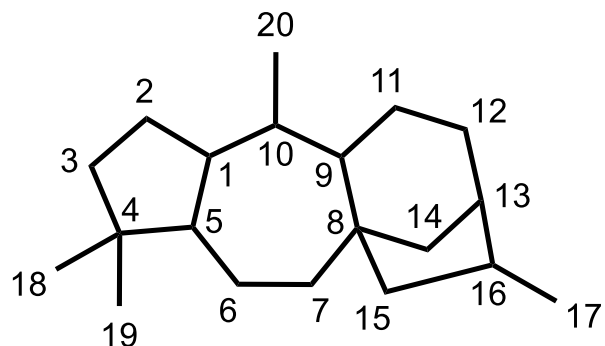
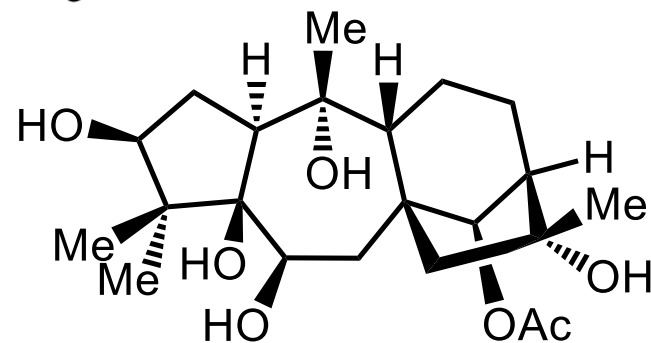


Total Synthesis of (–)-Principinol C

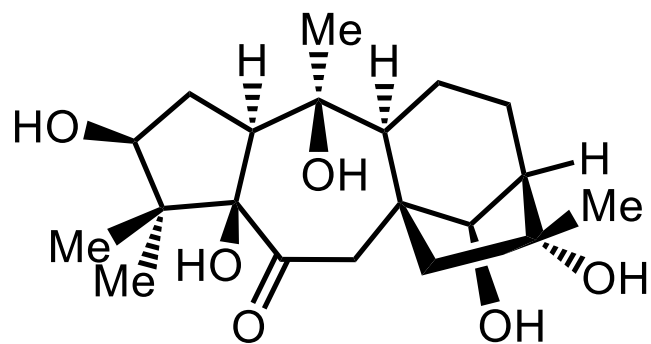
Tianhao Ma, Hao Cheng, Mallesham Pitchakuntla, Weihao Ma, and Yanxing Jia*



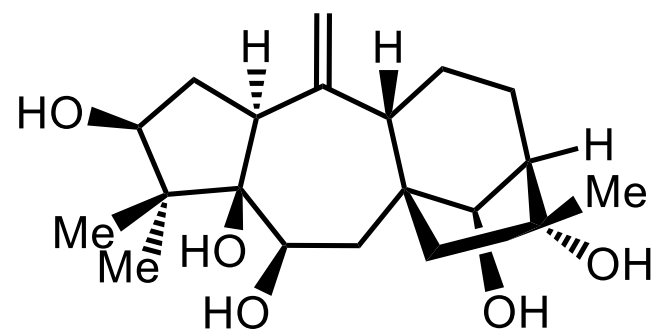
grayanane



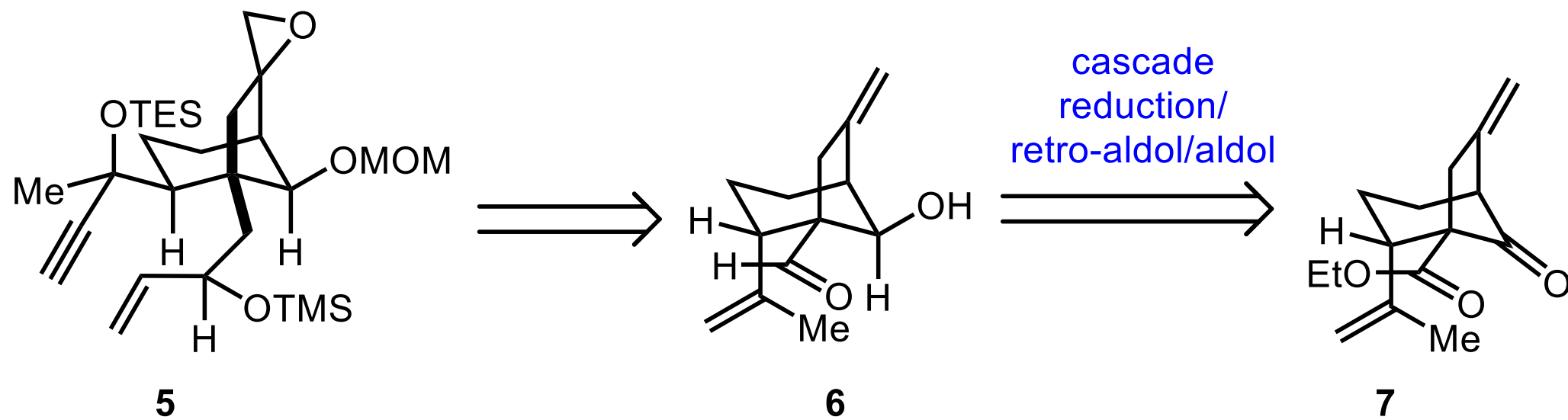
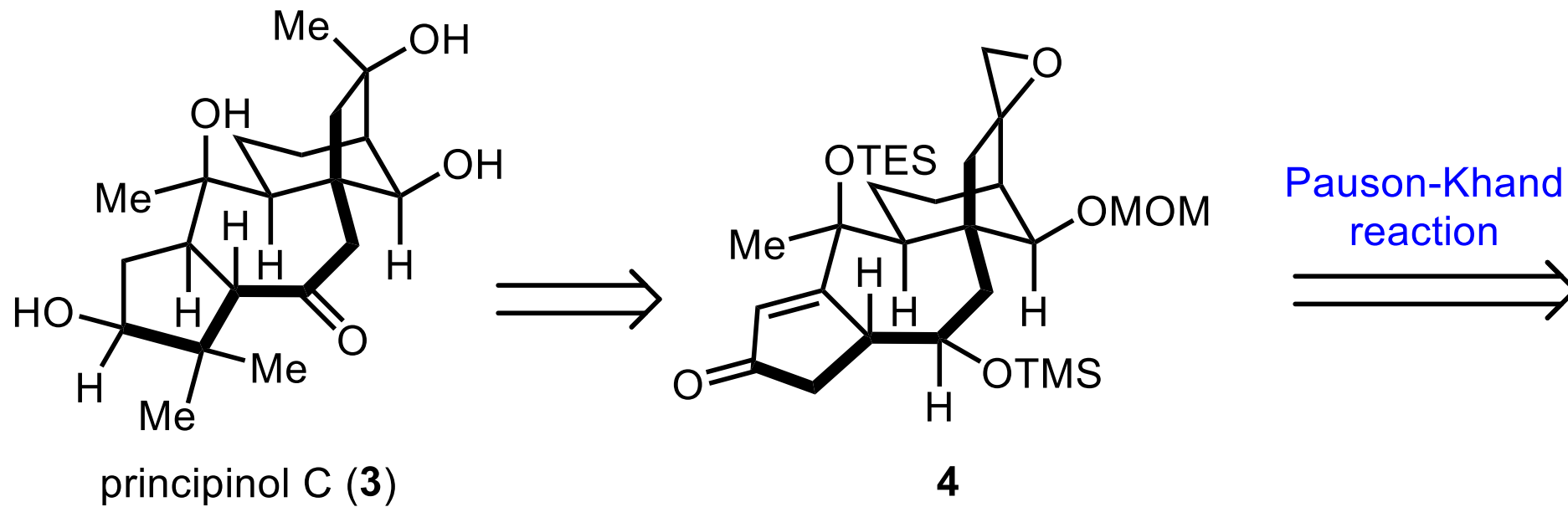
grayanotoxin I (1)



principinol C (3)



grayanotoxin II (2)



