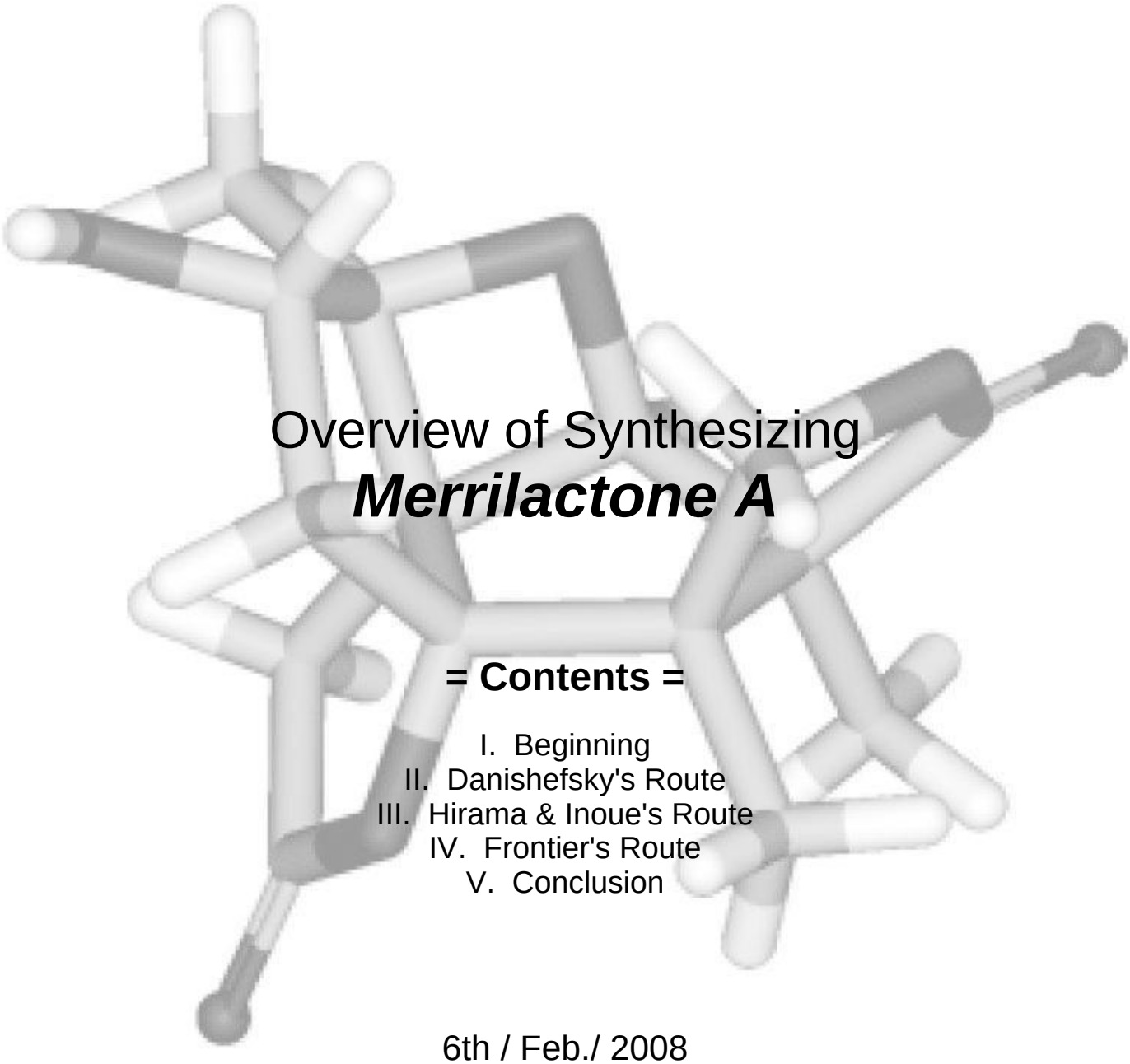


Overview of Synthesizing
Merrilactone A

= Contents =

6th / Feb./ 2008
Literature Seminar ~ B4 part ~

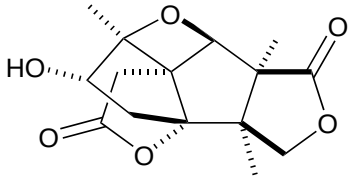
Takafumi Yukawa

I. Beginning

Merrilactone A

Illicium merrillianum

extraction



Merrilactone A only 0.004% yield

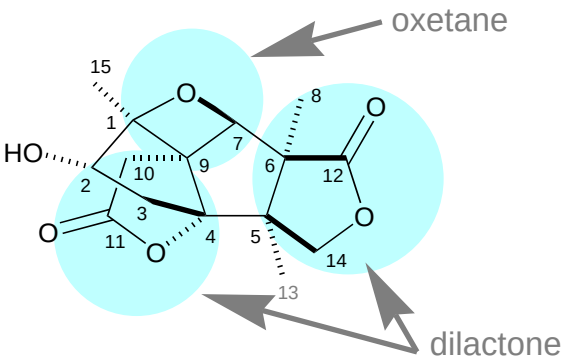
- Biological Feature
  - Neurotrophic
  - Neuritogenetic

⇒
- possibility for treatment of neuro-degeneration deseases (Alzheimer's and Perkinson's)
- potential alternative for nerve growth factor (NGF) and other expensive peptidal reagents

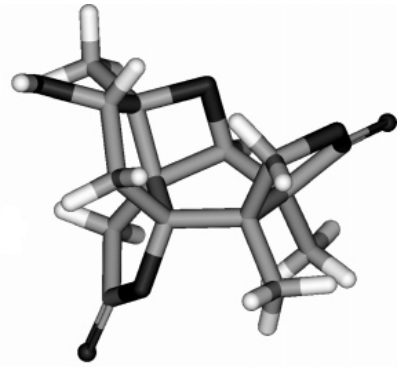
- Chemical Feature

  very interesting and challenging compound

Densely Oxygenated !



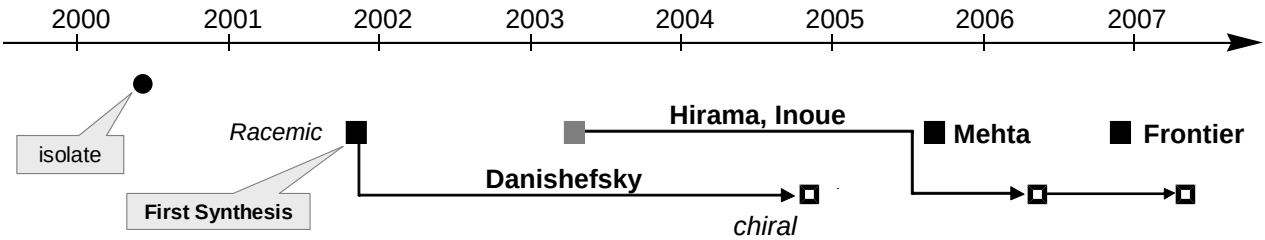
Highly compact and caged skeleton !



It is important to synthesize Merrilactone A in the place of both chemistry and biology.

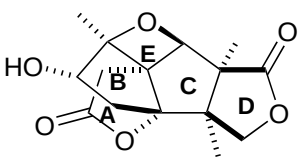
History

Isolation		Y. Fukuyama et al. *Tetrahedron Lett.* **2000**, *41*, 6111.	
Racemic	■	V. B. Birman and S. J. Danishefsky *J. Am. Chem. Soc.* **2002**, *124*, 2084.	→ Chap. II
	■	M. Hirama, M. Inoue et al. *J. Am. Chem. Soc.* **2003**, *125*, 10772.	→ Chap. III
	■	G. Mehta and S. R. Singh *Angew. Chem. Int. Ed.* **2006**, *45*, 953.	
	■	A. J. Frontier et al. *J. Am. Chem. Soc.* **2007**, *129*, 498.	→ Chap. IV
Chiral	□	Z. Meng and S. J. Danishefsky *Angew. Chem. Int. Ed.* **2005**, *44*, 1511.	
	□	M. Inoue et al. *Angew. Chem. Int. Ed.* **2006**, *45*, 4843.	
	□	M. Inoue et al. *J. Org. Chem.* **2007**, *72*, 3065.	→ Chap. III



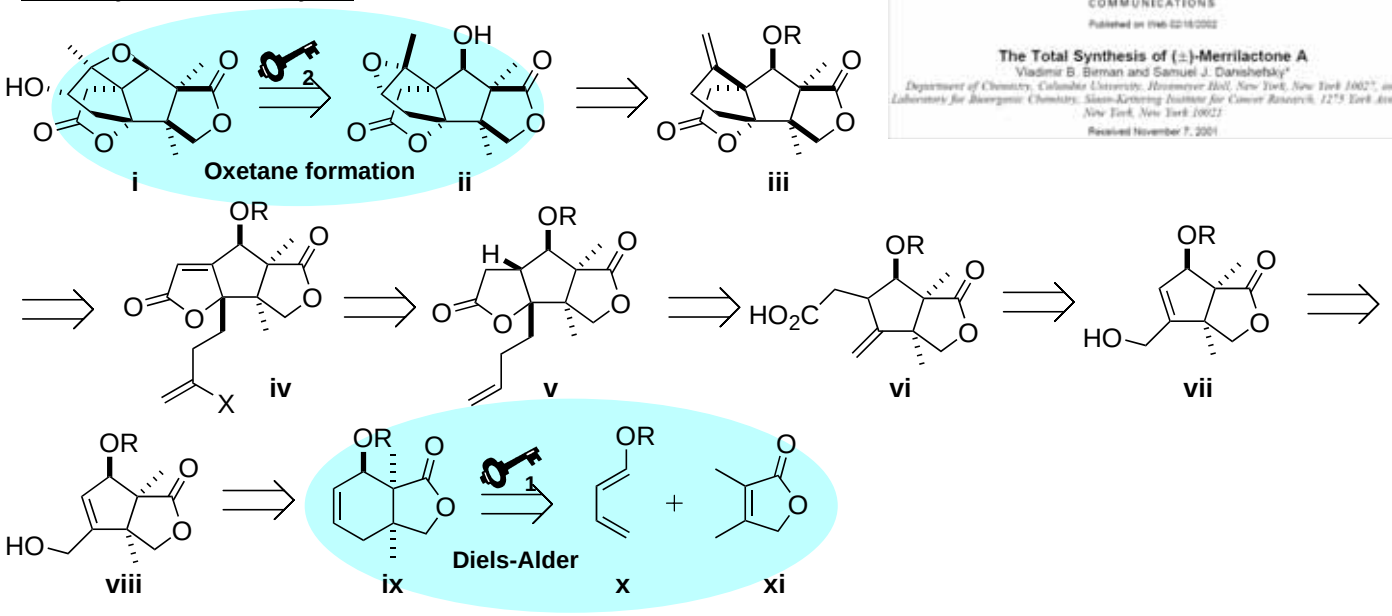
Strategy for Synthesis *~~ How to construct the five rings (A~E) ~~*

