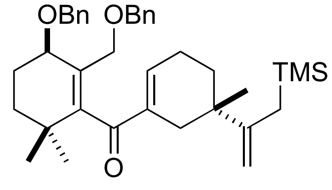
Problem Session (5)

2020/06/13 Shimizu Shinsuke

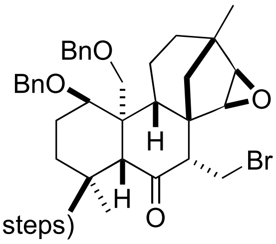
Please provide following reaction mechanisms and stereoselectivities

Problem 1



1-1

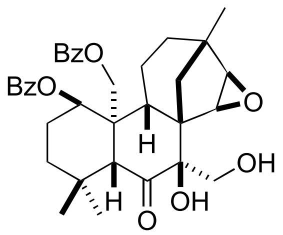
1. $EtAlCl_2$ (1.5 eq), CH_2Cl_2/THF (20/1), 40 °C
2. O_2, TPP (0.0056 eq), Fluorescent lamps, $CDCl_3$, rt
   ; Ac_2O (0.9 eq), pyridine (0.3 eq)
   DMAP (0.024 eq), rt, 43% (2 steps)
3. $RhCl(PPh_3)_3$ (1.0 eq), toluene, reflux, 67%
4. vinyl lithium, Et_2O, -78 °C to 0 °C
5. *m*-CPBA (2 eq), $NaHCO_3$ (10 eq), CH_2Cl_2, 0 °C, 70% (2 steps)
6. NBS (1.2 eq), silica gel (200 wt%), CH_2Cl_2, rt, 89%



1-2

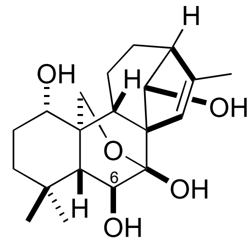
Vinyl lithium was prepared by mixing vinyl bromide (4 eq) and *t*-butyl lithium (7.5 eq).

Problem 2



2-1

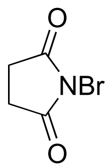
1. $EtAlCl_2$ (3 eq), toluene, 0 °C to rt, 57%
2. $LiAlH_4$ (5 eq), Et_2O, 0 °C to rt
3. $NaIO_4$ (1.38 eq), THF/pH 7 buffer (2/1)
   10 °C to rt, 69% (2 steps)
4. $(MeO)_2CMe_2$ (20 eq), PTSA (0.1 eq)
   acetone, rt; $NaHCO_3$ (20 eq); evaporation
   ; DMP (3.5 eq), CH_2Cl_2, 0 °C; DMP (2 eq), rt, 66%
5. *i*Bu_2AlH (2 eq), CH_2Cl_2/Et_2O (3/1), -100 °C to rt
   ; Red-Al (3 eq), THF, rt; aq.HCl, MeOH, rt, 56%
   (diastereomer at C6: 21%)



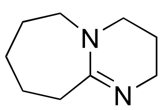
2-2

pH 7 buffer: 0.2 M aqueous solution of a 1:1 mixture of Na_2HPO_4:NaH_2PO_4

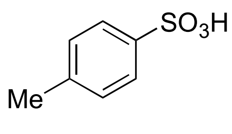
In these reactions, enantio excess (ee) were not mentioned.



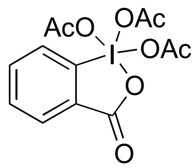
NBS



DBU



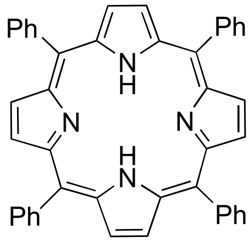
PTSA



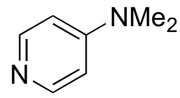
DMP

$NaAl(OC_2H_4OMe)_2H_2$

Red-Al



TPP



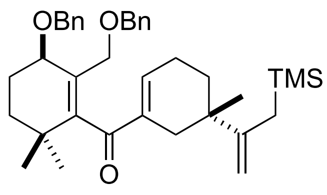
DMAP

Problem Session (5) Answer

2020/06/13 Shimizu Shinsuke

topic: Total synthesis of oridonin by Luo group
(Kong, L.; Su, F.; Yu, H.; Jiang, Z.; Lu, Y.; Luo, T. *J. Am. Chem. Soc.* **2019**, *141*, 20048.)

