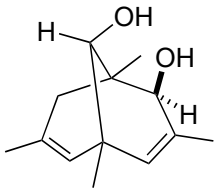
Problem Session (4)

2023.6.3. Kyohei Takaoka

Please provide the reaction mechanisms and explain why the chemical shifts of highlighted protons in **1-2** are low.

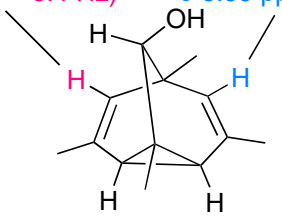
1



1-1

1. Cs_2CO_3 (3.0 eq), CDI (1.1 eq), THF, 60 °C
2. $KN(TMS)_2$ (3.0 eq), THF, 23 °C, 61% (2 steps)

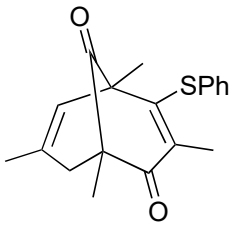
δ 3.41 ppm (d, *J* = 3.4 Hz) δ 3.55 ppm (d, *J* = 3.4 Hz)



1-2

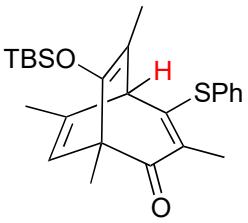
* coupling was observed between the two highlighted protons.

2

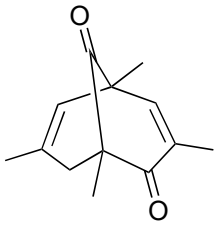


2-1

1. $KN(TMS)_2$ (3.0 eq), THF, −78 °C;
   TBSOTf (3.0 eq), −78 °C, 80%

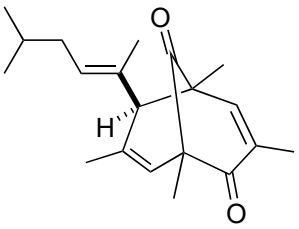


2-2

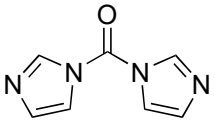


2-3

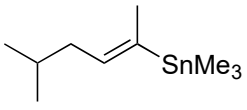
1. $KN(TMS)_2$ (2.0 eq), THF, −78 °C;
   TIPSOTf (2.0 eq), −78 °C, 70%
2. $PdCl_2(PhCN)_2$ (1.0 eq), CH_2Cl_2, 23 °C, 95%
3. **A** (4.0 eq), PPh_3 (2.2 eq), CuCl (10 eq), LiCl (12 eq)
   DMSO, 200 °C, microwave, 49%



2-4



CDI

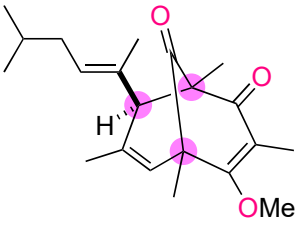


A

Problem Session (4) Answer

Topic: Total synthesis of ocellatusone C[1)]

2023.6.3 Kyohei Takaoka



ocellatusone C

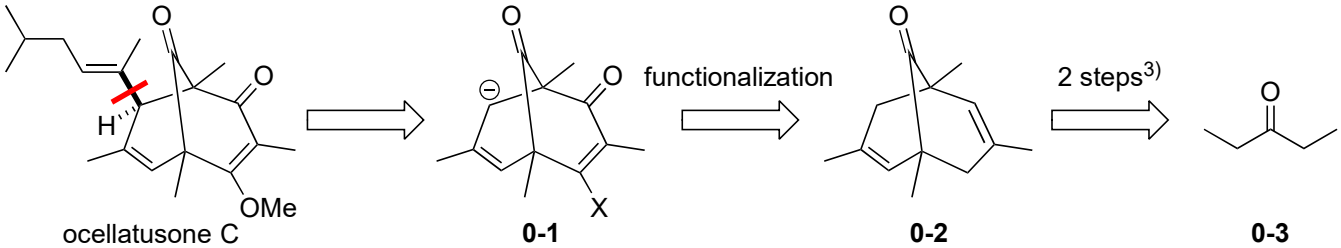
isolation: solar-powered sea slug, *Placobranchus ocellatus* (2020)[2)]

structural features: · bicyclo [3.3.1] nonane skeleton
· 3 oxygen-based functionalities
· 3 stereocenters with 2 quaternary carbons
· racemic

bioactivity: unknown

total synthesis: Maimone (2022)

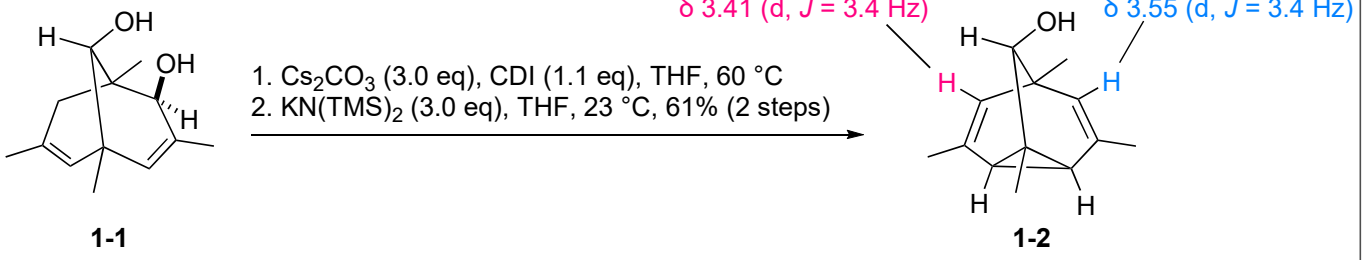
Retrosynthetic analysis:



Reference:

1. Sanchez, A.; Maimone, T. J. *J. Am. Chem. Soc.* **2022**, *144*, 7594.
2. Wu, Q.; Li, S.-W.; Xu, H.; Wang, H.; Hu, P.; Zhang, H.; Luo, C.; Chen, K.-X.; Nay, B.; Guo, Y.-W.; Li, X.-W. *Angew. Chem. Int. Ed.* **2020**, *59*, 12105.
3. Lee, G. S. **2014**, *PhD Thesis.* University of California, Los Angeles.

