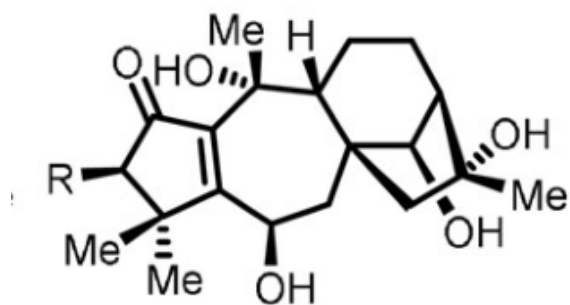


# Total Syntheses of Rhodomolleins XX and XXII: A Reductive Epoxide-Opening/Beckwith–Dowd Approach

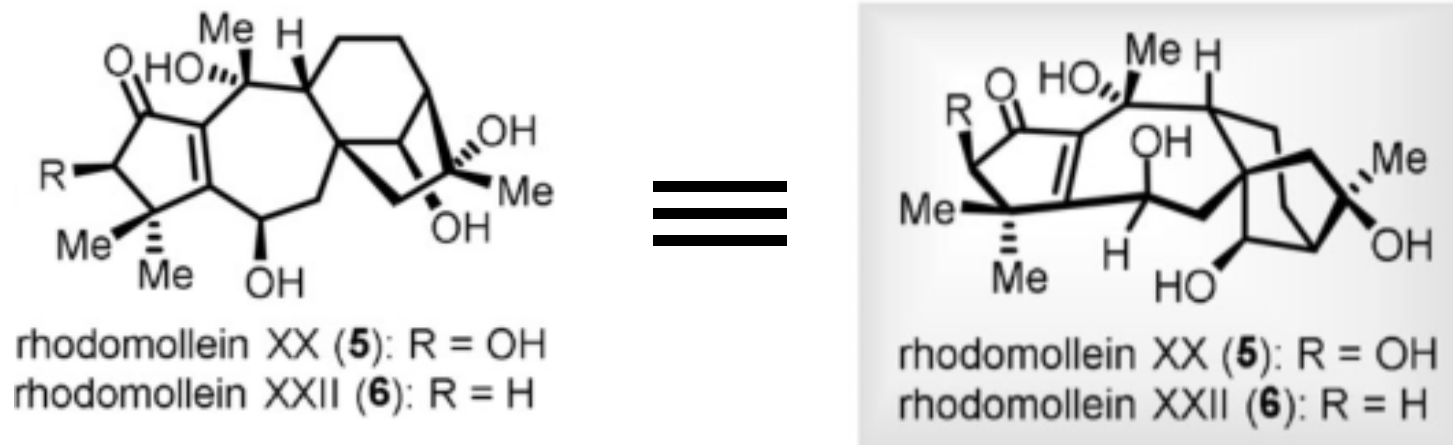
*Kuan Yu, Zhen-Ning Yang, Chun-Hui Liu, Shao-Qi Wu, Xin Hong, Xiao-Li Zhao, and Hanfeng Ding\**



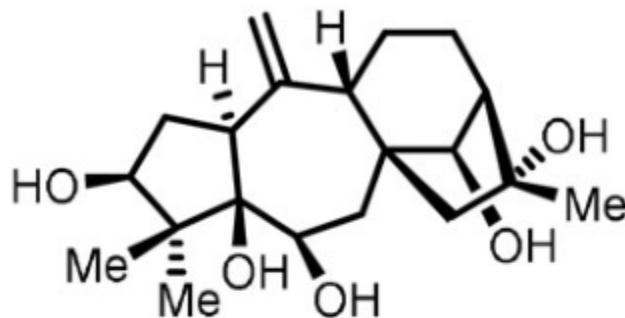
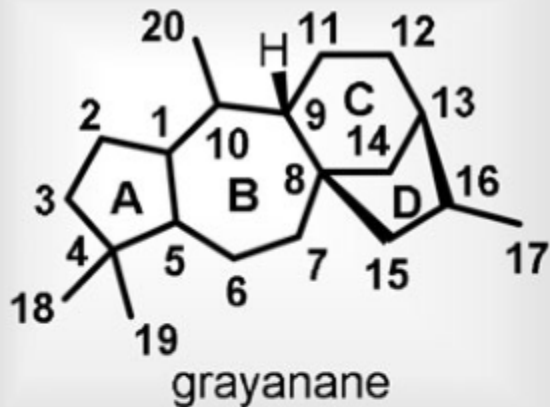
rhodomollein XX (**5**): R = OH

rhodomollein XXII (**6**): R = H

# Rhodomolleins XX and XXII

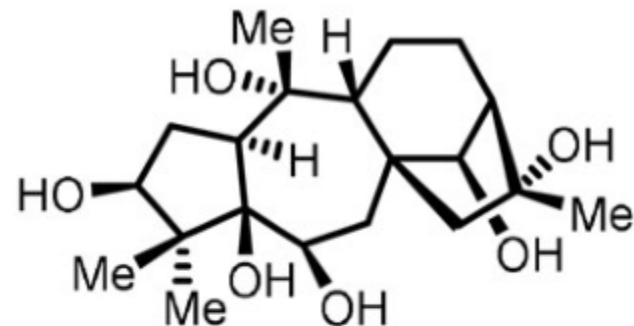


- Isolated from *Rhododendron molle* G. Don (Ericaceae).
- An unusual [5.7.6.5] tetracyclic carbon framework.
- 9 stereogenic centers.
- 3 quaternary carbons.



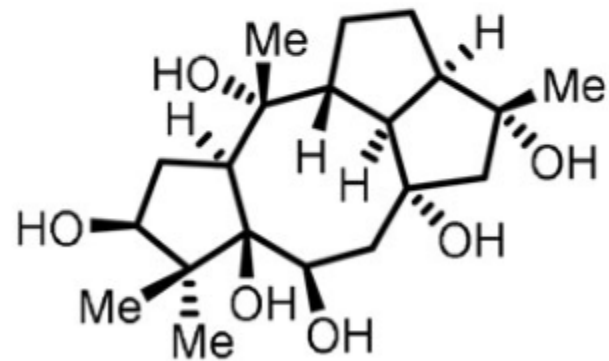
grayanotoxin II (1)

Matsumoto, 1972

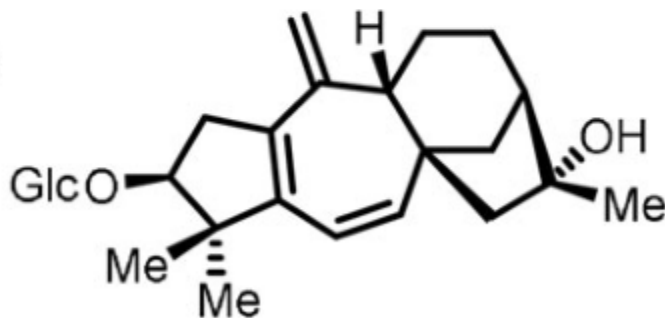


grayanotoxin III (2)

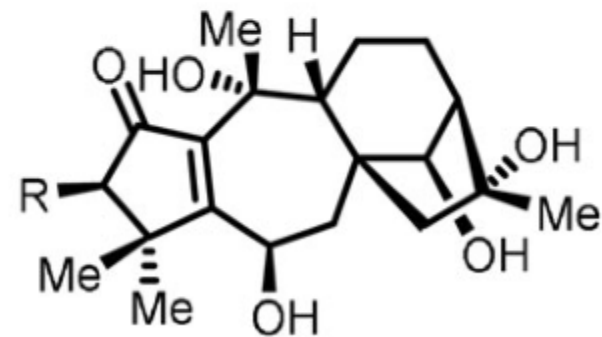
Shirahama, 1994



kalmanol (3)

