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Selective Oxidation of Monosaccharide Derivatives to Uronic Acids

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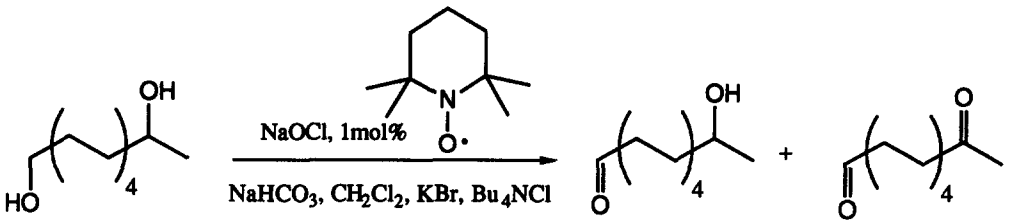
Abstract: Primary hydroxyl groups in partially protected monosaccharide derivatives were selectively oxidised to carboxylic acids using sodium hypochlorite in the presence of catalytic amounts of 2,2,6,6-tetramethyl-1-piperidinyl oxy, free radical (TEMPO). Acetal, benzyl and acyl- protection groups were unaffected during the oxidation reaction.

Oligo- and poly-saccharides containing uronic acid building blocks such as the glucosamino glycans heparin, heparan sulphate, chondroitin sulphate and dermatan sulphate have important physiological functions. Some of the proteins interacting with these negatively charged polysaccharides have been identified, such as antithrombin III (which is activated by heparin)[1] and fibroblast growth factor (which is activated by heparan sulphate).[2] In the case of the antithrombin/heparin system a unique pentasaccharide antithrombin binding sequence has been identified,[3] and chemically synthesised.[4] This work has demonstrated that small, chemically synthesised fragments can be used in therapy instead of oligo- and polysaccharides isolated from natural sources and has instigated synthetic studies on these negatively charged oligosaccharides with a view on their biological activity and possible therapeutic properties.

A key step in the synthesis of such oligosaccharides is the oxidation of the primary hydroxyl groups to carboxylic acids. This is usually achieved by chromium based oxidants, which are non-selective and require extensive protection of secondary hydroxyl groups.[5] Thus the oxidation of compound **1** to **6** (Table 1) would need five steps. We wanted to synthesise **6** from **1** in an ongoing research programme that aims to identify basic Fibroblast Growth Factor (bFGF) binding sequences[6] of heparan sulphate. Here we wish to report a selective one-step oxidation procedure for monosaccharide derivatives such as **1**, which is based on the use of oxyammonium mediated oxidations of primary alcohols with sodium hypochlorite.[7,8]

Our attention was drawn to this oxidation system by reports that it could be used to selectively oxidise the primary hydroxyl group in primary-secondary long chain diols such as 1,10-undecanediol to the hydroxy aldehydes (Scheme 1).[7,8] Recently, this system has been used as a mild oxidant for the synthesis of α-amino and α-alkoxy aldehydes.[9] The oxidising agent in this reaction is proposed to be the oxyammonium salt, which is continuously regenerated from the nitroxyl radical by hypochlorite.[10] This paper describes the application of this method to sugar chemistry with its more hydrophilic and polyfunctional monosaccharides, some of which bear base sensitive protection groups. We have investigated the oxidation of several partially protected monosaccharide derivatives (**1-5**) which are listed in Table 1.

Scheme 1:



58 : 15

Little product formation was observed when following the experimental procedure described for 1,10-undecanediol,[7] but good yields were obtained after modification of the reaction conditions, which were optimised for compound **1**.[11] Thus the reaction time was kept to a minimum in order to avoid hydrolysis of the acetyl group. Excess of hypochlorite (3 mole equivalents) needed to be added for best yields. The main difference from the reported results were that the main products were the carboxylic acids (*e.g.* **6** from **1**) rather than the aldehydes. This proved to be fortuitous to us since we could obtain the desired carboxylic acids directly and they could be isolated from the aqueous layer of the biphasic reaction system by extraction after separation and acidification of the aqueous layer. Only the product from the octyl glucoside oxidation precipitated out during the reaction and was isolated by filtration. The crude carboxylic acids contained little side product after this work up procedure. The organic layers of the biphasic reaction mixture were analysed by TLC and were found not to contain any of the carboxylates but just a mixture of several minor side products. The carboxylates were either isolated directly (**6**,**11**) or converted to their methyl esters (**7**,**8**,**9**,**10**)[12] to allow purification by silica chromatography. All yields are isolated yields. The products were fully characterised spectroscopically.[13-17]

Table 1 shows that a variety of monosacharide derivatives (**1** to **5**) could be selectively oxidised. Although minor side products resulting from the oxidation of secondary alcohols might be expected (see Scheme 1) these would have been already separated during the work up procedure. The oxidation leaves benzyl ethers (in compounds **1** and **2**), acetyl groups (in compound **1**) and acetonides (in compound **5**) intact.

The less protected methyl- and octyl- glucosides **3** and **4** , where three secondary hydroxyl groups were competing with the primary hydroxyl group still led to the carboxylates as the main products. The selectivity for primary hydroxyl groups in these sugars thus seems to be greater than expected from published examples such as shown in Scheme 1. This oxidation method might thus find its use as a simple and inexpensive alternative to PtO_2 catalysed oxidations.[18] Its application to the oxidation of primary hydroxyl groups in polysaccharide derivatives is currently being explored.

