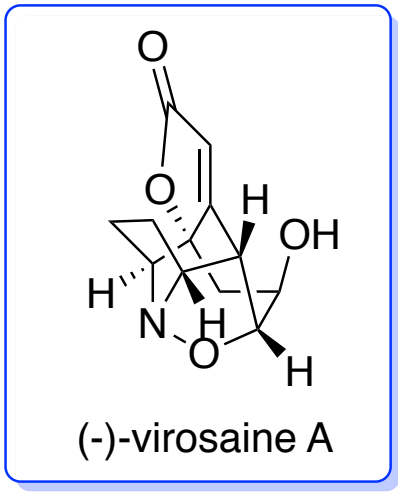
A Concise Enantioselective Total Synthesis of (-)-Virosaine A

Jonathan M. E. Hughes and James L. Gleason

Angew. Chem. Int. Ed. **2017**, 56, 1 – 6

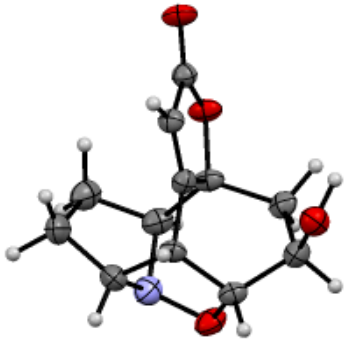


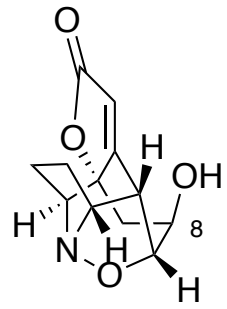
Ruiting Liu
Wipf Group Current Literature
08/05/2017

1

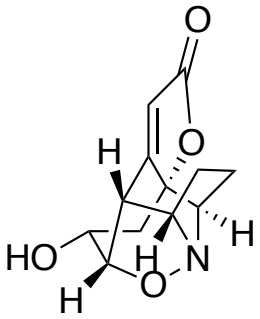
(-)-Virosaine A

- Virosaine **A** and **B** are both isolated from Flueggea virosa
- Among the most structurally complex Securinega alkaloids
- Neither **1** nor **2** showed cytotoxic activity against selected cancer cell lines (MCF-7, MDA-MB-231, HepG2, HepG2/ ADM, HL-60, K562 and Hep2)





virosaine A (**1**)

