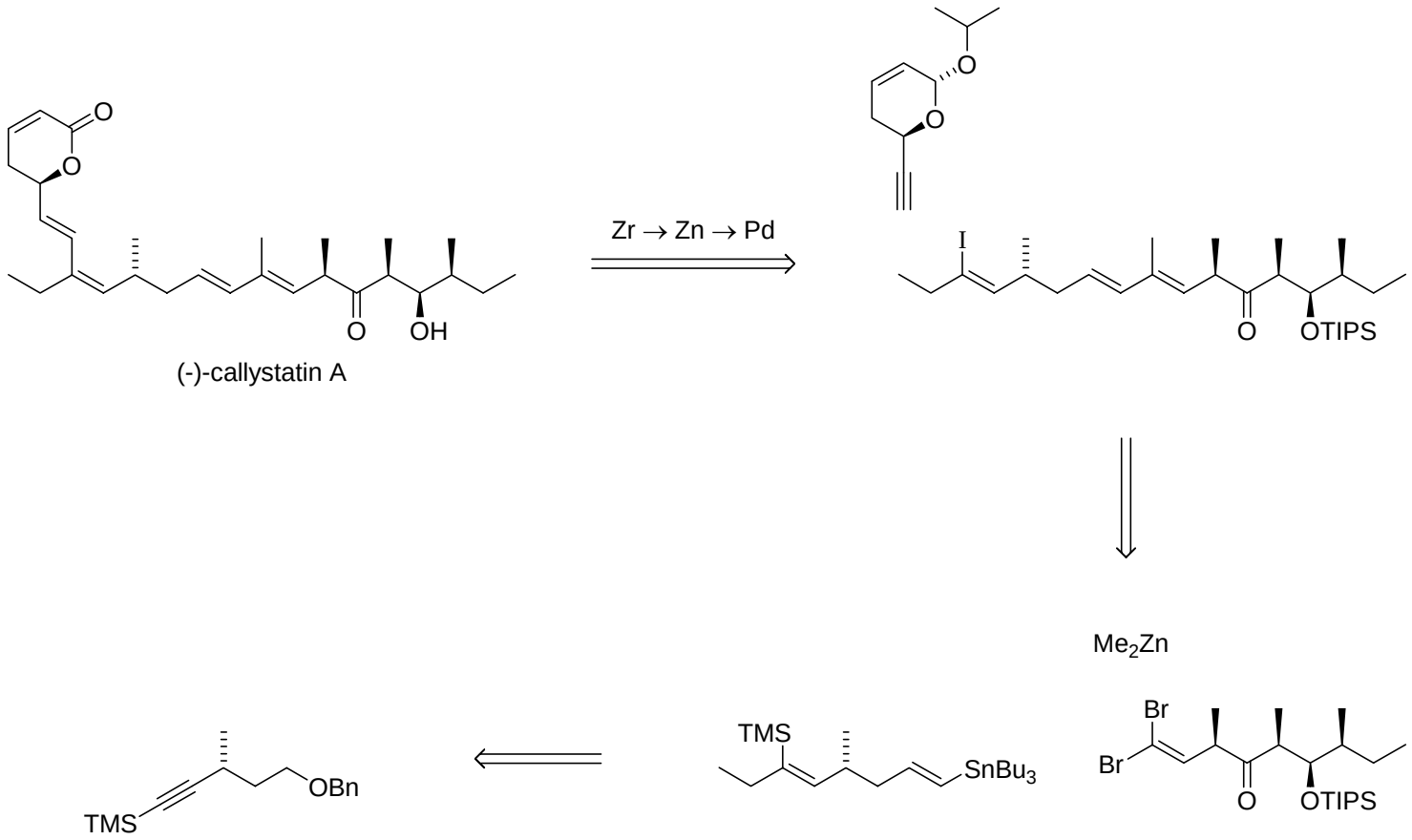
# Total Synthesis of (-)-Callystatin A

Langille, N. F.; Panek, J. S. *Org. Lett.* **2004**, *6*, 3203



• Isolated from marine sponge *Callyspongia truncata* (Goto Islands, Japan)
• Very cytotoxic vs. KB cells ($IC_{50}$ 0.01 ng/mL)

Kobayashi, M.; Higuchi, K.; Murakami, N.; Tajima, H.; Aoki, S. *Tetrahedron Lett.* **1997**, *38*, 2859

