Total Synthesis of Jerangolid D

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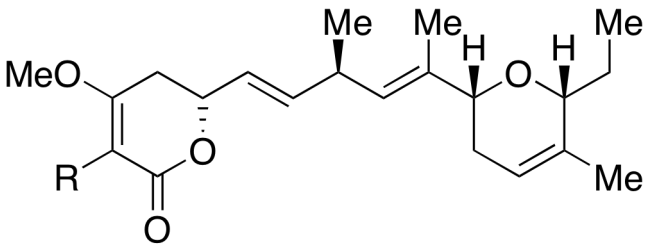
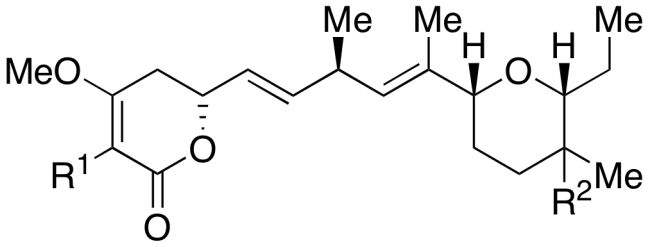
JACS ASAP

Jerangolid



Jerangolid A; R = CH_2OH
Jerangolid D; R = CH_3

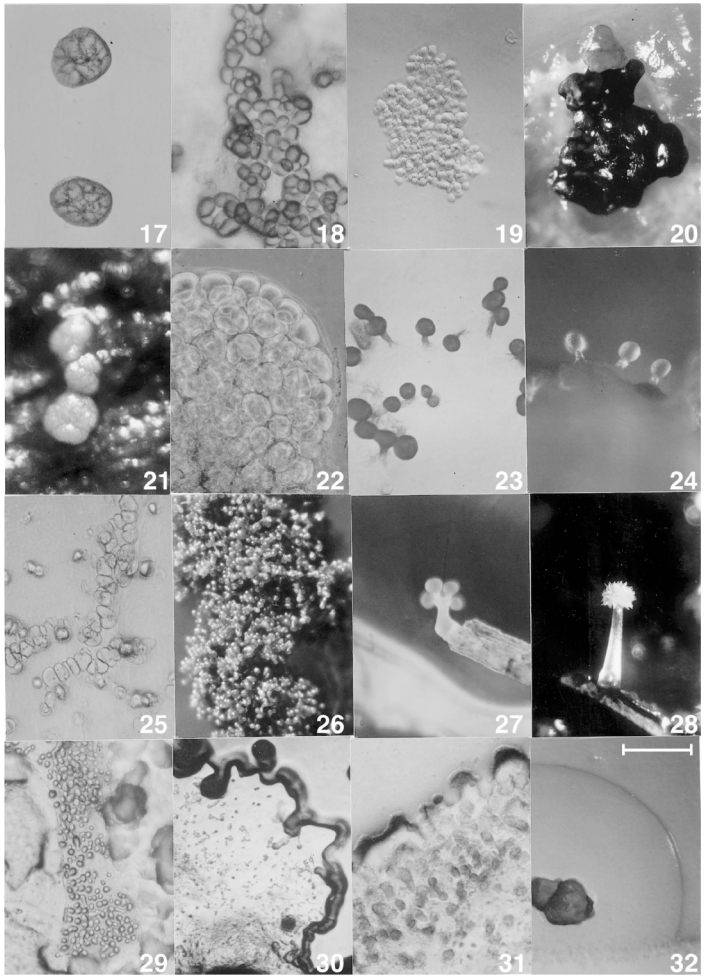


Jerangolid B; $R^1 = CH_3$, $R^2 = OH$
Jerangolid E; $R^1 = CH_3$, $R^2 = H$
Jerangolid H; $R^1 = CH_2OH$, $R^2 = H$

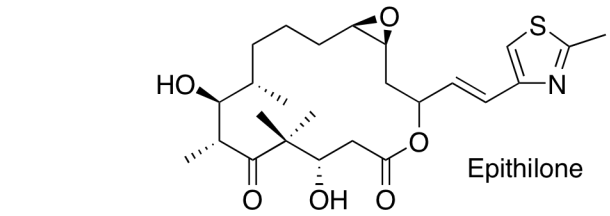
- Isolated from myxobacterium *Sorangium cellulosum*
- Anti-fungal agents activity against *Hansenula anolmala and Mucor hiemalis* (70 ng/mL); *Pichia membranaefaciens, Debaryomyces hansenii, Trichosoron terrestre* (0.1-0.4 μg/mL), and *Trichoderma hamata, Botritis cinerea*, and *Candida albicans* (4-7 μg/mL)
- Mechanism of action unknown

Gerth, K.; Washausen, P.; Hofle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1996**, *49*, 71-75.

