Electrochemical reduction of halogenosugars on silver: a new approach to *C*-disaccharide-like mimics

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Electrochemical reduction on silver of tri-*O*-acetyl-α-D-fucopyranosyl bromide 3 affords (1 → 1′)-linked *C*-disaccharide-like mimics 6–8; reduction of 1,2 : 3,4-di-*O*-isopropylidene-6-deoxy-6-iodo-α-D-galactopyranose 5 provides 1,2:3,4-di-*O*-isopropylidene-6-deoxy-6-(1′,2′ : 3′,4′-di-O-isopropylidene-6′-deoxy-α-D-galactopyranos-6′-yl)-α-D-galactopyranose 9; simultaneous reduction of 5 and tetra-*O*-acetyl-α-D-glucopyranosyl bromide 1 or tri-*O*-acetyl-α-L-fucopyranosyl bromide 4 gives 9 and methylene-bridged *C*-disaccharide-like mimics 11, 12 or 13, 14, respectively.

C-Glycosides are of interest as molecules of potential biological activity and are also useful for enzymatic and metabolic studies.[1] Some *C*-disaccharides have also been investigated.[2]

Here we describe an electrochemical approach to *C*-disaccharide-like mimics, the reduction of halogenosugars in MeCN at a silver electrode, a method already extensively applied to glycosides syntheses.[3,4] This approach was confirmed by the electroreduction using the above conditions of tetra-*O*-acetyl-α-D-glucopyranosyl bromide **1** which mainly provides 1,3,4,5,8,9,10,12-octa-*O*-acetyl-D-gluco-L-altro-L-erythro-2,6 : 7,11-dianhydrododecitol,[8] 1,3,4,5,8,9,10,12-octa-*O*-acetyl-D-gluco-D-galacto-L-erythro-2,6 : 7,11-dianhydrododecitol and 1,3,4,5,8,9,10,12-octa-*O*-acetyl-D-gluco-L-ido-L-erythro-2,6 : 7,11-dianhydrododecitol[8] with an overall yield of 50%, the ratio being *ca.* 2 : 1 : 1.[5] We can account for the formation of these biglucosyl derivatives *via* a radical pathway, *i.e.* the dimerisation of tetra-*O*-acetyl-D-glucopyranosyl radical **2**.[3,4]

The *O*-glucosides themselves formed in the electrolyses of **1** on silver in the presence of phenols can be accounted for by coupling of an anomeric radical and a phenoxyl radical.[3,5] These electrolyses were carried out in MeCN *via* cyclic voltammetry of **1** at a silver electrode which displays one irreversible peak at E_p = −1.3 V (*vs.* aq. SCE). Electrochemical reduction of **1** at a mercury electrode in DMF or MeCN was proposed by Vianello and co-workers as a new approach to 3,4,6-tri-*O*-acetyl-D-glucal, the cyclic voltammetry of **1** displaying one irreversible peak at E_p = −1.9 V (*vs.* SCE).[6] No dimers were observed. Different mechanisms are no doubt involved in electrolyses of **1** using mercury or silver electrodes. On mercury, the overall electrode process of **1** was interpreted as a two electron C–Br bond cleavage coupled to a very fast elimination of the acetate anion, which leads to 3,4,6-tri-*O*-acetyl-D-glucal. 1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranose was also isolated, *via* nucleophilic substitution.[6] The electrode process on the silver cathode appears more complex. Compound **1** undergoes a single electron-transfer reduction; the following elimination of the bromide anion leads to the intermediate radical **2**, which affords dimers (50%); 3,4,6-tri-*O*-acetyl-D-glucal (20%) and 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (15%) are also isolated, thus indicating that a further reduction of **2** occurs.

On the basis of these results, we have investigated whether silver cathodic reduction of halogenosugars could be suitable to generate carbohydrate radicals, with the aim of developing new synthetic methods. The voltammetric behaviour of **1**, tri-*O*-acetyl-α-D-fucopyranosyl bromide **3**,[7] tri-*O*-acetyl-α-L-fucopyranosyl bromide **4**[7] and 1,2 : 3,4-di-*O*-isopropylidene-6-deoxy-6-iodo-α-D-galactopyranose **5**[8] were studied both at silver and mercury electrodes in MeCN (Table 1).