• Inhibits the nuclear export signal (NES)-dependant transport of proteins from the nucleus to the cytoplasm by covalently binding to the CRM1 protein
• SAR showed that activity is dependant on the spatial arrangement between the α,β-unsaturated lactone (the active pharmacophore) and the conjugated diene, and that the β-hydroxy ketone is most likely involved in binding stabilization

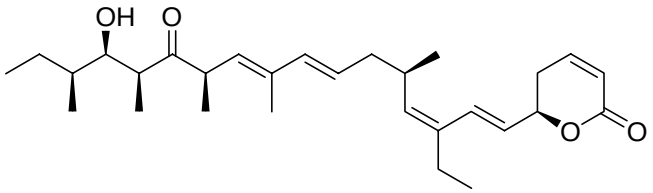
Murakami, N.; Sugimoto, M.; Nakajima, T.; Kawanishi, M.; Tsutsui, Y.; Kobayashi, M. *Bioorg. Med. Chem.* **2000**, *8*, 2651;

Murakami, N.; Sugimoto, M.; Kobayashi, M. *Bioorg. Med. Chem.* **2001**, *9*, 57

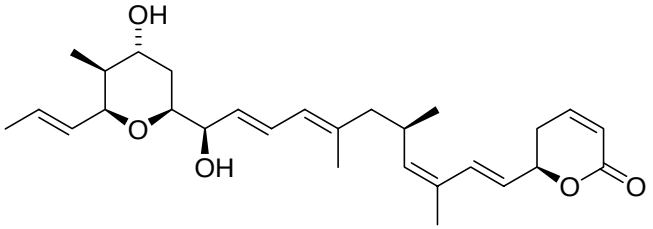
• member of the leptomycin family of natural products

reviw: Kalesse, M.; Christmann, M. *Synthesis* **2002**, 981

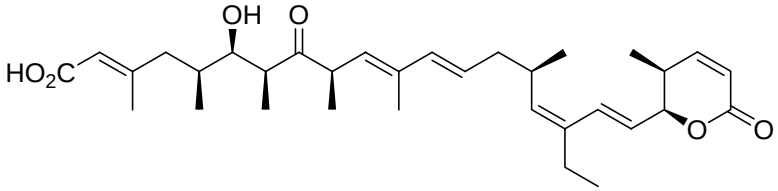
• 8 total syntheses of callystatin, and 2 of ratjadone




(-)-callystatin A

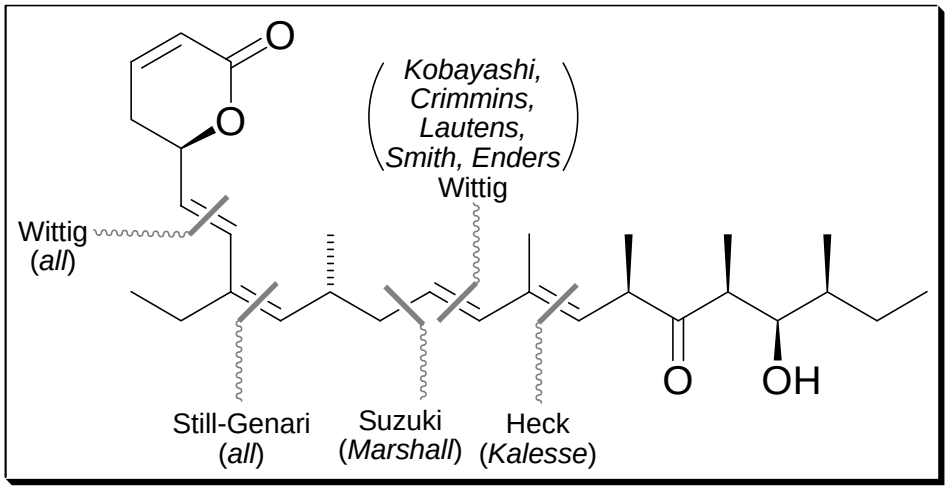



(+)-ratjadone




leptomycin B

Previous Total Syntheses of Callystatin A:




Kalesse, M.; Christmann, M. *Synthesis* **2002**, *981*

*Kobayashi*: Murakami, N.; Wang, W.; Aoki, M.; Tsutsui, Y.; Sugimoto, M.; Kobayashi, M. *Tetrahedron Lett.* **1998**, *2349*

