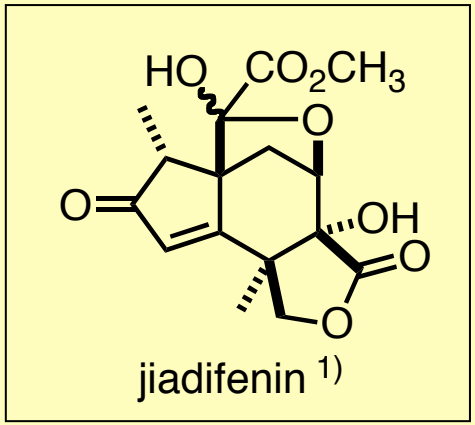
2AII-7

Pd触媒反応を活用したセコプレジザン型セスキテルペンジアジフェニンの合成研究

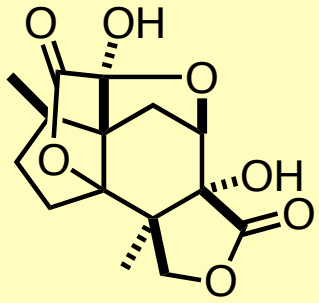
(徳島文理大薬)

○今井顕子・有井健視・原田研一・久保美和・日置英彰・福山愛保

Neurotrophic compounds isolated from Illicium species

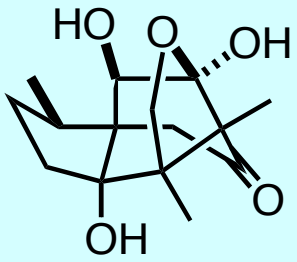


jiadifenin [1)]

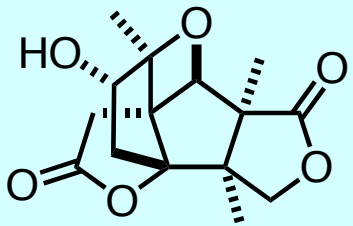


jiadifenolide [2)]

from *Illicium jiadifengpi*

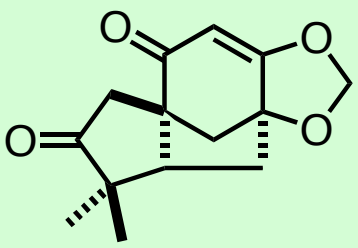


11-*O*-debenzoyltashironin[3)]

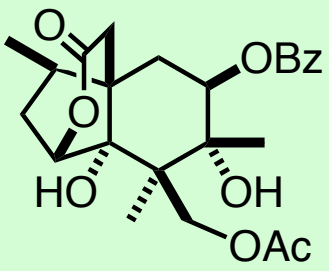


merrilactone A[4)]

from *Illicium merrillianum*



tricycloillicinone[5)]

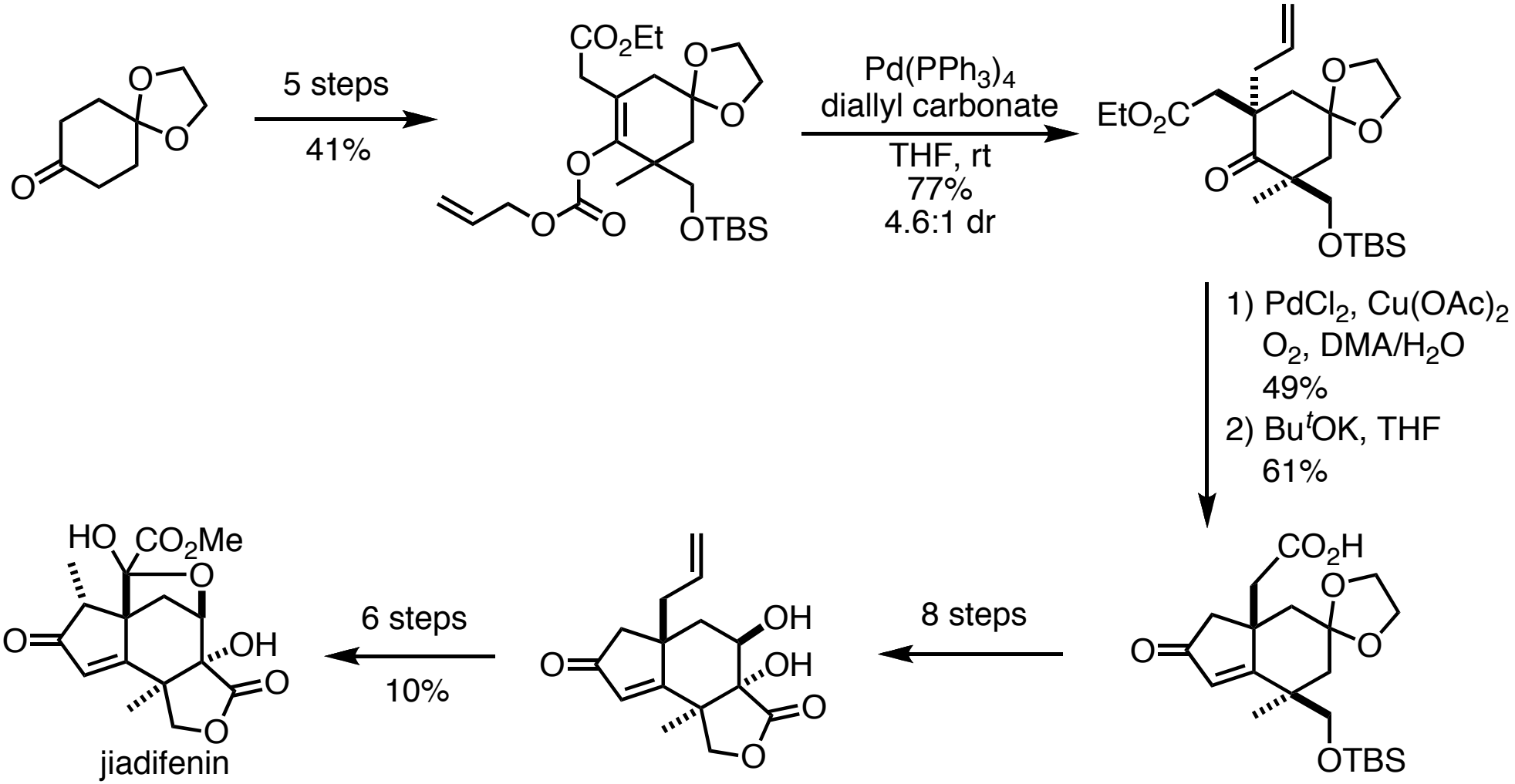


isodunnianine[6)]

from *Illicium tashiroi*

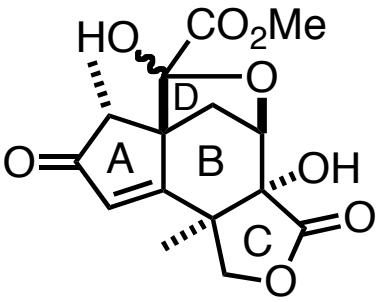
R. Yokoyama, J.-M. Huang, C.-S. Yang, Y. Fukuyama, *J. Nat. Prod.*, ***65***, 527-531 (2002).
M. Kubo, C. Okada, J.-M. Huang, K. Harada, H. Hioki, Y. Fukuyama, *Org. Lett.*, ***11***, 5190-5193 (2009).
J.-M. Huang, R. Yokoyama, C.-S. Yang, Y. Fukuyama, *J. Nat. Prod.*, ***64***, 428-431 (2001).
J.-M. Huang, R. Yokoyama, C.-S. Yang, Y. Fukuyama, *Tetrahedron Lett.*, ***41***, 6111-6114 (2000).
Y. Fukuyama, Y. Hata, M. Kodama, *Planta Medica*, ***63***, 2199-2201 (1997).
Y. Fukuyama, N. Shida, M. Kodama, *Planta Medica*, ***59***, 181-182 (1993).

Total synthesis of (±)-jiadifenin by Danishefsky's group

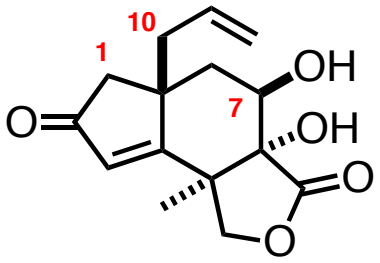


Y. S. Cho, D. A. Carcache, Y. Tian, Y.-M. Li, S. J. Danishefsky, *J. Am. Chem. Soc.*, ***126***, 14358-14359 (2004).
D. A. Carcache, Y. S. Cho, Z. Hua, Y. Tian, Y.-M. Li, S. J. Danishefsky, *J. Am. Chem. Soc.*, ***128***, 1016-1022 (2006)

Retrosynthetic analysis for jiadifenin

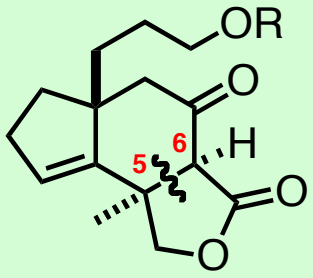


jiadifenin (**1**)



