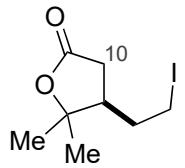
Problem Session (5)

2017.5.6 Haruka Fujino

Please fill in blanks, give the correct stereochemistry for **2-5**, and provide the mechanism of the following reactions.

(1)



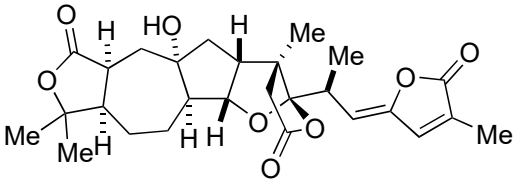
1-1

1. LiN(*i*-Pr)$_2$, THF, -78°C; **1-2**, 86% (dr at C19 1.5:1)
2. EDC, $CuCl_2$, toluene 80 °C, 83% (*E*/*Z* = 2/1)*
3. CuI, Zn, pyridine/H_2O sonication, **1-3**: 55% (and 10-*epi*-**1-3**: 4%)

($C_{21}H_{28}O_5$)

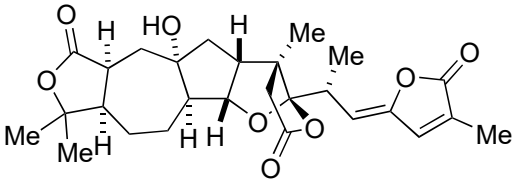
pentacyclic **1-3**

1. *m*CPBA, $NaHCO_3$ CH_2Cl_2, -15 °C, 51%
2. NaOMe, THF/MeOH, rt; $NiCl_2{\cdot}6H_2O$, $NaBH_4$, -15 °C, 73%
3. ICl, THF, 63%
4. **1-4**, AIBN, *n*-Bu_3SnH MS 4A, toluene, 100 °C



schilancitrilactone C (**1-5**, 36%)

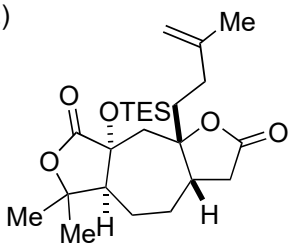
+



schilancitrilactone B (**1-6**, 9%)

* tips: A trace amount of water in the reaction system can cause the formation of (*Z*)-isomer.

(2)



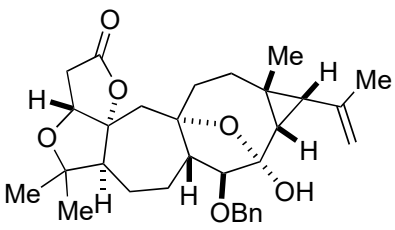
2-1

1. $LiN(SiMe_3)_2$, LiCl; MoOPH THF -78°C, 91%
2. BnBr, Ag_2O, CH_2Cl_2, 97%
3. CH_2=CHMgBr, THF
4. HG II, toluene, 80°C, 79%
5. Ac_2O, Et_3N, CH_2Cl_2, 97%
6. $LiN(SiMe_3)_2$, $CF_3CO_2CH_2CF_3$ THF, -78 °C to 0 °C
7. TsN_3, Et_3N, MeCN, 93% (3 steps)
8. $Cu(tbs)_2$, toluene, 80 °C, 65%

($C_{33}H_{46}O_7Si$)

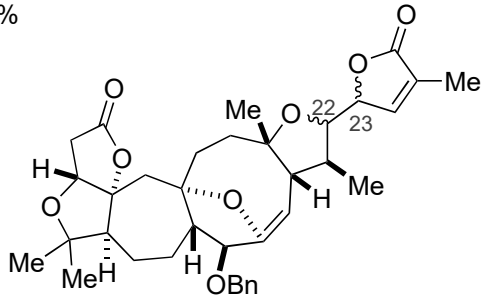
dilactone **2-2**

10 steps



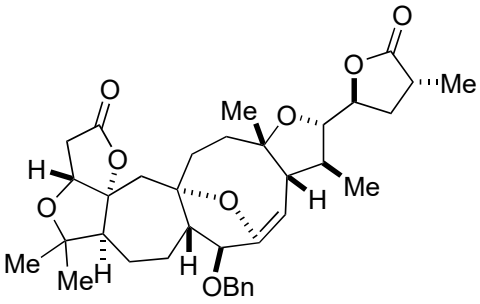
2-3

1. $BH_3{\cdot}SMe_2$, THF, 0 °C; $Na_2B_4O_7$, aq. H_2O_2, 65%
2. TPAP, CH_2Cl_2, 0 °C, 88%
3. **2-4**, $BF_3{\cdot}OEt_2$, CH_2Cl_2 -78 °C to -35 °C, 66%

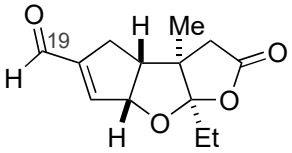


kinetic product **2-5** (single diastereomer)

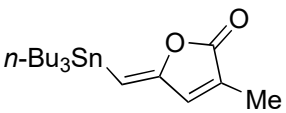
1. DBU, toluene, 65 °C, 70%
2. $NiCl_2{\cdot}6H_2O$, $NaBH_4$ MeOH, 0 °C, 62%
3. NaOMe, MeOH, brsm 73%



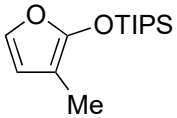
2-6



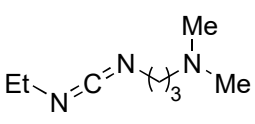
1-2



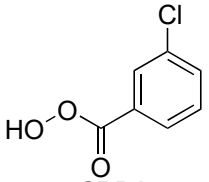
1-4



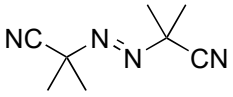
2-4



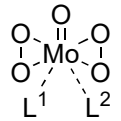
EDC



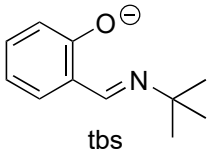
*m*CPBA



AIBN

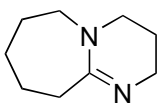


MoOPH (L^1 = pyridine, L^2 = HMPA)



tbs

HG II: Hoveyda-Grubbs 2nd catalyst



DBU

Problem Session (5) [Answer]

2017.5.6 Haruka Fujino

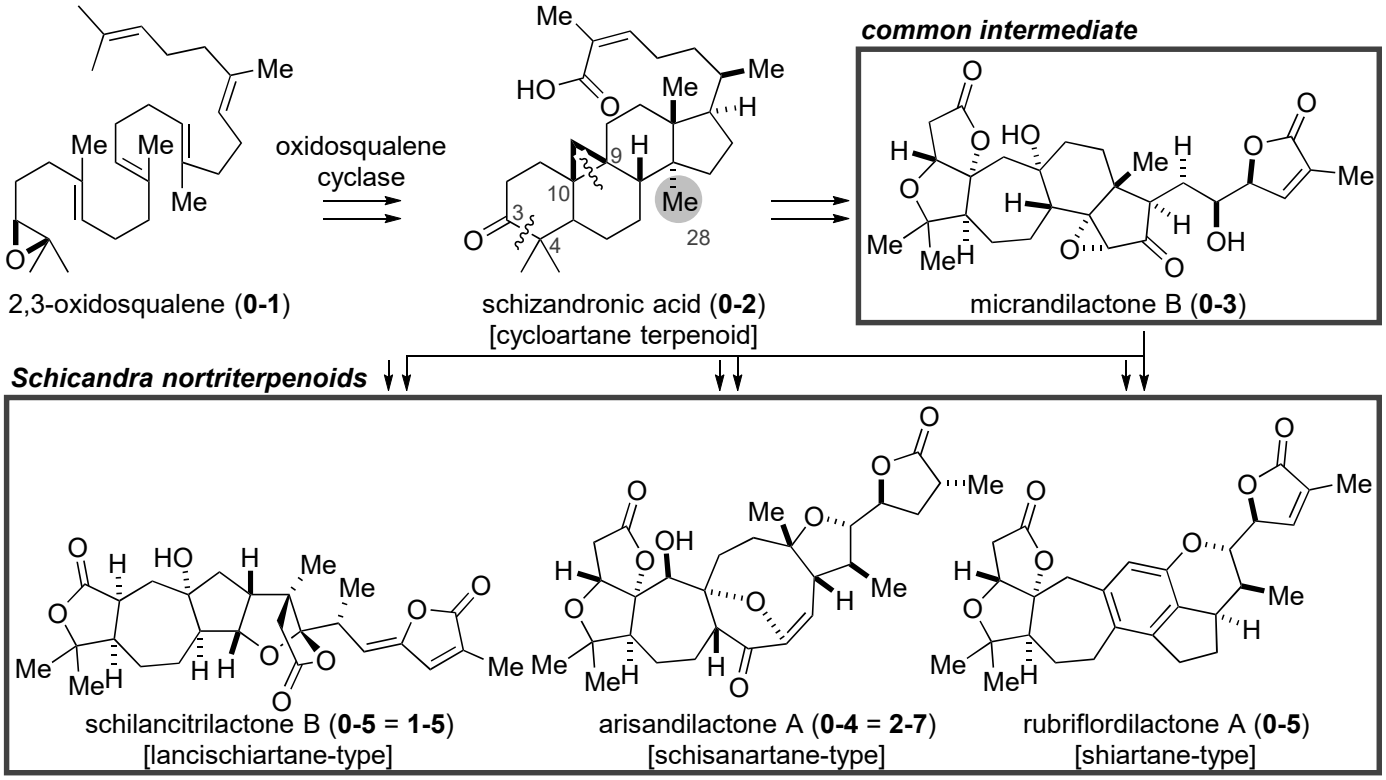
Topic: Total syntheses of *Schisandra* nortriterpenoids

(0) Introduction (Sun, H. D. *et al. Nat. Prod. Rep.* **2008**, *25*, 871.)

0.1 *Schicandra* nortriterpenoids

- a class of triterpenoid natural products with C_{26} to C_{29} framework found in plants of the *Schisandraceae* family
- > 70 highly oxygenated triterpenoids with various patterns of functinalized skeltons
- various phrmaceutical effects such as antihepatitis, antitumor, anti-HIV *etc*..

0.2 Outline of biosynthesis & classification



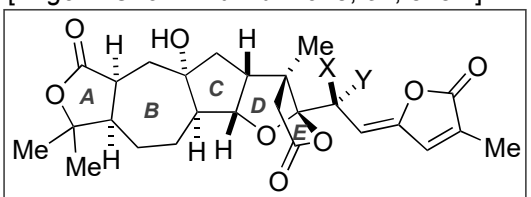
0.3 Synthetic study and total syntheses

- > 20 synthetic studies and total synthesis
- the most recent review; Li, X. and Carter, R. G. *et al. Angew. Chem. Int. Ed.* **2017**, *56*, 1704.
- the related LS: 160123_LS_Yinghua_Wang.

