

Total Synthesis of Taxol

2020. 10. 31.
Yusuke Imamura

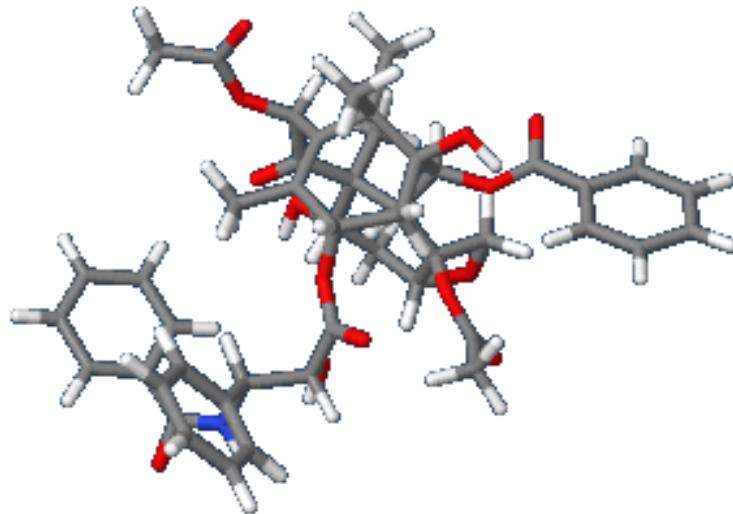
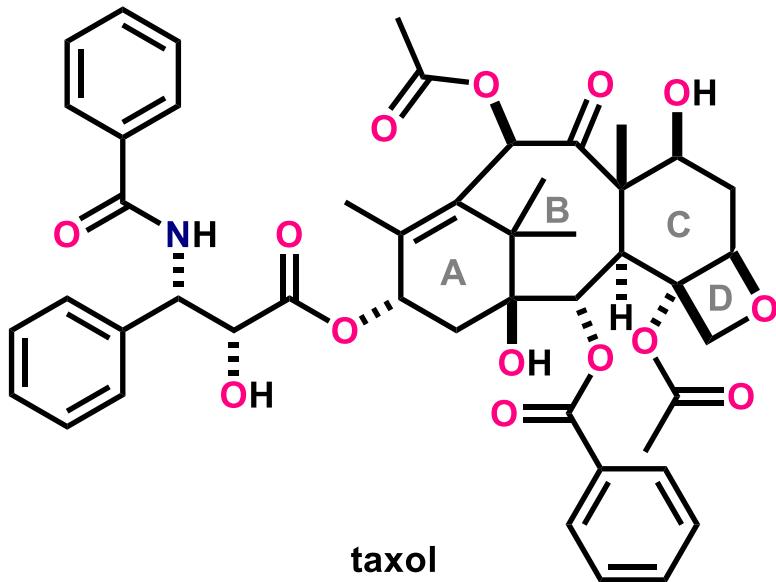
Contents

1. Introduction

2. Construction of core structure

3. Reactivity of functionalities

Taxol



Isolation

The bark of *Taxus brevifolia*

Biological activity

Stabilization of microtubules

Used as anticancer agent

Structural features

tricyclo[9.3.1.0^{3,8}]pentadecane

11 chiral centers

(3 tetrasubstituted carbons)

oxetane, bridgehead olefin

Total syntheses

Holton, R. A. et al. *J. Am. Chem. Soc.* **1994**, 116, 1597.

[mol]

Nicolaou, K. C. et al. *Nature* **1994**, 367, 630.

Danishefsky, S. J. et al. *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1723.

Wender, P. A. et al. *J. Am. Chem. Soc.* **1997**, 119, 2755.

Mukaiyama, T. et al. *Proc. Jpn. Acad.* **1997**, 73B, 95.

Kuwajima, I. et al. *J. Am. Chem. Soc.* **2000**, 122, 3811.

L. Jongwon, PhD thesis, Harvard University (USA), **2000**. (Kishi's group)

Takahashi, T. et al. *Chem. Asian. J.* **2006**, 1, 370.

Nakada, M. et al. *Chem. Eur. J.* **2015**, 21, 355.

Chida, N. et al. *Org. Lett.* **2015**, 17, 2570.

Baran, P. S. et al. *J. Am. Chem. Soc.* **2020**, 142, 10526.

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Contents

1. Introduction

2. Construction of core structure

- B-ring construction**
- D-ring construction**
- Tail part introduction**

3. Reactivity of functionalities

B-ring Construction

B-ring construction in previous syntheses

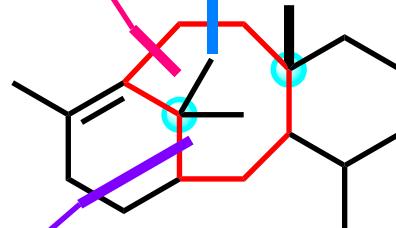
- Danishefsky
Heck 49%
- Kishi
NHK 48%
- Chida
 SmI_2 radical cyclization 66%
- Nakada
Pd cat alkenylation **97%**

- Nicolaou
pinacol coupling 23-25%
- Kuwajima
vinylogous Mukaiyama aldol 59%
- Takahashi
 α -alkylation of cyanide 49%

