

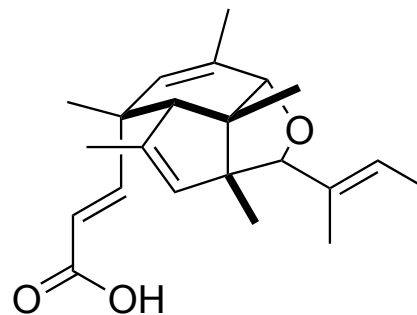
Divergent Total Synthesis of indoxamycins A, C and F

He, C.; Zhu, C.; Dai, Z.; Tseng, C.-C.; Ding, H. *Angew. Chem. Int. Ed.* **2013**, ASAP
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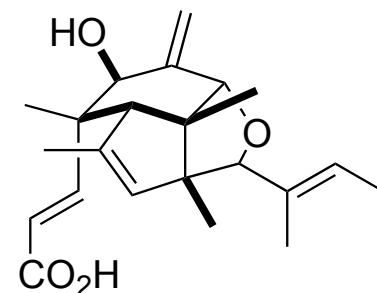
November, 14th 2013

Introduction

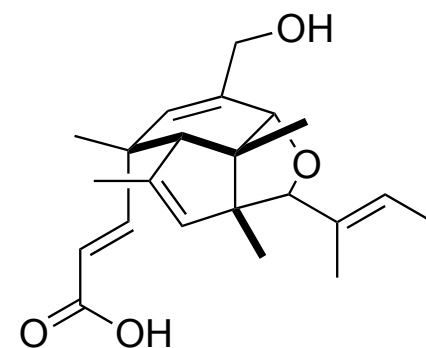
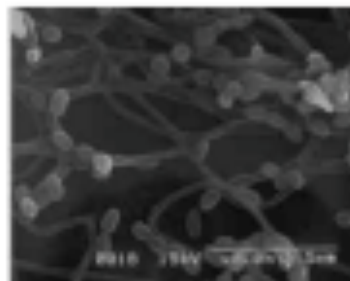
- Isolated from saline culture of marine-derived actinomycetes (Sato, 2009)
- Biologic activities :
 - HT-29 tumor cell :
 - $IC_{50} = 0.59$ (indoxamycin A)
 - $IC_{50} = 0.31$ (indoxamycin F)
 - Mitomycin : $IC_{50} = 0.66 \mu\text{m}$ (both)
- [5,5,6] tricyclic



