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Asymmetric Syntheses of Anthraquinonyl C-Glycosides

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Abstract

Syntheses of C2-anthraquinone aldehydes from the commercially available anthrarufin **11** have been investigated. A synthesis of the ketoaldehyde **5** in nine steps and 73% overall yield was achieved. Syntheses of **5** exploiting selective oxidations of either a C-bound allyl group *via* Wacker oxidation to introduce the methyl ketone functionality, or of a C-bound prop-1-enyl moiety *via* dihydroxylation and oxidative cleavage to generate the C2 formyl group were also developed. The aldehyde **81** was synthesised in seven steps and 81% overall yield from **11**, and syntheses of the phenolic aldehydes **82**, **95**, and **96**, the C1 benzyloxyaldehyde **104**, and the anthracene aldehyde **107** have been developed.

Hetero Diels-Alder reactions of several anthraquinone aldehydes with the dienes **6**, **120**, and **121** using catalysis by the complex (+)-VO(hfc)₂ **115** were studied. Reactions of the aldehydes **5** and **81** proceeded readily using catalytic amounts of **115** and dichloromethane, chloroform, or toluene as solvent to give the adducts **128** or **131** indicating an *endo* selective pericyclic reaction pathway. The enantioselectivities of these reactions were typically 20-50%, with a best ee of 56% for a reaction between **81** and **6** catalysed by 0.2 equivalents of **115** at -78°C. Reactions of the 1-silyloxydienes **120** and **121** with aldehyde **81** catalysed by **115** to give the enone **130** also proceeded readily with a best ee of 64% being obtained for a reaction between **81** and **121** in toluene at -78°C. Reactions of the phenolic aldehydes **95** and **96** and the diene **6**, catalysed by **115**, afforded good yields of cycloadducts, but with enantioselectivities identical to equivalent reactions of the aldehyde **81**. However reactions of the C1 benzyloxyaldehyde **104** with the dienes **6** and **120**, and **121** afforded cycloadducts with enantioselectivities lower than those from the equivalent reactions of the aldehyde **81**.

Elaboration of the cycloadduct **131** to the anthracene C-glycoside **149** established that the *hetero* Diels-Alder reaction had favoured the formation of the 2'*R*, 6'*R* enantiomer of **131**. This enantiofacial selectivity was correlated with the sense of anisochrony observed in ¹H NMR spectra of the ketone **129**, derived from **131**, in the presence of the chiral solvating agent (*S*)(+)-trifluoroanthrylethanol. The enone **130** was elaborated to the anthraquinone-olivose C-glycoside **154** demonstrating the utility of *hetero* Diels-Alder reactions involving silyloxydienes with C1 silyloxy and C1 methyl substituents for such syntheses.

Attempts to use chiral acyloxyborane complexes such as **168** and **169** as catalysts for *hetero* Diels-Alder reactions of the aldehydes **5**, **81** and **107** with the dienes **6** and **120** were unsuccessful. However two equivalents of the chiral acyloxyborane complex **168a**, in dichloromethane at -30°C , mediated a formal *hetero* Diels-Alder reaction between **81** and **120** affording the enone **130** in 45% yield, with a 79% ee in favour of the 6'*R* enantiomer. Reactions catalysed by the chiral acyloxyborane complex **169b** between benzaldehyde or *o*-anisaldehyde and the dienes **6**, **119**, and **120** gave products resulting from a Mukaiyama aldol addition rather than a *hetero* Diels-Alder reaction.

Hetero Diels-Alder reactions between **81** and **120** employing the chiral titanium complexes $\text{Ti}[(R)\text{-BINOL}]\text{Cl}_2$, $\text{Ti}[(R)\text{-BINOL}]_2$, and $\text{Ti}[(R,R)\text{-TADDOL}]\text{Cl}_2$ were investigated. No reaction was observed when 0.5, 1.2 and 2 equivalents of $\text{Ti}[(R)\text{-BINOL}]_2$ were used. However the complexes $\text{Ti}[(R)\text{-BINOL}]\text{Cl}_2$ and $\text{Ti}[(R,R)\text{-TADDOL}]\text{Cl}_2$ promoted the reaction between **81** and **120** at -30°C and -78°C , but induced low enantioselectivities (17-30%).

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