Total Synthesis of Bryostatins

(Previous Achievement and Krische's Work)

Literature seminar (2018.02.14)
B4 Hongyu Chen

Contents

1. Introduction

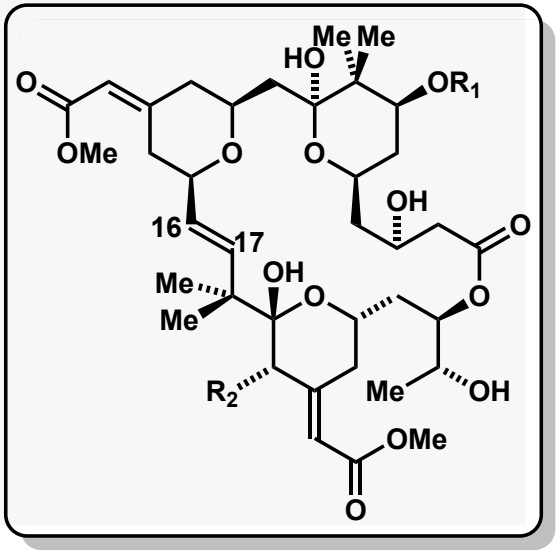
Introduction

Isolation :
From the marine bryozoan *Bugula neritina*
(フサコケムシ)

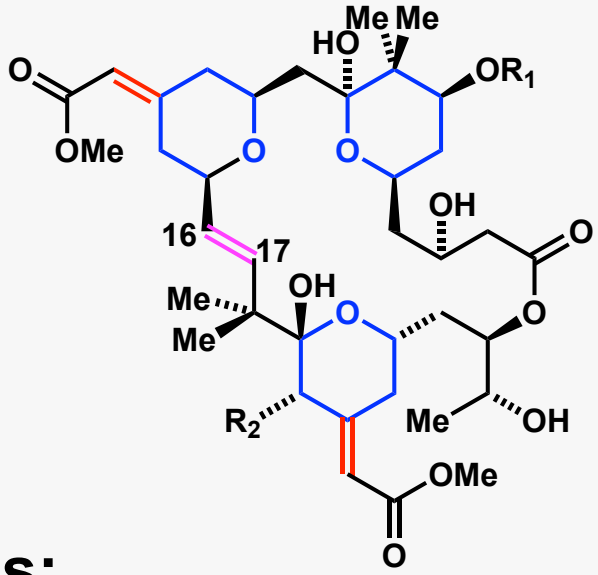
Biosynthesis :
Candidatus Endobugula sertula
(Symbiotic bacterium of *Bugula neritina*)

Biological activity :

- Potent modulator of protein kinase C (PKC)
- Anti-cancer effect
- Anti-HIV effect
- Life-prolonging effect on Alzheimer's disease



Introduction

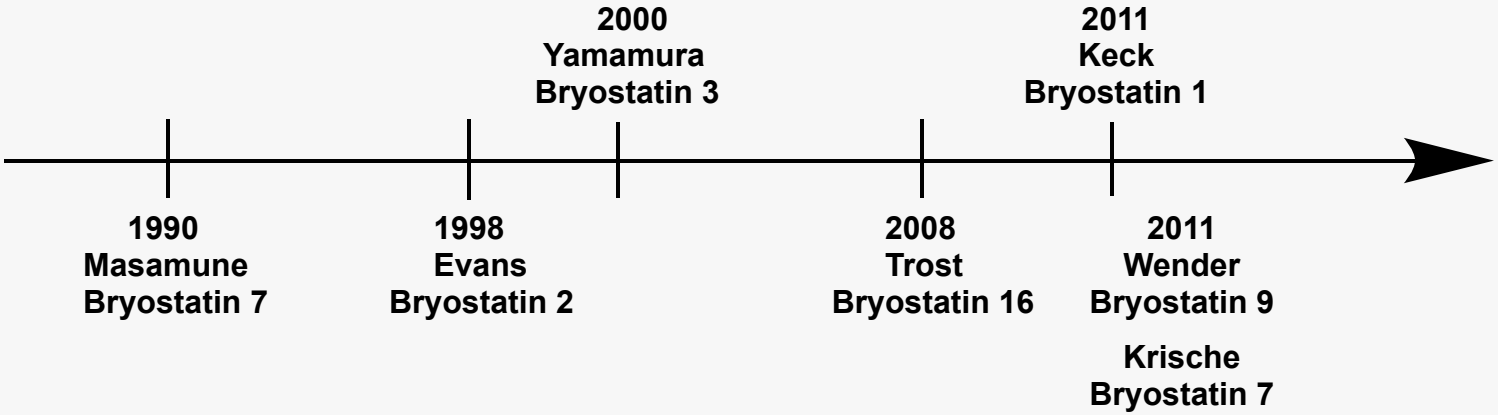


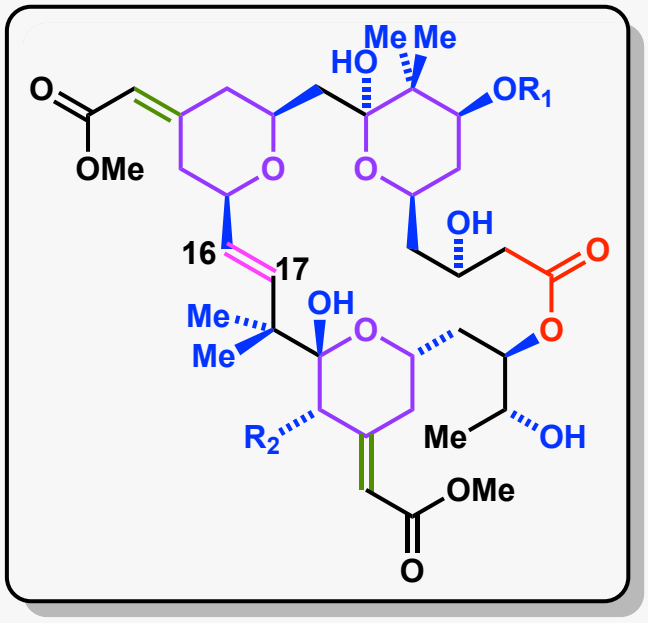
Structure features:

- A family of 20 marine natural products
- Three heavily substituted tetrahydropyran rings
- Two acid/base-sensitive *exo*-cyclic unsaturated esters
- One congested C16-C17 *trans*-alkene
- Numerous oxygen-containing functionalities on a 26-membered lactone

2. Previous work

Development of Bryostatin's Total Synthesis

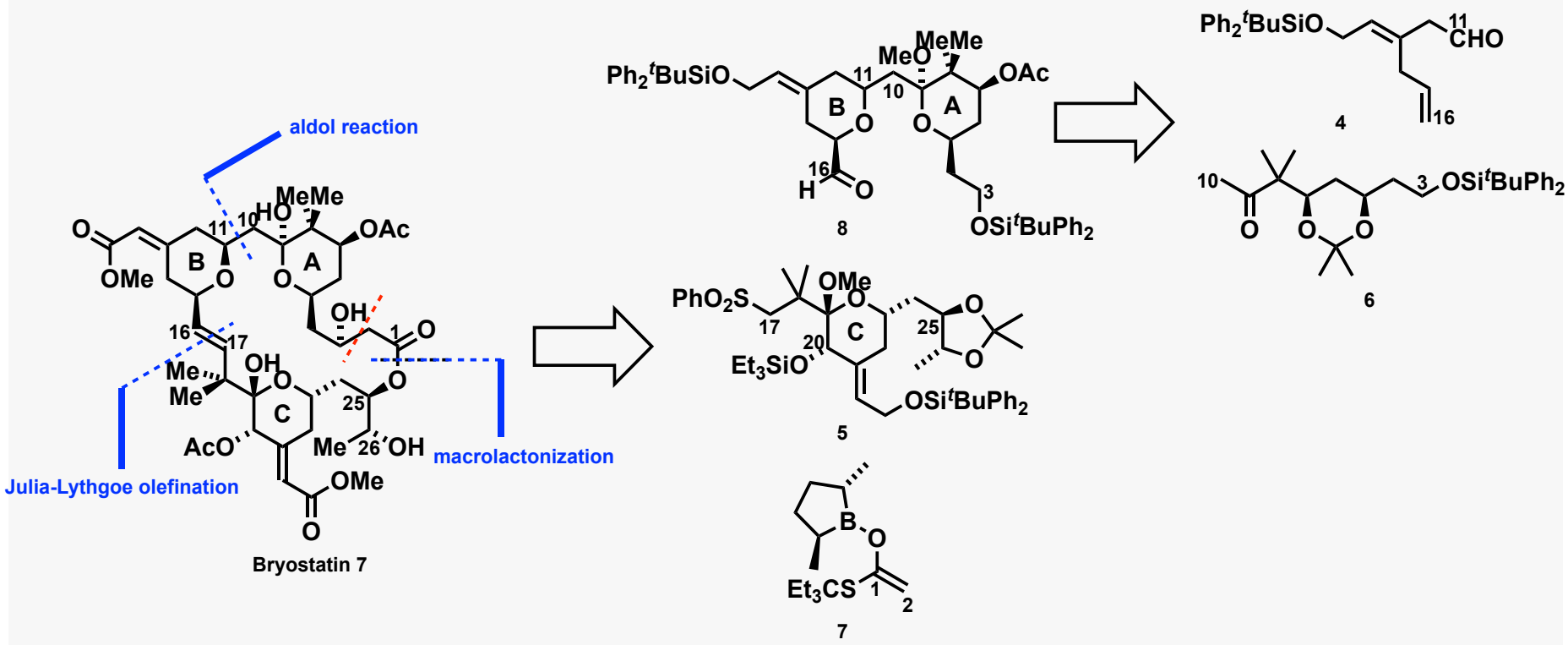




Synthesis points :

① *Exo*-cyclic unsaturated esters
② Congested C16-C17 *trans*-alkene
③ Macrolactonization
④ Complex steric structure

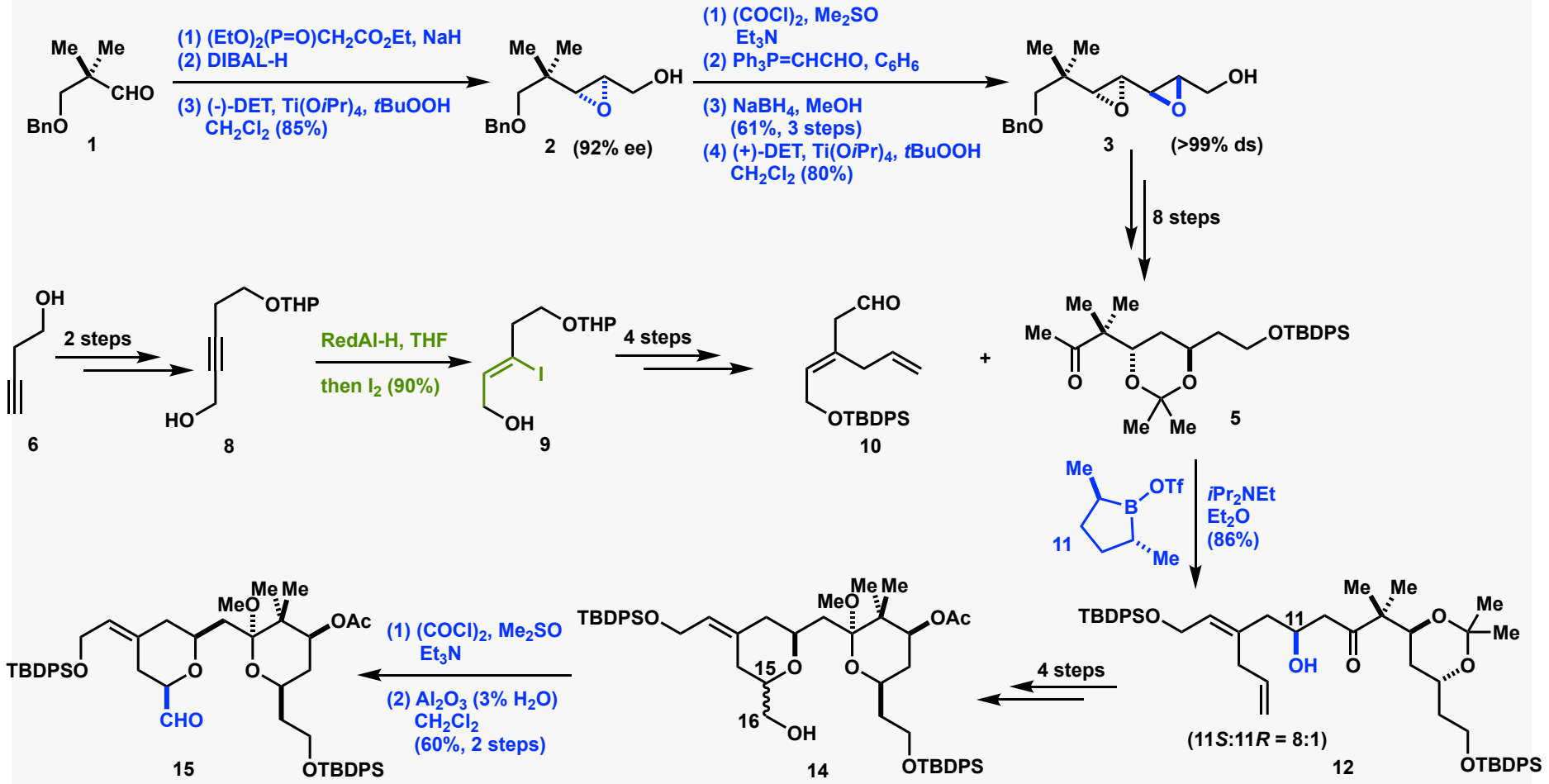
Total Synthesis of Bryostatin 7 by Masamune (1990) (1)



- First total synthesis of Bryostatin
- Bryostatin 7 was devided into 4 fragments and chiral enolate reagent 7 controlled enantioselectivity of the product
- 41 steps in total

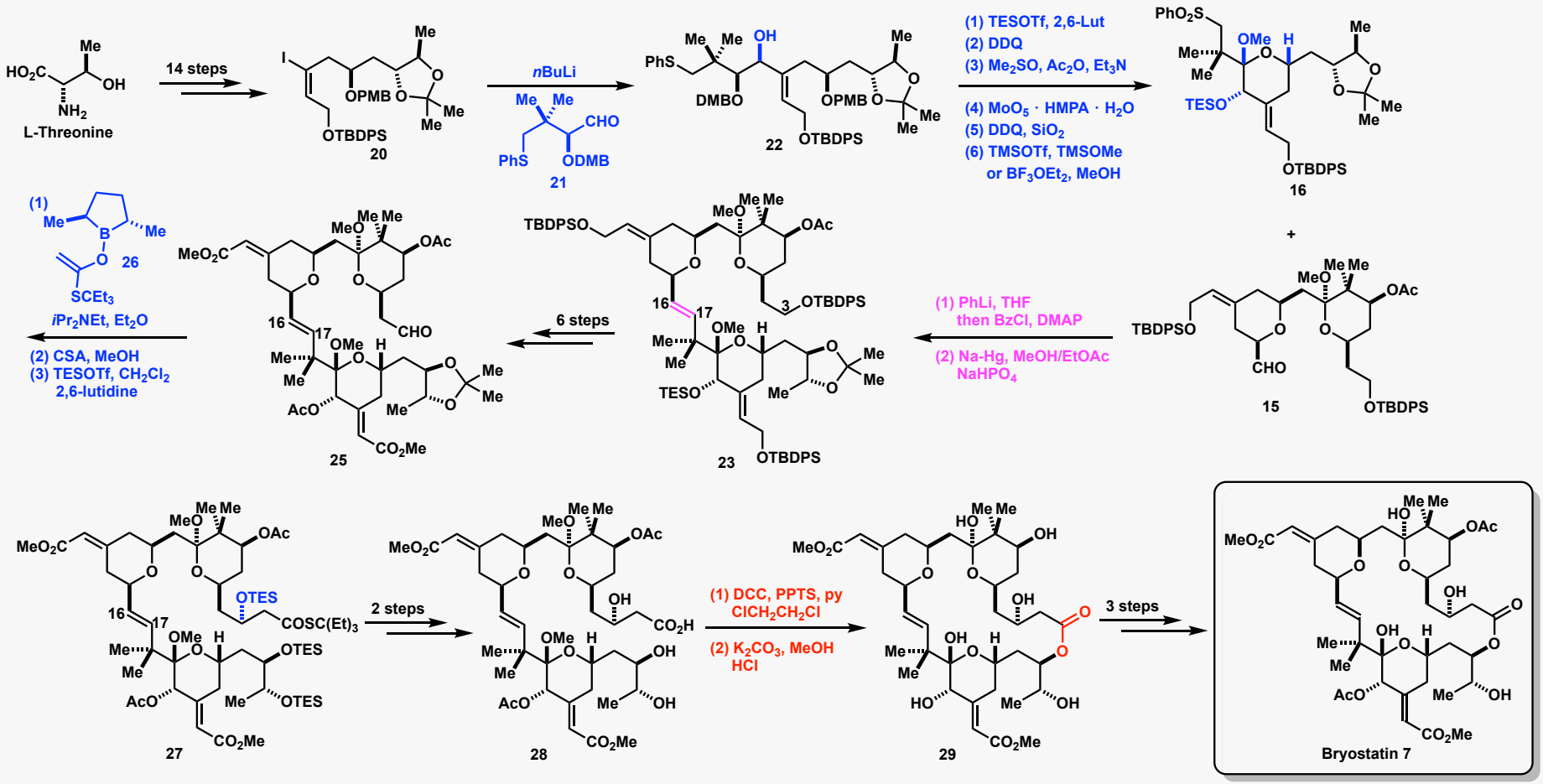
Masamune, S. et al. *J. Am. Chem. Soc.*, **1990**, 112, 7407.

Total Synthesis of Bryostatin 7 by Masamune (1990) (2)



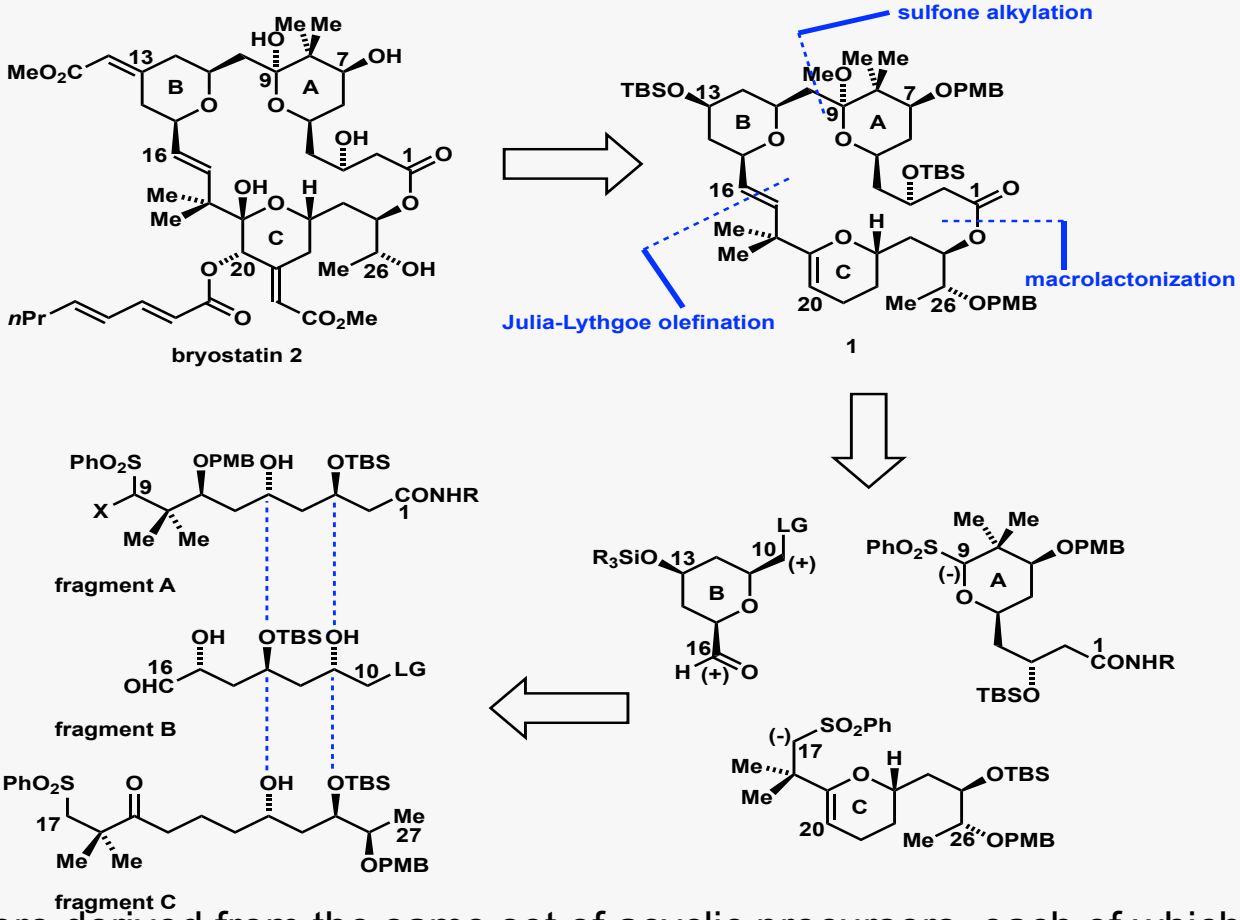
Masamune, S. et al. *J. Am. Chem. Soc.*, **1990**, 112, 7407.

Total Synthesis of Bryostatin 7 by Masamune (1990) (3)



Masamune, S. et al. *J. Am. Chem. Soc.*, **1990**, 112, 7407.

