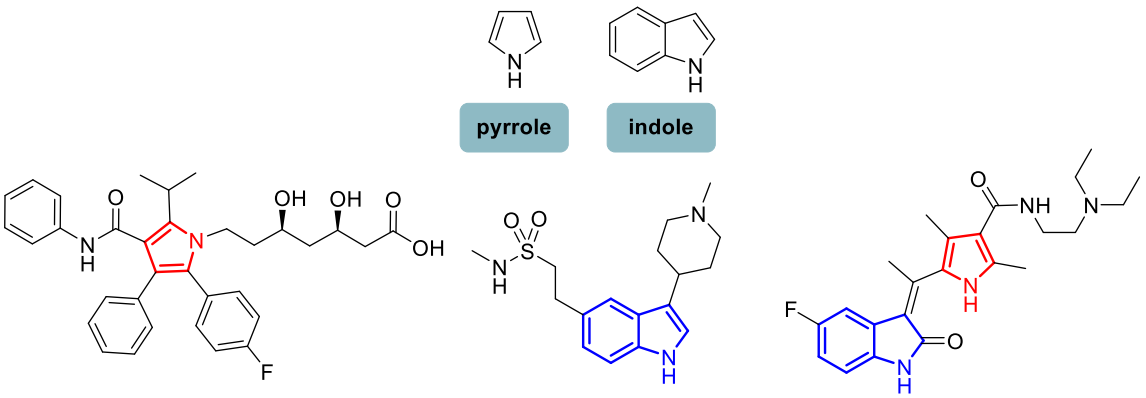
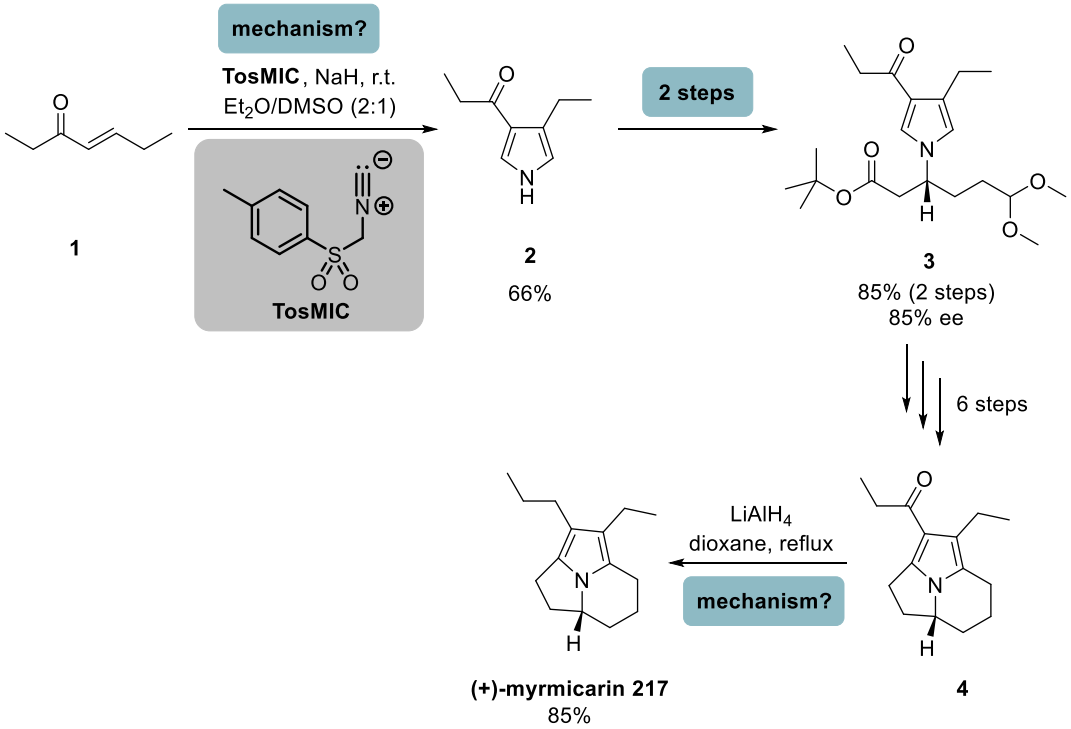
Pyrroles and Indoles