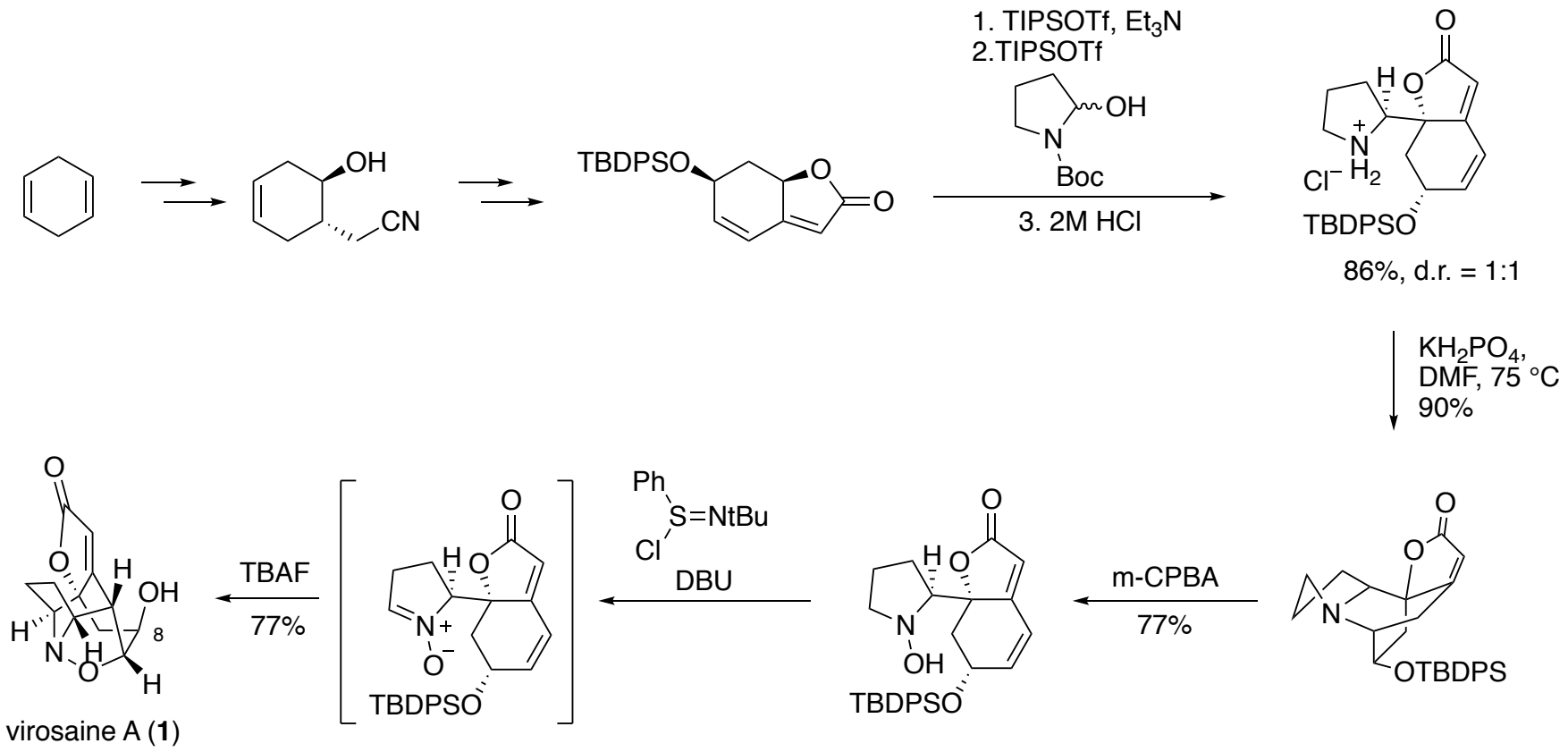


virosaine B (**2**)

