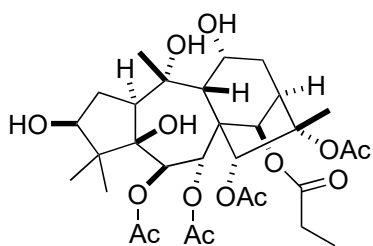
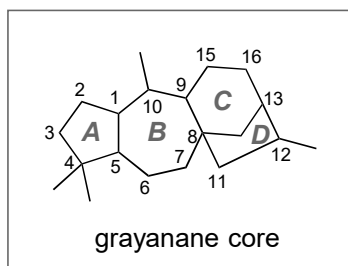
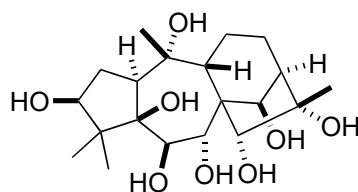


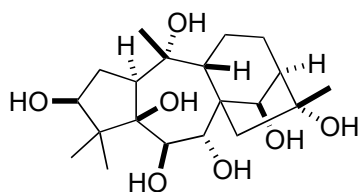
Please propose your synthetic route to one of grayane diterpenoids (**GD1-GD4**) from a commercial compound.



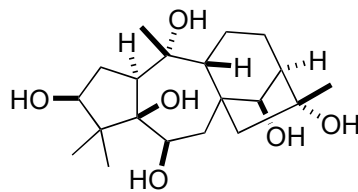
pierisformosoid B (**GD1**)



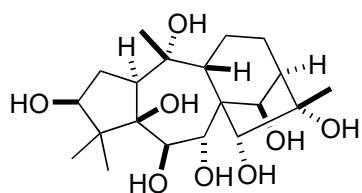
pierisformosoid D (**GD2**)



pieristoxin C (**GD3**)

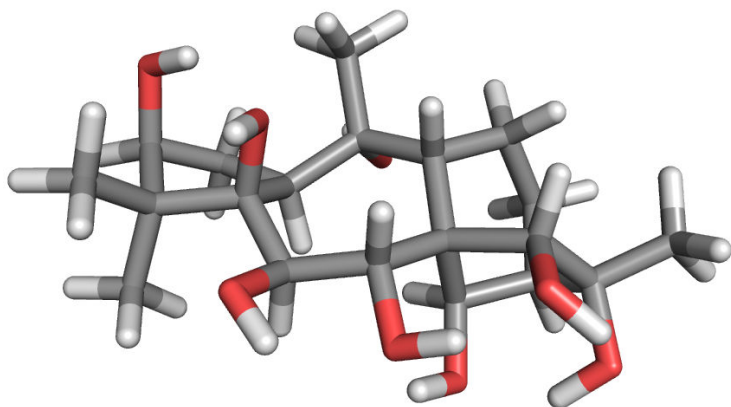


grayanotoxin III (**GD4**)

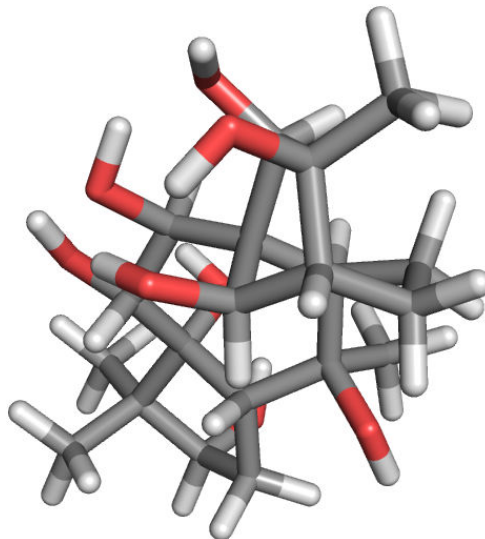


pierisformosoid D (**GD2**)

≡



≡



Topic: Synthetic Plan of Grayanotoxin III and more oxygenated congeners

### 1. Introduction

1-1 Grayanane diterpenoids - isolated from *Ericaceae* family



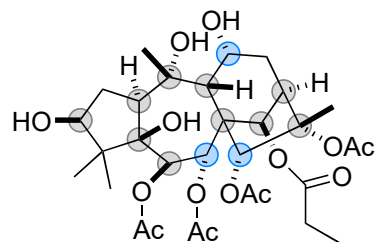
grayanane skeleton

- a unique 5/7/6/5 tetracyclic system containing bicyclo-[3,2,1]-octane system
- a broad range of bioactivities (toxic, analgesic, antitumor, antiviral, aminociceptive, anti-inflammatory, etc...)
- More than 290 grayanoids has been isolated.

