

HONOUR SCHOOL OF NATURAL SCIENCE

Final Examination

ORGANIC CHEMISTRY

OPTION 2

SAMPLE PAPER

Time: 2 hours

Candidates should answer *two* questions.

Please start each question in a new booklet.

The numbers in square brackets indicate the marks which examiners normally expect to assign to each part of the question.

Standard three letter abbreviations for amino acids are used throughout.

Aqueous work-up procedures are implied throughout, with concomitant protonation or deprotonation of charged intermediates. Assume reactions are carried out at ambient temperature unless otherwise indicated. A wavy line (\sim) indicates a mixture of stereoisomers.

Guide to Questions:

1. Chemoenzymatic synthesis and catalysis
 2. Natural Product synthesis
 3. Peptide chemistry
 4. Metabolism
 5. Mechanisms
-

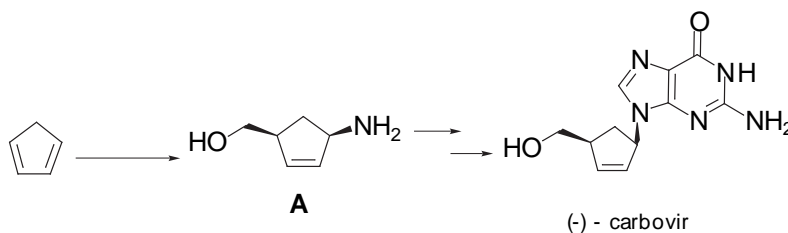
1. Answer **all** parts **A**, **B** and **C** of this question. *Note that this question is on **three** pages.*

Part A

In this question you are asked to devise chemoenzymatic syntheses of compounds **A-C** from achiral starting materials. In both parts you should indicate the source of chirality.

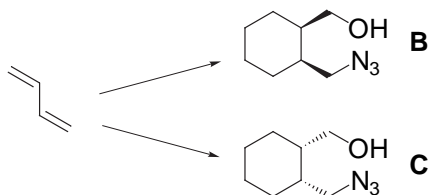
(a) **A** is a key intermediate in the synthesis of the antiviral reagent (-)-carbovir. Devise a chemoenzymatic synthesis of enantiopure **A** from cyclopentadiene or another starting material of your choice (more than one step may be required). *NB : You are **not** required to comment on the synthesis of carbovir from **A**.*

[9]



(b) Devise a chemoenzymatic synthesis of *both* enantiomers **B** and **C** from 1,3-butadiene or a starting material of your choice.

[9]



Part B

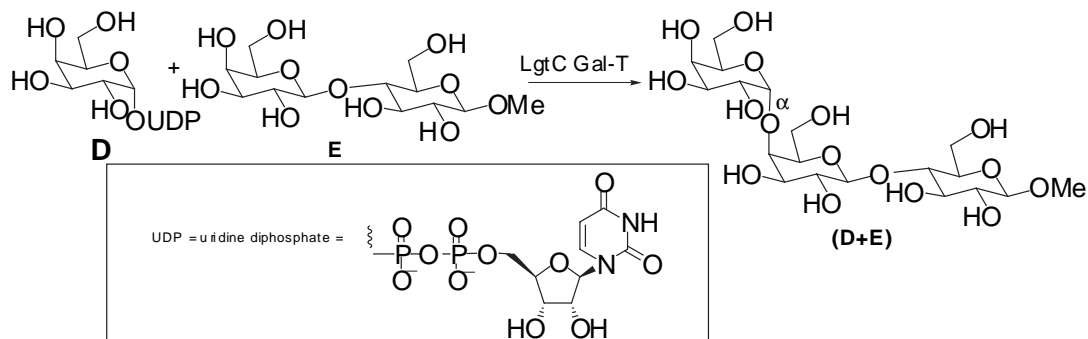
The galactosyltransferase enzyme from the LgtC gene of *Neisseria meningitidis*, LgtC Gal-T, has just been isolated and its X-ray crystal structure determined using **D** and the *substrate analogue* **F** bound to the active site. By examining the reaction that it catalyzes (**D** + **E**) and the representation of the 3D structure given opposite:

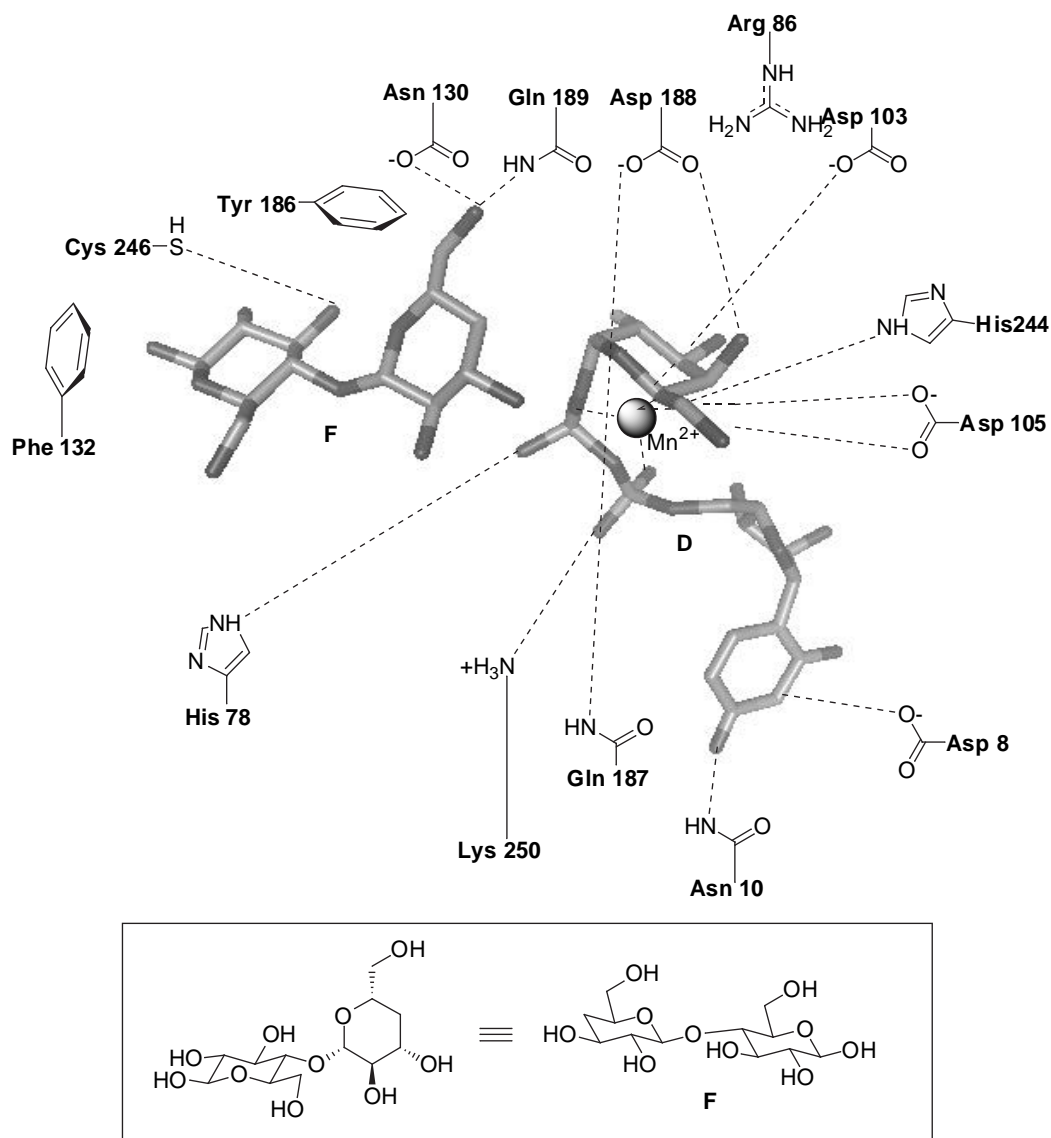
(a) Suggest a mechanism of action of LgtC Gal-T showing clearly the key active site residues that may be involved.

[8]

(b) Indicate how could you test your hypothesis.