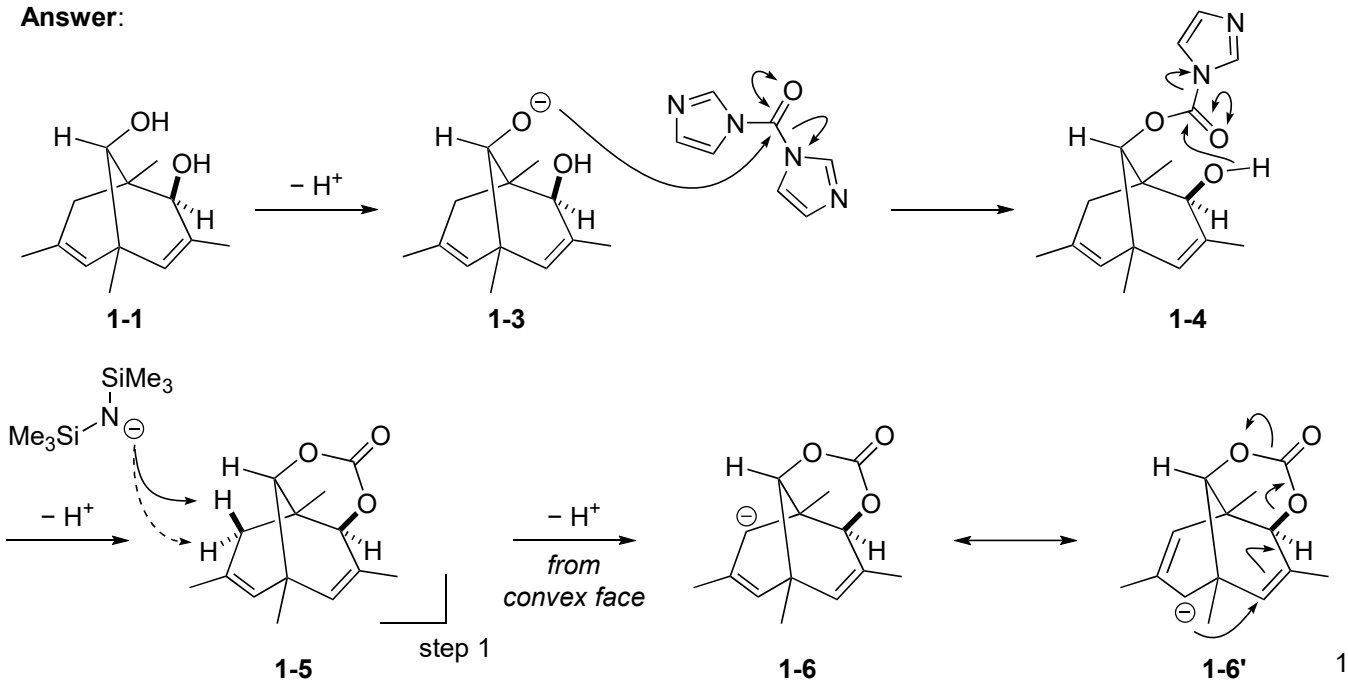
1

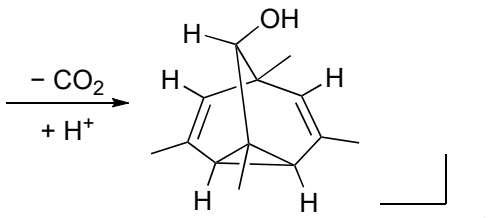


* coupling was observed between the two highlighted protons.

Sanchez, A.; Maimone, T. J. *J. Am. Chem. Soc.* **2022**, *144*, 7594.

Answer:



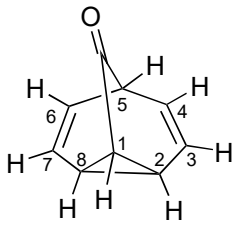


1-2

***discussion 1*: Chemical shift**

Discussion 1: Chemical shift

The compounds with tricyclo-[3.3.1.$0^{2,8}$]-3,6-diene skeleton, so called barbaralyl skeletone, have unique NMR spectral features.



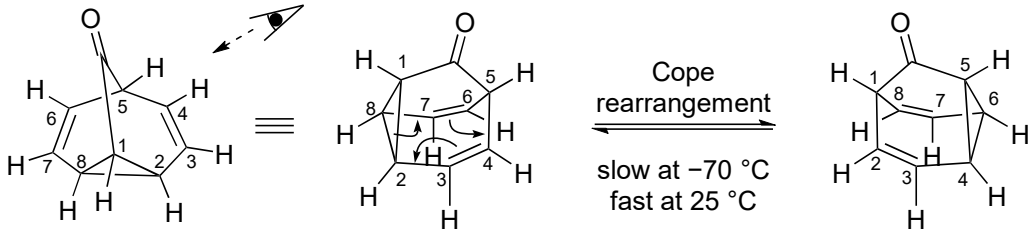
1-8 (barbaralone)

Table 1. ^{1}H NMR spectrum of **1-8**[2)]

No.	at −70 °C (δ)*	at 25 °C [δ, multi, *J* (Hz)]	Δ
1	2.46	2.60 (t, 6.5)	+0.14
2,8	2.91	4.20 (t, 7.0)	+1.29
3,7	5.71	5.69 (t, 7.3)	−0.02
4,6	5.92	4.20 (t, 7.0)	−1.72
5	2.91	2.60 (t, 6.5)	−0.31

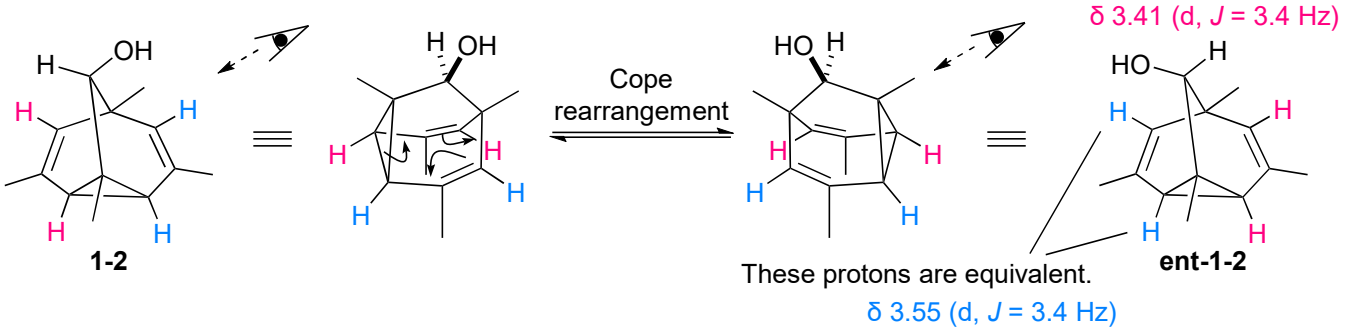
* signal patterns were not mentioned

At −70 °C, the peak of each proton is quite normal. However, at 25 °C, some peaks drastically shifted (H2 and 8, H4 and 6), and H1 and H5 showed the same peak patterns.



