



VYTORIN treats the 2 sources of cholesterol.

Your cholesterol.

It comes from pizza...and your parents.

VYTORIN lowered bad cholesterol
more than Lipitor or Zocor.



VYTORIN is
proven to lower
bad cholesterol
45% — 60%

(average effect
depending on dose;
52% at the usual
starting dose).

Erin Milner 2005

Crimmins Group Meeting

VYTORIN[™]
(ezetimibe/simvastatin) tablets

www.vytorin.com

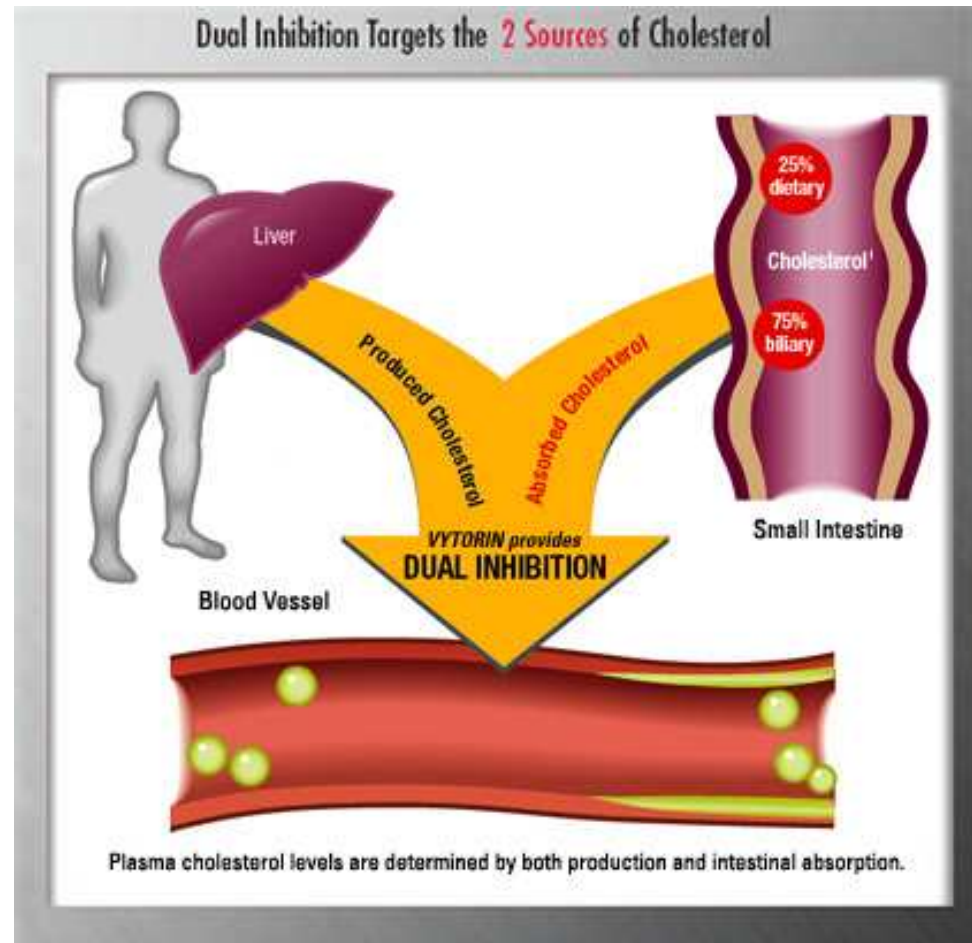
2 Sources of Cholesterol

The first is food, the second is your body.

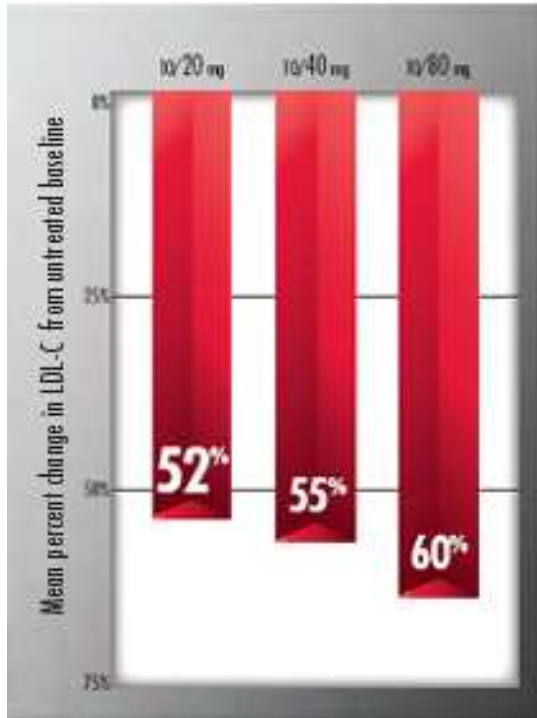
In humans, more than ½ of total body cholesterol is derived from de novo synthesis

LDL (low-density lipoprotein):
- can build up in the walls of your arteries and form a thick, hard plaque