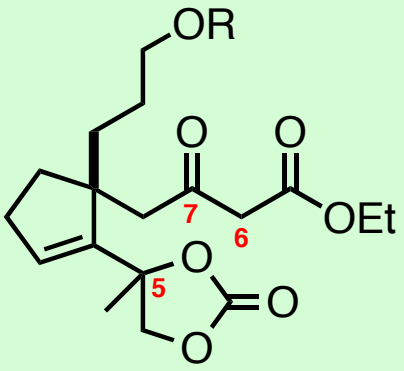
2

Danishefsky's intermediate



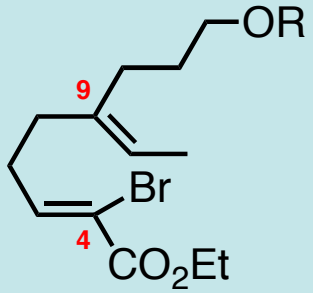
3

Tsuji-Trost reaction and lactonization

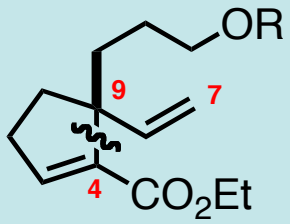


4

intramolecular Heck reaction

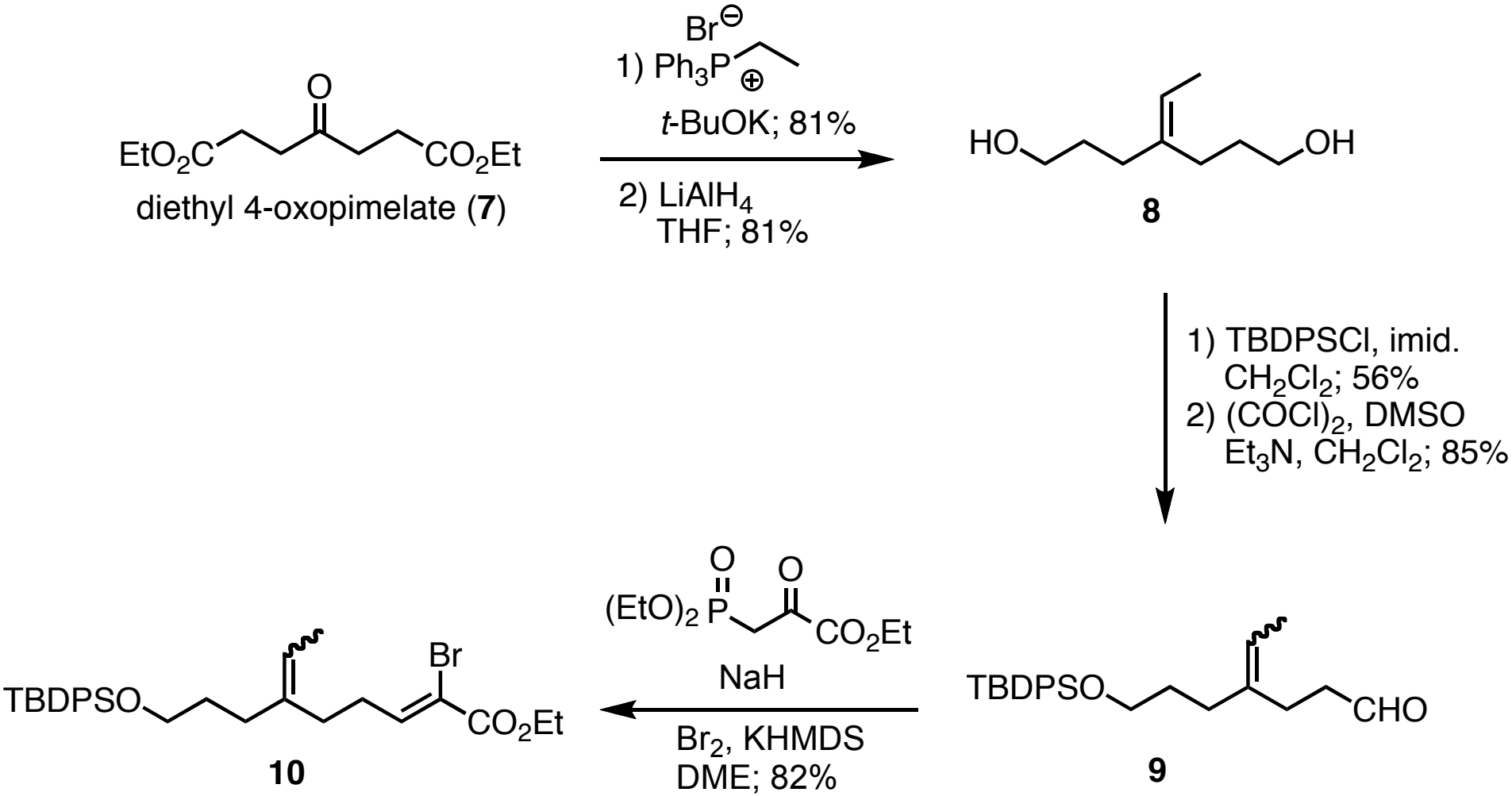


6

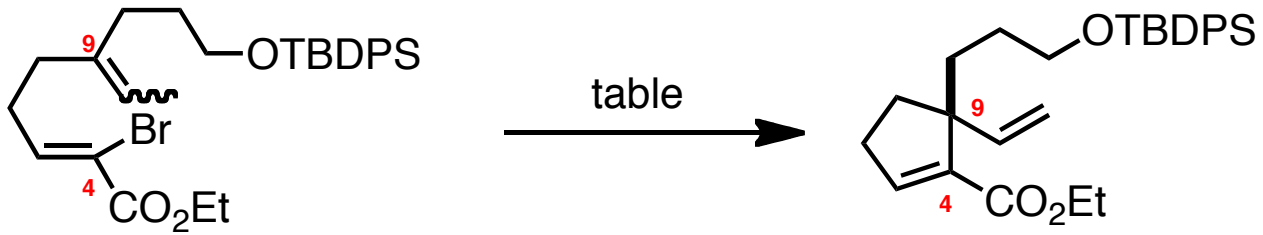


5

Preparation of 1,1-dibromo-1-alkene



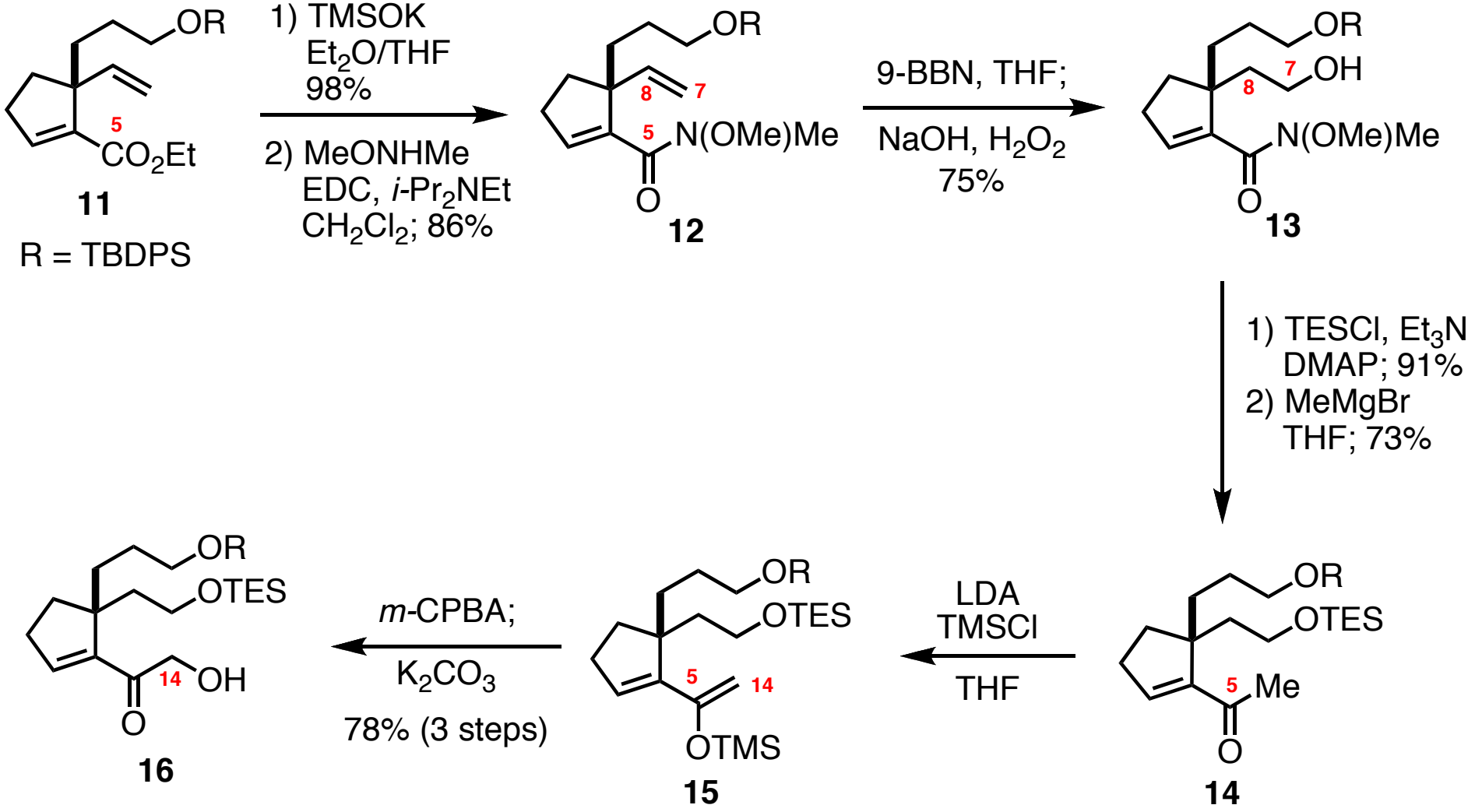
Effect of solvent on Mizoroki-Heck reaction