**comprehensive reviews:**

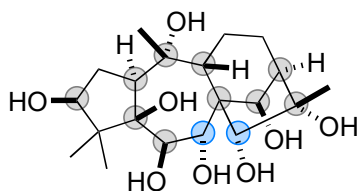
Li, S.-H. and Gao, J.-M. et al. *Eur. J. Med. Chem.* **2019**, 166, 400.  
 Yu, S.-S. et al. *Phytochem Rev.* **2013**, 13, 305.

1-2 Grayanotoxin III and more oxygenated congeners (GD1-GD4)



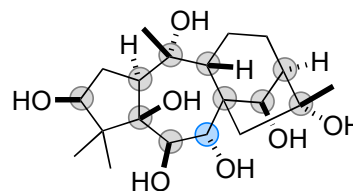
pierisformosoid B (**GD1**)  
[analgesic]

*Tetrahedron* **2018**, 74, 375.



pierisformosoid D (**GD2**)  
[analgesic]

*Tetrahedron* **2018**, 74, 375.

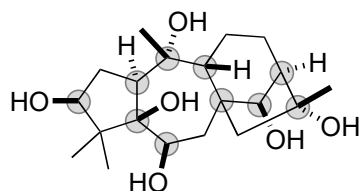


pieristoxin C (**GD3**)

[antifeedant, analgesic]

*Chem. Pharm. Bull.* **1980**, 28, 3124.

*Tetrahedron* **2018**, 74, 375.

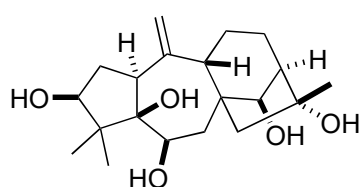


grayanotoxin III (**GD4**)

[sodium channel activation and cell depolarization]

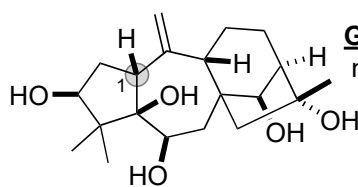
*J. Am. Chem. Soc.* **1954**, 79, 4548.

1-3 Related natural products



grayanotoxin II (=  $\Delta^{10,20}$ -**GD4**)  
[weaker activity than **GD4**]

*J. Am. Chem. Soc.* **1954**, 79, 4548.



principinol D (= 1-*epi*- $\Delta^{10,20}$ -**GD4**)  
(grayanane diterpenoids)

[weak PTP1B\* inhibitory]

*Tetrahedron* **2014**, 70, 4317.

**GD1-GD3**

no examples

\*PTP1B: protein tyrosine phosphatase 1B

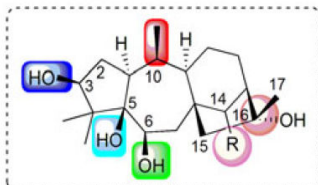
1-4 SAR study

**C3** 3 $\beta$ -OH: indispensable  
2 $\beta$ , 3 $\beta$ -epoxy: same level

5 $\beta$ -OH: indispensable  
**C5**  $\Delta^{1,5}$ : no activity  
5 $\beta$ , 9 $\beta$ -oxide: no activity

6 $\beta$ -OH: indispensable  
**C6** acetylation: no activity

optimal number of OH: 5  
1, 5-Seco: no activity  
B-homo-C-nor (kalmene): decrease  
A-homo-B-nor (leucothane): no activity