HDL (high-density lipoprotein):
- helps eliminate LDL

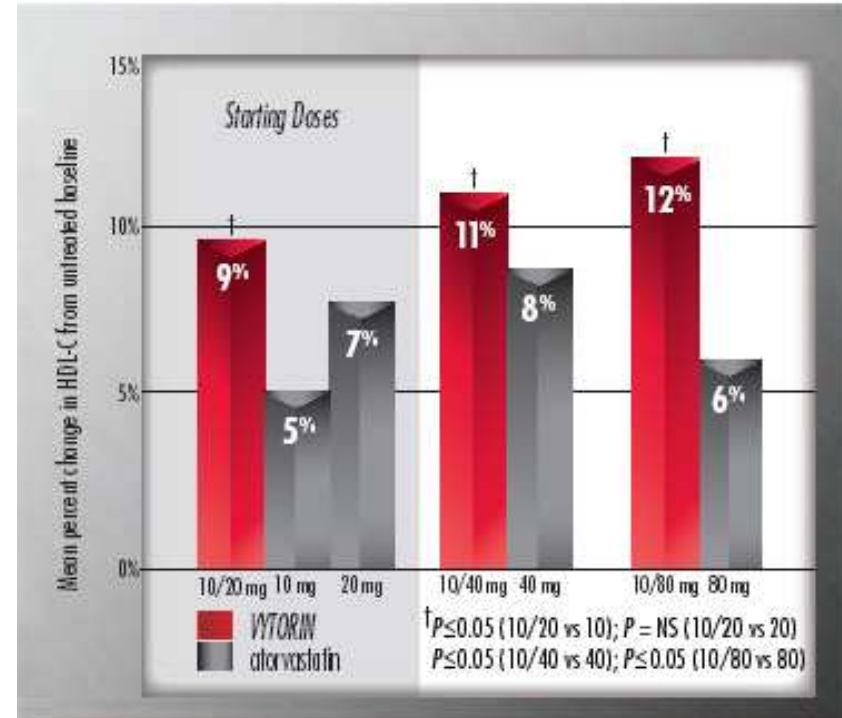


VYTORIN Lowered LDL-C by 52% With the Starting Dose*



**Lowered LDL cholesterol
Lowered triglycerides**

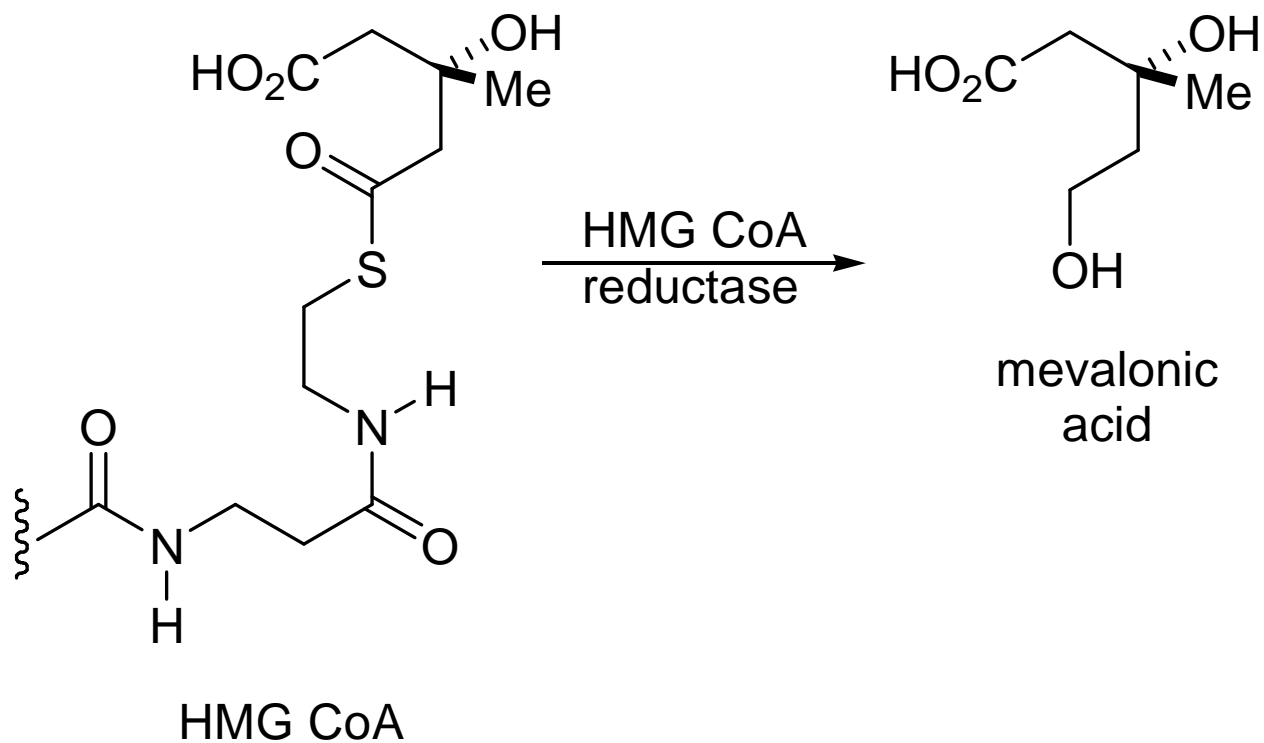
VYTORIN Provided Excellent HDL-C Efficacy vs Atorvastatin*



Raised HDL cholesterol

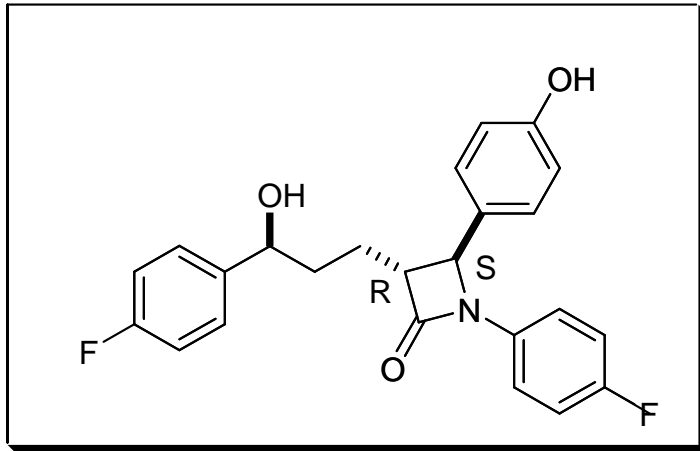
“VYTORIN was clinically proven to lower bad cholesterol more than Lipitor or Zocor alone.”

Cholesterol Biosynthesis



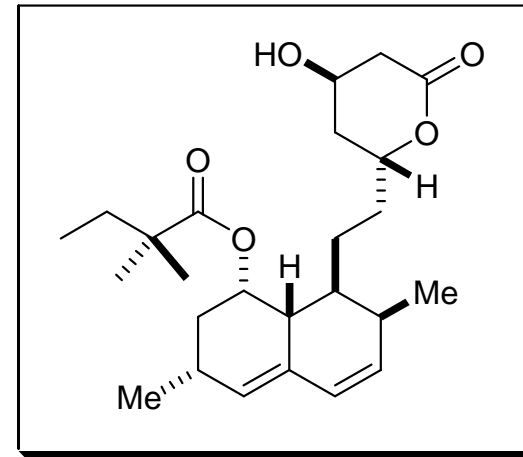
Review of synthetic approaches to mevinic acids:
Rosen & Heathcock, *Tetrahedron*, **1986**, 42, 4909

VYTORIN is a tablet containing two medicines



Zetia® (ezetimibe, SCH 58235)

