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Communication

A Convergent Total Synthesis of (+)-Ineleganolide

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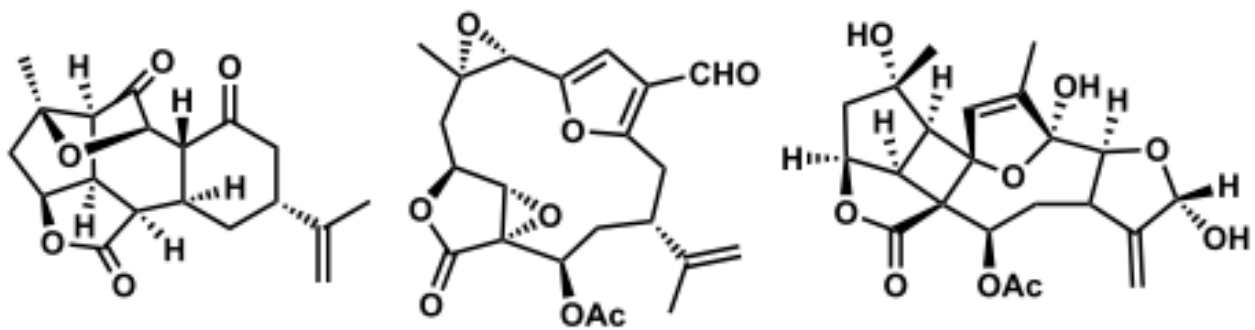


Ineleganolide (1)

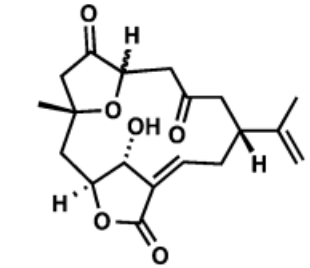
cytotoxic against
P-388 murine
leukeumia cells
(ED_{50} = 3.82 μg/mL)

Lophotoxin (2)

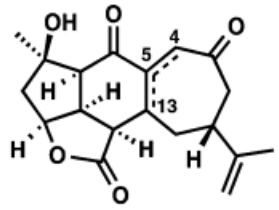
potent neurotoxin
irreversible inhibiton of
nicotinic
acetylcholine receptor

Bielschowskysin (3)

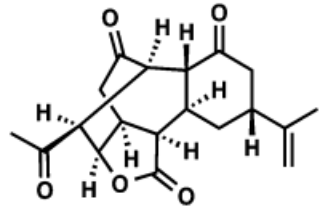
cytotoxic against
EKVX nonsmall cell lung cancer
(GI_{50} < 0.01 μM)
CAKI-1 renal cancer
(GI_{50} = 0.51 μM)



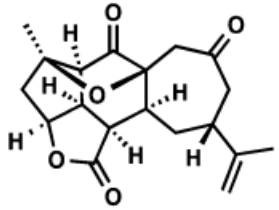
α-H: sinuleptolide (2)
β-H: 5-episinuleptolide (3)



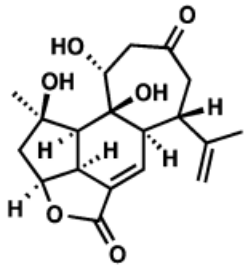
Δ 5-13: scabrolide A (4)
Δ 4-5: scabrolide B (5)



horiolide (6)

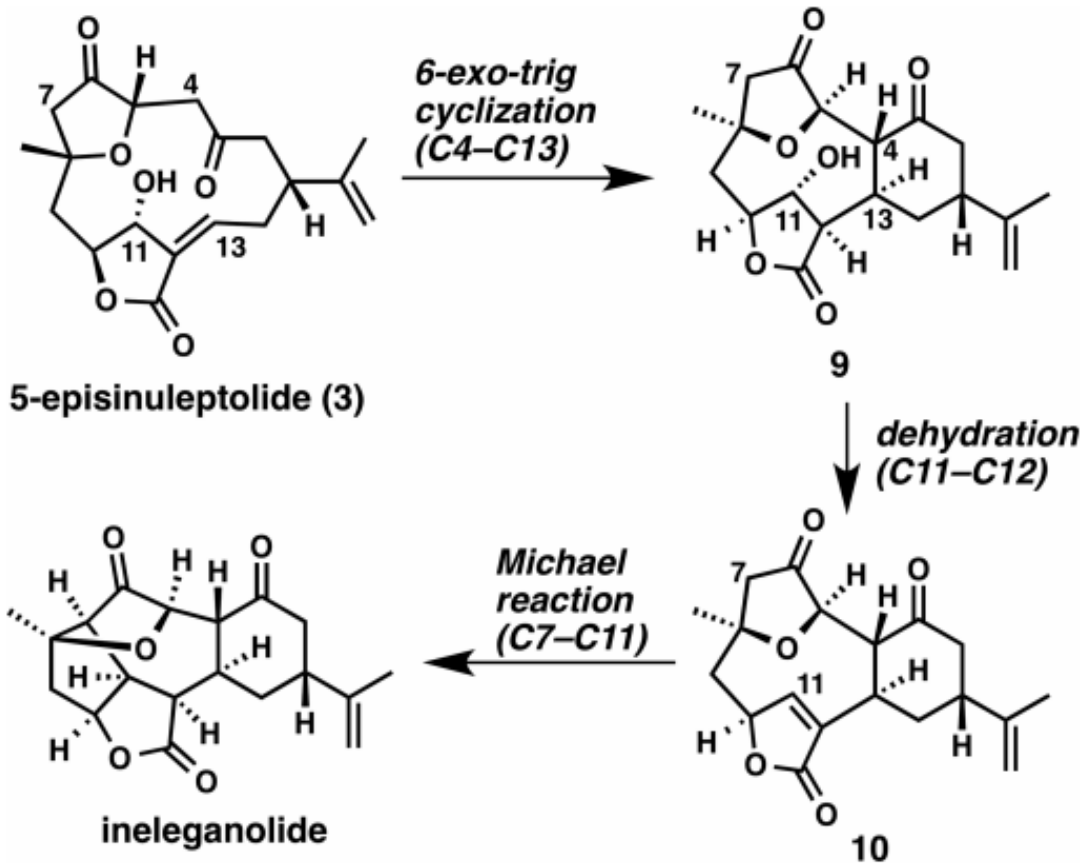


sinulochmodin C (7)



dissectolide (8)

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



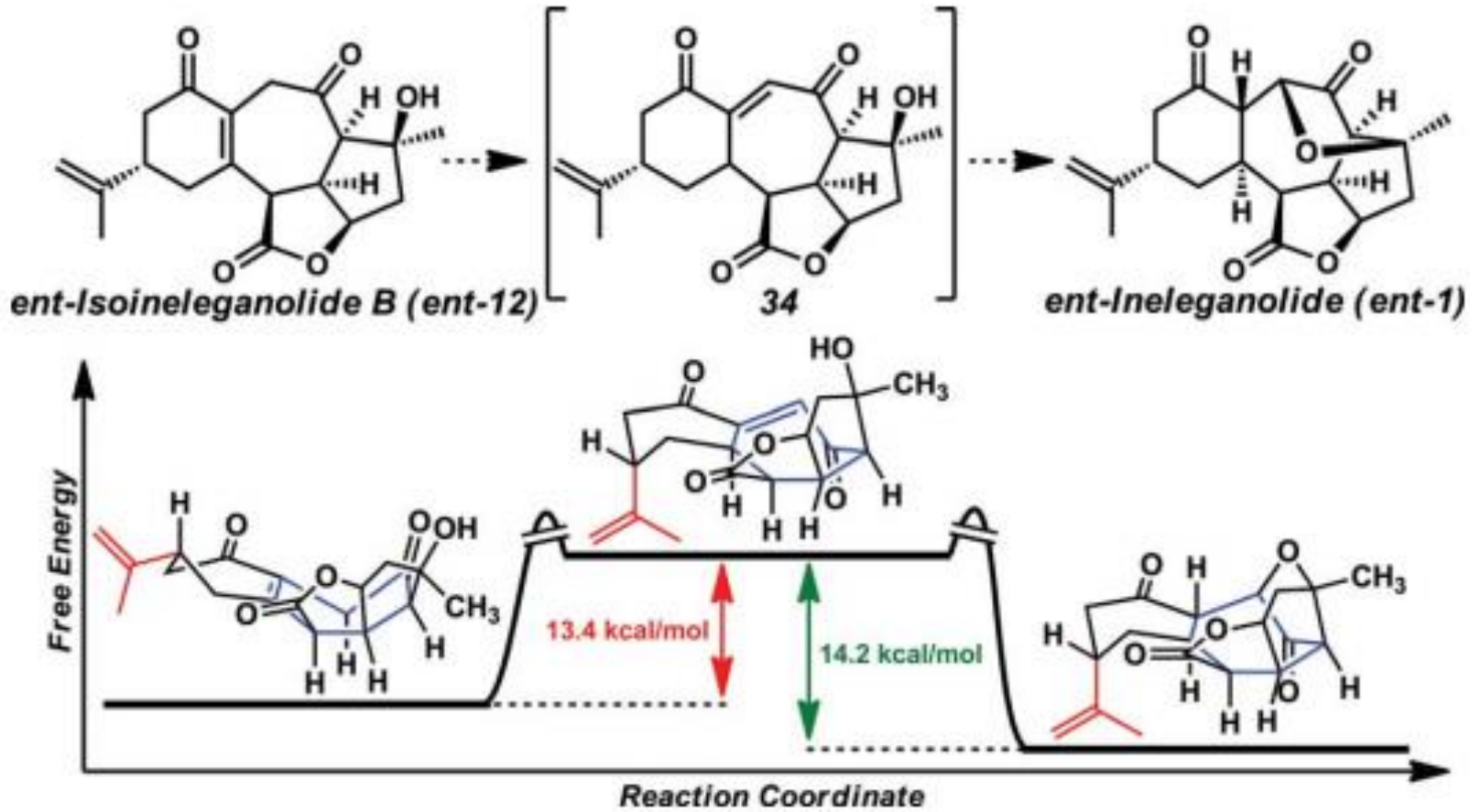
5-episinuleptolide (3)

