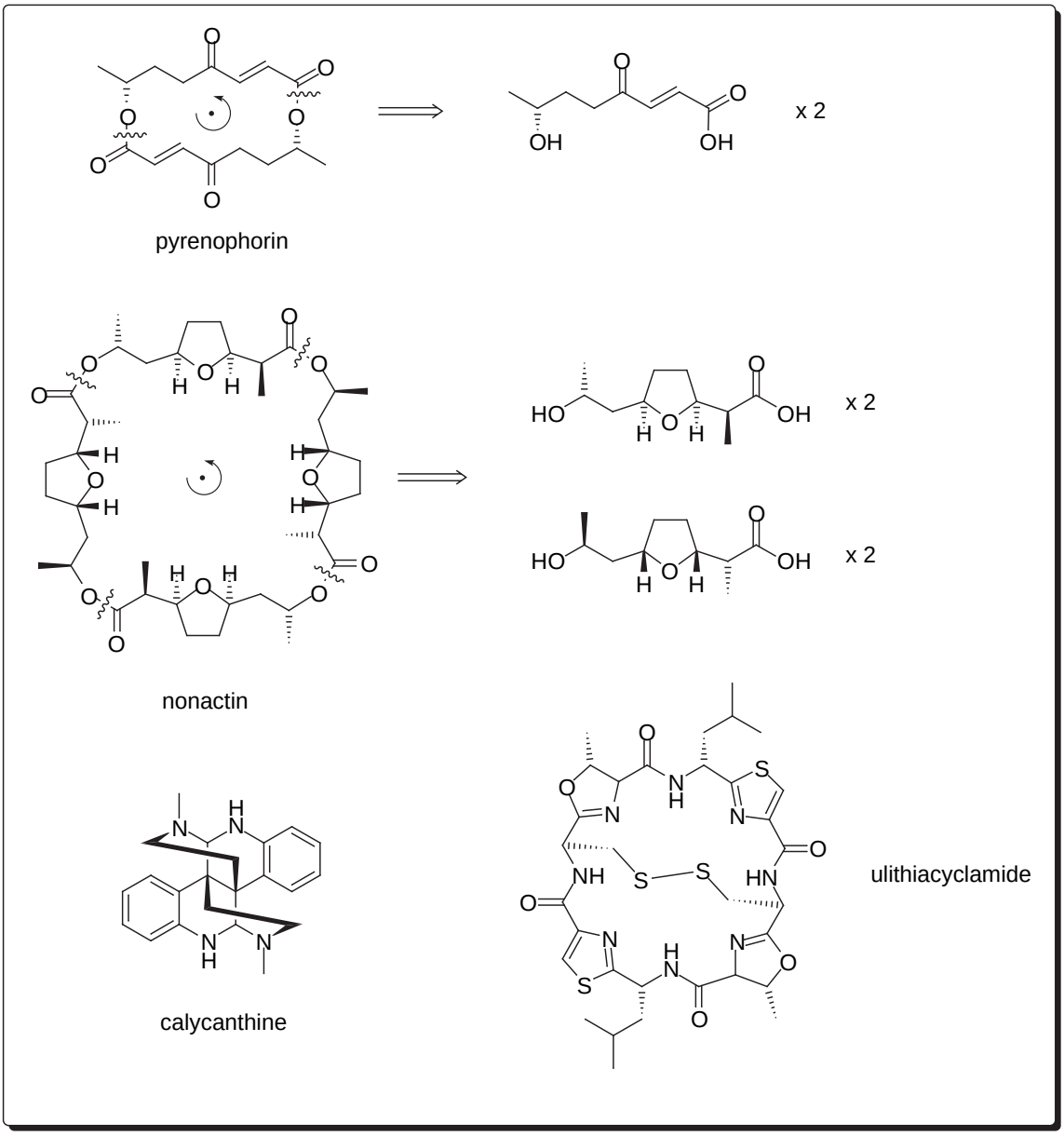
VIII Fortuitous Symmetry Elements and Pattern Recognition

