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Synthesis of Pseudo-disaccharides Related to Allosamidin

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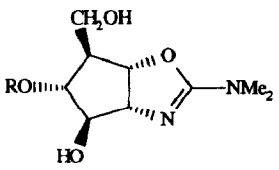
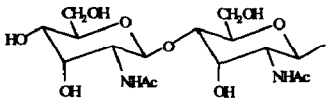
Abstract: *Suitably protected carbocyclic pseudo-sugars were synthesised from* D*-glucosamine via a Ferrier rearrangement. Stereospecific coupling with the glycosyl donor, 1,3,4,6-tetra-O-acetyl-2-deoxy-2-phthalimido-β-*D*-glucopyranoside and subsequent protecting group interconversions furnished β-1,4- pseudo-disaccharides related to the chitinase inhibitor, allosamidin.*

Since the discovery of allosamidin **1**[1], the first naturally occurring chitinase inhibitor, several related allosamidins have been described[2], including the glucoallosamidins where the central *N*-acetyl-D-allosamine residue in **1** is replaced by *N*-acetyl-D-glucosamine. Cleavage of the terminal sugar in the allosamidins results in pseudo-disaccharides which retain inhibitory activity to varying degrees against insect and fungal chitinases. For example, the *gluco* derivative **3** is a potent inhibitor of the chitinase from the yeast *Candida albicans*.[2] The potential use of chitinase inhibitors as insecticides[3] and antifungal agents[4] has prompted us to embark on the synthesis of related molecules which may have improved biological properties. We recently reported the synthesis of some 6-membered carbocyclic ring pseudo-sugar analogues of allosamizoline **2**[5], and we now describe the synthesis of related pseudo-disaccharides, including **18** which is a close analogue of the *gluco* pseudo-disaccharide **3**.

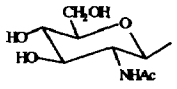


1 Allosamidin R =



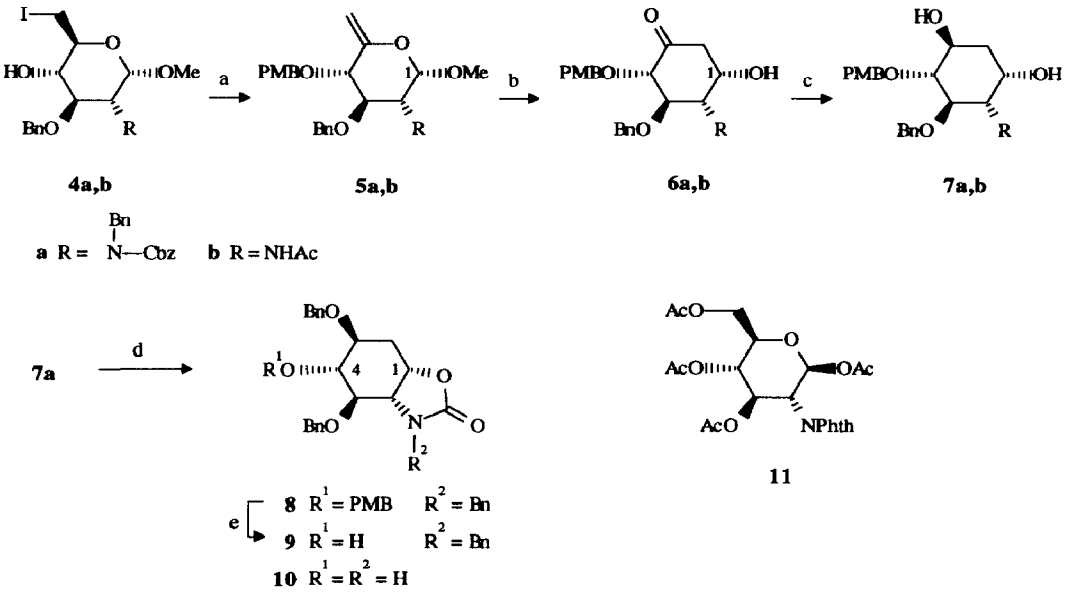
2 Allosamizoline R = H

3 Pseudo-disaccharide from Glucoallosamidin R =



The synthesis of the chiral C-4 hydroxy bicyclic oxazolidinone **9**[6] (Scheme 1), a convenient precursor to the target pseudo-disaccharides **14** and **18**, paralleled our recently described route to **10**[5], starting with the known primary iodide **4a**[7] and utilising the Ferrier rearrangement[8] (**5a** → **6a**) as a key step. Coupling between oxazolidinone **9** and the readily available glycosyl donor 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside **11** was conducted using Paulsen's procedure[9] [**9** (1 equiv), **11** (2 equiv), 4A mol. sieves, CH_2Cl_2, 0°C, TMSOTf (4 equiv), 4h] giving stereospecifically the β-1,4-linked product **12** in

