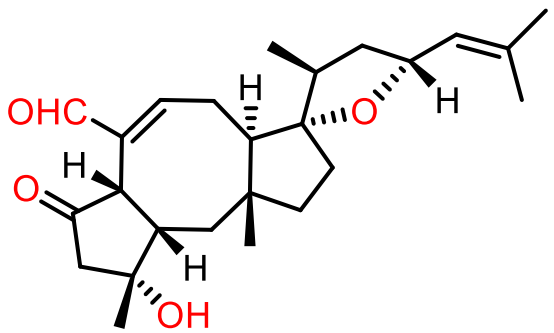
Total Synthesis of Ophiobolins

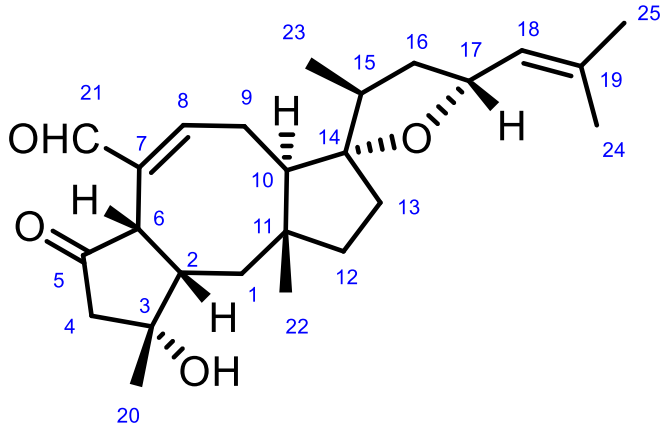


ophiobolin A

Li Bo

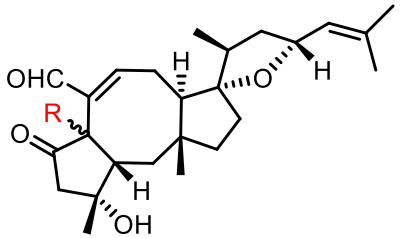
2021.12.23

Introduction of Ophiobolins

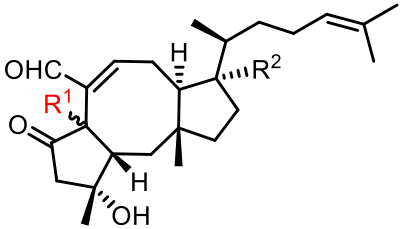


ophiobolin A (**8**)

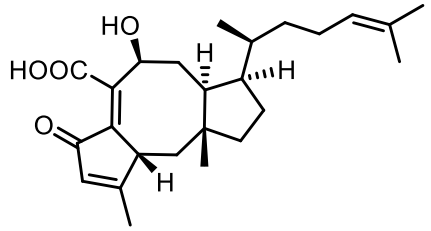
- A unique 5-8-5-5 tetracyclic ring system, including a tetrahydrofuran ring and eight stereocenters
- Isolated from a culture broth of the pathogenic plant fungus *Ophiobulus miyabeanus* in 1958
- Induces cell-death in the L1210 cell-line, inhibits calmodulin-activated cyclic nucleotide phosphodiesterase, and also shows cytotoxicity to cancer cell-lines A-549, Mel-20, and P-335



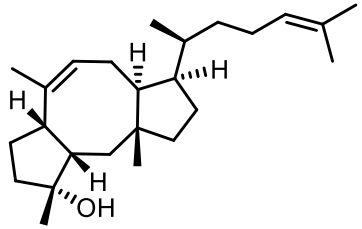
ophiobolin A	R = β-H
6-epi-ophiobolin A	R = α-H



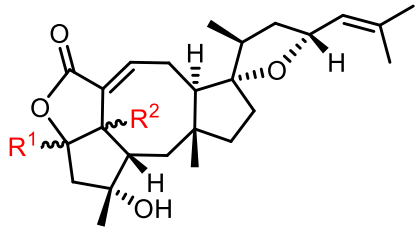
ophiobolin B	R^1 = β-H R^2 = OH
ophiobolin C	R^1 = β-H R^2 = H
6-epi-ophiobolin C	R^1 = α-H R^2 = H



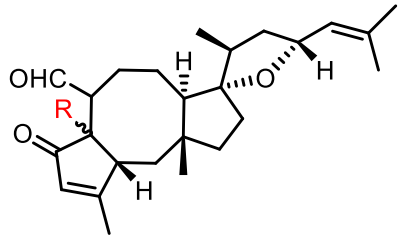
ophiobolin D



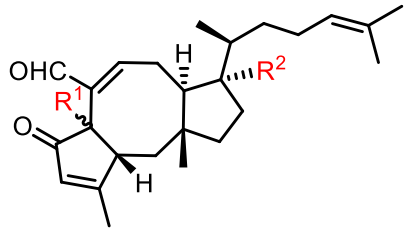
ophiobolin F



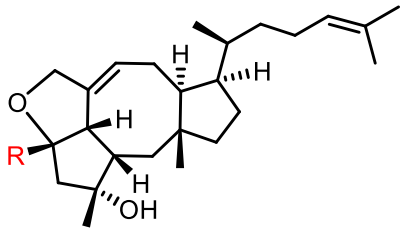
ophiobolin A lactone	R^1 = R^2 = β-H
ophiobolin L	R^1 = OH R^2 = β-H
6-epi-ophiobolin L	R^1 = OH R^2 = α-H



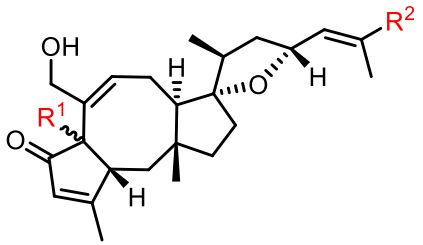
3-anhydroophiobolin A	R = β-H
3-anhydro-6-epi-ophiobolin A	R = α–H
3-anhydro-6-hydroxyophiobolin A	R = β-OH



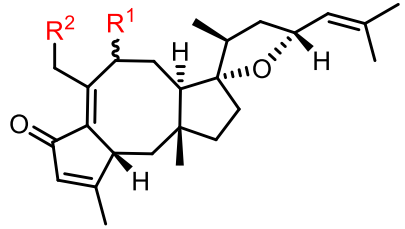
ophiobolin G	R^1 = β-H, R^2 = H
6-epi-ophiobolin G	R^1 = α-H, R^2 = H
3-anhydro-6-epi-ophiobolin B	R^1 = α-H, R^2 = OH



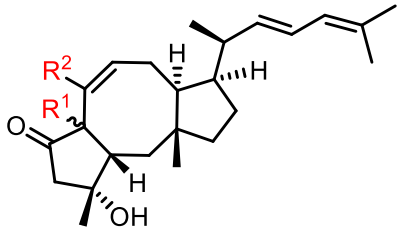
ophiobolin H	R = OH
5-O-methylophiobolin H	R = OCH_3



