Total Synthesis of Halichondrin A

Atsushi Ueda, Akihiko Yamamoto, Daisuke Kato and Yoshito Kishi

Department of Chemistry and Chemical Biology,
Harvard University, Cambridge, Massachusetts, USA

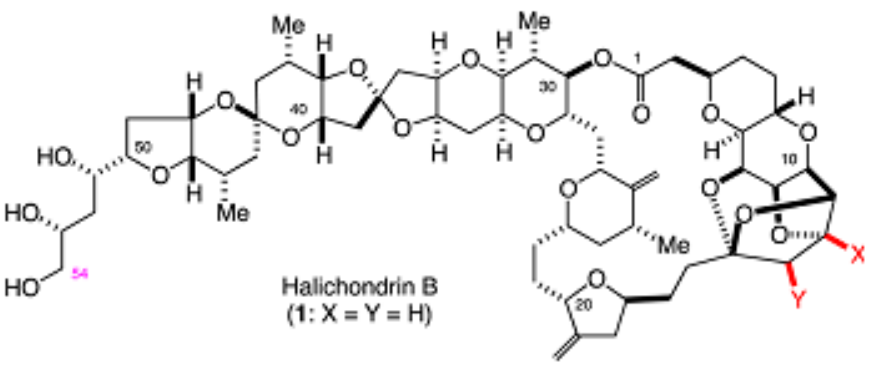
J. Am. Chem. Soc., 2014, 136, 5171–5176
DOI: 10.1021/ja5013307

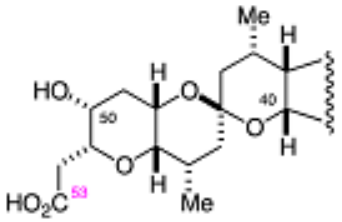
Halichondria okadai

Current literature
Andrey Kuzovlev
18.09.2014

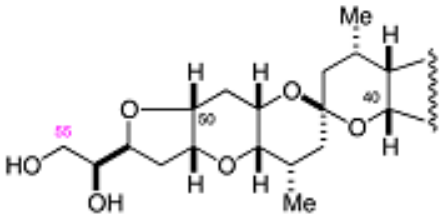
Introduction

- Halicondrins are polyether macrolides.
- Isolated from marine sponge *Halichondria okadai* by Uemura, Hirata and co-workers in 1985.
- Subgrouped into halichondrins A-C and norhalichondrin, halichondrin, homohalichondrin.
- Extraordinary in vitro and in vivo antitumor activity.





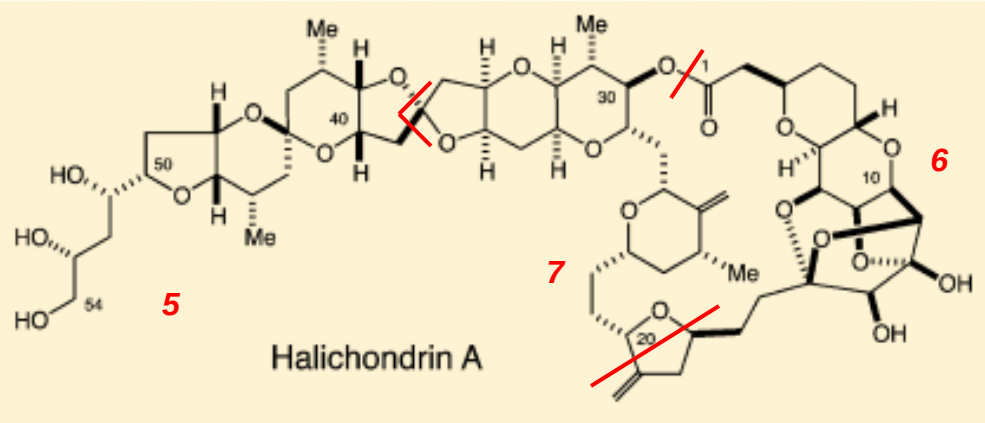
2 : Norhalichondrin B

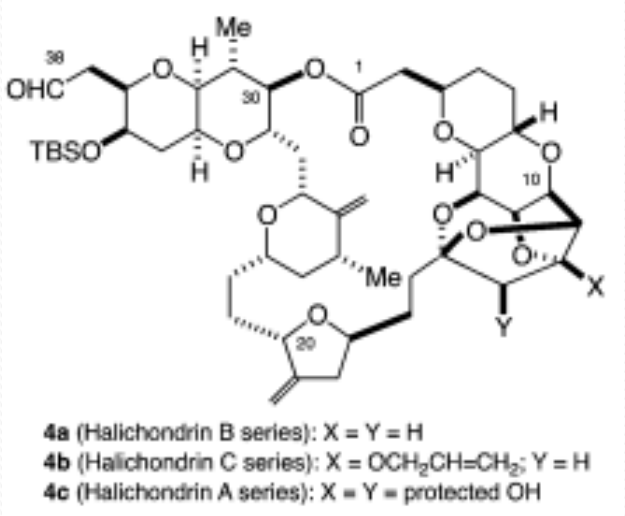


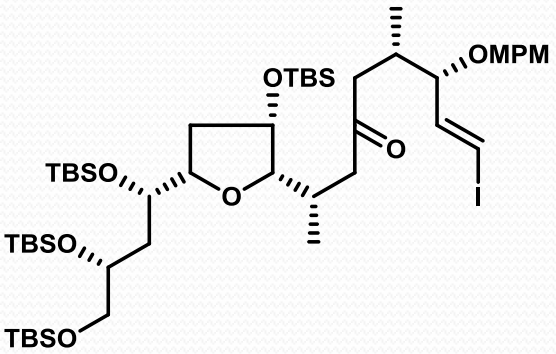
3 : Homohalichondrin B

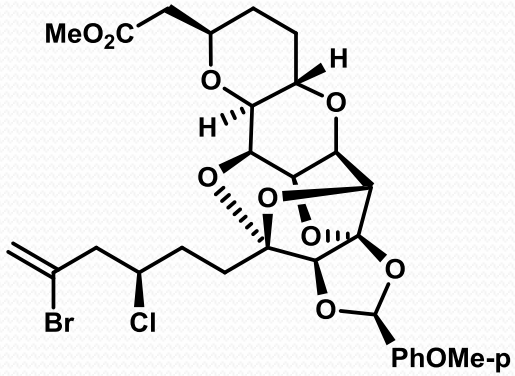
	A series (X = Y = OH)	B series (X = Y = H)	C series (X = OH; Y = H)
Halichondrin	unknown	known	known
Norhalichondrin	known	known	known
Homohalichondrin	known	known	known

