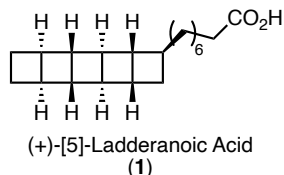
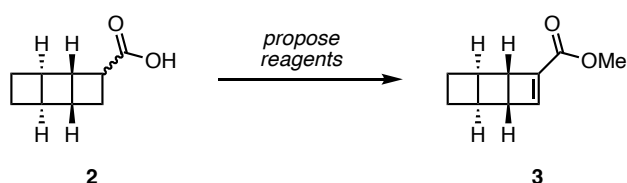


EAA Group Problems - Alistair Sterling – 19/11/2019

This set of problems is based on the recently-reported synthesis of (+)-[5]-Ladderanoic Acid (**1**) by the Brown group at Indiana University.



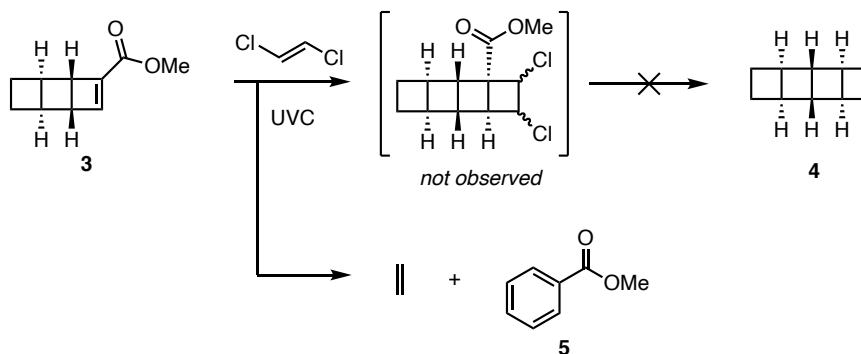
The first step of the synthesis relied on access to ester **3**, which they carried out starting from known carboxylic acid **2**.



1. How would you get from **2** to **3**? Reagents and plausible mechanisms required.

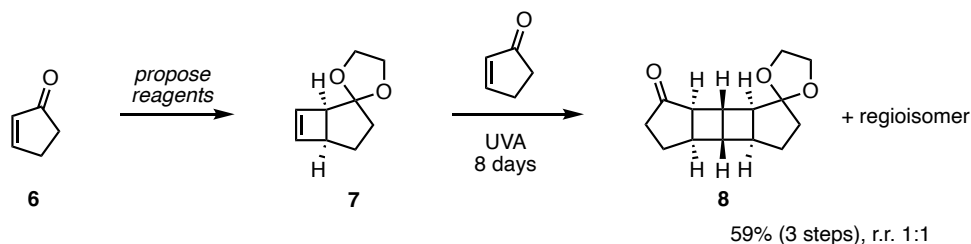
They then attempted to append an additional cyclobutane to the core. In the event, no desired product was observed. Instead, methyl benzoate and ethene were formed.

Intended route:



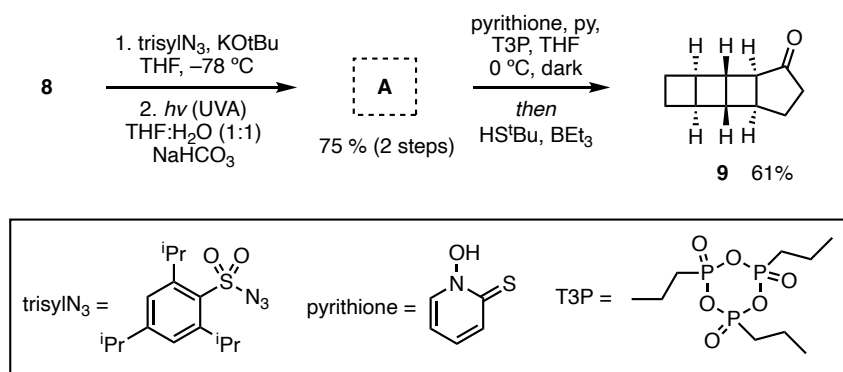
2. How are the alternative products (ethene and **5**) formed? Why was their original proposal destined to fail?

The group then employed a second strategy to avoid the issue discovered in question 2. Starting from 2-cyclopenten-1-one **6**, they built tetracyclic compound **8** in 3 steps.