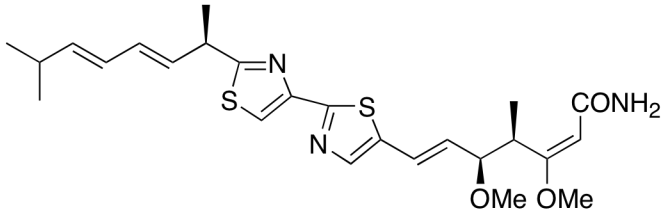
Myxobacteria



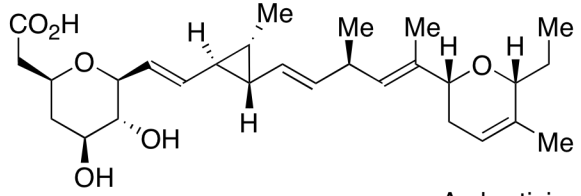
- Unicellular rod-shaped bacteria
- Found in soil
- Move by gliding
- Synthesize a large number of biologically active secondary metabolites



Epithilone



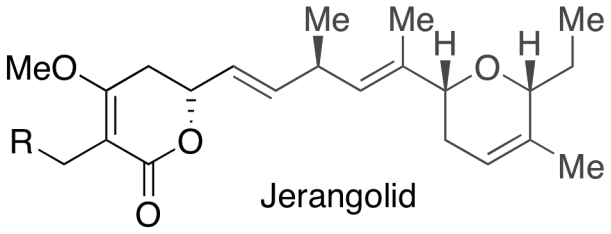
Myxothiazol

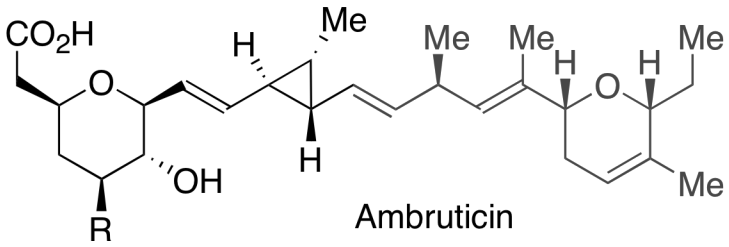


Ambruticin

Dawid, W.; *FEMS Microbiology Rev.* **2000**, *24*, 403-427.

Ambruticin/Jerangolid

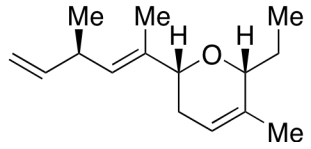




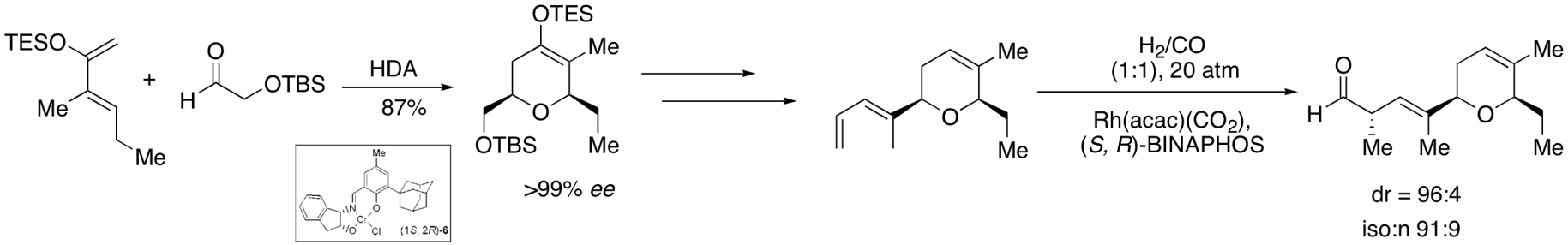
- Activity of Ambruticin and Jerangolid are similar
- Mode of action- affects the osmoregulation system of susceptible fungi
- Increase the amount of glycerol and accumulation of fatty acids, cells starts leaking results in cell death.

Genet, J-P.; Michelet, V. *Curr. Org. Chem.* **2005**, *9*, 405-418.

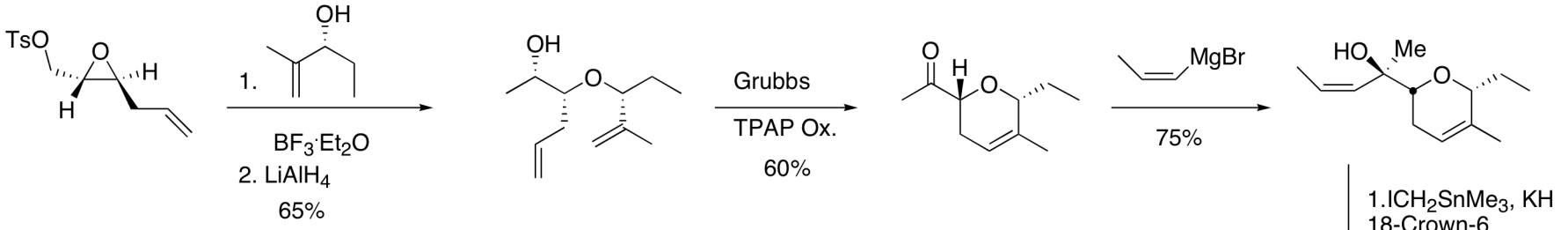
Previous synthesis of Abruticin-eastern fragment



Kende, 1990: Hetero-Diels Alder/Ireland-Claisen
Jacobsen 2001:



