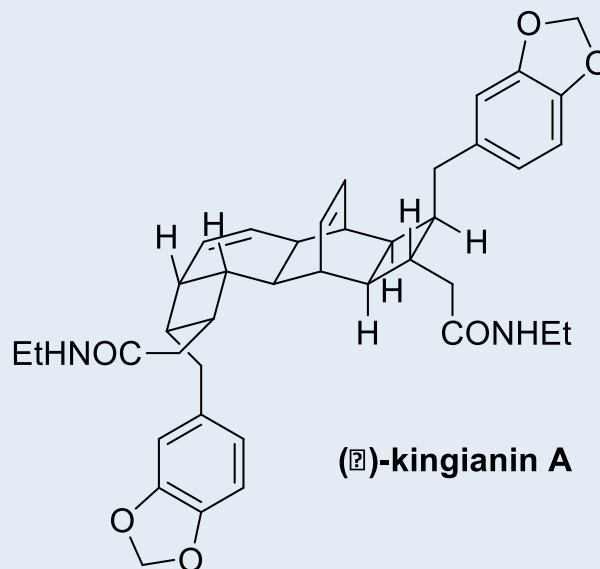


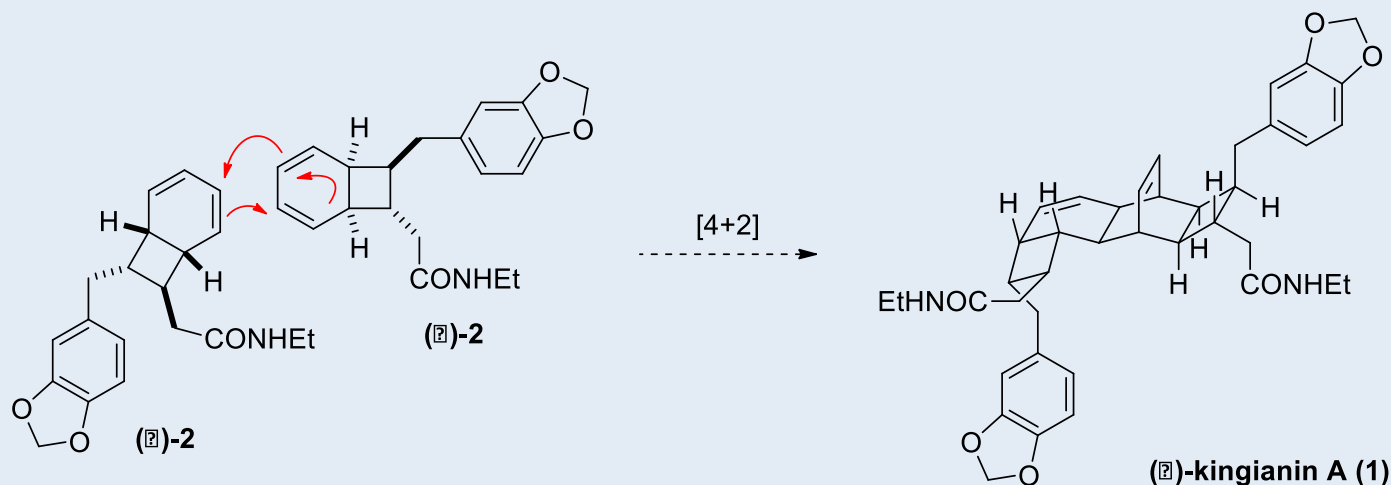
# Total Synthesis of Kingianins A, D and F