Essential structural elements  
Nonessential structural elements

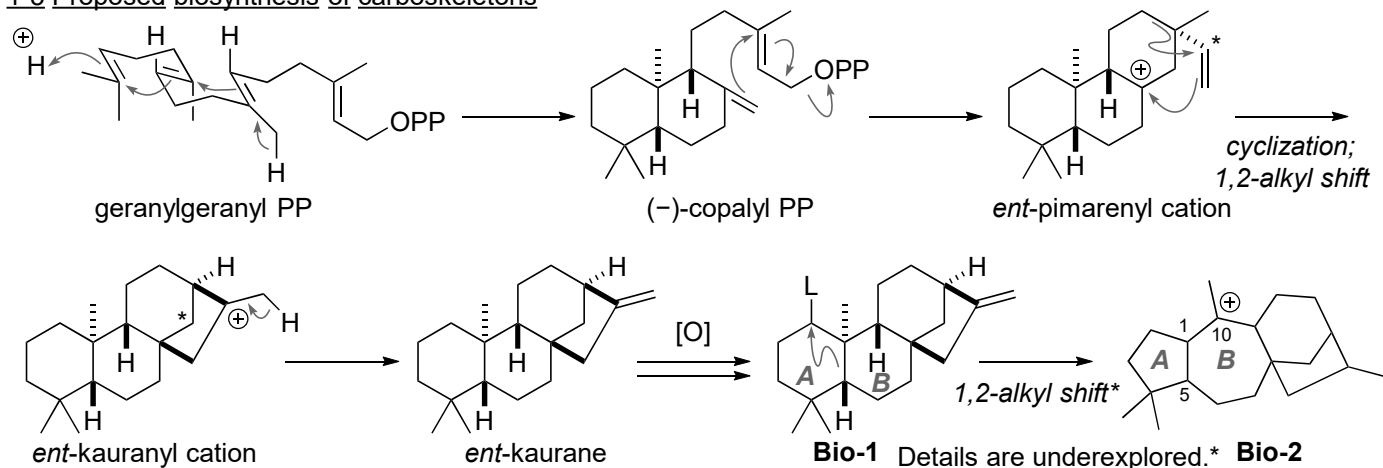
10 $\beta$ -CH<sub>3</sub>: indispensable  
**C10** 10 $\beta$ -CH<sub>3</sub>, 10 $\alpha$ -OH: decrease  
10 $\alpha$ -OH: no activity  
 $\Delta^{10,20}$ : no activity

**C14** R =  $\beta$ -OH >  $\beta$ -O-propionyl = H =  $\beta$ -NH<sub>2</sub> >  $\beta$ -OAc  
> carbonyl = oxime >  $\alpha$ -OH

16 $\beta$ -CH<sub>3</sub>, 16 $\alpha$ -OH = dehydroxy ( $\Delta^{15}$ ) = dehydroxy ( $\Delta^{16}$ )  
**C16** > 16 $\alpha$ -CH<sub>3</sub> = 17-nor > 16-carbonyl = 16-oxime  
15 $\alpha$ , 16 $\alpha$ -epoxy: no activity

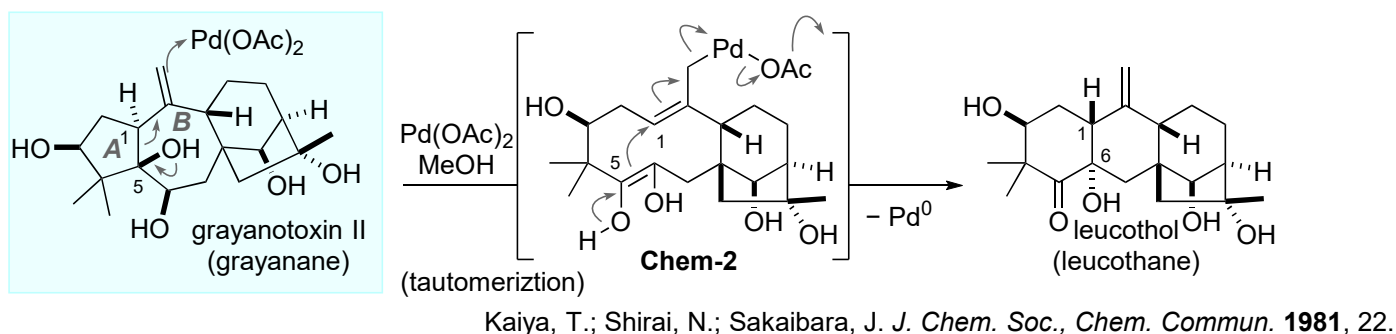
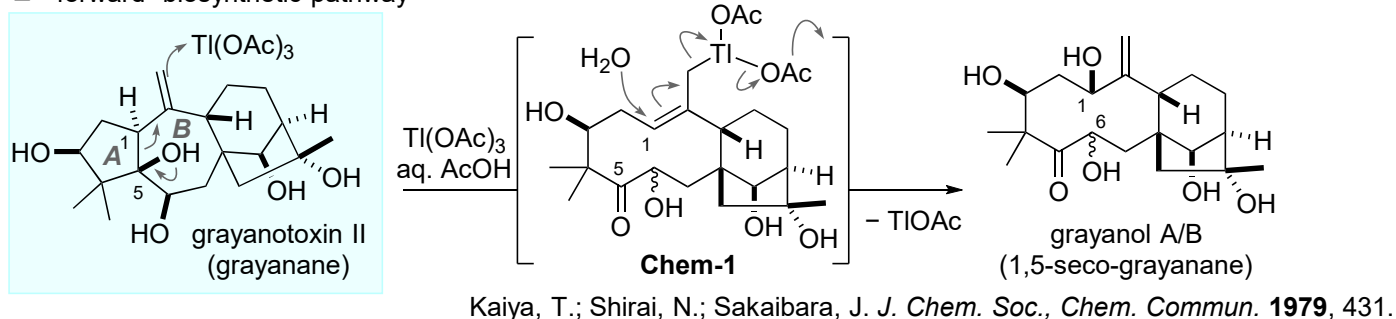
Fig. 21 A summary of the SAR profile of grayanane derivatives

