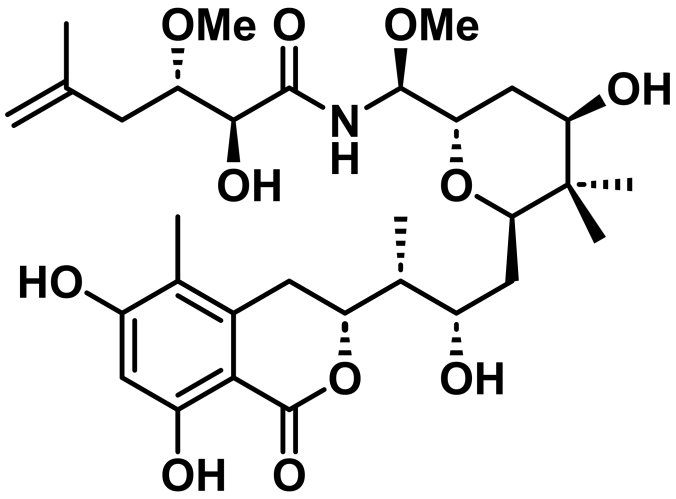
Total Synthesis of Psymberin

2026.01.15

张丰博



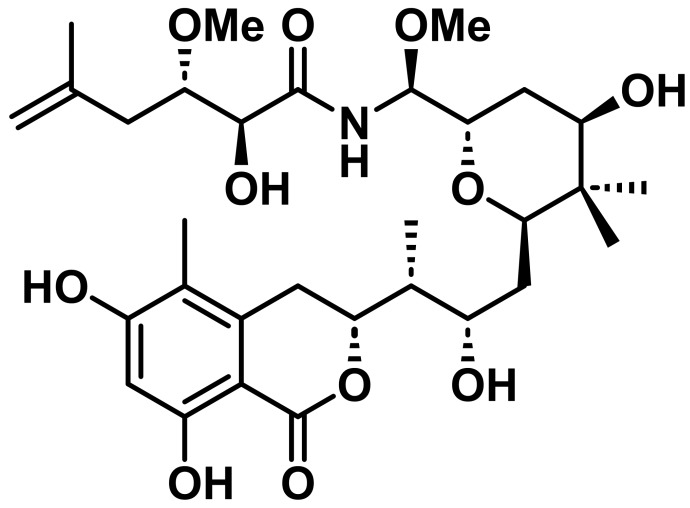
Psymberin/Irciniastatin A

Introduction of Author

- **叶涛**
- 首席研究员，教授
- 北京大学深圳研究生院化学生物学与生物技术学院副院长
- 1979 - 1983 华东理工大学 – 学士
- 1983 - 1986 华东理工大学 – 硕士
- 1989 - 1993 英国女王大学 - 博士
- 1993 - 1994 英国女王大学 - 博士后
- 1994 - 1998 诺丁汉大学 – 博士后
- 1998 - 2001 香港大学
- 2001 - 2015.8 香港理工大学
- 2015.9 北京大学深圳研究生院