Problem 1



1-1

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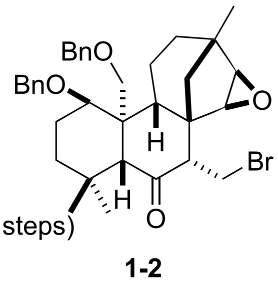
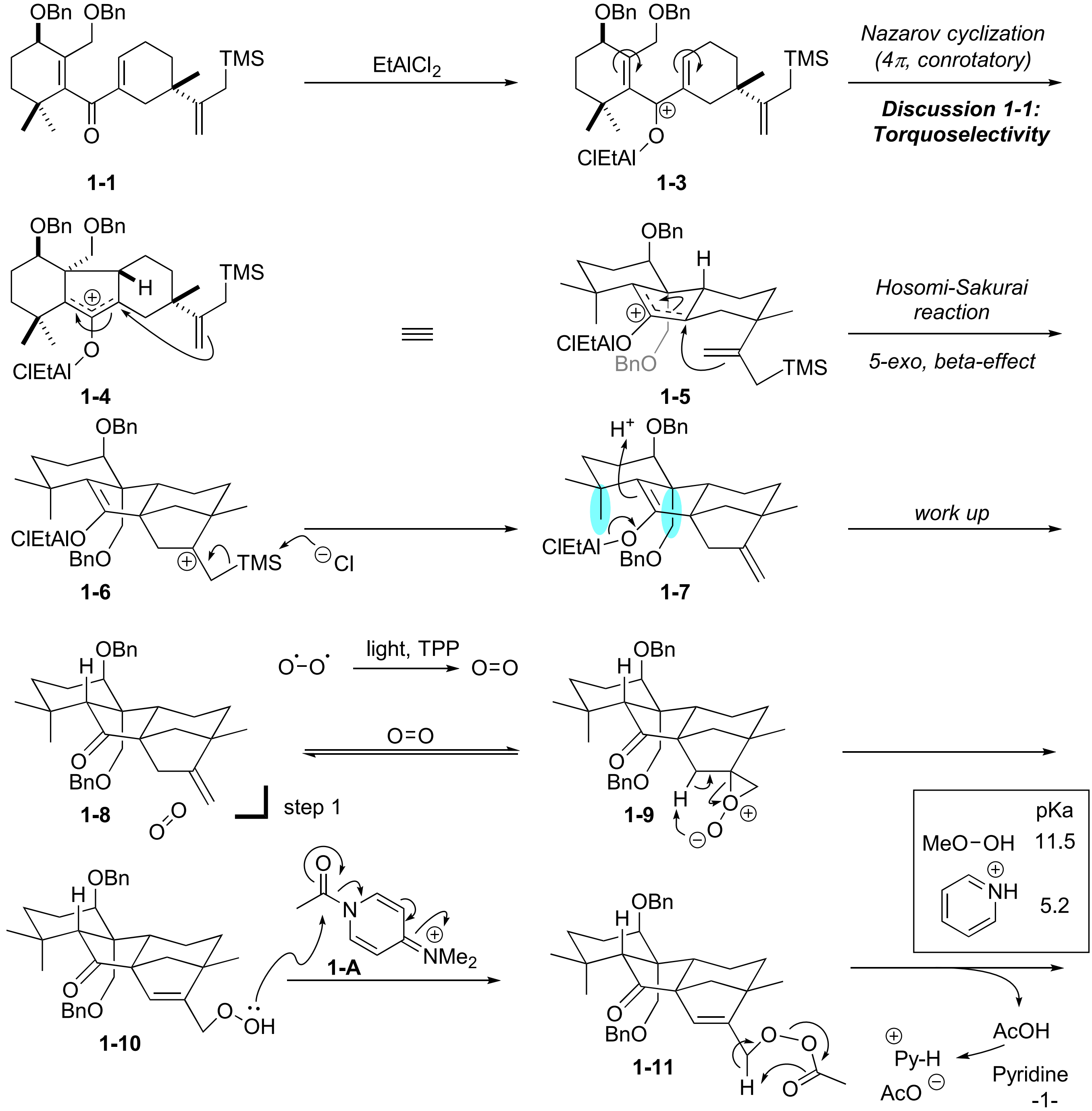
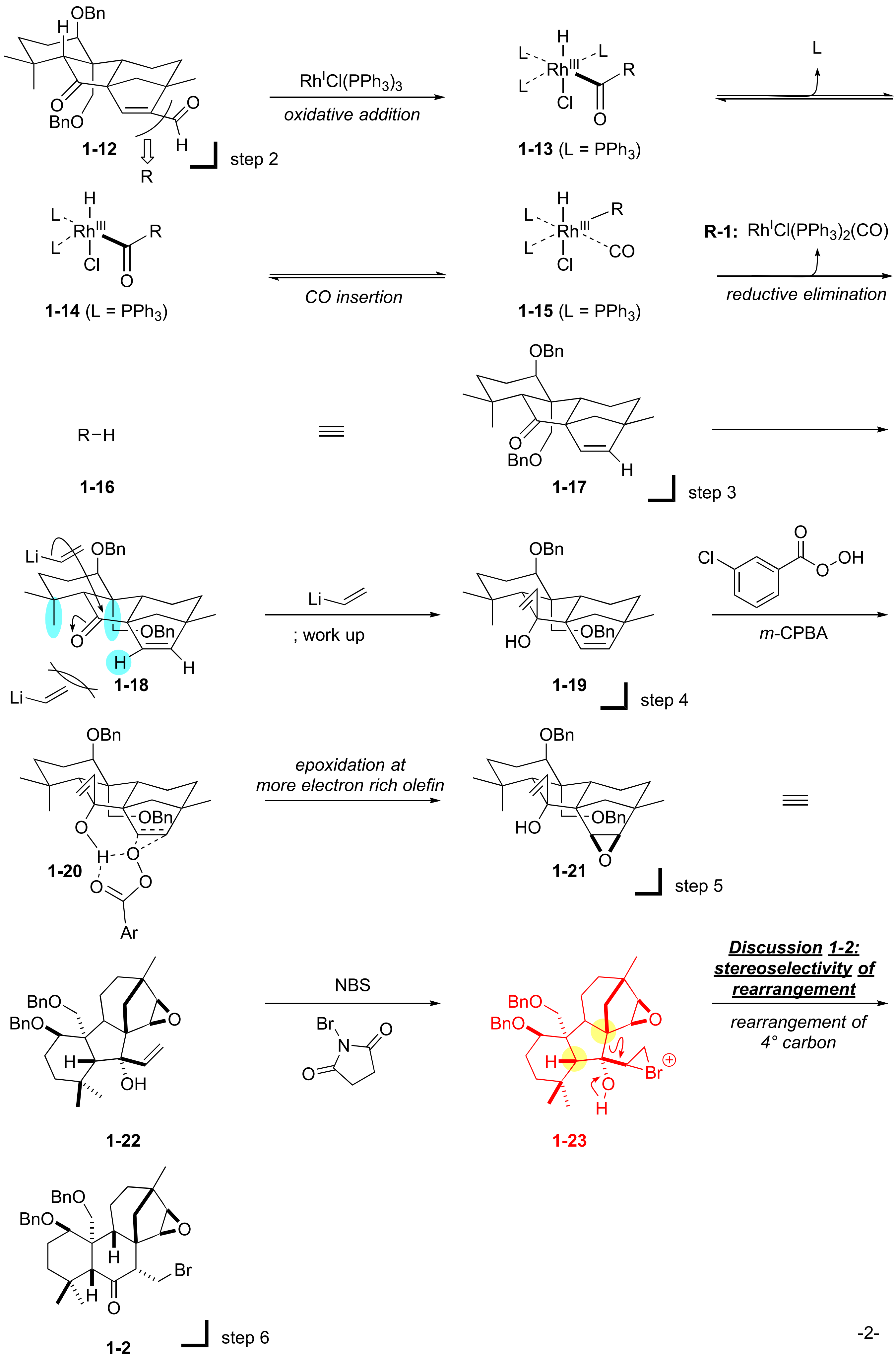


1-2

Vinyl lithium was prepared by mixing
vinyl bromide (4 eq) and *t*-butyl lithium (7.5 eq).