- Danishefsky's Route : D → C → A → B → E
- Hirama and Inoue's Route : B and C → D → A → E
- Frontier's Route : A and C → B → D → E



II. Danishefsky's Route

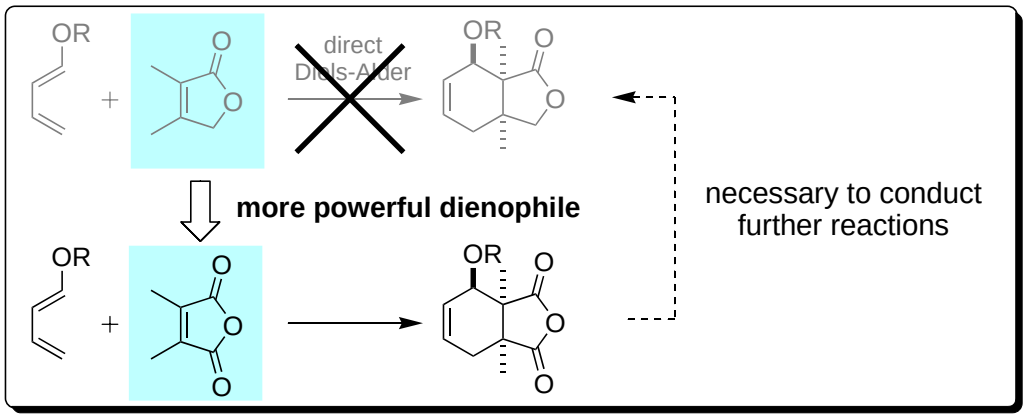
Retrosynthetic Analysis

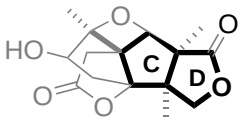


Key Reaction

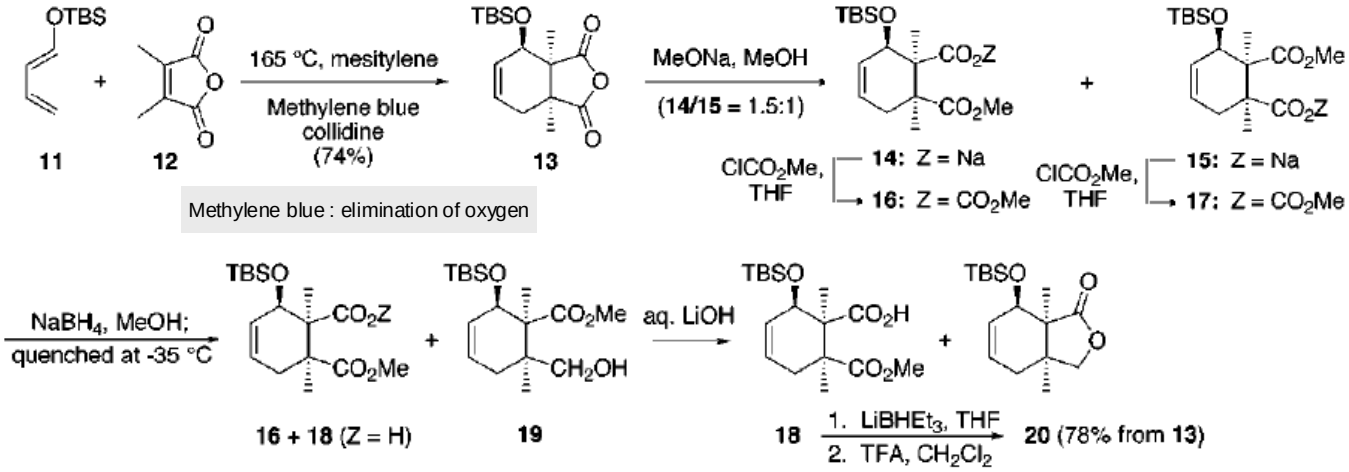
Diels-Alder Reaction

Diels-Alder reaction didn't directly proceed with the retro-synthesized compounds.



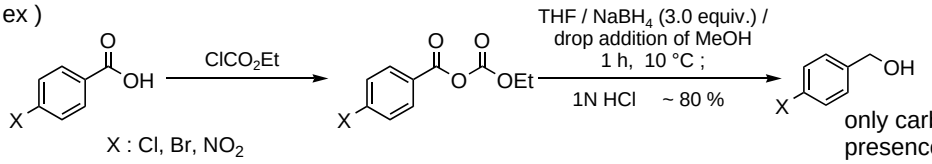


Scheme 1



15, 17→16, 19 : reduction under very mild condition with high chemoselectivity (*Synthesis* **1987**, 647)

ex)

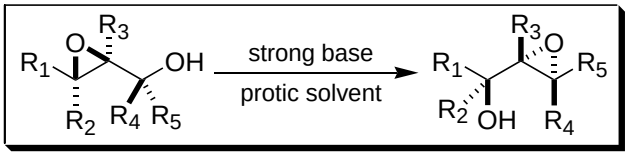


only carboxylic acid is reduced in the presence of halogen and nitro group.

2 Oxetane Formation

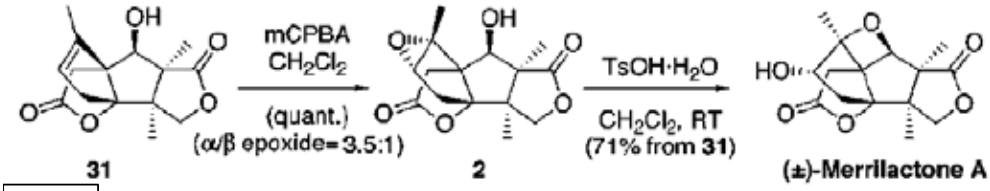
Largely, three methods are known for building-up oxetane

➢ Payne Rearrangement



⇨ This time, the situation has been slightly changed forming oxetane ring structure.

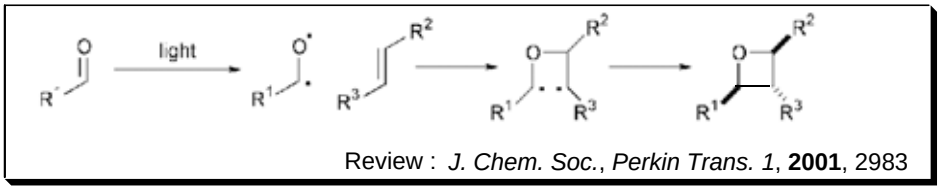
(Fukuyama et al. *Tetrahedron*, **2001**, *57*, 4691)



POINT

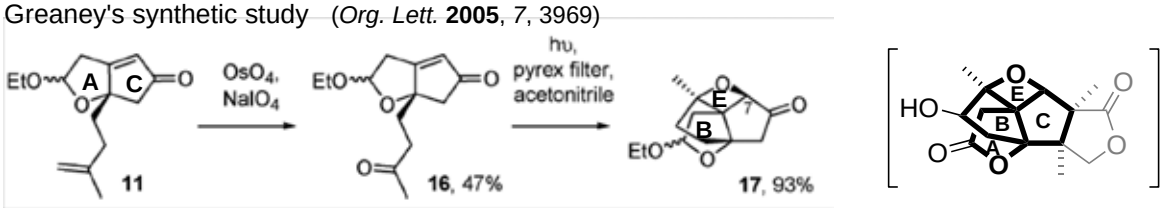
- C7-OH is located near C1. ⇨ C7-OH attacks C1 producing four-membered ring, not C2 doing five-membered ring.
- Strong base will open lactone ring. ⇨ Acid condition solves this problem, for tertiary C1 carbon is likely charging plus.

➢ Peternò-Büchi Reaction ([2+2] Photocycloaddition)

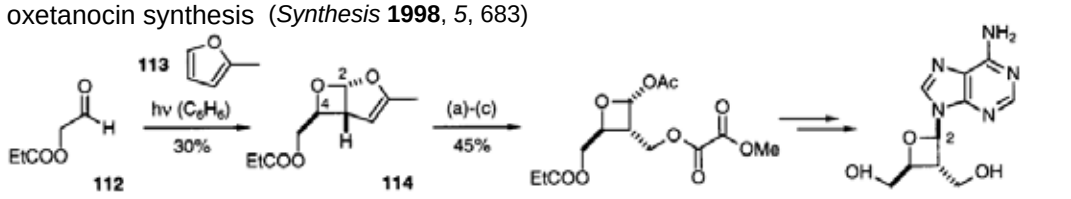


Review : *J. Chem. Soc.*, *Perkin Trans. 1*, **2001**, 2983

ex) Greaney's synthetic study (*Org. Lett.* **2005**, *7*, 3969)



cf) oxetanocin synthesis (*Synthesis* **1998**, *5*, 683)

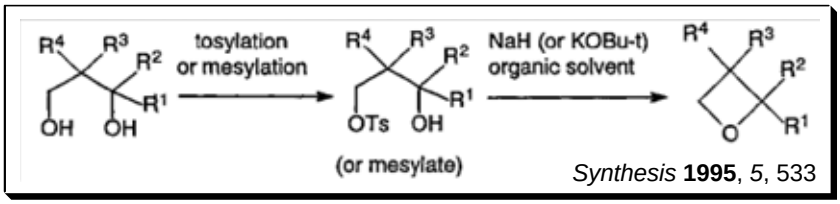


Reagents: (a) O_3 (CH_2Cl_2); Me_2S. (b) $NaBH_4$ on alumina (CH_2Cl_2). (c) MeOCOCOCl, NEt_3, DMAP CH_2Cl_2).