- Selective inhibitor of cholesterol in the small intestine
- Inhibited intestinal cholesterol absorption by 54% compared with placebo.
- Cholesterol inhibition in the small intestine decreased delivery to liver
- Caused an increase in clearance of cholesterol from the blood – complementary to HMG-CoA reductase inhibitor



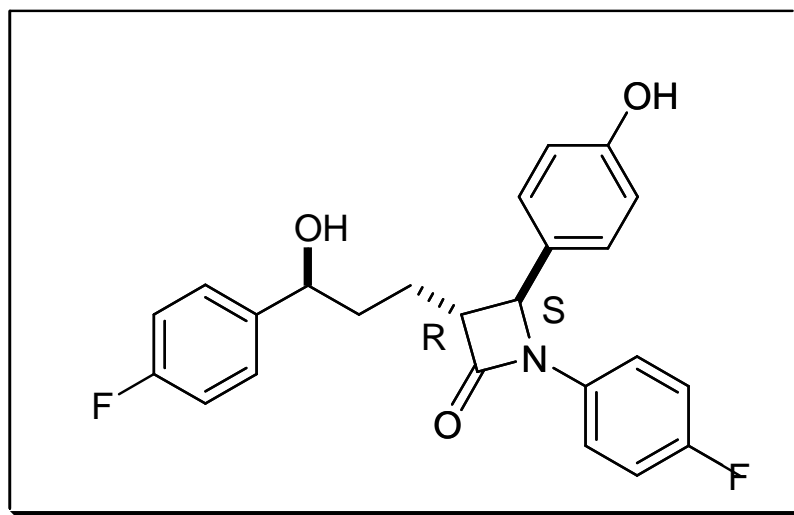
Zocor® (simvastatin)

- Inactive as the lactone
- Hydrolyzed to β -hydroxyacid form
- Reduces cholesterol by inhibiting the conversion of HMG-CoA to mevalonate by 45% (an early step in the biosynthetic pathway for cholesterol)
- Reduces LDL and increases HDL

Special Populations

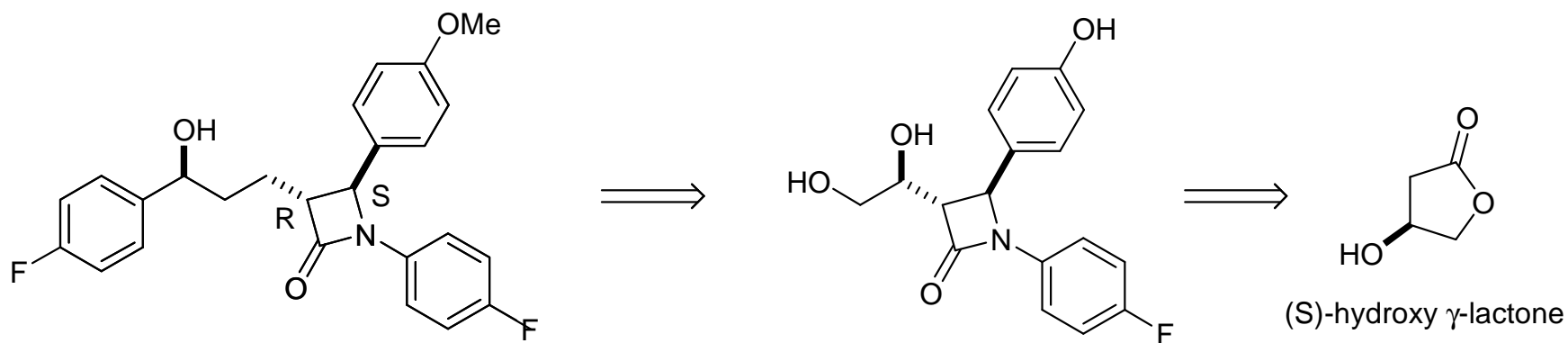
- Ezetimibe
 - Plasma concentrations for patients >65 years were 2-fold higher than younger subjects
 - Plasma concentrations were 10% higher in women than in men
- Simvastatin
 - HMG-CoA reductase inhibitory activity was increased 45% for patients >65 years were 2-fold higher than younger subjects

Ezetimibe (Zetia®), SCH 58235)

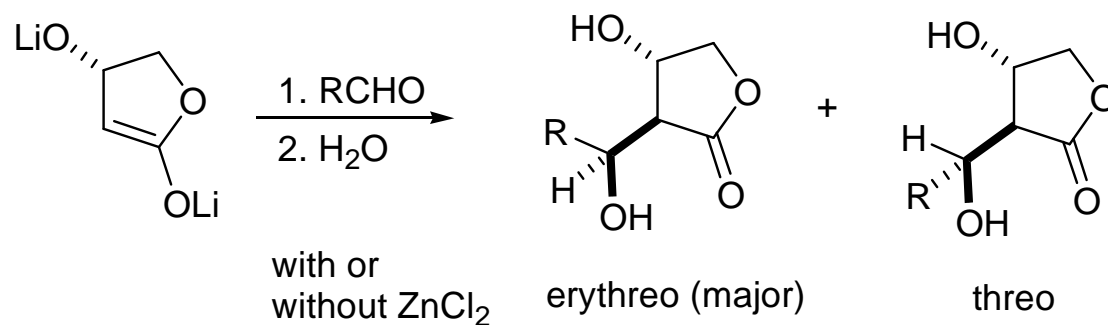


Chemical Process R & D
Schering-Plough Research Institute
Wu and coworkers, *JOC*, **1999**, *64*, 3714

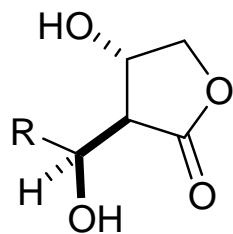
The Schering Plough Approach



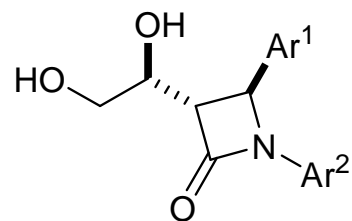
Condensation reaction of a chiral dianion with an electrophile



