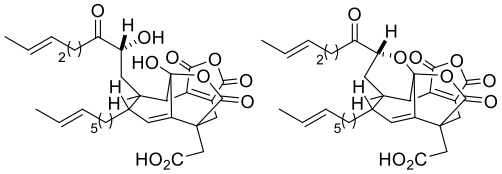
Problem Session (3) – Dead End and Detours -

2015.7.25 Haruka Fujino

Please solve the three following problems (**Problem 1 to 3**).

CP-molecules [(+)-CP-225,917 (Phomoidride A, **0-1**, Figure 1) and (–)-CP-263,114 (Phomoidride B, **0-2**)], two novel fungal metabolites reported by a research group at Pfizer in mid-1990s, have attracted a lot of organic synthetic chemists due to both of its intriguing biological activity and a unique complex structure.

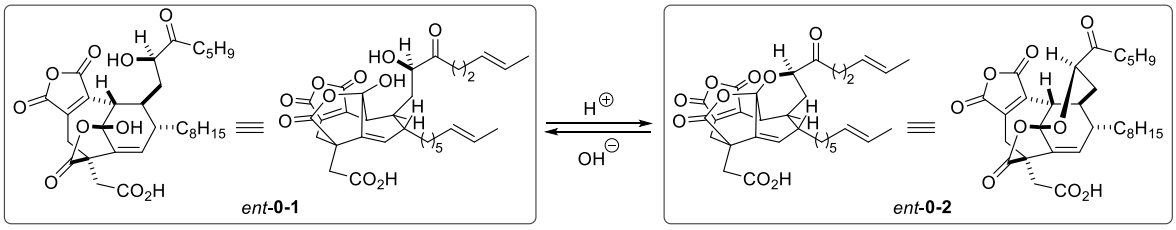
Figure 1. CP molecules



Phomoidride A (**0-1**) Phomoidride B (**0-2**)

K. C. Nicolaou *et al.* accomplished their first total synthesis (racemic form in 1999 and enantiopure (albeit enantiomers of natural ones; *ent*-**0-1** and *ent*-**0-2**) form in 2000). **0-1** and **0-2** can be mutually transformed under acidic ((*ent*-)**0-1** to (*ent*-)**0-2**) or basic ((*ent*-)**0-2** to (*ent*-)**0-1**) conditions (Scheme 1).

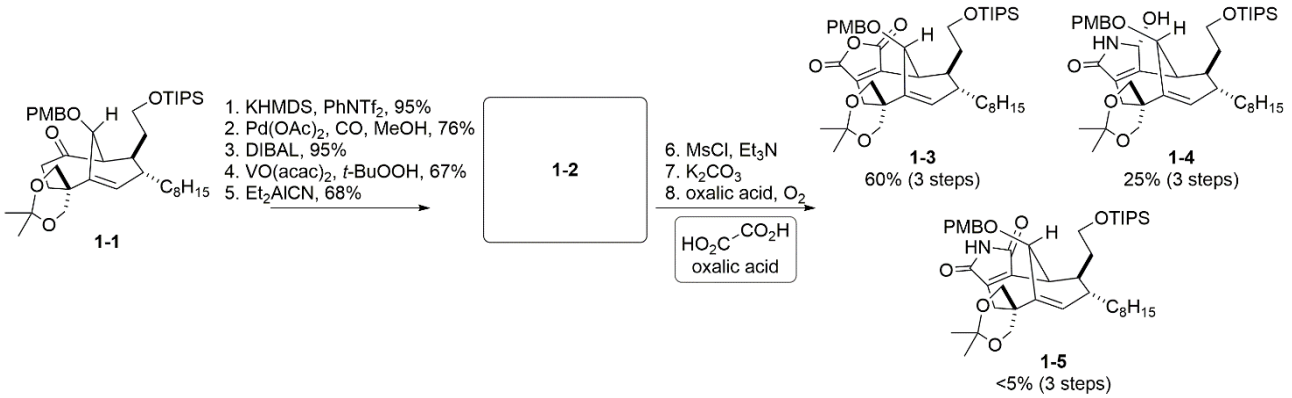
Scheme 1. Mutual conversion between (*ent*-)**0-1** and (*ent*-)**0-2**



<**Problem 1**: 1st Dead End ~ Construction of Maleic Anhydride>

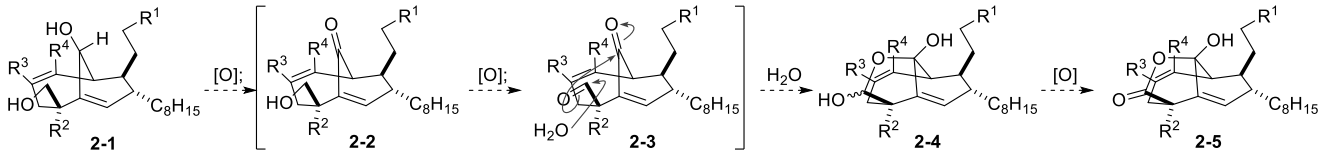
After several errors and traials, they finally accomplished construction of maleic anhydride moiety.

Problem 1. Please fill the blank and explain the reaction mechanism of the following reaction.



<**Problem 2**: 2nd Dead End ~ Construction of γ-hydroxylactone>

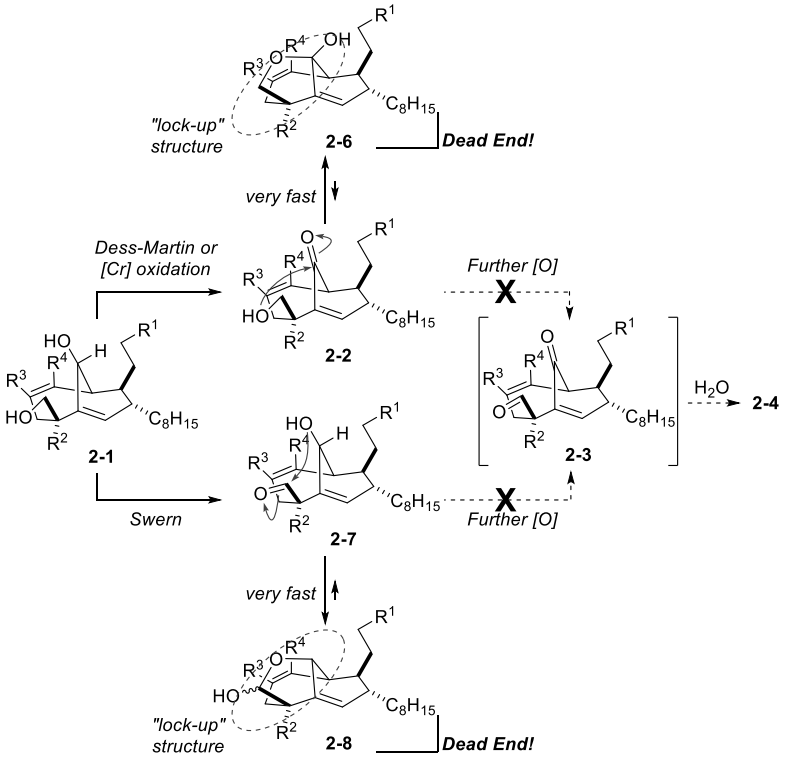
Scheme 2. First synthetic plan of γ-hydroxylactone ring



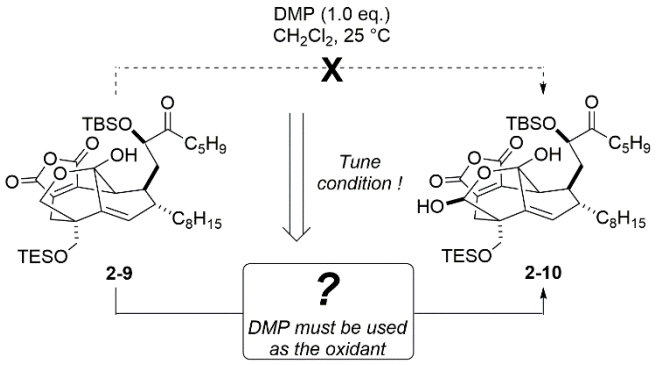
At first they planned to construct γ–hydroxylactone ring as shown in scheme 2. Successive oxidation of diol **2-1** to dialdehyde **2-3** via hydroxyl ketone **2-2** was expected. Unfortunatelly, this plan was failed (Scheme 3).

Oxidation of diol **2-1** afforded hydroxyenone **2-2** or hydroxyaldehyde **2-7** in good selectivity dependent on oxidating reagents. If further oxidation of another hydroxyl group on **2-2**/**2-7** was occurred, desired dialdehyde **2-3** (so unstable that immediately hydrolated to **2-4**) could be obtained. However, fast intramolecular hydroxyl group's attack to ketone (**2-2**)/aldehyde (**2-7**) was occurred. Afforded "cyclic-locked" compounds **2-6**/**2-8** were not able to be further oxidized to dialdehyde. Reverse reaction to **2-2**/**2-7** seemed very slow, and equilibrium is leaned towards locked compound **2-6**/**2-8**. That is why **2-6** and **2-8** are dead compounds.

Scheme 3. Attempted oxidation of diol **2-1** to dialdehyde **2-4**

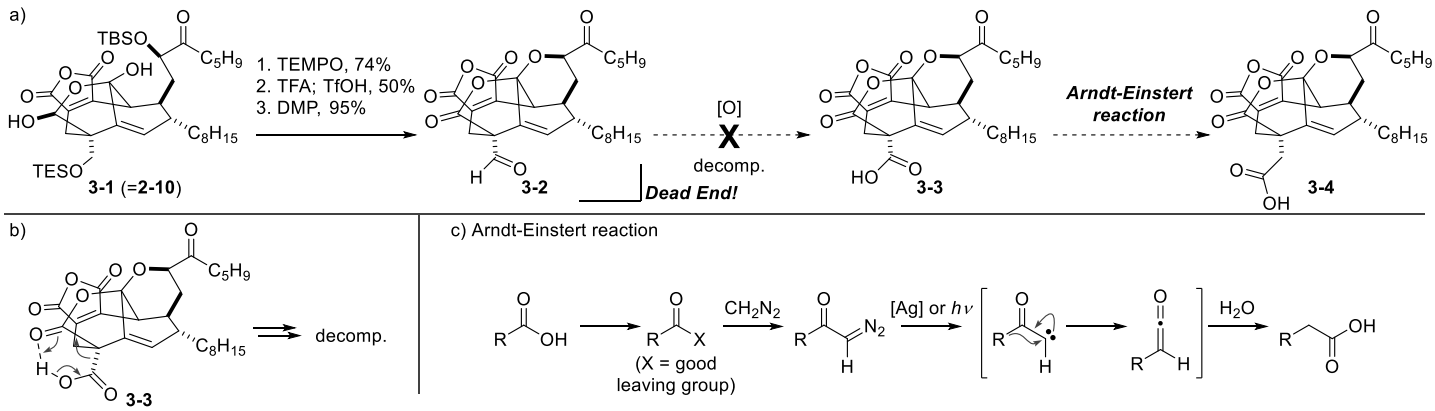


Problem 2. Further Dess-Martin oxidation of "locked" compound **2-9** to 2-10 could not be occurred under the shown condition (DMP (1.0 eq.), 25 °C). How should we **logically** tune the reaction condition in order to obtain desired compound **2-10**? One-step condition is desirable, but multi-step conversion is also acceptable. In any case, Dess-Martin periodinane (DMP) must be used as the oxidant.



<**Problem 3**: 3rd Dead End ~ Homologation>

Scheme 4. Attempted homologation by Arndt-Einstert reaction

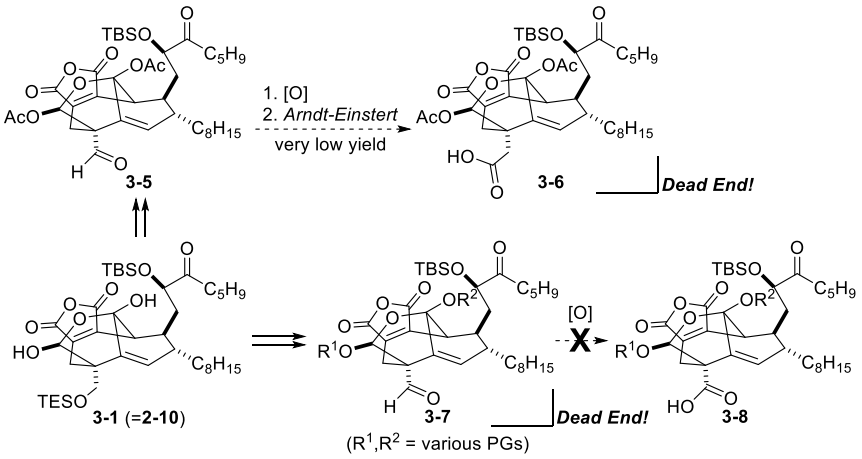


Towards the total synthesis of CP-molecules, Arndt-Einstert reaction (Scheme 4c) was chosen as homologating method. Nicolaou *et al.* designed carboxylic acid **3-3** as a substrate of Arndt-Einstert reaction. Conversion from **3-1** (=**2-10**) to aldehyde **3-2** smoothly proceeded in three steps (Scheme 4a). However, any attempts to oxidize **3-2** to **3-3** was all failed and decomposition of substrates was only observed. This unexpected results may be casued by rapid decarboxylative decomposition of **3-3** generated

in situ (Scheme 4b).

