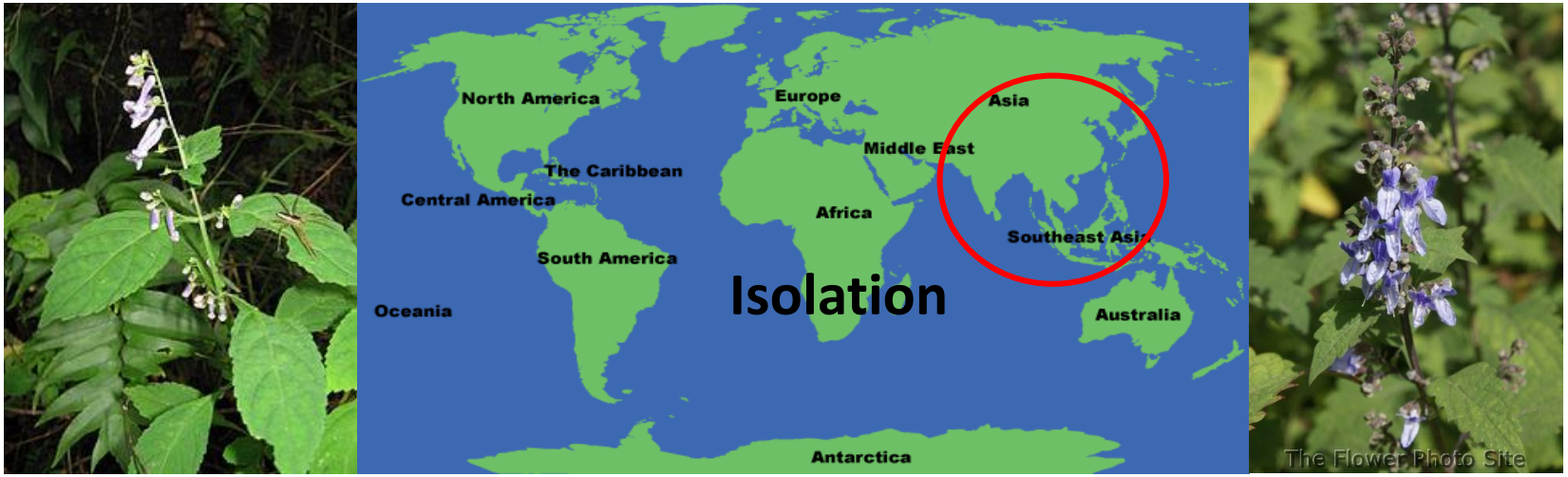
Isodon terpenoids :ent-kauranoids

Literature Talk
11/18/2015
Hee Nam Lim
Prof. Guangbin Dong Group

Major References: Sun, H.-D.; Huang, S.-X.; Han, Q.-B. *Nat. Prod. Rep.* **2006**, *23*, 673-698.
Lazarski, K. E.; Moritz, B. J.; Thomson, R. J. *ACIE* **2014**, *53*, 10588-10599.
Yeonman, J. T. S.'s Thesis, 2014, others in each slide

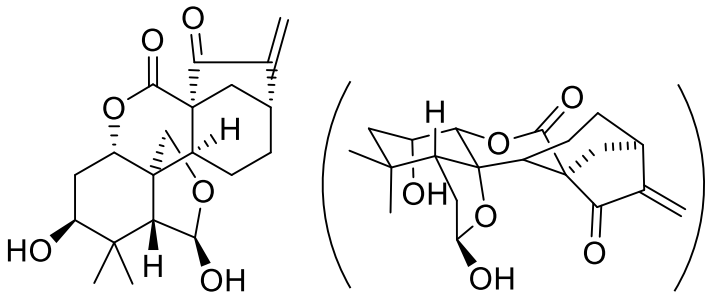


Isodon is a group of flowering plants in the family Lamiaceae

Traditional medicine for treatment of inflammation, gastric, respiratory, cancer, etc.

Yagi in **1910** “enmei-so” - first Isolation of Isodon diterpenoids from a mixture of leaves of *I. japonicus* and *I. trichocarpa*.

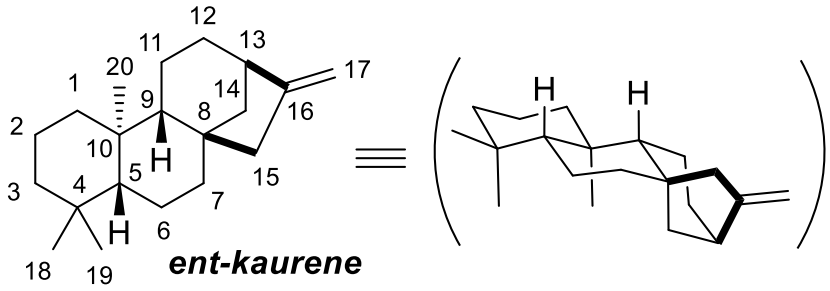
Three Japanese research groups in **1958** isolated enmein - First elucidation of structure by X-ray crystallography in **1966**



enmein

Since first discover, **>600 compounds** are reported in China mostly, Japan, and Korea. Experts in this field – E. Fujita (Japan), H. -D. Sun (China)

Basic Backbone



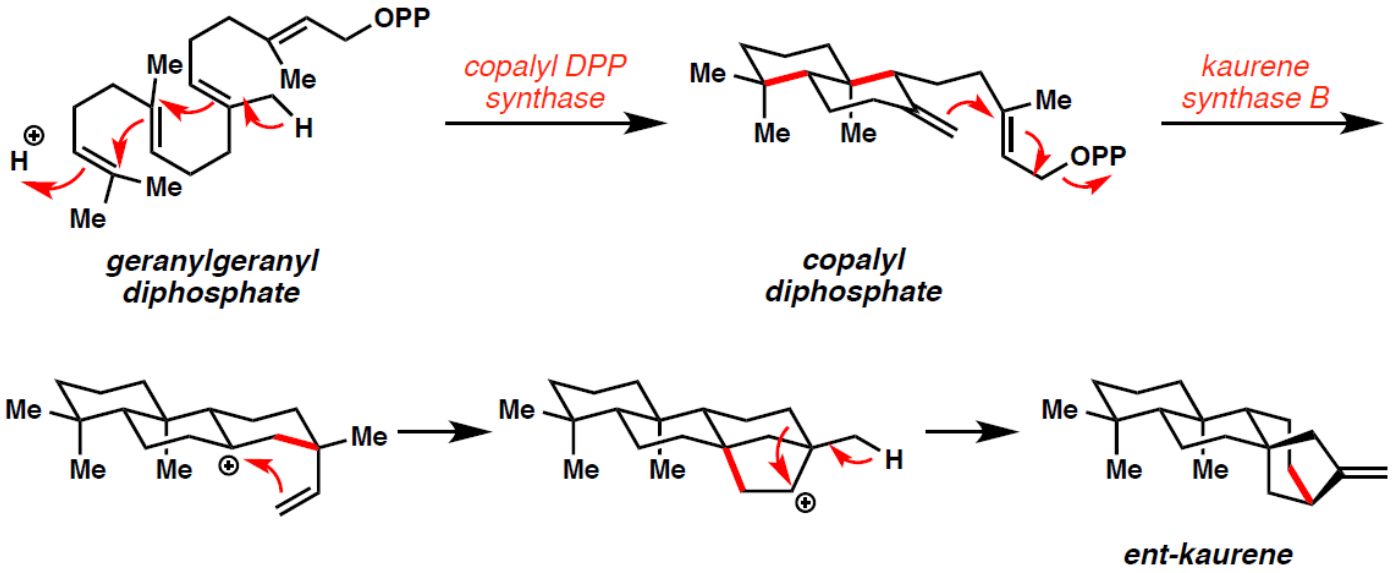
ent-kaurene

>212 compounds (majority) - non-oxidized at C20

C15 – generally functionalized with ketone or alcohol

C5, C9 – almost never functionalized except one case

Proposed biosynthesis



geranylgeranyl diphosphate

copalyl diphosphate

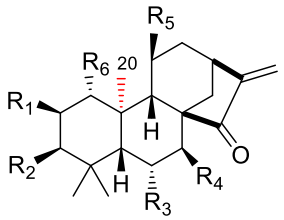
ent-kaurene

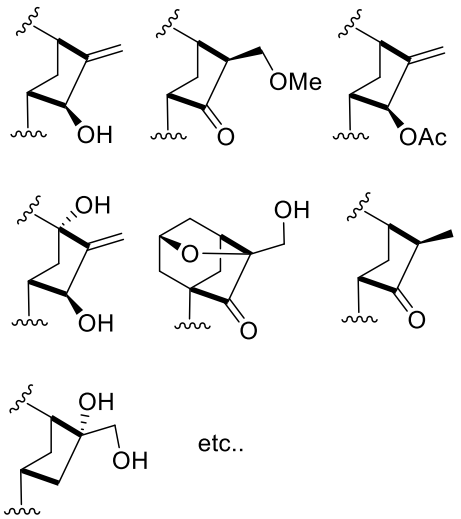
Yeonman, J. T. S.'s Thesis, 2014

Classification by Sun in 2006

three major classes

C-20 non-oxygenated ent-kauranes

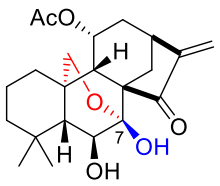




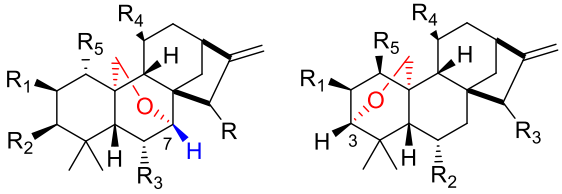
> 212 compounds

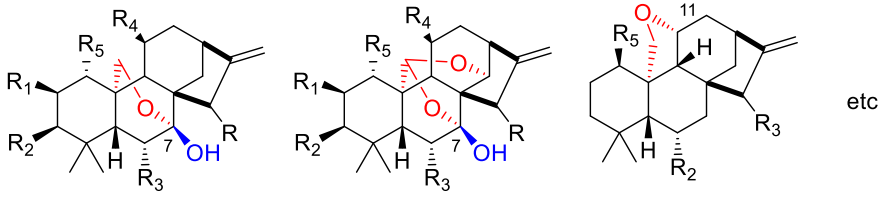
etc..

C-20 oxygenated ent-kauranes



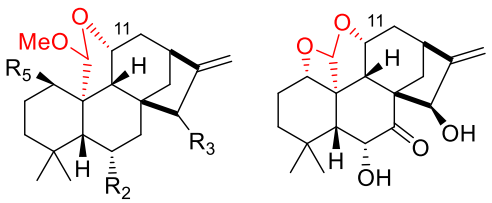
longikaurin E



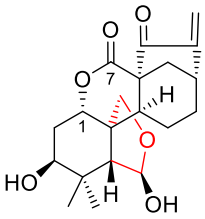


etc

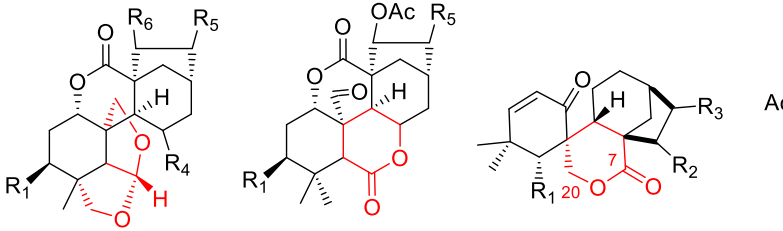
> 200 compounds

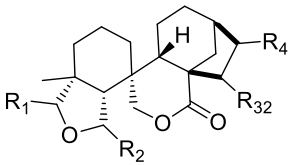


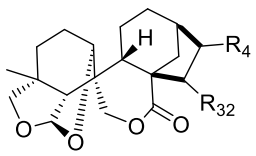
6,7-Seco-ent-kauranes



enmein

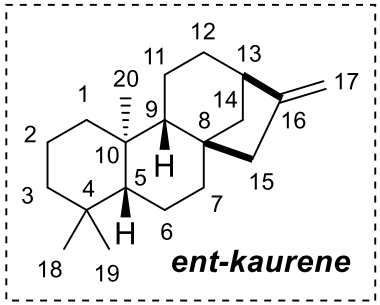






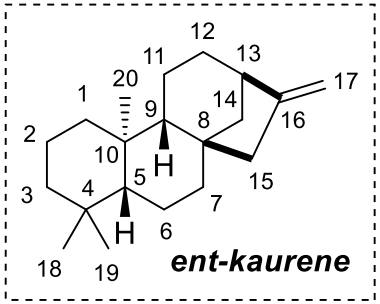
etc

> 105 compounds



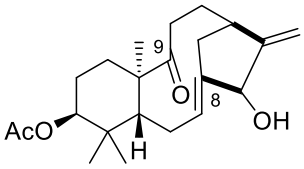
Sun, H.-D.; Huang, S.-X.; Han, Q.-B. *Nat. Prod. Rep.* **2006**, *23*, 673-698.

Classification by Sun in 2006

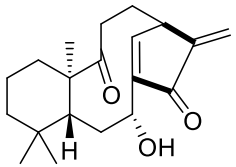


minor classes

8,9-Seco-ent-kauranes

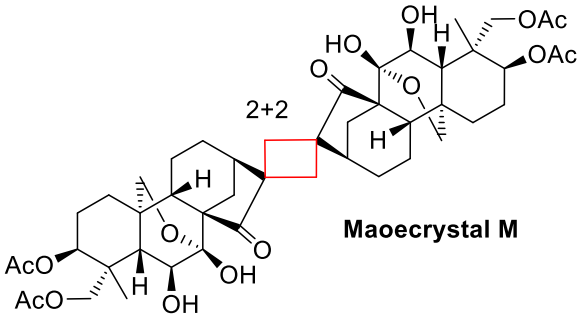


rabdohakusin

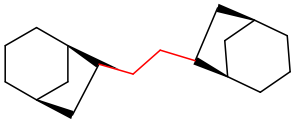


rabdoumbrosanin

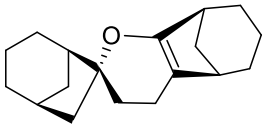
ent-Kaurane dimers



Maoecrystal M



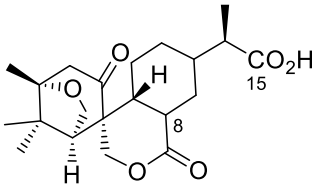
dehydrogenative



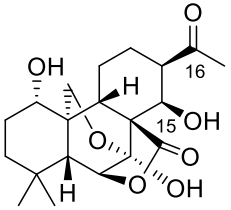
4+2

etc

8,15-or 15,16-Seco-ent-kauranes

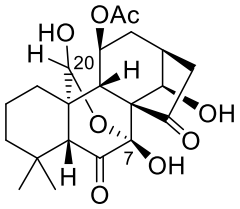


laxiflorin F



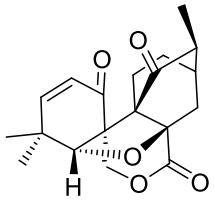
Rubescensin S

7,20-Cyclo-ent-kauranes



only one compound
xerophilusin F
cytotoxic to HL-60 and MKN-28 Human cancer cells

Miscellaneous ent-kauranes

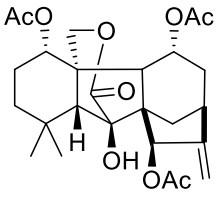


Maoecrystal V

highly selective to HeLa cells (anti-cancer, IC50 = 0.02 ug/mL)

etc...

ent-Gibbrellane

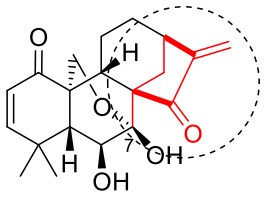


only compound
Rabdoepigibberellolide

Sun, H.-D.; Huang, S.-X.; Han, Q.-B. *Nat. Prod. Rep.* **2006**, *23*, 673-698.

Known Bioactivities: antibacterial, antitumor, anti-inflammatory, anti-feeding agents

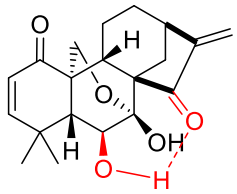
antibacterial



eriocalyxin B

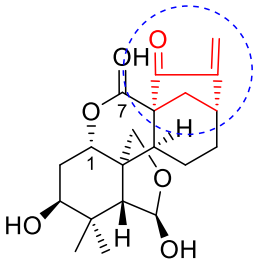
turned out this moiety is crucial
for antibacterial activity

; Michael acceptor of a sulfhydryl enzyme of bacteria



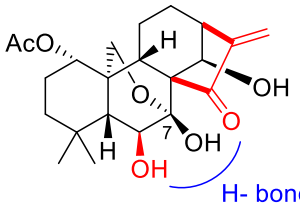
H-bonding is important: beta-OH has stronger H-bonding

antitumor



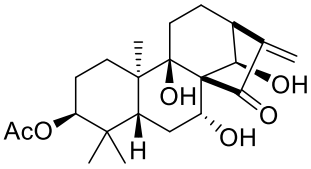
enmein

also important for antitumor activity

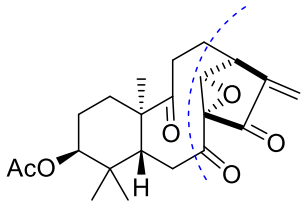


oridonin

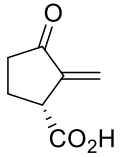
higher activity than enmein, but less toxicity



shikoccidin

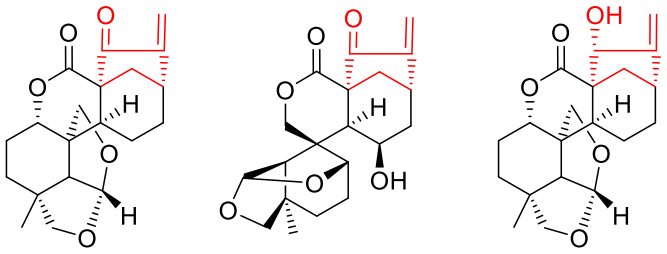


epoxyketoshikoccin



sarkomycin

-anitumor agent developed in 1980 in Japan



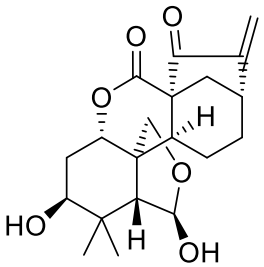
sculponeatin A = **sculponeatin C** > **sculponeatin B**

antitumor activity in vitro and in vivo

Sun, H.-D.; Huang, S.-X.; Han, Q.-B. *Nat. Prod. Rep.* **2006**, *23*, 673-698.

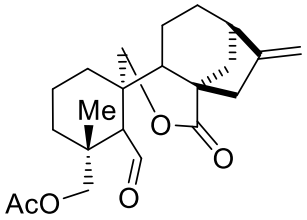
Total synthesis of ent-kauranoids

11 total synthesis papers regarding this family
>13 papers regarding synthetic study