1. Fundamental aspects of pyrroles and indoles.



   a. What are the pKa values (in DMSO) for pyrrole and indole?
   b. Outline the difference(s) between the indole anion and the *N*-methylindole anion.
   c. Label the preferred sites of electrophilic aromatic substitution for pyrrole and indole. Suggest methods for substituting pyrroles at less favoured positions.
   d. Suggest conditions for the sulfonation and nitration of pyrrole, respectively.

2. Pyrrole synthesis
   a. Many process-scale routes to atorvastatin (see Q1) proceed *via* a Paal-Knorr pyrrole synthesis. Propose a synthesis of the non-amine starting material needed for this step.
   b. The myrmicarin alkaloids contain highly substituted pyrrole cores. The Movassaghi group access these targets by functionalising 3,4-disubstituted pyrrole **2** (see below). Provide a mechanism for the formation of **2** from enone **1** and TosMIC.

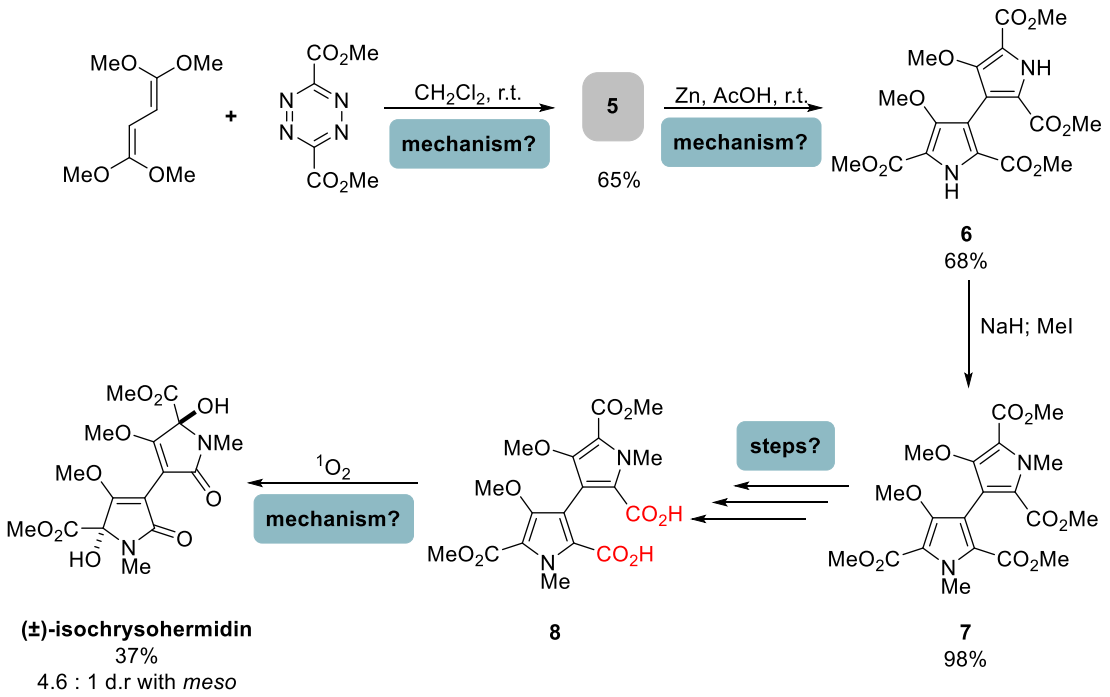


Org. Lett., **2005**, *7*, 4423

   c. Suggest conditions for the formation of *N*-alkylated pyrrole **3** from **2**.

d. Propose a mechanism for the reduction of **4** to give myrmicarin 217, as shown. What product(s) would result from addition of $LiAlH_4$ at -78 °C, followed by an acidic work-up?

e. The Boger synthesis of isochrysohermidin involves the formation of bis-pyrrole **6** (see below). Suggest a mechanism for the formation of **6** from the starting materials shown and identify intermediate **5**.