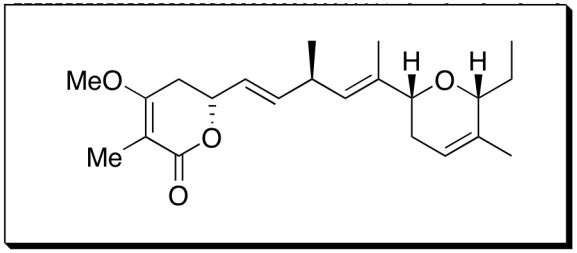
Martin, 2001:

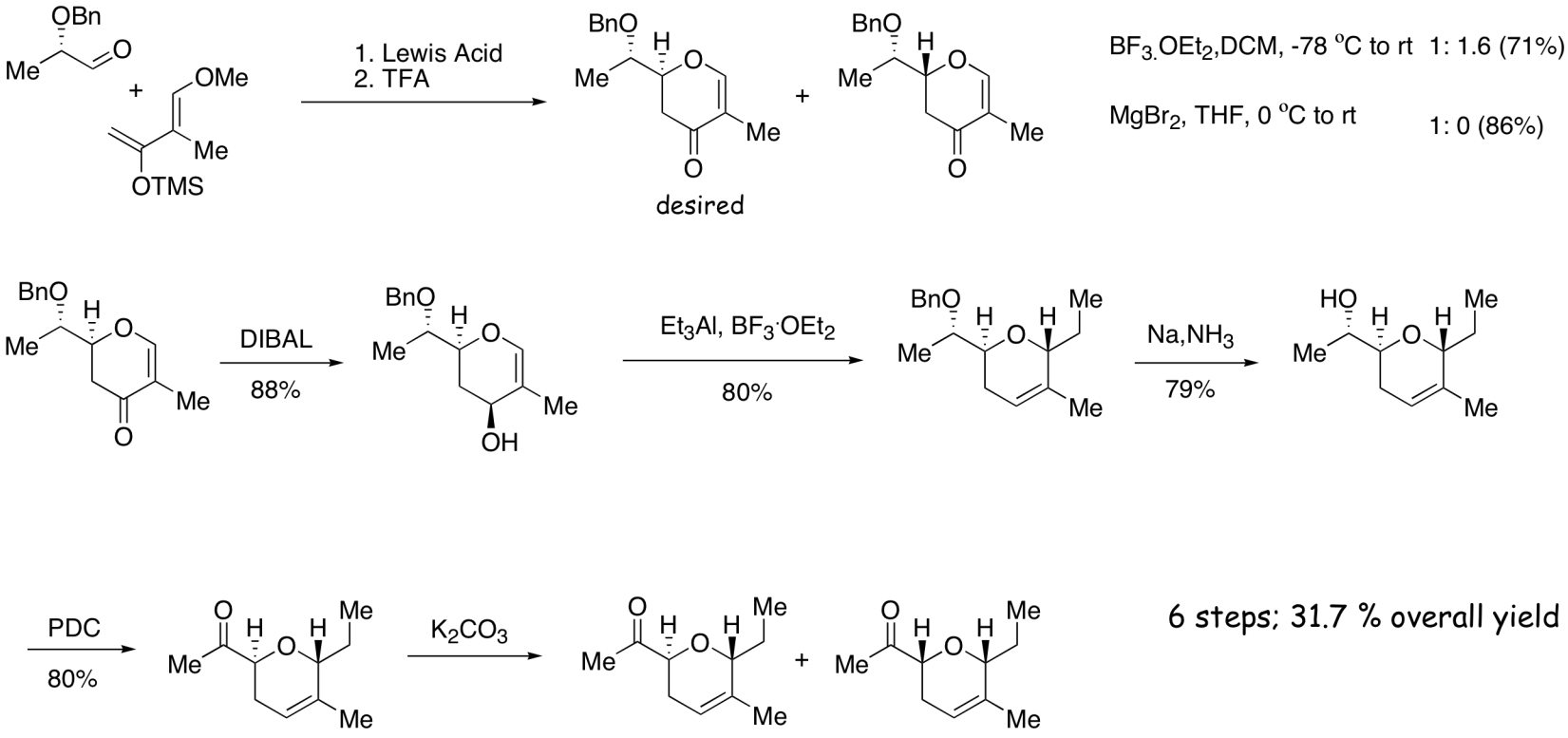


Lee, 2002: Auxiliary/Metathesis

Kende *et al. J. Am. Chem. Soc.* **1990**, *112*, 9645.;Jacobsen, E.; Liu, P. *J. Am. Chem. Soc.* **2001**, *123*, 10772; Martin, S *et al. Tetrahedron* **2003**, *59*, 6819.; Lee et al. *Angew. Chem. Int. Ed.* **2002**, *41*, 176.

