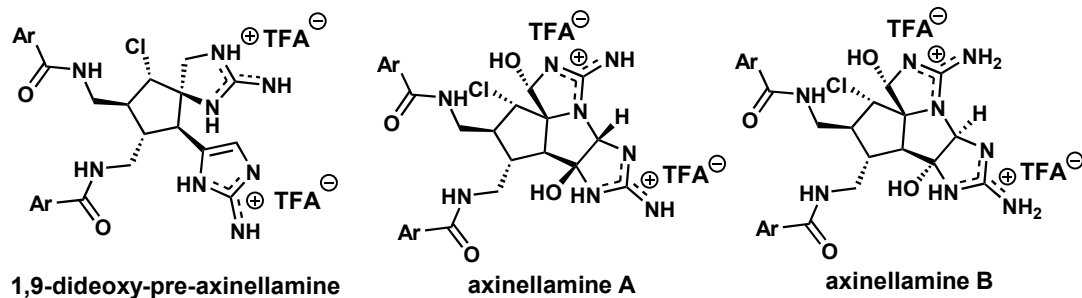


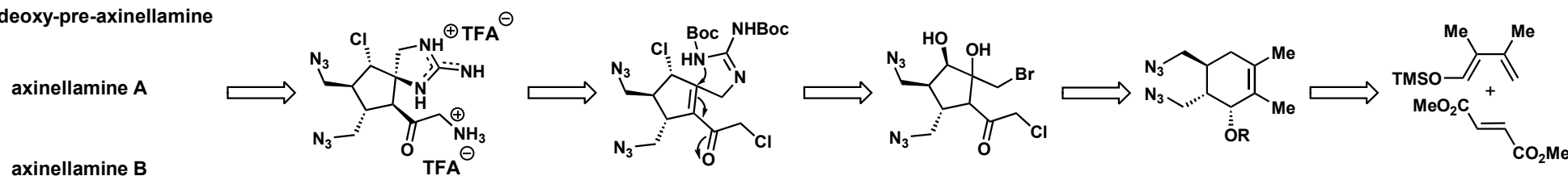
Synthesis of the Week: Axinellamines



- A pyrrole-imidazole alkyloid isolated from the *Axinella* marine sponges
- Axinellamine A was initially reported to have very poor antibiotic activity (1mM) against *H. pylori* with Axinellamine B having no activity.
- However, after biological evaluation of synthetic (racemic) material these compounds were found to possess submicromolar activity against both Gram-positive and Gram-negative bacteria as well as activity against hospital and community acquired MRSA.
- Interesting features include a tetracyclic bisguanidine core, two dibromopyrroles, and 8 stereocenters, all of which are contiguous.