Answer 1

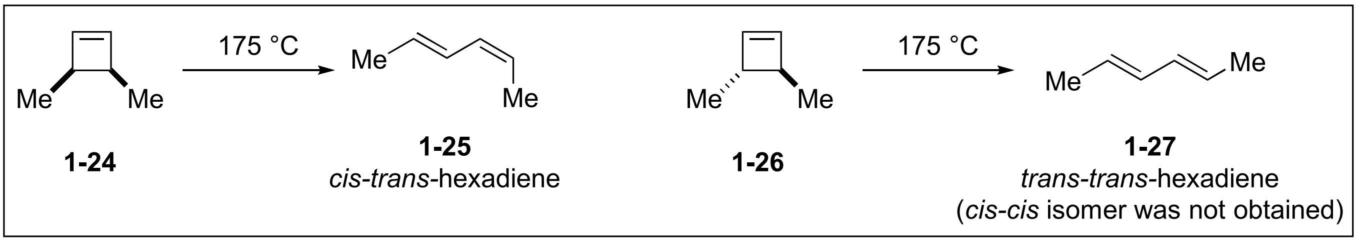


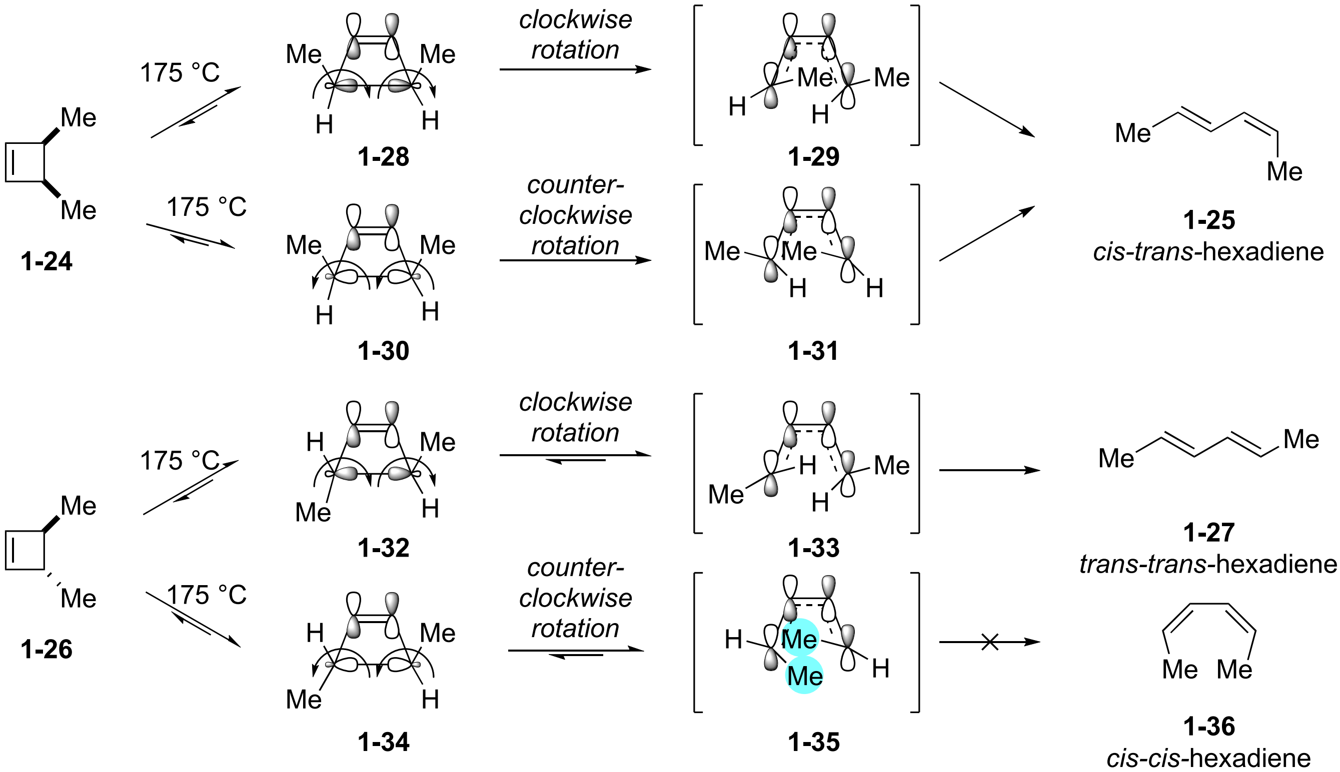

1-12
step 2
Rh^ICl(PPh3)3
oxidative addition
1-13 (L = PPh3)
1-14 (L = PPh3)
CO insertion
1-15 (L = PPh3)
R-1: Rh^ICl(PPh3)2(CO)
reductive elimination
R−H
1-16
1-17
step 3
1-18
; work up
1-19
step 4
m-CPBA
1-20
epoxidation at
more electron rich olefin
1-21
step 5
1-22
NBS
1-23
Discussion 1-2:
stereoselectivity of
rearrangement
rearrangement of
4° carbon
1-2
step 6

Discussion 1-1: Torquoselectivity of Nazarov cyclization *(clockwise or counterclockwise?)*

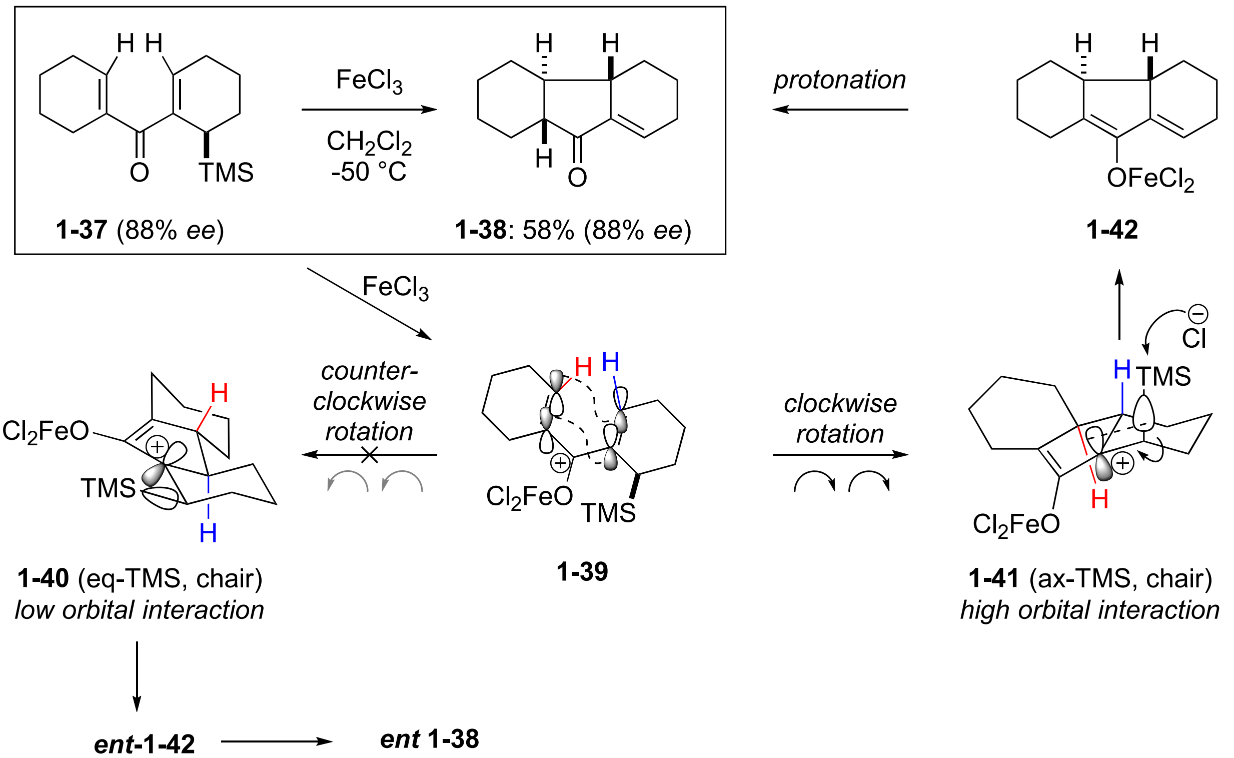
Torquoselectivity: steric repulsion and stereoelectronic effect are the driving force for the selectivity.

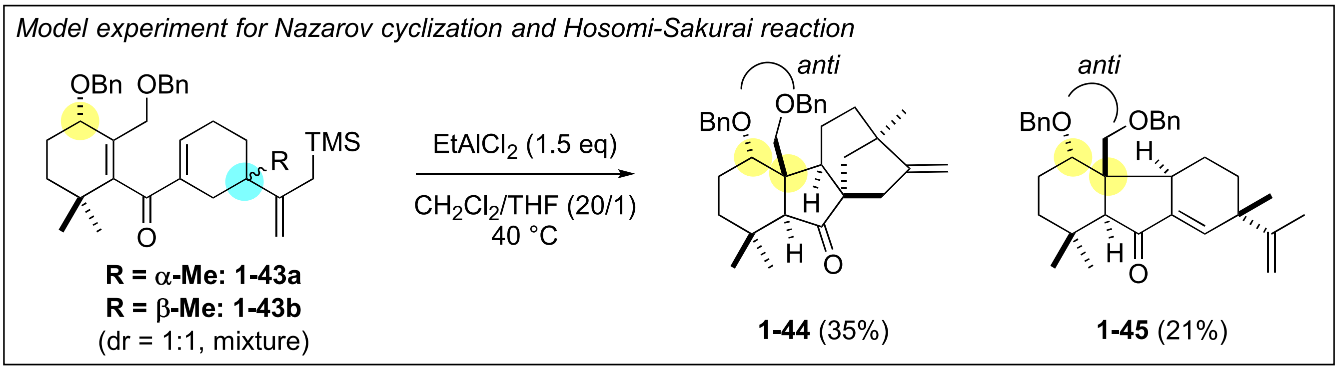
example of steric repulsion: Winter, R. E. K. *Tetrahedron Lett.* **1965**, *17*, 1207.