Donaldson-Dihydropyran

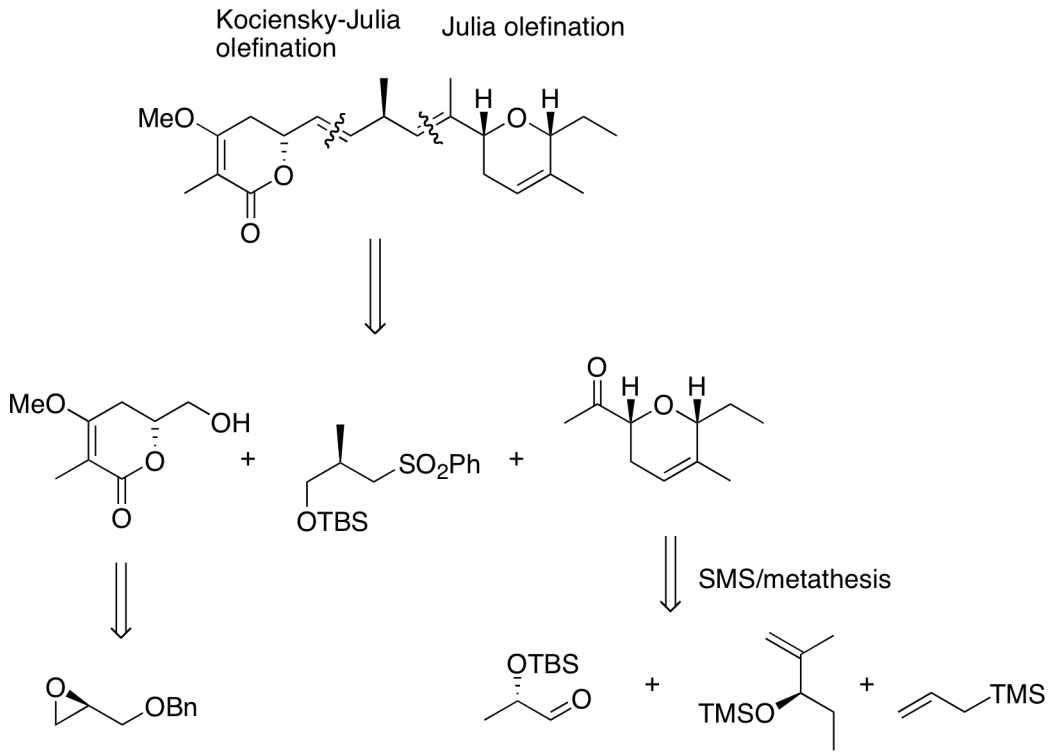


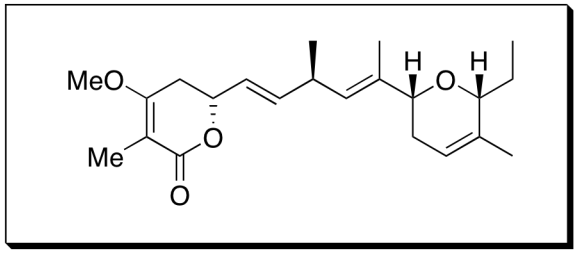


6 steps; 31.7 % overall yield

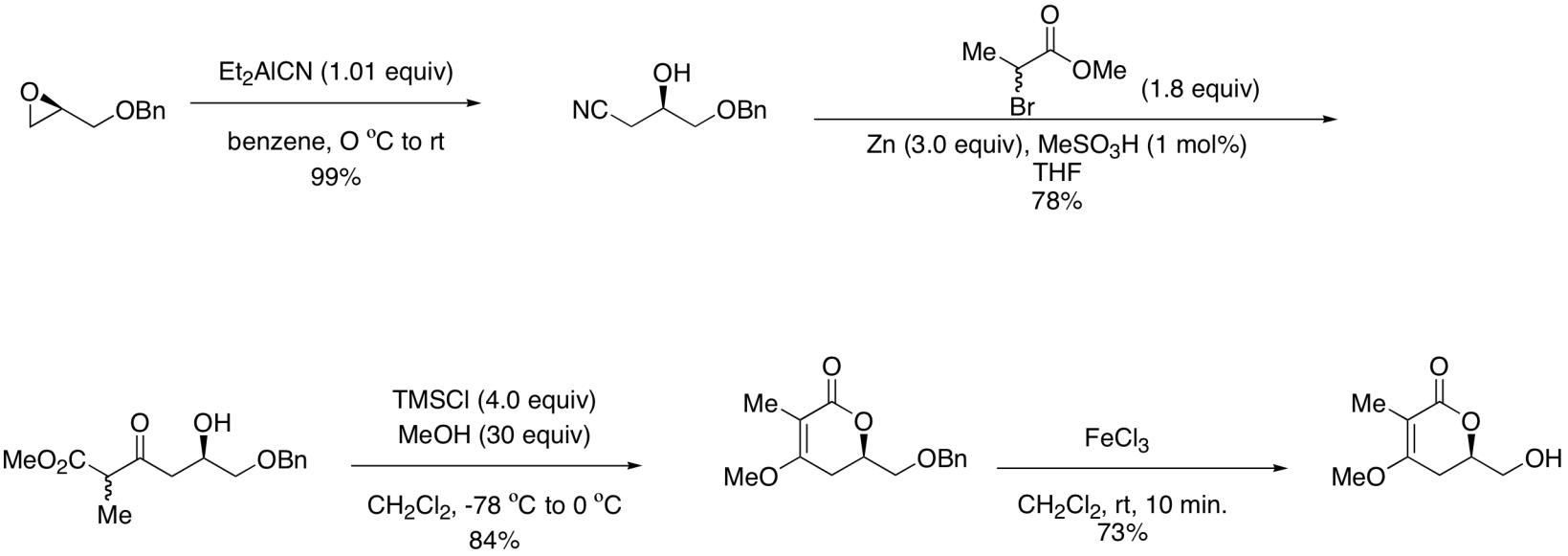
Donaldson, W. A.; Lukesh, J. M. *Tetrahedron Lett.* **2005**, *46*, 5529-5531.