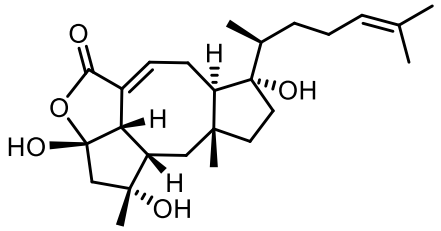
ophiobolin I	R^1 = β-H, R^2 = CH_3
6-epi-ophiobolin I	R^1 = α-H, R^2 = CH_3
25-hydroxyophiobolin I	R^1 = β-H, R^2 = CH_2OH



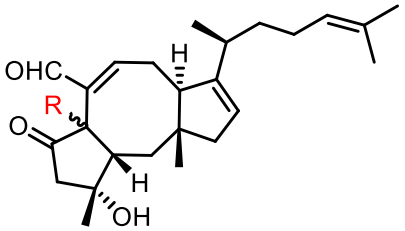
ophiobolin J	R^1 = β–OH, R^2 = OH
8-deoxyophiobolin J	R^1 = α-H, R^2 = OH
8-epi-Ophiobolin J	R^1 = α-OH, R^2 = OH



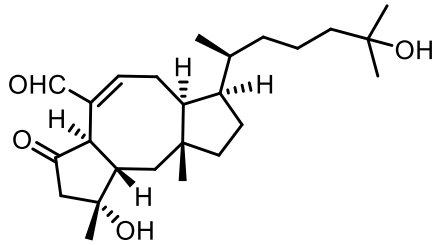
ophiobolin K R^1 = β-H, R^2 = CHO
6-epi-ophiobolin K R^1 = α-H, R^2 = CHO
21-deoxyophiobolin K R^1 = β-H, R^2 = CH_3



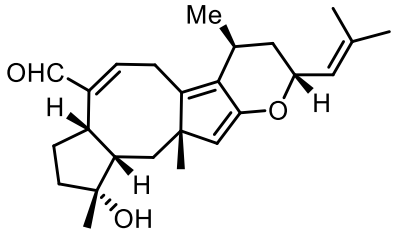
ophiobolin B lactone



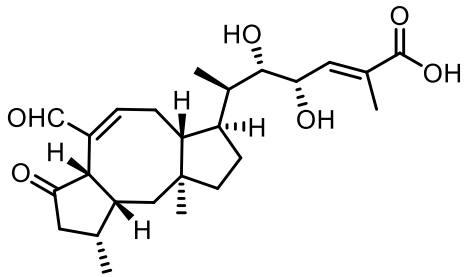
ophiobolin M R = β-H
6-epi-ophiobolin M R = α-H



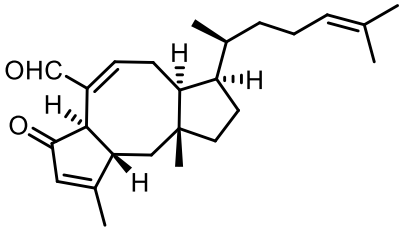
18,19-dihydroophiobolin C



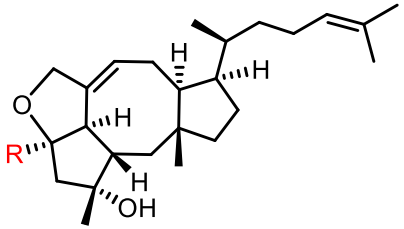
ophiobolin E



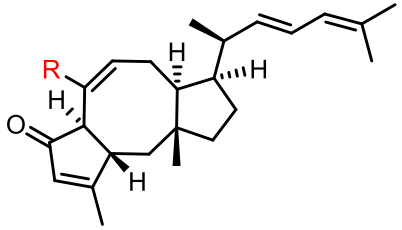
halorsenllinic acid



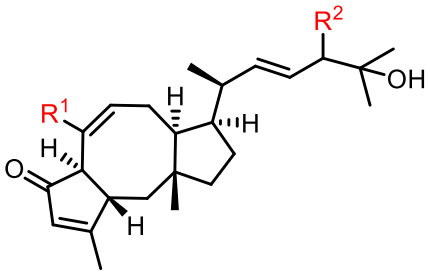
6-epi-ophiobolin N



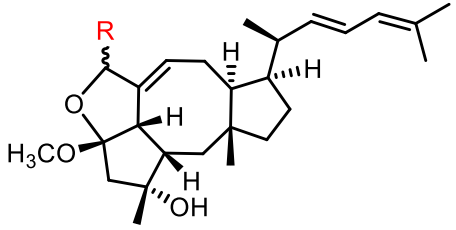
5 α,6 α-ophiobolin H R = OH
5 α,6 α-5-O-methylophiobolin H R = OCH_3



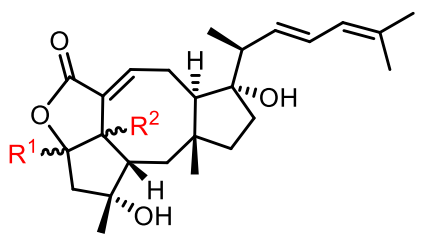
6α,21-deoxyophiobolin G R = CH_3
6α,21,21-dihydroophiobolin G R = CH_2OH



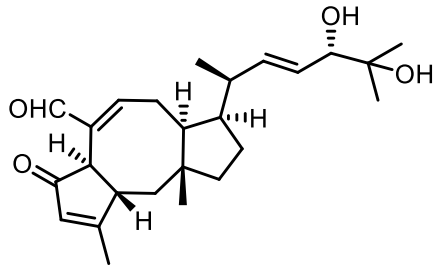
(6α)-18,19,21,21-O-tetrahydro
-18,19-dihydroxyophiobolin G R^1 = CH_2OH, R^2 = OH
ophiobolin R R^1 = CHO , R^2 = OCH_3



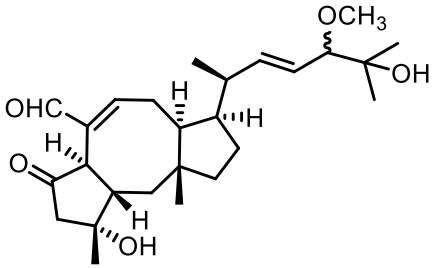
ophiobolin O R = α-OCH_3
21-epi-ophiobolin O R = β-OCH_3



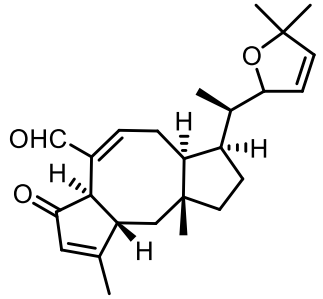
ophiobolin P R^1 = α-OH, R^2 = α-H
ophiobolin X R^1 = β-OH, R^2 = β-H



