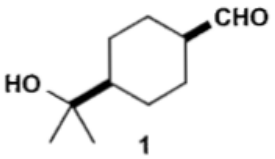
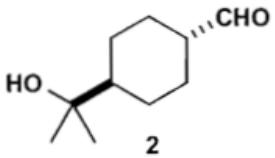
Lecture # 13

Strategy V: Stereoselectivity A

The biological properties of organic molecules depend on their stereochemistry. This is true for drugs, insecticides and insect pheromones, plant growth regulators, perfumery and flavouring compounds, as indeed for all compounds having biological activity. The *cis*-hydroxyaldehyde **1** has a strong and pleasant smell and is used in lily of the valley perfumes, whereas the *trans* isomer **2** is virtually odourless. Notice that these are diastereoisomers: the compounds are achiral. Any useful synthesis must give pure **1**, not a mixture of **1** with the more stable diequatorial **2**–at equilibrium there is 92% of **2** and only 8% of **1**.



1



2

3; chiral centres in multistriatin

The elm bark beetle pheromone multistriatin **3** is a more complicated example. You may recall from chapter 1 that a single isomer alone attracts the beetle. Making the right diastereoisomer by stereoselective synthesis is not enough. The compound must be a single enantiomer too. In this chapter we consider making the right diastereoisomer of compounds with several chiral centres and first address the question of making single enantiomers. This is only a brief discussion. You

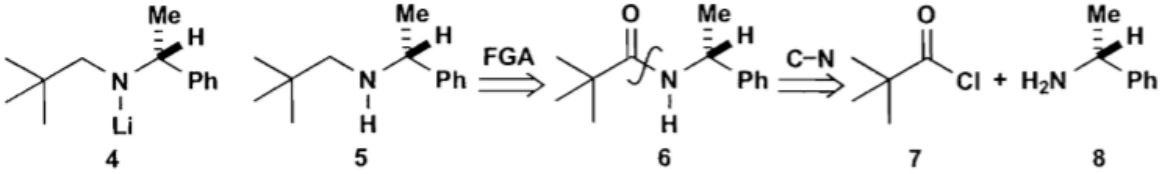
Enantiomerically Pure Compounds

We shall discuss two strategies in the making of single enantiomers. Either we can resolve a racemic compound somewhere in the course of the synthesis or we can use a single enantiomer as starting material. Other strategies are discussed in detail in *Strategy and Control*.

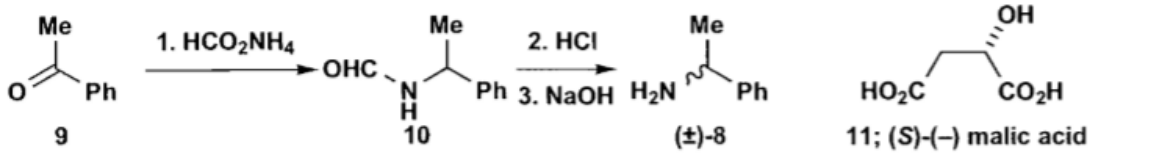
Resolution

Enantiomers cannot be separated by the normal processes of purification: crystallisation, distillation or chromatography. But diastereoisomers can. Resolution involves using an enantiomerically

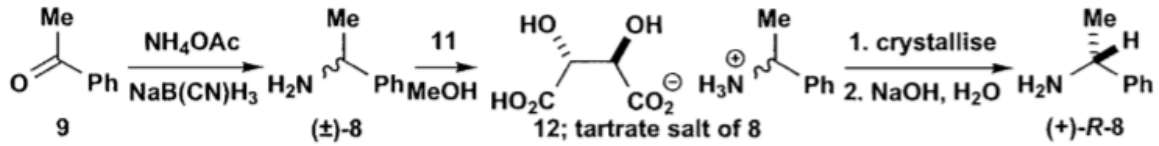
pure 'resolving agent' to convert our racemic compound into a mixture of diastereoisomers that can be separated by these processes. When Cram[3] wanted to study the stereochemistry of elimination reactions he needed a strong enantiomerically pure base that would not substitute. In other words an asymmetric version of LDA. He chose **4**, obviously obtained from **5** and BuLi. The usual FGI and C–N cleavage **6** led back to the acid chloride **7** of available pivalic acid (t-$BuCO_2H$) and the amine **8**.



