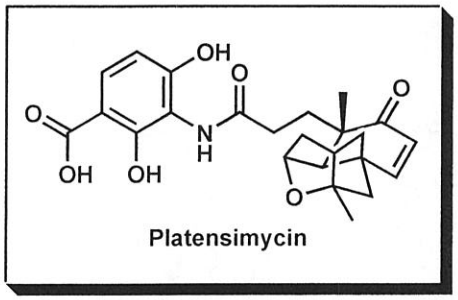
Tatsuhiko Yoshino (B4)
2009. 1. 28

Platensimycin ~ Synthesis and Bioactivity ~



Platensimycin

Isolation : from *Streptomyces platensis*
J. Wang *et al. Nature* **2006**, *441*, 358. Merck group.

Bioactivity : ***Antibiotics***

First Total Synthesis :
Racemic : K. C. Nicolaou *et al. ACIE* **2006**, *45*, 7086.
Asymmetric : K.C. Nicolaou *et al. ACIE* **2007**, *46*, 3942.

Other Syntheses :
B. B. Snider *et al. OL* **2007**, *9*, 1825.
K. C. Nicolaou *et al. Chem. Commun.* **2007**, 1922.
H. Yamamoto *et al. JACS* **2007**, *129*, 9534.
J. Mulzer *et al. ACIE* **2007**, *46*, 8074.
E. J. Corey *et al. OL* **2007**, *9*, 4921.
K.C. Nicolaou *et al. ACIE* **2008**, *47*, 944.
E. Lee *et al. ACIE* **2008**, *47*, 4009.
H. Ishibashi *et al. OL* **2008**, *10*, 4049.

Contents

1. Introduction

1.1 Antibiotics-Resistant Bacteria ~ Multi-drug Resistant Super Bugs

Vancomycin-Resistant *Staphylococcus aureus* (VRSA) was first reported in July In 2002 in U.S.

↓

How can bacteria get resistance to antibiotics?

↓

1. **Bacteria get the transporter to exclude antibiotics. (Erythromycin)**
2. **Bacteria get the enzymes to destroy or modify antibiotics. (Penicilin)**
3. **Target Structure mutates to have less affinity with antibiotics. (Methicillin, Vancomycin)**

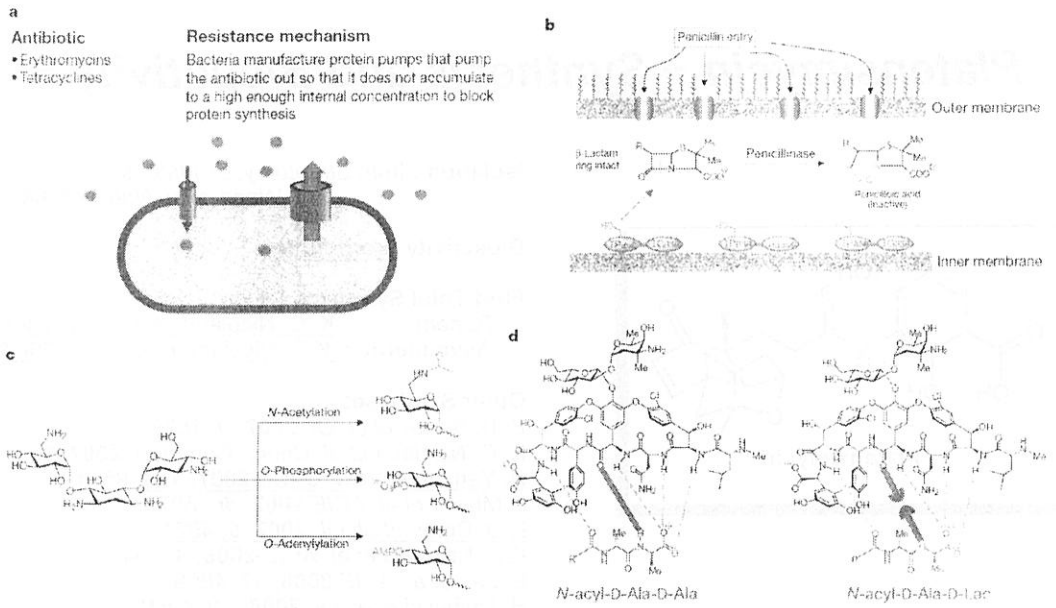


Figure 3 Principal resistance strategies for bacterial survival. **a**, Drugs such as tetracyclines or erythromycins are pumped back out of bacterial cells through efflux pump proteins to keep intracellular drug concentrations below therapeutic level. **b**, The antibiotic is destroyed by chemical modification by an enzyme that is elaborated by the resistant bacteria. This is exemplified here by the β-lactamase secreted into the periplasmic space to hydrolyse penicillin molecules before they reach their PBP targets in the cytoplasmic membrane of this Gram-negative bacterium. **c**, The aminoglycoside antibiotic kanamycin can be enzymatically modified at three sites by three kinds of enzymatic processing — *N*-acetylation, *O*-phosphorylation or *O*-adenylylation — to block recognition by its target on the ribosome. **d**, The target structure in the bacterium can be reprogrammed to have a low affinity for antibiotic recognition. Here the switch from the amide linkage in the D-Ala-D-Ala peptidoglycan termini to the ester linkage in the D-Ala-D-Lac termini is accompanied by a 1,000-fold drop in drug-binding affinity.

C. Walsh *Nature* **2000**, *406*, 775.

Multi-resistant "super bugs" are nightmare for humans.
Vancomycin was "Last Resort" for MRSA.
However, bacteria have got resistance even to Vancomycin.

1.2 Mechanism of Platensimycin ~ Why is Platensimycin a novel antibiotic ?

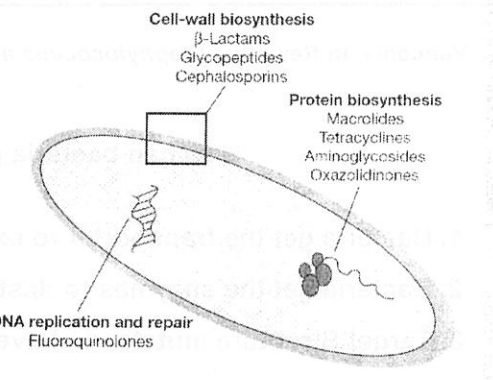
Mechanism of Major Antibiotics

Inhibition of cell wall synthesis, protein synthesis, DNA or RNA synthesis

Box 1
Targets, mode of action and mechanisms of resistance of the main classes of antibacterial drugs

Antibiotic	Target	Mode of action	Resistance mechanism
Cell wall			
β-Lactams	Transpeptidases/transglycosylases (PBPs)	Blockade of crosslinking enzymes in peptidoglycan layer of cell walls	β-Lactamases; PBP mutants
Vancomycin	D-Ala-D-Ala termini of peptidoglycan and of lipid II	Sequestration of substrate required for crosslinking	Reprogramming of D-Ala-D-Ala to D-Ala-D-Lac or D-Ala-D-Ser
Protein synthesis			
Macrolides of the erythromycin class	Peptidyl transferase, centre of the ribosome	Blockade of protein synthesis	rRNA methylation; drug efflux
Tetracyclines	Peptidyl transferase	Blockade of protein synthesis	Drug efflux
Aminoglycosides	Peptidyl transferase	Blockade of protein synthesis	Enzymatic modification of drug
Oxazolidinones	Peptidyl transferase	Blockade of protein synthesis	Unknown
DNA replication/repair			
Fluoroquinolones	DNA gyrase	Blockade of DNA replication	Gyrase mutations to drug resistance

Box 1 Figure Proven targets for antibacterial drugs. Cell-wall biosynthesis at the stage of crosslinking of peptidoglycan peptide strands by transpeptidases and transglycosylases is inhibited by the β-lactam antibiotics (penicillins and cephalosporins). Protein biosynthesis at the ribosome is targeted by several classes of antibiotics, including macrolides, tetracyclines, aminoglycosides and oxazolidinones, which block one or more steps involving rRNA and the proteins of the ribosome at the peptidyl transferase centre. The fluoroquinolone antibiotics interrupt DNA replication by trapping a complex of DNA bound to the enzyme DNA Gyrase, a type II topoisomerase.

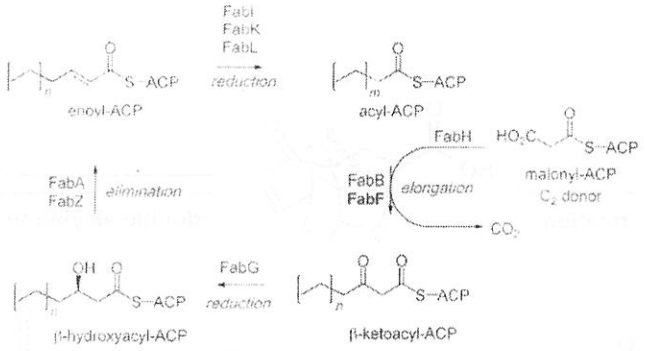


C. Walsh *Nature* **2000**, *406*, 775.

Drugs which have Completely differenet mechanism will cause less cross-resistance.

Taget of Platensimycin is fatty acid synthesis.

Fatty Acid Synthase type II (bacteria)



Scheme 1. Bacterial fatty acid biosynthesis.

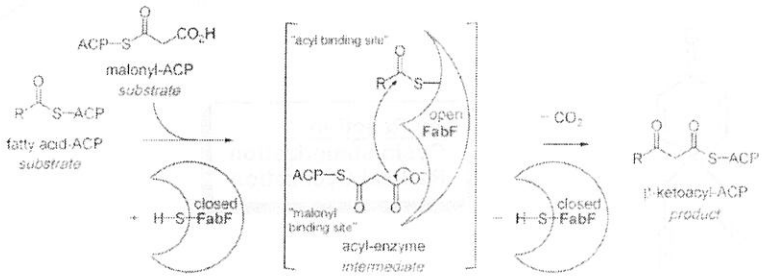
FAS is a good target !

FAS I (mammals)
Single huge protein can catalyze all the reactions.

Completely Different System !

FAS II (bacteria)
Each protein can catalyze one reaction.

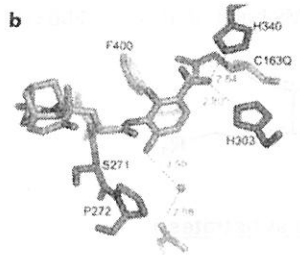
Platensimycin can specificially bind and block Acyl-FabF intermediate.



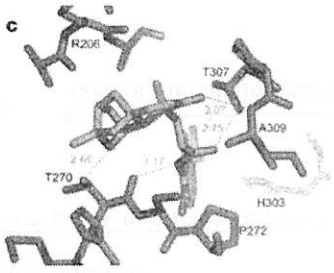
Scheme 2. FabF catalyzes C–C bond formation in the chain-elongation step of bacterial fatty acid biosynthesis.

D. Habich.; F. Nussbaum *ChemMedChem*. **2006**, *951*

X-ray structure of complex of Platencimycin and FabF(C163Q) , mimic of Acyl-FabF



Interactions of FabF(C163Q).with benzoic acid moiety of Platencimycin.



Interactions of FabF(C163Q).with amide linker and ketolide of Platensimycin.

Table 1 | Microbiological profiles and toxicity of platensimycin and linezolid

Organism and genotype	Platensimycin	Linezolid
Antibacterial activity (MIC, μg ml^{-1})*		
S. aureus (MSSA)	0.5	4
S. aureus + serum	2	4
S. aureus (MRSA)	0.5	2
S. aureus (MRSA, macrolide^R)	0.5	2
S. aureus (MRSA, linezolid^R)	1	32
S. aureus (VISA, vancomycin^I)	0.5	2
Enterococcus faecalis (macrolide^R)	1	1
Enterococcus faecium (VRE)	0.1	2
S. pneumoniae†	1	1
E. coli (wild-type)	>64	>64
E. coli (*tolC*)	16	32
Toxicity (μg ml^{-1})		
HeLa MTT (IC_{50})	>1,000	>100
Candida albicans (MIC)	>64	>64

*A concentration of 1 μg ml^{-1} equals 2.27 μM for platensimycin and 2.96 μM for linezolid.
†Cells were inoculated at 10^5 colony-forming units followed by incubation overnight at 37 °C with a serial dilution of compounds in Todd-Hewitt broth.
Linezolid is a synthetically derived agent that has been in clinical use since 2000. MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide; VISA, vancomycin-intermediate *S. aureus*; VRE, vancomycin-resistant *Enterococcus*.

Platensimycin showed antibacterial activities against Gram positive bacteria including MRSA, VISA and VRE.

However, pharmacokinetics profile is not so good. (In experiment with mice, continuous infusion was necessary)

Investigation of structure-activity relationship and modification of the structure is essential.

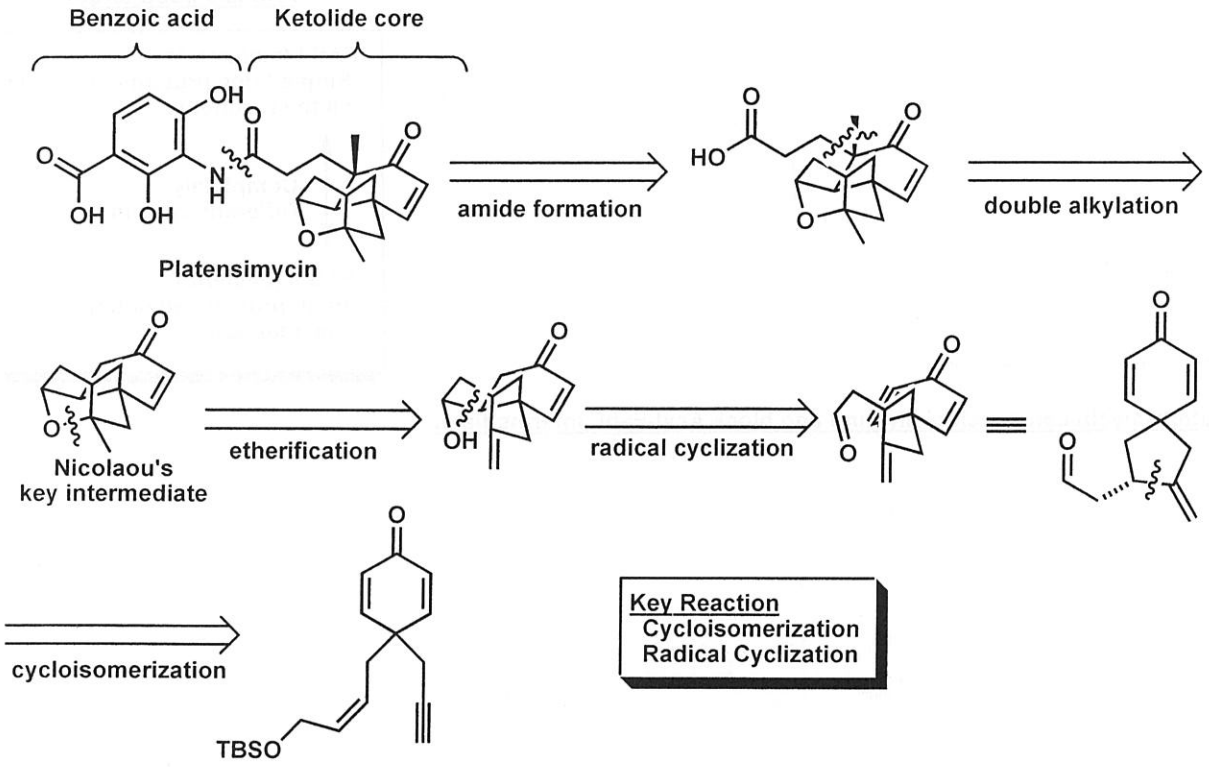
J. Wang *et al. Nature* **2006**, *441*, 358.