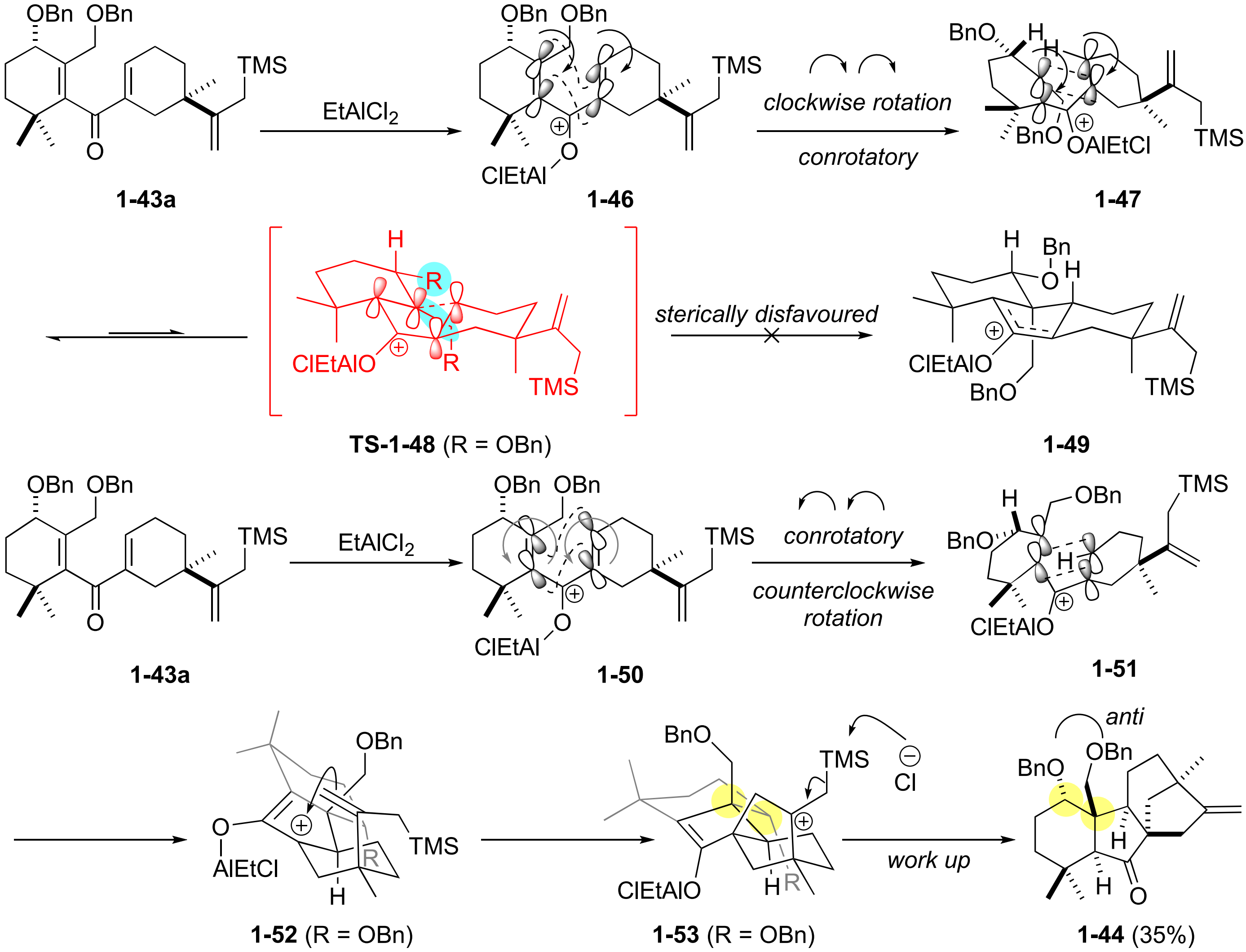


example of stereoelectronic effect: Denmark, S. E.; Wallace, M. A.; Walker, C. B. *J. Org. Chem.* **1990**, *55*, 5543.

