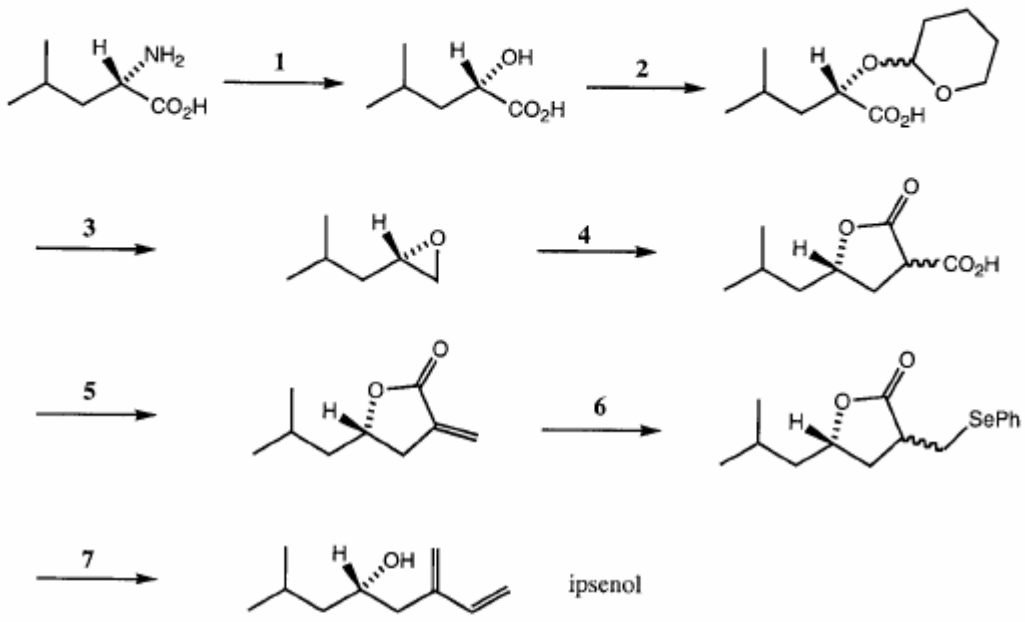
Synthesis

General Organic I 2002

3. Answer ***all*** parts **A-C** of this question which concerns a synthesis of ipsenol, the aggregation pheromone of the five spined engraver beetle.



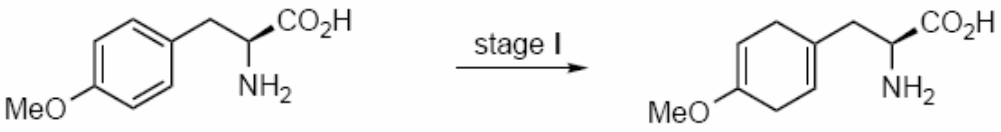
A. Suggest reagents with mechanisms for transformations **1**, **2**, **3**, **4**, **6** and **7**, some of which involve more than one step. **[6 x 2.5]**

B. The reagents for transformation **5** are CH_2O and Et_2NH: Suggest a mechanism. **[2.5]**

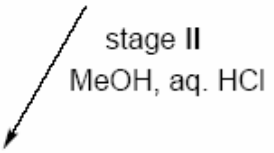
C. Suggest why the introduction of the PhSe group in transformation **6** was necessary. **[2.5]**

General Organic I 2001

4. Aeruginosin 298-A is a protease inhibitor isolated from blue-green algae. Part of a recent synthesis of Aeruginosin 298-A is outlined below.



A (single enantiomer)

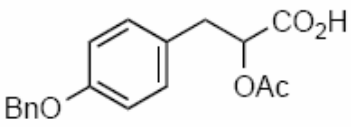


B **C**

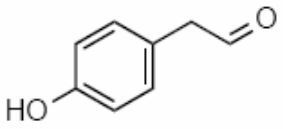
(a) Suggest reagents and mechanisms for stage **I**, and explain the regiochemistry observed. **[4]**

(b) Suggest mechanisms for the formation of **B** and **C** in stage **II**. **[10]**

(c) The structure of Aeruginosin 298-A includes a 4-hydroxyphenyllactic acid moiety, for which (*R*)-**D** was the starting material. Suggest reagents for the synthesis of racemic **D** from the phenol **E**. **[6]**



D



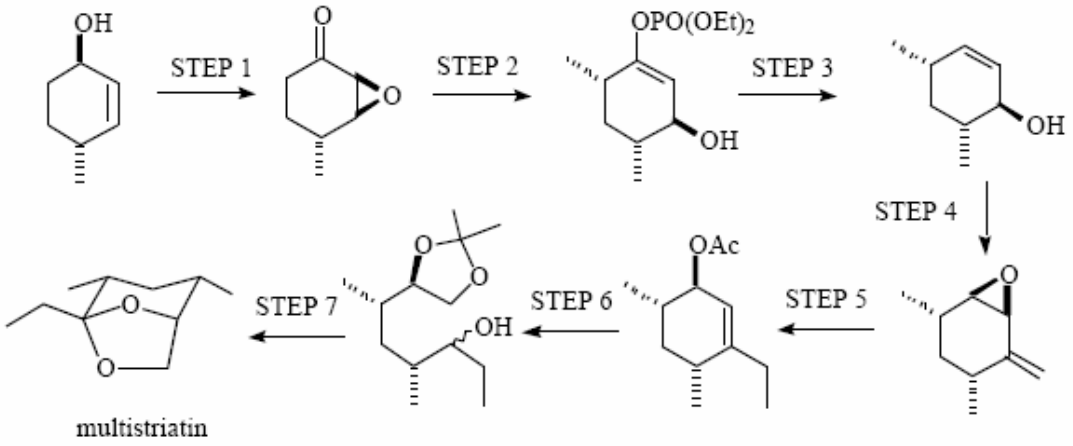
E

General Organic I 2000

5. Answer **all** parts of this question.

A synthesis of the insect pheromone multistriatin is shown:

Note you are NOT asked about STEP 3



(a) The reagents used to accomplish STEP 2 were:

(i) $(Me_2CH)_2NLi$ (ii) $(EtO)_2POCl$ (iii) Me_2CuLi

[4 marks]

Suggest a mechanism for this transformation and draw the structures of any intermediates.

(b) Suggest suitable reagents for carrying out **each** of the following, commenting on any points of stereoselectivity [more than one stage may be required for each step]:

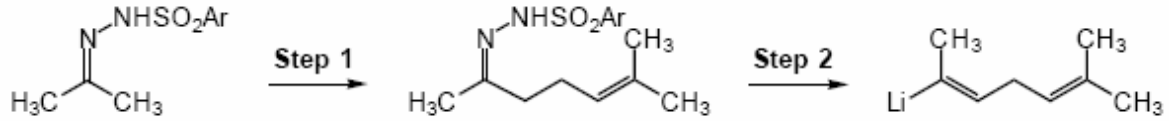
[16 marks]

(i) STEP 1
(ii) STEP 4
(iii) STEP 5
(iv) STEP 6
(v) STEP 7

General Organic II 2004

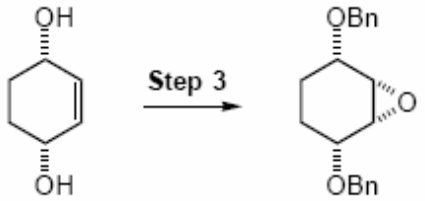
General Organic II 2002

6. Answer ***all*** parts of this question. Note that each synthetic transformation may require more than one step.



Ar = 2,4,6-triisopropylphenyl

A



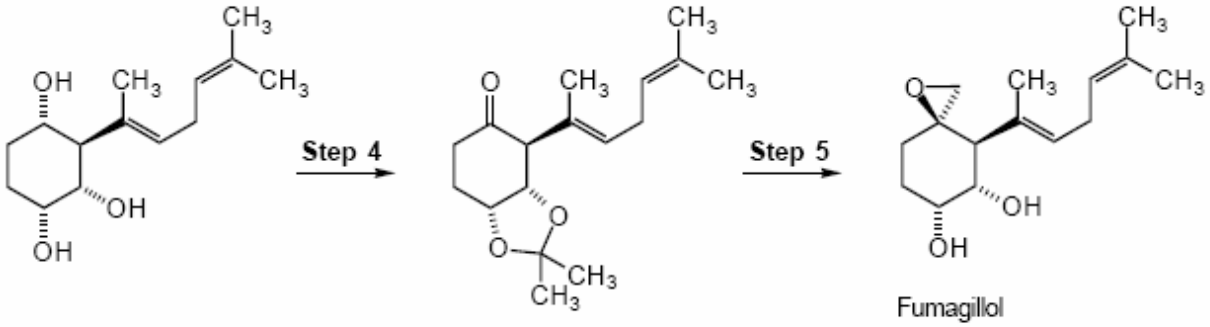
B

(a) Suggest reagents for Step 1. **[2]**

(b) Suggest reagents and give a mechanism for Steps 2 and 3 **[2 × 3]**

(c) Explain the stereoselectivity in Step 3. **[2]**

(d) Draw the product of the reaction between intermediates **A** and **B**.
Comment on the stereospecificity of this reaction. **[1]**



