Problem 4 25% of total	Question	4-1	4-2	4-3	4-4	4-5	4-6	4-7	Total
	Points	3	2	2	2	1	2	14	50
	Question	4-8	4-9	4-10	4-11	4-12	4-13	4-14	
	Points	1	2	2	12	4	2	1	

Problem 4: The wheels on the molecules go round and round…

by Lim Dillion, Singapore

Medium to large rings are hard to synthesise. However, these macrocyclic compounds often appear in natural products, and are a main target for chemists to synthesise. Let us look at some total syntheses that elegantly synthesise these macrocyclic natural products.

Part 1: Simple nine-membered rings

As a warm-up, let us consider a fairly old method in synthesising nine-membered rings: the Grob fragmentation (shown below). The Grob fragmentation is often used to generate macrocyclic rings by first synthesising a bicyclic compound. However, the synthesis of the bicyclic precursor required for the fragmentation proved to have little diversity.

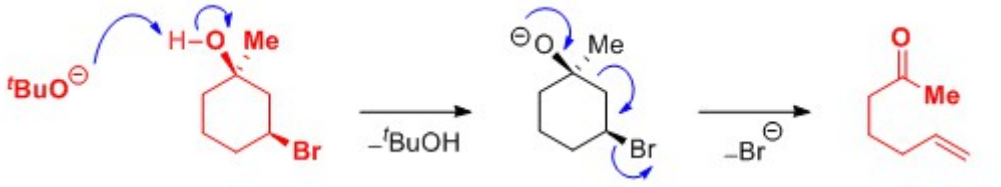


Figure 1: Grob Fragmentation

Consider the scheme for the synthesis of a 9-membered cycloalkyne, **5**, below:

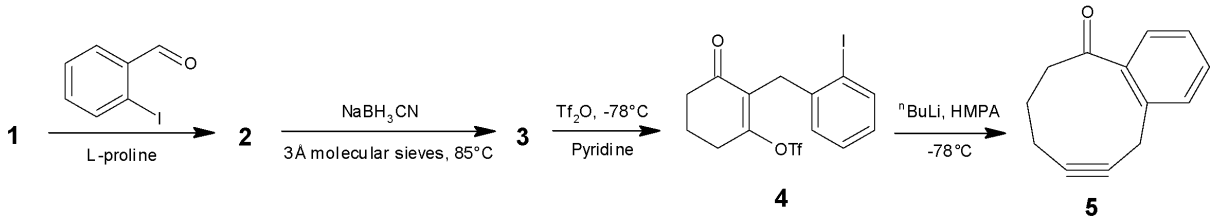


Figure 2: Synthesis of 9-membered cycloalkyne

4.1) **Deduce** the structures of **1** to **3**. You do **not** have to include stereochemistry.

4.2) **Draw** the mechanism for the conversion of **4** to **5**.

Part 2: Neocarzinostatin Chromophore

An interesting 9-membered ring formation is in the total synthesis of the neocarzinostatin chromophore (**N3**). In particular, the step below allows the correct stereoisomer of **N2** to be formed, where the -OH and -OTES groups are *trans* to each other.

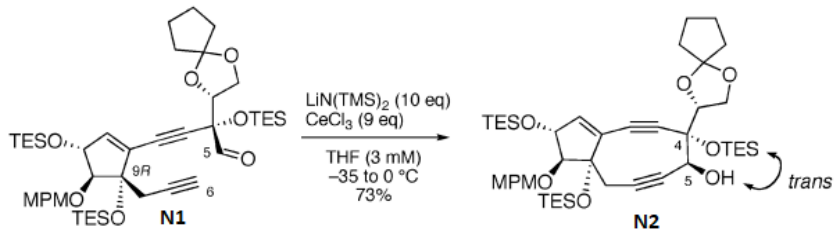
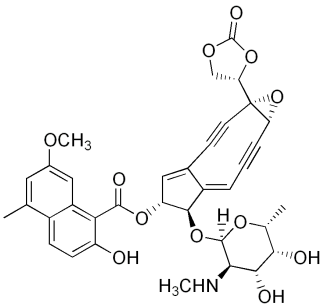


Figure 3: One step in the synthesis of neocarzinostatin chromophore



N3

Figure 4: Neocarzinostatin

4.3) By considering the Newman projection of the carbonyl carbon **5**, **<u>draw</u>** the mechanism for the formation of **N2** from **N1**, accounting for stereochemistry and **<u>explain</u>** why the correct stereochemistry is formed.

Neocarzinostatin belongs to a family of compounds known as enediyne antibiotics, and has been explored as a potential antitumour antibiotic. These compounds bind to DNA by interaction of parts of the molecule with the minor groove and activation to DNA-cleaving biradical species.