[4]



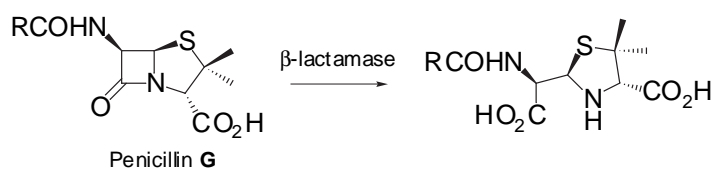


Notes:

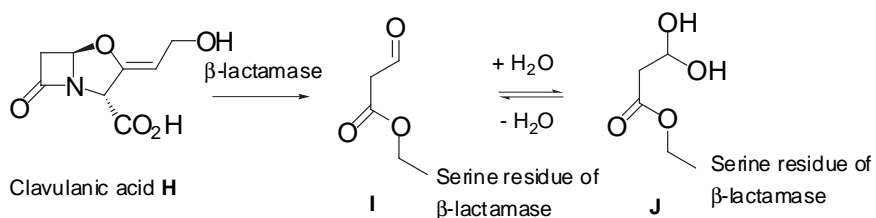
1. ----- indicates potential interaction within hydrogen bonding distance in the X-ray crystal structure
2. Protonation states of amino acid side chains have been assigned arbitrarily
3. Protein residues are represented schematically and do not necessarily represent their true positions in space but instead give an indication of their relative proximity to groups in the substrates

Part C

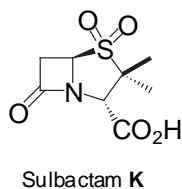
(a) Outline a mechanism for the serine β -lactamase enzyme catalysed hydrolysis of penicillin **G**. [4]



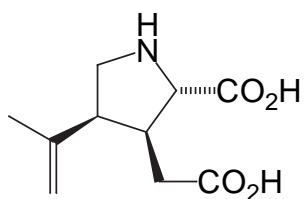
(b) Give a plausible mechanism for the production of **I** and **J**, which are formed during β -lactamase inhibition by clavulanic acid **H**. [10]



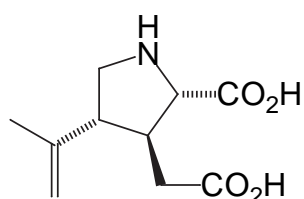
(c) Suggest how Sulbactam **K** inhibits β -lactamases. [6]



2.