indoxamycin A

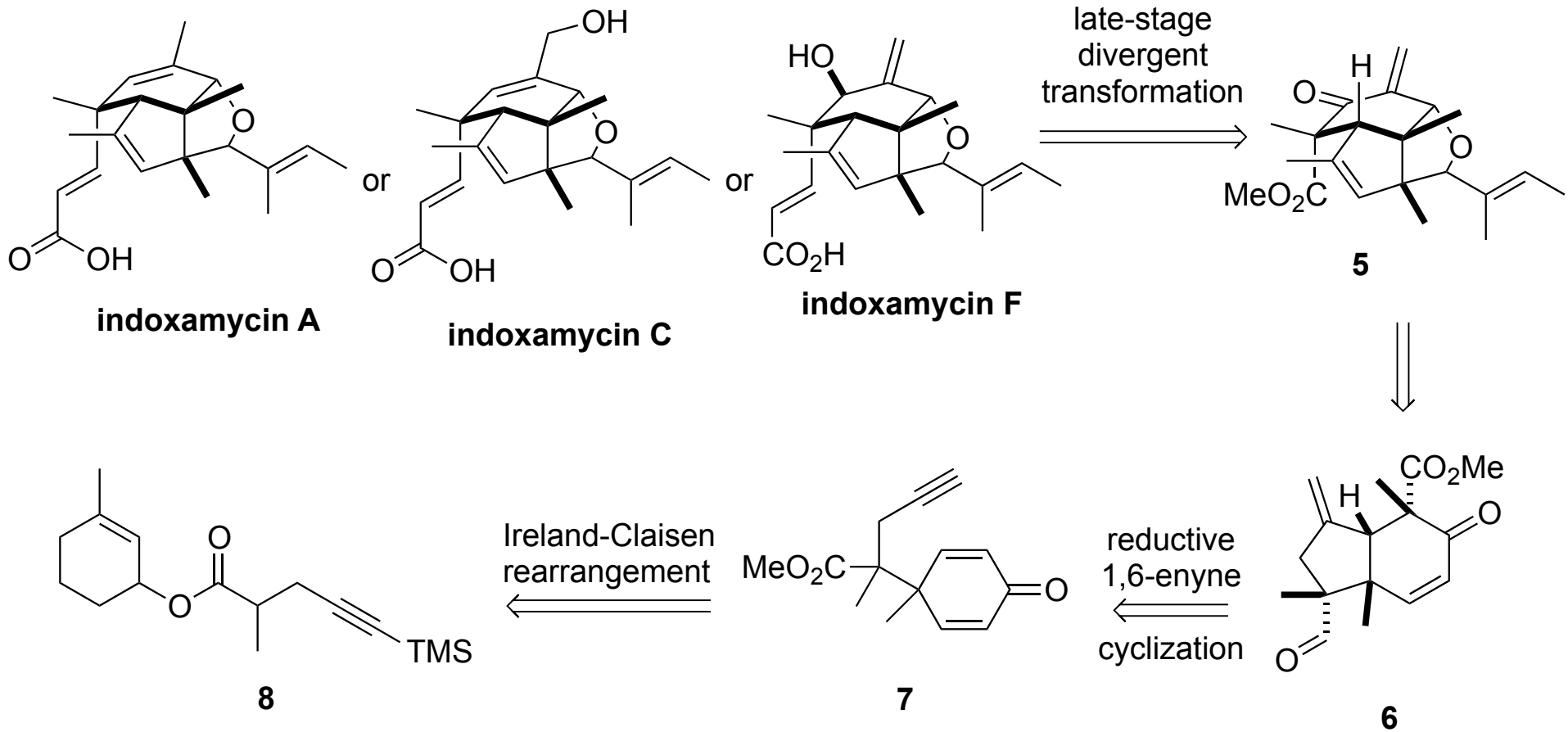


indoxamycin F

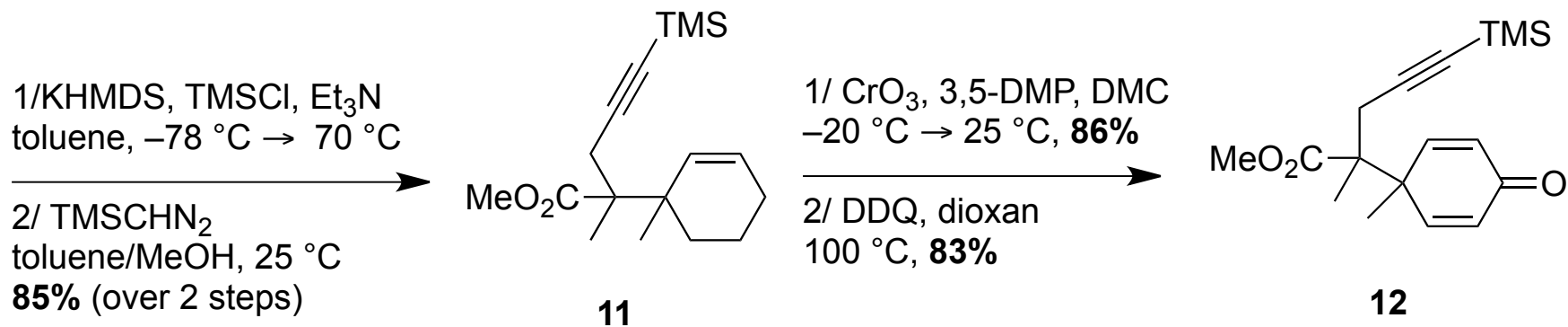
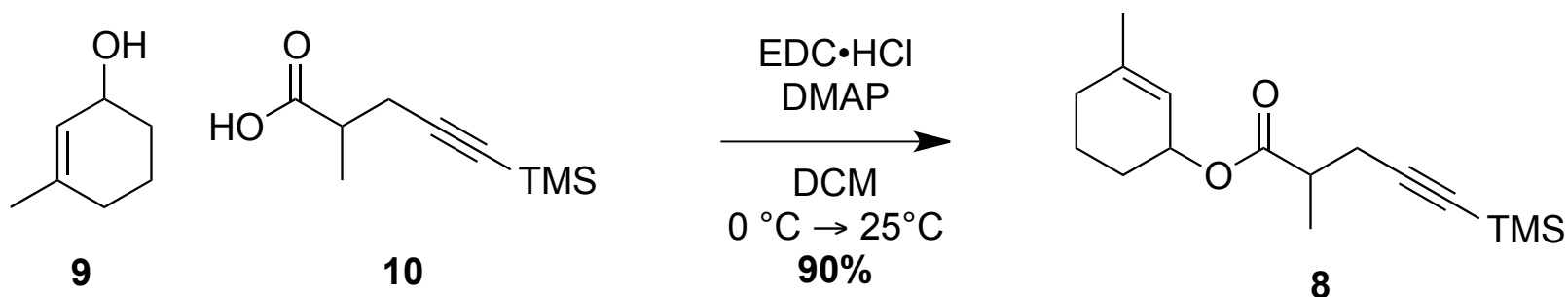


