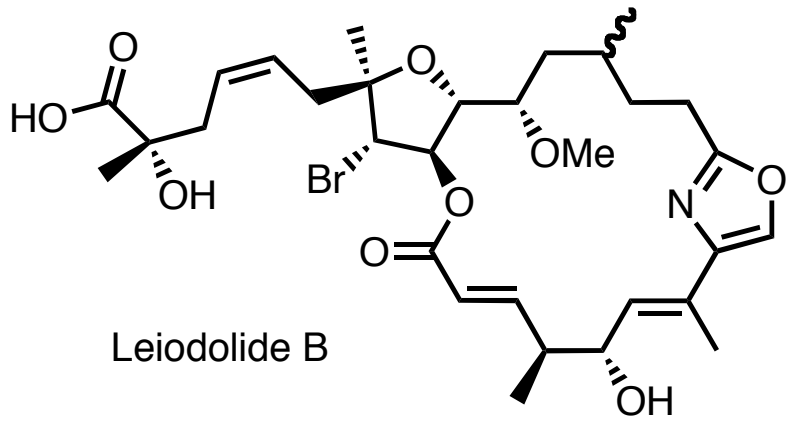
The Leiodolide B Puzzle

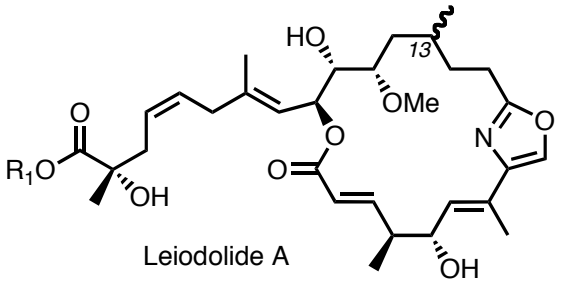


Leiodolide B

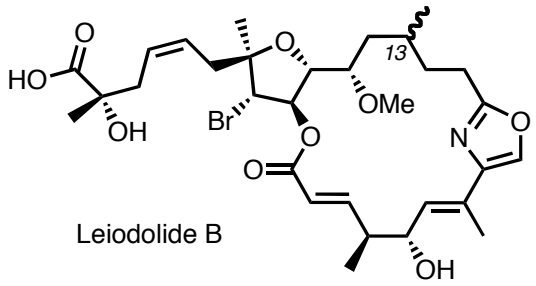
Alexandre Larivée, John B. Unger, Mikaël Thomas,
Conny Wirtz, Christophe Dubost, Shinya Handa, Alois Fürstner
Angew. Chem. Int. Ed. **2010**, 50, 304