Alice Gatland  
Literature Presentation 4<sup>th</sup> June 2013

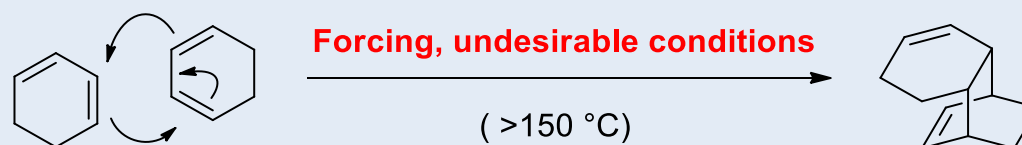
# Introduction

- The kingianins are a group of complex racemic bicyclo[4.2.0]octadiene dimers isolated from the bark of *Endiandra kingianai*.
- Kingianin A (**1**) was first isolated by the Litaudon group in 2010 who proposed a biosynthesis involving spontaneous Diels-Alder dimerisation of the bicyclo[4.2.0]octadiene precursor **2**:



*Org. Lett.* **2010**, *12*, 3638.

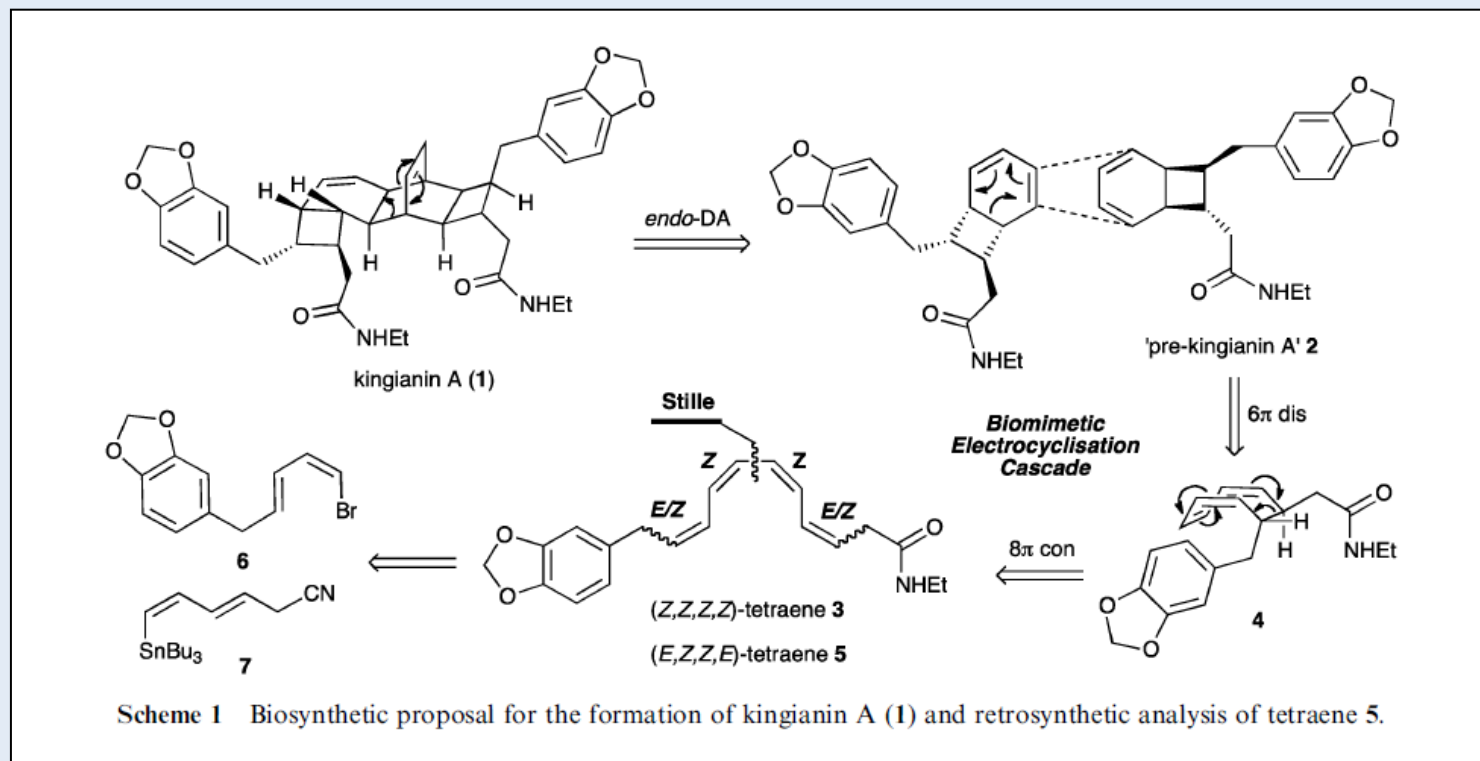
- But...



