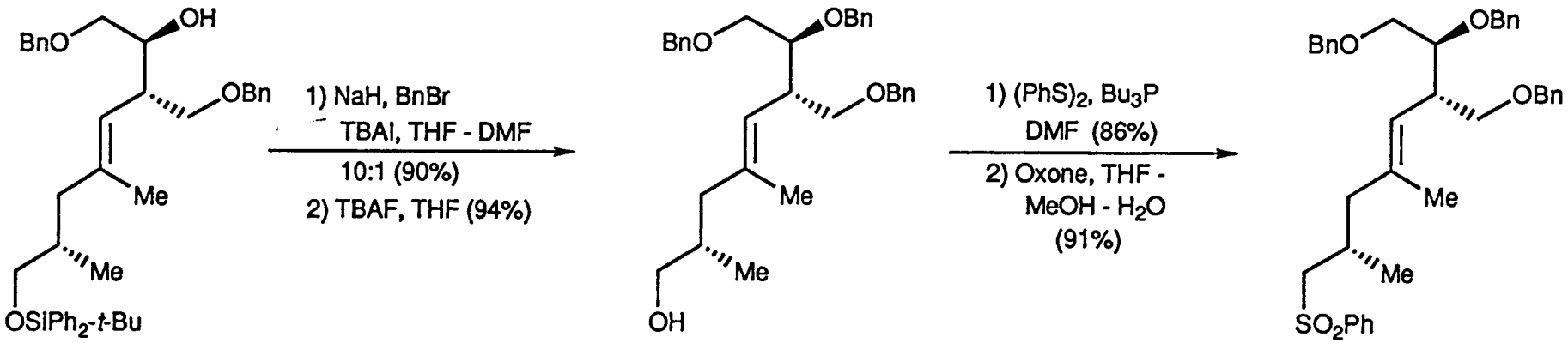


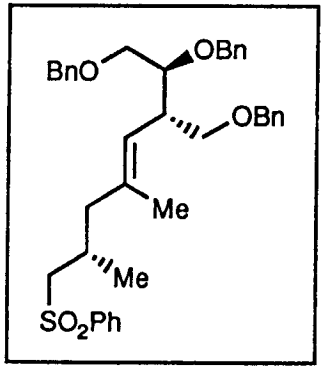

MOMO
OMOM
Me
Me
SO_2Ph

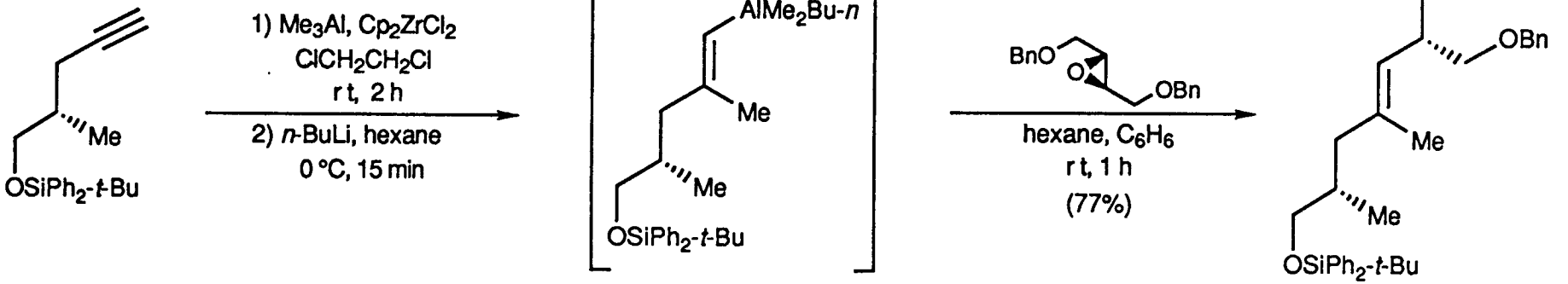

Me
$OSiPh_2$-*t*-Bu
1) Me_3Al, Cp_2ZrCl_2
$ClCH_2CH_2Cl$
rt, 2 h
2) *n*-BuLi, hexane
0 °C, 15 min
$AlMe_2Bu$-*n*
Me
Me
$OSiPh_2$-*t*-Bu
⊖
MOMO
O
hexane, 0 °C
1 h
MOMO
OH
Me
Me
$OSiPh_2$-*t*-Bu
OH
OMOM
Me
Me
$OSiPh_2$-*t*-Bu

(1 : 1)

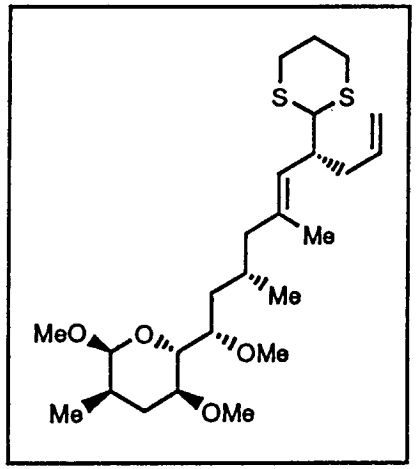

BnO
OBn
OBn
Me
Me
MeO
O
OMe
Me
OMe

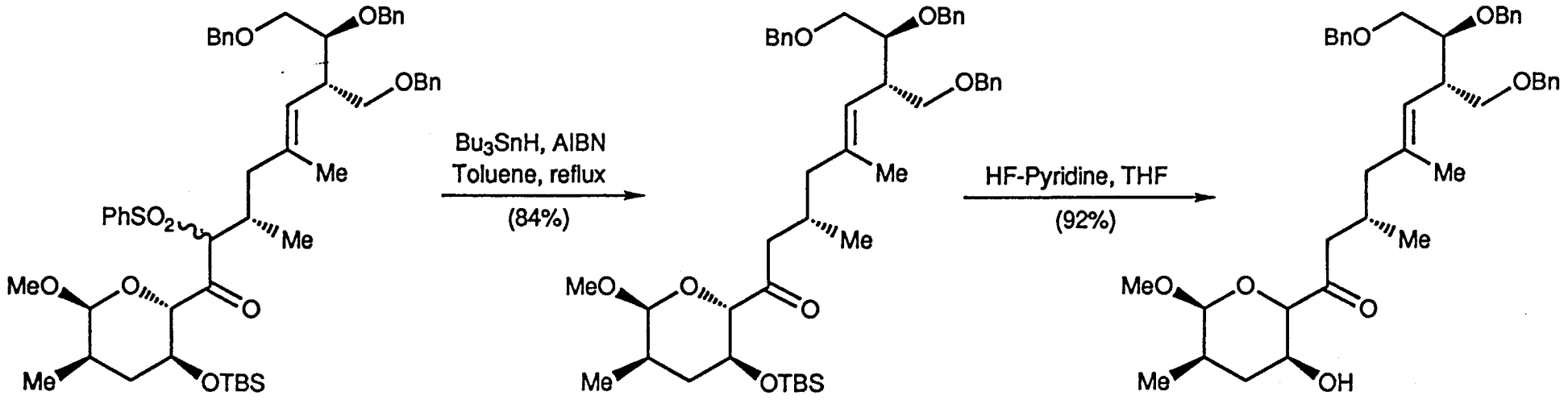

BnO
OH
OBn
Me
Me
OSiPh2-t-Bu
1) NaH, BnBr
TBAI, THF - DMF
10:1 (90%)
2) TBAF, THF (94%)
BnO
OBn
OBn
Me
Me
OH
1) (PhS)2, Bu3P
DMF (86%)
2) Oxone, THF -
MeOH - H2O
(91%)
BnO
OBn
OBn
Me
Me
SO2Ph


BnO
OBn
OBn
Me
Me
SO2Ph


Me
OSiPh2-t-Bu
1) Me3Al, Cp2ZrCl2
ClCH2CH2Cl
r t, 2 h
2) n-BuLi, hexane
0 °C, 15 min
AlMe2Bu-n
Me
Me
OSiPh2-t-Bu
Θ
BnO
O
OBn
hexane, C6H6
r t, 1 h
(77%)
OH
BnO
OBn
Me
Me
OSiPh2-t-Bu

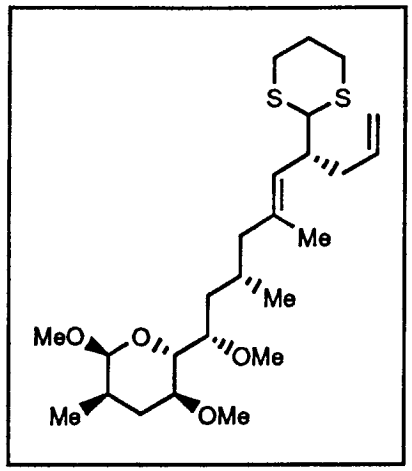
REDUCTIVE REMOVAL OF PHENYL SULFONE GROUP