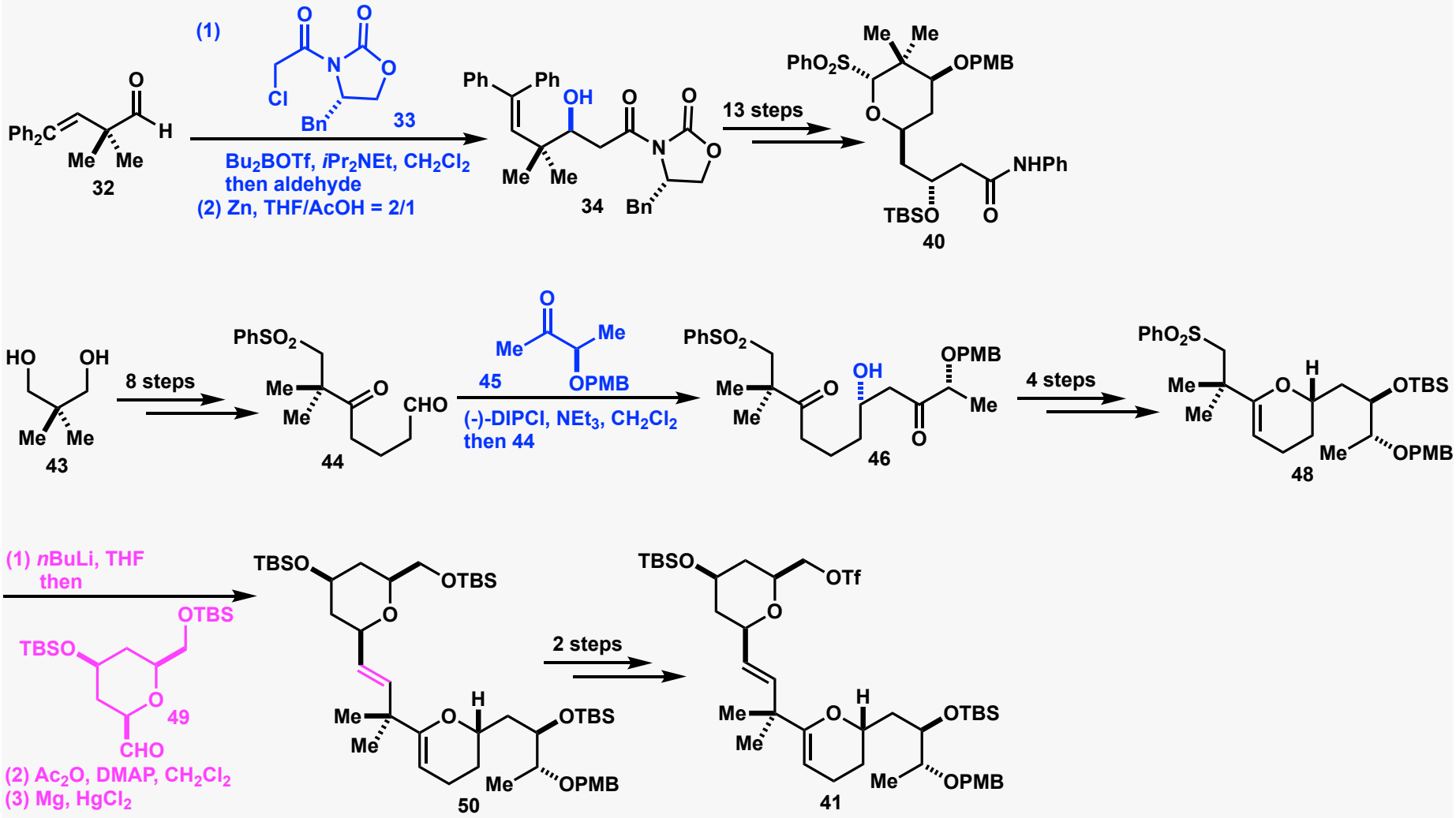
Total Synthesis of Bryostatin 2 by Evans (1998) (1)



- Rings A-C were derived from the same set of acyclic precursors, each of which contains a common *anti*-1,3-diol subunit
- This stereochemical motif can be effectively synthesized by sequential aldol and reduction reactions
- 42 steps in total

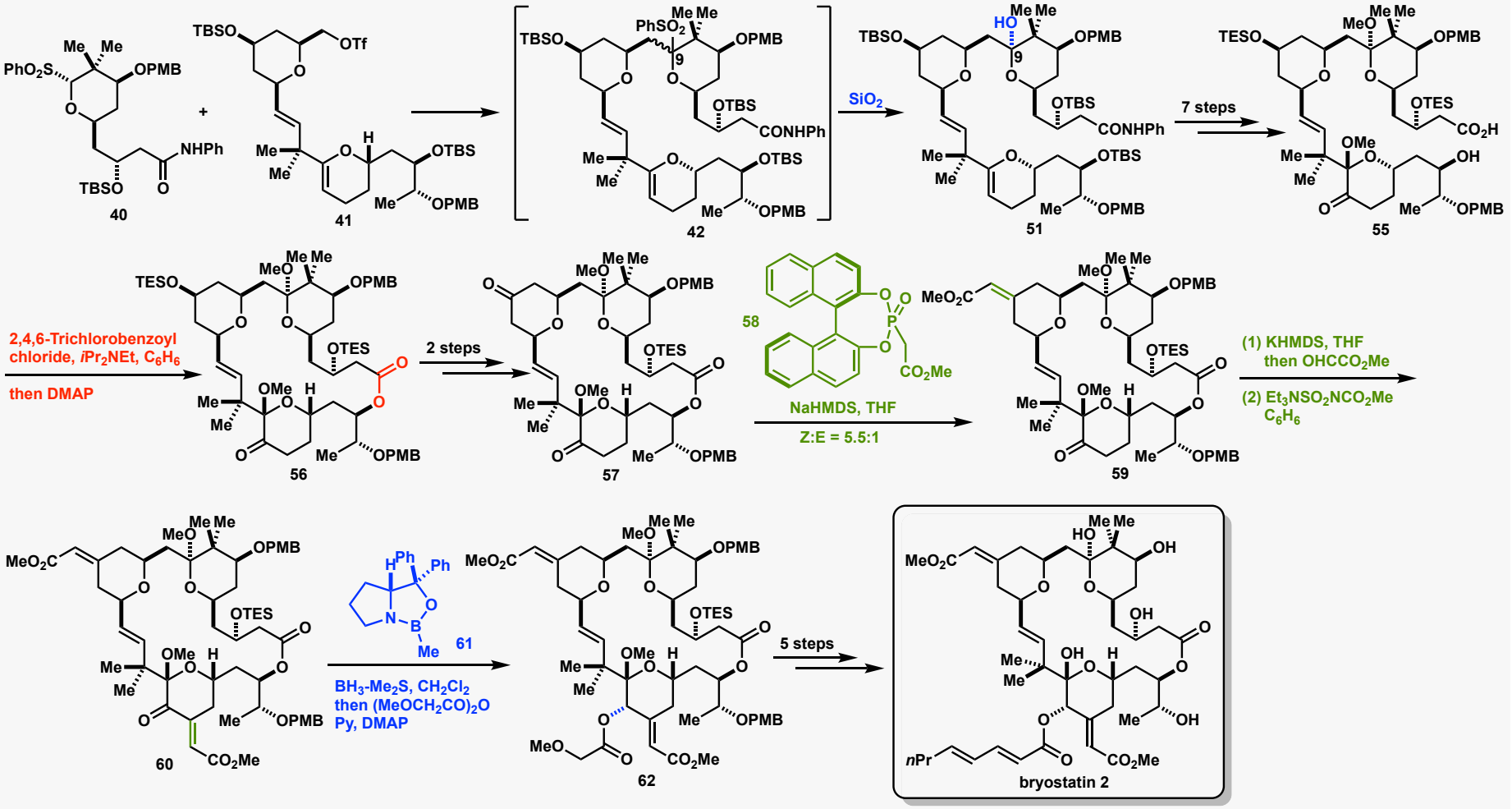
Evans, D. A. et al. *Angew. Chem., Int. Ed.* **1998**, 37, 2354.

Total Synthesis of Bryostatin 2 by Evans (1998) (2)



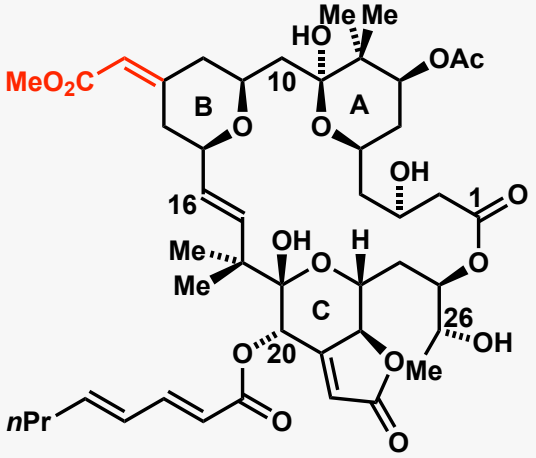
Evans, D. A. et al. *Angew. Chem., Int. Ed.* **1998**, 37, 2354.

Total Synthesis of Bryostatin 2 by Evans (1998) (3)



Evans, D. A. et al. *Angew. Chem., Int. Ed.* **1998**, 37, 2354.

Total Synthesis of Bryostatin 3 by Yamamura (2000) (1)

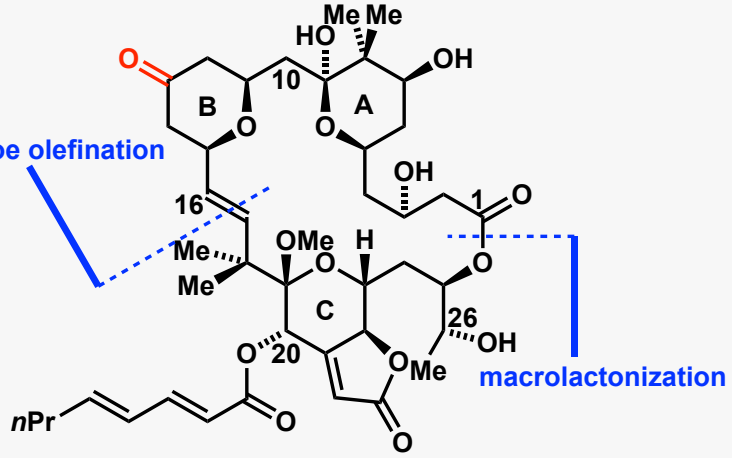


bryostatin 3

Horner-Wadsworth-Emmons reaction

Julia-Lythgoe olefination

macrolactonization



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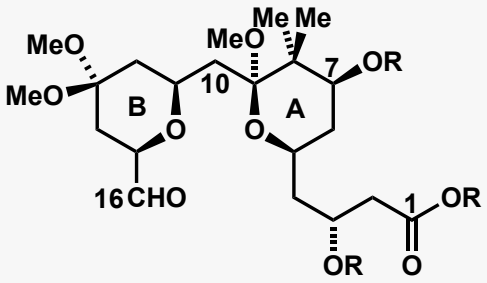
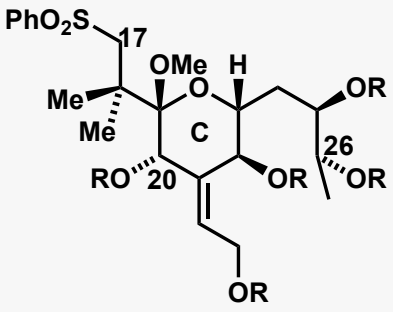


1

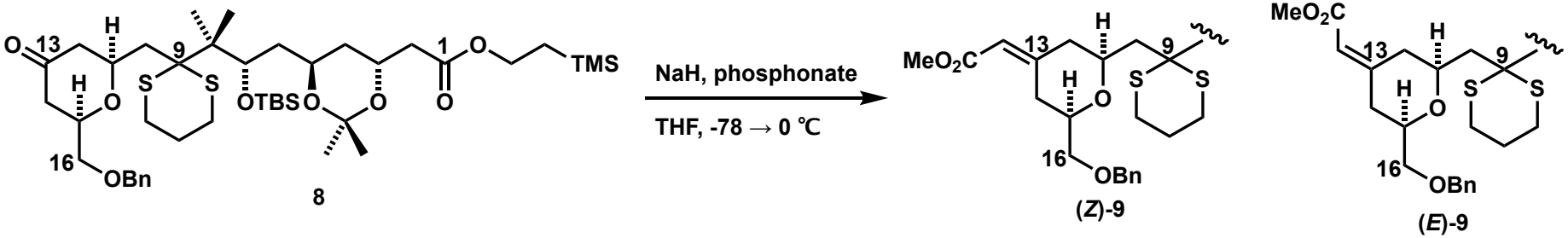


2

- The best condition for introducting a methoxycarbonylmethylene unit to the C13 position stereocontrolledly was studied
- 43 steps in total

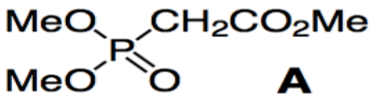
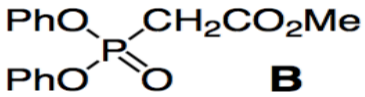
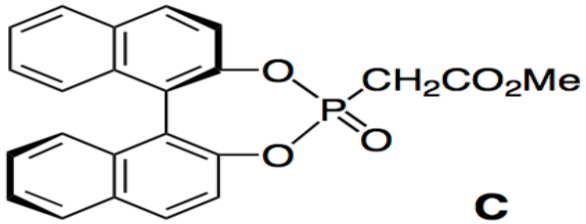
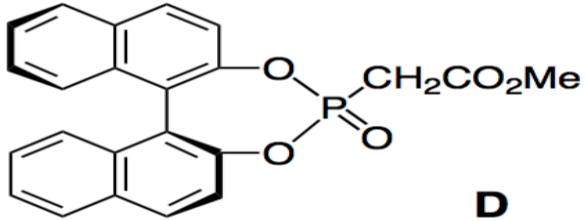
Yamamura, S. *Angew. Chem., Int. Ed.* **2000**, 39, 2290.

Total Synthesis of Bryostatin 3 by Yamamura (2000) (2)



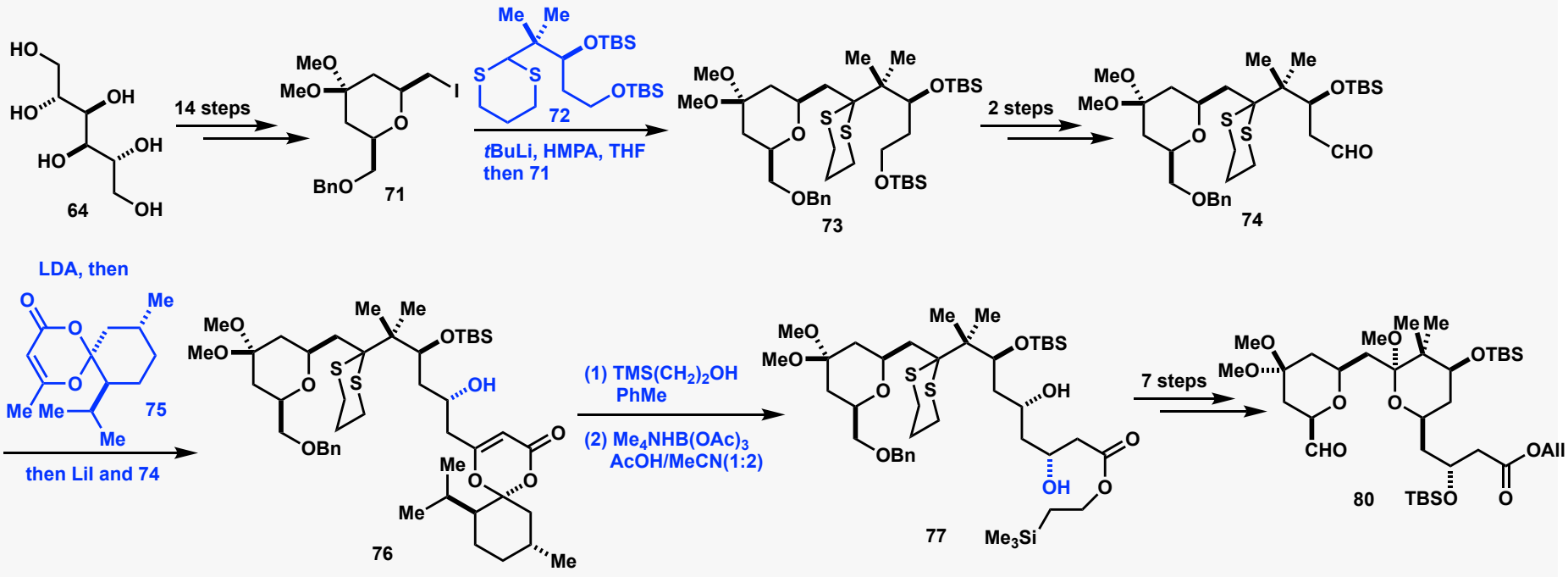
8 (*Z*)-9 (*E*)-9

Table 1. Horner-Wadsworth-Emmons reaction of **8** with various reagents.

Phosphonate	Yield [%]	*Z*:*E* ratio of **9**
 **A**	94	1.6:1
 **B**	90	2.0:1
 **C**	92	4.0:1
 **D**	85	2.3:1

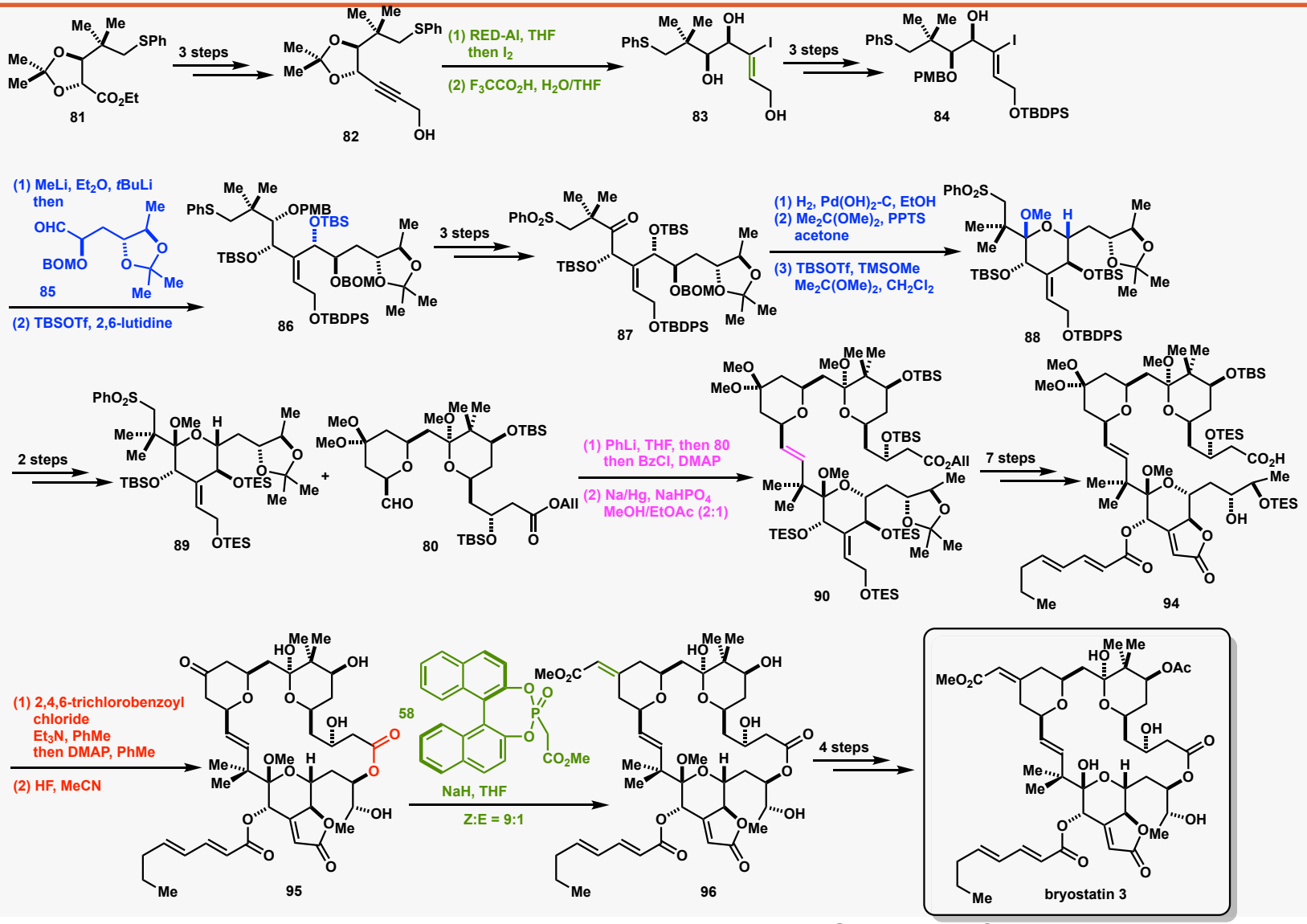
Yamamura, S. *Angew. Chem., Int. Ed.* **2000**, 39, 2290.

Total Synthesis of Bryostatin 3 by Yamamura (2000) (3)



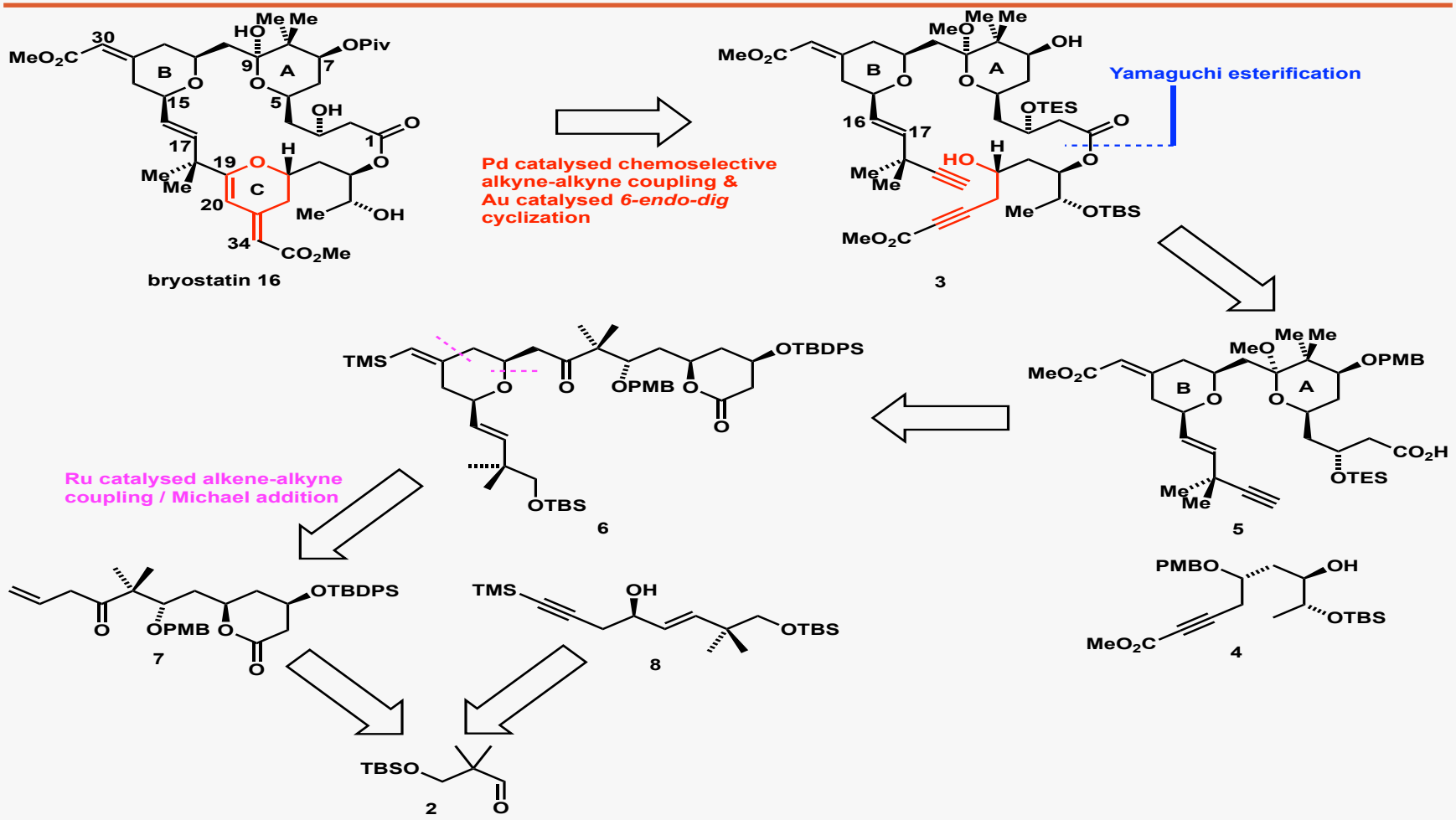
Yamamura, S. *Angew. Chem., Int. Ed.* **2000**, 39, 2290.

Total Synthesis of Bryostatin 3 by Yamamura (2000) (4)



Yamamura, S. *Angew. Chem., Int. Ed.* **2000**, 39, 2290.

