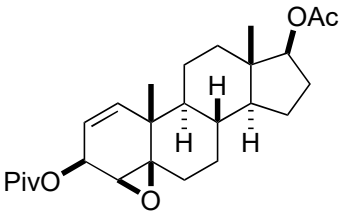
Problem Session (3)

2022.7.30 Kyohei Takaoka

Please provide the reaction mechanisms.

1

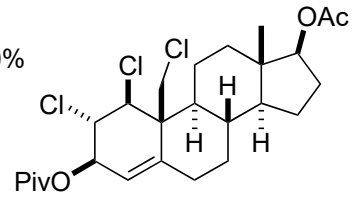


1-1

1. Et_4NCl (5 eq), Oxone (1.25 eq), CH_2Cl_2, 23 °C, 84%
2. 40% aqueous HBr (2 eq), CH_2Cl_2, 23 °C, 79%
3. $Pb(OAc)_4$ (1.2 eq), I_2 (1.5 eq), CH_2Cl_2, *hv*[a], 23 °C 80%
4. Zn (10 eq), THF/AcOH (5/1), 23 °C, 88%

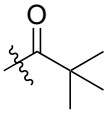
5. *n*-Bu_4NI (3 eq), PPh_3 (3 eq), $(CH_2Cl)_2$, 120 °C, 84%

[a] 300 W sunlight lamp

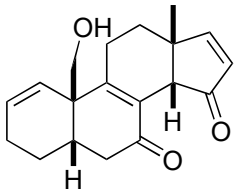


1-2

Oxone: $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$

Piv = 

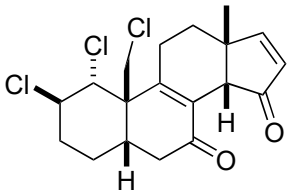
2



2-1

1. $SnCl_4$ (3 eq), *t*-BuOCl (2.5 eq), CH_2Cl_2, 0 °C; then $BF_3 \cdot OEt_2$ (2 eq), rt, 60%[b]
2. PPh_3 (3 eq), CCl_4, microwave 100 °C, 73%

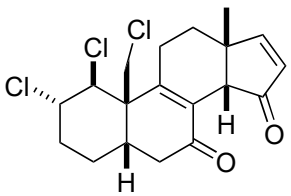
[b] 6% for minor diastereomer



2-2 (undesired)

1. $SOCl_2$ (3 eq), DMF (10 eq), CH_2Cl_2, rt, 79%
2. Et_4NCl_3 (2.5 eq), CH_2Cl_2, 0 °C, 61%[c]
3. $TiCl_4$ (5 eq), LiCl (5 eq), DMF, 90 °C, 79%
4. PPh_3 (3 eq), CCl_4, 90 °C, 35%

[c] 20% for minor diastereomer

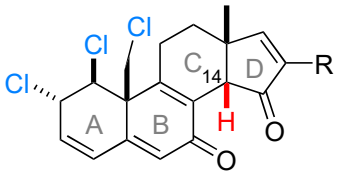


2-3 (desired)

Problem Session (3) Answer

2022.7.30 Kyohei Takaoka

Topic: Total syntheses of clionastatins (chlorinated natural product)



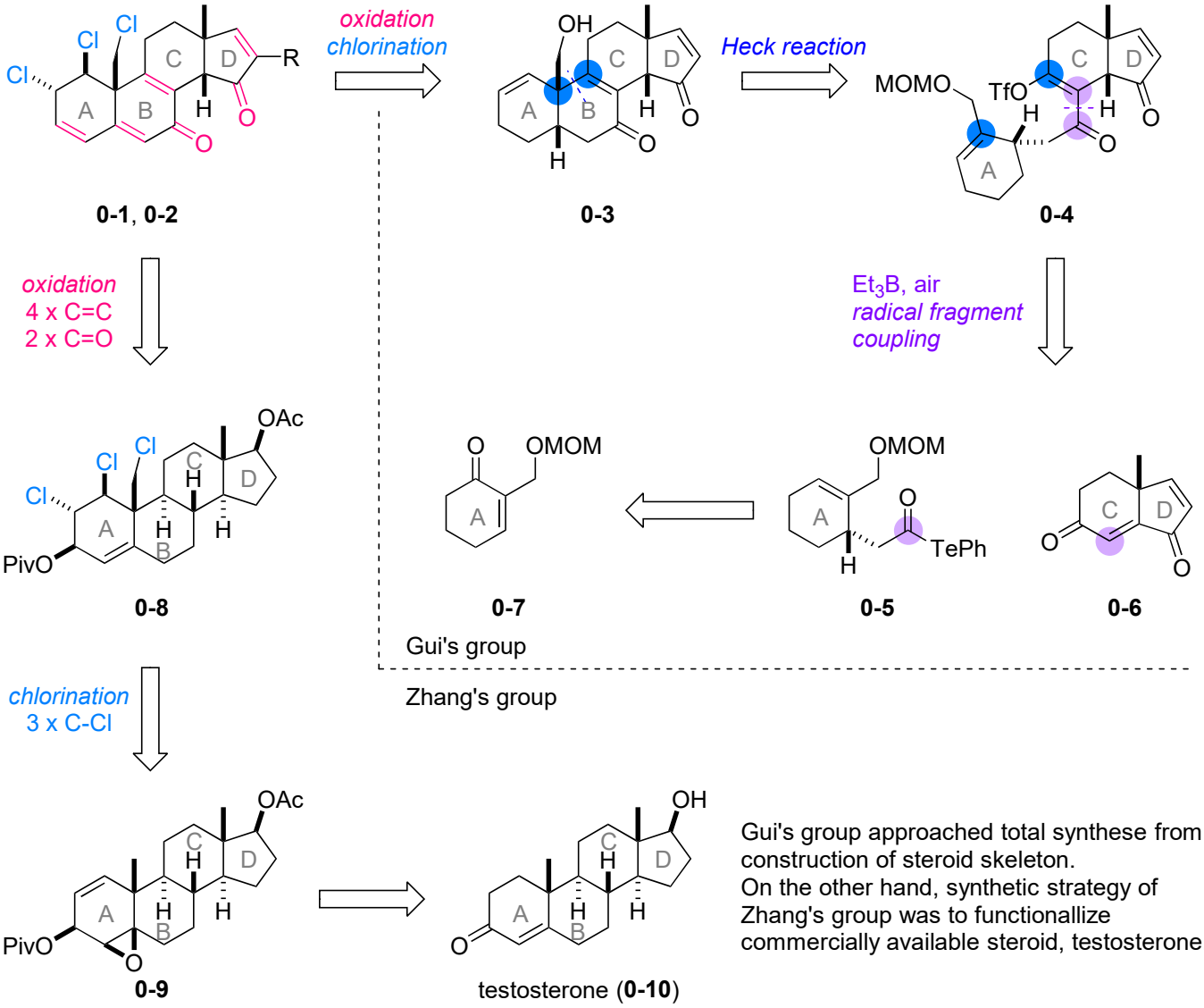
0-1: Clionastatin A (R = H)
0-2: Clionastatin B (R = Cl)

Isolated in 2004 fom burrowing sponge *Cliona nigricans*[2)]
(From 1.7kg (dried), 1.2 mg of **0-1** and 1.9 mg of **0-2** were isolated)

Total syntheses:
Gui's group (2021, 16-17 steps)[3)] with structural revision ← problem 2
Zhang's group (2022, 16 steps)[4)] ←problem 1
* Stereochemistry at C14 was incorrect in originally proposed structure.

cytotoxic acitivity (IC_{50}): 0.8-2.0 μg/mL

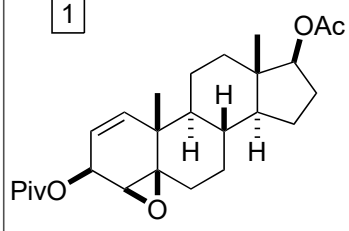
Retrosynthetic analysis:



Gui's group approached total synthese from construction of steroid skeleton.
On the other hand, synthetic strategy of Zhang's group was to functionallize commercially available steroid, testosterone.