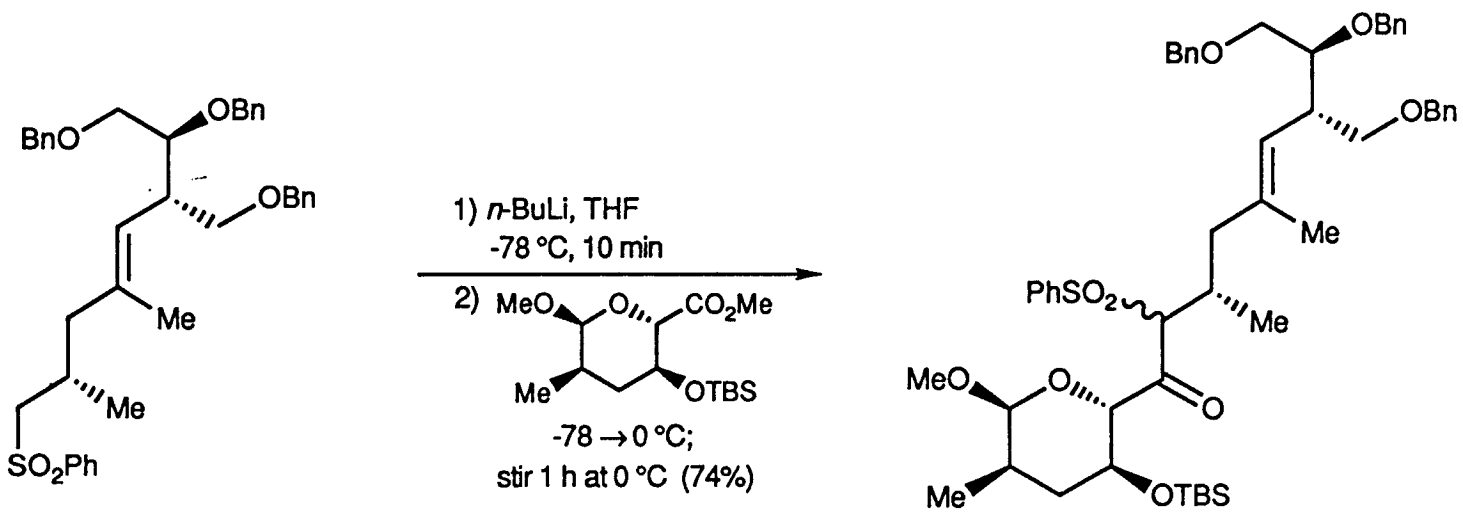




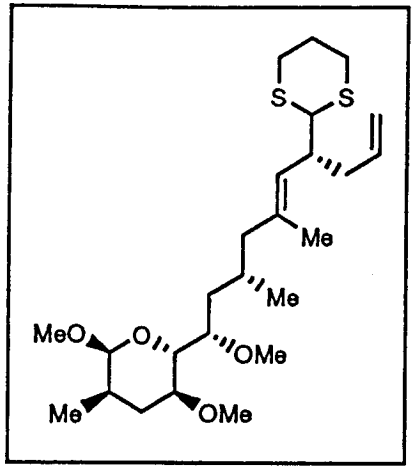
Smith, A. B., III; Hale, K. J.; McCauley, J. P., Jr. *Tetrahedron Lett.* **1989**, *30*, 5579.

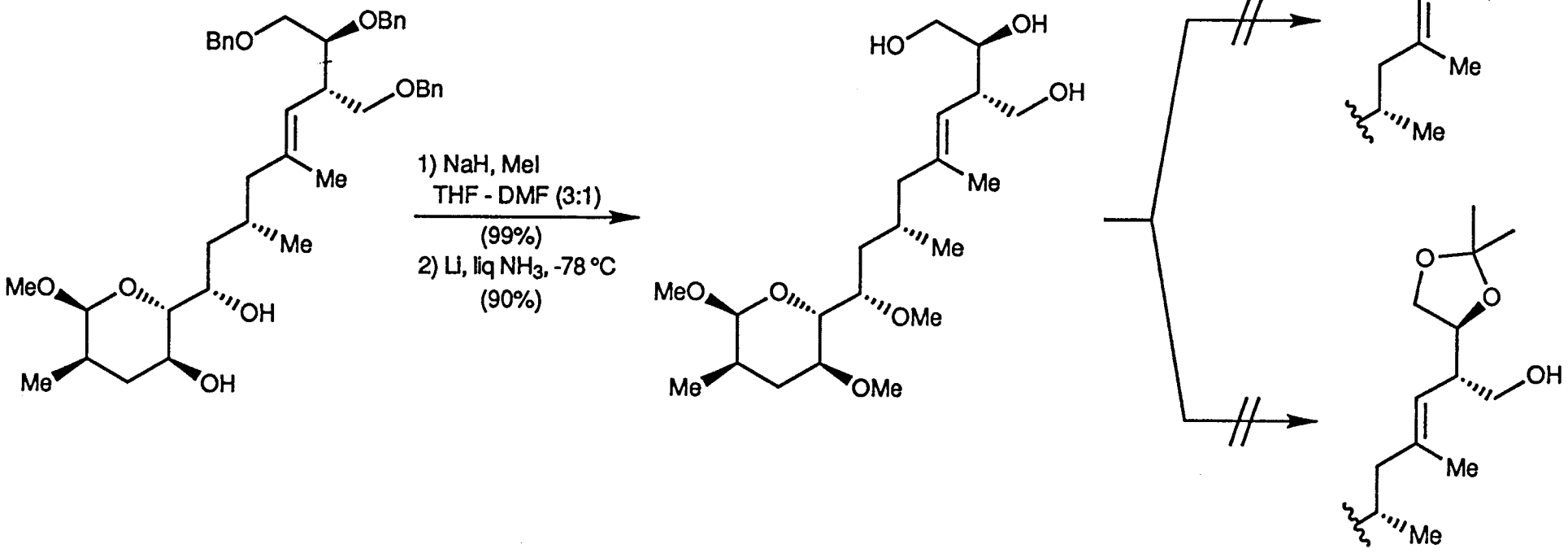
PREPARATION OF KETOSULPHONES



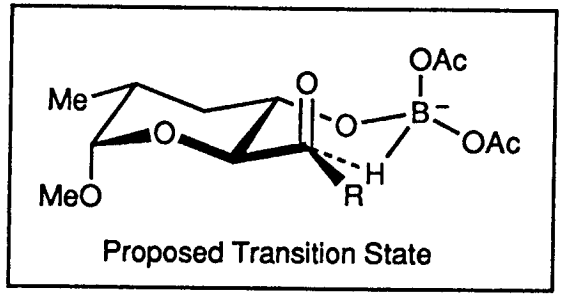


ATTEMPTED 1,2-DIOL FUNCTIONALIZATION

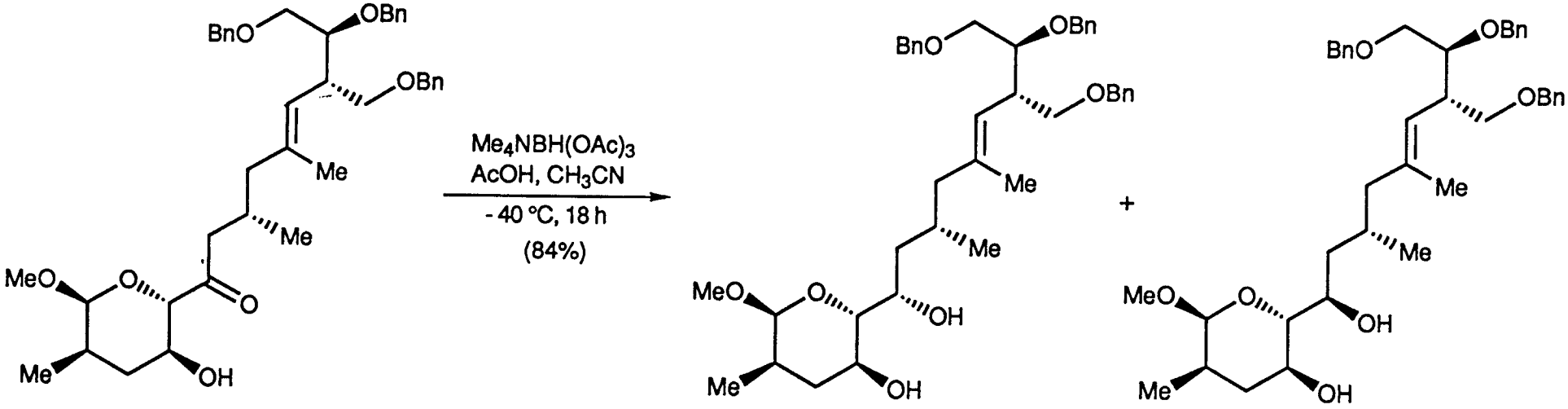




HYDROXYL DIRECTED REDUCTION OF THE β-HYDROXY KETONE



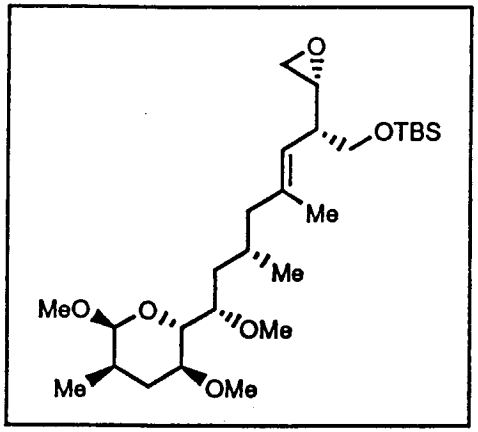
Proposed Transition State

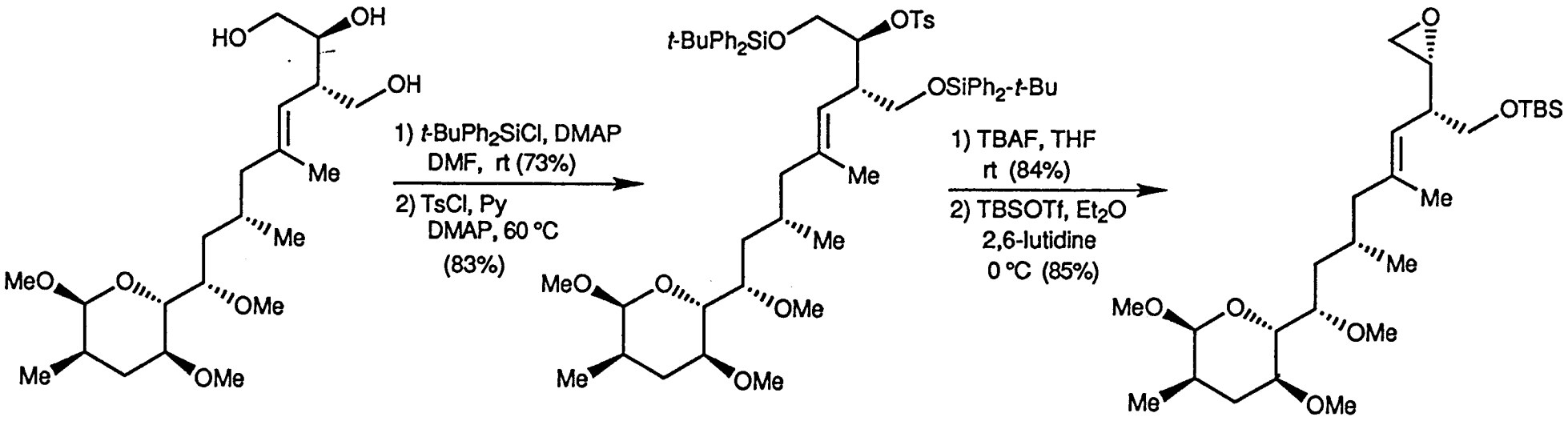


(20:1)