2. Total and Formal Syntheses

2.1 First Racemic Synthesis

K. C. Nicolaou *et al. ACIE* **2006**, *45*, 7086.

Retrosynthetic Analysis

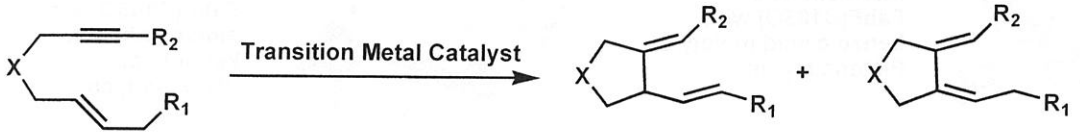


Key Reaction

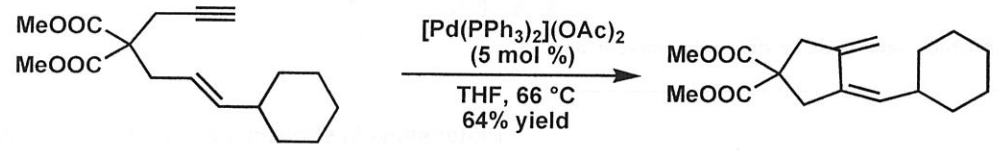
Transition Metal Catalyzed Cycloisomerization of Enynes

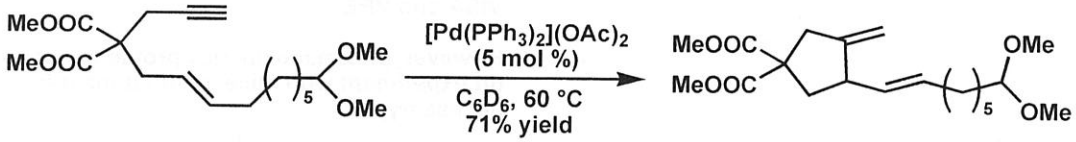
See also Previous Lit. Seminar Handouts (Sakaoka & Yanagida)

Review : V. Michelet *et al. ACIE* **2008**, *47*, 4268.



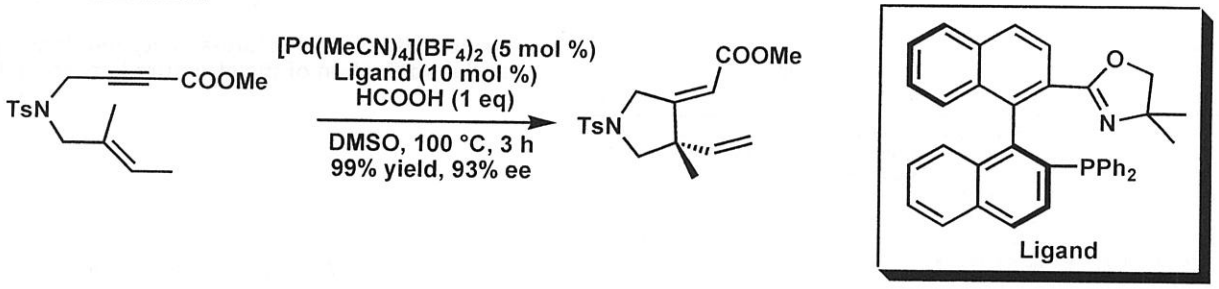
Pd Catalyzed Cycloisomerization for 1,3 or 1,4-diene (Selectivity mainly depends on substrates.)





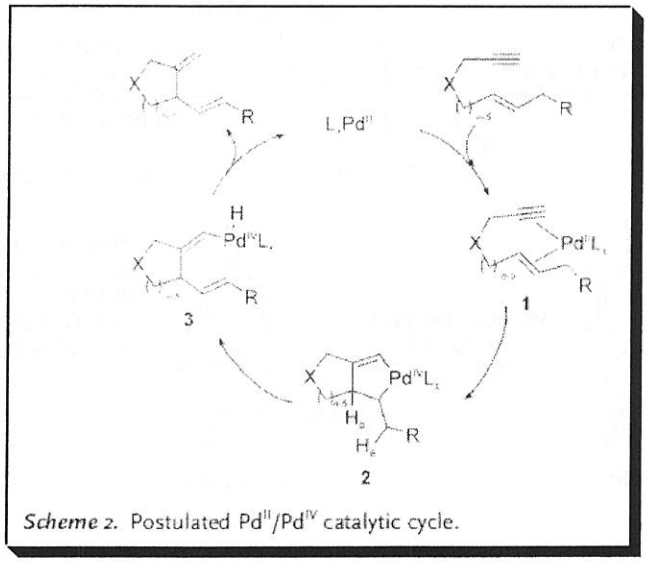
B. M. Trost *et al. JACS* **1994**, *116*, 4255.

Asymmetric Version

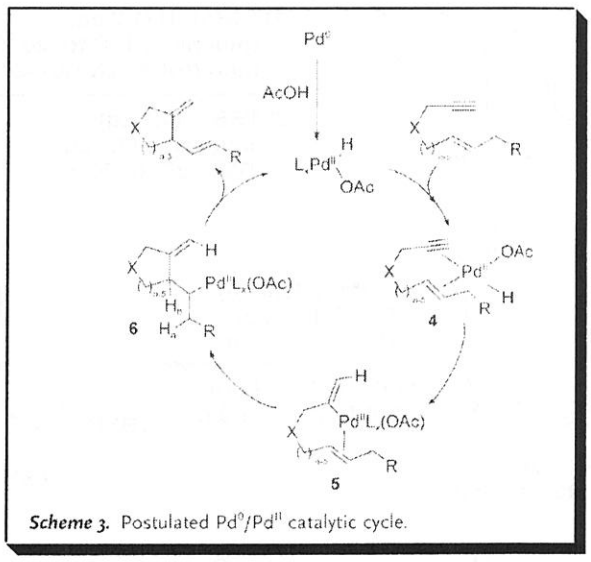


K. Mikami *et al. Org. Biomol. Chem.* **2003**, 3871.

Proposed Reaction Mechanism

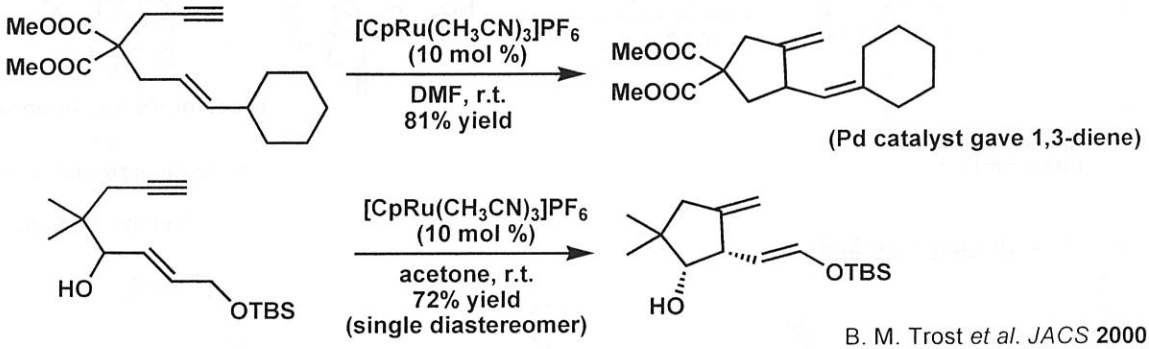


Scheme 2. Postulated Pd^{II}/Pd^{IV} catalytic cycle.



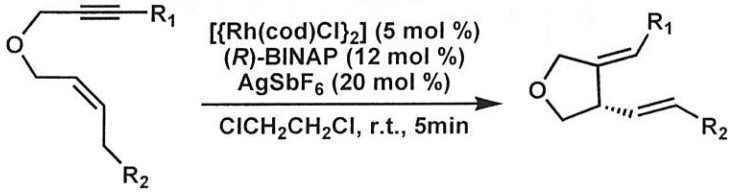
Scheme 3. Postulated Pd^{0}/Pd^{II} catalytic cycle.

Ru Catalyzed Cycloisomerization for 1,4-diene



B. M. Trost *et al. JACS* **2000**, *122*, 714.

Rh Catalyzed Asymmetric Cycloisomerization for 1,4-diene

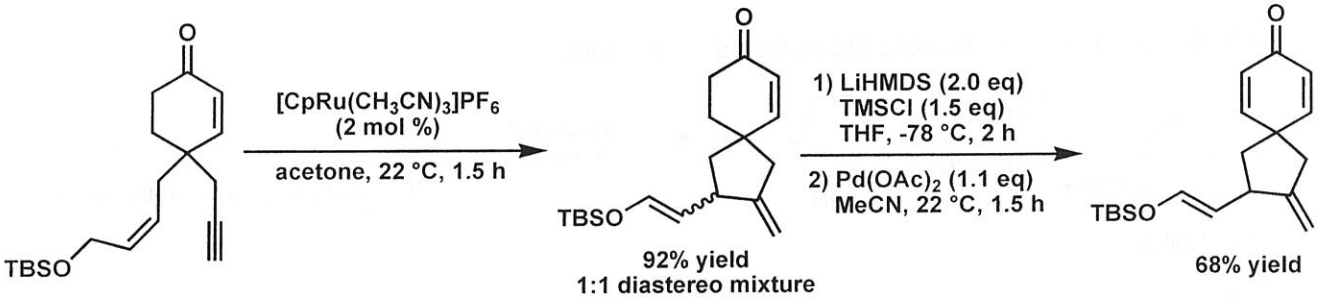


R_1 = Aryl, Alkyl, $-CH_2OMOM$, $-CH_2OH$
R_2 = H, Alkyl, -OPh, -OAc, -OH
81 - 98% yield
99 - >99.9% ee

X. Zhang *et al. ACIE* **2002**, *41*, 3457.

This catalyst gave excellent enantioselectivity with wide substrate scope.
However, terminal acetylene (R_1 = H) was not suitable. (in Nicolaou's asymmetric synthesis)

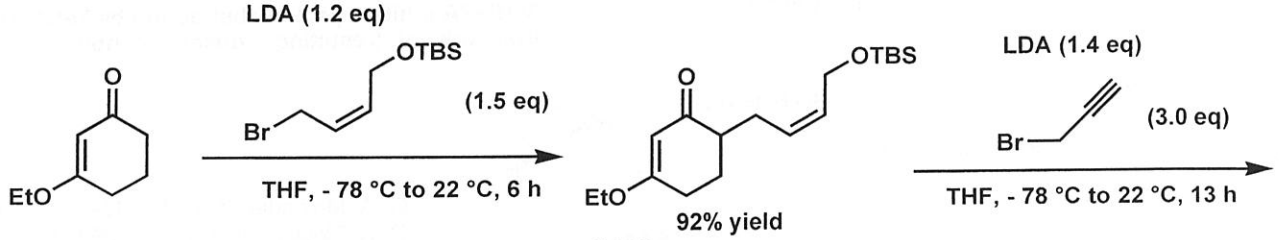
In Nicolaou's Racemic Synthesis of Platensimycin (Trost's Ru catalyst)