9

10

ineleganolide

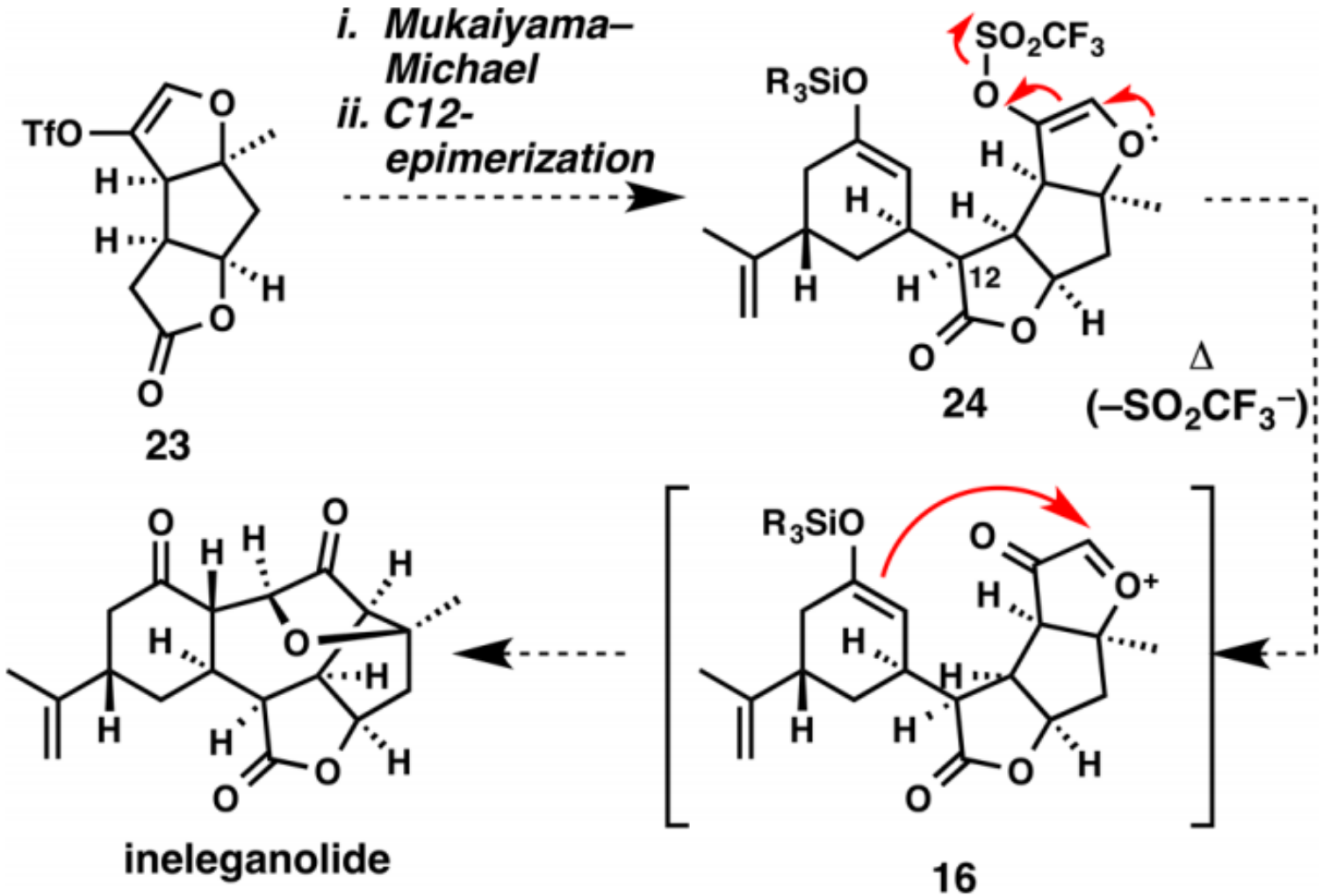
J. Org. Chem., **2016**, *81*, 1819.



Scheme 6 Conformational assessment and relative ground state energies.

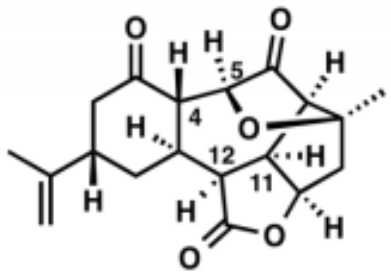
Chem. Sci., **2017**, *8*, 507.

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



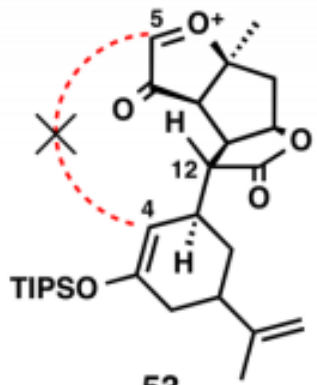
J. Org. Chem., **2016**, *81*, 1819.

a.



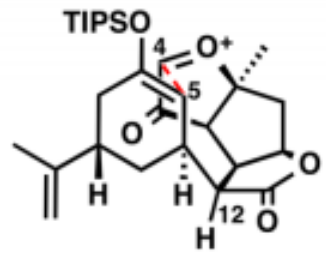
ineleganolide

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



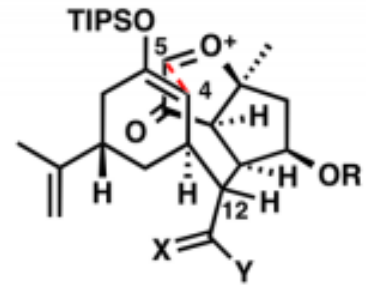
53
(epimeric C12 configuration to ineleganolide)

C4 and C5 held in close proximity to each other



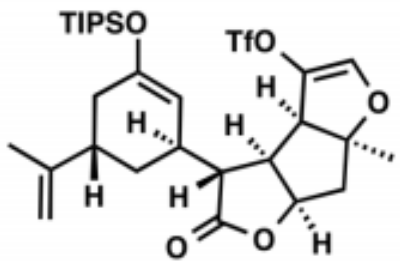
16
(same C12 configuration as ineleganolide)

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



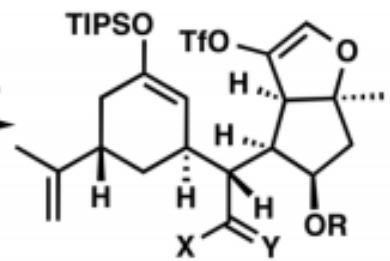
54
(epimeric C12 configuration to ineleganolide)

b.



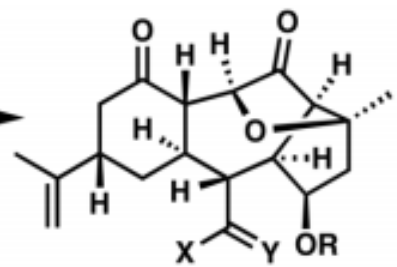
38

open lactone



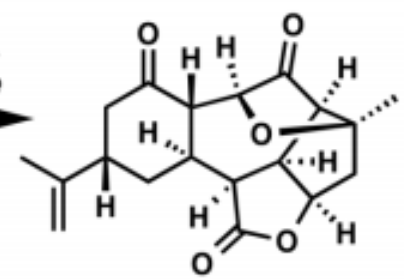
55

Δ
(–Tf⁻)