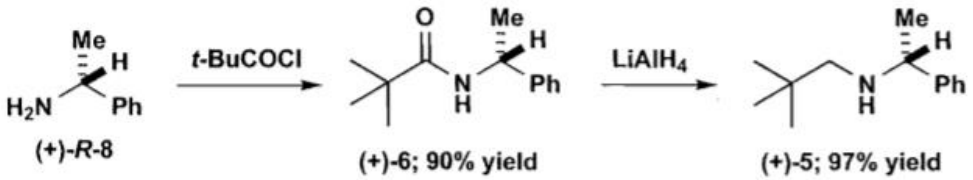
He prepared amine **8** by a kind of reductive amination of the ketone **9** via the N-formyl amine **10** and made it enantiomerically pure by resolution with malic acid **11**–a cheap enantiomerically pure compound.[4]



This would not be necessary nowadays as the preparation and resolution of **8** is an undergraduate experiment.[5] A more normal reductive amination gives racemic **8** and crystallisation of the tartrate salt **12** from methanol gives enantiomerically pure (+)-(*R*)-**8** after neutralisation. In fact this nearly perfect resolution gives both enantiomers of **8**. One tartrate salt crystallises out from MeOH and the other remains in solution. The salts are diastereoisomers and have different physical properties. Since no covalent bond is formed in making the salt **12**, simple neutralisation with NaOH gives pure amine **8** and the tartaric acid remains in solution as its sodium salt.

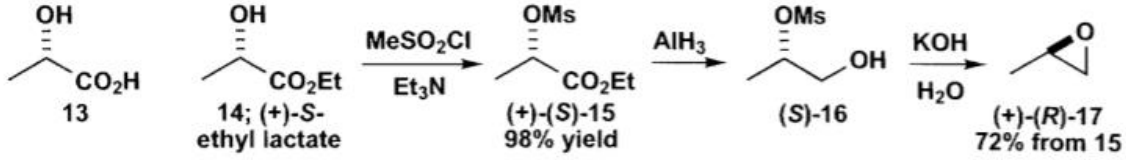


Cram finished his synthesis by making and reducing the amide **6**. Both steps go in excellent yield and, more importantly, without any racemisation as the chiral centre is not involved in either step. These principles are involved in all classical resolutions.



Enantiomerically Pure Starting Materials

There are very many enantiomerically pure starting materials available cheaply from nature. The amino acids are varied in structure and the hydroxyacids such as malic acid **11** and lactic acid **13** provide another resource. We shall give just one example of this kind of synthesis. Ethyl lactate **14** can be converted into the mesylate (a leaving group like tosylate) **15** and then reduced to the primary alcohol **16** with alane made from $LiAlH_4$ and concentrated H_2SO_4. This is not isolated but gives the epoxide **17** on treatment with base. The chiral centre is specifically inverted in the intramolecular S_N2 reaction.[6]

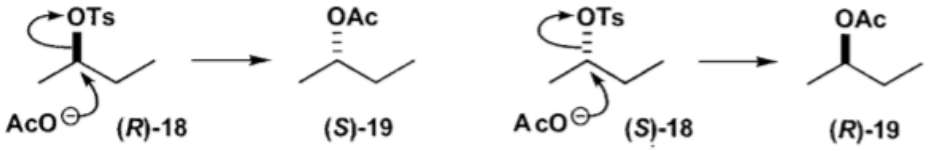


Stereospecific and Stereoselective Reactions

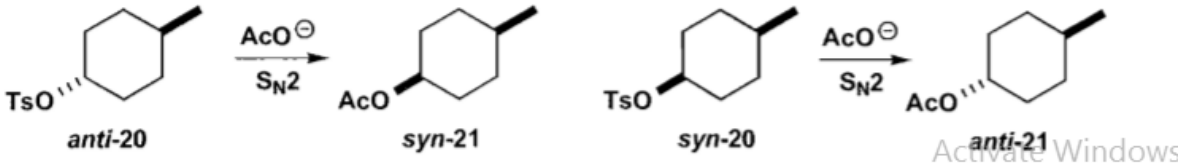
Stereospecific Reactions

Whether you are dealing with enantiomerically pure or racemic compounds, once the first chiral centre (or centres) is in place, new chiral centres must be introduced. Stereo*specific* reactions give specific and predictable stereochemical outcomes because the mechanism of the reaction demands this. The formation of **17** from **16** had to give that enantiomer as the nucleophilic oxyanion had to approach the chiral centre from the back (inversion) as all S_N2 reactions must go with inversion. Starting with enantiomerically pure materials, each enantiomer of the tosylate **18** must react in an S_N2 reaction to give an inverted acetate. One enantiomer of **18** gives one enantiomer of **19**

