University of Canterbury

Mid Year Examination and Test Period 2006

Prescription Number(s):	CHEM 325 BCHM 302
Paper Title:	Biological Chemistry

Time Allowed:	TWO HOURS
Number of pages:	NINE

Answer **ALL** questions

Total marks = 120. Allow 1 minute per mark.

TURN OVER

1. (17 marks)

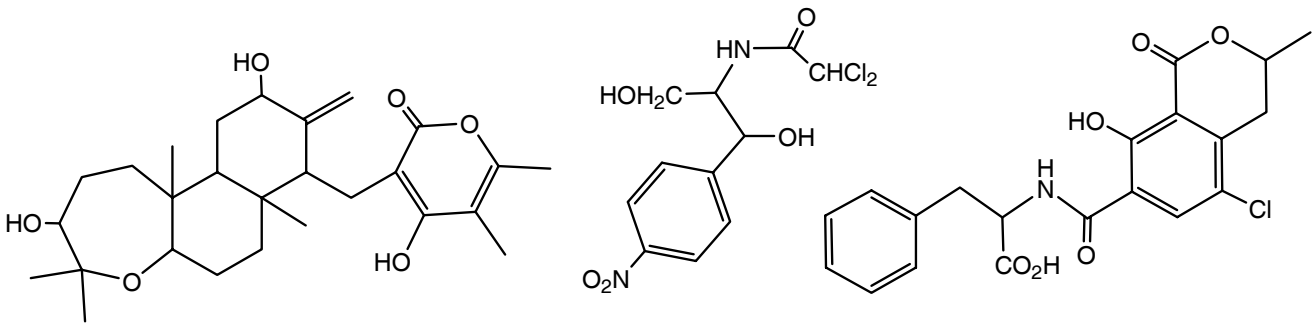
(a) What structural features do you consider to be important in recognising the origins of the following classes of natural product?

(i) isoprenoid,

(ii) polyketide,

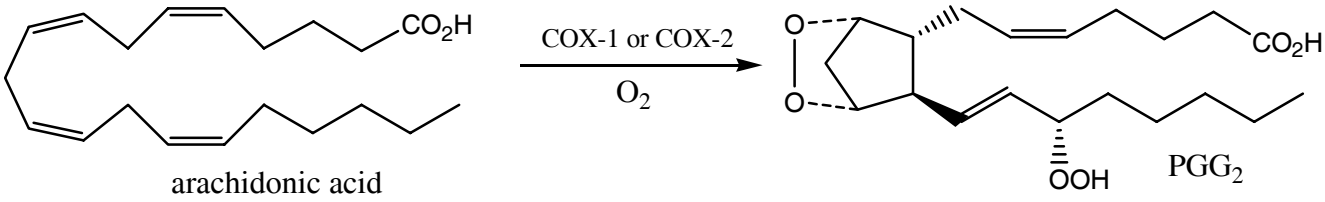
(iii) shikimate.

(b) What are the biosynthetic origins of **TWO** of the following compounds? **Note that some compounds could be of "mixed" biosynthetic origin.** For each compound indicate (delineate) the "building blocks" of each structure (*ie* the isoprene units, the polyketide chain, the starter unit, the repeat units, SAM, amino acid *etc*.) and any loss of O.



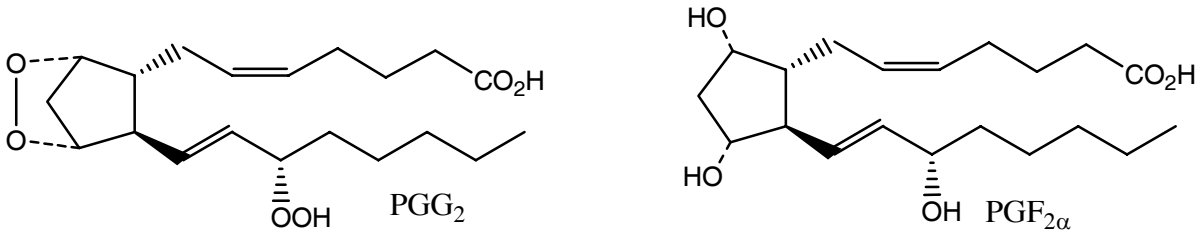
2. (13 marks)

(a) Draw the key steps in the cyclisation of arachidonic acid, by either of the cyclooxygenase enzymes COX-1 or COX-2, to form PGG_2.



arachidonic acid PGG_2

(b) Show how $PGF_{2\alpha}$ is formed from PGG_2.



