Enantioselective Total Syntheses of Manginoids A and C and Guignardones A and C

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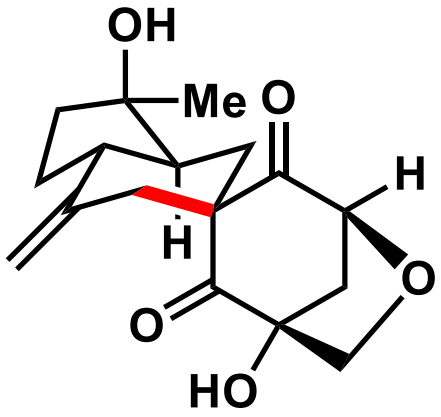
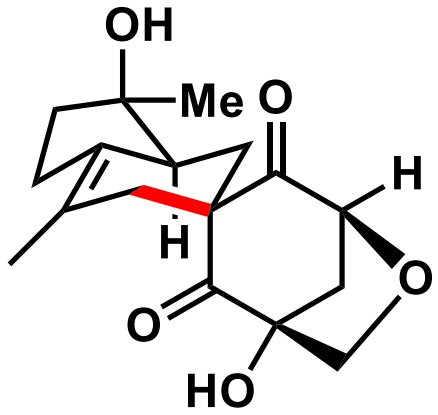
A) C-C bond cyclization

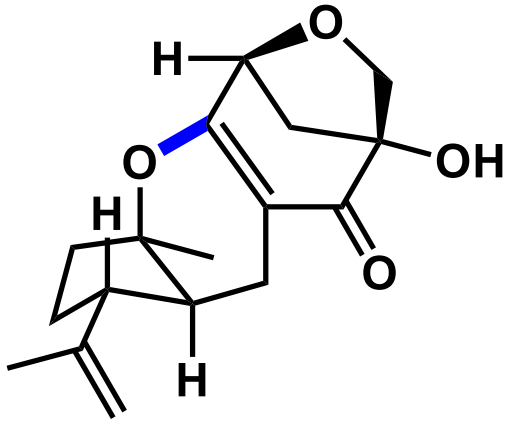


manginoid A (**1**)

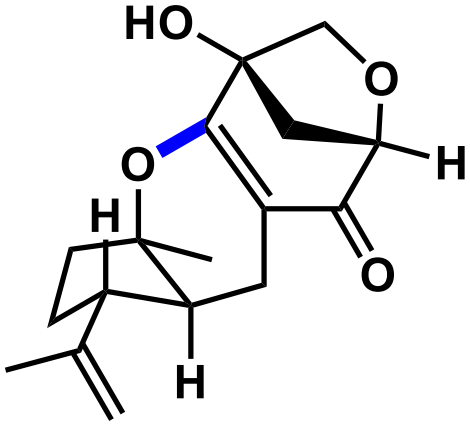


manginoid C (**2**)

B) C-O bond cyclization



guignardone A (**3**)



guignardone C (**4**)