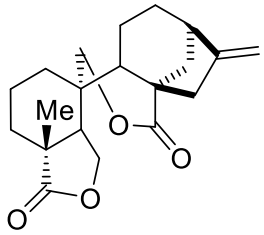
enmein

Fujita-1972



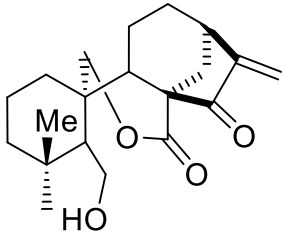
15-desoxy-effusin

Mander-1986



longirabdolactone

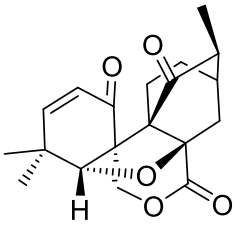
Mander-2003



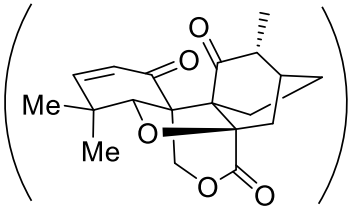
Sculponeatin

Zhai-2013

Thomson-2014



Maoecrystal V

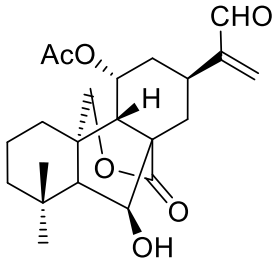


Yang-2010

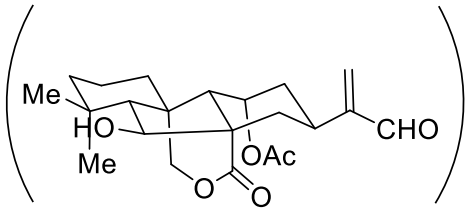
Danishefsky-2012

Zakarian-2013

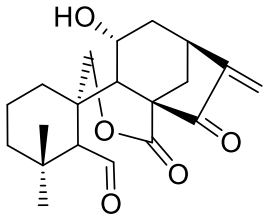
Thomson-2014



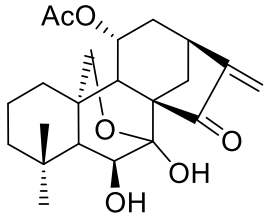
Maoecrystal Z



Reisman-2011



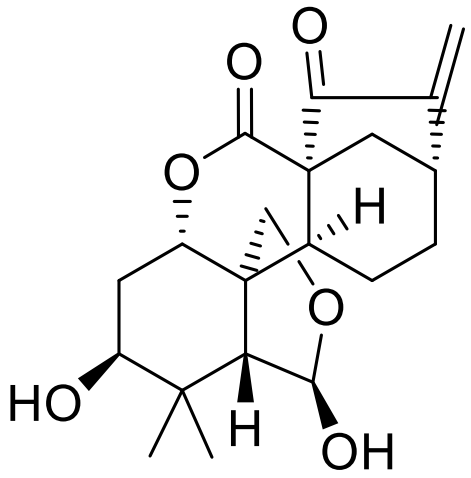
(-)-trichorabdal A



(-)-longikaurin

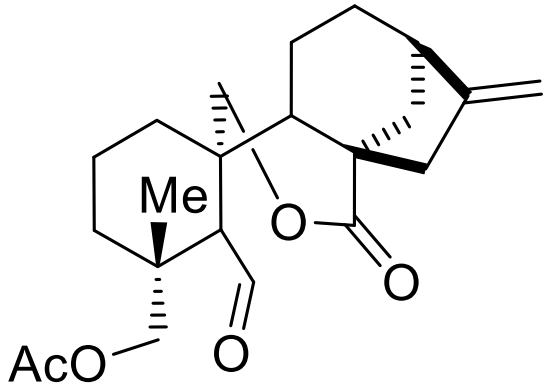
Reisman-2013

Early Synthesis based on step-by-step synthesis with classical chemistry



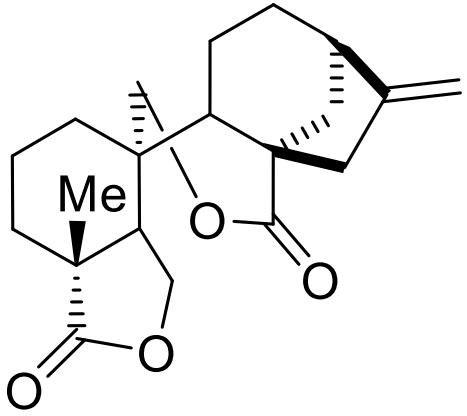
enmein

Fujita-1972



15-desoxy-effusin

Mander-1986

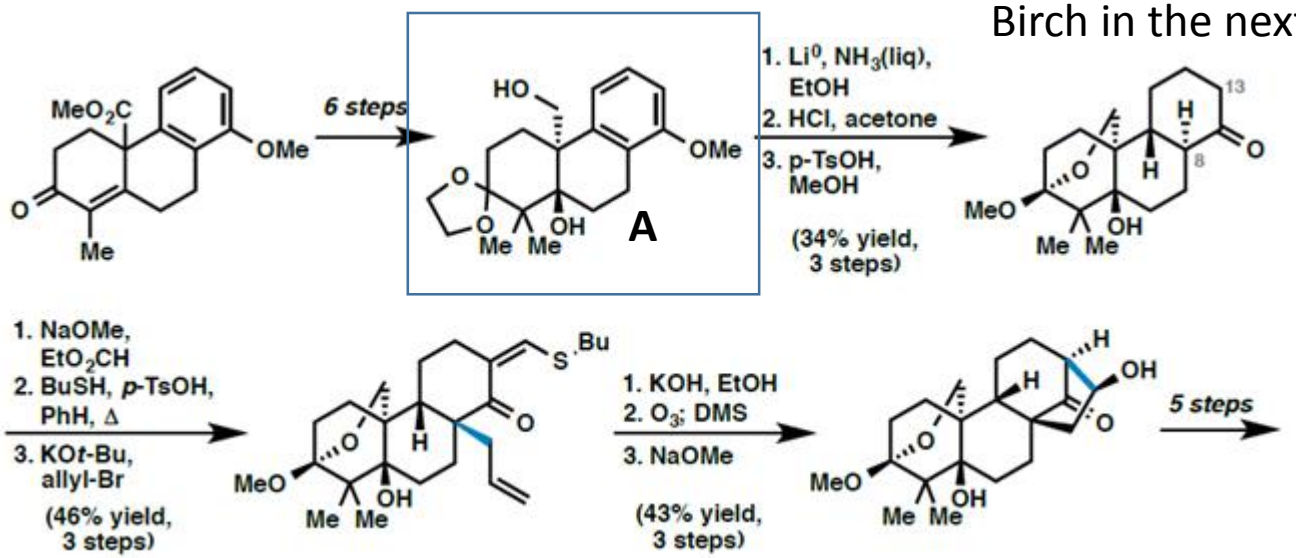


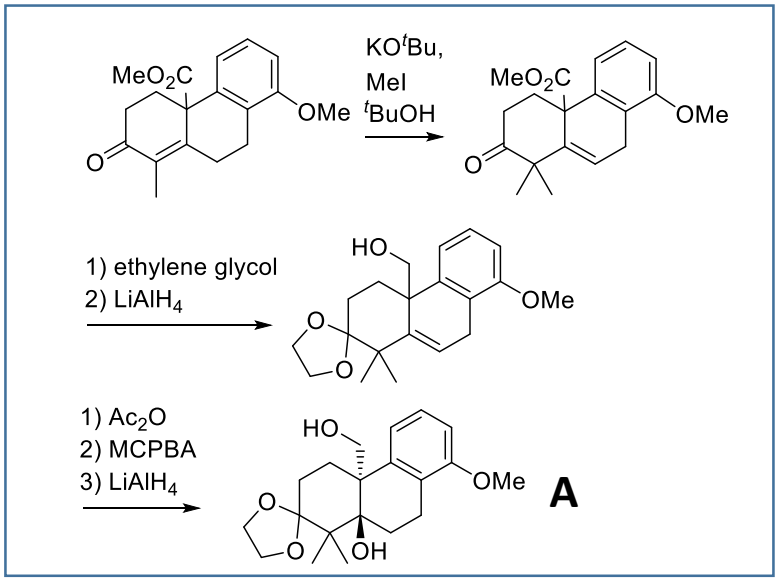
longirabdolactone

Mander-2003

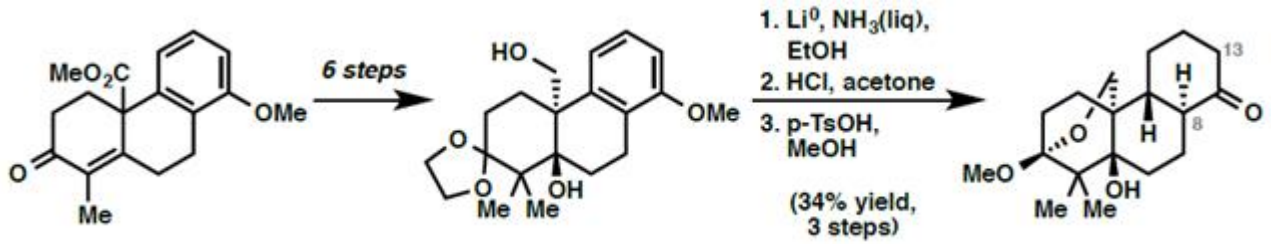
Fujita's Synthesis of Enmein in 1972

Birch in the next page



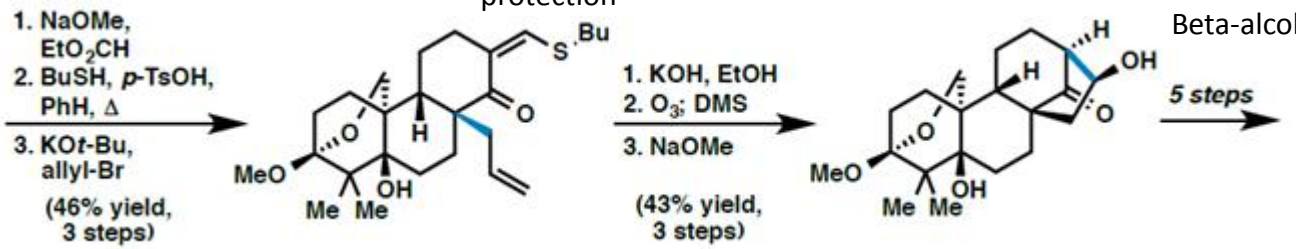


Fujita's Synthesis of Enmein in 1972

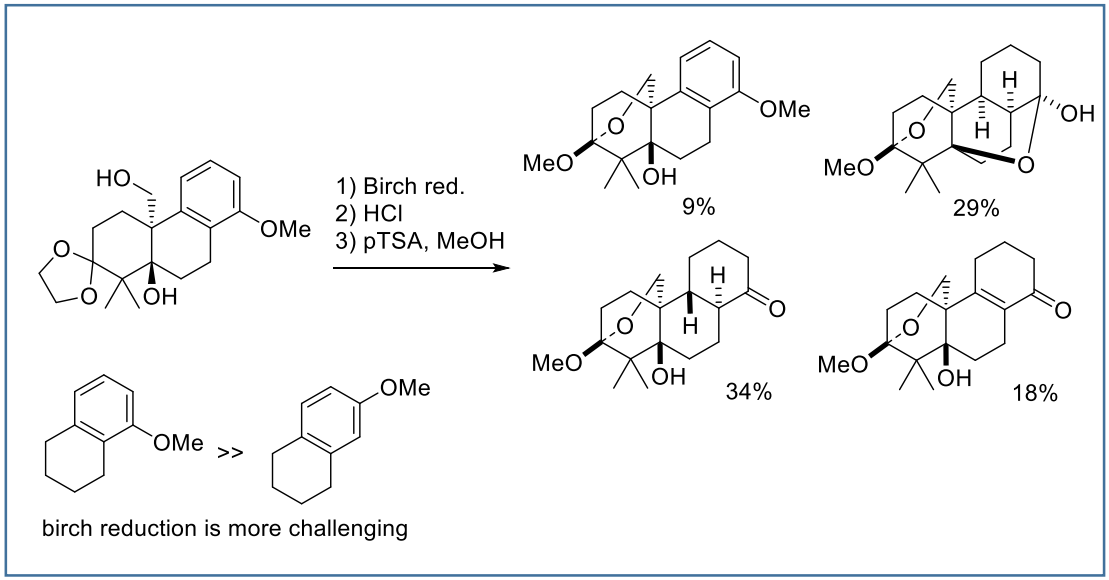


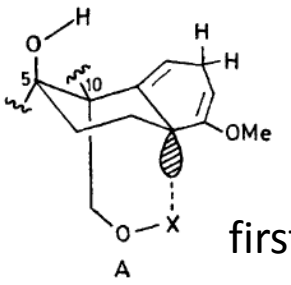
protection

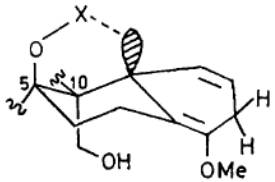
Beta-alcohol: kinetic product



role of alcohols

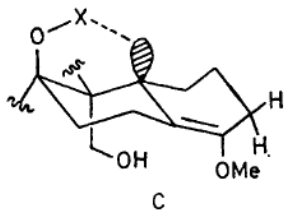






first step

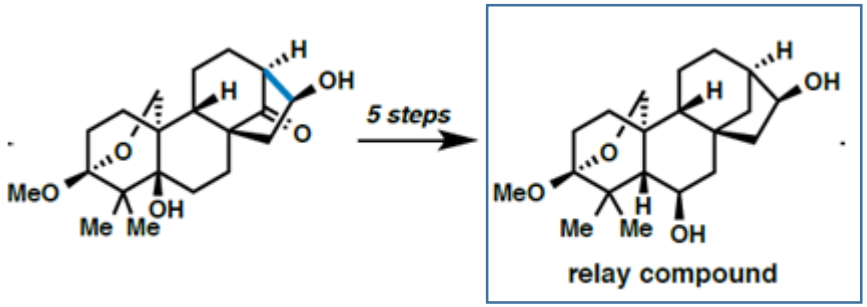
anions



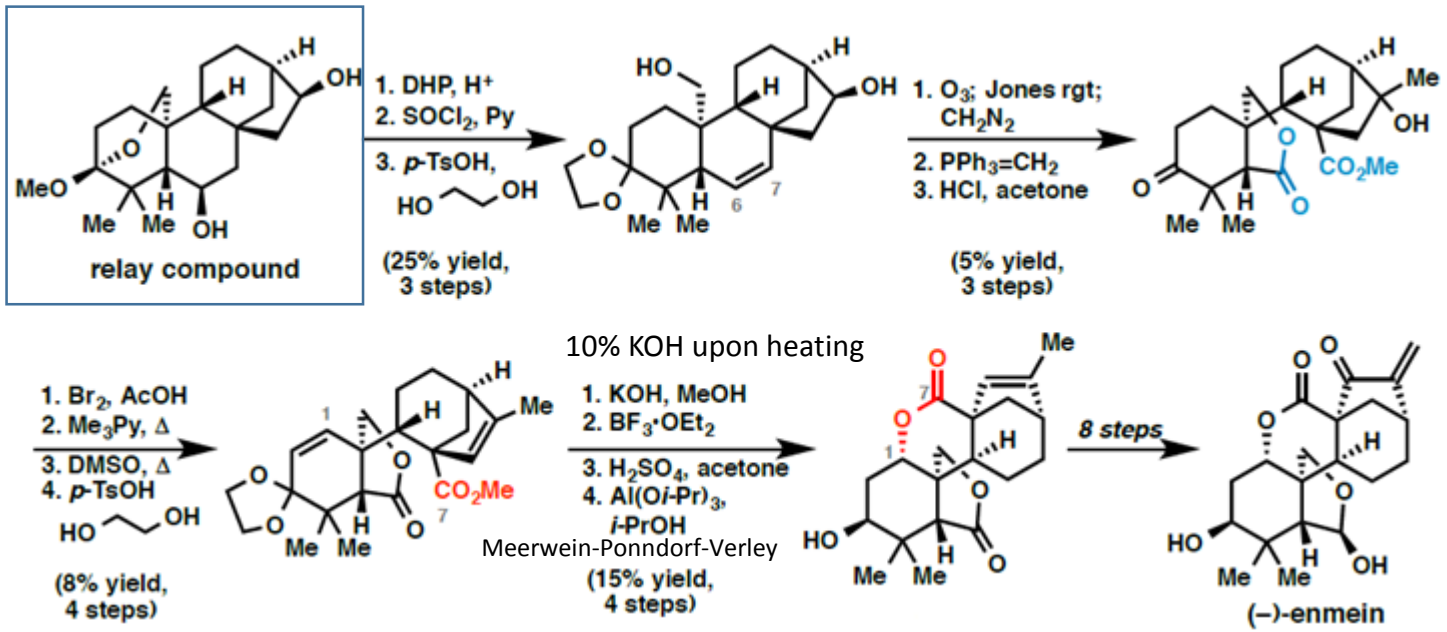
second step

Fujita's Synthesis of Enmein in 1972

obtained by degradation of enmein



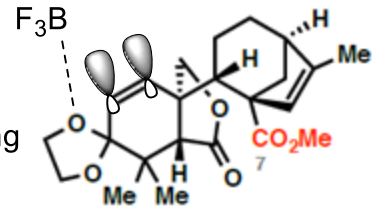
Huang-Minlon reduction/ dehydration w/SOCl2, hydroboration



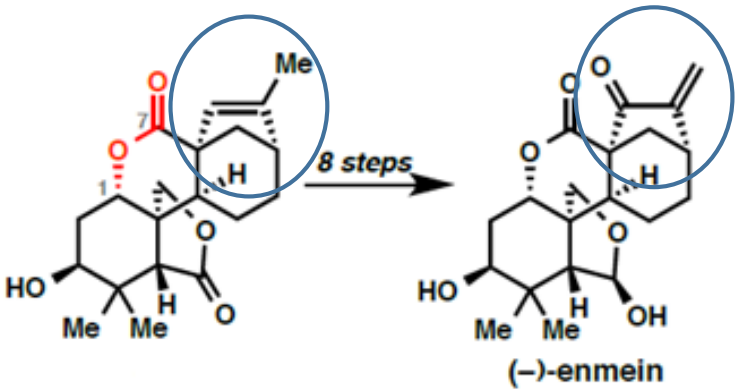
Introduction of double bond
Dehydration by heating

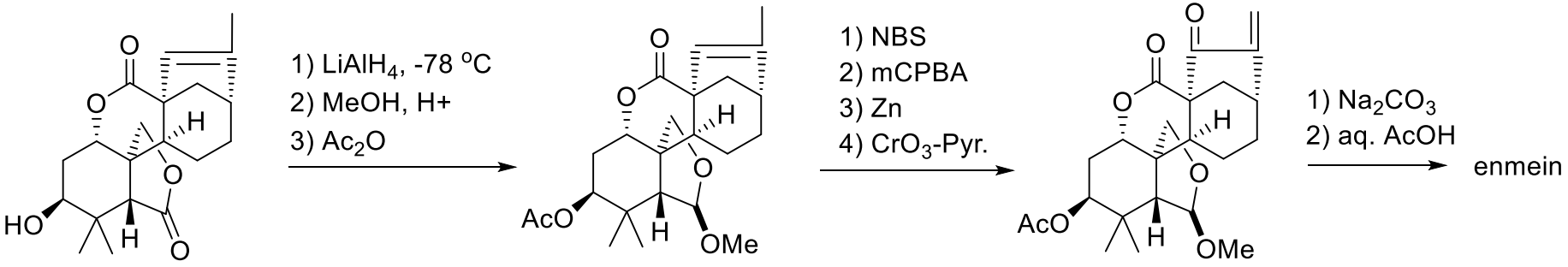
approaching from less hindered site

maximum orbital overlapping



Fujita's Synthesis of Enmein in 1972

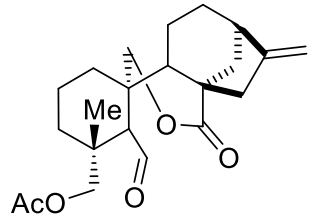




Total 44-steps from highly scalable phenanthrene derivative

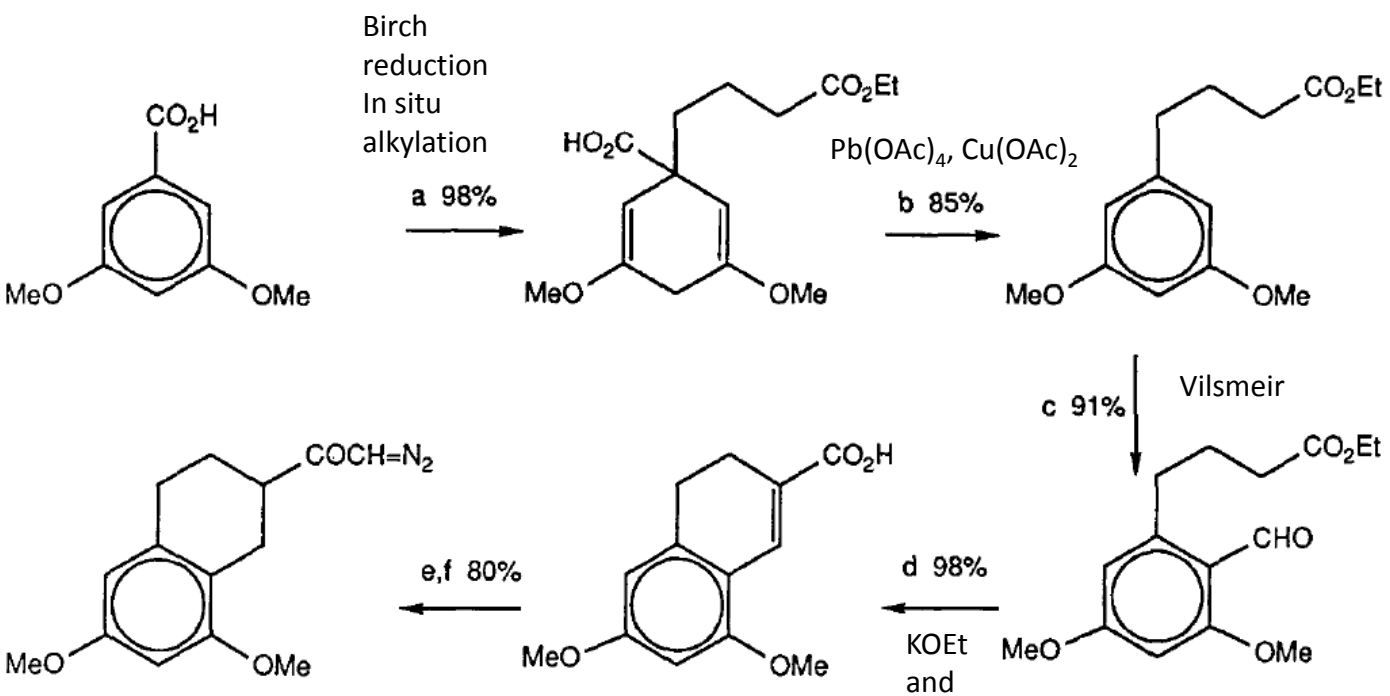
- too many steps – not efficient
- asymmetric synthesis was only achieved by semi-relay-synthesis
- Birch reduction and well studied reaction conditions for high stereoselectivity is still interesting.