3. Propose reagents and mechanisms for the transformation of **6** to **7**.

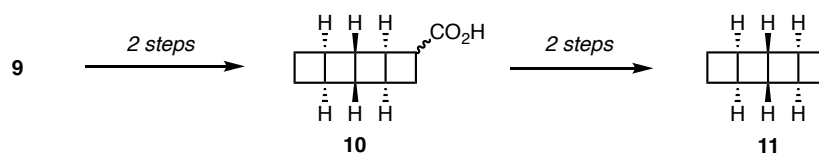
The next challenge in the synthesis was to contract the two cyclopentane rings. Conversion of the cyclopentyl ketone in **8** to the cyclobutane in **9** was achieved in 3 steps.



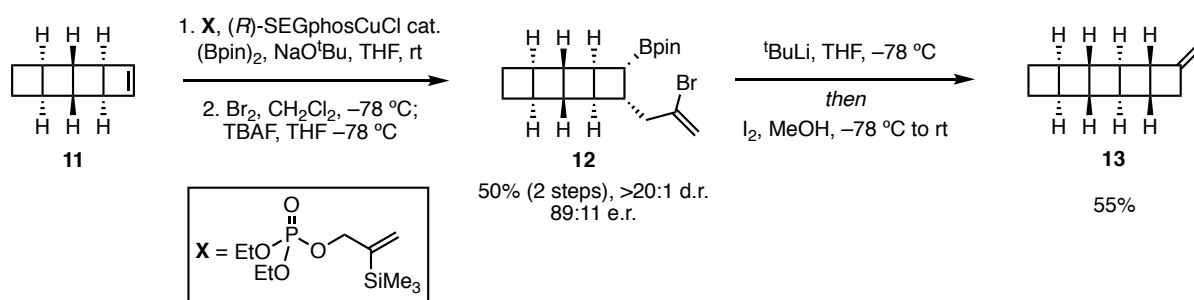
4. Suggest a structure for **A** by proposing mechanisms for:

- The conversion of **8** to **A** (note that the deprotection occurs in step 2)
- The conversion of **A** to **9**

A further ring contraction was employed to form carboxylic acid **10**. This was then transformed into hydrocarbon **11**, ready for the addition of the final ring. You do not need to comment on these steps.



To furnish the desired natural product **1**, a copper-catalysed desymmetrisation of **11** was followed by a few simple synthetic manipulations to complete the pentacyclic core.

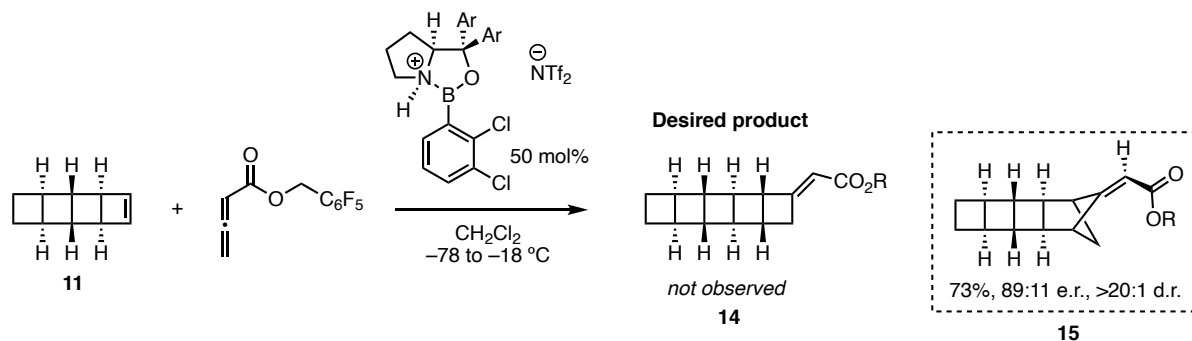


- Provide plausible mechanisms for the conversion of **11** to **12**. Stereochemical rationale is not required.
- Provide a mechanism for the conversion of **12** to **13**.

Product **13** was subsequently transformed into (+)-[5]-Ladderanoic Acid (**1**) through a further few trivial steps that will not be mentioned here.

Bonus:

On the way to the natural product, an interesting by-product was observed from the following reaction:



- Provide a plausible mechanism for the formation of **15** from **11**. Stereochemical rationale would be lovely but is not required.
Clue: olefin metathesis without the metal