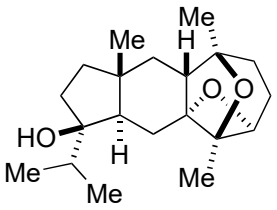
2017. 07. 22 D2 Kosuke Minagawa

Problem session (4) - Answer

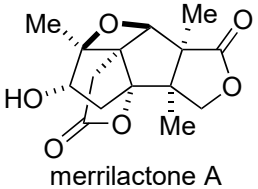
Topic: total synthesis of (+)-dictyoxetane, 7-membered ring

Natural products containing oxetanes

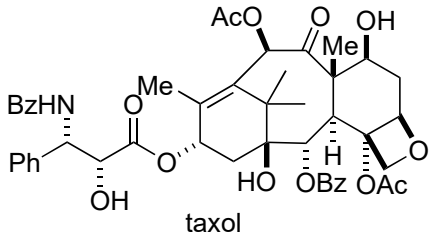
oxetane



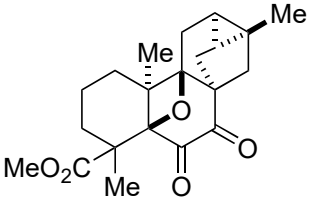
(+)-dictyoxetane
(activity unknown)



merrilactone A
(neurotrophic agent)



taxol
(anticancer)

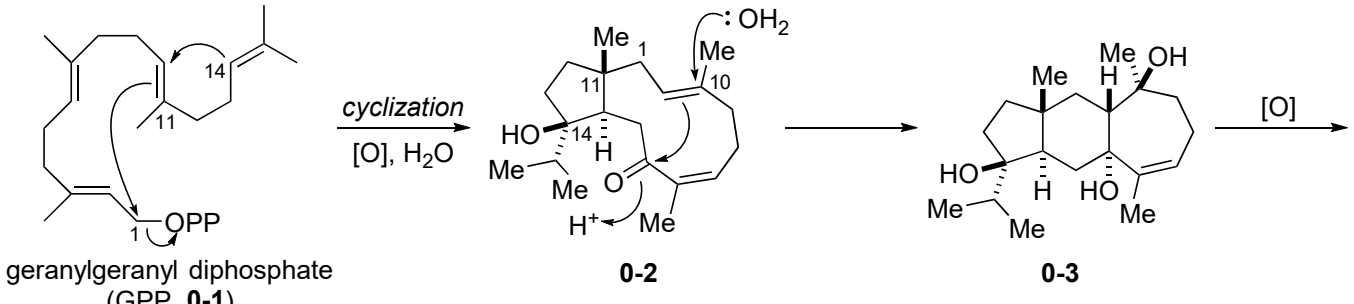


mitrephorone A
(anticancer)

·Isolation of (+)-dictyoxetane:
from the brown alga *Dictyota dichotoma* (Krusadai Island, India).
(Clardy, J. *et al J. Org. Chem.* **1985**, *50*, 3665.)

·Bioactivity of the dioxatricyclic subunit:
antitumor activity against HMO2 (human gastric carcinoma) and HEP G2 (human heptocellular carcinoma) cell lines.
(Hoffmann, H. M. R. *et al Tetrahedron Lett*. **1998**, *39*, 8259.)

·Proposed biosynthesis of (+)-dictyoxetane:
(Hoffmann, H. M. R. *et al Chem. Eur. J.* **1995**, *1*, 368.)

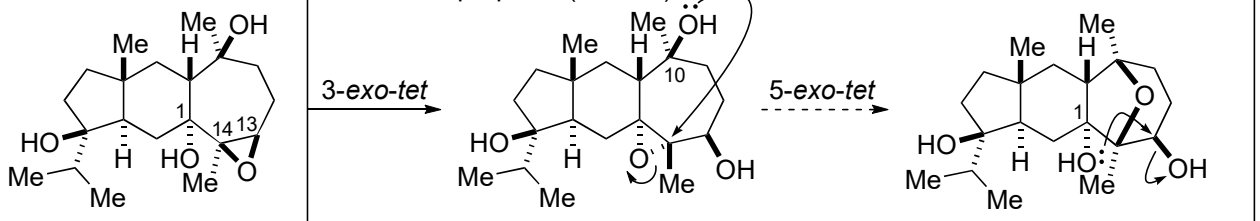


geranylgeranyl diphosphate
(GPP, **0-1**)

0-2

0-3

Hoffmann's proposal (in 1995)



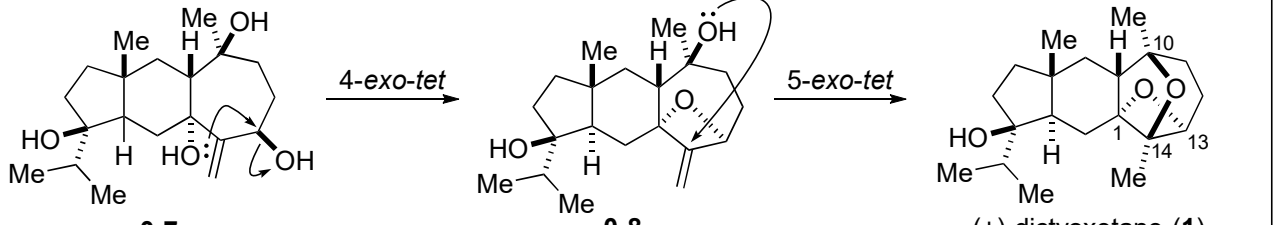
0-4

0-5

0-6

4-exo-tet

Magauer's proposal (in 2016)



