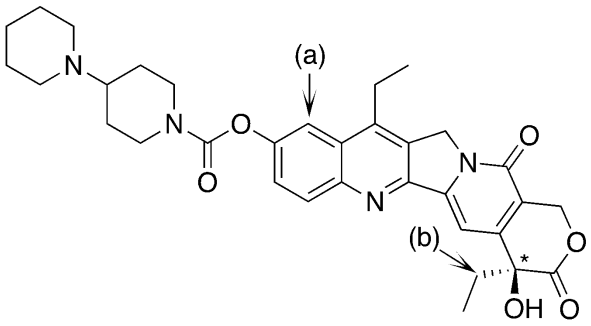
Problem Set 4

Irinotecan, shown below, is an anti-cancer prodrug that functions as a topoisomerase I inhibitor, leading to DNA damage and ultimately causing cell death. It is an analogue of camptothecin, a class of plant-derived compounds that show anti-cancer properties.



Questions 1-10 refer to the structure of Irinotecan:

1. How many degrees of unsaturation comprise Irinotecan?
   a) 7 b) 10 c) 12 d) 14 e) 17

2. How many sp^2-hybridized carbon atoms does Irinotecan have?
   a) 3 b) 13 c) 16 d) 18 e) 19

3. Which of the following functional groups are **not** in the molecule?
   a) amine b) alcohol c) alkane d) ether e) lactam

4. Which of the following statements about Irinotecan is false?
   a) It has two ethyl groups.
   b) It has one tertiary amine.
   c) The carbon labelled with an asterisk (*) is not a stereocentre/chirality centre.
   d) The carbon atom labelled (a) can be described as an sp^3-hybridized carbon.
   e) The carbon atom labelled (b) can be described as an sp^3-hybridized carbon.

5. Irinotecan is sensitive to changes in pH. Which of the following statements is true?
   a) The carbamate linkage is hydrolysed under acidic conditions.
   b) The ethyl group is deprotonated under basic conditions.
   c) The alcohol functional group is deprotonated under acidic conditions.
   d) The lactone is hydrolysed under acidic conditions to yield the carboxylate form.
   e) The lactone is hydrolysed under neutral/basic conditions to yield the carboxylate form.

6. Which of the descriptors below best characterize the carbon atom labelled with an asterisk (*)?
   a) *R* b) *S* c) sp-hybridized d) sp^2-hybridized e) primary

7. Irinotecan acts as a prodrug, with conversion to its active metabolite, SN-38, through enzymatic hydrolysis of the carbamate linkage. Which of the following is a byproduct of this hydrolysis reaction?

a) CO_2 b) H_2O c) H_3O^+ d) ^-OH e) no byproducts

8. Enzymes called carboxylesterases are required for hydrolysis of the carbamate linkage leading to drug activation. Which of the following is **not** a characteristic of enzymes?
   a) Enzymes are proteins
   b) Enzymes catalyse chemical reactions by lowering the activation energy
   c) Enzymes catalyse chemical reactions by making the reaction more energetically favourable
   d) Enzymes are not consumed by a reaction
   e) Enzymes only affect the kinetics of a reaction

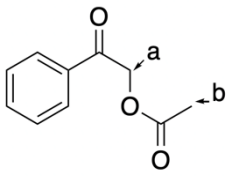
9. How many hydrogen bond donors does Irinotecan have?

a) 1 b) 2 c) 5 d) 10 e) 11

10. How many hydrogen bond acceptors does Irinotecan have?

a) 7 b) 8 c) 9 d) 10 e) 12

Consider the molecule, 2-acetoxyacetophenone, for questions 11-15.



11. In which range of ppm would you expect the aromatic protons of 2-acetoxyacetophenone to appear in a ^1H NMR spectrum?

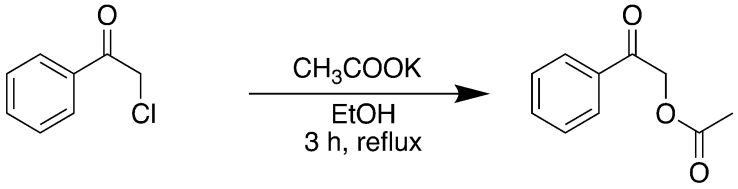
a) 1-2 b) 2-3 c) 3-4 d) 6-8 e) 10-12

12. What multiplicity would you expect protons from the site labelled **b** to display in a ^1H NMR spectrum?

a) singlet b) doublet c) triplet d) doublet of doublets e) multiplet

13. Which of the following statements is true regarding distinguishing protons labelled **a** from **b** by ^1H NMR?
   a) Protons **a** and **b** will integrate to the same number of protons.
   b) Protons **a** and **b** will display different chemical shifts.
   c) Protons **a** and **b** will both be multiplets.
   d) Protons **a** and **b** will both be doublets.
   e) Protons **a** and **b** cannot be distinguished from each other by NMR.

14. 2-acetoxyacetophenone is synthesized from 1-chloroacetophenone by the reaction below.



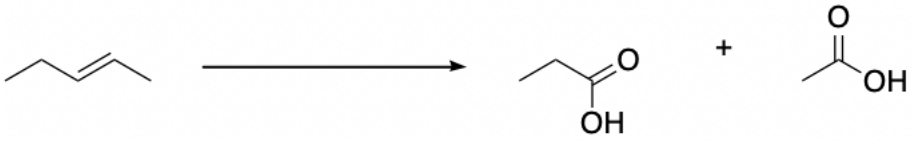
Which reaction class would this be classified as?

a) Elimination
b) Reduction
c) Oxidation
d) Substitution
e) Addition

15. You run the reaction shown in question 14 and decide to run an IR spectrum on an isolated product from the reaction and compare it to an IR of the starting material. Which of the following should you observe?