Application to Imine

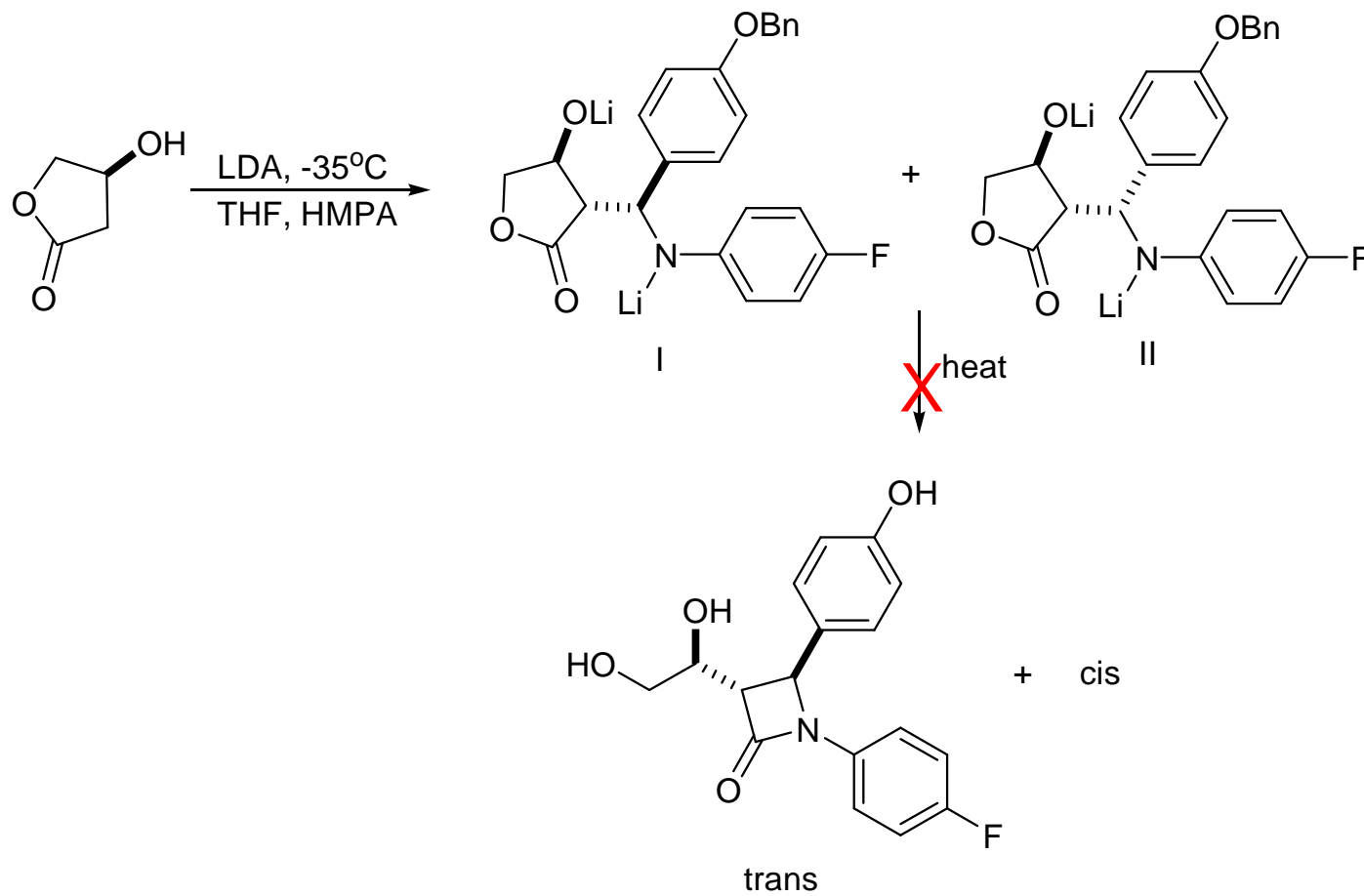


in the literature

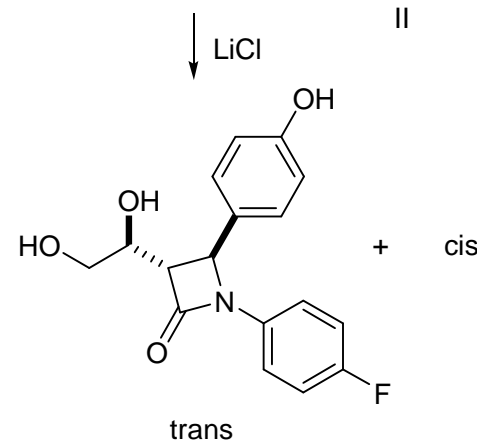
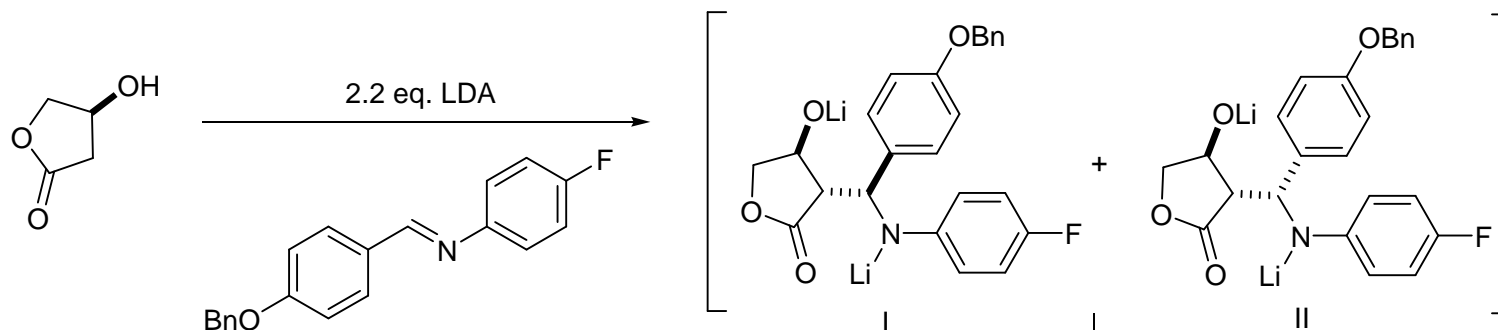