Reference:
1. Chung. W.-J.; Vanderwal, C. D. *Angew. Chem. Int. Ed.* **2016**, *55*, 4396.
2. Fattorusso, E.; Taglialatela-Scafati, O.; Petrucci, F.; Bavestrello, G.; Calcinai, B.; Cerrano, C.; Meglio, P. D.; Ianaro, A. *Org. Lett.* **2004**, *6*, 1633.
3. Ju, W.; Wang, X.; Tian, H.; Gui, J. *J. Am. Chem. Soc.* **2021**, *143*, 13016.
4. Cui, H.; Shen, Y.; Chen, Y.; Wang, R.; Wei, H.; Fu, P.; Lei, X.; Wang, H.; Bi, R.; Zhang,Y. *J. Am. Chem. Soc.* **2022**, *144*, 8938.

1



1-1

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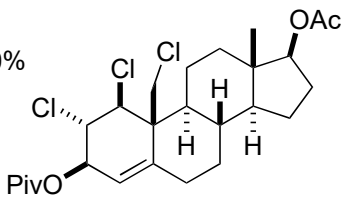
4. Zn (10 eq), THF/AcOH (5/1), 23 °C, 88%

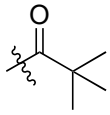
5. *n*-Bu_4NI (3 eq), PPh_3 (3 eq), $(CH_2Cl)_2$, 120 °C, 84%

[a] 300 W sunlight lamp



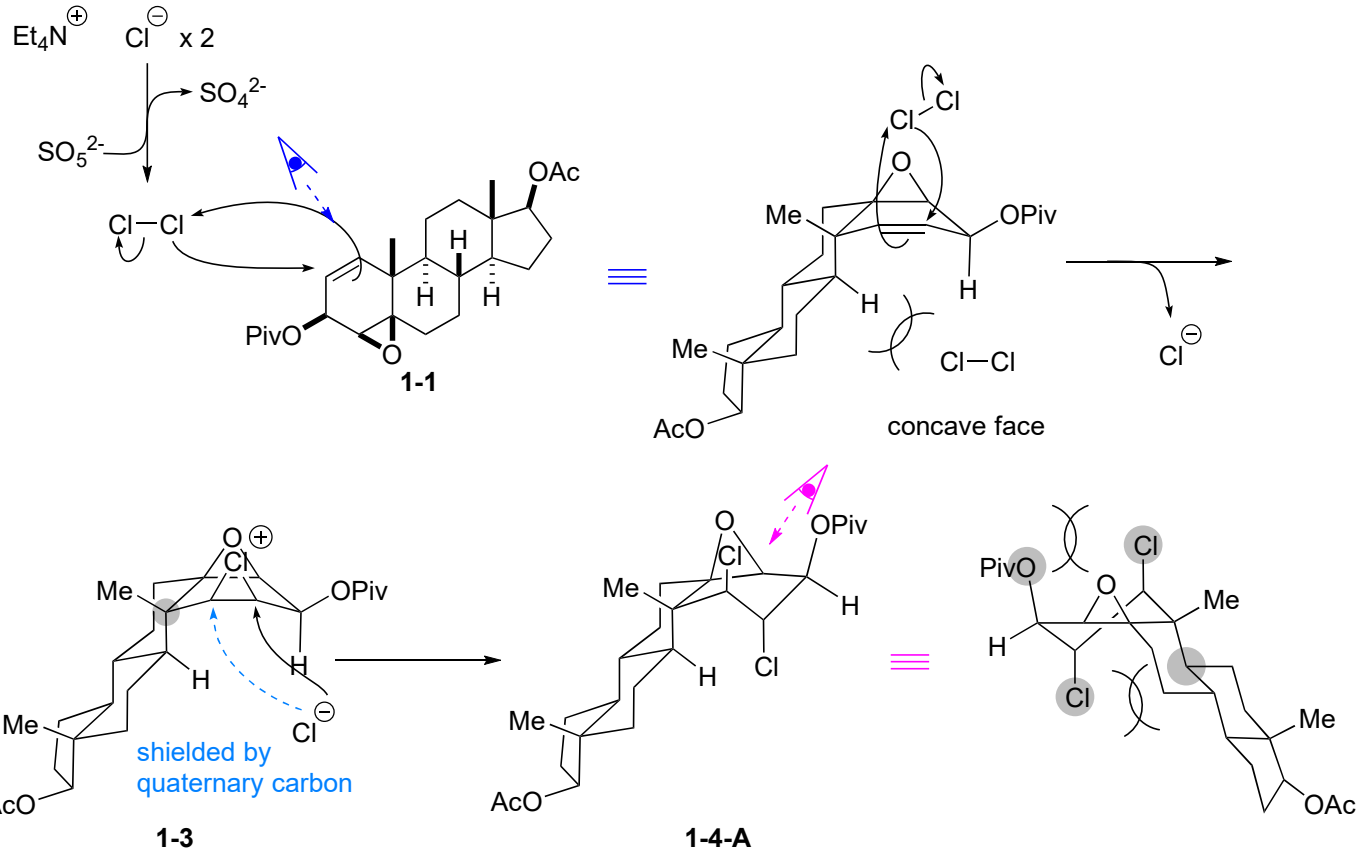
1-2

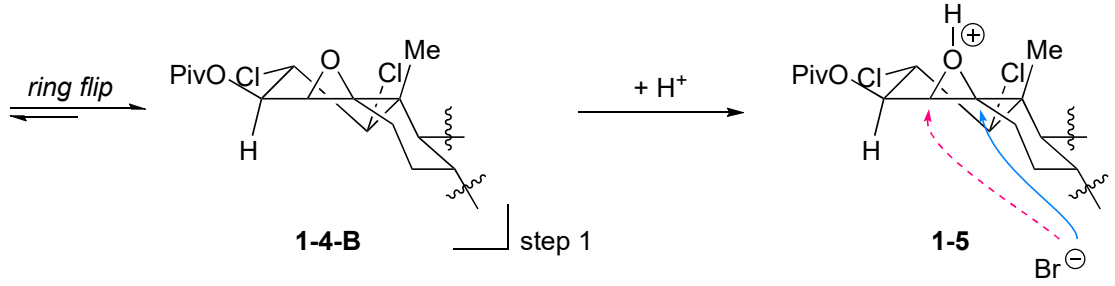
Oxone: $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$

