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Planning Synthetic Strategy and Retrosynthesis

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D111

Postgraduate Course
(Organic Problem Solving III)

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Terminology



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Disconnection: an analytical operation, which breaks a bond and converts a molecule into possible starting materials. The reverse of a chemical reaction.

Retrons: products of a reaction that are present in a molecule.

Partial retron: not the product of a reaction but close (can be converted to the full retron).

Synthon: a generalised fragment, usually an ion, produced by a disconnection.

Recap on the Basics

Polar Bond Theory: uses (+) or (-) to denote positional polar reactivity.

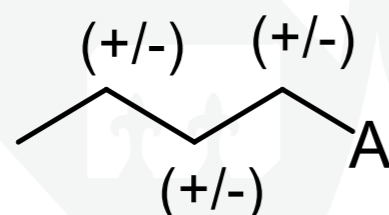
E = functional group with a greater electronegativity than C, so it induces a (+) charge on C. Conversely G induces a (-) charge.



E = OR, NR₂, =NR,
=O, halogen



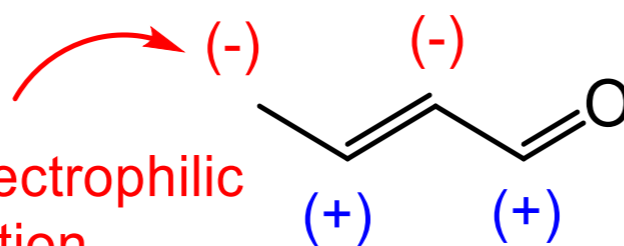
G = MgBr, Li



A = no charge preference, depends on conditions
SR, SO₂R, NO₂, PR₃, CN, *etc.*

e.g.:

latent sites for electrophilic
attack/deprotonation



sites of nucleophilic attack

Disconnection Selection



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1) Overall Goal: Decrease complexity!

Reduce: size of cyclic connectivity or topology, functional group content, stereocentre content/density

Remove: centres of high chemical reactivity, centre of kinetic/thermal instability.

Break target: into fragments of equal complexity.

2) Characteristics of Most Powerful Disconnections.

Disconnect molecular skeletons (rings or chains).

Remove functional groups and stereocentres.

Replace functional groups with hydrogen.

3) Non-Simplifying Transformations (moderately powerful)

Molecular skeleton connection or rearrangement.

Functional group interchange or transposition.

Stereocentre inversion or transfer.

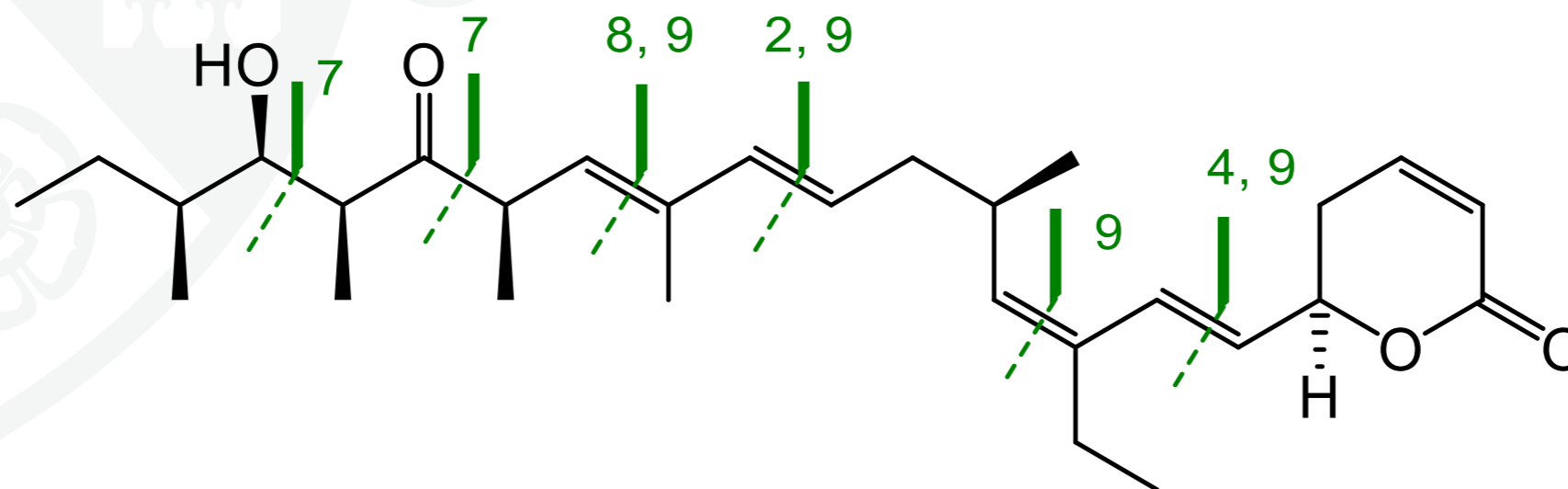
4) Transformations which increase complexity (least powerful)

Addition of rings, functional groups, protecting groups, stereocentres, temporary tethers, activating/deactivating groups.

Acyclic Systems



- 1) **Do not disconnect** building-block groups (alkyl, alkylaryl or aryl).
- 2) **Disconnect** to obtain symmetrical (or equal sized) precursors.
- 3) **Disconnect** bonds between C and heteroatoms
- 4) **Disconnect** bonds that attach rings to chains (can be 1, 2 or 3 bonds removed).
- 5) **Do not disconnect** skeletal bonds that are attached directly to remote stereocentres.
- 6) **Do not disconnect** stereocentres that are >3C removed from a functional group.
- 7) **Disconnect** bonds 1, 2 or 3C between functional groups.
- 8) **Disconnect** bonds 1, 2 or 3C away from functional groups.
- 9) **Disconnect** double bonds or double bond equivalents,.

