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
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

It really helps to count the carbon atoms to keep track on this one. The reagent is just a ketal of acetone. That way water does not have to be removed.

Step 2

This reaction starts with the reagents. Make a good leaving group on sulfur. Do an SN reaction using the alcohol to make another good leaving group and then do an elimination using the amine base.

Step 3

Reaction from our course.

Step 4

Reaction from our course.

Step 5

Reaction from our course.
Step 6

\[ \text{NaH} \quad \text{PhCH}_2\text{-Br} \rightarrow \text{Ph} = \text{phenyl} \]

Reaction from our course.

Step 7

\[ \text{Selective reaction on upper ketal. See step 12 for other part. Reaction from our course.} \]

Step 8

\[ \text{Mechanism is a cross between the CrO}_3 \text{ inorganic ester and the ozonolysis clipping of a double bond.} \]

Step 9

\[ \text{Think "aldol" reaction. See also step 13.} \]

Step 10

\[ \text{Mesyl chloride (like tosyl chloride) makes an OH into a good leaving group. The triethylamine is a good base, so think elimination.} \]
Step 11

Step 12

Step 13

Step 14

Step 16
Step 17

NBS (N-bromosuccinimide) in CH₃CN, H₂O

My guess on these - not shown.

Nucleophilic sulfur reacts with electrophilic bromine to make a better leaving group, then the usual hydrolysis with water.

Step 18

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Step 19

Think of silicon like carbon, but bigger and more electropositive. Looks like S₈ chemistry. Could be S₈₁ or S₈₂, but silicon has another option to expand octet with 5 groups and then collapse back to its tetrahedral shape. Not necessary for our course.

Step 20

Ozonolysis requires a double bond, which you can make using the strong base and C₄-H to the nitro group. The zinc workup is just like our CH₃SCH₃ workup. They both supply 2 electrons to reduce the ozonide.

Step 21

Think of palladium and hydrogen gas as a source of nucleophilic metal hydride, and the benzylic PhCH₂-Br are soooo reactive with good nucleophiles.

Step 23

The first step is an easy acid/base reaction. The second step is also acid/base, but perhaps harder to see. The third step is carbanion attack at a carbonoyl electrophile, and then workup.

Step 24

Use azide (N₃⁻) as a base, and then as a nucleophile. The first step is similar to the way we first made epoxides. After that look where the nucleophilic azide ends up. Attack there and do the elimination reaction.
Step 25

Think "step 19" with the CH$_3$OH solvent, and then release cyanide, which becomes a good nucleophile for the C=O bond.

Step 27

Reaction from our course.

Step 28

Make a hemiacetal first, using the acid, and then do the usual Jones CrO$_3$ reaction

Step 29

Think of palladium and hydrogen gas as a source of nucleophilic metal hydride, which "simplistically" reacts with one of the nitrogen atoms to release nitrogen gas. Proton transfers from that point on.

Step 30

Silicon loves fluorine (forms a very strong Si-F bond). Think $S_N$ chemistry.

Step 31

Sulfur loves Hg$^{2+}$, to help it become a good leaving group later on in the reaction. Think acyl substitution via addition followed by elimination.
First an aminol (addition reaction) forms with acid catalysis. Step 2 is an $S_N_1$ reaction to make the aminal.
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.

Hemiacetal 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.

These 3 steps = 66%

Wittig reaction joins nucleophilic carbon ylid with electrophilic C=O carbon. Phosphorous steals away oxygen atom to leave a very specific alkene.

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 Na⁺ HCO₃
CH₃OH/H₂O
85% (2 steps)
*“Aldol-like” reaction between C6 and C1.

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

15 TsOH / CH₂Cl₂
86%
Deprotects acetates and selectively reprotects the vicinal diol part as a ketal. Similar to steps 1 and 22.

16 93%

17 NBS (N-bromosuccinimide) CH₃CN, H₂O
Sulfur nucleophile brominates with electrophilic NBS, and becomes a leaving group, and is replaced by water at the Cα position. After the other sulfur repeats Cα becomes a carbonyl group (aldehyde).

18 NaBH₄ / CH₃OH
82%
(2 steps)
Aldehyde is reduced to a primary alcohol.

19 95%
Protection of alcohol as t-butyldiphenylsilyl ether (TBDDS). S₈ 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 20% Pd(OH)₂-Carbon
THF / H₂
Hydrogenolysis of benzyl groups (deprotection), possibly using “palladium hydride”-like S₈ reaction.

22 TsOH / CH₂Cl₂
79% (2 steps)
Reprotect vicinal diol as ketal (transketalization). Similar to steps 1 and 15.

23 LDA (lithium diisopropylamide)
CH₂Cl₂ / THF / -78°C
79% (2 steps)
Carbanion nucleophile made (inductive effects of the chlorine atoms), and it reacts with the C=O electrophile.

24 NaN₃ / DMSO (15-crown-5)
64%
Basic conditions makes alkoxide, followed by intramolecular S₈2 to form epoxide.
Trimethylsilyl cyanide (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.

Alcohol protected as MOM acetal (2nd one). Same as step 16.

DIBAH (diisobutylaluminium hydride) reduces the nitrile and workup makes aldehyde from imine intermediate.

Nitrogen substitutes for sulfur to make guanidine derivative. Doubly N-BOC protected nitrogen atoms. Hg²⁺ acts as Lewis acid for sulfur to make a better electrophile.

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.