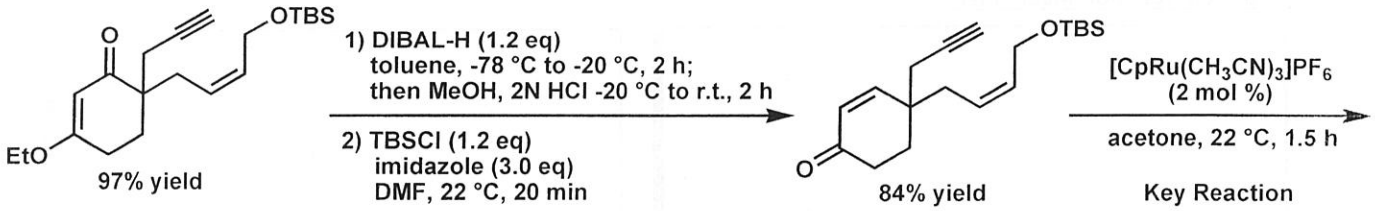


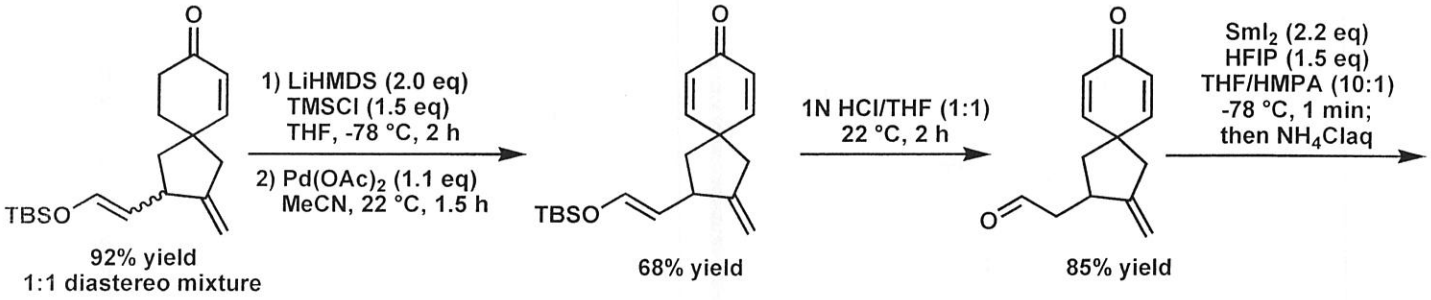
Total Synthesis

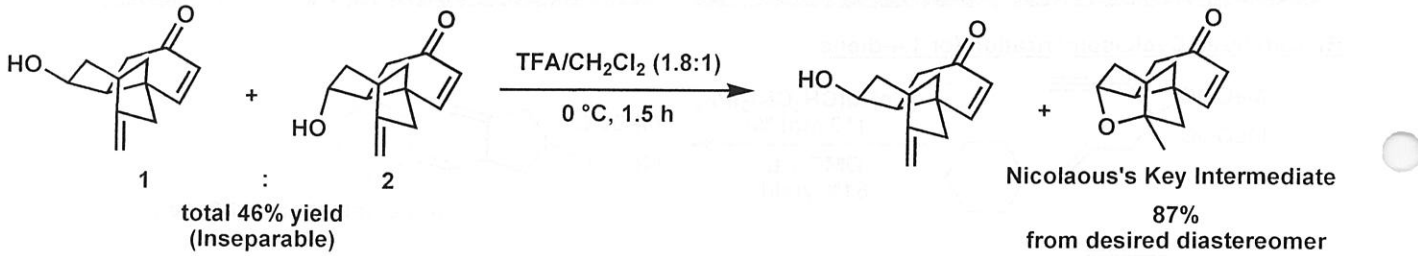
Synthesis of Ketolide Part

To Nicolaou's Key Intermediate

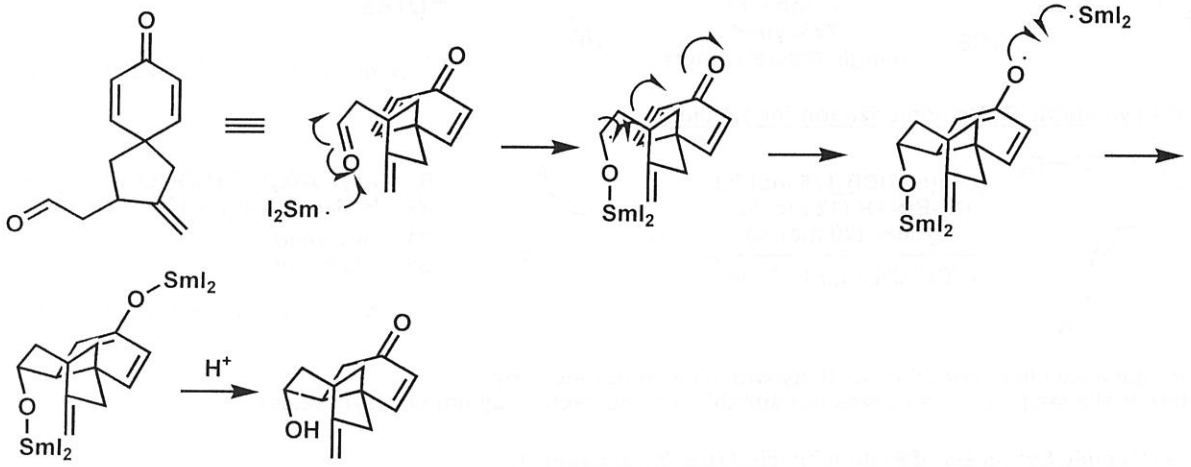




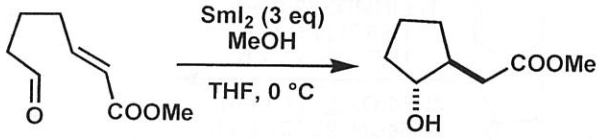




Ketyl Radical Cyclization with SmI_2



Ketyl Radical Cyclization of Aldehyde and Electron-Deficient Olefin

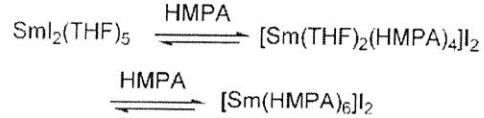


69% yield
dr = 3.1

E. J. Enholm *et al. TL* **1989**, *30*, 1063.

Effect of HMPA

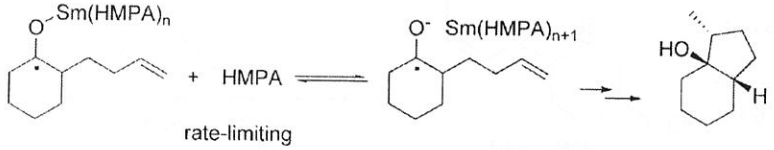
Scheme 1



1) [Sm[HMPA]$_n$] is more reductive species.

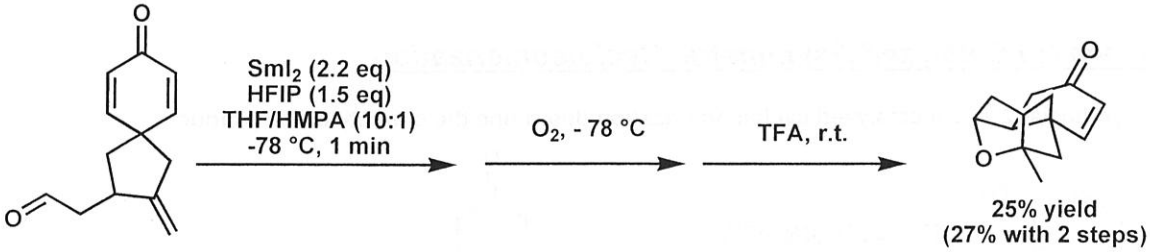
2) HMPA promotes cyclization by releasing solvent-seperated ion pair.

3) HMPA inhibits proton abstraction by ketyl radical from solvent. (resulting reduced alcohol)



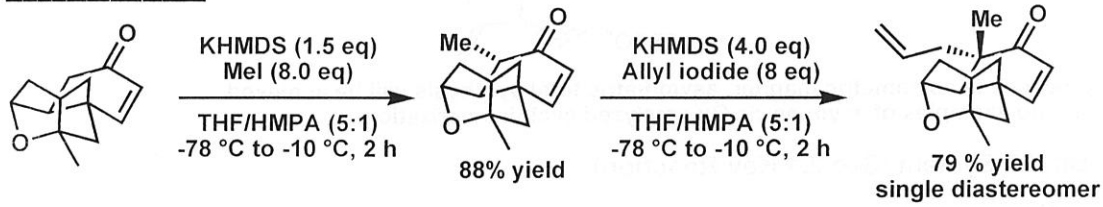
G. A. Molander *et al. JOC* **1992**, *57*, 3132.
R. A. Flowers *et al. JACS* **2008**, *130*, 7228.

One-pot Procedure for Ketyl Cyclization and Etherification



25% yield
(27% with 2 steps)

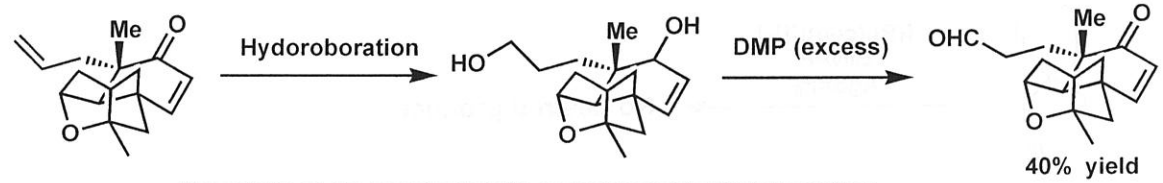
Double Alkylation



88% yield

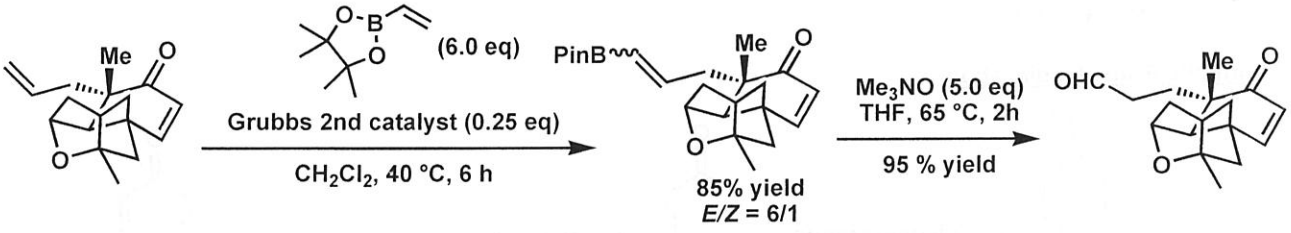
79 % yield
single diastereomer

Completion of Ketolide Part



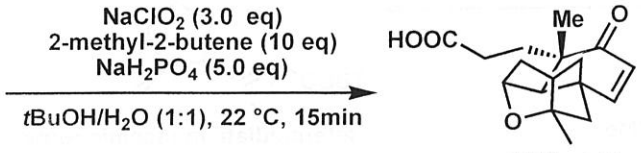
40% yield

Reactivity of the terminal olefin is low towards hydroboration.



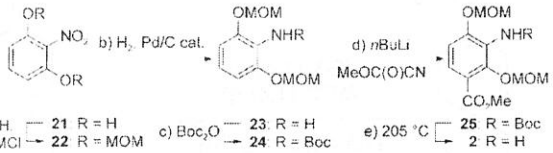
85% yield
E/*Z* = 6/1

95 % yield

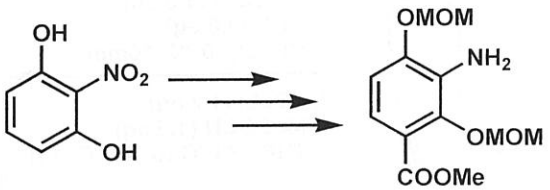


95 % yield

Synthesis of Benzoic Acid Part

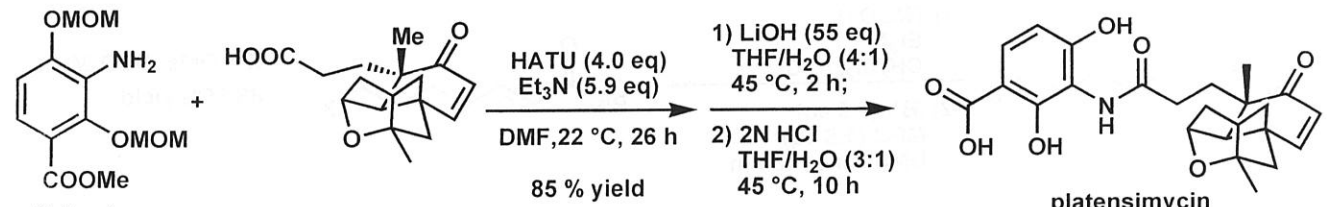


Scheme 3. Construction of the aromatic amine fragment **2**. Reagents and conditions: a) NaH (2.5 equiv), MOMCl (2.3 equiv), THF, 0—22 °C, 1.5 h, 82%; b) H_2 (balloon), 10% Pd/C (0.1 equiv), MeOH/EtOAc (10:1), 22 °C, 12 h, 99%; c) Boc_2O (3.0 equiv), 40 °C, 4 h, 99%; d) *n*BuLi (2.2 M in pentane, 1.0 equiv), TMSCl (1.0 equiv), −78 °C, 15 min; then *n*BuLi (2.2 M in pentane, 2.2 equiv), methyl cyanoformate (1.0 equiv), THF, −78 °C, 30 min; then 1 N aq HCl, 22 °C, 30 min, 54%; e) 1,2-dichlorobenzene, 205 °C (microwave), 5 min, 83%. Boc = *tert*-butoxycarbonyl.



5 steps
36 % yield

Completion of Total Synthesis



85 % yield

90 % yield

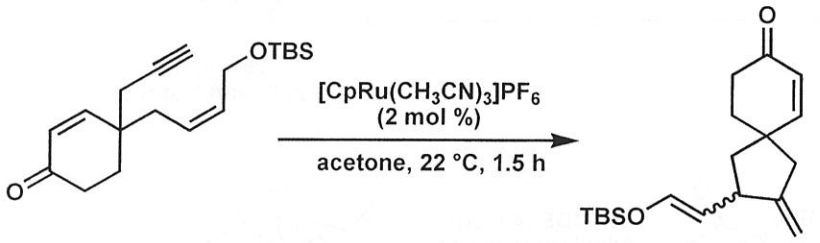
platensimycin
17 steps
overall yield 4.3 %

2.2 First Asymmetric Synthesis

K. C. Nicolaou *et al. ACIE* **2006**, *45*, 7086.

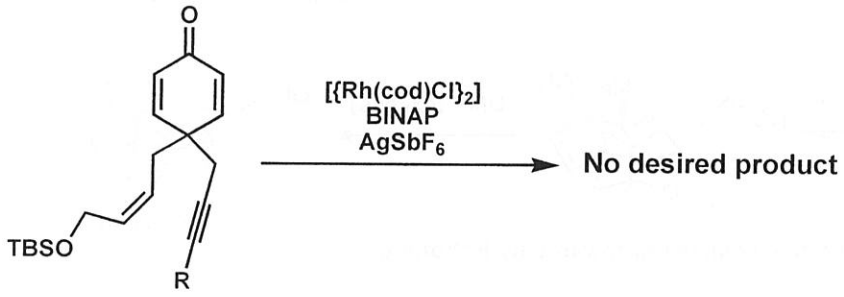
Synthesis via Rh Catalyzed Asymmetric Cycloisomerization

In racemic synthesis (2.1), Ru catalyzed cycloisomerization determine the chirality of the product.



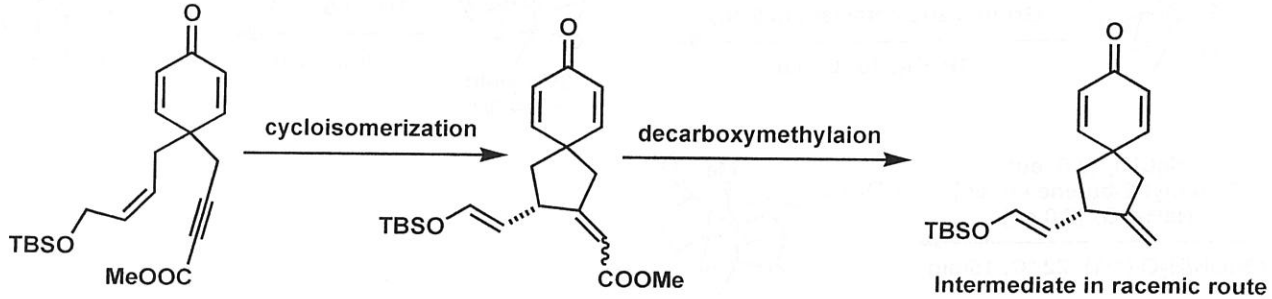
If this reaction proceeds in asymmetric manner, asymmetric total synthesis will be achieved.
However, there are no examples of asymmetric Ru catalyzed cycloisomerization.