1-5 Proposed biosynthesis of carboskeletons

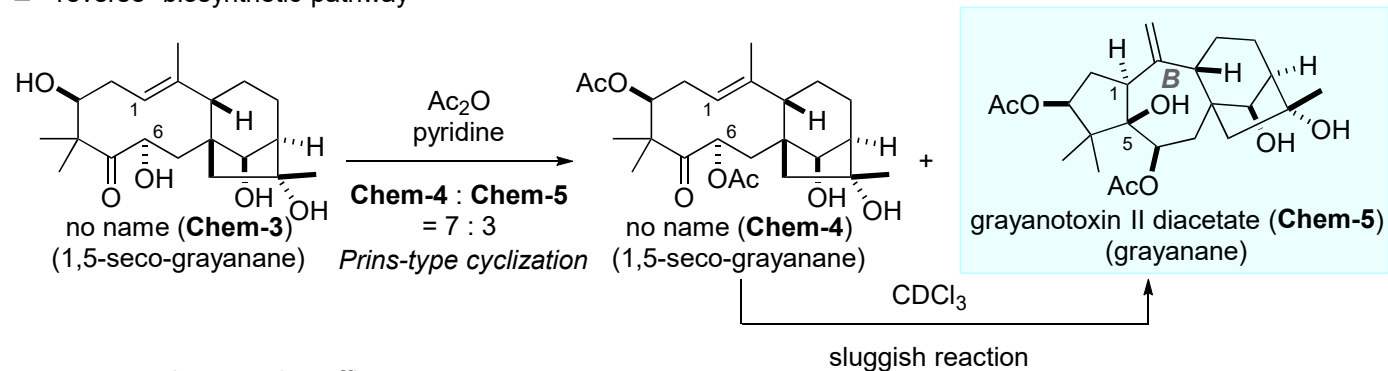


1-6 Chemical skeletal transformations of grayanane skeletons (Yields are not mentioned.)

