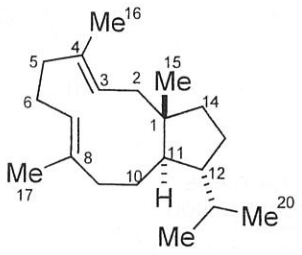
Xu Yingjie (M2)
2009/09/02

Dolabellane



Dolabellane skeleton

E. J. Corey *et al.* *J. Am. Chem. Soc.* **1996**, *118*, 1229.
J. Am. Chem. Soc. **2005**, *127*, 13813.
J. Am. Chem. Soc. **2006**, *128*, 740.

Dolabellane family

Structural feature

♦characteristic *trans*-bicyclo[9.3.0]tetradecane core

Isolation

♦The dolabellanes were originally isolated from the herbivorous sea hare *Dolabella californica.*

Bioactivity

♦The dolabellanes have exhibited an impressive range of biological properties, including significant cytotoxic, antibacterial, and antiviral activity.

Contents:

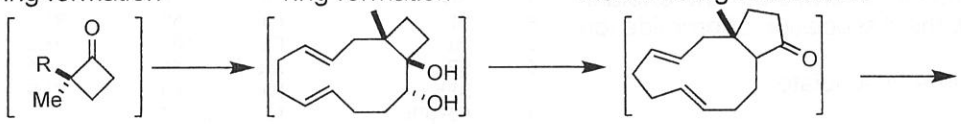
1. Corey`s synthetic strategies

strategy 1.

11-membered ring formation → 5-membered ring formation

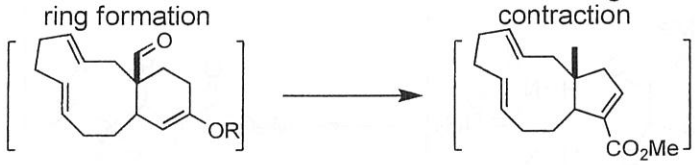
strategy 2.

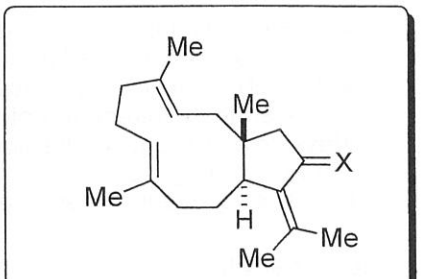
4-membered ring formation → 12-membered ring formation → small ring expansion and medium ring contraction



strategy 3.

11- and 6-membered ring formation → small ring contraction





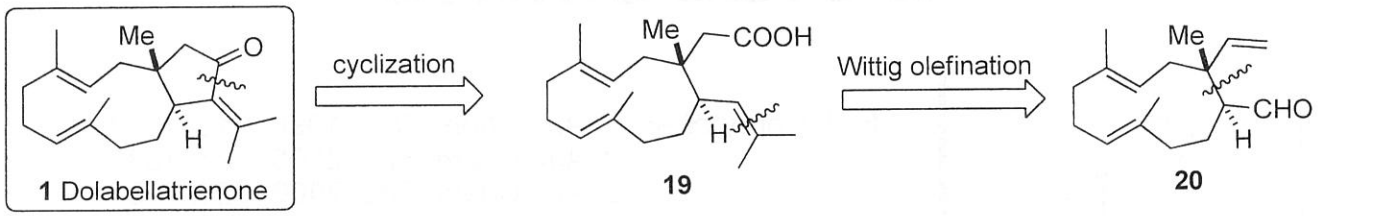
X = H, β-Araneosene
X = O, Dolabellatrienone

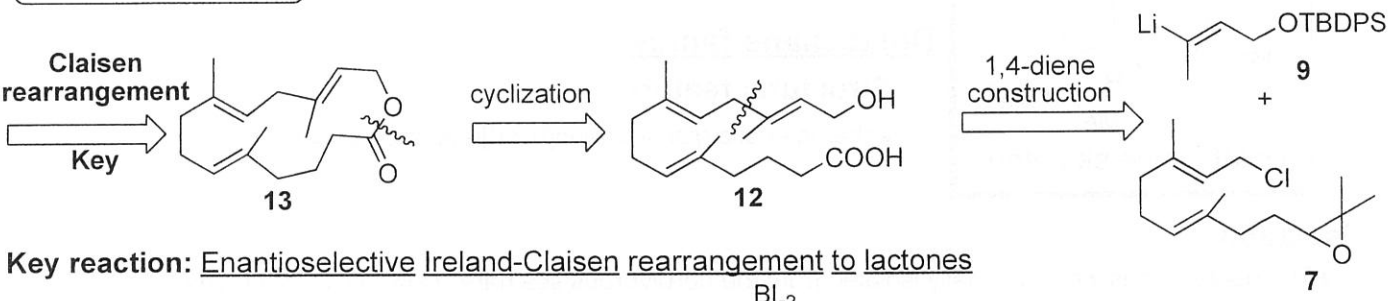
2. Total Syntheses

2-1 First Total Synthesis of Dolabellatrienone

E. J. Corey *et al.* *J. Am. Chem. Soc.* **1996**, *118*, 1229.

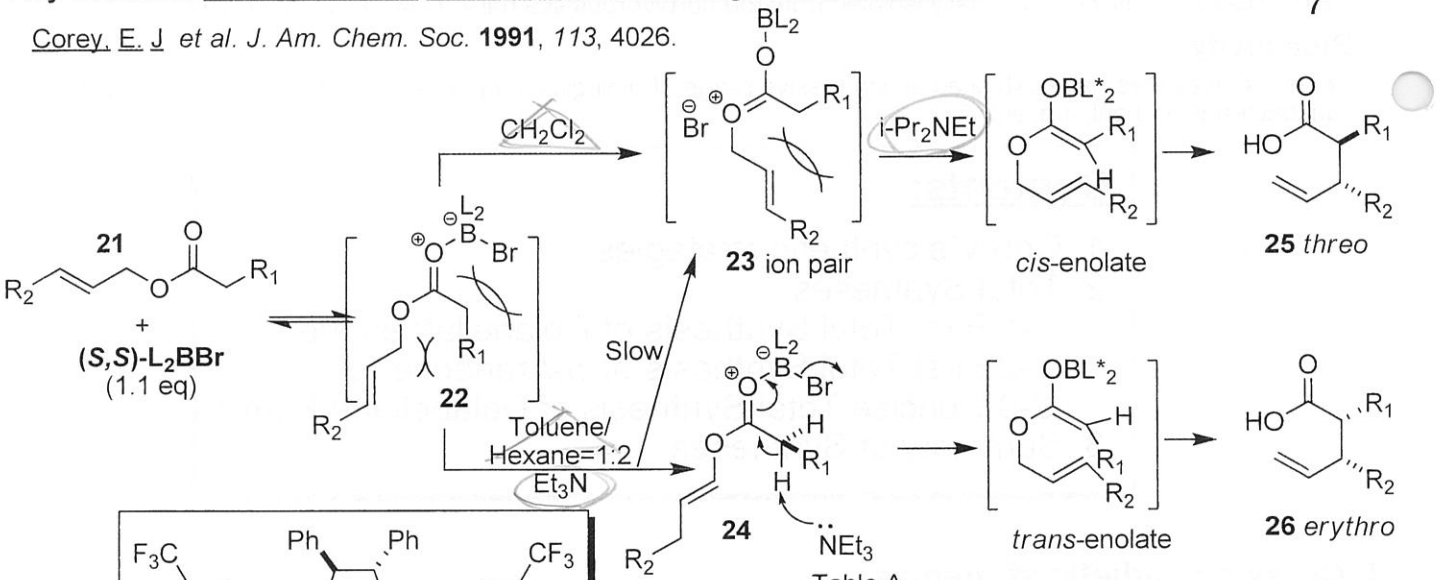
Retrosynthesis

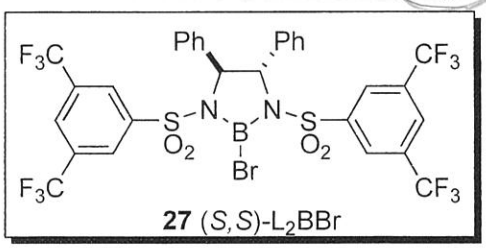




Key reaction: Enantioselective Ireland-Claisen rearrangement to lactones

Corey, E. J *et al. J. Am. Chem. Soc.* **1991**, *113*, 4026.





Corey, E. J *et al.*
J. Am. Chem. Soc. **1989**, *111*, 5493.
J. Am. Chem. Soc. **1990**, *112*, 4976.
J. Am. Chem. Soc. **1995**, *117*, 193.

Table A

entry	R_1	R_2	yield,[a] %	threo:erythro[b]	ee,[c] %
1	Me	Me	75	99:1	>97[f]
2	Et	Me	79	98:2	95[d]
3	Me	Ph	75	91:9	[illegible][f]
4	Et	Ph	72	91:9	>97[f]
5	Ph	Ph	100	23:77	>97[f]
6	SPh	Me	52	39:61	>97[f]
7	CH_2Ph	H	70		82[e]
8	CH_2-1-naphthyl	H	48		77[e]

[a]Reaction times at -20 °C: 14 days for entries 1, 2, 5, 7, and 8; 7 days for entries 3, 4, and 6.

- ♦simply by a change of the solvent and the tertiary amine used for enolate formation.
- ♦sterically smaller Et_3N(relative to DPEA) should accelerate the direct deprotonation to form the *trans*-enolate.
- ♦less polar solvent should slow the dissociation of bromide ion to from the ion pair.
- ♦increasing solvent polarity favors *cis*-enolate.