1-8

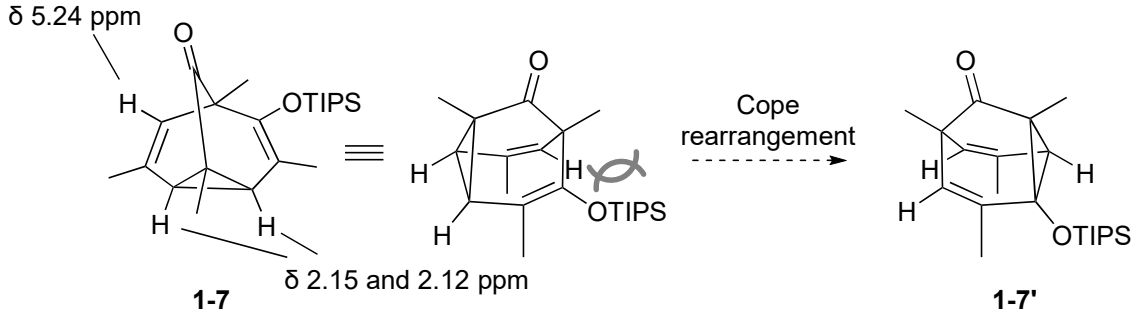
1-8 shows unique ^{1}H NMR spectrum because it can change its structure by Cope rearrangement. At −70 °C, this rearrangement is slow that H2 and H4 can be distinguished. As the temperature increases, this rearrangement proceeds at time-scale of NMR, these protons cannot be distinguished. Finally, at 25 °C, H1 and H5 showed the same peak pattern, as well as four protons (H2,4,6,8) showed the same peak pattern.



1-2 **ent-1-2**

Since **1-2** has barbaralyl skeletone, the rapid Cope rearrangement of **1-2** proceeds like **1-8**. Thus, there is in equilibrium between **1-2** and **ent-1-2** at room temperature, and it displays a spectrum consistent with a fluxional structure with averaged resonances and chemical shifts.

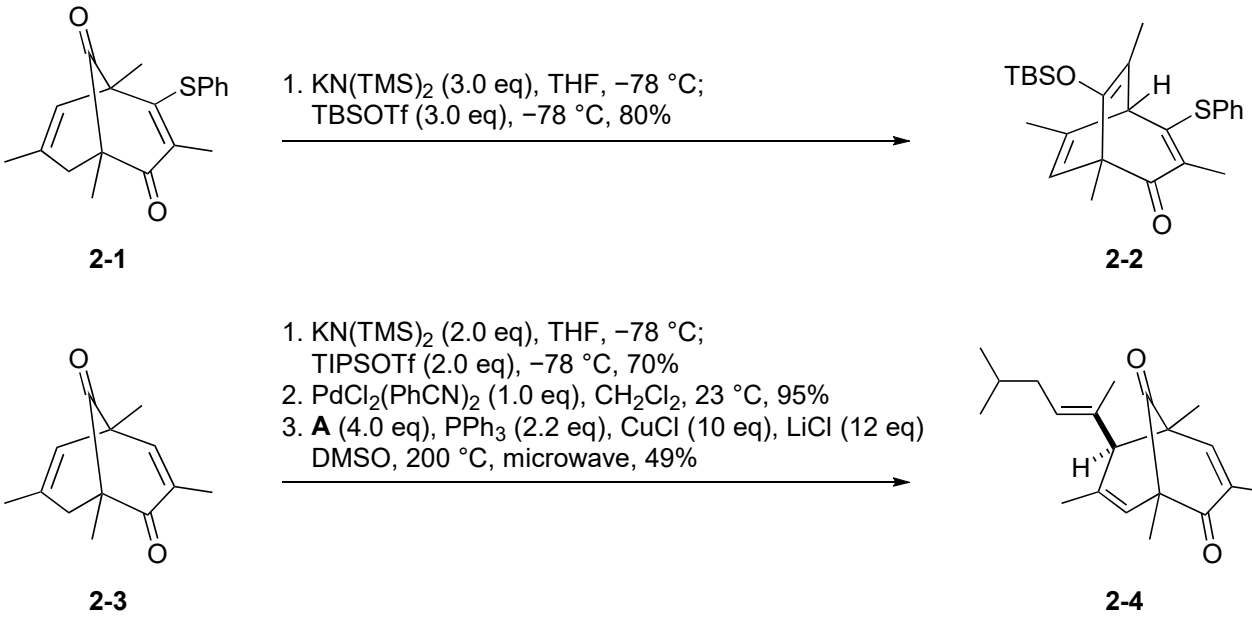
Appendix:



1-7 **1-7'**

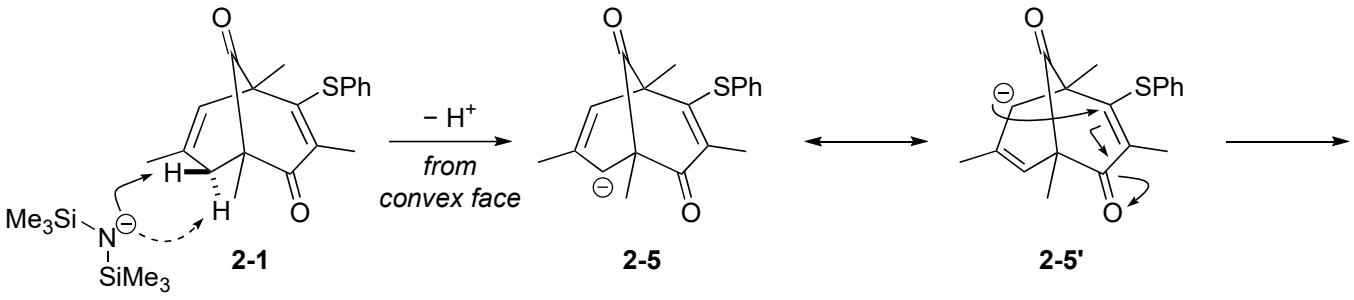
Unlike **1-2** and **1-8**, fluxional structure was not observed in **1-7**. This is because the size of OTIPS is too large to proceed Cope rearrangement. So normal chemical shift are observed in this compound.