*J. Am. Chem. Soc.* **1964**, *86*, 5202.

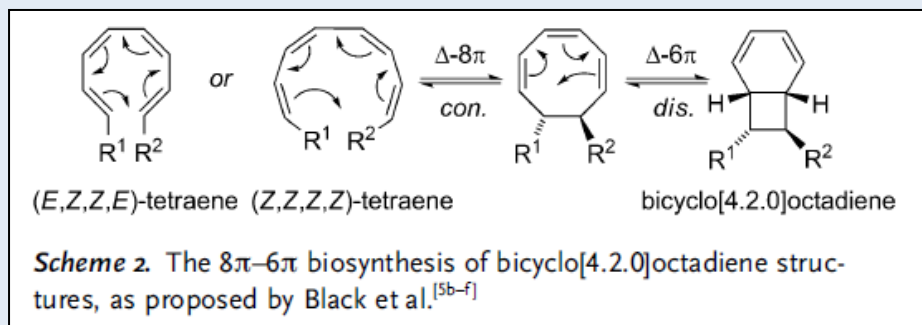
# First Synthetic Approach

- It was thought, however, that a structural feature within the Diels-Alder precursor **2** may lower the barrier to this transformation.
- Based on this biosynthetic speculation, the group of Moses published work on the synthesis of kingianin A in 2011.



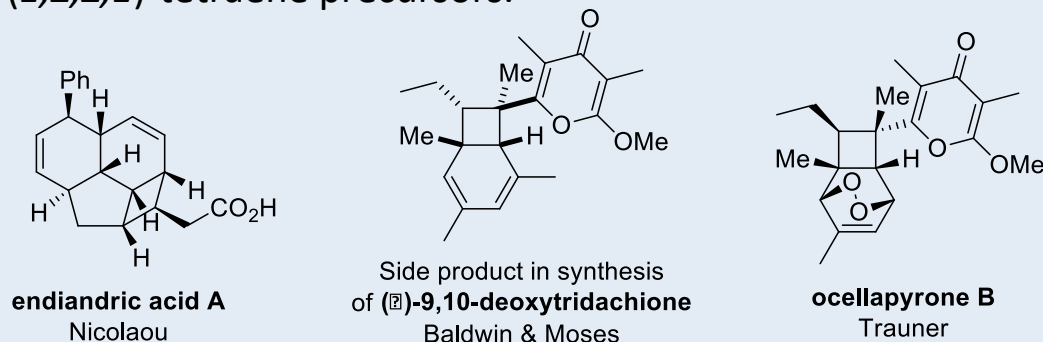
# Synthesis of Biosynthetic Monomer

- The bicyclo[4.2.0]octadiene skeleton is found in several natural products; the first to be isolated were the endiandric acids reported by Black and colleagues in the early 1980s.
- Black proposed that the bicyclo[4.2.0]octadiene structure was formed through a spontaneous  $8\pi$ - $6\pi$  domino electrocycloisalisation of either an (*E,Z,Z,E*)-tetraene or a (*Z,Z,Z,Z*)-tetraene.



*J. Chem. Soc. Chem. Commun.* **1980**, 902.