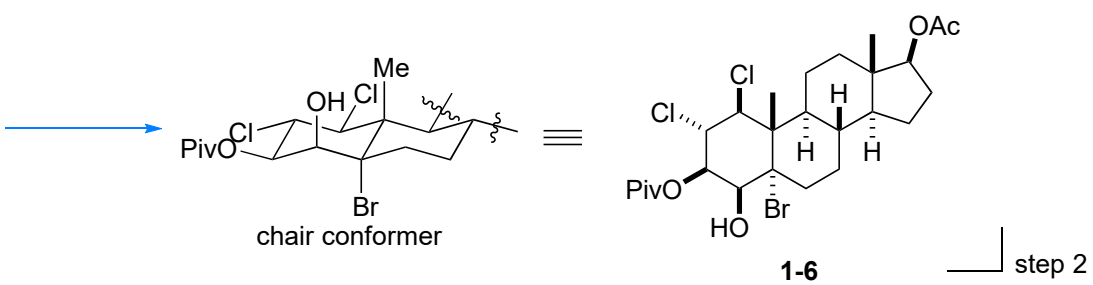
Piv = 

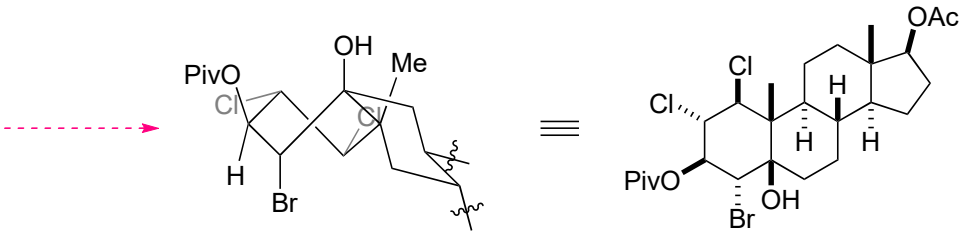
Cui, H.; Shen, Y.; Chen, Y.; Wang, R.; Wei, H.; Fu, P.; Lei, X.; Wang, H.; Bi, R.; Zhang,Y. *J. Am. Chem. Soc.* **2022**, *144,* 8938.

Answer:



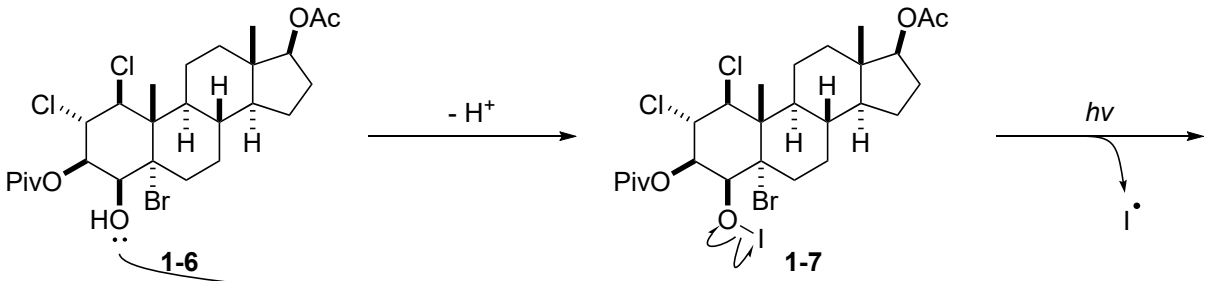




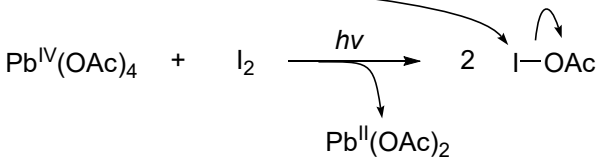


twisted boat conformer
(unfavored)