0-7

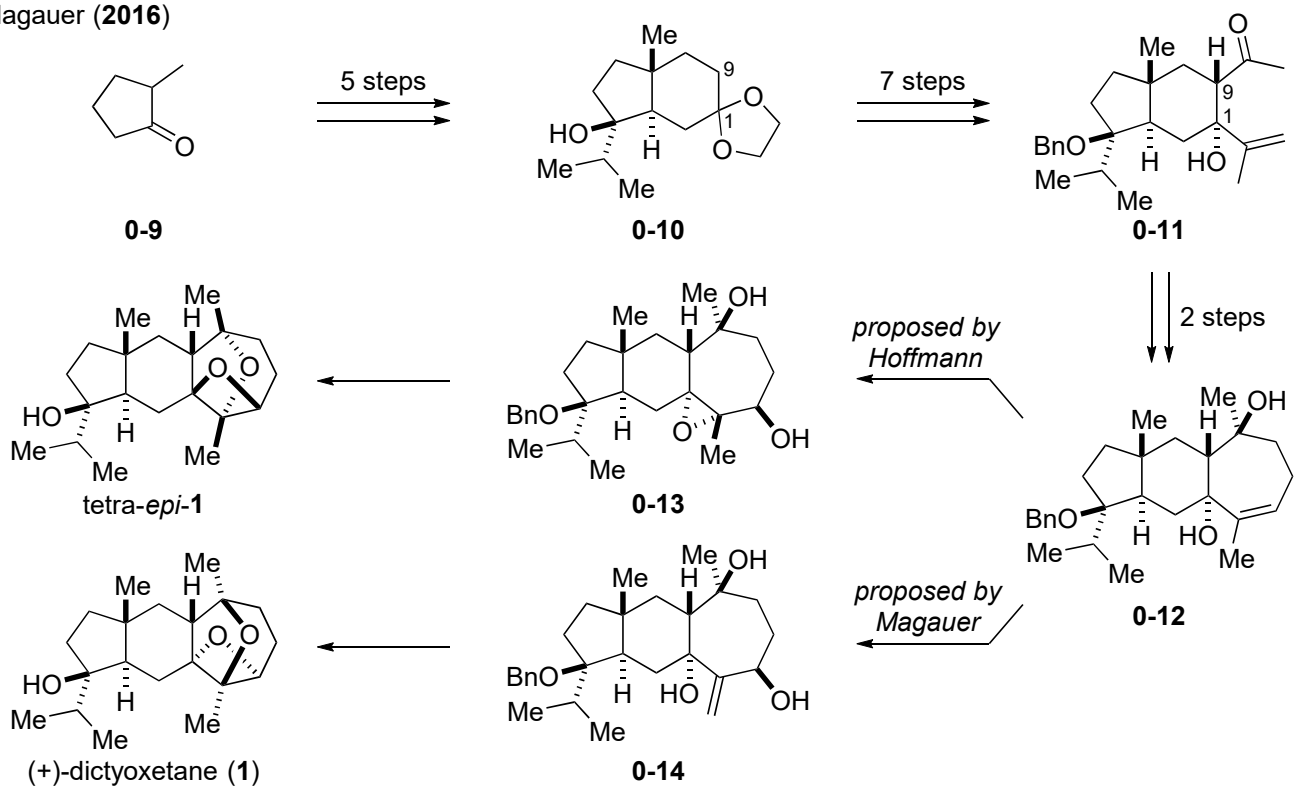
0-8

(+)-dictyoxetane (**1**)

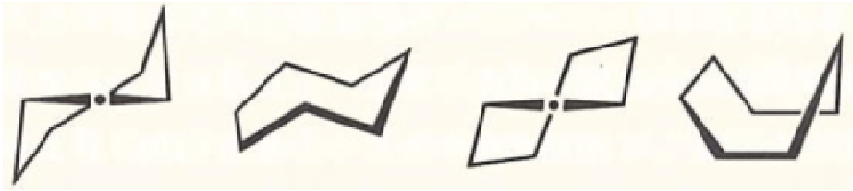
·Synthetic study of (+)-dictyoxetane
- Hoffmann, H. M. R. *et al. Chem. Eur. J.* **1995**, *1*, 368.
- Heathcock, C. H. *et al. J. Org. Chem.* **1996**, *61*, 9135.
- Hoffmann, H. M. R. *et al. Tetrahedron Lett.* **1998**, *39*, 8259.
- Hoffmann, H. M. R. *et al. Tetrahedron* **2002**, *58*, 6199.
- Grainger, R. S. *et al. Org. Biomol. Chem.* **2012**, *10*, 4926.
- Magauer, T. *et al. Chem. Eur. J.* **2016**, *22*, 15125.

·Total synthesis of (+)-dictyoxetane
- Magauer, T. et al. *J. Am. Chem. Soc.* **2016**, *138*, 6420.

Magauer (**2016**)



7-membered ring (relative stabilities in kcal/mol referred to the most stable conformer)

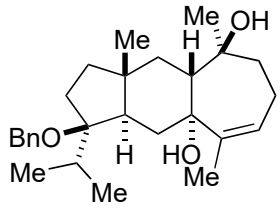


Twist Chair (TC)	**Chair (C)**	**Twist Boat (TB)**	**Boat (B)**
most stable (0)	(0.9 kcal/mol)	(3.8 kcal/mol)	(4.0 kcal/mol)

Pseudorotation between **TC** and **C** occur, easily. Pseudorotation between **TB** and **B** occur, easily.

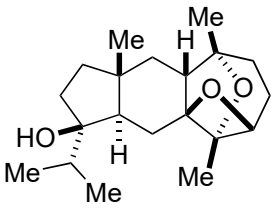
大学院講義有機化学 Ⅰ. 分子構造と反応・有機金属化学 p114-115

(1) Please provide the mechanism



1-1 (**0-12**)

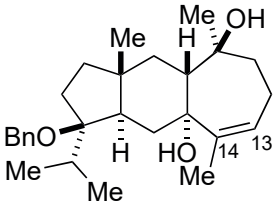
1) DMDO, CH_2Cl_2, -78 °C, 99%, dr>15:1
2) Cs_2CO_3, MeOH, 60 °C, 59% (75% brsm)
3) Martin sulfurane*,[a] , CH_2Cl_2, 0 °C;
4) H_2, Pd/C, THF, 23 °C, 60% (2 steps)



1-2 (tetra-*epi*-**1**)

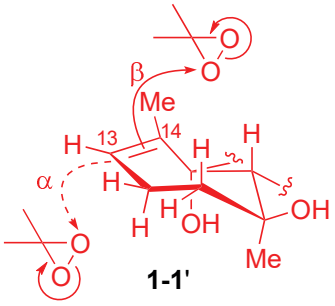
[a] In this reaction, olefination did not occur.

Answer



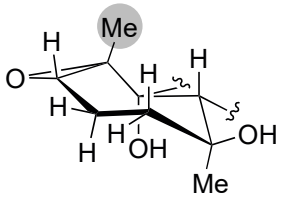
1-1 (**0-12**)

≡



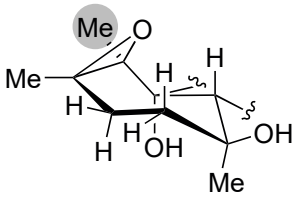
1-1'

α-*epoxidation*



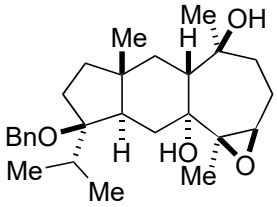
1-5 (chair-chair)
minor

β-*epoxidation*



1-7 (bort-chair)
major

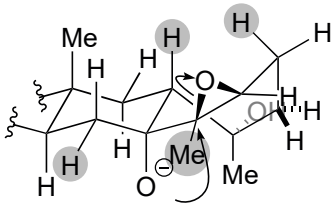
≡



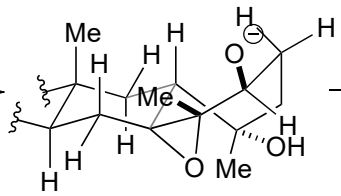
1-7' (major)

step 1

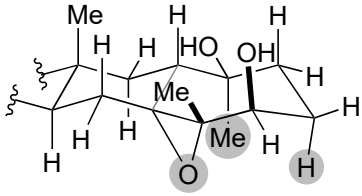
Cs_2CO_3
3-exo-tet



1-8 (twist boat)



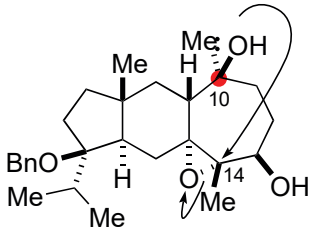
1-9 (twist boat)



1-10 (chair, X-ray)

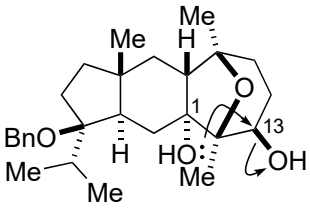
This equilibrium is biased toward chair comformation.