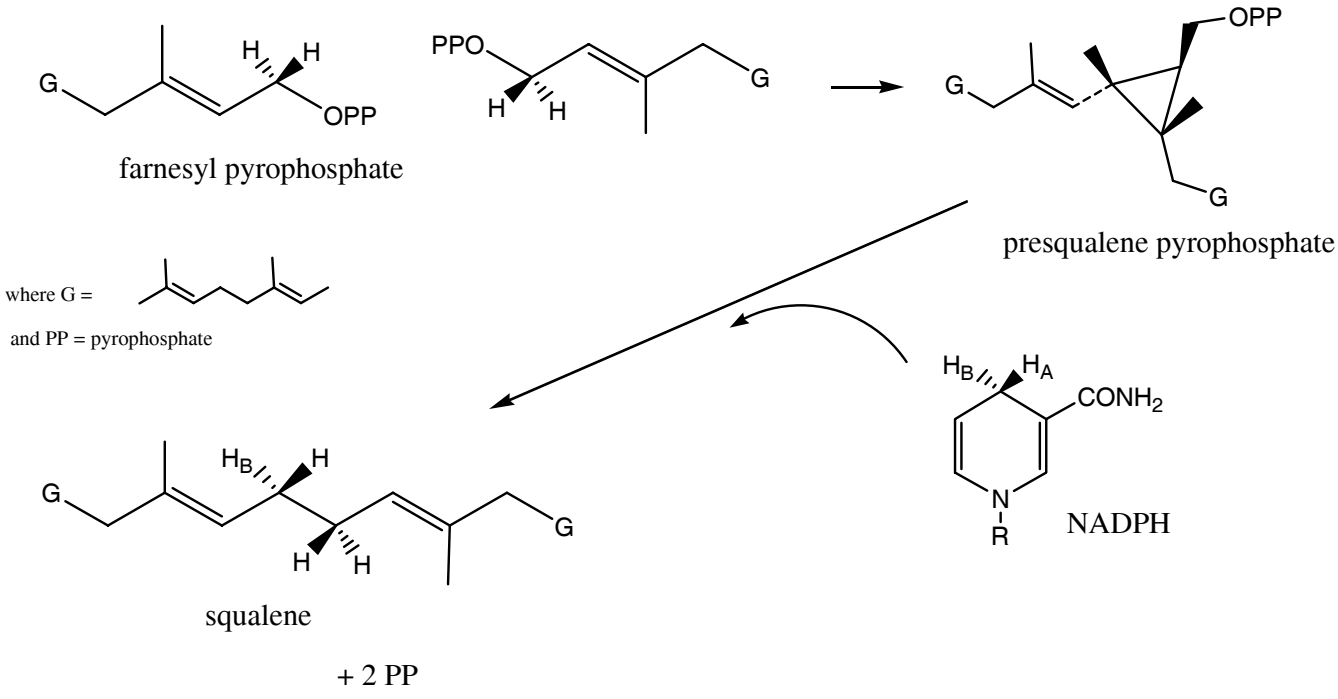
PGG_2 $PGF_{2\alpha}$

(c) If $^{18}O_2$ were used in the cyclooxygenase-catalysed step, which positions in $PGF_{2\alpha}$ would be labelled?

(d) What are the different roles ascribed to the COX-1 and COX-2 enzymes?

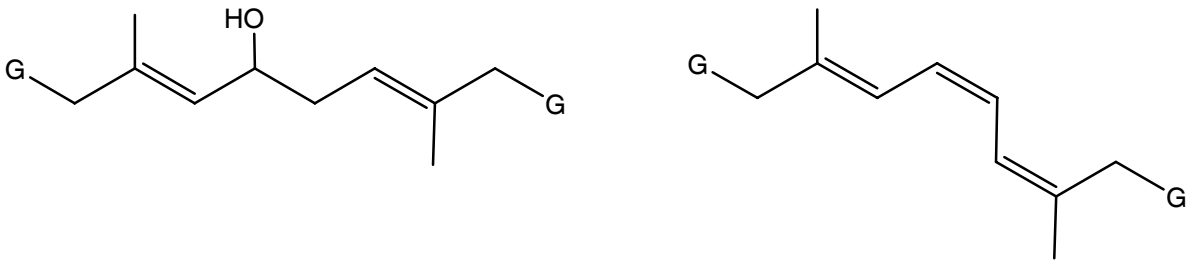
3. (15 marks)

Farnesyl pyrophosphate is converted in to squalene by squalene synthetase via presqualene pyrophosphate. An essential coenzyme for this reaction is NADPH.