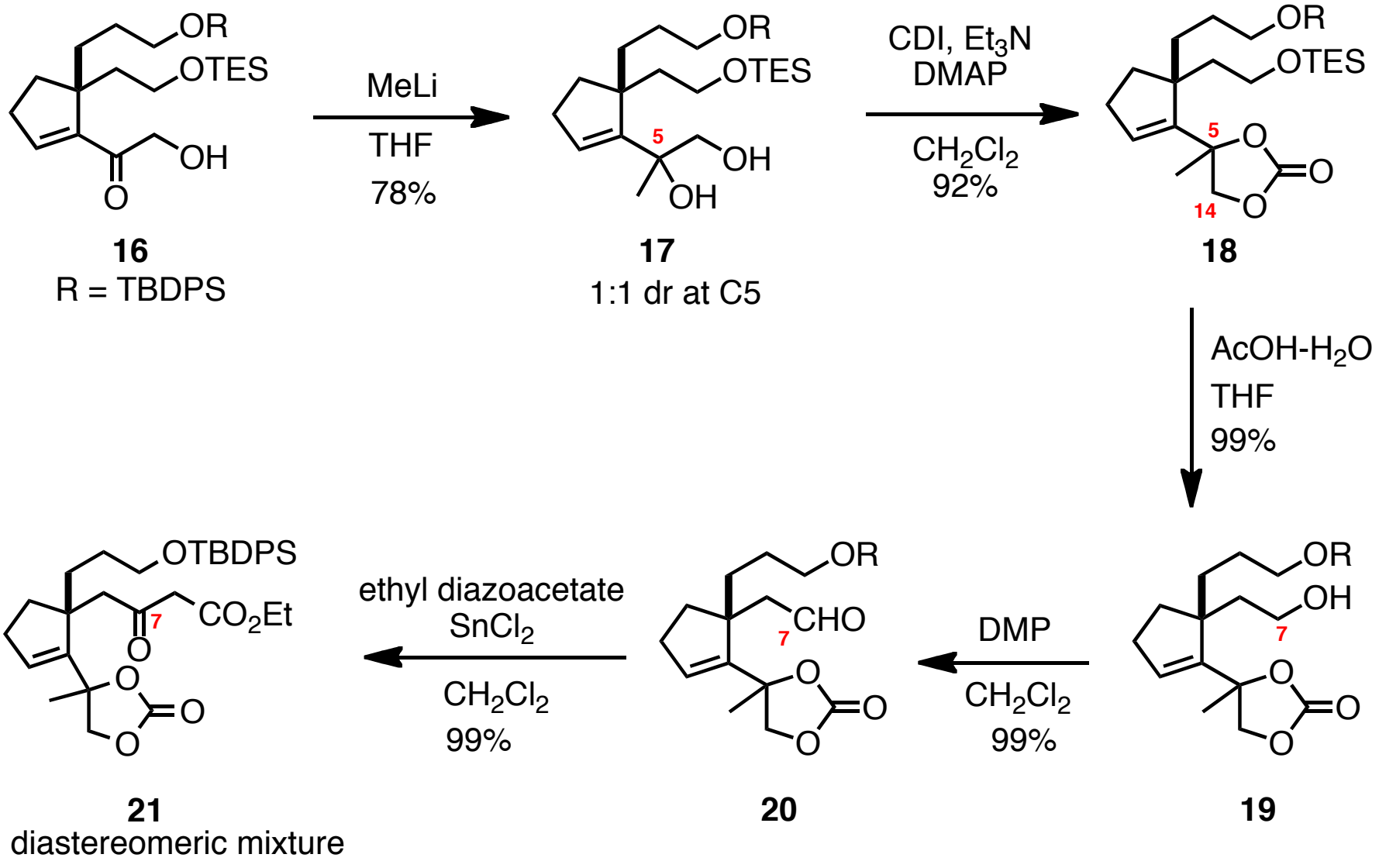
10 **11**

entry	$Pd(OAc)_2$	(*o*-tol)$_3$P	base	solvent	c (mol/L)	time (h)	yield
1	10 mol%	20 mol%	Et_3N	toluene	0.02	8	17%
2	10 mol%	20 mol%	Et_3N	CH_3CN	0.02	8	14%
3	10 mol%	20 mol%	Et_3N	dioxane	0.02	8	18%
4	10 mol%	20 mol%	Et_3N	DMF	0.02	8	39%
5	10 mol%	20 mol%	Et_3N	MeOH	0.02	1	99%
6	10 mol%	20 mol%	Et_3N	MeOH	0.1	1	98%
7	5 mol%	10 mol%	Et_3N	MeOH	0.02	1	99%
8	5 mol%	10 mol%	Et_3N	EtOH	0.02	1	88%
9	5 mol%	10 mol%	Et_3N	*t*-BuOH	0.02	2	99%

Preparation of allyl carbonate (No.1)



Preparation of cyclic carbonate (No.2)