difficulties

- 8-membered ring
- bridge head olefin
- neopentyl position

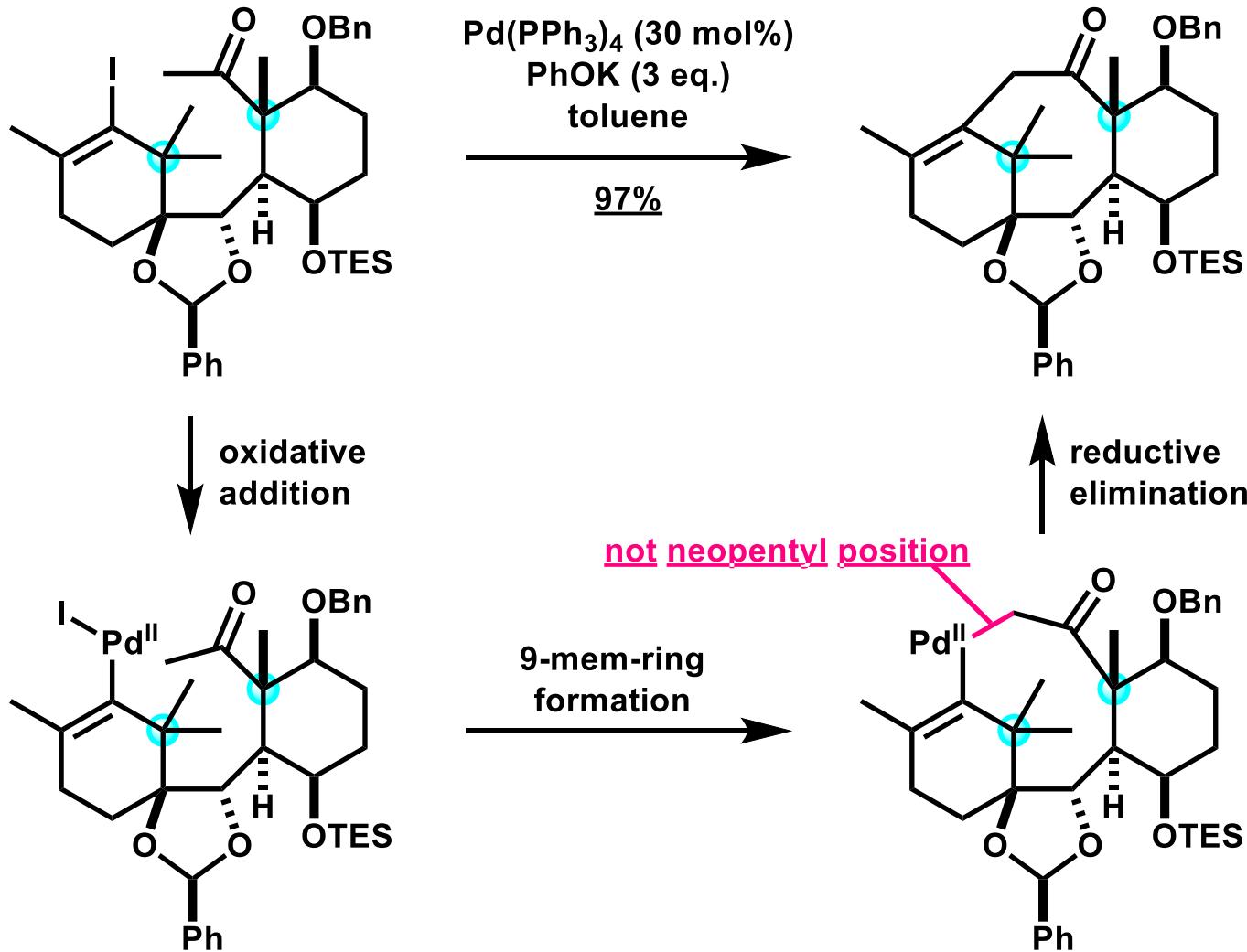
- Baran
DA 47%



- Other cyclization strategy
Holton AB->C
Wender AB->C
Mukaiyama BC->A

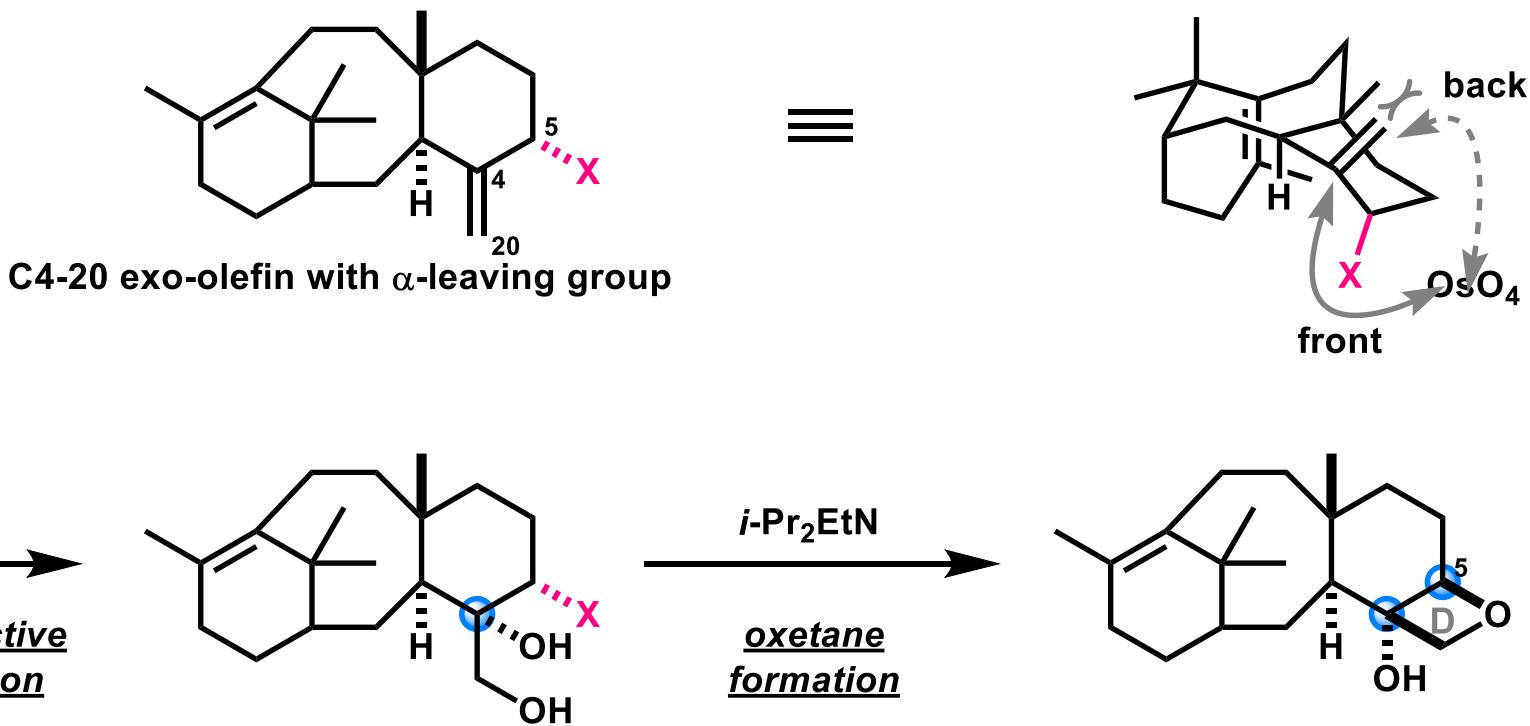
One of the most difficult challenges in construction of B-ring is bond formation at neopentyl position. The problem always arise, because there is 2 quaternary carbon atoms (highlighted) in 8-membered ring at 1,5-position.

Nakada's B-ring Construction



The efficacy of this B-ring construction should be attributed to expanded cyclization mode.

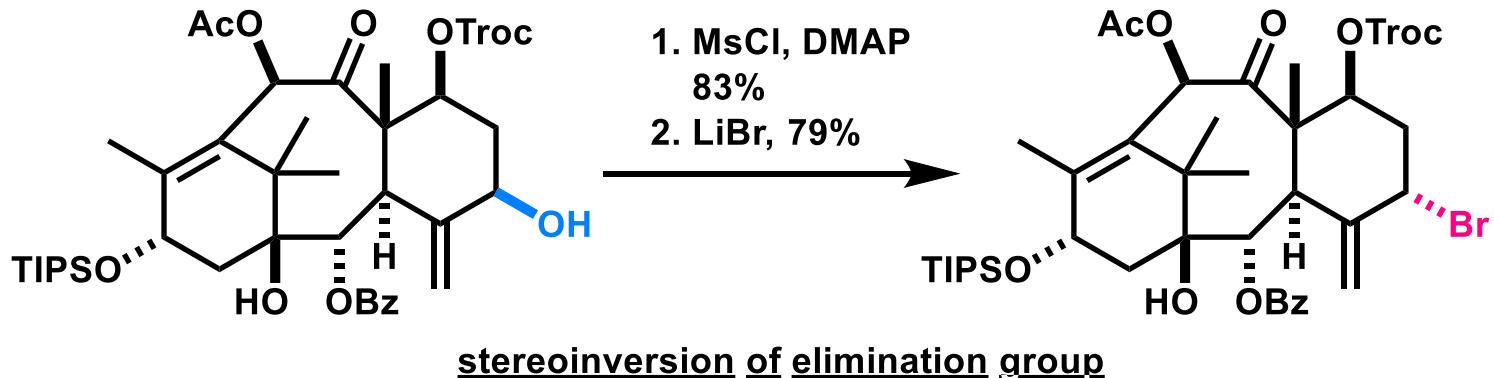
D-ring Oxetane Construction



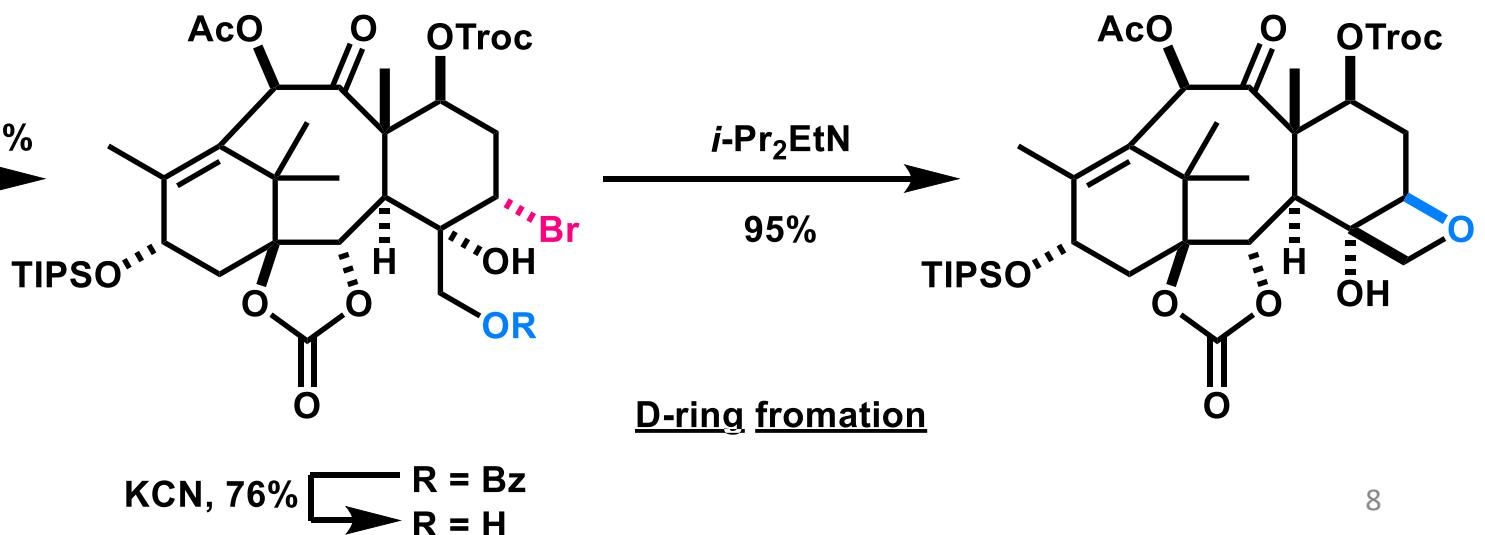
In the ALL syntheses, D-ring oxetane are constructed by nucleophilic addition of C20-OH. Although, Wender and Kishi synthesized C5- β -OH intermediate, they inverted it and used as leaving group.

D-ring Oxetane Construction

Wender's D-ring construction



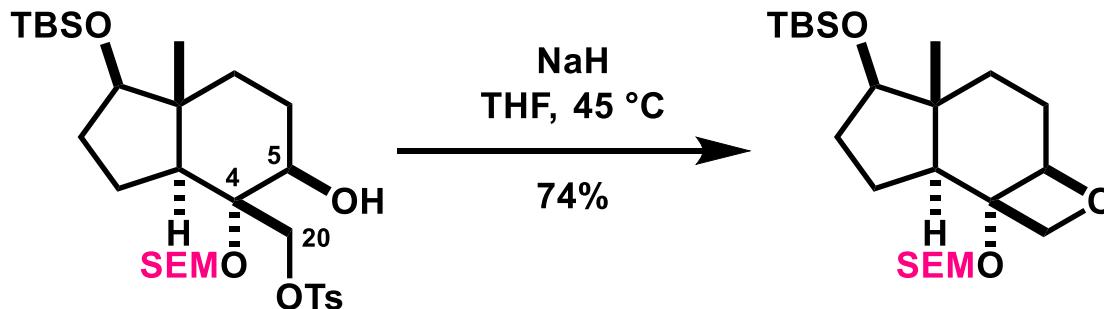
1. OsO_4 , pyridine;
 $\text{Na}_2\text{S}_2\text{O}_3$;
imidazole, 76%
2. triphosgene, 92%



