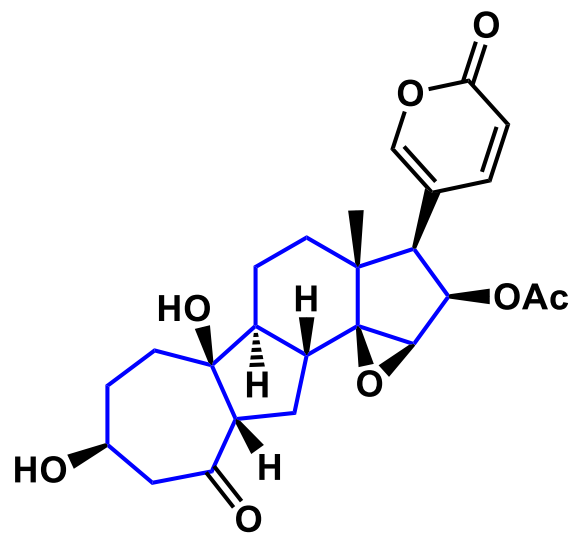
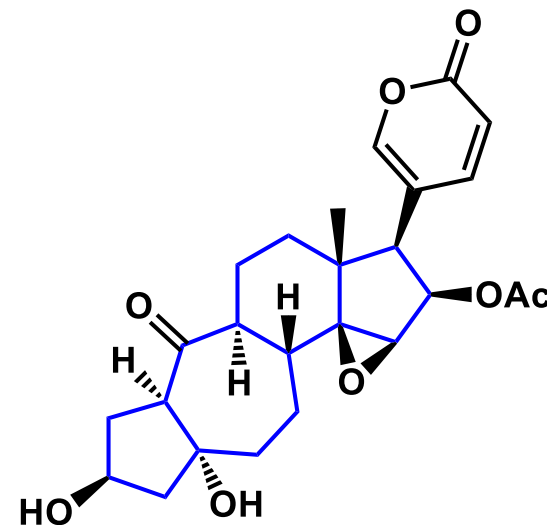


# Asymmetric Total Synthesis of Twin Bufogargarizins A and B

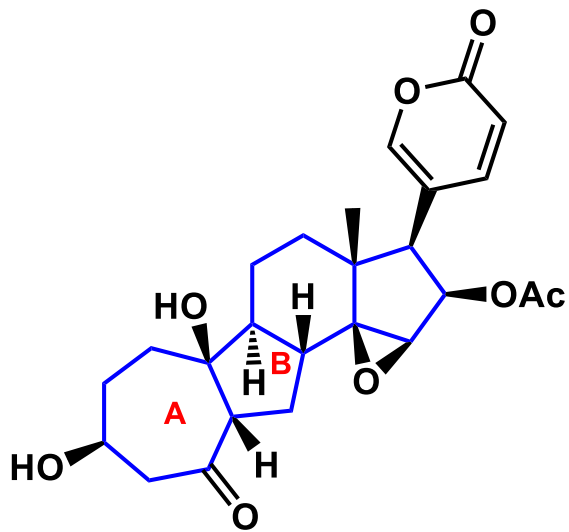
Li-Ping Zhong, Rui Feng, Jing-Jing Wang, and Chuang-Chuang Li\*



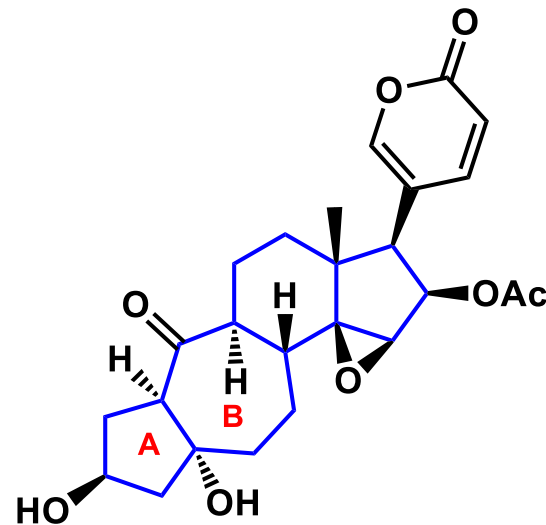
bufogargarizin A (1)



bufogargarizin B (2)



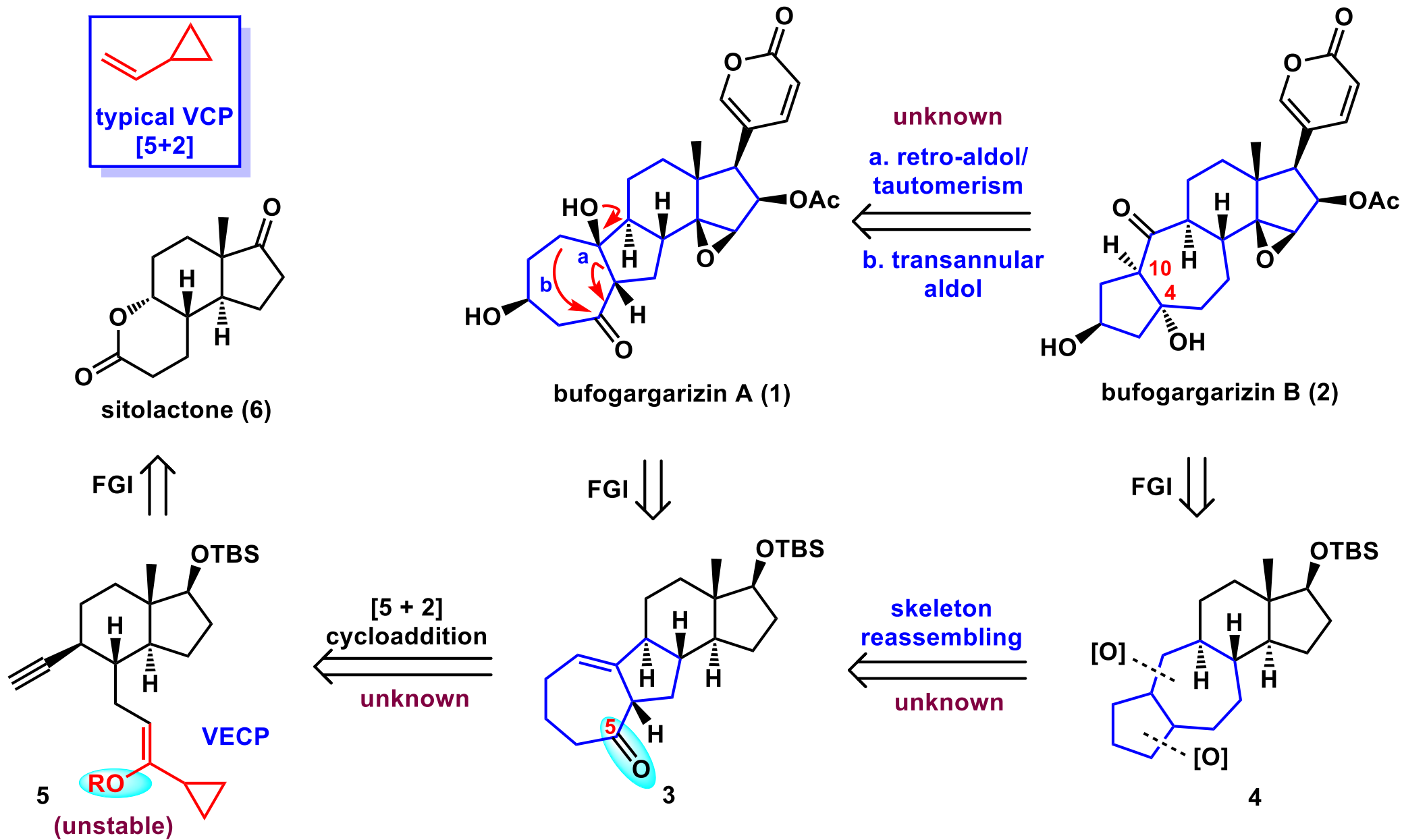
bufogargarizin A (1)