Nate Ware, Wipf Group Current Literature 01/29/11

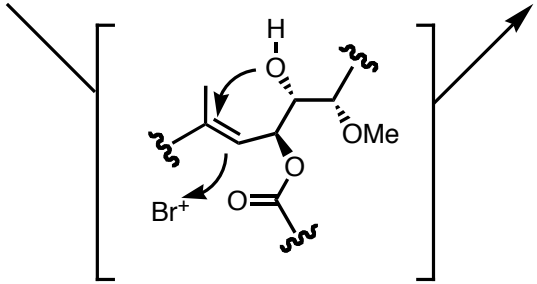
Leiodolides A and B

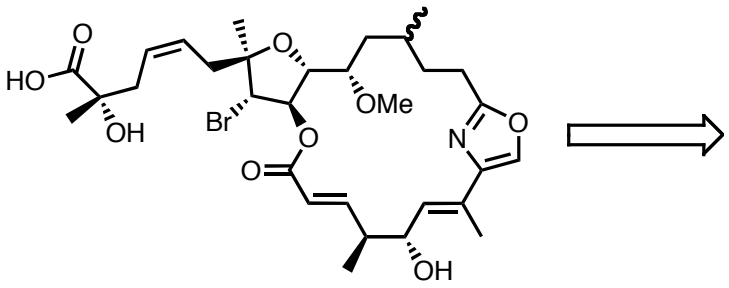


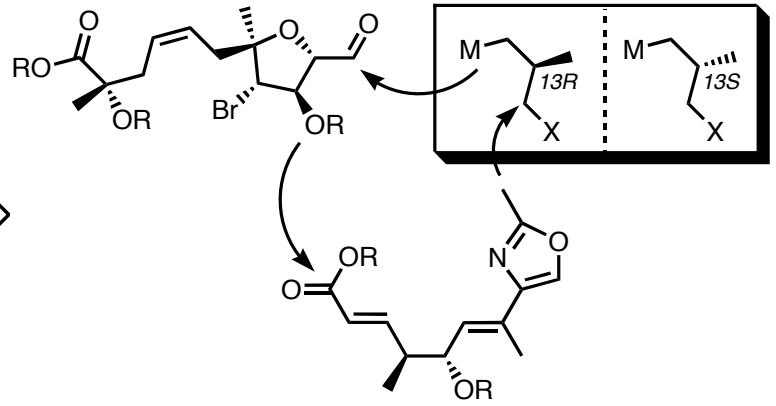
Leiodolide A



Leiodolide B







J. S. Sandler, P. L. Colin, M. Kelly, W. Fenical *J. Org. Chem.* **2006**, 71, 7245

Isolation and Activity

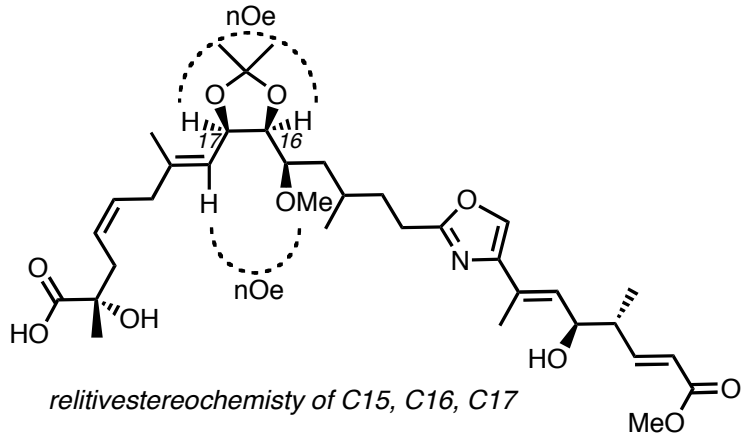
Deep Worker 2000

- Uchelbeluu Reef, Palau
- A new species of the genus *Leiodermatium*
- Isolated using *Deep Worker 2000* at 240 m (790 ft)
- 730 g of dry sponge gave 8 mg of leiodolide A (0.001%) and 0.8 mg of leiodolide B (0.0001%).
- Leiodolides A and B have IC_{50} values of 2.5 µM and 3.8 µM for HCT-116 human colon carcinoma.

http://www.nuytco.com/products/deepwater_photos.shtml#

J. S. Sandler, P. L. Colin, M. Kelly, W. Fenical *J. Org. Chem.* **2006**, 71, 7245

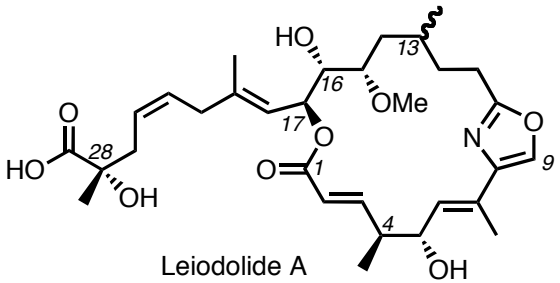
Degradation Experiments to Determine Structure



1. NaOMe, MeOH

2. 2,2-dimethoxypropane, PPTS, MeOH

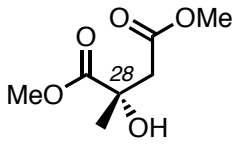
relitivestereochemisty of C15, C16, C17



Leiodolide A
(8 mg total material)

1. O_3, H_2O_2, MeOH

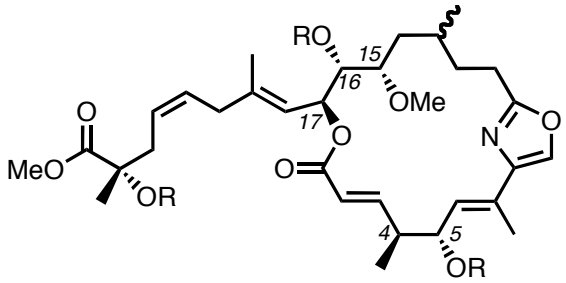
2. CH_2N_2



Identified by HPLC-MS and co-injected on chiral GC with authentic samples of both R- and S- dimethyl citramalate.

