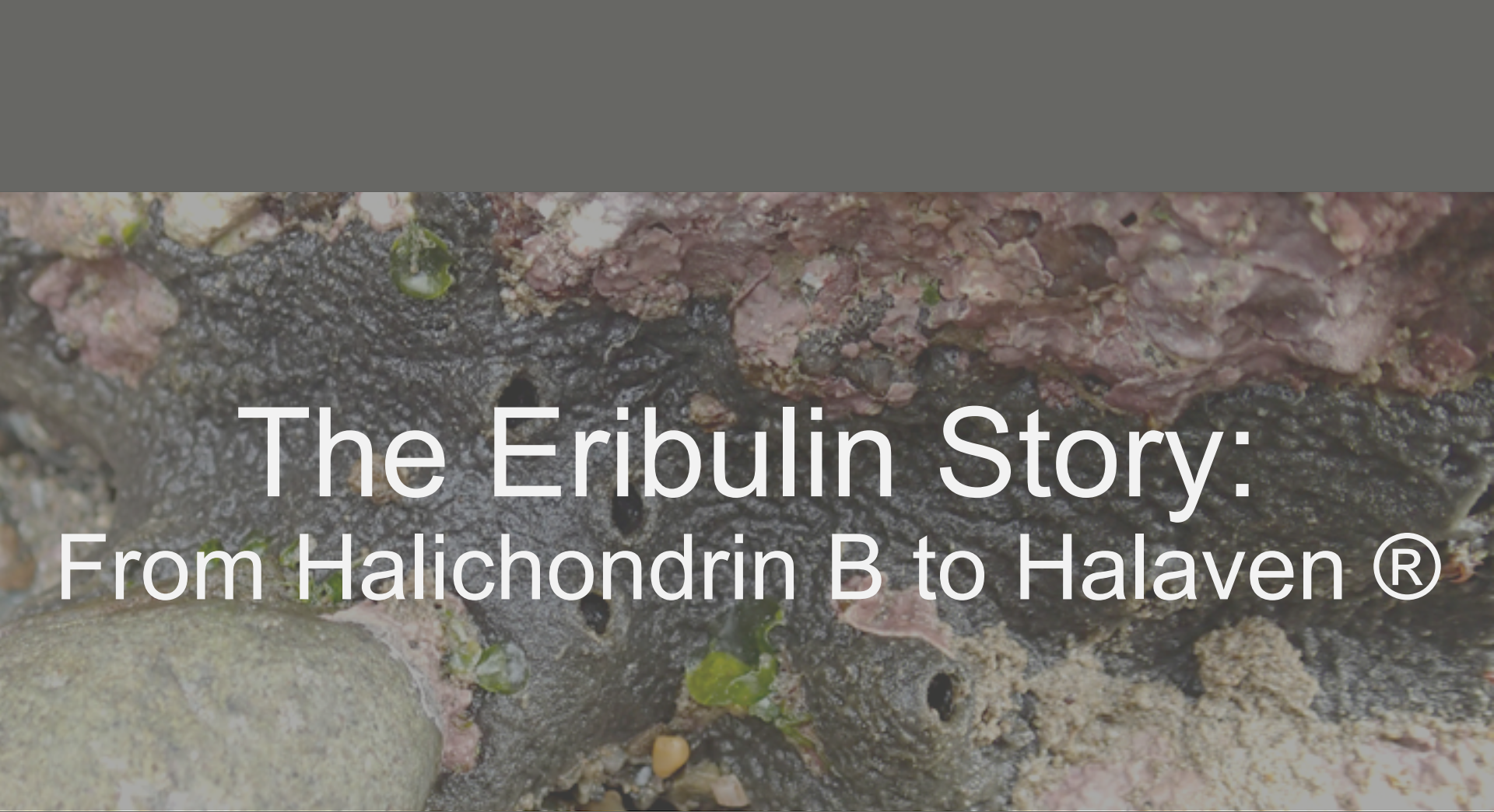




The Eribulin Story: From Halichondrin B to Halaven ®

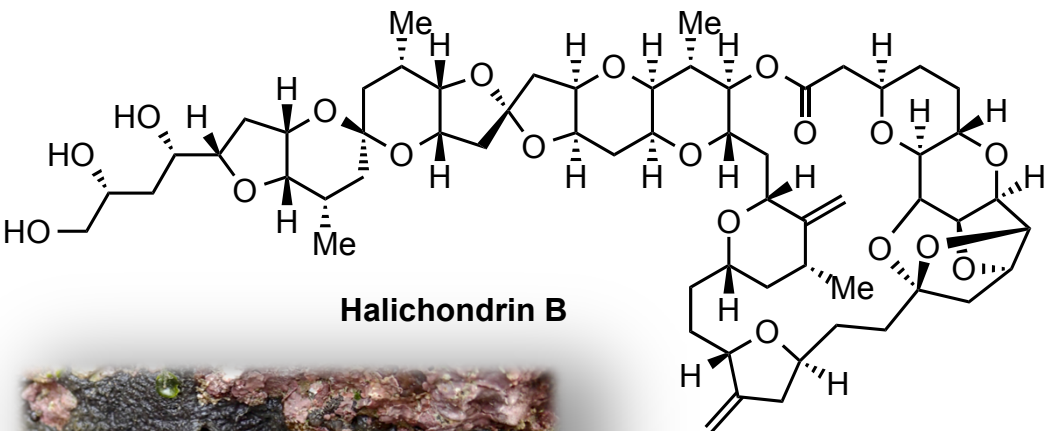
Chelsea Harmon

Looper Group

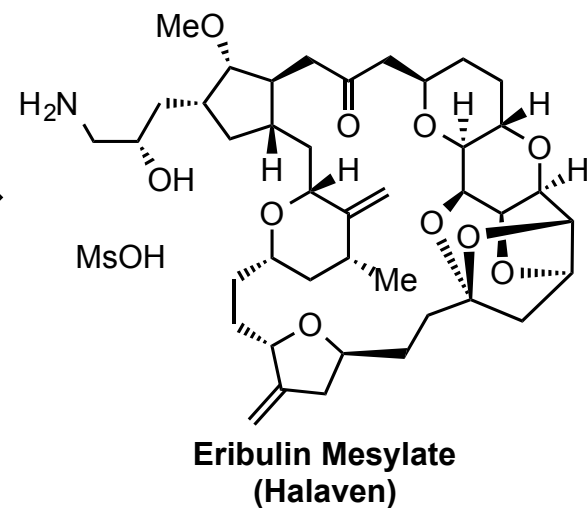
April

Synthesis Club

The Eribulin Story



Halichondrin B



Eribulin Mesylate (Halaven)



Halichondria okadai
Isolation 1986



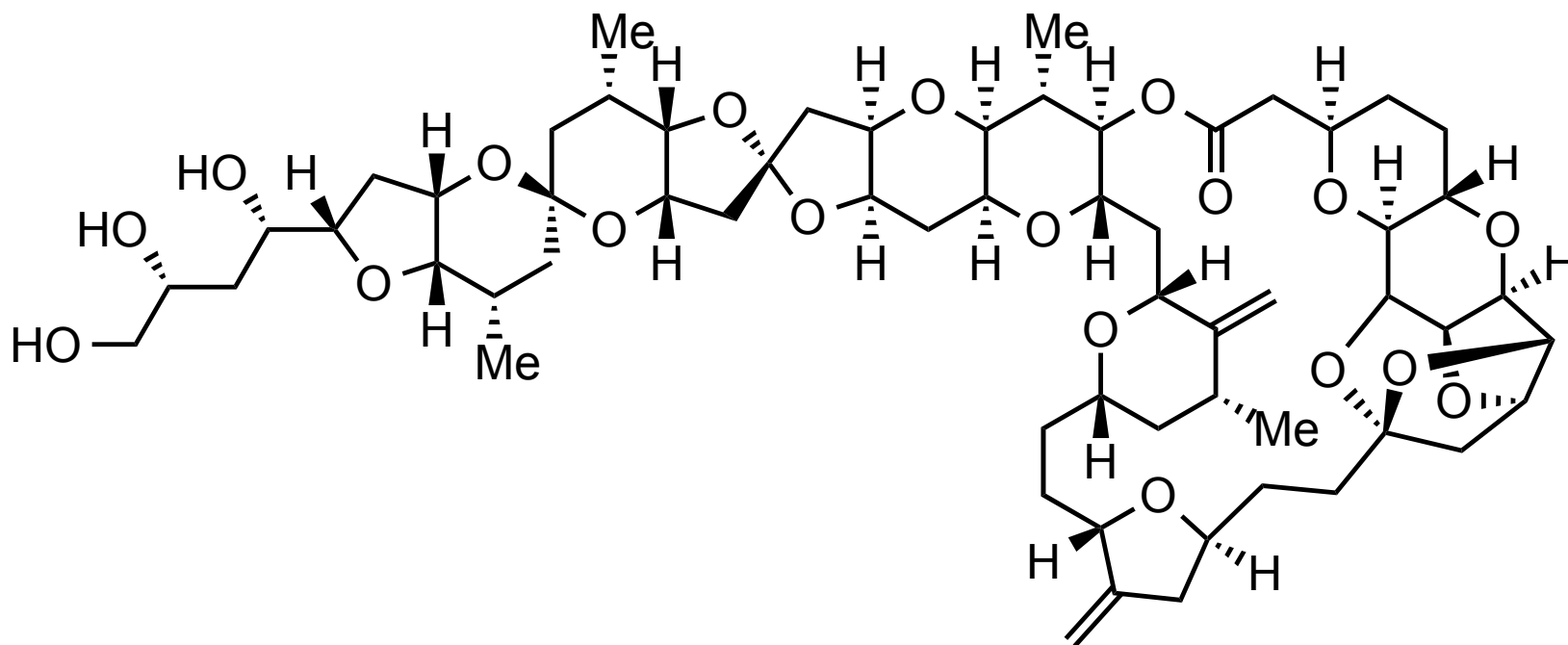
Kishi completed the first total synthesis in 1992