→ Rh-BINAP System (See 2.1 Key Reaction)



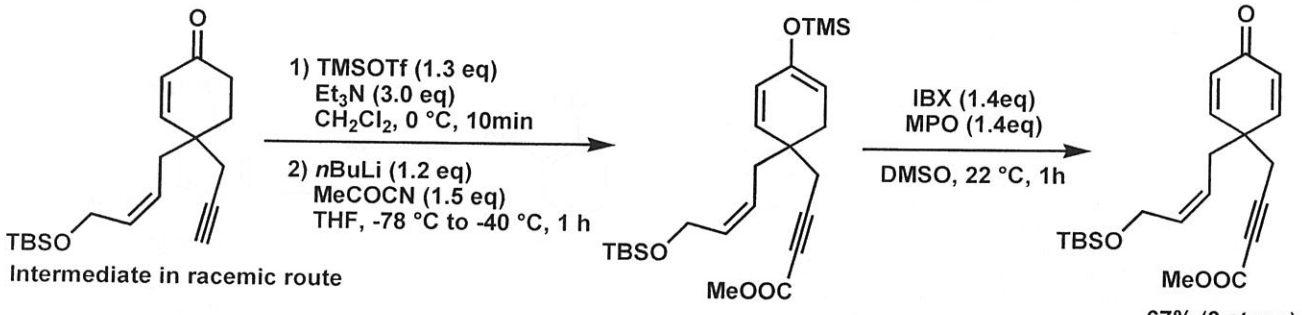
R = H or TMS

Synthetic Route Modification



Intermediate in racemic route

Synthesis of Carboxymethylated 1,5-Enyne

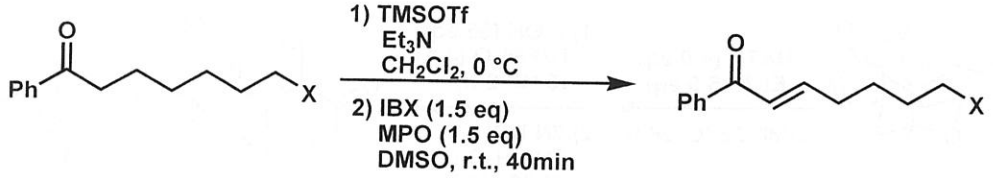


Intermediate in racemic route

67% (3 steps)

Oxidation of Silyl Enol Ether by IBX-MPO Complex

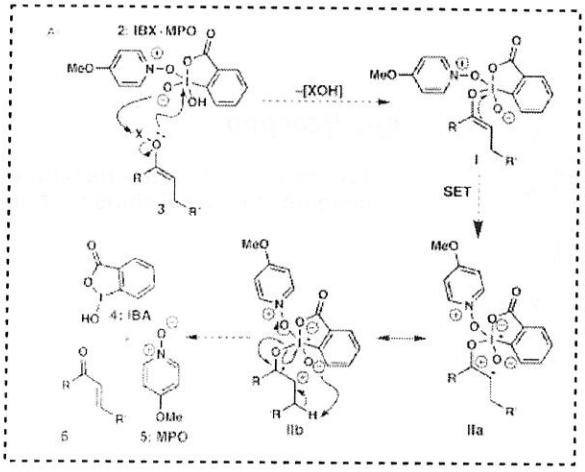
K. C. Nicolaou *et al. ACIE* **2002**, *41*, 996.

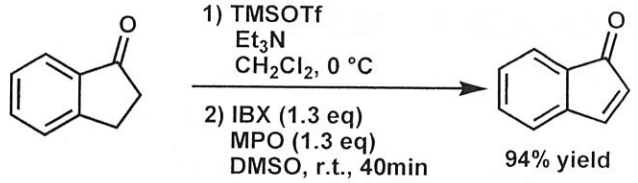


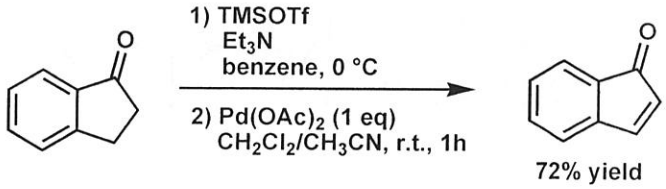
X = OMe, OSO_2Me, I
88-96% yield

Many functional groups can be tolerated.

Proposed Mechanism of Oxidation

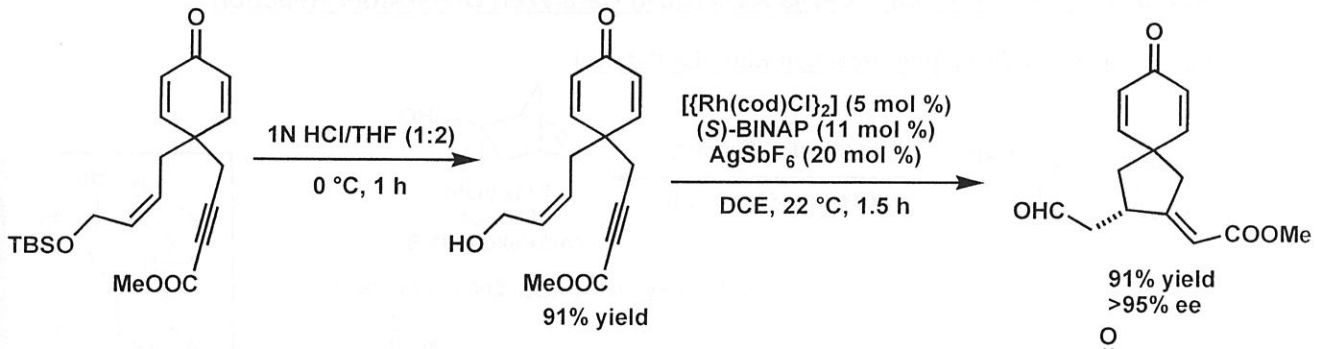


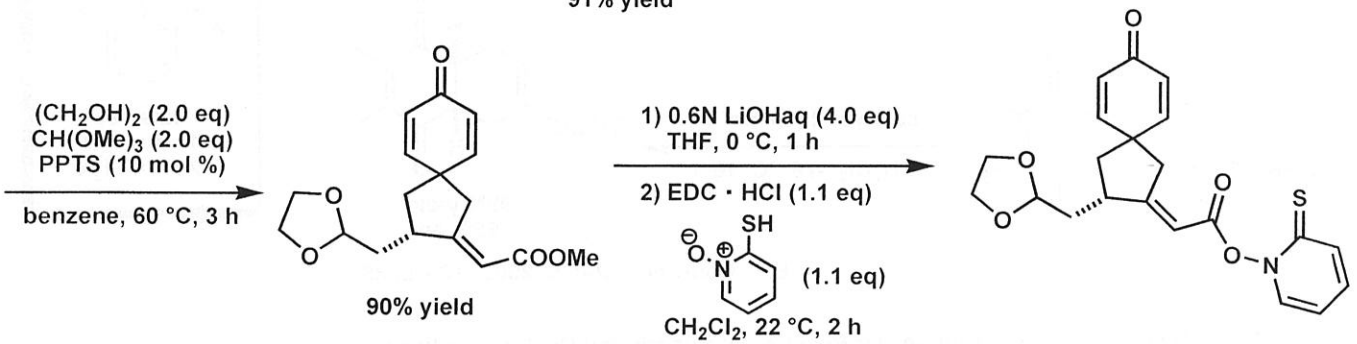


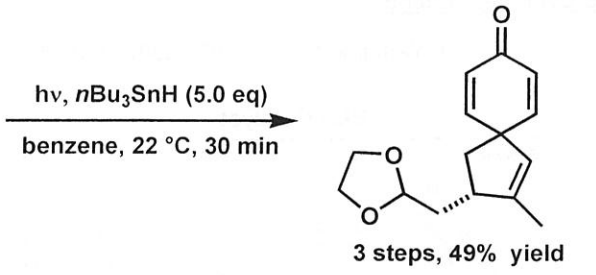


F. H. Hauser *et al. Synthetic. Comm.* **2001**, *31*, 77.

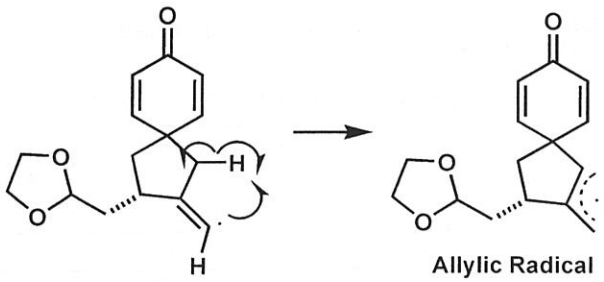
Asymmetric Cycloisomerization and Decarboxymethylation

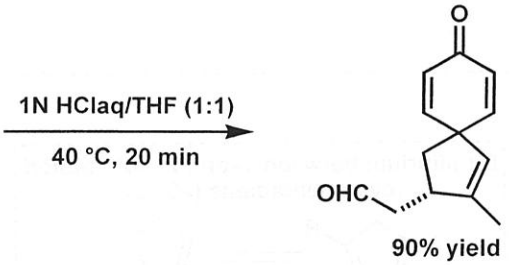


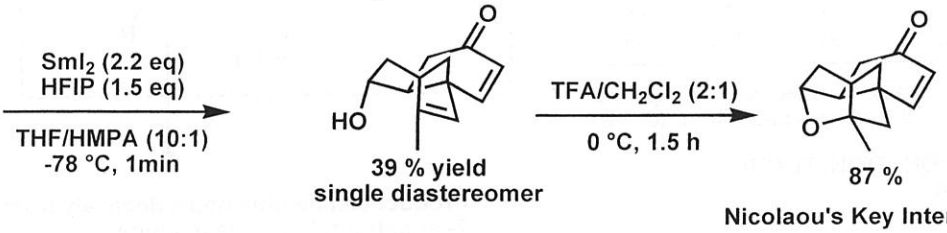




Unexpected 1,3-H-shift at Radical Decarboxylation Step





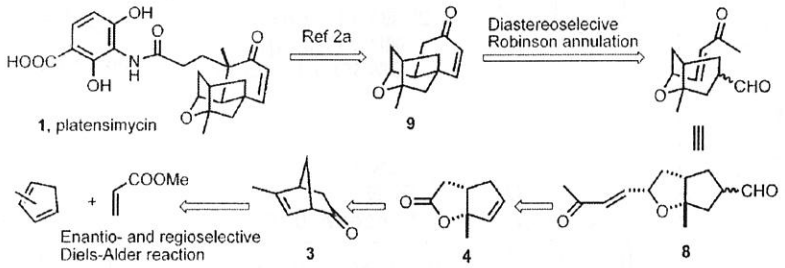


2.3 Yamamoto's Route

H. Yamamoto *et al. JACS* **2007**, *129*, 9534.

Retrosynthetic Analysis

Scheme 1. Retrosynthetic Analysis



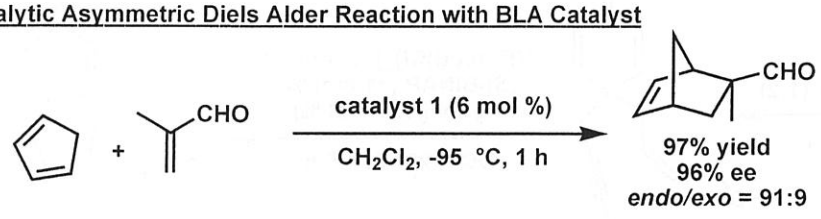
Key Reaction

Asymmetric Diels-Alder Reaction
Diastereoselective Robinson Annulation

Key Reaction

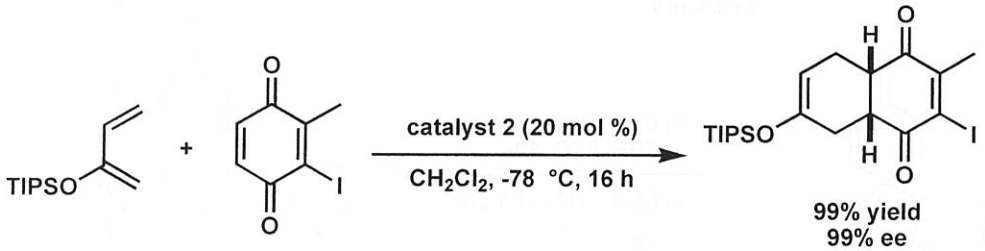
Bronsted Acid assisted Chiral Lewis Acid (BLA) Catalyzed Diels-Alder Reaction

Catalytic Asymmetric Diels Alder Reaction with BLA Catalyst



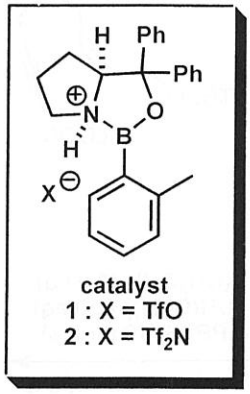
97% yield
96% ee
endo/exo = 91:9

E. J. Corey *et al. JACS.* **2002**, *124*, 3808.



99% yield
99% ee

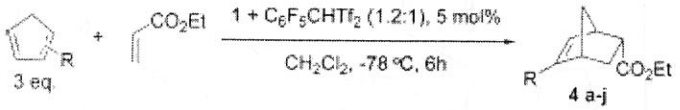
E. J. Corey *et al. JACS.* **2003**, *125*, 6388.



BLA Catalyzed Asymmetric Diels-Alder Reaction of Substituted Cyclopentadiene

H. Yamamoto *et al. JACS* **2007**, *129*, 9536.

Table 2. Diels–Alder Reaction of 2-Substituted Cyclopentadienes[a]

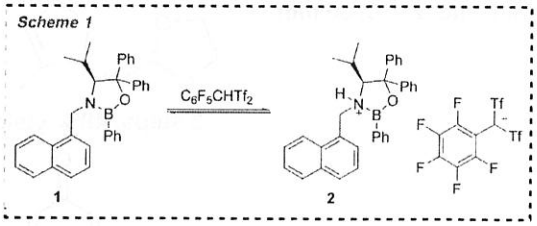


entry	diene	R	yield (%)[b]	dr	ee (%)
1	3a	Me–	96	99:1	99
2	3b	CH_2=$CHCH_2$–	98	99:1	97
3	3c	CH_2=$CBrCH_2$–	85	99:1	96
4[c,d]	3d	cyclohexyl	70	98:2	99
5	3e	$PhCH_2$–	97	99:1	97
6	3f	*p*-$MeOC_6H_4CH_2$–	96	99:1	99
7	3g	*p*-$BrC_6H_4CH_2$–	81	99:1	99
8	3h	$PhCH_2CH_2$–	97	99:1	99
9	3i	$(CH_2O)_2CHCH_2$–	98	99:1	98
10	3j	$MeO_2CCH_2CH_2$–	96	99:1	99

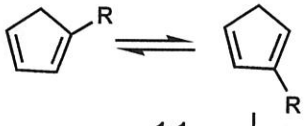
[a] See Supporting Information for details. [b] Isolated yield. [c] 5 equiv of diene used. [d] Reaction conducted at −78 °C for 6 h then −40 °C for 6 h.