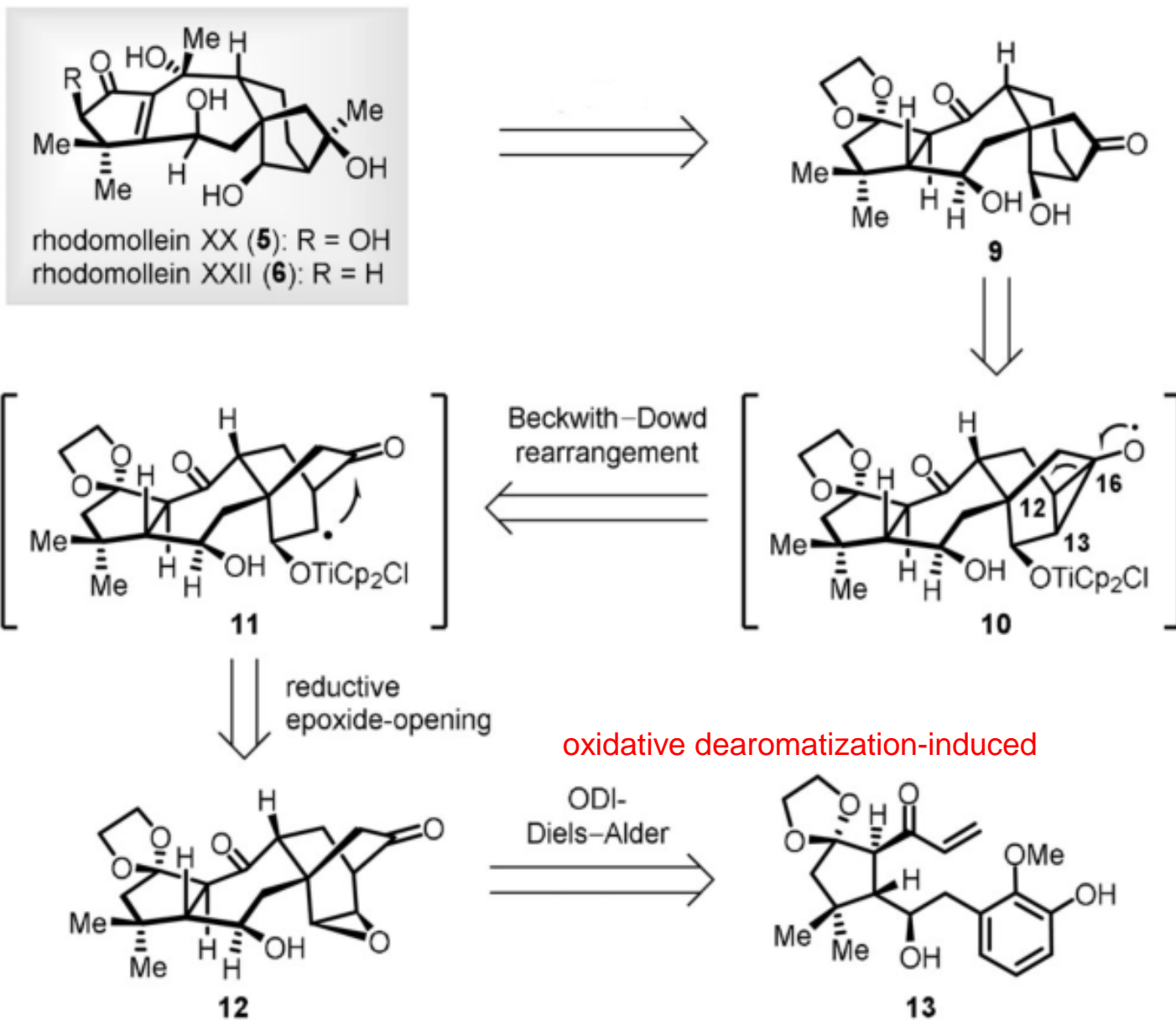


pierisformoside C (4)