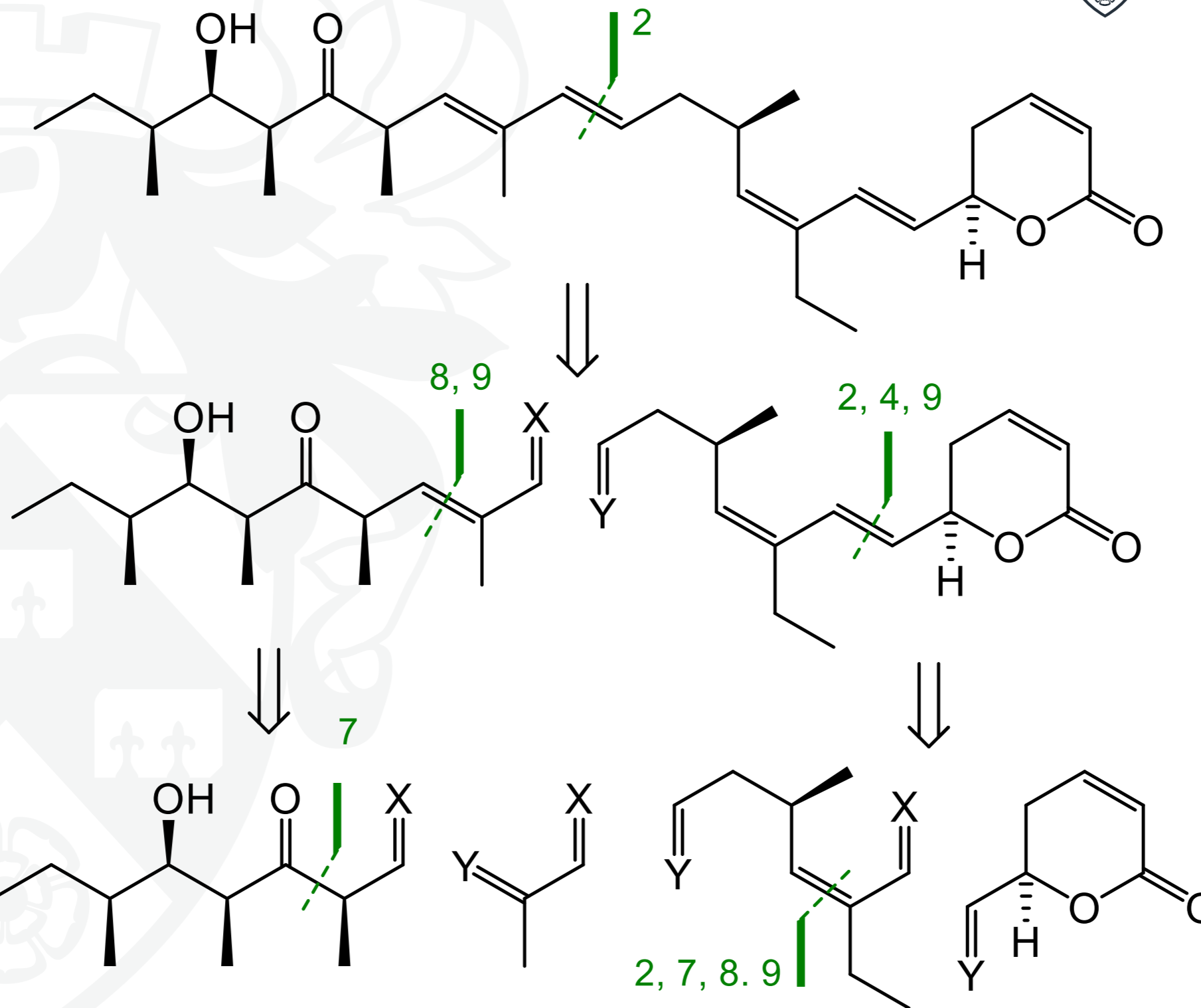


Acyclic Example

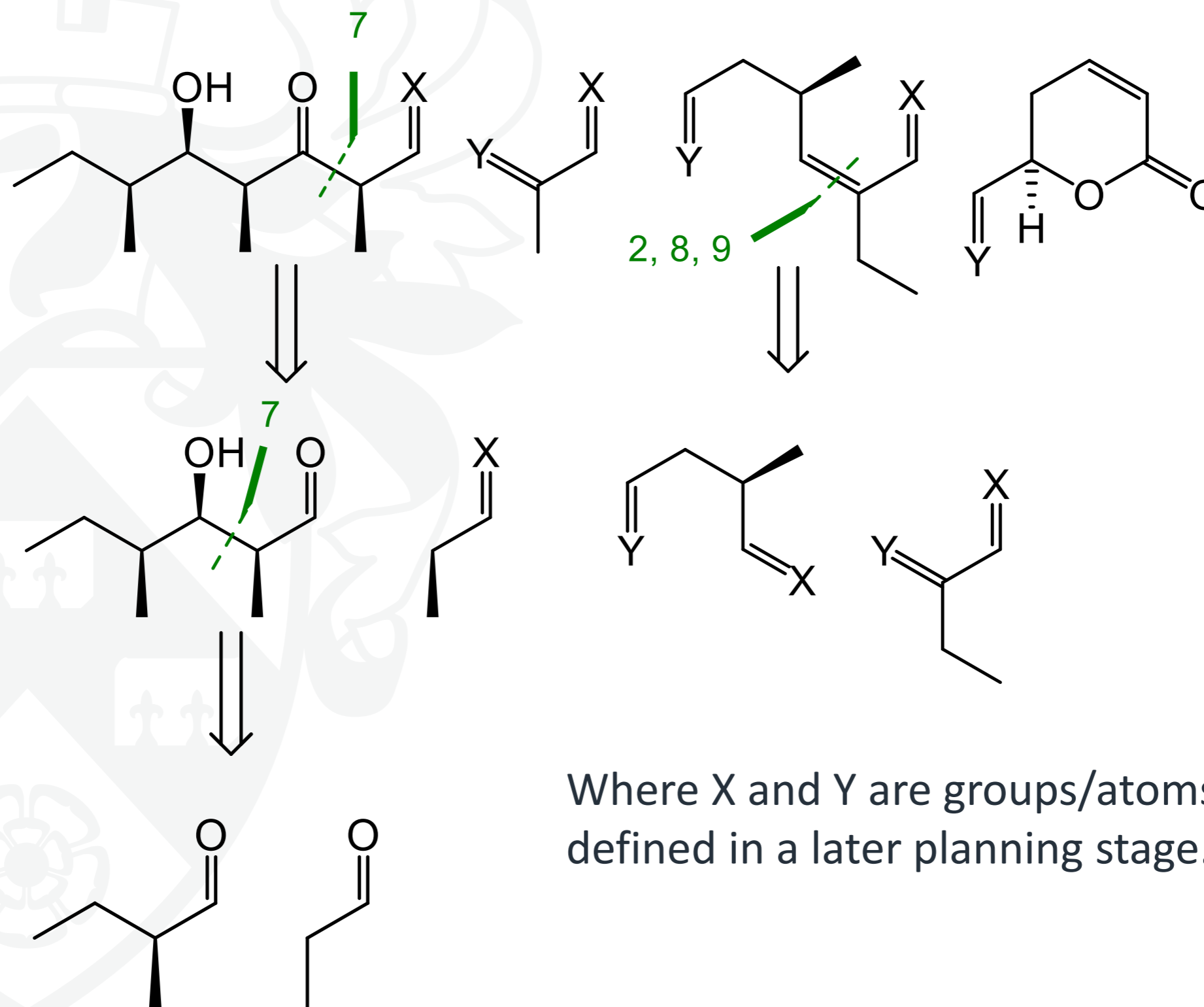
Primary strategic disconnection



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Acyclic Example



Where X and Y are groups/atoms to be defined in a later planning stage.

Disconnection of Isolated Rings



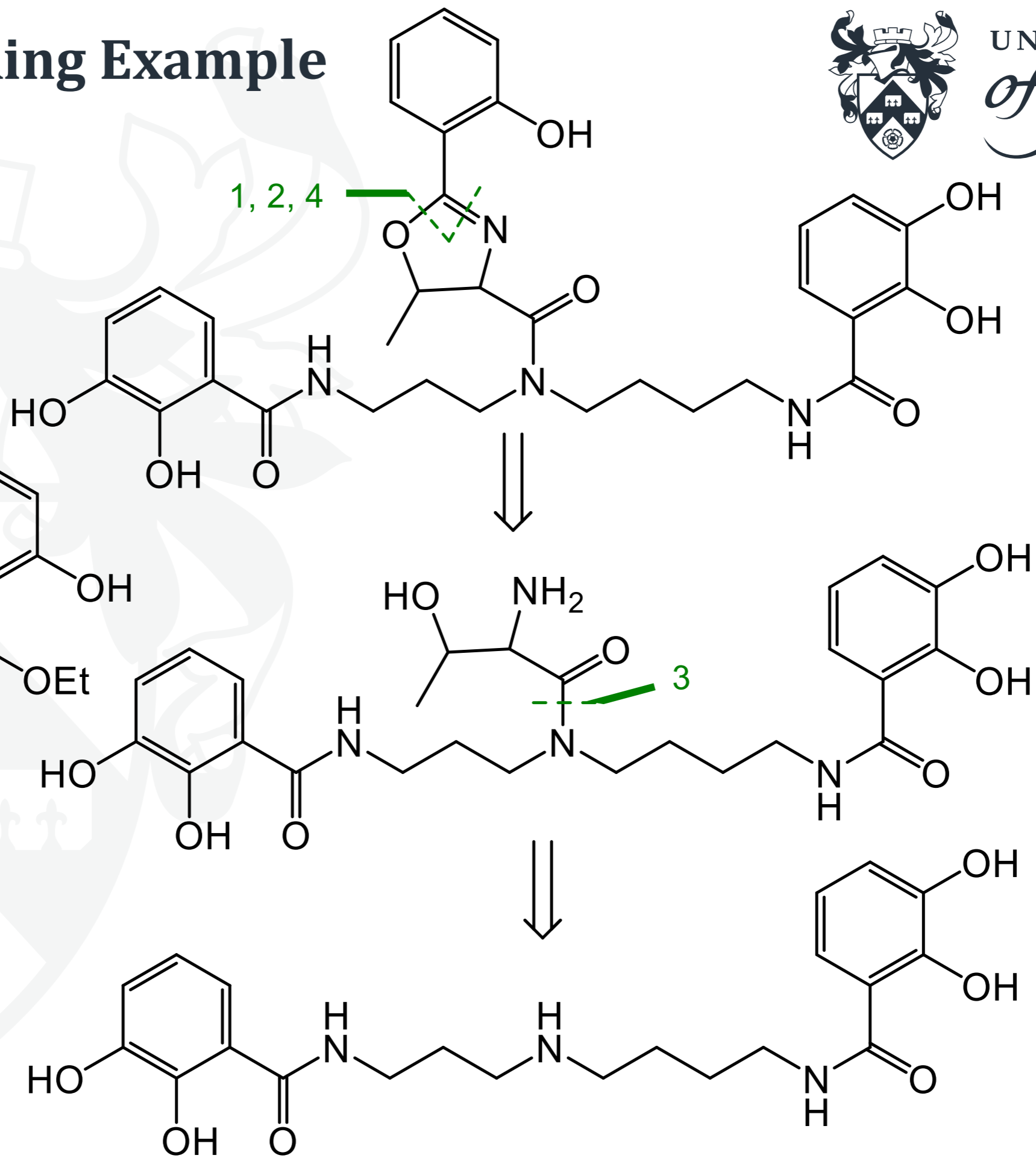
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- 1) **Disconnect** non building block rings which are embedded in a skeleton and centrally located.
- 2) **Disconnect** bonds between C and heteroatoms.
- 3) **Disconnect** bonds that create symmetrical or locally symmetrical, or a linear skeleton.
- 4) **Disconnect** easily formed rings such as lactones, acetals, hemiacetals embedded in the skeleton.
- 5) **TIP!** If several isolated rings are present the most strategic for disconnection will be the one that is most centrally located, especially if it allows you to disconnect back to an acyclic system (remember these rules!)

