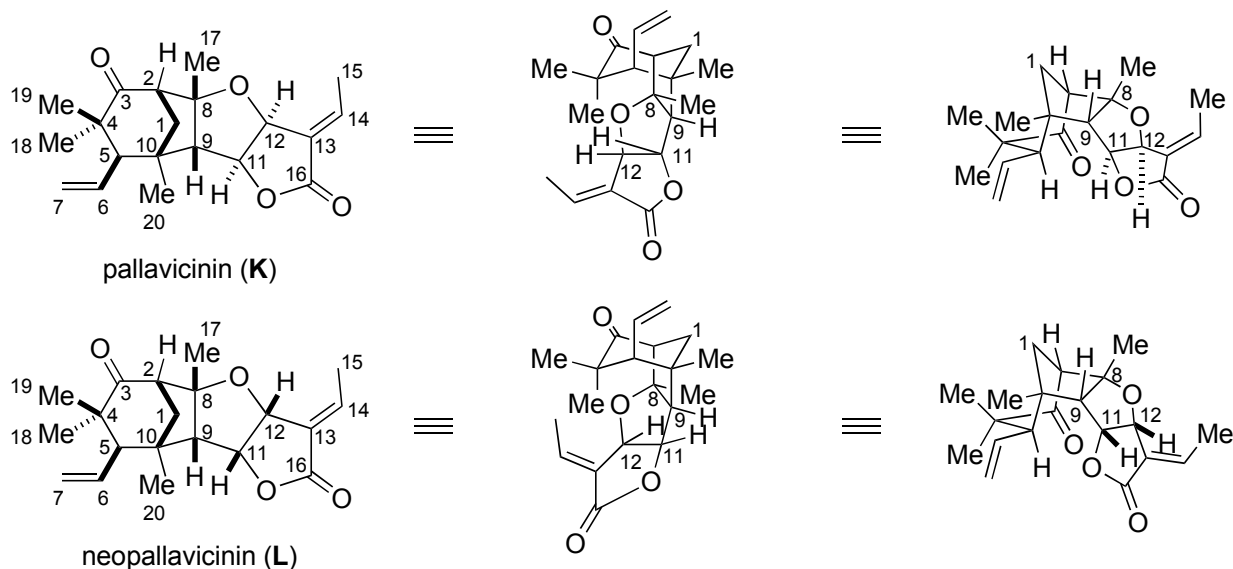


Topic: Total synthesis of pallavicinin and neopallavicinin



First isolation of pallavicinin: Taiwanese liverwort *Pallavicinia subciliata*
(Wu, C. L.; Liu, H.-J.; Uang, H.-L. *Phytochemistry* **2004**, 65, 623.)

First isolation of neopallavicinin: Chinese liverwort *Pallavicinia ambigua*
(Liu, H.-J.; Wu, C.-L. *J. Asian Nat. Prod. Res.* **1999**, 1, 177.)

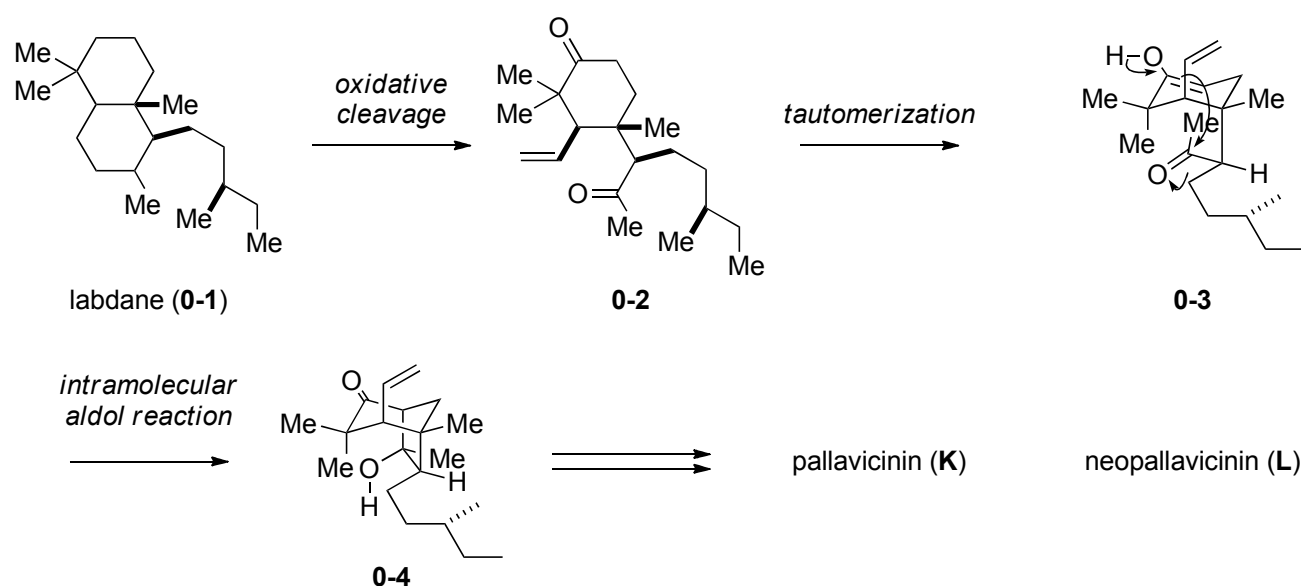
Determination of the absolute configurations: single X-ray diffraction and CD analysis
(Li, Z.-J.; Lou, H.-X.; Yu, W.-T.; Fan, P.-H.; Ren, D.-M.; Ma, B.; Ji, M. *Helv. Chim. Acta* **2005**, 88, 2637.)

Structural features: 6/5/5/5 tetracyclic skeleton
bicyclo[3,2,1] moiety (Please see Kawamata-kun's PS on 2013/0511)
7 contiguous stereocenters (1 quaternary carbon)

Total syntheses: Peng, X.-S.; Wong, H. N. C. *Chem. Asian. J.* **2006**, 1-2, 111. (racemic) →problem 1
Huang, B.; Guo, L.; Jia, Y. *Angew. Chem. Int. Ed.* **2015**, 54, 13599. (enantiomer of natural products)
→problem 2

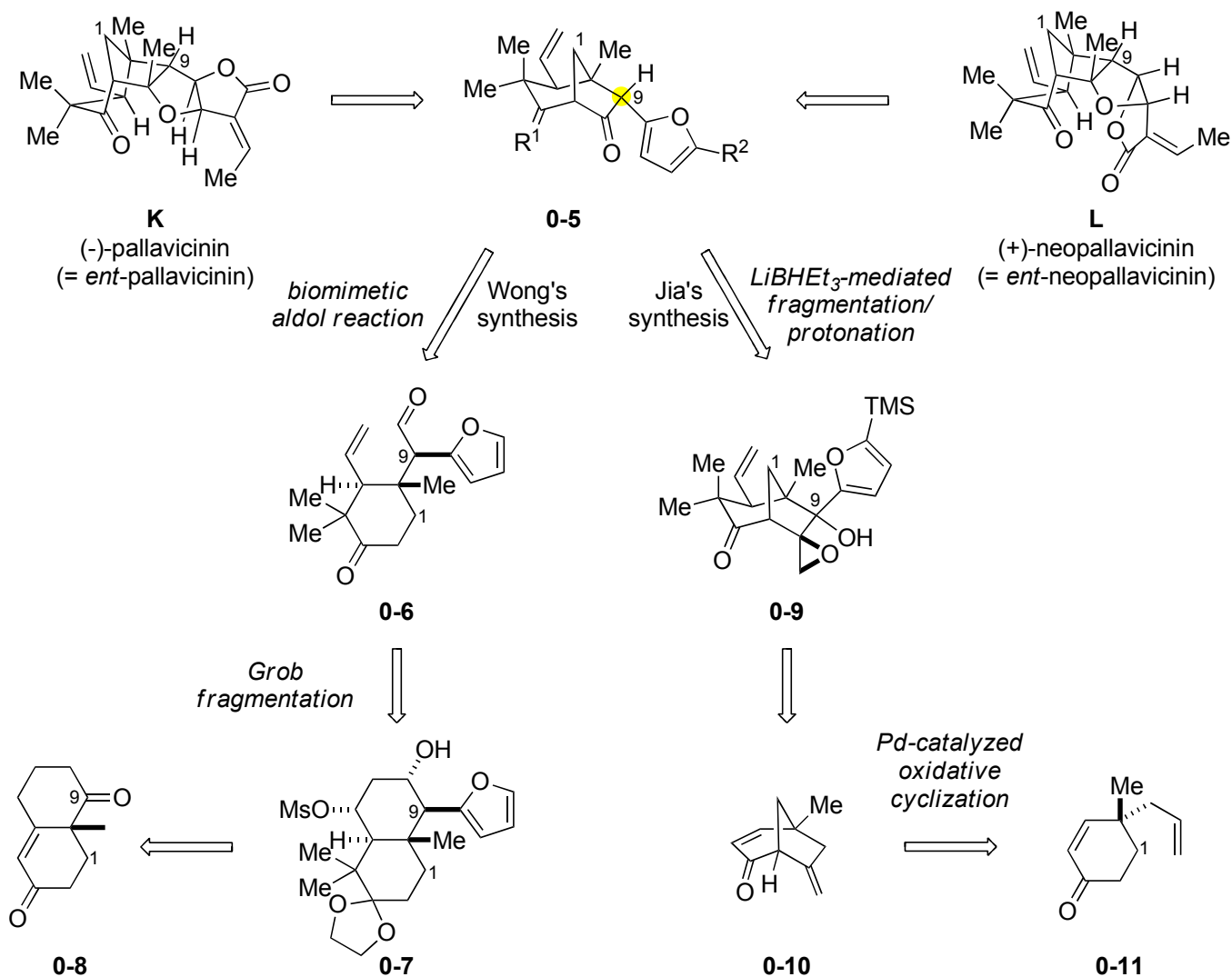
Synthetic study: Hardin-Narayan, A. R. *PhD Thesis*, University of California, Berkeley, **2011**. (Prof. Sarpong's group)

•Proposed biosynthesis



•Retrosynthetic analysis

Note: All compounds below are drawn in enantiomeric form of natural products.



(1) Please predict the structure of **B**.

A

1) *n*-Bu₄NF, THF, rt
 2) KO*t*-Bu, 18-crown-6, *t*-BuOH, 45 °C
 56% (2 steps)

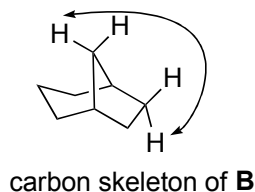
3) TsOH·H₂O (cat.), acetone, rt
 4) NaO*t*-Bu, *t*-BuOH, 60 °C
 5) IBX, CH₂Cl₂, rt
 56% (3 steps)