indoxamycin C

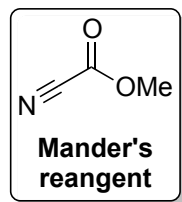
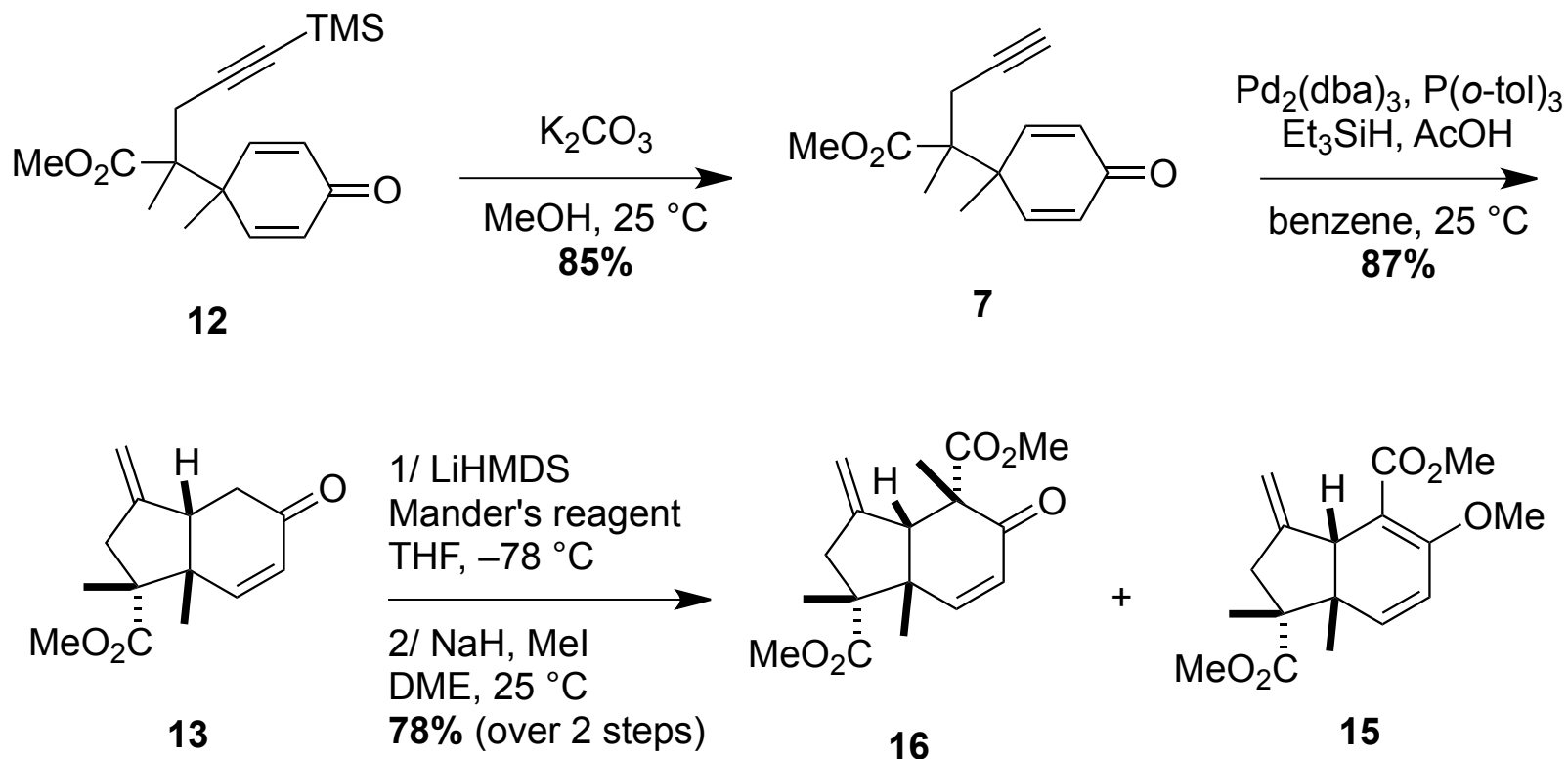
Retrosynthesis