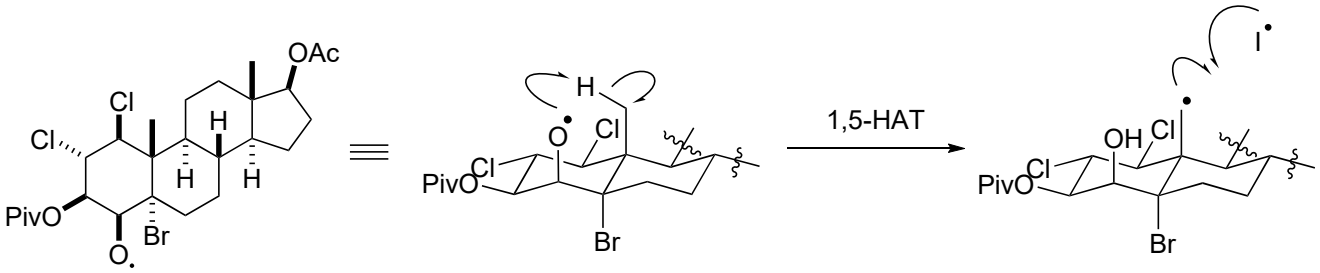
1-6'
not obtained



1-6 **1-7**

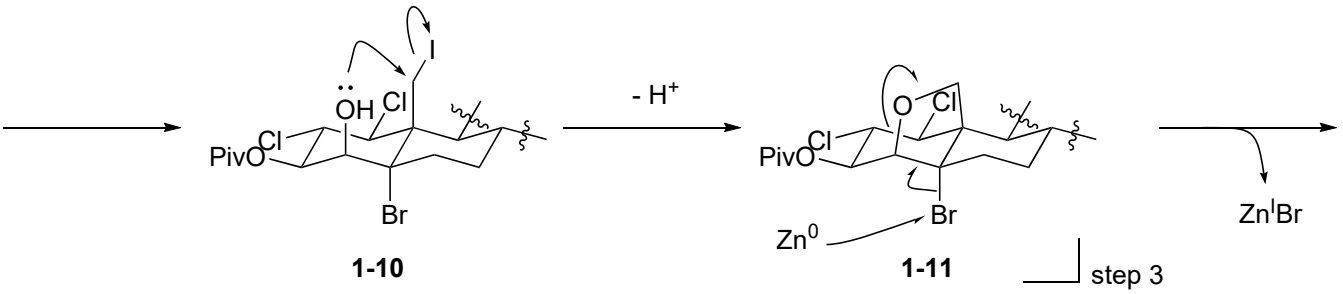


* Bond dissociation energy
O-I: 220 kJ/mol
C-Br: 270 kJ/mol
C-Cl: 330 kJ/mol

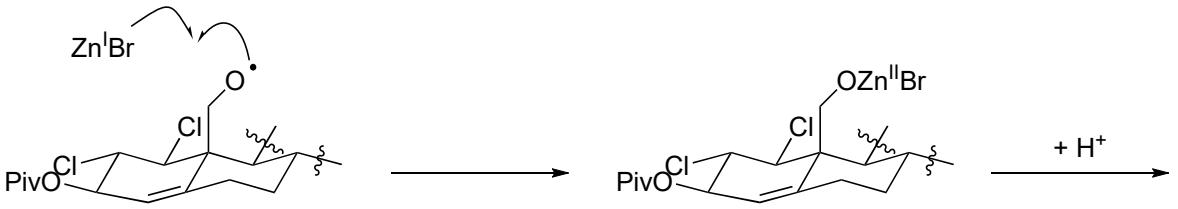


1-8 **1-9**

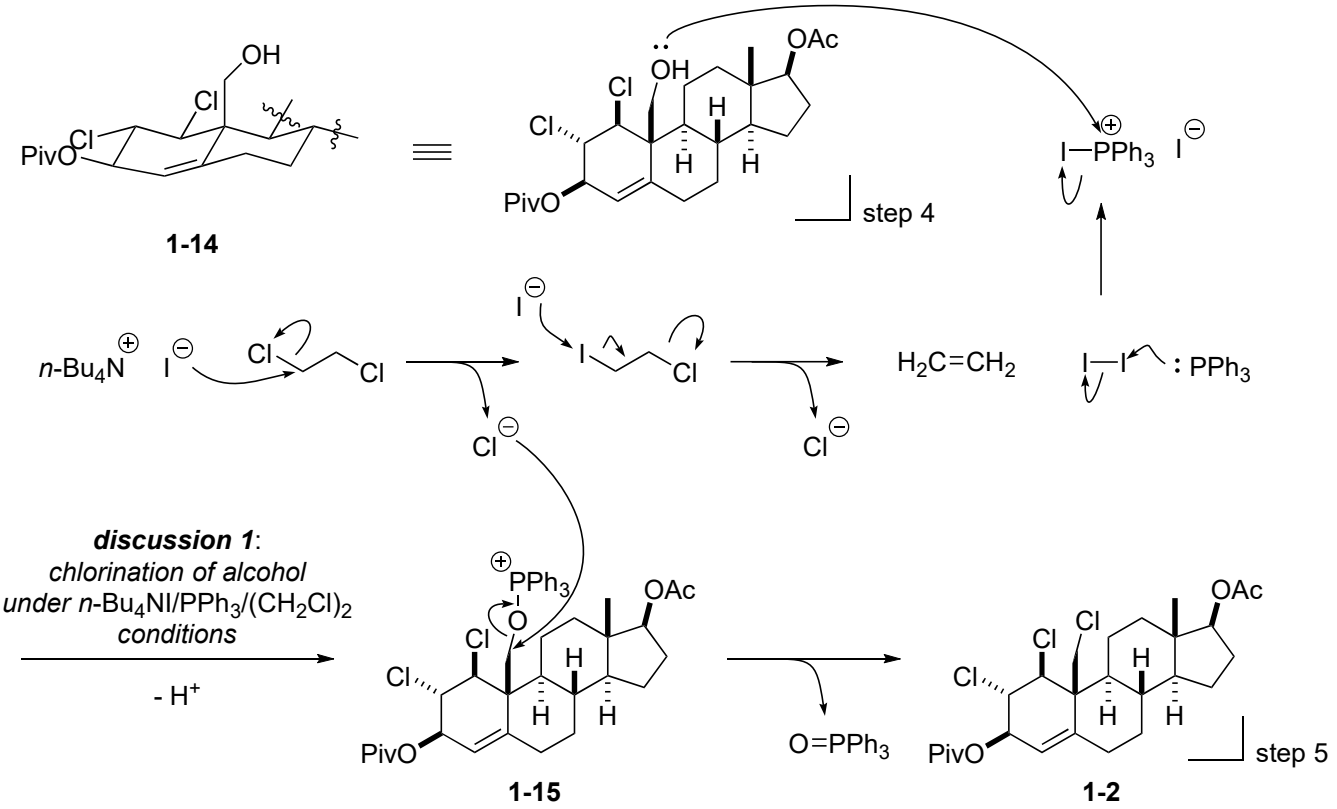
There is no proper hydrogen atom
that can proceed further HAT



1-10 **1-11** step 3

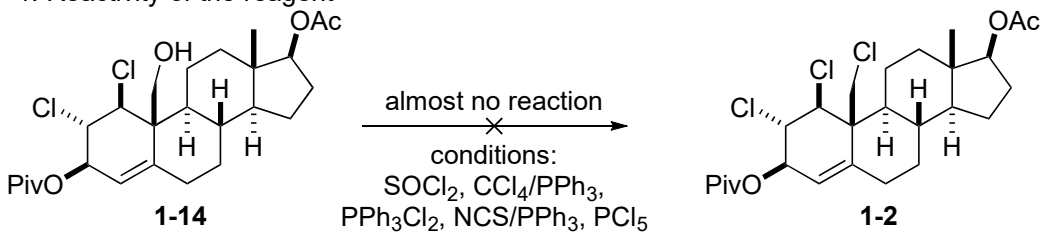


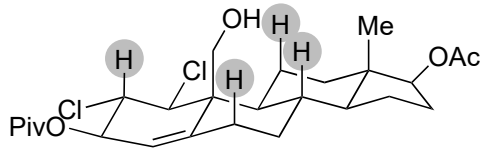
1-12 **1-13**



Discussion 1: Chlorination of alcohol under *n*-$Bu_4NI/PPh_3/(CH_2Cl)_2$ conditions[1)]

1. Reactivity of the reagent

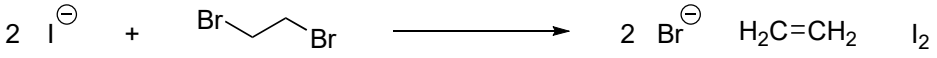




Alcohol is shielded by neighboring hydrogen atoms in **2-14**. So chlorination of this alcohol didn't proceeded with Ph_3P^+Cl, PCl_5 or $SOCl_2$. The reaction requires better reactive species than those reagent, and $PPh_3{}^+I$ would be such spicies (high reactivity with alcohol, and turned alcohol into good leaving group, $Ph_3P{=}O$.)

2. Reaction mechanism

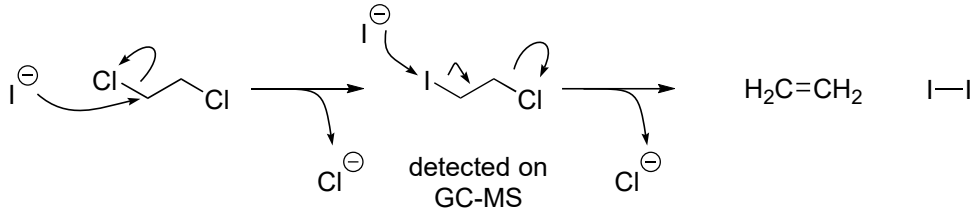
In previous study shows that $CH_2{=}CH_2$ and I_2 was genearated from $BrCH_2CH_2Br$ and I^-. [2)]



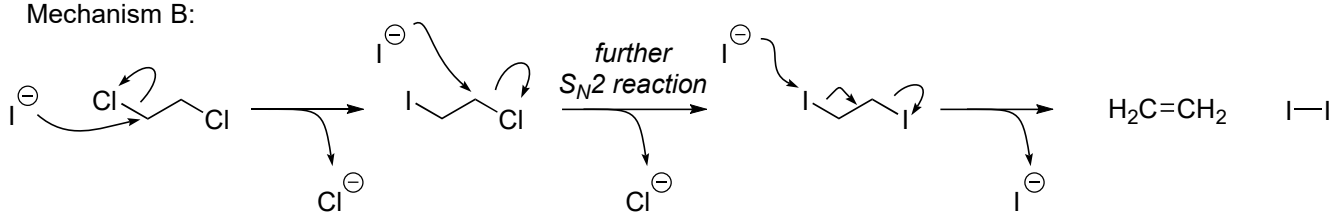
In the control experiment, $ClCH_2CH_2I$ was detected by GC-MS spectroscopy in the reaction mixture of *n*-BuNI and $(CH_2Cl)_2$. Thus, there could be 2 reaction mechanism (mechanism A, B) in the formation of I_2 and $CH_2{=}CH_2$.

