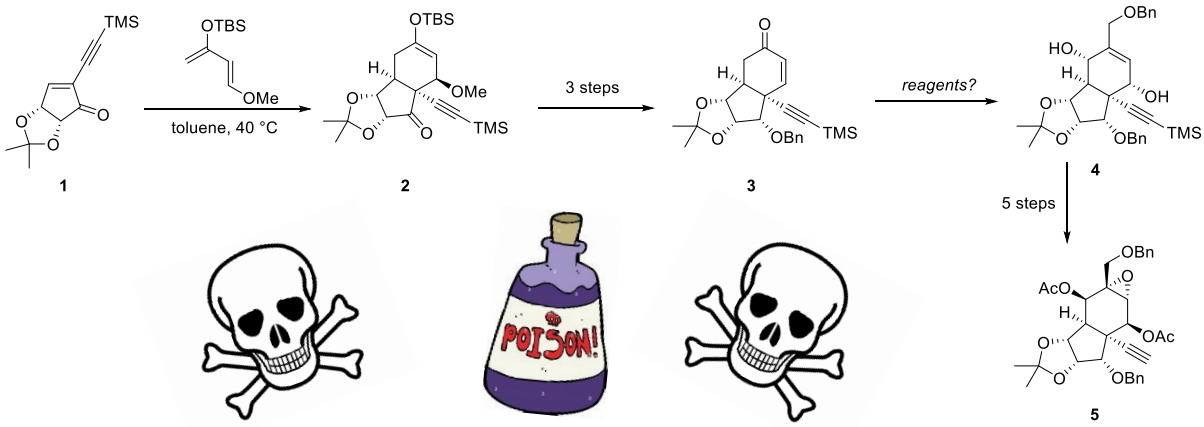
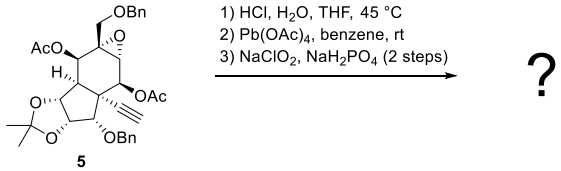
SYNTHESIS OF TETRODOTOXIN

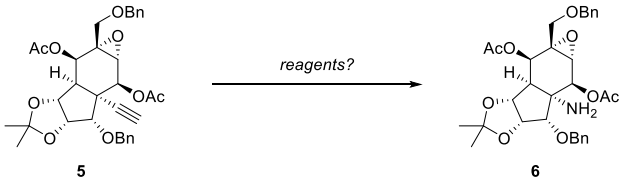
Tetrodotoxin is the toxin found in pufferfish, which acts by blocking voltage-gated sodium channels. Over 100 people a year die from pufferfish poison, almost all from consuming this deadly delicacy, but sometimes by more sinister means...



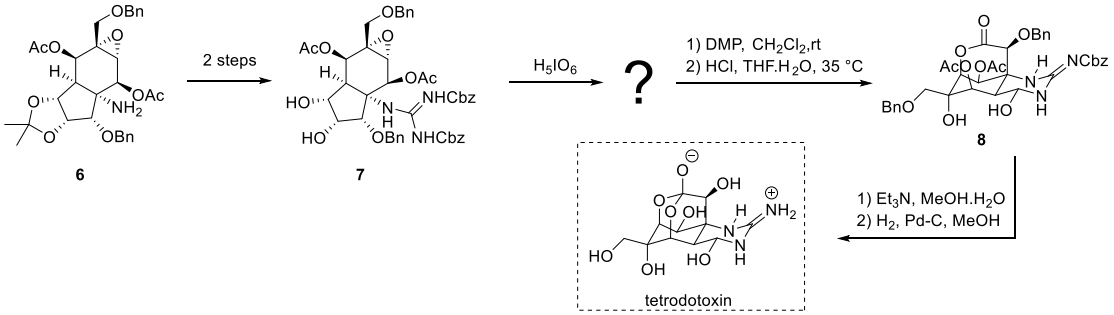
1. Rationalise the stereochemistry for the conversion of **1** to **2**.
2. Give reagents for the conversion of **3** to **4** (more than one step may be required).
3. With 5 more steps, they had intermediate **5** in hand. The first route they tried from this intermediate was unsuccessful. Can you identify the undesired product they formed?



4. Realising they would need to change the conformation of the ring, they tried another route. Provide reagents for the conversion of **5** to **6**. (More than one step may be required).

