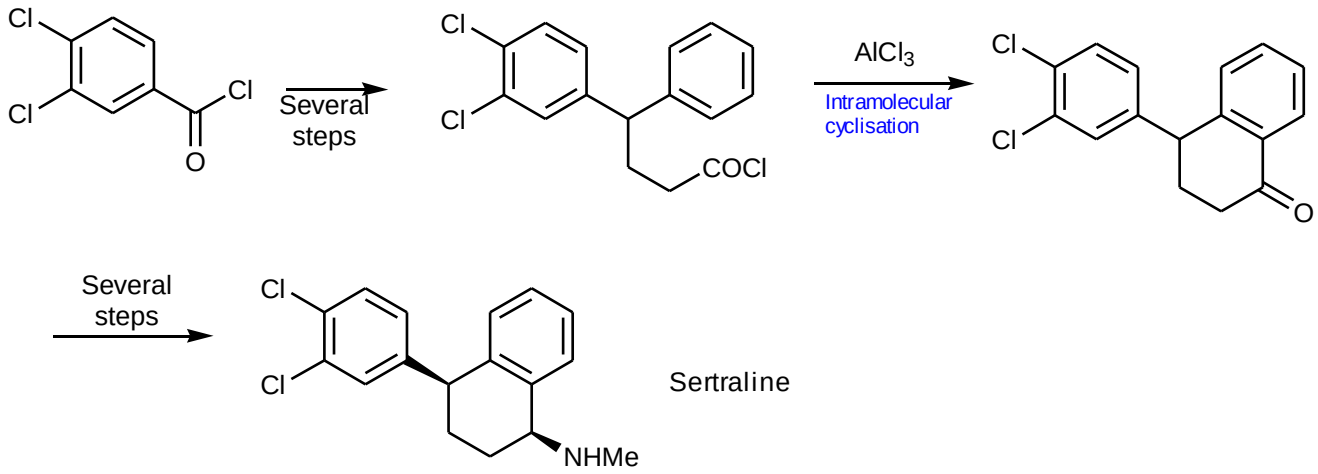
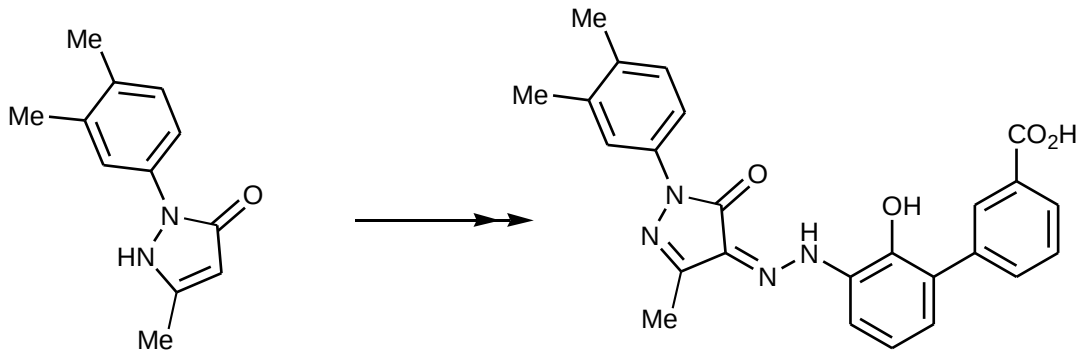
Chapter 4: Cyclic systems in drug synthesis

Question 4.1
In the synthesis of **sertraline** shown in Fig. 4.10, a Friedel Crafts acylation took place on one aromatic ring but not the other. Why?