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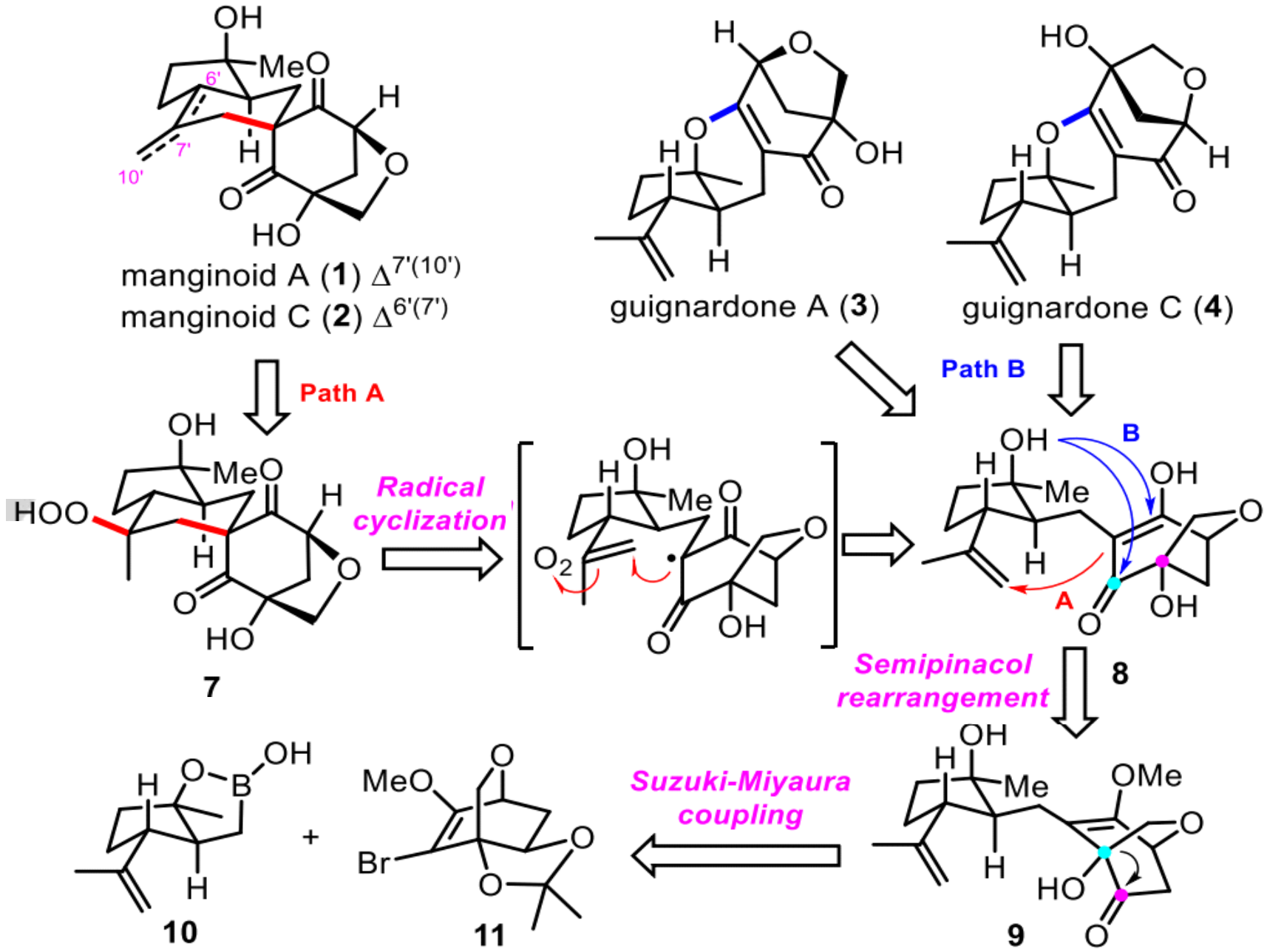
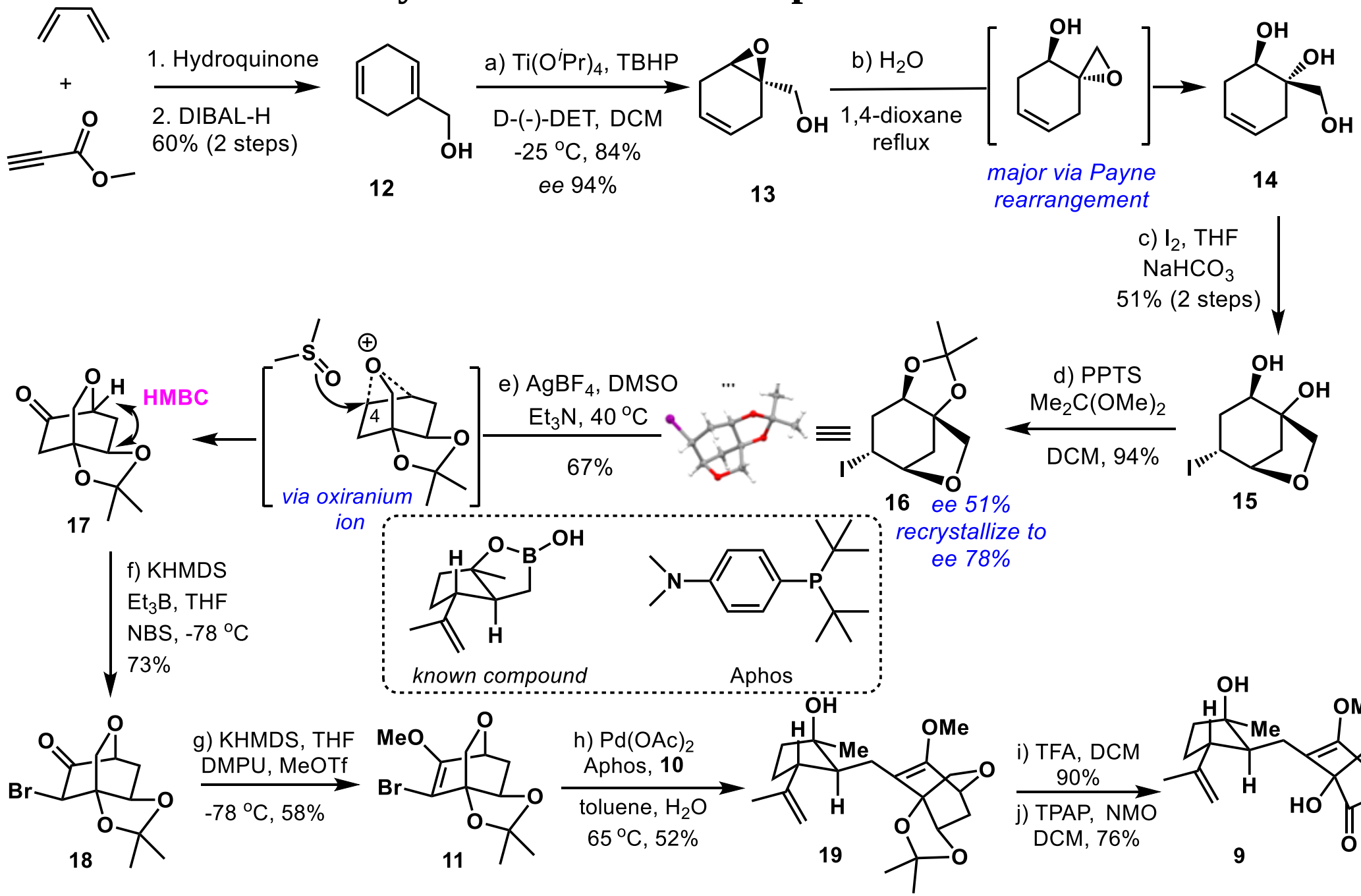
Snthetic analysis of manginoids and guignardones



