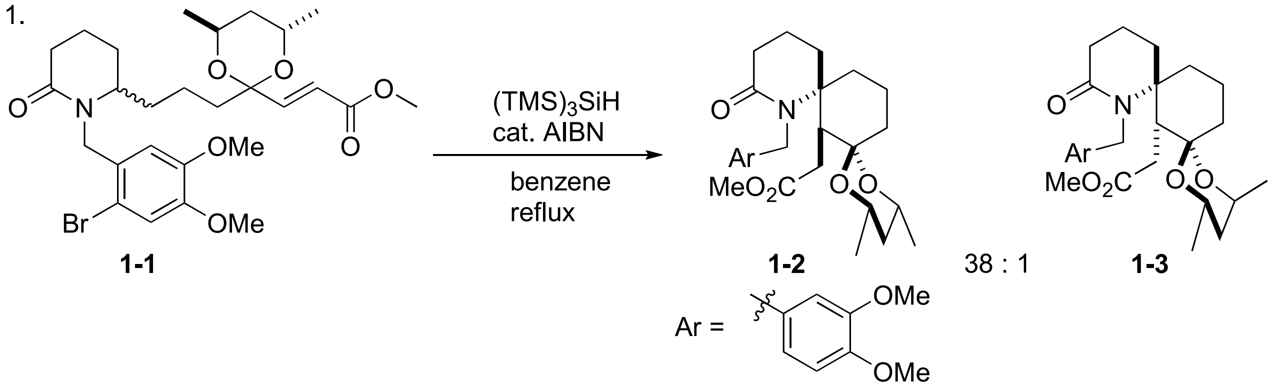
Problem session (2)

2017.9.2 Yuri Takada

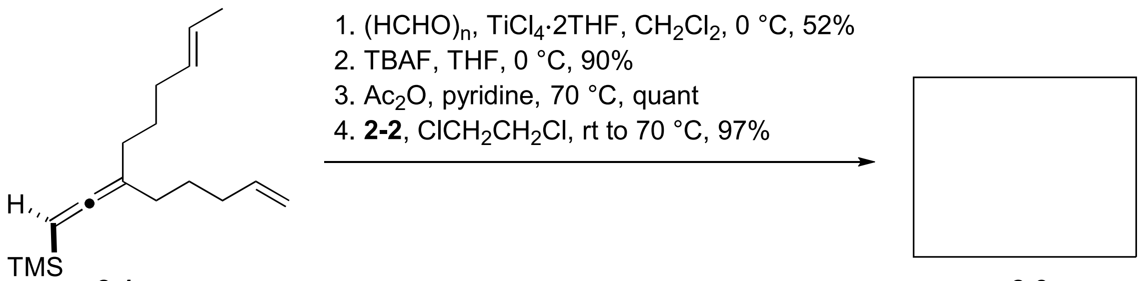
Please fill in a blank and provide the mechanism of the following reactions.

1.



1-1 → **1-2** : **1-3** = 38 : 1

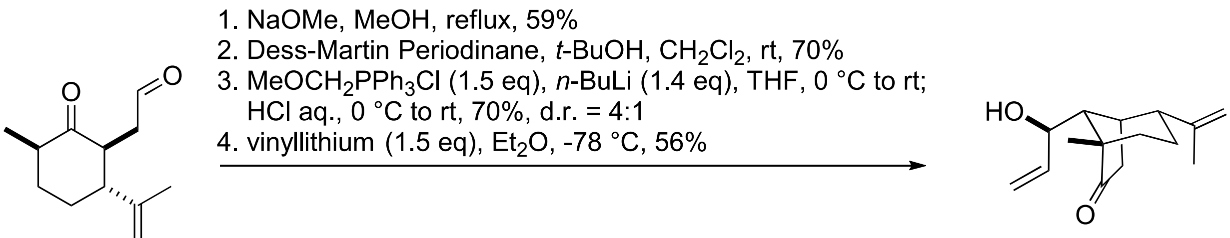
2.



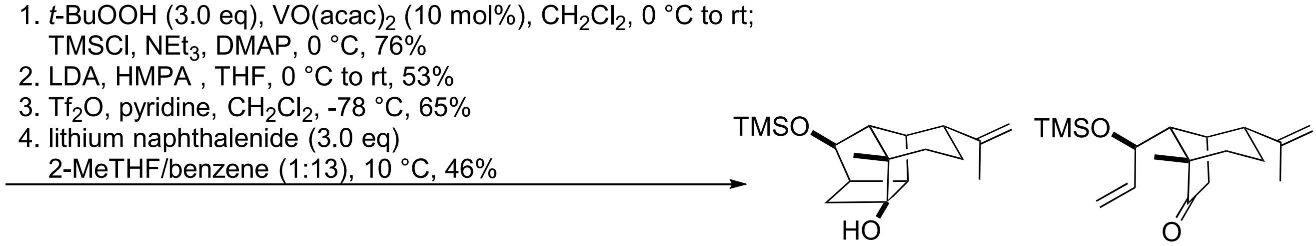
2-1
$C_{17}H_{30}Si$

2-3
bicyclic: $C_{14}H_{20}O_2$

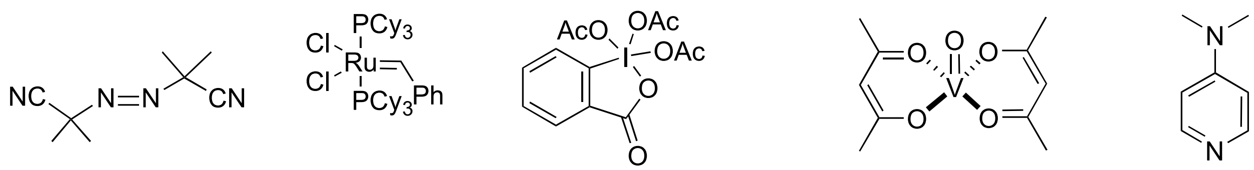
3.



3-1 → **3-2**



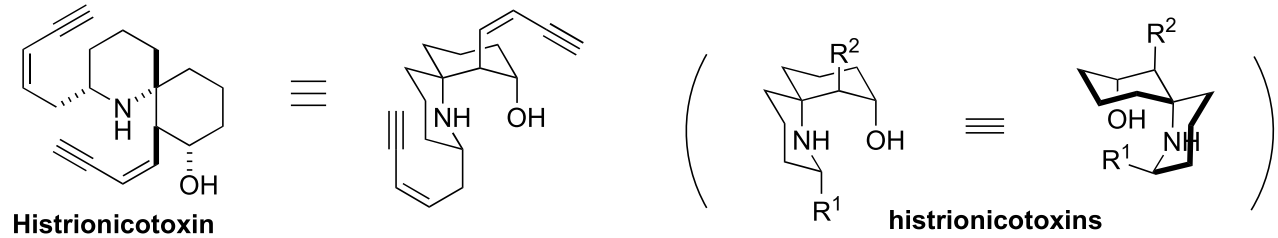
3-3 : **3-4** = 46 : 54



AIBN | **2-2** | Dess-Martin Periodinane | $VO(acac)_2$ | DMAP

Problem session (2)-Answer

2017.9.2 Yuri Takada



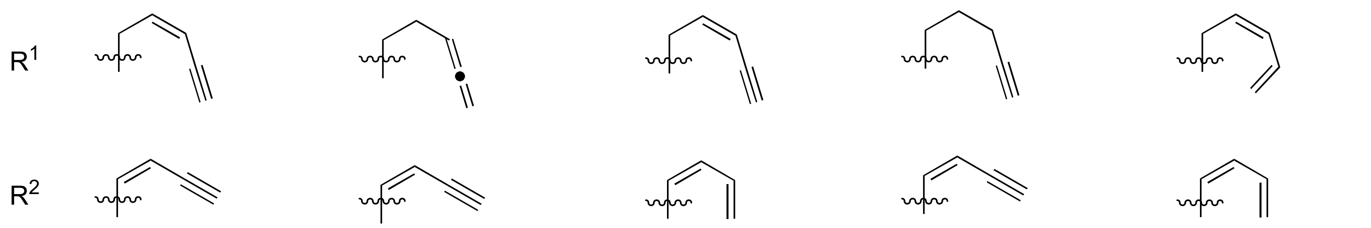
Histrionicotoxin **histrionicotoxins**

<Isolation and Structual determination>
From the poison frog *Dendrobates histrionicus*
(Daly, J.; Karle, I.; Myers, C.; Tokuyama, T.; Waters, J.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1870.)

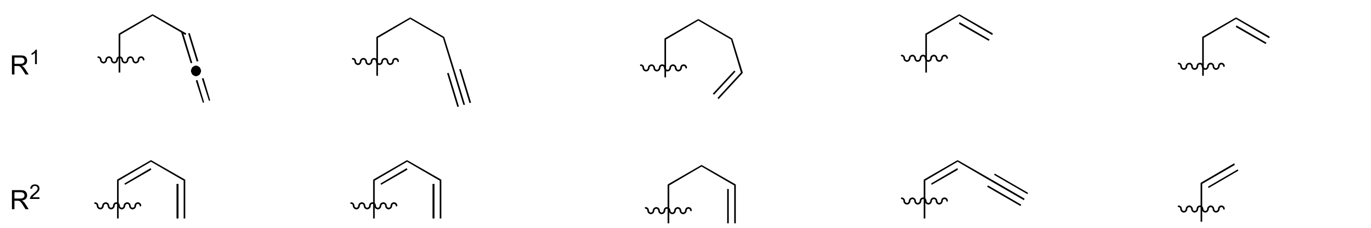
<Bioactivity>
noncompetitive inhibitor of the acetylcholine receptor (neural toxicity)
(Takahashi, K.;Witkop, B.; Brossi, A.; Maleque, M.; Albuquerque, E. *Helv. Chim. Acta* **1982**, *65*, 252.
Gessner, W.; Takahashi, K.; Witkop, B.; Brossi, A.; Albuquerque, E. *Helv. Chim. Acta* **1985**, *68*, 49.)