2

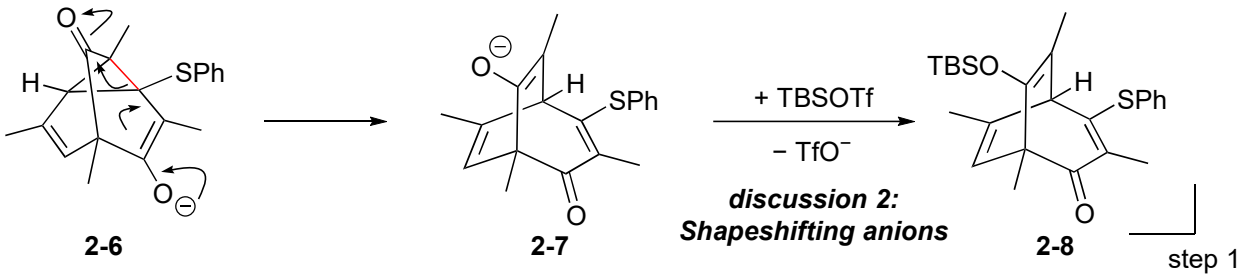


2-1 **2-2** **2-3** **2-4**

Answer:

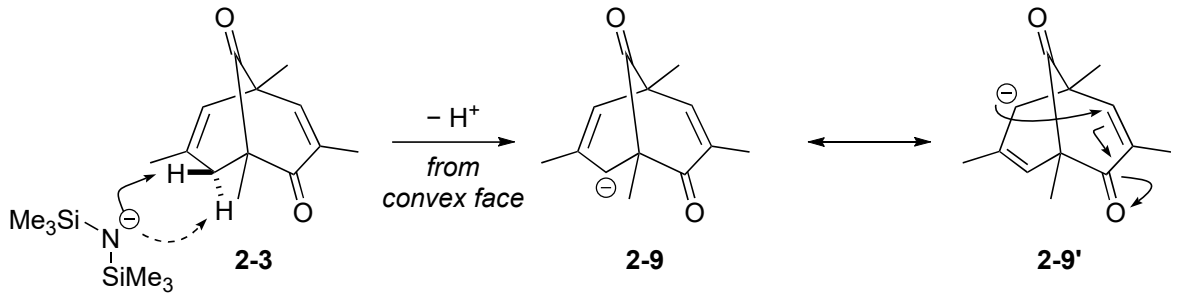


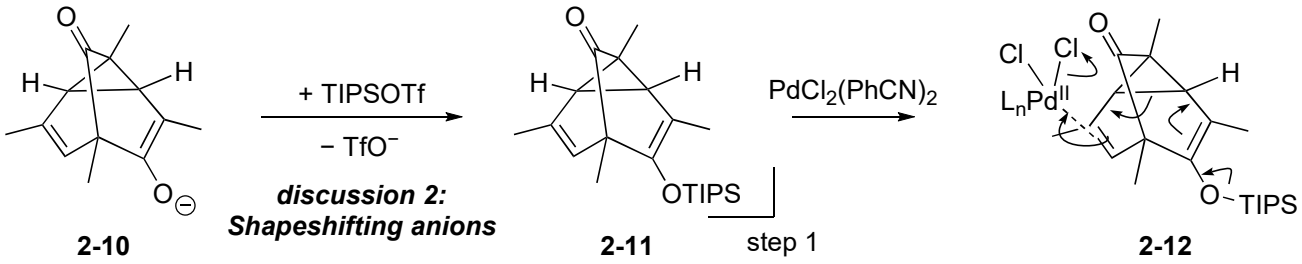
2-1 **2-5** **2-5'**

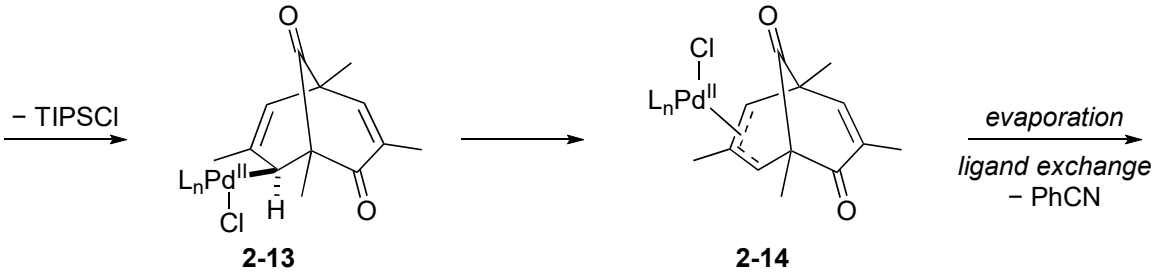


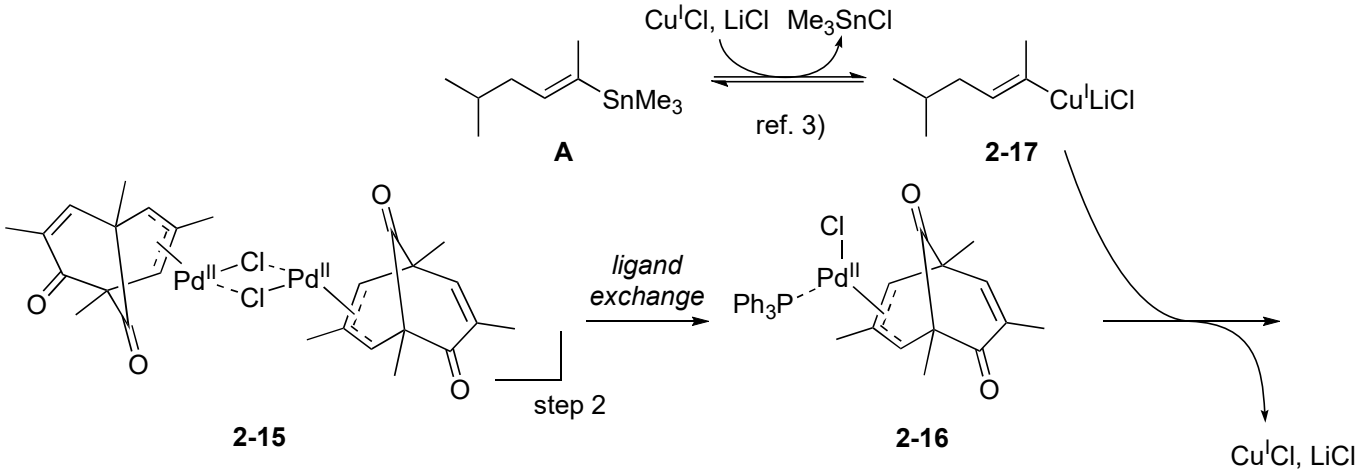
2-6 **2-7** ***discussion 2: Shapeshifting anions*** **2-8**

