C-Glucosyl quinones and related spacer-connected *C*-disaccharide

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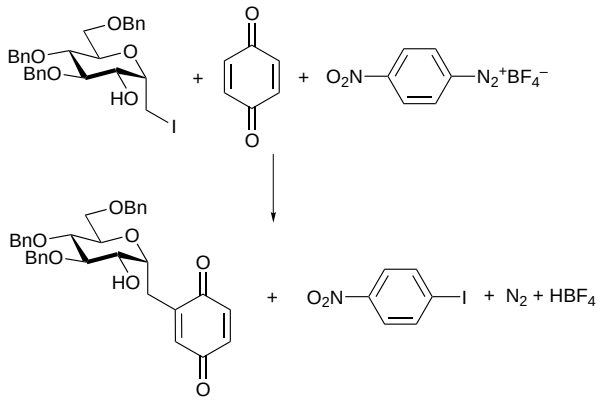
***C*-Glycosyl radicals obtained from iodide 1 react with benzo- and naphtho-quinone to afford, after deprotection, *C*-glycosyl quinones 4 and 6 which inhibit yeast α-glucosidase; employing a naphthoquinone linked to the non-reducing end of a sugar 7, a spacer-connected *C*-disaccharide 8 is obtained.**

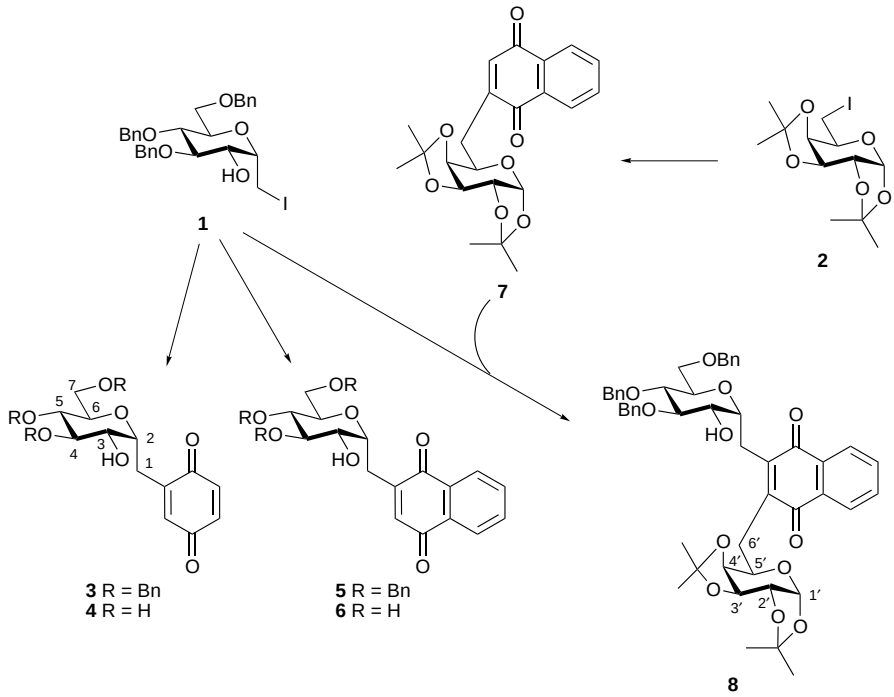
There is a growing interest in *C*-glycosides and *C*-disaccharides as potential inhibitors and regulators of carbohydrate processing enzymes and as stable mimics of saccharidic structures involved in recognition phenomena.[1] In this context, particular attention has been devoted to molecules that interfere in the biosynthesis of N-linked glycoproteins, so inhibiting pathologic processes such as HIV replication,[2] or tumour growth and metastasis formation.[3] The biosynthesis of N-linked glycoproteins involves a common asparagine-linked oligosaccharide intermediate which undergoes a trimming process, the first two trimming enzymes being α-glucosidases (I and II).[4] As a consequence α-glucoside mimics, among them α-*C*-glucosides, are potential inhibitors of N-linked glycoprotein biosynthesis.



