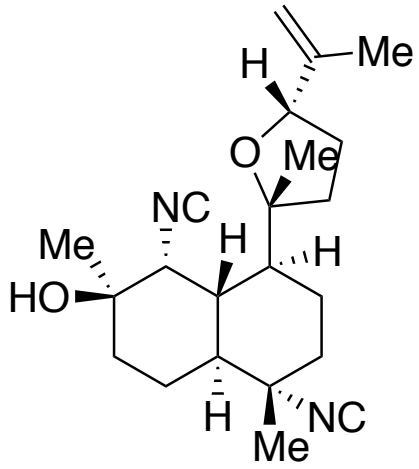
Stereocontrolled Synthesis of Kalihinol C

Christopher A. Reiher and Ryan A. Shenvi
JACS. **2017**, 3647

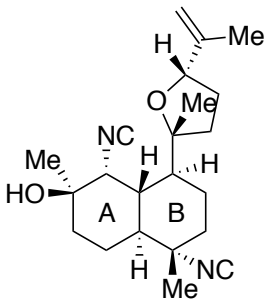


Kalihinol C

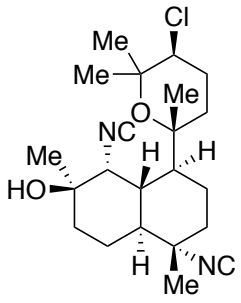
Ruiting Liu
Wipf Group Current Literature
04/15/2016

Kalihinol C

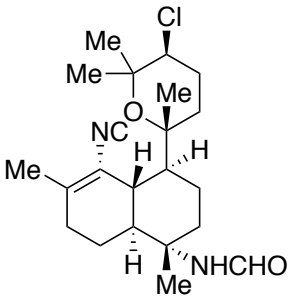
- Kalihinol C, isolated from the sponge *Acanthella* sp., is a member of marine diterpenoids known as the kalihinanes
- Kalihinol A exhibits the highest reported potency of the ICTs against Plasmodium falciparum
- Antimalarial activity of kalihinol C not known



