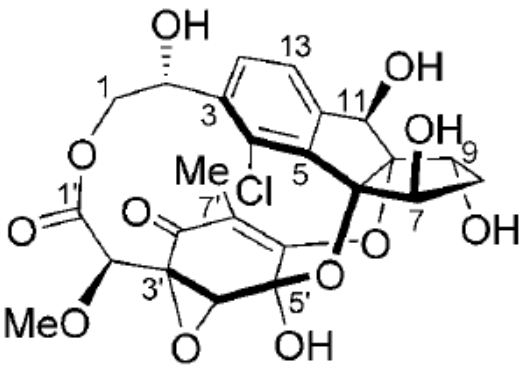
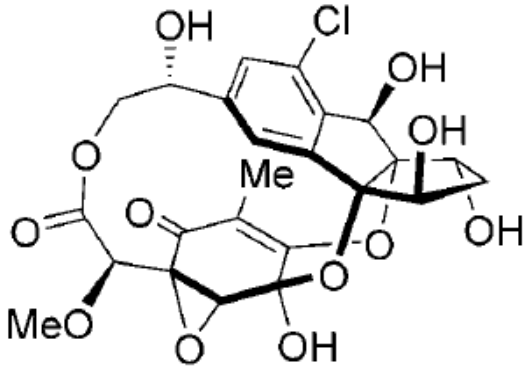
Nov. 10th 2010
Junya Kawai (B4)

Total Synthesis of Sporolide B



1a: sporolide A



1b: sporolide B

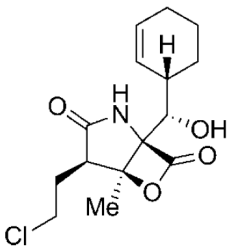
Isolation: from *Salinospora tropica* (a marine actinomyceta),
and it also produces salinosporamide A, a potent inhibitor of the 20S proteasome.

Structure: determined in 2005 (Fenical *et al., Org. Lett.,* 2005, *7,* 2731-2734)
7 rings, 10 stereogenic centers, and 22 out of 24 carbons are either oxygenated or sp^2 hybridized.
Including highly substituted indane system, a 1,4-dioxane ring, an epoxy cyclohexenone hemiacetal, and 13-membered macrolide moiety.
Difference between sporolide A and B is only the location of chlorine atom on the benzenoid structure.

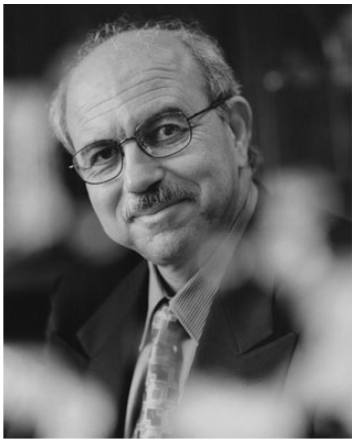
Biological activity: None (but the precursor enediyne compound is considered to have an antitumor activity)

Synthetic study: K. Gademann *et al., Synthesis,* 2010, *4*, 631-642 (Biomimetic method)
Total synthesis: K. C. Nicolaou *et al., Angew. Chem. Int. Ed.* 2009, *48,* 3449-3453 (Sporolide B)
K. C. Nicolaou *et al., J. Am. Chem. Soc.* 2010, *132,*11350-11363 (Sporolide B, 9-*epi*-sporolide B)
Synthesis of sporolide A has never been reported.

Contents



salinosporamide A

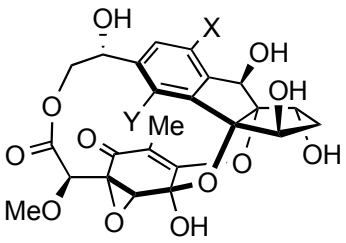


K. C. Nicolaou

Angew. Chem. Int. Ed., 2010, *49*, 2 *Chem. Soc. Rev.*, 2009, *38*, 2993

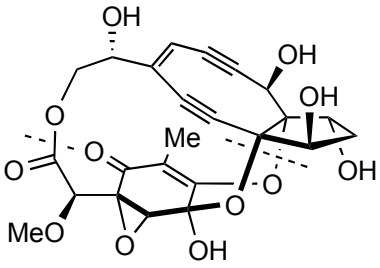
1. Biomimetic approach

1-1. Hypothetical biosynthesis of sporolides



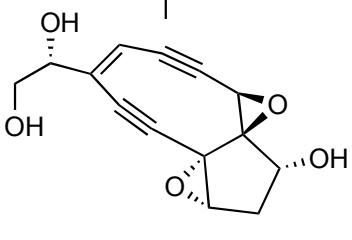
1a: sporolide A (X=H, Y=Cl)
1b: sporolide B (X=Cl, Y=H)

Bergman cycloaromatization

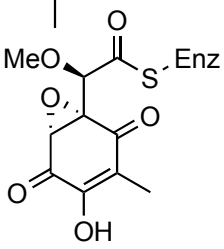


pre-sporolide

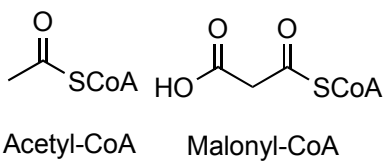
derived
from 2 building blocks.



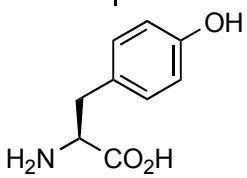
3
9-membered enediyne



2
cyclohexenone epoxide



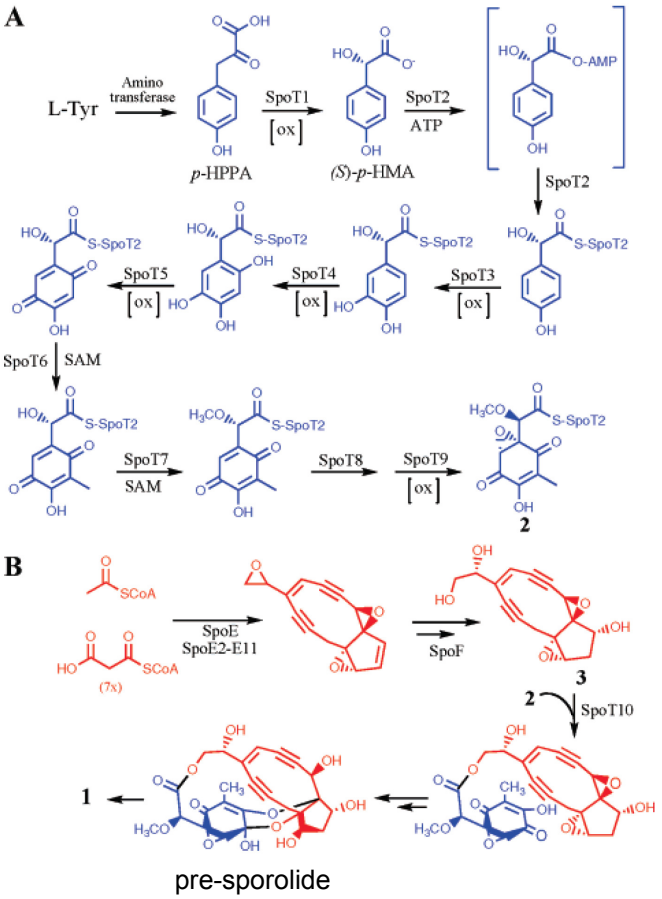
Acetyl-CoA Malonyl-CoA



L-Tyrosine

Biosynthesis toward pre-sporolide is catalyzed by several polyketide synthases encoded in *spo* gene cluster.

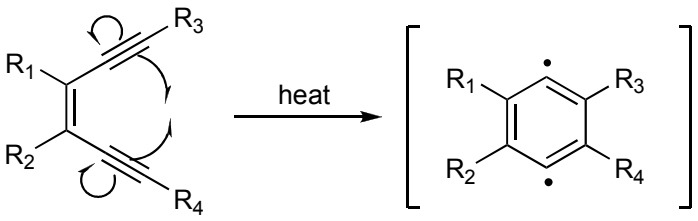
Moore *et al., PNAS*, 2007, *104*, 10376-10381
Moore *et al., J. Am. Chem. Soc.*, 2008, *130*, 2406-2407



pre-sporolide

1-2. Bergman cycloaromatization

R. G. Bergman, *Acc. Chem. Res.*, 1973, *6*, 25-31
Basak *et al., Chem. Rev.*, 2003, *103*, 4077-4094

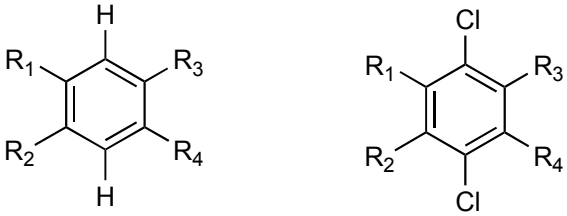


enediyne
(Z)-hex-3-ene-1,5-diyne

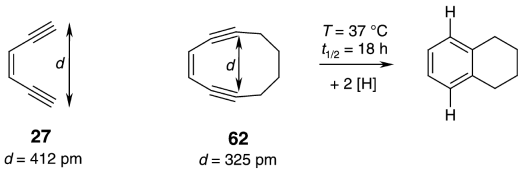
biradical intermediate
"*para*-benzyne"

1,4-cyclohexadiene
(hydrogen donor)

CCl_4



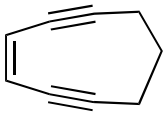
Nicolaou *et al., J. Am. Chem. Soc.,* 1988, *110*, 4866
Sander *et al., Angew. Chem. Int. Ed.,* 2003, *42,* 502-528



27 d = 412 pm **62** d = 325 pm

Scheme 19. The transition from the acyclic enediyne **27** to the cyclic enediyne **62** leads to a drastic reduction of the barrier for cycloaromatization.[78h,87] However, the distance *d* between the acetylenic carbon atoms seems to be only one of the factors governing the activation enthalpy of the Bergman cyclization.[88]

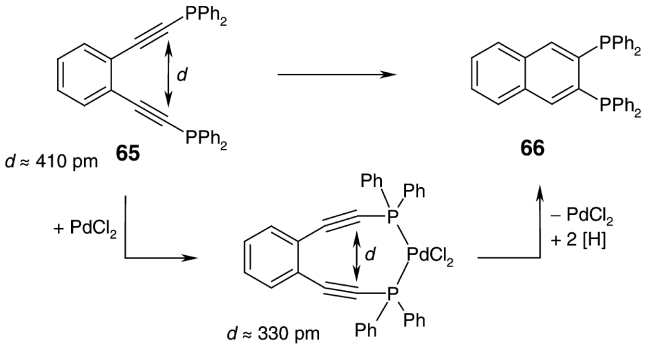
Distance between two terminal alkyne moiety is one of the key factors of reactivity.
Cyclization of **27** requires 200°C ($t_{1/2}$ = 30 s), while 10-membered enediyne **62** proceeds smoothly even at 37°C.



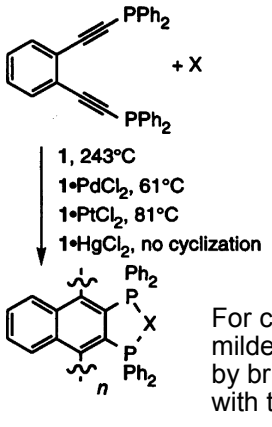
Fenical *et al., Org. Lett.,* 2006, *8*, 1024

9-membered enediynes are much more unstable.
In nature, they are stabilized as chlomoprotein.
Once separated from their protein complex, cyclization occurs rapidly.

Buchwald *et al., Science,* 1995, *269,* 814



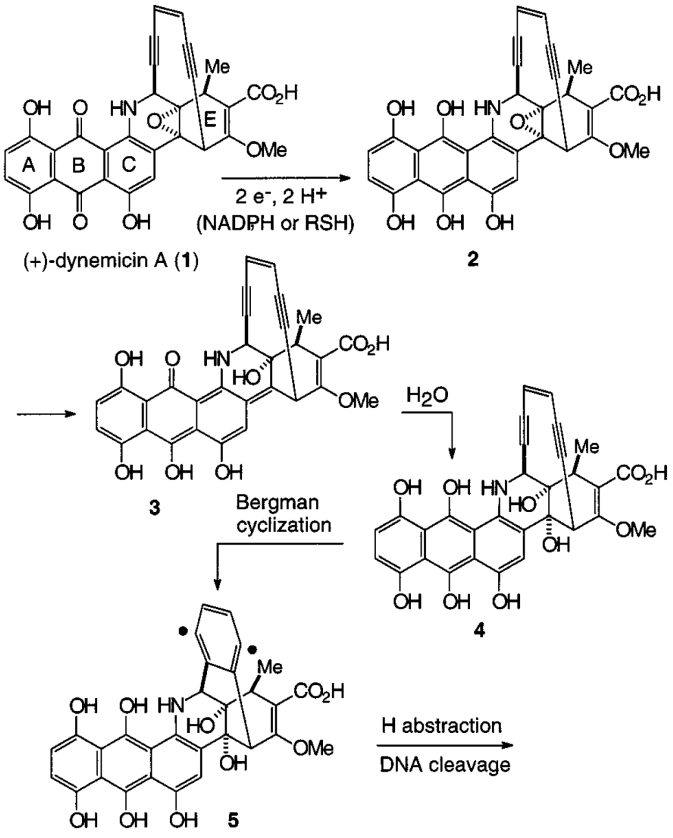
Scheme 20. The cyclization temperature of **65** is drastically reduced by metal complexation.[95]



Scheme 3

For cyclization of the acyclic enediyne, milder temperature can be adopted by bridging two alkyne moiety with transition metals.

Niestroj *et al., Eur. J. Org. Chem.,* 1999, 1-13



Scheme 2

Smith and Nicolaou, *J. Med. Chem.*, 1996, *39*, 2103-2117

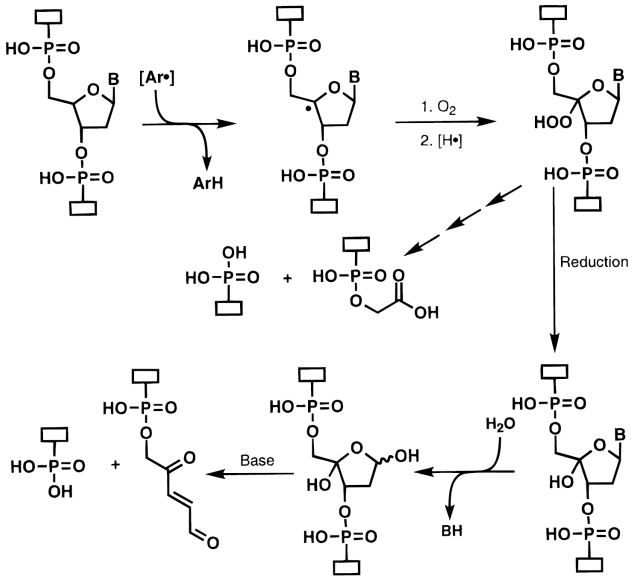


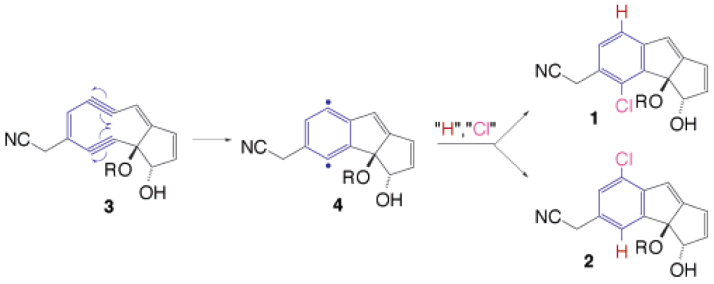
Figure 6. DNA cleavage by C(4′) hydrogen atom abstraction.