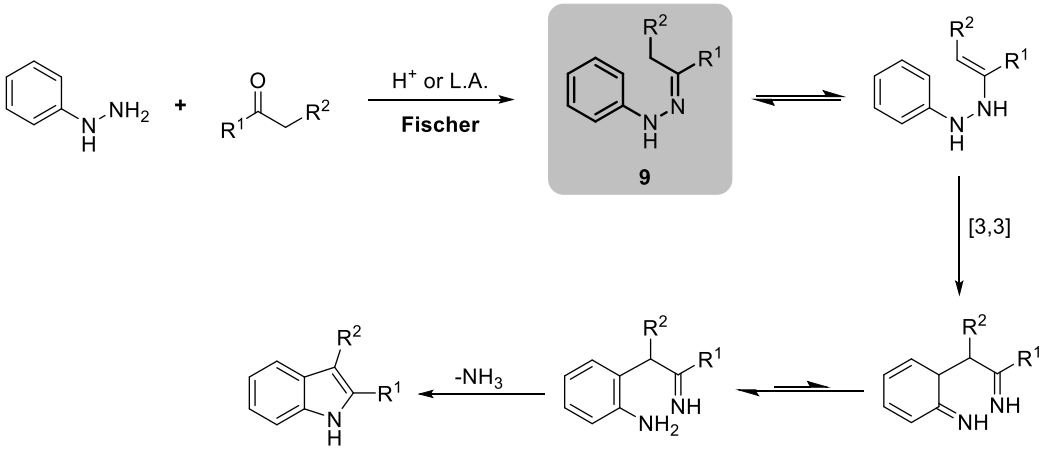
J. Am. Chem. Soc., **1993**, *115*, 11418

f. Outline a strategy for the selective formation of diacid **8** from **7**.

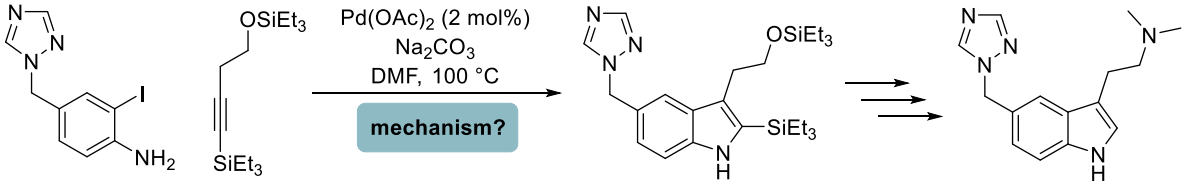
g. Propose a mechanism for the formation of isochrysohermidin from **8** with singlet oxygen.

3. Indole synthesis

a. The Fischer indole synthesis proceeds *via* a hydrazone intermediate such as **9**. Propose another method by which intermediates of this kind could be accessed (i.e. not from a phenylhydrazine).