natural product core

Preliminary Studies

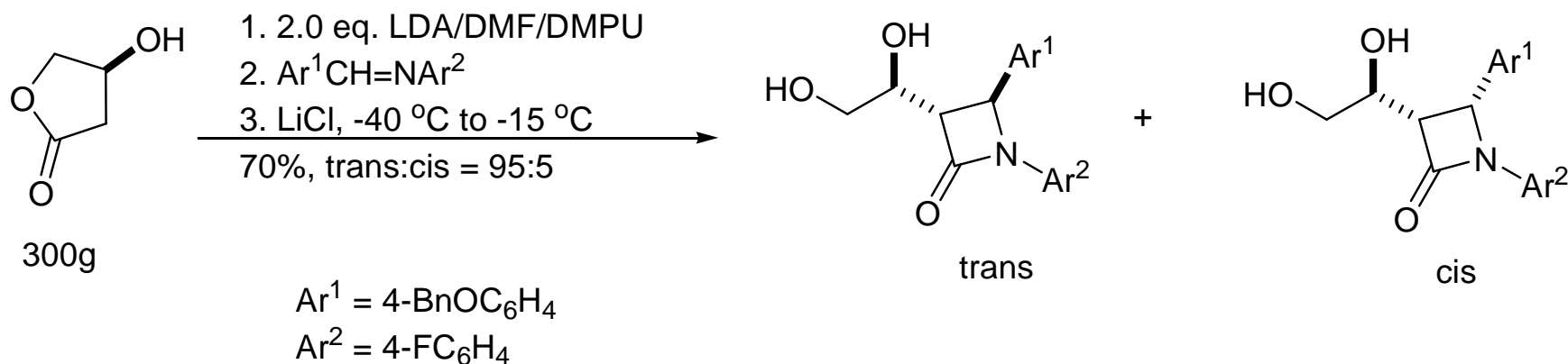


Metal and Temperature Effects on Diastereoselectivity



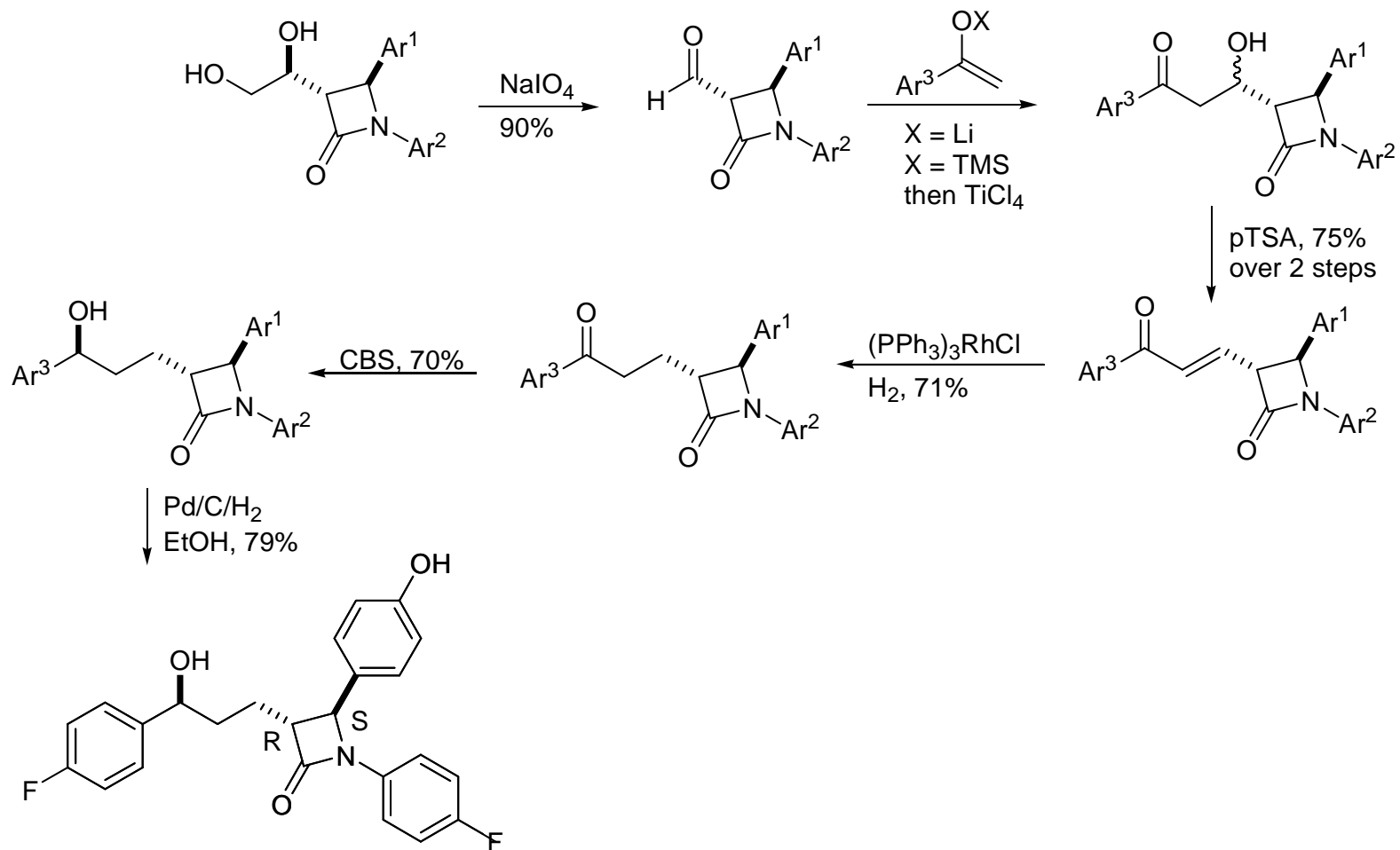
#	base	T (°C)	% Conv	I:II	Trans: cis	% yield
1	Et ₂ Zn	-25	80	11:89	40:60	7
2	LDA	-25	99	73:23	87:13	76
3	NaHMDA /LiHMDA	-25	65	86:14	99:1	46
4	LDA	-15	98	69:31	90:10	68
5	LDA	-35	99	79:21	90:10	78