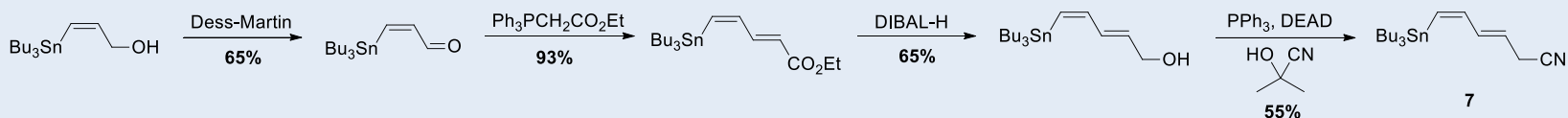
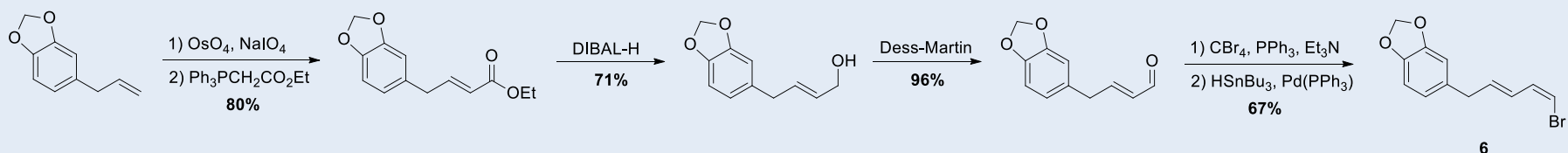
- A number of biomimetic syntheses of bicyclo[4.2.0]octadiene natural products have utilised the proposed (*E,Z,Z,E*)-tetraene precursors.



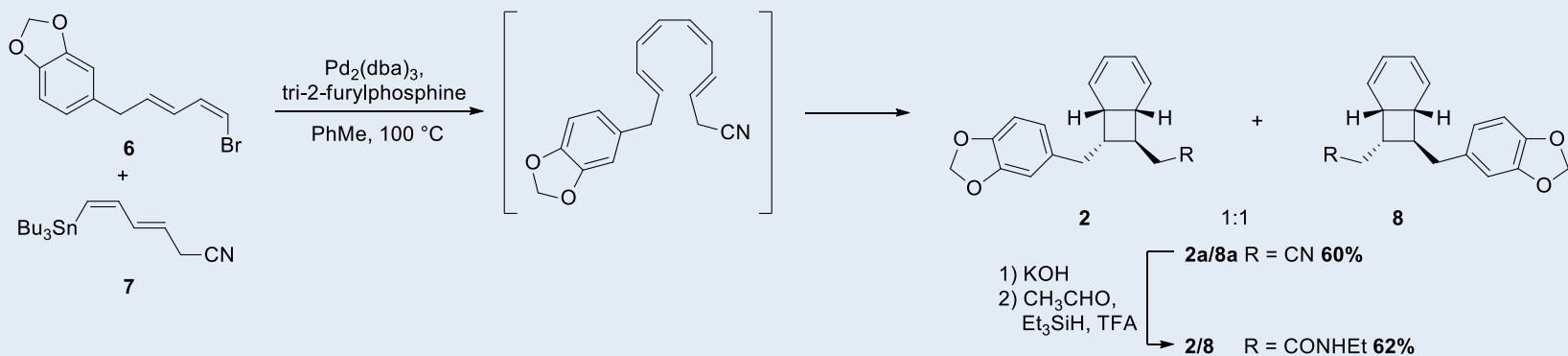
*J. Am. Chem. Soc.* **1982**, *104*, 5555; *Chem. Commun.* **2005**, 1687; *Angew. Chem. Int. Ed.* **2005**, *44*, 4602.

# Synthesis of Biosynthetic Monomer

- First synthesis of Diels-Alder precursor:

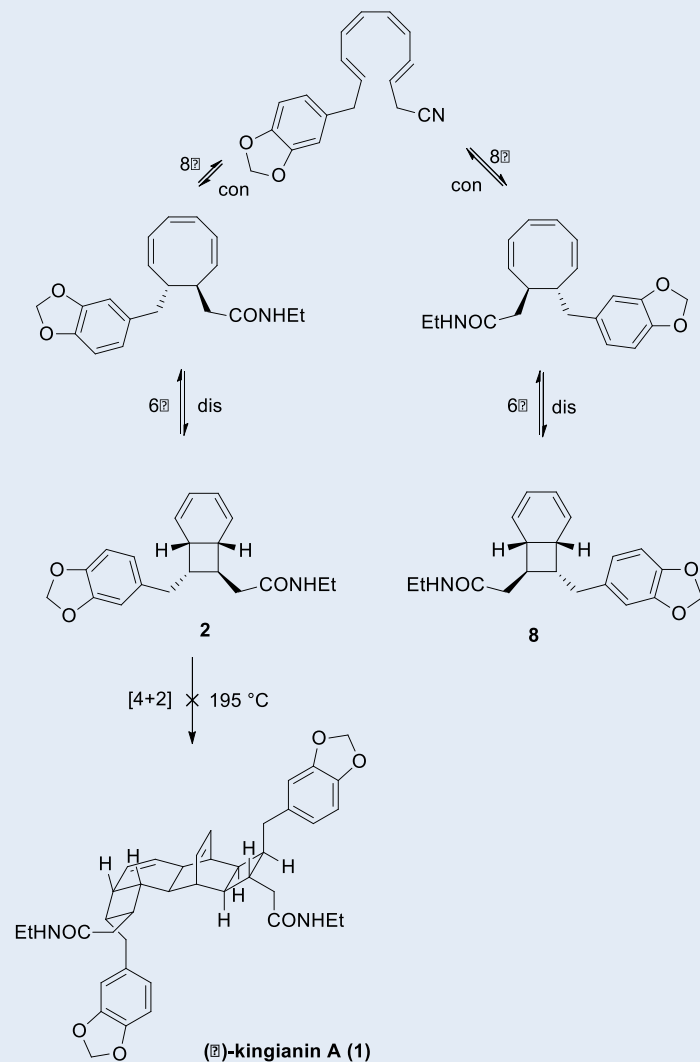


- Fragments **6** and **7** were found to undergo Stille coupling followed by rapid *in situ* electrocyclicisation to give a mixture of diastereoisomers of bicylcooctadienes.



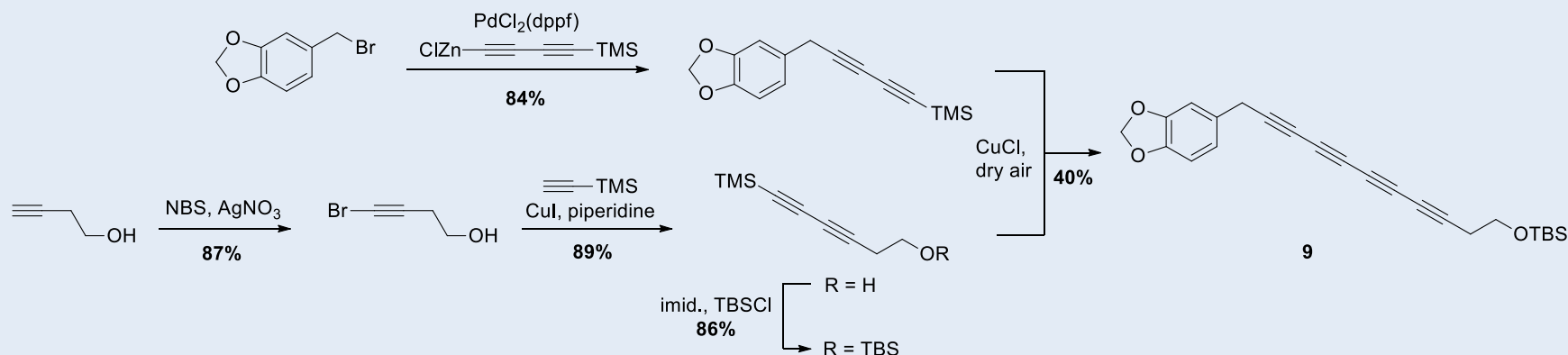
# Diels-Alder Dimerisation

- Diels-Alder precursor **2** was stable at room temperature over several weeks, showing no sign of dimerisation to kingianin A (**1**).
- Heating solutions of bicyclooctadienes **2** and **8** up to 195 °C provided no evidence for the formation of Diels-Alder dimers.
- Compounds **2** and **8** underwent interconversion, presumably *via* retro  $6\pi$ - $8\pi$  electrocyclicisation.
- The use of Grieco's conditions (addition of  $\text{LiClO}_4$  solution) was also unsuccessful.
- It was concluded that the biosynthesis of the kingianins probably does not proceed *via* a simple [4+2] cycloaddition.