POINT

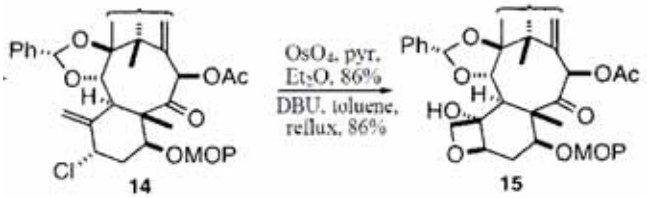
- generally low yield
- difficult to control the position of olefin and carbonyl group

➢ From 1,3-Diol



Synthesis **1995**, *5*, 533

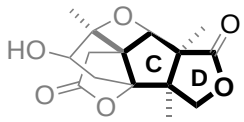
cf) Taxol Synthesis

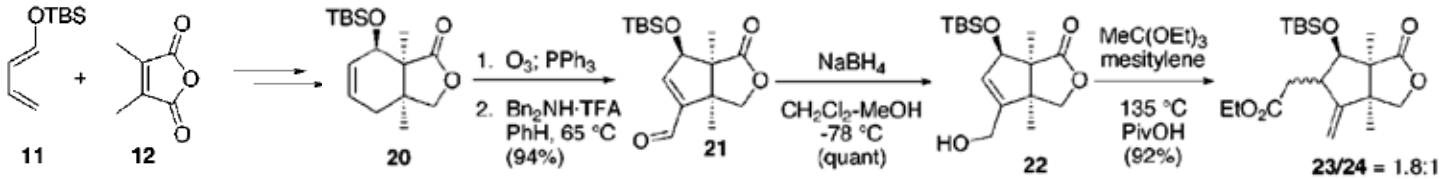


POINT Installation of 1,3-diol moiety should be prior to oxetane formation.

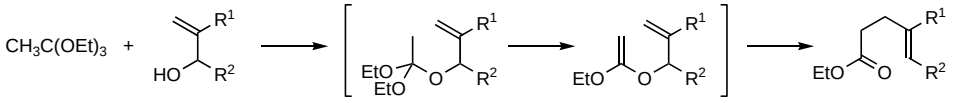
Total Synthesis

Ring C, D Synthesis

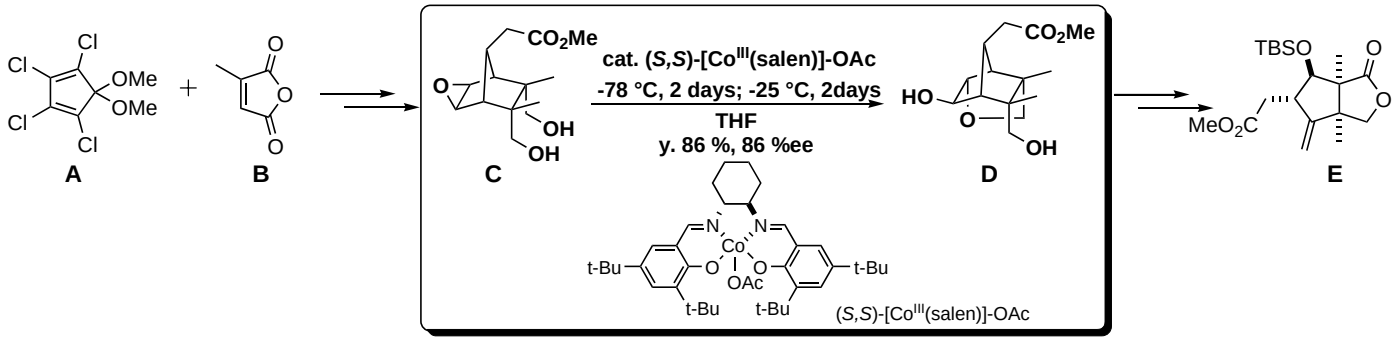




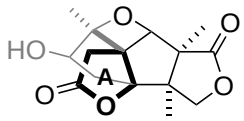
22 → **23, 24** : Claisen rearrangement by Johnson *ortho* protocol (*J. Am. Chem. Soc.* **1970**, *92*, 741)

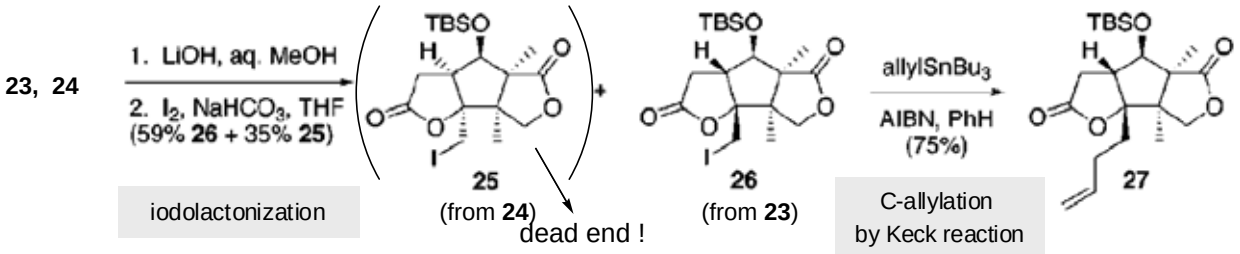


cf) Danishefsky developed this strategy for asymmetric synthesis. (*Angew. Chem. Int. Ed*. **2005**, *44*, 1511)

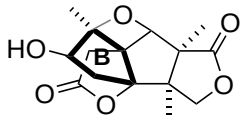


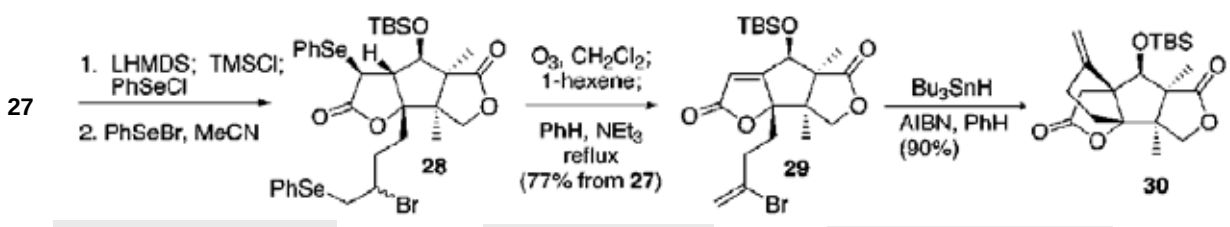
Ring A Synthesis





Ring B Synthesis



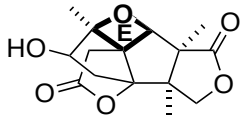


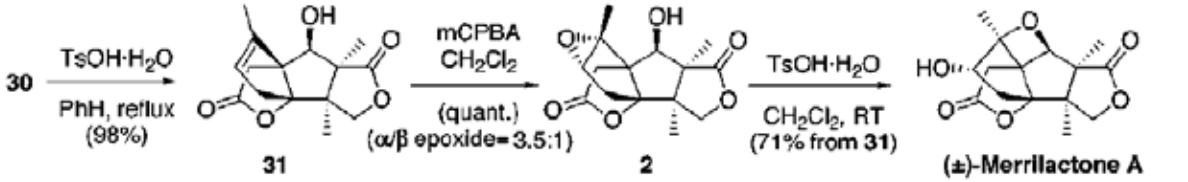
selenenylation and bromoselenenylation

oxidative deselenenylation

free radical cyclization

Ring E Synthesis



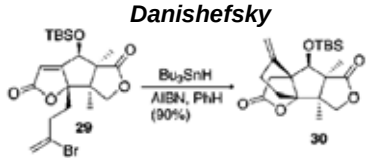


toal 20 steps
10.7 % overall yield

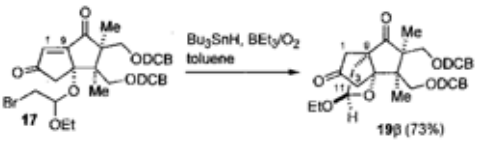
< Free Radical Cyclization >

Free radical cyclization is another key reaction for all synthesis route.

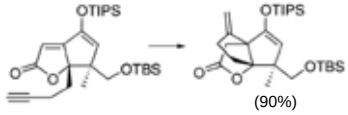
Danishefsky



Hirama and Inoue

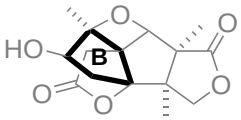


Frontier



AIBN, Bu_3SnH, PhH, reflux; *p*-TsOH, H_2O (one pot)

⟹ Important method to construct ring B



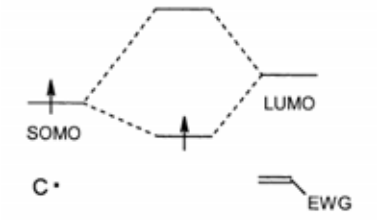
General Feature

react under mild conditions
attack the closest reactive site
irreversible

⇨

undamage the other functional groups
high regio and stereoselectivity
retro reaction doesn't occur

Frontier Molecular Orbital



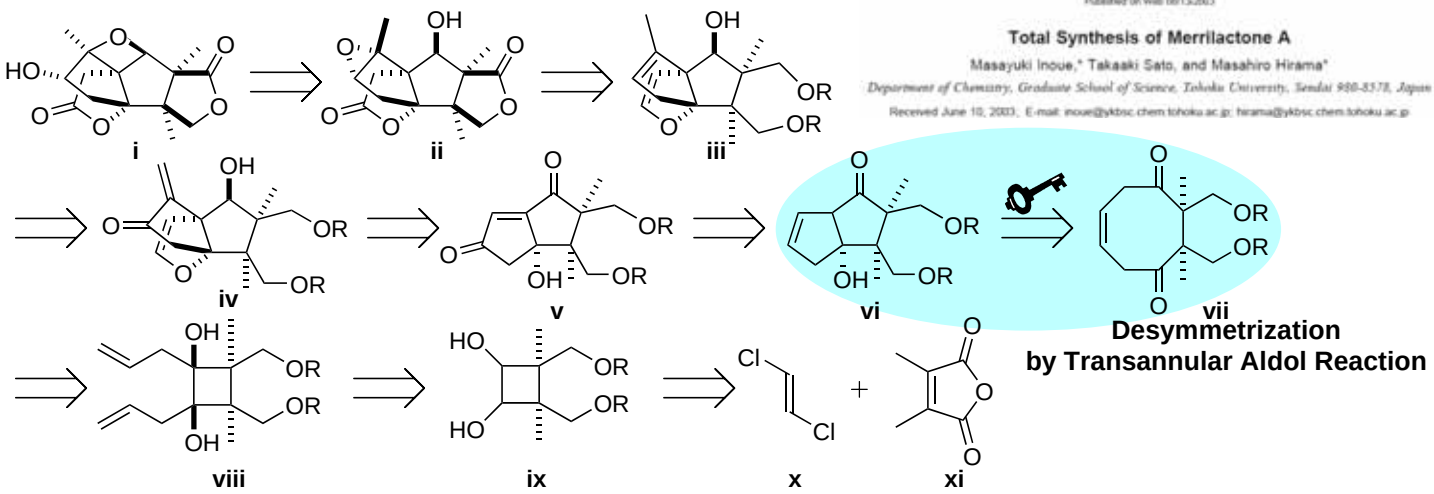
FMO intereaction of a nuclephilic radical with an electron-poor alkene