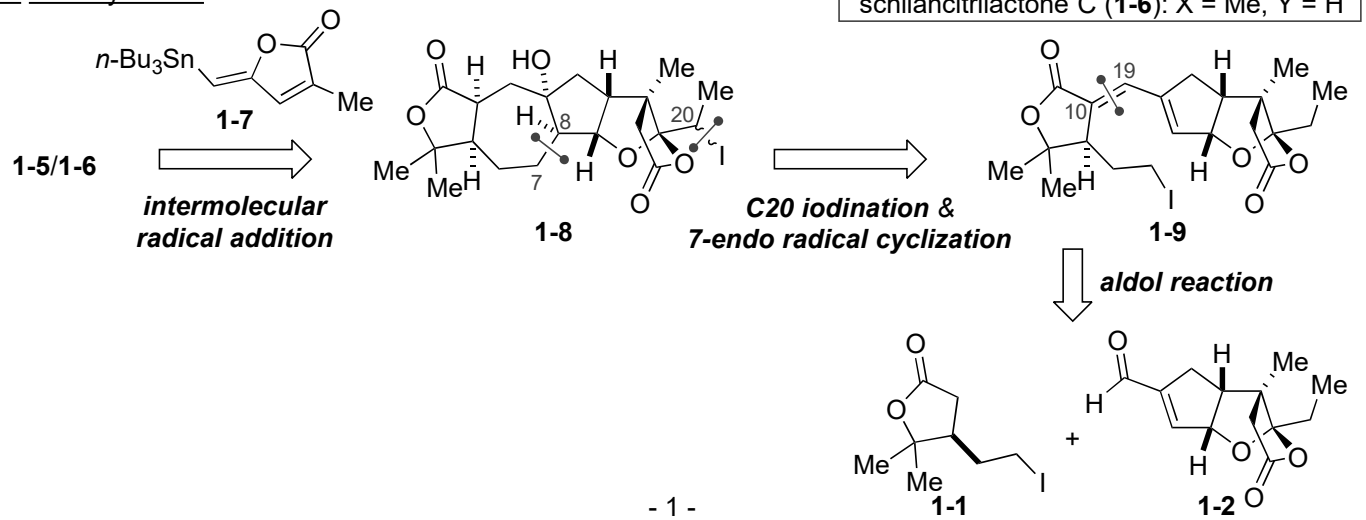
(1) Total synthesis of schilancitrilactones B and C by Tang, P. *et al.* [*Angew. Chem. Int. Ed.* **2015**, *54*, 5732.]

1.1 Information

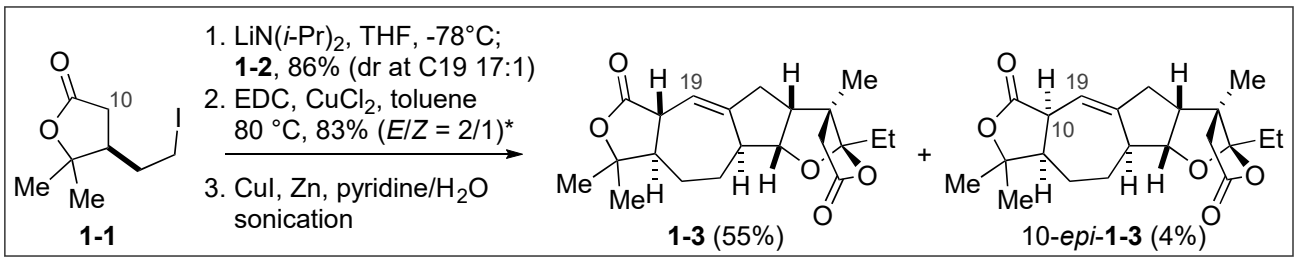
- isolation: *S. Lancifolia* [Sun, H. D. *et al. Org. Lett.* **2012**, *14*, 1286.]
- bioactivity: anti-HIV 1 for **1-6**, no activity for **1-5**
- structural features: 5/7/5/5/5-fused pentacyclic core
  9 stereocenters
- total synthesis: not reported

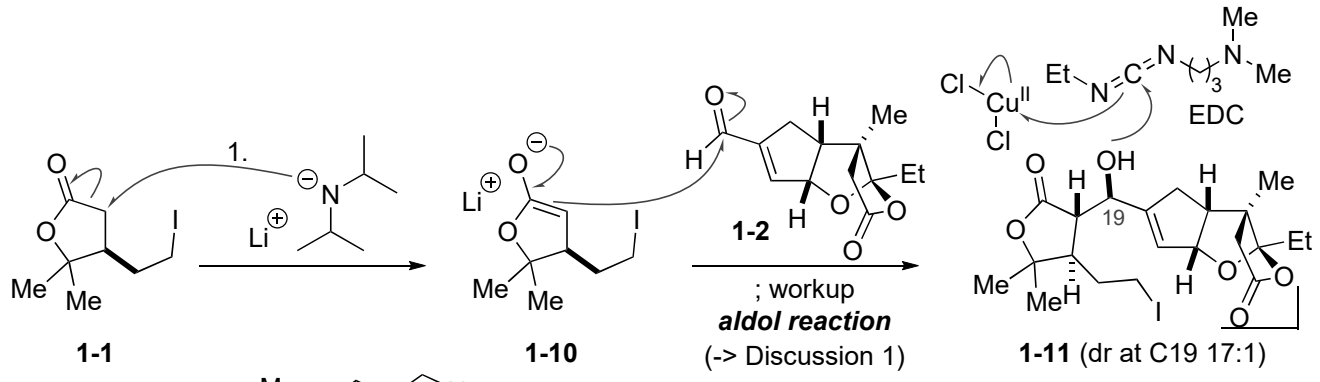


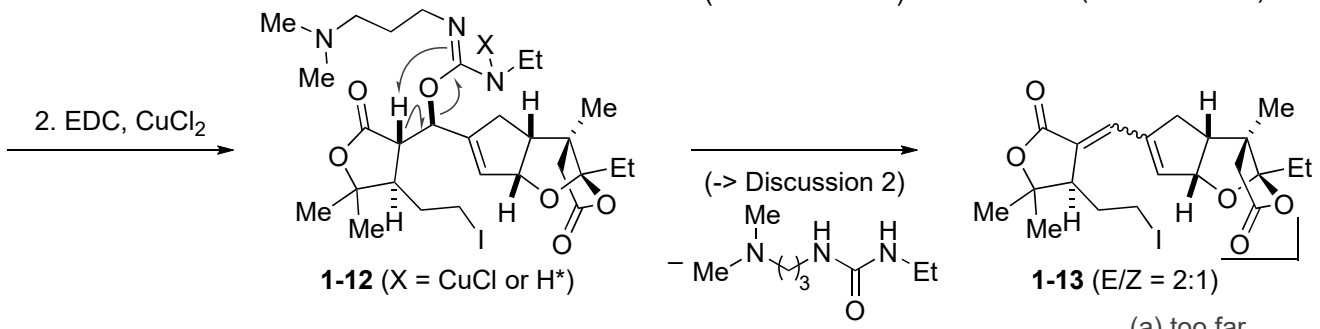
1.2 Retrosynthesis

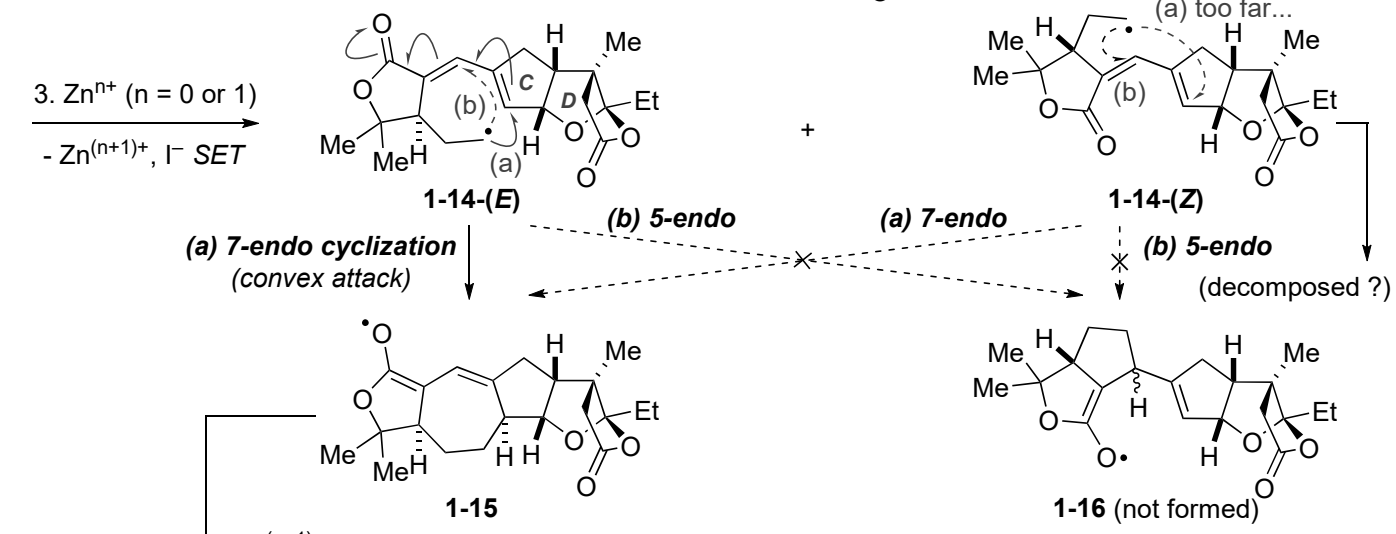


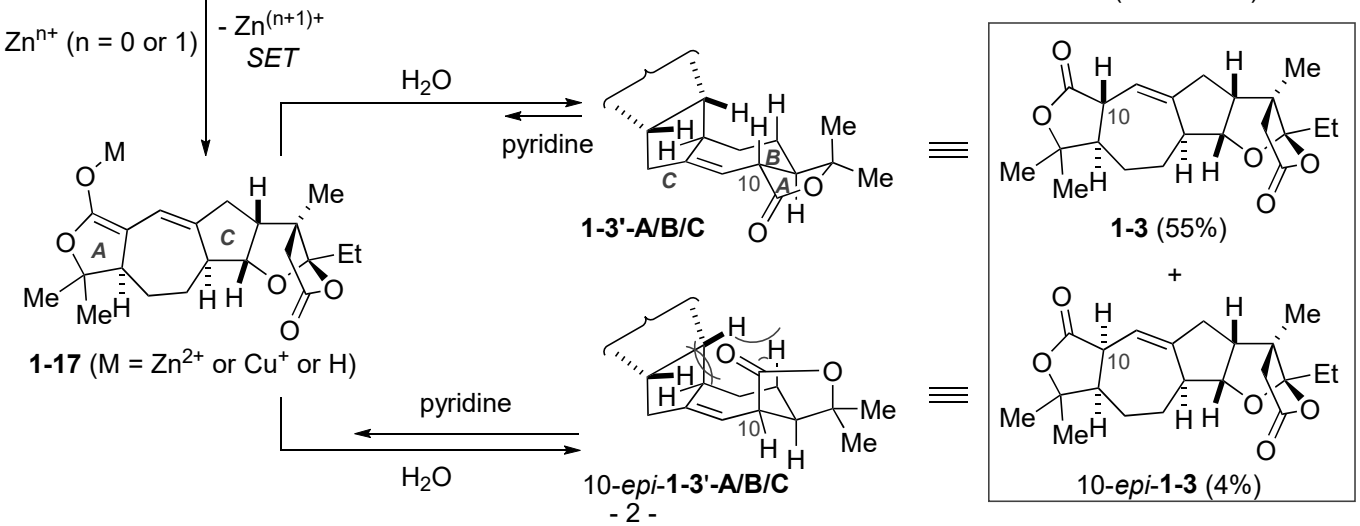
1.3 Transformation from **1-1** to **1-4**