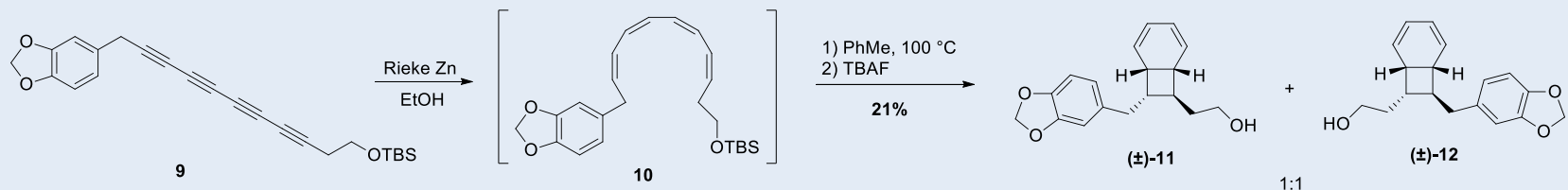


# A Second Attempt

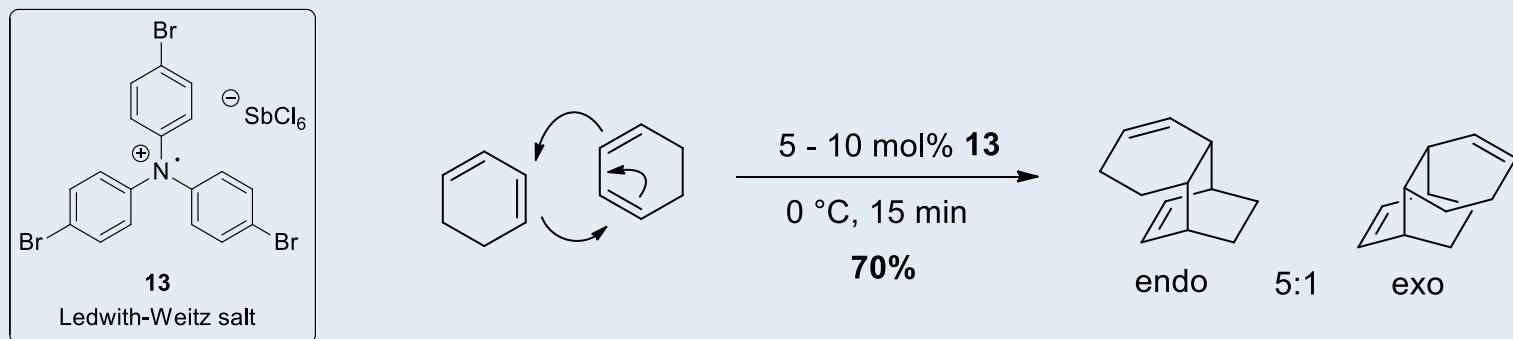
- A second investigation into the puzzling biosynthetic origin of the kingianins was published by Sherburn and colleagues this year.
- As well as probing the dimerisation of cyclooctadiene fragments, the group also took the opportunity to investigate the use of the *(Z,Z,Z,Z)*-tetraene in the synthesis of these fragments. Most synthetic work in the literature has utilised *(E,Z,Z,E)*-tetraenes.
- To this end, a gram-scale preparation of unsymmetrical tetrayne **9** and its unprecedented reduction to a *(Z,Z,Z,Z)*-tetraene was developed.



