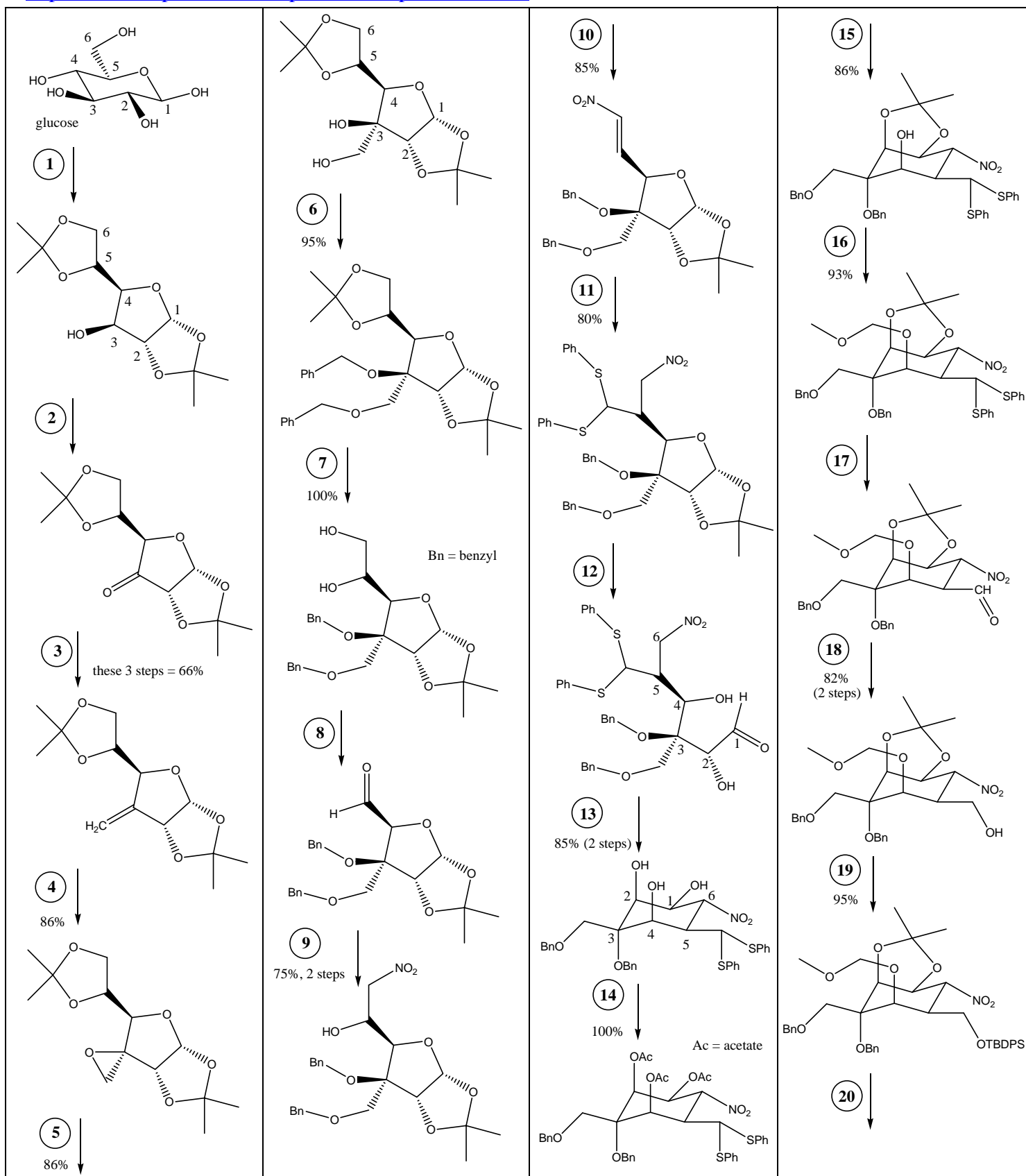
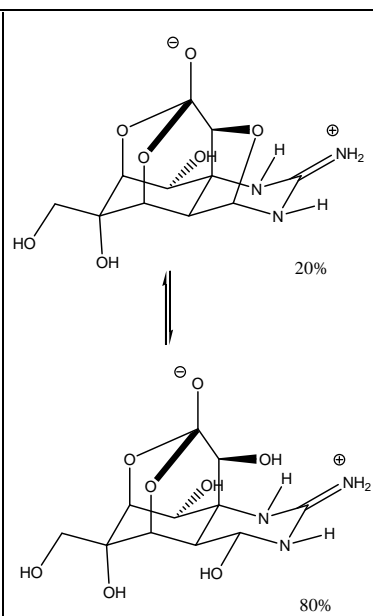
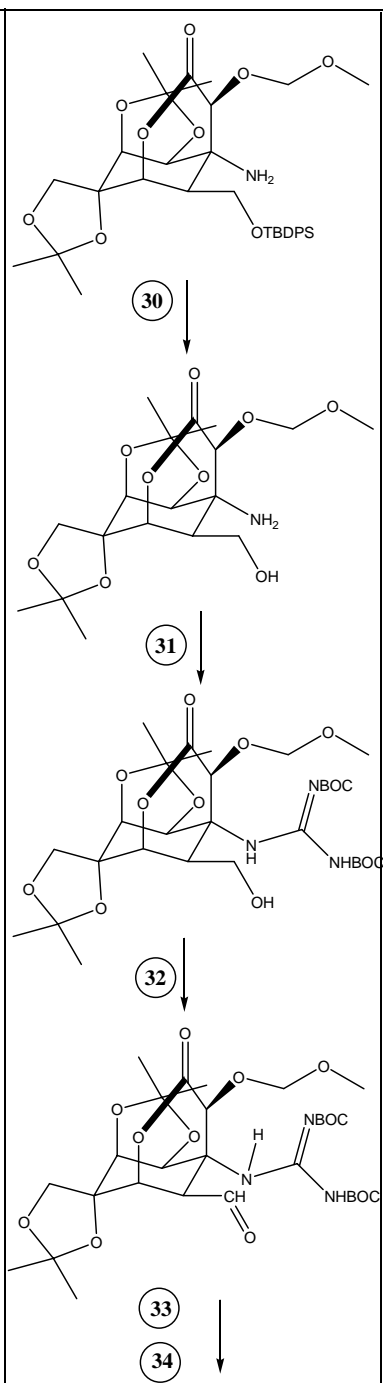
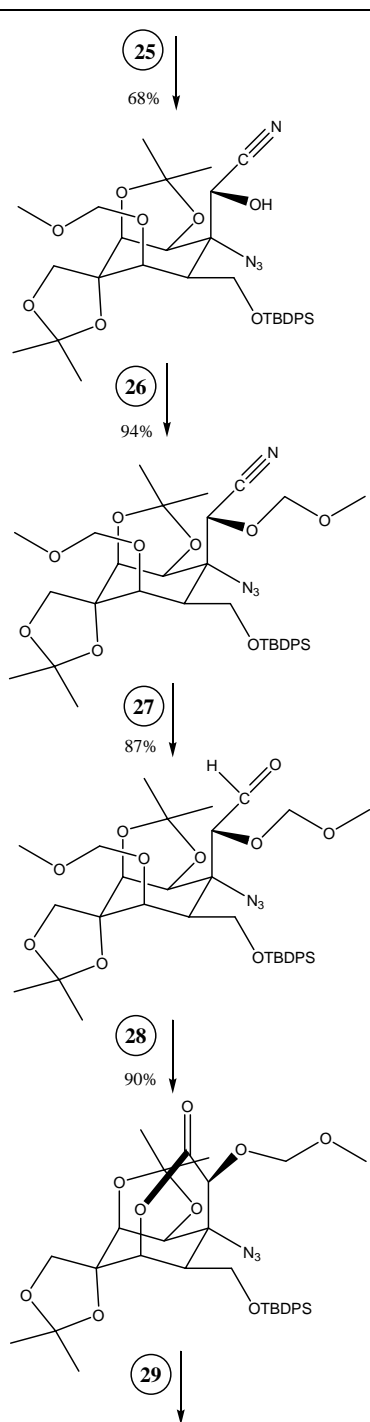
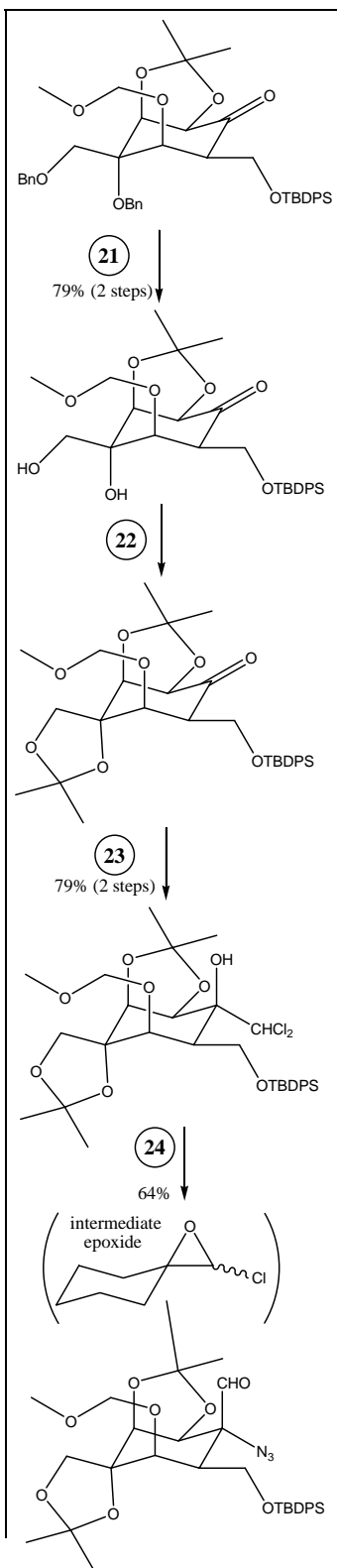