B

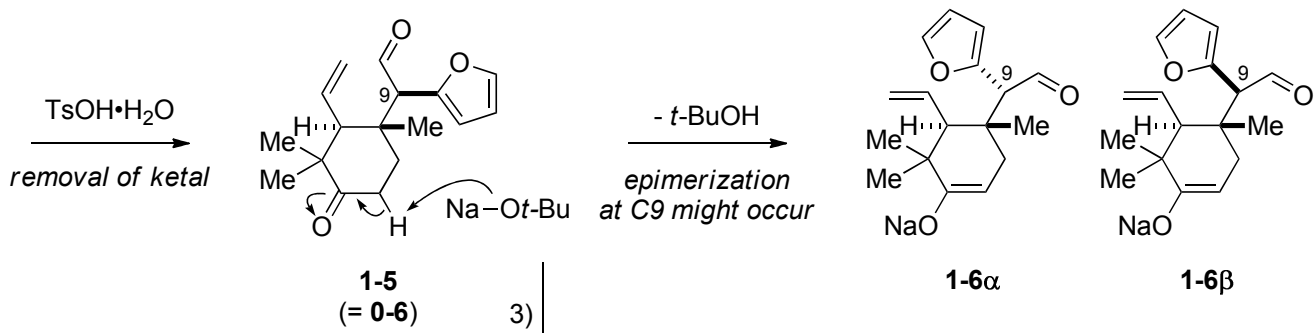
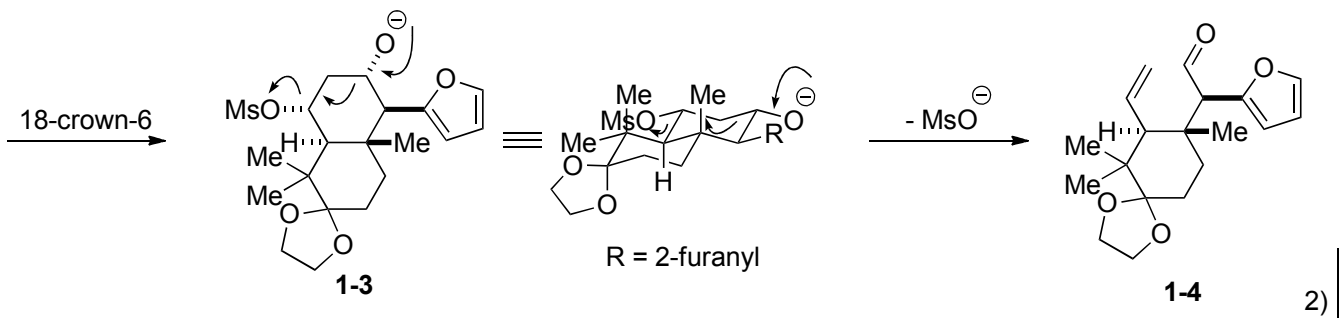
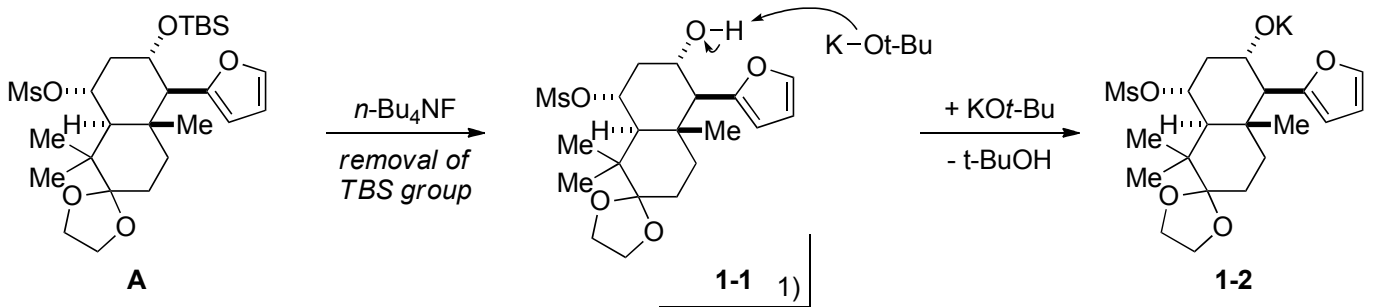
B'

B: authors' proposal
B': my proposal

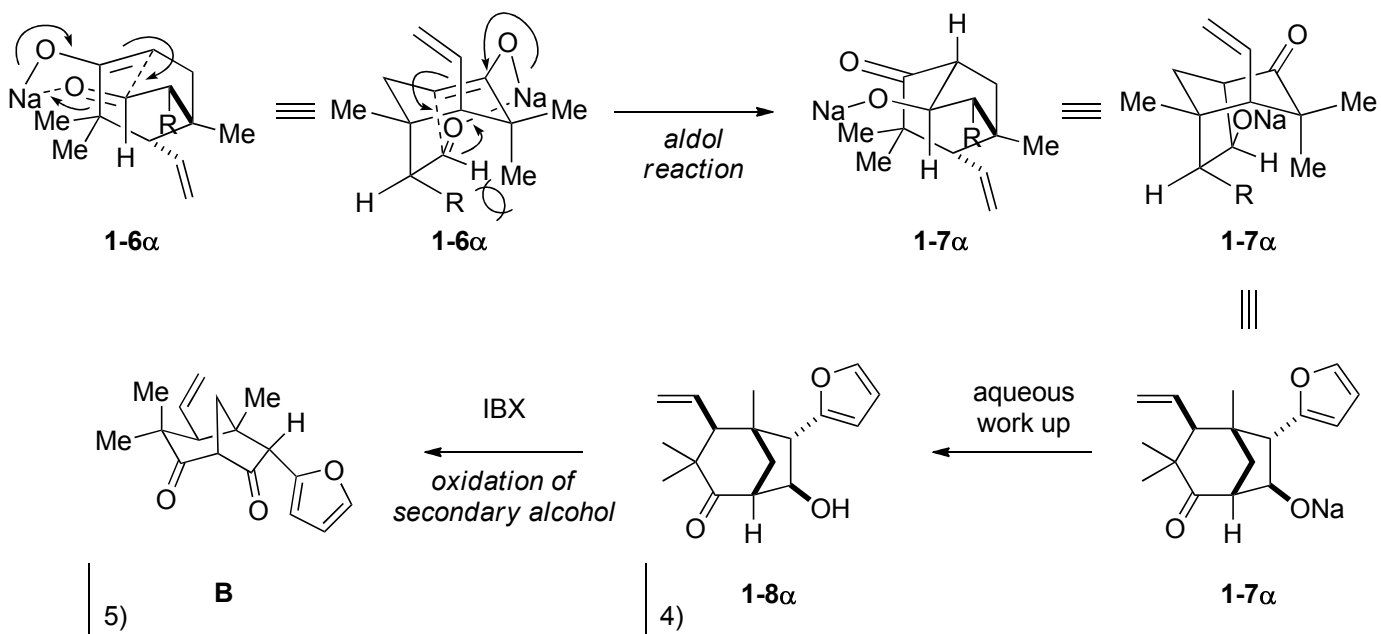
Authors say there is a W-type coupling correlation between 1-H and 9-H in **B**, but...



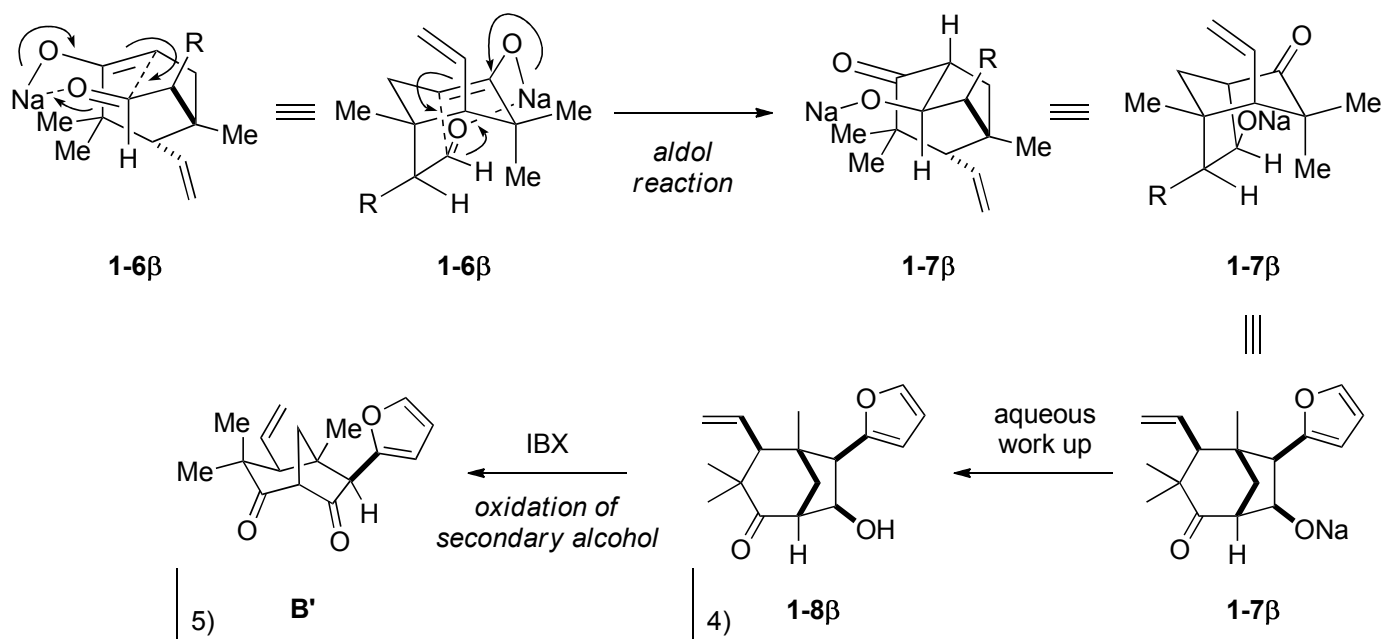
if there is a W-shape coupling, coupled protons should be shown ones.



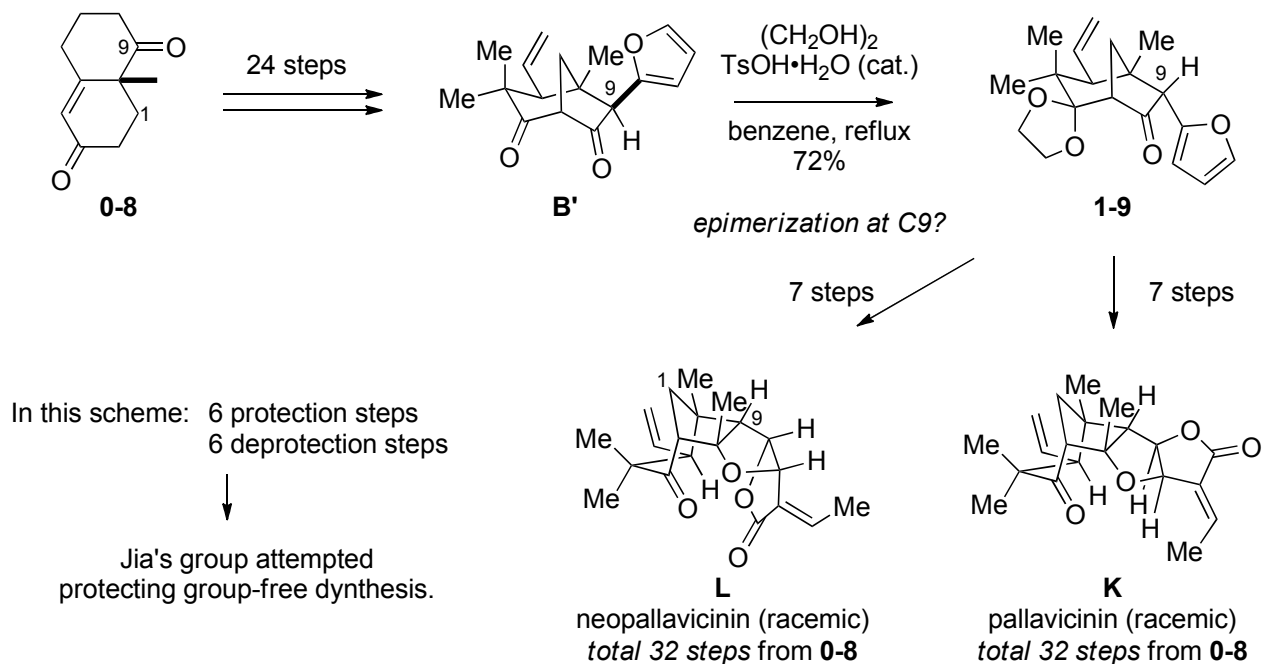
From **1-6α** (R = 2-furanyl)