*Crimmins*: Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084

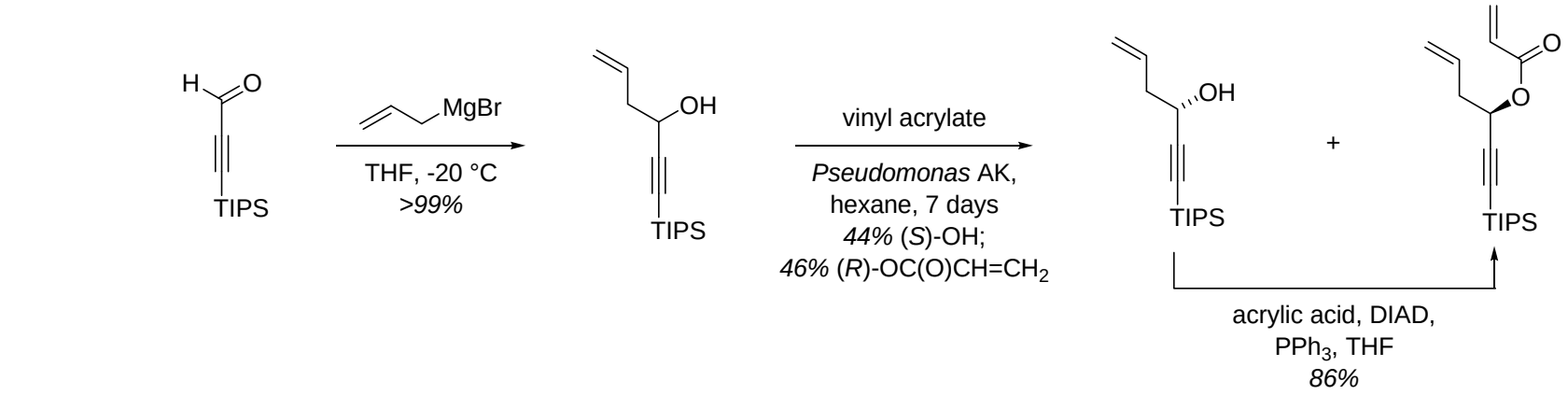
*Smith*: Smith III, A. B.; Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685

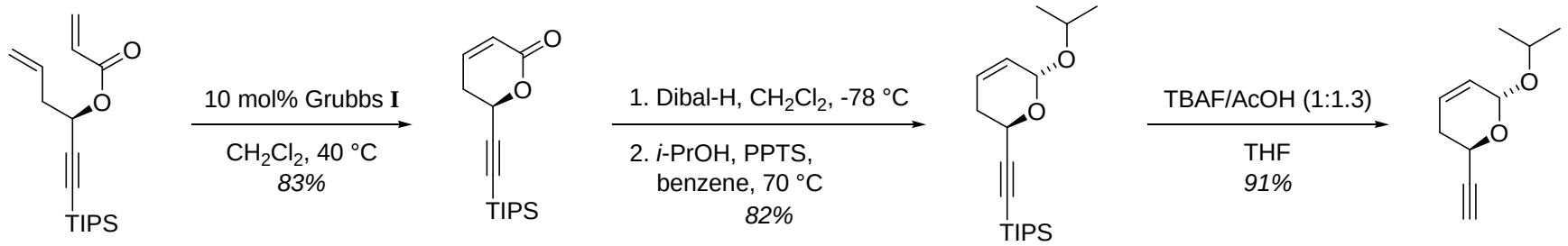
*Kalesse*: Kalesse, M.; Quitschalle, M.; Khandavalli, C. P.; Saeed, A. *Org. Lett.* **2001**, *3*, 3107; Kalesse, M.; Chary, K. P.; Quitschalle, M.; Burzlaff, A.; Kasper, C.; Scheper, T. *Chem. Eur. J.* **2003**, *9*, 1129

*Enders*: Vicario, J. L.; Job, A.; Wolberg, M.; Müller, M.; Enders, D. *Org. Lett.* **2002**, *4*, 1023; Enders, D.; Vicario, J. L.; Job, A.; Wolberg, M.; Müller, M. *Chem. Eur. J.* **2002**, *8*, 4272

*Marshall*: Marshall, J. A.; Bourbeau, M. P. *J. Org. Chem.* **2002**, *67*, 2751; Marshall, J. A.; Bourbeau, M. P. *Org. Lett.* **2002**, *4*, 3931