In the presence of thiols or a base, neocarzinostatin undergoes a reaction to form biradicals of the form:

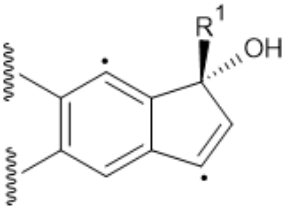


Figure 5: Biradical formed from both reactions with thiol and bases

4.4) **<u>Propose</u>** a mechanism, respectively, for the formation of the biradical shown above when a (a) thiol (**R**SH), (b) generic base (**B**) is added. You may abbreviate irrelevant parts of the structure, but label them **clearly**.

4.5) **<u>Explain</u>** why neocarzinostatin and other similar compounds do not undergo the reaction shown above naturally, but only when an activation reaction is carried out (such as the addition of a thiol).

Part 3: (+)-Byssochlamic Acid

Another method of synthesising 9-membered rings (and even larger rings) are pericyclic ring-expansion reactions. An example of this is the synthesis of (+)-byssochlamic acid, a compound isolated from *Byssochlamys fulva*, commonly associated with spoiled canned fruits.

9-membered rings can adopt many conformations, and some are shown below:

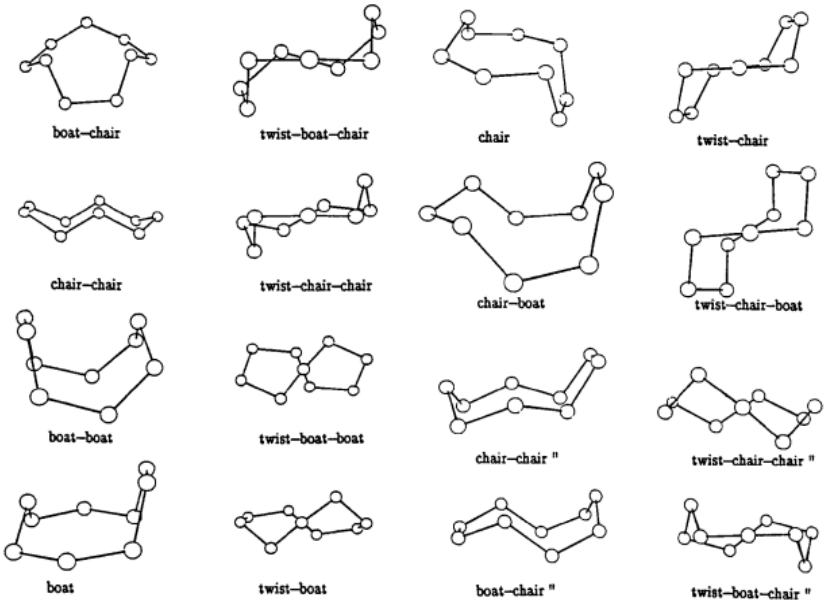
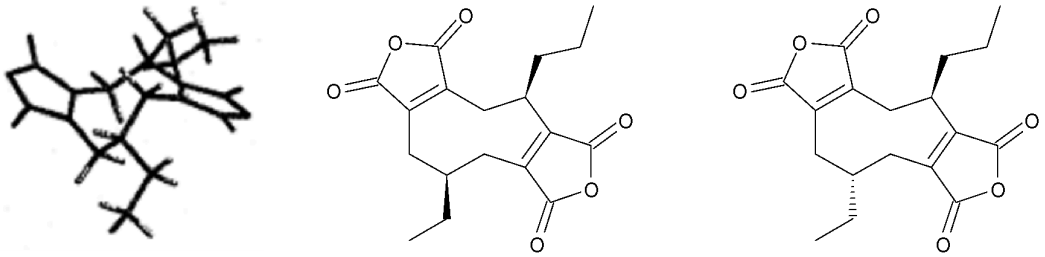


Figure 6: 9-membered ring conformers

In particular, it was found that byssochlamic acid has a cis- (**6c**) and a trans- (**6t**) isomer, depending on the relative orientation of the ethyl and propyl group, as shown below. Based on energy minimization using a PM3 algorithm, it was predicted that the 9-membered ring in **6c** and **6t** both exhibited a similar chair-like conformation. The computed 3-dimensional structure of **6c** is shown on its left.



6c (3D) **6c** **6t**

Figure 7: Structures of 6c and 6t

4.6) Based on the computed 3-dimensional conformer of **6c** shown, **6c (3D)**, **<u>propose</u>** the computed 3-dimensional conformer of **6t**. Hence, **<u>explain</u>** why **6t** is unstable relative to **6c** based on the conformer of **6t**.

Thus, the authors found that if the centre bearing the propyl group is stereomutable, they could easily do an asymmetric synthesis of byssochlamic acid by controlling the orientation of the remote ethyl substituent.

Hence, they attempted a synthesis of byssochlamic acid with this in mind.