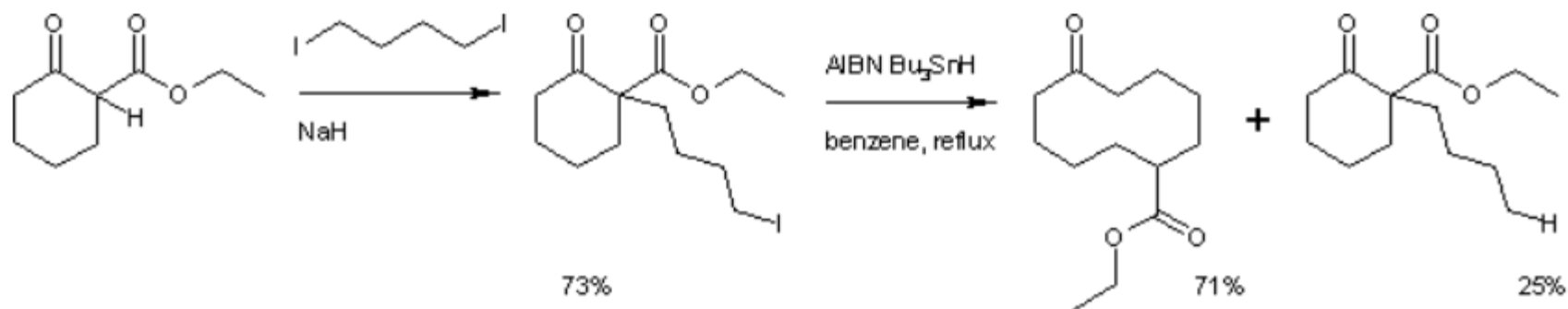
rhodomollein XX (5): R = OH

rhodomollein XXII (6): R = H

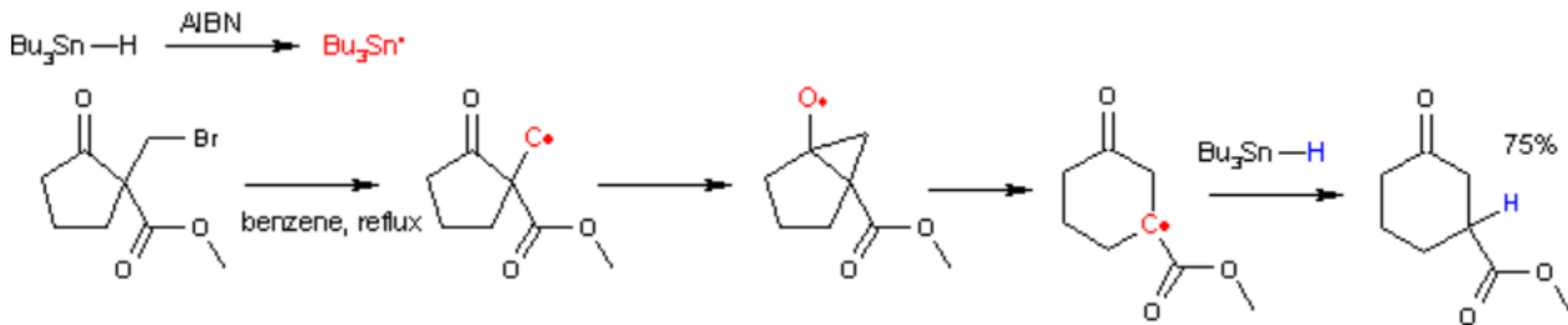


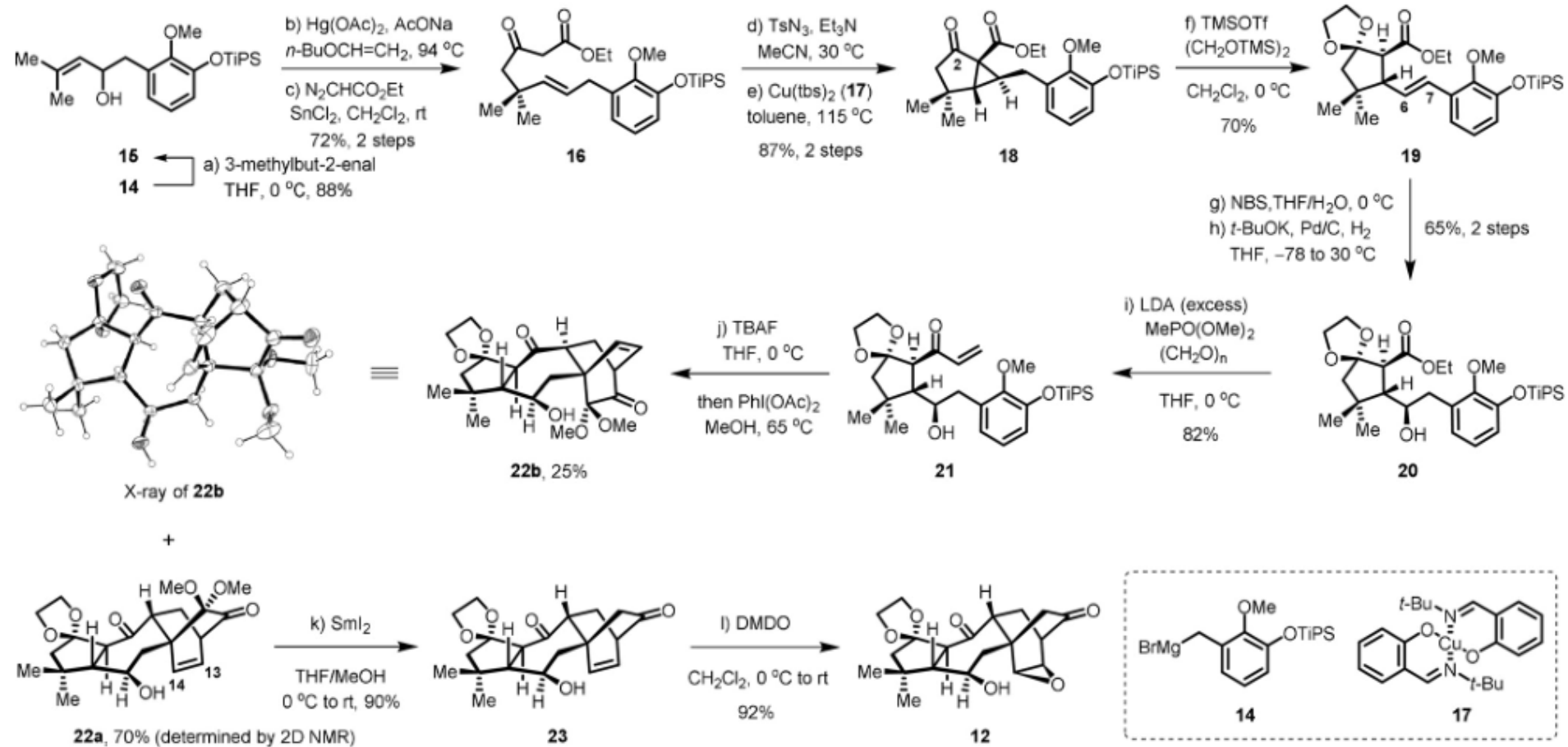
**Scheme 1.** Retrosynthetic analysis of rhodomolleins XX (**5**) and XXII (**6**).

## Dowd–Beckwith ring-expansion reaction

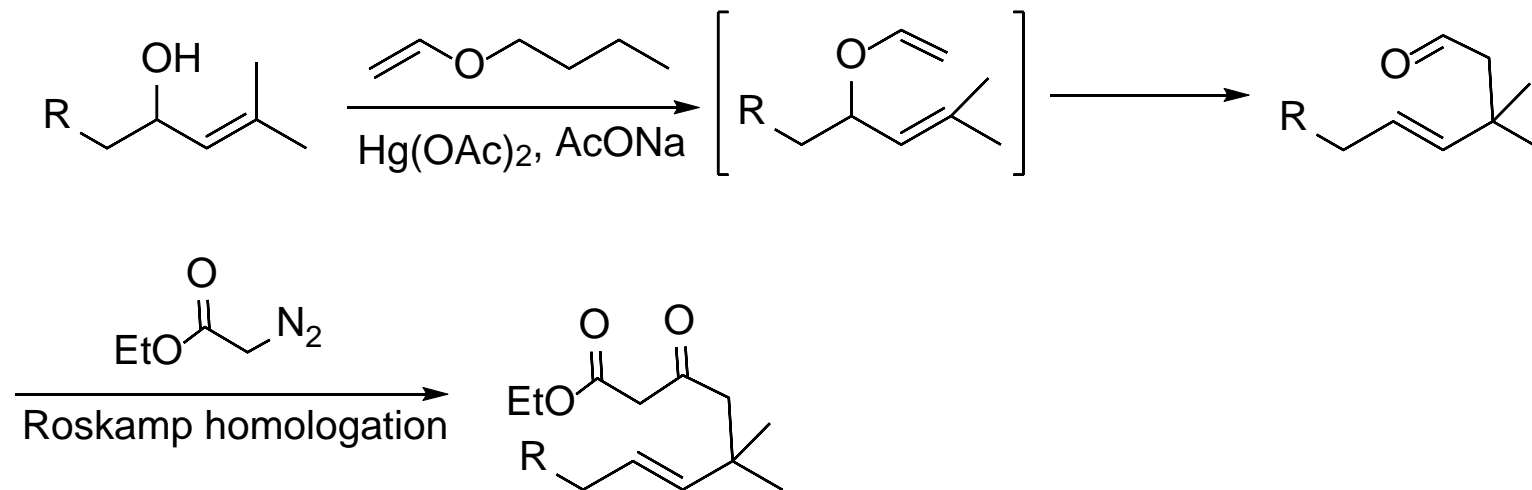
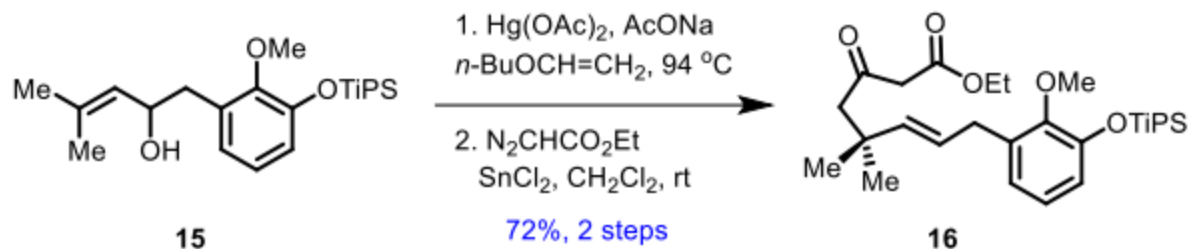