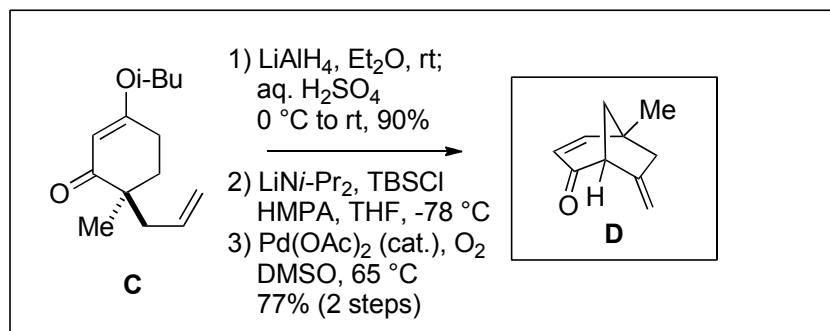
From **1-6 β**



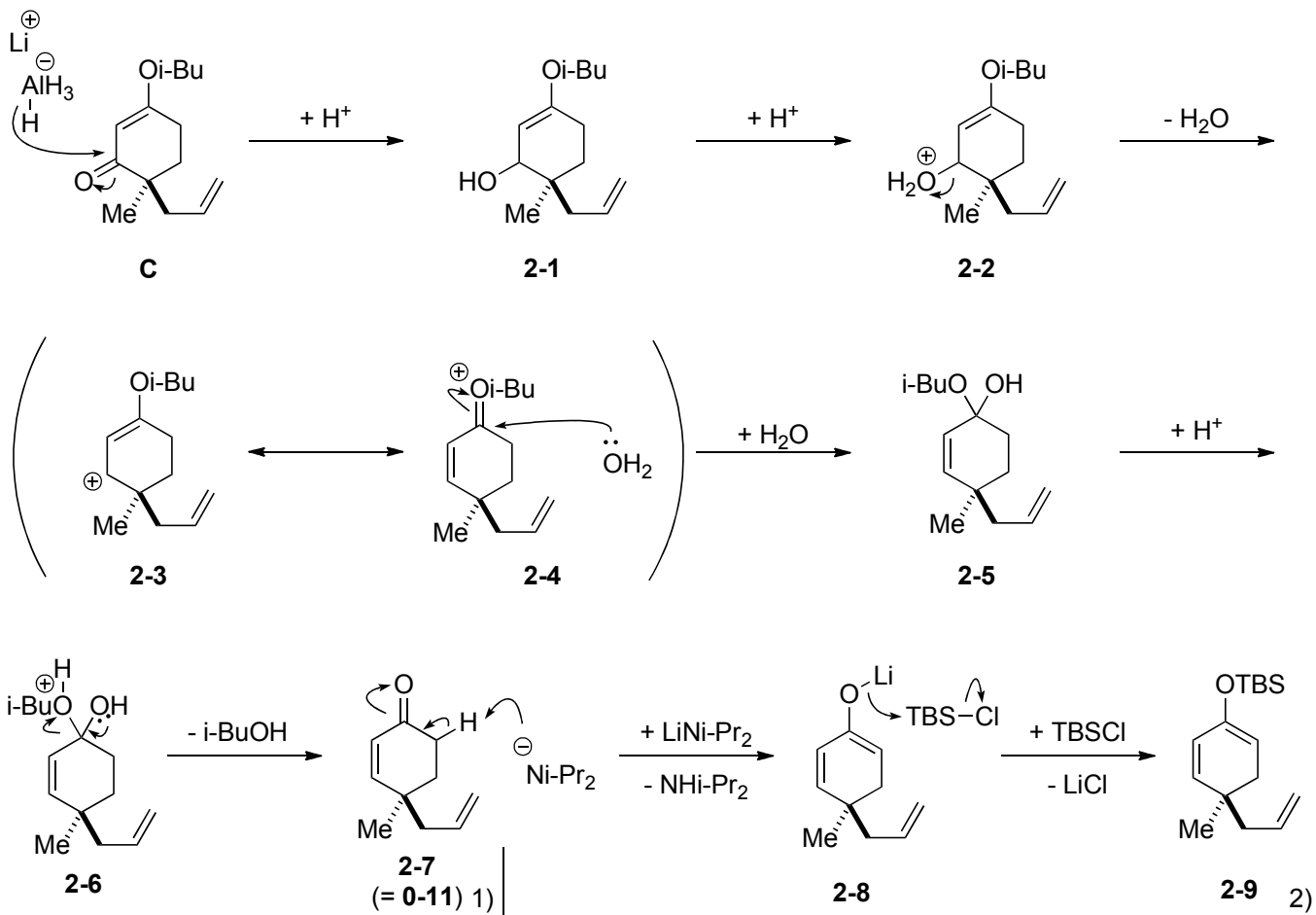
•Wong's synthesis



(2) **C** to **D**

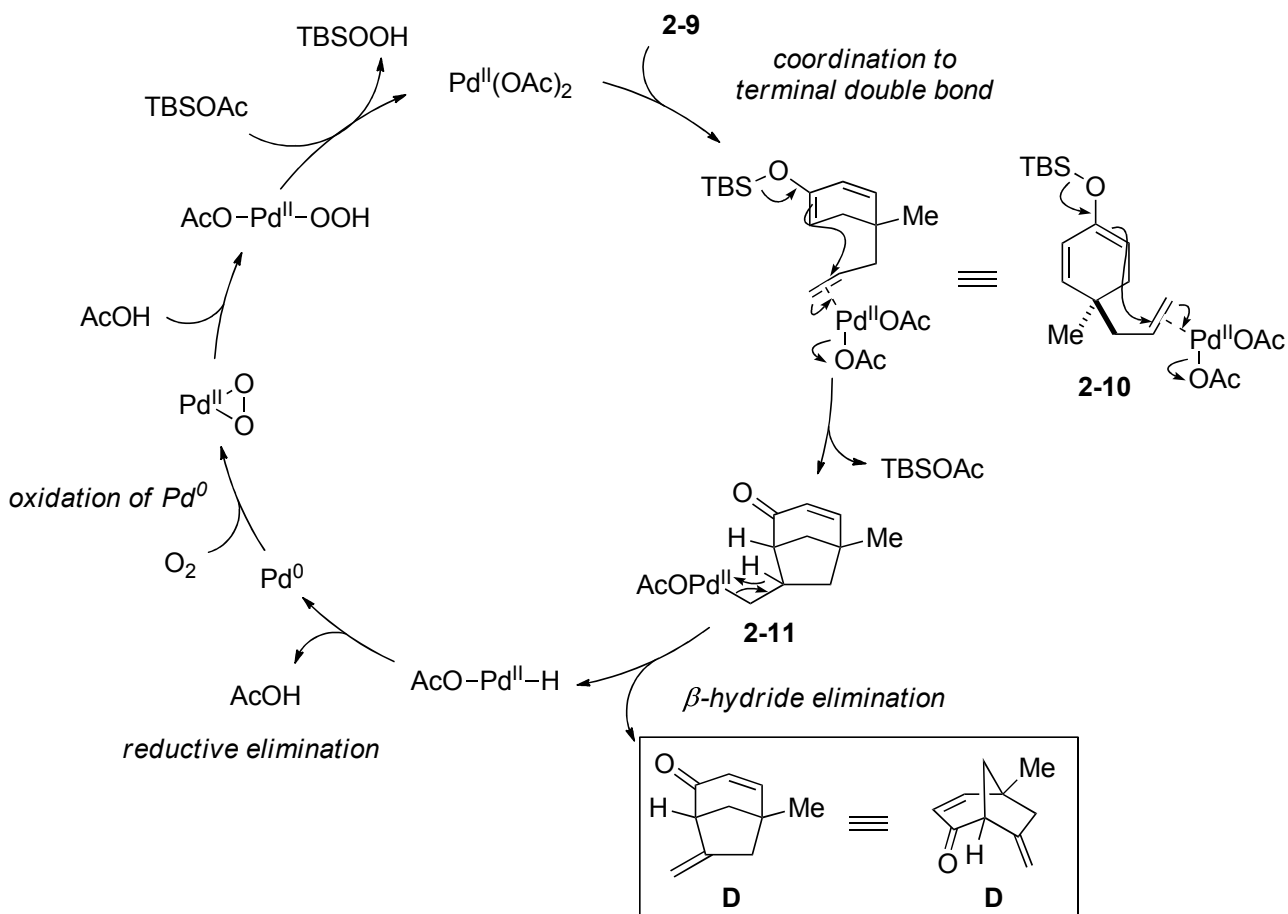


Key step: Pd-catalyzed oxidative cyclization

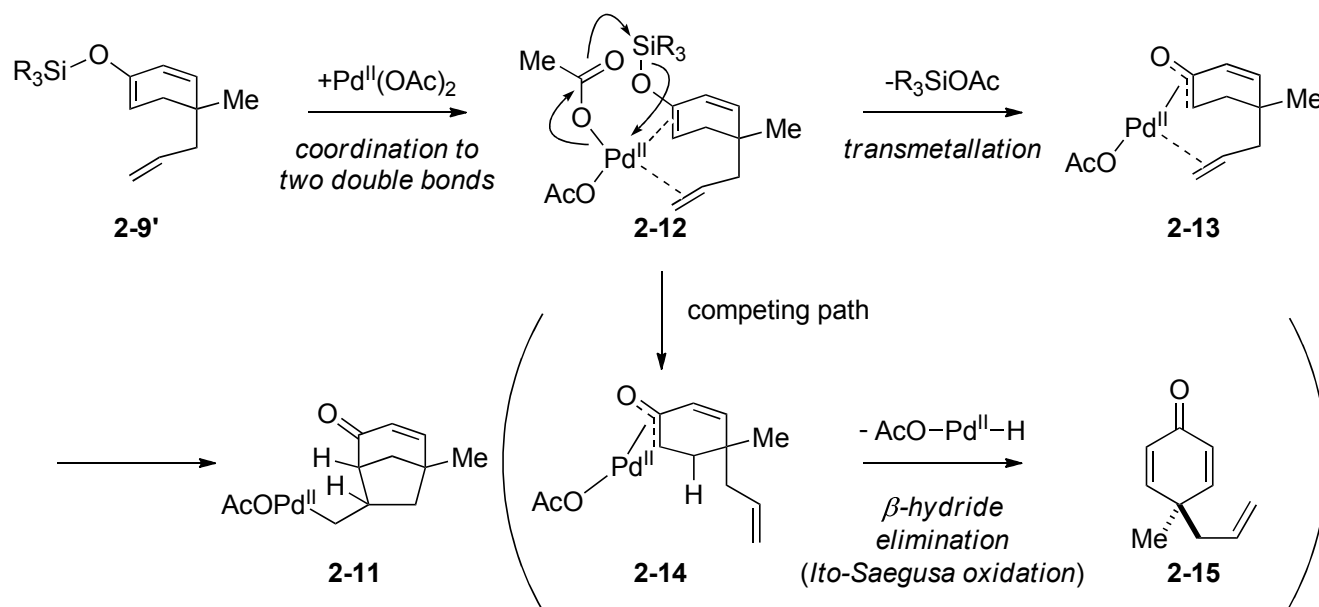


HMPA might reduce the aggregation state of this lithium enolate.

•Cycle of Pd-catalyzed oxidative cyclization (path a)



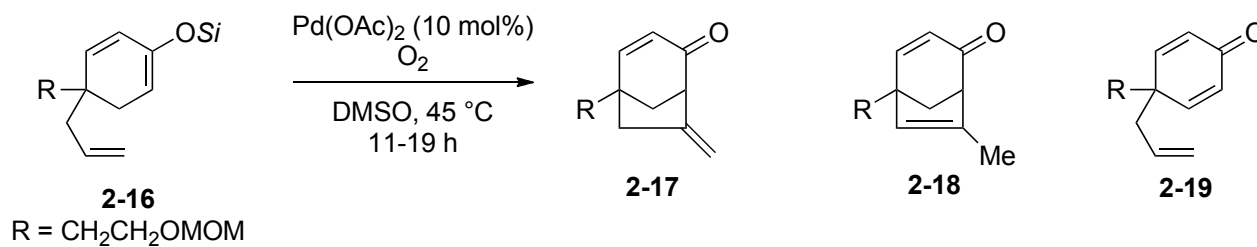
•Alternative path from **2-9** to **D** (path b)



In case of bulkier silyl group (TBS), transmetallation becomes slower.

→ Above reaction mechanism (path a) is more plausible.