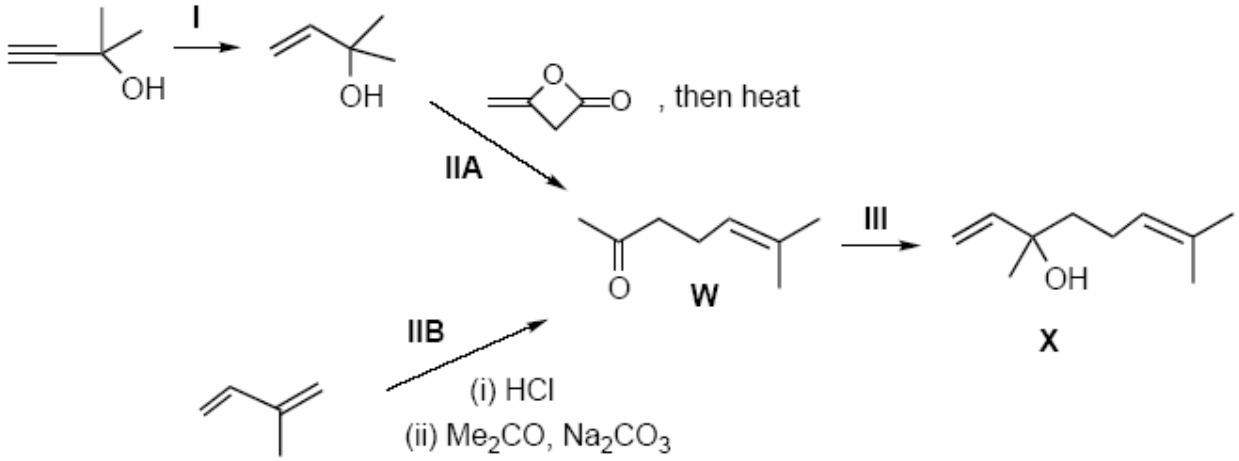
Fumagillol

(e) Suggest reagents, give mechanisms, and explain the selectivity achieved in Step 4. **[5]**

(f) Suggest reagents for Step 5, paying attention to the epoxide stereochemistry. **[4]**

General Organic II 2001

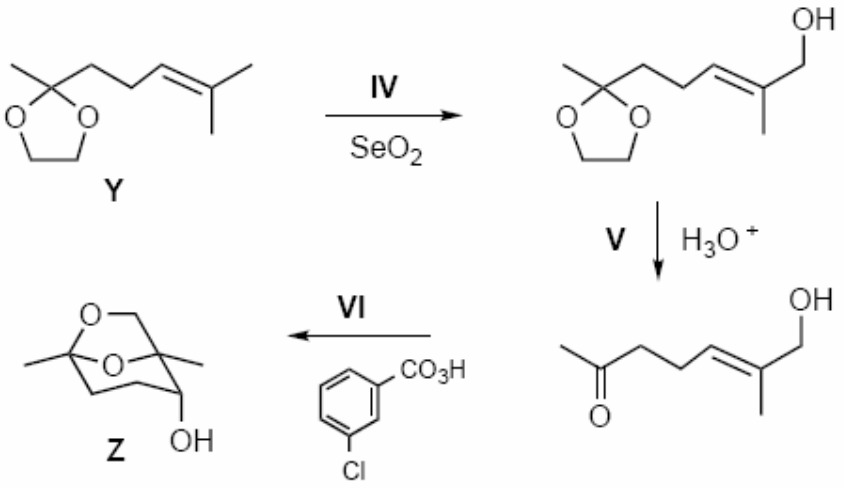
7. Two routes to the perfume ingredient linalool, **X**, are shown below. Both go *via* the intermediate **W**.



(a) Give reagents for stages **I** and **III**. **[2]**

(b) Suggest mechanisms for stages **IIA** and **IIB**. **[5 + 5]**

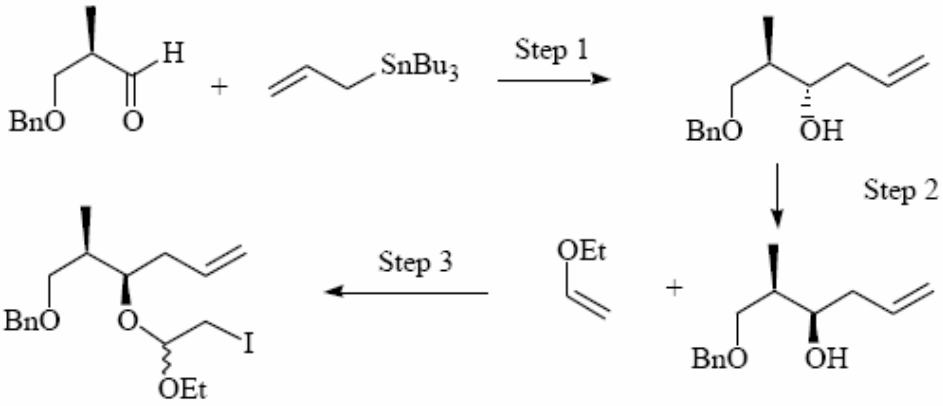
(c) Intermediate **W** can be converted into the ketal **Y** and then into compound **Z**. Suggest mechanisms for stages **IV** and **VI** in this process. (You are *not* required to comment on stage **V**). **[4 + 4]**



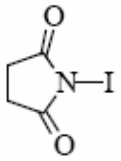
General Organic II 2001

7. Answer **BOTH** parts **A** and **B** of this question which concern the synthesis of the antimicrobial and antifungal macrolide Rhizoxin.

Part A



Reagents and conditions:
Step 1: $SnCl_4$, CH_2Cl_2, -90°C
Step 3: *N*-iodosuccinimide, CH_2Cl_2, -20°C

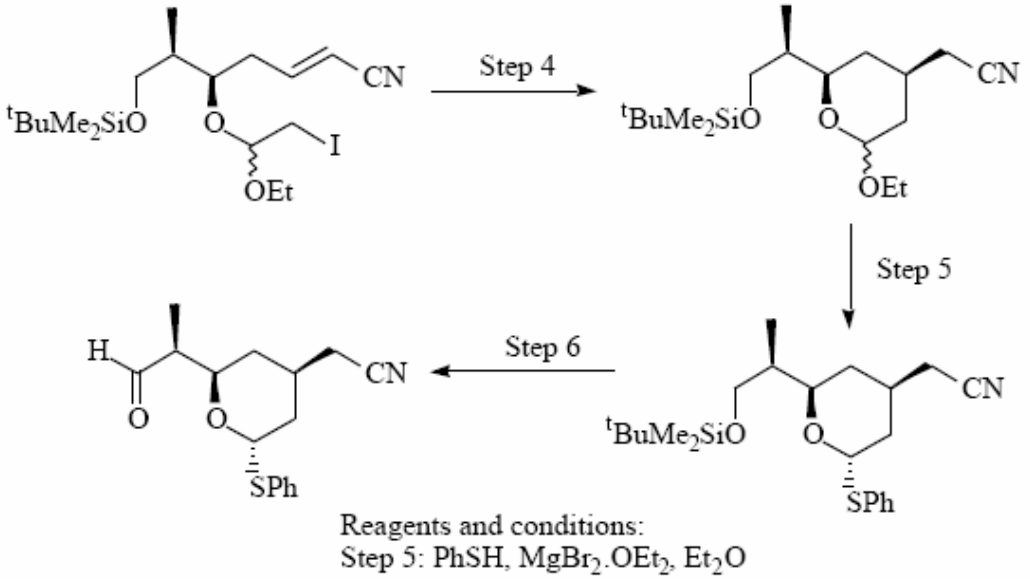
N-iodosuccinimide = 

(i) Give a mechanism for Step 1; explain the stereochemical outcome of this reaction. **[5 marks]**