■ "forward" biosynthetic pathway



■ "reverse" biosynthetic pathway



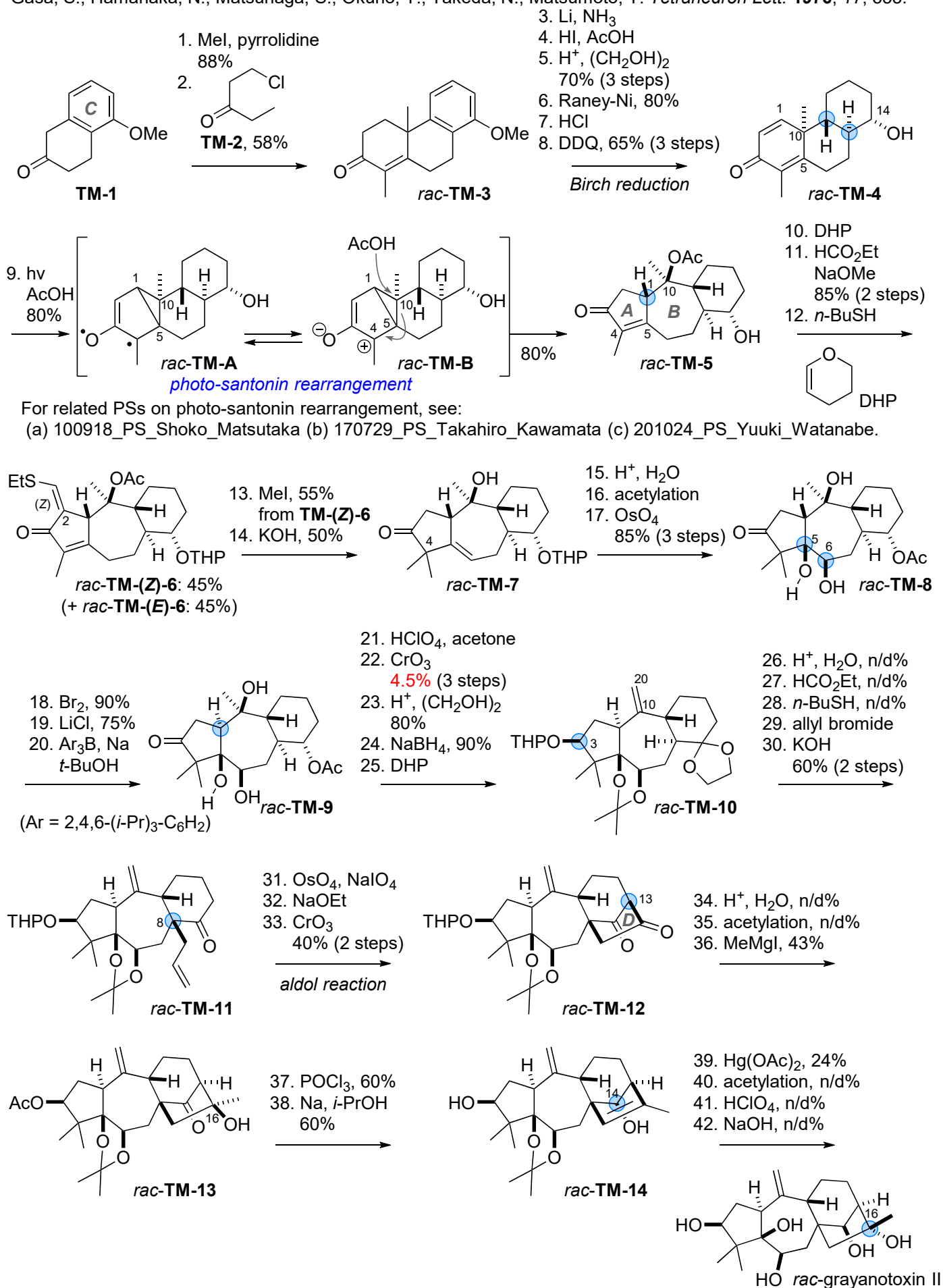
not good conversion efficacy  
 ← The conformation of Chem-3 might be flexible.

Katai, M.; Terai, T.; Meguri, H. *Chem. Lett.* **1985**, 443.