Optimized Procedure: 1-Step Formation of trans β -lactams

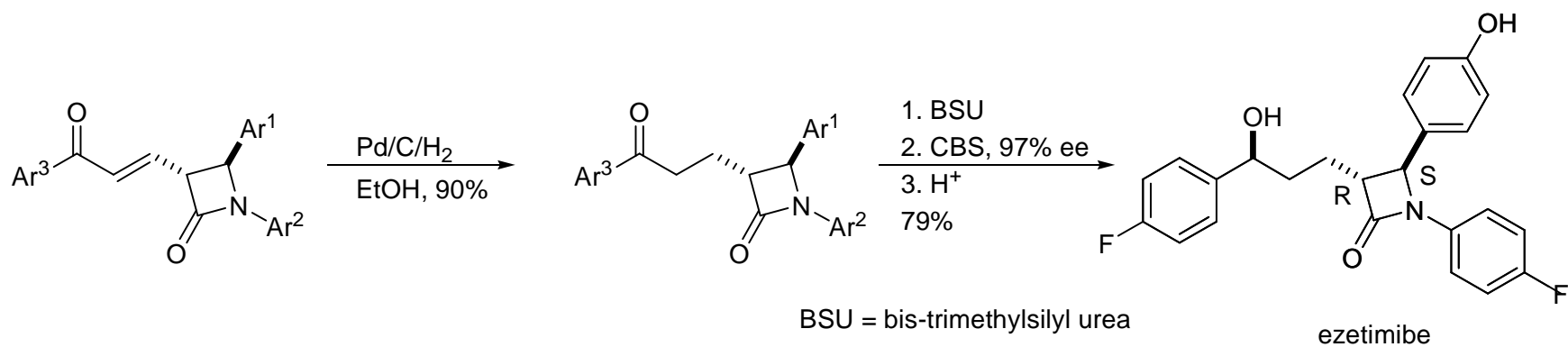


DMPU: N,N-dimethyl propyl urea (lower toxicity than HMPA)

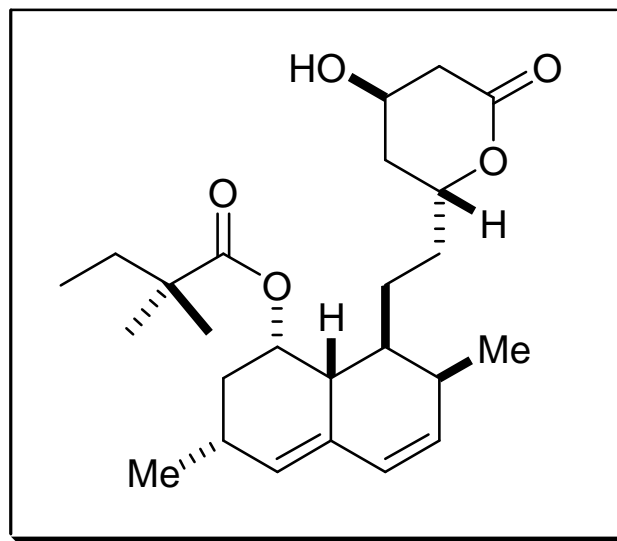
Elaborating the β -lactam Core



Novel 3-step 1-pot Procedure



Simvastatin (Zocor®)



Chemistry Research Department

Hoffmann La Roche, Inc.

Wovkulich and coworkers, *JACS*, **1989**, 111, 2596

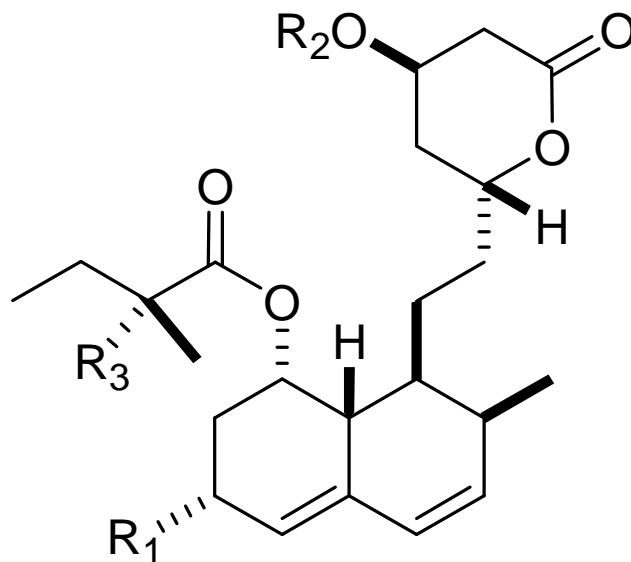
Review of synthetic approaches to mevinic acids:

Rosen & Heathcock, *Tetrahedron*, **1986**, 42, 4909

Initial Discoveries

- 1976 – Isolation of competitive inhibitor of hydroxymethylglutaryl coenzyme A reductase (**HMG CoA**)
 - Endo et al. at Sankyo Co. from *Penicillium citrinum* (ML236B)
 - Brown et al. at Beecham Pharmaceuticals from *P. brevicompactum* (compactin)
- 1980 – Alberts et al. at Merck, Sharp & Dohme from *Aspergillus terreus* (mevinolin)
- 1981 – 1st synthesis of (+)-compactin

Common HMG-CoA Reductase Inhibitors

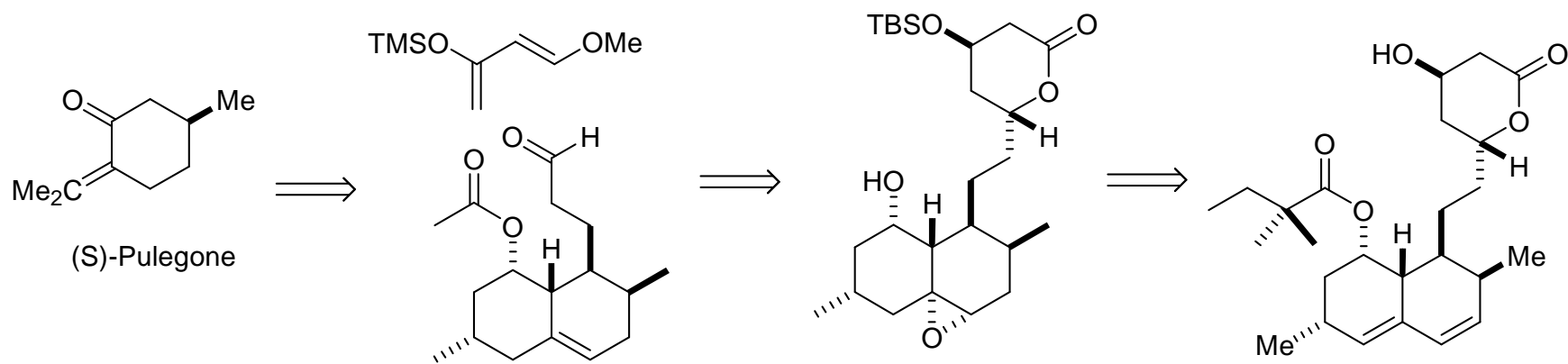


$R_1 = \text{Me}$, $R_2 = \text{H}$, $R_3 = \text{H}$ (mevinolin)

