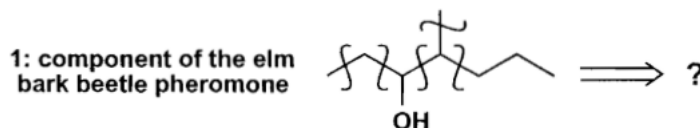


## Lecture # 12

# General Strategy A: Choosing a Disconnection

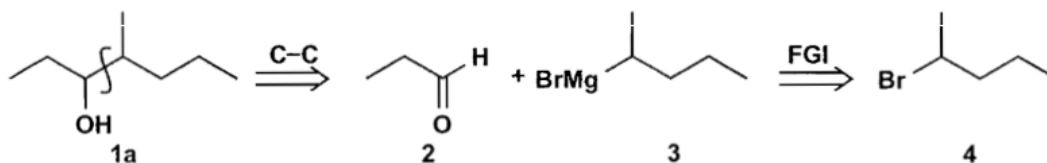
This is the first of four *General Strategy* chapters in which we discuss important points that apply to the whole of synthetic design rather than one particular area. This chapter concerns general principles to help you choose one C–C disconnection rather than another. Even a simple molecule like the alcohol **1**, introduced in chapter 1 as a component of the elm bark beetle pheromone, can be disconnected at any of the five marked bonds.



## Greatest Simplification

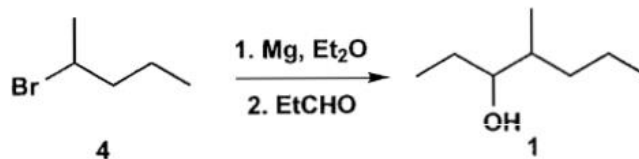
Only one of the five bonds **1a** is a good choice and for two reasons. We aim to achieve the greatest simplification in our disconnections so that we get back quickly to simple starting materials. This makes the synthesis as short as possible. So we disconnect bonds that are:

- Towards the middle of the molecule. This breaks the molecule into two reasonably equal parts and is much better than simply lopping one atom off the end.
- At a *branchpoint* in the molecule: this is more likely to give simple straight chain starting materials. Here we get the aldehyde **2** and the Grignard reagent **3** coming from the straight chain halide **4**. Both **2** and **4** are commercially available.

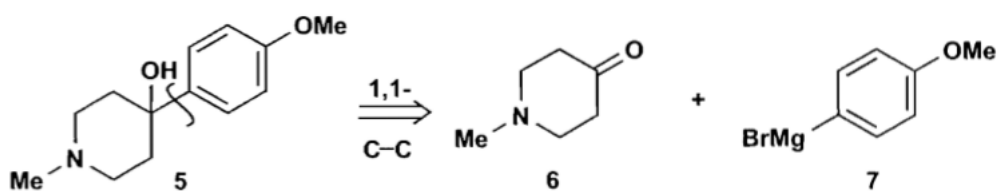


The synthesis is a one-step process derived from the chemistry we were discussing in the last chapter.<sup>1</sup>

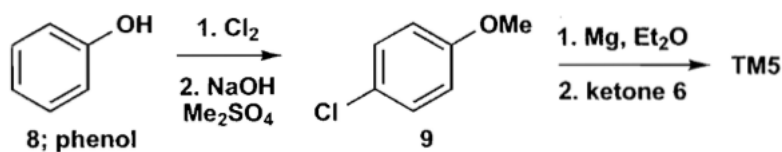
The synthesis is a one-step process derived from the chemistry we were discussing in the last chapter.<sup>1</sup>



We can extend these guidelines when we realise that a junction between a ring and a chain and, even more, a junction between two rings, is always at a branchpoint. The series of drugs based on bicyclic structure 5 has an excellent disconnection between the two rings.

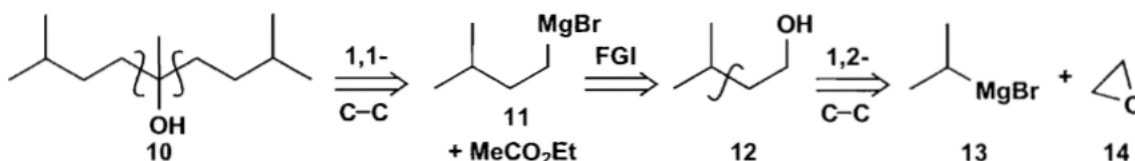


The Grignard reagent 7 is made from the halide that comes eventually from phenol by chlorination and methylation.<sup>2</sup> We shall discuss the synthesis of ketones like 6 in chapter 19.