## 2. Past Total Syntheses of Grayanotoxin III and Related Analogs

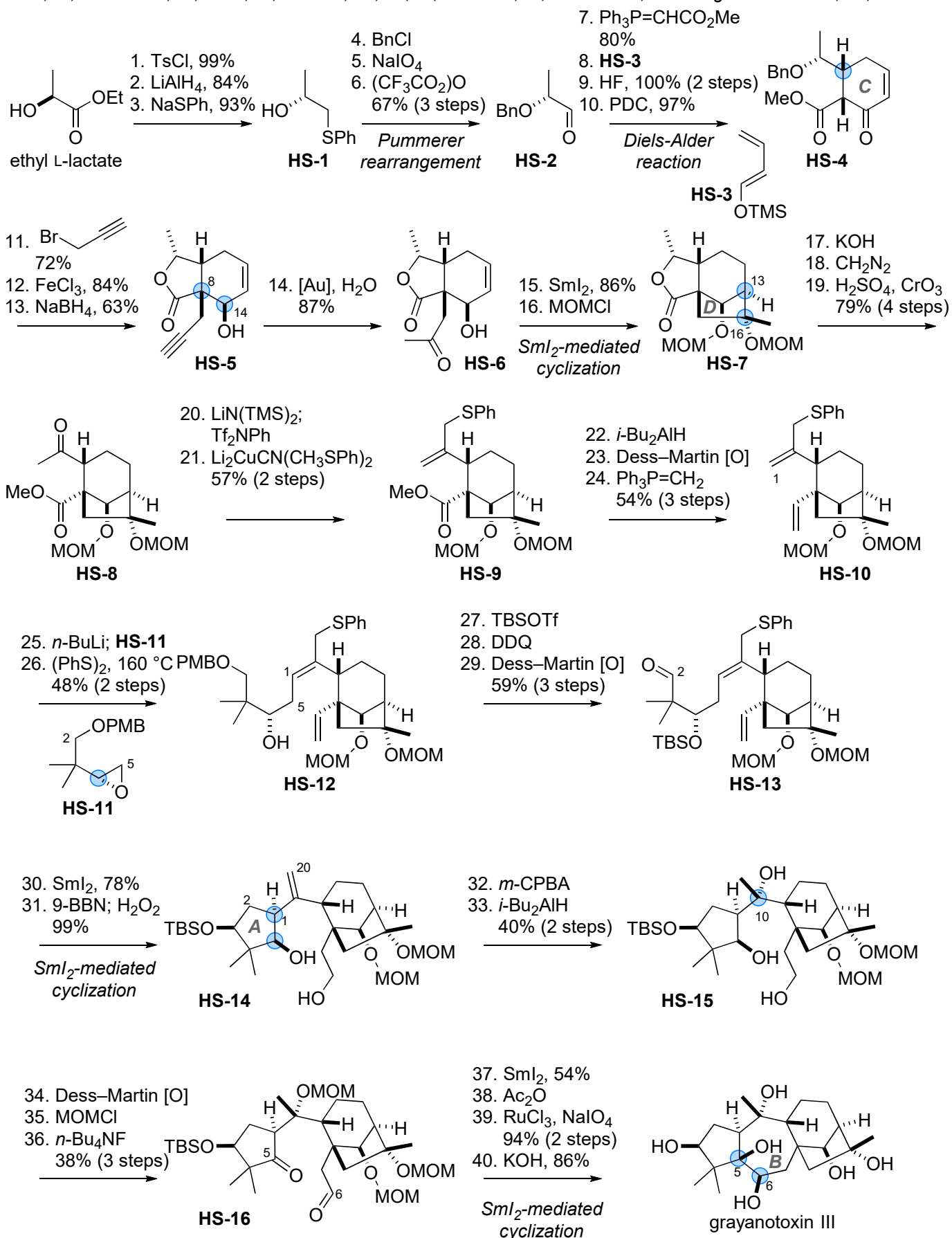
### Matumoto Group (grayanotoxin II, racemic)

Gasa, S.; Hamanaka, N.; Matsunaga, S.; Okuno, T.; Takeda, N.; Matsumoto, T. *Tetrahedron Lett.* **1976**, *17*, 553.