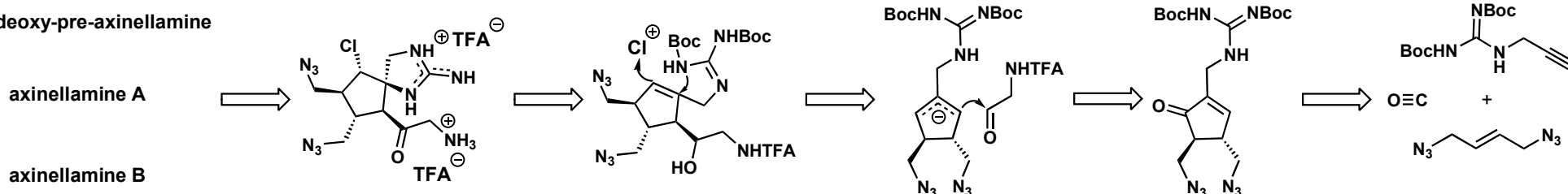
Initial disconnect

1,9-dideoxy-pre-axinellamine

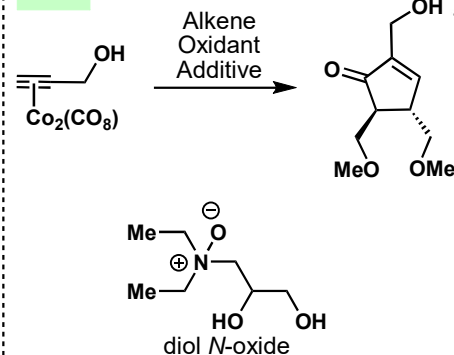


Scalable disconnect

1,9-dideoxy-pre-axinellamine

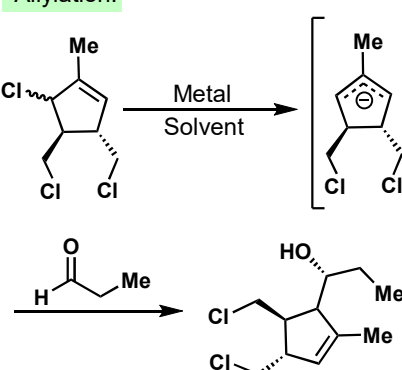


PKR:



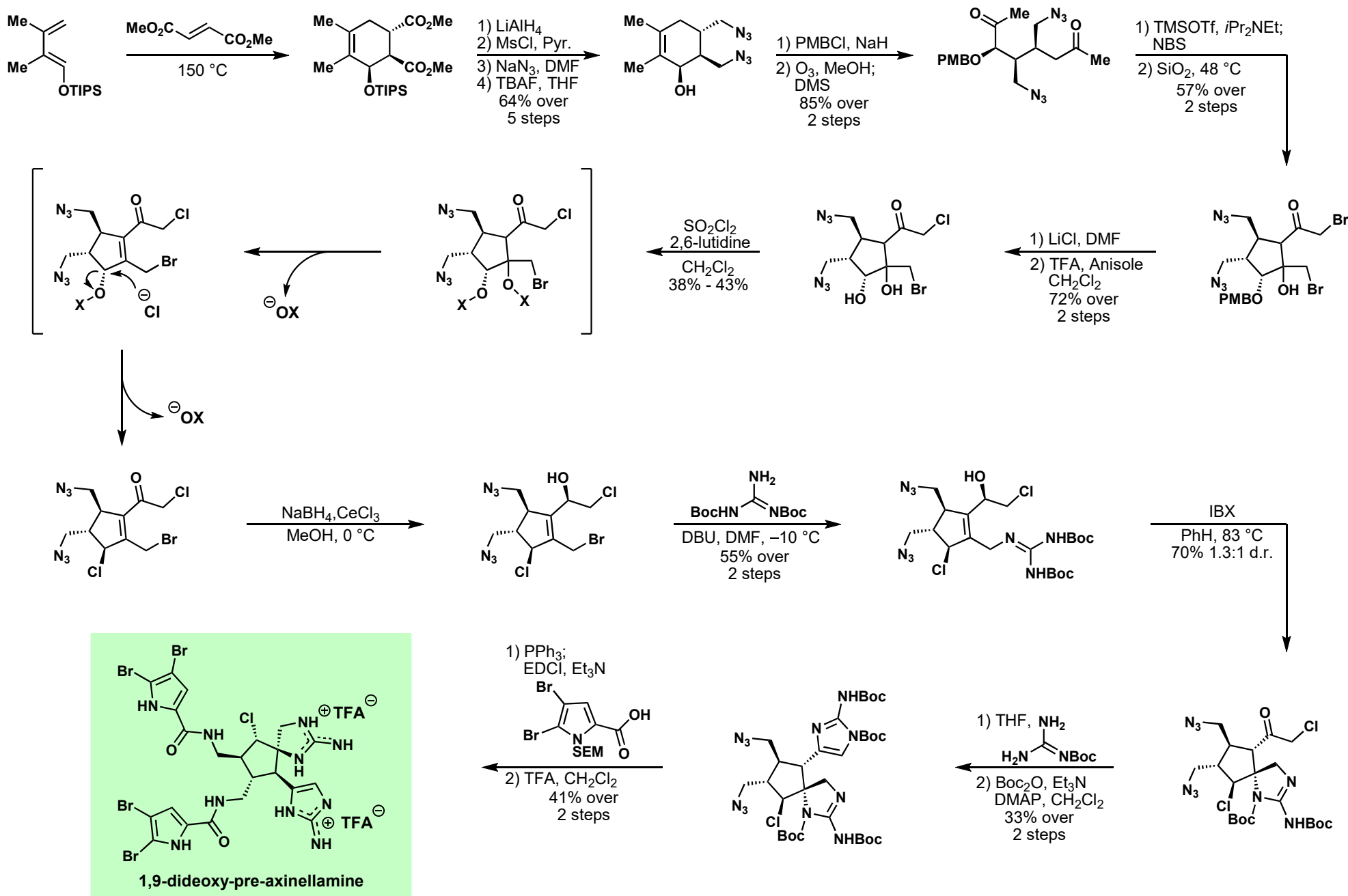
entry	change from standard conditions	yield (24)
1	oxidant = Silver (II)	decomp
2	oxidant = Iron (III) Chloride	decomp
3	oxidant = NMO (slow addition)	15-20%
4	additive = none	15-20%
5	additive = mercaptans: PhSH, 1,2-Ethanedithiol	decomp
6	additive = 1°/2° polyamines: ethylenediamine, 1,2-Diaminocyclohexane, diethylenetriamine	0% (rsm)
7	additive = 3° amines: dimethylethanolamine, tetramethylethylenediamine, TEA	16%
8	additive = 2° alkyl sulfides: nBuSMe, 2-(methylthio)ethanol	16-20%
9	additive = 1° alcohols: MeOH, BnOH	16-20%
10	additive = 1,2-Dimethoxyethane	15%
11	additive = unhindered diols and triols: ethylene glycol, propane-1,3-diol, glycerol	45-49% ^a
12	additive/oxidant = diol N-oxide (33)	48%

