

# A Convergent Total Synthesis of (+)-Ineleganolide

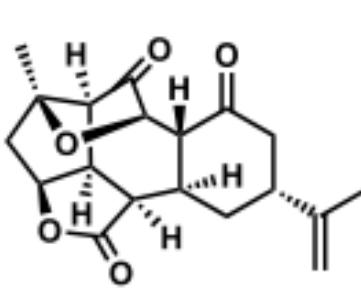
Benjamin M. Gross, Seo-Jung Han, Scott C. Virgil, and Brian M. Stoltz\*



Cite This: <https://doi.org/10.1021/jacs.3c02142>

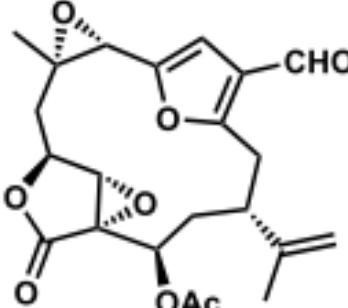


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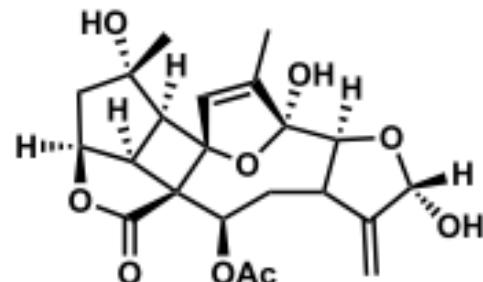
*Ineleganolide (1)*

cytotoxic against  
P-388 murine  
leukemia cells  
( $ED_{50} = 3.82 \mu\text{g/mL}$ )



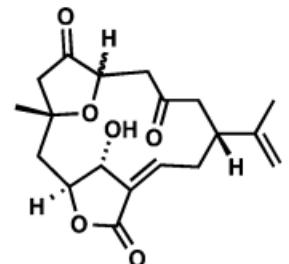
*Lophotoxin (2)*

potent neurotoxin  
irreversible inhibitor of  
nicotinic  
acetylcholine receptor

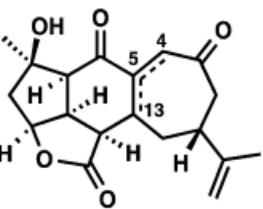


*Bielschowskysin (3)*

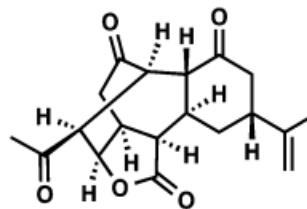
cytotoxic against  
EKVX nonsmall cell lung cancer  
( $GI_{50} < 0.01 \mu\text{M}$ )  
CAKI-1 renal cancer  
( $GI_{50} = 0.51 \mu\text{M}$ )



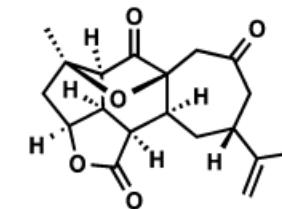
$\alpha$ -H: sinuleptolide (2)  
 $\beta$ -H: 5-episinuleptolide (3)



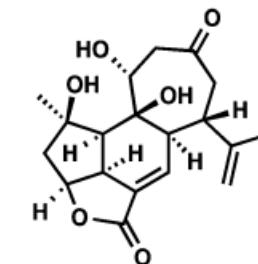
$\Delta$  5-13: scabrolide A (4)  
 $\Delta$  4-5: scabrolide B (5)



holiolide (6)

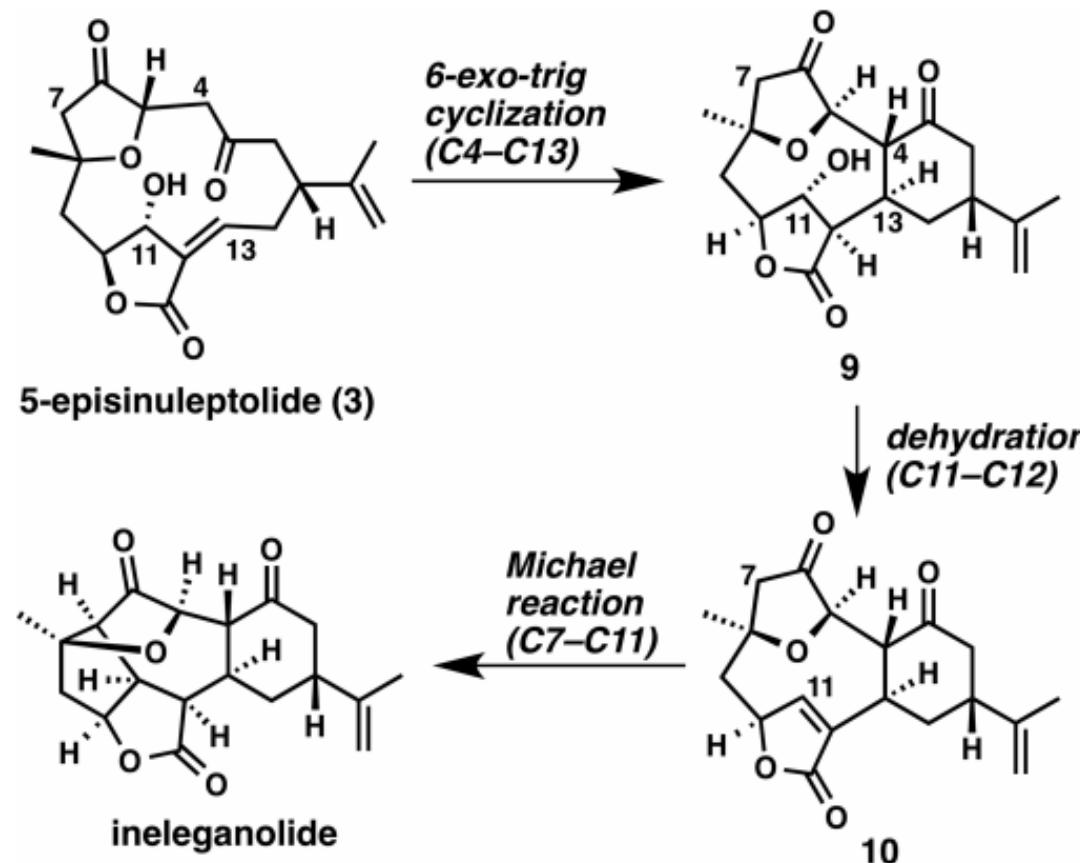


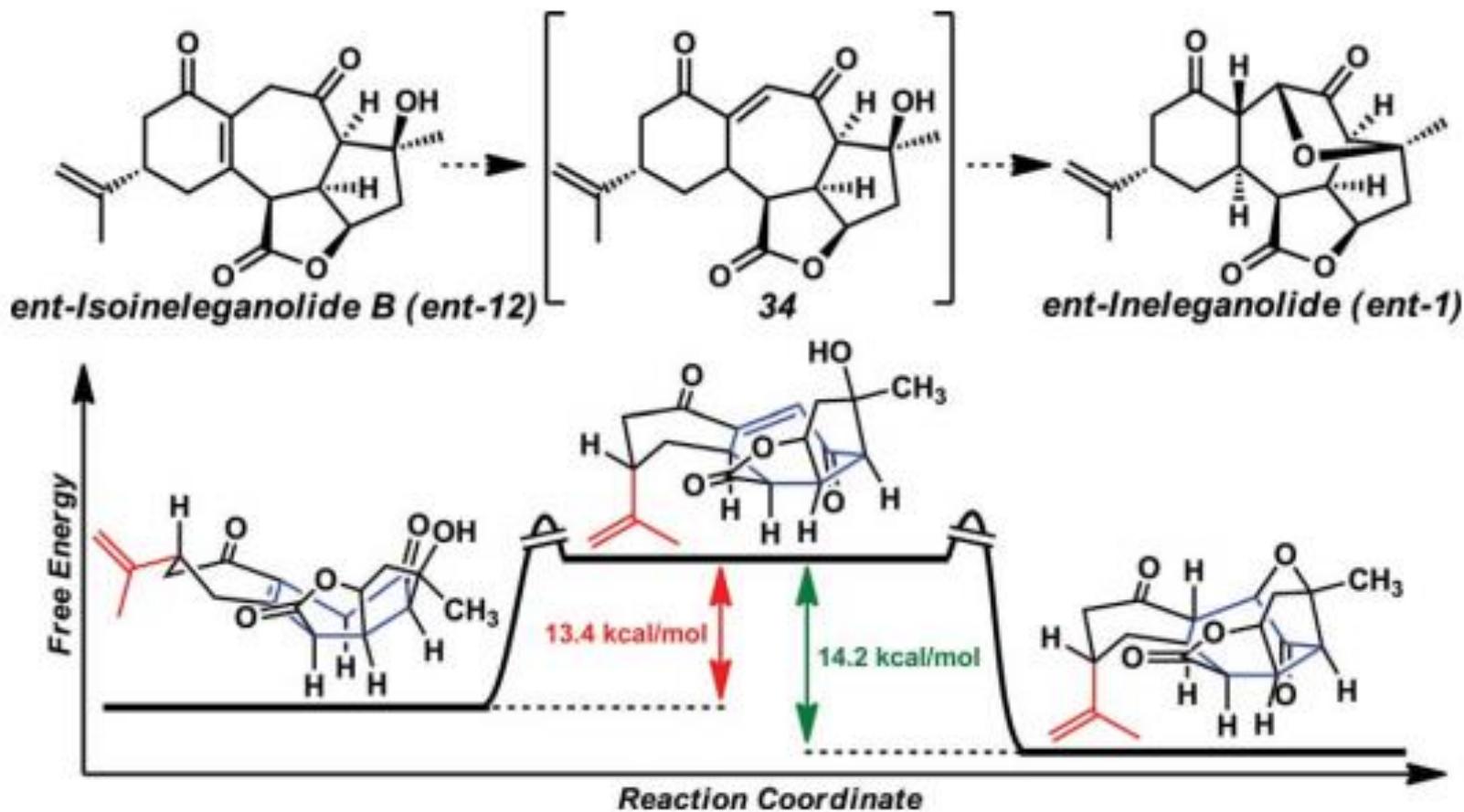
sinulochmodin C (7)



dissectolide (8)