Isolated Ring Example



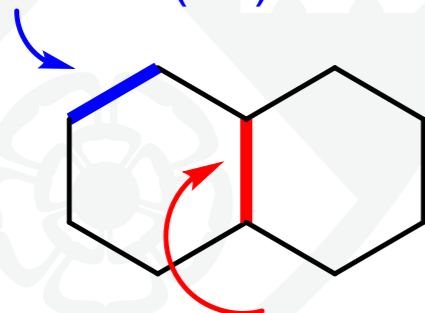
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Disconnection of Fused Rings

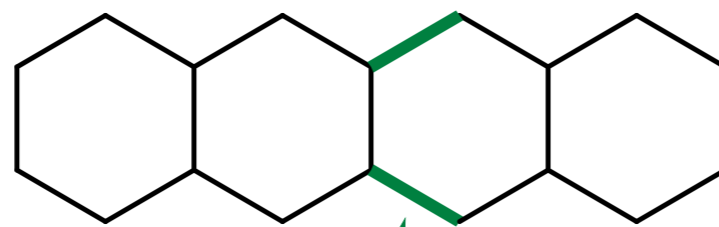
- 1) **Disconnect** two co-cyclic bonds: the fusion bond and an *offexendo* bond (one beta to it). If ring size 3-7 these must be *cis*!
- 2) **Disconnect** co-cyclic bond pair in a central ring.
- 3) **Do not disconnect** building block rings.
- 4) **Disconnect** [2+1] and [2+2] retrons (3 and 4 membered rings).
- 5) **Do not disconnect** fusion bonds that create >7 member rings.
- 6) **Disconnect** directly linked *exendo* bonds in rings that contain alternating *exendo* and *fusion* bonds.
- 7) **Disconnect** hetero rings: lactones, acetals, lactams, etc.
- 8) **Do not disconnect** bonds that create stereocentres unless they can be removed with stereocontrol.

offexeno (oe)



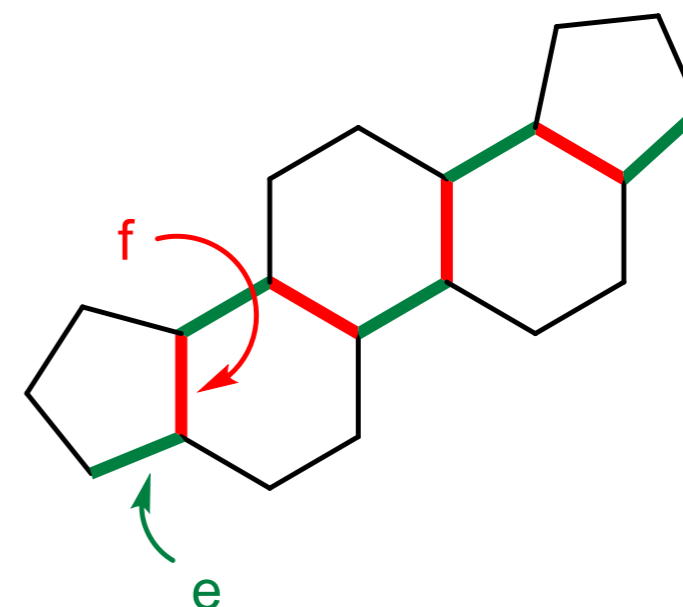
fusion (f)

rule 1



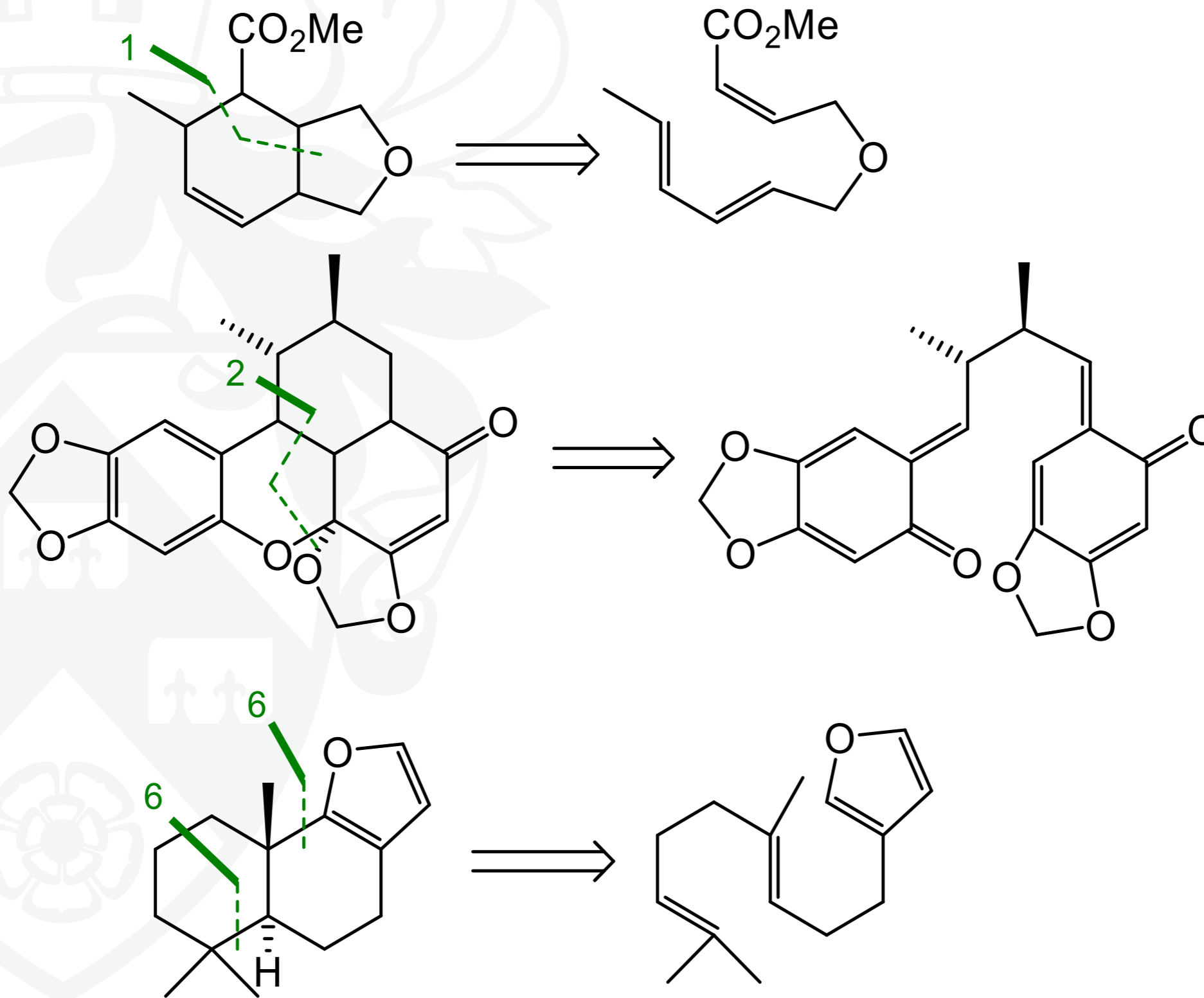
exendo (e)

