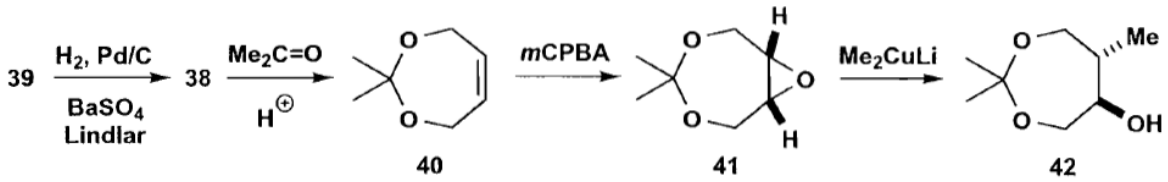
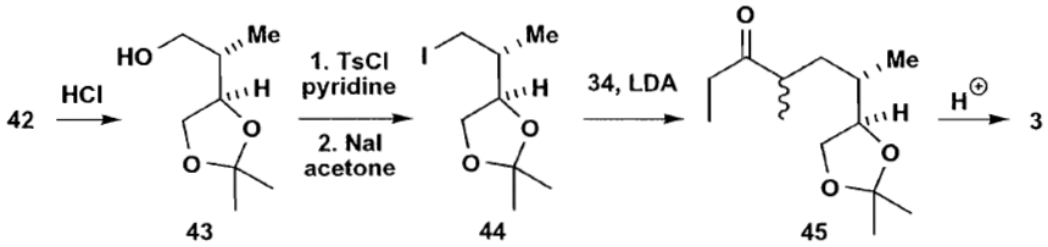
Lecture # 14

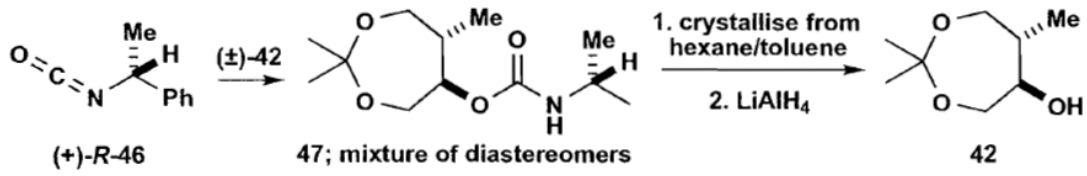
The alkyne is actually available as it is easily made from acetylene and formaldehyde. Two decisions remain: how do we distinguish the three alcohols in **36** and what reagent do we use for Me^- in the reaction on the epoxide? Protection as the cyclic acetal **40** makes epoxidation straightforward and Me_2CuLi turned out to be the best reagent for opening the epoxide. We now have two of the OHs protected **42** but they are the wrong two!



Acetal formation is thermodynamically controlled and five-membered rings are more stable than seven-membered. So the ingenious solution was to submit **42** to acid when it rearranged by acetal exchange to **43**. Now the right OH group is unprotected and it can be transformed into the iodide **44** ready for alkylation of the lithium enolate of **34**. Treatment with acid again isomerises the acetal **45** into multistriatin **3** with loss of acetone. No attempt was made to control the centre next to the carbonyl group in **45**: cyclisation gave 85% of **3** with an equatorial methyl group[8] and only 15% of the other diastereoisomer resulting from the uncontrolled centre in **45**.



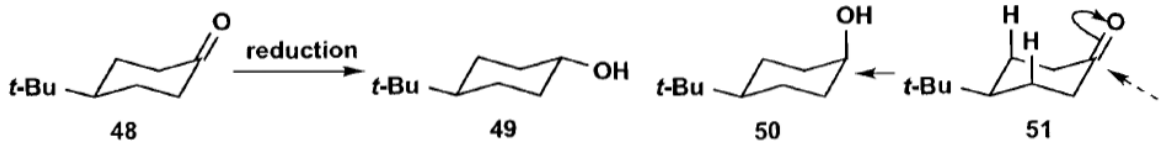
But it is important that multistriatin be made in enantiomerically pure form as well as one diastereomer. Looking back over the synthesis, the first chiral intermediate is **42** and, after some failures, reaction with the isocyanate (+)-(*R*)-**46** gave a mixture of the urethanes **47** that could be separated by crystallisation. Removal of the urethane by reduction with $LiAlH_4$ gave enantiomerically pure alcohol **42** from which enantiomerically pure (>99%) multistriatin **3** could be made by the methods above.



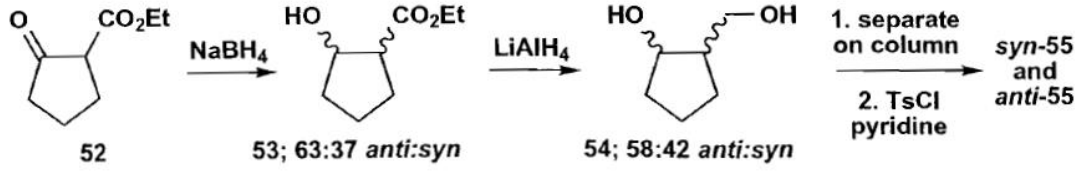
Stereoselective Reactions

We shall use *stereoselective* to describe reactions that have two mechanistically acceptable but stereochemically different pathways so that the molecule may *select* the more favourable—i.e. faster—pathway (kinetic control) or the more stable product (thermodynamic control). These reactions commonly involve setting up one or more new chiral centres in the presence of others.

