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Synthesis and chemistry of the insect antifeedant azadirachtin

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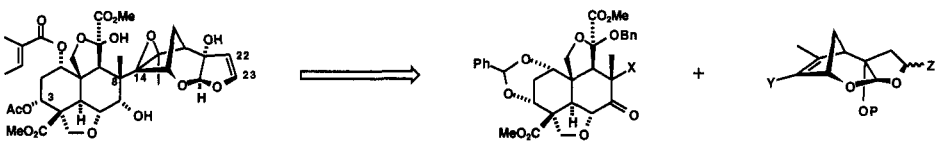
Abstract

The synthesis of key fragments towards the total synthesis of the insect antifeedant azadirachtin is described, including the decalin portion of this molecule, which was also obtained by natural product degradation using an oxidative and retro-aldol process.

The natural product azadirachtin, which was isolated from the neem tree *Azadirachta indica* A. Juss (Meliaceae),[1] has generated enormous worldwide interest due to its potential as a new insect pest control agent. The compound is extremely active as an antifeedant and growth disruptant in a large range of insect species, whilst retaining very low mammalian toxicity. Commercial formulations of azadirachtin and neem extracts have been shown to be highly effective in the field. Both the chemistry[2] and biological properties[3] of azadirachtin have been the subject of several symposia and recent reviews.



Azadirachtin — *Decalin portion* — *Hydroxyfuran acetal portion*

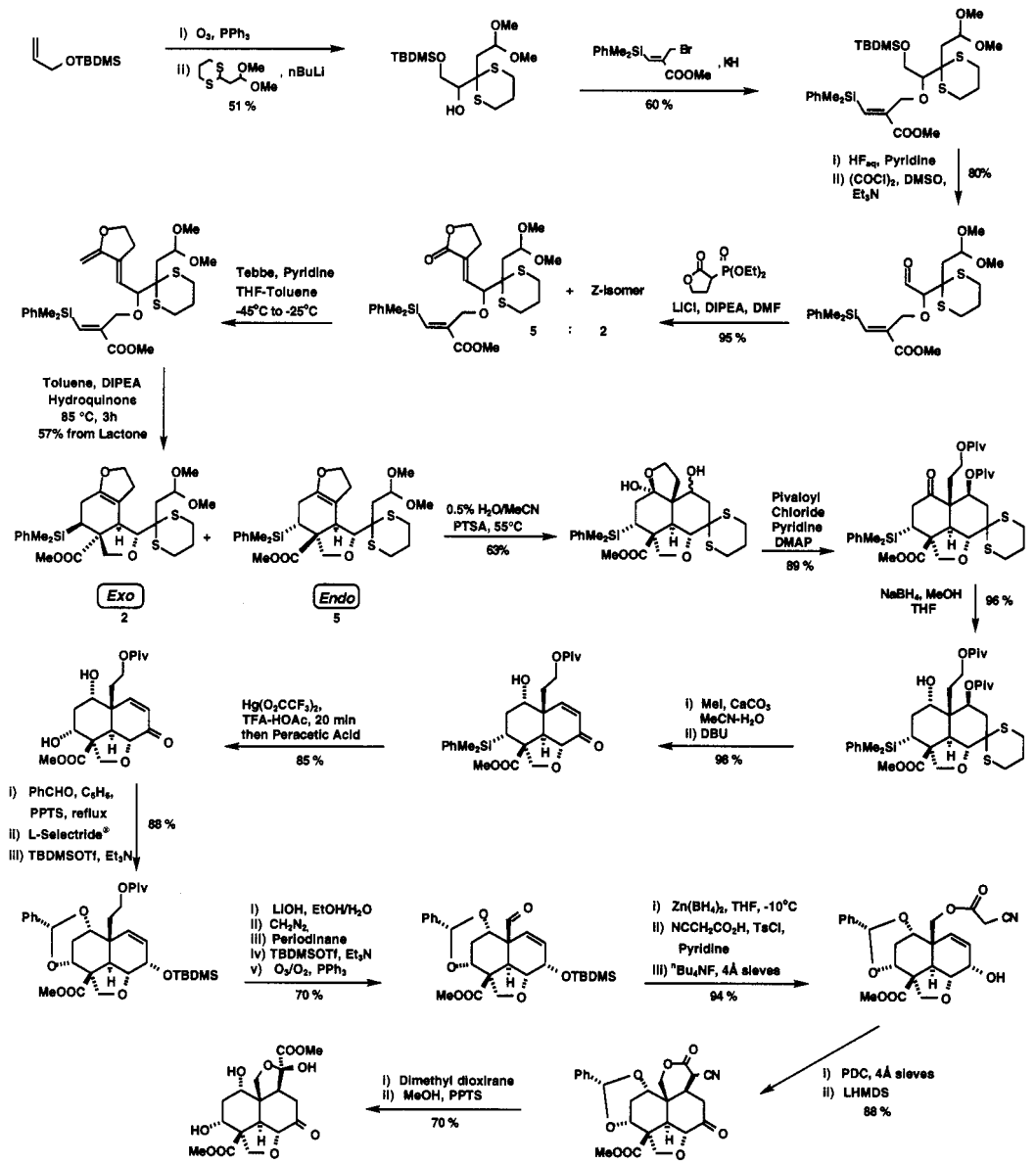
Scheme 1

Owing to the activity of azadirachtin and its fascinating structure,[4] we have become interested in the functional groups responsible for its biological activity. We have therefore devised substantial structure modification programs,[5] along with synthetic studies leading to several key fragments and potential mimics of azadirachtin.[6] These studies are designed to give a deeper understanding of the feeding mechanisms and host plant recognition by insects at a molecular level. We have published extensively on the structural changes we have made to the natural product, together with the subsequent effects on activity and on the preparation of various sub-structures of this complex molecule.[2] Here we report on some of our studies towards the total synthesis of azadirachtin.