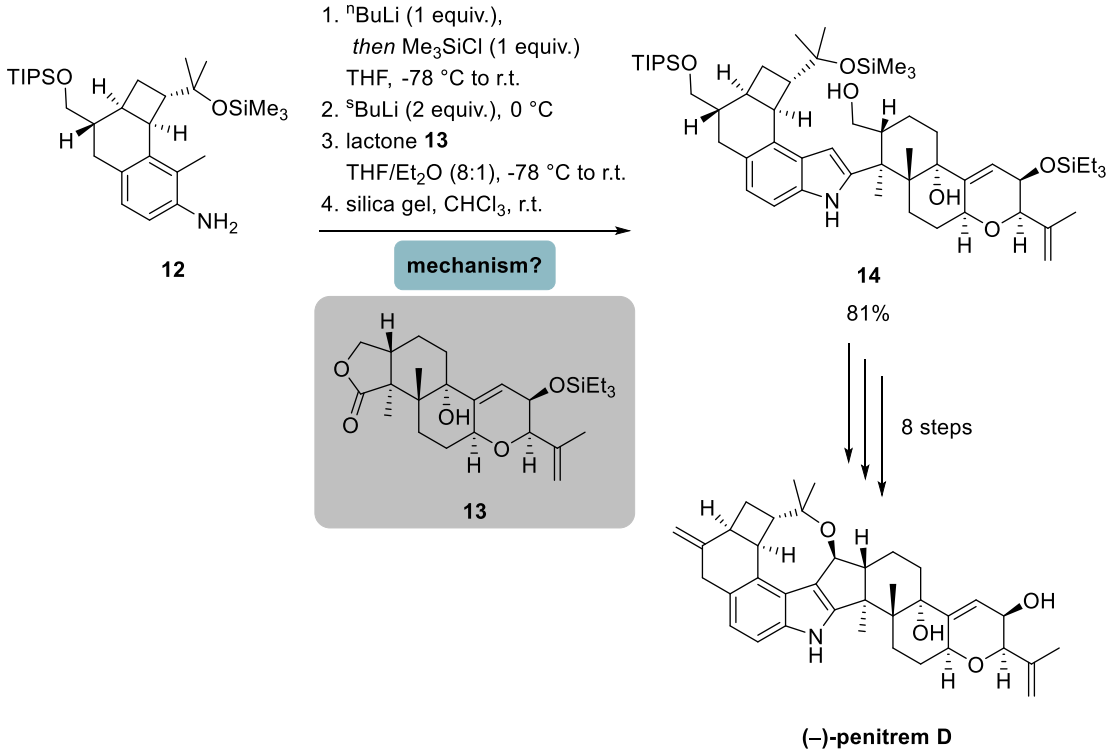


b. Provide a mechanism for the Larock indole synthesis of **11** from **10**.



Tetrahedron Lett., **1994**, *35*, 698

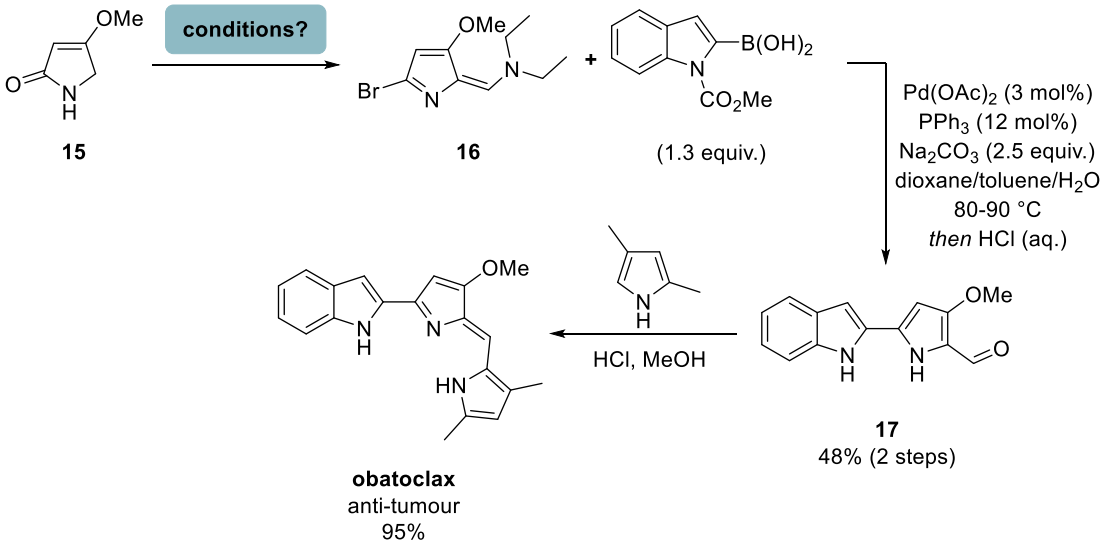
c. Propose a mechanism for the synthesis of indole **14** from the starting materials shown.