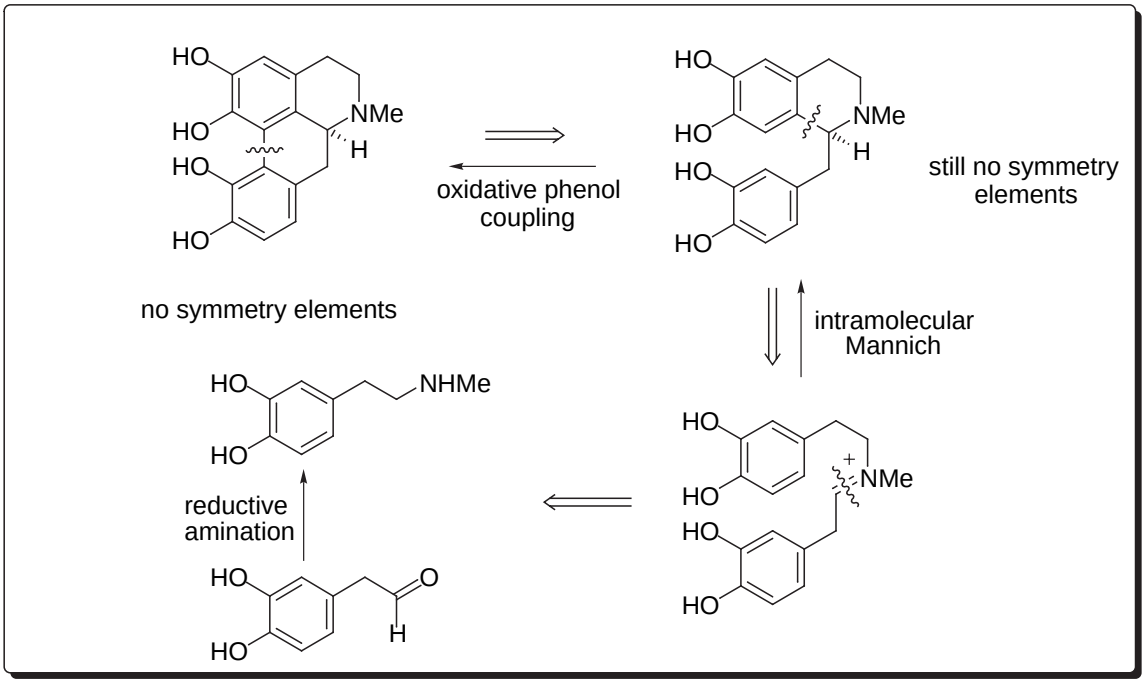
Many natural products, or sub-units within them, possess elements of symmetry; some are very obvious, others less so. However if they can be recognised and exploited in a synthetic strategy, they usually reduce the number of steps and greatly simplify the problem.

Examples:

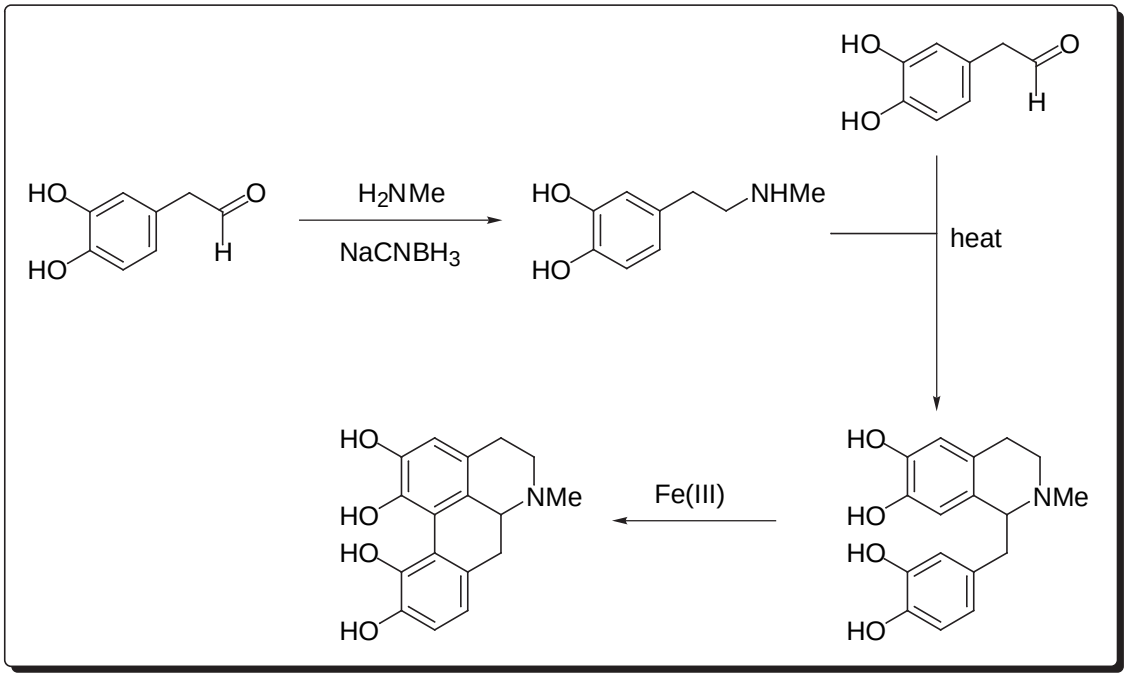


Symmetry in molecules is often disguised. Dimerisation reactions are frequently observed in biosynthetic pathways. Subsequent transformations however can make the two monomers difficult to identify.

Consider a retrosynthesis for the following benzyl *iso*quinoline alkaloid:



The molecule looks as though it may be a dimer of a functionalised catechol but in its natural form there are no obvious symmetry elements. Two strategic disconnections reveal a possible synthetic approach starting from the catechol aldehyde.



This synthetic approach would be described as **BIOMIMETIC** in that Nature constructs this molecule in a similar way, although obviously with different reagents and under milder conditions.

VIII.A Two-Directional Synthesis

Using two-directional synthesis, a molecule is constructed by starting from a central core and moving outwards in *two* – rather than just one – directions. Two reactions are therefore performed at a time installing two identical functional groups in each step. This strategy is therefore only applicable to molecules possessing a relatively high degree of symmetry. Two-directional syntheses generate symmetrical products; however at some point it is usually necessary to break up the symmetry, most commonly by differentiating the chain termini. This can be achieved in a number of interesting and creative ways depending on the type of symmetry element present in the chain. We will see later how two-directional chain synthesis has been applied with particular success to the preparation of the skipped (1, 3, (2n+1)) polyol motif found in an important class of polyketide macrolide antibiotics.

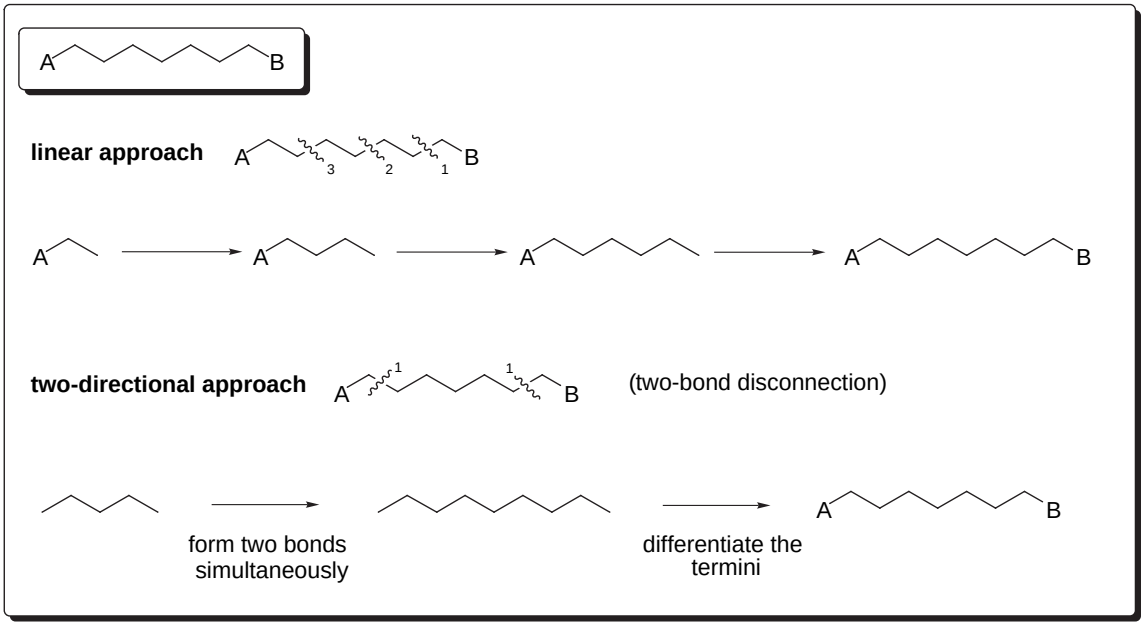
For good reviews:

i) S. R. Magnuson, *Tetrahedron*, 1995, **51**, 2167-2213.

ii) C. S. Poss, S. Schreiber, *Acc. Chem. Res*., 1994, **27**, 9-17.

