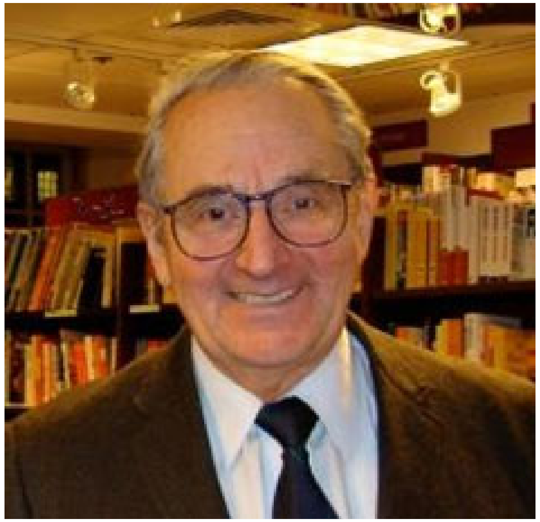


"…To them and to those starting careers in chemistry, I would offer the following advice: Never underestimate what you can accomplish if you prepare yourself well, continue to learn, work hard and optimistically, and value your integrity."

1951 Instructor @ UI
1953 Assistant Prof. @ UI
1956 Prof. @ UI
1959 Prof. @ Harvard
1965 Chairman, Department of Chemistry @ Harvard; Sheldon Emery Prof. @ Harvard
1997 Todd Prof. @ Cambridge
2000 Sheldon Emery Research Prof. @ Harvard

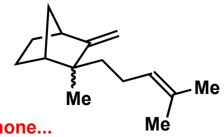
Representative Award:

National Medal of Science
Nobel Prize
Priestley Medal
...

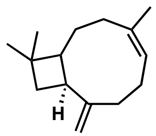
Major Academic Interests

Total Synthesis of Natural Product
Biosynthesis of Natural Product
Synthetic Methodology
Computer-Aided Drug Design
...

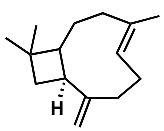
30 articles in 10 years
from CxHy to CxHyOz,
including hydrocarbon, terpene, hormone...



β-santalene&
epi-*β*-santalene
JACS, 1962, 84, 2611

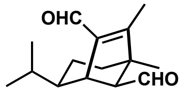


(±)-caryophyllene

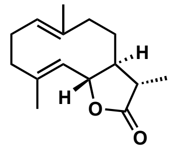


(±)-isocaryophyllene

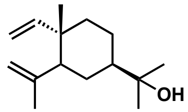
JACS, 1963, 85, 362
JACS, 1964, 86, 485



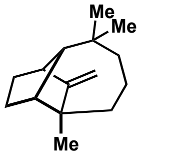
helminthosporal
JACS, 1963, 85, 3527



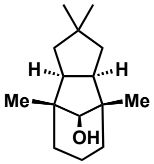
Dihydrocostunolide
JACS, 1963, 85, 4033
JACS, 1965, 87, 5736



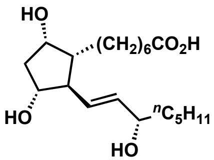
(±)-elemol
TL, 1969, 10, 1779



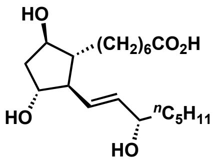
(±)-longifolene
JACS, 1961, 83, 1251
JACS, 1962, 84, 2938
JACS, 1964, 86, 478



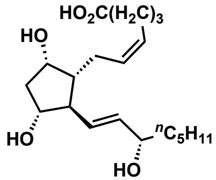
meso-*α*-caryophyllene alcohol
JACS, 1964, 86, 1652
JACS, 1965, 87 ,5733



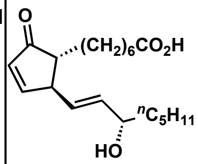
$F_{1\alpha}$



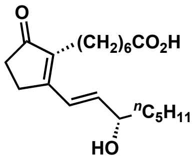
$F_{1\beta}$



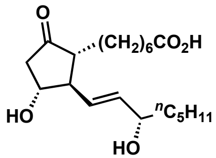
$F_{2\alpha}$



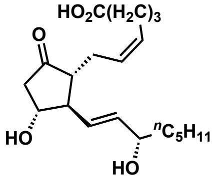
A_1



B_1



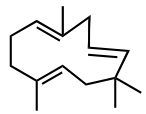
E_1



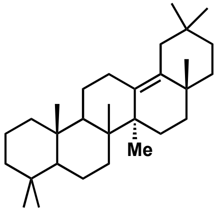
E_2

prostaglandin

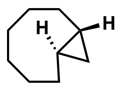
JACS,1968, 90, 3245
JACS,1968, 90, 3247
JACS,1969, 91, 535
JACS,1969, 91, 5675
JACS,1970, 92, 397(optical modification)
JACS,1970, 92, 2586



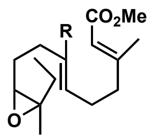
humulene
JACS,1967,89,2758



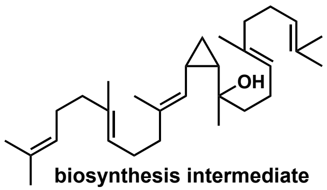
Olean-11,12;13,18-diene
JACS, 1963, 85, 3979



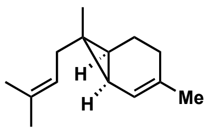
trans-bicycle[6.1.0]
TL, 1968, 9, 3655



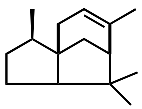
(±)-cecropia juvenile hormone
R=Me or Et
JACS, 1968, 90, 5618
JACS, 1970, 92, 6636
JACS, 1970, 92, 6637