rule 2



rule 6

Fused Examples



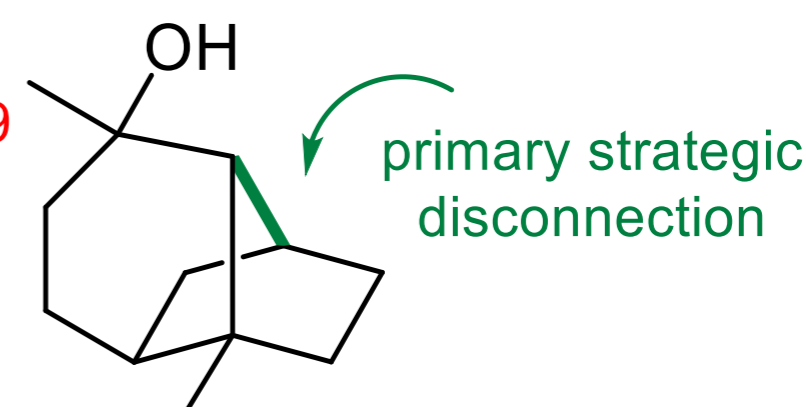
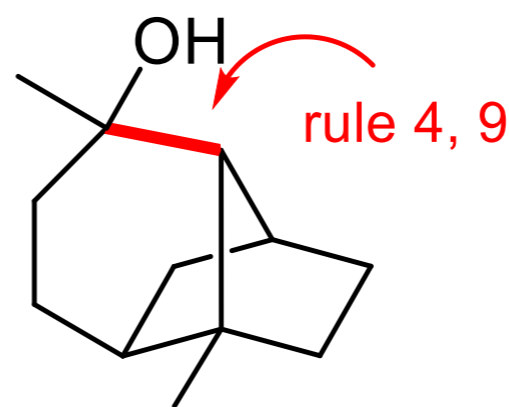
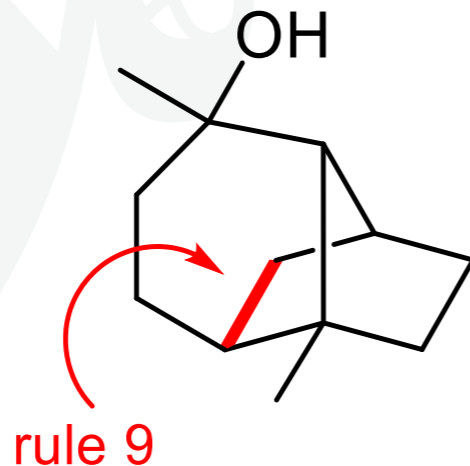
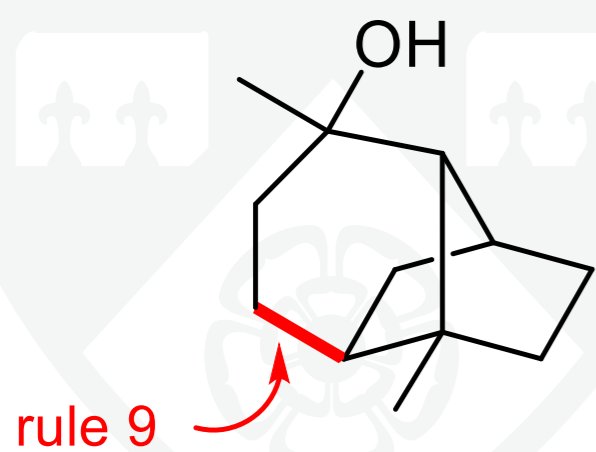
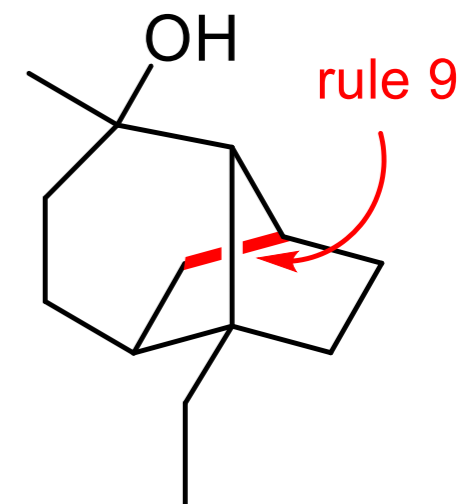
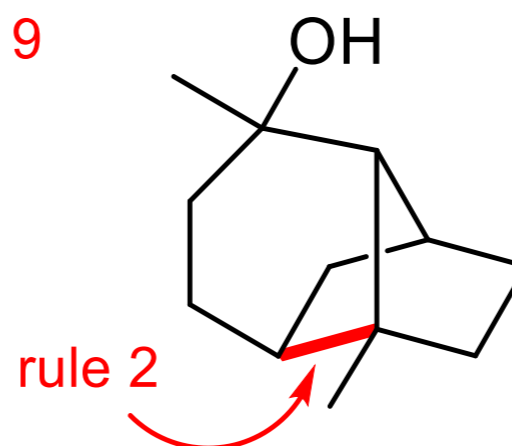
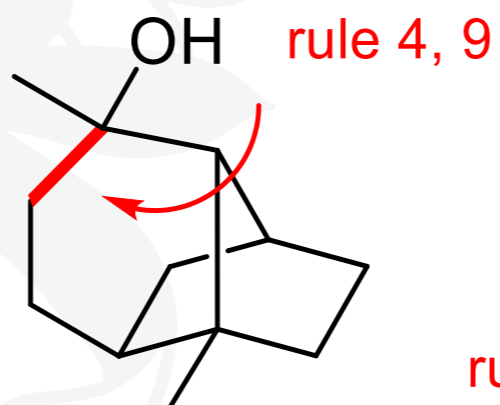
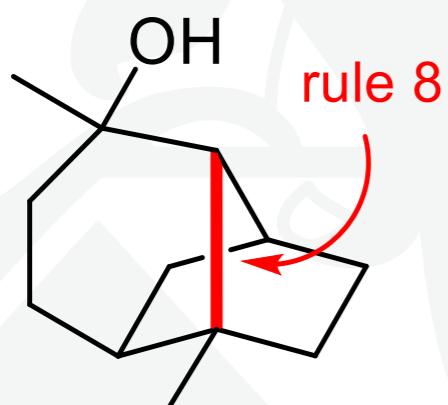
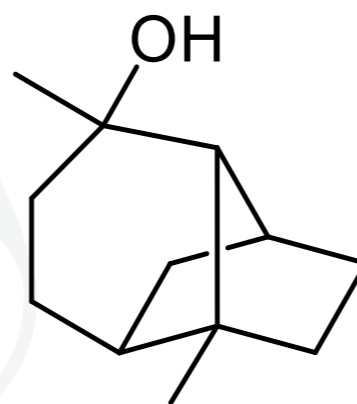
Disconnection of Bridged Rings



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- 1) **Disconnect** *exendo* bonds in 4-7 membered rings. **But do not disconnect** bonds *exo* to 3-membered rings.
- 2) **Do not disconnect** bridges which result in >7 membered rings.
- 3) **Disconnect** bonds in rings that contain the most bridgehead atoms, **but do not** break rule 2.
- 4) **Do not disconnect** bonds that result in stereocentres. **OK if at point of** attachment.
- 5) **Do not disconnect** bonds within aromatic rings and heteroaromatic rings.
- 6) **Disconnect** C-O, N or S bonds.
- 7) **Disconnect** to reduce bridges.
- 8) **Do not disconnect** bonds that lead to medium-sized rings.
- 9) **Do not disconnect** bonds that create pendant chains.

