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The Synthesis of Pseudo-sugars Related to Allosamizoline

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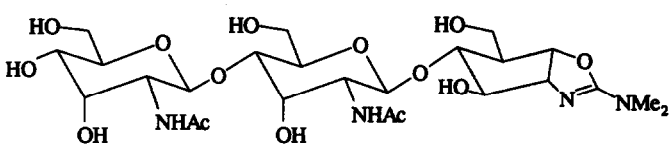
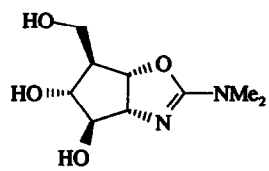
Abstract: *The syntheses of two bicyclic pseudo-sugars related to allosamizoline, the aminocyclitol component of the chitinase inhibitor allosamidin, are described. These carbocyclic pseudo-sugars containing a cyclohexane ring were synthesised from* D*-glucosamine via a Ferrier rearrangement .*

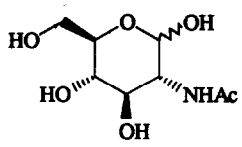
The allosamidins[1] are a family of naturally occurring pseudo-trisaccharides which are inhibitors of chitinase enzymes from a variety of sources. Because chitin is an essential structural component of the exoskeleton of insects and the cell wall of many fungi, inhibitors of chitinase have potential utility both as insecticides[2] and antifungal agents.[3] Allosamidin **1**, the first reported member of the series, consists of a β-1,4-linked array of two molecules of *N*-acetyl-D-allosamine and a novel aminocyclitol, termed allosamizoline **2**. Both allosamidin **1** and the much weaker chitinase inhibitor, allosamizoline **2**,[4] have been the subject of considerable synthetic interest, Vasella[5] and Danishefsky[6] having completed total syntheses of **1** and several enantiospecific syntheses of **2** also having been reported.[7] As part of a study aimed at the synthesis of potentially more potent inhibitors of chitinases, we now describe routes to some 6-membered carbocyclic ring analogues of allosamizoline **2** starting from D-glucosamine.



1 Allosamidin



2 Allosamizoline



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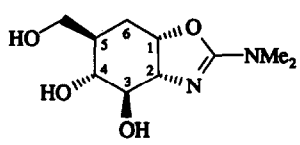

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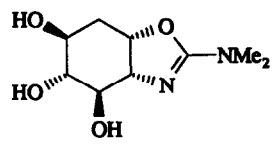

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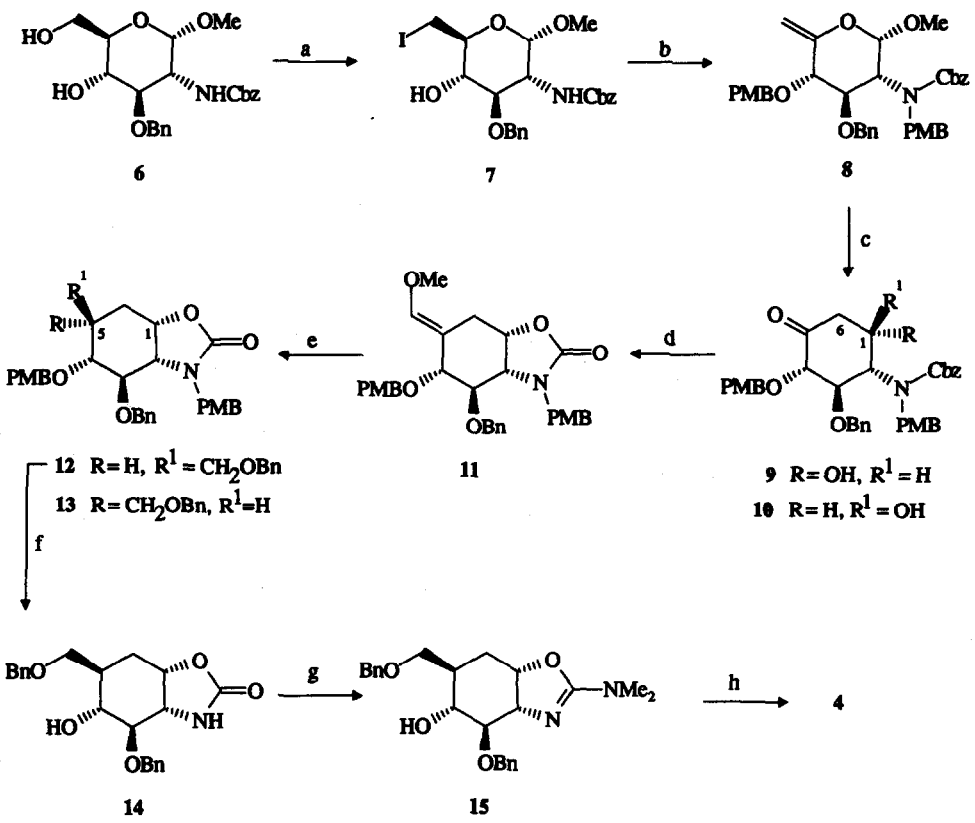
In view of the fact that allosamizoline **2** can be considered to be a pseudo-sugar derivative with *gluco*-stereochemistry,[8] we wished to prepare analogues of **2** in which the pseudo-sugar more closely resembles *N*-