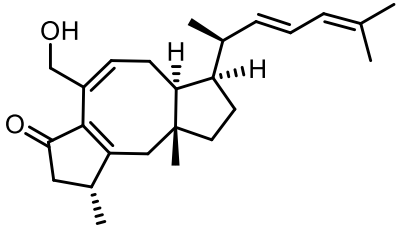
ophiobolin Q



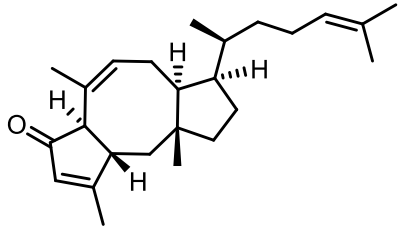
ophiobolin S



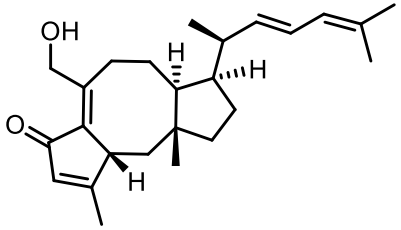
ophiobolin T



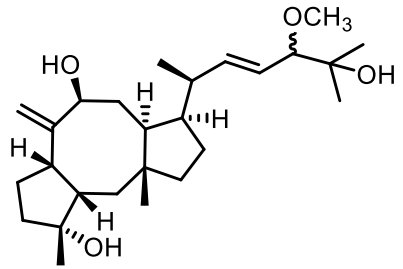
ophiobolin U



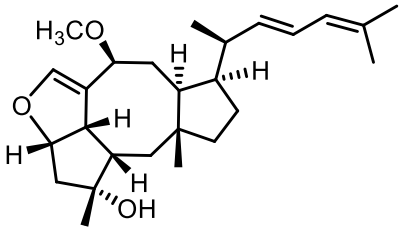
6α,16,17-dihydro-21-deoxyophiobolin G



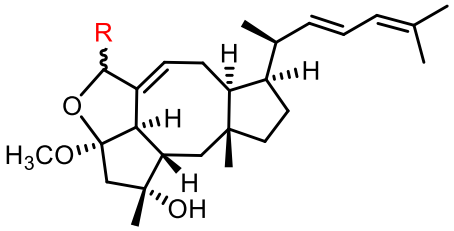