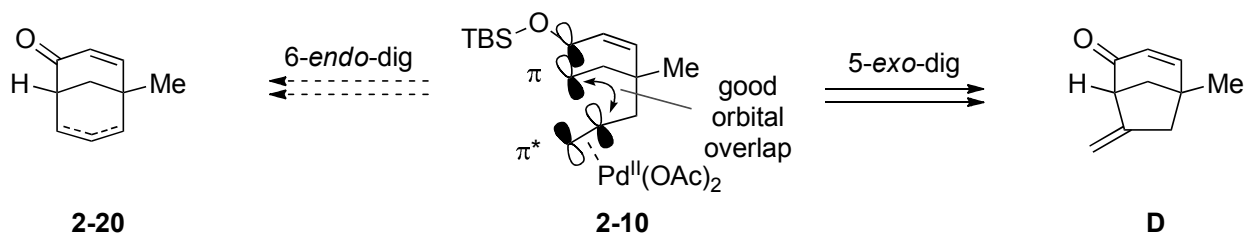
•Effect of silyl group



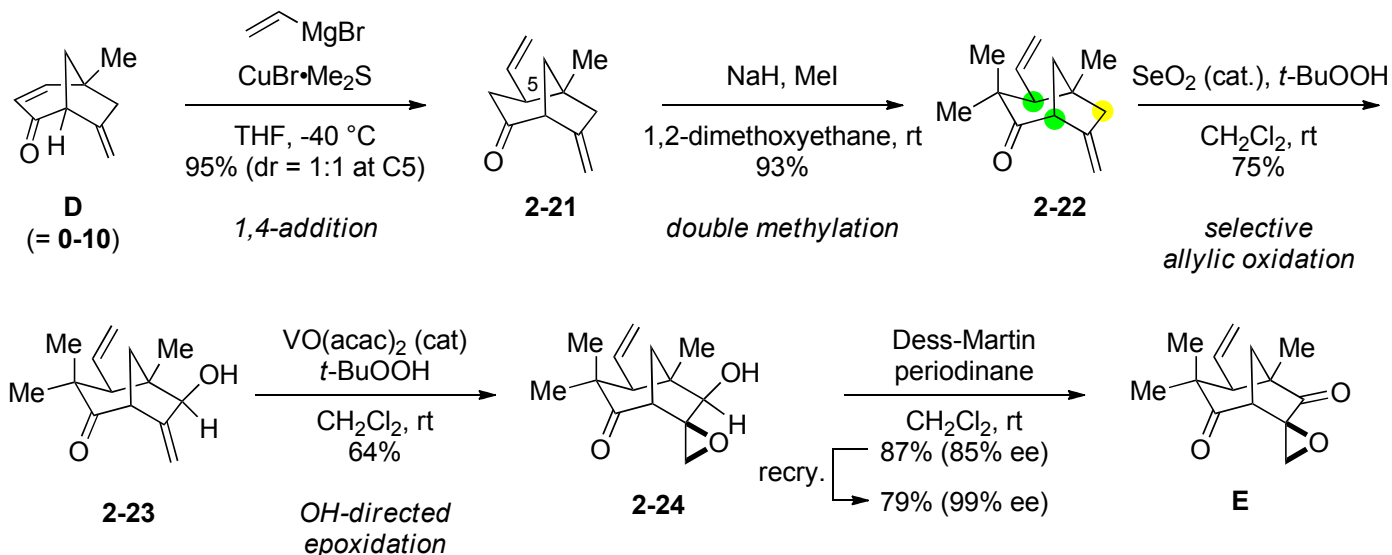
entry	Si	yield		
		2-17	2-18	2-19
1	TMS	62%	trace	21%
2	TES	76%	trace	14%
3	TBS	81%	4%	5%

Toyota, M.; Ihara, M. *Synlett* **2002**, 1211.

