Organic Synthesis and Carbon-Carbon Bond Forming Reactions

1. To introduce basic concepts of organic synthesis:

Retrosynthesis – thinking backwards from relatively complex molecules to simpler ones – the disconnection approach.

2. To classify and extend the main carbon-carbon bond forming reactions (CCBFR) introduced in CHE1C1Y.

3. To illustrate the importance of organic synthesis with real examples.

Organic Synthesis

Introduction

Why bother?!

Ca. 7 million organic compounds known – most have been made by synthesis rather than isolated from nature.

Reasons for Synthesising Organic Compounds:

a) Proof of structure of a natural compound by ‘putting it together’ from simpler molecules.
b) To prepare compounds that are useful to mankind e.g. pharmaceuticals, polymers, dyes etc.
c) To prepare specific compounds to study reaction mechanisms or biological metabolism (e.g. labelled compounds).
d) For the intellectual challenge – new problems demand new solutions and can lead to the development of NEW CHEMISTRY, reagents etc.

When faced with the challenge of preparing a specific organic compound how do we go about it?

This is the art of synthesis!

e.g. How might we attempt to make Z jasmone – an important constituent of many perfumes?

\[
\begin{align*}
\text{Target Molecule} & \longrightarrow \text{Precursors} \\
\text{n.b.} & \\
\end{align*}
\]

Solomons p169 - 172

\[\alpha,\beta \text{ unsaturated ketone, alkene, 5-membered ring}\]
In fact one synthesis uses the following as carbon sources

![Chemical structure]

It is not clear from this however, how the chemistry might be done! Therefore just being given the **starting materials** is not sufficient to help plan a synthesis. Note the importance of CCBFR.

We need a logical planning method.

**Retroynthetic Analysis (The Disconnection Approach)**

Originated by E.J. Corey (Nobel Prize 1990)  

p169 – 172  
p259 – 260  
p354 – 359

**Definition of Terms**

**Target Molecule (TM)** – the compound we wish to prepare e.g.

![Methylphenyl ketone](image)

**Retroynthetic Analysis** – the process of WORKING BACKWARDS from the TM in order to devise a suitable synthetic route (or routes) on paper.  

Note:  

\[ \longrightarrow \] denotes disconnection of TM to its most immediate precursor.

Multiple steps are required so this needs to be repeated.

\[ TM \longrightarrow 1st \text{ Precursor} \longrightarrow 2nd \text{ Precursor} \longrightarrow \text{ Starting compounds} \]

- readily available

After writing possible routes we would need to evaluate each one before deciding which to follow.
Readily Available Starting Materials (RASM) – cheap, commercially available compounds.

Disconnection – a paper operation involving an imagined cleavage of a bond (yielding ‘synthons’) to suggest a method and possible SM’s for making the bond, ultimately leading to possible SM’s for the overall synthesis.

\[ X \rightleftharpoons Y \rightarrow X^+ + Y^- \]
\[ \text{OR} \quad X^- + Y^+ \]
\[ \text{OR} \quad X^+ + Y^- \]

Note: There must be a good chemical reaction corresponding to the reverse of the disconnections.

Synthon – an idealised fragment, usually a cation or anion, resulting from a disconnection.

\[ X^+ Y^- \]
\[ X^- Y^+ \]
\[ X \; Y \]

Usually synthons don’t exist as such, but help in the correct choice of reagent.

In our example:

Looks possible because it implies electrophilic attack on benzene ring

Does not look so good (nucleophilic attack less usual)

Synthetic Equivalent – the actual compounds used to function as synthons.

