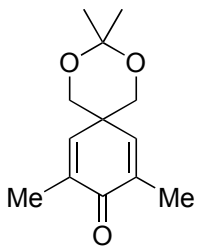
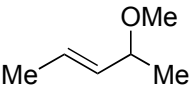
Problem Session (5)

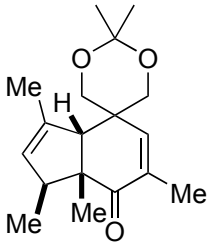
2016. 5. 7 Masaki Koshimizu

Please provide reaction mechanisms (**1**→**2**, **3**→**4**, **5**→**6, 7**→**8**)



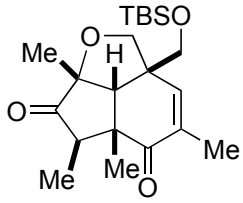
1

1. 
   Cp_2TiCl_2, *n*-BuLi, THF, -78 °C to rt;
   then **1**, -40 °C to 10 °C
   3.8:1 ratio of olefin diastereomers, 62%
2. *t*-BuOK, [18]crown-6, THF
   -78 °C to -40 °C, then Et_3SiCl, -78 °C
   d.r.=3.6:1, 70%
3. $Pd(OAc)_2$, O_2, DMSO, 45 °C, 74%



2

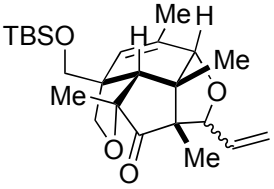
4 steps



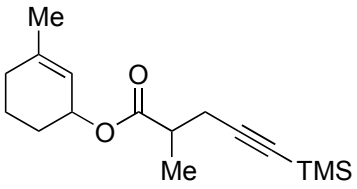
3

1. KH, THF, rt; then [18]crown-6
   propargyl bromide, 0 °C, 87%
2. $[(Ph_3PAu)_3O]BF_4$
   1,2-dichloroethane, 75 °C, 84%
3. $LiBHEt_3$, THF, -78 °C, 80%
4. AuClL, AgOTs, toluene, 60 °C
   d.r.=3.2:1, 72%

L = 2-(di-*tert*-butylphosphino)biphenyl

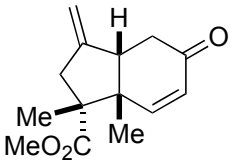


4



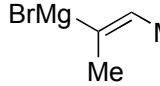
5

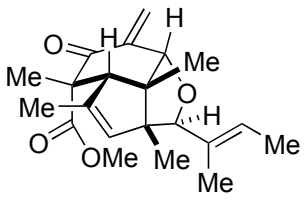
1. $KNTMS_2$, TMSCl
   Et_3N, toluene
   -78 to 70 °C; then
   $TMSCHN_2$, CH_2Cl_2
   25 °C, 85% (ca. 1.5:1 d.r.)
2. CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2
   -20 to 25 °C, 86%, (ca. 1.5:1 d.r.)
3. DDQ, 1,4-dioxane, 100 °C, 83%
4. K_2CO_3, MeOH, 25 °C, 85%
5. $[Pd_2(dba)_3]$, P(*o*-tol)$_3$, Et_3SiH, AcOH
   benzene, 25 °C, 87%



6

4 steps

1. 
   (1.2 eq)
   THF, -78 °C; then
   $=\overset{\oplus}{N}Me_2\ Cl^{\ominus}$ (3 eq), -78 to -25 °C, 80%
2. $TsOH\cdot H_2O$, toluene, 60 °C, 82%



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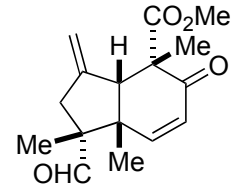
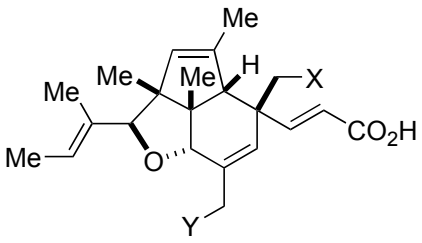


7

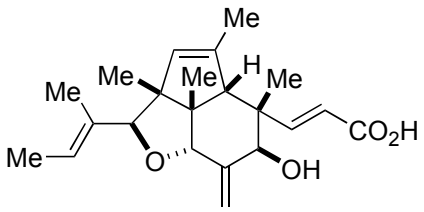
Problem Session (5) - Answer -

2016. 5. 7 Masaki Koshimizu

Synthetic Study of indoxamycins



indoxamycin A: X = H, Y = H
indoxamycin B: X = OH, Y = H
indoxamycin C: X = H, Y = OH



indoxamycin F

0. Introduction

0-1. Isolation

from saline cultures of marine-derived actinomycetes by Sato in 2009
S. Sato, F. Iwata, T. Mukai, S. Yamada, J. Takeo, A. Abe, H. kawahara, *J. Org. Chem*. **2009**, *74*, 5502.

0-2. Bioactivities

growth-inhibition activitiy against HT-29 tumor cell lines
indoxamycin A: IC_{50} = 0.59 μM mitomycin: IC_{50} = 0.66 μM
indoxamycin F: IC_{50} = 0.31 μM

0-3. Total synthesis

・Total synthesis of indoxamycin B in 2012 by Carreira => problem 1
O. F. Jeker, E. M. Carreira, *Angew Chem. Int. Ed.* **2012**, *51*, 3474.
・Total syntheses of indoxamycin A, C and F by Ding => problem 2
C. He, C. Zhu, Z. Dai, C-C. Tseng, H. Ding, *Angew Chem. Int. Ed.* **2013**, *52*, 13256.