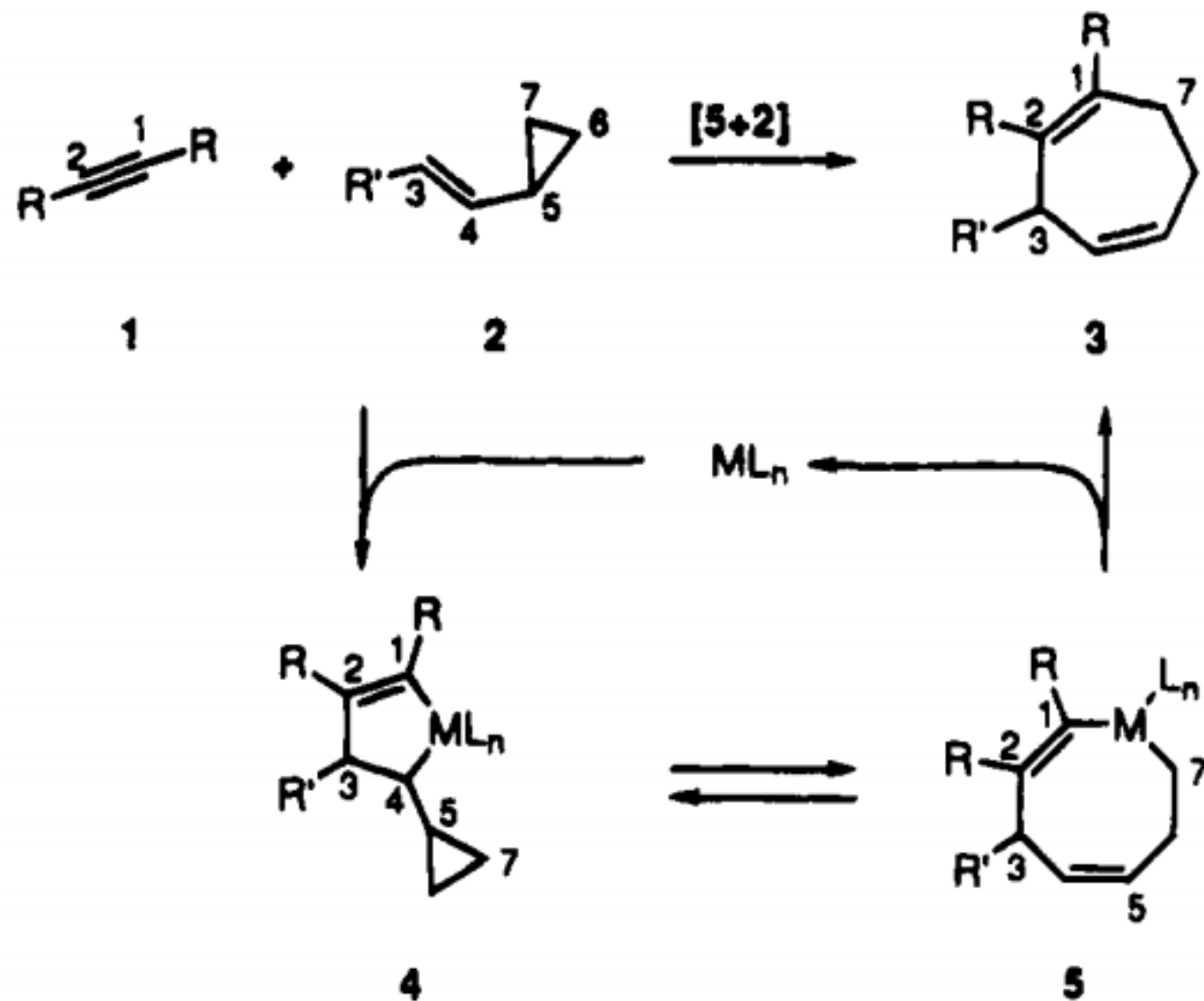
bufogargarizin B (2)

- ❑ Unusual [7/5/6/5] or [5/7/6/5] tetracyclic skeleton
- ❑ Highly oxygenated
- ❑ 10 Stereocenters: 9 contiguous, 3 quaternary
- ❑ No Total Synthesis

