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LETTERS

An Unprecedented entry to 5, 6-Dihydroxy-2-azabicyclo[2.2.1]heptan-3-one.

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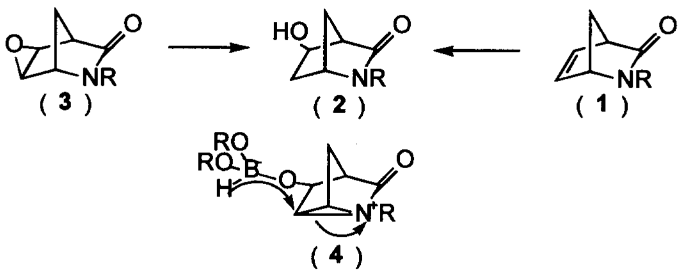
Abstract:- A catecholborane mediated reaction of the lactam epoxide unexpectedly gave the *cis*-diol a useful intermediate for adenosine agonists. The origin of this reaction is postulated to arise from the formation of a boronic anhydride which is transferred to the electron deficient C-6 *via* transannular attack by the amide nitrogen.

The importance of carbocyclic nucleosides as mimetics in biological processes (1, 2) has been well documented since the first reported synthesis of aristeromycin by Shealy and co-workers having the complete hydroxyl functionality corresponding to ribose. (3) Several strategies have been employed to prepare carbocyclic nucleosides.(4) Of these an osmium tetroxide catalysed dihydroxylation of the bicyclic lactam, 2-azabicyclo[2.2.1hept-5-en-3-one and the hydroboration of a derived cyclopenteneyl amine have been reported on a multi-kilogram scale. (5)

As part of our continuing interest in the use of the bicyclic lactam (**1, R =H**) to prepare carbocyclic nucleoside precursors we recently reported the synthesis of the 5-*exo* hydroxy lactam (**2, R=H**).(6) This was accomplished utilising either a microbial biohydroxylation of the saturated lactam or an oxymercuration reaction, opening the way to a synthesis of carbocyclic 2'-deoxy nucleosides. It was envisaged that an alternative approach could be based on the rearrangement chemistry previously exploited to provide access to 3'-deoxy carbocyclic nucleosides. (7) Thus treatment of the known *exo*-epoxide (**3**) (8) with catecholborane (CAB) followed by intramolecular hydride delivery to the resulting aziridinium species (**4**) would be expected to give the key alcohol (**2**). (Scheme 1)



Scheme 1. Proposed mechanism for the synthesis of 5-*exo*-alcohol.

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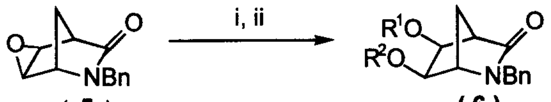
Of the published procedures (8) for preparing the epoxide (5) oxidation with 3-chloroperoxybenzoic acid was found to be a more reproducible procedure than Oxone ® in allowing preparation of multigram quantities. The epoxide was treated with catecholborane in THF at -78°C and the reaction mixture was then allowed to warm to room temperature. Following a methanol quench and partial purification by silica gel filtration to remove polar by-products, a product was isolated by silylation and chromatography. The ^1H NMR was highly symmetrical suggesting that the desired monohydroxylated species had not been formed and the product was in fact the silyl ether (**6, R^1=R^2=TBS**) isolated in 27% yield. (Scheme 2)

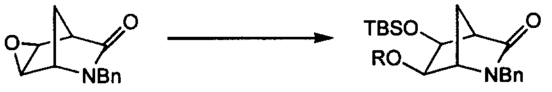


(5) (6)

Scheme 2 i. catecholborane / THF, -78°C - RT, ii. tBDMSCl / imidazole / DMF.

In order to confirm this result and provide an insight into the probable mechanism, two series of reactions were carried out. It was considered that the diol could result from donation of an oxygen nucleophile rather than hydride from the boron, which could have occurred if there had been partial degradation of the borane by moisture. Thus first of all addition of water was investigated as one of the potential intermediates would be a boronic acid/anhydride resulting from addition of water to CAB. Secondly alcohols and acids were added to the catecholborane to provide an insight into the regio- and stereochemistry of the reaction.