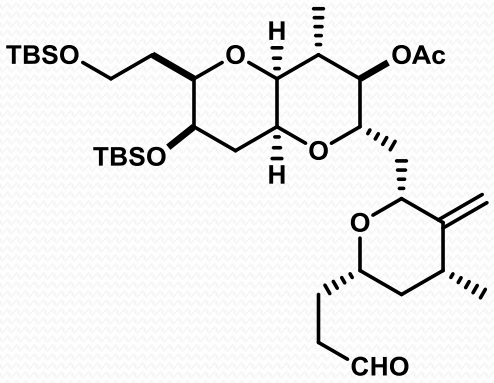
Retrosynthetic Analysis of Halichondrin A



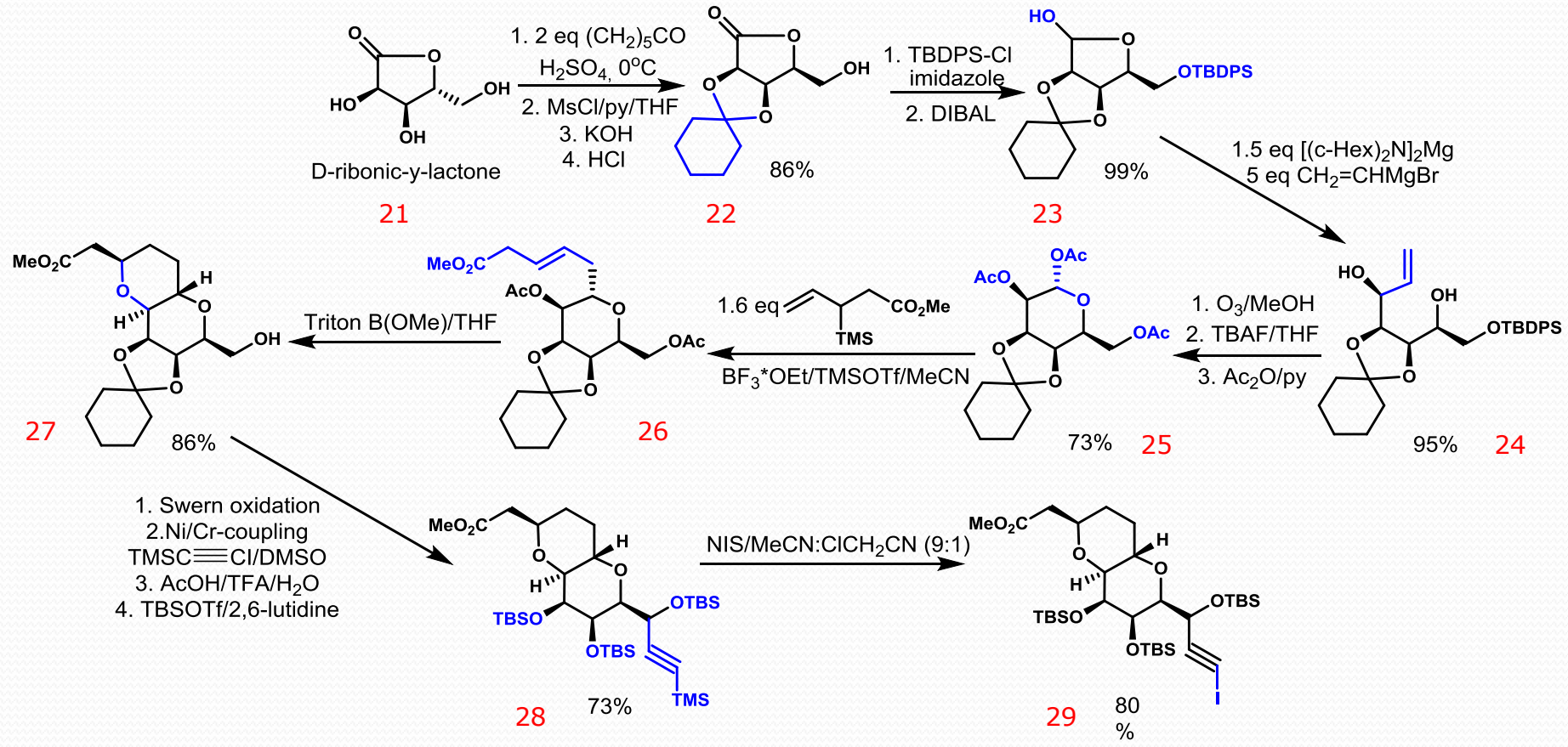