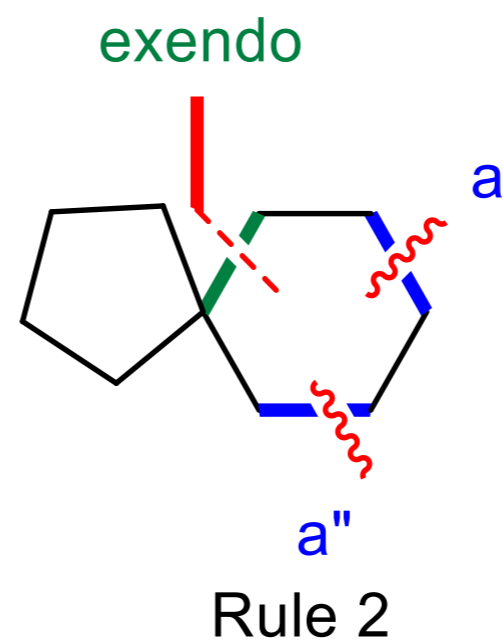
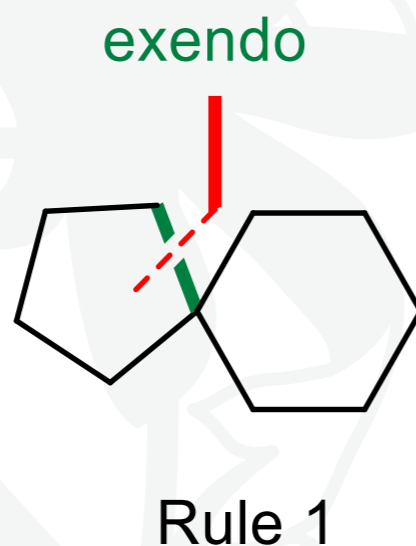
Bridged Example



Spiro Rings Disconnections

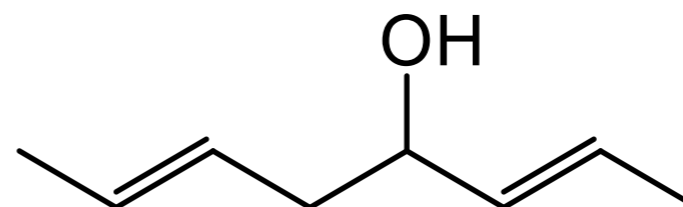
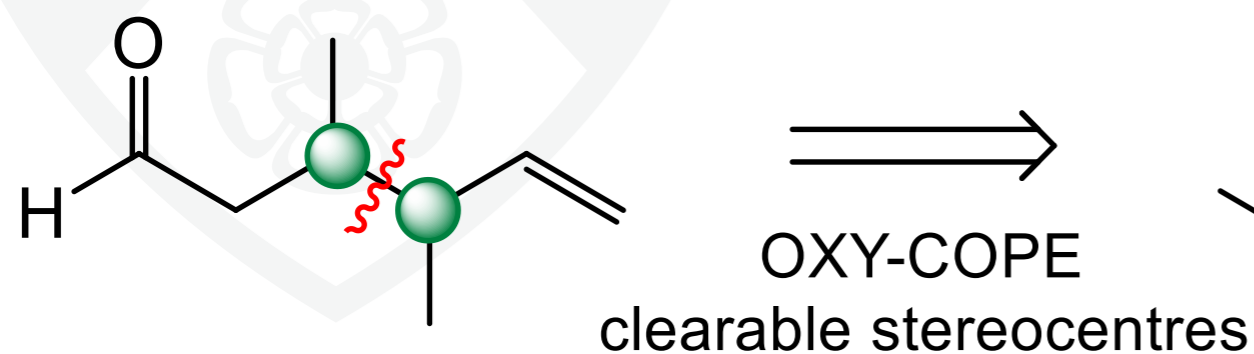
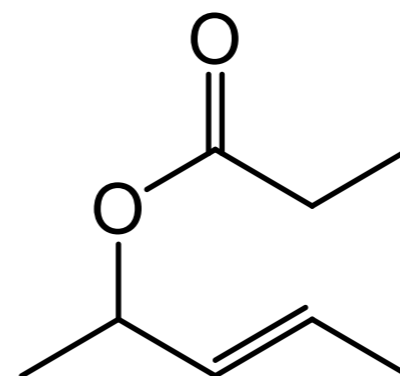
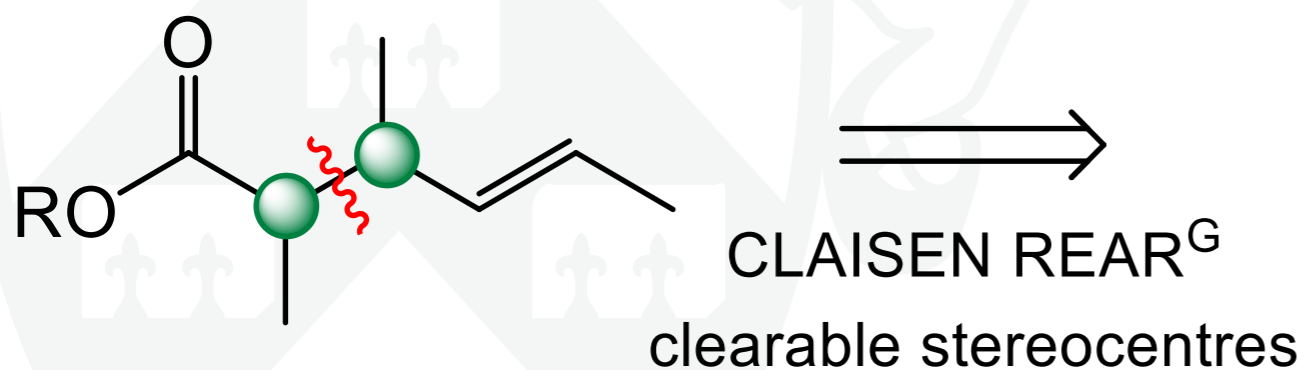
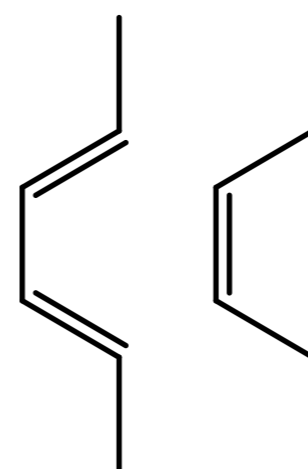
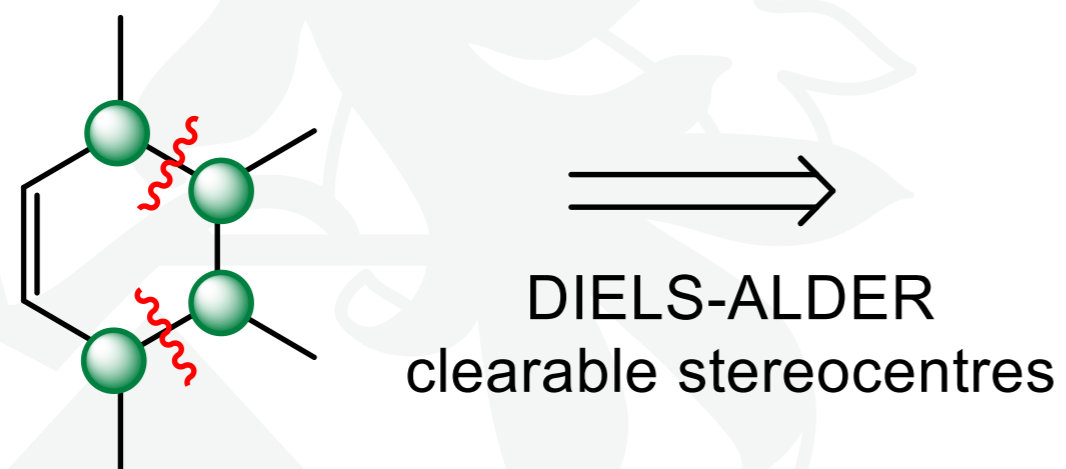
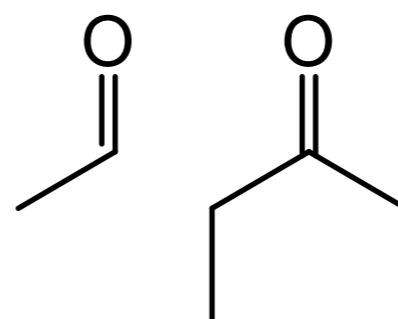
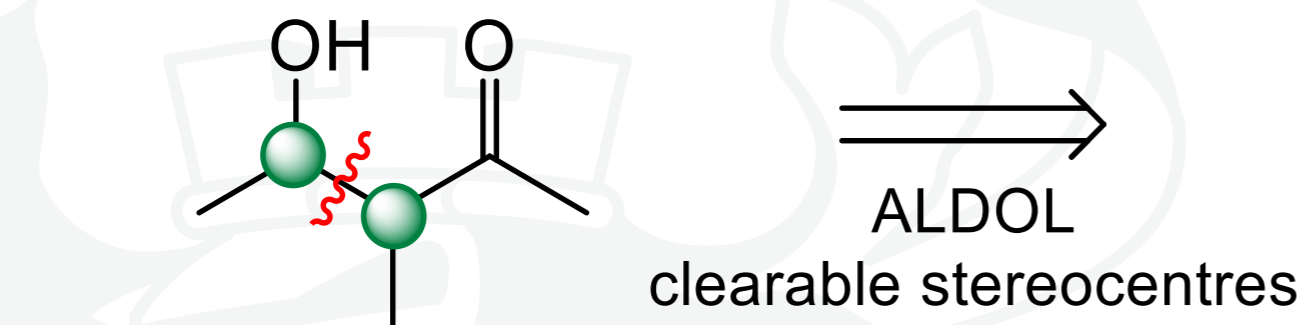


- 1) **Disconnect** 1 *exendo* bond.
- 2) **Disconnect** 1 *exendo* bond and one co-cyclic bond beta to it.

