# RING EXPANSION CASCADE

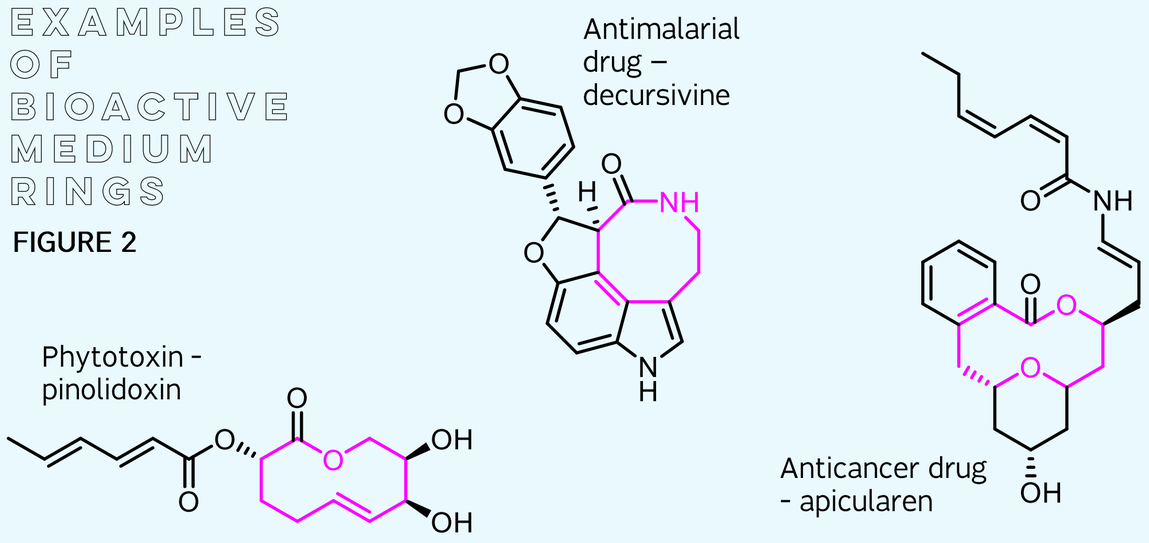
## Streamlining the synthesis of novel medium rings through a new undergraduate teaching labs project

## INTRO & AIM

**Organic chemistry** (the study of carbon-containing molecules) is an important branch of chemistry, underpinning much of biology and medicine.
**Medium sized rings** (8-11 atoms) are super important in this area of chemistry, with many potential applications. (SEE FIGURE 2)
However, making them is hard and so their potential hasn't been explored fully yet.
Research by the Unsworth group at the University of York found an effective new method to make these rings via a **ring expansion cascade** reaction. This involves linear starting materials containing **internal nucleophilic catalysts**, which allow the ring to be formed via a smaller cyclic intermediate. (SEE FIGURE 1)
In my research I have designed a new Teaching Labs Project which will enable year 3 chemistry students to seamlessly select and synthesise the starting materials for novel ring expansion cascades. This means that many more interesting and useful products will be made.

## EXAMPLES OF BIOACTIVE MEDIUM RINGS

FIGURE 2




## BACKGROUND

**As you can see from the diagrams in FIGURE 2, medium sized rings are very useful for biological applications, like drugs.** This is due to their more rigid structures in comparison to their linear equivalents, but more flexible than typical smaller rings. This means they can adjust in order to bind to enzymes and receptors without losing much entropy.

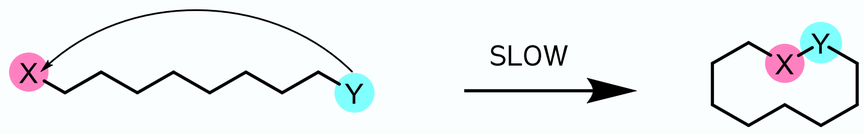
**However, medium sized rings are difficult to make for numerous reasons.** Two ends of a long linear molecule coming together is unfavourable due to the loss of entropy (molecule becomes less disordered). There is also an enthalpic barrier to the cyclisation of medium rings, which is caused by strain: bond angles forced away from their optimal geometry, interactions between atoms/groups separated by 3 covalent bonds (torsional strain) and repulsive interactions between close atoms in a ring (transannular strain).