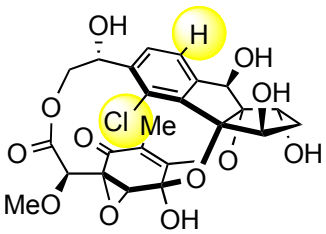
Hydrogen atom abstraction from DNA leads to double-strand cleavage.
So, many compounds possesing the enediyne structure has an antitumor activity.

1-3. Nucleophilic addition to *p*-benzyne

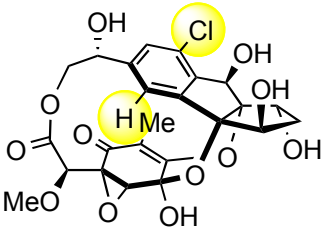
O'Connor *et al., J. Am. Chem. Soc.*, 2007, *129*, 4795-4799

Scheme 1. Proposed (Partial) Mechanism for Formation of Cyanosporasides (**1**, **2**; R = 3-oxo-4-methyl-β-fucosyl) from an Enediyne Precursor, **3**





sporolide A



sporolide B

Cyanosporaside A/B (products of *S. pacifica*), sprolide A/B were isolated as a 1:1 mixture of Cl-positional isomers. (No dihydro nor dichloro compound was detected.)

→ Not radicalic pathway.

→ How is only one Cl incorporated ?

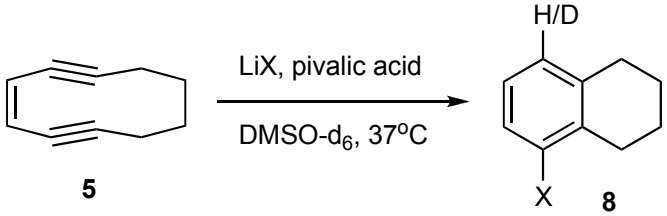


Table 1. Rate Constants and Yields of **8** (X = Cl, Br, I) for Reactions of Enediyne **5** with Halide and Pivalic Acid in DMSO-d_6 at 37 °C

MX	$[\mathbf{5}]_o$/mM	$[X^-]$/mM	[HA]/mM	$10^5 k/s^{-1}$	%yield
LiI	75	750	90	1.42	100
LiI[a]	4	550	20	1.38	100
LiI	4	55	20	1.31	100
LiI	75	370	90	1.35	98
LiI[b]	4	550	20	1.23	55
LiBr	3.8	550	15	1.51	100
LiBr	19	576	20	1.46	100
LiBr[a]	3.8	550	15	1.56	92
LiBr[a]	14	584	20	1.30	92
LiBr	24	360	190	1.21	77
LiBr	28	420	84	1.32	71
LiCl	3.8	550	15	1.30	99
LiCl[a]	3.8	550	15	1.59	37
none	15.5	0	0	2.07	0

[a] + 20% D_2O. [b] + 50% D_2O.

8 is partially deuterated, even in absent of D_2O.
Reaction rate is just first order in [**5**] (*i.e.* $-d[\mathbf{5}]/dt = k[\mathbf{5}]$) and independent of [HA], [LiX], and the kind of halides.

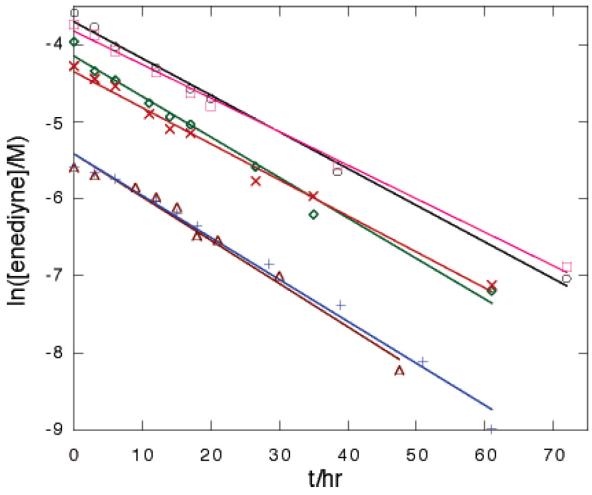
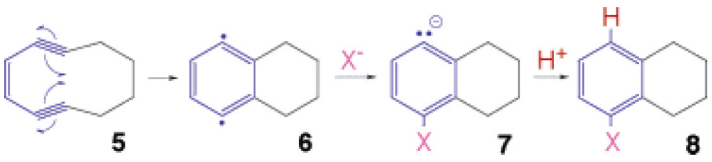


Figure 1. Plot of ln[enediyne] vs time for reaction of **5** with LiBr under conditions of entries 6−11 in Table 1 (+, ◇, △, ×, ○, and □, respectively).

Slopes are clearly the same for all.

Plausible mechanism



→ The intermediate is haloaryl anion **7** (strong base) which can abstract D^+ cation from DMSO-d_6.

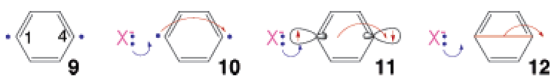
→ The rate-limiting step is the cycloaromatization of **5** to **6.**

Alternative mechanisms of cyclization can be excluded due to the reaction rate order.

Electron transfer from halide to *p*-benzyne can be rejected, because it is endothermic (>170 kJ/mol).

If the protonation occured before the chlorination, deuterium abstraction from DMSO-d_6 would be unreasonable.

Scheme 4. Detailed Mechanism of Halide Addition to *p*-Benzyne **9**



A mix of transfers of an electron pair and a single electron.(**10**)

Singlet biradical forms a new weak sigma bond between position 1 and 4, and halide approachs to the sigma antibond, then nucleophilic displacement occurs. (**11**, **12**)

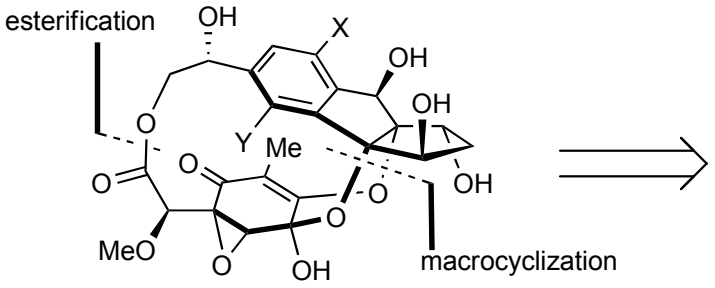
Calculated study shows this halide addition step is exothermic, even in water.

→ Thus, only one chlorine is introduced to either of the two possible positions.

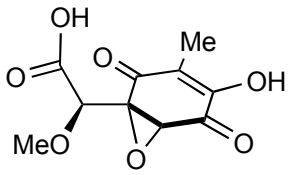
1-4. Gademann's synthetic study

Retrosynthetic analysis Biomimetic approach through Bergman cycloaromatization of 9-membered enediyne ring. If this route succeeded, a 1:1 mixture of both isomers could be obtained at the same time.

The most challenging point is the high rigidity of 9-membered enediyne moiety.



1a: sporolide A (X=H, Y=Cl)
1b: sporolide B (X=Cl, Y=H)



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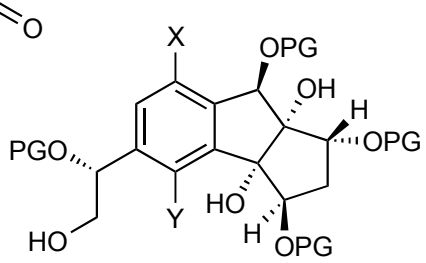

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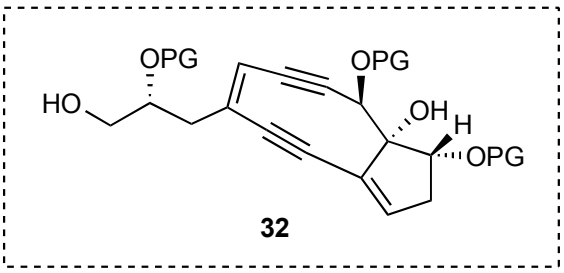
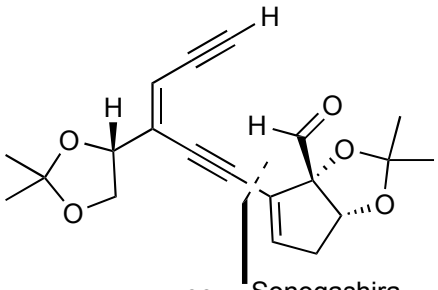
Bergman cycloaromatization



32

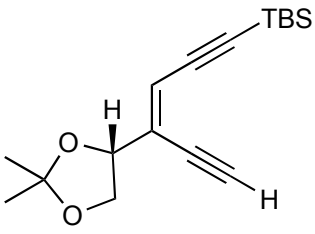
9-membered enediyne intermediate

Acetylide attack

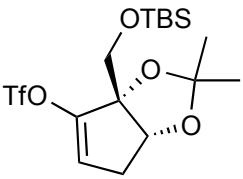


33

Sonogashira cross-coupling



34



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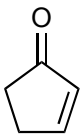
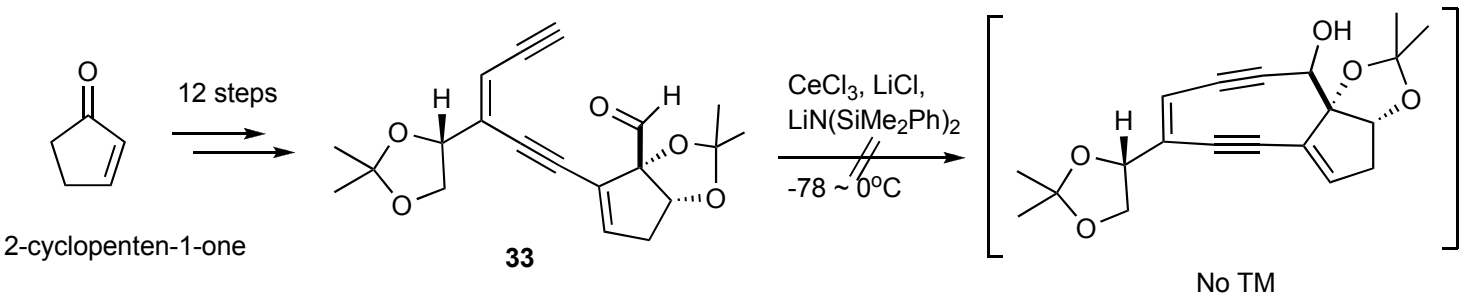
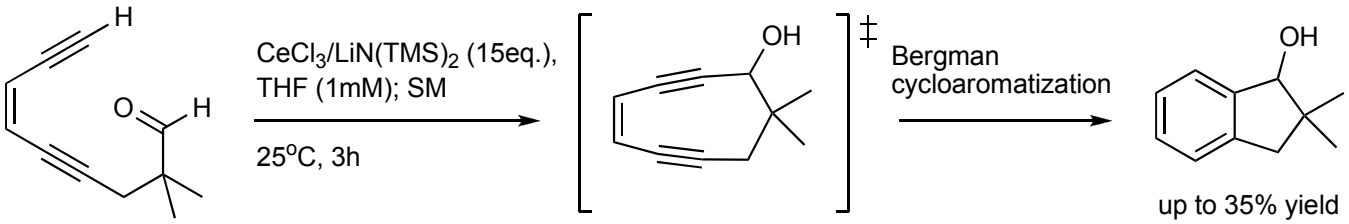


2-cyclopenten-1-one

Strategy 1) 9-membered enediyne ring K. Gademann *et al., Synthesis,* 2010, *4,* 631-642



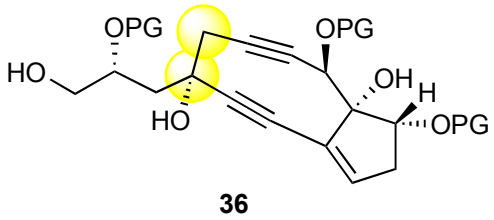
Hirama *et al., Chem. Lett.,* 1998, *27,* 959



Lower temperature (<20°C), or higher concentration (5mM) only yielded dimer or oligomer.
A large excess of $CeCl_3/LiN(TMS)_2$ was necessary to obtain TM in >10% yield.

Thus, high temp. is required for intramolecular acetylide attack to enediyne, because of the rigidity of structure which came from two sp^2 hybridized centers. But in this case, higher temp. made serious side reactions.

Strategy 2) 9-membered diyne ring



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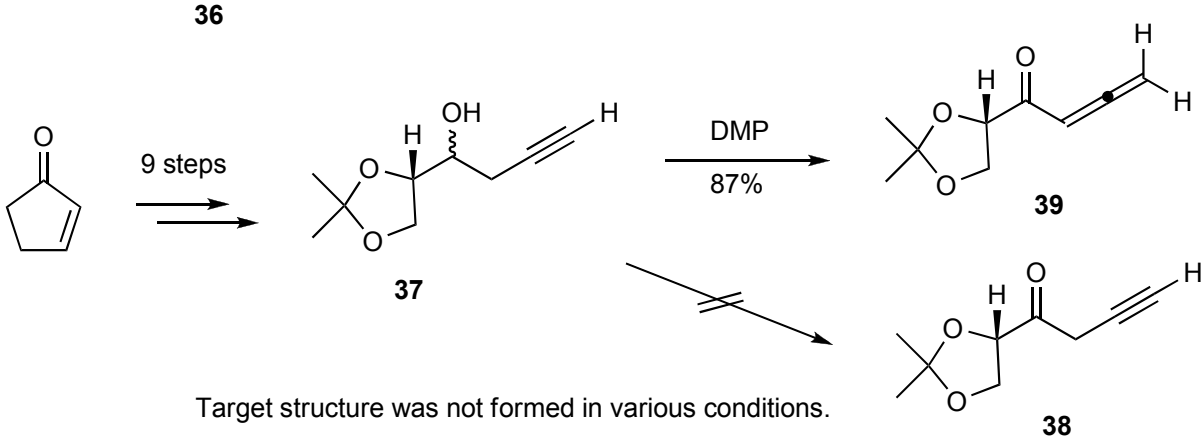
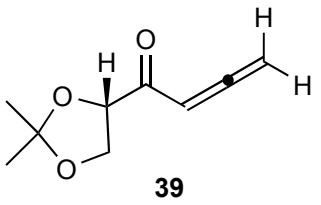
Target structure;
9-membered ring diyne core without two sp^2 hybridized centers
(Less rigid structure than enediyne)

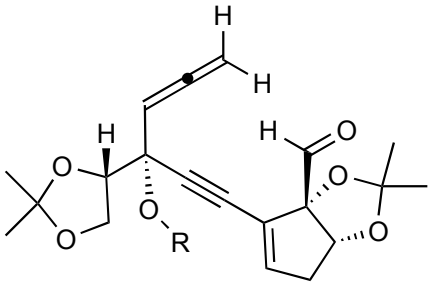


Target structure was not formed in various conditions.