Author's desired pathway (from **1-10'** to **1-12**)

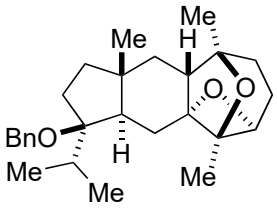


1-10'

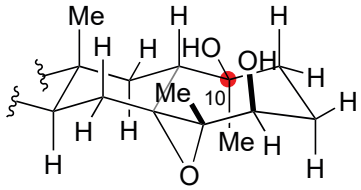
acid, base, neutral...



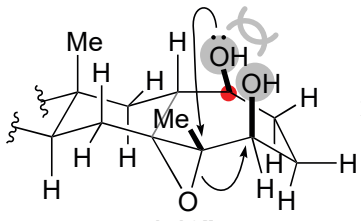
1-11



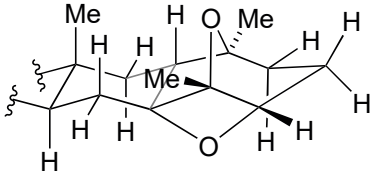
1-12 (desired)



1-10 (X-ray)
● C10: equat. OH



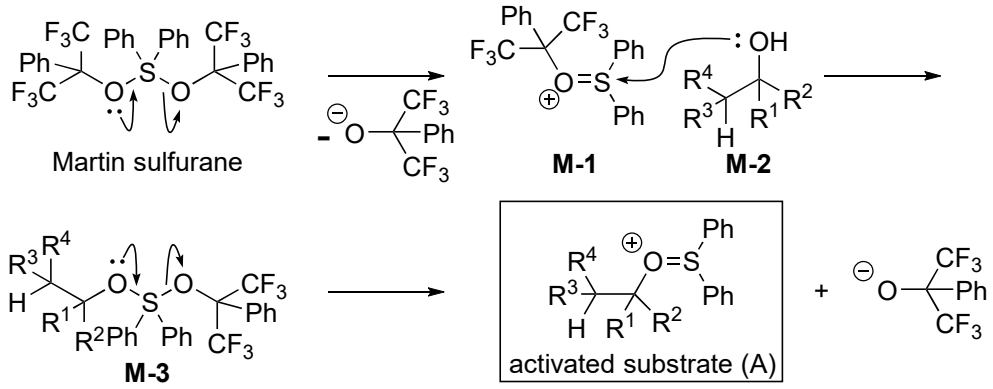
1-10"
● C10: axial OH



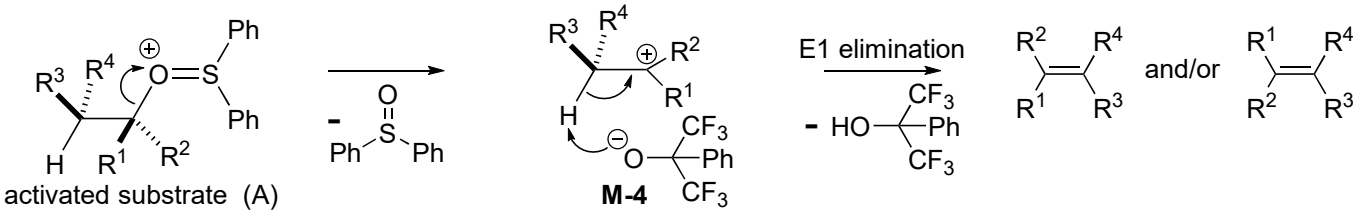
1-12' (desired)

- 3 - step 2

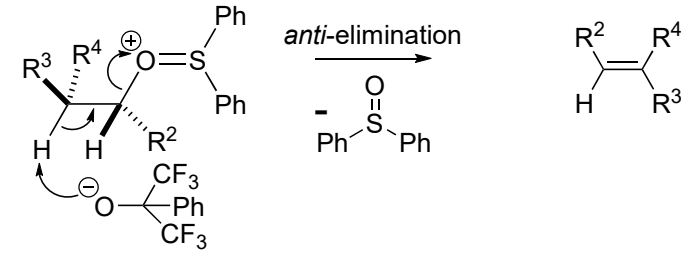
· Martin sulfurane



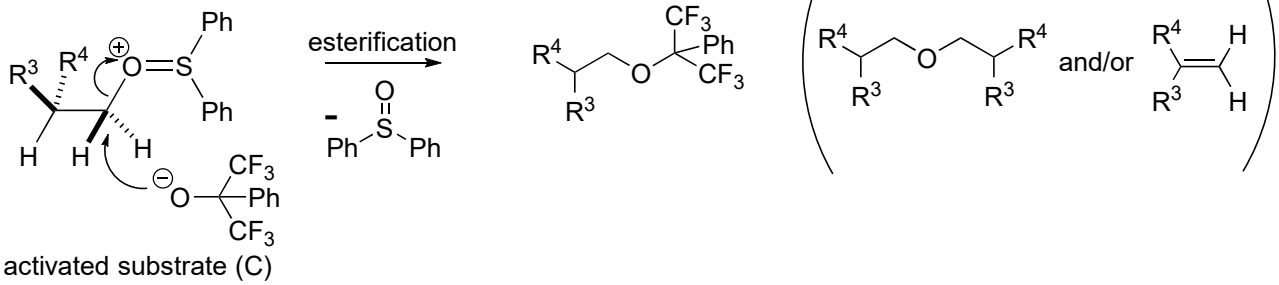
1. in case of 3° alcohol



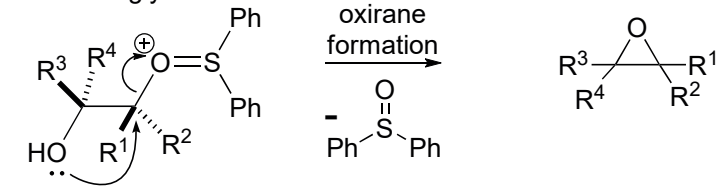
2. in case of 2° alcohol



3. in case of 1° alcohol

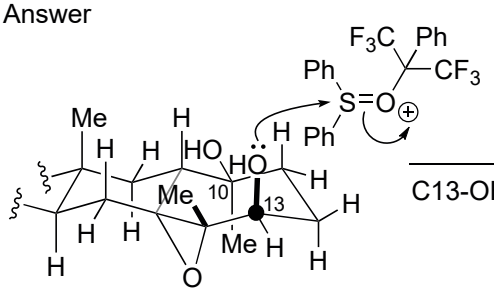


4. in case of glycol



a) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327.
b) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003.
c) Martin, J. C.; Franz, J. A.; Arhart, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 4604.
-120128_LS_Masanori NAGATOMO