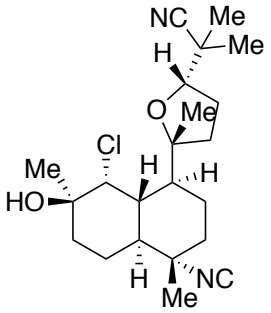
Kalihinol C



Kalihinol A
FCR-3 :1.2 nM



Kalihineno Y

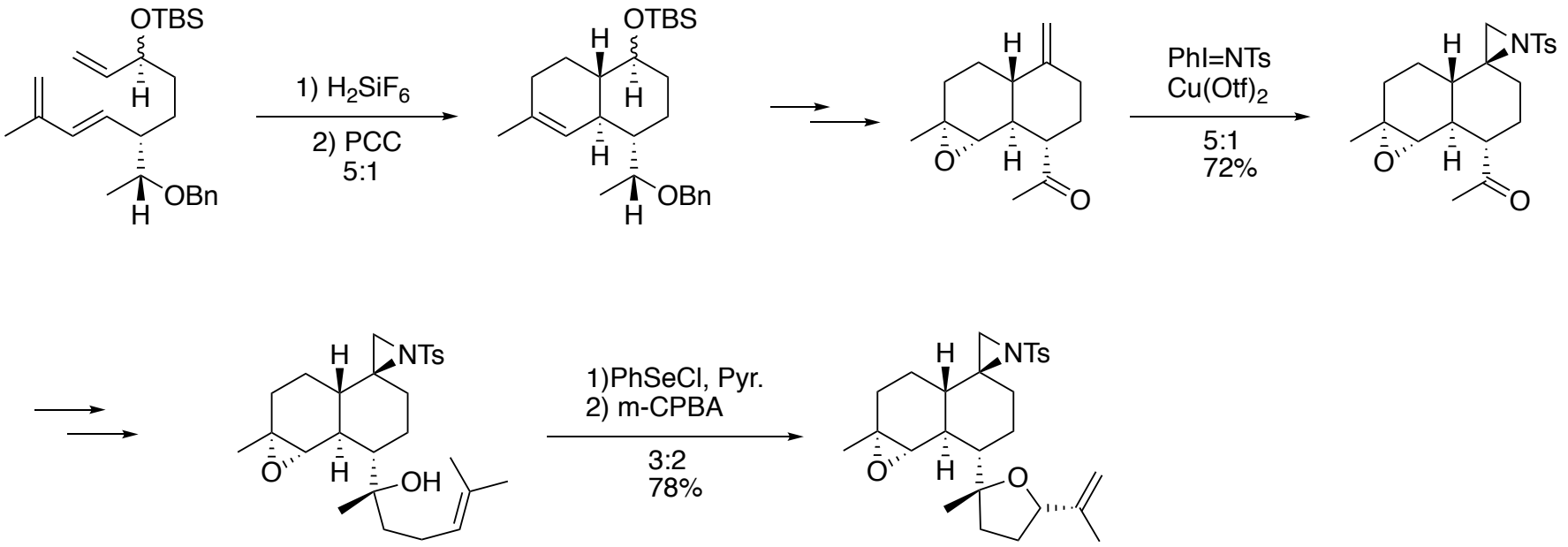


Kalihinol D

Structurally related Kalihinols

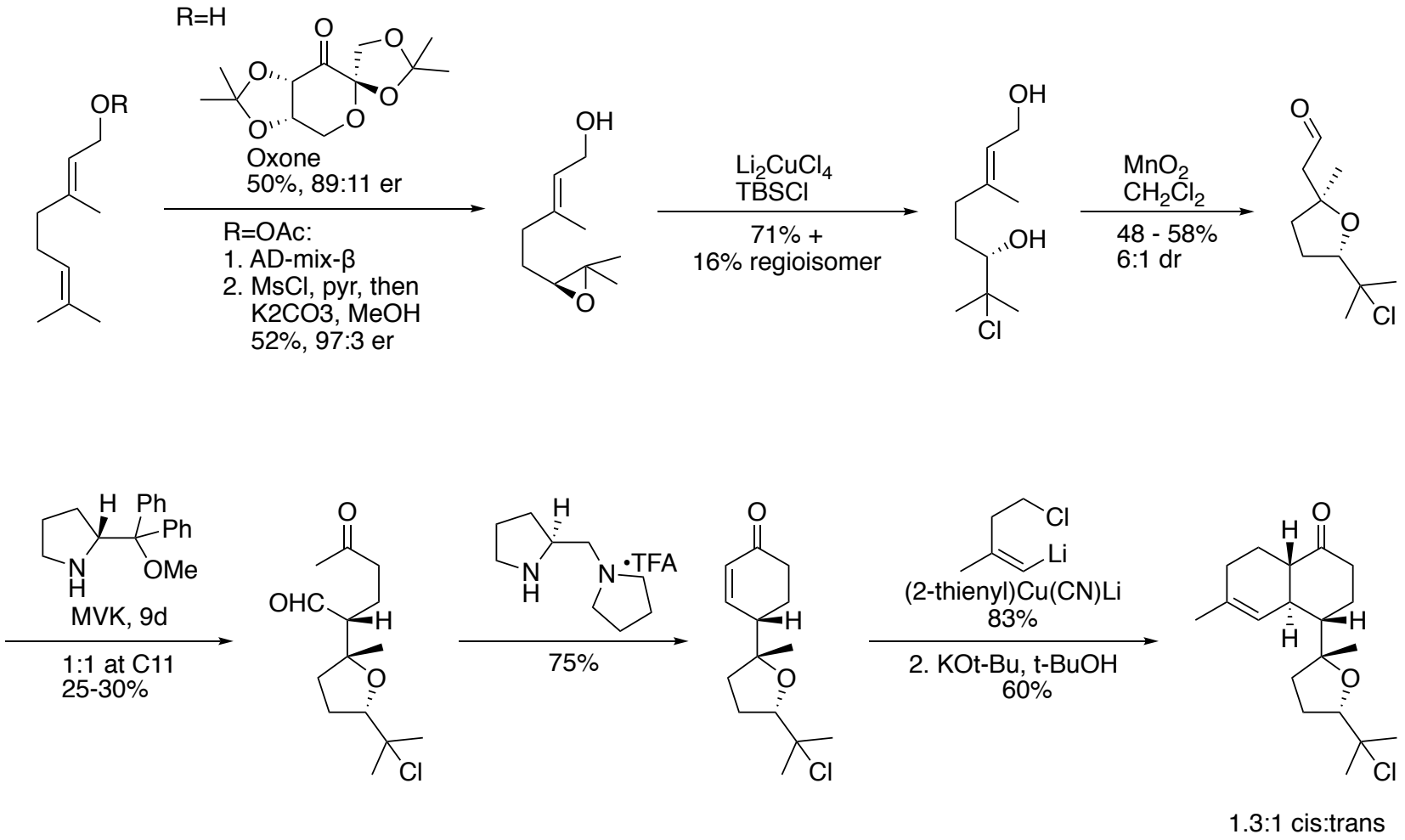