a. (*S*)-MTPACl, DMAP, MeOH

b. (*R*)-MTPACl, DMAP, MeOH



R = (*S*)-MTPA
R = (*R*)-MTPA

absolute stereochemisty of C4, C5, C15, C16, C17

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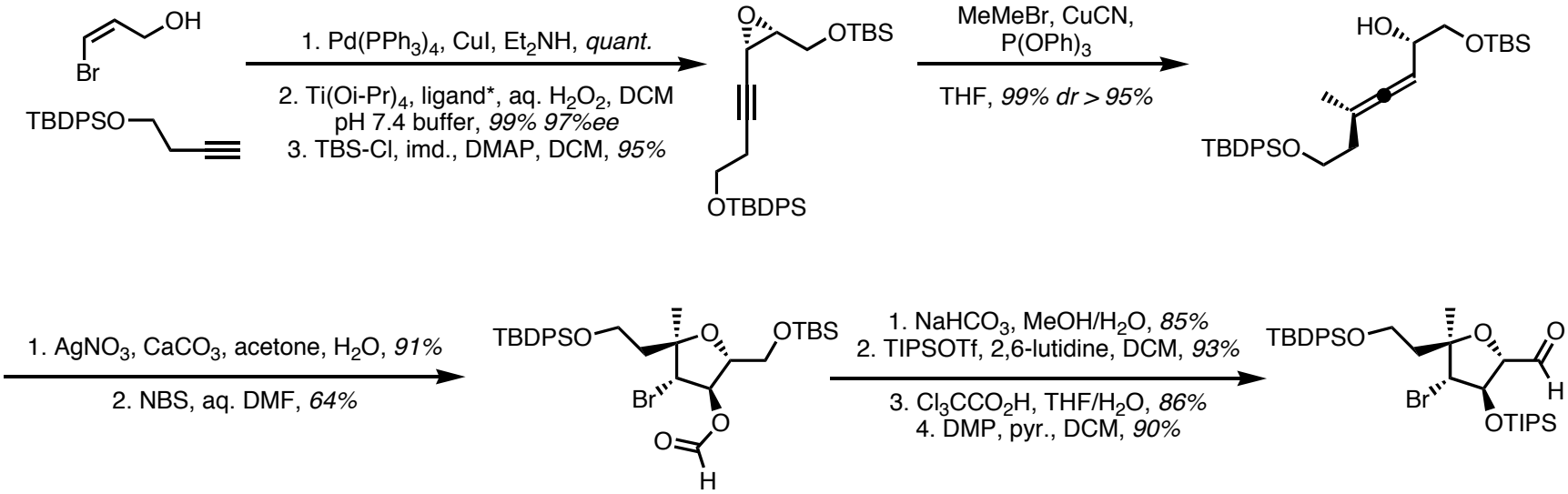
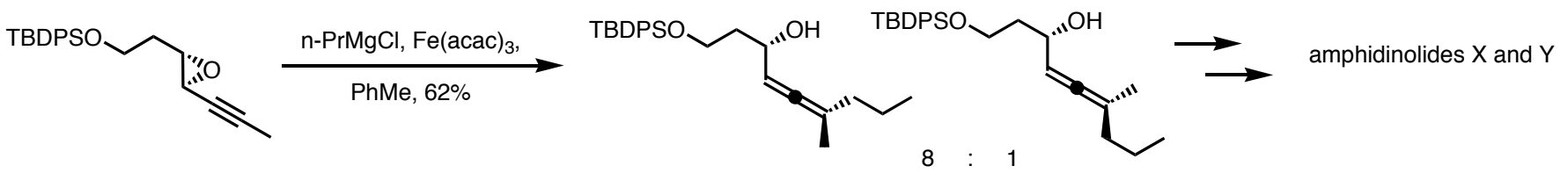
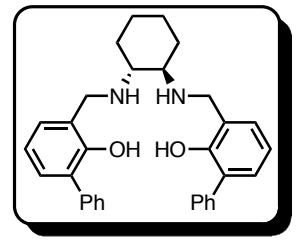
Formation of Furan Fragment



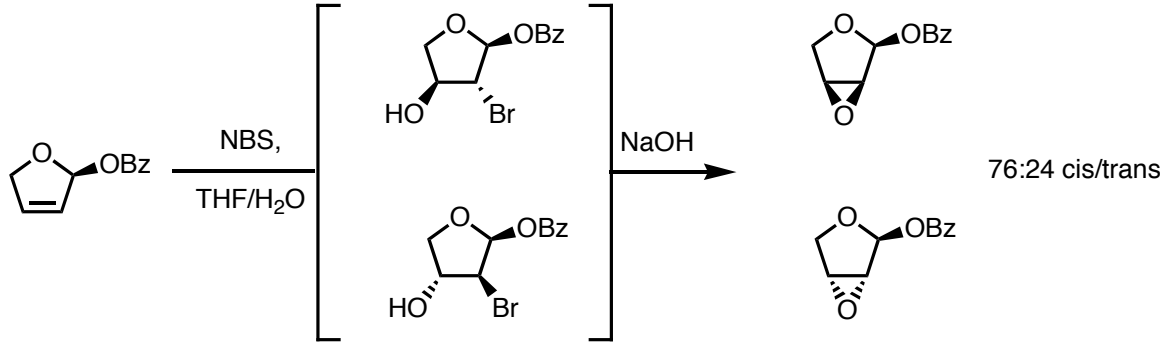


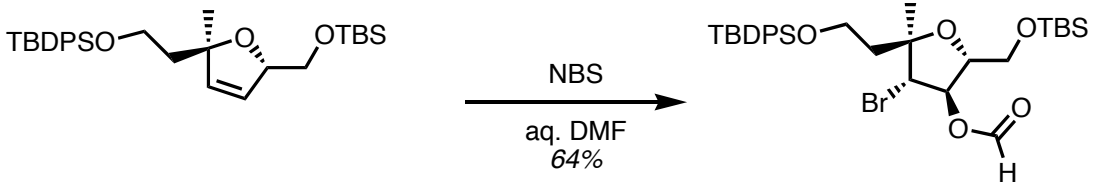
A. Furstner, E. Kattnig, O. Lepage *JACS* **2006**, 128, 9194
C. Deutsch, A. Hoffmann-Roder, A. Domke, N. Krause, *Synlett*, **2007**, 737