*Lautens*: Lautens, M.; Stammers, T. A. *Synthesis* **2002**, 1993

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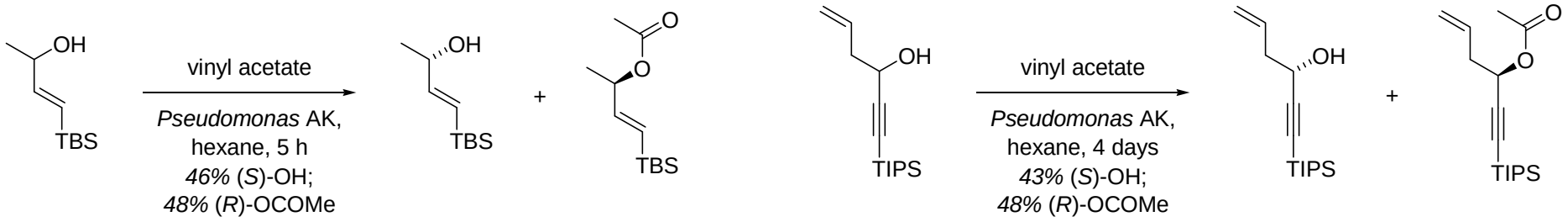
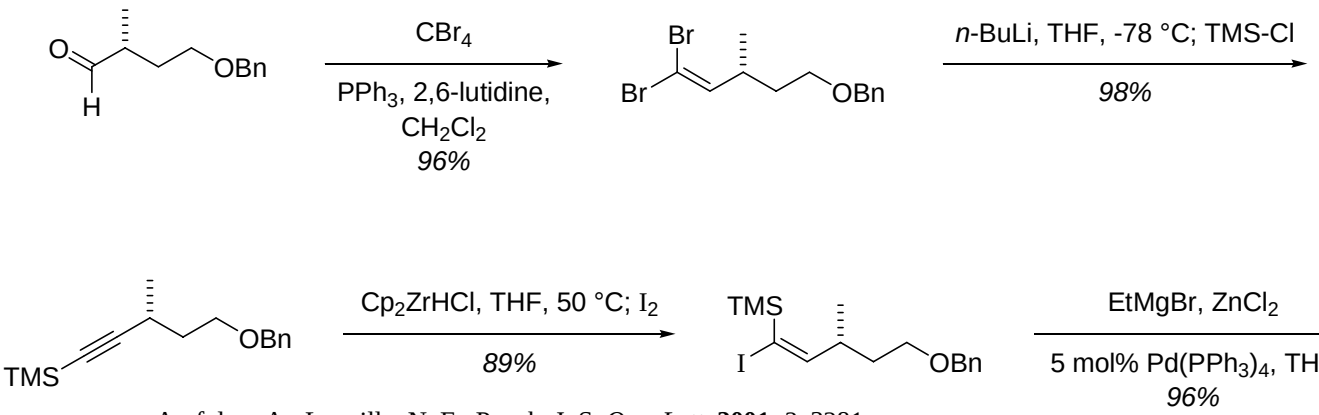
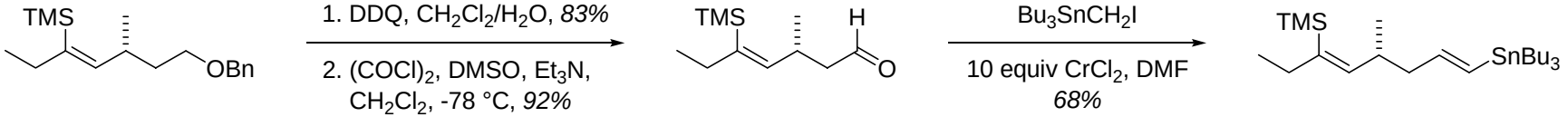



