PROBLEM 1
Suggest a mechanism for this reaction, commenting on the selectivity and the stereochemistry.

Purpose of the problem
The opportunity to explore the consequences of the intramolecular version of an important reaction.

Suggested solution
The ylid forms in the usual way but can’t reach across the ring to attack the carbonyl group directly so it has to do conjugate addition instead. It also has to attack from the top face as it is tethered there. Completion of the cyclopropane forming reaction leaves the sulfur still attached to the angular methyl group. Raney nickel reduces the C–S bond (this reagent is commonly used for this purpose). This reaction shows that simple sulfonium ylids can do conjugate addition—they just prefer to add to carbonyl groups if that possibility is available.

PROBLEM 2
Explain the regiochemistry and stereochemistry of this reaction.

Purpose of the problem
Exploration of sulfur ylid chemistry.

Suggested solution
The ylid is stabilised by conjugation with the ester group—you can think of it also as an enolate. We can expect reversible addition to the carbonyl group and hence conjugate addition under thermodynamic control. The stereochemistry of the ring junction is inevitable: only a cis ring can be made (a trans-fused ring would be too strained). The interesting centre is that of the ester on the three-membered ring. It too is in a more stable configuration: on the outside of a folded molecule. The intermediate is probably a mixture of diastereoisomers, but as the conjugate addition is reversible the cyclopropane may be formed by cyclisation of only the diastereoisomer that can give the more stable product.
**PROBLEM 3**

Give mechanisms for these reactions, explaining the role of sulfur.

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**Purpose of the problem**

Sulfur acetics as good nucleophiles: in the terminology of chapter 28, ‘acyl anion equivalents’ or ‘d¹ reagents’.

**Suggested solution**

The first reaction is an acetal exchange controlled by entropy: three molecules go in and four come out (the product, two molecules of methanol and one of water). We show just part of the mechanism.

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This chemistry was used to make the perfume *cis*-jasmone by R. A. Ellison and W. D. Woessner, *J. Chem. Soc., Chem. Commun.*, 1972, 529.
Now the sulfur atoms work to stabilise an anion (organolithium) formed by deprotonation. Alkylation and hydrolysis with a mercury catalyst gives the product.

PROBLEM 4
Suggest a mechanism by which this cyclopropane might be formed.

Attempts to repeat this synthesis on the related compound below led to a different type of product. What is different this time?

Purpose of the problem
Can you disentangle a curious variation on a simple mechanism?
**Suggested solution**

The first reaction is a straightforward cyclopropane formation with a sulfoxonium ylid and a conjugated ketone. The only unusual feature, the MeO group, makes no difference.

![Chemical structure](image)

In the second example, the bromine atom and the phenolic OH evidently *do* make a difference. No doubt the reaction starts in the same way and a cyclopropane is formed. Under the reaction conditions, the phenol will exist as an anion and this displaces the bromine. This unusual S_N2 reaction at a tertiary centre is possible because of activation by the carbonyl group.

![Chemical structure](image)

**PROBLEM 5**

Deduce the structure of the product of this reaction from the NMR spectra and explain the stereochemistry. Compound A has δH 0.95 (6H, d, J 7 Hz), 1.60 (3H, d, J 5), 2.65 (1H, double septuplet, J 4 and 7), 5.10 (1H, dd, J 10 and 4), and 5.35 (1H, dq, J 10 and 5).

![Chemical structure](image)

**Purpose of the problem**

A simple way to make Z-alkenes, with a bit of NMR revision.

**Suggested solution**

This is obviously a Wittig reaction and we should expect a Z-alkene as the ylid is not stabilized by further conjugation. The evidence is plain:
the signals at 5.10 and 5.35 are the alkene hydrogens and the coupling constant between them is 10 Hz. This is definitely a Z-alkene.

PROBLEM 6
A single geometrical isomer of an insect pheromone was prepared in the following way. Which isomer is formed and why?

Purpose of the problem
Testing your knowledge of the stereochemistry of the Wittig reaction.

Suggested solution
The first Wittig with a stabilised ylid gives the $E$-enal A. The second, with an unstabilised ylid, gives a $Z$ alkene so the final product is an $E,Z$-diene.
PROBLEM 7
How would you prepare samples of both geometrical isomers of this compound?