(ii) Suggest how you would carry out Step 2. **[3 marks]**

(iii) Explain Step 3. **[3 marks]**

Part B



Reagents and conditions:
Step 5: PhSH, $MgBr_2.OEt_2$, Et_2O

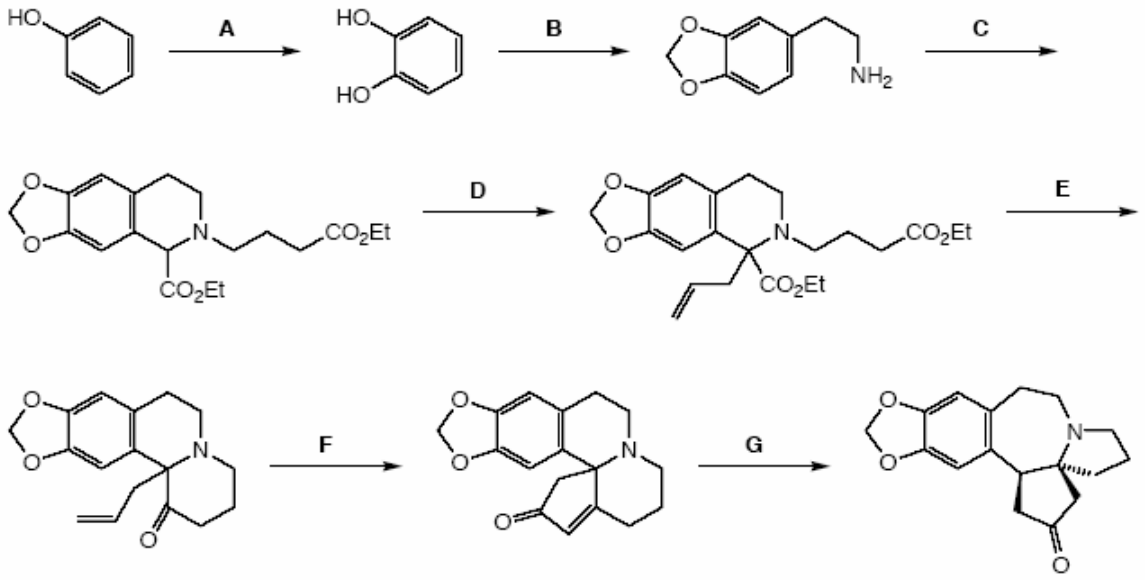
(i) Explain how you would carry out Step 4. **[2 marks]**

(ii) Give a mechanism for Step 5. **[3 marks]**

(iii) Suggest reagents for Step 6 (more than step may be necessary). **[4 marks]**

Advanced Organic 2004

6. Answer *all* parts of this question that concerns the synthesis of a key intermediate in a potential commercial synthesis of cephalotaxine, a Chinese drug in advanced clinical trials for the treatment of acute human leukaemia.



(a) Give plausible mechanisms for the reactions in transformations **A**, **D**, **E**, and **G** for which the reagents are:

A (i) $CHCl_3$, NaOH, H_2O; (ii) H_2O_2, NaOH, H_2O

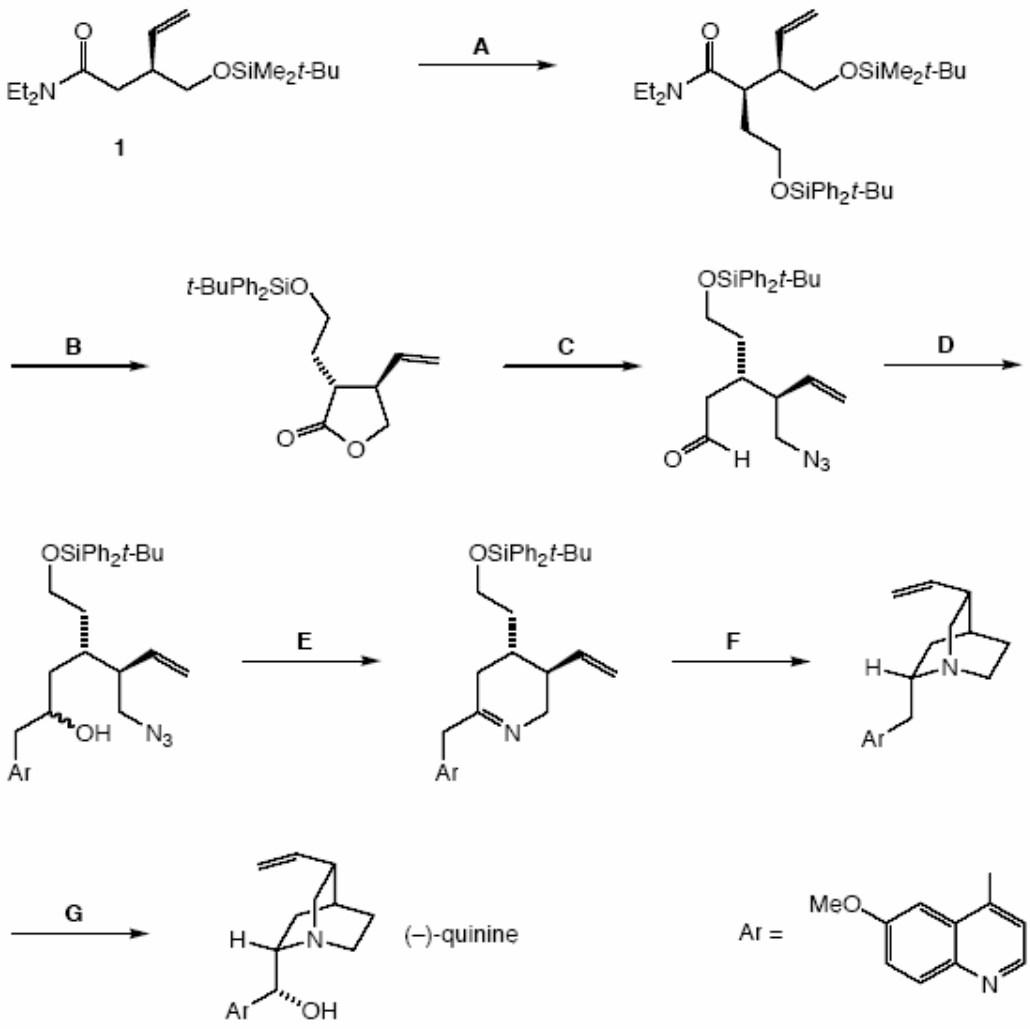
D (i) CH_2=$CHCH_2Br$, DMSO; (ii) KO*t*-Bu, DMSO/THF

E (i) KO*t*-Bu, toluene; (ii) $CaCl_2$, DMSO

G Zn, AcOH **[4 × 5]**

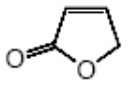
(b) Suggest suitable reagents and give mechanisms for *two* of the transformations **B**, **C**, and **F** (more than one step will be necessary in each case). **[2 × 7]**

10. Answer *all* parts of this question that concerns a recent total synthesis of (–)-quinine, a historically important antimalarial plant alkaloid and ingredient of tonic water.



Note: You are *not* required to comment on transformation **D**.

(a) Suggest a synthesis of amide **1** (as the racemate) from lactone **2**. **[6]**



2

(b) Explain the stereochemical outcome in reaction **A** for which the reagents are: $LiN(i\text{-}Pr)_2$, then $ICH_2CH_2OSiPh_2t\text{-}Bu$. **[4]**

(c) Give a mechanism for reaction **B** for which the reagents are: cat. H^+, EtOH. Comment on the selectivity in this step. **[3]**

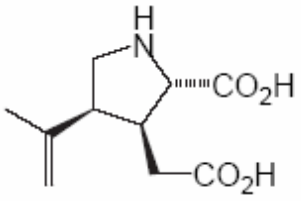
(d) Suggest suitable reagents for transformation **C** (more than one step will be necessary). **[8]**

(e) The reagents for transformation **E** are: (i) DMSO, $(COCl)_2$ then Et_3N; (ii) Ph_3P, heat. Give plausible mechanisms for these reactions. **[5]**

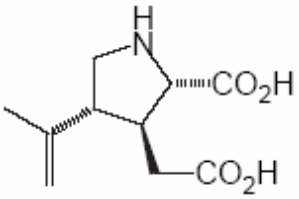
(f) The reagents for transformation **F** are: (i) $NaBH_4$; (ii) HF; (iii) CH_3SO_2Cl, heat. Explain the stereoselectivity in step (i) of this sequence and give mechanisms for steps (ii) and (iii). **[5]**

(g) The oxidation reaction **G** was achieved by adding the bicyclic amine to a mixture of NaH and DMSO and then bubbling O_2 through the solution. Suggest a reasonable mechanism for this process. You are ***not*** required to comment on the stereoselectivity in this step. **[3]**