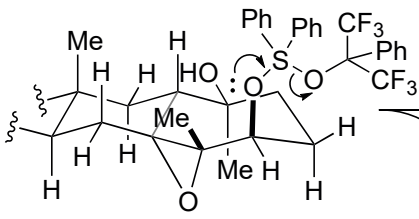
Answer



1-10 (X-ray)

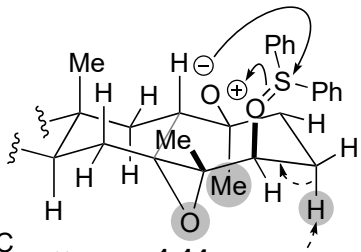
(● C13: 2°-axial OH
C10: 3°-equat. OH)

C13-OH

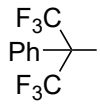


1-13

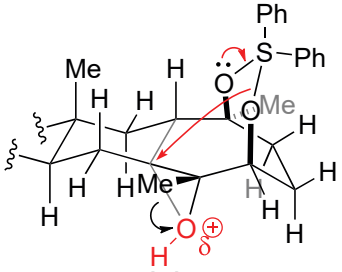
±H⁺



1-14

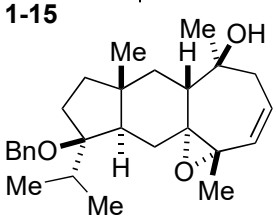


·Intramolecular reaction is faster than inter-.
·Steric repulsions facilitate to synthesize **1-15**

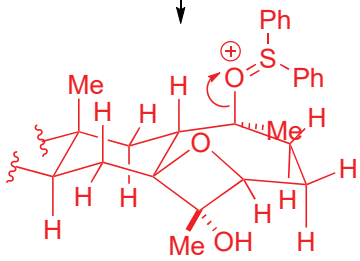


1-15

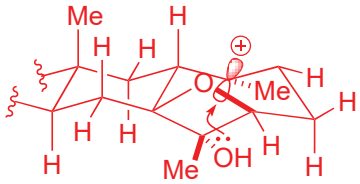
strain release of epoxide



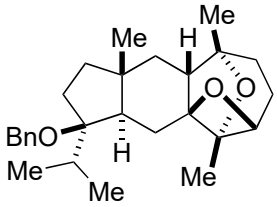
1-16



1-16



1-17



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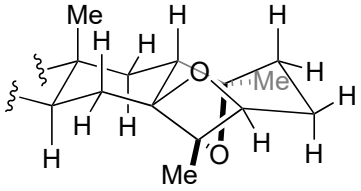
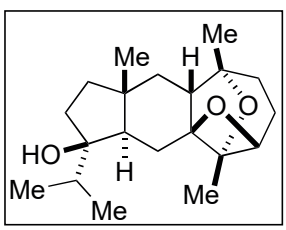


1-18

step 3

H_2, Pd/C

deprotection of Bn group



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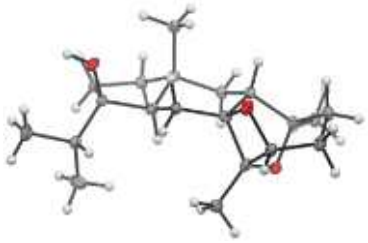
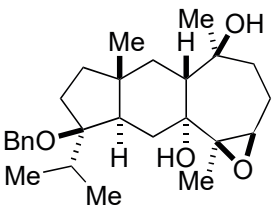


1-2 (tetra-*epi*-**1**)

1-2 (X-ray)

step 4

(2) Please fill in the blank and provide the mechanism.

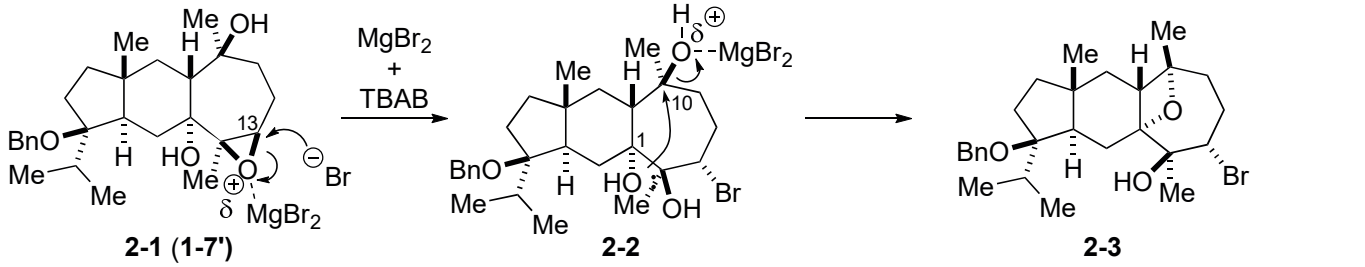


2-1 (**1-7'**)
($C_{27}H_{40}O_4$)

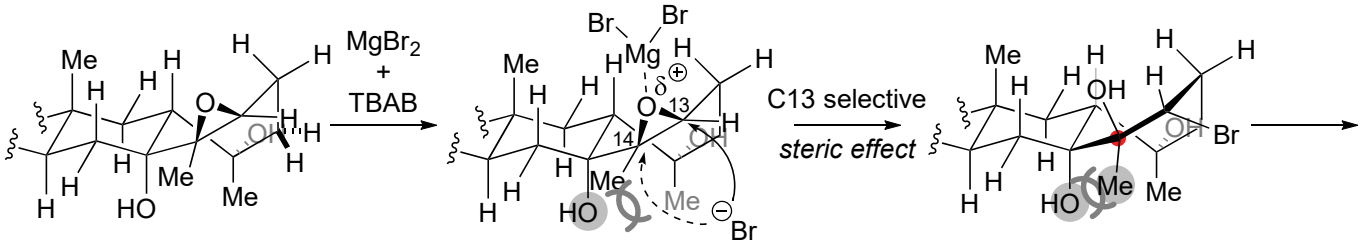
1) $MgBr_2 \cdot Et_2O$, TBAB*, CH_2Cl_2, 23 °C, 51%
2) K_2CO_3, MeOH, 0 °C 94%
3) $Cu(BF_4)_2 \cdot xH_2O$ CH_2Cl_2, 23 °C, 36%

2-2
($C_{27}H_{38}O_3$)

Answer
mechanism of step1 (plane figure)