Mander's Synthesis of 15-desoxy effusin in 1986



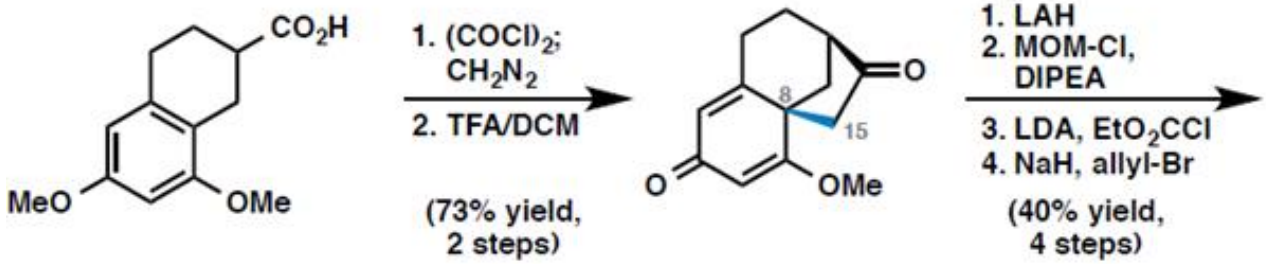
15-desoxy-effusin

Mander-1986

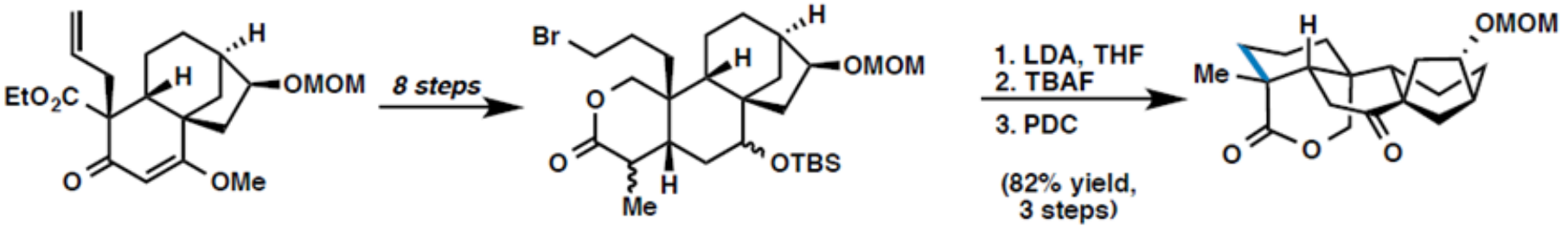


hydrogenation didn't work
reduction w/Na gave saturated carboxylic acid

Mander's Synthesis of 15-desoxy effusin in 1986

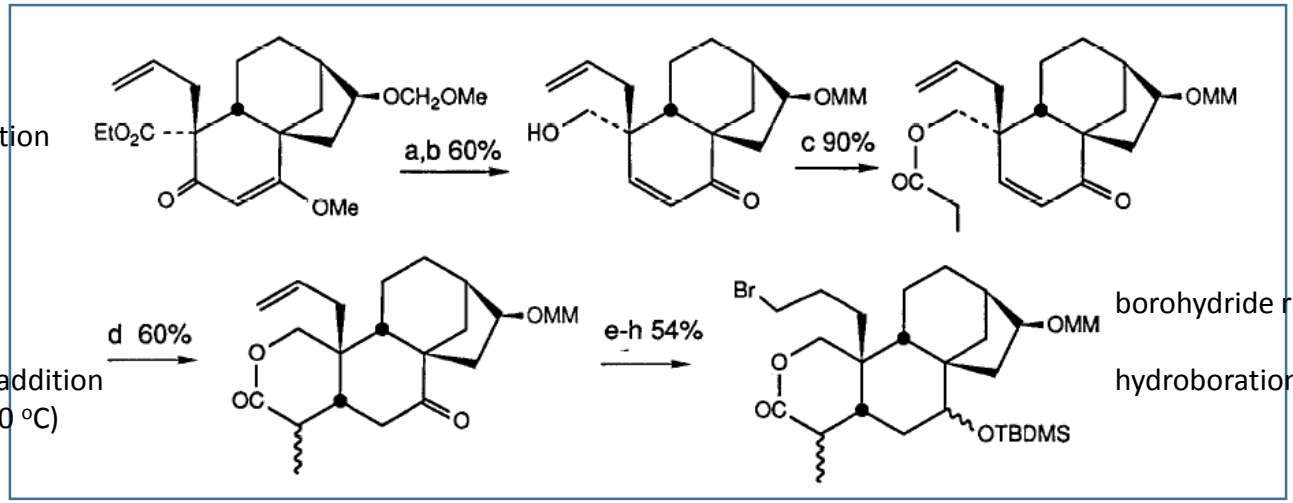


Dearomatized C-C bond formation



Red-Al reduction
hydrolysis

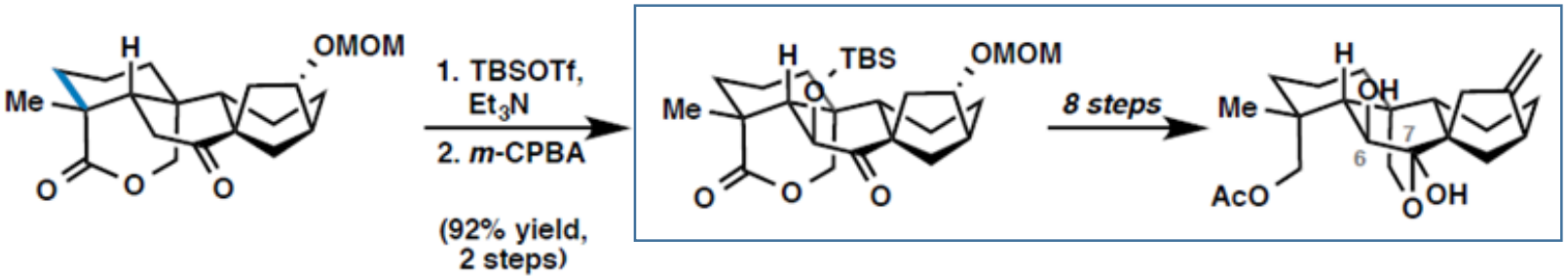
propionate
and Michael addition
(KH, DMF, -30 °C)

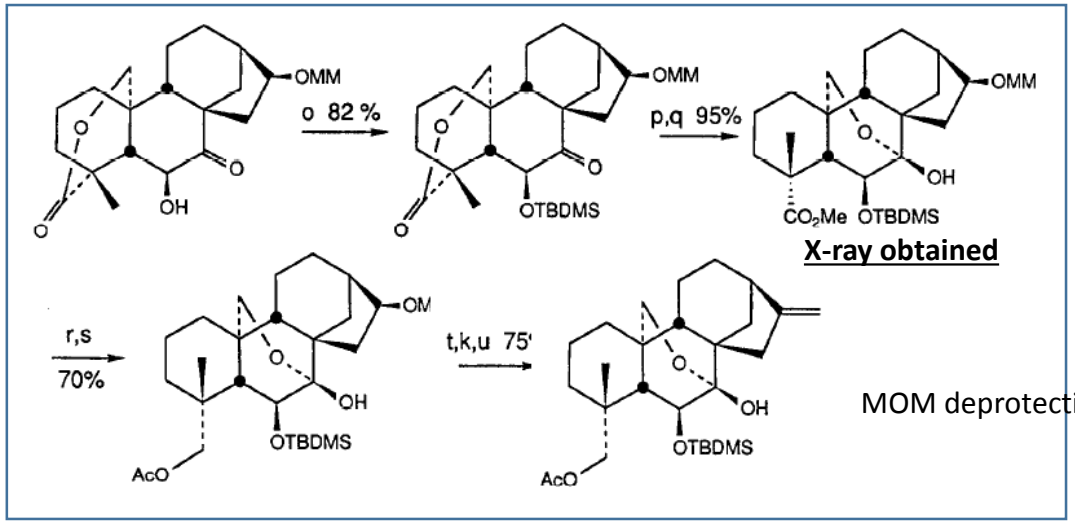


borohydride reduction/protection

hydroboration/ bromination w/ CBr_4

Mander's Synthesis of 15-desoxy effusin in 1986

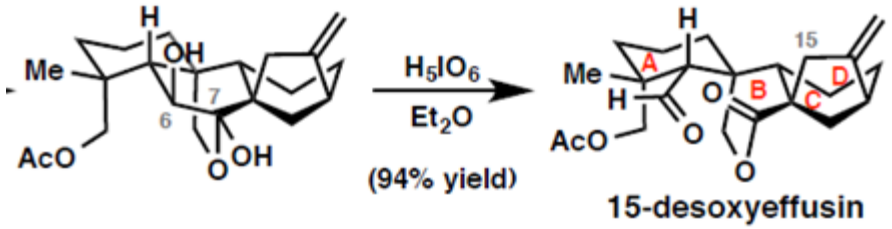




r = LAH
s = Ac_2O

P = KOH, q = CH_2N_2

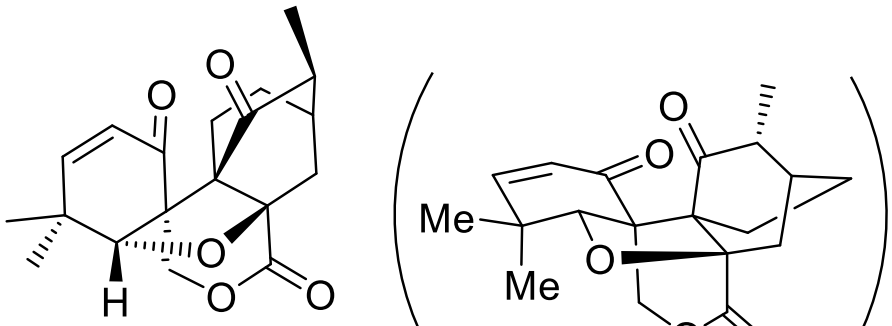
MOM deprotection/oxidation/wittig



oxidative cleavge

Total **29 steps** from dihydronaphthoic acid

New Design and Synthesis: Cascade and Catalysis



Maoecrystal V

- isolated in 2004 by Sun and co-workers from the leaves of a Chinese medicinal herb called Isodon eriocalyx

- IC50 60 nM, selective to HeLa cells

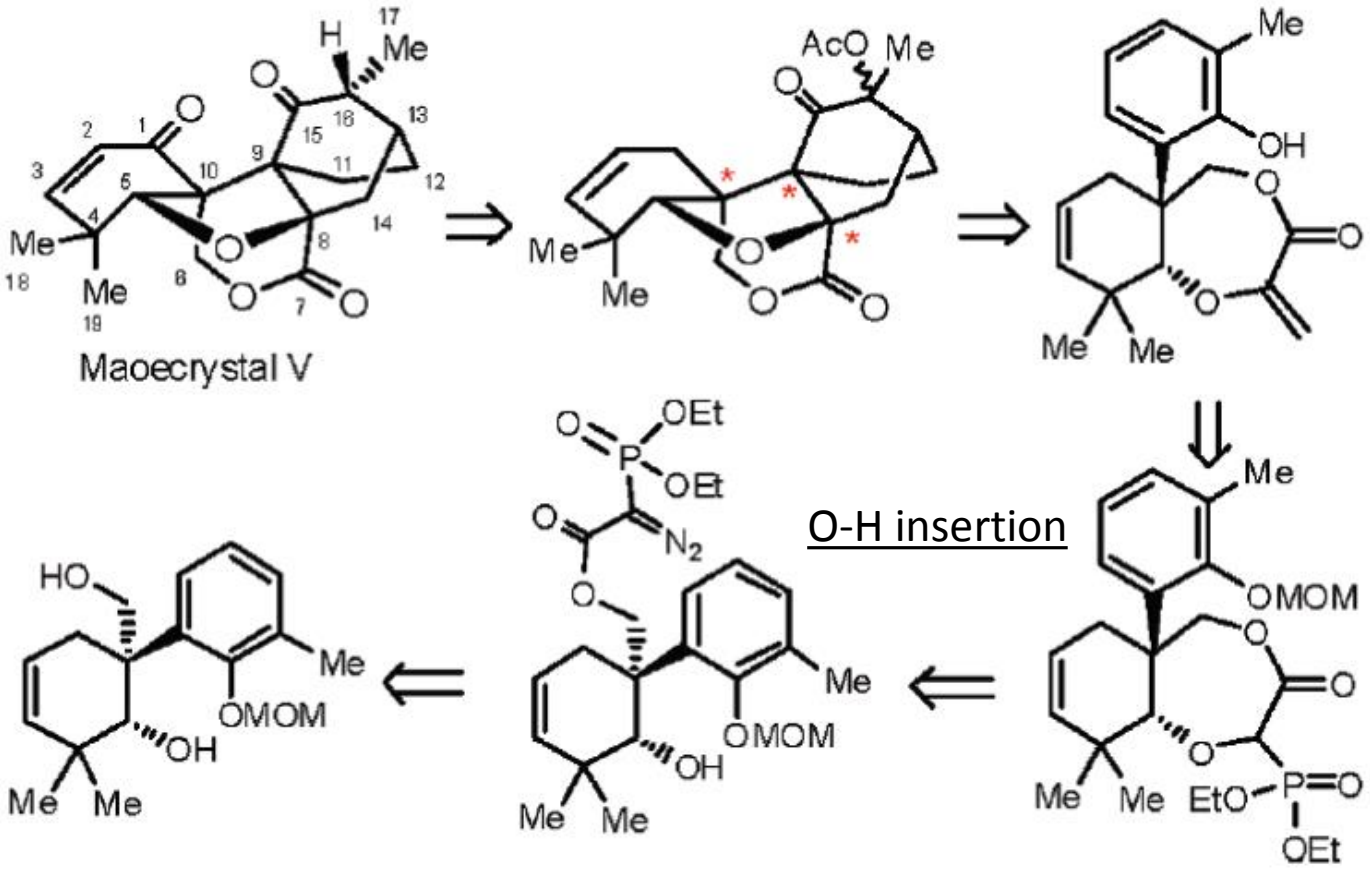
- 6 stereogenic centers (three vicinal quaternary stereocenters)- confirmed by X-ray crystallography.

- pentacyclic framework

First total synthesis: Yang's Synthesis of Maoecrystal V in 2010

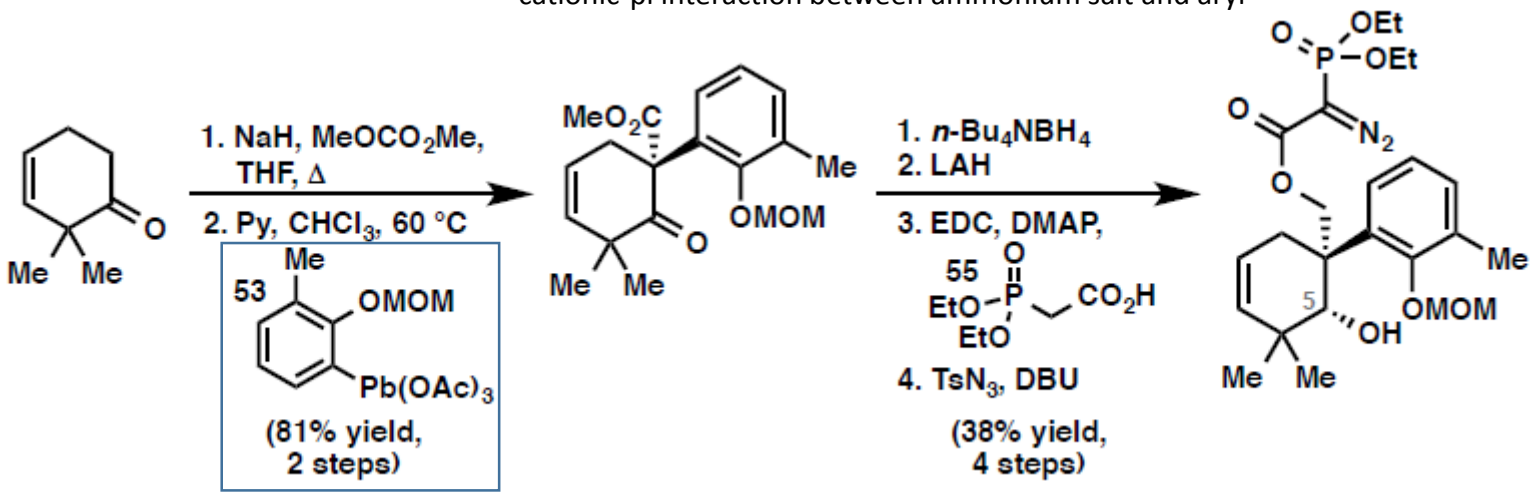
Retrosynthesis

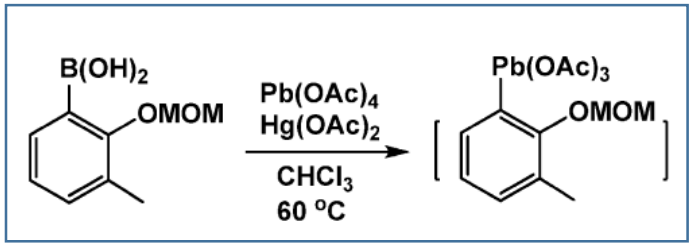
Key: Wessely oxidative dearomatization of a pheol followed by IMDA reaction



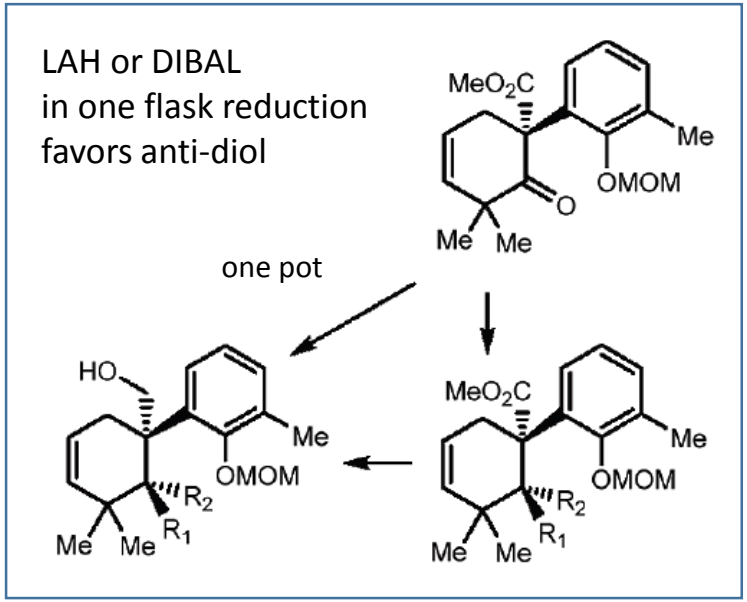
Yang's Synthesis of Maoecrystal V in 2010

other reducing agents – organoboranes,
$NaBH_4$/Lewis acid/ hydrosilane different isomer
cationic-pi interaction between ammonium salt and aryl

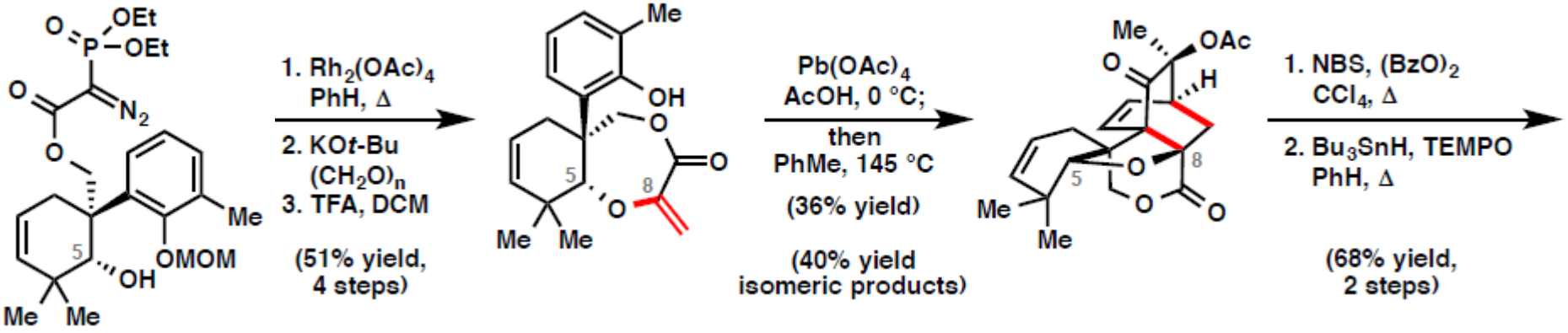


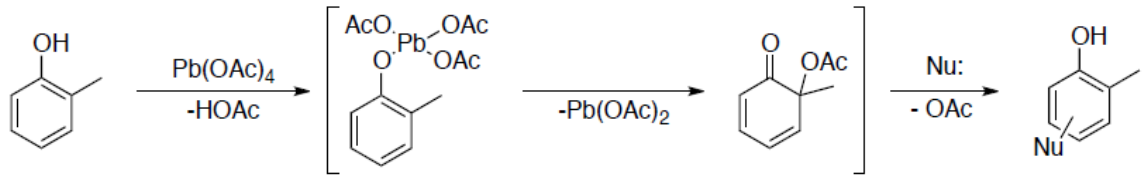


LAH or DIBAL
in one flask reduction
favors anti-diol

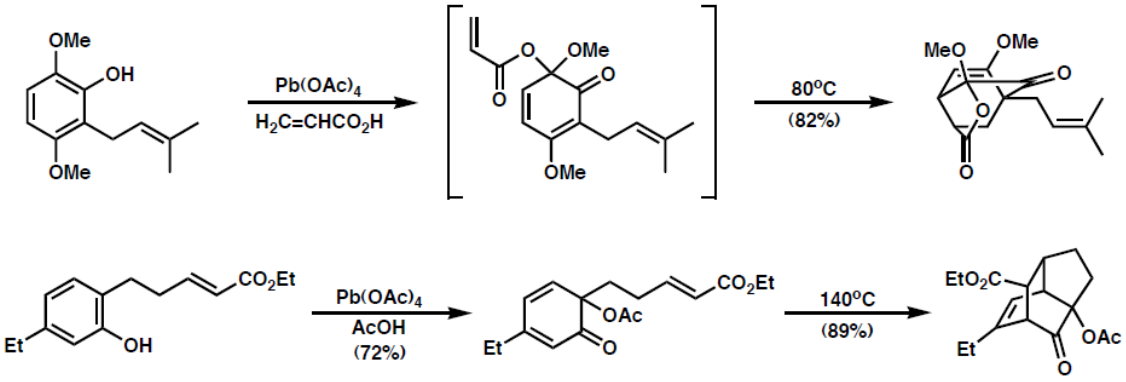


Yang's Synthesis of Maoecrystal V in 2010



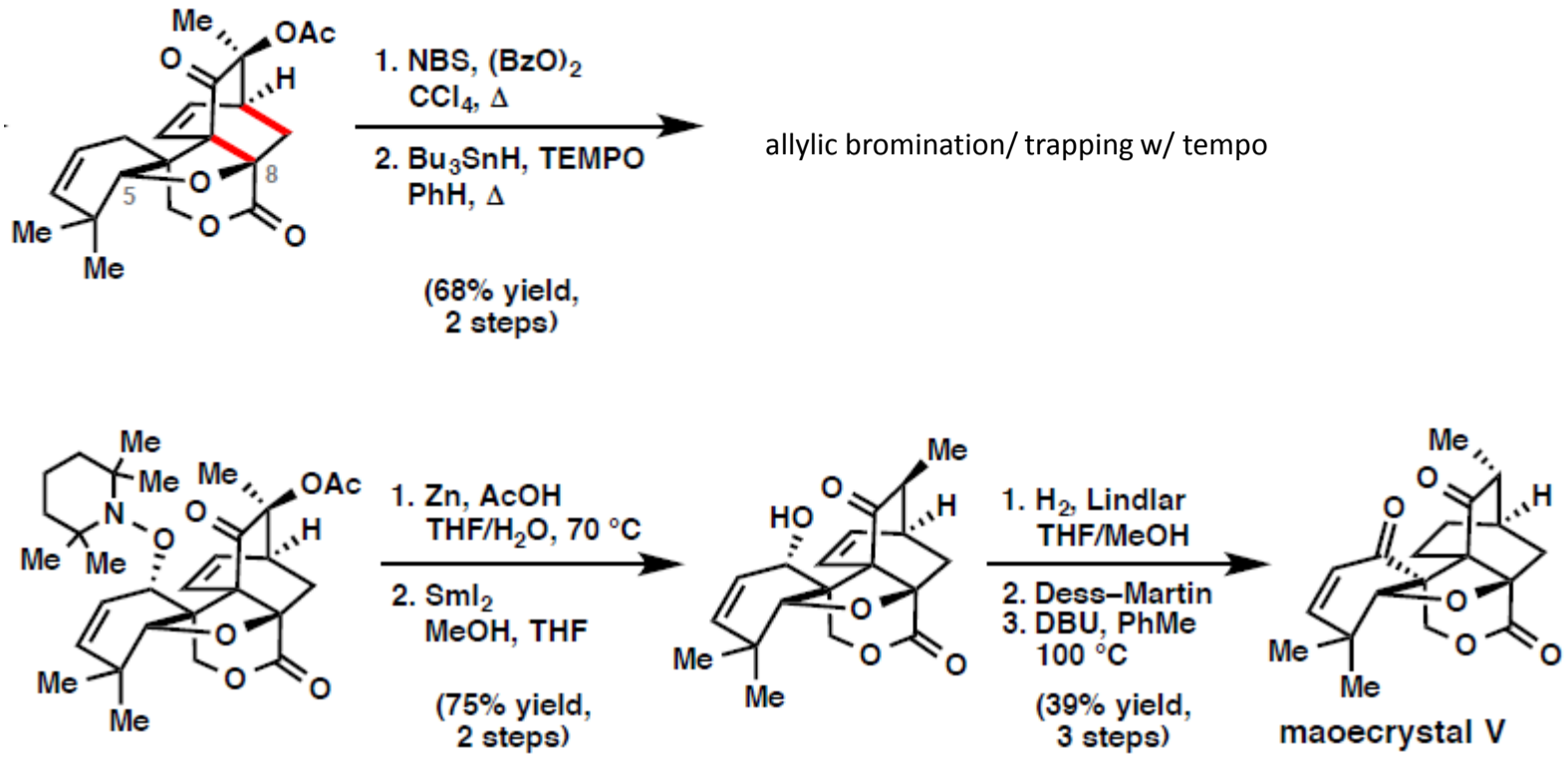


Wessely et al. *Monatsch. Chem*. **1950**, *81*, 811.