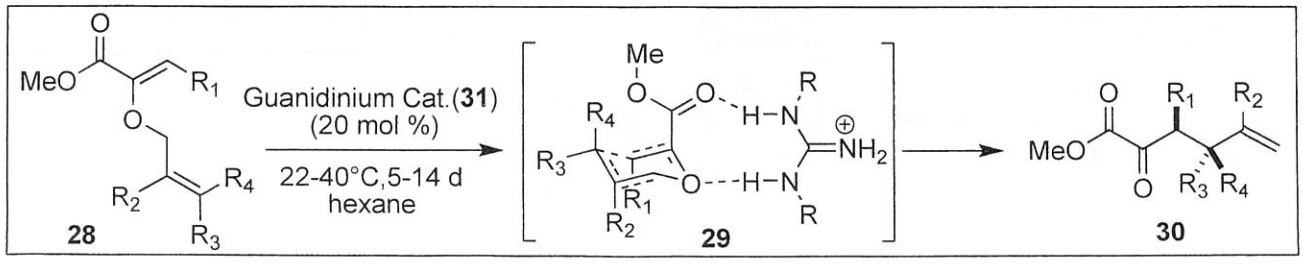
Table B

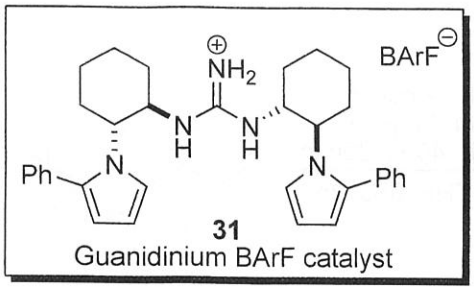
entry	R_1	R_2	yield,[a] %	erythro:threo[b]	ee,[c] %
1	Me	Me	65	90:10	96[h]
2	Et	Me	79	89:11	>97[d]
3	Me	Ph	88	96:4	>97[h]
4	Et	Ph	69	95:5	>97[h]
5	Ph	Ph	100	98:2	>97[e]
6	SPh	Me	56	95:5	>97[f]
7	SPh	Ph	45	91:9	>97[f]
8	CH_2Ph	H	57		84[g]
9	CH_2-1-naphthyl	H	63		79[g]

[a]Reaction times at -20 °C: 14 days for entries 1, 2, 5, and 7-9; 7 days for entries 3, 4, and 6.

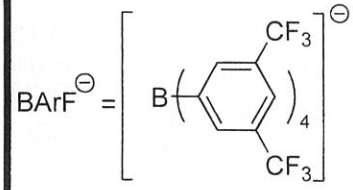
Recent studies

Jacobsen, E. N. *et al. J. Am. Chem. Soc.* **2008**, *130*, 9228.



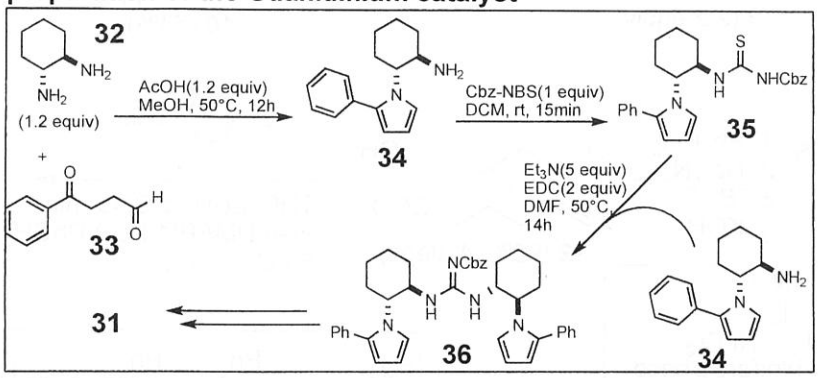


31
Guanidinium BArF catalyst

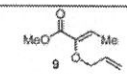
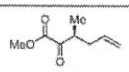
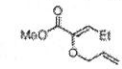
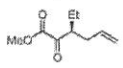
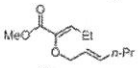
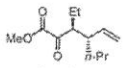
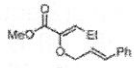
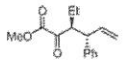
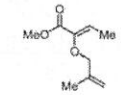
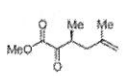
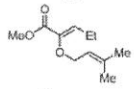
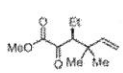
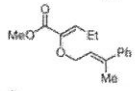
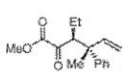
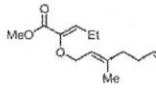
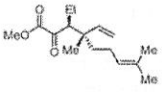


- optimal rates and enantioselectivities were observed in hexanes; catalyst is virtually insoluble in this solvent.
- only guanidinium ions associated to the non-coordinating BArF counterion were found to be effective.

preparation of the Guanidinium catalyst

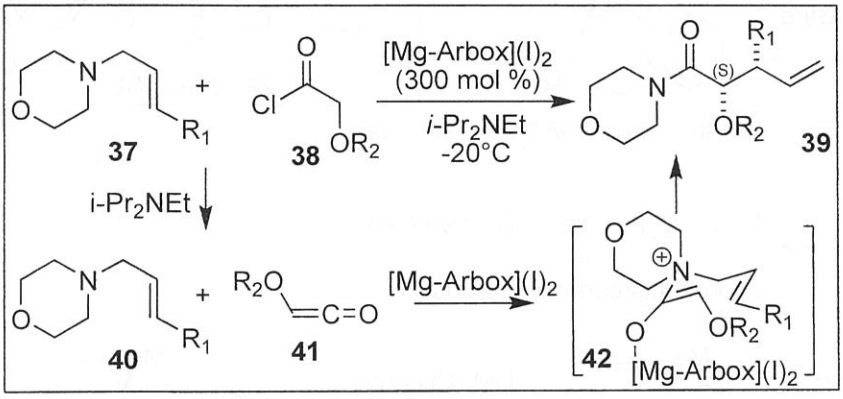


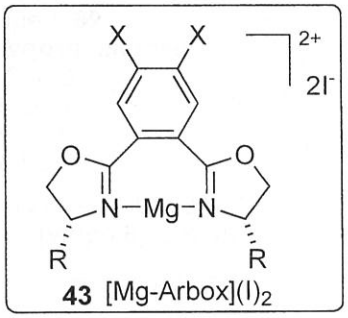
Table

entry	substrate	product[b]	yield[c,d] (%)	ee[e] (%)
1			80	92
2			86	92
3			92 > 20:1 dr	85
4			91 19:1 dr	81
5			73	96
6			89	81
7			89 > 20:1 dr	82
8			73 > 20:1 dr	84

Reactions run on a 0.1 mmol scale in 2 mL of hexanes.

MacMillan, D. W. C. *et al. J. Am. Chem. Soc.* **2001**, *123*, 2911.





43 [Mg-Arbox](I)$_2$

Table A (R_1 = H; R_2 = Bn)

entry	chiral Lewis acid complex	R	X	mol % LA	time (h)	% yield	% ee[a]
1	**1**	–	–	200	24	87	56
2	**2a**	Ph	H	200	24	88	83
3	**2b**	Ph	Cl	200	24	65	86
4	**2c**	*p*-MeOPh	Cl	50	24	81	42
5	**2c**	*p*-MeOPh	Cl	100	24	63	81
6	**2c**	*p*-MeOPh	Cl	200	24	80	91
7	–	–	–	–	24	42	

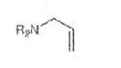
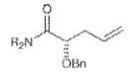
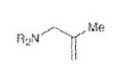
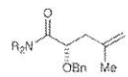
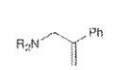
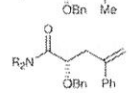
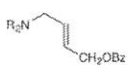
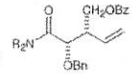
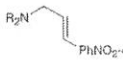
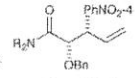
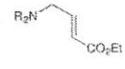
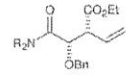
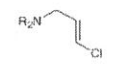
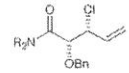
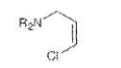
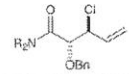
[a] Enantiomeric excess was determined by chiral GLC.

Table B (R_1 = H)

entry	OR2	time (h)	% yield	% ee[a]
1	OAc	20	44	37
2	OTBS	20	67	38
3	OPhCl-4	20	59	71
4	OPh	20	48	78
5	OMe	24	28	80
6	OBn	24	80	91

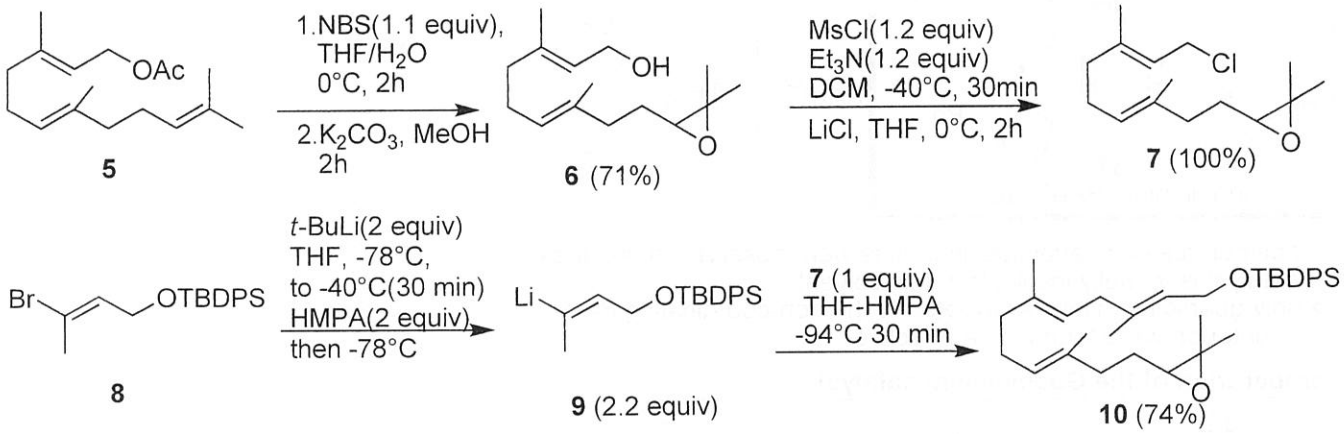
[a] Enantiomeric excess was determined by chiral GLC or HPLC.