# Radical Cation Diels-Alder



- As a standard Diels-Alder reaction between this class of substrates had failed in the past, it was hypothesised that a radical cation Diels-Alder dimerisation may be required to form the kingianins in nature.

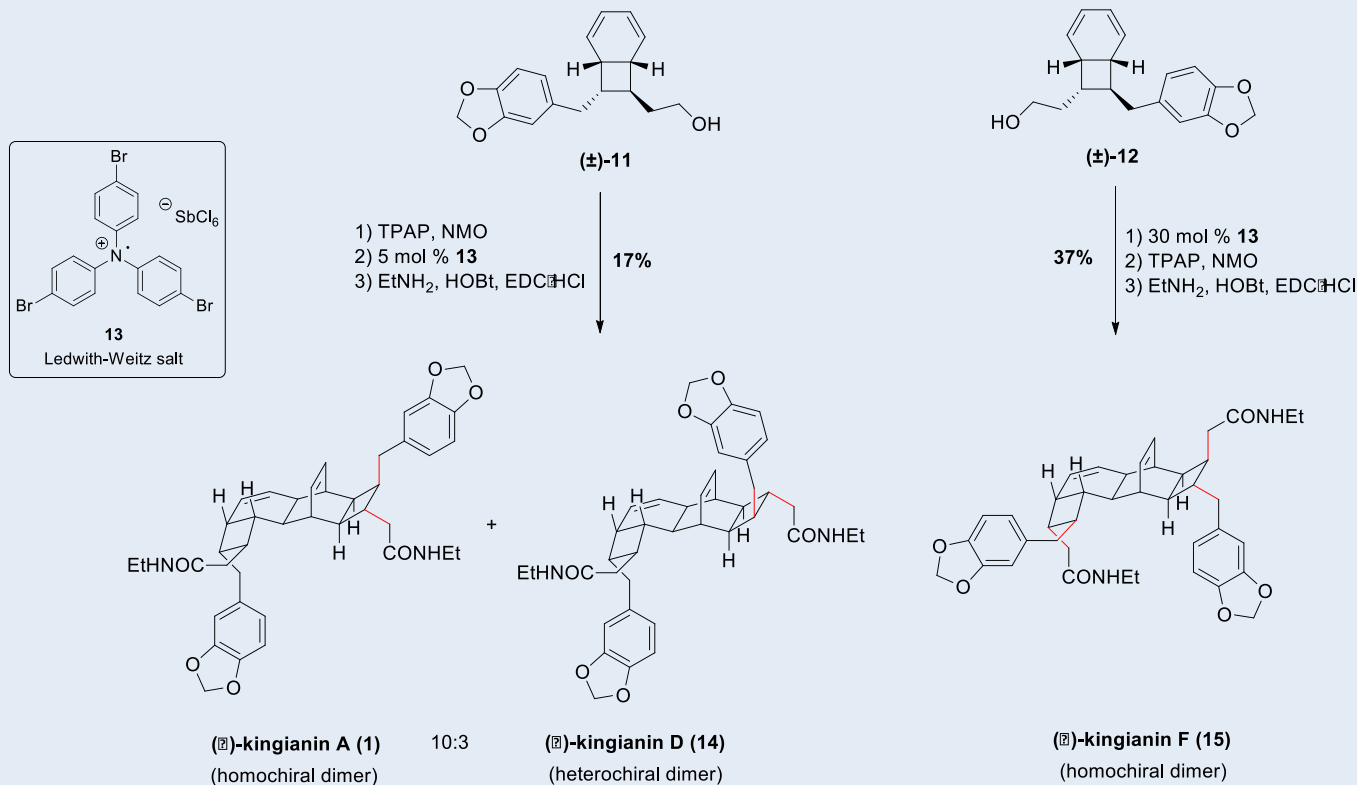


- Radical cation salt **13** converts dienophiles to radical cations which are highly electron deficient and add readily to dienes. This is especially effective when the dienophile is a conjugated diene.