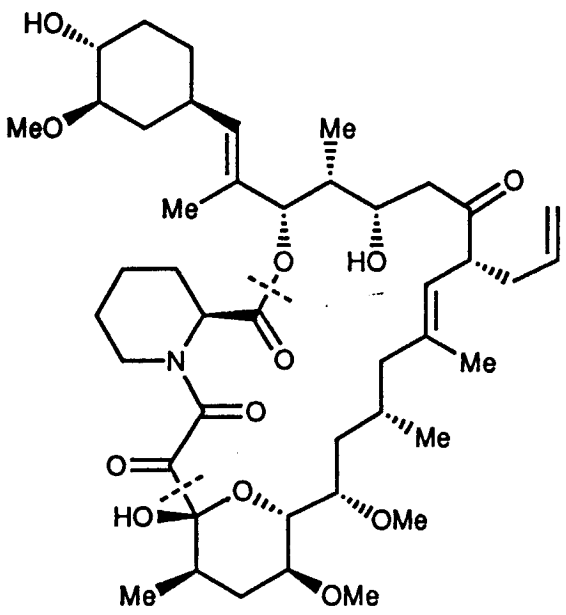
Evans, D. A.; et al. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

EPOXIDE FORMATION

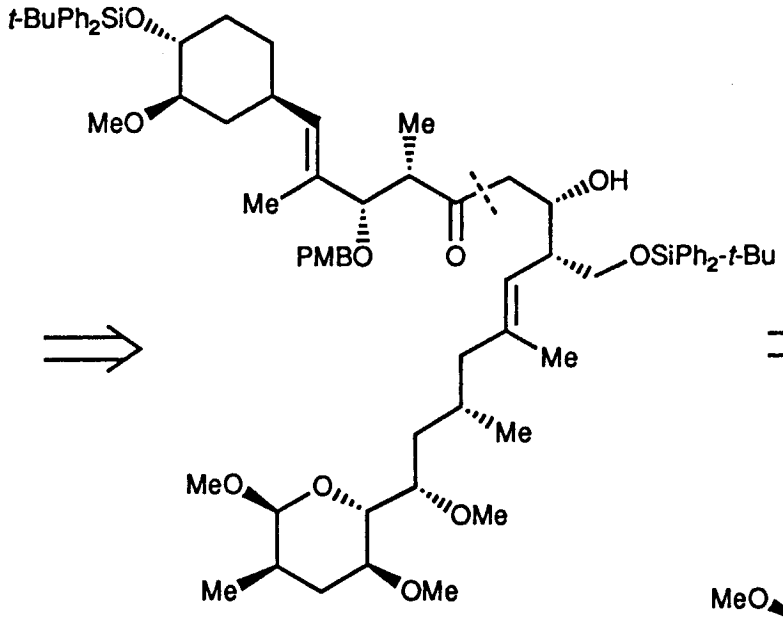


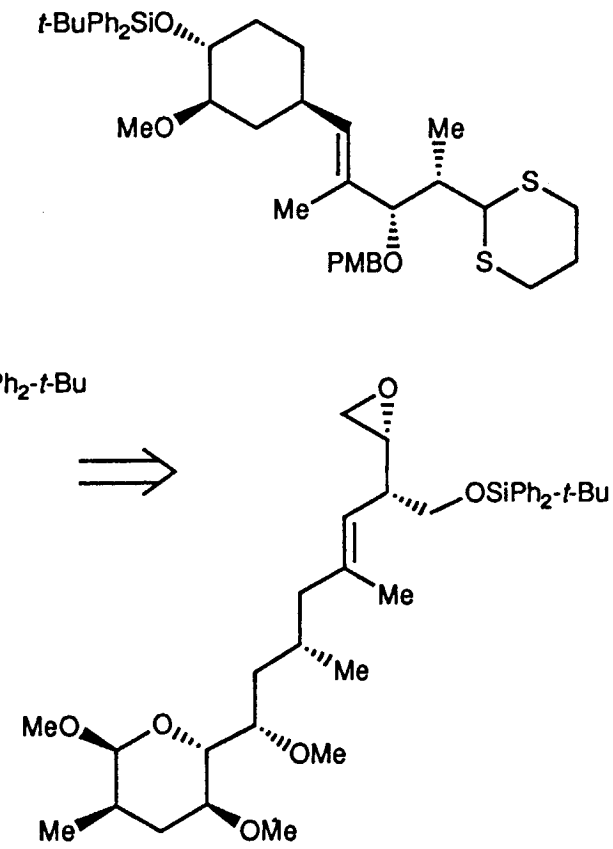


SECOND GENERATION RETROSYNTHETIC ANALYSIS OF FK506

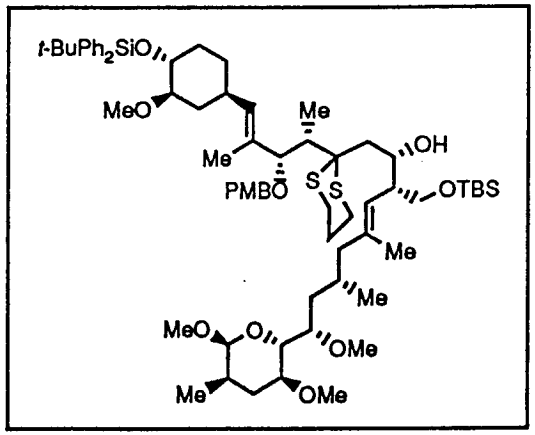


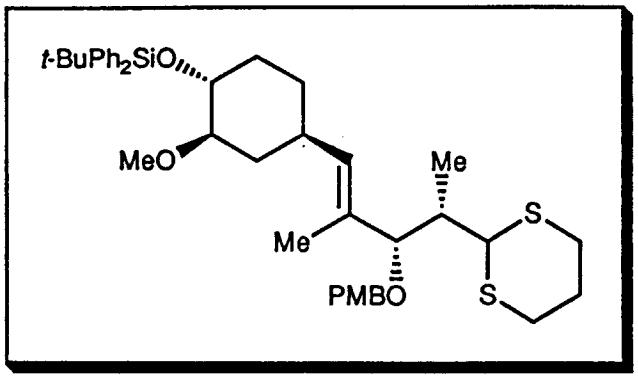
FK 506

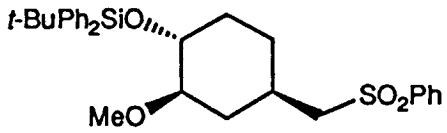


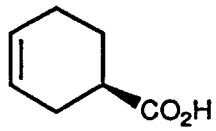


RETROSYNTHETIC ANALYSIS OF DITHIANE SUBTARGET

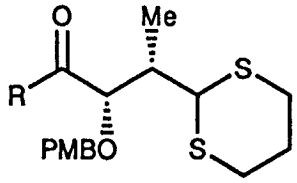


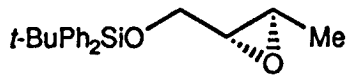






Asymmetric Diels-Alder

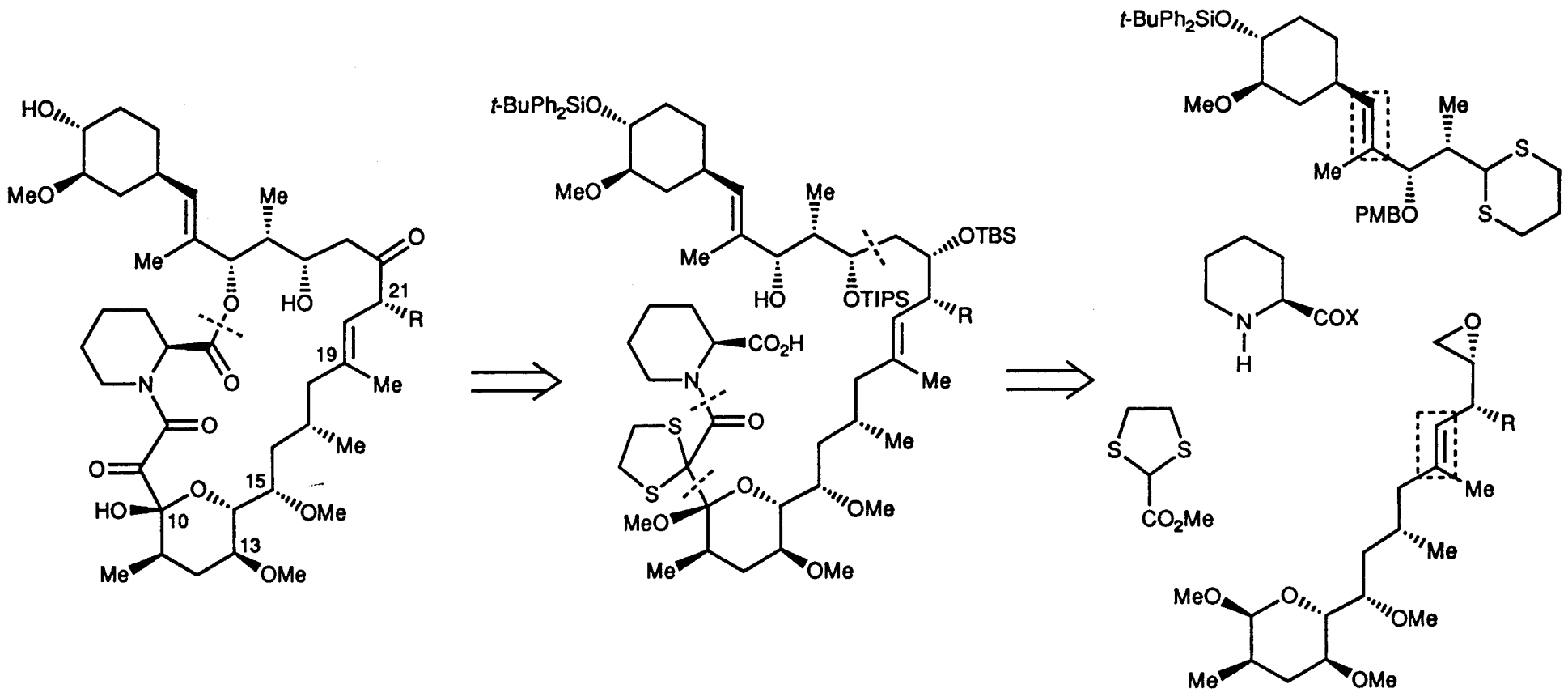




Sharpless Asymmetric Epoxidation

R = Me (Julia Coupling)
R = H (Methylation of Enol Triflate)