0-4. Structural revision of indoxamycins

0-4-1. Carreira's achievement (2012)

indoxamycin B
(originally proposed)

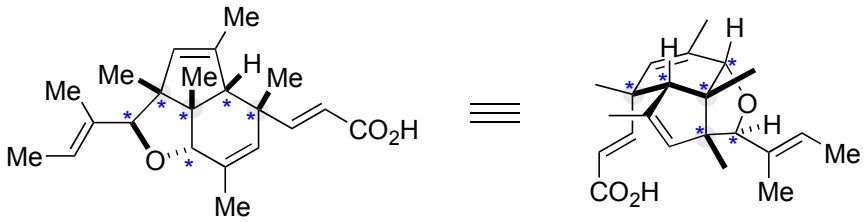
indoxamycin B
(revised)

0-4-2. Ding's achievement (2013)
elucidation of the stereochemistry of indoxamycin A, C and F

indoxamycin F
(originally proposed)

indoxamycin F
(revised)

0-5. Strutural features



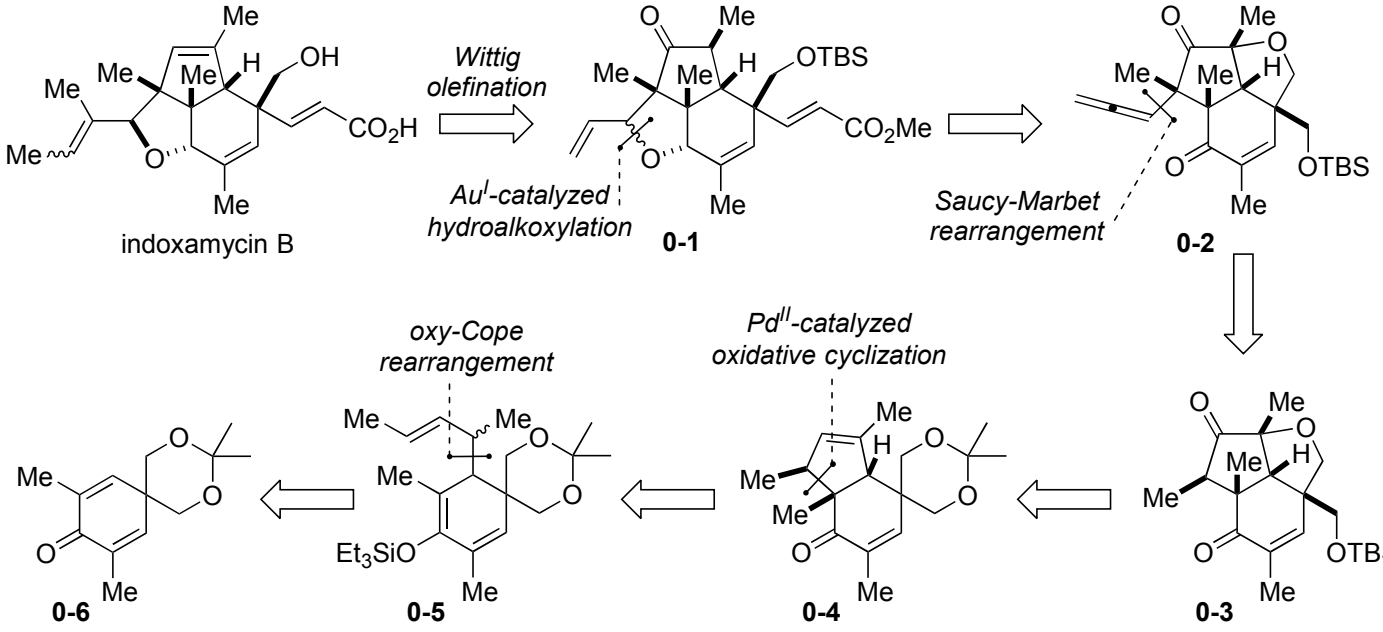
indoxamycin A

unprecedented [5,5,6]
tricyclic cage-like carbon framework

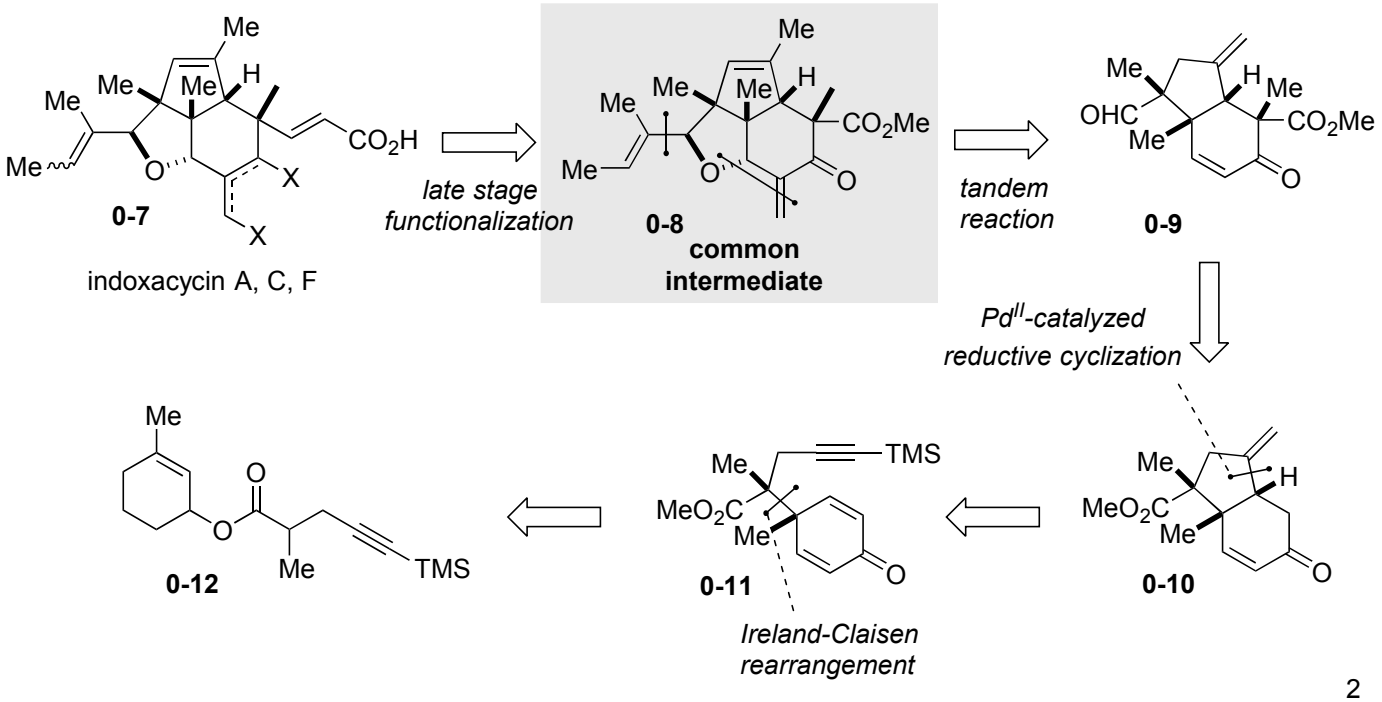
- six contiguous stereogenic centers
- three quaternary carbon atoms including two vicinal carbon atoms
- tetrasubstituted olefin
- unsaturated carboxylic acid