Allylation:

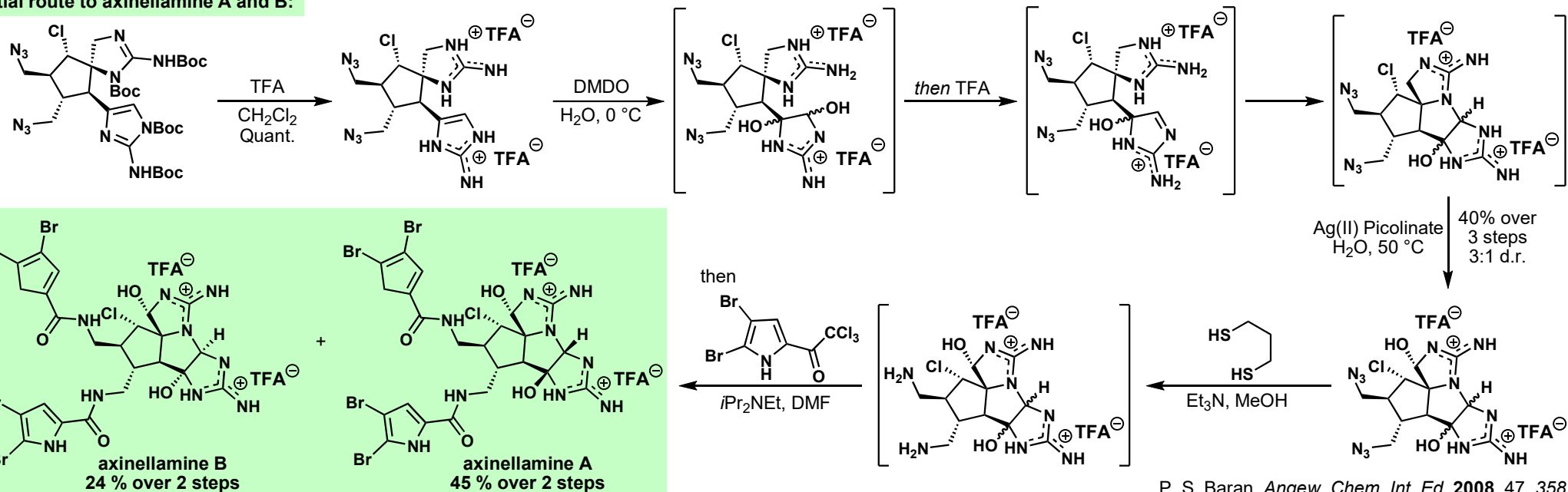


entry	metal (3-5 equiv)	solvent (0.1M)	yield (43:44)
1	Sn	THF	NR
2	Fe	THF	NR
3	In	THF	NR
4	Zn	THF	trace
5	Mg	THF	decomp.
6	Mg/I ₂	THF	decomp.
7	Zn	aq. NH ₄ Cl	20%
8	Zn	THF/20% aq. NH ₄ Cl	50%
9	Mg/Zn	THF	decomp.
10	Mg/In	THF	decomp.
11	Zn/In	THF	16%
12	Zn/In	H ₂ O	NR
13	Zn/In	THF/20% aq. NH ₄ Cl	62% (7:1)
14	Zn/In	THF/6% aq. NH ₄ Cl	67% (9:1)
15	InCl ₃	THF	NR
16	InCl ₃	THF/6% aq. NH ₄ Cl	NR

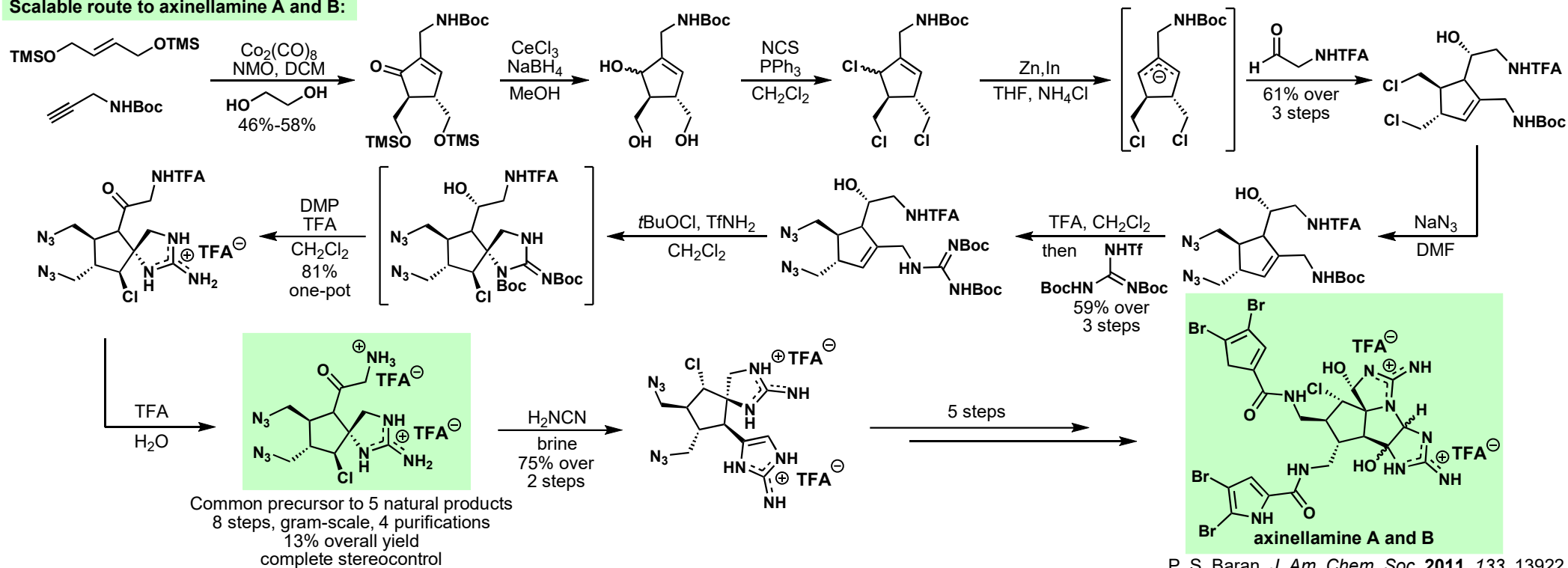
Initial route to 1,9-dideoxy-pre-axinellamine:



Initial route to axinellamine A and B:

P. S. Baran, *Angew. Chem. Int. Ed.* **2008**, *47*, 3581

Scalable route to axinellamine A and B:

P. S. Baran, *J. Am. Chem. Soc.* **2011**, *133*, 13922