ophiobolin V



ophiobolin W

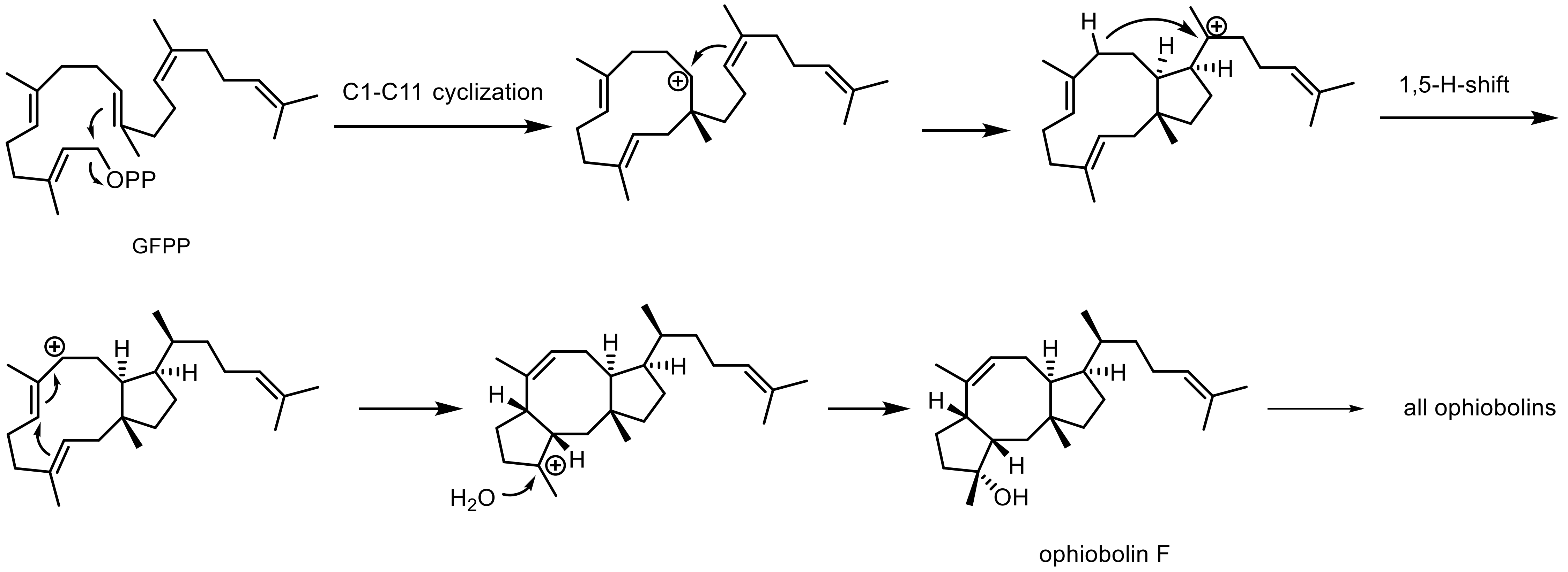


ophiobolin Y



ophiobolin Z R = β-OCH_3
21-epi-ophiobolin Z R = α-OCH_3

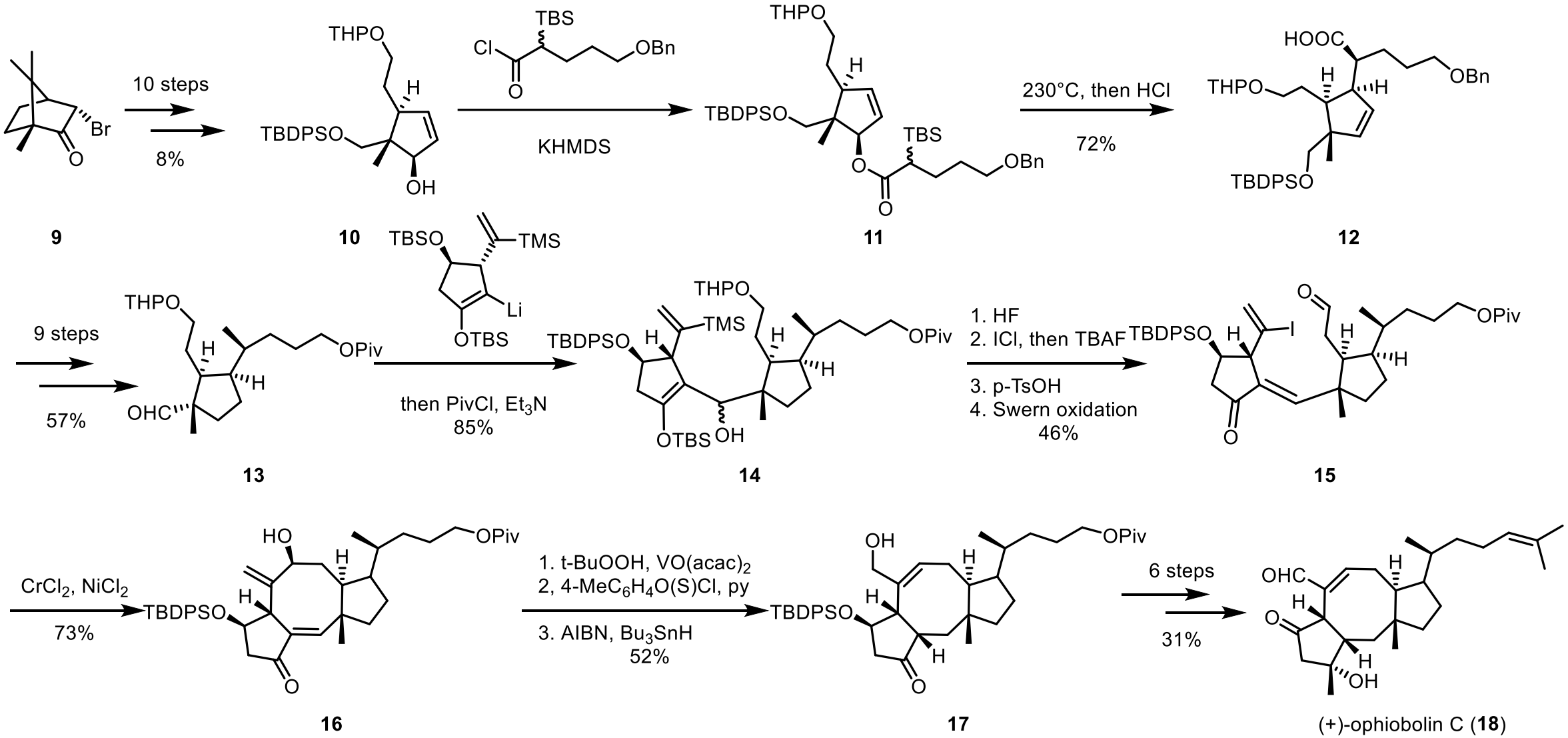
Introduction of Ophiobolins



Proposed biosynthetic pathway of ophiobolins

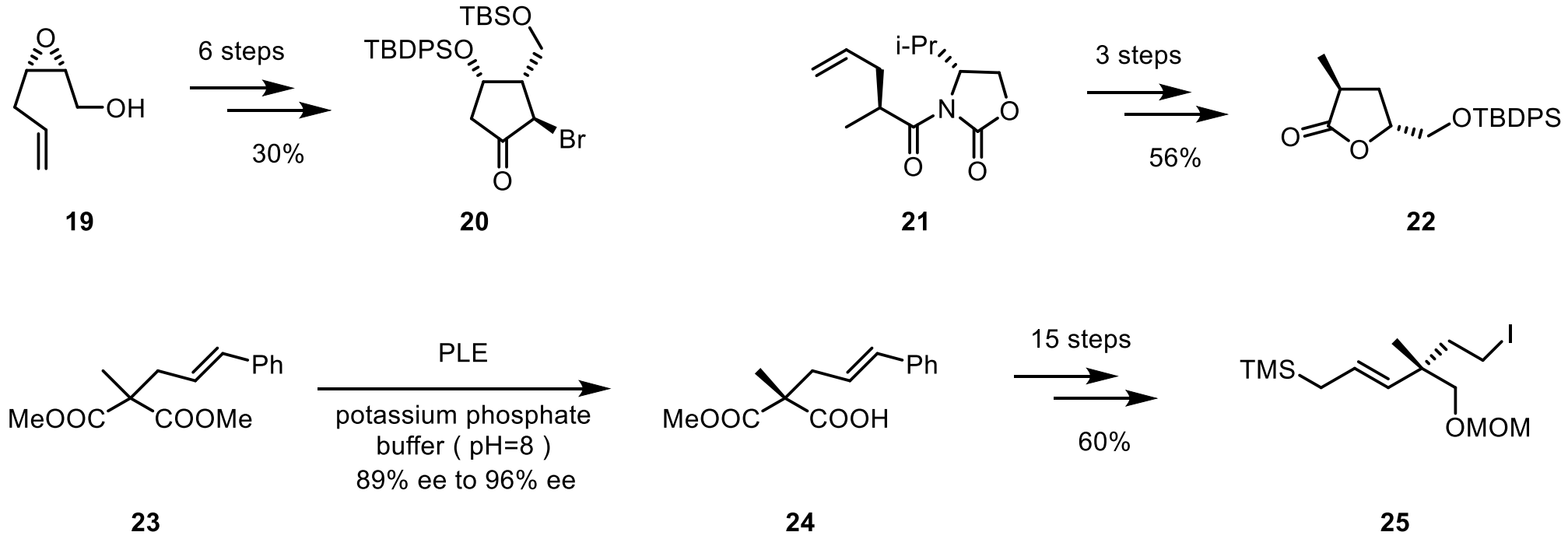
H. Oikawa *et al*, *Org. Lett*. **2013**, *15*, 594–597