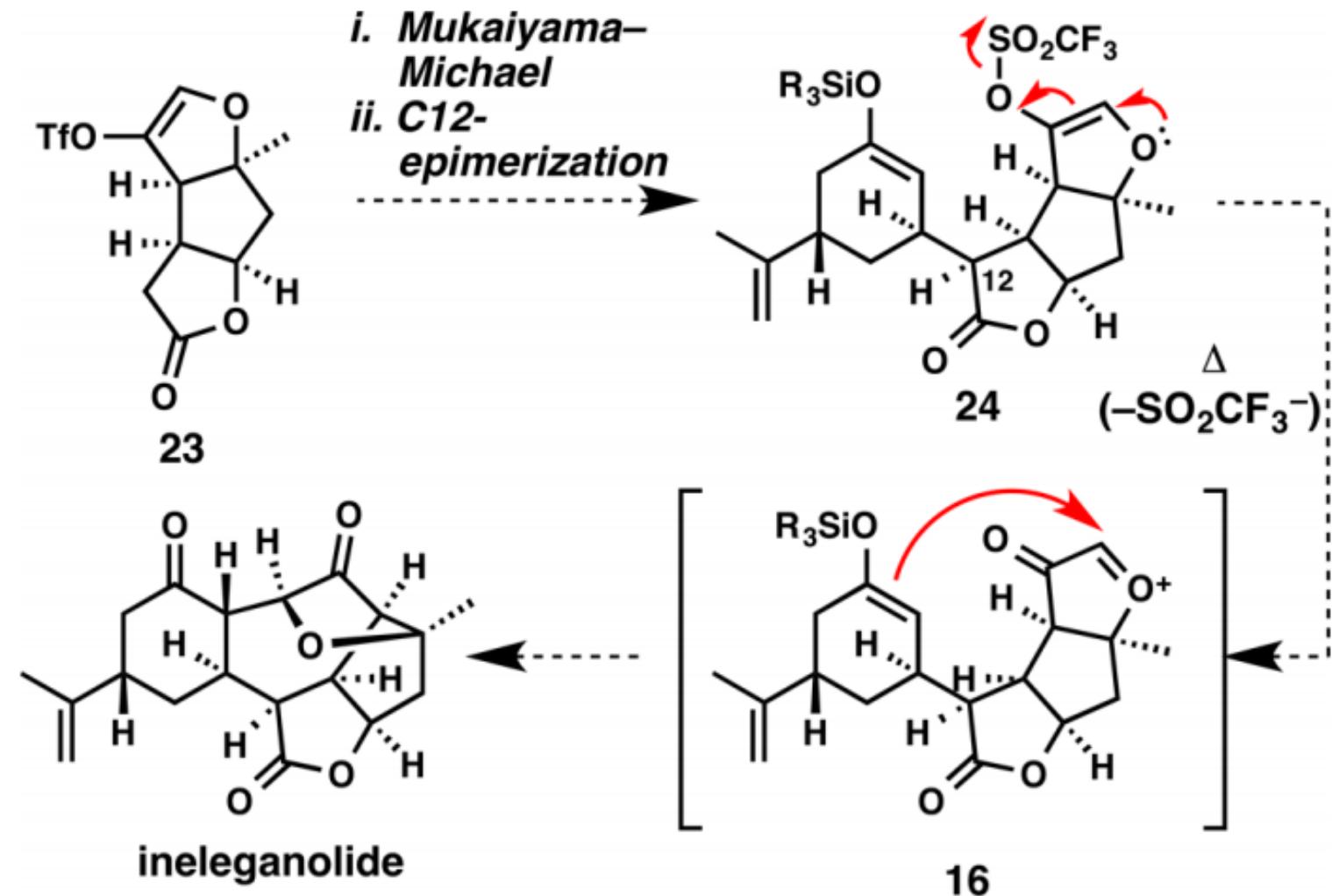
**Scheme 1. Proposed Biosynthesis of Ineleganolide and Sinulariadiolide from 5-Episinuleptolide**



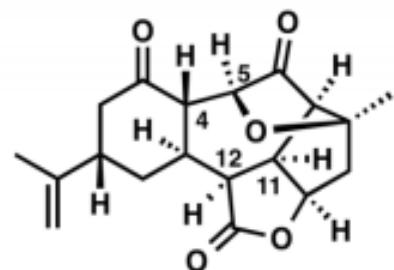


Scheme 6 Conformational assessment and relative ground state energies.

**Scheme 4. Proposed Implementation of Triflate Fragmentation in Our Synthesis of Ineleganolide**

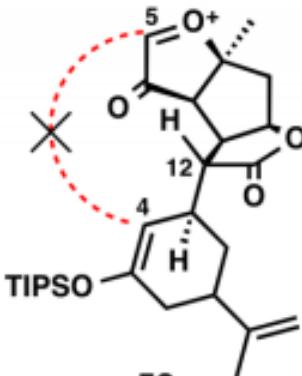


a.



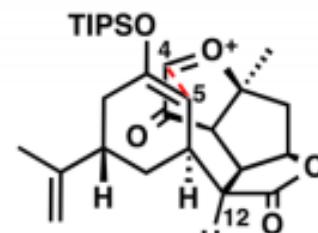
ineleganolide

C4 and C5 cannot reach each other owing to rigidity of tricycle



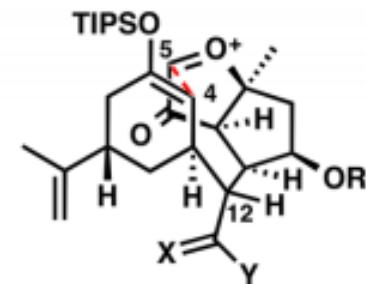
53  
(epimeric C12 configuration to ineleganolide)

C4 and C5 held in close proximity to each other



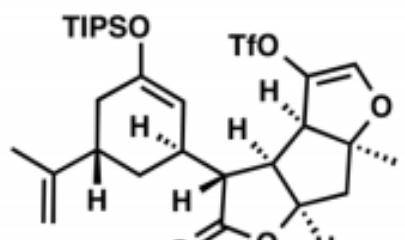
16  
(same C12 configuration as ineleganolide)

opening the lactone ring allows C11–C12 bond rotation; C4 and C5 can reach each other regardless of C12 configuration



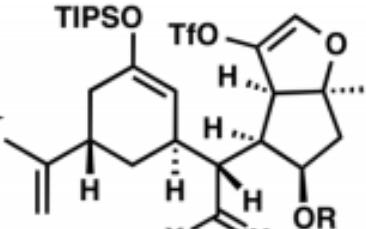
54  
(epimeric C12 configuration to ineleganolide)

b.