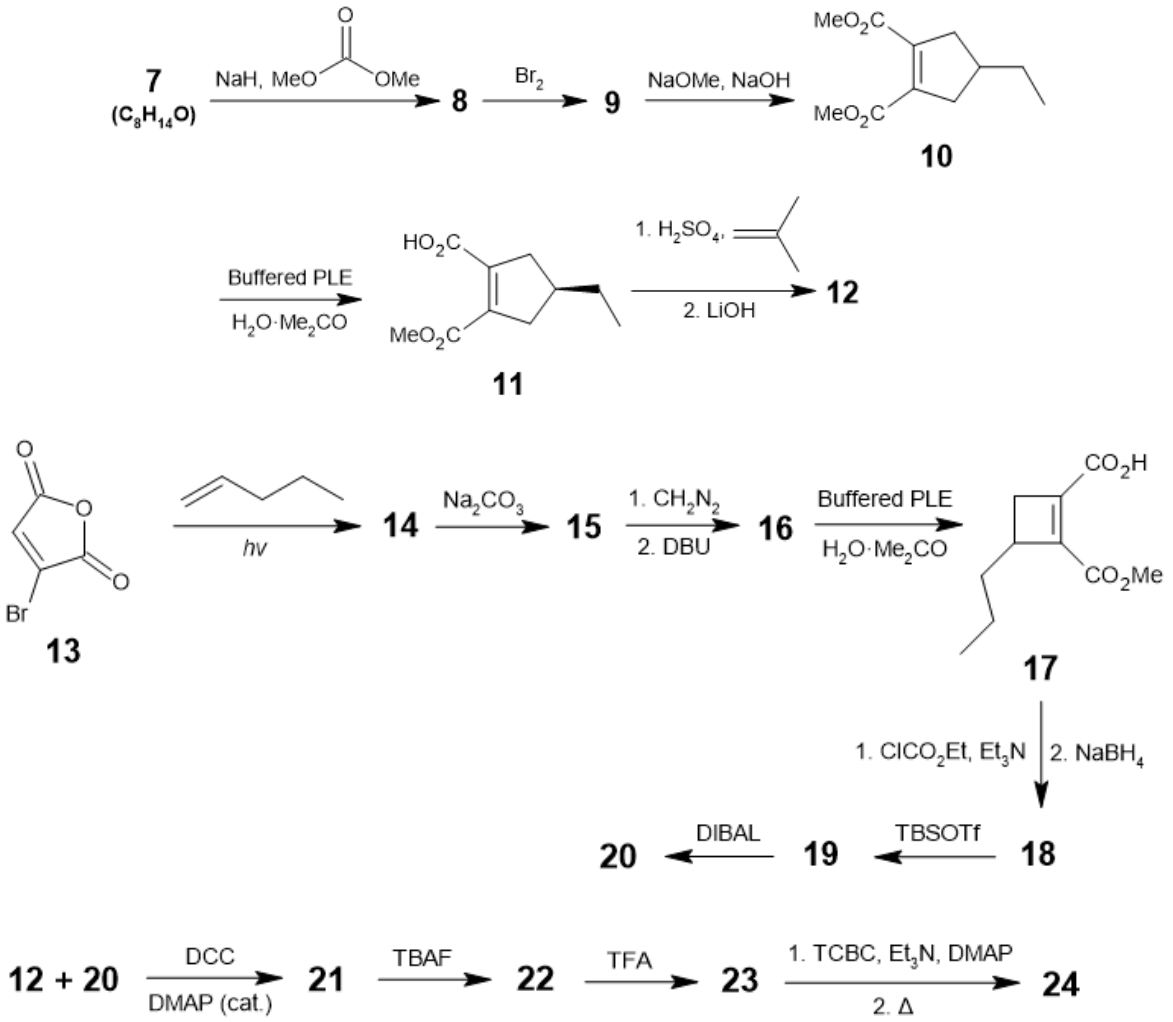


Figure 8: Attempt of Total Synthesis of (+)-Byssochlamic Acid

4.7) **<u>Deduce</u>** the structures of **7** to **9**, **12**, **14** to **16** and **18** to **24**. Stereochemistry is **not** required.

On irradiation of **23** with light, **23** was expected to become the desired product, **6**. However, upon initial irradiation, no reaction occurred. It was discovered that **23** required a much stronger source of light, but upon increasing the intensity of the light used, **23** turned back into its component reactants instead. Hence, the authors had to change the approach of the total synthesis.

4.8) By considering the conformation of **23**, **<u>propose</u>** a reason why a greater intensity of light was required for the reaction than expected.

By considering the conformation of **23**, the authors proposed the following alternative total synthesis of (+)-byssochlamic acid. With the use of porcine liver esterase (PLE), a pair of two regioisomers, **27** and **28** were formed.

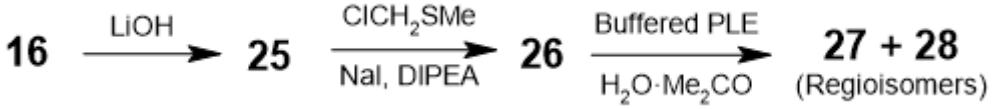


Figure 9a: Total Synthesis of (+)-Byssochlamic Acid (Part 1)

4.9) **<u>Deduce</u>** the structures of **25** and **26**. Stereochemistry is **not** required.