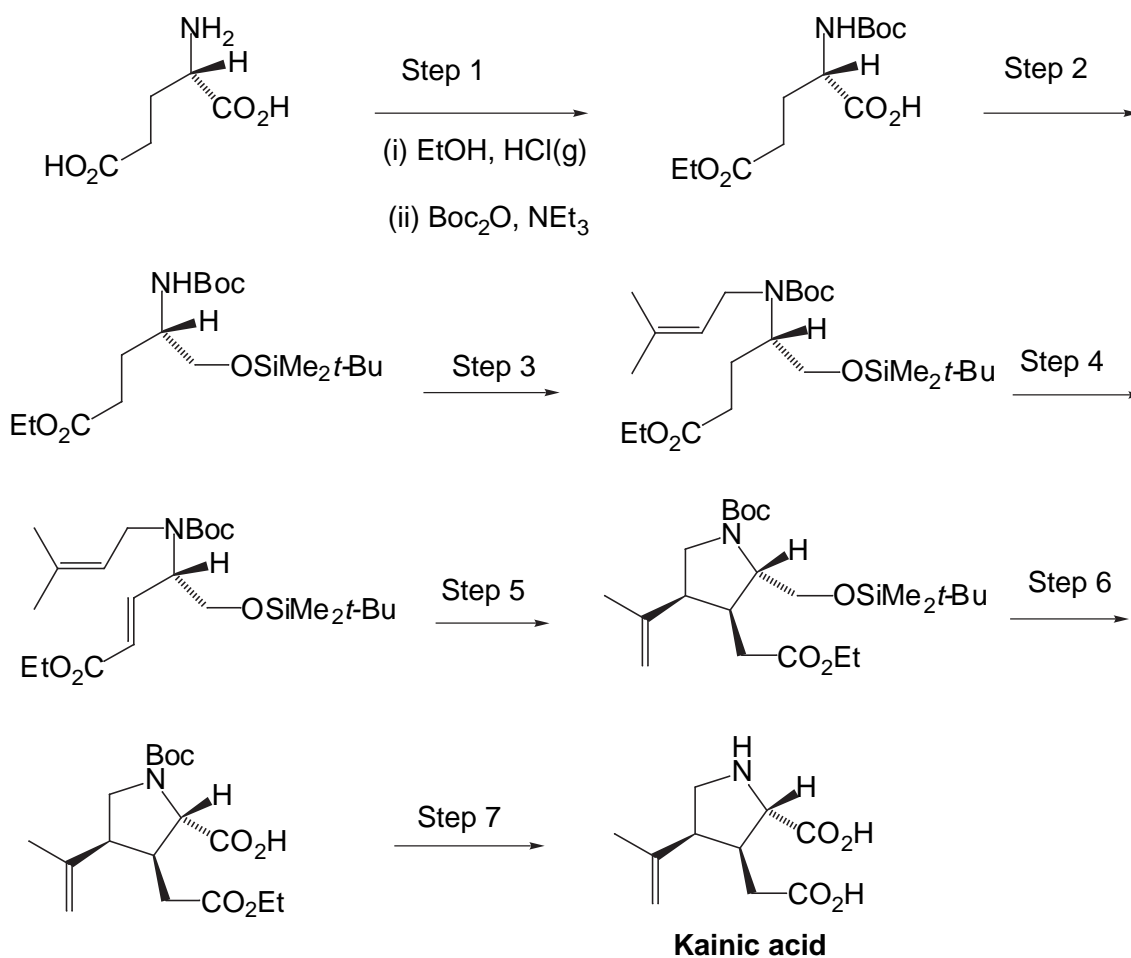


Kainic acid



Allo-kainic acid

Kainic acid, a powerful neurotoxin, occurs in a marine algae along with its biologically inactive isomer Allo-kainic acid. The enantioselective synthesis of Kainic acid was achieved from natural (*S*)-glutamic acid as follows:



Question continues

- (a) Explain the transformation achieved in Step 1. [3]
- (b) Suggest reagents to achieve Step 2 and explain the mechanisms. [5]
- (c) Suggest reagents to achieve Step 4 and explain the mechanisms. Why is it essential to reduce the carboxyl group in Step 2 before carrying out Step 4? [5]
- (d) Suggest conditions for achieving Step 5 and explain the stereochemical outcome. [6]
- (e) Suggest reagents to achieve the transformations in Step 6. Explain the mechanisms involved. [5]
- (f) Suggest reagents to achieve the transformations in Step 7. Explain the mechanisms involved. [4]
- (g) Given a sample of Kainic acid, explain how you could convert it into the more stable isomer, Allo-kainic acid. [5]

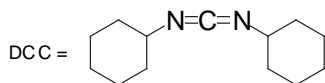
[You are not expected to comment upon Step 3]

3. Answer *all* parts of this question.

Part A

Outline the mechanism of coupling of protected amino and carboxylic acid components using DCC.

Discuss how this coupling can be made more efficient with one additive of your choice.

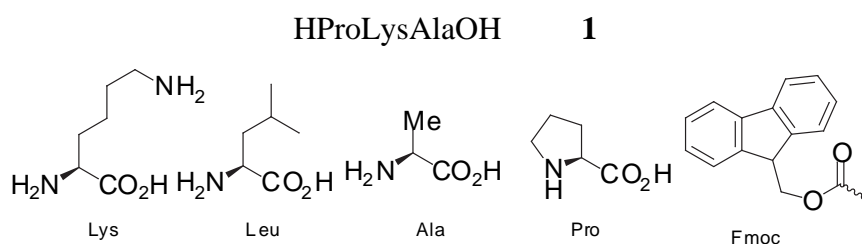


[10]

Part B

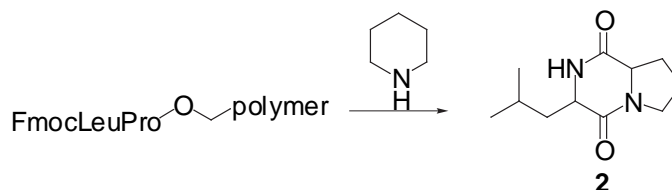
Provide a solution phase synthesis of the tripeptide **1** starting from unprotected component amino acids.

[12]



Part C

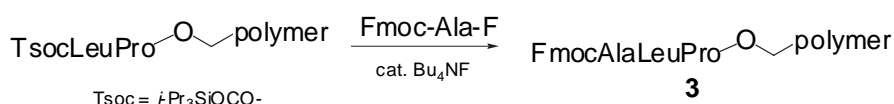
During a solid phase synthesis the following problem was found during deprotection of the second amino acid residue.