Scheme 1

Many α-*C*-glucosides have been synthesised, among them aryl *C*-glucosides, in which the aromatic group is directly linked to the anomeric centre of the sugar.[5] Molecules of this kind, with quinones (especially flavonoids) directly linked to the anomeric centre of the sugar, are found in nature and are believed to form stable complexes with DNA. On the other hand, the presence of a naphthoquinone aglycon in *O*- and *S*-glycosides is responsible for antitumour[6] and antifungal[7] activity, and irreversible glycosidase inhibition.[8]

To mimic natural α-*O*-glucosides, and at the same time to produce a stable *C*-glycosidic linkage between the sugar and a quinone, we decided to synthesise α-*C*-glucosidic compounds in which the quinone is linked to the anomeric carbon through a methylene bridge. In the light of the fact that the conversion of this methylenic carbon into a nucleophile often gives rise to undesired elimination reactions or epimerization, we decided to use a radical approach. Quinones were in fact extensively studied as radical scavengers both from a mechanistic and a synthetic point of view.[9] In this context we decided to investigate the substitution by *C*-glycosyl radicals derived from



Scheme 2

C-glycosyl iodides and diazonium tetrafluoroborate according to Scheme 1. As this kind of quinone substitution is governed by enthalpic and, to a minor extent, steric effects, a radical at a methylenic carbon linked to the anomeric centre of a sugar appeared to be an attractive reagent.

An α-*C*-glucosyl radical can be obtained from the corresponding iodide provided that the hydroxy group at C-2 is not benzylated,[10] otherwise an abstraction of the benzylic hydrogen occurs with formation of the more stable benzyl radical. We synthesised (3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl)iodomethane **2**, which lacks the benzyl protecting group at C-2, exploiting a vinylation–electrophilic cyclisation procedure[11] using 2,3,5-tri-*O*-benzyl-D-arabinose **1**.

In a typical experimental procedure (Scheme 2), a solution of 4-nitrobenzenediazonium tetrafluoroborate (2 mmol) in degassed DMSO (7 ml) was added dropwise to a solution of **1** (1 mmol), the quinone (1 mmol) and powdered $FeSO_4 \cdot 7H_2O$ (2 mmol) in degassed DMSO (15 ml). The solution was stirred until the evolution of nitrogen ceased. Usual work-up and chromatography afforded **3** {oil, $[\alpha]_D$ + 31.3 (*c* 1, $CHCl_3$)}‡ or **5** {oil, $[\alpha]_D$ + 47.6 (*c* 1, $CHCl_3$)}§ in 30–35% yield (80–85% yield based on converted **1**), and unreacted **1** was resubmitted to the reaction. Catalytic hydrogenation of **3** and **5** (Pd/C in EtOH) afforded **4** {oil, $[\alpha]_D$ − 9.7 (*c* 1, MeOH)} and **6** {mp 108–109 °C; $[\alpha]_D$ + 86.5 (*c* 1, acetone)}, respectively, in quantitative yield.

The biological activities of **4** and **6** as inhibitors of yeast α-glucosidase were tested according with the procedure reported by Wong.[12] Compound **4** is a poor competitive inhibitor (K_i = 2.9 mM) but interestingly the presence of a further aromatic ring in **6** strongly enhances the inhibitory activity (K_i = 0.17 mM).

The radical generated from **1** was also trapped (50% yield) by the sugar-substituted naphthoquinone **7**¶ (obtained from **2** *via* the procedure above). This reaction provided the naphthoquinone-connected *C*-disaccharide **8** {oil, [α] + 39.2 (*c* 1, $CHCl_3$); *m/z* 846}‖ in which two sugars are permanently linked through a naphthoquinone spacer. Recently, different saccharides connected with aliphatic[13] and aromatic[14] spacers have been synthesised to mimic biologically active natural oligosaccharides; this is the first example in which two saccharides are permanently connected *via* C–C linkages to a quinone spacer.