Eribulin
discovered in
2004

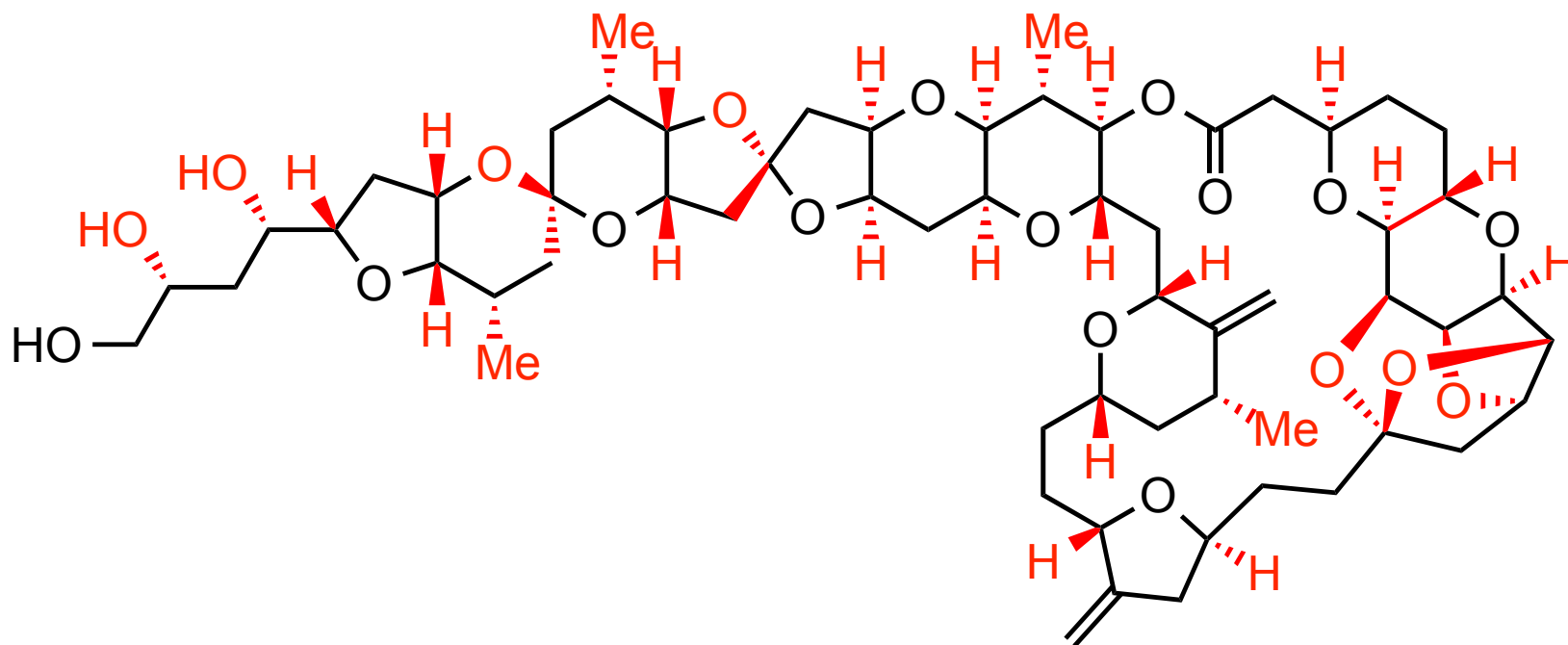
Halichondrin B

IC₅₀ of 0.0093 ng/mL in B-16 melanoma cell cytotoxicity assay



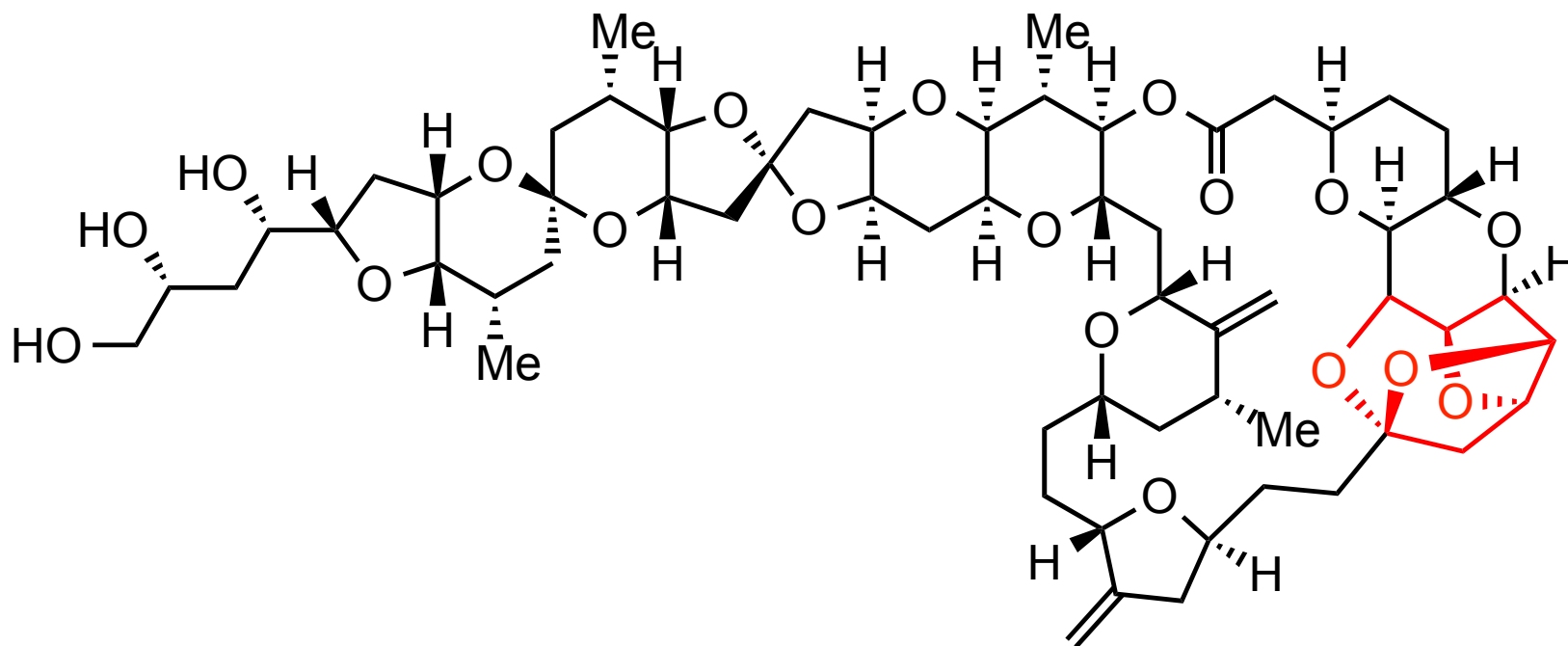
Halichondrin B

31 Stereocenters



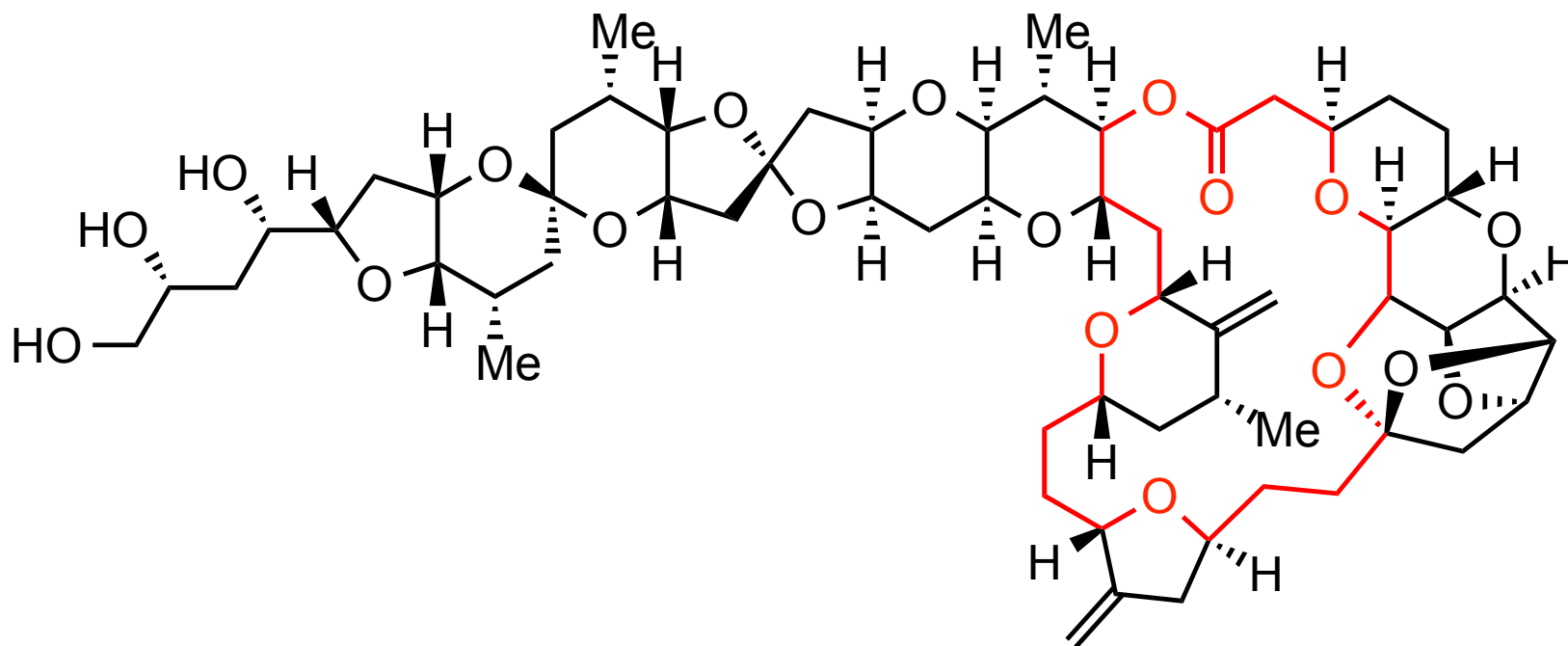
Halichondrin B

2,6,9-trioxatricyclo[3.3.2.0]decane ring system



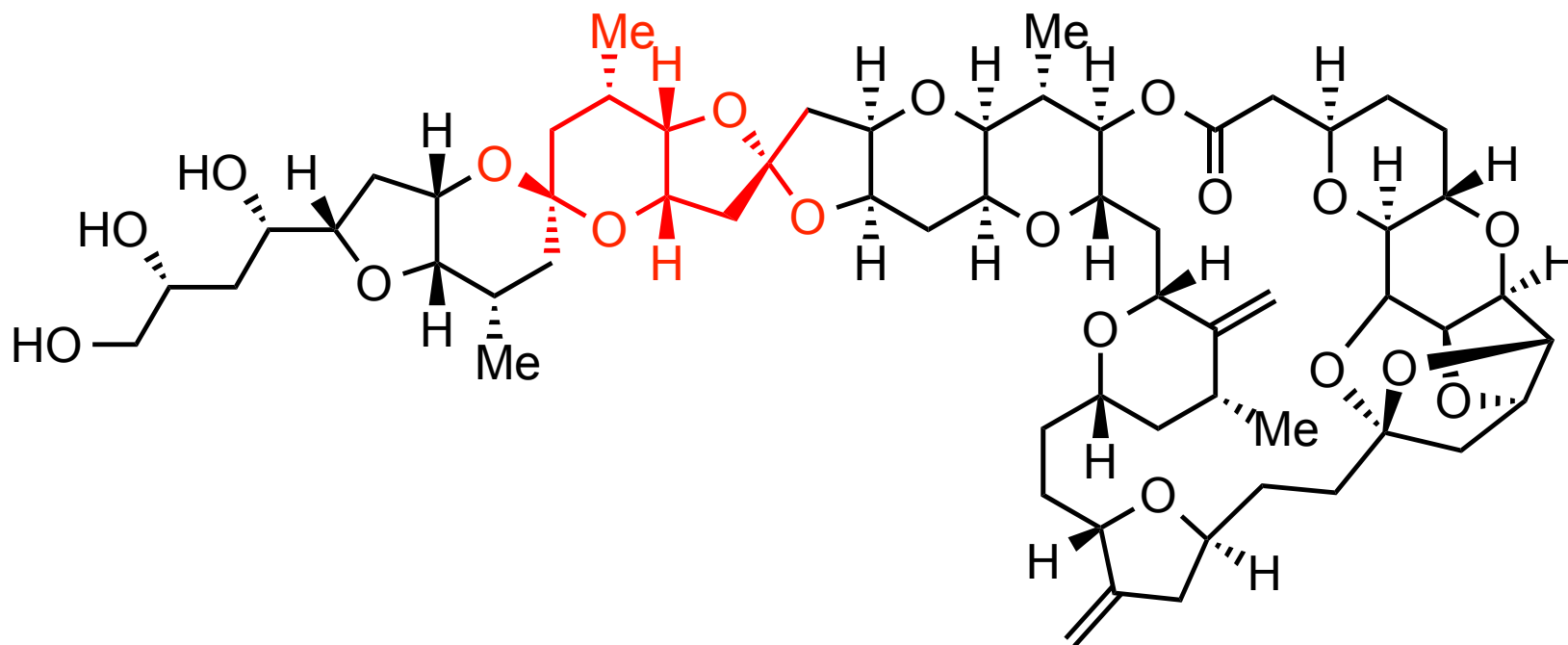