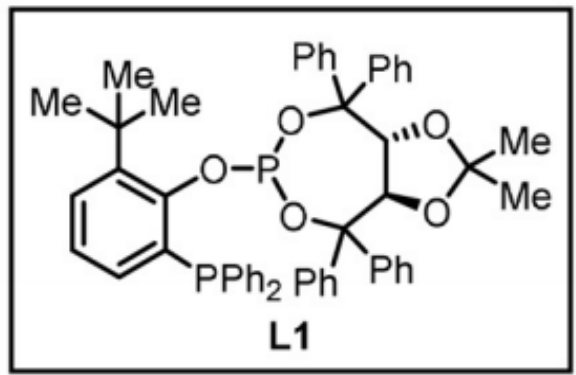
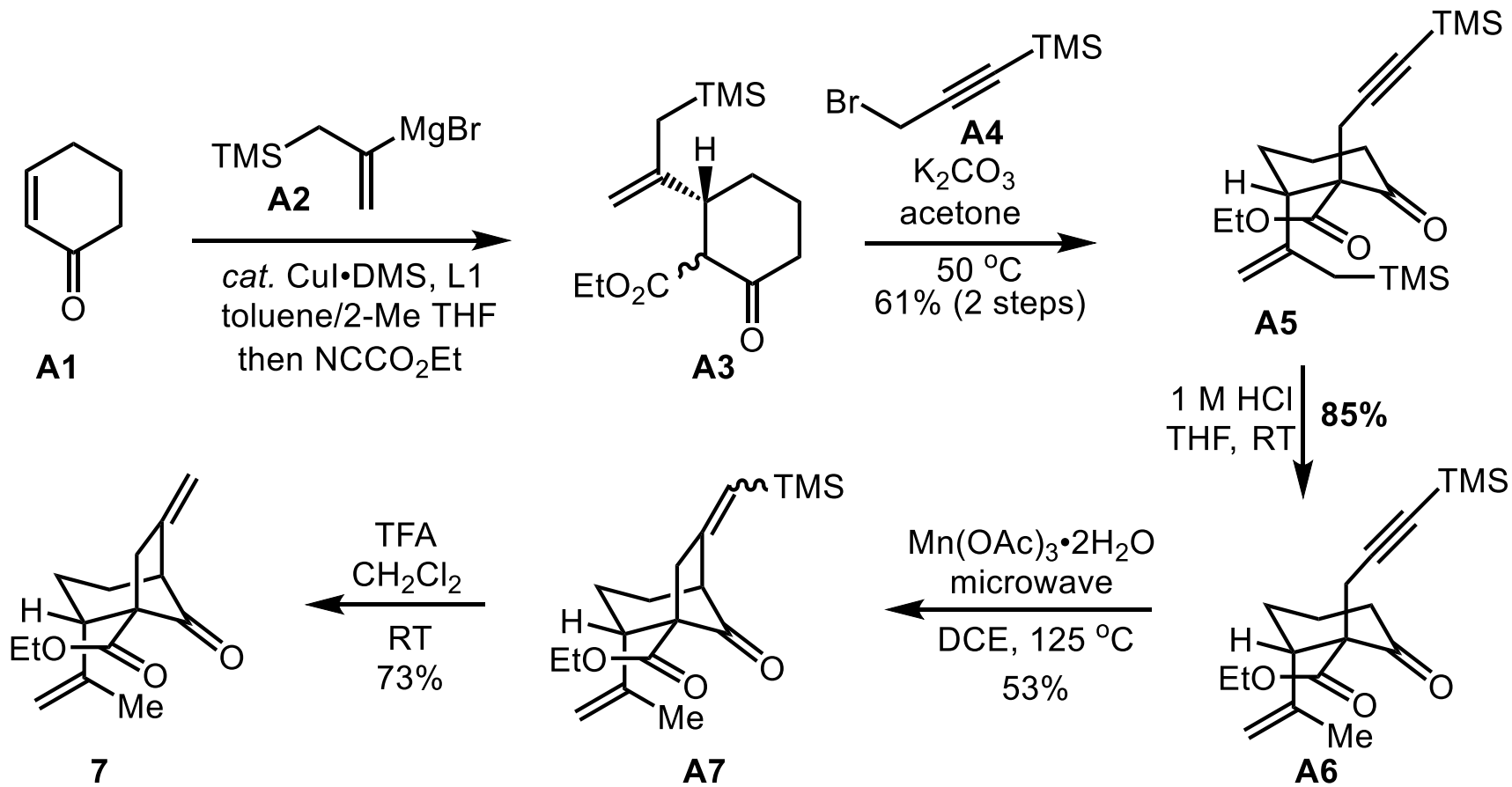
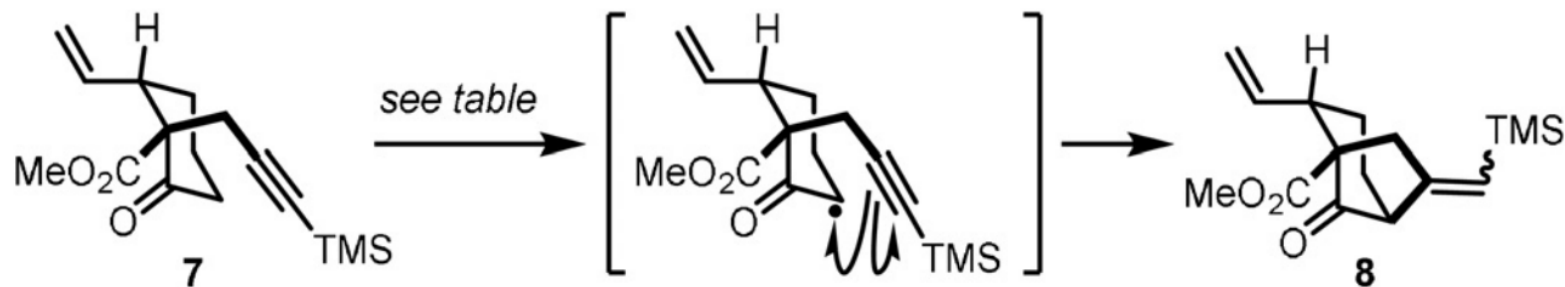