A. Yamashita *et al., J. Am. Chem. Soc.,* 1975, *97,* 891
Allenes are known to undergo isomerization to alkynes under strong base condition.
So, they continued the synthesis using allene **39**.

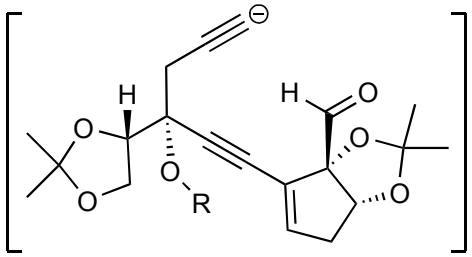


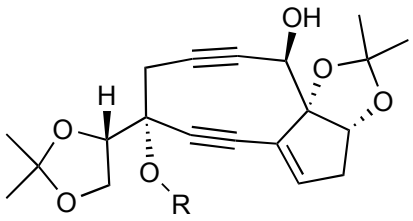
39



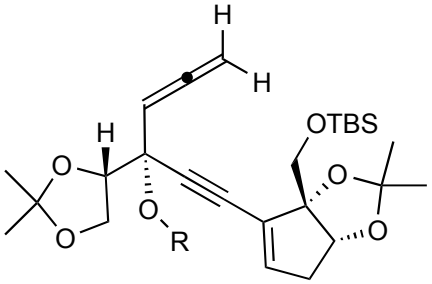
40: R = H
41: R = TMS
42: R = Me

Strong base
Lewis acid
Temperature





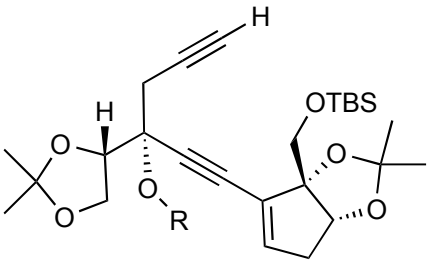
Cascade system toward formation of
9-membered ring failed under 22 conditions.



43: R = H
44: R = Me
45: R = TBS

KAPA

Simple isomerization also failed.



KAPA: Potassium 3-(aminopropyl)amide; prepared from KH & 3-aminopropylamine *in situ.*
Yamishita *et al., Chem. Commun.,* 1976, 959

Conclusion

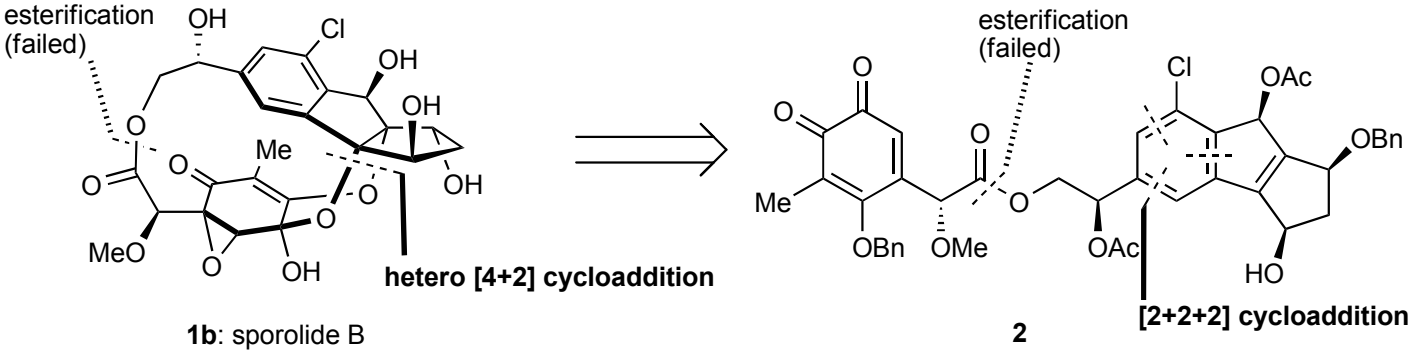
9-membered enediyne ring is very difficult to construct due to the high rigidity of the structure.
It is still uncertain whether the strategy of forming 9-membered diyne ring is promising or not.

2. Nicolaou's approach

K. C. Nicolaou *et al., Angew. Chem. Int. Ed.,* 2009, *48*, 3449-3453
K. C. Nicolaou *et al., J. Am. Chem. Soc.,* 2010, *132,* 11350-11363

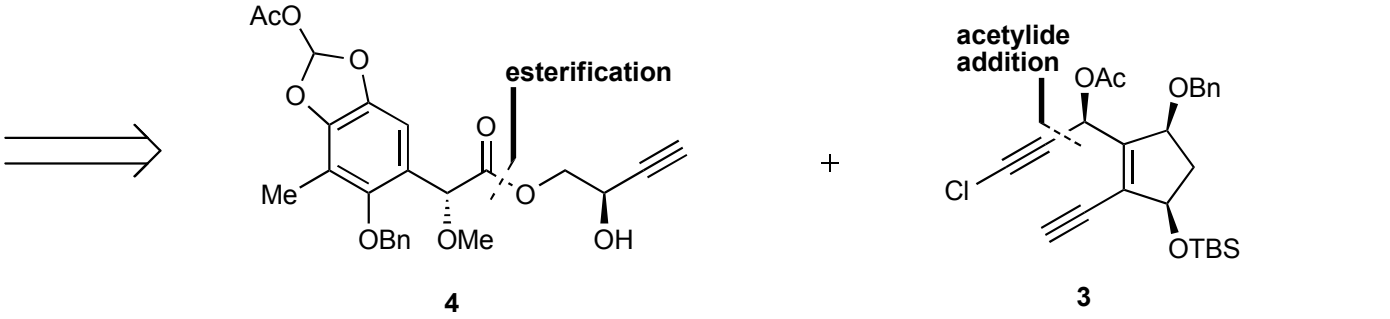
2-1. Retrosynthetic analysis

Instead of biomimetic way, they proposed the approach through two unusual cycloadditions; Intramolecular hetero [4+2] cycloaddition, and ruthenium-catalyzed [2+2+2] cycloaddition.



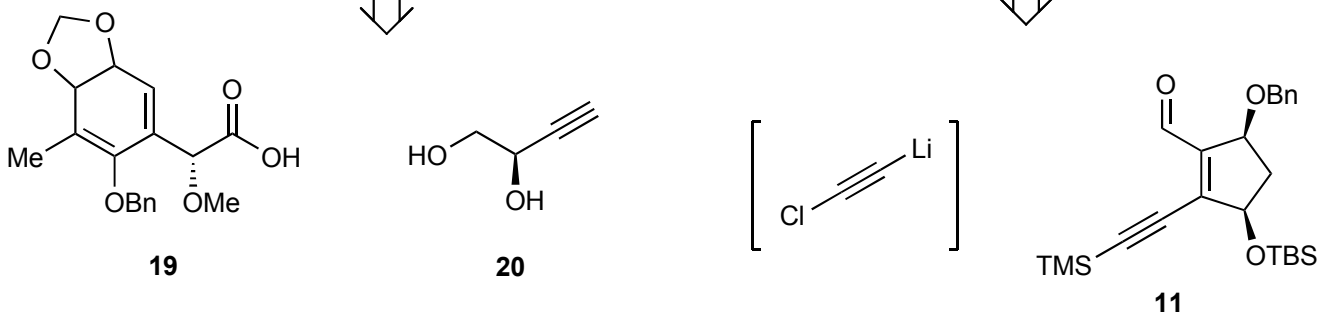
1b: sporolide B

2



4

3



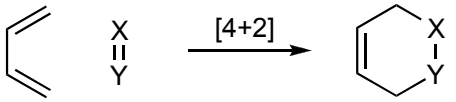
19

20

11

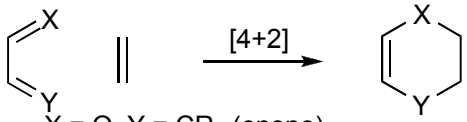
2-2. Hetero [4+2] cycloaddition

(a) hetero 2e component



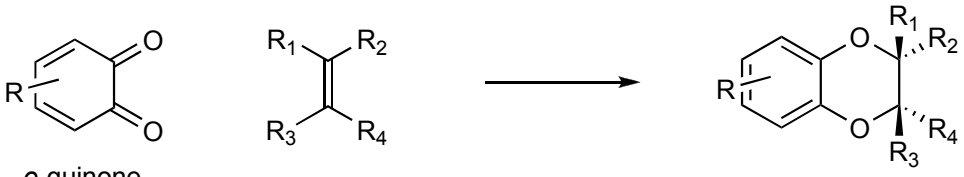
X = O, Y = CR_2 (carbonyl)
X = Y = NR

(b) hetero 4e component



X = O, Y = CR_2 (enone)
X = Y = O (1,2-dicarbonyl)
Nicolaou's Method

[4+2] cycloaddition of 1,2-dicarbonyl moiety



o-quinone
(*o*-benzoquinone)

1,4-dioxane derivative

Cycloaddition of substituted *ortho*-quinones has only been reported.
(Simple *o*-quinones are so unstable that they are rapidly dimerized.)

Difficulties: (1) Two stable C=O bonds
(2) Lower HOMO energy than C=C bond
(3) Existence of other 2e/4e systems

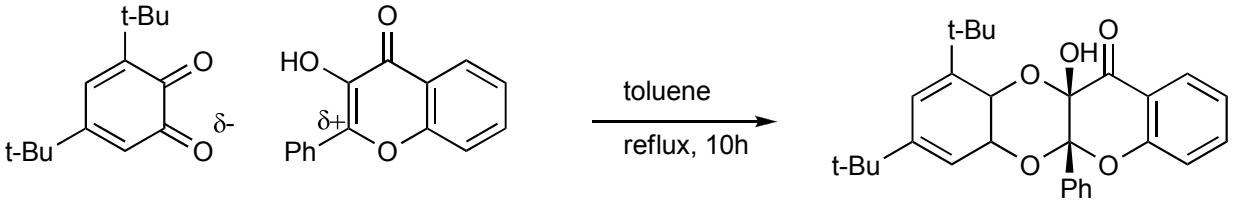
In order to overcome: (1) Aromatization of *o*-quinones
(2) Introduction of EDG / Using LUMO of *o*-quinone
(3) Steric effect

C-C : 340-350 kJ/mol
C-O : 350-380 kJ/mol
C=C: 600-625 kJ/mol
C=O: 725-760 kJ/mol
aromatization : 140 kJ/mol
(Ref. Warren)

V. Nair *et al., Synlett.,* 1996, 1143-1147
o-quinone has 4 possible reactive points.

Carbodiene **Heterodiene** **Dienophile** **Heterodienophile**

Reglier *et al., Tet. Lett.,* 2004, *45*, 8011-8013

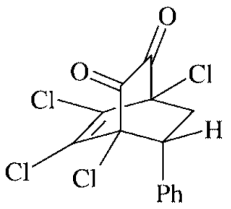


flavonol

55% (racemic)

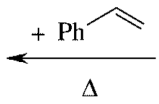
Regioselectivity seems to be based on the partial polarization.

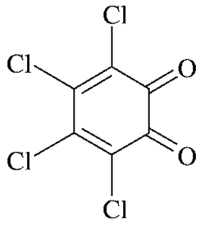
P. G. Jones *et al., Eur. J. Org. Chem.,* 2006, *335-350*



43

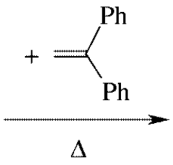
all-carbon diene as 4e system

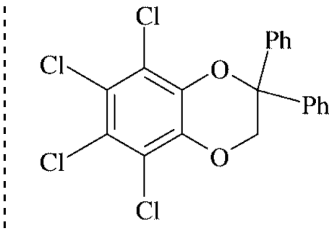




10f

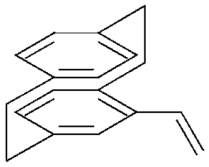
o-quinone derivative



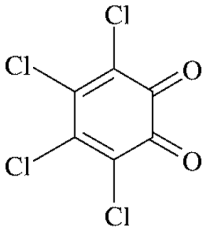


44

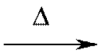
heterodiene moiety as 4e system

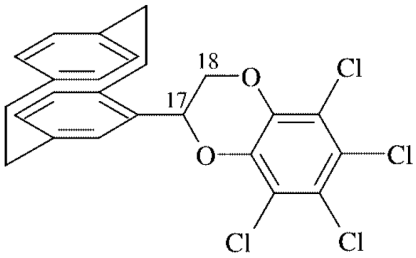


7



10f

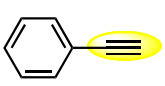


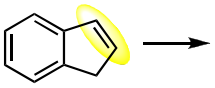


49

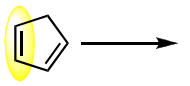
62% yield

Reactivity of each diene-system seems to depend on the structural bulkiness of dienophile.

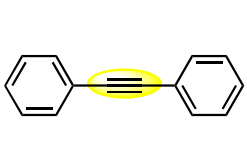


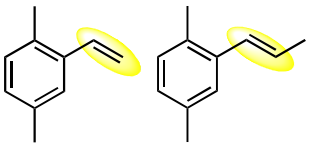


reacts with all-carbon diene



reacts with both (gives mixture)



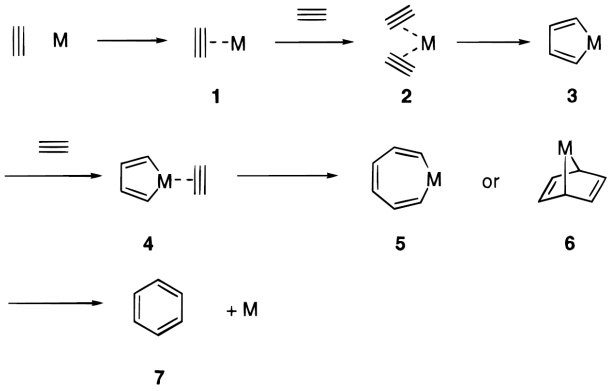


reacts with heterodiene moiety

2-3. Regioselective [2+2+2] cycloaddition

Y. Yamamoto *et al., Chem. Rev.,* 2000, *100,* 2901-2915

Scheme 1 General mechanism

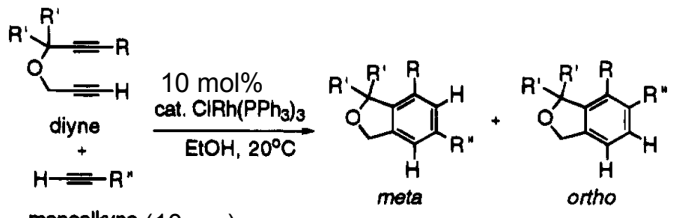


M = Co, Ni, Rh, Ru, Pd and many other kinds of metals are available today.