4.10) By considering the results of using PLE in the conversion of **10** to **11** and **16** to **17**, **<u>propose</u>** the structures of **27** and **28** respectively, given that **27** was the major regioisomer, with the ratio of **27**:**28** formed being 7:1.

The total synthesis of (+)-byssochlamic acid, **6**, was then concluded using **11** and **27**. It was known that the cyclopentane ring in **37** exhibited puckering.

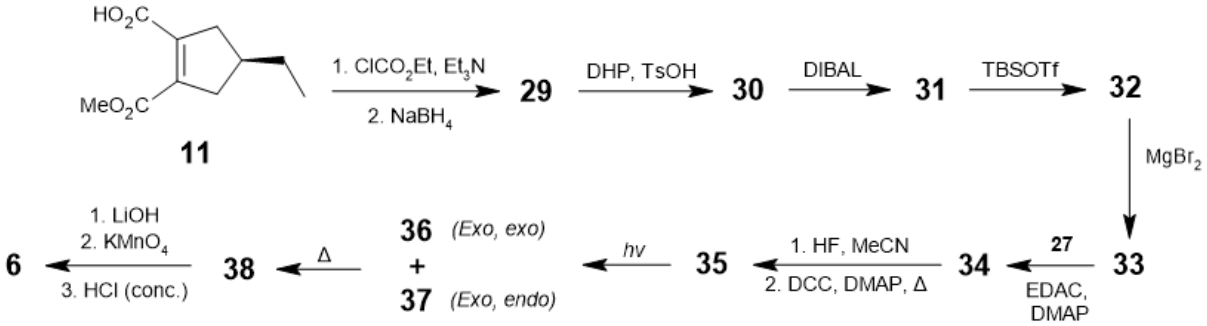


Figure 9b: Total Synthesis of (+)-Byssochlamic Acid (Part 2)

4.11) **<u>Deduce</u>** the structures of **29** to **38**. Stereochemistry is **not** required, except for the 3-dimensional structures of **36** and **37** being required.

4.12) **<u>Draw</u>** the mechanism for the conversion of **35** to **38**.

4.13) By considering the conformation of the product formed, **<u>explain</u>** why the *exo*, *exo* and *exo*, *endo* products are formed, but the alternative *endo*, *exo* product from the conversion of **35** to **38** is **not** formed.

It is also known that when (+)-byssochlamic acid was irradiated, it underwent a reaction to give a saturated isomer, known as photobyssochlamic acid. Upon thermolysis, **6** was **not** regenerated.

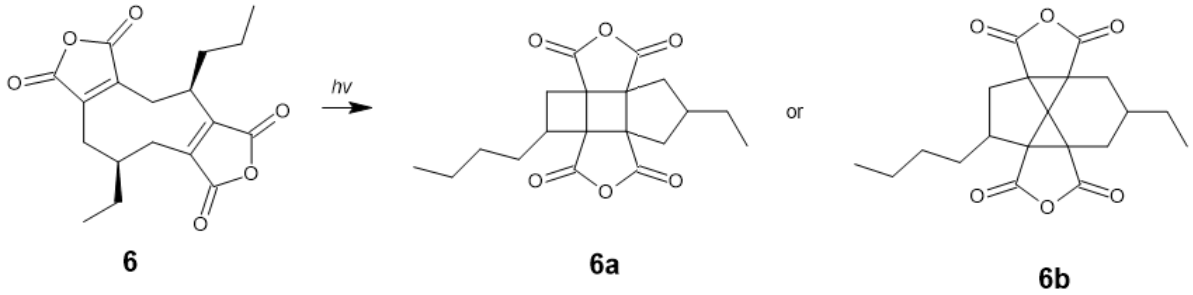


Figure 10: Possible structures of photobyssochlamic acid

4.14) **Deduce** and **explain** whether **6a** or **6b** is more likely to be the correct structure of photobyssochlamic acid.