Friedel Crafts reagent

Functional Group Interconversion (FGI) – the process of writing one functional group for another to help synthetic planning and to help disconnection. Note, there must be a good reaction in the reverse (forward!) direction.
E.g.

\[
\begin{align*}
\text{NH}_2 & \quad \text{?} \quad \text{OH} \\
\text{N} & \quad \text{NO}_2 \\
\text{O} & \quad \text{O}=\text{N} = \text{O}
\end{align*}
\]

Easy! Nitration of benzene (HNO\(_3\)/H\(_2\)SO\(_4\))

Alternative synthesis of

\[
\begin{align*}
\text{O} & \quad \text{HO} \quad \text{H} \\
\text{CH} & \quad \text{CH} \\
\text{MgBr} & \quad \text{CH}_3
\end{align*}
\]

Many ways to make alcohols (e.g. via Grignard reagents) - suggests alternative synthesis to Friedel Crafts.

In planning a synthetic strategy, apart from devising a means of constructing the carbon skeleton with the required functionality as above, there are other subtle factors, which we must address.

Control of Regiochemistry

\[
\begin{align*}
X & \quad Y \\
\text{AND NOT} & \quad \text{AND NOT}
\end{align*}
\]

(Control of Stereochemistry)

\[
\begin{align*}
\text{O} & \quad \text{HO} \quad \text{H} \\
\text{CH}_3 & \quad \text{MgBr}
\end{align*}
\]

(Good summary p169 – 172, 259 – 260, 354 – 359)
We will illustrate this approach with examples, starting with synthesis of benzene derivatives. Starting point is usually fairly obvious – simple benzene derivatives or perhaps benzene itself.

**The Synthesis of Substituted Benzene Derivatives** (Solomons p655 – 695)

Reactions are usually straightforward ($\text{S}_{\text{E}}\text{Ar}$) and you will have met most of them before. Synthesis is simplified because the nature of the starting materials is usually clear. Thus, most reactions correspond to the following disconnection:

\[
\begin{align*}
\text{X} & \quad \text{X S} \quad \text{E} \quad \text{Ar} \\
\end{align*}
\]

**Example 1**

1st decision – which bond to disconnect first!

---

Problem! No good synthetic equivalent for NH$_2^+$

(but o/p directing effect of Br sub is OK)

Br$^+$ - can use Br$_2$/FeBr$_3$

o/p directing effect of NH$_2$ is OK

BUT, problem is overbromination

However, we can carry out monobromination on the N-acyl derivative of the amine:

\[
\begin{align*}
\text{NHCOCH}_3 & \quad \text{Br}_2 \\
\end{align*}
\]

(some o-isomer - separate)

then we can remove the protecting group (HO'/H$_2$O) to give the required product.
So formally:

\[ \text{NH}_2 \quad \text{FGI} \quad \text{NHCOCH}_3 \quad \text{FGI} \quad \text{NO}_2 \quad \text{FGI} \quad \text{HNO}_3\text{H}_2\text{SO}_4 \]

Is there an alternative route? Try a different FGI!

Example 2

Synthesis
Guidelines for designing a synthesis

1. Use retrosynthetic analysis to work backwards from TM to the precursors and eventually to RASM.

2. Locate the functional groups in the TM – for most functional groups there are good DISCONNECTIONS (the reverse of real chemical reactions).

3. Examine all possible disconnections – check which are chemically sound (correspond to known reactions, reagents, directing effects etc.)

4. If you can make no progress try FGI: (NO₂/NH₂; CH₃/COOH; C-Br/C-OH; CHO/CH₂OH etc.)

5. Having obtained precursors to TM, repeat the process on these intermediates.

Clearly you will need a good knowledge of your basic chemistry and an appreciation of reaction mechanisms, directing effects etc.

With Aromatic systems the SM’s are usually fairly obvious. Usually benzene or a benzene derivative such as toluene, phenol etc. bond to be disconnected is almost always the bond joining the aromatic ring to the rest of the molecule.

