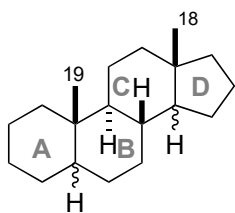


Topic: Traditional reactions and skeleton transformation of steroidal compounds

•Brief introduction of steroids



0-1

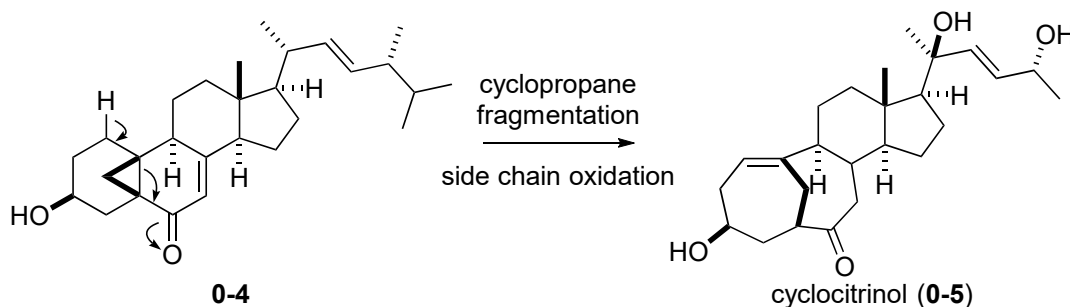
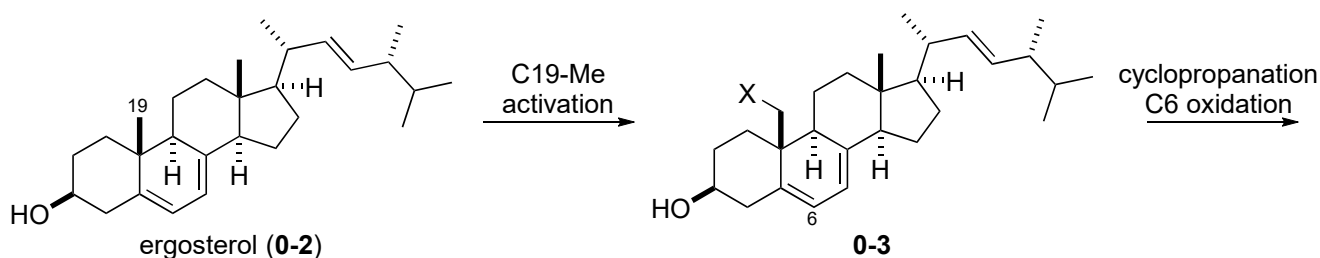
common skeleton of steroids

biologically and pharmaceutically important class of natural products  
used as a membrane lipid and hormone.  
show various bioactivities such as cardiac, antitumor, and anti-inflammatory effect

structural features  
6/6/6/5-membered ABCD-tetracyclic  
B/C is mainly *trans*-fused  
C18, C19 methyl groups

Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*, 3rd ed.; Wiley: London, U.K., 2009.

It is proposed that steroids are precursors of other classes of natural products.

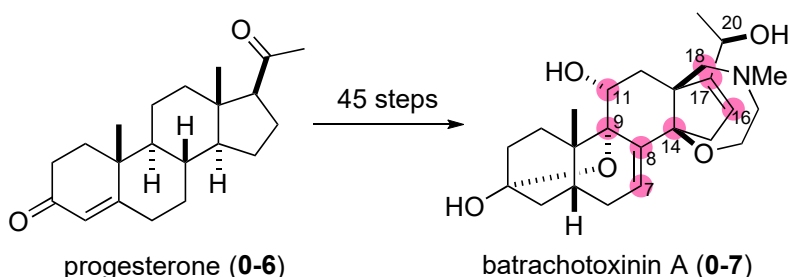


Gui, J. et al. *J. Am. Chem. Soc.* **2018**, *140*, 9413.

Rodrigues-Filho, E. et al. *J. Braz. Chem. Soc.* **2005**, *16*, 1343.

•Examples for synthesis of steroids and related natural products from steroidal natural compound

synthesis of batrachotoxinin A (Wehril, H. et al. *Helv. Chim. Acta* **1972**, *55*, 1151. *Helv. Chim. Acta* **1973**, *56*, 139.)



C7,8: dehydrogenation (C6,7)  
epoxidation, dehydration

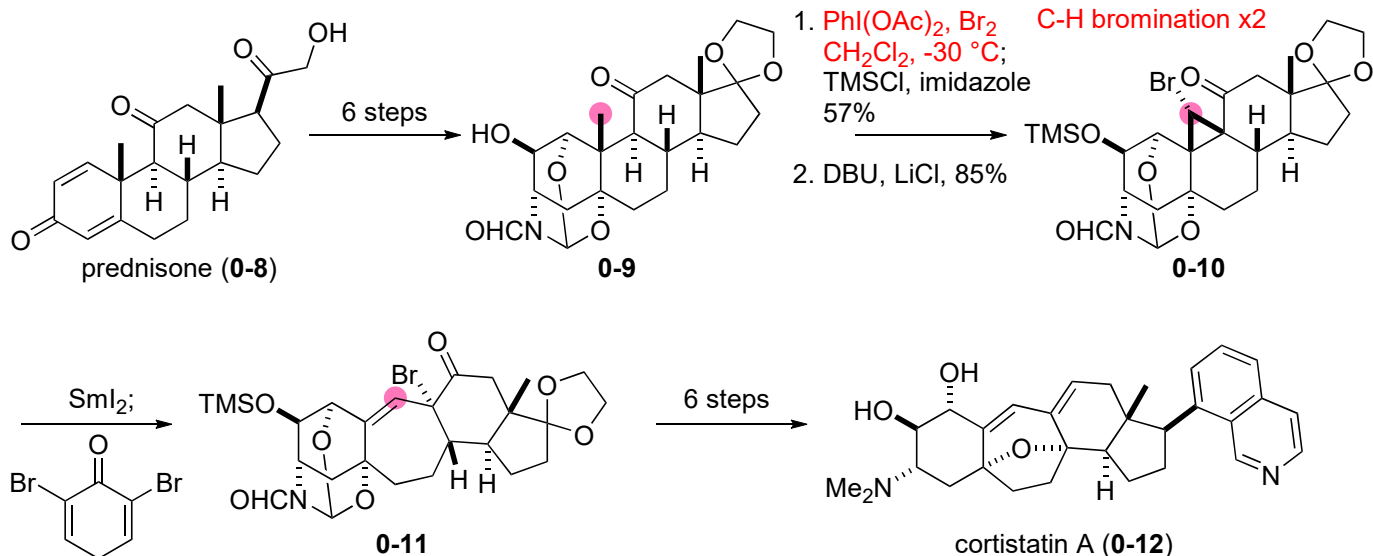
C9,11: bio-oxidation at C11  
dehydration, dihydroxylation

C16,17: olefination via radical bromination

C14: olefination via radical bromination  
epoxidation

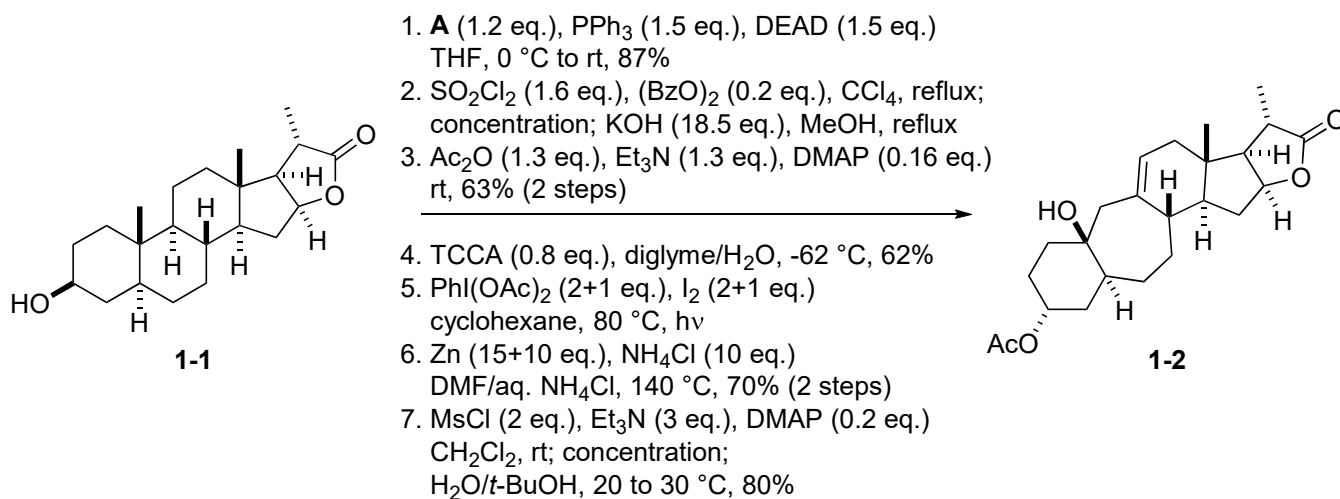
C18: oxidation utilizing C20-OH  
( $\text{Pb}(\text{OAc})_4$ ,  $\text{CaCO}_3$ ,  $\text{I}_2$ ,  $h\nu$ )