75% yield (Scheme 2). No attempts were made to utilise alternative glycosyl donors[10] in this work since glycosidation reactions involving anomeric acetate **11** proceeded in satisfactory yields to give only the β-1,4-isomers.[11] Elaboration of **12** into the target compound **14** proceeded smoothly utilising established protecting group interconversions. Thus, hydrazinolysis of **12**, and subsequent acetylation, followed by *O*- and *N*-benzyl group removal (Li, NH_3, THF) and further acetylation afforded oxazolidinone **13**, in 30% overall yield. *O*-Deacetylation of **13** then gave the pseudo-disaccharide **14**.[12]

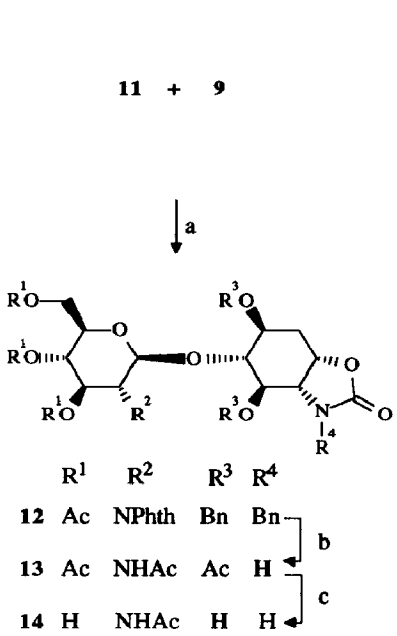


Reagents: (a) PMBCl, NaH, DMF, 87%(**5a**), 65%(**5b**). (b) $HgSO_4$, H_2SO_4, dioxan, H_2O, 80°C, 65%(**6a**), 79%(**6b**). (c) $NaBH_4$, HOAc, 94%(**7a**), 93%(**7b**). (d) NaH, DMF, then BnBr, 78%. (e) DDQ, CH_2Cl_2, H_2O, 88%.

Scheme 1

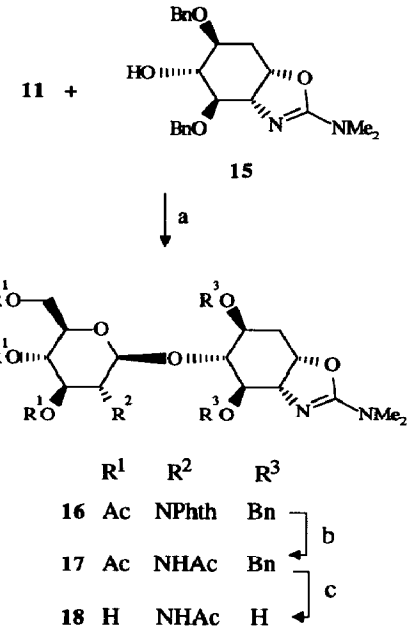
Attempted conversion of the oxazolidinone group in **13** directly into the corresponding *N,N*-dimethylamino oxazoline derivative using the procedure reported by Trost[13] in his synthesis of (±)-allosamizoline (MeOTf, CH_2Cl_2, then, Me_2NH) led to cleavage of the glycoside bond. The pseudo-disaccharide **18** was more conveniently prepared from our previously reported *C*-4 hydroxy bicyclic oxazoline **15**[5] (Scheme 3). Coupling between **15** and glycosyl donor **11** proceeded smoothly giving the β–1,4-coupled product **16** in 80% yield. In common with Vasella's work[14] on the total synthesis of allosamidin, problems were experienced with the attempted conversion of the phthalimido group in **16** to the corresponding *N*-acetyl compound **17**. Mild and strictly anhydrous conditions were required to avoid concomitant opening of the *N,N*-dimethylamino oxazoline ring. Treatment of **16** with freshly condensed methylamine in dry ethanol (room temp., 48h) gave an intermediate amine which was acetylated with Ac_2O-pyridine-DMAP (0°C, 30 min) giving **17** in 67% yield. In contrast, acetylation of the intermediate amine with Ac_2O-pyridine in the absence of DMAP was considerably slower (room temp., 18h) and gave the oxazoline ring opened product **21**

(85%) with only small amounts of **17** (10%). Hydrogenolysis of **17** followed by *O*-deacetylation yielded the target pseudo-disaccharide **18**.