Stereoselective Total Synthesis of Optically Active Tetrodotoxin (Puffer fish toxin) JOC, 2008, 1234-42

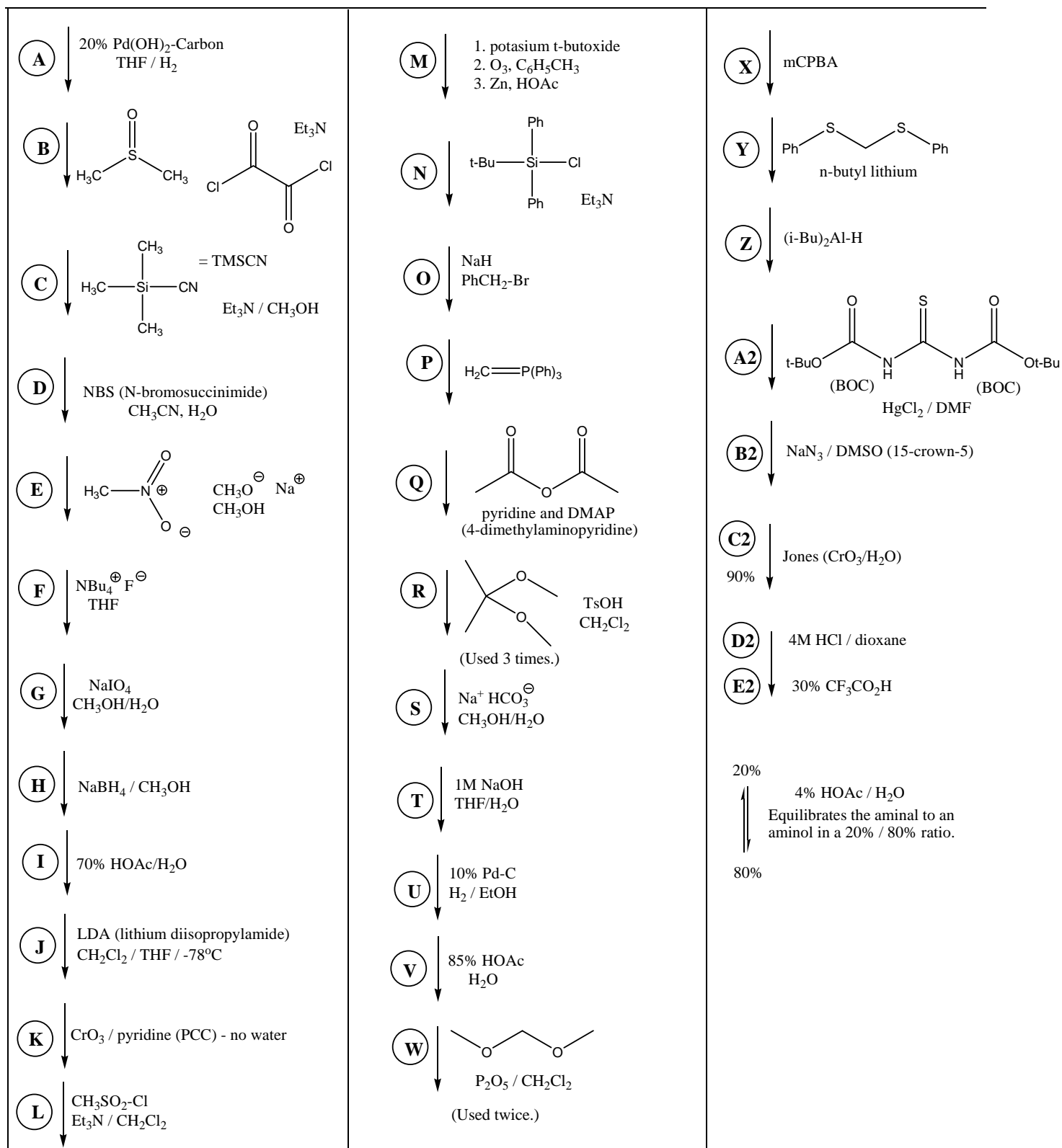
Match the list of reagents (letters) to the synthetic steps (numbers). A key is available at:

<http://www.csupomona.edu/~psbeauchamp/courses.html>





Reagents used in synthetic steps above are shown below. Simplistic structures are used to present possible mechanisms, just below.