(a) Show all of the steps in the conversion of farnesyl pyrophosphate into squalene.

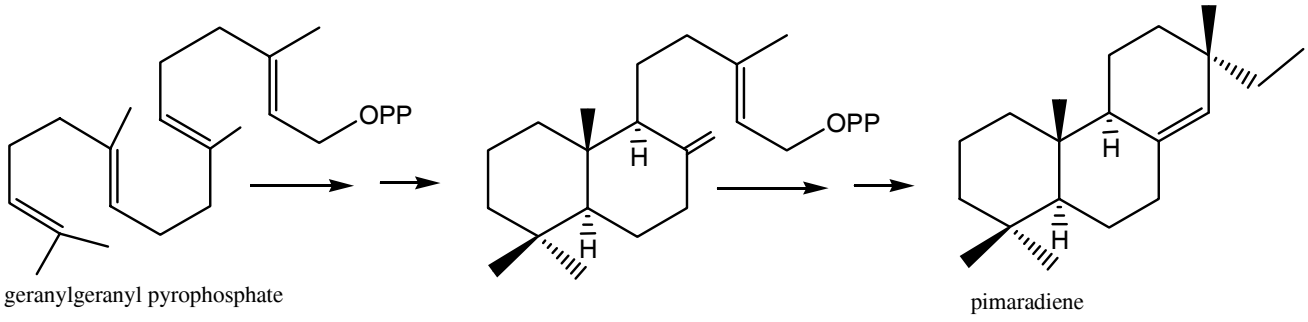
(b) In the absence of NADPH, the following two compounds are formed. Suggest a rational pathway for their formation.



4. (15 marks)

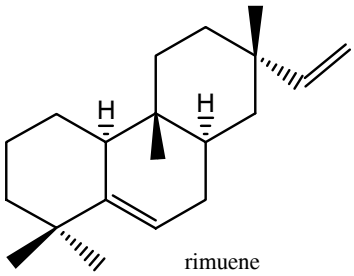
Answer **EITHER:**

Diterpenes such as pimaradiene are formed by polyolefin cyclisation from geranylgeranyl pyrophosphate.



geranylgeranyl pyrophosphate

pimaradiene



rimuene

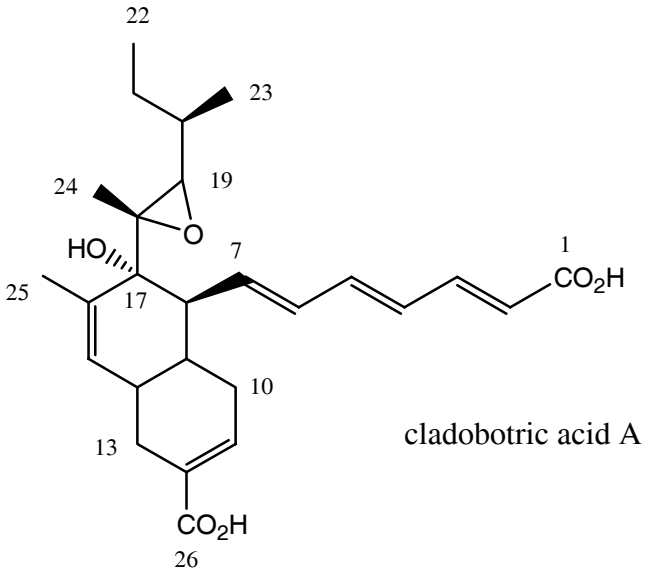
(a) What are the steps involved in the formation of pimaradiene?

(b) Account for the stereochemistry observed in pimaradiene.

(c) Co-occuring with pimaradiene is rimuene. Suggest a pathway that accounts for the structure and stereochemistry of rimuene.

OR:

The discovery of a new polyketide skeleton, cladobotric acid A, was announced earlier this year in the *Journal of Organic Chemistry*.



cladobotric acid A

(a) Suggest a folding pattern for the C22 polyketide precursor that would lead to cladobotric acid A.

(b) Biosynthetic experiments were carried out that confirmed the polyketide origin of cladobotric acid A.

(i) If 2-^{13}C-acetate was used in the biosynthetic experiments, which carbons in cladobotric acid A would be labelled?