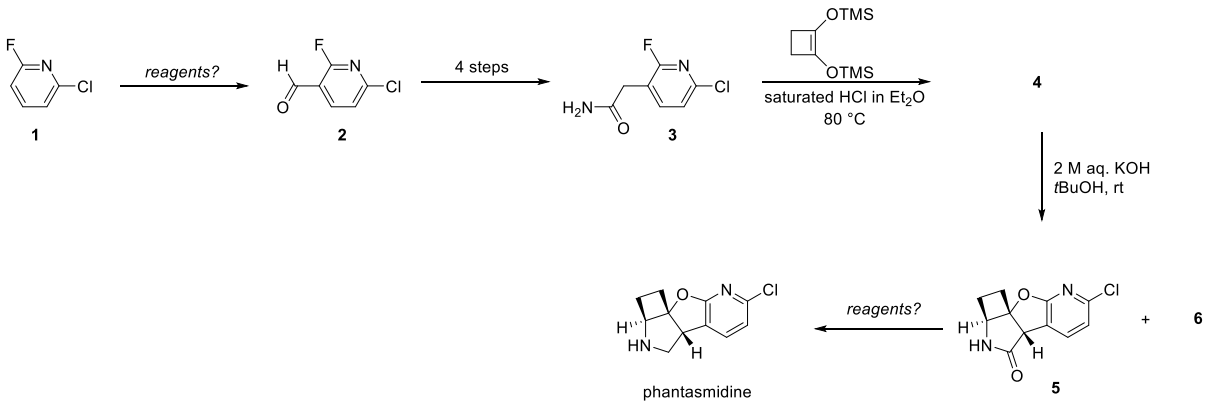


5. From **6**, they were able to access **7** in 2 steps. Identify the unknown intermediate on reaction of **7** with H_5IO_6.
6. Give the mechanism of conversion of the unknown intermediate into **8**.



SYNTHESIS OF PHANTASMIDINE

Phantasmidine is a poison produced by the phantasmal poison frog (figure **1a**) and also ghosts (figure **1b**).



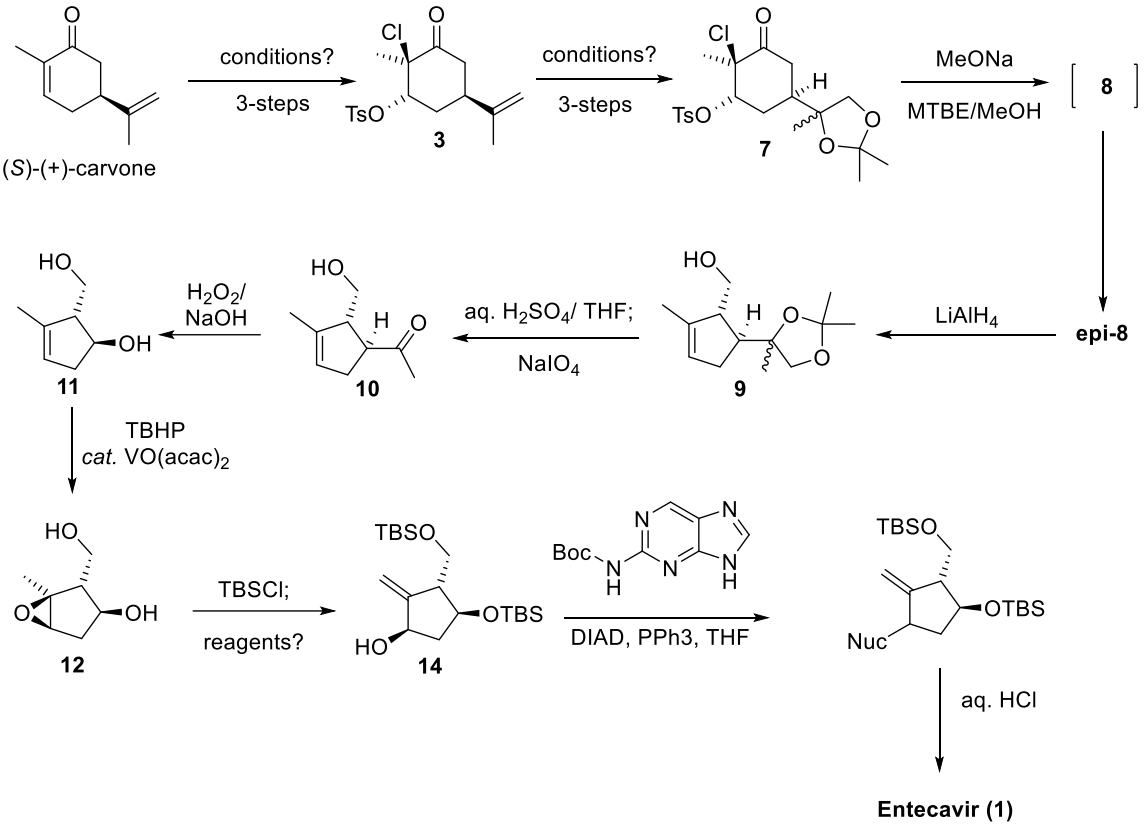
1. Suggest reagents for the conversion of **1** to **2** (more than one step may be required.
2. Identify the structure of intermediate **4** and give the mechanism for it's formation.
3. Give the mechanism for the formation of **5** and identify unwanted byproduct **6**.
4. The authors originally tried to synthesis phantasmidine starting from 2,6-dichloropyridine using the same route, however they were unable to form compound **5**, why do you think this is?
5. How would you convert **5** into phantasmidine (more than one step may be required).