## Reaction mechanism



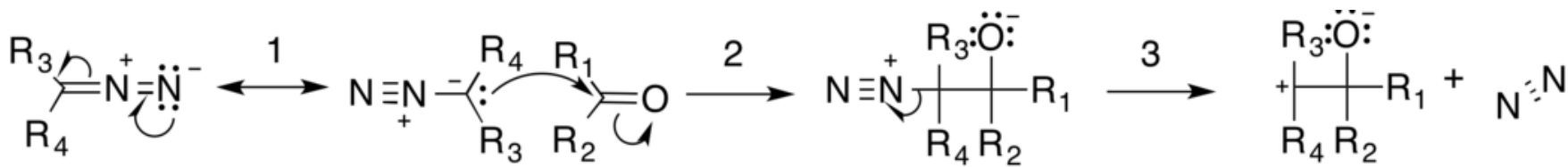


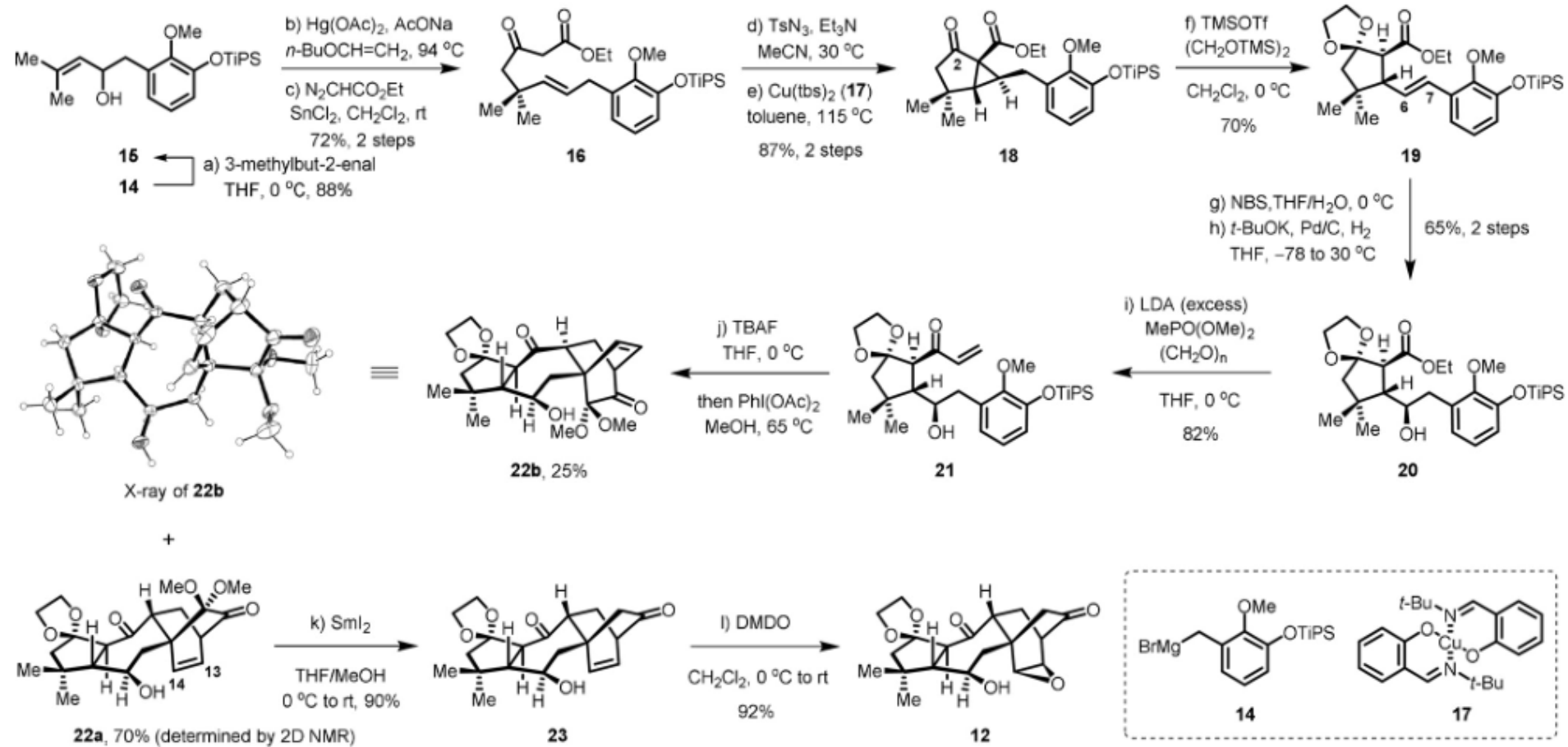
**Scheme 2.** Construction of keto-epoxide **12**. DMDO = dimethyldioxirane, LDA = lithium diisopropylamide, NBS = *N*-bromosuccinimide, TBAF = tetra-*n*-butylammonium fluoride, tbs = *N*-*tert*-butylsalicylaldiminato, THF = tetrahydrofuran, TiPS = triisopropylsilyl, TMSOTf = trimethylsilyl trifluoromethanesulfonate, Ts = 4-toluenesulfonyl.



*Synth. Commun.* **2002**, 32, 869.

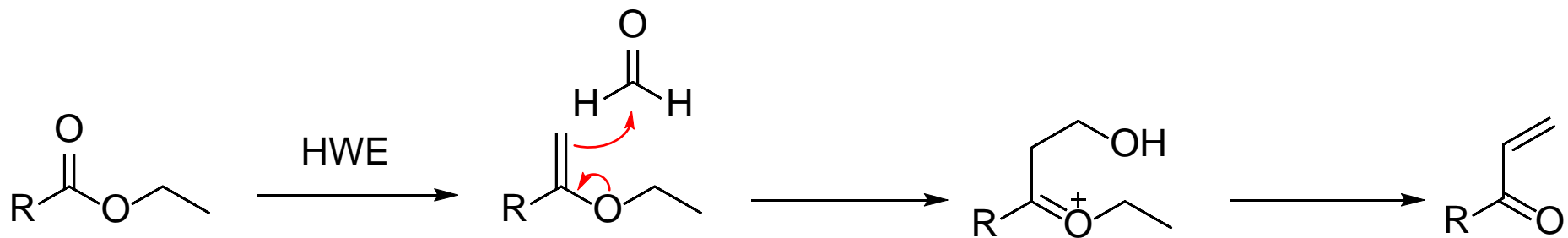
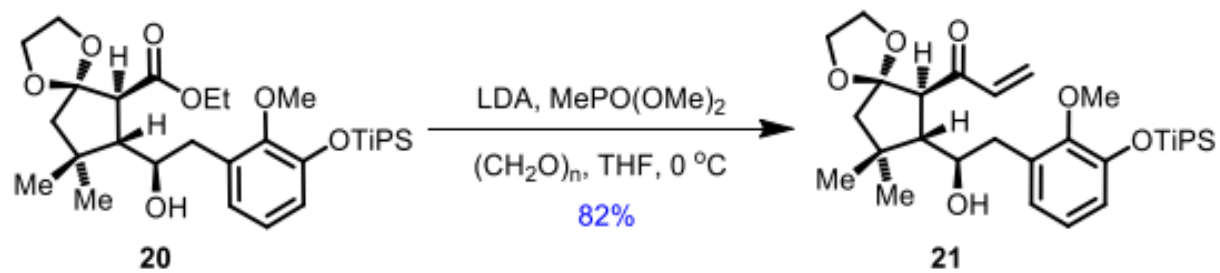
Roskamp homologation