J. Am. Chem. Soc., **2003**, *125*, 8228

4. Compounds containing both pyrrole and indole moieties

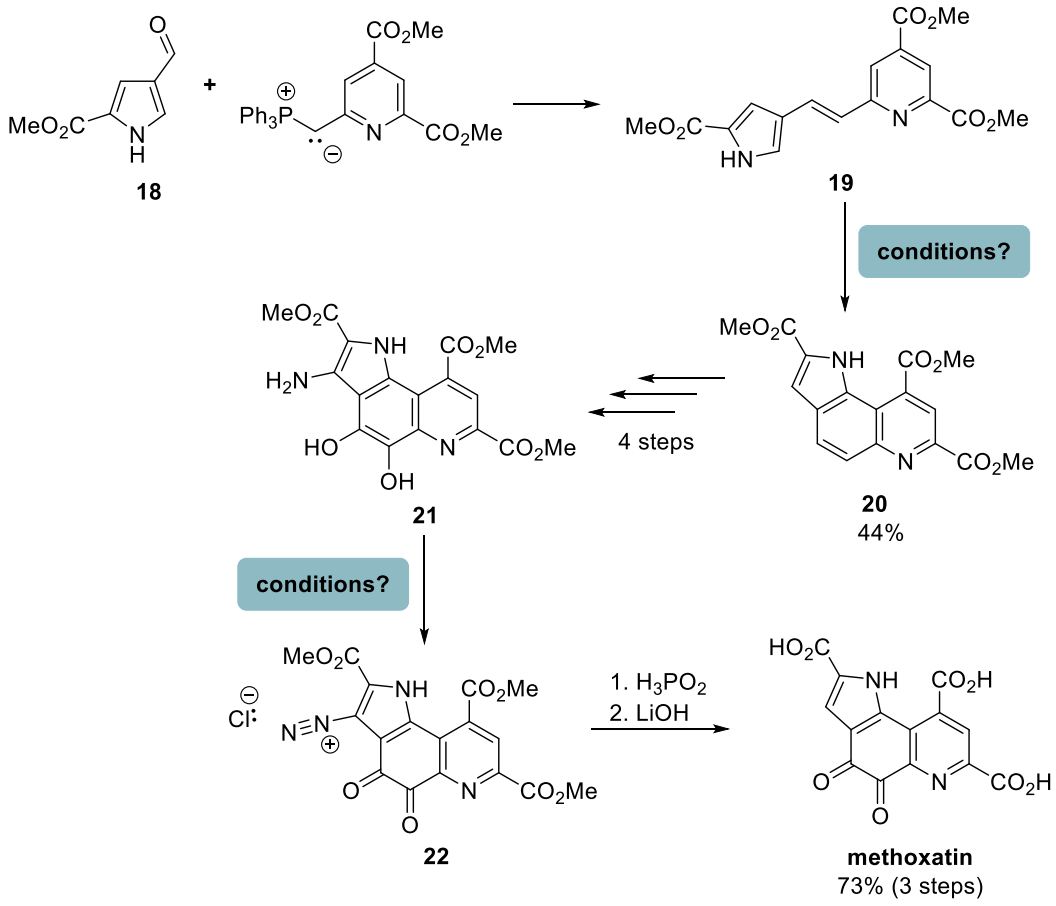
a. Consider the Gemin X route to obatoclax (shown below). Suggest conditions for the formation of bromide **16**. Why was this compound chosen as a coupling partner for the Suzuki step rather than, e.g., the corresponding 2-bromo-5-formylpyrrole?