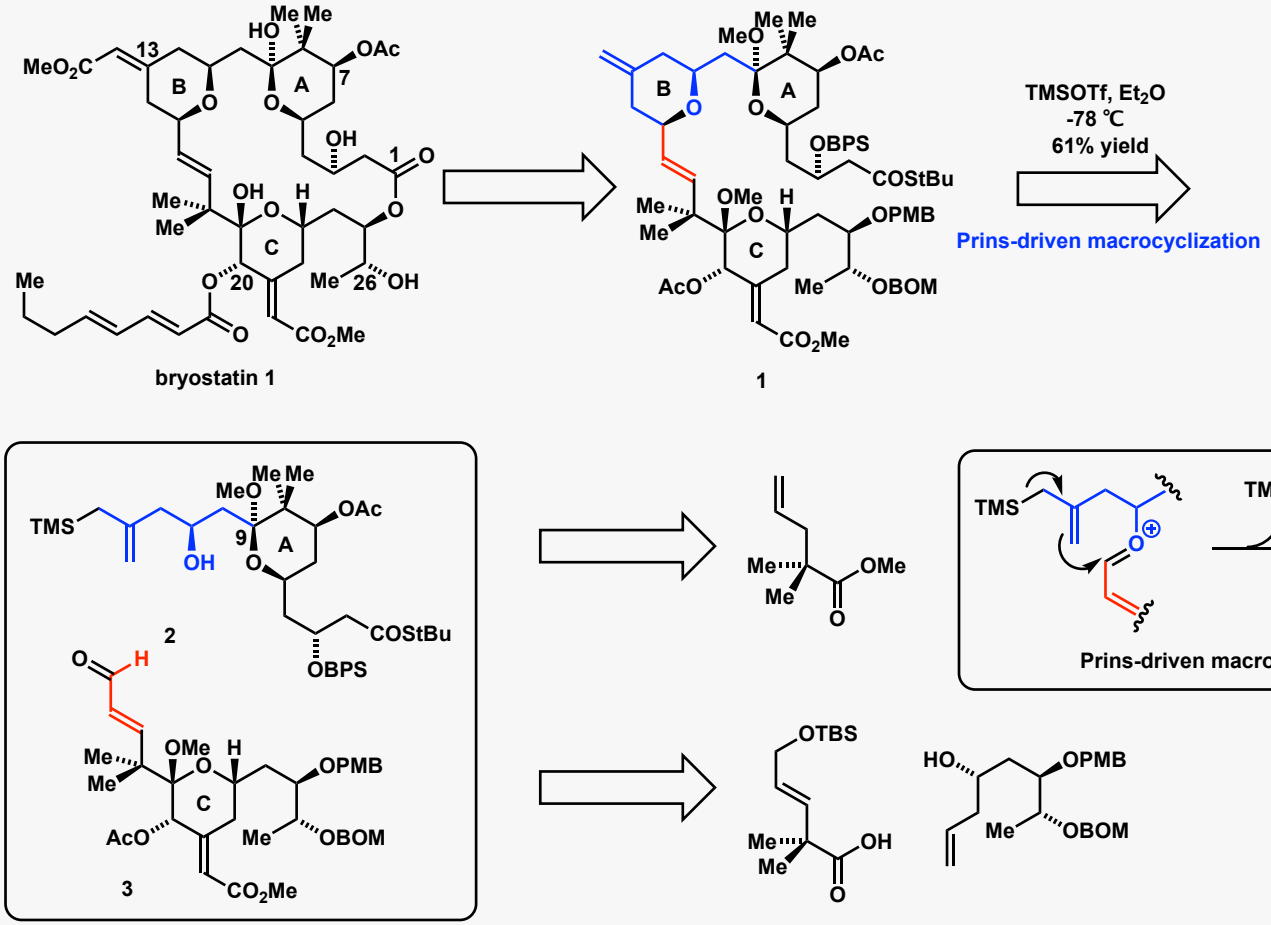
Total Synthesis of Bryostatin 16 by Trost (2008)



- Pd-catalysed chemoselective alkyne-alkyne coupling followed by Au-catalysed *6-endo-dig* cyclization efficiently produced both the macrocycle and the C ring of Bryostatin 16
- Ru-catalysed tandem alkene-alkene coupling / Michael addition generated *cis*-tetrahydropyran 6
- 28 steps in total

Trost, B. M. et al. *Nature*. **2008**, 456, 485.

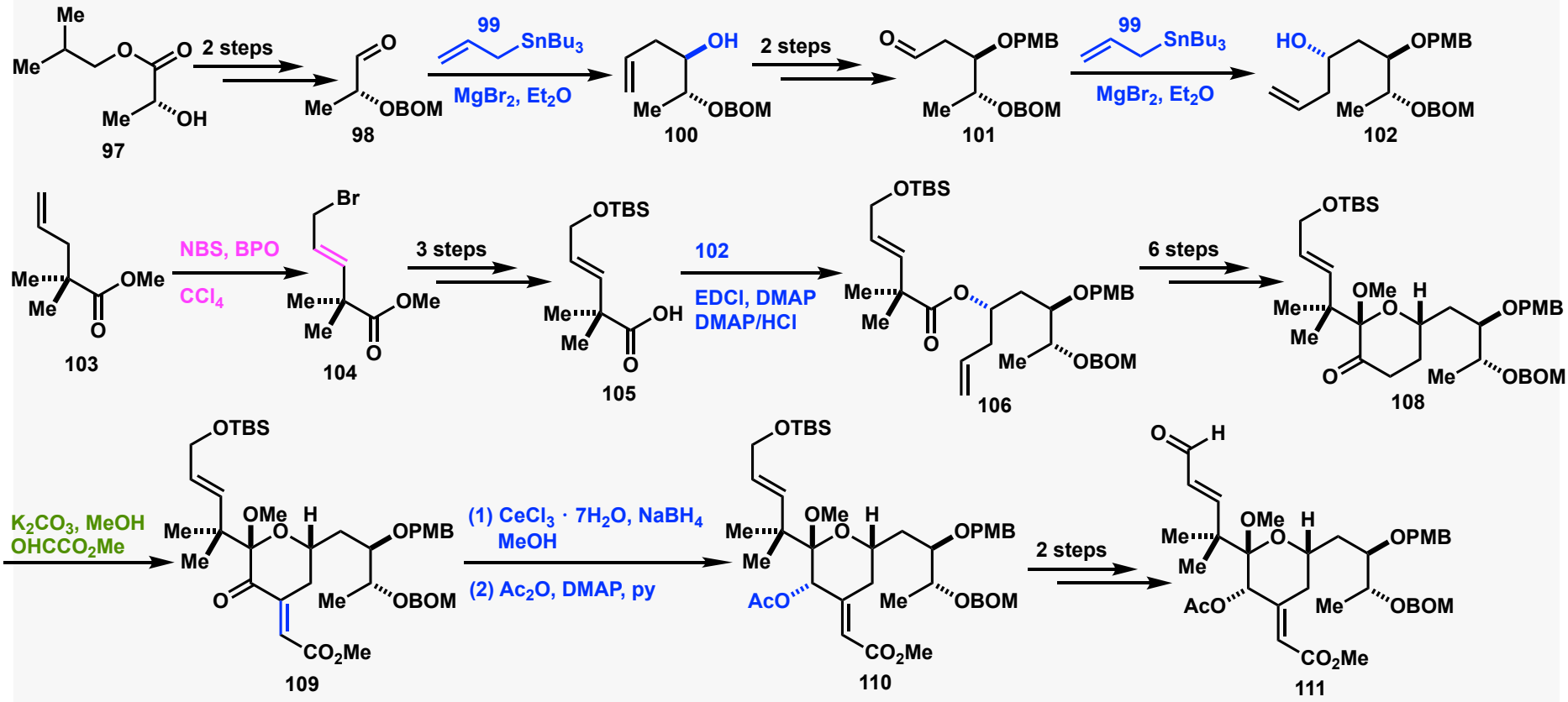
Total Synthesis of Bryostatin 1 by Keck (2011) (1)



- A strategy of combining an A-ring hydroxyallylsilane and a C-ring aldehyde was selected for an attempted synthesis of Bryostatin 1
- A spirocylic structure formed via intramolecular cyclization of the silane at the C9 position was a major byproduct
- 31 steps in total

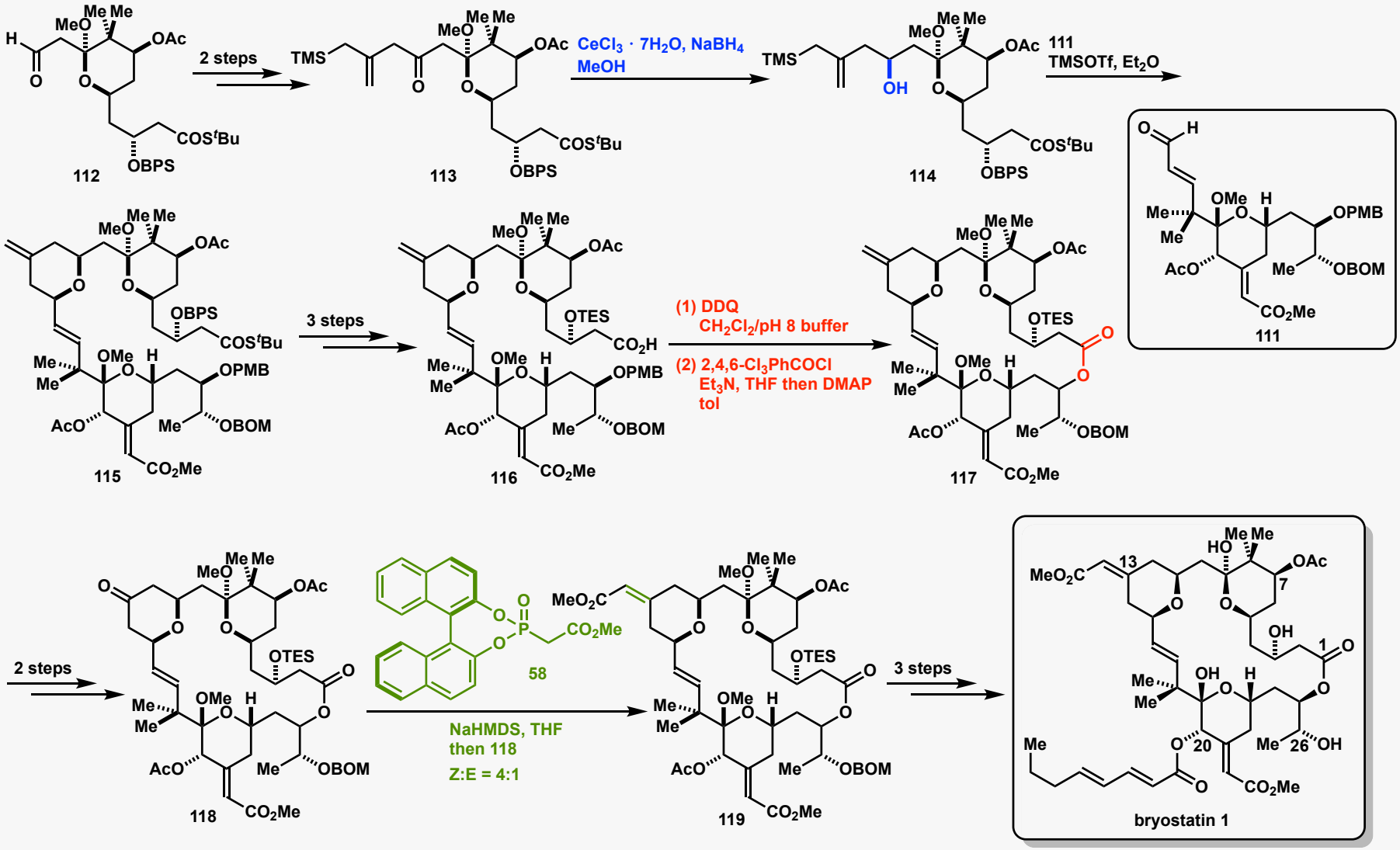
Gary E. Keck. et al. *J. Am. Chem. Soc.*, **2011**, 133 (4), 744.

Total Synthesis of Bryostatin 1 by Keck (2011) (2)



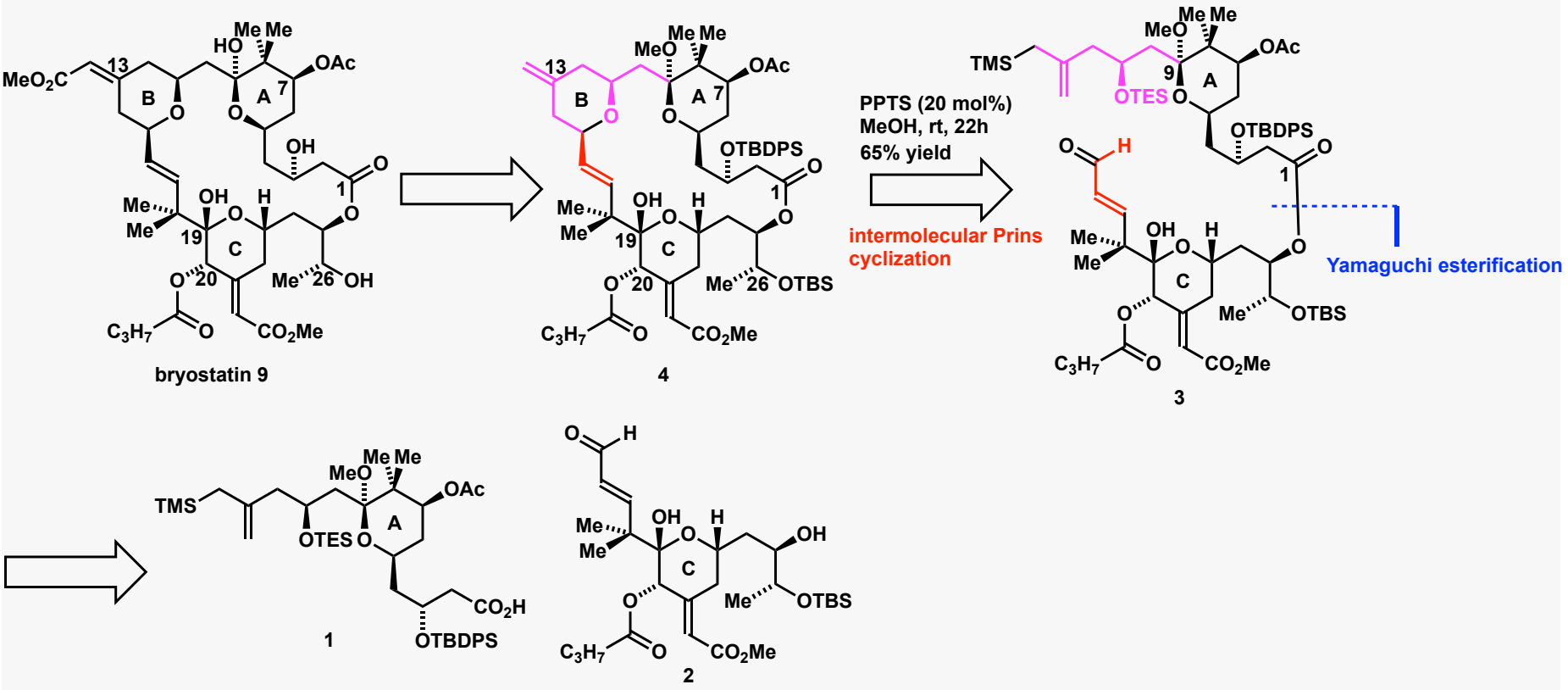
Gary E. Keck. et al. *J. Am. Chem. Soc.*, **2011**, 133 (4), 744.

Total Synthesis of Bryostatin 1 by Keck (2011) (3)



Gary E. Keck. et al. *J. Am. Chem. Soc.*, **2011**, 133 (4), 744.

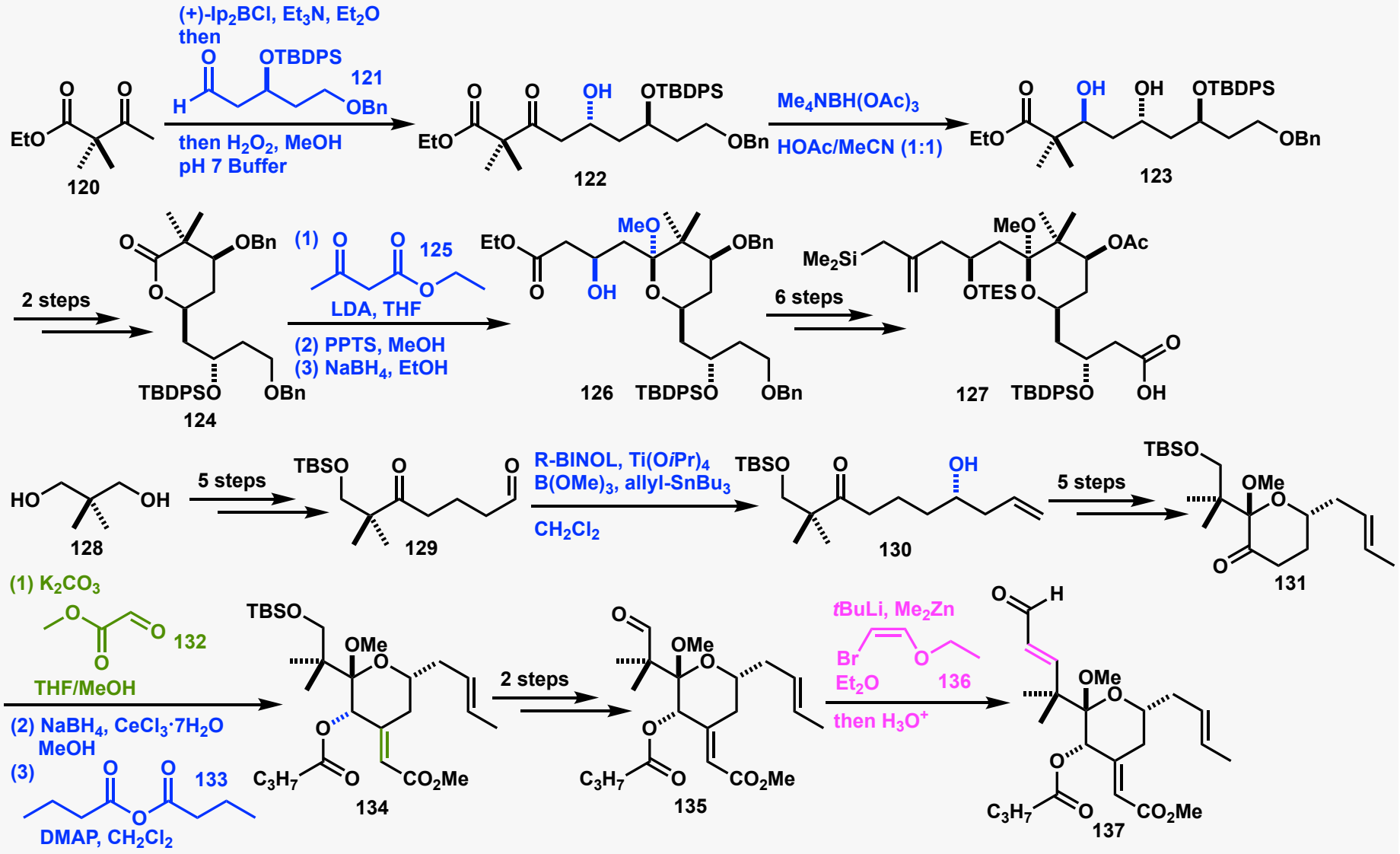
Total Synthesis of Bryostatin 9 by Wender (2011) (1)



- An intermolecular Prins cyclization to anneal the B ring was investigated, which prevented the spirocyclic byproduct from synthesizing
- 25 steps in total

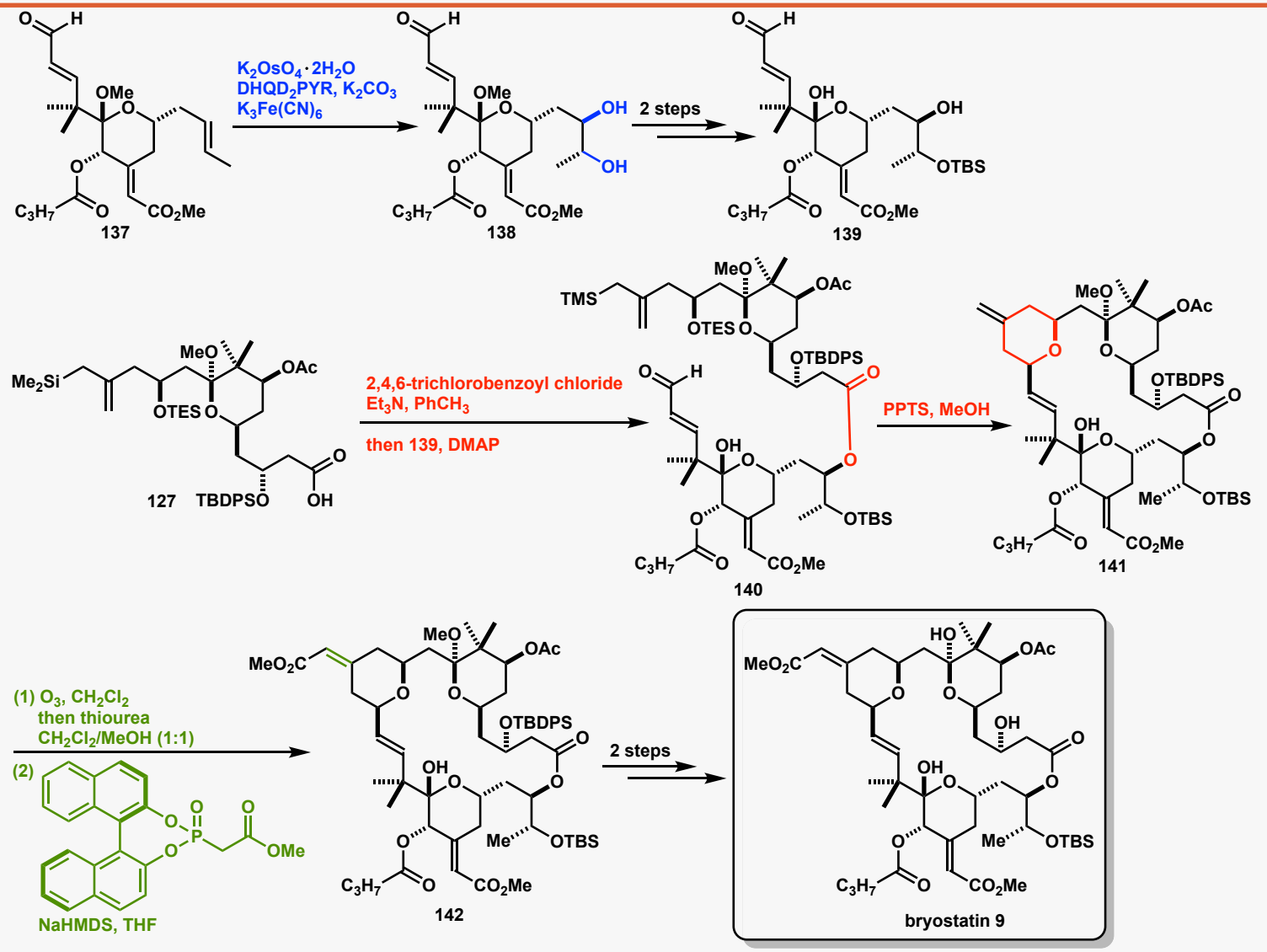
Wender, P. A. et al. *J. Am. Chem. Soc.*, **2011**, 133, 9228.

Total Synthesis of Bryostatin 9 by Wender (2011) (2)



Wender, P. A. et al. *J. Am. Chem. Soc.*, **2011**, 133, 9228.

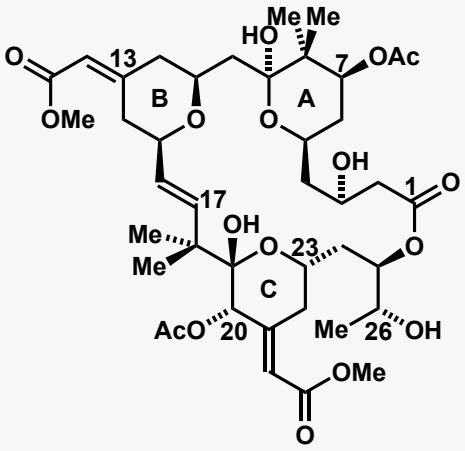
Total Synthesis of Bryostatin 9 by Wender (2011) (3)



Wender, P. A. et al. *J. Am. Chem. Soc.*, **2011**, 133, 9228.