Possible reaction mechanism

Mechanism A:

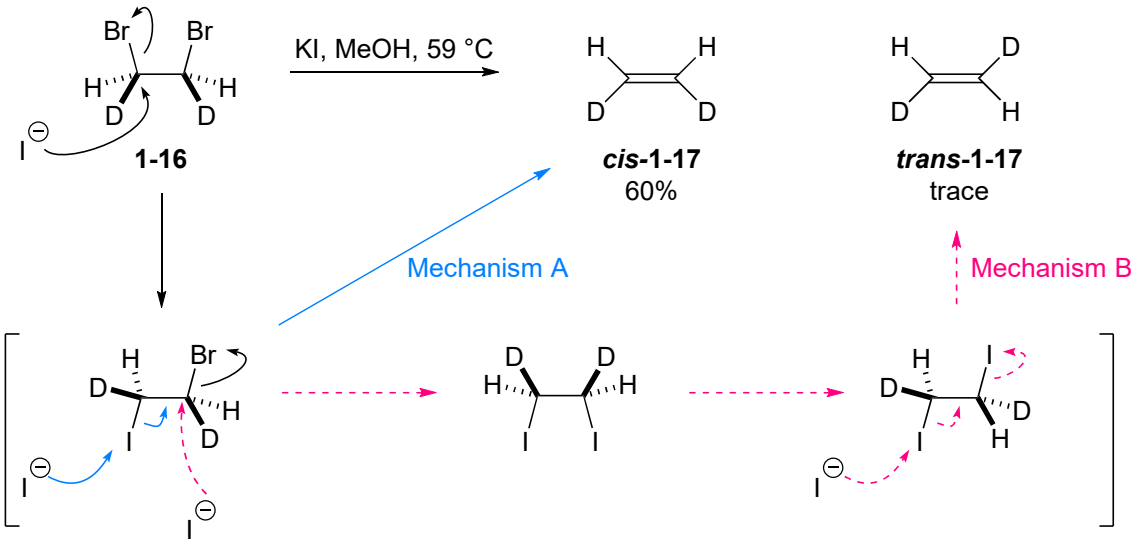


Mechanism B:



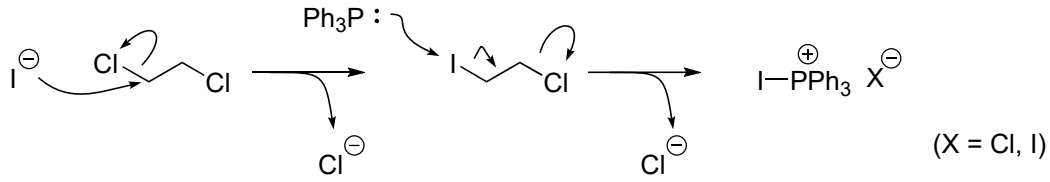
Deuterium labeling experiment supports mechanism A, not mechanism B.

Deuterium labeling experiment[3)]

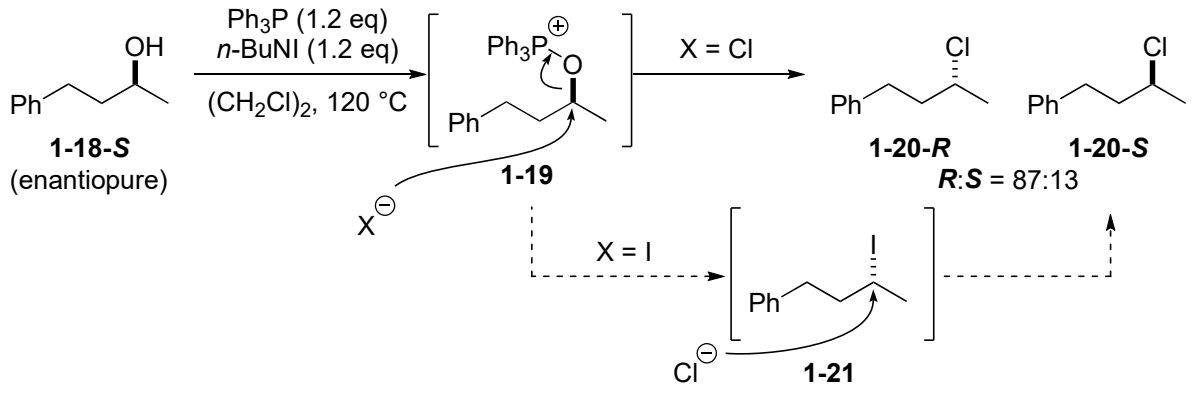


On the other hand, nucleophilic atack from PPh_3 instead of I^- can be possible reaction pathway.

Other plausible reaction mechanism:



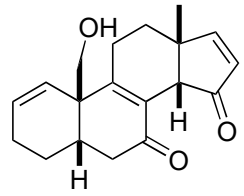
The following result suggested that chlorination from **1-19** is the major pathway, not iodinating pathway.



Reference:

1. Chen, J.; Lin, J.-H.; Xiao, J.-C. *Org. Lett.* **2018**, *20*, 3061.
2. Hine, J.; Brader, W. H. *J. Am. Chem. Soc.* **1955**, *77*, 361.
3. Schubert, W. M.; Steadly, H.; Rabinovitch, B. S. *J. Am. Chem. Soc.* **1955**, *77*, 5755.