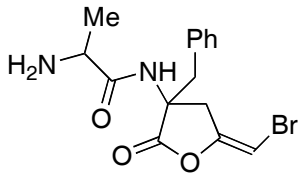
2-^{13}C-acetate = $^{13}CH_3-CO_2H$

Note: 2-^{13}C-acetate is converted into 2-^{13}C-malonate during biosynthesis.

(ii) Which carbons in cladobotric acid A are derived from SAM?

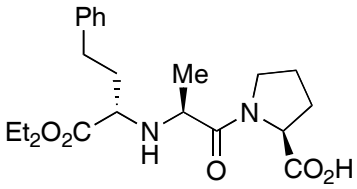
5. (30 marks)

For **two** of the three compounds below, propose a **detailed** mechanism of action against the specified biological target. Include a **brief** discussion on the medicinal importance of the biological targets in your chosen examples.

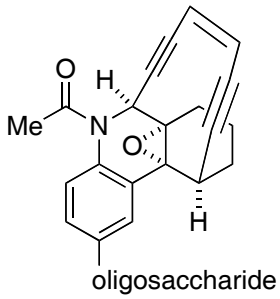


Biological Target

serine protease



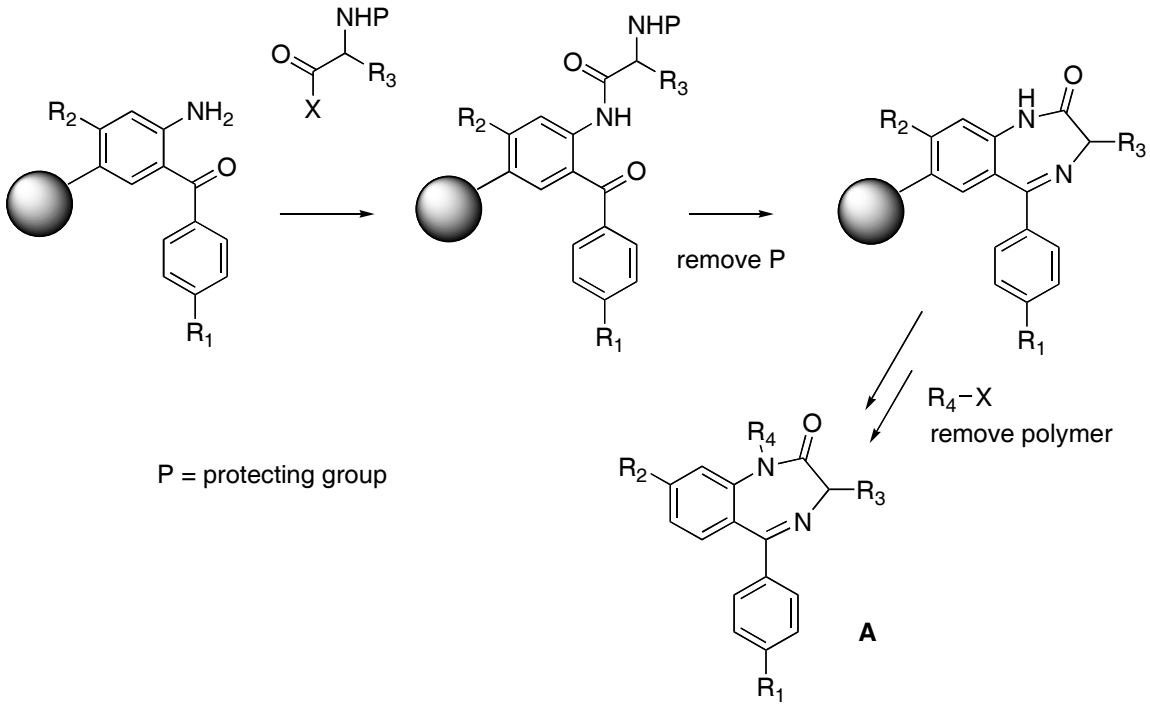
angiotensin-converting enzyme



DNA

6. (30 marks)

Compounds **A** are an important class of biologically active compound that can be prepared by solid phase synthesis as indicated below. There are four points of variability in structures **A** (R_1, R_2, R_3, and R_4) that can be used to generate a library of structures.



(a) Describe, in principle, how you would use the split synthesis method to construct a library of compounds **A**. Include discussion on molecular tagging where appropriate.

(b) Describe, in principle, how you would use your library of compounds to optimize the potency of this class of inhibitor against a biological target.

(c) Discuss the role of the protecting group (P) in the synthesis. Include discussion on what chemical properties it should possess and give an example of a suitable group.

END OF PAPER