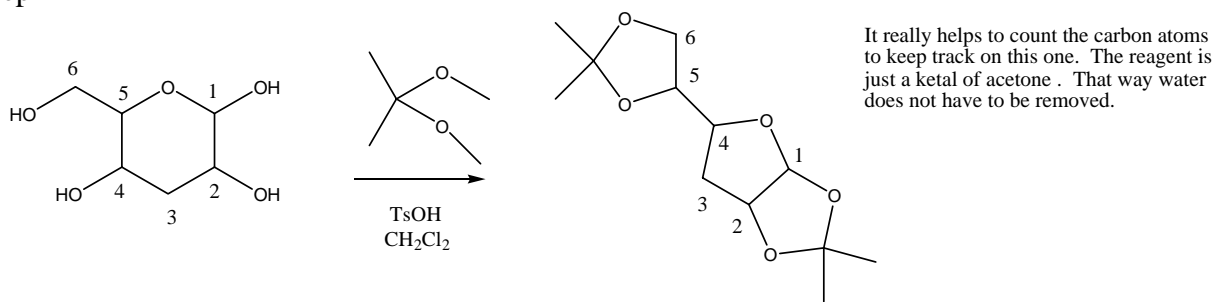


This is how you learn the logic of synthetic organic chemistry. You study the masters at work (literature synthesis papers) to discover options and experimental details. You also discover that many of the first year reactions that you learn don't always work the way you were taught. You learn alternate methods,

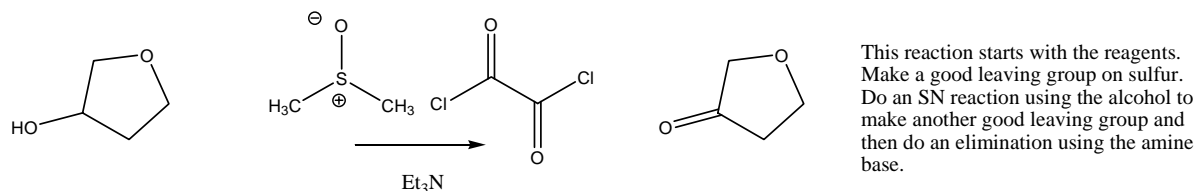
and sometimes you have to invent your own reaction to make a transformation work. There are also lots of lab skills that only come from actually working in the lab, doing reactions from start to finish: purifying your solvents and reagents, monitoring reactions, working up reactions, collecting spectra and physical properties on your compounds, etc. Being a synthetic chemist requires healthy doses of optimism, persistence and patience.

Several interesting mechanism problems from simplified structures in the synthesis.

