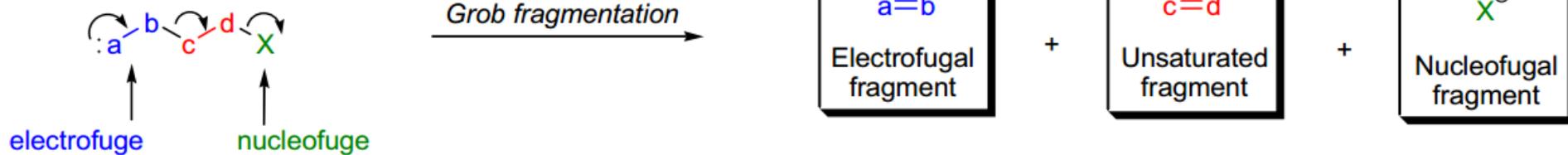


The Grob Fragmentation



Cyril A. Grob (1917 – 2003)

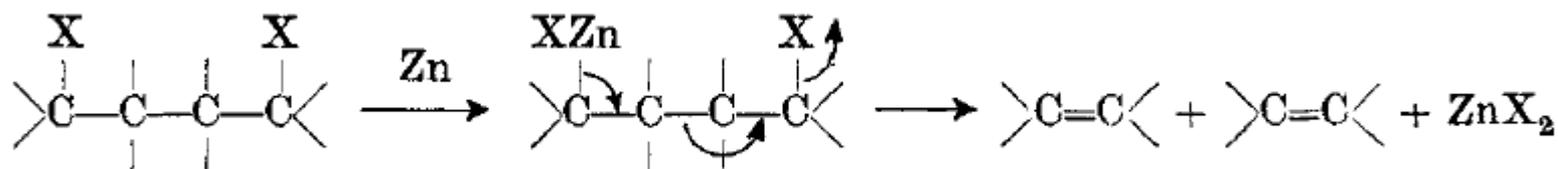
- Born in London to Swiss parents in 1917
- Studied Chemistry at ETH Zurich
- Carried out a PhD for Leopold Ruzicka (Nobel Prize in Chemistry 1939) in 1943 on artificial steroidal antigens
- Moved to Basel and worked with Taddeus Reichstein at a Pharmaceutical Institute then for the Organic Chemistry section of the University in 1947
- Became director of the Institute then in 1960 became the chair
- In 1987 he was given emeritus status
- 15th December 2003 he died at home in Basel aged 86



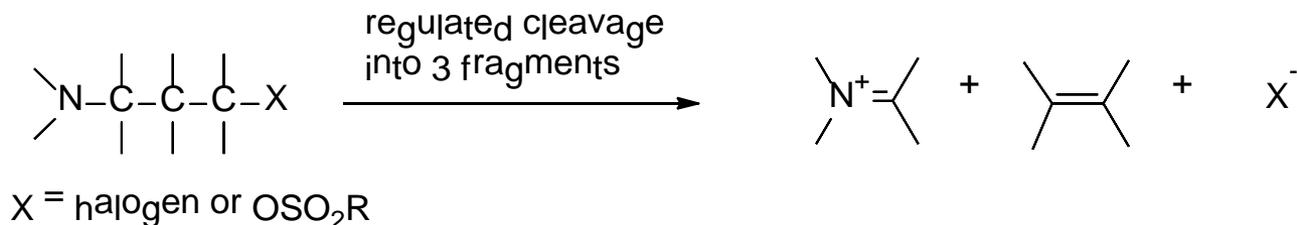
Cyril A. Grob

Discovery of the Grob fragmentation

An investigation of the reductive elimination of bromine from 1,4-dibromides in the presence of zinc led in 1955 to the recognition of heterolytic fragmentation as a general reaction principle. The elimination of the halogen from saturated 1,4-dihalides led to the formation of two olefinic bonds.



The structural and stereochemical prerequisites for a fragmentation to occur were investigated with model systems, such as γ -aminohalide or γ -aminosulfonates:

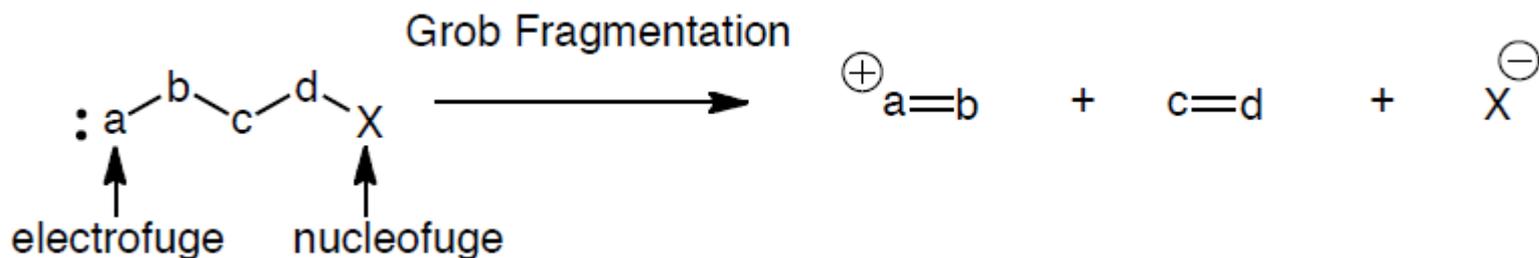


The heterolytic fragmentation is now termed the Grob fragmentation

These studies also led to the elucidation of the mechanism of the Beckmann rearrangement.