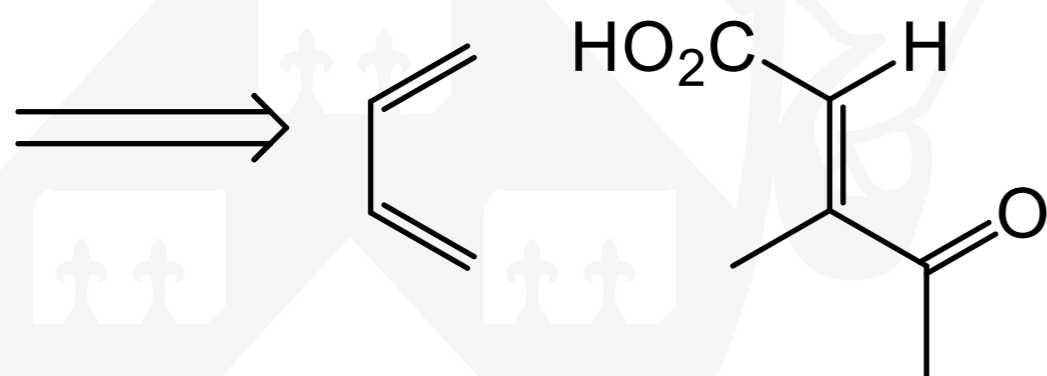
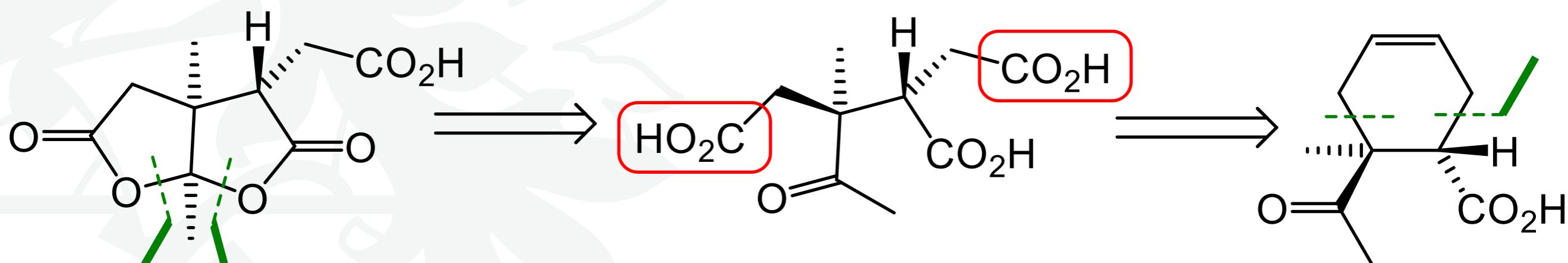


break exendo and *either* a' or a''

Some Powerful Disconnections

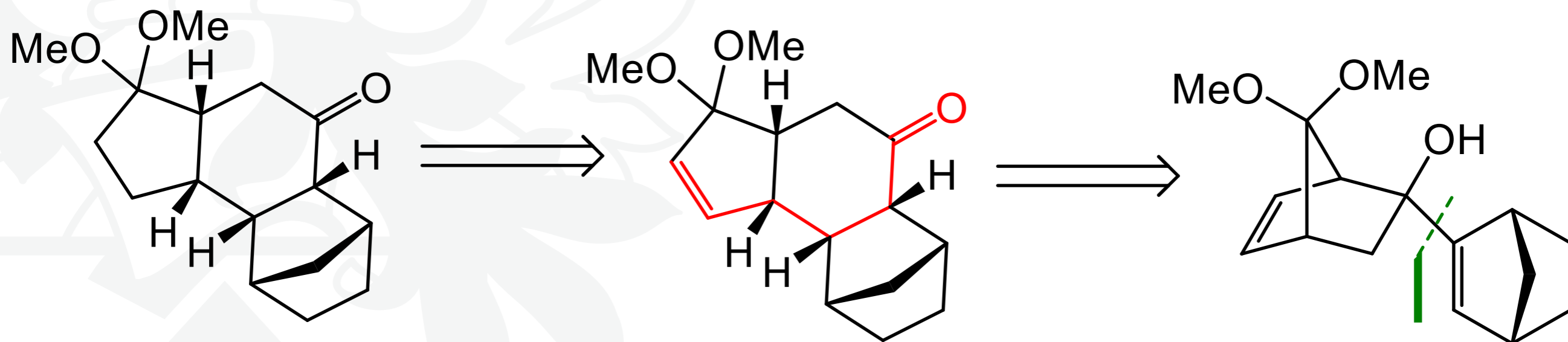


Some Not-So-Obvious Examples: Diels-Alder

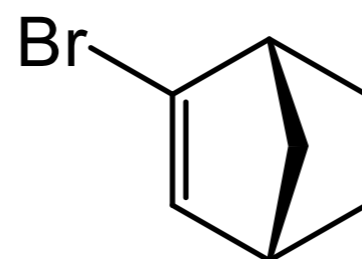
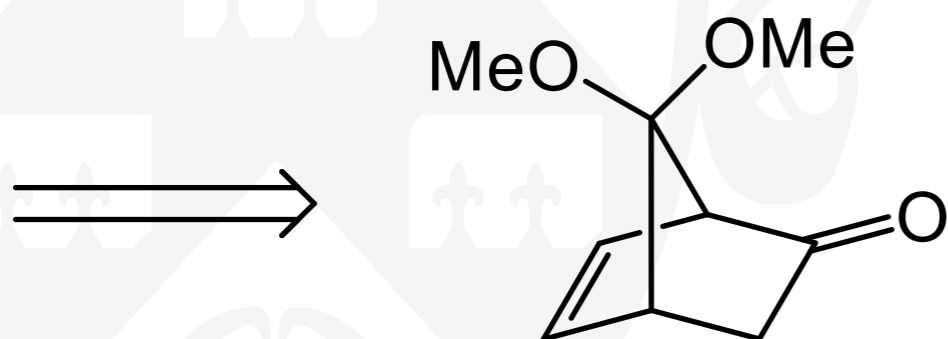


- 1) 1,6-functionality can arise from oxidative cleavage of a cyclohexene.
- 2) Cyclohexenes are easily formed by Diels-Alder reactions.