<structual feature>
1) 1-azaspiro [5.5] undecane core
2) *Z* enyne side chains

Histrionicotoxin **isodihydro-HTX** **neodihydro-HTX** **allodihydro-HTX** **tetrahydro-HTX**

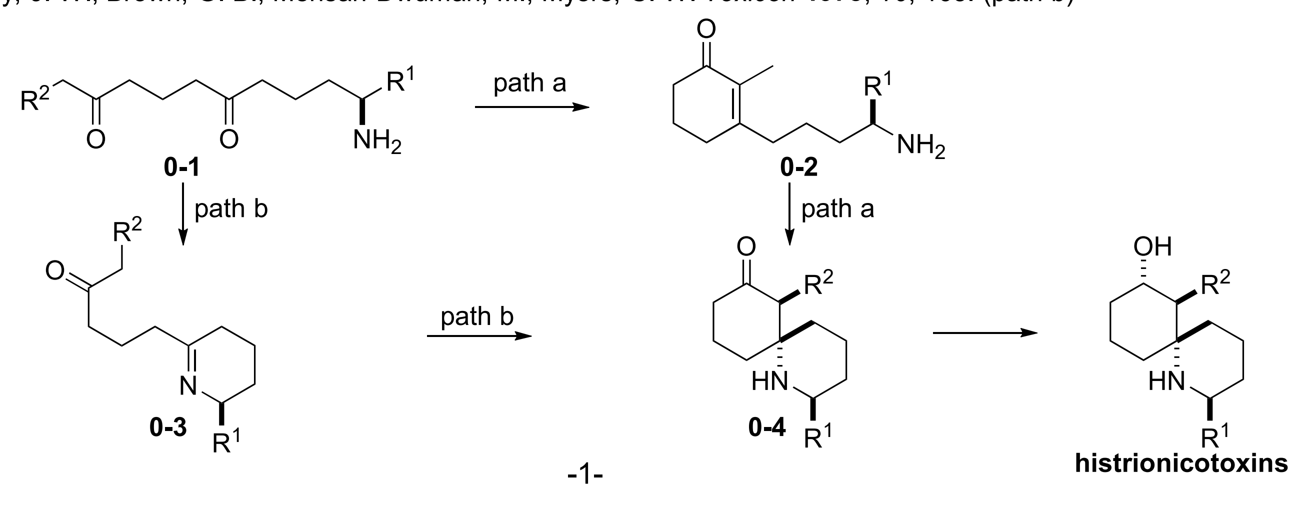


isotetrahydro-HTX **allotetrahydro-HTX** **octahydro-HTX** **HTX-259** **HTX-235A**



<Biosyhthesis of Histrionicotoxin>

Winterfeldt, E. *Heterocycles* **1979**, *12*, 1631. (path a)
Daly, J. W.; Brown, G. B.; Mensah-Dwumah, M.; Myers, C. W. *Toxicon* **1978**, *16*, 163. (path b)



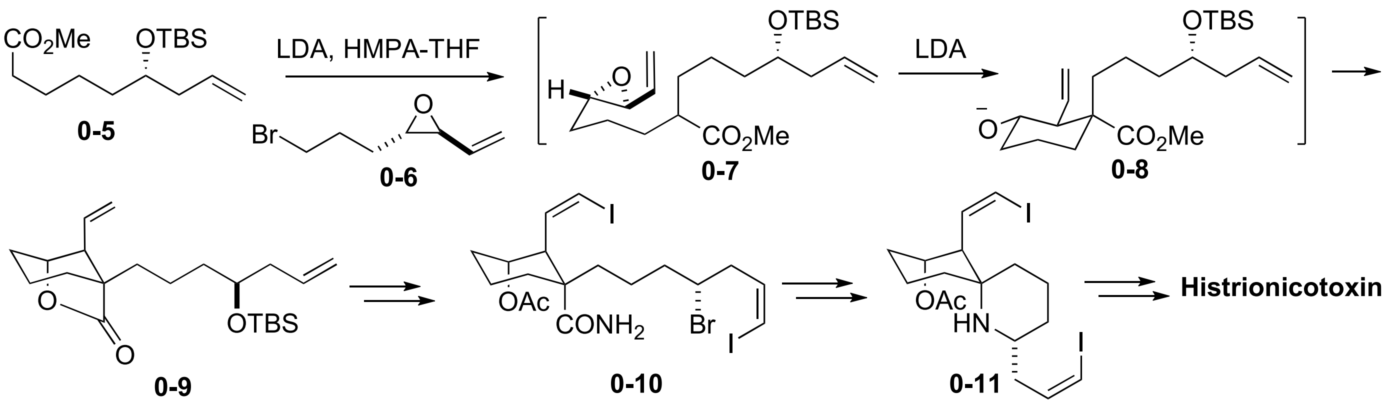
<Total synthesis>

For the total synthesis of (-)-HTX
Stork, G.; Zhao, K. *J. Am. Chem. Soc.* **1990**, *112*, 5875.
Williams,G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B. *J. Am. Chem.Soc.* **1999**, *121*,4900.
Adachi, Y.; Kamei, N.; Yokoshima, S.; Fukuyama, T. *Org.Lett.* **2011**, *13*, 4446. (***problem 2***)
Sato, M.; Azuma, H.; Daigaku, A.; Sato, S.; Takasu, K.; Okano, K.; Tokuyama, H. *Angew.Chem. Int. Ed.* **2017**, *56*, 1087.(***problem 1***)

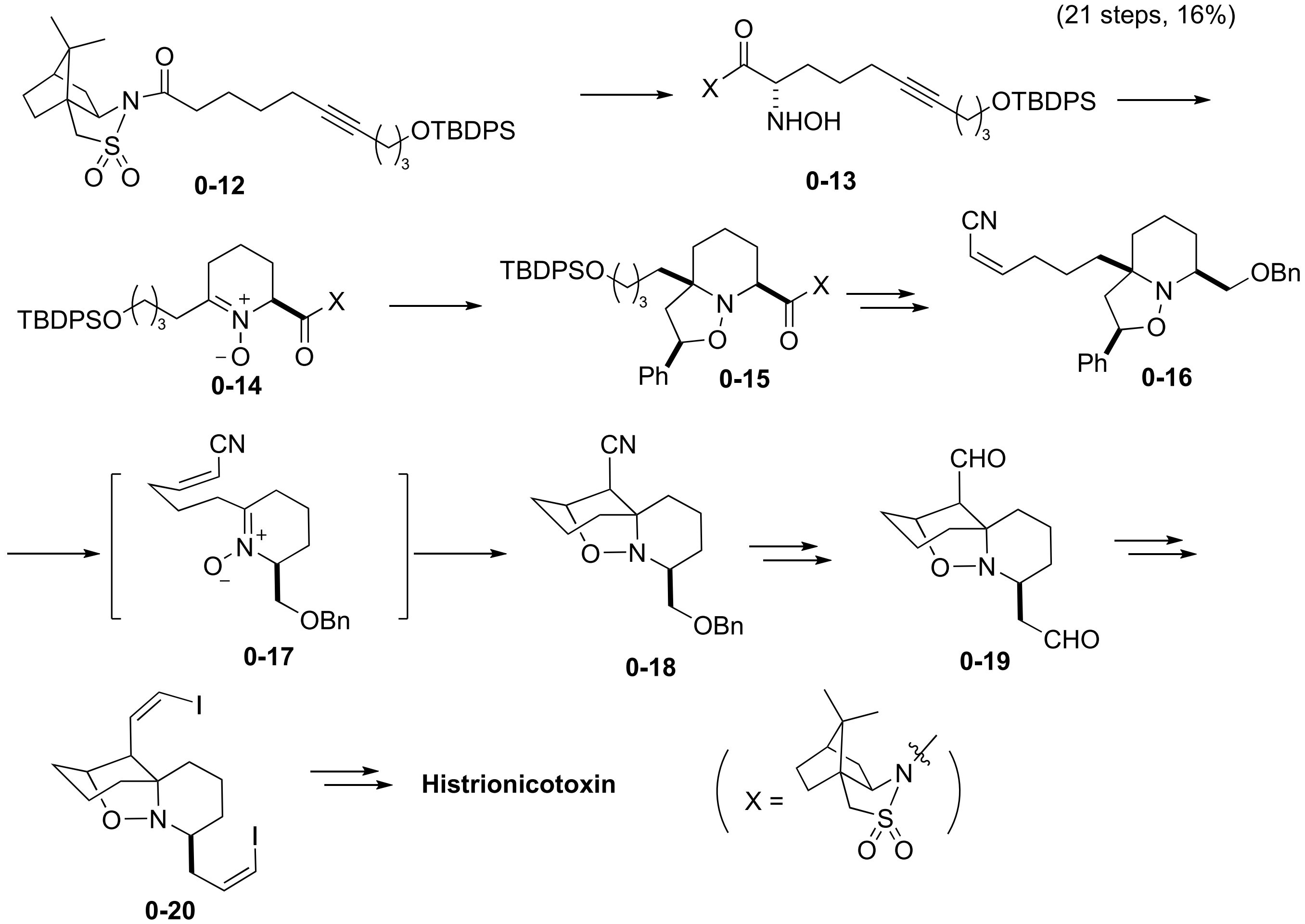
For the total synthesis of (±)-HTX
Carey, S. C.; Aratani, M.; Kishi, Y. *TetrahedronLett.* **1985**, *26*, 5887.
Karatho-luvhu, M. S.; Sinclair, A.; Newton, A. F.; Alcaraz, M.-L.; Stock-man, R. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **2006**, *128*, 12656.

For a review, see: Sinclair, A.; Stockman, R. A. *Nat. Prod. Rep.* **2007**, *24*, 298.

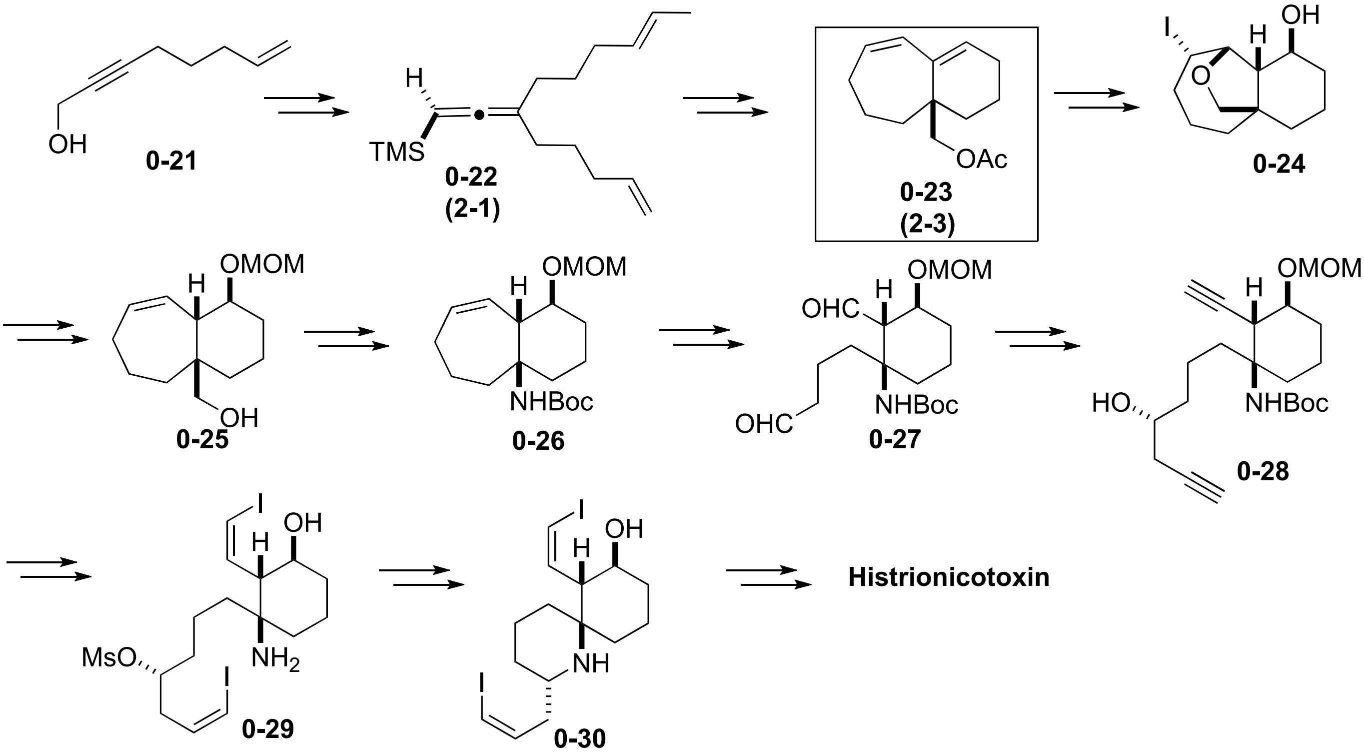
Stork *et. al* Stork, G.; Zhao, K. *J. Am. Chem. Soc.* **1990**, *112*,5875. (14 steps, 0.44%)