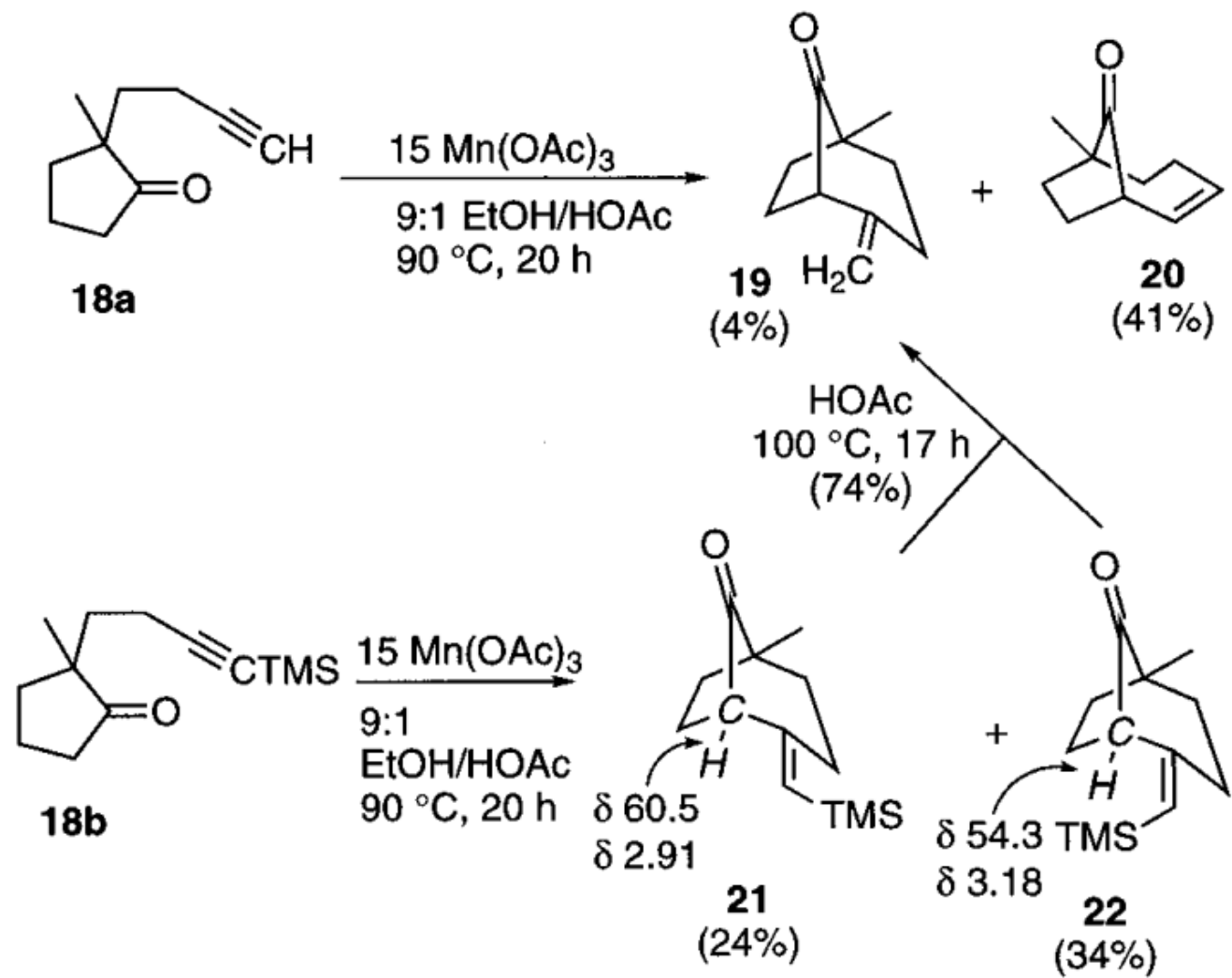
Table 1: Condition optimization for the formation of the oxygenated Bicyclo[3.2.1]octane System.^[a]



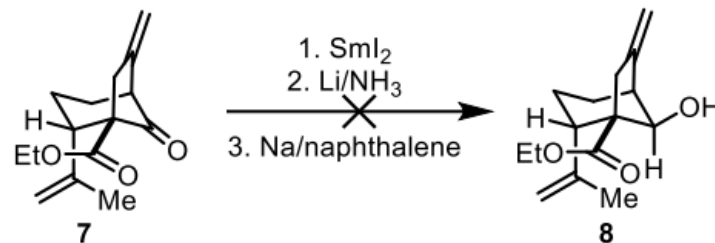
Entry	Equiv. of Mn ^{III}	Solvent	T [°C]	t	Yield [%] ^[b]
1	6	EtOH/HOAc (9:1)	100 (heat)	3 d	23
2	6	EtOH/HOAc (9:1)	100 (MW)	6 h	27
3	3	HOAc	100 (MW)	30 min	32
4	3	THF/HOAc (9:1)	100 (MW)	6 h	40
5	3	THF	110 (MW)	6 h	47
6	3	DCE	110 (MW)	6 h	58
7	3	DCE	120 (MW)	3 h	60
8	2.5	DCE	125 (MW)	3 h	60

[a] Reaction conditions: **7** (0.3 mmol), Mn(OAc)₃, solvent (3 mL).

[b] Yield of isolated product. TMS = trimethylsilyl, THF = tetrahydrofuran, DCE = 1,2-dichloroethane.



Section 1.1 Attempts to reduce **7** by using some single electron donor reductants.

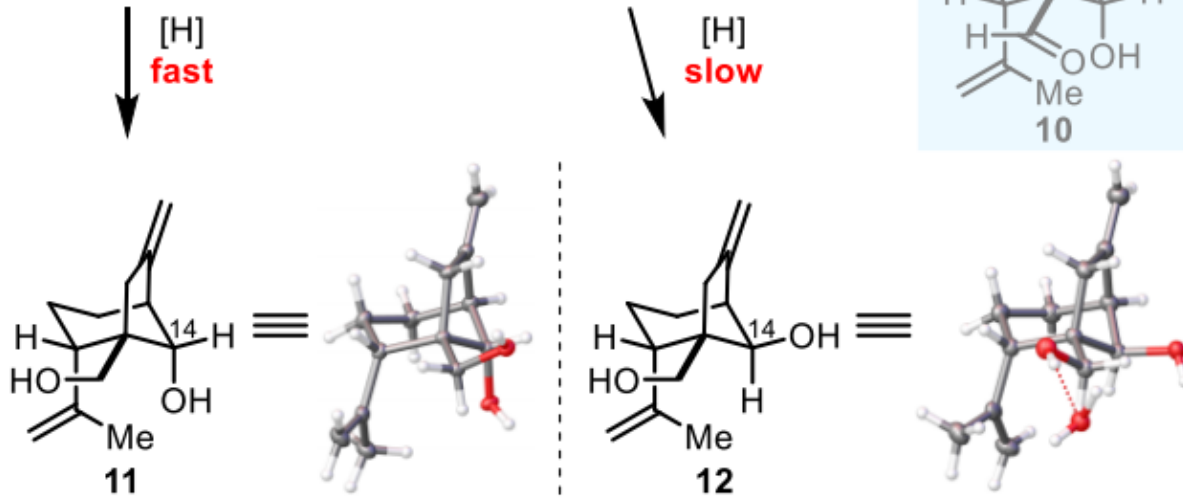
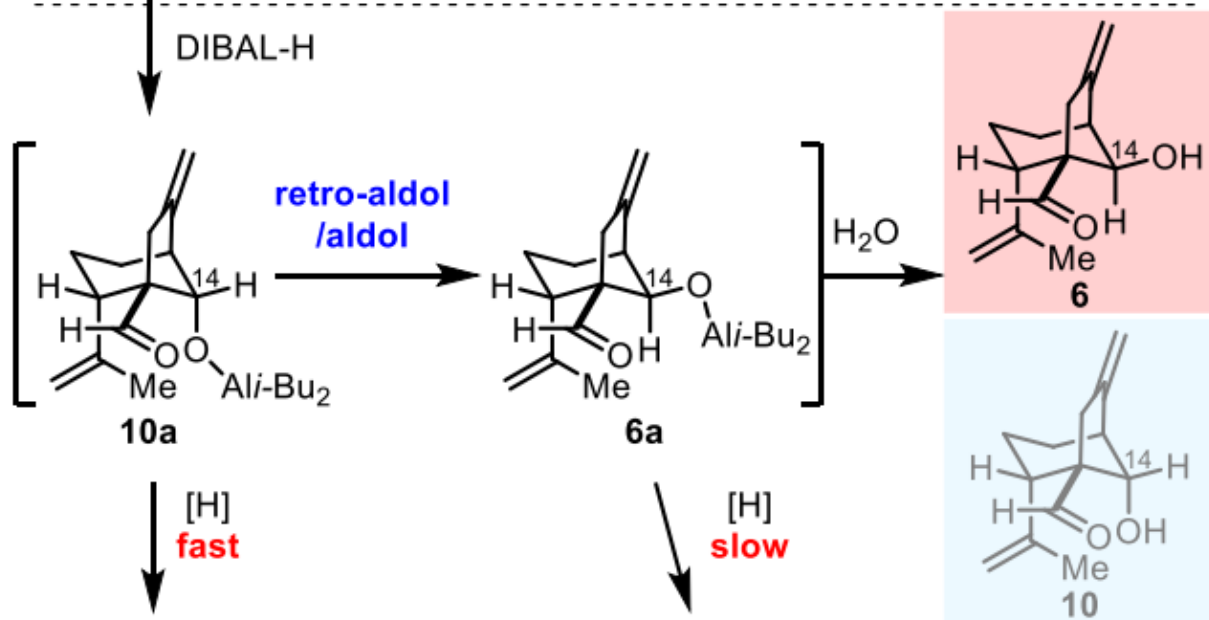
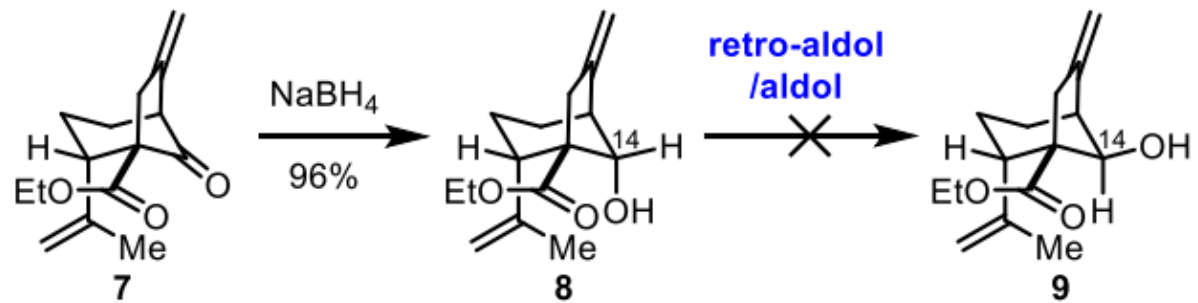