https://fr.wikipedia.org/wiki/Flueggea_virosa
Org.Lett., **2012**, *3096*

2

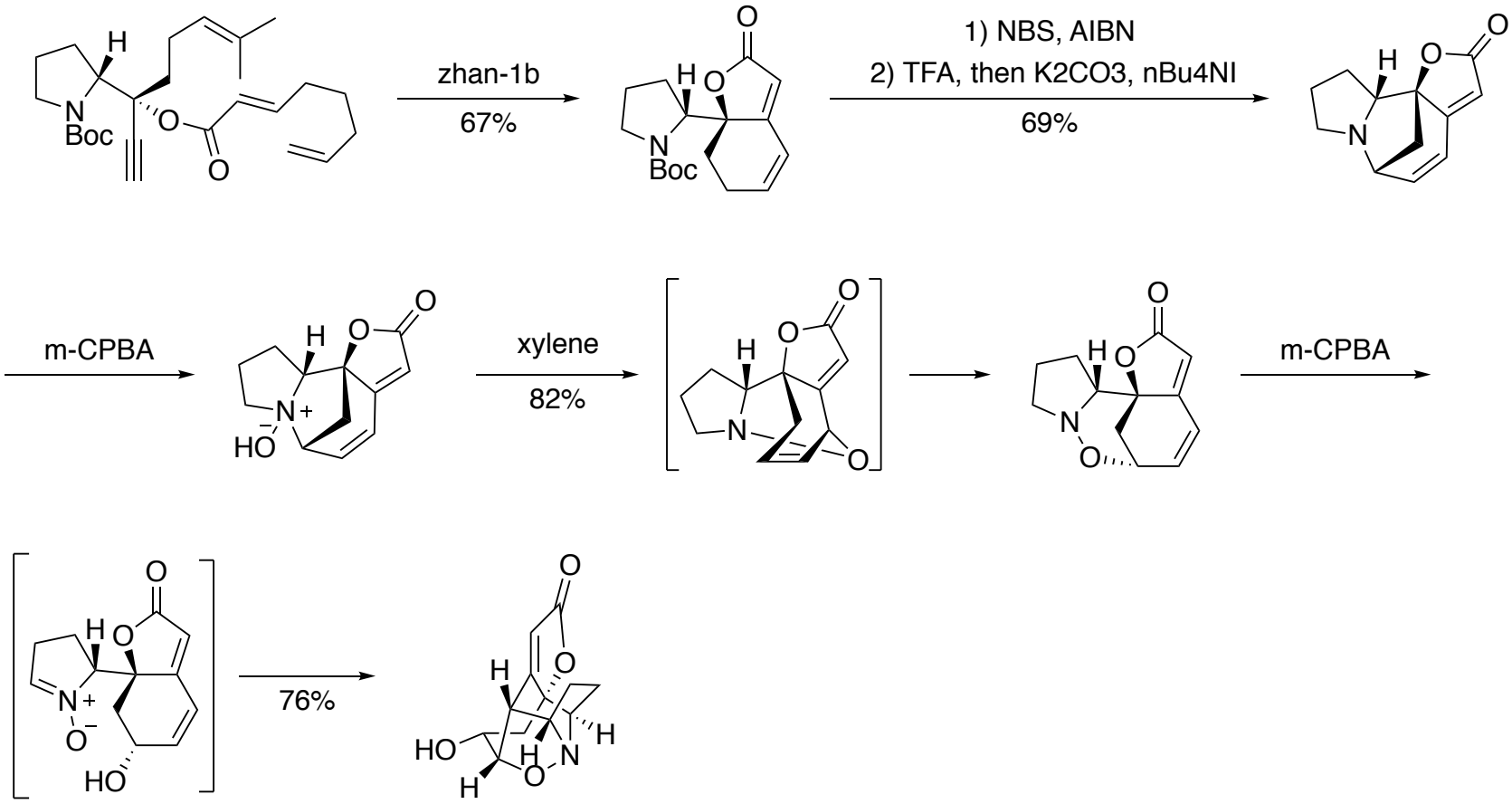
Previous Reported Synthesis



18 steps employing aza-Michael addition and Cope elimination