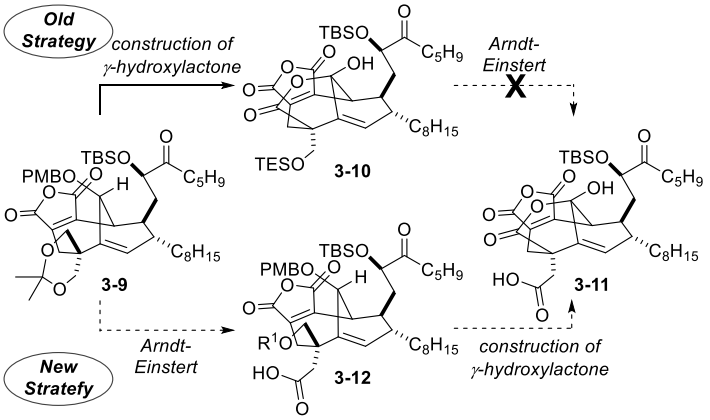
Considering the instability of β-ketocarboxylic acid structure in **3-3**, it is natural that they conceived the usage of protected γ-hydroxylactol (ex. **3-5** and **3-7**, Scheme 5), though a number of protecting groups were all insuitable in this system (Scheme 5).

Scheme 5. Attempted conversion of protected γ-hydroxylactol



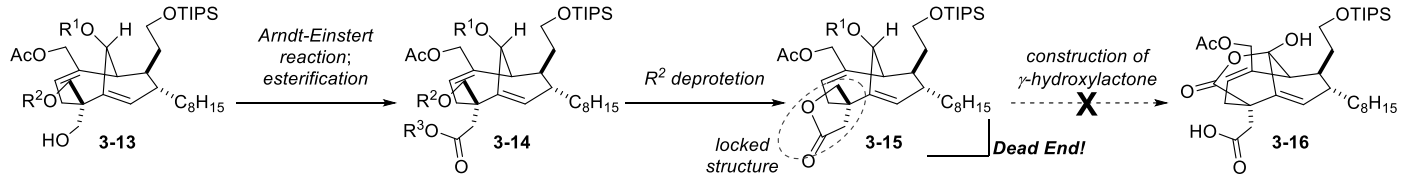
That is why they moved the next strategy, changing the order of conversion (**Old strategy**: at first construction of γ-hydroxylactone (**3-9** to **3-10**), then homologation (to **3-11**) → New strategy: at first homolagation (**3-9** to **3-12**), then construction of γ-hydroxylactone (to **3-11**)) (Scheme 6).

Scheme 6. Plan of new strategy

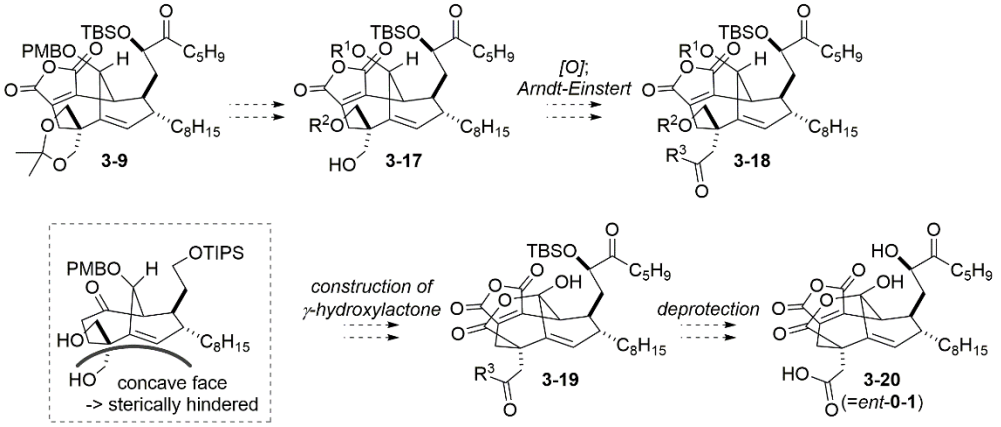


Along with this new strategy, they first conducted model study against **3-13**. Arndt-Einstert homolagation and subsequent esterification smoothly affored desired ester **3-14** (Scheme 7). However, in deprotecting R^2 group to construct γ-hydroxylactone moiety, the 1,4-diol system from **3-14** rapidly collapsed into γ-lactone **3-15**, and this "locking device" would not open nomatter what they tried.

Scheme 7. Dead-end locked structure **3-15**

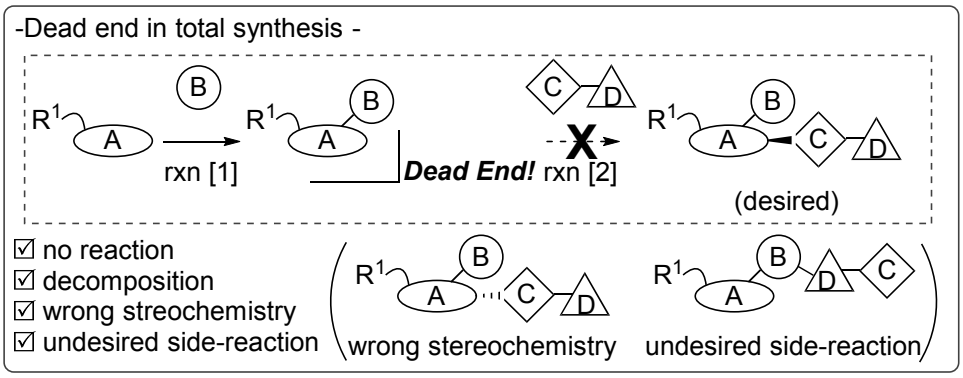


Problem 3. Choose the proper protecting groups (R^1-R^3) from the view point of inhibiting undesired reaction (like shown **Scheme 7**), shorter total steps and easily deprotection. Please note that α-face of CP molecules scheme is sterically very hindered because α-face is a concave face.



Problem Session (3) [Answer] - Dead Ends and Detours -

2015.7.25 Haruka Fujino



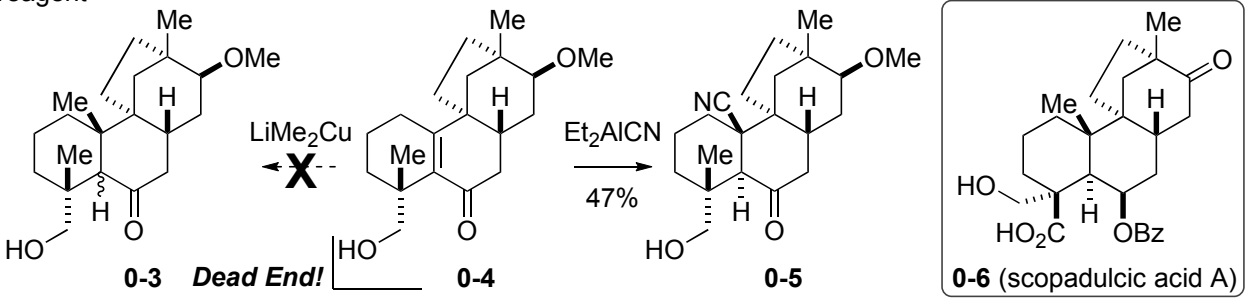
Reference:

Sierra, M. A.;de la Torre, M. C. *Dead Ends and Detours*, **2004**, Wiley-VCH, Weinheim.

(0) Introduction

0.1 Tuning reactions (-> **Problem 2**)

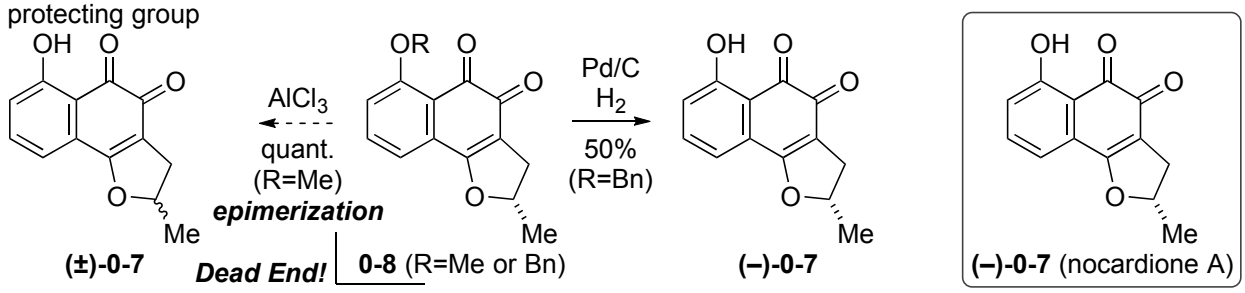
♣ reagent



Overman, L. E. *et al. J. Am. Chem. Soc.* **1997**, *119*, 12032.

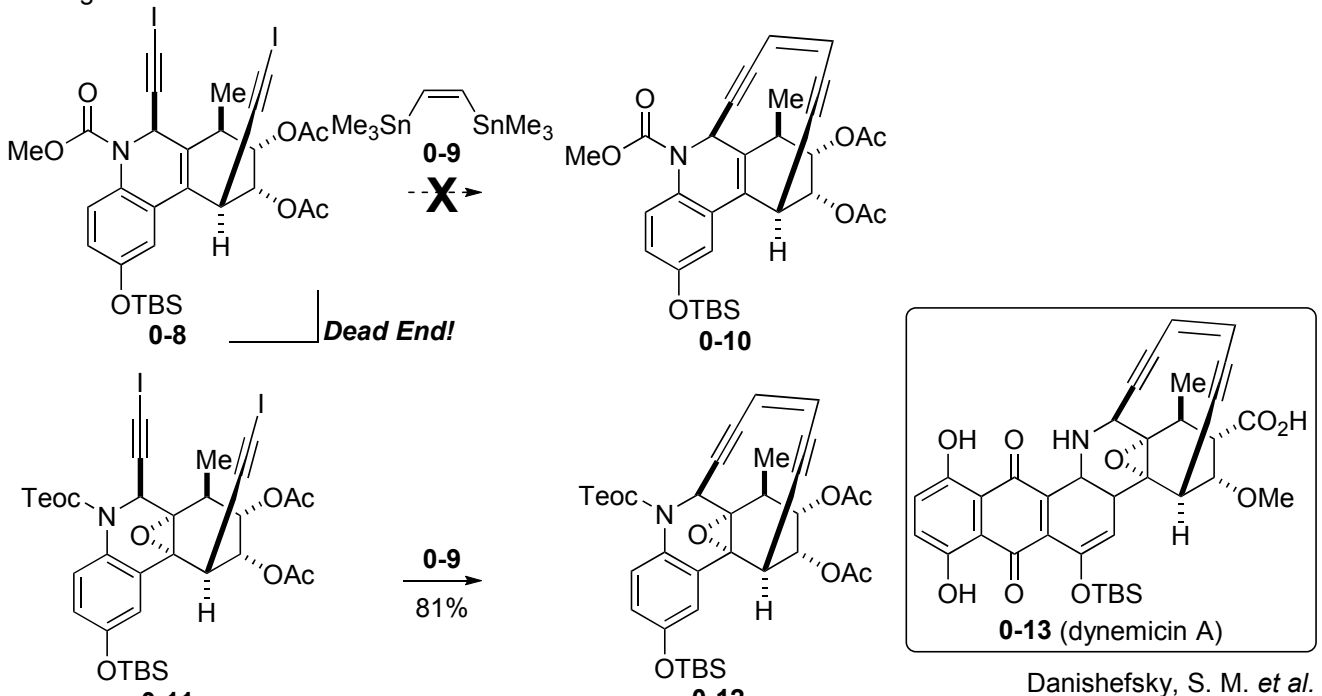
♣ substrate

◆ protecting group



Davis. F. A. *et al. Tetrahedron Lett.* **1978**, 5171.; *J. Org. Chem.* **1990**, *55*, 1254.

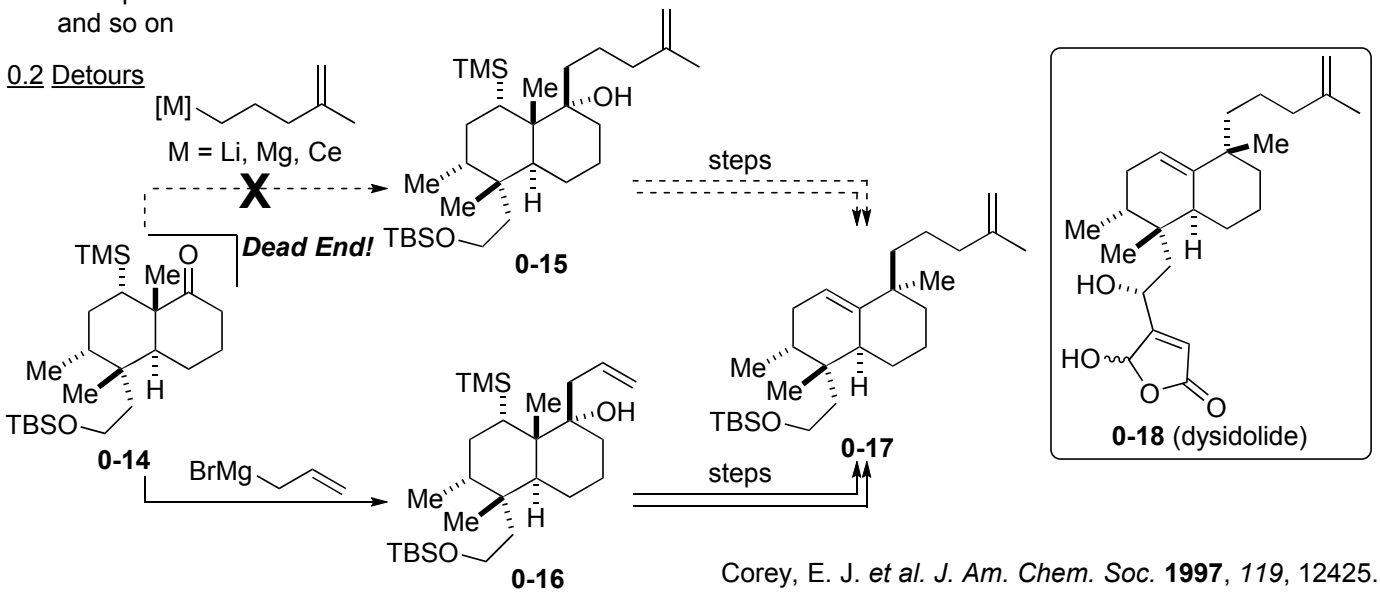
◆ redesign of scheme



Danishefsky, S. M. *et al.*
J. Am. Chem. Soc. **1996**, *118*, 9509.