16
R = TBDPS

17
1:1 dr at C5

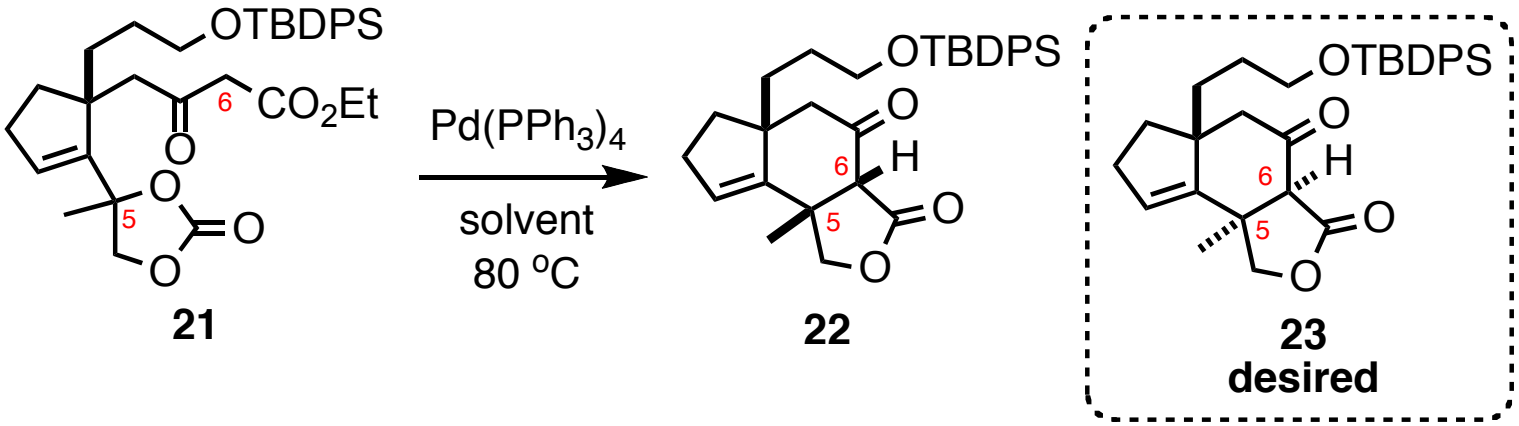
18

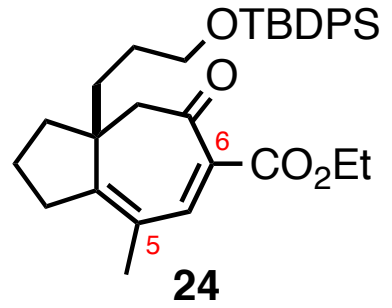
19

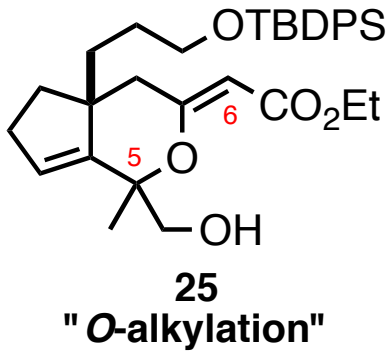
20

21
1: 1 diastereomeric mixture

Effect of solvent on Pd-catalyzed cyclization of carbonate

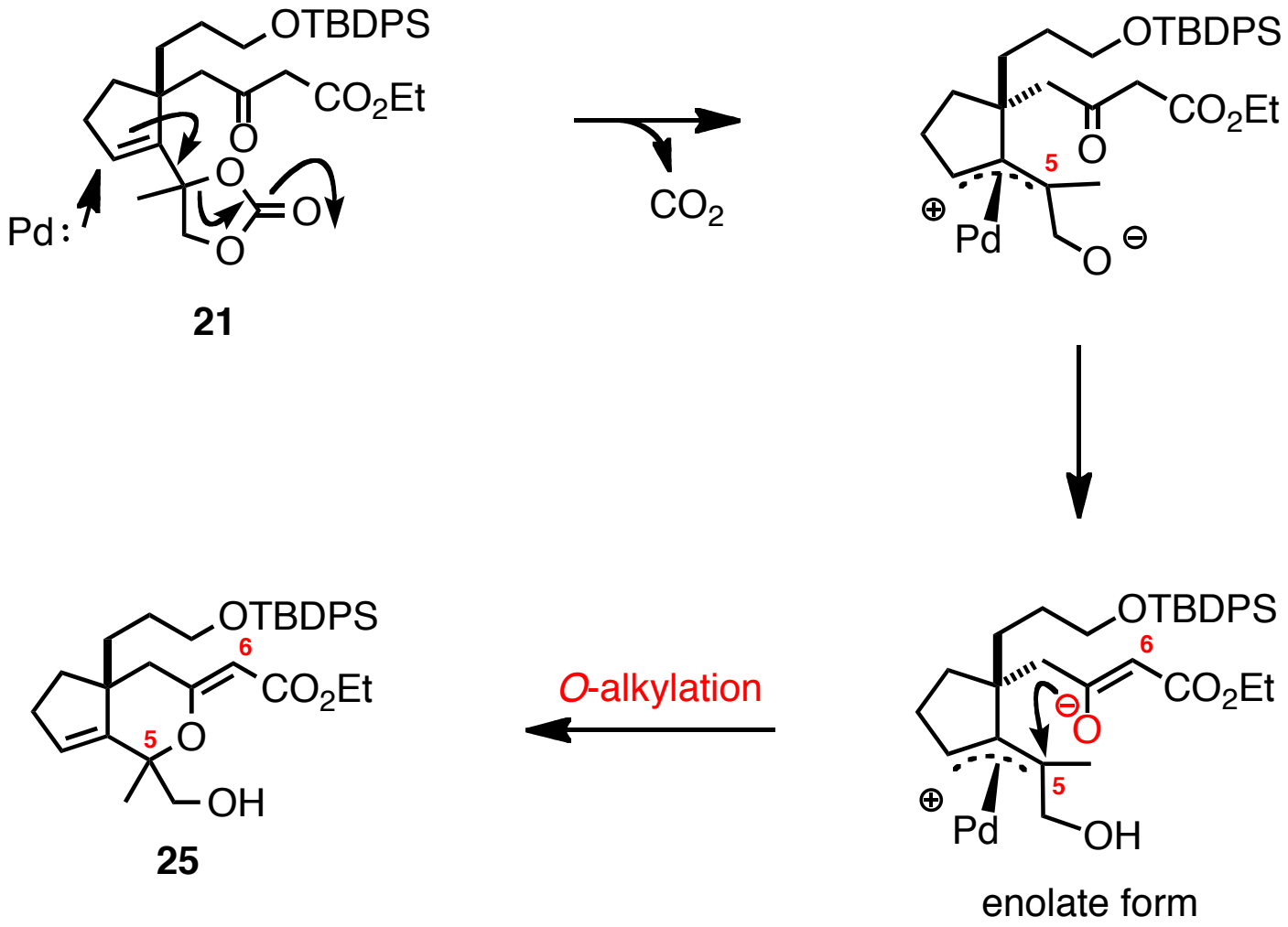




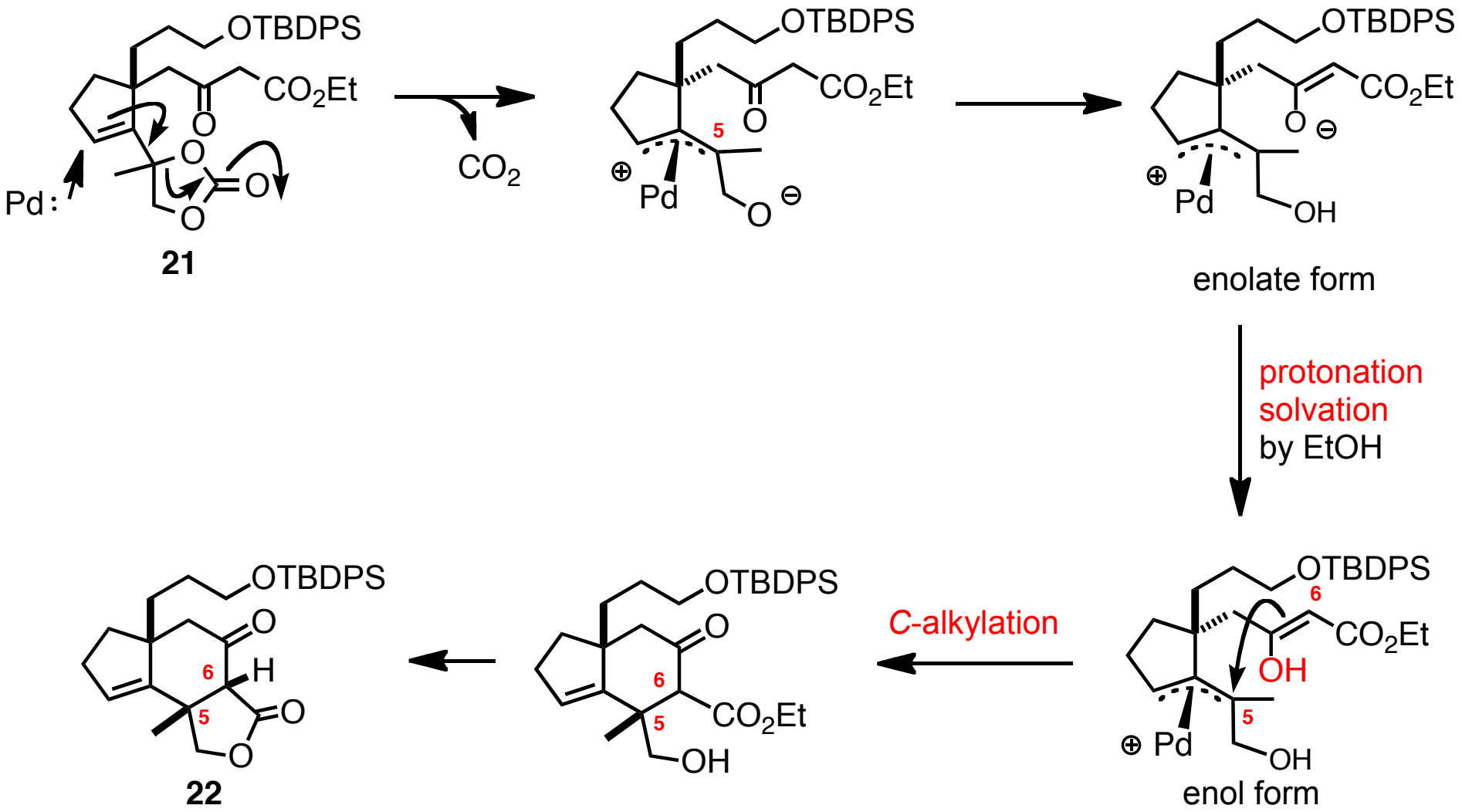


entry	solvent	**22**	**23**	**24**	**25**
1	toluene	-	-	-	-
2	THF	-	-	-	-
3	dioxane	-	-	-	-
4	CH_3CN	-	-	-	-
5	DMSO	trace	-	-	12%
6	DMF	8%	-	trace	56%
7	EtOH	48%	-	32%	-

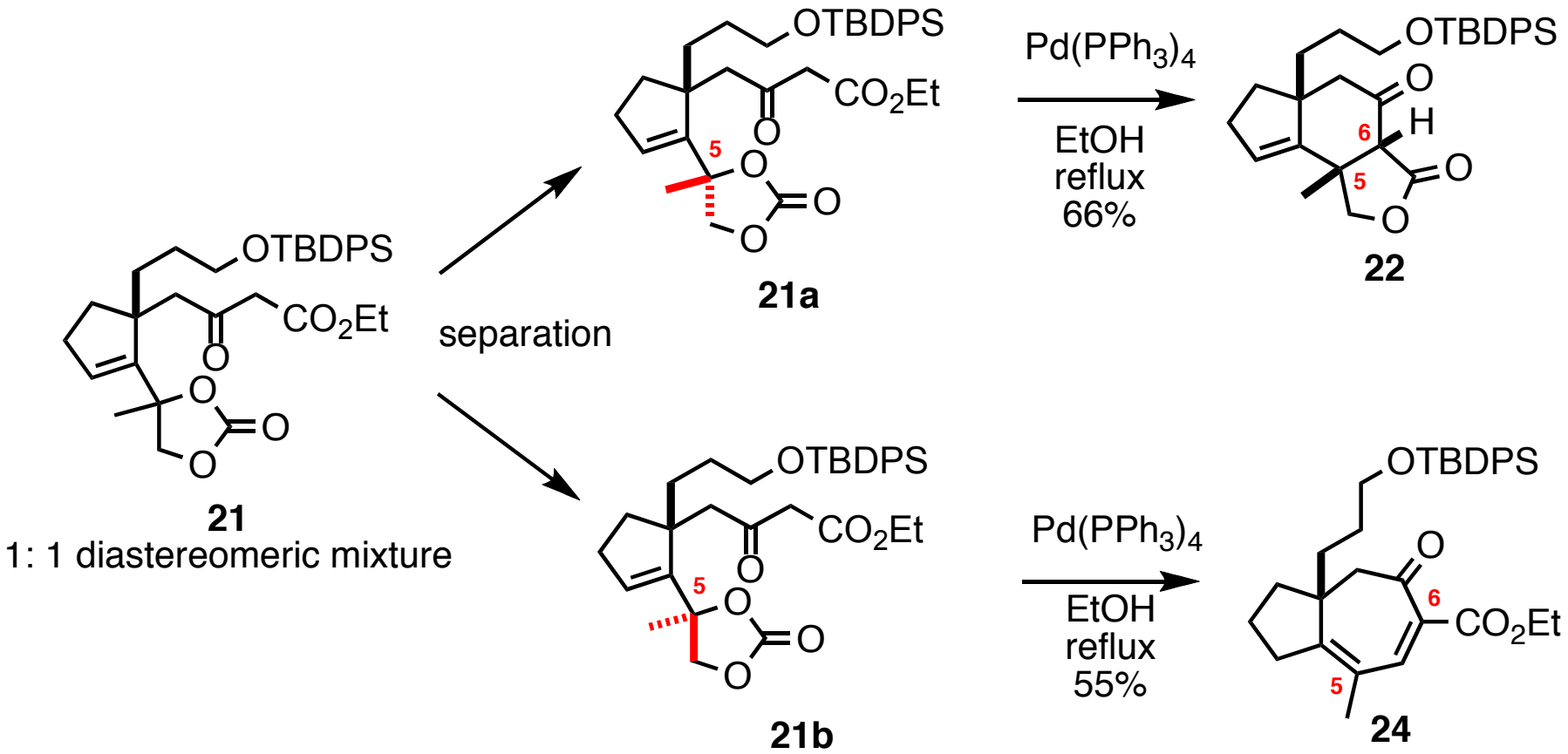
Mechanism of O-alkylation in aprotic solvent



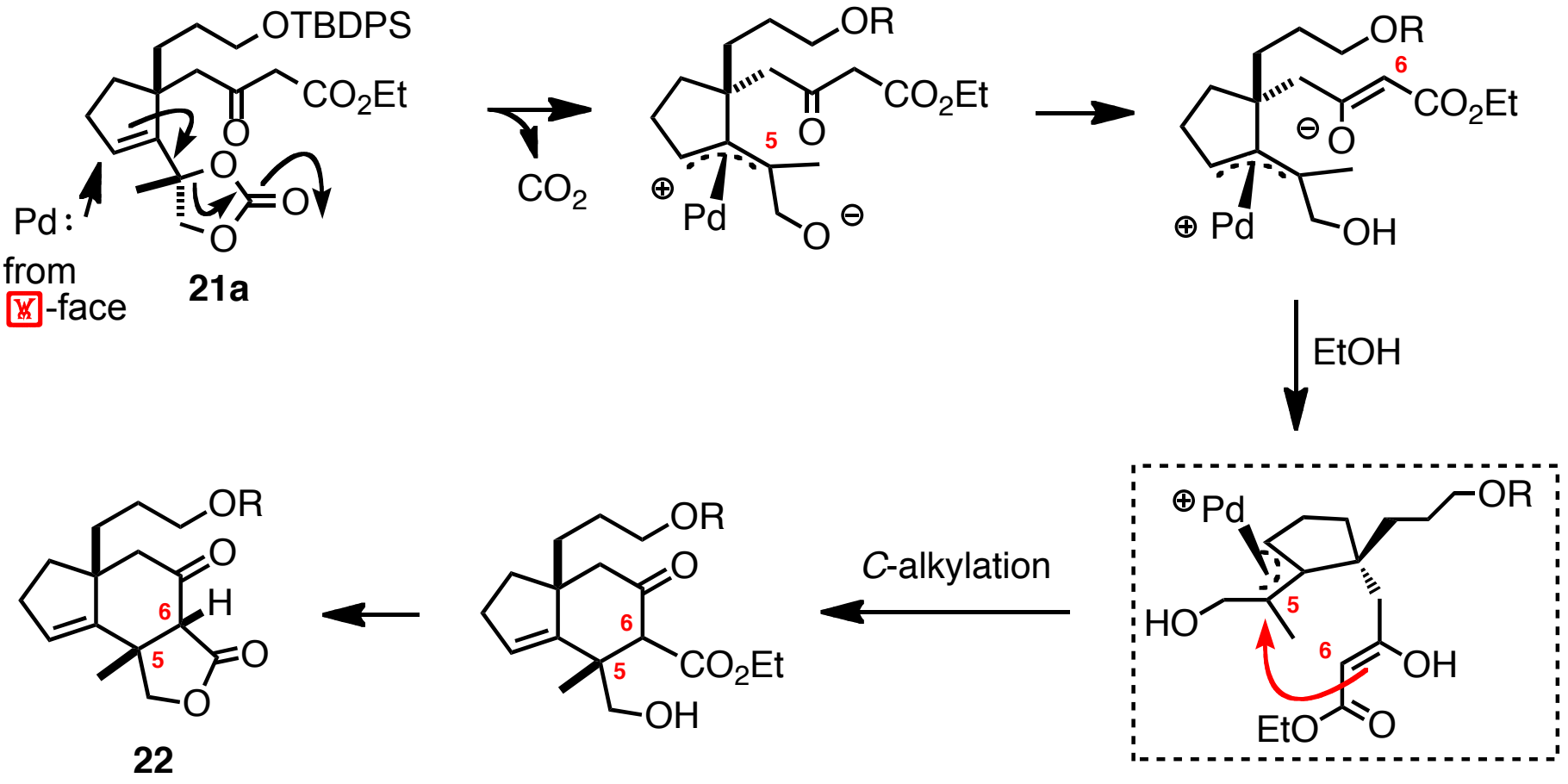
Mechanism of C-alkylation in protic solvent