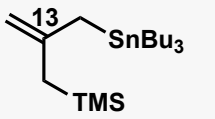
3.Total synthesis of Bryostatin 7 by Krische

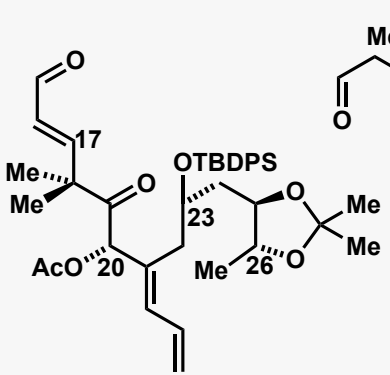
Retrosynthetic Analysis of Bryostatin 7



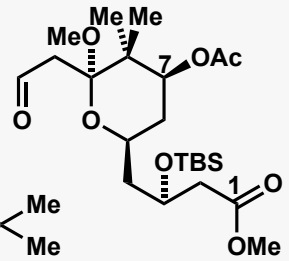
Bryostatin 7

20 Steps (LLS), 36 Total Steps
5 C-C Bonds Formed via
Hydrogen-Mediated C-C Coupling





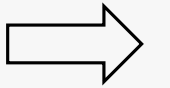
Fragment A
(10 Steps)

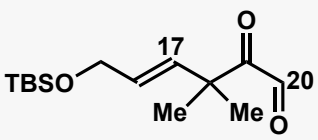


Fragment B
(10 Steps)

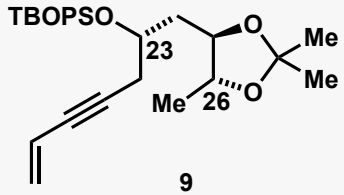
Fragment A

1 C-C Bond Formed via
Hydrogenative Coupling
C20-C21





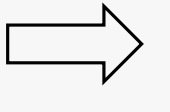
6
(6 Steps)

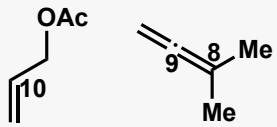


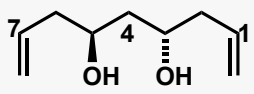
9
(6 Steps)

Fragment B

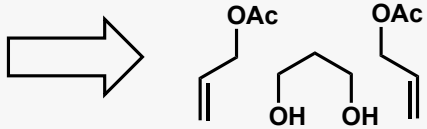
4 C-C Bonds Formed via
Hydrogenative Coupling
C2-C3, C5-C6, C7-C8,
C9-C10





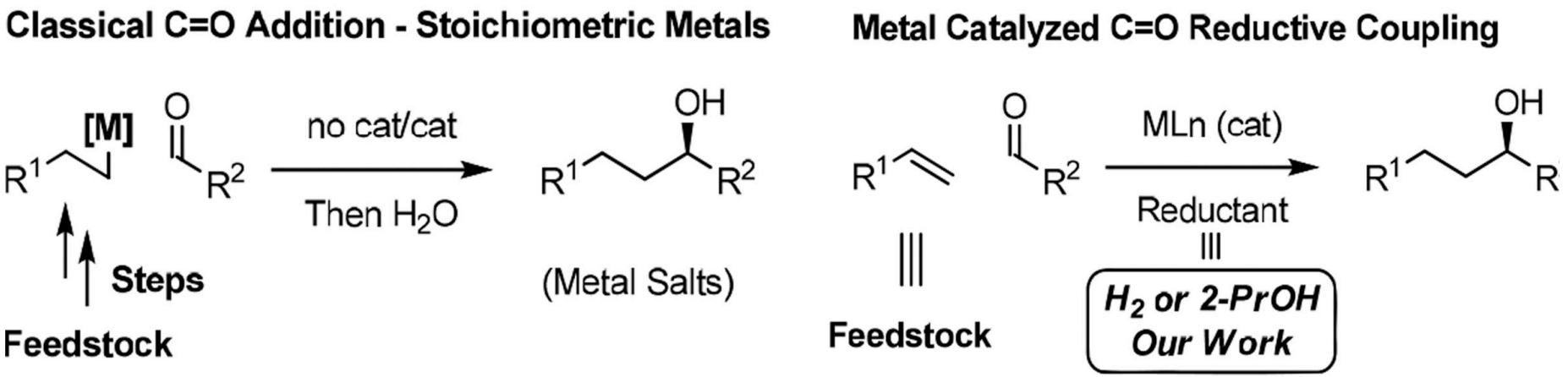


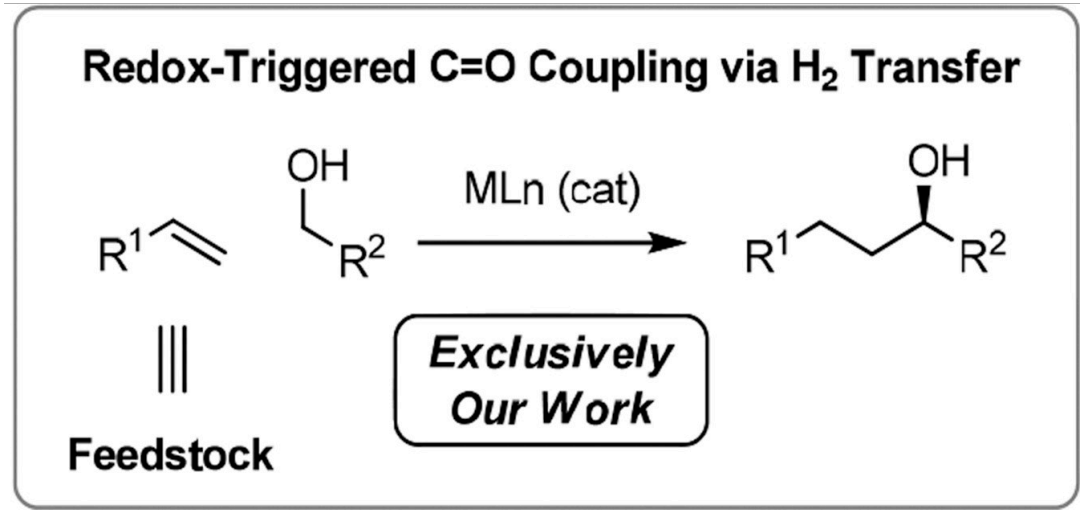
11
(1 Step)



Michael J. Krische. et al. *J. Am. Chem. Soc.*, **2011**, 133, 13876.

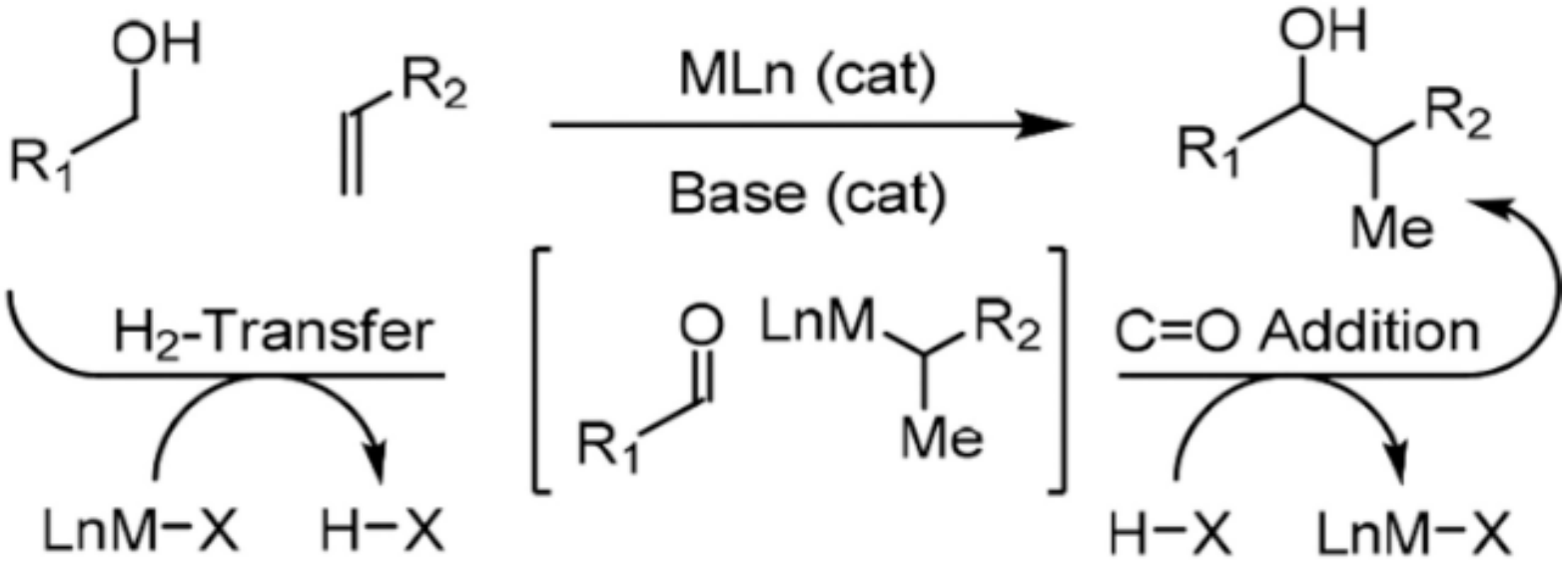
Krische's Work (Key Reaction)





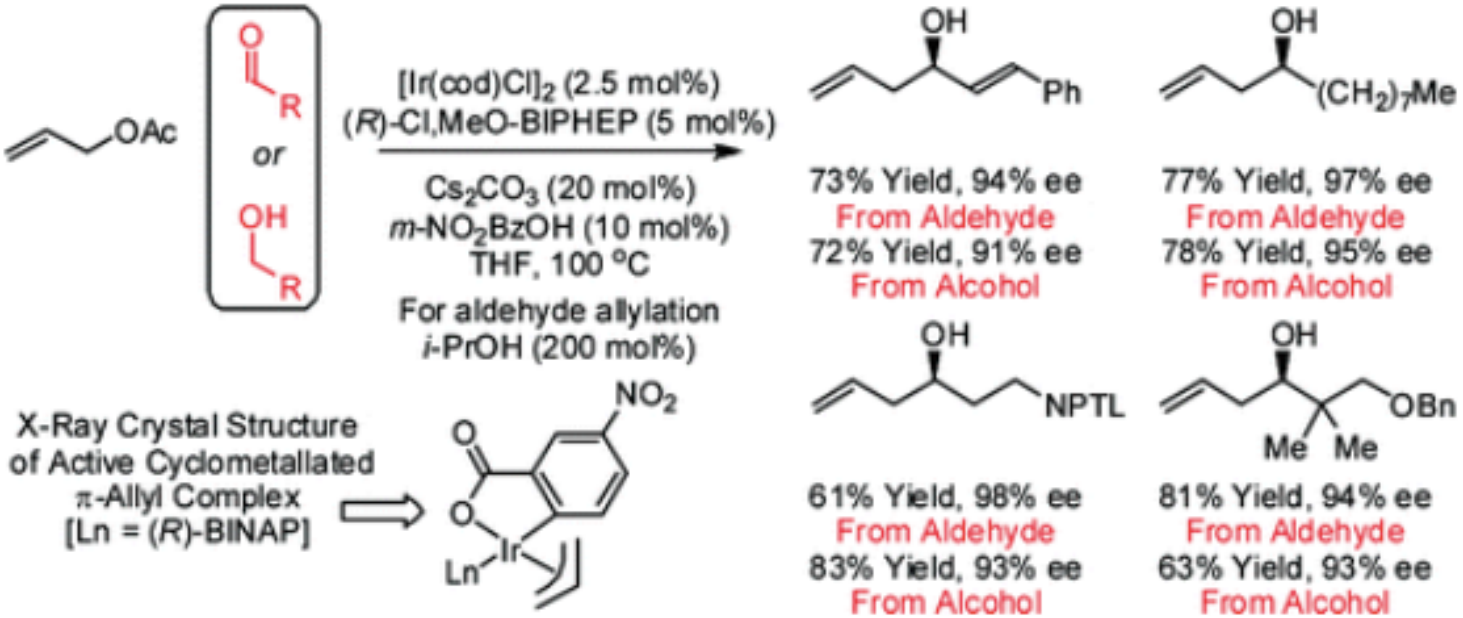
Michael J. Krische. et al. *Acc. Chem. Res.*, **2017**, 50, 2371.

Conception of Krische's Work



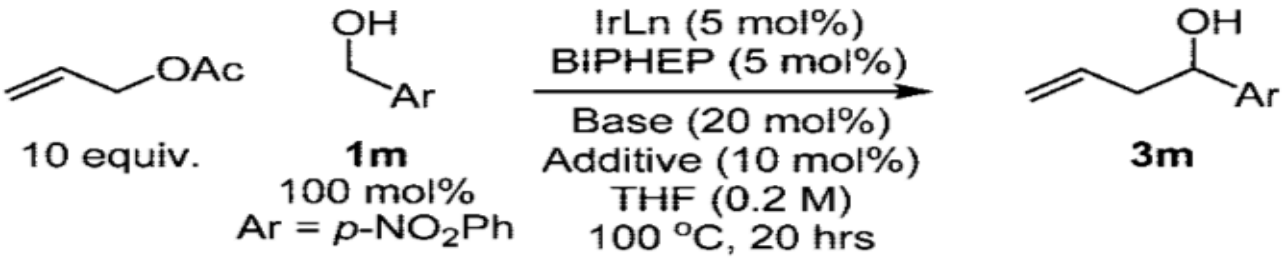
Michael J. Krische. et al. *Acc. Chem. Res.*, **2017**, 50, 2371.

Enantioselective Ir-Catalyzed Carbonyl Allylation via Transfer Hydrogenative Coupling of Allyl Acetate

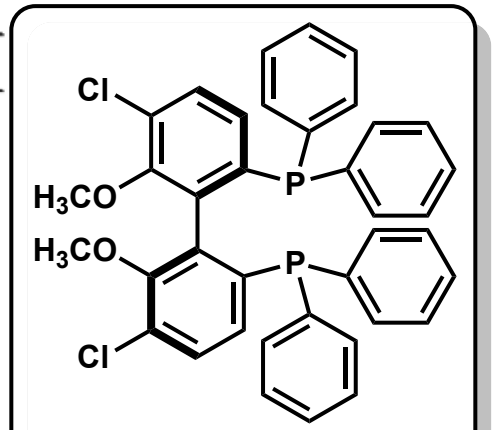


Michael J. Krische. et al. *J. Am. Chem. Soc.*, **2008**, 130, 14891.

Effect of Basic and Acidic Additives and Iridium Source in the Transfer Hydrogenative Allylation



	Entry	Base	Additive	Iridium Source	Yield (%)
⇨	**1**	**Cs_2CO_3**	***m*-NO_2BzOH**	**$[Ir(cod)Cl]_2$**	**80**
Additive-Base	2	K_2CO_3	*m*-NO_2BzOH	$[Ir(cod)Cl]_2$	21
	3	Na_2CO_3	*m*-NO_2BzOH	$[Ir(cod)Cl]_2$	15
	4	Li_2CO_3	*m*-NO_2BzOH	$[Ir(cod)Cl]_2$	12
	5	---	*m*-NO_2BzOH	$[Ir(cod)Cl]_2$	≤ 5
	6	Cs_2CO_3	---	$[Ir(cod)Cl]_2$	47
	7	---	---	$[Ir(cod)Cl]_2$	10
	8	---	*m*-NO_2BzOCs	$[Ir(cod)Cl]_2$	72
	9	Cs_2CO_3	*m*-NO_2BzOCs	$[Ir(cod)Cl]_2$	79
	10	Cs_2CO_3	*o*-NO_2BzOH	$[Ir(cod)Cl]_2$	39
	11	Cs_2CO_3	*p*-NO_2BzOH	$[Ir(cod)Cl]_2$	49
	12	Cs_2CO_3	BzOH	$[Ir(cod)Cl]_2$	39
	13	Cs_2CO_3	*p*-MeOBzOH	$[Ir(cod)Cl]_2$	42
	14	Cs_2CO_3	*m*-FBzOH	$[Ir(cod)Cl]_2$	41
	15	Cs_2CO_3	*m*-NO_2BzOMe	$[Ir(cod)Cl]_2$	47
IrLn	16	Cs_2CO_3	---	[Ir(cod)(BIPHEP)]BARF	41
	17	Cs_2CO_3	*m*-NO_2BzOH	[Ir(cod)(BIPHEP)]BARF	72



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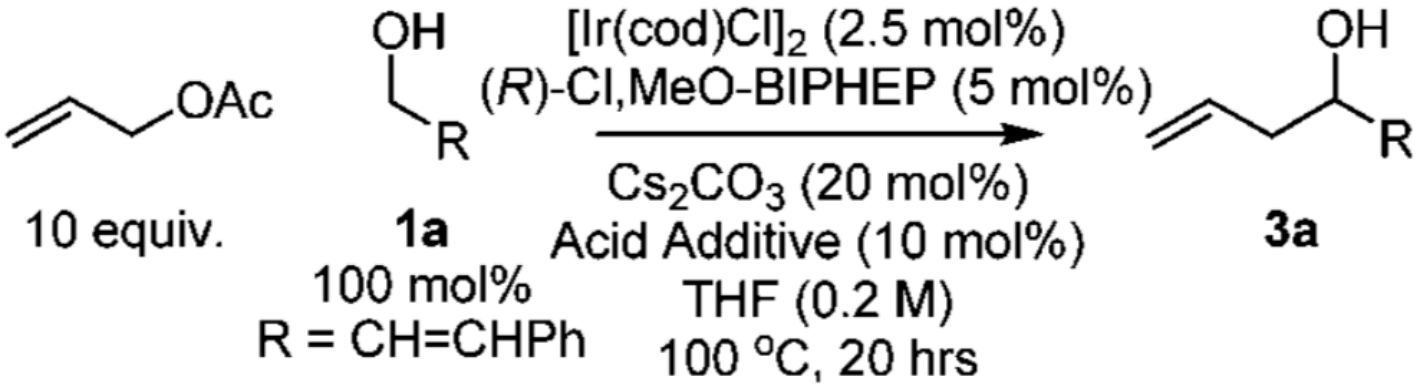
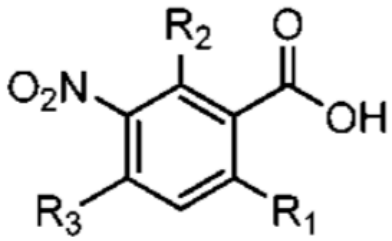
Effect of Substitution of *m*-Nitrobenzoic Acid in the Transfer Hydrogenative Allylation



Entry	Carboxylic Acid	Yield (%)	ee (%)
⇨ **1**	**$R_1 = R_2 = R_3 = H$**	**71**	**91 (*R*)**
2	No Acid Additive	8	47 (*S*)
3	R_1 = Me, $R_2 = R_3 = H$	18	65 (*S*)
4	R_2 = Me, $R_1 = R_3 = H$	50	67 (*R*)
5	R_3 = Me, $R_1 = R_2 = H$	69	91 (*R*)



- Substituents of *m*-NO_2BzOH are important for enantioselectivity
- R1 is the preferred site of cyclometalation and the enantioselectivity would be reversed if it is blocked

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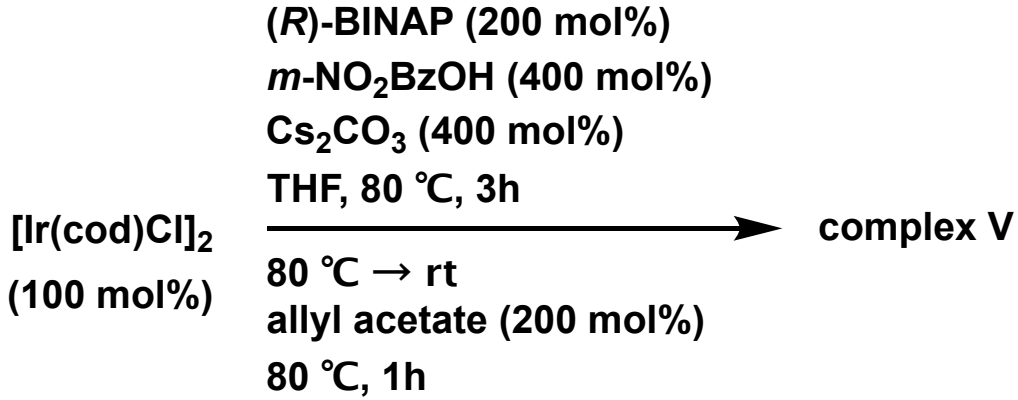
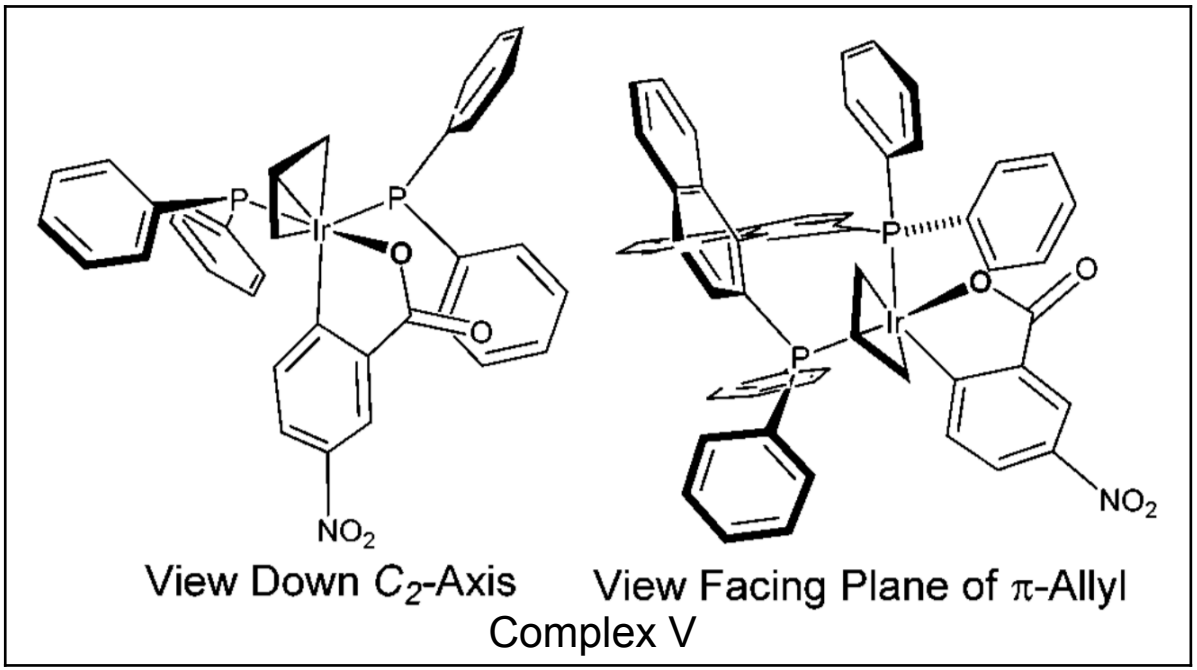
Catalytically Active *ortho*-cyclometalated iridium(Ⅲ)-π-allyl complex V