Total synthesis of (+)-Ophiobolin C by Kishi

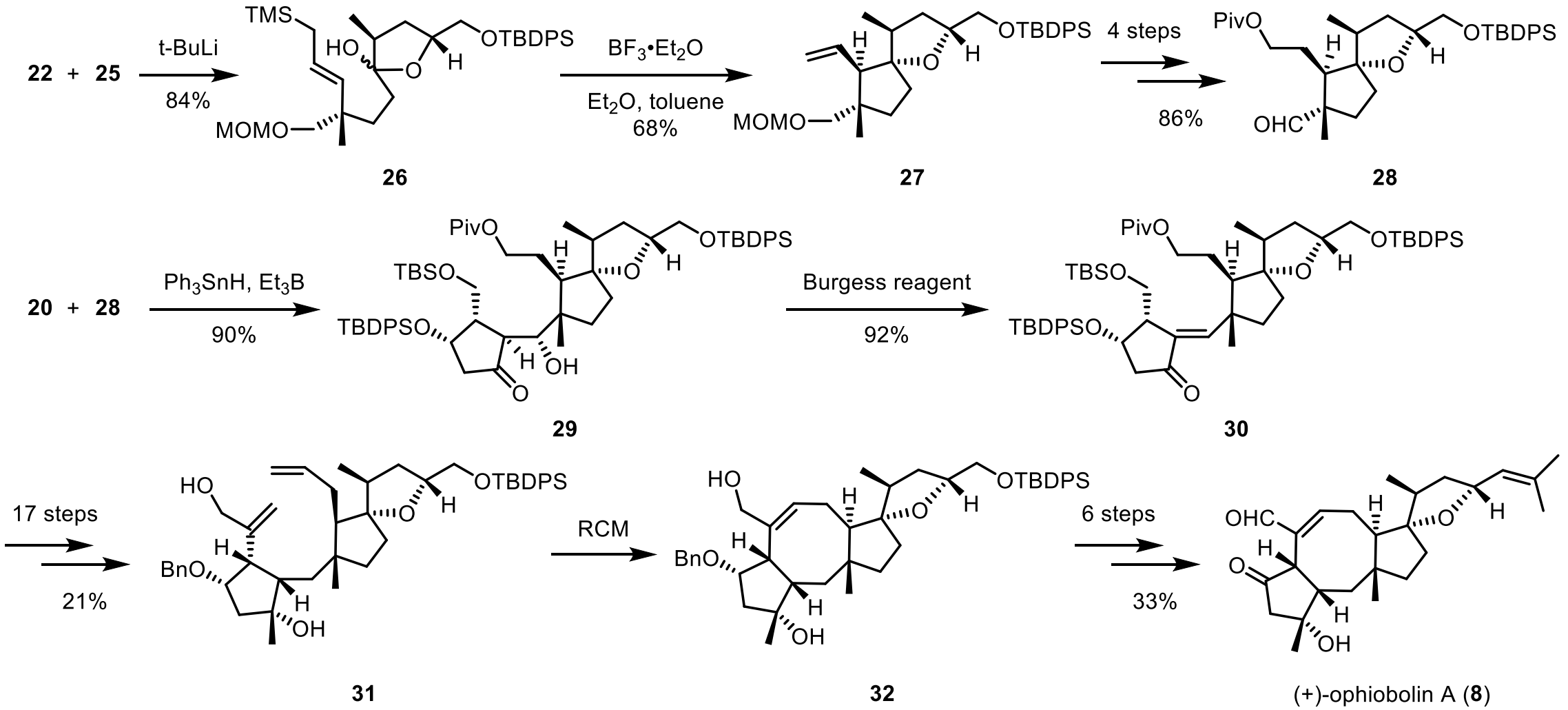


Y. Kishi *et al*, *J. Am. Chem. Soc*. **1989**, *111*, 2735

Total synthesis of (+)-Ophiobolin A by Nakada



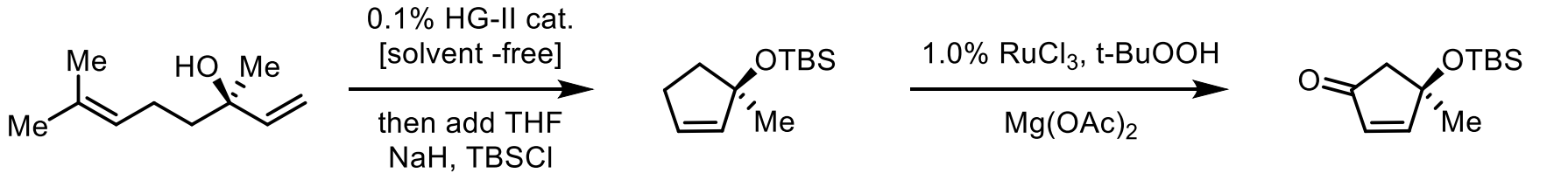
Total synthesis of (+)-Ophiobolin A by Nakada



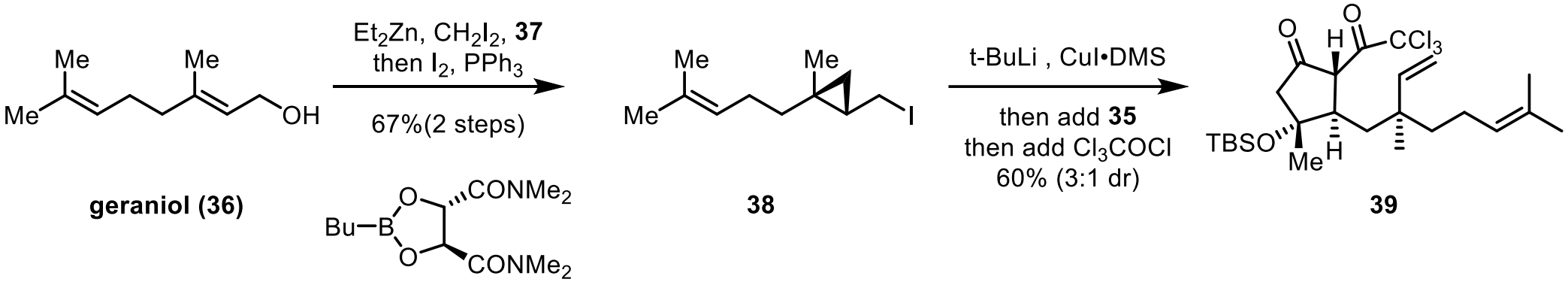
M. Nakada *et al*, *Angew. Chem. Int. Ed*. **2011**, *50*, 9452

M. Nakada *et al*, *Chem. Eur. J*. **2013**, *19*, 5476

Total synthesis of (-)-6-epi-Ophiobolin N by Maimone



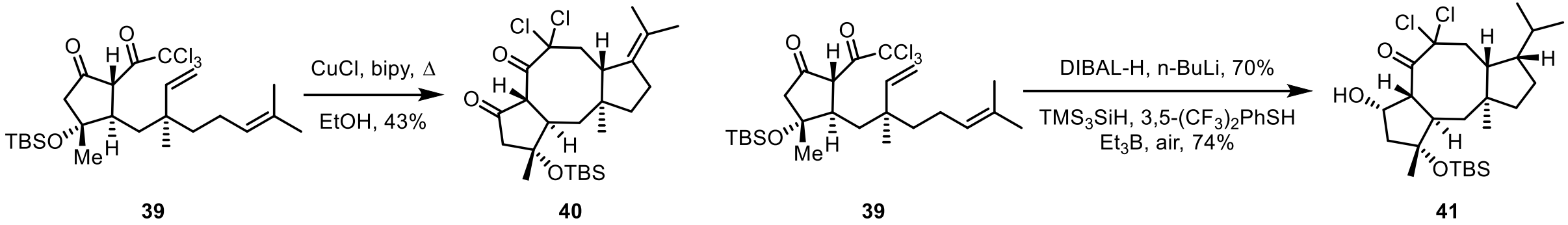
(-)-linalool (**33**) **34** **35** (56% over two-steps)