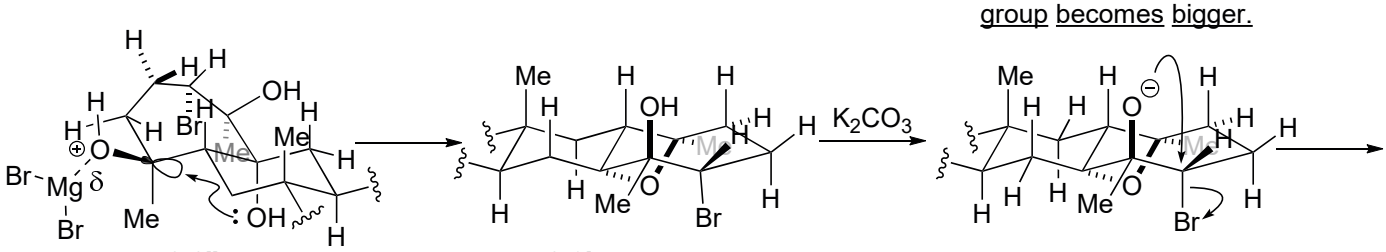
2-1 (**1-7'**) **2-2** **2-3**



2-1' (**1-7**) **2-4** **2-2'** (front view)

●C14: $sp^2 \rightarrow sp^3$

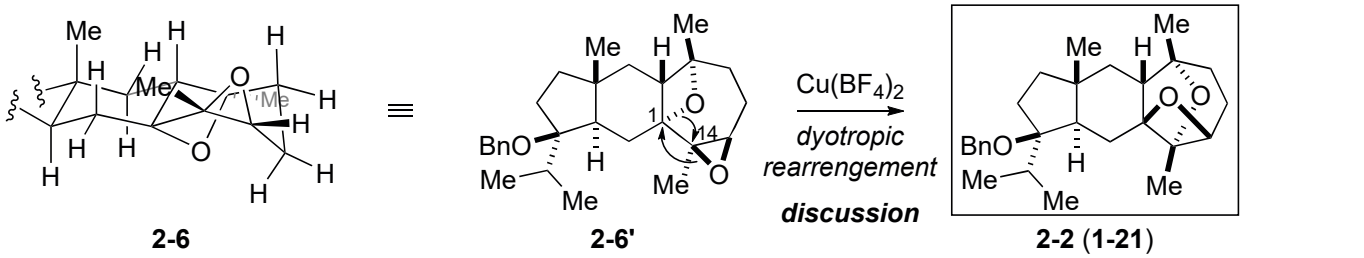
Steric repulsion between OH and Me group becomes bigger.



2-2''
(backside view)
→ Cyclization was accelerated.

2-3' (chair like)
(front view)

step 1



2-6 **2-6'** **2-2** (**1-21**)

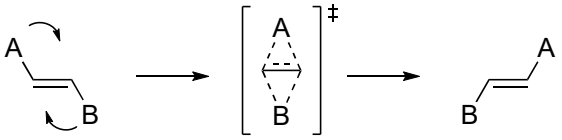
step 2 step 3

·Dyotropic rearrengement (100501_PS_Koichi MURAI)

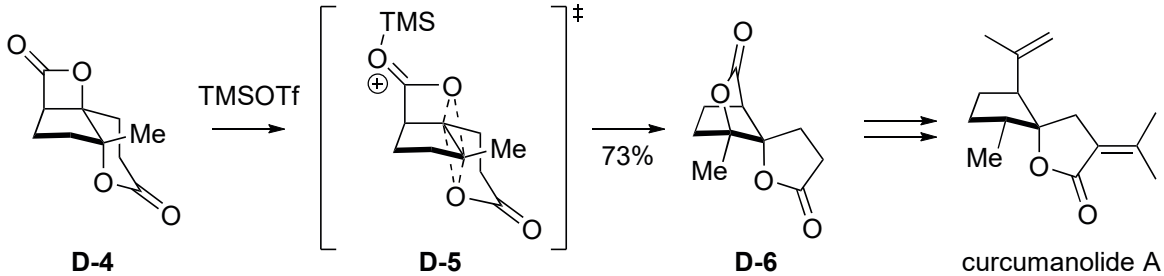
-In this reaction, two σ-bonds simultaneously migrate, intramolecularly.

(Reetz, M. T. *Angew. Chem. Int. Ed.* **1972**, *22*, 129.)

Type I: 1,2-shift in which two migrating groups interchange their relative positions in a stationary scaffold. Migrating bonds must be antiperiplanar.



D-1 **D-2** **D-3**

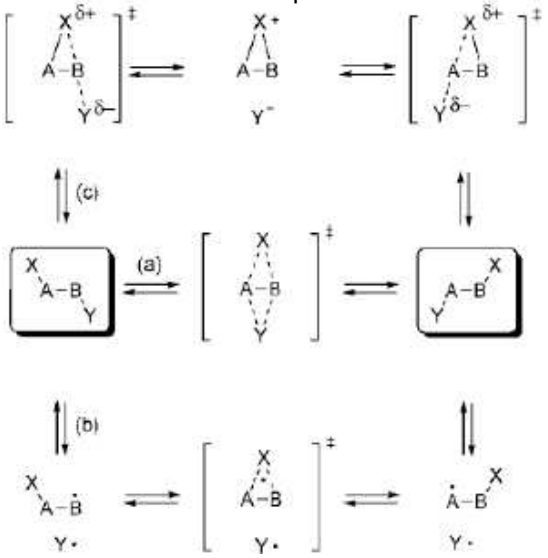


D-4 **D-5** **D-6** curcumanolide A

total synthesis of (-)-curcumanolide A (Romo, D. *et al J. Am. Chem. Soc.* **2012**, *134*, 13348.)

- 121102_LS_Yusuke Sesoko

- Reaction mechanisms: depends on the nature of reaction framework



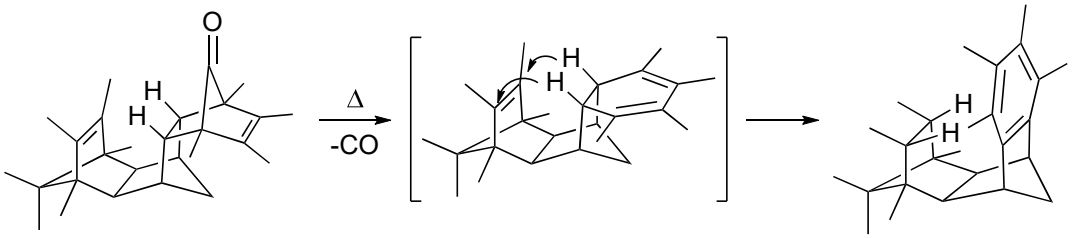
path (a): concerted

path (b): radical

path (a): ionic

Type II: migration to new bonding sites without positional interchange

D-7 **D-8** **D-9** **D-10** **D-11** **D-12**



D-13 **D-14** **D-15**

(Mackenzie, K. *J. Chem. Soc.* **1965**, 4646.)

