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Cycloaddition reactions for the synthesis of piperidine and indolizidine alkaloids

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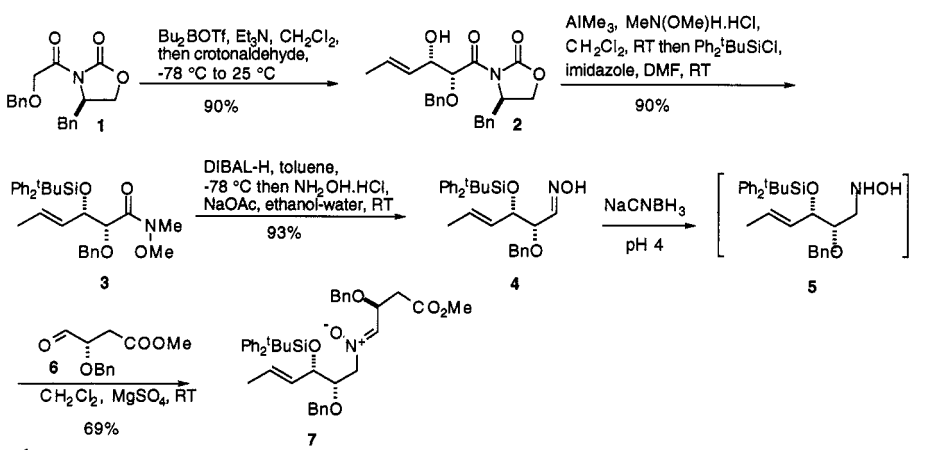
Abstract: The intramolecular nitrone dipolar cycloaddition of *N*-alkenylnitrones has been utilised in approaches to the synthesis of a family of indolizidines such as castanospermine and a tethered swainsonine analogue. Examples of a tandem hydroxylamino-alkyne cyclisation/dipolar trapping experiment in the synthesis of (±)-adaline and (±)-euphococcinine are outlined.

Introduction

In recent years we have developed a general intramolecular nitrone dipolar cycloaddition approach to all-*cis*-2,3,6-trisubstituted piperidines [1] and related indolizidines [2-4]. We then investigated the possibility of using the same approach for the synthesis of polyhydroxylated piperidines and indolizidines of the family of glycosidase inhibitors, which culminated in a successful total synthesis of deoxynojirimycin [5]. In this paper we describe an approach to the synthesis of castanospermine **16** and a tethered analogue **26** of swainsonine for binding studies on mannosidases. We also report the tandem intramolecular 6-*endo-dig* cyclisation of hydroxylamino-alkynes followed by intramolecular dipolar cycloaddition of a pendant alkene to synthesise the bicyclic alkaloids adaline **43** and euphococcinine **51**.

Approach to Castanospermine

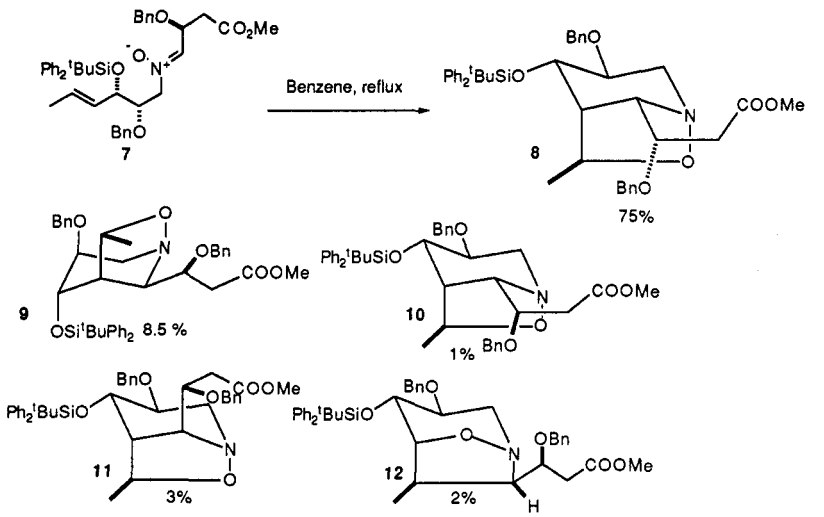
Castanospermine **16** is an attractive synthetic target owing to its glucosidase inhibitory activity and potential for interfering with glycoprotein trimming and processing in the cellular recognition process involving the HIV virion [6].