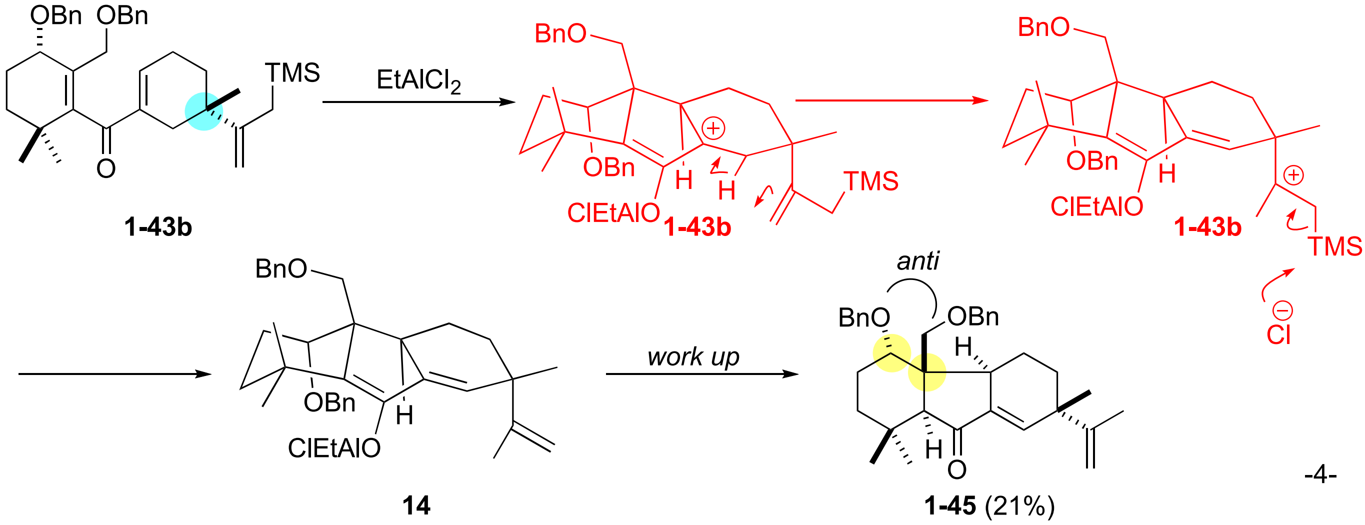


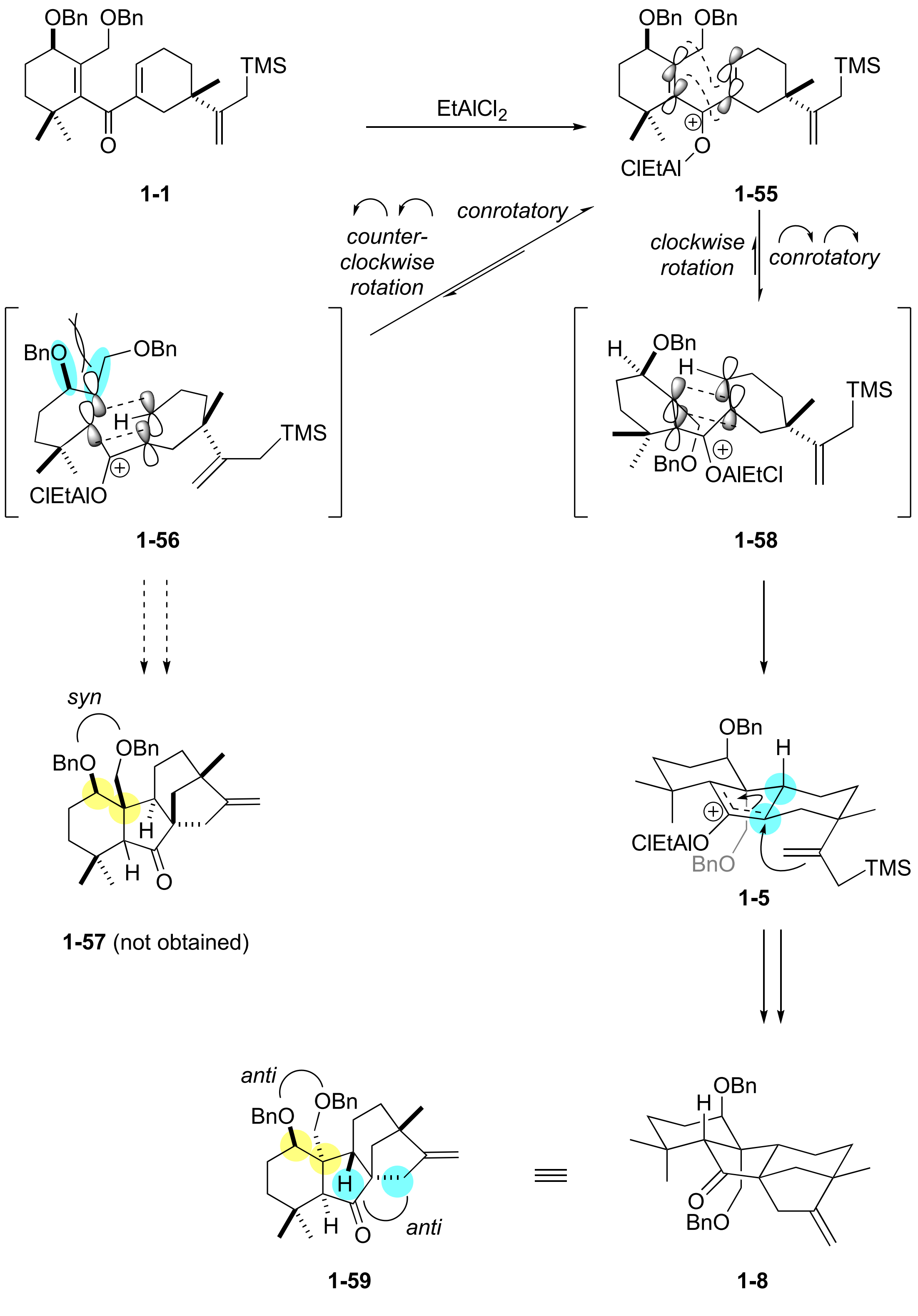


Torquoselectivity

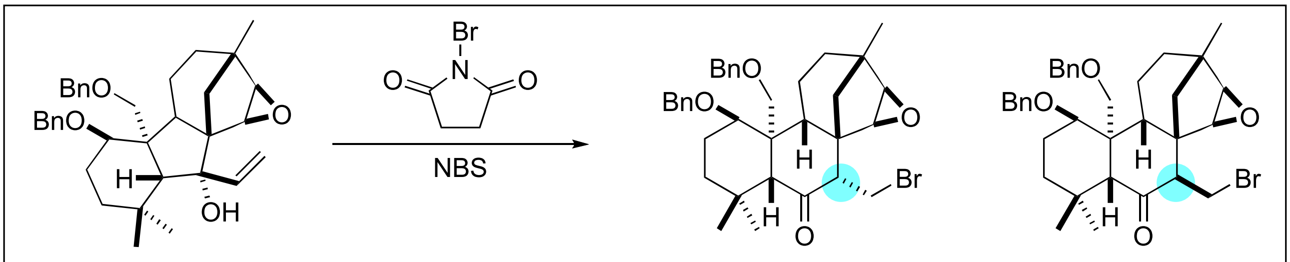


Hosomi-Sakurai reaction



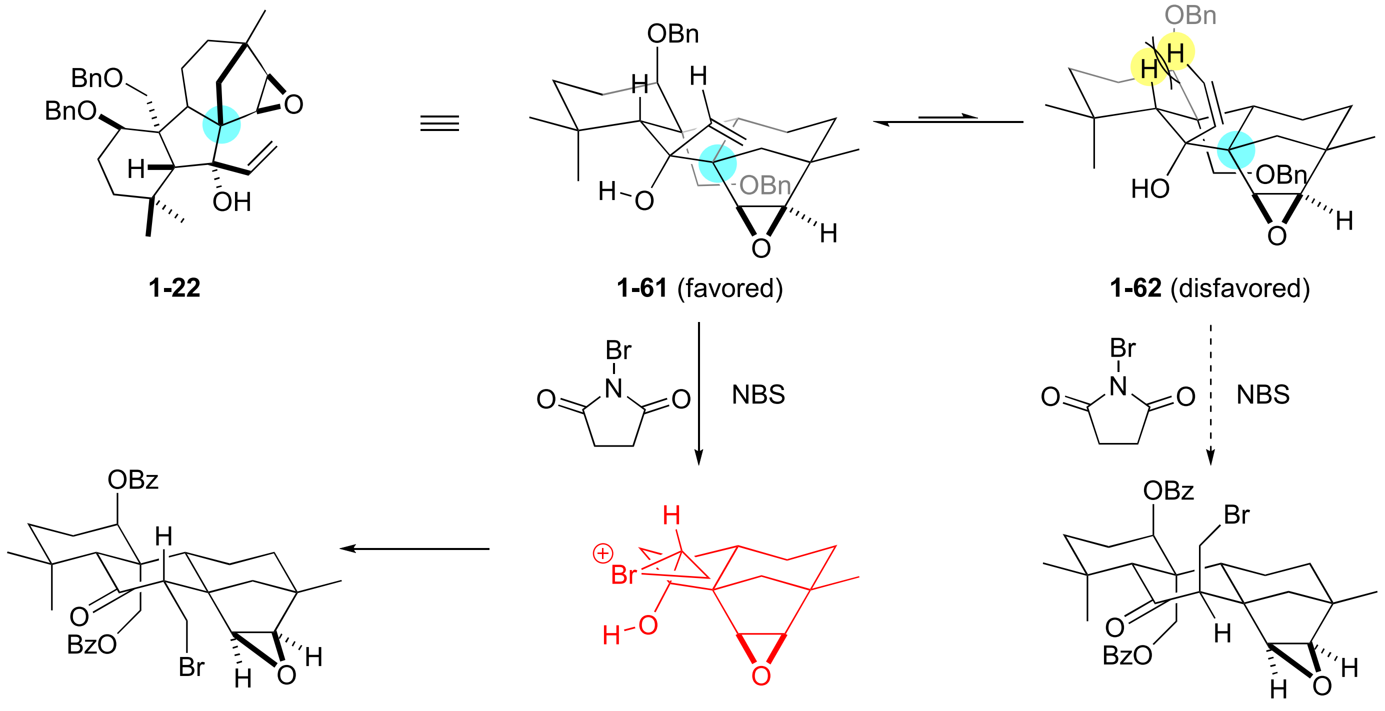

OBn OBn
TMS
O
1-1
EtAlCl2
1-55
ClEtAl
conrotatory
counter-
clockwise
rotation
clockwise
rotation
BnO
OBn
H
ClEtAlO
1-56
1-58
OAlEtCl
syn
1-57 (not obtained)
1-5
anti
1-59
1-8

Discussion 1-2: stereoselectivity of rearrangement



1-22 **1-2** (89%) **1-60** (not obtained)