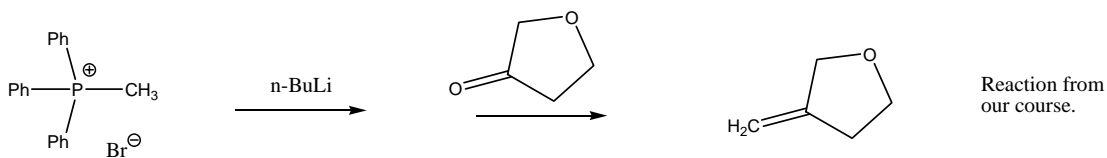
Step 1



Step 2



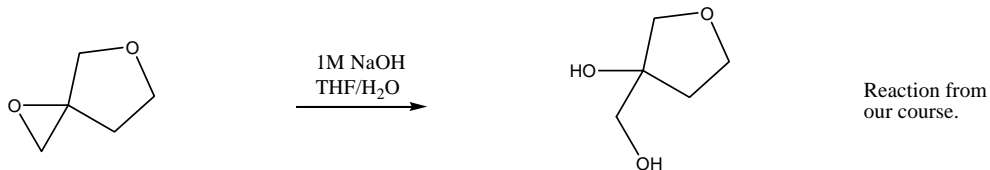
Step 3



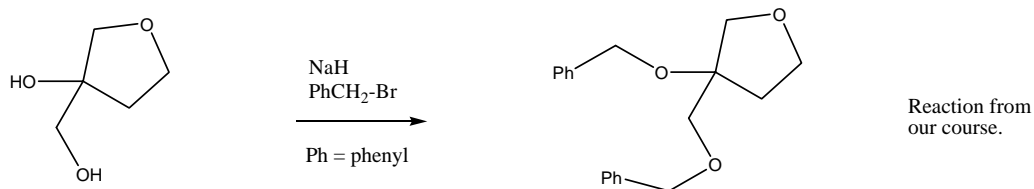
Step 4



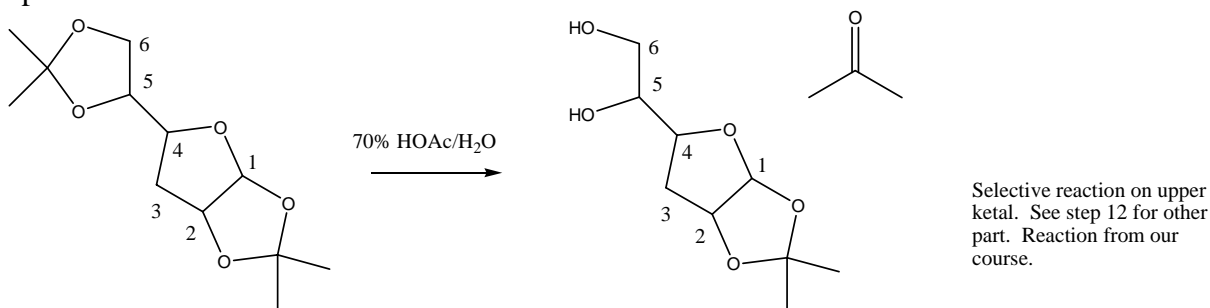
Step 5



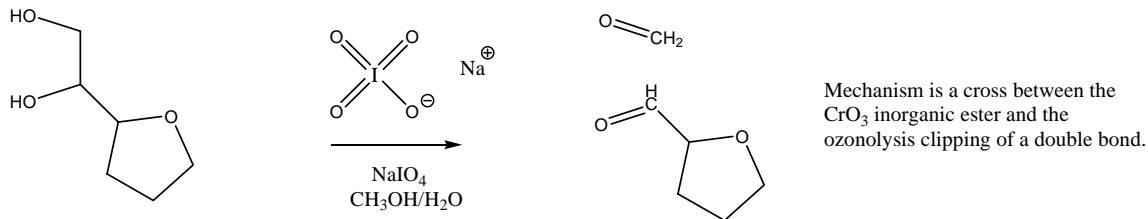
Step 6



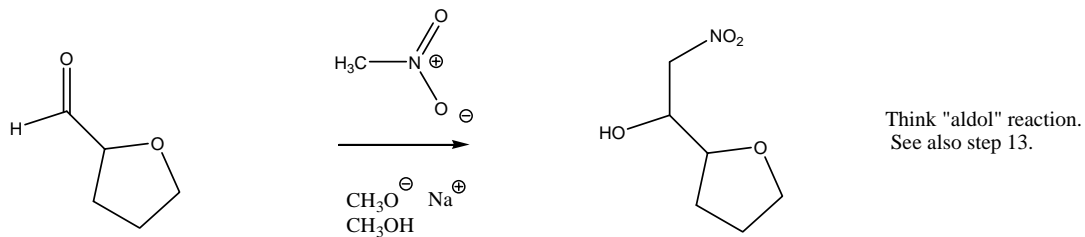
Step 7



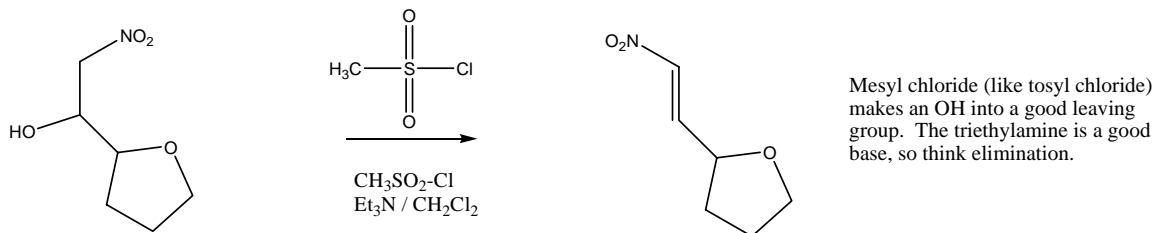
Step 8



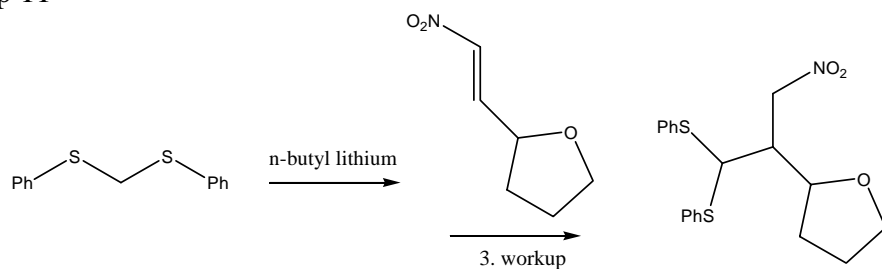
Step 9



Step 10

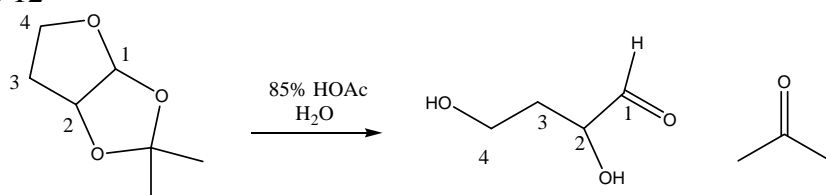


Step 11



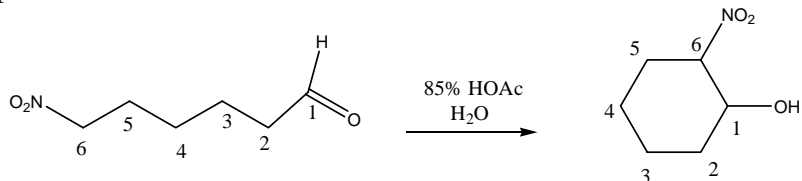
Make a good carbanion nucleophile, and then think "Michael reaction" ...or conjugate addition.

Step 12



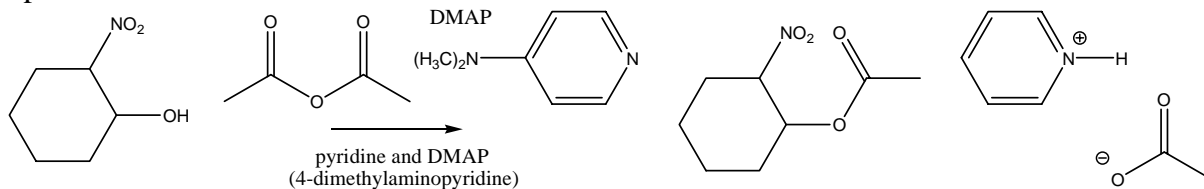
Remember the selective ketal hydrolysis in step 7? This is the hydrolysis of the other ketal. Requires a little stronger acid solution.

Step 13



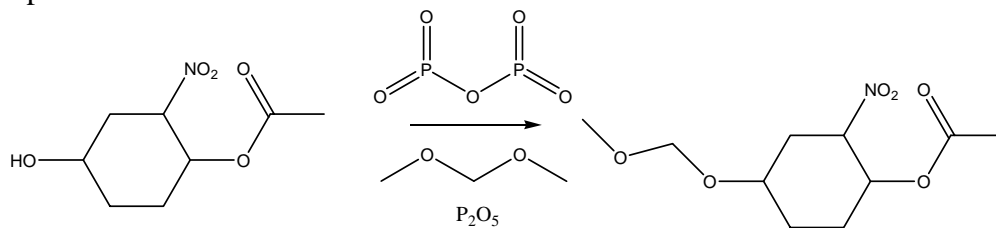
Think "aldol" reaction...or look back at step 9.