Section 1.2 Attempts to invert the C14-OH of **8** by retro-aldol/aldol reaction.

Table S1. Attempts of the retro-aldol/aldol reaction of ester **8**.

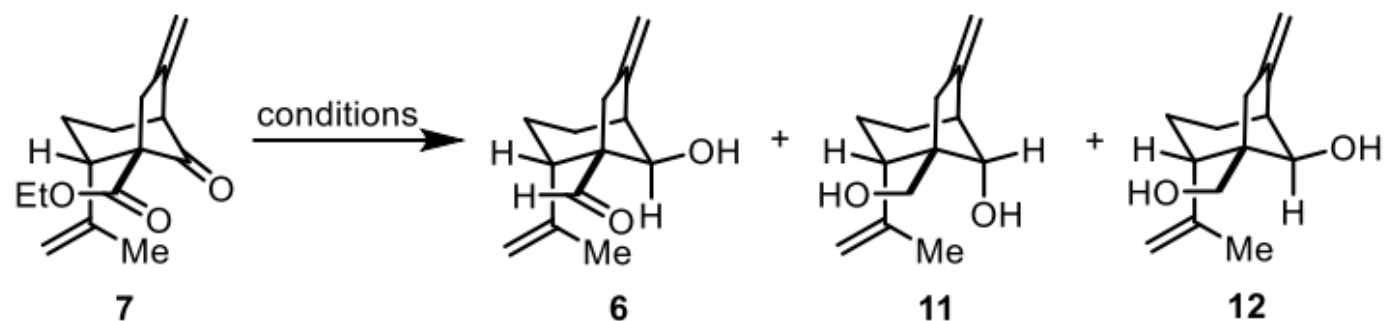


entry	conditions	results
1	PPTS, DCM, rt	SM recovered
2	<i>p</i> -TSA, DCM, rt	SM recovered
3	Et ₂ AlCl, THF, 0 °C - rt	decomposed
4	K ₂ CO ₃ , MeOH, rt	SM recovered
5	Et ₃ N, MeOH, rt - 60 °C	decomposed
6	NaH, THF	decomposed



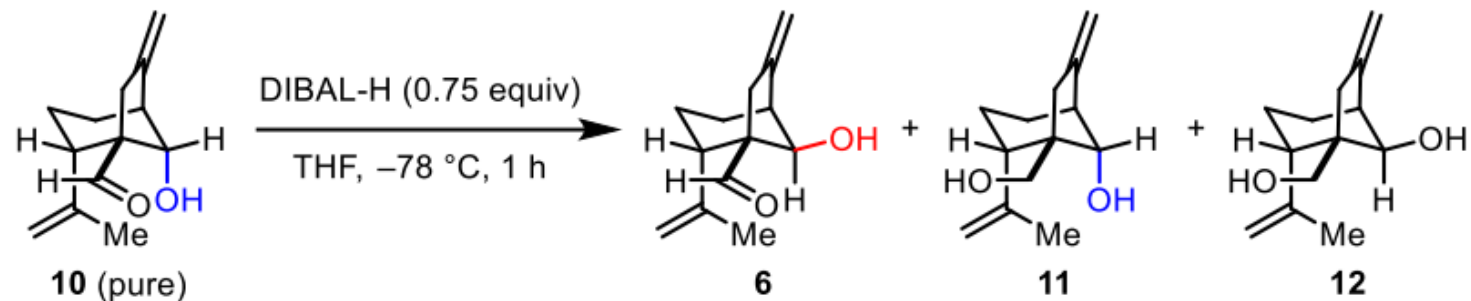
Section 1.3 Optimization of the cascade reduction/retro-aldol/aldol reaction.

Table S2. Optimization of the cascade reduction retro-aldol/aldol reaction.



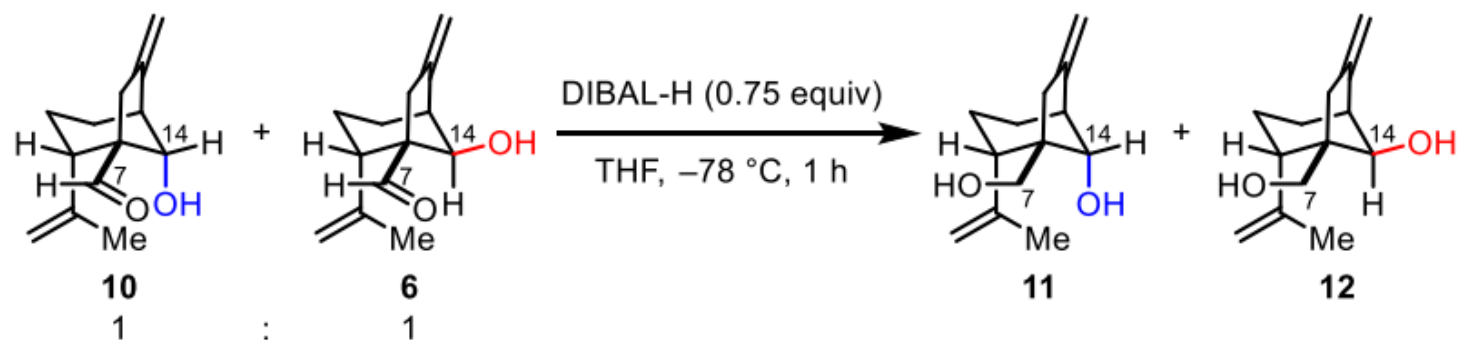
entry	conditions	yield (%) ^a		
		6	11	12
1	DIBAL-H (5.0 equiv), THF, -78 °C - rt, 12 h	-	82	14
2	DIBAL-H (4.0 equiv), THF, -78 °C - rt, 12 h	-	80	12
3	DIBAL-H (4.0 equiv), THF, -78 °C - rt, 1 h	12	79	trace
4	DIBAL-H (3.0 equiv), THF, -78 °C - rt, 1 h	33	58	-
5	DIBAL-H (2.5 equiv), THF, -78 °C - rt, 1 h	14	43	-
6	DIBAL-H (3.0 equiv), MeTHF, -78 °C - rt, 1 h	2	69	-
7	DIBAL-H (3.0 equiv), DCM, -78 °C - rt, 1 h	-	75	-
8	DIBAL-H (3.0 equiv), toluene, -78 °C - rt, 1 h	-	73	-

^aIsolated yield.