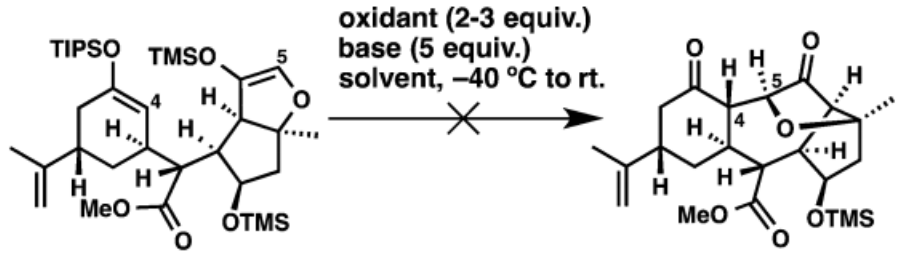
56

epimerize C12, reform lactone



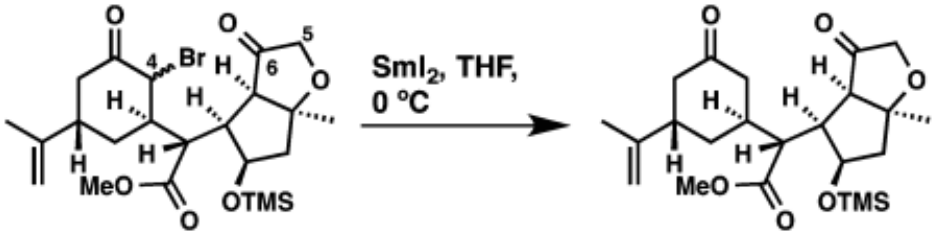
ineleganolide

J. Org. Chem., **2016**, *81*, 1819.

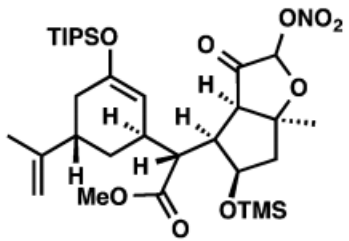


66 68

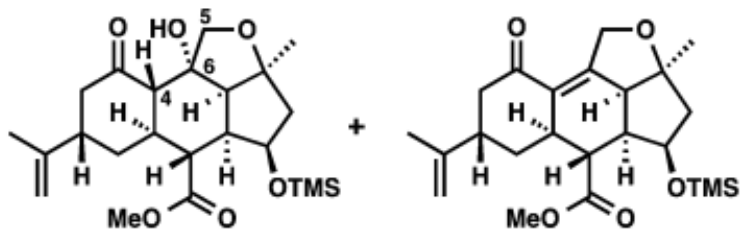
oxidants include: CAN, TBACN, Ag_2O,$Mn(acac)_3$, $Mn(hfacac)_3$, CrO_3, $Pb(OAc)_4$, NBS, I_2



73 (3:1 *dr*) 78 not observed

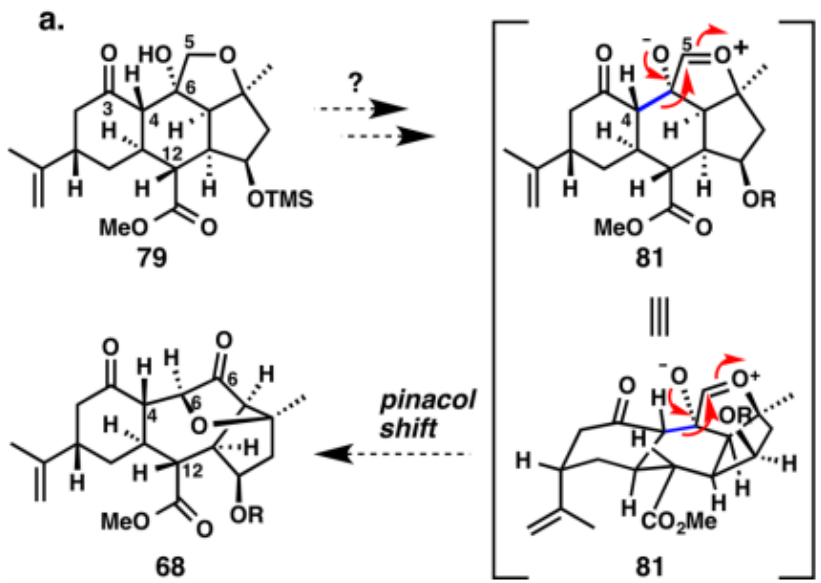


69



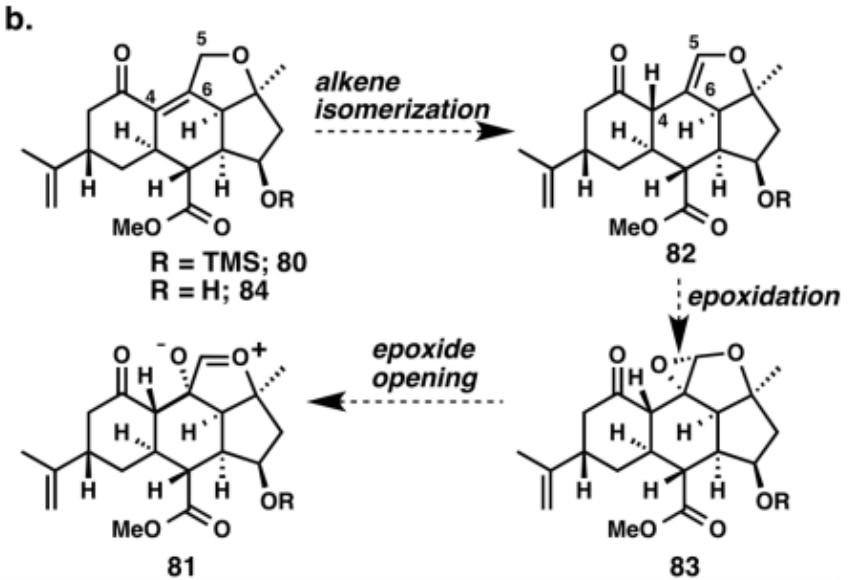
79 (86%) 80 (5%)

a.



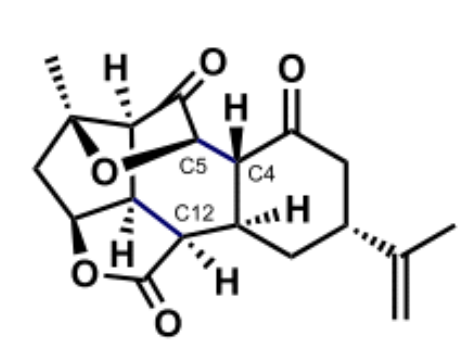
79 81 68 81

b.



82 83 81

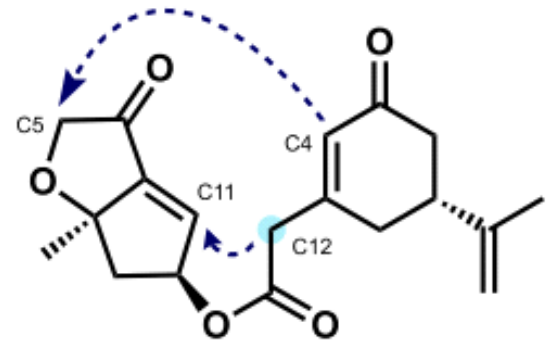
J. Org. Chem., **2016**, *81*, 1819.



(+)-ineleganolide (1)

1,4 Addition

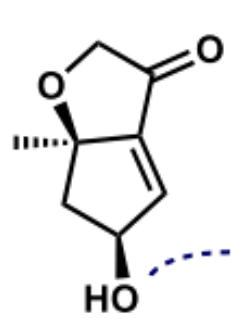
C4–C5 bond formation



4

vinylogous β-ketoester at C12

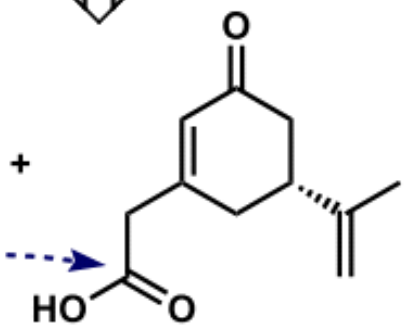
convergent coupling



5

from (*R*)-linalool

+



6

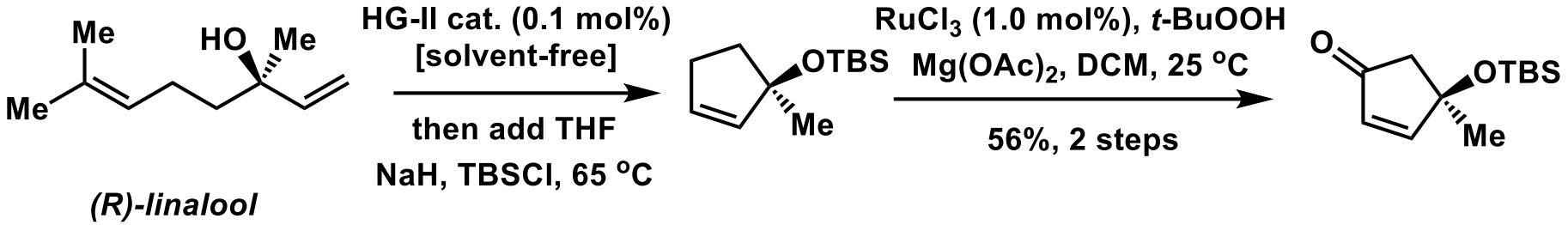
from (*S*)-norcarvone

Ref [15] Semisynthesis (Pattenden, 2011)