The general mechanism

Grob fragmentation: An interesting and generally useful skeletal transformation, involving specific carbon-carbon bond cleavage with accompanying conversion of certain sigma-bonds to pi-bonds.

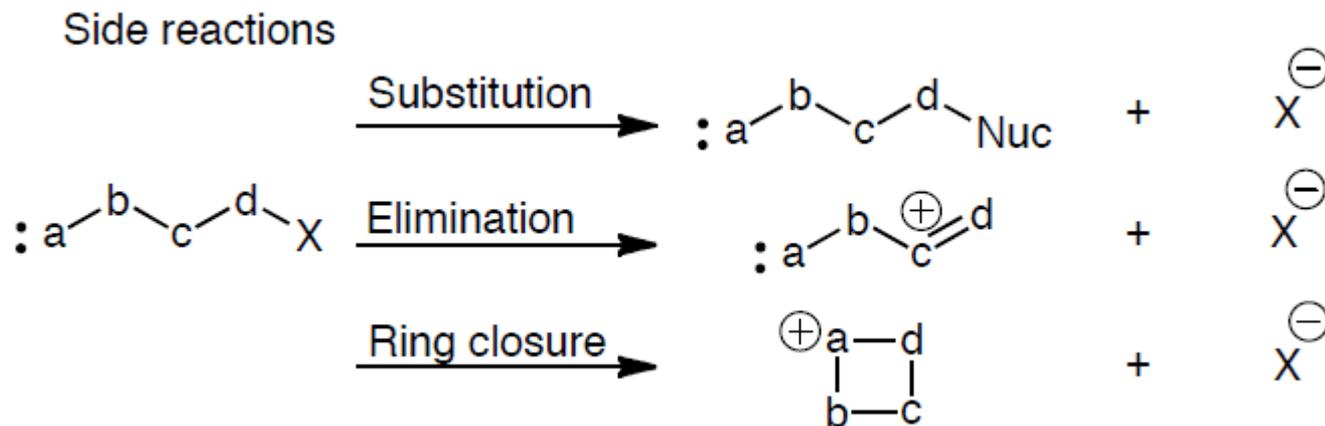


An **electrofuge** is a leaving group, which does not retain the bonding pair of electrons from its previous bond with another species.

A **nucleofuge** is a leaving group, which retains the lone pair from its previous bond with another species



Other reaction paths for this system



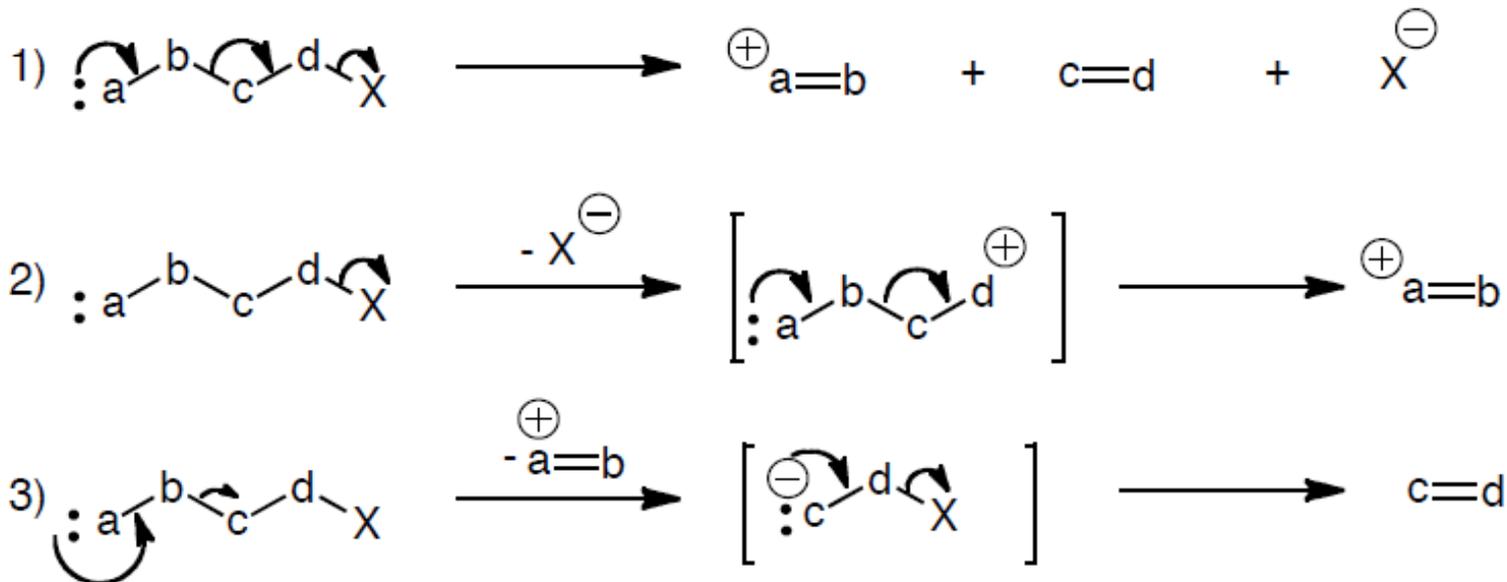
In nucleophilic solvent; water or alcohol it is possible for alternative reactions to occur:

- 1) Substitution of the nucleofugal group X with the solvent
- 2) Elimination of the nucleofugal group X
- 3) Attack of the lone pair on the electrofugal group (a) on d and loss of the nucleofugal group X resulting in ring closure

Fragmentation is the main pathway, as the alternative routes can be disfavoured or excluded by optimisation of the stereoelectronic geometries or due to ring strain in cyclic substrates.