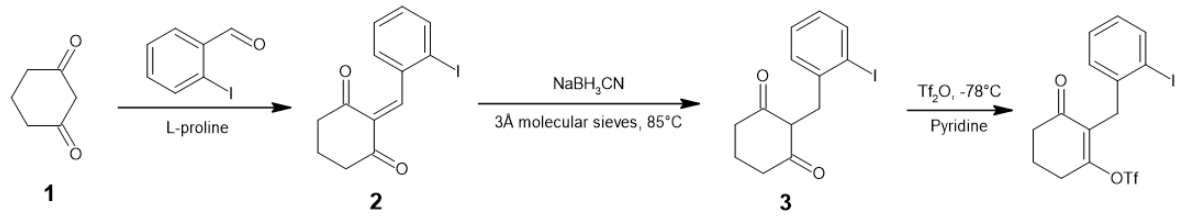
Problem 4: Solution

Grading guidelines for mechanisms

No penalty if the side products (e.g. OTf^-, ^nBuI) are not shown

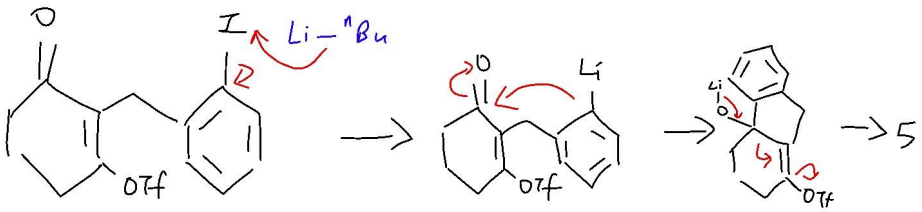
- 0.5 points if base used is not specified (e.g. B^-) or wrong base is used (e.g. water instead of ^nBuLi),
- 0.5 points if electrons are not pushed to an electron sink (e.g. inappropriate use of carbanions)
- 0.5 points for every general minor error in mechanism (e.g. missing H, missing charges),
-1 point for every general major error in mechanism (e.g. direction of arrow is wrong, expanded octet for period 2 elements)

4.1) **Deduce** the structures of **1** to **3**. You do **not** have to include stereochemistry.



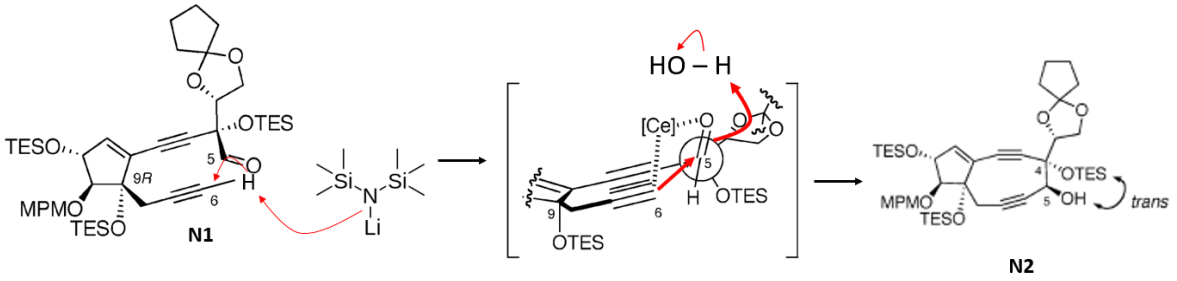
Grading guidelines
1 point each for each correct structure. (Total 3 points)
Drawing an alcohol instead of alkene for **2** will be accepted

4.2) **Draw** the mechanism for the conversion of **4** to **5**.



Grading guidelines
Any reasonable mechanism for the halogen-lithium exchange will be accepted.
0.5 points for halogen-lithium exchange
0.5 points for the intramolecular nucleophilic addition to the ketone
1 point for the Grob fragmentation to form 5.

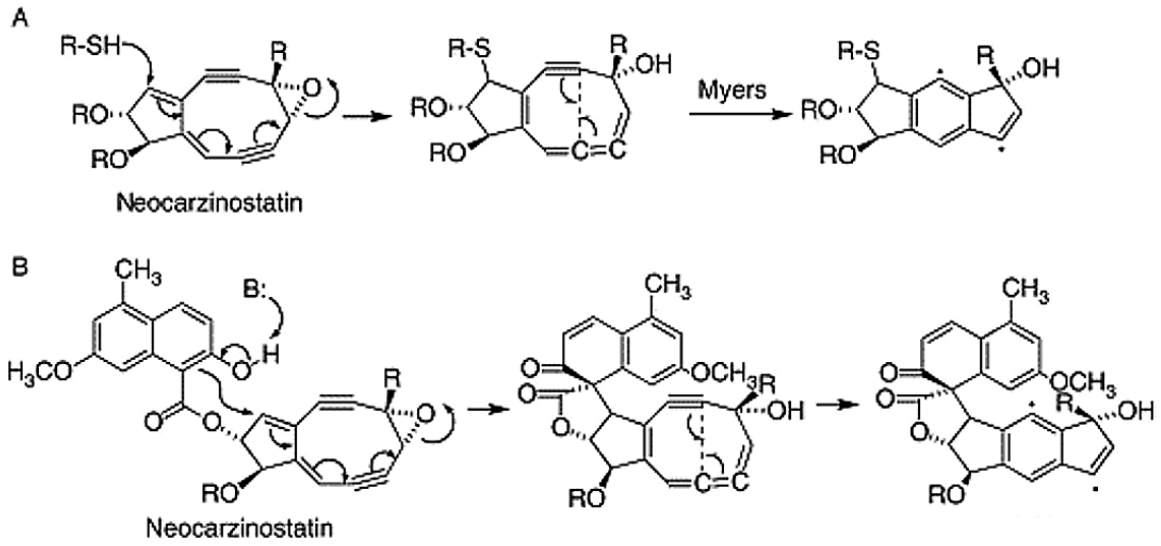
4.3) By considering the Newman projection of the carbonyl carbon **5**, **<u>draw</u>** the mechanism for the formation of **N2** from **N1**, accounting for stereochemistry and **<u>explain</u>** why the correct stereochemistry is formed.