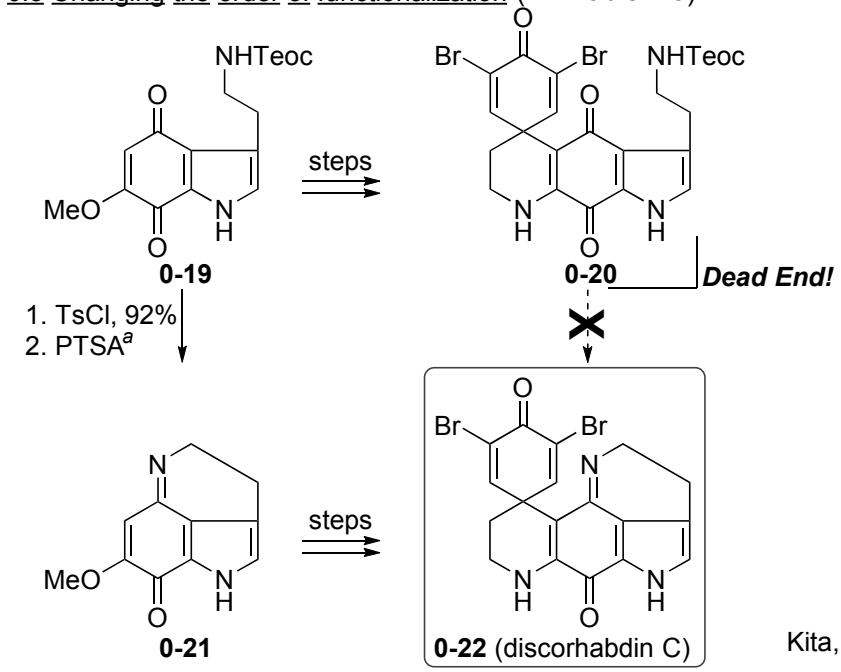
♣ additive
♣ solvent (concentration, non-polar vs polar vs protic, aromotic, coordination (ether, HMPA, DMPU...))
♣ temperature
and so on

0.2 Detours



Corey, E. J. *et al. J. Am. Chem. Soc.* **1997**, *119*, 12425.

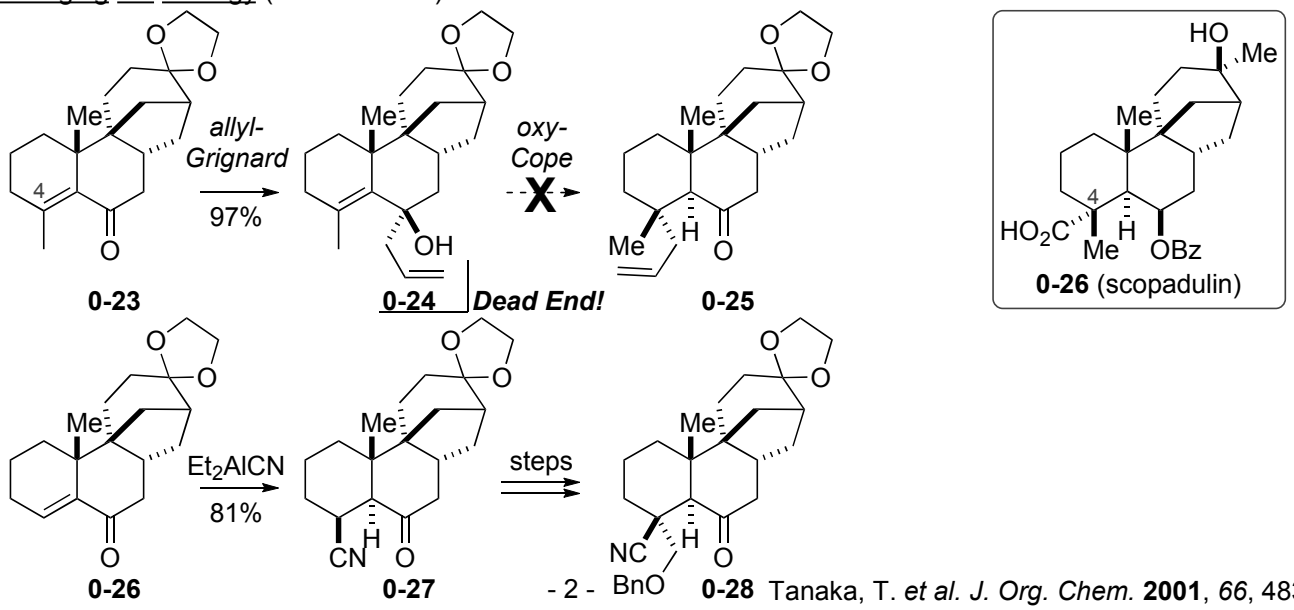
0.3 Changing the order of functionalization (-> **Problem 3**)



[a] Yield was not mentioned in this step.

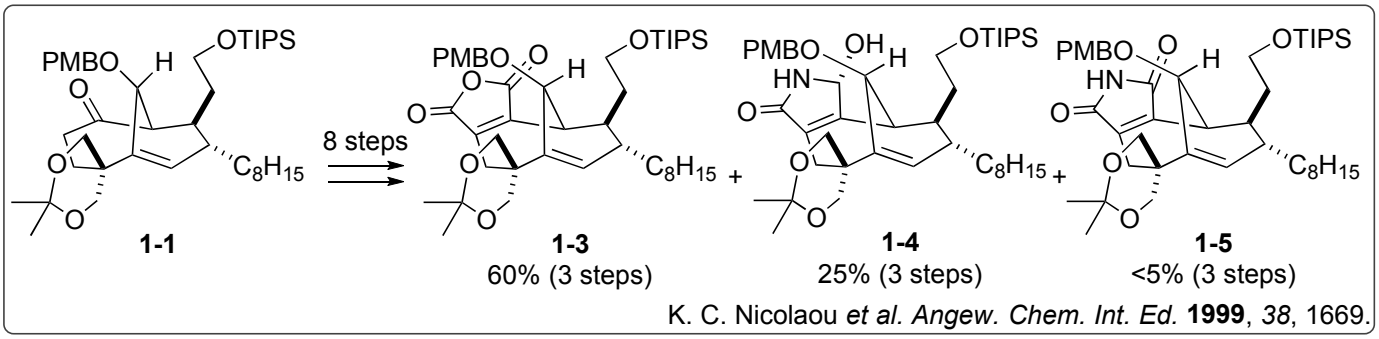
Kita, Y. *et al. J. Am. Chem. Soc.* **1992**, *114*, 2175.

0.4 Changing the strategy (-> **Problem 1**)



Tanaka, T. *et al. J. Org. Chem.* **2001**, *66*, 4831.

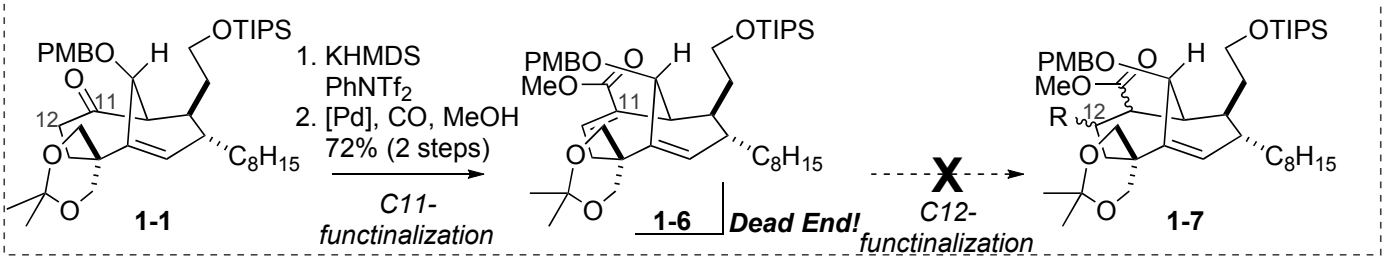
(1) Problem 1



K. C. Nicolaou *et al. Angew. Chem. Int. Ed.* **1999**, *38*, 1669.

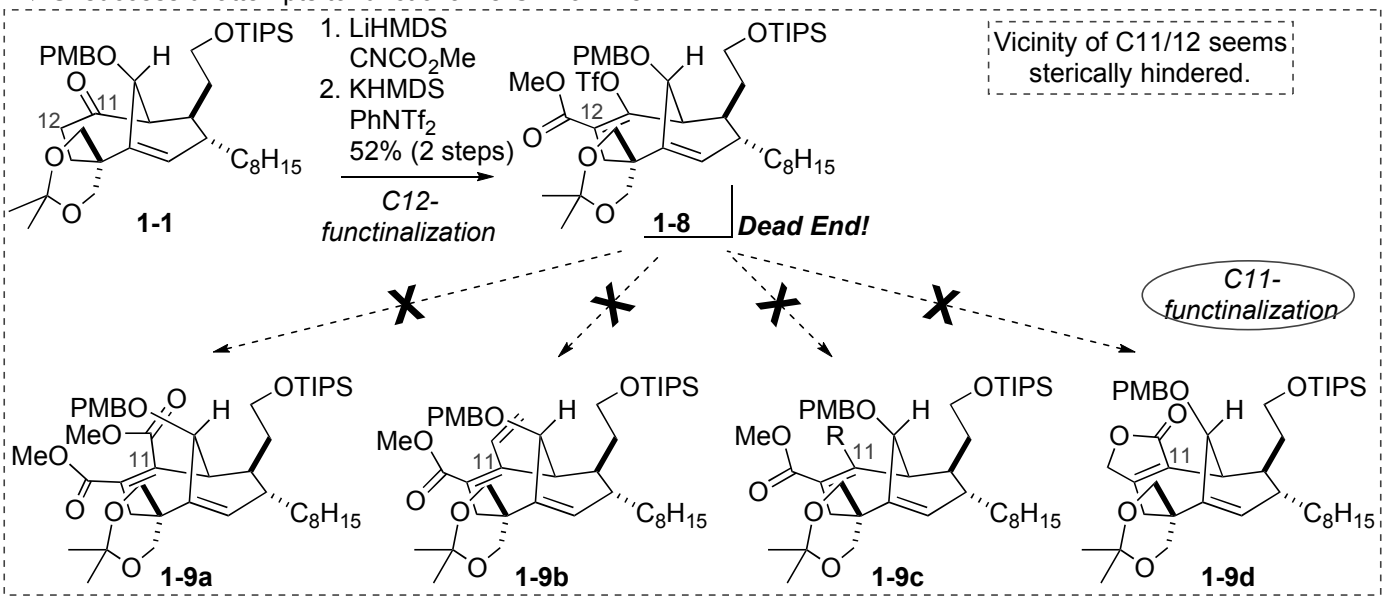
1.1 Background ~ A lot of dead ends ~ [K. C. Nicolaou *et al. Angew. Chem. Int. Ed.* **2002**, *41*, 2678.]