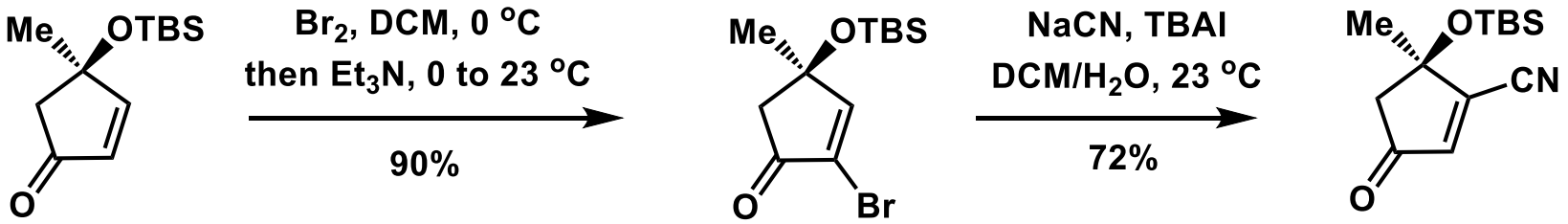
Ref [14] Total Synthesis (Wood, 2022)

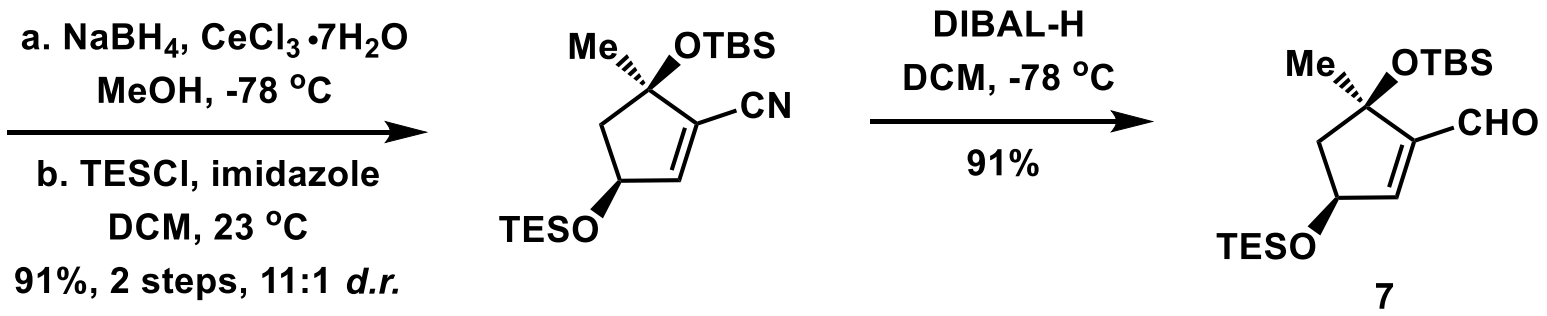
macrocyclic precursors

previous research



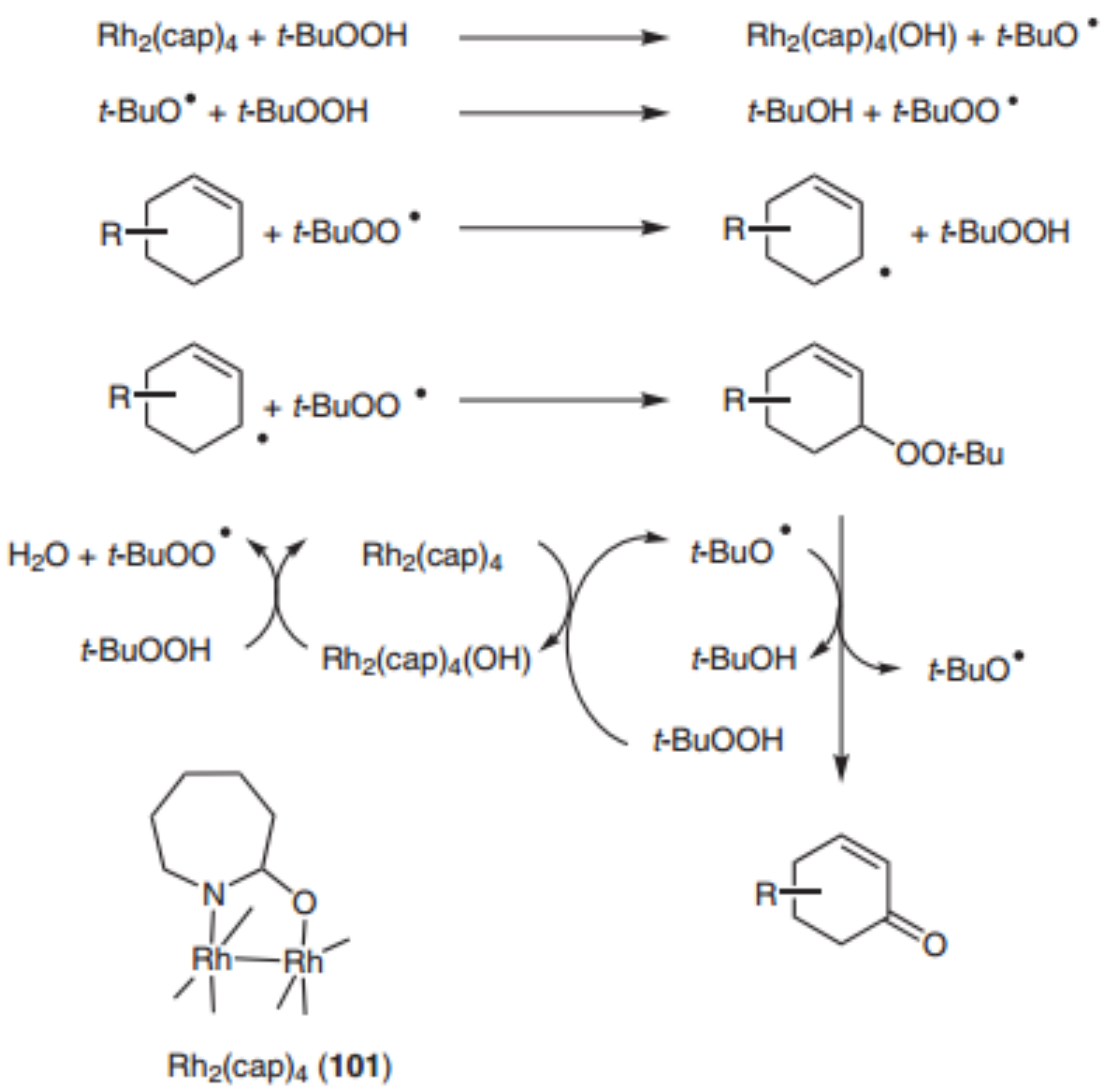
science, **2016**, *352*, 20232.





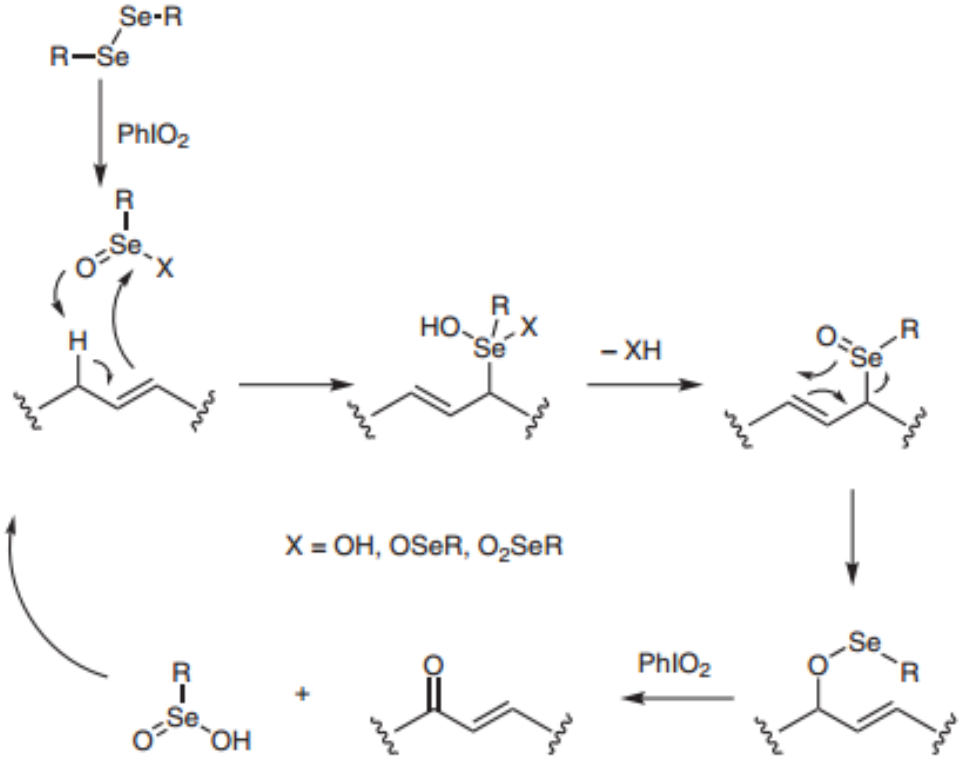
J. Am. Chem. Soc., **2022**, *144*, 20232.

