Massachusetts Institute of Technology

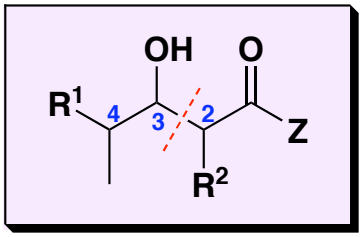
Organic Chemistry 5.512

May 3, 2006
Prof. Rick L. Danheiser

Unit 6

Stereocontrolled Aldol Reactions

- ★ Overview of the Stereochemistry of the Aldol Reaction and Substrate Control
- ★ Reagent Control: Chiral Auxiliary Strategies
- ★ Reagent Control: Chiral Controller Strategies
- ★ Reagent Control: Chiral Lewis Acid Catalyzed Aldol Reactions

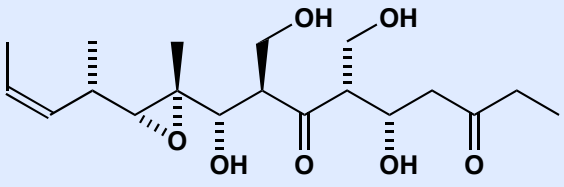


The Aldol Retron

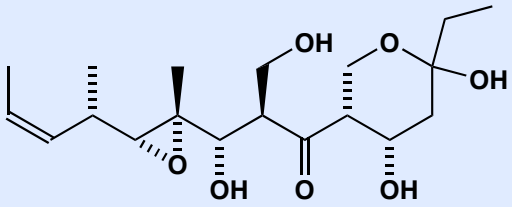
Case Study

Total Synthesis of Myriaporones

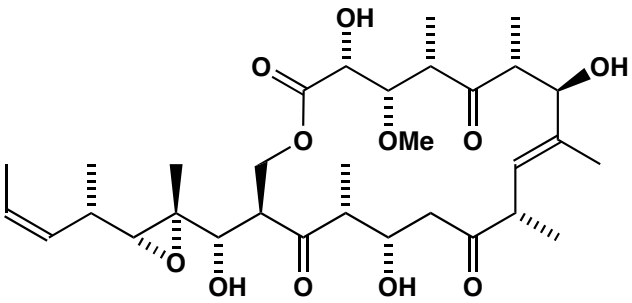
Fleming, K. N.; Taylor, R. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 1728