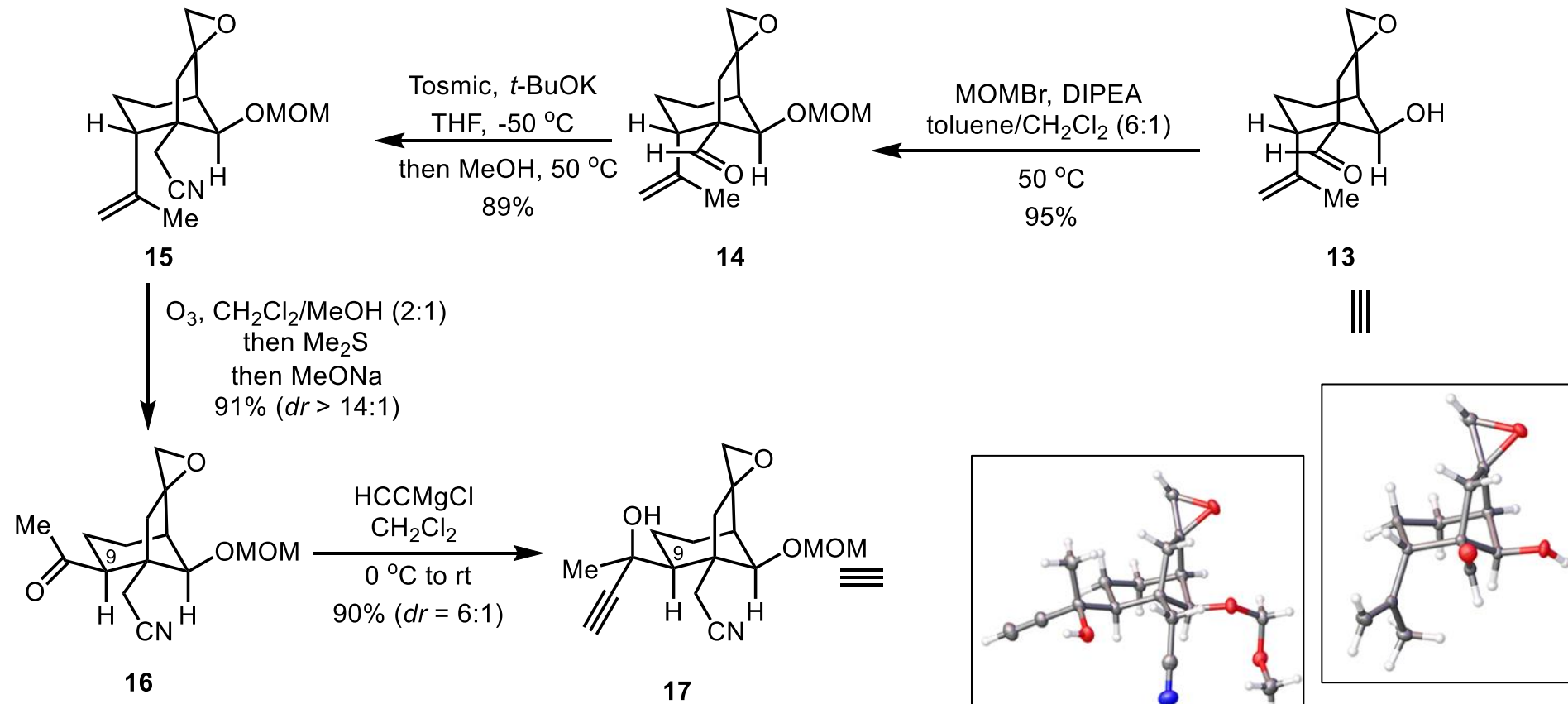
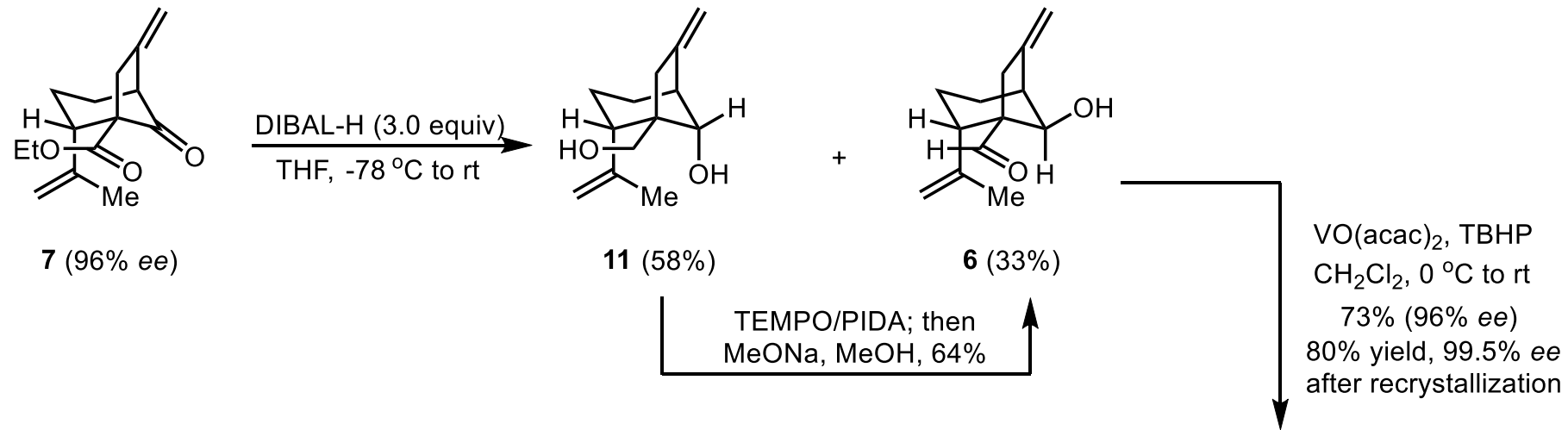
ratio (%)			
10	6	11	12
73	16	11	-

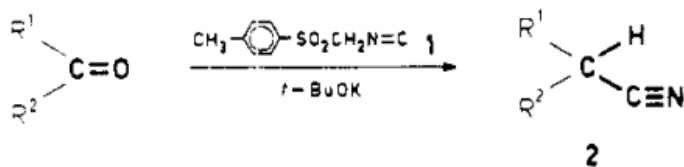
The ratio (**10**: **6**: **11**: **12**) was determined by the crude of $^1\text{H-NMR}$.