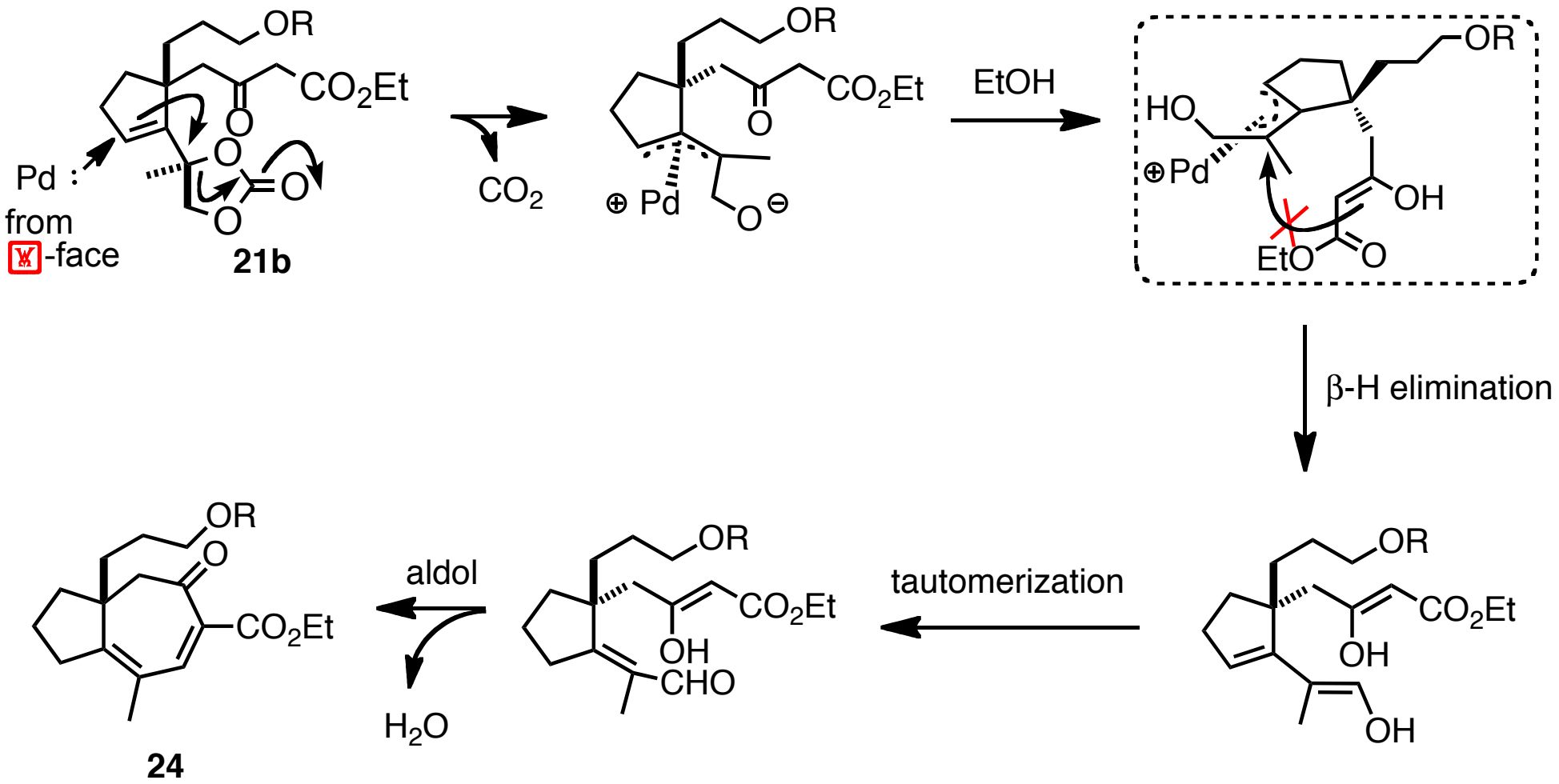
Difference between 21a and stereoisomer 21b in Pd-catalyzed reaction



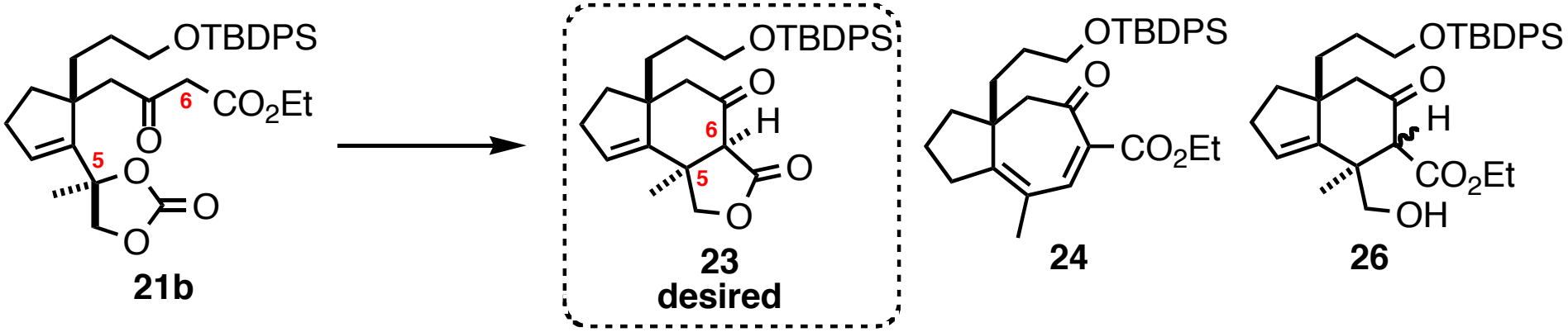
Mechanism of successive Tsuji-Trost reaction and lactonization



Mechanism of construction of seven-membered ring from 21b



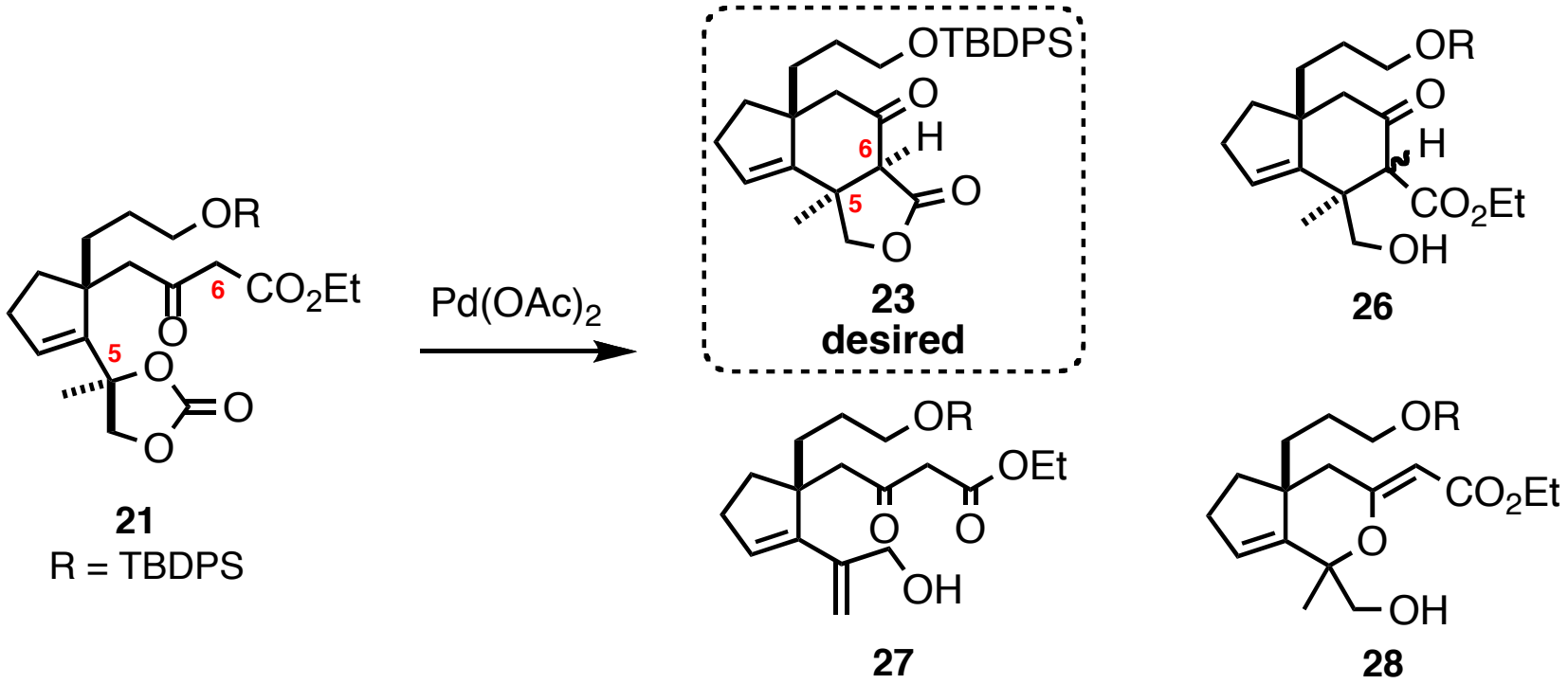
Effect of ligand on Pd-catalyzed cyclization of carbonate



entry	catalyst	ligand	solvent	temp.	**23**	**24**	**26**
1	$Pd(OAc)_2$	*n*-Bu_3P	EtOH	reflux	-	M. P.	-
2	$Pd(OAc)_2$	*t*-Bu_3P	EtOH	reflux	-	M. P.	-
3	$Pd(OAc)_2$	Cy_3P	EtOH	reflux	-	M. P.	-
4	$Pd(OAc)_2$	DPPB	EtOH	reflux	22%	28%	-
5	$Pd(OAc)_2$	DPPF	EtOH	reflux	-	40%	-
6	$Pd(OAc)_2$	(*R*)-BINAP	EtOH	reflux	27%	-	23%