synthesis of cortistatin A (Baran, P. S. et al. *J. Am. Chem. Soc.* **2008**, *130*, 7241.)



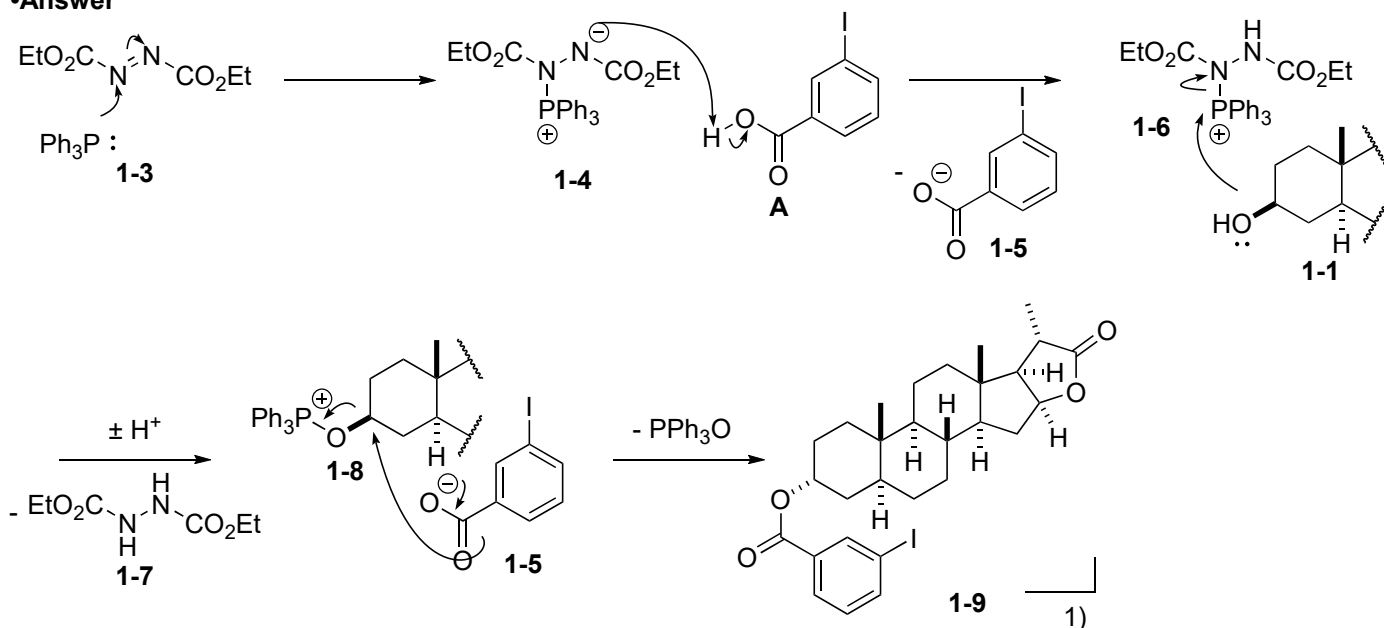
Please see, 141101\_PS\_Akinori\_YAMAGUCHI.

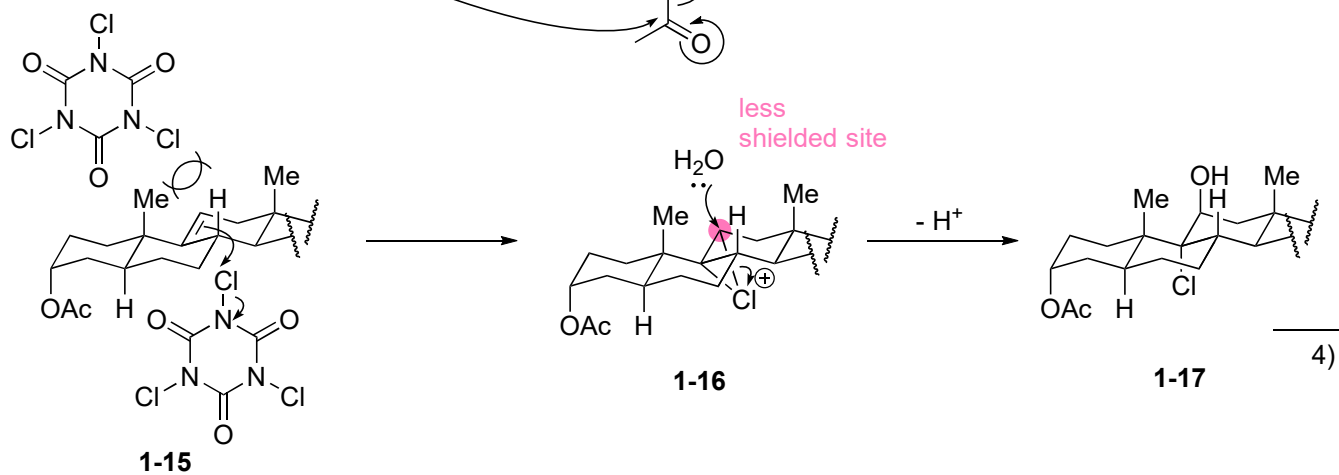
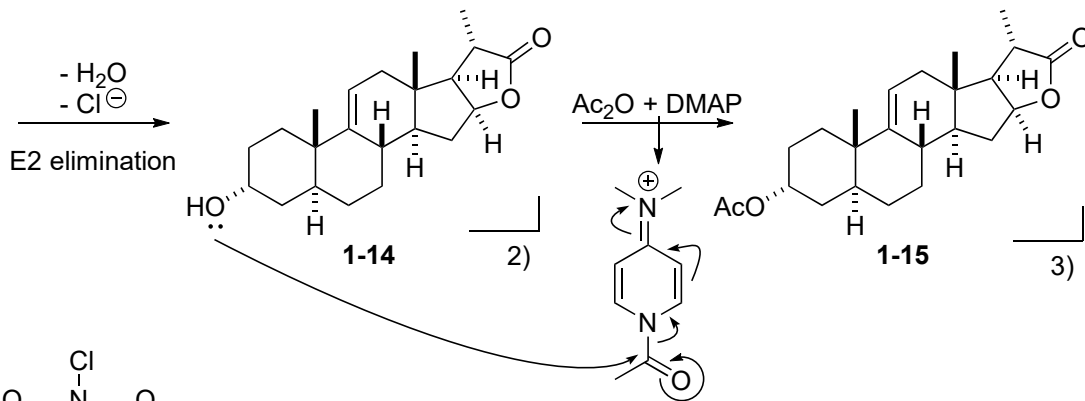
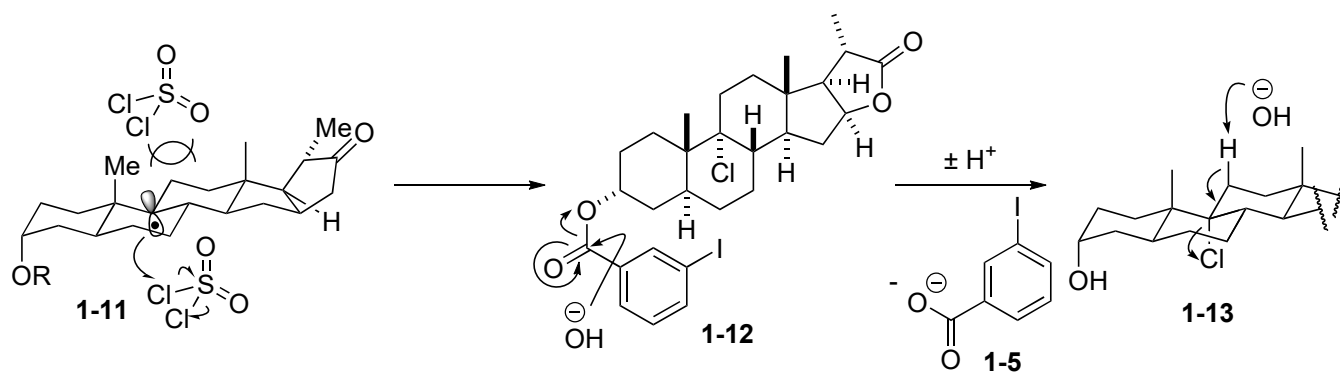
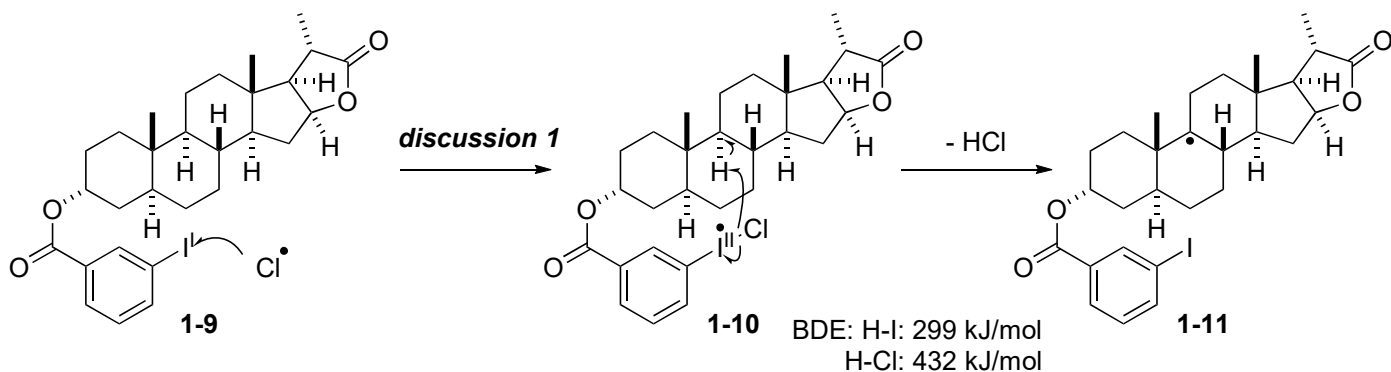
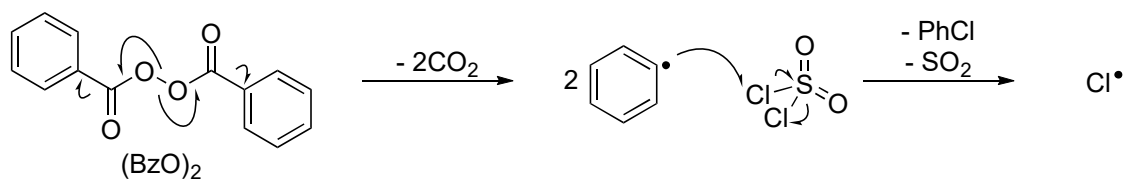
(1) Please explain the reasonable reaction mechanisms.