Halichondrin B

22-Membered Macrocycle

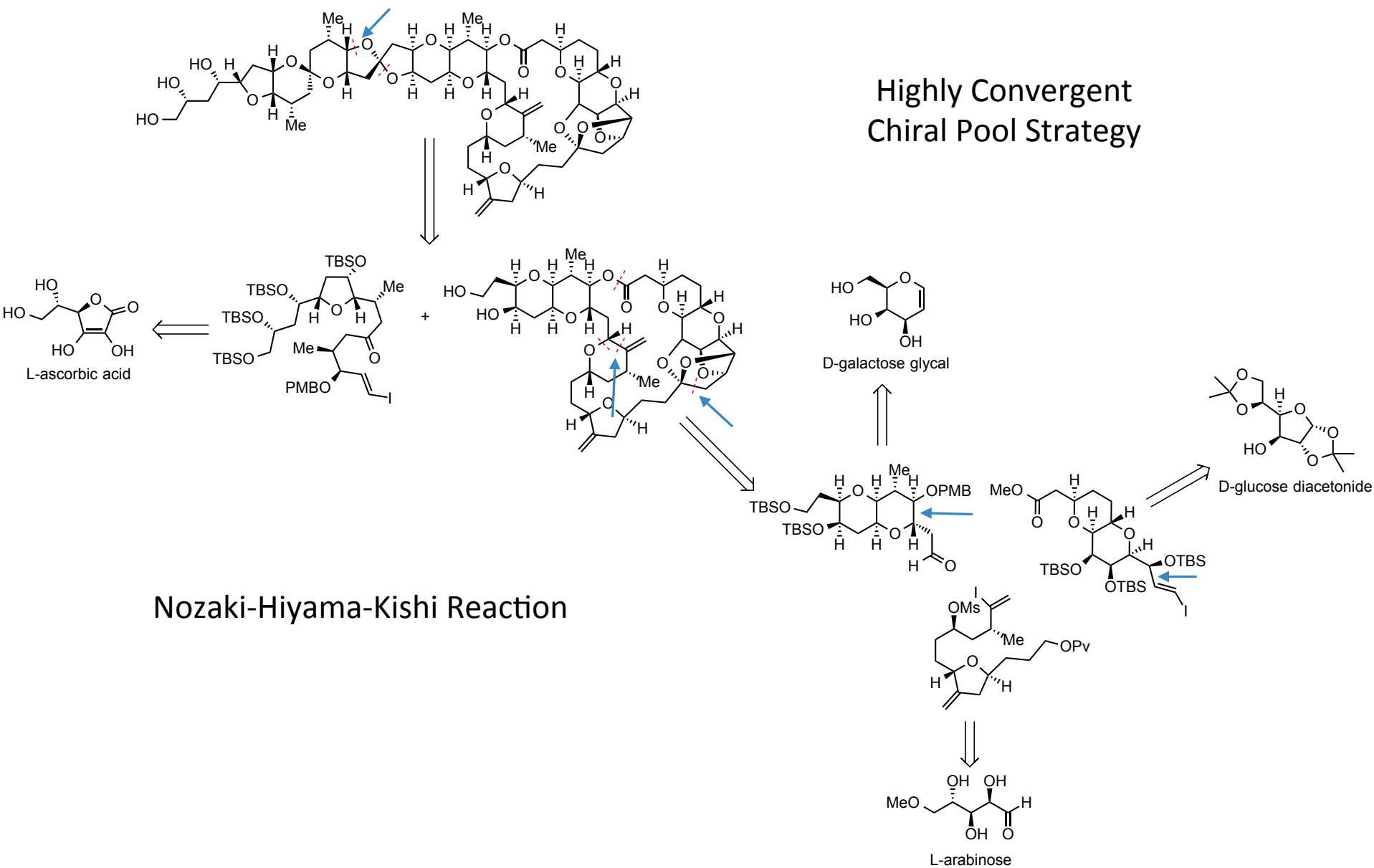


Halichondrin B

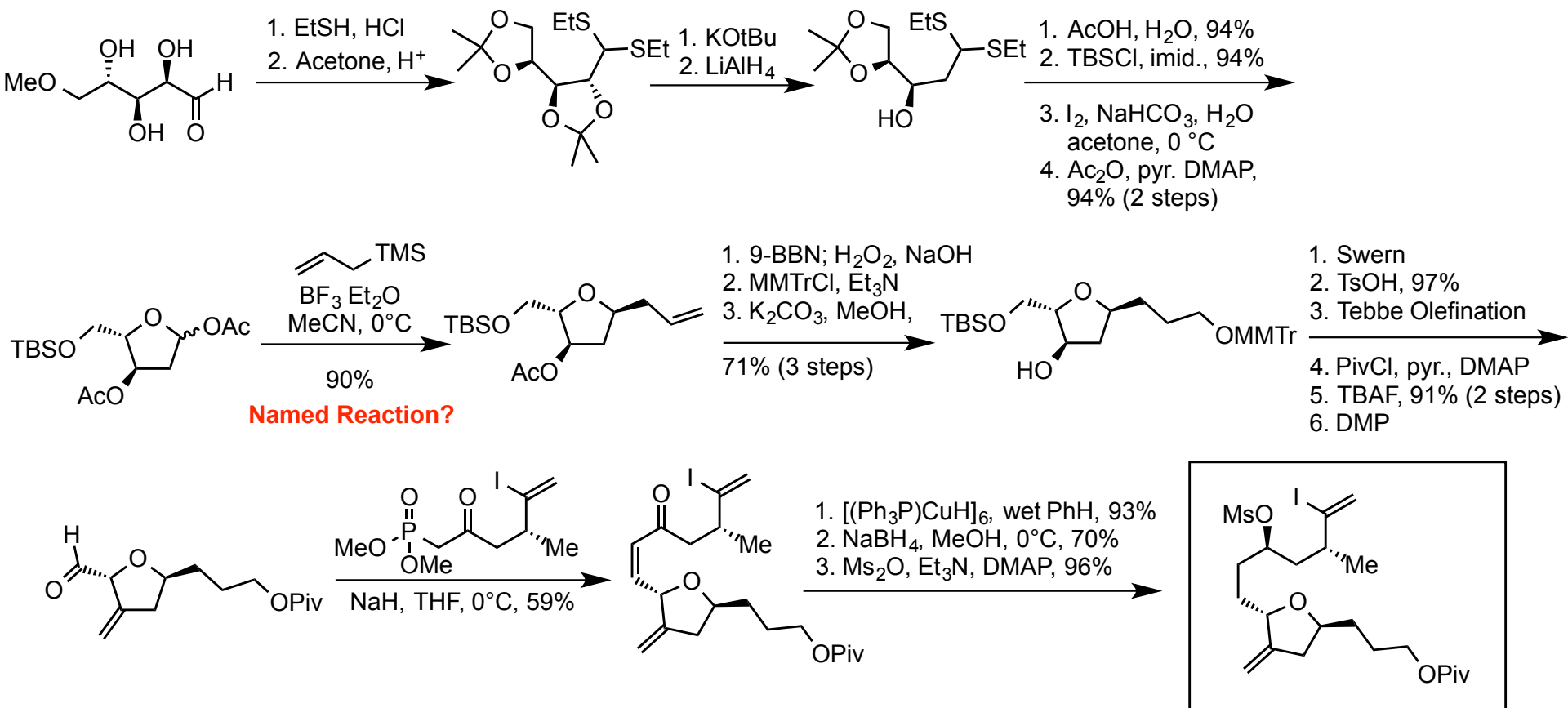
Two Spiro-Ketal Formations



Kishi Total Synthesis of Halichondrin B

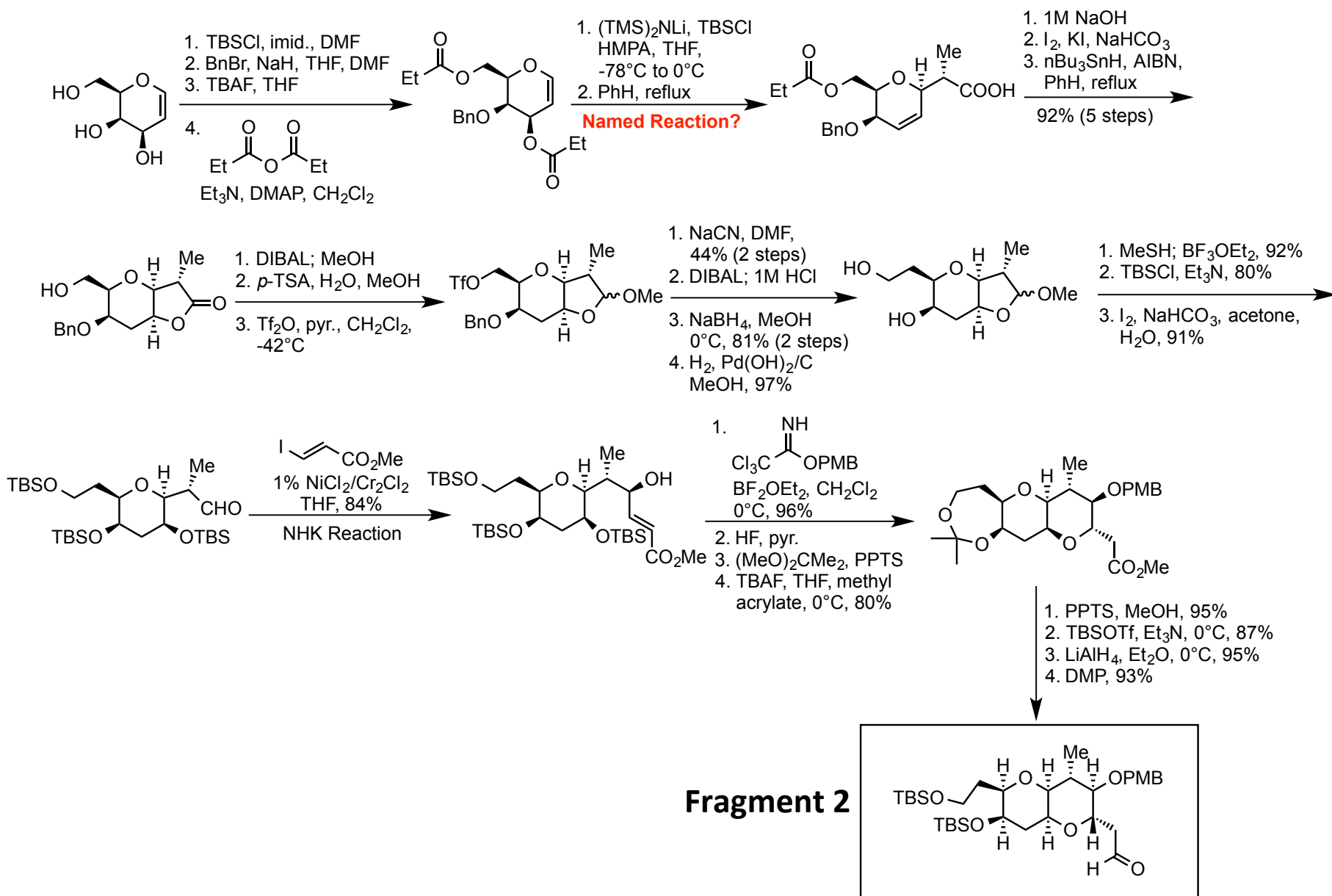


Kishi Total Synthesis of Halichondrin B

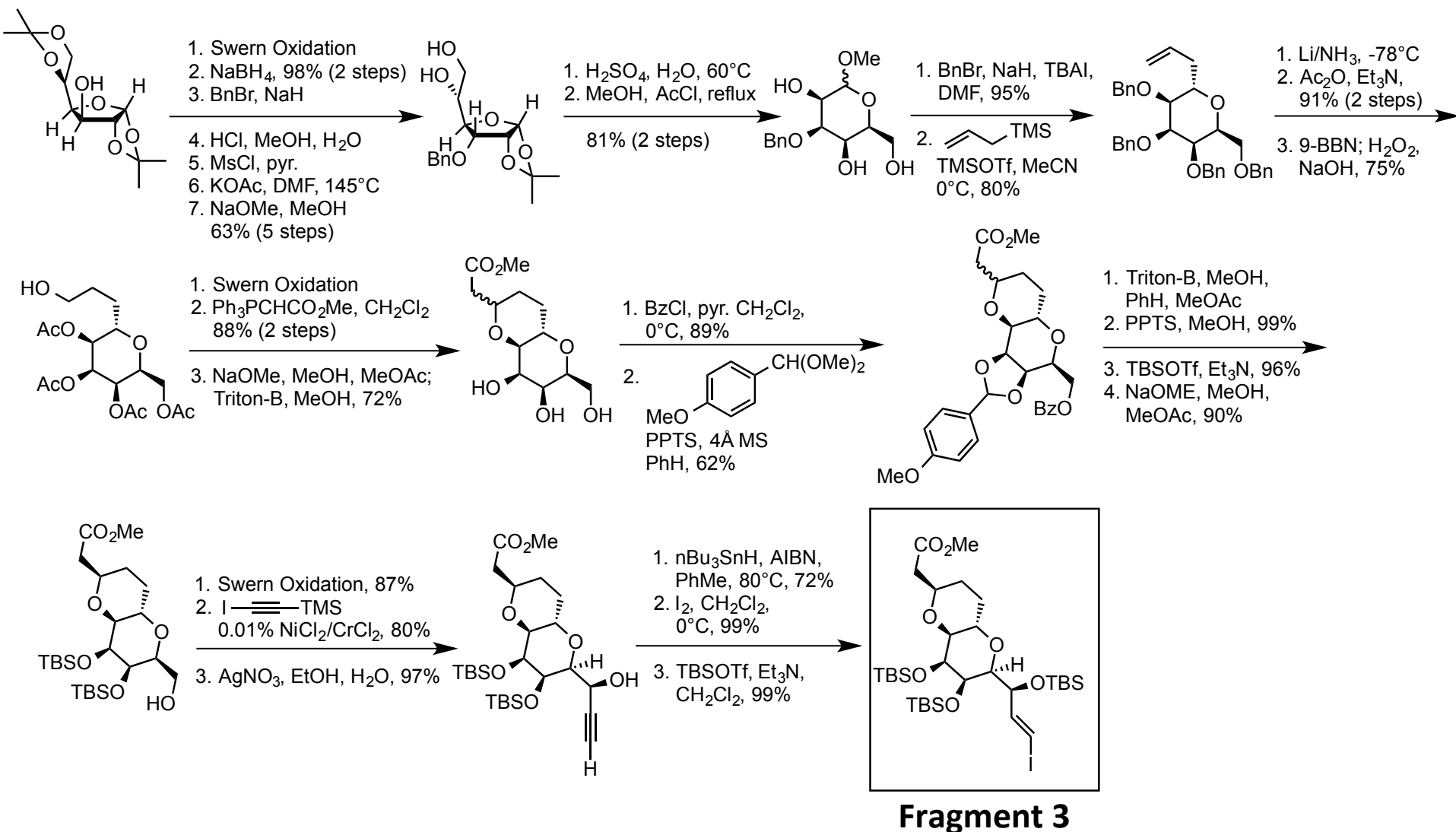


Named Reaction?