♣ C11 functionalization -> C12 functionalization

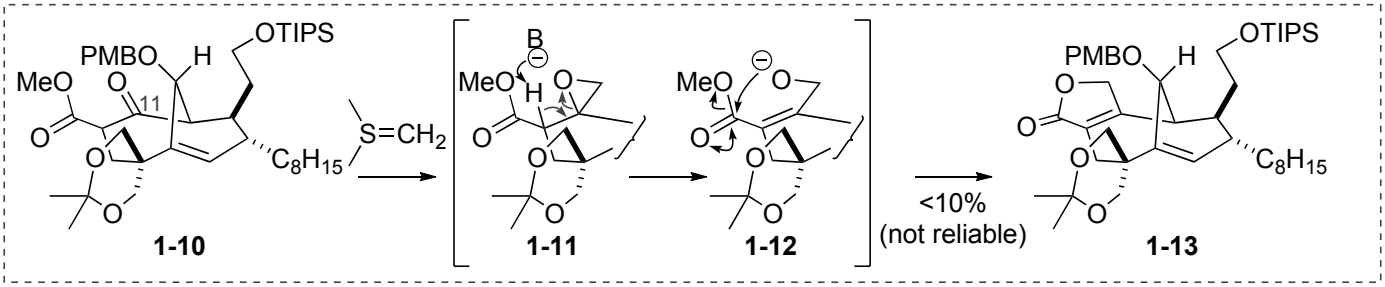


♣ C12 functionalization -> C11 functionalization [cf. 0.3 Changing the order]

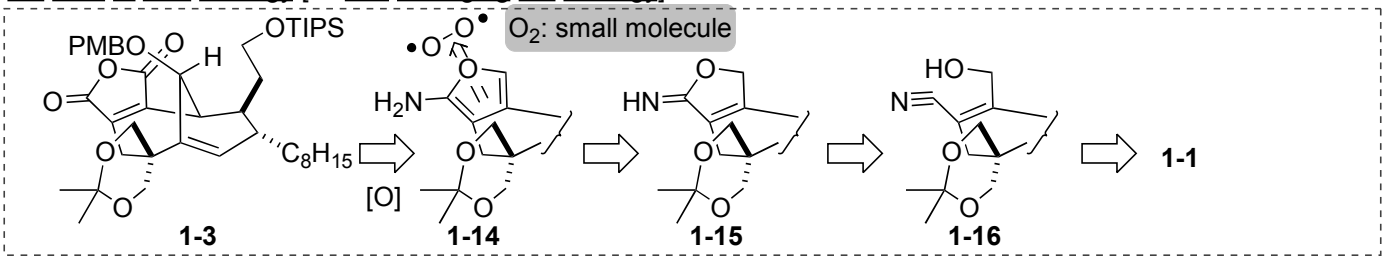
♦ Unsuccessful attempts to functionalize C11 on **1-8**



♦ Attempt to functionalize C11 on **1-10**

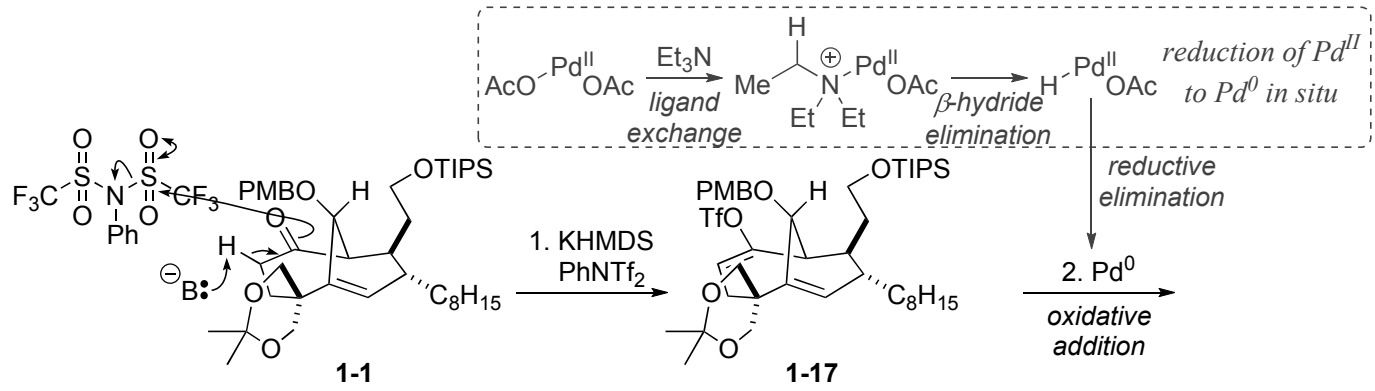


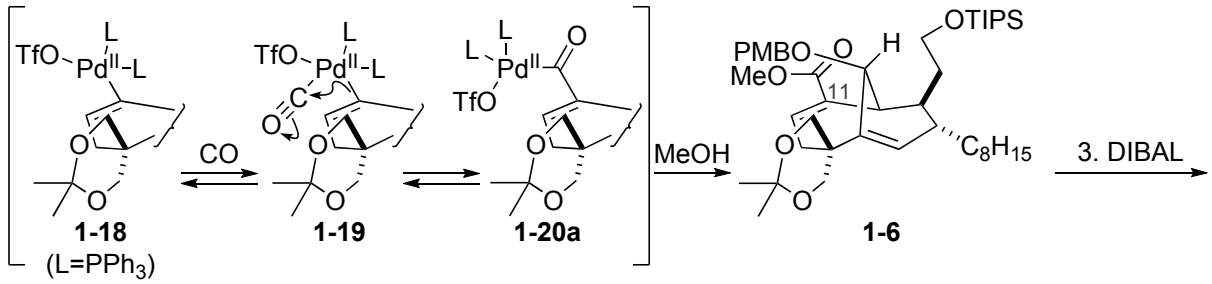
1.2 Plan of new strategy [cf. 0.4: Changing the strategy]

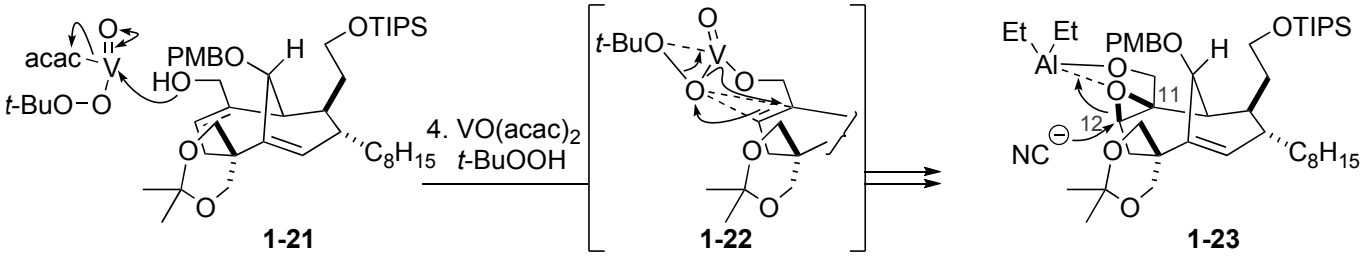


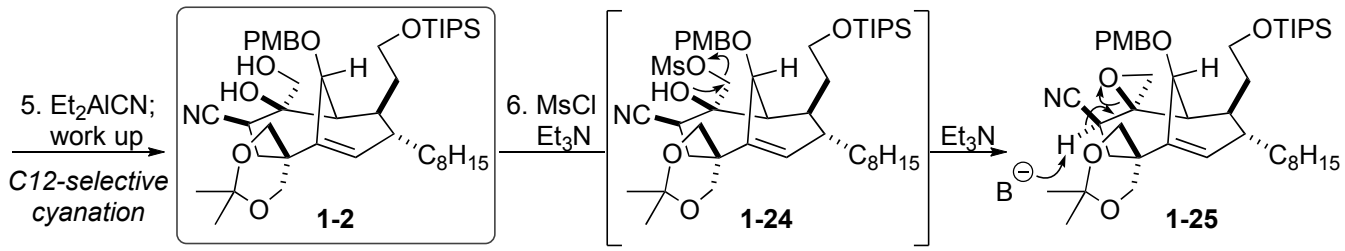
1.4 Answer

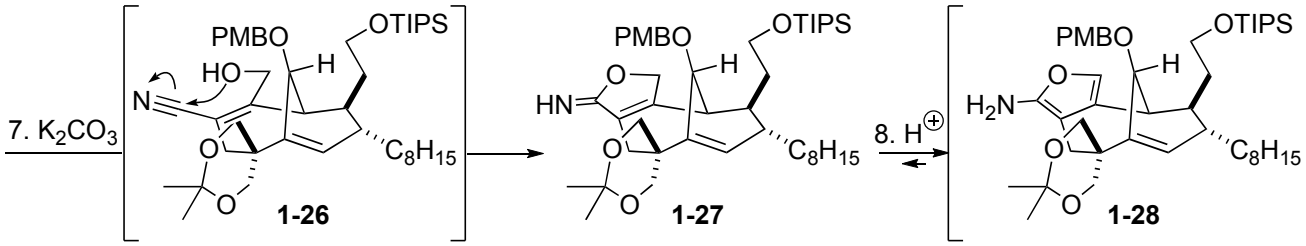
For details of oxidation by moleculer oxygen, see;
100703_LS_Tamaki_Hoshikawa ($^1O_2$/$^3O_2$) and 140620_PS_Komei_Sakata ($^1O_2$)

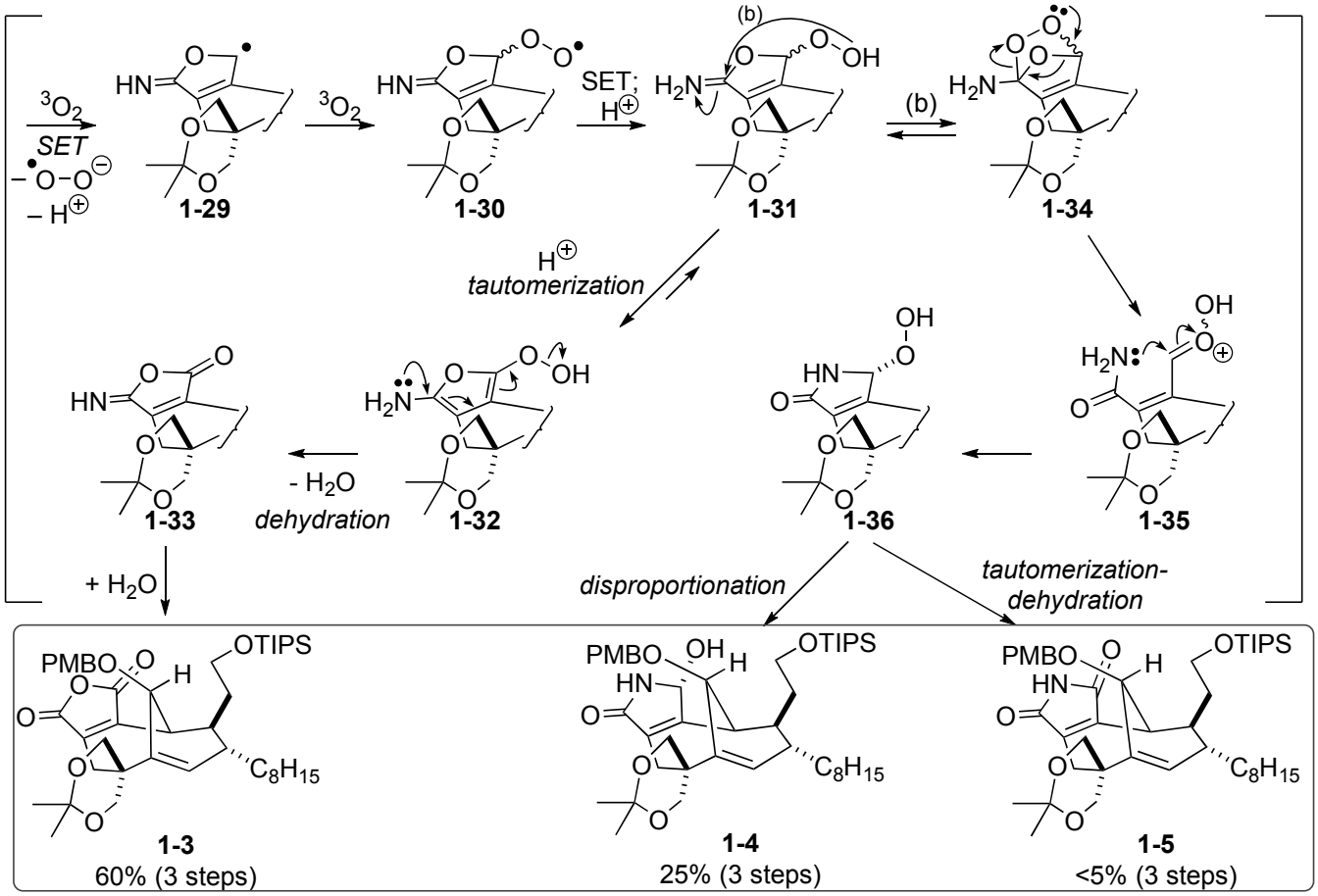






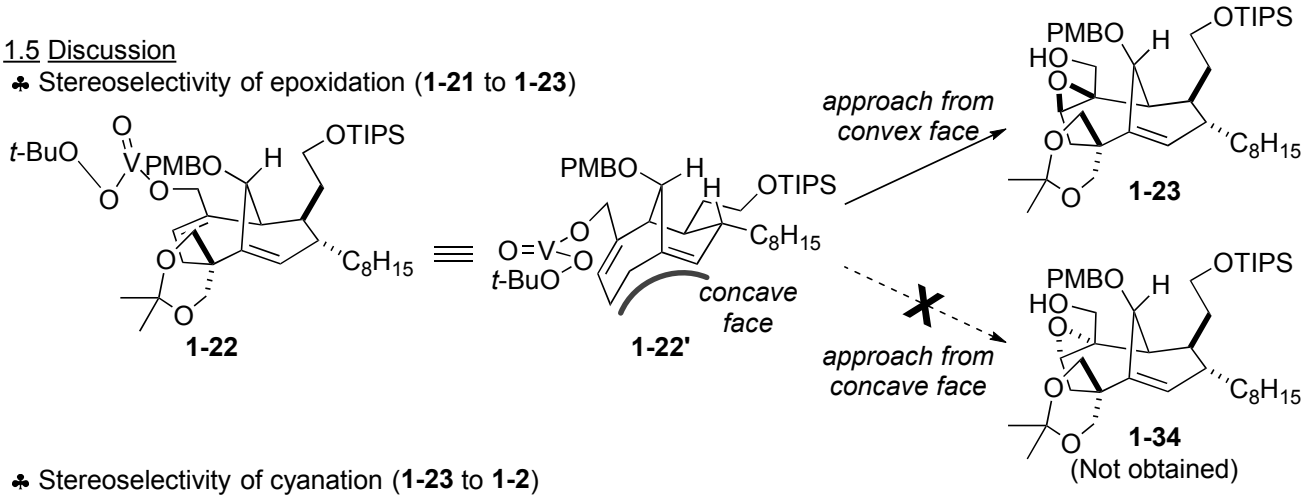






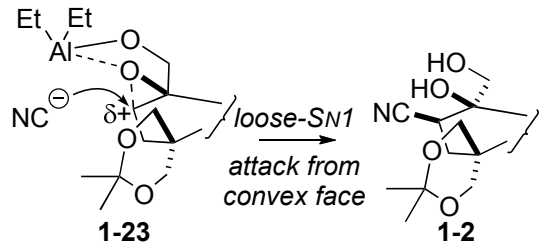
1.5 Discussion

♣ Stereoselectivity of epoxidation (**1-21** to **1-23**)