Retrosynthesis:

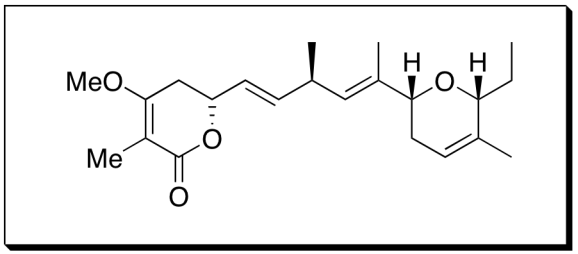


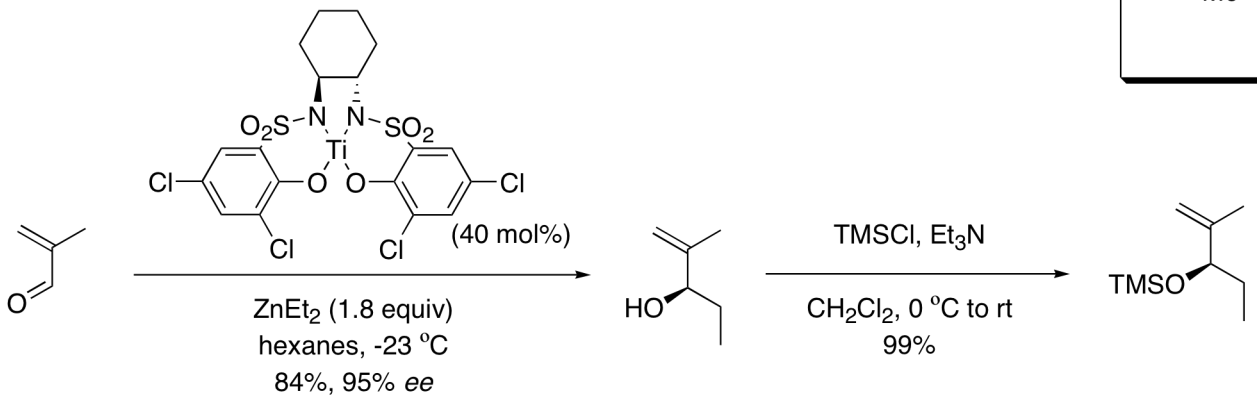


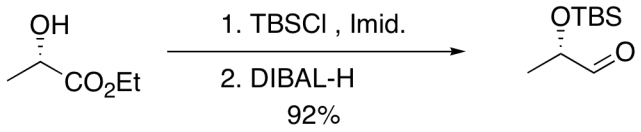
Lactone:

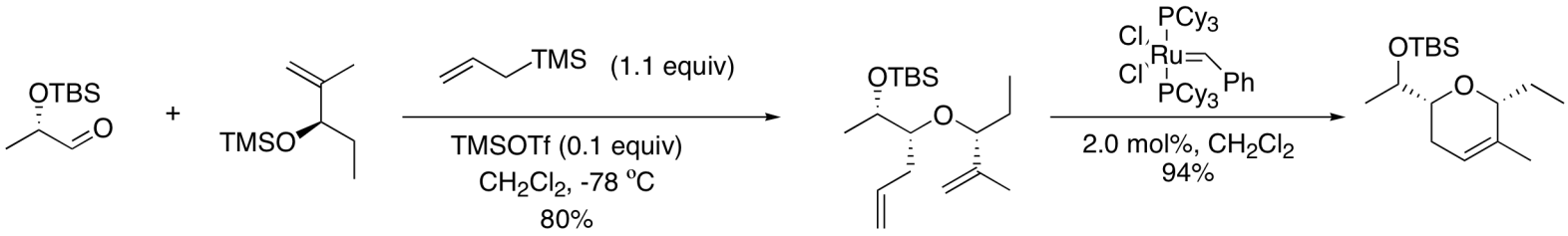

Et2AlCN (1.01 equiv)
benzene, O °C to rt
99%
(1.8 equiv)
Zn (3.0 equiv), MeSO3H (1 mol%)
THF
78%
TMSCl (4.0 equiv)
MeOH (30 equiv)
CH2Cl2, -78 °C to 0 °C
84%
FeCl3
CH2Cl2, rt, 10 min.
73%

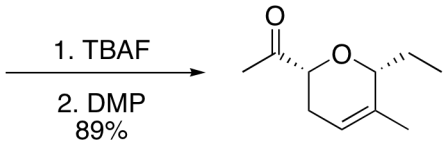
Pyran:


MeO
Me
O
O
H
O
H


O2S
N
N
SO2
Ti
Cl
O
O
Cl
Cl
Cl
(40 mol%)
O
ZnEt2 (1.8 equiv)
hexanes, -23 °C
84%, 95% ee
HO
TMSCl, Et3N
CH2Cl2, 0 °C to rt
99%
TMSO

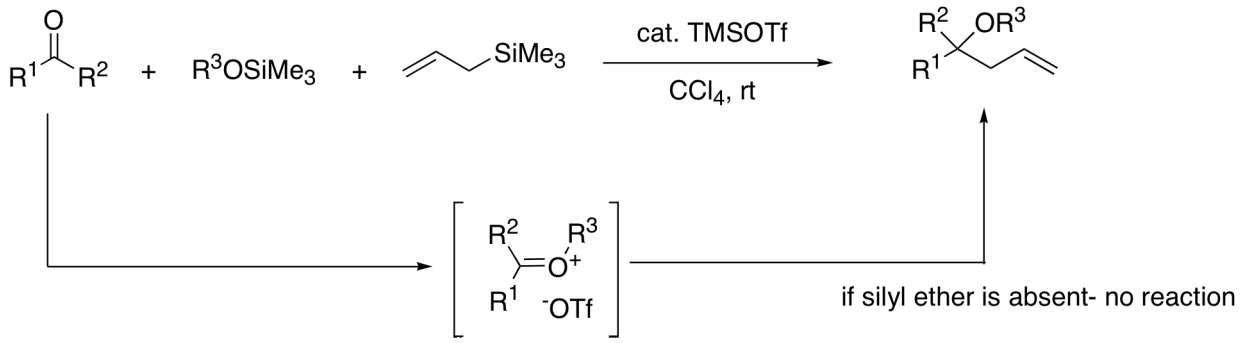

OH
CO2Et
1. TBSCl , Imid.
2. DIBAL-H
92%
OTBS
O


OTBS
O
+
TMSO
TMS
(1.1 equiv)
TMSOTf (0.1 equiv)
CH2Cl2, -78 °C
80%
OTBS
O
PCy3
Cl
Ru
Cl
Ph
PCy3
2.0 mol%, CH2Cl2
94%
OTBS
O