https://scbb.pkusz.edu.cn/info/1157/2116.htm
https://web.pkusz.edu.cn/ye/tao-ye/

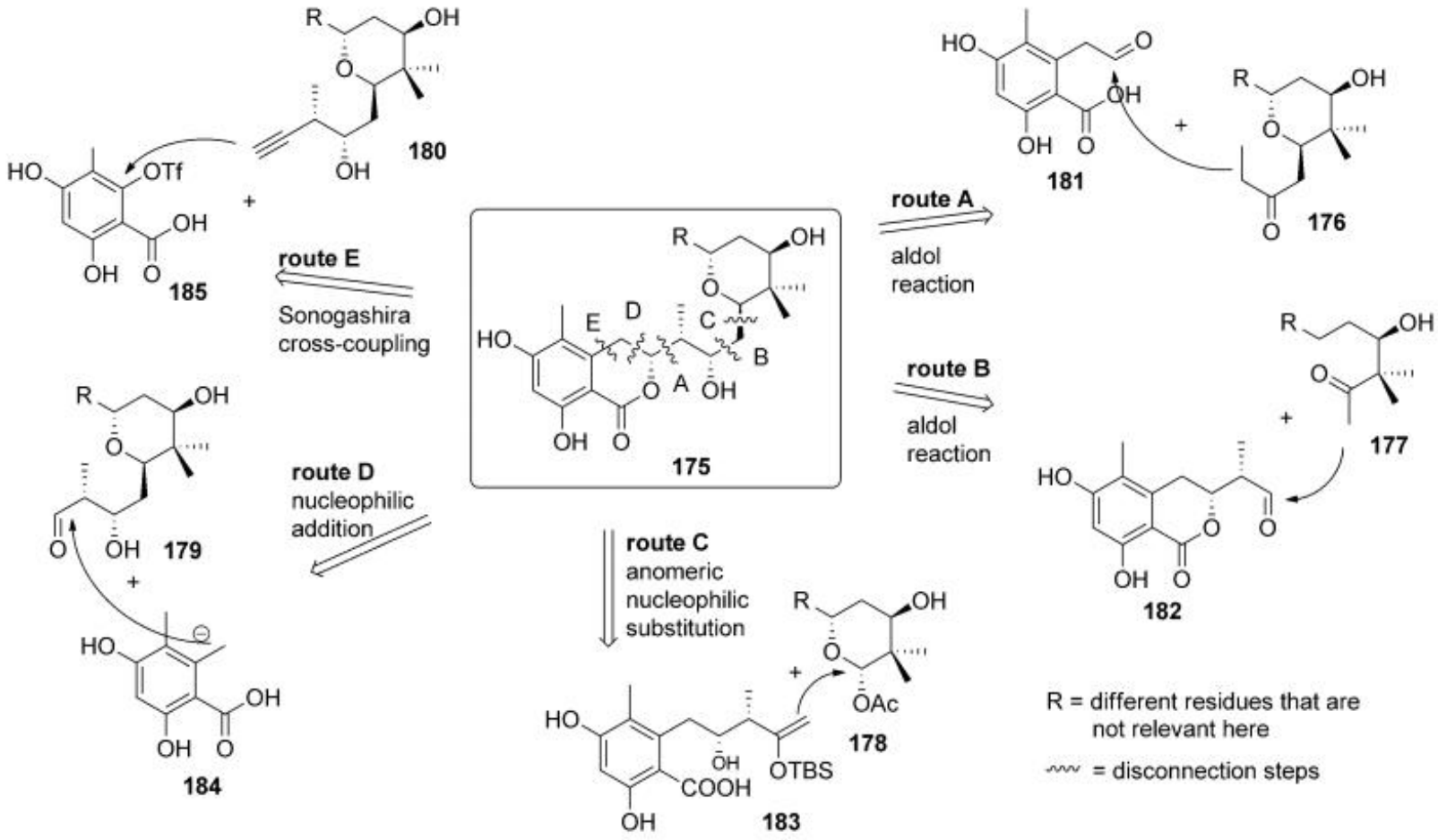
Features of Psymberin



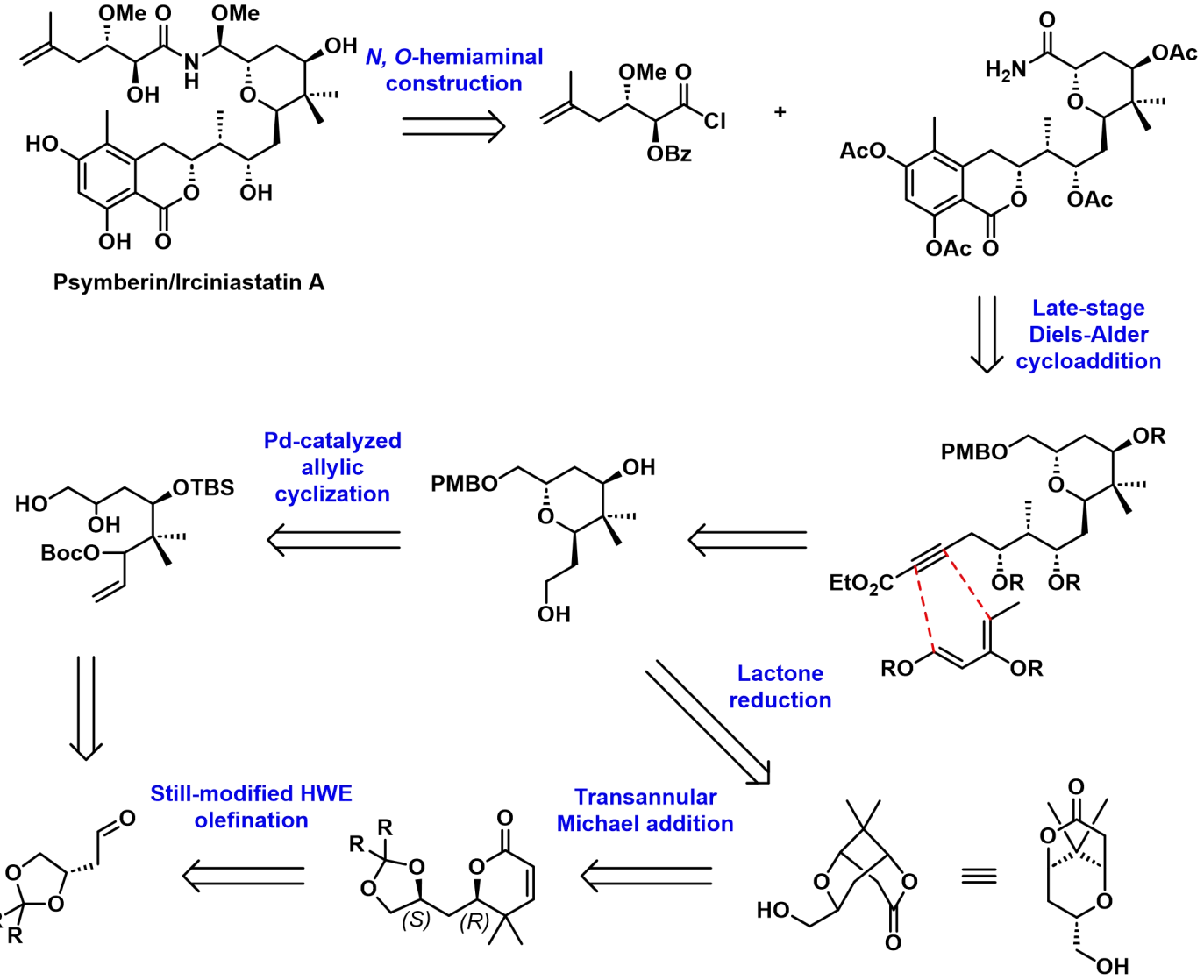
Psymberin/Irciniastatin A

- four distinct components:
- a psymberic acid side chain,
- a dihydroisocoumar in (DHIC) unit,
- an N,O-hemiaminal moiety,
- a highly functionalized 2,6-trans-tetrahydropyran (2,6-trans-THP) core.

