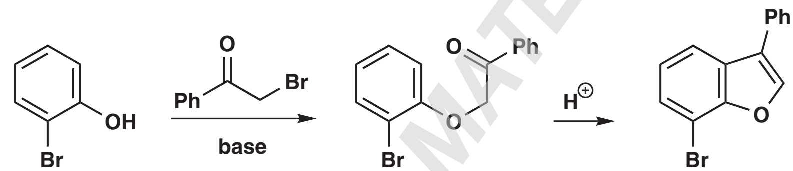
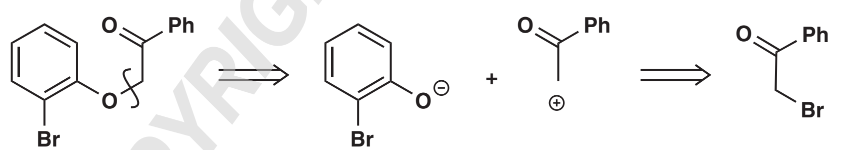
1 The Disconnection Approach

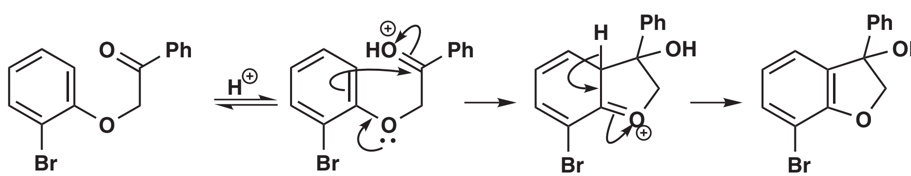
We start with a few simple problems to set you at ease with disconnections. **Problem 1.1:** Here is a two-step synthesis of the benzofuran **3**. Draw out the retrosynthetic analysis for the synthesis of **2** from **1** showing the disconnections and the synthons.



Answer 1.1: As this is a simple S_N2 reaction, the disconnection is of the C–O bond **2a** and the synthons are nucleophilic phenolate anion **4**, which happens to be an intermediate in the reaction, and the cation **5**, which happens not be an intermediate in the reaction but is represented by the α-bromoketone **6**.



Problem 1.2: Draw the mechanism of the cyclisation of **2** to **3**. This is an unusual reaction and it helps to know what is going on before we analyse the synthesis. **Answer 1.2:** The first step is an acid-catalysed cyclisation of the aromatic ring onto the protonated ketone **7**. Loss of a proton **8** completes the electrophilic aromatic substitution giving the alcohol **9**.



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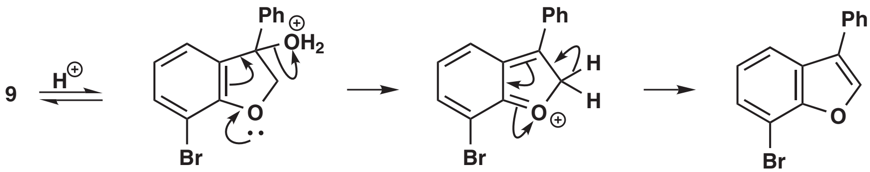
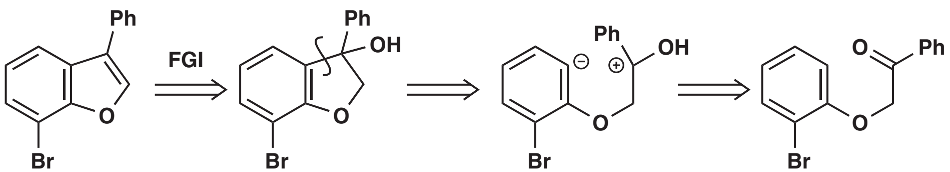
Now protonation of the alcohol leads to loss of water **10** to give a stabilised cation that loses a proton **11** to give the new aromatic system **3. Problem 1.3:** Now you should be in a position to draw the disconnections for this step.



10 **11** **3**

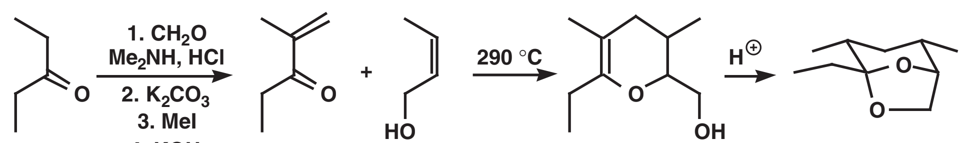
Answer 1.3: We hope you might have drawn the intermediate alcohol **9**. Changing **3** into **9** is not a disconnection but a Functional Group Interconversion (FGI) – changing one functional group into another. Now we can draw the disconnection revealing the synthons **12** represented in real life by **2**.



3 **9** **12** **2**

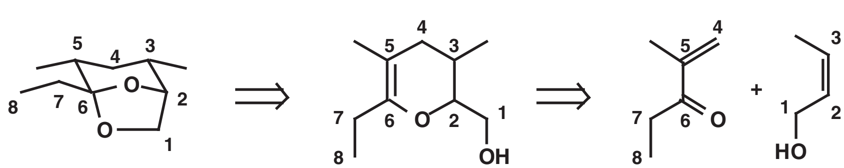
A Synthesis of Multistriatin

In the textbook we gave one synthesis of multistriatin **17** and here is a shorter but inferior synthesis as the yields are lower and there is little control over stereochemistry.[1] **Problem 1.4:** Which atoms in the final product **17** come from which starting material and which bonds are made in the synthesis? *Hint*: Arbitrarily number the atoms in multistriatin and try to trace each atom back through the intermediates. Do not be concerned over mechanistic details, especially of the step at 290 °C.



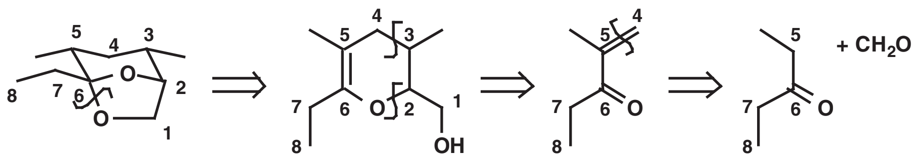
13 **14** **15** **16** **17; multistriatin**

Answer 1.4: However you numbered multistriatin, the ethyl group (7 and 8 in **17a**) finds the same atoms in the last intermediate **16a** and the rest falls into place. It then follows which atoms come from **14** and which from **15**. Finally, you might have said that C-4 in our diagrams comes from formaldehyde.



17a **16a** **14a** **15a**

So the disconnections also fall into place. Just one C–O bond was disconnected at first **17b** then one C–O and one C–C **16b** and finally the alkene was disconnected **14b** in what you may recognise as an aldol reaction with formaldehyde. If you practise analysing published syntheses like this, you will increase your understanding of good bonds to disconnect.



17b **16b** **14b** **13b**

References

1. W. E. Gore, G. T. Pearce and R. M. Silverstein, *J. Org. Chem.*, 1975, **40**, 1705.