过渡金属催化过氧化物氧化烯丙位

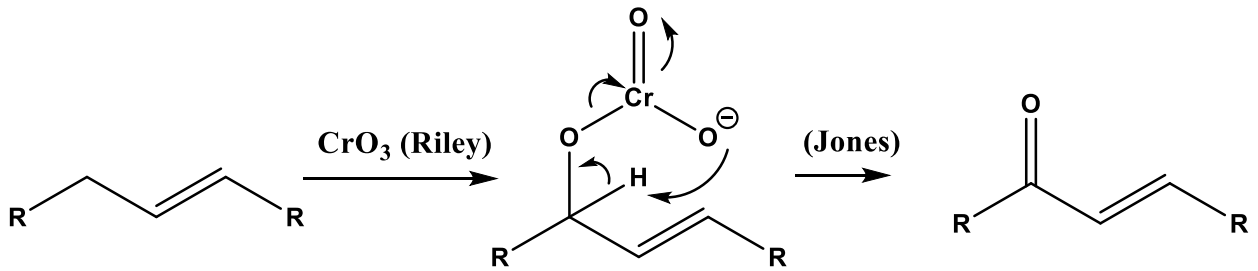


$Rh_2(cap)_4$ (**101**)

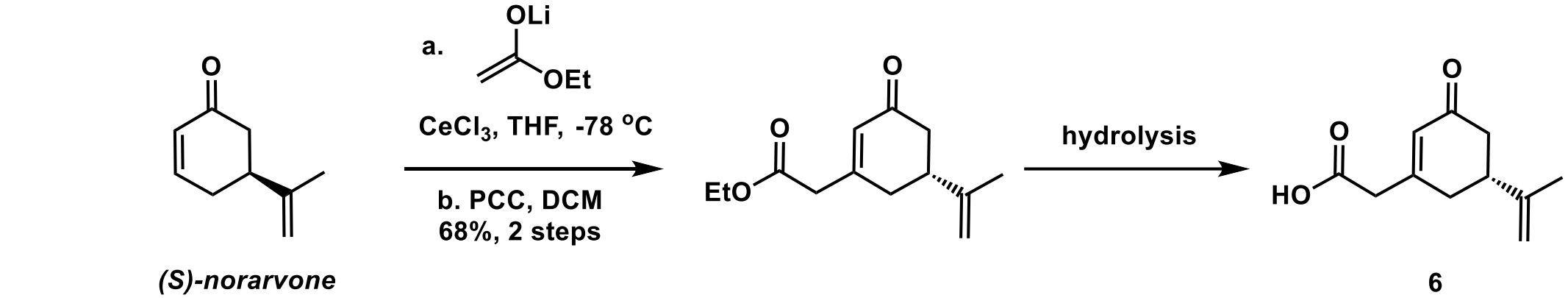
硒氧化烯丙位(Riley Oxidation)



铬氧化烯丙位(Jones Oxidation)



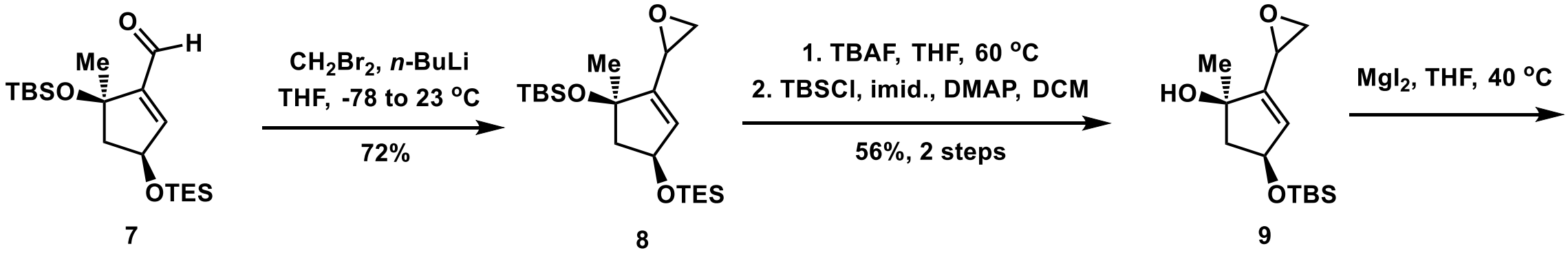
Sythesis, **2013**, *45*, 2201.