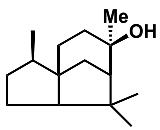


biosynthesis intermediate
TL, 1968, 9, 5113

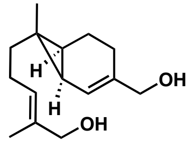


(±)-sesquicarene
TL, 1969, 10, 1837
TL, 1969, 10, 3257

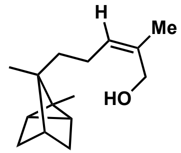




(±)-cedrene & cedrol
JACS, 1969, 91, 1557

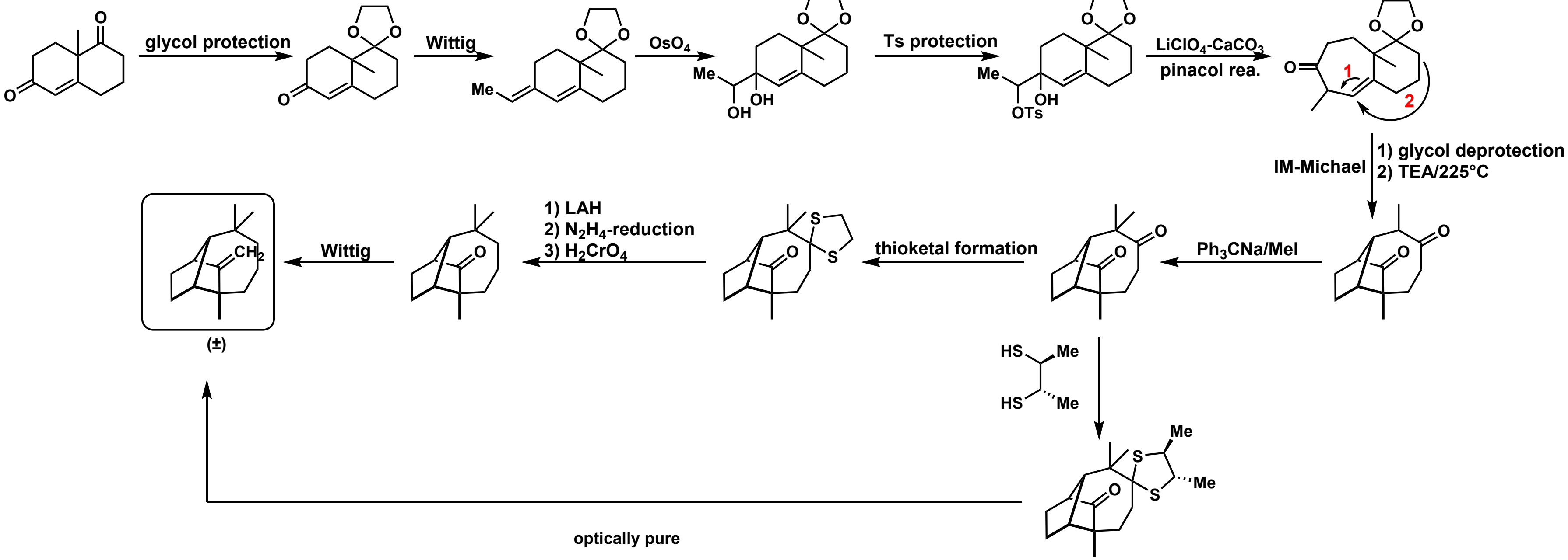


(±)-sirenin
JACS, 1969, 91, 4318
TL, 1970, 11, 2245

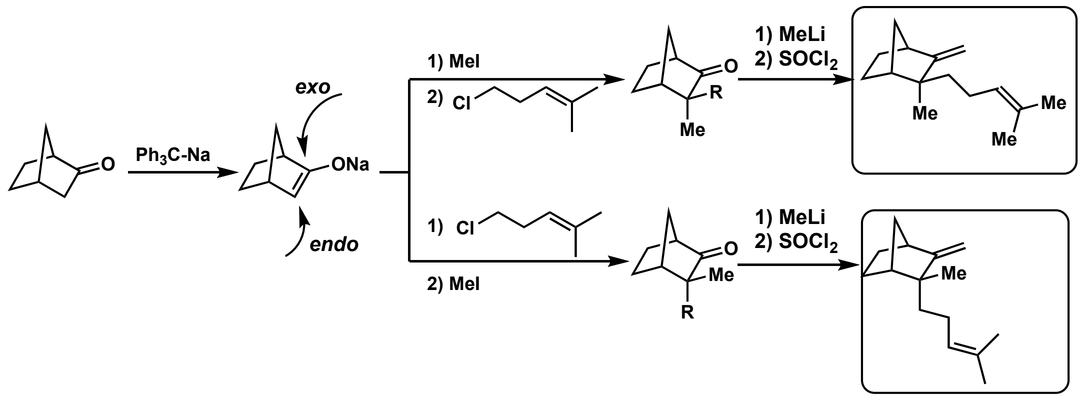


α-santalol
JACS, 1970, 92, 6314

(±)-Longifolene

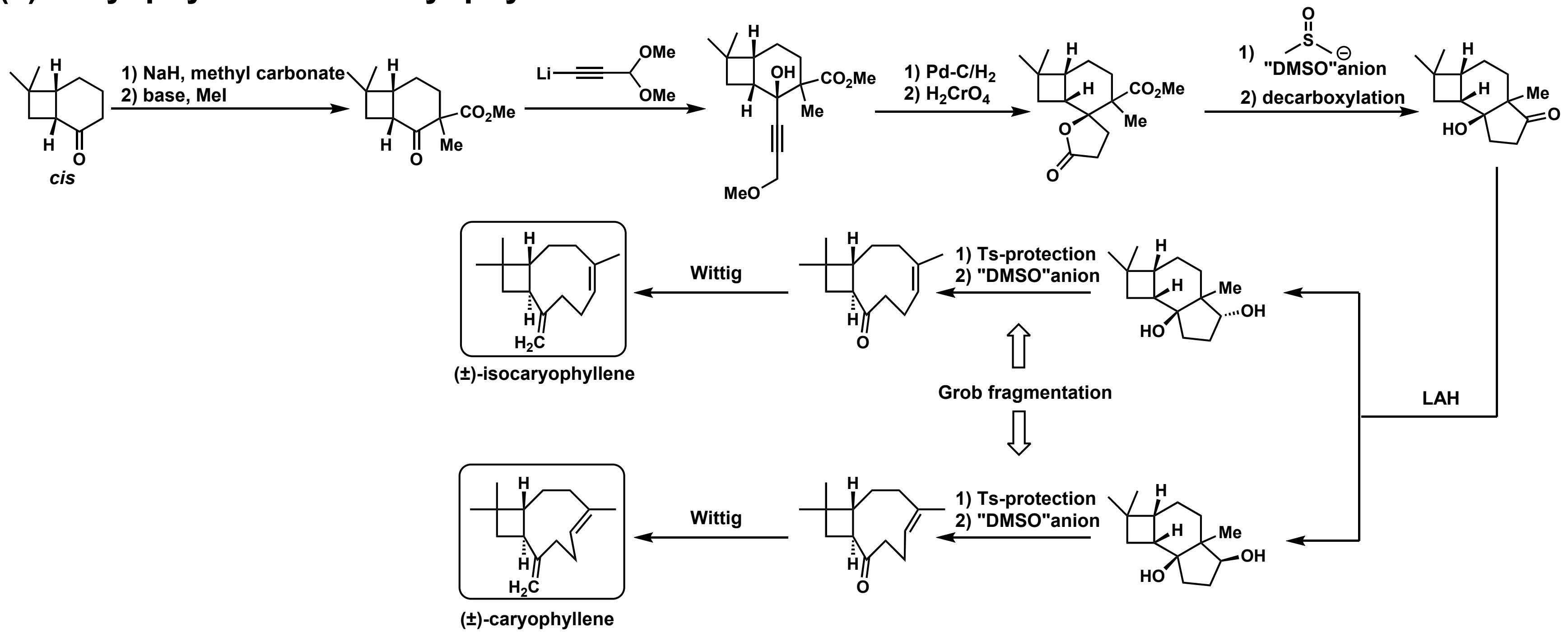


β-Santalene

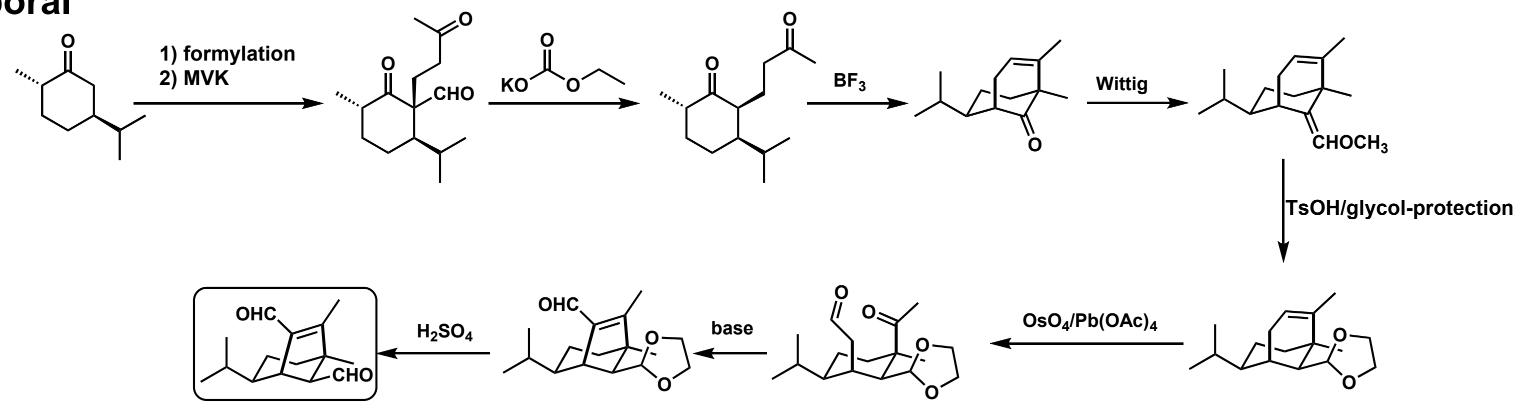


Nucleophilic attack rate:exo>endo
(kinetic control)