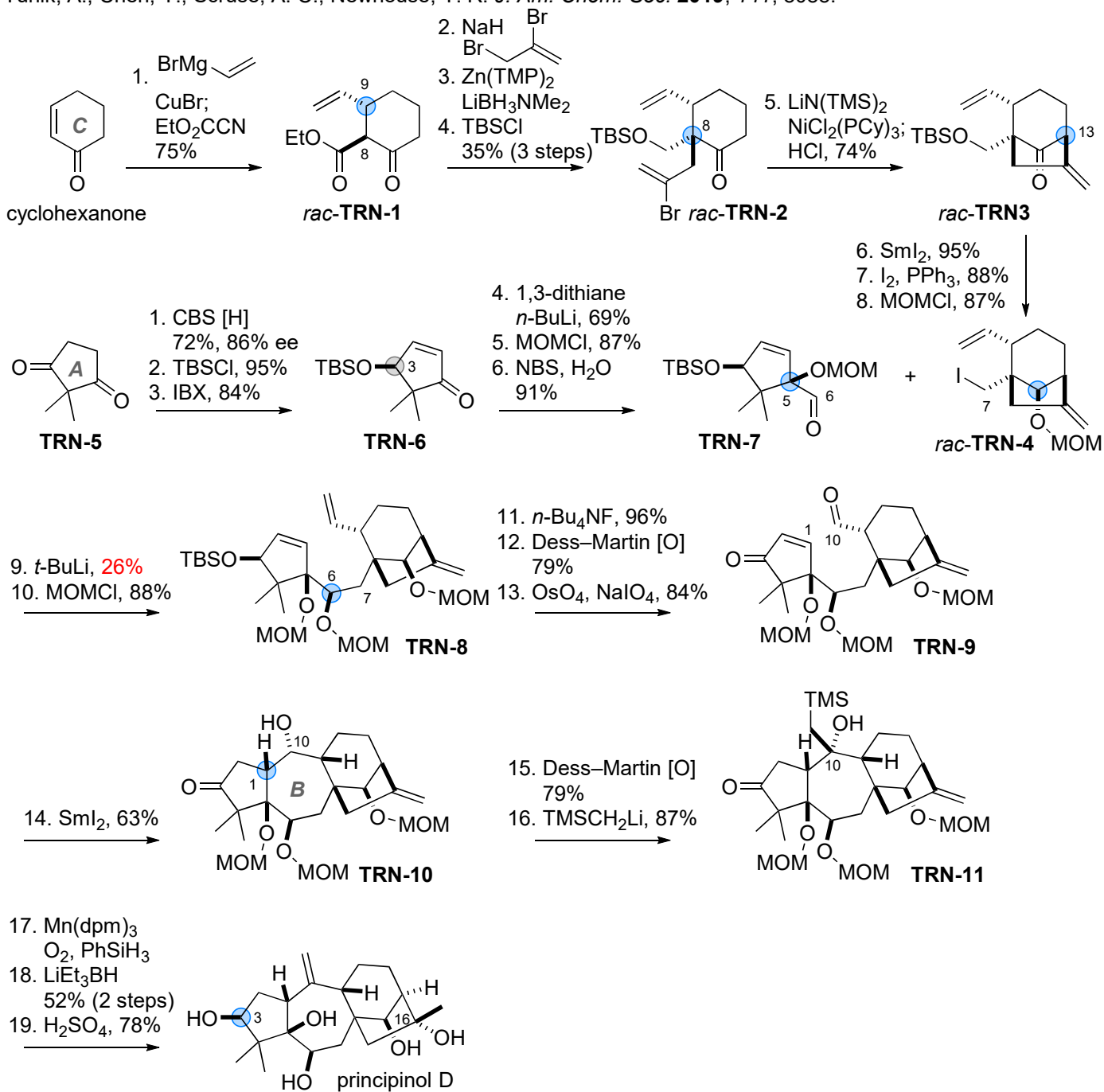
## Shirahama Group (grayanotoxin III)

Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5532.



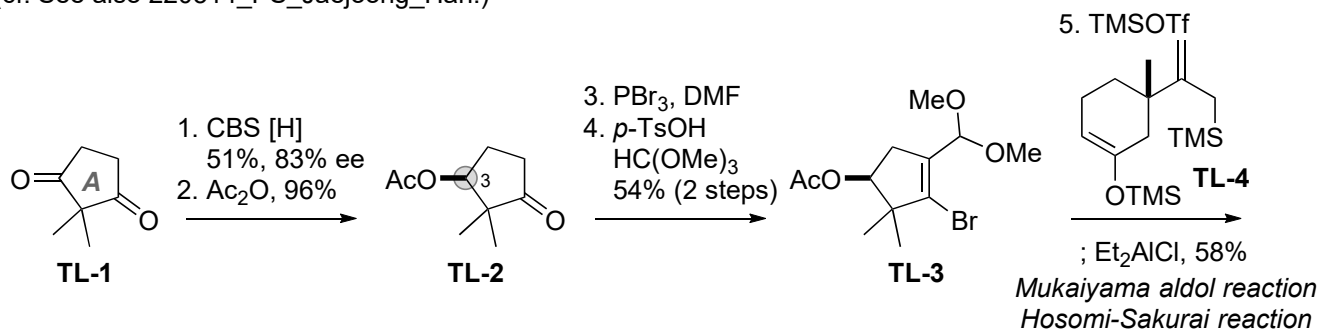
## Newhouse Group (principinol D)