Tisdale, E. J. et al. *Org. Lett.* **2002**, *4*(6), 909.
Bhamare, N. K. et al. *J. Chem. Soc., Chem. Commun.*. **1990**, 739.

Yang's Synthesis of Maoecrystal V in 2010

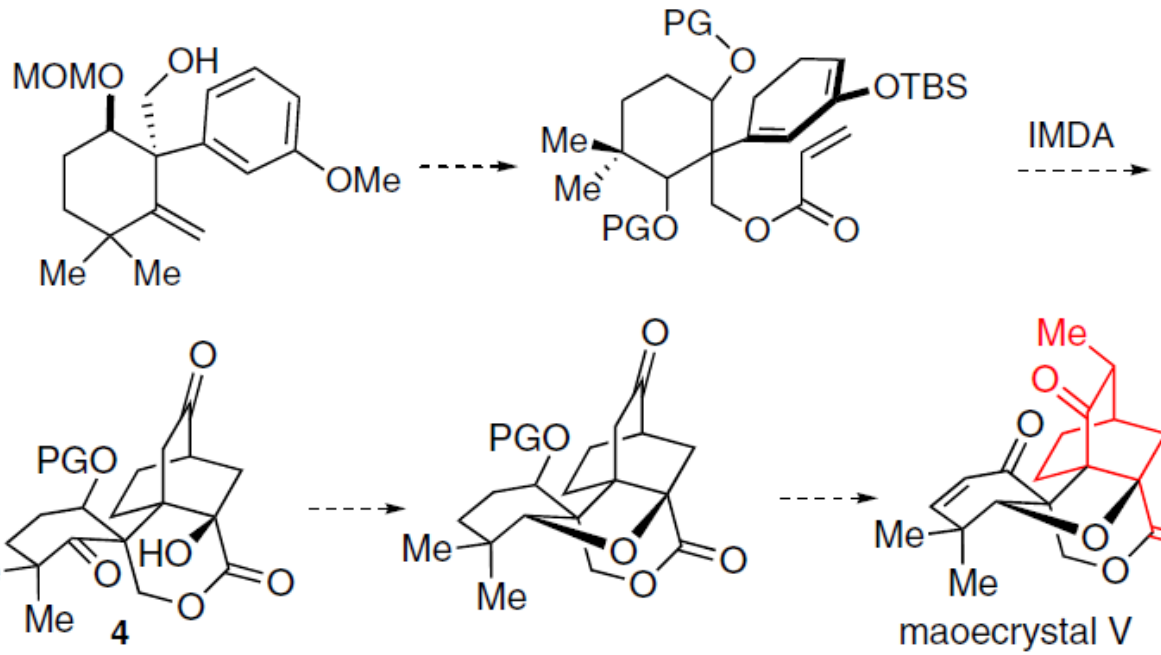


no epimerization

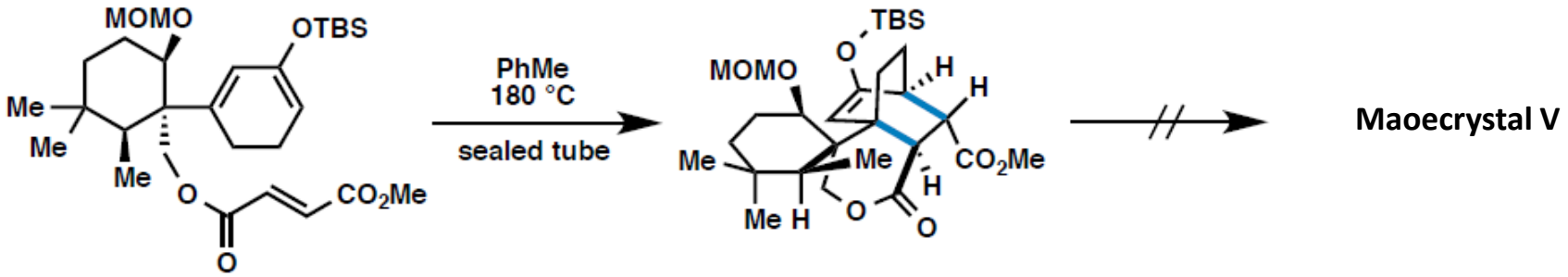
TO summarize….

17 steps *longest linear sequence*
features Rh(II)-catalyzed O-H insertion
Wessely's oxidation/ IMDA cascade
, but not asymmetric

Danishefsky's synthesis of Maoecrystal V in 2012



bicyclo [2.2.2] octane - IMDA

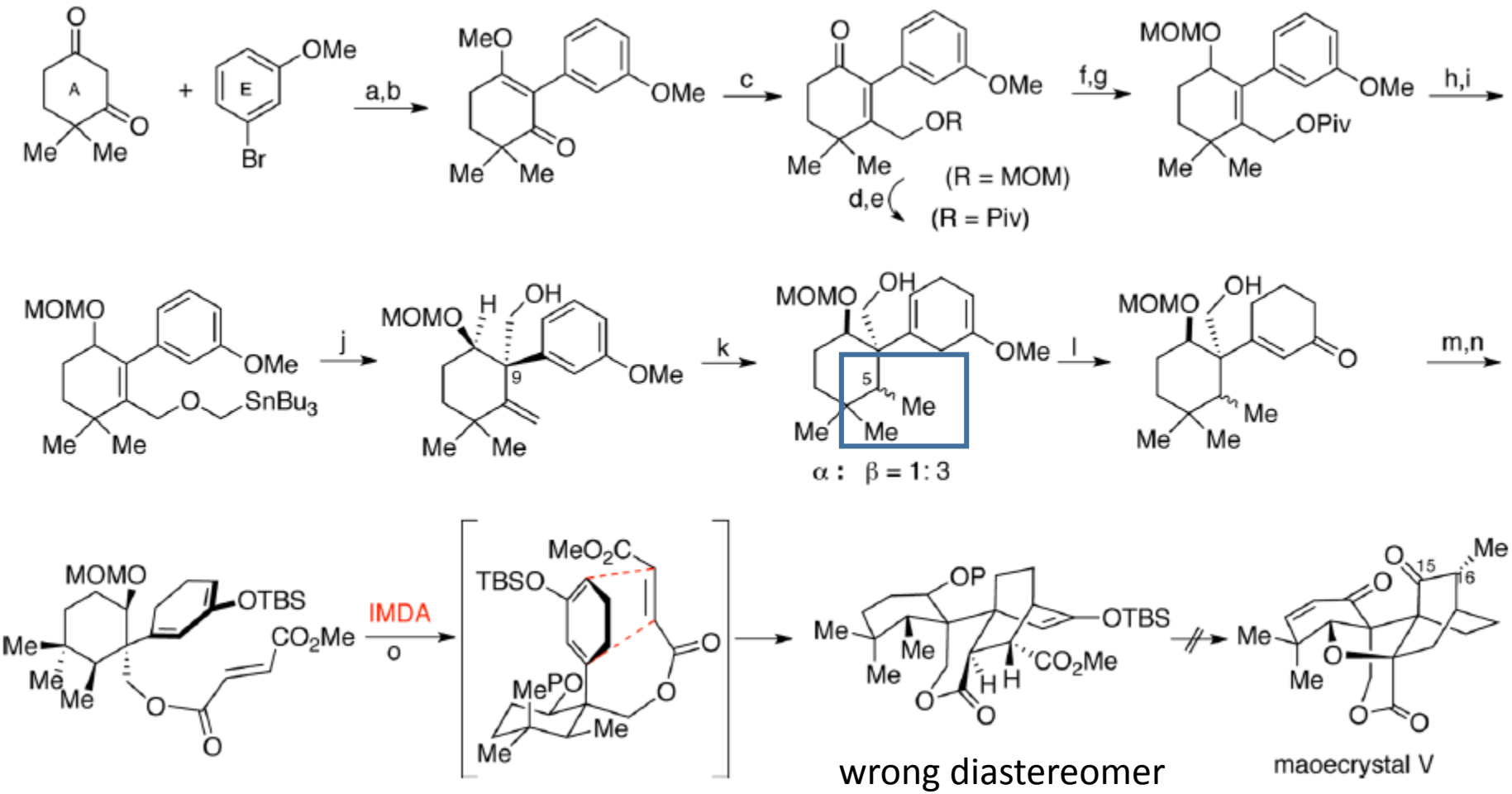


Maoecrystal V

Peng, F.; Yu, M.; Danishefsky, S. J., *Tetrahedron Lett*. **2009**, *50*, 6586-6587.

Danishefsky's synthesis of Maoecrystal V in 2012

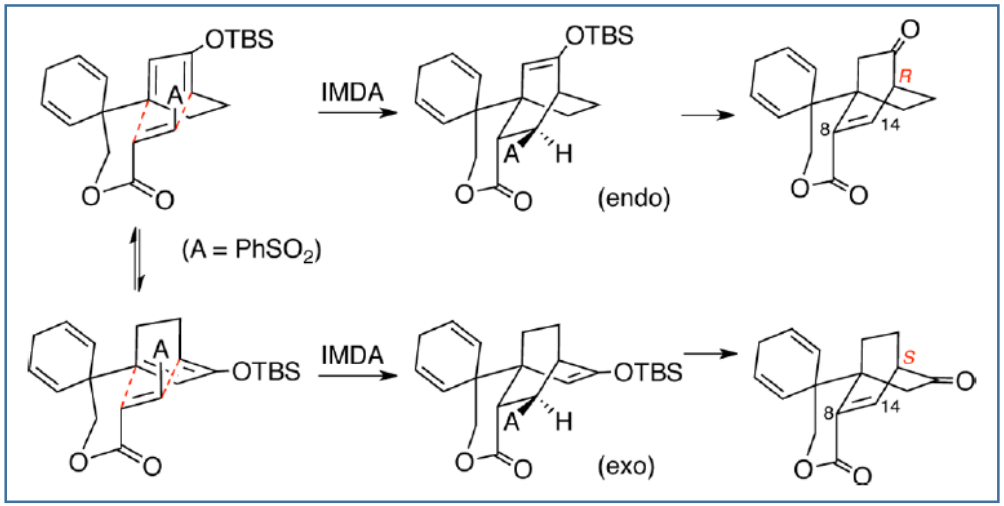
First approach- frustrated

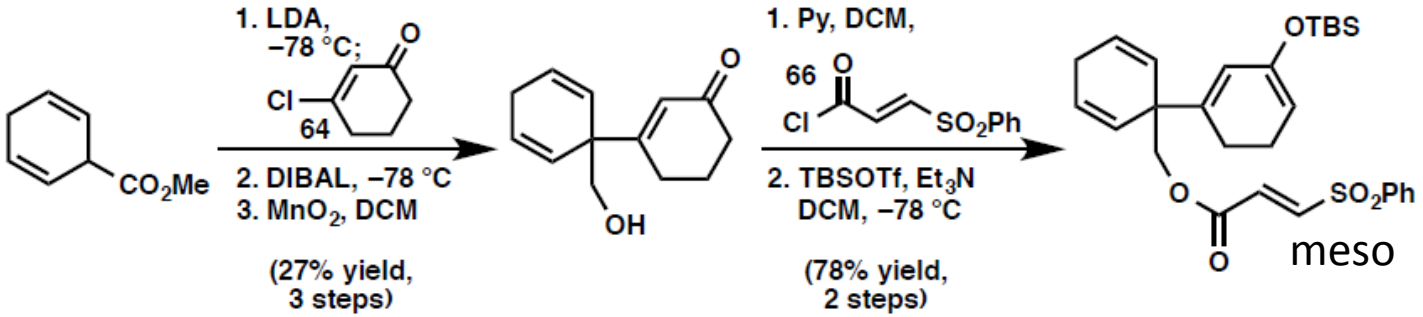


Danishefsky's synthesis of Maoecrystal V in 2012

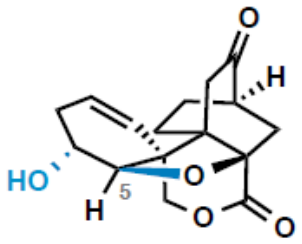
Second approach

Simplified structure
to avoid chiral influence of cycloxane
New strategy to induce C8-C14

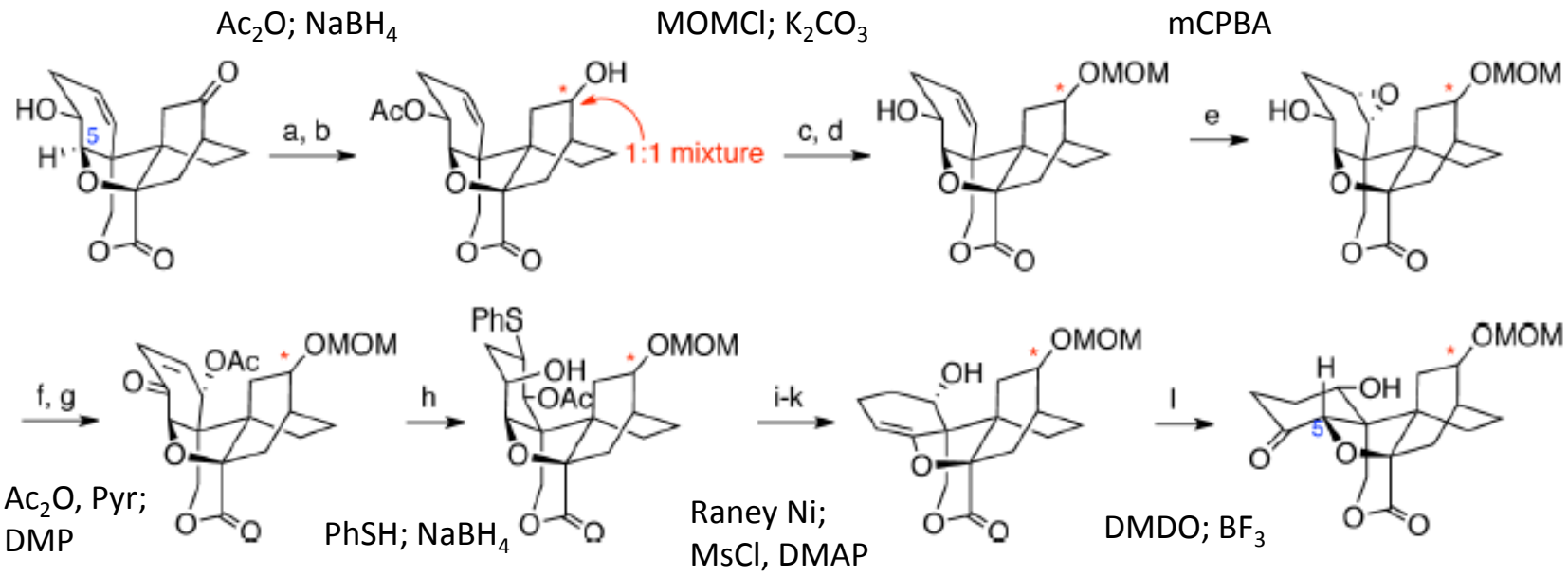




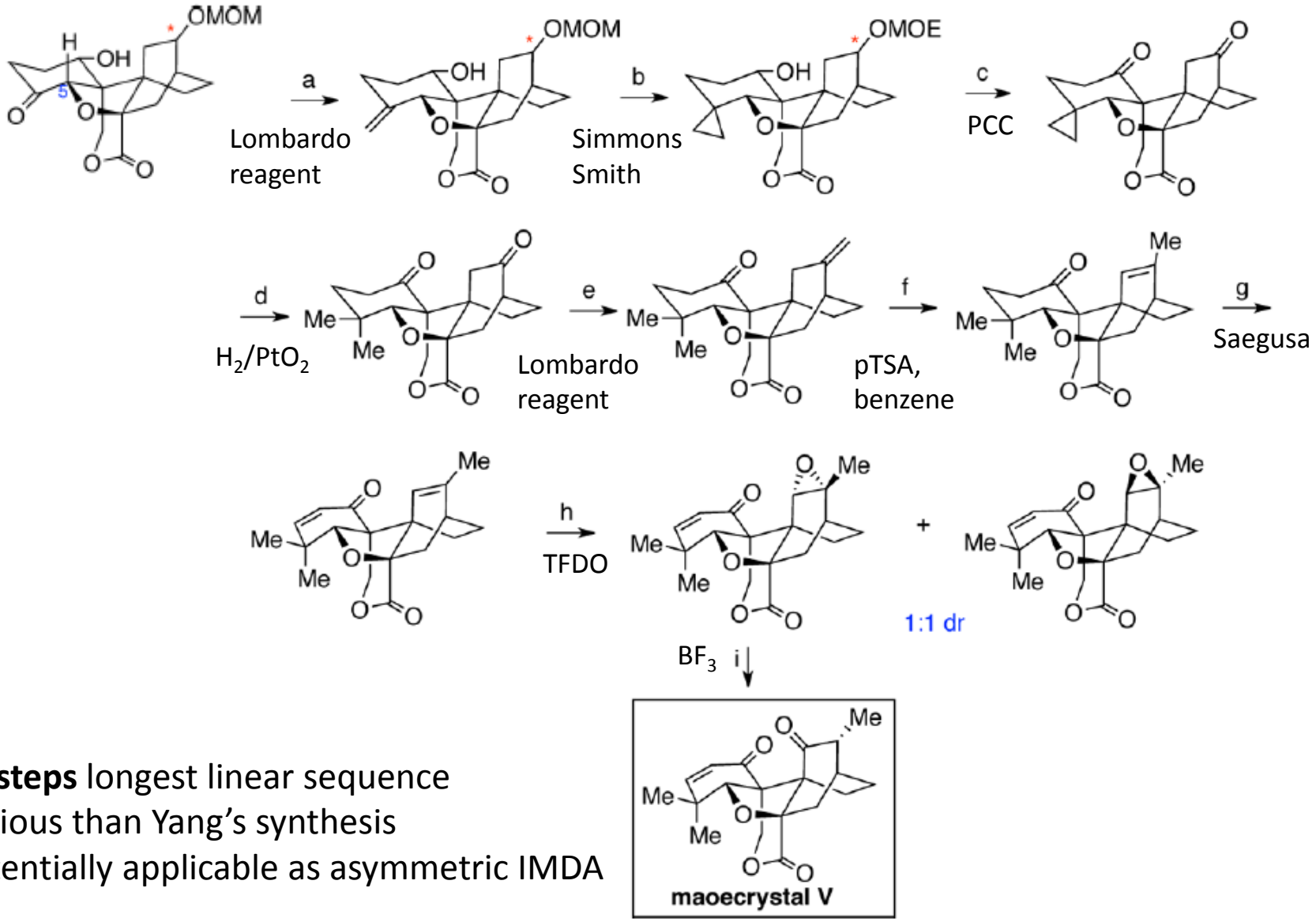
Danishefsky's synthesis of Maoecrystal V in 2012



from here… 21 steps…



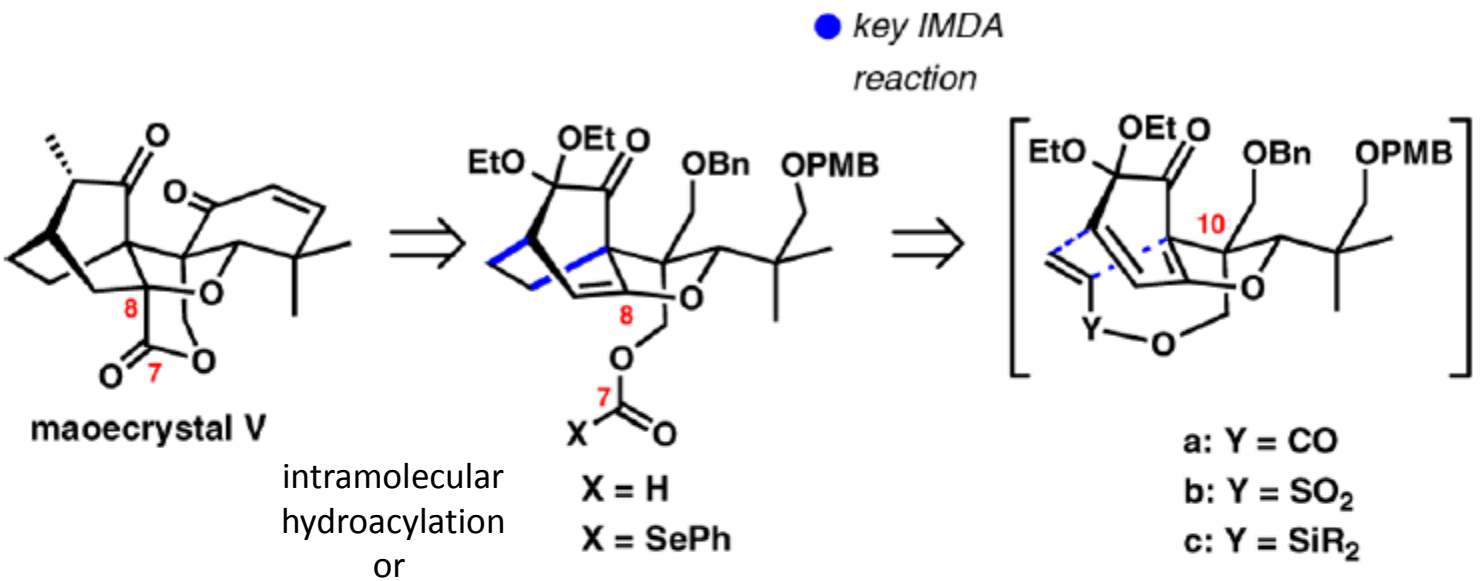
Danishefsky's synthesis of Maoecrystal V in 2012



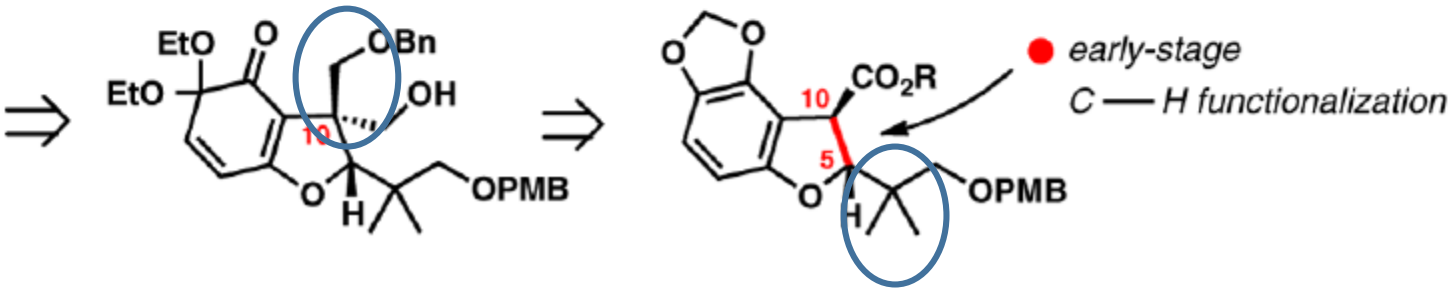
31 steps longest linear sequence
tedious than Yang's synthesis
potentially applicable as asymmetric IMDA