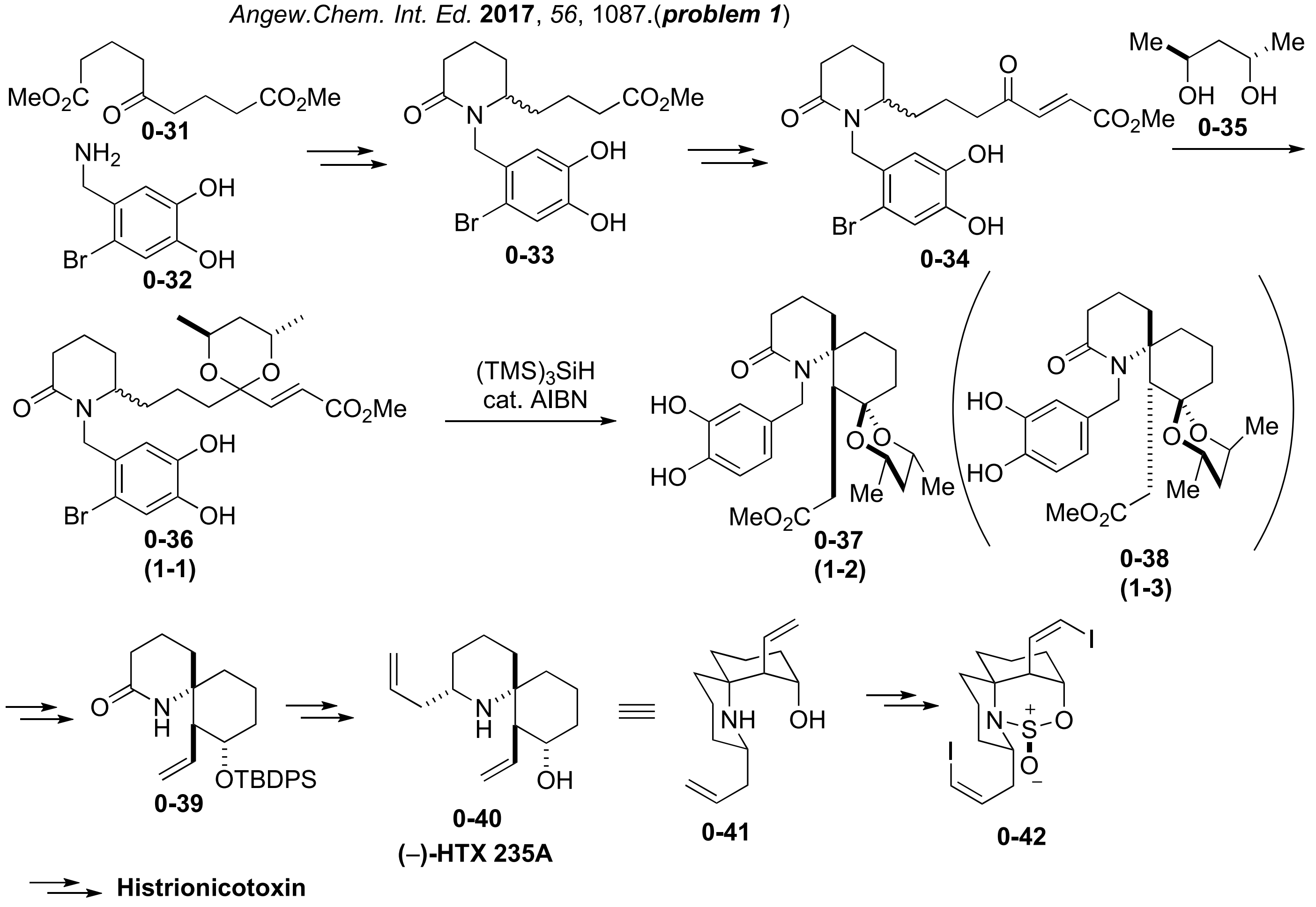
Holmes *et. al* Williams,G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B. *J. Am. Chem.Soc.* **1999**, *121*,4900. (21 steps, 16%)



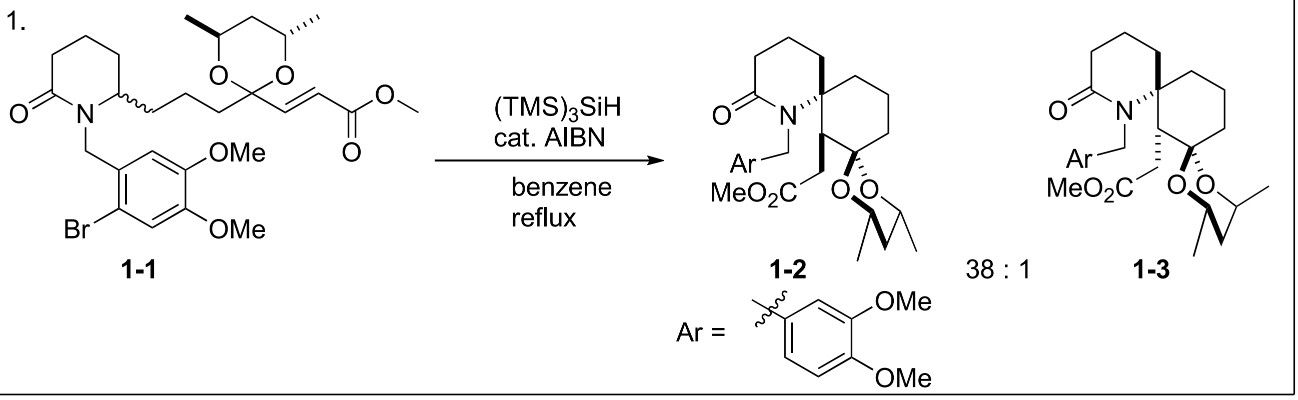
Fukuyama *et. al* Adachi, Y.; Kamei, N.; Yokoshima, S.; Fukuyama, T. *Org.Lett.* **2011**, *13*, 4446. (***problem 2***)

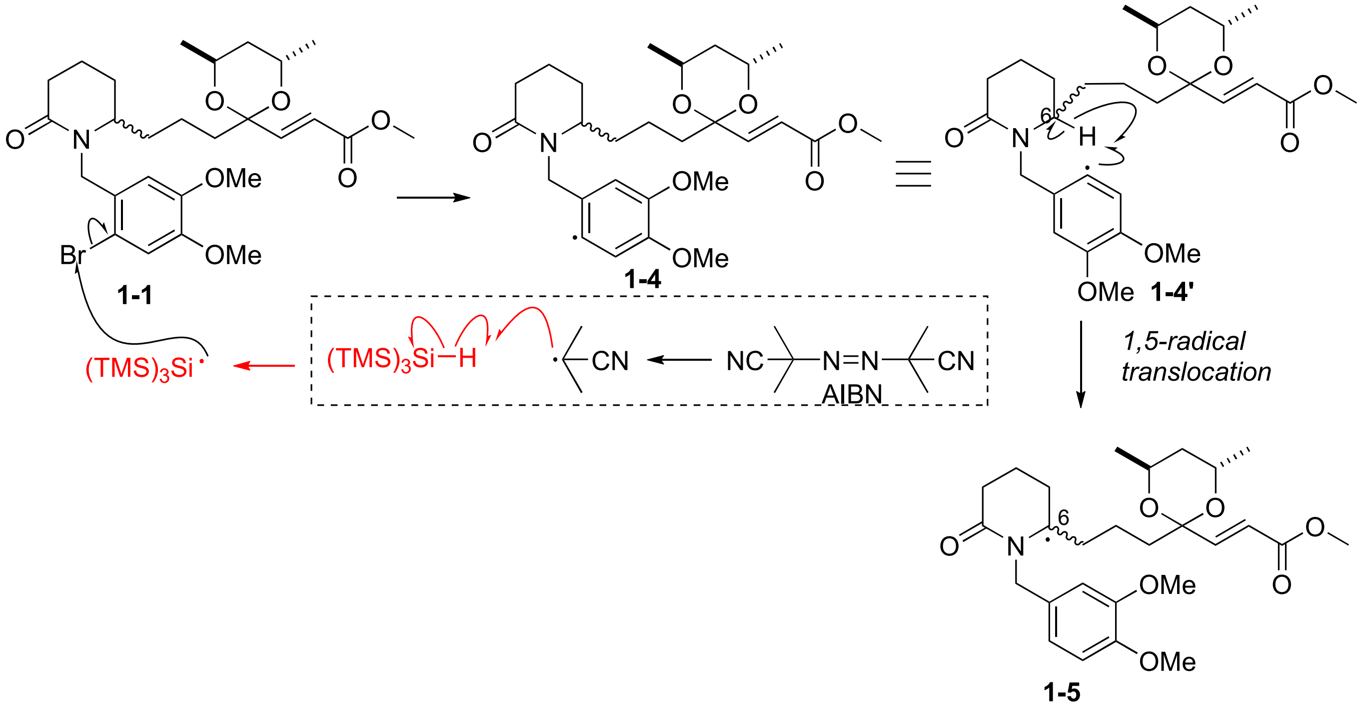


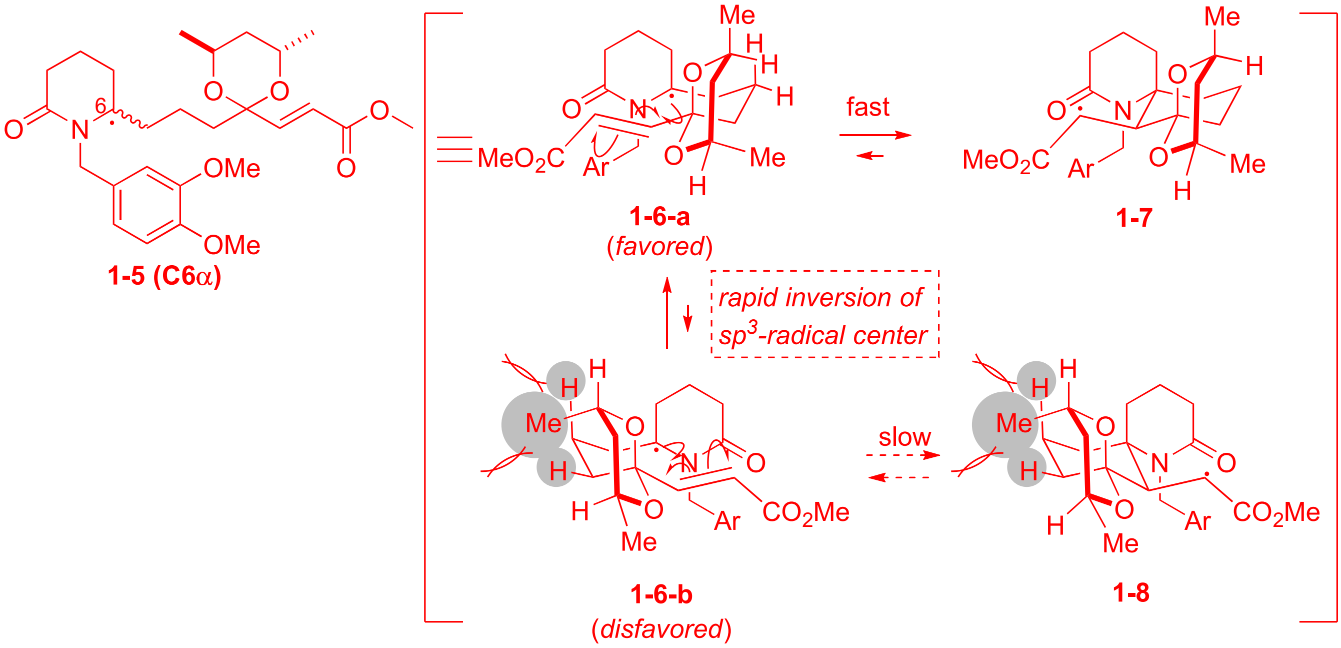
Tokuyama *et. al* Sato, M.; Azuma, H.; Daigaku, A.; Sato, S.; Takasu, K.; Okano, K.; Tokuyama, H. *Angew.Chem. Int. Ed.* **2017**, *56*, 1087.(***problem 1***)