K. Gademann etc, *Chem. Commun.* **2013**, 1921

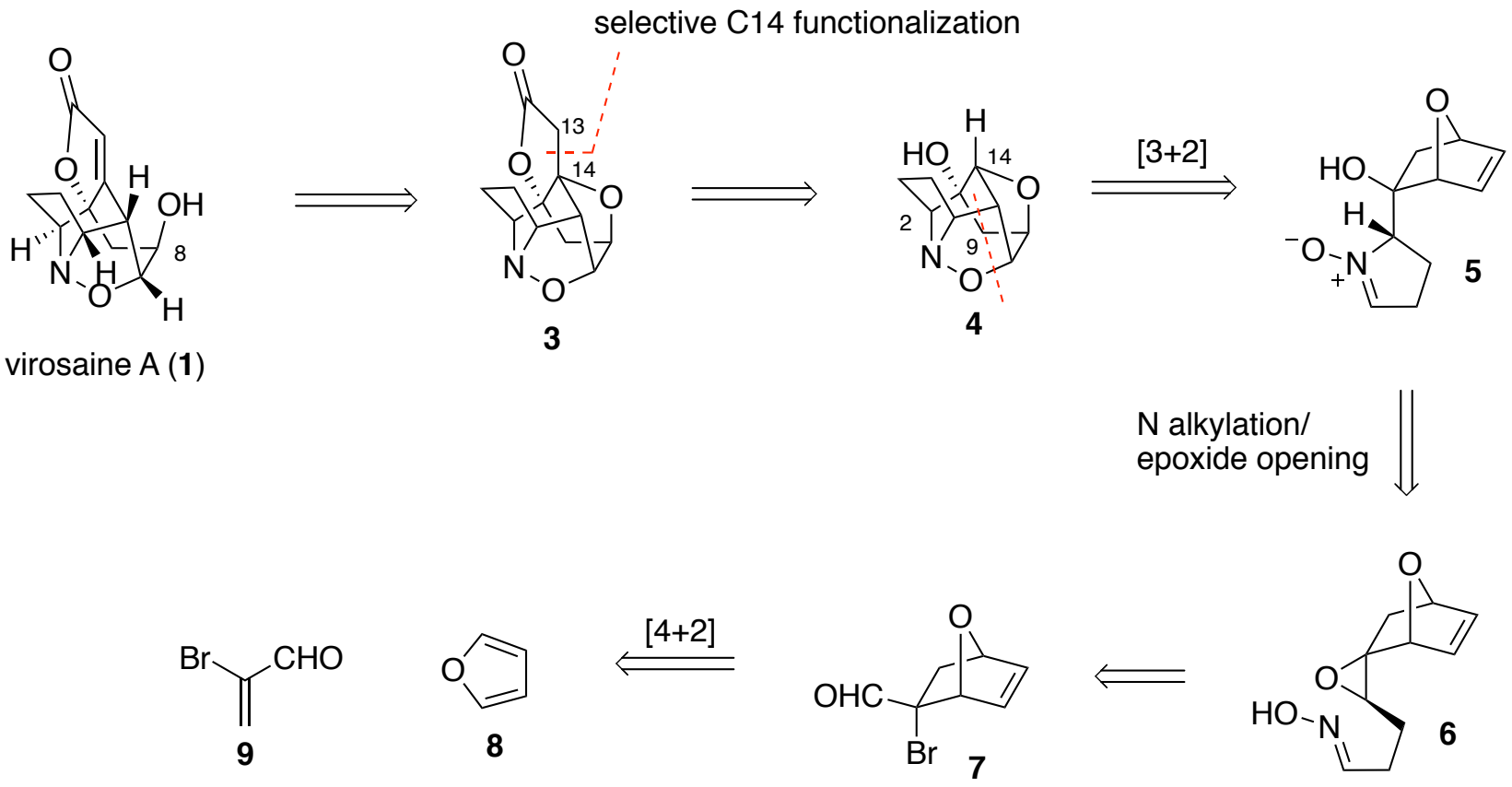
(+)-Virosaine B



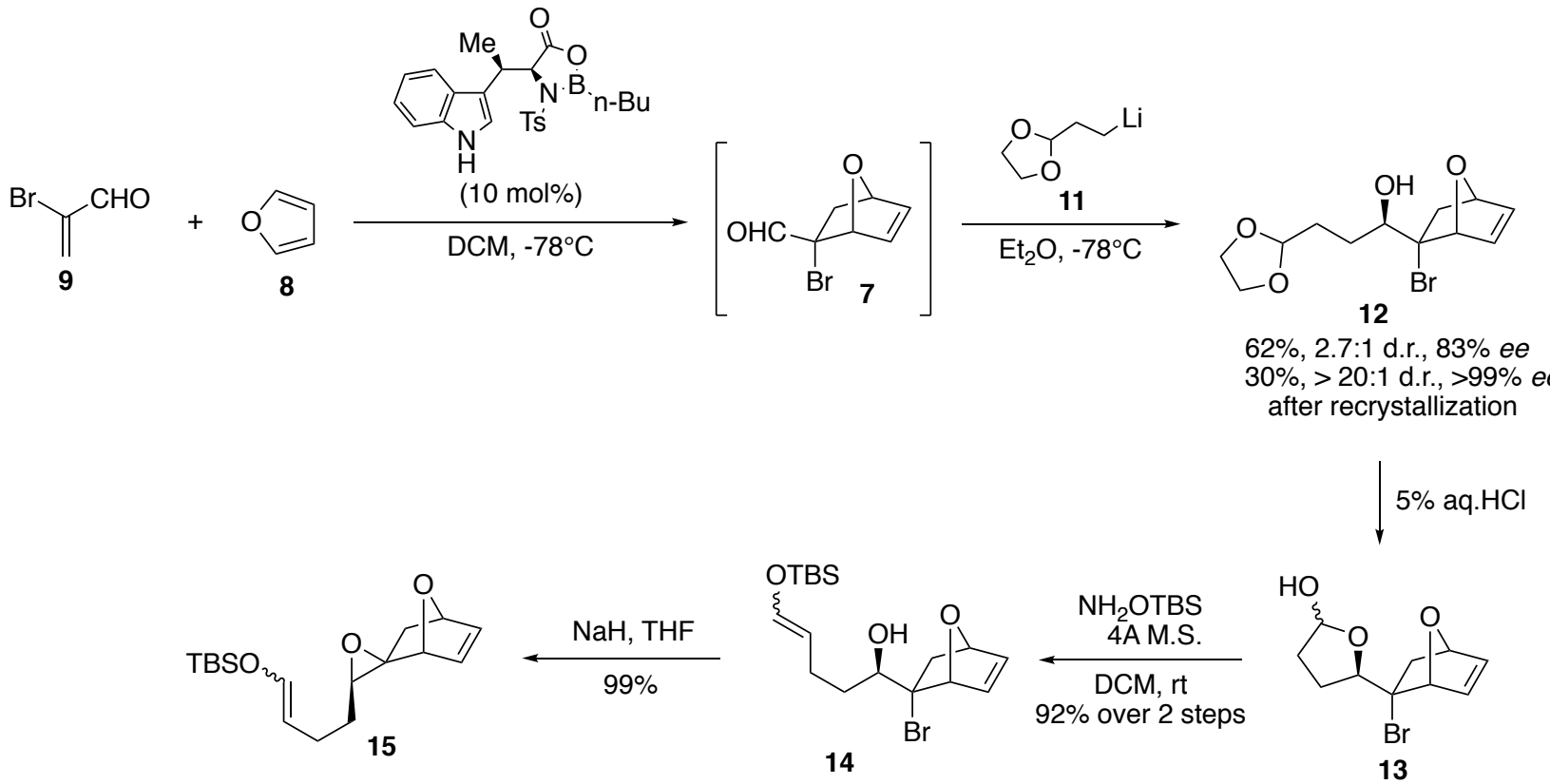
10 steps 6.68% overall yield

Z. Yang etc*, Angew. Chem. Int. Ed*, **2013**, 620