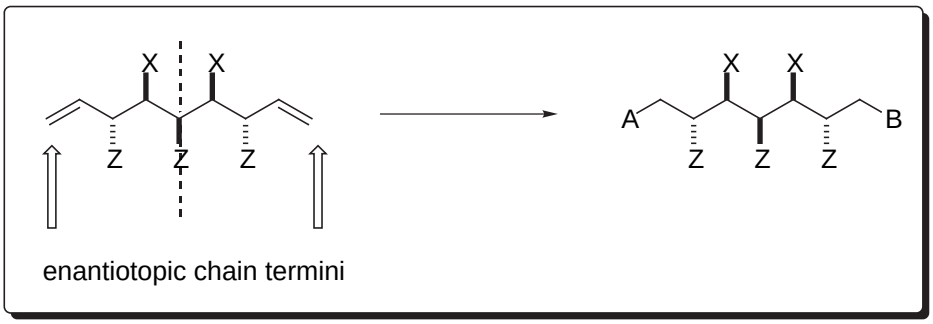
Two-Directional Approach to Acyclic Chain Preparation

Compare the linear and two-directional approaches.



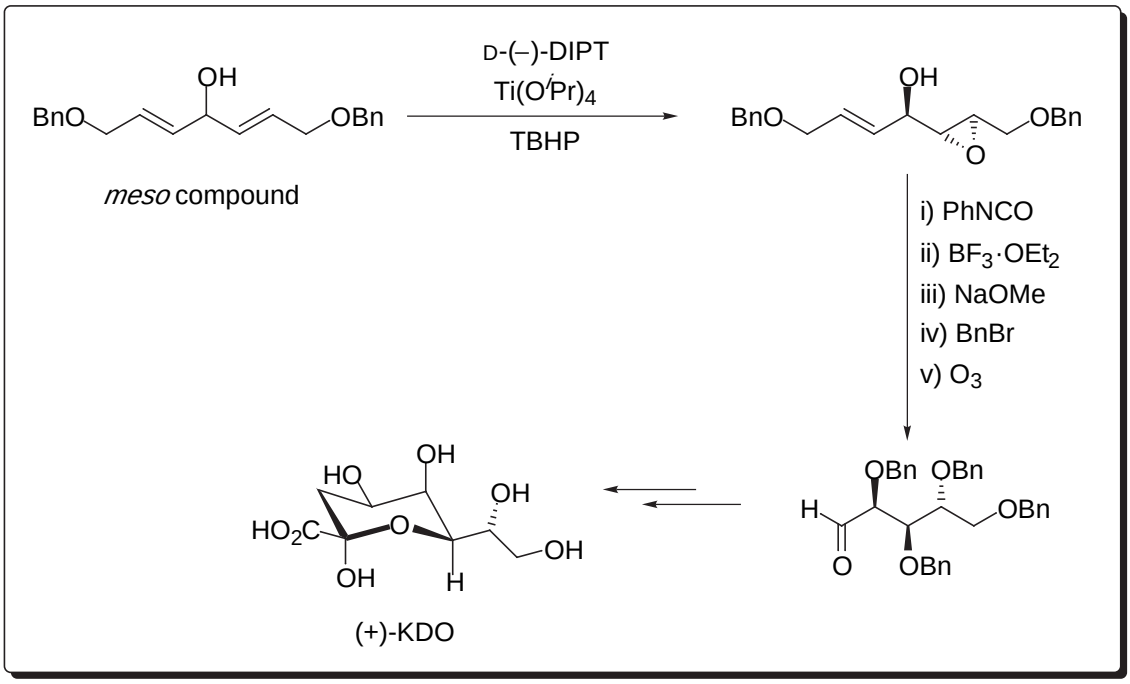
A number of approaches can be used to differentiate the chain termini. These are best illustrated by example.