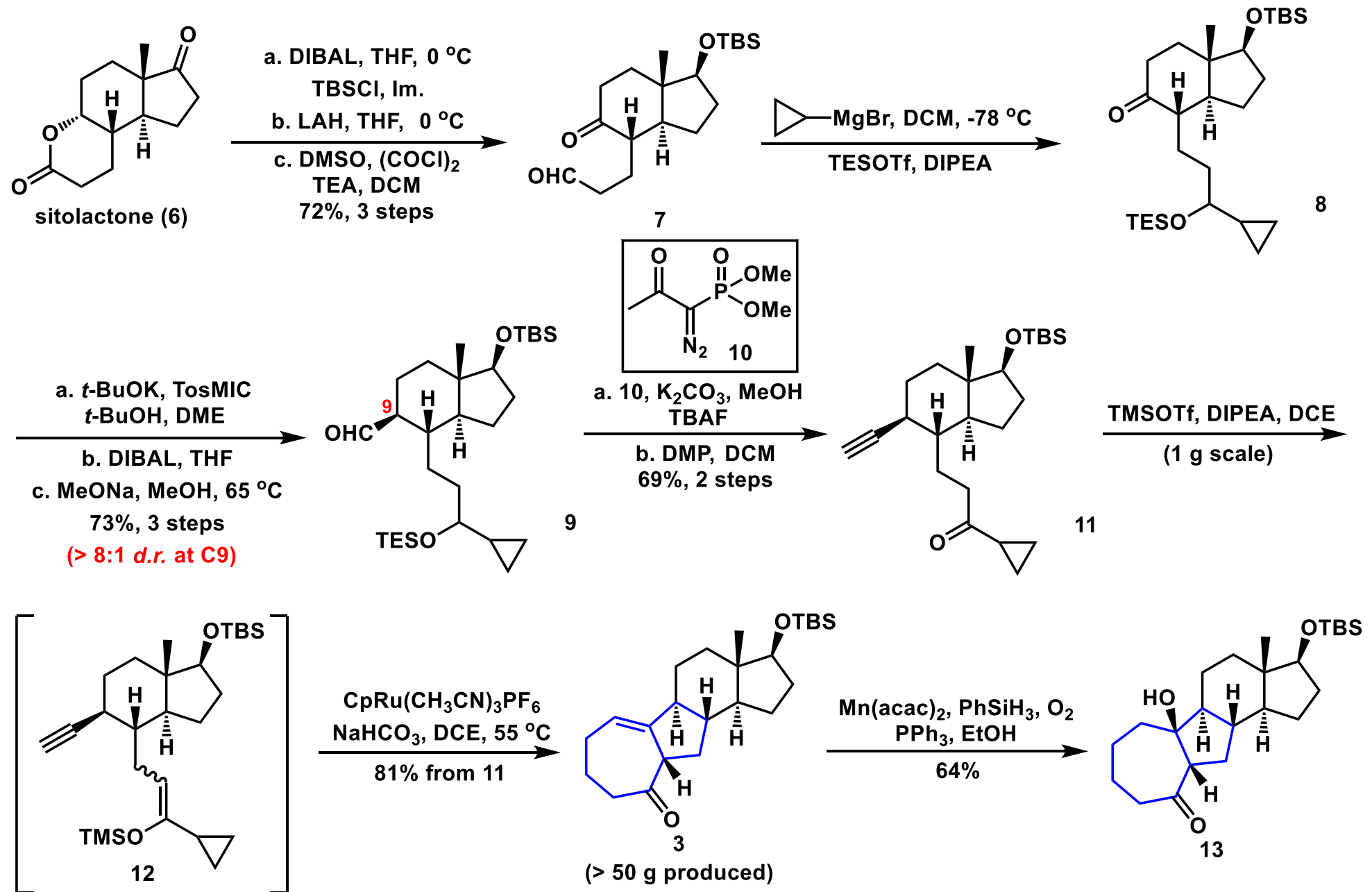
# Scheme 1. Retrosynthetic Analysis of Bufogargarizins A and B



## Transition Metal Catalyzed [5 + 2] Cycloadditions of Vinylcyclopropanes and Alkynes

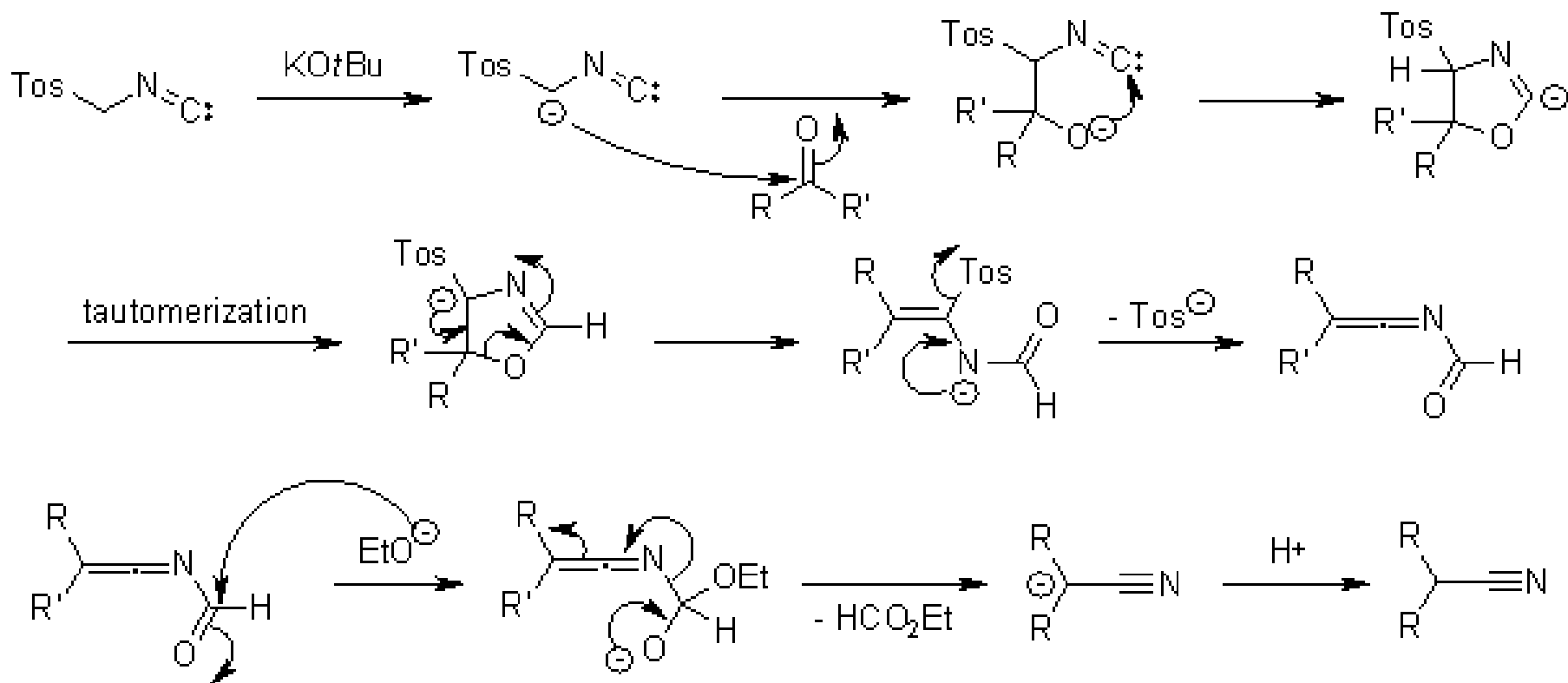
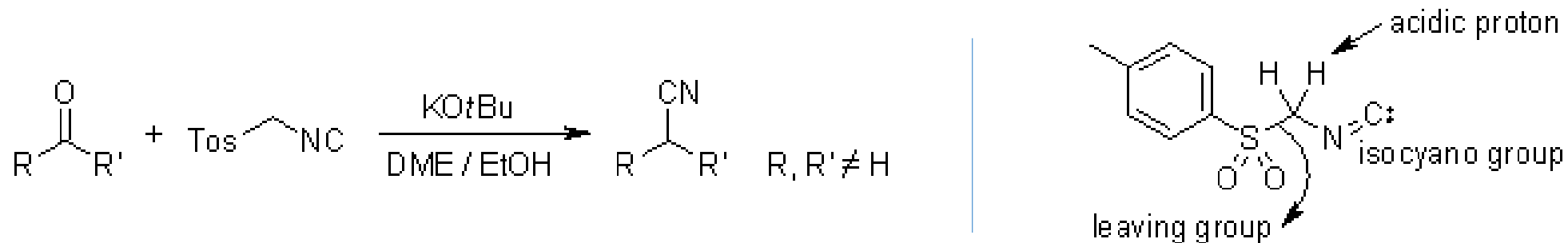