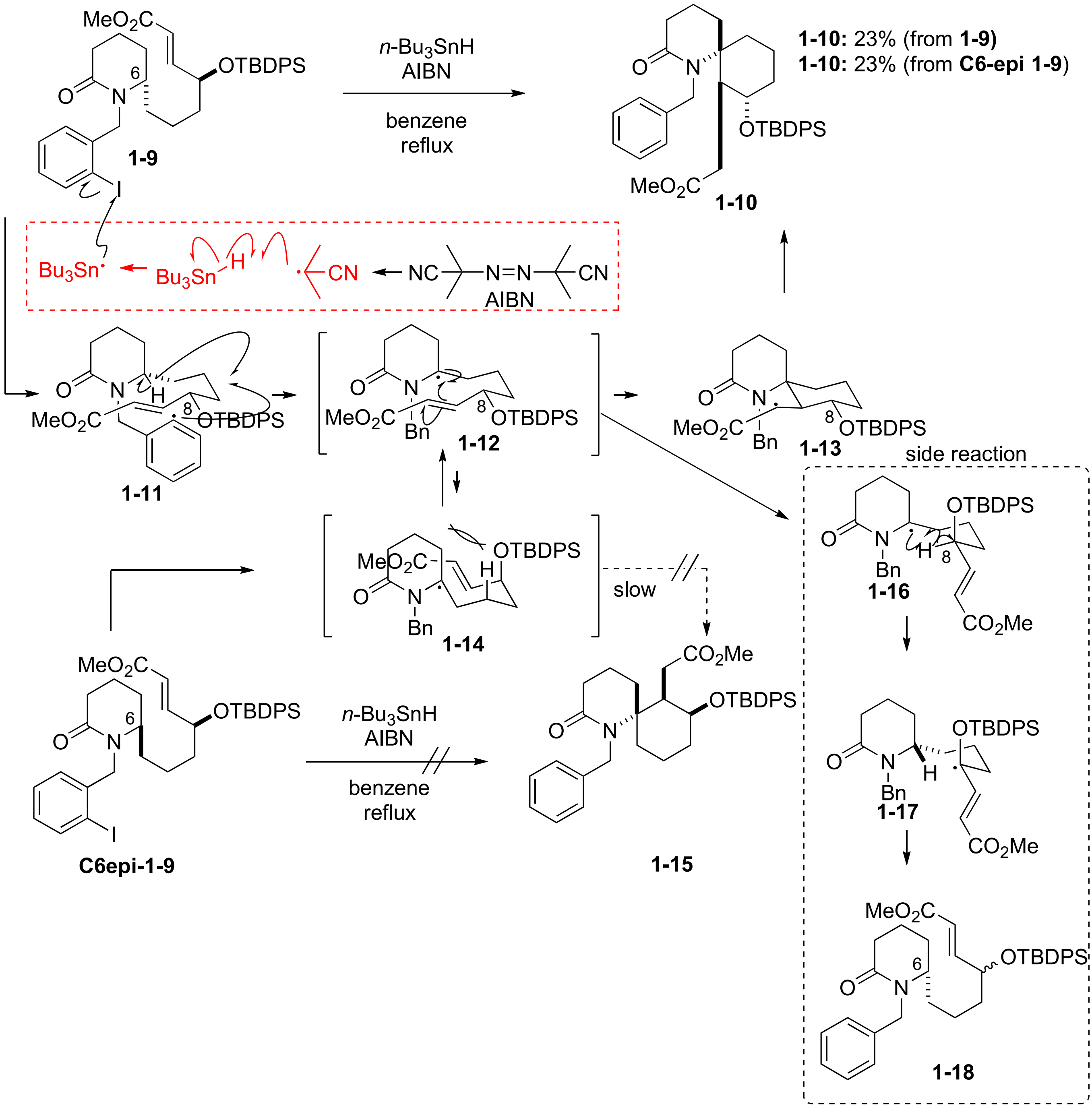
1.

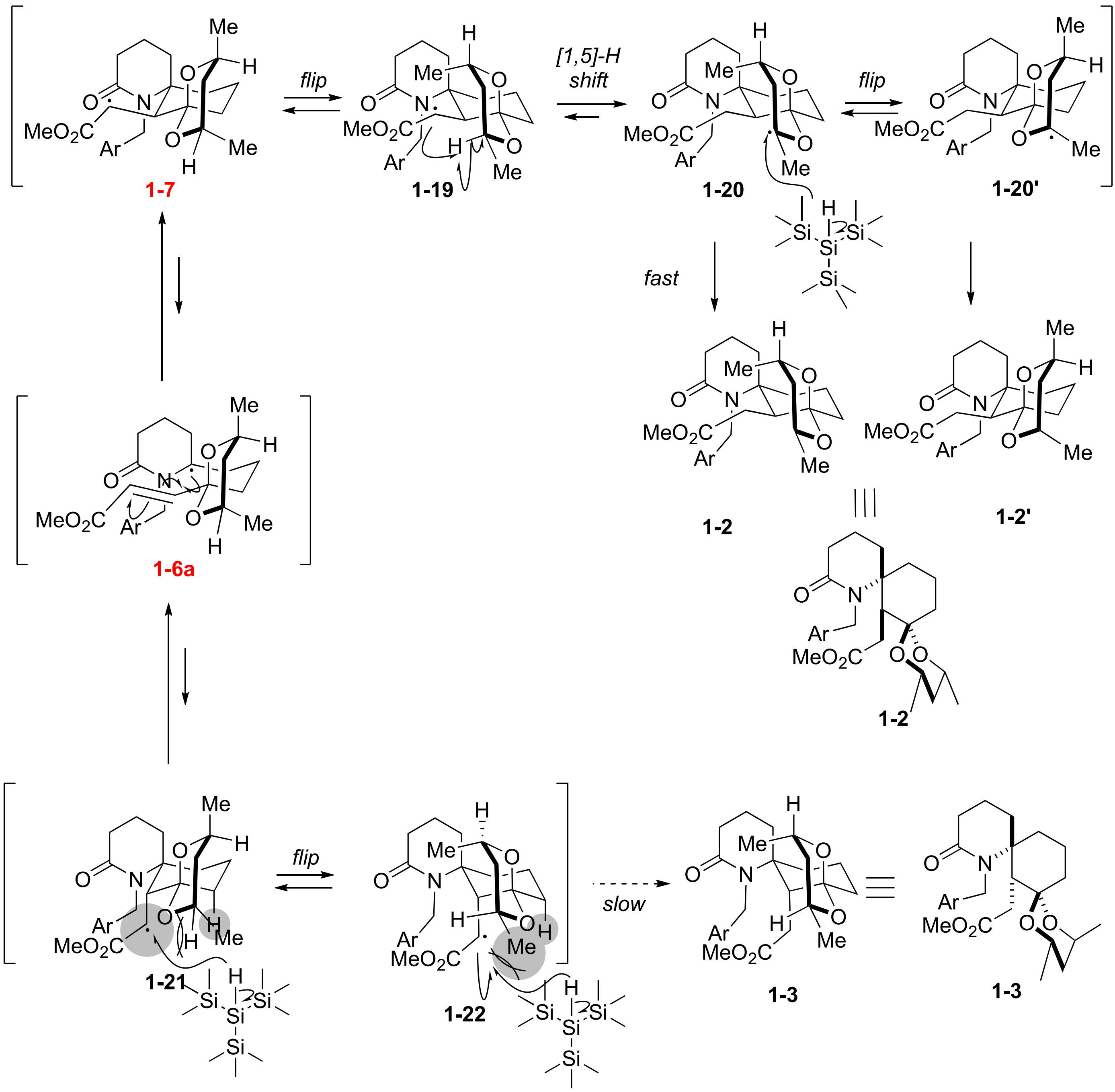

(TMS)$_3$SiH
cat. AIBN
benzene
reflux
1-1
1-2
38 : 1
1-3
Ar =
OMe
OMe


1-1
1-4
1-4'
(TMS)$_3$Si·
(TMS)$_3$Si–H
NC–N=N–CN
AIBN
1,5-radical translocation
1-5


1-5 (C6α)
fast
1-6-a
(favored)
1-7
rapid inversion of sp^3-radical center
slow
1-6-b
(disfavored)
1-8