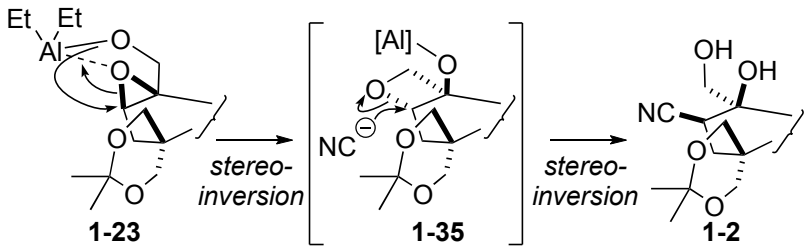


♣ Stereoselectivity of cyanation (**1-23** to **1-2**)

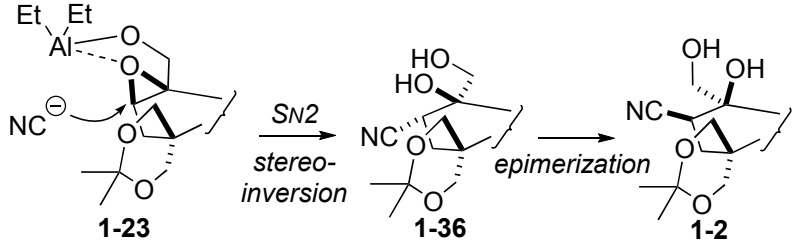
♦ mechanism 1 (loose-SN1)

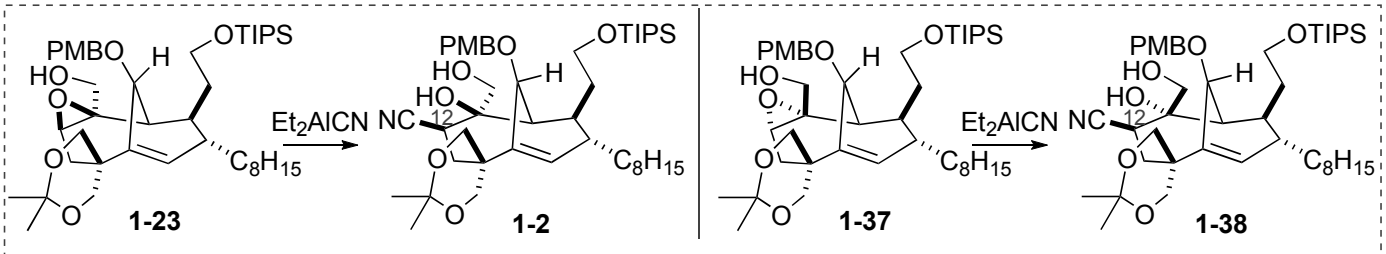


♦ mechanism 2 (intramolecular participation)



♦ mechanism 3 (SN2 -> epimerization)

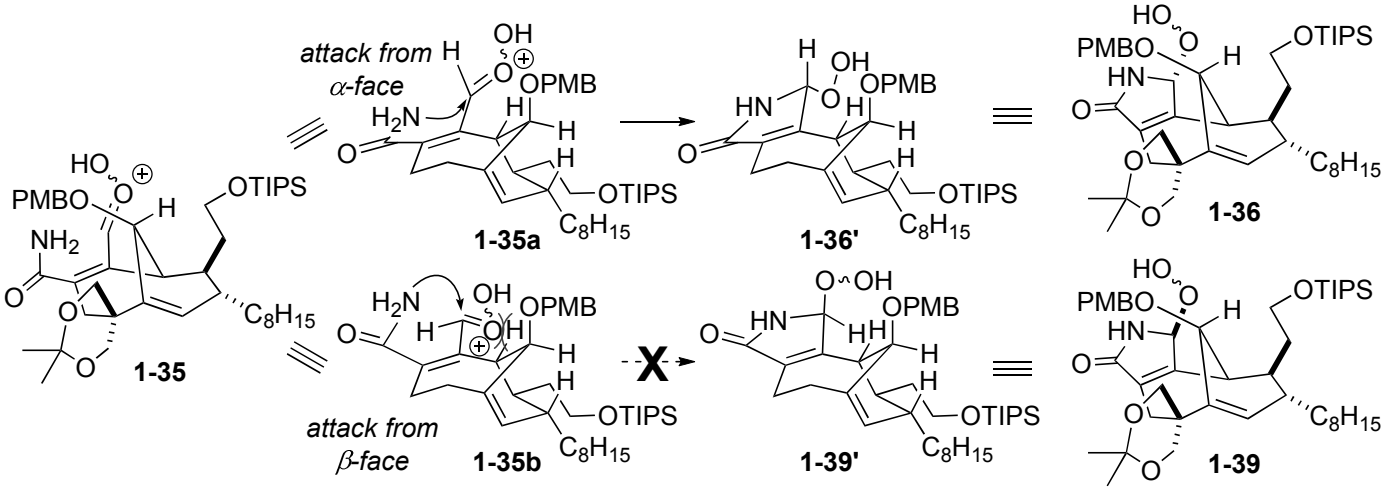




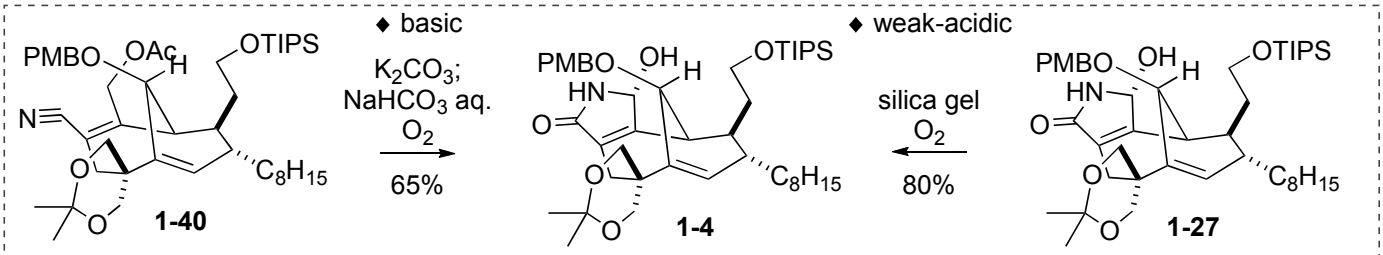
K. C. Nicolaou *et al. J. Am. Chem. Soc.* **2002**, *124*, 2190.

-> Mechanism 2 is implausible.

♣ Stereoselectivity from **1-35** to **1-36**



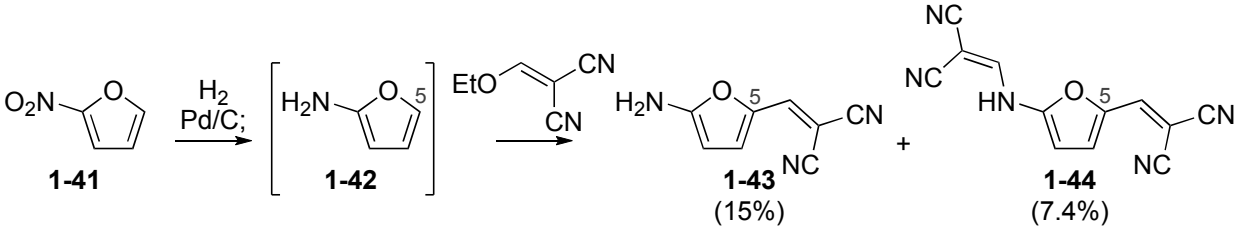
♣ auto-oxidation under basic/weak-acidic conditions



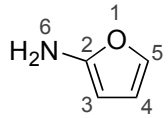
K. C. Nicolaou *et al. J. Am. Chem. Soc.* **2002**, *124*, 2190.; *Angew. Chem. Int. Ed.* **2002**, *41*, 2678.

-> Acidic condition is important for promotiong tautomerization.

♣ Reaction of 2-aminofuran



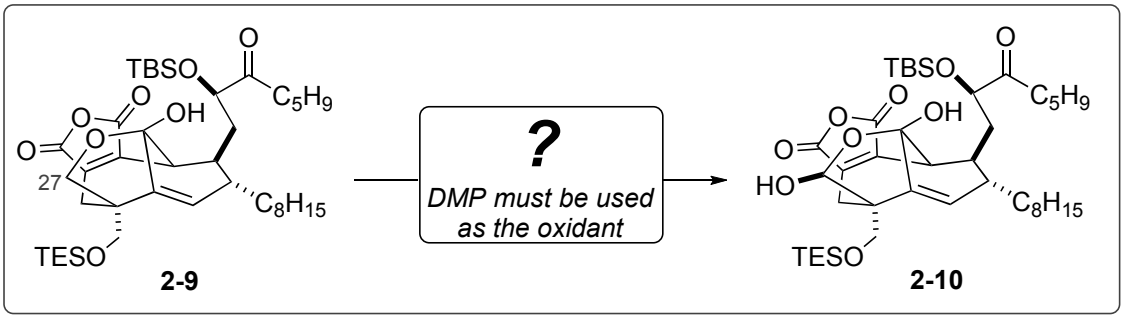
HOMO coefficient of 2-aminofuran (calculated with AM1)



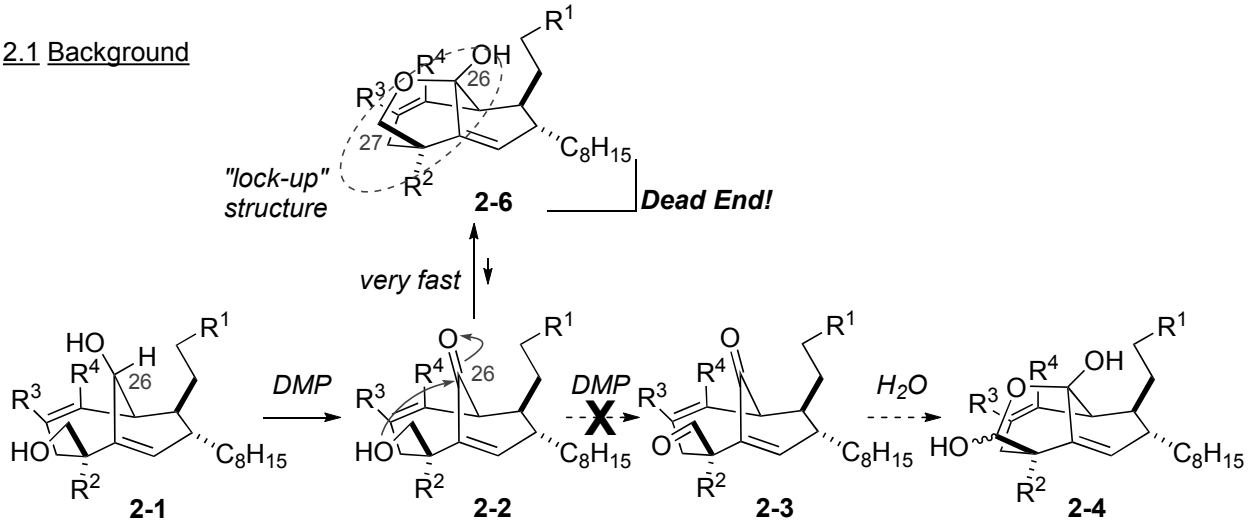
C^2	C^3	C^4	C^5
0.46	0.49	-0.26	-0.52

Ramsden, C. A. *et al. J. Heterocyclic. Chem.* **1993**, *113*, 30.