J. Am. Chem. Soc. **1984**, *106*, 4644

(±)-Kalihinol C



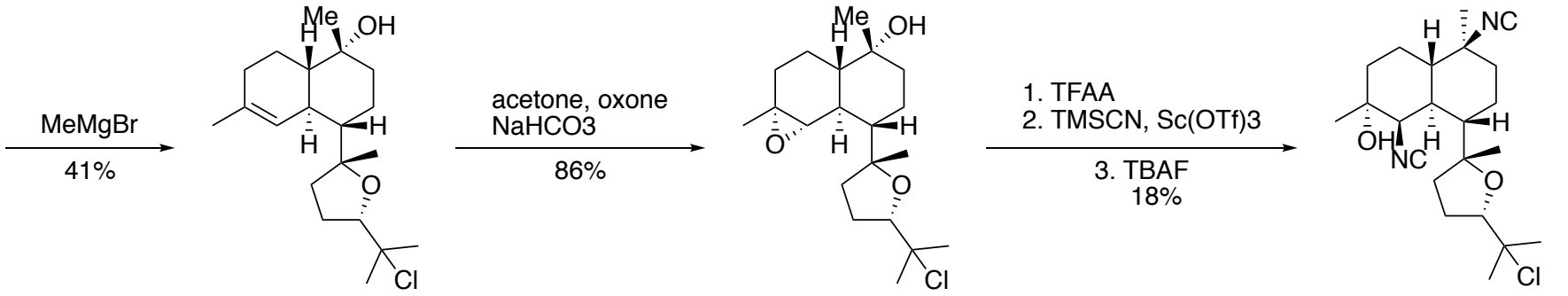
J.Wood, Org Lett. **2004**, 1123

Kalihinol B



Vanderwal, JACS, **2015**, 4912

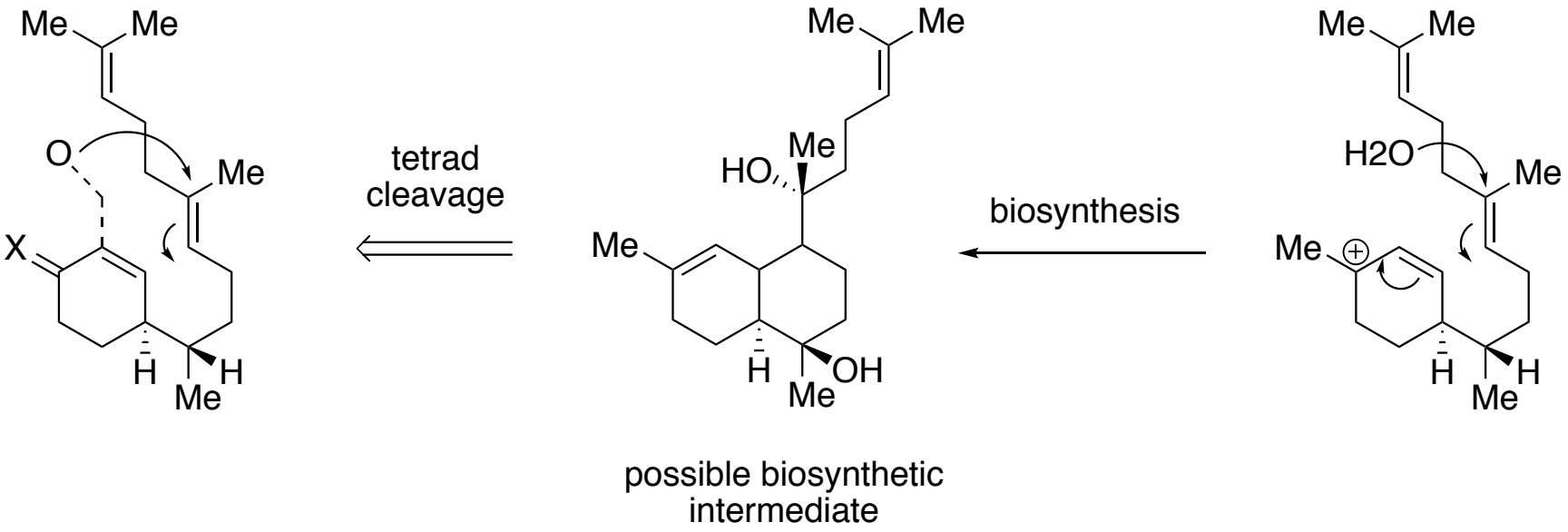
Kalihinol B