Generally, highly regioselective synthesis is achieved in partially / totally intramolecular system.

Holmquist *et al., J. Am. Chem. Soc.,* 1995, *117,* 6605-6606

Table 1. Regioselectivity of $ClRh(PPh_3)_3$-Catalyzed Cyclotrimerization

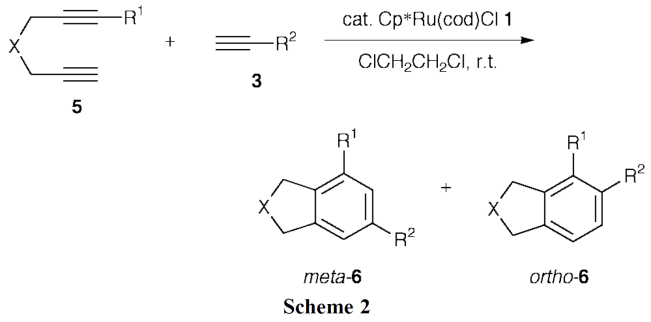


entry	diyne	monoalkyne	yield of aromatic products (isomer ratio)
1	R = CH_3, R' = H (**17**)	R" = *n*-Bu (**20**)	35% (*m* : *o* = 1.7 : 1)
2	**17**	R" = $C(CH_3)_2OH$ (**21**)	54% (*meta* only)
3	**17**	R" = CH_2OH (**22**)	53% (*m* : *o* = 1.8 : 1)[a]
4	R = $C(CH_3)_2OH$, R' = H (**18**)	**20**	36% (*meta* only)
5	**18**	**21**	60% (*meta* only)[b]
6	**18**	**22**	52% (*meta* only)[b, c]
7	R = OEt, R' = CH_3 (**19**)	**20**	61% (*m* : *o* = 4 : 1)
8	**19**	**21**	53% (*meta* only)
9	**19**	**22**	59% (*m* : *o* = 4 : 1)

[a] 2 mol % $ClRh(PPh_3)_3$ was used for this entry. [b] Analytically pure compounds were obtained by conversion of aromatic products to the corresponding bis-*O*-trimethylsilyl ethers (excess 1-(trimethylsilyl)imidazole, THF, 20 °C, 16 h) followed by flash chromatography. [c] The yield was 95% based on recovered diyne **18**.

Willkinson's catalyst was used.
Steric repulsion causes regioselectivity.
→ *meta*-substituted benzene can be synthesized through this approach.

K. Itoh *et al., Chem. Commun.*, 2000, 549-550
K. Itoh *et al., J. Am. Chem. Soc.*, 2003, *125*, 12143-12160



Scheme 2

Table 2 Cp*Ru(cod)Cl-catalyzed cycloaddition of 1,6-diynes **5a–c** with terminal alkynes **3**[a]

Entry	X	R^1	R^2	Catalyst (mol%)	Yield[b] (%) *t*	(*meta* : *ortho*)[c]
1	$C(CO_2Me)_2$	Me	Bu	1	1 h	**6a**, 85 (93 : 7)
2	$C(CO_2Me)_2$	Me	Me[d]	3	18 h	**6b**, 80 (94 : 6)
3	$C(CO_2Me)_2$	Me	CH_2OMe	1	3 h	**6c**, 86 (94 : 6)
4	$C(CO_2Me)_2$	Me	Ph	3	24 h	**6d**, 82 (88 : 12)
5	$C(CO_2Me)_2$	Ph	Bu	10	24 h	**6e**, 80 (95 : 5)
6	$C(CO_2Me)_2$	$SiMe_3$	Bu	5	7 h	**6f**, 94 (98 : 2)
7	NTs	Me	Bu	1	10 min	**6g**, 82 (93 : 7)
8	O	Me	Bu	1	30 min	**6h**, 75 (95 : 5)

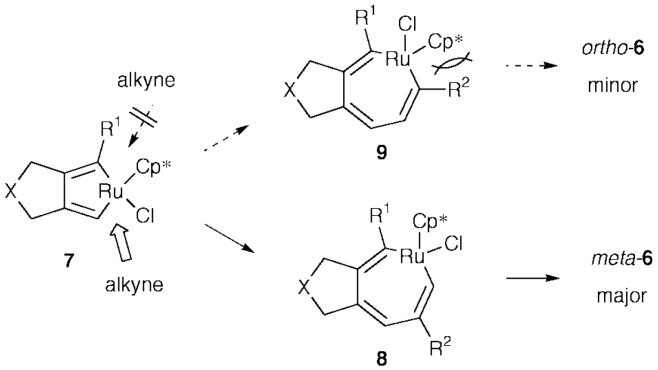
[a] All reactions were carried out with a terminal alkyne (2 equiv.) in 1,2-dichloroethane at r.t. [b] Isolated yield. [c] Ratios in parentheses were determined by GC analyses of isolated products. [d] Under propyne gas (balloon).

Catalyst screening in entry 1 (above)

run	precatalyst (mol %)	t (h)	6a yield (%)[b] (meta:ortho)[c]
1	Cp*RuCl(cod) **1a** (1)[a]	1	85 (93:7)
2	$[Cp^*RuCl_2]_2$ **1b** (0.5)[a]	2	81 (94:6)
3	CpRuCl(cod) **1c** (1)[a]	24	76 (87:13)
4	$RhCl(PPh_3)_3$ (5)[d]	72	61 (63:37)
5	$Ni(cod)_2/4PPh_3$ (15)[e]	4	83 (30:70)
6	CpCo(cod) (20)[f]	15	70 (54:46)

[a] A solution of **5a**(0.5 mmol) in DCE (3 mL) was added dropwise to a solution of **1** and **3a** (2 equiv) in DCE (2 mL) for 15 min and stirred for the time specified above at room temperature. [b] Isolated yields. [c] Isomer ratios were determined by GC analysis of isolated products. [d] In EtOH at 60 °C. [e] In THF at room temperature. [f] The reaction was carried out with 10 equiv of **3a** in a sealed xylene solution at 150 °C.

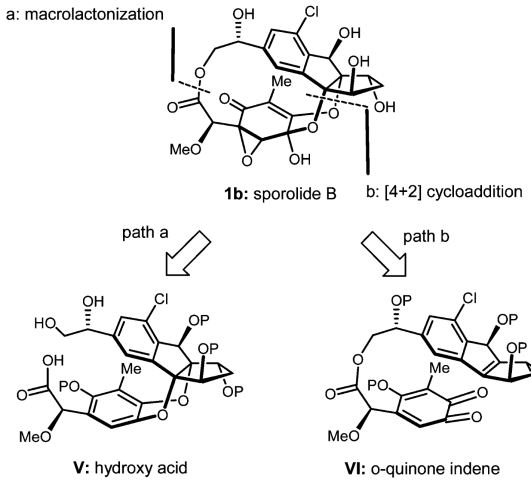
Cp*RuCl(cod) gives the greatest *meta*-selectivity.



The bulky Cp* ligand is important for the high selectivity.
(Cp* = pentamethylcyclopentadienyl)

For regioselective synthesis of pyridine derivatives, see Mr. Saito's literature seminar.

2-4. Model studies about cycloaddition



In the first retrosynthetic analysis, they proposed 2 pathways.

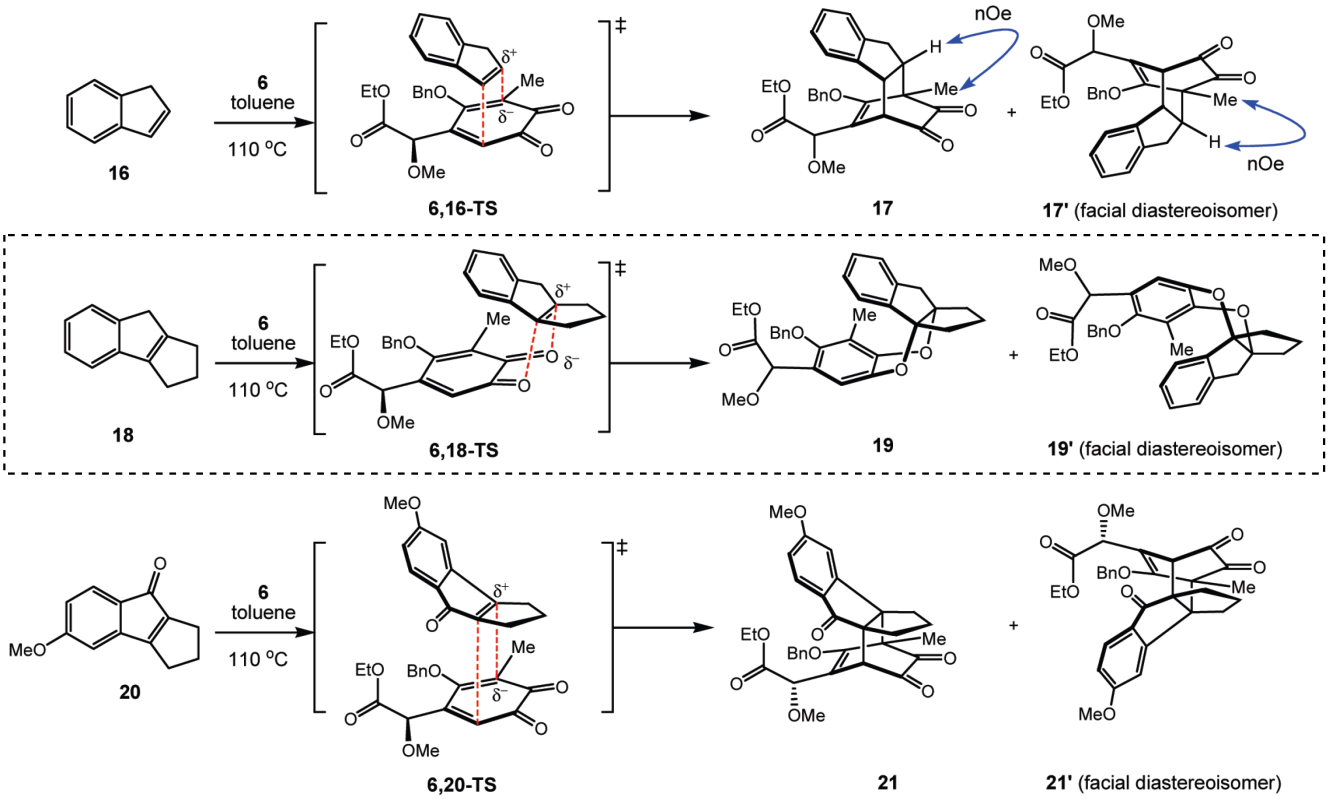
Path a: Intermolecular [4+2] and following lactonization
Path b: Esterification and following intramolecular [4+2]

But intramolecular [4+2] cycloaddition might be problematic, due to the limited conformation.

So they adopted the intermolecular [4+2] system (Path a) as an initial study.

Intermolecular [4+2] cycloaddition ~ model study

Scheme 2. Intermolecular [4+2] Cycloaddition Reaction between Indene Derivatives and *o*-Quinone **6**[a]



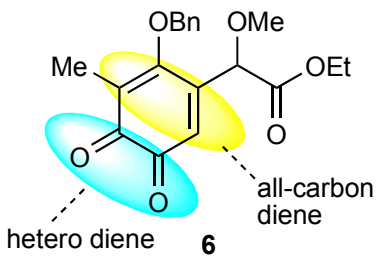
[a] Reagents and conditions: indene derivatives **16**, **18**, **20** (1.0 equiv), *o*-quinone **6** (1.2 equiv), toluene, 115 °C, 4 h **17**,**17′**, 82%, ca. 1.5:1 dr; **19**,**19′**, 57%, ca. 1:1 dr; and **21**,**21′**, 80%, ca. 10:1 dr.

o-quinone has two kinds of diene system: all-carbon diene, and hetero diene moiety.
All-carbon diene has much higher reactivity for [4+2], but is more sterically hindered.

Indene **16** gives only undesired products. (all-carbon diene is much more reactive.)

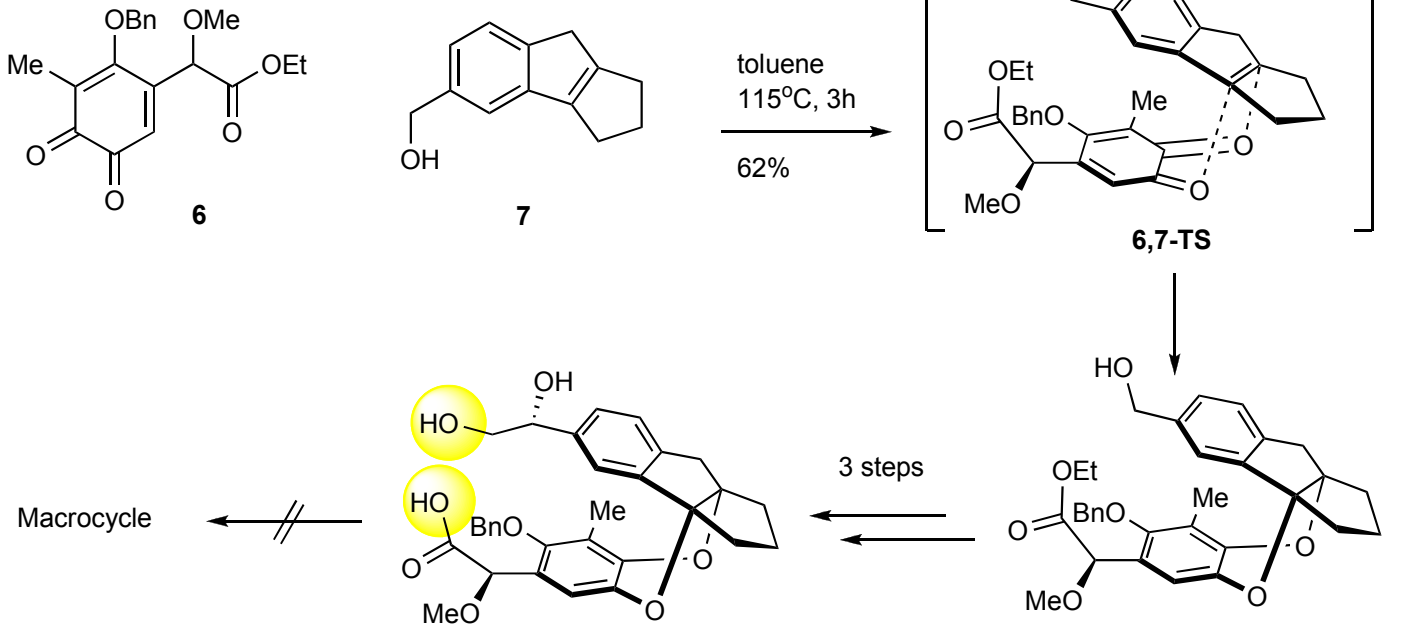
But more crowded indene derivative **18** gives desired products in good yield.
→ Steric repulsion of dienophile can reverse the reactivity of diene system !

In case of enone **20**, all-carbon diene reacts, despite the steric repulsion.