## Scheme 2. Asymmetric Synthesis of 13

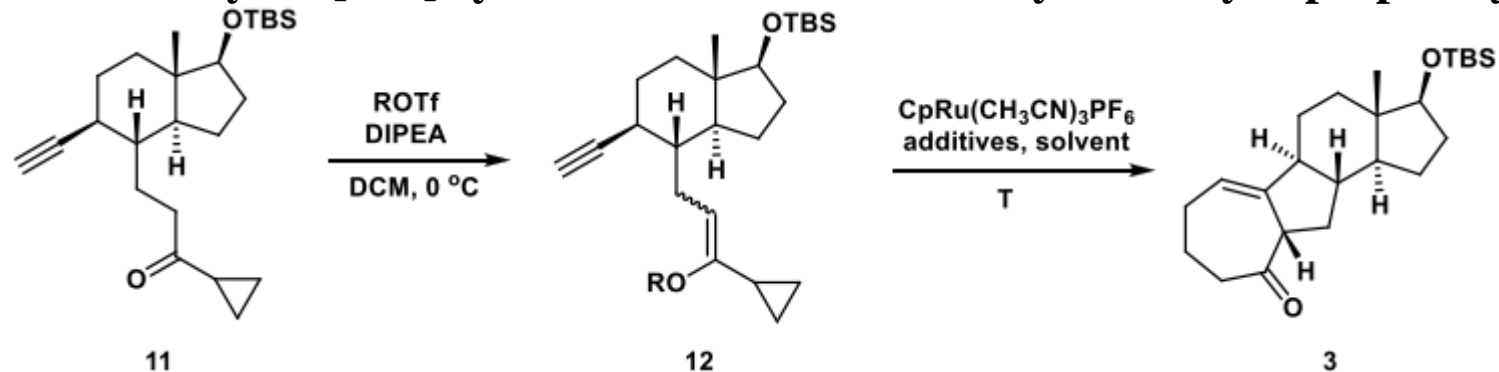


## Van Leusen反应

酮和对甲苯磺酰甲基异腈（TosMIC）一锅法反应得到多一个碳的腈的反应。



**Table S1. Optimization of Ru-catalyzed [5+2] cycloaddition reaction of vinyl ether cyclopropane-yne on compound 11 .**



Entry	Catalyst (eq.)	R group	Additives (1.0 eq.)	Solvents	T/°C	Conc. (mol·L <sup>-1</sup> )	Yield/%
1	0.2 eq.	TIPS	NaHCO <sub>3</sub>	DCE	55	0.02	64 <sup>a</sup>
2	0.2 eq.	TBS	NaHCO <sub>3</sub>	DCE	55	0.01	65 <sup>a</sup>
3	0.2 eq.	TES	NaHCO <sub>3</sub>	DCE	55	0.02	50 <sup>a</sup>
<b>4</b>	<b>0.2 eq.</b>	<b>TMS</b>	<b>NaHCO<sub>3</sub></b>	<b>DCE</b>	<b>55</b>	<b>0.01</b>	<b>82<sup>a</sup></b>
5	0.2 eq.	TMS	NaHCO <sub>3</sub>	DCE	25	0.01	59 <sup>a</sup>
6	0.2 eq.	TMS	–	DCE	55	0.01	46 <sup>a</sup>
7	0.1 eq.	TMS	NaHCO <sub>3</sub>	DCE	55	0.01	37 <sup>a</sup>
8	0.2 eq.	TMS	NaHCO <sub>3</sub>	DCE	55	0.05	63 <sup>a</sup>
9	0.2 eq.	TMS	NaHCO <sub>3</sub>	DCE	83	0.01	74 <sup>a</sup>
<b>10</b>	<b>0.2 eq.</b>	<b>TMS</b>	<b>NaHCO<sub>3</sub></b>	<b>DCE</b>	<b>55</b>	<b>0.01</b>	<b>81<sup>b</sup></b>
11	0.2 eq.	TMS	K <sub>2</sub> CO <sub>3</sub>	DCE	55	0.01	N.D. <sup>a</sup>
12	0.2 eq.	TMS	NaHCO <sub>3</sub> DPPP	DCE	55	0.01	N.D. <sup>a</sup>

**Table S1. Optimization of Ru-catalyzed [5+2] cycloaddition reaction of vinyl ether cyclopropane-yne on compound 11 .**

13	0.2 eq.	TMS	NaHCO <sub>3</sub>	DCM	39	0.01	Trace <sup>a</sup>
14	0.2 eq.	TMS	NaHCO <sub>3</sub>	acetone	55	0.01	Trace <sup>a</sup>
15	0.2 eq.	TMS	NaHCO <sub>3</sub>	toluene	110	0.01	N.R. <sup>a</sup>
16	0.2 eq. <sup>c</sup>	TMS	NaHCO <sub>3</sub>	toluene	55	0.01	RSM
17	0.2 eq. <sup>c</sup>	TMS	NaHCO <sub>3</sub>	toluene	110	0.01	Decomposed

**Note:** N.D.: not detected; N.R.: no reaction; RSM: recovering starting materials; DCE: 1,2-dichloroethane; DPPP: 1,3-bis(diphenylphosphino)propane;