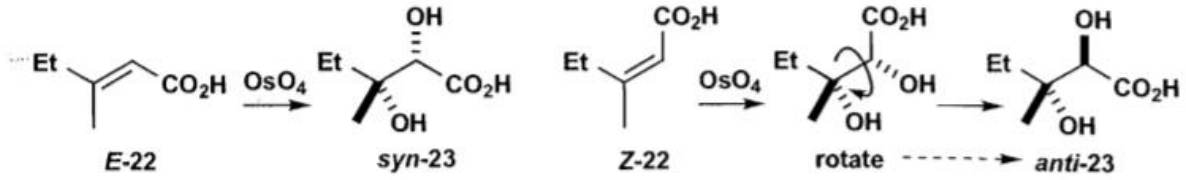
and the other enantiomer of **18** gives the other enantiomer of **19** by stereospecific inversion.



If we are dealing with diastereoisomers the same thing applies. Compound **20** is not chiral so the question of enantiomers doesn't arise but each diastereomer of **20**, *syn* or *anti* gives a different diastereomer of **21** with inversion.

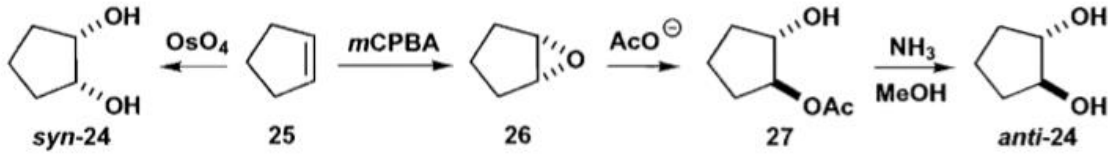


Dihydroxylation of an alkene with OsO_4 is a specifically *cis* reaction: the two OH groups add to the same side of the alkene. So *E*-**22** gives one diastereomer (*syn* as drawn) of the diol **23** while *Z*-**22** gives, by *syn* addition, a diol that can be re-drawn after rotation of a bond, as *anti*-**23**.



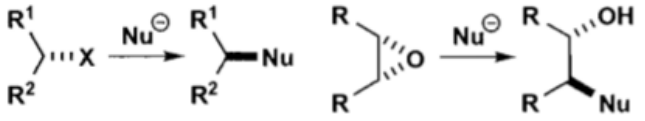
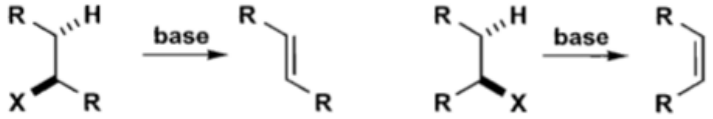
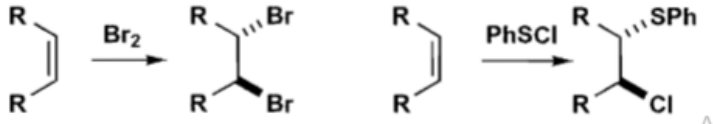
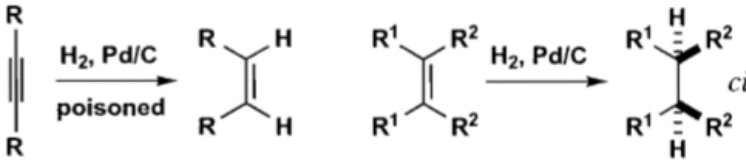
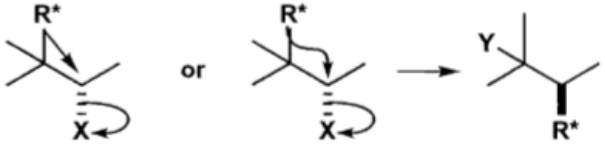
However, should you wish to make both *syn* and *anti*-diols from an alkene when only one isomer (*E*- or *Z*-) can be made, such as cyclopentene **25**, you need another method. Epoxidation

is also a *syn*-specific method but opening the epoxide ring by an S_N2 reaction inverts one of the centres to set up an *anti* relationship. Strongly basic reagents are best avoided so acetate can be used as the nucleophile and the ester **27** can be cleaved with ammonia in methanol with attack only at the carbonyl group.