0-6. Synthetic strategies

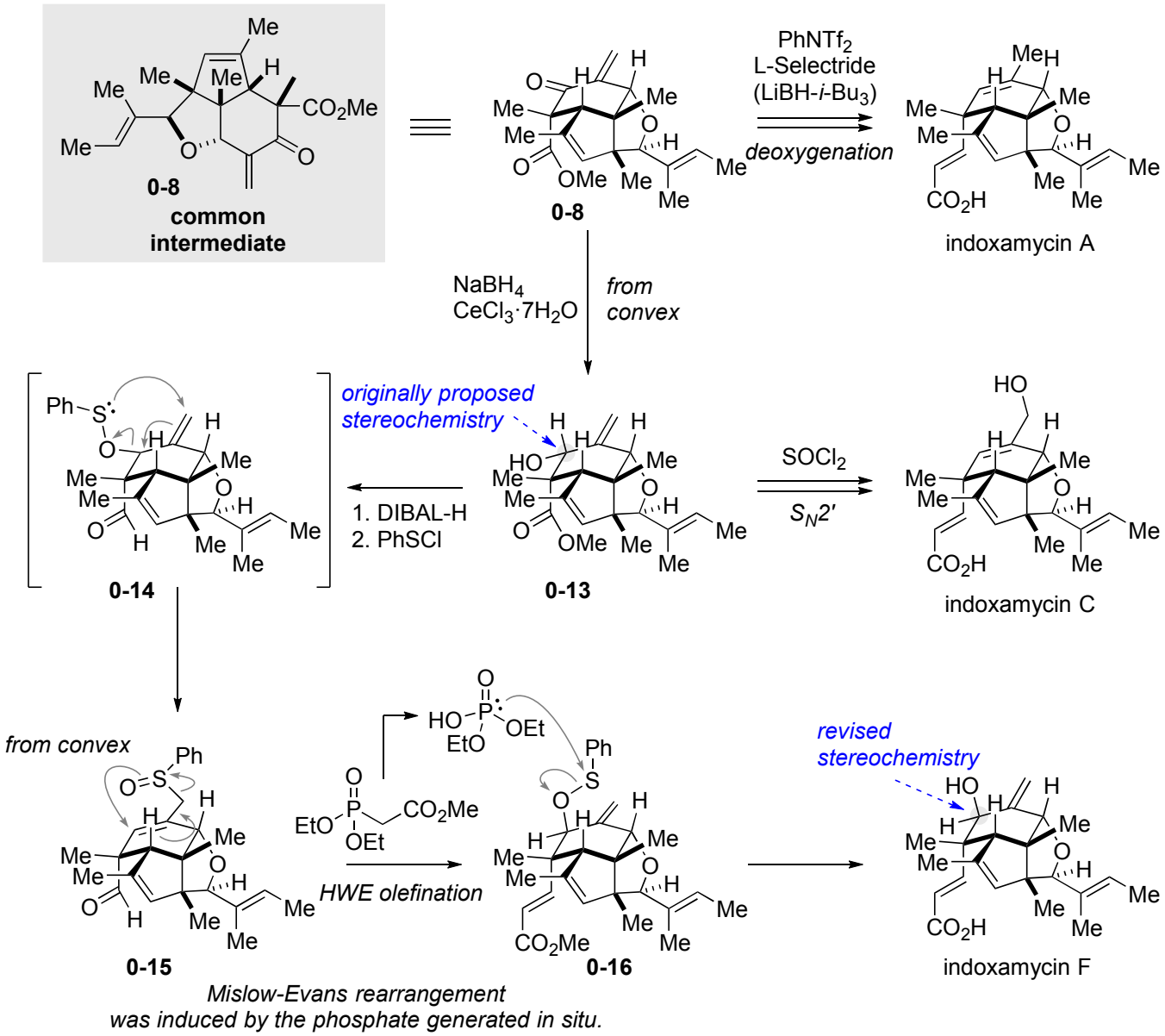
0-6-1. Carraira's approach



0-6-2. Ding's approach

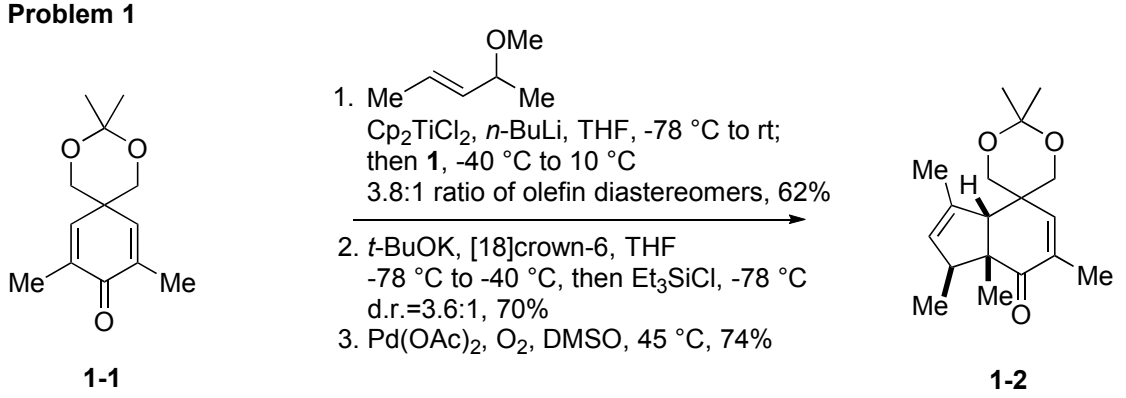


Ding's divergent total synthesis



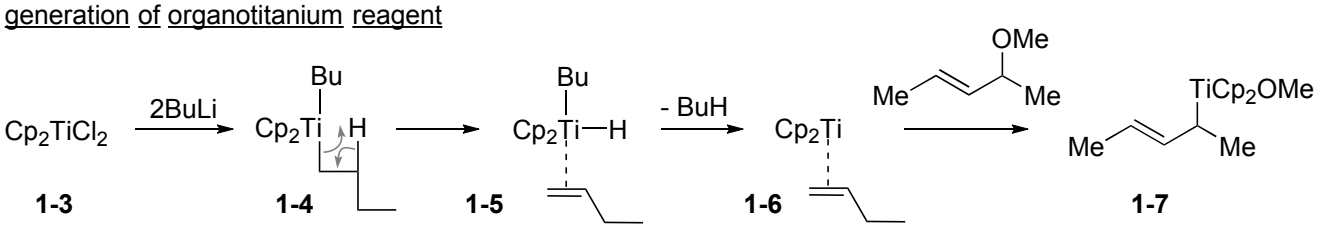