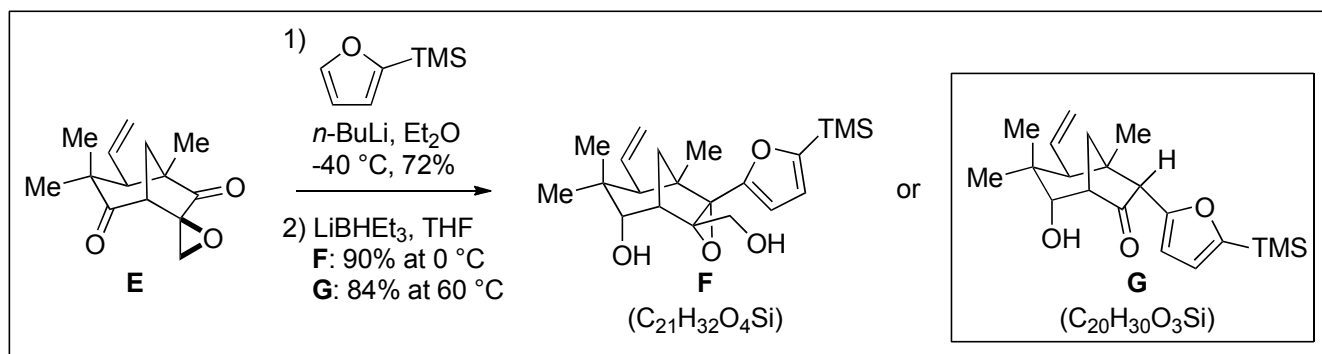
•5-*exo* vs 6-*endo*



•Scheme from **D** to **E**

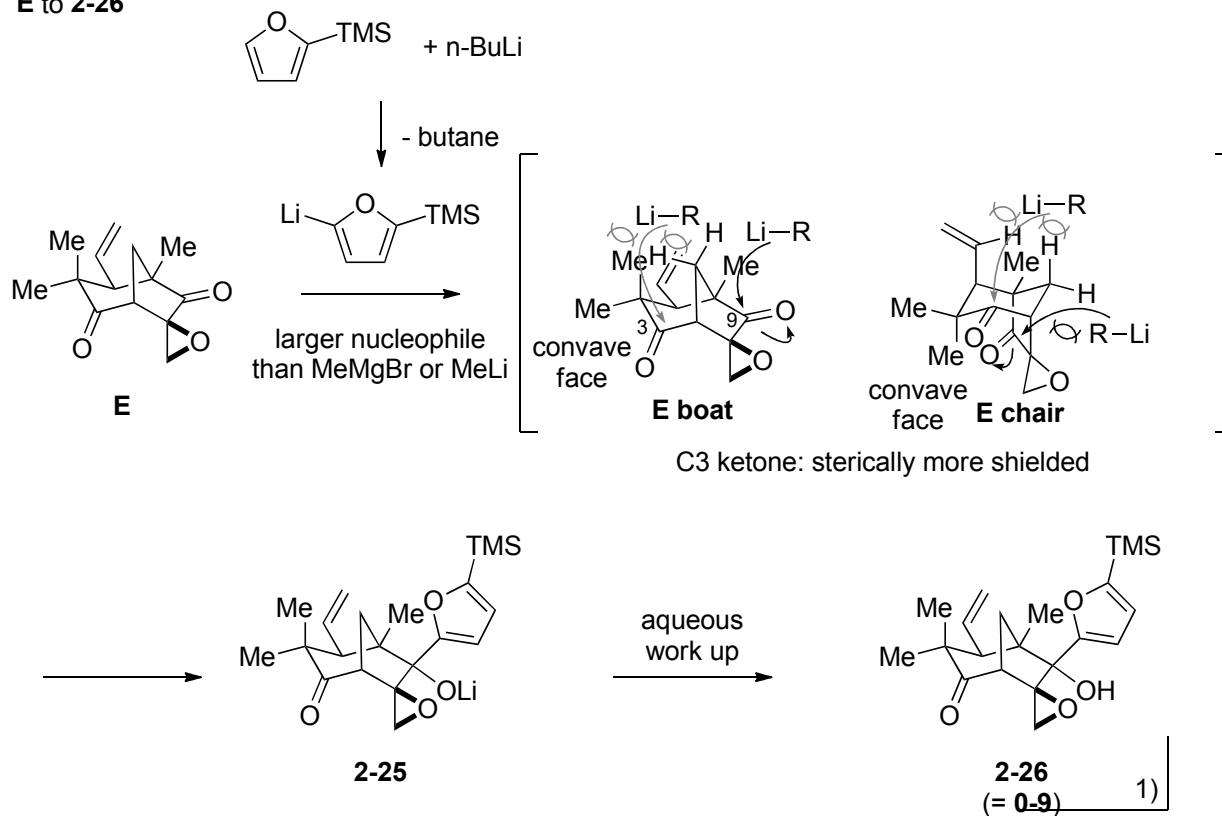


•**E** to **F** and **G**

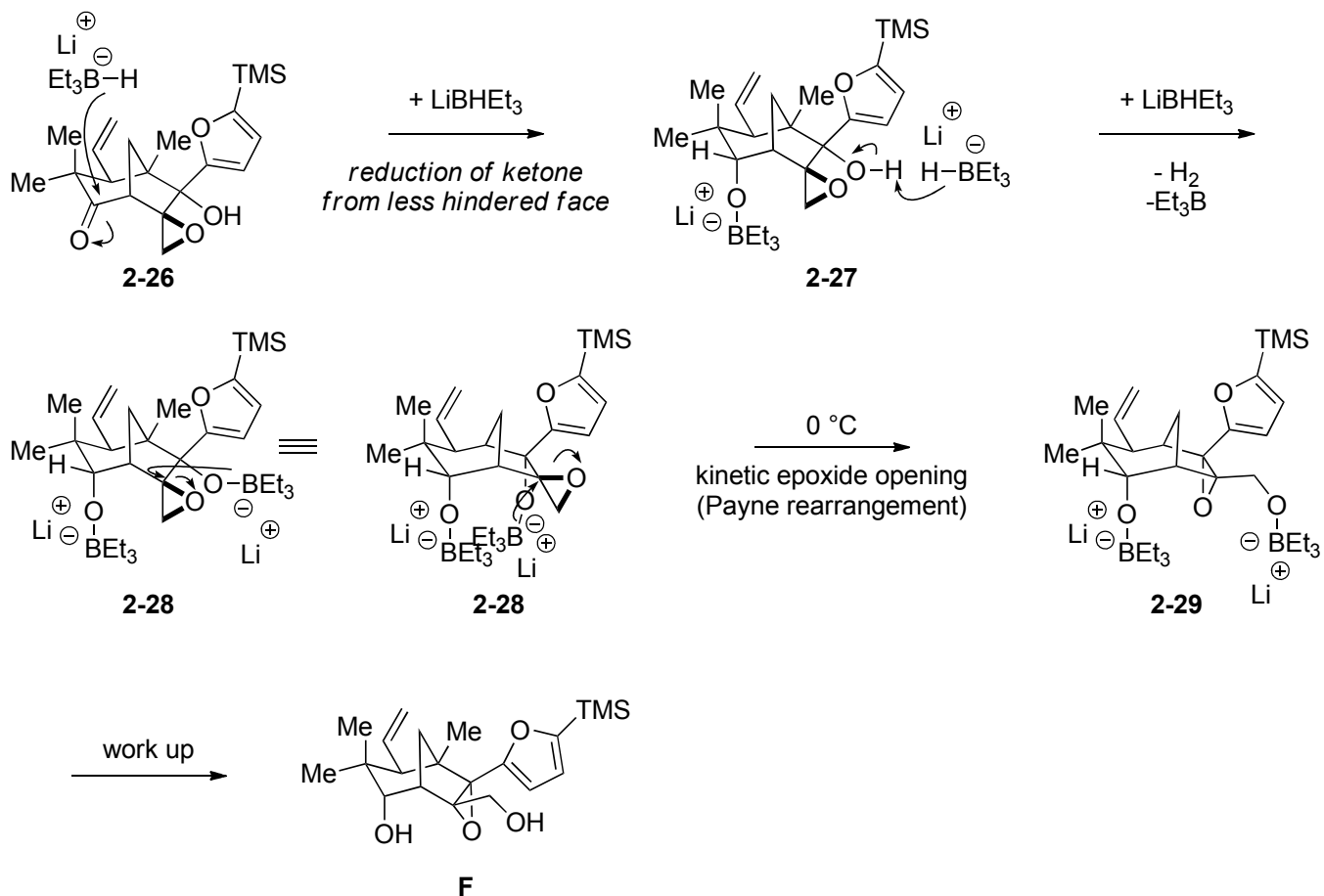


Key step: LiBHET_3 -mediated fragmentation/protonation

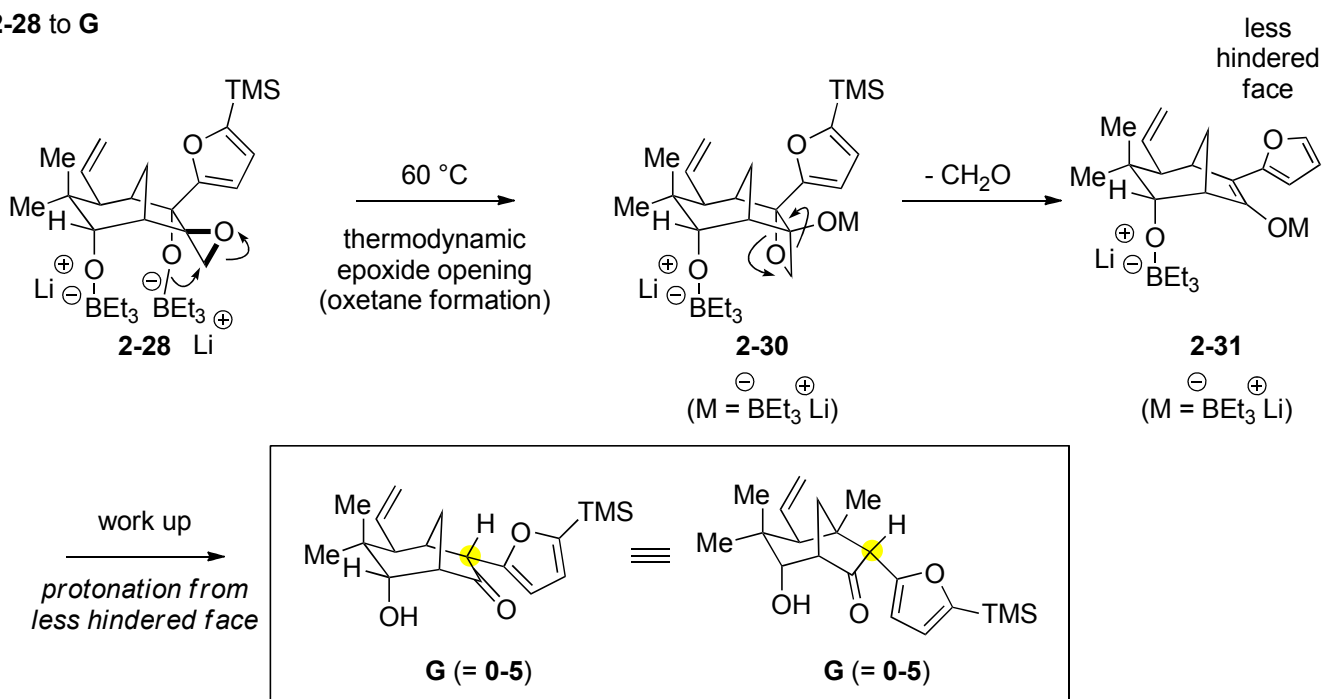
E to **2-26**



2-26 to F

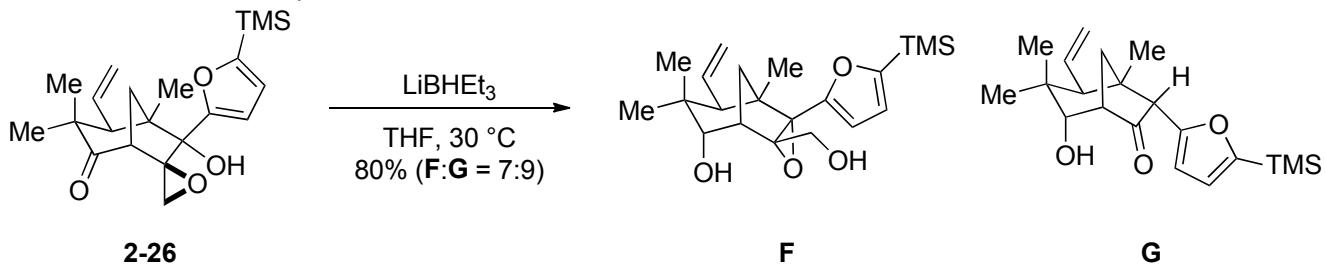


2-28 to G

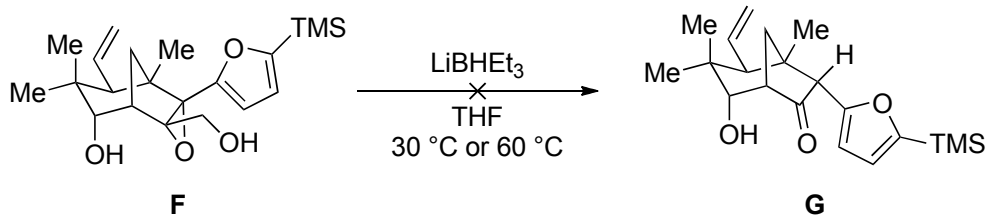


•Experimental results

Generation of **F** and **G** completed at 30 °C.



F did not convert to **G**

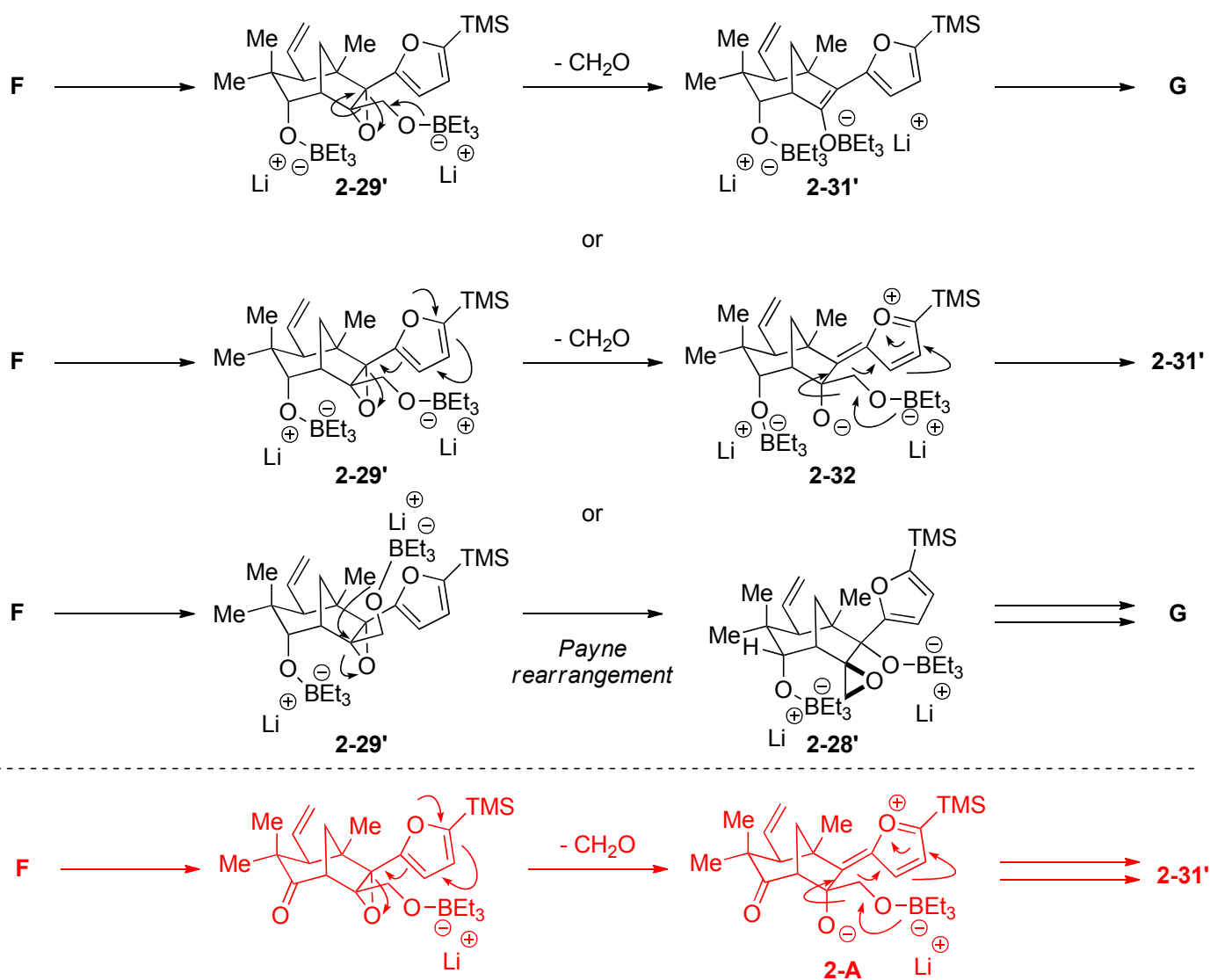


→**F** is not the exact precursor of **G**. The generation of **G** seemed not to be under thermodynamic control.

But this reaction is not suitable as a negative control.

There is the possibility that reduction of ketone occurred after **2-A** was formed.

From this result reactions below did not occur. (Author's claim)



•Validity of oxetane intermediate.

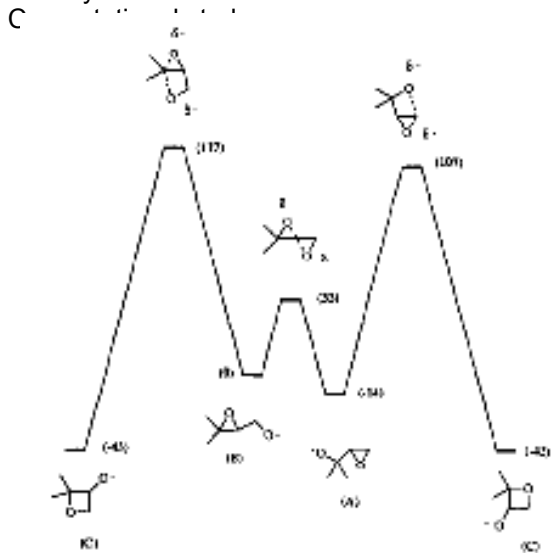


Fig. 1. Ab initio [G2 (MP2) 0K] calculations (Gaussian 94) for the interconversions of A, B and C. Energies in kJ mol^{-1} . Details of geometries of A, B, C and the three transition states, see Table 1.