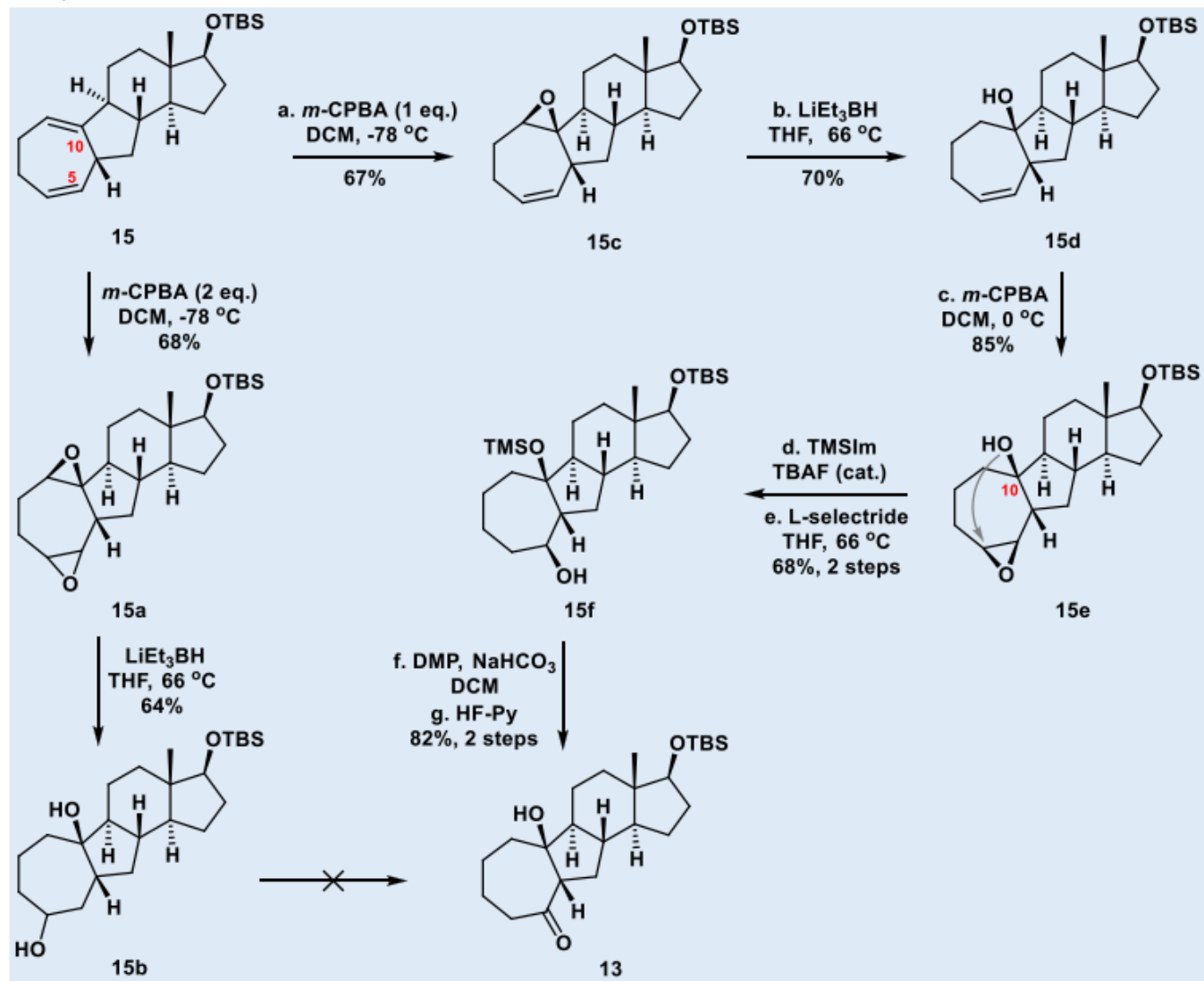
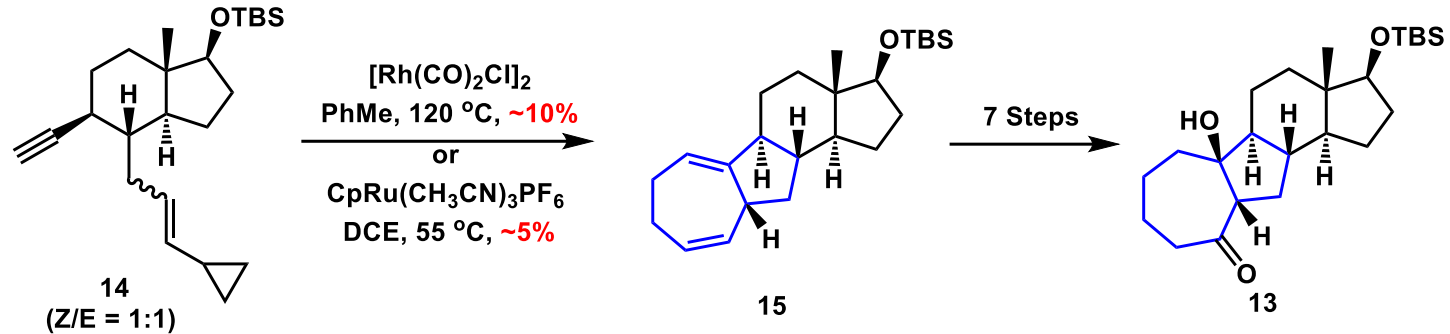
a. **Stepwise procedure:** The reaction was performed under 0.1 mmol substrate scale according to similar procedure as General procedure for vinyl ether cyclopropane-yne [5+2] reaction in Page S26;

b. **One-pot sequence procedure:** The reaction was performed under 0.1 mmol substrate scale according to similar procedure as Synthesis of compound 3 in Page S10;

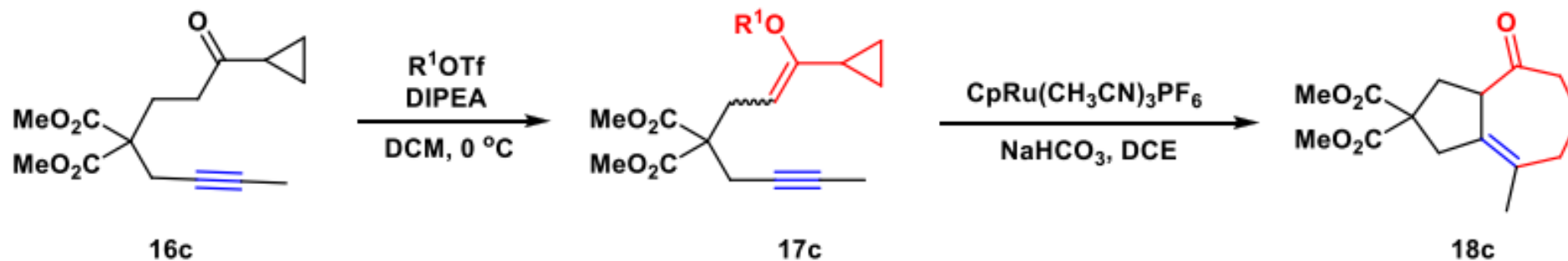
c. **[Rh(CO)<sub>2</sub>Cl]<sub>2</sub>** was used as a catalyst, the procedure is similar to the stepwise procedure.

**Note:** Compound **12** could be purified by neutral alumina column chromatography, the configuration of silyl enol ether was determined by 2D-NOESY spectrum analysis.