step 1

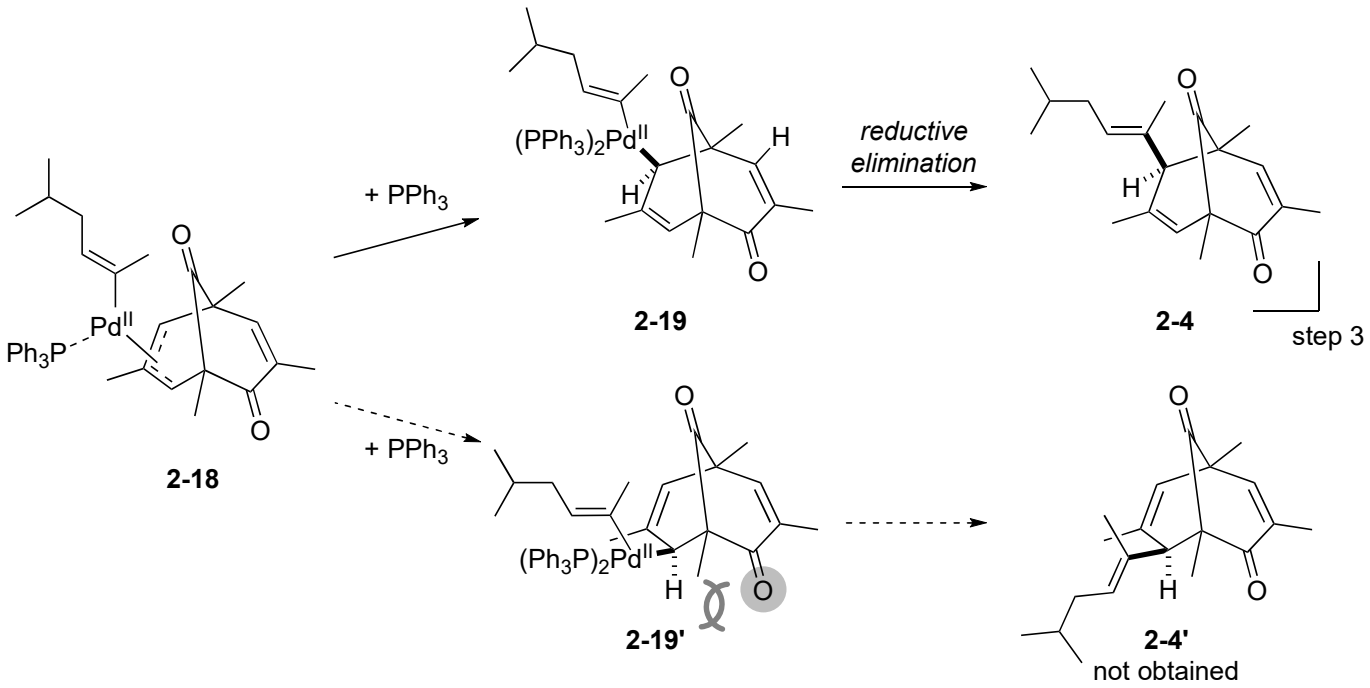




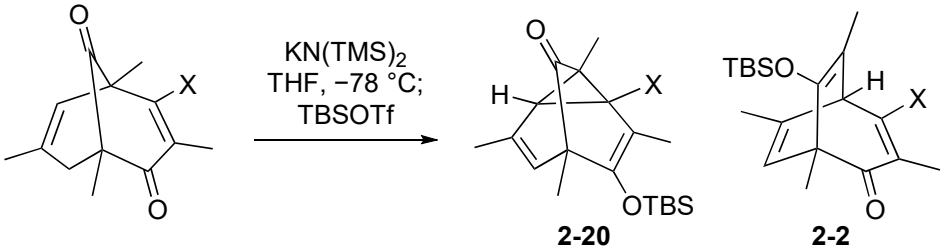




* The Authors say **2-15** must be complexed with PPh_3 prior to addition of **A**, suggesting that **2-16** was generated in the reaction.

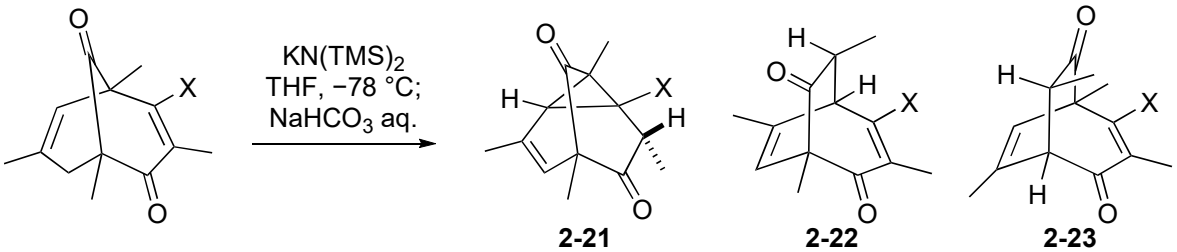


Discussion 2: Shapeshifting anions
2.1. Experimental results



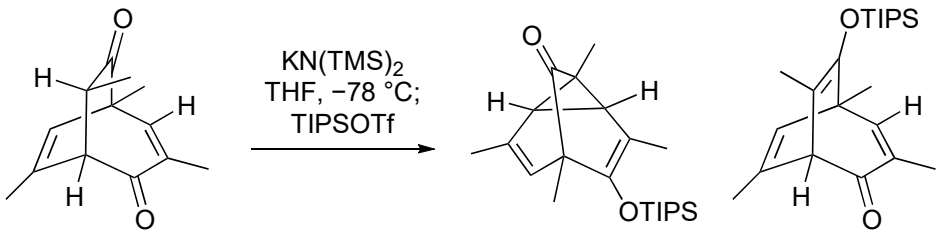
2-1 (X = SPh) **2-3** (X = H)	X = SPh X = H	**2-20** not obtained 70%	**2-2** 80% not obtained