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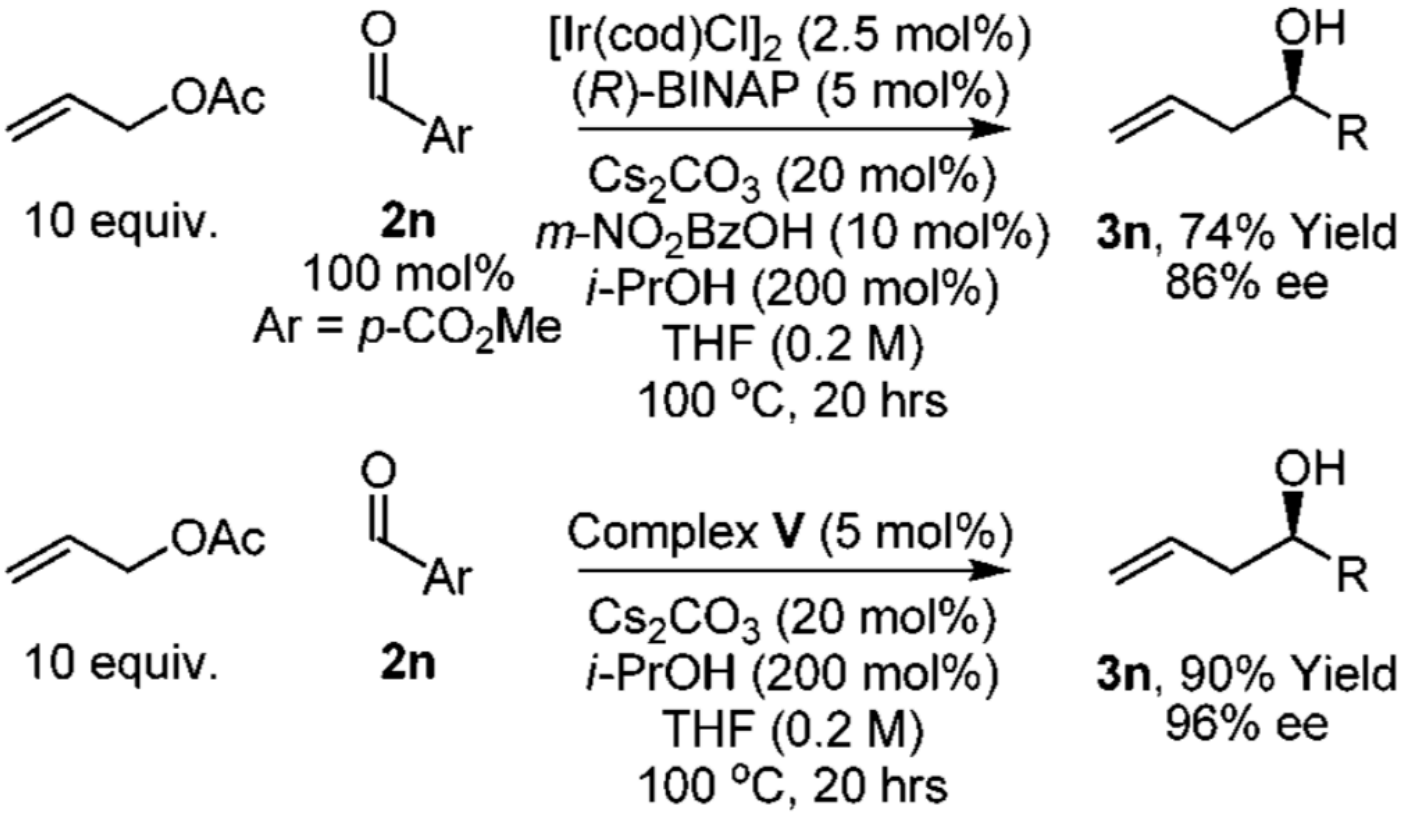
Experiments Corroborating Intervention of *Ortho*-Cyclometalated Iridium(Ⅲ)-π-Allyl Complex(V) as a Catalytically Relevant Entity



- Carbonyl allylation products are also accessible from aldehydes when employing isopropanol as a hydrogen donor
- Complex V serves as an active catalyst in the transfer hydrogenative carbonyl allylation of aldehyde 2n under standard conditions, suggesting that complex V is indeed catalytically relevant

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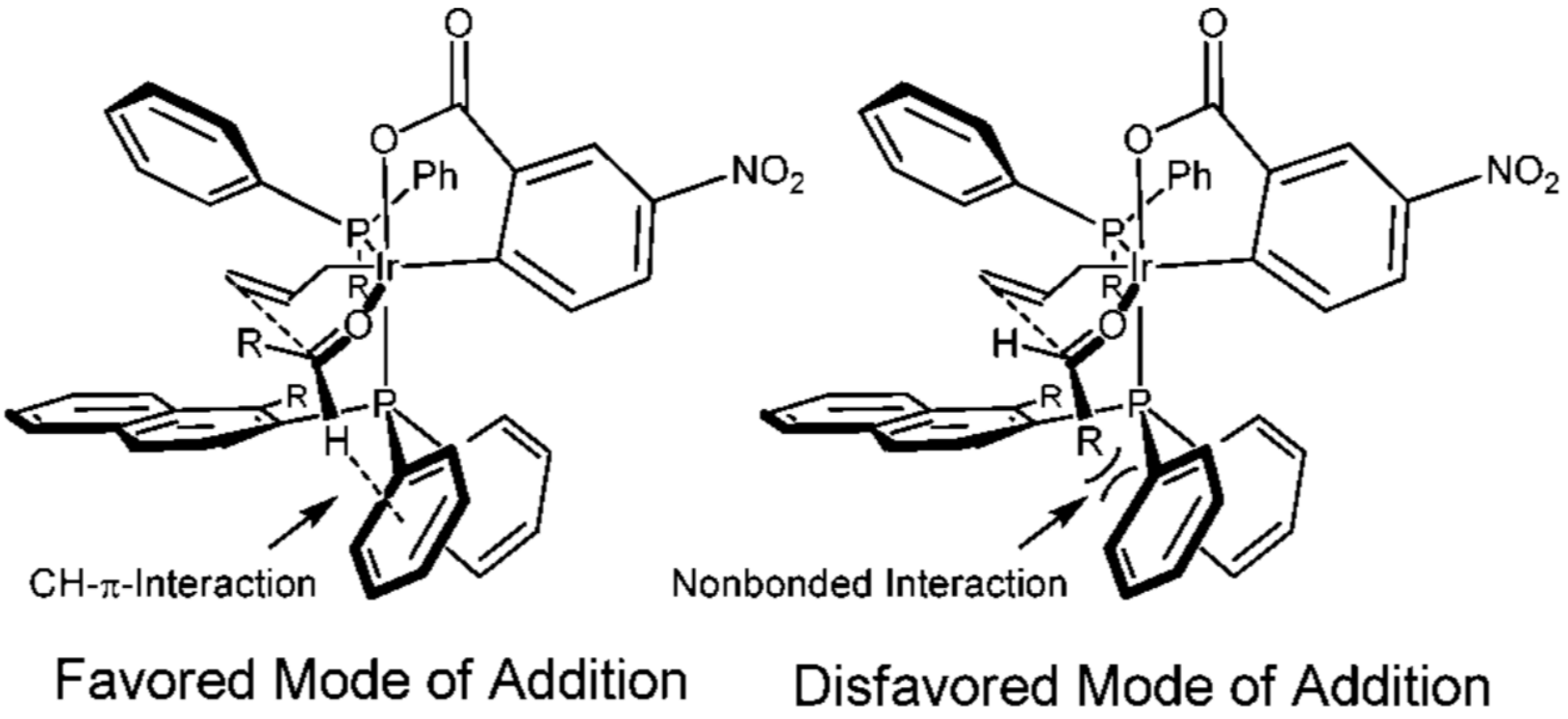
Proposed Stereochemical Model



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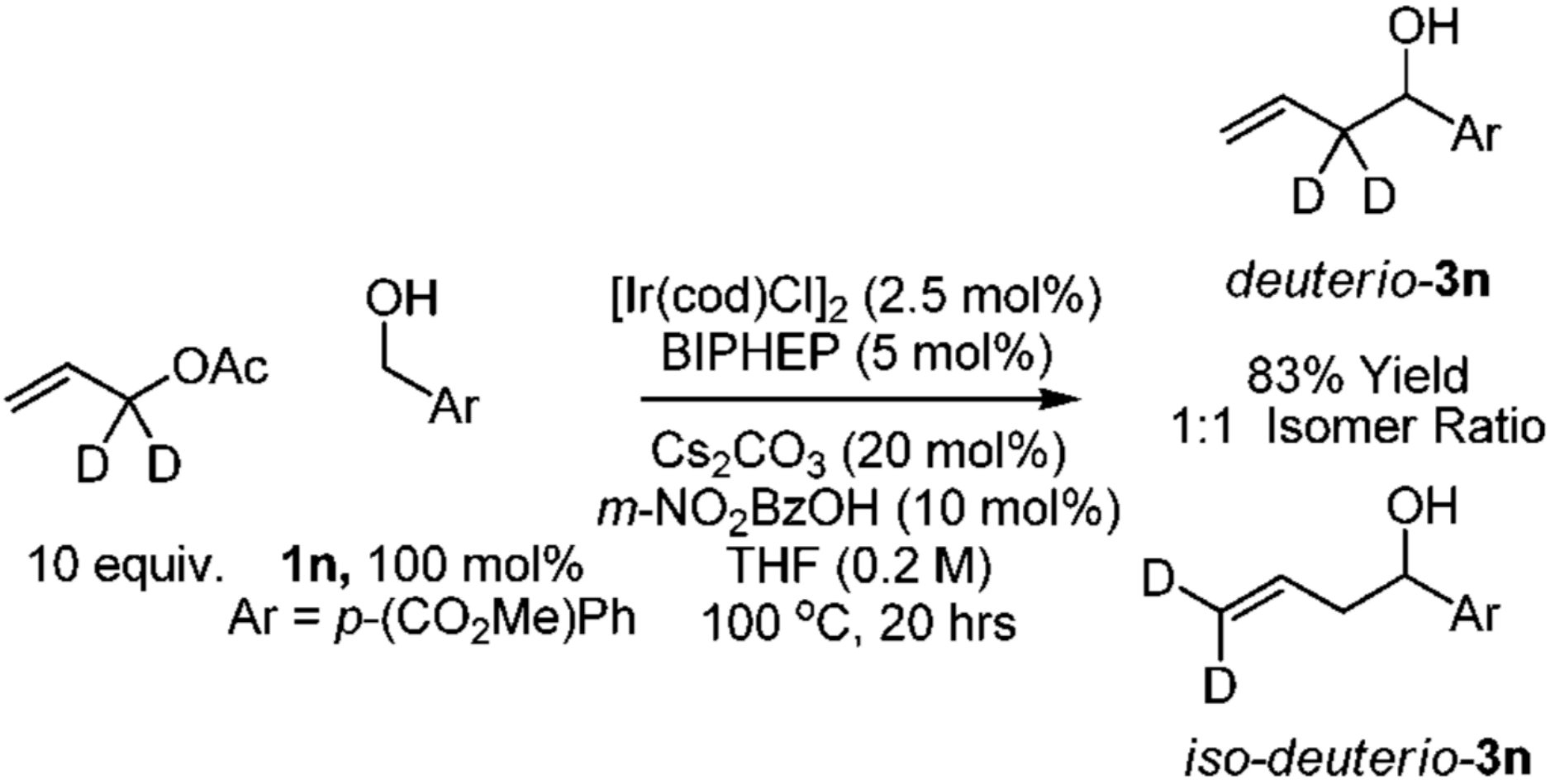
Ir-Catalyzed Transfer Hydrogenative Allylation of Benzylic Alcohol Employing Isotopically Labeled Allyl Acetate



- Intervention of rapid interconversion of allyl haptomers through the agency of a symmetric π-allyl is supposed

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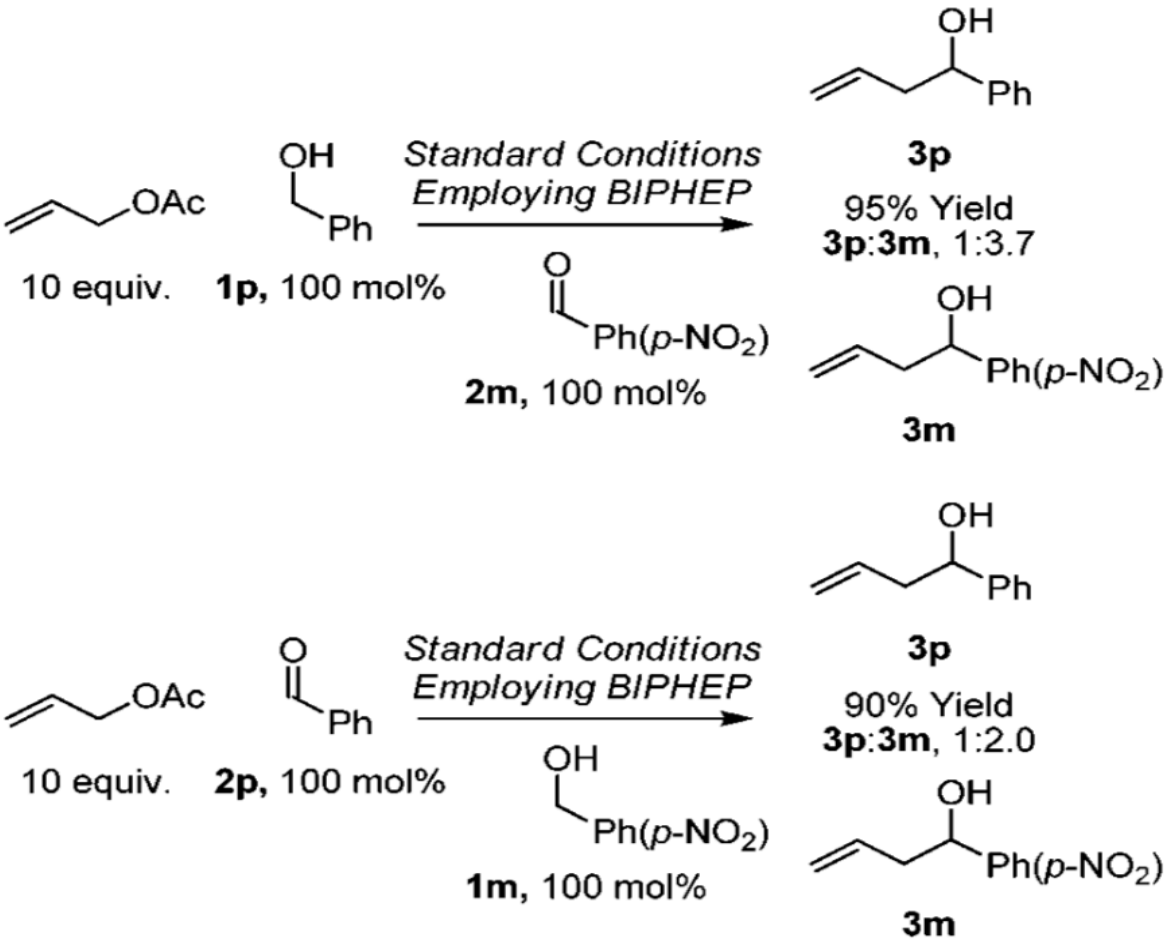
Experiments Establishing Rapid Redox Equilibration in Advance of Carbonyl Addition



- A very similar product distribution and yield are obtained, establishing rapid redox equilibration in advance of C-C coupling

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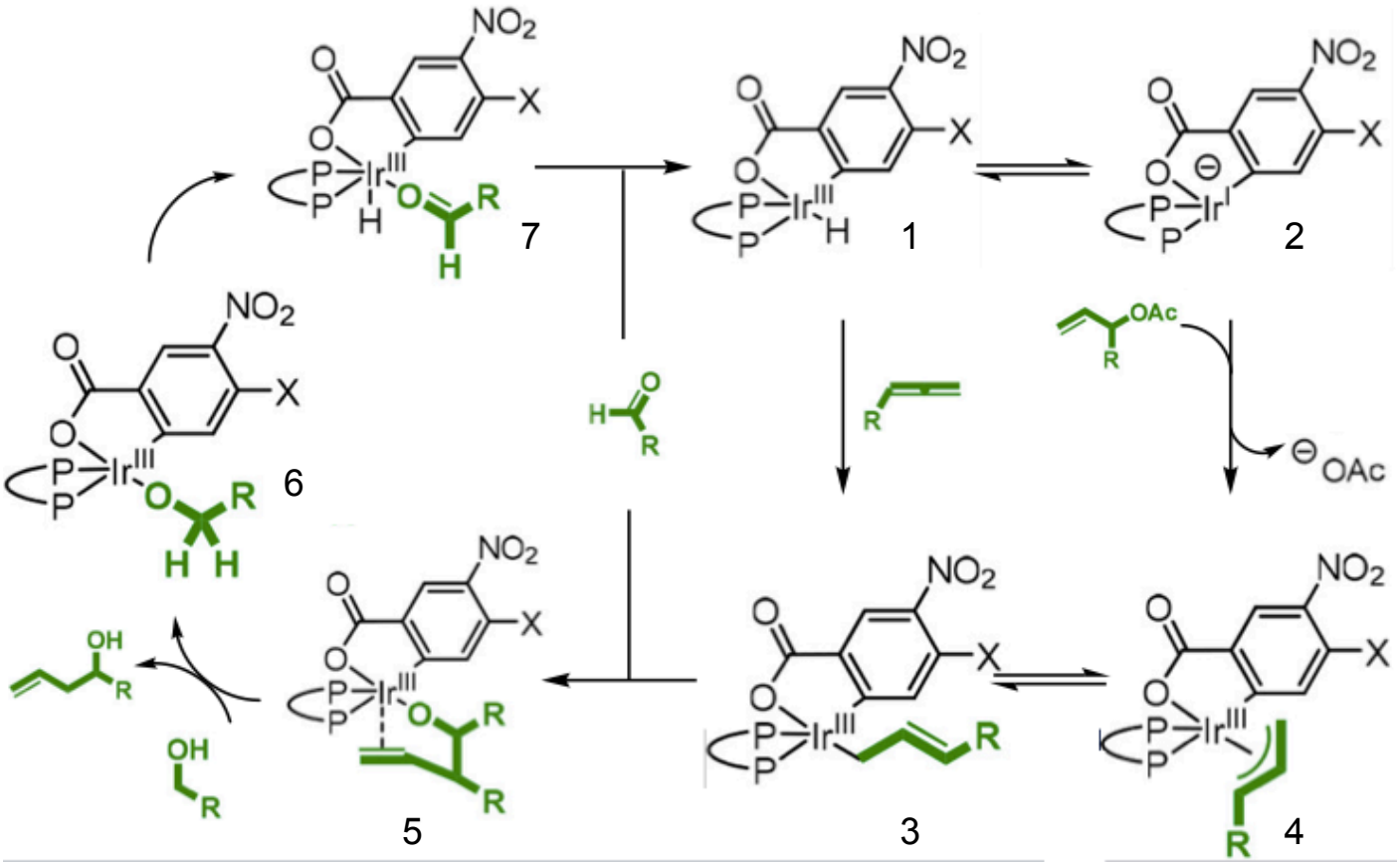
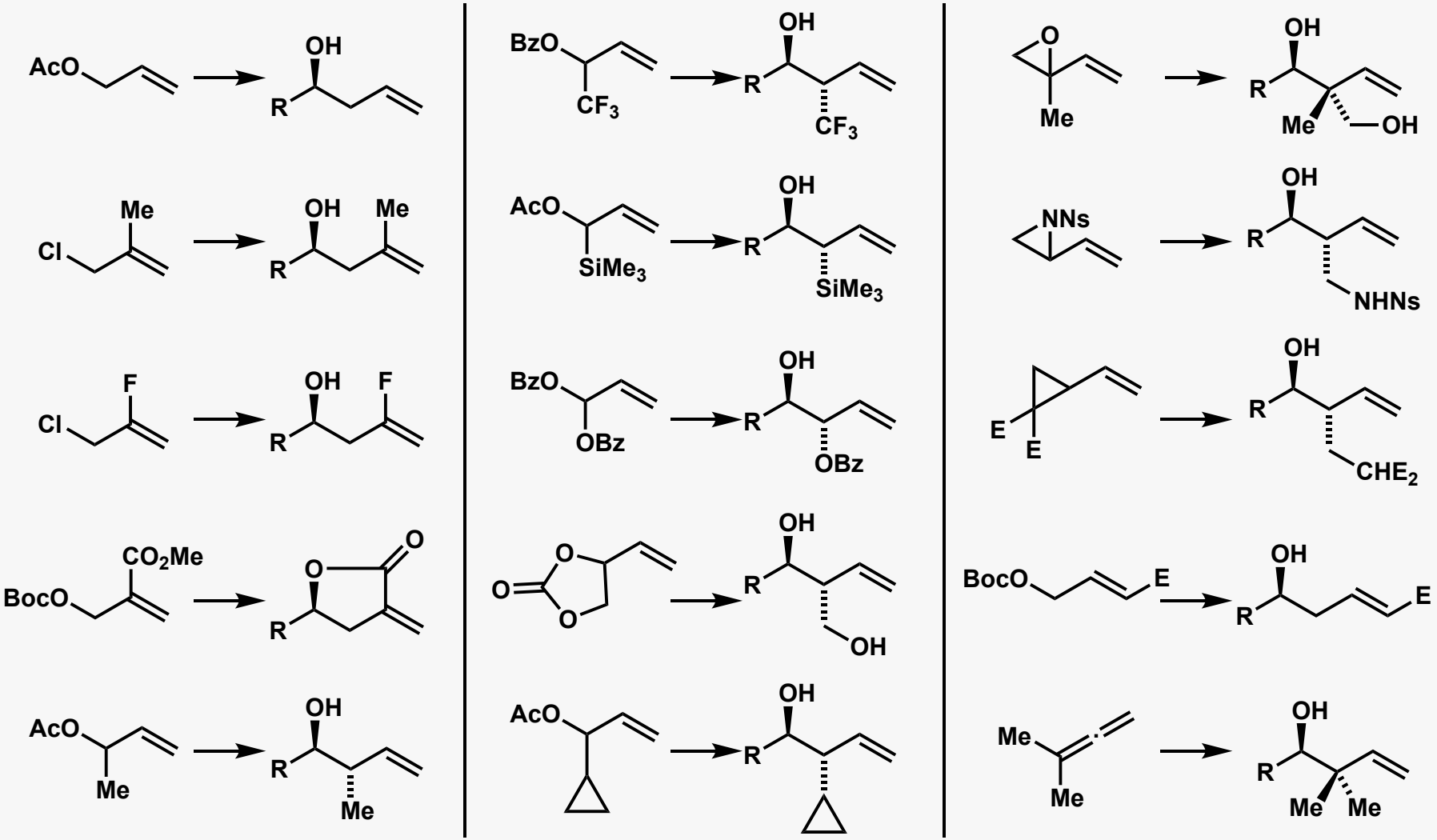
Proposed Catalytic Mechanism



- Dehydrogenation of the secondary alcohol products is prevented by internal chelation of the homoallylic olefin

Michael J. Krische. et al. *Acc. Chem. Res.*, **2017**, 50, 2371.

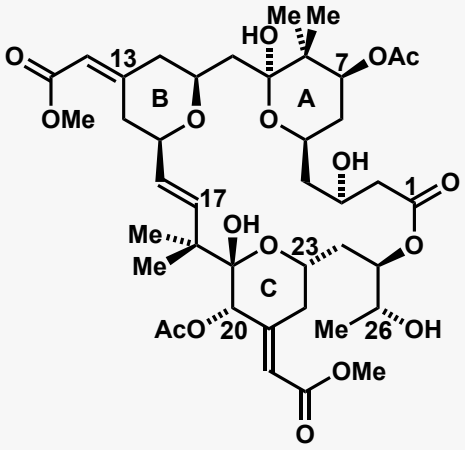
Survey of Enantioselective Alcohol C-H Allylations via Iridium-Catalyzed Hydrogen Transfer



E = CO_2Me > 99% ee

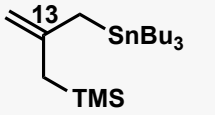
Michael J. Krische. et al. *Acc. Chem. Res.*, **2017**, 50, 2371.