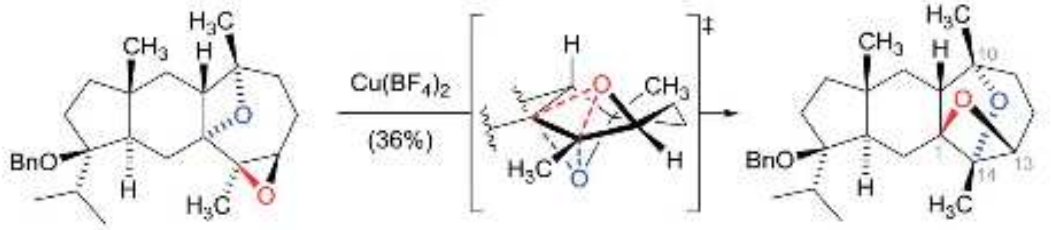
- Reaction mechanisms: almost all concerted.

discussion: Concerted vs Stepwise (steps 3: dyotropic rearrengement)

Author says...

epoxide-oxetane **2-6'** converted to dioxatricycle **2-2** by mild Lewis acid activation via a type I dyotropic rearrangement.

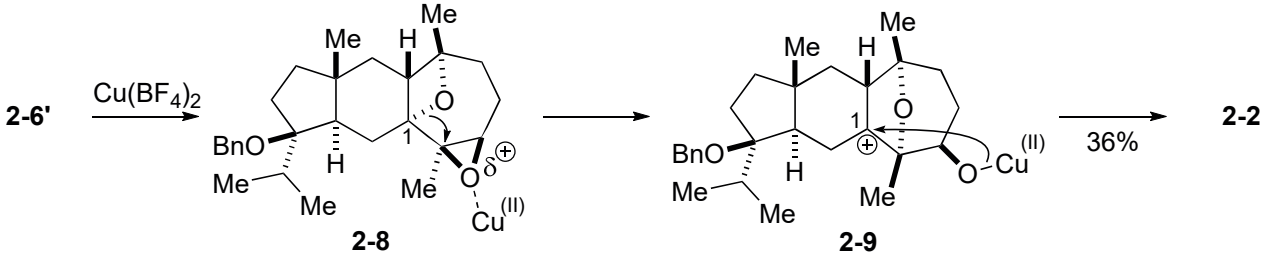
It is currently unkown, if **2-2** is the product of a concerted dyotropic reaction or a stepwise rearrangement.

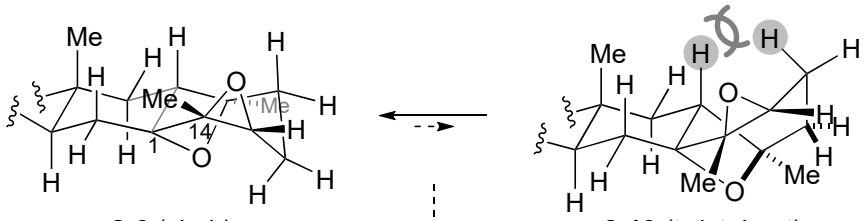


2-6' **2-7** **2-2** (**1-21**)

Hugelshofer, C. L.; Magauer T. Dyotropic rearrangements in natural product total synthesis and biosynthesis. *Nat. Prod. Rep.* **2017**, *34*, 228.

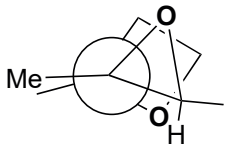
·My proposal: Stepwise rearrangement



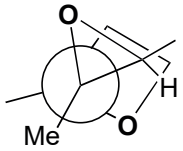


2-6 (chair)
more stable

2-10 (twist boat)
less stable



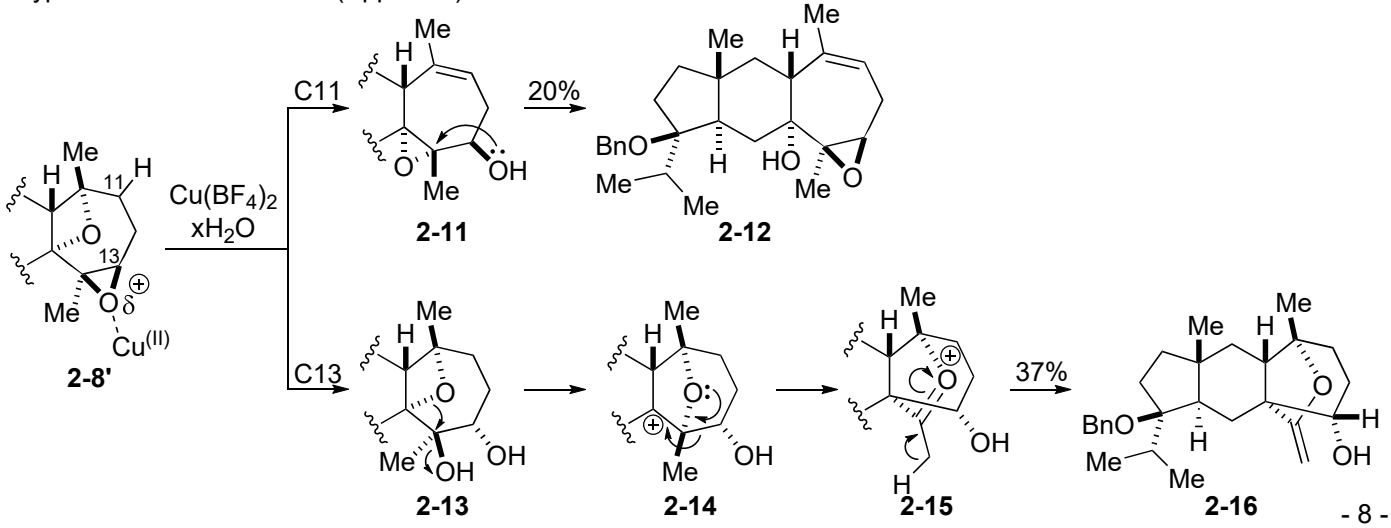
2-6" (chair)
(C14-C1)
the orbital overlap of **C-O** bonds is bad



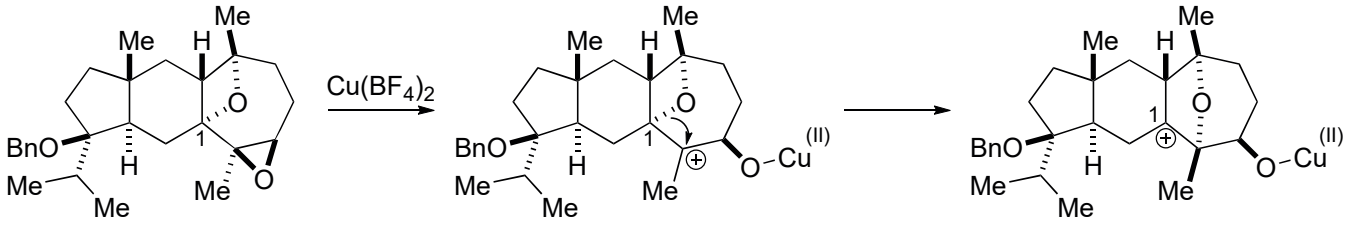
2-10' (twist boat)
(C14-C1)
the orbital overlap of **C-O** bonds is not bad

→ Concerted dyotropic reaction is difficult ?