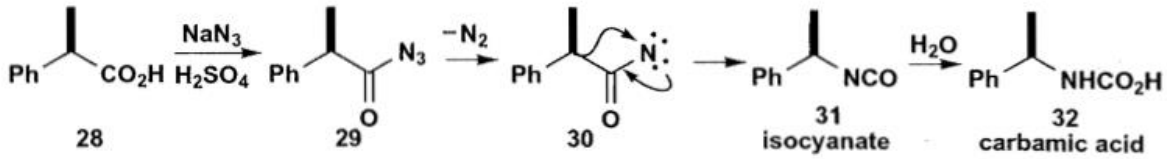


The table gives a list of a few stereospecific reactions but a knowledge of the mechanism of any reaction you contemplate in a synthesis is the one essential way to be sure of the stereochemical outcome.

Stereospecific Reactions

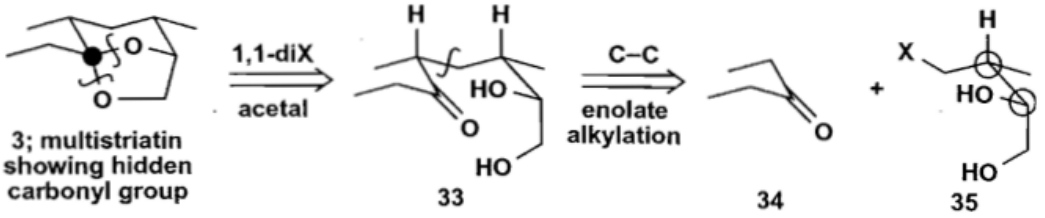
Reaction	Chemistry	Result
Substitution S_N2		inversion
Elimination E2		anti-peri-planar H and X
Electrophilic addition to alkenes		*cis* addition
Electrophilic addition to alkenes		*trans* addition
Hydrogenation of alkynes and alkenes		*cis* addition
Rearrangements		retention at R* inversion at migration terminus
Reactions not involving chiral centre(s)	anything	retention

The entry 'rearrangement' may surprise you but it can be very valuable as in an alternative synthesis[7] of the amine **8**. Enantiomerically pure acid **28** is converted into the azide **29** that loses nitrogen to give a nitrene. This nitrogen atom has only six electrons and an empty orbital into which the whole side chain can migrate **30**. It does so with at least 99.6% retention of configuration to give the isocyanate **31** that picks up water to give the unstable carbamic acid **32** which loses CO_2 spontaneously to give the amine **8**. The acid **28** is not now available in enantiomerically pure form so the resolution with tartaric acid is now preferred. In any case, both enantiomers of the amine **8** are available and we would now probably use it to resolve the acid **28**.



Diastereoselective Synthesis of Multistriatin

We promised in chapter 1 that a synthesis of the elm bark beetle would appear and here it is. It has four chiral centres but one of them (marked as a hidden carbonyl group) is unimportant. Disconnecting the acetal reveals keto-diol **33**. If we make **33** it must cyclise to **3**—no other stereochemistry is possible. Further C–C disconnection with alkylation of an enolate in mind reveals symmetrical ketone **34** and a diol **35** with a leaving group (X) at one end and the two chiral centres (marked with circles) adjacent.



The leaving group will come from an alcohol so the basic skeleton is a 1,2,3-triol **36** that is nearly symmetrical and becomes symmetrical with a C–C disconnection to the symmetrical epoxide **37**. Both starting materials **34** and **37** are available and are symmetrical: we just have to make **37**. The epoxide comes from the *Z*-alkene **38** and that can be made by Lindlar reduction of the alkyne **39**.