Also FGI’s often correspond to some simple types of reaction e.g. reduction (NO₂ to NH₂), oxidation (CH₃ to COOH), diazonium chemistry (NH₂ → N₂⁺ → Ar-X).
In aromatic chemistry CCBFR revolve around:

1) Friedel Crafts type reactions

\[
\begin{align*}
\text{ROCl} \\
\text{Ar—H} & \longrightarrow \text{Ar—COR}
\end{align*}
\]

2) Displacements on aromatic diazonium salts

\[
\begin{align*}
\text{Ar}^+ & \stackrel{\text{CN}}{\longrightarrow} \text{Ar—C—N}
\end{align*}
\]

3) Not forgetting Grignard reagents + carbonyls)

With aliphatic acyclic and cyclic systems – the process is not always as straightforward – need to consider a greater array of CCBFR’s and FGI’s.

Retrosynthesis In An Aliphatic Molecule – A Guide To Alternative Disconnections.

Retrosynthetic analysis 1

Synthesis
Retrosynthetic analysis 2

Synthesis
Retrosynthetic analysis 3

Synthesis

Ph\(\text{BrMg} \rightarrow \text{Ph} \quad \text{Ph} \quad \text{OH} \quad \text{H}_2\text{O}

Path A

Path B
Retrosynthetic analysis 4

Synthesis

Ph\text{CH}_3\text{CO} \rightarrow \text{PhCH}_3\text{Br} \quad \text{base} \rightarrow \text{PhCOCH}_2\text{Ph} \quad \text{NaBH}_4 \rightarrow \text{PhOH}
We shall discuss possible synthesis later, but we will concentrate on CCBFR in aliphatic systems.

Review and extend CCBFR from 1C1Y, in particular:
- Aldol and Claisen condensations
- Alkylation of β-keto esters (RCHOCH₂CO₂R’)
- Grignard reactions
And illustrate their use in synthesis.
Classification of CCBFR in aliphatic chemistry

There are several ways of doing this. We shall consider the following:

a) **Carbanion Alkylation**

i) **Alkylation of enolate ions**

\[
\text{O} + \text{R} \xrightarrow{\text{X}} \text{R}
\]

p 867 - 879

ii) **Alkylation of acetylide or cyanide**

\[
\text{R} \xrightarrow{\text{C} = \text{C}} \xrightarrow{\text{X}} \text{R} \xrightarrow{\text{R}} \text{R'}
\]

p 321 - 322

\[
\text{R} \xrightarrow{\text{N} = \text{C}} \xrightarrow{\text{X}} \text{R} \xrightarrow{\text{CN}}
\]

p 804

iii) **Organometallic alkylation**

\[
\text{R} \xrightarrow{\text{MgX}} \xrightarrow{\text{O}} \text{R} \xrightarrow{\text{OH}}
\]

p 483

**Note** iv) **Direct alkylation of carbanions is possible in some cases**

\[
\text{R}_2\text{CuLi} + \text{R'} \xrightarrow{\text{X}} \text{R} \xrightarrow{\text{R'}} \text{R'}
\]

p 167 - 169

Where R' = methyl or 1° alkyl halide

(Not a typical substitution mechanism!)

b) **Carbonyl Addition And Carbonyl Substitution Reactions**

i) **Aldol and related reactions (Add\textsuperscript{n})**

\[
\text{2} \xrightarrow{\text{O}} \xrightarrow{\text{OH}} \text{p 762 - 774}
\]

ii) **Claisen condensation and related reactions (Sub\textsuperscript{n})**

\[
\text{2} \xrightarrow{\text{O}} \xrightarrow{\text{O}} \text{p 860 - 867}
\]
iii) Organometallic reactions (Add\(^n\))

\[
\text{O} + \text{RMgBr} \rightarrow \text{OH} \quad \text{R} \quad \text{p 483 - 492}
\]

iv) Acetylide/cyanide addition

\[
\text{O} + \text{R} \equiv \text{R} \quad \text{OH} \quad \text{R} \quad \text{p 492}
\]
\[
\text{O} + \text{R} \equiv \text{N} \quad \text{OH} \quad \text{CN} \quad \text{p 732 - 734}
\]

v) Wittig reaction (Add\(^n\))

\[
\text{O} + \text{R} \equiv \text{CHPPPh}_3 \quad \text{O} \quad \text{PPh}_3 \quad \text{R} \quad \text{p 734 - 737}
\]