Scheme 1

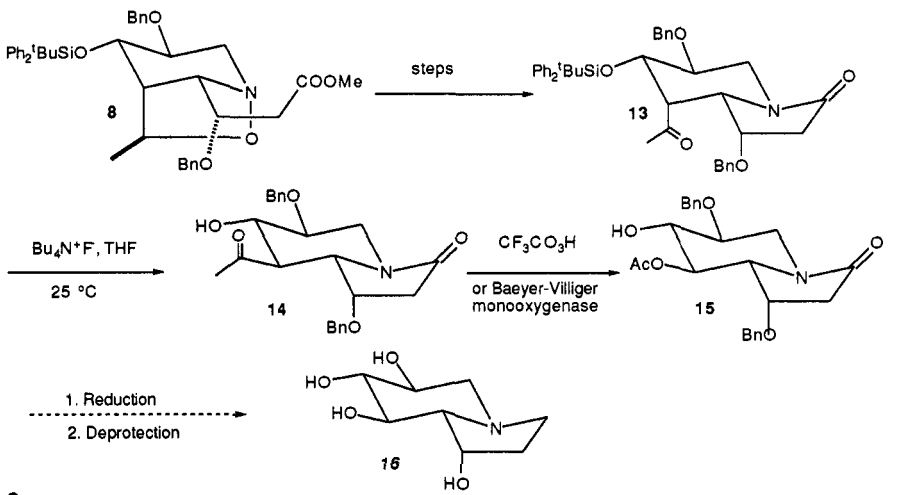
Our synthetic approach depends on the synthesis of the nitrone **7** and its intramolecular cycloaddition via a transition state in which the equatorial preference for the alkoxy substituents was expected to control the chair-like folding. The synthesis of the nitrone is summarised in Scheme 1. The relative and absolute stereochemistry of the alkoxy substituents in **3** are determined by the Evans *syn*-aldol reaction.

The nitrone **7** is formed from the hydroxylamine **5** and the aldehyde **6** derived from (*S*)-malic acid. Model reactions had established that the intramolecular cycloaddition was largely controlled by the preference for two alkoxy substituents to be equatorial in the chair-like transition state [4]. This was largely the case (Scheme 2) for the nitrone **7**; other adducts formed included that (**9**) derived from the alternative chair transition state as well as the adduct **11** from (*E*)-(*Z*)-isomerisation of the nitrone and the adduct **10** from epimerisation of the benzyloxy substituent adjacent to the nitrone.



Scheme 2

The end strategy used for deoxynojirimycin [5] called for the reductive cleavage of the N-O bond followed by elimination of the resulting alcohol, ozonolysis of the alkene, and stereoselective reduction of the carbonyl group . In the event this was unsuccessful for castanospermine, and it was decided to attempt the Baeyer-Villiger approach (Scheme 3).



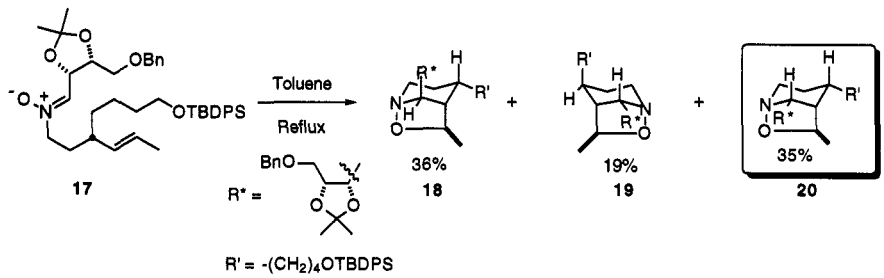
Scheme 3

Reductive cleavage of the N-O bond of **8**, oxidation of the resulting secondary alcohol, and cyclisation to the indolizidinone afforded an intermediate **13** for Baeyer-Villiger studies. This Reductive cleavage of the N-O bond of **8**, oxidation of the resulting secondary alcohol, and cyclisation to the indolizidinone afforded an intermediate **13** for Baeyer-Villiger studies. This proved totally unreactive to all oxidising reagents. Attempts to epimerise the methyl ketone resulted in β-elimination of the alkoxy group except under the novel conditions of fluoride-induced

desilylation of the TBDPS ether. Under these conditions a moderate yield of the diequatorial hydroxyketone **14** was obtained, presumably by a retro-aldol/aldol pathway. At the time of writing we are attempting both chemical and enzymic Baeyer-Villiger oxidations of this substrate to complete the synthesis of castanospermine.