Step 14



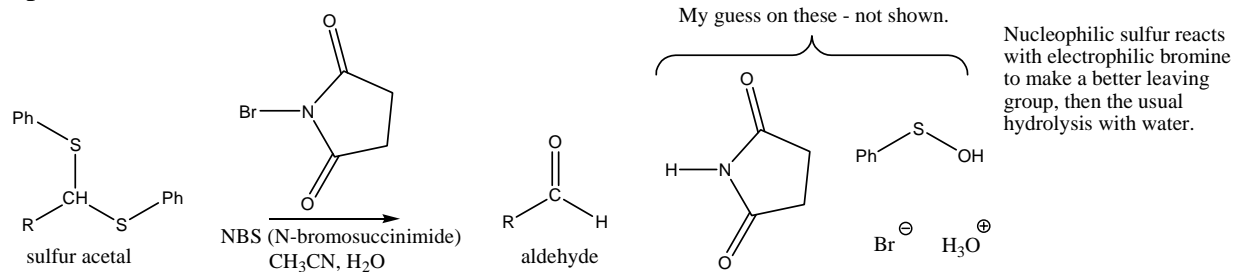
DMAP makes acetic anhydride into an even more reactive acylating electrophile, which reacts with the OH to make an ester.

Step 16



Think of P₂O₅ as an anhydride reacting with the other reagent. Then think S_N1 chemistry (...or S_N2 chemistry).

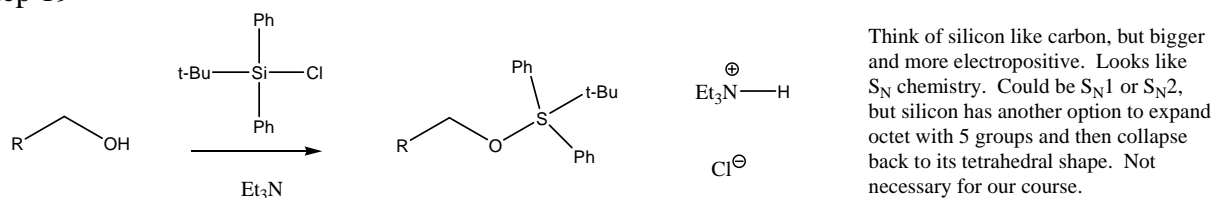
Step 17



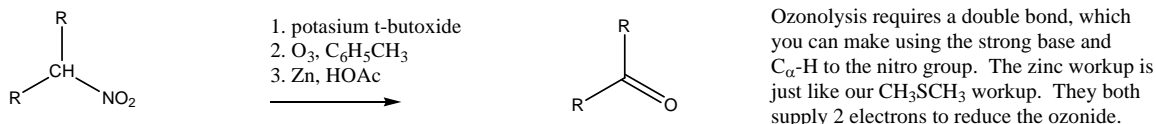
Step 18



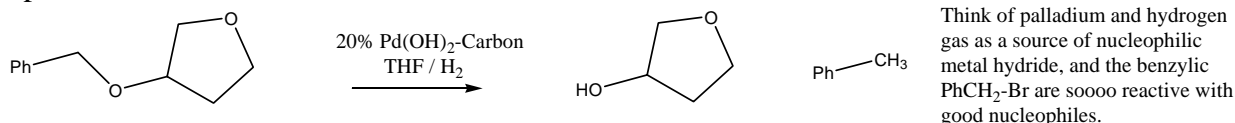
Step 19



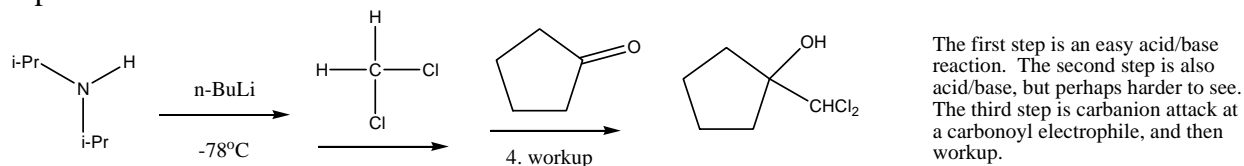
Step 20



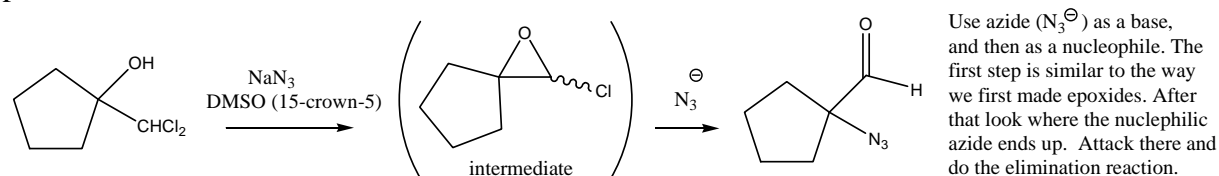
Step 21



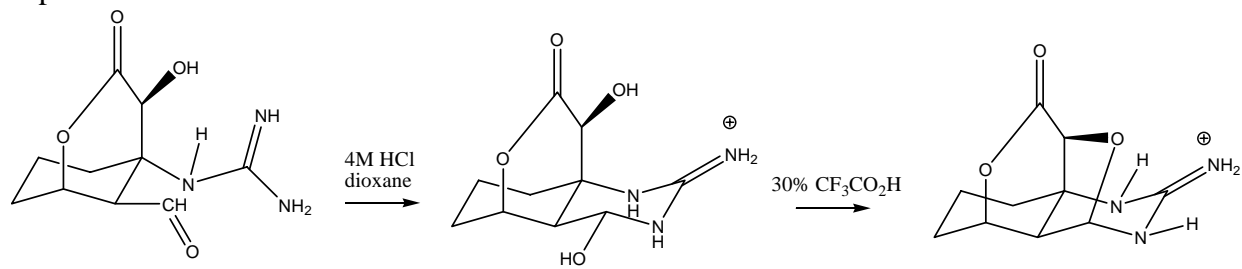
Step 23



Step 24

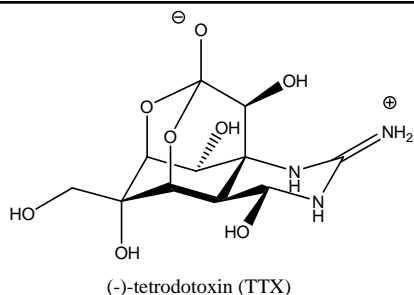


Step 33-34

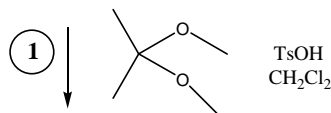
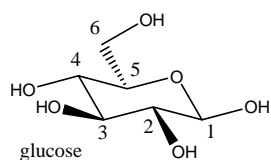


First an aminal (addition reaction) forms with acid catalysis. Step 2 is an S_N1 reaction to make the aminal.