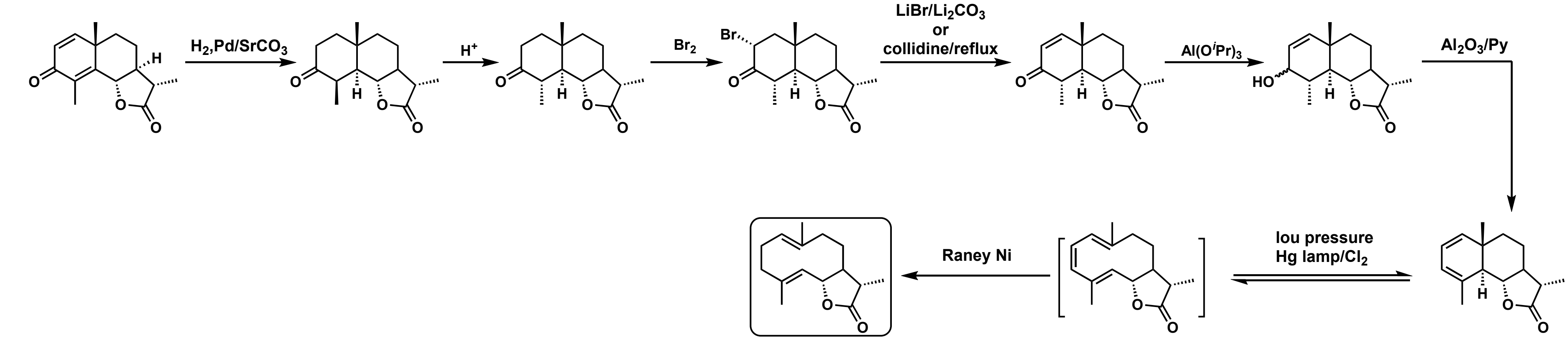
(±)-Caryophyllene & Isocaryophyllene



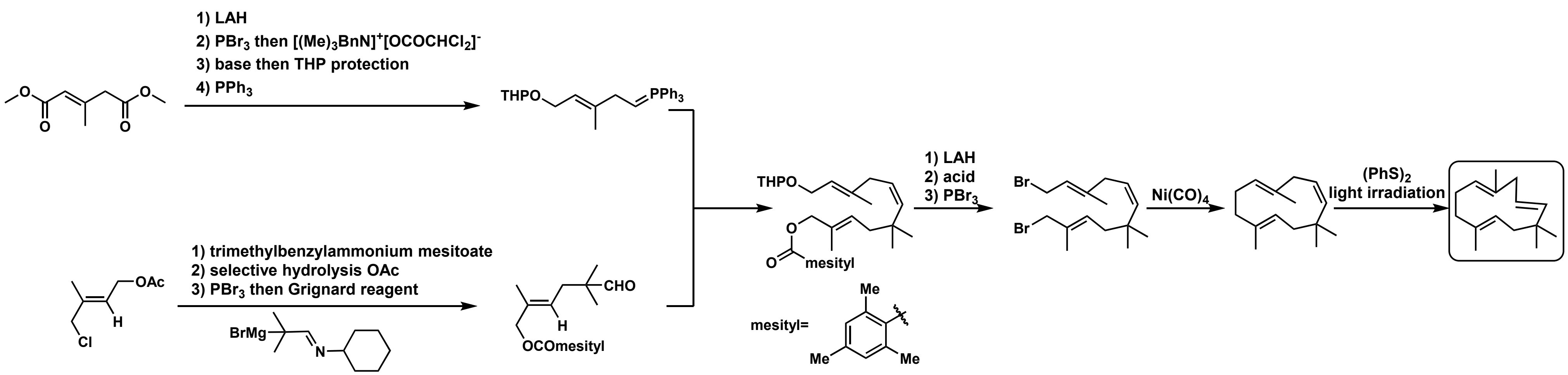
Helminthosporal



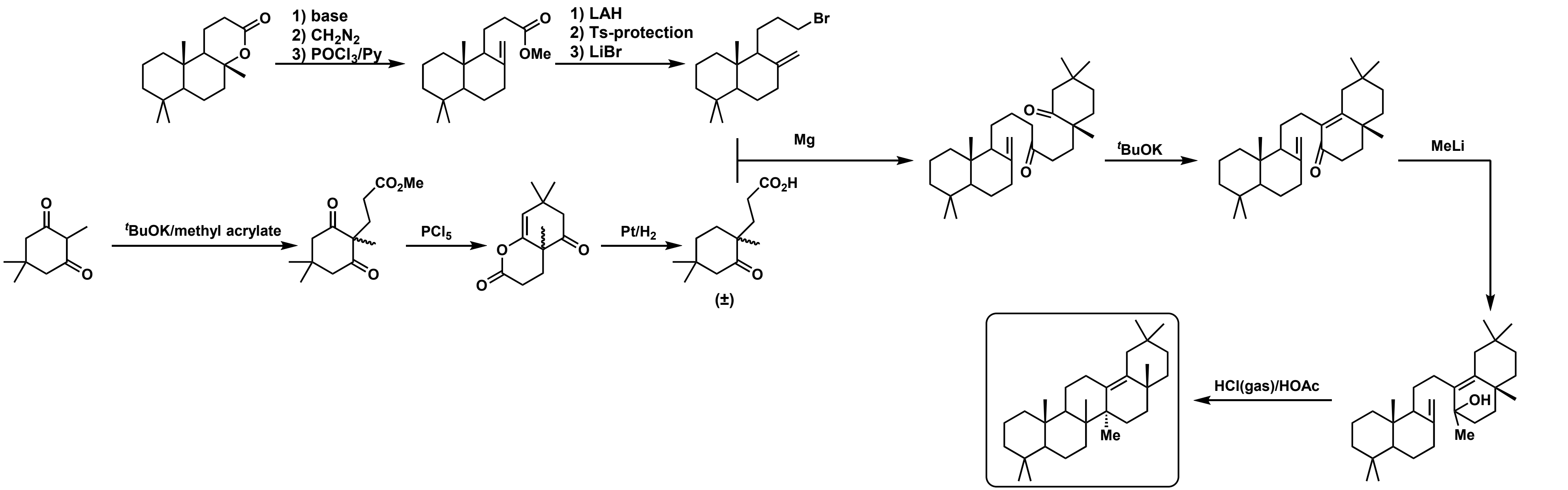
Dihydrocostunolide



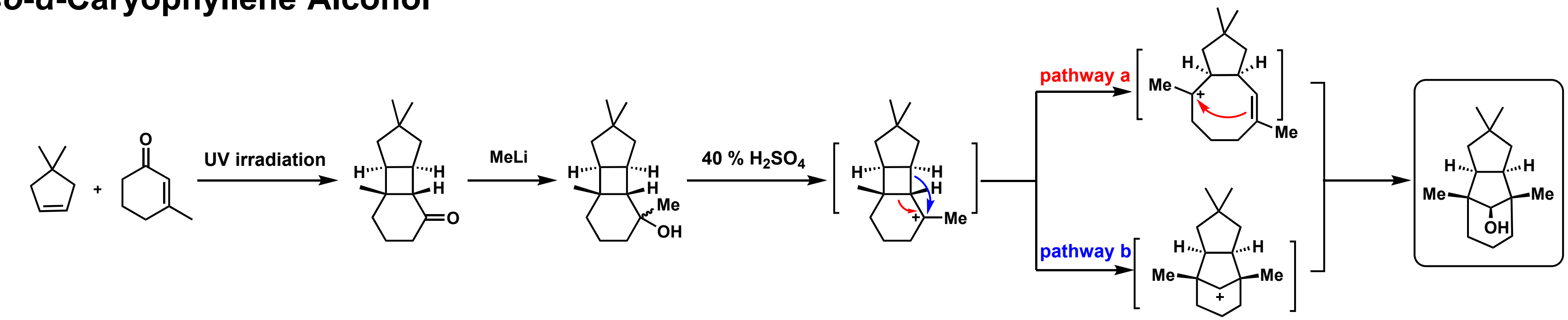
Humulene



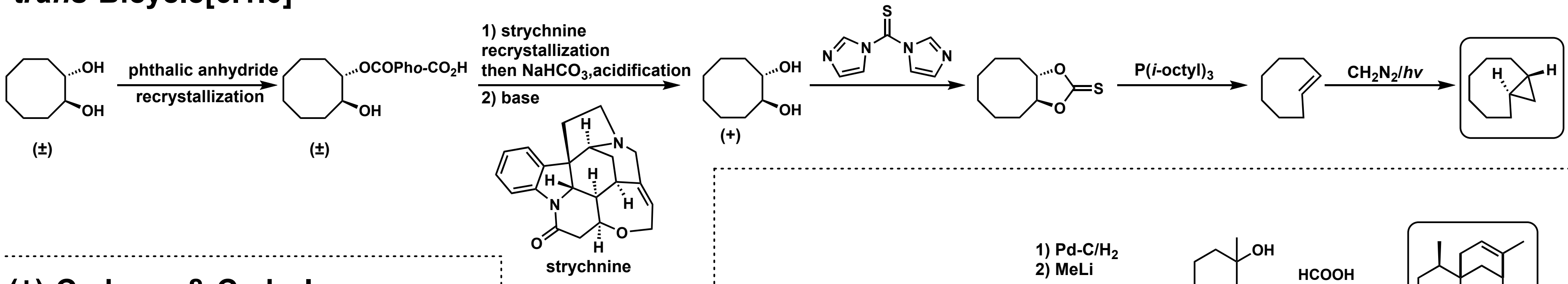
Olean-11,12;13,18-Diene



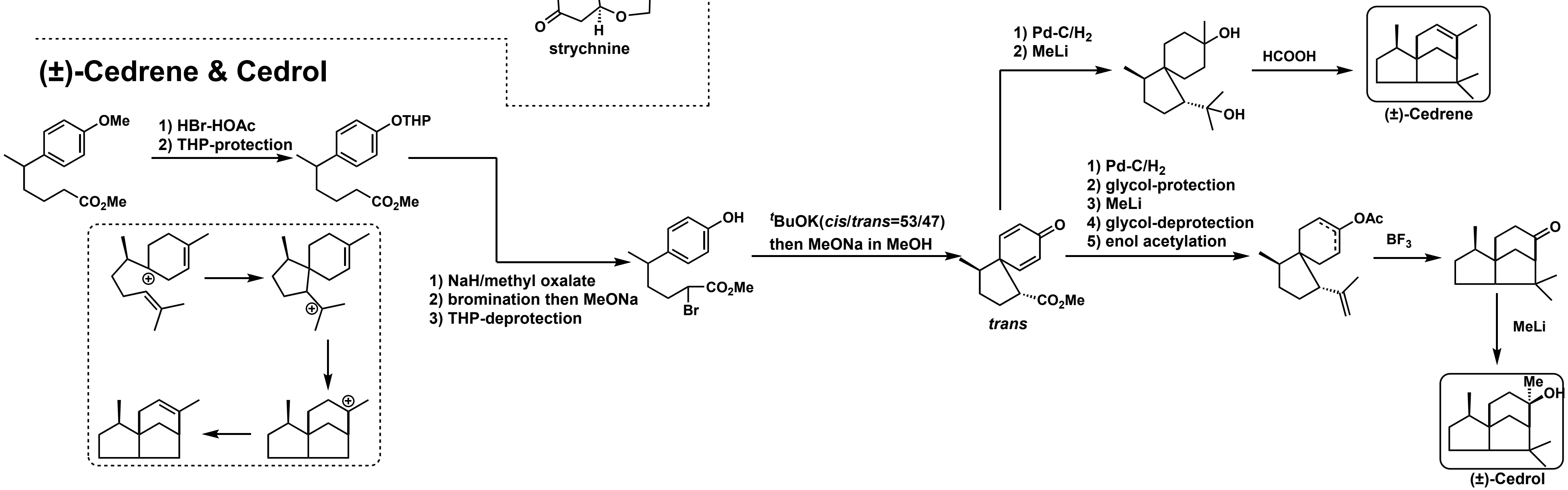
meso-α-Caryophyllene Alcohol



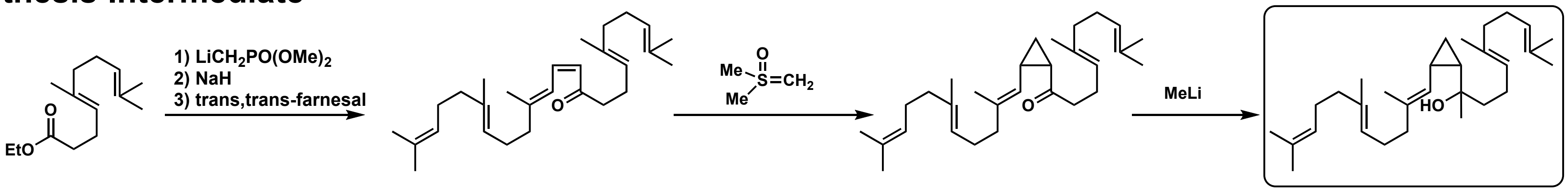
trans-Bicycle[6.1.0]