(c) Conjugate Addition Reactions - ‘Michael’ (1,4 Addition)

\[
\text{O} + \text{CH(CO}_2\text{Et})_2 \quad \text{O} \quad \text{CO}_2\text{Et} \quad \text{CO}_2\text{Et} \quad \text{p 774 - 778}
\]
\[
\text{O} + \text{RMgBr} \quad \text{R}_2\text{CuLi better} \quad \text{O} \quad \text{R} \quad \text{p 777}
\]

(d) Reaction Of Alkenes, Alkynes And Aromatics

i) Pericyclic reactions:

Cycloadditions

\[
\text{R} \quad \text{R} \quad \text{R} \quad \text{R} \quad \text{Diels Alder}
\]
Electrocyclic reactions

\[
\begin{array}{c}
\text{MJC}
\end{array}
\]  

Sigmatropic reactions

Cope Rearrangement

ii) Friedel Crafts and related reactions

\[
\begin{array}{c}
\text{RCO}^+ \\
\text{R}
\end{array}
\]

iii) Addition of carbenes to alkenes

Simmons Smith (carbenoid)

In the main we will be looking at ionic reactions.

In CCBFR the carbonyl group is very important

as an electrophile  as a nucleophile

Also in CCBFR, organometallic compounds are important.

\[
\begin{array}{c}
\text{RMgBr - Grignard Reagents, Lithium alkyls LiR etc} \\
\text{R}_2\text{CuLi - Organocuprates}
\end{array}
\]
Carbonyl Chemistry for Forming C-C Bonds

Carbonyl compounds having an α-hydrogen act as weak (protic) acids and react with a base to yield enolate anions.

\[
\text{base} \rightarrow \text{enolate anion} \rightarrow \text{base-H}
\]

\[
\text{O} \quad \text{H} \quad \text{O} \quad \text{H} \quad \text{H} \quad \text{O} \quad \text{H}
\]

\[
\text{Ka} = \frac{[\text{H}^+][\text{CH}_3\text{COCH}_2^-]}{[\text{CH}_3\text{COCH}_3]} \quad \text{pKa} = \log\text{Ka}
\]

Presence of neighbouring carbonyl group increases the acidity of a ketone over an alkane by a factor of \(10^{40}\)!

The use of such enolate anions from carbonyl compounds is fundamental to organic synthesis and you will already have met them as intermediates in the aldol reaction and claisen condensation.

When we have two carbonyl groups adjacent to a methylene group, the acidity of the α-H is greatly increased. Because of the acidity of their methylene (CH\(_2\)) hydrogens, malonic esters, ethylacetoacetate and β-dicarbonyl compounds etc are often called active hydrogen compounds.
Active Methylene Compounds

ethylacetooacetate (ethyl 3-oxobutanoate)

diethyl malonate (diethyl propandioate)

acetyl acetone (2,4-pentandione)

2-methoxycarbonylcyclohexanone

1,3-cyclohexanedione

pKα

9 (2 x ketones)

11 (1 x ketone, 1 x ester)

13 (2 x ester)

19

25

Compare:

RCOOH 5

CH₃CH₂OH 16

HOH 16

H–C=C–H 25

CH₃CH₃ 60
Such compounds are often used in synthesis because:

1) They are readily made and cheap
2) The anion can be generated quantitatively
3) Self condensation does not occur with 1 mole of base – OH is deprotonated
4) The site of deprotonation is unambiguous
5) The enolate ions formed on deprotonation can be alkylated and acylated offering useful products.