Sparks, M. A.; Panek, J. S. *Tetrahedron Lett.* **1991**, *32*, 4085




Arefolov, A.; Langille, N. F.; Panek, J. S. *Org. Lett.* **2001**, *3*, 3281

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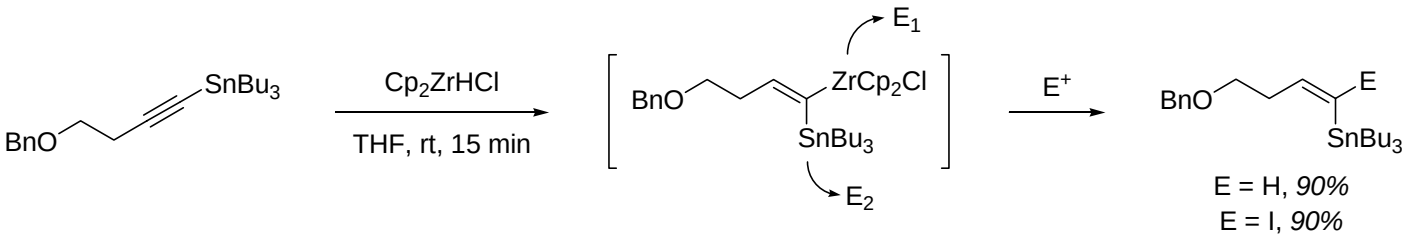
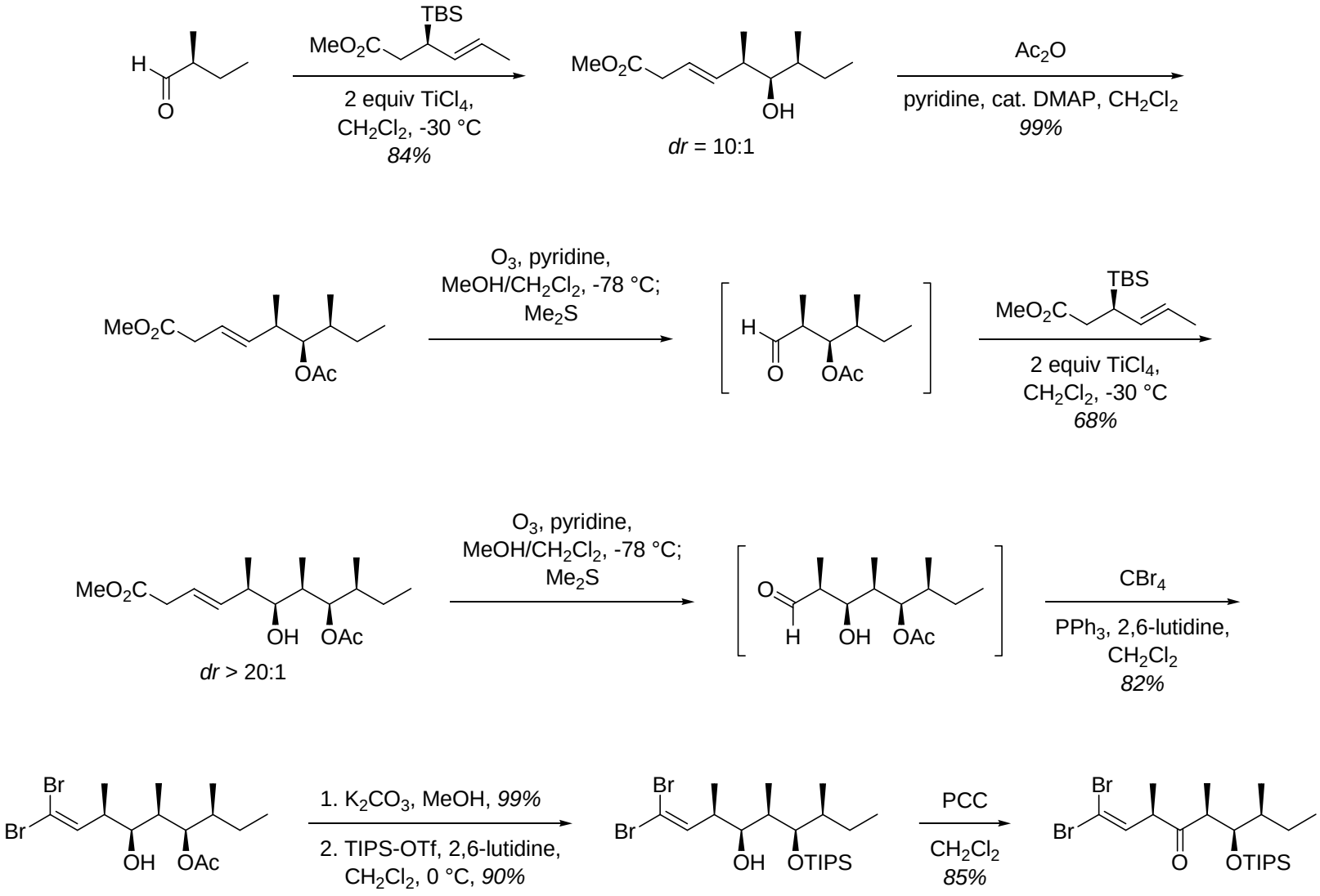
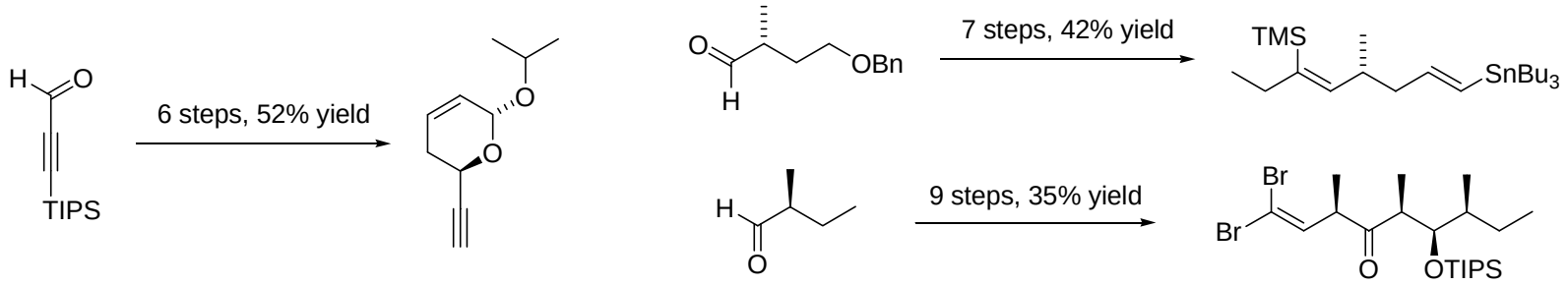
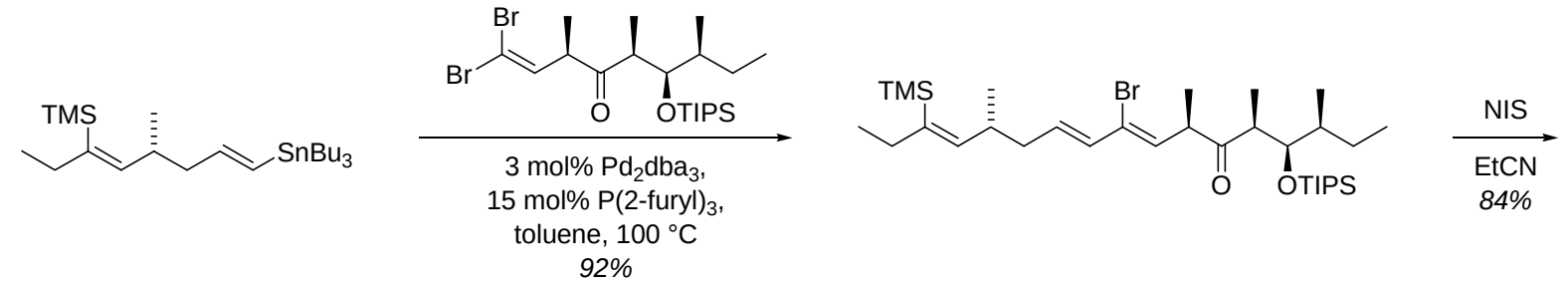
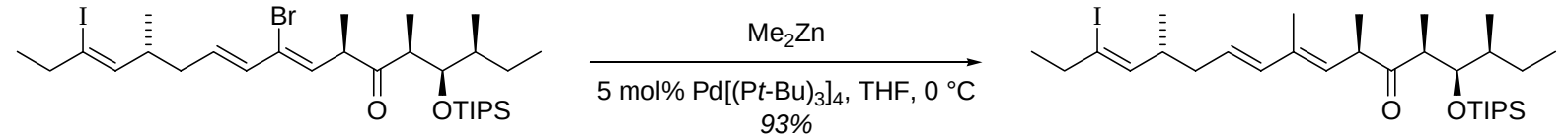