Zakarian's synthesis of Maoecrystal V in 2013

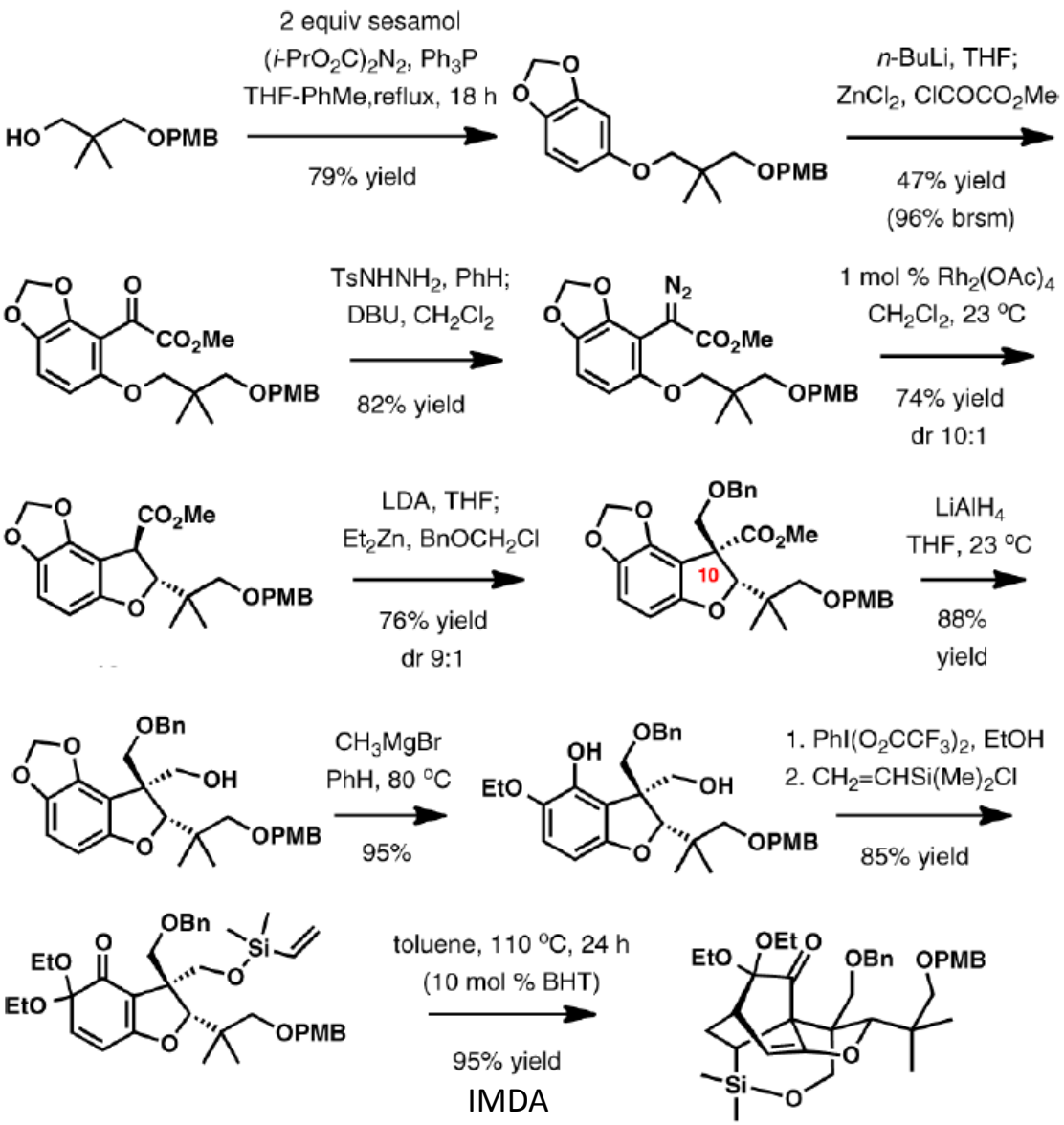
<u>a different disconnection for Diels-Alder using silyl-tethered precursor ; early construction of tetrahydrofuran</u>



efficiency of tether removal and distance



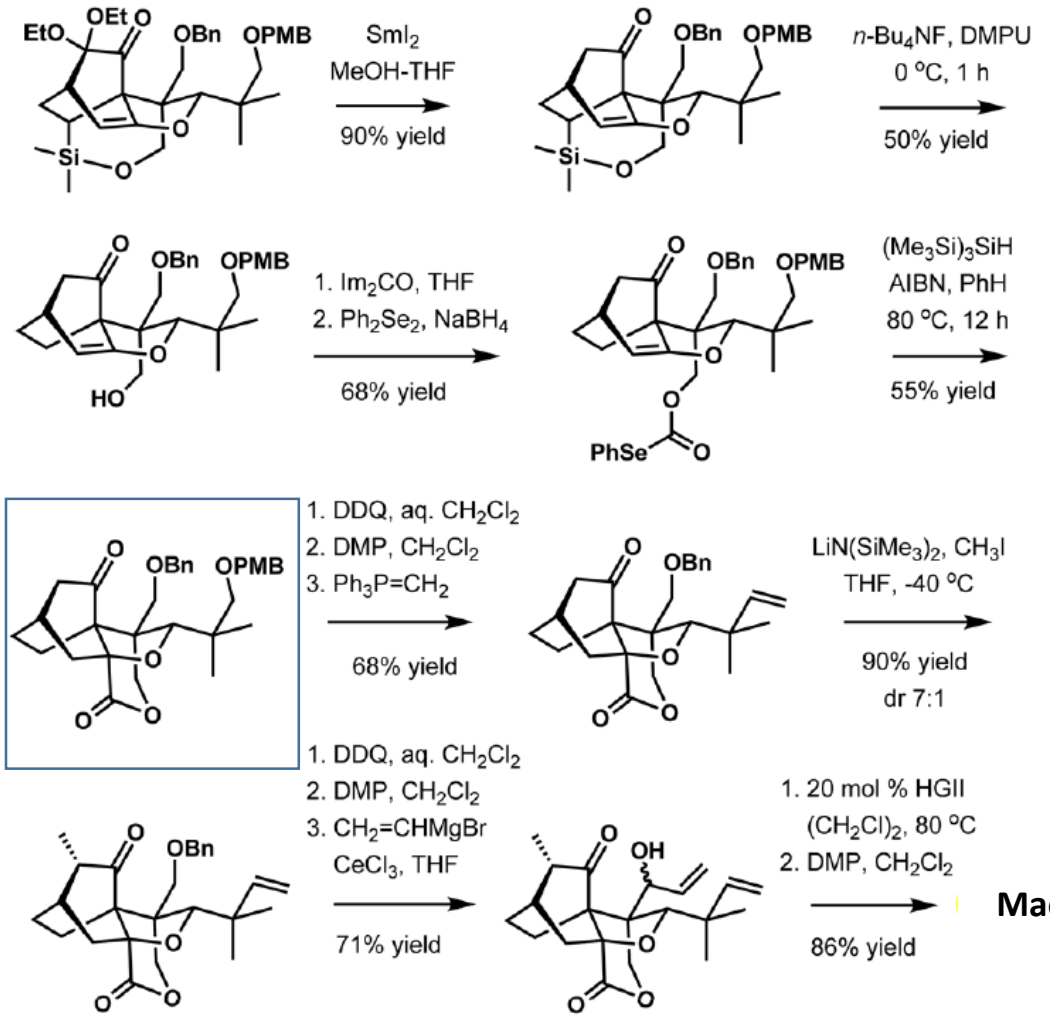
Zakarian's synthesis of Maoecrystal V in 2013

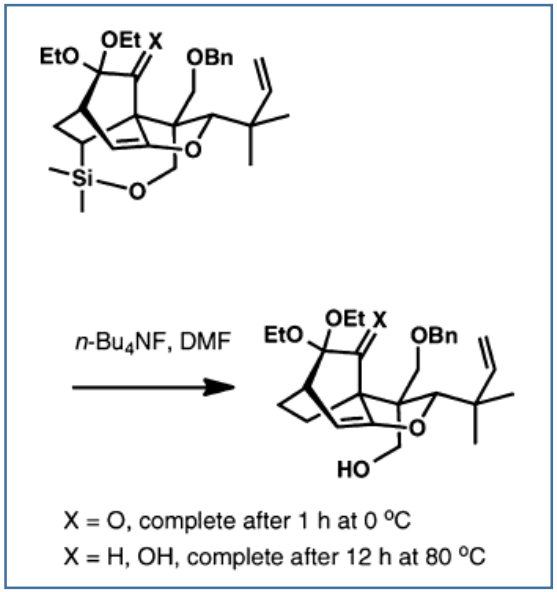


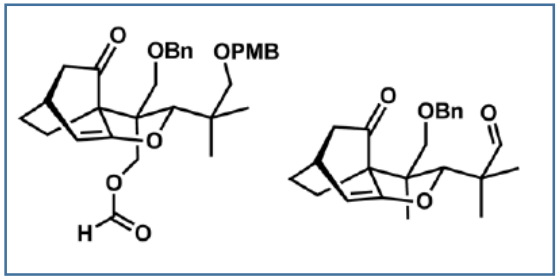
controlled by steric

another Wessely type

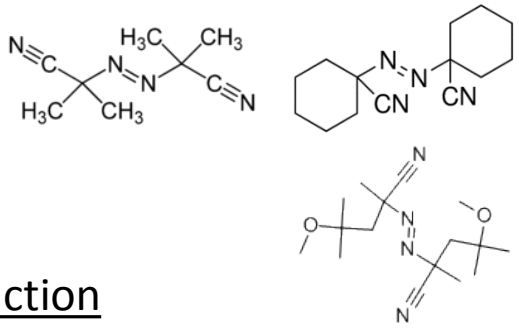
Zakarian's synthesis of Maoecrystal V in 2013





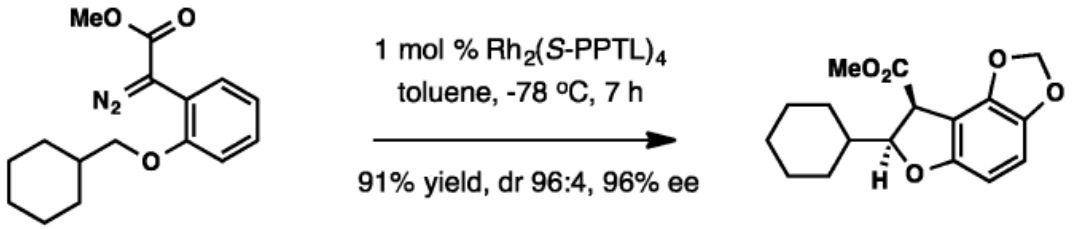


Bu_3SnH- too reactive
under many types of initiators

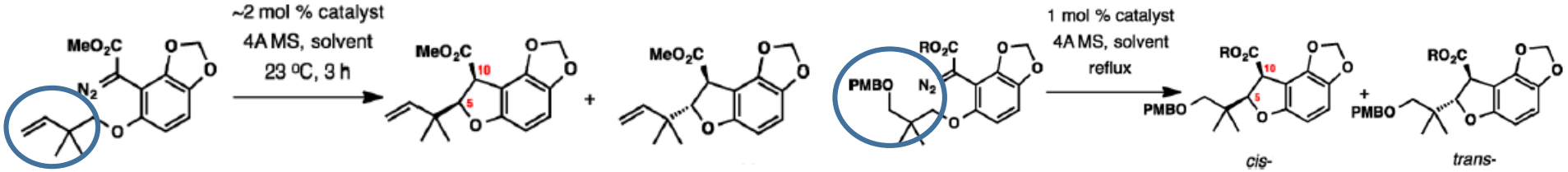


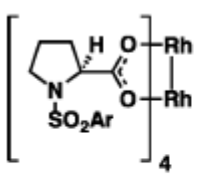
24 steps longest LS; tether mediated DA reaction

Zakarian's enantioselective synthesis of (-)-Maoecrystal V in 2014



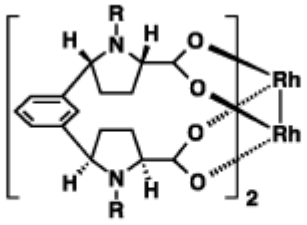
developed by Davies – benzylic ether C-H insertion





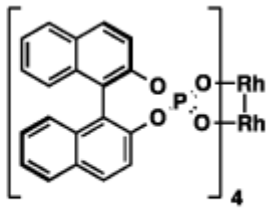
Ar = *p*-$C_{12}H_{25}C_6H_4$

Rh_2(*S*-DOSP)$_4$

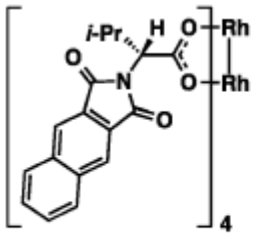


R = SO_2-2,4,6-tri-*i*-PrC_6H_2

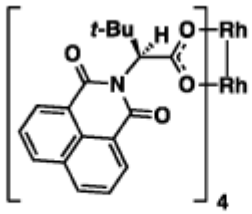
Rh_2(*S*-biTISP)$_2$



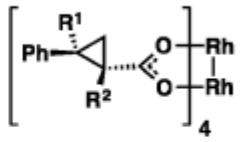
Rh_2(R-BNP)$_4$



Rh_2(*R*-BPTV)$_4$

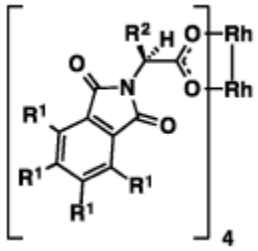


Rh_2(*S*-NTTL)$_4$



R^1 = Ph, R^2 = 4-BrPh **Rh_2(*R*-BTPCP)$_4$**

R^1 = H, R^2 = Ph **Rh_2(*R*-DPCP)$_4$**

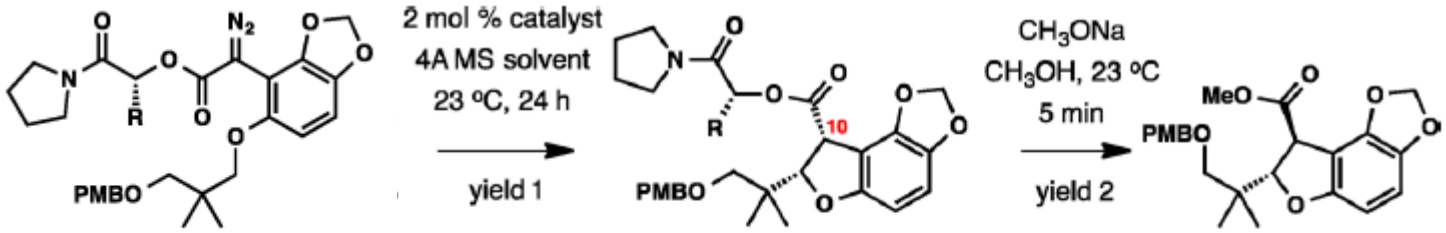


R^1 = H, R^2 = *t*-Bu	**Rh_2(*S*-PTTL)$_4$**
R^1 = H, R^2 = adamantyl	**Rh_2(*S*-PTAD)$_4$**
R^1 = H, R^2 = *i*-Pr	**Rh_2(*S*-PTV)$_4$**
R^1 = Cl, R^2 = *t*-Bu	**Rh_2(*S*-TCPTTL)$_4$**
R^1 = Cl, R^2 = adamantyl	**Rh_2(*S*-TCPTAD)$_4$**

Chiral ligand screening

low dr or ee for all cases

Zakarian's enantioselective synthesis of (-)-Maoecrystal V in 2014



22a: R = CH_3
22b: R = Ph

23a: R = CH_3
23b: R = Ph

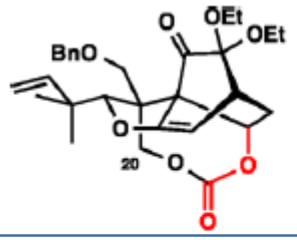
24

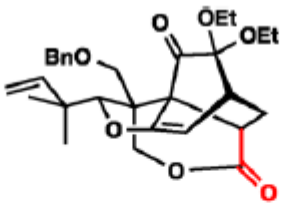
Chiral Auxiliary screening

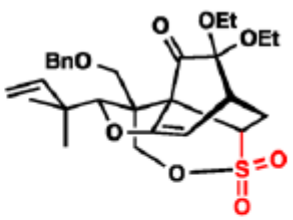
entry	starting material	catalyst	solvent	yield 1 (%)[a]	yield 2 (%)[b]	ee %[c]
1	22a	Rh_2(*S*-PTAD)$_4$	CH_2Cl_2	<10		
2	22a	Rh_2(*R*-PTAD)$_4$	CH_2Cl_2	<10		
3	22a	Rh_2(*S*-DOSP)$_4$	CH_2Cl_2	63	83	62
4	22a	Rh_2(*R*-DOSP)$_4$	CH_2Cl_2	74	86	70
5	22a	$Rh_2(OAc)_4$	CH_2Cl_2	84	84	65
6	22a	$Rh_2(O_2CC_4F_9)_4$	CH_2Cl_2	0		
7	22a	Rh_2(*R*-DOSP)$_4$	$(CH_2Cl)_2$	72		
8	22a	Rh_2(*R*-DOSP)$_4$	PhMe	61		
9	22a	Rh_2(*R*-DOSP)$_4$	*c*-C_6H_{12}	<10		
10	22a	Rh_2(*R*-DOSP)$_4$	CH_3CN	0		
11	23b	Rh_2(*S*-DOSP)$_4$	CH_2Cl_2	84	89	59
12	23b	Rh_2(*R*-DOSP)$_4$	CH_2Cl_2	57	77	52
13	23b	$Rh_2(OAc)_4$	CH_2Cl_2	72	85[c]	76
14	23b	Rh_2(OAc)4	CH_2Cl_2	61[d]	84	84

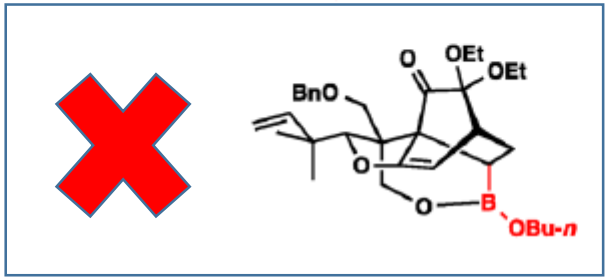
Zakarian's enantioselective synthesis of (-)-Maoecrystal V in 2014

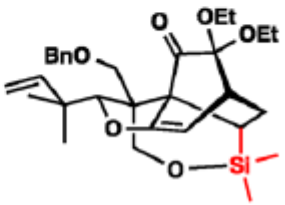
potential tethers

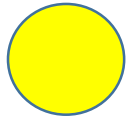


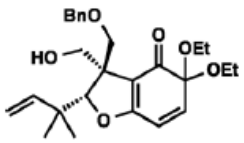


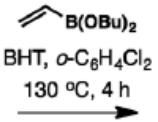


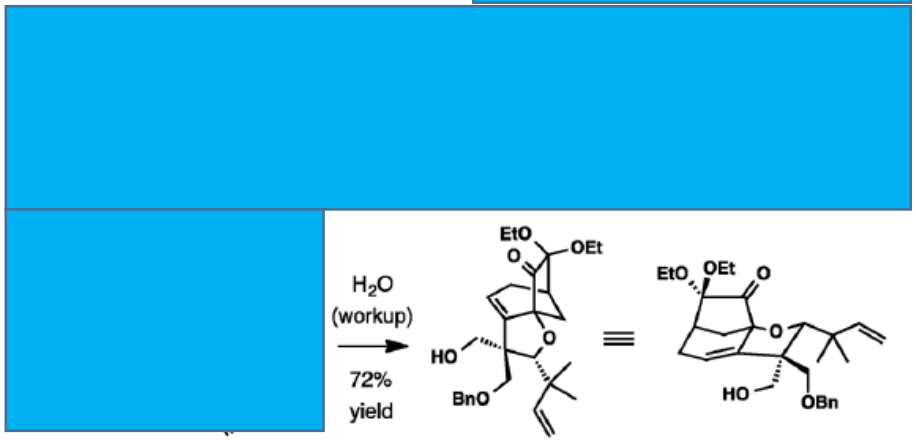




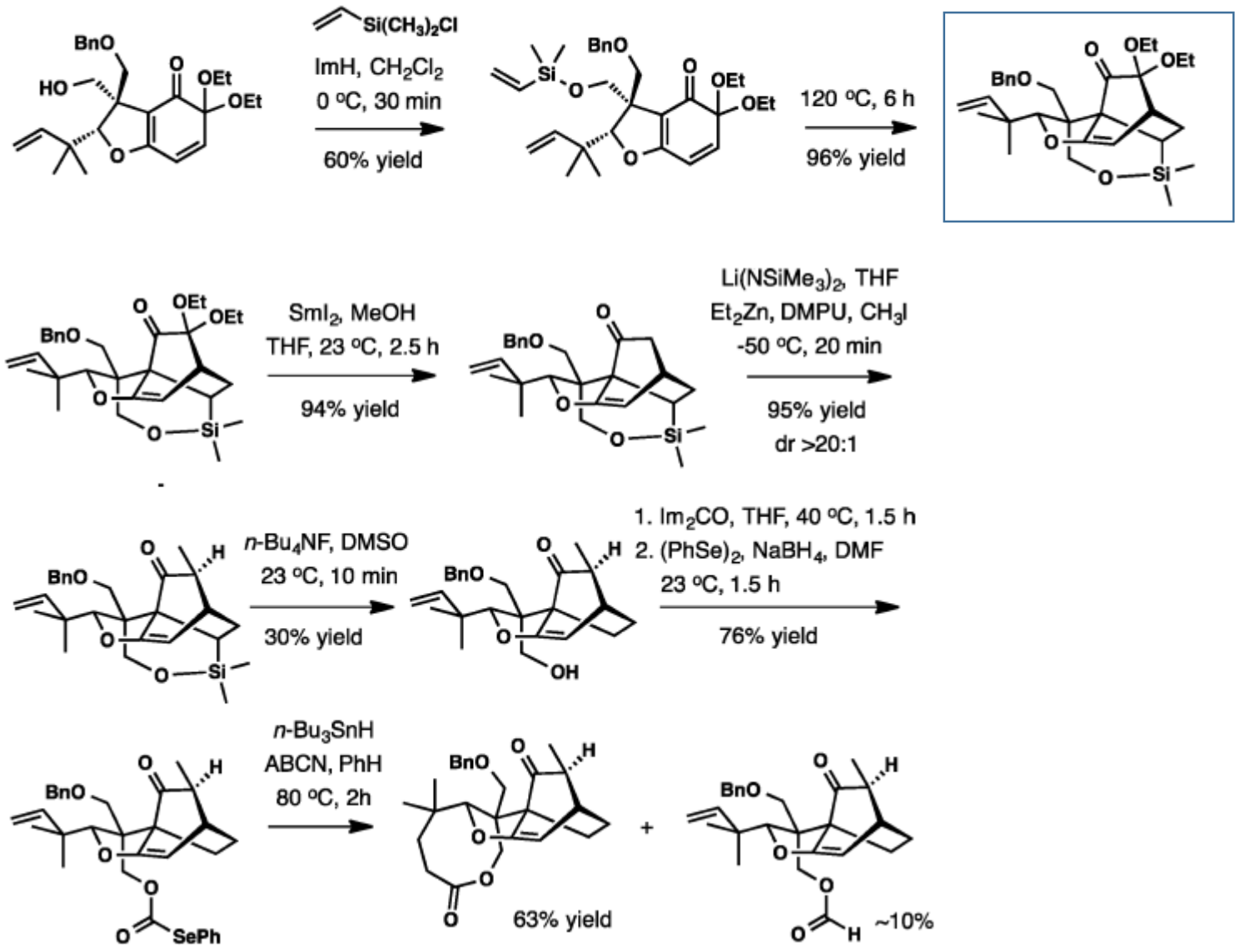




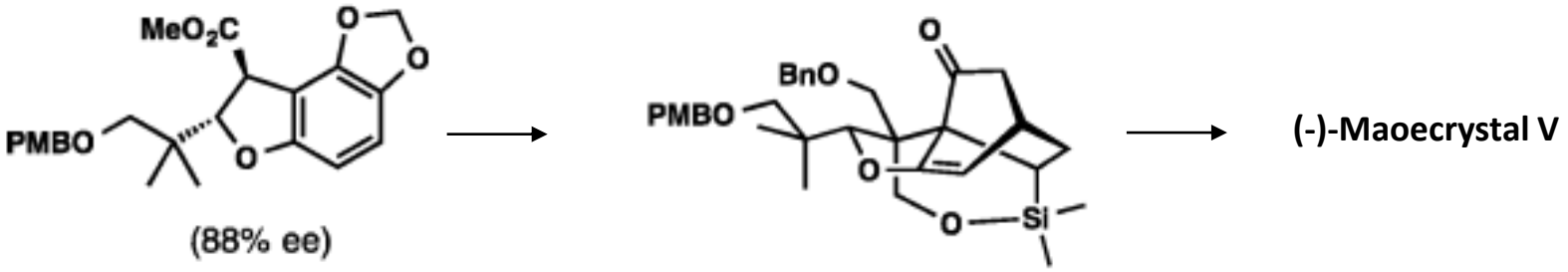




Zakarian's enantioselective synthesis of (-)-Maoecrystal V in 2014



Zakarian's enantioselective synthesis of (-)-Maoecrystal V in 2014



10 mg of the natural products

$[\alpha]_D^{25}$ −101.1° (*c* 0.3, CH_3OH)