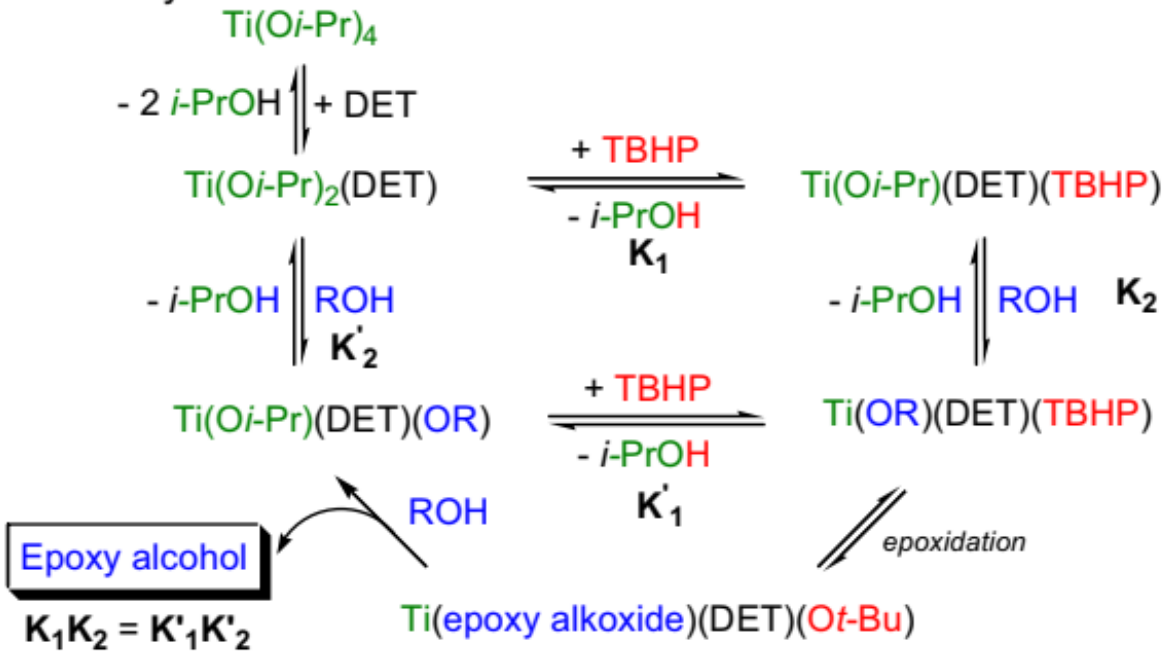
Synthesis of all carbon precursor 9



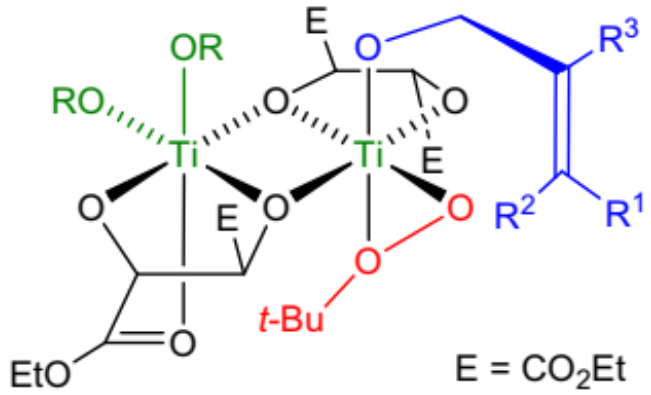
Sharpless Asymmetric Epoxidation

Mechanism: [36,3,37-39,18]

The first step is the rapid ligand exchange of Ti(O*i*-Pr)$_4$ with DET. The resulting complex undergoes further ligand exchange with the allylic alcohol substrate and then TBHP. The exact structure of the active catalyst is difficult to determine due to the rapid ligand exchange but it is likely to have a dimeric structure. The hydroperoxide and the allylic alcohol occupy the axial coordination site on the titanium and this model accounts for the enantiofacial selectivity.



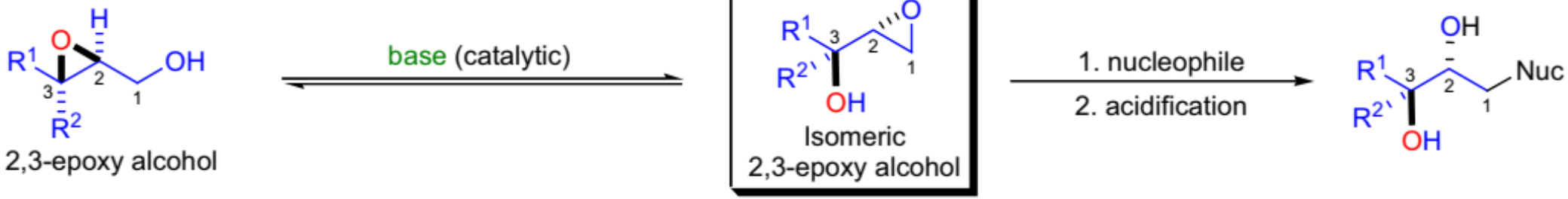
Transition state of epoxidation:



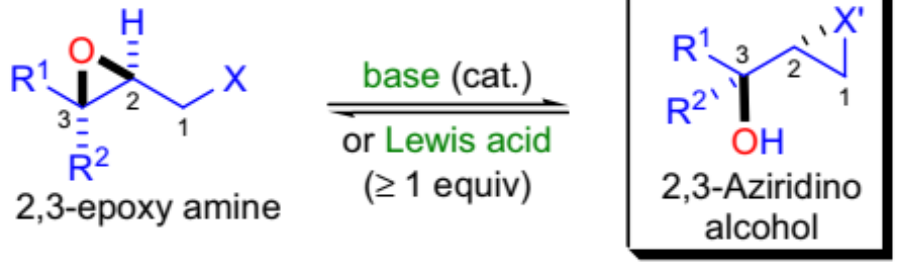
$$\text{Rate} = \frac{[\text{Ti(O}i\text{-Pr)}_2\text{(DET)}]\,[\text{TBHP}]\,[\text{ROH}]}{[i\text{-PrOH}]^2}$$

Payne Rearrangement

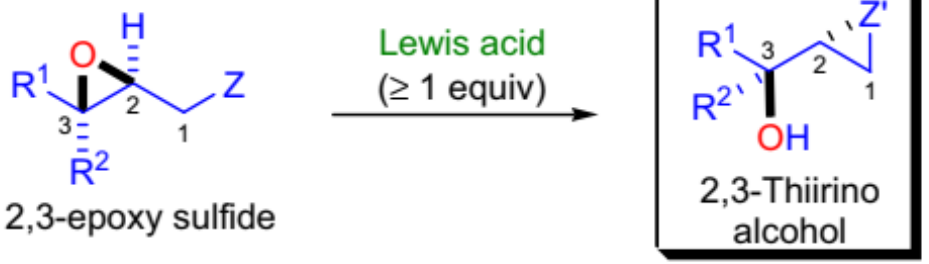
Payne rearrangement followed by nucleophilic epoxide ring-opening:



Aza-Payne rearrangement (can be true equilibrium):

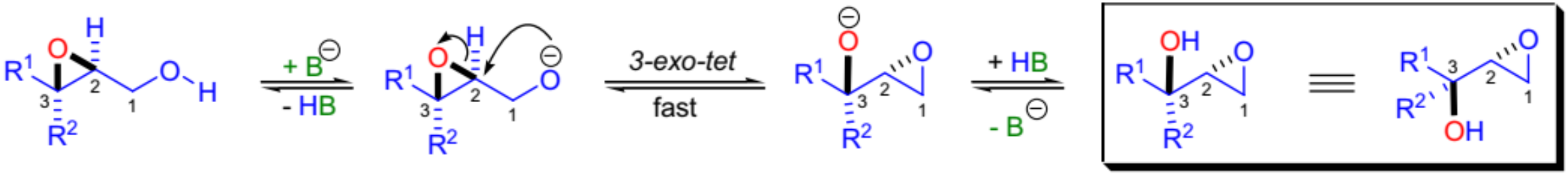


Thia-Payne rearrangement (only forward direction):



$R^{1\text{-}2}$ = H, alkyl, aryl; when X = NR_2, X' = NR_2^+; when X = NHMs, X' = NMs; when Z = SAc, Z' = S; when Z = SR, Z' = SR^+

base: NaOH, KOH, NaOR, NaH, KH; Lewis acid: $AlMe_3$, TMSOTf, $PhB(OH)_2$, $BF_3{\cdot}OEt_2$, $Ti(O\textit{i}\text{-}Pr)_4$

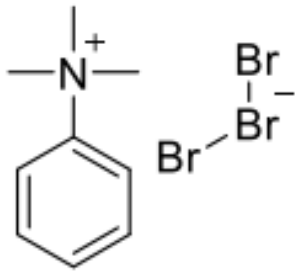


Bromination Screening of 17

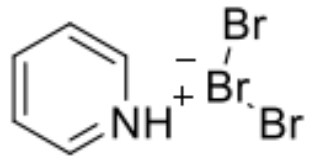
17 18

Entry	Reagent	Result
1	**PTAP**, THF, 0 °C, 0.5 h	trace
2	**Py•HBr$_3$**, THF, 0 °C, 0.5 h	N.D.
3	**CuBr$_2$**, 30 °C	N.D.
4	**DDB**, ether, r.t.	N.D.
5	LHMDS, **NBS**, THF	26%
6[a]	LDA, DMPU, TMSCl then **NBS**, THF	56%
7	KHMDS, Et_3B, **NBS**, THF	**73%**

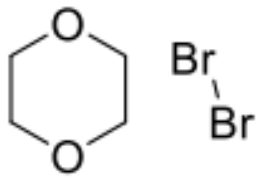
[a]All reagents should be freshly prepared or opened