With other Bronsted acid (MsOH, TfOH, Tf_2NH) lower reactivity was observed.

BLA Catalyst

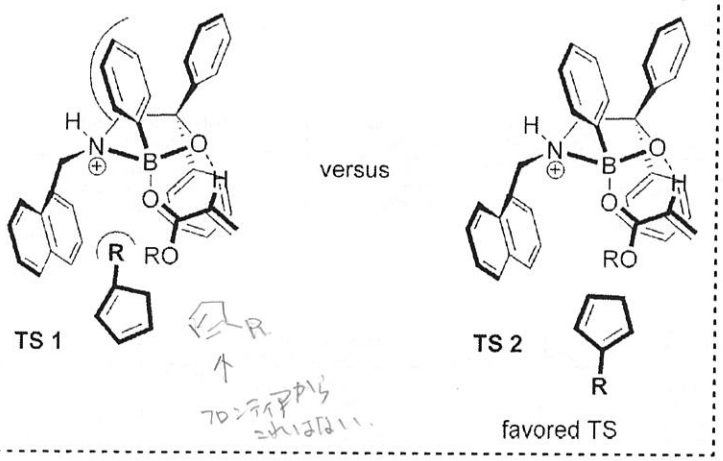


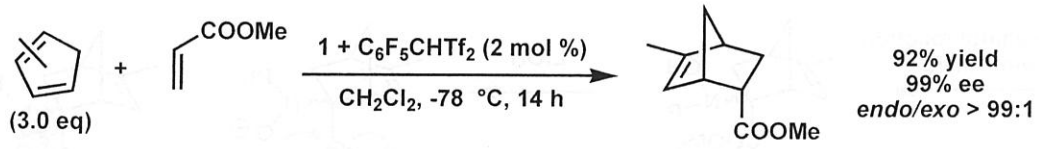
Equilibrium between 1- and 2- substituted cyclopentadiene (>0 °C)



Product can be obtained selectively from 2- substituted cyclopentadiene. (at -78 °C, isomerization does not occur)

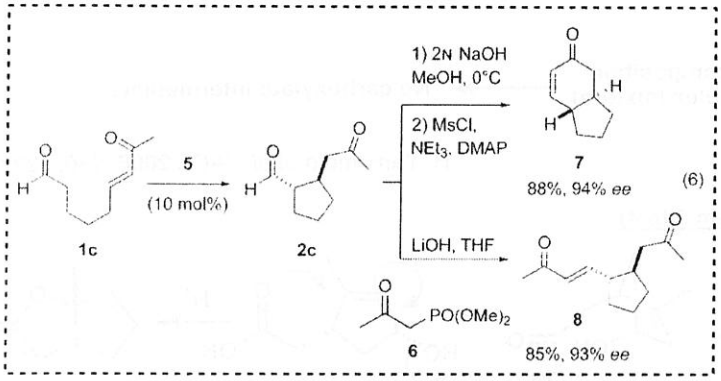
Scheme 2. Hypothetical Transition State **A** (*endo* Approach)

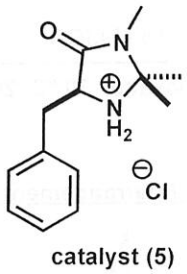




Diastereoselective Intramolecular Robinson Annulation by Proline

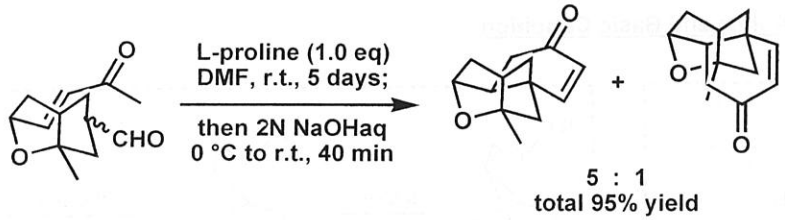
Reported Organocatalytic Asymmetric Intramolecular Robinson Annulation





B. List *et al. ACIE* **2004**, *43*, 3958.

Diastereoselective Robinson Annulation by Proline



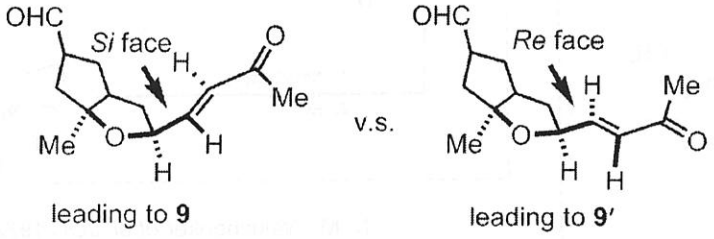


Figure 1. Facial selectivity for the intramolecular Michael addition.

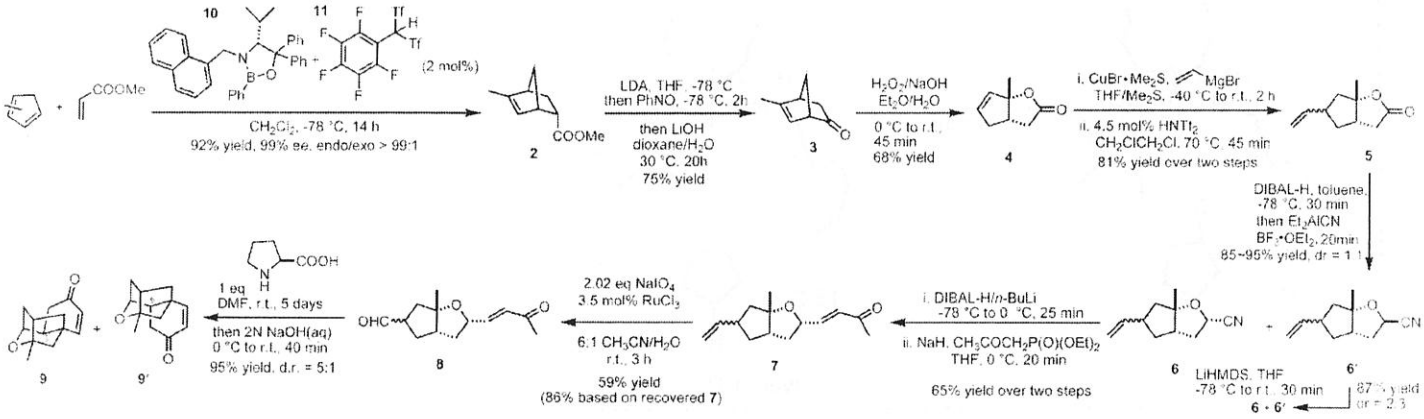
Hyper conjugation between...

Left (desired)
π of enone and C-O σ* bond works as electron-withdrawing.

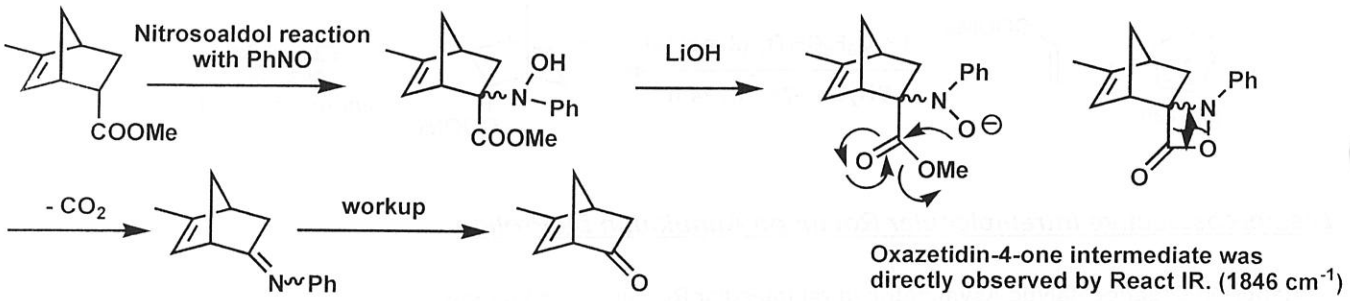
Right (undesired)
π* of enone and C-C σ bond works as electron-donating.

Desired Product **Undesired Product**

Scheme 2. Synthetic Route toward Tetracyclic Compound **9**



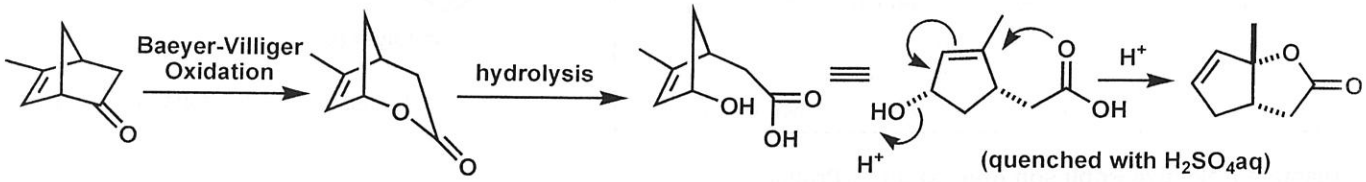
Decarboxymethylation via Nitroso aldol-Hydrolysis Sequence (2 to 3)



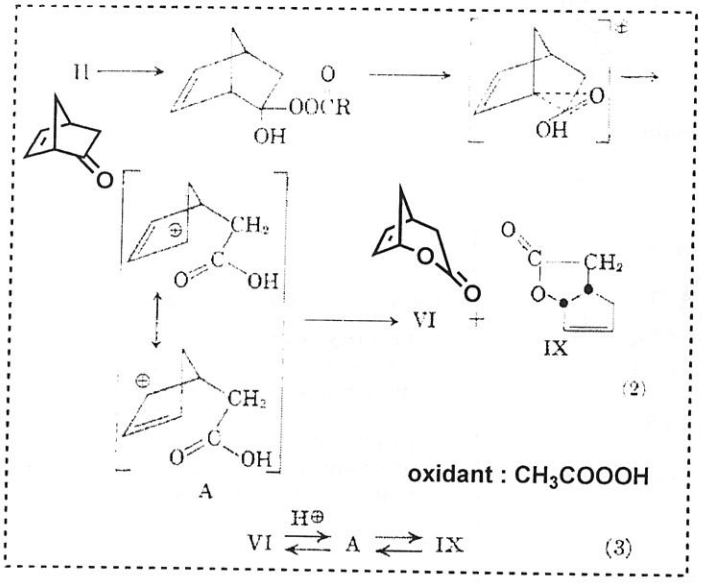
Oxazetidin-4-one intermediate was directly observed by React IR. (1846 cm^{-1})

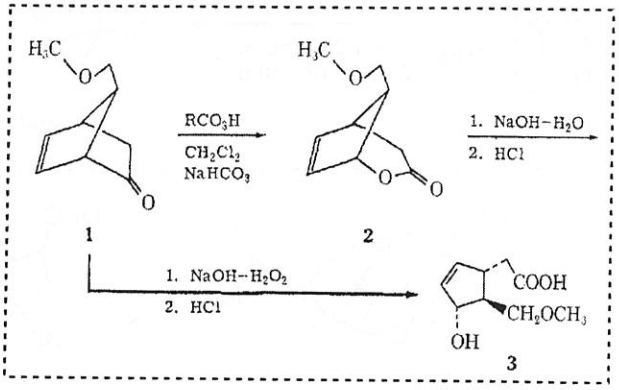
H. Yamamoto *et al. JACS* **2008**, *130*, 12276.

Baeyer-Villiger Oxidation - Rearrangement (Mechanism 3 to 4)



Baeyer-Villiger Oxidation - Rearrangement with Acidic and Basic Condition





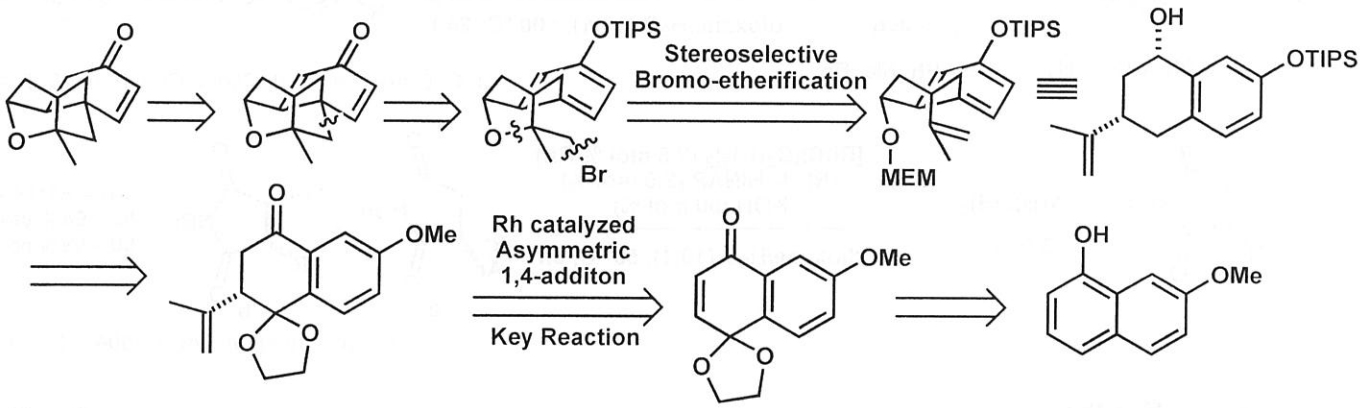
N. M. Weinshenker *et al. JOC* **1972**, *37*, 3741.

J. Meiwald. *et al. JACS* **1958**, *80*, 6303.

2.4 Corey's Route

E. J. Corey *et al. OL* **2007**, *9*, 4921.

Retrosynthetic Analysis

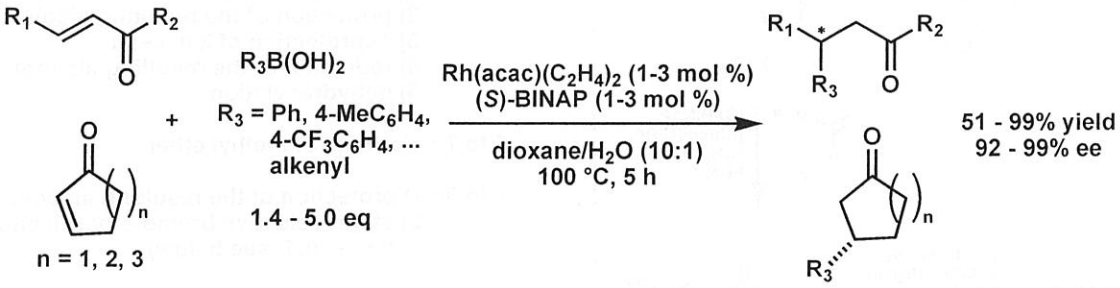


Key Reaction

Rh Catalyzed Asymmetric 1,4-addition of Borate

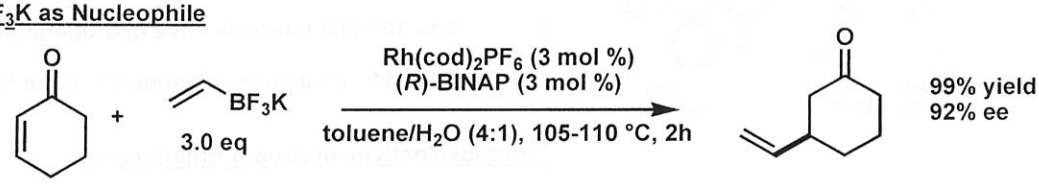
Review : T. Hayashi.; K. Yamasaki. *Chem. Rev.* **2003**, *103*, 2829.