The reaction is accerated as LUMO becomes lower by the effect of electron withdrowng group.

rxn rate : EWG = -CHO > $-CO_2R$ > -Ph

III. Hirama and Inoue's Route

Retrosynthetic Analysis



J|A|C|S COMMUNICATIONS

Published on Web 08/13/2003

Total Synthesis of Merrilactone A

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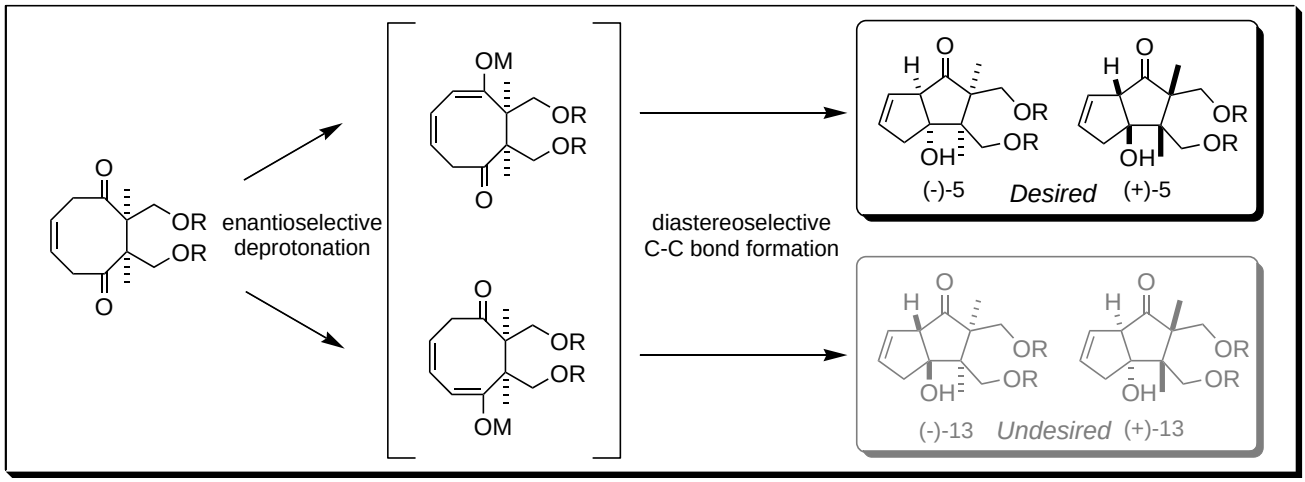
Key Reaction

Desymmetrization by Transannular Aldol Reaction

Advantage of taking desymmetrization strategy

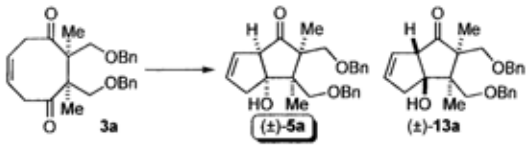
- making the process shorter
- possibility to achieve enantioselectivity by desymmetrization



☑ Condition Check

optimization of base reagent

Table 1 Diastereoselective transannular aldol reaction: Base effect.

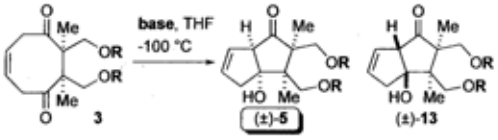


entry	reagents and conditions	(±)-5a : (±)-13a	combined yield
1	DBU, CH_2Cl_2, 0 °C	1.1 : 1	63%
2	LiN(TMS)$_2$, THF, -100 °C	3.1 : 1	85%
3	LiN(TMS)$_2$, THF, -40 °C	2.6 : 1	78%
4	MgBrN(TMS)$_2$, Et_2O, rt	1 : 3.0	81%
5	LiN(TMS)$_2$/Et_3N, toluene, -78 °C	1 : 5.1	79%
6	LiNMePh, THF, -100 °C	5.7 : 1	99%*
7	LiNMe(*m*-ClPh), THF, -100 °C	5.8 : 1	87%*
8	LiNMe(*p*-ClPh), THF, -100 °C	11.2 : 1	89%

* The yields were based on recovered starting material. [80% conversion (entry 6), 92% conversion (entry 7)]

optimization of protecting group

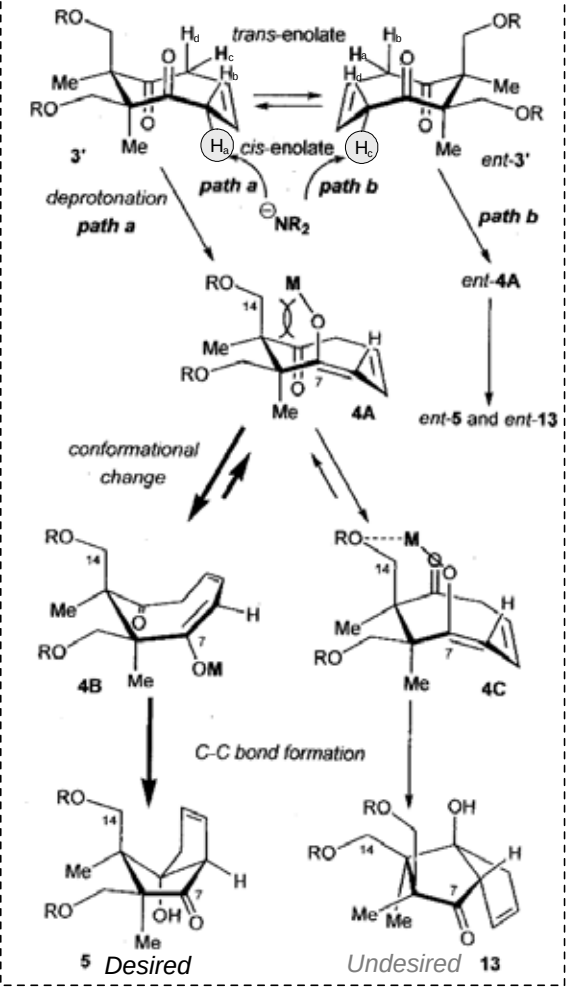
Table 2 Diastereoselective transannular aldol reaction: Protective group effect.



entry	3	base	(±)-5 : (±)-13	combined yield
1	3a: R =	LiN(TMS)$_2$	3.1 : 1	85%
2	3b: R =	LiN(TMS)$_2$	3.2 : 1	92%
3	3c: R =	LiN(TMS)$_2$	3.9 : 1	93%
4	3d: R =	LiN(TMS)$_2$	6.0 : 1	88%
5	3d: R =	LiNMe(*p*-ClPh)	16.0 : 1	97%

(DCB)

Possible Mechanism



From condition check

Table 1 entry 1 and 2 : $LiN(TMS)_2$ was better than DBU in selectivity
entry 2 and 3 : high selectivity under lower rxn temp.

⇨ **Diastereoselectivity is achieved under kinetic control.**

+

Table 2 entry 1~ 4 : selectivity was changed under protecting group

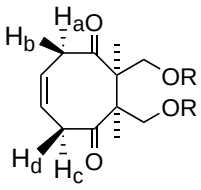
⇨ **Diastereoselectivity depends on the size of ortho-substituent.**

⇩

The mechanism (shown left) can be supported.

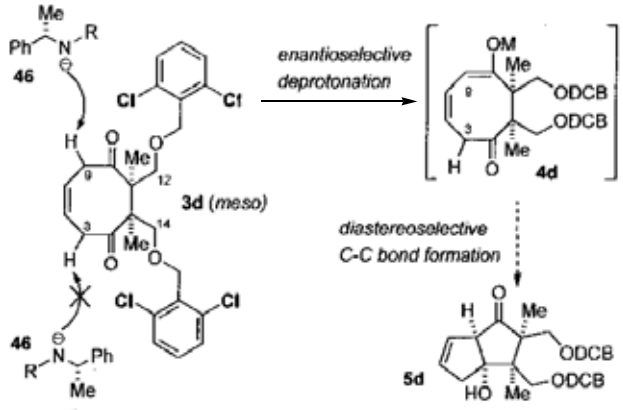
Explanation of Possible Mechanism

1. Only 2 protons circled (a and c) in the chart will actually be deprotonated and stable *cis*- enolate (4A and *ent*-4A) should be formed.
2. After deprotonation, steric interaction occurs between C7-O bond and C14 in the conformation of **4A** to generate **4B**.
3. Enolate flips downward kinetically before stabilization by chelation like **4C**.

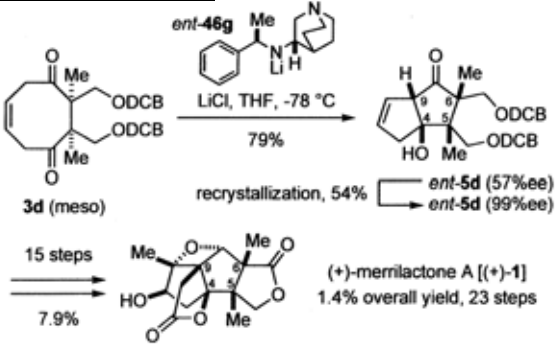


Moreover, Hirama and co-workers succeeded in synthesizing chiral Merrilactone A by using chiral base in desymmetrization process. (*J. Org. Chem.* **2007**, *72*, 3005)

Asymmetric Desymmetrization

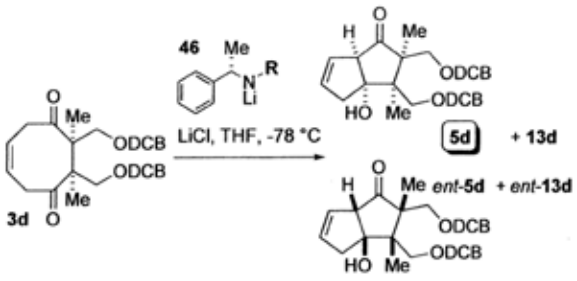


Apply to Total Synthesis



☑ Condition Check

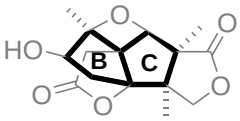
Table 4 Enantioselective transannular aldol reaction.