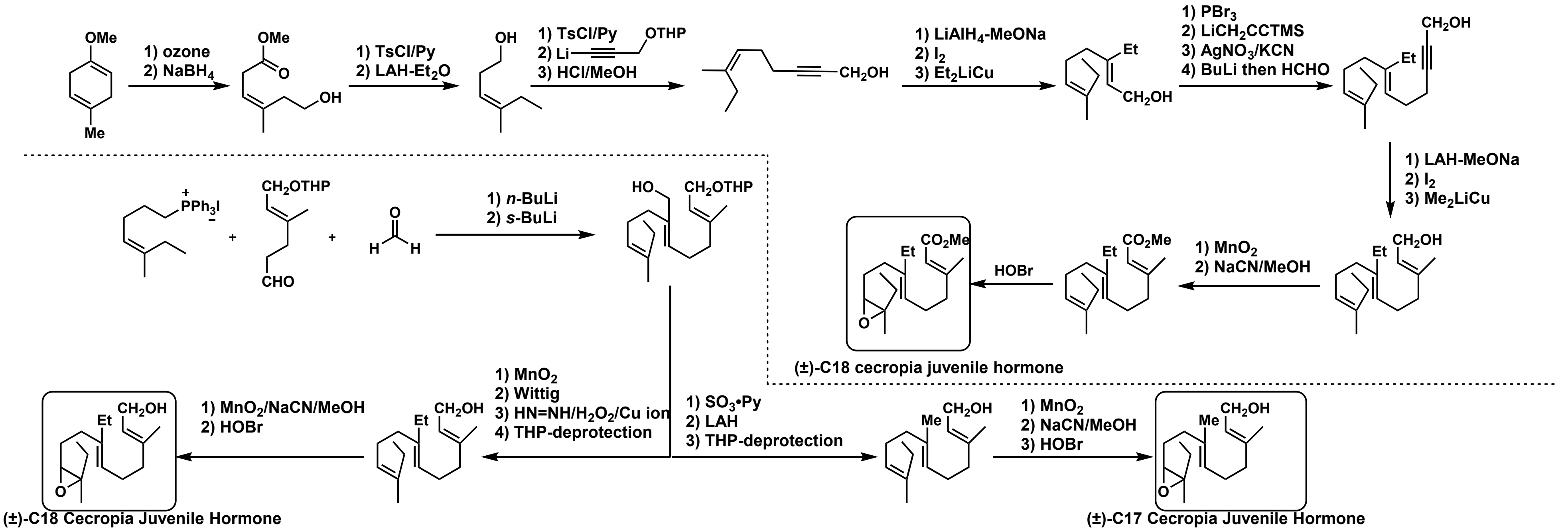
(±)-Cedrene & Cedrol



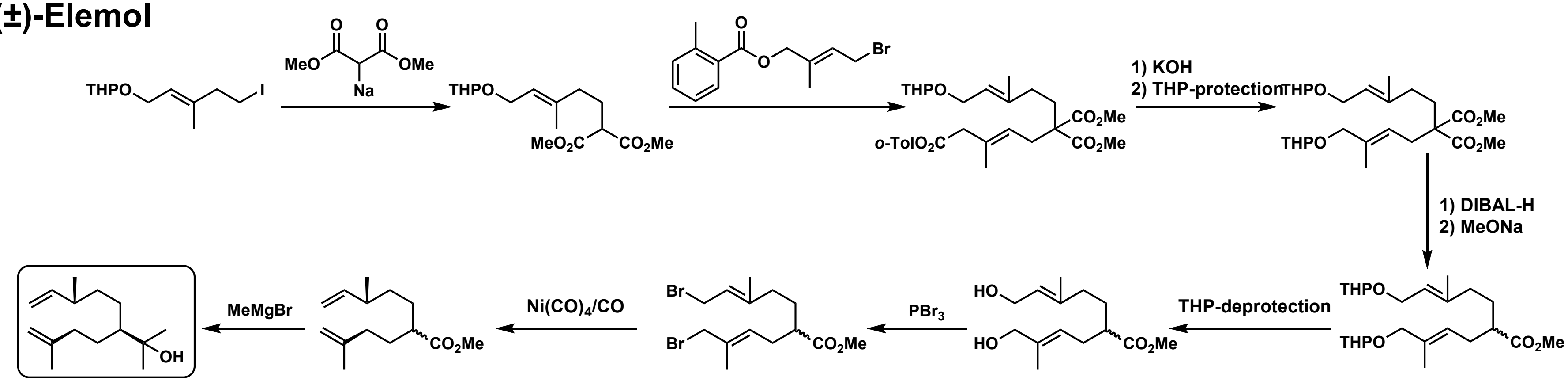
Biosynthesis Intermediate



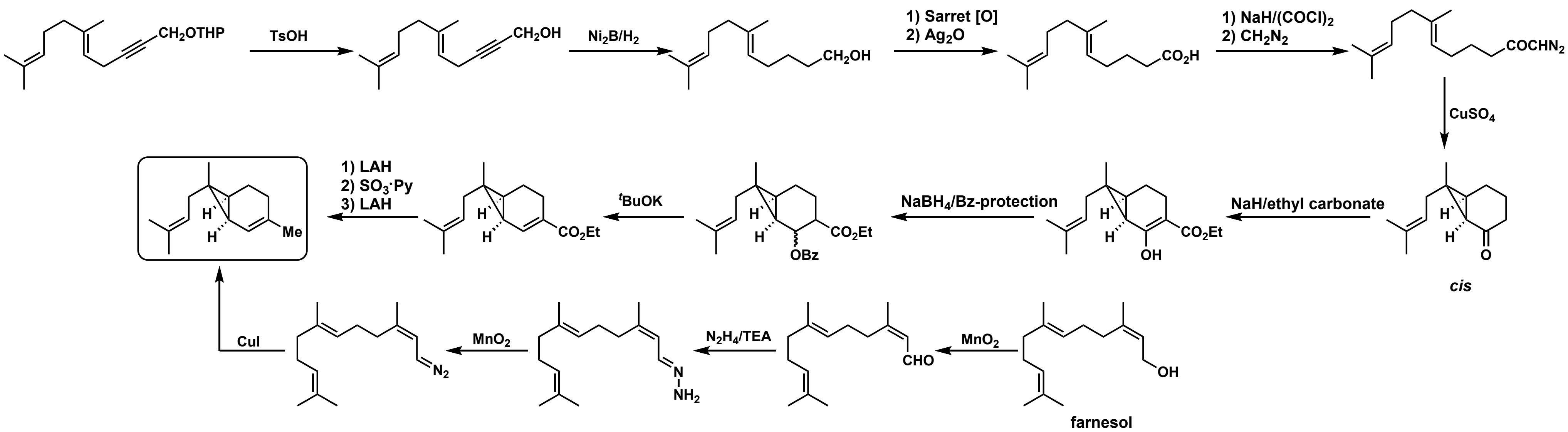
(±)-Cecropia Juvenile Hormone(C_{17}:R=Me;C_{18}:R=Et)



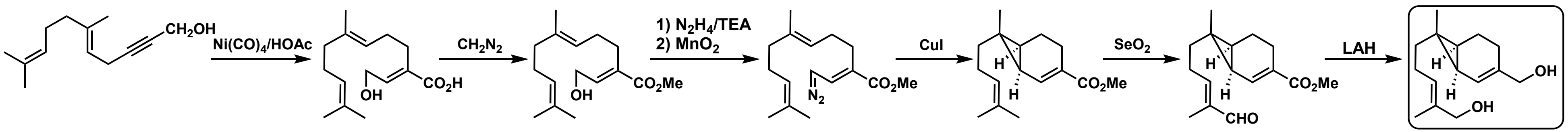
(±)-Elemol



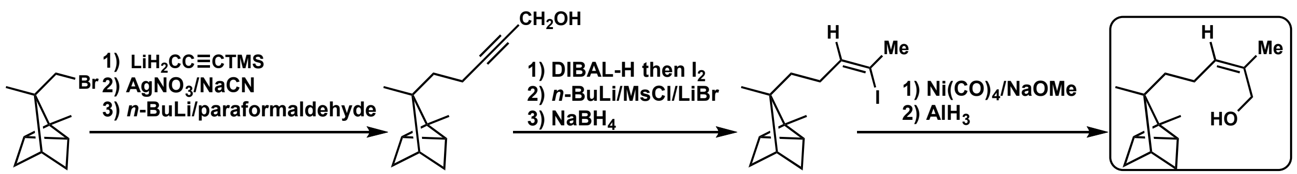
(±)-Sesquicarene



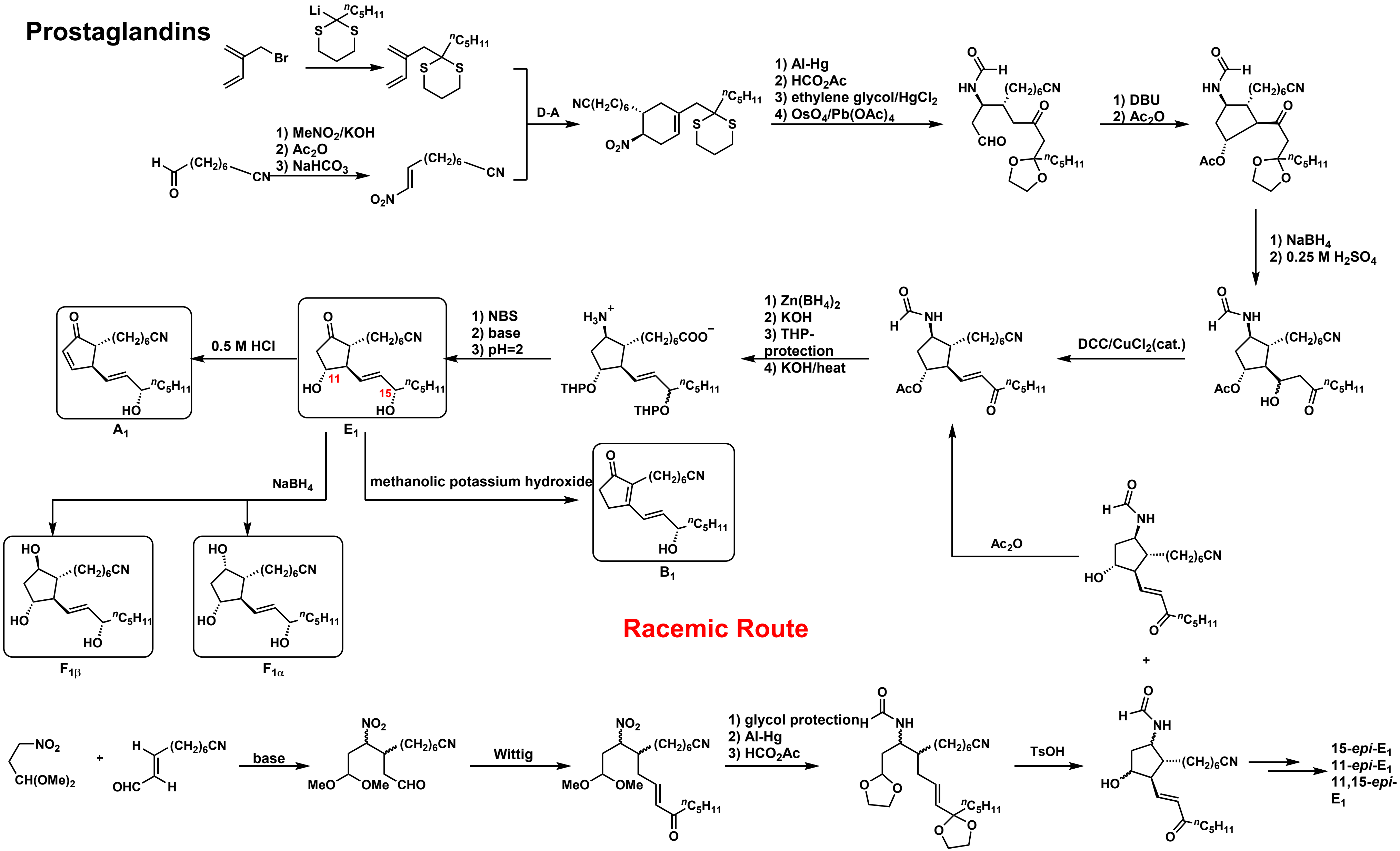
(±)-Sirenin

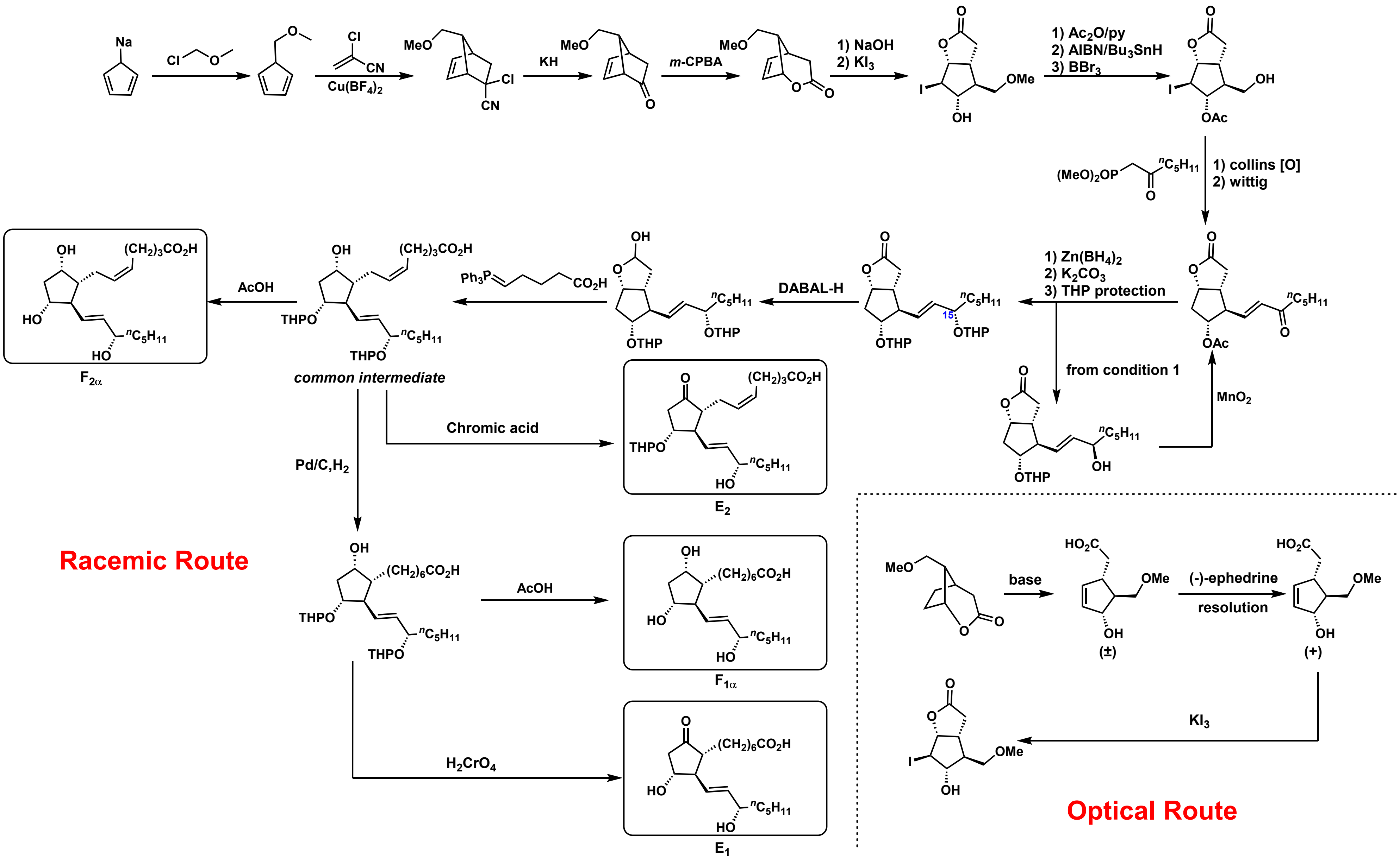


α-Santalol



Prostaglandins



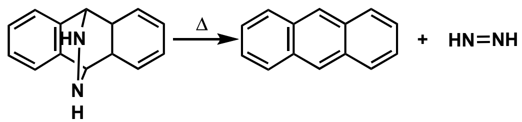


Na
Cu(BF4)2
KH
m-CPBA
1) NaOH
2) KI3
1) Ac2O/py
2) AIBN/Bu3SnH
3) BBr3
(MeO)2OP
1) collins [O]
2) wittig
1) Zn(BH4)2
2) K2CO3
3) THP protection
from condition 1
MnO2
DABAL-H
Ph3P
AcOH
F2α
common intermediate
Chromic acid
E2
Pd/C,H2
F1α
H2CrO4
E1
Racemic Route
base
(±)
(-)-ephedrine
resolution
(+)
KI3
Optical Route