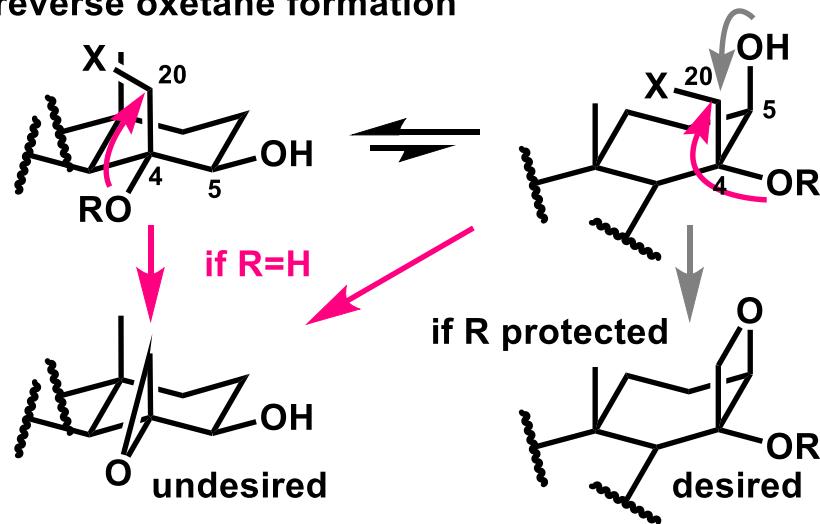
Reverse D-ring Construction

Example of reverse oxetane formation¹

- point: C4-OH are protected in all of these substrates

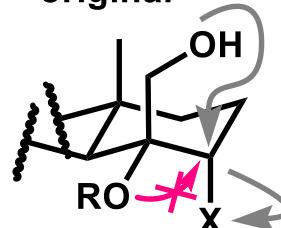


reverse oxetane formation



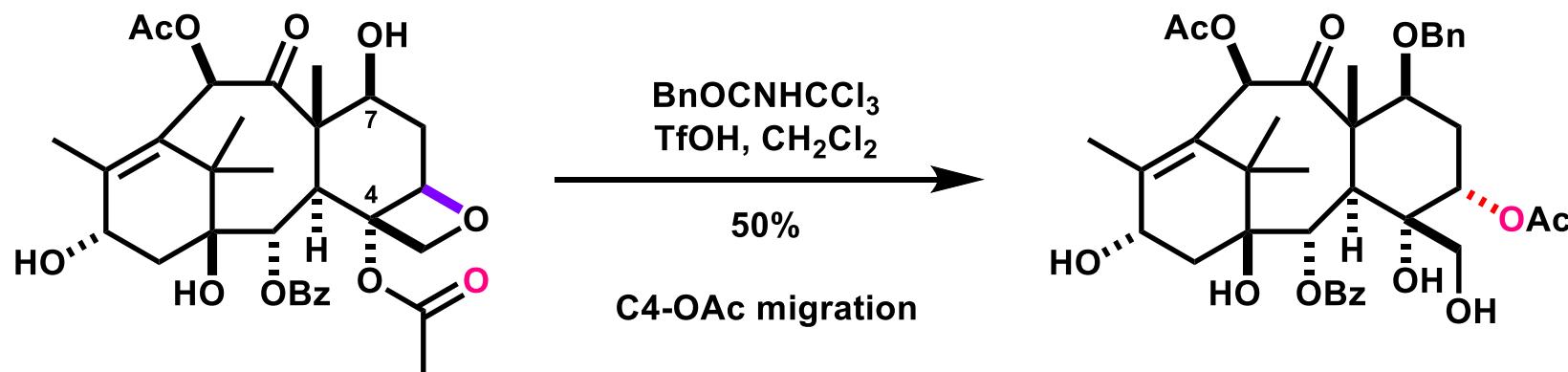
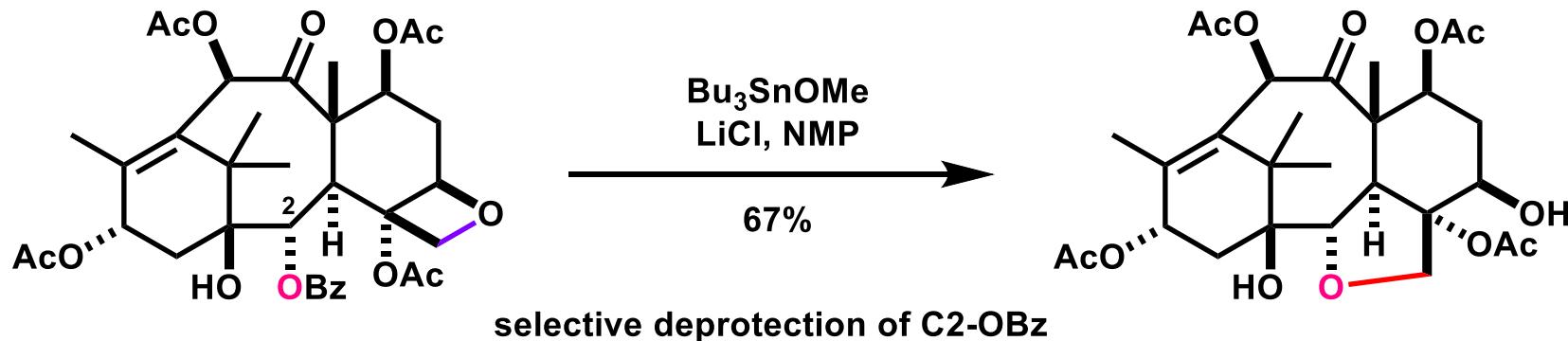
Conformational change is needed to form oxetane.
If R = H, epoxide formaion compete.
However, protection of tert-OH before the
formation of oxetane is difficult.

original



No conformational change needed.
Epoxide can't be formed.

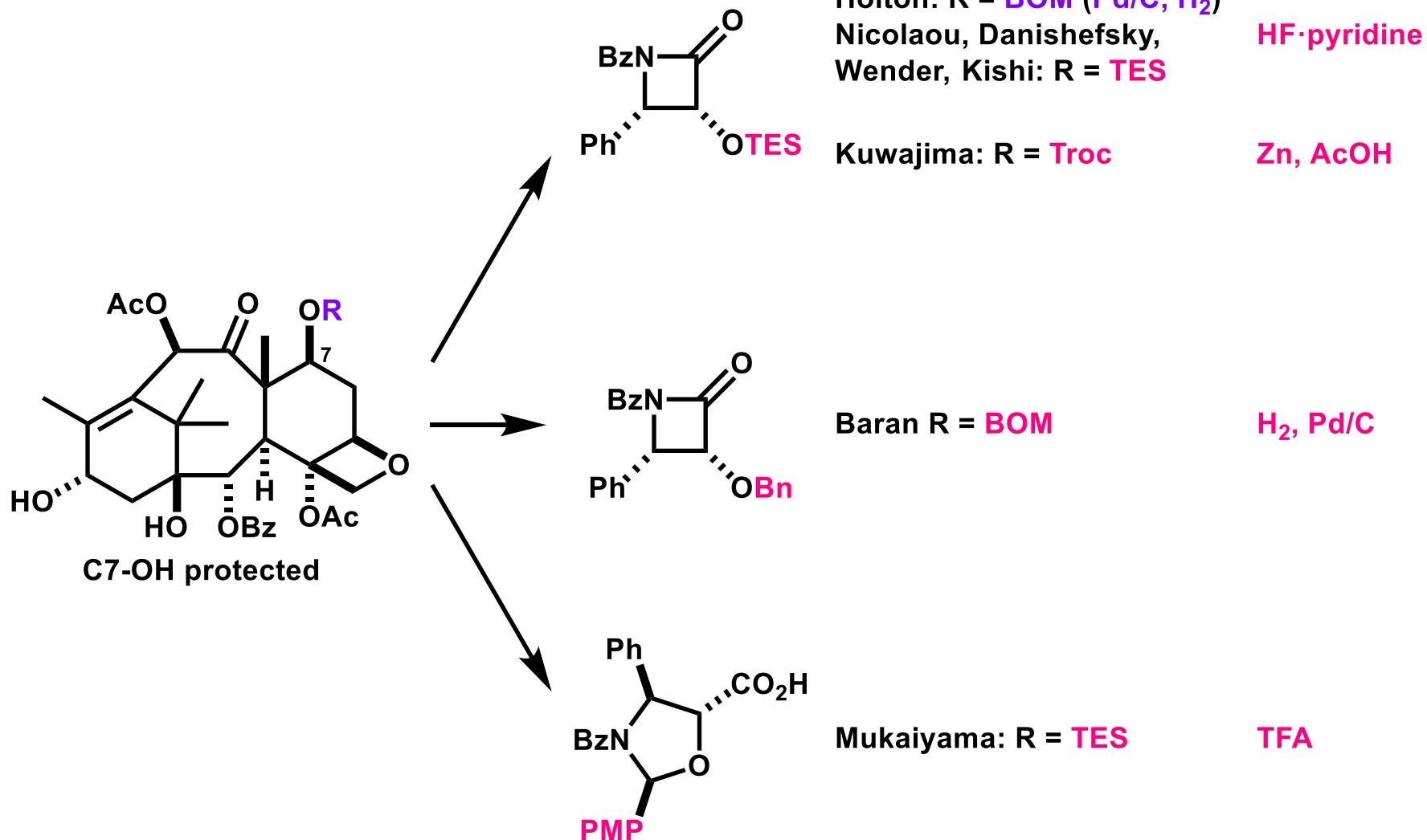
Oxetane Opening



Oxatane are liable to be opened by neighboring oxygen functionality under acidic conditions.

1. Farina, V.; Huang, S. *Tetrahedron Lett.* **1992**, 33, 3929. 2. Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, 117, 624.

Introduction of Tail Part

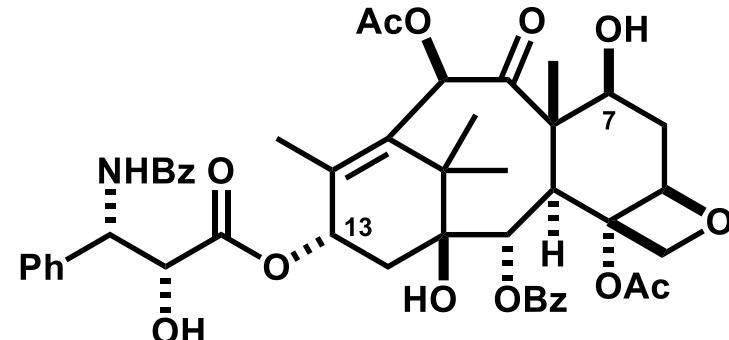


In all syntheses other than Holton, simultaneous deprotection of tail part and C7-OH was conducted.

C7-OH Protection

Holton and Baran used BOM only.

Change of C7-protection
(which uses more than 1 protecting group)



Professor	2 nd last	Last	comment
Nicolaou	Bn (H ₂ , Pd(OH)/C)	TES (HF · py.)	Chemoselectivity vs olefin?
Danishefsky	TBS (TBAF)	TES (HF · py.)	Too robust?
Wender	Troc (PhLi)	TES (HF · py.)	Accidental?
Kuwajima	TES (HF · py.)	Troc (Zn, AcOH)	Orthogonality to C13-OTBS
Mukaiyama	TES (HF · py.)	TES (TFA)	Deprotected with C13-OTES
Takahashi	BOM (H ₂ , Pd/C)	TES (HF · py.)	For Danishefsky intermediate
Chida	Bz (K ₂ CO ₃ , MeOH)	TES (HF · py.)	Chemoselectivity vs Ac? For Danishefsky intermediate
Nakada	Bn (H ₂ , Pd(OH)/C)	TES (HF · py.)	For Nicolaou intermediate