Figure **1a**: Phantasmal poison frog in the wild

Figure **1b**: Ghost in the wild

Pilot production total synthesis of entecavir (ente-cadaver?)

Entecavir is an antiviral medication used in the treatment of hepatitis B and zombification.

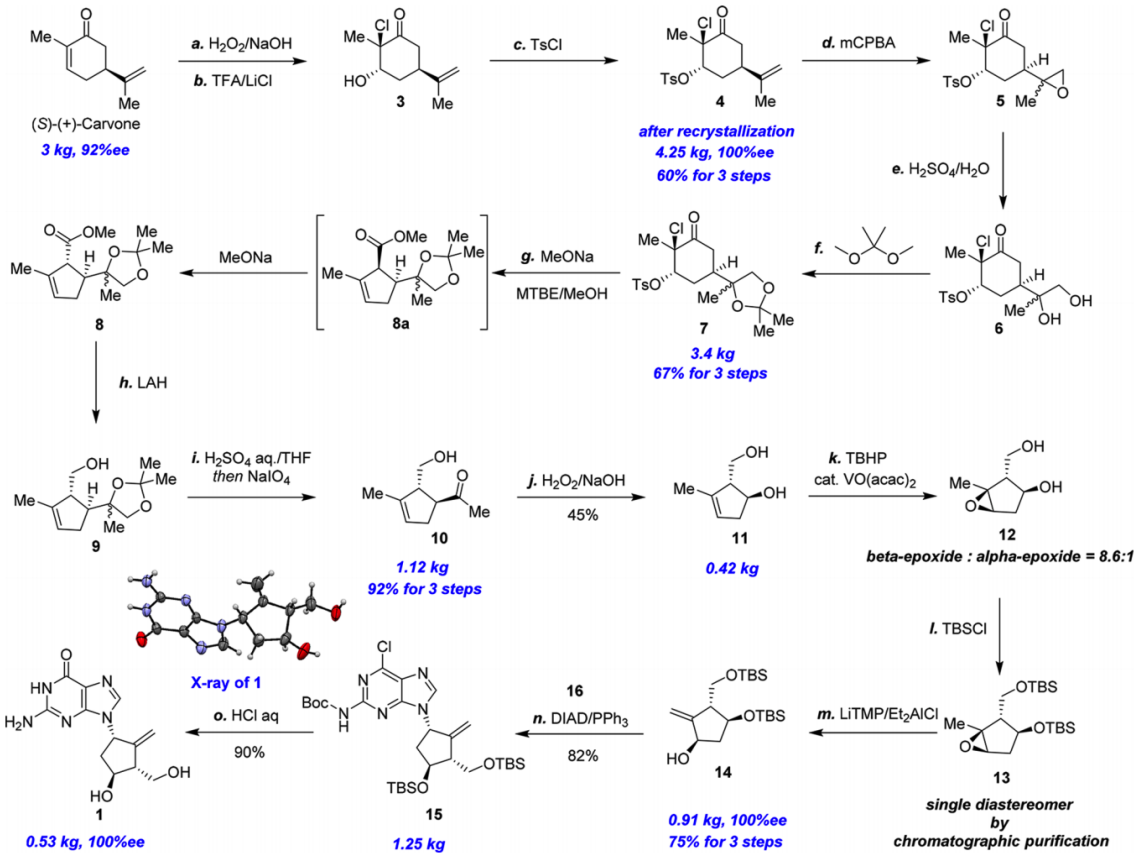


1. Suggest conditions for the transformation of carvone into **3**. Don't forget to rationalize stereochemistry!
2. Suggest conditions for the transformation of **3** into **7**.
3. Provide a mechanism for **7** going to **epi-8** via **8**. Can you explain why **epi-8** is the thermodynamic sink, and why (with aide of a stereochemical model/TS) it isn't initially formed? How is this named reaction called?
4. Give mechanism for the formation of **10**.
5. The two subsequent transformations are slightly unusual. Can you explain **10** to **11** and **11** to **12** (usually what sort of double bonds are oxidized by $VO(acac)_2$?) Why does diastereoselectivity work well in this case?
6. Suggest reagents for the epoxide opening to yield **14**. Give justification for your choice.
7. Give the name and mechanism for the substitution of alcohol **14**. Through which atom would nucleophile **16** react? What is the missing stereochemistry in **15**? Thereby provide the structure of Entecavir (**1**).

SOLUTIONS

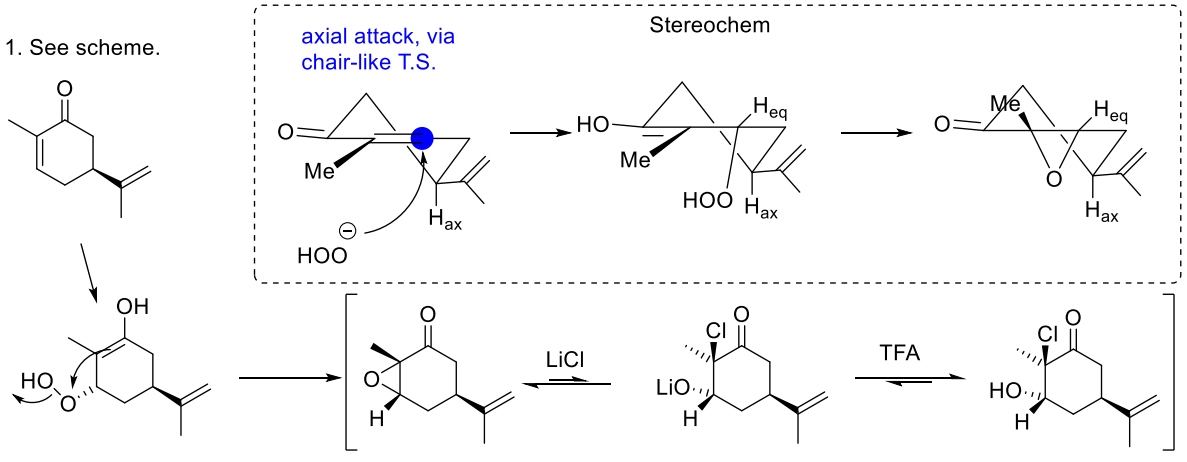
Yehua Jin et al. **OPR&D 2018,** 22, 377. doi: 10.1021/acs.oprd.8b00007

Scheme 2. Synthesis of Entecavir (1)[a]



[a]Reagents and conditions: (a) 30% $H_2O_{2(aq)}$, 4N $NaOH_{(aq)}$, MeOH, 0 °C; (b) TFA, LiCl, THF, 0–5 °C; (c) TsCl, DMAP, CH_2Cl_2, 25 °C (60% for 3 steps); (d) mCPBA, CH_2Cl_2, 25 °C; (e) H_2SO_4, H_2O, THF, 25 °C; (f) 2,2-dimethoxypropane, cat. PSA, CH_2Cl_2, 25 °C (67% for 3 steps); (g) MeONa, MTBE/MeOH, 0–25 °C; (h) LAH, THF, 5–10 °C; (i) 20% $H_2SO_{4(aq)}$, THF, 25 °C, then $NaIO_4$ 25 °C (92% for 3 steps); (j) 30% $H_2O_{2(aq)}$, 10% $NaOH_{(aq)}$, MeOH, 70 °C (45%); (k) cat. $VO(acac)_2$, TBHP, CH_2Cl_2, 0 ± 5 °C; (l) TBSCl, imidazole, cat. DMAP, DMF, 25 °C; (m) LiTMP, Et_2AlCl, toluene, 0 °C (75% for 3 steps); (n) **16**, DIAD, PPh_3, THF, 0 °C (82%); (o) 3 N $HCl_{(aq)}$, THF, 55 °C (90%).