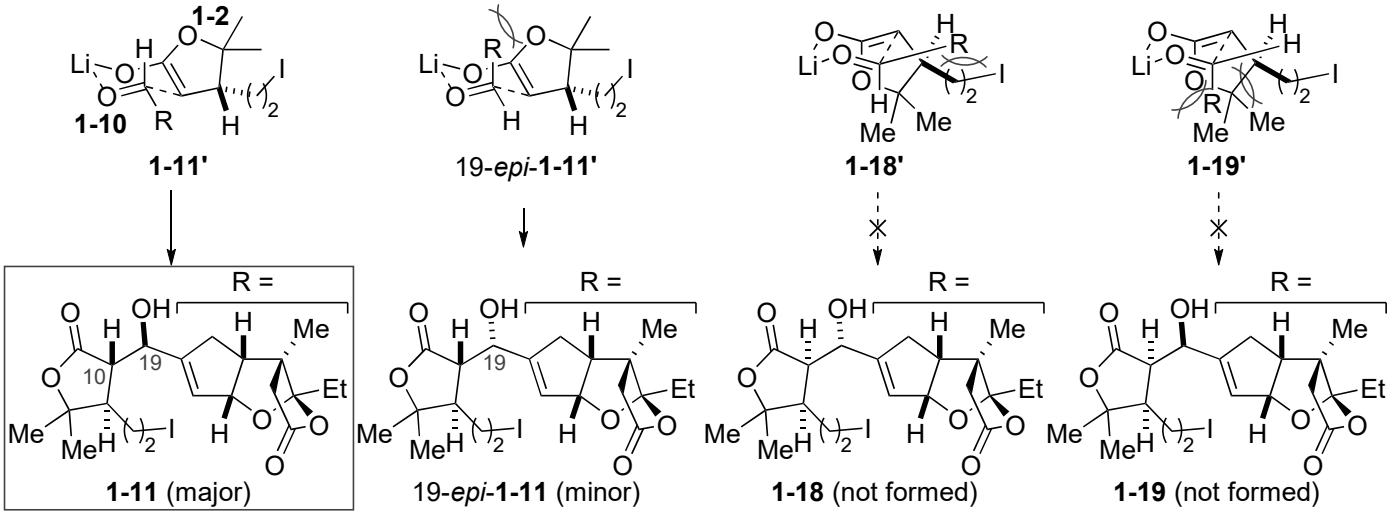




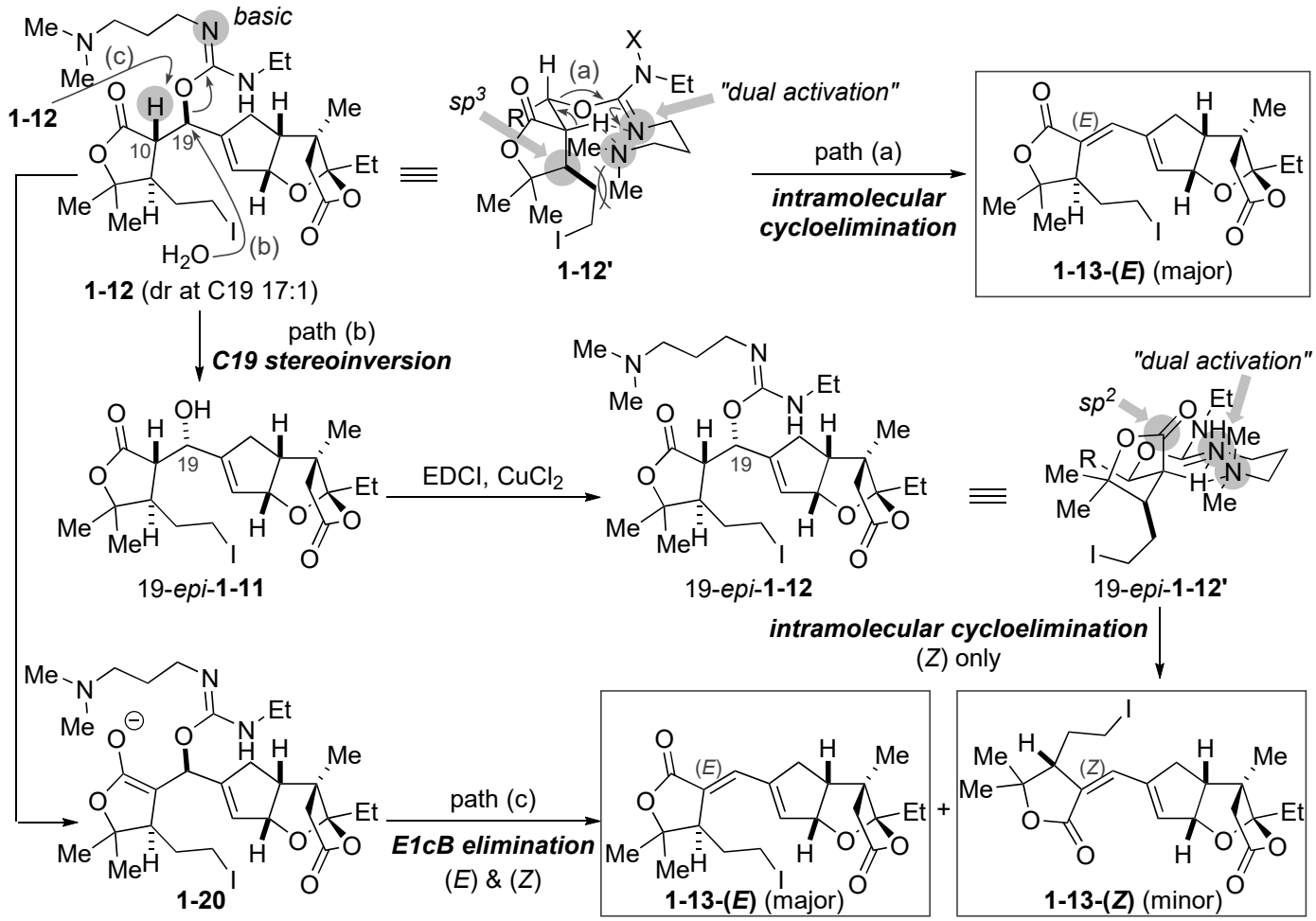


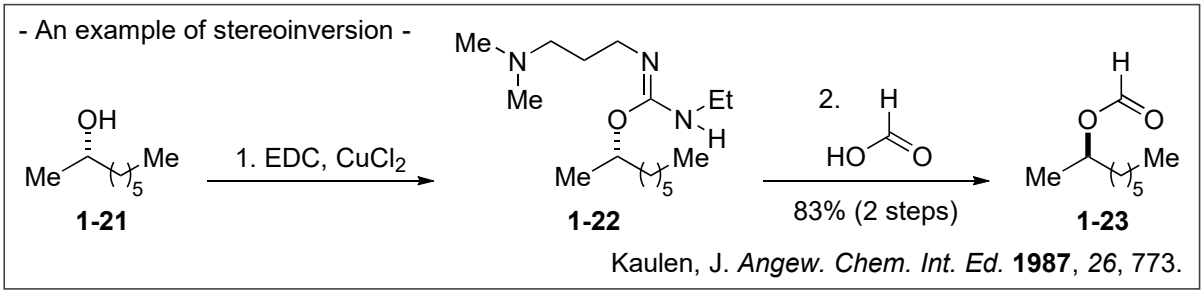


<Discussion 1: Stereoselectivity in Aldol reaction>

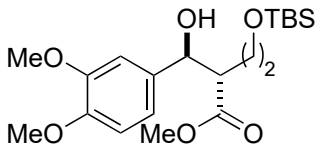


<Discussion 2: Stereoselectivity in C10–C19 olefin formation>

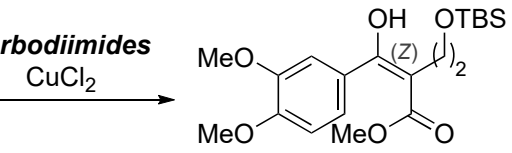




- Effect of "dual actiation" -

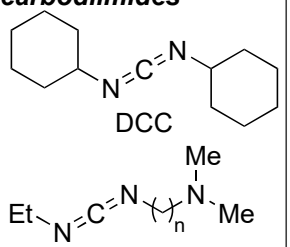


1-24



1-25

carbodiimides



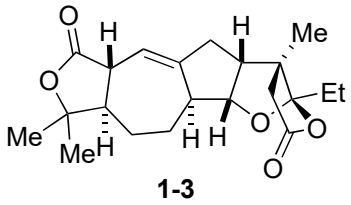
1-26 (n = 2)
EDC (n = 3)
1-27 (n = 4)

Table 1-1.

entry	***carbodiimides***	**1-22** (*Z*:*E*)
1	DCC	45% (33:67)
2	DCC + Et_3N	37% (60:40)
3	**1-26**	42% (82:18)
4	EDC	95% (96:4)
5	EDC·HCl	17% (15:85)
6	**1-27**	43% (88:12)

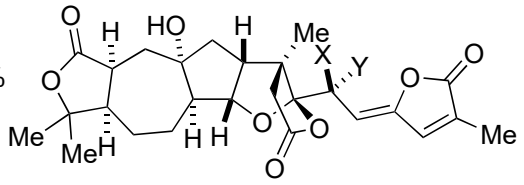
Sai, H. *et al. Tetrahedron* **2007**, *63*, 10345.

1.4 Transformation from **1-3** to **1-6**/**1-5**

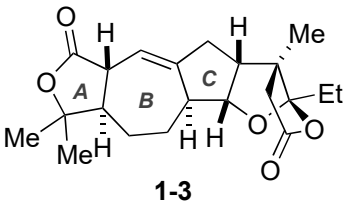


1-3

1. *m*CPBA, $NaHCO_3$
CH_2Cl_2, -15 °C, 51%
2. NaOMe, THF/MeOH, rt;
$NiCl_2·6H_2O$, $NaBH_4$, -15 °C, 73%
3. ICl, THF, 63%
4. **1-4**, AIBN, *n*-Bu_3SnH
MS 4A, toluene, 100 °C

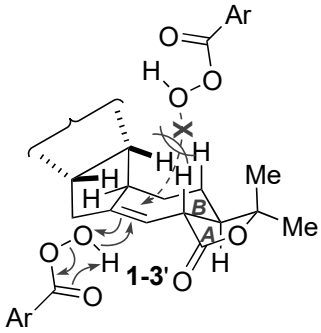


schilancitrilactone C (**1-6**, X = Me, Y = H): 36%
schilancitrilactone B (**1-5**, X = H, Y = Me): 9%



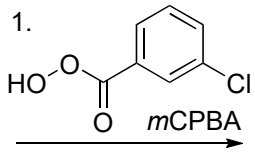
1-3

≡

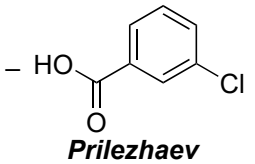


1-3'

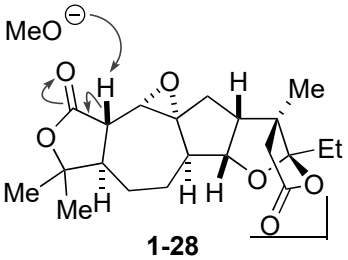
1.