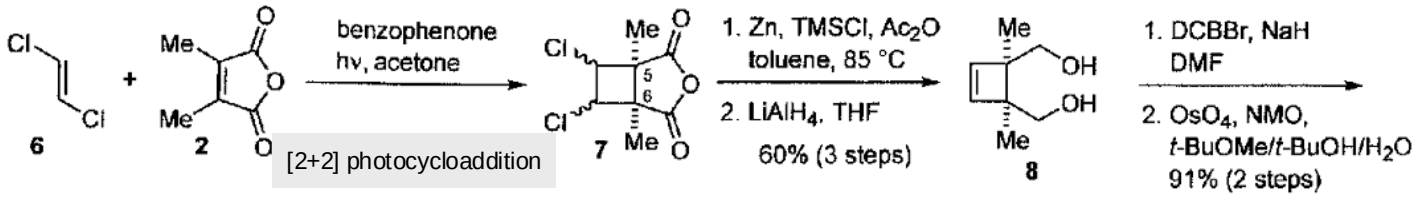


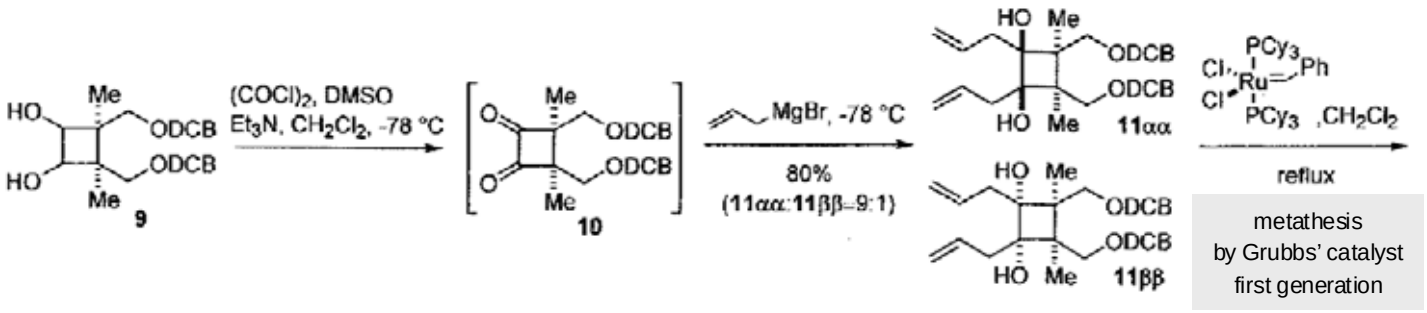
entry	R		(5d+*ent*-5d) : (13d+*ent*-13d)	5d : *ent*-5d	combined yield
1		**46a**	19 : 1	1 : 2.4	87%
2		**46b**	15 : 1	1 : 1.3	73%
3		**46c**	6.0 : 1	1 : 1	100%
4		**46d**	7.0 : 1	1.9 : 1	88%
5		**46e**	8.1 : 1	2.2 : 1	94%
6		**46f**	3.0 : 1	2.7 : 1	94%
7		**46g**	6.0 : 1	4.7 : 1	90%

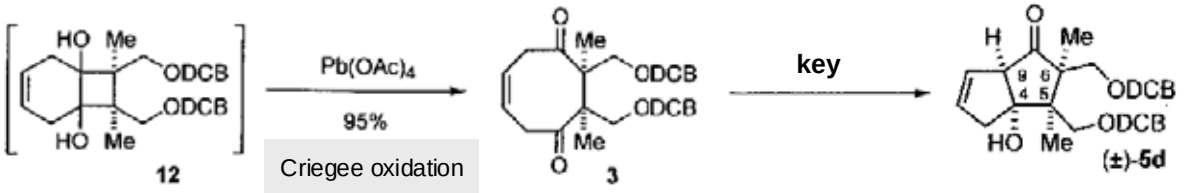
Total Synthesis

Ring B, C Synthesis

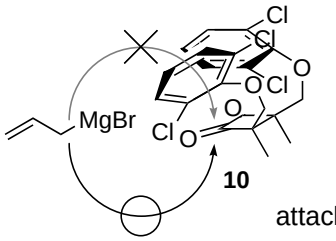




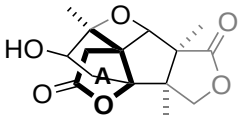


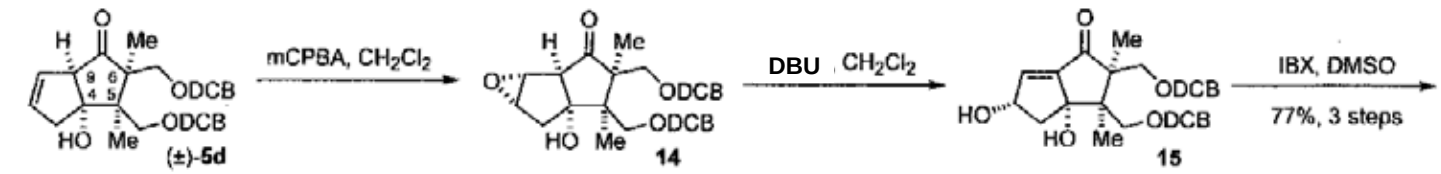


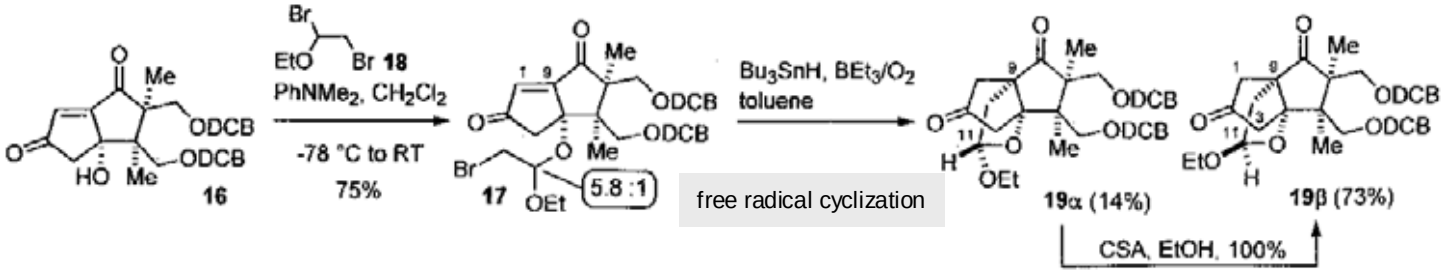
10→11 : attack from down side because of the steric effect of DCB



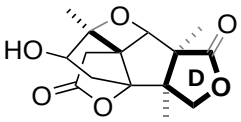
Ring A Synthesis

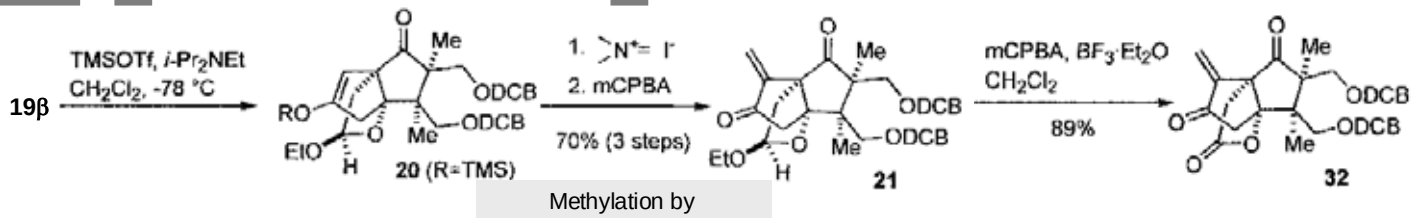




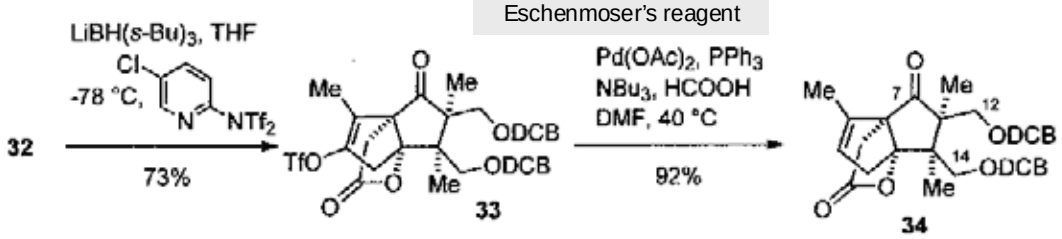


Ring D Synthesis





Methylation by Eschenmoser's reagent



19→20 : stereoselective enolization

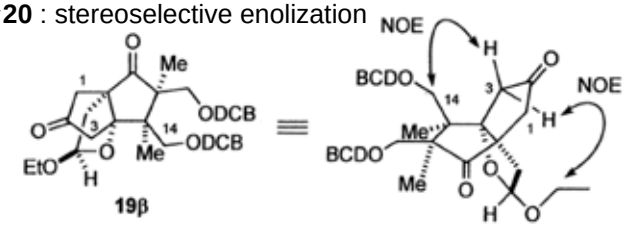


Fig. 2 NOESY data of 19β.

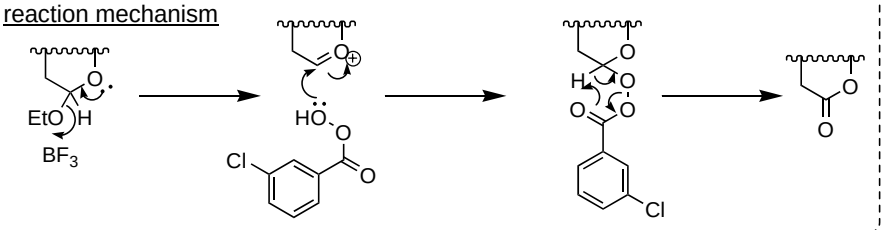
C3 protons are hidden by DCB or ethyl moiety.

⇩

C1 proton can be regioselectively deprotonated.

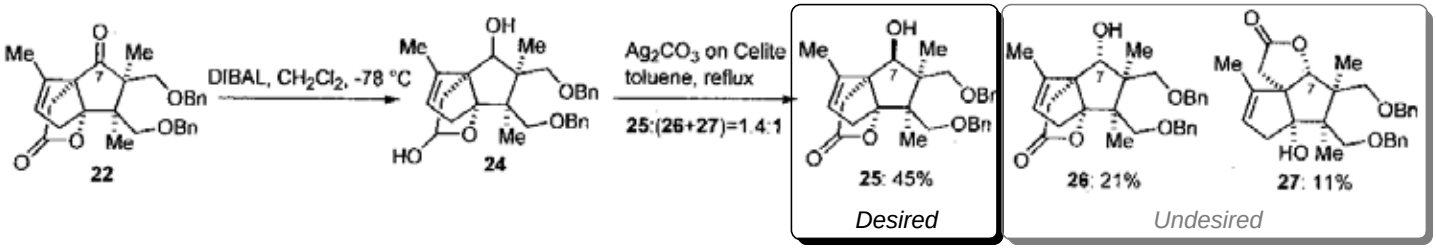
21→32 : oxidation of ketal (*Tetrahedron lett.* **1978**, *19*, 419)

reaction mechanism

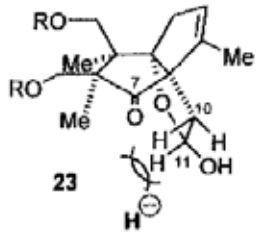


At this stage, the problem is how to reduce C7 carbonyl group.