(a) Explain the chemistry involved in the formation of **2**.

[7]

The successful synthesis used the following chemistry to attach the third amino acid residue.



(b) Suggest a synthesis of Fmoc-Ala-F from alanine.

[7]

(c) Provide an explanation for the formation of **3**.

[7]

(d) Why is the formation of products such as **2** usually only a problem during *N*-deprotection of the second (rather than later) residues of a growing peptide?

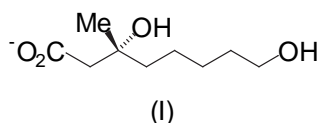
[7]

4. Answer **all** parts **A**, **B**, **C** and **D** of this question.

Part A

Explain how mevalonic acid (I)(MVA) is biosynthesised from Acetyl CoA.

[8]



Part B

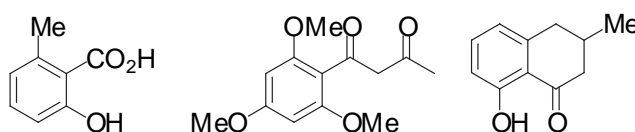
Explain what is understood by the acetate hypothesis. Include an explanation of how the structural diversity of polyketide natural products arises.

[8]

Part C

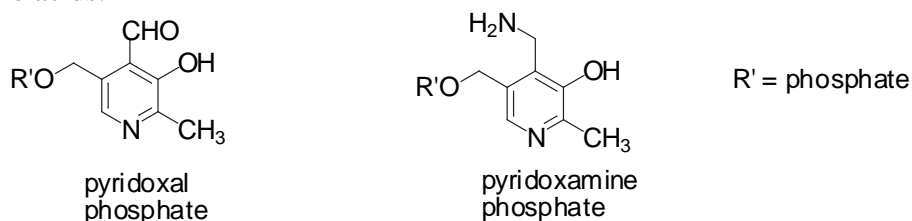
For *two* of the following polyketide natural products, illustrate which pairs of carbon atoms would be labelled as the result of a feeding experiment with [1,2-¹³C]labelled acetate. Use this information to propose a plausible forward biosynthetic pathway for each of the compounds that you choose.

[2 x 10]



Part D

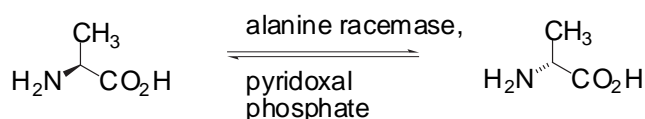
Pyridoxal phosphate and pyridoxamine phosphate are important cofactors for many enzyme-catalysed reactions of amino acids.



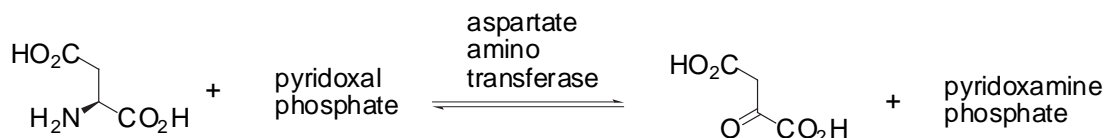
Give mechanistic explanations for *both* of the following:

[2 x 7]

(a) The enzyme alanine racemase and the cofactor pyridoxal phosphate cause racemisation of the amino acid alanine.