Contents

1. Introduction

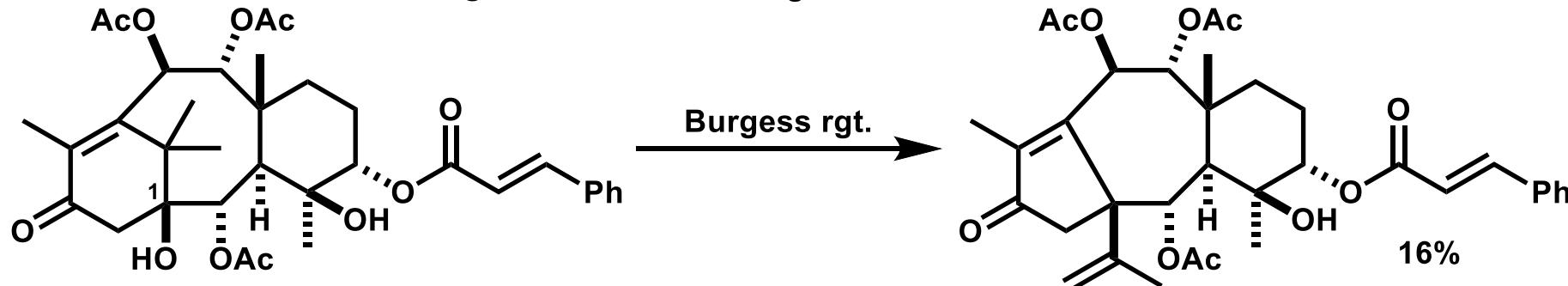
2. Construction of core structure

3. Reactivity of functionalities

C1 skeletal rearrangement

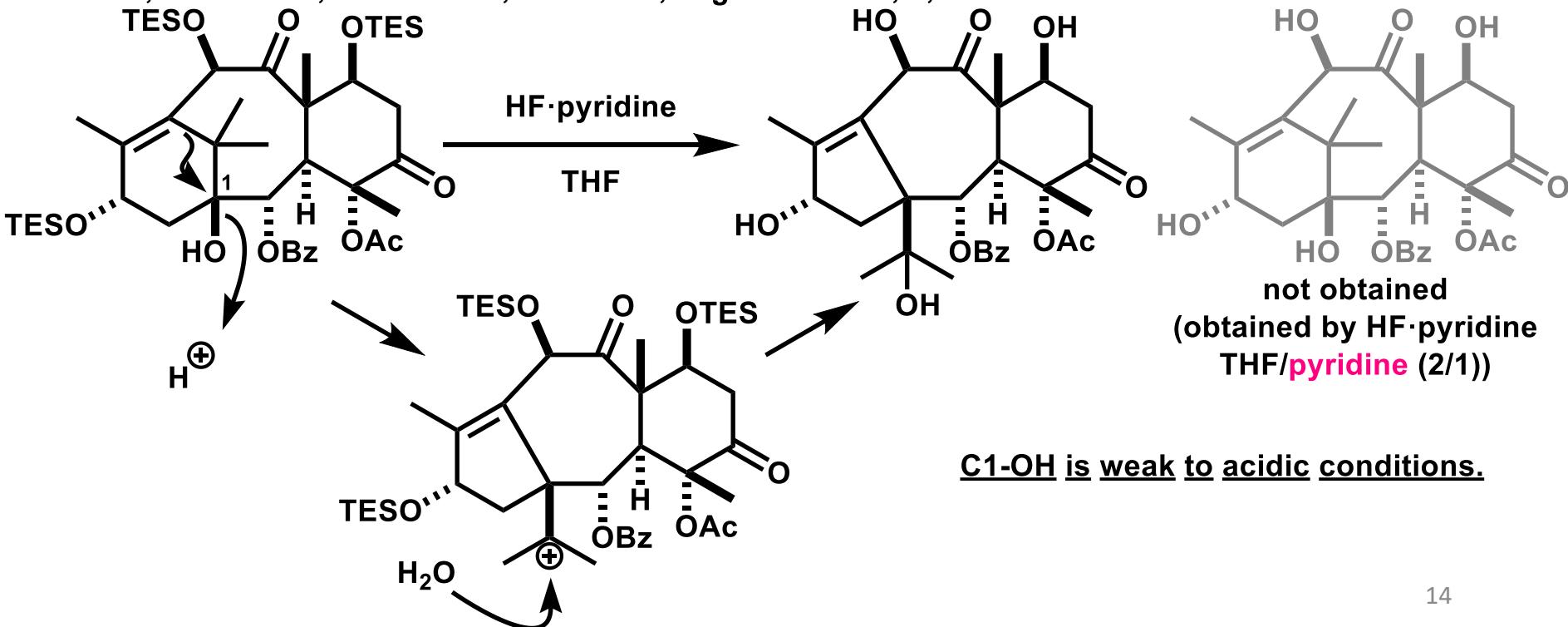
- Regioselective dehydration

Y. Imamura, S. Yoshioka, M. Nagatomo, M. Inoue, *Angew. Chem. Int. Ed.* 2019, 58, 12159.



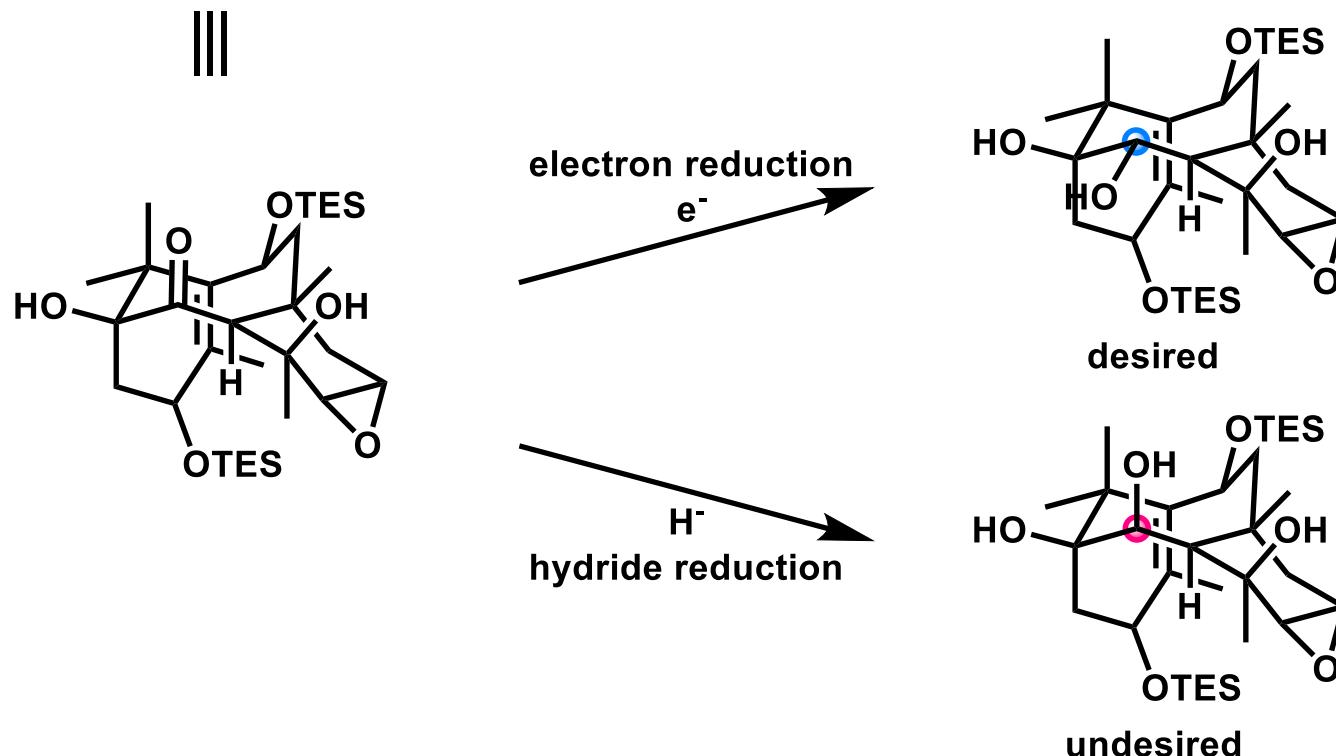
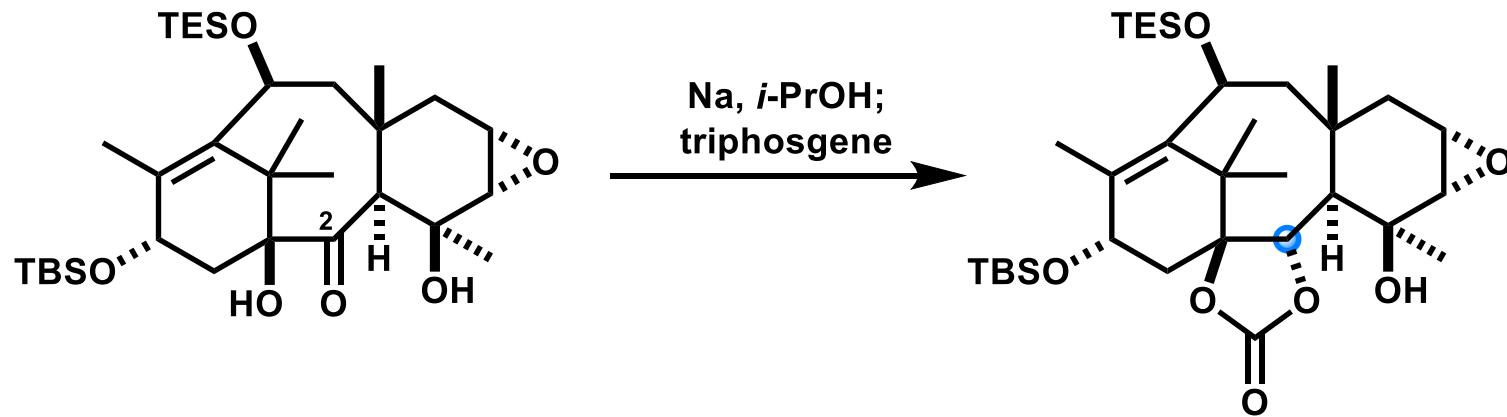
- Silyl deprotection