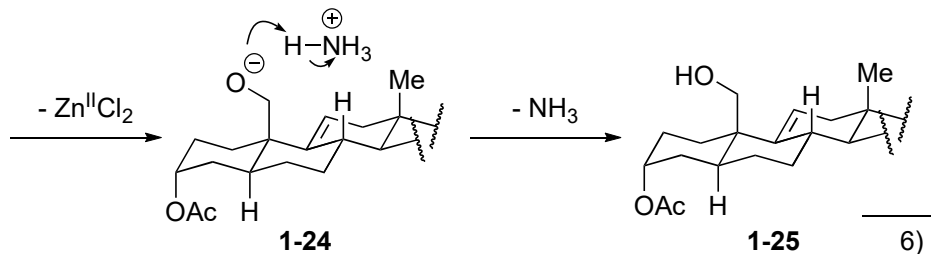
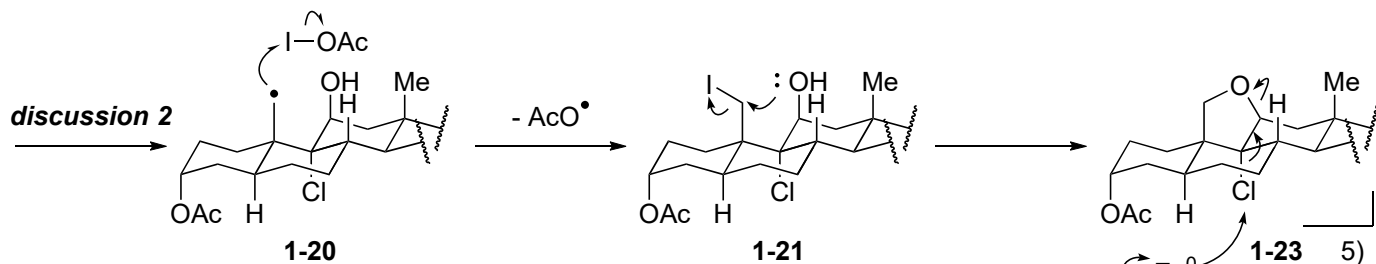
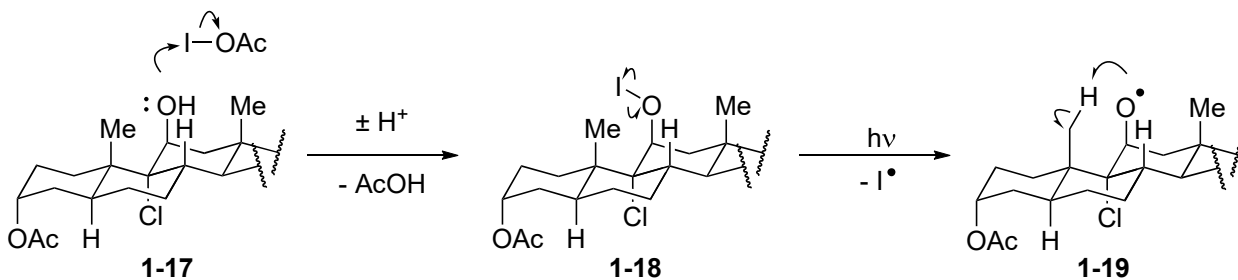
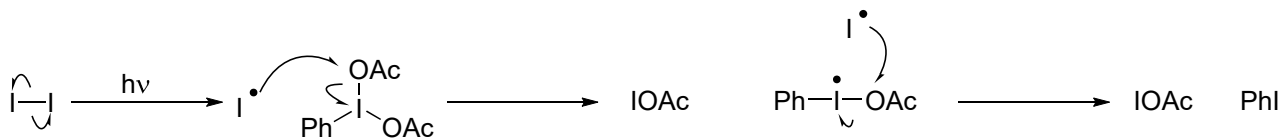


Wang, Y.; Chen, B.; He, X.; Gui, J. *J. Am. Chem. Soc.* **2020**, *142*, 5007.