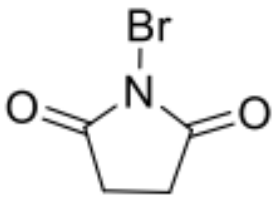
PTAP



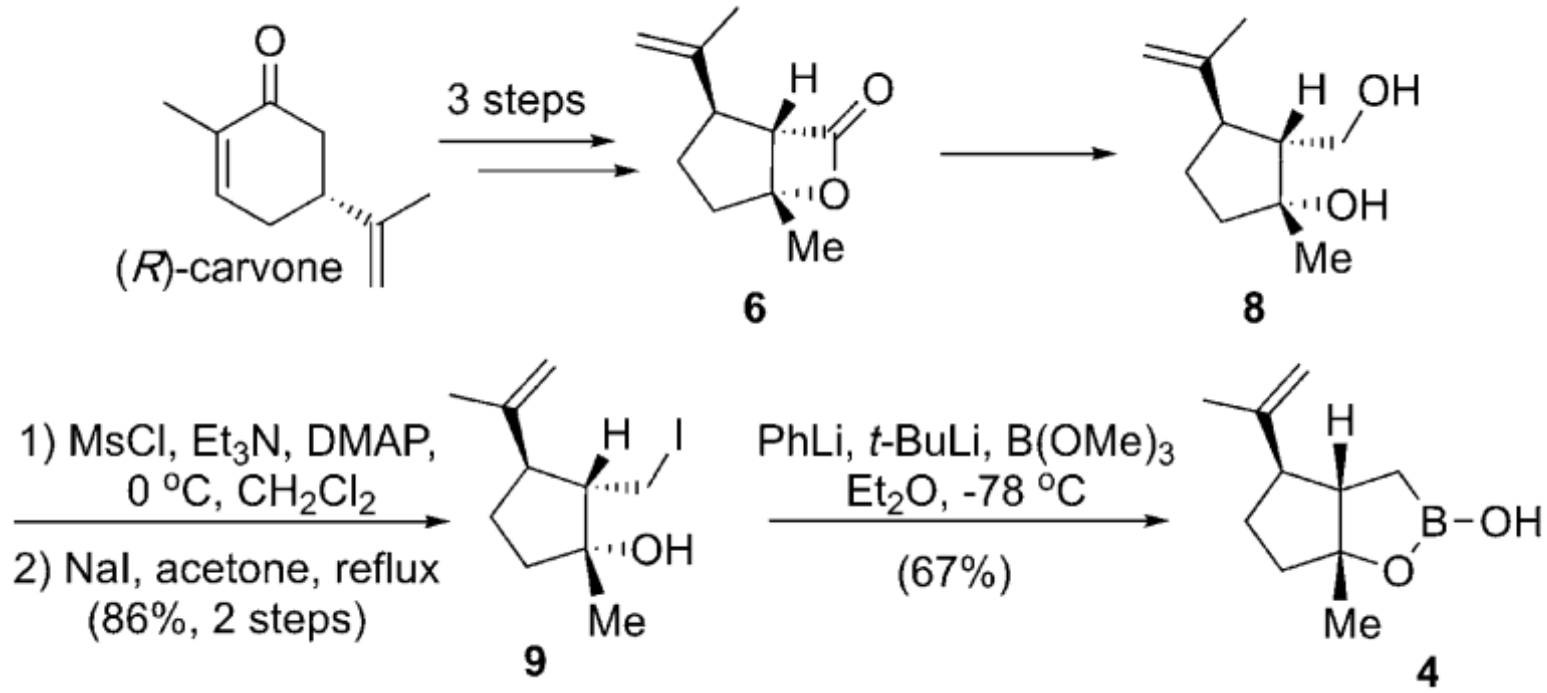
Py•HBr$_3$



DDB



NBS