··· (a)



2-1 (X = SPh) **2-3** (X = H)	X = SPh X = H	**2-21** not obtained 16%	**2-22** 40% not obtained	**2-23** not obtained 50%

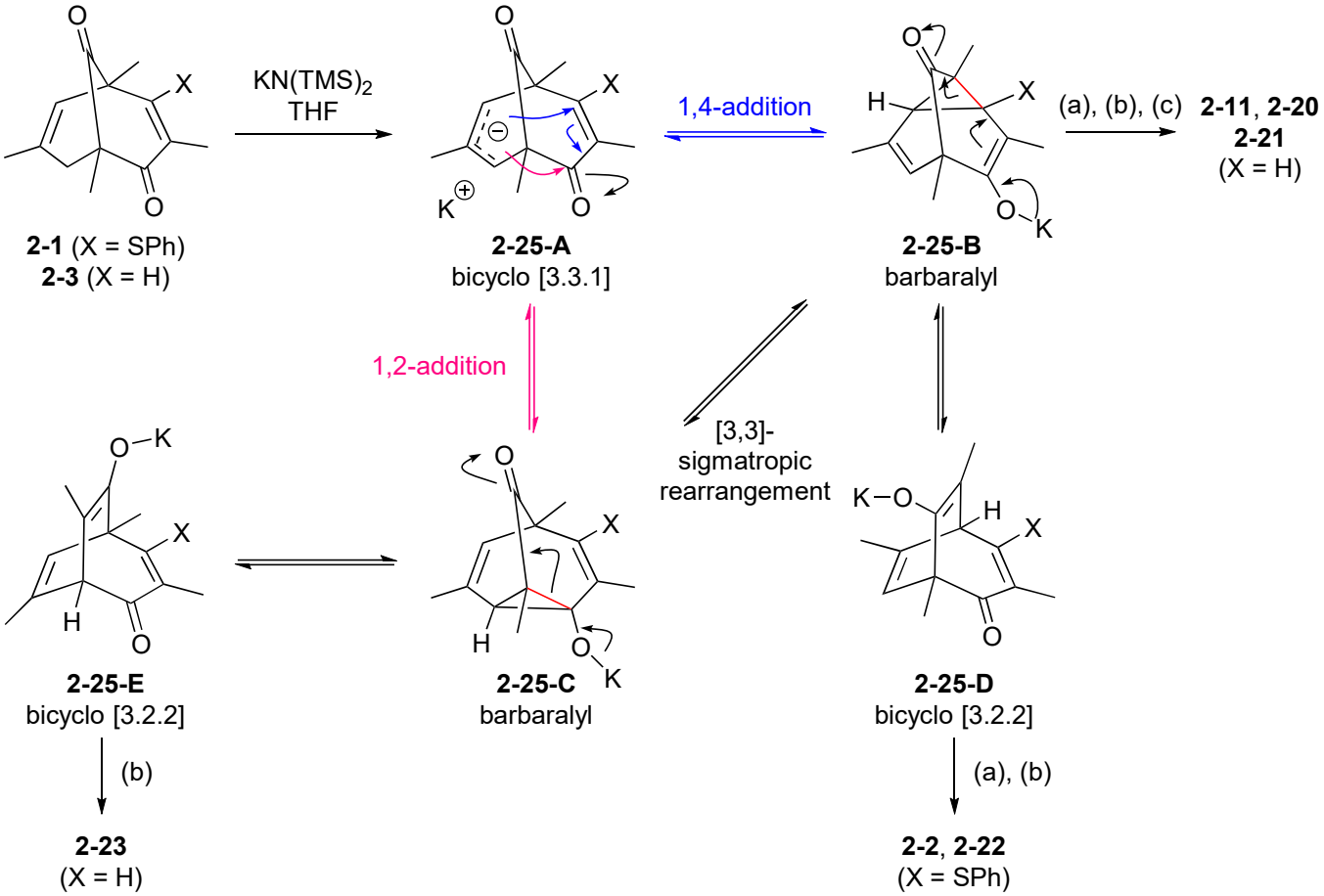
··· (b)



2-23-H		**2-11** 73%	**2-24** not obtained

··· (c)

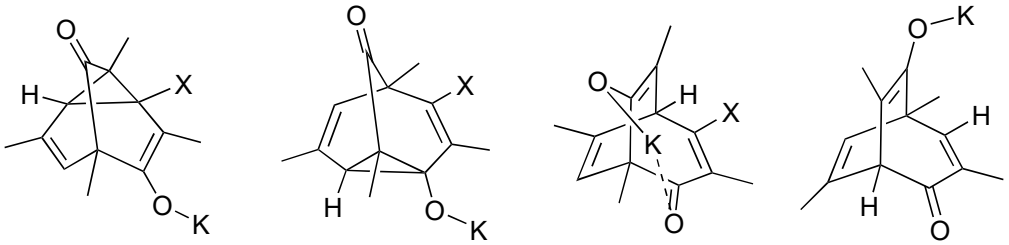
Results (a) and (b) suggest that there exist at least 5 intermediates (**2-25-A** to **E**) from deprotonation of **2-1** or **2-3**. Based on the result (c), an equilibrium should exist between the five isomers, and equilibrium is shifted when different substituent is introduced (X = H: **2-25-B** and **2-25-E** are in favor. X = SPh: **2-25-D** is in favor.)



2.2. Computational calculation

For better understanding, the authors employed DFT calculations for each isomer.