S. Thoret, F. Gueritte, D. Guenard, J. Dubois, *Org. Lett.* 2016, 8, 2301.



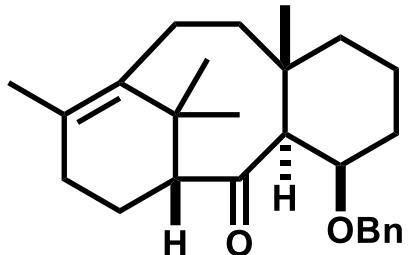
C2 reduction

Baran's synthesis



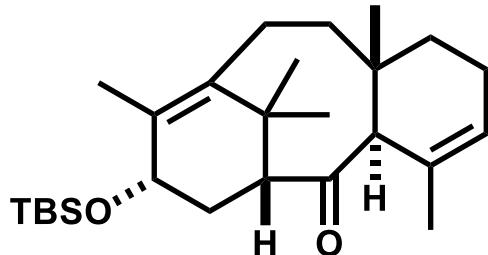
Difficulty in C2 reduction

Limited examples of successful reduction



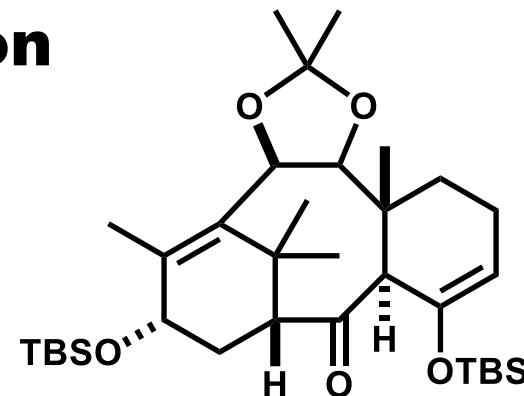
Na, EtOH
Williams

J. Org. Chem.
2000, 65, 7865.



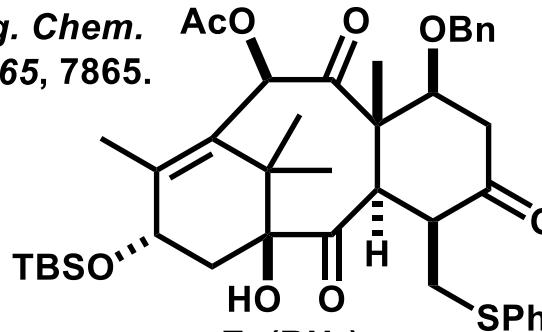
Na, i-PrOH
Baran

Angew. Chem. Int. Ed.
2016, 55, 8280.



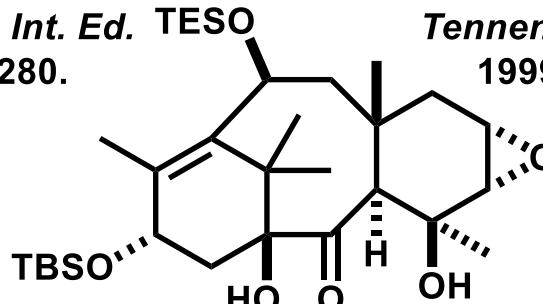
Na, CF3CH2OH
Kuwajima

Tennentou Abstract
1999, 41, 463.



Zn(BH4)2
Danishefsky

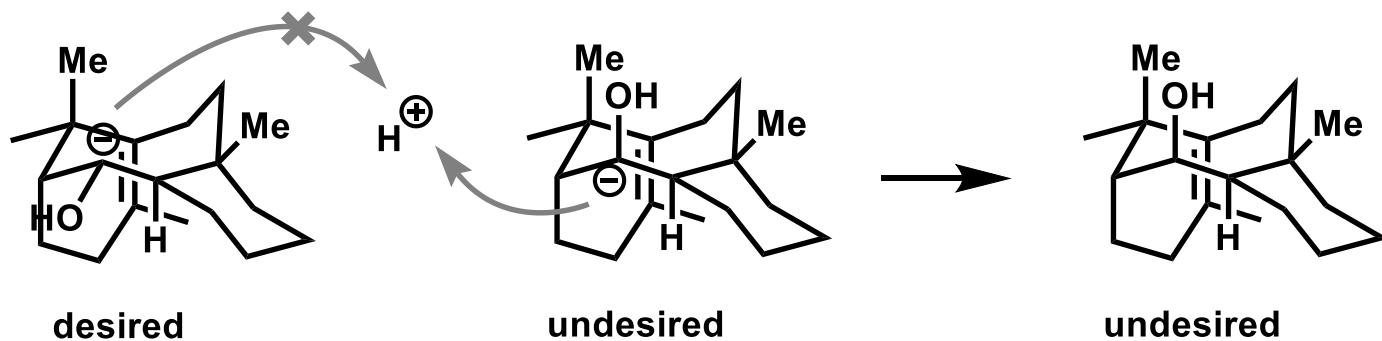
WO1993020036 A1
1993.



Na, i-PrOH
Baran

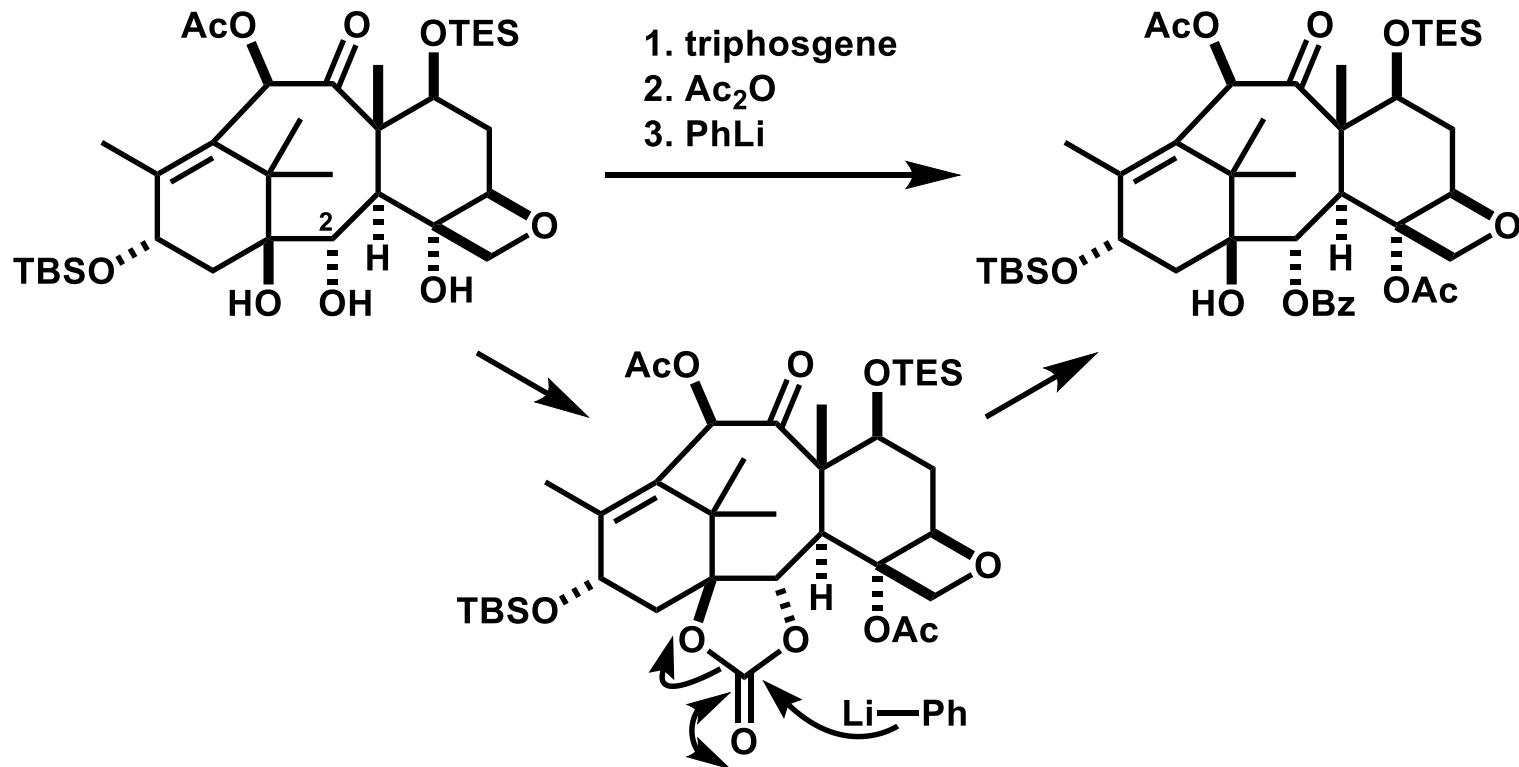
J. Am. Chem. Soc.
2020, 142, 10526.

difficulty in electron reduction



C2 benzylation

Kuwajima's synthesis



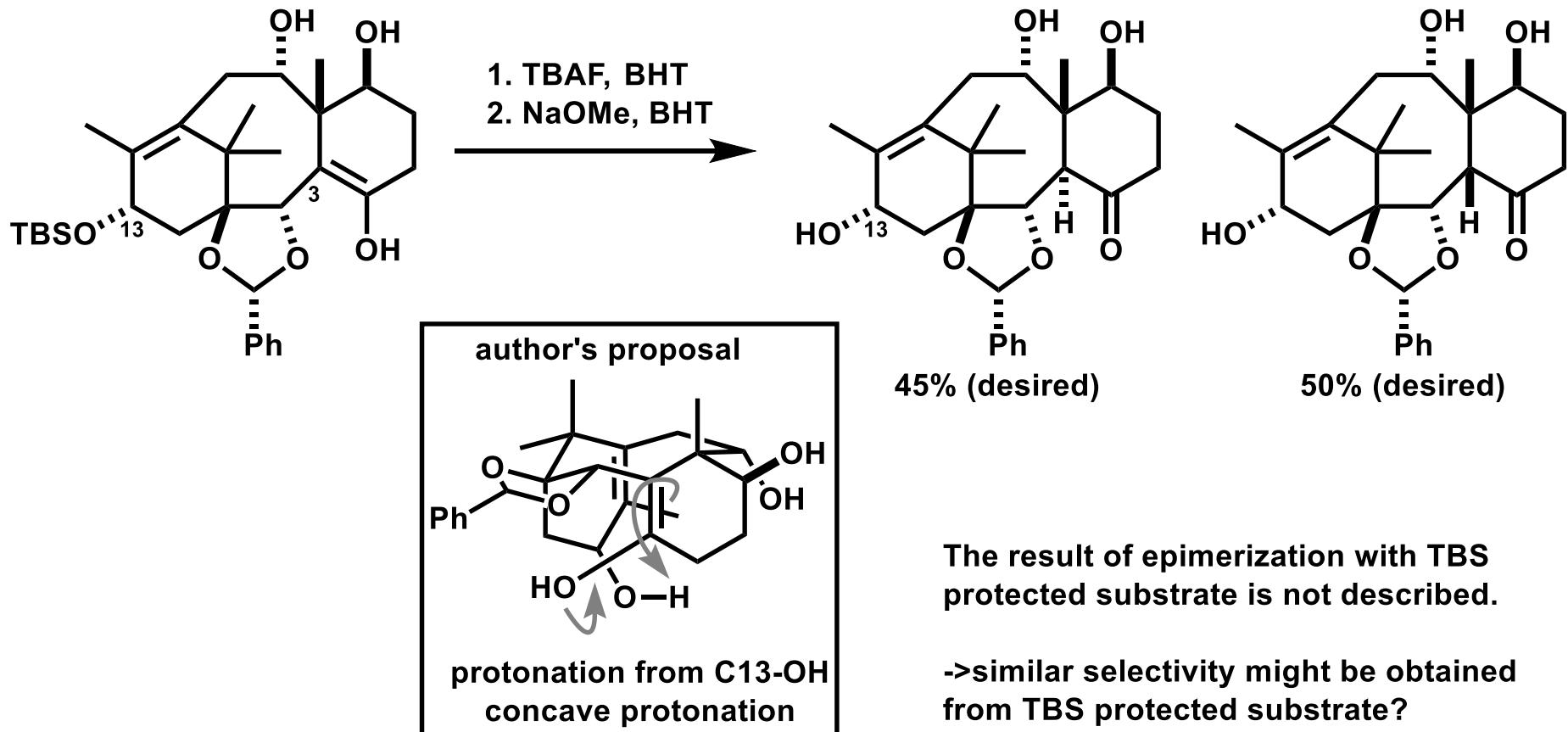
In the ALL total syntheses of taxol, C2-benzoyl was installed via carbonate.