⇨ At first, they use DIBAL-H for compound **22** (model substrate), but desired product wasn't selectively obtained.



22→24 : reduction by DIBAL-H



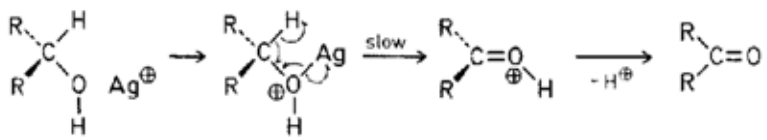
Ketal blocks the attack of hydride from downward

⇩

Undesired products (**26**, **27**)

24→25 : Ag_2CO_3/Celite oxidation (*Synthesis*, **1979**, 401)

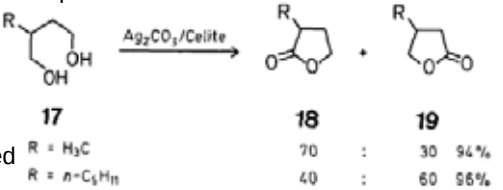
mechanism



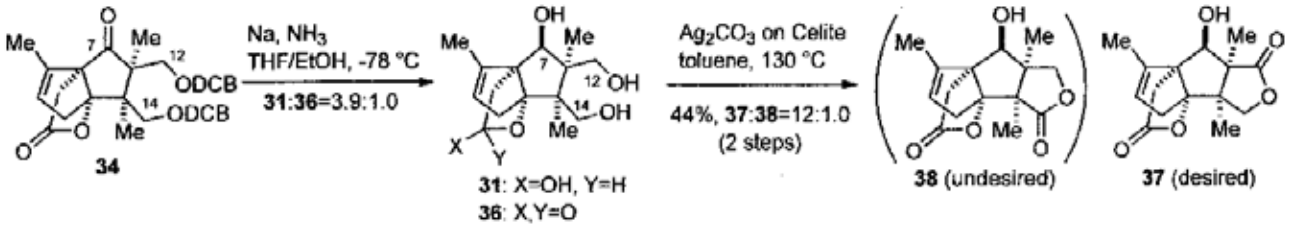
Celite : easy to separate Ag residue from product

advantage
very mild condition (neutral)

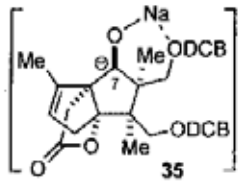
disadvantage
excess amount of Ag_2CO_3 is needed
low selectivity



⇨ Then, try another reductant : Birch reduction.



34 → **31** : Birch reduction

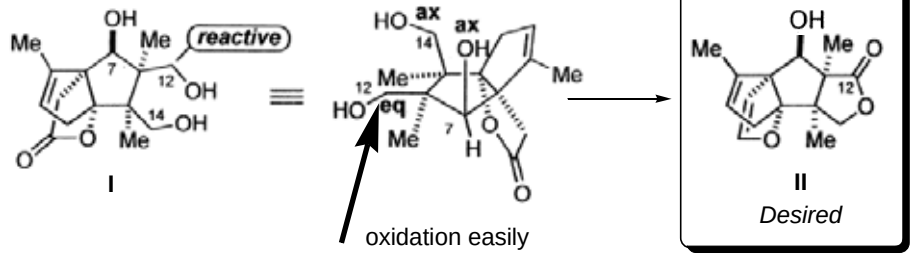


Sodium cation is chelated as shown in the chart above

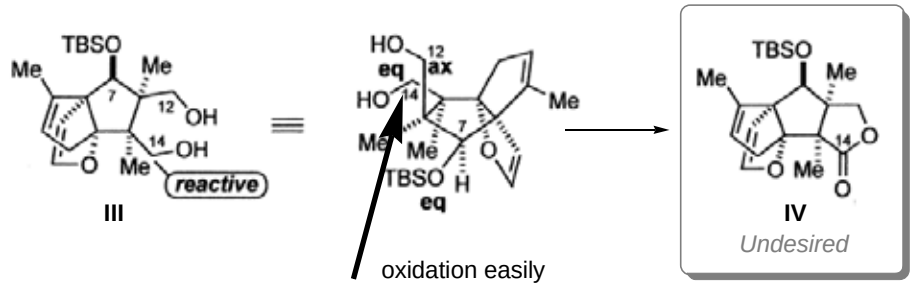
⇩

high stereoselectivity

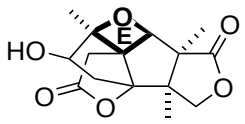
31, 36 → **37** : regioselective oxidation

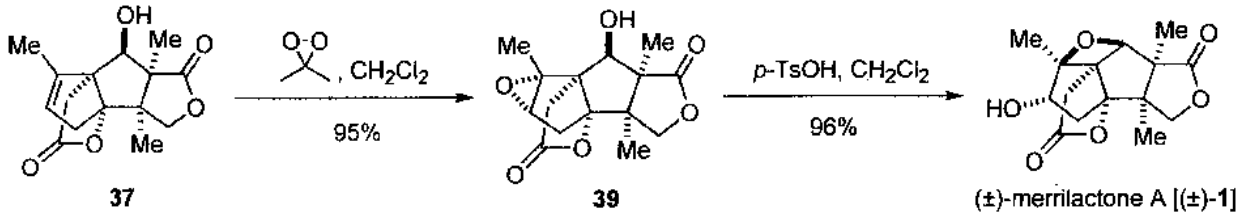


cf) if the alcohol is protected by TBS, the structure is changed that TBSO directs *pseudo*-equatorial way.



Ring E Synthesis

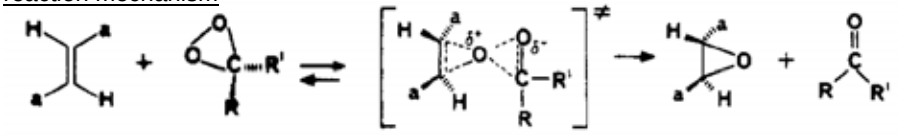




total 23 steps
3.0 % overall yield

37 → **38** : epoxidation by dimethyldioxirane (DMDO) (*Chem Rev*. **1989**, *89*, 1187)

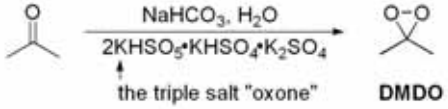
reaction mechanism



not commercially available ; preparation by oxidation of acetone is inefficient (y. ~ 3%).

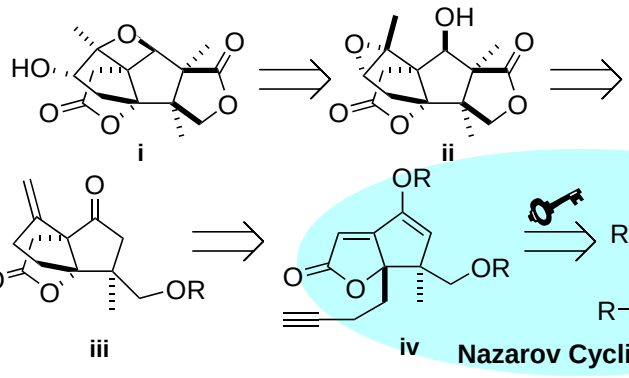
however, advantage is larger.
byproduct is only acetone
good selectivity despite of high reactivity
inexpensive for preparation

preparation



IV. Frontier's Route

Retrosynthetic Analysis



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Total Synthesis of (±)-Merrilactone A via Catalytic Nazarov Cyclization

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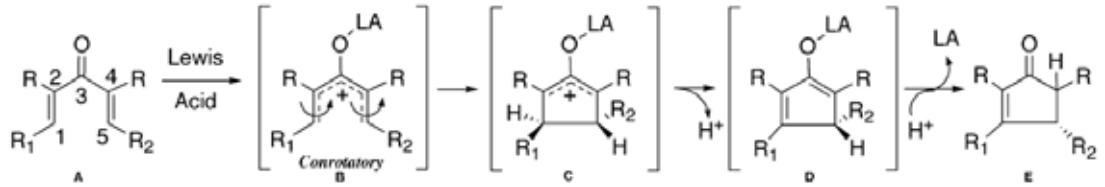
Ref. *J. Am. Chem. Soc.* **2008**, *130*, 300

Key Reaction

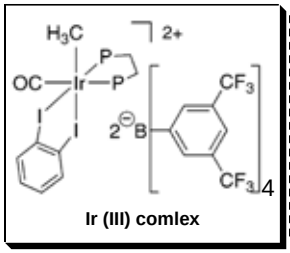
Nazarov Cyclization

Lewis acid-catalyzed Nazarov cyclization

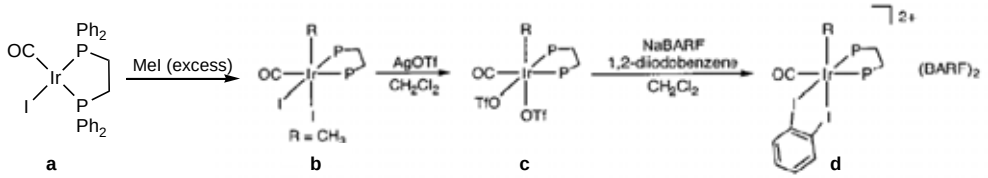


general Lewis acids : $FeCl_3$, BF_3 Et_2O, $SnCl_4$, $Cu(OTf)_2$, $PdCl_2(MeCN)_2$, $AlCl_3$, $Sc(OTf)_3$, etc

Eisenberg and Frontier developed more powerful Lewis acid ; Ir (III) complex.



synthesis of Ir (III) complex (*Inorg. Chem.* **2002**, *41*, 2095)