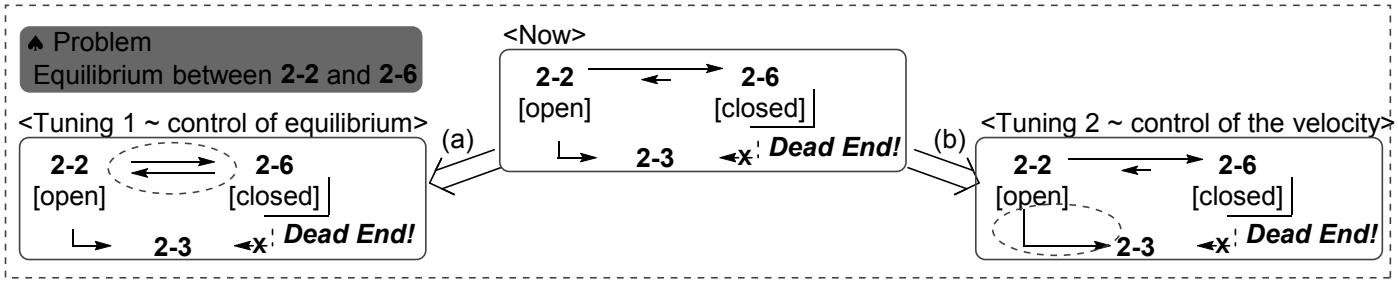
(2) Problem 2



2.1 Background

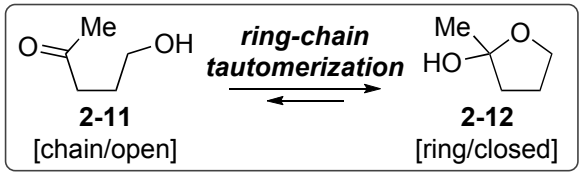


K. C. Nicolaou *et al. J. Am. Chem. Soc.* **2002**, *124*, 2191.



2.2 Answer [cf. 0.1 Tuning reaction conditions]

♣ Control of equilibrium ~ ring(closed)-chain(open) tautomerization



♦ solvent effect

	E_T [a]	**2-12** (%)
cyclohexane	30.9	43.8
CCl_4	32.5	42.7
dioxane	36.0	45.5
$CHCl_3$	39.1	42.7
acetonitrile	42.2	44.0
DMSO	45.0	36.0
formamide	56.6	45.8
water	63.1	0.0

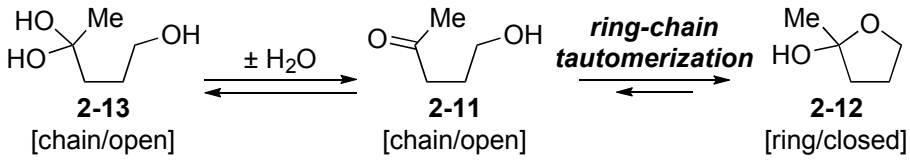
[a] Dimroth's E_T value of polarity

♦ effect of water

H_2O:dioxane	**2-12** (%)
0.00:1.00	45.5
0.40:0.60	43.9
0.61:0.39	42.7
0.81:0.19	39.6
0.93:0.07	27.1
0.96:0.04	8.0
1.00:0.00	0.0

H_2O:DMSO	**2-12** (%)
0.00:1.00	36.0
0.16:0.84	32.5
0.36:0.64	23.0
0.52:0.48	12.5
0.61:0.39	7.5
0.72:0.28	0.0
1.00:0.00	0.0

Whiting, J. E. *et al. Can. J. Chem.* **1971**, *49*, 3799.



2-13 [chain/open] **2-11** [chain/open] **2-12** [ring/closed]

-> Addition of H_2O inhibited ring-closing.

♦ effect of temperature

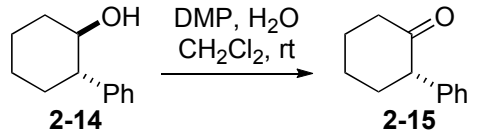
solvent	**2-12** (%) 15 °C	25 °C	50 °C
dioxane	46.1	45.5	42.8
DMSO	37.2	36.0	32.9
H_2O:dioxane = 0.96:0.04	11.6	8.0	4.5
H_2O:DMSO = 0.96:0.04	4.4	0.8	1.0

Whiting, J. E. *et al. Can. J. Chem.* **1971**, *49*, 3799.

♣ Control of the velocity of DMP oxidation

♦ increase in the amount of DMP
♦ elebation of temperature

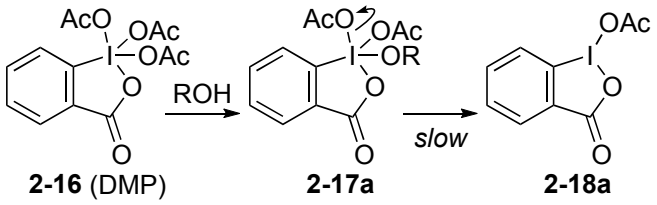
♦ effect of water in DMP oxidation



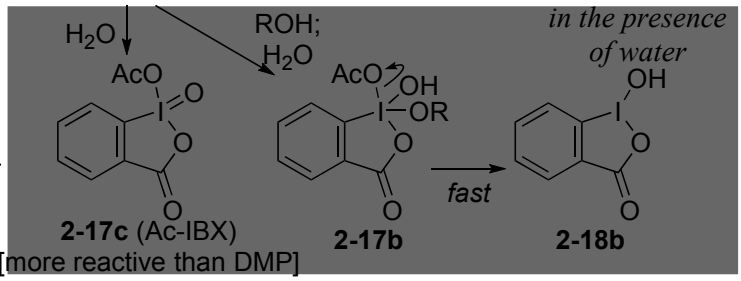
2-14 **2-15**

entry	DMP	H_2O	time	**2-15**
1	1.5 eq.	0 eq.	14 h	97%
2[a]	1.5 eq.	1.1 eq.	0.5 h	97%
3	4.9 eq.	excess	1.2 h	98%

-> Addition of H_2O (1.1 eq.) accelerates DMP [O].



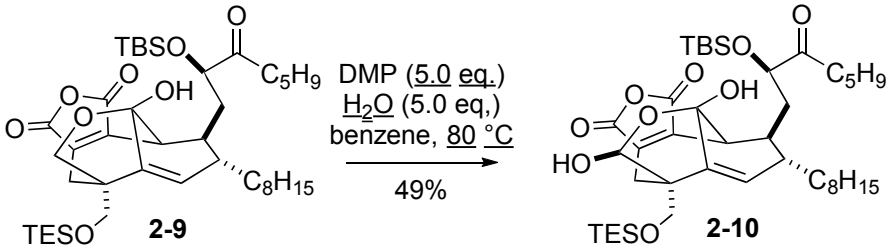
2-16 (DMP) **2-17a** **2-18a**



2-17c (Ac-IBX) [more reactive than DMP] **2-17b** **2-18b**

Martin, J. C. *et al. J. Am. Chem. Soc.* **1991**, *113*, 7277.; Schreiber, S. L. *et al. J. Org. Chem.* **1994**, *59*, 7549.

♣ Nicalaou's success

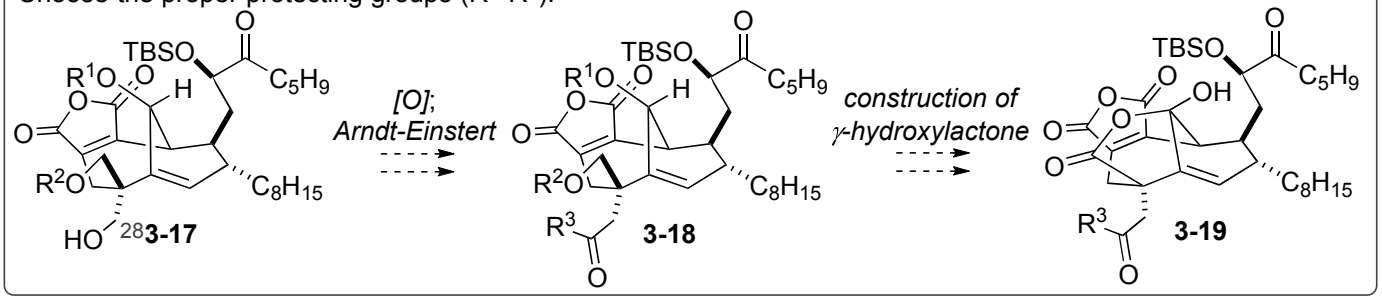


2-9 **2-10**

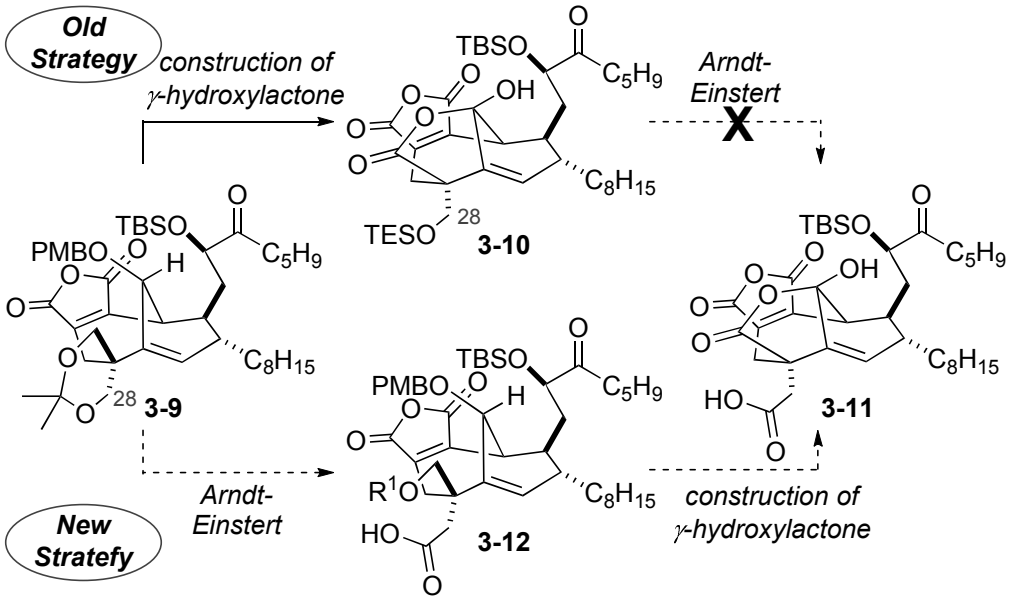
K. C. Nicolaou *et al. J. Am. Chem. Soc.* **2002**, *124*, 2190.

(3) Problem 3

Choose the proper protecting groups (R^1-R^3).

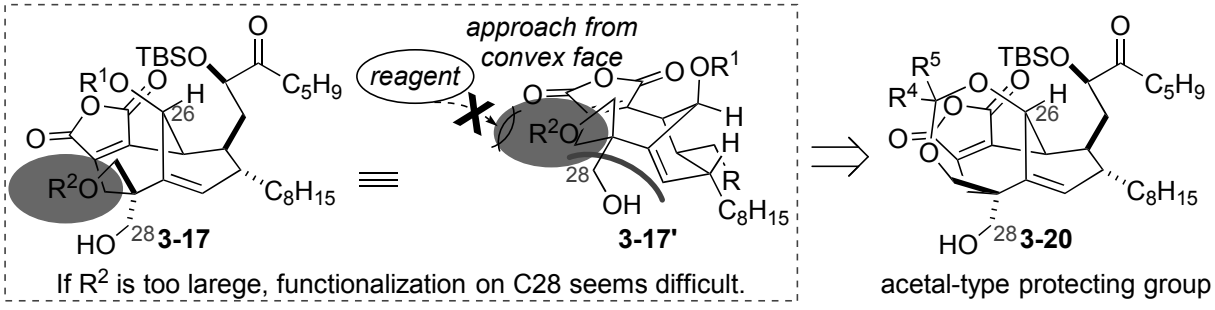


3.1 Background - Dead end and new plan [cf. 0.3 Changing the order]

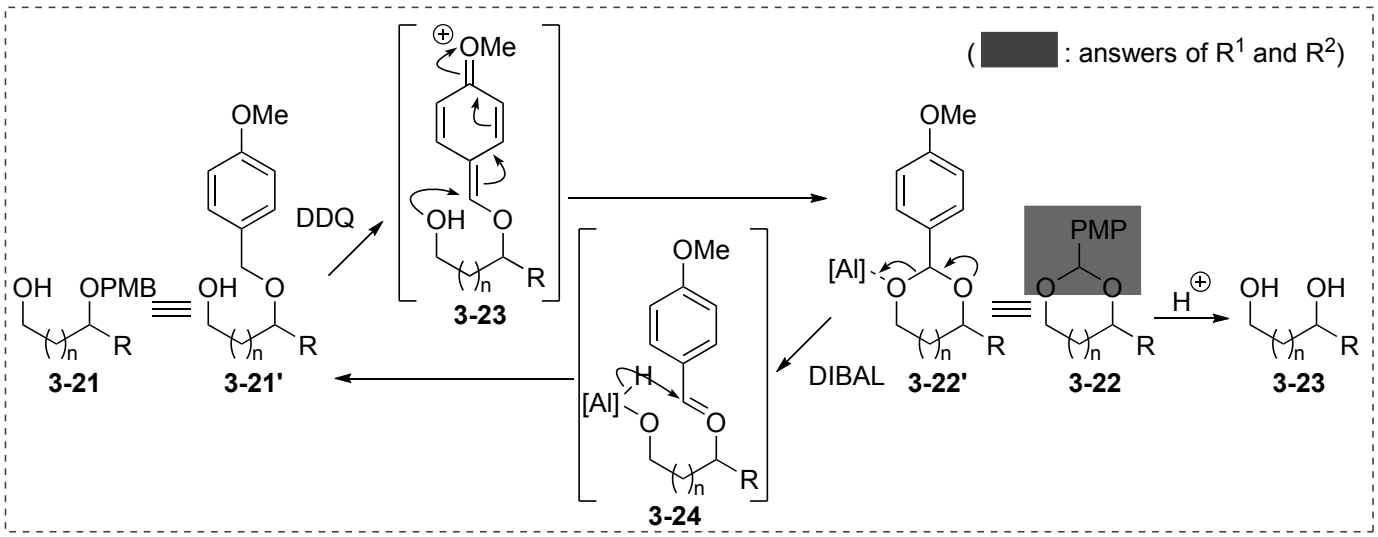


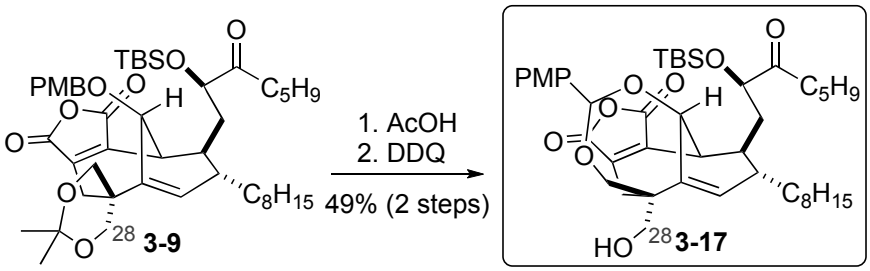
3.2 Answer

♣ R^1 and R^2



To shoeten a number of total steps, use of PMB-group on C26...