When catecholborane/water (2:1 ratio) was added to the epoxide the product obtained after silylation was (**6**), the same as that previously obtained. This could imply that an intermediate boronic acid or equivalent reagent is formed and this might function as a Lewis acid. (9) In order to probe this theory further, catecholborane was decomposed with methanol and the resulting solution added to a solution of the epoxide. After silylation and chromatography the expected mono-silyl species (**7, R^1=Me, R^2=TBS**) was obtained with the regiochemistry as shown. In a similar manner, addition of benzoic acid to CAB gave the mono benzoate (**7, R=Bz**)

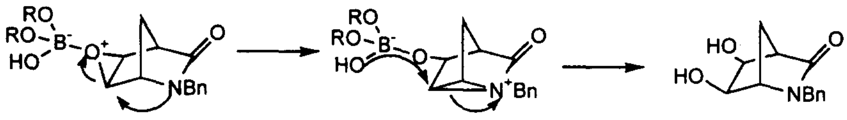


(5)

(7a) R = Me 6%
(7b) R = Bz 24%

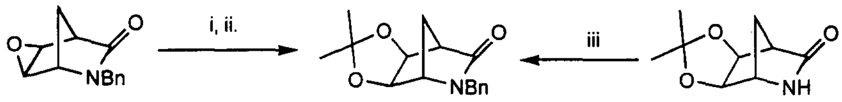
Scheme 3. Preparation of Monoprotected Diols.

These results would suggest that the following mechanism in which epoxide complexation, anchimerically assisted nitrogen-mediated ring opening and oxygen migration from boron takes place is a valid explanation. Scheme 4



Scheme 4

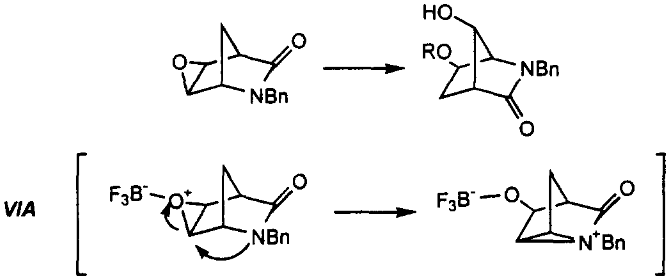
To prove unequivocally the formation of a *cis*-diol product, the reaction mixture from a catecholborane/water reaction was treated with 2,2-dimethoxypropane to give the acetonide (**8**), identical by ^{1}H NMR and chromatography to a sample prepared by benzylation of the known acetonide (**9**). (10) (Scheme 5)



(**8**) (**9**)

Scheme 5. i. CAB / H_2O / THF, ii. 2,2-dimethoxypropane/ TsOH, iii. BnBr/NaH

A key feature of the above reaction is the surprisingly unexpected outcome compared with when the epoxide is treated with other Lewis acid nucleophile combinations. Thus treatment of the epoxide with BF_3 and alcohols or carboxylic acids (R = AcO, MeO, 3-chloropropyloxy) (Scheme 6) gave the rearranged 6,7 diol monoprotected at C-7, thus opening up a potential route to differentially functionalised analogues of carbocyclic cordycepin. (7) This result is analogous to that reported by Holmes in the acid catalysed epoxide ring opening in a related azabicyclo[2. 2. 2.]octane system. (11) Another example of where retention of configuration without rearrangement taking place in this type of system is the fluorination of the related 6,7-bromohydrin where retention of configuration is observed following treatment of the alcohol with DAST. Nucleophilic ring opening of the intermediate aziridinium cation occurs at the more favoured C-1 position to give retention of configuration and regiochemistry suggesting that substrate control determined by the bromine dictates the mode of attack, while in our case reagent control is effective for the first time. (12)



Scheme 6

In conclusion we have demonstrated that a catecholborane/water complex mediated epoxide ring opening provides an alternative route to the 5,6-diol required for adenosine agonists whereas a reductive approach to the 5-*exo* alcohol remains elusive.

References and Notes.

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