Three potential mechanisms for the Grob

There are three potential mechanisms as the bond break sequence may occur as a one or two stepped process:



Certain structural and stereoelectronic requirements determine which mechanism is used. These are similar mechanisms to the known 1,2 elimination to give olefins.

Three potential mechanisms for the Grob

- 1) One stepped process, simultaneous loss of the electrofugal group and nucleofugal group



Three potential mechanisms for the Grob



2) Two stepped process, firstly loss of X generating a carbocation then break down to the two olefinic species if following the fragmentation route (similar to E1 or S_N1)

However the carbonium ion can further react via elimination, substitution, or ring-closure.

The rate-determining step is the ionization to the carbonium ion. The tendency to ionize is greater when a tertiary and thus stable carbonium ion is formed.

The leaving ability of X^- is important as it can lead to an increased ionization rate (e.g. $Cl < Br < I$)

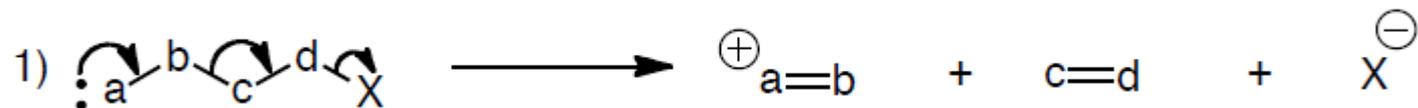
Three potential mechanisms for the Grob



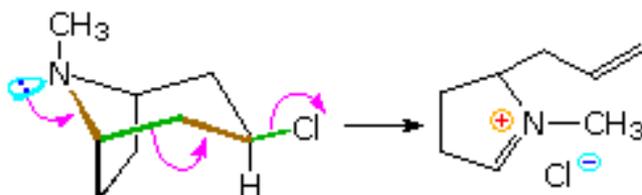
3) Two stepped process, firstly loss of electrofugal group generating a carbanionic species then break down to give olefin and release of X (rarer)

This can only occur if the carbanion is stabilized by electron-withdrawing substituents and if X is a poorer leaving group.

The synchronous mechanism

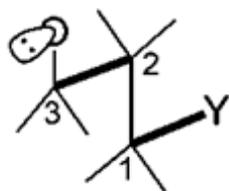
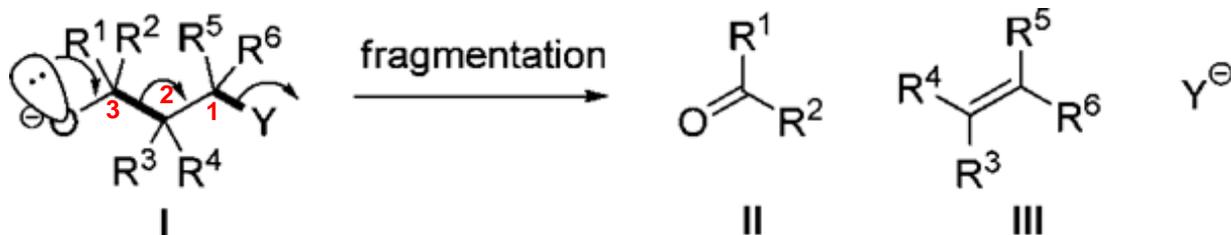


- Involves 5 atomic centres of 1 molecule in a transition state therefore requiring rigorous structural and stereoelectronic requirements.

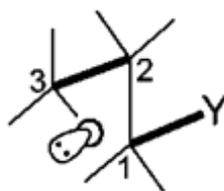


- The orbitals of the bonding and non-bonding electron pairs participating in the reaction must be aligned properly, i.e. the non-bonding pair of the nitrogen (e.g. **a**) and the bonding pairs in the green-coloured covalent bonds (the reacting electron pairs, **b-c** and **d-x**) are anti relative to the brown bonds (**a-b** and **c-d**). This is the preferred configuration for maximum overlap.

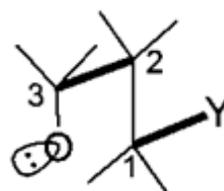
The anti-peri planar configuration



IVa



IVb

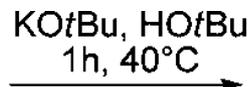
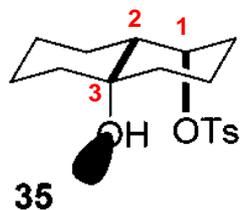


