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Preliminary communication

The synthesis of tri- and tetra-saccharide oxazolines*

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Oligosaccharides having the structure of the carbohydrate "core" of *N*-glycoproteins[1] are currently important compounds for studies on the biosynthesis of glycoproteins. Unfortunately, this structure is complex, and as a result, synthesis of suitable compounds is difficult. One way to overcome this problem is to take advantage of naturally occurring compounds in which many of the required structural features are already present, such as the partially degraded, glycoprotein-derived oligosaccharides that accumulate in the urine of mannosidosis patients[2]. These compounds have the general structure **1**, and, for the synthesis of the core structure, it is necessary to (*a*) add another 2-acetamido-2-deoxy-D-glucose residue linked β-D-(1→4) to the reducing end of the mannosidosis oligosaccharides, to form a chitobiose derivative at that end, and (*b*) convert the product into an intermediate compound that can be readily converted into an α-D-glycosyl phosphate, ready for the synthesis[3] of a "lipid intermediate".

Previous work has shown that oxazolines can conveniently be used for the synthesis of chitobiose derivatives[4] and for subsequent conversion into α-D-glycosyl phosphates[5]. The present communication reports the use of **2**, isolated from mannosidosis urine[2], for the preparation of a trisaccharide oxazoline (**4**), and conversion of **4** into a tetrasaccharide oxazoline (**13**).

To a stirred suspension of *O*-α-D-mannopyranosyl-(1→3)-*O*-β-D-mannopyranosyl-(1→4)-2-acetamido-2-deoxy-D-glucose (**2**) in acetyl chloride was added conc. hydrochloric acid to a concentration of 2%, to give the per-*O*-acetylglycosyl chloride **3** (t.l.c. gave no indication of scission of glycosidic bonds during this reaction). Compound **3**, without purification, was suitable for conversion into the oxazoline **4** by chloride-ion catalysis[6].

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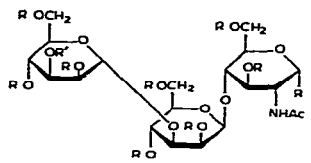
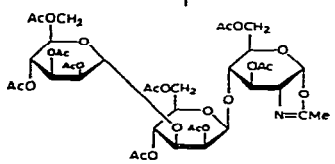
$(\alpha\text{-D-Man}p)_n\text{-}\beta\text{-D-Man}p\ (1\rightarrow4)\text{-GlcNAc}$ $n = 1\text{-}8$

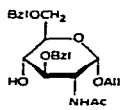
1



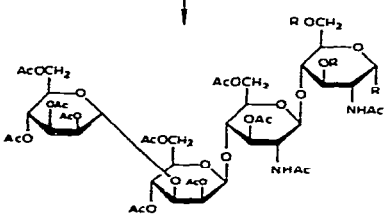
2 R = H OH R = H
3 R = Cl R = Ac



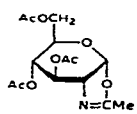
4



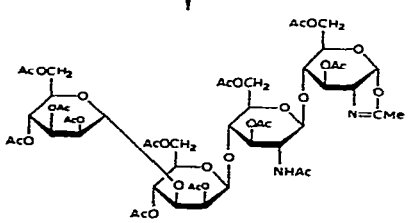
5
Bzl = CH_2Ph
All = $CH_2{-}CH{=}CH_2$



6 R = $OCH_2{-}CH{=}CH_2$ R = Bzl
7 R = $OCH{=}CH{-}Me$ R = Bzl
8 R = $O(CH_2)_2Me$ R = Bzl
9 R = H OH R = Bzl
10 R = H OH R = H
11 R = Cl R = Ac



12



13

In t l c., **4** was clearly separated from the per-*O*-acetyl oxazolines derived from 2-acetamido-2-deoxy-D-glucose[6], 2-acetamido-4-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-deoxy-D-glucose[4], and 2-acetamido-2-deoxy-4-*O*-β-D-mannopyranosyl-D-glucopyranose[7,8], and it was pure enough for synthetic purposes without chromatography, for characterization, a sample of **4** was purified by t.l c (42% yield from **2**), m p 75–77°, $[\alpha]_D^{13}$ -10° (*c* 1.4, 1,2-dichloroethane), giving the expected ν_{max}^{KBr} at 1675 cm^{-1} (C=N), and ^{1}H-n.m r. signal (δ 6 14, $J_{1,2}$ 7 5 Hz, H-1).

The glycosylation by oxazoline **4** of OH-4 of a derivative of 2-acetamido-2-deoxy-D-glucopyranose was expected to be difficult, because of the extremely poor nucleophilicity of this group[9] and the extra steric hindrance due to the unusually large molecular size of the oxazoline, but these problems were overcome by careful choice of the reaction conditions Thus, treatment of allyl 2-acetamido-3 6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside* (**5**) with **4** in 1,2-dichloroethane in the presence of anhydrous *p*-toluenesulfonic acid[4] gave glycoside **6** (22% yield based on **4**), separated from unchanged **5** (75%) by deacetylation, preparative layer chromatography (p l c), and reacetylation, **6** had m p 95–97°, $[\alpha]_D^{20}$ +5° [*c* 2 1, 5 1 (v/v) chloroform–methanol], and the expected i r and ^{1}H-n.m r spectra

To remove the allyl group, **6** was treated with tris(triphenylphosphine)rhodium chloride[10], giving the 1-propenyl glycoside **7**, and some propyl glycoside[4] **8** This mixture was treated with mercuric chloride[11], giving **9** from **7** Isolation of **9** by p l c gave a solid, m p 115–118°, $[\alpha]_D^{20}$ −7 → −8° [*c* 1 8, 5 1 (v/v) chloroform–methanol], having the expected i r and ^{1}H-n m r spectra As the yield of **9** was quite variable (52 to 77%), the allyl group was also removed by treatment with palladium-on-charcoal in aq ethanol–acetic acid[12], which gave **9** directly (47%) Catalytic hydrogenation of **9** gave **10** in almost quantitative yield, m p 184–184 5°, $[\alpha]_D^{20}$ −11° [*c* 1 6, 5 1 (v/v) chloroform–methanol, no change in 4 h), as a mixture of anomers (by t l c)

Conversion of **10** into the tetrasaccharide oxazoline **13**, was achieved by treatment with hydrochloric acid–acetyl chloride, to give **11**, followed by chloride-ion catalysis[6]. T l c. showed that oxazolines **4** and **12** were minor by-products, indicating some scission of the chitobiose bond P l c gave **13** (53% from **10**), m p 117–119°, $[\alpha]_D^{20}$ −12° (*c* 1 05, dichloromethane), having ν_{max}^{KBr} 1675 cm^{-1} (C=N) and ^{1}H-n m r signal for H-1 (δ 5 81, $J_{1,2}$ 8 Hz)

All of the compounds described gave elemental analyses in agreement with assigned structures Oxazoline **4** was further characterized by acid hydrolysis, per(trimethylsilyl)ation of the products, and g l c analysis for the content of D-mannose and 2-acetamido-2-deoxy-D-glucose

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*An allyl glycoside was chosen, because of its properties as a "tracer" in t l c , see ref 4

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