Relative free energy differences of isomeric anions:



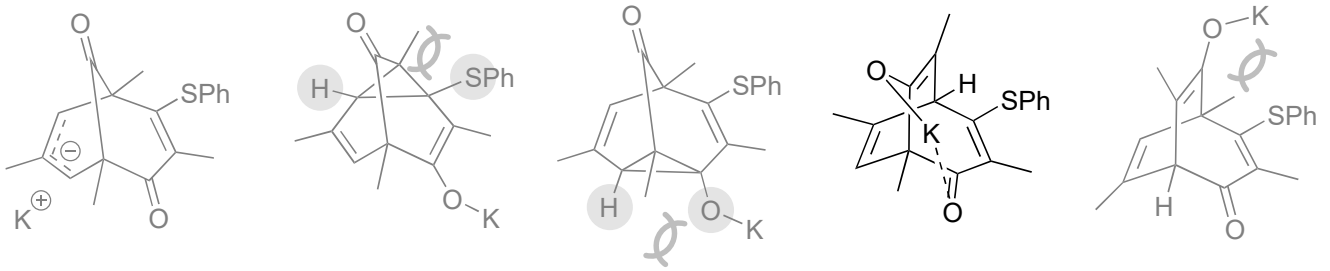
	Δ G° (kcal/mol)			
X	**2-25-B**	**2-25-C**	**2-25-D**	**2-25-E**
SPh	0.0	+7.1	−4.0	+0.4
OMe	0.0	+8.3	−6.6	−3.0
F	0.0	+9.2	−3.3	−3.3
H	0.0	+8.2	+0.3	−0.9
CN	0.0	+4.5	−1.7	−2.5

* calculated at B3LYP-D3(BJ)/6-311+G(d,p)/PCM(THF)//B3LYP-D3(BJ)/6-31+G(d,p)/PCM(THF) at 195 K

Calculations showed that the chelating form is the most stable conformer of **2-25-D**. When X is an electron-donating substituent (e.g., SPh, OMe), the stabilizing effect of chelation is enhanced, making **2-25-D** the most stable of the five isomers.

On the other hand, when X is an electron-withdrawing substituent, this stabilizing effect is weaken, making **2-25-D** less stable. As a result, **2-25-E** became the most stable conformer (X = CN).

2.3. In case of **2-1** (X = SPh)



2-25-A-SPh
(disfavored)
(allylic anion)

2-25-B-SPh
(disfavored)
ΔG^o = 0.0 kcal/mol

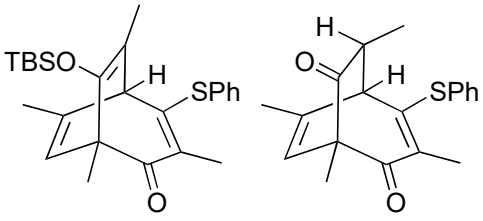
2-25-C-SPh
(disfavored)
ΔG^o = +7.1 kcal/mol

2-25-D-SPh
(favored)
ΔG^o = −4.0 kcal/mol

2-25-E-SPh
(unfavored)
ΔG^o = +0.4 kcal/mol

(a), (b)

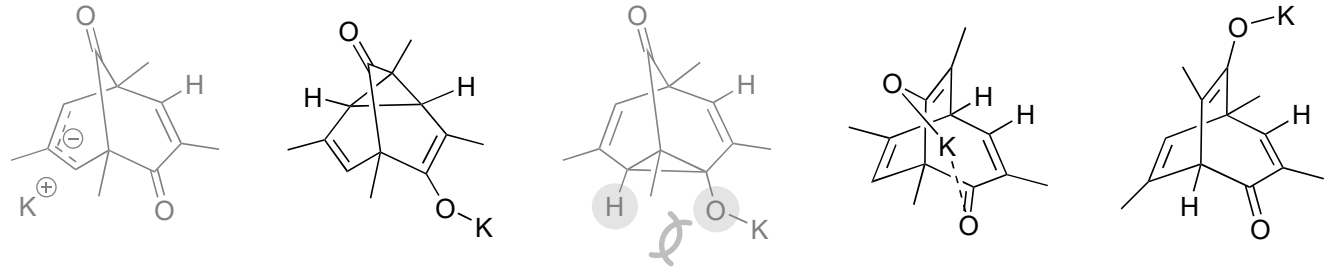
no further reaction proceeds



2-2 **2-22**

2-25-A, **2-25-B** and **2-25-C** are thought to be disfavored due to unstable allylic anion (**A**) or large steric repulsion between highlighted atoms of cyclopropane (**B** and **C**).
2-25-D is more favored in comparison with **2-25-E**, because potassium enolate can be stabilized by adjacent carbonyl groups in the presence of electron donating group, SPh.
Calculation suggests that **2-25-D** is by far the most stable isomer, so the anions are present almost only in the form of **2-25-D-SPh** during the reaction, yielding **2-2** or **2-22** as a major product.

2.4. In case of **2-3** (X = H)



2-25-A-H
(disfavored)
(allylic anion)

2-25-B-H
(favored)
ΔG^o = 0.0 kcal/mol

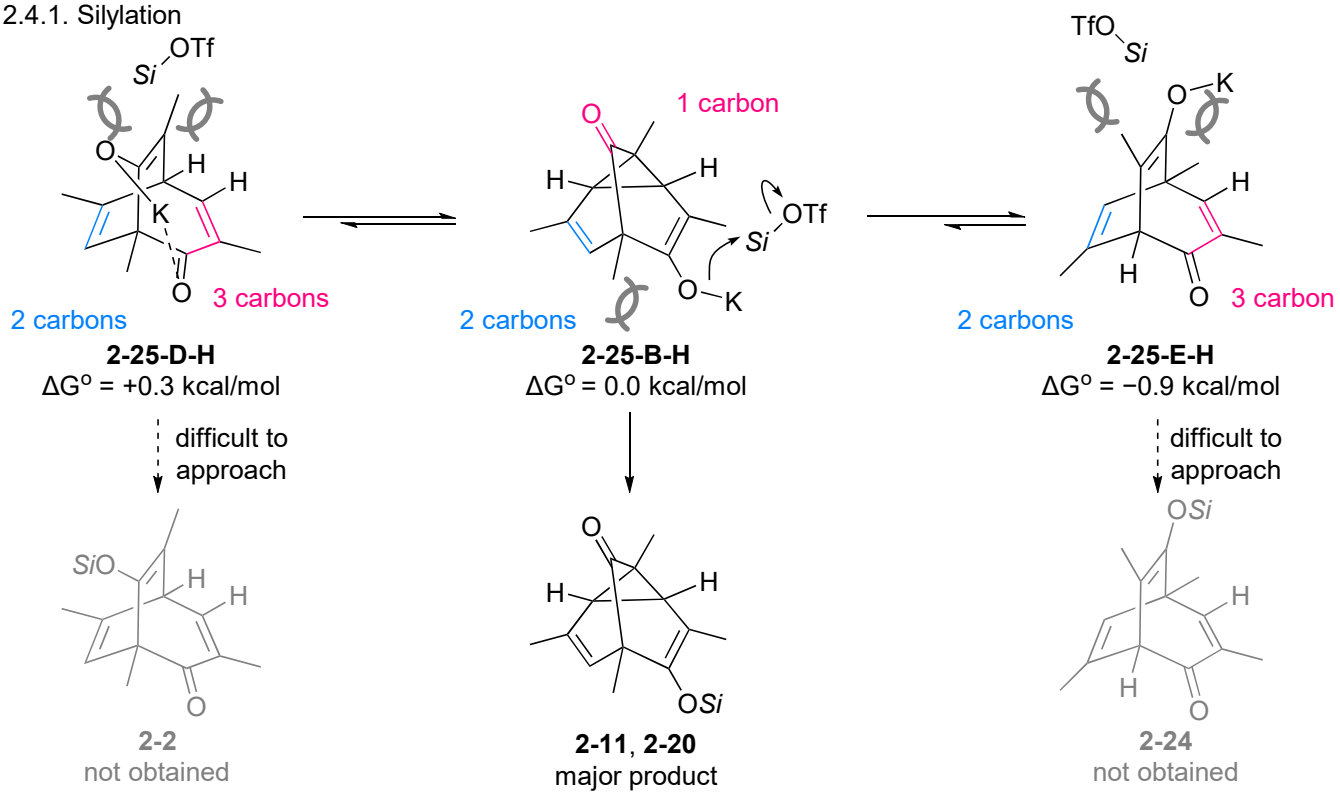
2-25-C-H
(disfavored)
ΔG^o = +8.2 kcal/mol