In all cases, regioselectivity can be explained by assuming polarization.
(diene: electron donation from OBn group. dienophile: conjugation with phenyl or carbonyl group.)

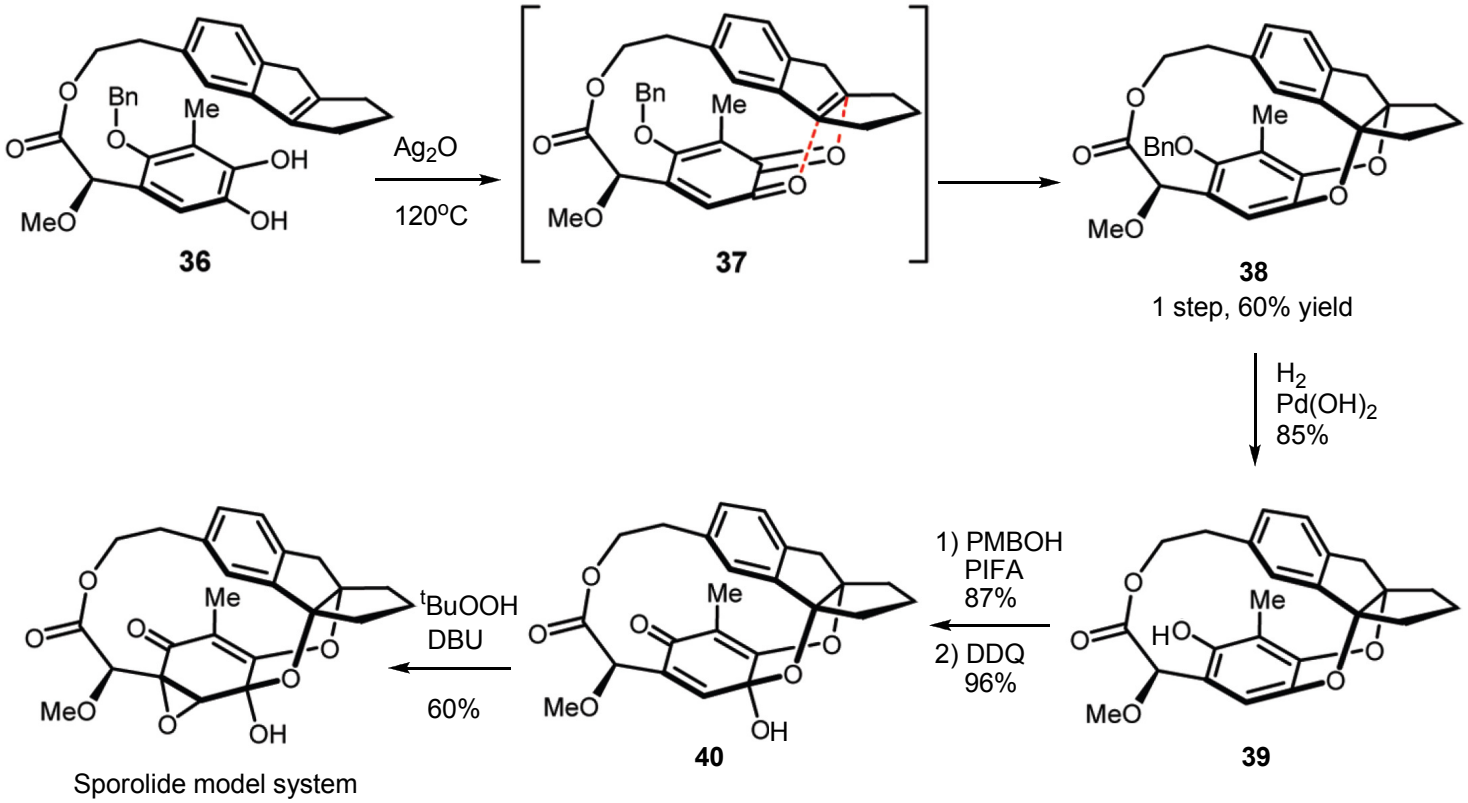
Failed attempts through macrolactonization



Macrolactnization failed in 6 activation conditions (Corey-Nicolaou, Mukaiyama salt, Mitsunobu, etc.)
Due to overwhelming strain within the expected transition state for the macrolactonization...?

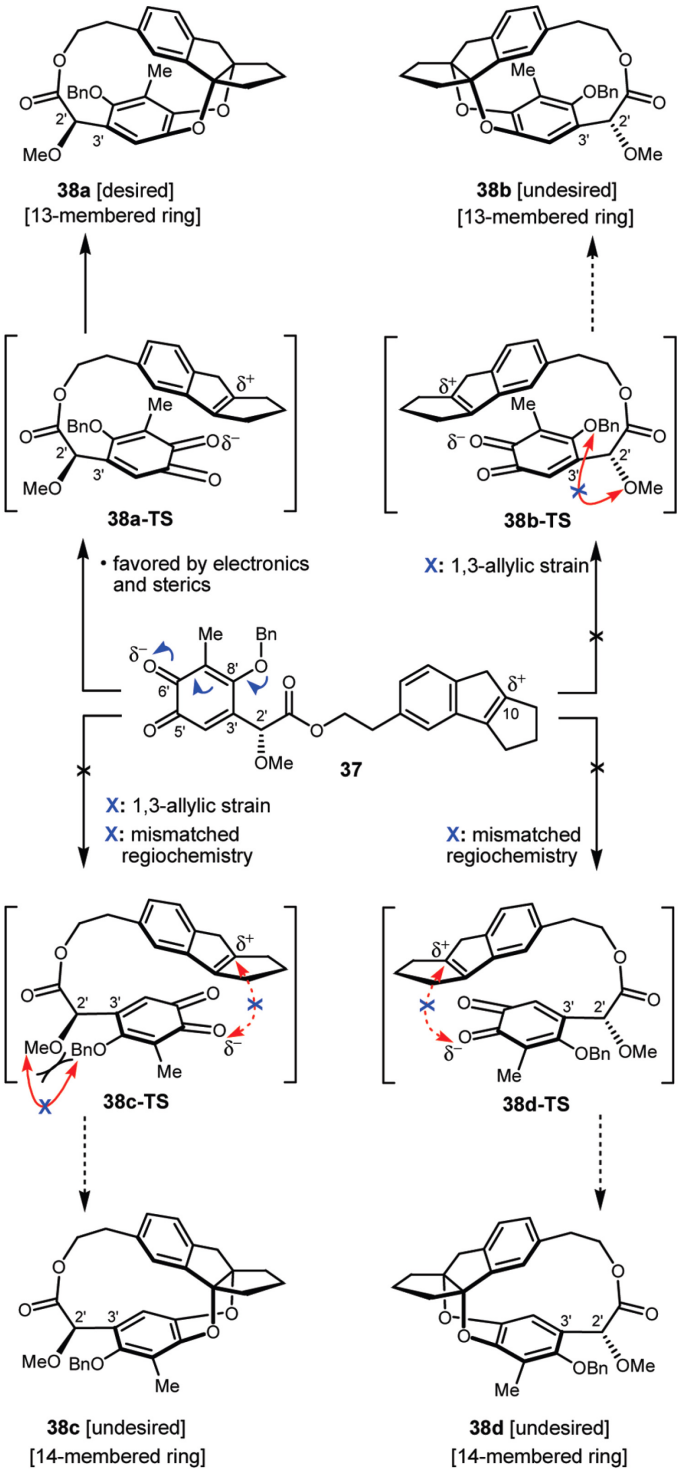
→ Change the method to Path b (esterification & following intramolecular [4+2] cycloaddition)

Intramolecular [4+2] cycloaddition ~ model study



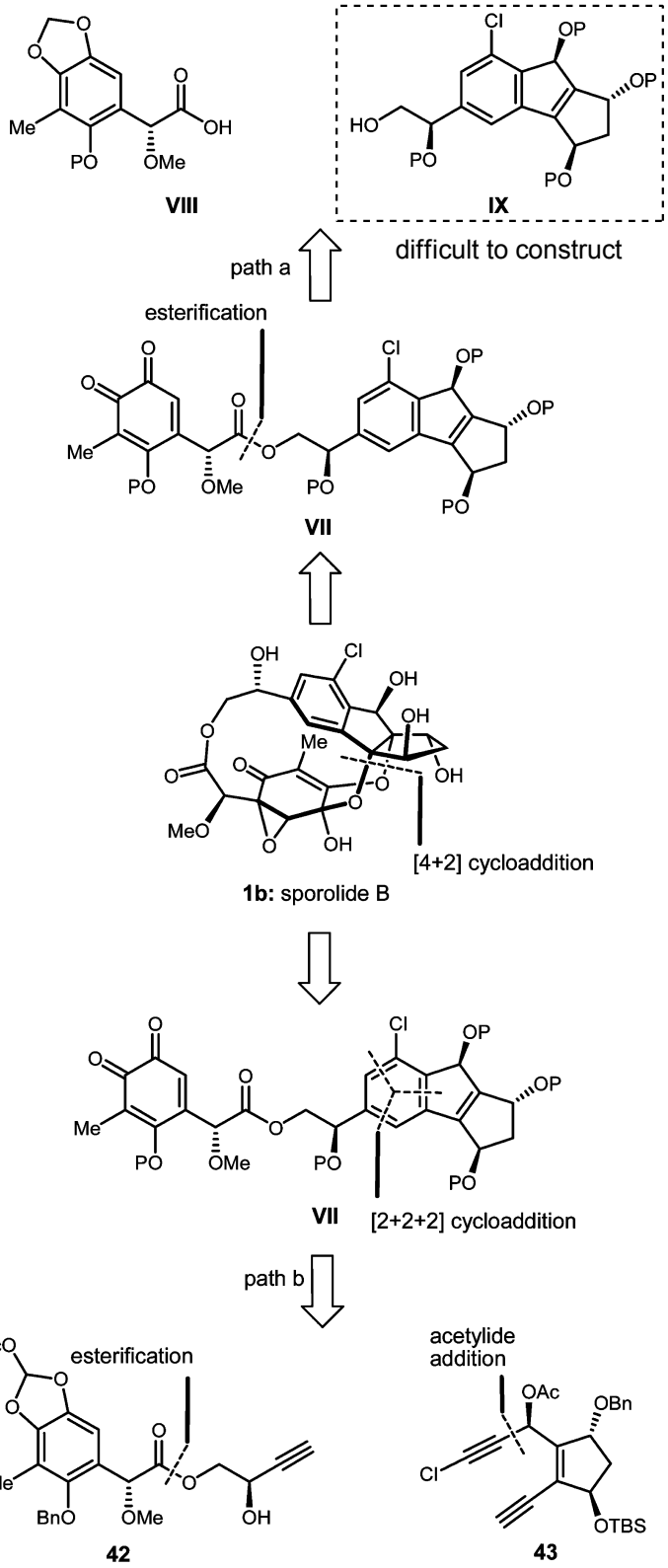
In model study, desired macrocycle was formed as a single diastereoisomer.

Diastereoselectivity of model study



Diastereo- & regioselectivity is fully controled by partial polarization and 1,3-allylic strain.

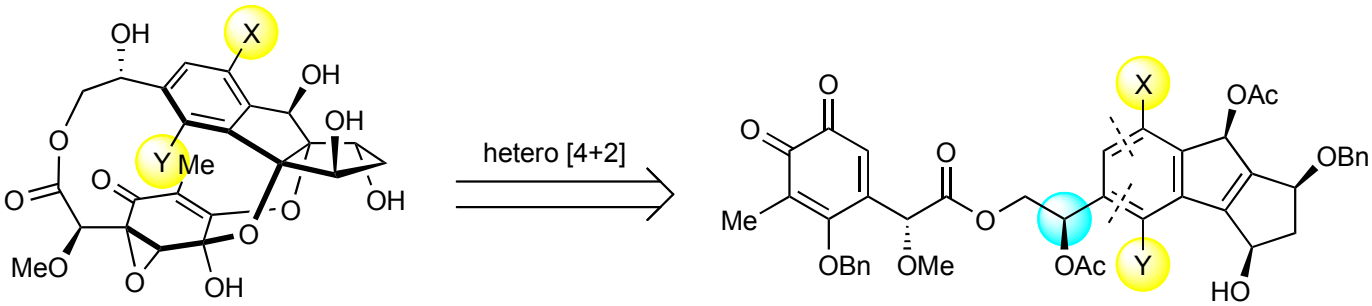
Strategy change from esterification to [2+2+2] cycloaddition



To synthesize precursor VII through esterification, VIII and IX is necessary.
Though synthesis of VIII was achieved, IX was difficult to construct, presumably due to sensitive & crowded nature.

→ As an alternative strategy to synthesize precursor VII, metal-catalyzed [2+2+2] cycloaddition was adopted.

Possible selectivity of [2+2+2] cycloaddition

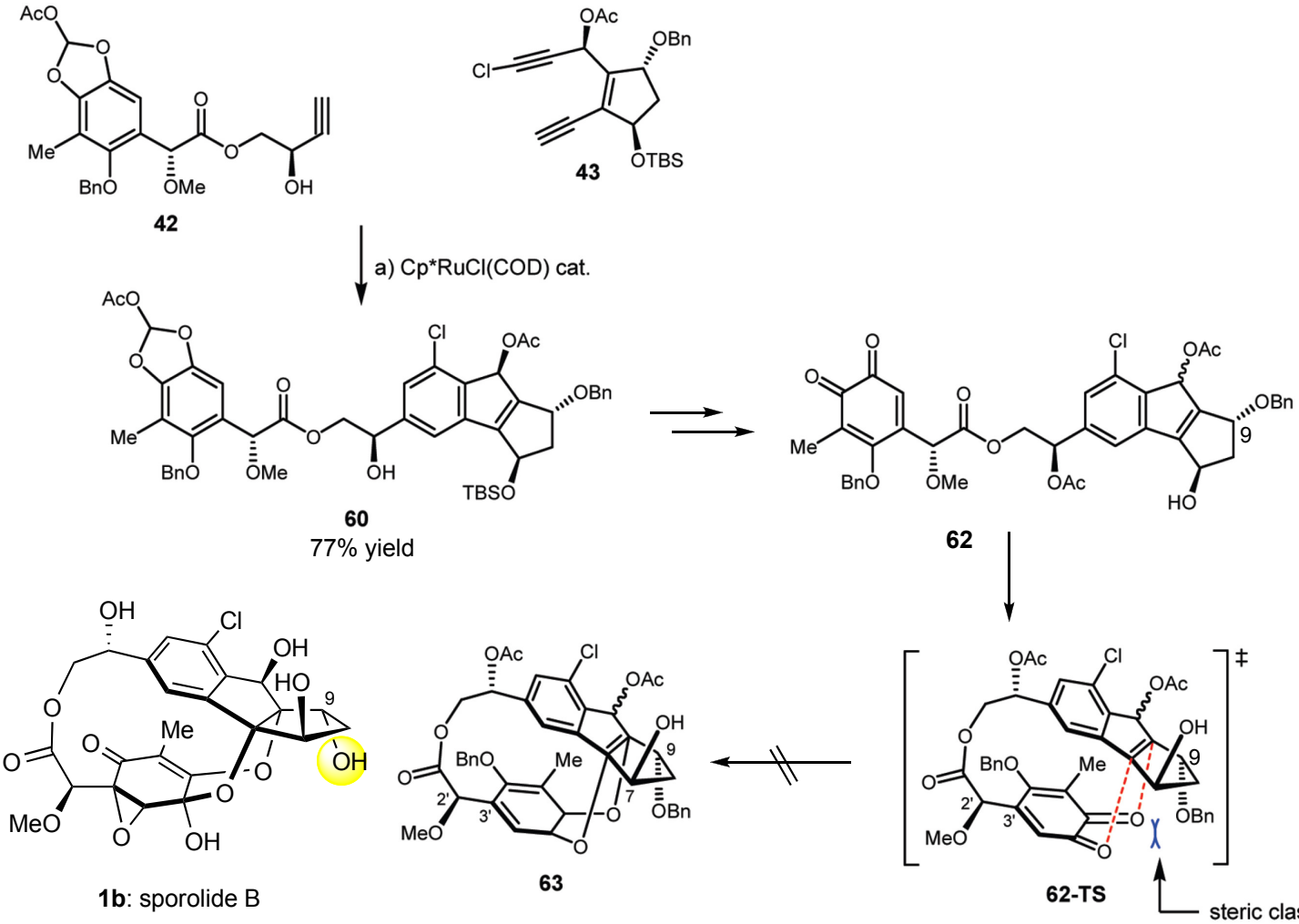


1a: sporolide A (X = H, Y = Cl)
2a: sporolide B (X = Cl, Y = H)

sporolide A: *ortho* position (unfavor)
sporolide B: *meta* position (favor)

Considering the regioselectivity of [2+2+2] cycloaddition,
the substituted group (*o*-quinone moiety) and chlorine atom will locate in *meta* position.
→ Only sporolide B can be synthesized through [2+2+2] cycloaddition !