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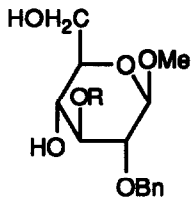
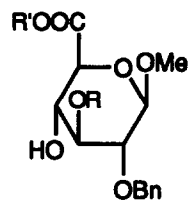
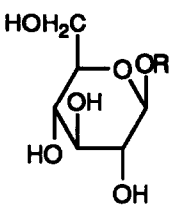
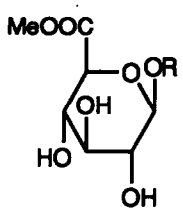
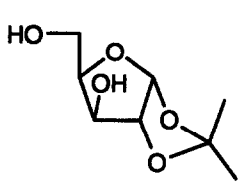
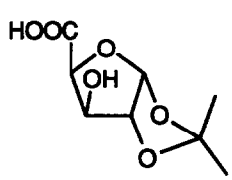
Table 1:

STARTING MATERIALS	PRODUCTS (Yield)
	
1: R = -acetyl	**6**: R = -acetyl, R' = -H (83% crude) **7**: R = -acetyl, R' = -Me (50% from **1**)[13]
2: R = -benzyl	**8**: R = -benzyl, R' = -Me (61%)[14]
	
3: R = -Me	**9**: R = -Me (55% from **3**)[15]
4: R = -n-octyl	**10**: R = -n-octyl (67% from **4**)[16]
	
5	**11**: (64%)[17]

References and Notes

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11. General Oxidation Procedure: To a solution of the alcohol (6×10^{-4} mole) in dichloromethane (1.8 ml) containing TEMPO (1mg) was added a solution of saturated aqueous sodium bicarbonate (1.2 ml) containing potassium bromide (6.6mg) and tetrabutyl ammonium chloride (8.8mg). The mixture was cooled to 0°C and a solution of sodium hypochlorite (1.3M, 1.5 ml), sodium bicarbonate (0.66ml) and brine (1.32 ml) were added dropwise over 45 min. The two layers were separated and the organic extracts washed with water (3 x 5ml). The combined aqueous extracts were acidified with 4 M hydrochloric acid and extracted with ethyl acetate (5 x 25 ml), dried over sodium sulphate and concentrated.
12. General esterification procedure: Acid (3.5×10^{-4} mol) and Dowex $50H^+$ (0.33g) were stirred in dry MeOH (11 ml) at room temperature under Argon for 20 - 48 hours. The mixture was filtered, concentrated and purified by silica chromatography.
13. Selected spectroscopic data for **7**: (Found: C 57.68, H 6.21, $C_{17}H_{22}O_8$ requires C 57.62, H 6.26); δ_H/ppm (500 MHz; $CDCl_3$) 2.03 (3H, s, -OAc), 3.39 (1H, dd, *J 7.67, 7.62*, H-2), 3.60 (3H, s, -OMe), 3.84 (3H, s, $-CO_2Me$), 4.43 (1H, d, *J 7.62*, H-1), 4.61, 4.84 (2 x 1H, 2d, *J 11.84*, $PhCH_2$-), 5.05 (1H, m, H-3), 7.26-7.37 (5H, m, Ph); m/z CI(NH_3) MNH_4^+ 372 (23%), MH^+ 355 (4%).
14. Selected spectroscopic data for **8**: (Found: C 65.41, H 6.82, $C_{22}H_{26}O_7$ requires C 65.66, H 6.51); υ_{max} ($CHCl_3$)/cm^{-1} 1750 (C=O); δ_H/ppm (500 MHz; $CDCl_3$) 3.44 (1H, dd, *J 7.60, 7.56* H-2), 3.52 (1H, m, H-3), 3.59 (3H, s, -OMe), 3.83 (3H, s, $COOCH_3$), 3.85-3.89 (2H, m, H-4, H-5), 4.37 (1H, d, *J 7.52*, H-1), 4.71-4.92 (4H, m, 2 x $PhCH_2$-), 7.27-7.37 (10H, m, Ph); δ_C/ppm (200 MHz; $CDCl_3$) 170.09 (C=O); m/z CI(NH_3) MNH_4^+ 420 (31%).
15. Selected spectroscopic data for **9**: υ_{max} ($CHCl_3$)/cm^{-1} 1750 (C=O); δ_H/ppm (500 MHz; $CDCl_3$) 3.46 (1H, m, H-2), 3.56 (3H, s, -OMe), 3.60 (1H, m, H-3), 3.75 (1H, m, H-4), 3.83 (3H, s, $-CO_2Me$), 3.91 (1H, d, *J 9.70*, H-5), 4.29 (1H, d, *J 7.75*, H-1); δ_C/ppm (200 MHz; $CDCl_3$) 170.12 (C=O); m/z CI(NH_3) MNH_4^+ 240.108, $C_8H_{14}O_7NH_4^+$ requires 240.233.
16. Selected spectroscopic data for **10**: υ_{max} ($CHCl_3$)/cm^{-1} 1750 (C=O); δ_H/ppm (500 MHz; $CDCl_3$) 3.84 (3H, s, CO_2Me); δ_C/ppm (200 MHz; $CDCl_3$) 170.13 (C=O); m/z CI(NH_3) MNH_4^+ 338.218, $C_{15}H_{28}O_7NH_4^+$ requires 338.420.
17. Selected spectroscopic data for **11**: υ_{max} ($CHCl_3$)/cm^{-1} 1770 (C=O); δ_H/ppm (500 MHz; $CDCl_3$) 1,34, 1.50 (6H, 2s, 2 x -Me), 4.57 (1H, d, *J 2.61*, H-3), 4.61 (1H, d, *J 2.60*, H-2), 4.82 (1H, d, *J 2.83*, H-4), 6.08 (1H, d, *J 2.81*, H-1); δ_C/ppm (200 MHz; $CDCl_3$) 171.21 (C=O); m/z CI(NH_3) MNH_4^+ 222.098, $C_8H_{12}O_6NH_4^+$ requires 222.217.
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