2-25-D-H
(favored)
ΔG^o = +0.3 kcal/mol

2-25-E-H
(favored)
ΔG^o = −0.9 kcal/mol

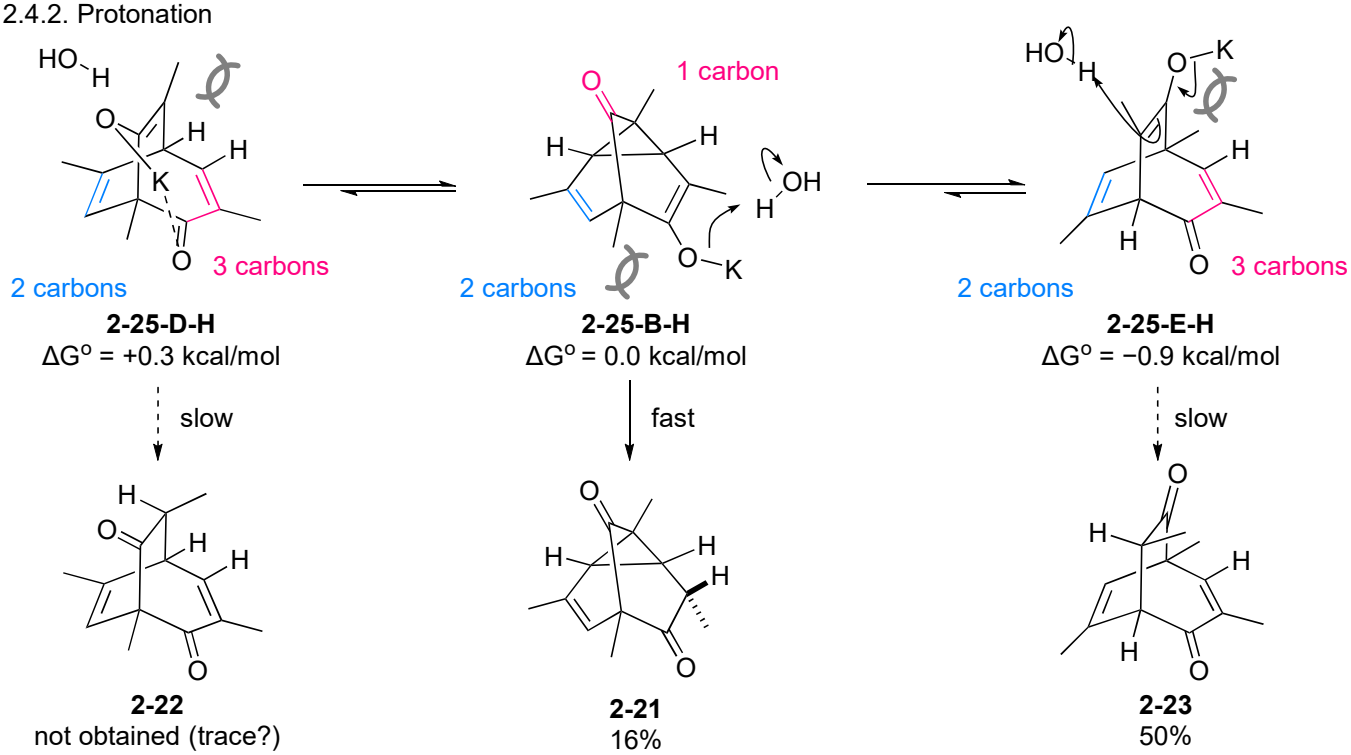
2-25-B, **2-25-D** and **2-25-E** are in favor. Calculation shows that there are only small energy differences among these 3 isomers, so there are 3 isomers in the reaction mixture.

2.4.1. Silylation



The α and β faces of enolate are shielded in all isomers. Among them, the β-face of **2-25-B-H** is relatively uncrowded because it has only one sp^2 carbon (the others have two or three sp^2 carbons). SiOTf is too large to access to the other faces, so silyl etherification proceeds only from the β-face of **2-25-B-H**, with **2-11** (X = TIPS) or **2-20** (X = TBS) being obtained as a major product.

2.4.2. Protonation



Compared to *Si*OTf, proton is small, so protonation can be proceed from all of 3 isomers. **2-24-E-H** is the most stable conformer, but the protonation is relatively slow because of steric hindrance. **2-24-B-H** is the second most stable conformer, and the protonation is faster than from **2-24-E-H**. As a result, **2-21** was obtained as well as **2-23**. (If ΔG° = 0.9, the ratio of **2-24-B-H**: **2-24-E-H** would be 18: 82).

Reference:

1) Sanchez, A.; Maimone, T. J. *J. Am. Chem. Soc.* **2022**, *144*, 7594.
2) von E. Doring, W.; Ferrier, B. M.; Fossel, E. T.; Hartenstein, J. H.; Jones, M.; Klumpp, G.; Rubin, R. M.; Saunders, M. *Tetrahedron* **1967**, *23*, 3943.
3) Han, X. J.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.