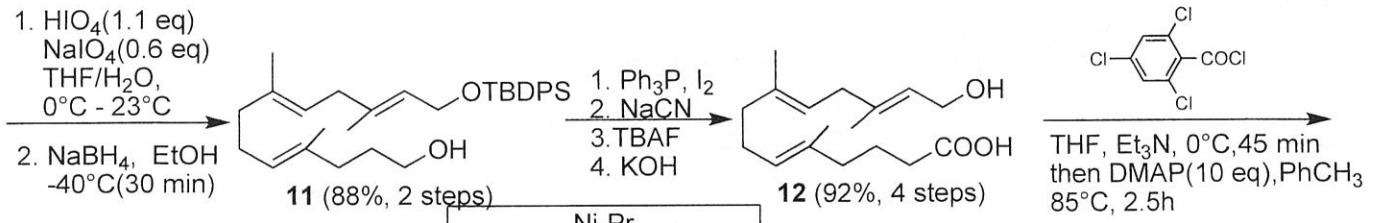
Table C (R_1 = H; R_2 = Bn)

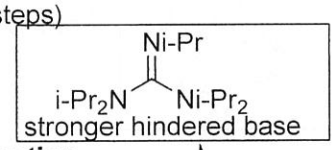
entry	amine[a]	product[a]	% yield	*syn:anti*[b]	% ee[b]
1			80	--	91[c]
2			78	--	91[c]
3			79	--	90
4			86	92:8	86[c]
5			82	99:1	97
6			84	97:3	96
7			95	98:2	91
8			74	3:97	91

[a] NR_2 = N-morpholine. [b] Ratios determined by chiral GLC or HPLC. Absolute stereochemistry determined by chemical correlation or by analogy. [c] Reaction performed with 200 mol % Cat..