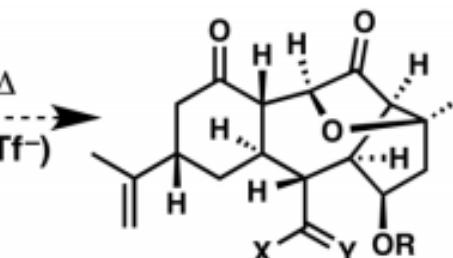
38

open lactone



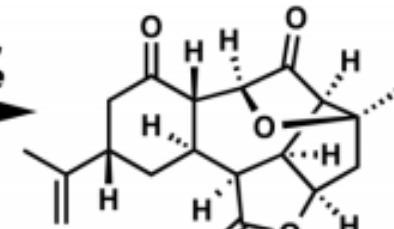
55

$\Delta$

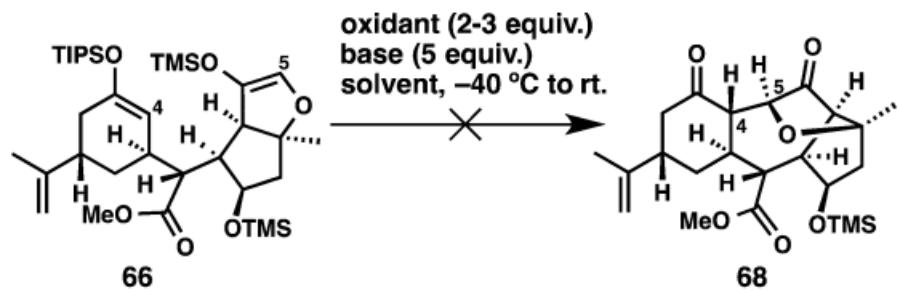


56

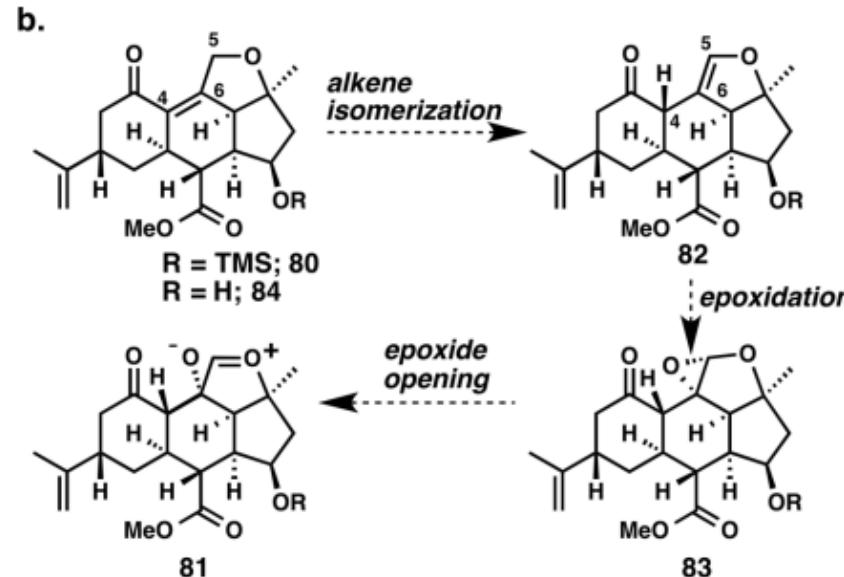
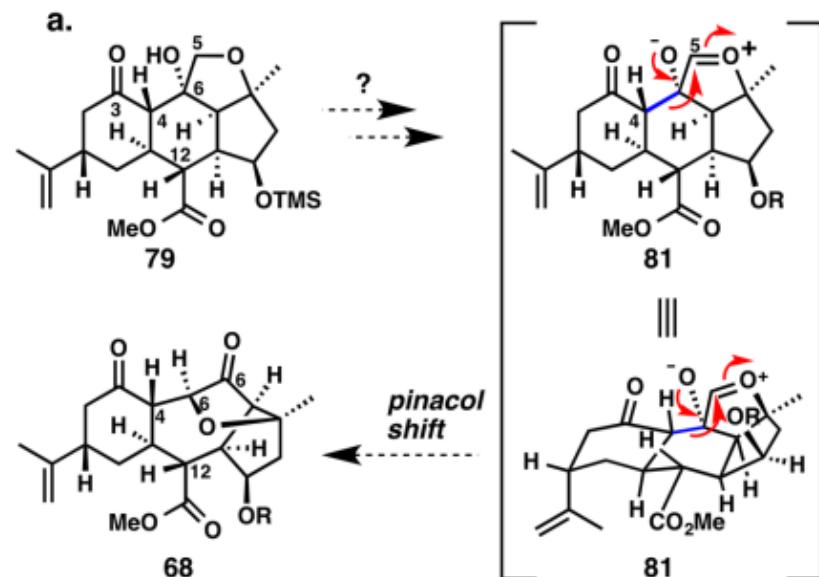
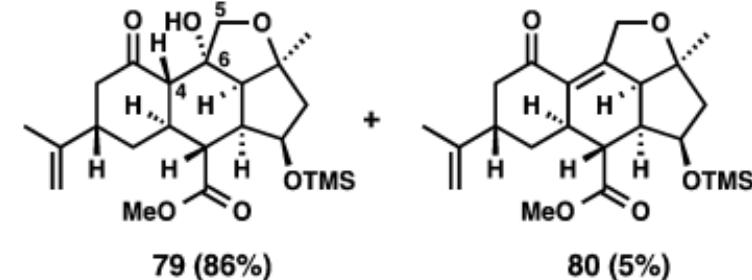
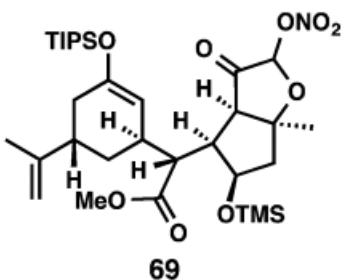
epimerize C12, reform lactone