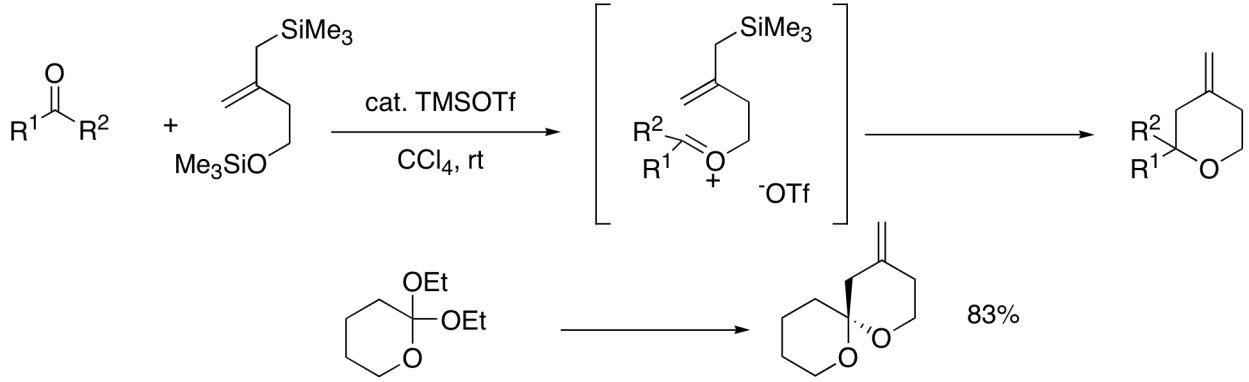

1. TBAF
2. DMP
89%
O
O

Silyl modified Sakurai

-1990

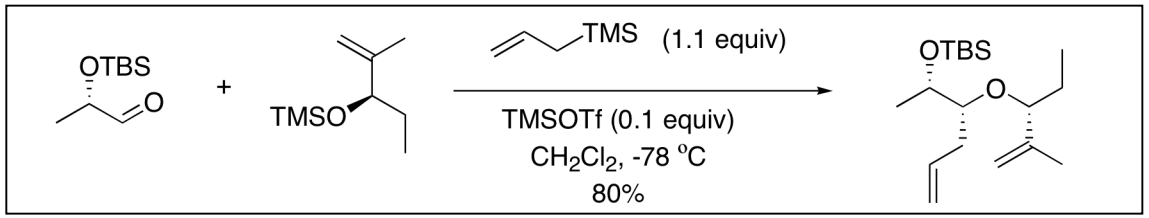


-1991: Intramolecular



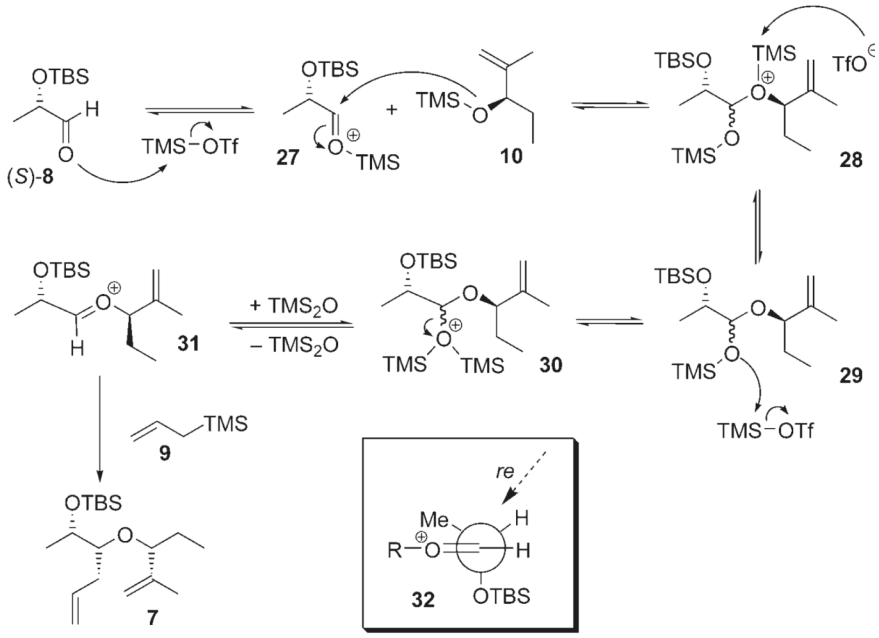
Marko, I.; Mekhalfia, A. *Tetrahedron Lett.* **1991**, *32*(36), 4779-4782.
Marko, I.; Mekhalfia, A.; Adams, H. *Tetrahedron Lett.* **1991**, *32*(36), 4779-4782.

Sakurai AMCR

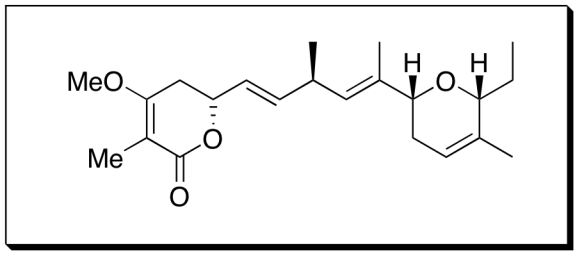


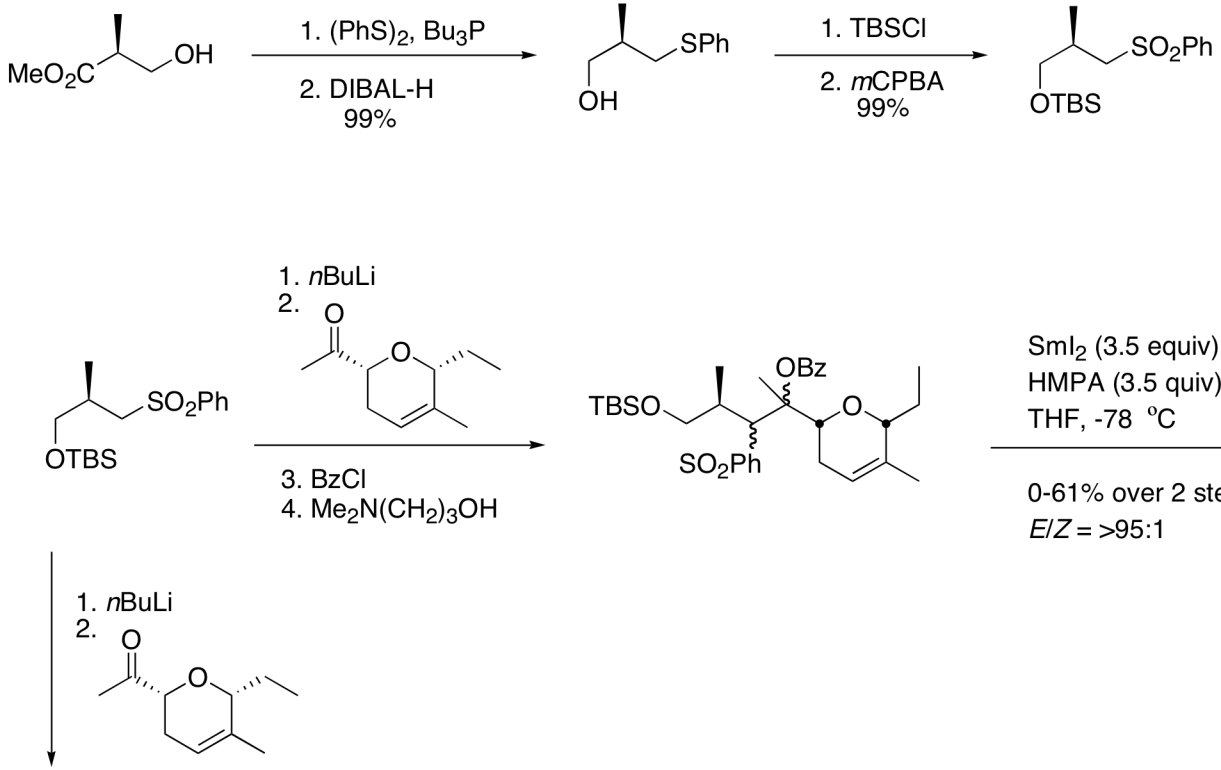
Entry	Aldehyde	Silyl ether	Product	Yield[a] [%]
1	OTBDPS, CHO, (*S*)-**8**	OTMS, (*R*)-**10**	OTBDPS, O, (2*S*,3*R*,5*R*)-**7**	81
2	OTBDPS, CHO, (*S*)-**8**	OTMS, (*S*)-**10**	OTBDPS, O, (2*S*,3*R*,5*S*)-**7**	82
3	OTBDPS, CHO, (*R*)-**8**	OTMS, (*R*)-**10**	OTBDPS, O, (2*R*,3*S*,5*R*)-**7**	75
4	OTBDPS, CHO, (*R*)-**8**	OTMS, (*S*)-**10**	OTBDPS, O, (2*R*,3*S*,5*S*)-**7**	76