advantages

1. selective protection of 1,2-diol
2. protection of C1-OH (difficult to be protected other than cyclic protection)

C3 epimerization

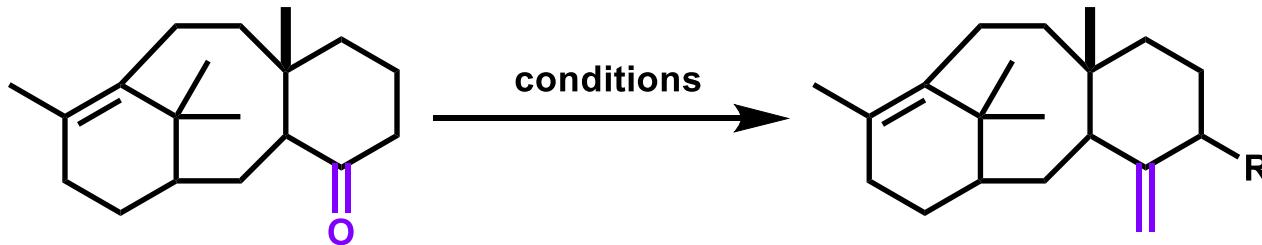
Kuwajima's synthesis



The result of epimerization with TBS protected substrate is not described.

->similar selectivity might be obtained from TBS protected substrate?

C4-20 carbon extension



◆ Holton, Baran

1. MeMgBr
2. Burgess reagent

◆ Kuwajima

1. $\text{KN}(\text{TMS})_2, \text{PhN}(\text{TMS})_2$
2. $\text{Pd}(\text{PPh}_3)_4, \text{TMSCH}_2\text{MgCl}$
3. NCS

◆ Chida

1. $\text{TMSCH}_2\text{MgCl}$
- ...
2. $\text{BF}_3 \cdot \text{OEt}_2$

◆ Nakada

- $$\text{CH}_2\text{I}_2, \text{Zn}, \text{TiCl}_4$$

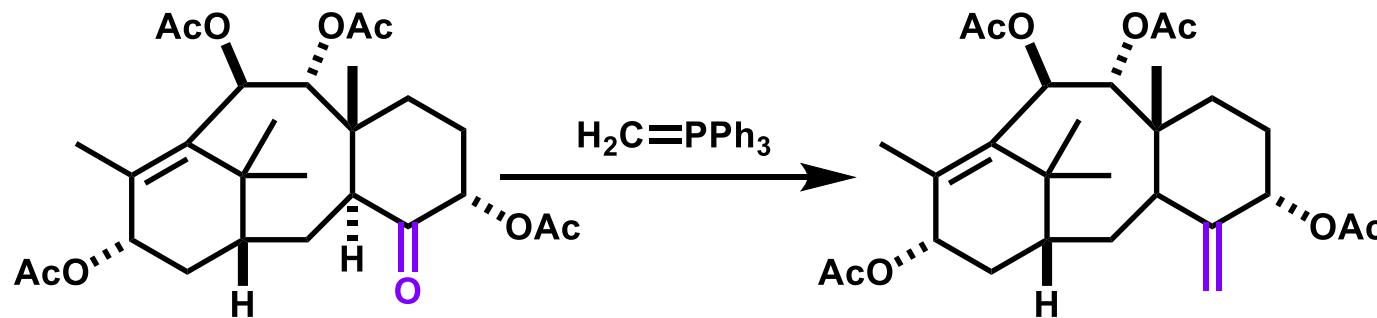
takes >2 steps

1 steps

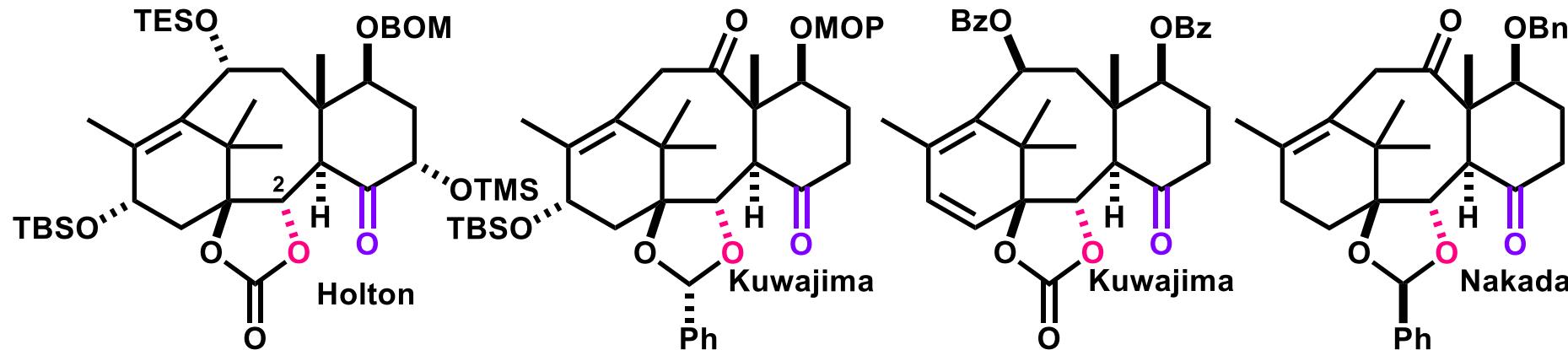
◆ Nicolaou, Danishefsky, Wender, Mukaiyama, Kishi, Takahashi
preinstalled before the construction of tricycle

C4-20 Wittig reaction

Total synthesis of taxusin (Holton and Kuwajima)



Substrate for olefination in the total syntheses of taxol

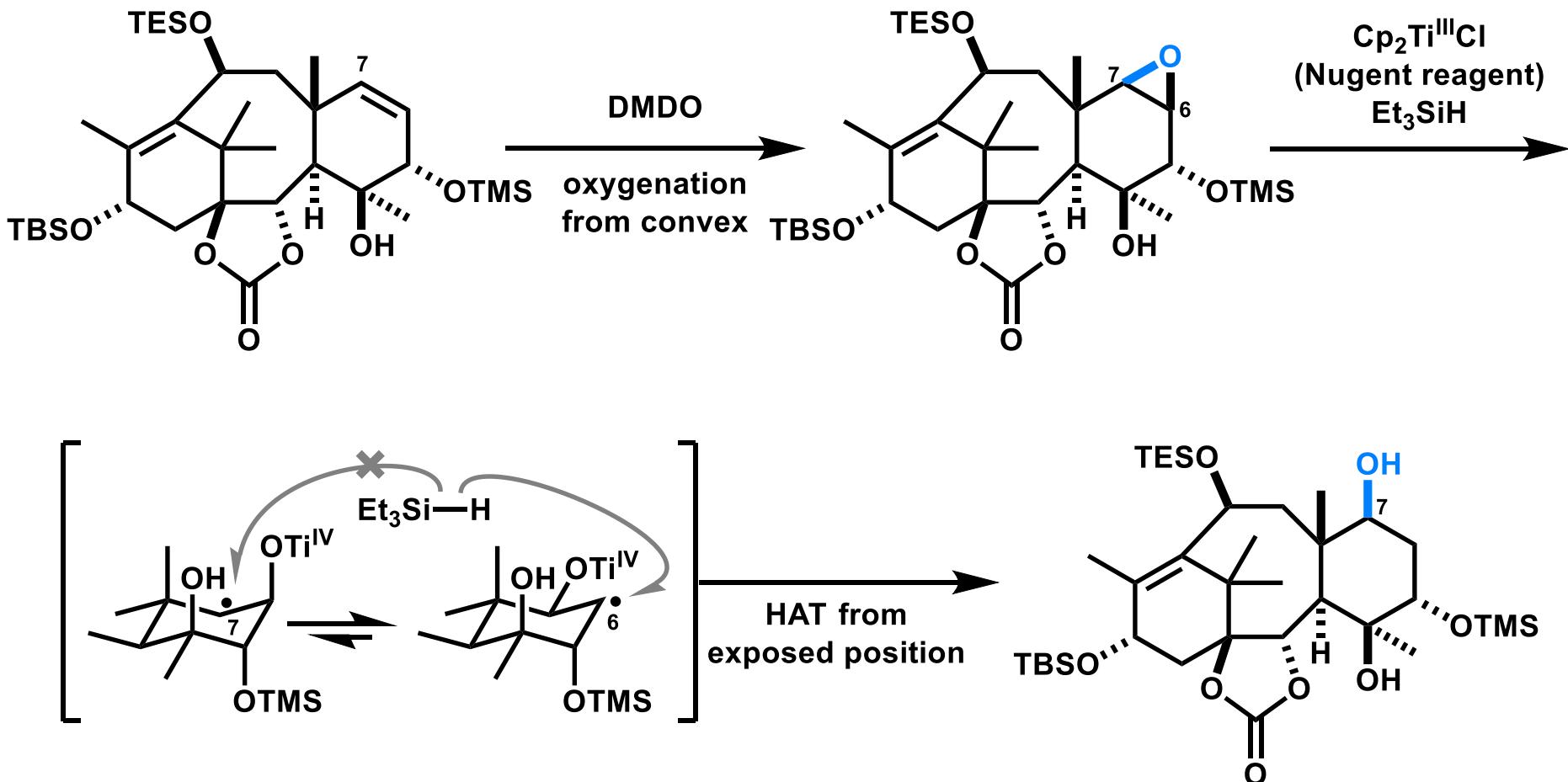


All the substrates contain C2-oxygen functionality (β -oxygen) and weak to basic conditions?