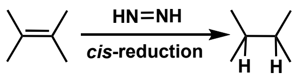
Diimide Reduction

TL, 1961, 2, 347
JACS, 1961, 83, 2957
JACS, 1962, 84, 685

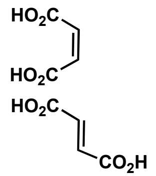
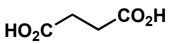
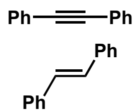
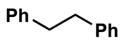
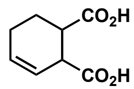
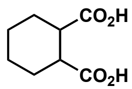
Preparation



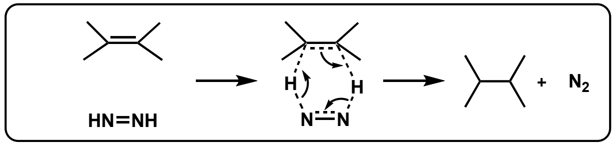
General Formula



con 1:N_2H_2-O_2-copper ion
con 2:N_2H_2-H_2O_2-copper ion

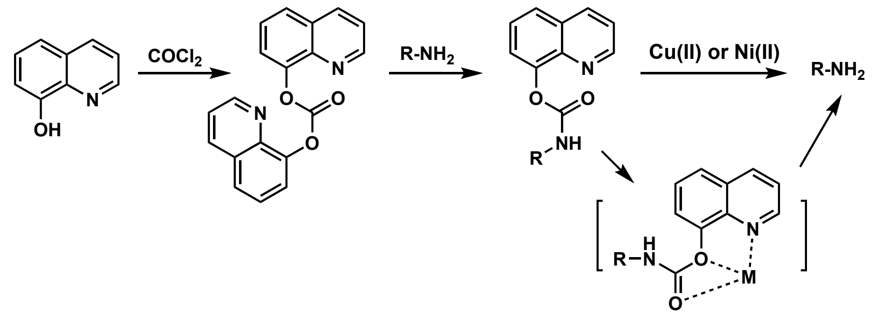
		82%[1] 76%[2]
		80%[1] 88%[1]
gibberellic acid cholesterol 	tetrahydrogibberellic acid cholestanol 	74%[2] 20%[1] 78%[2]

Mechanism



Protection Group of Amino Acid

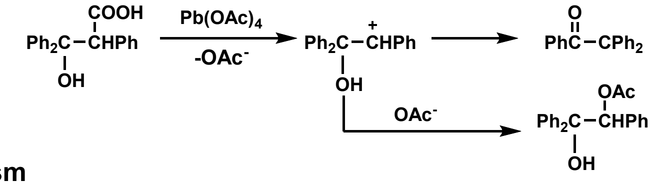
JACS, 1962, 84, 4899



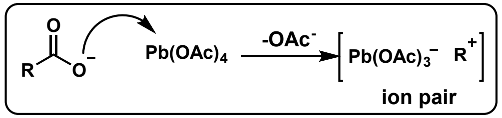
Oxidative Decarboxylation by Pb(IV)

Angew Chem, 1962, 74, 88

General Formula



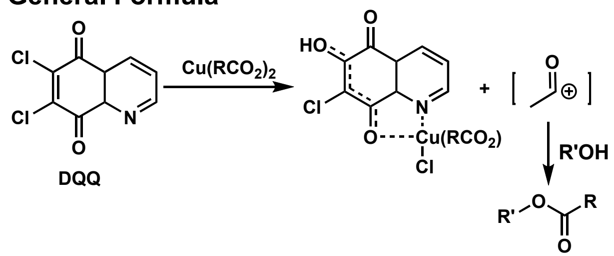
Mechanism



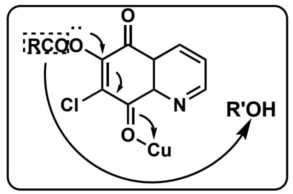
Acylation of Alcohol by DQQ

JACS, 1962, 84, 4904

General Formula



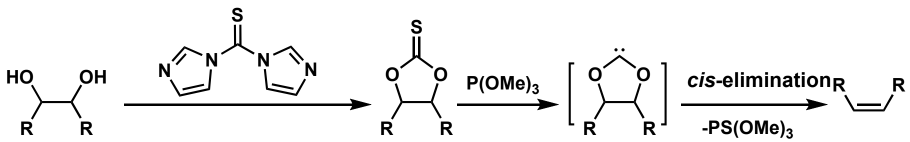
Mechanism

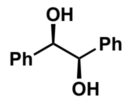
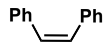
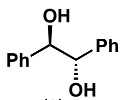
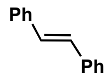
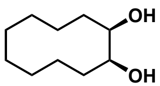
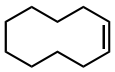
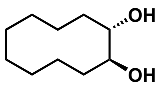
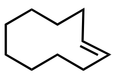


1,2-Diol-*cis*-Elimination

JACS, 1963, 85, 2677
JACS, 1965, 87, 934

General Formula

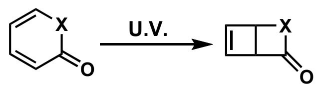


 *meso*		92%
 (±)		87%
		84%
		81%

Isomerization of 2-Pyrone and *N*-methyl-2-pyridone

JACS, 1964, 86, 950

General Formula

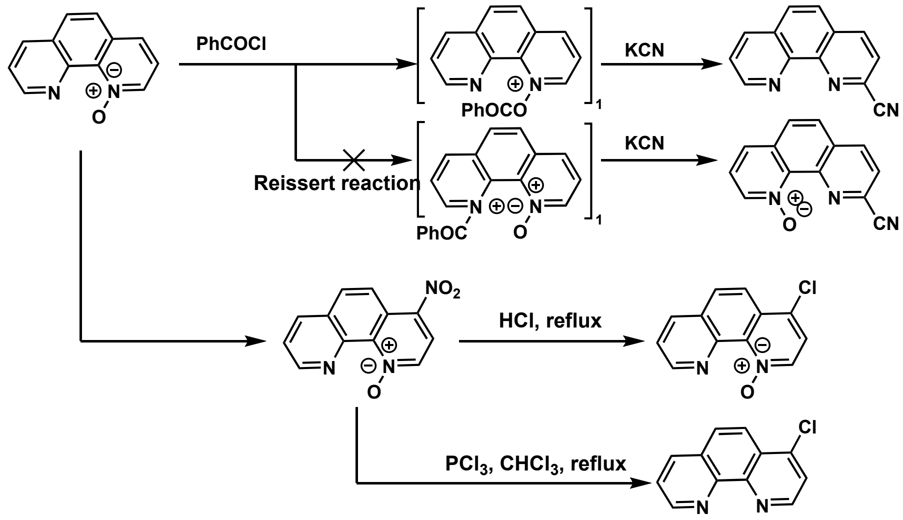


X=O or N-Me

Convertion of 1,10-Phenanthroline *N*-oxide

JOC, 1965, 30, 288

GeneralFormula



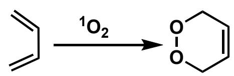
Singlet O_2 Peroxidation

JACS, 1964, 86, 3881

Preparation

$$O_2 \xrightarrow{\text{electrodeless discharge}} {}^1O_2$$

General Formula



Tested Substrates

1) 9,10-disubstituded anthracene:dimethyl, diphenyl rate:Me>Ph>H

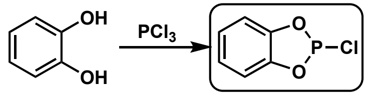
2) reactive 1,3-diene:α-terpinene, 2,5-Di-phenyl-3,4-isobenzofuran

Tips:

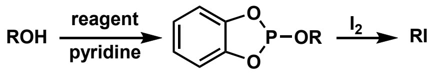
1. Solvent effect is important. Chlorobenzene/bromobenzene/nitrobenzen are better than iodobenzene/anisole/DMSO(reaction rate).
2. Olefins can not be converted into allylic hydroperoxides.

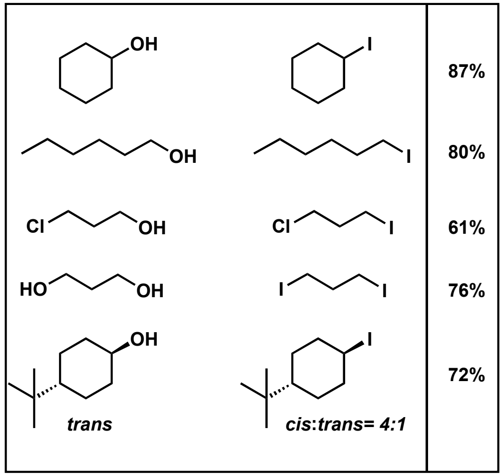
Reagent for Converting Alcohol into Alkyl Iodide

Preparation JOC, 1967, 32, 4160



General Formula

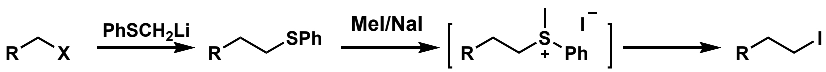




Homologation of Primary Halide

TL, 1968, 9, 5787

General Formula



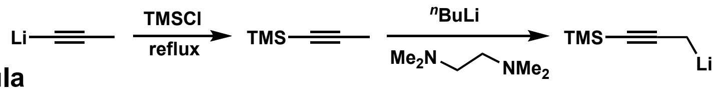
X=Br or I

Lithio-1-substituded Propyne

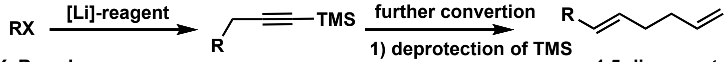
TL, 1968, 9, 5041

1. Lithio-1-TMS-propyne

Preparation



General Formula



X=Br or I

1,5-diene system

Advantages Compared with Allylic Coupling Reagents

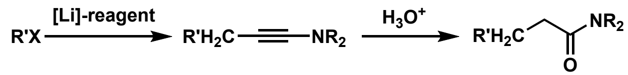
1. TMS served as bulky group and blocked the acidic proton at C_1 making metallation occured at C_3(stereo&regioselectivity)
2. suppressing the formation of allen product(controlling of 1,3-allylic transposition)