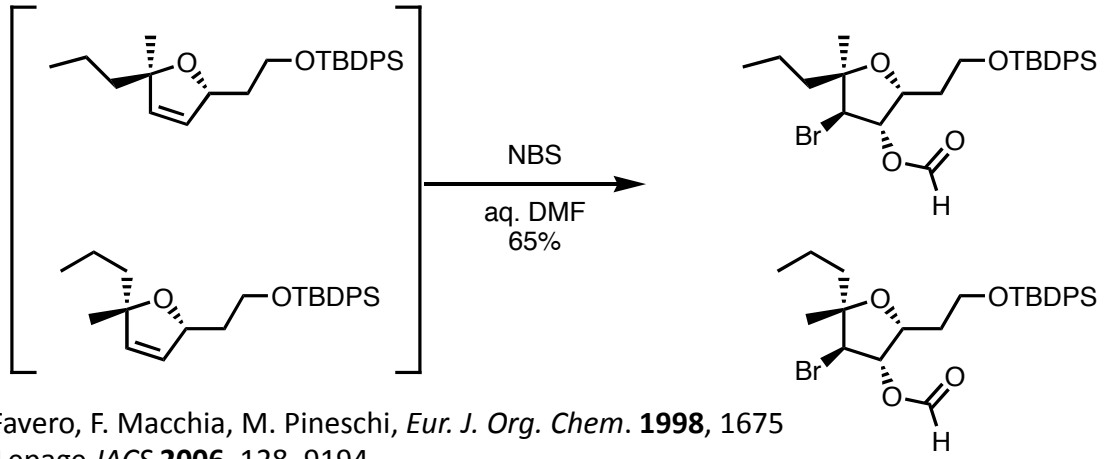


ligand

Bromo-esterification

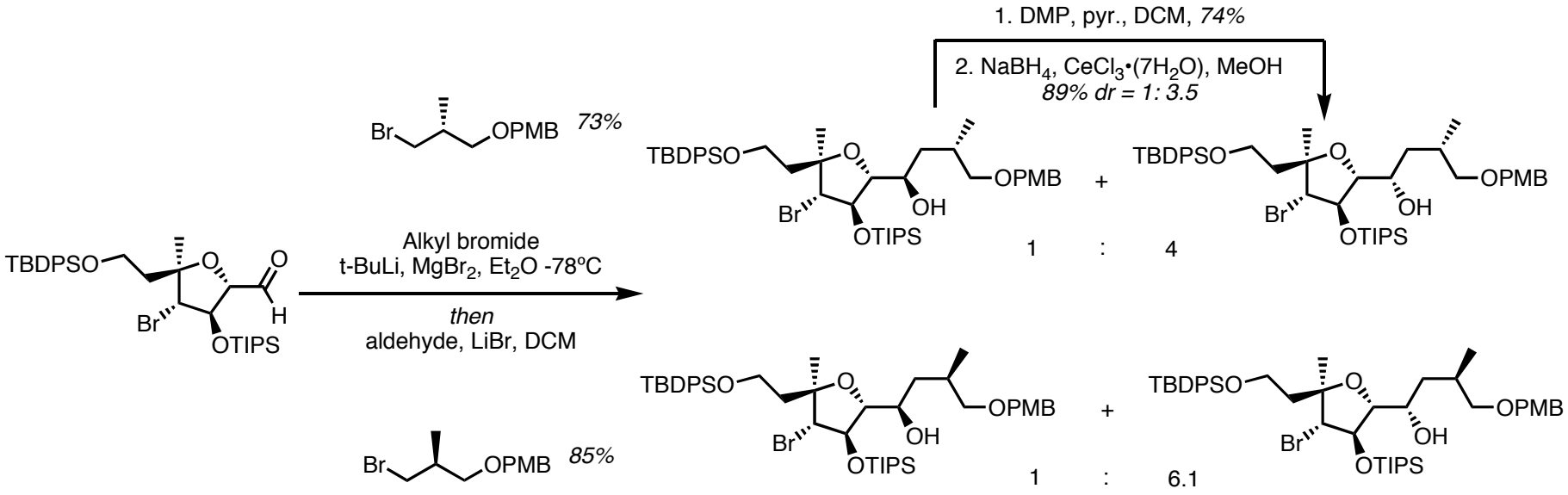


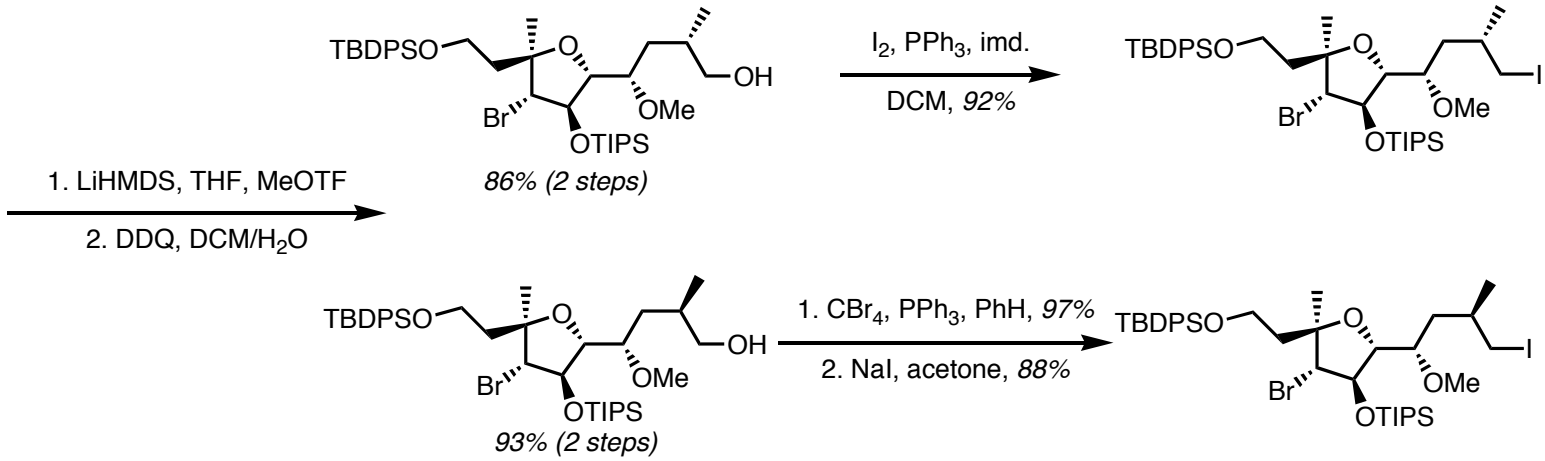