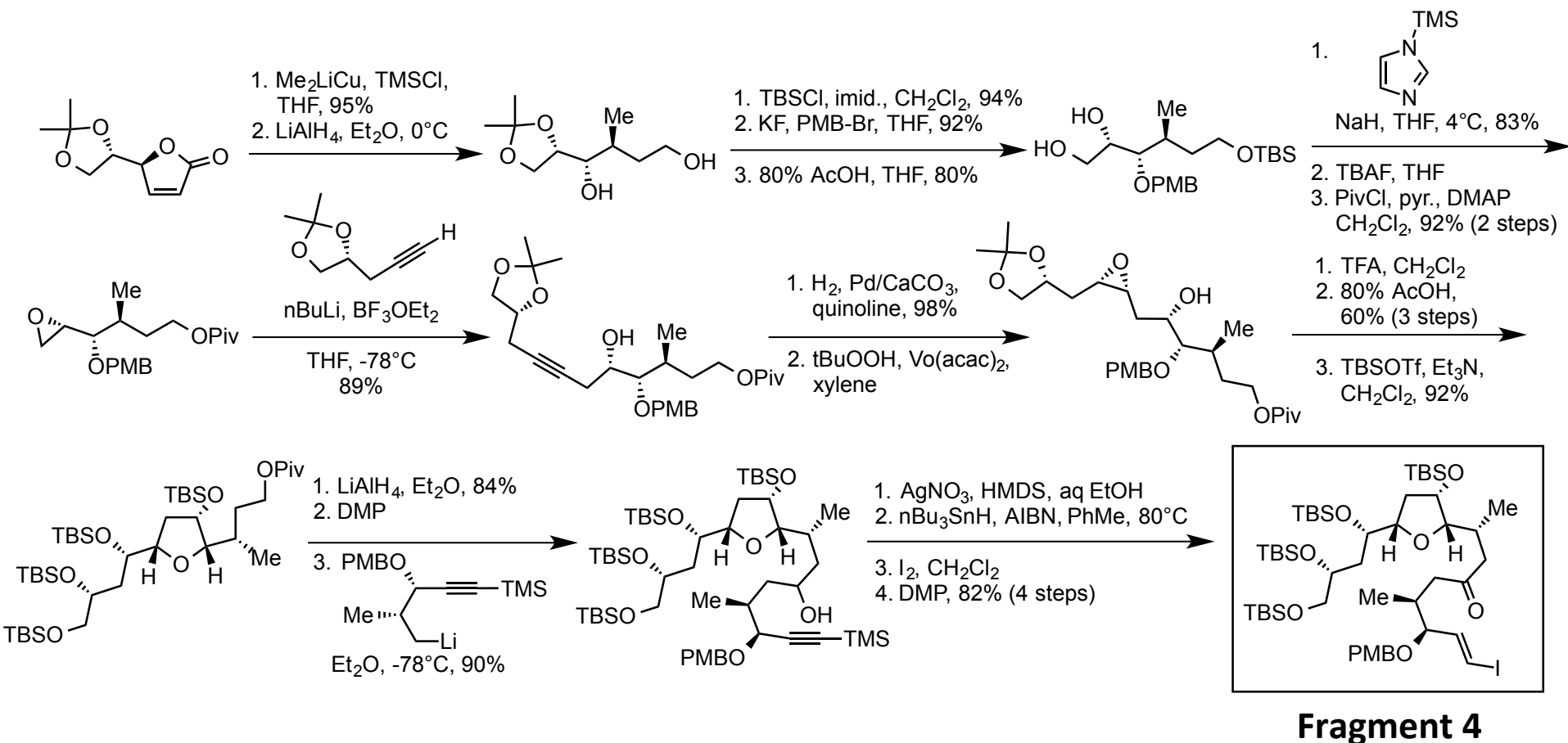
Kishi Total Synthesis of Halichondrin B



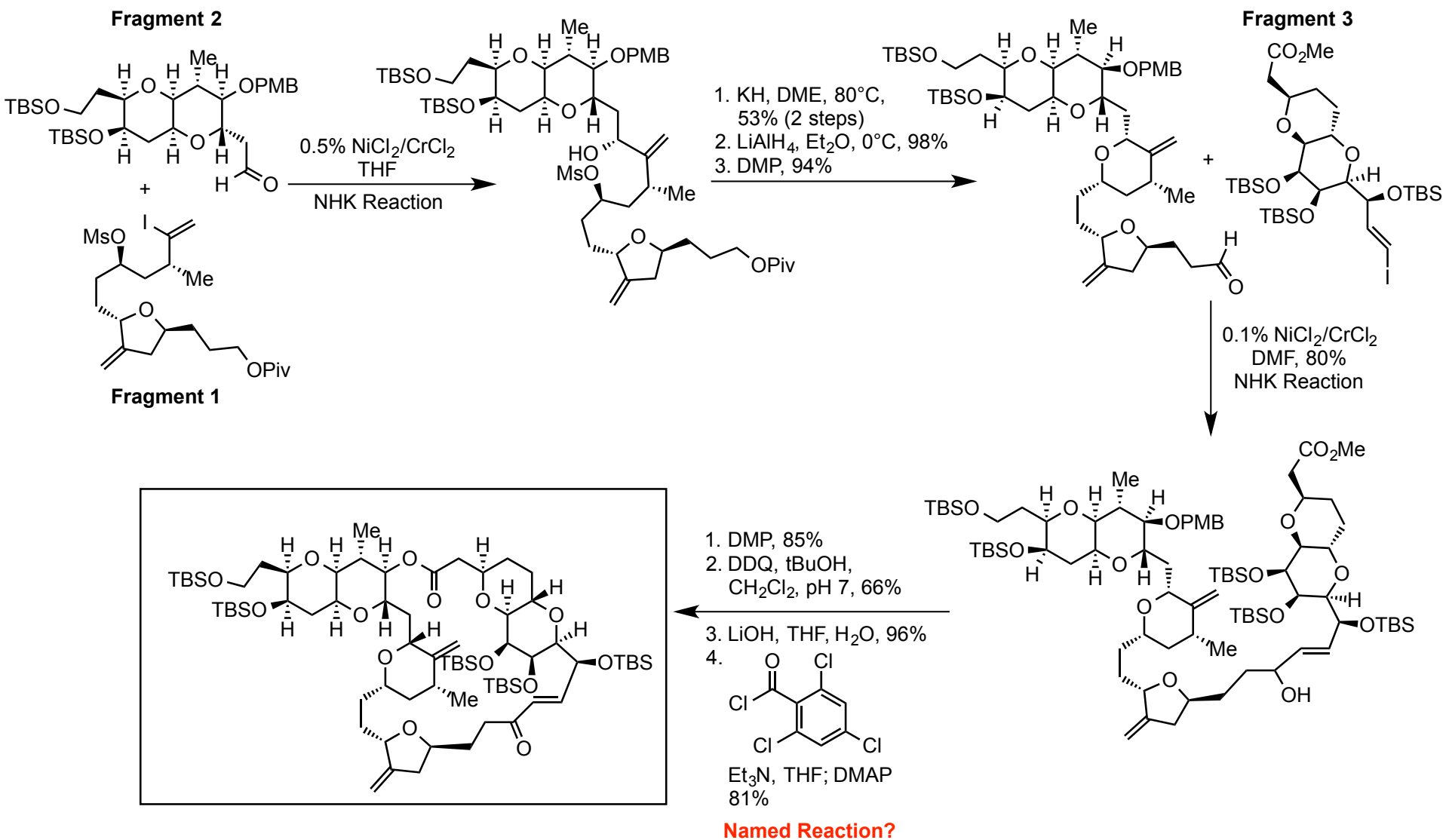
Kishi Total Synthesis of Halichondrin B



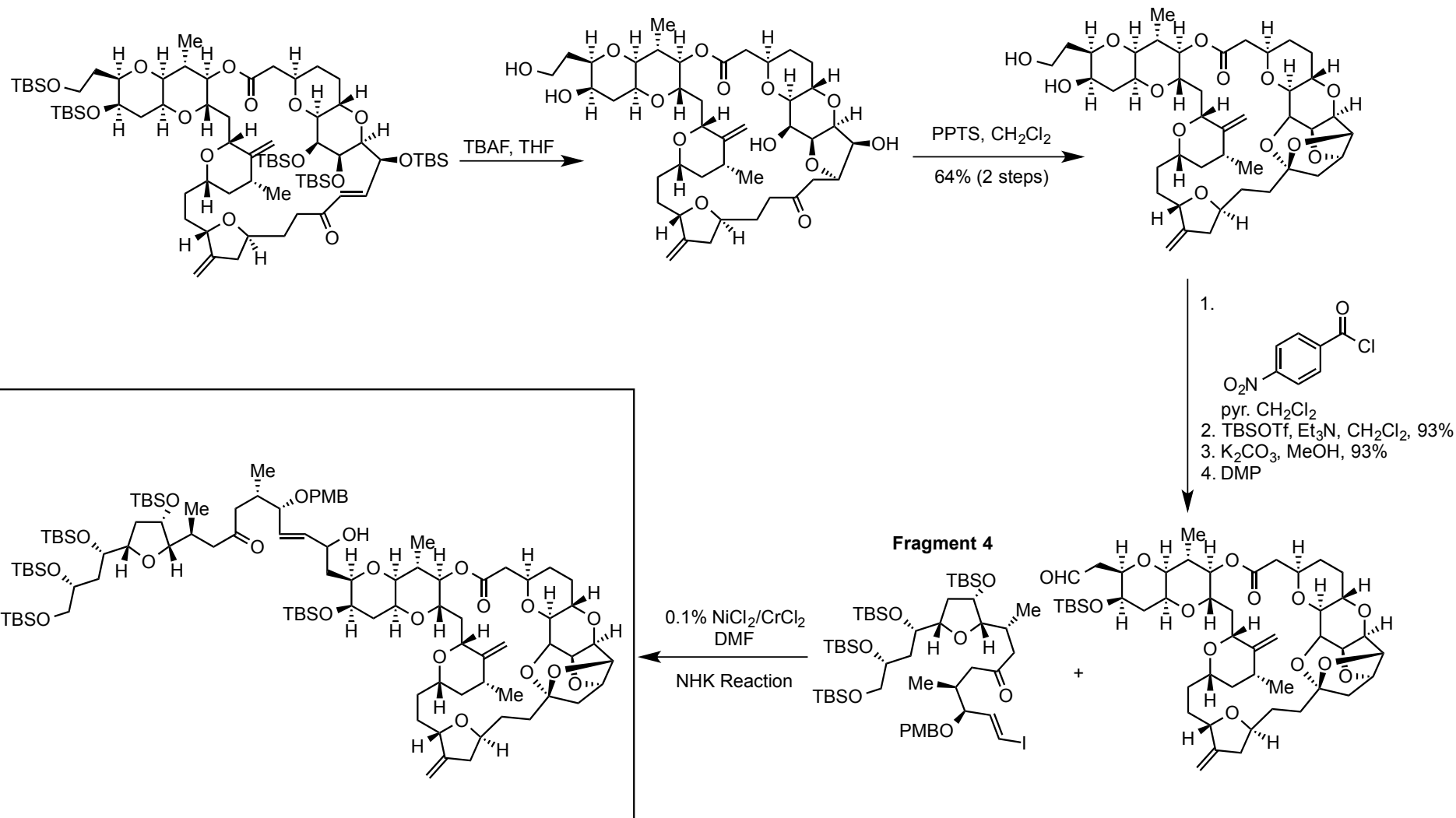
Kishi Total Synthesis of Halichondrin B



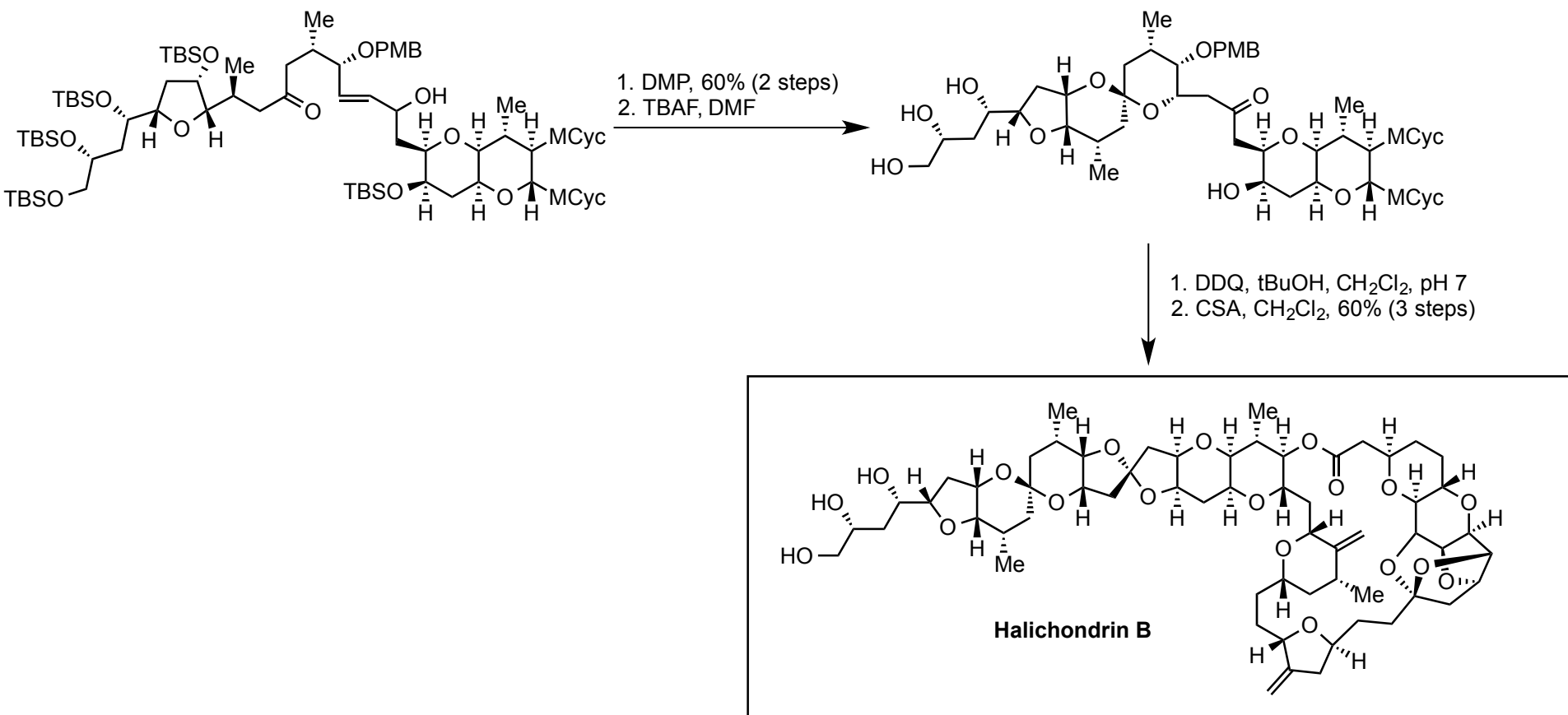