Standard Reaction Condition Using Boronic Acid



T. Hayashi *et. al. JACS* **1998**, *120*, 5579.

RBF_3K as Nucleophile



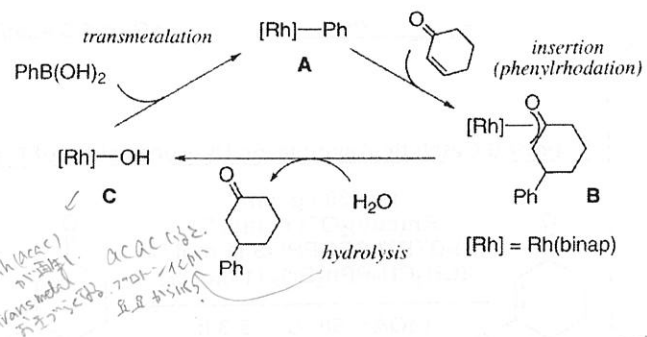
and many examples
(cyclic and acyclic enone,
aryl and alkenyl borate)

RBF_3K is generally more stable than boronic acid and is also more reactive.

S. Darses.; J. Genet. *et. al. Eur. J. Org. Chem.* **2002**, *3552*

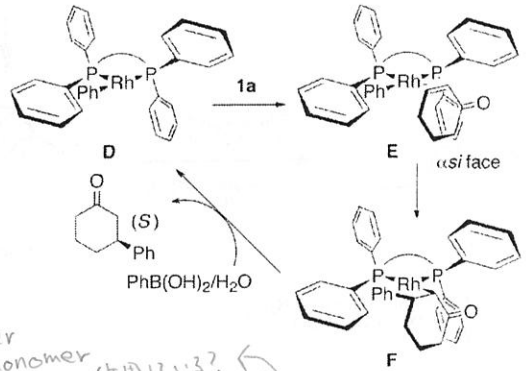
Proposed Reaction Mechanism

Scheme 12

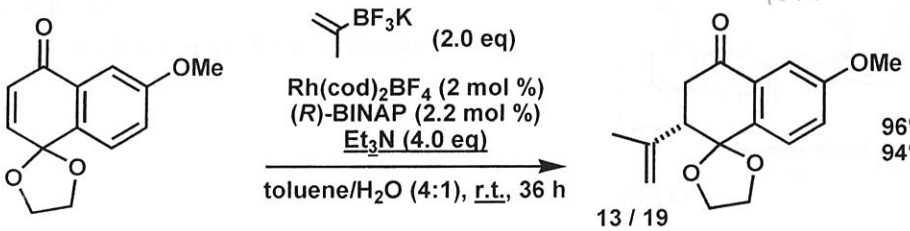


Structure of Rh/(*S*)-BINAP and Enantioselectivity

Scheme 15



In Corey's Synthesis

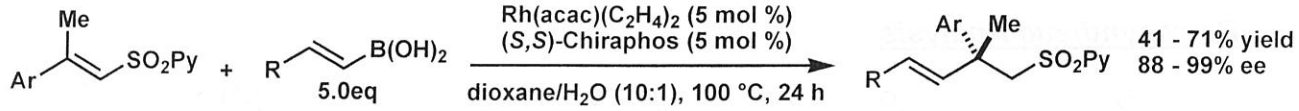


96% yield
94% ee

Et_3N and low temperature was necessary.

w.o. Et_3N : No Reaction
High Temperature : decomp

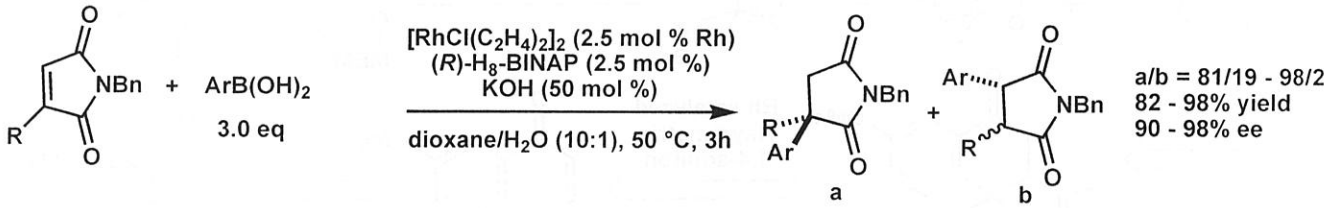
Recent Examples (Construction of Quaternary Carbon Center)



Ar = Ph, 4-Cl-C_6H_4 R = Ph, Me, Bn

41 - 71% yield
88 - 99% ee

J. C. Carretero *et. al. Chem. Commun.* **2005**, 4961.

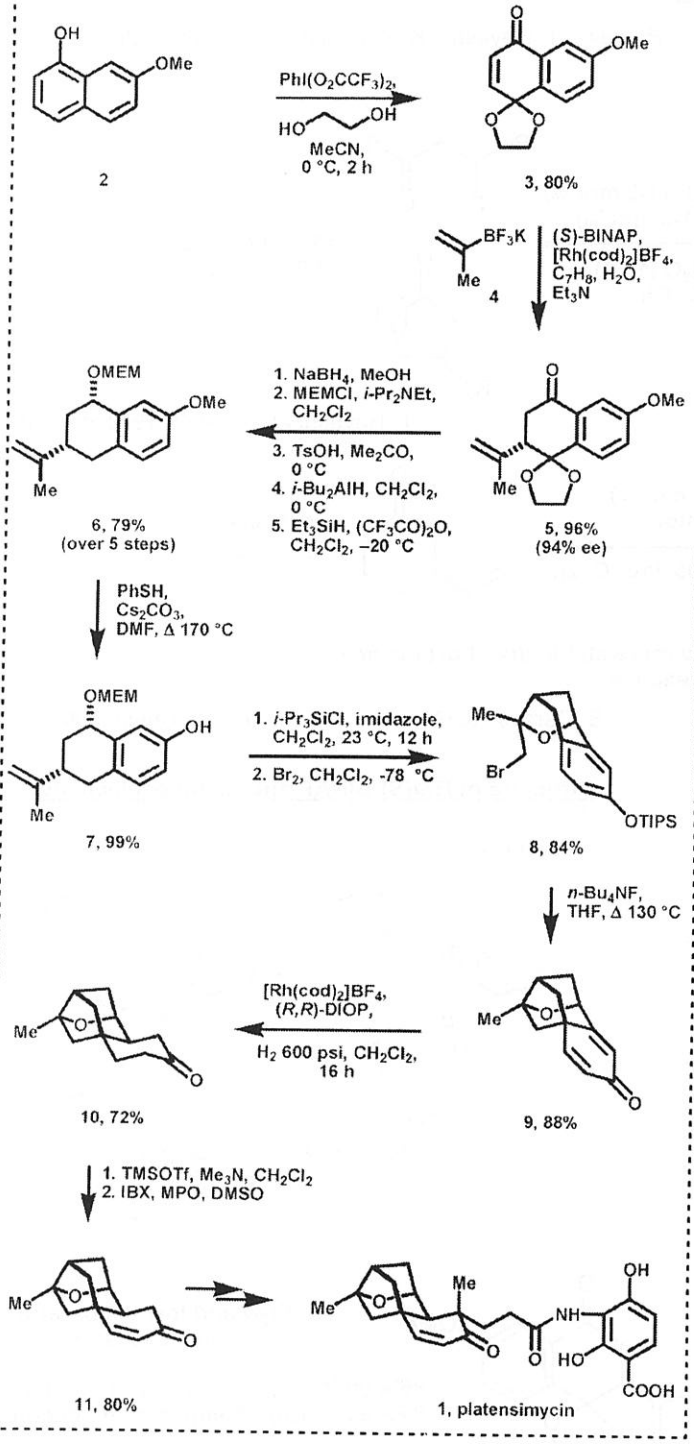


a/b = 81/19 - 98/2
82 - 98% yield
90 - 98% ee

T. Hayashi *et. al. JACS* **2006**, *128*, 5628.

Formal Synthesis

Scheme 1



2 to 3 : oxidative ketalization

3 to 5 : Key Reaction

5 to 6 : 1) stereoselective reduction of ketone
2) protection of the resulting alcohol
3) deprotection of ketacetal
4) reduction of the resulting alcohol
5) dehydroxylation

6 to 7 : cleavage of methyl ether

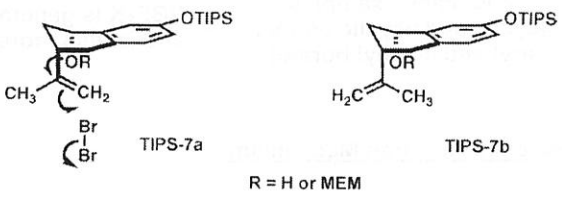
7 to 8 : 1) protection of the resulting alcohol
2) stereoselective bromo-etherification
d.r. > 10:1 (see below)

8 to 9 : phenolic nucleophilic substitution

9 to 10 : diastereoselective hydrogenation

10 to 11 : oxidation of ketone to enone by IBX-MPO

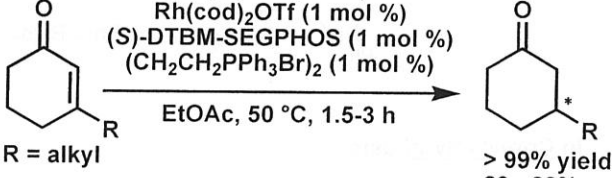
Stereoselectivity of Bromo-Etherification



R = H or MEM

7a ⇌ 7b ΔG_0 = 1.5 kcal/mol

Reported Catalytic Asymmetric Hydrogenation of Enone

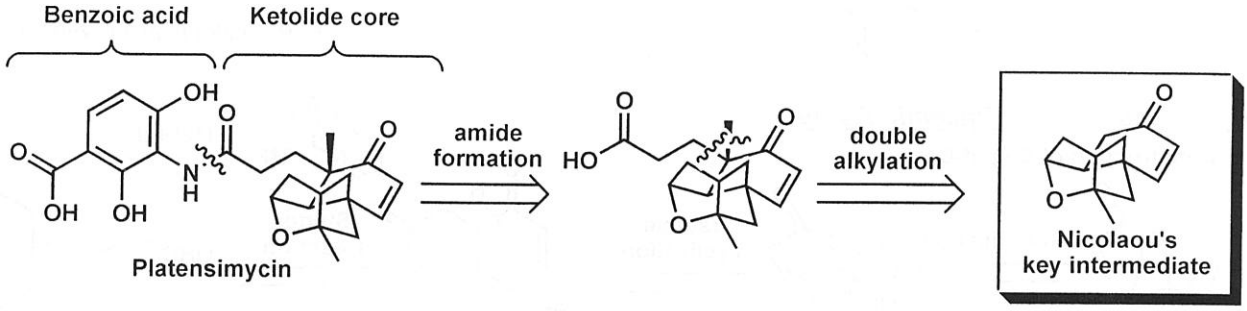


> 99% yield
83 - 88% ee

K. Mashima *et. al. Chem. Eur. J.* **2008**, *14*, 2060

2.5 Summary of Syntheses

Common Strategy

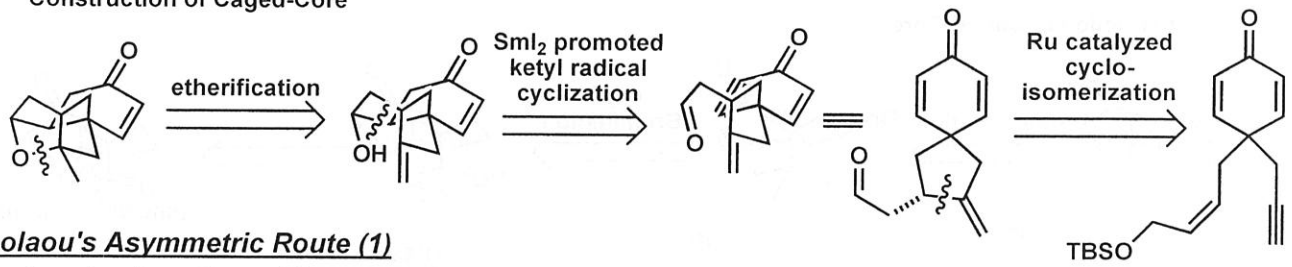


Summary of Routes to Nicolaou's Key Intermediate

Nicolaou's Racemic Route

K. C. Nicolaou *et al. ACIE* **2006**, *45*, 7086.

Construction of Caged-Core



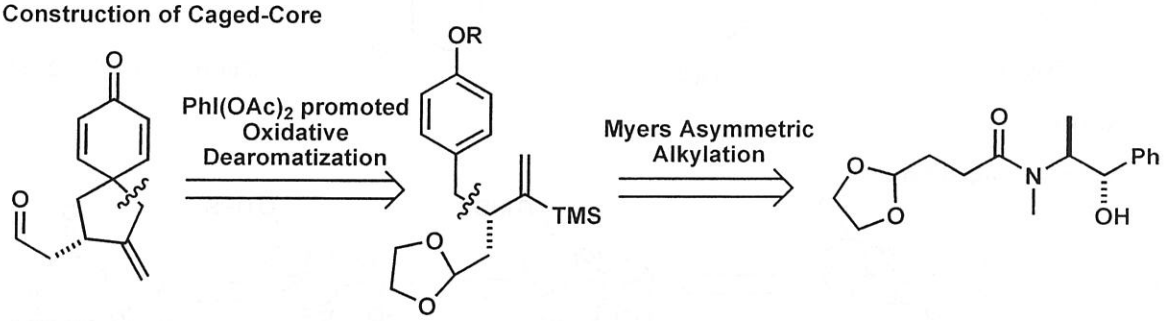
Nicolaou's Asymmetric Route (1)

Construction of Caged-Core : Directl modification of racemi route
Chirality Introduction : Rh catalyzed asymmetric cycloisomerization

K.C. Nicolaou *et al. ACIE* **2007**, *46*, 3942.