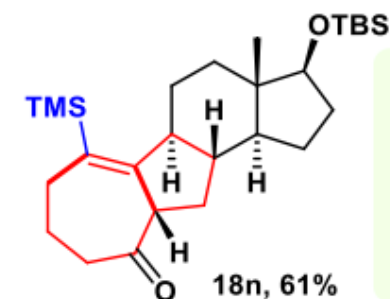
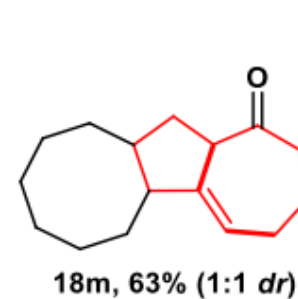
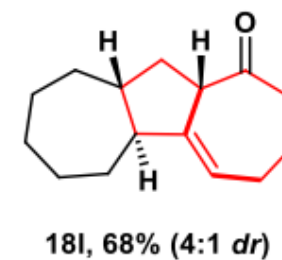
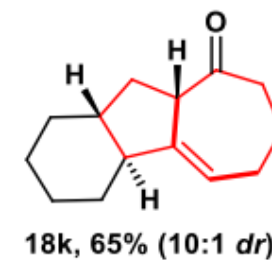
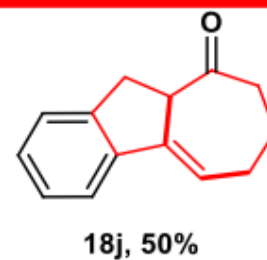
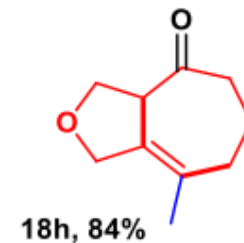
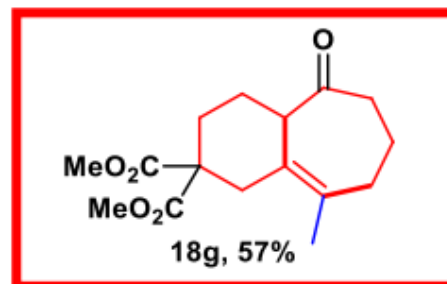
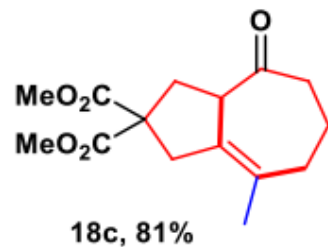
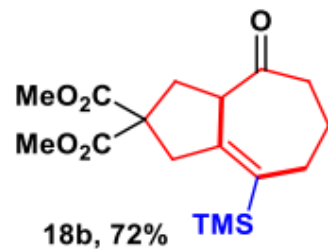
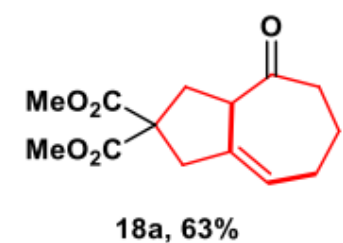
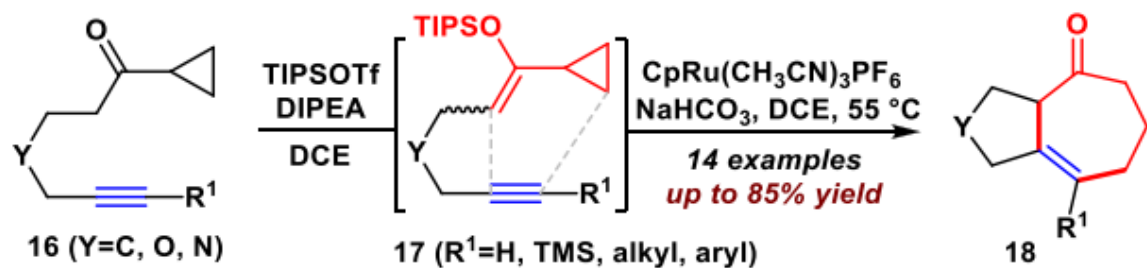


**Table S2. Optimization of Ru-catalyzed [5+2] cycloaddition reaction of vinyl ether cyclopropane-yne reaction on general substrate**



Entry	Catalyst (eq.)	R <sup>1</sup> Group	Additives (1.0 eq.)	Solvents	T/°C	Yield/%	12	0.25	TIPS	NaHCO <sub>3</sub>	DCE	25	81
1	0.40	TIPS	NaHCO <sub>3</sub>	DCE	50	75	13	0.25	TIPS	NaHCO <sub>3</sub>	DCE	15	72
2	0.25	TIPS	NaHCO <sub>3</sub>	DCE	50	73	14	0.25	TIPS	NaHCO <sub>3</sub>	DCE	0	N.R.
3	0.20	TIPS	NaHCO <sub>3</sub>	DCE	50	65	15	0.25	TIPS	NaHCO <sub>3</sub>	DCM	25	68
4	0.10	TIPS	NaHCO <sub>3</sub>	DCE	50	67	16	0.25	TIPS	NaHCO <sub>3</sub>	CDCl <sub>3</sub>	25	53
5	0.05	TIPS	NaHCO <sub>3</sub>	DCE	50	57	17	0.25	TIPS	NaHCO <sub>3</sub>	acetone	25	45
6	0.25	TMS	NaHCO <sub>3</sub>	DCE	50	60	18	0.25	TIPS	NaHCO <sub>3</sub>	DMF	25	33
7	0.25	TES	NaHCO <sub>3</sub>	DCE	50	66	19	0.25	TIPS	NaHCO <sub>3</sub>	toluene	25	N.R.
8	0.25	TBS	NaHCO <sub>3</sub>	DCE	50	74	20	0.25	TIPS	-	DCE	83	57
9	0.25	TIPS	NaHCO <sub>3</sub>	DCE	100	55	21	0.25	TIPS	K <sub>2</sub> CO <sub>3</sub>	DCE	83	N.D.
11	0.25	TIPS	NaHCO <sub>3</sub>	DCE	83	67	22	0.25	TIPS	DPPP	DCE	83	Trace

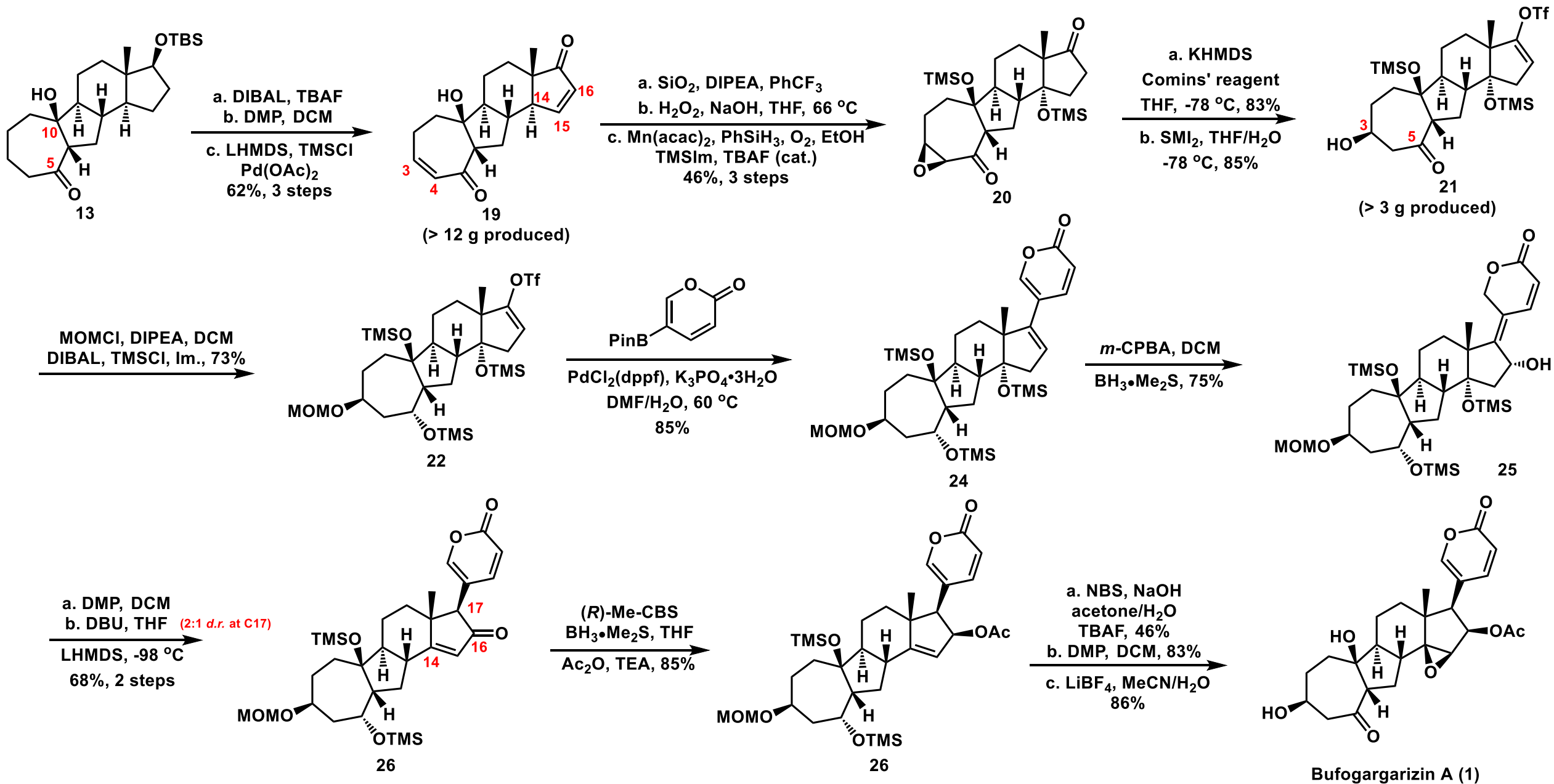
### Scheme 3. Substrate Scope of the Ru-Catalyzed [5 + 2] Cycloaddition Reaction of Vinyl Ether Cyclopropane-yne