Previous Synthesis of Psymberin

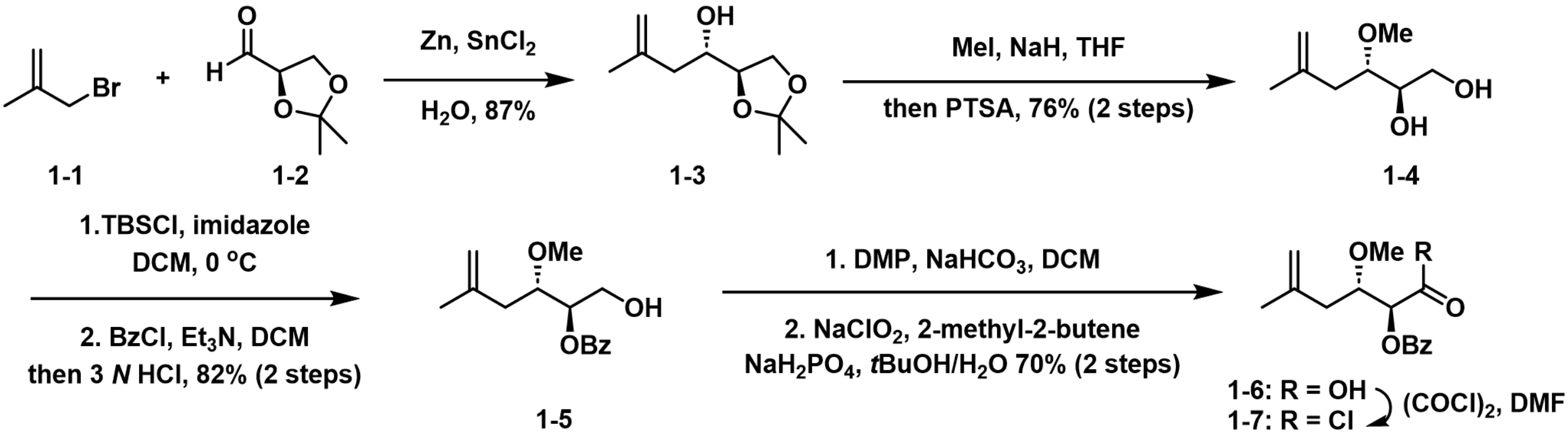


First Generation Synthesis of Psymberin Retrosynthetic Disconnections

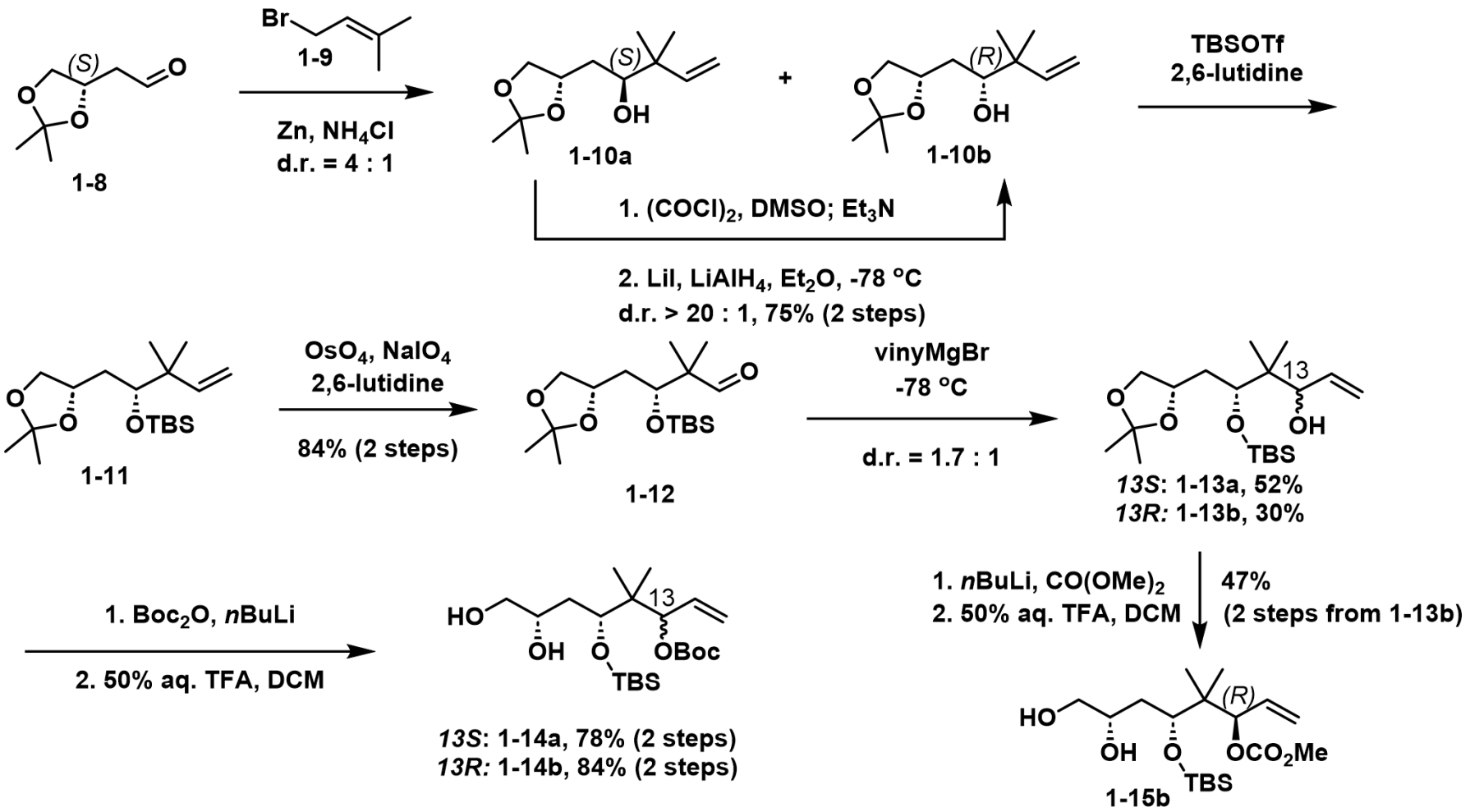


J. Org. Chem. **2025**, *90*, 17332−17356

Synthesis of Psymberic Acid Chloride

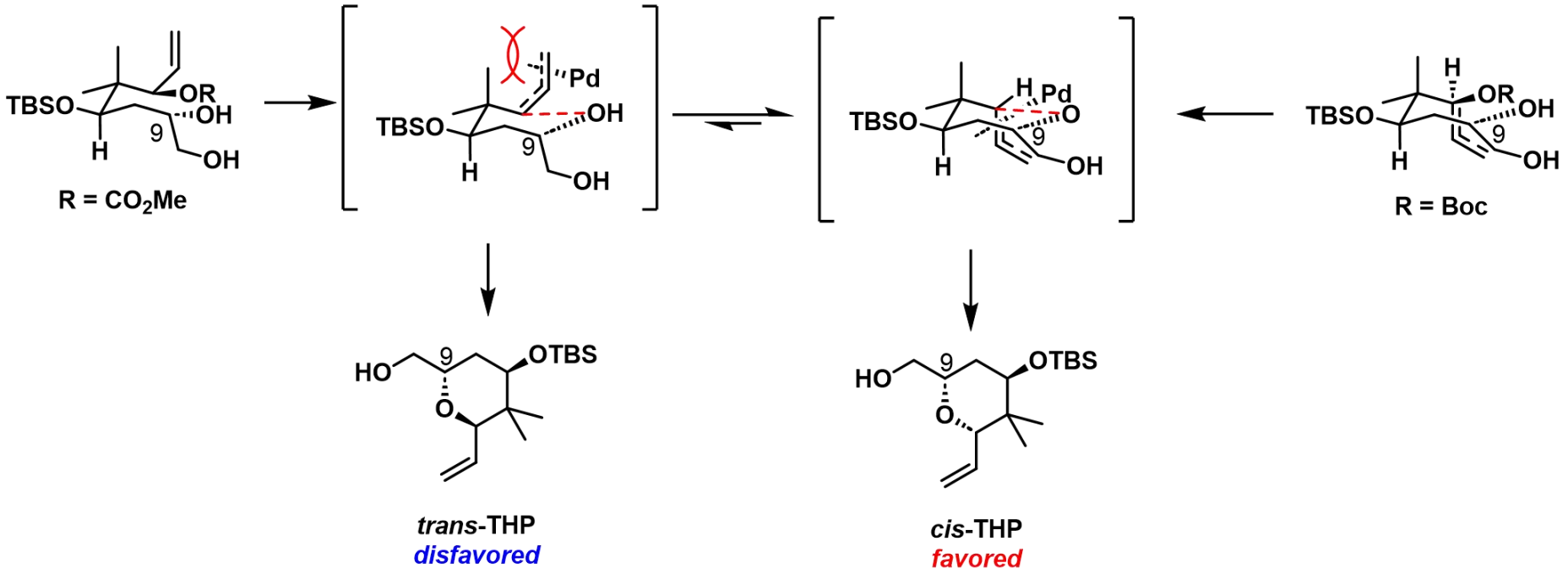


Synthesis of Cyclization Precursors



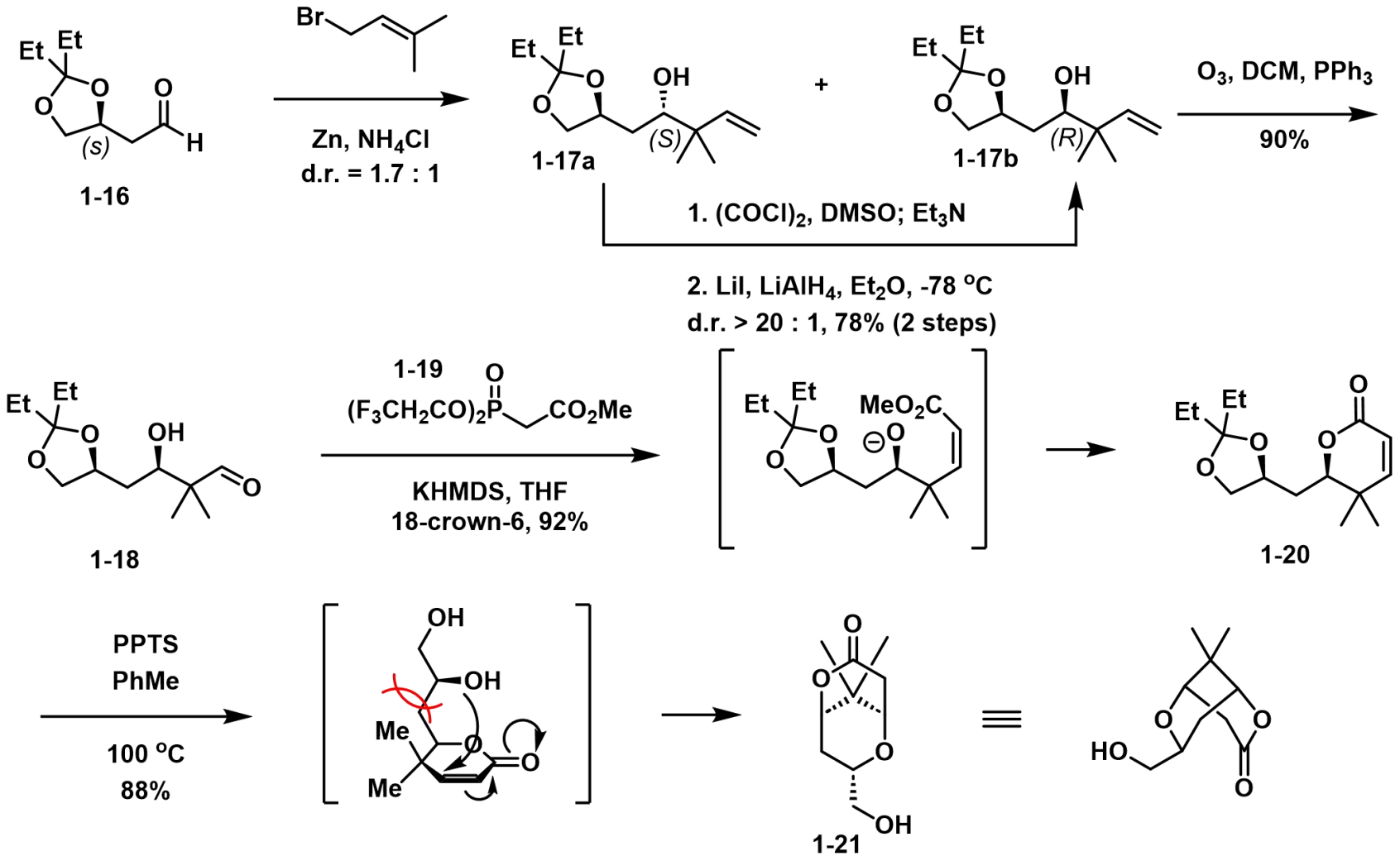
J. Org. Chem. **2025**, *90*, 17332−17356