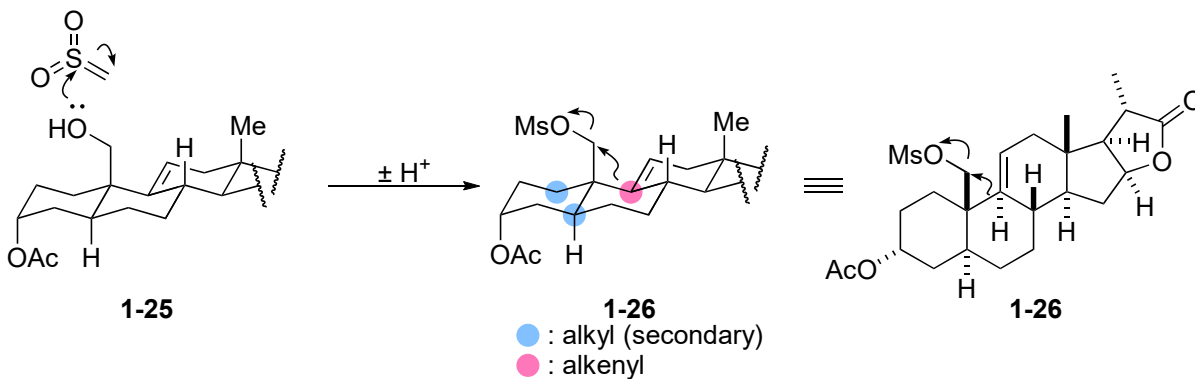
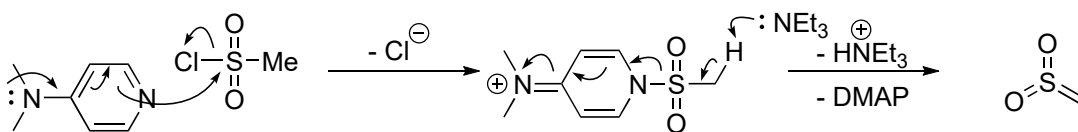
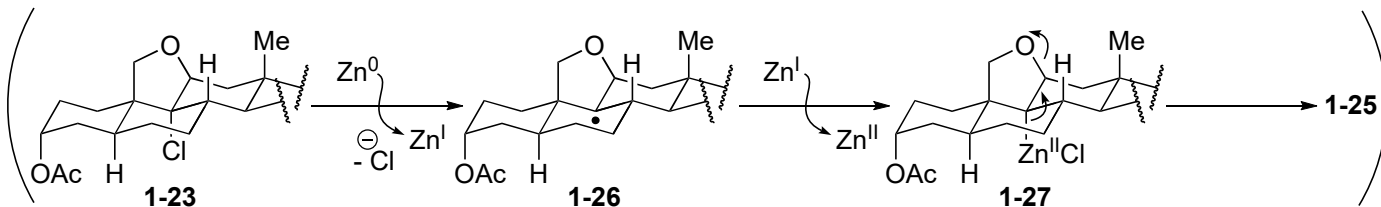
•Answer

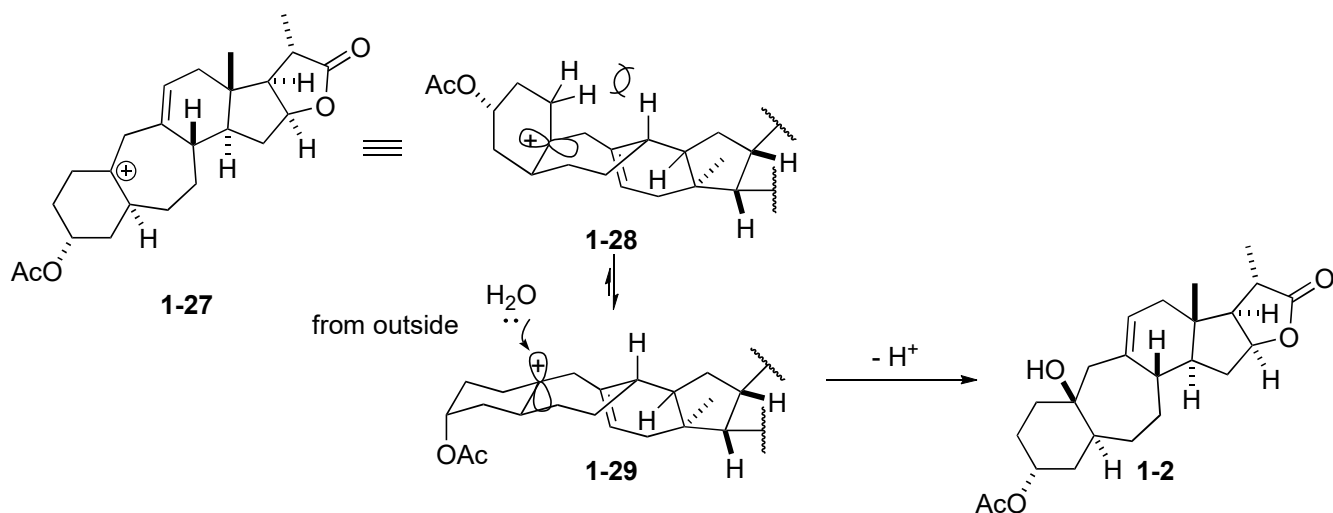






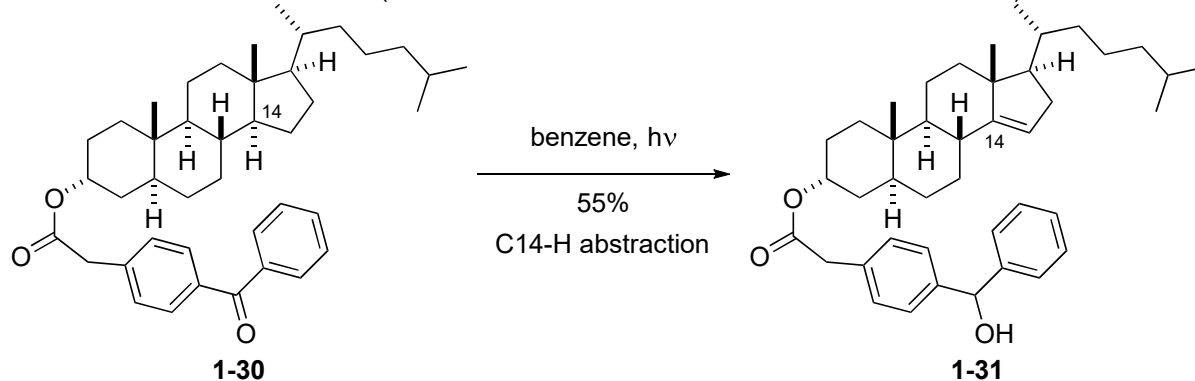
another pathway





### Discussion 1

•Breslow's first remote oxidation (Breslow, R. et al. *J. Am. Chem. Soc.* **1973**, *95*, 3251.)



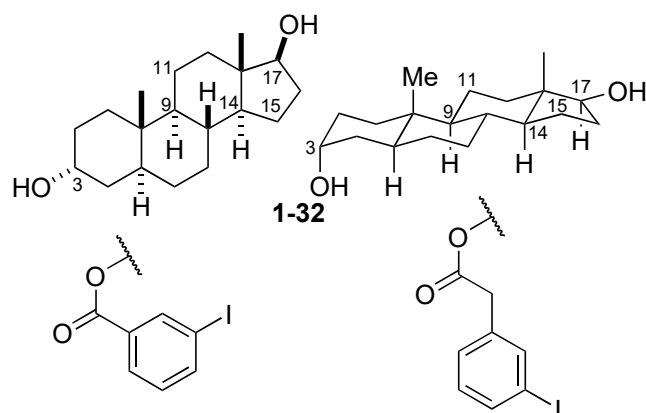
•Regioselectivity of remote oxidation utilizing iodoarene unit

**Table II.** Calculated Distances in Steroids and Reagents

Oxygen	Steroids (A/B trans) Hydrogen	Distance, Å <sup>a</sup>	a'
3 $\alpha$	5 $\alpha$	2.68	
3 $\alpha$	9 $\alpha$	4.41	4.44
3 $\alpha$	14 $\alpha$	6.52	6.62
3 $\alpha$	17 $\alpha$	8.49	8.72
7 $\alpha$	17 $\alpha$	5.04 <sup>b</sup>	