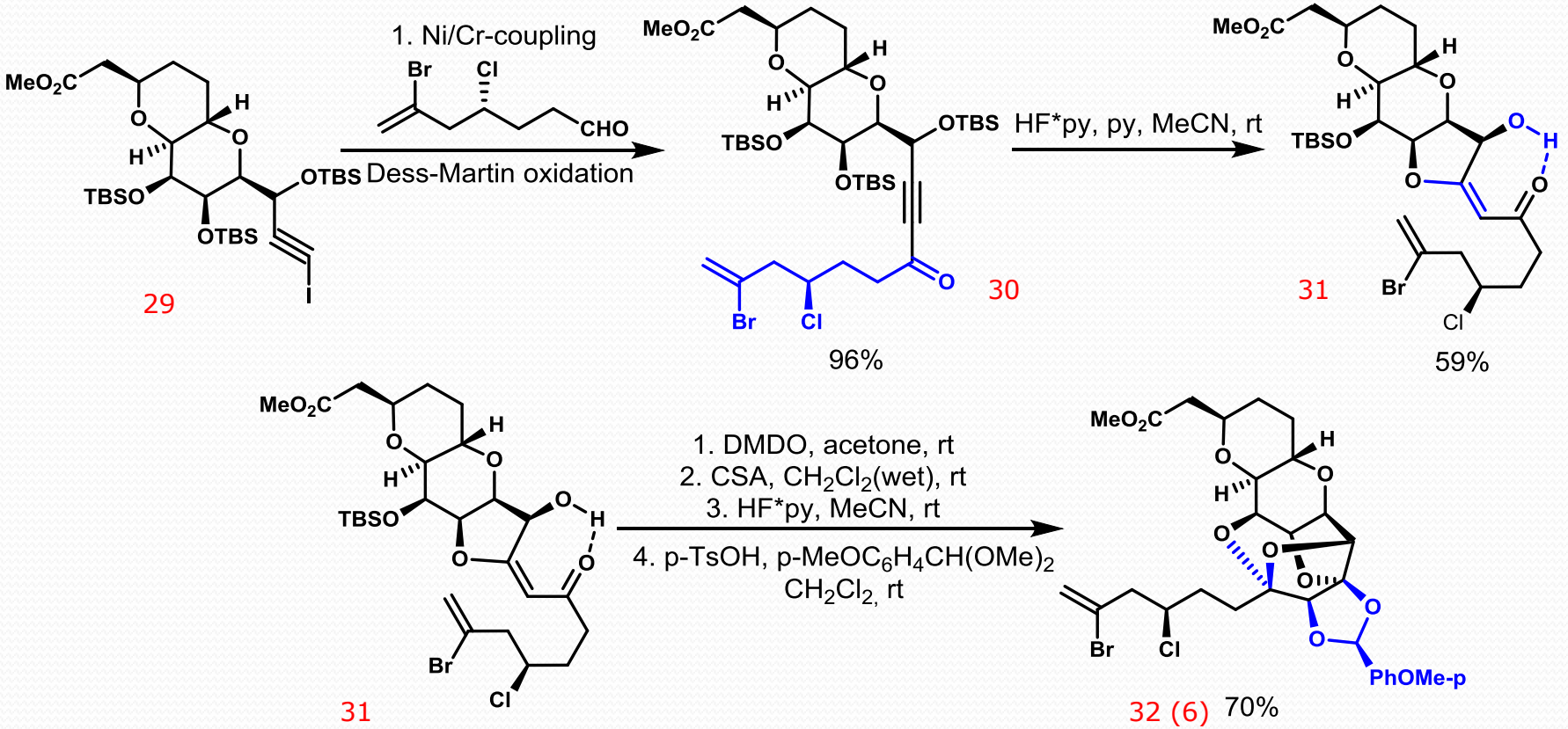




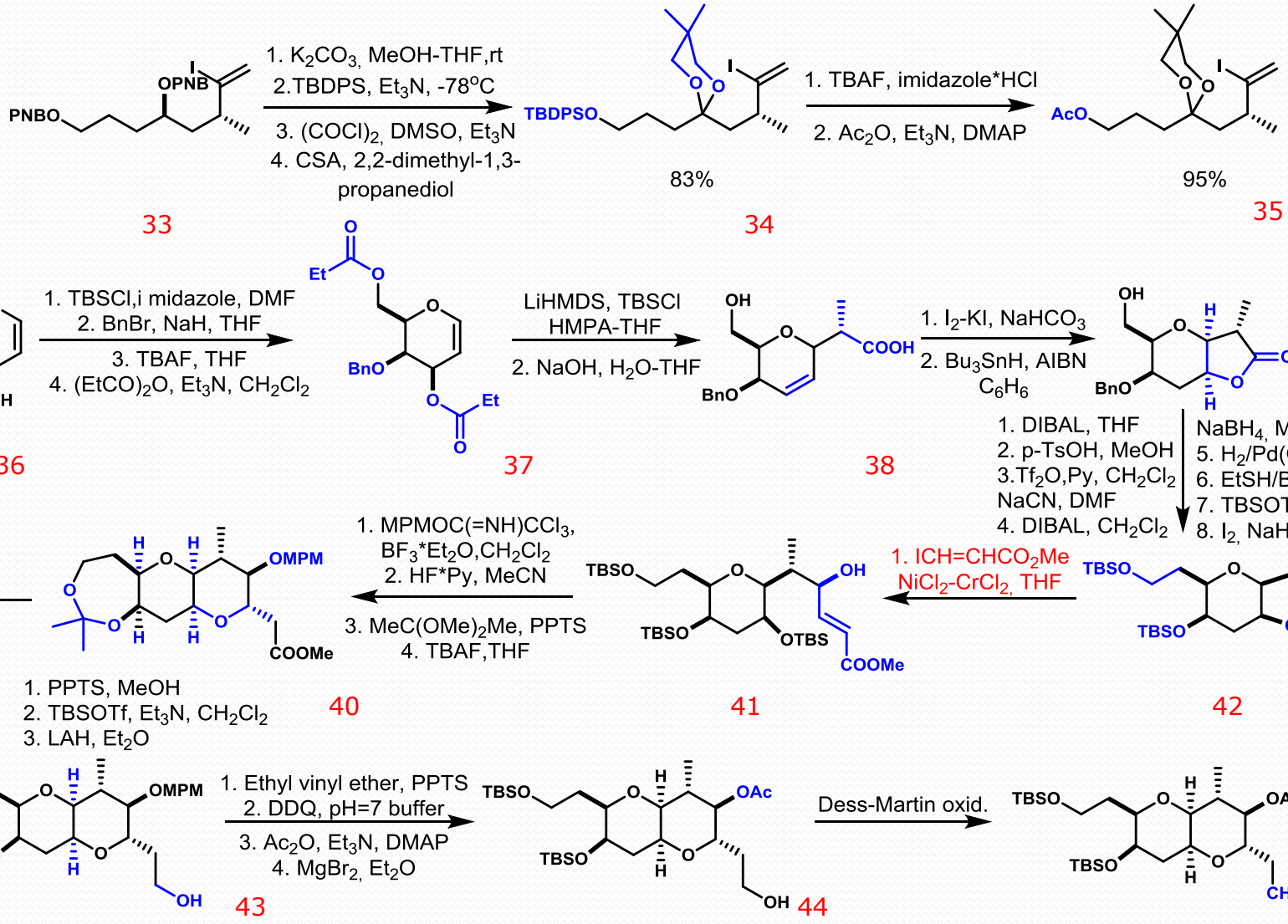
Synthesis of Precursor for Building Block 6