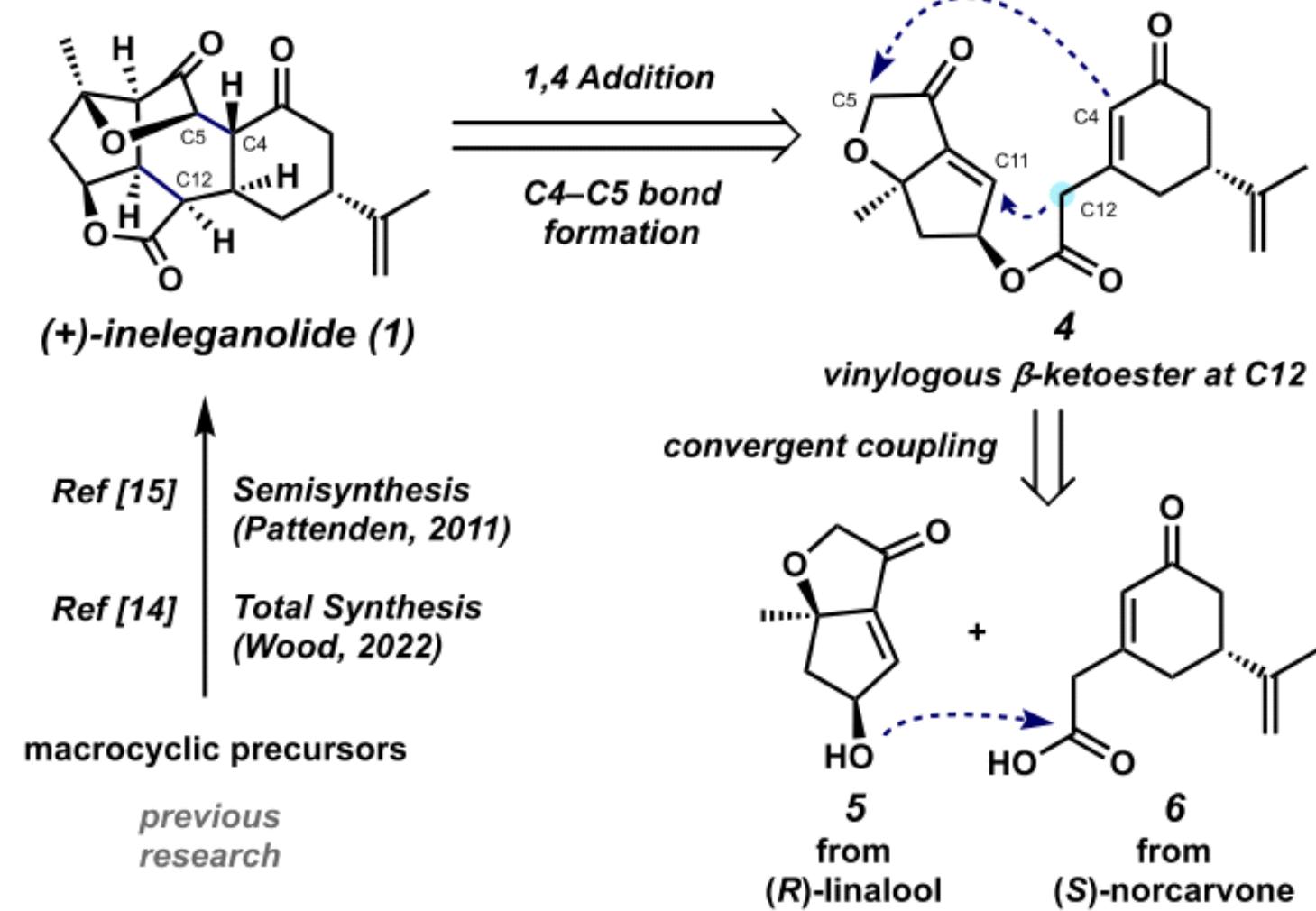


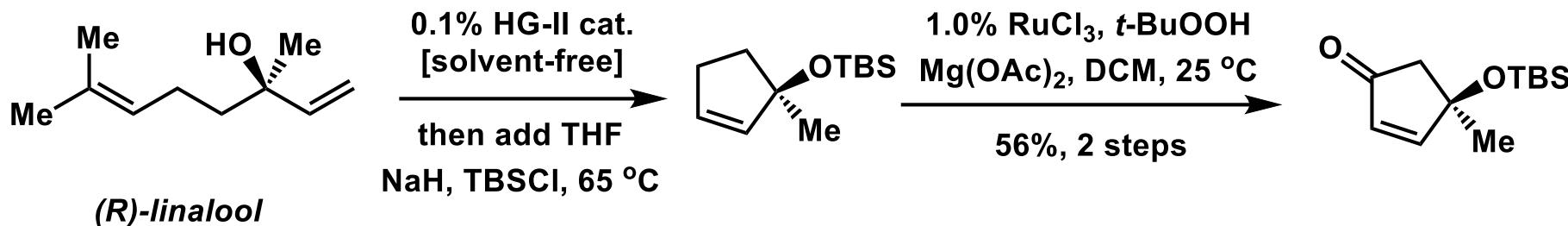
ineleganolide



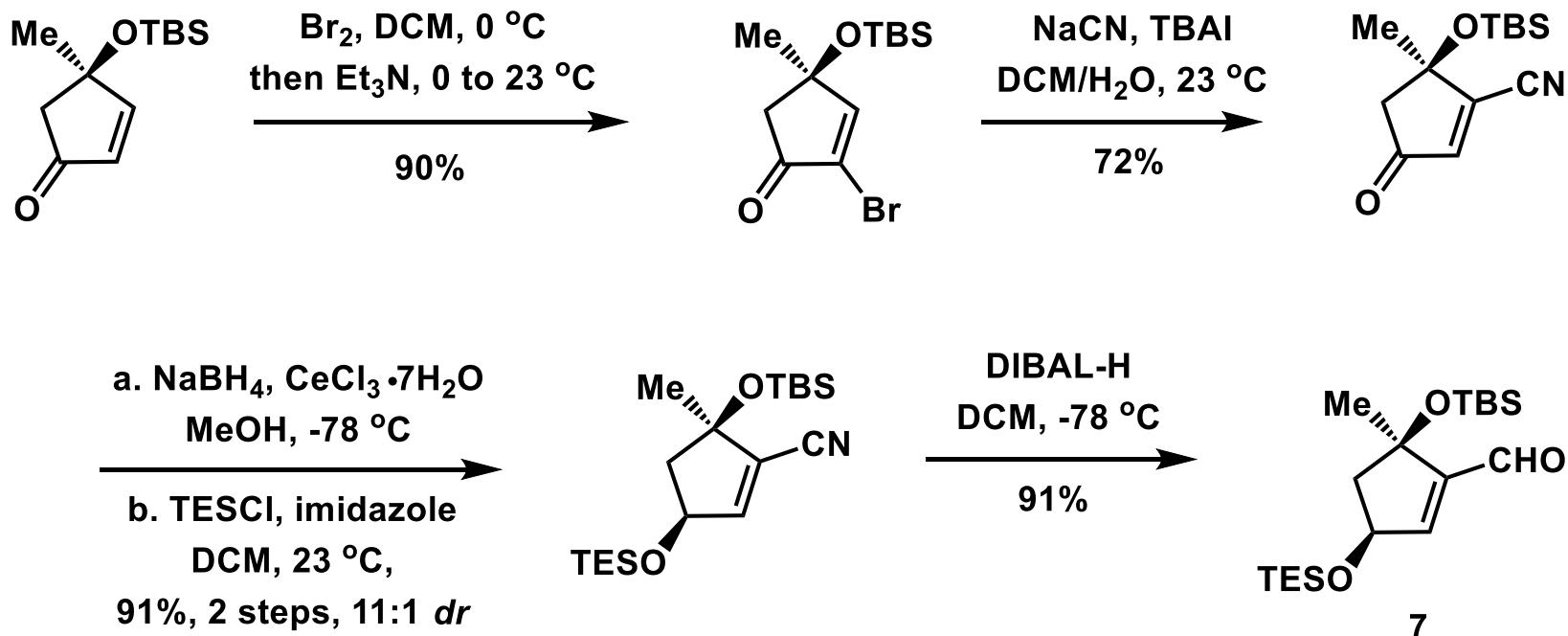
oxidants include: CAN, TBACN,  $\text{Ag}_2\text{O}$ ,  $\text{Mn}(\text{acac})_3$ ,  $\text{Mn}(\text{hfacac})_3$ ,  $\text{CrO}_3$ ,  $\text{Pb}(\text{OAc})_4$ , NBS,  $\text{I}_2$