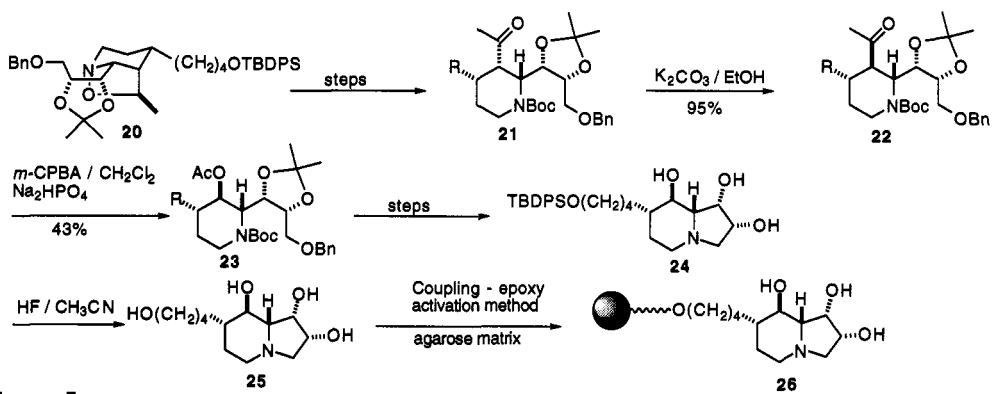
Synthesis of a Tethered Swainsonine Analogue

Swainsonine has been identified as a powerful inhibitor of lysosomal α-mannosidase [7]. Various studies have shown that the introduction of substituents at C-7 has no effect on the binding of swainsonine analogues, and we have designed the analogue **25** with a potential tether for attachment to an agarose matrix to explore the potential of such a substrate **26** in affinity chromatography of mannosidases. Our synthesis of the analogue **25** again depended on the intramolecular nitrone dipolar cycloaddition of the nitrone **17** followed by the usual strategy of formation of a methyl ketone **21**, epimerisation and Bayer-Villiger oxidation to introduce the final secondary alcohol group. The required nitrone **17** is derived from an aldehyde obtained from D-isoascorbic acid and a hydroxylamine in which the allylic stereocentre is generated by a Johnson-Claisen rerrangement of a chiral allylic alcohol precursor (Scheme 4).



Scheme 4

Surprisingly, the cycloaddition was quite non-stereoselective, and considerable quantities of the adducts **18** and **19** were observed in which the cycloaddition had taken place either from the alternative (*E*)-nitrone stereoisomer or from the alternative chair transition state respectively. Evidently the required all-equatorial adduct **20** arises form a mismatched transition state in which there is severe steric interaction between the acetonide and the allylic substituents. The epimer at the allylic stereocentre of the nitrone **17** undergoes smooth cycloaddition to give the corresponding all-equatorial adduct suggesting a matched situation. As it transpires the unwanted diastereoisomers **18** and **19** can also be used to make epimeric tethered swainsonine analogues, as the absolute stereochemistry at C-7, C-8 and C-8a is not important for the mannosidase binding properties.