Example:

![Diagram of active methylene compounds reaction]

Reactions of Active Methylene Compounds

1) Carbanion Alkylation

Most important use is for preparation of ketones (from β-keto esters RCOCH₂CO₂Et) and of acids from malonic esters (CH₂(CO₂R)₂).
Note:

\[ \text{OEt} \]

is the synthetic equivalent to \[ \text{CO}_2\text{Et} \]

The CO\(_2\)Et group is used to activate \(\alpha\)-carbon atom

**So Retrosynthesis**

\[ \begin{array}{ccc}
\text{R} & \rightarrow & \text{R}^+ \\
\text{CO} & \rightarrow & \text{COEt} \\
\text{RBr} & \text{synthetic equivs} \\
\end{array} \]

**Why not just use** 

\[ \text{OEt} \]

Seems OK but problems

1) In unsymmetrical case, which \(\alpha\)-position reacts?
2) Product may alkylate
3) \[ \text{OEt} \]

may prefer to react with starting ketone or product

**The use of activating group stabilises the required enolate**

so that conversion is complete with Et\(^+\)

reaction with SM cannot therefore occur

The alkyl halide is added in a separate step—no base remains to form anion of product

**Note.** The activating group is easily removed
Acids

\[
\begin{align*}
\text{CO}_2\text{Et} + \text{RBr} & \xrightarrow{1) \text{NaOEt}} \text{R}\text{CO}_2\text{Et} + \text{NaBr} + \text{EtOH} \\
\text{R}\text{CO}_2\text{Et} & \xrightarrow{1) \text{KOH} \ 2) \text{H^+}/\Delta} \text{R}\text{COOH} + \text{CO}_2 \\
\text{R}\text{CO}_2\text{Et} + \text{R'}\text{Br} & \xrightarrow{1) \text{KOH} \ 2) \text{H^+}/\Delta} \text{R}\text{COOH} + \text{CO}_2
\end{align*}
\]

**Note:** with 2 equivalents of NaOEt and a dihalide (e.g. Br(CH\text{2})_4\text{Br}) - can get cycloalkane carboxylic acids.

* e.g.

\[
\text{COOH}
\]

So *Retrosynthesis*:

\[
\text{RCH}_2\text{CO}_2\text{H} \xrightarrow{\Theta} \text{CO}_2\text{Et} + \text{CH}_2\text{CO}_2\text{H} \equiv \text{CO}_2\text{Et} \equiv \text{CO}_2\text{Et}
\]

**Practice with**

\[
\begin{align*}
\text{C}_1\text{H}_7\text{C}_2\text{H}_5\text{CO}_2\text{H} & \xrightarrow{(\text{LiAlH}_4)} \text{C}_1\text{H}_7\text{C}_2\text{H}_5\text{CH}_2\text{OH} \equiv \text{R}_1^1\text{R}_2^2\text{CO}_2\text{Et} \equiv \text{FGL} \equiv \text{R}_1^1\text{R}_2^2\text{CH}_2\text{OH} \\
& \equiv \text{1,3 diol}
\end{align*}
\]

**Note:** FGI's can be carried out on intermediates/products.

**Note especially:**

Helps in the synthesis of 1,3 diols.
Enolate Anions as Ambident Nucleophiles

e.g.

\[
\begin{align*}
\text{reacts as alkoxide} & \quad \text{acts as carbanion} \\
\text{H}_3\text{C}-\text{C}=\text{O} & \quad \text{H}_3\text{C}-\text{CH}_2
\end{align*}
\]

Site of alkylation depends, in part, on substrate

<table>
<thead>
<tr>
<th>Alkyl halides</th>
<th>C-alkylation</th>
<th>O-alkylation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CH\text{₃})\text{₂}SiCl</td>
<td></td>
<td>(CH\text{₃})\text{₂}SiCl</td>
</tr>
</tbody>
</table>

silyl enol ether

(strong Si-O bond formed)

2. Reaction of Active Methylene Compounds with Carbonyl Compounds (Knoevenagel Condensation)

\[
\begin{align*}
\text{RCH=CH}_2+\text{CO}_2\text{Et} & \rightarrow \text{RCH=CHCO}_2\text{Et} \\
\text{RCH=CHCO}_2\text{Et} & \rightarrow \text{RCH=CHCO}_2\text{H} + \text{H}_2\text{O}
\end{align*}
\]

Usually uses weak base/weak acid as catalyst, (R\text{₂}NH/HOAc). Any combination of stabilising groups can be used (CN, CO\text{₂}Et etc).
3. Michael Reaction with Active Methylene Compounds (Conjugate Addition Reaction)

Carbanions derived from active methylene compounds react with $\alpha,\beta$-unsaturated compounds by 1,4-(conjugate) addition known as Michael addition.