IVc

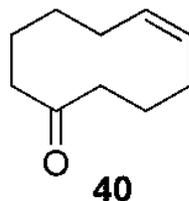
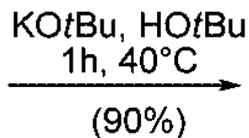
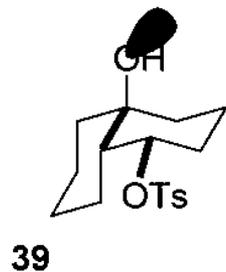
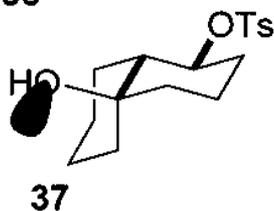
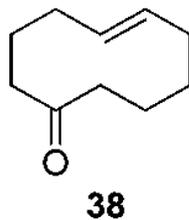
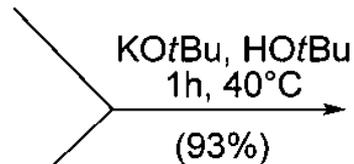
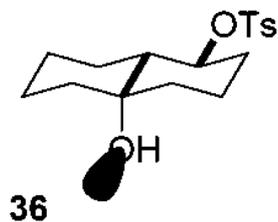
The lone pair on O, the $C2-C3$ and $C1-Y$ σ -bonds must be *anti*-periplanar for maximal orbital overlap in the transition state of the p-orbitals in the newly formed π -bond.

The relative configuration at $C1$ and $C2$ is transformed into the *E/Z* geometry of the olefin. The all-*anti*-periplanar arrangement is met in the staggered conformation **IVa** and its rotamers **IVb** and **IVc** around $C2-C3$, but rotation around $C1-C2$ leads to unfavorable conformations.

An example of anti-peri planar



elimination products

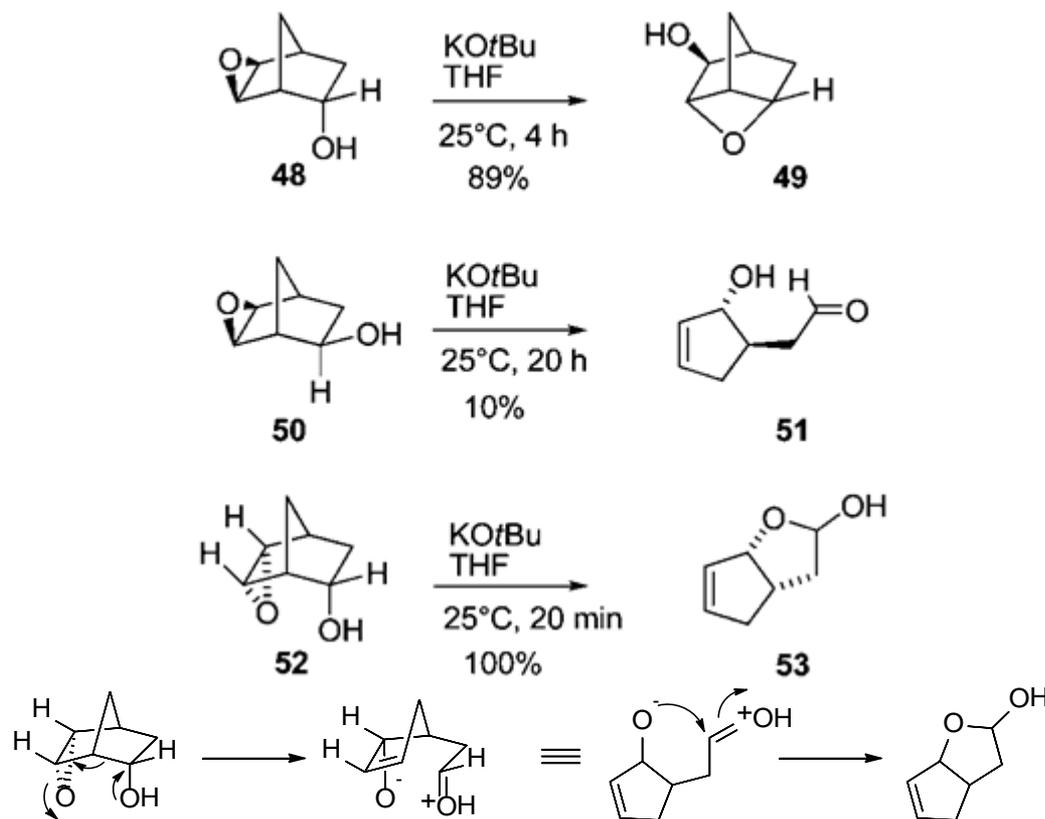


In the cyclic templates **35-39**, the C1-C2-C3-conformations are fixed. The anti-peri planar arrangement is present in **36-39**, but not in **35**. **36-39** undergo Grob fragmentation, and **35** does not.

Exceptions

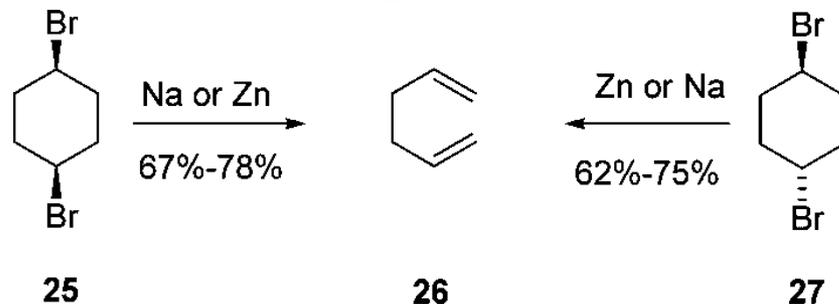
As with any rules there are always exceptions and for some molecules the *syn* geometry is preferred.

An example of this is the Grob fragmentation occurs for the *endo* epoxide (**52**) but not the *exo*. It is thought the *endo* is better suited to the fragmentation due to the high co-planarity of the orbitals.