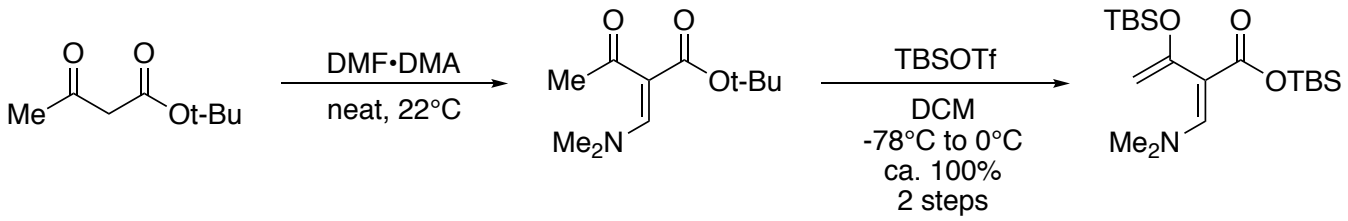
Kalihinol B
12 steps, 0.13%

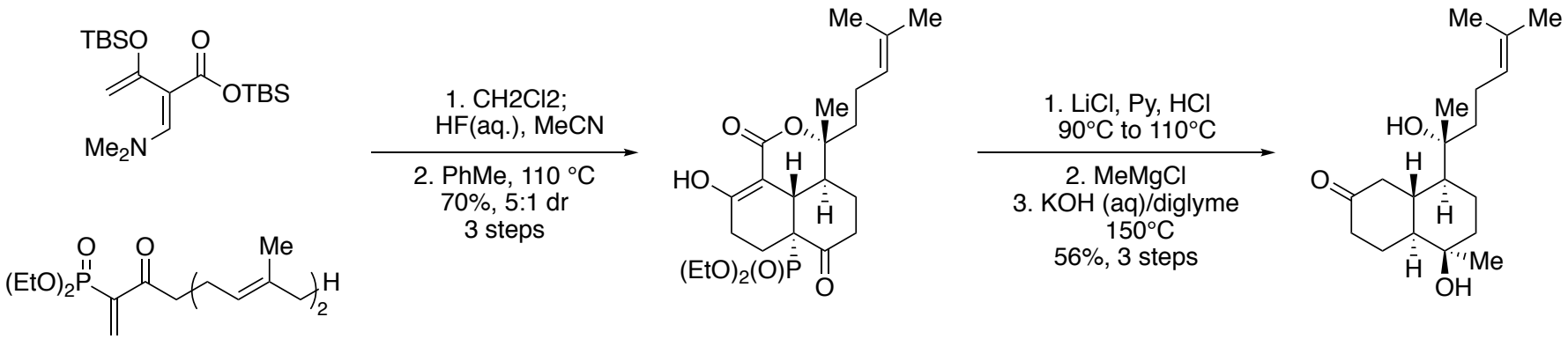
Vanderwal, JACS, **2015**, 4912

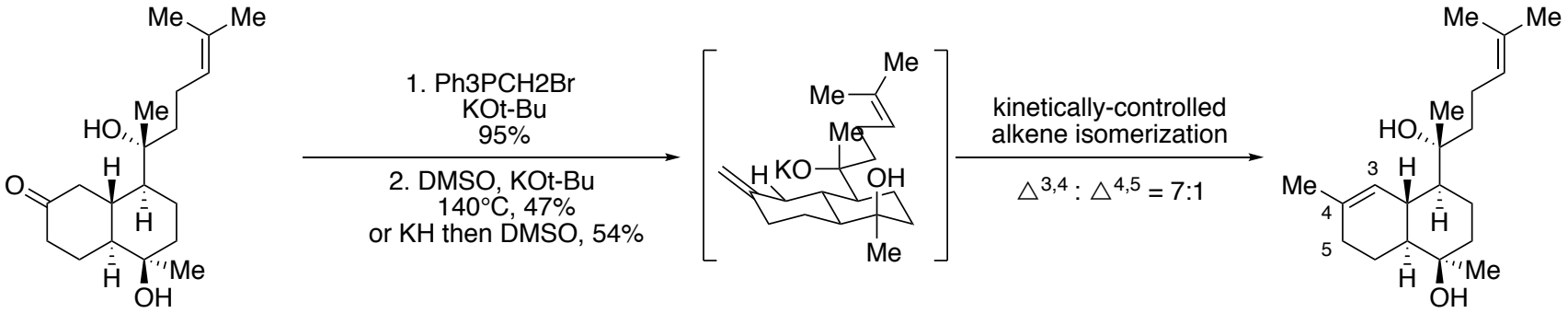
Biosynthesis and retrosynthetic analysis