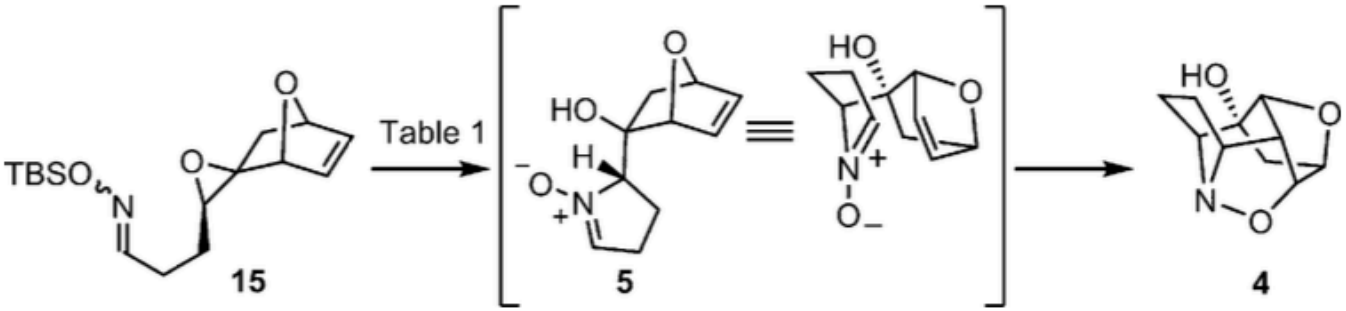
Retrosynthesis



Synthesis of (-)-Virosaine A



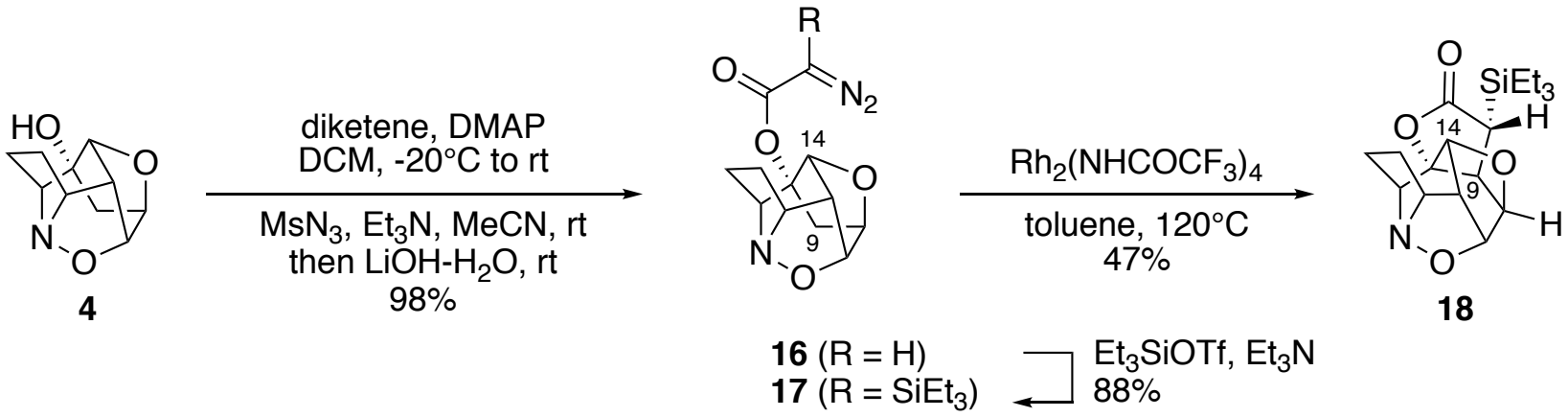
Optimation of the Cascade Reaction

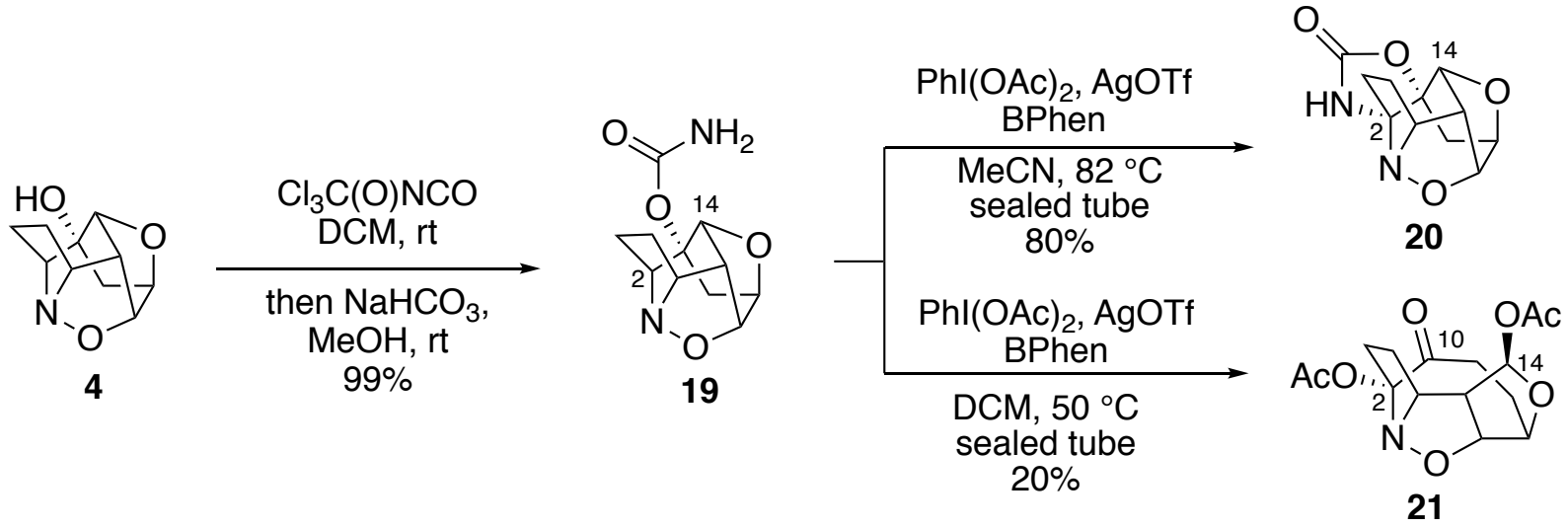


Entry	Solvent	Acid (equiv)	*T* [°C]	*t*	Yield [%][a]
1[b]	xylenes	PPTS (0.2)	140	8 h	26
2	THF	PPTS (1)	70	12 h	40
3[c]	THF	PPTS (1)	100	1 h	45
4[c]	MeOH	PPTS (1)	120	1 h	28
5[c]	MeCN	PPTS (1)	120	1 h	50
6[c]	MeCN	AcOH (5)	120	1 h	<10
7[c]	**AcOH**	**–**	**120**	**30 min**	**92**
8[d]	AcOH	–	120	40 min	82

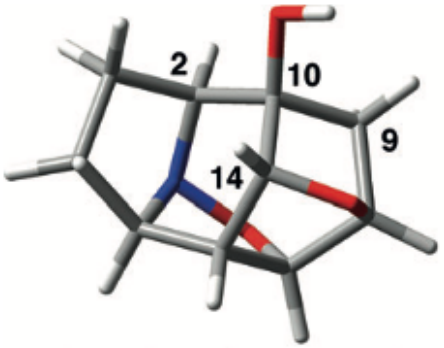
[a] Yield of isolated **4**. [b] Oxime **6** was used as the starting material. [c] Microwave heating. [d] On 5 mmol scale.