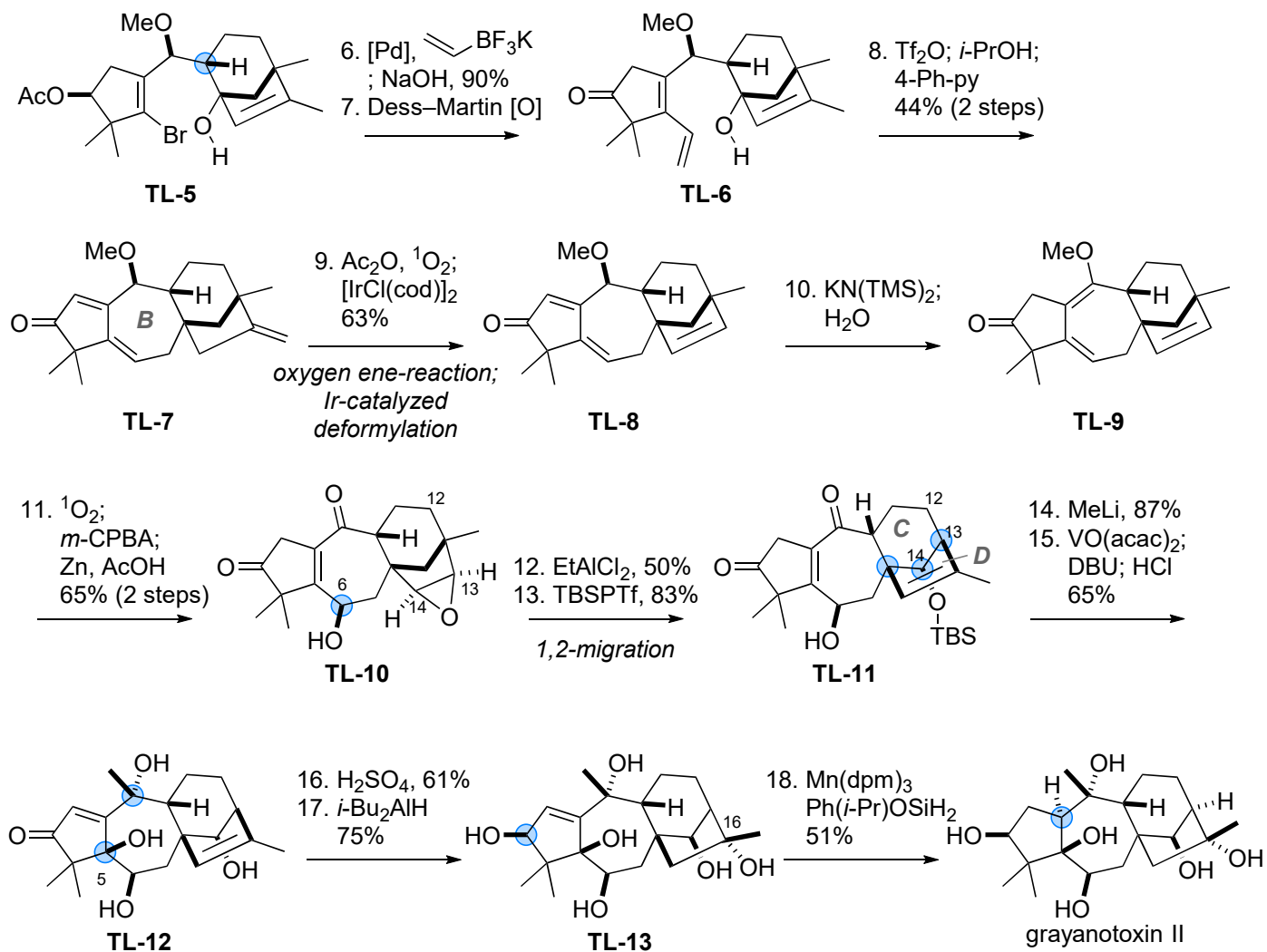
Turlik, A.; Chen, Y.; Scrusse, A. C.; Newhouse, T. R. *J. Am. Chem. Soc.* **2019**, *141*, 8088.



## Luo Group (grayanotoxin III)

Kong, L.; Yu, H.; Deng, M.; Wu, F.; Jiang, Z.; Luo, T. *J. Am. Chem. Soc.* **2022**, *144*, 5268.  
(cf. See also 220514\_PS\_Jaejoong\_Han.)





*Our original synthetic plans are closed to the public.*