1. See scheme.



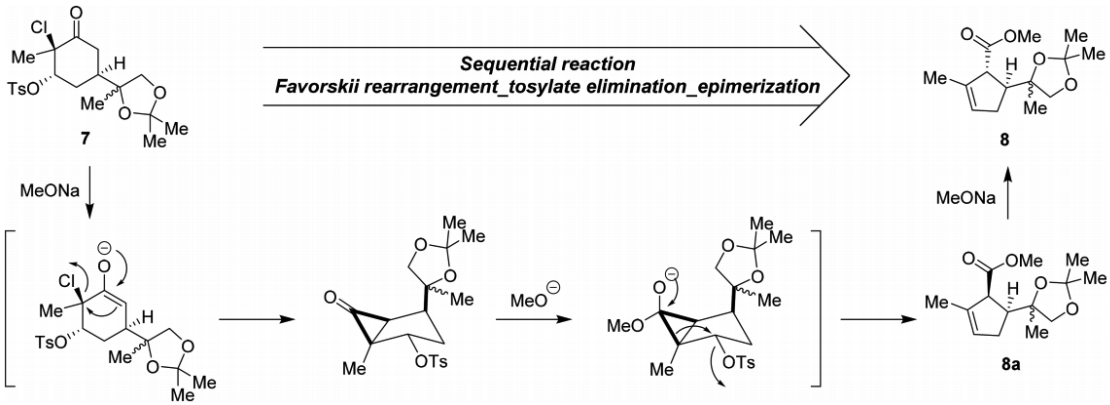
equilibirum displaced: Badjwa and Anderson **TL** 1991, *32*, 3021
carvone application: Ley **ACIE** 2003, *42*, 599; **Chem. - Eur. J.** 2007, *13*, 5688

2. See scheme.

in two steps with OsO4 (but this is presumably too toxic for a pilot synthesis of a pharmaceutical). mCPBA is well be

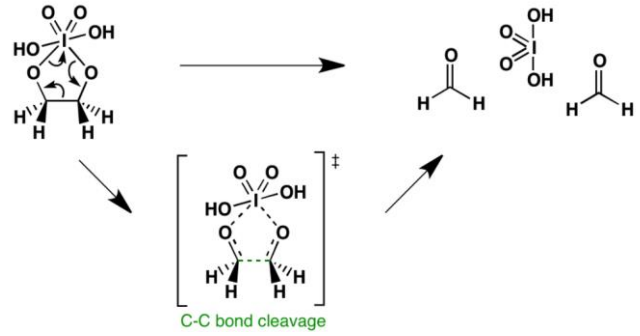
3.