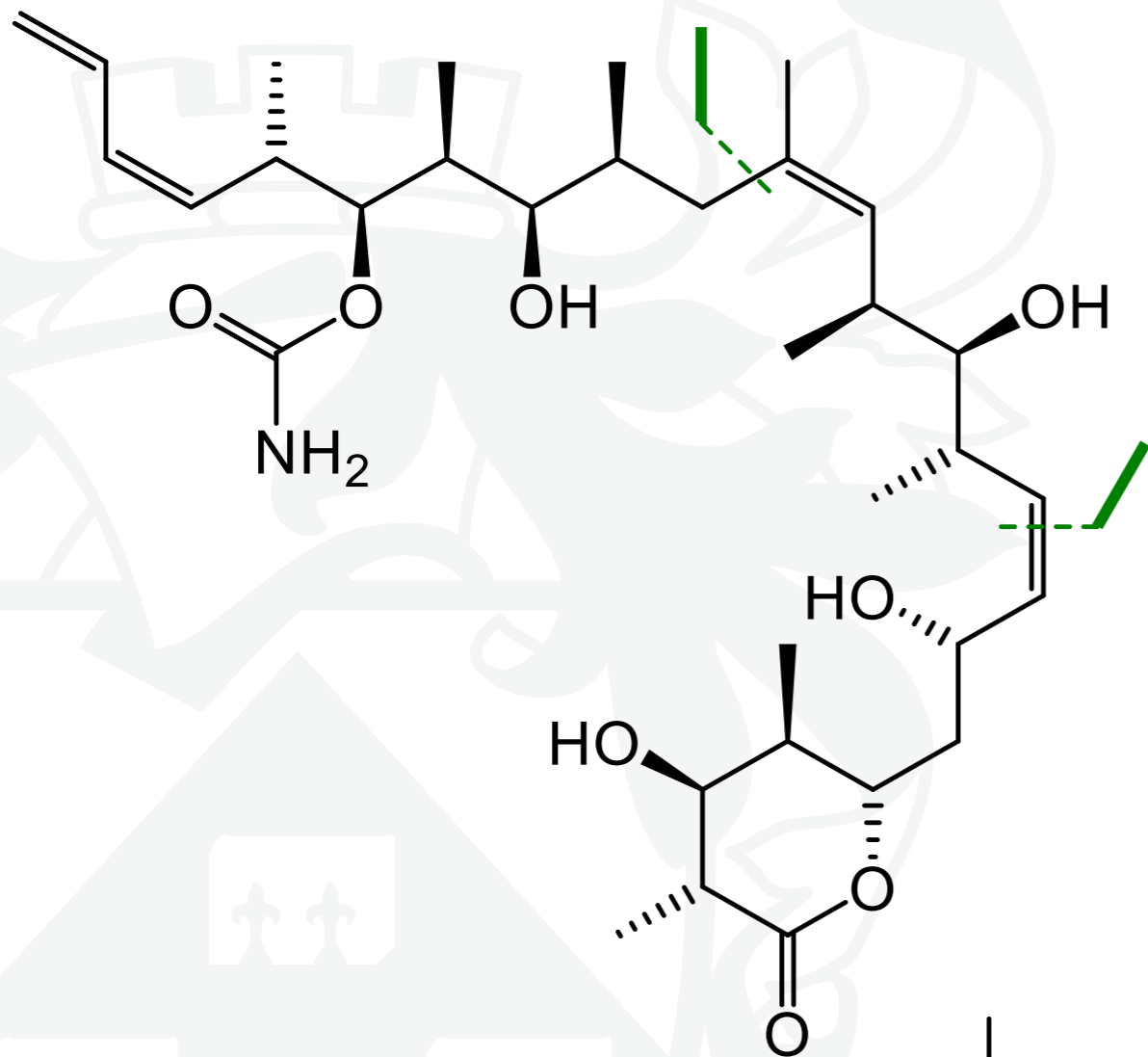
Some Not-So-Obvious Examples: Oxy-Cope



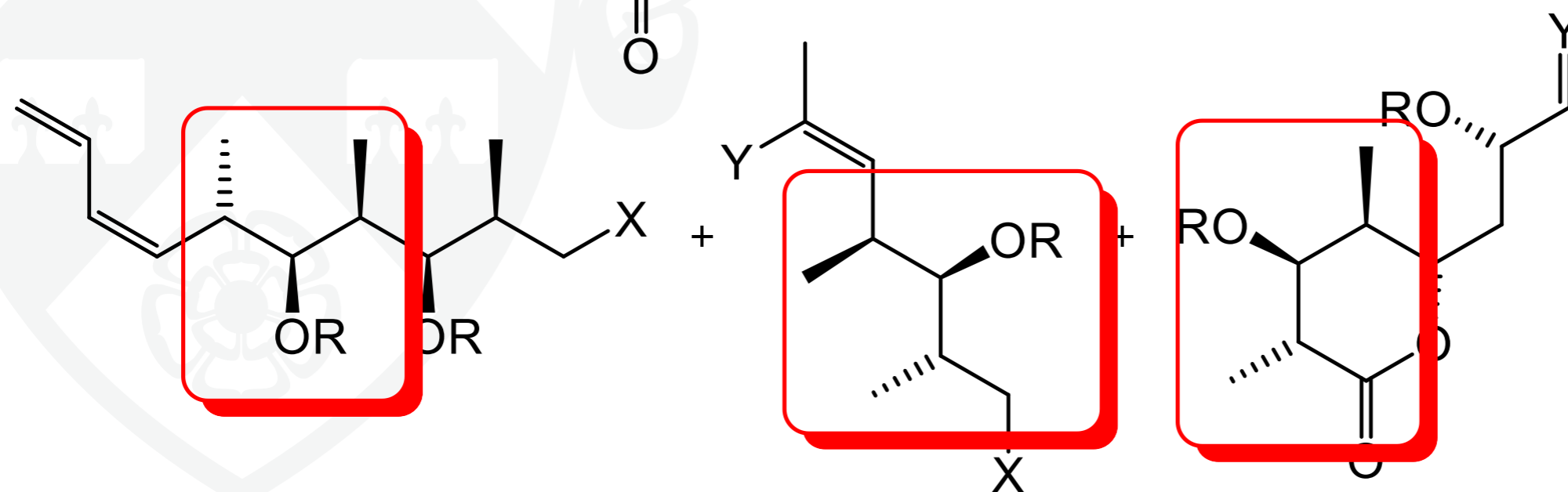
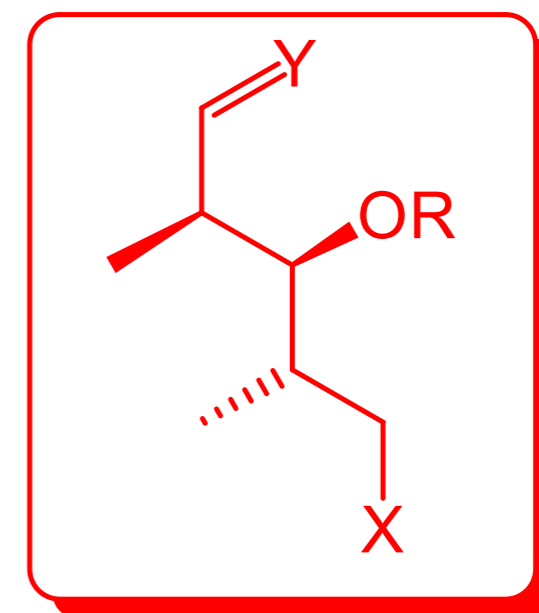
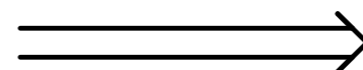
Oxy-Cope retron



Worked Example: Discodermolide



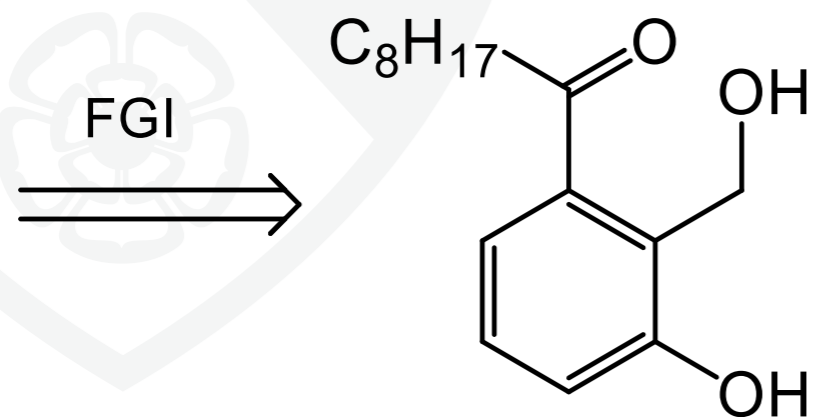
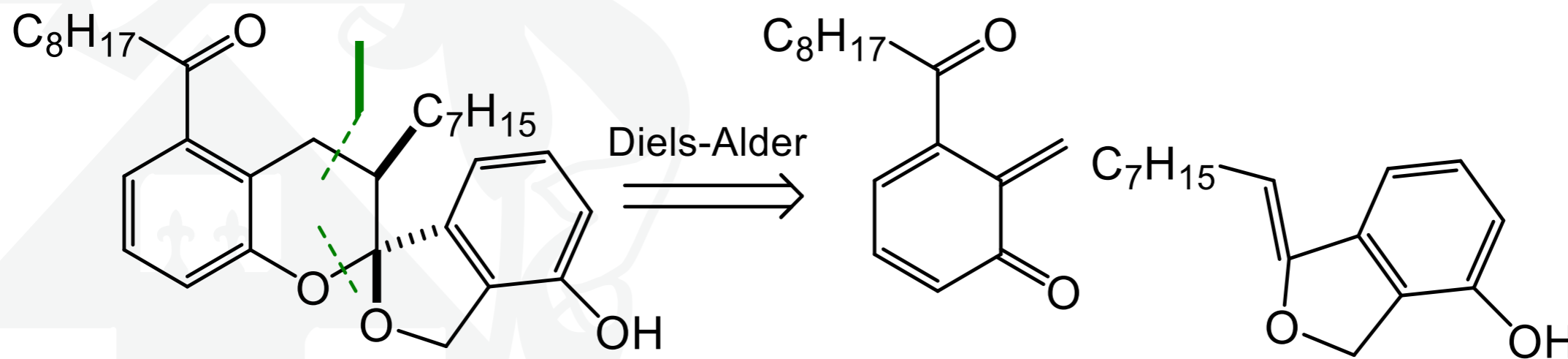
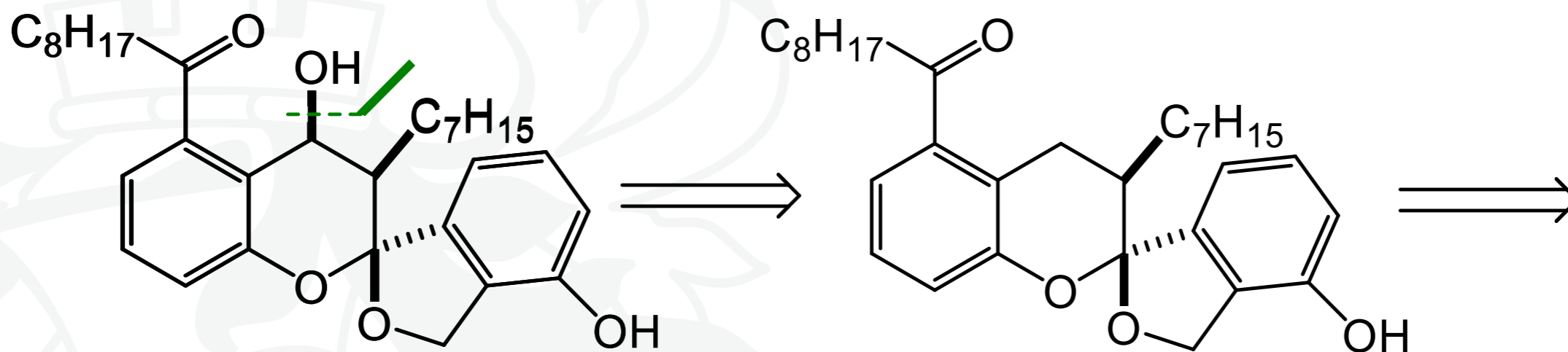
primary strategic
disconnections



