Preliminary communication

Retention of the anomeric configuration in the imidate procedure: synthesis of disaccharides containing α -L-rhamnopyranosyl and α -D-mannopyranosyl groups*

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The imidate procedure¹ has proved to be an efficient method of glycosylation in the synthesis of oligosaccharides: β -glycosyl imidates, prepared from α -glycosyl halides, give α -glycosides on acid-catalysed reactions with alcohols. Direct preparation of β - as well as some α -glycosyl imidates has been reported², and each type of imidate reacts with inversion at the anomeric center during glycosidation, provided that neighbouringgroup participation is not possible.

Relatively few sugar imidate derivatives have been described and we now report on the synthesis and reactions of such compounds in the *manno* series.

Treatment of 2,3,4-tri-O-benzyl-L-rhamnopyranose³, prepared⁴ (61%) from Lrhamnose, with sodium hydride and trichloroacetonitrile in dichloromethane for 30 min at room temperature readily gave 85% of syrupy 2,3,4-tri-O-benzyl-1-O-trichloroacetimidoyl- α -L-rhamnopyranose^{**} (1), $[\alpha]_D - 34^\circ$; ¹³C-n.m.r. data: 96.4 p.p.m. (C-1). Similarly, 2.3,4,6-tetra-O-benzyl-D-mannopyranose⁵ afforded 86% of syrupy 2,3,4,6-tetra-O-benzyl-1-O-trichloroacetimidoyl- α -D-mannopyranose (2), $[\alpha]_D + 39^\circ$; ¹³C-n.m.r. data: 96.5 p.p.m. (C-1). The α configurations were verified by the $J_{C-1,H-1}$ value⁶ of 177 Hz for 1 and 2, and no β -imidate could be detected in the above reactions.

Treatment of benzyl 2,3,4-tri-O-benzyl- β -D-glucopyranoside⁷ (3) in dichloromethane with a slight excess of 1 and a catalytic amount of anhydrous toluene-*p*sulfonic acid in the presence of molecular sieves (4 Å) for 1 day gave benzyl 2,3,4-tri-Obenzyl-6-O-(2,3,4-tri-O-benzyl- α -L-rhamnopyranosyl)- β -D-glucopyranoside (86%), m.p.

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^{**}Optical rotations were determined for solutions in chloroform. N.m.r. spectra were recorded for solutions in CDCl₃. All new compounds gave satisfactory elemental analyses.



128–129° (from ethyl acetate–light petroleum), $[\alpha]_D$ –22°; ¹³C-n.m.r. data: 98.6 p.p.m. (C-1'). $J_{C-1'H-1'}$ 168 Hz. Similar reactions of 1 with the partially protected L-rhamnose derivatives⁸ 4–6 yielded the following α -linked disaccharide derivatives. Benzyl 2.3-0isopropylidene-4-O-(2,3,4-tri-O-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (96%). syrup. [α]_D -33°; ¹³C-n.m.r. data: 97.4 p.p.m. (C-1'), J_{C-1',H-1'} 170 Hz. Benzyl 2,4-di-Obenzyl-3-O-(2,3,4-tri-O-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (82%), m.p. 100–102° (from ethyl acetate–light petroleum), $[\alpha]_{D}$ –44°; ¹³C-n.m.r. data: 100.0 p.p.m. (C-1'), J_{C-1'H-1'} 169 Hz. Benzyl 3,4-di-O-benzyl-2-O-(2,3,4-tri-O-benzyl-α-Lrhamnopyranosyl)- α -L-rhamnopyranoside (70%), syrup, $[\alpha]_D -25^\circ$; ¹³C-n.m.r. data: 99.3 p.p.m. (C-1'). $J_{C-1',H-1'}$ 168 Hz. The imidate 2 also reacted with 4 to afford an α linked disaccharide, benzyl 2,3-O-isopropylidene-4-O-(2,3,4,6-tetra-O-benzyl-a-D-mannopyranosyl)- α -L-rhamnopyranoside (93%). syrup, $[\alpha]_{D}$ +31°; ¹³C-n.m.r. data: 99.1 p.p.m. (C-1'), $J_{C-1',H-1'}$ 167 Hz. No β isomer could be isolated in the above reactions. A byproduct obtained in the glycosylation of 5 proved to be 1,5-anhydro-2,3,4-tri-O-benzyl-6deoxy-L-arabino-hex-1-enitol (7), m.p. $91-92^{\circ}$ (from light petroleum). $[\alpha]_{D}$ +7°, which was a β -elimination product of 1.