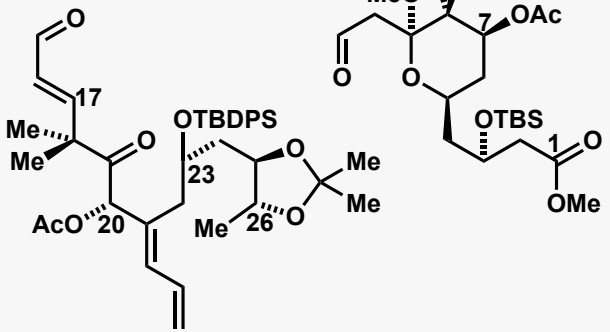
Retrosynthetic Analysis of Bryostatin 7



Bryostatin 7

20 Steps (LLS), 36 Total Steps
5 C-C Bonds Formed via
Hydrogen-Mediated C-C Coupling



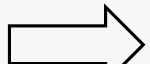


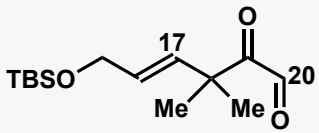
Fragment A
(10 Steps)

Fragment B
(10 Steps)

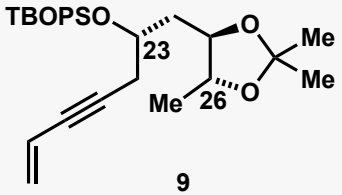
Fragment A

1 C-C Bond Formed via
Hydrogenative Coupling
C20-C21





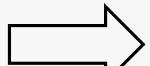
6
(6 Steps)

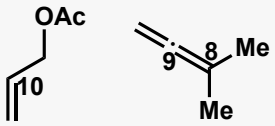


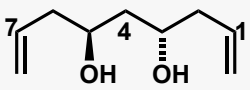
9
(6 Steps)

Fragment B

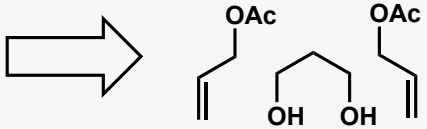
4 C-C Bonds Formed via
Hydrogenative Coupling
C2-C3, C5-C6, C7-C8,
C9-C10





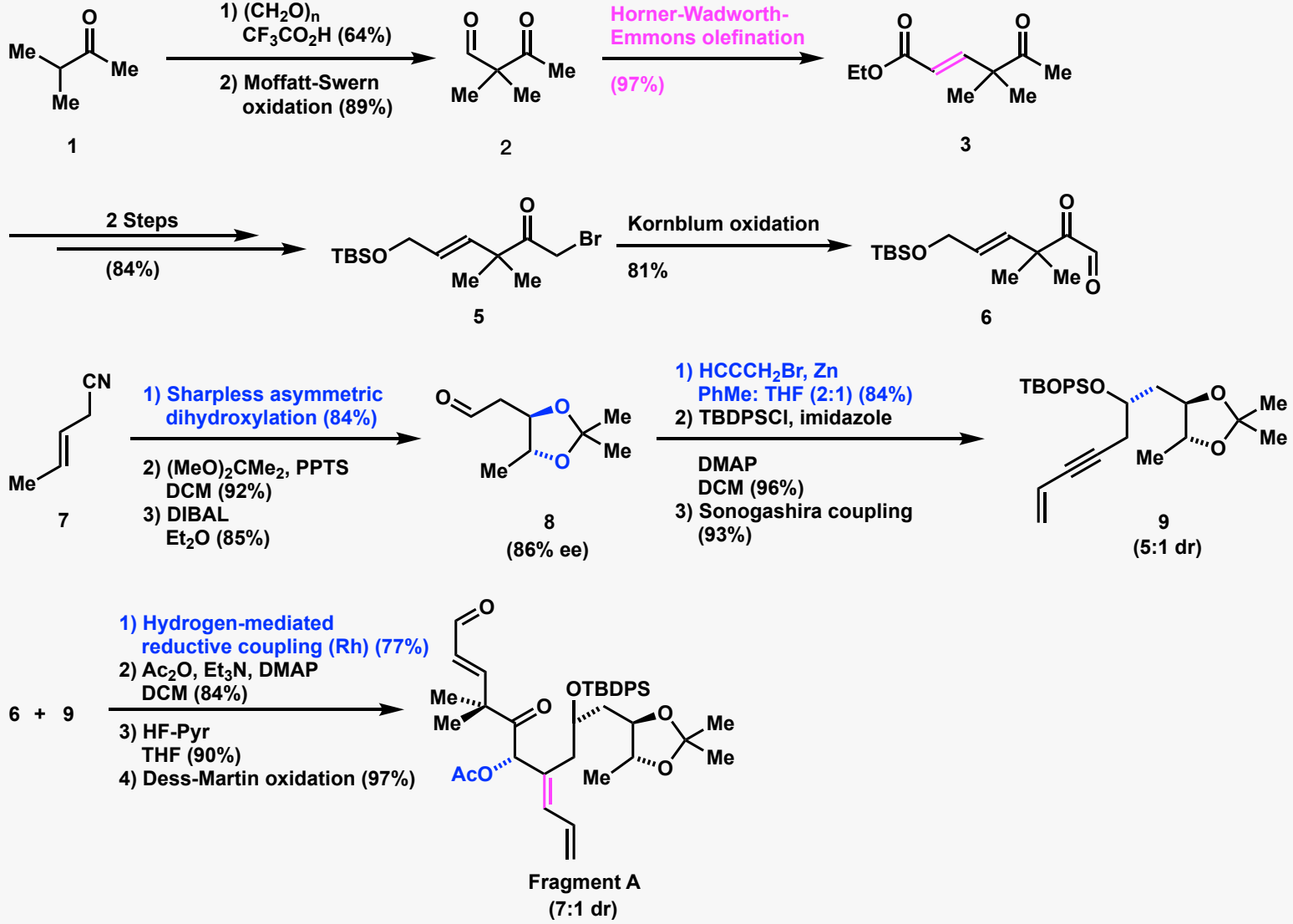


11
(1 Step)



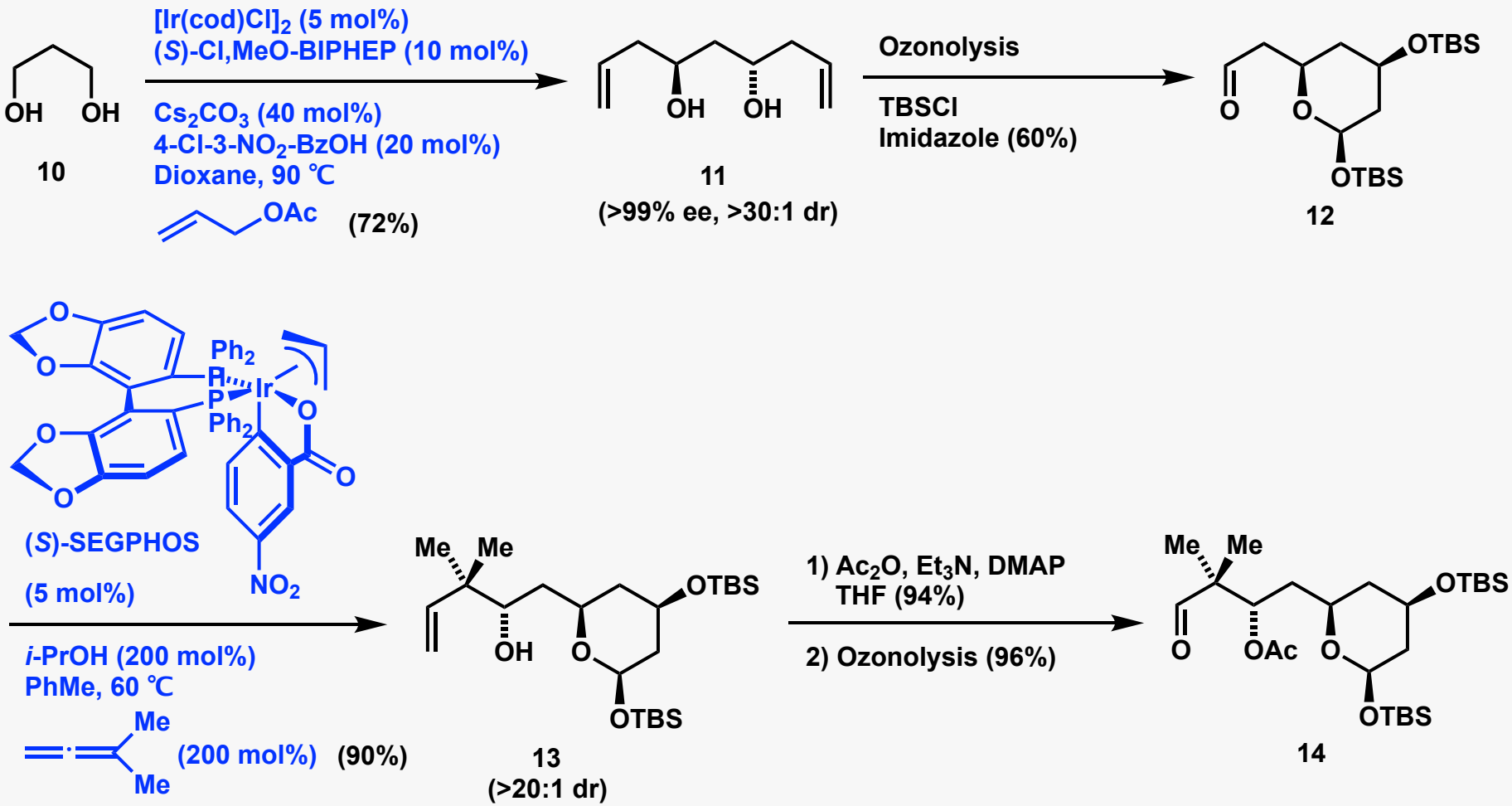
Michael J. Krische. et al. *J. Am. Chem. Soc.*, **2011**, 133, 13876.

Synthesis of Fragment A



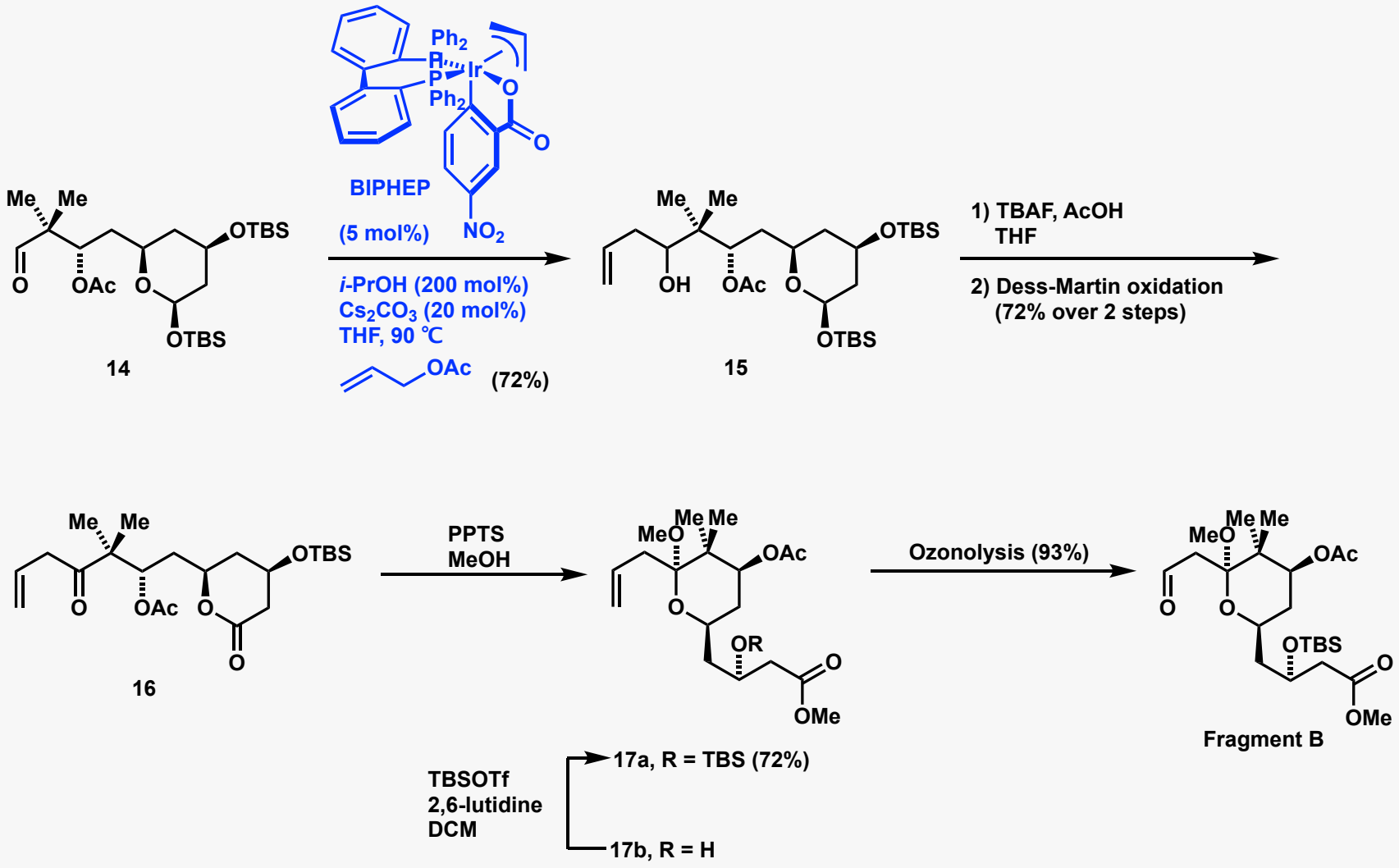
Michael J. Krische. et al. *J. Am. Chem. Soc.*, **2011**, 133, 13876.

Synthesis of Fragment B Employing Multiple Transfer Hydrogenative C-C Bond Formations (1)



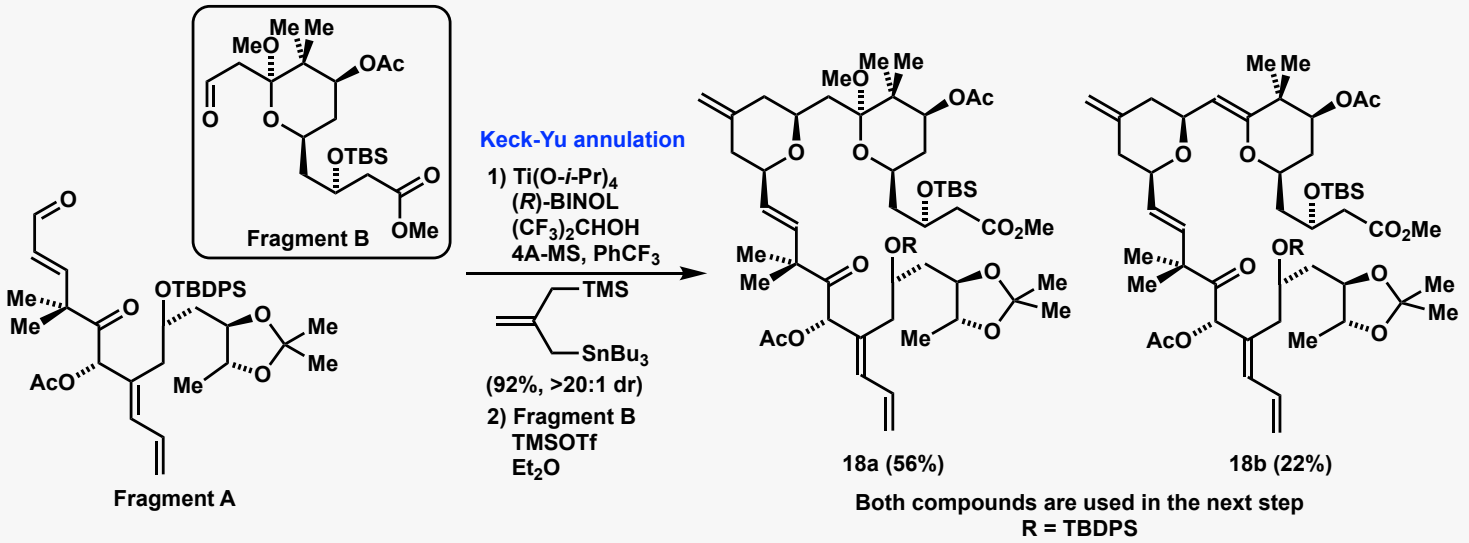
Michael J. Krische. et al. *J. Am. Chem. Soc.*, **2011**, 133, 13876.

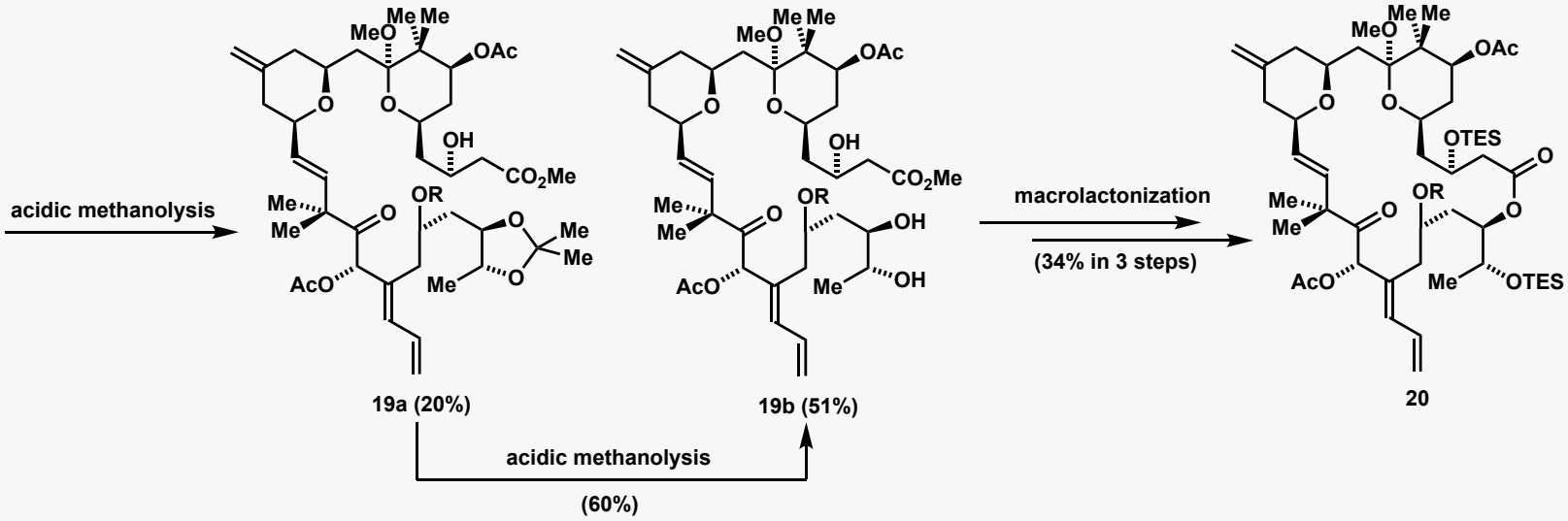
Synthesis of Fragment B Employing Multiple Transfer Hydrogenative C-C Bond Formations (2)



Michael J. Krische. et al. *J. Am. Chem. Soc.*, **2011**, 133, 13876.

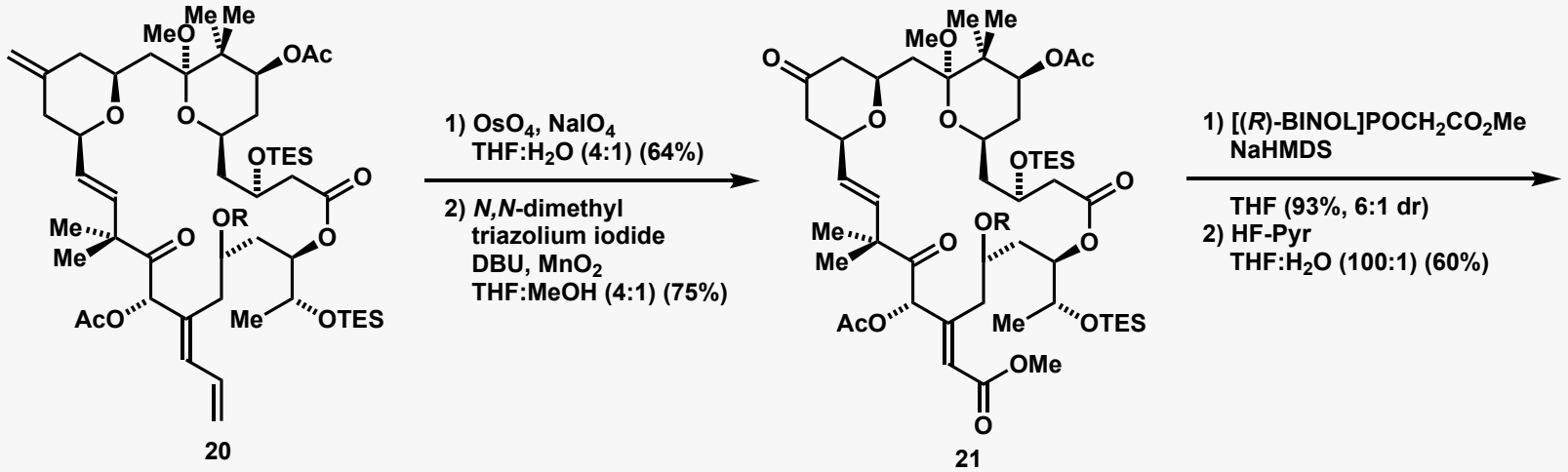
Union of Fragment A and Fragment B and Total Synthesis of Bryostatin 7 (1)

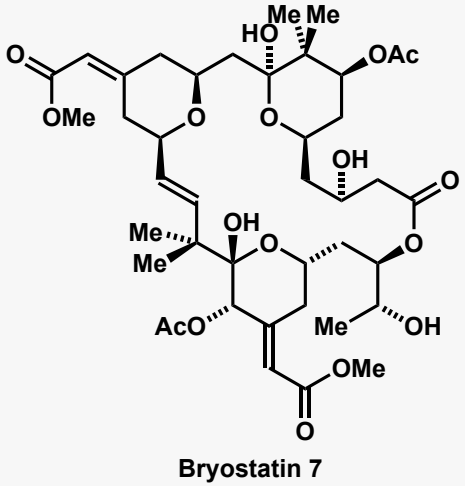




Michael J. Krische. et al. *J. Am. Chem. Soc.*, **2011**, 133, 13876.

Union of Fragment A and Fragment B and Total Synthesis of Bryostatin 7 (2)





Bryostatin 7

- Prepared in 20 steps (longest linear sequence) and 36 total steps, representing the most concise route to any bryostatin reported, to date
- Carbonyl allylation products could generate in a single manipulation and form as single enantiomers by utilizing hydrogenative methods
- Hydrogenative methods could bypass the requirement of stoichiometric metals

Michael J. Krische. et al. *J. Am. Chem. Soc.*, **2011**, 133, 13876.

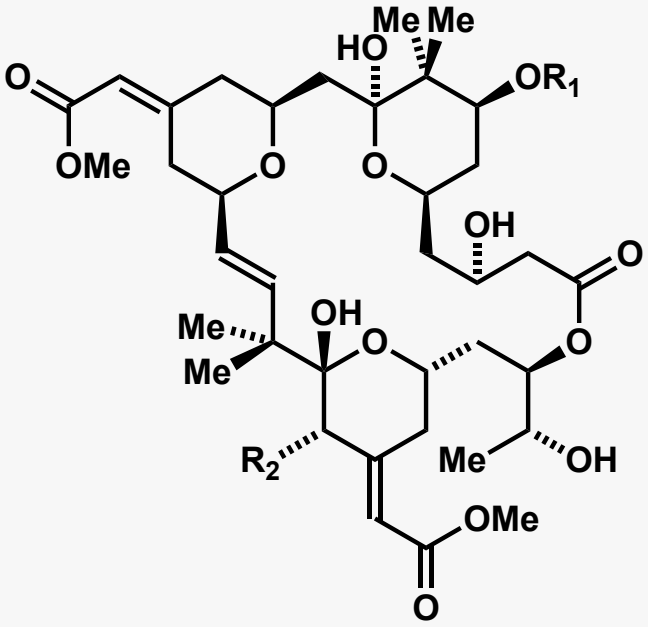
4. Summary

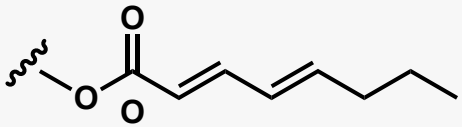
Summary

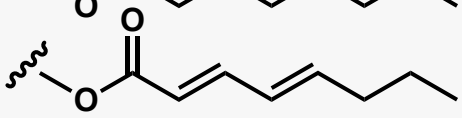
- Bryostatins are potent modulators of protein kinase C with promising biological activity.
- Total synthesis of Bryostatins 1, 2, 3, 7, 9, and 16 has been reported.
- Multiple transfer hydrogenative C-C bond formations reported by Krische, which was utilized in the total synthesis of Bryostatin 7 in 2011 simplified the total synthesis of Bryostatins.