·Byproducts in this reaction (Appendix)



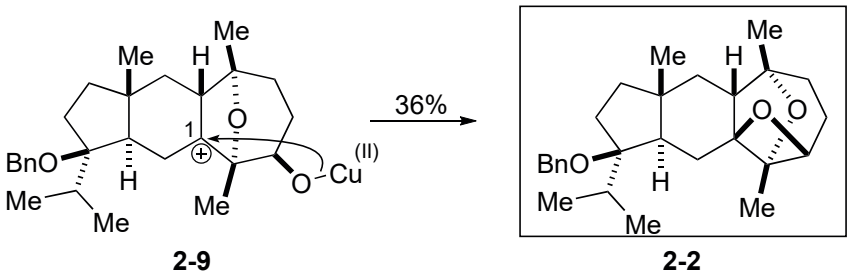
Prof. Inoue's suggestion: Concerted vs Stepwise



2-6' **2-8** **2-9**
more stable 3° cation

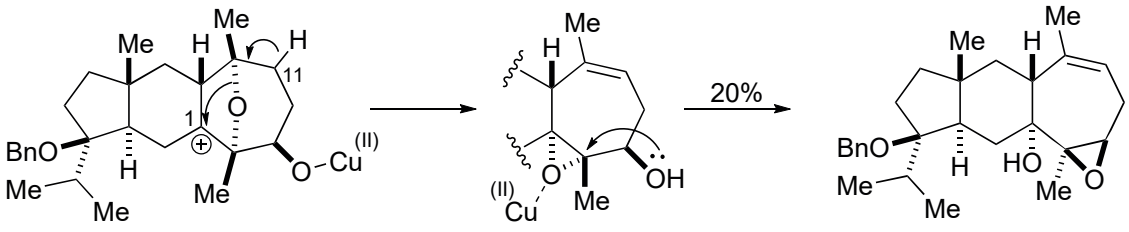
These products should be synthesized via the same carbocation **2-9**. That is,
the reaction mechanism (Concerted or Stepwise) for the three compounds (**2-2**, **2-12** and **2-16**) should be same.

1. to compound **2-2**



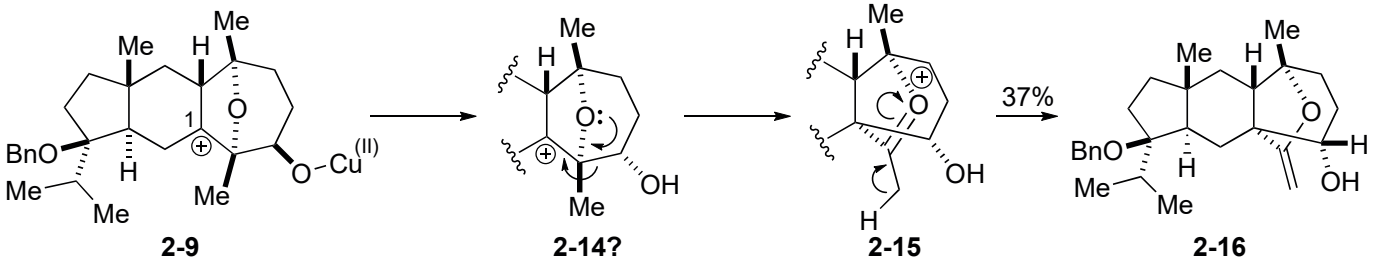
2-9 **2-2**

2. to compound **2-12**



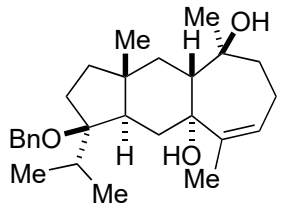
2-9 **2-11** **2-12**

3. to compound **2-12**



2-9 **2-14?** **2-15** **2-16**

(3) Please fill in the blank and provide the mechanism.

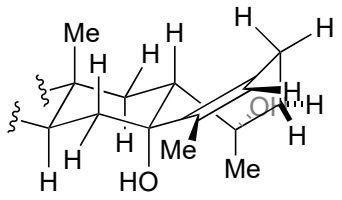


3-1 (1-1)
($C_{27}H_{40}O_3$)

1) TMS-imidazole, CH_2Cl_2, 0 to 23 °C, 92%
2) O_2 (bubbled), TPP* hν, $(CH_2Cl)_2$, 0 °C; PPh_3, 23 °C, 71%
3) MsCl, Et_3N, CH_2Cl_2, -78 °C
4) NaH, THF, 66 °C, 88% (2 steps)
5) NIS*, CH_2Cl_2, 23 °C
6) H_2, Pd/C, THF, 23 °C, 80% (2 steps)

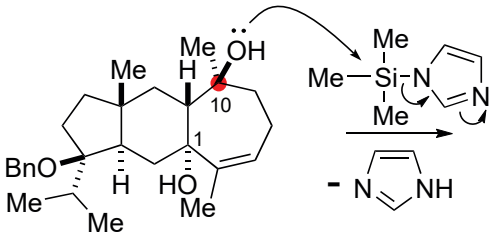
3-2
($C_{20}H_{32}O_3$)

Answer

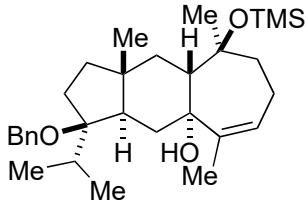


3-1' (**1-6**, twist boat)
(cf. page 3)

≡

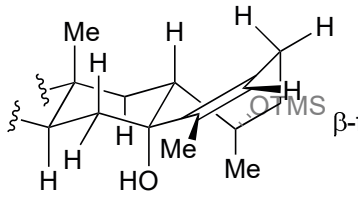


3-1 (**1-1**)
● C10: less hindered 3° OH



3-3 (C10-OTMS)

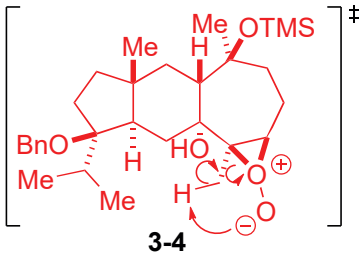
≡



3-3' (C10-OTMS)