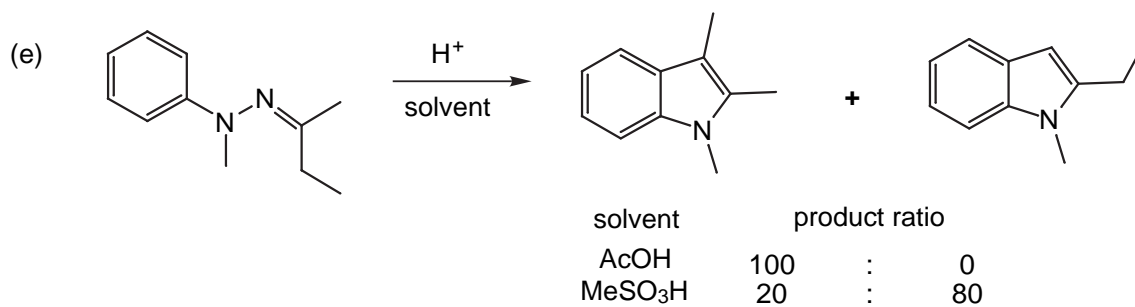
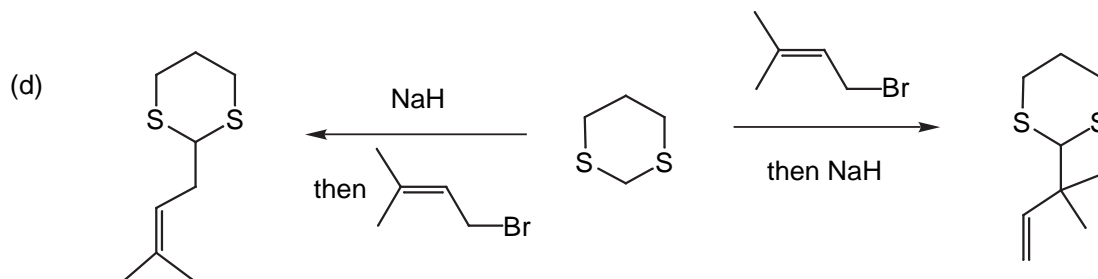
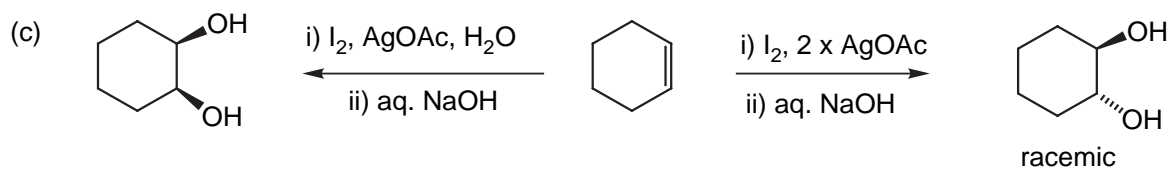
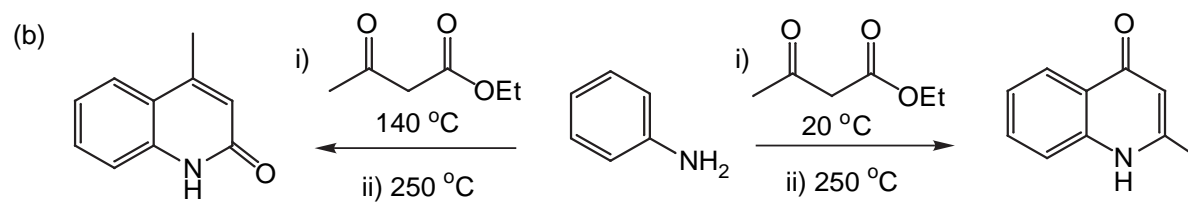
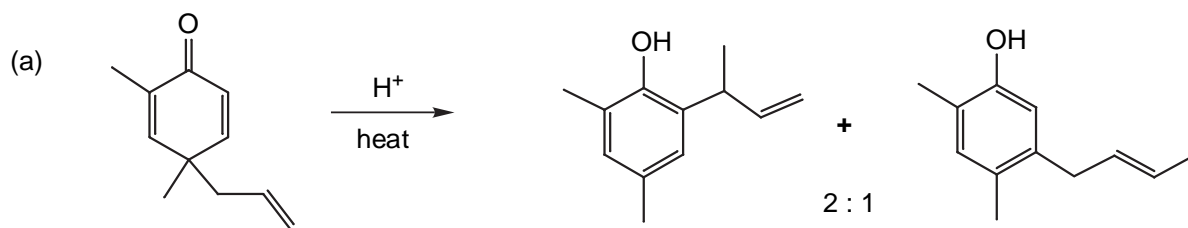
(b) The enzyme aspartate amino transferase and the cofactor pyridoxamine phosphate cause the following reaction:



5. Answer *both* parts **A** and **B** of this question.

Part A Explain the chemistry in *four* of the following

[4 x 7]



Part B

Explain the chemistry in *two* of the following.

[2 x 11]