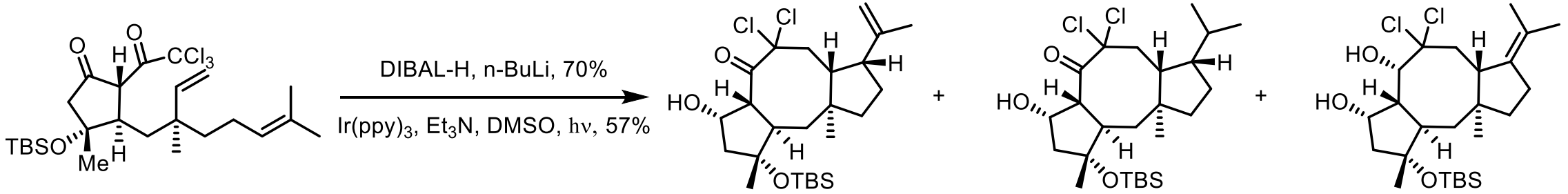
geraniol (36) **38** **39**

37

Total synthesis of (-)-6-epi-Ophiobolin N by Maimone

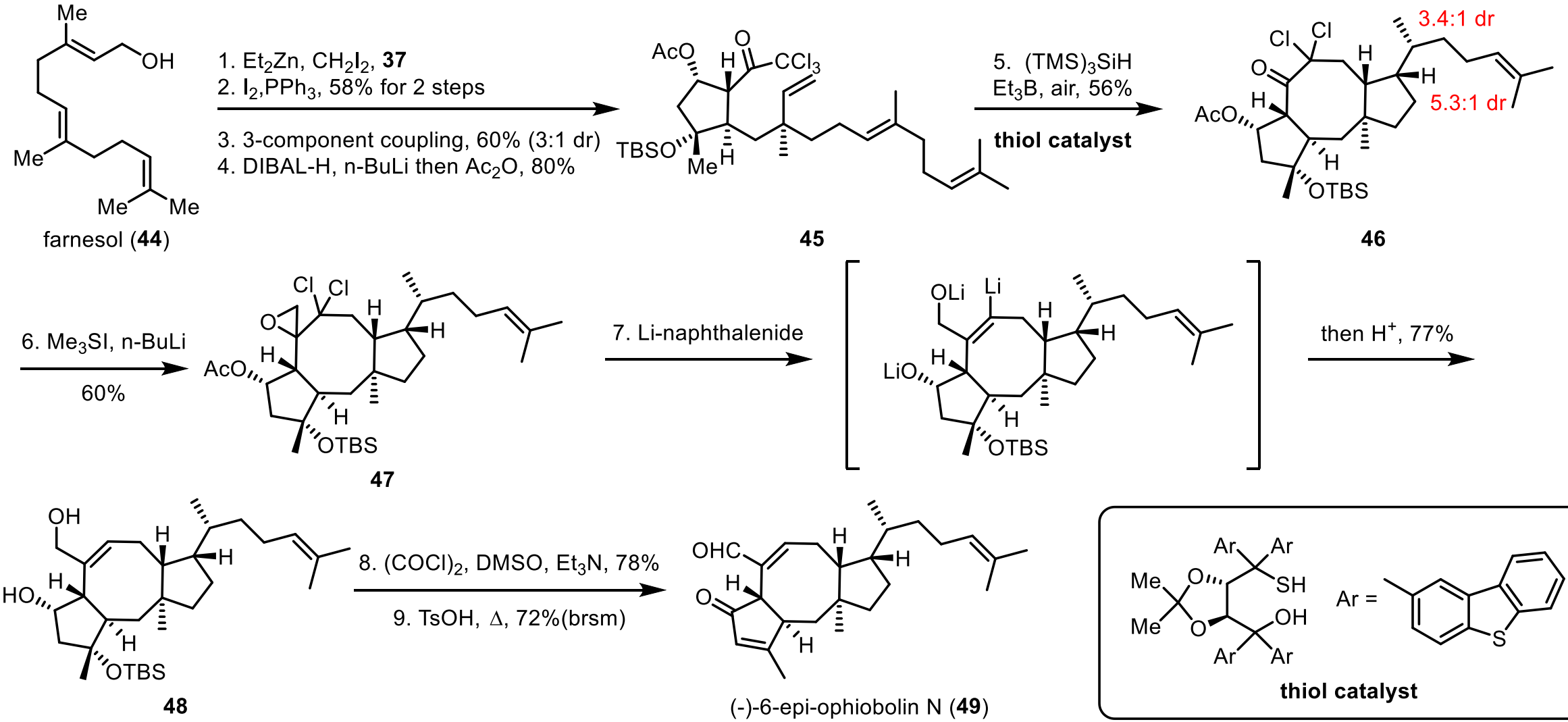


39 **40** **39** **41**



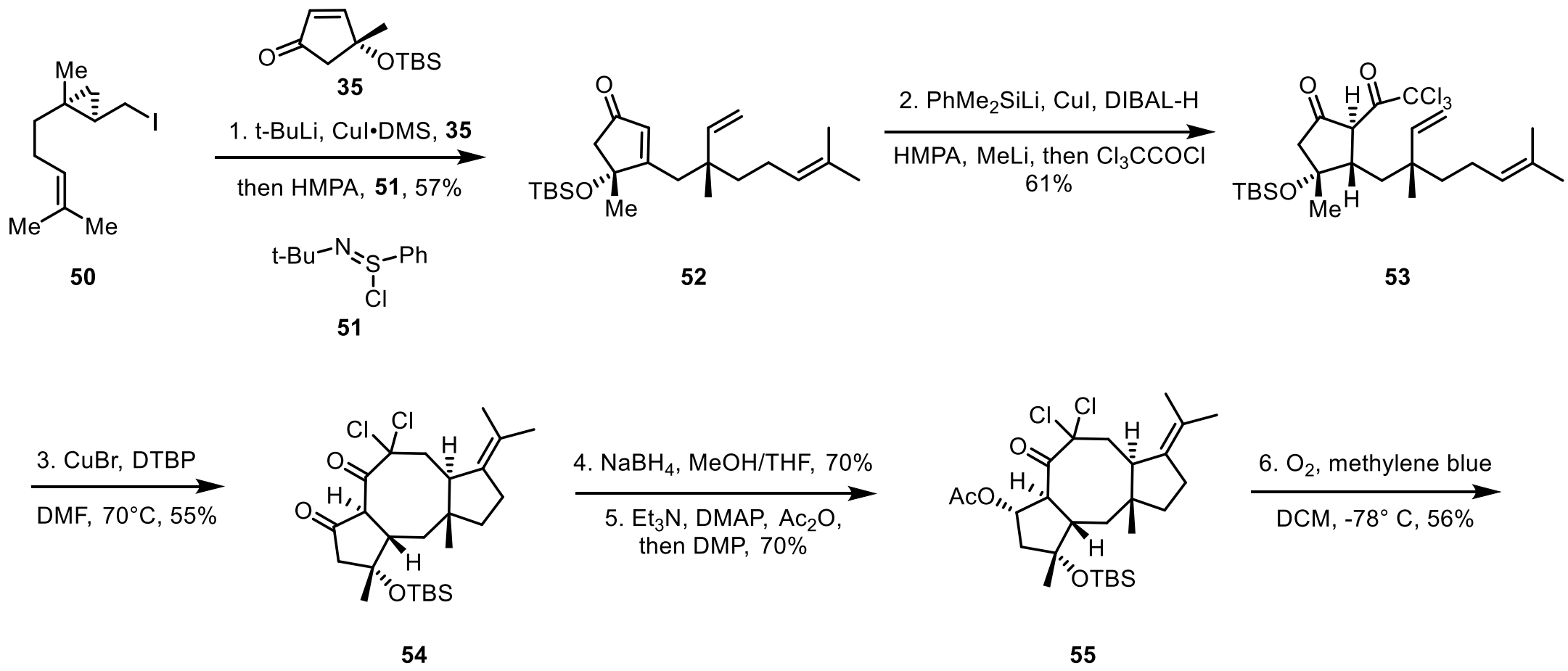
39 **42** **41 (10%)** **43 (15%)**

Total synthesis of (-)-6-epi-Ophiobolin N by Maimone

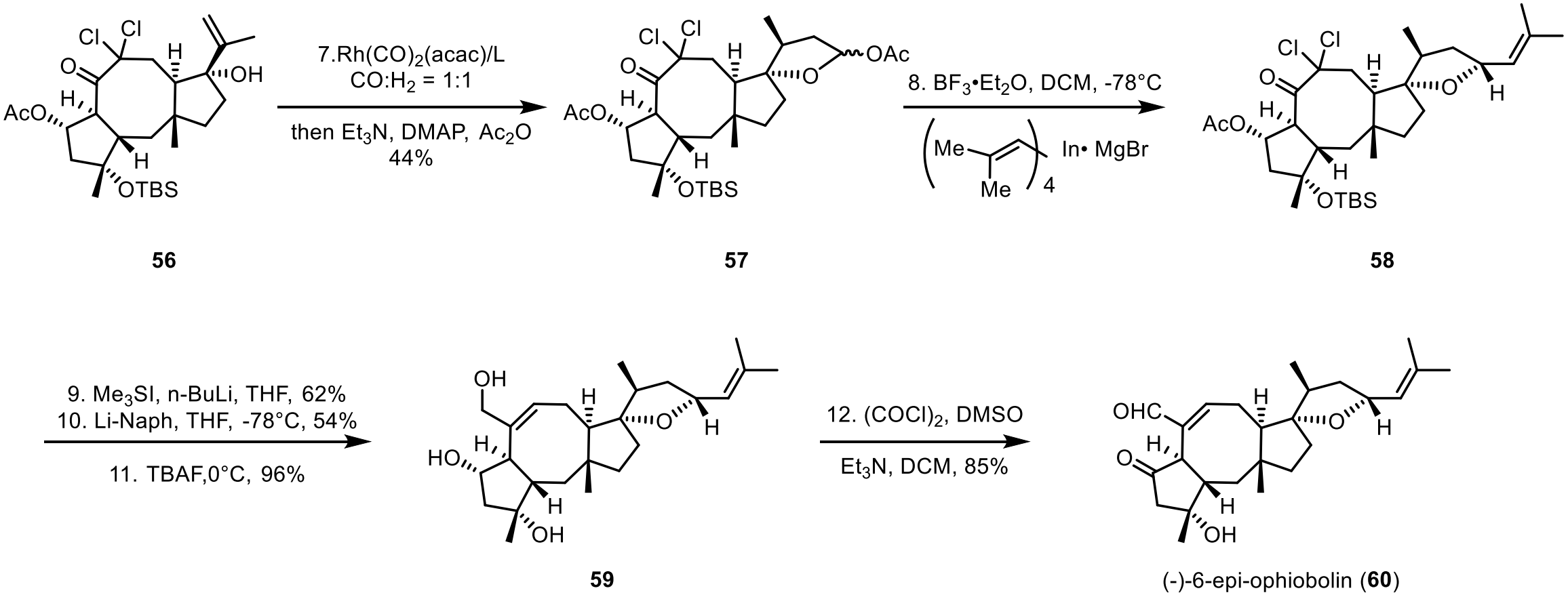