UNIFIED RETROSYNTHETIC ANALYSIS OF FK506, FR900520, AND FR900523



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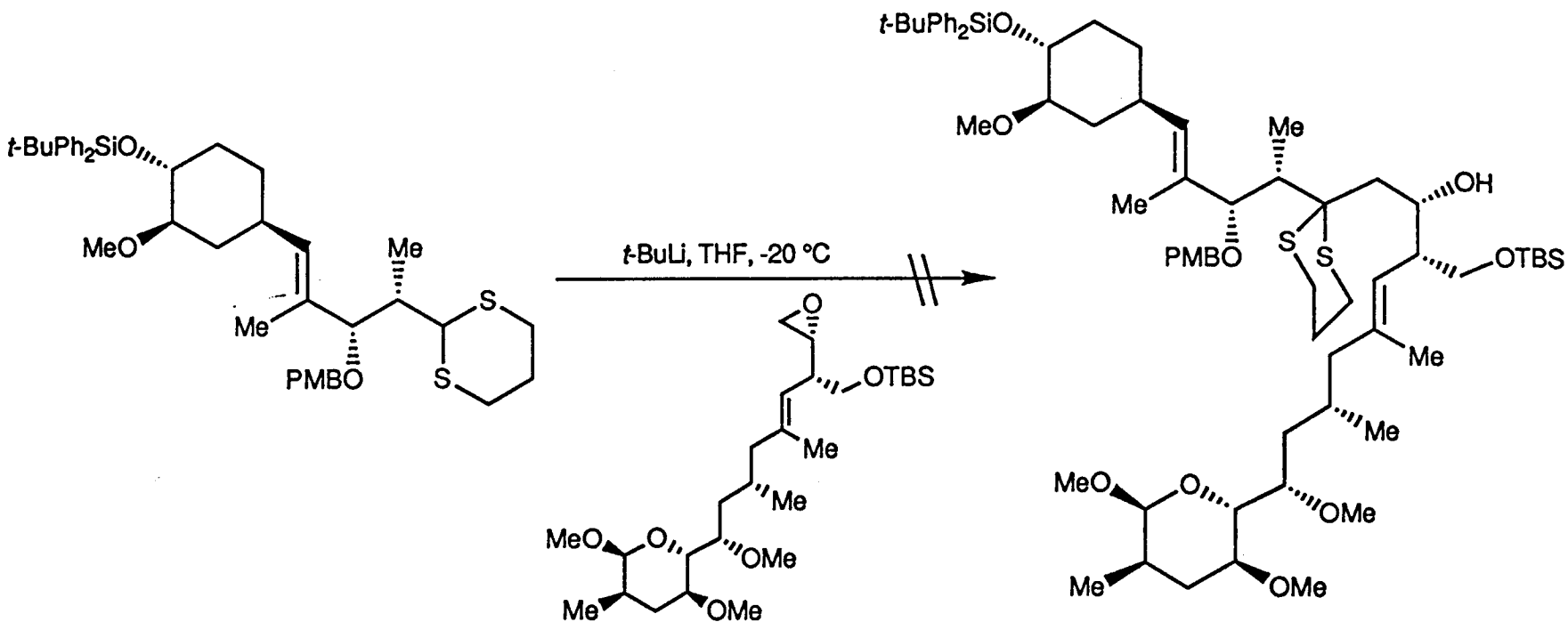
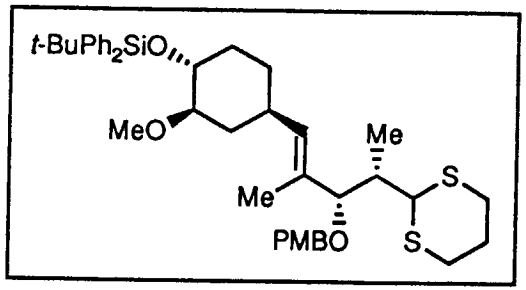
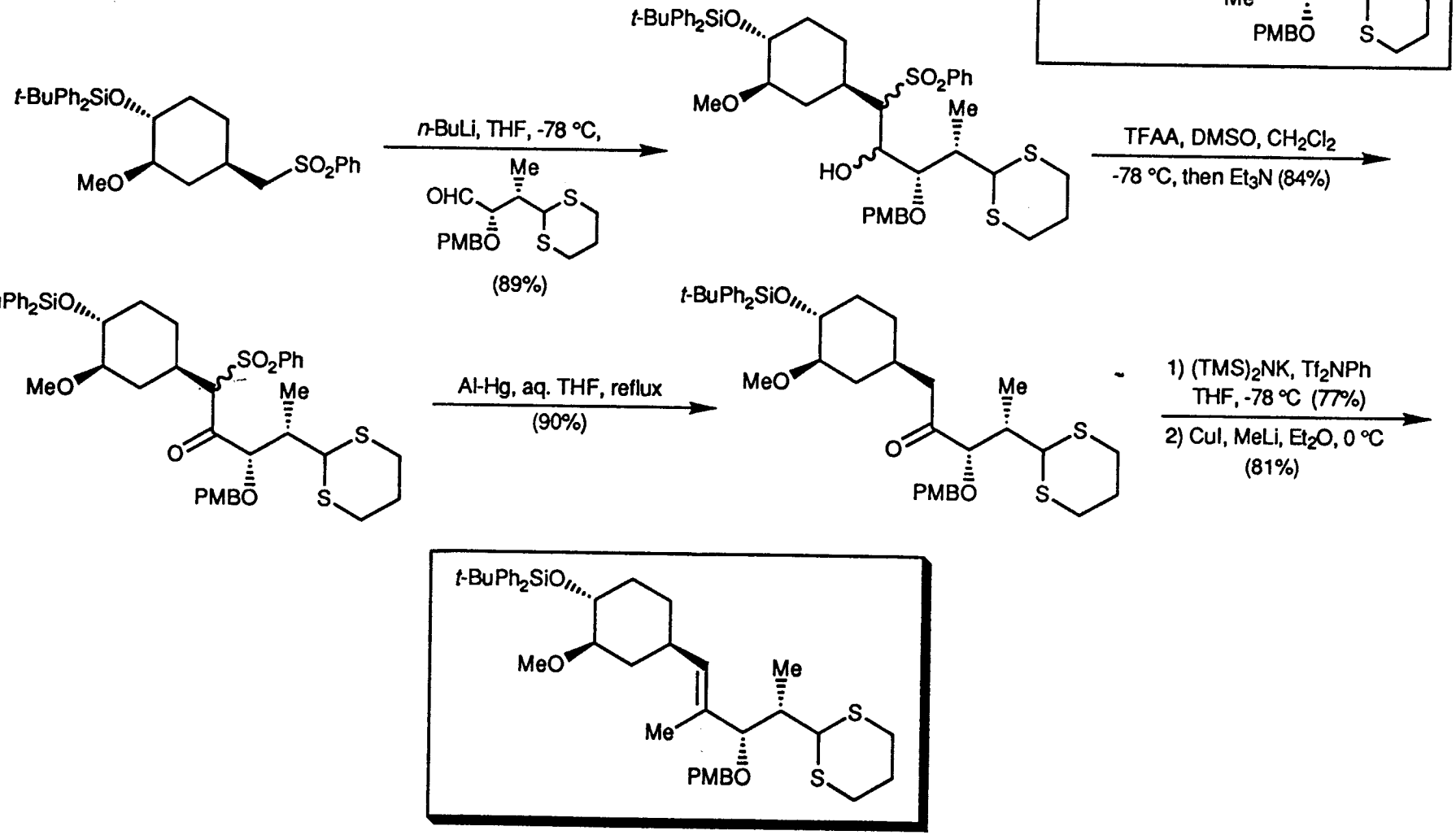
COUPLING OF NORTHERN AND EASTERN UNITS



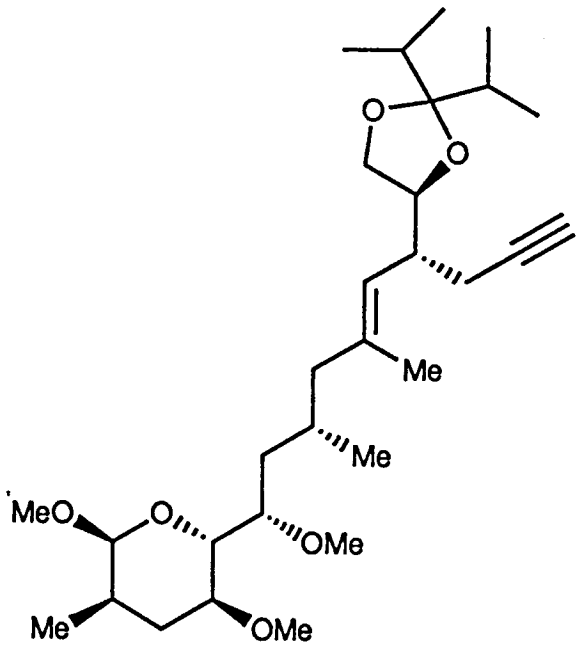
COMPLETION OF NORTHERN DITHIANE





Smith, A. B., III; Hale, K. J.; Laakso, L. M.; Chen, K.; Riéra, A. *Tetrahedron Lett.* **1989**, *30*, 6963.