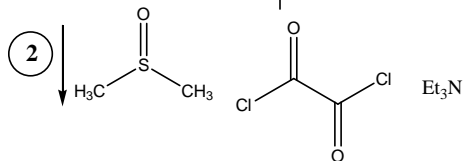
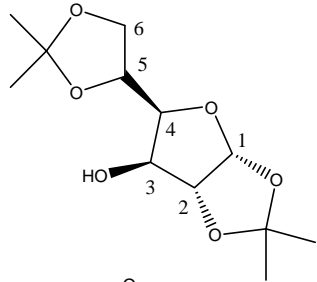
Key - Stereoselective Total Synthesis of Optically Active Tetrodotoxin (Puffer fish toxin) JOC, 2008, 1234-42



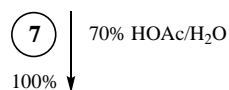
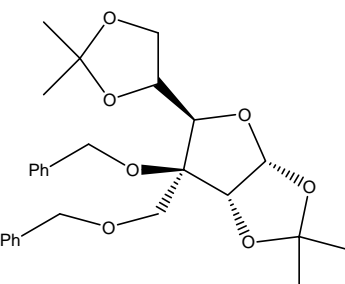
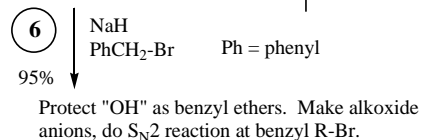
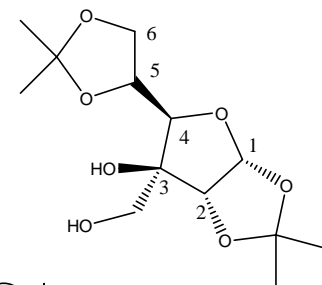
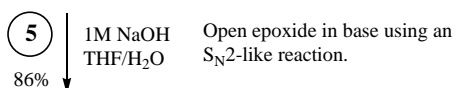
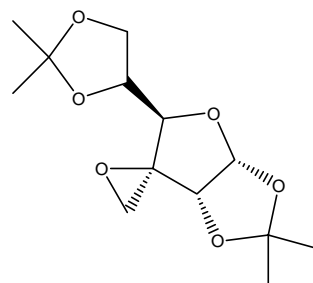
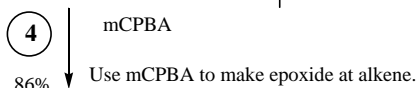
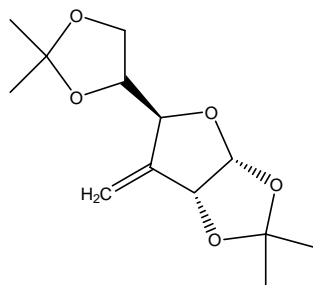
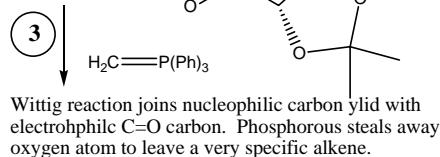
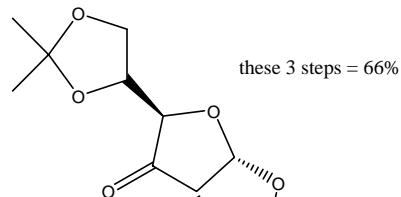
Tetrodotoxin is one of the best known marine toxins. It is found in puffer fish. It is also found in newts, frogs, octopi, crabs, shellfish and several other animals. It is not actually produced by the animals, but produced by various kinds of bacteria in the animals. Larger amounts are wanted for pharmaceutical studies. It interacts with elements of the sodium ion channel in cell membranes and has been used as a tool to study molecular events that occur there.



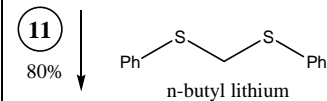
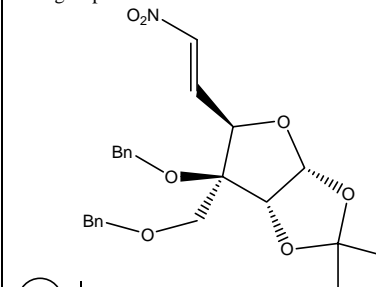
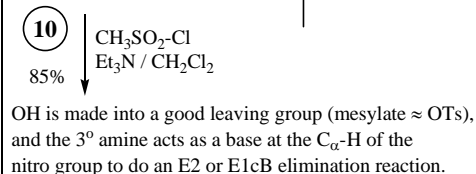
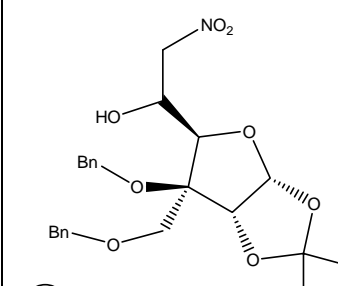
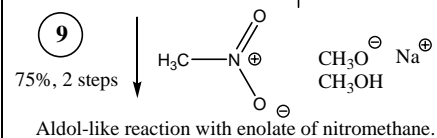
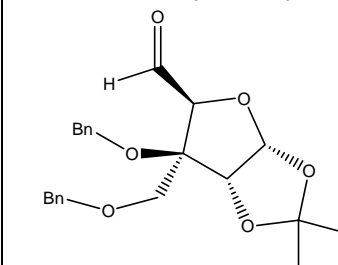
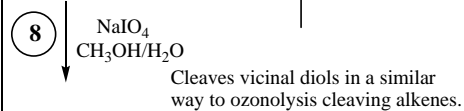
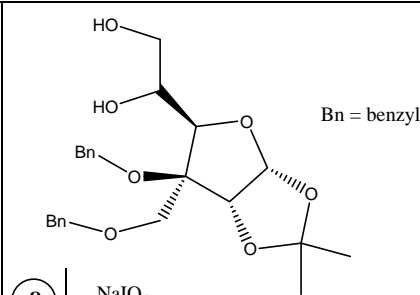
Hemiactal of glucose using C₅-OH opens and recloses to di-ketal using C₄-OH. Similar to steps 15 and 22.



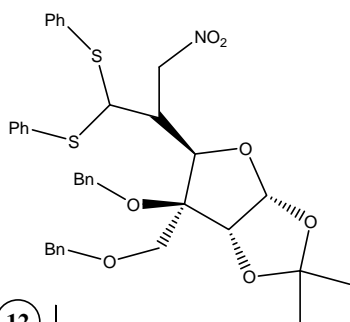
Swern oxidation makes a good leaving group on the oxygen atom. Elimination makes a C=O pi bond.