Nicolaou's Asymmetric Route (2)

Construction of Caged-Core

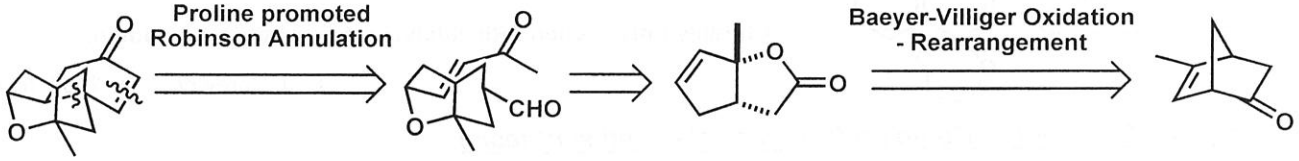


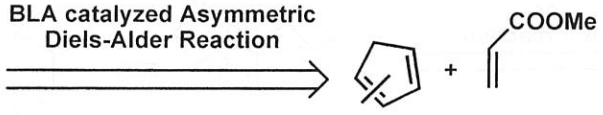
Chirality Introduction : Myers Asymmetric Alkylation (Chiral Auxiliary)

Yamamoto's Route

H. Yamamoto *et al. JACS* **2007**, *129*, 9534.

Construction of Caged-Core

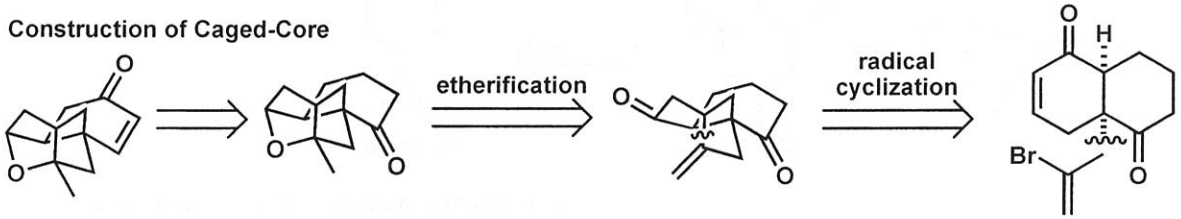


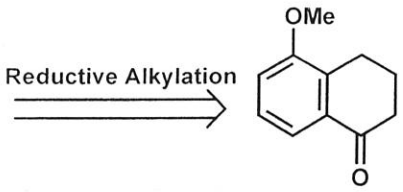


Chirality Introduction : BLA catalyzed Asymmetric Diels-Alder Reaction

Snider's Route (racemic)

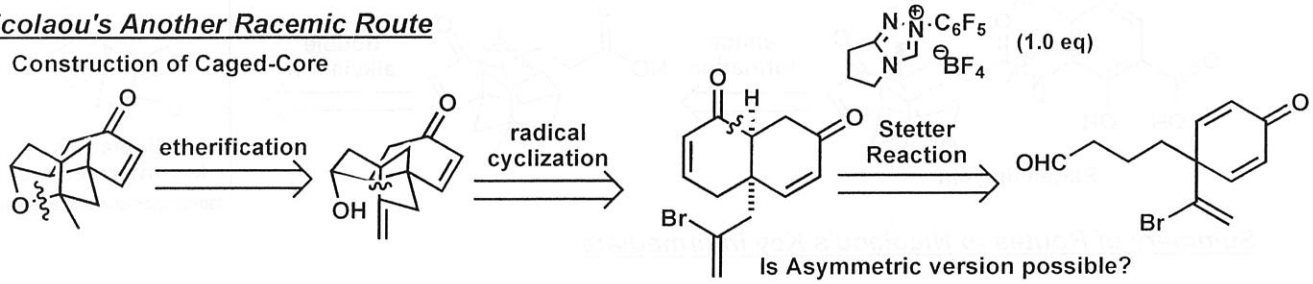
Construction of Caged-Core





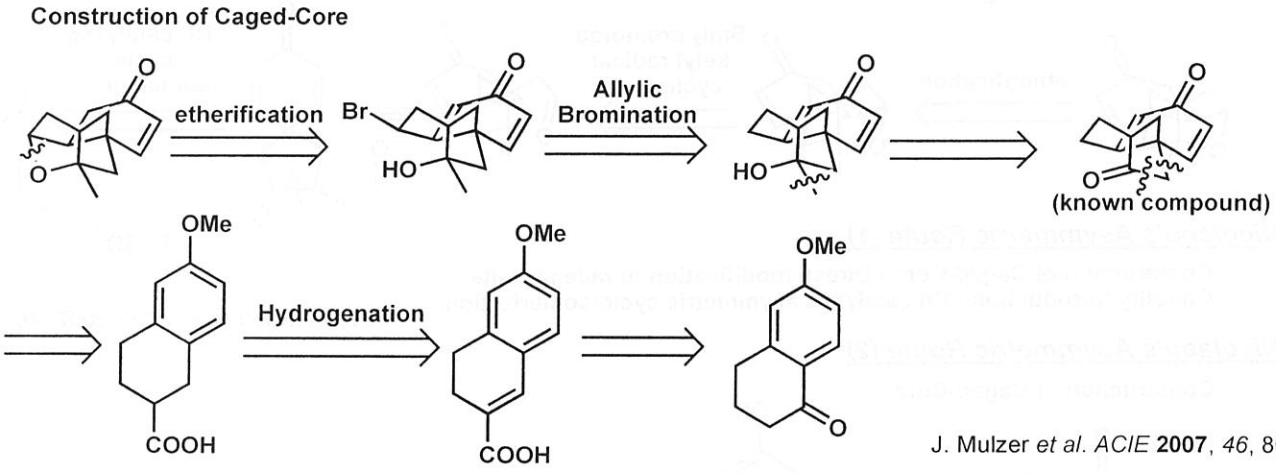
B. B. Snider *et al. OL* **2007**, *9*, 1825.

Nicolaou's Another Racemic Route



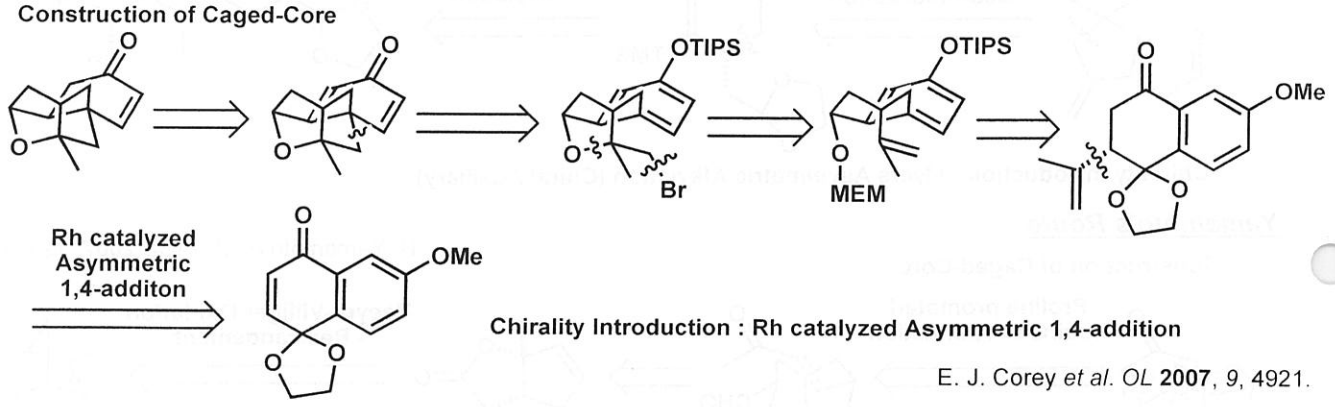
K. C. Nicolaou *et al. Chem. Commun.* **2007**, 1922.

Mulzer's Route (racemic)



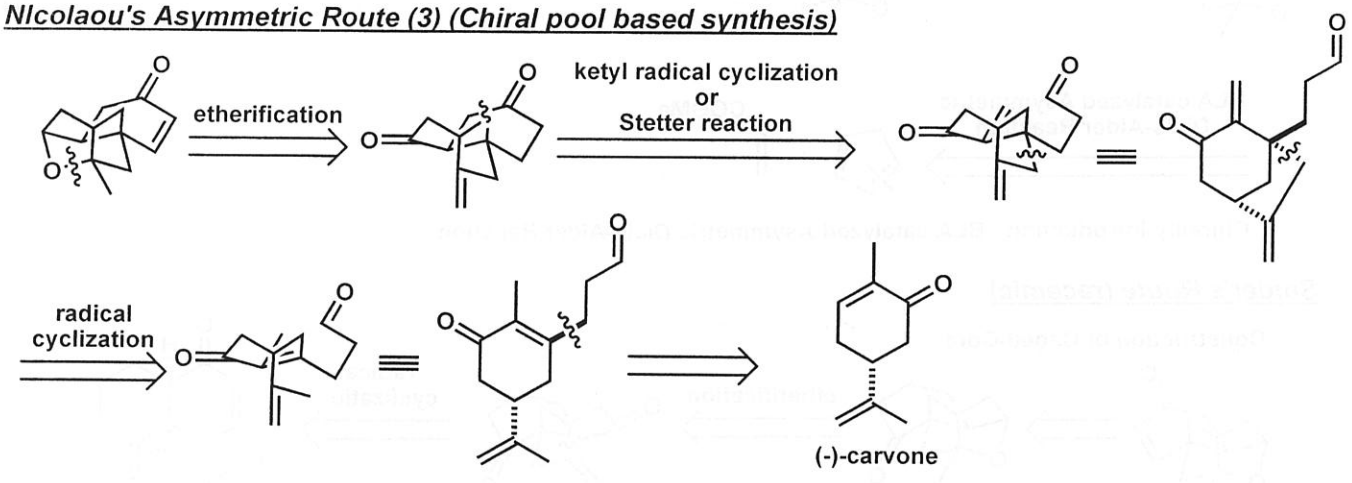
J. Mulzer *et al. ACIE* **2007**, *46*, 8074.

Corey's Route



E. J. Corey *et al. OL* **2007**, *9*, 4921.

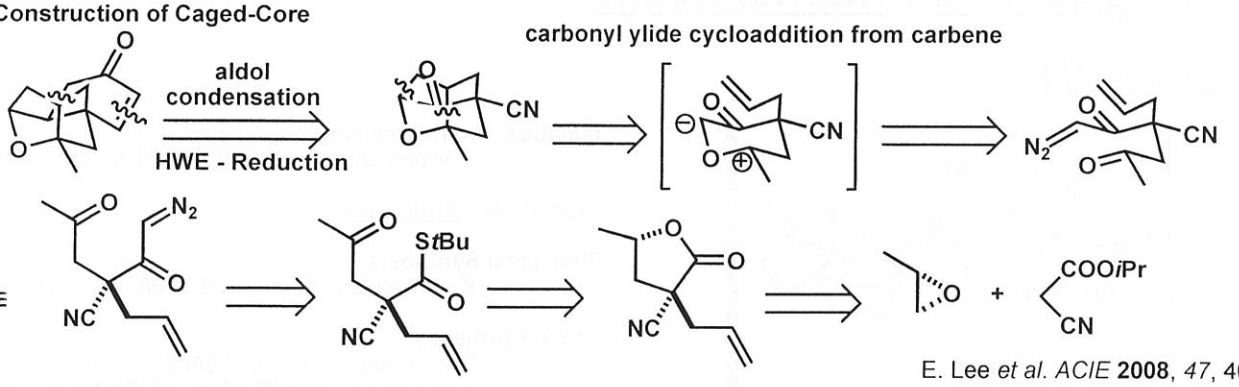
NIcolaou's Asymmetric Route (3) (Chiral pool based synthesis)



K.C. Nicolaou *et al. ACIE* **2008**, *47*, 944.

Lee's Route

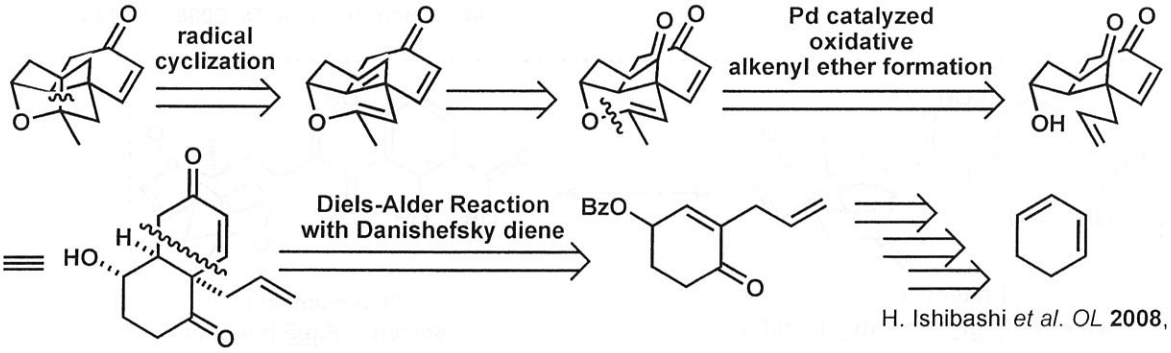
Construction of Caged-Core



E. Lee *et al. ACIE* **2008**, *47*, 4009.

Ishibashi's Route (racemic)