T. J. Maimone *et al*, *Science*, **2016**, *352*, 1078

Total synthesis of (-)-6-epi-Ophiobolin A by Maimone



Total synthesis of (-)-6-epi-Ophiobolin A by Maimone



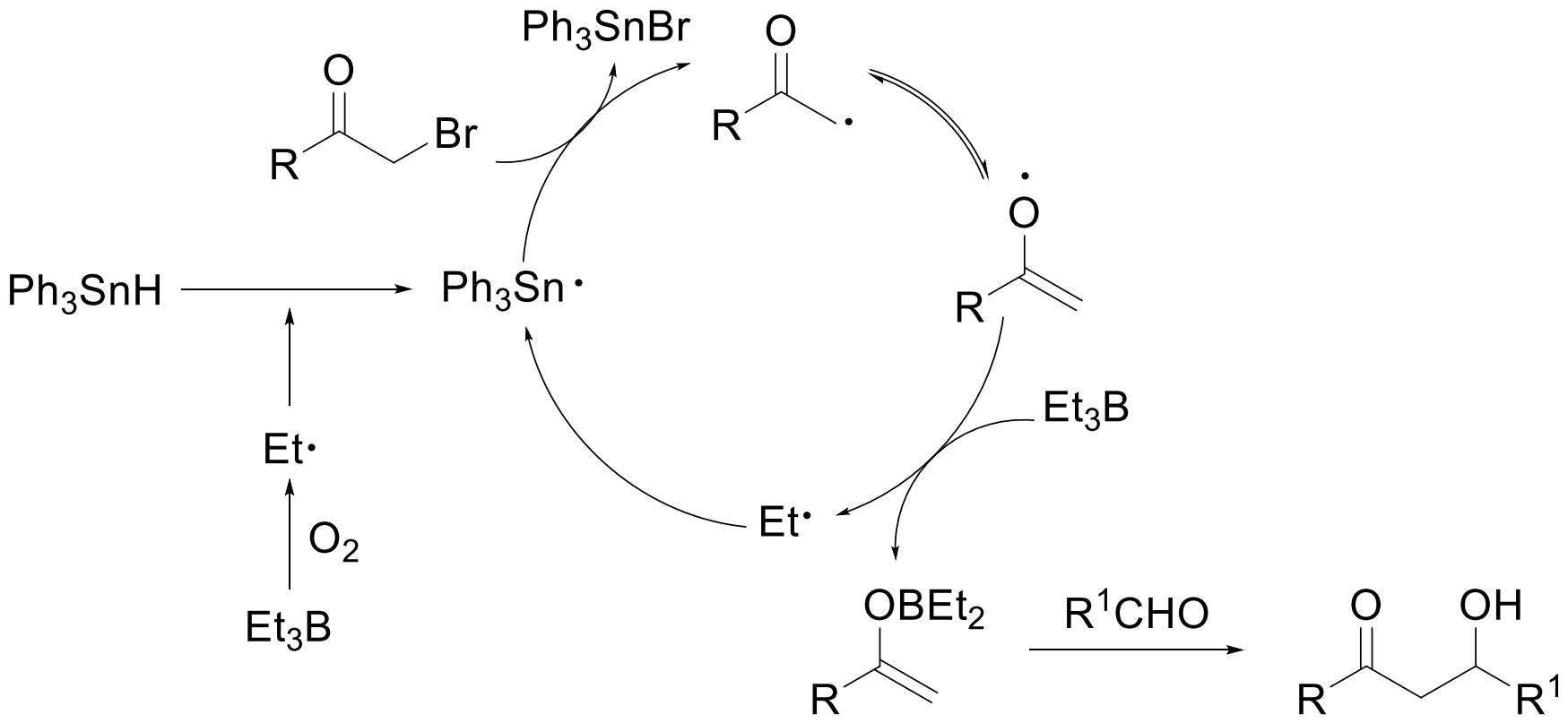
56 **57** **58**

59

(-)-6-epi-ophiobolin (**60**)

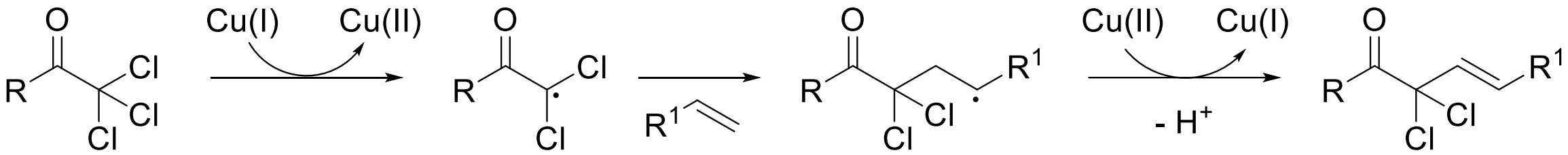
T. J. Maimone *et al*, *Angew.Chem. Int. Ed*. **2020**, *59*, 1532