Using 70% acetic acid deprotects one ketal. Later the other ketal is deprotected in 85% acetic acid.

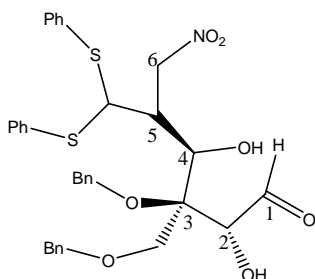


Anion forms at carbon between the two sulfur atoms (inductive and/or resonance) and undergoes conjugate addition at the beta carbon to the nitro group. Dithiane gives a lower yield (the normal "sulfur" group used).



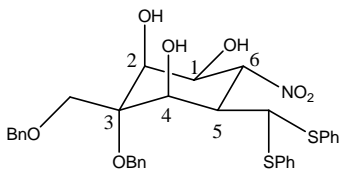
12
85% HOAc
H₂O

Deprotection of ketal to release alcohol and aldehyde. Stronger acid needed than first ketal removal.



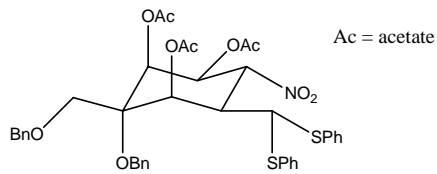
13
85% (2 steps) Na⁺ HCO₃[⊖]
CH₃OH/H₂O

"Aldol-like" reaction between C6 and C1.



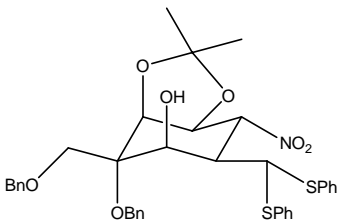
14
100% pyridine and DMAP
(4-dimethylaminopyridine)

Protects free alcohol groups as acetate ester groups. DMAP catalyzes the acyl substitution reaction.



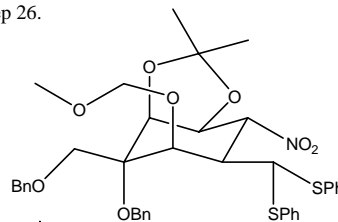
15
86% TsOH / CH₂Cl₂

Deprotects acetates and selectively reprotects the vicinal diol part as a ketal. Similar to steps 1 and 22.



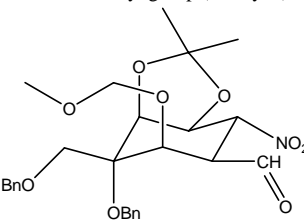
16
93% MOM group (methoxymethyl acetal). P₂O₅

Protection of free OH as MOM group (methoxymethyl acetal). P₂O₅ acts as a Lewis acid catalyst. Similar to step 26.



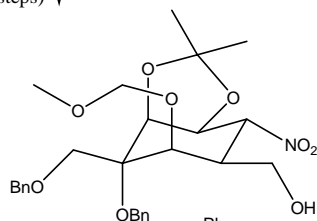
17
NBS (N-bromosuccinimide) CH₃CN, H₂O

Sulfur nucleophile brominates with electrophilic NBS, and becomes a leaving group, and is replaced by water at the C_α position. After the other sulfur repeats C_α becomes a carbonyl group (aldehyde).



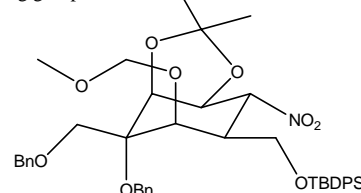
18
82% (2 steps) NaBH₄ / CH₃OH

Aldehyde is reduced to a primary alcohol.



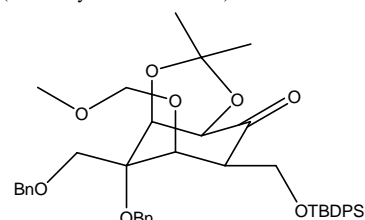
19
95% t-Bu-Si-Cl
Ph Et₃N

Protection of alcohol as t-butyl-diphenylsilyl ether (TBDPS). S_N substitution at silicon with chloride leaving group.



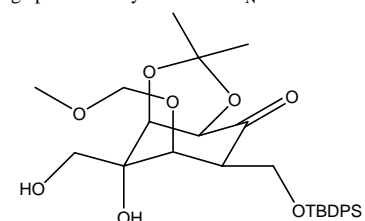
20
1. potassium t-butoxide
2. O₃, C₆H₅CH₃
3. Zn, HOAc

"Enolate-like" anion generated using RO[⊖] is ozonized and reduced with zinc to ketone (McMurry's transformation).



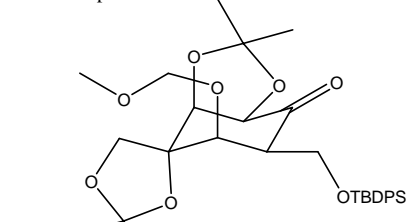
21
79% (2 steps) 20% Pd(OH)₂-Carbon
THF / H₂

Hydrogenolysis of benzyl groups (deprotection), possibly using "palladium hydride"-like S_N2 reaction.



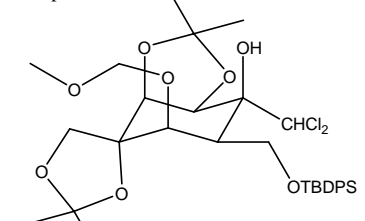
22
TsOH / CH₂Cl₂

Reprotect vicinal diol as ketal (transketalization). Similar to steps 1 and 15.



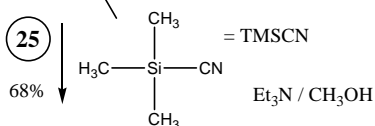
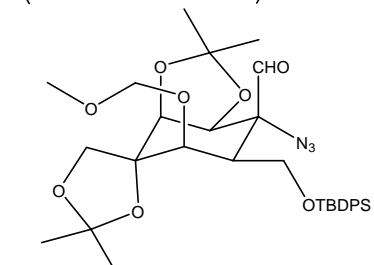
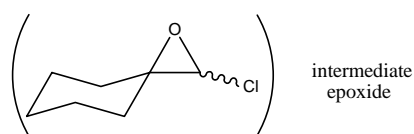
23
79% (2 steps) LDA (lithium diisopropylamide)
CH₂Cl₂ / THF / -78°C

Carbanion nucleophile made (inductive effects of the chlorine atoms), and it reacts with the C=O electrophile.

