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Unexpected Stereoselectivity in the *cis* Dihydroxylation of Some 2-Cyclopentene-1-carboxamides.

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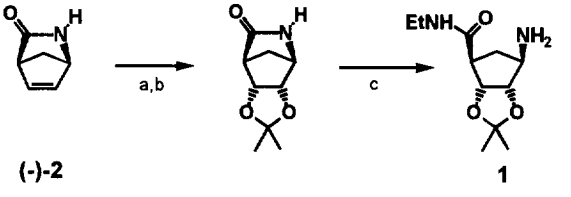
Abstract:- While 4-substituted-2-cyclopentene-1-carboxylate esters gave no facial selectivity in the *cis* dihydroxylation of the olefin function with osmium tetroxide/N-methylmorpholine-N-oxide, the corresponding carboxamides unexpectedly gave high diastereoselectivity for the isomer useful for carbocyclic ribofuranosyl nucleosides.

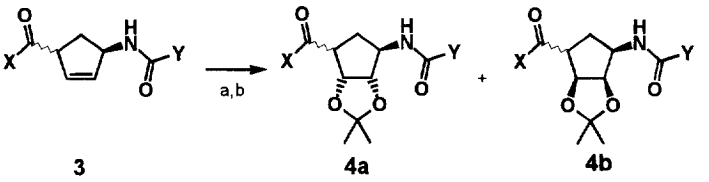
Carbocyclic ribofuranosyl nucleosides have attracted considerable synthetic interest as potential therapeutic agents[1]. During the course of our studies into the synthesis of intermediates for vasodilator adenosine agonists we investigated routes to the acetonide **1**, the preparation of which has been reported from the racemic bicyclic lactam, 2-azabicyclo[2.2.1]hept-5-en-3-one **2** with a late stage resolution[2]. Similarly this compound could be prepared from the resolved bicyclic lactam **(-)-2**[3] where the key osmium tetroxide catalysed *cis* dihydroxylation is *exo* selective by virtue of the constraints of the bicyclic framework[4] and where ethylamine is introduced in the last stage (Scheme 1).



(-)-2 **1**

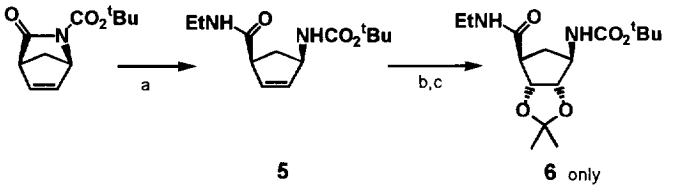
Scheme 1. a, OsO_4, *N*-methylmorpholine-*N*-oxide, acetone-water; b, $(MeO)_2CMe_2$, TsOH; c, $EtNH_2$.

As an alternative approach we investigated a route with the ethylamine introduced before the dihydroxylation. However that requires a monocyclic cyclopentene intermediate where the literature indicates that both faces of the olefin are dihydroxylated to give a mixture of products.[5] Indeed, when the *cis* and *trans* methyl esters **3** (X=MeO, Y=Ph) were individually subjected to dihydroxylation with catalytic osmium tetroxide and *N*-methylmorpholine-*N*-oxide as secondary oxidant, followed by acetonide formation, both gave a 1 : 1 ratio of isomeric acetonides **(4a)** and **(4b)** as determined by GCMS or HPLC. The separate products were subsequently isolated by chromatography and characterized.



Scheme 2. a, OsO_4 , NMO; b, $(MeO)_2CMe_2$, TsOH.

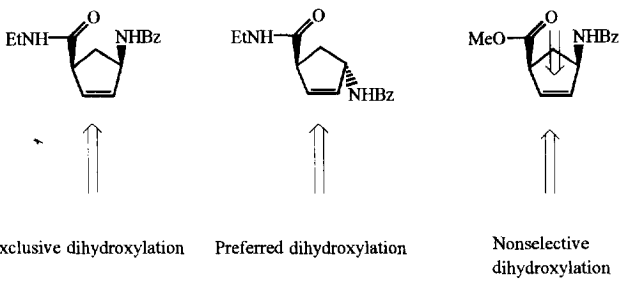
In order to obtain the carboxamide **5**, the lactam **(-)-2** was activated to nucleophilic attack by N-t-butoxycarbonylation[6] then cleaved by anhydrous ethylamine in dichloromethane. To our surprise dihydroxylation under the standard conditions gave the acetonide (**6**) unexpectedly as a single diastereisomer as determined by ^{1}H NMR analysis af the crude reaction mixture (Scheme 3),[7] thus opening up a further practical route to compounds having the ribose configuration. The above result prompted us to investigate more closely the origin of the stereoselectivity. In the first instance we examined some other carboxamide derivatives prepared by ring opening of the *N*-t-BOC lactam (**5**) with methylamine or dimethylamine in aqueous THF . In each case the only product after dihydroxylation/ acetonide formation was an acetonide analogous to **6** as shown by ^{1}H NMR of the crude reaction mixtures.



Scheme 3. a, $EtNH_2$, b, OsO_4, NMO, acetone; c, $(MeO)_2CMe_2$ / TsOH.