Advanced Organic 2003

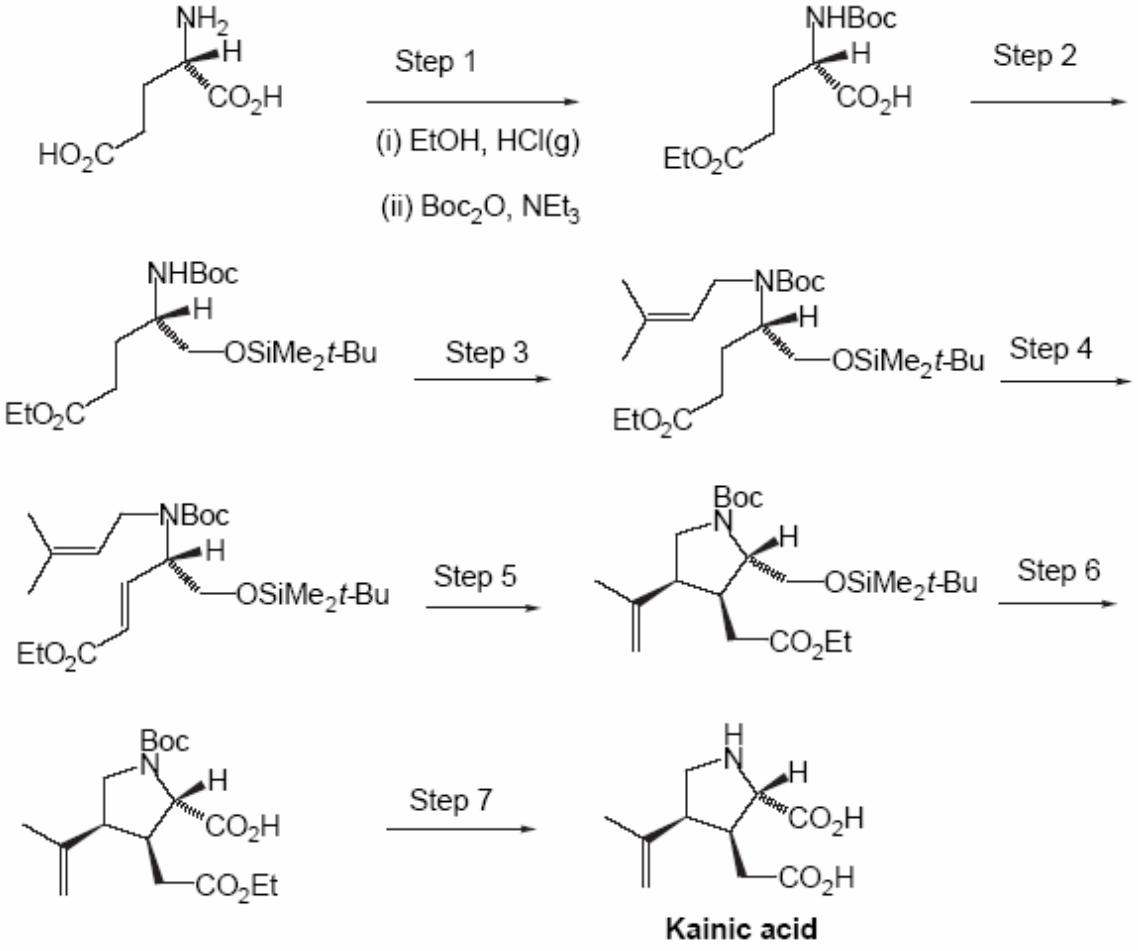


Kainic acid



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:



Kainic acid

(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]**

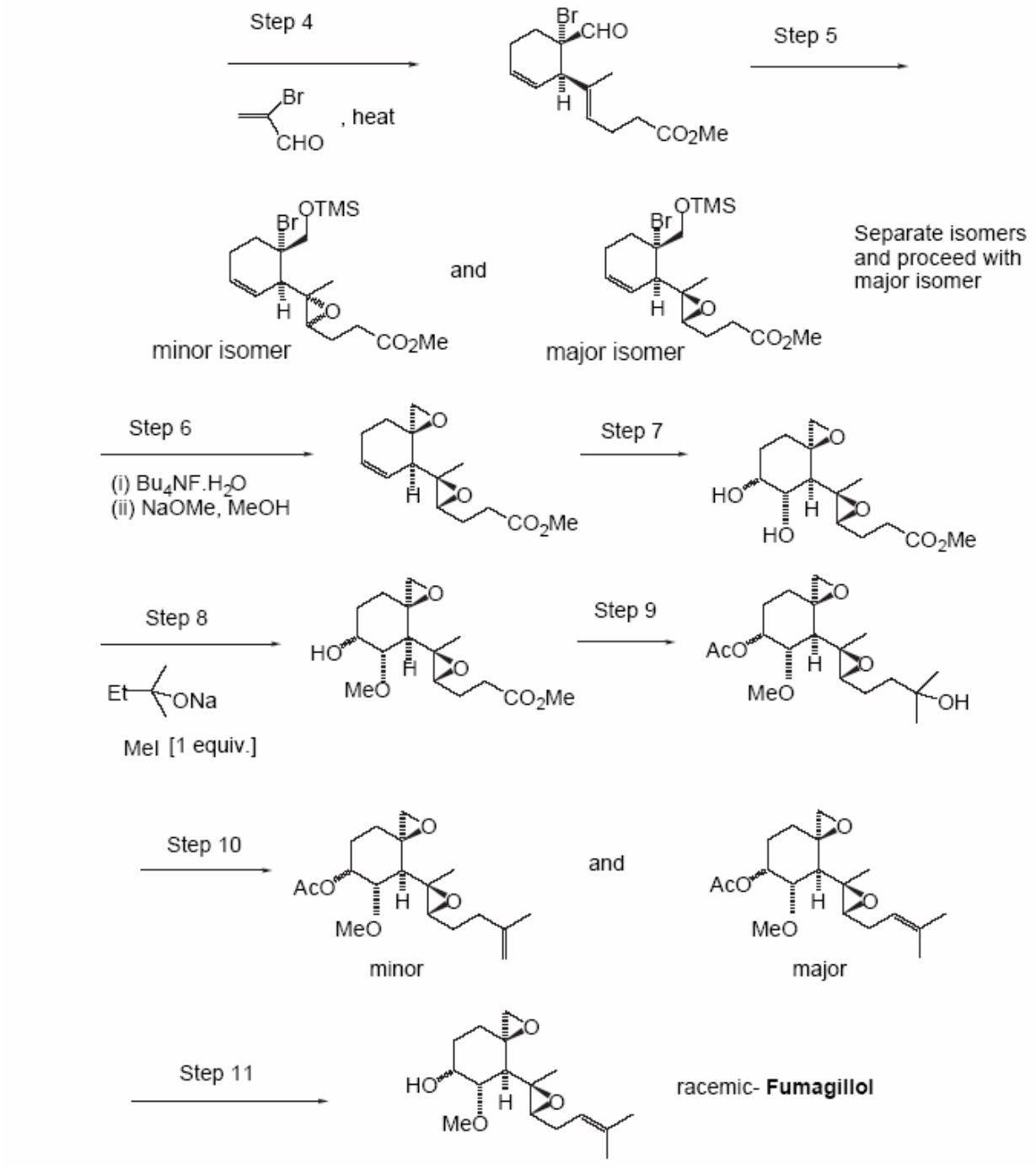
(d) Suggest conditions for achieving Step 5 and explain the stereochemical outcome. **[6]**

(e) Suggest reagents to achieve the transformations in Step 6. Explain the mechanisms involved. **[5]**

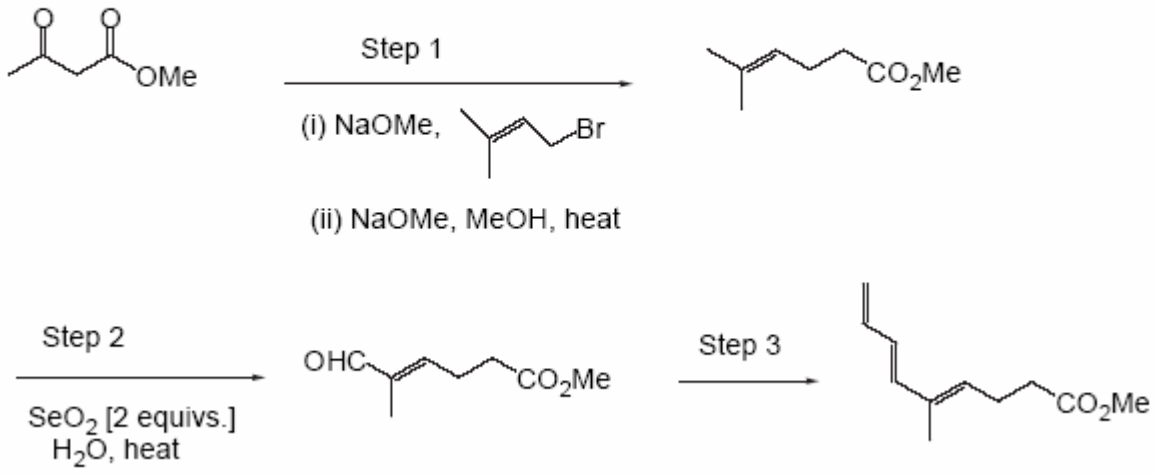
(f) Suggest reagents to achieve the transformations in Step 7. Explain the mechanisms involved. **[4]**

(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]


Step 4
Br
CHO
, heat
Br
CHO
Step 5
Br
CHO
H
CO2Me
OTMS
Br
H
O
CO2Me
minor isomer
and
OTMS
Br
H
O
CO2Me
major isomer
Separate isomers and proceed with major isomer
Step 6
(i) Bu4NF.H2O
(ii) NaOMe, MeOH
O
H
O
CO2Me
Step 7
HO
O
H
HO
O
CO2Me
Step 8
Et
ONa
MeI [1 equiv.]
HO
O
H
MeO
O
CO2Me
Step 9
AcO
O
H
MeO
O
OH
Step 10
AcO
O
H
MeO
O
minor
and
AcO
O
H
MeO
O
major
Step 11
HO
O
H
MeO
O
racemic- **Fumagillol**