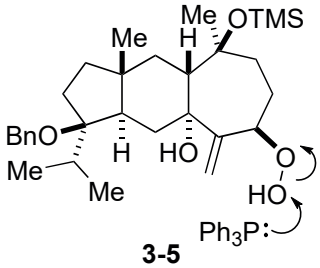
step 1

$^3O_2$ → $^1O_2$ (hν, TPP)
β-face selective (cf. page 3)

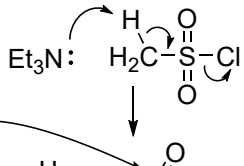


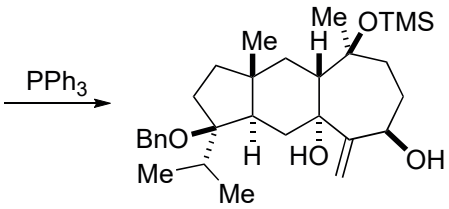
3-4

Ene reaction



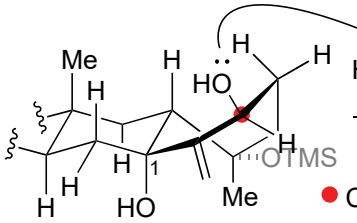
3-5





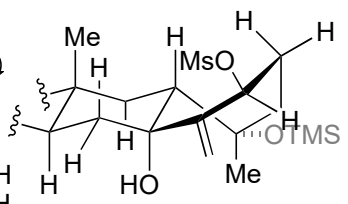
3-6

≡



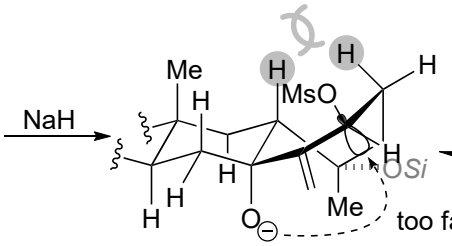
3-6' (twist boat)
● C13: 2° OH
C1: 3° OH

step 2



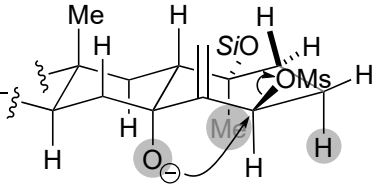
3-7 (twist boat)

step 3

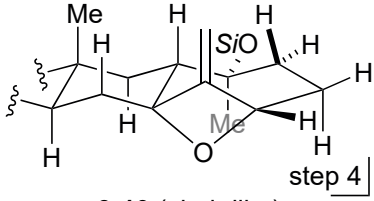


3-8 (twist boat)

too far



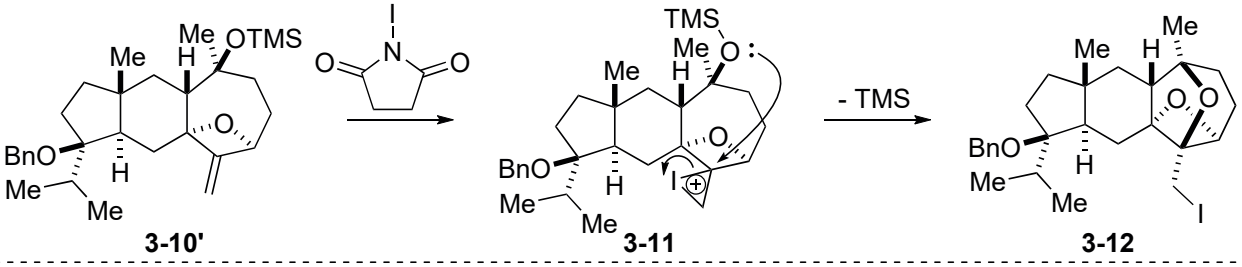
3-9 (chair like)



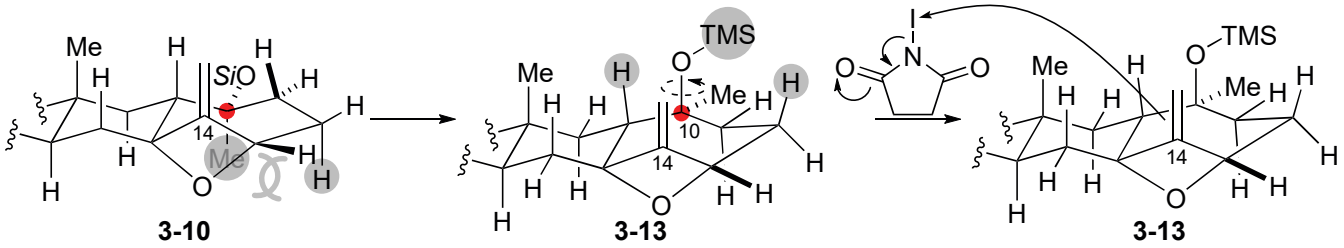
3-10 (chair like)

step 4

mechanism of step 5 (plane figure)



3-10' **3-11** **3-12**



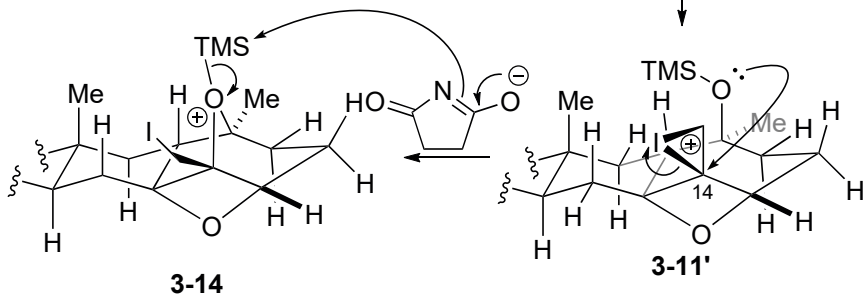
3-10 (C10: axial Me) **3-13** (C10: axial OTMS) **3-13**

Author says...

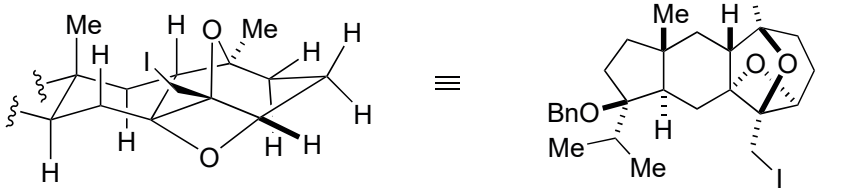
3-10' showed severe signal broadening in the ^{1}H-NMR spectrum at ambient temperature.

↓

C10-OTMS moiety had been brought into close proximity of the *exo*-methylene (C14) and could no longer freely rotate.



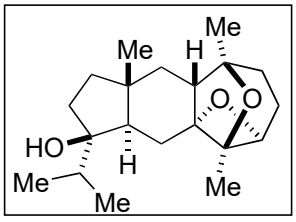
3-14 **3-11'**



3-12' ≡ **3-12**

step 5

H_2, Pd/C | - Bn - I



3-2 (**1**)

step 6