1) Carreira's total synthesis of indoxamycin B

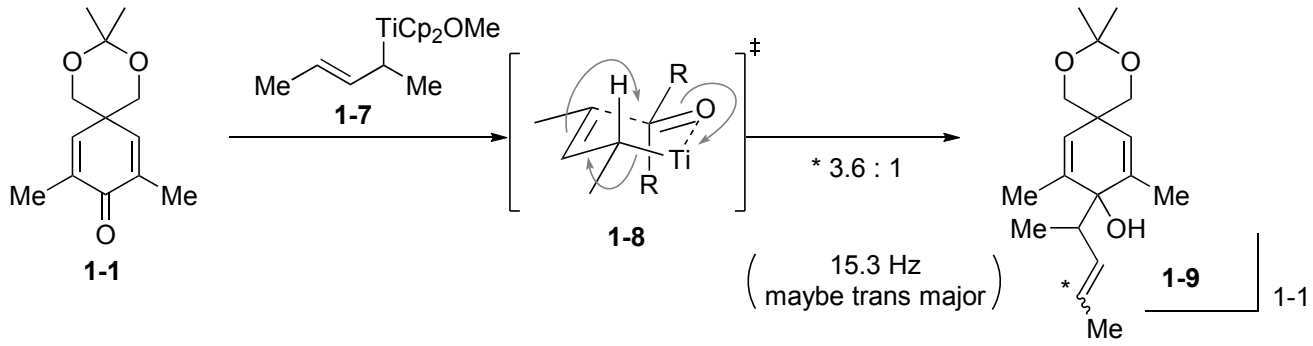
Problem 1

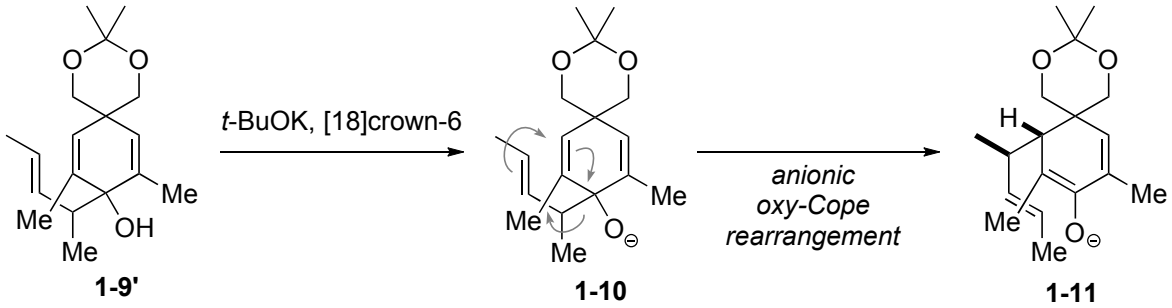


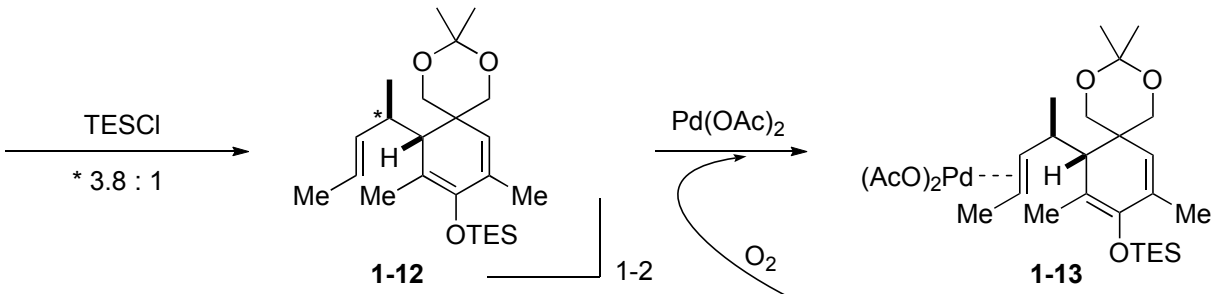
<key reactions>
- Anionic oxy-Cope rearrangement
- Pd-mediated oxidative cyclization