VIII.A.1 Achiral Chain (including *meso* compounds)



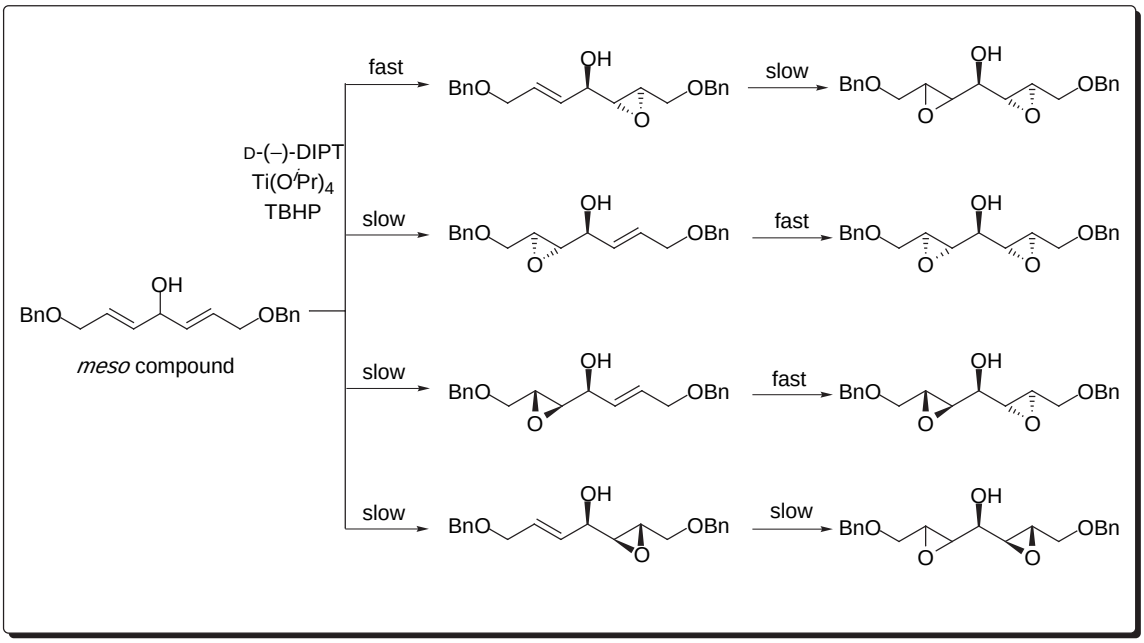
In this case the molecule is not chiral until the enantiotopic termini have been differentiated.

Schreiber's synthesis of (+)-KDO:



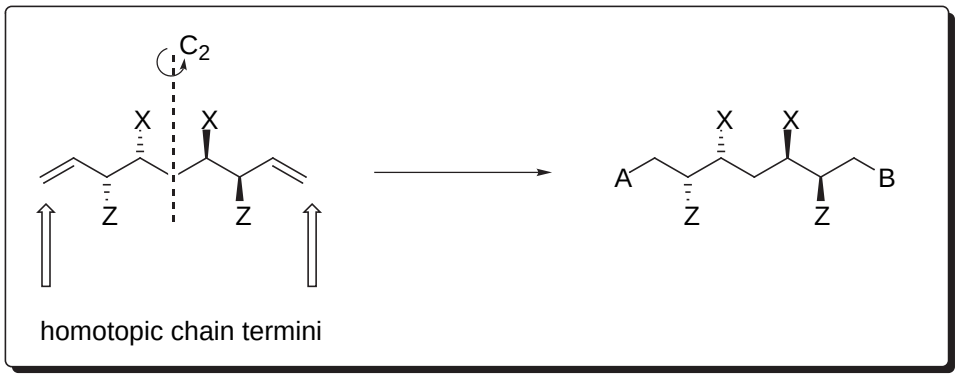
The key step involves a Sharpless Asymmetric Epoxidation, which is an excellent method for desymmetrising this type of system:

- the reaction exhibits very high diastereo- and enantiofacial selectivity.
- minor stereoisomers are 'destroyed' in a kinetic resolution:



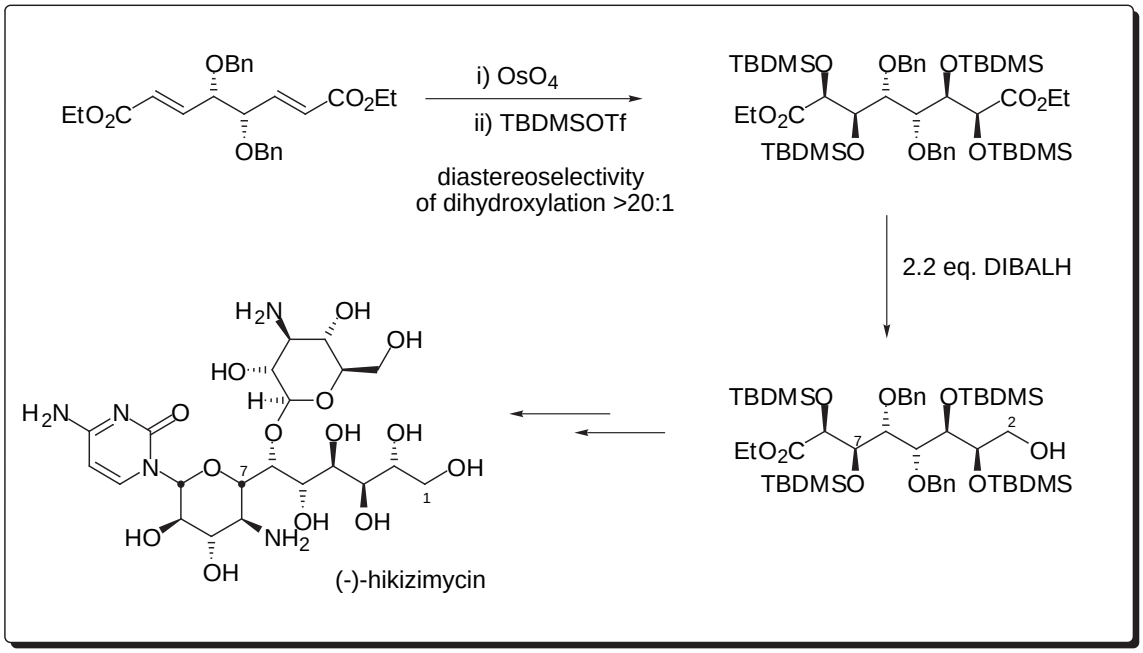
VIII.A.2 C_2-Symmetrical Chain

In this case the terminal groups are homotopic and therefore monofunctionalisation is sufficient to differentiate the chain termini.



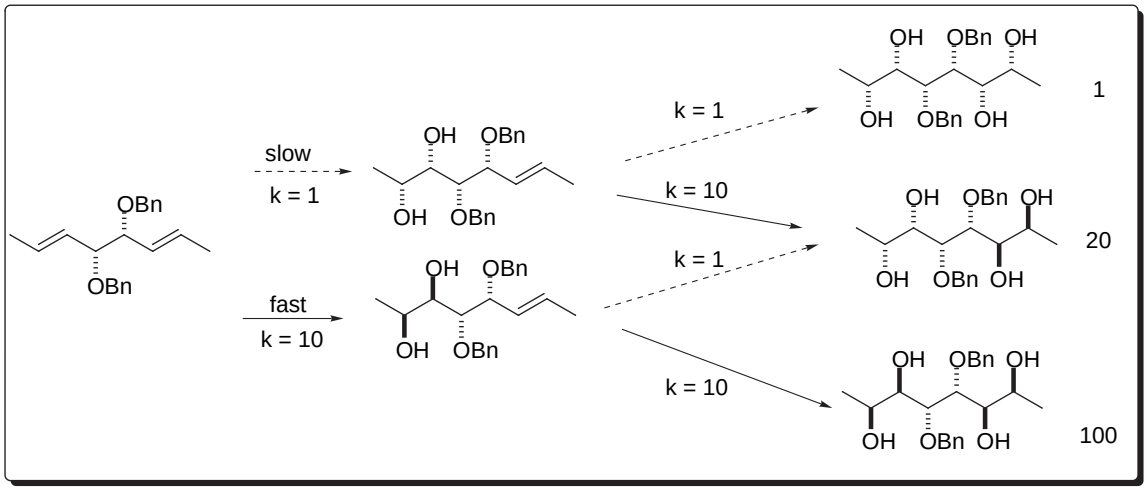
One way in which this type of chain can be prepared, is by simultaneous homologation of a C_2-symmetrical starting material.