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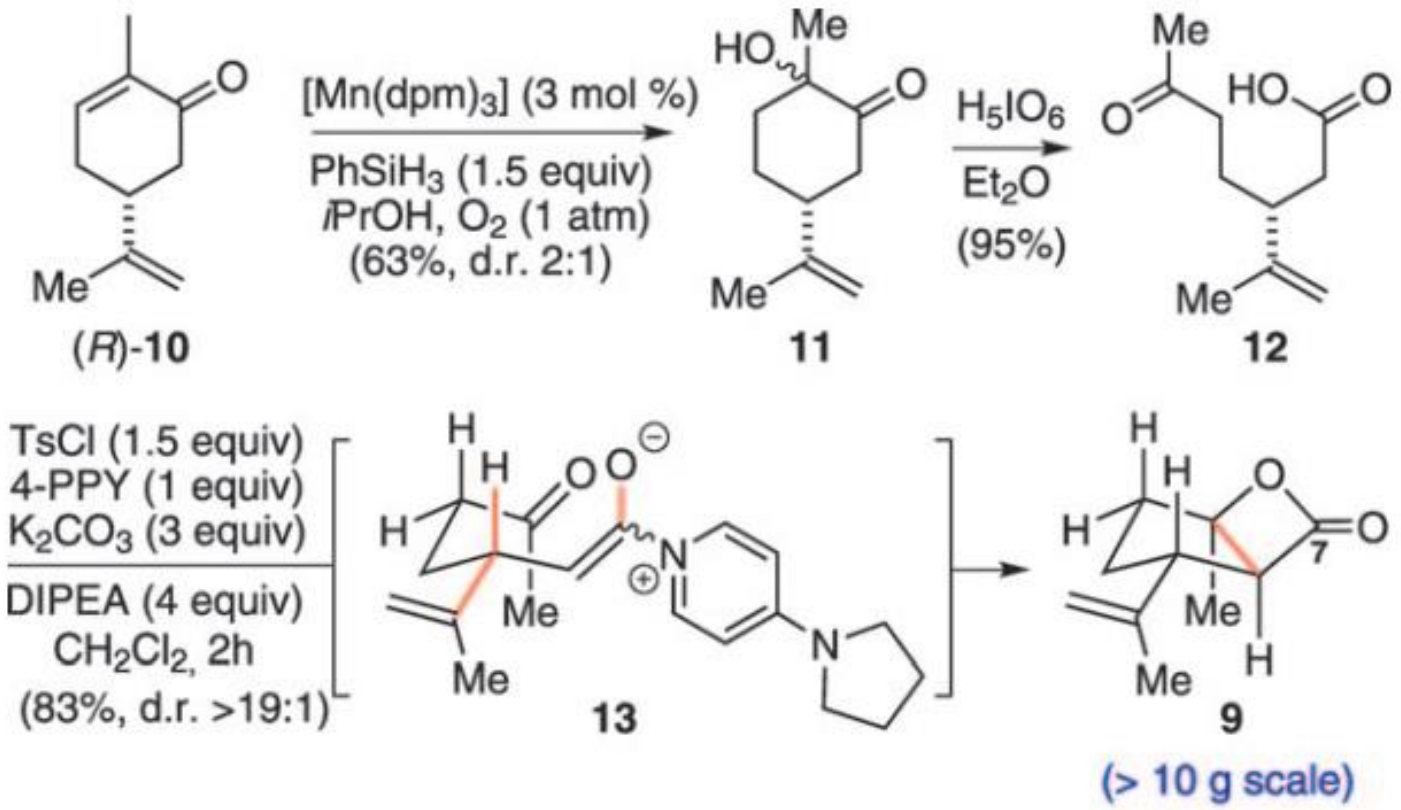
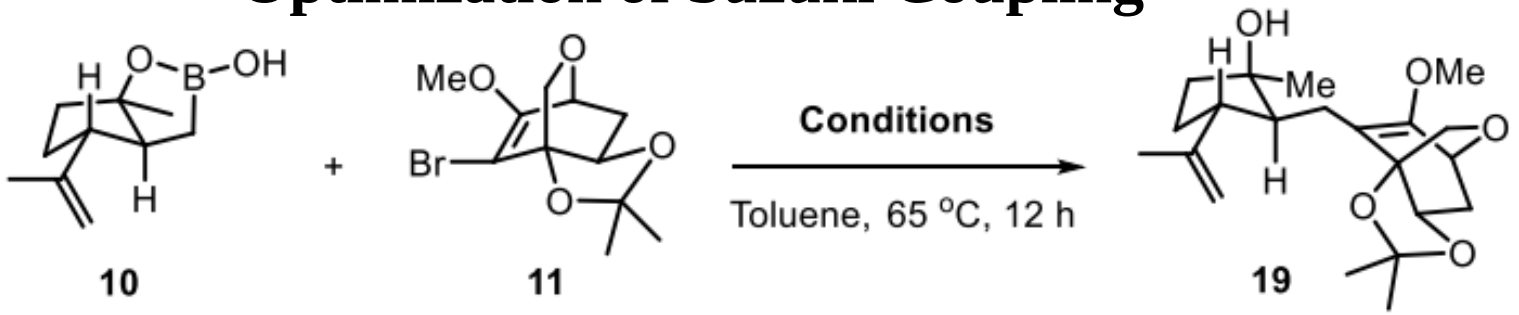