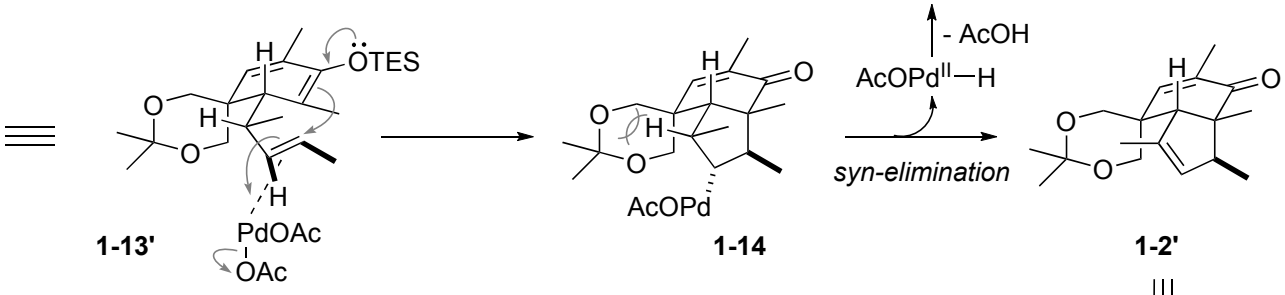
generation of organotitanium reagent

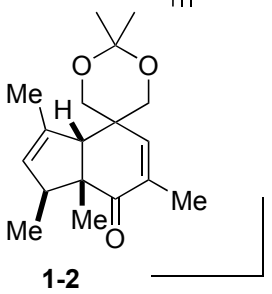




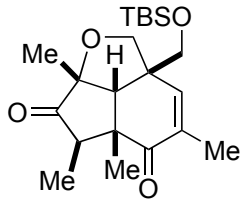








Problem 2



2-1

1. KH, THF, rt; then [18]crown-6 propargyl bromide, 0 °C, 87%
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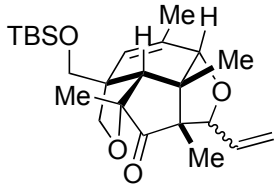
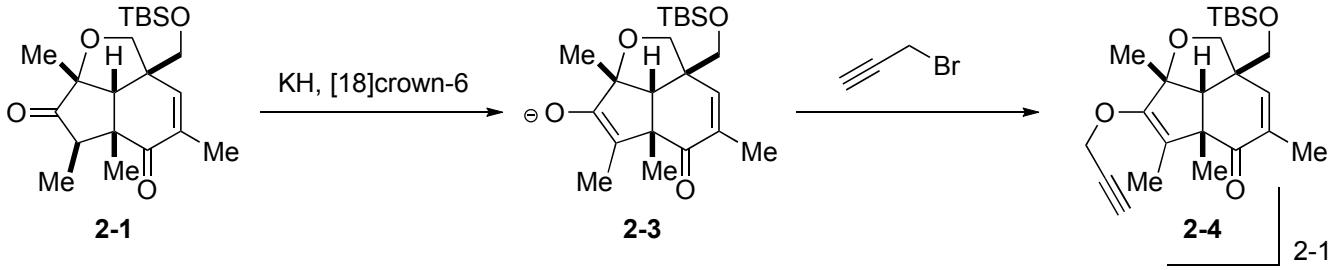
3. $LiBHEt_3$, THF, -78 °C, 80%
4. AuClL, AgOTs, toluene, 60 °C d.r.=3.2:1, 72%

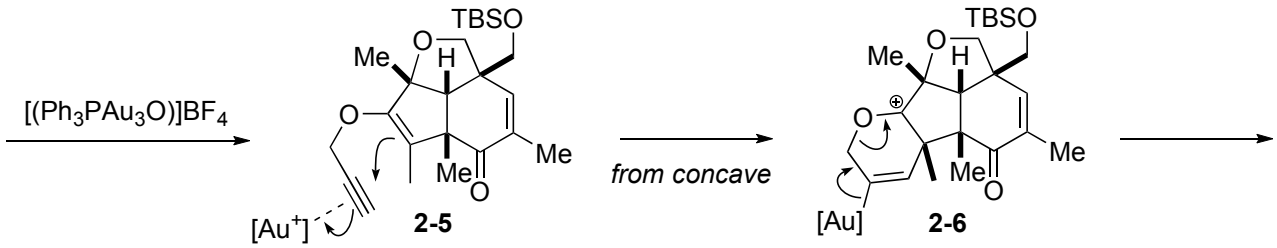
L = 2-(di-*tert*-butylphosphino)biphenyl