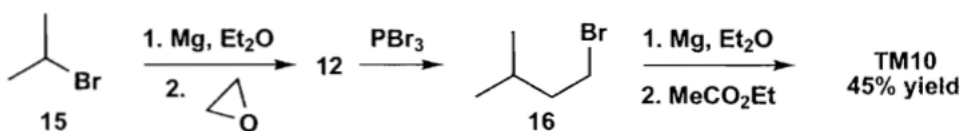


## Symmetry

We saw symmetry put to good use at the end of the last chapter and it may well help if we can do two identical disconnections at once. The symmetrical tertiary alcohol **10** can be made from two molecules of a Grignard reagent **11** and one of ethyl acetate. Then back to the alcohol **12** by FGI and a disconnection at the branchpoint gives the starting materials.



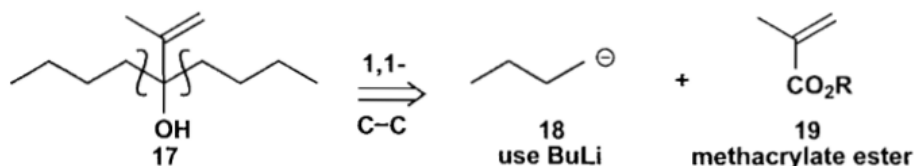
This synthesis was carried out by Grignard himself.<sup>3</sup> The bromide **16** was made from the alcohol **12** with  $\text{PBr}_3$ —a good reagent when an  $\text{S}_{\text{N}}2$  displacement is needed.



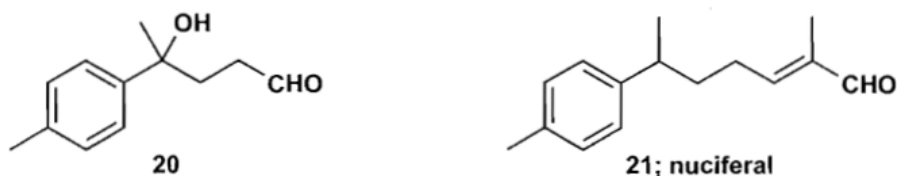
## Recognisable Starting Materials

A very practical guideline is to look for starting materials you can buy. It is obviously impossible to give a list of such compounds (though we've done our best with some simple compounds) or for any individual chemist to know what's available. In addition, what's available varies from year to year and sometimes from week to week. Then the requirements of research chemists, who often need only a gram of something, development chemists, who need kilograms, and production chemists who need tonnes are very different indeed, especially in the price they are prepared to pay. The solution is to use suppliers' catalogues. They are free on request from the main suppliers such as Aldrich or Fluka.

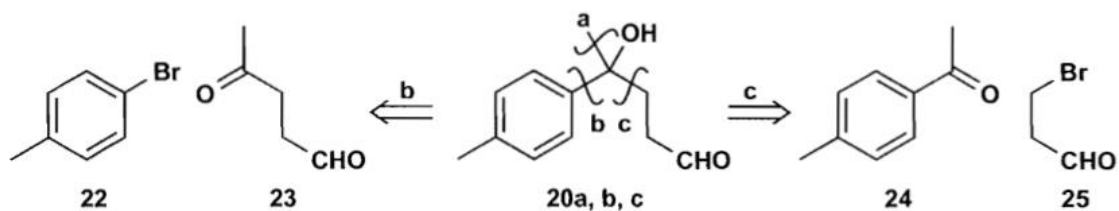
Still using symmetry, the tertiary alcohol **17** needs a butyl nucleophile and a methacrylate ester.<sup>4</sup> You can buy a railway tanker full of BuLi if you want and methacrylate esters are used in enormous quantities to make polymers. You won't always be as lucky as this.



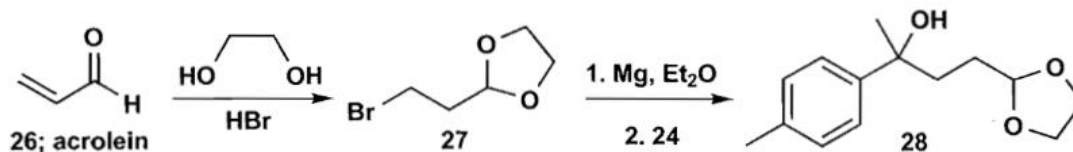
In less favourable circumstances, look for starting materials that can easily be made. The hydroxyaldehyde **20** was an intermediate in Büchi's synthesis<sup>5</sup> of the natural product nuciferal **21**.