Myriaporone 4

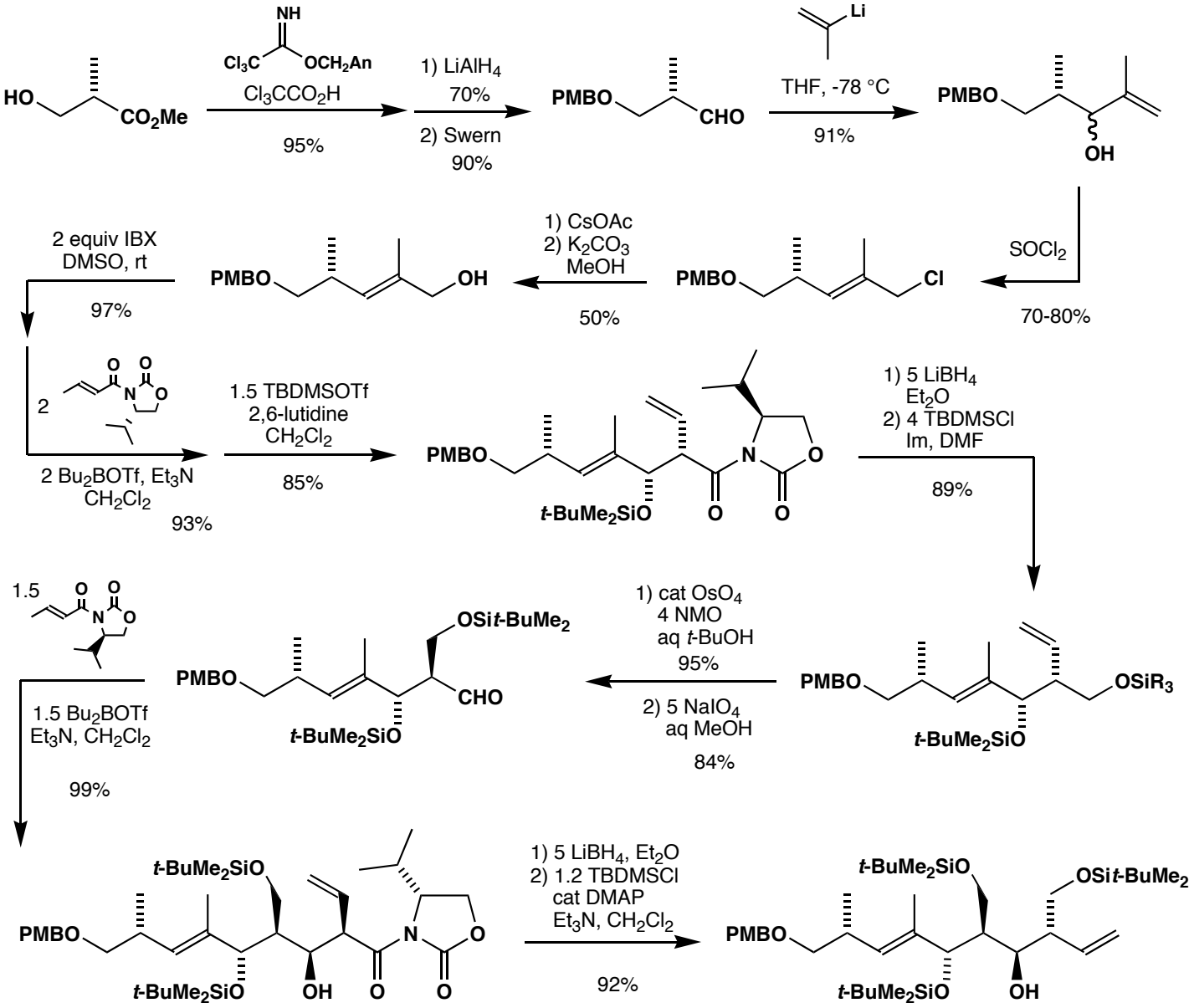


Myriaporone 3



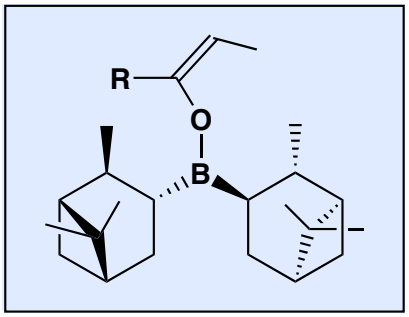
Tedanolide

Tactics


HO
CO2Me
NH
Cl3C
OCH2An
Cl3CCO2H
95%
1) LiAlH4
70%
2) Swern
90%
PMBO
CHO
Li
THF, -78 °C
91%
PMBO
OH
SOCl2
70-80%
PMBO
Cl
1) CsOAc
2) K2CO3
MeOH
50%
PMBO
OH
2 equiv IBX
DMSO, rt
97%
2
2 Bu2BOTf, Et3N
CH2Cl2
93%
1.5 TBDMSOTf
2,6-lutidine
CH2Cl2
85%
PMBO
t-BuMe2SiO
1) 5 LiBH4
Et2O
2) 4 TBDMSCl
Im, DMF
89%
PMBO
OSiR3
t-BuMe2SiO
1) cat OsO4
4 NMO
aq t-BuOH
95%
2) 5 NaIO4
aq MeOH
84%
PMBO
OSit-BuMe2
CHO
t-BuMe2SiO
1.5
1.5 Bu2BOTf
Et3N, CH2Cl2
99%
t-BuMe2SiO
PMBO
t-BuMe2SiO
OH
1) 5 LiBH4, Et2O
2) 1.2 TBDMSCl
cat DMAP
Et3N, CH2Cl2
92%
t-BuMe2SiO
OSit-BuMe2
PMBO
t-BuMe2SiO
OH

III. Chiral Controller Strategies

(1) Paterson Boron Enolates



Ian Paterson
Cambridge University

(2) Enamine Aldol Reactions

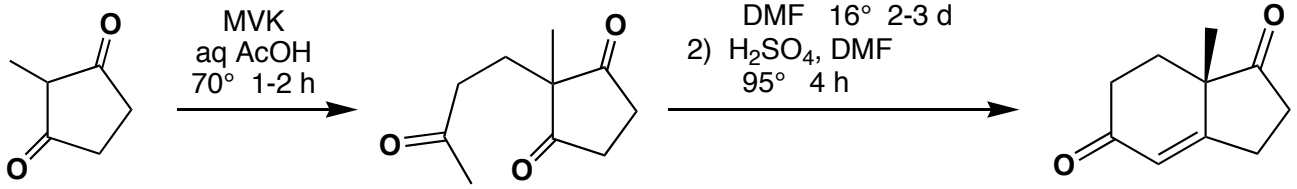
Reviews

(1) "Proline-Catalyzed Asymmetric Reactions" List, B. *Tetrahedron* **2002**, *58*, 5573

(2) "Enamine Catalysis Is a Powerful Strategy for the Catalytic Generation and Use of Carbanion Equivalents" List, B. *Acc. Chem. Res.* **2004**, *37*, 548

(3) "Enamine-Based Organocatalysis with Proline and Diamines" Notz, W.; Tanaka, F.; Barbas, C. F. *Acc. Chem. Res.* **2004**, *37*, 580