acetyl-D-glucosamine **3**, the repeating sugar unit of the enzyme substrate chitin. Our target compounds were the pseudo-*N*-acetyl-D-glucosamine analogue **4** and the related C-5[9] hydroxyl derivative **5**, each containing a cyclohexane derived pseudo-sugar in place of the functionalised cyclopentane in allosamizoline. Barton[10] has synthesised the carbocyclic analogue of D-glucosamine employing the Ferrier rearrangement[11] of a carbohydrate to a cyclohexane as the key step. We have exploited this methodology for the synthesis of our target molecules, but as the ultimate aim of our work was to prepare β-1,4-linked saccharides of **4** and **5**, we required a protecting group strategy which allowed selective manipulation of the C-4 hydroxyl group. The synthesis of both target allosamizoline analogues **4** and **5** via the key cyclohexanone intermediate **9** (Scheme 1) was achieved as follows:



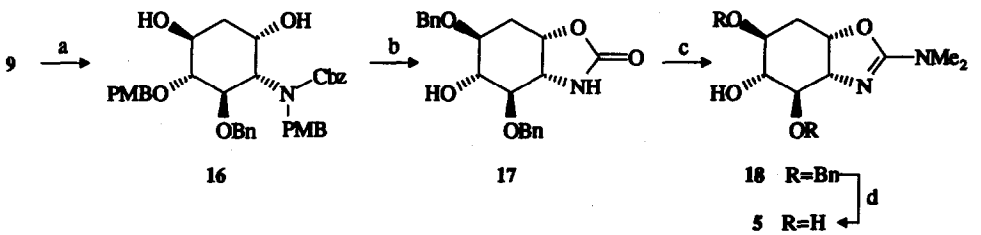
Reagents and conditions: (a) PPh_3, imidazole, I_2, PhMe, 80°C, 75%. (b) PMBCl, NaH, DMF, 82%. (c) $HgSO_4$, H_2SO_4, dioxan, H_2O, 80°C, 65%. (d) $Ph_3P^+CH_2OMe\ Cl^-$, *n*-BuLi, DME, 0°C, 35%. (e) *i*. $Hg(OAc)_2$, MeCN, H_2O; *ii*. KI; *iii*. $NaBH_4$, THF, 69%; *iv*. BnBr, NaH, DMF, 85%. (f) CAN, MeCN, H_2O, 69%. (g) MeOTf, CH_2Cl_2, 20°C, then Me_2NH, 0°C, 40% (38% of **14** recovered). (h) H_2, Pd-C, MeOH, HOAc, 74%.

Scheme 1

D-Glucosamine hydrochloride was converted in 5 steps into methyl 3-*O*-benzyl-2-*N*-Cbz-2-deoxy-α-D-glucopyranoside **6**,[12] which was selectively transformed to the primary iodide **7**[13] by the method of Garegg.[14] Treatment of **7** with sodium hydride and *p*-methoxybenzyl chloride in DMF gave the enol ether **8**. The utilisation of *p*-methoxybenzyl (PMB) group protection at the 2-*N* and 4-*O* positions in **8** allows selective deprotection later in the synthesis and subsequent manipulation at these centres. Ferrier rearrangement[11] of enol ether **8** using mercuric sulphate catalysis afforded a 6:1 mixture of diastereoisomeric cyclohexanones **9** and **10**. The C-1 α-OH isomer **9**,[15] which was readily separable from the mixture, possessed the required stereochemistry for the construction of the *cis*-1,2-fused oxazoline ring in the target molecules **4** and **5**.