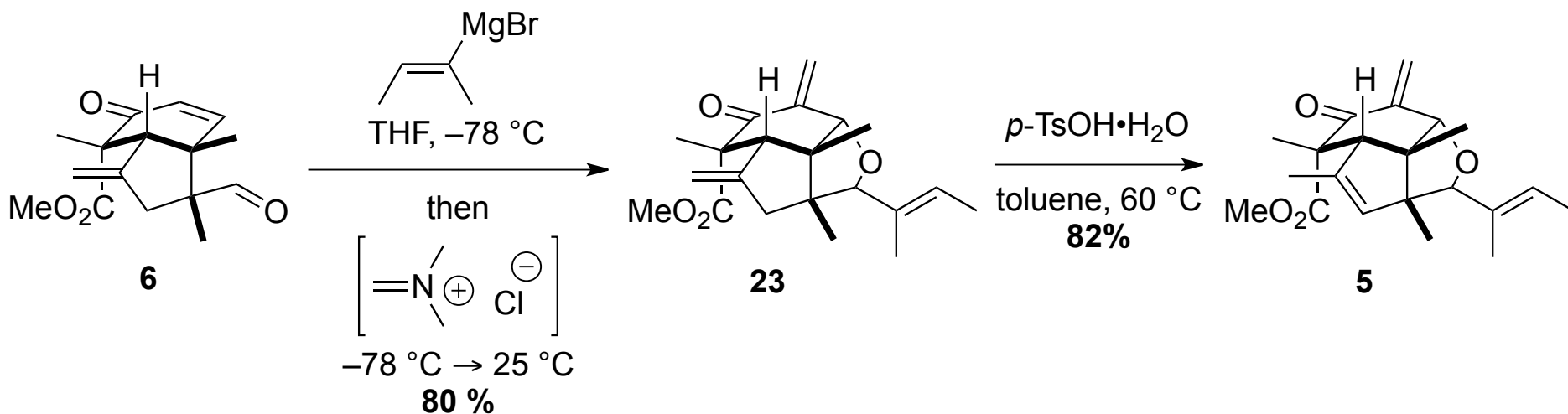
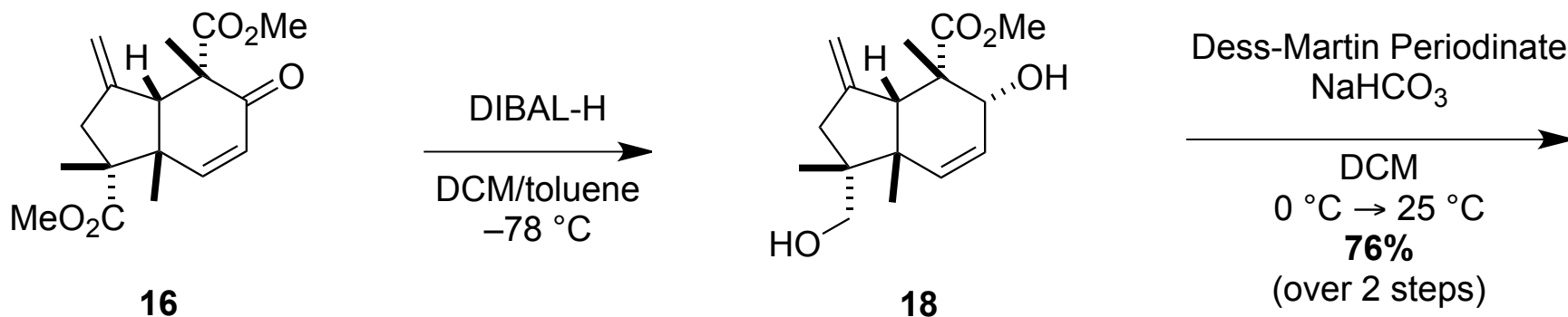
Synthesis of the common intermediate