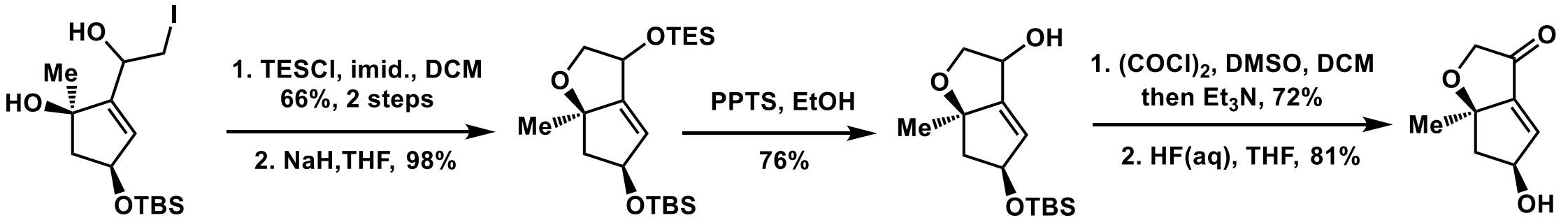
(S)-norarvone

6

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

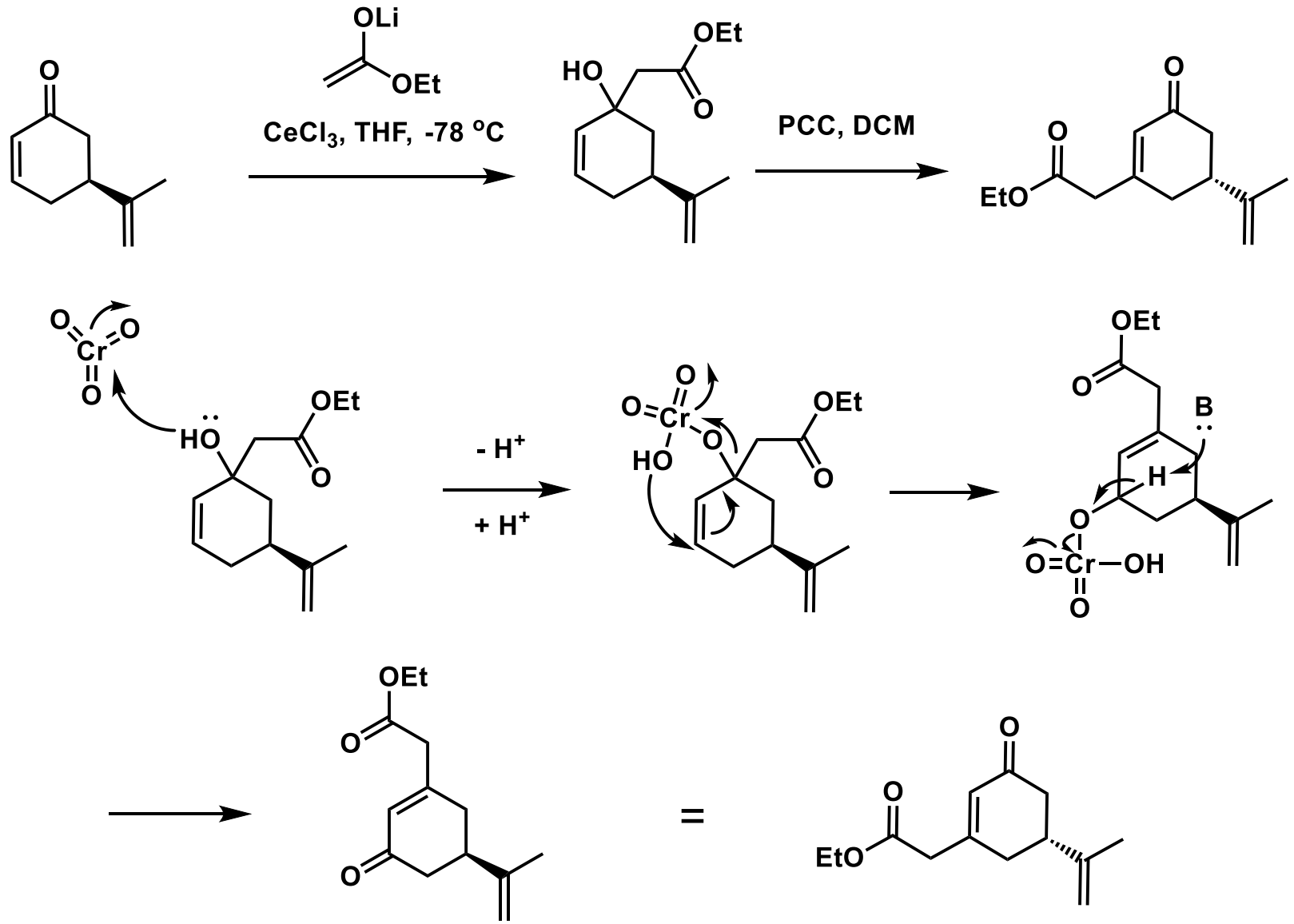


7 8 9

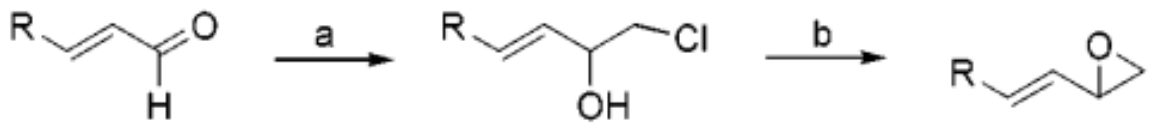


10 11 12 5

Babler–Dauben 氧化重排

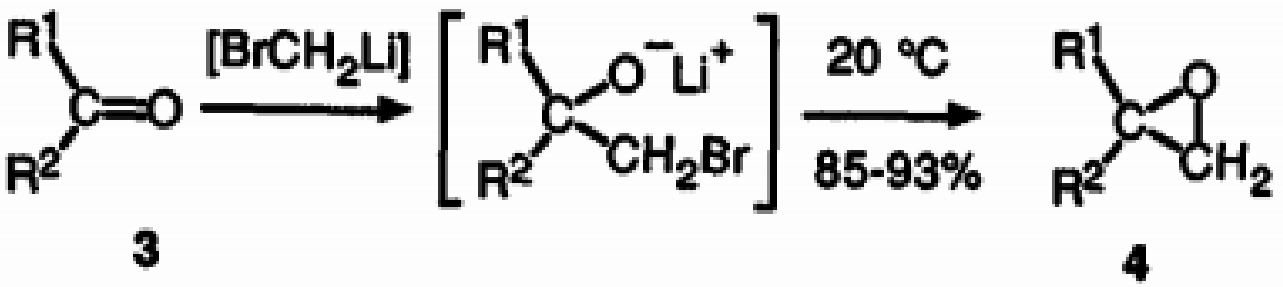


Scheme 2. Approach to Synthesis of 2-Vinyloxiranes[a]



R = Aryl, or Alkyl

[a] (a) $ClCH_2I$ (1.5 equiv), *n*-BuLi (1.5 equiv), THF, −78 °C, ~1 h; (b) NaH (95%, 1.1 equiv), NaI (10%), THF, 0 °C, ~1 h.



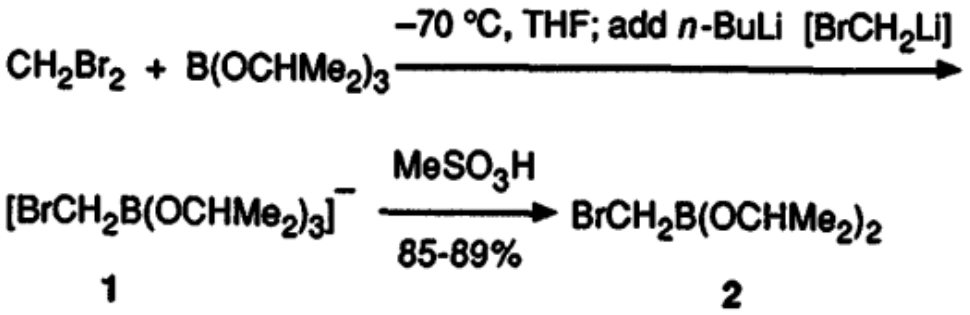


Table 1. Oxiranes (4) from $R^1R^2C{=}O$ (3), $ClCH_2I$ or CH_2Br_2, and BuLi.[a]

Oxirane	bp, °C (mbar)	Yield from $ClCH_2Li$, %	from $BrCH_2Li$
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

[a] Isolated yields, high purity indicated by 200-MHz ^1H NMR. Cpds. 4a-c are known.[1,3] 4d has been partially characterized previously.[8]

Synlett, **1991**, *9*, 631.

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

SWERN OXIDATION

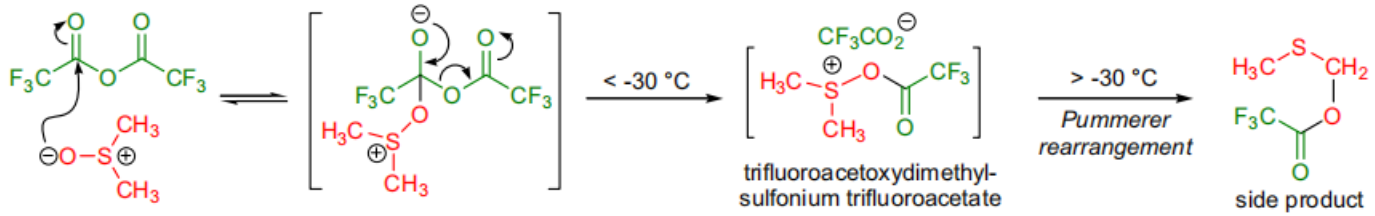
(References are on page 692)

Importance:

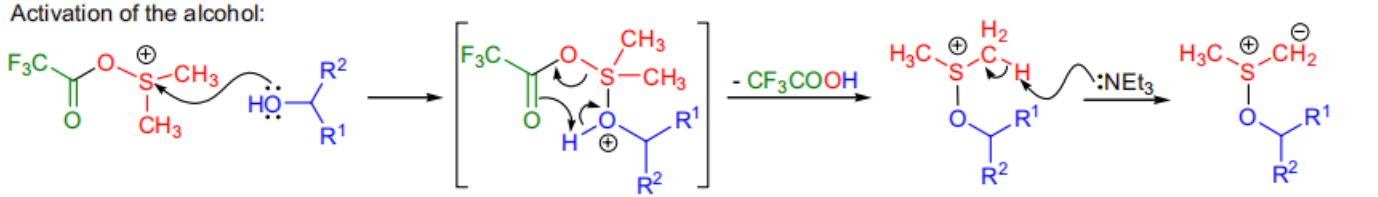
[*Seminal Publications*[1-6]; *Reviews*[7-10]; *Modifications & Improvements*[11-16]]

Mechanism:[6-9]

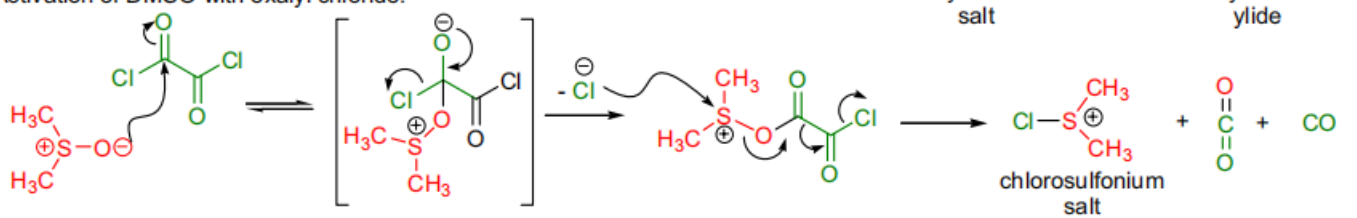
Activation of DMSO with TFAA:



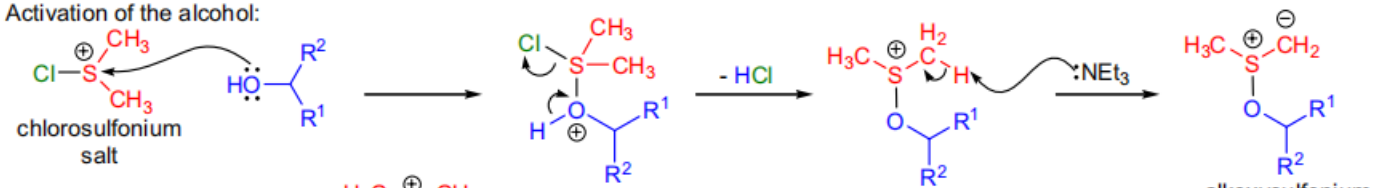
Activation of the alcohol:



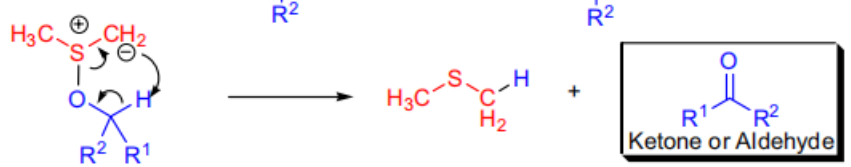
Activation of DMSO with oxalyl chloride:

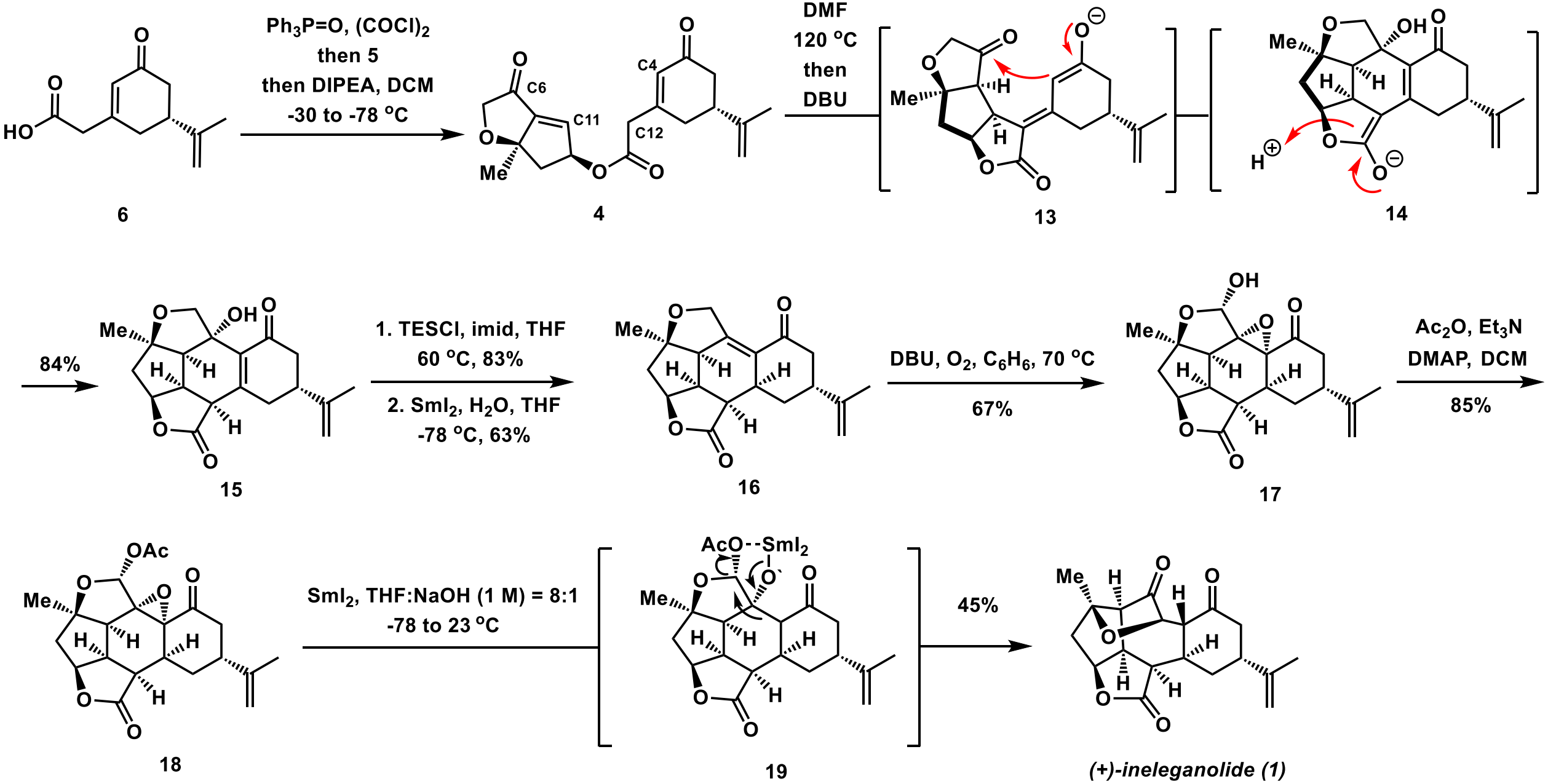


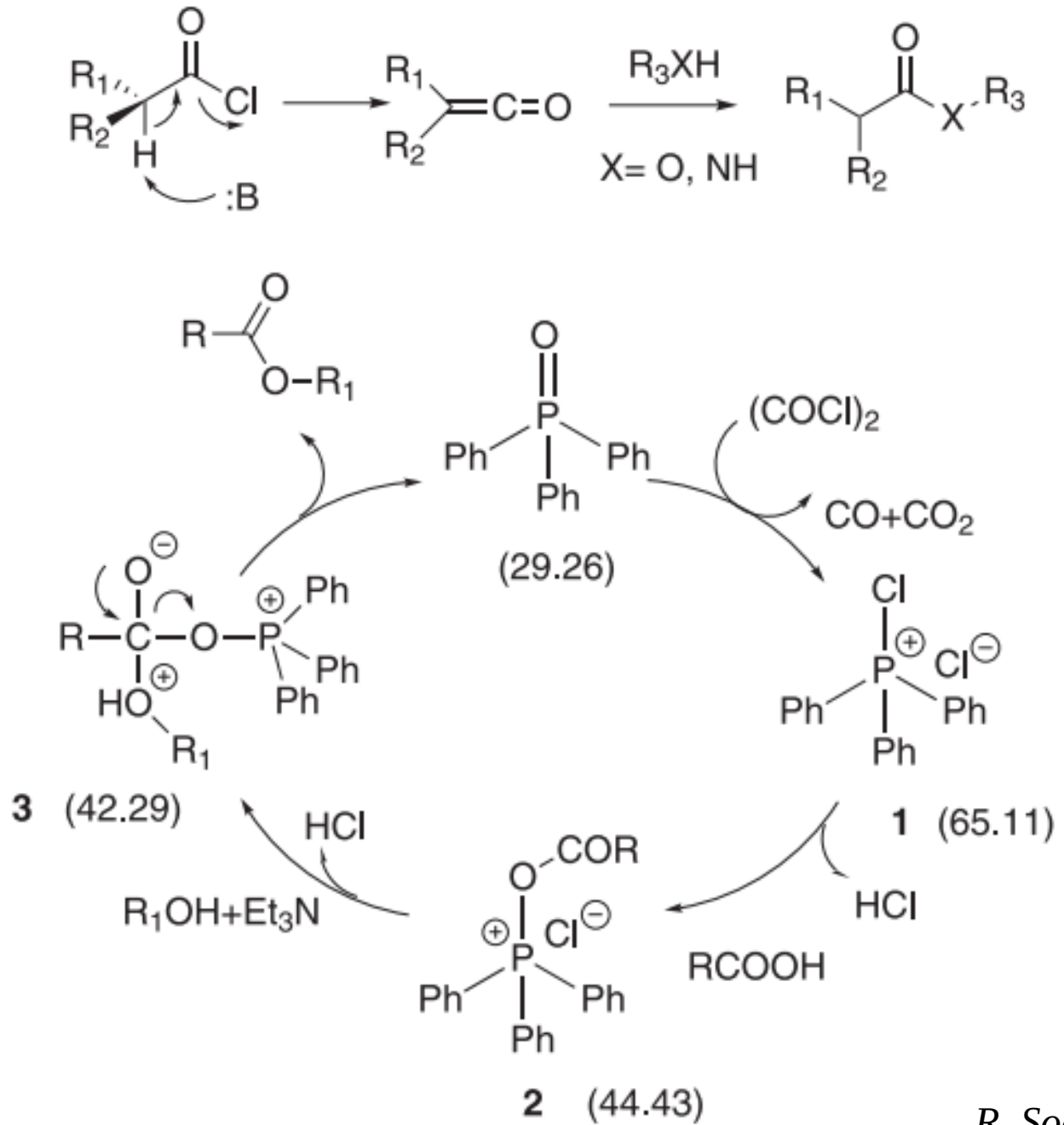
Activation of the alcohol:



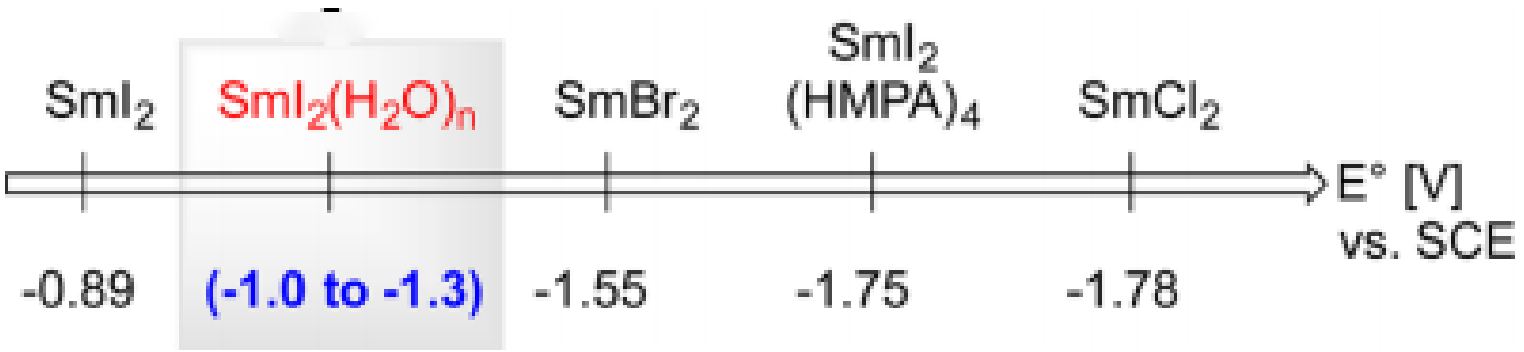
Formation of the product:

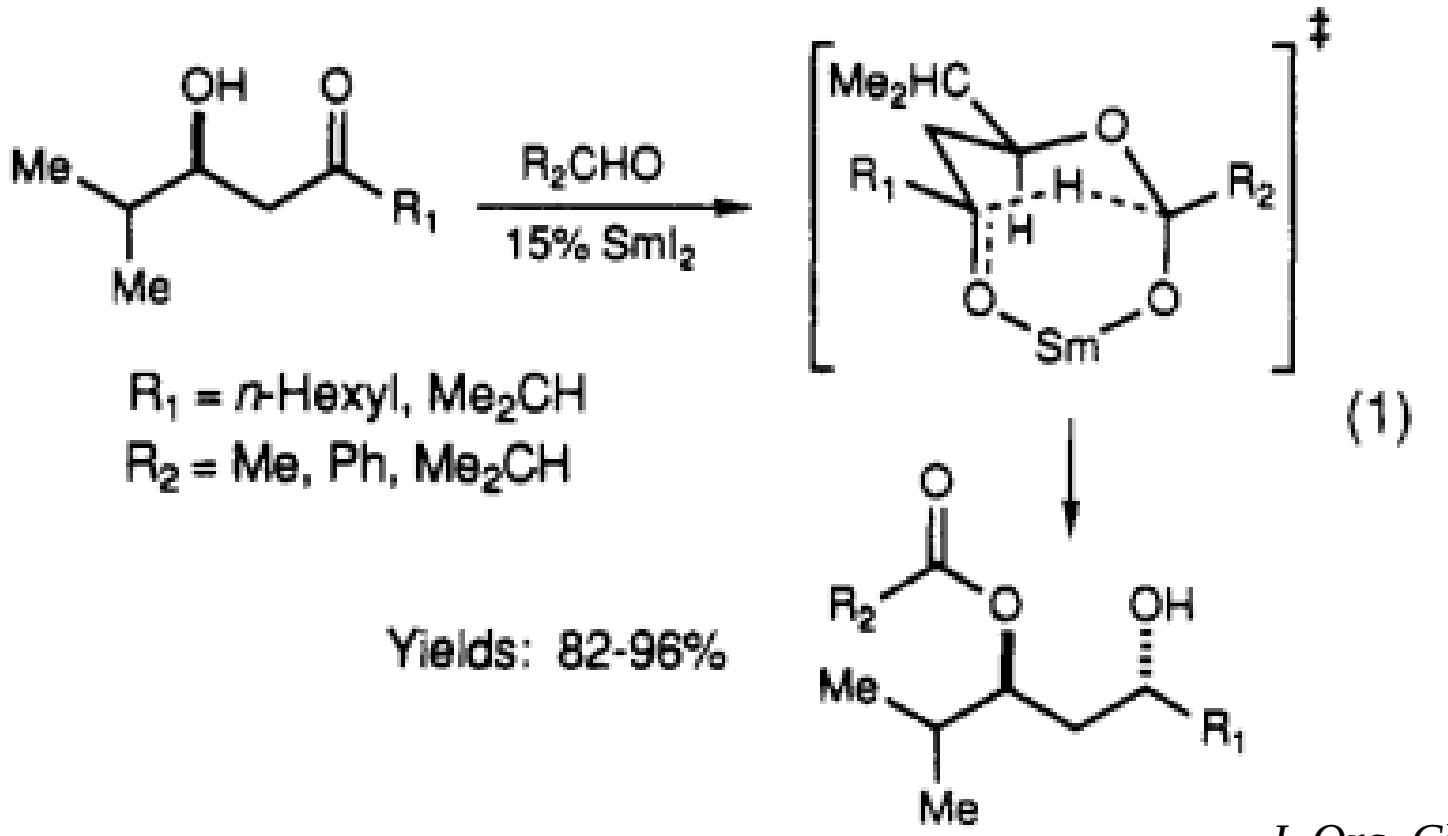



Ph3P=O, (COCl)2
then 5
then DIPEA, DCM
-30 to -78 °C
DMF
120 °C
then
DBU
6
4
13
14
84%
15
1. TESCl, imid, THF
60 °C, 83%
2. SmI2, H2O, THF
-78 °C, 63%
16
DBU, O2, C6H6, 70 °C
67%
17
Ac2O, Et3N
DMAP, DCM
85%
18
SmI2, THF:NaOH (1 M) = 8:1
-78 to 23 °C
19
45%
(+)-ineleganolide (1)



R. Soc. Open Sci., **2018**, *5*, 171988.





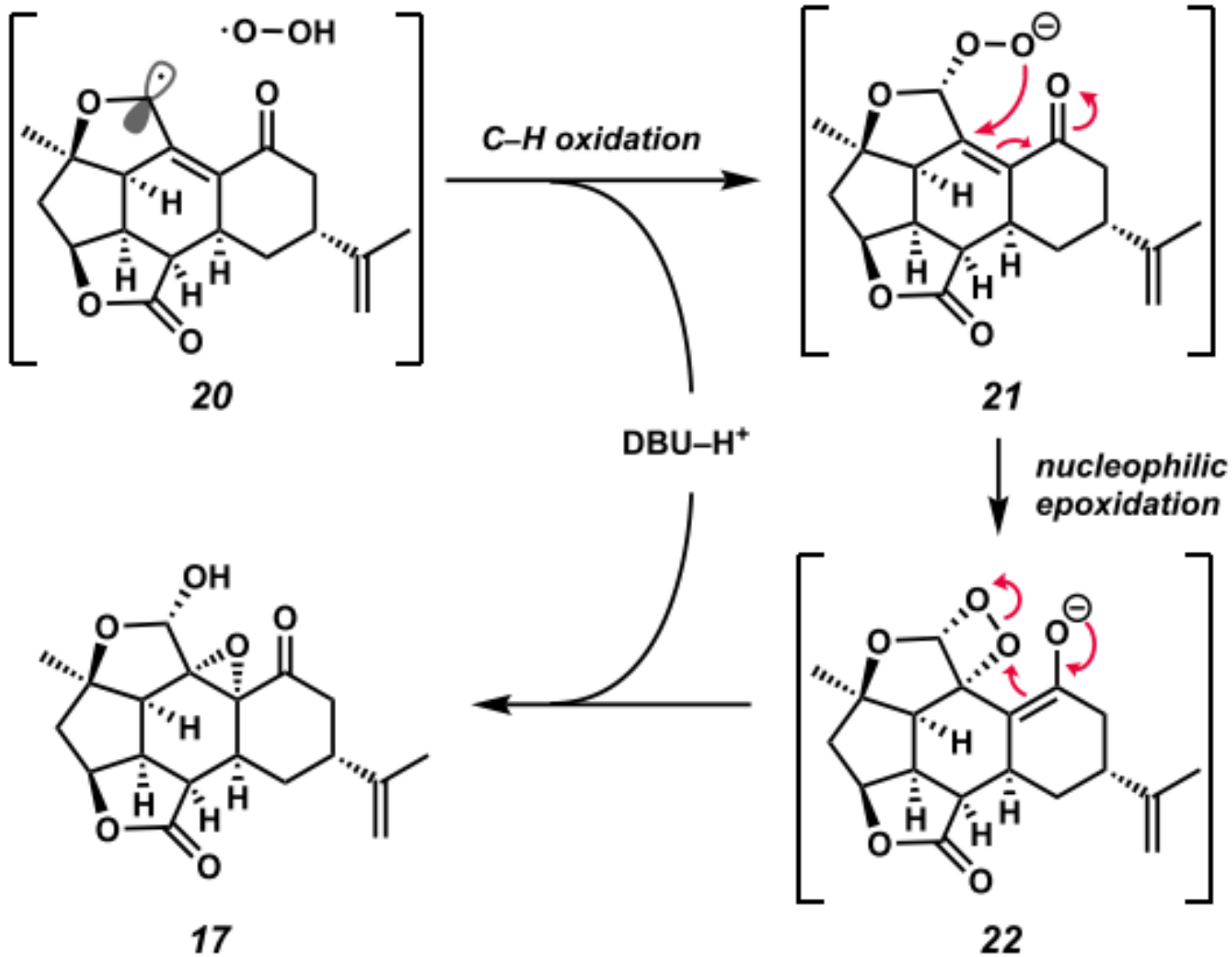
R_1 = *n*-Hexyl, Me_2CH

R_2 = Me, Ph, Me_2CH

Yields: 82-96%

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

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



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