2



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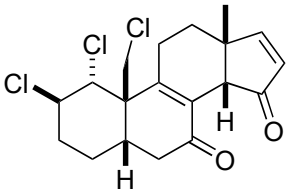
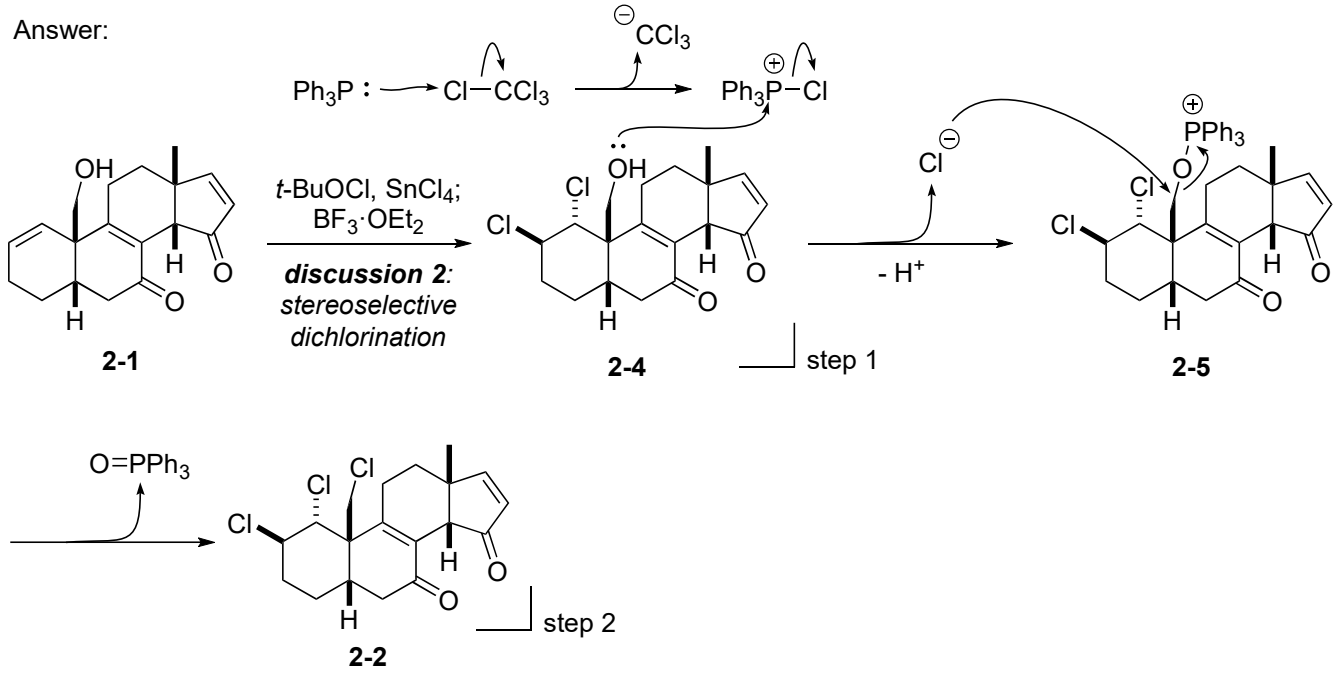
[b] 6% for minor diastereomer



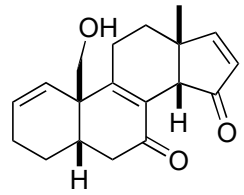
2-2 (undesired)

Ju, W.; Wang, X.; Tian, H.; Gui, J. *J. Am. Chem. Soc.* **2021**, *143*, 13016.

Answer:



2-1 **2-4** **2-5** **2-2**



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3. $TiCl_4$ (5 eq), LiCl (5 eq), DMF, 90 °C, 79%
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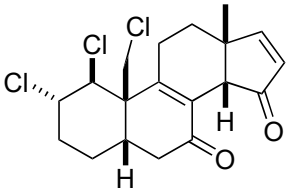
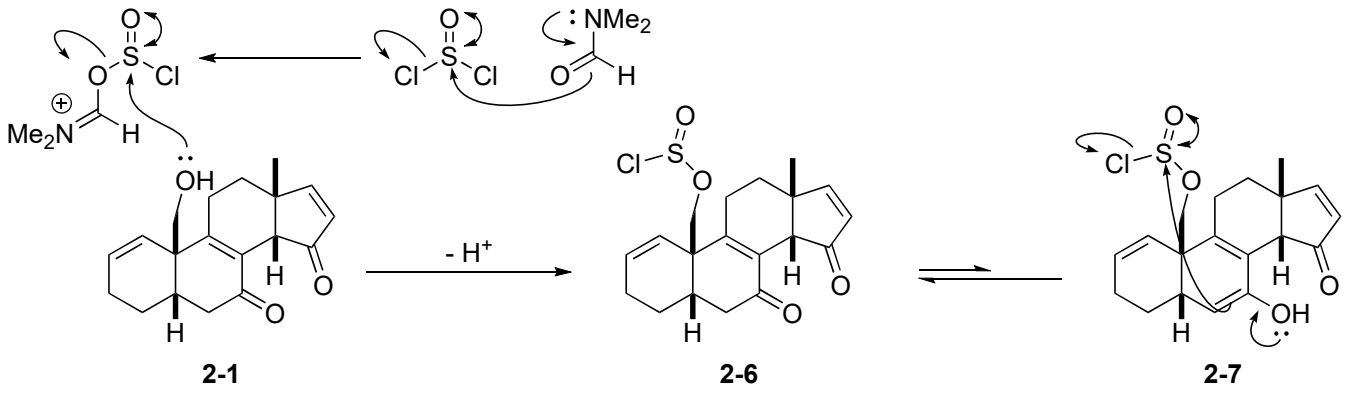
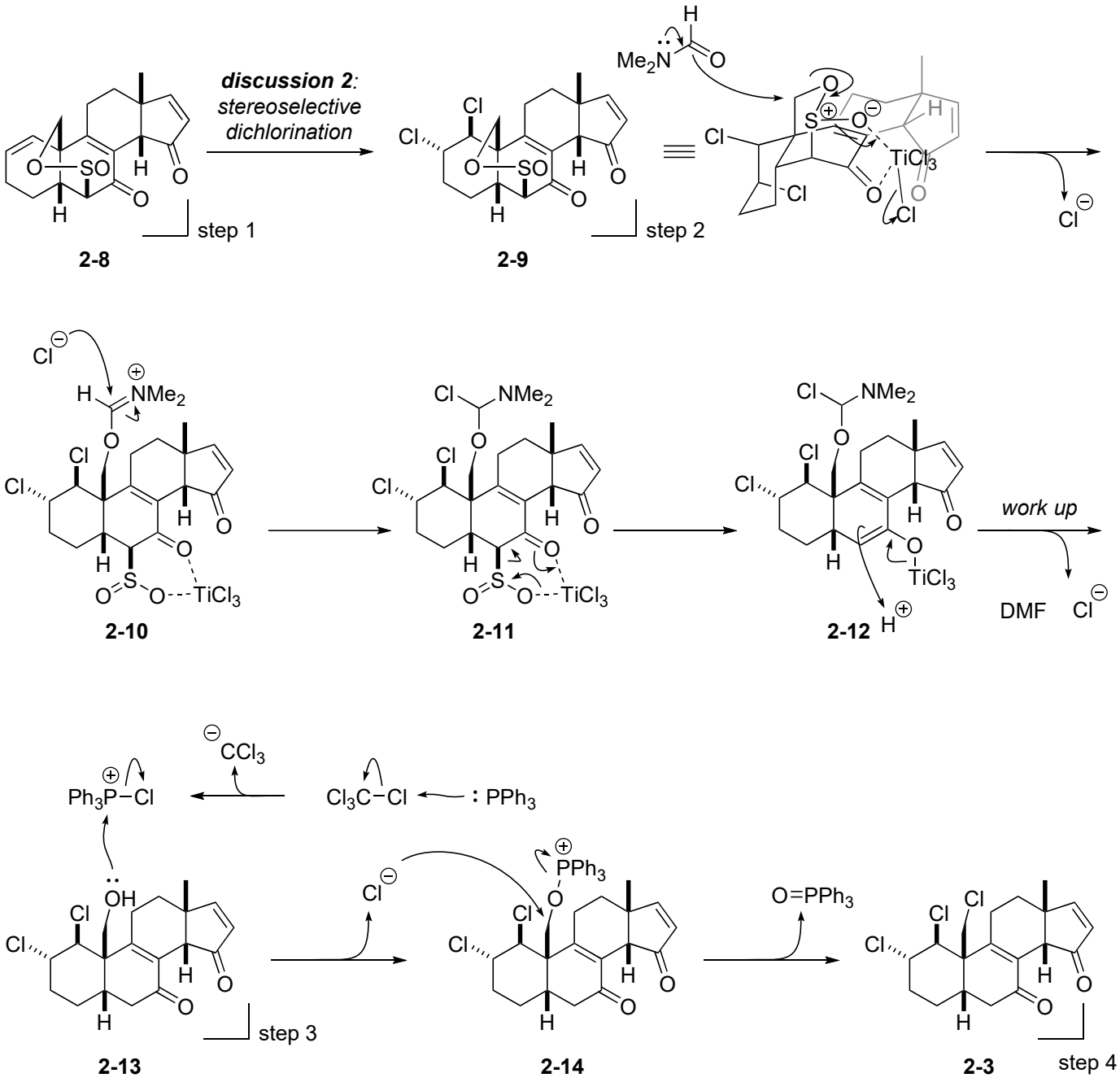