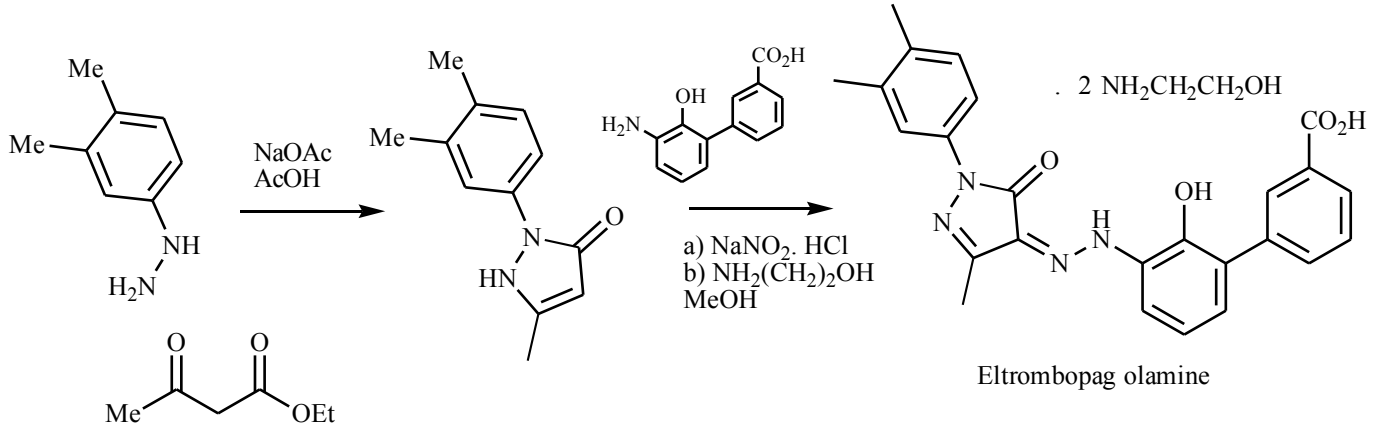
Answer
This is due to the different reactivies of the rings to electrophilic substitution. Chloro substituents have an elecron withdrawing effect on an aromatic ring making it less electron rich and less liable to undergo electrophilic substitutions such as the Friedel Crats acylation.

Question 4.2
Eltrombopag is a drug that was approved in 2008 for the treatment of patients having low platelet counts. It acts as an agonist at the receptor for the hormone **thrombopoietin.** The synthesis of the compound involves intermediate I. Suggest how this intermediate could be synthesised.