*m*CPBA

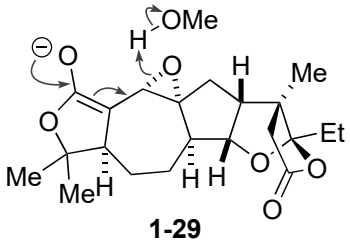
– 

Prilezhaev epoxiadtion



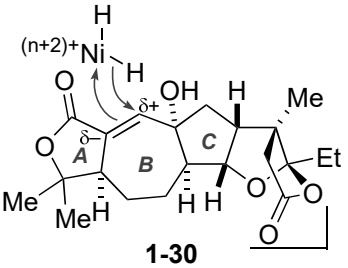
1-28

2. NaOMe, MeOH



1-29

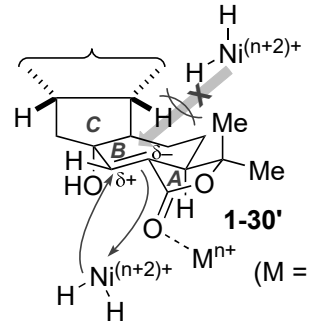
– $^{\ominus}$OMe



1-30

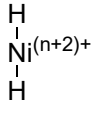
$(2NiCl_2 + 4NaBH_4 + 9H_2O \longrightarrow Ni_2B + 3H_3BO_3 + 4NaCl + 12.5H_2)^{ref.}$

≡



1-30'

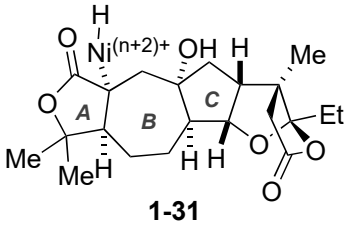
(M = Na or Ni)

Ni^{n+} $\xrightarrow{H_2}$ 

oxidative addition

3. $NiCl_2·9H_2O$, $NaBH_4$

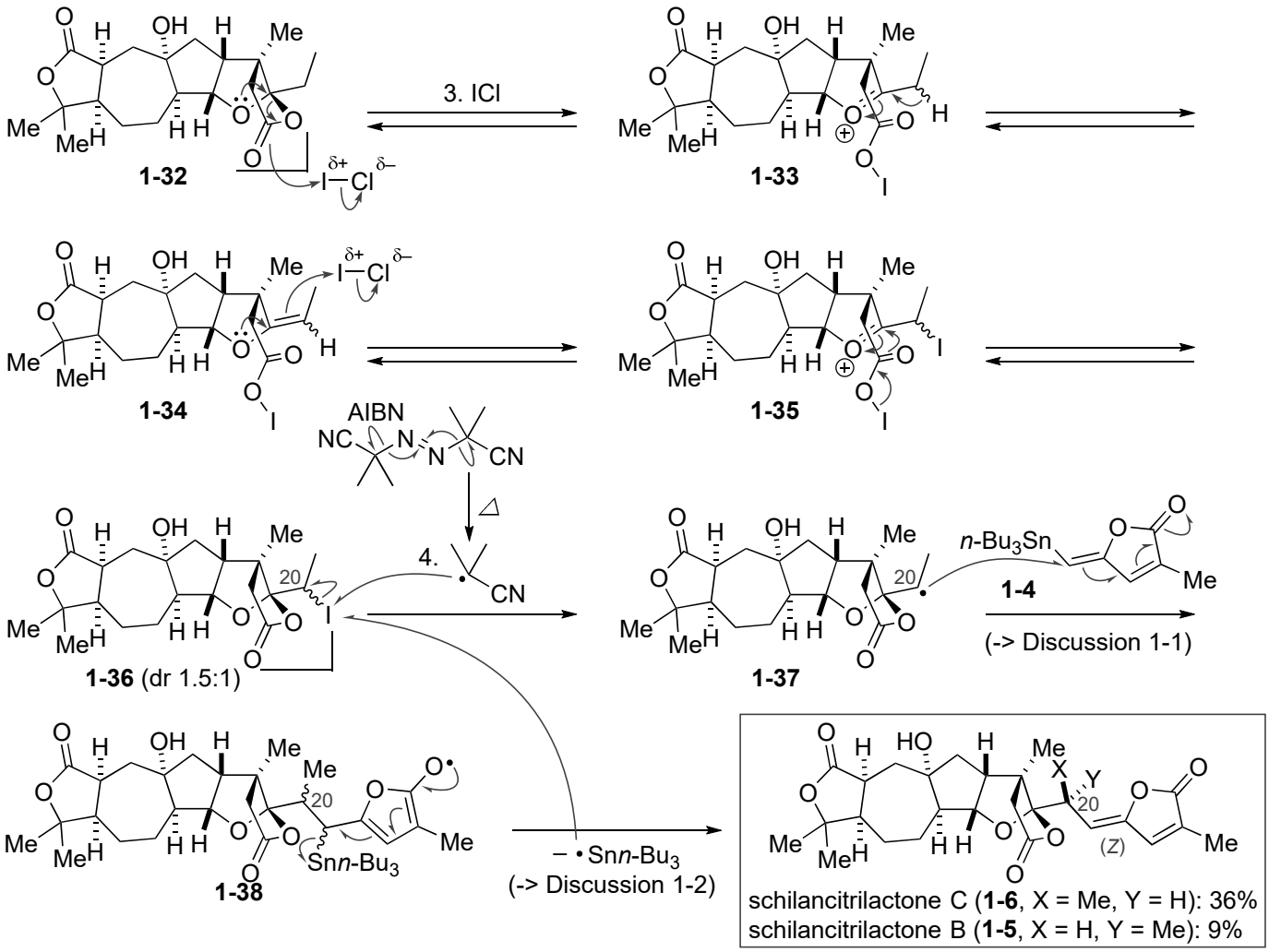
insertion



1-31

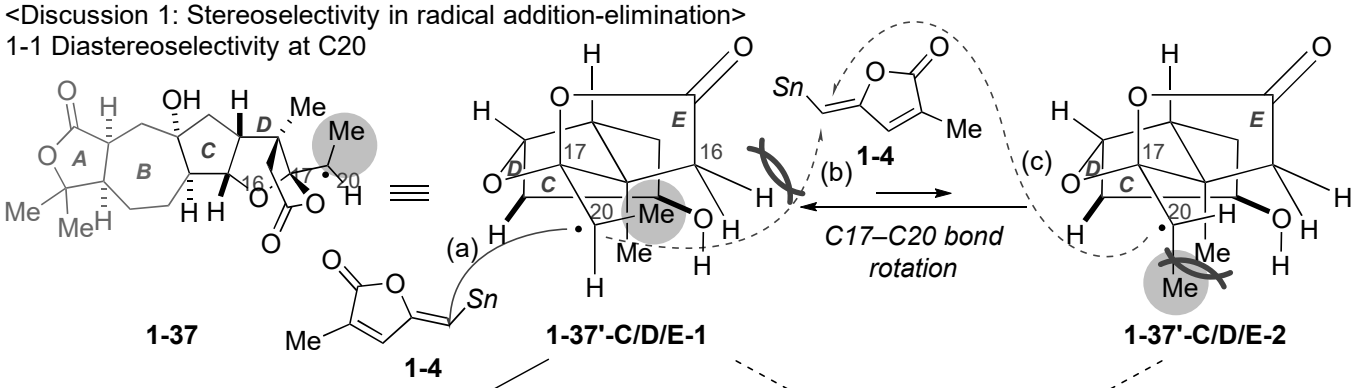
reductive elimination
– Ni^{n+}

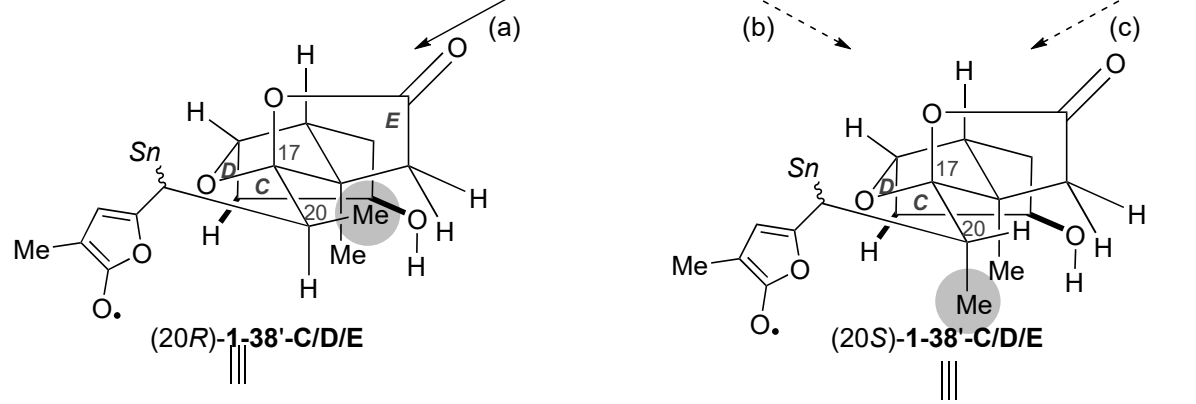
ref. Schlesinger, H. I. *et al. J. Am. Chem. Soc.* **1953**, *75*, 215.