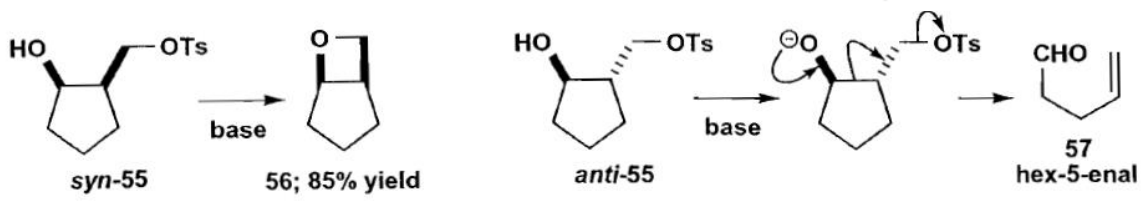
The ketone **48** could be reduced to either alcohol **49** or **50**. The equatorial alcohol **49** is more stable and so equilibrating reducing agents like *i*-PrOH with $(i\text{-PrO})_3\text{Al}$ give[9] mainly **49**. But the equatorial approach **51** is kinetically favoured as the two marked axial Hs hinder approach from the other side. Large reducing agents like $\text{LiAlH}(\text{O}t\text{-Bu})_3$ give[10] mostly the axial alcohol **50**.



Sometimes both diastereomers of a compound are needed and then poorly diastereoselective reactions are a boon. Both *syn* and *anti* tosylates **55** were needed to study the stereochemistry of reactions.[11] Reduction of the ketoester (see preparation in chapters 19 and 21) in two stages gave a mixture of *syn* and *anti* diols **54**, separable by column chromatography.

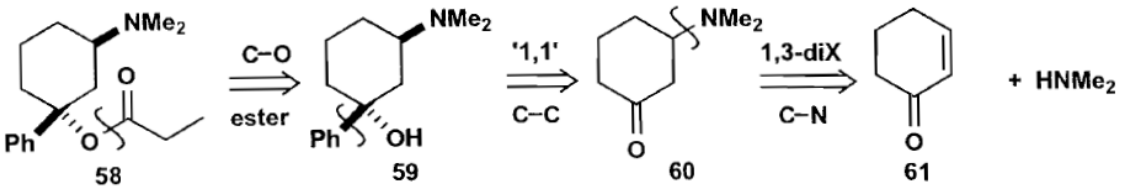


Each diol was selectively tosylated on the primary alcohol to give *syn* and *anti* tosylates **55** which were each treated with base [the anion of DMSO: MeS(O)CH_2^-]—*syn*-**55** cyclised to give the bicyclic ether **56** in good yield while *anti*-**55** fragmented to give volatile hexenal **57**.

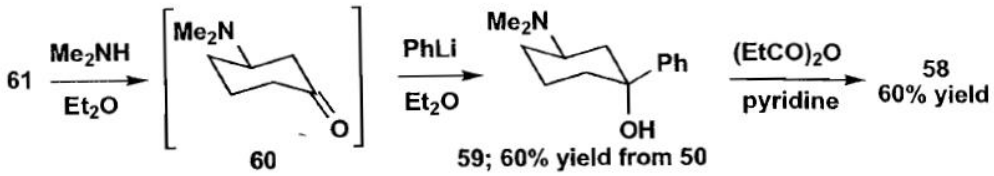


Conformational Control in Six-Membered Rings

If a new chiral centre is formed on a saturated six-membered ring, conformational control is a possibility. We have already seen conformational effects in the reduction of ketone **48** and the same kind of arguments apply to attack on ketones by carbon nucleophiles. The alcohol **59**, needed to make an analgesic **58**, can obviously be made from the ketone **60** and that is the result of conjugate addition to cyclohexenone.[12]