2. Lithio-1-propyn amine

JOC, 1970, 35, 3405

Preparation

General Formula

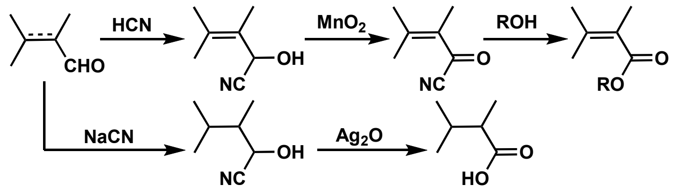


Features:

1. R=bulky (eg. *i*-Pr,)
2. X=I>Br>Cl (N.R)
3: lithium-halogen exchange could be side-reaction

Oxidation of α,β-unsaturated Aldehyde

General Formula JACS, 1968, 90, 5616

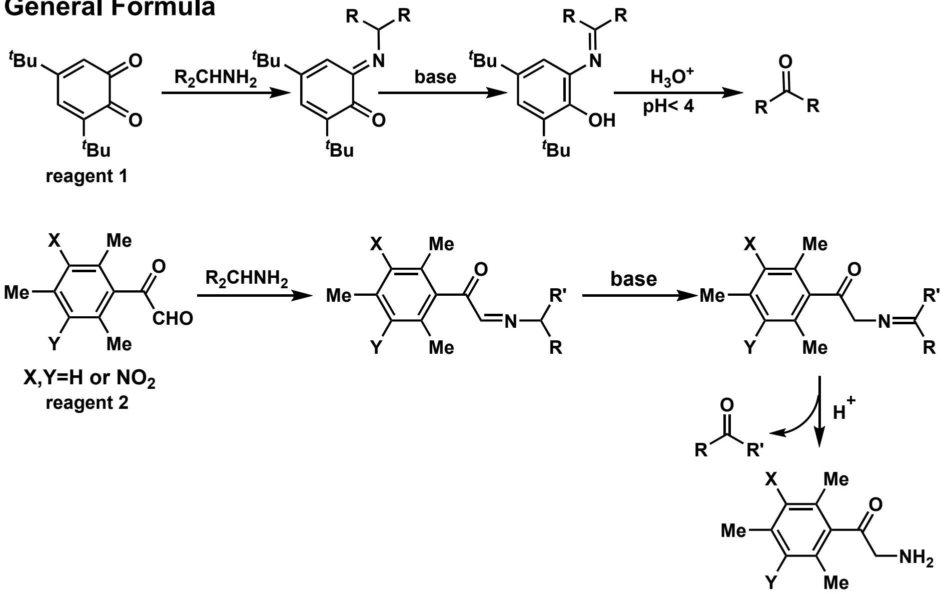


no *cis-trans* isomerization

Oxidation of Primary Amines to Ketones

JACS, 1969, 91, 1429

General Formula

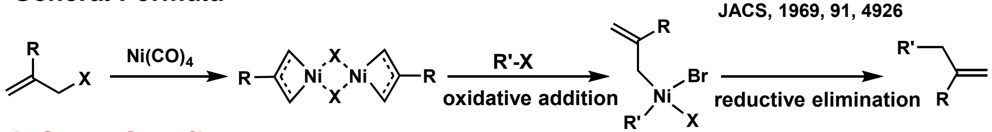


Benzhydrylamine	ketone, 83% - 90%	reagent 1 & reagent 2
α-Phenylethylamine	ketone, 84% - 98%	reagent 1 & reagent 2
2-*exo*-Bornylamine	ketone, 69% - 92%	reagent 1 & reagent 2
Cyclopentylamine	ketone, 75% - 93%	reagent 1 & reagent 2
Cyclohexylamine	ketone, 58% - 97%	reagent 1 & reagent 2
Cyclododecylamine	ketone, 75% - 97%	reagent 1 & reagent 2
Benzylamine	aldehyde, 55% - 78%	reagent 2
^{n}Dodecylamine	aldehyde,low yield	reagent 2

Nickel Carbonyl

JACS, 1964, 86, 1641
TL, 1966, 7, 6237
JACS, 1967, 89, 2755
JACS, 1967, 89, 2757
JACS, 1969, 91, 1233
JACS, 1969, 91, 4926

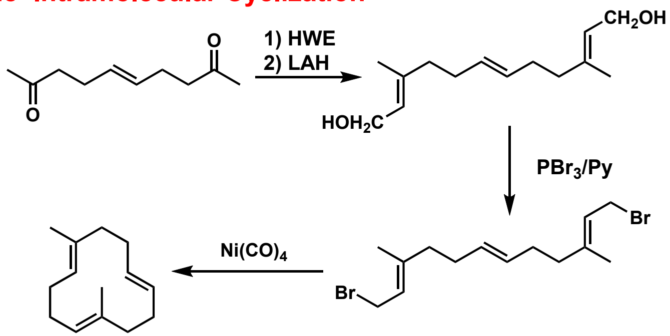
General Formula



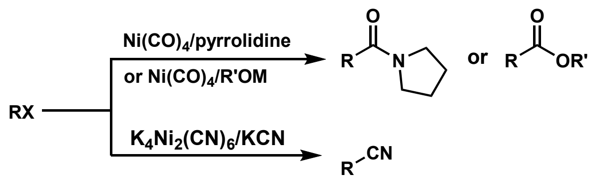
1. Cross Coupling

R=Me, CO_2Et, H
X=Cl, Br, I

2. Dibromide Intramolecular Cyclization

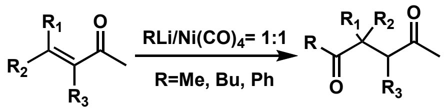


3. Homologation(carbonyl insertion)



X=I>Br>Cl
R=vinyl or phenyl
M=Na,K..

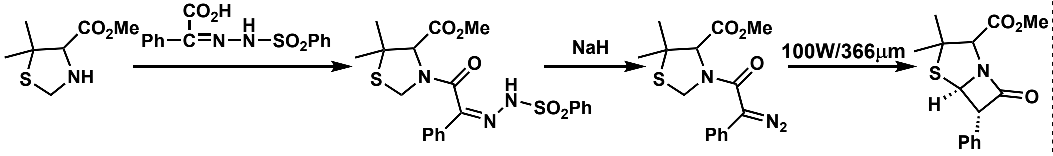
4. 1,4 Addition of Acyl Groups to Conjugated Enones



Tested Substrate: benzalacetone, methyl cinnamate, 2-cyclohexenone, 3-buten-2-one, 3-methyl-3-penten-2-one, mesityl oxide, methyl crotonate

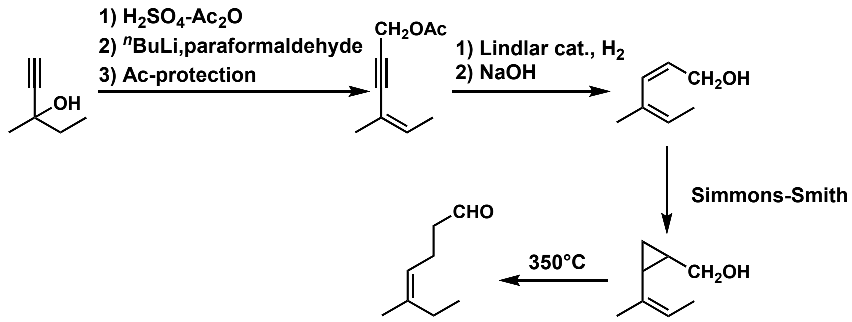
A New Synthetic Approach to the Penicillin

JACS, 1965, 87, 2518



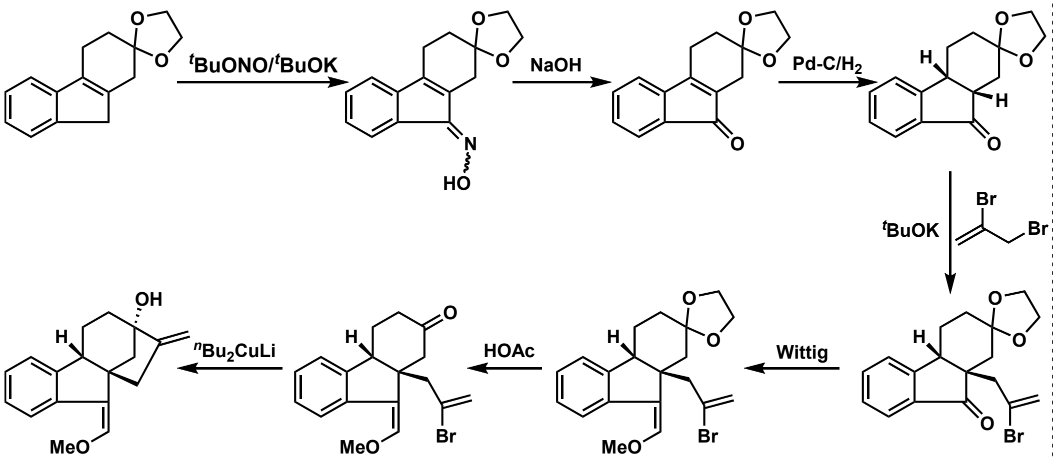
Trisubstituted Olefin Synthesis

JACS, 1970, 92, 6635



Route to the Gibberellic Acids Skeleton

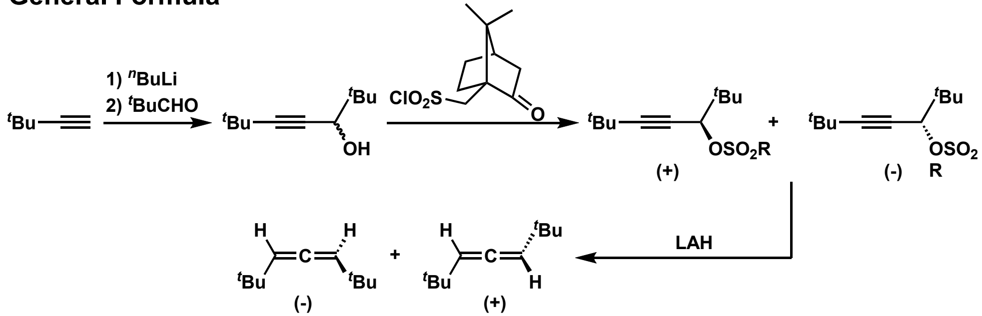
JACS, 1970, 92, 396



Synthesis of Optically Active Allene

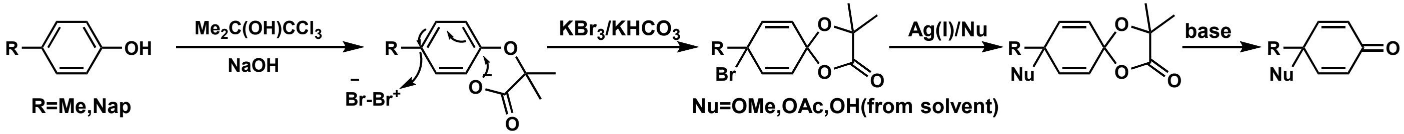
TL, 1969, 10, 313

General Formula



Conversion of Phenoxy Grouping into Cyclic Polyfunctional System

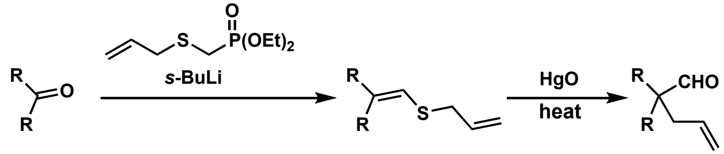
JACS, 1969, 91, 4782



Spiro Annulation of a Carbonyl Group

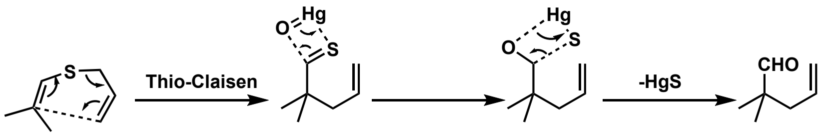
General Formula

JACS, 1970, 92, 5522



cyclohexanone	83%	82%
cyclooctanone	19%	72%
cyclododecanone	54%	74%
fluorenone	81%	43%
norbornanone	65%	83%
adamantanone	72%	45%
benzaldehyde	83%	39%
camphor	trace	