Possible Mechanism for the Stereoselectivity of Pd-Catalyzed Allylic Cyclization



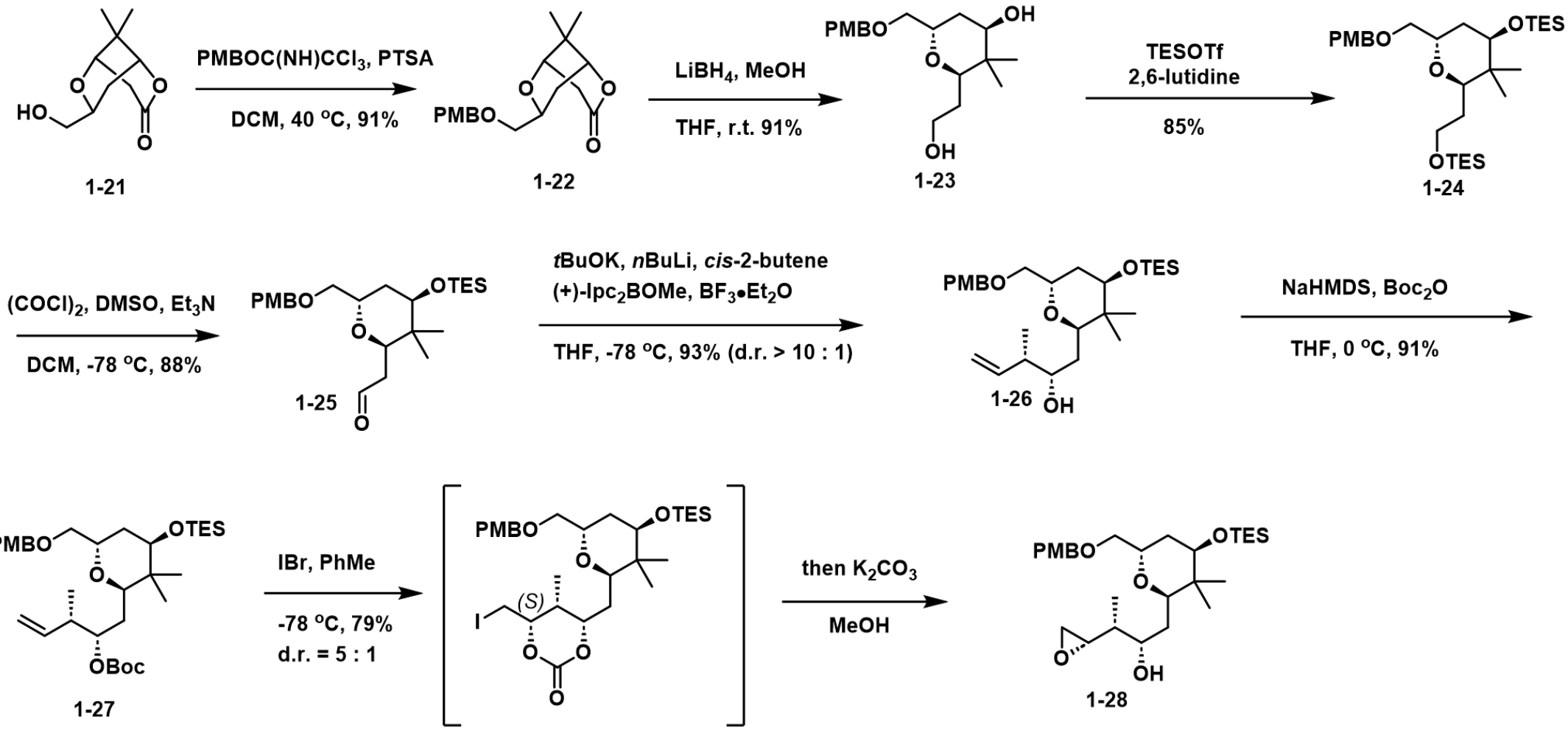
J. Org. Chem. **2025**, *90*, 17332−17356

Synthesis of 2,6-trans-THP Derivative



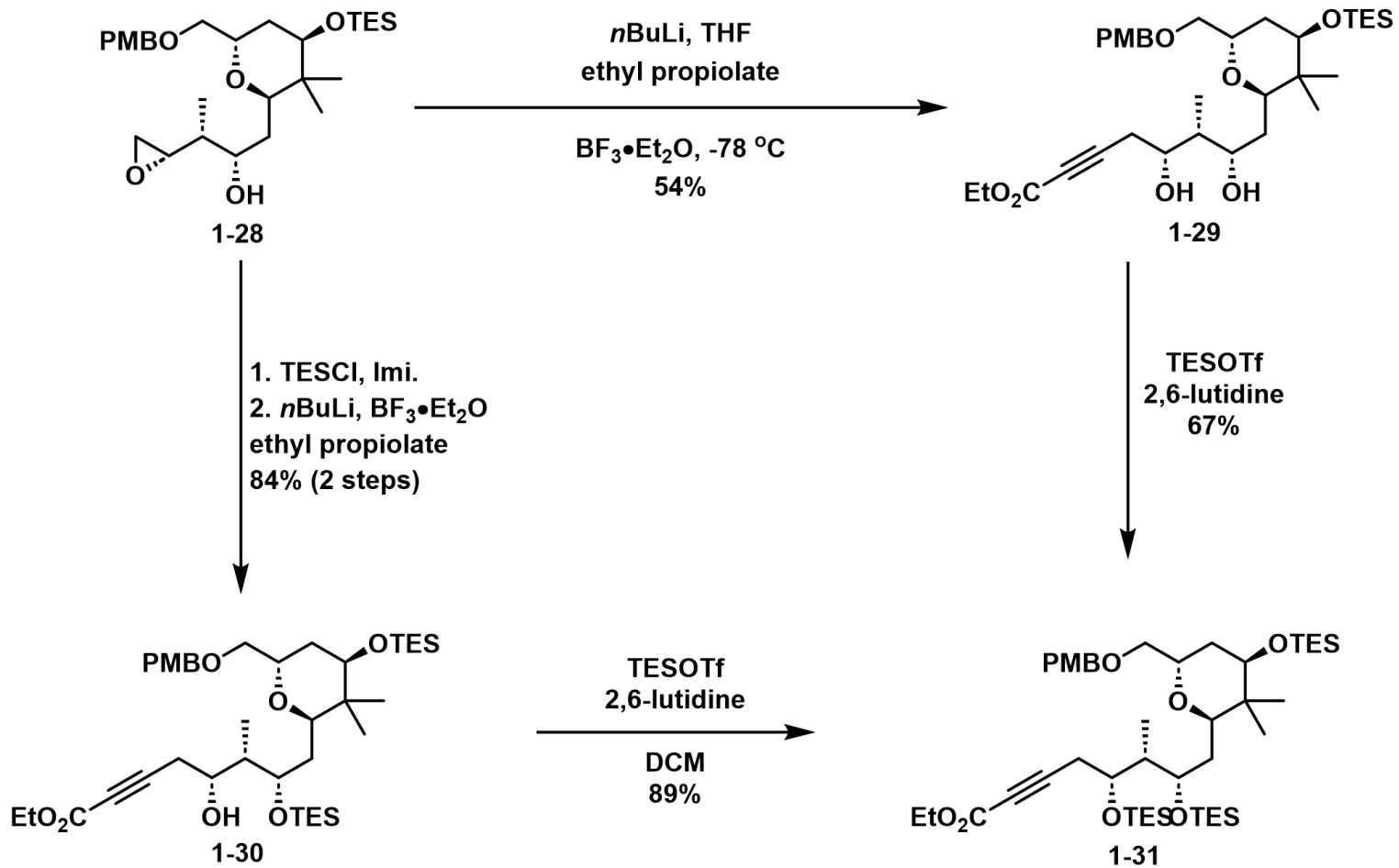
J. Org. Chem. **2025**, *90*, 17332−17356

Synthesis of 2,6-trans-THP Derivative



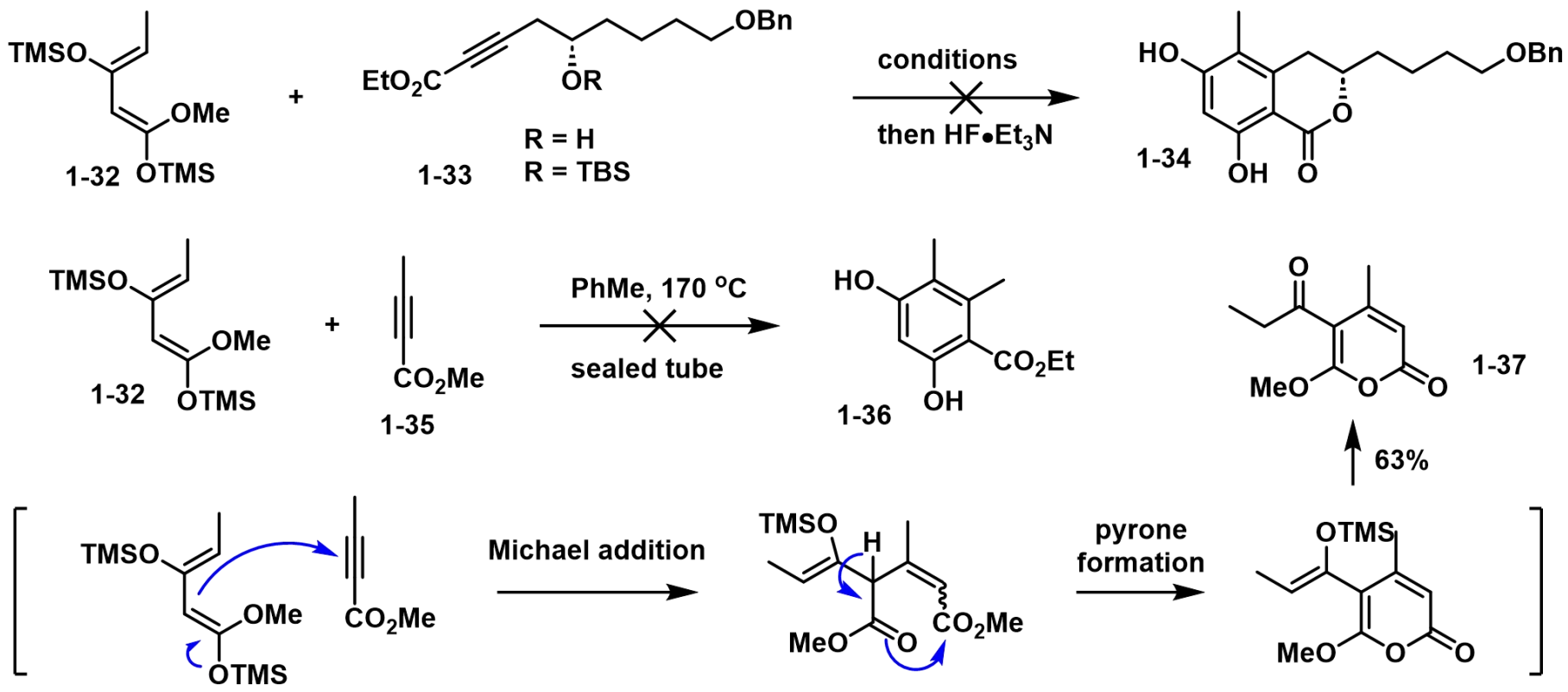
J. Org. Chem. **2025**, *90*, 17332−17356