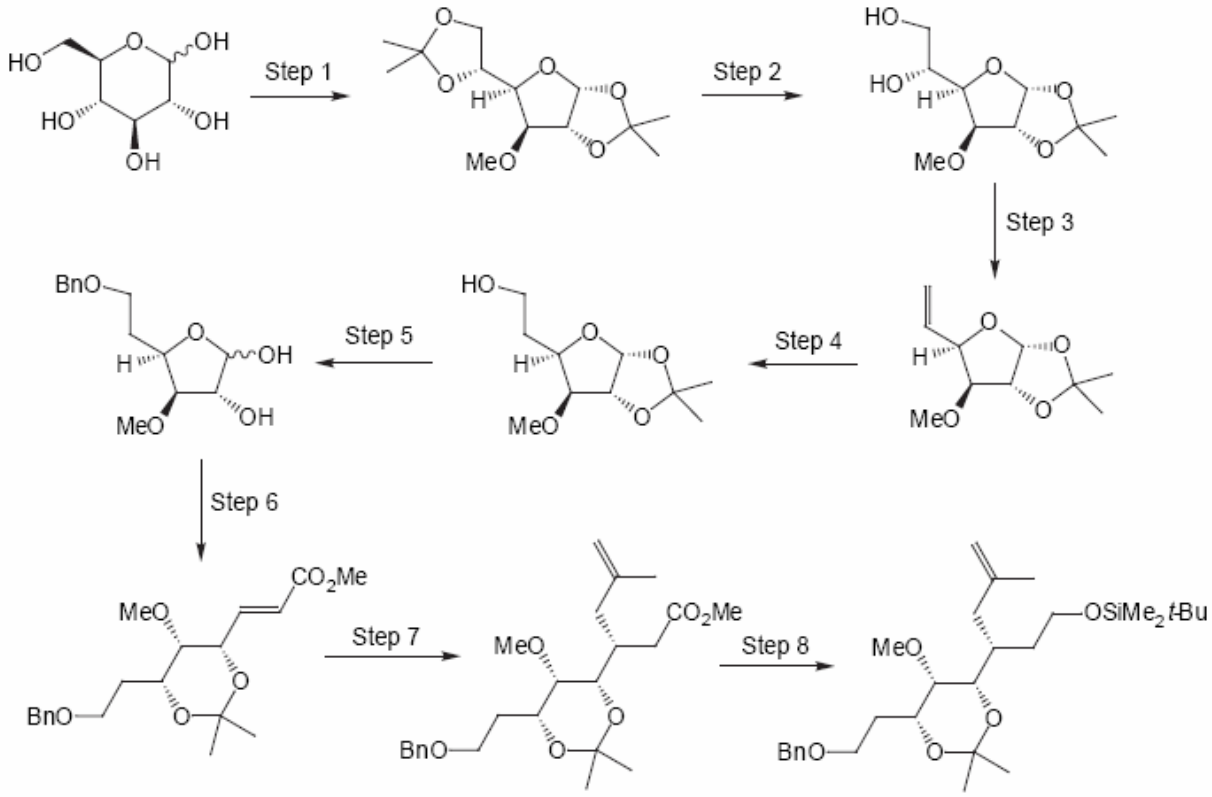
2. The synthesis of racemic-Fumagillol, the alcohol from which the antibiotic Fumagillin is derived, is shown below:



Advanced Organic 2002

3. Answer ***all*** parts of this question.

Answer the following questions concerning part of the total synthesis of the macrolide antibiotic carbomycin B. Each step may require more than one synthetic transformation.



Note: You are **not** required to comment on Step 2

(a) The reagents for Step 1 were (i) Me_2CO / H^+; then (ii) NaH, MeI. Give mechanisms for and explain the selectivity of these transformations. **[5]**

(b) Suggest reagents for Step 3. **[2]**

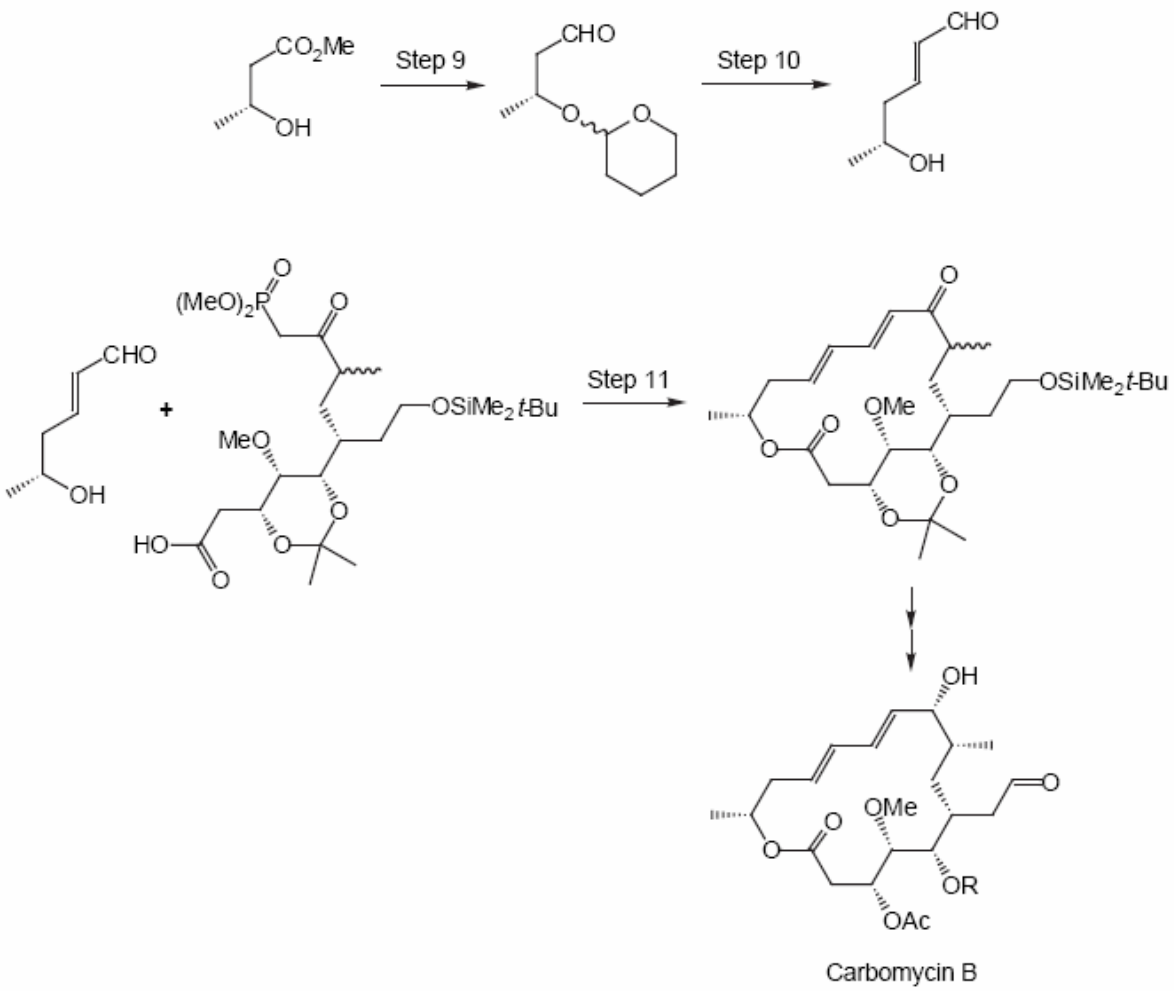
(c) Suggest reagents and give a mechanism for Step 4. Explain the regioselectivity of this reaction. **[4]**

(d) Suggest reagents for, and explain the chemistry involved in Step 5. **[4]**

(e) Suggest reagents for, and explain the chemistry involved in Step 6. Comment on the stereoselectivity of this transformation. **[6]**

(f) Suggest a reagent and give mechanisms for Step 7. You are *not* required to comment on the stereoselectivity of this step. **[2]**

