Massachusetts Institute of Technology

Organic Chemistry 5.512

April 25, 2007
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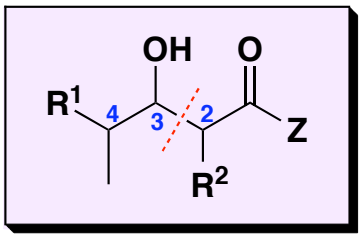
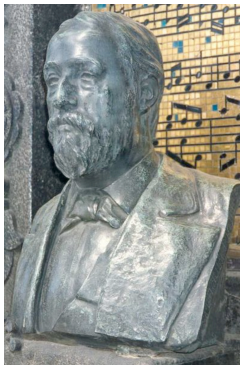
Unit 6

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



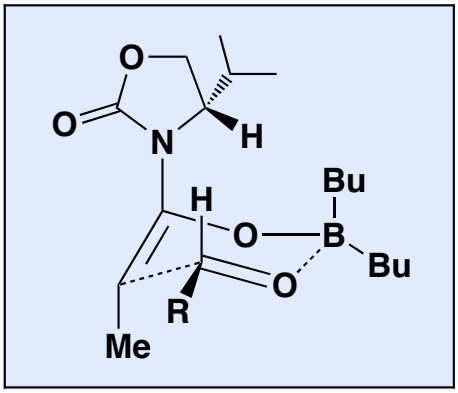
Alexsander Borodin

II. Chiral Auxiliary Strategies

★ 2,3-Syn Aldols

Evans Oxazolidinone Boron Enolates

Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83



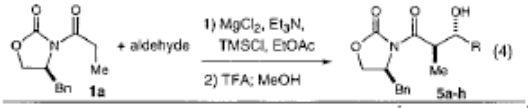
Review
"Asymmetric Aldol Reactions Using Boron Enolates"
Cowden, C. J.; Paterson, I. *Organic Reactions* **1997**, *51*, 1

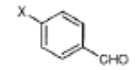
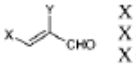
★ 2,3-Anti Aldols

(1) Evans Dones

D. A. Evans et al.
J. Am. Chem. Soc. **2002** *124*, 392
and *Org. Lett.* **2002**, *4*, 1127

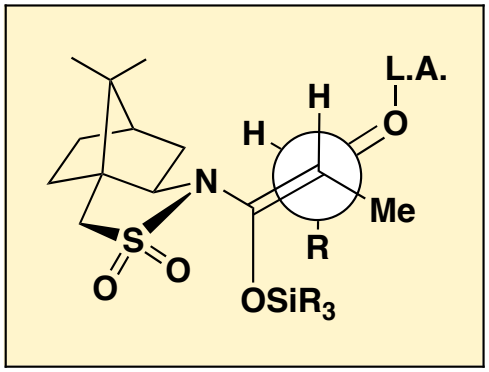
Table 2. Mg-Catalyzed *anti*-Aldol Reactions of **1a** with Representative Aldehydes (Eq 4)[a]

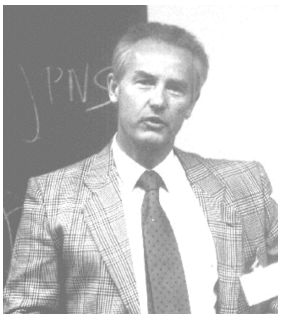


aldehyde		product	procedure[a,b]	dr[c]	yield (%)[d]
	X = Me	5a	A	24:1	-
	X = OMe	5b	A	32:1	91
	X = NO_2	5c	B	7:1	71
	X = Ph, Y = H	5d	B	21:1	92
	X = Ph, Y = Me	5e	A	28:1	92
	X = H, Y = Me[j]	5f	B	16:1	77
α-naphthaldehyde		5g	A	14:1	91
furfural		5h	B	6:1	80

[a] Procedure A: reactions were conducted with 1.0 equiv **1**, 0.2 equiv $MgCl_2$, 2.0 equiv of triethylamine, 1.5 equiv of TMSCl, 1.2 equiv of RCHO at 0.5 M in EtOAc for 24 h. [b] Procedure B: reaction conducted as in Procedure A but with 0.1 equiv $MgCl_2$ and the addition of 0.3 equiv of $NaSbF_6$ at 0.2 M in ethyl acetate. [c] Table 1 footnote b. [d] Isolated yield of a single diastereomer.