Synthesis of Diels–Alder Precursor



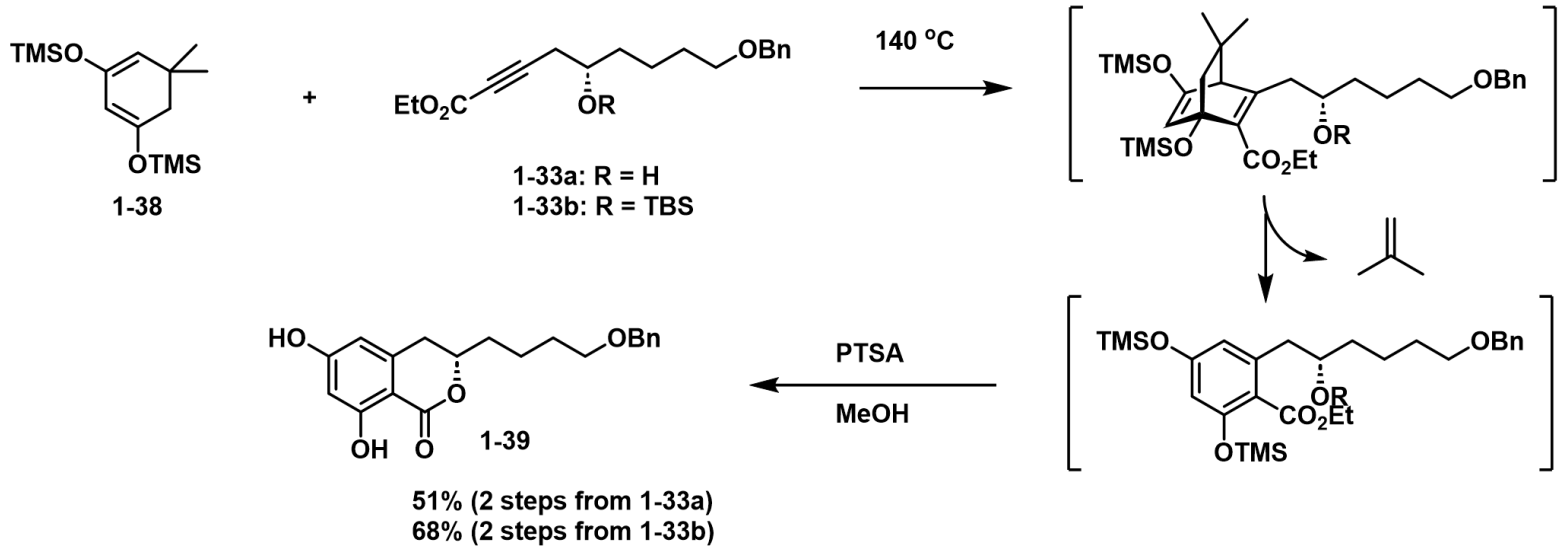
J. Org. Chem. **2025**, *90*, 17332−17356

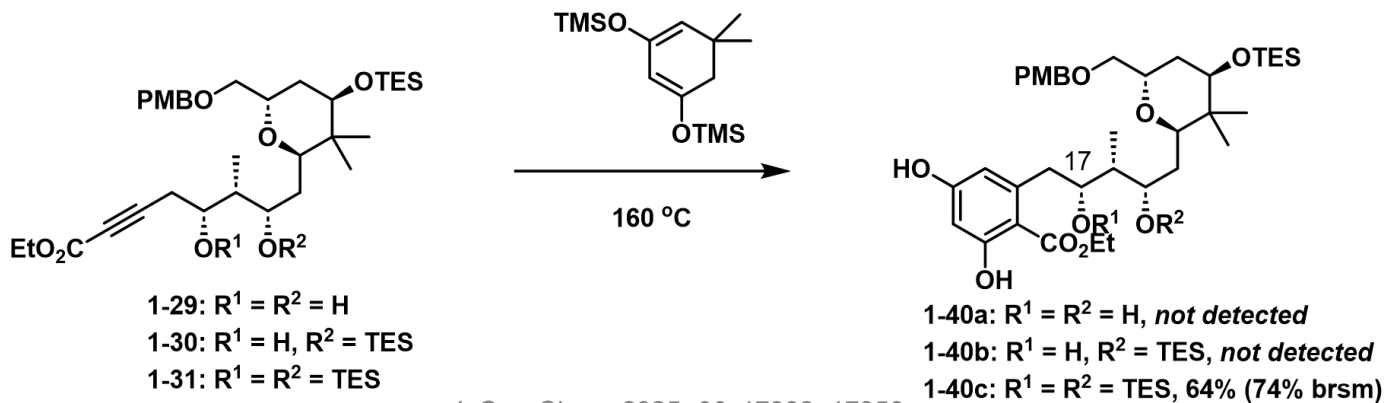
Diels–Alder Reaction to Construct the Dihydroisocoumarin Unit



J. Org. Chem. **2025**, *90*, 17332−17356

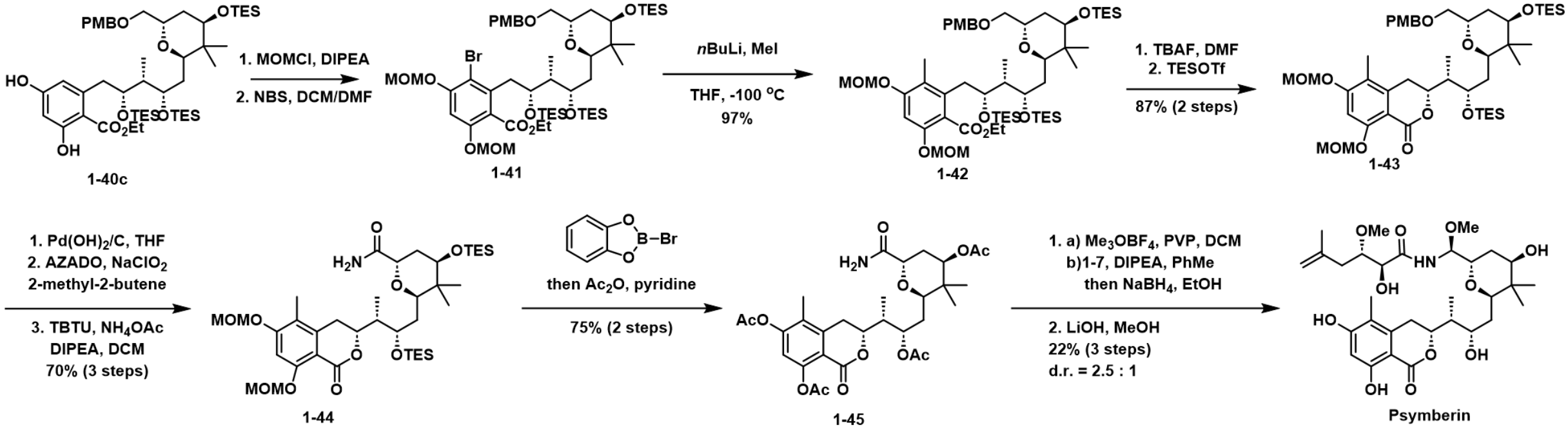
Diels–Alder Reaction to Construct the Dihydroisocoumarin Unit