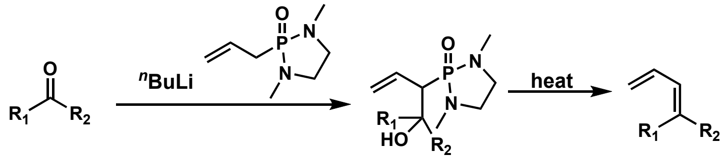
Proposed Mechanism



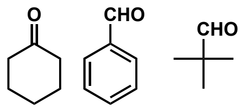
Reagent for Synthesis of 1,1-Disubstituted Diene

General Formula

JOC, 1969, 34, 3053



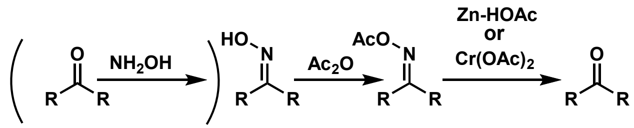
Tested Substrates



Conversion of Ketoximes to Ketones by Chromous Acetate

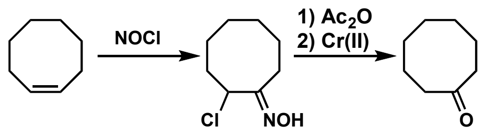
JACS, 1970, 92, 5276

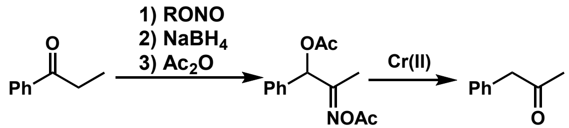
General Formula



cyclohexanone	84%
phenylacetone	74%
camphor	88%
propiophenone	80%
2-methyl-2-cyclohexenone	80%
progesterone 20-monoxime *O*-acetate	84%
1,4-cyclohexanedione mono-hemithioethylene ketal	92%
4-benzoyloxycyclohexanone	95%

Other Application





Dehydroxylation of Allylic and Benzylic Alcohols

JOC, 1969, 34, 3667

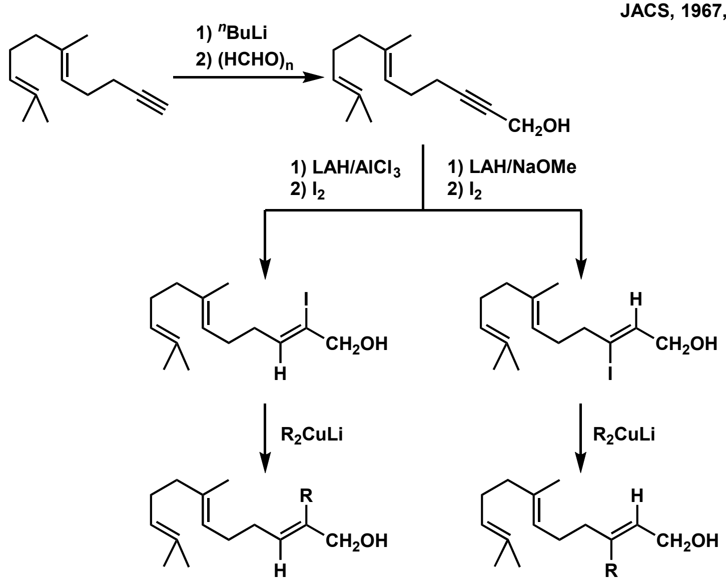
$ROH \xrightarrow{SO_3 \cdot Py} RO\overset{-}{S}O_3C_5H_5\overset{+}{N}H \xrightarrow{LAH} RH$

geraniol	98%
farnesol	95%
benzyl alcohol	75%
indanol	64%

features: no *cis-trans* isomerization and allylic transposition were observed

Stereospecific Synthesis of Trisubstituted Olefins

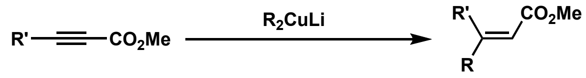
JACS, 1967, 89, 4245



Organocopper Reagent

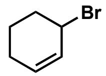
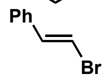
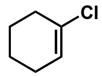
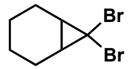
JACS, 1967, 89, 3911
JACS, 1968, 90, 5615
JACS, 1969, 91, 1851
JACS, 1970, 92, 395
TL, 1970, 11, 315

General Formula



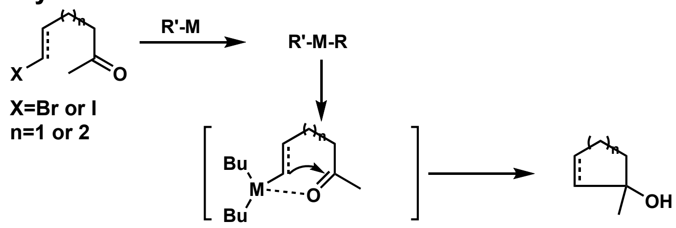
Features:

1. *cis* addition when reacts in THF at -80°C while a mixture of *cis*/*trans* product was formed in Et_2O
2. when equivalent of [Cu] is less than 0.5 eq. of [Li], 1,2-addition will dominate.
3. when R=Me, coppor-halogen exchange will become a serious side reaction.
4. carboxylic acid and amide are tolerated

$C_{10}H_{21}I$	80%
$C_7H_{15}Cl$	75%
	60%
	65%
	60%
	60%
$I(CH_2)_{10}CO_2H$	76%
$I(CH_2)_{10}CON(Me)Ph$	82%
PhI	75%

Other metal ion(Manganese\cobalt) were also tested, leading to a unsatisfactory resluts

Intramolecular Cyclization



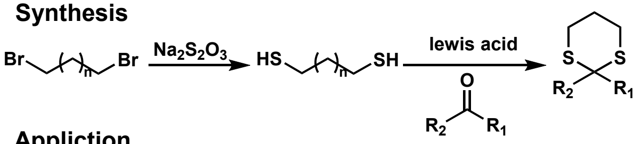
Bu_2CuLi ⇨	C_{sp2} halides
$NiTPP^{2-}$ ⇨	C_{sp3} halides

nickel tetraphenylporphine $\xrightarrow{Li\text{-}Nap}$ $NiTPP^{2-}$

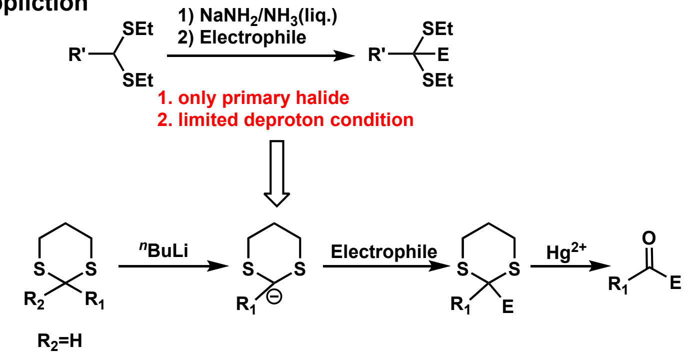
Sulfur Chemistry

1. 1,3-Dithiane

Synthesis

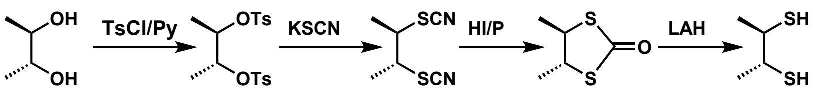


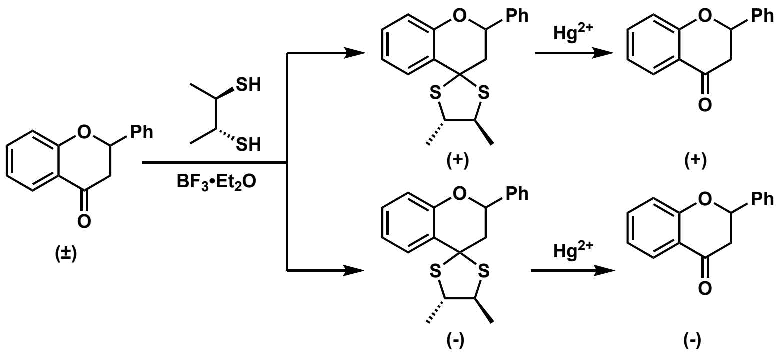
Application



Electrophile=aldehyde, ketone, alkyl halide, epoxide,TMSCl chloroformate, DMF, CO_2....

Resolution Reagent: L(+)-2,3-Butanedithiol

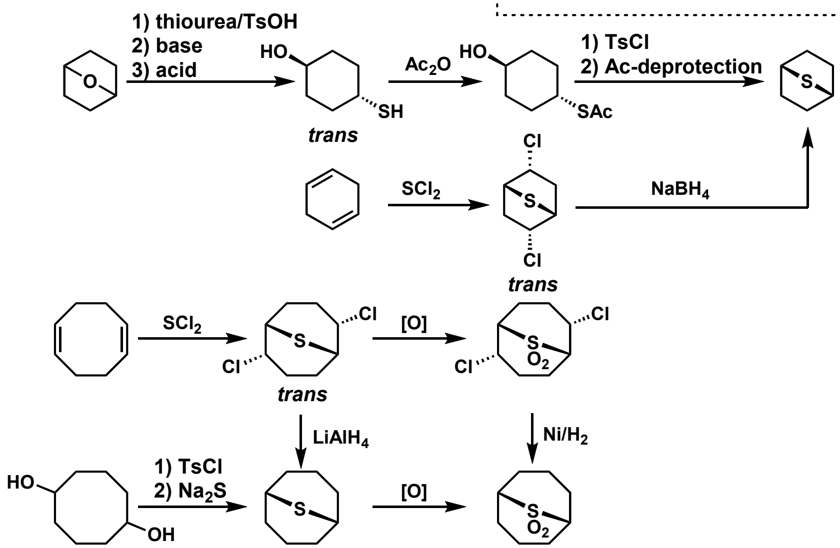




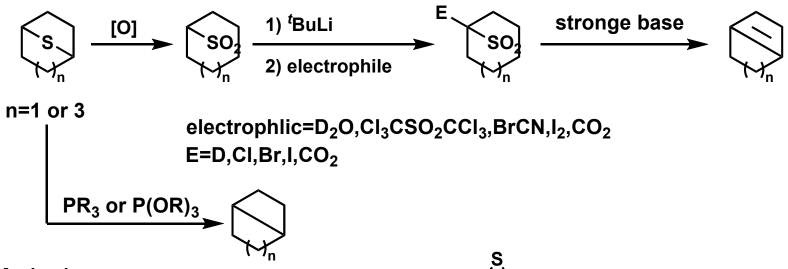
2. Sulfur-Bridged Carbocycle Synthesis

JACS, 1962, 84, 866
JACS, 1962, 84, 867
JACS, 1962, 84, 2938
JACS, 1962, 84, 3782
JOC, 1963, 28, 254
Angew, 1965, 4, 1075
Angew, 1965, 4, 1077
JOC, 1966, 31, 1663
JACS, 1966, 88, 5656
JOC, 1966, 31, 4097
JACS, 1967, 89, 434
TL, 1967, 8, 2325
JOC, 1968, 33, 298
JACS, 1968, 90, 5548
JACS, 1968, 90, 5553
JOC, 1969, 34, 896
JOC, 1969, 34, 1233
Org Syn, 1970, 50, 72