Worked Example Fused/Spirocyclic: Paecilospirone



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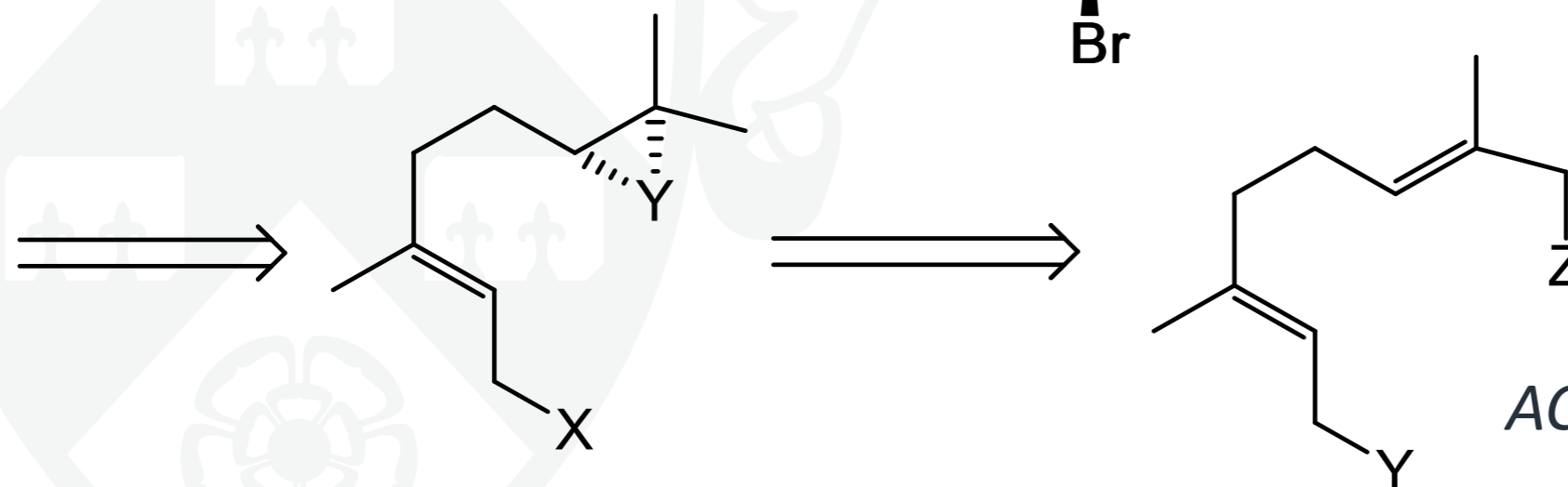
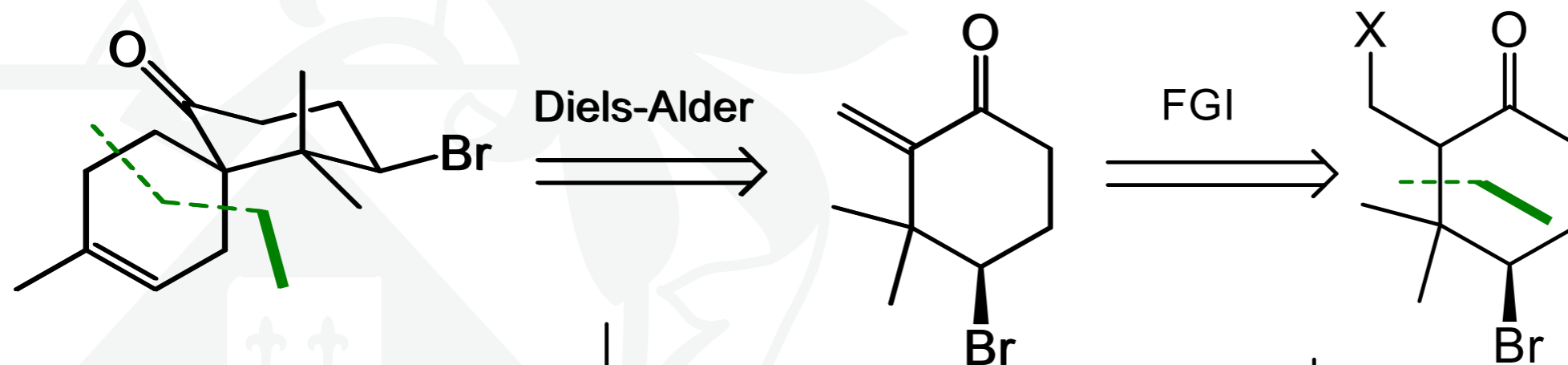
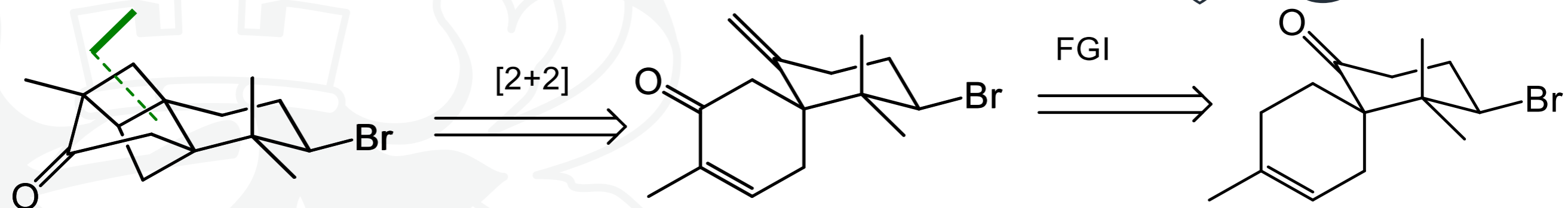


Synlett **2018**, 29, 1517.

Worked Example Fused/Spirocyclic: Aplydactone



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ACIE 2016, 55, 11476.



Final Notes

Remember to reduce complexity:

Look for the most simplifying bond disconnection, this may become evident after consideration of functional group topological relationships.

Disconnect the molecule into fragments of equal size and complexity.

Look for latent symmetries.

Continually read the literature.

Continually practice – go through your ideas with group members and supervisors.

Homework: For next session identify the ‘allowed’ disconnections (p. 5, 8, 9, 10 and 13) highlighted in: i) Discodermolide, ii) Paecilospirone and, iii) Aplydactone

Have fun!