Scheme 3. Proposed Mechanism of the Tandem Reaction Sequence from 7 to 8

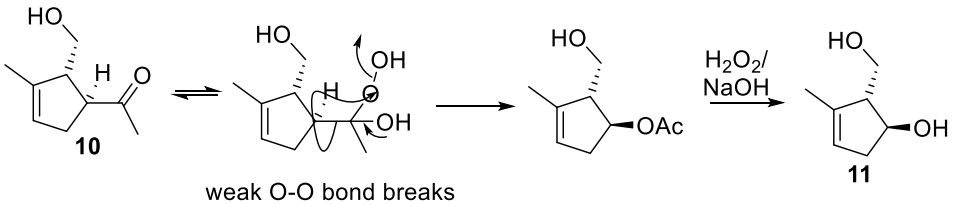


epimerization puts two groups in cyclopentene ring in a trans relationship

4. hypervalent iodine oxidation/ glycol cleavage

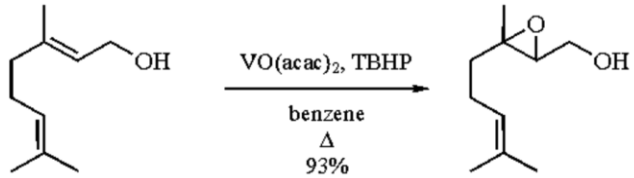


5. Baeyer-Villiger oxidation (slightly unusual conditions - usually a peracid is used).

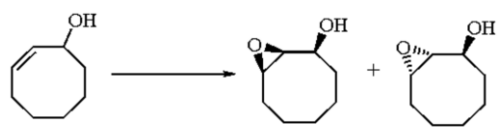


weak O-O bond breaks
reform carbonyl
conserve stereochem

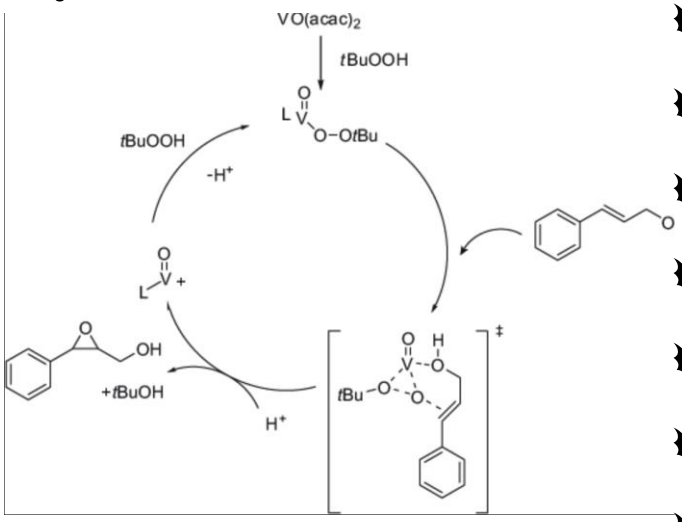
"vanadium acac" is selective for allylic alcohols:



it is also stereoselective. This is important for understanding the mechanism/ TS:



	% *cis*	% *cis*
$VO(acac)_2$, TBHP	97	3
m-CPBA	0.2	99.8
$MoO_2(acac)_2$	42	58

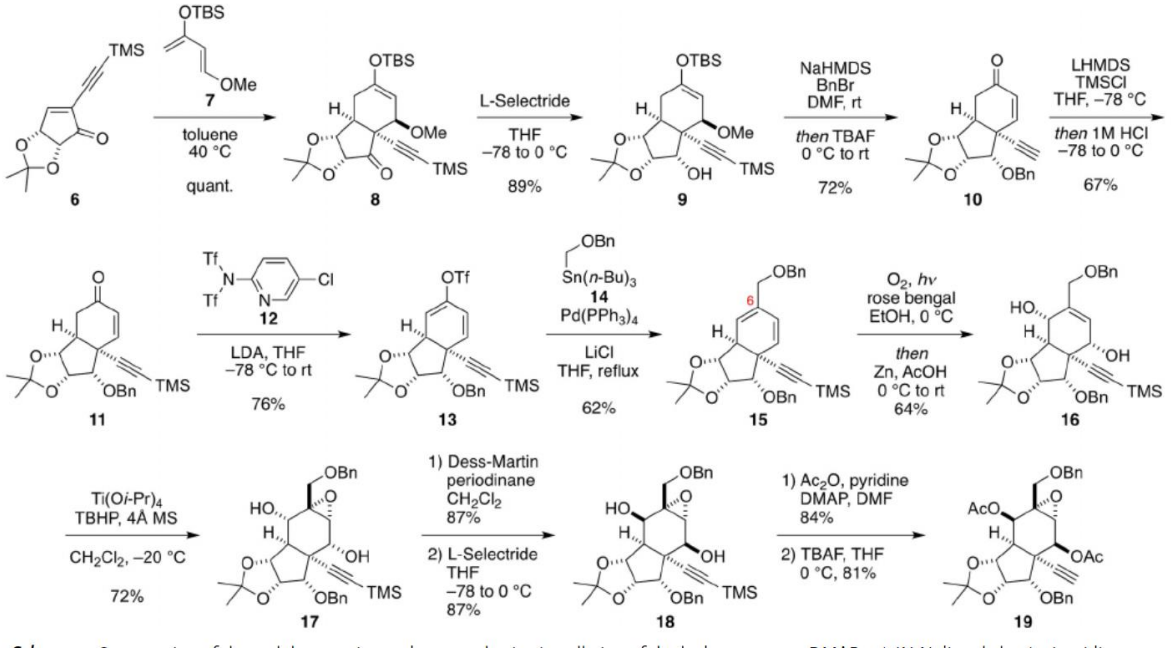


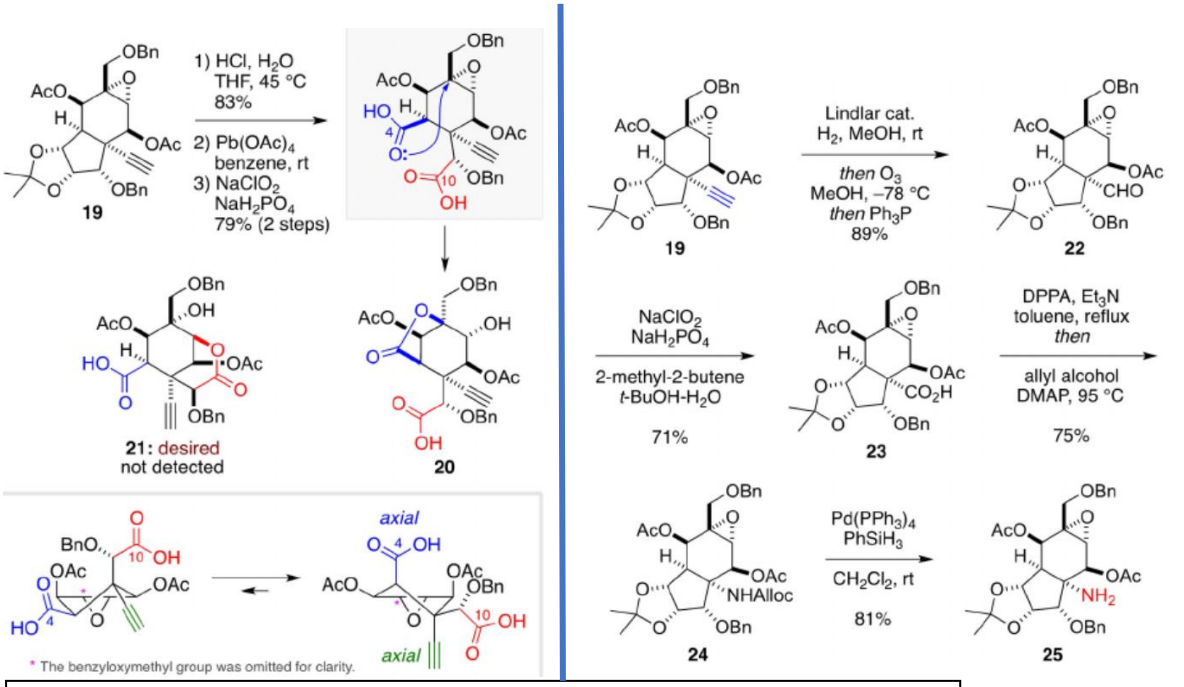
standard mech.

Our alcohol is homoallylic but there are other