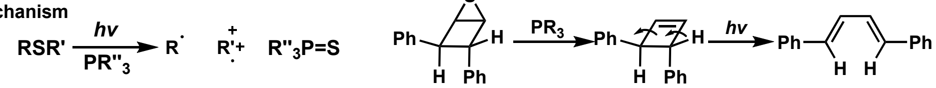
Synthesis



Sulfur Extrusion



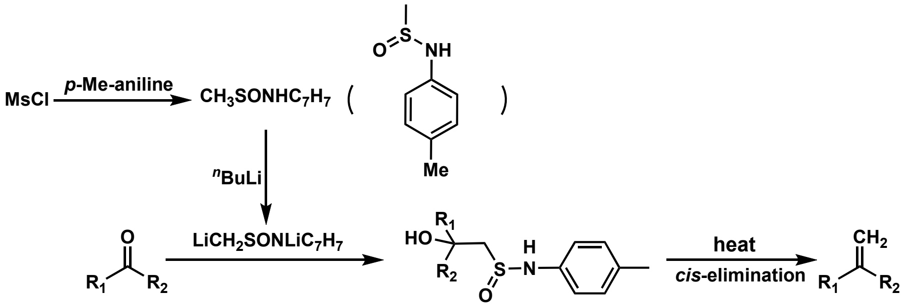
Mechanism



Substrate Scope

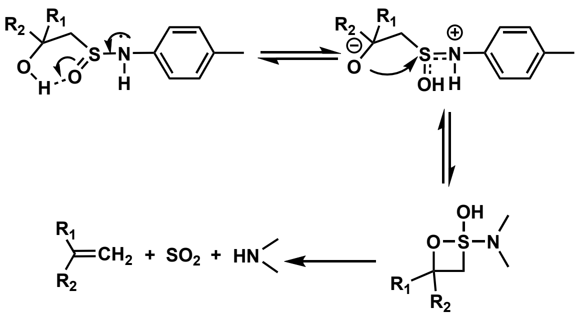
3. Sulfinamide

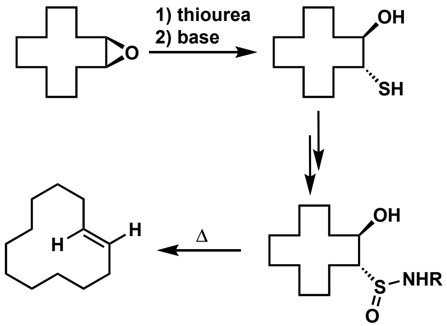
General Formula

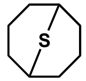
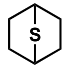
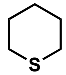


Thermal Elimination of β-Hydroxy Sulfinamide

Mechanism

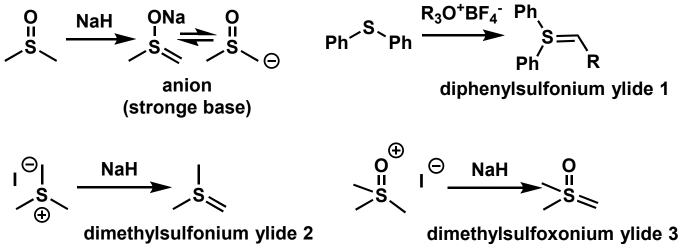




reactant	solvent	yield
	$P(C_8H_{17}O)_3$	47%
	$P(C_8H_{17}O)_3$ $P(Bu)_3$	49% 49%
Bn_2S	$P(OMe)_3$	59%
$(allyl)_2S$	$P(C_8H_{17}O)_3$	38%
(allyl)S(pseudoallyl)	$P(Bu)_3$	68%
	$P(C_8H_{17}O)_3$	trace
	$P(C_8H_{17}O)_3$	complex

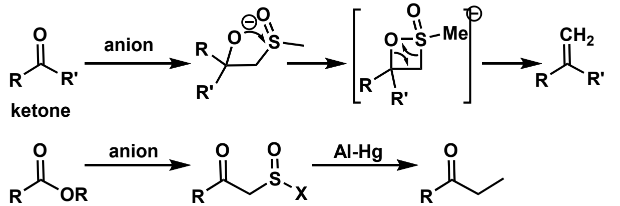
4. Methylsulfinyl Carbanion & Dimethylsulfoxonium Methylide

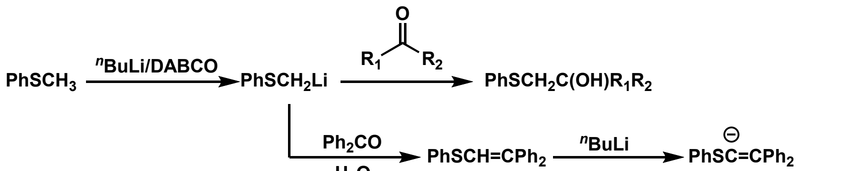
Synthesis



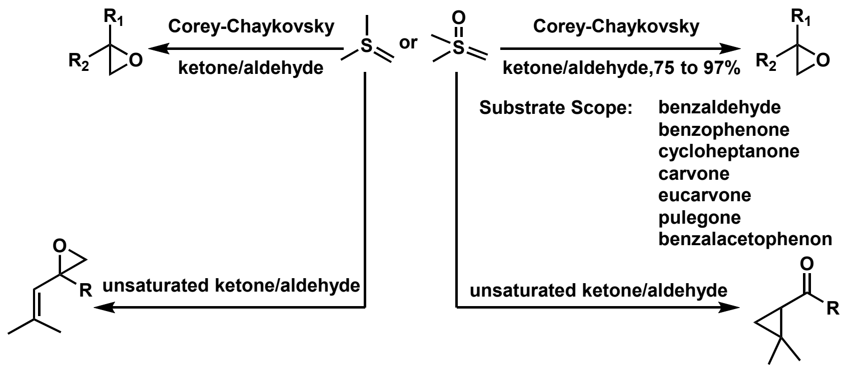
Application

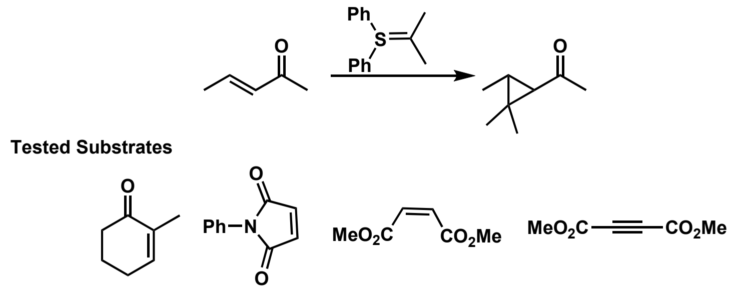
S_N2 Reaction





Corey-Chaykovsky Reaction

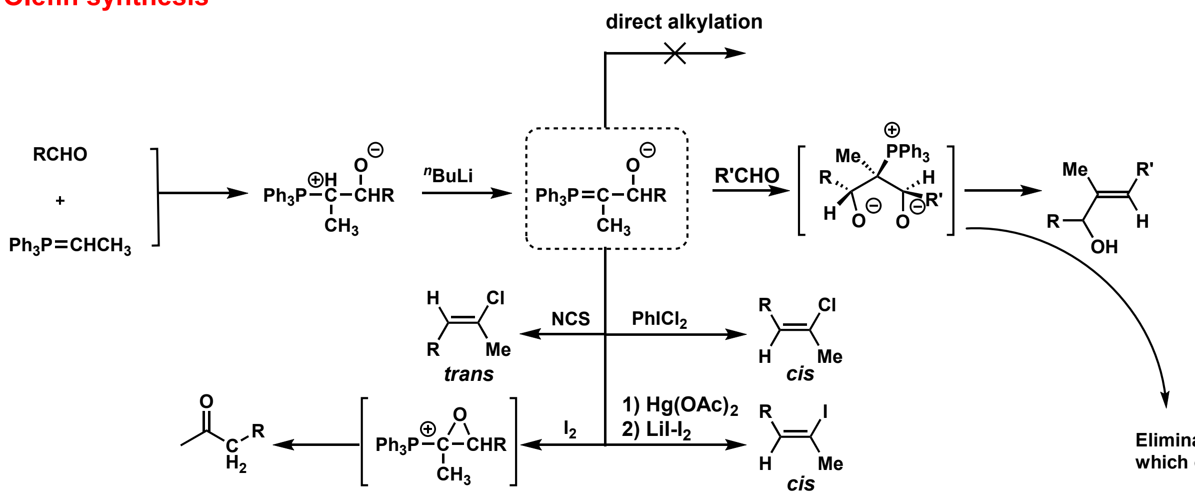




Modification of Wittig-Type Reaction

1. Trisubstituted Olefin synthesis

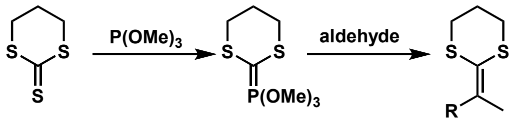
JACS, 1964, 86, 1639
JACS, 1964, 86, 1640
TL, 1967, 8, 3201
JACS, 1966, 88, 5652
JACS, 1966, 88, 5654
JACS, 1966, 88, 5656
JACS, 1968, 90, 6816
JACS, 1970, 92, 226
TL, 1970, 11, 447
JOC, 1970, 35, 777



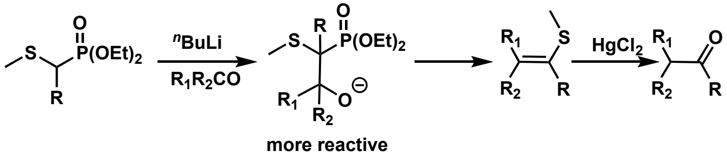
Elimination of dianion involves highly selective loss of oxygen which originated in the **second** aldehyde used in the sequence

2. New Phosphorus Ylide

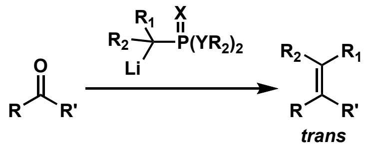
Dithiane-containing Ylied



α-Thio Phosphate Ylied



Heteroatom-containing Phosphate Ylied



Things I didn't cover:

- Biochemistry researches
- Computer-Aided drug design
- Some mechanism researches(including NMR methodologies)