other experiment



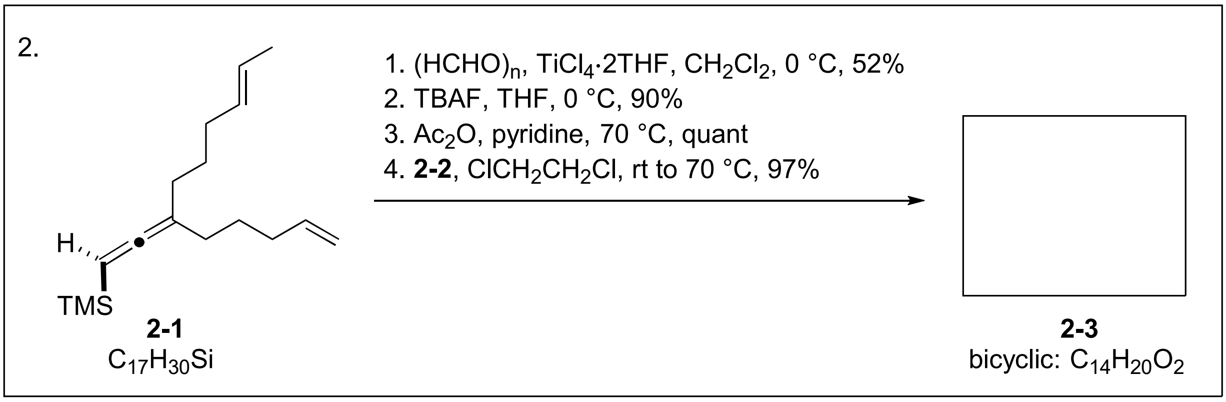


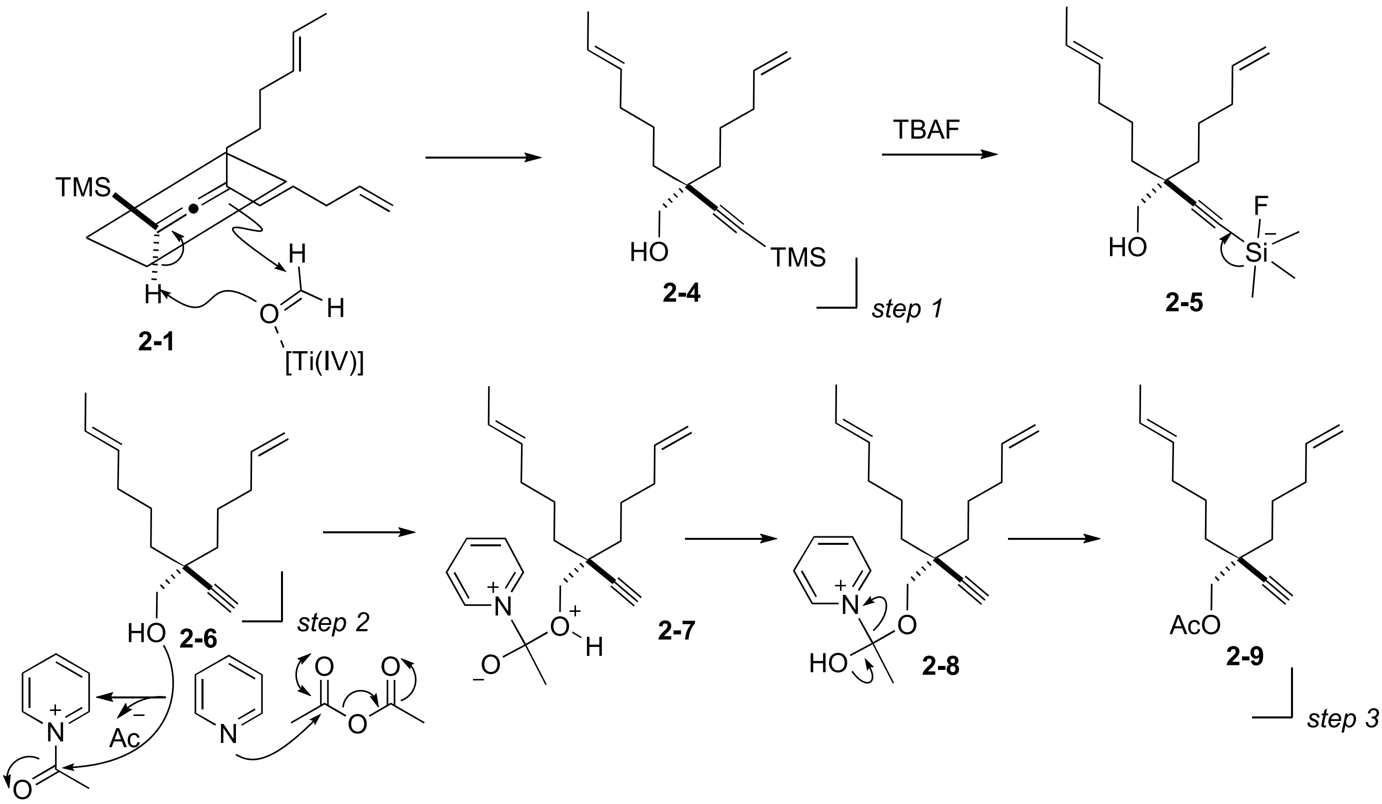
bulky $(TMS)_3SiH$ could be due to smooth H-atom transfer to the radical spieces **1-20**,
which is more readily accessible than other radical spieces in the equilibrium between **1-6** and **1-22**.

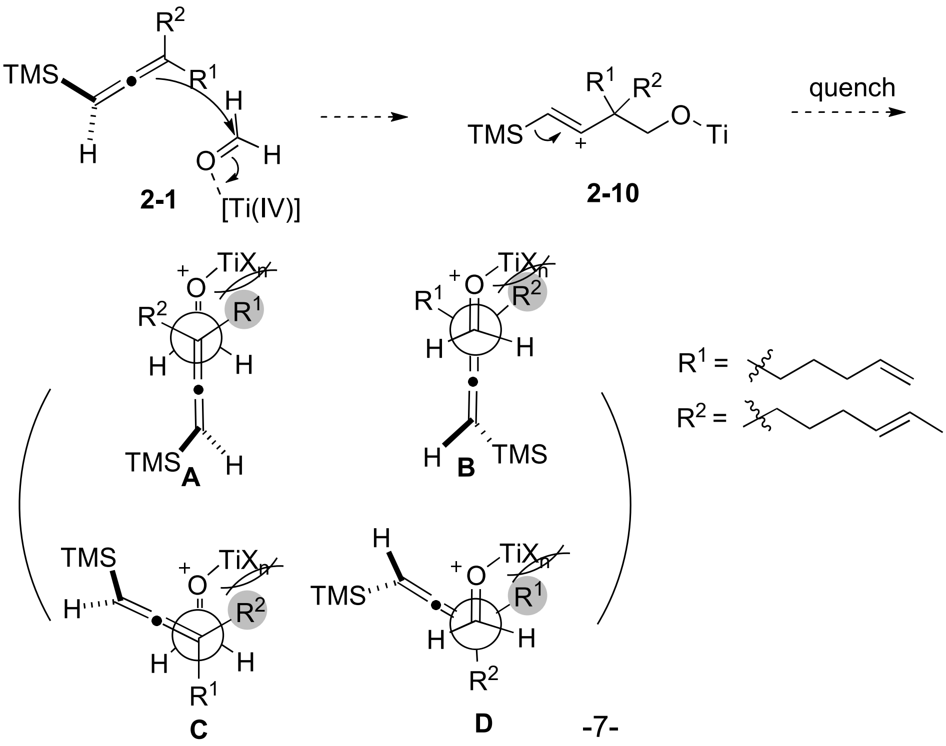
Table

Entry	Reagent	Yield [%]	**1-2/1-3**
1	nBu$_3$SnH	79	3:1
2	Ph$_3$SnH	84	1.7:1
3	(TMS)$_3$SiH	68	38:1

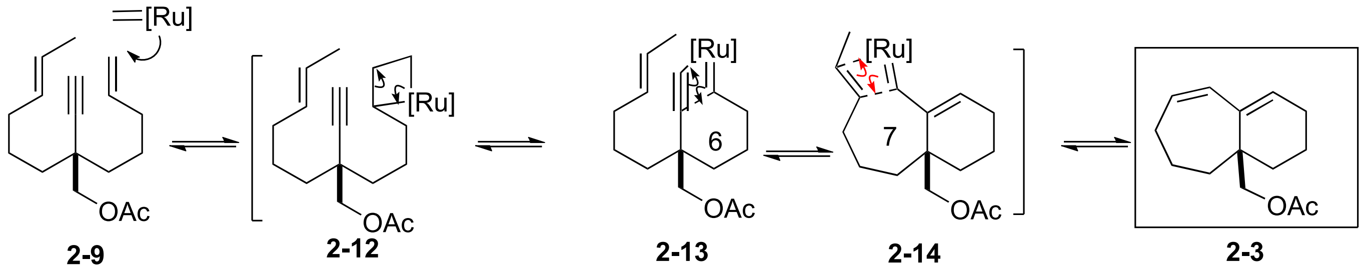
2.


1. (HCHO)$_n$, TiCl$_4$·2THF, CH$_2$Cl$_2$, 0 °C, 52%
2. TBAF, THF, 0 °C, 90%
3. Ac$_2$O, pyridine, 70 °C, quant
4. **2-2**, ClCH$_2$CH$_2$Cl, rt to 70 °C, 97%
H
TMS
2-1
$C_{17}H_{30}Si$
2-3
bicyclic: $C_{14}H_{20}O_2$

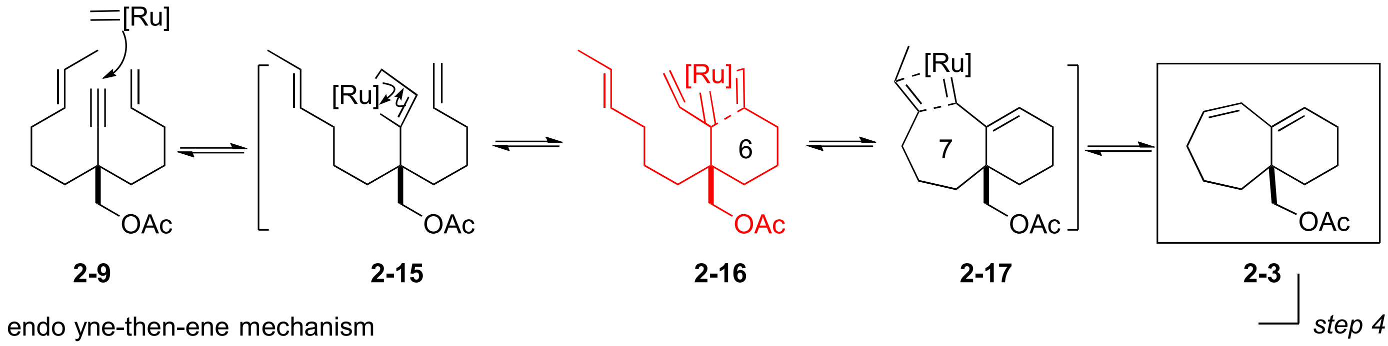

TMS
H
H
H
O
[Ti(IV)]
2-1
HO
TMS
2-4
step 1
TBAF
HO
F
Si
2-5
HO
2-6
step 2
Ac
O
N
O
O
O
N
O
H
2-7
HO
O
2-8
AcO
2-9
step 3


TMS
R^2
R^1
H
H
O
H
[Ti(IV)]
2-1
R^1
R^2
TMS
O
Ti
2-10
quench
R^1
R^2
OH
2-11
TiX$_n$
O
R^2
R^1
H
H
TMS
A
H
R^1
R^2
H
H
B
TMS
R^1 =
R^2 =
TMS
H
R^2
R^1
C
H
TMS
R^1
R^2
D

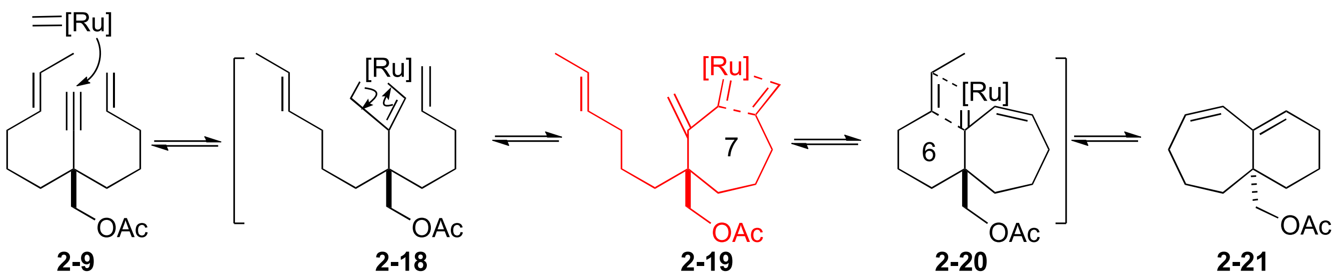
ene-then-yne mechanism

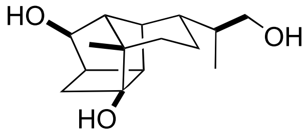


exo yne-then-ene-mechanism



endo yne-then-ene mechanism





(+)-dendrowardol C

<Isolation and Structual determination>

from the stems of *Dendrobium wardianum* Warner, an orchid endemic to southern China and Southeast Asia
(Fan, W.-W.; Xu, F.-Q.; Dong, F.-W.; Li, X.-N.; Li, Y.; Liu, Y.-Q; Zhou, J.; Hu, J.-M. *Nat. Prod. Bioprospect.* **2013**, *3*, 89.)