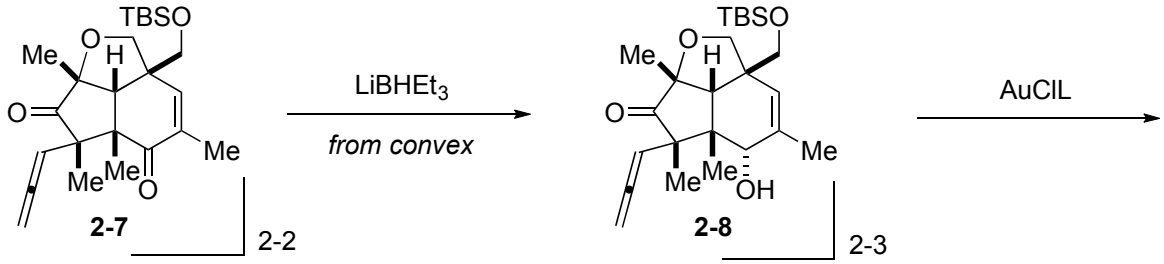
2-2

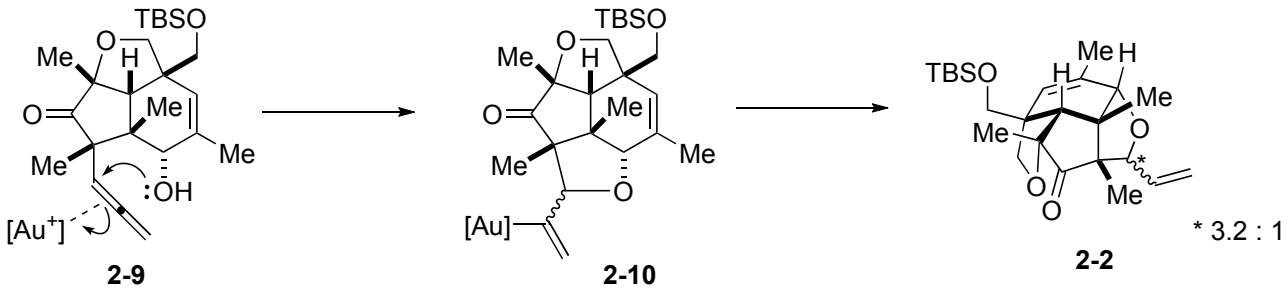
<key reactions>
・Saucy-Marbet rearrangement
・Au-catalyzed hydroalkoxylation





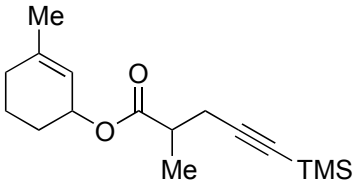
propargyl Claisen rearrangement
(Saucy-Marbet rearrangement)





2) Ding's total syntheses of indoxamycin A, C and F

Problem 3



3-1

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   -78 to 70 °C; then
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   25 °C, 85% (ca. 1.5:1 d.r.)
2. CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2
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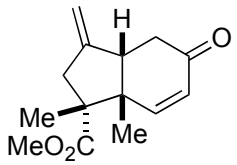
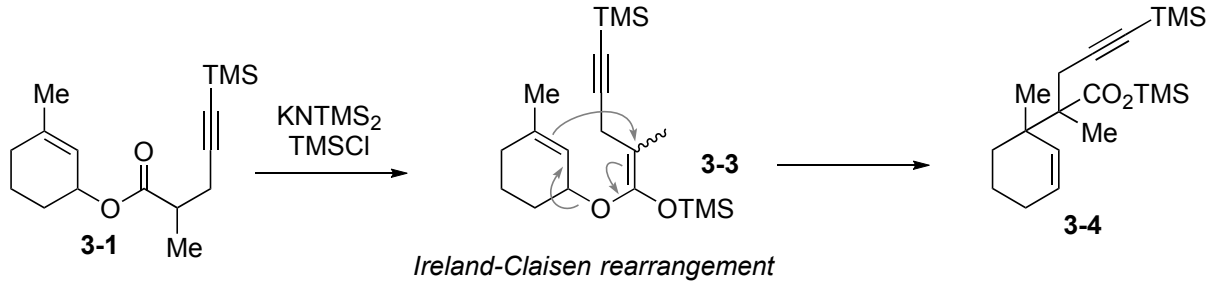
3. DDQ, 1,4-dioxane, 100 °C, 83%
4. K_2CO_3, MeOH, 25 °C, 85%
5. $[Pd_2(dba)_3]$, P(*o*-tol)$_3$, Et_3SiH, AcOH
   benzene, 25 °C, 87%

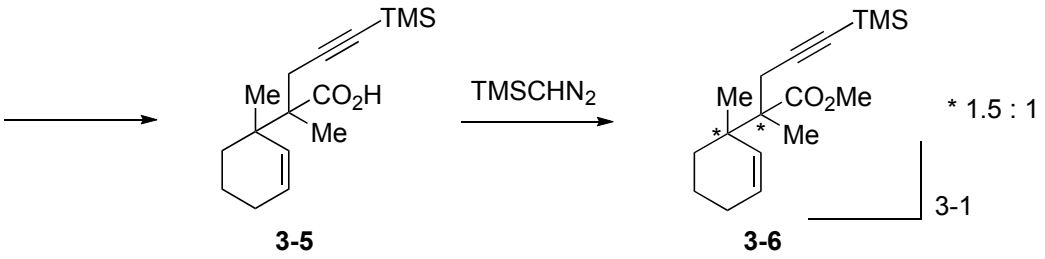


3-2

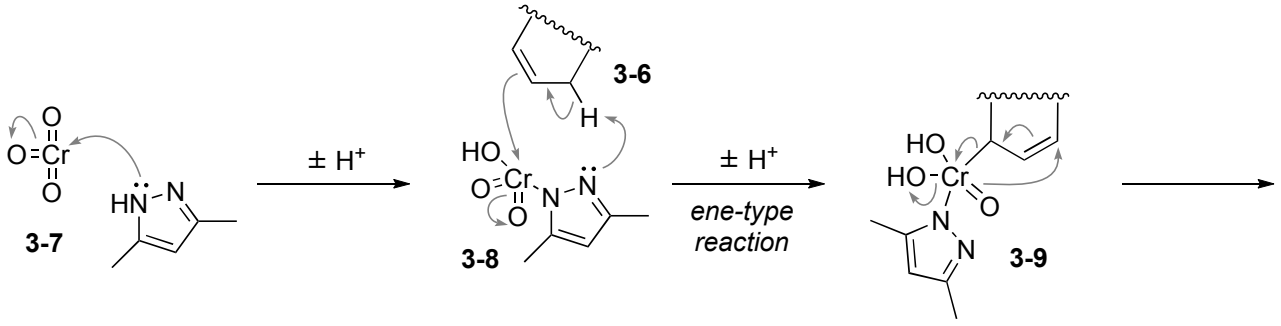
<key reactions>
- Ireland-Claisen rearrangement
- Pd-catalyzed reductive cyclization