Failed attempt to sporolide B system through intramolecular [4+2] cycloaddition



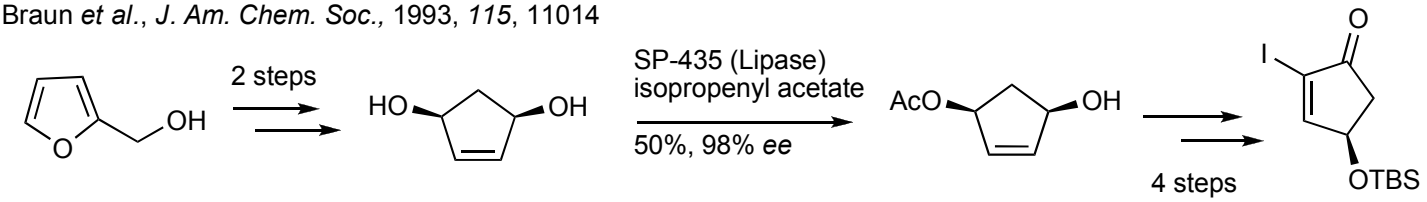
In case of fully substituted precursor **62**, [4+2] cycloaddition didn't occur at all,
due to the steric clash between o-quinone moiety and down-directed OBn group at C-9 position.

→ To overcome this problem, new substrate with the C-9 inverted stereochemistry was essencial.

2-5. Total synthesis of sporolide B

Synthesis of building block 3

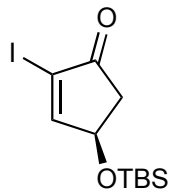
Curran *et al*., *Tetrahedron,* 1997, *53*, 1983
Braun *et al*., *J. Am. Chem. Soc.,* 1993, *115*, 11014



furfuryl alcohol
4,200 YEN/ 50G (Ald)

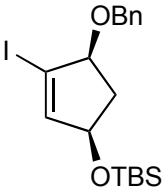
cis-1,4-cyclopentenediol
68,500 YEN/ 2.5g (Ald)

5



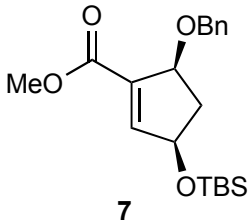
5
>99% ee

1) $NaBH_4$, $CeCl_3{\cdot}7H_2O$
MeOH, -78°C, 1h
2) NaH, THF; BnBr, TBAI
0°C to rt, 16h
(95%, *ca*. 10:1 *dr*)



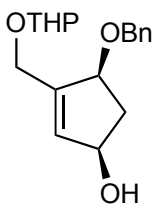
6

$PdCl_2(PPh_3)_2$ (5 mol%)
CO (balloon), Et_3N
MeOH, 70°C, 3h (95%)



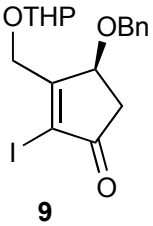
7

1) DIBAL (2.5eq.), toluene
-78°C to -10°C, 1h (95%)
2) DHP, $TsOH{\cdot}H_2O$, CH_2Cl_2, 0°C, 30min.
3) TBAF, THF, rt, 3h



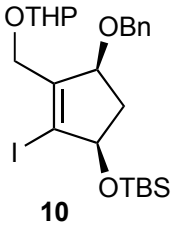
8

1) DMP, $NaHCO_3$, CH_2Cl_2, rt,
30min. (83% over 3 steps)
2) I_2, CH_2Cl_2/Pyridine (1:1)
rt, 15h (80%)



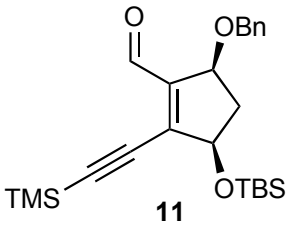
9

1) $NaBH_4$, $CeCl_3{\cdot}7H_2O$
MeOH, -78°C, 1h
2) TBSCl, imid., DMAP
CH_2Cl_2, rt, 3h
(94%, *ca.* 10:1 *dr*)



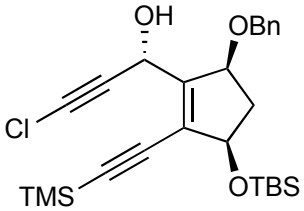
10

1) ≡—TMS $PdCl_2(PPh_3)_2$ (2 mol%),
CuI (4 mol%), Et_2NH, rt, 16h (98%)
2) Et_2AlCl, CH_2Cl_2, -25°C to rt, 2h (99%)
3) DMP, $NaHCO_3$, CH_2Cl_2, rt, 1h (79%)



11

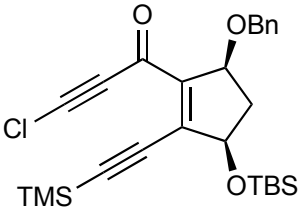
Cl—Cl (4.5 eq.)
MeLi (3.0 eq.), Et_2O
0°C, 30min.;
then **11**, 0°C, 10min.
(*ca.* 5:1 *dr)*



12

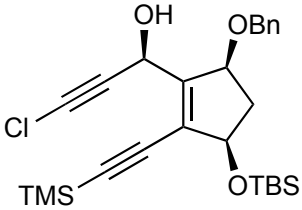
undesired diastereomer

DMP, $NaHCO_3$
CH_2Cl_2, rt, 1h
93% (2 steps)



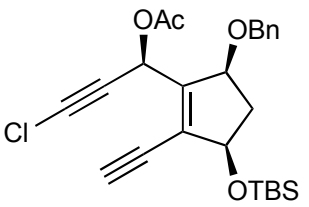
13

DIBAL (1.5 eq.), toluene
-78°C, 30min. (*ca*. 7:1 *dr*)



14 (81% pure isomer)

1) K_2CO_3, MeOH
rt, 1h (99%)
(TMS deprotection)
2) Ac_2O, Et_3N, DMAP
CH_2Cl_2, 0°C, 30min.
(98%)

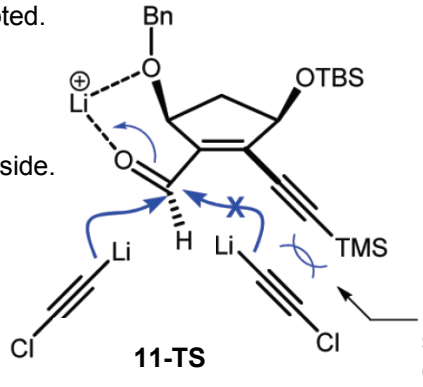


3

stereoselectivity of propargylic alcohol **12** and **14**

12 → **14**: direct Mitsunobu rxn failed.
oxidation-reduction was adopted.

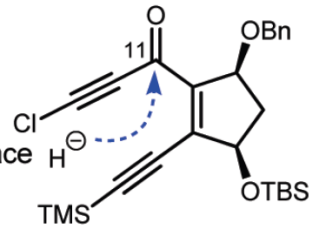
Chelation-controled TS
→ carbonyl group is directed to up-side.



11-TS

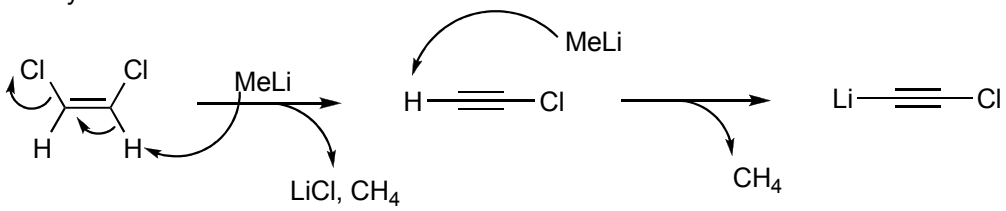
top face blocked
by OBn

bottom face
attack

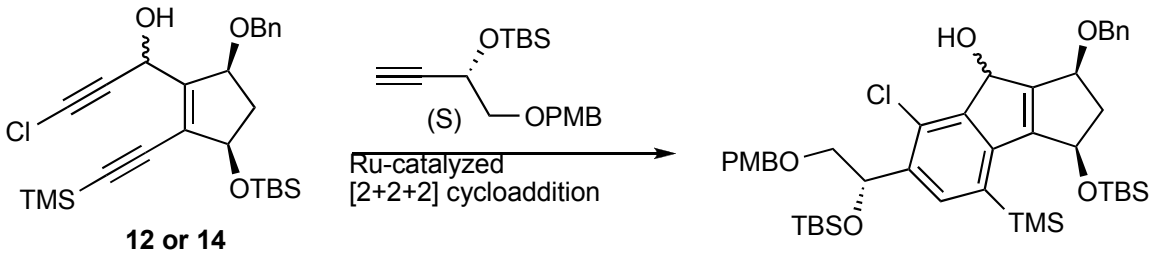


13

Lithium chloroacetylide is formed *in situ*.



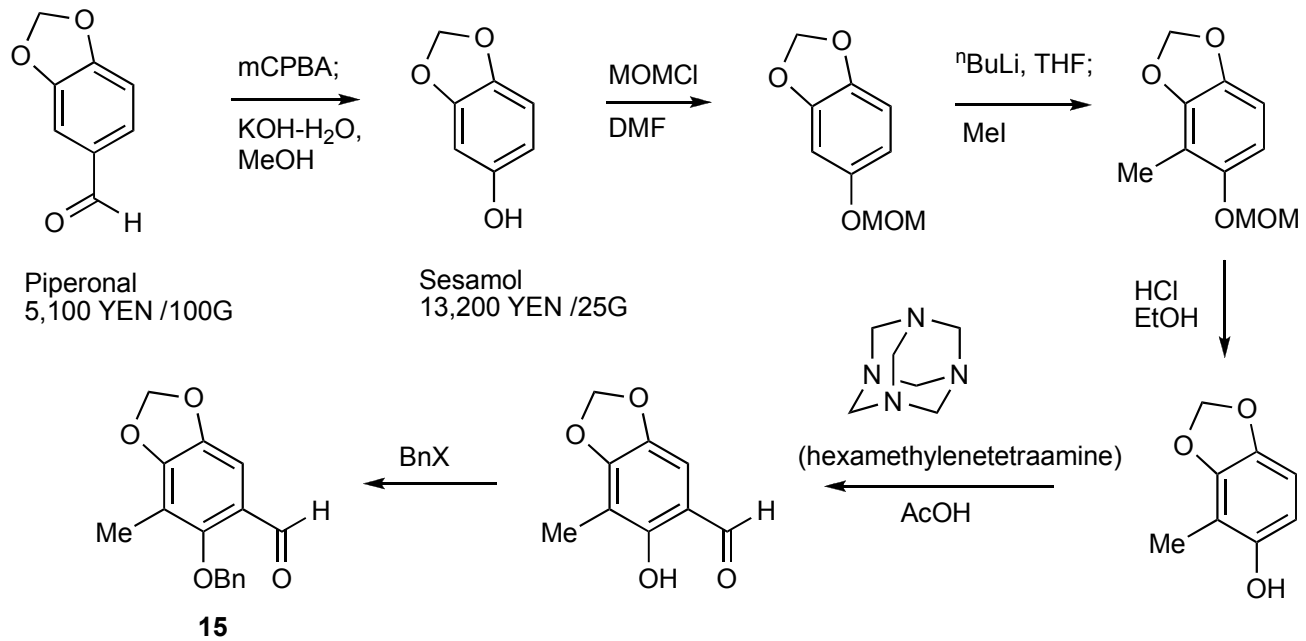
The configurations of **12**/**14** were determined by NMR (NOE?) of derivatives, prepared by [2+2+2] cycloaddition.