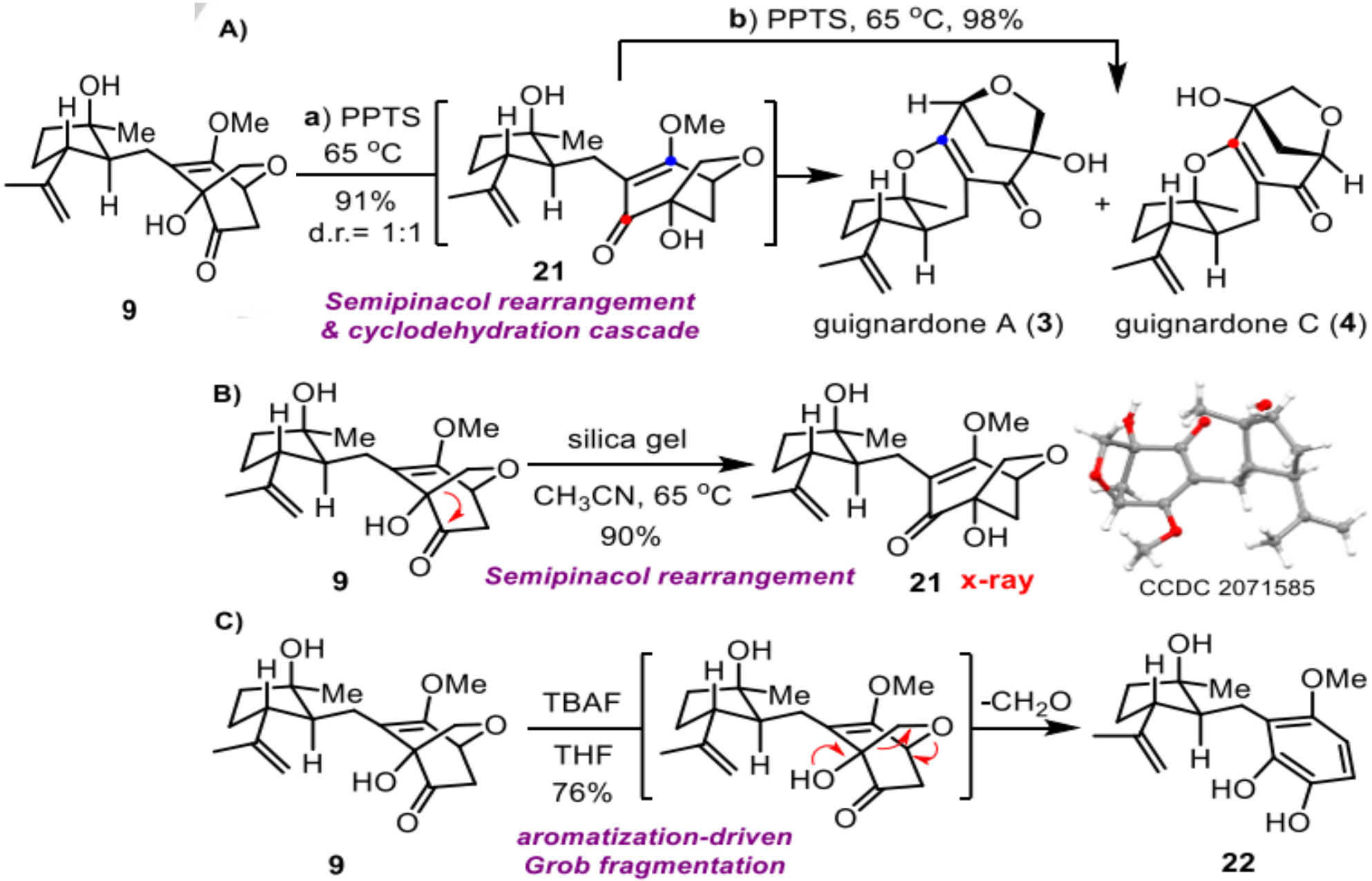
Angew. Chem. Int. Ed. **2011**, *50*, 7537.