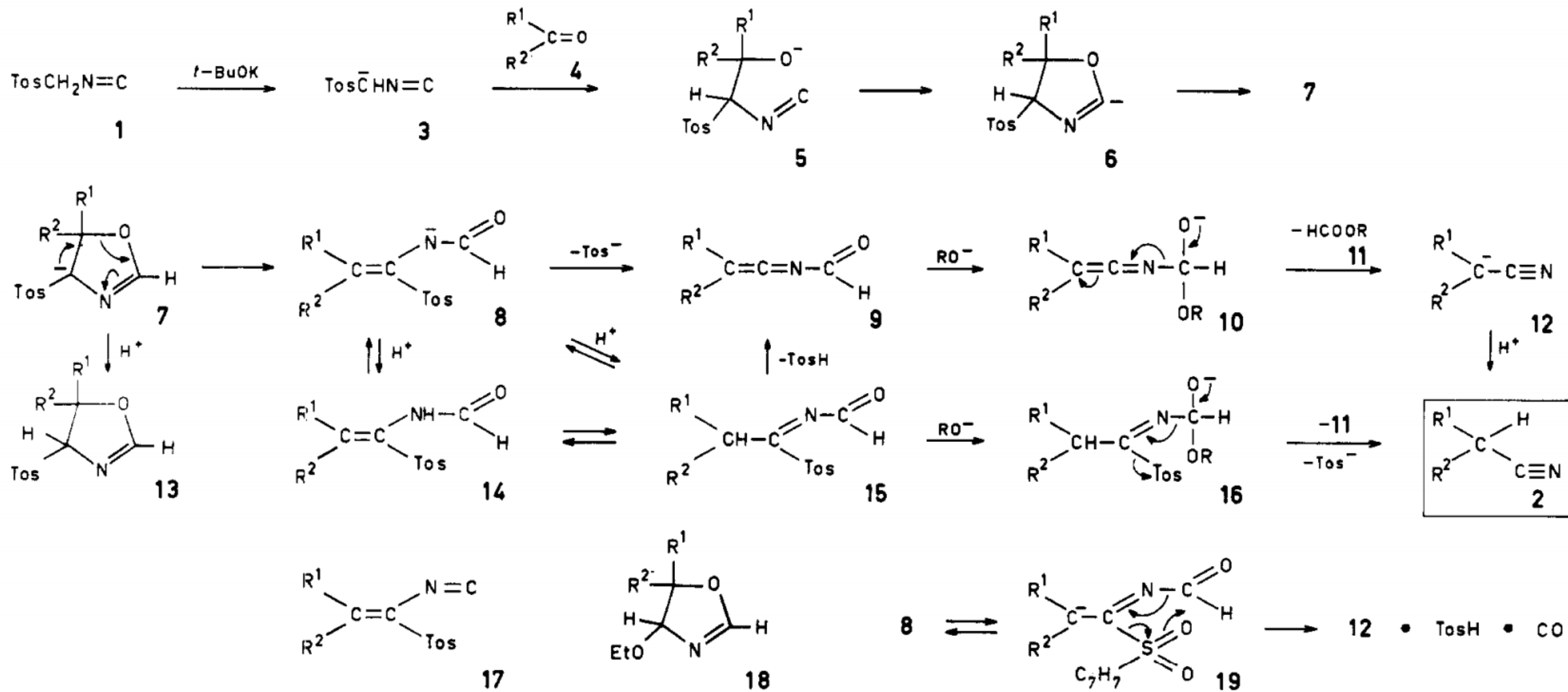
ratio (%)			
10	6	11	12
38	46	10	6

The ratio (**10**: **6**: **11**: **12**) was determined by the crude of $^1\text{H-NMR}$.



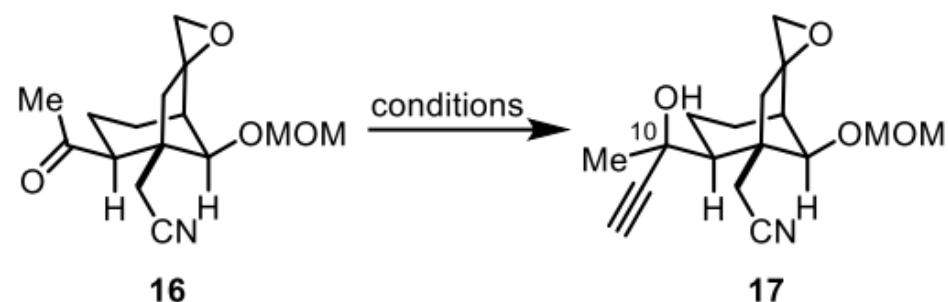


Scheme I. Proposed Mechanism for Conversion of Ketones to Nitriles with TosMIC According to Equation 1



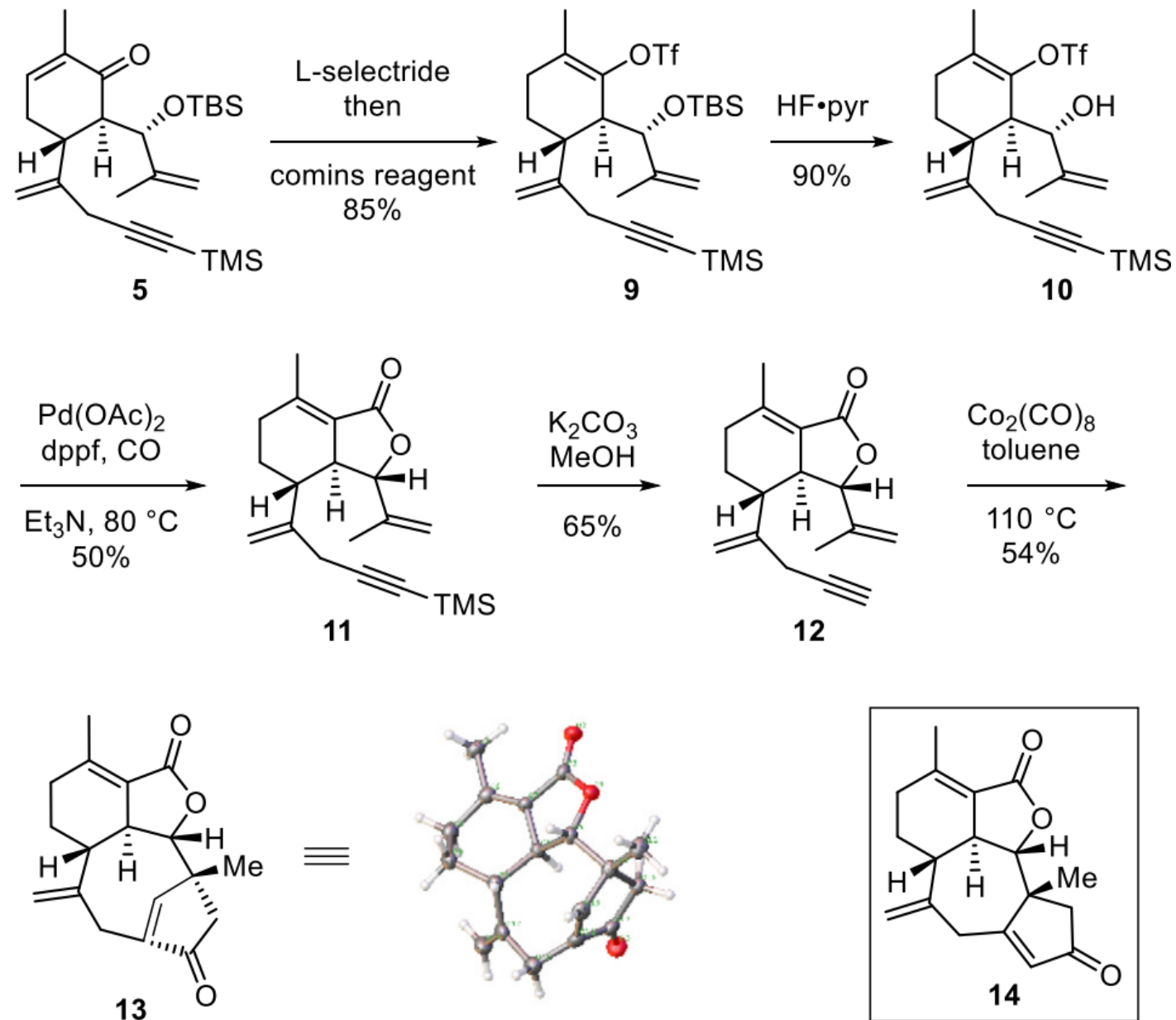
Section 1.5 Optimization of the addition reaction of ketone **16**.