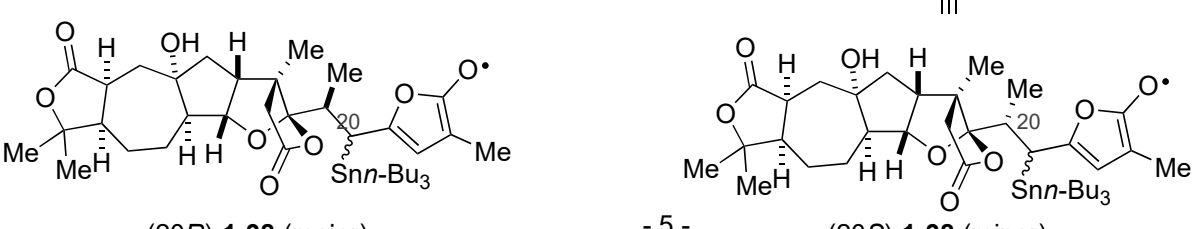


<Discussion 1: Stereoselectivity in radical addition-elimination>

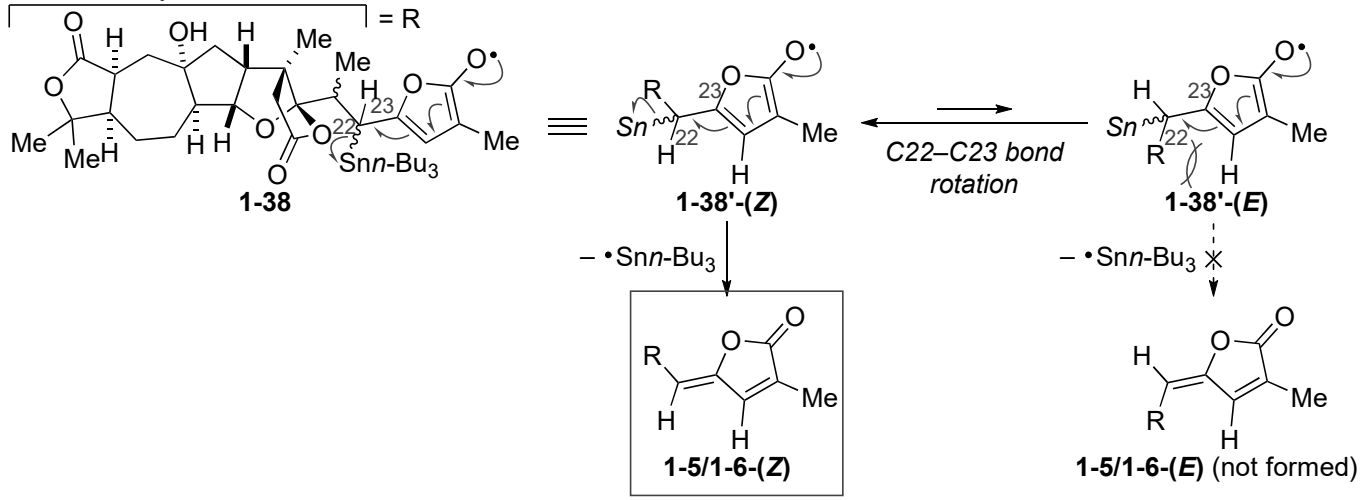
1-1 Diastereoselectivity at C20







1-2 *Z*-selectivity of **1-5**/**1-6**

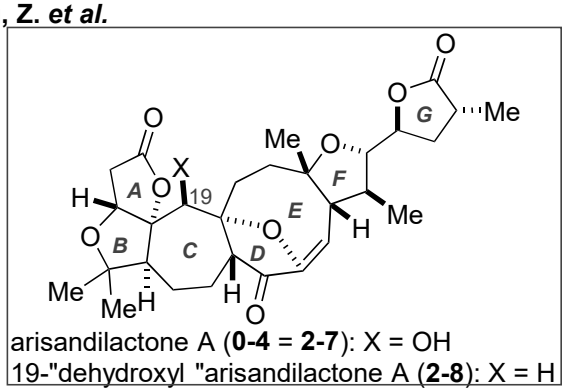


(2) **Total synthesis of 19-"dehydroxyl" arisandilactone A by Yang, Z. *et al.***

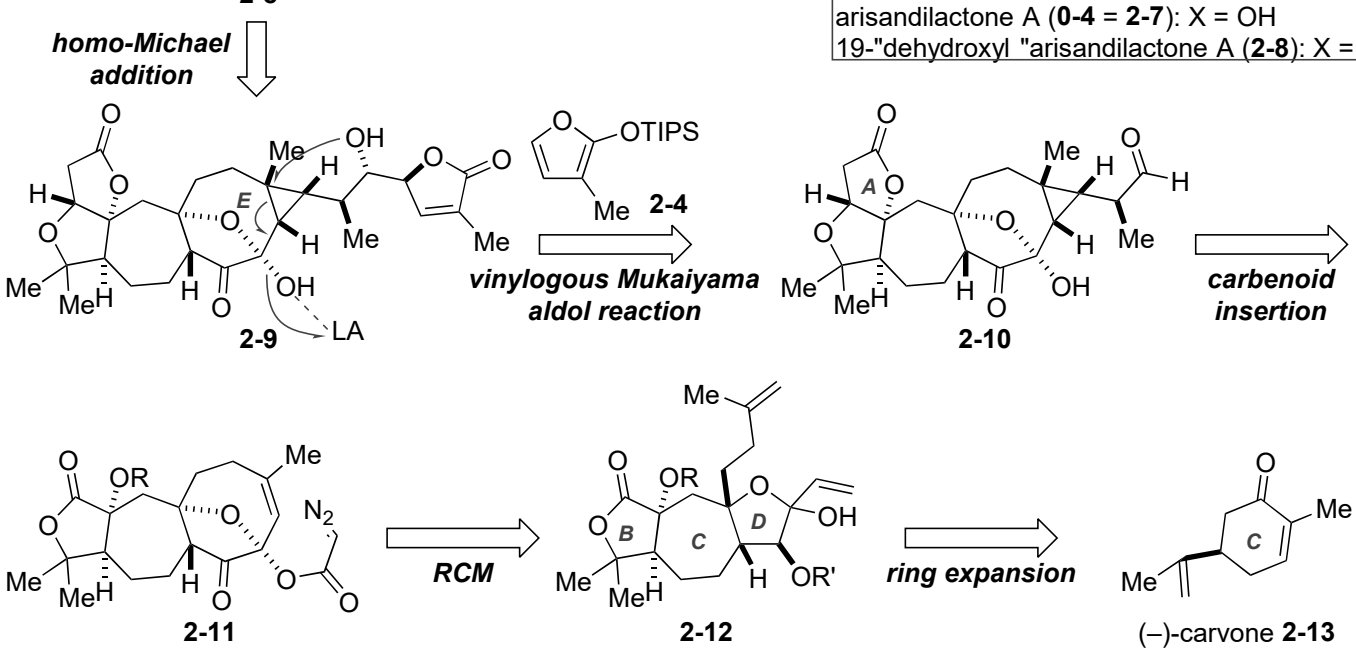
[Nat. Commun. doi: 10.1038/ncomms14233]

2.1 Information of arisandilactone A (**2-7**)

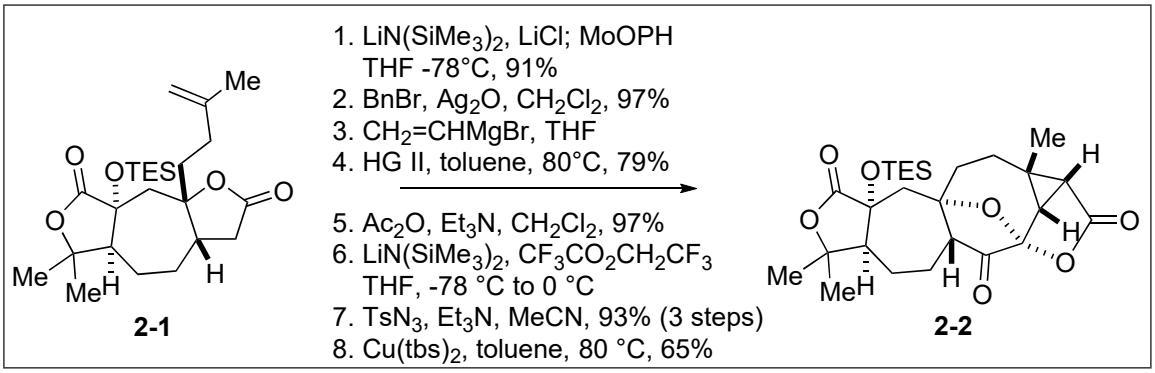
- isolation: *S. aresanensis*
  (Shen, Y.-C. *et al. Org. Lett.* **2010**, *12*, 1016.)
- bioactivity: unknown
- structural features: 7/9/5-oxa-bridged core, 12 stereocenters
- total synthesis: not reported