In retrosynthesis terms

How would you prepare
4. Dianions in Synthesis

We have discussed the regioselective reactions of this active methylene carbon (C-2) in ethylacetoacetate. Can regiospecifically trap C-4 via the dianion.

\[ \text{OEt} \quad \text{OEt} \]

\[ \text{O} \quad \text{O} \]

or \[ 2 \times \text{LiN} \text{iPr}_2 \text{(LDA)} \]

\[ \text{LiN} \]

1) NaH, 2) BuLi

or \[ 2 \times \text{LiN} \text{Pr}_2 \text{(LDA)} \]

lithium diisopropylamide

least acidic forms most reactive anion

Need two equivalents of base and second one needs to be strong (pKa>20)

\[ \text{OMe} \]

\[ \text{OMe} \]

\[ \text{R} \]

1) RX (1 equiv)

2) H^+
Carbonyl Addition and Carbonyl Substitution – Aldol and Claisen Reactions.

Usually self-condensations, these reactions combine nucleophilic attack and α-substitution as the first step.

The Aldol Condensation of Aldehydes and Ketones

![Aldol Condensation Reaction]

General for aldehydes and ketones with α-H

NB Reversible

Product favoured with RCH₂CHO

SM favoured with R₂CHCHO

Reason for dehydration

1) Acidity of α-H
2) Stability of conjugated product

Note the Aldol condensation can also be performed with acid catalysis in which dehydration usually follows (enol form is involved – mechanism p 773). NB dehydration drives the reaction when the equilibrium is unfavourable.

In retrosynthesis terms

Recognise aldol or aldol product
Unsymmetrical ketone? Regioselectivity is a problem!

Hence different products from acid and basic conditions

Claisen Condensation of Esters

Note: the only difference between the Aldol and Claisen reaction is the fate of the tetrahedral intermediate – Claisen expels alkoxide, Aldol alkoxide is protonated.
**Mixed Aldol and Mixed Claisen Condensations**

These are not very useful generally as there are four potential products. However, they can be useful if one component has no $\alpha$-H.

**Mixed Aldol**

![Mixed Aldol Reaction](image)

**Mixed Claisen Condensations**

Only successful when one of the ester components has no $\alpha$-H e.g. PhCO$_2$Et OR HCOOEt.

![Mixed Claisen Reaction](image)

Can also carry out mixed Claisen between ester and ketone

![Mixed Claisen Reaction](image)

**Synthesis of dimerone**

![Synthesis of dimerone](image)
C-C Bond Formation to Make Rings

**Intramolecular Aldol Reactions and Claisen Condensations**

When certain dicarbonyl compounds are treated with base intramolecular Aldol reactions can occur. Similarly diesters can undergo intramolecular Claisen Condensations (this reaction is known as the Dieckmann cyclisation).

### Aldol

![Aldol Reaction Diagram](attachment:image.png)

- 5 and 6 membered rings preferred

The intramolecular Aldol condensation forms the basis of a very useful method for making rings – The **Robinson Annulation Reaction**:

![Robinson Annulation Reaction Diagram](attachment:image.png)
Intramolecular Claisen Condensations – The Dieckmann Cyclisation

Reaction works best with 1,6 or 1,7 diesters to give 5 or 6 membered rings.