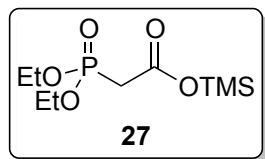
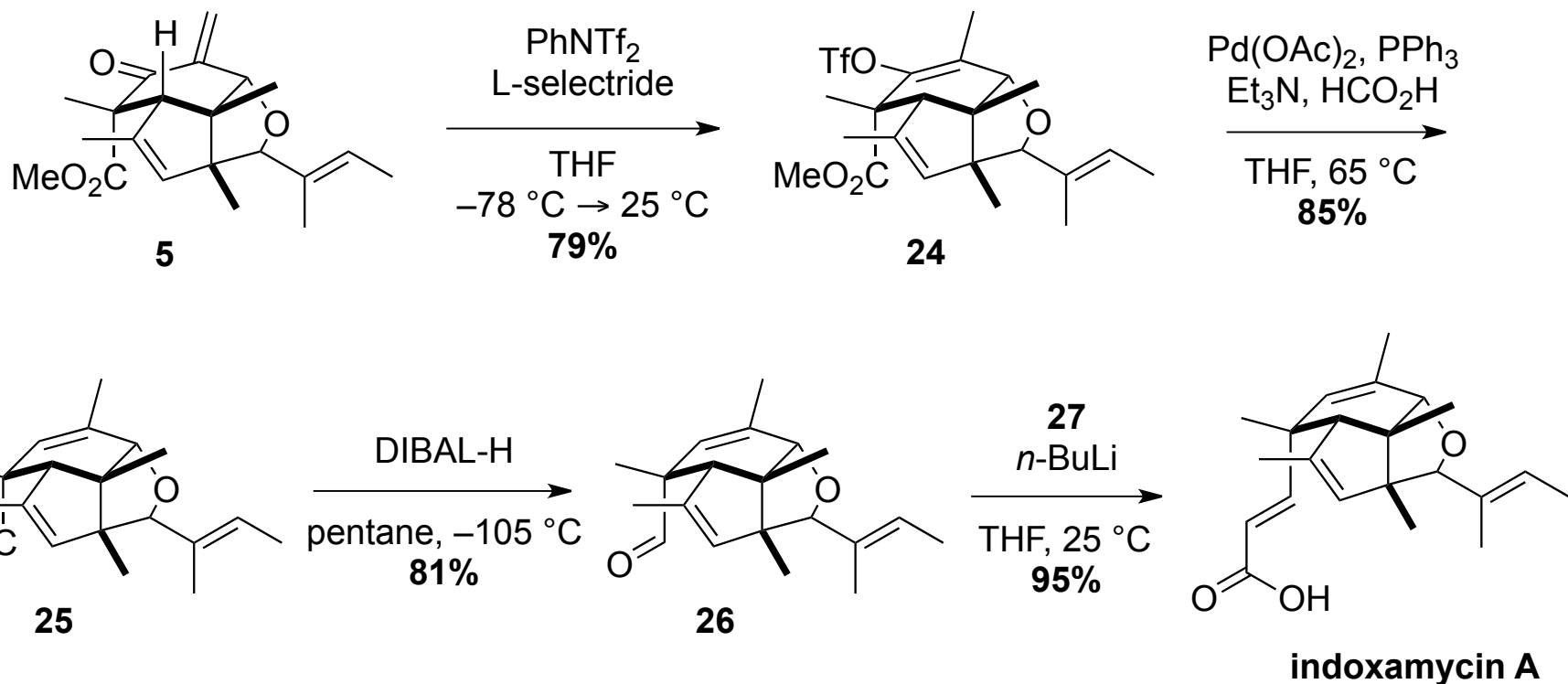
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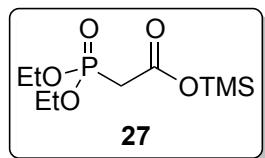
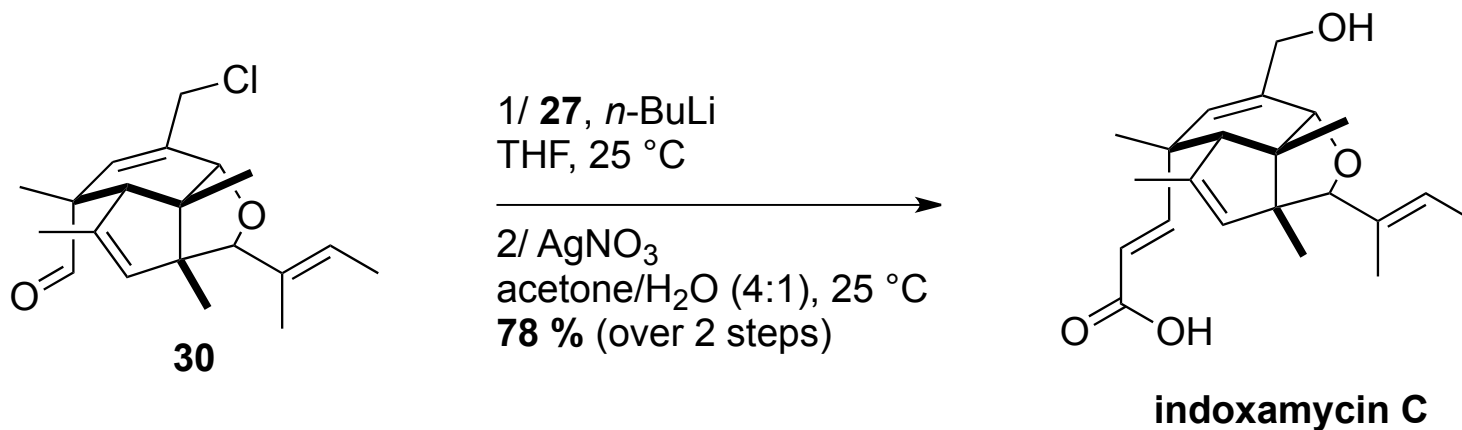
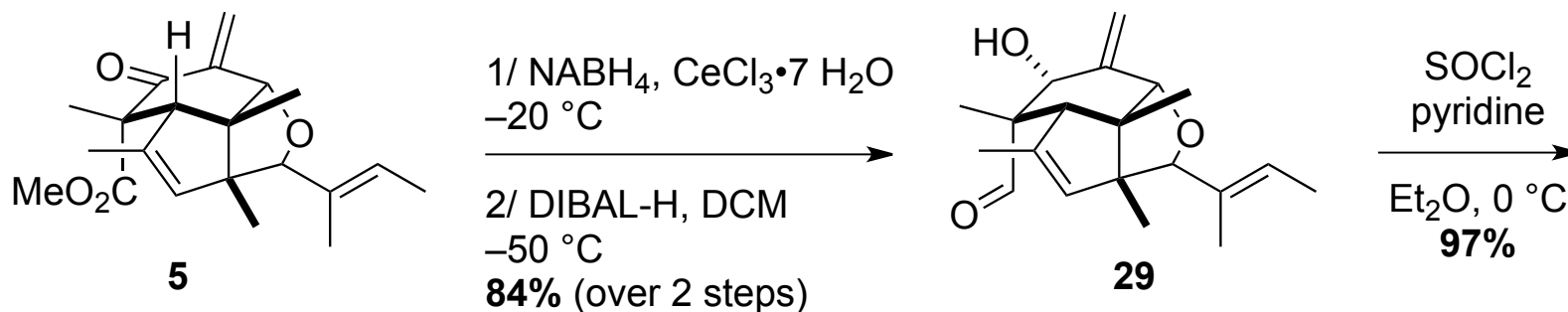
Synthesis of the common intermediate