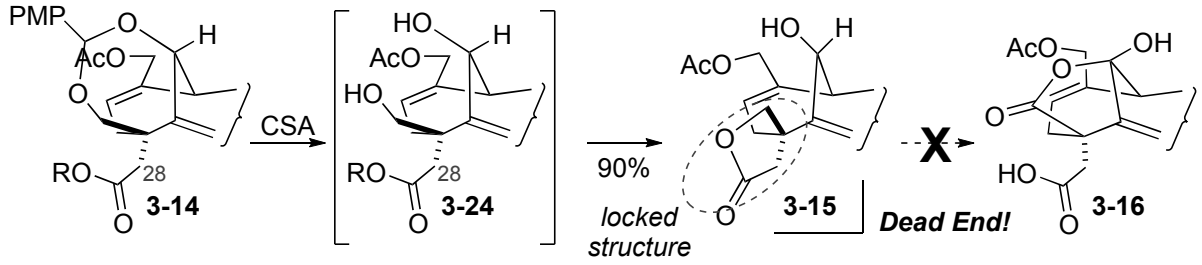




K. C. Nicolaou *et al. Angew. Chem. Int. Ed.* **1999**, *38*, 1669.

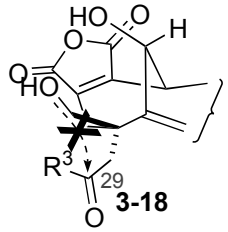
♣ R^3

unexpected reaction

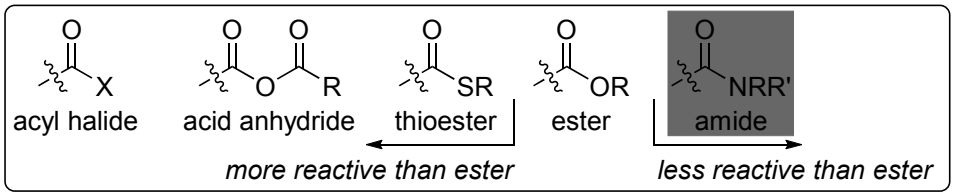


K. C. Nicolaou *et al. J. Am. Chem. Soc.* **2002**, *124*, 2202.

new protecting group



♦ R^3 should be the same degree of oxidation as carboxylic acid (For shortening steps)



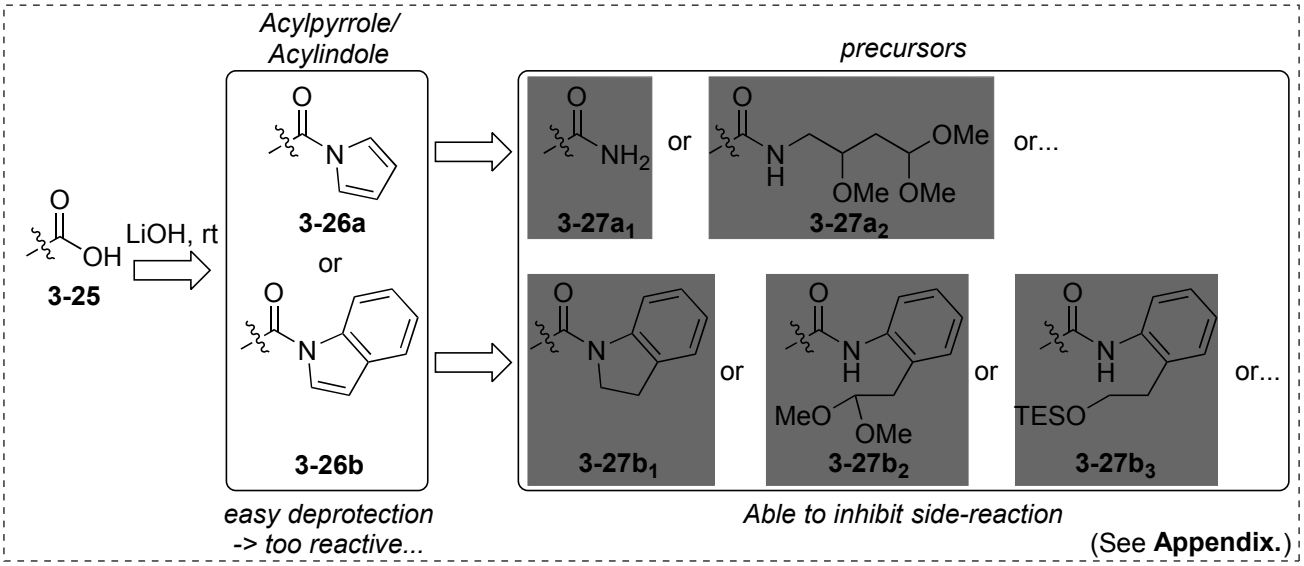
-> Generally, the deprotection of amide requires harsh (△ + H^+/OH^-) conditions.

R^3 ... ♦ can be deprotected under mild condition.
♦ should be stable to oxidation (construction of γ-hydroxylactone).

<Easily deprotectable amide groups>

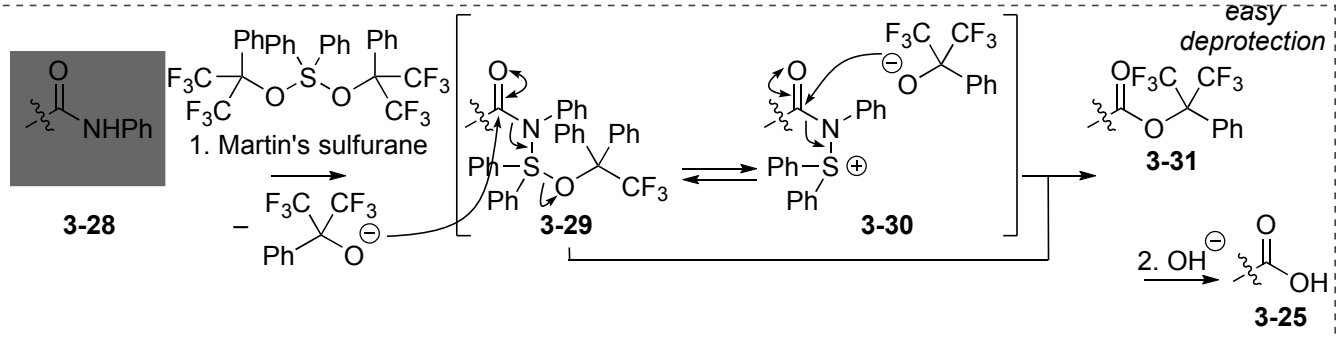
♦ use of aromaticity

(: answers of R^3)



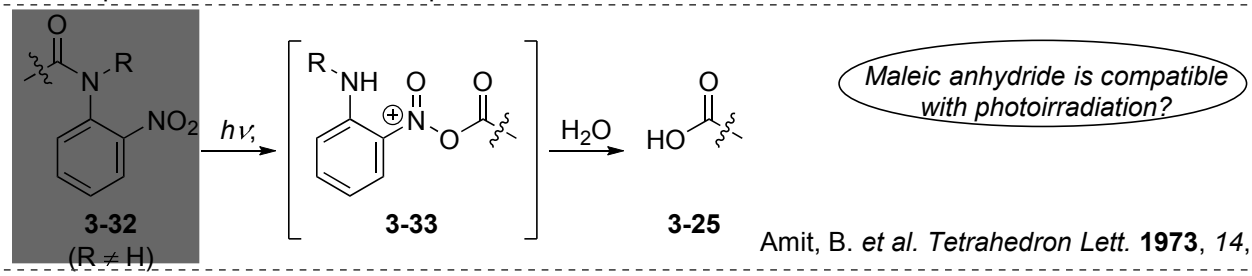
(See **Appendix.**)

◆ Use of Martin's sulfurane



Martin, J. C. *et al. J. Am. Chem. Soc.* **1975**, *97*, 6137.

◆ Use of photo-labile *ortho*-nitro compounds

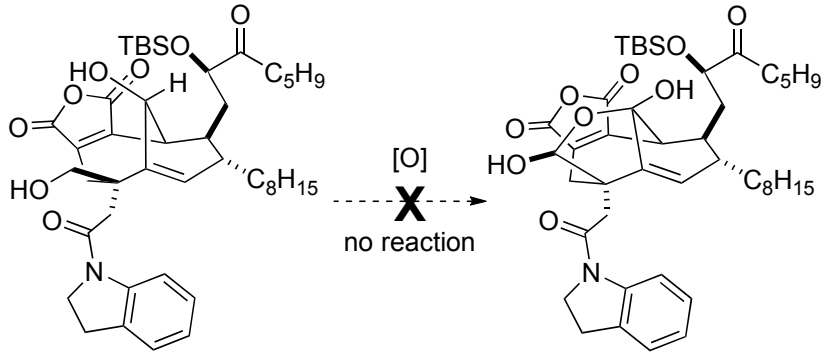


Amit, B. *et al. Tetrahedron Lett.* **1973**, *14*, 2205.

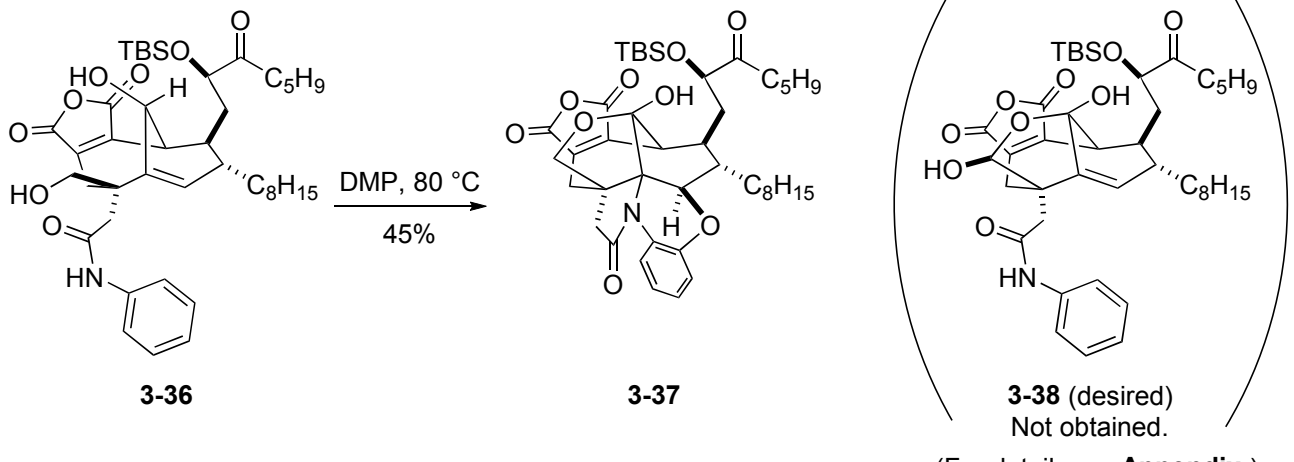
Answer of R^3:
amide (easy to remove, compatible with oxidation, ...) = ex. **3-27**, **3-28**, **3-32**