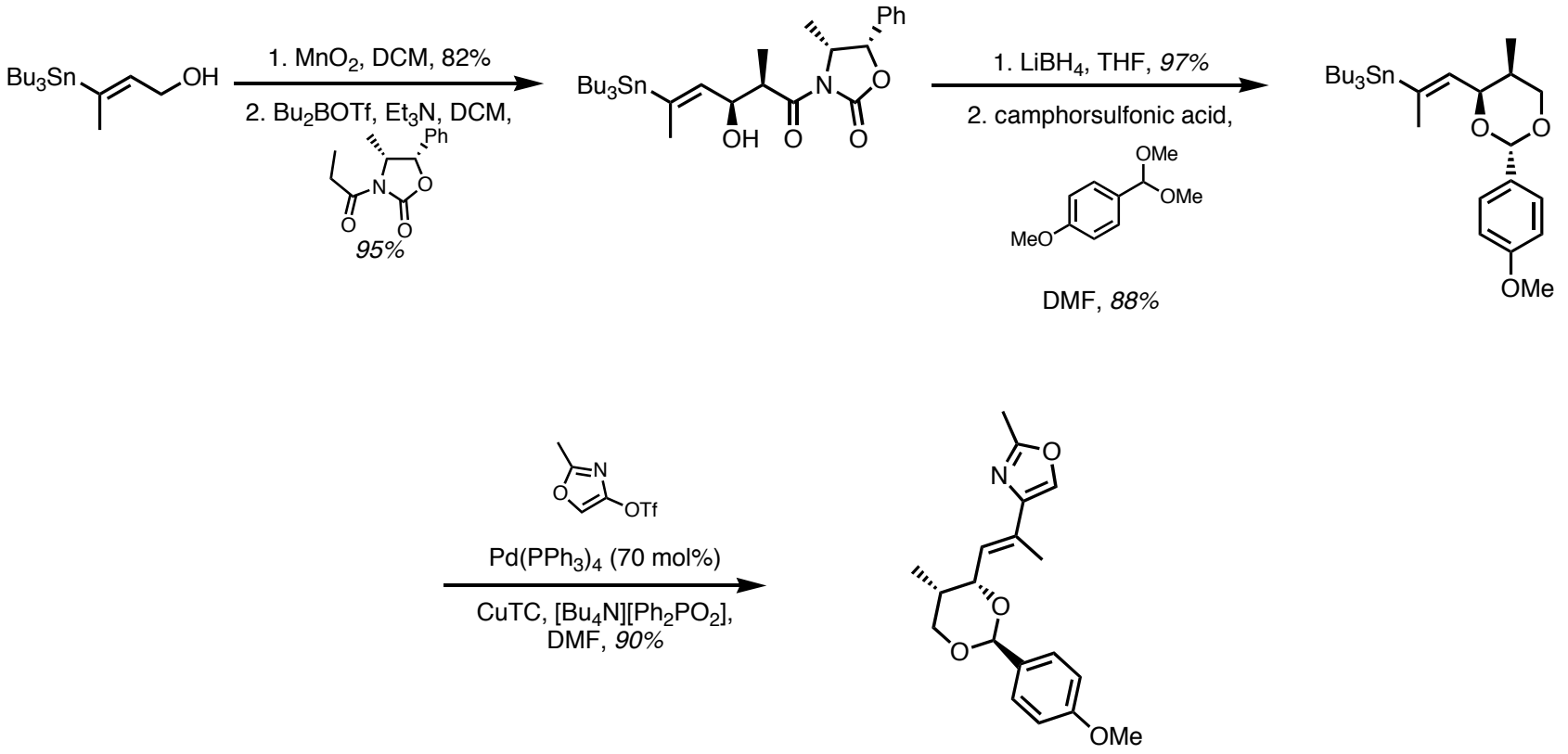
P. Crotti, V. Di Bussolo, L. Favero, F. Macchia, M. Pineschi, *Eur. J. Org. Chem*. **1998**, 1675
A. Furstner, E. Kattnig, O. Lepage *JACS* **2006**, 128, 9194