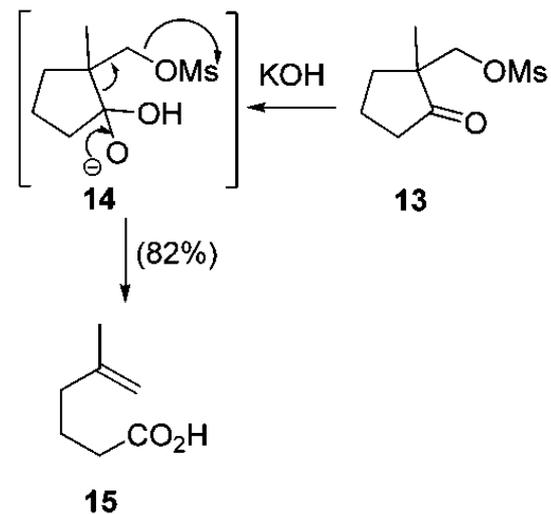


Examples of the Grob fragmentation

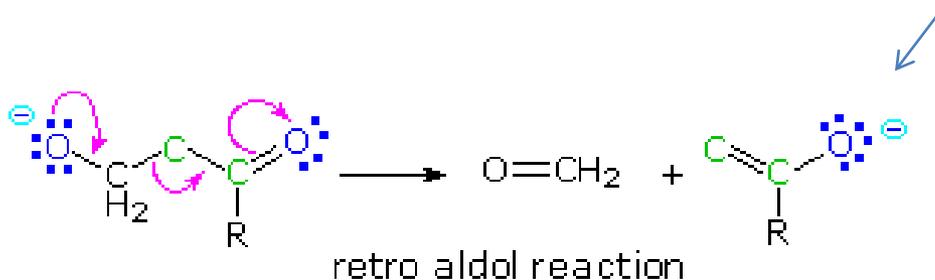
In 1955 this was one of the first fragmentation reactions discovered by Grob:



However in 1952 Eschenmoser had discovered a base catalysed reaction, despite the previous work, this elimination reaction taking place when an electrofuge and nucleofuge are situated in positions 1 and 3 on an aliphatic chain was termed the Grob fragmentation.



Another example of a Grob fragmentation is the retro-aldol reaction:

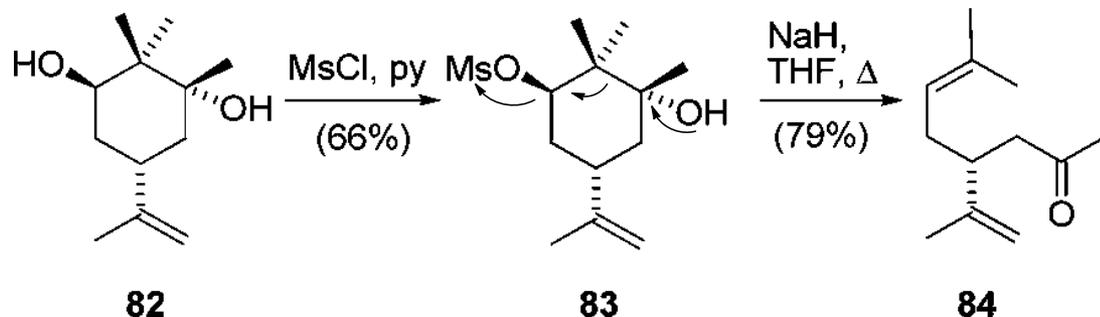


Carbonyl generating Grob fragmentation

Carbonyl generation via ring cleavage reactions:

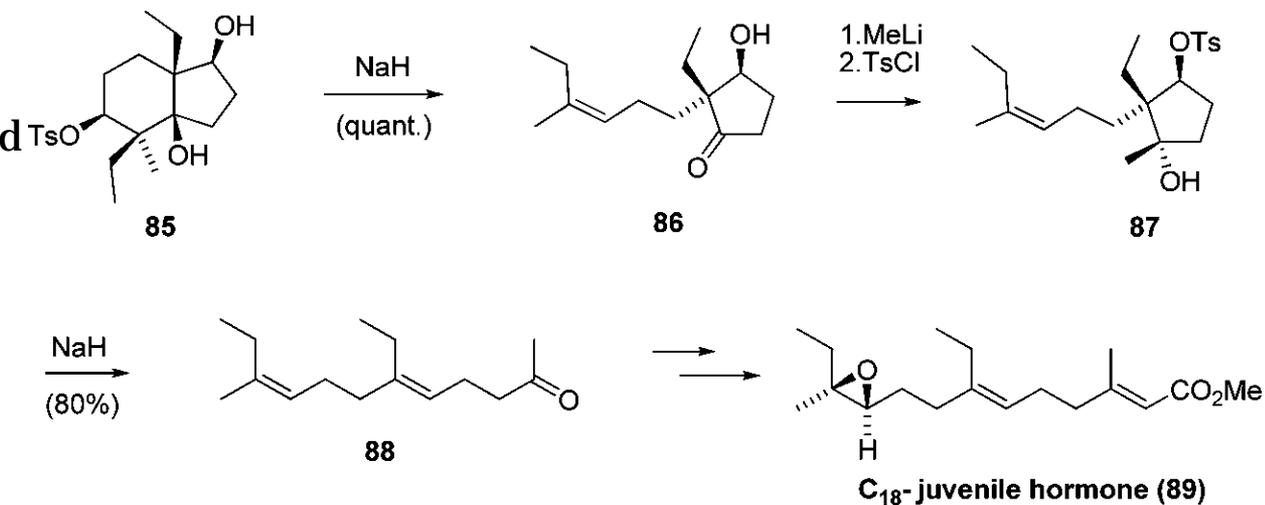
Monosulphanated 1,3,diols:

Basic deprotonation then
fragmentation from anion formed
Forming a lavandulyl system



Stereospecific synthesis of acyclic trisubstituted olefin subunits in
cecropia juvenile hormone:

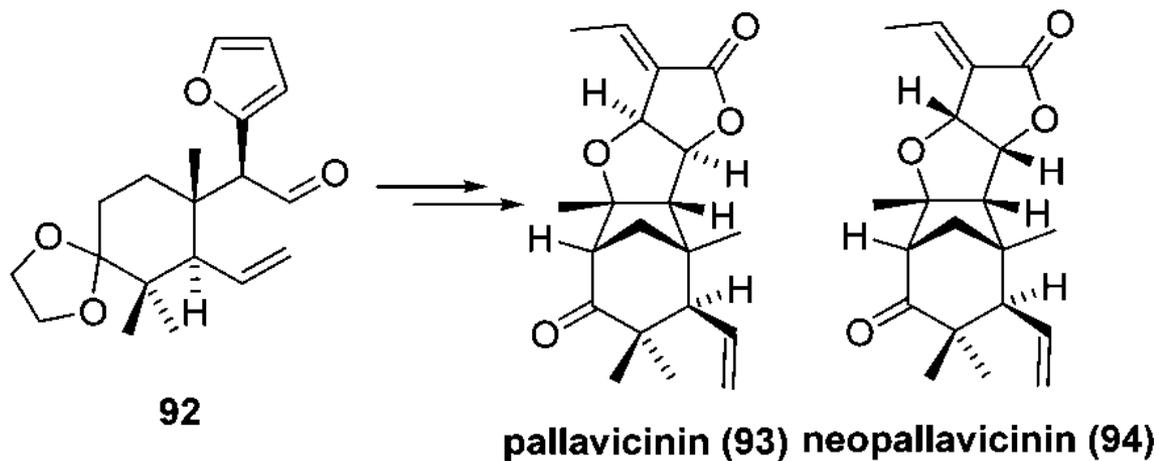
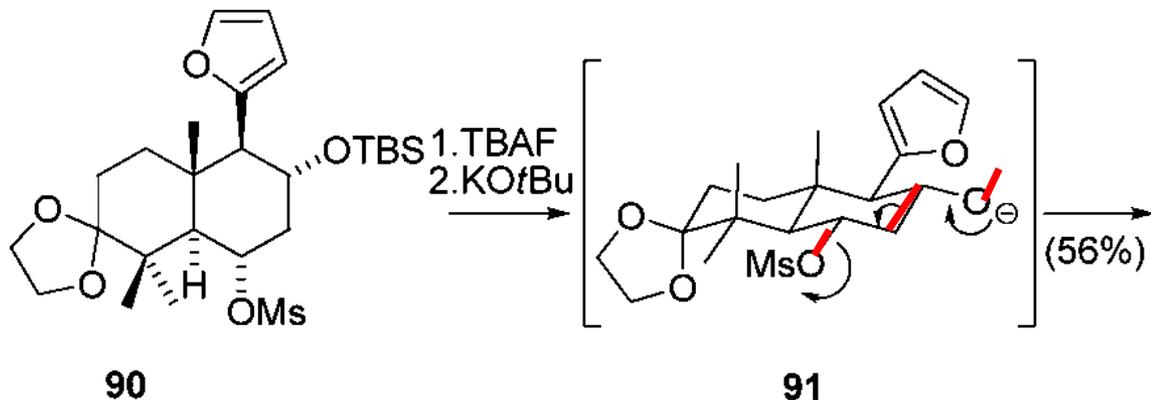
This fragment was built based
on a repetition sequence



In total synthesis

In total synthesis:

The total synthesis of pallavicinin and neopallavicinin relied on a Grob fragmentation to generate the vinyl moiety in, which is present in both targets:

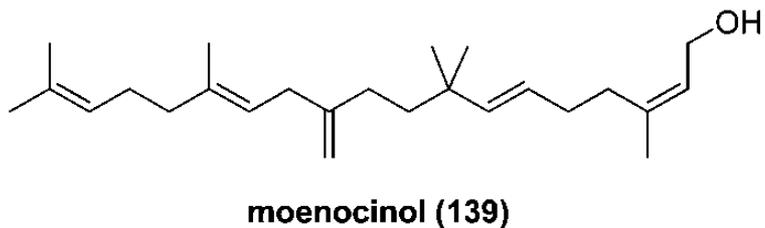
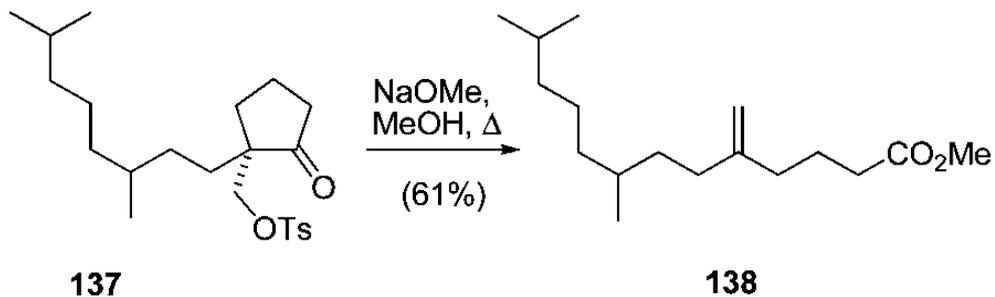
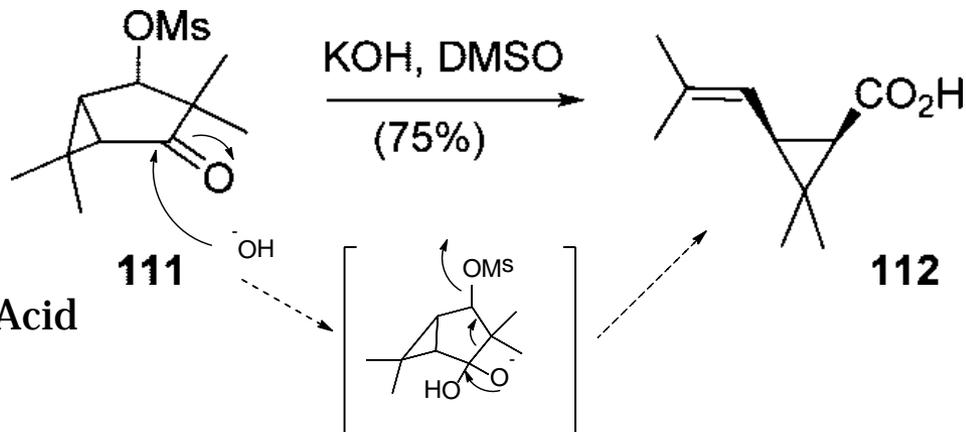


B-hydroxy ketones

Fragmentation from β -hydroxy ketones:

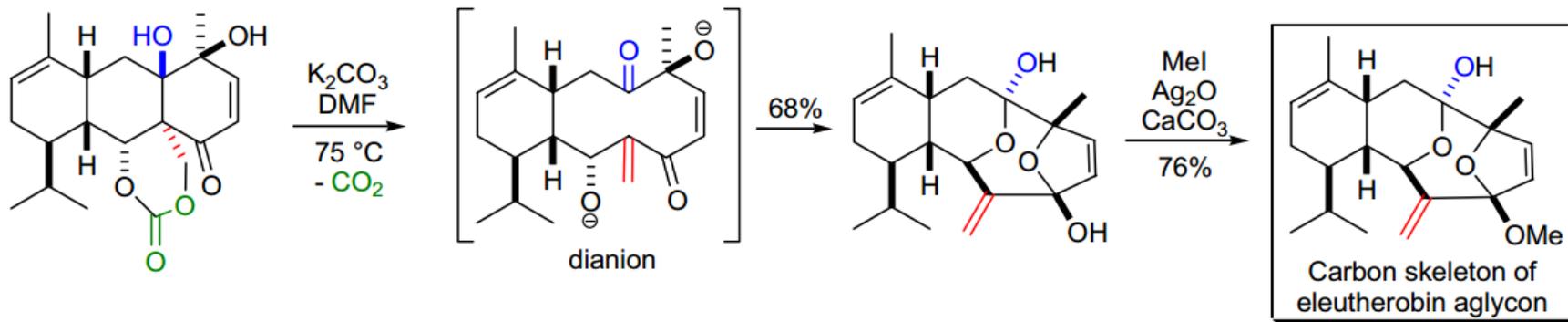
Addition of OH nucleophile to carbonyl
followed by fragmentation:

Applied to the formation of *cis*-Chrysanthemic Acid



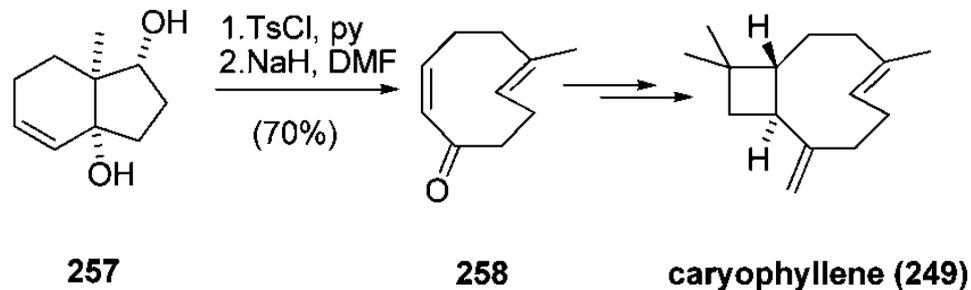
In a model system for the synthesis of moenocinol, Grob fragmentation was used to introduce the exomethylenemoiety

Total synthesis



In the laboratory of J.D. Winkler, the synthesis of the carbon framework of the the tricyclic fragmentation precursor was subjected to potassium carbonate in DMF at $75^\circ C$ to afford the fragmentation product in 68% yield via a dianion intermediate that underwent a spontaneous hemiketalization.

In 2008, Corey published an enantioselective synthesis of caryophyllene . The nine membered ring was generated by fragmentation of diol to dienone. Dienone **258** was also an intermediate in his synthesis of coraxeniolide A.