Azadirachtin contains sixteen stereogenic centres, seven of which are fully substituted and this, together with the facts that it is acid and base labile, prone to rearrangement,[7] photosensitive and contains a high density of oxygen atoms, make it a formidable synthetic challenge. We have chosen to prepare this compound by a convergent approach which will bring together a decalin fragment with a hydroxyfuran acetal portion (Scheme 1). We recognise this coupling involves the formation of a difficult bond, but therein lies the challenge.

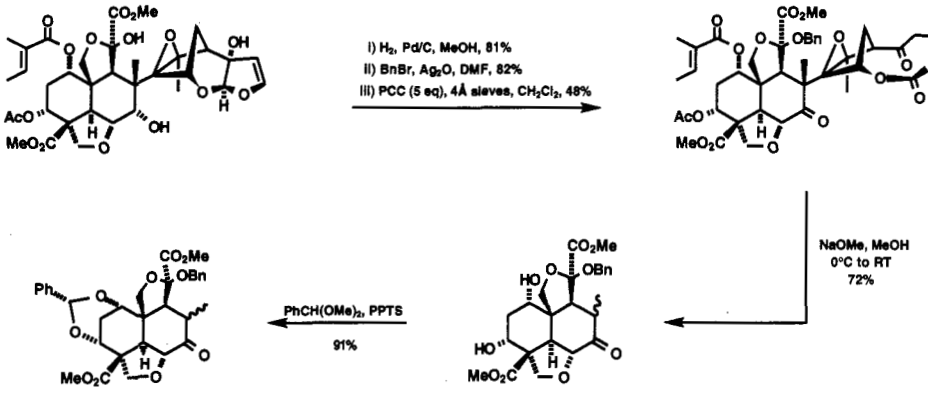
As a prelude to the total synthesis, we have formulated relay schemes which permit the preparation, from the natural product, of an advanced intermediate which we also hope to obtain by synthesis. Methods to convert this intermediate back to the natural product have also been developed, in particular the re-introduction of the C22-C23 enol double bond which makes use of an acetal exchange process.[8]

For the preparation of the decalin portion required for the total synthesis, we devised the route shown in Scheme 2.[9] This synthetic work incorporates some interesting new chemistry, particularly the use of the dimethylphenylsilyl substituent which controls much of the inherent stereochemistry of the decalin fragment and can be unmasked at a later stage as the C-3 hydroxyl substituent.



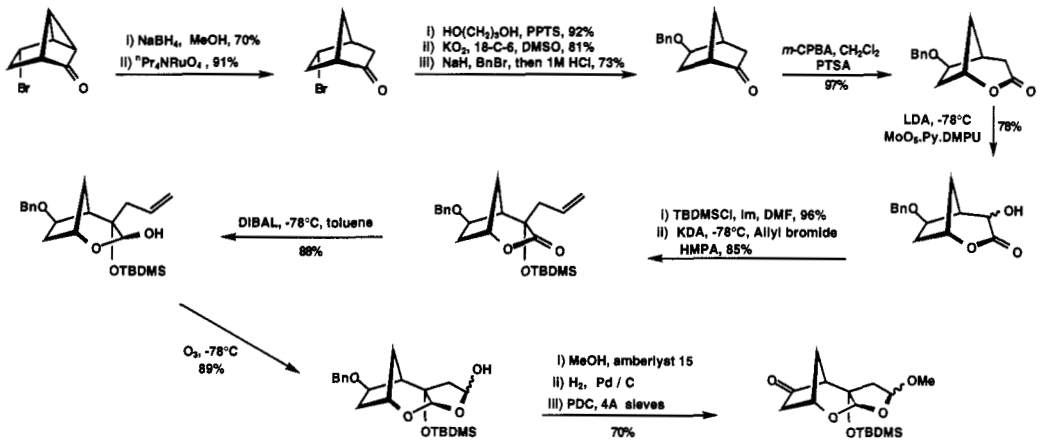
Scheme 2

We have also devised a route by which we can degrade the natural product to provide further quantities of the decalin fragment (Scheme 3). This chemistry uses an interesting oxidative cleavage reaction followed by a sequence of reactions designed to eventually cleave the C8-C14 bond, giving the decalin by a retro-aldol process.[10]



Scheme 3

The synthesis of the hydroxyfuran acetal portion has also been achieved (Scheme 4) and this fragment can be elaborated further to provide more substituted coupling partners.[11]



Scheme 4

We are now in the process of using a radical tether approach to bring together the two components to form the crucial C8-C14 bond and hence complete the synthesis of azadirachtin utilising a relay route.

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