12 or 14

Synthesis of building block 4

A. Kubo *et al.*, *J. Chem. Soc. Perkin Trans. 1,* 1997, 53-69

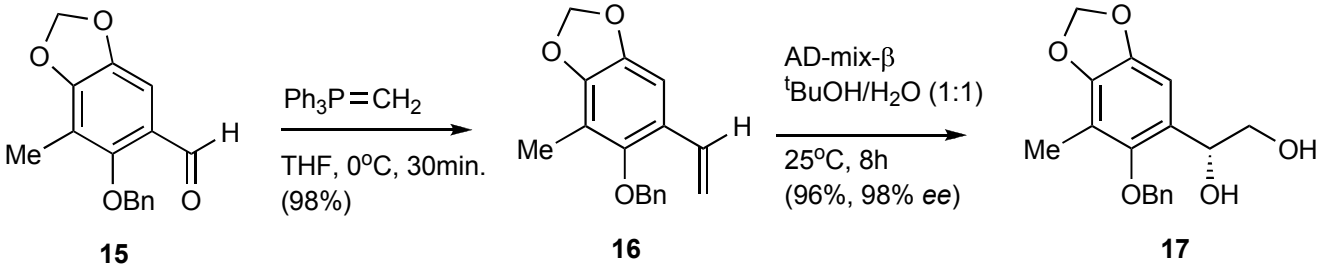


Piperonal
5,100 YEN /100G

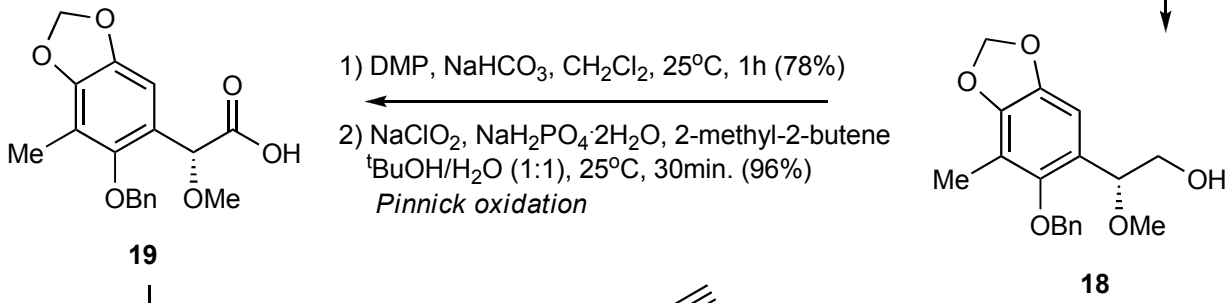
Sesamol
13,200 YEN /25G

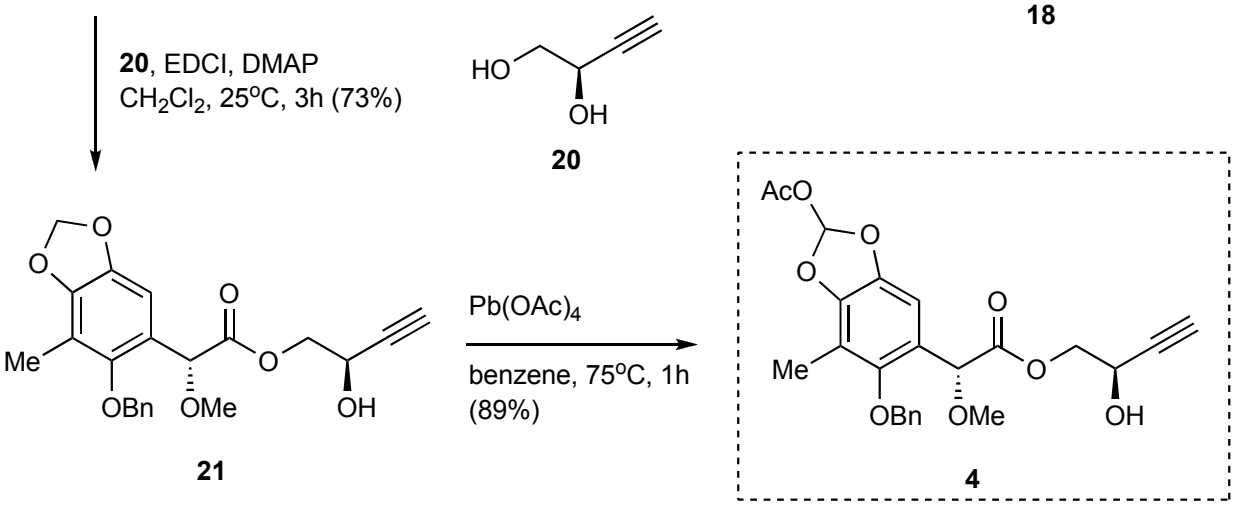
15

Synthesis of building block 4



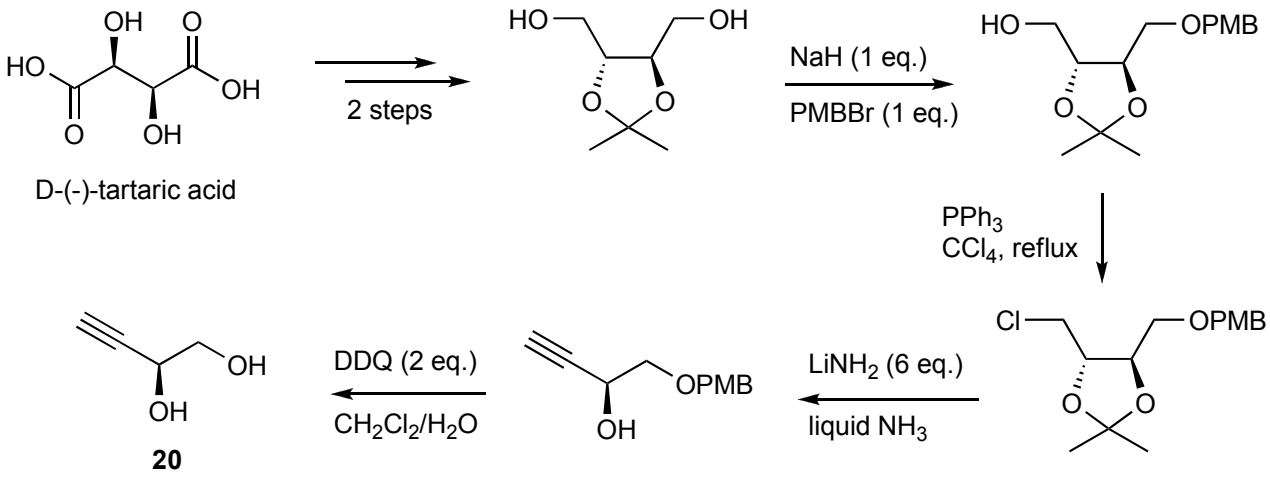
1) TBSCl, Et_3N, DMAP, CH_2Cl_2, 25°C, 8h (99%)
2) ^tBuOK, MeI, MeCN, 0 to 25°C, 16h (95%)
3) TBAF, THF, 25°C, 16h (99%)





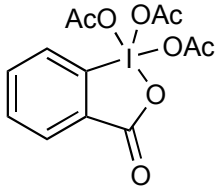
Preparation of **20**

Yadav *et al.*, *Tet. Lett.*, 1988, *29,* 2737

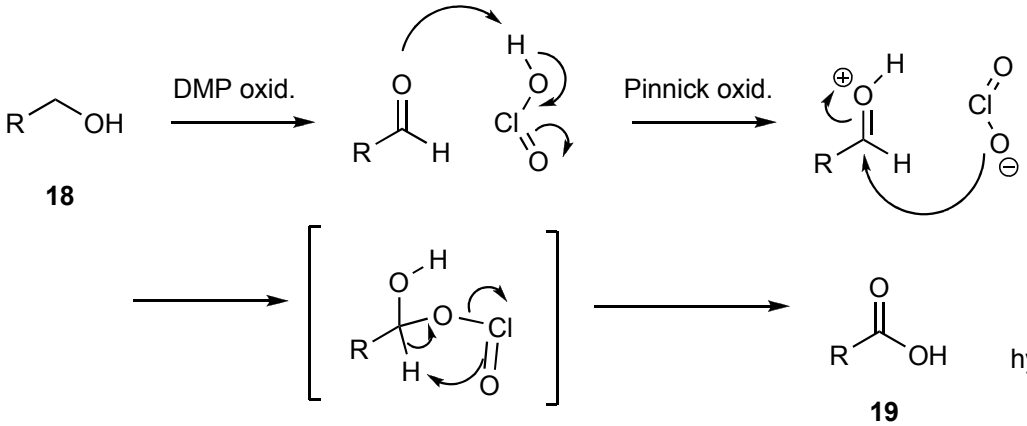


18 ⟶ **19** : Dess-Martin oxidation & Pinnick Oxidation

Dess-Martin oxidation: A milder oxidation method of alcohol ⟶ aldehyde (cf. Swern oxid.)
Pinnick oxidation: A milder oxidation method of aldehyde ⟶ carboxylic acid
Aldehyde-selective oxidation (alcohol, alkene etc. are not oxidized.)
(2-methyl-2-butene is the hypochlorous acid scavenger.)
If Mn(VII) or Cr(VI) is used (1 step oxidation), benzylic oxidation may also occur.



Dess-Martin Periodinane



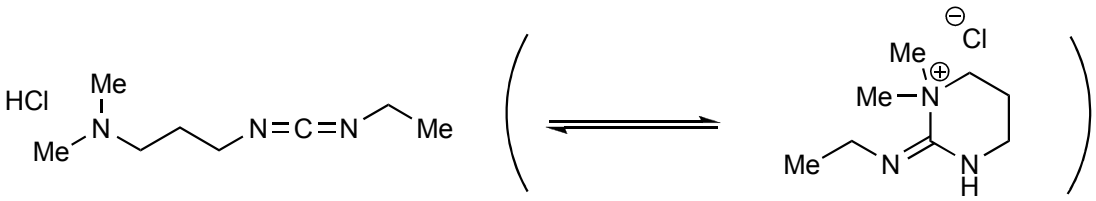
18

19

hypochlorous acid

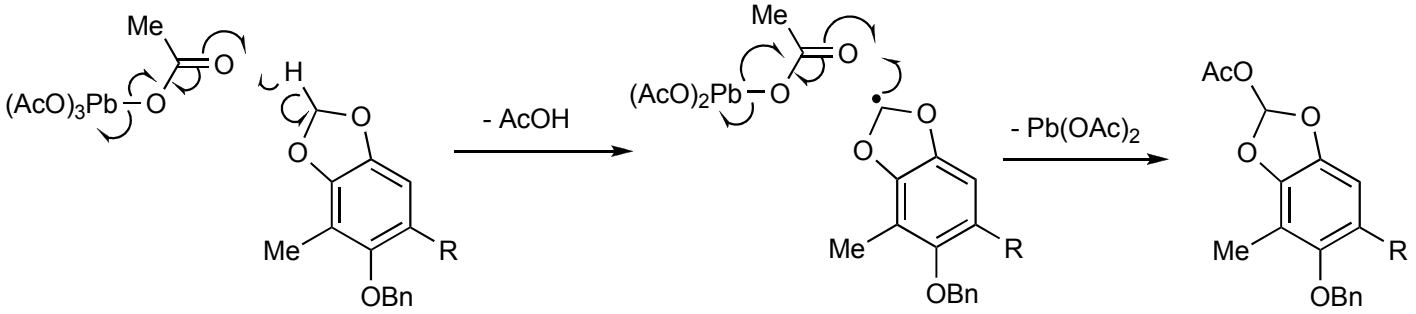
19 ⟶ **21** : Milder condensation

EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride



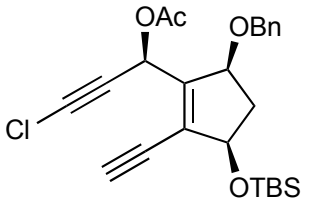
21 ⟶ **4**: Radicallic cleavage?

Chepelev *et al., J. Org. Chem.*, 2003, *68*, 7023-7032

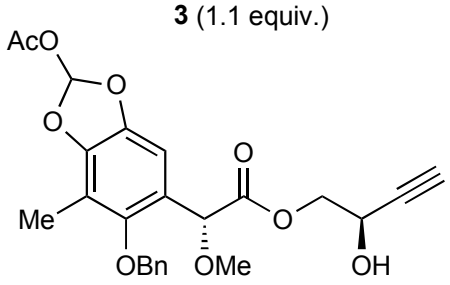


21 **4**

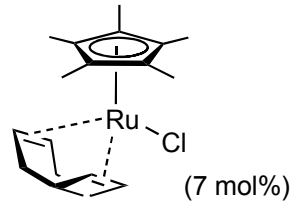
Synthesis of *o*-quinone derivative 2 (through Ru-catalyzed [2+2+2] cycloaddition)



3 (1.1 equiv.)



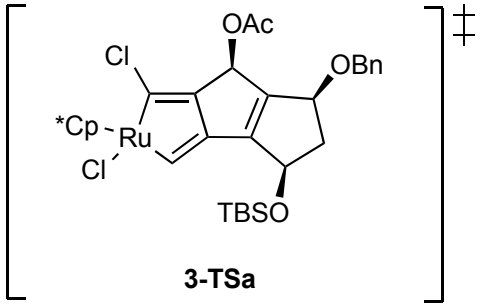
4 (1.0 equiv)



(7 mol%)

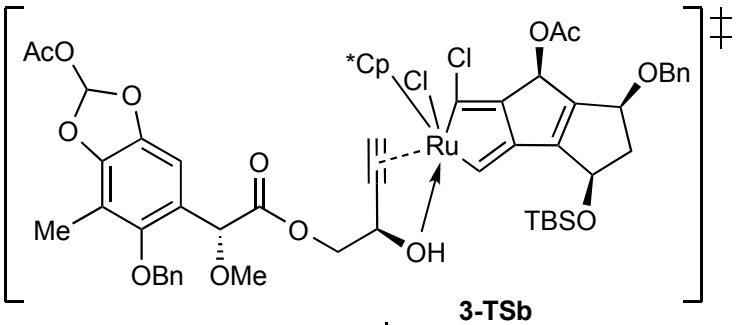
DCE, 25°C, 30min.

Oxidative addition



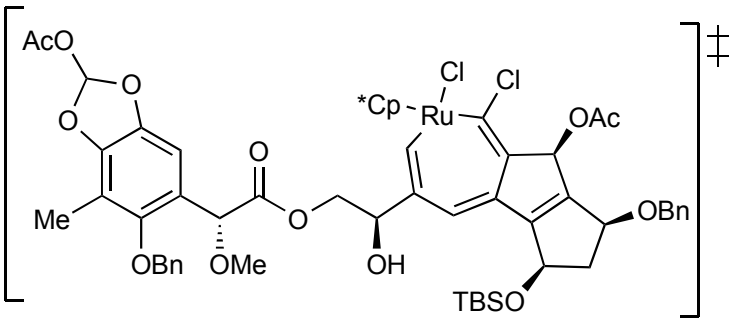
3-TSa

Free-hydroxy group directing alkyne coordination



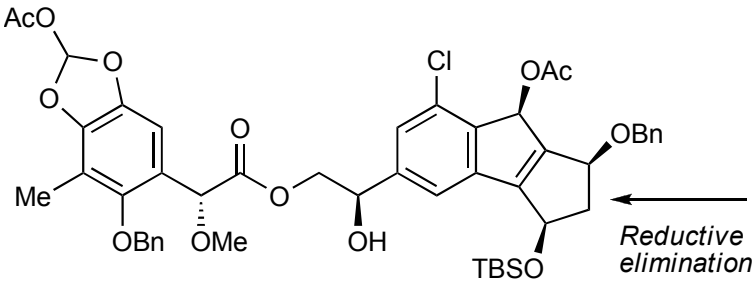
3-TSb

Alkyne insertion to metallacycle



3-TSc

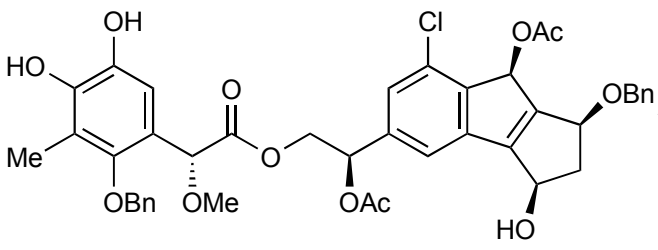
Reductive elimination



22 (87% yield)

1) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0°C, 30min. (92%)
2) aq. HF (excess), MeCN, 25°C 30min.;
then MeOH(excess), 25°C, 3h (74%)