# Radical Cation Diels-Alder

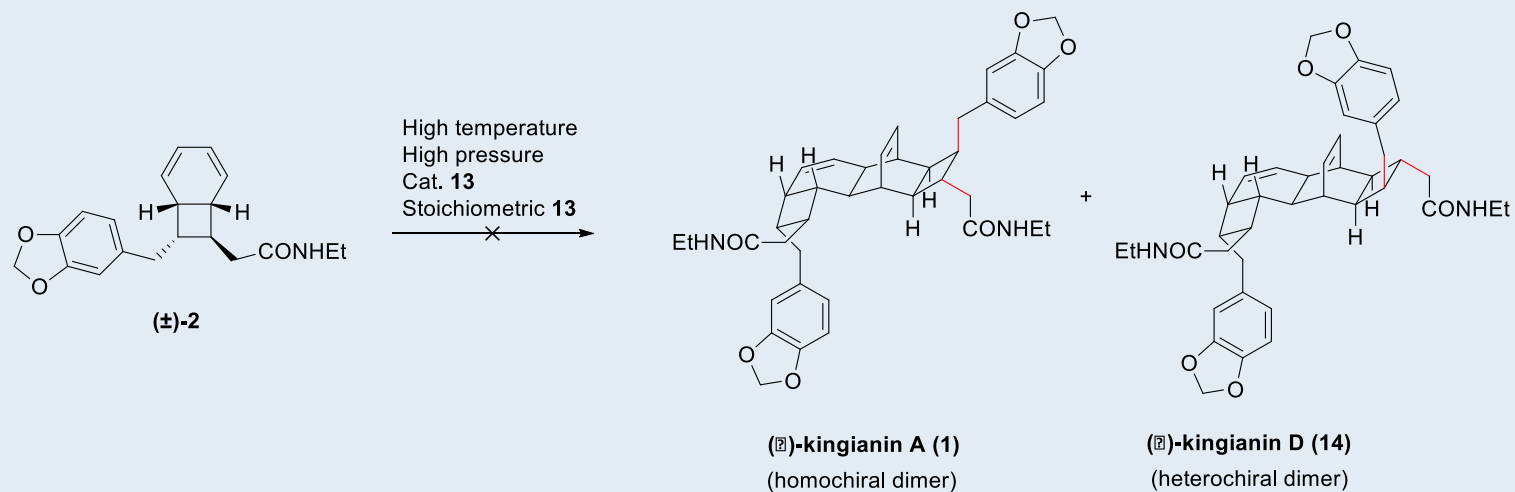
- It was found that both dicyclooctadiene diastereoisomers could indeed be converted into kingianins using this methodology.



- Although other products were observed in the reaction mixtures, only 3 of the possible 32 isomeric products could be isolated. These 3 all result from *endo*-selective Diels-Alder reactions on the convex face of both diene and dienophile.

# Radical Cation Diels-Alder

- Interestingly, the proposed biosynthetic intermediate **2**, which was the Diels-Alder precursor in Moses' work, failed to cyclise even under radical cation conditions:



# Summary

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- Bicyclo[4.2.0]octadienes are found in a number of natural products.
- It is proposed that they are biosynthesised by an  $8\pi$ - $6\pi$  electrocyclisation sequence which has been shown to be effective in the laboratory synthesis of a number of natural products.
- The electrocyclisation precursor can be either an (*E,Z,Z,E*)-tetraene or a (*Z,Z,Z,Z*)-tetraene.
- Sherburn and colleagues developed a novel method for the gram-scale synthesis of an unsymmetrical tetrayne and its reduction to the (*Z,Z,Z,Z*)-tetraene.
- Moses found that the bicyclo[4.2.0]octadiene intermediates would not undergo thermal Diels-Alder dimerisation, so this is unlikely to be the biosynthetic mechanism for kingianin natural products.
- Sherburn determined that the natural products can form under radical cation Diels-Alder conditions using Ledwith-Weitz salt, although further work is required to explain the site and orientational regioselectivity observed, and how this occurs in nature.