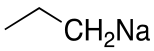
a) 2 sharp peaks are observed with wavenumber between 1680 and 1750
b) Appearance of a broad band with wavenumber between 3200 and 3550
c) Appearance of a band with wavenumber above 3000
d) Loss of sharp peak with wavenumber between 1680 and 1750
e) No change will be observed by IR

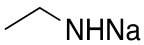
16. Which reagents can be used to carry out the following reaction?

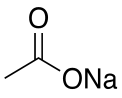


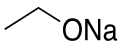
a) O_3/H_2O_2
b) HCl, H_2O
c) H_2, Pd/C
d) Br_2, DCM
e) NaOH, H_2O

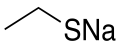
17. Which of the following is the strongest nucleophile?

a) 

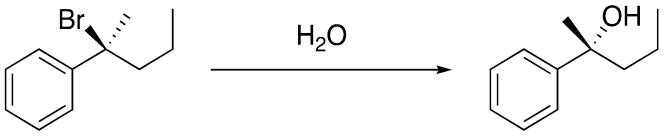
b) 

c) 

d) 

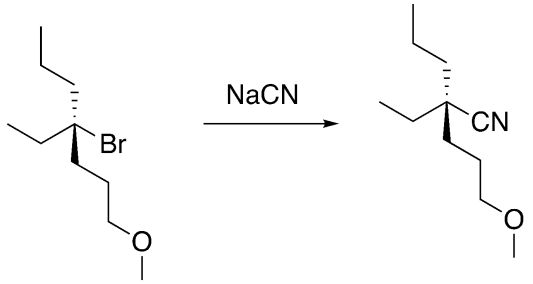
e) 

18. Which of the descriptors below best describes the stereocenter of the product from the following reaction?



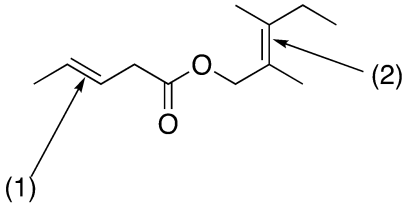
a) *R* b) *S* c) sp-hybridized d) sp^2-hybridized e) a primary carbon p

19. Which of the following would be a suitable choice of solvent for the shown reaction?



a) EtOH b) DMSO c) MeOH d) water e) hexanes

20. Which of the following best describe the isomerization in order of the numbered carbons in the molecule shown below?



a) (1) *E* (2) *E* b) (1) *E* (2) *Z* c) (1) *Z* (2) *E* d) (1) *Z* (2) *Z* e) no need for E/Z description

21. Tris (or tris(hydroxymethyl)aminomethane) has a pK_a of around 8.1 at room temperature. It is commonly used as a basis for buffers. Which pH range would Tris be most useful for buffering?

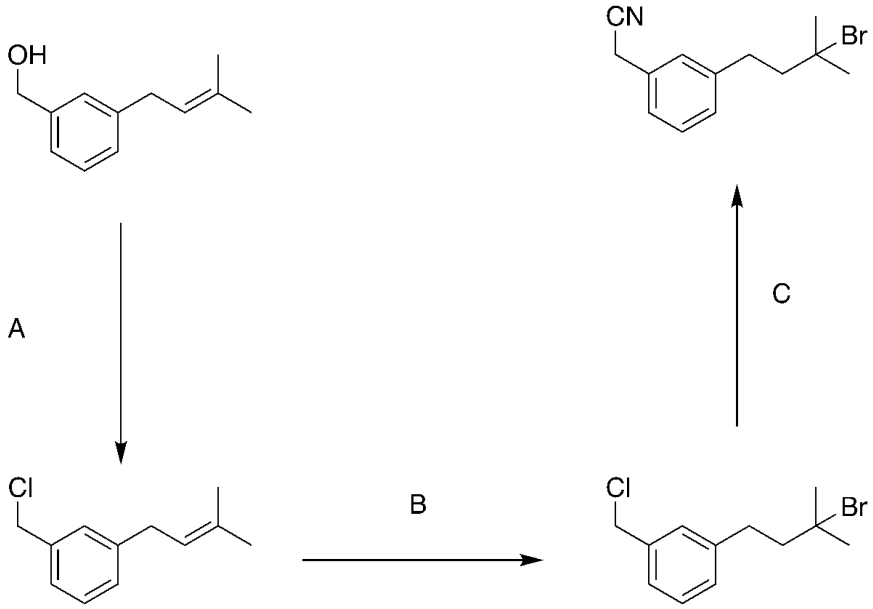
a) 1-2 b) 3-4 c) 5-6 d) 7-8 e) 9-10

22. Drug candidate A binds to its receptor with a K_d of 4.6 nM. In order for drug candidate B to be stronger than A if they bind to the same receptor, which of the following statements must be true?

a) K_d must be less than 4.6 nM
b) K_d must be equal to 4.6 nM
c) K_d must be greater than 4.6 nM

d) K_d must be negative
e) These two drug candidates cannot be compared

Questions 23-25 refer to the scheme presented below.



23. Which of the following reagents would perform the reaction labelled A?
a) PBr_3
b) $SOCl_2$
c) HCl
d) Cl_2
e) Cl_2, H_2O

24. Which of the following reagents would perform the reaction labelled B?
a) HBr without peroxides
b) HBr with peroxides
c) Br_2
d) Br_2, H_2O
e) H_2, Pt

25. Which of the following reagents would promote the reaction labelled C?
a) NaCN, EtOH
b) HNO_3
c) NaCN, acid
d) NaCN, DMSO
e) HNO_3, H_2O