Regioselective Formation of Enolate Ions (p786)

Thermodynamically favoured
(More stable due to more substituted double bond)

Kinetically Favoured
Sterically hindered base rapidly removes proton from less substituted α position (where there are more of them also)

Alkylation is regiospecific:

Other Useful CCBFR’s
The Wittig Reaction (p 734)

\[
\begin{align*}
  \text{O} & \quad \text{R} \quad \text{R'} \\
  \quad \text{+} & \quad \text{R'} \quad \text{X} \quad \text{R''} \\
  \quad \text{PPh}_3 & \quad \text{Base} \\
\end{align*}
\]

Very useful method for alkene synthesis as the position of the double bond is known. The first step is formation of a Phosphorus Ylide (a neutral compound with C\(^-\) and P\(^+\)).

\[
\begin{align*}
\text{Ph}_3\text{P:} & \quad \text{BrCH}_2\text{CO}_2\text{Et} \\
& \quad \text{Ph}_3\text{P} \equiv \text{CHCO}_2\text{Et} \quad \text{Br} \\
\text{Base} & \quad \text{PH}_3\text{P} \equiv \text{CHCO}_2\text{Et} \quad \text{Br} \\
\text{Does not} & \quad \text{contribute much} \\
\text{CH}_3\text{CH} \equiv \text{CHCO}_2\text{Et} & \quad \text{Acetylene anion as a synthon for CH}_{3}\text{C} = \text{O} \\
\text{RCOR'} & \quad \text{HgSO}_4 \quad \text{H}_2\text{O} \\
\text{OH} & \quad \text{OH} \\
\text{Dithiane Anions} & \\
\text{Acyl anion equivalents which exhibit Umpolung (reversed polarity p 907). Two S} \\
\text{atoms attached to the same carbon atom of a 1,3-dithiane cause the H atoms to be} \\
\text{more acidic (pKa \(\approx 32\)) than normal alkyl C-H.}
1,3-dithianes are easily prepared from aldehydes, they are thioacetals.

\[
\text{RCHO} + \begin{array}{c}
  \text{SH} \\
  \text{SH}
\end{array} \xrightarrow{H^+} \begin{array}{c}
  \text{R} \\
  \text{S}
\end{array} \
\stackrel{\text{BuLi}}{\longrightarrow} \begin{array}{c}
  \text{R} \\
  \text{S}
\end{array} \xrightarrow{1) \text{R'}CHO} \begin{array}{c}
  \text{R} \\
  \text{S}
\end{array} \xrightarrow{2) \text{Hg}^{2+}/\text{H}_2\text{O}} \begin{array}{c}
  \text{R} \\
  \text{S}
\end{array} \xrightarrow{\text{Hg}^{2+}/\text{H}_2\text{O}} \begin{array}{c}
  \text{R} \\
  \text{S}
\end{array}
\]

Radical Dimerisation Reactions Leading To 1,2-diO Pattern

1. Pinacol Formation

Retrosynthesis

\[
\begin{array}{c}
  \text{OH} \\
  \text{OH}
\end{array} \
\xrightarrow{\text{OH}} \
\begin{array}{c}
  \text{C} \\
  \text{C}
\end{array} \rightarrow \
\begin{array}{c}
  \text{C} \\
  \text{C}
\end{array}
\]

Synthesis

\[
\begin{array}{c}
  \text{Mg/ether} \\
  \text{electon transfer}
\end{array} \xrightarrow{\text{OH}} \begin{array}{c}
  \text{Mg} \\
  \text{O}
\end{array} \xrightarrow{\text{OH}} \
\begin{array}{c}
  \text{Mg} \\
  \text{O}
\end{array} \xrightarrow{\text{H}_2\text{O}} \begin{array}{c}
  \text{OH} \\
  \text{OH}
\end{array}
\]
2. Acyloin Condensation

Similar to ester dimerisation, used traditionally to make large rings.

Now improved by addition of Me₃SiCl which traps the intermediate dianion.
So to finish -cis jasmone (Can J. Chem. 1978, Vol 56, p2301)