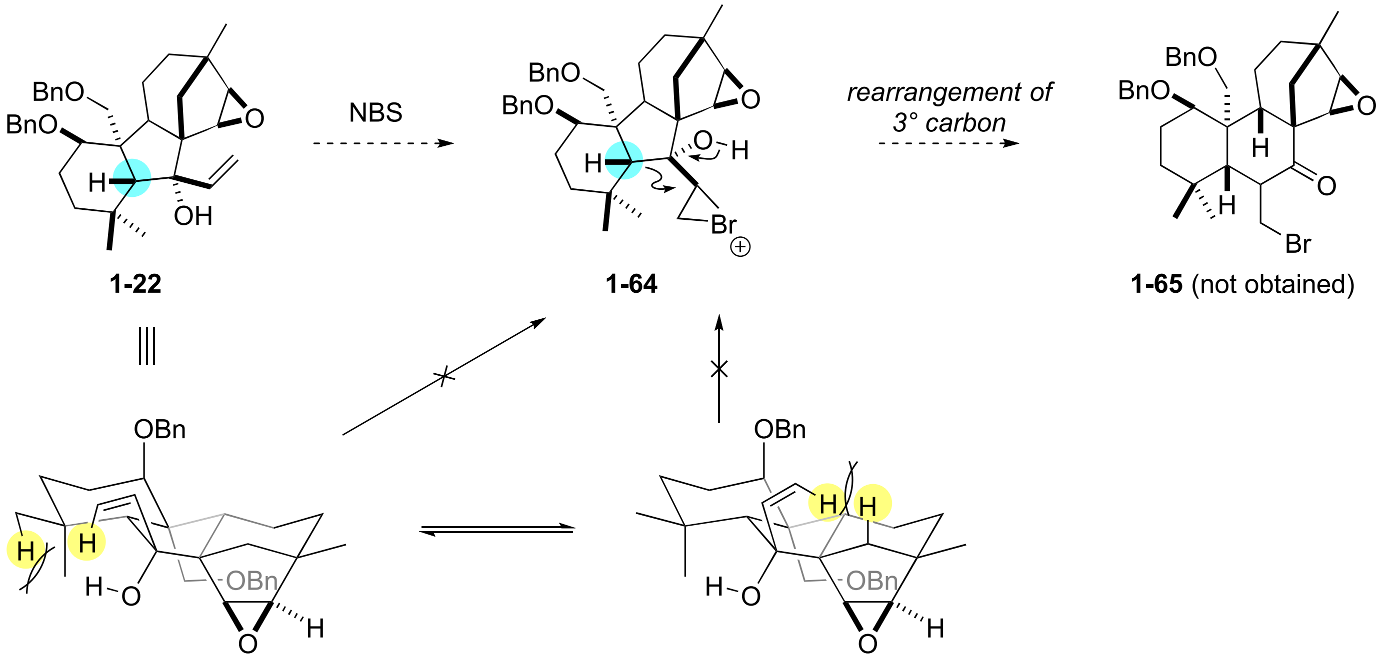
Stereoselectivity



1-22 **1-61** (favored) **1-62** (disfavored)

1-2 (89%) **1-63** (some substituents were omitted) **1-60** (not obtained)

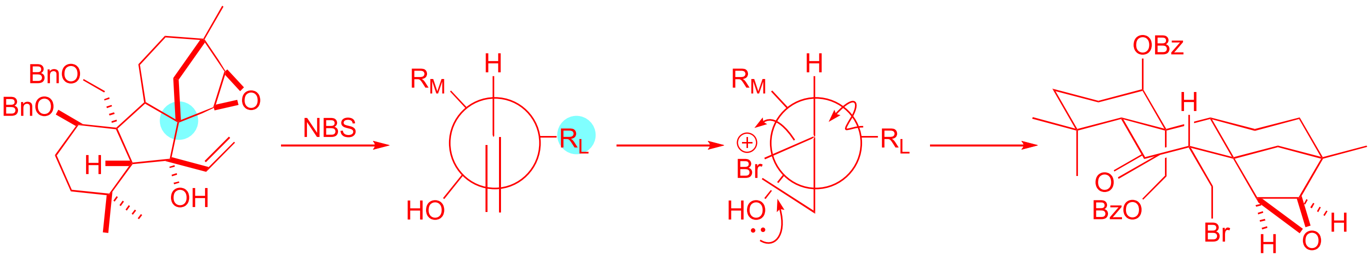
Regioselectivity



1-22 **1-64** **1-65** (not obtained)

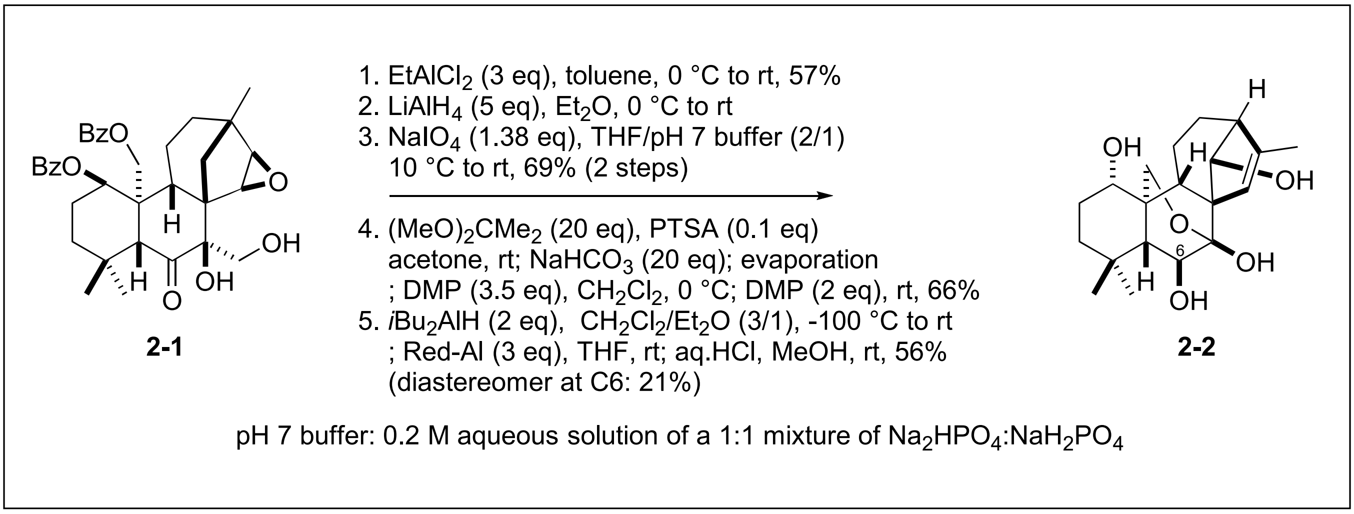
1-66 (disfavored) **1-66** (disfavored)