Kishi Total Synthesis of Halichondrin B



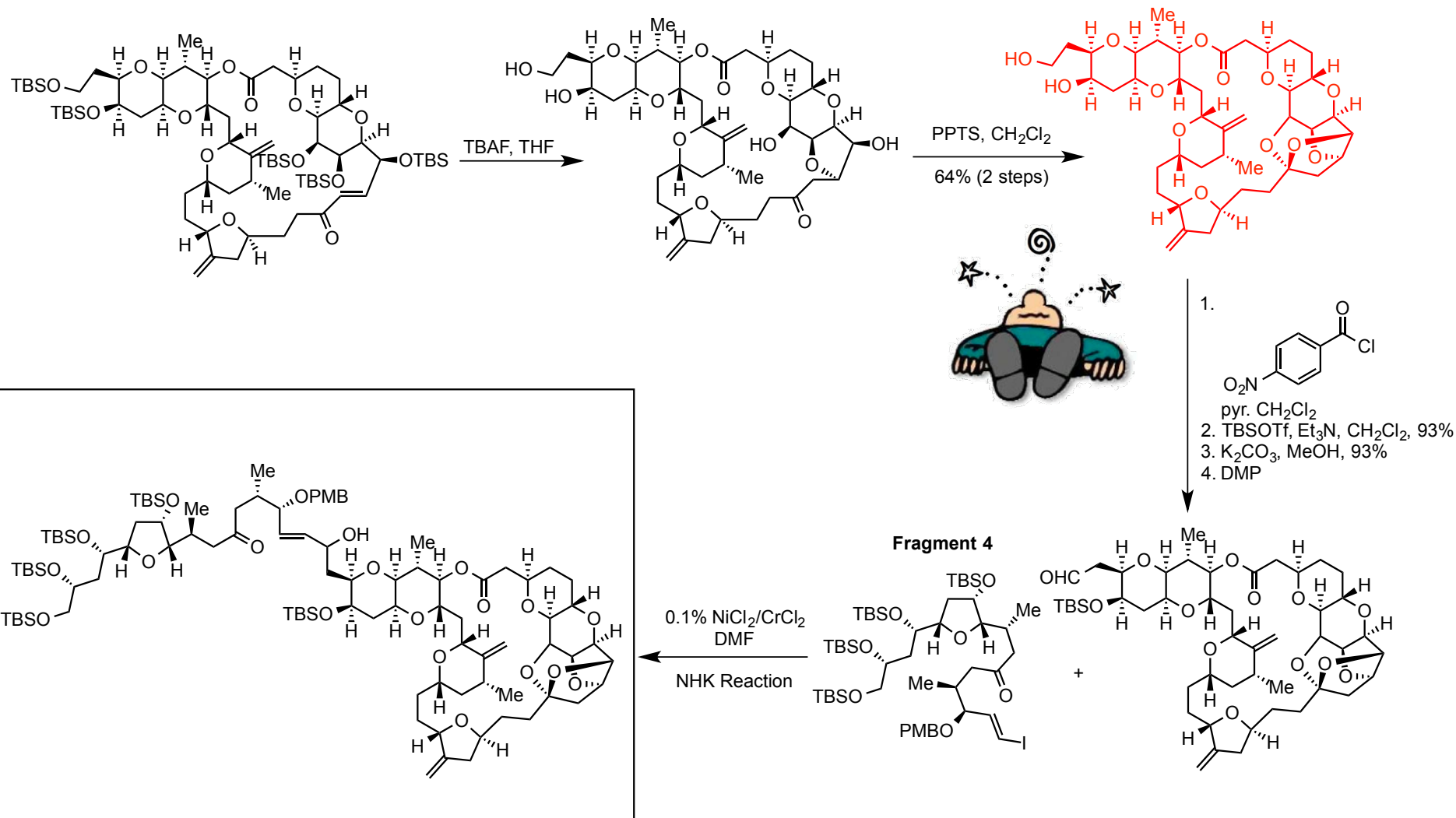
Kishi Total Synthesis of Halichondrin B



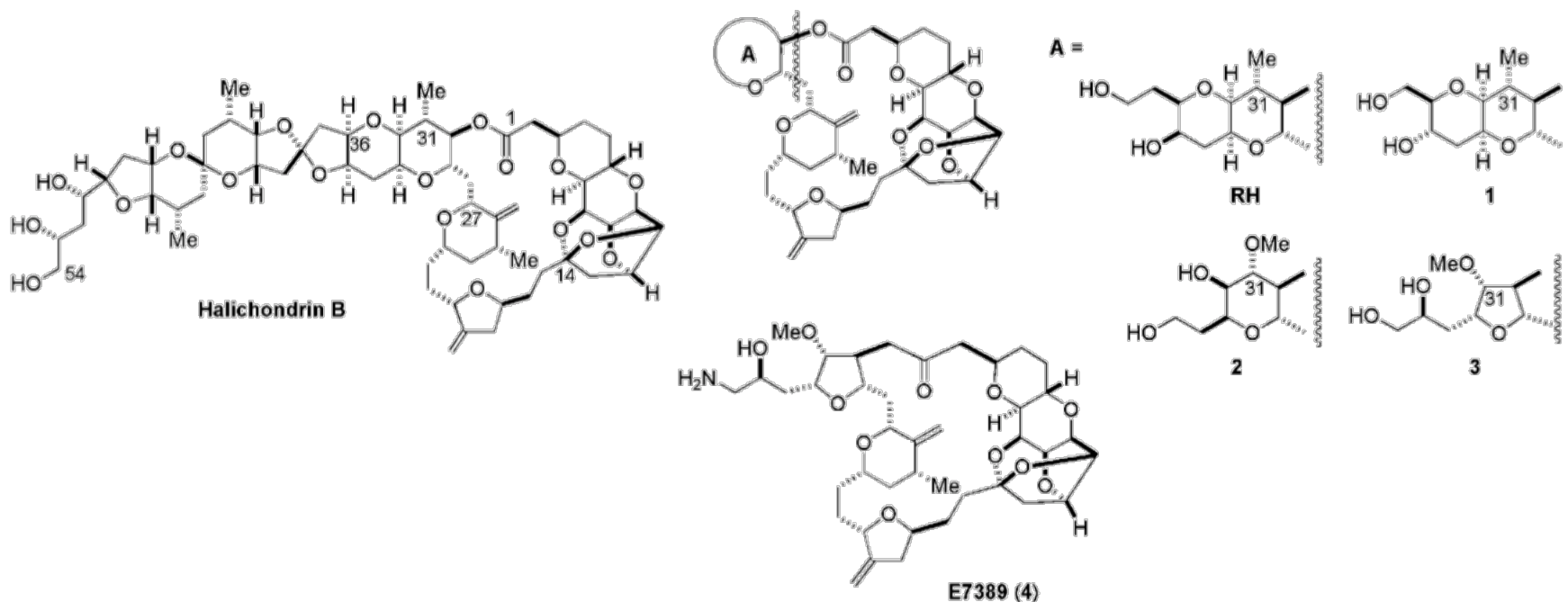
Kishi Total Synthesis of Halichondrin B



Eastern Fragment Discovery

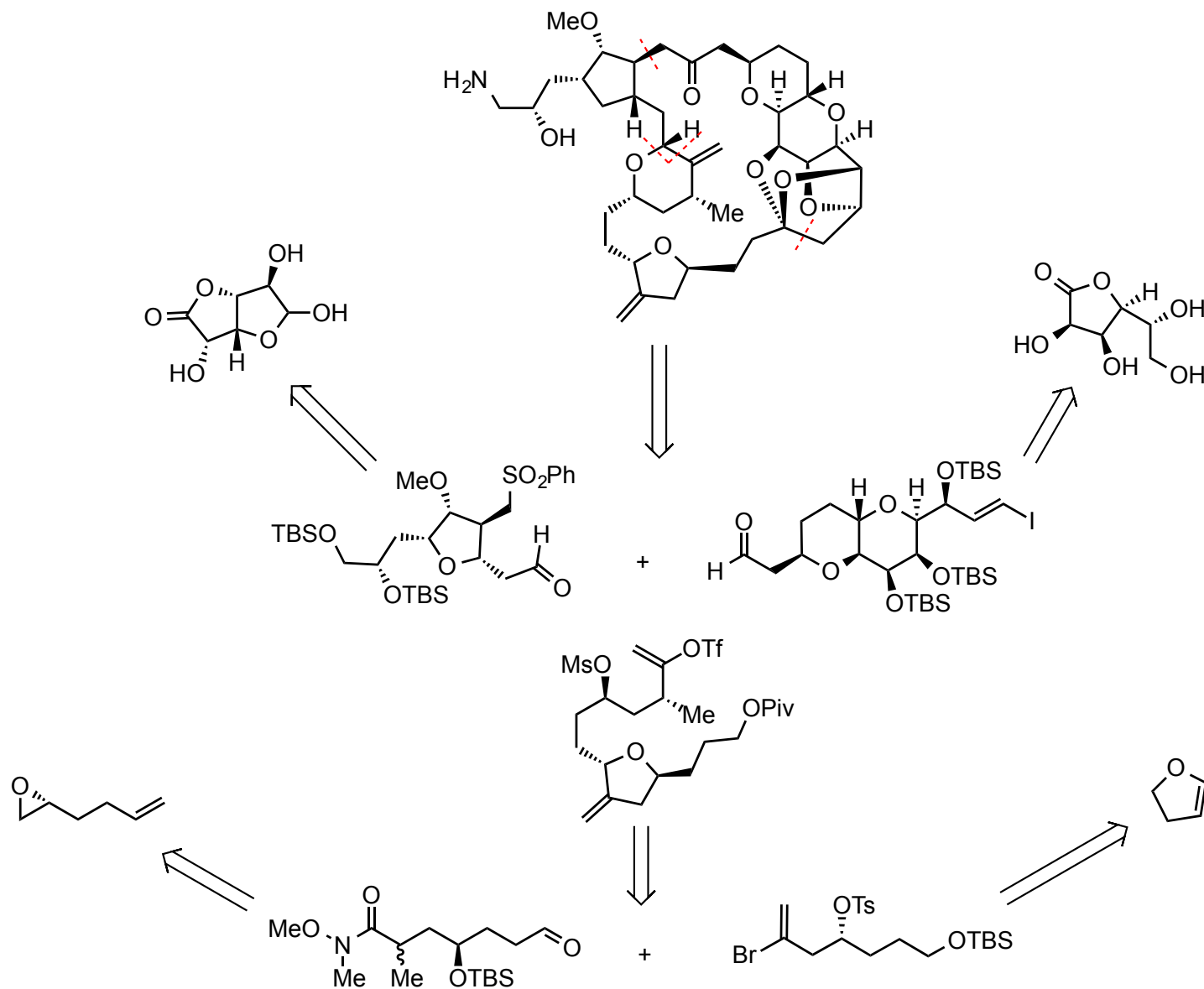