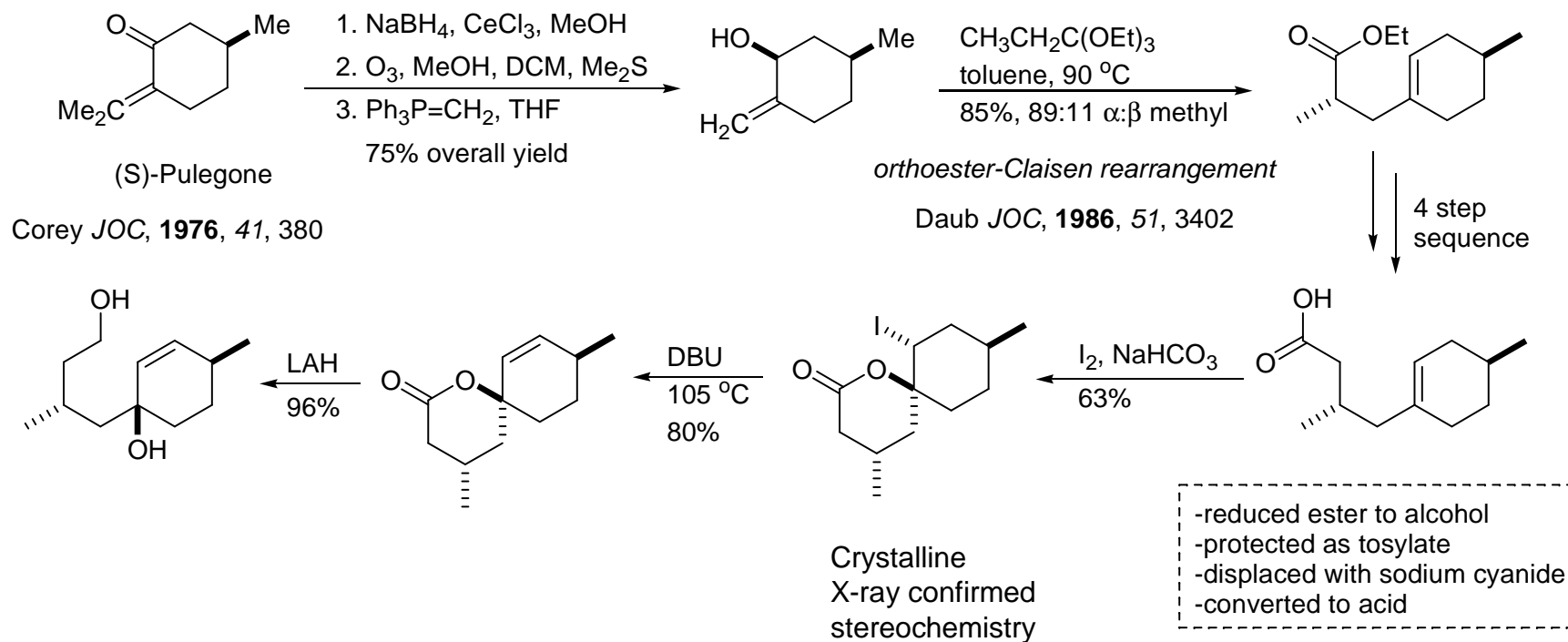
$R_1 = \text{Me}$, $R_2 = \text{H}$, $R_3 = \text{Me}$ (**Simvastatin**)

$R_1 = R_2 = \text{H}$, $R_3 = \text{H}$ (compactin)