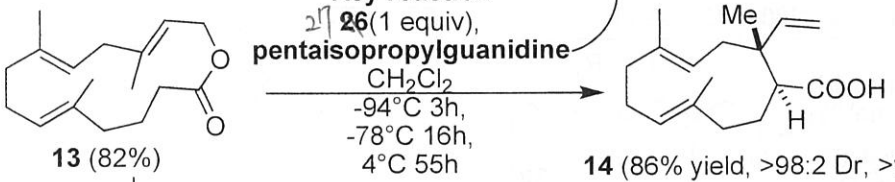
Total synthesis

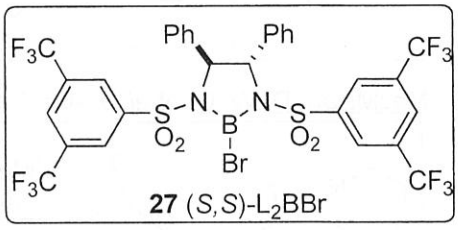


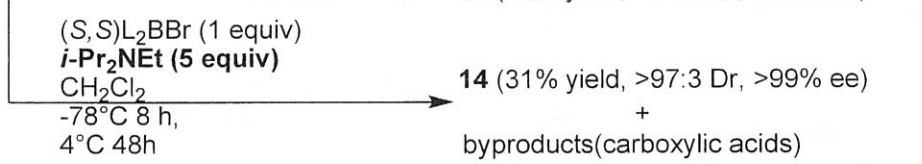


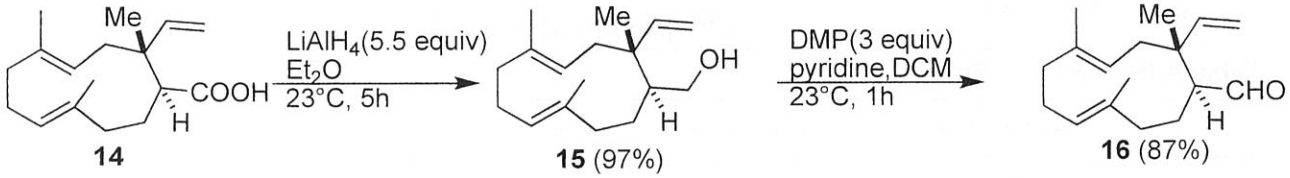


Key reaction

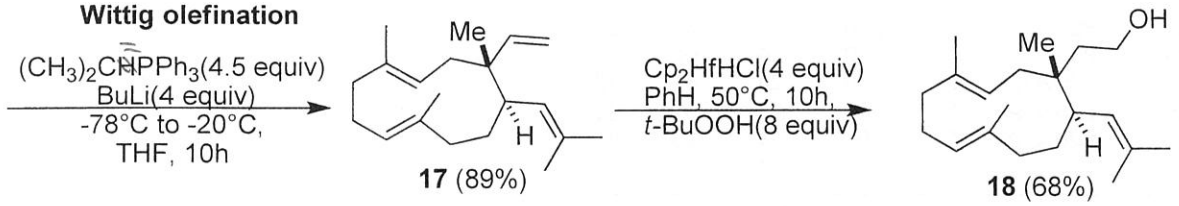


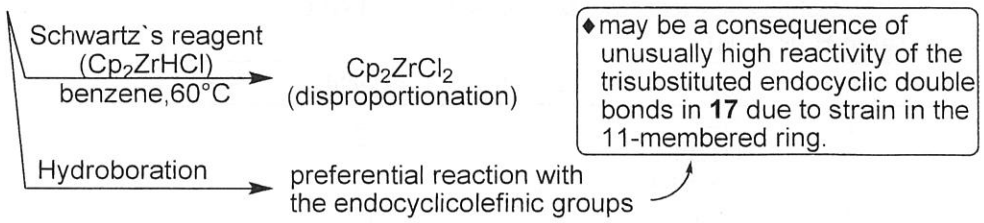


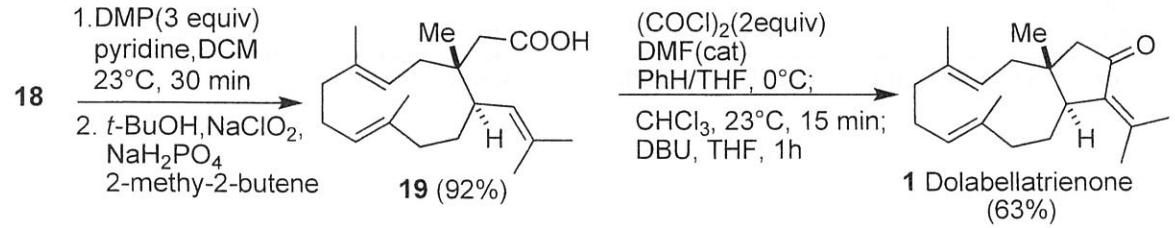




Wittig olefination



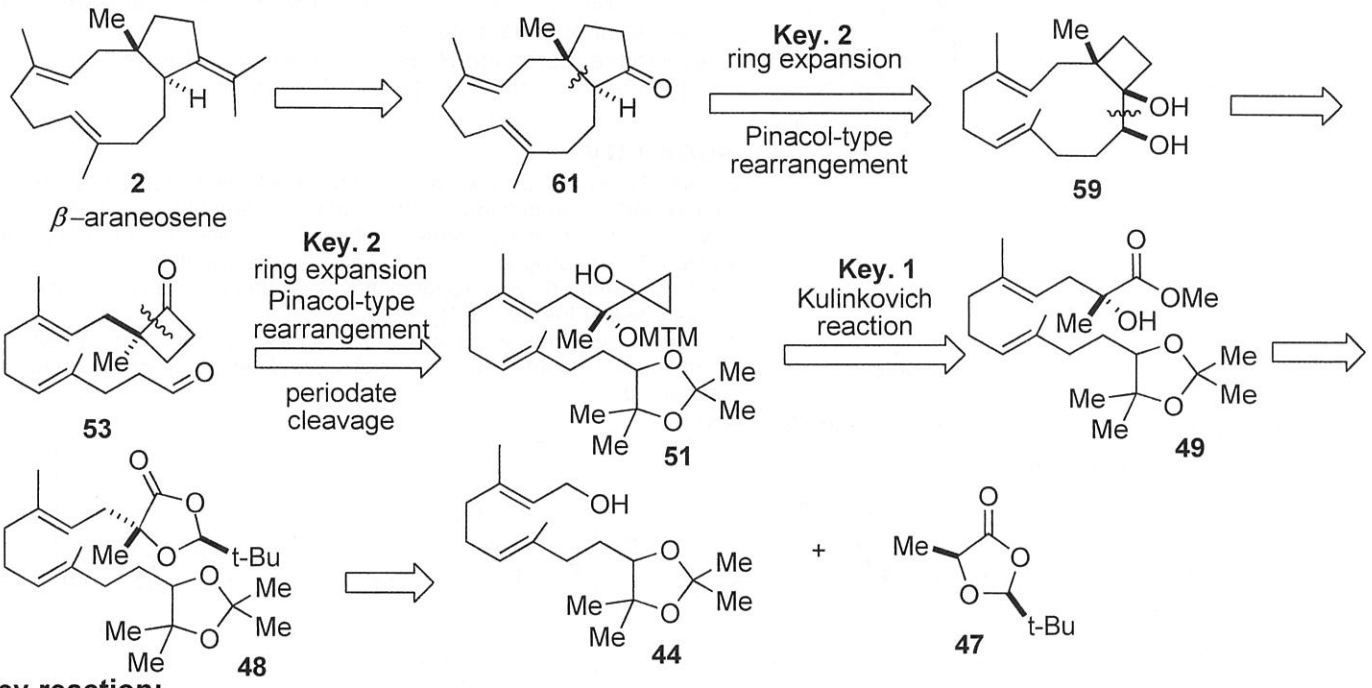




2-2 First Total Synthesis of β-Araneosene

E. J. Corey *et al.* *J. Am. Chem. Soc.* **2005**, *127*, 13813.

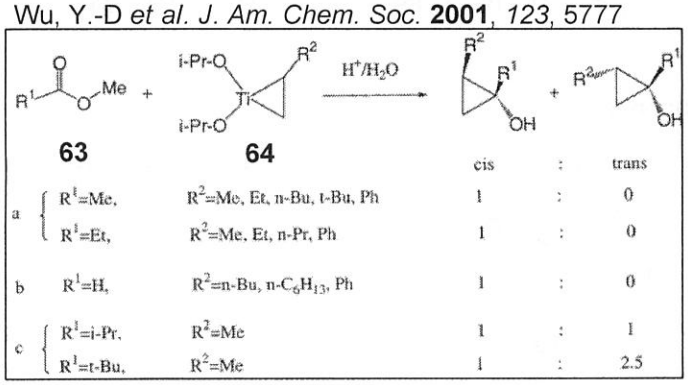
Retrosynthesis

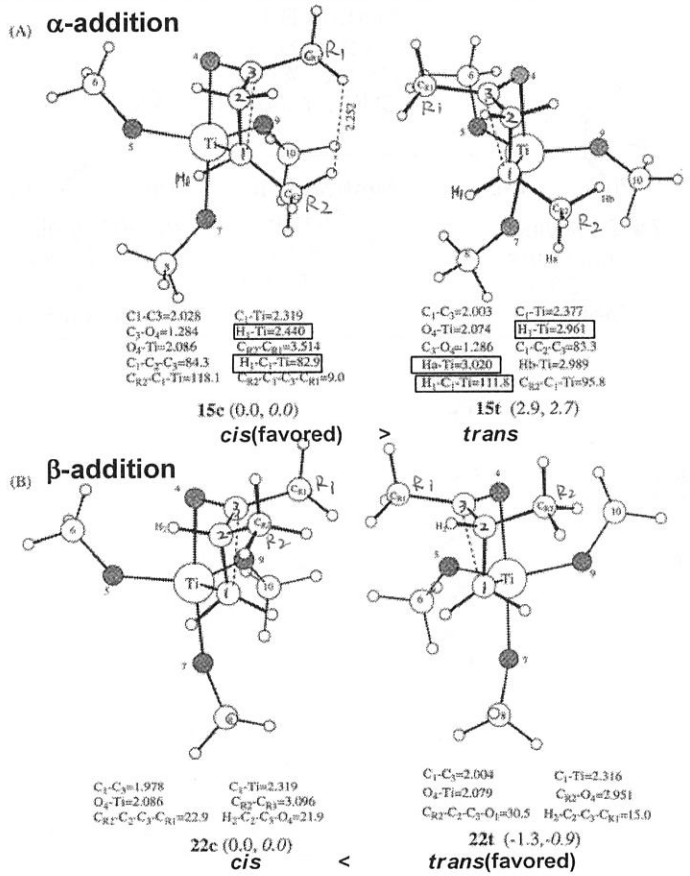


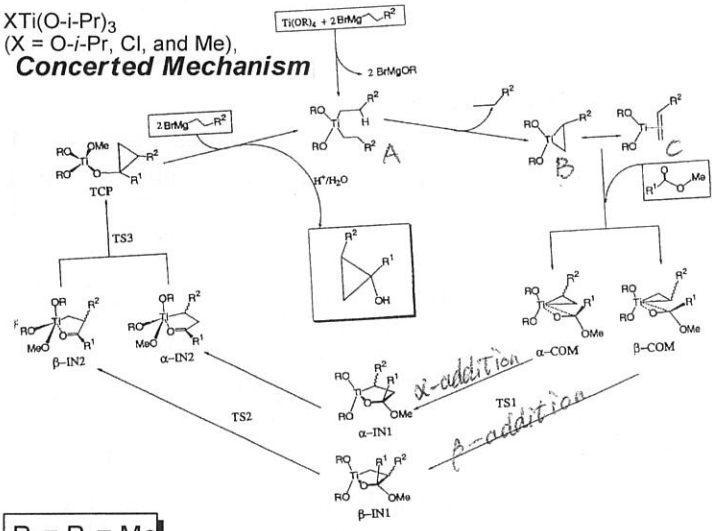
Key reaction:

1. Kulinkovich cyclopropanation(**49** ⟶ **51**)

Wu, Y.-D *et al. J. Am. Chem. Soc.* **2001**, *123*, 5777



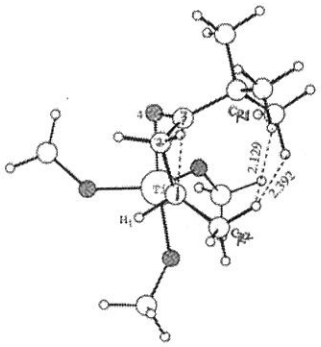




R_1= R_2= Me

- ♦α-addition manifold(A) is generally favored.
- ♦If β-addition manifold were the favored pathway, trans-R_1/R_2 cyclopropanol(22c) would be the major product.
  TS_3 22c:C_2-C_3 bond becomes nearly eclipsed in TS_3, It is about 1.3 kcal/mol less stable than TS_3 22t.
- ♦This is in contradiction to experimental observations, further supporting the conclusion that the α-addition manifold is the favored pathway.
- ♦α-addition:the cis-R_1/R_2 cyclopropane-forming transition state is stabilized by the (C_1)H-Ti **agostic interaction** [a] but destabilized by the R_1-R_2 repulsion.
- ♦TS_3 15c benefits from an agostic interaction. (denoted as (H_1-Ti = 2.440Å ,Ti-C_1-H_1 = 83°).
- ♦The agostic interaction in TS3 15t is absent (H1-Ti = 2.961Å ,Ti-C1-H1 = 112°).
- ♦R_2 methyl group in 15t suffers from steric interactions with the metal center.(Ha-Ti = 3.020Å, Ti-C_1-CR_2 = 96°)

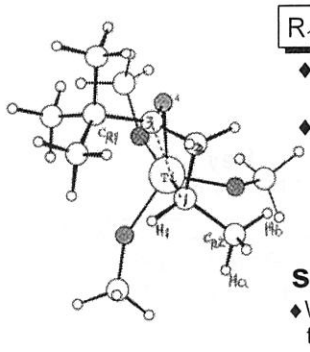
[a] ***Agostic interaction*** is a term in organometallic chemistry for the interaction of a coordinately-unsaturated transition metal with a C-H bond, when the two electrons involved in the C-H bond enter the empty d orbital of a transition metal, resulting in a two electron three center bond.



C_1-C_3=2.007 O_4-C_3=1.297
H_1-Ti=2.355 C_1-C_3=2.007
C_1-Ti=2.351 O_4-Ti=2.035
H_1-C_1-Ti=76.7 C_{R2}-C_1-Ti=122.5

24c (0.0, *0.0*)
cis

≈



C_1-C_3=2.032 H_a-Ti=3.135
C_1-Ti=2.421 H_b-Ti=3.164
O_4-Ti=2.040 C_3-O_4=1.290
H_1-C_1-Ti=113.3 C_{R2}-C_1-Ti=99.9

24t (0.1, *0.2*)
trans

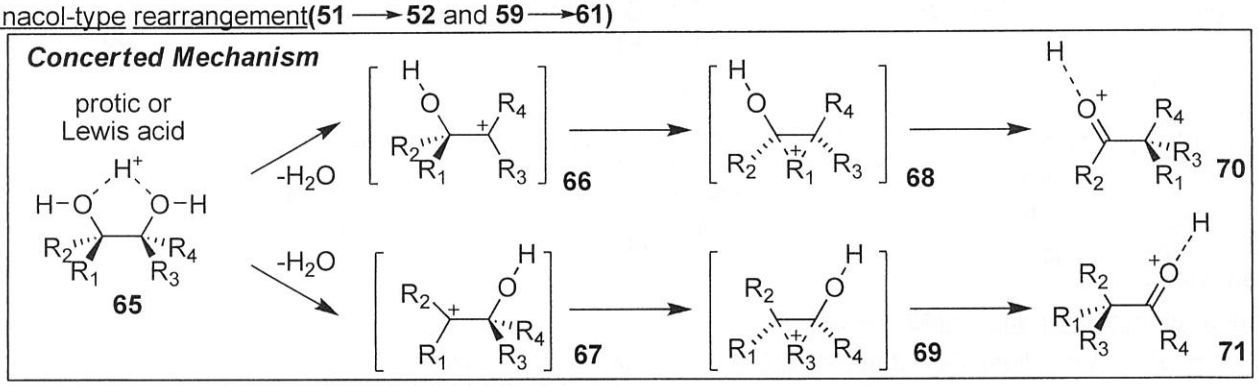
R_1=*t*-Bu, R_2= Me

- The β-addition should be excluded due to R_2-ester repulsion in its cycloinsertion TS_1,larger than TS_3 22t.
- The preference for the cis-R_1/R_2 TS_3 24c over the trans-R_1/R_2 TS_3 24t almost disappears.
  due to the increased R_1-R_2 repulsion in the former, which has two close (R_1)H—H(R_2) contacts. (2.129Å and 2.392Å)

summary

- When R_1 and R_2 are alkyl groups, the Kulinkovich reaction favors the α-addition manifold over the β-addition manifold since the cycloinsertion transition states of the latter involves R_2–ester repulsion.
- When R_1 is hydrogen or primary alkyl groups, the final 1,2-disubstituted cyclopropanol has its R_1 and R_2 in a *cis* relationship, regardless of the size of R_2 group.
- When R_1 becomes secondary or tertiary alkyl groups, and R_2=Me, a mixture of cis and trans 1,2-disubstituted cyclopropanols can be observed.