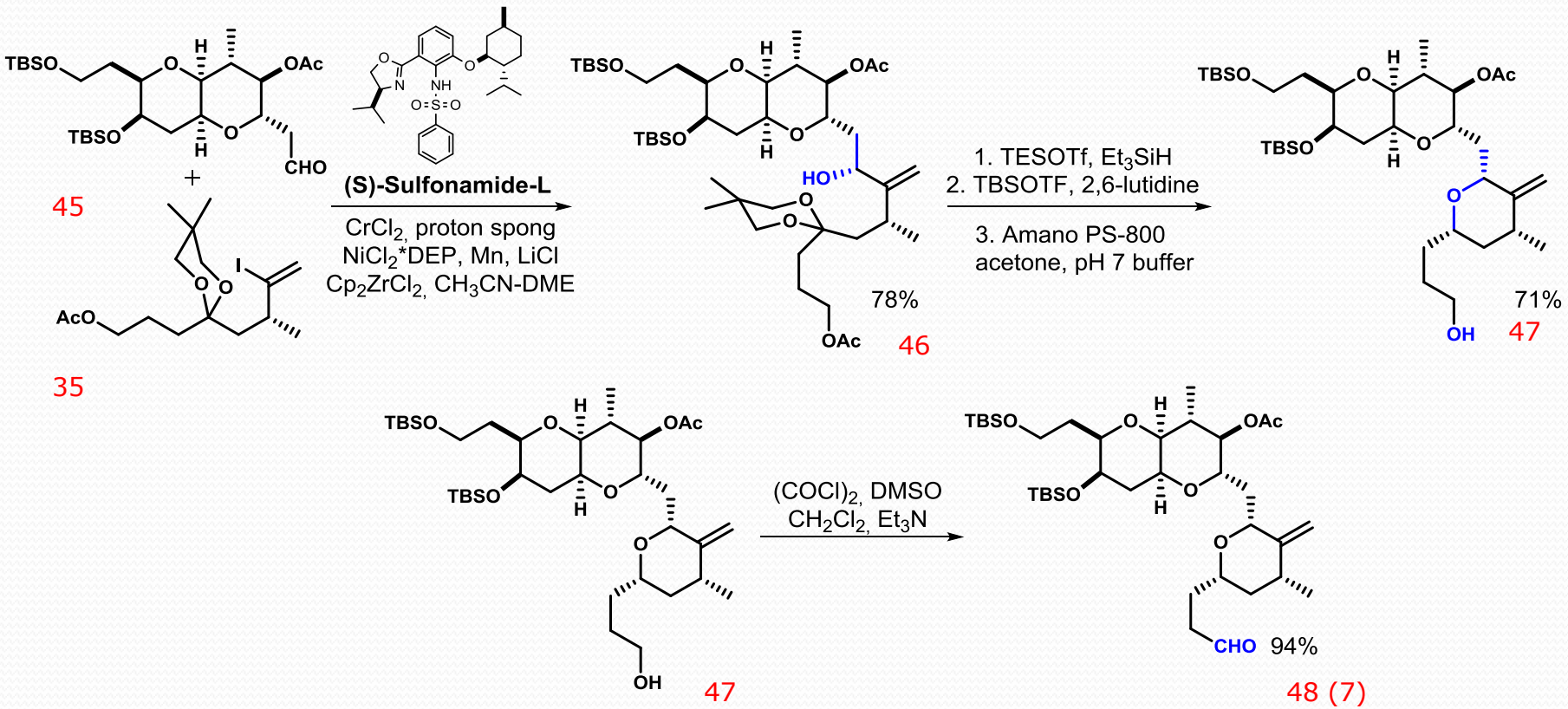
Synthesis of Building Block 6



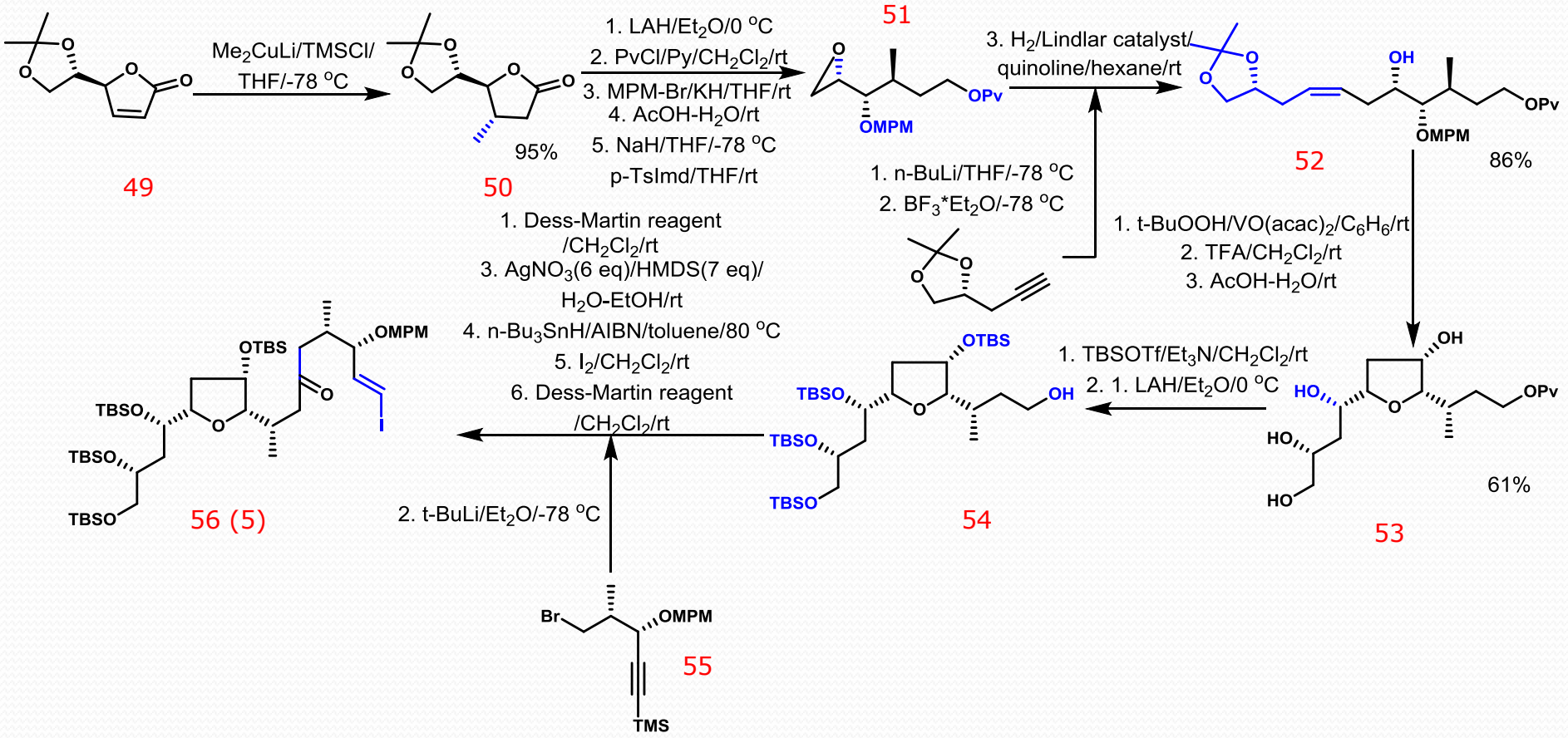
Synthesis of Precursors for Aldehyde 7



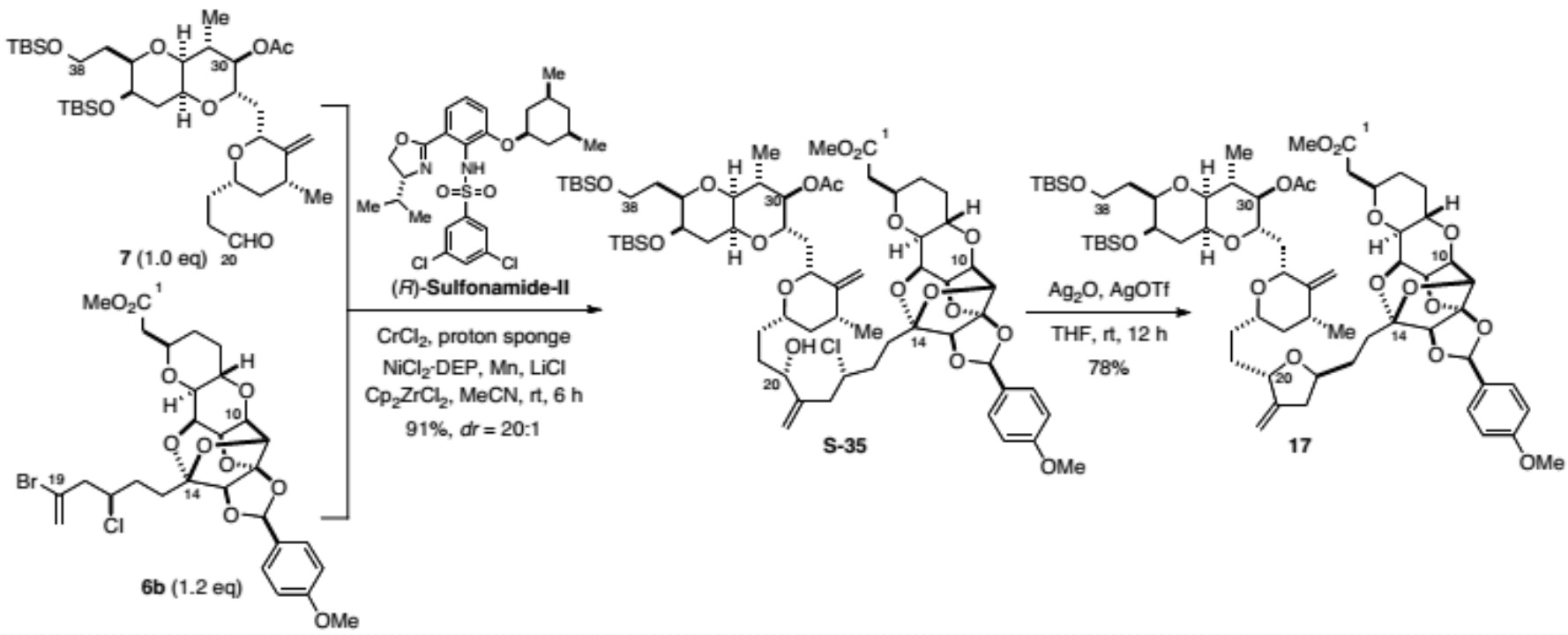