STRUCTURAL CONFIRMATION: ORTEP OF ADVANCED INTERMEDIATE



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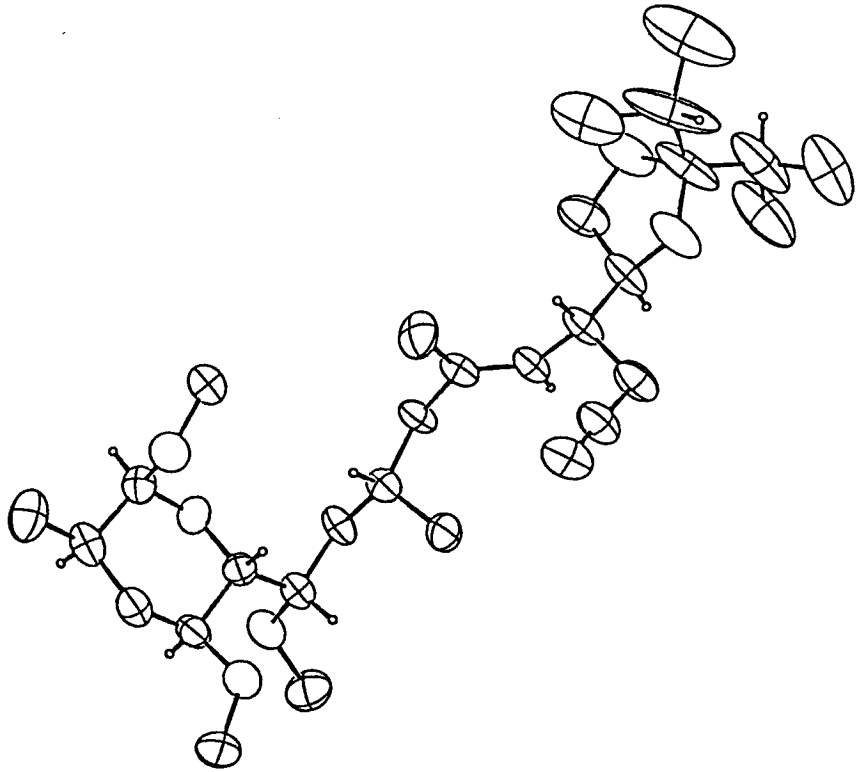
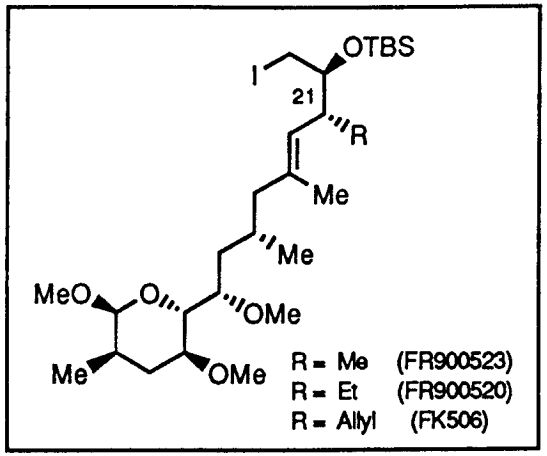
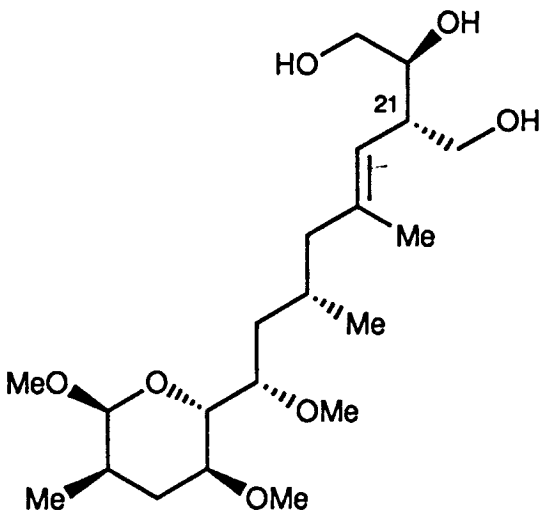
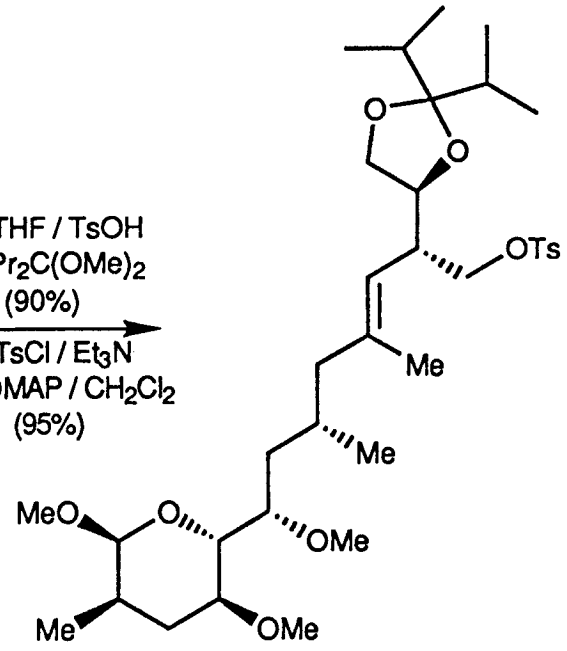


A UNIFIED SYNTHETIC STRATEGY TO FK506, FR900523, AND FR900520(INTRODUCTION OF THE C(21) SIDE CHAINS)

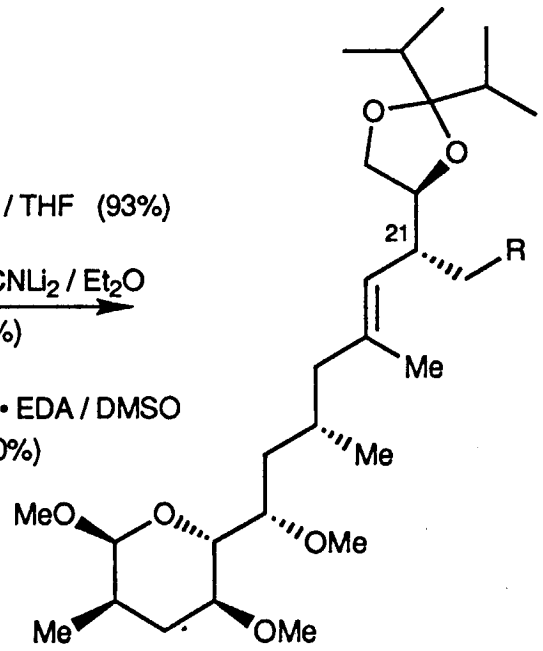




1) THF / TsOH
i-$Pr_2C(OMe)_2$
(90%)
2) TsCl / Et_3N
DMAP / CH_2Cl_2
(95%)



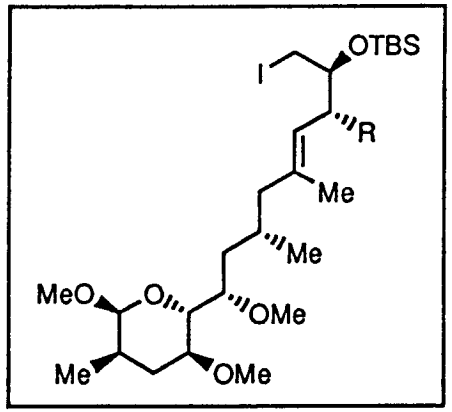
(a) $LiEt_3BH$ / THF (93%)
or
(b) $Me_2CuCNLi_2$ / Et_2O
(83%)
or
(c) LiC≡CH • EDA / DMSO
(70 - 80%)

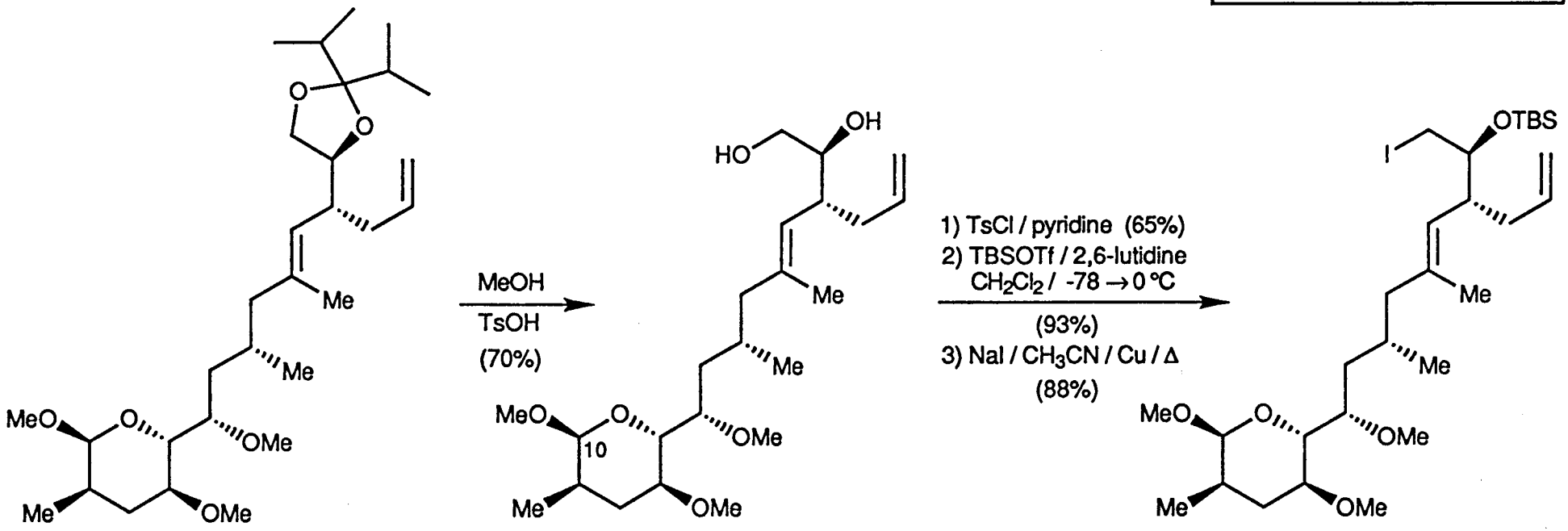


(a) R = H (FR900523)
(b) R = CH_3 (FR900520)
(c) R = C≡CH
R = $CH{=}CH_2$ (FK506)