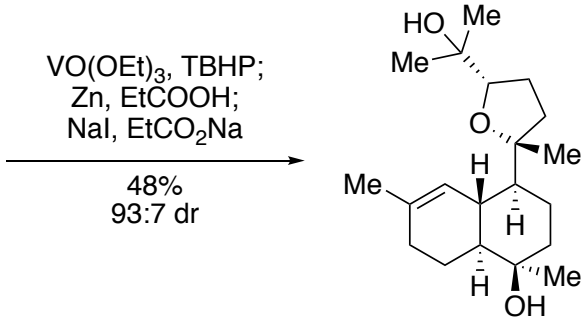


Synthesis of Kalihinol C



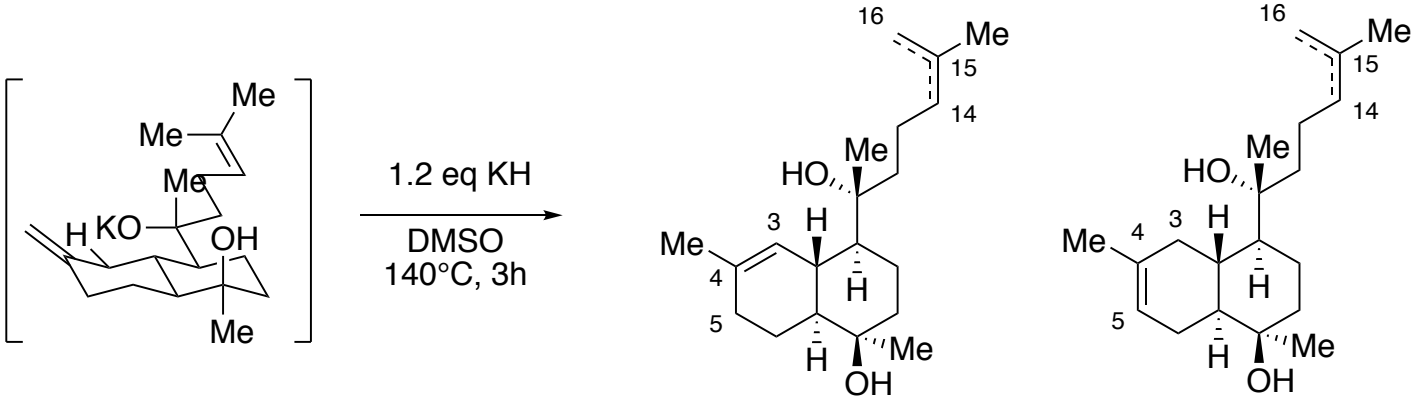



1. Ph3PCH2Br
KOt-Bu
95%
2. DMSO, KOt-Bu
140°C, 47%
or KH then DMSO, 54%
kinetically-controlled
alkene isomerization
△3,4 : △4,5 = 7:1