examples in literature of stereoselectivity in these cases (see citations in c

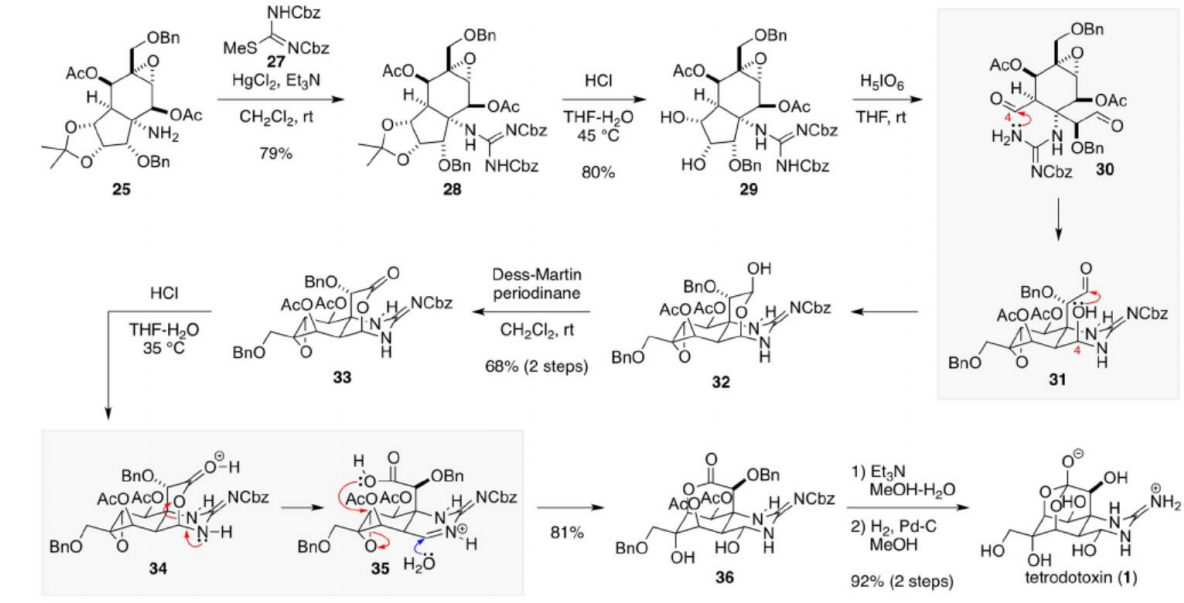
For a more in depth discussion of the epoxidation with TBHP, see: Journal of Catalysis 294 (2012) 1–18