2-1 **2-3** (desired)

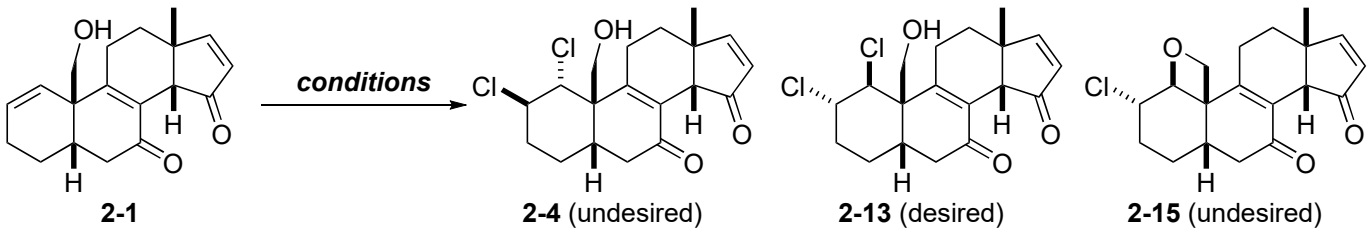
Answer:



2-1 **2-6** **2-7**



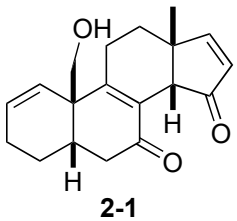
Discussion 2: Stereoselective dichlorination



entry	conditions	result
1	Et_4NCl_3 (2 eq), CH_2Cl_2, −78 °C (conditions A)	**2-4**: **2-12**: **2-15** = 5: 4: 1 (in NMR)
2	$SnCl_4$ (3 eq), *t*-BuOCl (2.5 eq), CH_2Cl_2, 0 °C; $BF_3{\cdot}EtO_2$ (2 eq) (conditions B)	**2-4**: 60% **2-13**: 6% **2-15**: trace

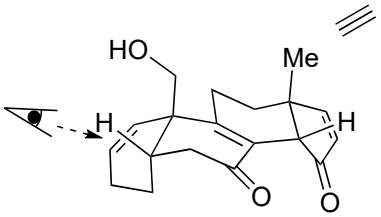
When Et_4NCl_3 was used as a chlorinating source, in addition to **2-4**, desired **2-12** and oxetane **2-15** were obtained (entry 1).

In the conditions under Et_4NCl_3 in CH_2Cl_2:

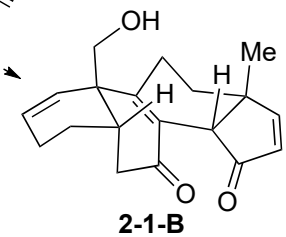


2-1

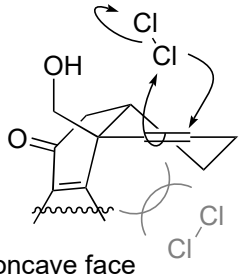
There could be 2 conformers, **2-1-A** and **2-1-B**.



2-1-A

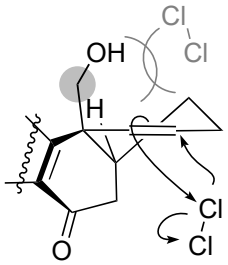


2-1-B



concave face

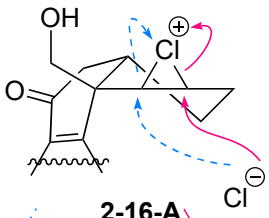
2-1-A



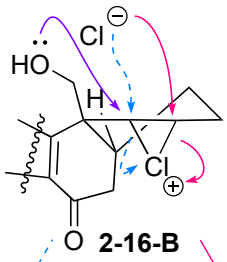
2-1-B

Cl_2 reacts from convex face in **2-1-A**.

CH_2OH locates *psuedo-axial* and shields convex face in **2-1-B**. Steric hindrance in cocave face is relatively small, thus Cl_2 reacts from concave face.

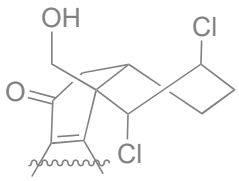


2-16-A

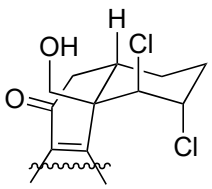


2-16-B

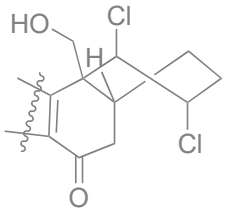
2-15



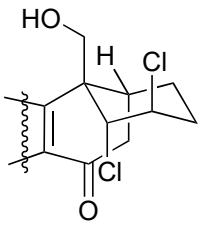
twisted boat conformer (unfavored)



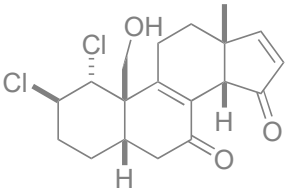
chair conformer



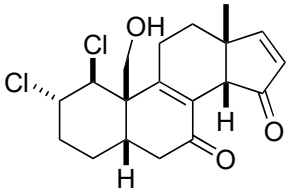
twisted boat conformer (unfavored)



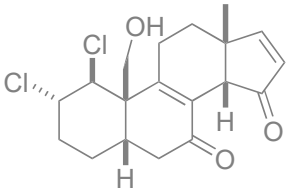
chair conformer



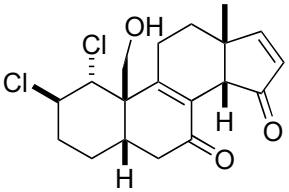
2-4 (undesired)



2-13 (desired)