Org. Process Res Dev, **2007**, *11*, 1051

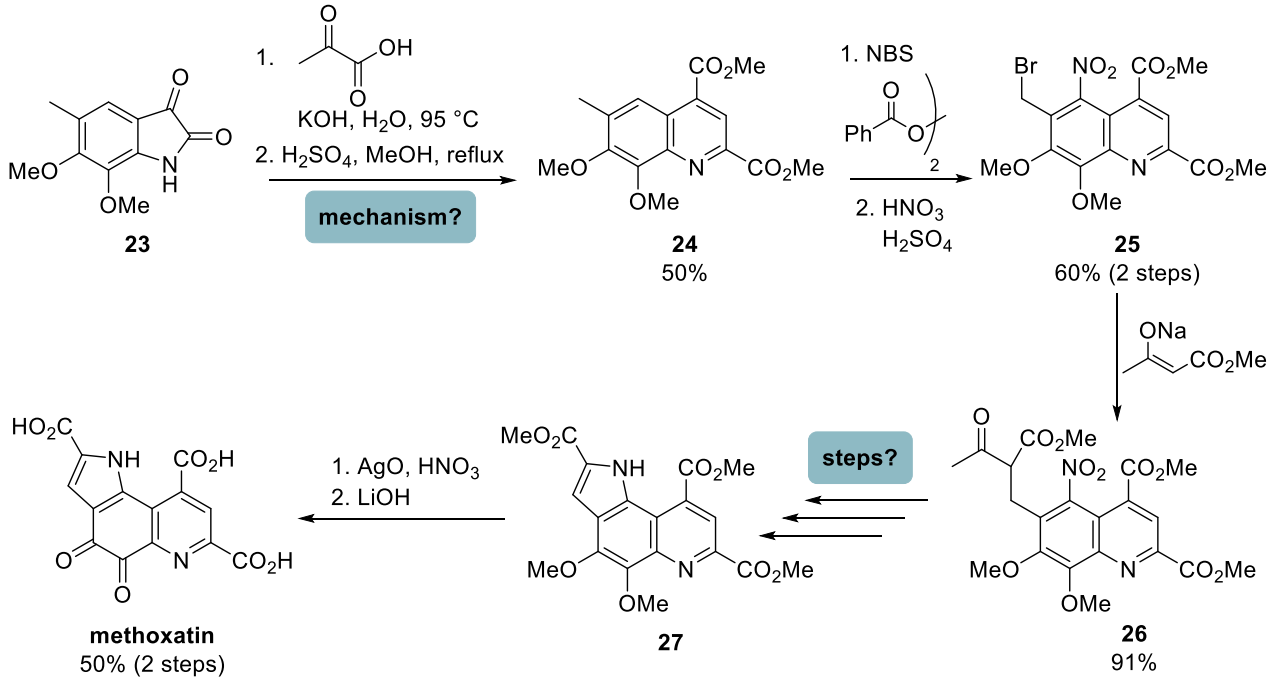
b. The cross-coupling step shown resulted in moderate yields due to a competing side reaction. What is this side reaction likely to be?

c. The Hendrickson synthesis of methoxatin (see below) starts from pyrrole **18**. Suggest a practical method for the preparation of **18**.



J. Org. Chem., **1982**, *47*, 1150

d. Suggest conditions for the conversion of **19** to deoxymethoxatin ester **20**. What kind of process occurs here?
e. Suggest conditions for the conversion of hydroquinone **21** to diazonium salt **22**.
f. The Weinreb synthesis of methoxatin proceeds by ring expansion of isatin **23** to give pyridine **24** (see below). Propose a mechanism for this transformation.



J. Org. Chem., **1982**, *47*, 2833

g. Propose a sequence for the conversion of nitroquinoline **26** to compound **27**.