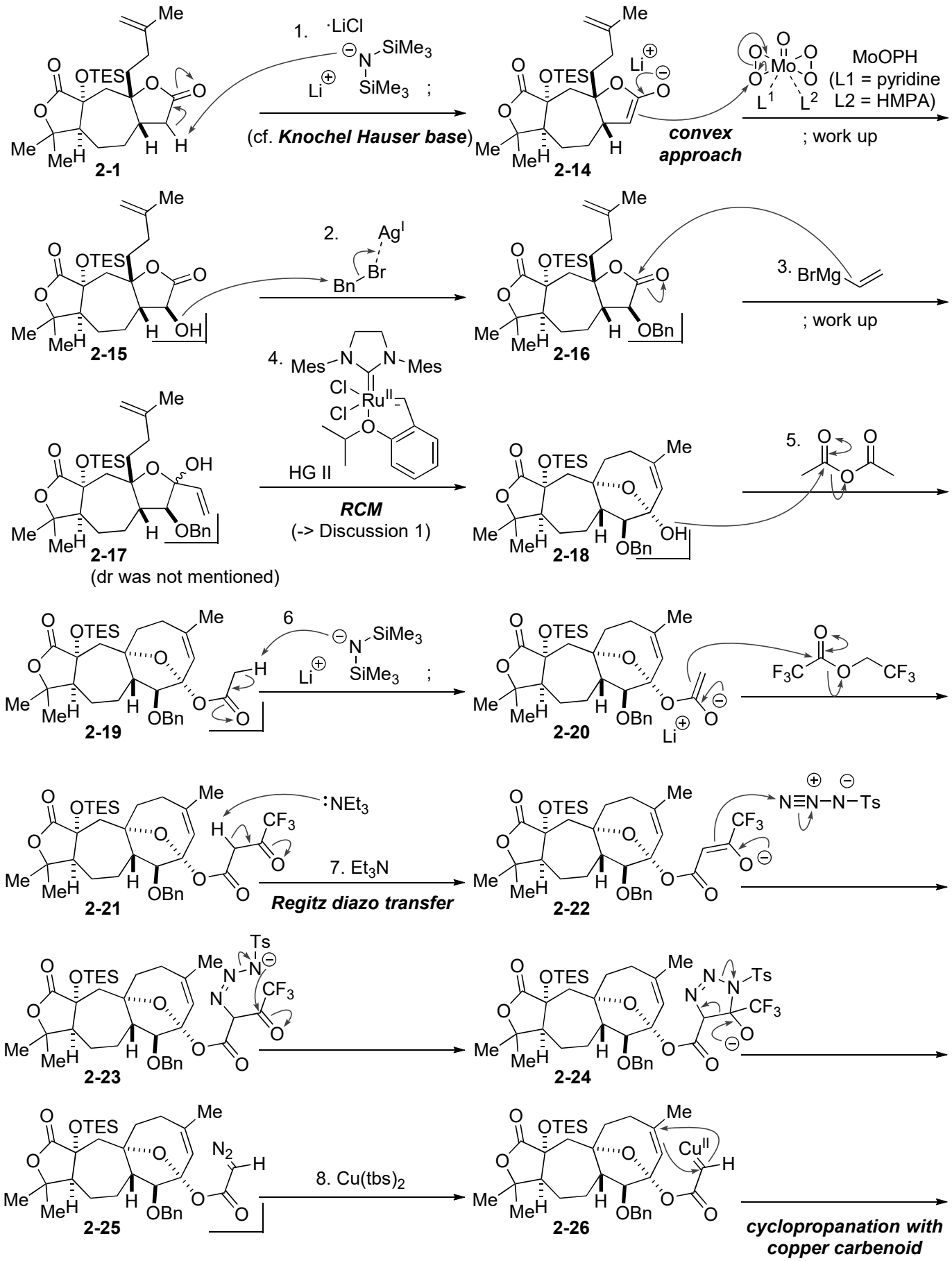


2.2 Retrosynthesis of 19-"dehydroxyl" arisandilactone A (**2-8**)

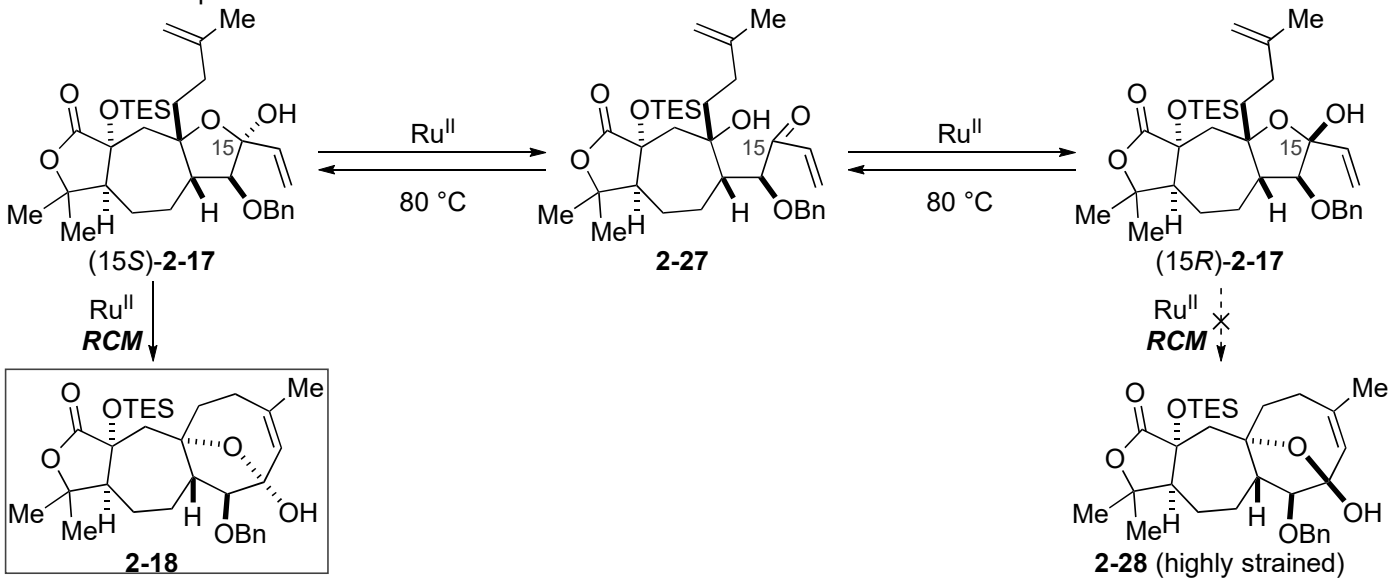


2.3 Transformation from **2-1** to **2-2**

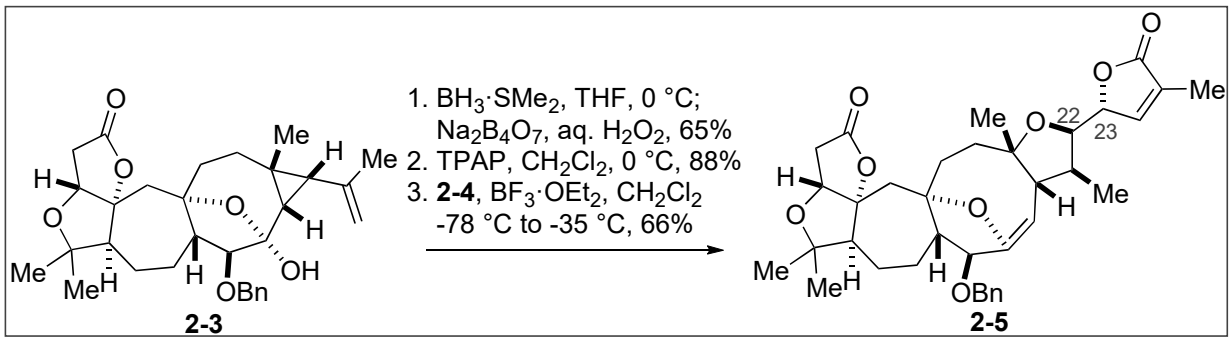


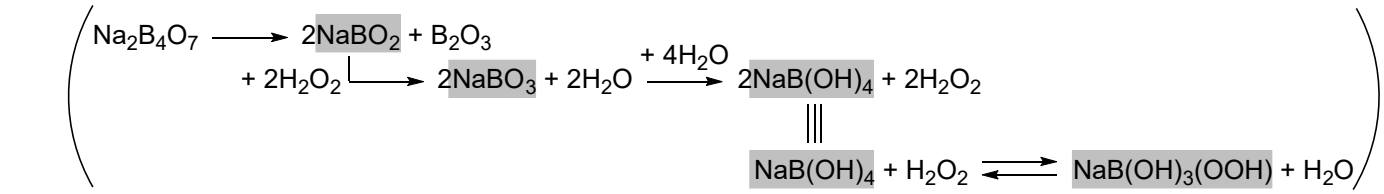

2-1
1. ·LiCl
(cf. Knochel Hauser base)
2-14
convex approach
MoOPH
(L1 = pyridine
L2 = HMPA)
; work up
2-15
2. Ag(I)
2-16
3. BrMg
; work up
2-17
(dr was not mentioned)
4. HG II
RCM
(-> Discussion 1)
2-18
5.
2-19
6
2-20
2-21
7. Et3N
Regitz diazo transfer
2-22
2-23
2-24
2-25
8. Cu(tbs)2
2-26
cyclopropanation with copper carbenoid
2-2

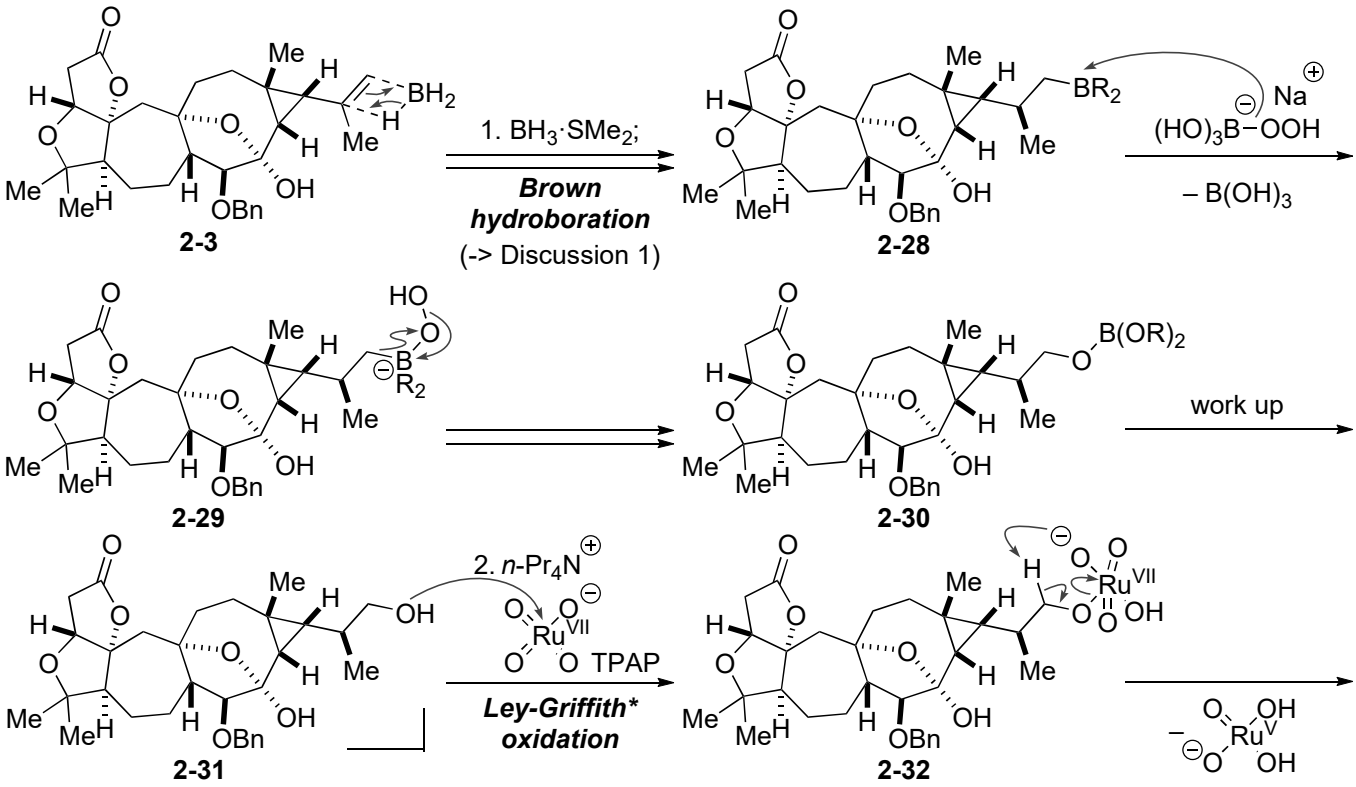
<Discussion 1: epimerization of hemiketal in RCM>



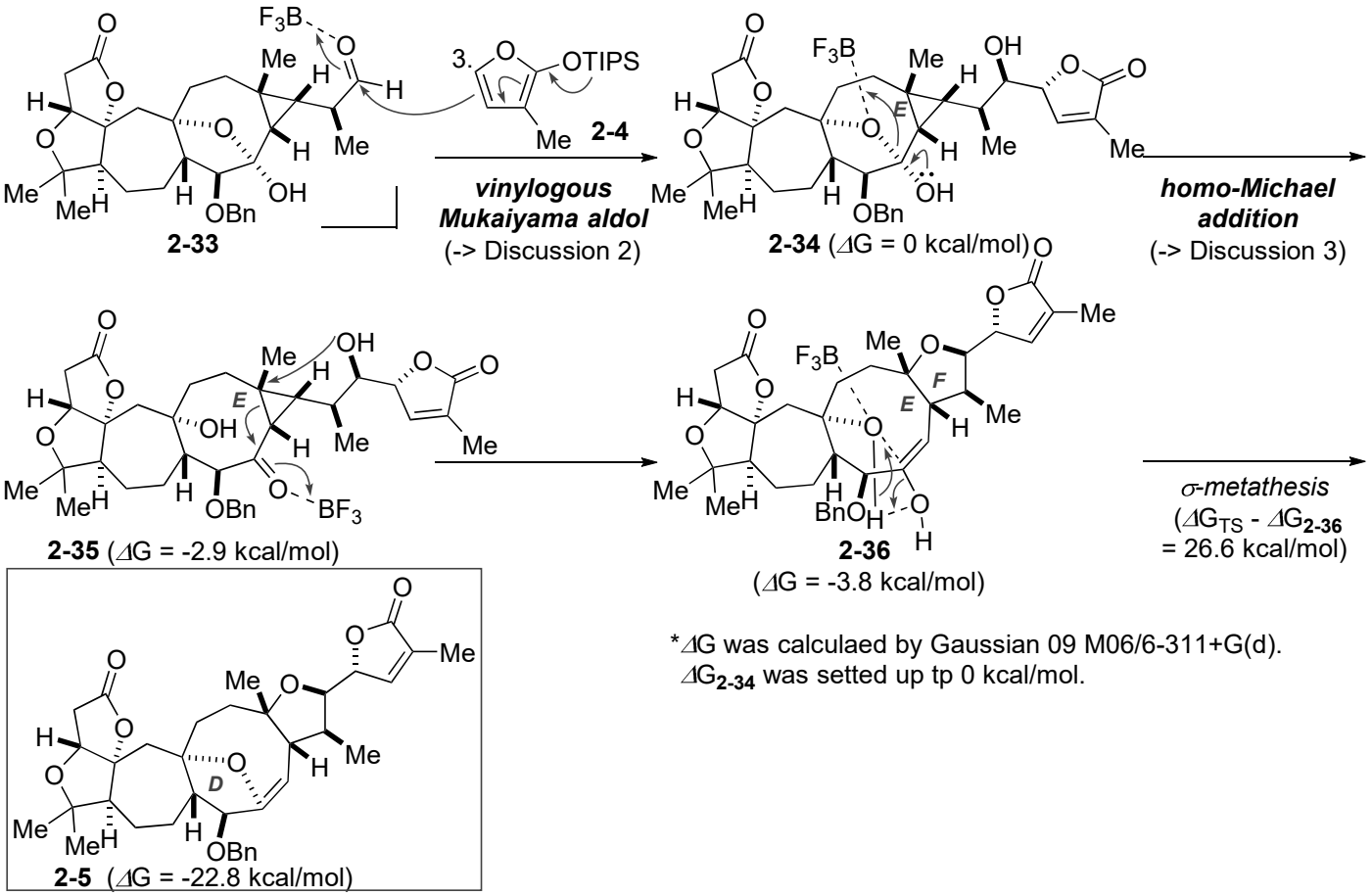
2.4 Transformation from **2-3** to **2-5**