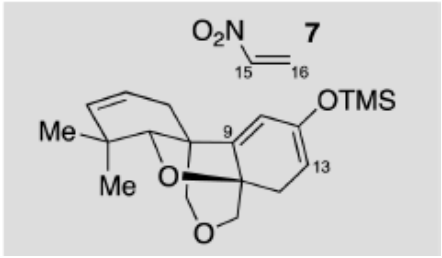
lit.[6] $[\alpha]_D^{25}$ −92.9° (*c* 0.7, CH_3OH)

chiral auxiliary with simple non-chiral catalyst solved low ee-problem

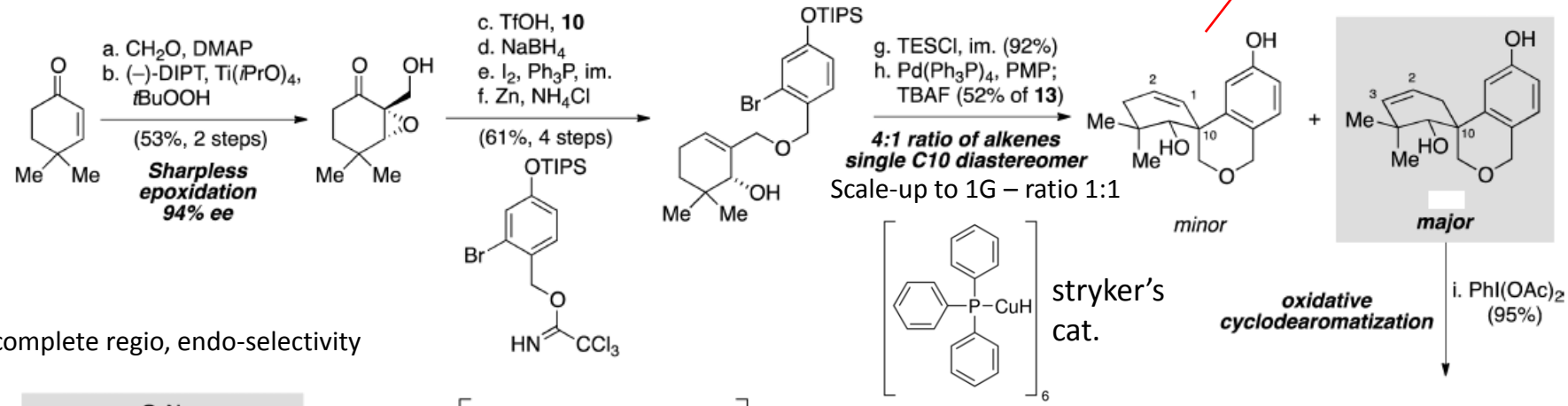
; less efficient than asymmetric catalysis , but can be alternative way

Thomson's enantioselective synthesis of (-)-Maoecrystal V in 2014

another Diels-Alder; but asymmetric and intermolecular reaction



no ring closure
under the same conditions

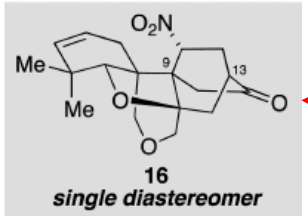


complete regio, endo-selectivity

one pot

fragmentation to pheol was not observed.

Thomson's enantioselective synthesis of (-)-Maoecrystal V in 2014



early attempts by other reductions – poor conversion, reproducibility, decomposition

developed by Nicolaou

a. HS SH $BF_3 \cdot Et_2O$; Zn/HCl (89%)

b. IBX; HCl (87%)

c. Raney-Ni (98%)

d. LHMDS, MeI (95%) *1:1 dr*

First try; inseparable

e. K_2CO_3, $(CH_2O)_n$ (97%)

f. $NaBH_4$; Raney-Ni (95%) ***>15:1 dr***

g. NBS, $(BzO)_2$; $AgBF_4$, DMSO (73%) ***allylic oxidation***

kornblum oxidation

h. CrO_3, AcOH ***late-stage C–H oxidation***

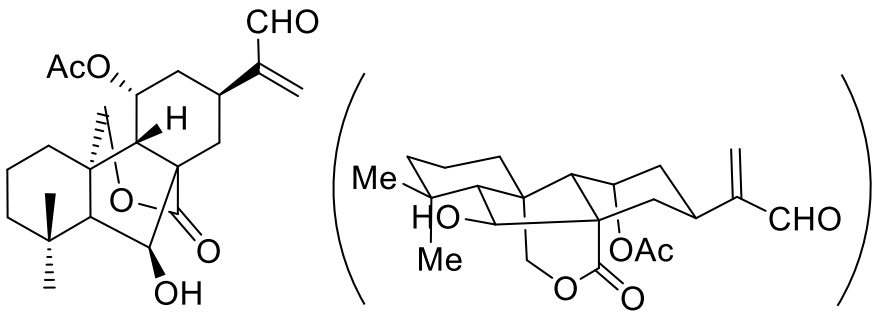
maoecrystal V (28%)

(47%)

electronic factor (at C1) is very important in C-H oxidation step

18 steps LS, sharpless epoxidation; Heck; intermolecular DA; beautiful

Reisman's concise synthesis of (-)-Maoecrystal Z in 2011



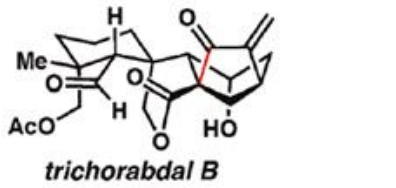
Maoecrystal Z

- isolated in 2006 by Sun and coworkers from the herb Isodon eriocalyx.

- in vivo cytotoxicity to A 2780 ovarian cancer cell line

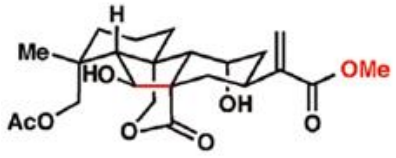
- tetracyclic core structure

- 6 vicinal stereogenic centers, 2 quaternary Carbons



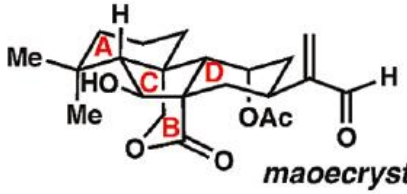
NaOH, MeOH

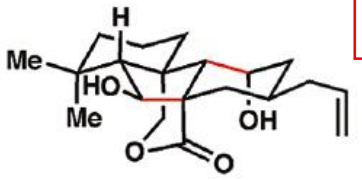
retro-Dieckmann/ aldol reaction



report by Fujita in 1981
- retro Dieckmann/aldol cascade

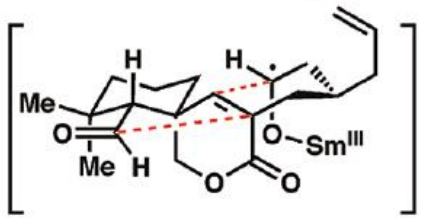
Retrosynthesis

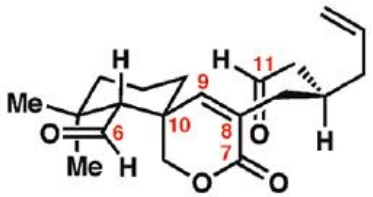




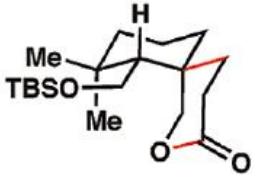
reductive cascade cyclization

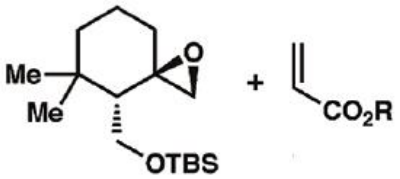
selective initiation due to steric?





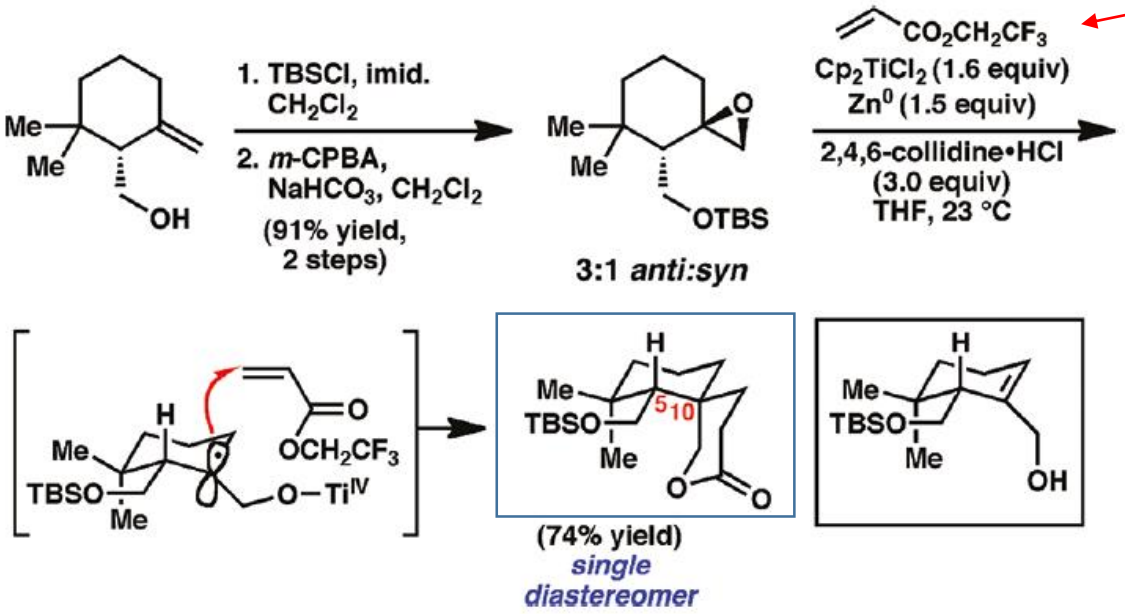
reductive epoxide coupling

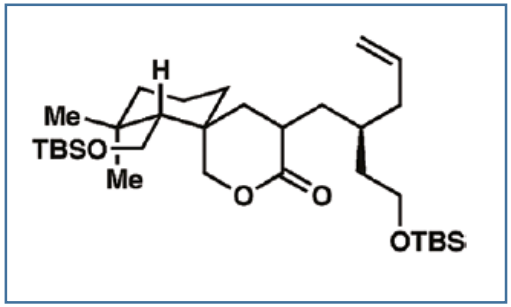


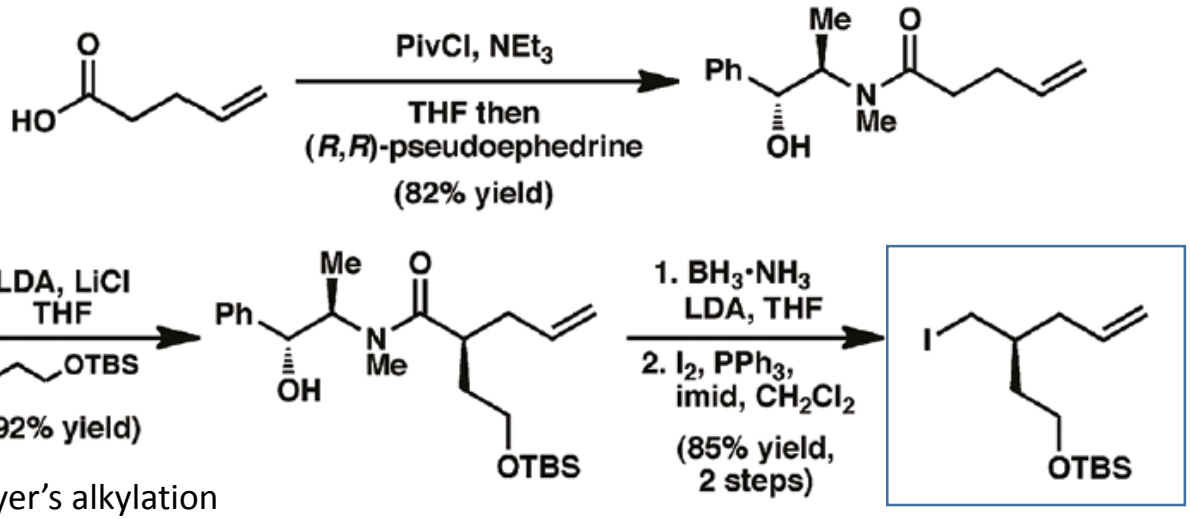


Reisman's concise synthesis of (-)-Maoecrystal Z in 2011

more electrophilic MA/
portionwise addition

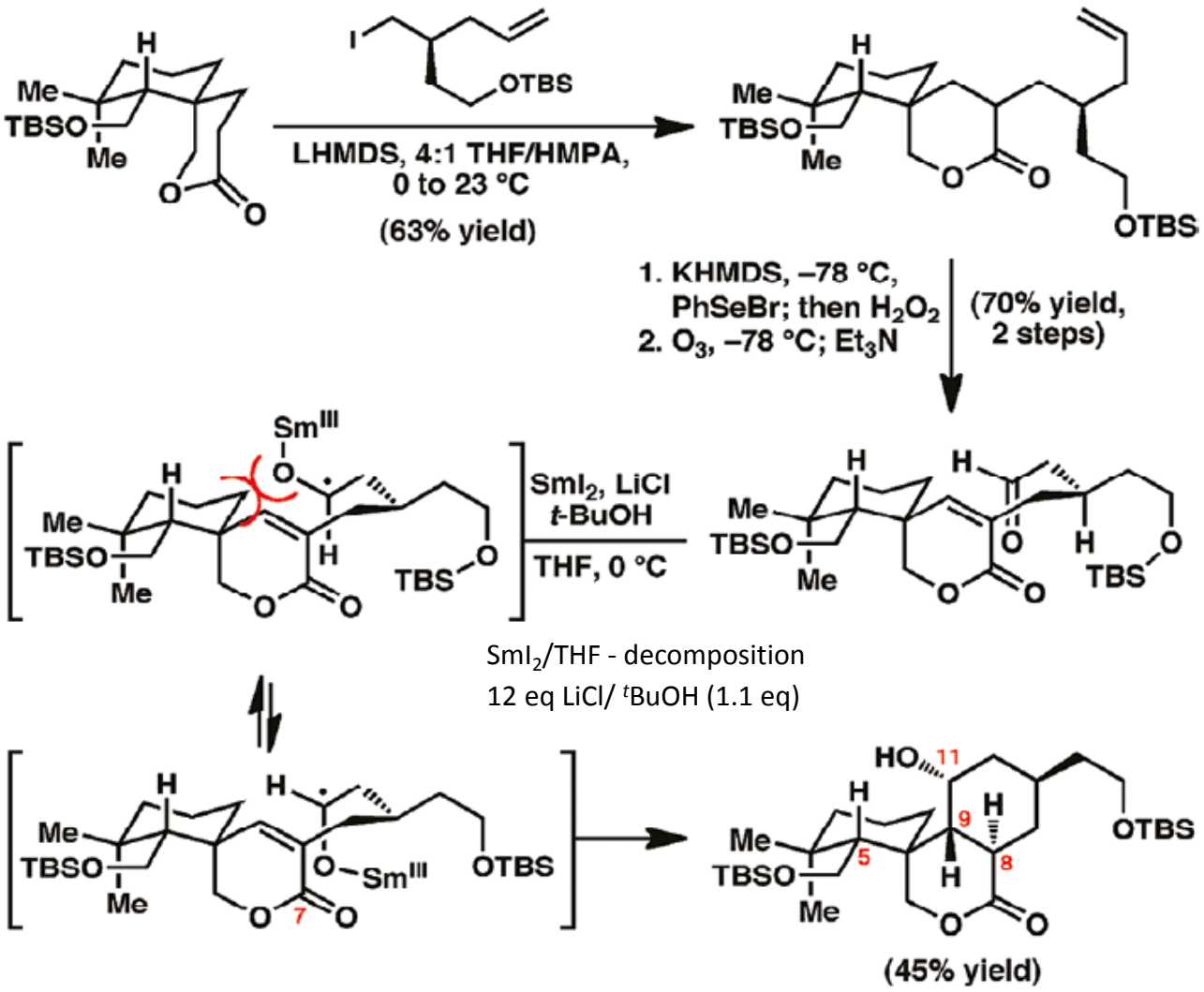






Myer's alkylation

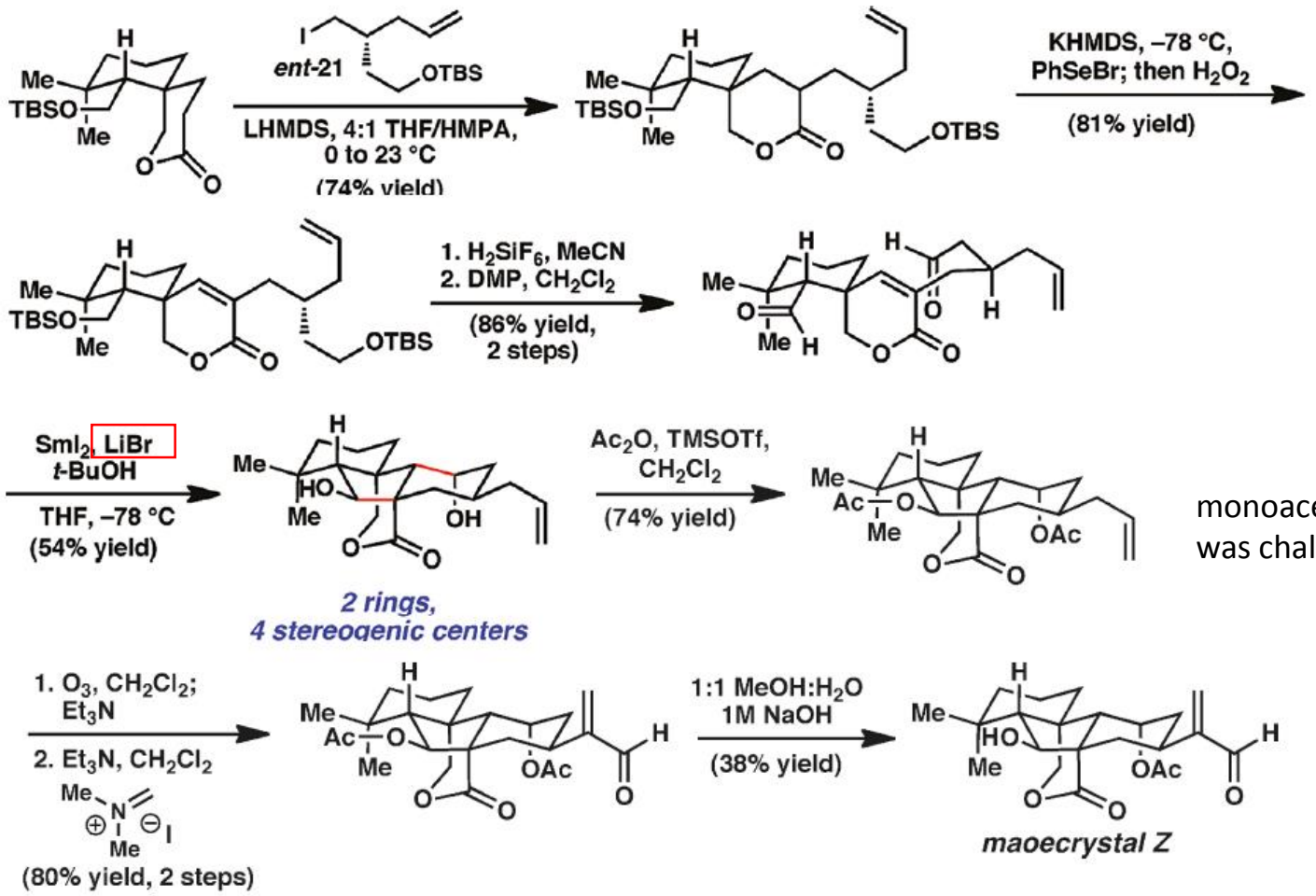
Reisman's concise synthesis of (-)-Maoecrystal Z in 2011



SmI_2/THF - decomposition
12 eq LiCl/ ^{t}BuOH (1.1 eq)

(1) The lithium cation may coordinate
to the carbonyl and make it easier to reduce;
(2) the bromide and chloride anions may coordinate
to the Sm(II) and alter its reactivity;
(3) the lithium salts may enhance or prevent aggregation of SmI2, making it more or less reactive

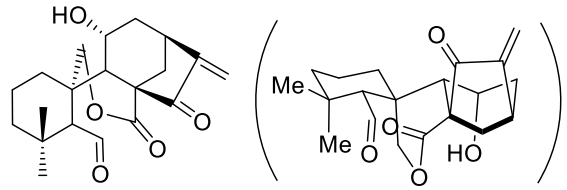
Reisman's concise synthesis of (-)-Maoecrystal Z in 2011



monoacetylation was challenging

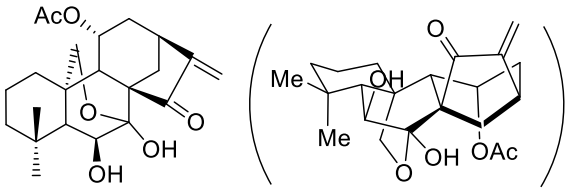
highly efficient, well designed, **12 steps** from (-)-cyclogeraniol, Ti(III)-mediated spiro-lactone formation/SmI_2-mediated cascade successful monoacetylation could cut one more step.