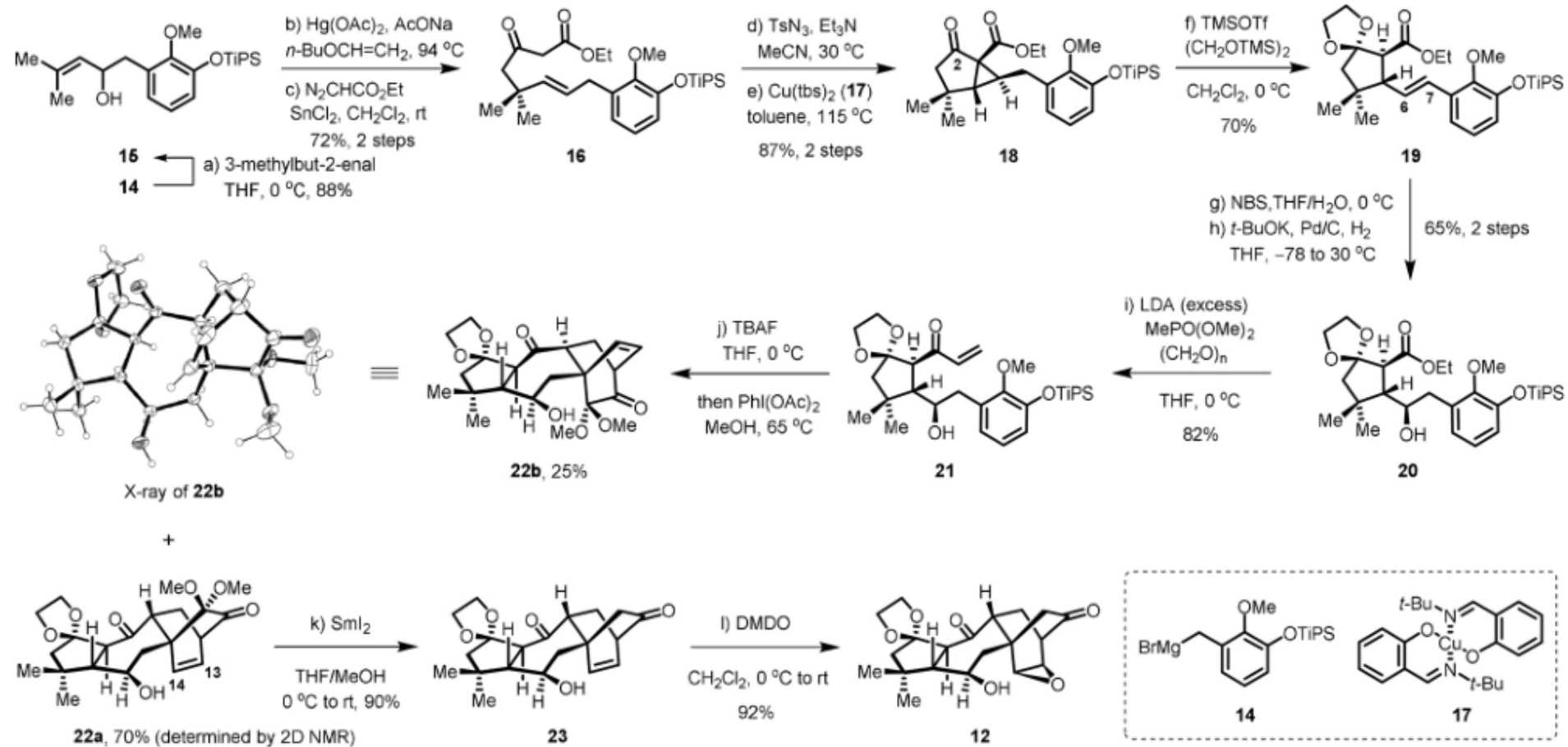




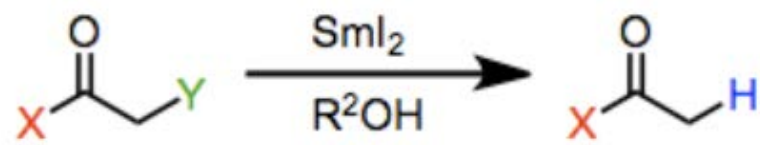
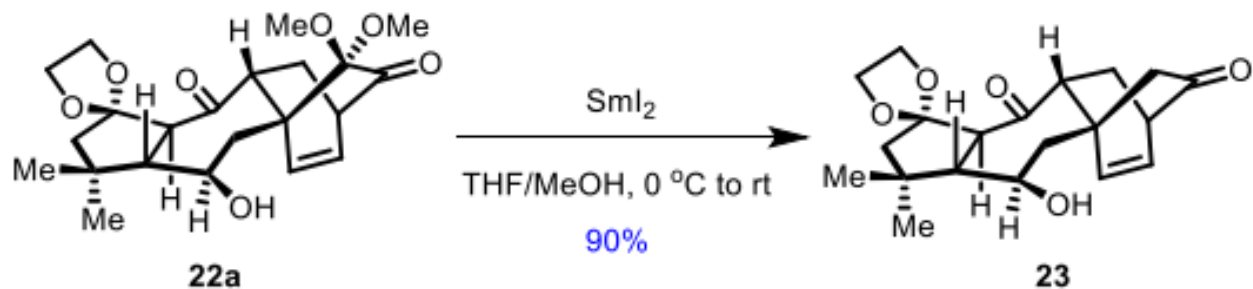
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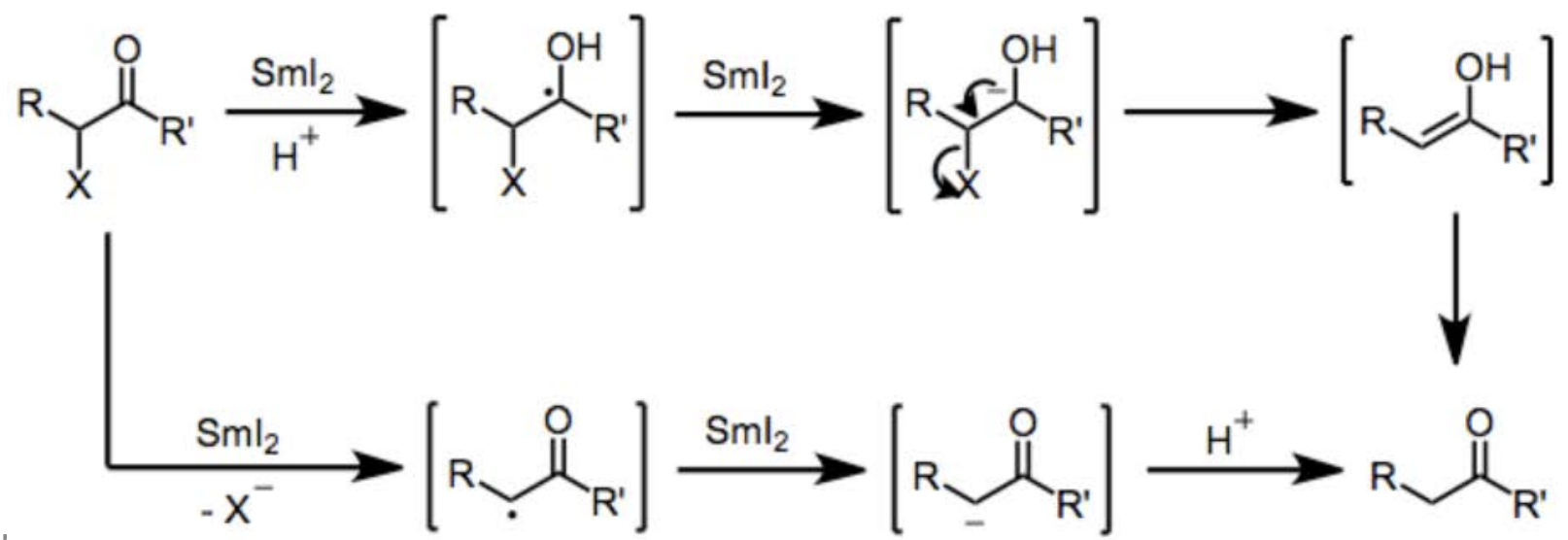