The cerium-chelated carbonyl oxygen is sterically remote from the neighbouring TES group.

Grading guidelines
0.5 points for the deprotonation of the alkyne.
0.5 points for the formation of **N2**.
1 point for the correct explanation about sterics.

4.4) **<u>Propose</u>** a mechanism, respectively, for the formation of the biradical shown above when a (a) thiol (**R**SH), (b) generic base (**B**) is added. You may abbreviate irrelevant parts of the structure, but label them **clearly**.



Grading guidelines
0.5 points for the conjugate nucleophilic addition of part (a).
0.5 points for the base-catalyzed intramolecular addition reaction of part (b).
1 point for the correct Myers cycloaromatization, present in the second step of both parts.

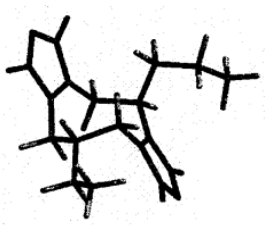
4.5) **Explain** why neocarzinostatin and other similar compounds do not undergo the reaction shown above naturally, but only when an activation reaction is carried out (such as the addition of a thiol).

These processes do not take place in neocarzinostatin and other similar compounds because their spatial arrangement prevents coplanarity of the three bonds involved in the Myers cycloaromatization, and therefore an activation reaction or cascade of reactions that alters the compound geometry is necessary.

Grading guidelines
1 point for mentioning the coplanar geometry needed for the reaction to occur.

4.6) Based on the computed 3-dimensional conformer of **6c** shown, **6c (3D)**, **propose** the computed 3-dimensional conformer of **6t**. Hence, **explain** why **6t** is unstable relative to **6c** based on the conformer of **6t**.

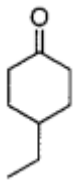
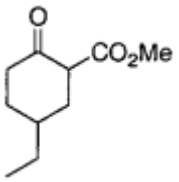
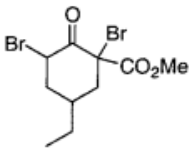
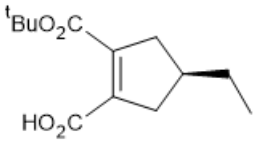
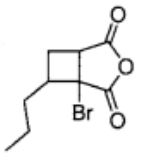
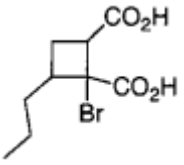
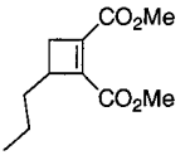
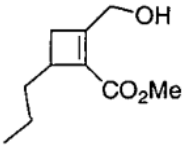
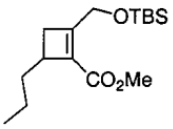
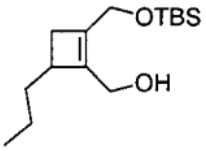
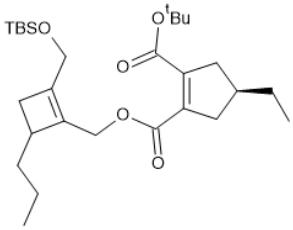
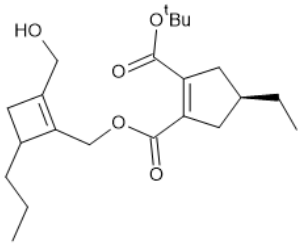
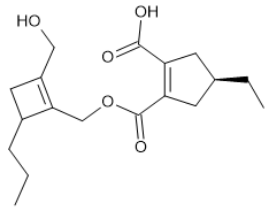
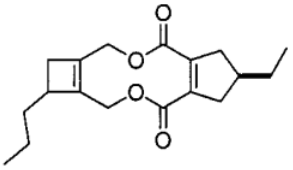
The 3-dimensional conformer of **6t** is shown on the right.



The factor which destabilizes **6t** relative to **6c** is the pseudoaxial orientation of the propyl chain, which creates a transannular steric interaction with an endo hydrogen of the methylene adjacent to the ethyl substituent.

Grading guidelines
1 point for the correct drawing of the conformer.
1 point for correct explanation about the transannular steric interaction.

4.7) **Deduce** the structures of **7** to **9**, **12**, **14** to **16** and **18** to **24**. Stereochemistry is **not** required.

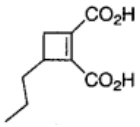
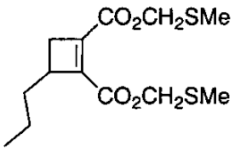
7 	**8** 
9 	**12** 
14 	**15** 
16 	**18** 
19 	**20** 
21 	**22** 
23 	**24** 

Grading guidelines
1 point for each correct structure. (Total 14 points)

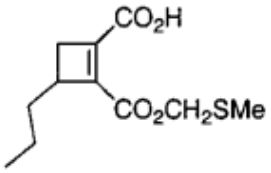
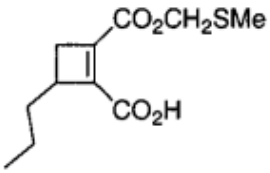
4.8) By considering the conformation of **23**, **propose** a reason why a greater intensity of light was required for the reaction than expected.

