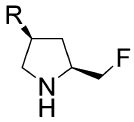
Problem Sheet - Fluorine when it's good and when it's bad.

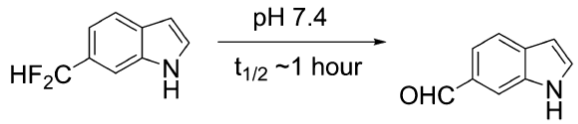
1.



1, R = alkyl

The compound above is unstable in water at pH 7.4 at 50 °C. What are the decomposition products? Give a synthesis of compound **1** when R=Me.

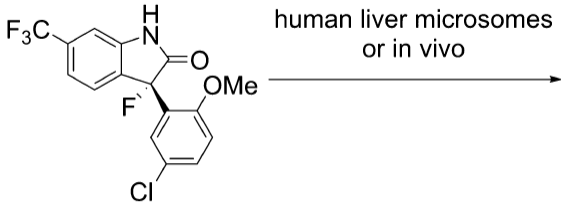
2.



11

Give a mechanism for the decomposition process above. Give a synthesis of **11**.

3.

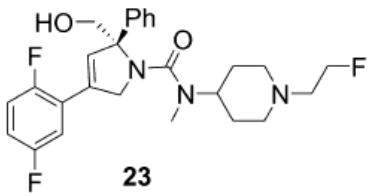


12

Compound **12** is unstable in vivo with respect to demethylation. Des-methyl **12** is further unstable with respect to a rearrangement reaction that generates a Michael acceptor with an empirical formula of $C_{15}H_7O_2NF_3Cl$.

Give the mechanism and structure of the Michael acceptor. Explain why this is not good in the context of drug discovery/toxicity.

4.

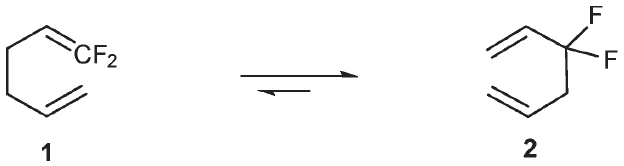


23

Explain how in vivo fluoroacetate can be generated from compound **23** and why this is bad.

Give an asymmetric synthesis of **23**.

5.



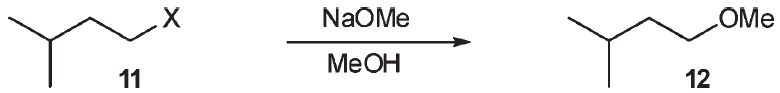
1 **2**

favoured by 5.0 kcal mol^{-1}

Explain why **2** is favoured over **1**.

6.

Table 5 Rates of halide ions as leaving groups in an S_N2 reaction

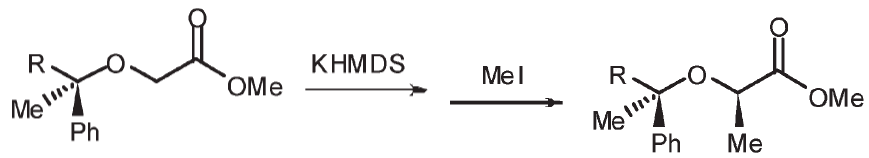


11 **12**

Halide ion	Relative reaction rate
F^-	1
Cl^-	71
Br^-	3500
I^-	4500

Explain these data.

7.



R = CH_2F **39**
R = CF_2H **40**
R = CF_3 **41**

R = CH_2F, 82% de **43**
R = CF_2H, 88% de **44**
R = CF_3, 90% de **45**

Explain these data.