J. Org. Chem. **2025**, *90*, 17332−17356

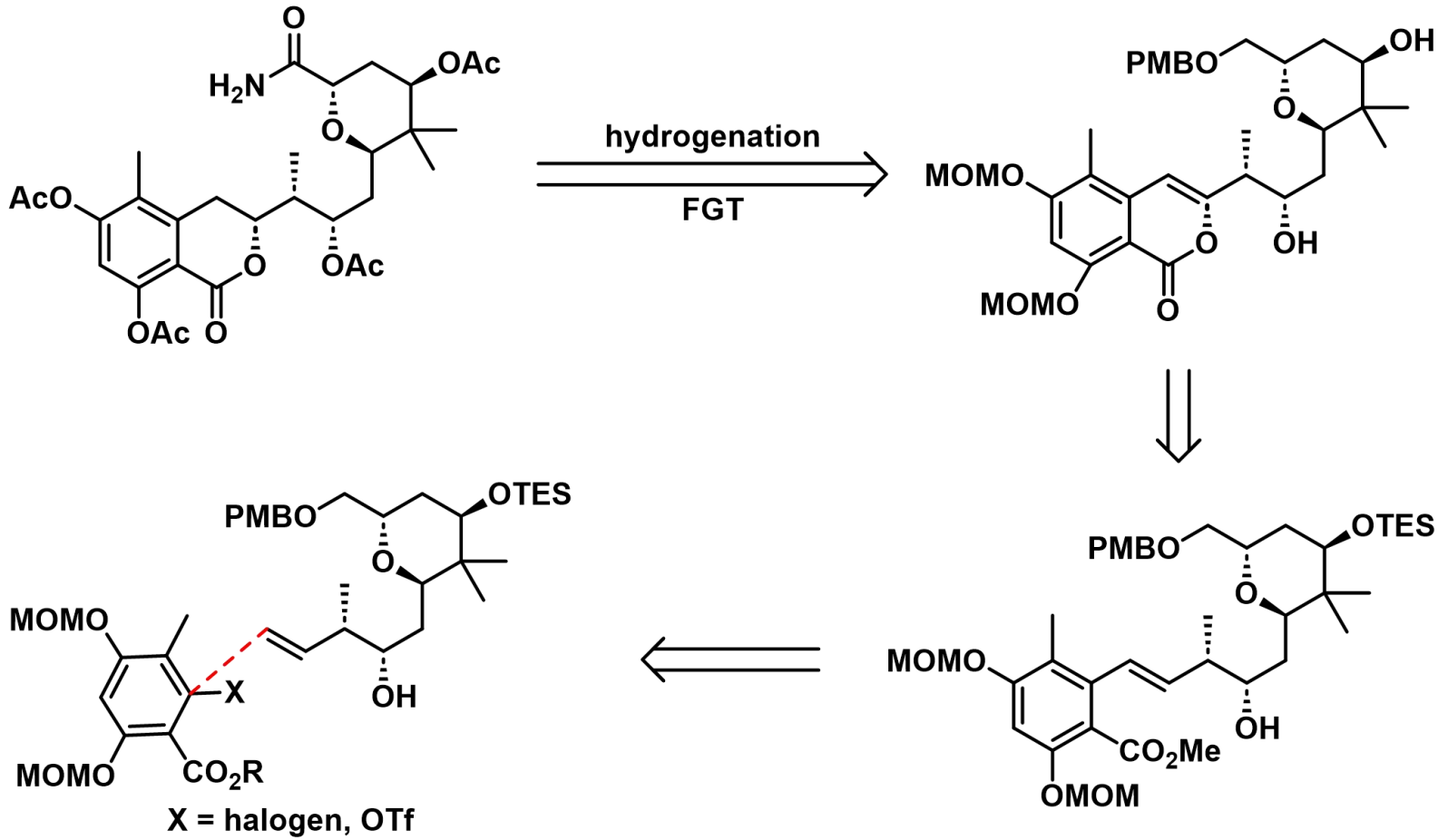
Completion of the Total Synthesis



J. Org. Chem. **2025**, *90*, 17332−17356

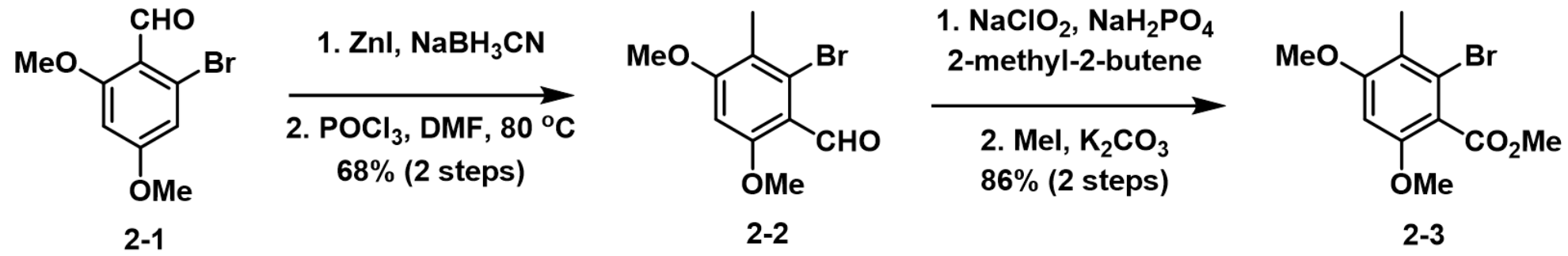
Second Generation Synthesis of Psymberin