Other explanation

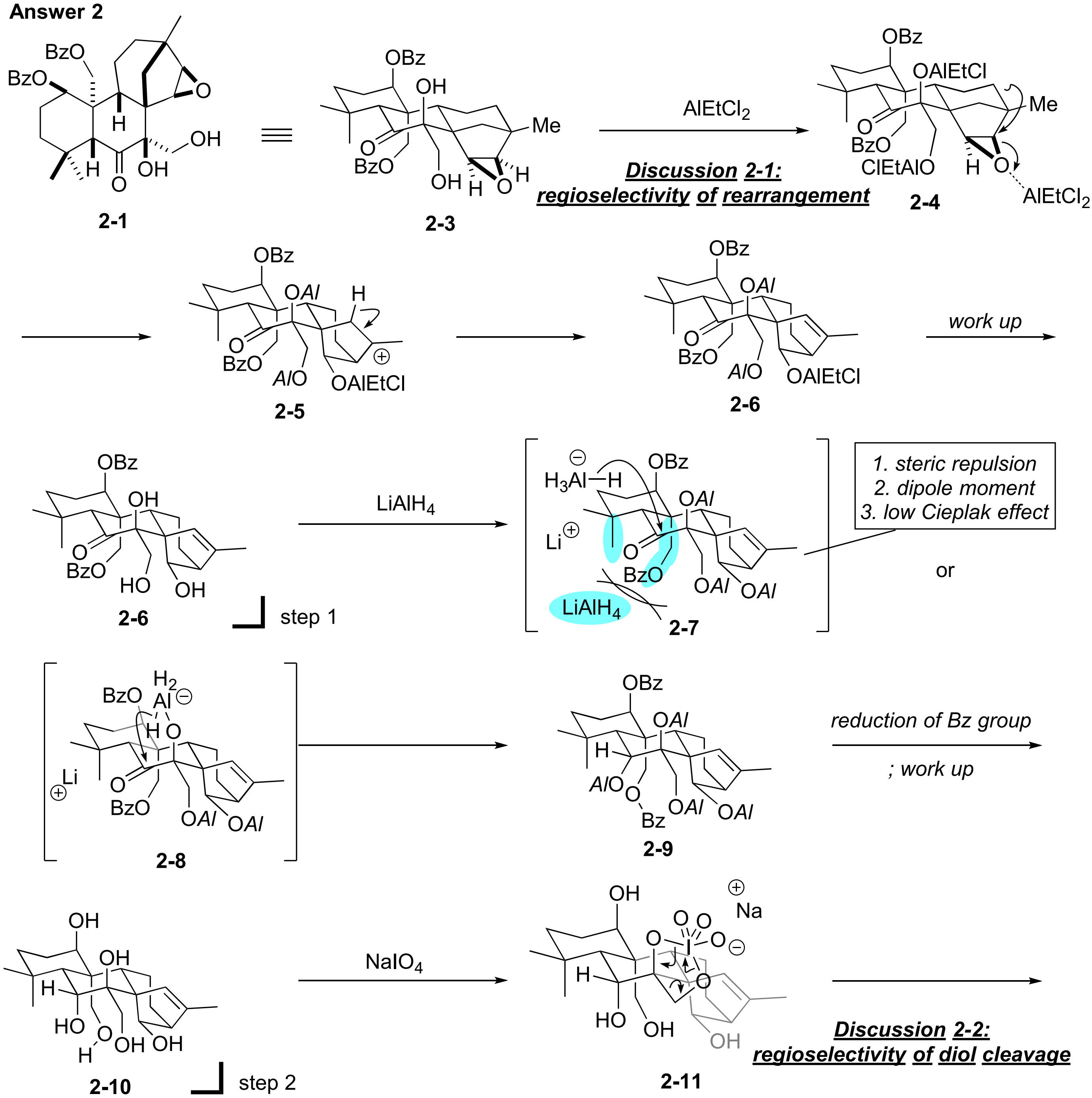


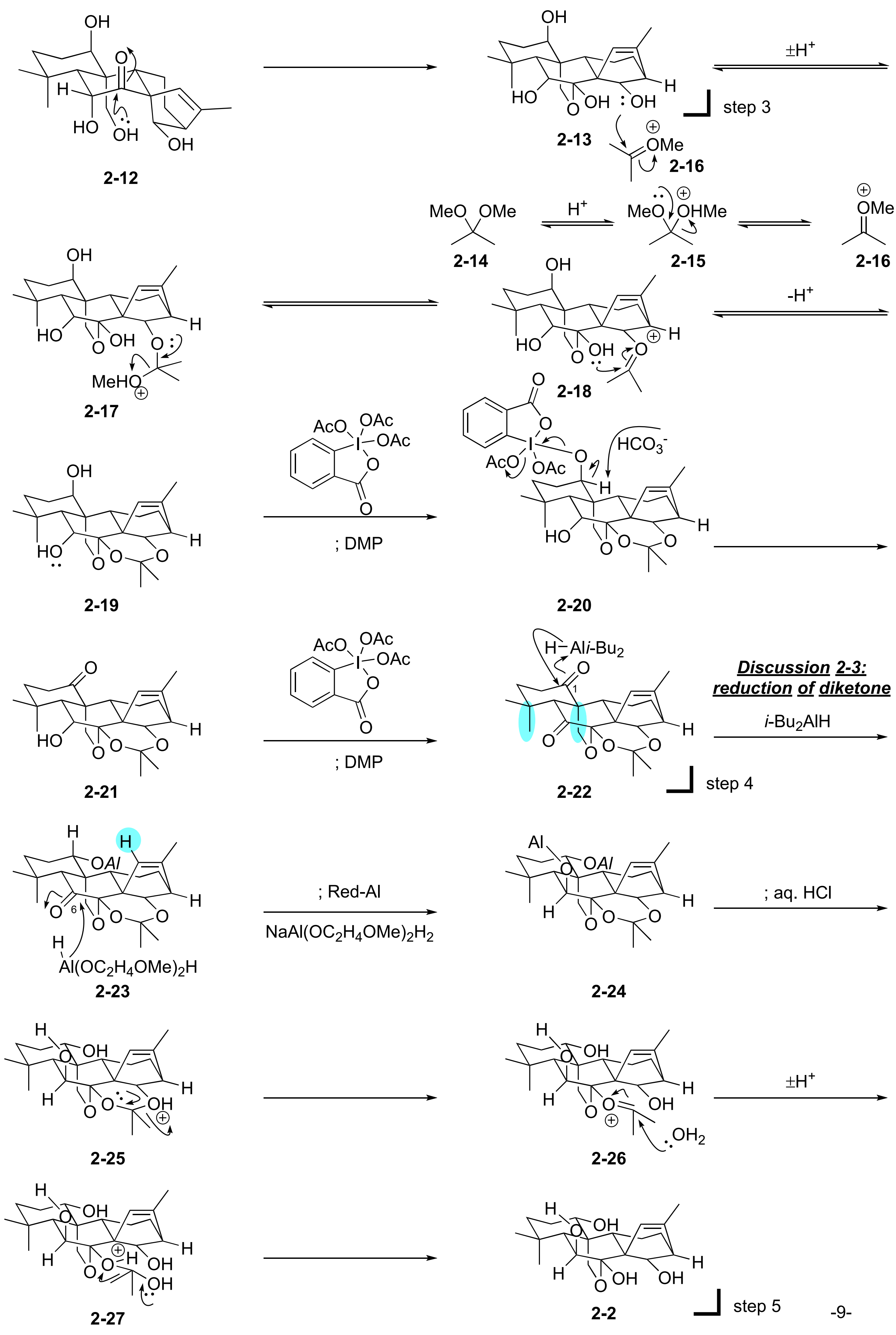
1-22 **1-71** **1-72** **1-2** (89%)