**Often, rather than forming a ring, a linear reagent will react with another molecule and dimerise. High dilution conditions prevent this but are impractical for large scale synthesis and so another method is required.**

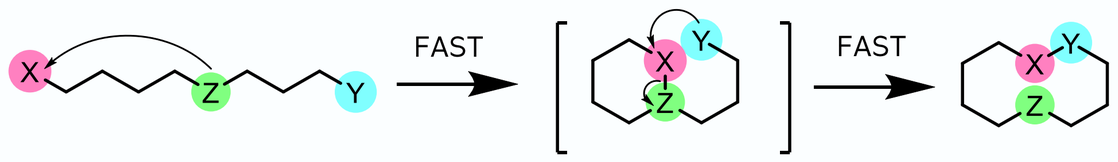
**Cascade ring expansion reactions (see reaction b in FIGURE 1) help to solve this problem by using an internal nucleophilic catalyst (atom Z) which both increases the reaction rate and the yield, making it a much better option.**

## SYNTHESIS (MAKING) OF MEDIUM RINGS

a) **traditional end-to-end cyclisation** – 1 long complicated step




b) **ring expansion using internal nucleophilic catalyst** – 2 simple steps




Option b is more efficient as the conditions required are simpler and the reaction occurs at a faster rate.

FIGURE 1: typical synthesis of medium rings

## BUILDING BLOCKS

It can take a long time to figure out the best way to synthesise the linear starting materials but by introducing the idea of 'building blocks' this time is completely cut out. We have designed 2 sets of building blocks – alkyl bromides containing an electrophilic centre (A) and secondary amines which act as nucleophiles (B).

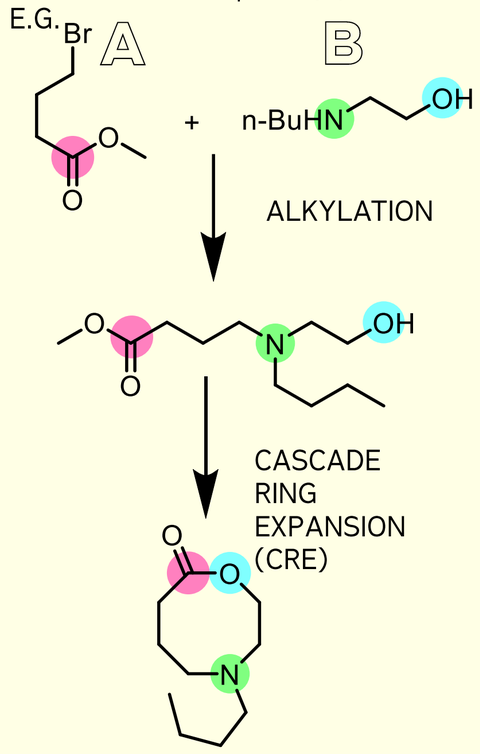



FIGURE 3: example reaction scheme using building blocks

**General Procedures:**
These are the methods students will use to make the desired rings. All combinations of building blocks can be reacted together in the same way.

*ALKYLATION* –

- Potassium carbonate (3 equivalents) is added to a solution of amine, B, (1 equiv.) and alkyl bromide, A, (1 equiv.) in acetonitrile (ca. 5.0mL/mmol).
- The reaction mixture is heated at reflux (85°C) and monitored by thin layer chromatography. This is typically complete in ~16h.
- The mixture is then cooled to room temperature, filtered through celite and the solvent evaporated under reduced pressure.
- Purification by flash column chromatography forms the desired tertiary amine product.

*RING EXPANSION* –

- Methyl ester (1 equiv.) is stirred in a mixture of 0.5 M aq. LiOH (1.1 equiv.) and methanol (an equal volume to the 0.5 M aq. LiOH used) for 1 hour at 50 °C.
- The mixture is then cooled to room temperature and the solvent evaporated under reduced pressure to afford the intermediate lithium carboxylate.
- To this mixture in the same flask, chloroform (10 mL/mmol of ester), DIPEA (1.85 equiv.) and T3P (1.5 equiv.) are added sequentially.
- The mixture is stirred at RT for 1 h, and then quenched with water (20 mL) and extracted with DCM (3 × 20 mL).
- The combined organics are dried over $MgSO_4$ and the solvent evaporated under reduced pressure.
- The final product is formed through purification by flash column chromatography.