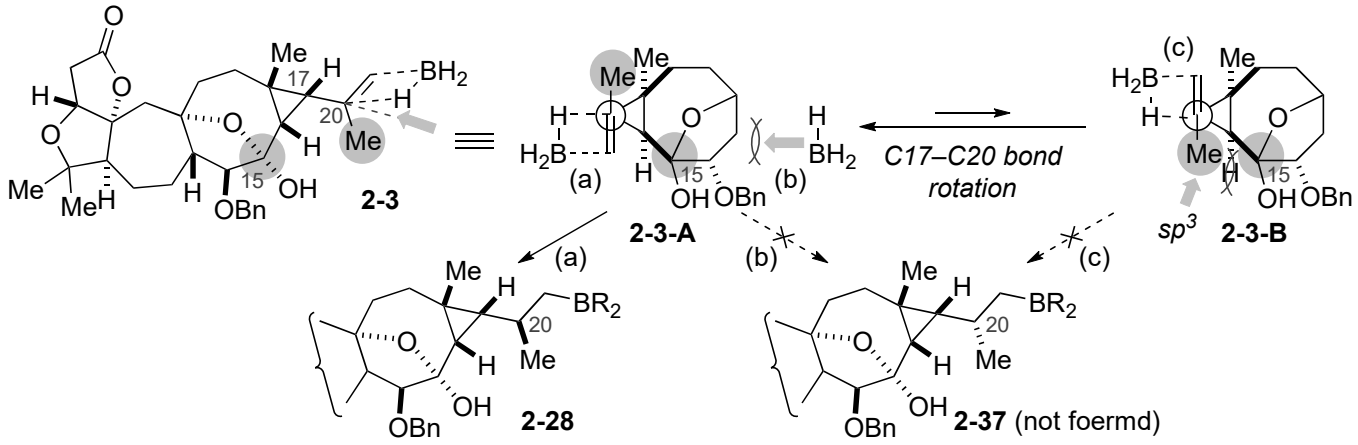


*The actual reaction mechinism is much more complex than the above-drawn, and is still unclear for details.

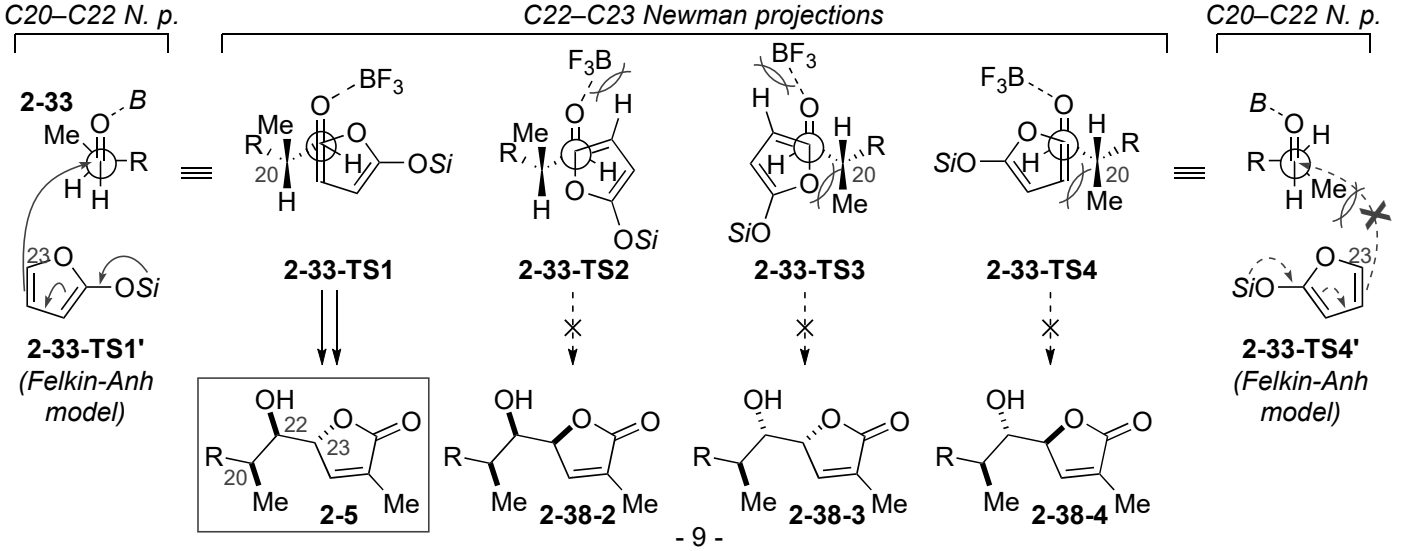


*⊿G was calculaed by Gaussian 09 M06/6-311+G(d).
$\Delta G_{\mathbf{2\text{-}34}}$ was setted up tp 0 kcal/mol.

<Discussion 1: Stereoselectivity in hydroboration>

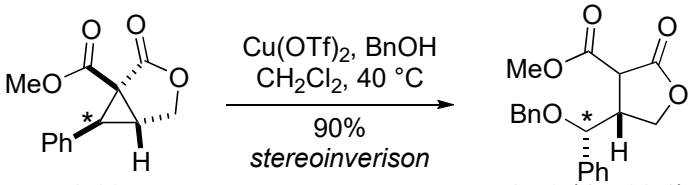


<Discussion 2: Stereoselectivity in vinylogous Mukaiya aldol reaction>



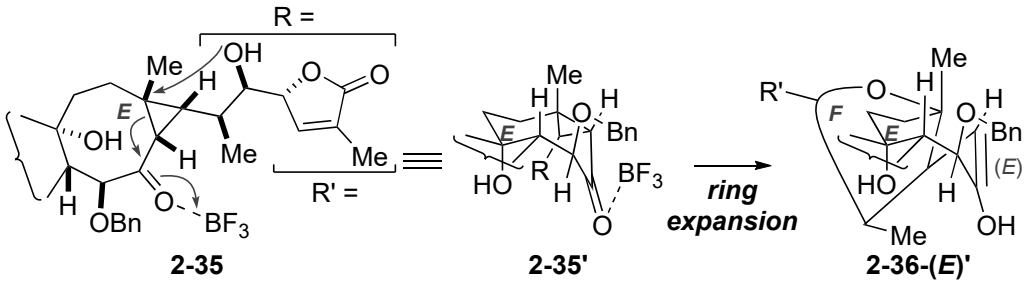
<Discussion 3: homo-Michael addition>

3-1 An exapmle of intermolecular homo-Michael addition with stereoinversion

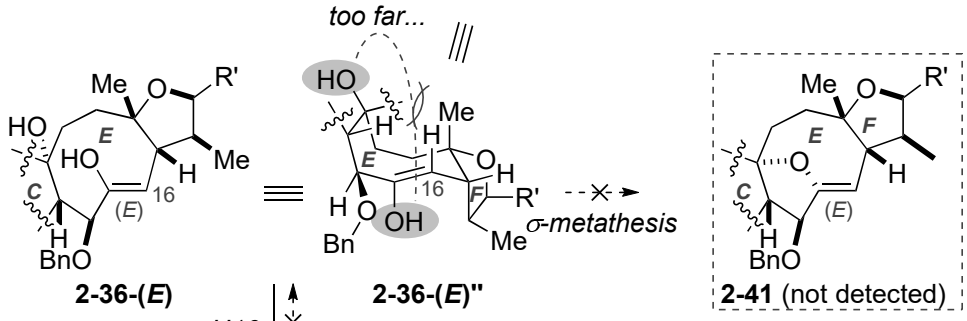


2-39 **2-40** (dr >99:1) Takada, S. *et al.Tetrahedron Lett.* **2016**, *57*, 2422.

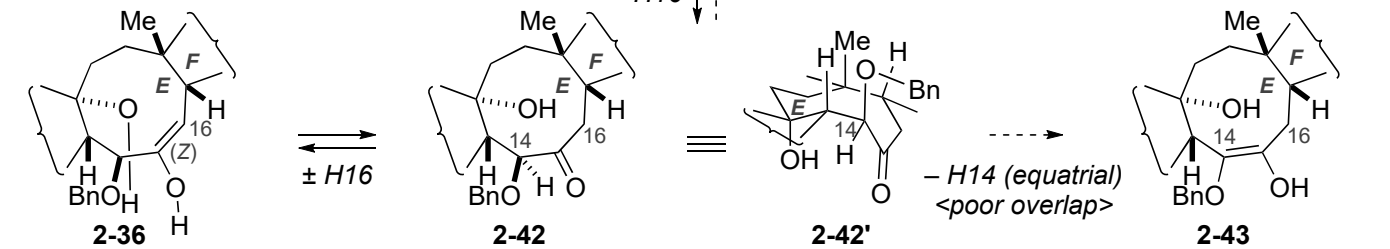
3-2 Ring expansion & DE ring formation (⊿G was calculaed by Gaussian 09 M06/6-311+G(d)).