Reagent-chlorine atom $\sigma$ complex <sup>c</sup>	Oxygen-chlorine distance, Å <sup>d</sup>
<i>m</i> -Iodobenzoate	4.27
<i>p</i> -Iodophenylacetate	6.84
<i>m</i> -Iodophenylacetate	5.24
4'-Iodo-3-biphenylcarboxylate (3)	8.68
4-( <i>p</i> -Iodophenyl)butyrate	8.11



*m*-Iodobenzoate

*p*-Iodophenylacetate

*m*-Iodophenylacetate

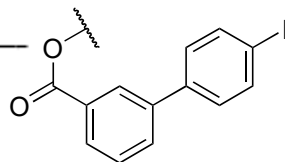
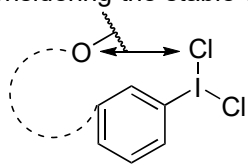
4'-Iodo-3-biphenylcarboxylate (3)

4-(*p*-Iodophenyl)butyrate

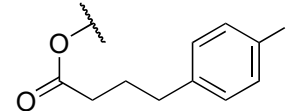
<sup>a</sup> Calculated from X-ray structure of 1-32

<sup>a'</sup> Calculated from MacroMidel

<sup>d</sup> Estimated O-Cl distance considering the stable conformation

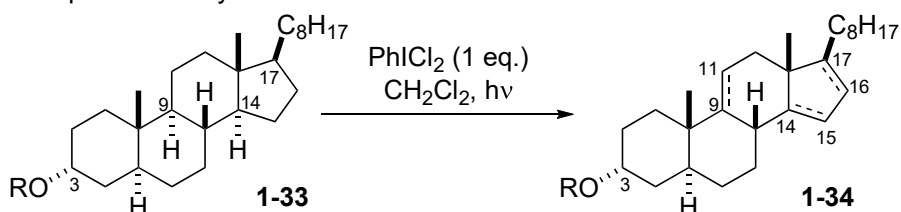


$\Delta_{16,17}$  37%



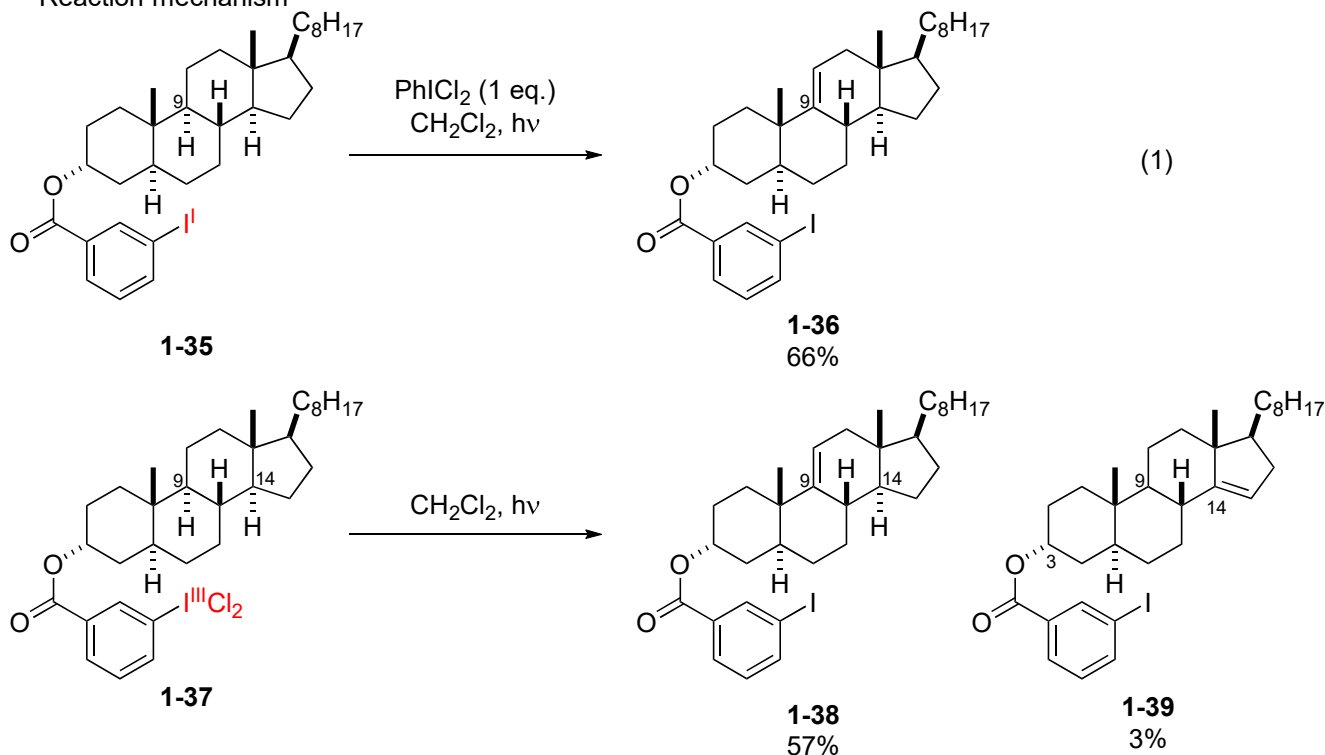
$\Delta_{9,11}$  2%,  $\Delta_{14,15}$  10%,  $\Delta_{16,17}$  11%

The product and yield of the reaction below.



The regioselectivity of C-H abstraction depended on the length of attached acyl groups.

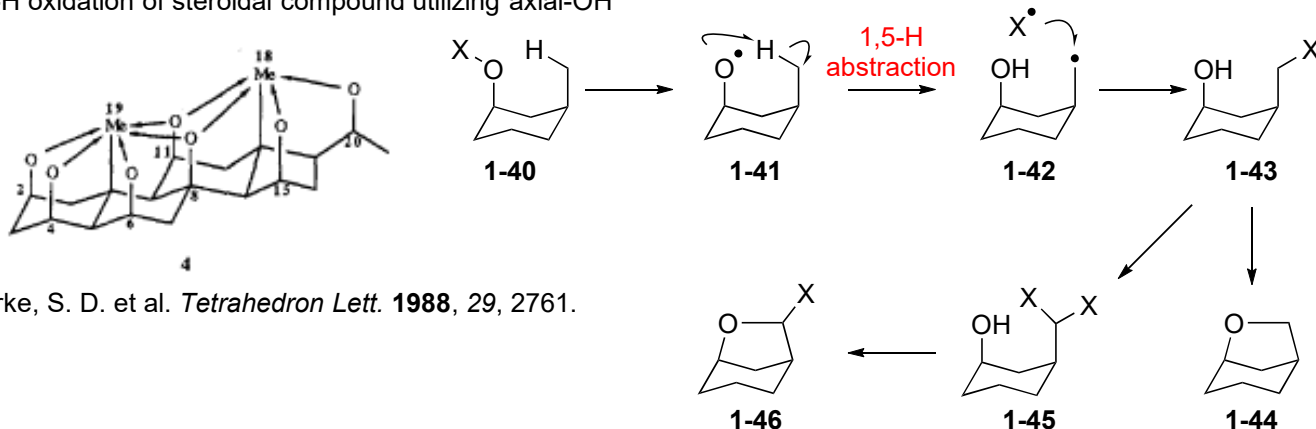
•Reaction mechanism



From these similar results, authors proposed that these reactions proceed via the same intermediate. In the reaction (1), they did not observe the formation of **X** in  $^1\text{H}$  NMR. Thus they proposed the reaction mechanism as described above.

Discussion 2

•C-H oxidation of steroidal compound utilizing axial-OH



Burke, S. D. et al. *Tetrahedron Lett.* **1988**, 29, 2761.

Similar strategy was first applied to steroidal compound by E. J. Corey (N instead of O,  $\text{NCS}$ ,  $h\nu$ , *JACS* **1958**, 80, 2903.)

$\text{Pb}(\text{OAc})_4$  conditions were first applied to steroidal compound by G. Cainelli (*Helv. Chim. Acta* **1959**, 42, 1124.)

For reviews on this type C-H functionalization using steroidal compound, see:

Majetich, G. et al. *Tetrahedron* **1995**, 51, 7095.