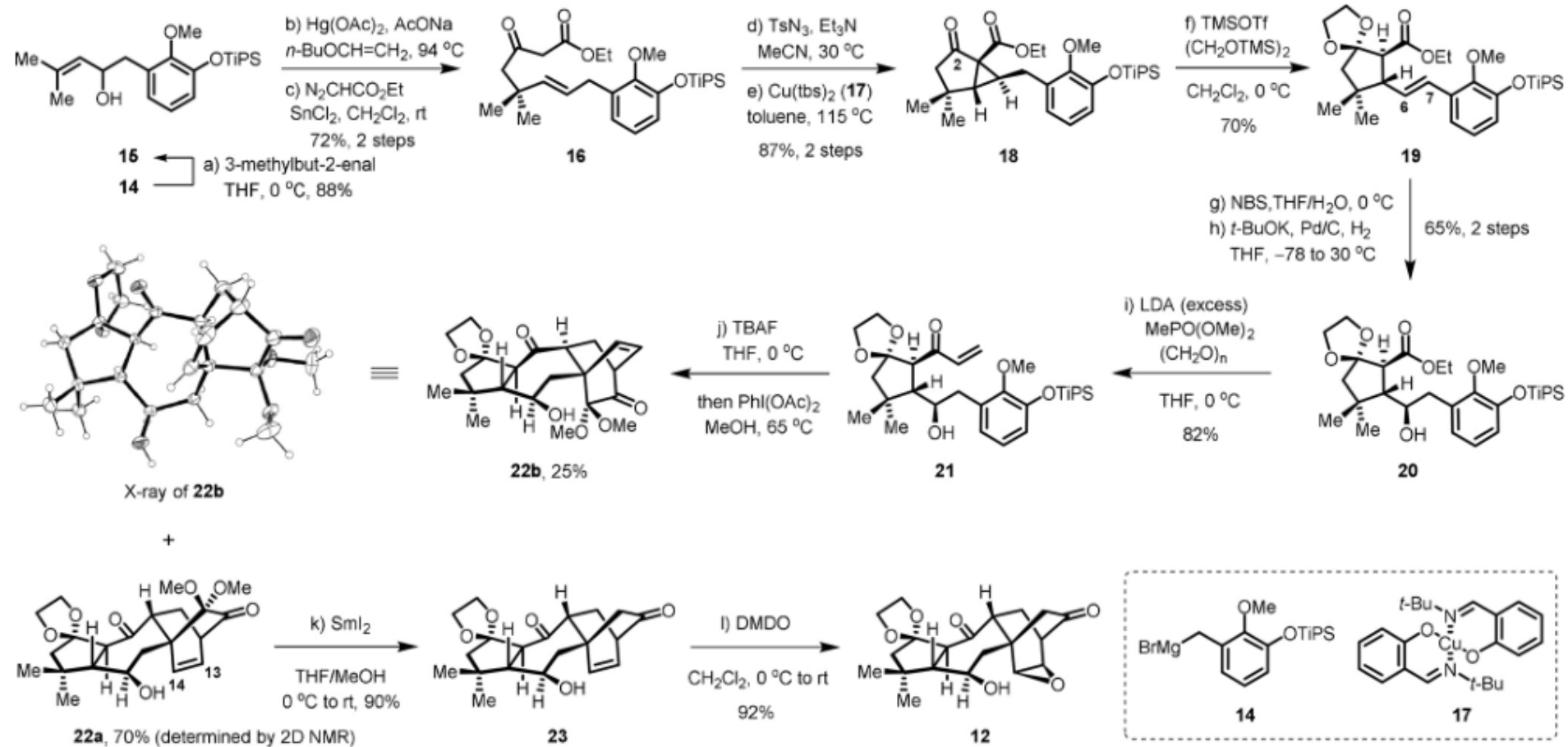


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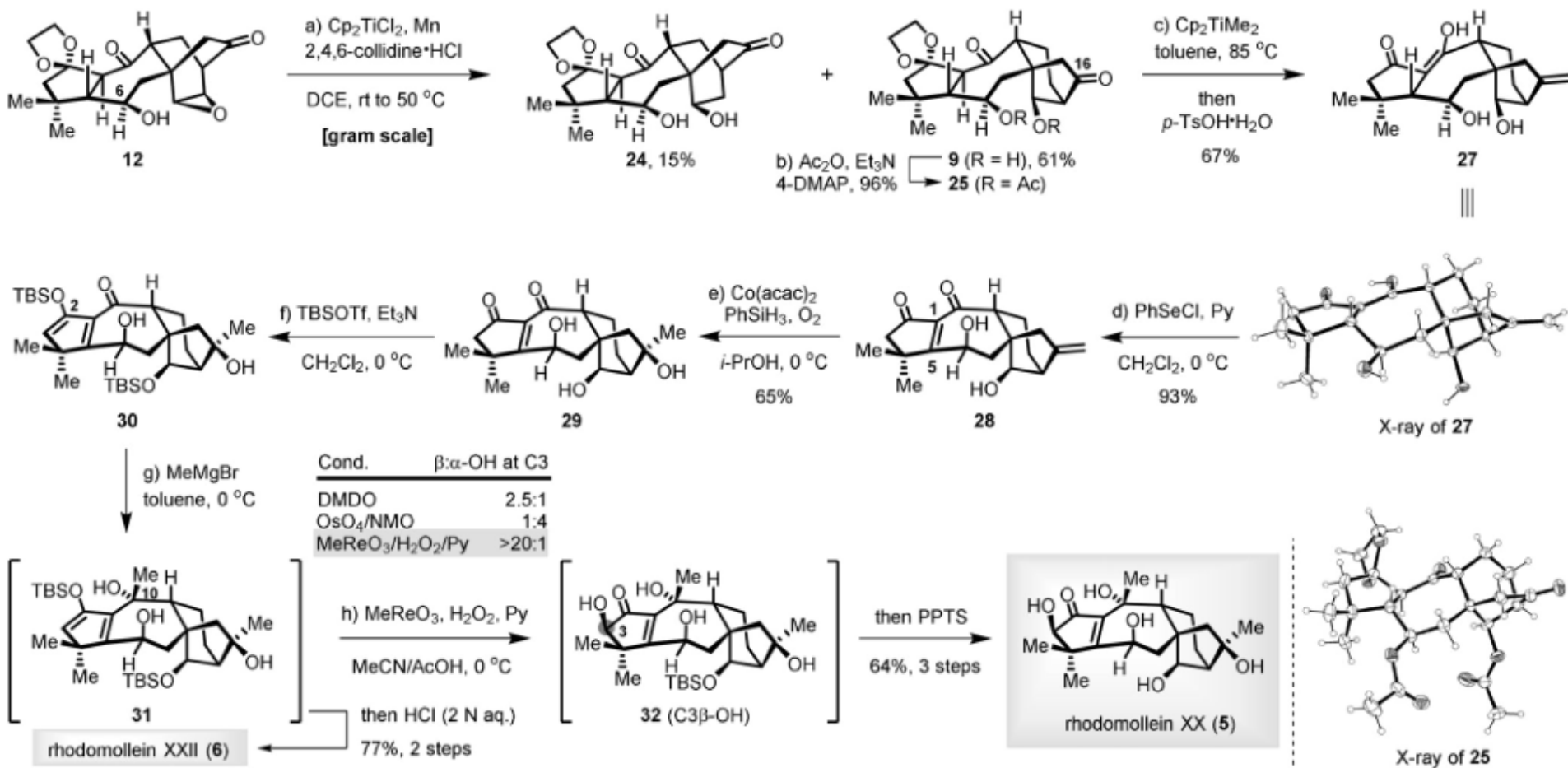


**X = R, OR**  
**Y = OH, OR, O<sub>2</sub>CR, halide, OSiR<sub>3</sub>, OSO<sub>2</sub>Ar, SAr, S(O)Ar, SO<sub>2</sub>Ar, OP(O)(OR)<sub>2</sub>**