Table S3. Optimization of the addition reaction of ketone **16**.

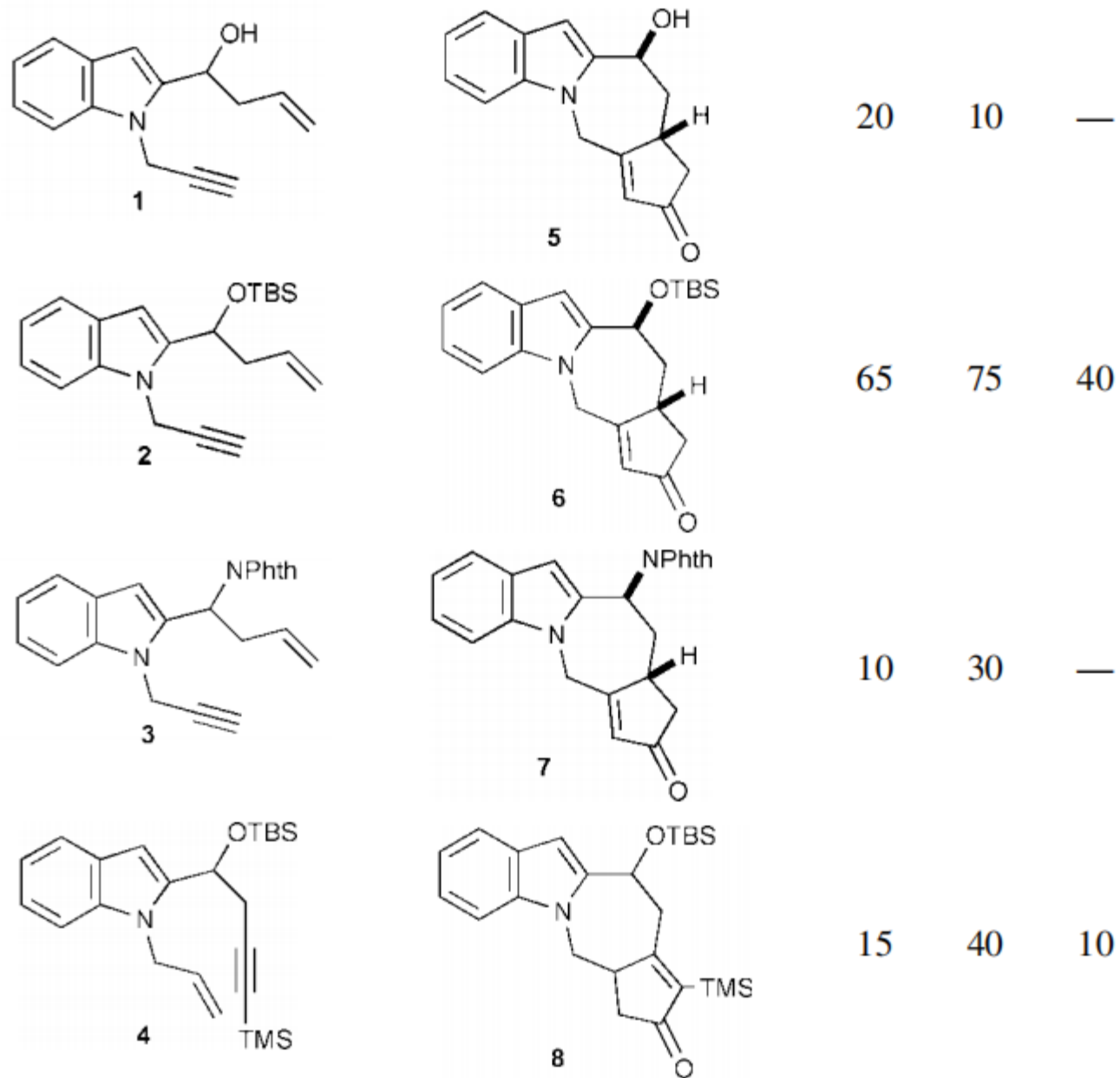


entry	conditions	yield (%) ^a	dr ^b
1	HCCMgBr (2.0 equiv), THF, 0 °C - rt	73	1:3
2	TMSCCLi (2.0 equiv), THF, 0 °C, then TBAF	51	1:4
3	Lithium acetylide ethylenediamine complex, THF, 0 °C	-	-
4	HCCMgBr (2.0 equiv), toluene, 0 °C - rt	71	4:1
5	HCCMgBr (2.0 equiv), DCM, 0 °C - rt	69	6:1
6	HCCMgCl (2.0 equiv), toluene, 0 °C - rt	93	4:1
7	HCCMgCl (2.0 equiv), DCM, 0 °C - rt	90	6:1
8	HCCMgCl (2.0 equiv), Et ₂ O, 0 °C - rt	49	2:1
9	HCCMgCl (2.0 equiv), MeTHF, 0 °C - rt	71	1:3

^aIsolated yield. ^bRatio of dr was determined by ¹H NMR of the pure isolated product.



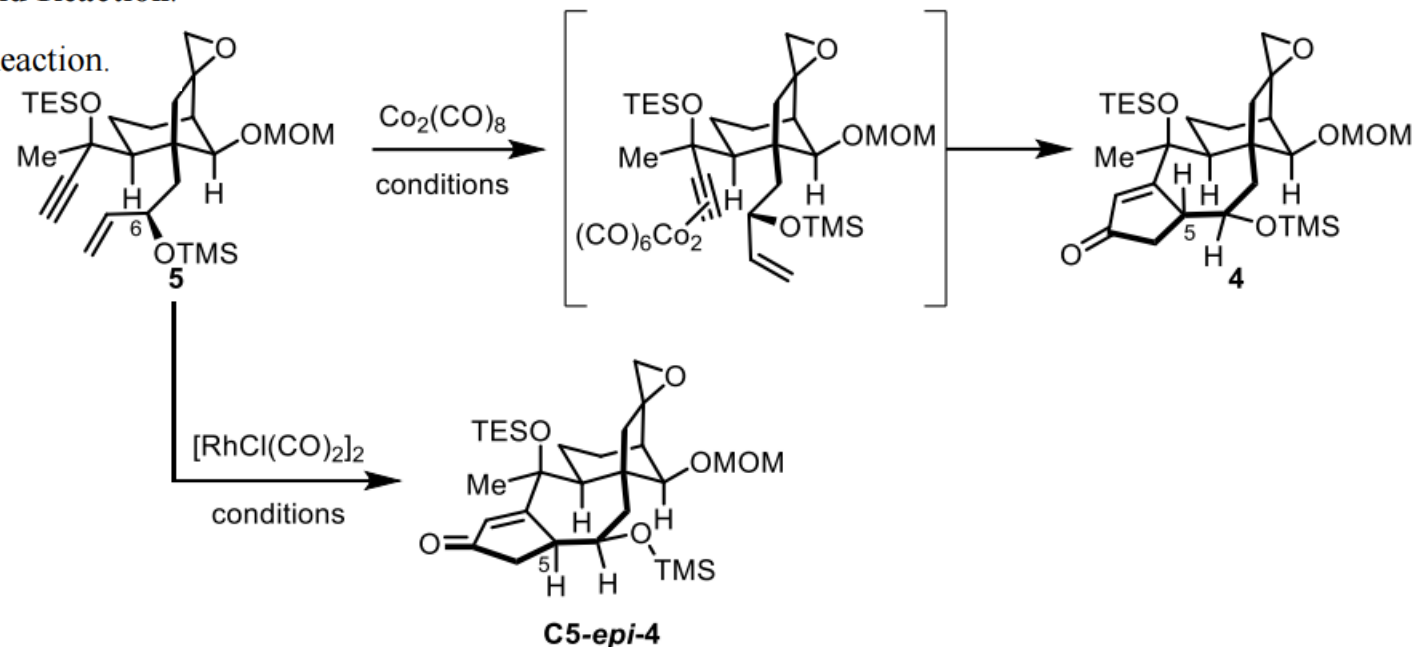
Scheme 3. Synthesis of compound **13**.