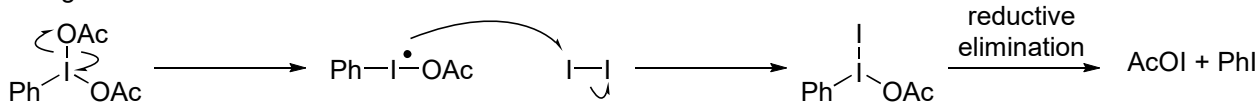
Pellissier, H.; Santelli, M. *Org. Prep. Proced. Int.* **2001**, 33, 455.

$\text{X} = \text{Y} = \text{NO}$  ( $\text{NOCl}$ ,  $h\nu$ , Barton reaction)  
 $\text{X} = \text{I}$  ( $\text{PhI}(\text{OAc})_2$ ,  $\text{I}_2$ ,  $h\nu$  or  $\text{Pb}(\text{OAc})_4$ ,  $\text{I}_2$ ,  $h\nu$  or  $\text{AgOAc}$ ,  $\text{I}_2$ ,  $h\nu$  or  $\text{HgO}$ ,  $\text{I}_2$ ,  $h\nu$ )

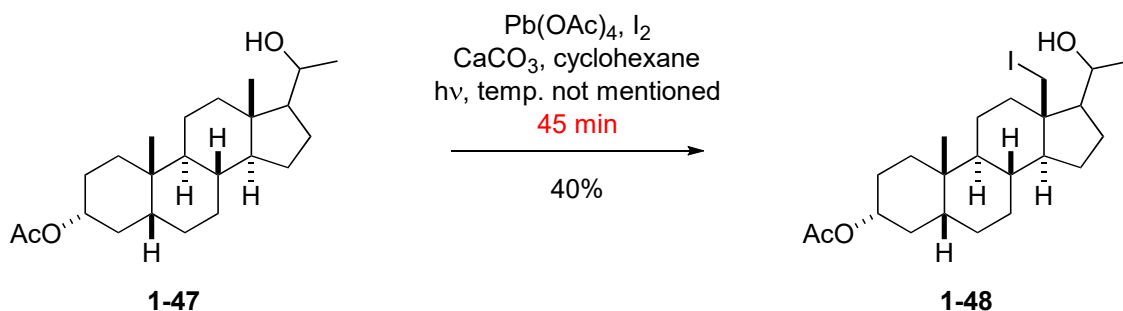
•Generation of AcOI

confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR (Luszytk, J. et al. *Tetrahedron Lett.* **1994**, 35, 1003.)

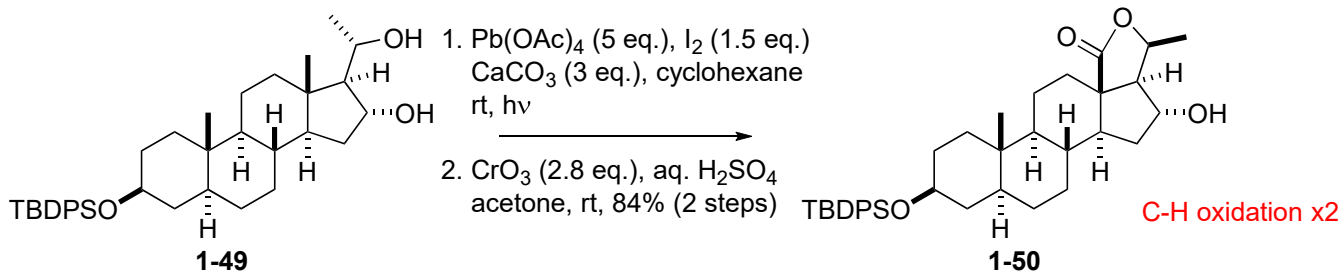
another generation mechanism



The product structure seems to depend on the reaction conditions.

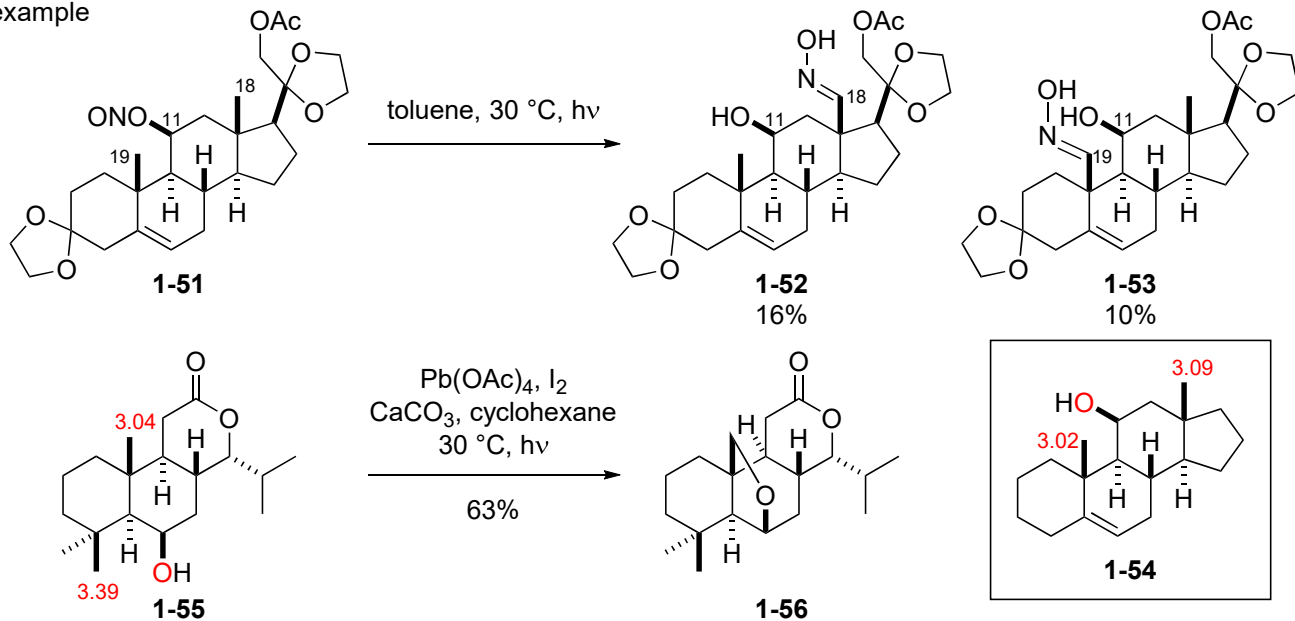


Bogan, P.; Gall, R. E. *Aust. J. Chem.* **1979**, *32*, 2323.



Gui, J.; Wang, D.; Tian, W. *Angew. Chem. Int. Ed.* **2011**, *50*, 7093.

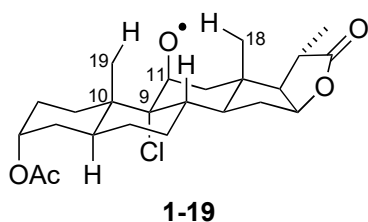
•Regioselectivity - C18 vs C19 - example



red number: distance from red oxygen to carbon (MM2 calculation)  
closer C-H would react.

Burke, S. D. et al. *Tetrahedron Lett.* **1988**, *29*, 2761.

In this problem case, C-H at C19 selectively reacted.

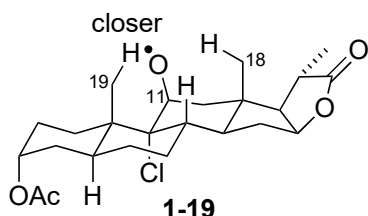


In this all chair conformation, the distance of C18H-C11O and C19H-C11O should be almost the same.

An oxyl radical would react electron rich C-H bond.

In terms of stereoelectronic effect, C10-C19 $\sigma$  orbital is parallel to C9-Cl $\sigma^*$ , thus C-H at C18 should be more electron-rich than that at C19.