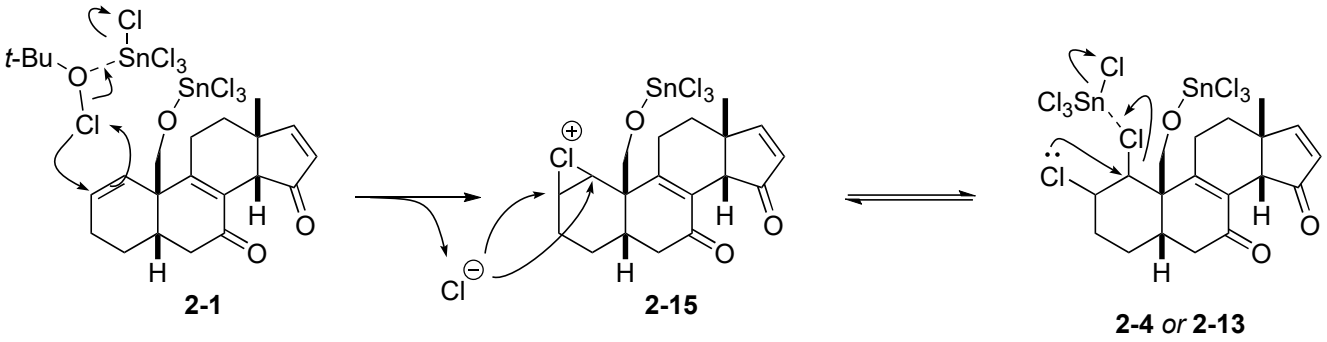
2-13 (desired)



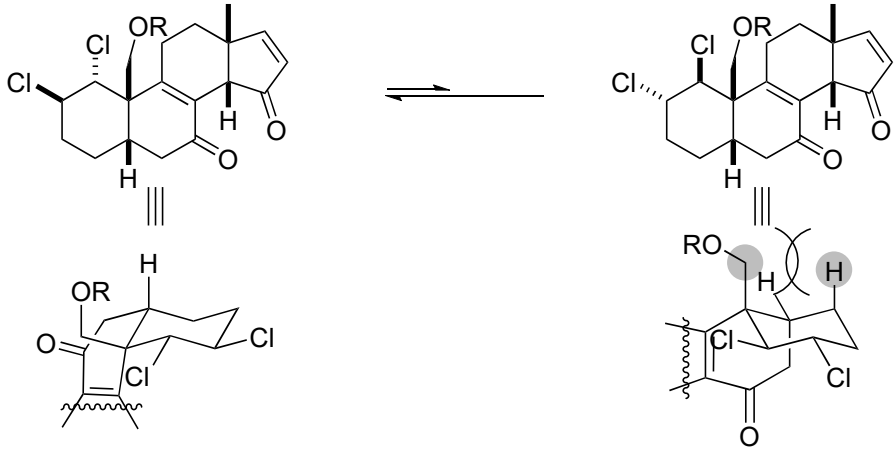
2-4 (undesired)

Since **2-1-A** and **2-1-B** is in equillibrium, **2-4**: **2-13**: **2-15** was generated in the ratio of 5: 4: 1.
(Considering **2-13** was from **2-1-A** and **2-4** and **2-15** were from **2-1-B**, **2-1-A** : **2-1-B** ~ 4 : 6)

In the conditions under *t*-BuOCl/$SnCl_4$ in CH_2Cl_2:
In the presence of $SnCl_4$, dichlorination could be reversible due to Lewis acidity of $SnCl_4$.



2-1 **2-15** **2-4** *or* **2-13**

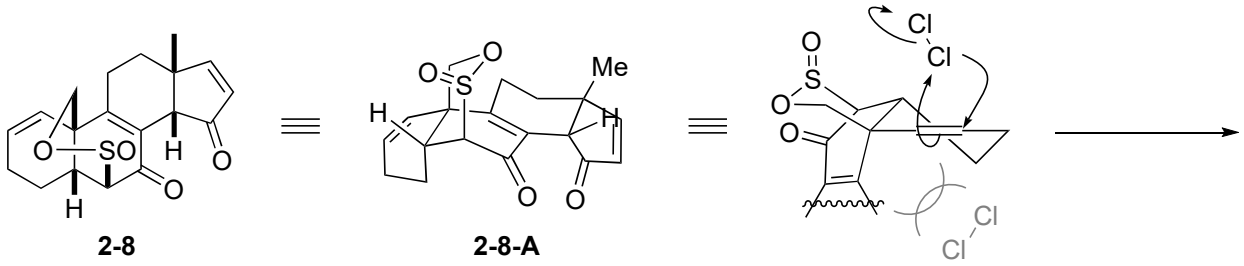


2-4
(favored)

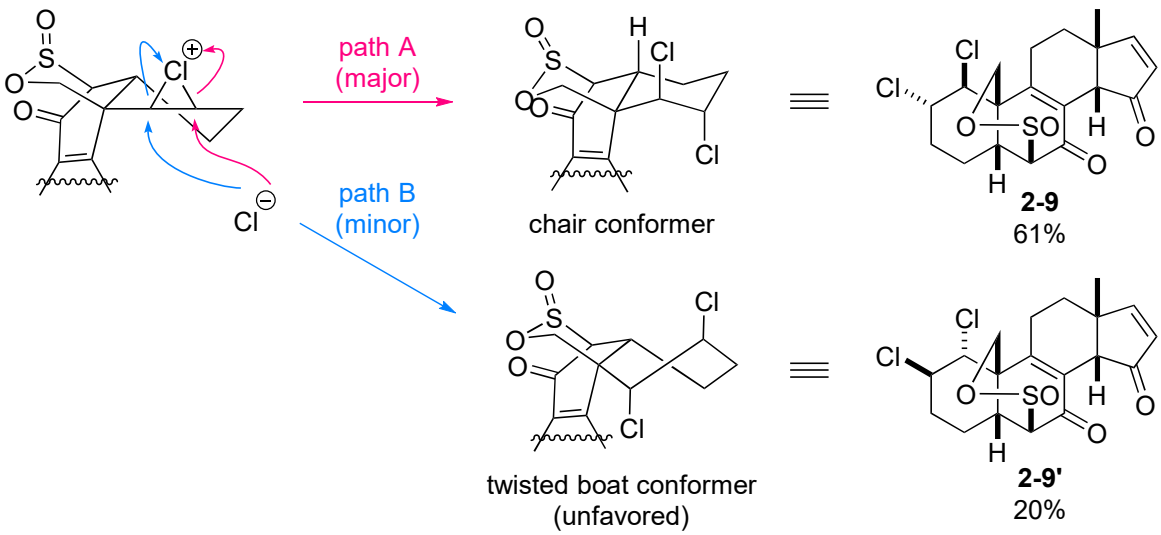
2-13
(disfavored)

As a result, more stable **2-4** was obtained as a major isomer.
The role of $BF_3{\cdot}OEt_2$ would be reducing the amount of HCl. ($BF_3{\cdot}OEt_2$ + HCl → HBF_3Cl + Et_2O)

In **2-8**, since conformation is fixed, reaction proceeded only from **2-8-A**.
In comparison to path B, path A is more favorable and desired **2-9** was obtained as a major product.



2-8 **2-8-A**



chair conformer

2-9
61%

twisted boat conformer
(unfavored)

2-9'
20%