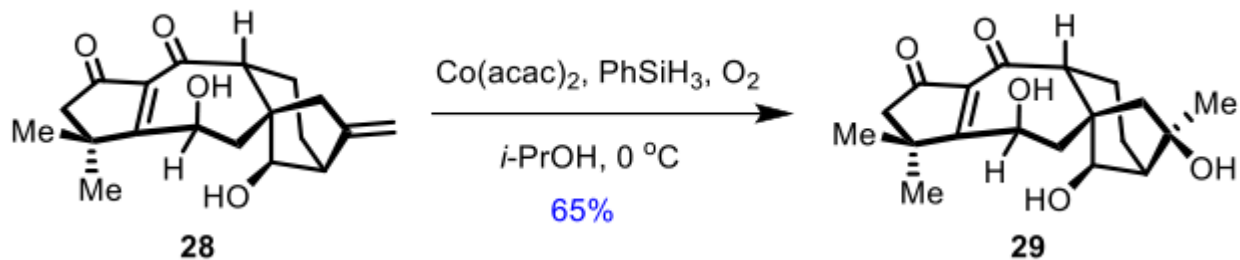




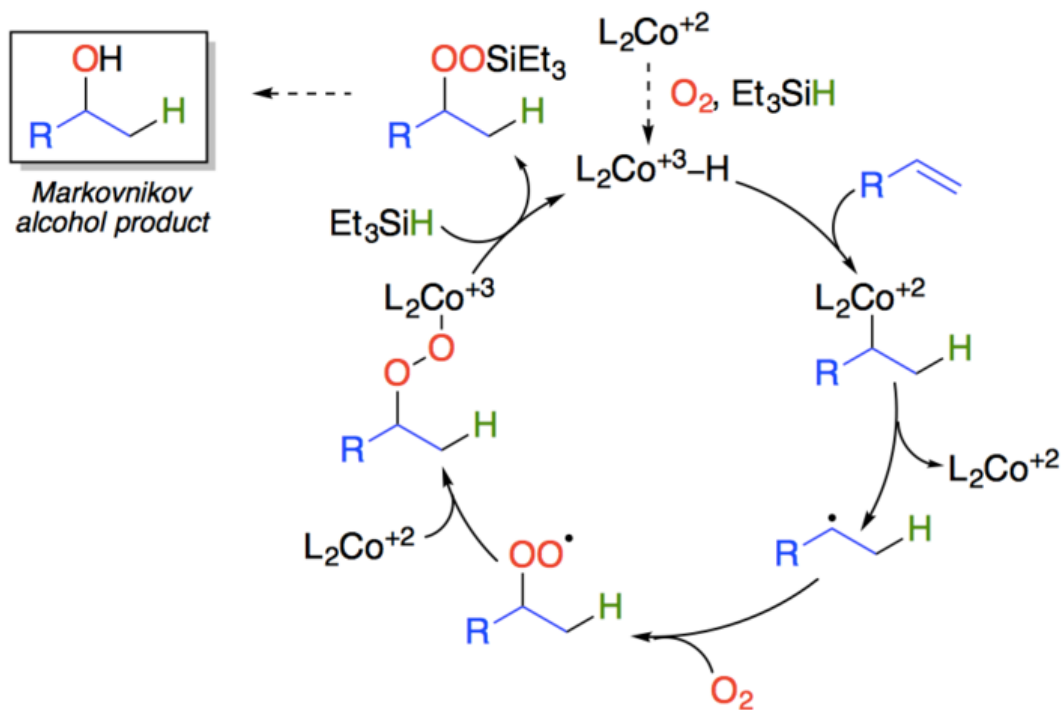
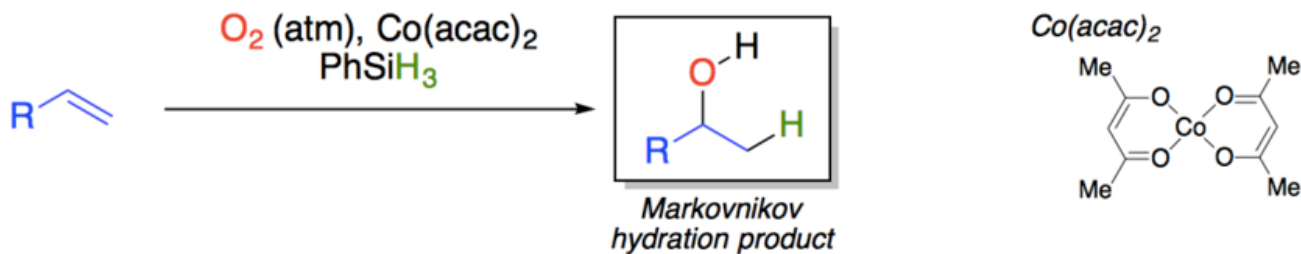
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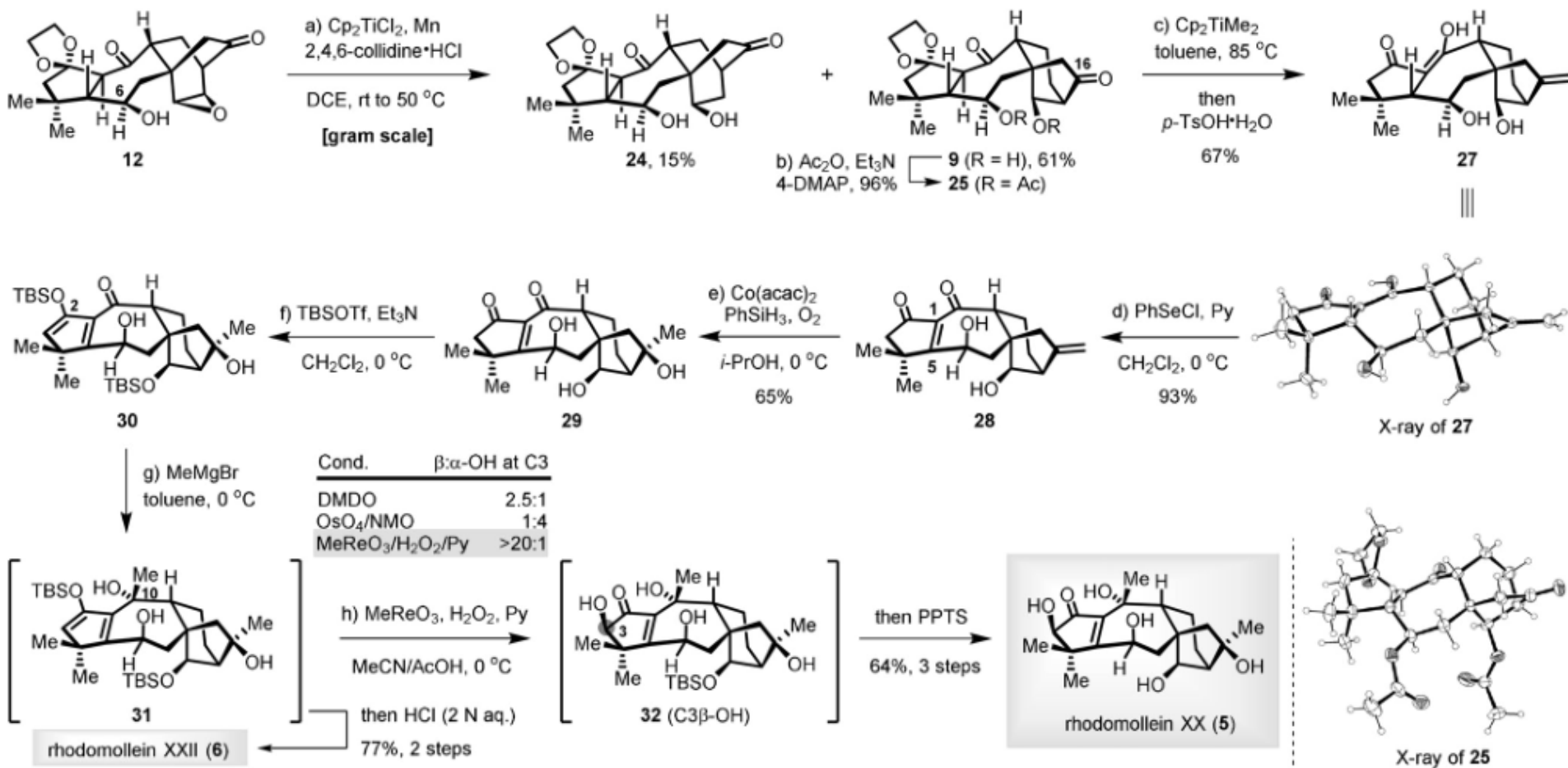


**Scheme 3.** Late-stage syntheses of rhodomolleins XX (5) and XXII (6). acac = acetylacetonate, collidine = trimethylpyridine, Cp = cyclopentadiene, DCE = 1,2-dichloroethane, 4-DMAP = *N,N'*-dimethylaminopyridine. NMO = *N*-methylmorpholine *N*-oxide, PPTS = pyridinium 4-toluenesulfonate, Py = pyridine, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate.