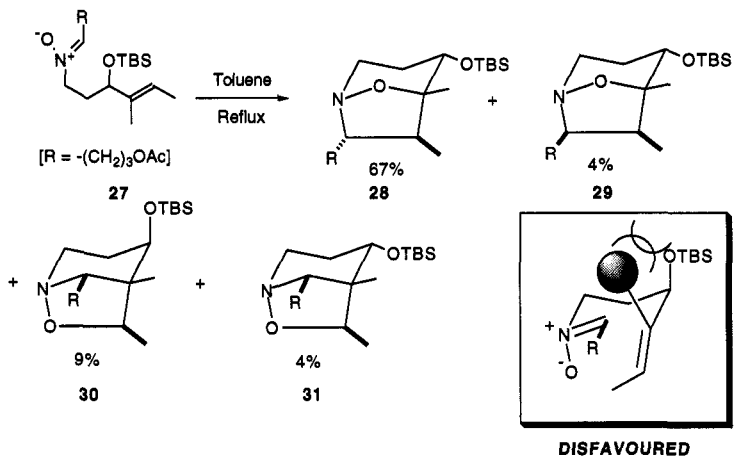


Scheme 5

Scheme 5 illustrates the elaboration of the adduct to the tethered swainsonine analogue. Noteworthy is the observation that the epimerisation of the axial methyl ketone **21** to the equatorial ketone **22** occurs smoothly, there being no offending β-alkoxy substituent to undergo elimination. Furthermore the Bayer-Villiger oxidation of the methyl ketone **22** occurs in reasonable yield. The swainsonine analogue **25** has been tethered to an agarose matrix for evaluation as an affinity material for mannosidases. Results of the binding studies will be reported in due course.

Influence of Allylic Substituents on Regiochemistry of Cycloaddition

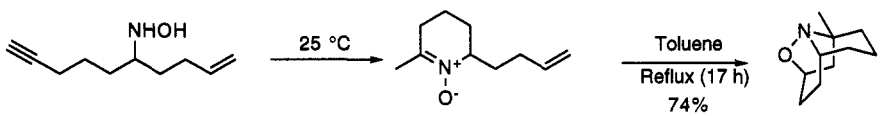
The examples of nitrone cycloaddition above illustrate the subtle effects that allylic substituents can have on both the regiochemistry of the cycloaddition and the chair-folding of the transition state. In an approach to the indolizidine core of allopumiliotoxin 323B' we have been studying the model nitrone cycloaddition illustrated in Scheme 6. Oppolzer [8] had previously proposed that the regiochemistry of addition of nitrones such as **27** was largely determined by a kinetic preference for the nitrogen atom to be within a six-membered ring, and that this could only be overturned if the internal substituent was cation-stabilising. The nitrone **27** allows a test of these competing influences, and shows a surprising preference for the unexpected regioisomer **28** having nitrogen in the seven-membered ring. We attribute this influence to the allylic strain in the transition state leading to the expected adduct **30**, and this is confirmed when the offending internal methyl group is not present; the adduct then reverts to the regiochemistry of **30**.



Scheme 6

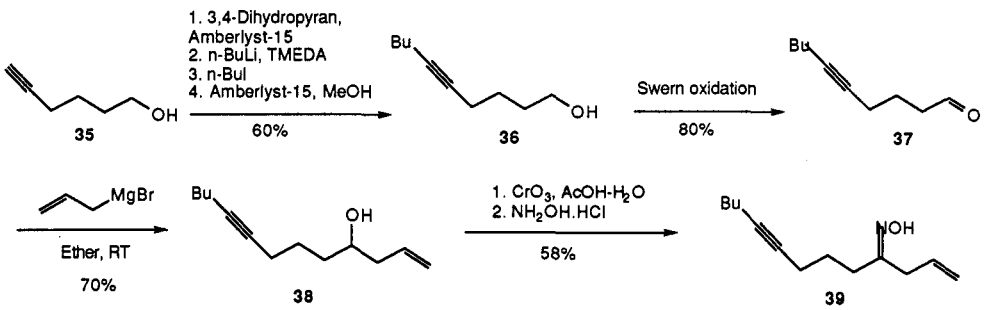
Intramolecular Hydroxylamine-Alkyne Cyclisations and Tandem Dipolar Cycloadditions