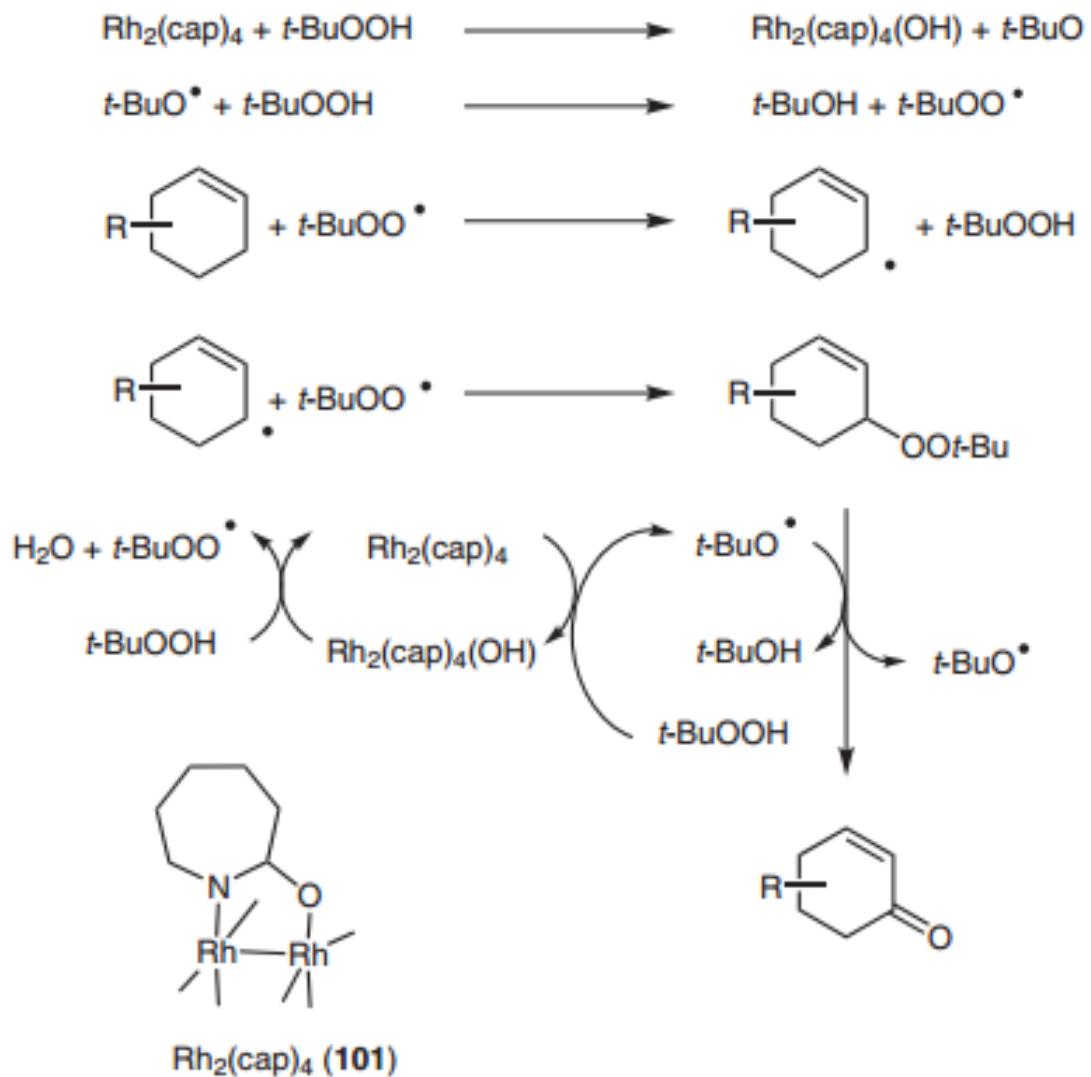


*science, 2016, 352, 20232.*

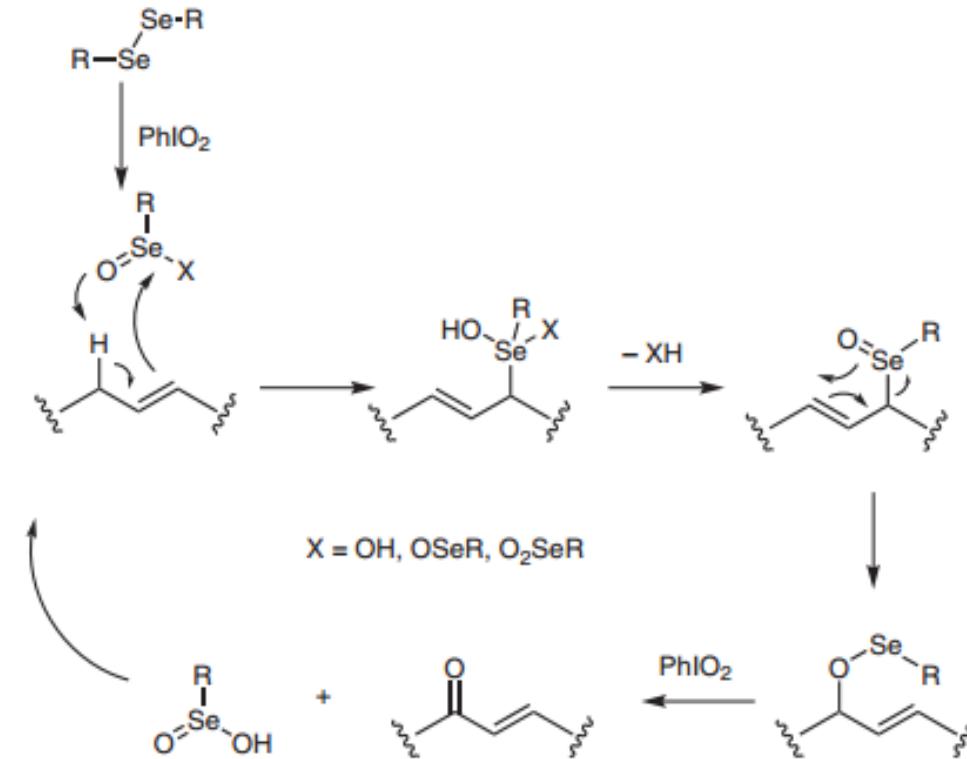


*J. Am. Chem. Soc., 2022, 144, 20232.*

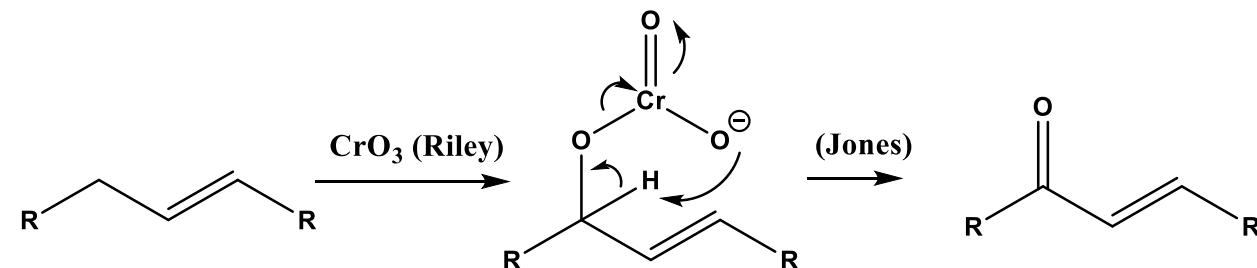
## 过渡金属催化过氧化物氧化烯丙位

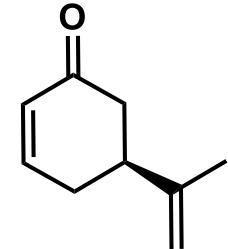


## 硒氧化烯丙位(Riley Oxidation)

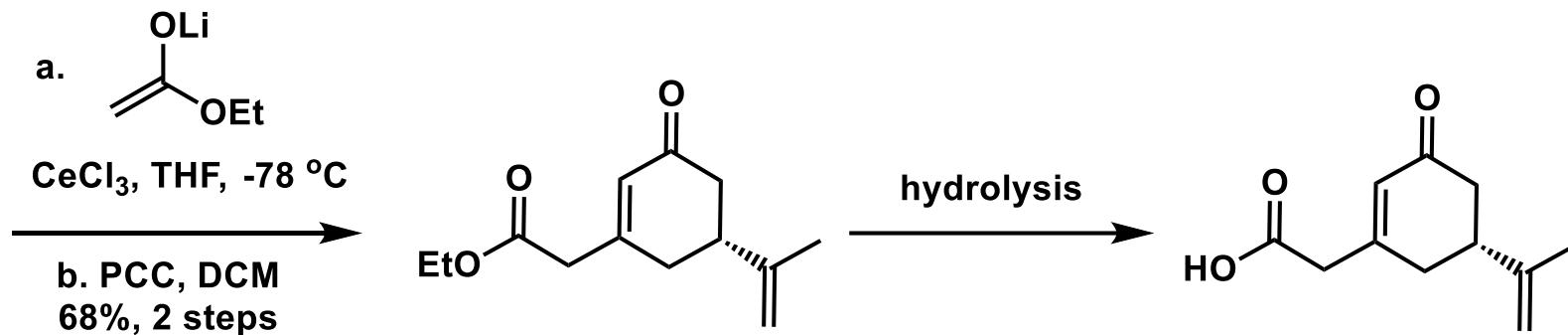


## 铬氧化烯丙位(Jones Oxidation)



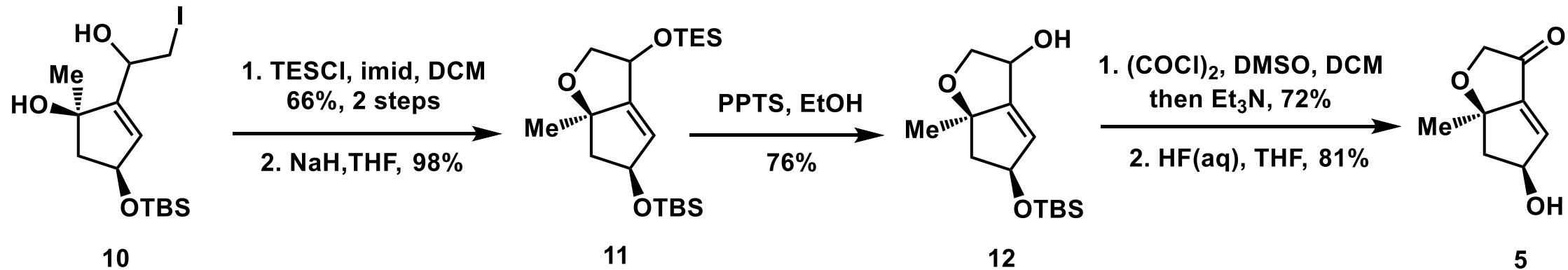
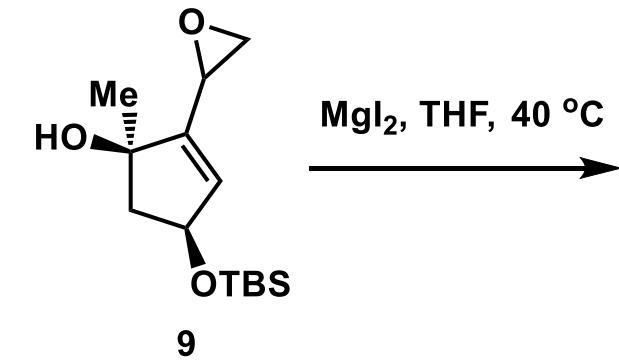
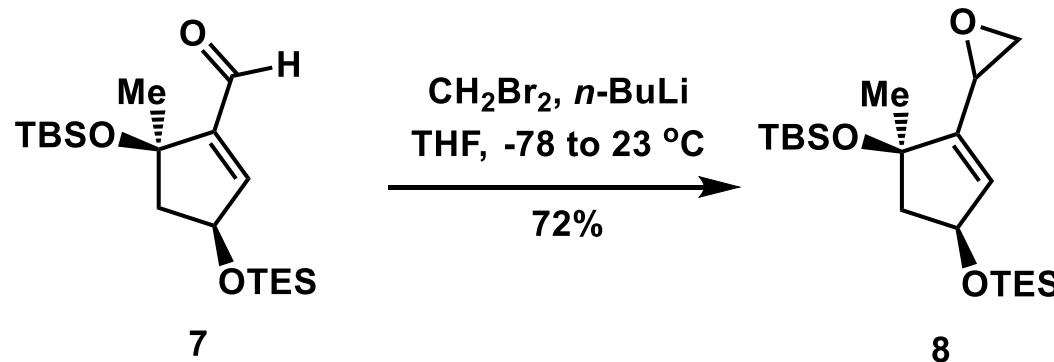