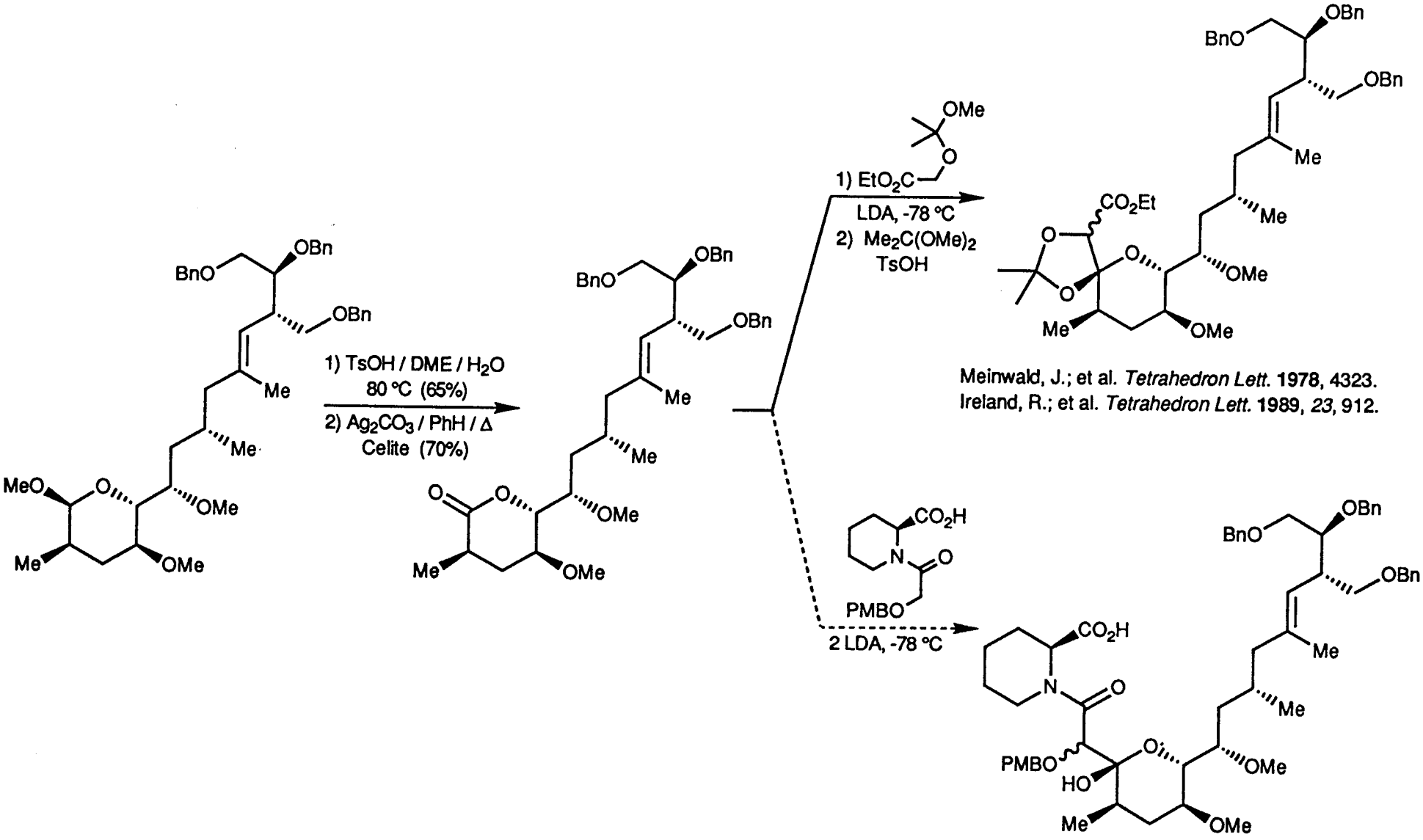
H_2 / Lindlar
quinoline / hexane
(97%)

SYNTHESIS OF EASTERN IODIDE





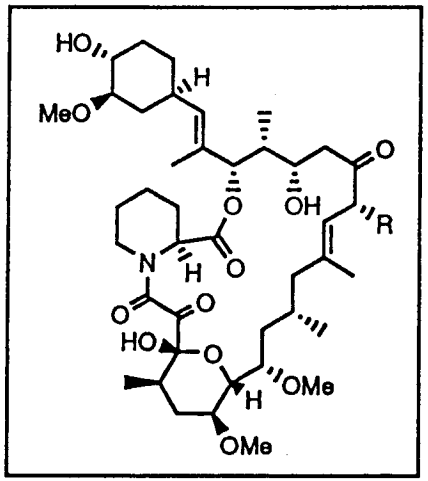
MODEL STUDY FOR TRICARBONYL INTRODUCTION

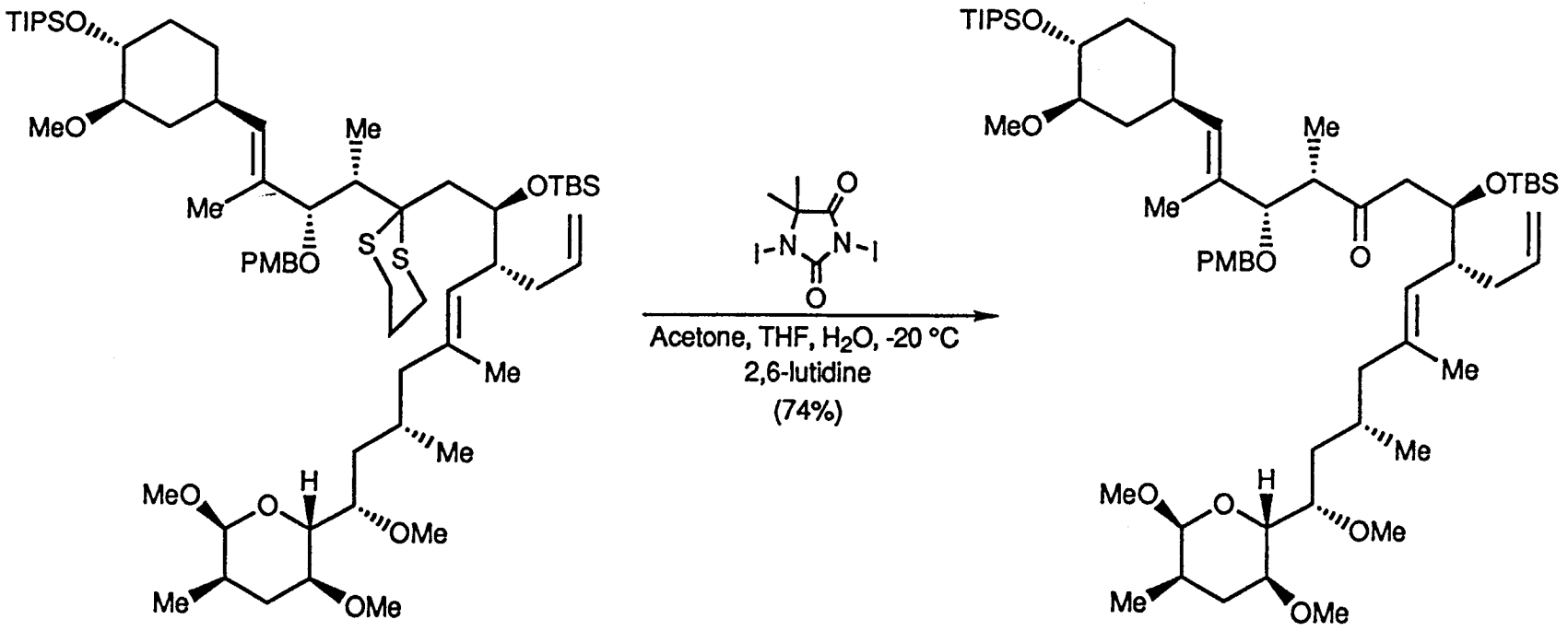


Meinwald, J.; et al. *Tetrahedron Lett.* **1978**, 4323.
Ireland, R.; et al. *Tetrahedron Lett.* **1989**, *23*, 912.

Shirahama, H.; et al. *Tetrahedron Lett.* **1991**, *25*, 2909.

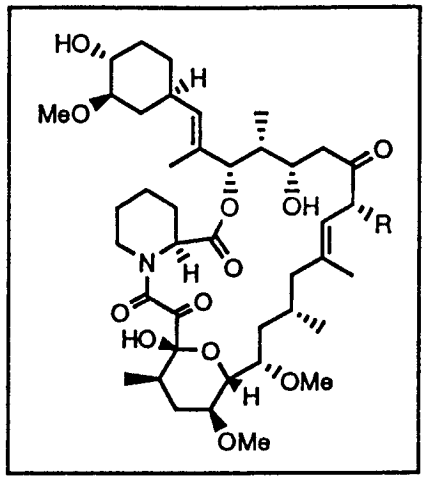
DITHIANE HYDROLYSIS

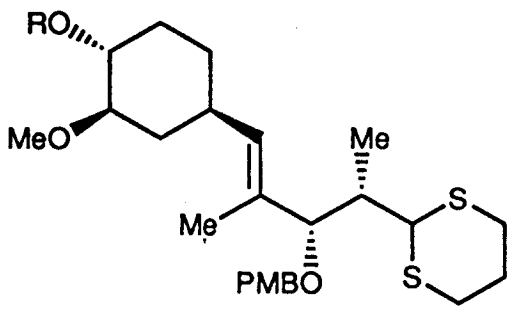




Corey, E. J.; et al. *J. Am. Chem. Soc.* **1980**, *102*, 1743.