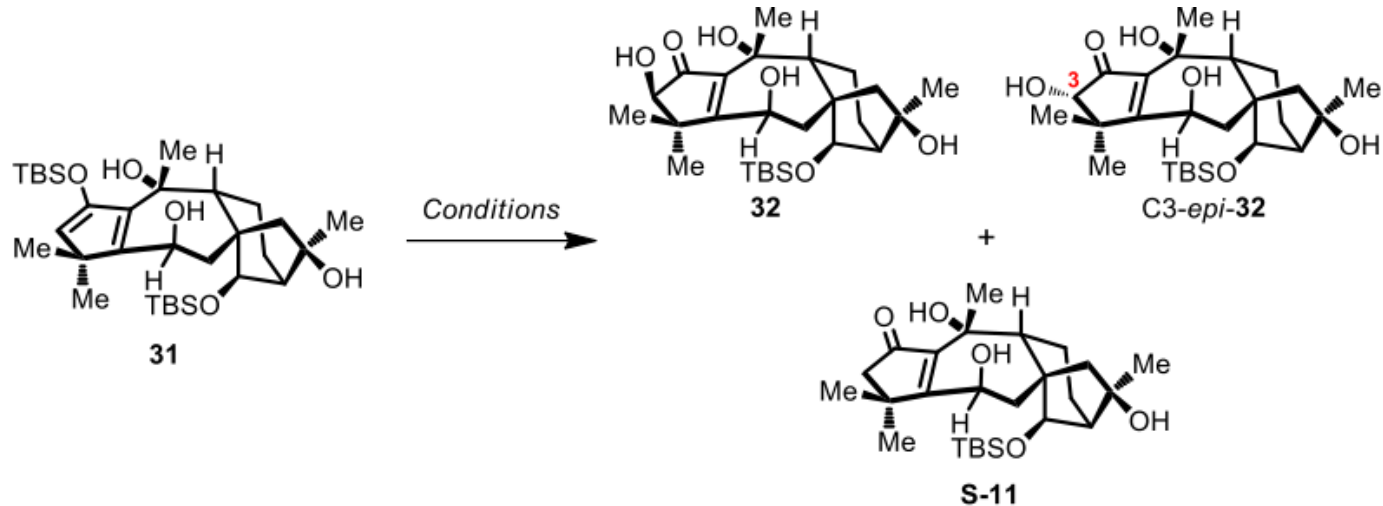


## Mukaiyama hydration



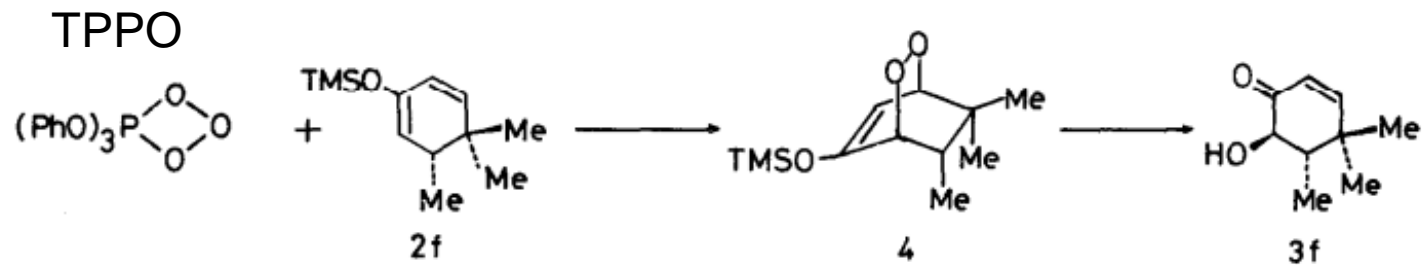


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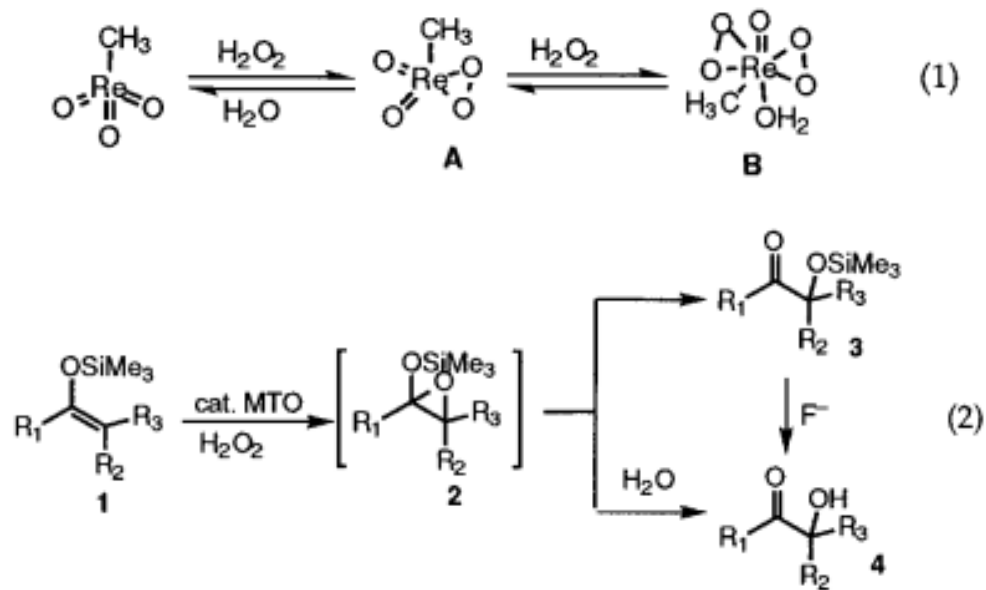


Entry	Conditions	Yield [%] <sup>[b]</sup>		
		<b>32</b>	<b>C3-epi-32</b>	<b>S-11</b>
1	DMDO, CH <sub>2</sub> Cl <sub>2</sub> , -78 °C	15	6	0
2	<i>m</i> -CPBA, NaHCO <sub>3</sub> , hexane, 0 °C	0	0	70
3	Davis' oxaziridine, CHCl <sub>3</sub> , rt	0	0	62
4	CuCl, <i>t</i> -BuOOH, benzene, 0 °C	0	0	85
5	oxone, NaHCO <sub>3</sub> , acetone/H <sub>2</sub> O (1:1 v/v), 0 °C	13	5	0
6	OsO <sub>4</sub> , NMO, acetone, rt	16	65	0
7	OsO <sub>4</sub> , NMO, pyridine, <i>t</i> -BuOH, rt	13	54	0
8 <sup>[c]</sup>	TPPO, CH <sub>2</sub> Cl <sub>2</sub> , rt	0	0	0
<b>9</b>	<b>MeReO<sub>3</sub>, H<sub>2</sub>O<sub>2</sub>, pyridine, MeCN/HOAc (95:5 v/v), 0 °C</b>	<b>87</b>	<b>0</b>	<b>0</b>



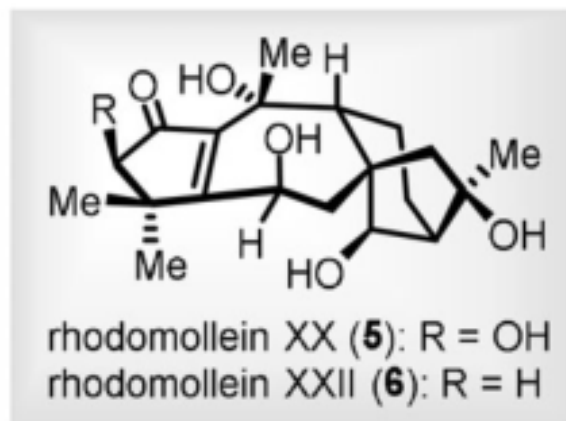


*J. Org. Chem.* **1980**, *45*, 3000-3004



*J. Org. Chem.* **1998**, *63*, 4129-4130

# Conclusion



- A new titanium(III)-mediated reductive epoxide-opening/Beckwith–Dowd rearrangement process.
- A  $\text{Cu}(\text{tbs})_2$  -catalyzed intramolecular cyclopropanation, a diastereoselective ODI-Diels–Alder cycloaddition, and a  $\text{MeReO}_3$  -catalyzed Rubottom oxidation.
- First total syntheses of rhodomolleins XX and XXII in 23 and 22 steps.