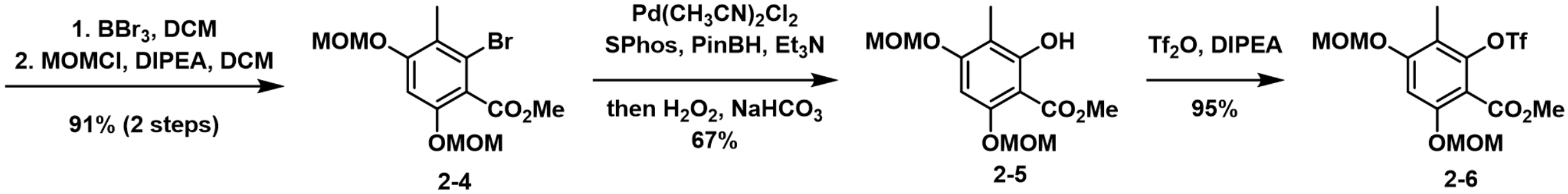
Retrosynthetic Disconnections



J. Org. Chem. **2025**, *90*, 17332−17356

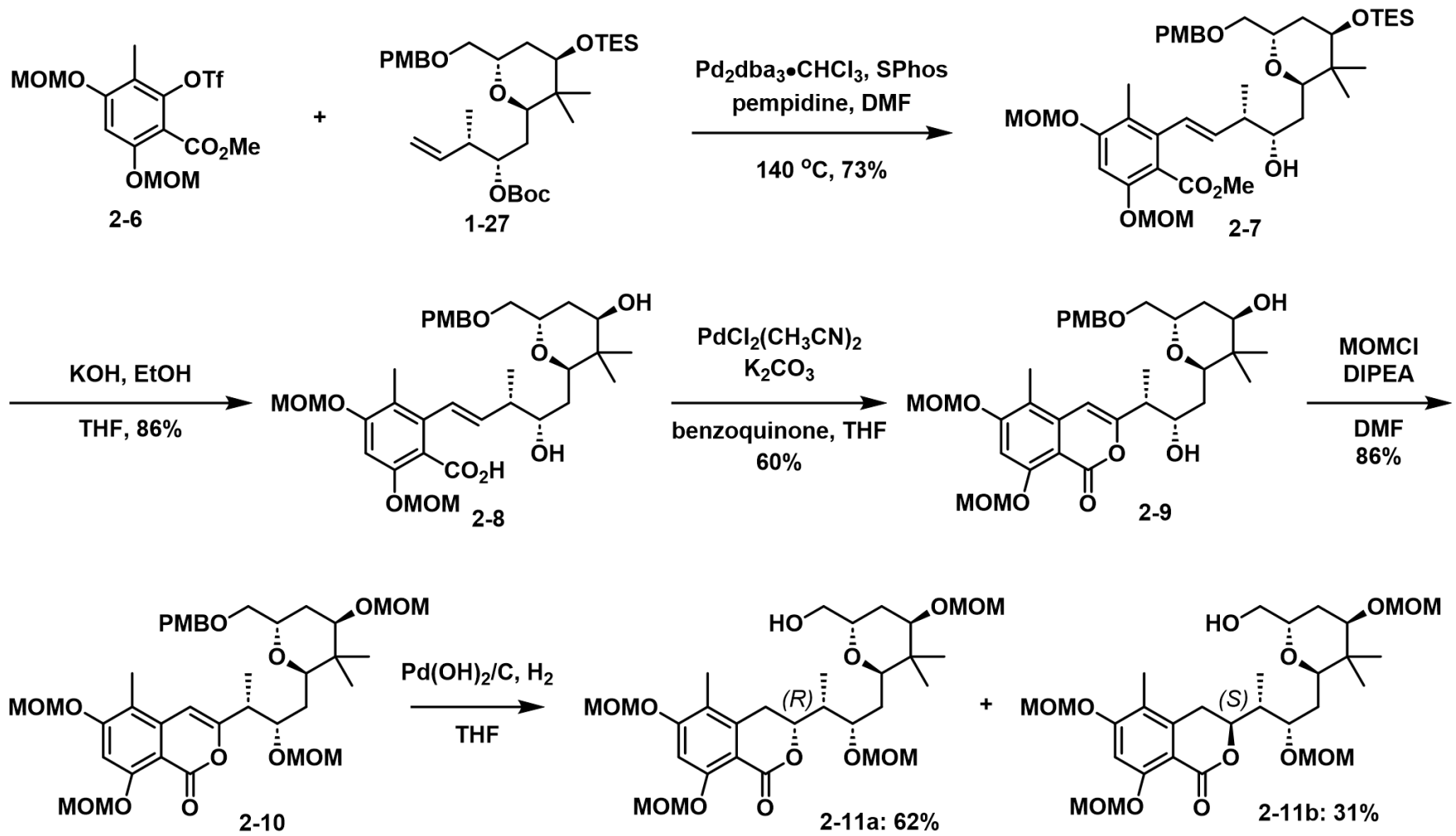
Synthesis of Aryl Moiety





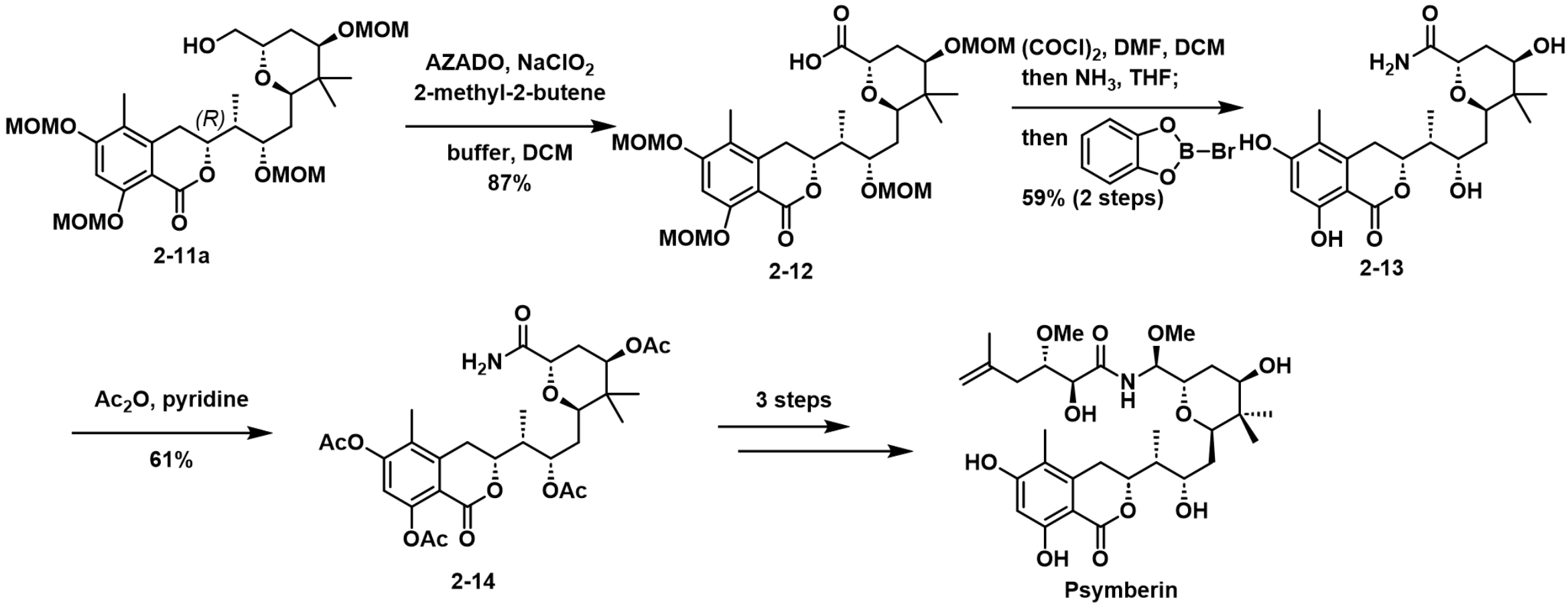
J. Org. Chem. **2025**, *90*, 17332−17356

Synthesis of Dihydroisocoumarin



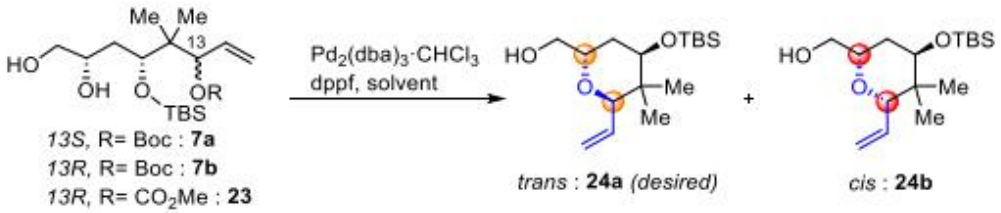
J. Org. Chem. **2025**, *90*, 17332−17356

Completion of the Total Synthesis



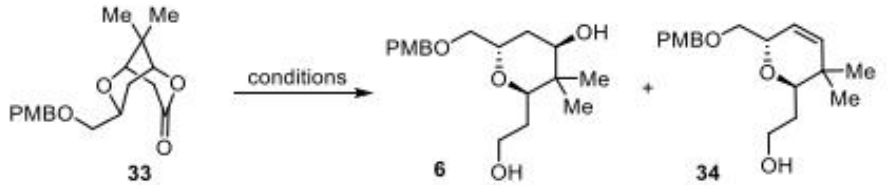
补充

Table 1. Attempts on the Pd-Catalyzed Allylic Cyclization for Access to 2,6-*trans*-THP



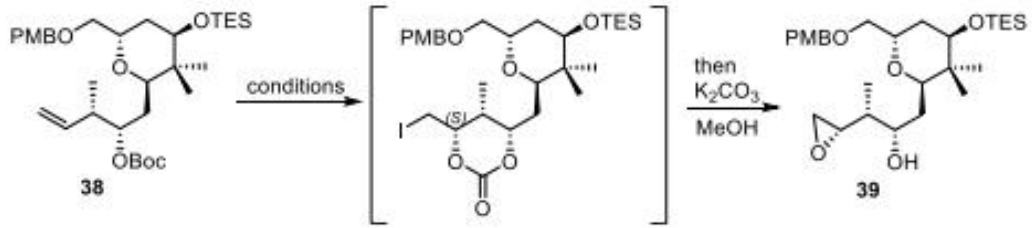
entry	substrates	solvent	temp.	yields (*trans/cis*)
1	**7a**	DCE	70 °C	no conversion
2	**7a**	DCE	83 °C	trace
3	7a	PhMe	110 °C	90% (1:2.2)
4	**7b**	PhMe	110 °C	no conversion
5	**23**	PhMe	110 °C	94% (1:2.5)

Table 2. Conditions for the Reduction of Lactone 33



entry	condition	6	34
1	$LiAlH_4$, THF, 0 °C to r.t.	30%	20%
2	$LiAlH_4$, THF, 0 °C	44%	12%
3	DIBAL-H, DCM, −78 °C to r.t.	50%	
4	$LiBH_4$, MeOH, THF, r.t.	91%	