Formation of Furan Fragment

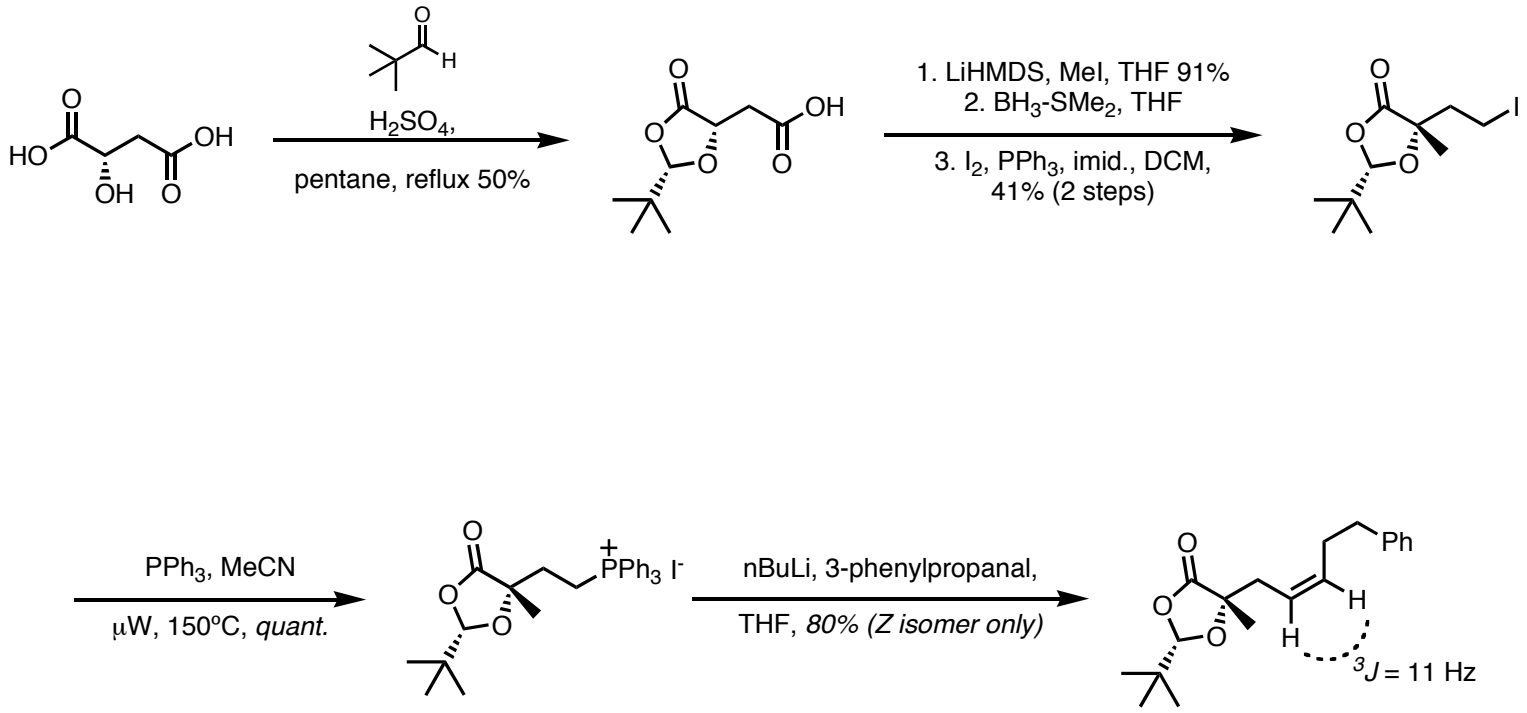




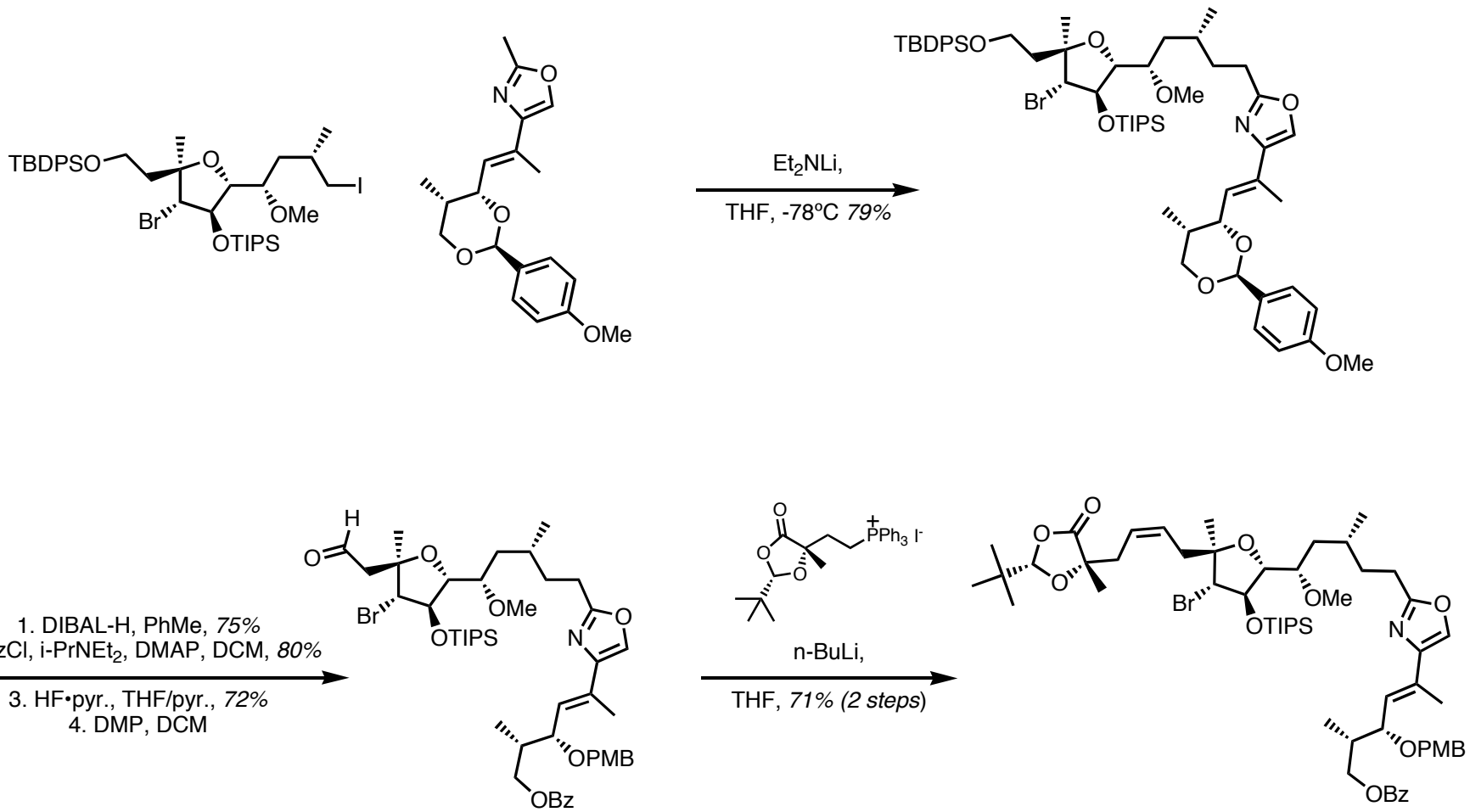
Formation of the Oxazole Fragment



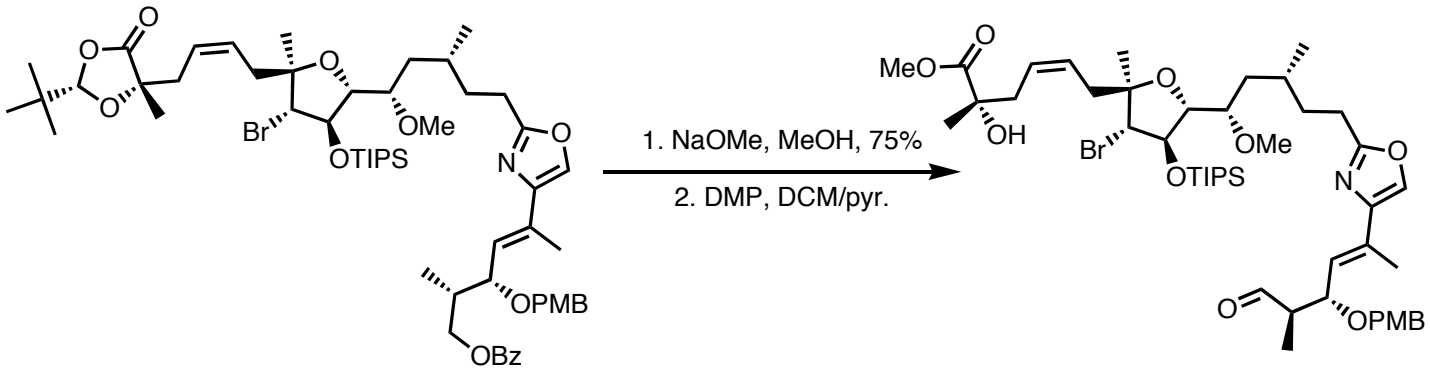
Formation of the Terminal Acid

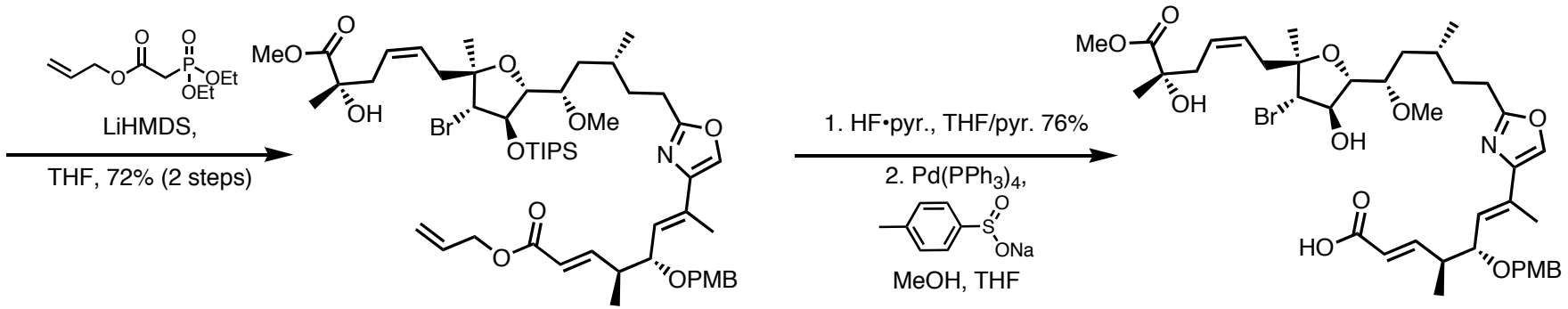


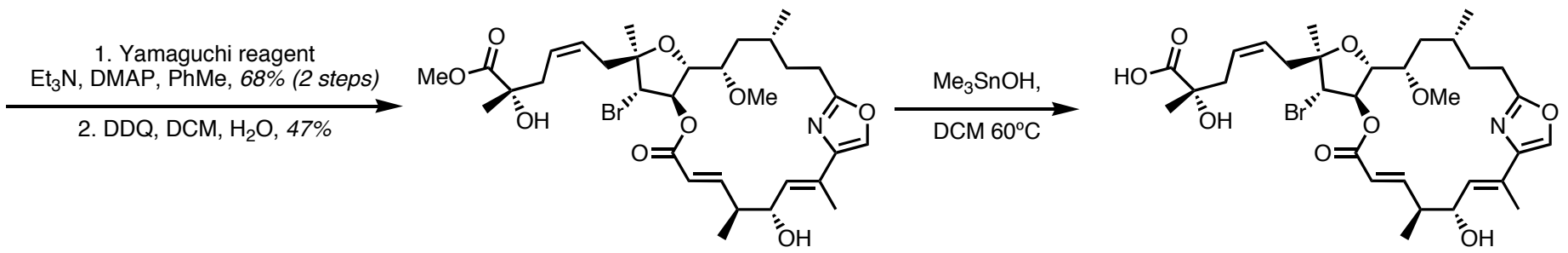
Coupling of the Fragments



Cyclization and Completion







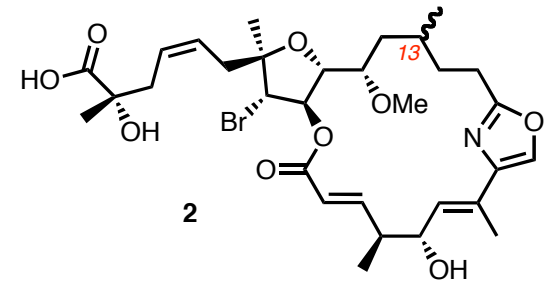
Doesn't match isolation data.

^{13}C Comparison

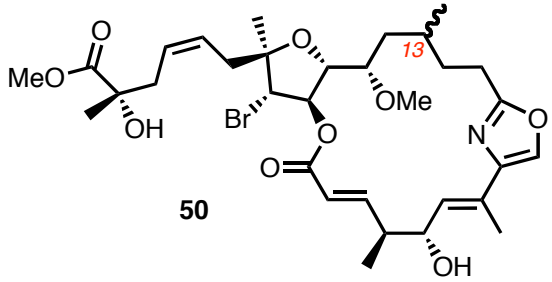
Table 1: Comparison of the ^{13}C NMR data of leiodolide B in [D_4]MeOH reported in the literature (75 MHz)[2] with the recorded data (150 MHz) for acid (13*R*)-**2** and the four diasteromeric esters **50** and **51** shown in Scheme 6.[a]

Position	Ref.	(13*R*)-**2**	(13*R*)-**50**	(13*S*)-**50**	(13*R*)-**51**	(13*S*)-**51**