(g) Suggest reagents for Step 8. **[2]**



Carbomycin B

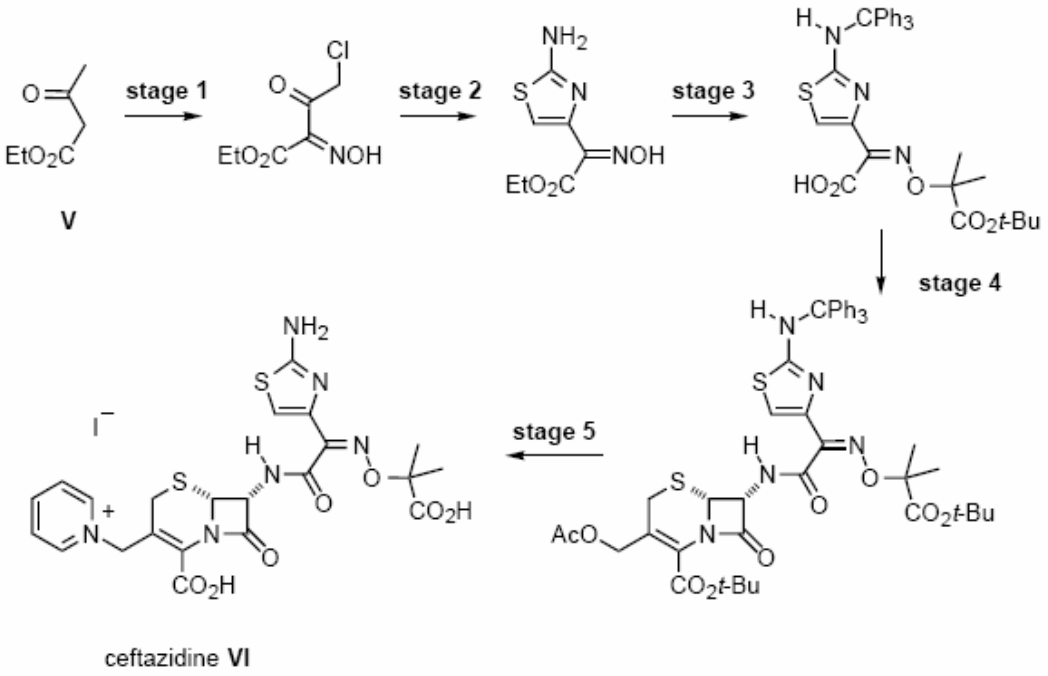
Note: you are **not** required to comment on Step 10

(h) Suggest reagents for Step 9. **[3]**

(i) Suggest reagents and give mechanisms for Step 11. **[6]**

Advanced Organic 2001

B) A synthesis of the antibiotic ceftazidine **VI** from ethyl acetoacetate **V** is outlined below (each stage may involve more than one step).



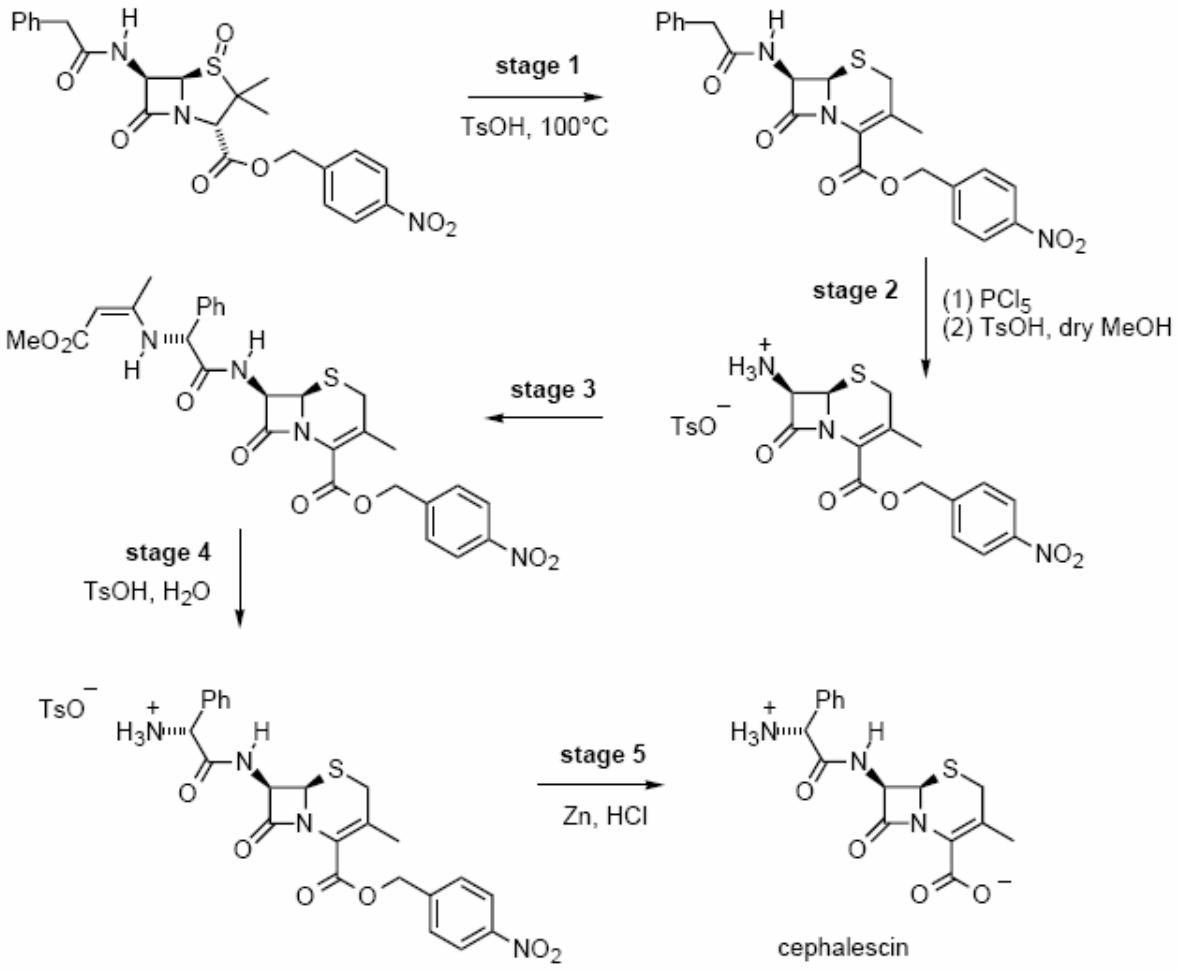
[Note. You are not required to comment on stage 4.]

(a) Suggest reagents and mechanisms for stages **1** and **2**. **[5+4]**

(b) Give reagents for stages **3** and **5**. **[4+4]**

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

A) The following scheme shows part of the commercial synthesis of the antibiotic cephalescin.



[Note. You are not required to comment on stage 3.]

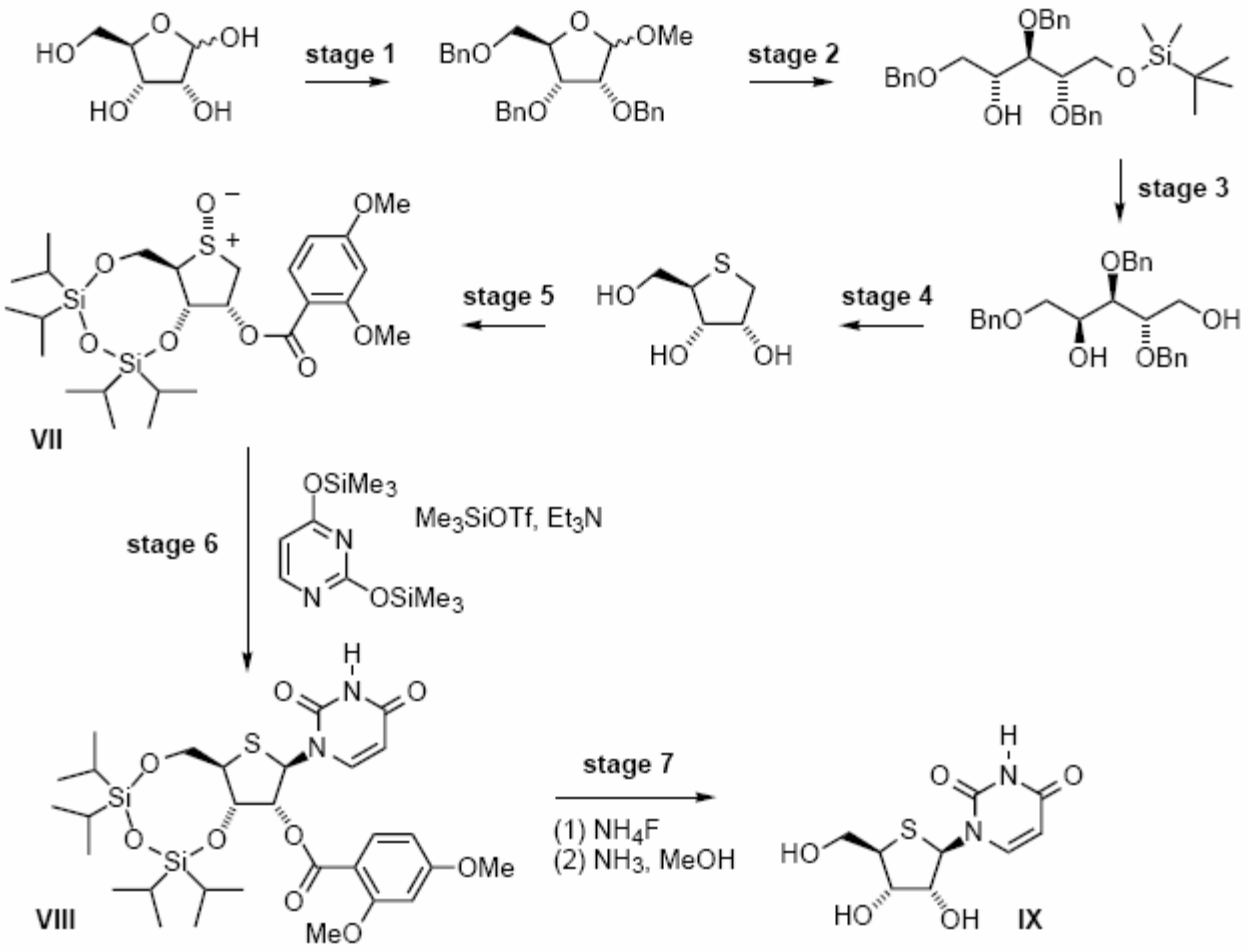
(a) Propose a mechanism for stage **1**, and suggest an experiment to test your proposal. **[3+3]**

(b) Suggest mechanisms for stage **2**, and state the other products formed. **[4]**

(c) Give mechanisms for stages **4** and **5**. **[3+3]**

9. Thioribonucleosides are important potential anticancer and antiviral agents. A range of these compounds can be made stereoselectively from key intermediates via reaction with suitable derivatives of nucleic acid bases.