The two carbonyl groups are able to twist out of coplanarity with the cyclopentene to a degree which would disrupt conjugation, hence significantly reducing the light absorption properties of the diolide. **Grading guidelines** 1 point for a reasonable explanation that involves the conformation of **23**.

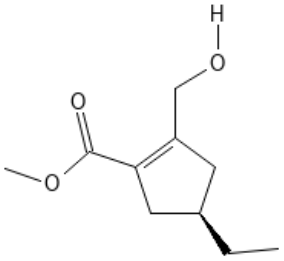
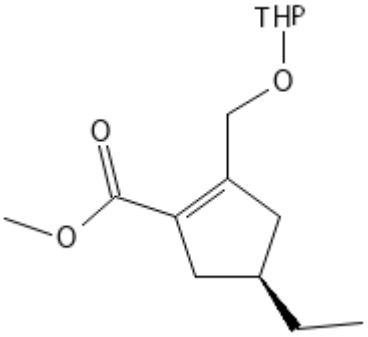
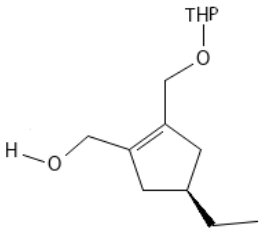
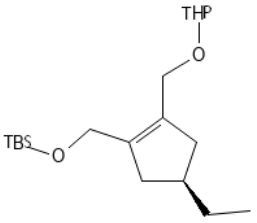
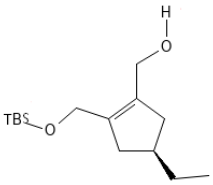
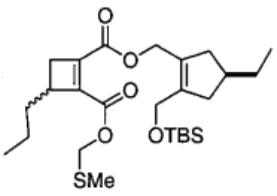
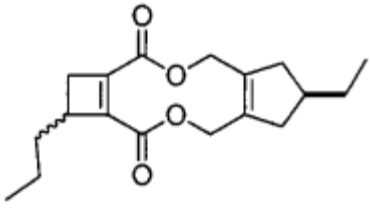
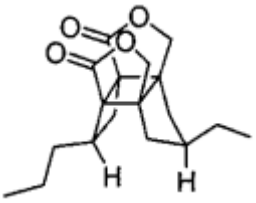
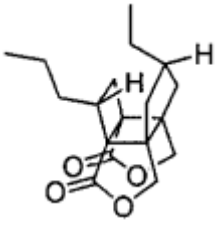
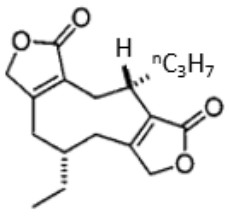
4.9) **Deduce** the structures of **25** and **26**. Stereochemistry is **not** required.

25 	**26** 
Grading guidelines 1 point for each correct structure. (Total 2 points)	

4.10) By considering the results of using PLE in the conversion of **10** to **11** and **16** to **17**, **propose** the structures of **27** and **28** respectively, given that **27** was the major regioisomer, with the ratio of **27**:**28** formed being 7:1.

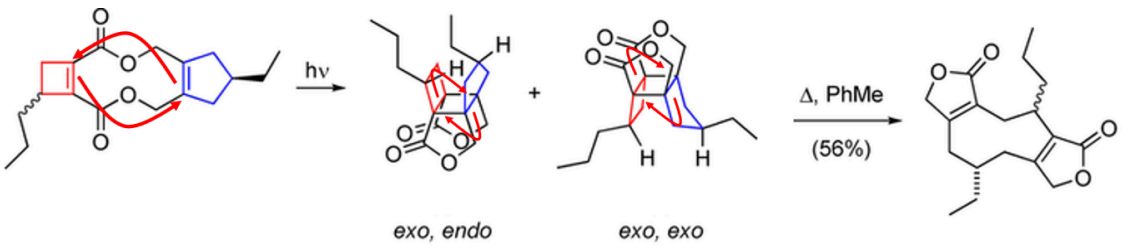
27 	**28** 
Grading guidelines 1 point for each correct structure. (Total 2 points)	

4.11) **Deduce** the structures of **29** to **38**. Stereochemistry is **not** required, except for the 3-dimensional structures of **36** and **37** being required.

29 	**30** 
31 	**32** 
33 	**34** 
35 	**36** 
37 	**38** 

Grading guidelines
1 point for each correct structure of **31** to **35** and **38**. (Total 8 points)
2 points for each correct structure of **36** and **37**. (Total 4 points)

4.12) **Draw** the mechanism for the conversion of **35** to **38**.