VO(OEt)3, TBHP;
Zn, EtCOOH;
NaI, EtCO2Na
48%
93:7 dr

15

Alkoxide-directed Alkene Isomerization



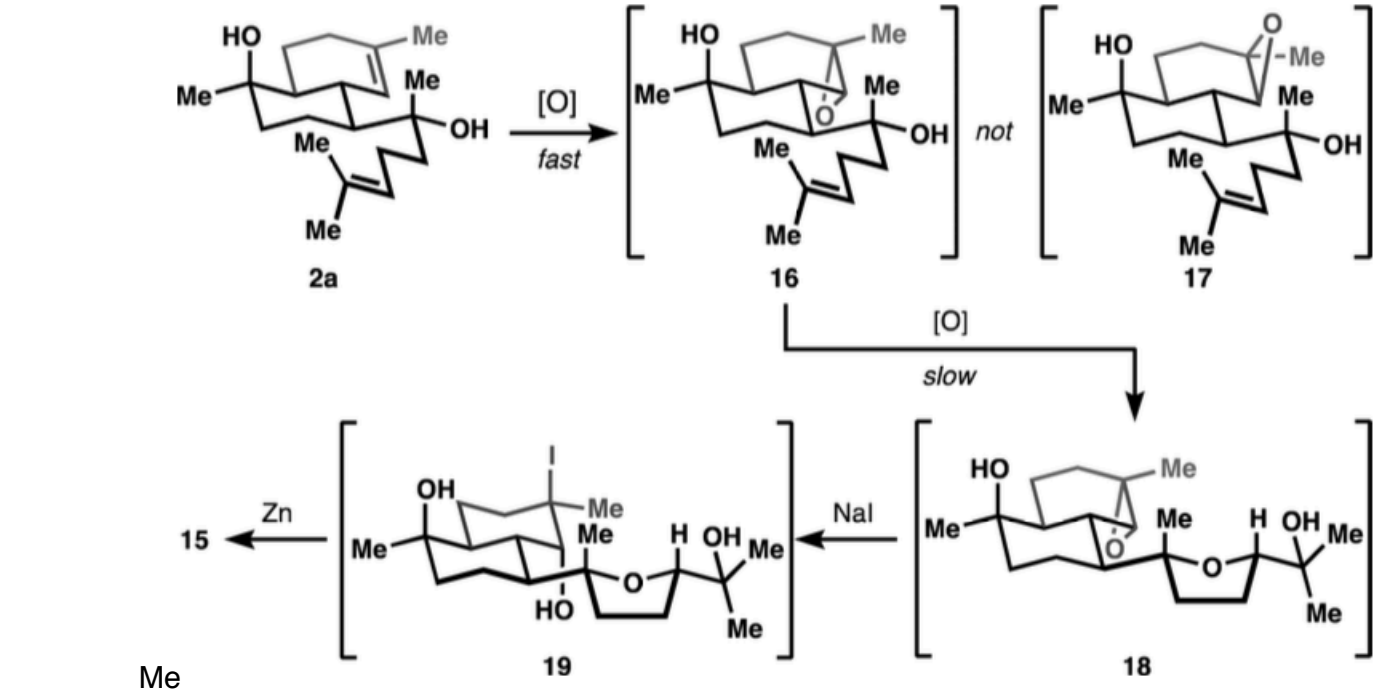
$\triangle^{3,4}$ (**2a, b**)
2a: $\triangle^{14,15}$
2b: $\triangle^{15,16}$

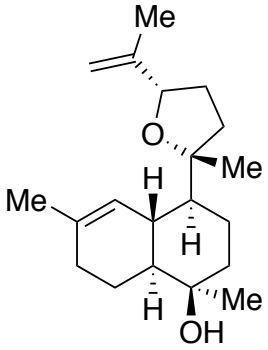
$\triangle^{4,5}$ (**14a, b**)
14a: $\triangle^{14,15}$
14b: $\triangle^{15,16}$

entry	variations (and % conversion)	2:14	%2a
1	none (78)	7:1	54
2[a]	4 equiv. KO*t*-Bu, no KH (82)	5:1	55
3[a]	16 equiv. KO*t*-Bu, no KH (86)	1:1	28
4	1.2 equiv. *n*-BuLi, no KH (0)		0
5	DMPU instead of DMSO (0)		0
	alternate conditions		
6[b]	20 mol % $RhCl_3$, $EtOH/H_2O$, 70 °C (56)	1:1	28
7[a]	2 mol % [Co],[c] 4 mol % $PhSiH_3$, PhH (42)	<1:20	<5