3.3 Result

♣ Use of acylindole precursor **3-27b$_1$**



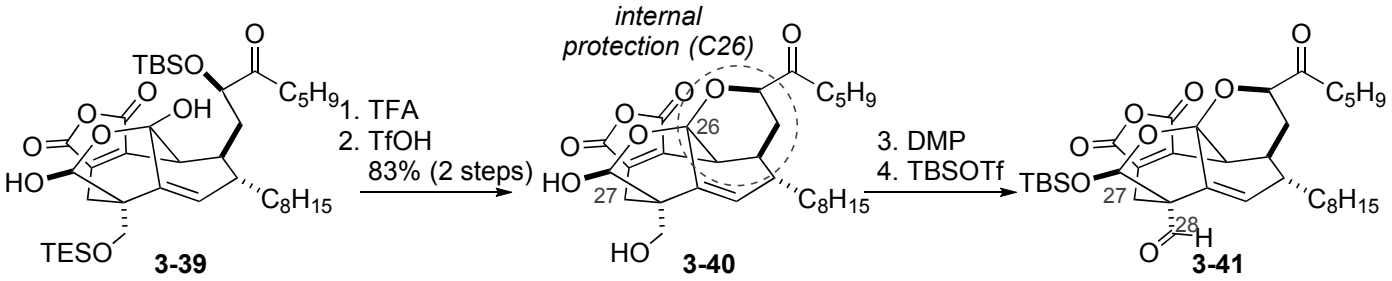
♣ Use of phenylanilide **3-28**

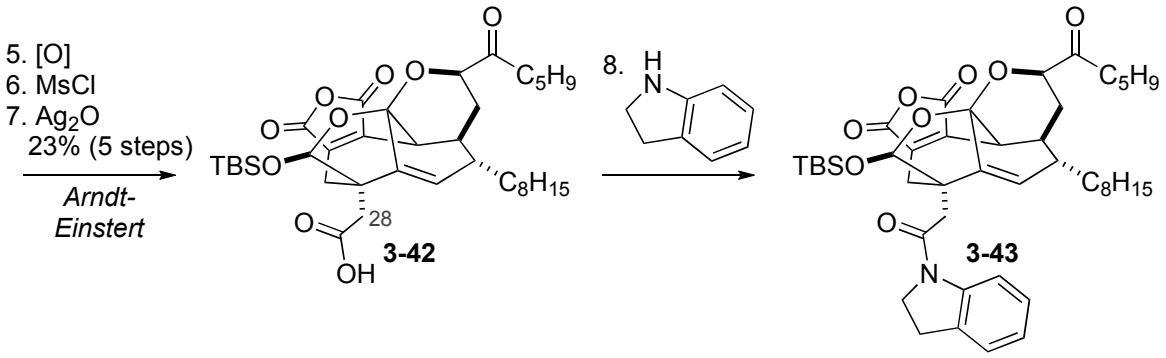


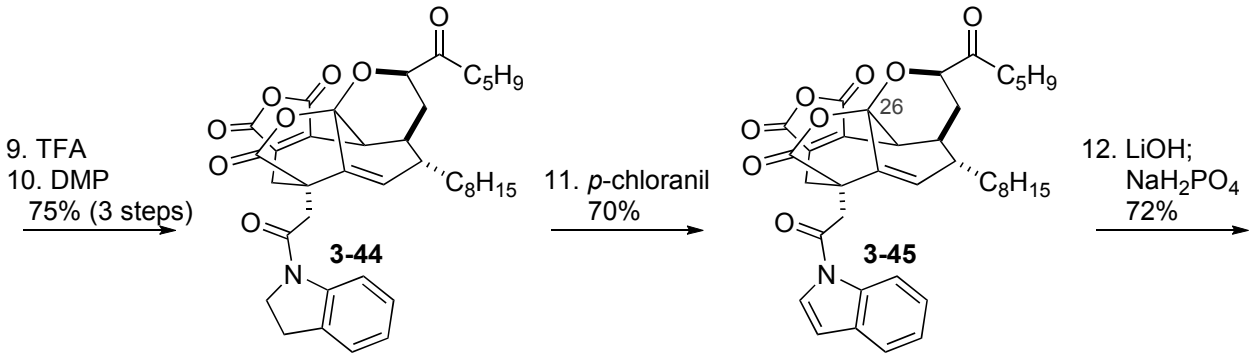
(For detail, see **Appendix**.)

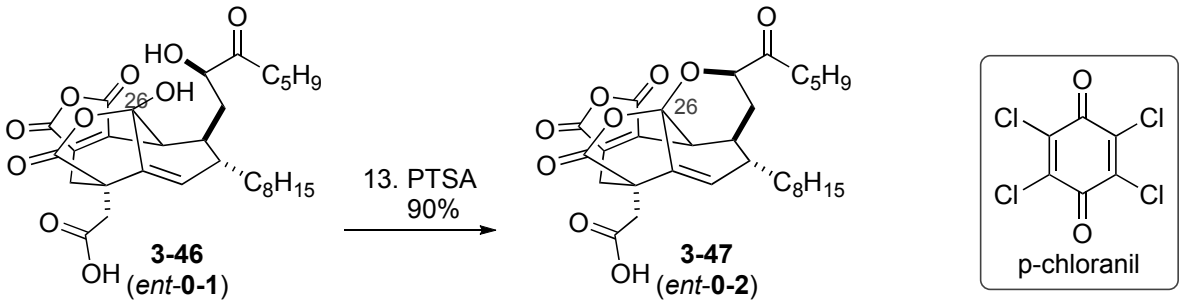
K. C. Nicolaou, *et al. Angew. Chem. Int. Ed.* **2002**, *41*, 2678.

3.4 Successful Route









Appendix:

(1) CP molecules

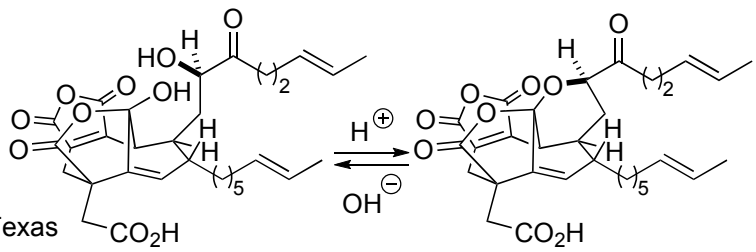
♣ **CP molecules**
- ♦ (+)-CP-225,917 (**0-1**, Phomoidride A)
- ♦ (–)-CP-263,114 (**0-1**, Phomoidride B)

♣ **Isolation**
- ♦ by Pfizer Central Research (Dr. Kaneko's group)
- ♦ from an unidentified fungus on a Juniper twig in Texas

J. Am. Chem. Soc. **1997**, *119*, 1594.

♣ **Bioactivity**
- ♦ Inhibition of squalene synthase
- ♦ Inhibition of Ras-farnesyl transferase

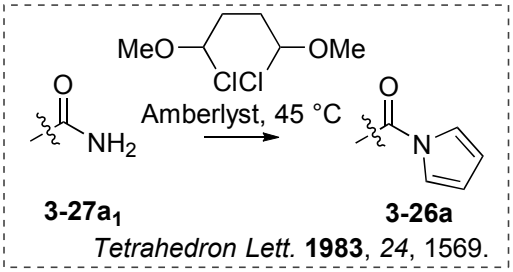
J. Am. Chem. Soc. **1997**, *119*, 1594.



ent-**0-1** (*ent*-Phomoidride A) ⇌ *ent*-**0-2** (*ent*-Phomoidride B)

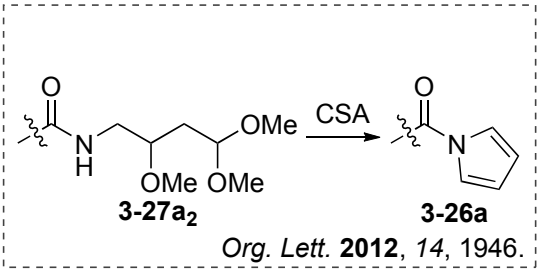
♣ **Four total syntheses**
- ♦ ***Prof. Nicolaou*** <rac. form> *ACIE*, **1999**, *38*, 1669; 1676. <ent. form> *ACIE*, **2000**, *39*, 1829.
- ♦ ***Prof. Fukuyama*** <as. form, 1st> *JACS*, **2000**, *122*, 7825. <as. form, 2nd> *OL*, **203**, *5*, 2235.
- ♦ ***Prof. Shair*** <as. form> *JACS*, **2000**, *122*, 7424.
- ♦ ***Prof. Danishefsky*** <rac. form> *ACIE*, **2000**, *39*, 4509.

(2) Convestion to acylindole



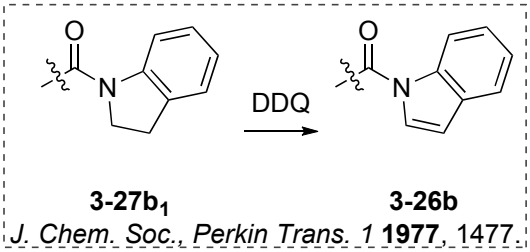
3-27a$_1$ **3-26a**

Tetrahedron Lett. **1983**, *24*, 1569.



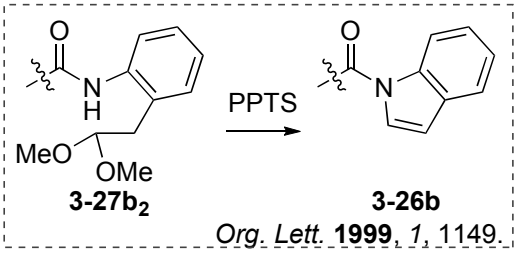
3-27a$_2$ **3-26a**

Org. Lett. **2012**, *14*, 1946.



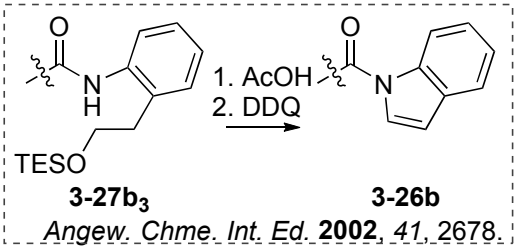
3-27b$_1$ **3-26b**

J. Chem. Soc., Perkin Trans. 1 **1977**, 1477.



3-27b$_2$ **3-26b**

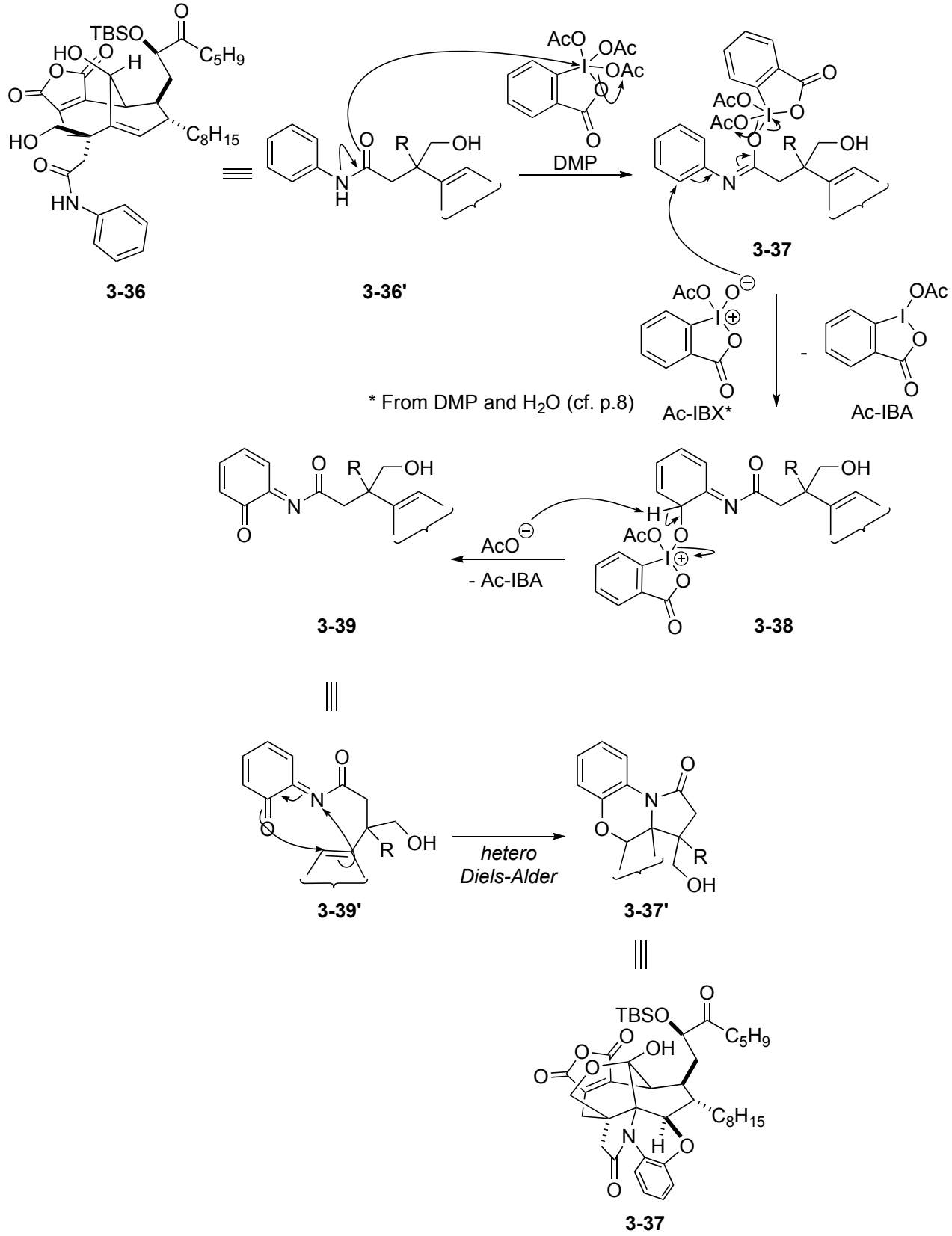
Org. Lett. **1999**, *1*, 1149.



3-27b$_3$ **3-26b**

Angew. Chme. Int. Ed. **2002**, *41*, 2678.

(3) Side-reation of phenylanilide with DMP
(cf. 130216_PS_Hidenori_Todoroki)



K. C. Nicolaou *et al. Angew. Chem. Int. Ed.* **2000**, *39*, 622.; **2001**, *40*, 202.