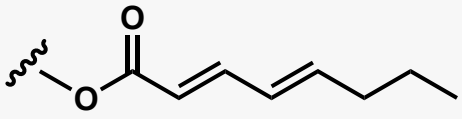
Appendix

Appendix 1. Structure of Bryostatins (1)

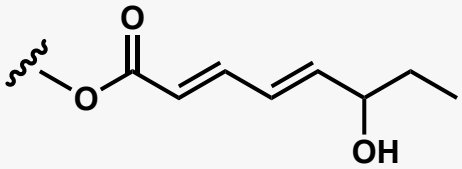


1: R_1 = Ac, R_2 = 

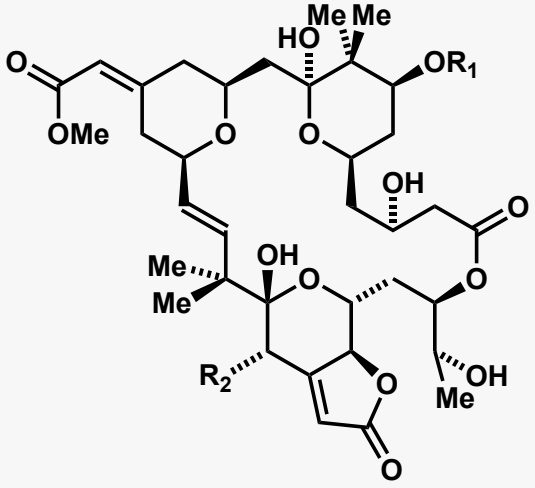
2: R_1 = H, R_2 = 

4: R_1 = $OCOCH_2CH(CH_3)_2$, R_2 = $OCO(CH_2)_2CH_3$
5: R_1 = $OCOCH_2CH(CH_3)_2$, R_2 = OAc
6: R_1 = $OCO(CH_2)_2CH_3$, R_2 = OAc
7: R_1 = OAc, R_2 = OAc
8: R_1 = $OCO(CH_2)_2CH_3$, R_2 = $OCO(CH_2)_2CH_3$
9: R_1 = Ac, R_2 = $OCO(CH_2)_2CH_3$
10: R_1 = Piv, R_2 = H
11: R_1 = Ac, R_2 = H
12: R_1 = $CO(CH_2)_2CH_3$, R_2 = 

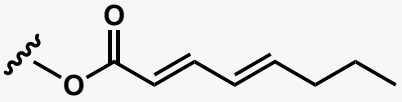
13: R_1 = $CO(CH_2)_2CH_3$, R_2 = H
14: R_1 = Piv, R_2 = OH

15: R_1 = Ac, R_2 = 

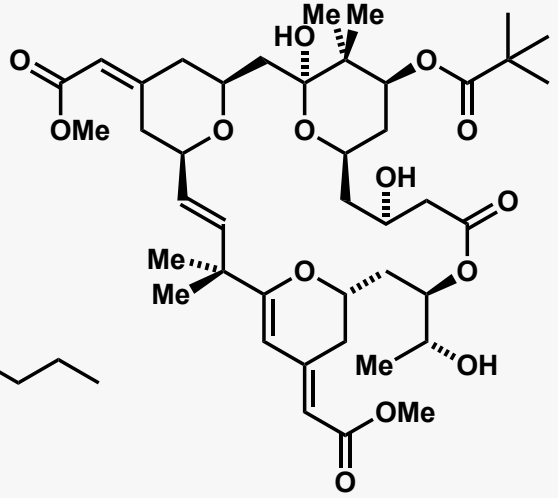
Appendix 1. Structure of Bryostatins (2)



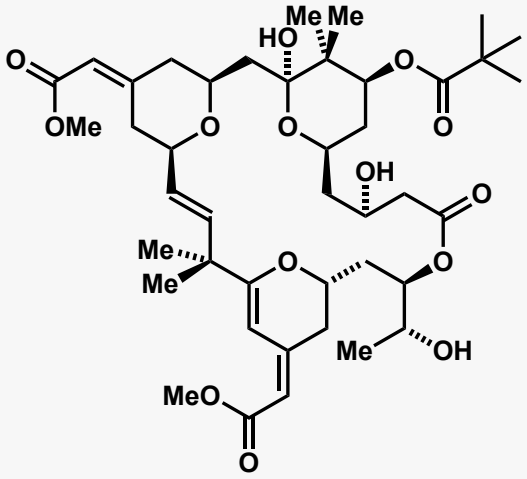
3: R_1 = Ac, R_2 =



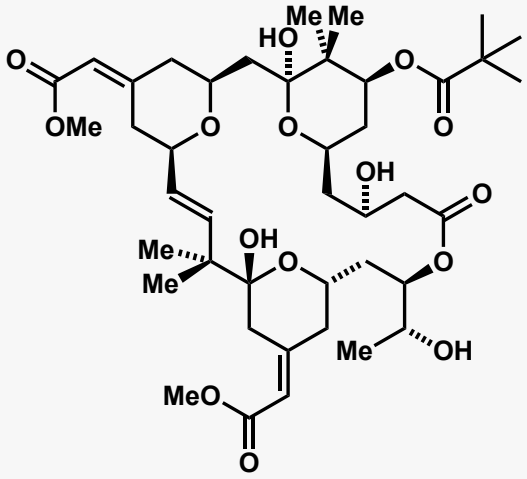
20: R_1 = Piv, R_2 = H



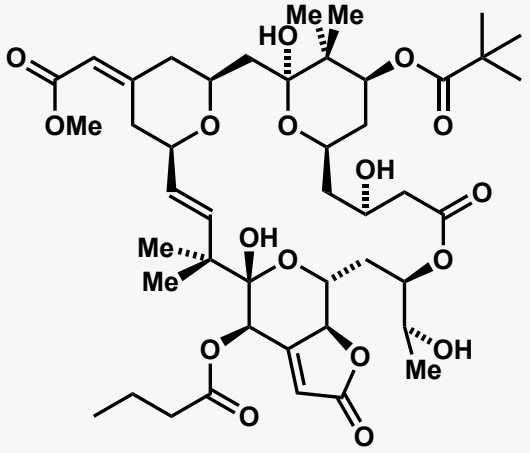
Bryostatin 16



Bryostatin 17

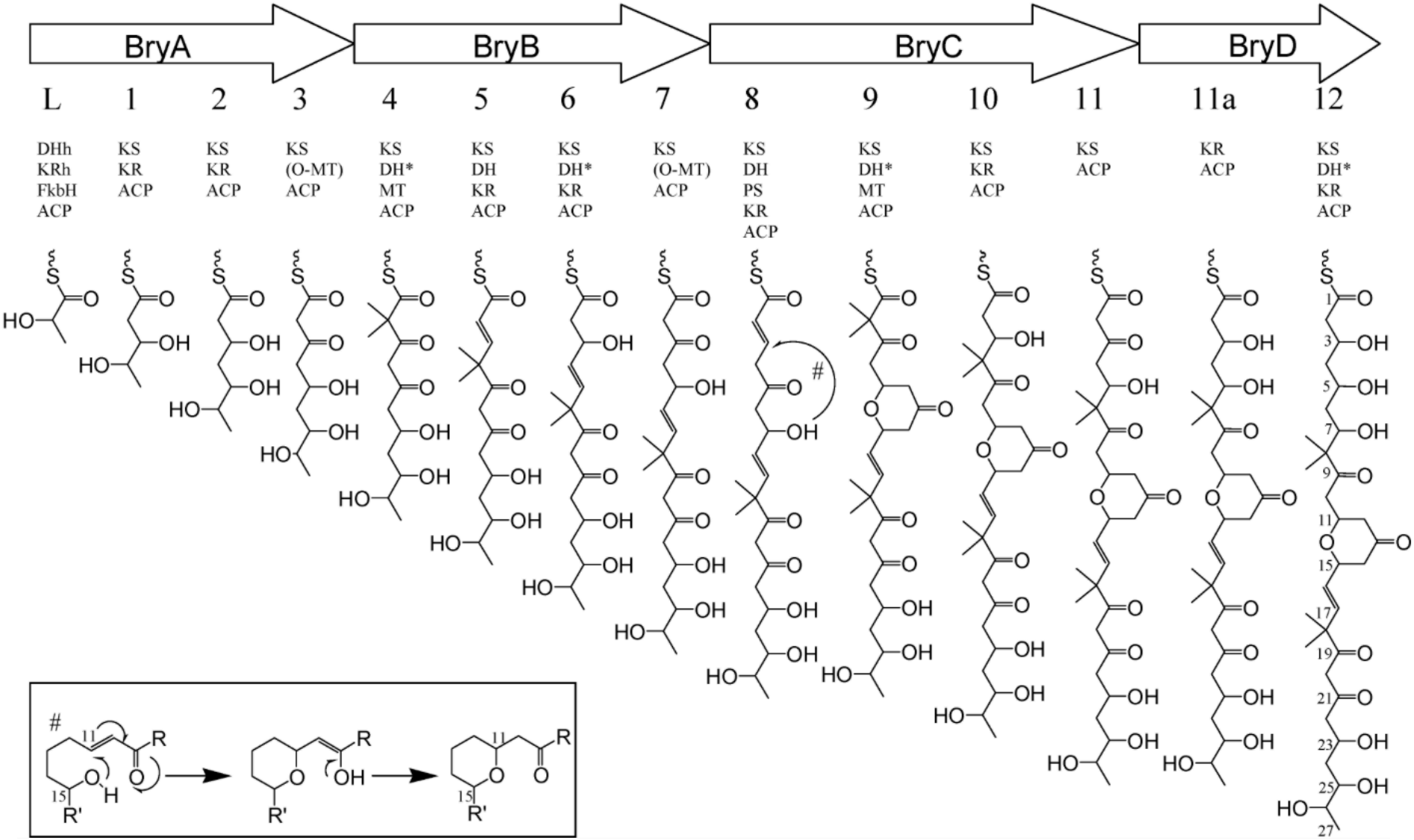


Bryostatin 18



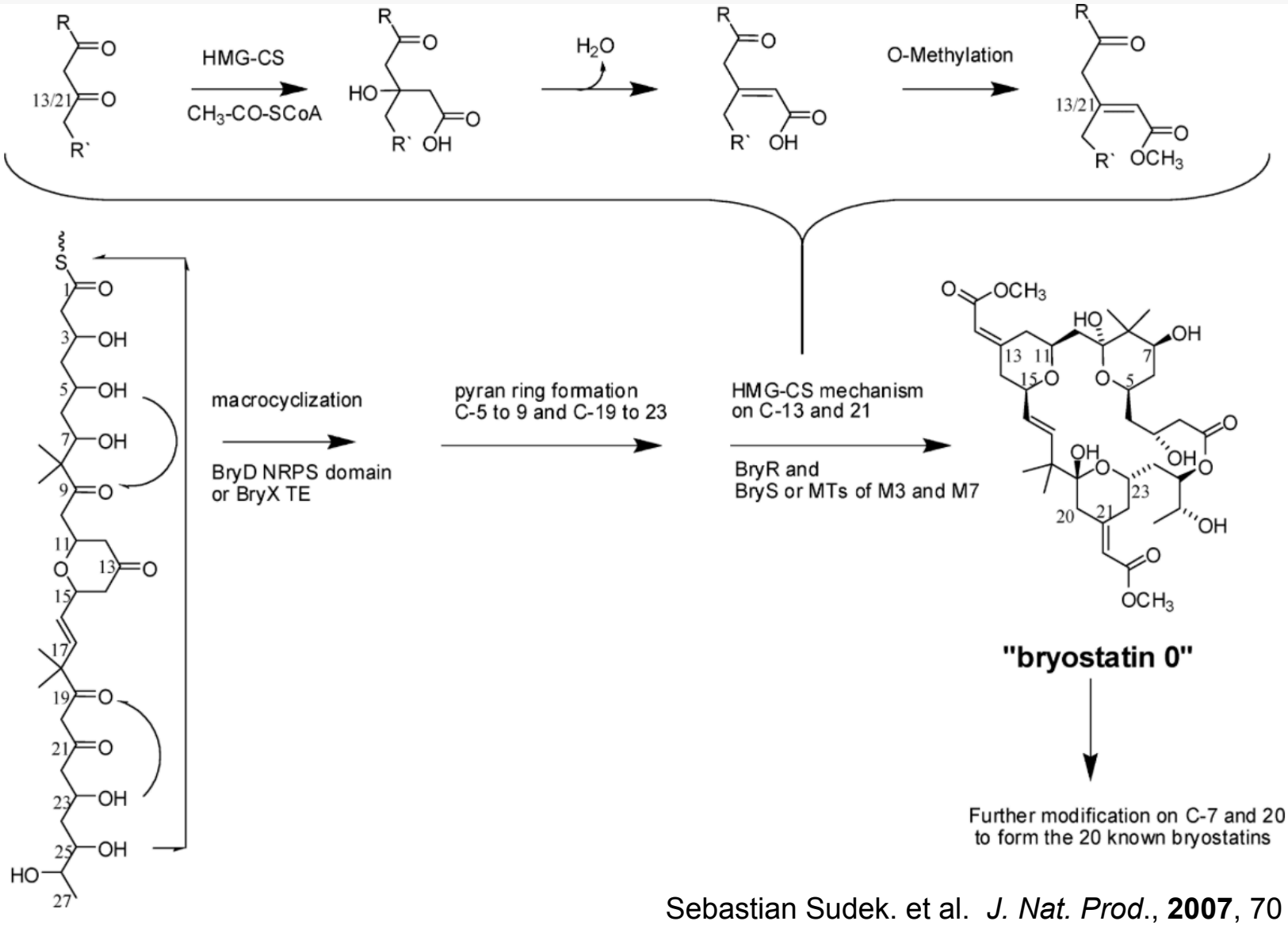
Bryostatin 19

Appendix 2. Biosynthesis of Bryostatin (1)



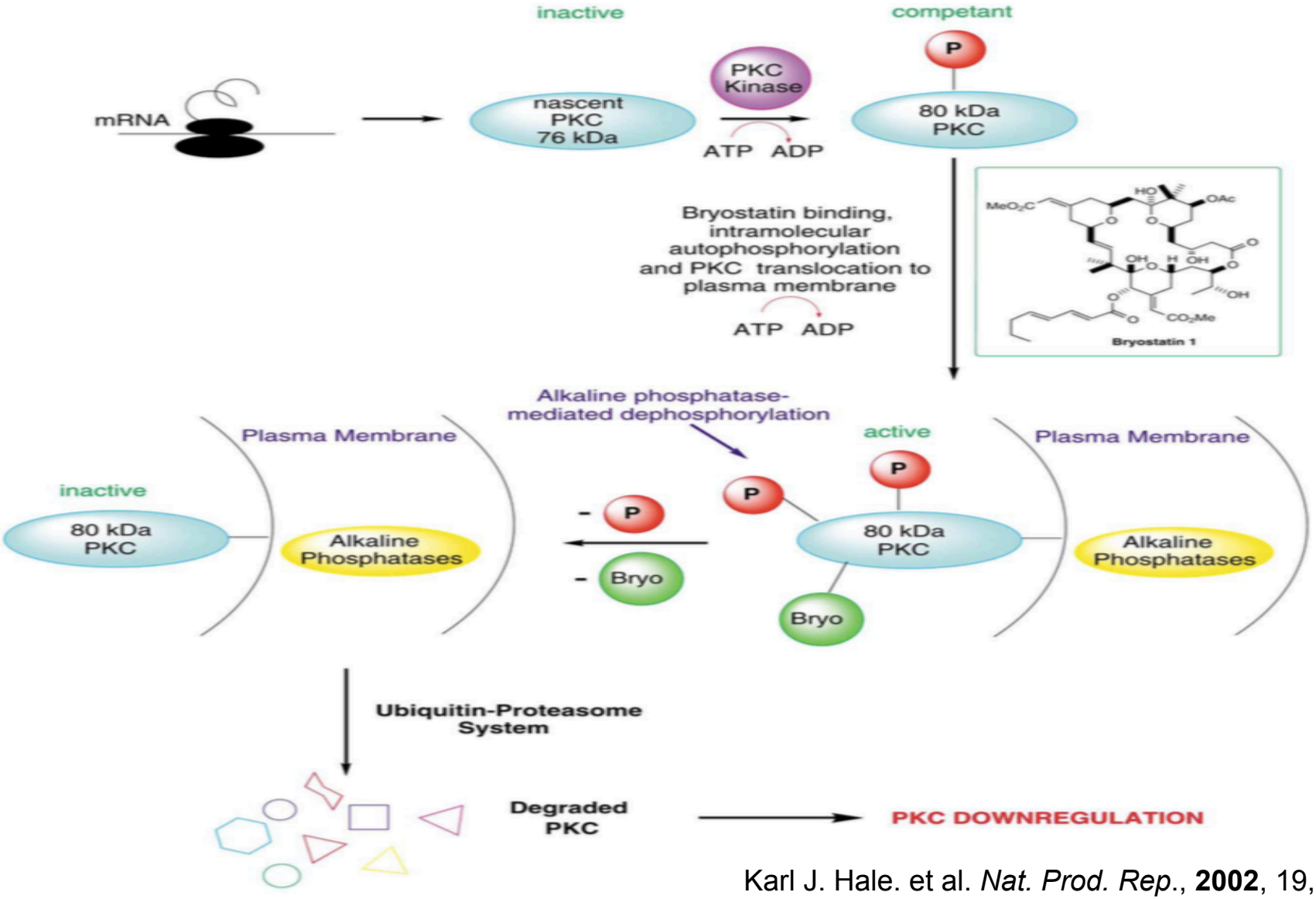
Sebastian Sudek. et al. *J. Nat. Prod.*, **2007**, 70 (1), 67.

Appendix 2. Biosynthesis of Bryostatin (2)



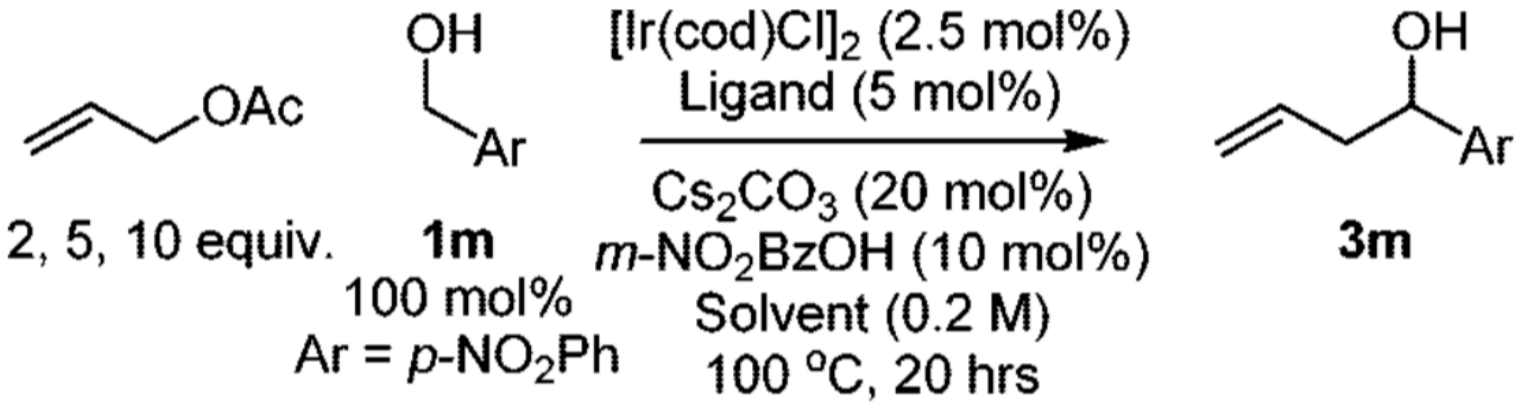
Sebastian Sudek. et al. *J. Nat. Prod.*, **2007**, 70 (1), 67.

Appendix 3. Hypothetical pathway of PKC synthesis and downregulation by bryostatin 1



Karl J. Hale. et al. *Nat. Prod. Rep.*, **2002**, 19, 413.

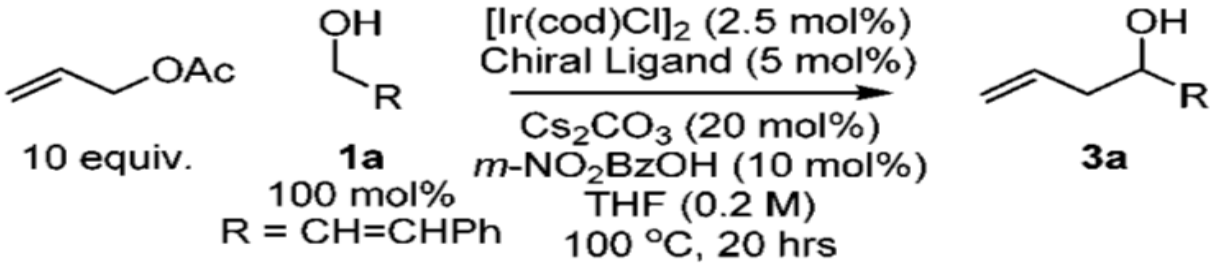
Appendix 4. Effect of Allyl Acetate Loading, Solvent, and Ligand in the Transfer Hydrogenative Allylation



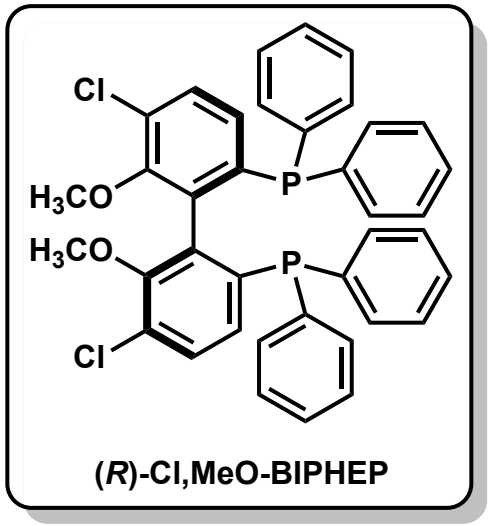
Entry	Solvent	Ligand	Allyl Acetate (mol%)	Yield (%)
1	**THF**	**BIPHEP**	**1000**	**80**
2	THF	BIPHEP	500	68
3	THF	BIPHEP	200	67
4	Dioxane	BIPHEP	200	68
5	Toluene	BIPHEP	200	13
6	DCE	BIPHEP	200	15
7	THF	PPh_3	1000	8

Michael J. Krische. et al. *J. Am. Chem. Soc.*, **2008**, 130, 14891.

