NOVEL SYNTHETIC ANTHRACYCLINONES

A thesis

presented to the University of Auckland

for the Degree of

DOCTOR OF PHILOSOPHY

by

STEPHEN EYRE HOLROYD

Department of Chemistry

University of Auckland

December 1991

TABLE OF CONTENTS

ABSTRACT

Lewis acid mediated cyclisations of the *ortho* allyl substituted homochiral hydroxyanthraquinone acetals (37), (38), (43), and (44), prepared via optimised reductive Claisen rearrangements have been investigated. The mono and dichloro tetracyclic species (71-74), (76), (77), (83), (84), (87-90) and novel dioxepins (97), (98), (101), (102) have been synthesised and their stereochemistries assigned using NMR techniques. Mechanisms have been proposed for the formation of most of the products. An S_N2-like process in which the dioxolane ring structure is maintained in an ion pair intermediate is favoured when tin(IV) or titanium(IV) chloride are used at lower temperatures (-78°C). Such a path explains the good C7 stereoselectivity in the generation of the anthracyclinones. Thereafter the direction of chloride addition is governed by the orientation of this ion pair which provides the chloride to C-9 on the A-ring. An alternative path predominates when boron trifluoride etherate is used and at higher temperatures. This probably involves a free oxocarbenium ion which explains the poor C7 stereoselectivity, since either face of the oxocarbenium ion is equally accessible to the incoming nucleophilic olefin. An adjacent methoxy group on the anthraquinone ring lowers the stereoselectivity at both C7 and C9. This effect is explained by invoking bidentate coordination of either tin(IV) or titanium(IV) chloride to the quinone carbonyl, the methoxy oxygen and the acetal. The resultant steric interactions raise the energy of the favoured transition state and thus the acetal reacts via a different conformation, or the S_N1-like path may be favoured, both of which afford a lower stereoselectivity. When titanium(IV) chloride is used with the isobutylene substituted methoxy anthraquinonyl acetal (37) a reversal in C7 stereoselectivity is found which has been explained as due to a favouring of reaction in which the other acetal oxygen has become complexed. With these substrates trimethylsilyl triflate does not induce the desired acetal/alkene cyclisation, rather the isobutylene substituted acetals (37) and (38) giving the dimethyl furans (68) and (69), while the vinyl chlorides (43) and (44) were largely unreactive.

Preliminary studies on modifications aimed at introducing oxygen bearing functionality at C9 in the mono and dichloro tetracyclic species have been carried out.

The potential of the acetal from condensation of the conduritol dimethyl ether (140) and the aldehyde (35) in syntheses of novel anthracyclines bearing a 7-cyclitol substituent has been studied. The cyclohexenyl acetals (143), (153), (154), and (157) have been prepared but their reactions with a variety of Lewis acids give the appropriate napthacenediones (67), (91), (133), and (155) as the only tetracyclic products isolated. It is proposed that coordination of the α-methoxy groups to the Lewis acid diverts the reaction paths.

A one-pot reductive Claisen/Ene reaction of the aldehyde (35) has been optimised as a method for preparing the tetracyclic anthracyclinone (163). Further modifications of this tetracycle have been investigated.

Preliminary studies of a route aimed at utilising a Dieckmann condensation to furnish anthracyclinone precursors were side-tracked when rather than the desired furans an iodoetherification reaction gave a series of novel iodomethylfurans and furanocyclopropanes.

The use of palladium(II) bisacetonitrile to simultaneously cleave the allyl ether and conjugate the C-allyl double bond of (33) to afford (217) has been investigated.