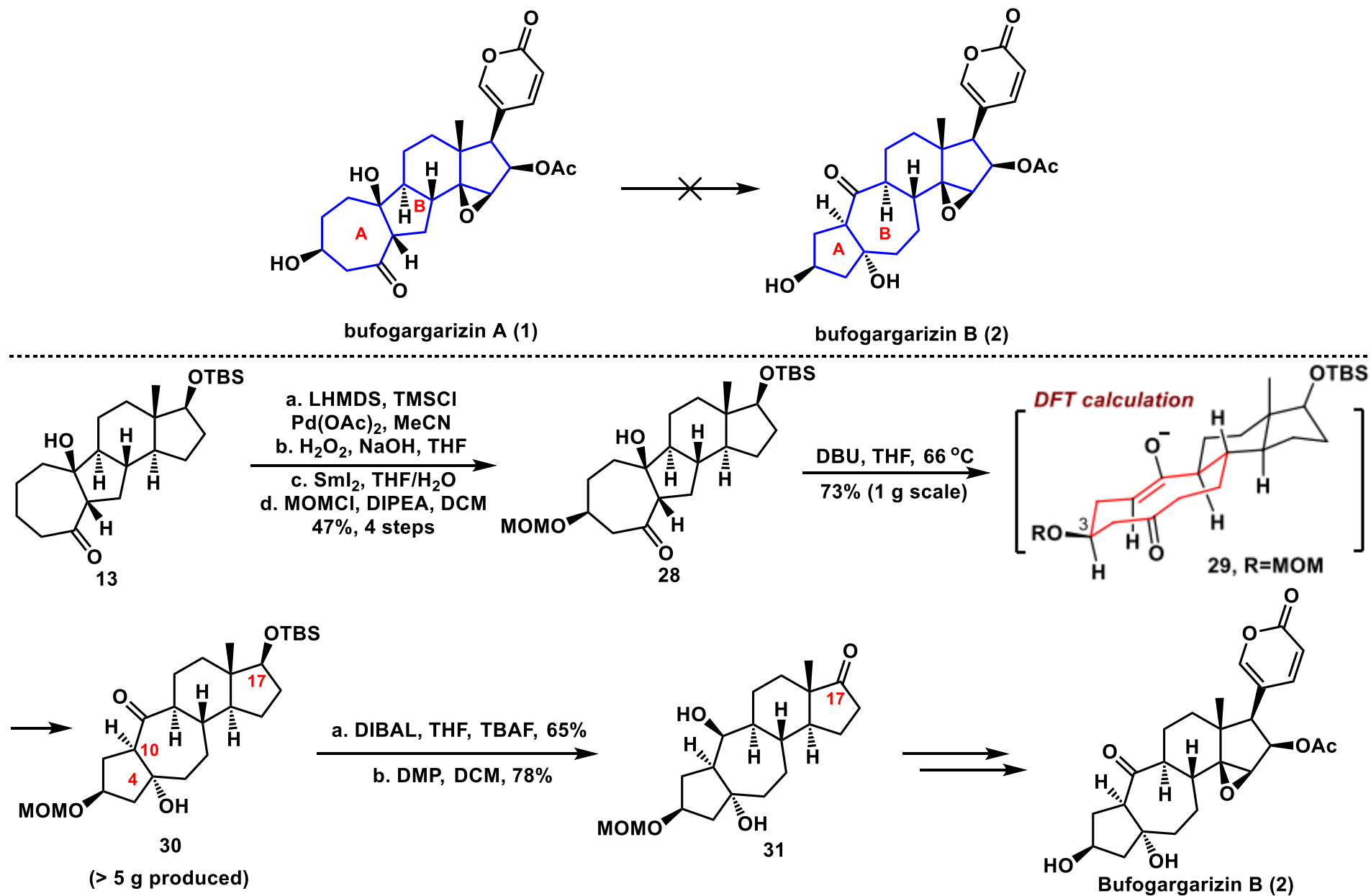
a step delivers:

- ◆ [7-5-X] ring systems
- ◆ 2 new C-C bonds
- ◆ 1 new stereocenter
- ◆ 1 newly formed polysubstituted olefin