Reactions of imidates 1 and 2 with a large excess of methanol gave ~1:1 mixtures (g.l.c., h.p.l.c.) of the corresponding α - and β -glycosides. Methyl 2,3,4-tri-O-benzyl- α -L-rhamopyranoside (49%), syrup, $[\alpha]_{\rm D} -26^{\circ}$; lit.³ $[\alpha]_{\rm D} -27.8^{\circ}$; ¹³C-n.m.r. data:



99.1 p.p.m. (C-1), $J_{C-1,H-1}$ 169 Hz. Methyl 2,3,4-tri-*O*-benzyl- β -L-rhamnopyranoside (38%), m.p. 65–67° (from light petroleum), $[\alpha]_D$ +81°; ¹³C-n.m.r. data: 102.7 p.p.m. (C-1), $J_{C-1,H-1}$ 152 Hz. Methyl 2,3,4,6-tetra-*O*-benzyl- α -D-mannopyranoside (51%), syrup, $[\alpha]_D$ +28°; lit.⁵ $[\alpha]_D$ +27°; ¹³C-n.m.r. data: 99.0 p.p.m. (C-1), $J_{C-1,H-1}$ 166 Hz. Methyl 2,3,4,6-tetra-*O*-benzyl- β -D-mannopyranoside (46%), m.p. 71–72° (from light petroleum), $[\alpha]_D$ -59°; lit.⁹ m.p. 69–70°, $[\alpha]_D$ -55.1°; ¹³C-n.m.r. data: 102.6 p.p.m. (C-1), $J_{C-1,H-1}$ 156 Hz.

Thus, the imidate procedure of glycosylation does not necessarily result in the inversion of the anomeric configuration, as α -imidates of sugars having the manno configuration react with retention (see also ref. 10). Therefore, an S_N2 or push-pull mechanism can be excluded and the formation of α -glycosides may involve a double inversion. Protonation of the trichloroacetimidoyl group, which is a good leaving-group¹¹, is followed by cleavage with the formation of a β -tosylate (or the equivalent tight ion-pair) which, in turn, reacts with alcohols to give α -glycosides. The stereoselective reaction of a free carbonium ion intermediate with the poorly nucleophilic, bulky alcohols cannot be excluded. Loss of the trichloroacetimidoyl group and formation of ionic intermediates is facilitated by the reverse anomeric effect of the protonated imidate.

The above reactions offer a new stereoselective method for the synthesis of oligosaccharides containing α -L-rhamno- and α -D-manno-pyranosyl residues. Since the preparation and reactions of imidates are compatible with the presence of a series of blocking groups, "functionalised imidates" {*e.g.*, 4-O-acetyl-2,3-O-isopropylidene-1-O-tri-chloroacetimidoyl- α -L-rhamnopyranose (8; 79%), m.p. 100–102° (from light petroleum), $[\alpha]_D -22°$ } useful for the synthesis of higher oligosaccharides can readily be prepared from the corresponding hydroxy derivatives.

The above method can be extended to furanosides; thus, 2,3:5,6-di-O-isopropylidene-1-O-trichloroacetimidoyl- α -D-mannofuranose (9), m.p. 113–114° (from ethyl acetate-light petroleum), $[\alpha]_D$ +51°; n.m.r. data: δ 6.27 (s, H-1, $J_{1,2}$ <1 Hz); reacted with 3 to afford benzyl 2,3,4-tri-O-benzyl-6-O-(2,3:5,6-di-O-isopropylidene- α -D-mannofuranosyl)- β -D-glucopyranoside (81%), m.p. 121–122° (from ethyl acetate-light petroleum), $[\alpha]_D$ +19°; n.m.r. data: δ 5.12 (s, H-1', $J_{1',2'}$ <1 Hz).

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