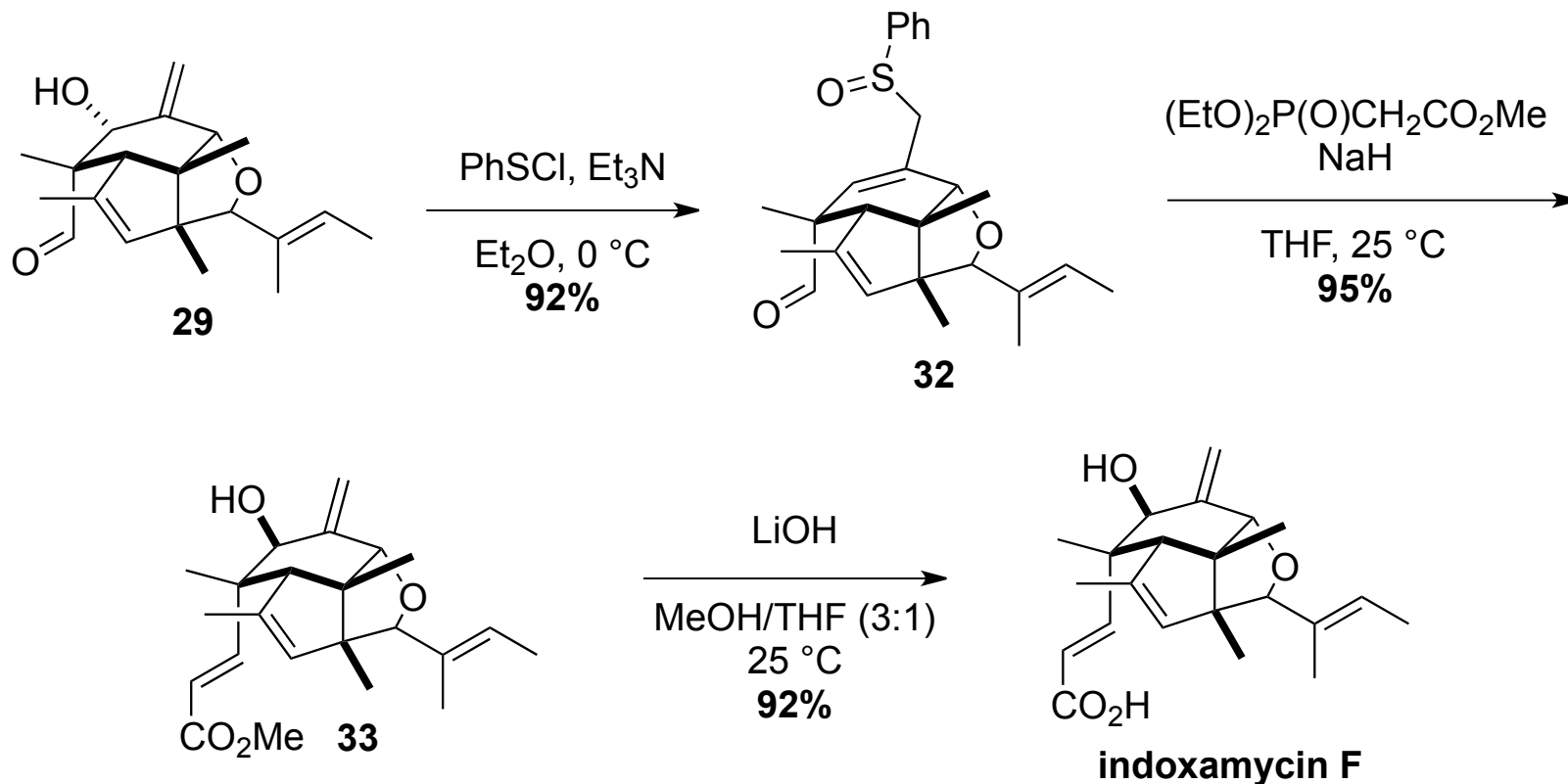
Synthesis of the indoamycin A



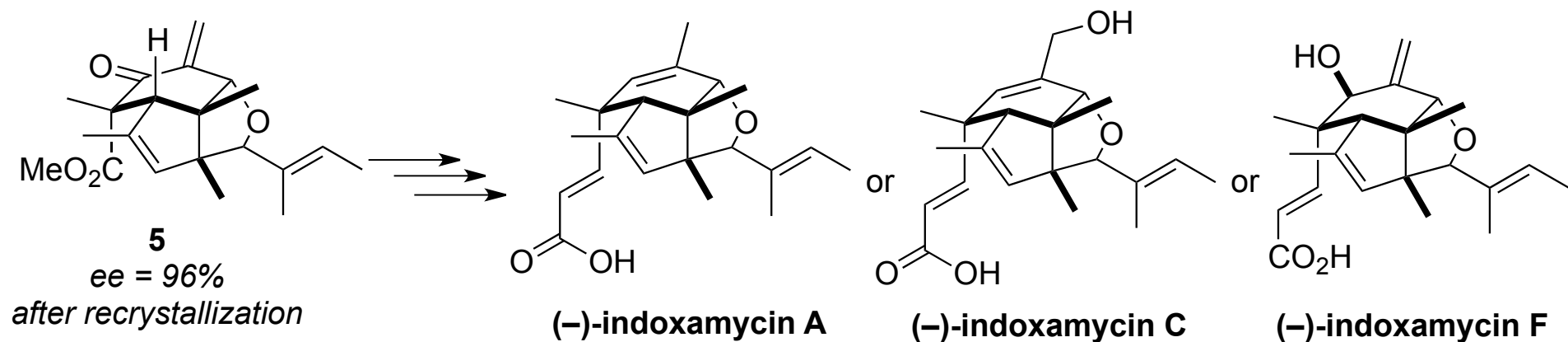
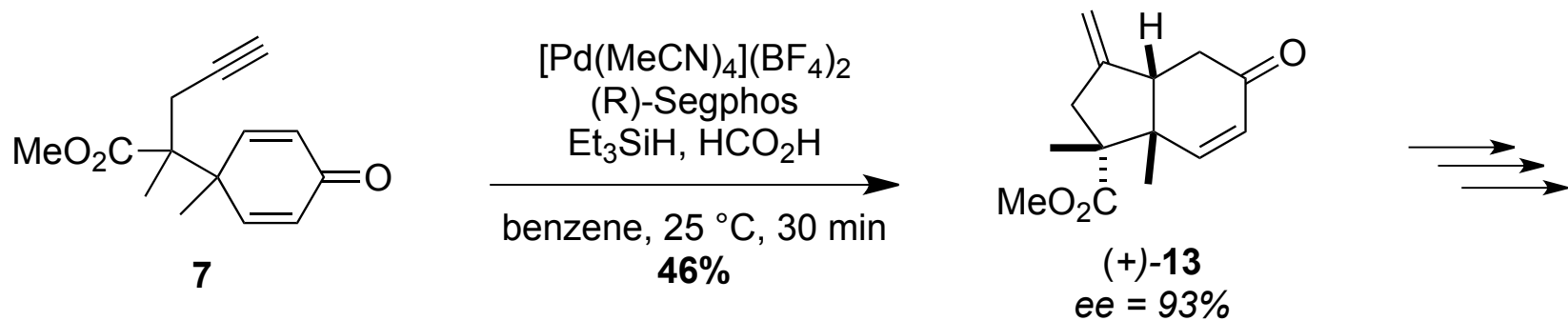
Synthesis of the indoxamycin C