For the synthesis of **4** (Scheme 1) the hydroxymethyl group at C-5 was introduced by Wittig chemistry. The reaction of cyclohexanone **9** with (methoxymethylene)triphenylphosphorane[10] was accompanied by cyclisation of the C-1 hydroxyl onto the amine Cbz group with concomitant loss of benzyl alcohol giving the *E*-enol ether-oxazolidinone **11**. Oxymercuration of enol ether **11**, followed by borohydride reduction and subsequent benzylation gave a 5:1 mixture of the protected C-5 hydroxymethyl compounds **12** and **13**. The desired 5β-isomer **12**[15] was isolated in 45% yield from **11** after preparative hplc.

Oxidative removal of the *O*- and *N*-PMB groups [cerium (IV) ammonium nitrate (CAN), MeCN, H_2O][16] afforded the deprotected oxazolidinone **14**, which was converted into the *N,N*-dimethylamino oxazoline **15** using a method developed by Trost[17] in his synthesis of allosamizoline **2**. Finally, hydrogenolysis of the benzyl groups in **15** gave the target allosamizoline analogue **4**.[18]



Reagents and conditions: (a) $NaBH_4$, HOAc, 85%. (b) *i.* NaH, DMF, then BnBr, 73%; *ii.* CAN, MeCN, H_2O, 61%. (c) MeOTf, CH_2Cl_2, then Me_2NH, 60%. (d) H_2, Pd-C, MeOH, HOAc, then IRA 400 (OH^-), H_2O, 87%.

Scheme 2

The related pseudo-sugar **5**, having a hydroxyl group at C-5 , was also prepared from the Ferrier rearrangement product **9** (Scheme 2). Hydroxyl-directed reduction[19] of the cyclohexanone **9** with sodium triacetoxyborohydride gave exclusively the *trans* 1,5-diol **16**. In this case, oxazolidinone formation was accomplished by treatment of **16** with NaH in DMF, and sequential benzylation of the C-5 hydroxyl group and oxidative removal of both PMB groups furnished the bicyclic intermediate **17**. Elaboration of **17** to the selectively protected *N,N*-dimethylamino oxazoline **18** as before and subsequent hydrogenolysis gave the allosamizoline analogue **5**.[18] While **5** showed no detectable inhibitory activity against the chitinase from *Candida albicans*, the pseudo-sugar **4** is a weak inhibitor of the enzyme, comparable with allosamizoline **2**.[4]

We have described the synthesis of allosamizoline analogues **4** and **5** in which the cyclopentanoid pseudo-sugar is replaced by related pseudo-hexoses. The strategy employed allows control of stereochemistry to give products with the *gluco*-configuration found in allosamizoline **2**, and in addition affords selectively

protected advanced intermediates **15** and **18**, which are suitable precursors for the synthesis of β-1,4-linked pseudo-disaccharides related to allosamidin **1**. The synthesis of such compounds will be reported elsewhere.

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18. **4** : Hygroscopic solid; $[\alpha]_D^{25}$ +30° (c=0.5, MeOH); ν_{max} (KBr) 3500-3200, 1647cm^{-1}; ^{1}H-NMR (CD_3OD, 400MHz) δ: 1.70 (2H, m, *H*-5, *H*-6a), 2.26 (1H, dt, *J*=11.2, 2.8Hz, *H*-6b), 2.90 (6H, s, N*Me*$_2$), 3.19 (2H, m, *H*-3, *H*-4), 3.53 (1H, t, *J*=7.0Hz, *H*-2), 3.62 (1H, dd, *J*=10.8, 5.3Hz, 5-C*Ha*), 3.74 (1H, dd, *J*=10.8, 3.4Hz, 5-C*Hb*), 4.61 (1H, ddd, *J*=7.0, 3.6, 2.8Hz, *H*-1) ppm. **5** : Gum; $[\alpha]_D^{25}$ +40° (c=0.1, H_2O); ν_{max} (film) 3400(b), 1640cm^{-1}; ^{1}H-NMR (d_6-DMSO, 270MHz) δ: 1.67 (1H, ddd, *J*=14.5, 9.6, 4.8Hz, *H*-6a), 2.03 (1H, dt, *J*=14.5, 4.4Hz, *H*-6b), 2.78 (6H, s, N*Me*$_2$), 2.95-3.05 (2H, m, *H*-3, *H*-4), 3.41 (1H, m simplifies to ddd with D_2O, *J*= 9.6, 4.4, 2.6Hz, *H*-5), 3.49 (1H, t, *J*=7.4Hz, *H*-2), 4.55 (1H, ddd, *J*=7.4, 4.8, 4.4Hz, *H*-1), 4.3-4.8 (3H, b exchanged with D_2O, 3 x *OH*) ppm.
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