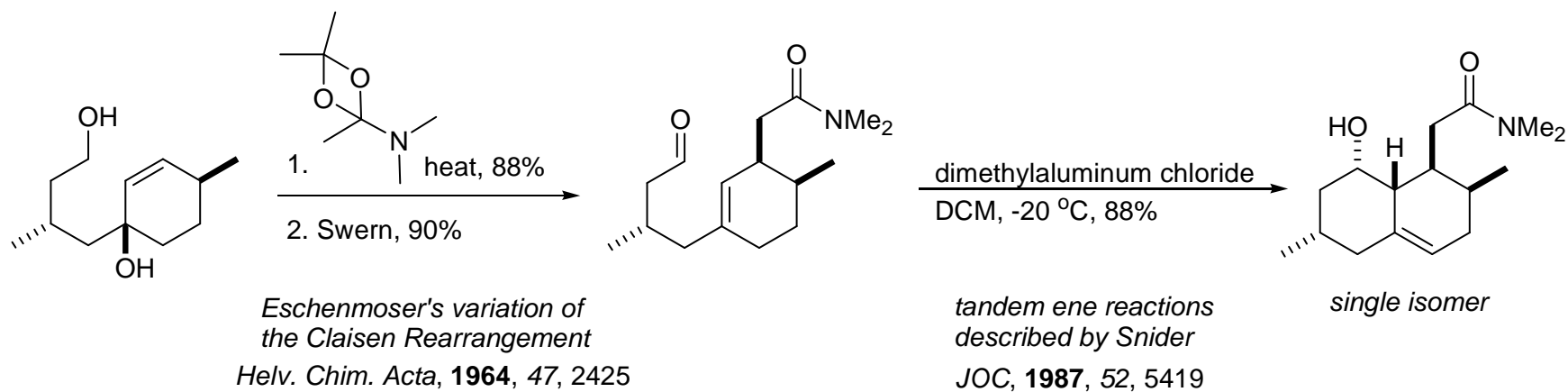
The Hoffmann La Roche Approach



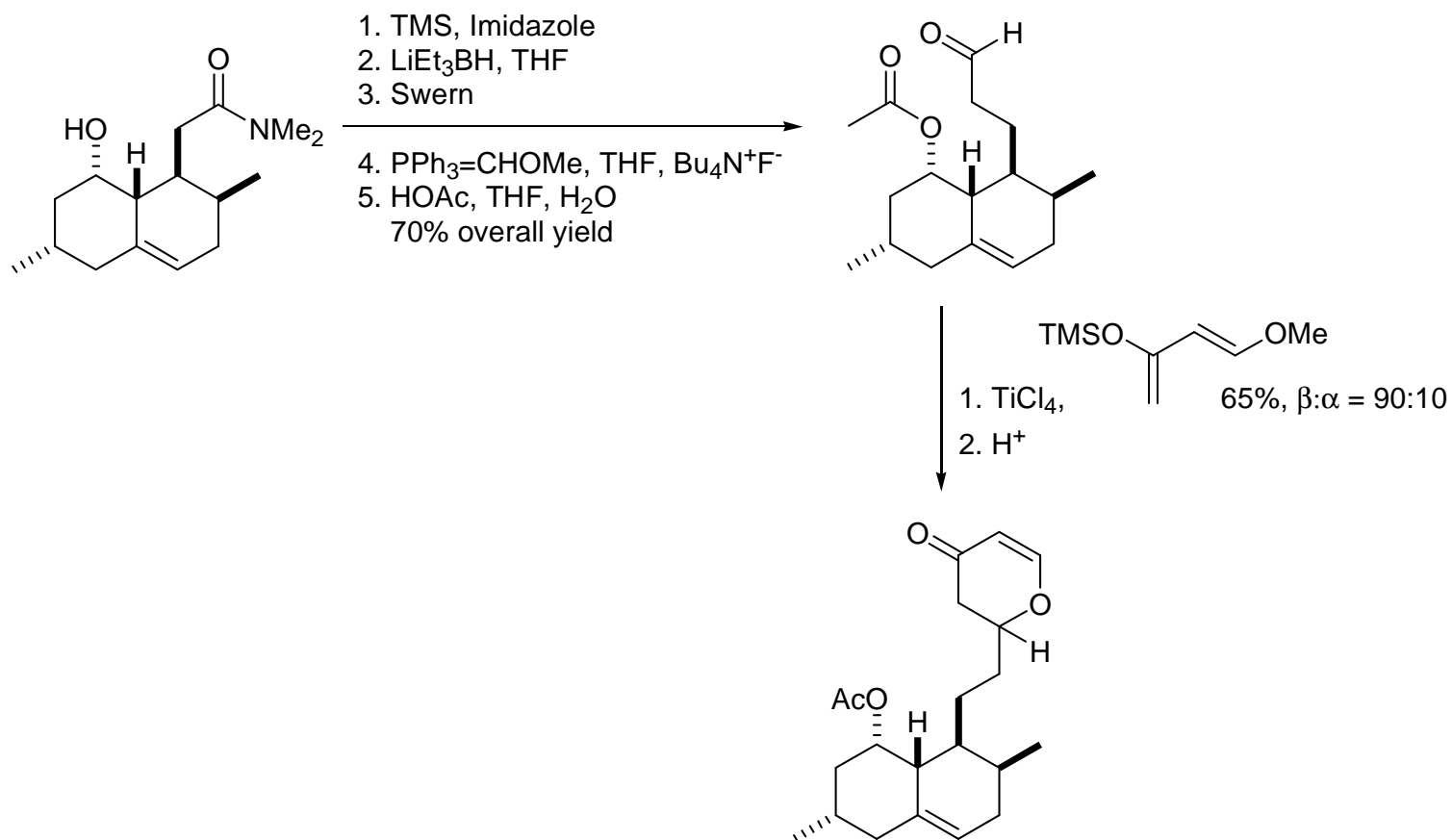
Orthoester-Claisen Rearrangement



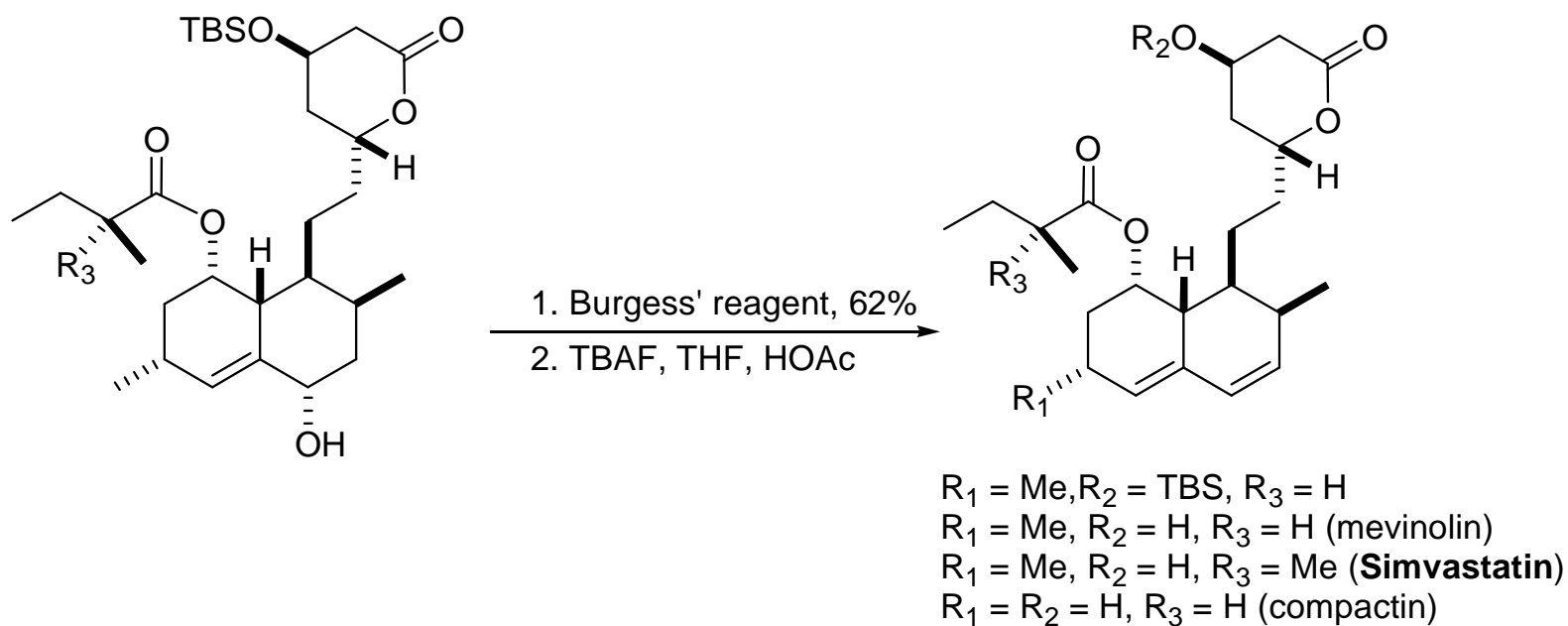
Forming the Bicyclic Structural Motif



Construction of the Lactone Moiety



Elimination and Deprotection





Germany; September 9, 2005