<Bioactivity>

no cytotoxic activity against human tumor cell lines HL-60, SMMC-7721, A-549, MCF-7, and SW480
(Fan, W.-W.; Xu, F.-Q.; Dong, F.-W.; Li, X.-N.; Li, Y.; Liu, Y.-Q; Zhou, J.; Hu, J.-M. *Nat. Prod. Bioprospect.* **2013**, *3*, 89.)

<structual feature>

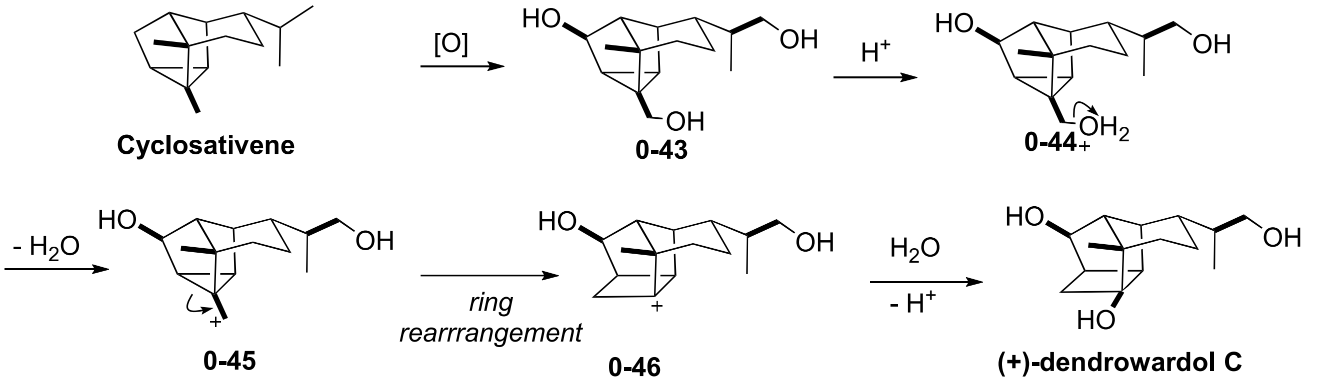
unprecedented 4/5/6/6 tetracyclic ring system
highly congested carbon skeleton
9 contiguous stereogenic centersf

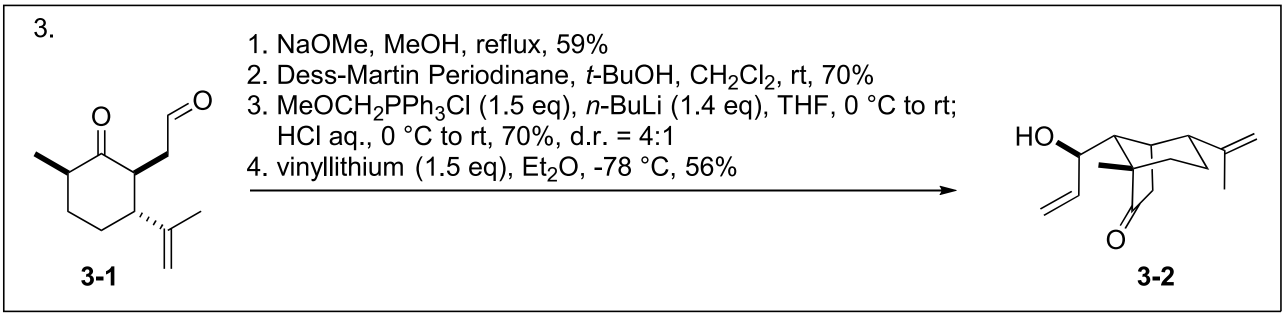
<Total synthesis>

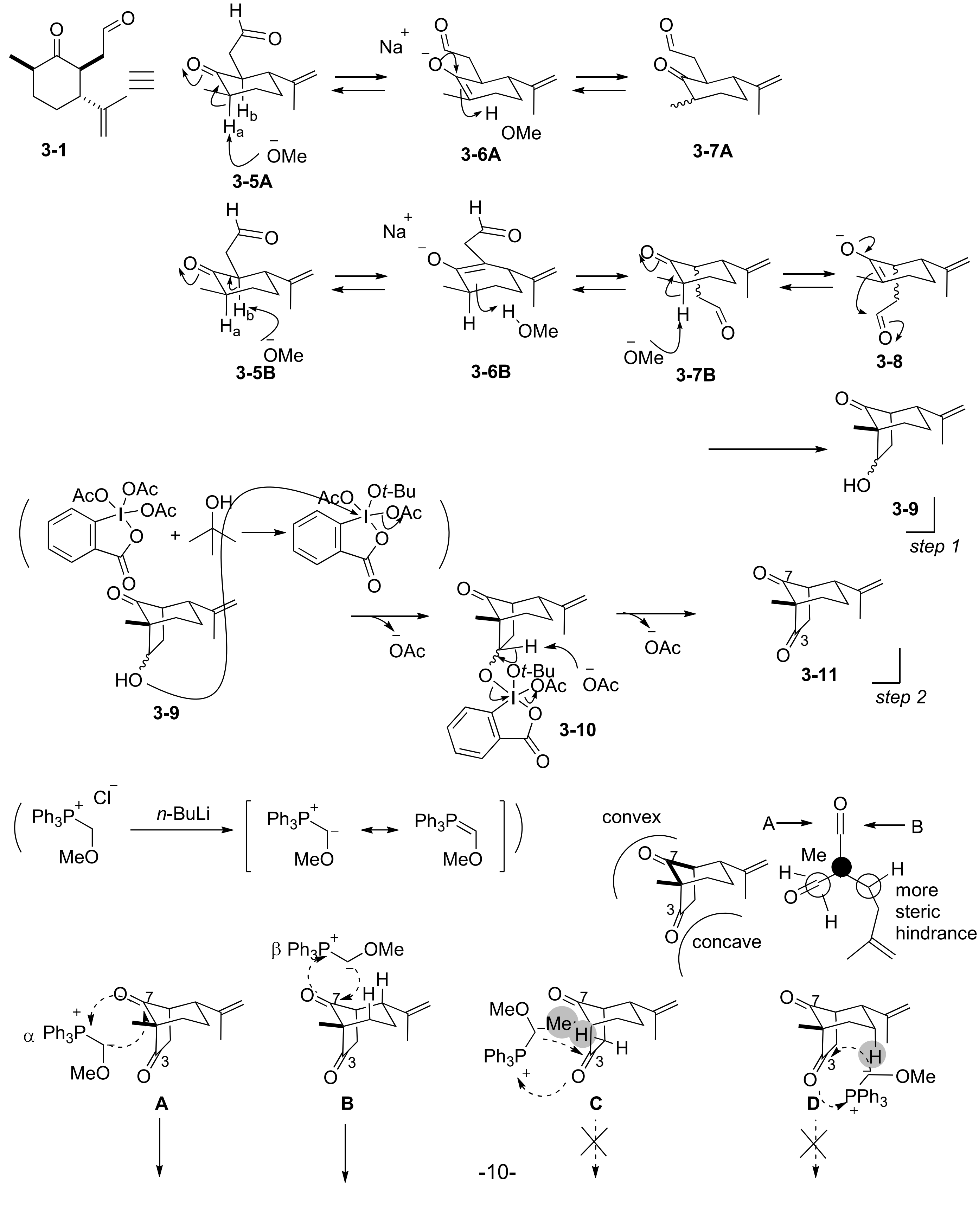
First total synthesis
Wolleb, H.; Carreira, E. M. *Angew.Chem. Int. Ed.* **2017**, *56*, 10890.(***problem 3***)