Synthesis of the indoxamycin F



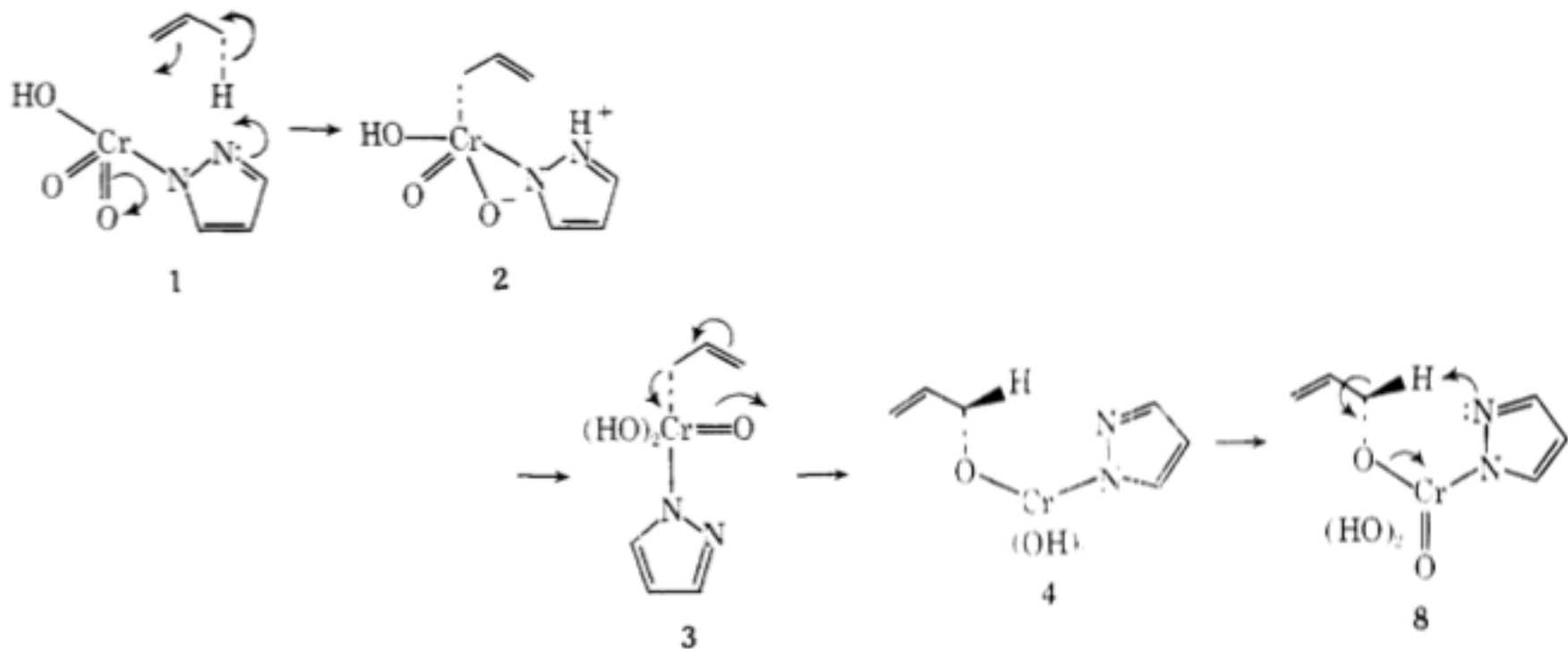
Asymmetric synthesis



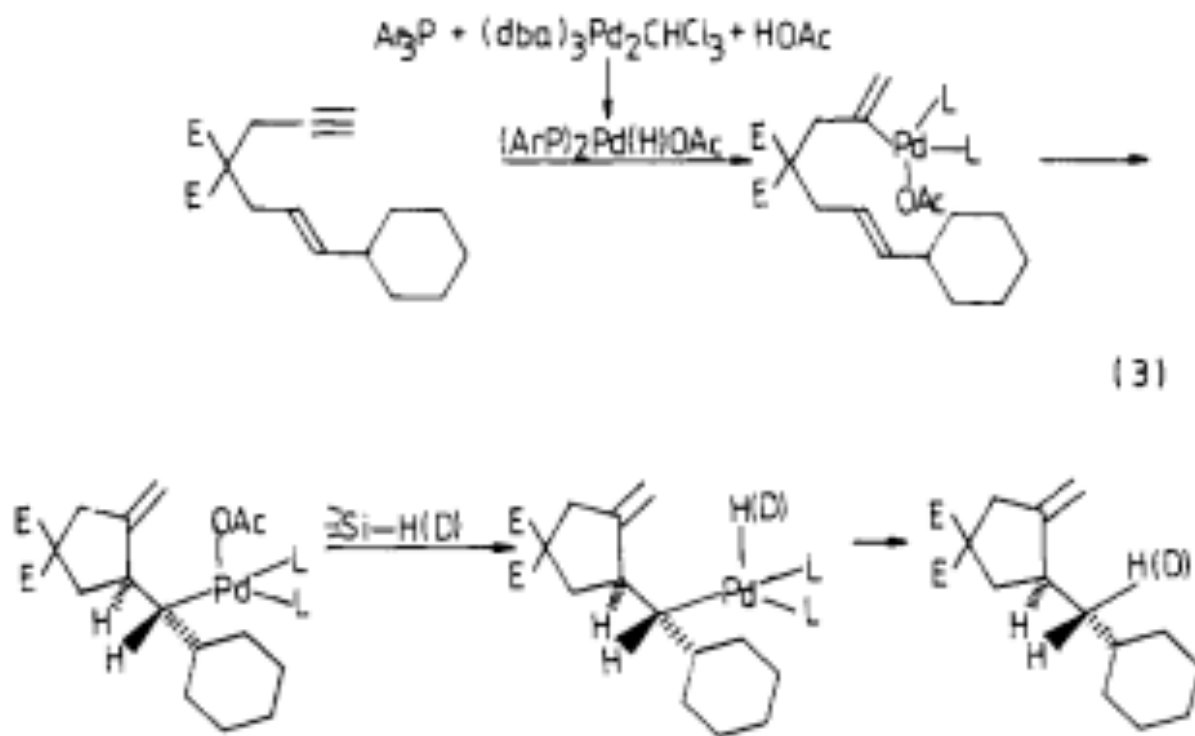
Conclusion

- 3 totals synthesis with 1 commun intermediated :
 - Indoxamycin A : 16 steps
 - Racemic :Yield = 8%
 - Enantioselective : Yield = 4%
 - Indoxamycin C : 17 steps
 - Racemic : Yield = 10%
 - Enantioselective : Yield = 5%
 - Indoxamycin F : 17 steps
 - Racemic : Yield = 11%
 - Enantioselective : Yield = 5%
- 3 keys steps :
 - Ireland-Claisen rearrangement,
 - Stereodivergent reductive 1,6-enyne cyclization,
 - Tandem 1,2-addition/oxa-Michael/methylenation reaction