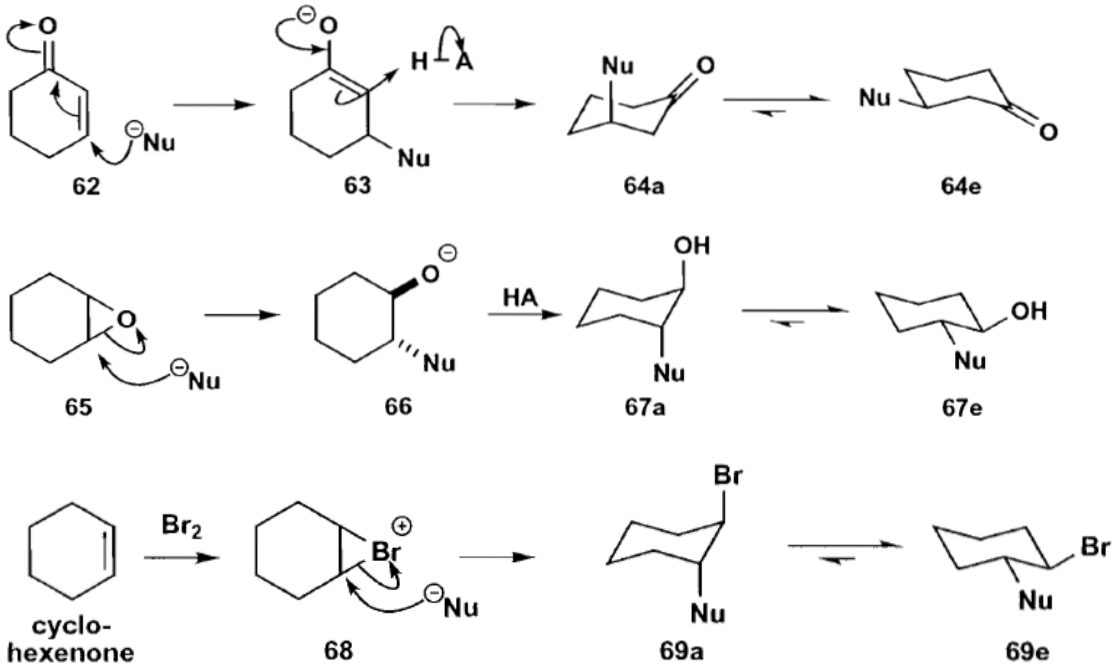
Addition of Me_2NH to cyclohexenone followed by reaction with PhLi, without isolation of **60**, gives **59** in 60% overall yield. As you would expect, a large nucleophile such as PhLi prefers to add from the equatorial side. Notice that it adds to **60** on the *same* side as the Me_2N group—obviously nothing to do with steric hindrance. The Me_2N group merely fixes the conformation and the PhLi then adds equatorially. Acylation with the anhydride gives the drug **58**.



Axial Attack to Make a Chair

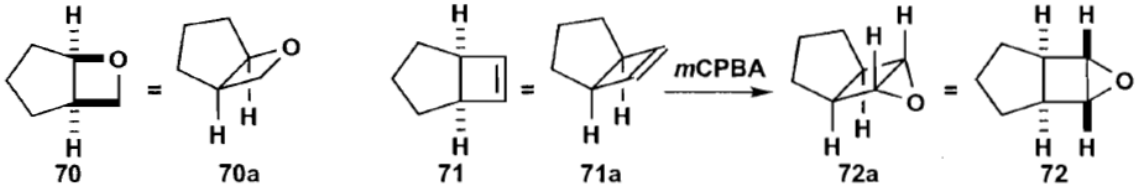
When the starting material is not a chair but a flattened chair, the first priority is to make a proper chair for the product. Strangely this means axial attack by nucleophiles on such electrophiles as

cyclohexenone **62**, epoxides **65**, and bromonium ions **68**. Though the products rapidly equilibrate to all equatorial conformations **64e**, **67e** and **69e**, they are formed initially in axial **64a** or *trans*-di-axial conformations **67a** and **69a**.

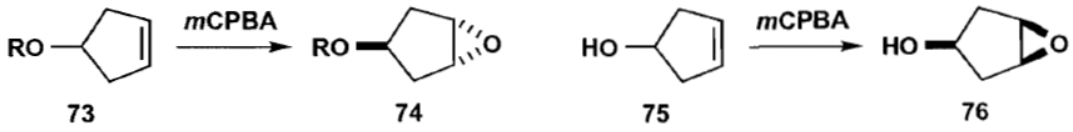


Stereochemical Control in Folded Molecules

If two small rings (3-, 4- or 5-membered) are fused together (that is with two adjacent atoms common to both) they must have *cis* stereochemistry at the ring junction and a folded conformation like a half-opened book. We saw earlier that **70** had to have a *cis* ring junction: the compound *anti*-55 that might have cyclised to the *trans* ring junction fragmented instead. This compound has a folded conformation **70a**. We shall deal with folded conformations in chapter 38 but meanwhile, notice that **70a** and **72a** show an 'outside' (the cover of the book) and an 'inside' (the pages of the book). Epoxidation of **71** goes on the outside of the folded molecule to give **72.**



Control in epoxidation of small rings by another substituent is easy to understand as the rings are virtually flat and we do not have to worry about axial and equatorial substituents. So the simple (achiral) cyclopentene **73**, with a large substituent (R = *t*-BuMe$_2$Si) on the ring, gives the *anti*-epoxide 74 because of steric hindrance. However, the free alcohol **75** epoxidises on the same face as the OH group to give **76**. The only reasonable explanation is that the OH group hydrogen bonds to the reagent and delivers it to the same face.[13]



73 **74** **75** **76**