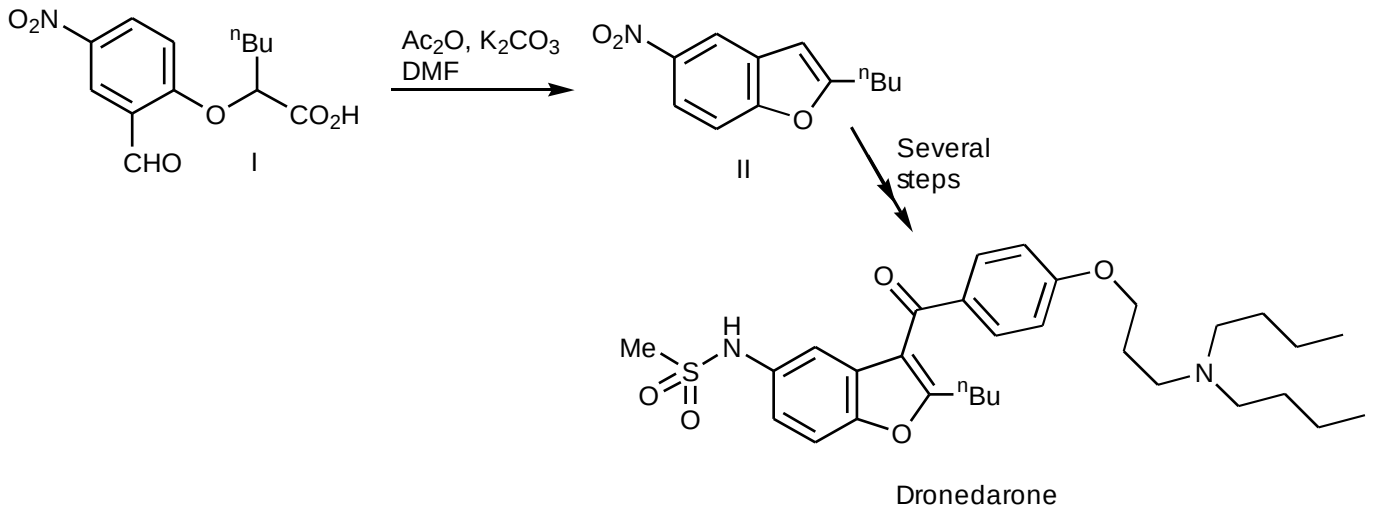
Answer

The intermediate contains a 5-membered heterocycle which could be formed by an intermolecular cyclisation involving a hydrazine and a β-keto ester. The hydrazine would act as a dual nucleophile and the β-keto ester as a dual electrophile.



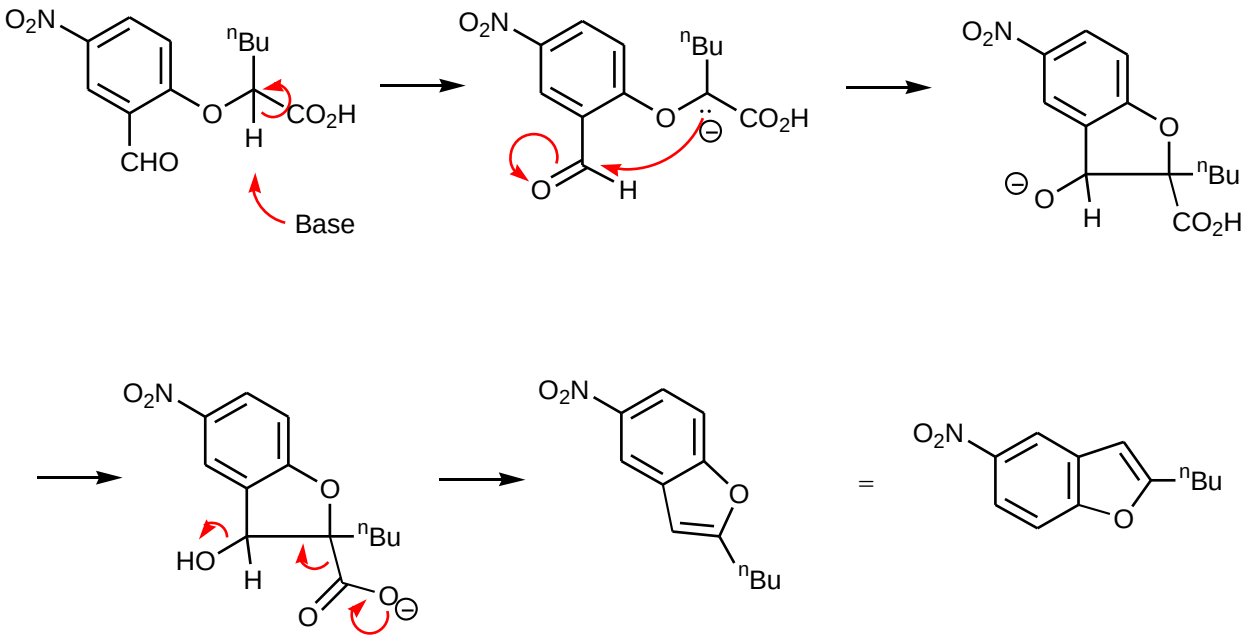
Eltrombopag olamine

Question 4.3
The following synthesis of a benzofuran (II) was involved in the synthesis of **dronedarone,** which is used in the treatment of cardiac arrythmias. Propose a mechanism by which the benzofuran intermediate is formed.