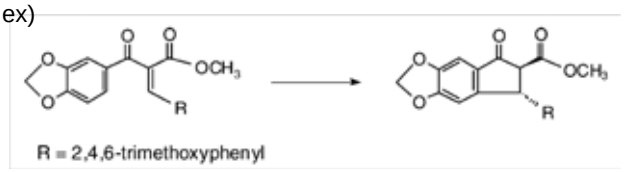


Feature

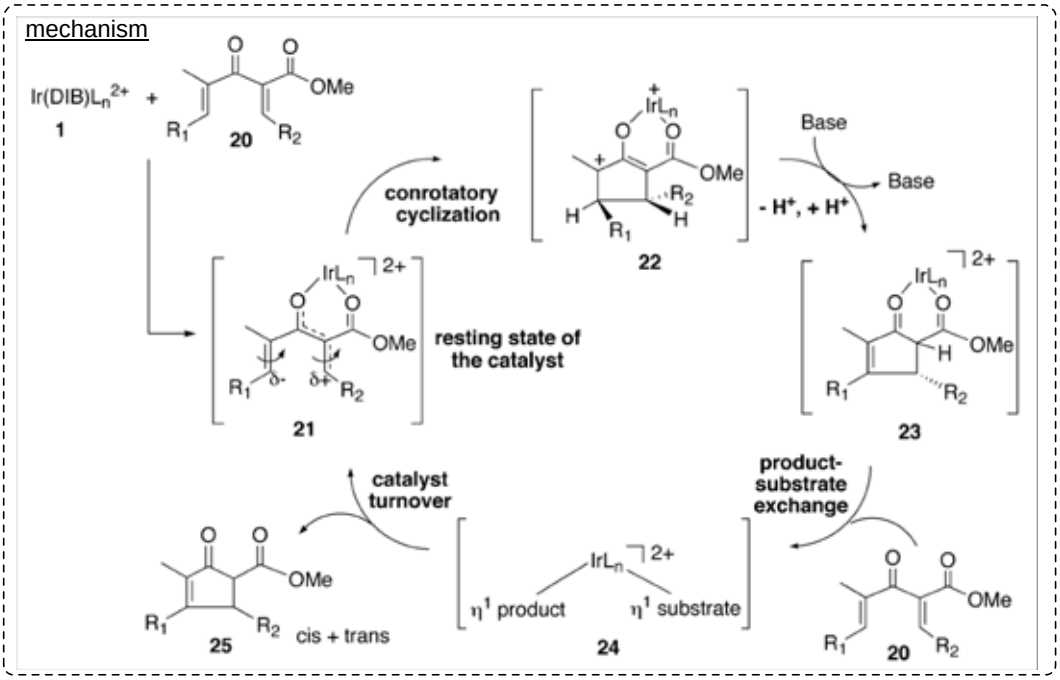
Strong Lewis Acid ⇨

- increase the reactivity
- lessen byproducts under mild condition

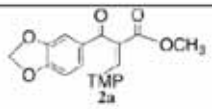
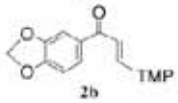
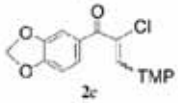
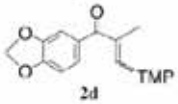
ex)



mechanism



Reactivity compared to $Cu(OTf)_2$

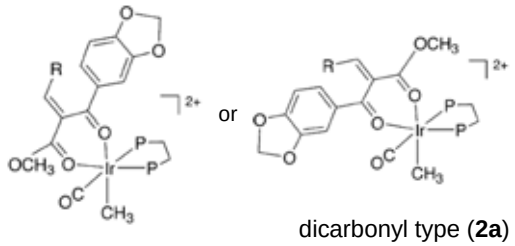
Substrate	Catalyst	Time (min.)	Temperature (°C)	Yield (%)
 2a	1	8.0	25.7	>99
	$Cu(OTf)_2$	30	65.0	90
 2b	1	—	—	—
	$Cu(OTf)_2$	—	—	—
 2c	1	41.5	25.4	99
	$Cu(OTf)_2$	90	65.0	82
 2d	1	125	25.5	96
	$Cu(OTf)_2$	270	65.0	71

1 : Ir (III) complex

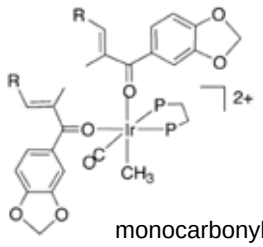
(*Tetrahedron* **2005**, *61*, 6193)

active spieces

substrates coordinate to Ir (III) by O, O' chelation.



dicarbonyl type (**2a**)



monocarbonyl type (**2c**, **2d**)

compound **2a, 2c, 2d**

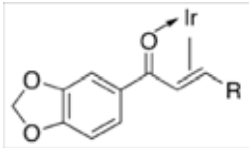
- short reaction time
- low temperature
- high yield

⇒ Ir (III) complex is superior to $Cu(OTf)_2$

compound **2b**

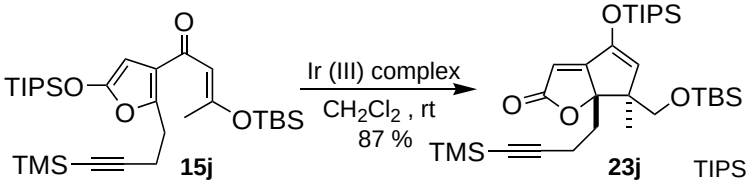
Cyclization didn't proceed with **2b**.
The possible chelate structure is shown right.

possible structure of Ir (III) chelation

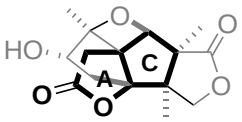


cyclization can't proceed in this binding

In Merrilactone synthesis, **15j** is the substrate for the key reaction forming ring C.

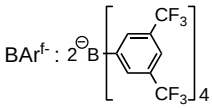


TIPS : triisopropylsilyl



However, Ir(III) complex can not be the only catalyst of Nazarov cyclization. $TIPS^+$ produced is also thought to be a catalyst.
This presumption is suggested by these experiments.

entry	Ir(III) complex	TIPSOTf	$TIPS^+ \cdot BAr^{f-}$	reaction
0	○	×	×	○
1	○	×	○	○
2	×	○	×	×
3	×	×	○	○



- entry 0 : using Ir (III) for general substrate (unprotected by TIPS)
- entry 1 : using Ir (III) for **15j** (protected by TIPS)
- entry 2 : using TIPSOTf for general substrate
- entry 3 : using $TIPS^+ \cdot BAr^{f-}$ for general substrate

entry 0 : Ir (III) complex works as a catalyst.
entry 2 : TIPSOTf doesn't work as a catalyst.
entry 3 : $TIPS^+$ BAr^{f-} works as a catalyst.

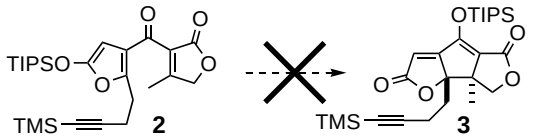
⇒

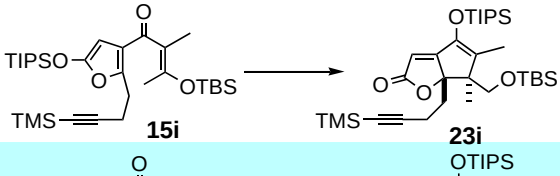
Possibility

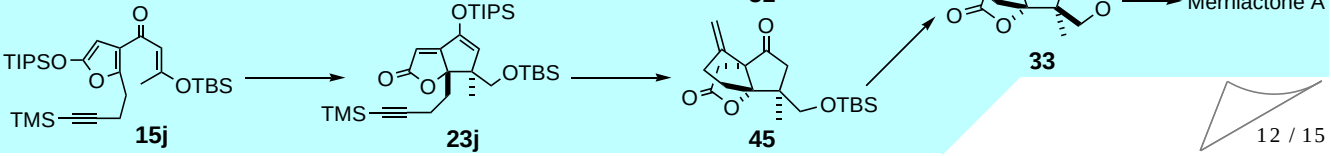
1. Ir (III) initiates and catalyzes.
2. Ir (III) initiates only and $TIPS^+$ catalyzes, in stead.
3. Both Ir (III) and $TIPS^+$ catalyze.

Total Synthesis

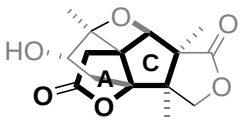
They examined three procedures, and only No.3 was gone well.

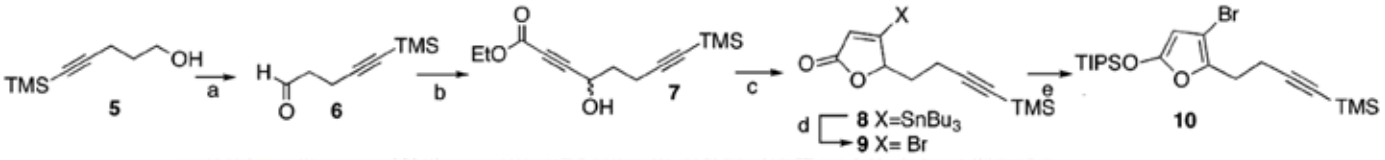
1. 

2. 

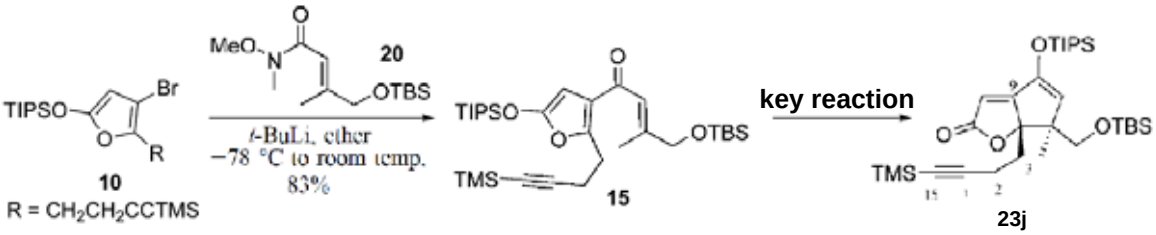
3. 