Appendix 5. Effect of Chiral Ligand and Temperature in the Transfer Hydrogenative Allylation



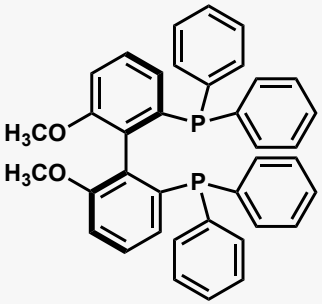
	Entry	T °C	Chiral Ligand	Yield (%)	ee (%)
T °C ⇩	**1**	**100**	**(*R*)-Cl,MeO-BIPHEP**	**71**	**91 (*R*)**
	2	80	(*R*)-Cl,MeO-BIPHEP	61	93 (*R*)
	3	120	(*R*)-Cl,MeO-BIPHEP	59	90 (*R*)
Chiral Ligand	4	100	(*R*)-MeO-BIPHEP	69	80 (*R*)
	5	100	(*R*)-BINAP	64	90 (*R*)
	6	100	(*R*)-tol-BINAP	51	88 (*R*)
	7	100	(-)-TMBTP	59	82 (*R*)
	8	100	(*S*)-C1-TUNEPHOS	80	70 (*S*)
	9	100	(*R*)-C2-TUNEPHOS	77	77 (*R*)
	10	100	(*S*)-C3-TUNEPHOS	72	78 (*S*)
	11	100	(*S*)-C4-TUNEPHOS	57	80 (*S*)
	12	100	(*R*)-H8-BINAP	68	85 (*R*)
	13	100	(*S*)-BIPHEMP	68	80 (*R*)
	14	100	CTH-(*S*)-P-PHOS	71	86 (*S*)
	15	100	(*R*)-SOLPHOS	41	40 (*R*)
	16	100	(*S*)-SEGPHOS	69	78 (*S*)
	17	100	(*R*)-SYNPHOS	69	83 (*R*)



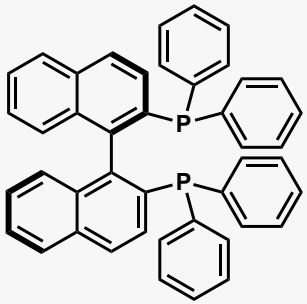
(*R*)-Cl,MeO-BIPHEP

Michael J. Krische. et al. *J. Am. Chem. Soc.*, **2008**, 130, 14891.

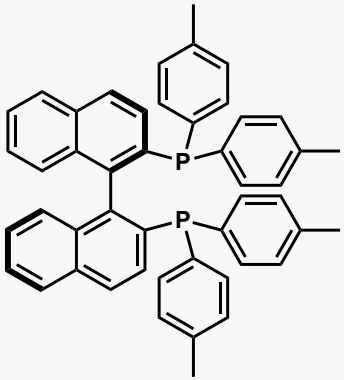
Appendix 6. Chiral Ligands



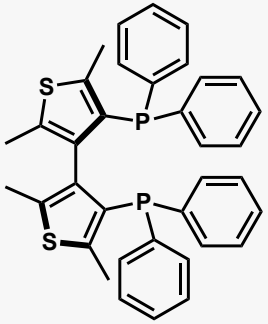
(*R*)-MeO-BIPHEP



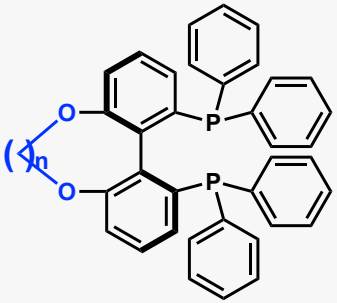
(*R*)-BINAP



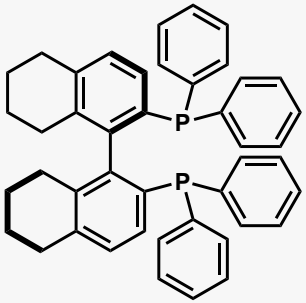
(*R*)-tol-BINAP



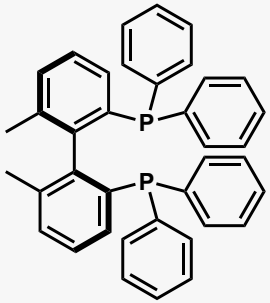
(-)-TMBTP



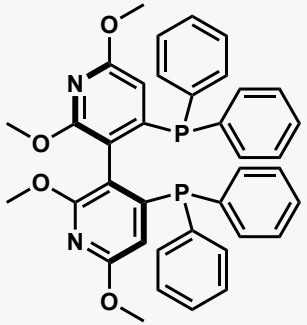
(*S*)-Cn-TUNEPHOS



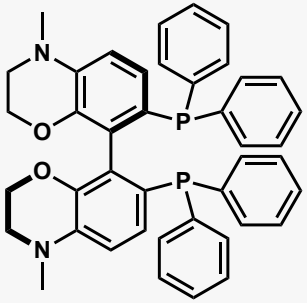
(*R*)-H8-BINAP



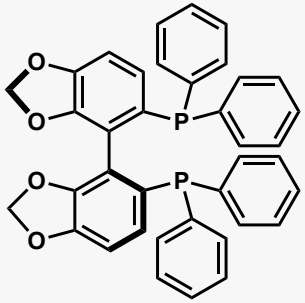
(*S*)-BIPHEMP



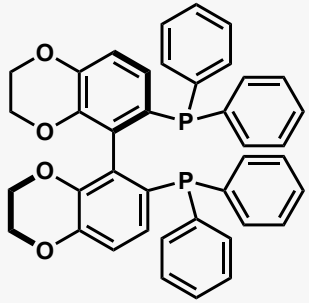
CTH-(*S*)-P-PHOS



(*R*)-SOLPHOS

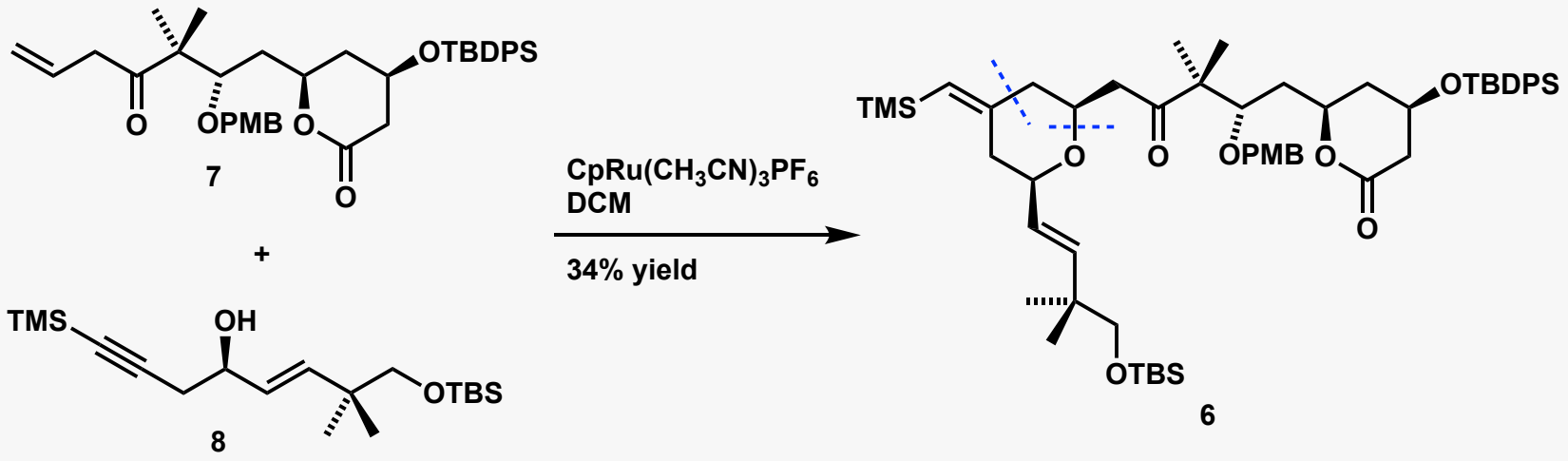


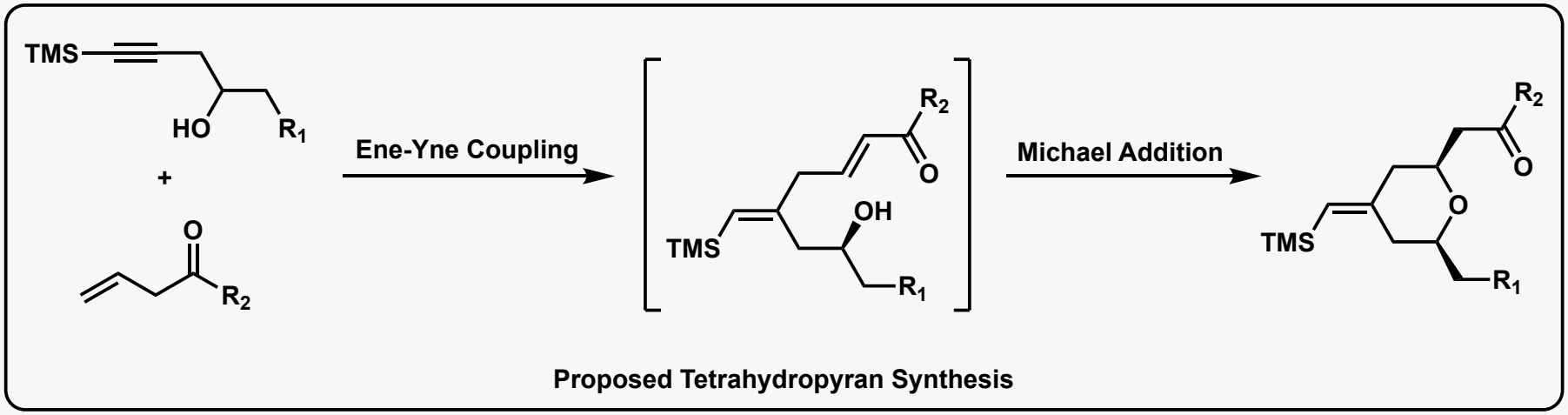
(*S*)-SEGPHOS



(*R*)-SYNPHOS

Appendix 7. Total Synthesis of Bryostatin 16 by Trost (2008) (1)

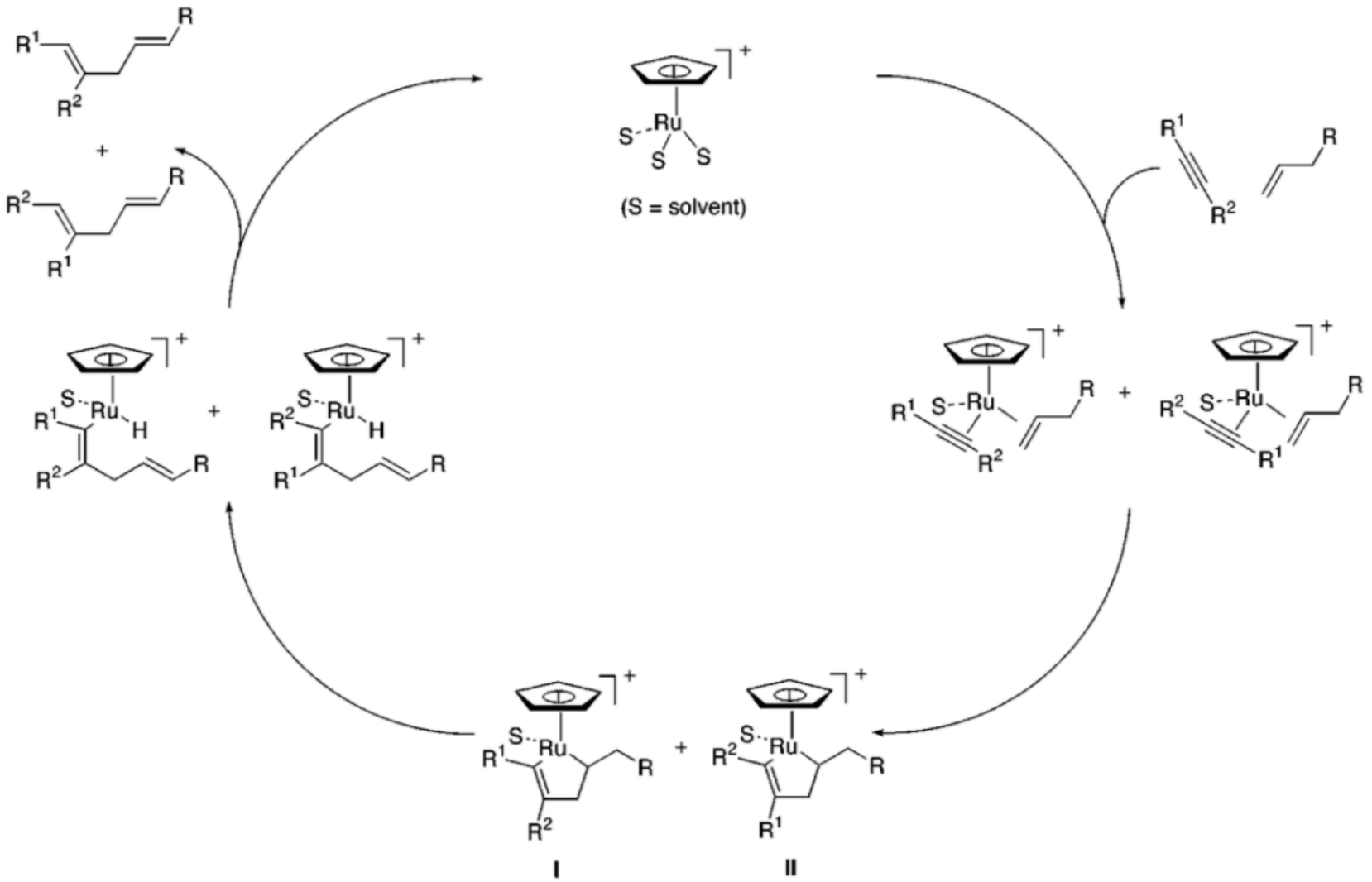




Trost, B. M. et al. *Nature*. **2008**, 456, 485.

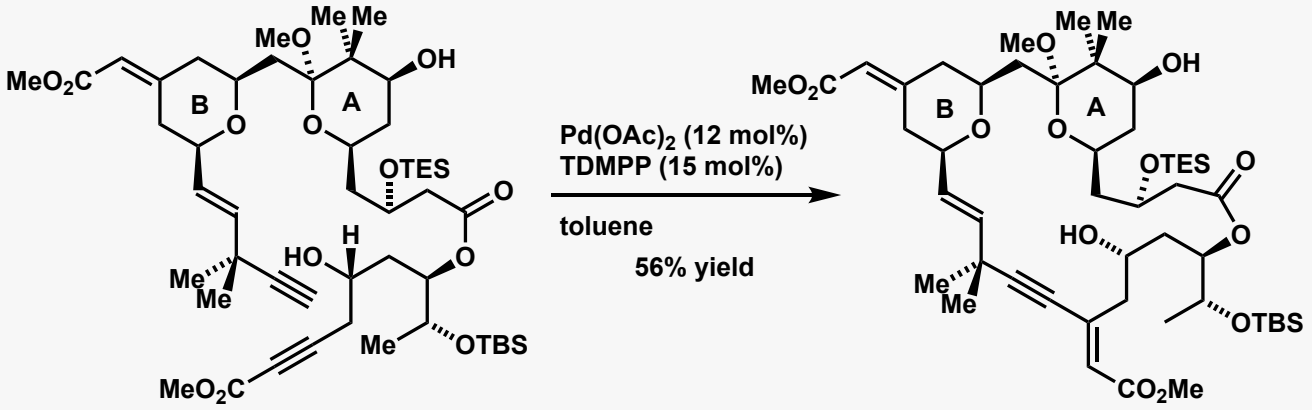
Appendix 8. Mechanistic Proposal for Ru-Catalyzed Alkene-Alkyne Addition

Scheme 1. Mechanistic Proposal for Ru-Catalyzed Alkene−Alkyne Addition

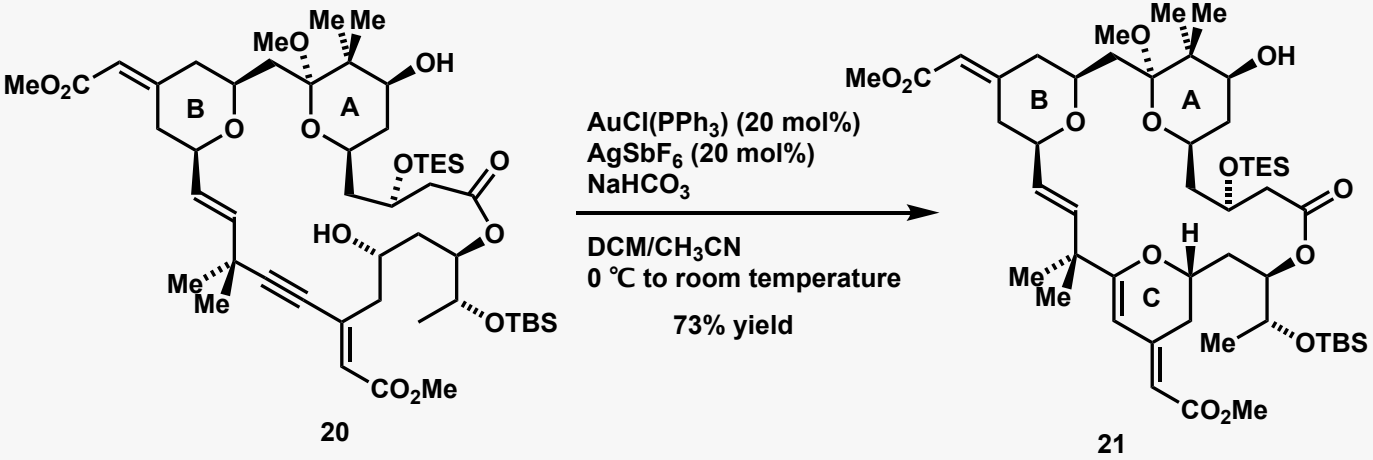


Trost, B. M. et al. *Org. Lett.*, **2000**, 2 (12), 1761.

Appendix 9. Total Synthesis of Bryostatin 16 by Trost (2008) (2)



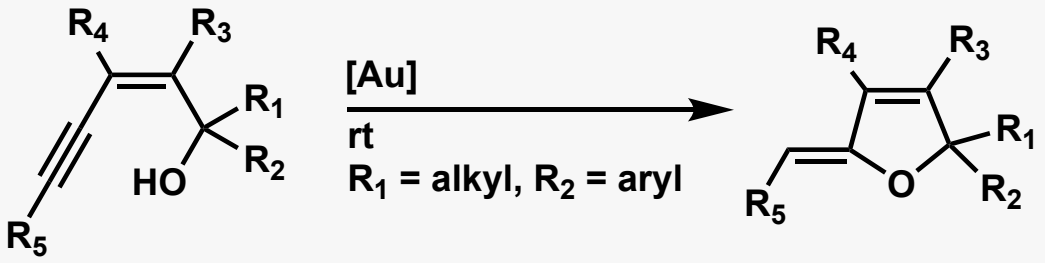
- Pd catalyst chemoselectively inserts into the carbon-hydrogen bond of the terminal alkyne



- Au catalyst gives *6-endo-dig* cyclization product selectively

Trost, B. M. et al. *Nature*. **2008**, 456, 485.

Appendix 10. *5-exo-dig* & *Z*-isomer Selectivity of Gold-Catalyzed Cyclization



1a **2a**

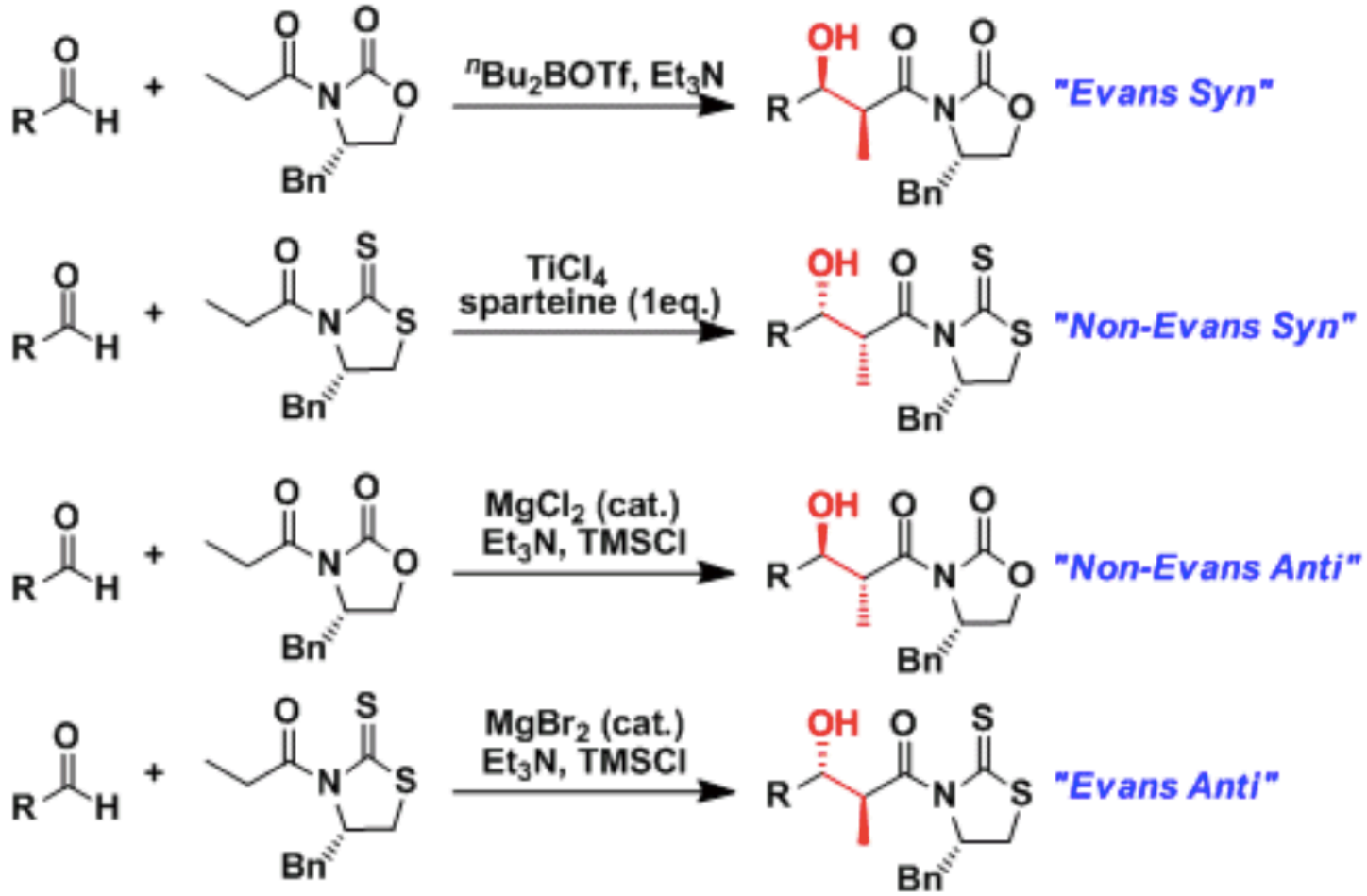
Condition A: 1% $AuCl_3$, in CH_2Cl_2
Condition B: 1% $(PPh_3)AuCl$, 1% AgOTf, in THF

enynol	R_1	R_2	R_3	R_4	R_5	condition	yield
1a	Me	*o*-ClC_6H_4	Ph	Ph	Ph	A, 3h	97%
1b	Me	Ph	Ph	Ph	Cy[c]	A, 1h	92%
1c	Me	*p*-FC_6H_4	Ph	Ph	Bu	A, 1h	89%
1d	Me	Ph	Ph	Ph	Ph	A, 3h	91%
1e	Me	*p*-FC_6H_4	C_3H_7	C_3H_7	Ph	B, 3h	84%
1f	Me	2-thienyl	Ph	Ph	*p*-MeC_6H_4	B, 3h	87%
1g	Me	*o*-ClC_6H_4	Ph	Ph	Bu	A, 1h	83%

- In all cases, only *5-exo-dig* cyclization occurred and stereoisomerically pure compounds (*Z*)-2 were found to be the only reaction products

YH. Liu. et al. *Org. Lett*., **2005**, 7 (24), 5409.

Appendix 11. Evans Aldol Reaction



https://www.chem-station.com/odos/2009/06/evans-evans-aldol-reaction.html