COUPLING OF NORTHERN DITHIANE WITH EASTERN IODIDE

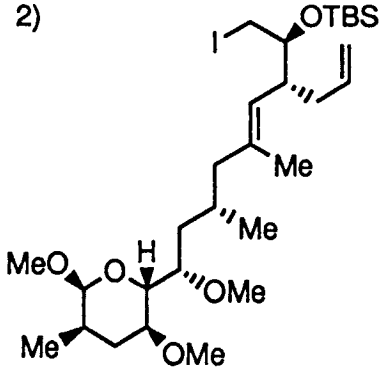


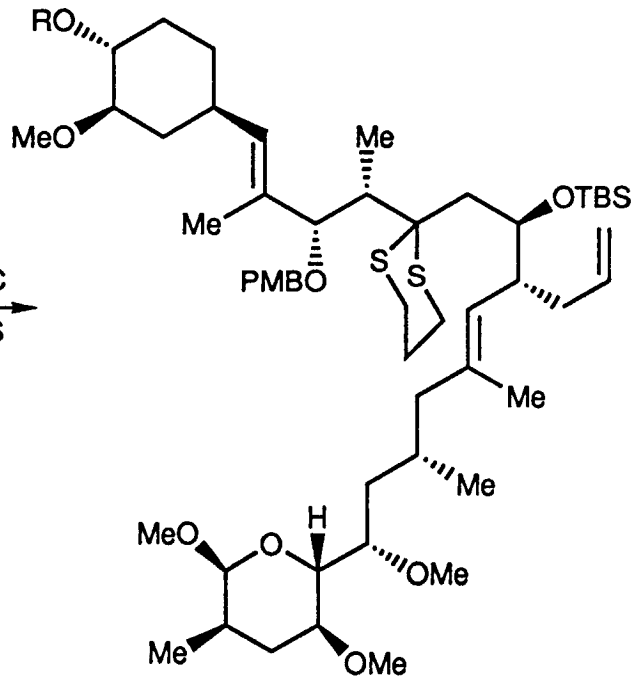


1) TBAF
2) TIPSOTf
(97%)

R = *t*-BuPh$_2$Si
R = TIPS

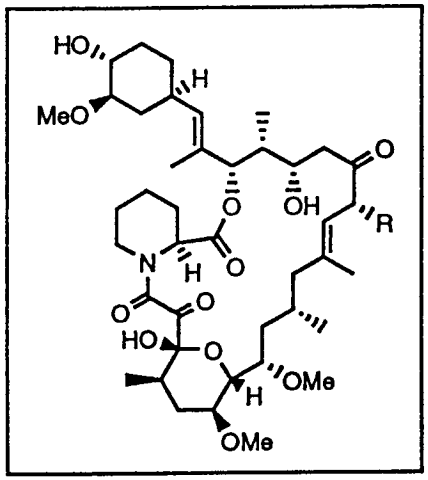
1) *t*-BuLi, HMPA, THF, -78 °C
2)

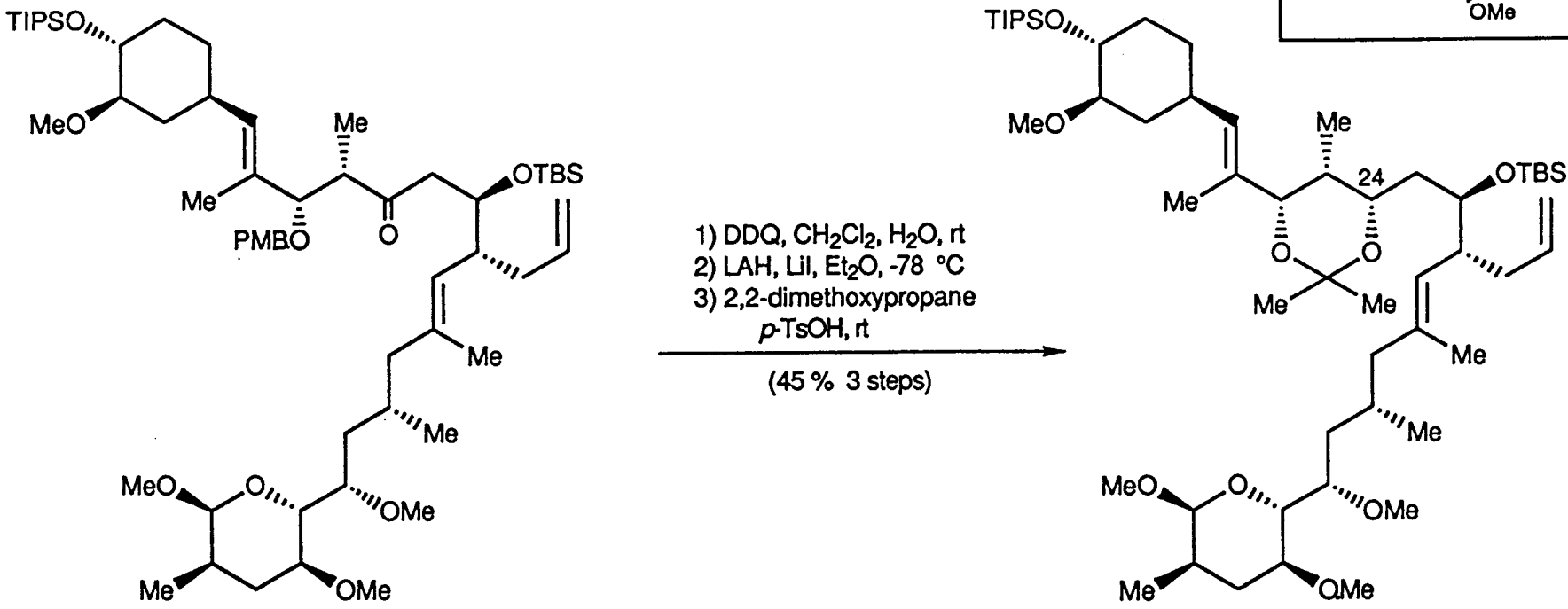




R = *t*-BuPh$_2$Si (82%)
R = TIPS (82%)

DETERMINATION OF C(24) STEREOCENTER

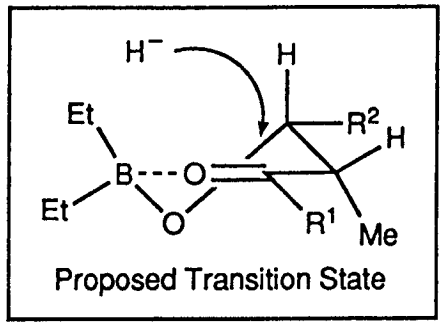




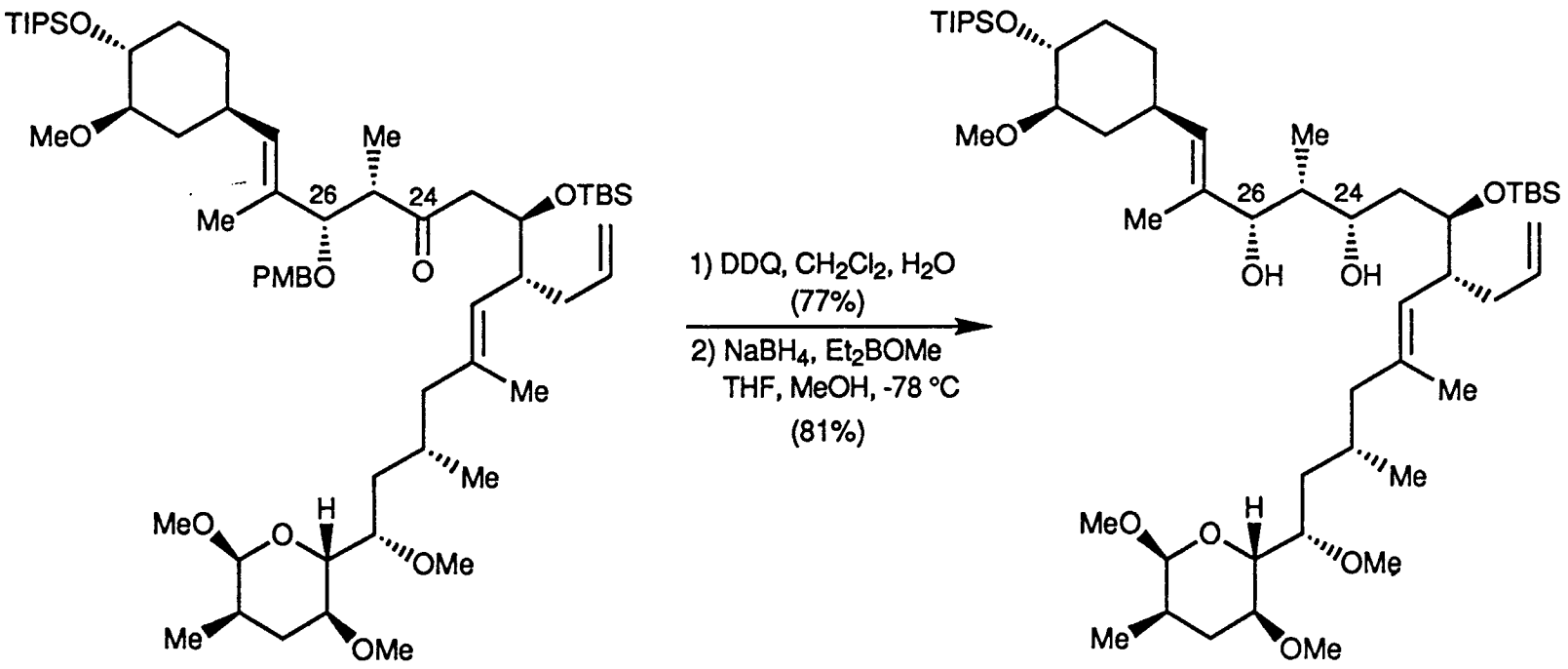
* $^{13}C \rightarrow$ **no signals between 21-25 ppm**

* Evans, D. A.; et al. *Tetrahedron Lett.* **1990,** 31, 7099.
Rychnovsky, S. D.; et al. *Tetrahedron Lett.* **1990,** 31, 945.

C(26) HYDROXYL DIRECTED REDUCTION OF C(24) KETONE

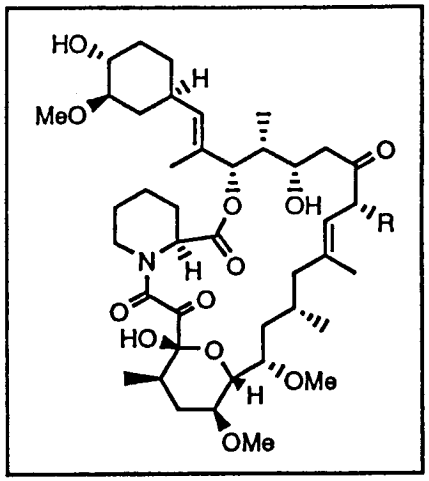


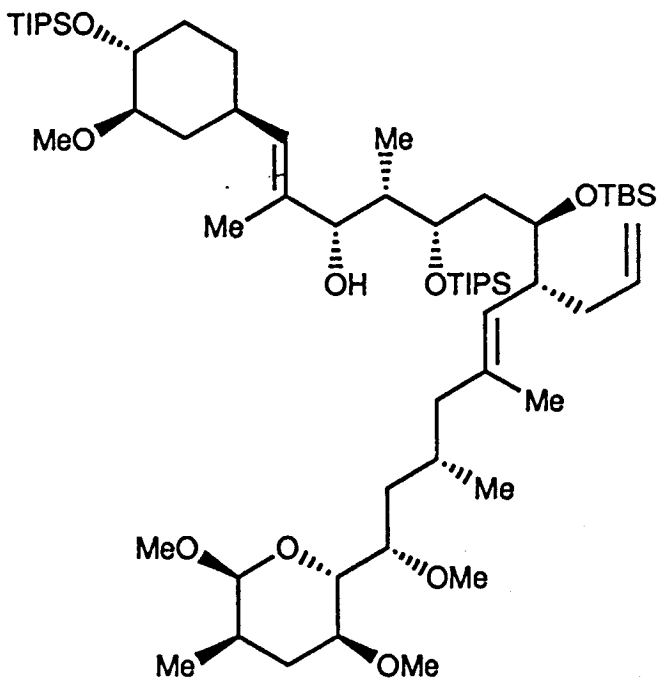
Proposed Transition State



Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.