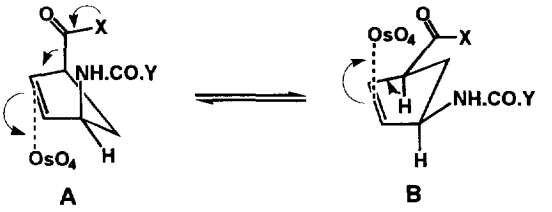
In further exploration of the origin of the stereoselectivity, cyclopentenes (**3**, X= EtNH-, Y=Ph) were obtained from treatment of the benzoylamide (**3**, X=MeO-, Y=Ph, *cis/trans* mixture) with aqueous ethylamine in THF at room temperature. Dihydroxylation of a sample that was 1.5 :1 *cis : trans* under standard conditions gave three acetonide products in which it was shown by GCMS that the *cis* alkene had given a single product (**4a**) where hydroxylation was *anti* to the carboxamide, while the *trans* alkene had given a 1:3 mixture of diastereoisomers (**4a**):(**4b**), the major product again resulting from dihydroxylation *anti* to the carboxamide.[8] The corresponding *N*-carboxybenzyl ethylamide (**3**, X=EtNH-, Y=-OPh, *cis*) behaved similarly. The results for the *trans*-1,4-substituted-2-cyclopentenes show that the carboxamide function maintains a strong *anti* directing influence in spite of the different relative position of the protected amino group.

In explanation of the profound *anti*-directing effect of the carboxamide function summarized in Scheme 4, it is possible to imagine that this may in part be due to the planarity of the amide bond causing this function to be more effective at shielding the upper face of the cyclopentene ring than an ester with the result that dihydroxylation occurs on the opposite face.



Scheme 4. The preferred mode of dihydroxylation of 1,4-disubstituted cyclopentenes.

A more attractive explanation, however, arises from consideration of the olefinic substrate as a pair of equilibrating conformers (Scheme 5) and where dihydroxylation can be activated by electron release from the allylic pseudoaxial bonds. The product composition will reflect the conformer which is the more reactive. In the case of conformer **B,** such activation would be from the hyperconjugative electron release from the axial hydrogen atoms, this phenomenon known as the Cieplak effect[9] has effectively explained the preferred electrophilic attack *syn* to substituents in certain cyclopentene derivatives.[5] Alternatively in conformer **A** the axial substituents could promote the electrophilic attack and in this regard the donation of electrons from bridging of the carbonyl oxygen of the amino substituent has been invoked.[10] While our results are consistent with such an effect from the amino substituent, such effect seems less significant than that from a carboxamide substituent since *trans*-1,4-disubstituted cyclopent-2-enes give predominantly dihydroxylation *anti* to the carboxamide substituent.



Scheme 5

For conformer **A**, electron release from the conjugated electron pair of the carboxamide function could increase reactivity of the olefin, while for conformer **B** the greater electron withdrawal by the carboxylate ester and consequent greater acidity of the adjacent proton would increase the reactivity of that conformer. Thus relative to the ester the carboxamide will favour reaction through conformer **A** leading to the observed *anti* product

In conclusion we have shown the profound effect of a carboxamide function in controlling the stereochemistry of products obtained in the dihydroxylation of the adjacent olefin function in 2-cyclopentene-1-carboxamides which gives products useful for the preparation of carbocyclic nucleosides.

References and Notes.

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7. A representative experimental procedure is as follows: A solution of (-)-BOC lactam (2.72 g, 13 mmol) in dichloromethane (30 ml) was treated with ethylamine (5 ml) at 20°C, stoppered and allowed to stand for 10 hr. The solution was concentrated to dryness and the residue recrystallized from ethyl acetate / hexane. The solid was collected by filtration, washed with t-butyl methyl ether and dried to give the ethylamide **5** (1.58g, 48%). This amide (218 mg, 0.9 mmol) was disolved in acetone (10 ml) and osmium tetroxide (0.07 ml of a 4% aqueous solution, 0.001 mol eq) added followed by a solution of trimethylamine-*N*-oxide (105 mg, 1.4 mmol) in water (0.6 ml). The resulting solution was heated at 55°C for 1hr, then cooled to ambient temperature and filtered through Florosil. The filtrate was concentrated and the resulting white solid (92 mg) was suspended in 2,2-dimethoxypropane (10 ml) and p-toluenesulfonic acid (10 mg) added. The mixture was heated at reflux for 1hr, cooled to ambient temperature and ethyl acetate (10 ml) added. The solution was then washed with saturated sodium hydrogen carbonate (5 ml), water (5 ml), and brine (5 ml), dried ($MgSO_4$), and concentrated under reduced pressure to give the acetonide **6** (117 mg, 40%)
8. Detailed analytical studies (HPLC, GCMS and ^1H NMR) were carried out to confirm the presence or absence of other diastereoisomers. The *anti* relationship of the acetonide to the carboxamide function in **6** is apparent from the ^1H NMR spectrum where the protons at the carbon atoms bearing the acetonide are doublets since they couple only to each other and not to the other vicinal protons which are in in a *trans* relationship.
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