Optimization of Suzuki Coupling

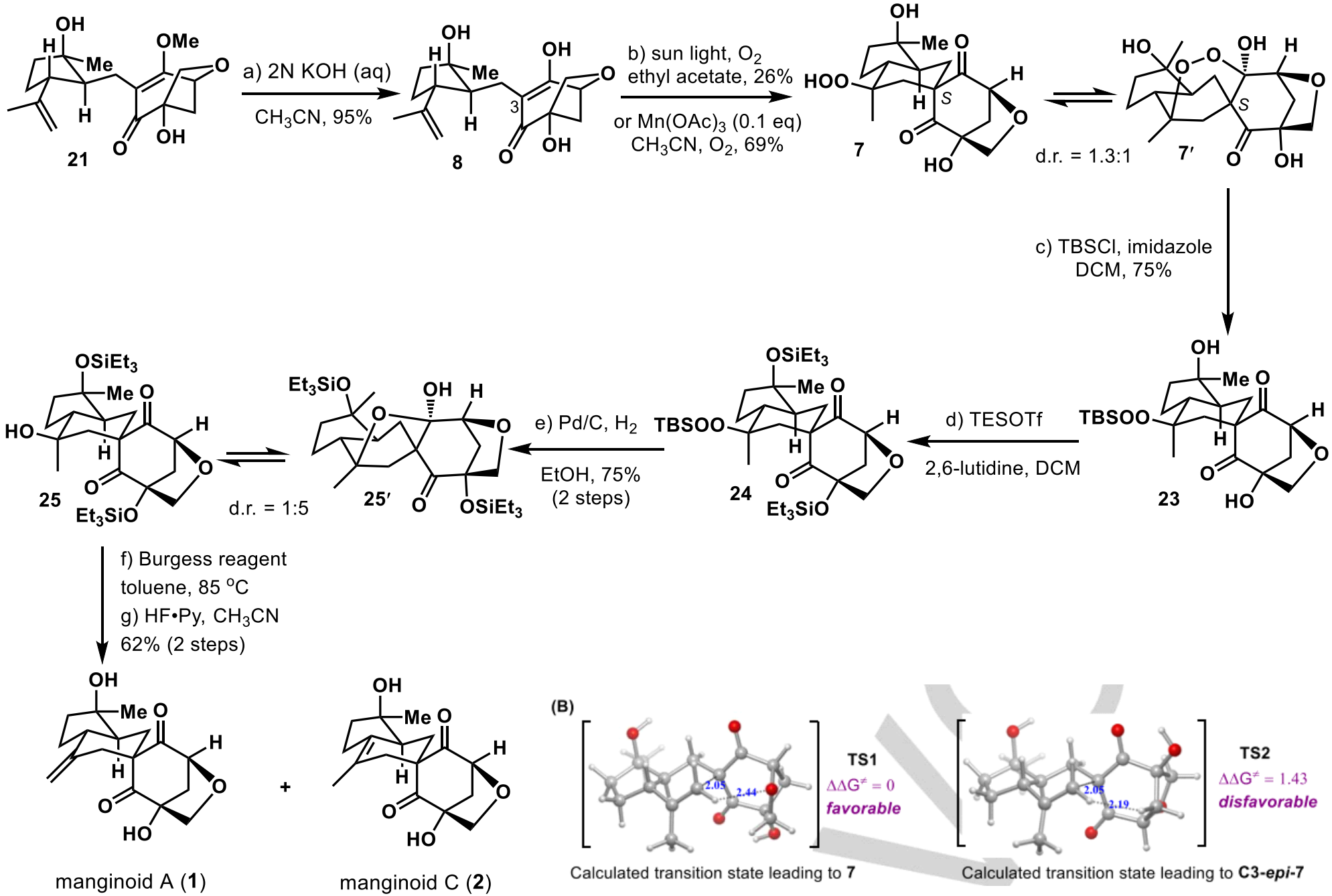


Entry	Pd source	Ligand	Base	Additive[b]	Yield
1	$Pd(OAc)_2$ 10 mol %	Aphos	Cs_2CO_3	/	30%
2	$Pd(OAc)_2$ 10 mol %	Sphos	Cs_2CO_3	/	25%
3	$PdCl_2$ 10 mol %	dppf	Cs_2CO_3	/	trace
4	$Pd(OAc)_2$ 10 mol %	Aphos	Cs_2CO_3	H_2O	43%
5	$Pd(OAc)_2$ 10 mol %	Aphos	CsF	H_2O	37%
6	$Pd(OAc)_2$ 10 mol %	Ruphos	$K_3PO_4 \cdot H_2O$	/	26%
7	$Pd(OAc)_2$ 10 mol %	Aphos	$K_3PO_4 \cdot H_2O$	/	28%
8	$Pd(OAc)_2$ 20 mol %	Aphos	*t*-BuONa	H_2O	50%
9	**$Pd(OAc)_2$ 20 mol %**	**Aphos**	**Cs_2CO_3**	**H_2O**	**61%**
10	$Pd(OAc)_2$ 20 mol %	Aphos	Cs_2CO_3	H_2O[c]	40%
11[d]	**$Pd(OAc)_2$ 20 mol %**	**Aphos**	**Cs_2CO_3**	**H_2O**	**52%**

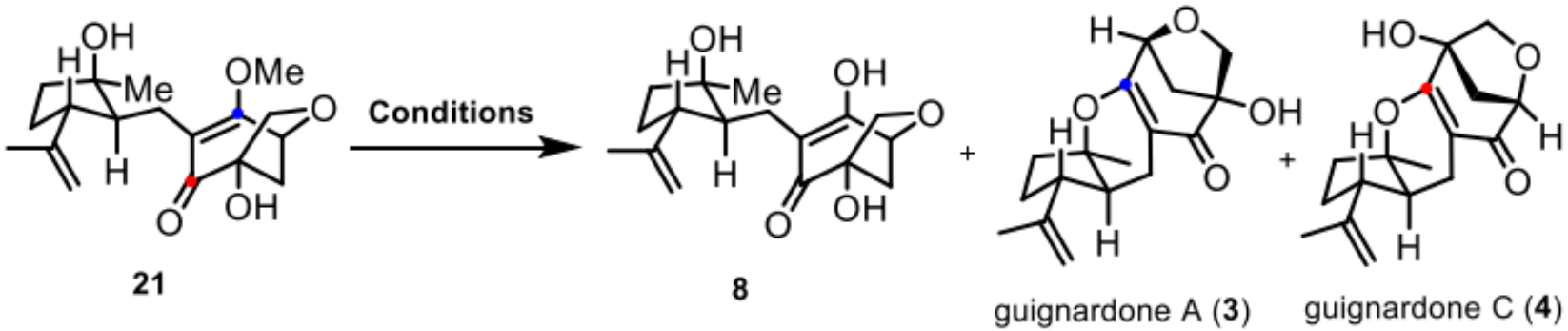
Total Syntheses of (+)-guignardones A (3) and C (4)



Total Syntheses of (+)-manginoid A (1) and (-)-manginoid C (2)



Reaction Screening for Demethylation of 21



21 8 guignardone A (**3**) guignardone C (**4**)

Entry	Reagent	Temp (°C)	Solvent	Yield[b] (%)		
				8	**3**	**4**
1	LiCl	120	DMSO	0	0	0
2	CAN	80	Acetonitrile/H_2O	0	0	0
3	PPTS	65	Toluene	0	50	48
4	AcOH	50	AcOH	0	40	47
5	3 N HCl	23	Acetone	0	71	16
6	4 N KOH	70	Acetonitrile	70	0	0
7	4 N KOH	23	Acetonitrile	85	0	0
8	**2 N KOH**	**23**	**Acetonitrile**	**95**	**0**	**0**