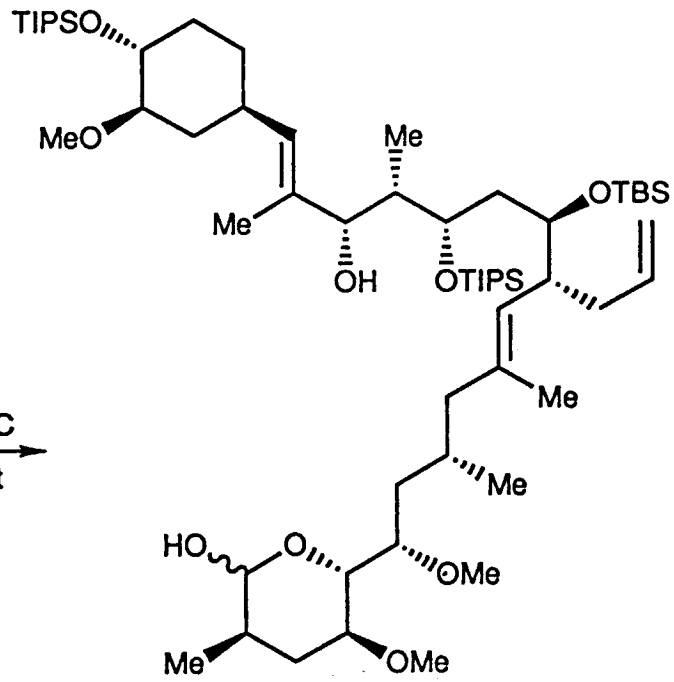
HYDROLYSIS OF THE METHYL ACETAL



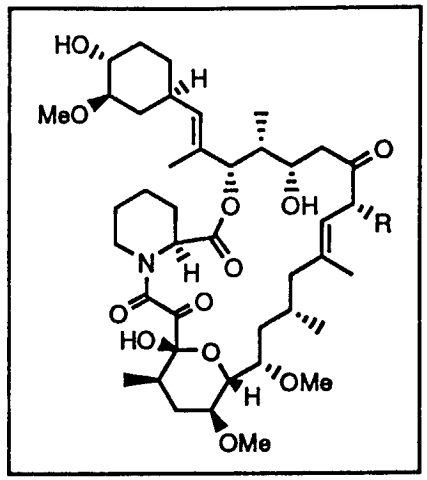


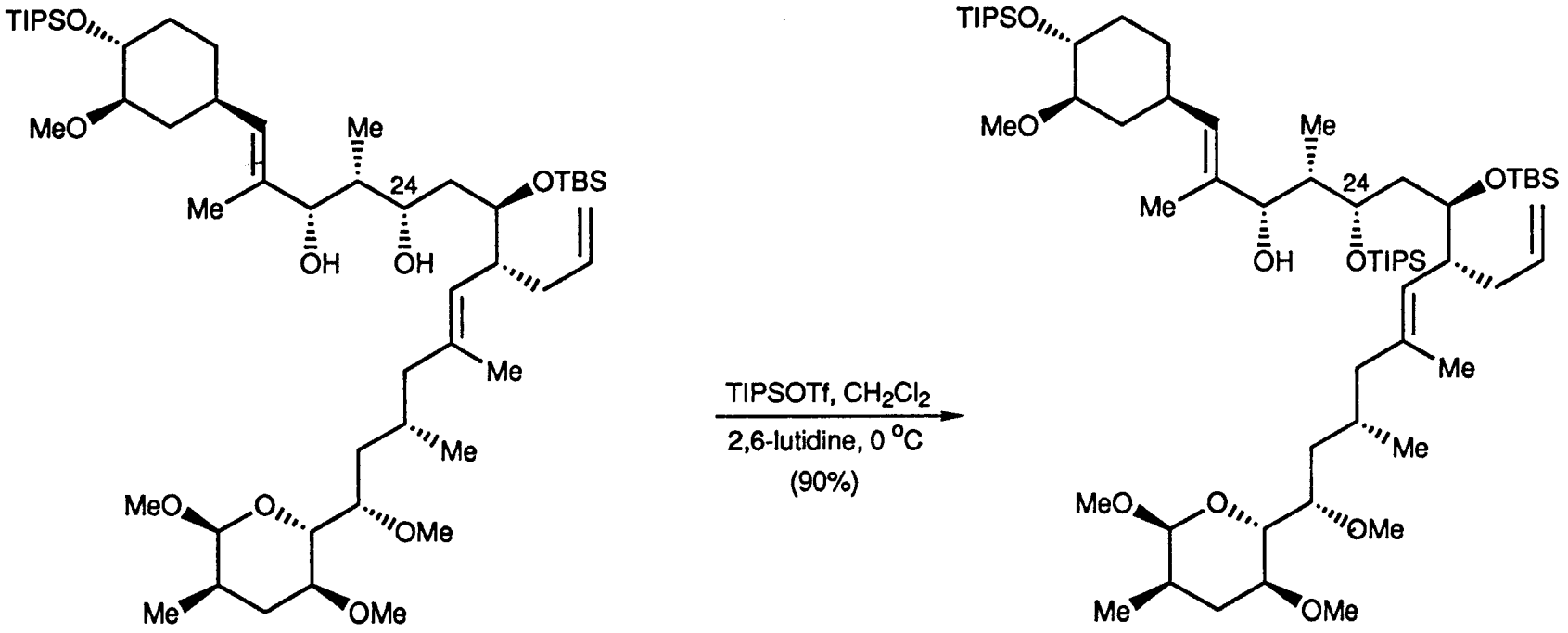
1) H_2SO_4, Ac_2O, 0 °C

2) K_2CO_3, MeOH, rt



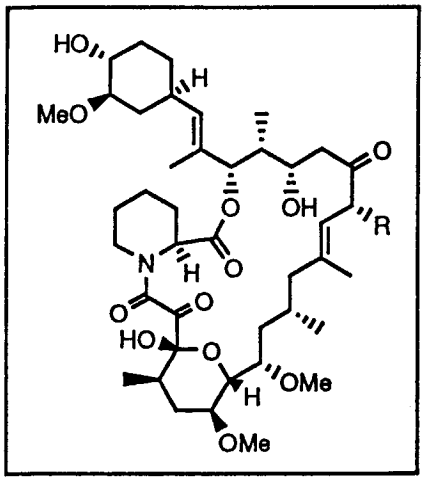
SELECTIVE PROTECTION OF THE C(24) HYDROXYL

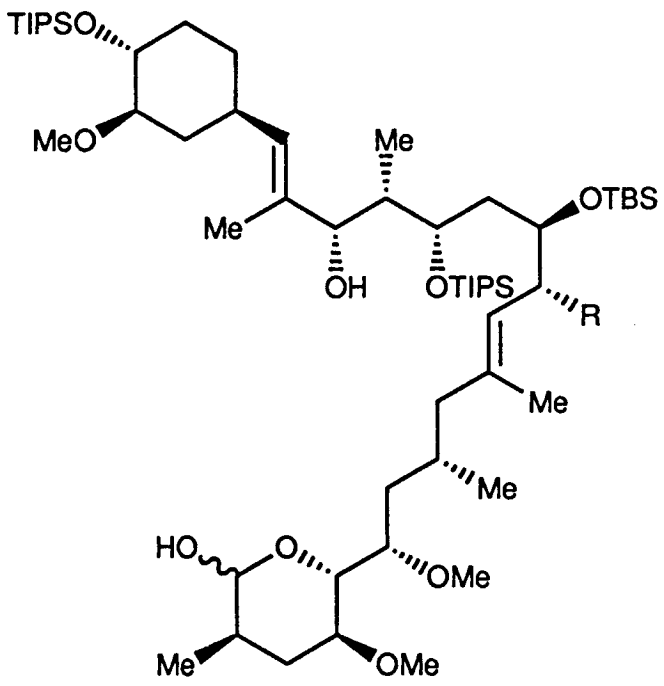


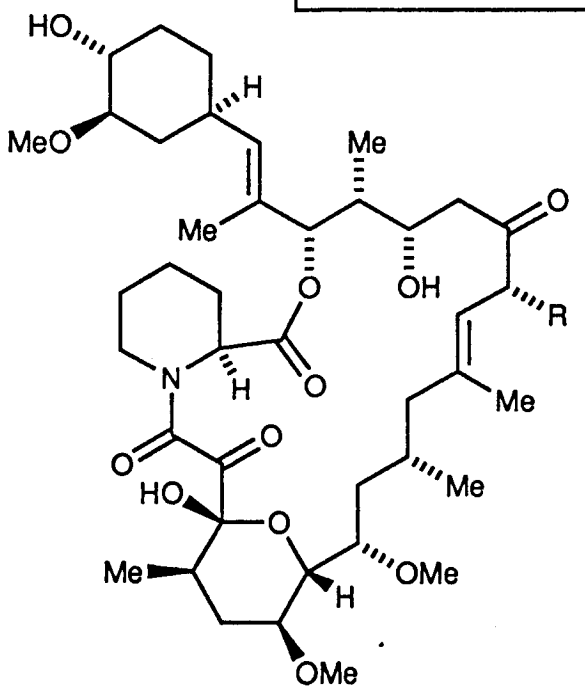


Jones, A. B.; Villalobos, A.; Linde, R. G. II; Danishefsky, S. J. *J. Org. Chem. Soc.* **1990**, *55*, 2786.

UNIFIED END GAME FOR FK506, FR900520, AND FR900523







FK506 R = $CH_2CH{=}CH_2$
FR900520 R = CH_2CH_3
FR900523 R = CH_3