1. Holton, R. A.; Juo, R. R.; Kim, H. B.; Williams, A. D.; Harusawa, S.; Lowenthal, R. E.; Yogai, S. *J. Am. Chem. Soc.* **1988**, 110, 6558. 2. Hara, R.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1996**, 118, 9186.

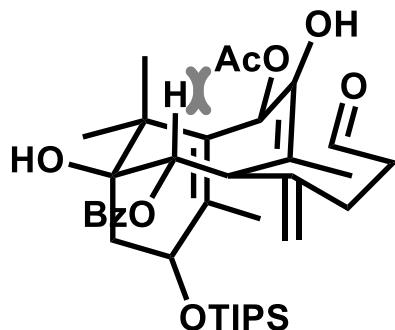
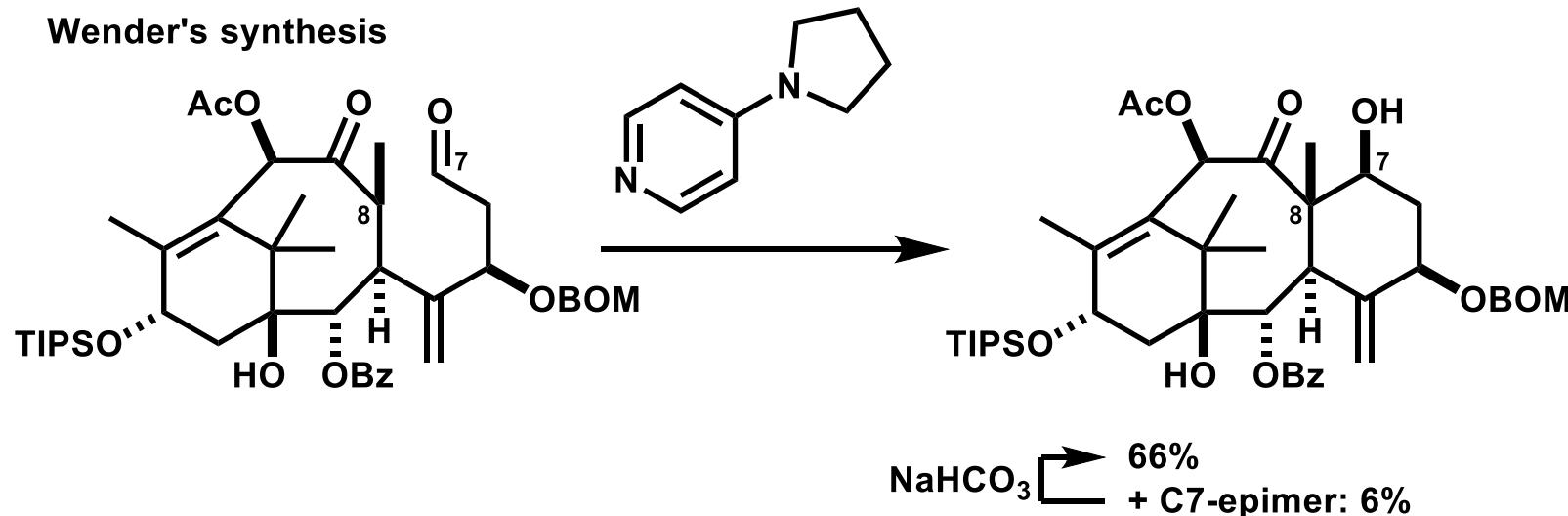
C7 oxygen introduction

Baran's synthesis

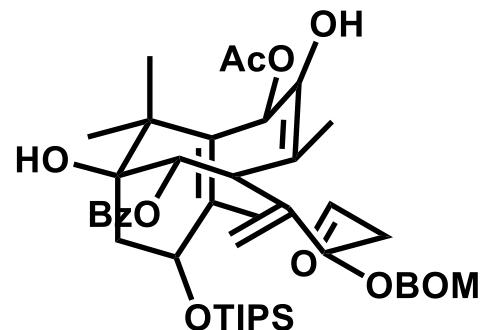


C7 epimerization

Wender's synthesis



C8-epimer
impossible to form
transannular interaction

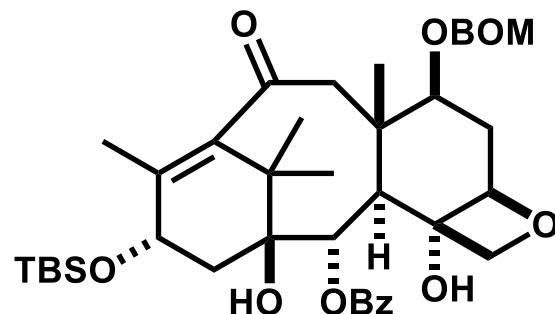


O-axial

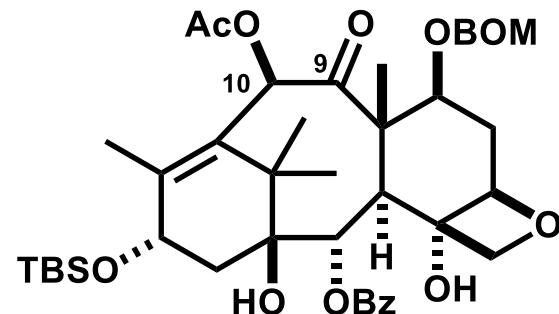
O-equatorial

C9,10 acetoxy ketone

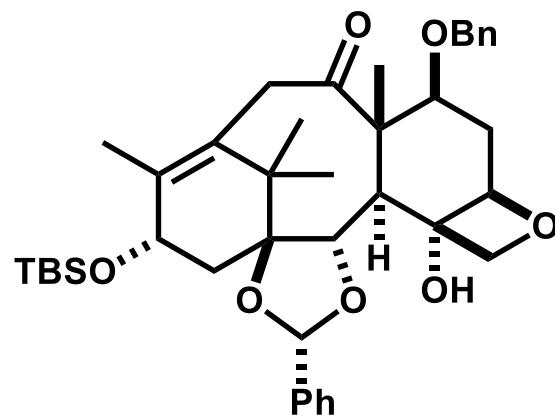
Holton



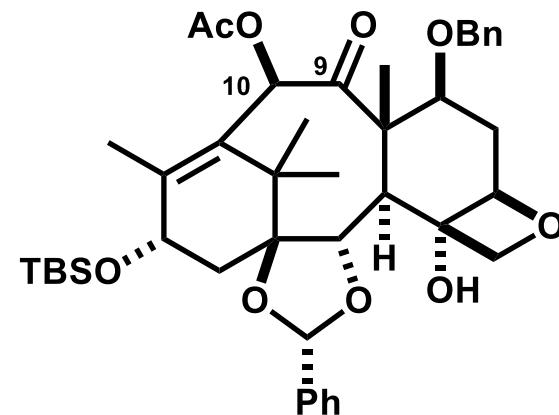
1. KOt-Bu, (PhOSe)₂O
2. **KOt-Bu**
3. Ac₂O



Nakada

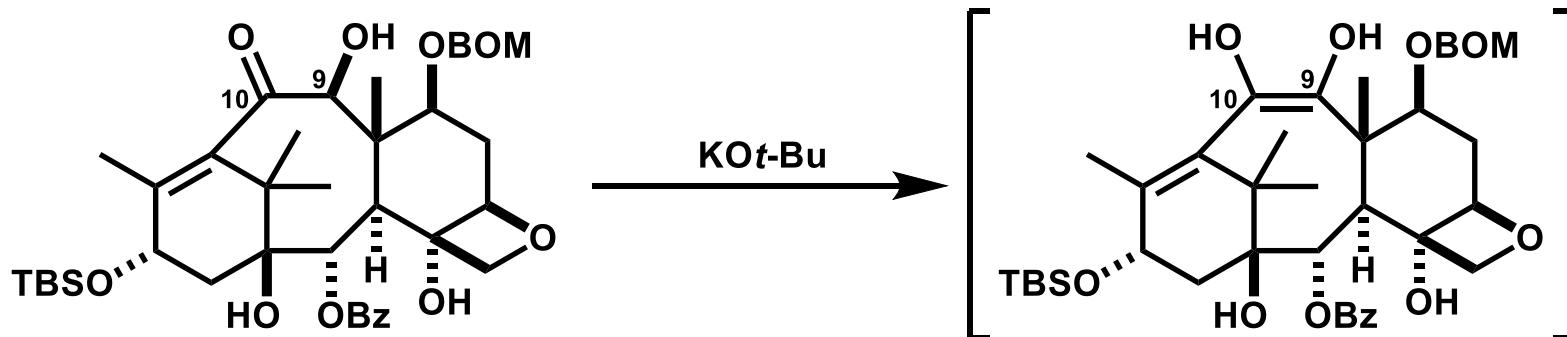


1. KN(TMS)₂; Davis
2. Ac₂O; **DBU**

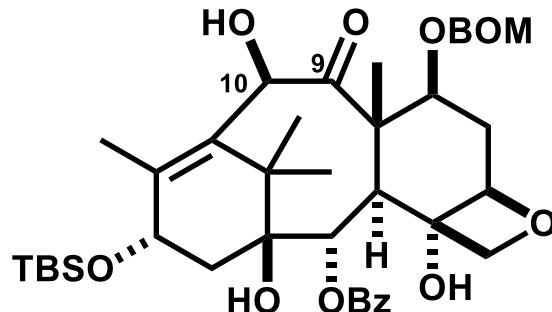
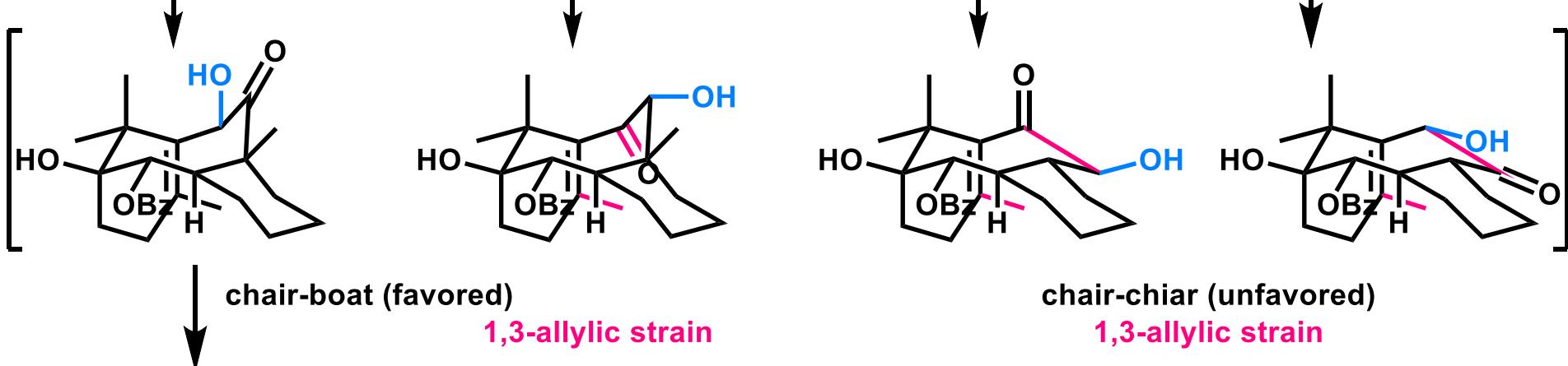


Hydroxy ketone were isomerized to desired diastereomer.