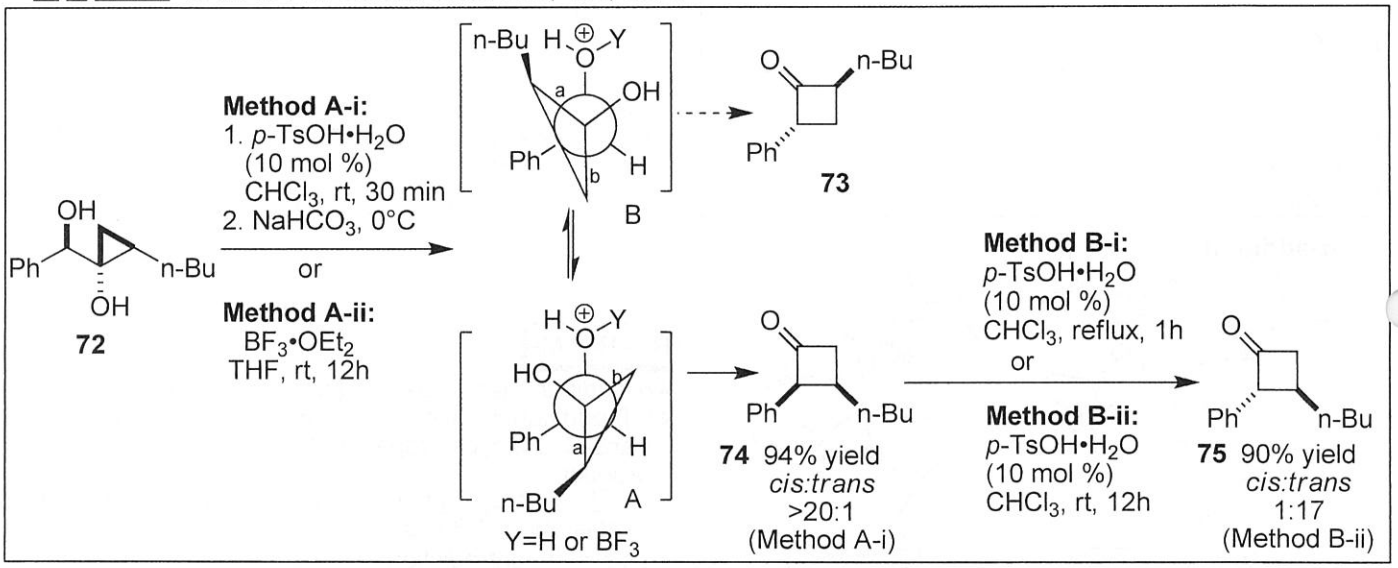
2. Pinacol-type rearrangement(**51** ⟶ **52** and **59** ⟶ **61**)



3 ⟶ 4 ring formation

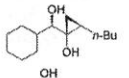
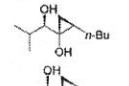
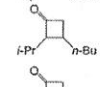
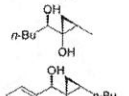
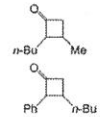
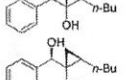
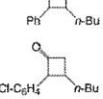
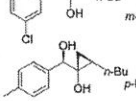
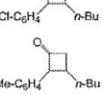
Diastereoselective Synthesis of 2,3-Disubstituted Cyclobutanones

P. J. Walsh *et al. J. Am. Chem. Soc.* **2009**, *131*, 6516



- conformer A is less hindered
- migration of the more substituted C-C bond (a) is favorable
- the *cis* isomer can be rationalized by the rearrangement of conformer A with breakage of bond (a)
- the *trans* isomer can be explained by isomerization of the kinetic *cis* product to the thermodynamic *trans* product via enol formation.
- *cis* product can be equilibrated to the *trans*

cis/*trans* >20:1	prolonged treatment with *p*-TsOH ⟶	*cis*/*trans* = 1:17

entry	α-hydroxy cyclopropyl carbinol	cyclobutanones	Method	*cis*:*trans*[a]	isolated yield (%)
1			A-i	>20:1	94
			B-ii	>1:20	90
2			A-i	>20:1	95
			B-i	>1:20	80
3			A-i	>20:1	99
			B-i	1:5	89
4			A-i	>20:1	99
			B-ii	1:17	90
5			A-i	17:1	99
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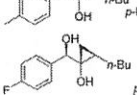
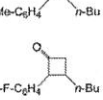
6			A-i	>20:1	94
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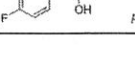
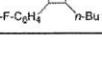
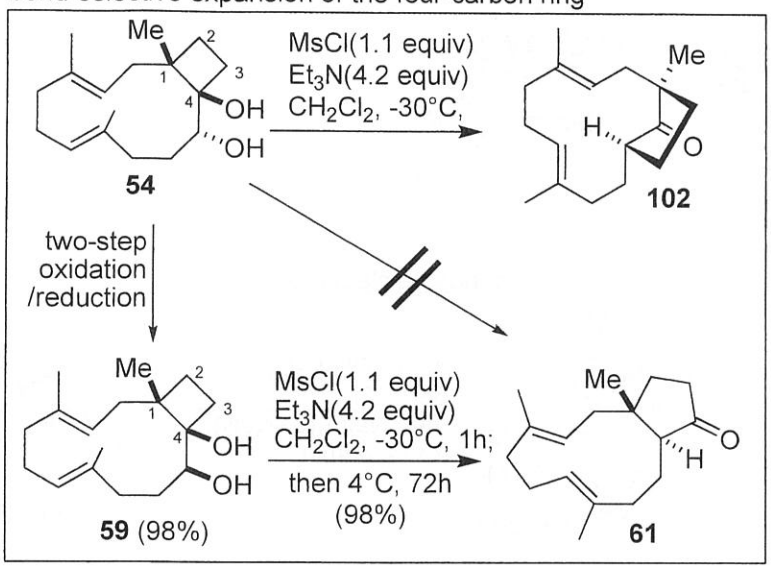
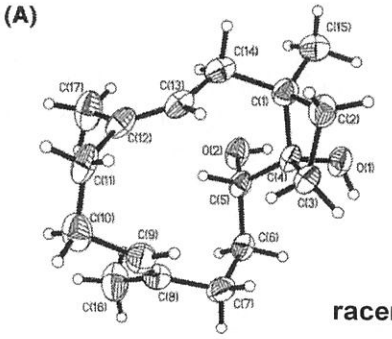
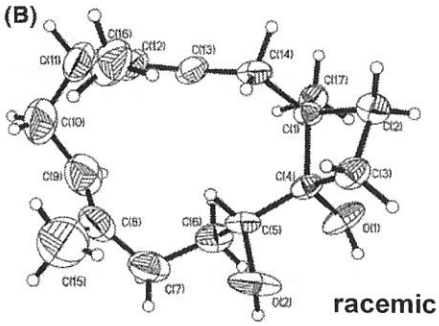
7			A-i	>20:1	99
			B-i	20:1	80

4 → 5 ring formation

bond-selective expansion of the four-carbon ring





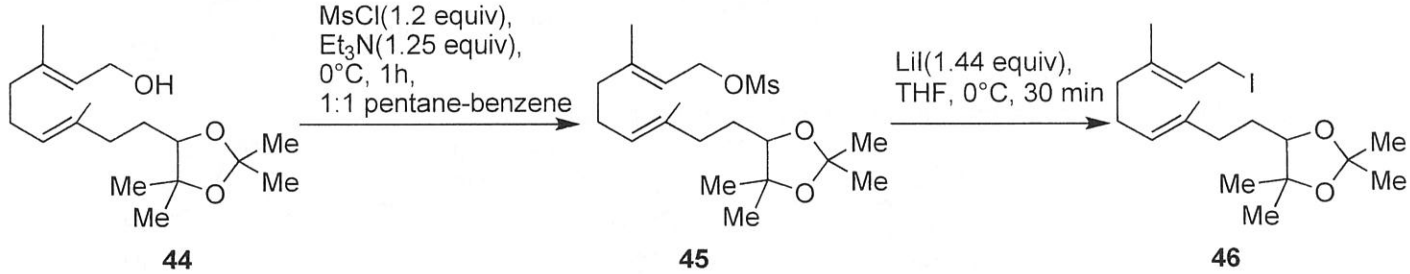


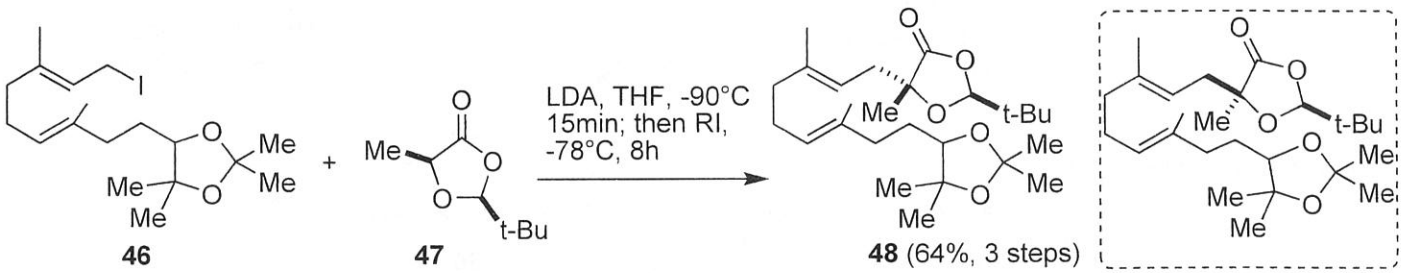
- although the trans diol **54** might serve as a direct precursor to key intermediate **61**, it transpired that the exclusive pinacol rearrangement product formed upon activation of the secondary hydroxyl is the *bridged* 5,12-bicyclopentanone **102**.

54: conformational rigidity enforced by the 12-membered ring results in a stereoelectronic preference for 1,2-migration of the less substituted, exocyclic cyclobutane bond (C4-C3, bond length 1.543(3) Å), even though the internal σ bond (C1-C4, 1.567(3) Å) is considerably weaker.

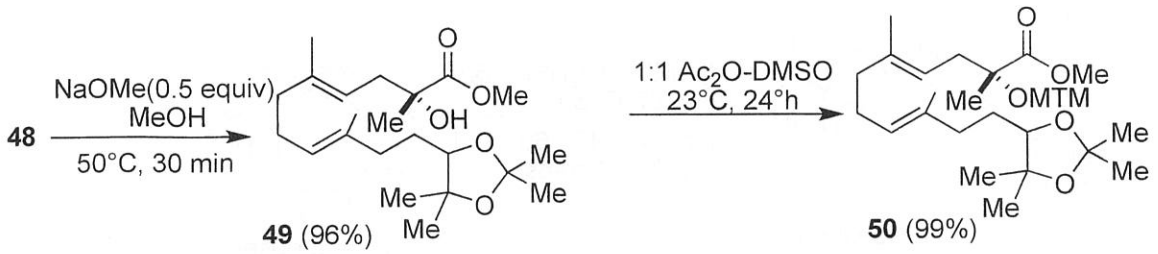
59: situates the longer C1-C4 linkage antiperiplanar to the secondary C-O bond.