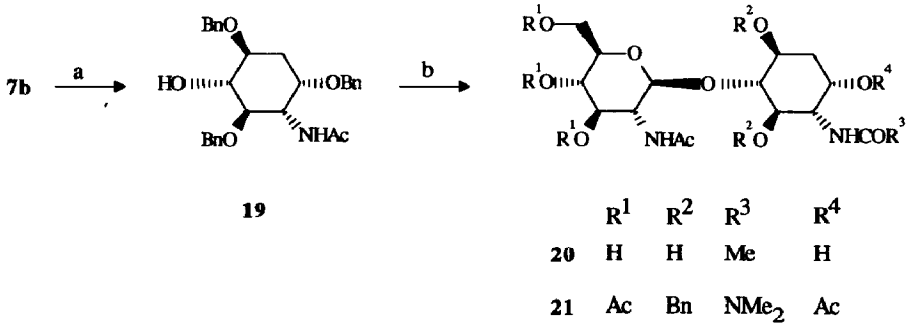
Reagents: (a) TMSOTf, 4A mol. sieves, CH_2Cl_2, 0°C. (b) *i.* $N_2H_4.H_2O$, EtOH, then Ac_2O, py; *ii.* Li, NH_3, THF, then Ac_2O, py. (c) NaOMe, MeOH, 64%.

Scheme 2



Reagents: (a) TMSOTf, 4A mol. sieves, CH_2Cl_2, 0°C. (b) *i.* $MeNH_2$, EtOH; *ii.* Ac_2O, py, DMAP. (c) *i.* H_2, Pd-C, MeOH, HOAc, 94%; *ii.* NaOMe, MeOH, 77%.

Scheme 3



Reagents: (a) *i.* NaH, BnBr, DMF, 59%; *ii.* DDQ, CH_2Cl_2, H_2O, 77%. (b) *i.*TMSOTf, **11**, 4A mol. sieves, CH_2Cl_2, 0°C, 50%; *ii.* $N_2H_4.H_2O$, EtOH, then Ac_2O, py, 91%; *iii.* H_2, Pd-C, MeOH, HOAc, 76%; *iv.* NaOMe, MeOH, 95%.

Scheme 4

Pseudo-saccharides in which the ring oxygen of a sugar is replaced by a methylene group have attracted interest in view of their potential biological properties.[7] Consequently, we have extended the stereospecific glycosidation-deprotection methodology described above to synthesise the carbocyclic chitobiose analogue **20** (Scheme 4) utilising the chiral cyclohexanol **7b** (Scheme 1). Of the 3 pseudo-disaccharides **14**, **18** and **20**, only **18** was a weak inhibitor of the chitinase enzyme from *Candida albicans*.

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11. The β-stereochemistry of the glycoside bond was deduced from ^{1}H-NMR coupling constants and was consistent with literature precedent (see ref. 9). For example; **12** ($CDCl_3$, 270MHz) $J_{1',2'}$ 8.3Hz; **16** ($CDCl_3$, 270MHz) $J_{1',2'}$ 8.2Hz.
12. **14**: M.p. 210-215°C; (Found: C, 46.1; H, 6.2; N, 7.2. $C_{15}H_{24}N_2O_{10}$ requires C, 45.9; H, 6.2; N, 7.1%); $[\alpha]_D^{20}$ +8° (c=0.05, MeOH); ν_{max} (KBr) 3400(br), 1740, 1640, 1560cm^{-1}; ^{1}H-NMR (CD_3OD, 400MHz) δ: 1.96 (1H, m, *H*-6a), 2.00 (3H, s, NH*Ac*), 2.23 (1H, dt, *J*=14.9, 4.1Hz, *H*-6b), 3.35-3.90 (10H, m), 4.72 (1H, d, *J*=8.4Hz, *H*-1') and 4.78 (1H, m, *H*-1) ppm; ^{13}C-NMR (CD_3OD, 100.6MHz) δ: 23.1, 35.6, 49.9, 57.9, 58.7, 62.7, 69.3, 72.1, 75.9, 76.9, 78.0, 85.1, 102.8, 161.8 and 174.6 ppm; *m/z* (FAB, glycerol, Na matrix) 415 (MNa^+).
18: Hygroscopic solid; (Found: C, 48.5; H, 7.1; N, 9.9. $C_{17}H_{29}N_3O_9$ requires C, 48.7; H, 7.0; N, 10.0%); $[\alpha]_D^{25}$ +32° (c=0.05, MeOH); ν_{max} (KBr) 3400(br), 1645, 1560cm^{-1}; ^{1}H-NMR (d_6-DMSO/D_2O, 400MHz) δ: 1.78 (1H, m, *H*-6a), 1.80 (3H, s, NH*Ac*), 1.93 (1H, dt, *J*=14.2, 4.5Hz, H-6b), 2.78 (6H, s, N*Me*$_2$), 3.07-3.70 (10H, m), 4.49 (1H, d, *J*=8.0Hz, *H*-1'), 4.59 (1H, ddd, *J*=8.5, 4.9, 4.5Hz, *H*-1) ppm; ^{13}C-NMR (d_6-DMSO, 100.6MHz) δ: 23.0, 32.1, 37.1, 56.0, 61.0, 66.7, 67.6, 70.6, 74.1, 75.5, 76.8, 78.1, 86.8, 101.3, 161.3 and 169.7 ppm; *m/z* (FAB, glycerol, Na matrix) 442 (MNa^+).
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