Problem 2



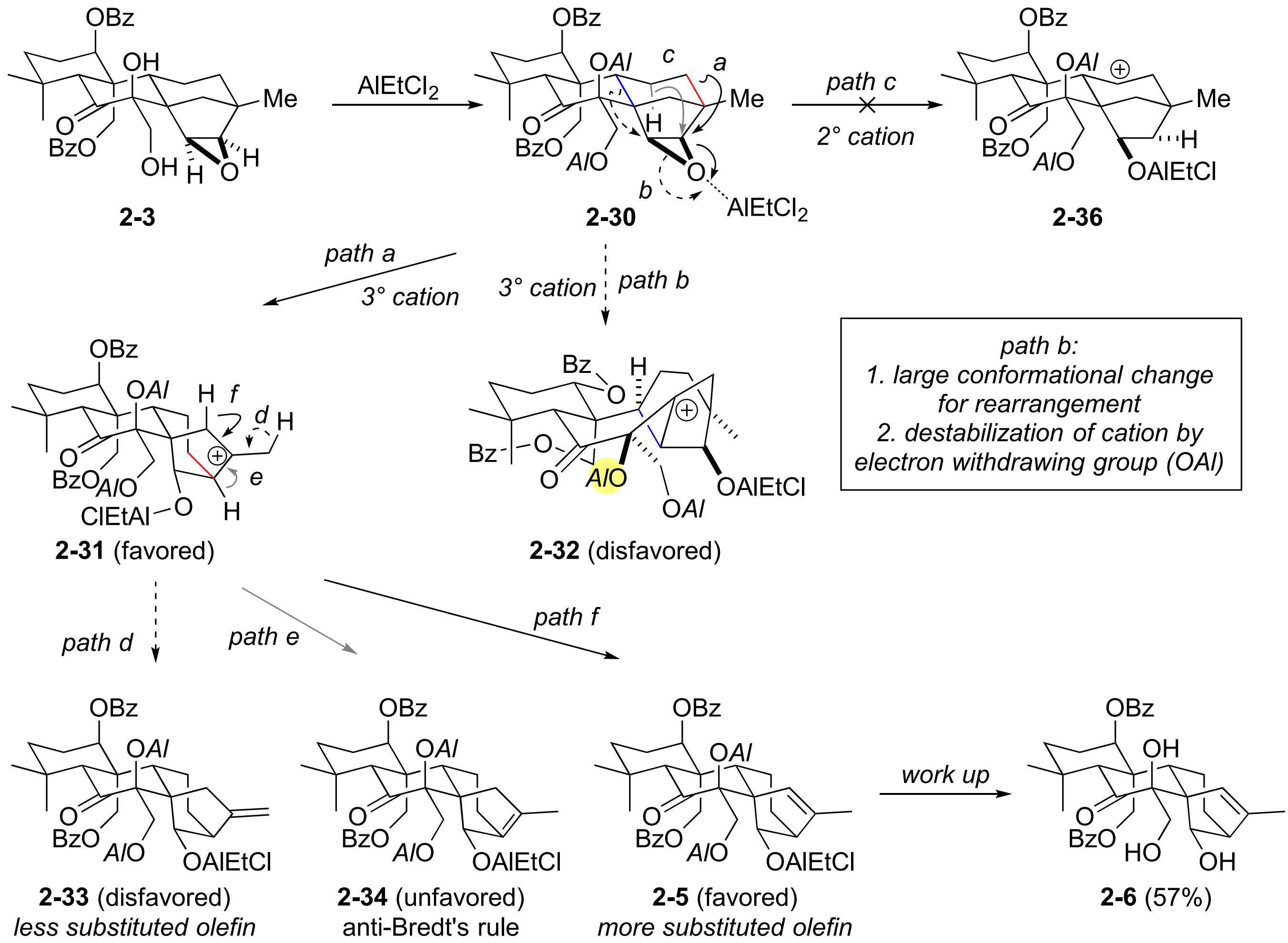
Answer 2



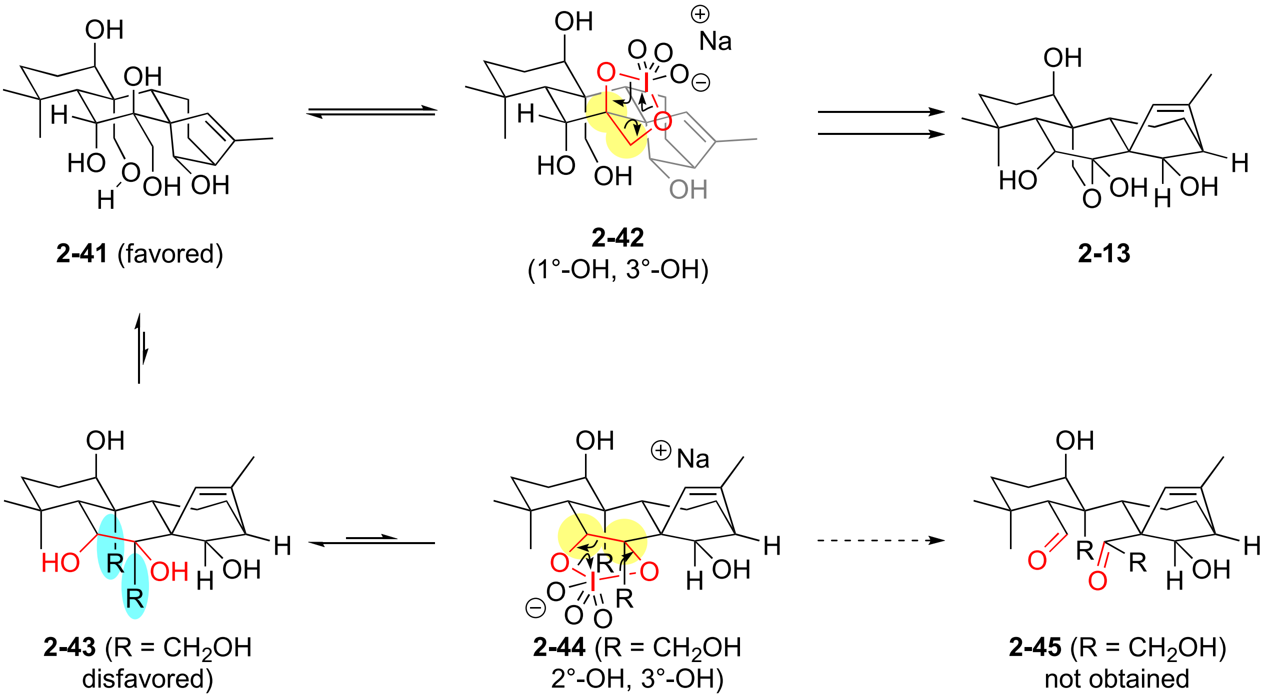


2-12
2-13
±H+
step 3
2-16
MeO OMe
H+
MeO OHMe
OMe
2-14
2-15
2-16
2-17
2-18
-H+
2-19
; DMP
AcO OAc OAc
HCO3-
2-20
2-21
2-22
Discussion 2-3: reduction of diketone
i-Bu2AlH
H–Ali-Bu2
step 4
2-23
; Red-Al
NaAl(OC2H4OMe)2H2
Al(OC2H4OMe)2H
2-24
; aq. HCl
2-25
2-26
OH2
2-27
2-2
step 5

Discussion 2-1: regioselectivity of rearrangement



Discussion 2-2: regioselectivity of diol cleavage



Discussion 2-3: reduction of diketone

The order of reduction:
-> Reduction at C1-ketone proceeded first.

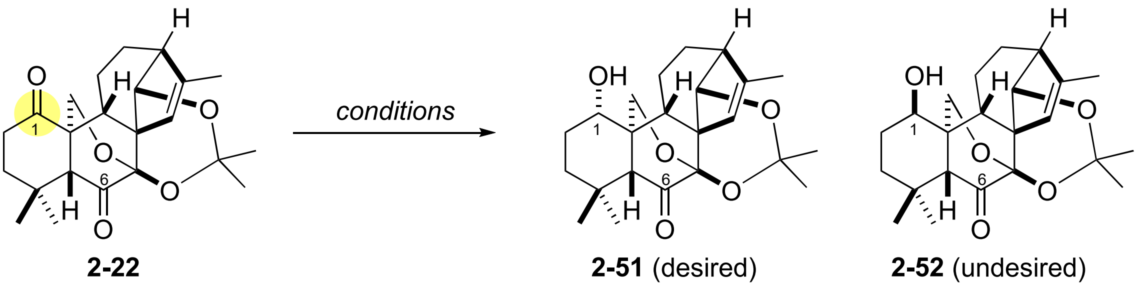
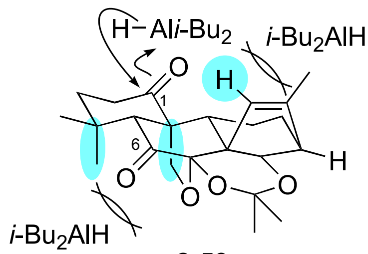


Table 2-1

entry	*conditions*	results
1	$LiAlH_4$ (3 eq), THF, -78 °C	**2-51**:**2-52**=2.5:1
2	*i*-Bu_2AlH (3 eq), CH_2Cl_2/THF (3/1), -100 °C	**2-51**:**2-52**=8:1



2-53