M.P.= main product

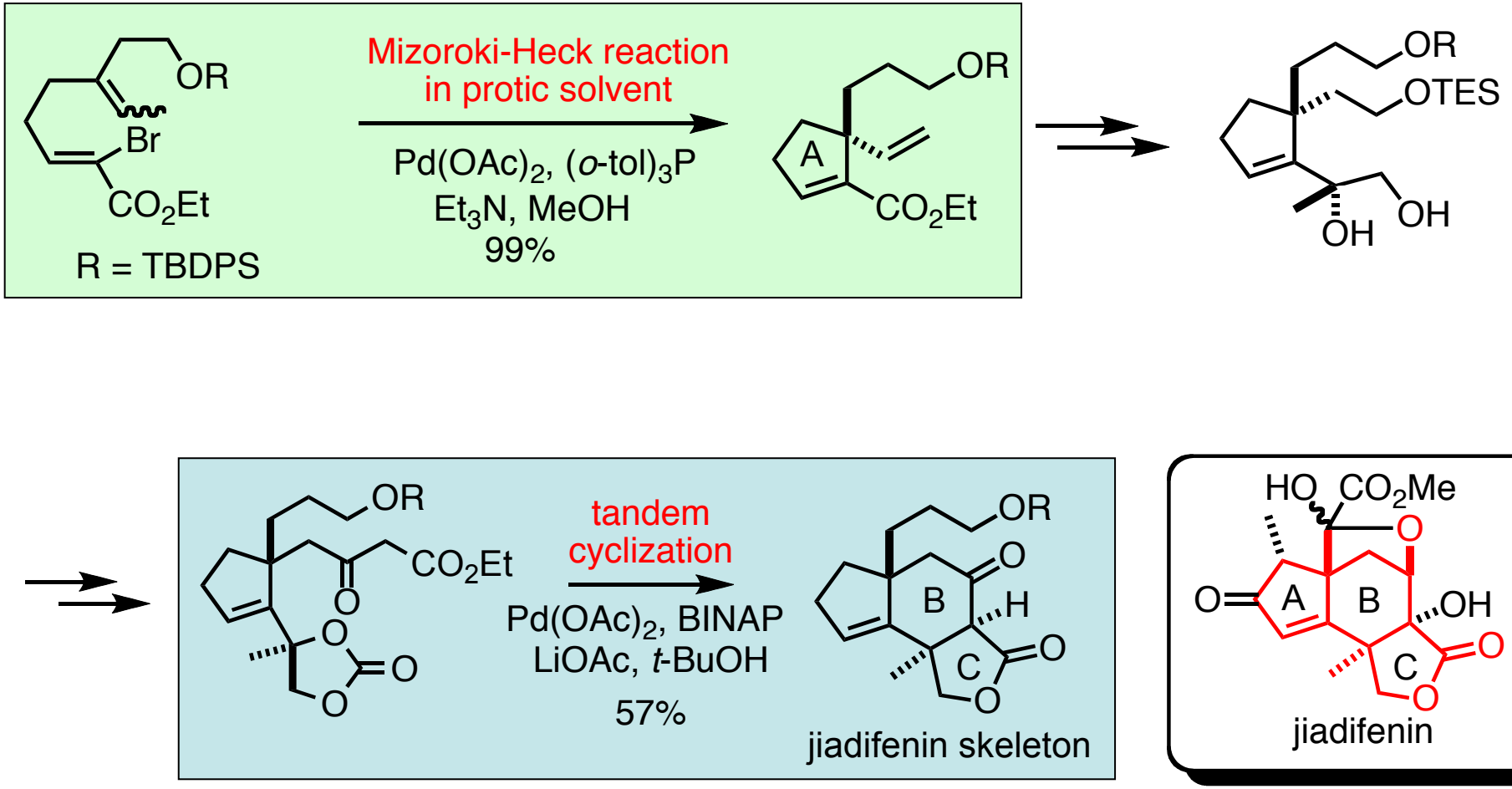
Effects of solvent and base on Pd-catalyzed cyclization of carbonate



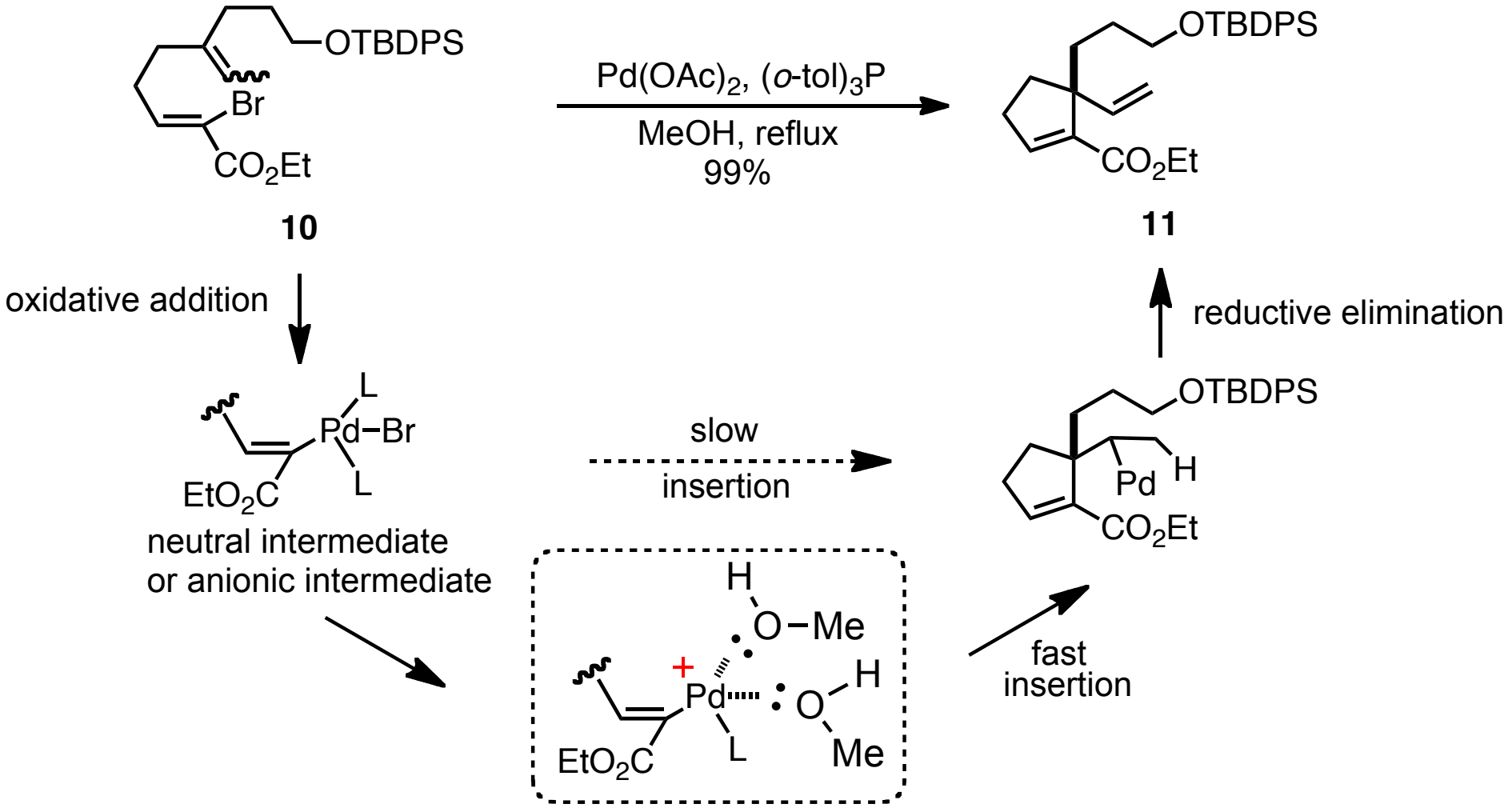
entry	ligand	base	solvent	temp.	**23**	**26**	**27**	**28**
1	(*R*)-BINAP	-	*t*-BuOH	80 °C[a]	38%	14%	13%	-
2	(*R*)-BINAP	LiOAc (1.2 eq)	*t*-BuOH	80 °C	48%	-	20%	7%
3	(*R*)-BINAP	LiOAc (0.5 eq)	*t*-BuOH	80 °C	45%	-	13%	16%
4	(*R*)-BINAP	LiOAc (2.4 eq)	*t*-BuOH	80 °C	57%	-	9%	trace
5	(±)-BINAP	LiOAc (2.4 eq)	*t*-BuOH	80 °C	55%	-	9%	9%

[a]No reaction was observed at lower temperature (eg. 65 °C)

Conclusion


OR
Br
CO_2Et
R = TBDPS
Mizoroki-Heck reaction
in protic solvent
$Pd(OAc)_2$, (*o*-tol)$_3$P
Et_3N, MeOH
99%
A
OR
CO_2Et
OR
OTES
OH
OH
OR
CO_2Et
O
O
O
O
tandem
cyclization
$Pd(OAc)_2$, BINAP
LiOAc, *t*-BuOH
57%
B
C
H
O
O
jiadifenin skeleton
HO
CO_2Me
O
O
A
B
C
OH
O
O
jiadifenin