2-35 **2-35'** **2-36-(*E*)'**

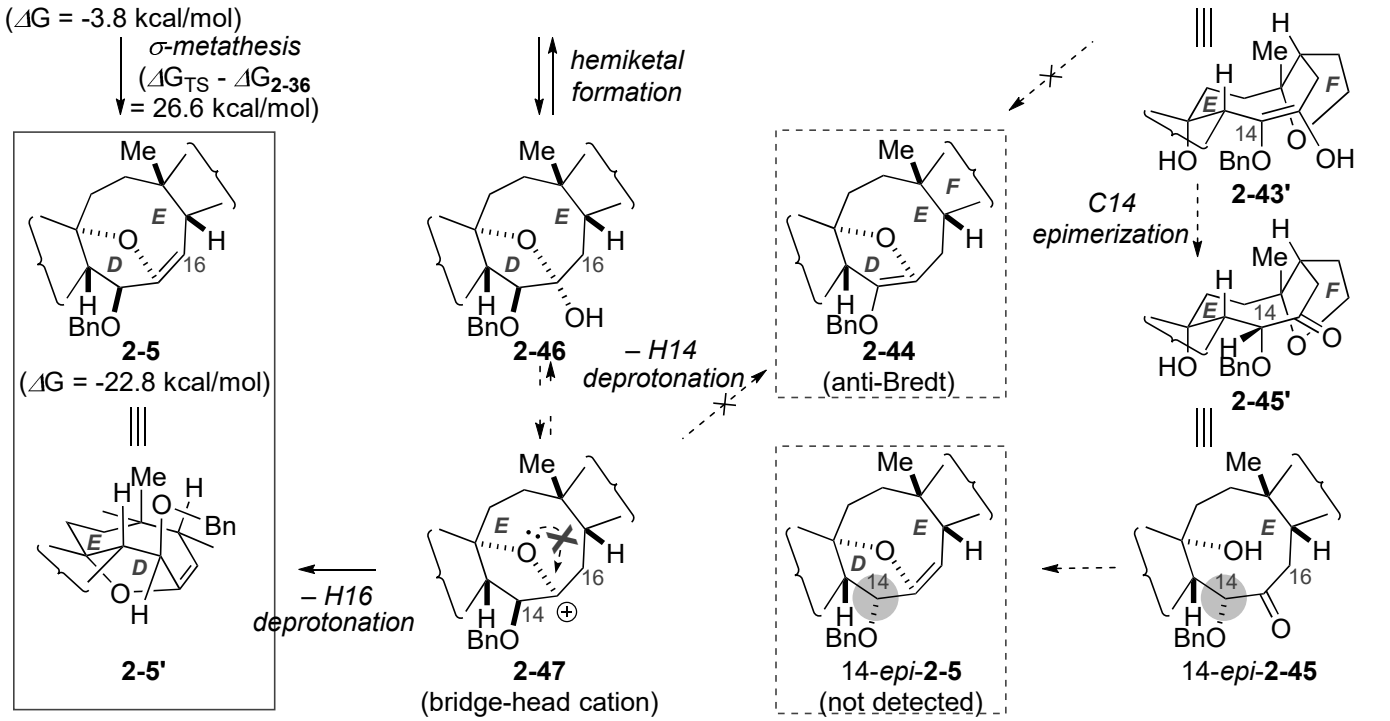


2-36-(*E*) **2-36-(*E*)"** **2-41** (not detected)



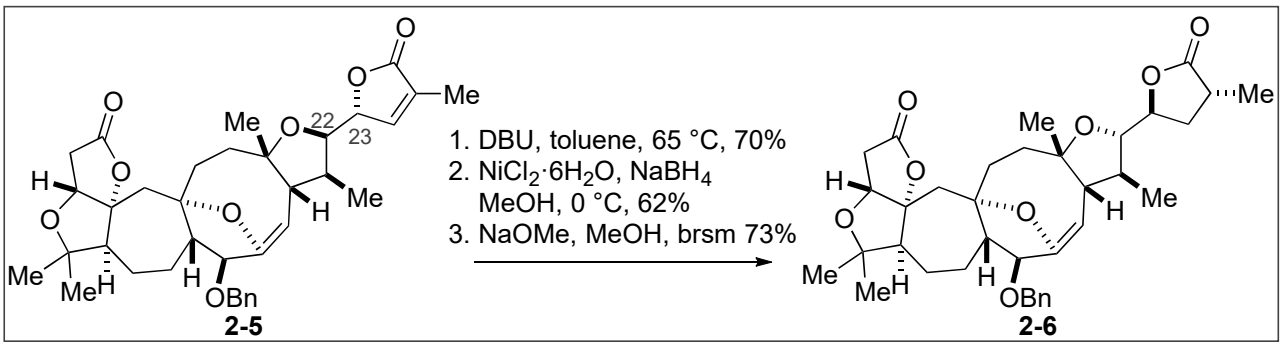
2-36 **2-42** **2-42'** **2-43**

(⊿G = -3.8 kcal/mol)

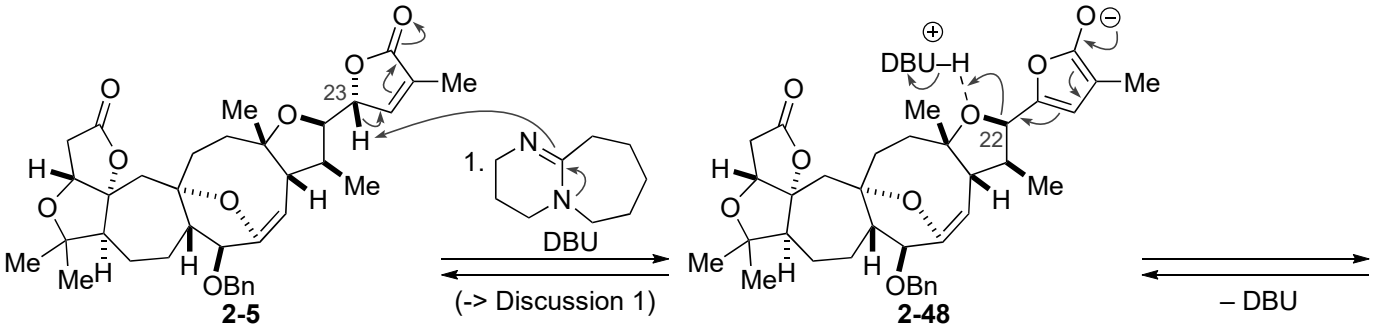


2-5 (⊿G = -22.8 kcal/mol) **2-5'** **2-46** **2-47** (bridge-head cation) **2-44** (anti-Bredt) **2-43'** **2-45'** 14-*epi*-**2-5** (not detected) 14-*epi*-**2-45**

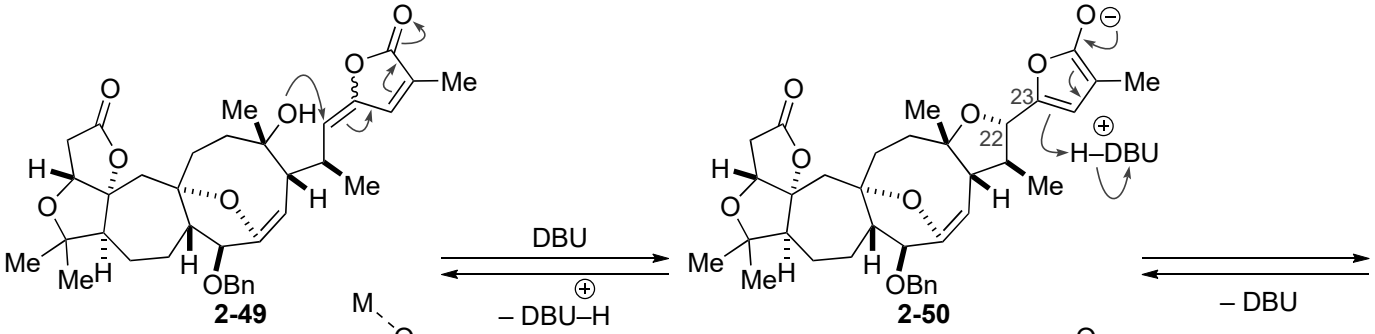
2.5 Transformation from **2-5** to **2-6**



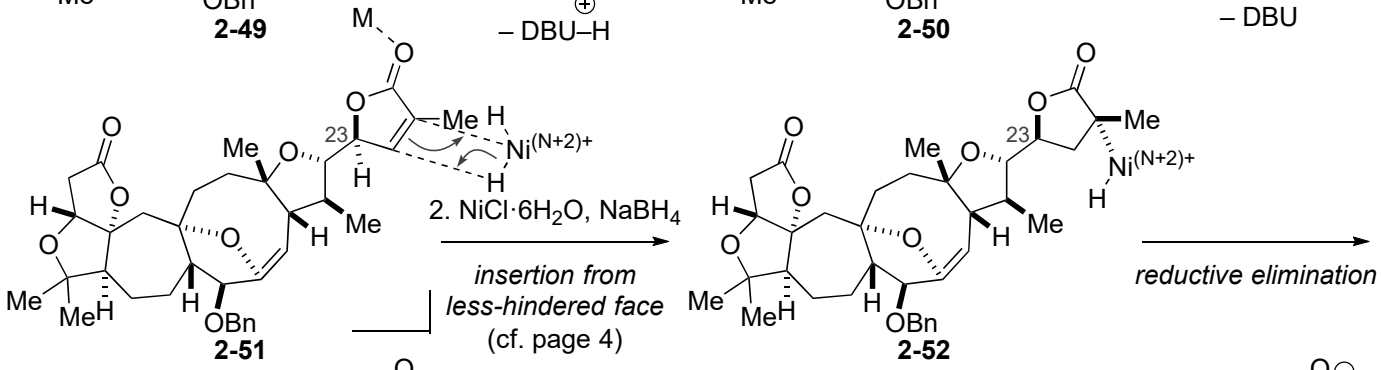
2-5 **2-6**



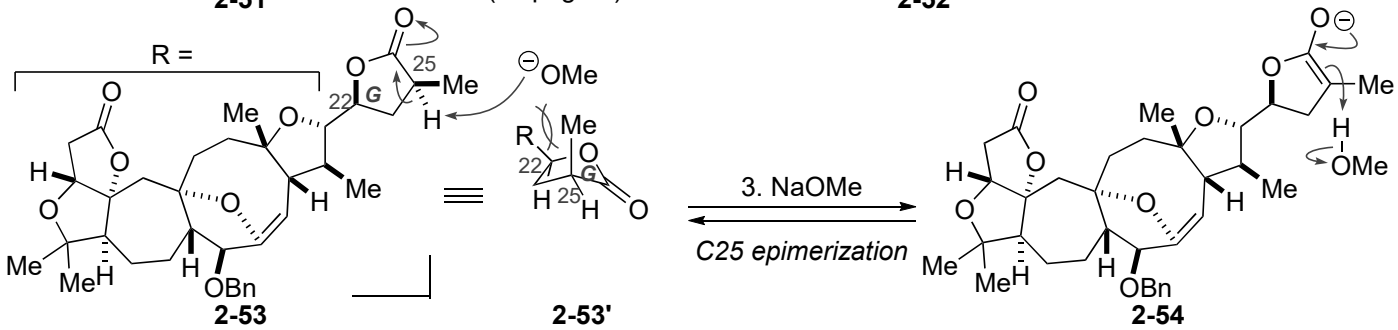
2-5 **2-48**



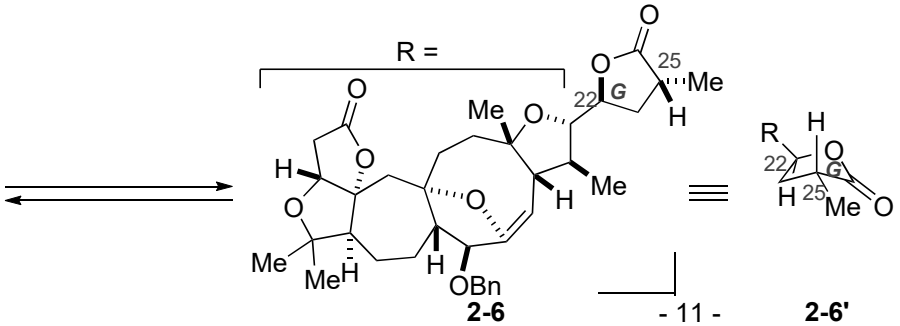
2-49 **2-50**



2-51 **2-52**



2-53 **2-53'** **2-54**



2-6 **2-6'**

<Discussion:1 Thermodinamically-controlled isomerization at C22 & C23>
(⊿G was calculaed by Gaussian 09 M06/6-311+G(d))