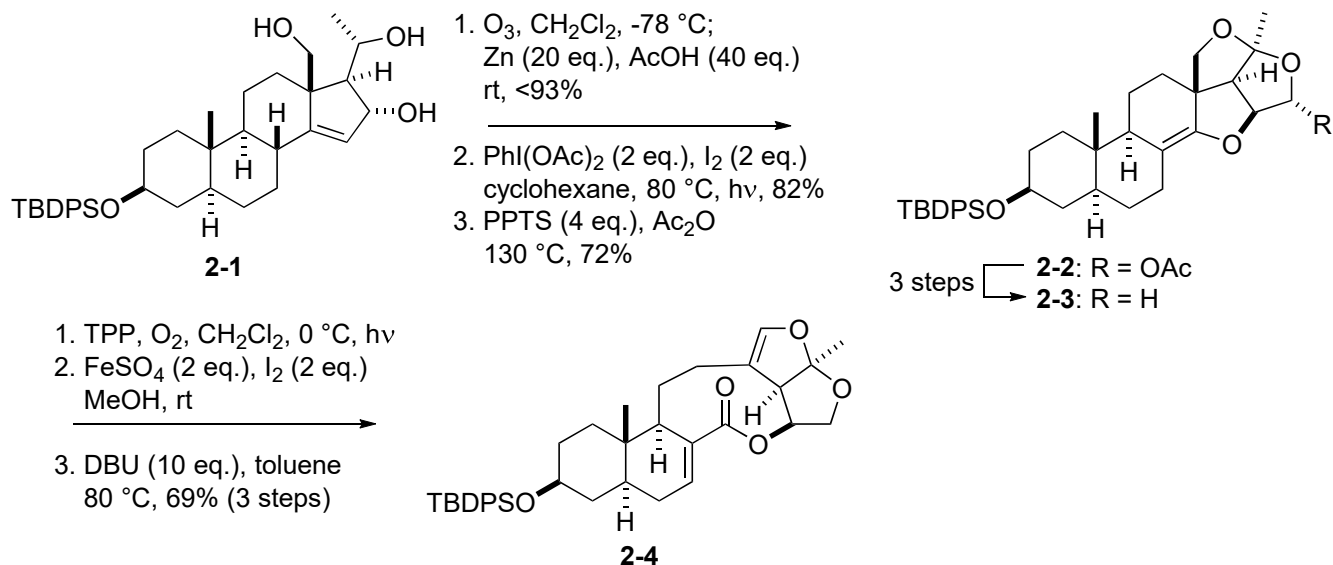
C18 C-H would react?



I assume that the conformation of C-ring is not chair to avoid 1,3-diaxial interaction between two methyl groups.

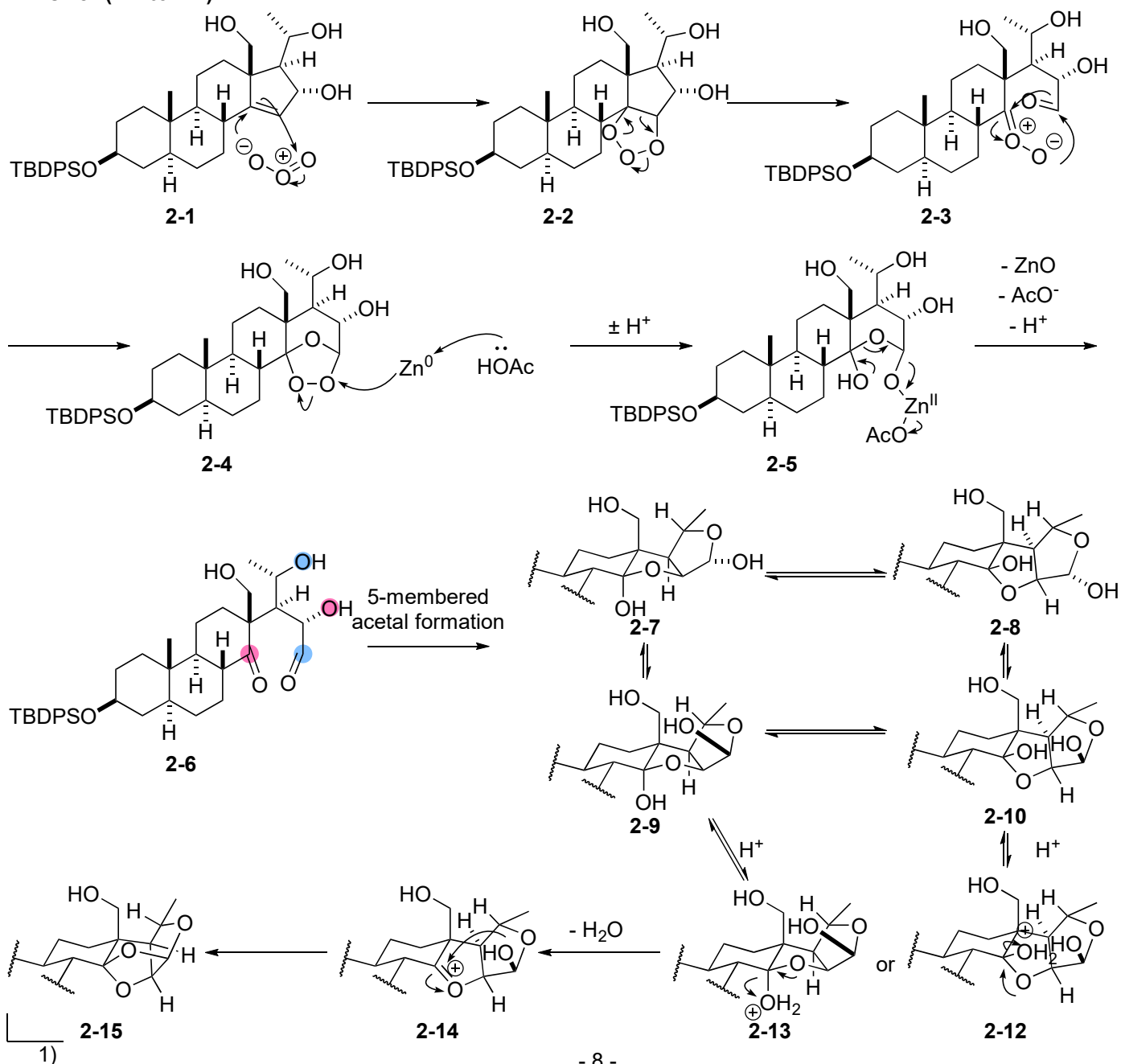
In this case, C-H at C19 would be located closer than that at C18, thus the reaction proceeded at C19 dominantly.

(2) Please explain the reasonable reaction mechanisms from **2-1** to **2-2** and **2-3** to **2-4**.