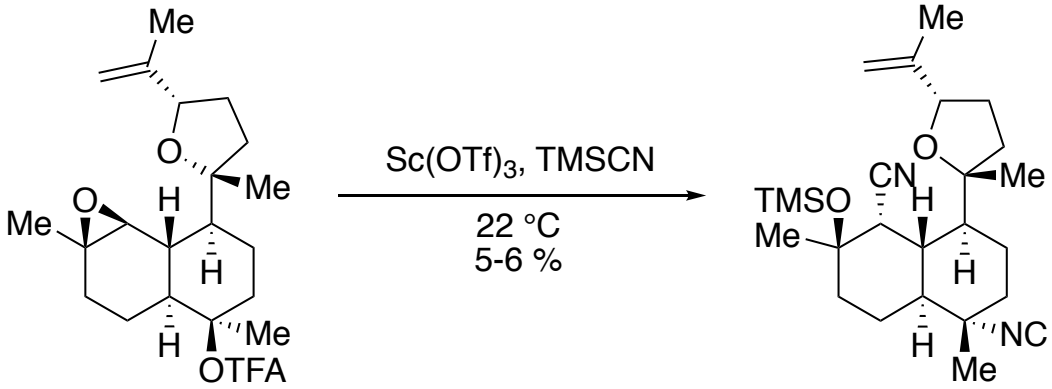
[a] ^{1}H NMR. [b] GC–MS. [c] $Co(Sal^{t\text{-}Bu,t\text{-}Bu})Cl\cdot H_2O$.