Ring A, C Synthesis

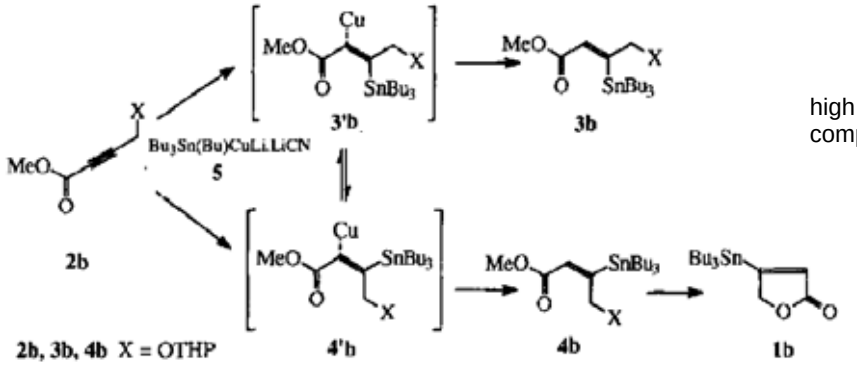




[a] Reaction conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −50 °C, 90%; (b) ethyl propiolate, *n*-BuLi, THF, −78 °C, then **6** 88%; (c) (Bu_3Sn)-$Cu(CN)Li_2$, THF, −78 °C, 90%; (d) Br_2, CH_2Cl_2, room temp, 93%; (e) TIPSOTf, Et_3N, CH_2Cl_2, −78 to 0 °C, quant



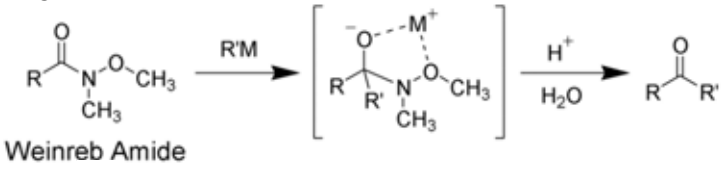
7→8 : lactonization by higher-order stannylcuprate



high stereo- and regioselectivity compared with general stannylcuprate

- 1,4-addition of tributylstannane
- high temp. : *E*-isomer (**3'b**)
- low temp. : *Z*-isomer (**4'b**)

10→15



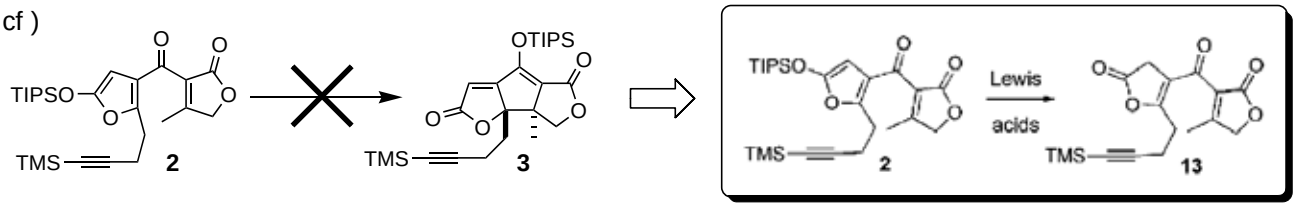
Weinreb Amide

The metal is strongly chelated by the amide moiety.

⇓

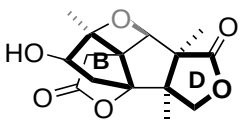
make it possible not to overadd to the substrate, producing a tertiary alcohol.

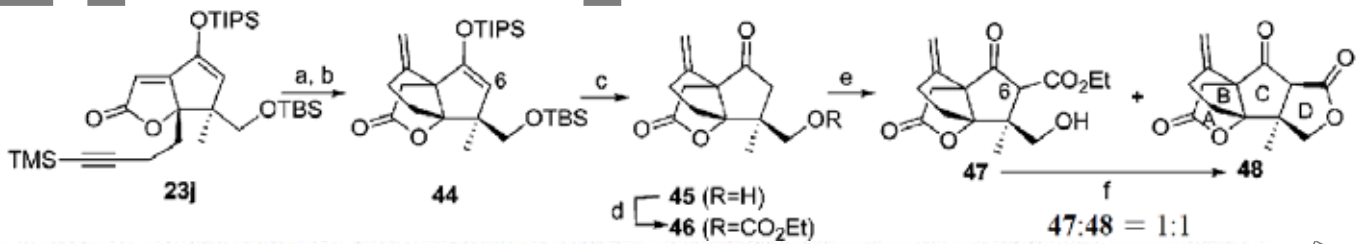
cf)



Using a variety of Lewis acids, all attempts were failed and only hydrolyzed compound **13** was obtained.

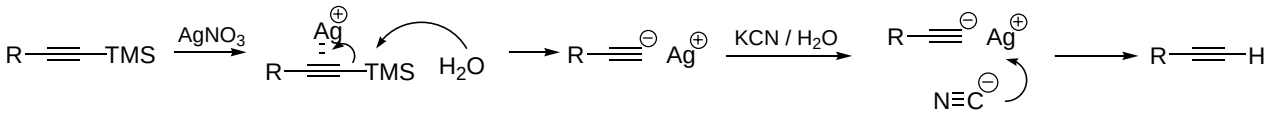
Ring B, D Synthesis



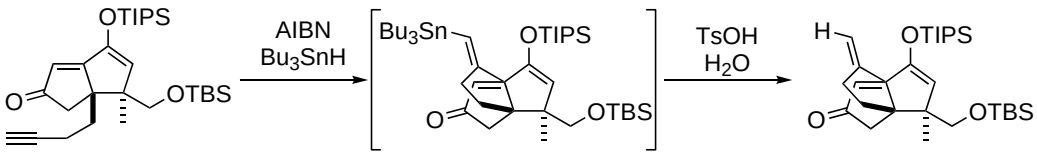


(a) $AgNO_3$, then KCN, $THF/H_2O/EtOH$, 87%; (b) (i) AIBN, Bu_3SnH, PhH, reflux, then (ii) *p*-$TsOH{\cdot}H_2O$ (one pot), 91%; (c) 3 equiv TBAF, 0 °C, 99%; (d) DMAP, Py, $ClCO_2Et$, 95%; (e) 20 equiv NaH, THF ; (f) *p*-$TsOH{\cdot}H_2O$ (90% from **46**).

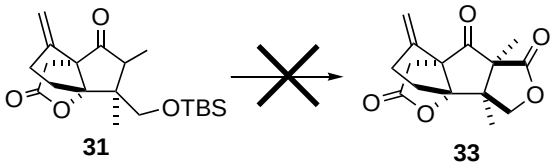
23i → 44 : selective desilylation of alkyne

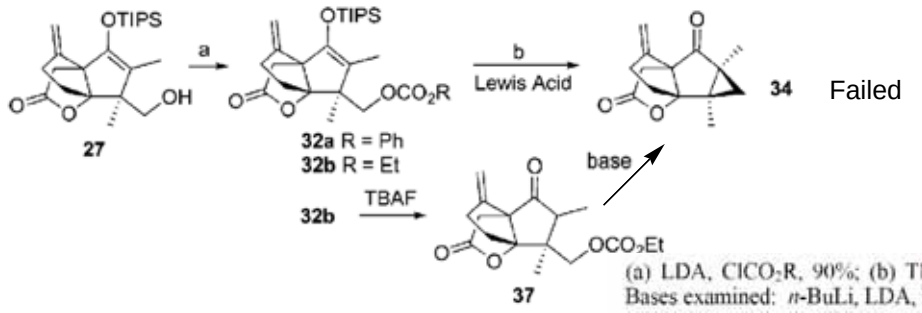


23i → 44 : free radical cyclization

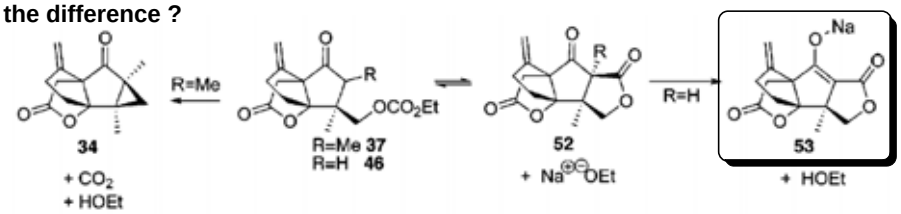


cf) When Me group was pre installed (31), desired lactone formation didn't proceed.



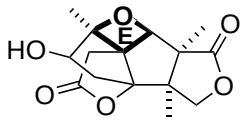


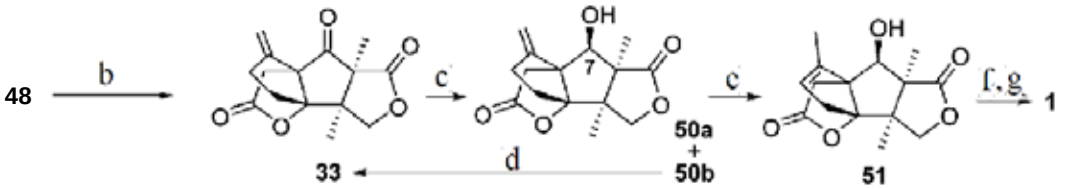
What is the difference ?



In the case of R=H, stabilization makes the equilibrium shift rightward.

Ring E Synthesis

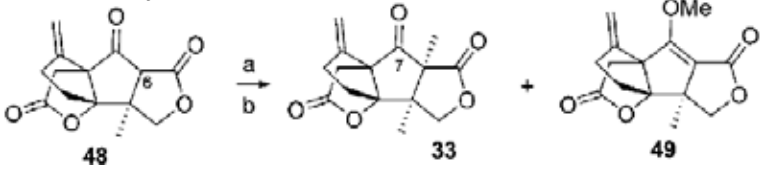




total 17 steps,
14.4 % overall yield

(b) NaH, MeI, and then HMPA (97% yield); (c) $NaBH_4$, MeOH gave **50a** (42% yield) and **50b** (51% yield); (d) Dess–Martin periodinane (99% yield); (e) *p*-TsOH·H_2O, benzene, reflux, 4 h, 92% yield; (f) *m*-CPBA; (g) *p*-TsOH·H_2O, 68% yield over two steps.

48 → 33 : methylation



(a) NaH, MeI, gave **33** (84% yield) and **49** (14% yield); 6:1 ratio;
(b) NaH, MeI, and then HMPA, gave **33** only (97% yield);

V. Conclusion

Evaluate these three routes by Baran's 8 rules → see Mr. Kuramochi's lit. seminar

By Baran, short synthesis is defined as follow.

short synthesis : maximized C-X(C) bond forming, minimized redox and protection-deprotection.

This time, three total synthesis are summerized

Route	**Total Steps**	**Yield (%)**	C-X Forming (steps)	Ratio (%)	Redox (steps)	Ratio (%)	protection & deprotection (steps)	Ratio (%)
Danishefsky	**20**	**10.7**	10	50	2	10	3	15
Hirama & Inoue	**23**	**3.3**	12	52	7	30	3	13
Frontier	**17**	**14.4**	10	59	2	12	3	18

⇒ Frontier's route will be good.

Danishefsky : Formation of A ring by Diels-Alder is difficult. Stereoselective direct Diels-Alder would be nice.

Hirama & Inoue : After desymmetrization, formation of ring B was problematic.

Frontier : Smart synthesis, but asymmetric Nazarov cyclization should be the key for asymmetric total synthesis.