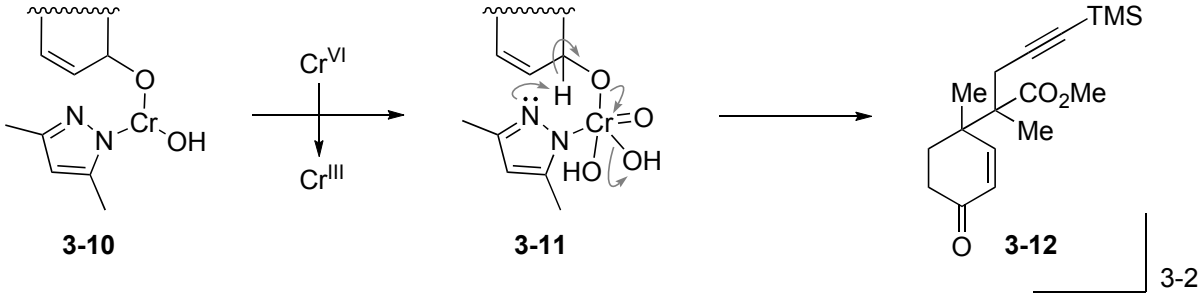
Ireland-Claisen rearrangement



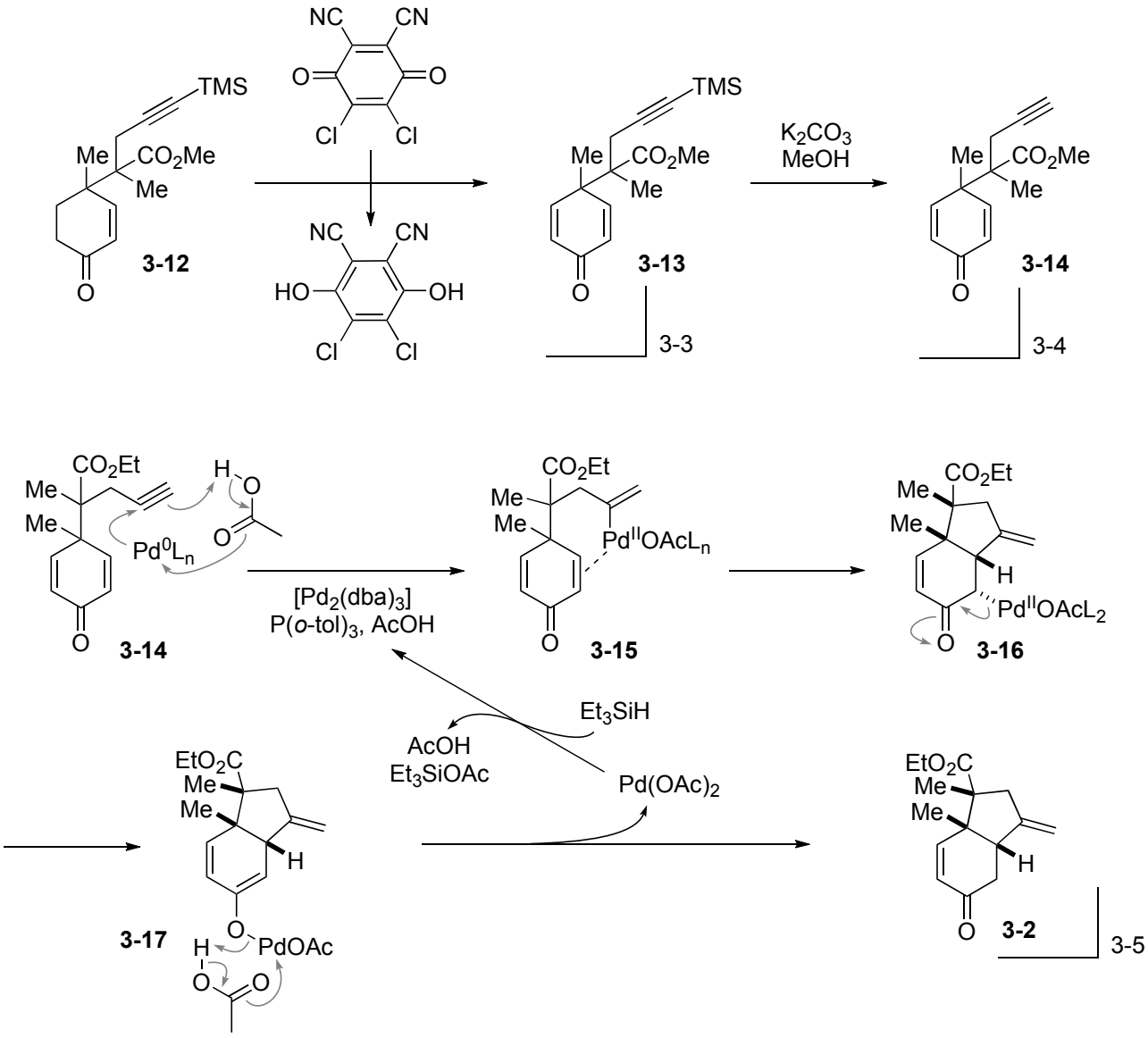
3-5 **3-6** * 1.5 : 1 3-1



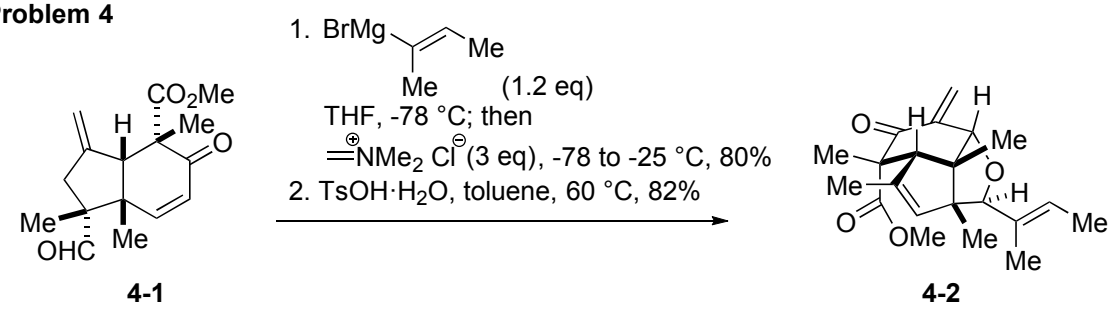
3-7 **3-8** **3-9**



3-10 **3-11** **3-12** 3-2