Total synthesis

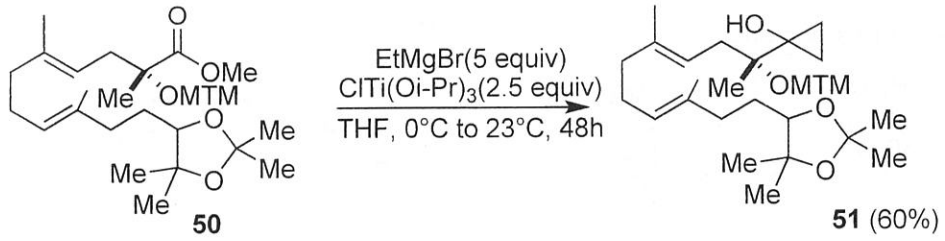




- The diastereomer that would result from electrophilic attack at the more screened face of the chiral metal enolate could not be detected in the unpurified reaction mixture.

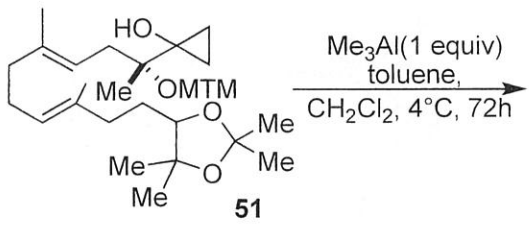


Kulinkovich cyclopropanation



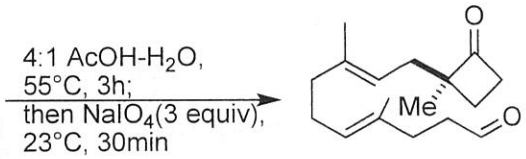
50 **51** (60%)

Pinacol-type rearrangement



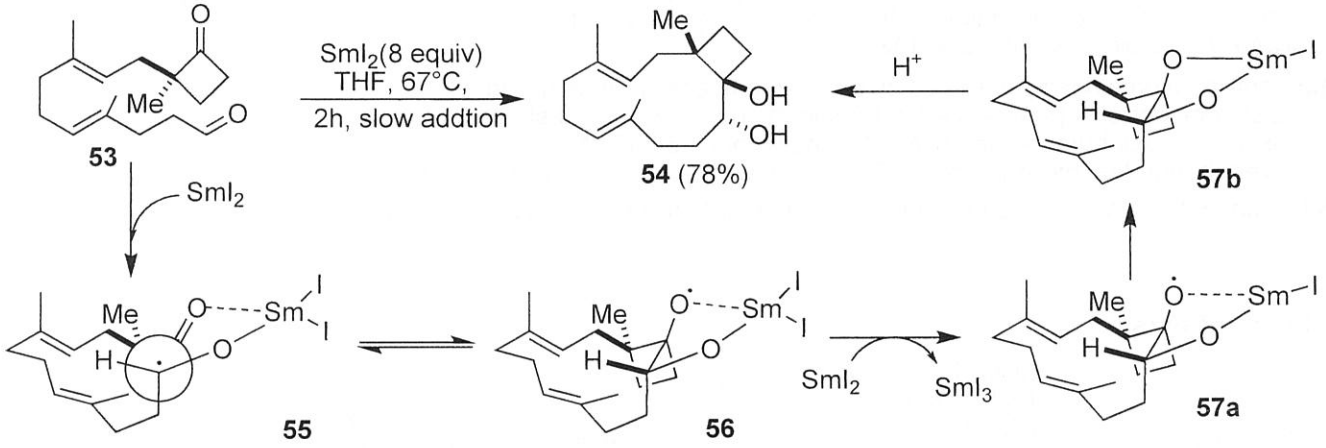
51 **52** (90%)

periodate cleavage



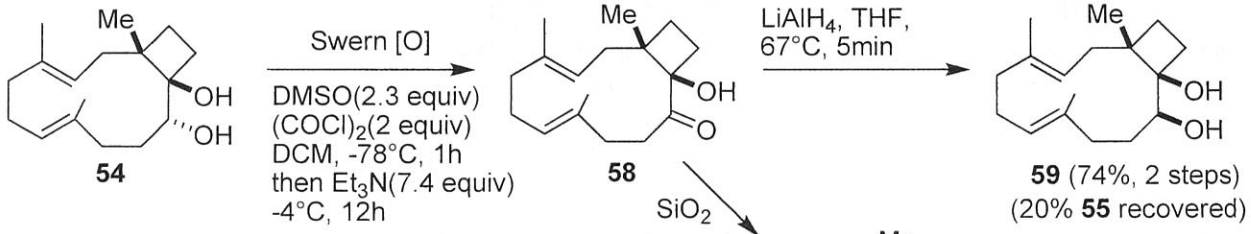
53 (92%)

reductive macrocyclization with SmI_2



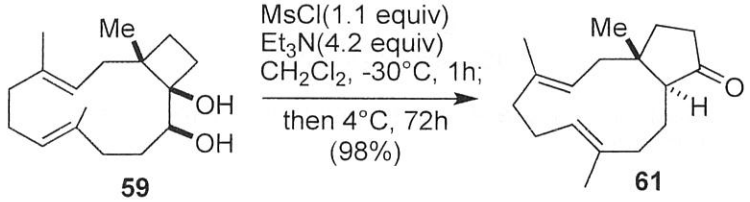
53 **54** (78%) **55** **56** **57a** **57b**

oxidation/reduction—structural change for bond-selective expansion

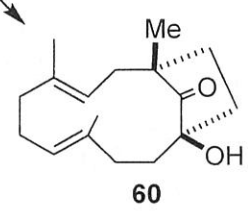


54 **58** **59** (74%, 2 steps)
(20% **55** recovered)

second
Pinacol-type rearrangement

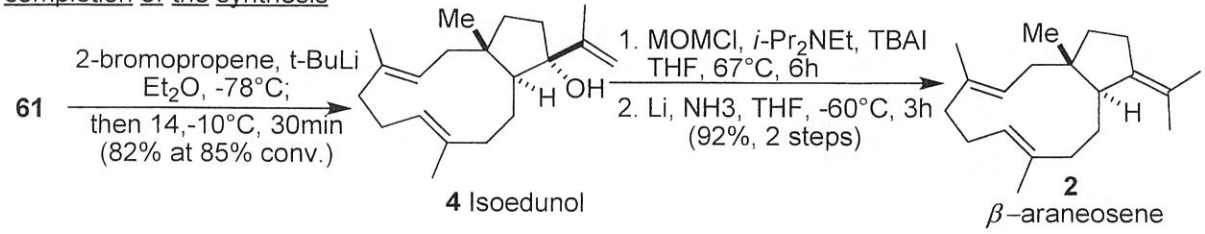


59 **61**



(>98%) **60**

completion of the synthesis

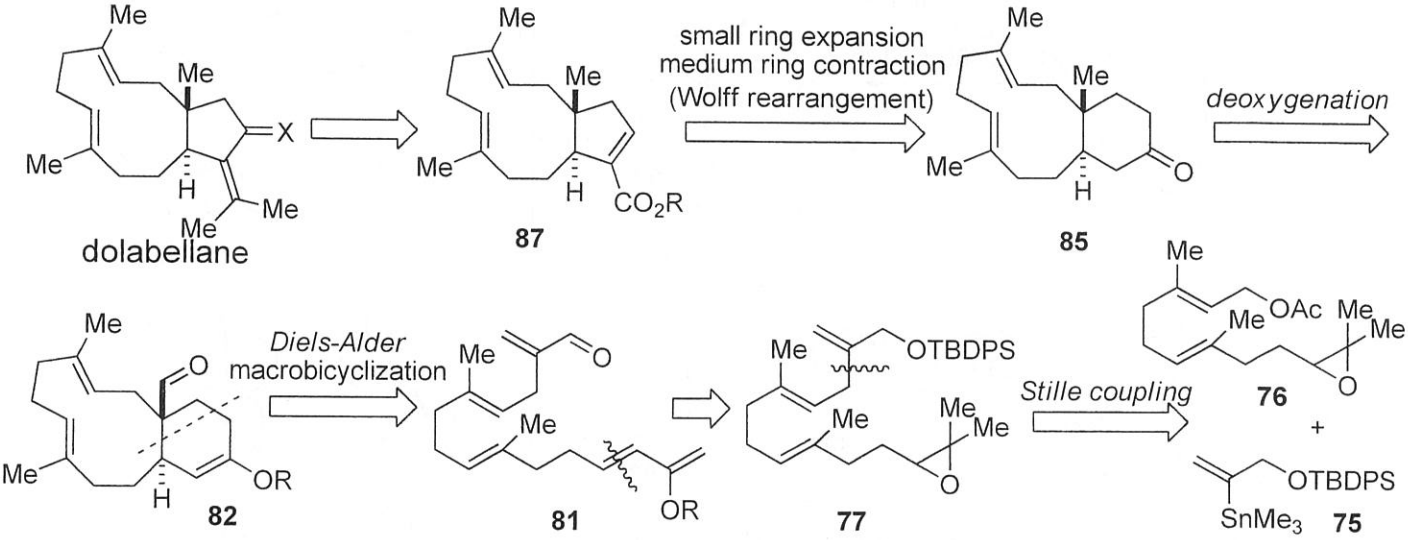


4 Isoedunol **2** β–araneosene

2-3. Concise Total Synthesis of dolabellane family

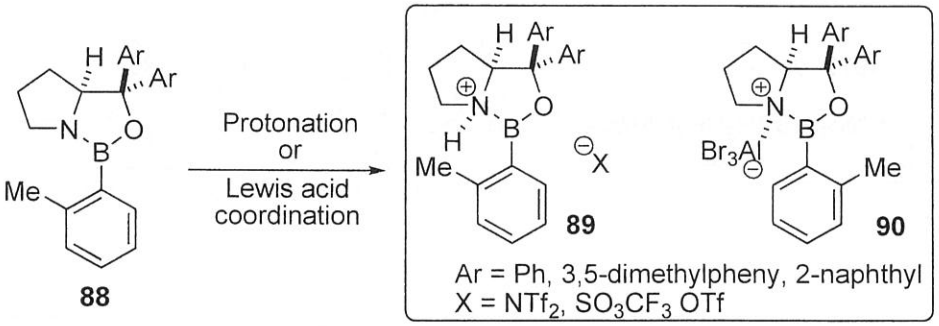
E. J. Corey *et al. J. Am. Chem. Soc.* **2006**, *128*, 740.