The role of protic solvent

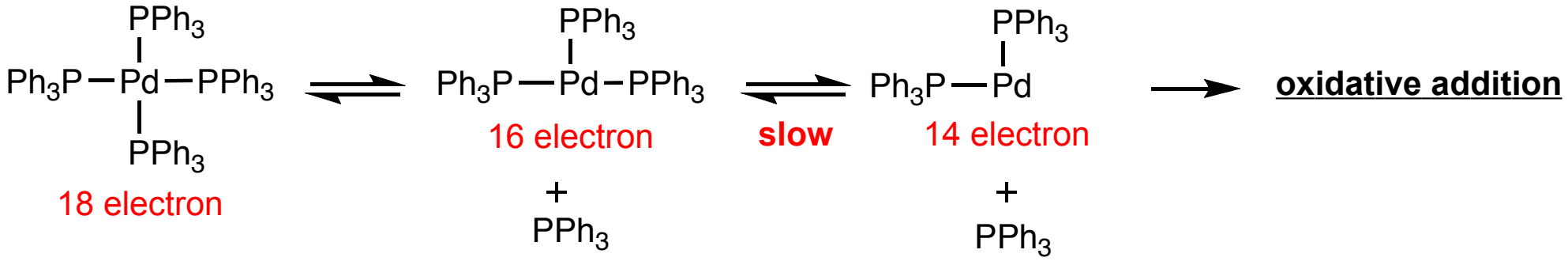


Replacement of ligand and/or Br with MeOH

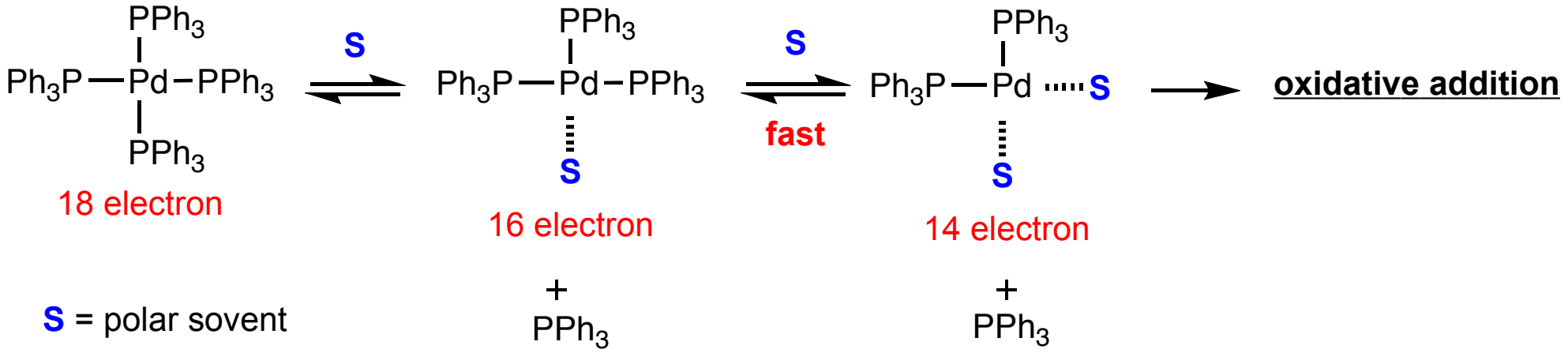
1) cationic palladium species
2) compact ligand

Difference between polar solvent and non-polar solvent

In non-polar solvent

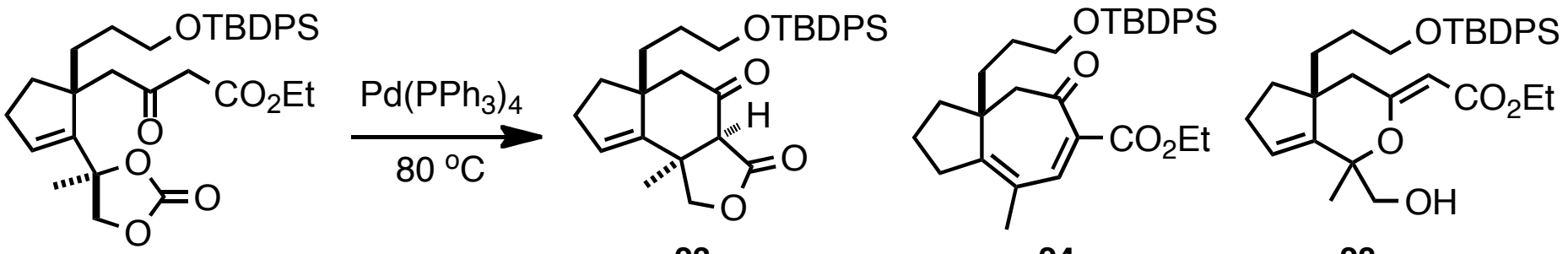


In polar solvent



S = polar sovent

Using Pd_2dba_3 as a catalyst for cyclization of carbonate



21b **23** **24** **28**

entry	catalyst	ligand	solvent	temp.	**23**	**24**	**28**
1	Pd_2dba_3	*n*-Bu_3P	EtOH	80 °C	-	-	-
2	Pd_2dba_3	*t*-Bu_3P	EtOH	80 °C	-	-	-
3	Pd_2dba_3	Cy_3P	EtOH	80 °C	-	30%	-
4	Pd_2dba_3	(*S*,*S*)-Trost ligand	EtOH	80 °C	-	-	-
5	Pd_2dba_3	(*R*)-BINAP	EtOH	80 °C	-	-	-

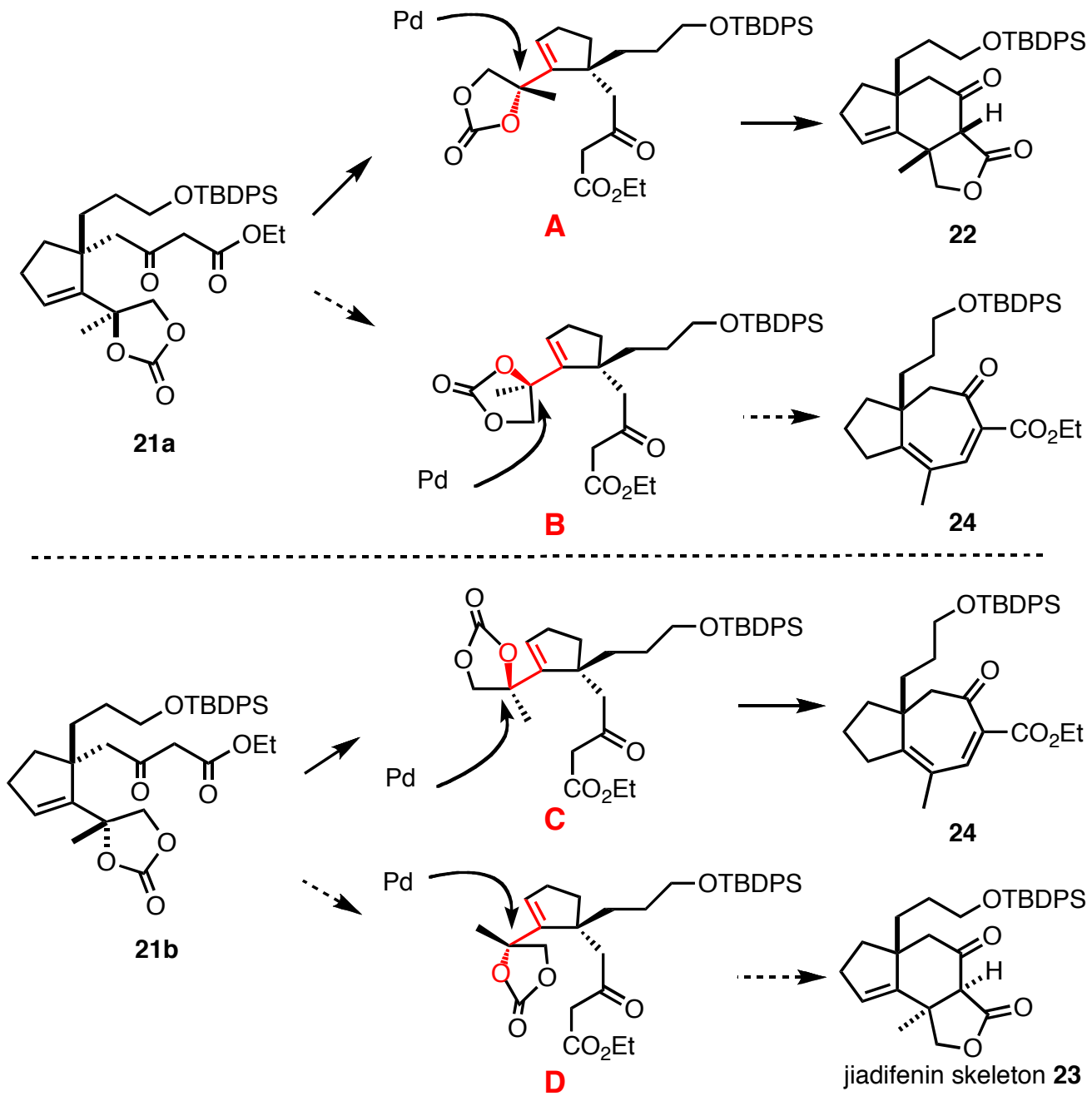
Difference between Pd_2dba_3 and $Pd(OAc)_2$ as precatalyst

$$Pd_2dba_3 + n PPh_3 \rightleftharpoons Pd(PPh_3)n \rightleftharpoons Pd(PPh_3)_2 + {}_{n-2}PPh_3$$

neutral Pd species

$$Pd(OAc)_2 + n PPh_3 \rightleftharpoons [Pd(PPh_3)_3(OAc)]^- \rightleftharpoons [Pd(PPh_3)_2(OAc)]^- + PPh_3$$