Reisman's synthesis of (-)-Trichorabdal A and (-)-Longikaurin E in 2013



(-)-trichorabdal A

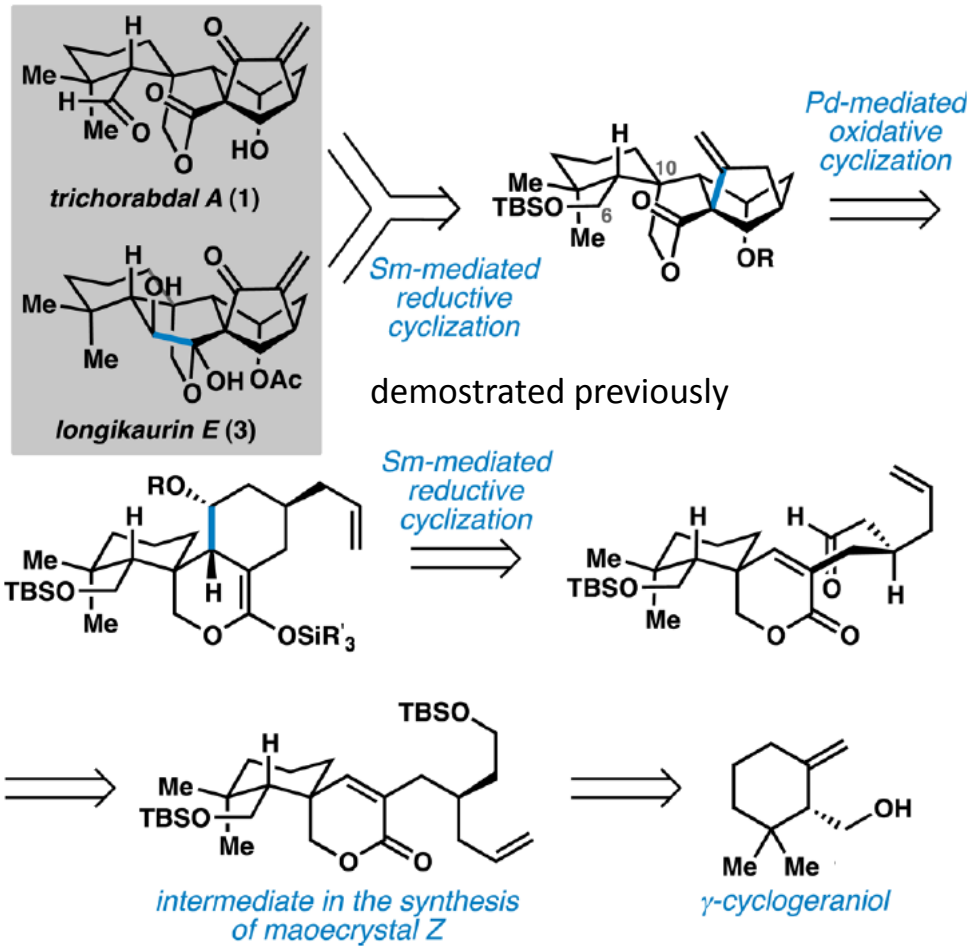
- inhibit tumor growth in vivo in mice



(-)-longikaurin

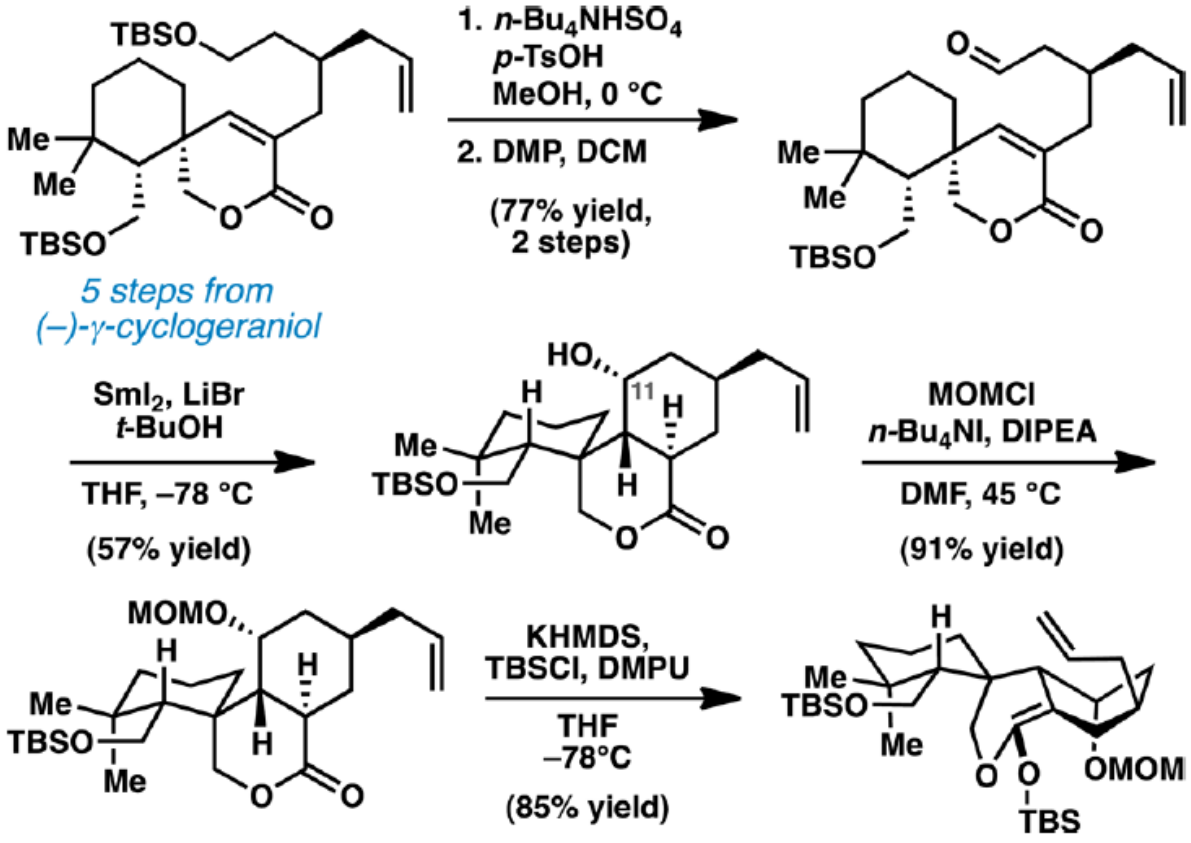
- showed in vivo cytotoxicity against several human cancer cell lines

Retrosynthesis

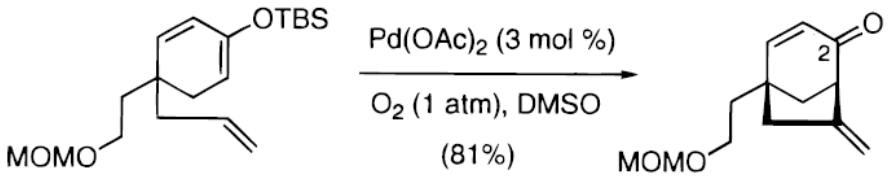


same intermediate in Maoecrystal Z

Reisman's synthesis of (-)-Trichorabdal A and (-)-Longikaurin E in 2013

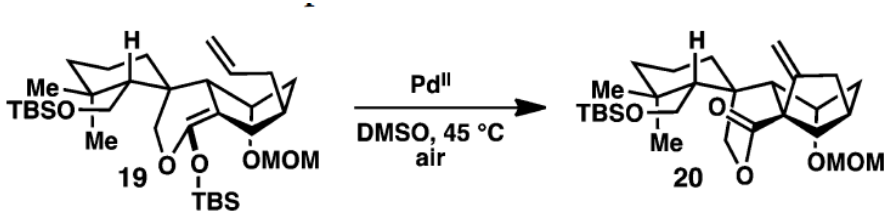


Reisman's synthesis of (-)-Trichorabdal A and (-)-Longikaurin E in 2013



Ihara et al. *JACS* **1998**, *120*, 4916.

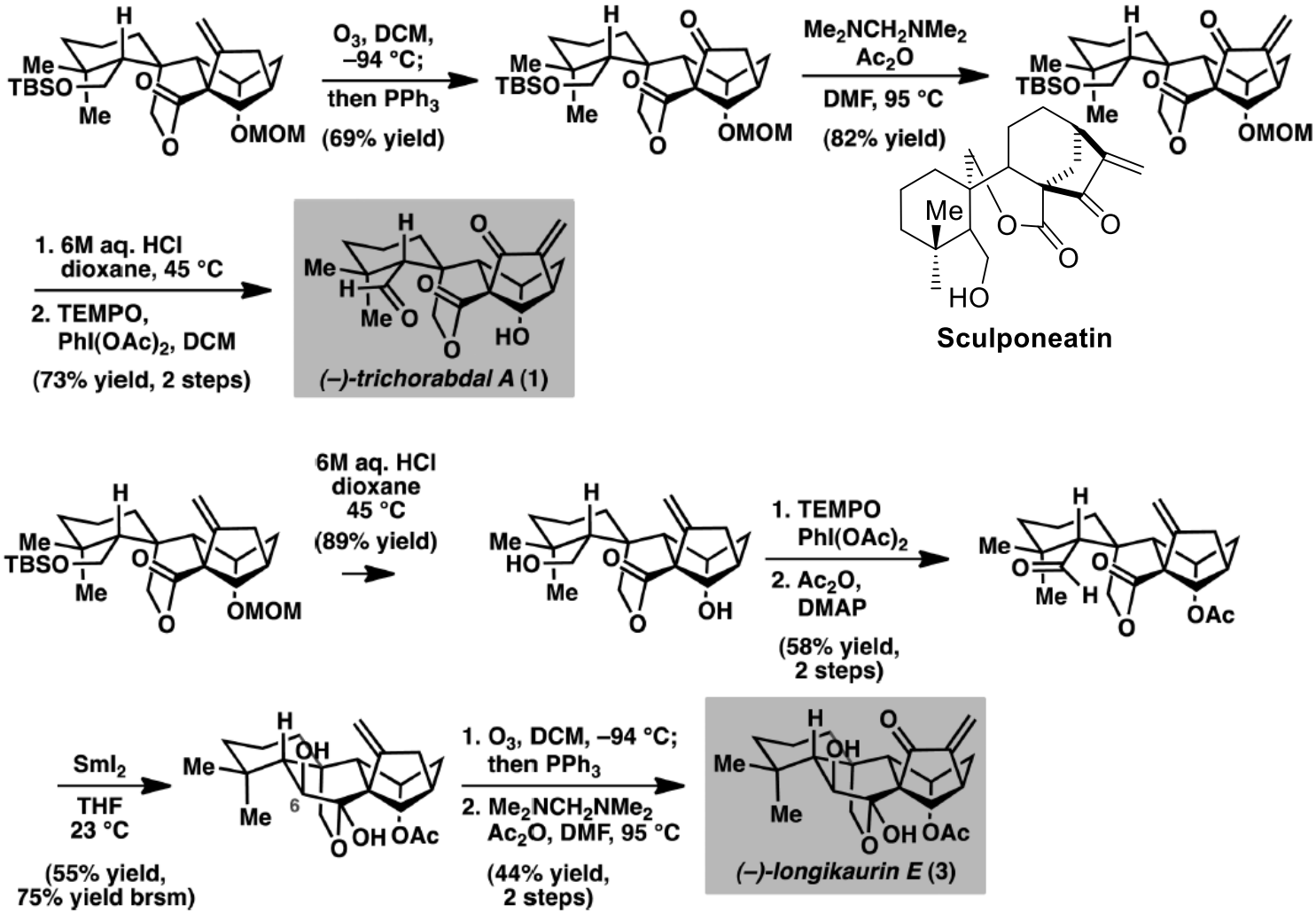
silyl ketene acetal more challenging ; few example



entry	Pd source (equiv)	additive (equiv)	yield **20** (%)[a]
1	$Pd(OAc)_2$ (0.1)	–	7
2	$Pd(OAc)_2$ (1.0)	–	35
3[b]	$Pd(OAc)_2$ (1.0)	–	28[c]
4	$Pd(TFA)_2$ (1.0)	–	19
5	$PdCl_2$ (1.0)	–	0
6	$PdCl_2$ (1.0)	$AgBF_4$ (2.0)	5[d]
7[e]	$Pd(OAc)_2$ (1.0)	H_2O (5.0)	38
8	$Pd(OAc)_2$ (1.0)	K_2CO_3 (5.0)	0
9	$Pd(OAc)_2$ (1.0)	AcOH (0.5)	56
10	$Pd(OAc)_2$ (0.1)	AcOH (0.5)	7
11	$Pd(OAc)_2$ (1.0)	AcOH (1.0)	31
12	$Pd(OAc)_2$ (1.0)	*p*-TsOH (0.5)	46
13	$Pd(OAc)_2$ (1.0)	BzOH (0.5)	32
14	$Pd(OAc)_2$ (1.0)	PivOH (0.5)	40

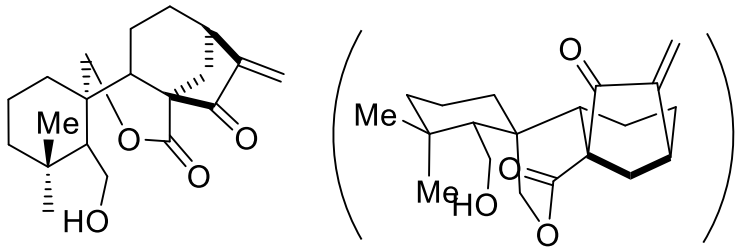
[a]Isolated yield. [b]Reaction conducted in MeCN at 23 °C. [c]Product isolated as an inseparable 4.3:1 mixture with an olefin isomerization side product. [d]13% yield of a Wacker oxidation product was also isolated. See Supporting Information. [e]Run under a N_2 atmosphere.

Reisman's synthesis of (-)-Trichorabdal A and (-)-Longikaurin E in 2013



concise and reliable now; PdII-mediated oxidative cyclization ;**15 and 17 steps** from (-)-γ-cyclogeraniol

Zhai's synthesis of Sculponeatin N in 2014

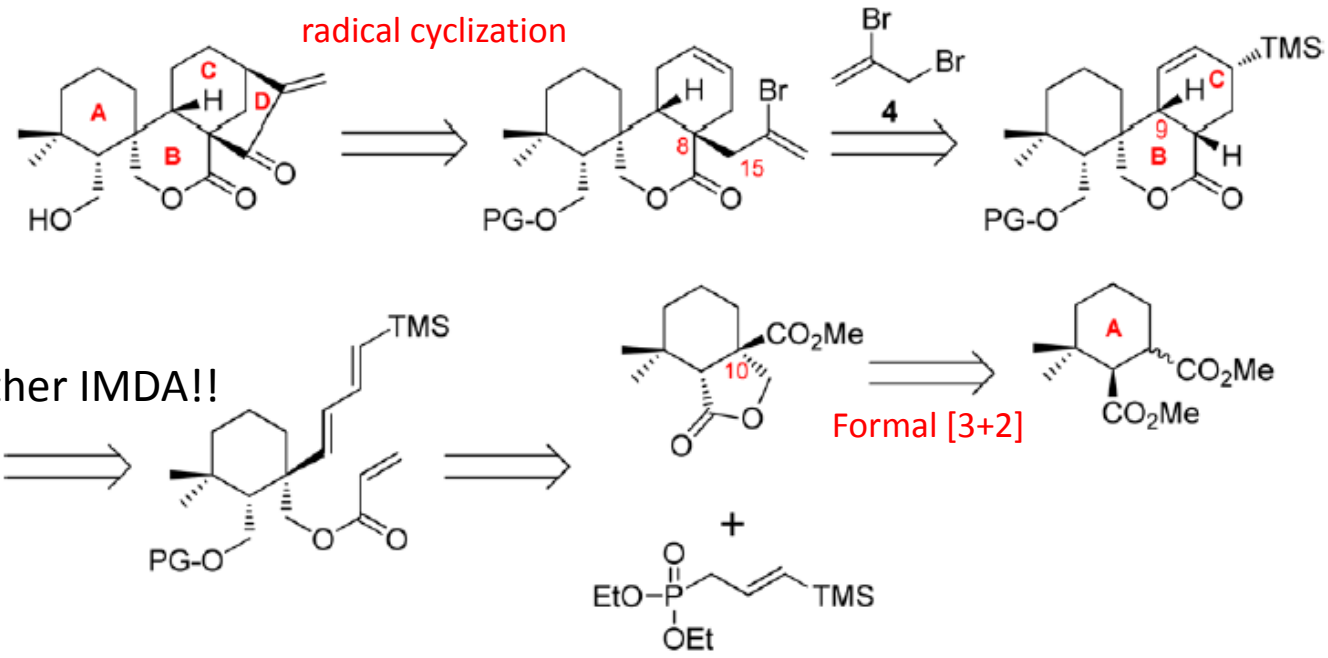


Sculponeatin

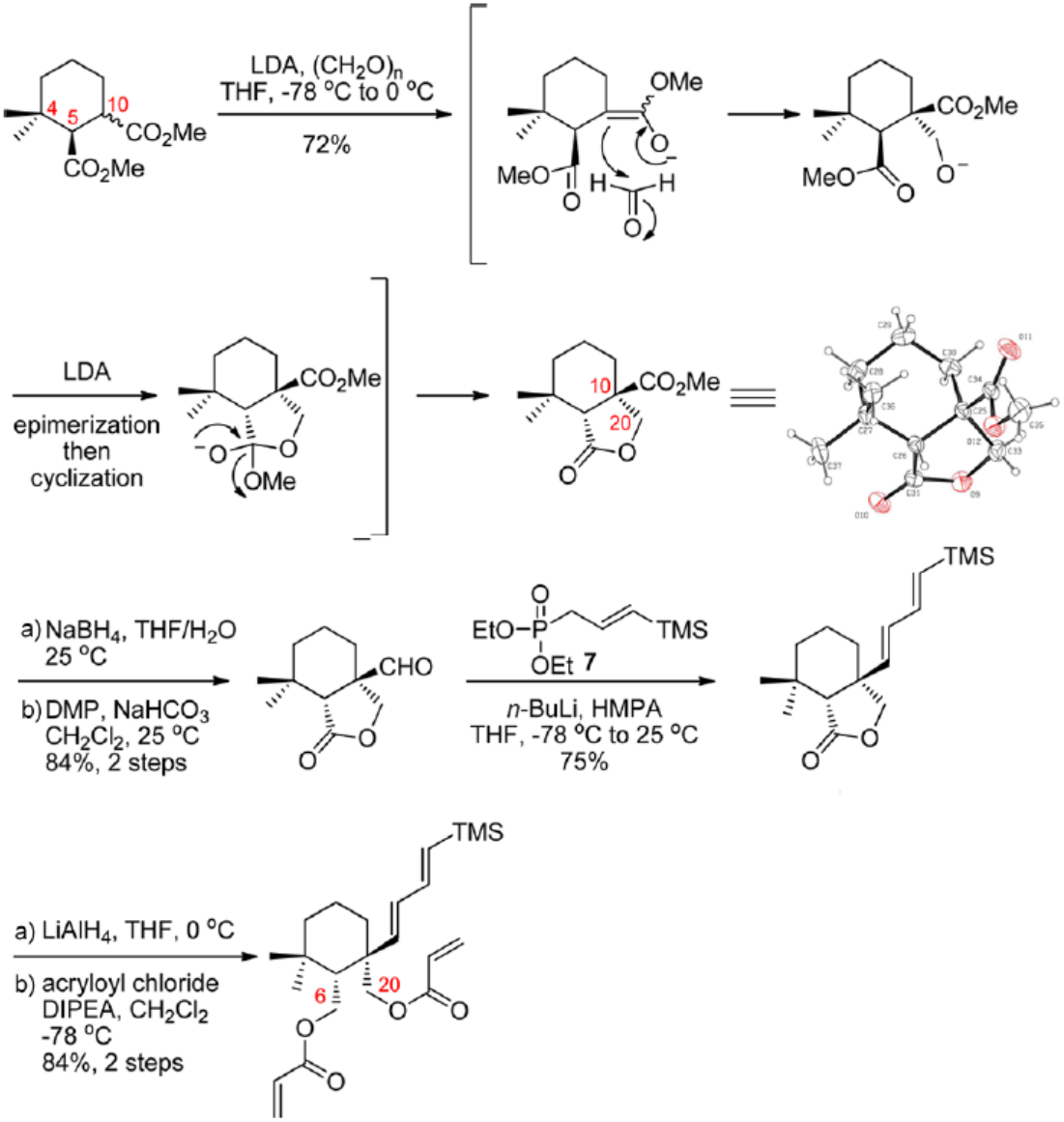
- isolated by Sun and coworkers in 2010

- cyctotoxic against K562 and HepG2 human cancer cell lines (IC_{50} = 0.21 and 0.29 uM)

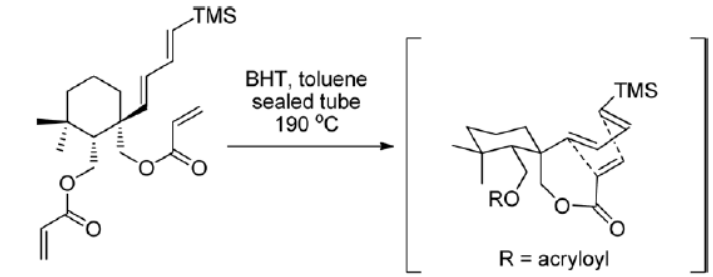
Retrosynthesis

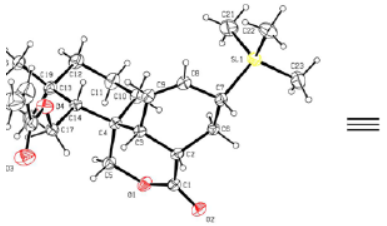


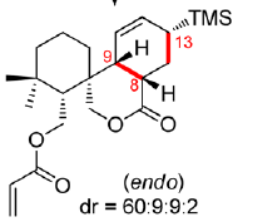
Zhai's synthesis of Sculponeatin N in 2014



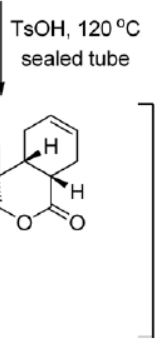
Zhai's synthesis of Sculponeatin N in 2014

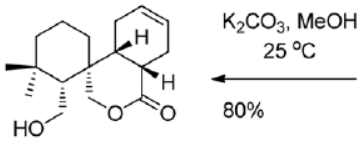




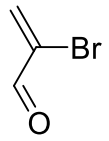


protodesilyation



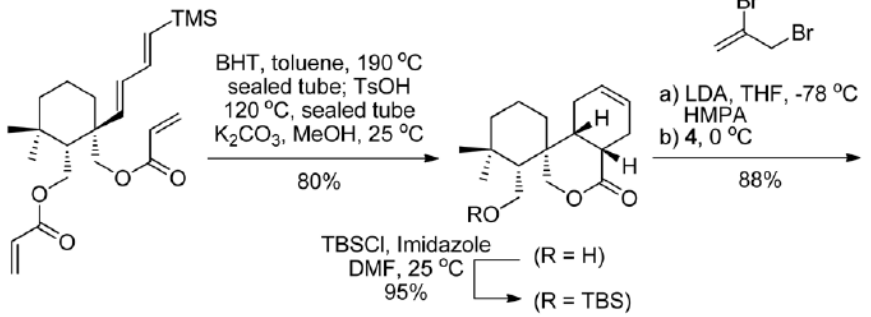


Single isomer!!!