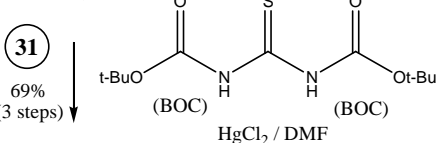
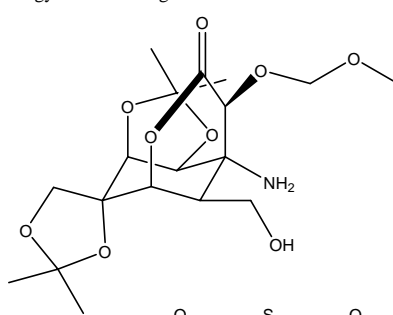
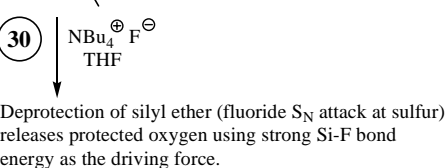
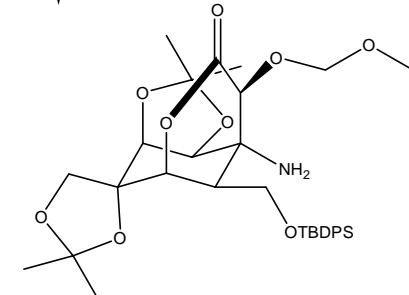
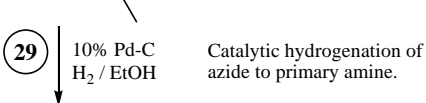
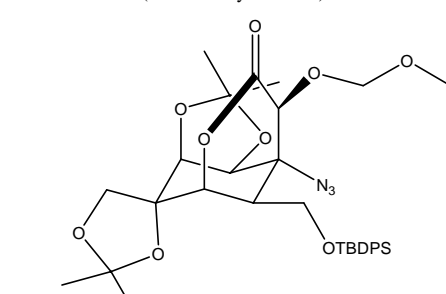
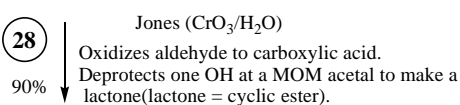
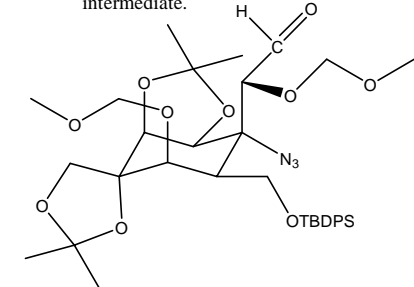
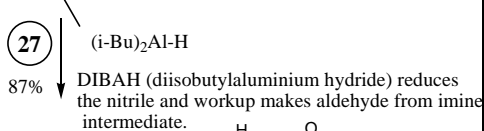
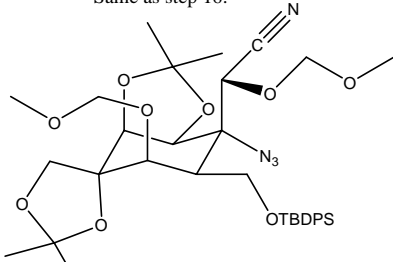
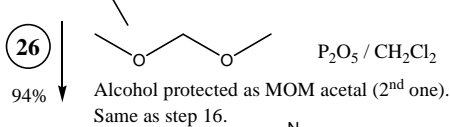
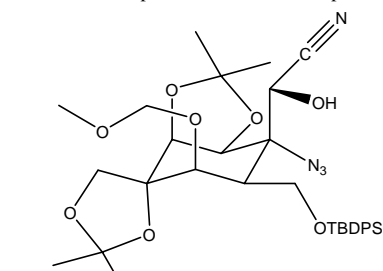


24
64% NaN₃ / DMSO (15-crown-5)

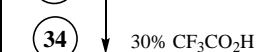
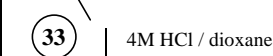
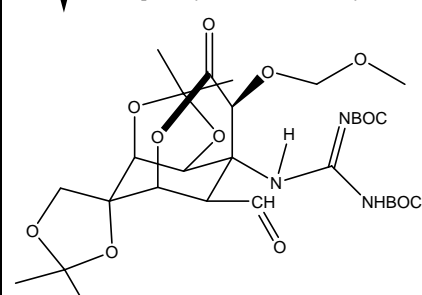
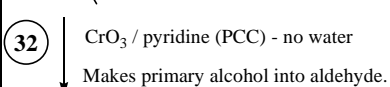
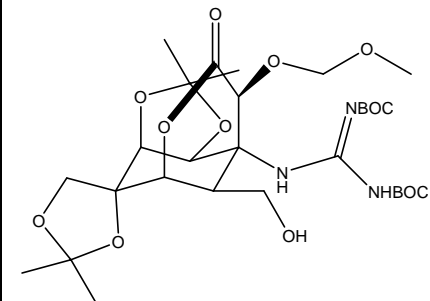
Basic conditions makes alkoxide, followed by intramolecular S_N2 to form epoxide.



Trimethylsilylcyanide (TMSCN) makes the cyanohydrin with 56% desired epimer (stereochemistry). The other 17% epimer could be epimerized to 12% more of the desired stereoisomer. TMSCN likely acts as a Lewis acid with the C=O group, releasing cyanide, which attacks the C=O. The TMS part is lost in the workup.

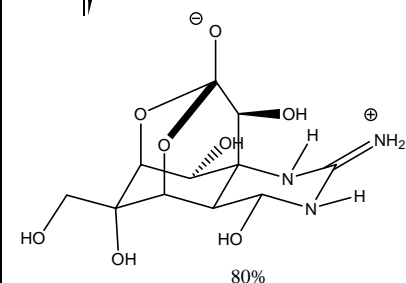
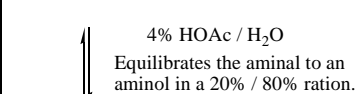
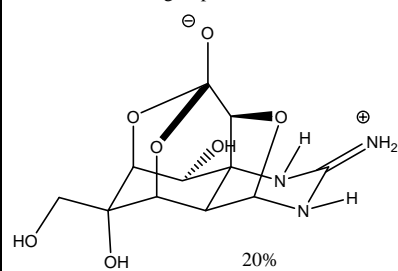


Nitrogen substitutes for sulfur to make guanine derivative. Doubly N-BOC protected nitrogen atoms. Hg^{+2} acts as Lewis acid for sulfur to make a better electrophile.



50% (3 steps)

Aqueous acid solutions deprotect ketals and MOM acetals and liberated alcohols react with lactone. The aldehyde makes an aminal with the guanidinium group and one of the OH groups.



Tetradotoxin is the extremely poisonous puffer fish toxin. The overall yield of 34 steps in this synthesis is 0.38%. That's an average yield of about 85% per step overall.