Synthesis of Aldehyde 7



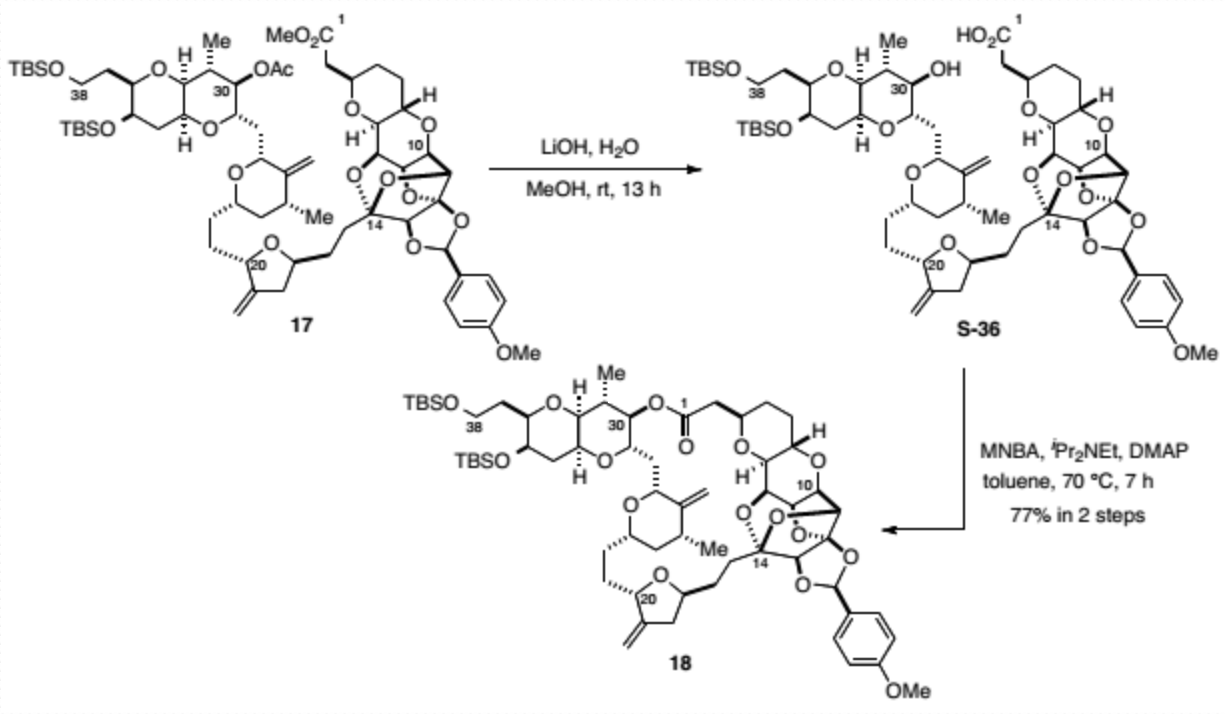
Synthesis of Building Block 5



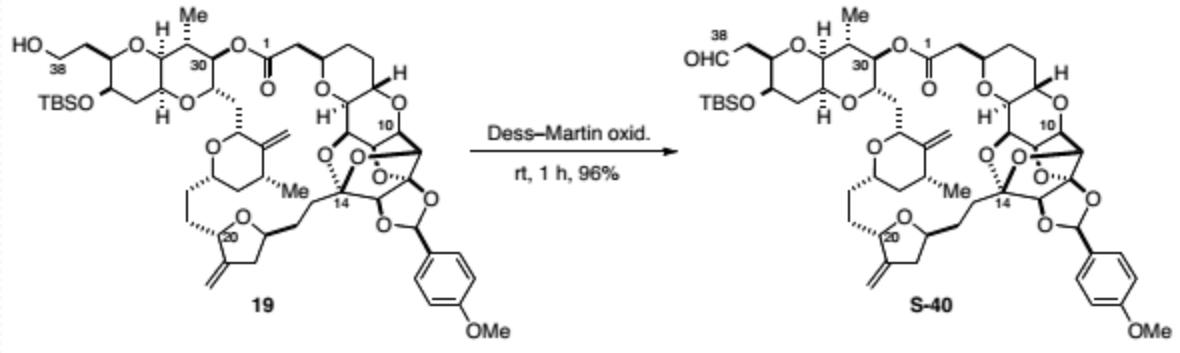
Synthesis of Building Block 19 (6+7)