A synthesis of thioribonucleoside **IX** from ribose is shown below. (More than one step may be required for each stage.)



(a) Suggest reagents for stage **1**. **[2]**

(b) Suggest reagents for stage **2**. **[3]**

(c) Suggest reagents and mechanisms for stage **3**. **[6]**

(d) The reagents for stage **4** were:

(i) excess $MeSO_2Cl$, pyridine;

(ii) Na_2S;

(iii) BCl_3, –90°C.

Explain the chemistry of this stage. **[6]**

(e) The reagents for stage **5** were:

(i) $ClSi(i\text{-}Pr)_2OSi(i\text{-}Pr)_2Cl$, pyridine;

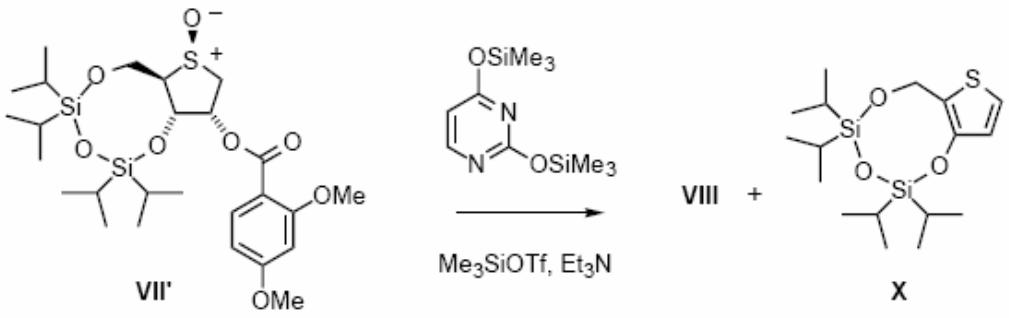
(ii) 2,4-dimethoxybenzoyl chloride, pyridine;

(iii) O_3, –78°C.

Explain the chemistry of this stage. **[6]**

(f) Give mechanisms for stage **7**. **[4]**

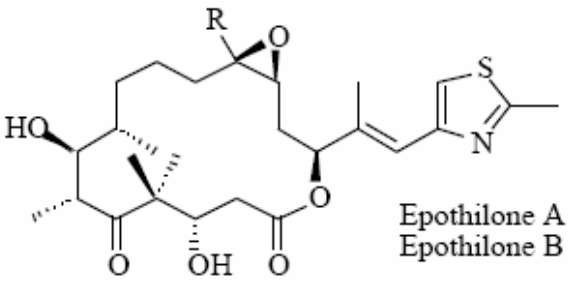
(g) Suggest a mechanism for stage **6**. Your mechanism should explain the stereoselectivity shown in this reaction, and your answer should include an explanation for the following observation:
When the epimeric sulfoxide **VII'** was subject to the reagents for stage **6**, a mixture of the required product **VIII** and a thiophene by-product **X** was obtained.
No **X** was isolated from the corresponding reaction of **VII**. **[6]**



Advanced Organic 2000

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

The potent anti-tumour agents Epothilones A and B were recently isolated from the myxobacteria *Sorangium cellulosum*. Answer the following questions, which concern approaches to the total synthesis of these natural products.



Epothilone A R= H
Epothilone B R= Me

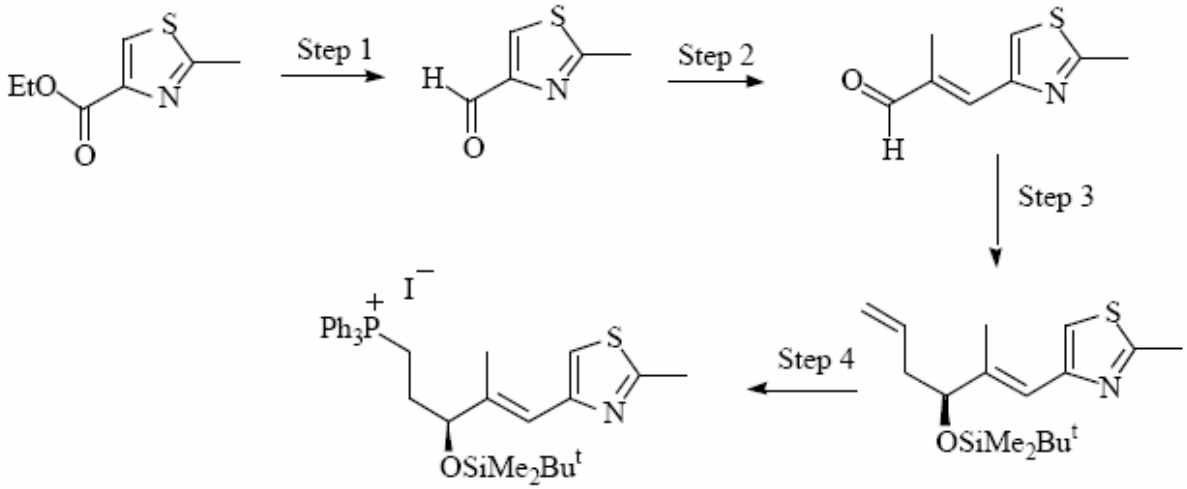
Part A

(a) Suggest a reagent for Step 1. **[2]**

(b) Suggest reagents and give mechanisms for Step 3. **[3]**

Explain how this reaction could be performed in an asymmetric manner. **[2]**

(c) Suggest reagents for Step 4 (more than 1 step is required). **[5]**



Part B

(a) Give a mechanism for Step 1. **[2]**

Explain the stereochemical outcome of this reaction sequence. **[3]**

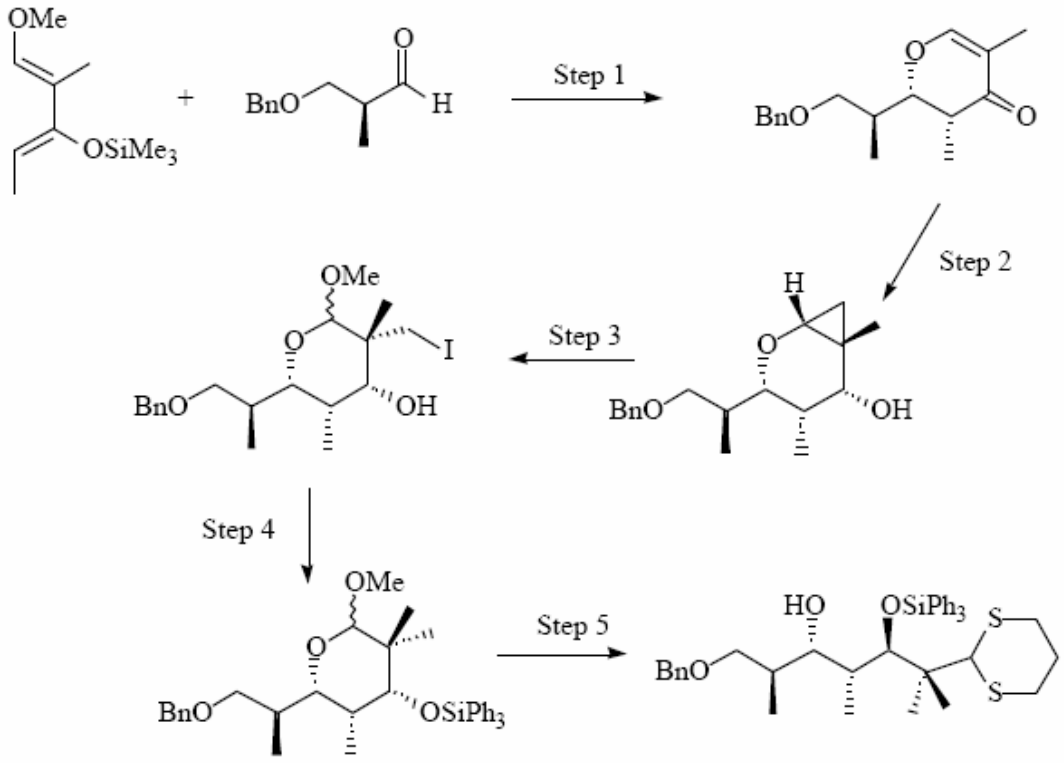
(b) Suggest reagents and give mechanisms for Step 2 (more than 1 step is required). **[5]**