(2) Oppolzer Sultams

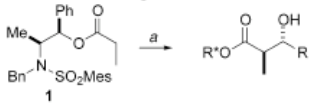




(3) Masamune Esters

Review
"Boron-Mediated Aldol Reaction of Carboxylic Esters"
Abiko, A. *Acc. Chem. Res.* **2004**, *37*, 387
see also *Org. Synth.* **2002**, *79*, 109 and 116

Table 4. anti-Selective Asymmetric Aldol Reaction of Compound 1



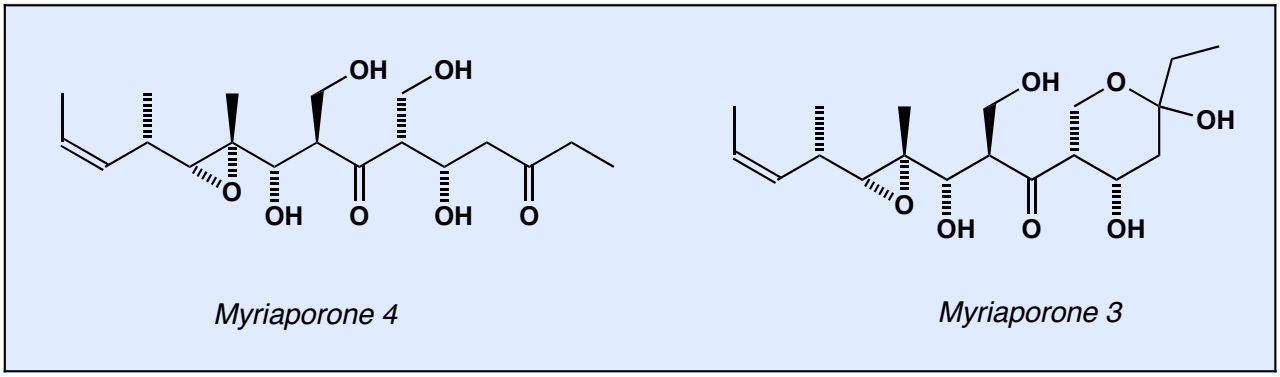
RCHO	yield (%)	ds for anti[b]
MeCHO	92	97:3
EtCHO	90	96:4
n-PrCHO	95	95:5
i-PrCHO	95	98:2
c-HexCHO	91	95:5
t-BuCHO	96	>99:1
PhCHO	93	95:5
(*E*)-$CH_3CH{=}CHCHO$	96	98:2
$CH_2{=}C(CH_3)CHO$	97	96:4
$BnOCH_2CH_2CHO$	94	95:5
$BnOCH_2C(CH_3)_2CHO$	98	96:4

[a] *c*-Hex_2BOTf (2.0 equiv), Et_3N (2.4 equiv), −78 °C for 2 h; then RCHO, −78 °C for 1 h, 0 °C for 1 h. [b] anti/syn = >98:2; ds = diastereoselectivity.