active anionic Pd species



Boltzmann Distribution (%)*

A:**B** = 99 : 1

A: dihedral angle = 10-170°

B: dihedral angle = 190-350°

Boltzmann Distribution (%)*

C:**D** = 76 : 24

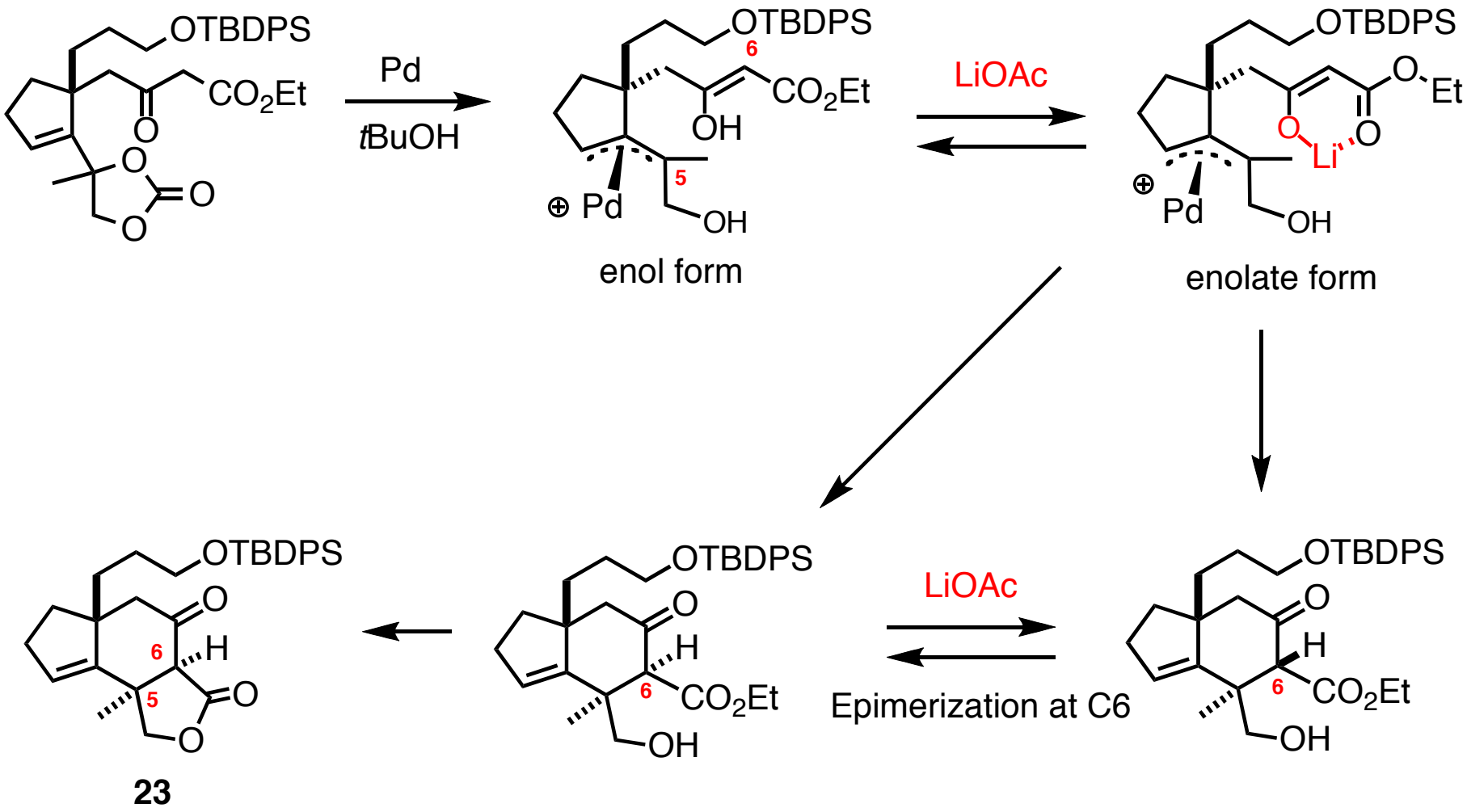
C: dihedral angle = 190-350°

D: dihedral angle = 10-170°

*The ratio was calculated with spartane '08

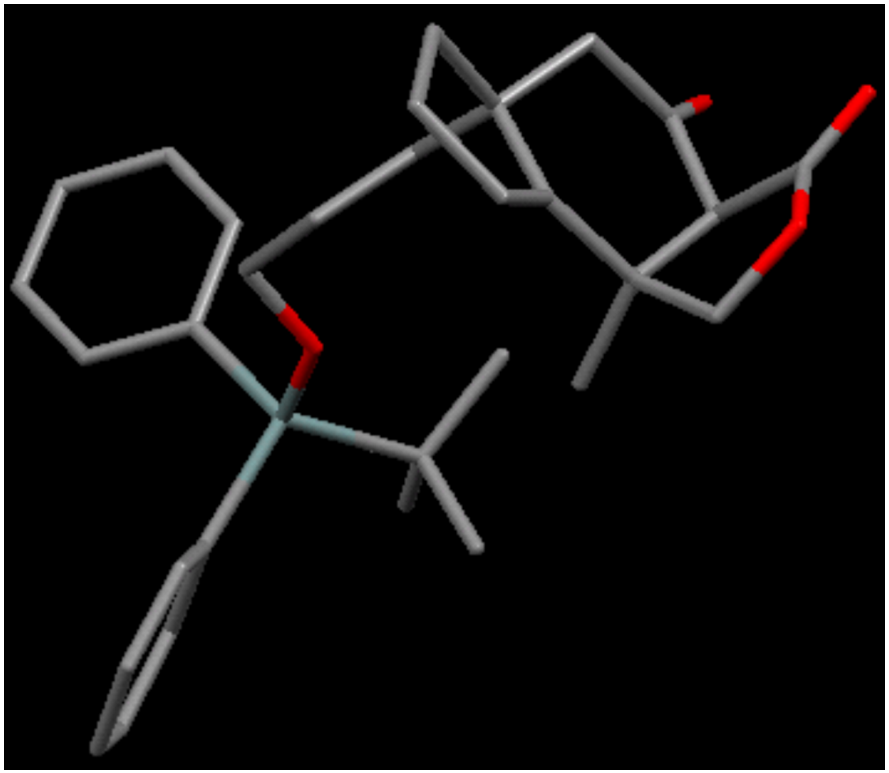
The role of LiOAc in tandem cyclization*

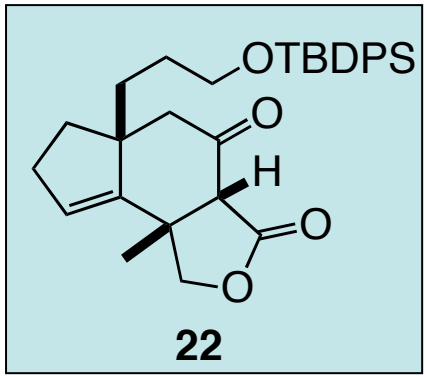
1. Formation of lithium enolate
2. Promoting the epimerization at C6



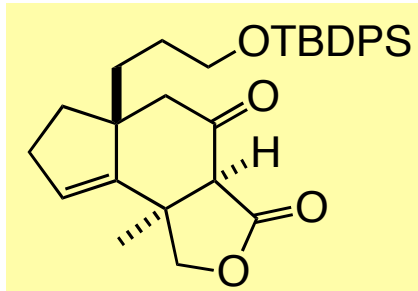
*Using K^+ as a counter ion, *O*-alkylation was preference.

Relative stereochemistry of compound 22





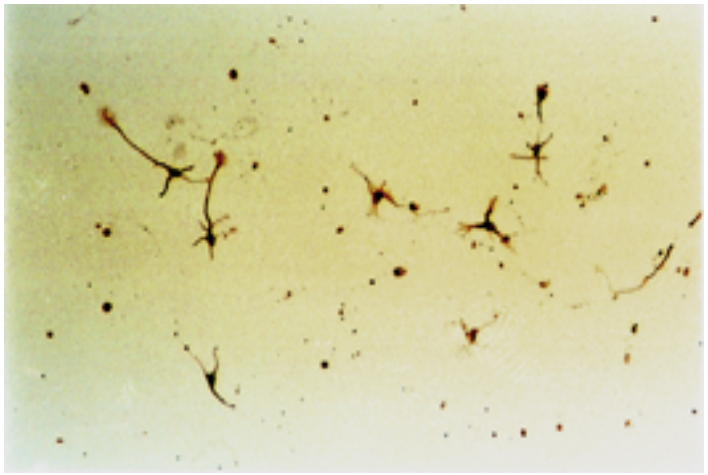
22



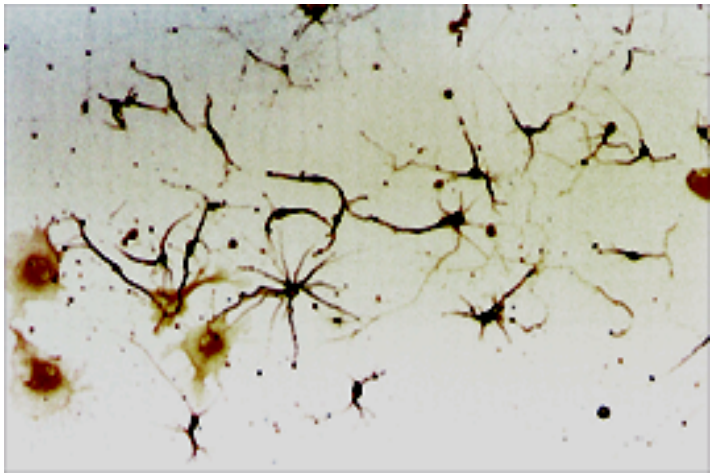
Desired isomer **23**

crystal data
crystal: monoclinic, space group: P2(1)
dimensions: a = 8.0156(14) Å
b = 8.0900(15) Å, c = 42.519(8) Å
V = 2757.2(9) Å, Z = 4, final *R*: 0.0704

Neurite outgrowth promoting activity of jiadifenin in primary cultured rat cortical neurons



control



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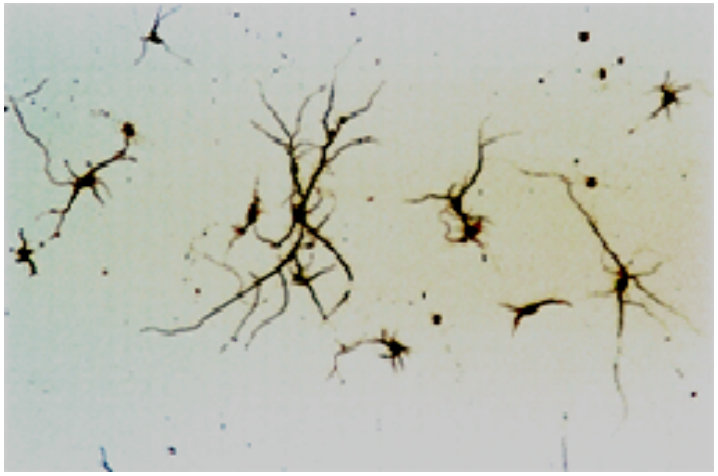
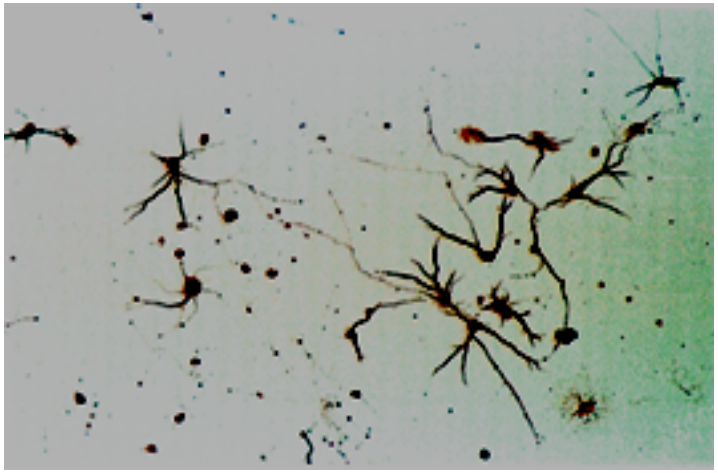


1.0 μM



10 μM