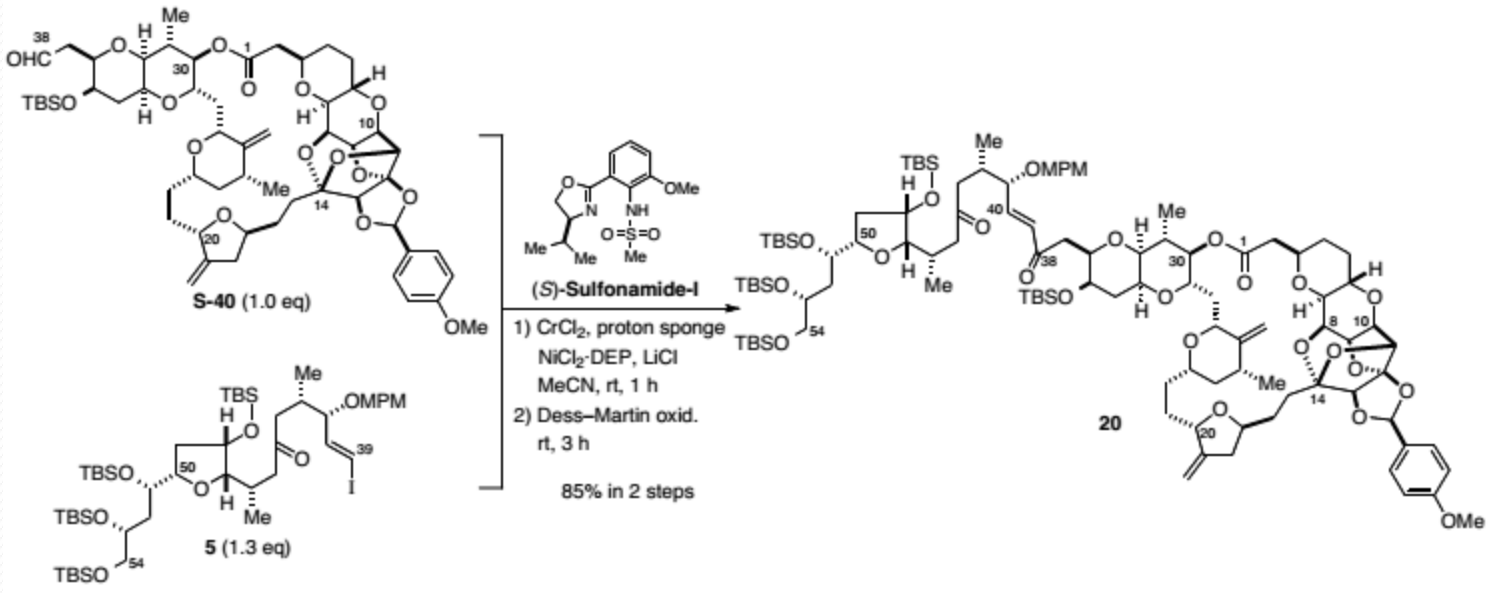


Synthesis of building block 19

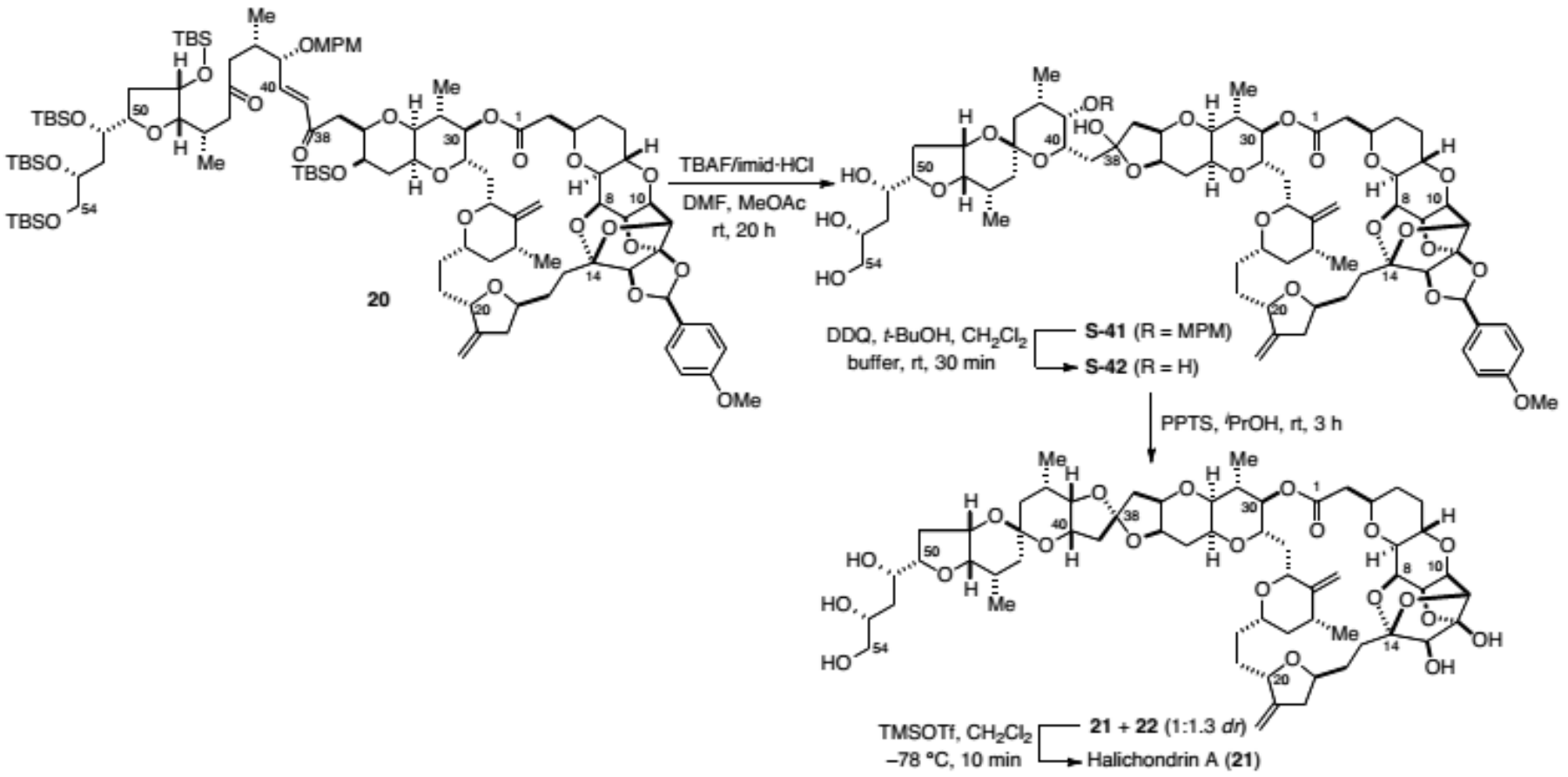


Completion of the Total Synthesis (5+19)