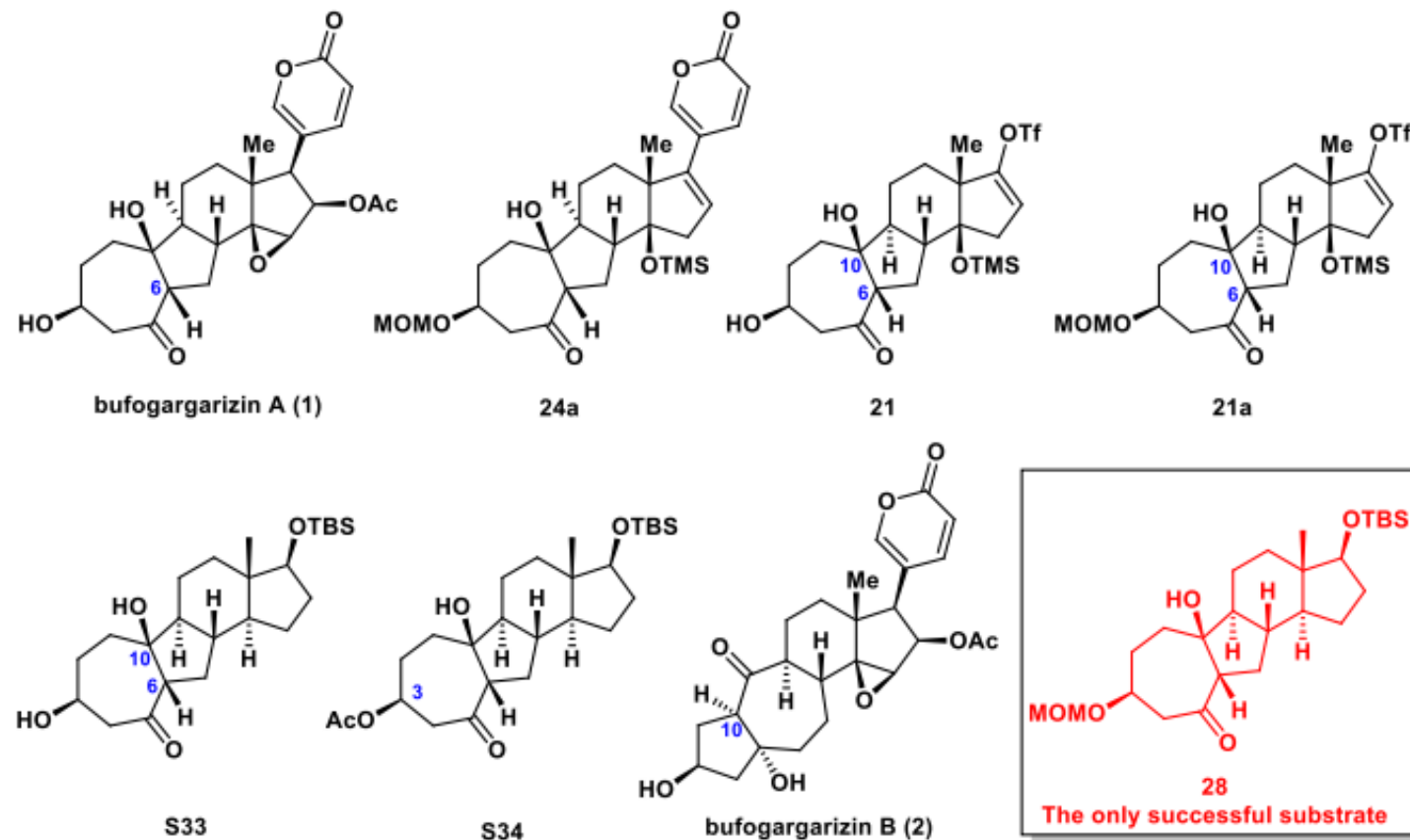
## Scheme 4. Asymmetric Total Synthesis of Bufogargarizin A



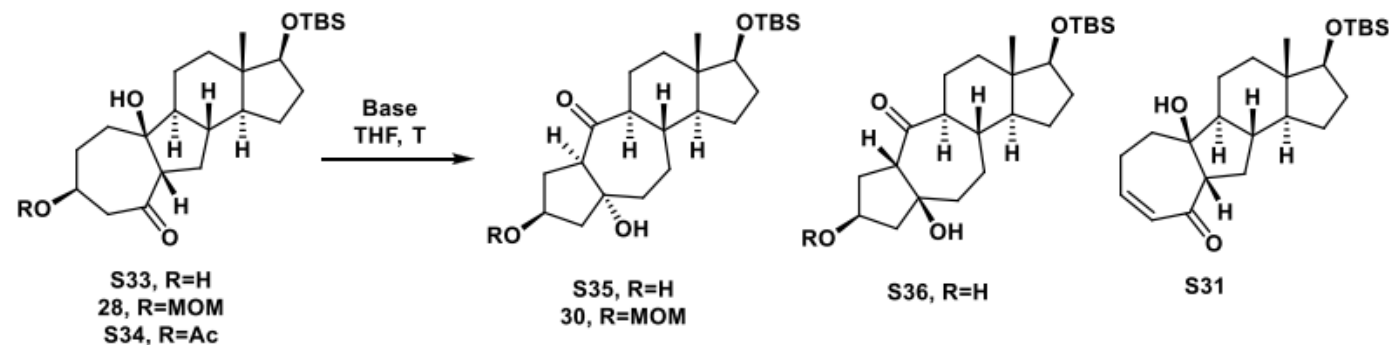
## Scheme 5. Asymmetric Total Synthesis of Bufogargarizin B



Summary of attempted substrates for retro-aldol/transannular aldol cascade reaction.



There are several substrates (see above) we have tried for the retro-aldol/transannular aldol cascade reaction. In some substrates (such as 1, 24a, 21, 21a, S33), undesired C10 or C6 diastereoisomers were obtained. Under more harsh conditions, substrates 1, 24a, and 2 were decomposed. This would be due to some undesired reactions occurring, such as the pyranone ring opening, epoxide ring opening, or ester hydrolysis. For S34, C3 -elimination was the main by-reaction. The compound 28 was the only substrate with satisfactory stereoselectivity and yield after extensive investigation. Thus, we think that 28 with lower oxidation state and simpler functional groups can effectively avoid unnecessary by-reactions.

**Table S5: Optimization of retro-aldol/transannular aldol cascade reactions<sup>a,b</sup>**

Entry	Compound	Base	Solvents	T/°C	Ratio (S35:S36:S31)	Yield S35(%) <sup>c</sup>
1	S33	LHMDS	THF	-78	–	N.R.
2	S33	LHMDS	THF	0	–	N.R.
3	S33	TBAF	THF	66	1:2:1	21
4	S33	DBU	THF	66	–	Trace
5	S33	DBU (7 eq.)	THF	66	1.5:1	30
6	S33	DBU (15 eq.)	THF	66	1:1	45
7	S33	DBU (15 eq.)	dioxane	102	1:1.2	40
8	S33	TBD (15 eq.)	THF	50	1:1	42
9	S33	K <sub>2</sub> CO <sub>3</sub>	MeOH	50	–	Mess
10	S33	NaOH	EtOH	50	–	Mess
11	28	DBU (15 eq.)	THF	66	only 30	75
12	S34	K <sub>2</sub> CO <sub>3</sub>	THF	83	only S31	45 <sup>d</sup>

Note: a. N.D., not detected; N.R., no reaction; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene;

b. To a solution of S33, 28 or S34 (0.1 mmol, 1.0 equiv.) in solvent (2 mL) was added base (0.2 mmol, 2.0 equiv., unless otherwise stated), and the reaction mixture was stirred for 20 hours at the temperature as showed in table;

c. Isolated yield;

d. Isolated yield of S31.