Equilibrium between **2-33** and **2-34** seems to be very fast. Activation energies to oxetanolate from epoxy alkoxide are very high, but oxetane intermediate might exist in this condition.

collisional activation mass spectra

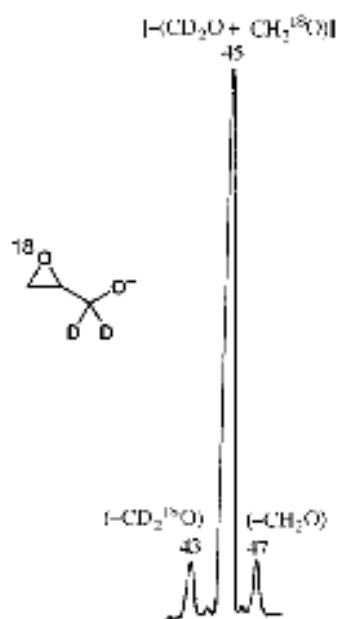
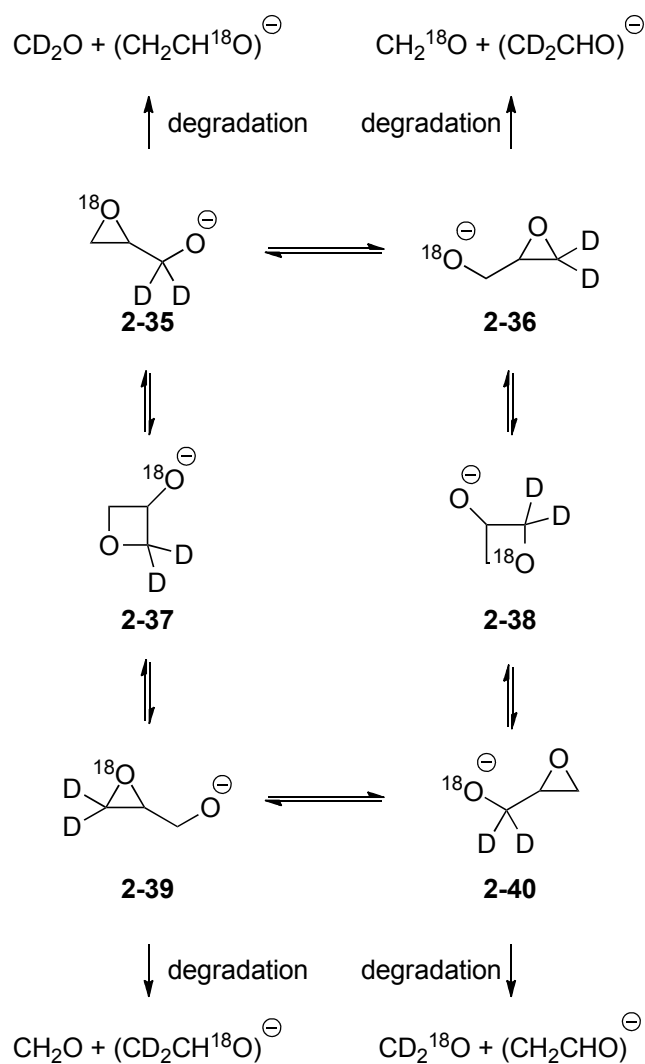


Fig. 4 Partial MS/MS data for the 2,3 $[^{18}\text{O}]$ epoxy[1,1- $^2\text{H}_2$]propoxide anion. VG ZAB 2HF instrument.

collisional activation mass spectra of X
(gas phase)



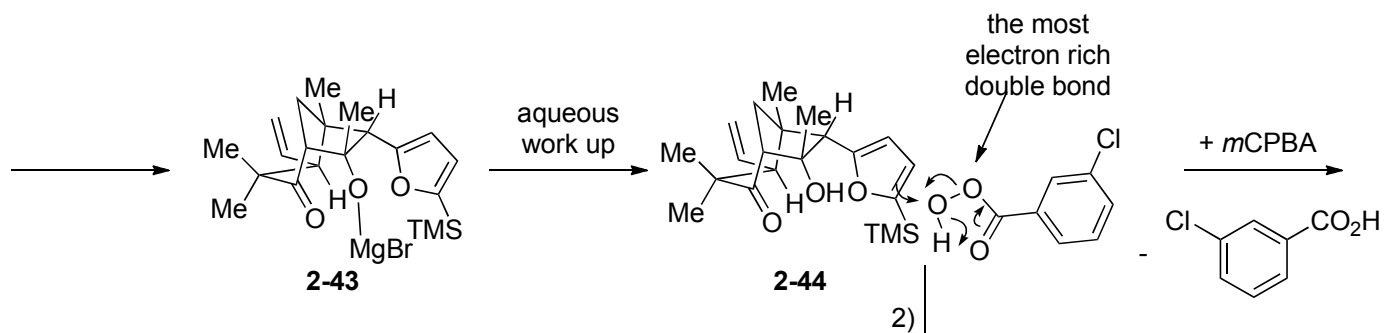
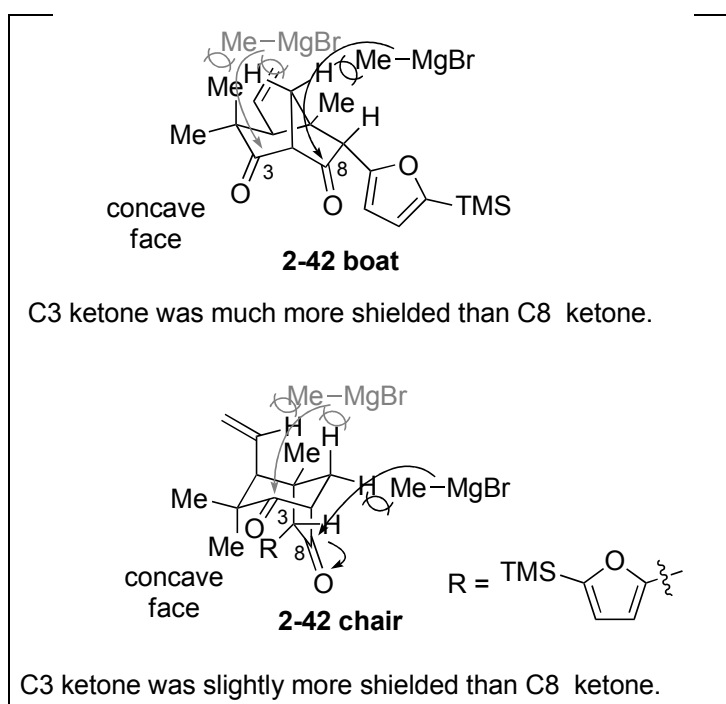
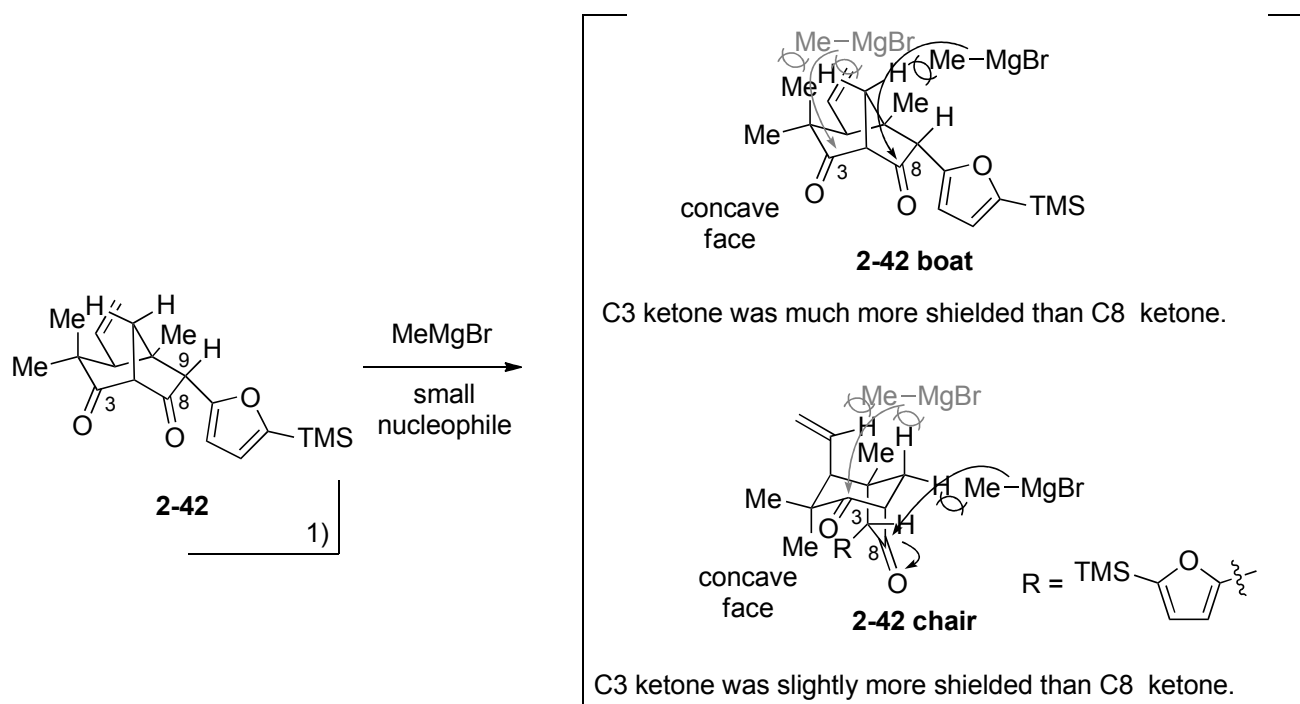
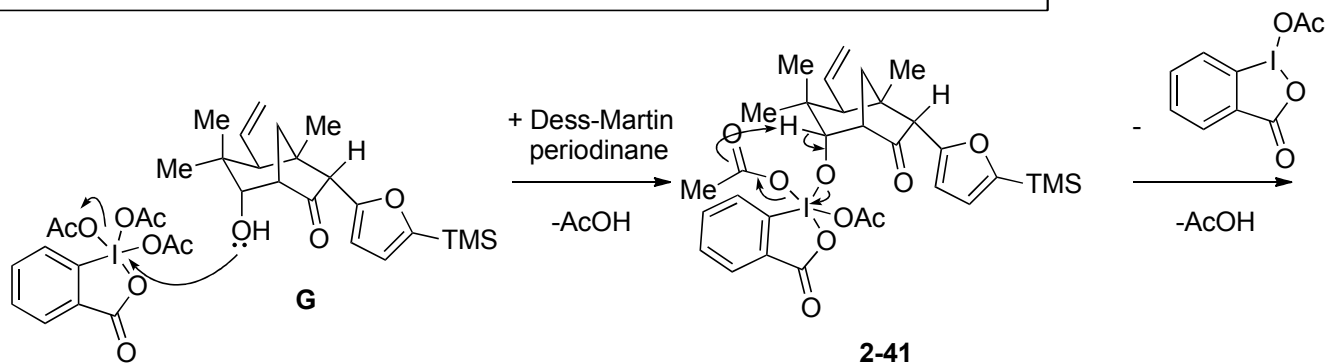
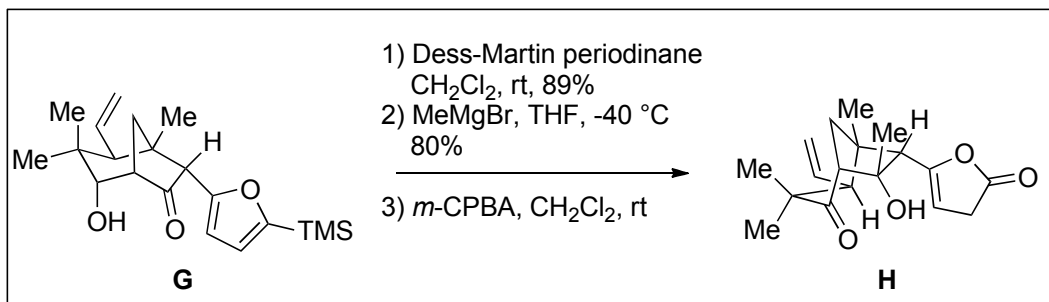
The mass peaks of $(-\text{CD}_2^{18}\text{O})$ and $(-\text{CH}_2\text{O})$ were detected.