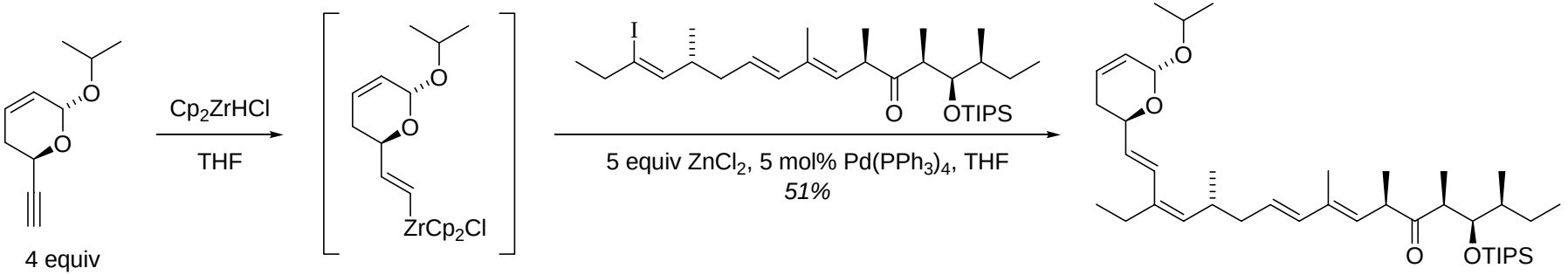

Lipshutz, B. H.; Kell, R.; Barton, J. C. *Tetrahedron Lett.* **1992**, *33*, 5861
*see also* Mapp, A. K.; Heatchcock, C. H. *J. Org. Chem.* **1999**, *64*, 23 (total synthesis of myxalamide A)

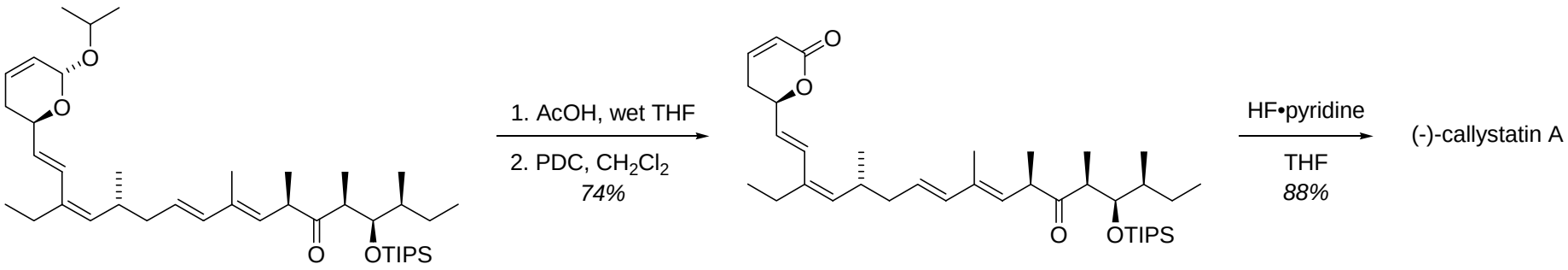

TBS
MeO2C
H
O
2 equiv TiCl4,
CH2Cl2, -30 °C
84%
MeO2C
OH
dr = 10:1
Ac2O
pyridine, cat. DMAP, CH2Cl2
99%
MeO2C
OAc
O3, pyridine,
MeOH/CH2Cl2, -78 °C;
Me2S
H
O
OAc
TBS
MeO2C
2 equiv TiCl4,
CH2Cl2, -30 °C
68%
MeO2C
OH
OAc
dr > 20:1
O3, pyridine,
MeOH/CH2Cl2, -78 °C;
Me2S
O
H
OH
OAc
CBr4
PPh3, 2,6-lutidine,
CH2Cl2
82%
Br
Br
OH
OAc
1. K2CO3, MeOH, 99%
2. TIPS-OTf, 2,6-lutidine,
CH2Cl2, 0 °C, 90%
Br
Br
OH
OTIPS
PCC
CH2Cl2
85%
Br
Br
O
OTIPS


6 steps, 52% yield
7 steps, 42% yield
9 steps, 35% yield


3 mol% Pd2dba3,
15 mol% P(2-furyl)3,
toluene, 100 °C
92%
NIS
EtCN
84%


Me2Zn
5 mol% Pd[(Pt-Bu)3]4, THF, 0 °C
93%


Cp2ZrHCl
THF
4 equiv
5 equiv ZnCl2, 5 mol% Pd(PPh3)4, THF
51%




- 16 steps (longest linear sequence), 29 steps total
- 2.6 mg of natural product prepared in final step of experimental section
- 9 of 11 C-C bond forming steps involved either stoichiometric or [catalytic] metals (2 Corey-Fuchs)
- efficient preparation of trisubstituted alkenes of the 2 dienes using Pd-catalyzed cross coupling