1	166.6	166.7	166.7	166.7	166.6	166.9
2	122.8	121.5	121.5	121.5	121.8	121.7
3	153.1	153.1	153.2	153.5	153.3	153.5
4	45.1	44.7	44.7	44.5	45.6	46.2
5	71.7	72.0	72.0	72.0	71.9	71.6
6	131.2	128.3	128.3	128.0	128.9	129.5
7	125.5	128.4	128.4	129.2	129.1	128.4
8	143.3	143.4	143.1	143.6	143.7	143.5
9	134.5	135.2	135.2	135.1	134.8	135.5
10	166.4	166.5	166.5	166.5	166.6	167.1
11	25.7	25.8	25.8	25.1	25.2	26.0
12	33.9	33.9	33.9	34.0	34.5	35.6
13	30.5	29.4	29.4	30.4	29.2	31.5
14	36.7	37.0	37.0	38.7	36.7	39.9
15	78.0	77.9	77.9	79.0	78.3	79.6
16	80.5	80.9	80.9	83.7	80.9	83.7
17	78.4	78.7	78.5	79.2	78.3	77.8
18	16.3	15.5	15.5	15.6	15.9	16.7
19	13.7	14.1	14.1	14.3	14.4	14.2
20	20.7	20.9	20.9	20.2	20.9	21.1
21	58.0	58.0	58.0	59.1	58.0	59.9
22	56.2	56.1	55.9	56.0	55.8	55.4
23	84.0	84.5	84.5	84.7	84.4	84.2
24	37.6	37.4	37.3	37.3	37.5	37.8