Retrosynthesis



Key reaction:

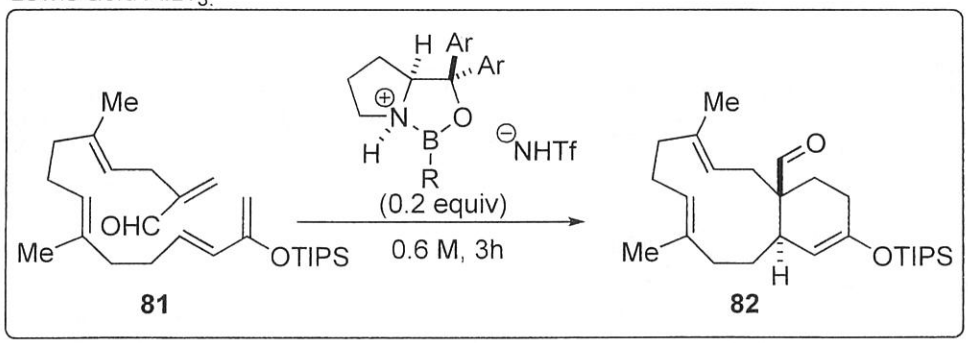
1. Enantioselective Diels-Alder Reactions catalyzed by **a chiral oxazaborolidinium cation** .



Corey, E. J et al.
J. Am. Chem. Soc. **2007**, *129*, 1499.
J. Am. Chem. Soc. **2004**, *126*, 4800.
J. Am. Chem. Soc. **2003**, *125*, 6388.
J. Am. Chem. Soc. **2002**, *124*, 9992.
J. Am. Chem. Soc. **2002**, *124*, 3808.

Oxazaborolidine is quite a weak base, its full protonation can only beachieved using a very strong acid such as $HNTf_2$, HSO_3CF_3, HOTf or strong Lewis acid $AlBr_3$.

chiral oxazaborolidinium cation is an extraordinarily useful broad-spectrum catalyst for numerous highly enantioselective Diels-Alder reactions.



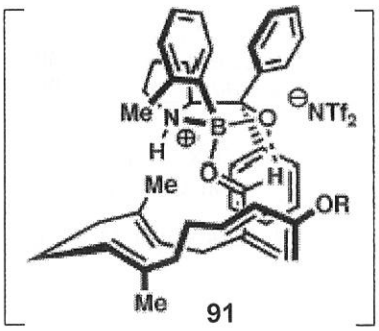


Table. Optimization of the enantioselectivity of the Diels-Alder reaction converting **81** into **82**.

Entry	Catalyst	Solvent	Temp	Ar	R	*endo/exo*	*e.e.*
1	(*S*)	toluene	-78 °C	Ph	2-MePh	20:1	80.3
2	(*R*)	toluene	-78 °C	Ph	2-MePh	20:1	86.4
3	(*S*)	CH_2Cl_2	-78 °C	Ph	2-MePh	20:1	55.8
4	(*S*)	toluene	-78 °C	Ph	Ph	13:1	87.2
5	(*S*)	CH_2Cl_2	-78 °C	Ph	Ph	12:1	69.6
6	(*S*)	toluene	-93 °C	Mes	Ph	12:1	87.8
7	(*S*)	toluene	-93 °C	Mes	2-MePh	12:1	87.7
8	(*S*)	toluene	-93 °C	Ph	2-MePh	20:1	90.4

♦standard achiral initiators: such as Me_2AlCl, $MeAlCl_2$, $EtAlCl_2$, or heat deprotected and/or polymerized **81**, without detectable conversion to **82** or any other Diels-Alder-type product

2. Novel methodology of deoxygenation

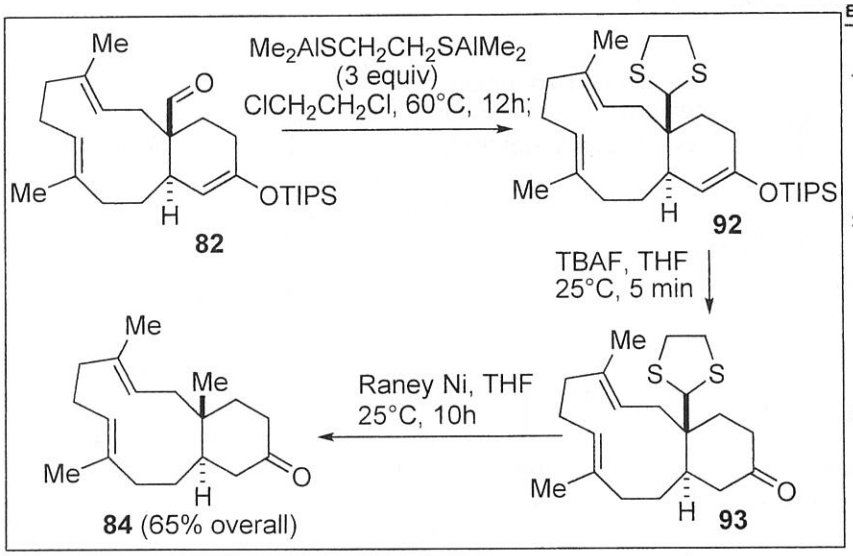
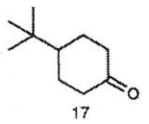
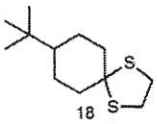
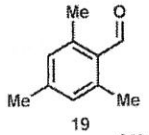
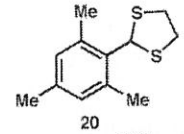
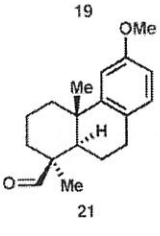
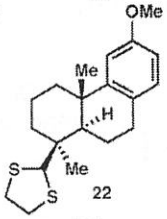
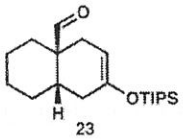
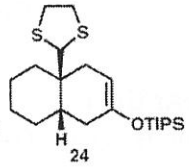
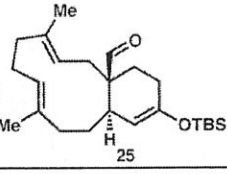
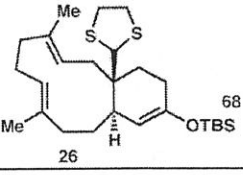


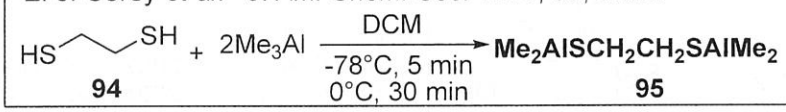
Table. $Me_2AlSCH_2CH_2SAlMe_2$-Induced Dithiane Formationa

Entry	Starting material	Product	Yield (%)
1	 17	 18	83
2	 19	 20	87
3	 21	 22	79
4	 23	 24	72
5	 25	 26	68

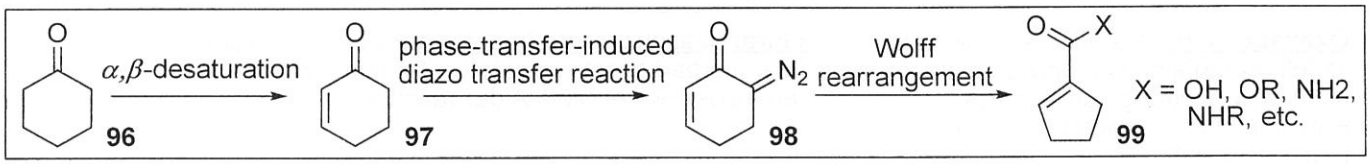
[a] With 3 equiv of sulfide reagent at 60°C in 1,2-dichloroethane for 2-12h

- many other reagents and methods for *thioacetalization* failed because of vinyl ether cleavage and further reaction.
- alternative protocols, such as Wolff-Kishner reduction and Barton-McCombie deoxygenation,also failed.

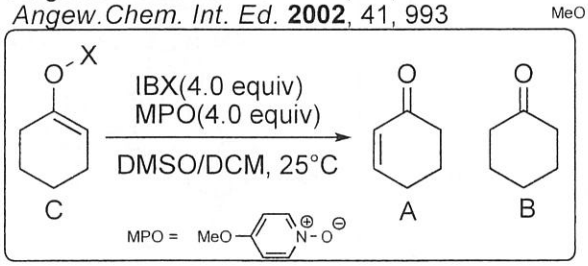
E. J. Corey *et al.* *J. Am. Chem. Soc.* **1973**, *95*, 5829.



3. Ring contraction { α,β-desaturation; Wolff rearrangement



K. C. Nicolaou et al.
Angew.Chem. Int. Ed. **2002**, 41, 996
Angew.Chem. Int. Ed. **2002**, 41, 993



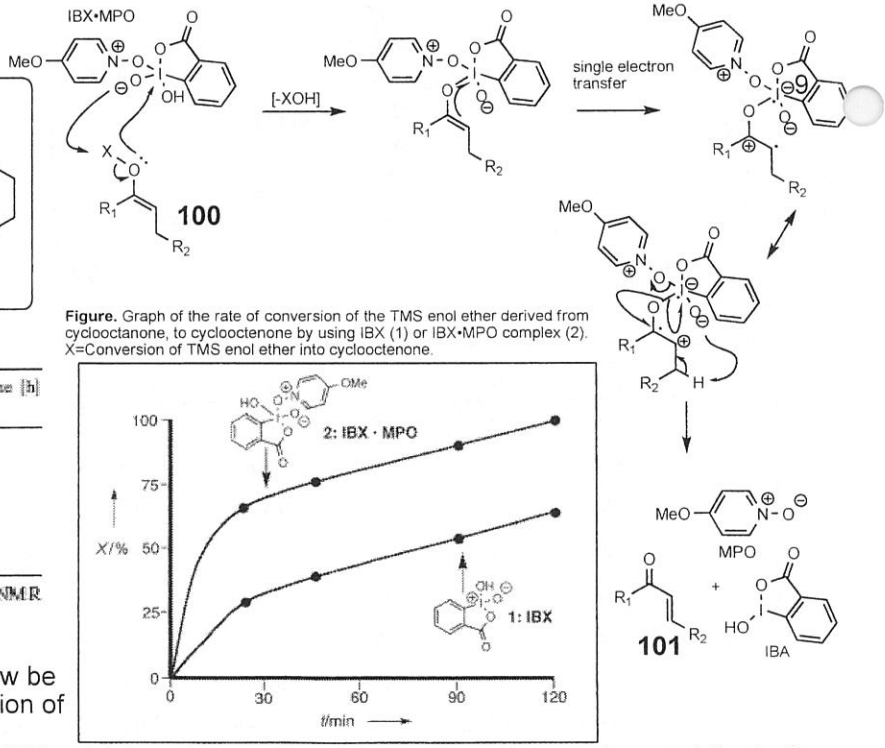


Table. Reactions of various enol ether derivatives of cyclohexanone with IBX•MPO complex.