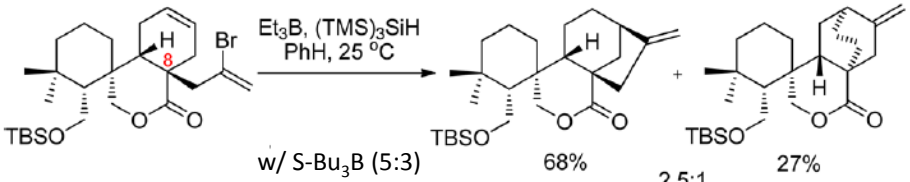
first try with acrolein
low yield

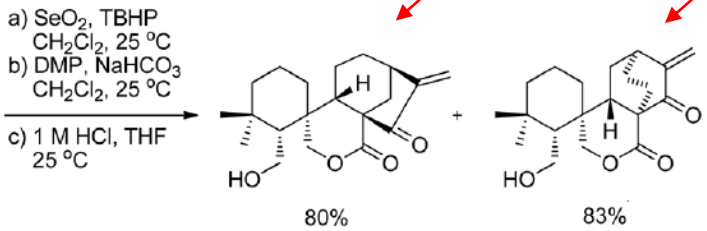
Second try with propargyl bromide low dr



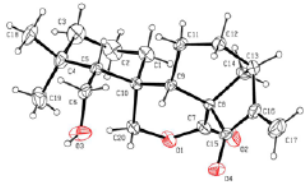
reductive Heck – unsuccessful

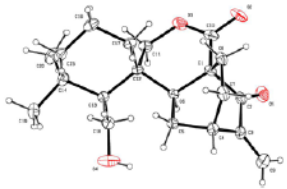
AIBN as an initiator – thermodynamically more favorable [2.2.2] bicycle as a major





13 steps from known sm

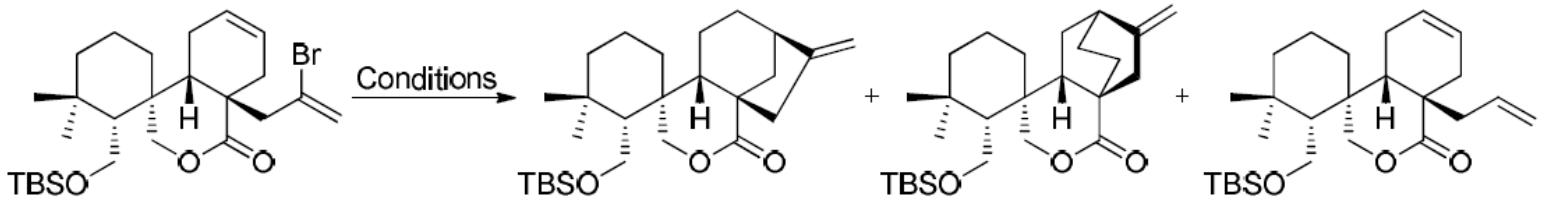




smart setting for the preparation of substrate, concise, radical cycl to form [3.2.0] briged cycle

Zhai's synthesis of Sculponeatin N in 2014

from SI of Zhai's paper



entry	conditions	ratio[a]	yield (%)
1	*n*-Bu_3SnH, AIBN, PhH, reflux, 2 h	**17**:**17a** = 1:3	92
2	$(TMS)_3SiH$, AIBN, PhH, reflux, 2 h	**17**:**17a** = 1:1.2	60
3	*n*-Bu_3SnH, Et_3B, PhH, 25 °C, 2 h	**17**:**17a**:**17b** = 1:1.2:0.3	95
4	*n*-Bu_3SnH, Et_3B, PhMe, –20 °C, 5 h	**17**:**17a**:**17b** = 10:1:5	93
5	*n*-Bu_3SnH, Et_3B, PhMe, –78 °C, 24 h	**17**:**17a**:**17b** = 34:1:17	92
6	$(TMS)_3SiH$, *s*-Bu_3B, PhH, 25 °C, 2 h	**17**:**17a** = 5:3	90
7	$(TMS)_3SiH$, Et_3B, PhH, 25 °C, 2 h	**17**:**17a** = 2.5:1	95

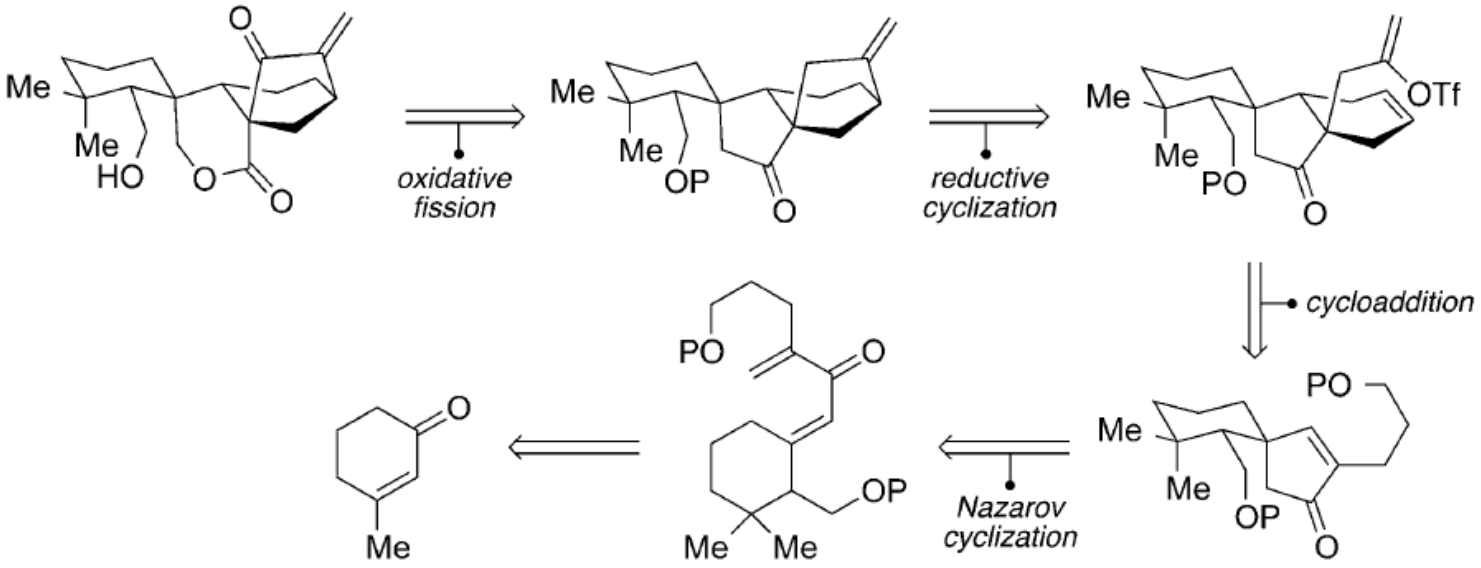
nBu_3SnH seems to be very good H-donor

Et_3B – seems to induce kinetic product

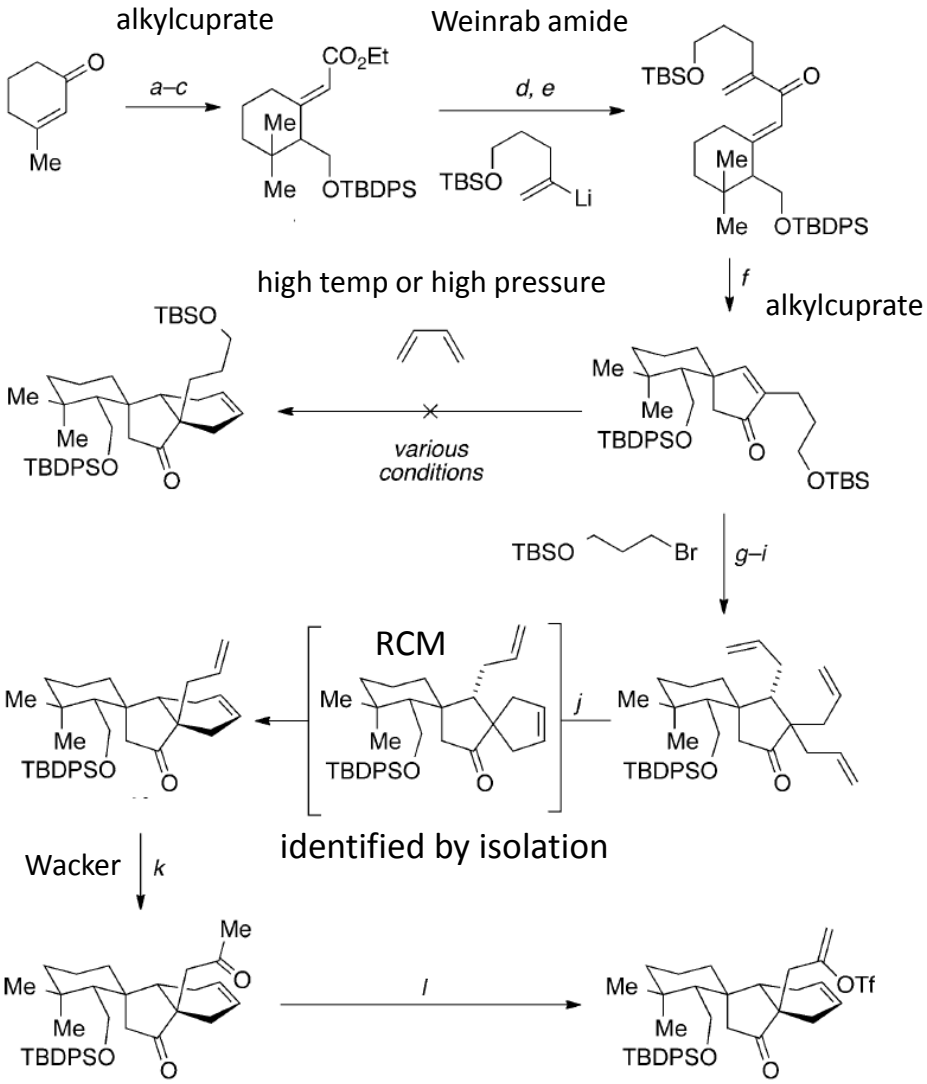
AIBN – resulted in thermodynamic product (maybe due to stabilized radical?)

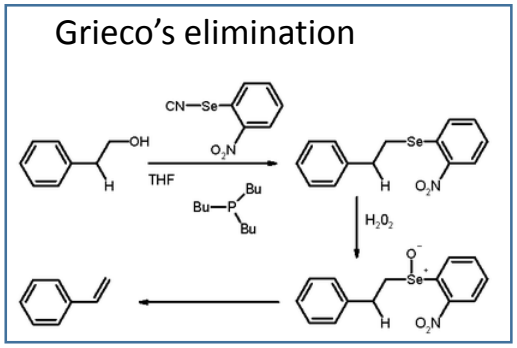
Thomson's synthesis of Sculponeatin N in 2014

Retrosynthesis

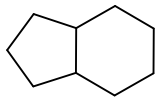


Thomson's synthesis of Sculponeatin N in 2014



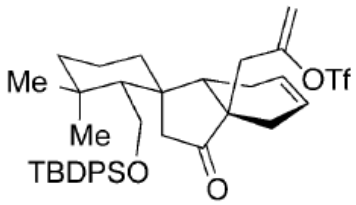


a) MeMgBr (1.2 equiv), CuI (5 mol%), LiCl (10 mol%); then CH_2O, 88%; b) TBDPSCl (1.1 equiv), Im (2.1 equiv), 98%); c) $TMSCH_2CO_2Et$ (2.0 equiv), LDA (2.0 equiv), 57% (87% brsm); d) Me(OMe)NH·HCl (2.0 equiv), *i*PrMgCl (4.0 equiv), 85%; e) **11** (1.2 equiv), 95%; f) 1) $AlCl_3$ (2.0 equiv); 2) TBSCl (1.1 equiv), Im (2.1 equiv), 80%; g) **16** (4.0 equiv), *t*BuLi (8.0 equiv), (2-thiophene)-Cu(CN)Li (4.0 equiv), $BF_3{\cdot}Et_2O$ (4.0 equiv), 78%; h) 1) 10% HF, acetonitrile; 2) the Grieco reagent (2.5 equiv), Bu_3P (3.0 equiv); then H_2O_2 (50 equiv), 71%; i) 1) TMSOTf (6.0 equiv), NEt_3 (8.0 equiv); 2) MeLi (1.2 equiv), allyl iodide (5.0 equiv) 57%; j) Grubbs II (5 mol%), 91%; k) $PdCl_2$ (25 mol%), CuCl (1.5 equiv), O_2; l) KHMDS (1.5 equiv),

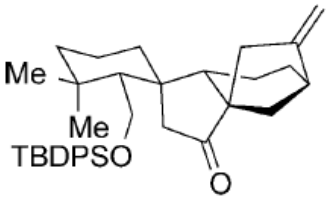


hydrindane

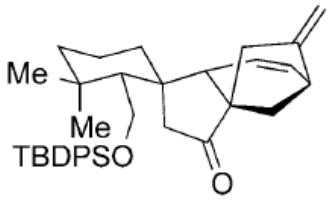
Thomson's synthesis of Sculponeatin N in 2014



conditions



22



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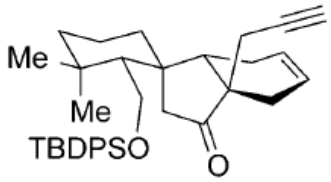


24

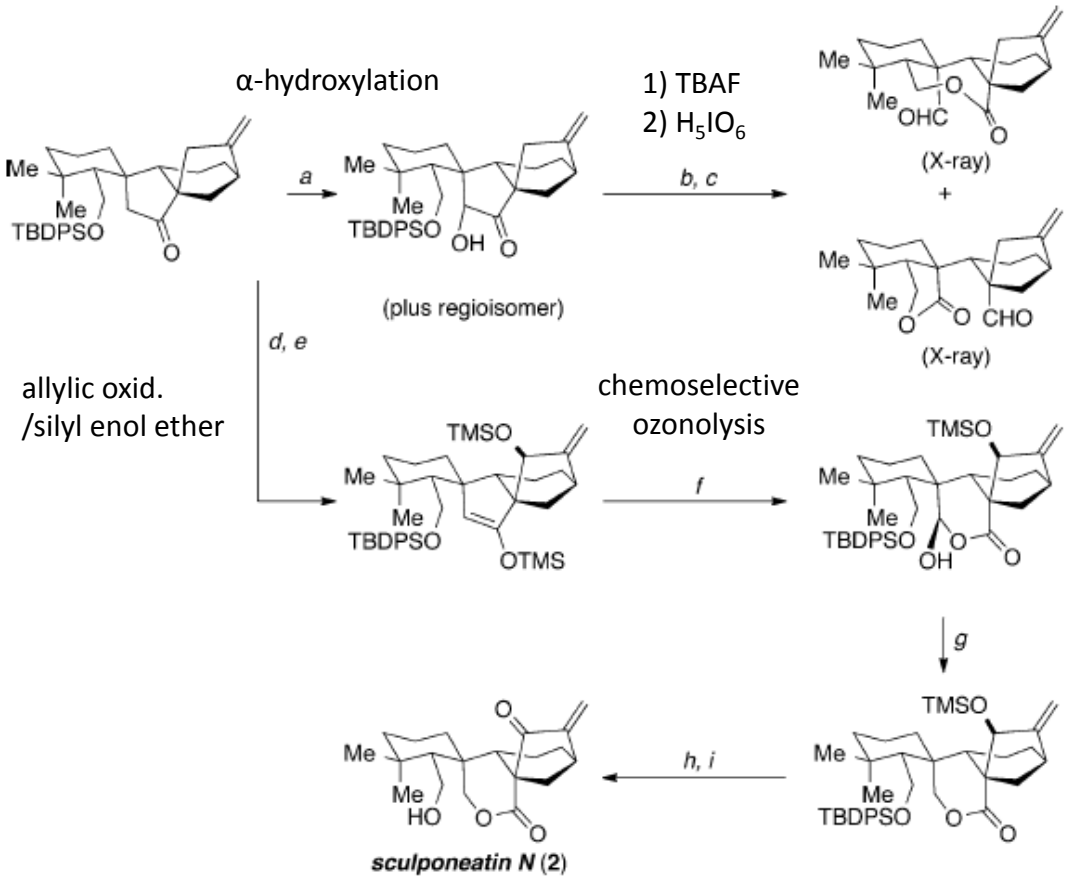
Entry	Reaction conditions	Product(s)	Yield
1	$Pd(PPh_3)_4$ (50 mol%), K_2CO_3, 4 Å MS, MeCN, RT	**23**	43
2	$Pd(OAc)_2$ (10 mol%), TBACl (3.0 equiv) HCO_2Na (2.5 equiv), 4 Å MS, DMF, RT	**22**:**23**:**24** (3:1:6)[b]	68[c]
3	1) TBAF (2.5 equiv), THF, RT 2) Bu_3SnH (4.0 equiv), AIBN (0.1 equiv), toluene, reflux; silica gel	**22**	71

significant by-product

Heck or Reductive Heck – not successful

solution – radical cycl.

Thomson's synthesis of Sculponeatin N in 2014



END GAME
- cyclopentanone to lactone

attempted oxidative cleavage/
re-ring closure upon reduction

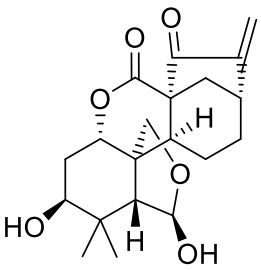
a) 1) TMSOTf (15 equiv), NEt_3 (20 equiv); 2) MeLi (3.0 equiv) MoO_5·Py·HMPA (5.0 equiv), 67%; b) TBAF (10 equiv), 80%; c) H_5IO_6 (3.0 equiv), 42% (**26**), 29% (**27**); d) SeO_2 (2.0 equiv), *t*BuOOH (1.2 equiv); e) TMSOTf (15 equiv), NEt_3 (20 equiv); f) O_3, Py, methanol, chloroform 49% over 3 steps from **22**; g) $LiBH_4$ (5.0 equiv), 50 °C, 47%; h) TBAF (5.0 equiv), 38%; i) MnO_2 (5 equiv by mass), 95%.

23 steps from
3-methyl cyclohexanone;

featuring Nazarov, RCM
to construct two quaternary
carbon centers,
radical cyclization for [3.2.0]bicycle

IN SUMMARY

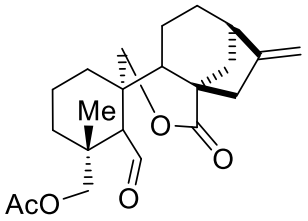
So far 11 total synthesis….Who will be the next??



enmein

Fujita-1972

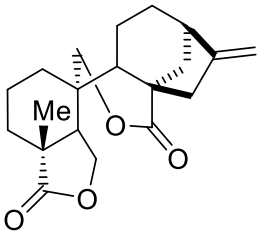
44 steps + α



15-desoxy-effusin

Mander-1986

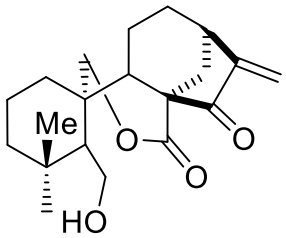
29 steps



longirabdolactone

Mander-2003

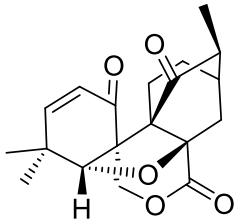
27 steps



Sculponeatin

Zhai-2013 **13 steps + α**

Thomson-2014 **23 steps**



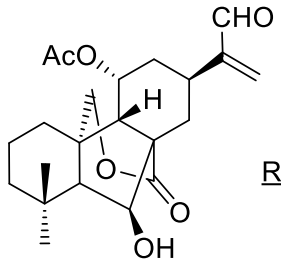
Maoecrystal V

Yang-2010 **31 steps**

Danishefsky-2012 **17 steps**

Zakarian-2013 **18 steps**

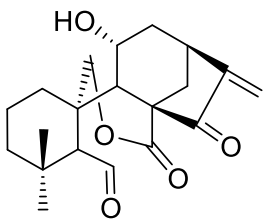
Thomson-2014 **24 steps**



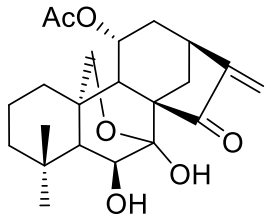
Maoecrystal Z

Reisman-2011 **12 steps + 4**

Diels-Alder
is still predominant!!



(-)-trichorabdal A



(-)-longikaurin

Reisman-2013

15 steps + 4 and 17 steps + 4

THANK YOU FOR YOUR ATTENTION.. Q & A