Grading guidelines
2 points for the cycloaddition to form **36** and **37**.
1 point for each cycloreversion to form **38**. (Total 2 points)

4.13) By considering the conformation of the product formed, **explain** why the *exo*, *exo* and *exo*, *endo* products are formed, but the alternative *endo*, *exo* product from the conversion of **35** to **38** is **not** formed.

In **36**, the ethyl and propyl substituents are directed away from the interior of the cage. In **37**, the ethyl substituent rather than the propyl group occupies the interior space, and puckering of the cyclopentane ring of **37** moves the ethyl group away from the congested cage interior.

However, the alternative *endo*, *exo* photoadduct in which the propyl group is endo would create severe compression between the propyl substituent and a CH_2 group of the cyclopentane ring.

Grading guidelines
0.5 points for explanation of ethyl and propyl groups being directed away from the cage in **36**.
0.5 points for explanation of ethyl group being directed into from the cage in **37**.
0.5 points for explanation that the cyclopentane ring is puckered to reduce the steric hindrance in **37**.
0.5 points for explanation that the propyl group will have compression with a CH_2 group in the cyclopentane ring in the alternative photoadduct.

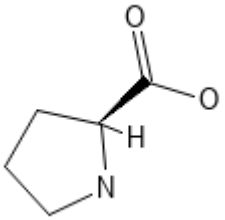
4.14) **Deduce** and **explain** whether **6a** or **6b** is more likely to be the correct structure of photobyssochlamic acid.

6b is the correct structure of photobyssochlamic acid, because **6a** reverts to byssochlamic acid upon pyrolysis, as seen in its total synthesis.

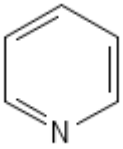
Grading guidelines
0.5 points for the correct structure chosen.
0.5 points for correct explanation about **6a** reverting to byssochlamic acid with reference to the total synthesis.

CHART CHART CHART

L-Proline

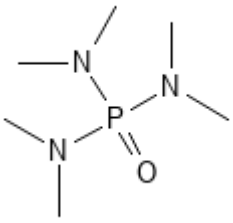


Pyridine



-Tf

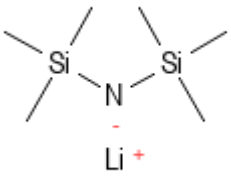
HMPA



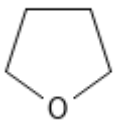
-TES

-MPM

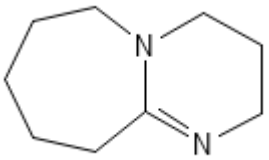
LiN(TMS)2



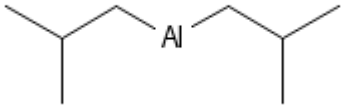
THF



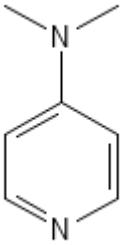
DBU



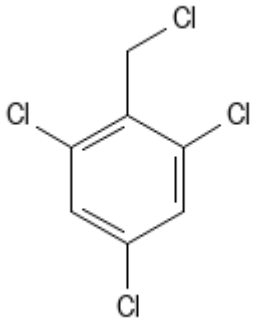
-TBS
DIBAL



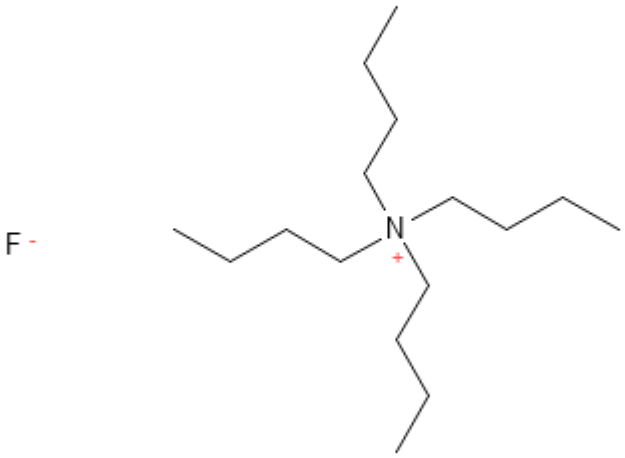
DMAP



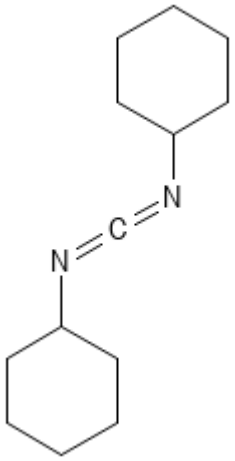
TCBC



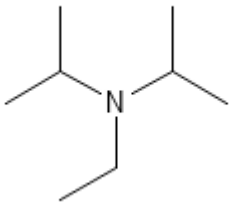
TBAF



DCC

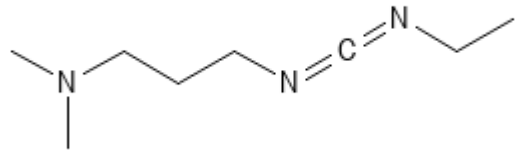


DIPEA



-Ts

EDAC



DHP