Attempted C14 C-H Functionalization





Evaluation of the Potential Sites of Reactivity

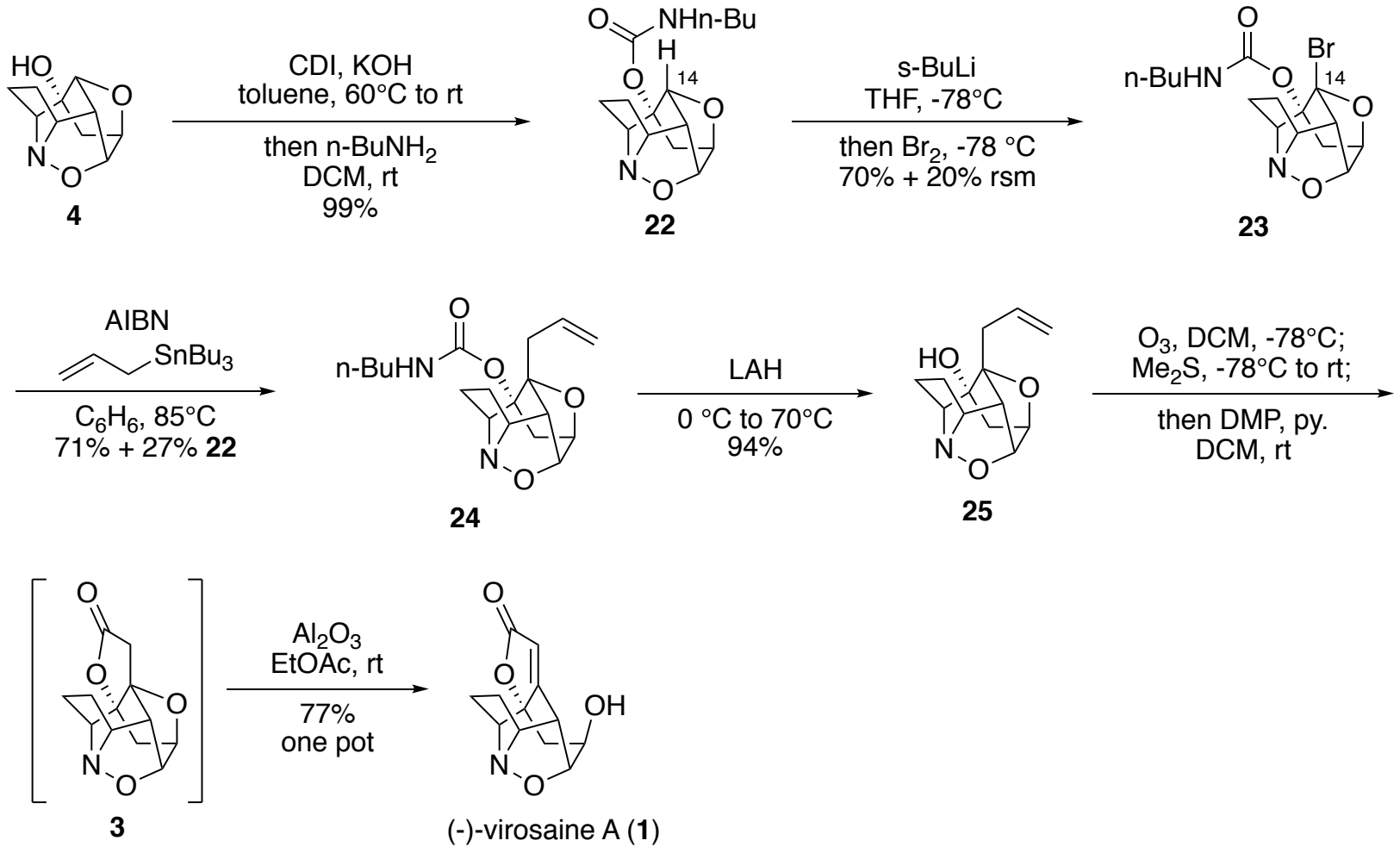


4: "top-down" perspective

Site	^{1}H (δ, ppm)	^{13}C (δ, ppm)	NPA partial atomic charge on carbon	C-H HOMO Energy (eV)
2	3.59	66.8	-0.037	-13.69
9	1.73	45.5	-0.423	-13.71
14	4.72	85.7	+0.095	-14.48

- the lone pair from the bridging oxygen atom donate into the C14-H14 s* orbital results in only inductive deactivation
- NPA charge analysis indicated that C14 has a relatively high positive charge
- NBO analysis showed that the C14 H14 bond has the lowest-energy HOMO of all of the C-H bonds in **4**

Site-directed Deprotonation Approach



Conclusion

- 10 steps, 9 % overall yield
- an efficient epoxide opening/nitrone cycloaddition cascade process to rapidly construct the core
- selectively manipulate the C14-H14 bond by a directed lithiation/bromination sequence