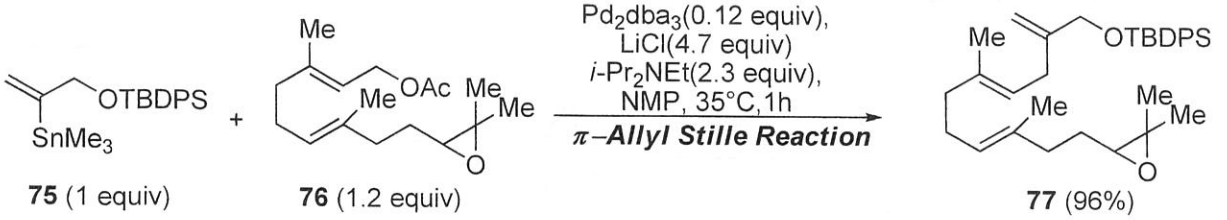
Enol ether 58	X	58	Products[b] A		B	Time [h]
a:	TMS	0	0	:	1	1
b:	TES	0	1	:	18	8
c:	TBS	1	0	:	0	12
d:	Ac	8	1	:	0	12
e:	Me	3	6	:	1	2
f:	$CH_2CH=CH_2$	3	8	:	1	1

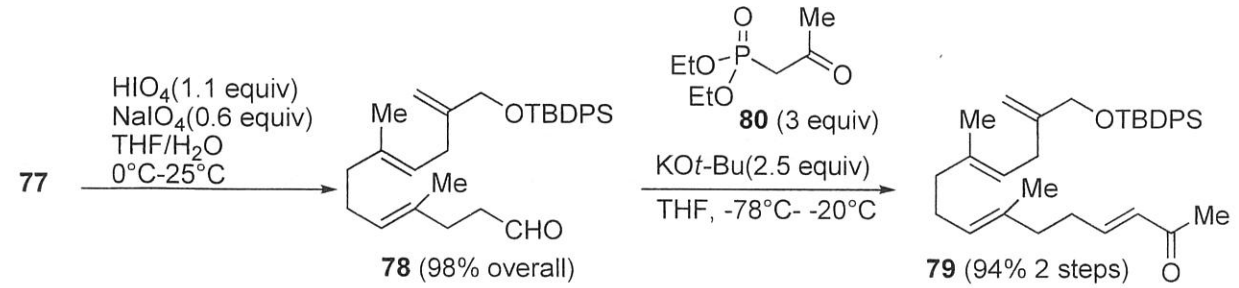
[a] see main text for discussion. [b] Ratios determined by ^1H NMR spectroscopy.

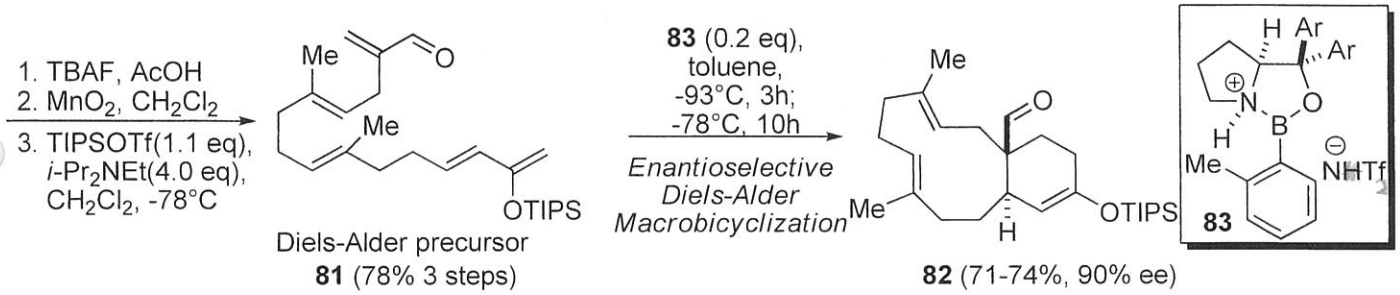
Figure. Graph of the rate of conversion of the TMS enol ether derived from cyclooctanone, to cyclooctenone by using IBX (1) or IBX•MPO complex (2). X=Conversion of TMS enol ether into cyclooctenone.

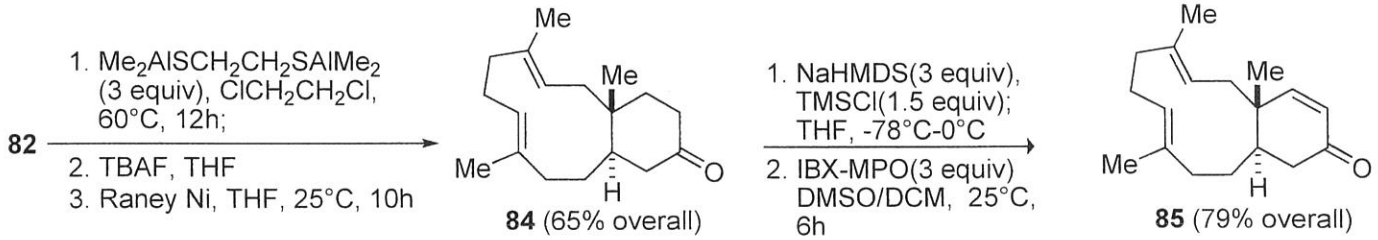
- A diverse set of carbonyl compounds can now be dehydrogenated with ease by the fast oxidation of the corresponding TMS enol ethers.
- when heteroatom oxide ligands appended to IBX, might provide a unique electronic environment around the iodine center which could enhance the propensity of these reagents to serve as electron sinks.

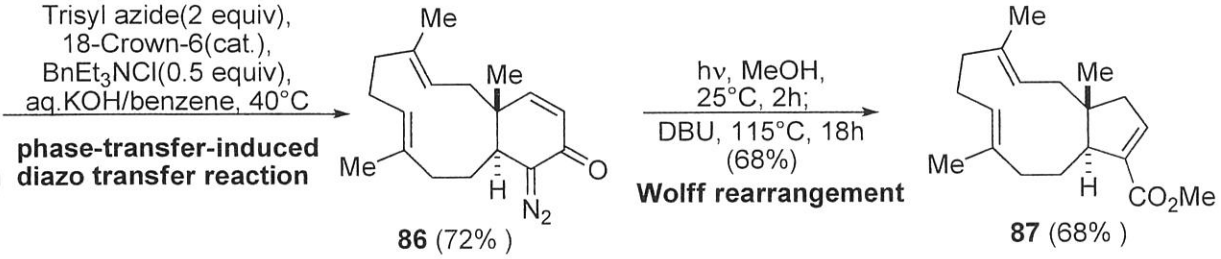
Total synthesis

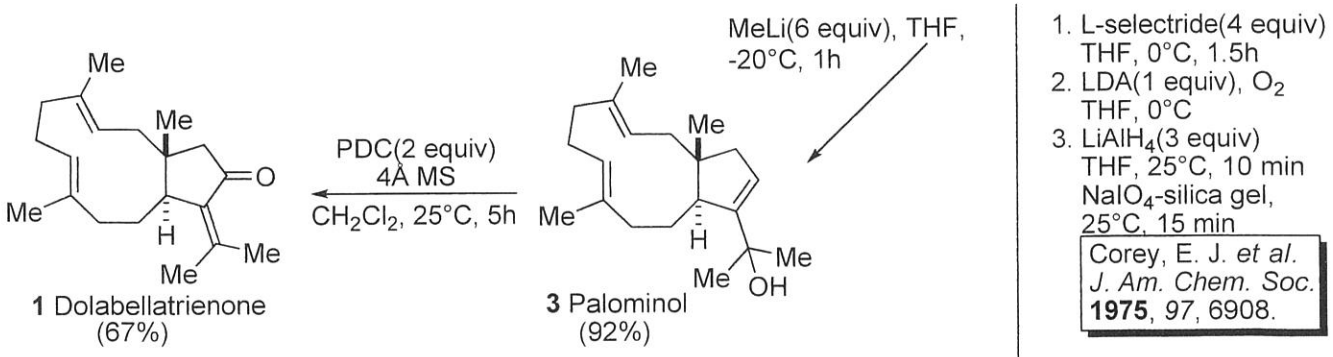












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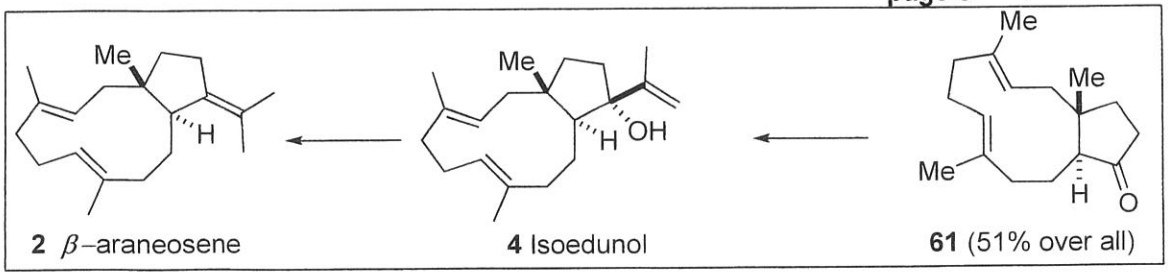

3. Summary of Syntheses