Example:



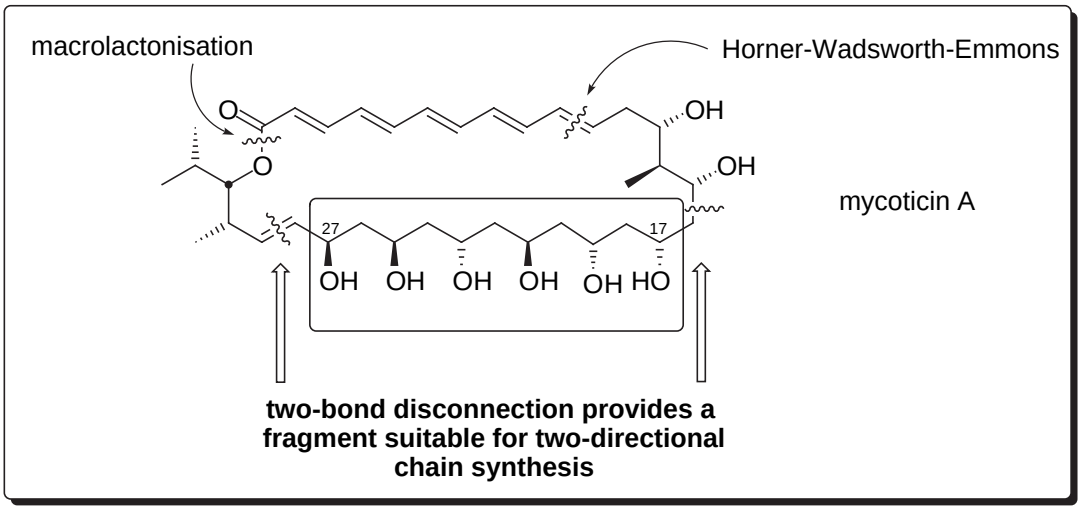
N. Ikemoto, S. L. Schreiber, *J. Am. Chem. Soc.*, 1992, **114**, 2524-2536

Note the effect of carrying out the reaction twice: if the diastereoselectivity of dihydroxylation for each olefin is 10:1, then the expected diastereoselectivity of the double reaction (assuming the intermediates react at a similar rate and selectivity) is 100:20:1 as illustrated below.