Discovery of the Eastern Fragment's Activity

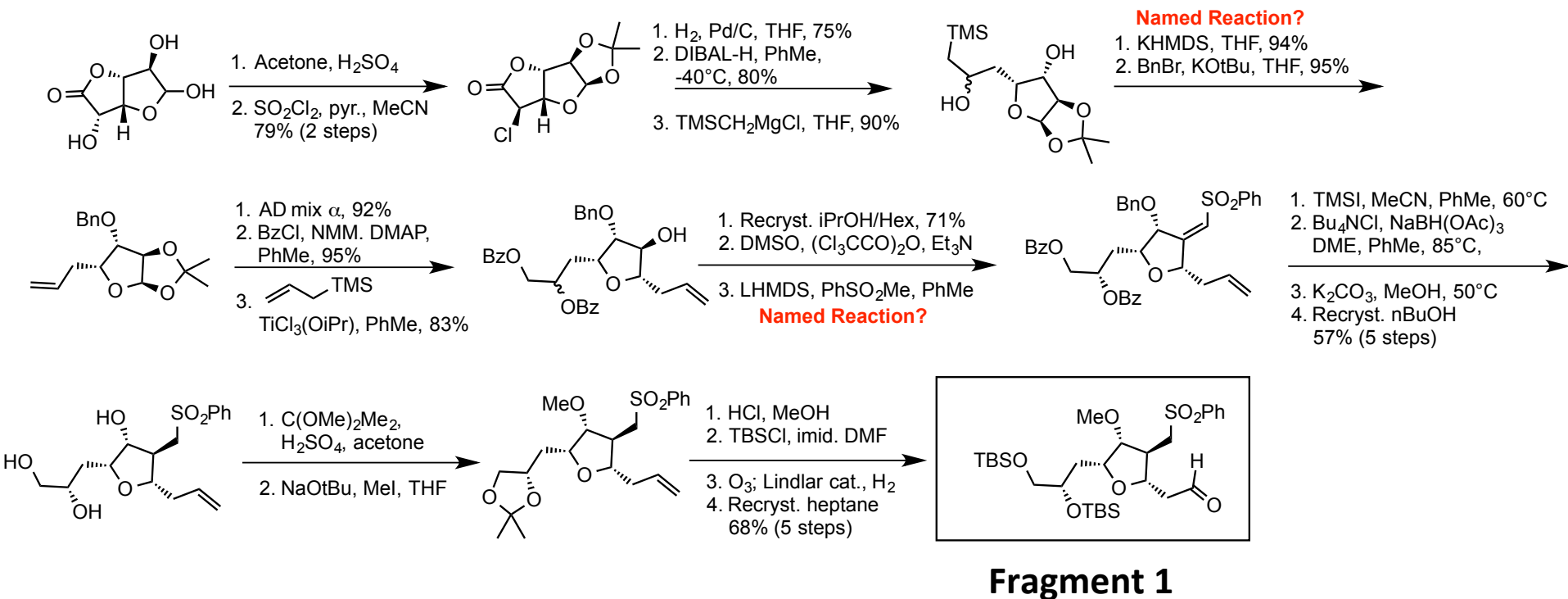


Compound	DLD-1 IC ₅₀ , nM	U937 IC ₉₉ , 0h, nM	U937 IC ₉₉ , 10h, nM	Reversibility Ratio	Fold Resistance
HB	0.74 ± 0.03	8	25	3	2.8
1	3.4 ± 0.40	9	220	24	12
2	1.8 ± 0.00	10	300	30	10
3	0.67 ± 0.09	2	15	8	6.2
4	13.0 ± 0.20	10	10	1	15