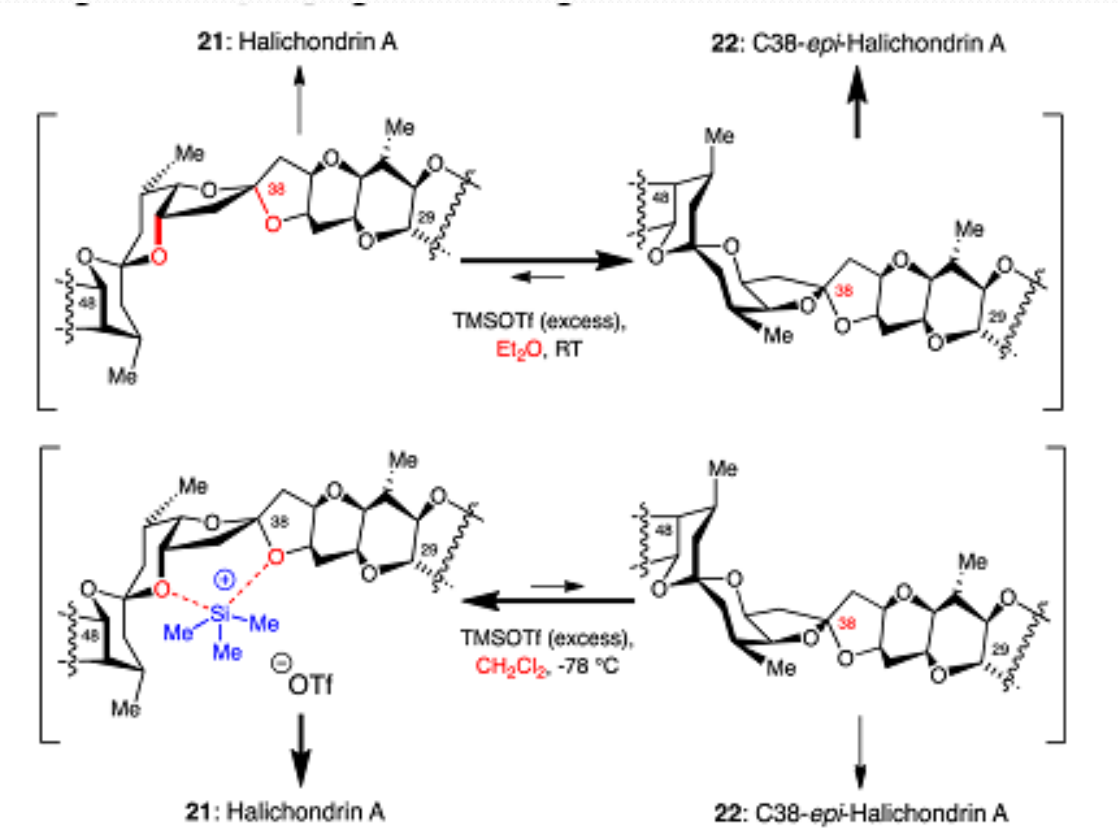




Completion of the Total Synthesis



[5,5]-Spiroketal Equilibration

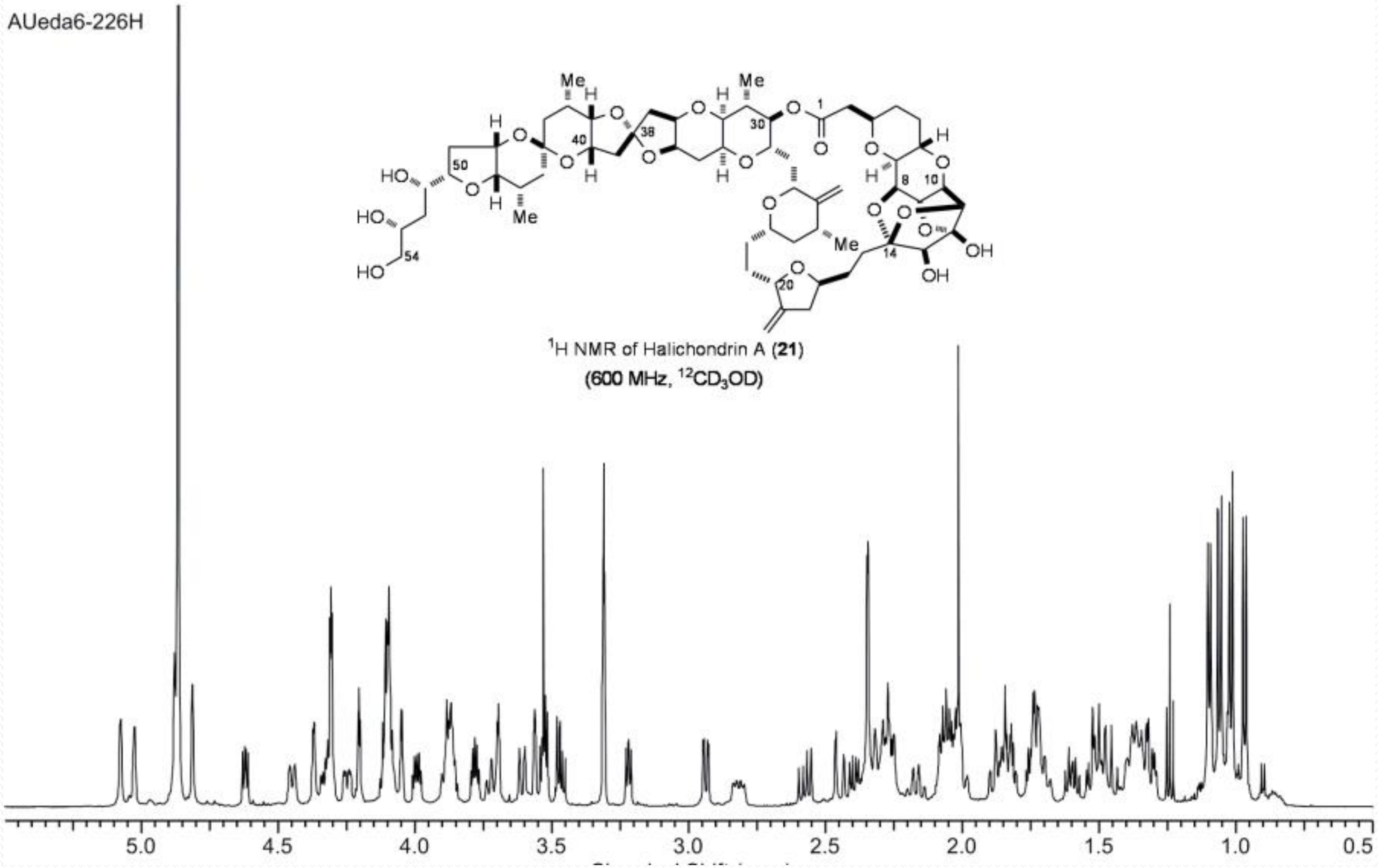


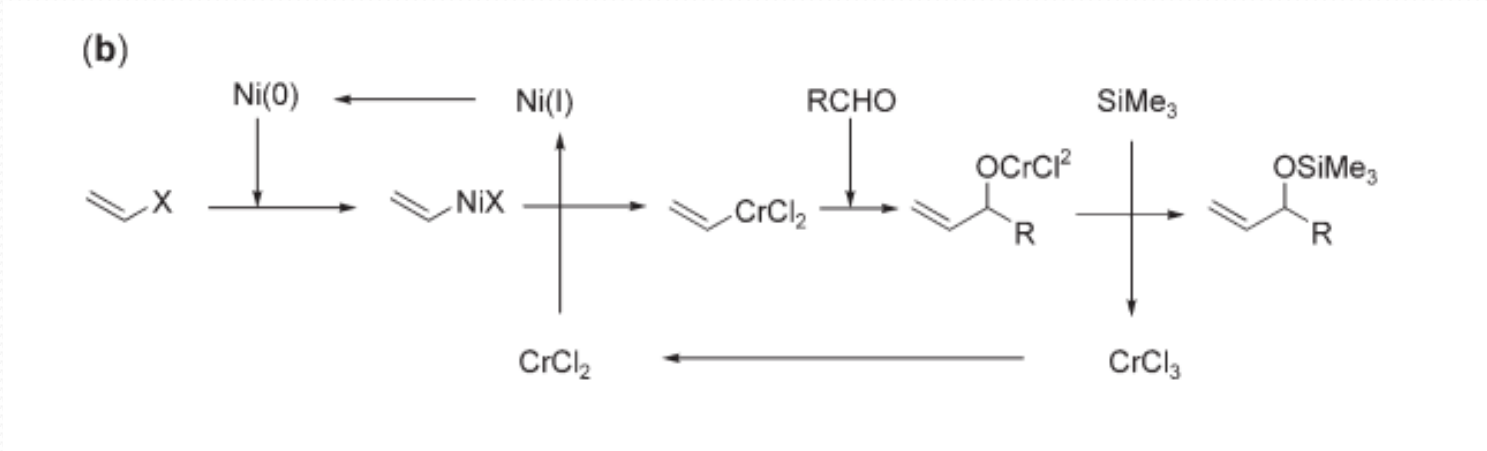
Conclusions

Total synthesis of halichondrin A, included followed key-steps:

- Catalytic asymmetric Ni/Cr-mediated coupling
- Shiina macrolactonization
- Dess-Martin oxidation
- Newly discovered highly selective TMSOTf-mediated equlibration

Thank you for your attention!




(b)
Ni(0)
Ni(I)
RCHO
SiMe3
X
NiX
CrCl2
OCrCl2
R
OSiMe3
R
CrCl2
CrCl3

Ni/Cr coupling