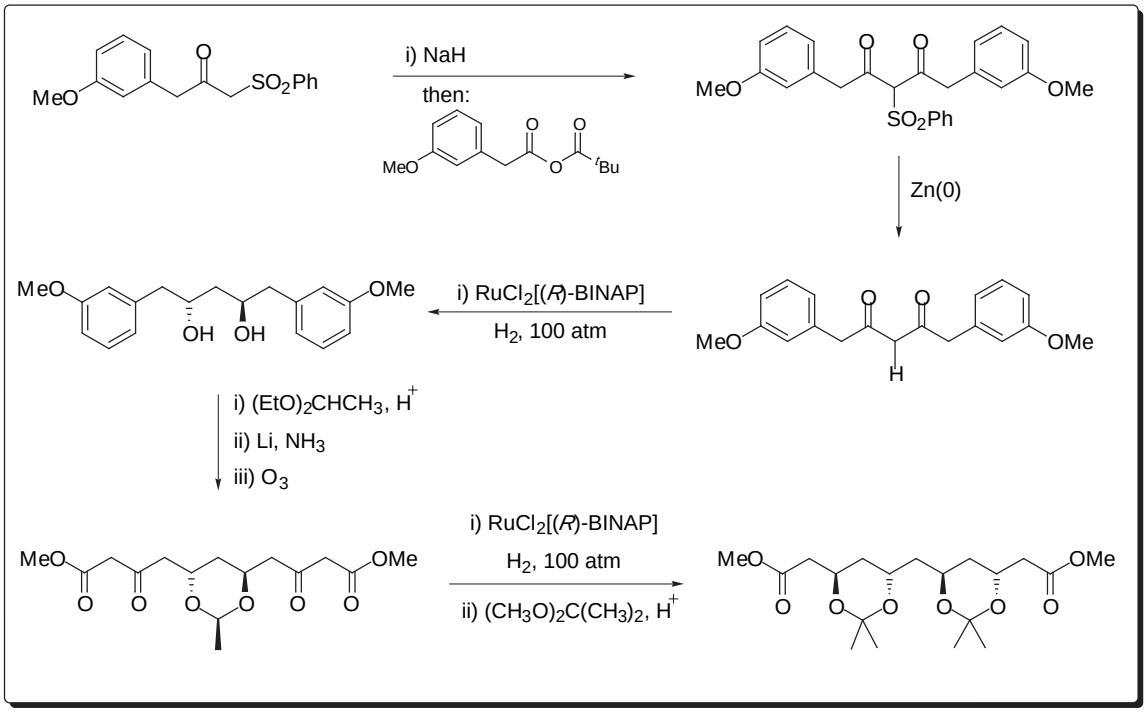


Synthesis of (+)-Mycoticin A

C. S. Poss, S. D. Rychnovsky, S. L. Schreiber, *J. Am. Chem. Soc.*, 1993, **115**, 3360-3361



We will only consider the preparation of the symmetrical polyol fragment.



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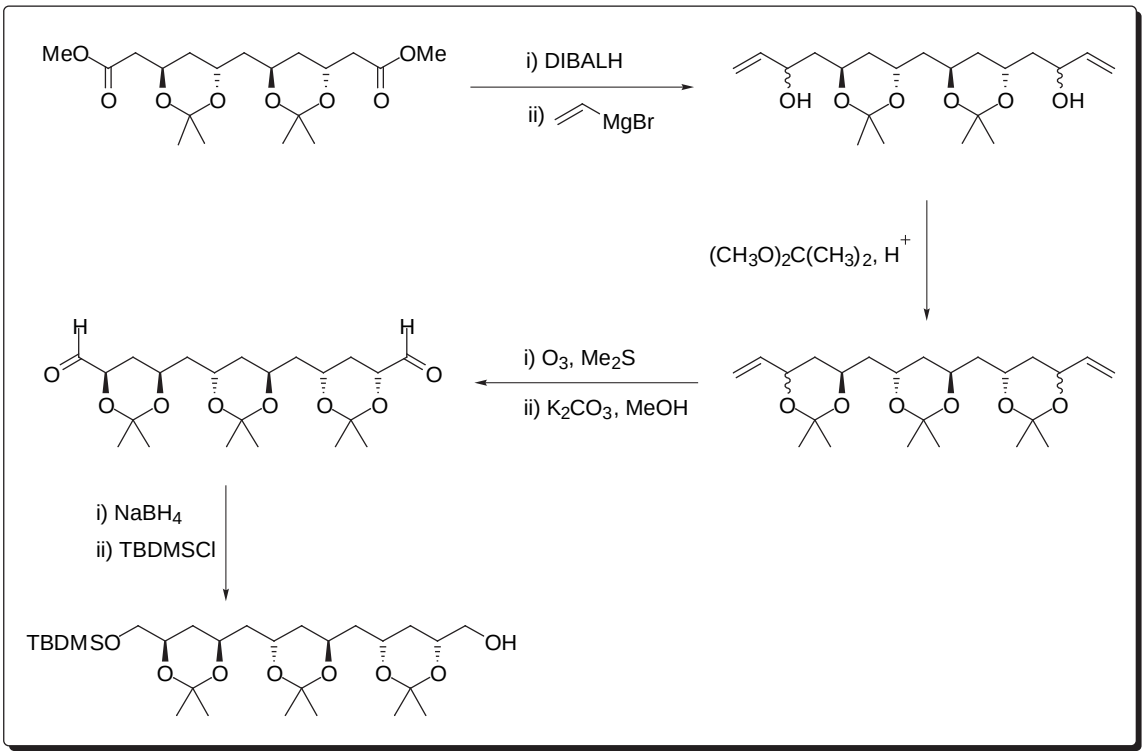

Make sure you can rationalise each step in this synthetic sequence.

Summary

Many molecules or sub-units within molecules possess elements of symmetry, which, if recognised, can be very helpful in designing efficient synthetic sequences. We have concentrated on one approach, two-directional synthesis. Clearly this strategy can only be applied to a limited number of molecules; however, when suitable symmetry elements are present, it provides a very efficient synthetic strategy.