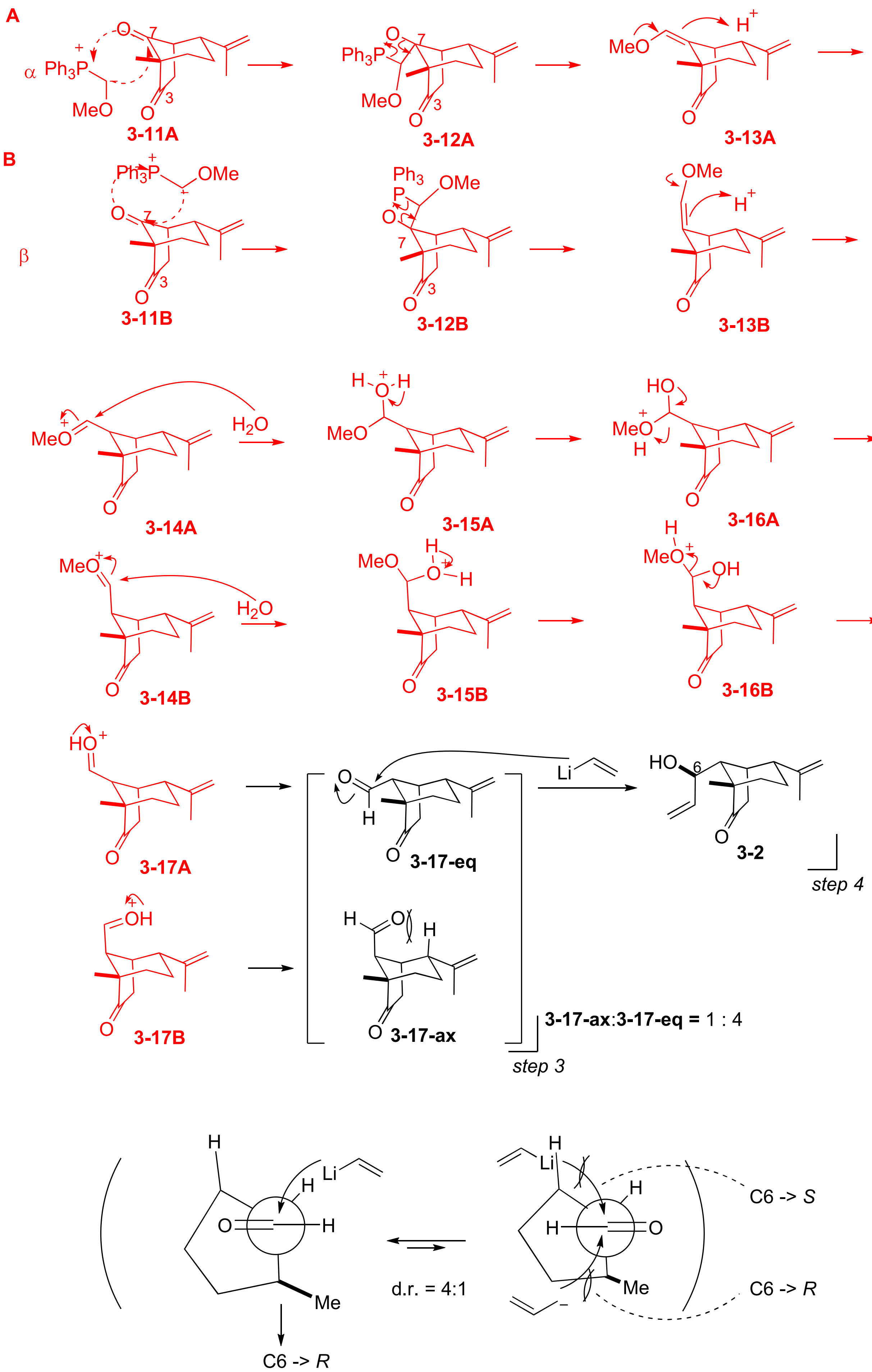
<Biosyhthesis of (+)-dendrowardol C>

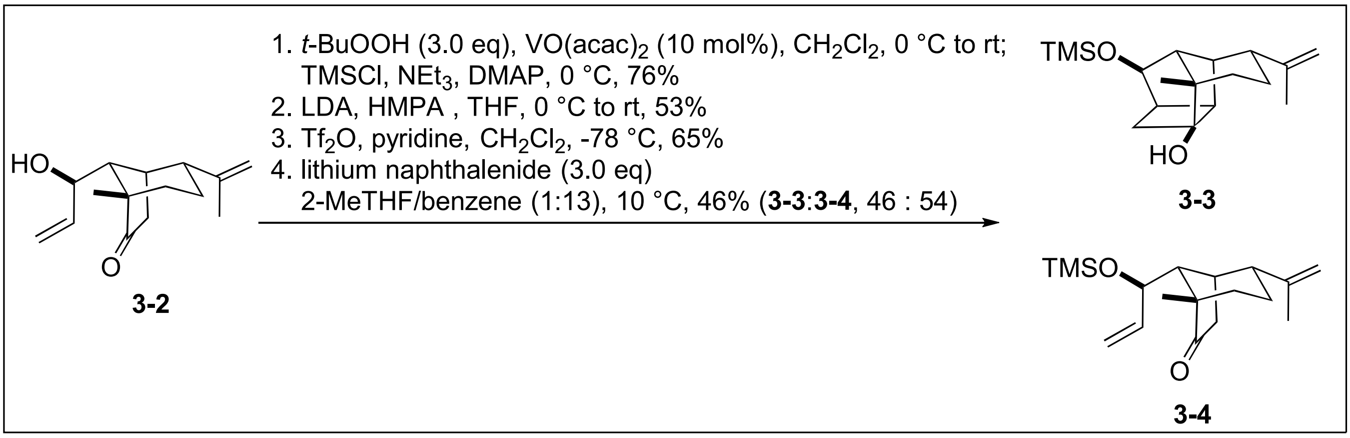
(Fan, W.-W.; Xu, F.-Q.; Dong, F.-W.; Li, X.-N.; Li, Y.; Liu, Y.-Q; Zhou, J.; Hu, J.-M. *Nat. Prod. Bioprospect.* **2013**, *3*, 89.)

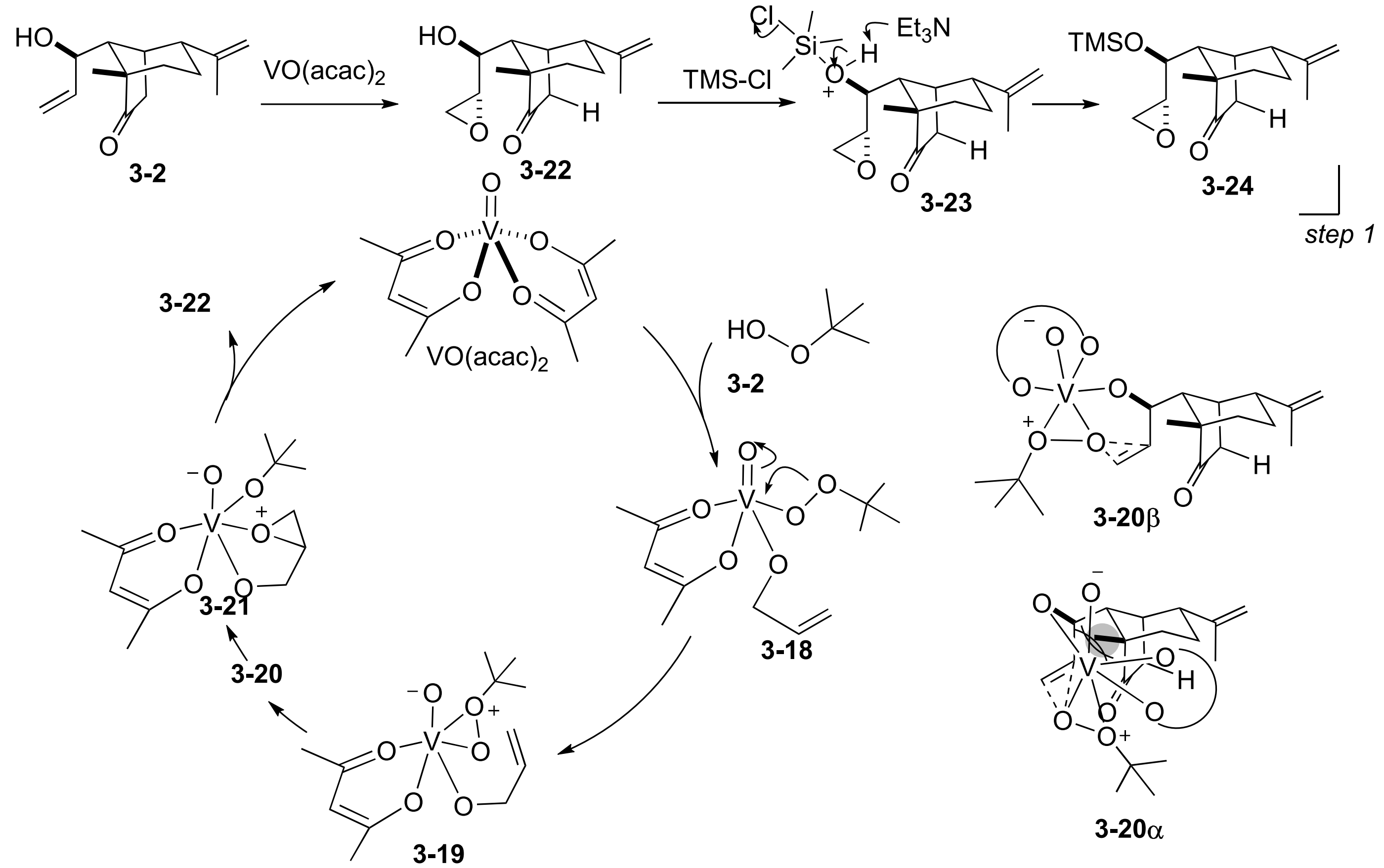


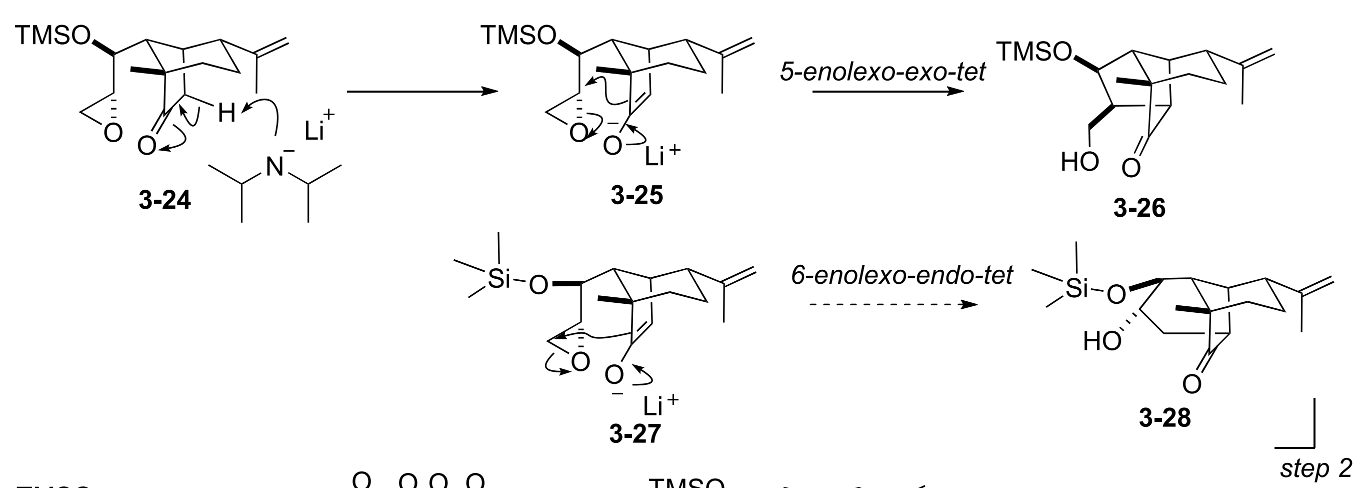

3.
1. NaOMe, MeOH, reflux, 59%
2. Dess-Martin Periodinane, t-BuOH, CH2Cl2, rt, 70%
3. MeOCH2PPh3Cl (1.5 eq), n-BuLi (1.4 eq), THF, 0 °C to rt; HCl aq., 0 °C to rt, 70%, d.r. = 4:1
4. vinyllithium (1.5 eq), Et2O, -78 °C, 56%
3-1
3-2

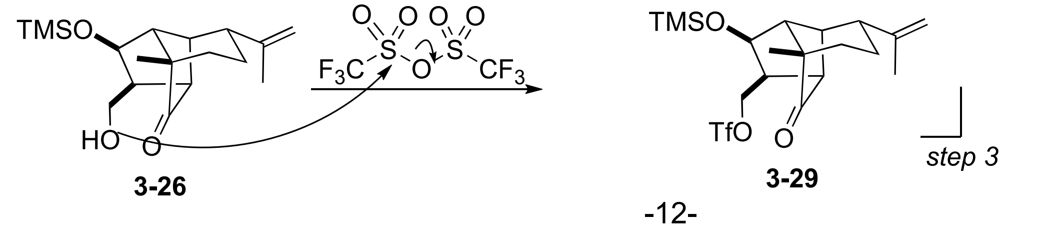

3-1
3-5A
3-6A
3-7A
3-5B
3-6B
3-7B
3-8
3-9
step 1
3-10
3-11
step 2
n-BuLi
convex
concave
more steric hindrance
A
B
C
D