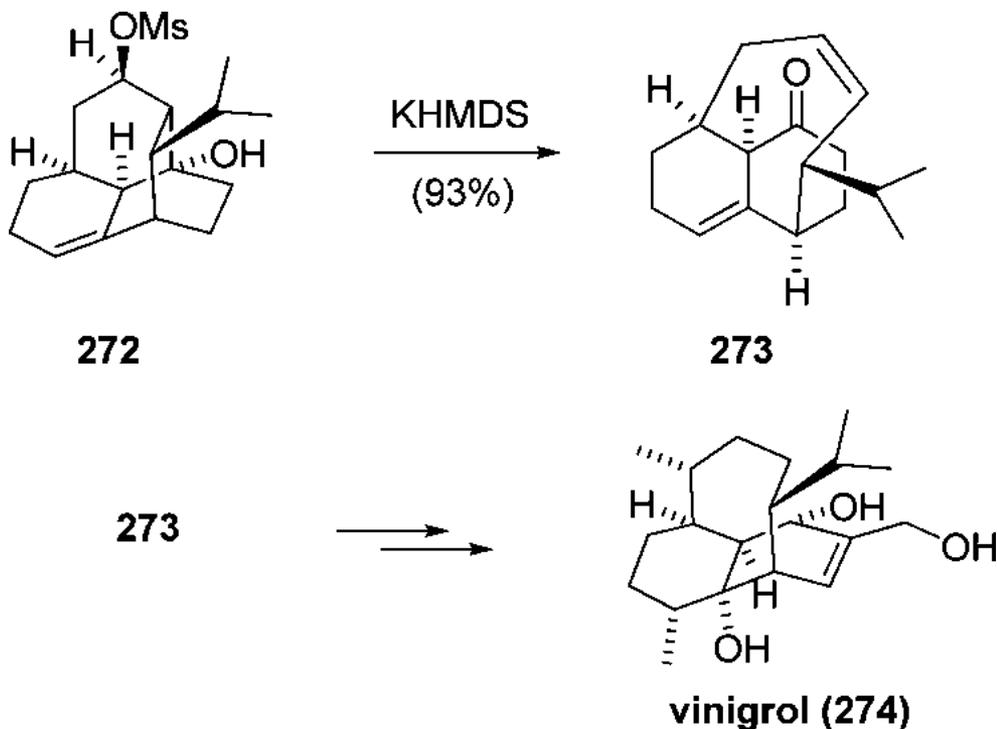


Total synthesis

Barans approach to Vinigrol:

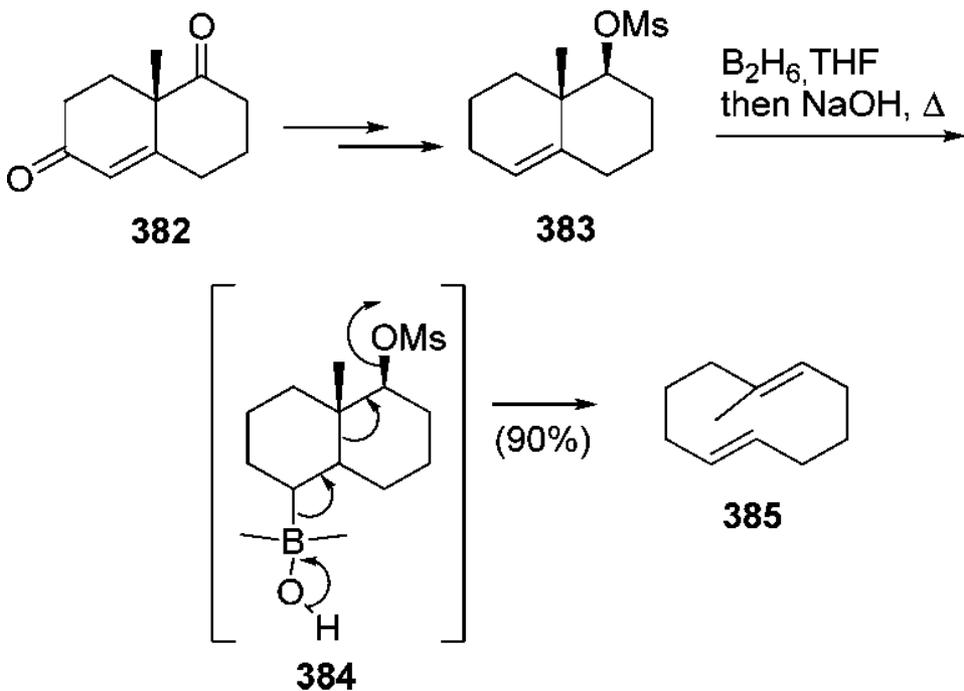
A fragmentation was used to overcome the inherent ring strain of the decahydro-1,5-butanonaphthalene system in intermediate **273**.

The tetracyclic precursor **272** was prepared by two Diels-Alder reactions. Grob fragmentation of monomesylated diol **272** with KHMDS was used to form the tricyclic core



Different electrofugal groups

Boronic esters can also be used as electrofugal groups as shown in the e.g. below:



Eschenmosers synthesis of macrolides: Decarboxylative fragmentation can occur a double Grob type fragmentation occurs of an amidinium salt forming an unsaturated lactone