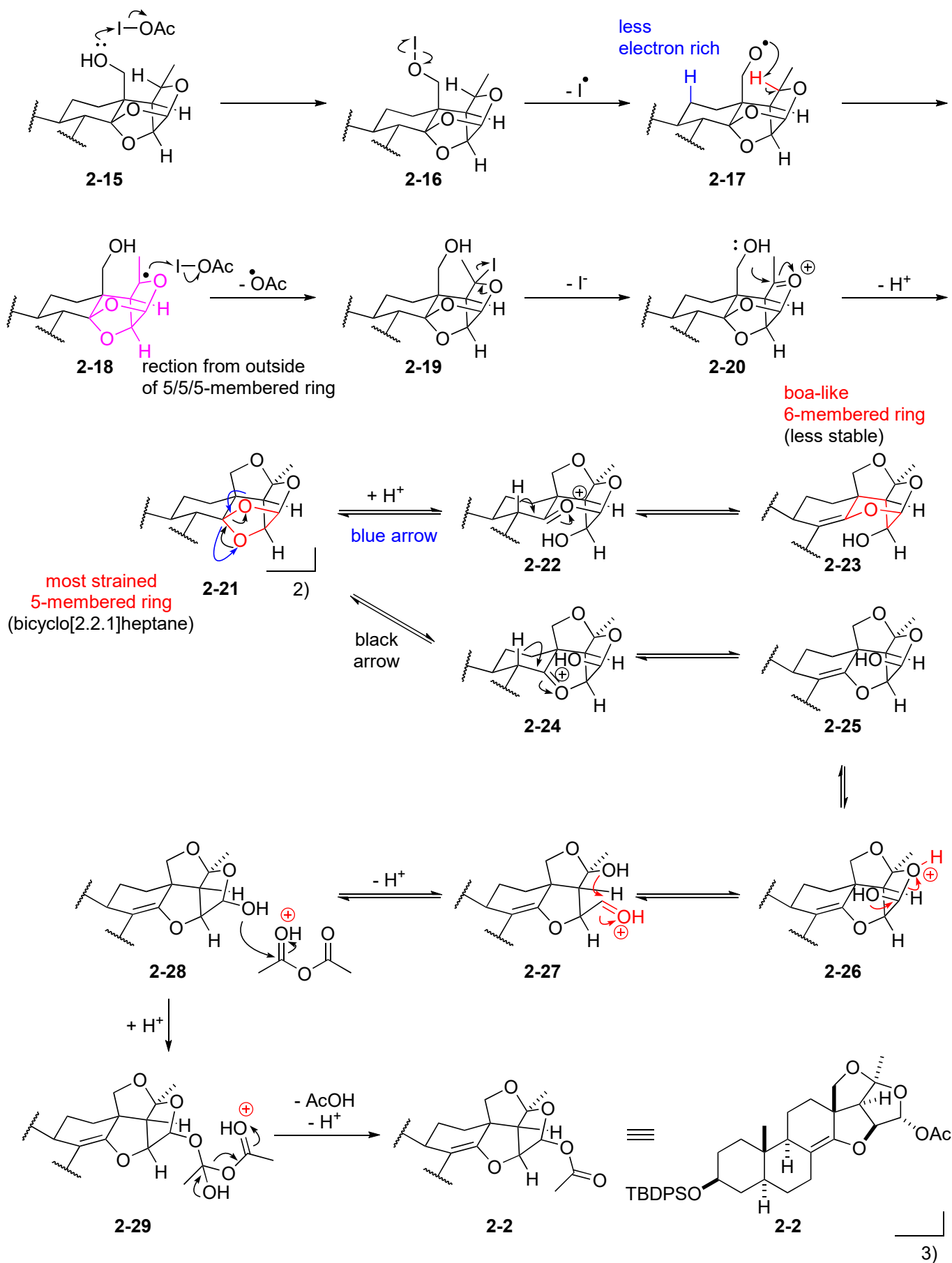
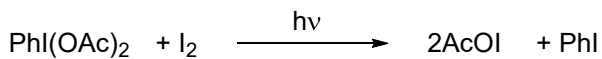


Gui, J.; Wang, D.; Tian, W. *Angew. Chem. Int. Ed.* **2011**, *50*, 7093.

•Answer (2-1 to 2-2)

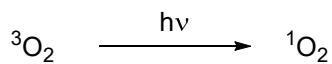




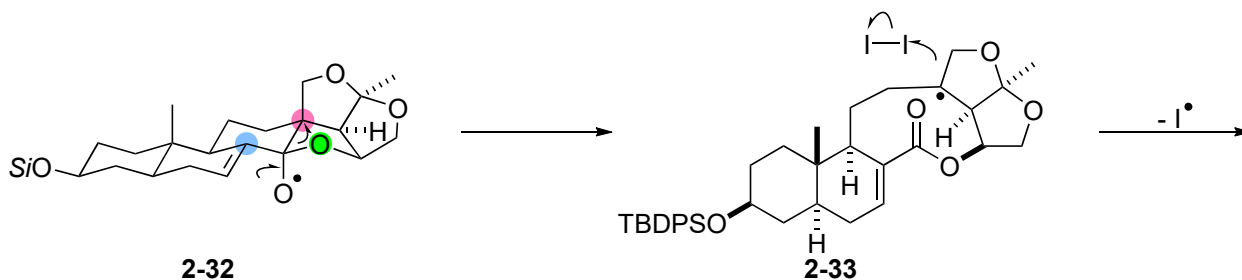
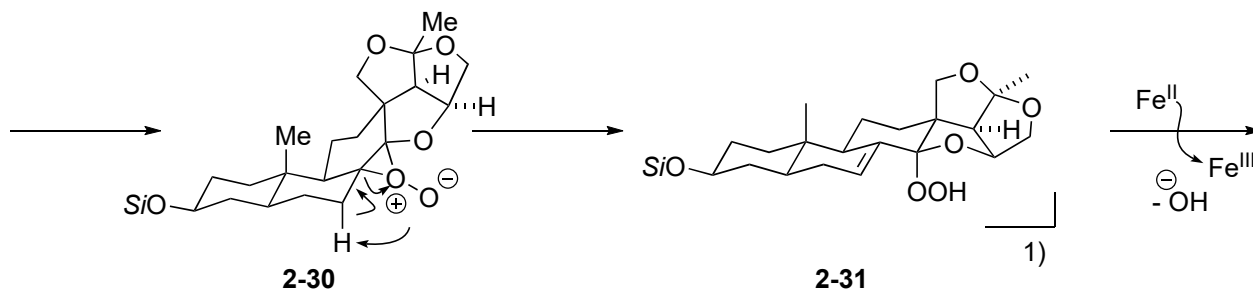
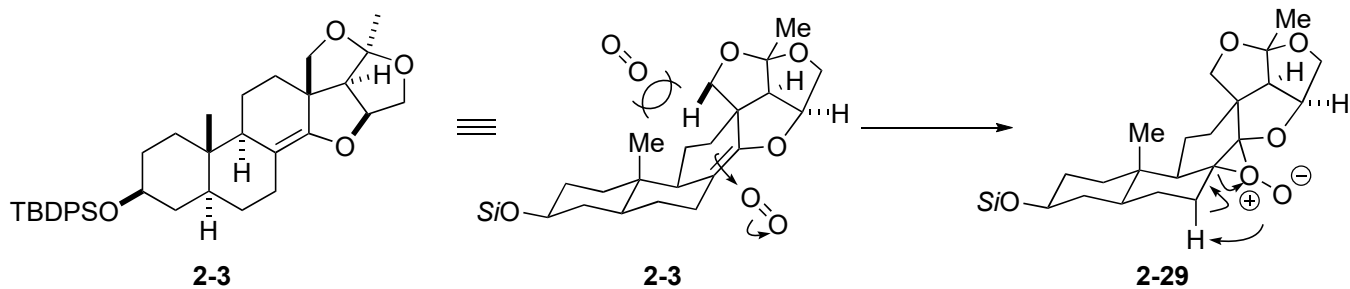


3)

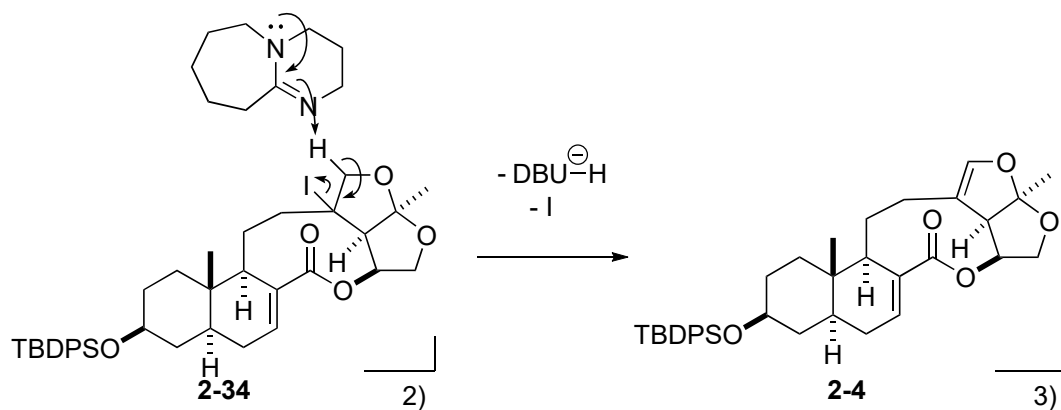
•Answer (2-3 to 2-4)



TPP: photosensitizer



- : form  $\text{sp}^2$  radical (disfavored)
- : form oxyl radical (disfavored)
- : form  $\text{sp}^3$  tertiary radical (favored)



For the  ${}^1\text{O}_2$  reaction, please see 200613\_PS\_Shimizu\_Shinsuke