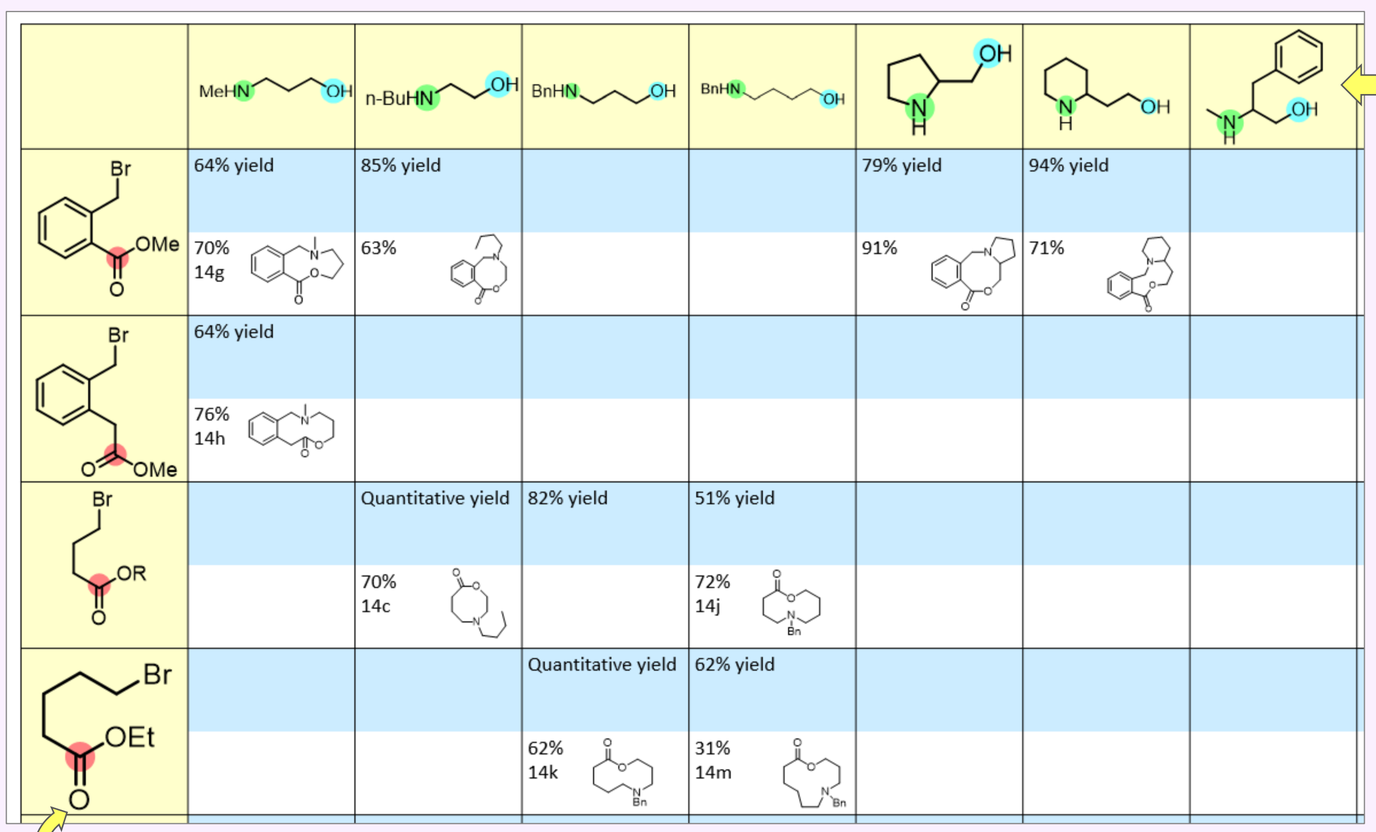
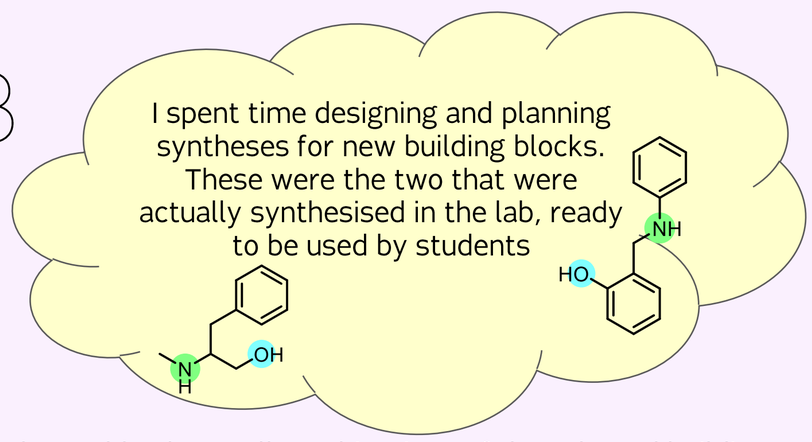



FIGURE 4: example showing a small section of the table of building blocks, their products and yields of each step

BLUE – alkylation details
WHITE – CRE details




The complete table shows all combinations of the selected building blocks. It is designed so students can easily select reagents, one from each axis, then use the general procedures to make their rings. Following the experiment, the students will input reaction details into the relevant box.

I reviewed existing research results to populate the table where combinations had already been carried out. This includes the yield of each step (%) and a diagram of the final product.

**This Teaching Labs Project will commence in January 2022 and continue for the foreseeable future. Hopefully it will be successful and enjoyable and I am excited to see what positive impact it will have in this area of chemistry. I'm looking forward to seeing the project grow as well as joining in with it myself during my third year.**

LAIDLAW SCHOLARS

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