*(S)-norarvone*

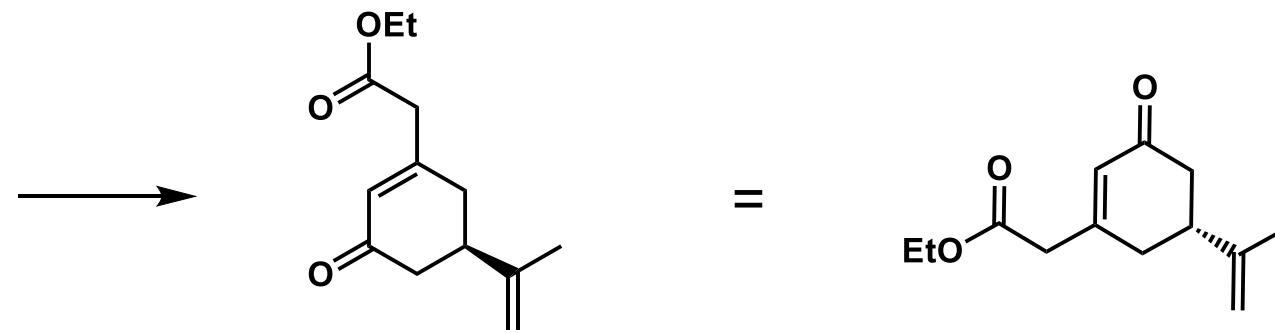
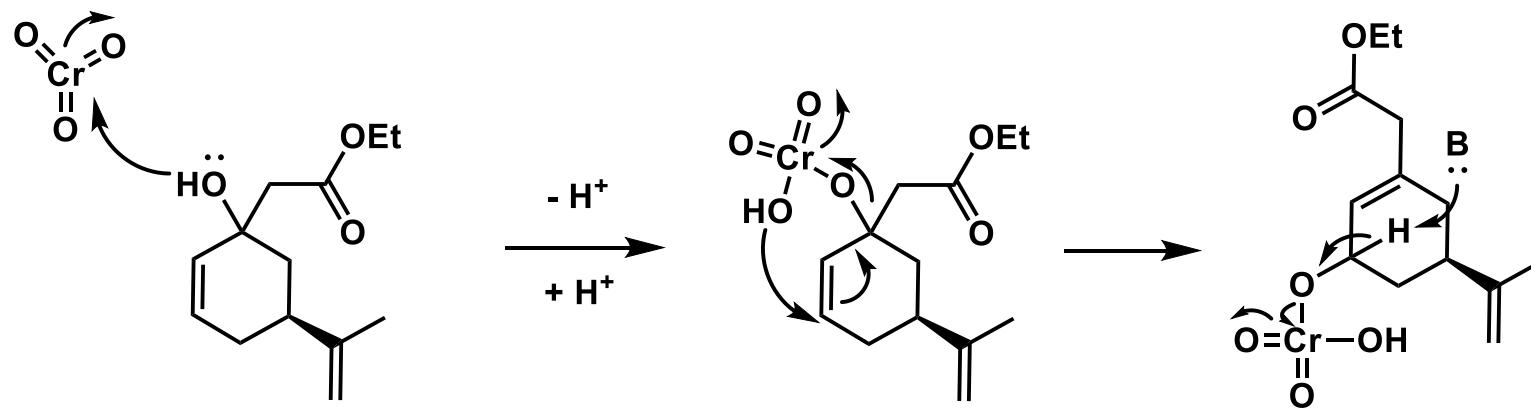
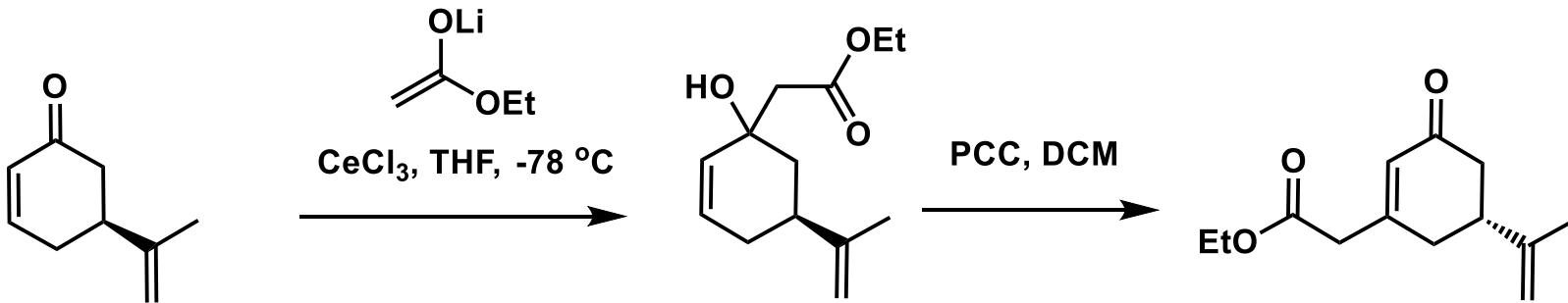


6

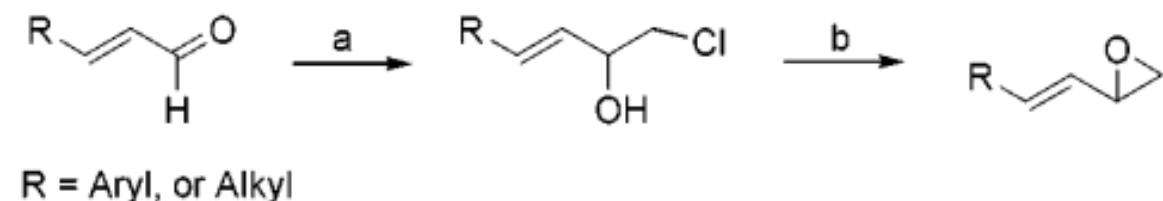
*Chem. Sci.*, 2017, 8, 507.



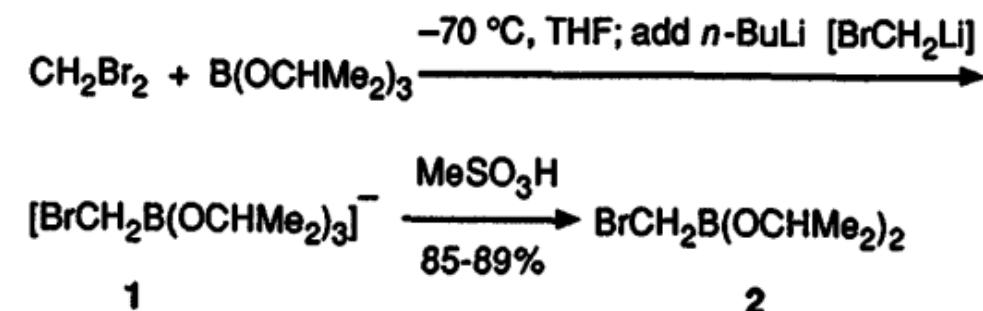
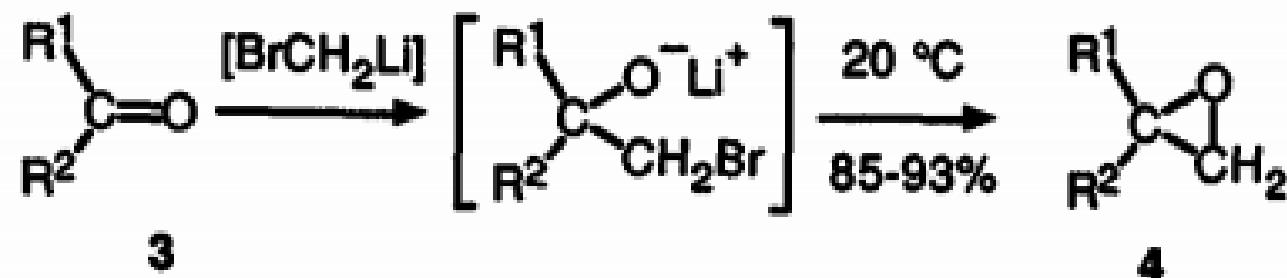
Babler–Dauben 氧化重排



**Scheme 2.** Approach to Synthesis of 2-Vinyloxiranes<sup>a</sup>



<sup>a</sup> (a)  $\text{ClCH}_2\text{I}$  (1.5 equiv),  $n\text{-BuLi}$  (1.5 equiv), THF,  $-78^\circ\text{C}$ ,  $\sim 1$  h; (b)  $\text{NaH}$  (95%, 1.1 equiv),  $\text{NaI}$  (10%), THF,  $0^\circ\text{C}$ ,  $\sim 1$  h.



**Table 1.** Oxiranes (4) from  $\text{R}^1\text{R}^2\text{C=O}$  (3),  $\text{ClCH}_2\text{I}$  or  $\text{CH}_2\text{Br}_2$ , and  $\text{BuLi}$ .<sup>a</sup>

Oxirane	bp, °C (mbar)	Yield from $\text{ClCH}_2\text{Li}$ , %	from $\text{BrCH}_2\text{Li}$
4a	48-51 (0.2)	89	93
4b	60-63 (50)	88	91
4c	46-49 (0.3)	93	93
4d	57-65 (1.7)	40	93

<sup>a</sup> Isolated yields, high purity indicated by 200-MHz  $^1\text{H}$  NMR. Cpd. 4a-c are known.<sup>1,3</sup> 4d has been partially characterized previously.<sup>8</sup>

*Synlett*, 1991, 9, 631.

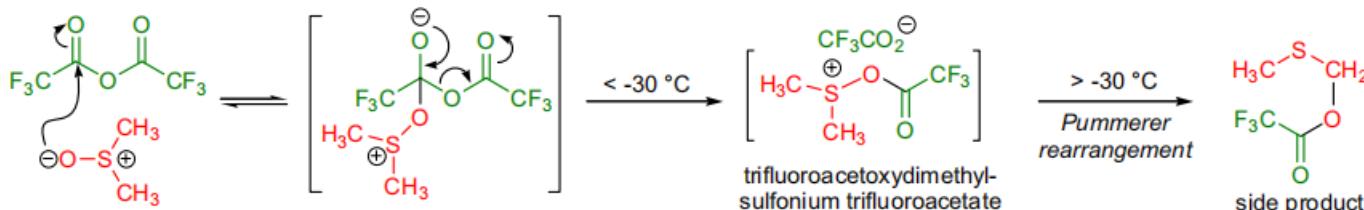
*Org. Lett.*, 2002, 4, 1.