Answers for tetrodotoxin - Angew. Chem. Int. Ed. 2020, 59, 6253 –6257



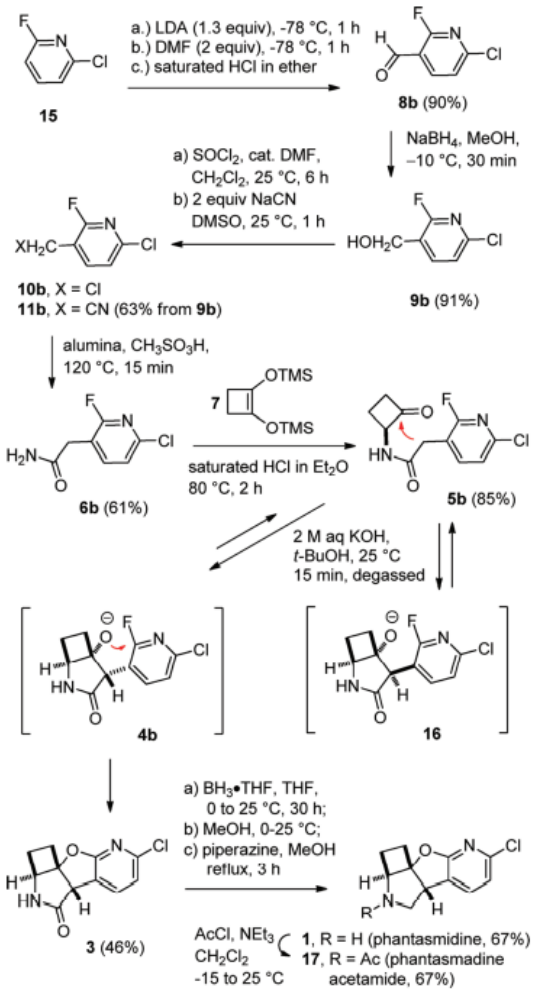


3. Attempted oxidation of the dialdehyde with sodium chlorite induced epoxide opening by the C4 carboxyl group instead of the C10 carboxyl group, leading to exclusive production of the undesired lactone. This result might be attributed to the sterically less demanding ethynyl group which assumed the axial conformation in the cyclohexane ring and therefore the C4 carboxyl also adopted axial conformation and attacked the epoxide.

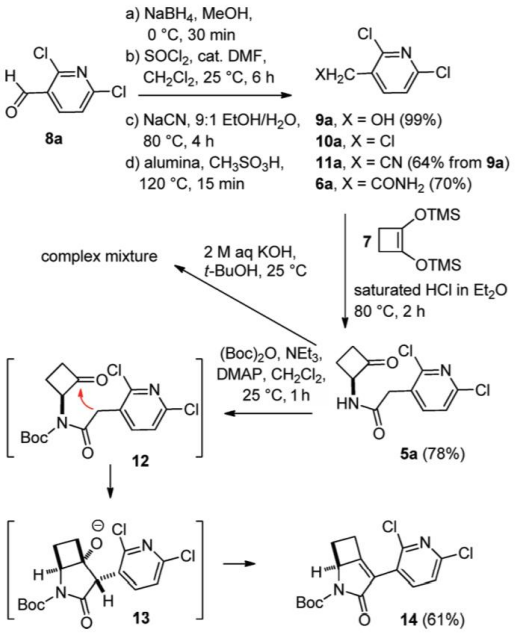


Synthesis of Phantasmidine - Org. Lett., Vol. 13, No. 3, 2011

Scheme 3. Synthesis of (±)-Phantasmidine (**1**)



Scheme 2. Unsuccessful Route to (±)-Phantasmidine (**1**)



4. Dichloropyridine: nucleophilic aromatic substitution with displacement of the chloride was sufficiently slow so that only the unstable R,-unsaturated lactam resulting from dehydration of the aldol product was isolated in 61% yield. (see next scheme)