^a In pure product after purification by column chromatography with correct spectroscopic data (¹H, ¹³C NMR, IR).^b Phth = Phthalimido

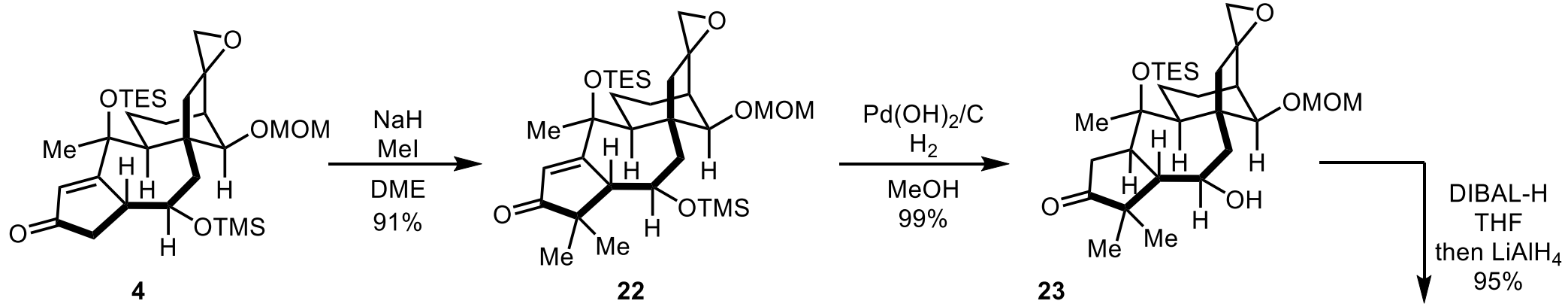
Section 1.6 Optimization of the Pauson-Khand Reaction.

Table S4. Optimization of the Pauson-Khand Reaction.

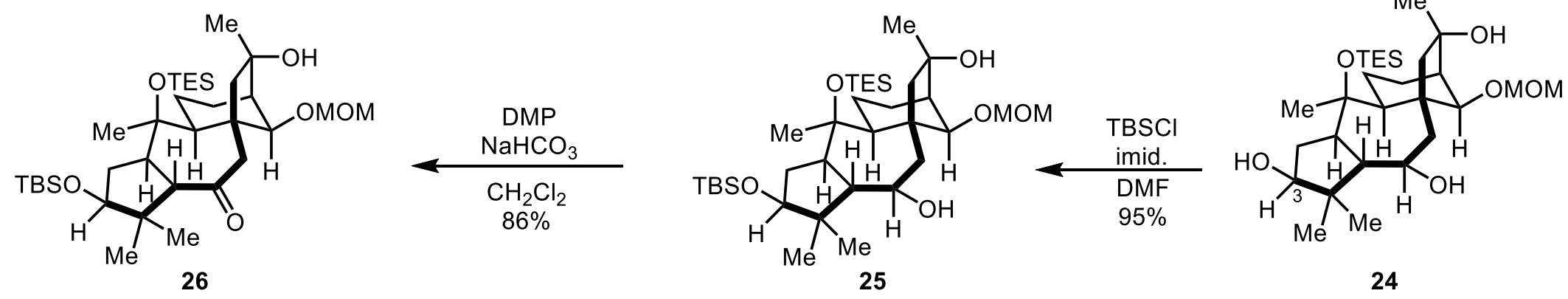


entry	conditions	yield 4 (%) ^a
1 ^b	$\text{Co}_2(\text{CO})_8$, toluene, 40 °C	<5
2	$\text{Co}_2(\text{CO})_8$, toluene, 40 - 60 °C	45
3	$\text{Co}_2(\text{CO})_8$, toluene, 110 °C	21
4	$\text{Co}_2(\text{CO})_8$, THF, 40 - 60 °C	20
5 ^c	$\text{Co}_2(\text{CO})_8$, toluene, 40 °C; then NMO, 60 °C	-
6 ^c	$\text{Co}_2(\text{CO})_8$, toluene, 40 °C; then TMTU, rt	-
7 ^c	$\text{Co}_2(\text{CO})_8$, toluene, 40 °C; then TMAO, rt	-
8 ^c	$\text{Co}_2(\text{CO})_8$, toluene, 40 °C; then DMSO, rt	-
9 ^d	$[\text{RhCl}(\text{CO})_2]_2$ (5 mol %), CO, toluene, rt - 90 °C	-
10 ^e	$[\text{RhCl}(\text{CO})_2]_2$ (5 mol %), CO, toluene, 110 °C	-
11 ^f	$[\text{RhCl}(\text{CO})_2]_2$ (1.5 equiv), CO, toluene, 110 °C	-

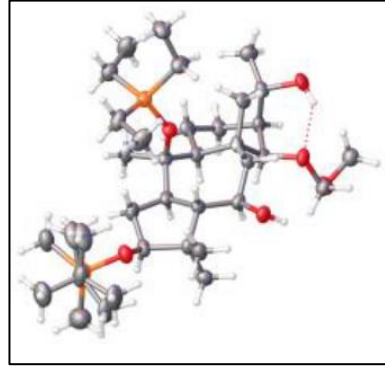
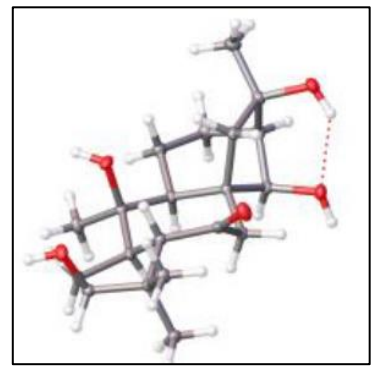
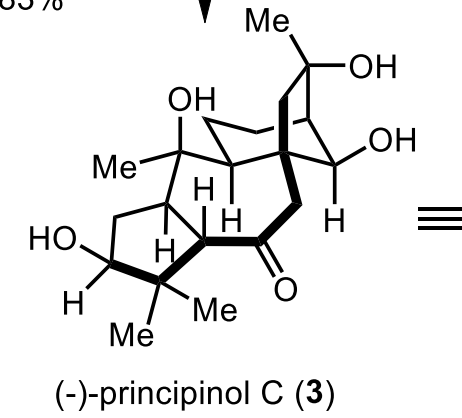
^aIsolated yield. ^bMost of dicobalt alkyne complex was remained. ^cDicobalt alkyne complex was converted back to **5** after additive was added. ^dNo reaction. ^eThe reaction was very slow and **C5-epi-4** was observed in a trace amount. ^f**C5-epi-4** was obtained in 21% yield.



DIBAL-H
 THF
 then LiAlH₄
 95%



TBAF, THF
 then
 H₂SO₄, 1,4-Dioxane
 83%



≡