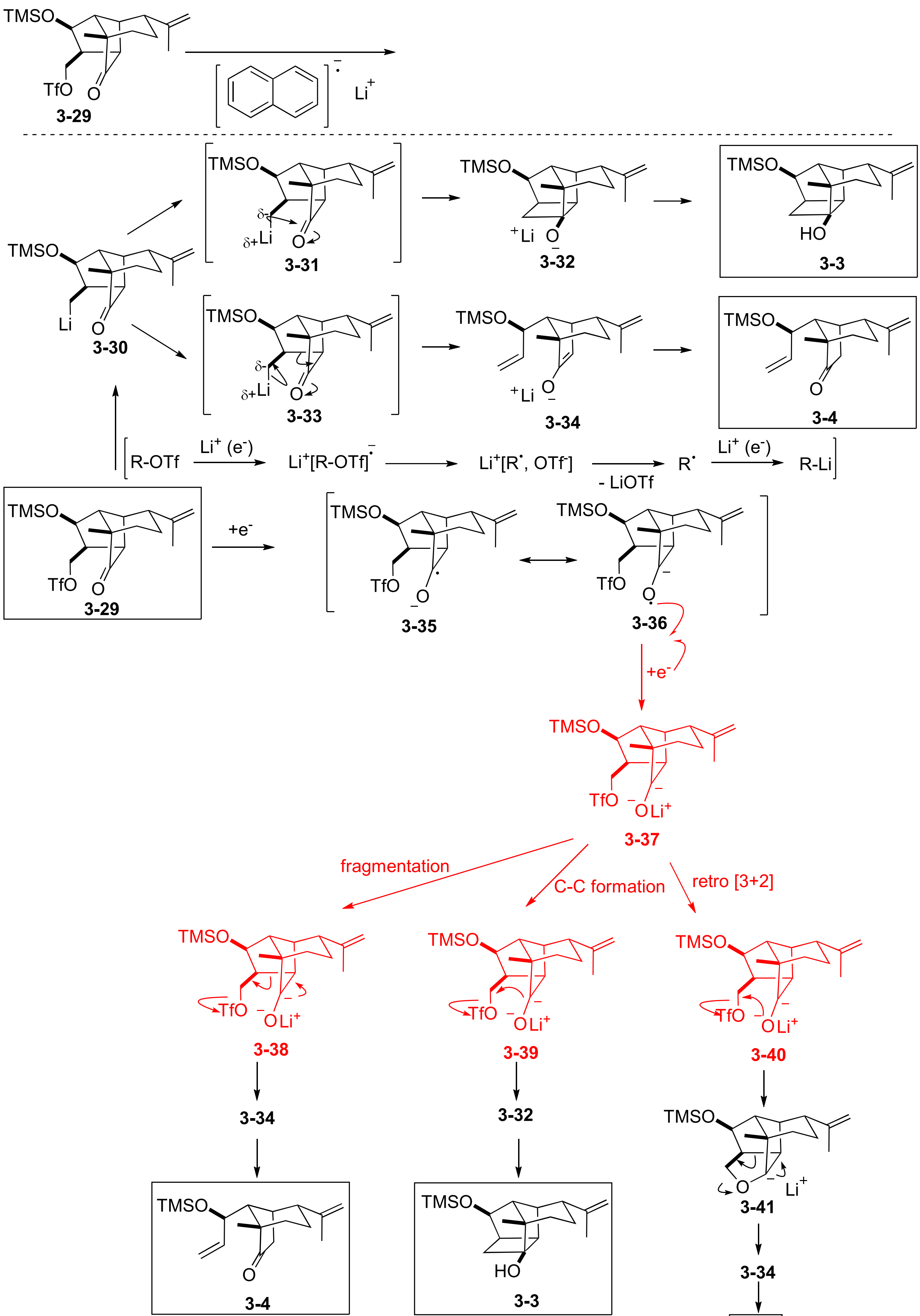

A
α
Ph_3P
MeO
3-11A
3-12A
3-13A
B
β
OMe
3-11B
3-12B
3-13B
H_2O
3-14A
3-15A
3-16A
3-14B
3-15B
3-16B
3-17A
3-17B
3-17-eq
3-17-ax
Li
HO
3-2
step 4
3-17-ax:3-17-eq = 1 : 4
step 3
Me
d.r. = 4:1
C6 -> R
C6 -> S
C6 -> R

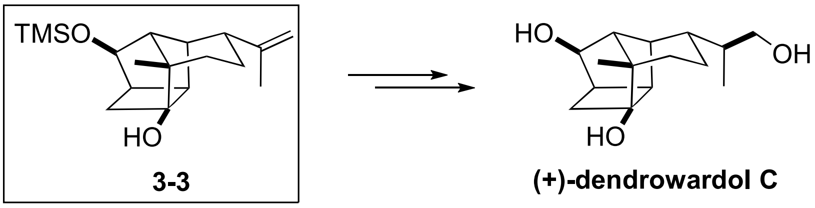

1. t-BuOOH (3.0 eq), VO(acac)2 (10 mol%), CH2Cl2, 0 °C to rt;
TMSCl, NEt3, DMAP, 0 °C, 76%
2. LDA, HMPA , THF, 0 °C to rt, 53%
3. Tf2O, pyridine, CH2Cl2, -78 °C, 65%
4. lithium naphthalenide (3.0 eq)
2-MeTHF/benzene (1:13), 10 °C, 46% (3-3:3-4, 46 : 54)
HO
O
3-2
TMSO
HO
3-3
TMSO
O
3-4


HO
VO(acac)2
3-2
3-22
TMS-Cl
Et3N
3-23
TMSO
3-24
step 1
VO(acac)2
3-22
3-2
3-18
3-21
3-20
3-19
3-20β
3-20α

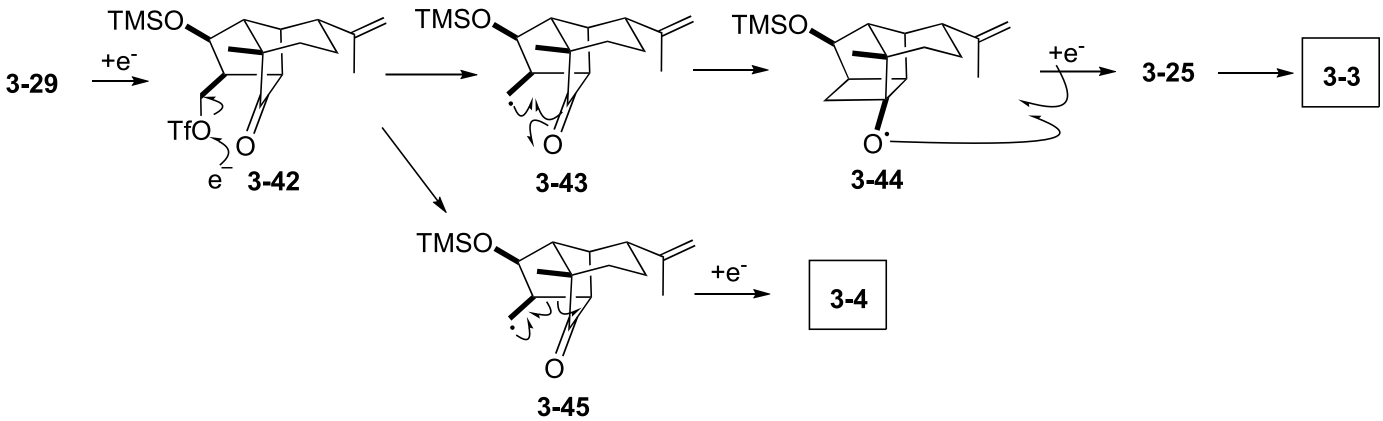

TMSO
Li+
3-24
3-25
5-enolexo-exo-tet
3-26
3-27
6-enolexo-endo-tet
3-28
step 2


TMSO
HO
3-26
F3C
CF3
TfO
3-29
step 3


TMSO
TfO
O
3-29
Li+
3-30
δ-
δ+Li
3-31
3-32
3-3
HO
3-33
3-34
3-4
R-OTf
Li+ (e-)
Li+[R-OTf]·−
Li+[R·, OTf−]
- LiOTf
R·
R-Li
+e-
3-35
3-36
3-37
OLi+
fragmentation
C-C formation
retro [3+2]
3-38
3-39
3-40
3-41

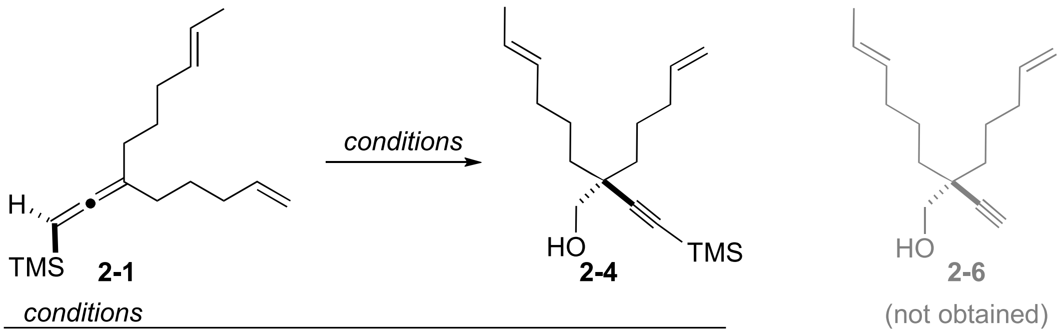


other mechanism



Appendix

ene reaction

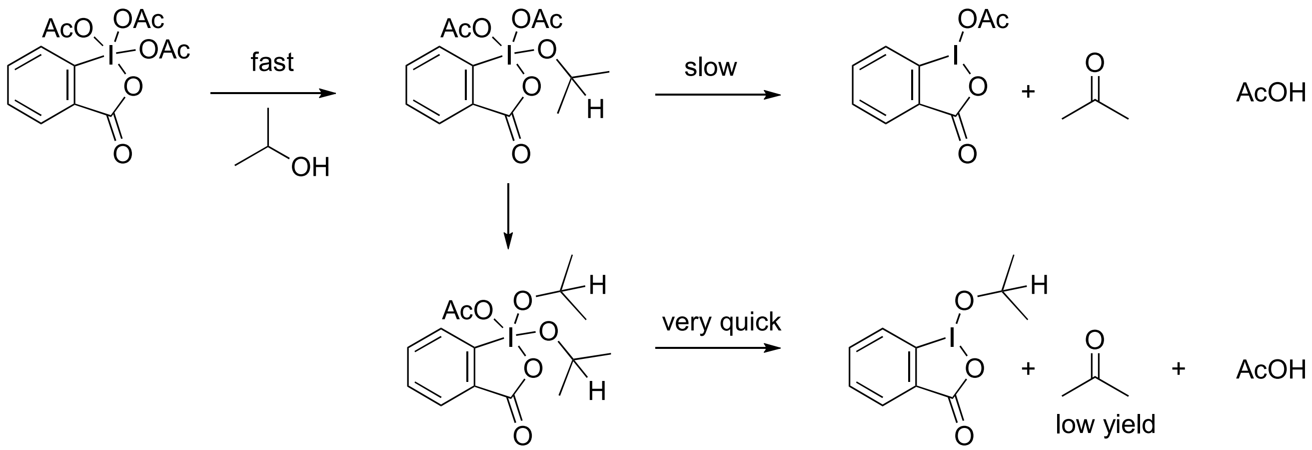


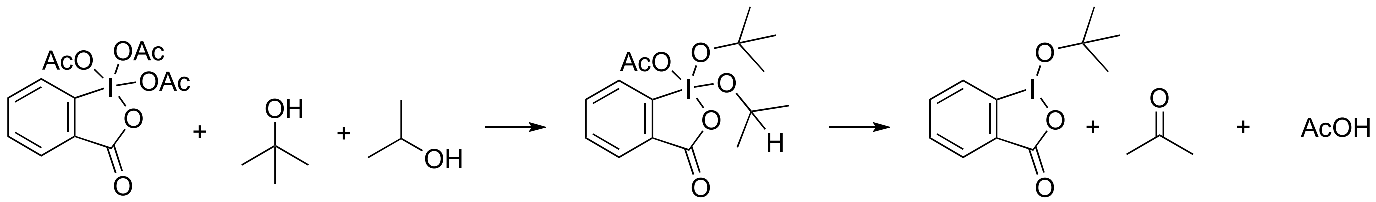
conditions

entry	electrophile	Lewis acid	result
1	trioxane	$BF_3{\cdot}OEt_2$	decomp.
2	$(HCHO)_n$	$BF_3{\cdot}OEt_2$	unknown product
3	trioxane	TMSOTf	decomp.
4	$(HCHO)_n$	TMSOTf	decomp.
5	trioxane	$TiCl_4$	irreproducible
6	$(HCHO)_n$	$TiCl_4$	22%
7	trioxane	$TiCl_2{\cdot}2THF$	52%

Adchi, Y. Doctor thesis The University of Tokyo **2013**

Dess-Martin Oxidation (addition of *t*-BuOH)





Tojo, G.; Fernandez, M. *Oxidation of Alcohols to Aldehydes and Ketones: A Guide to Current Common Practice* **2006**

Dess, D. B.; Martin, J. C. *J. Org, Chem.* **1983**, *48*, 4156.