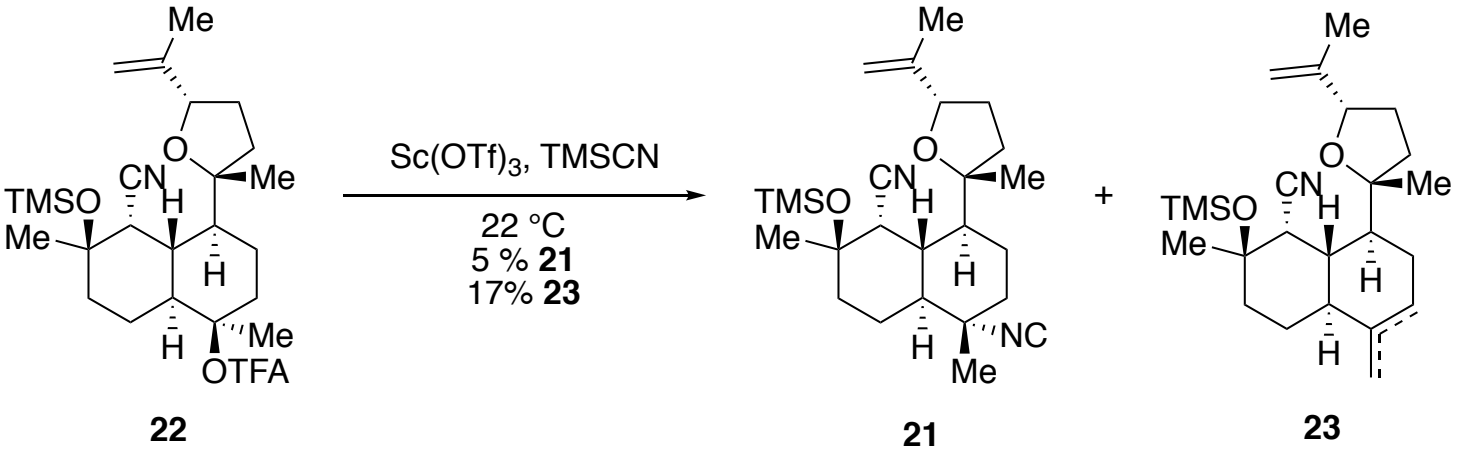
Steroselctive Oxidative Cyclization





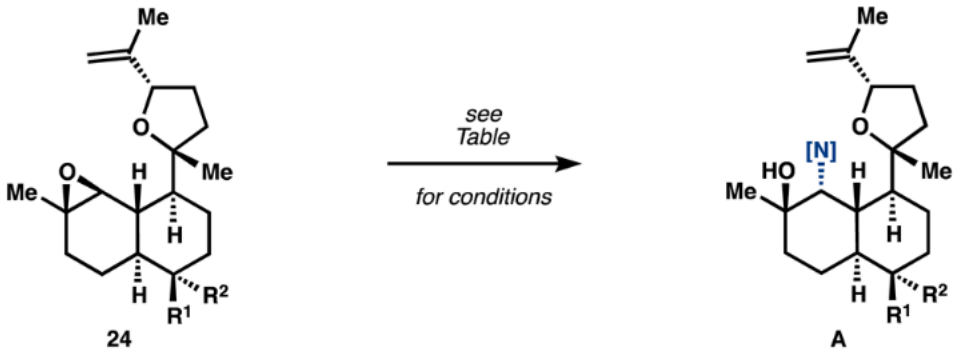
Isocyanohydrin Installation





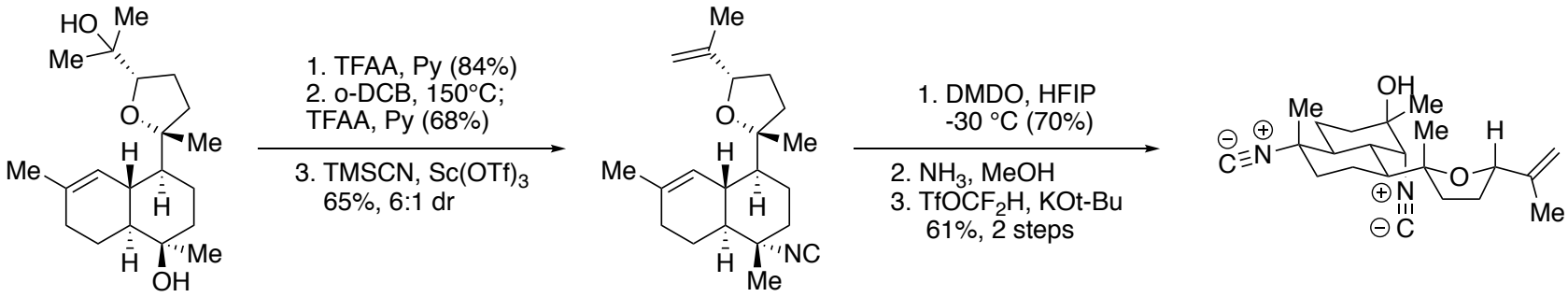
22 **21** **23**

Epoxidation followed by isonitrile installation is low yielding, competitive elimination occurs



R^1/R^2	conditions [N]	R^1/R^2	A:B:C:D
OTFA/Me	TMSCN, $Sc(OTf)_3$ [NC]	OTFA/Me	83:0:17:0
OH/Me	TMSCN, $Sc(OTf)_3$ [NC]	OTMS/Me	100:0:0:0
Me/NC	TMSCN, $Sc(OTf)_3$ [NC]	Me/NC	61:0:39:0
Me/NHCHO	TMSCN, $Sc(OTf)_3$ [NC]	Me/NHCHO	54:31:0:15
Me/NC	NH_3, MeOH [NH_2]	Me/NC	100:0:0:0

[a]Any silylethers were converted to alcohols with TBAF.


HO
Me
Me
O
Me
H
Me
H
H
Me
OH
1. TFAA, Py (84%)
2. o-DCB, 150°C;
TFAA, Py (68%)
3. TMSCN, Sc(OTf)3
65%, 6:1 dr
Me
O
Me
H
Me
H
H
NC
Me
1. DMDO, HFIP
-30 °C (70%)
2. NH3, MeOH
3. TfOCF2H, KOt-Bu
61%, 2 steps
OH
Me
Me
Me
H
N
C
O
N
C
Me

Conclusion

- 17 steps, 1.3%
- Double cycloaddition for A,B ring
- An alkoxide-directed isomerization method to access the thermodynamically disfavored $\Delta^{3,4}$ unsaturated trans-bifloran skeleton
- A short, high-yielding, regio and stereoselective strategy for installing the A-ring isocyanohydrin motif, including difluorocarbene-mediated isonitrile synthesis.