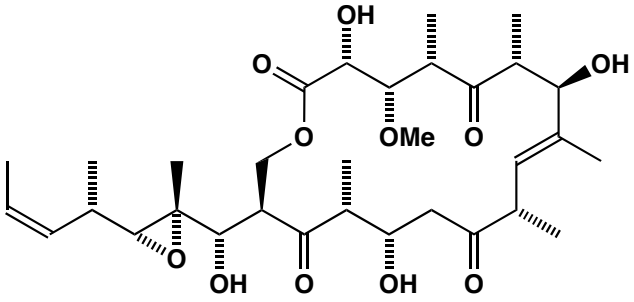
Case Study

Total Synthesis of Myriaporones

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

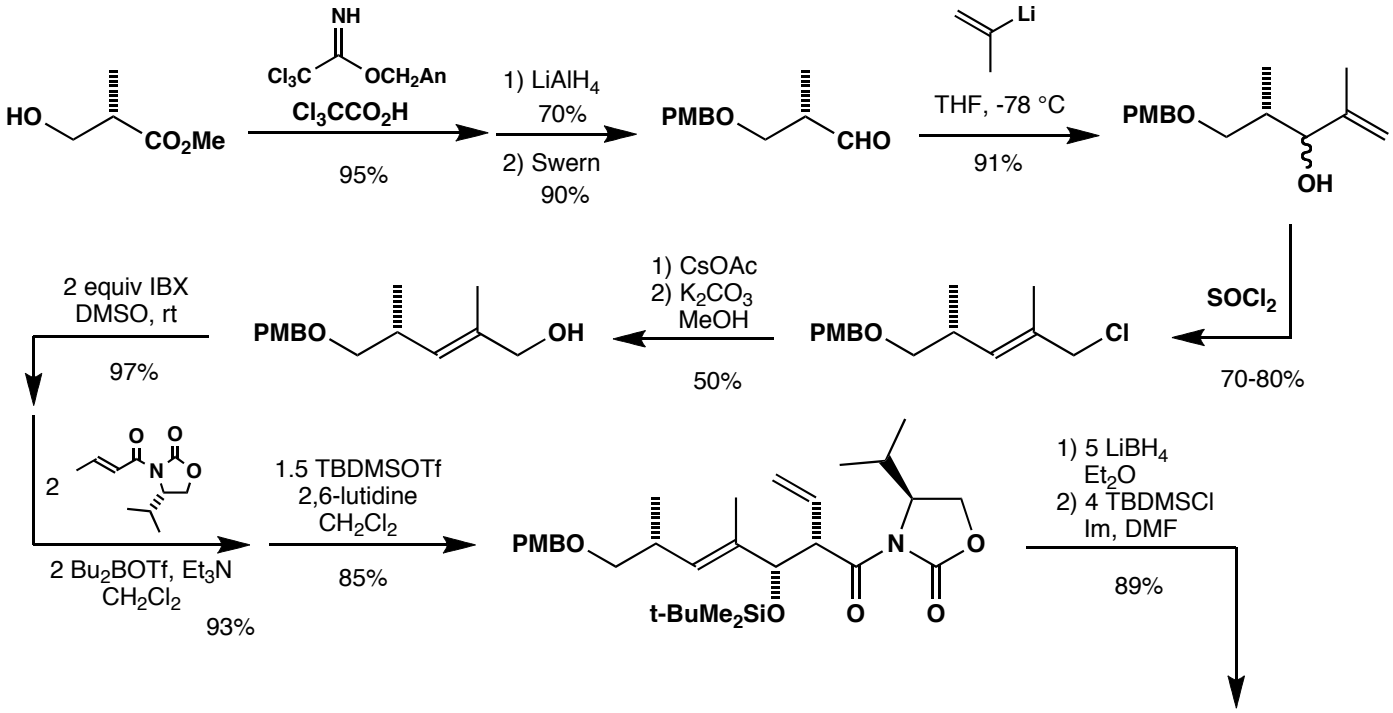


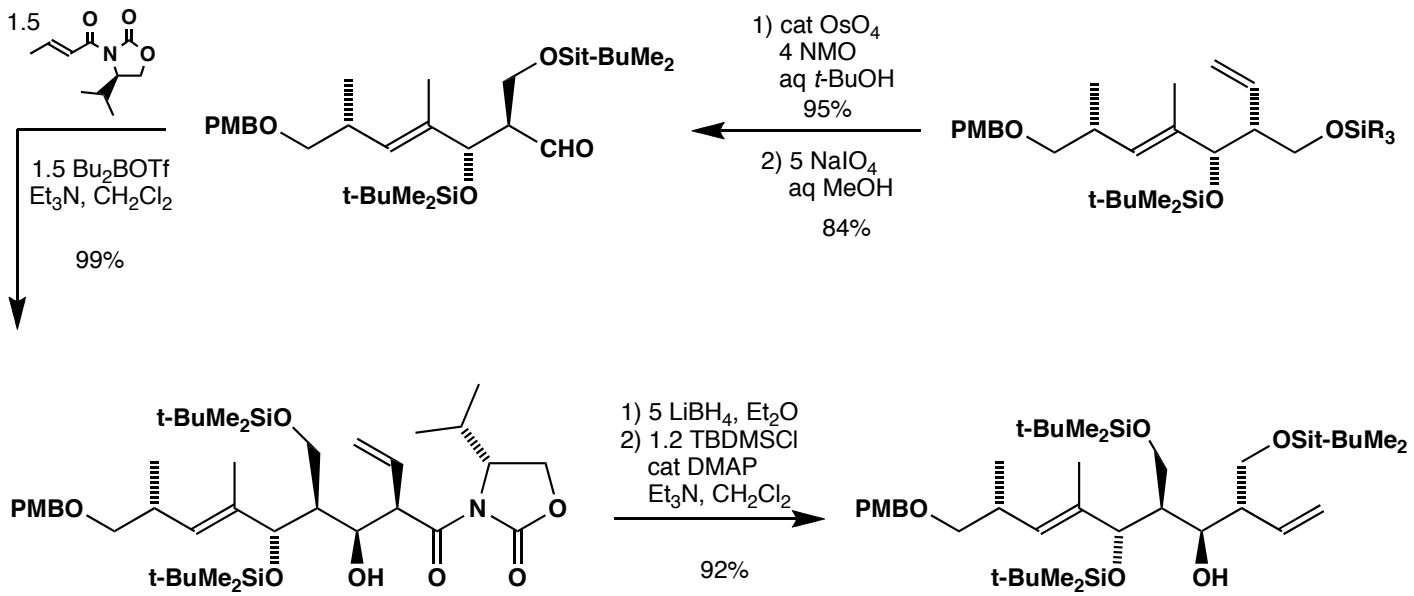
Myriaporone 4 *Myriaporone 3*



Tedanolide

Tactics




1.5
1.5 Bu2BOTf
Et3N, CH2Cl2
99%
PMBO
OSit-BuMe2
CHO
t-BuMe2SiO
1) cat OsO4
4 NMO
aq t-BuOH
95%
2) 5 NaIO4
aq MeOH
84%
PMBO
OSiR3
t-BuMe2SiO
t-BuMe2SiO
PMBO
t-BuMe2SiO
OH
N
O
O
1) 5 LiBH4, Et2O
2) 1.2 TBDMSCl
cat DMAP
Et3N, CH2Cl2
92%
t-BuMe2SiO
OSit-BuMe2
PMBO
t-BuMe2SiO
OH