C9,10 acetoxy ketone

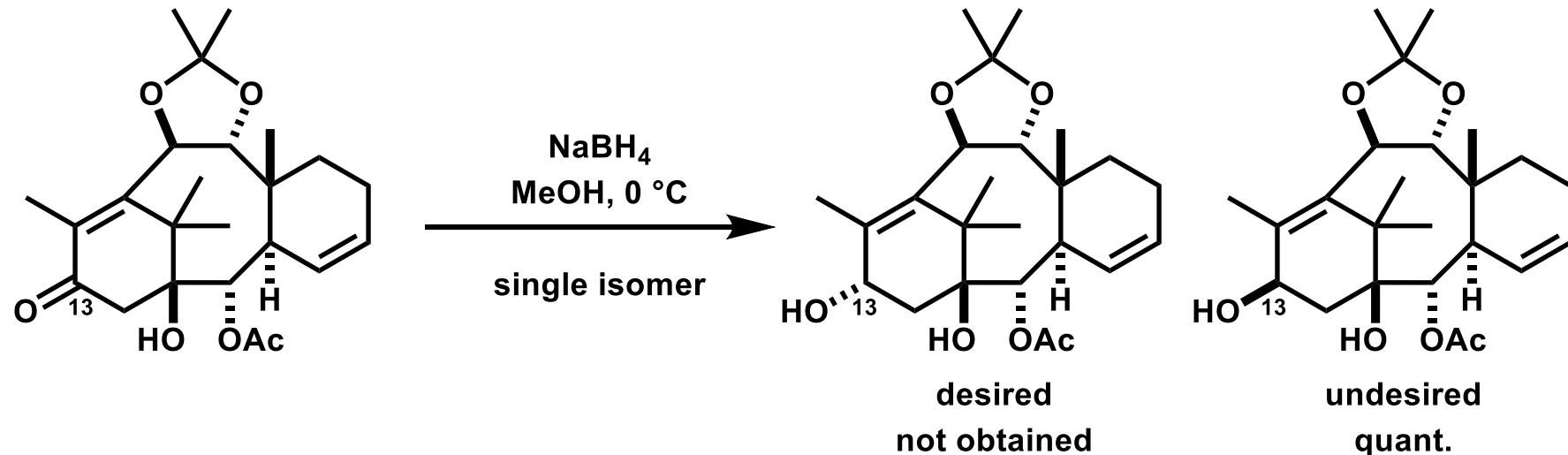


All OHs (blue) are positioned to equatorial to minimize transannular interaction.

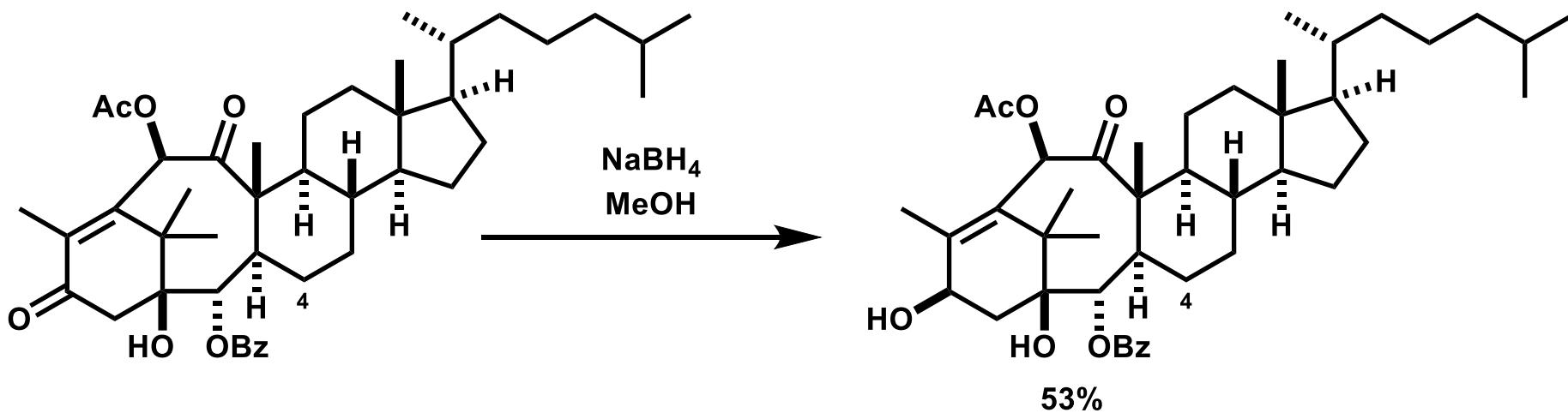


C13 reduction

200425_RR_Yusuke_Imamura

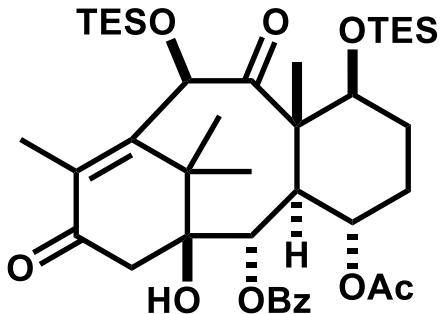


Young, W. B.; Lingk, J. J.; Snyder, L. B.; Danishefsky, S. J.; De Gala, S. *Tetrahedron Lett.* 1995, 36, 4963.

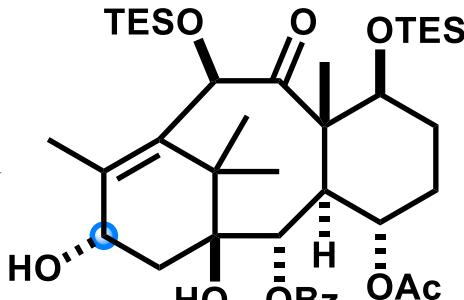


Substrate without C4- α -OAc gave undesired diastereoselectivity.

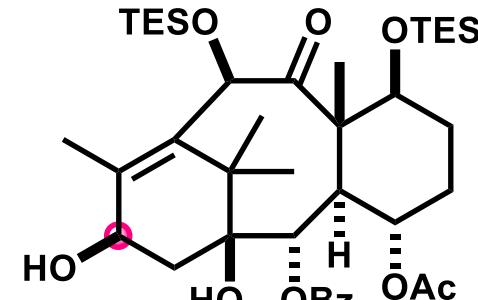
C13 reduction



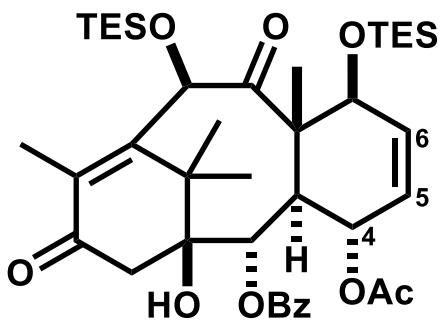
NaBH_4
MeOH/THF



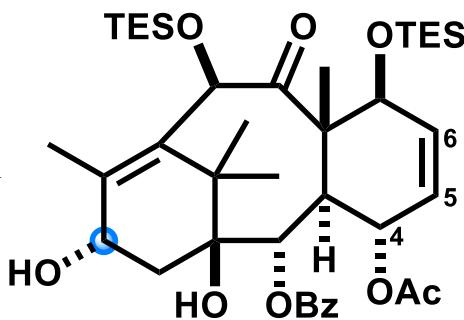
desired: 30%



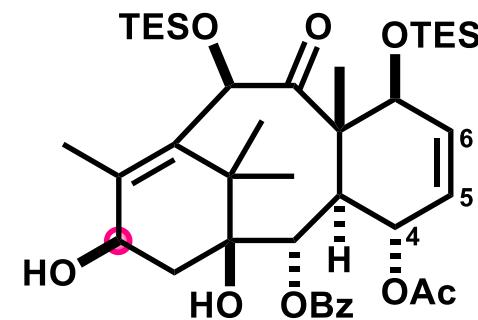
undesired: 47%



NaBH_4
MeOH/THF

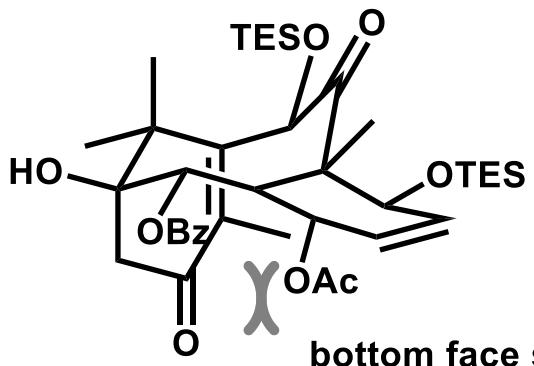
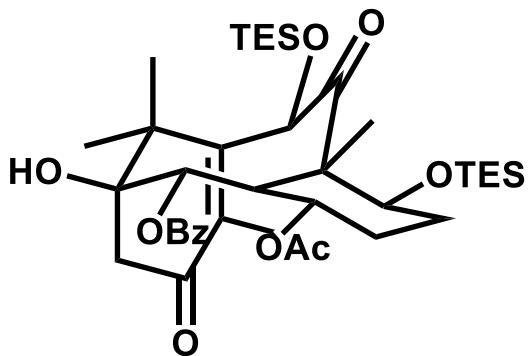


desired: 45%



undesired: 20%

Conformational change modified the position of acetoxy group.



(C4) substitution of C-ring affects
the selectivity of C13 reduction

bottom face shielded

Summary