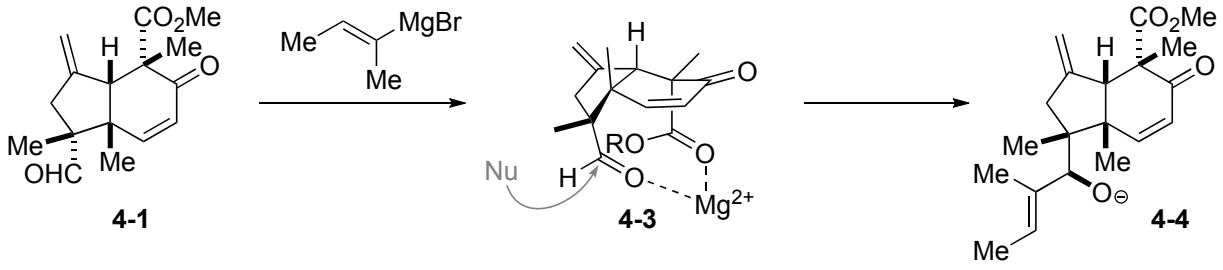


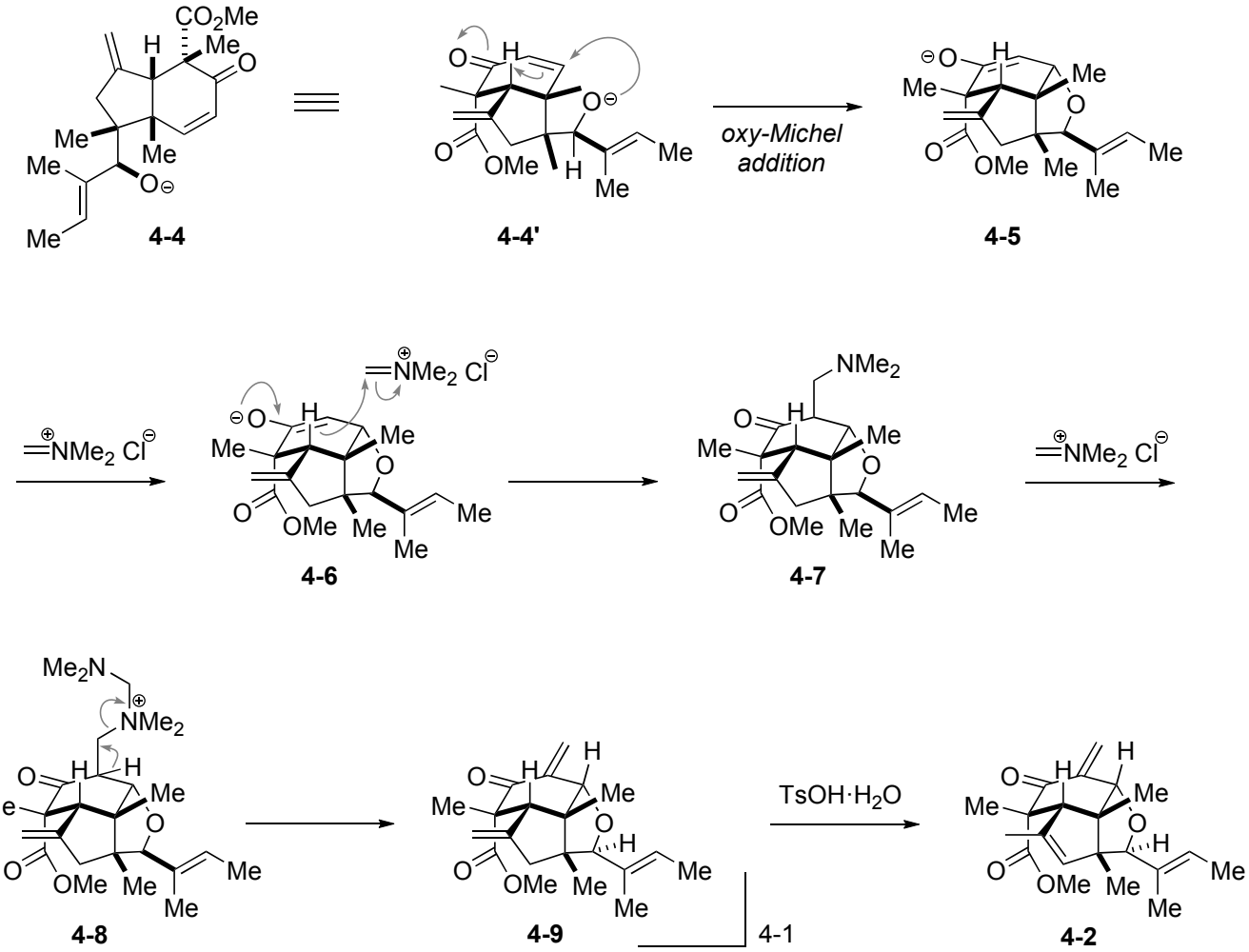
Problem 4



<key reactions>

・Tandem reaction (Grignard addition, oxy-Michael addition, methylenation)




4-4
4-4'
oxy-Michel addition
4-5
4-6
4-7
4-8
4-9
TsOH·H2O
4-2
4-1