![Chemical structure]

**Purpose of the problem**
A simple stereocontrolled alkene synthesis but both isomers are needed.

**Suggested solution**
There are many methods that can be used to tackle this question. The only snags are protecting the OH group if necessary and care in isolating the Z-compound as it may isomerise easily to the E-compound by reversible conjugate addition. One way to the Z-alkene uses reduction of an alkyne to control the stereochemistry. The OH group is protected as a benzyl ether removed by hydrogenation, perhaps under the same conditions as the reduction of the alkyne.

![Chemical reaction]

The E-alkene might be produced by reduction of the alkyne with an alkali metal in liquid ammonia but a Wittig reaction is probably easier. Either a phosphonium ylid or a phosphonate ester could be used. Protection of the alcohol as an ester allows hydrolysis of both esters in one step.

![Chemical reaction]
PROBLEM 8
Which alkene would be formed in each of these elimination reactions? Explain your answer mechanistically.

Purpose of the problem
Revision of the three main methods for stereoselective (or stereospecific) alkene bond formation.

Suggested solution
The first is sort of a Wittig reaction (the starting material is made by opening an epoxide with \( \text{Ph}_3\text{P} \)), the second a Julia reaction and the third and the fourth are Peterson reactions under different conditions. Each is described in detail in chapter 27 of the textbook. The Wittig reaction is under kinetic control and is a stereospecific cis elimination. In this case the product is a \( Z \)-alkene.

The Julia reaction is under thermodynamic control as equilibration occurs under the reaction conditions. The stereoselective product is the \( E \)-alkene.
The Peterson reaction is a syn elimination under basic conditions, giving the Z-alkene from this starting material, but an E2 anti-elimination under acidic conditions, giving the E-alkene from this starting material.

![Diagram of syn elimination and base mechanism](image)

**PROBLEM 9**

Give mechanisms for these reactions, explaining the role of silicon.

![Reactions](image)

**Purpose of the problem**

Reminder of the anion-stabilizing role of sulfones and the excellence of the mesylate leaving group plus the special role of fluoride as a nucleophile for silicon.

**Suggested solution**

Sodium hydride removes a proton from the sulfone to give an anion that can act as a nucleophile. Displacement of mesylate gives an allyl silane, which is converted into an allylic anion by fluoride. Addition to the ketone gives a 5/5 fused system with the more stable cis ring junction.

![Mechanisms](image)
**PROBLEM 10**

Give mechanisms for these reactions, explaining the role of silicon. Why is this type of lactone difficult to make by ordinary acid- or base-catalysed reactions?

![Chemical structures](image)

**Purpose of the problem**

Basic organosilicon chemistry: the Peterson reaction and allyl silanes as nucleophiles.

**Suggested solution**

Acylation of the Grignard reagent is followed by a second attack on the ketone as expected but the tertiary alcohol is a Peterson intermediate and eliminates to give the alkene.

![Chemical structures](image)

Now a Lewis acid catalysed reaction of the allyl silane via a β-silyl cation gives the lactone. The double bond in these ‘exo-methylene’ lactones easily moves into the ring in acid or base so mild conditions are ideal for these reactions.

![Chemical structures](image)
PROBLEM 11

How would you carry out the first step in this sequence? Give a mechanism for the second step and suggest an explanation for the stereochemistry. You may find that a Newman projection helps.

Purpose of the problem

An important way to make an allyl silane and an important reaction of the product.

Suggested solution

The best route to the allyl silane is the Wittig reaction (p. 675). The ylid is not stabilised by and extra conjugation so the Z-isomer is favoured.

The reaction with EtAlCl2 is a Lewis acid-catalysed conjugate addition of the allyl silane to the enone. Conjugate addition is preferred because the nucleophile (the allyl silane) is tethered to the electrophile (enone) and the five-membered ring is preferred to a seven-membered ring.

The stereochemistry comes from the way the molecule prefers to fold and the Newman projection below should make that clear. The hydrogen atom on the allyl silane tucks underneath the six-membered
ring while the double bond of the allyl silane projects out into space to give the stereochemistry found in the product. The ratio between this diastereoisomer and the other varies from 2:1 to 7.5:1 depending on conditions so the preference is really quite weak.