Comment on the stereochemical outcome of these reactions **[3]**

(c) Give a mechanism for Step 3. **[3]**

(d) Suggest reagents for Step 4 (more than 1 step is required). **[3]**

(e) Give a mechanism for Step 5. **[3]**



Reagents and conditions:

Step 1: $TiCl_4$, -78°C then acid, RT

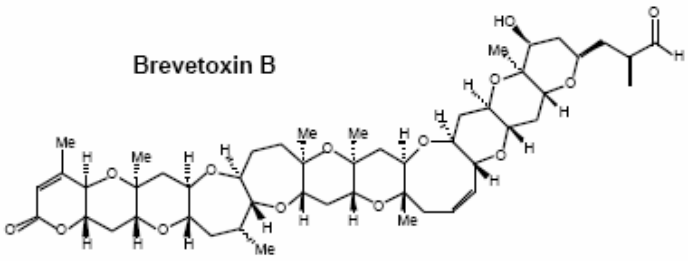
Step 3: *N*-iodosuccinimide, MeOH, RT

Step 5: 1,3-propanedithiol, $TiCl_4$, CH_2Cl_2, -78°C to -40°C

12. Answer *both* Parts A *and* B of this question

Brevetoxin B is a marine neurotoxin associated with the so-called 'red tide' catastrophes which are periodically responsible for the killing of massive amounts of marine life. Answer the following questions which concern synthetic approaches to fragments of the polyether ring systems of Brevetoxin B.

Brevetoxin B



Part A

(a) Give a mechanism for Step 1. **[3]**

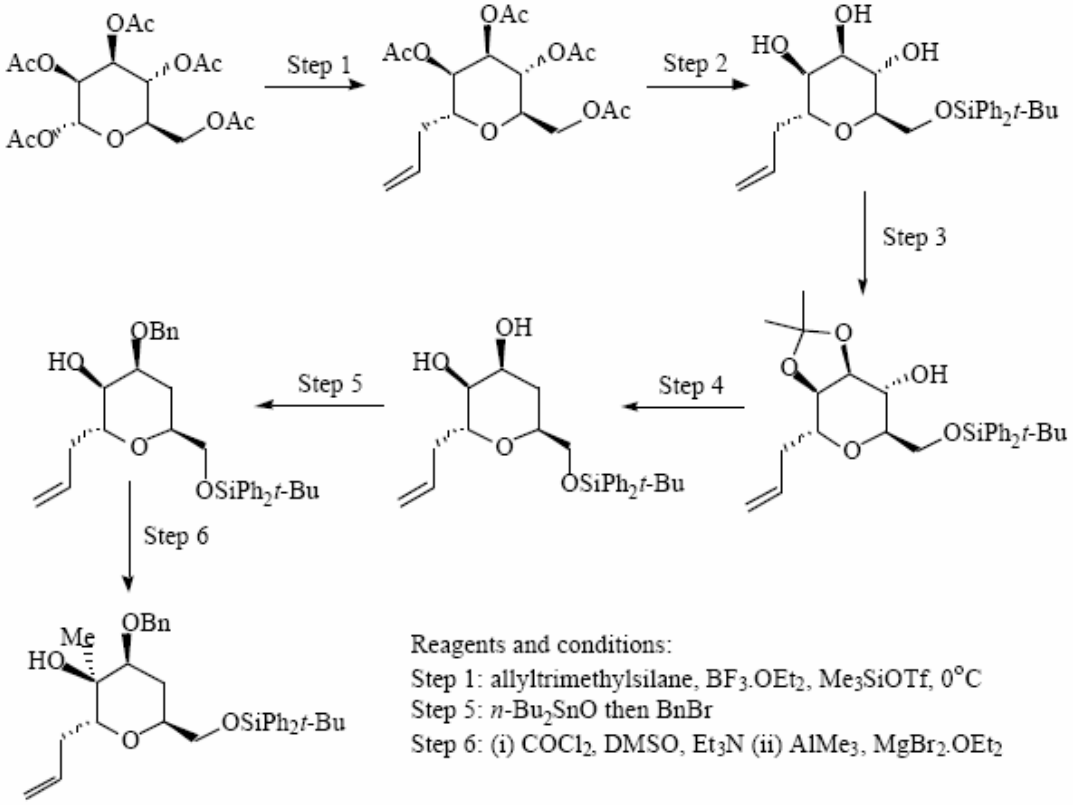
(b) Suggest reagents for Step 2 (more than one step is necessary). Comment on the choice of silyl protecting group. **[3]**

(c) Suggest reagents and give a mechanism for Step 3. Explain the regioselectivity of this reaction. **[3]**

(d) Suggest reagents for, and explain the chemistry involved in Step 4. **[4]**

(e) Explain Step 5 as fully as possible. **[3]**

(f) Give mechanisms for, and explain Step 6. **[3]**



Reagents and conditions:
Step 1: allyltrimethylsilane, $BF_3.OEt_2$, Me_3SiOTf, 0°C
Step 5: n-Bu_2SnO then BnBr
Step 6: (i) $COCl_2$, DMSO, Et_3N (ii) $AlMe_3$, $MgBr_2.OEt_2$

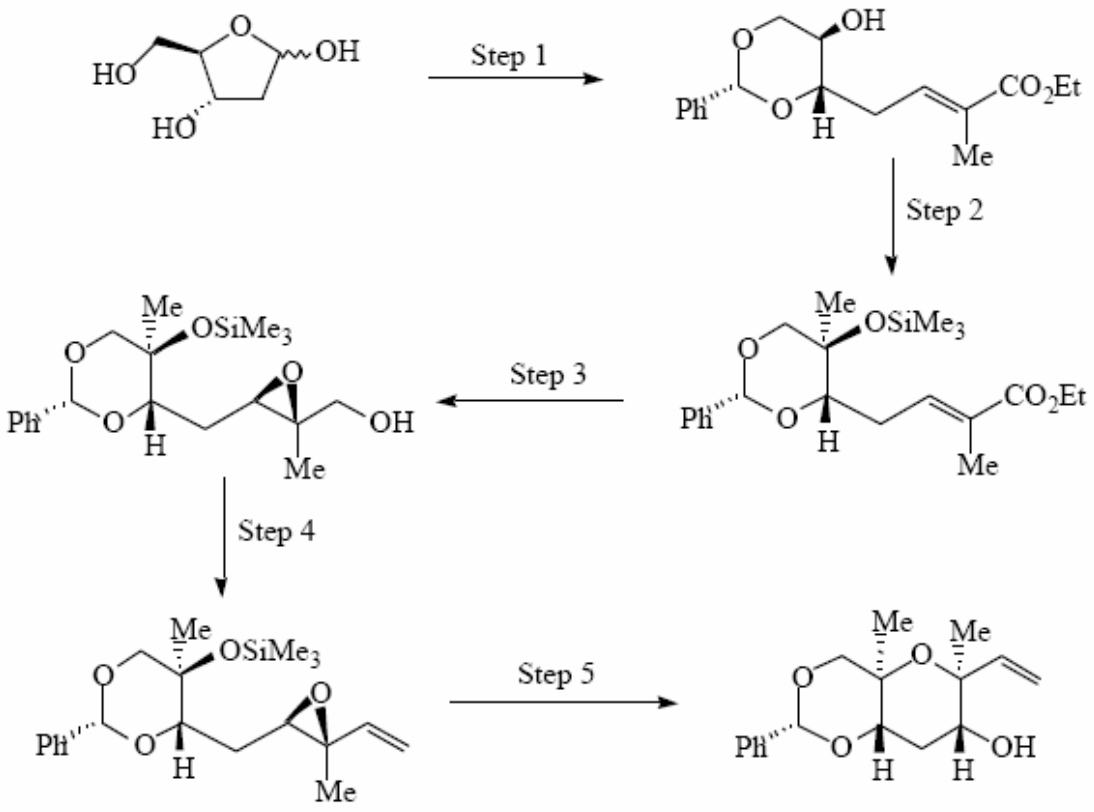
Part B

Note: You are NOT expected to comment on either Step 2 or Step 4

(a) Suggest reagents for, and explain Step 1 (more than one step is necessary). **[6]**

(b) Explain Step 3 as fully as possible. **[6]**

(c) Suggest reagents and give a mechanism for Step 5. **[3]**



Reagents and conditions:
Step 3: (i) DIBAL, CH_2Cl_2 (ii) (-)-Diethyltartrate, *t*-BuOOH, $Ti(O\textit{i}\text{-}Pr)_4$, CH_2Cl_2