[a] Yields of the isolated products.

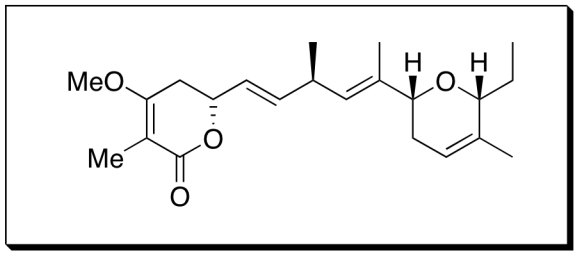


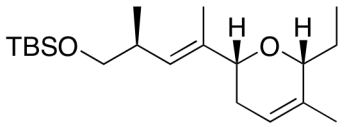
Scheme 4. Proposed reaction mechanism for the Sakurai MCR.


MeO
Me
O
O
H
O
H

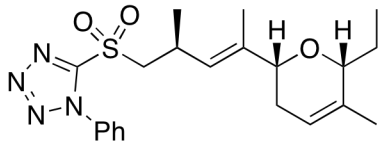

MeO2C
OH
1. (PhS)2, Bu3P
2. DIBAL-H
99%
SPh
OH
1. TBSCl
2. mCPBA
99%
SO2Ph
OTBS
1. nBuLi
2.
O
O
SO2Ph
OTBS
3. BzCl
4. Me2N(CH2)3OH
OBz
TBSO
SO2Ph
SmI2 (3.5 equiv)
HMPA (3.5 quiv)
THF, -78 °C
0-61% over 2 steps
E/Z = >95:1
TBSO
H
O
H
1. nBuLi
2.
O
O
OH
TBSO
PhO2S
Bz2O (3.0 equiv)
Sc(OTf)3 (10 mol%)
OBz
TBSO
SO2Ph
SmI2 (3.5 equiv)
HMPA (3.5 quiv)
THF, -78 °C
52-67% over 3 steps
E/Z = >95:1
TBSO
H
O
H

Putting it all together:

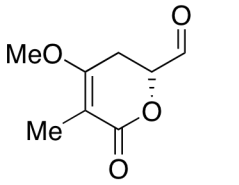


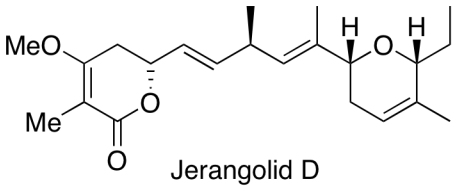


1. TBAF
2. PT-SH (1.2 equiv), PPh_3, DIAD
then 30% H_2O_2
$(NH_4)_6Mo_7O_{24}.H_2O$(0.2 equiv), EtOH
0 °C to rt
72% over 2 steps



KHMDS,

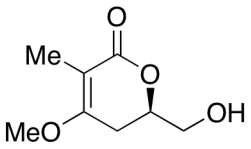




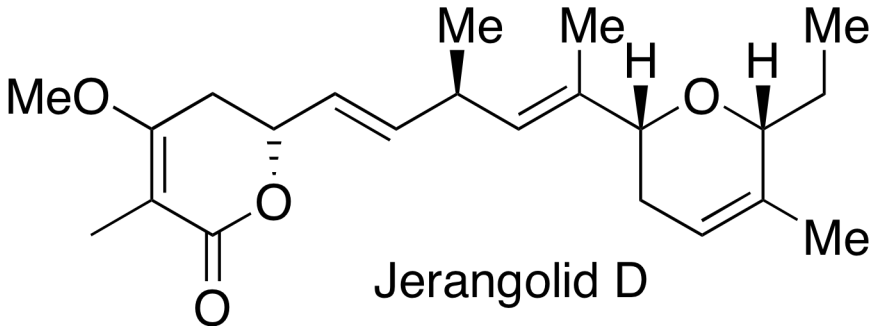
Jerangolid D

54% *E*/*Z* = >95:1

Oxalyl chloride,
DMSO, Et_3N



Summary



Jerangolid D

- First total synthesis of Jerangolid in 22 steps in 6.1% overall yield.
- Utilized the silyl modified sakurai reaction
- Synthesis of analogues and other members of the Jerangolid family