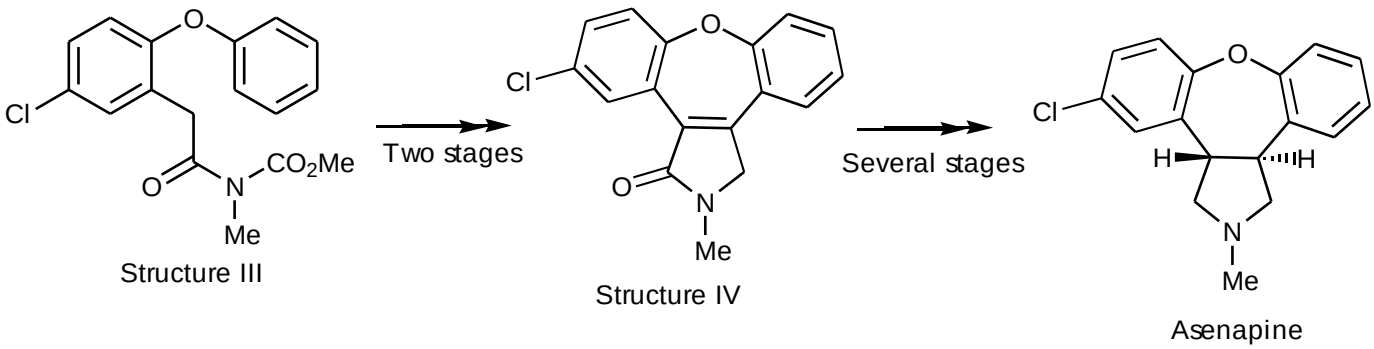
Dronedarone

Answer
One possible mechanism is the following



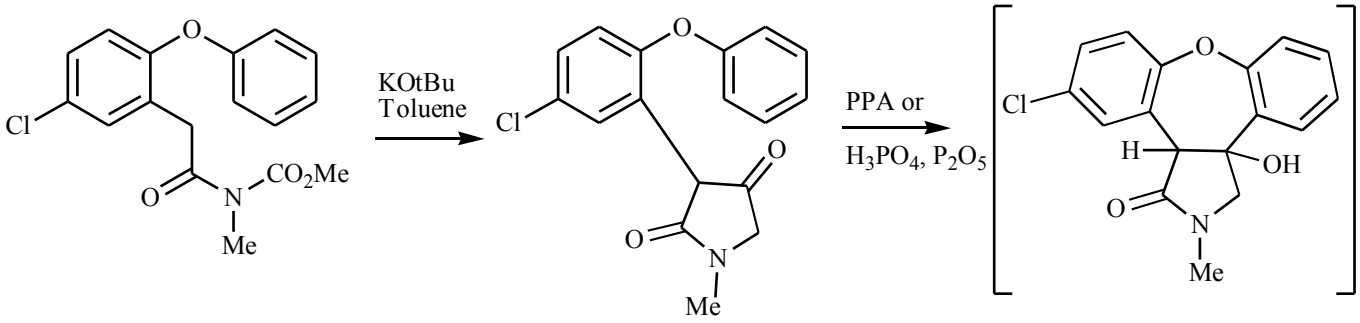
Question 4.4

Structure III was prepared as part of a synthesis to **asenapine,** which has been approved in the US as an atypical antipsychotic agent. Structure III was converted in two stages to the tetracyclic structure IV. Suggest how this might have been carried out.

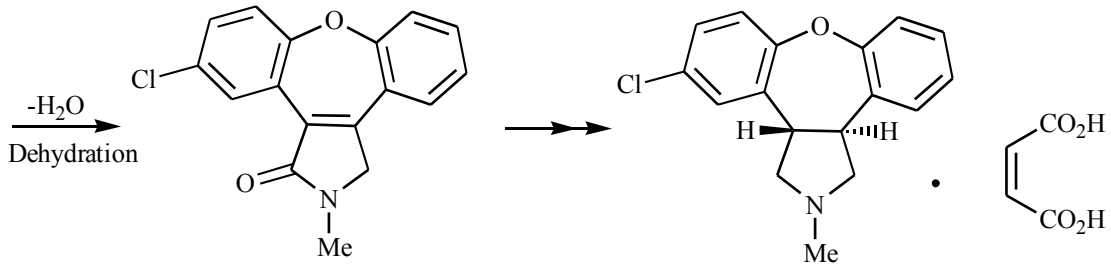


Answer

It involves a Diekmann like cyclisation to give an oxo lactam, which is then treated with acid to promote an intramolecular Friedal crafts reaction followed by a dehydration.



Oxo lactam



Asenapine maleate