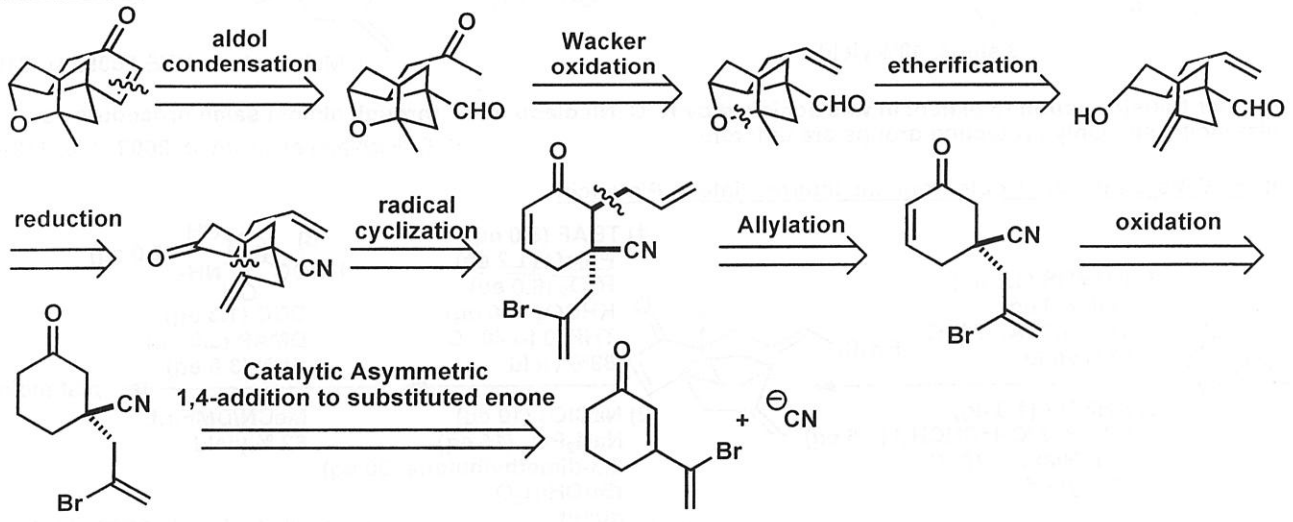
Construction of Caged-Core



H. Ishibashi *et al. OL* **2008**, *10*, 4049.

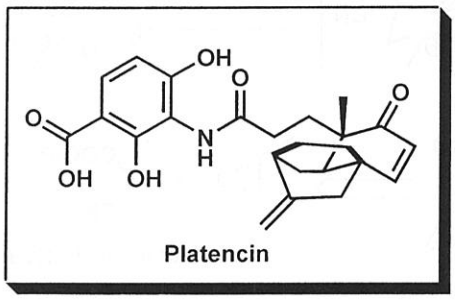
entry	Route	Steps	Yield	Chirality
1	Nicolaou racemic (1)	10	11%	racemic
2	Nicolaou asymmetric (1)	16	6.2%	catalytic asymmetric
3	Nicolaou asymmetric (2)	10	11%	chiral auxiliary
4	Yamamoto	10	4.9%	catalytic asymmetric
5	Snider	8	31%	racemic
6	Nicolaou racemic (2)	15	5.2%	racemic
7	Mulzer	12	4.4%	racemic
8	Corey	14	26%	catalytic asymmetric
9	Nicolaou asymmetric (3)	14	2.0%	chiral pool based
10	Lee	11	20%	chiral pool based
11	Ishibashi	15	11%	racemic

My Opinion



3. Analogues of Platensimycin

3.1 Platencin



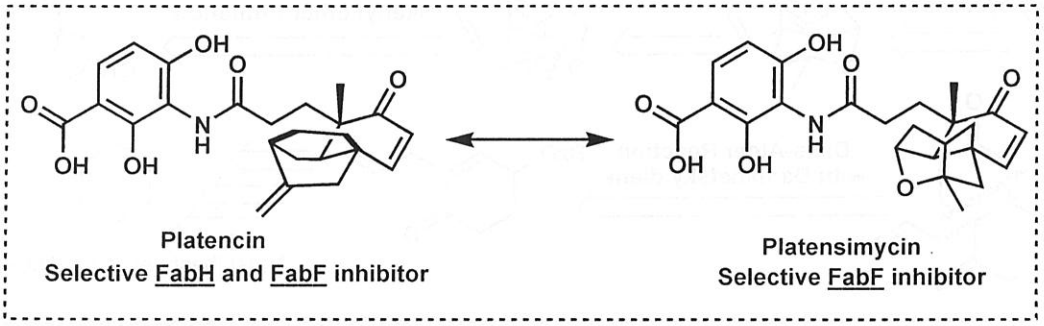
Platencin

Isolation : from *Streptomyces platensis*
J. Wang *et al. Proc. Natl. Sci. USA*. **2007**, *119*, 4768.

Bioactivity : ***Antibiotics***

First Total Synthesis :
K. C. Nicolaou *et. al. ACIE* **2008**, *47*, 1780.

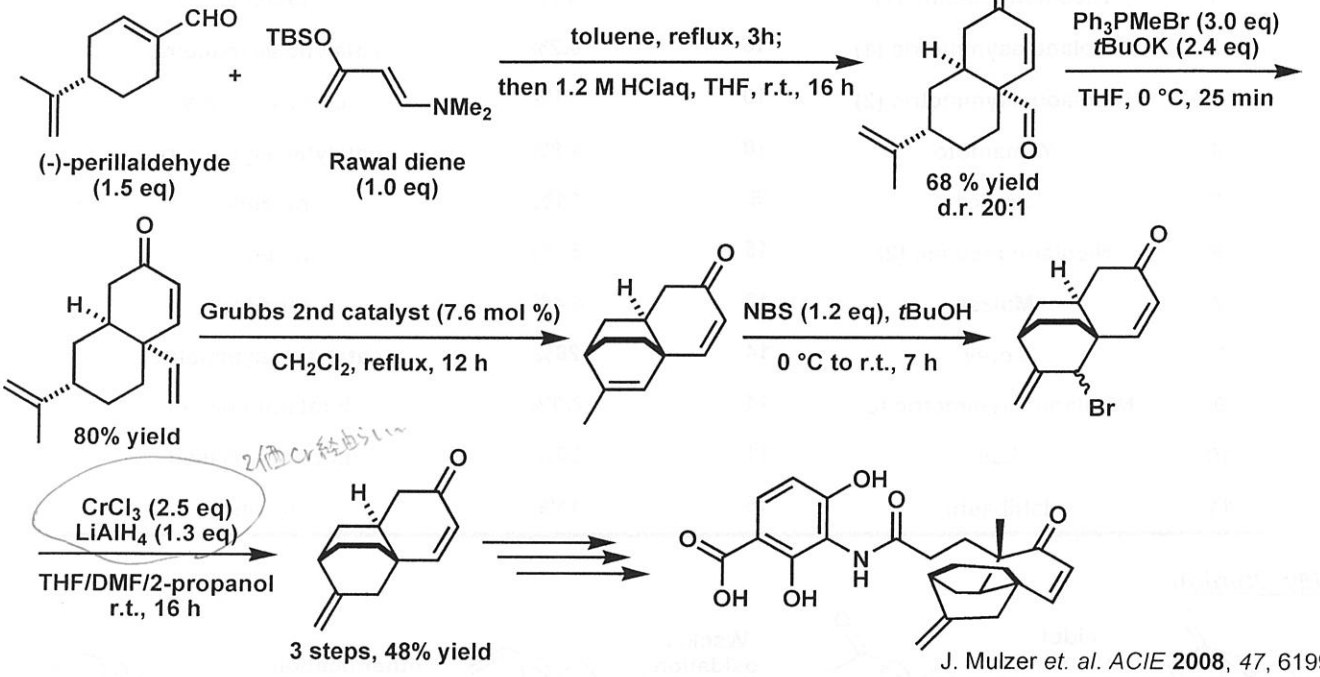
Other Syntheses :
V. H. Rawal *et. al. ACIE* **2008**, *47*, 4373.
J. Mulzer *et. al. ACIE* **2008**, *47*, 6199.
D. Lee *et. al. ACIE* **2008**, *47*, 6201.
F. P. J. T. Rutjes *et. al. ACIE* **2008**, *47*, 6576.
K. C. Nicolaou *et. al. JACS* **2008**, *130*, 11292.
M. G. Banwell *et. al. OL* **2008**, *10*, 4465.



Platencin
Selective FabH and FabF inhibitor

Platensimycin
Selective FabF inhibitor

Mulzer's Formal Synthesis



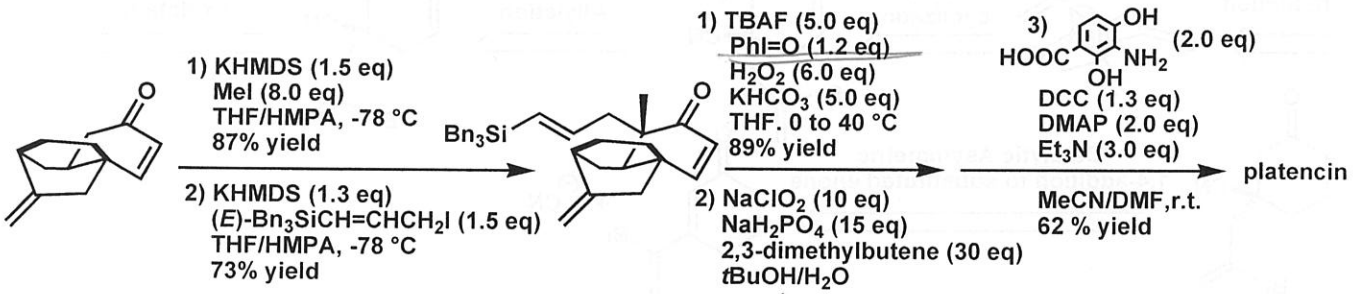
(-)-perillaldehyde (1.5 eq)

Rawal diene (1.0 eq)

J. Mulzer *et. al. ACIE* **2008**, *47*, 6199.

Further transformation to platencin was achieved by K. C. Nicolaou *et. al.* through almost same procedure as platencimysin. Only protecting groups are different.
K. C. Nicolaou *et. al. JACS* **2008**, *130*, 11292.

Reported More Efficient Route from the Intermediate to Platencin



V. H. Rawal *et. al. ACIE* **2008**, *47*, 4373

3.2 Other Synthesized Analogues

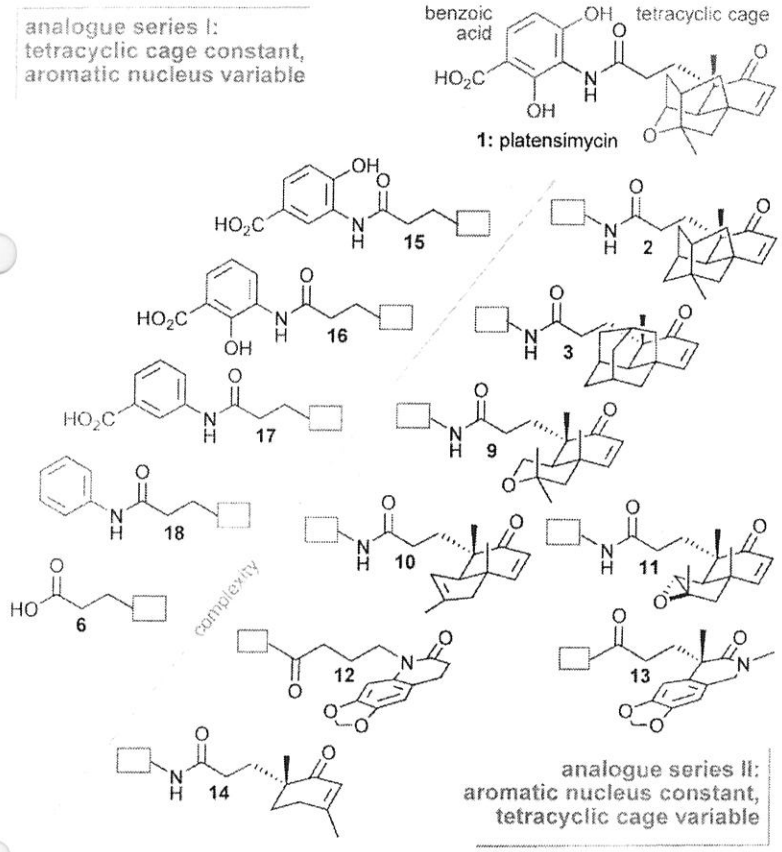
Platensimycin and Platencin showed high *in vitro* anti-biotic effect. However, it seems difficult to use directly for clinical purpose because of their non-ideal phamacokinetic profiles.

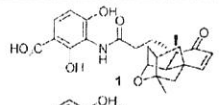
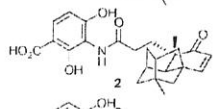
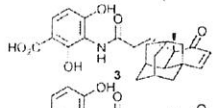
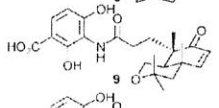
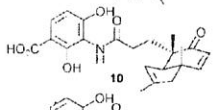
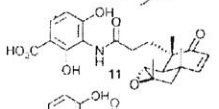
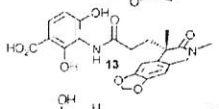
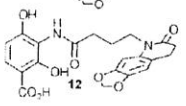
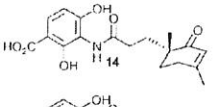
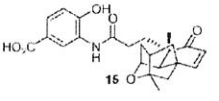
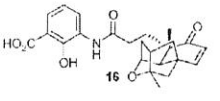
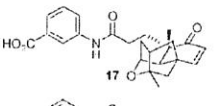
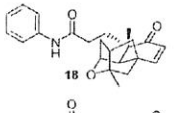
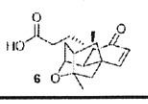
↓

Investigation of *Structure - Activity Relationship* (SAR) and Structure Modification are Essencial.

Synthesis of Many Analogues and Evaluation by Nicolaou

K. C. Nicolaou *et. al. ACIE* **2007**, *46*, 4712.
K. C. Nicolaou *et. al. JACS* **2007**, *129*, 14850.
K. C. Nicolaou *et. al. JACS* **2008**. *130*. 13110.

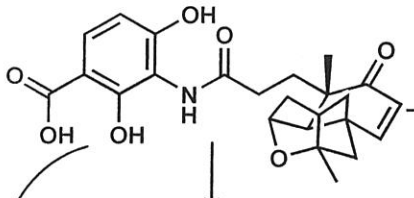


Entry	Compound	MRSA	VREF	*E. coli*
1[a]		0.2–0.4	0.4–0.8	>88
2[a]		1.1–2.2	1.1–2.2	>88
3[a]		1.3–1.8	1.3–1.8	>88
4[a]		3.5–4.3	6.5–8.6	>86
5[b]		8.0–10	>80	>80
6[c]		17–20	>83	>83
7[a]		>88	>88	>88
8		>86	>86	>86
9[a]		>69	>69	>69
10[a]		>85	>85	>85
11[a]		>85	>85	>85
12[a]		>82	>82	>82
13[a]		>73	>73	>73
14[a]		37–58	>58	>58

[a] Only the isomer shown was tested in the antibacterial assay. [b] Both the isomer shown and its enantiomer were tested separately in the antibacterial assay. The latter isomer was found to be inactive in the investigated range. [c] The compound was tested as a racemic mixture in the antibacterial assay.

From entry 2 (carbaplatensimycin), 3 (adamantaplatensimycin) and 4, Caged-Core structure is NOT essential.
Similar bulky lipophilic structure would be effective.

On the other hand, benzoic acid structure seems very important for anti-biotic activity.



Similar bulky but easy to synthesize structure ?
Enone moiety is essential?

Amide bond can be replaced?

OH and COOH groups can be replaced with other polar functional group?

platencin's MIC (μg/ml)		
MRSA	VREF	*E.coli*
~ 1	0.06	>64