## SWERN OXIDATION

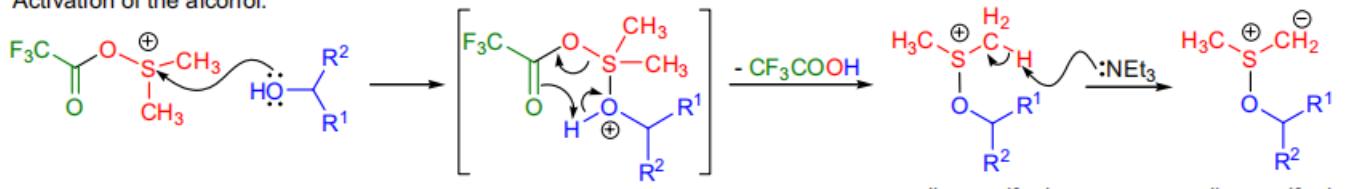
(References are on page 692)

Importance:[Seminal Publications<sup>1-6</sup>; Reviews<sup>7-10</sup>; Modifications & Improvements<sup>11-16</sup>]Mechanism:<sup>6-9</sup>

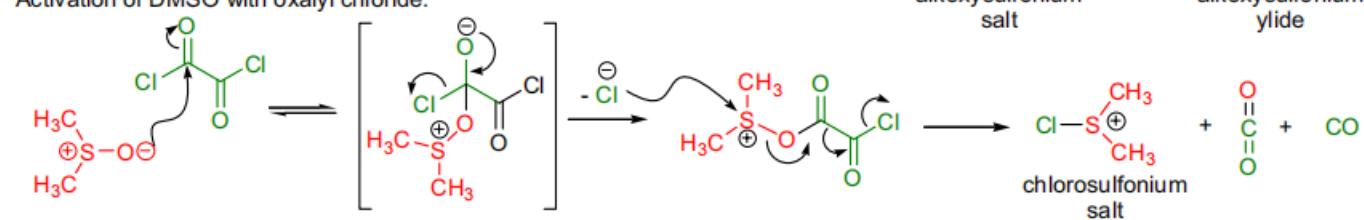
Activation of DMSO with TFAA:



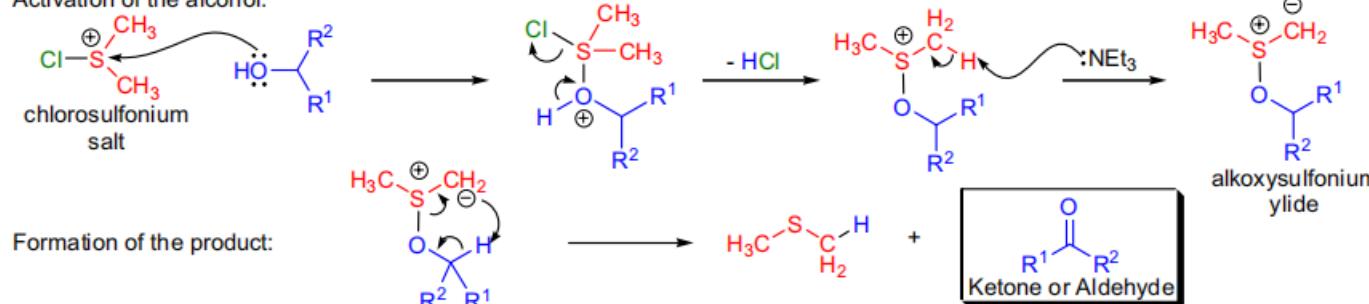
Activation of the alcohol:

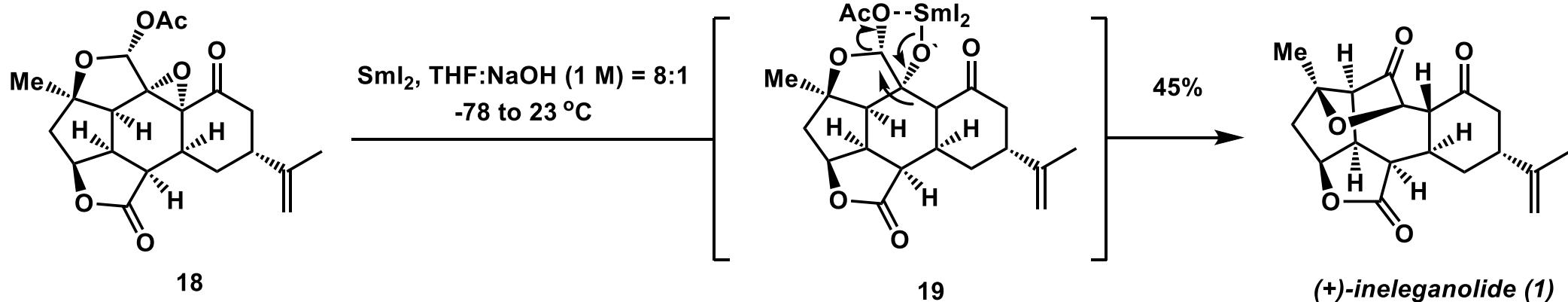
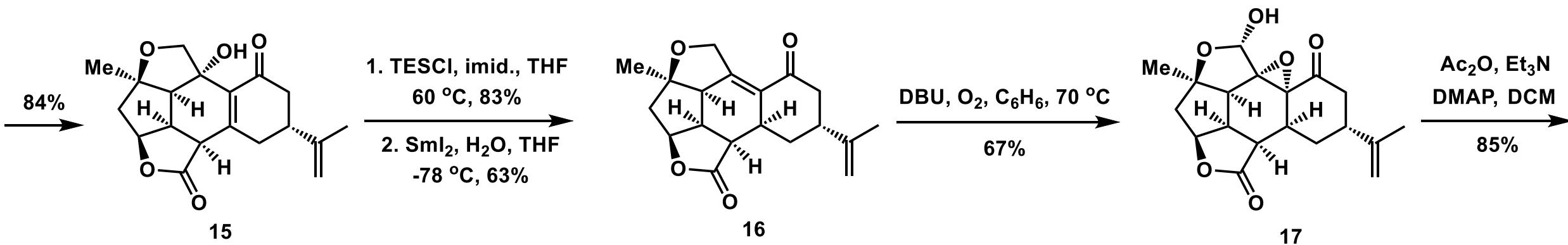
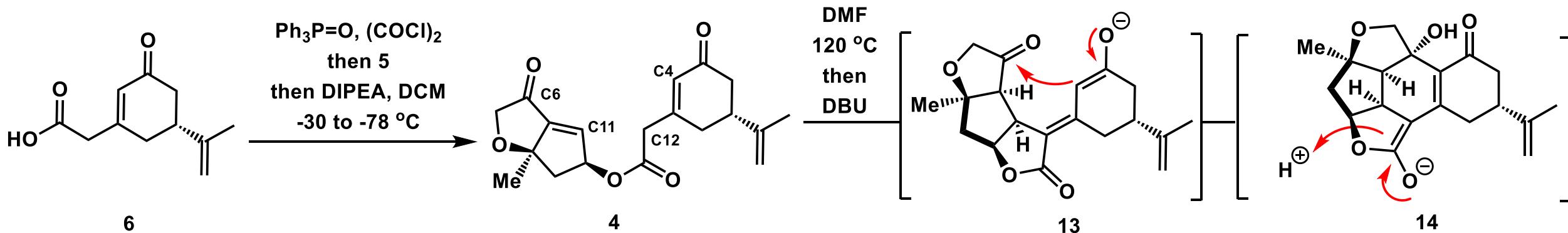