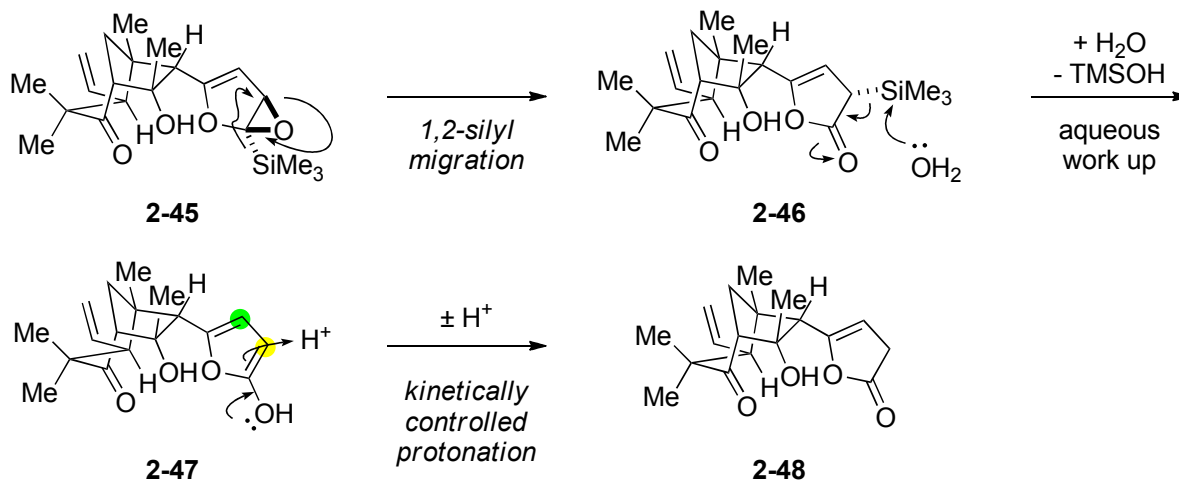
A small amount of **2-39** and **2-40** existed via oxetane **2-37** and **2-38**.

Dua, S.; Taylor, M. S.; Buntine, M. A.; Bowie, J. H. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1991.

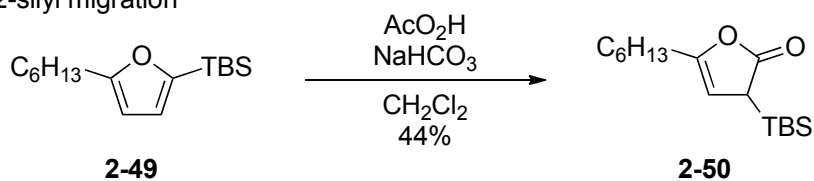
Dua, S.; Bowie, J. H.; Taylor, M. S.; Buntine, M. A. *Int. J. Mass Spectrom. Ion Processes* **1997**, 165/166, 139.

•G to H



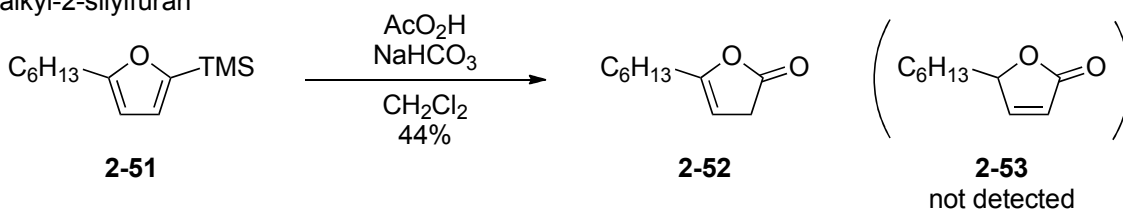


•Oxidation of 2-silylfuran
-1,2-silyl migration



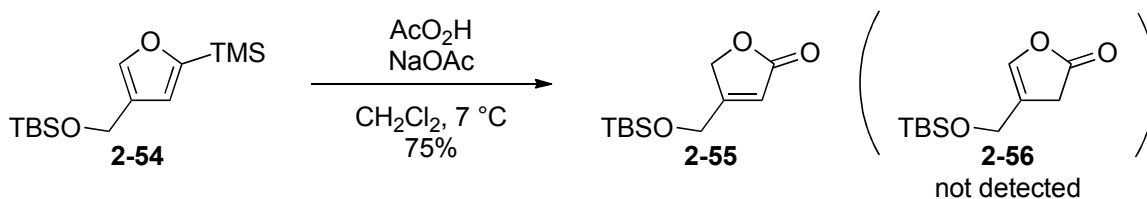
Kuwajima, I.; Urabe, H. *Tetrahedron Lett.* **1981**, 22, 5191.

-Regioselectivity of protonation
5-alkyl-2-silylfuran



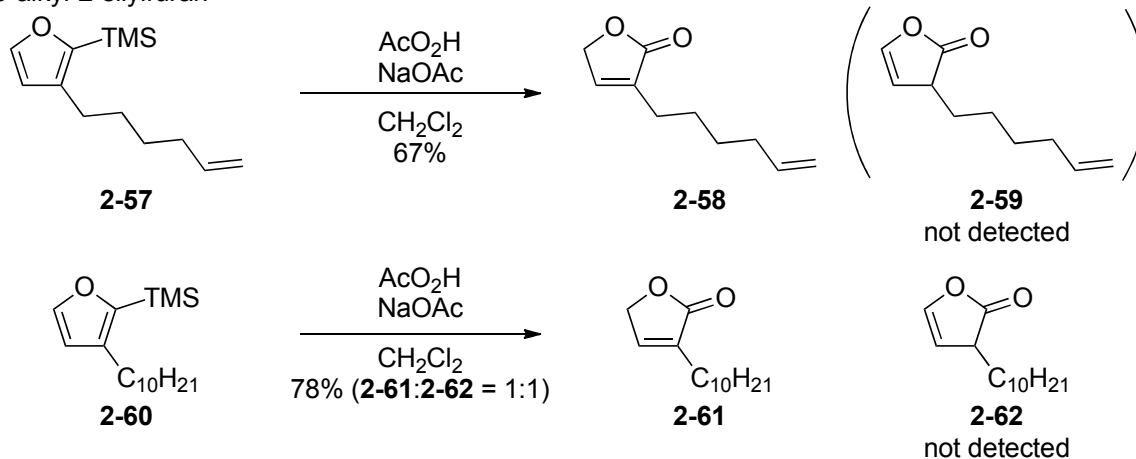
Kuwajima, I.; Urabe, H. *Tetrahedron Lett.* **1981**, 22, 5191.

4-alkyl-2-silylfuran



Goldsmith, D.; Liotta, D.; Saindane, M.; Waykole, L.; Bowen, P. *Tetrahedron Lett.* **1983**, 24, 5835.

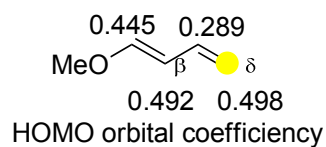
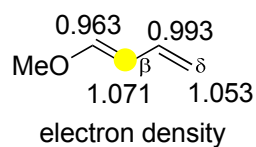
3-alkyl-2-silylfuran



Tanis, S. P.; Head, D. B. *Tetrahedron Lett.* **1984**, 25, 4451.

→ As for 4- or 3-alkyl-2-silylfuran, conjugate olefins tend to generate in many cases (thermodynamic control).
 As for 5-alkyl-2-silylfuran, non-conjugate olefins tend to generate in many cases (kinetic control).

cf. Electron density and HOMO orbital coefficient of methyl enol ether

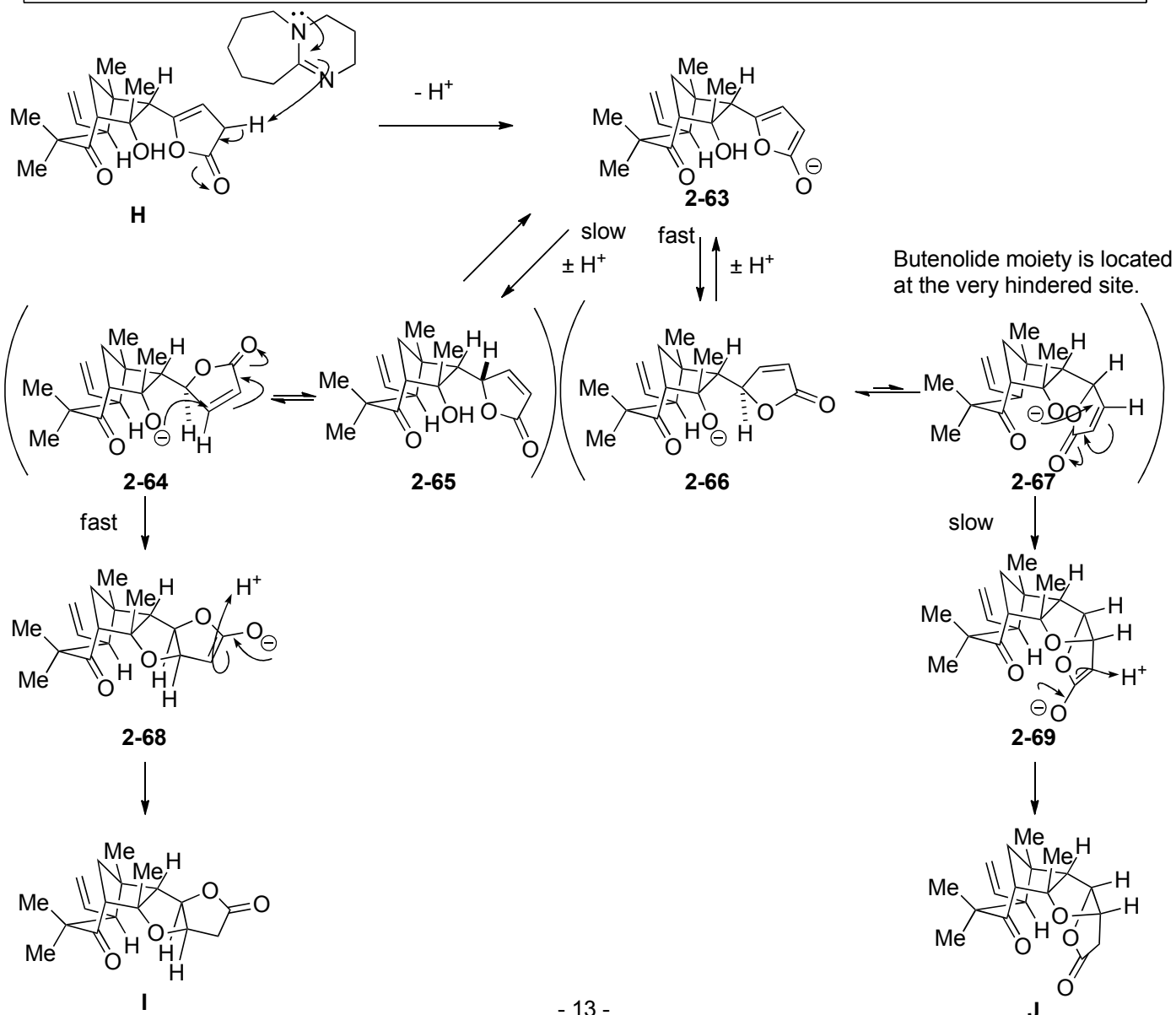
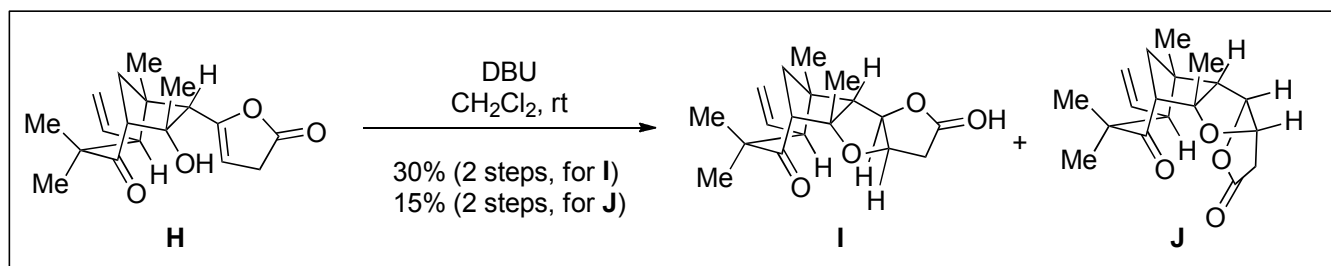


Rogers, N. A. J.; Sattar, A.
Tetrahedron Lett. **1965**, *20*, 1471.