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Footnotes and References

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‡ *Selected data* for **3**: ^{1}H NMR (500 MHz, C_6D_6, *J* values in Hz): δ 2.72 (dd, 1 H, *J* 15.1, 3.5, H-1a), 2.81 (dd, 1 H, *J* 15.1, 9.8, H-1b), 2.97 (d, 1 H, *J* 8.5, OH), 3.53 (t, 1 H, *J* 5.0, H-5), 3.57 (dd, 1 H, *J* 4.8, 10.3, H-7a), 3.64 (ddd, 1 H, *J* 8.5, 3.3, 5.0, H-3), 3.72 (t, 1 H, *J* 5.0, H-4), 3.77 (dd, 1 H, *J* 10.3, 6.2, H-7′a), 4.13 (br q, 1 H, *J* 5, H-6), 4.18 (dt, 1 H, *J* 9.8, 3.5, H-2), 4.25–4.42 (6 d, 6 H, OCH_2Ph), 6.03 (dd, 1 H, *J* 9.6, 3.0, =CH–C=O), 6.08 (d, 1 H, *J* 9.6, =CH–C=O), 6.63 (d, 1 H, *J* 3.0, =CH–C=O), 7.02–7.25 (m, 15 H, ArH).

§ *Selected data* for **5**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.85 (d, 2 H, *J* 6.7, H-1), 2.99 (d, 1 H, *J* 8.3, OH), 3.53 (m, 2 H, H-5, H-7a), 3.64 (ddd, 1 H, *J* 8.3, 5.5, 2.9, H-3), 3.71 (m, 2 H, H-4, H-7b), 4.03 (q, 1 H, *J* 5.0, H-6), 4.18 (dt, 1 H, *J* 6.7, 2.9 Hz, H-2), 4.37–4.60 (6 H, OCH_2Ph), 6.92 (s, 1 H, ArH, quinone), 7.12–7.27 (m, 15 H, $OCH_2C_6H_5$), 7.63 (2 H, Ar-H, quinone), 7.99 (2 H, Ar-H, quinone).

¶ *Selected data* for **7**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30, 1.36, 1.48 (4 s, 12 H, CH_3), 2.84–2.89 (m, 2 H, H-6a, H-6b), 4.15 (m, 1 H, H-5), 4.22 (dd, 1 H, *J* 7.8, 1.8, H-4), 4.30 (dd, 1 H, *J* 5.4, 2.5, H-2), 4.63 (dd, 1 H, *J* 7.8, 2.5, H-3), 5.50 (d, 1 H, *J* 5.4, H-1), 7.02 (t, 1 H, *J* 1.2, =CH–C=O), 7.70–7.75 (m, 2 H, ArH), 8.04–8.11 (m, 2 H, ArH).

‖ *Selected data* for **8**: ^{1}H NMR (500 MHz, C_6D_6, COSY): δ 0.92, 1.13, 1.41, 1.56 (4 s, 12 H, CH_3), 3.09 (dd, 1 H, *J* 13.6, 3.7, H-1a), 3.18 (d, 1 H, *J* 6.9, OH), 3.28 (dd, 1 H, *J* 13.5, 3.1, H-6′a), 3.49 (dd, 1 H, *J* 13.6, 10.3, H-1b), 3.71 (m, 1 H, H-5), 3.72 (m, 2 H, H-7a, H-6′b), 3.88 (m, 2 H, H-4, H-7b), 3.92 (m, 2 H, H-3, H-4′), 4.07 (dd, 1 H, *J* 2.4, 5.0, H-2′), 4.40 (m, 1 H, H-6), 4.45 (m, 2-H, H-2, H-3′), 4.57 (m, 1 H, H-5′), 4.24–4.60 (6 d, 6 H, OCH_2Ph), 5.31 (d, 1 H, *J* 5.0, H-1′), 6.95–7.20 (m, 15 H, $OCH_2C_6H_5$), 7.93 (d, 2 H, *J* 5.0, ArH), 8.03 (d, 2 H, *J* 5.0, ArH); ^{13}C NMR (125.721 MHz, C_6D_6): δ 24.53, 24.89, 25.92, 26.41 (CH_3), 26.41 (C-6′), 29.48 (C-1), 67.35 (C-3′), 69.26 (C-7), 70.99 (C-2′), 71.22 (C-3), 71.65 (C-2), 73.20–73.85 (OCH_2Ph), 73.21 (C-4′), 73.38 (C-5′), 74.16 (C-6), 76.16 (C-5), 79.57 (C-4), 96.98 (C-1′), 108.51 (O–C–O), 109.34 (O–C–O), 126.02–148.23 (aromatic), 185.04 (C=O), 185.44 (C=O).

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