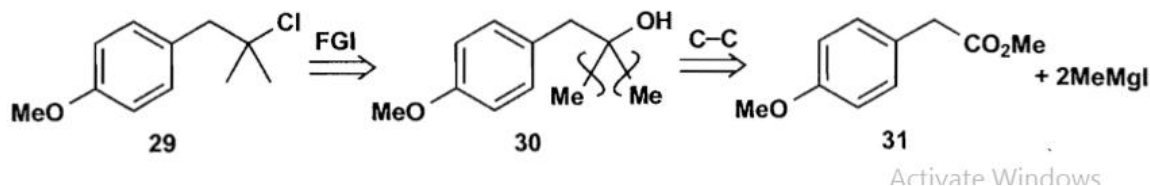
The tertiary alcohol is an obvious place to disconnect. Rejecting the poor disconnection of one carbon atom **20a**, we have a choice between **20b** and **20c** giving one of two ketones **23** or **24** and Grignard reagents made from one of two halides **22** or **25**. We can easily make **22** and **24** by halogenation or Friedel-Crafts acylation of toluene. But what about **23** and **25**?



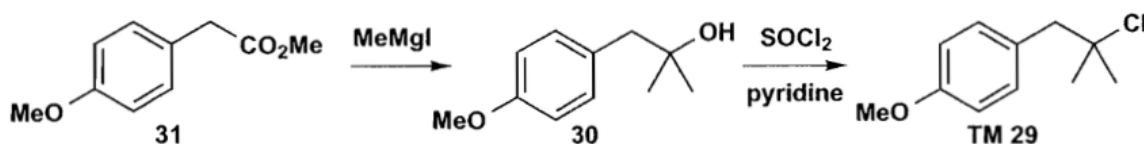
We have not met methods to make **23** and, though it could be made, there is a serious chemoselectivity problem in getting the Grignard reagent to attack the less reactive ketone in the presence of the aldehyde. Büchi preferred route **c** as he knew how to make the protected version **27** of **25** that will be needed for the Grignard reagent. We know this too as it was compound **32** in chapter 10. The Grignard reagent from **27** was combined with the ketone **24** to give a protected version of the intermediate **20**. Büchi preferred to keep the acetal in the remaining steps of the synthesis.



Returning to a series of compounds from the last chapter, Bunnett and Sridharan made one of them **29** by a different route. They went back to the alcohol as before but then disconnected the two methyl groups **30**. One reason was that it is difficult to add a MeO group to a benzene ring, but the main reason was that the methyl ester **31** is readily available.



The synthesis is straightforward but no yields are given in the paper.<sup>6</sup>



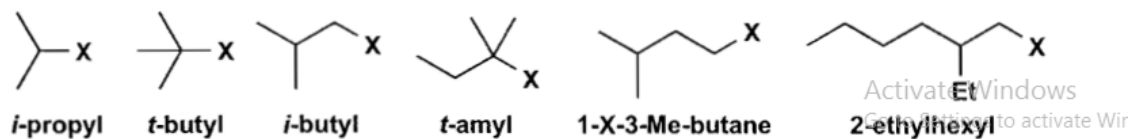
## Available Compounds

A small selection of commonly used compounds but the Aldrich catalogue has over 34,000 entries.

*Straight Chain Compounds:* C<sub>1</sub> to about C<sub>10</sub> and more in many cases

Alcohols, alkyl halides, acids, aldehydes, amines, nitriles, ketones.

*Branched Chain Compounds:* as above based on these skeletons (and others):



*Cyclic Compounds:* C<sub>4</sub> to C<sub>10</sub> and others:

Ketones, alcohols, alkenes, halides, amines.

*Aromatic Compounds:* Very considerable variety—see catalogues.

*Heterocyclic Compounds:* Saturated and unsaturated in great variety.

*Monomers for Polymers:* Butadiene, isoprene, styrene

Acrylates, methacrylates, unsaturated nitriles, chlorides and aldehydes.

## Summary of Guidelines for Good Disconnections

1. Make the synthesis as short as possible.
  2. Use only disconnections corresponding to known reliable reactions.
  3. Disconnect structural C–X bonds first and try to use two-group disconnections.
  4. Disconnect C–C bonds using the FGs in the molecule.
    - (a) Aim for the greatest simplification. If possible
      - disconnect near the middle of the molecule
      - disconnect at a branch point
      - disconnect rings from chains
    - (b) Use symmetry (if any).
  5. Use FGI to make disconnections easier.
- 
6. Disconnect back to available starting materials or ones that can easily be made.

Only some of these guidelines may apply to any given target molecule and they may well contradict each other. Developing judgement in choosing good disconnections can come only with practice. There are many different approaches to any reasonably complicated target and no 'right' answer.