First Generation Process Synthesis of Eribulin Mesylate by Eisai

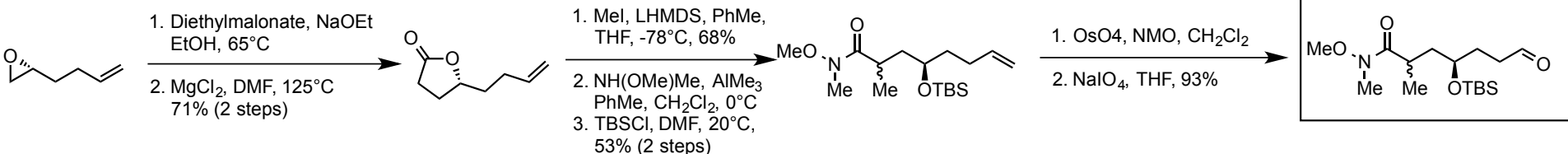


First Generation Process Synthesis of Eribulin Mesylate by Eisai

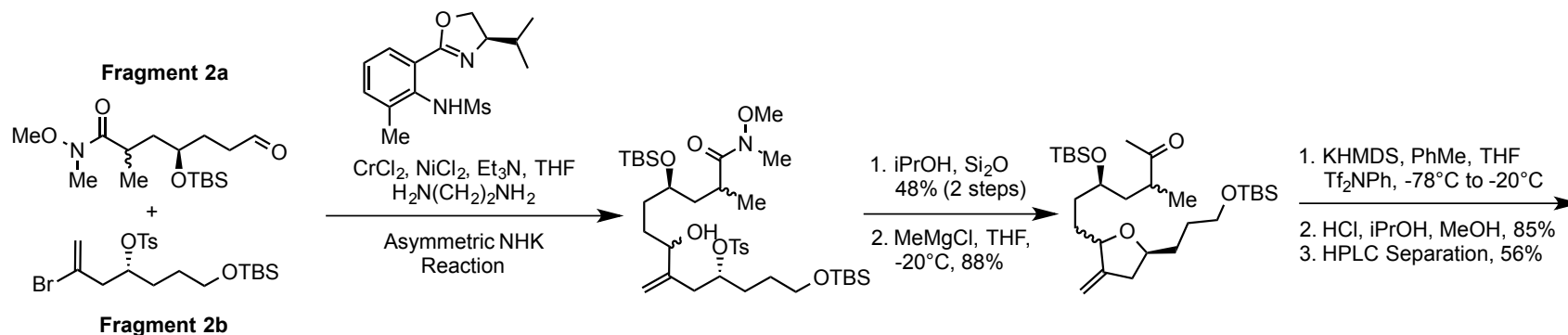
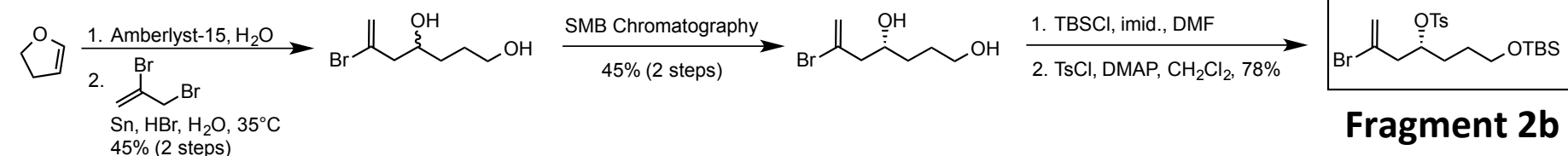