25	126.5	127.8	127.9	127.9	127.9	127.8
26	130.4	128.6	128.4	128.4	128.5	128.5
27	39.2	39.1	39.2	39.2	39.2	39.2
28	76.4	75.4	75.7	75.7	75.8	75.7
29	182.7	179.1	177.5	177.5	177.5	177.5
30	26.0	25.9	25.9	26.1	26.0	26.4
31	26.4	26.0	25.9	25.9	25.9	25.9

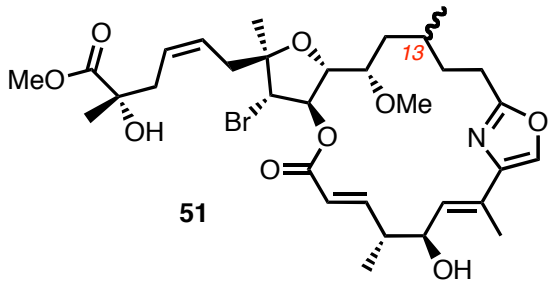
[a] The heat map color-codes differences in chemical shift considered to be beyond the experimental error as follows: red: $\Delta\delta \geq 1$ ppm; blue: 0.5 ppm $\leq \Delta\delta < 1$ ppm; green: 0.3 ppm $\leq \Delta\delta < 0.5$ ppm. For a comparison of the ^1H NMR data, see the Supporting Information.



2



50



51

Summary

- Completed the proposed structure of leiodolide B.
- The actual structure of leiodolide B is left ambiguous.
- Aim to complete the more carefully characterized leiodolide A to assess the structure of this family of compounds.