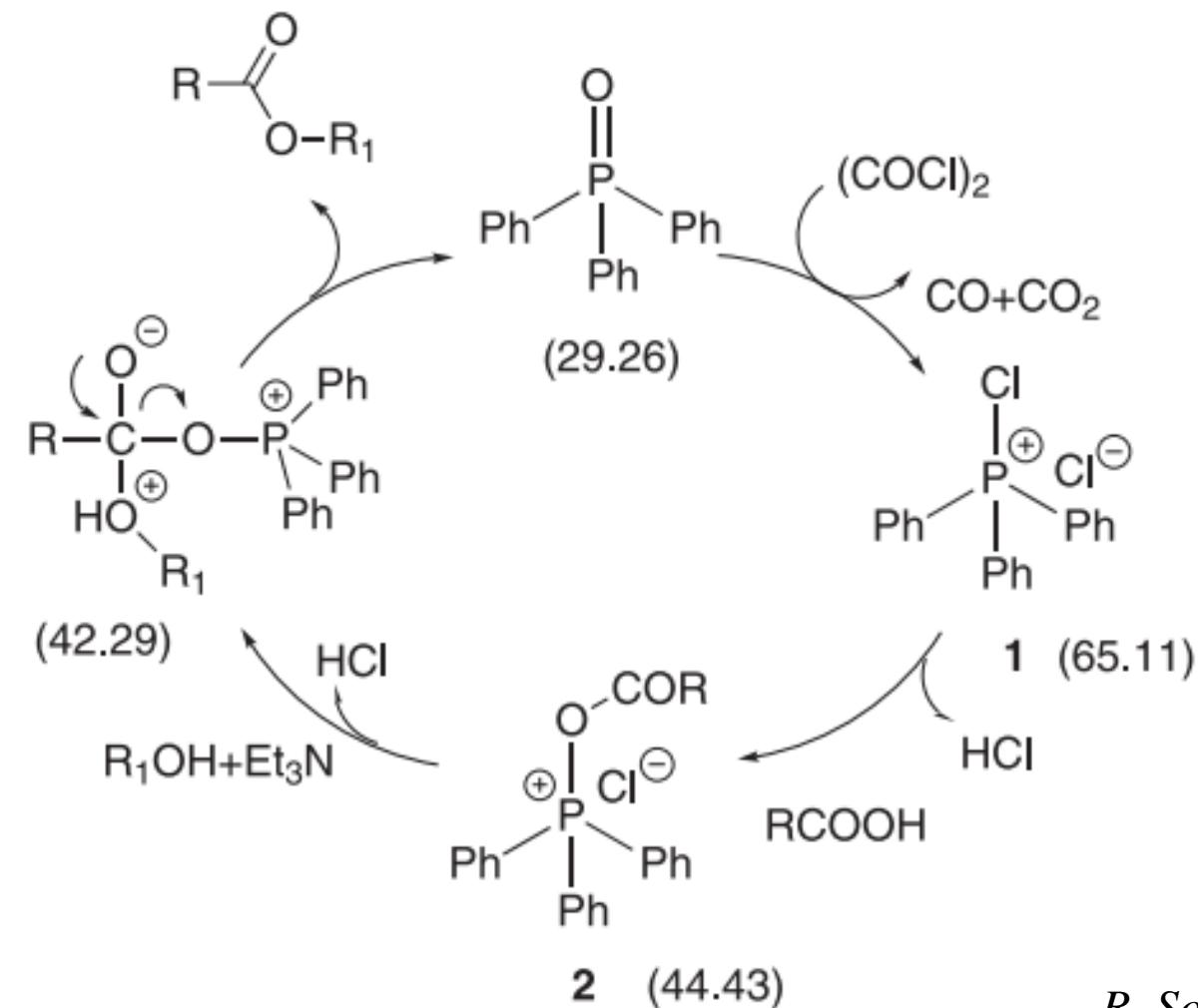
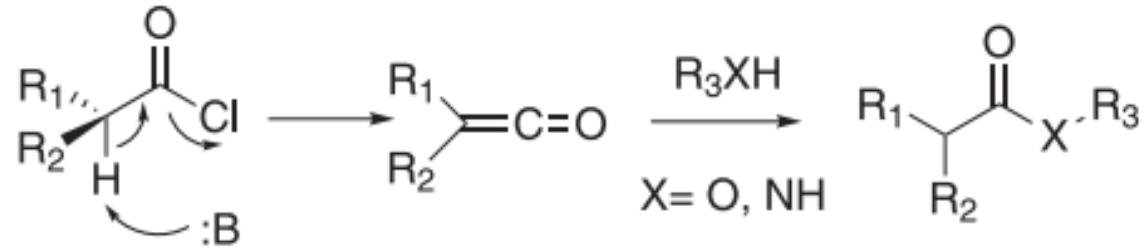
Activation of DMSO with oxalyl chloride:

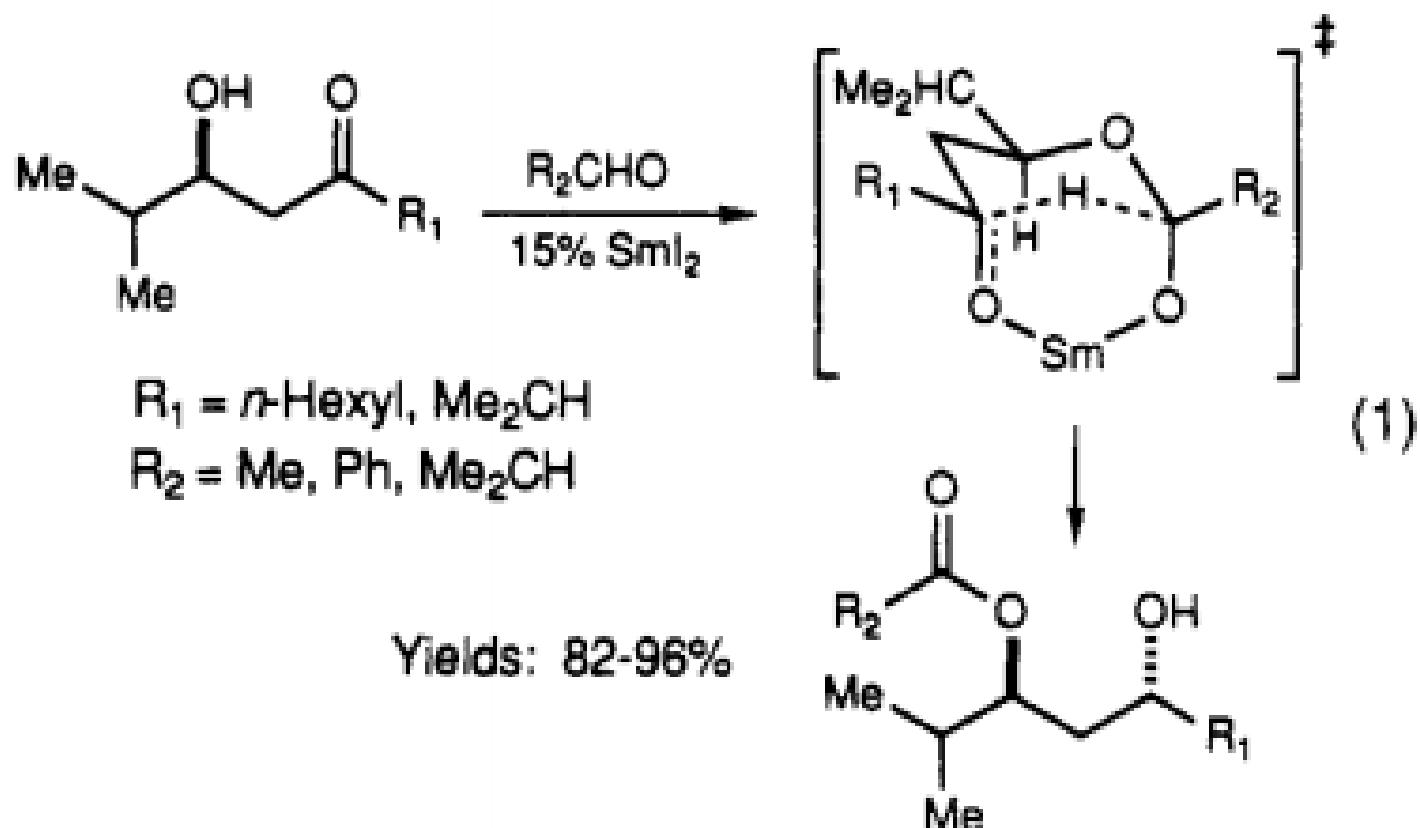
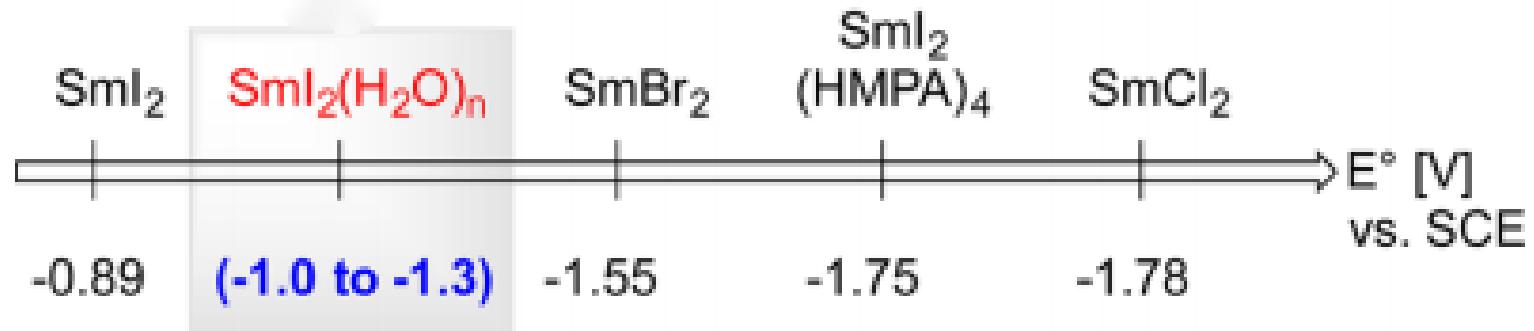


Activation of the alcohol:









*J. Org. Chem.*, 2014, 79, 2522.

*J. Am. Chem. Soc.*, 1990, 112, 6447.