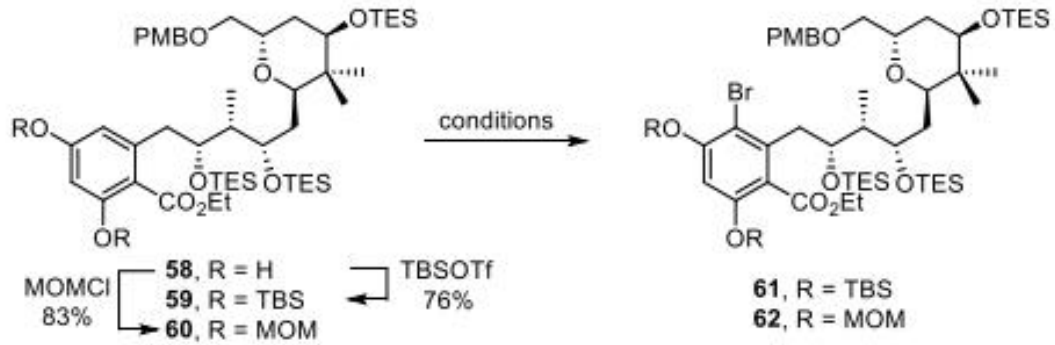
Table 3. Condition Optimization for the Epoxidation of Alkene 38



entry	reagent	solvent	temp.	yields (d.r.)
1	NIS	CH_3CN	R.T	77% (2.5:1)
2	NIS	CH_3CN	0 °C	80% (3:1)
3	NIS	CH_3CN	−20 °C	81% (4:1)[a]
4	I_2	CH_3CN	−20 °C	70% (3:1)[b]
5	ICl	DCM	−78 °C	58% (2.6:1)
6	ICl	PhMe	−78 °C	70% (5:1)
7	IBr	PhMe	−78 °C	79% (5:1)

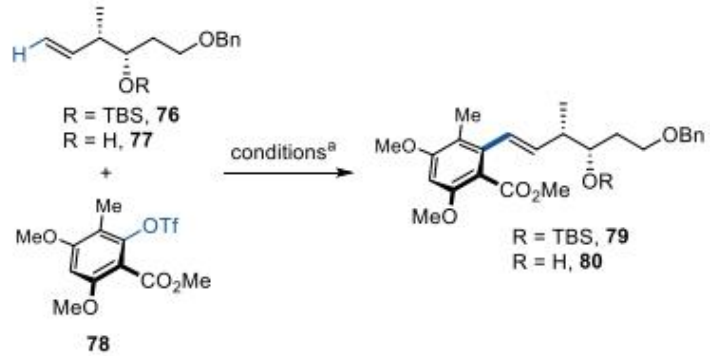
[a]Yield based on recovered starting material. [b]TES was deprotected.

Table 4. Bromination of Aryl Moiety



entry	substrate	conditions	product (yield)
1	**59**	NBS, DCM	no conversion
2	**60**	NBS, DCM	no conversion
3	**60**	NBS, THF	no conversion
4	**60**	NBS, DCM/DMF (5:1)	**62** (91%)
5	**60**	NBS, DCM/DMF (10:1)	**62** (trace)
6	60	NIS, DCM/DMF (5:1)	no conversion
7	**59**	NBS, DCM/DMF (5:1)	complicated

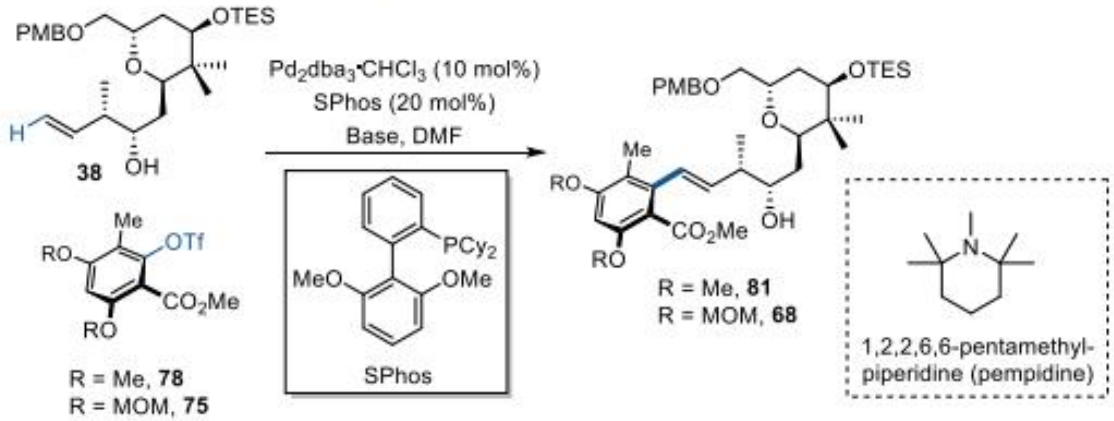
Table 5. Model Reaction between Aryl Unit 78 and Simplified Alkenes 76 and 77



entry	alkene	catalyst/ligand/additive	base	product (yield)
1	**76**	$PdCl_2(PPh_3)_2$/LiCl	Et_3N	N.R.[b]
2	**76**	$PdCl_2(PPh_3)_2$//LiCl	Et_3N	N.R.
3	**76**	$PdCl_2$dppf	Et_3N	N.R.
4	**76**	$Pd(OAc)_2/P(o\text{-tol})_3$	Et_3N	N.R.
5	**76**	$Pd(OAc)_2/PCy_3$	Et_3N	N.R.
6	**76**	$Pd(OAc)_2$/dppp	Et_3N	N.R.
7	**76**	$Pd_2dba_3{\cdot}CHCl_3$/BINAP	Et_3N	N.R.
8	**76**	$Pd_2dba_3{\cdot}CHCl_3$/SPhos	Et_3N	**79** (10%)
9	**77**	$Pd_2dba_3{\cdot}CHCl_3$/SPhos	Et_3N	**80** (33%)
10	**77**	$Pd_2dba_3{\cdot}CHCl_3$/Xphos	Et_3N	trace
11	**77**	$Pd_2dba_3{\cdot}CHCl_3$/*t*Buphos	Et_3N	N.R.
12	**77**	$Pd_2dba_3{\cdot}CHCl_3$/Ruphos	Et_3N	N.R.
13	**77**	$Pd_2dba_3{\cdot}CHCl_3$/SPhos	$NaHCO_3$	N.R.
14	**77**	$Pd_2dba_3{\cdot}CHCl_3$/SPhos	K_2CO_3	N.R.
15	**77**	$Pd_2dba_3{\cdot}CHCl_3$/SPhos	Cs_2CO_3	N.R.
16	**77**	$Pd_2dba_3{\cdot}CHCl_3$/SPhos	DIPEA	**80** (58%)
17	**77**	$Pd_2dba_3{\cdot}CHCl_3$/SPhos	2,6-lut.	trace

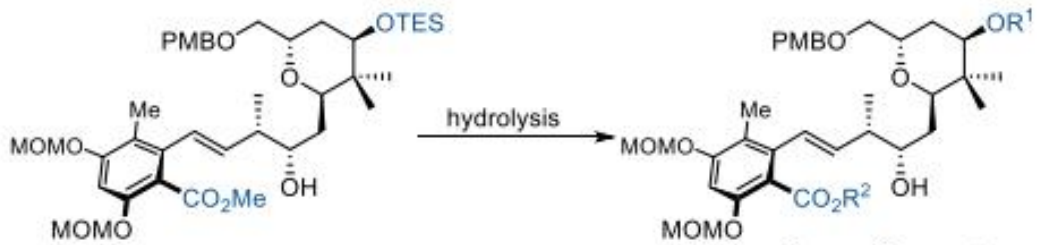
[a]All reactions were conducted in refluxing DMF. [b]The reaction temperature was 120 °C.

Table 6. Further Optimization of the Heck Reaction



entry	R	base	temp.	product (yield)
1	Me	DIPEA	155 °C	**81** (40%)
2	Me	DIPEA	140 °C	**81** (42%)
3	Me	DIPEA	120 °C	**81** (29%)
4	Me	Cy_2NMe	140 °C	NR
5	Me	pempidine	140 °C	**81** (65%)
6	MOM	pempidine	140 °C	**68** (73%)

Table 7. Hydrolysis of the Methyl Ester in 68



68

R^1 = H, R^2 = Me, **84**
R^1 = R^2 = H, **85**

entry	conditions	temp.	yield
1	Me_3SiOK (10 equiv), THF	reflux	NR
2	Me_3SnOH (3 equiv), PhMe	reflux	NR
3	NaOH (20 equiv), THF/H_2O/MeOH (v:v:v = 1:1:1)	80 °C	**84** (84%)
4	THF/*aq*.KOH(10M)/MeOH (v:v:v = 1:1:1)	80 °C	**85** (33%)(brsm 77%)
5	THF/*aq*.KOH(20 M)/EtOH (v:v:v = 1:1:1)	80 °C	**85** (86%)