First Generation Process Synthesis of Eribulin Mesylate by Eisai

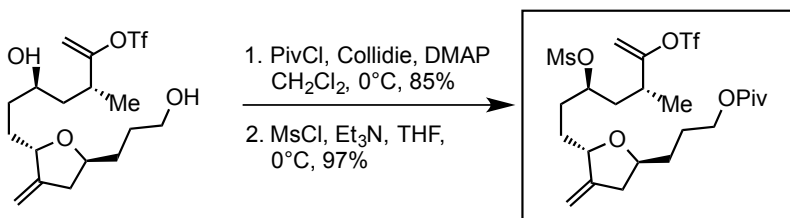
Fragment 2a



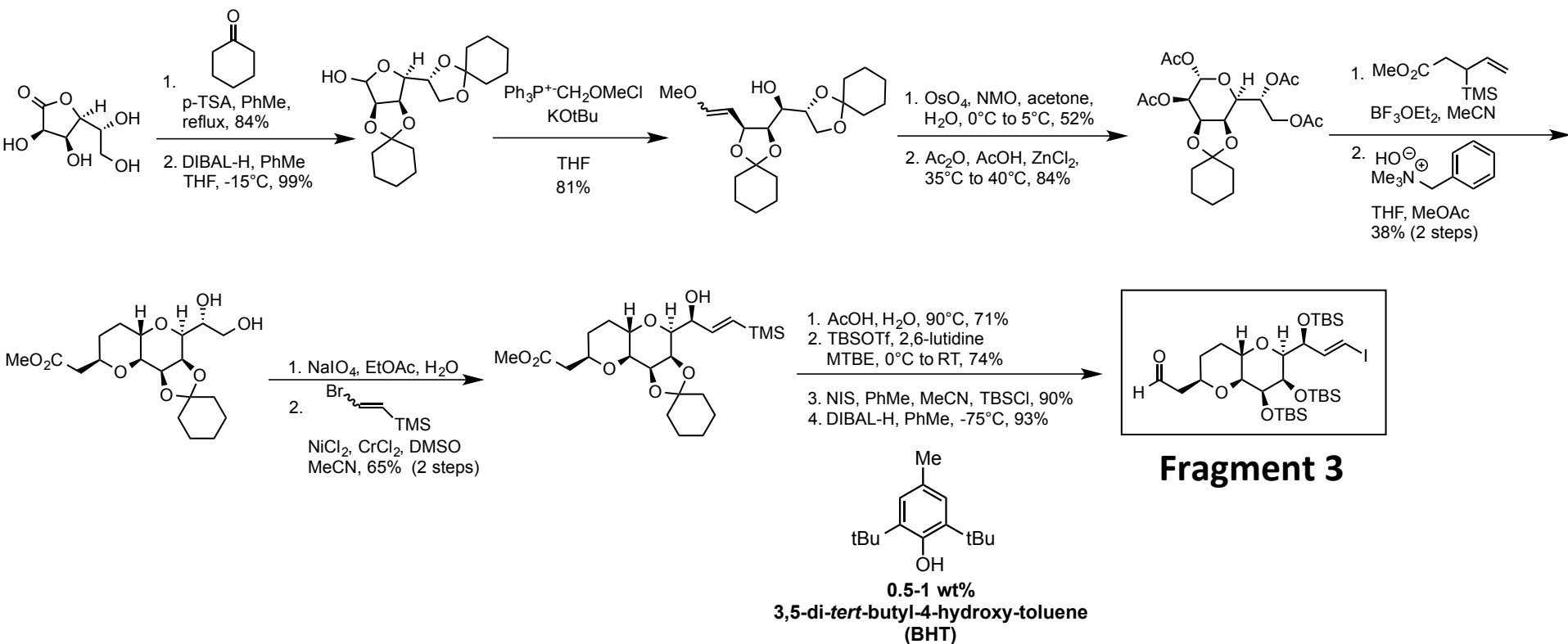
Fragment 2b



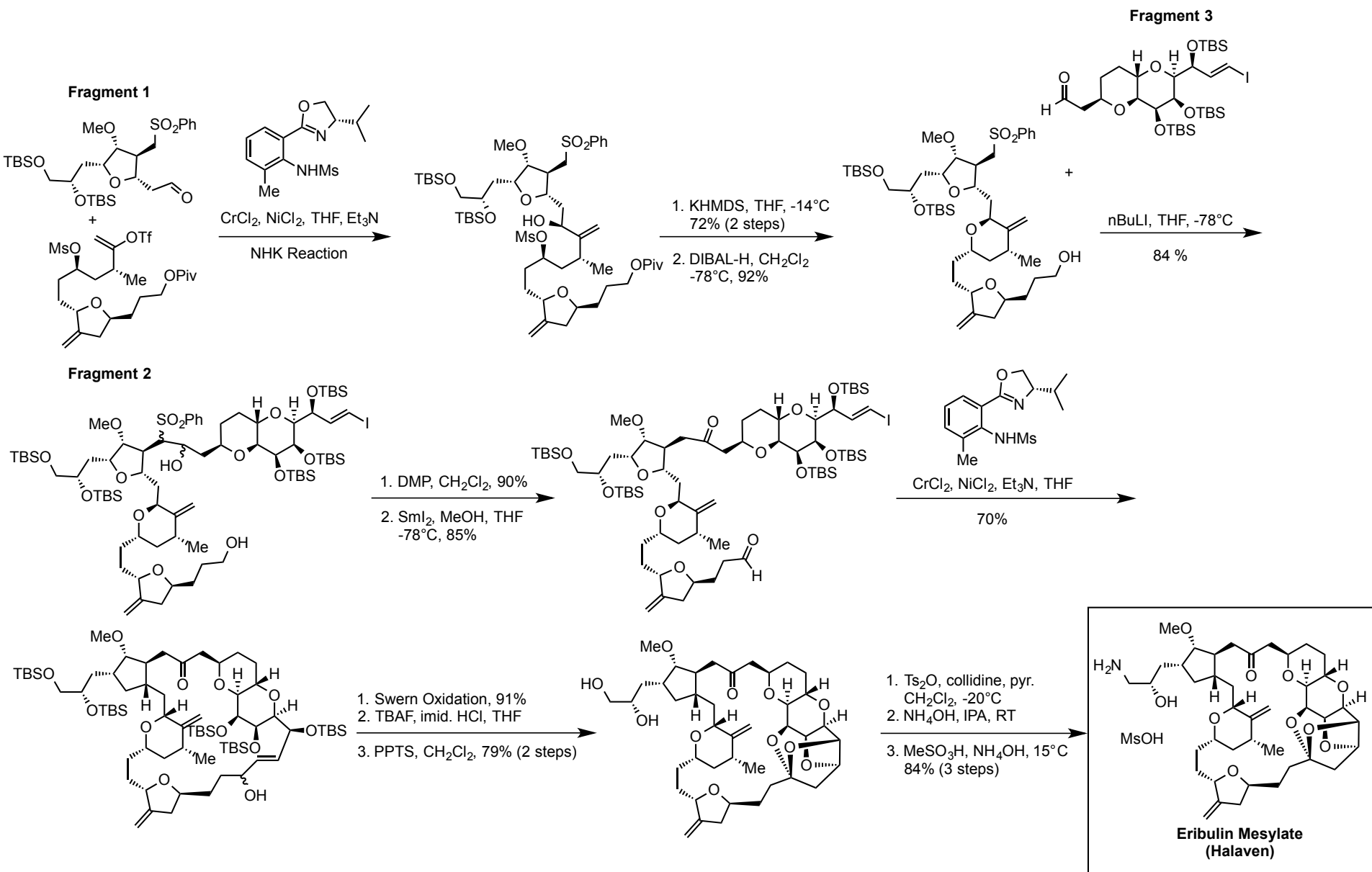
Fragment 2



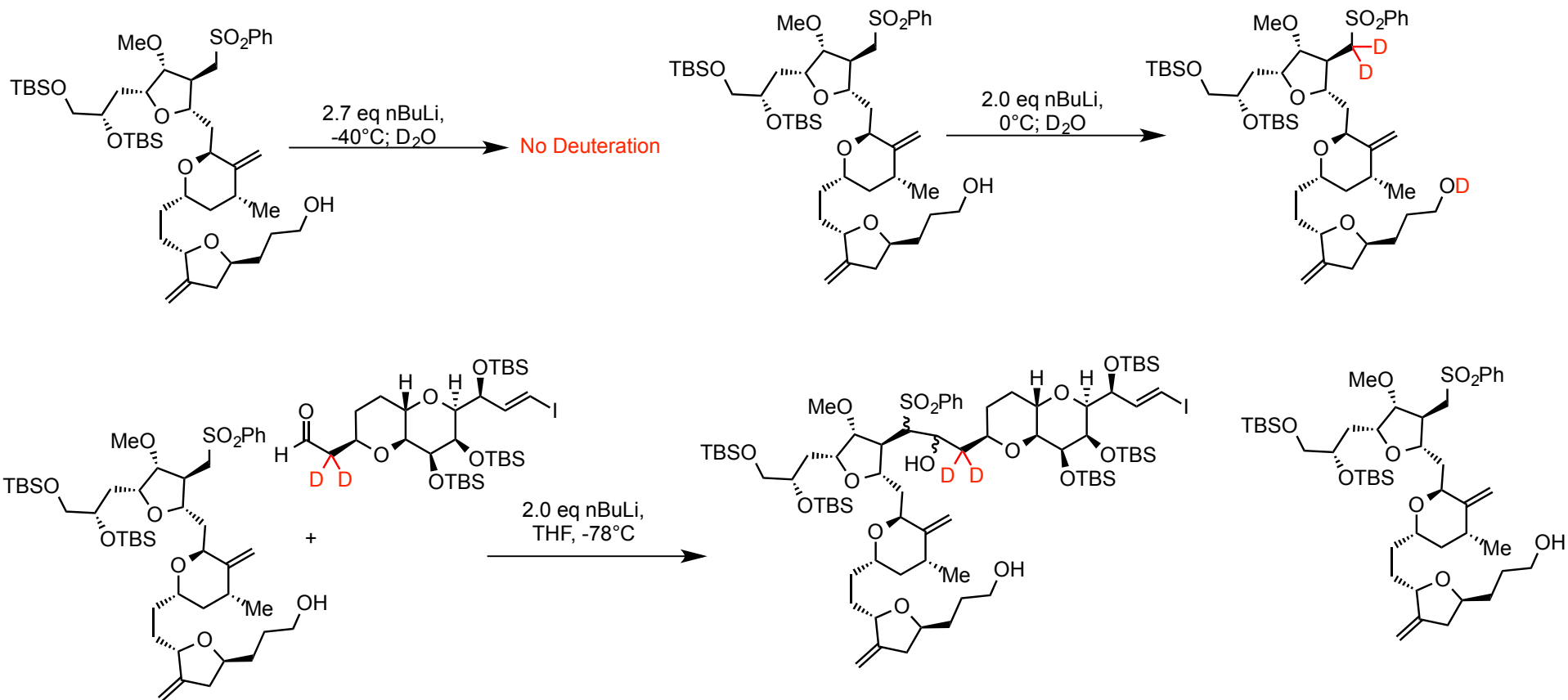
First Generation Process Synthesis of Eribulin Mesylate by Eisai



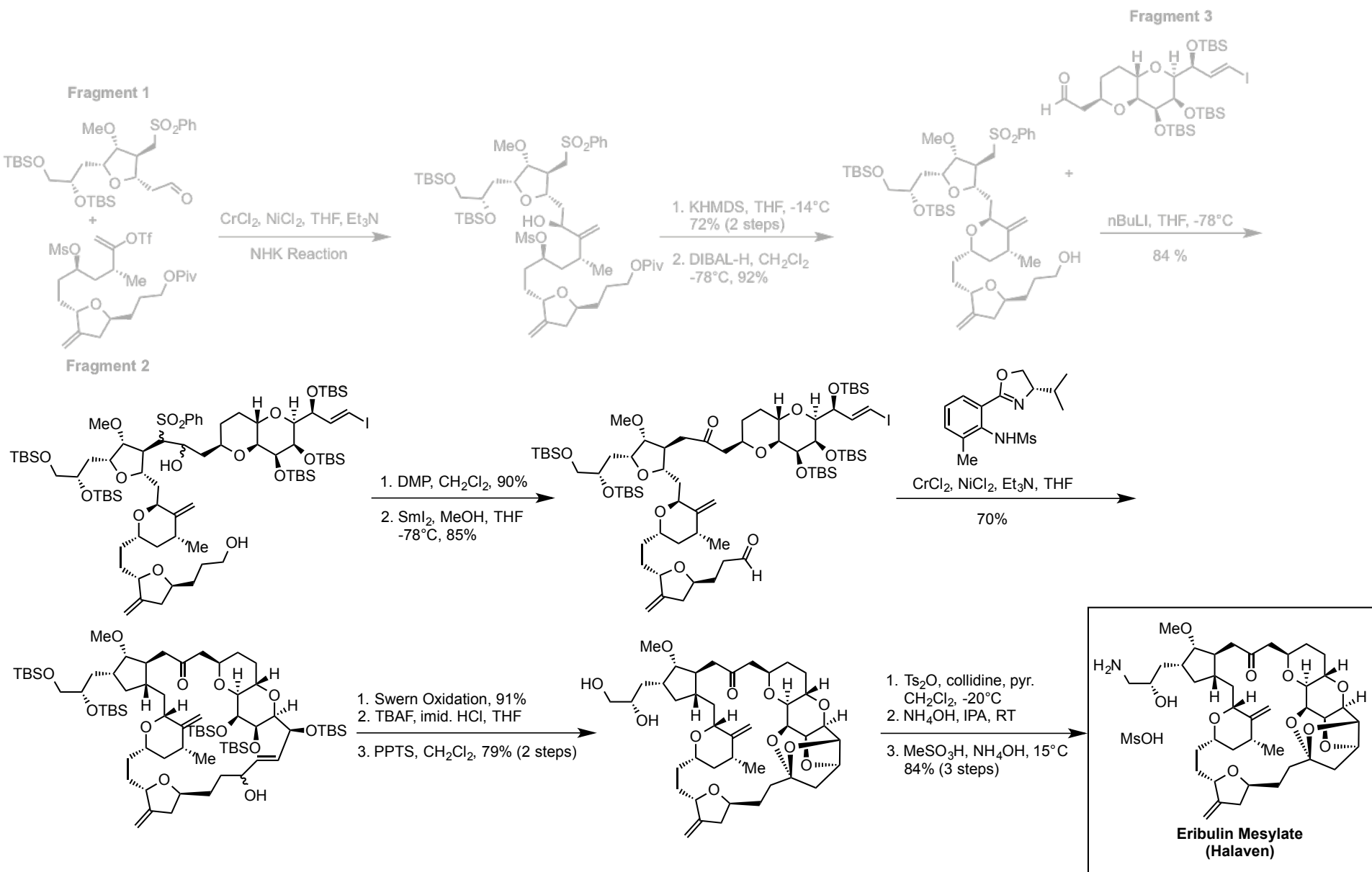
First Generation Process Synthesis of Eribulin Mesylate by Eisai



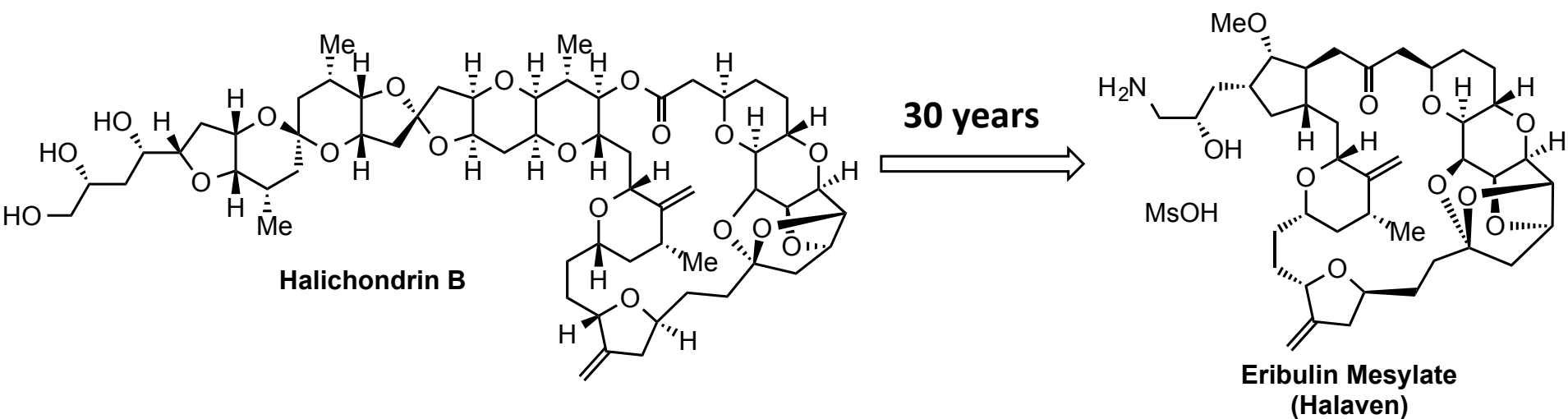
Deuterium Studies



First Generation Process Synthesis of Eribulin Mesylate by Eisai



Summary



Questions?