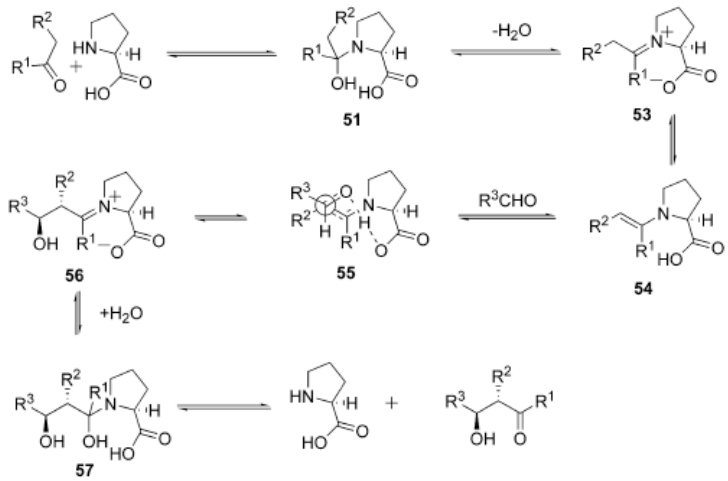
Hajos-Parrish-Eder-Sauer-Wiechert Reaction

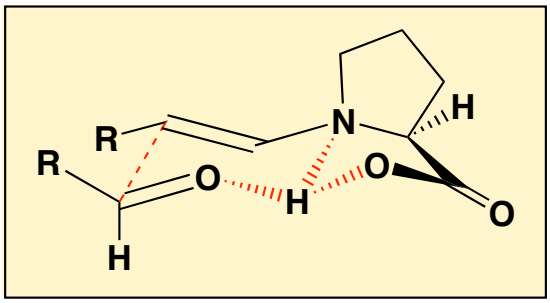


70-76%
92-94% enantiomeric purity

Hajos, Z. G.; Parrish, D. R. *Org. Synth. Coll. Vol.* **7**, 363

Scheme 8. Proposed Mechanism of the Proline-Catalyzed Intermolecular Aldol Reaction





III. Chiral Lewis Acid Strategies

(1) Carreira Chiral Ti Catalyst

Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994,** *116*, 8837

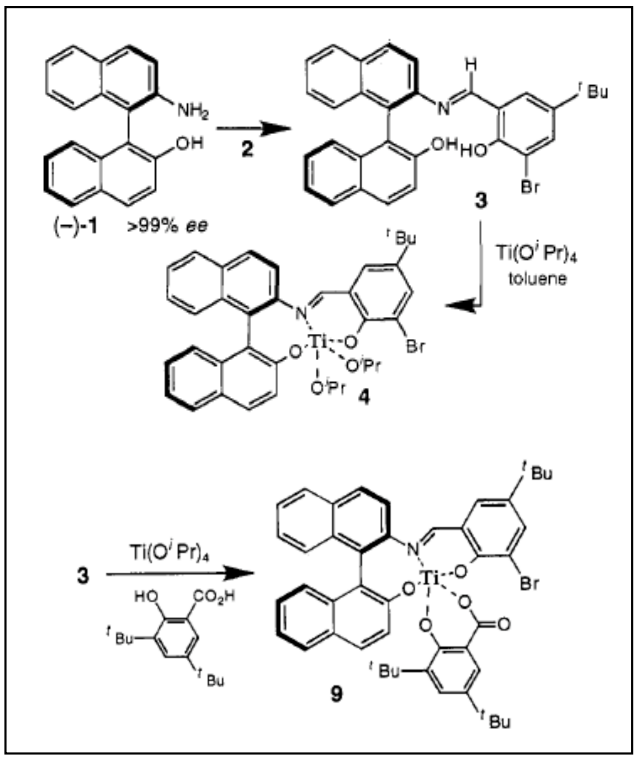
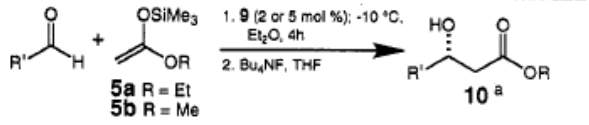


Table 1. Catalytic Asymmetric Aldol Additions of Alkyl Aceate Ketene Acetal[b,c]



Entry	Aldehyde	ee: R = Et [d]	ee: R = Me [e]
1		92%	97%
2		88%	95%
3		93%	97%
4		89%	94%
5	$C_6H_{11}CHO$	94%	95%
6	PhCHO	93%	96%

[a] Absolute configuration was determined by reduction to the known 1,3-diols.[1h] [b] Yields for two steps (addition and desilylation) range from 72 to 98%. [c] For each entry, the *ee* was determined by preparation of the derived (*S*)-MTPA ester and analysis by ^{1}H NMR spectroscopy. [d] 5 mol % catalyst used. [e] 2 mol % catalyst used.

(2) Evans Copper BOX and PYBOX Catalysts

D. A. Evans et al. *J. Am. Chem. Soc.* **1999,** *121*, 669
Reviewed in: J. S. Johnson and D. A. Nicewicz In *Modern Aldol Reactions,* Vol 2; Mahrwald, R., Ed.; Wiley-VCH, 2004; pp 69-103.