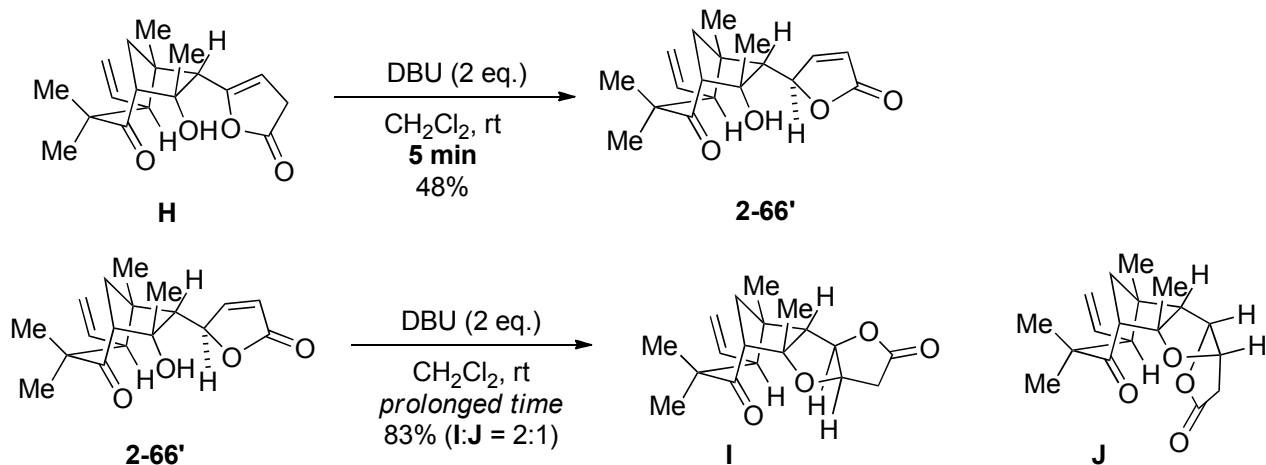
Alston, P. V.; Ottenbrite, R. M.
J. Org. Chem. **1975**, *40*, 1111.

→ Hard reagents (H^+) tend to react at β position under kinetic control condition.

•H to I and J



•Experimental result

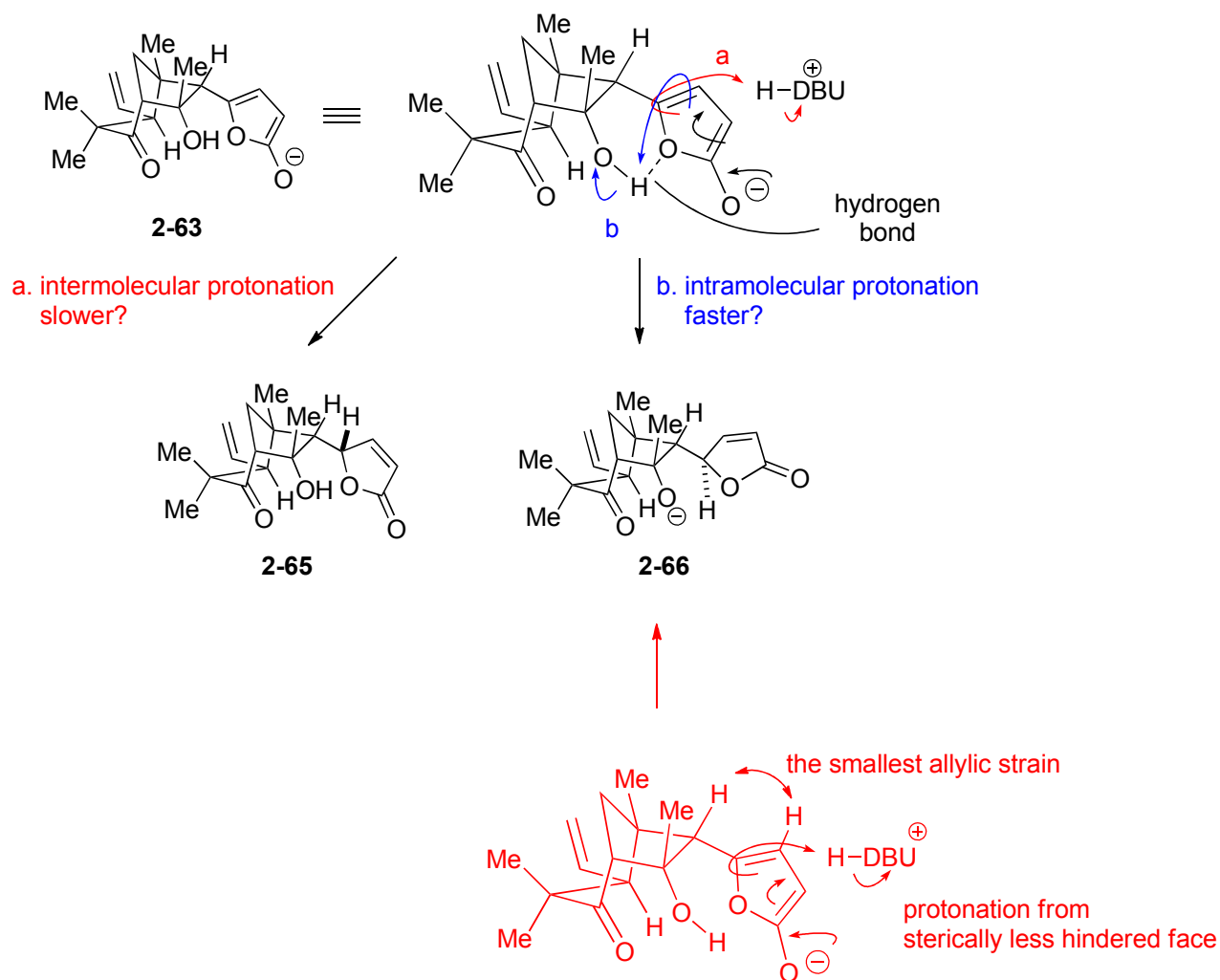


→ Equilibrium between **2-64** (**2-65**) and **2-66** (**2-67**) existed.

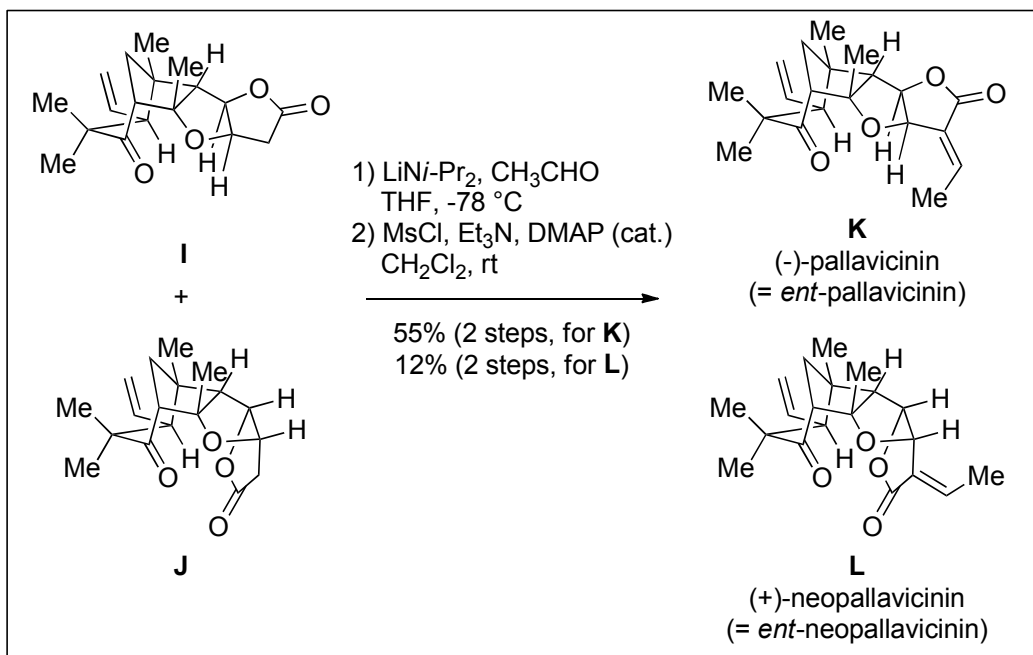
The product ratio depended on energies of products (thermodynamic control)

or
energy difference between conformers **2-64** or **2-66** and transition states leading to **2-68** or **2-69**, respectively. (kinetic control, Curtin-Hammett principle)

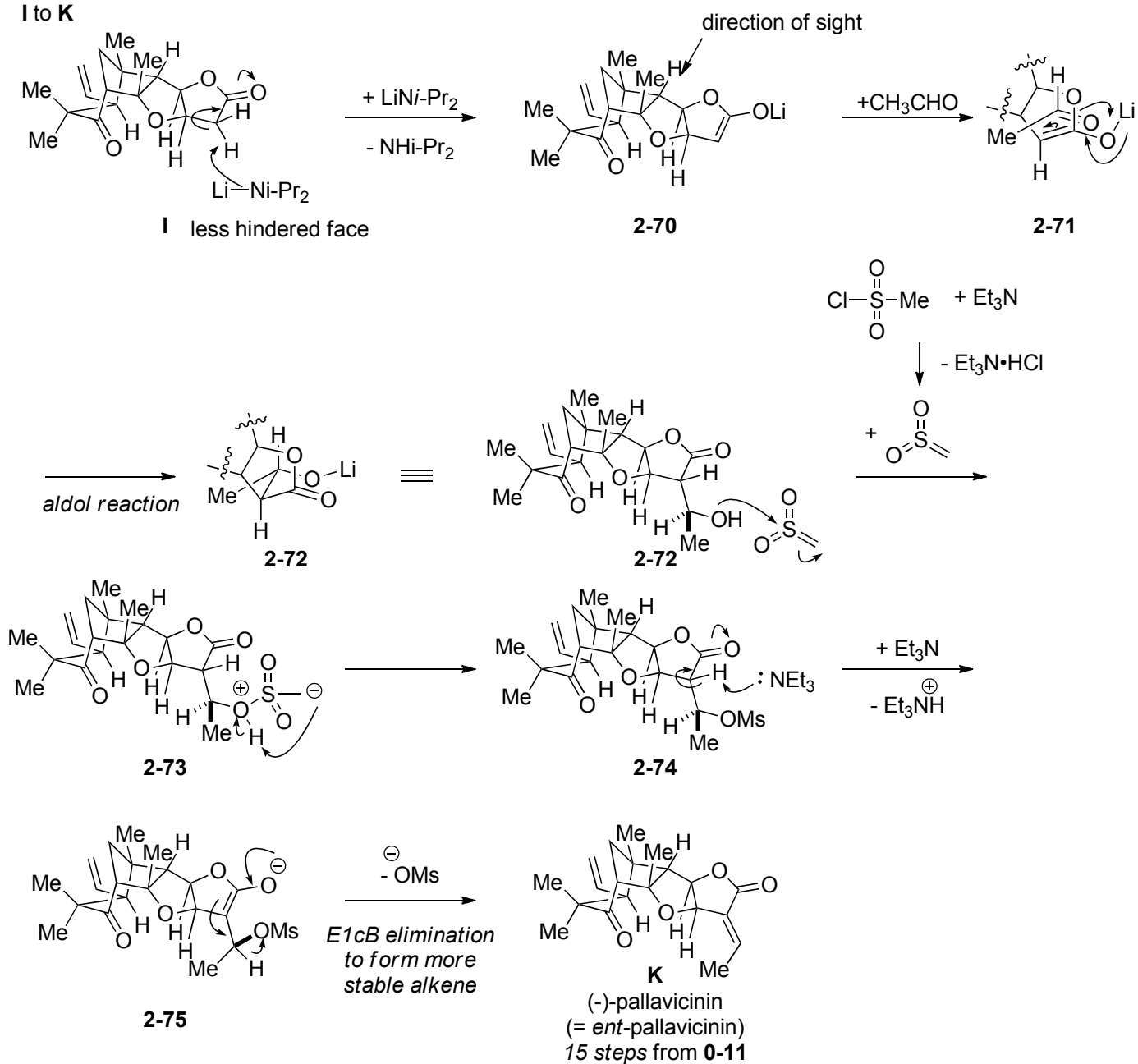
•Stereoselectivity of protonation of **2-63** (face selectivity of furanolate) (my proposal)



•I, J to K, L



I to K



J to L