Et_3B-Mediated Reformatsky type reaction



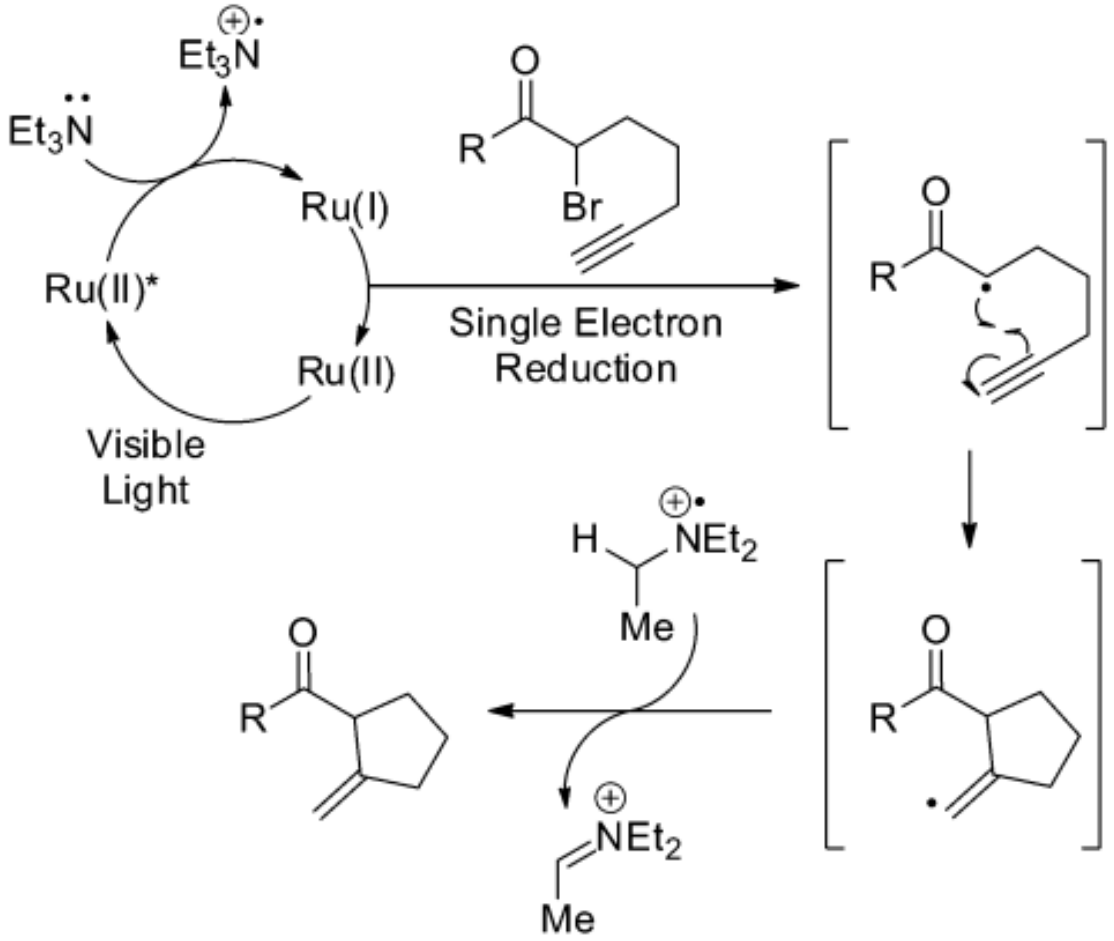
K. Oshima *et al*, *Tetrahedron Lett*, **1988**, *29*, 1041

CuCl/bpy mediated intermolecular ATRA reactions



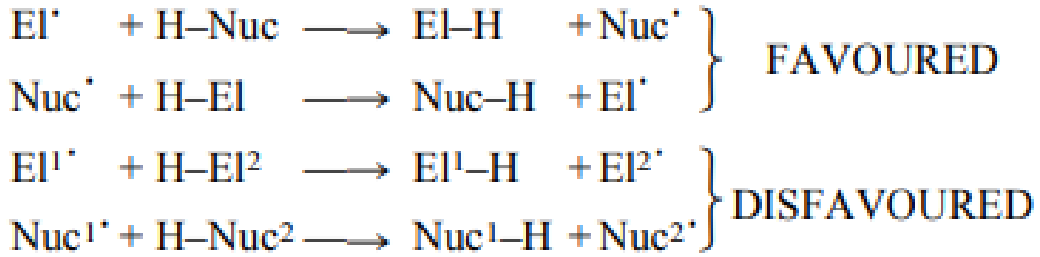
X. D. Hu *et al*, *Tetrahedron*, **2015**, *71*, 2313

Radical cyclization initiated by visible light photoredox catalysis



C. R. J. Stephenson, *Chem. Commun.*, **2010**, *46*, 4985

Mulliken-type electronegativity



Mulliken-type electronegativity

$$\chi_X = (IE_X + EA_X)/2$$

IE : ionisation energy
EA : electron affinity

Radical (X•)	D_{HX}/kJ mol^{-1}	IE^a/eV	EA^a/eV	χ_X/eV	s_X
$NC\dot{C}H_2$	389[b]	10.0[c]	1.54[c]	5.77	2.5
$MeC(O)\dot{C}H_2$	385[d]	8.8[e]	1.86[c]	5.33	
Me•	439[f]	9.84[c]	0.08[c]	4.96	
$Ph\dot{C}H_2$	368[g]	7.20[c]	0.90[c]	4.05	
Et•	421[f]	8.38	−0.39	4.00	
$HO\dot{C}H_2$	393[b]	7.56[c]	−0.38[h]	3.59	
Pr^{i}•	411[f]	7.57	−0.48	3.55	
c-C_6H_{11}•	400[g]	7.21[i]	−0.48[j]	3.37	
c-C_3H_9•	400[g]	7.21[c]	−0.48[j]	3.37	
Bu^{t}•	402[f]	6.93	−0.30	3.32	
$Bu^tO\dot{C}H_2$	389[k]	6.94[l]	−0.38[m]	3.28	
$MeO\dot{C}H_2$	389[b]	6.94[c]	−0.38[m]	3.28	
$O[CH_2]_3\dot{C}H$	385[b]	—	—	3.28[l]	
F_3C•	446[b]	9.25	1.8	5.53	0.0
Cl_3C•	401[b]	8.78	1.90	5.34	0.7
Cl_3Si•	382[b]	7.92	2.50	5.21	2.2
Me_3Sn•	310[g]	7.10[c]	0.97[n]	4.04	
Bu_3Sn•	310[o]	7.10[p]	0.97[n]	4.04	
Me_3Si•	388[q]	6.81[r]	0.97[s]	3.89	
Et_3Si•	388[q]	6.81[m]	0.97[n]	3.89	
H_2N•	449[g]	11.40	0.74	6.07	0.5
HO•	499[g]	13.17	1.83	7.50	0.6
Bu^{t}O•	440[b]	11.9[t]	1.91[c]	6.91	
MeO•	440[b]	11.9[e]	1.62[c]	6.76	
PhO•	356[u]	8.85	2.35	5.60	
PhS•	343[g]	8.63	2.47	5.55	
F•	570[g]	17.42	3.40	10.41	0.0
Cl•	431[g]	13.01	3.62	8.32	
Br•	366[g]	11.84	3.36	7.60	
H•	436[g]	13.59	0.74	7.17	

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