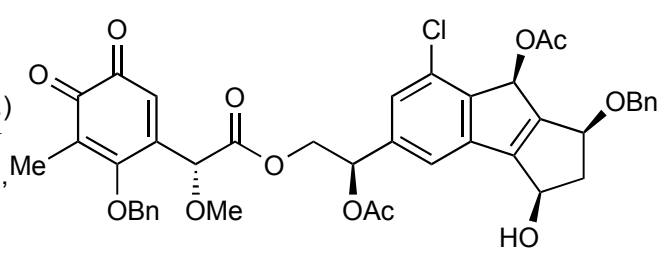
deprotection of TBS & acetoxy acetal group



23

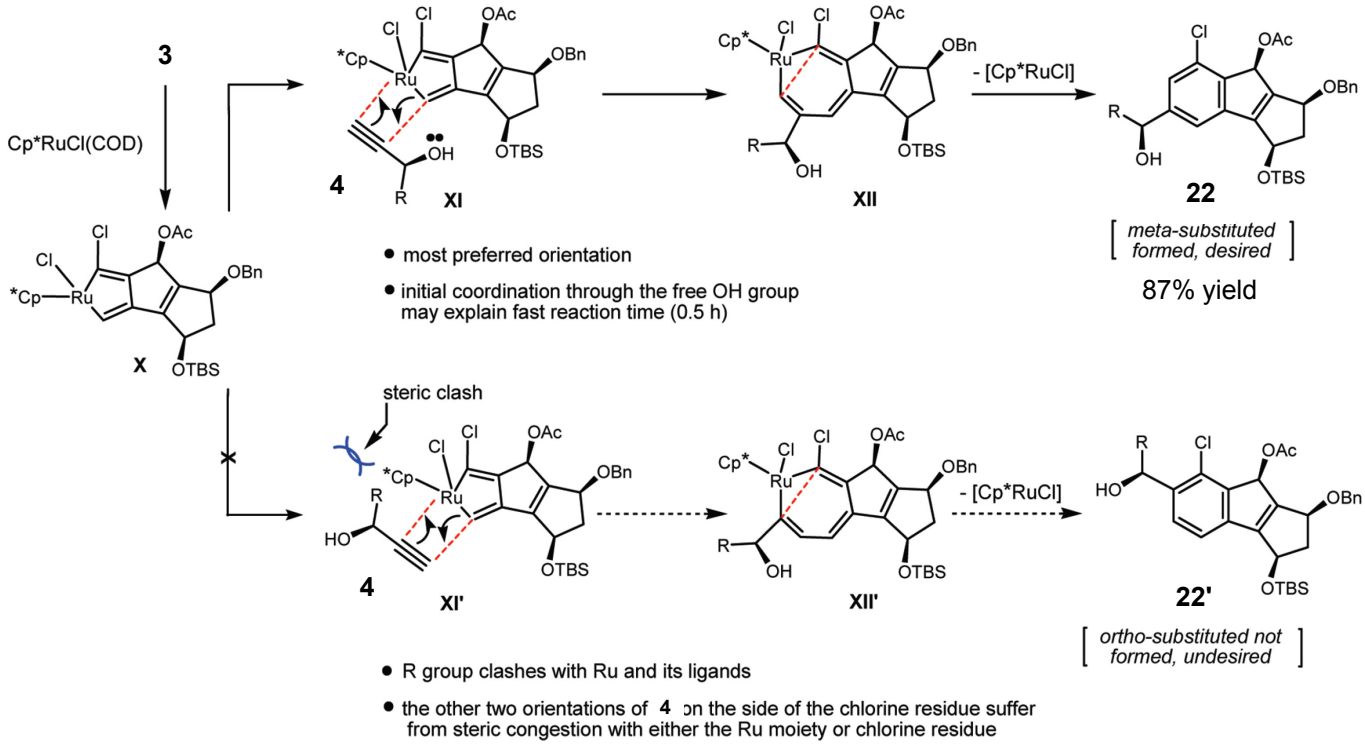
Ag_2O (2.5 eq.)

CH_2Cl_2, 25°C, 30min. (94%)



2

Several Studies about [2+2+2] cycloaddition step

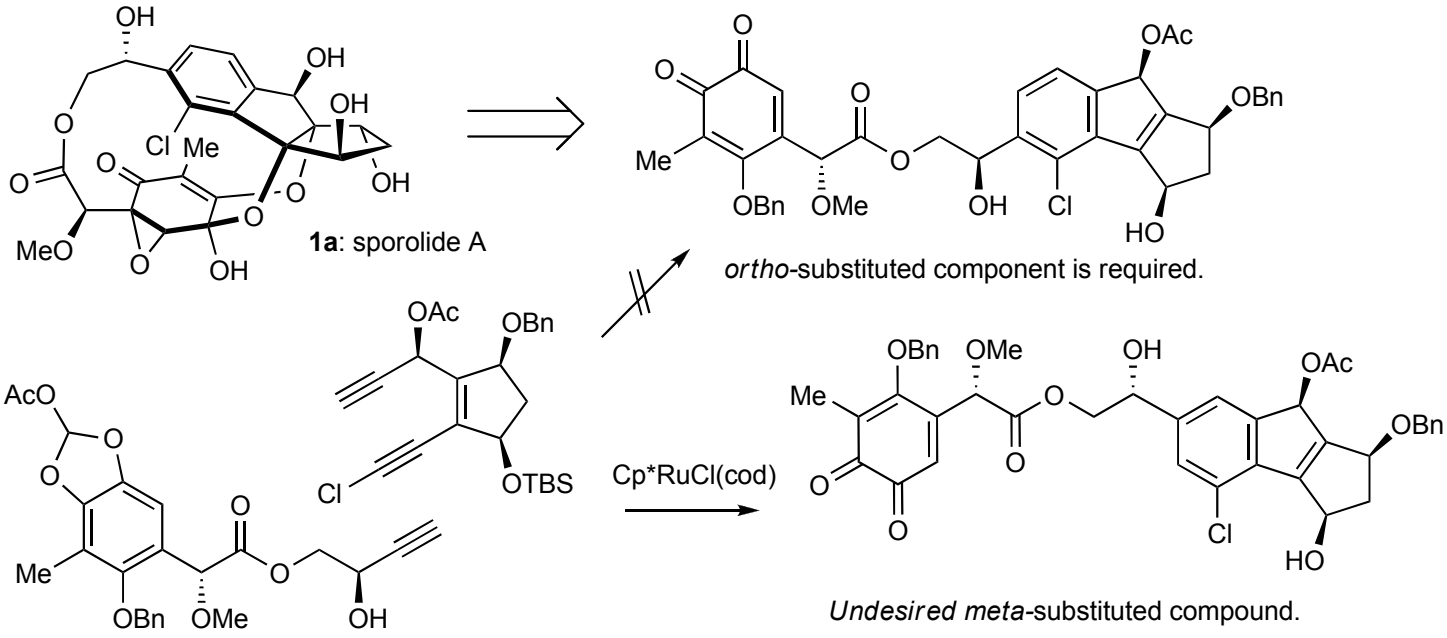


Regioselectivity is completely controled by steric effect ! (No *ortho*-regioisomer was observed at all)

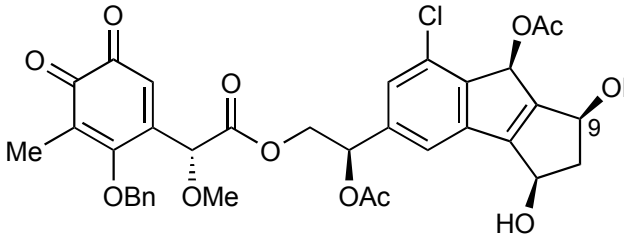
Free hydroxy group of **4** fastens the reaction, because of the possible coordination onto ruthenium nucleus. When propargylic alcohol **4** was acetylated in advance, reaction rate got significantly slower (*ca.* 10-fold) and regioselectivity decreased (*ca.* 10:1).

Wilkinson's catalyst $Rh(PPh_3)_3Cl$ can also catalyze this cycloaddition (*meta*:*ortho* 20:1, 85% combined yield). For this time, erosion of regioselectivity was also observed (20:1 → 10:1), when acetyl-protected **4** was used.

Sporolide A cannot be synthesized through the same method !

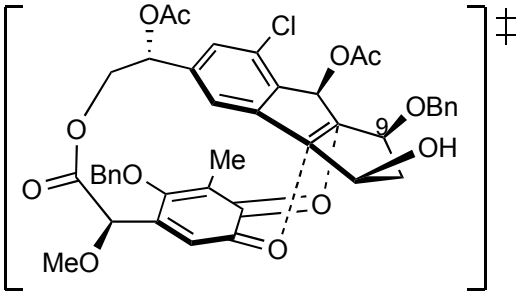


Synthesis of Sporolide B from 2 (through hetero [4+2] cycloaddition)



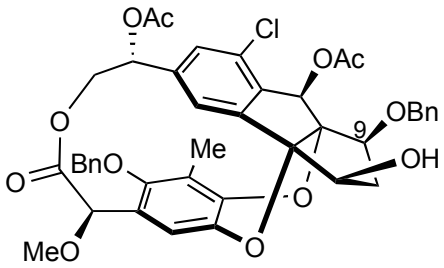
2

toluene, 110°C, 1.5h



2-TS

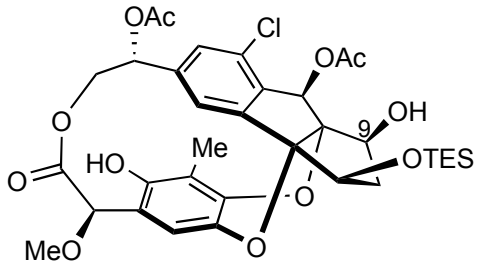
Intramolecular hetero [4+2] *cycloaddition*



24
(40% yield based on *ca.* 50% conversion)

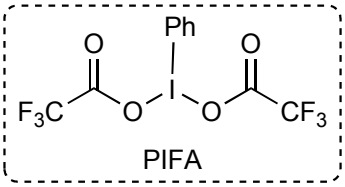
1) TESOTf, Et_3N, CH_2Cl_2
0°C, 30min. (90%)

2) H_2, $Pd(OH)_2/C$
EtOAc, 25°C, 4h (92%)

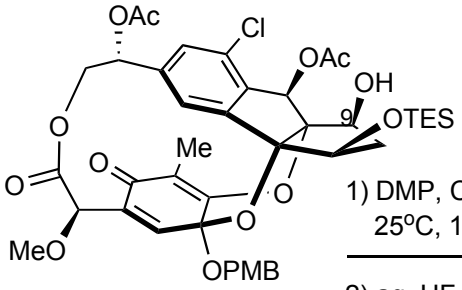


25

PIFA (1.5 eq.), PMBOH, K_2CO_3
MeCN, 0°C, 30min. (75%)
Oxidative dearomatization



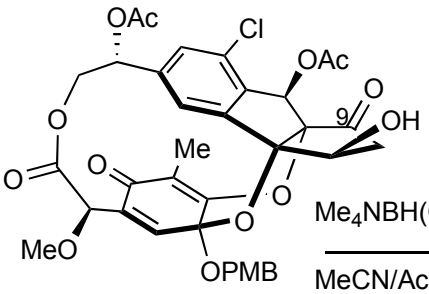
PIFA



26

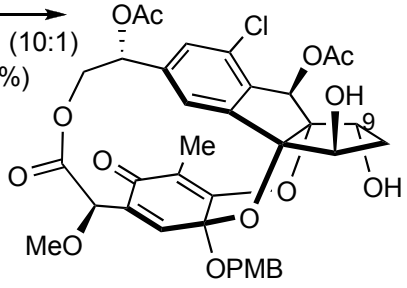
1) DMP, CH_2Cl_2,
25°C, 1h (90%)

2) aq. HF (excess)
MeCN, 25°C, 2h
(85%)



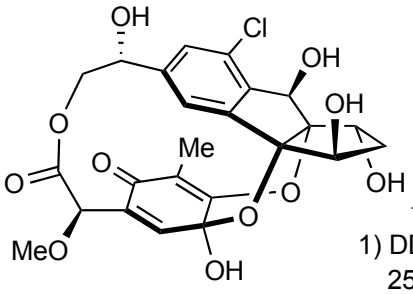
27

$Me_4NBH(OAc)_3$ (10 eq.)
MeCN/AcOH (10:1)
25°C, 2h (85%)



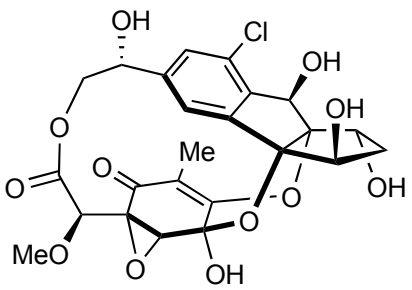
28

1) DDQ (5 eq.), CH_2Cl_2/H_2O (10:1)
25°C, 5h (70%)
2) DBU, CH_2Cl_2/MeOH (3:1)
40°C, 4h (78%)



29

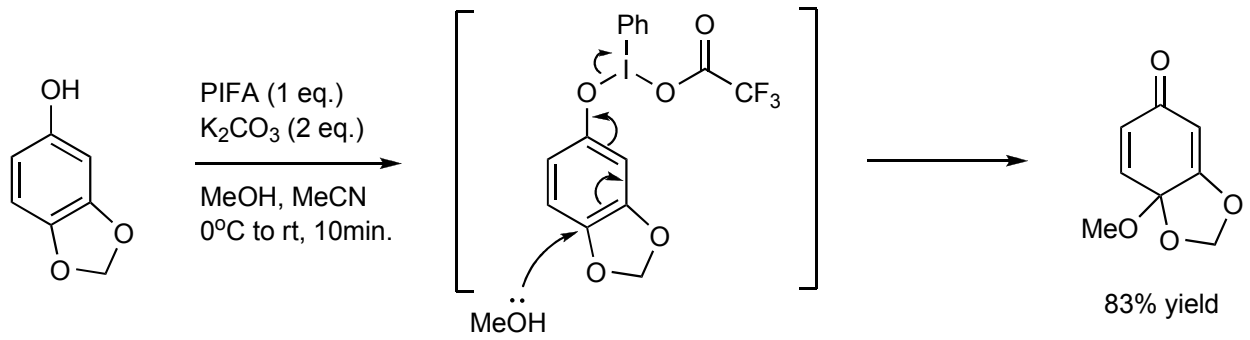
^{t}BuOOH (10 eq.)
DBU, CH_2Cl_2,
40°C, 3h (63%)



1b: sporolide B

25 ⟶ **26**: Oxidative dearomatization by PIFA (formation of *p*-benzoquinone monoacetal)

Y. Kita *et al., J. Org. Chem.*, 1987, *52*, 3927-3930



Conclusion

Hetero [4+2] cycloaddition of *o*-quinone is sometimes useful for construction of benzodioxin moiety, but there seems to be much room to improve in this reaction.

Partially-intramolecular [2+2+2] cycloaddition of alkynes has now become one of the most powerful way to synthesize highly substituted benzene derivatives under mild conditions.

In both cycloadditions, chemo- & regioselectivity highly depends on the steric effect of the substrates and the catalyst.