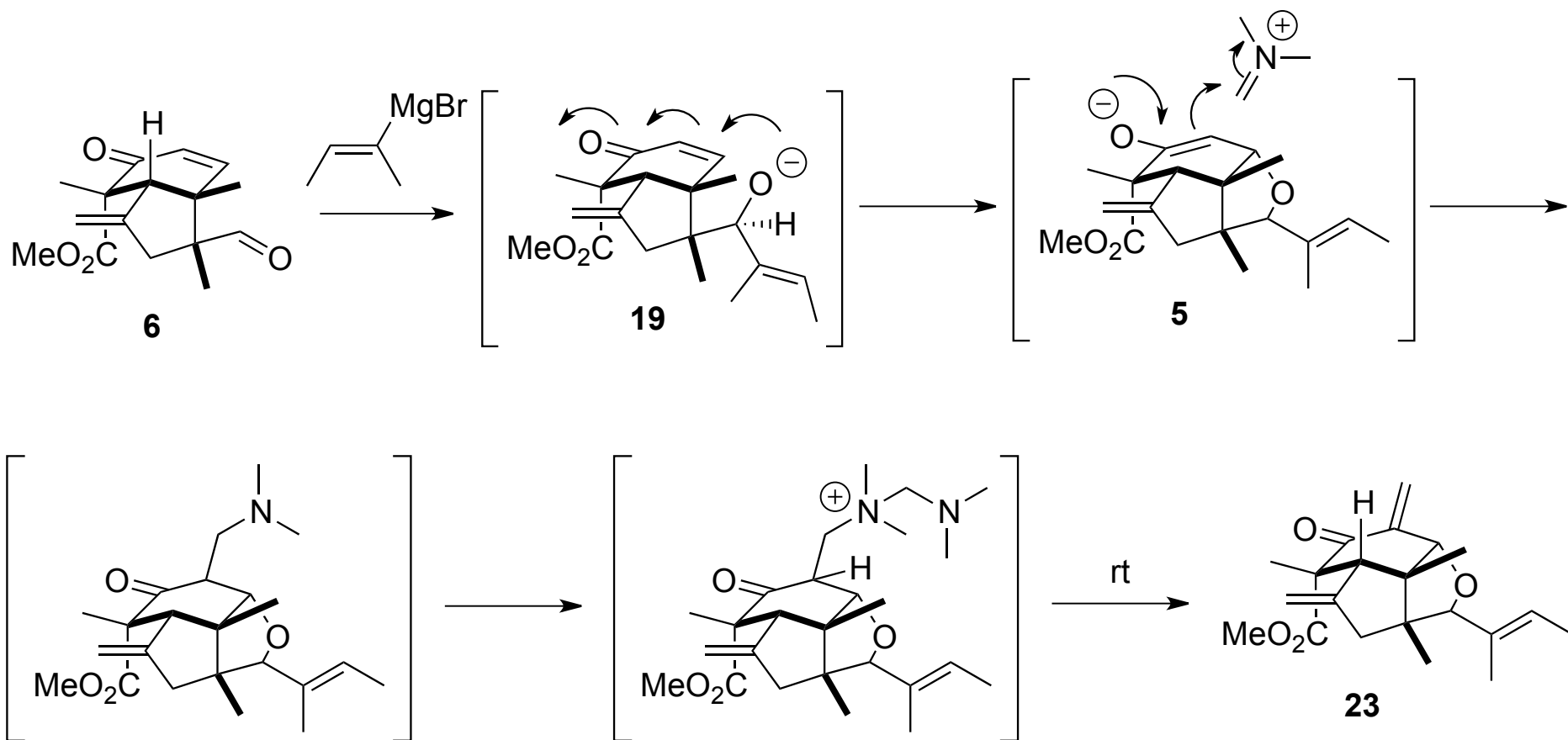
Allylic oxidation



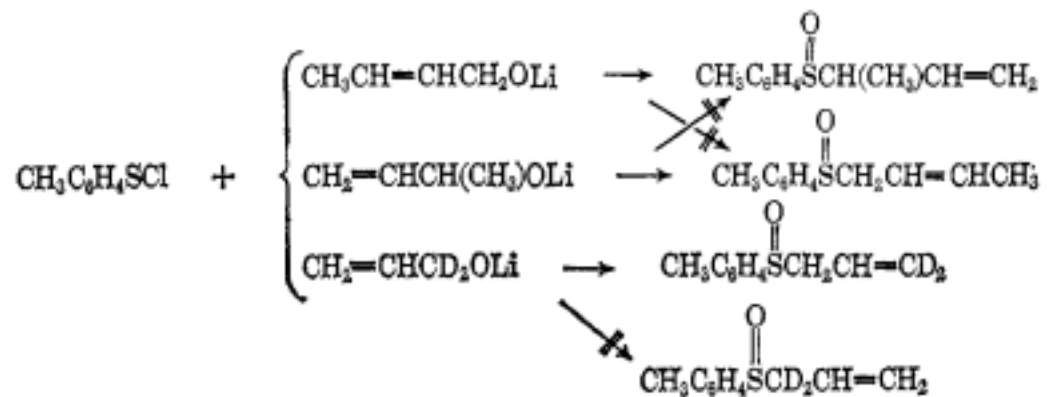
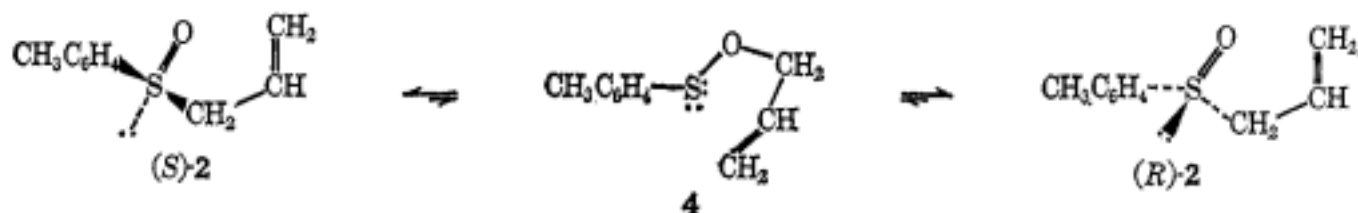
Reductive 1,6-enyne cyclization



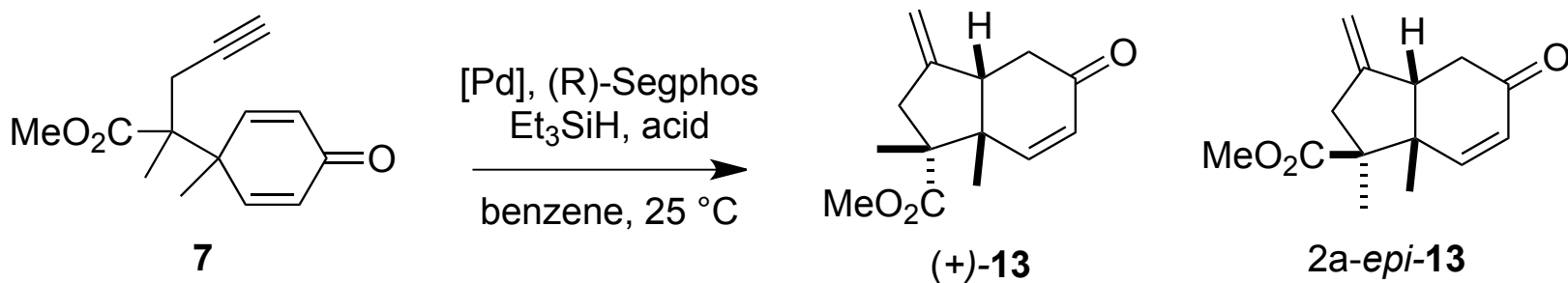
Mechanism



Mislow rearrangement



Asymmetric synthesis



Entry	[Pd]	acid	t (h)	(+)-13, 2a-epi-13	
				Yield (%)	ee (%)
1	Pd ₂ dba ₃	AcOH	24	15, n.d.	65, —
2	Pd(tfa) ₂	AcOH	10	40, 32	72, 64
3	[Pd(MeCN) ₄](BF ₄) ₂	AcOH	0.5	42, 33	84, 71
4	[Pd(MeCN) ₄](BF ₄) ₂	HCO ₂ H	0.5	46, 43	93, 80