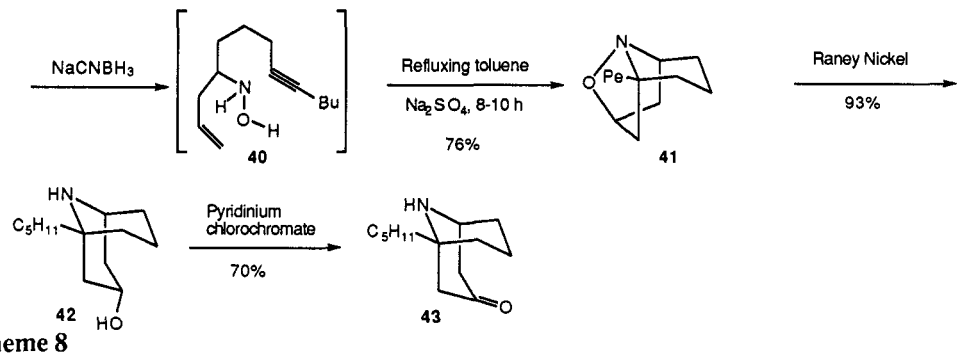
The influence of double bond substituents on the rate of reverse Cope elimination of hydroxylamines is also significant [9-13]. We have studied a related cyclisation of hydroxylamines onto triple bonds which can in the presence of pendant dipolarophiles lead to the trapping of the resultant nitrones as cycloadducts [2]. Scheme 7 illustrates an example. Much indirect evidence is available to suggest that the cyclisation step is a concerted 'ene' reaction [14].



Scheme 7

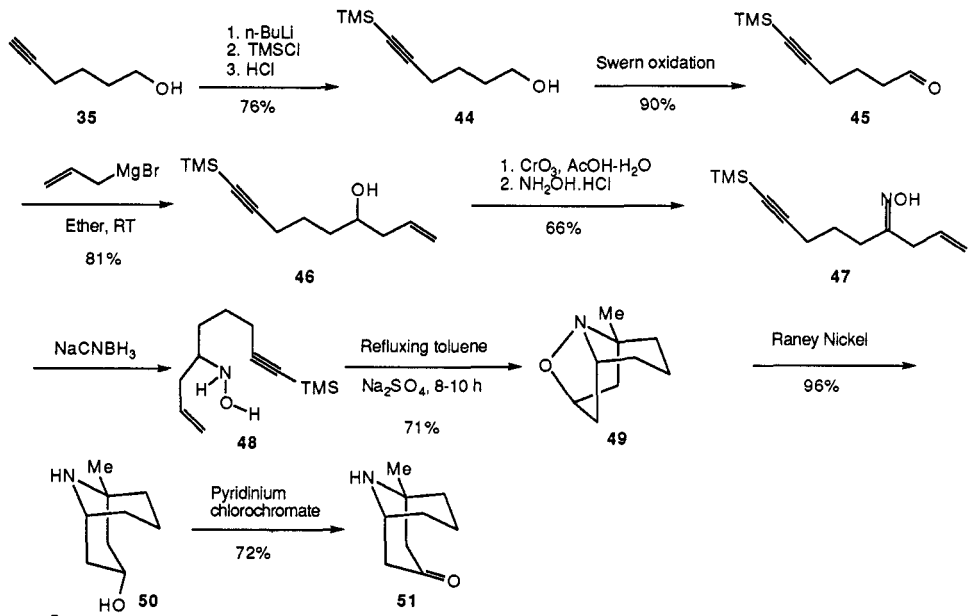
The conversion in Scheme 7 is attractive because it allows construction of complex polycycles from precursors having one stereocentre, and it is an example of the maximisation of molecular complexity. We have therefore selected two target alkaloids, (±)-adaline and (±)-euphococcinine, to demonstrate applications of the tandem process in synthesis [15]. The synthesis of adaline is summarised in Scheme 8.





Scheme 8

The synthesis of euphococcinine is quite analogous. Both series are racemic, and therefore for illustrative purposes the appropriate enantiomer corresponding to the correct absolute configuration of the target molecule is depicted. In principle each synthesis could now be completed from a single enantiomerically pure hydroxylamine precursor.



Scheme 9

Summary

The work described in this article has shown how relatively complex piperidine and indolizidine alkaloid structures can be assembled using the stereocontrol imparted by one stereocentre in a nitrone or hydroxylamine precursor, together with chair-like concerted transition states. Many more structurally complex alkaloids can be designed using these principles. In particular the hydroxylamine-alkyne cyclisation may be a particular example of a much more general process, not just restricted to hydroxylamines and alkynes (alkenes).

Acknowledgements

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