Table 1 Reduction peak potentials

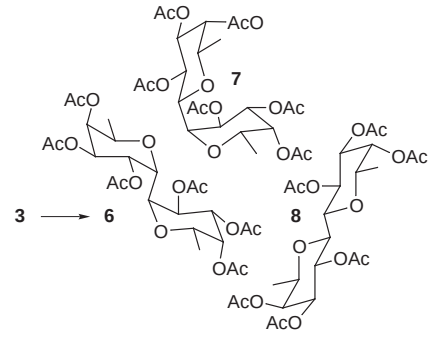
Halogenosugar	E_p (Ag)/V (*vs.* SCE)	E_p (Hg)/V (*vs.* SCE)
1	−1.30	−1.95
3[a]	−1.20	−1.95
5	−1.23	−1.81

[a] Compound **4** is reduced at the same E_p as **3**.

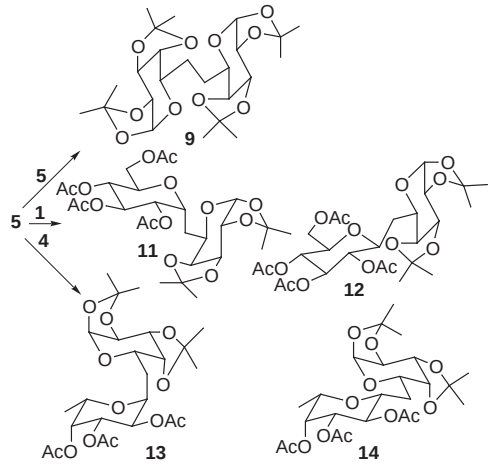
Data in Table 1 confirm the remarkable electrocatalytic activity of silver with respect to mercury. Compounds **1**,**3**–**5** were submitted to preparative electrolyses on a silver cathode in MeCN. Tri-*O*-acetyl-α-D-fucopyranosyl bromide **3** was electrolysed at −1.5 V. 3,4,5,8,9,10-Hexa-*O*-acetyl-D-galacto-L-ido-D-threo-1,12-deoxy-2,6 : 7,11-dianhydrododecitol **6**‡ (15%), 3,4,5,8,9,10-hexa-*O*-acetyl-D-galacto-L-altro-D-threo-1,12-deoxy-2,6 : 7,11-dianhydrododecitol **7**‡ (15%) and 3,4,5,8,9,10-hexa-*O*-acetyl-D-galacto-D-galacto-D-threo-1,12-deoxy-2,6 : 7,1-dianhydrododecitol **8**‡ (4%) (Scheme 1) were recovered, together with 3,4-di-*O*-acetyl-D-fucal (11%) and fucose tetraacetate (10%).

The product distribution of **3** appears similar to that of **1**, except for the dimer ratio. 1,2 : 3,4-Di-*O*-isopropylidene-6-deoxy-6-iodo-α-D-galactopyranose **5** is suitable for generating a non-anomeric radical and for derivatisation to occur at the other end of the sugar skeleton. The reduction of **5** at −1.7 V provides 1,2 : 3,4-di-*O*-isopropylidene-6-deoxy-6-(1′,2′ : 3′,4′-di-*O*-isopropylidene-6′-deoxy-α-D-galactopyranos-6′-yl)-α-D-galactopyranose **9**[4,9] as the only product (Scheme 2). Once again its formation can be explained by the presence of an intermediate radical like 1,2 : 3,4-di-*O*-isopropylidene-6-deoxy-α-D-galactopyranos-6-yl radical **10**.

On the basis of these results and of the similar redox potentials of the investigated substrates (Table 1), we asked



Scheme 1



Scheme 2

ourselves if it was possible to couple two different radicals generated at the same stage. Our goal was the synthesis of non-symmetrical *C*-disaccharides-like mimics. Radical **2** is a secondary radical, to some extent stabilised by an O atom in the α-position, while **10** is an unstabilized primary radical. So could the so-called anomeric radical **2** behave as a persistent radical[10] and act as a scavenger of the more reactive **10**? Compounds **1** and **5** were simultaneously reduced at −1.5 V in the ratio 1.5 : 1. 1,2 : 3,4-Di-*O*-isopropylidene-6-deoxy-6-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-glucopyranosyl)-α-D-galactopyranose **11**§ (9%) and 1,2 : 3,4-di-*O*-isopropylidene-6-deoxy-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-galacto-pyranose **12**§ (9%) were isolated (Scheme 2) together with **9** (17%), with only a very small amount of glucosyl dimers (> 3%).

Compounds **4**[7] and **5** in the ratio 2 : 1 were also simultaneously reduced at −1.5 V. 1,2 : 3,4-Di-*O*-isopropylidene-6-deoxy-6-(2′,3′,4′-tri-*O*-acetyl-α-L-fucopyranosyl)-α-D-galactopyranose **13**¶ (11%) and 1,2:3,4-di-*O*-isopropylidene-6-deoxy-6-(2′,3′,4′-tri-*O*-acetyl-β-L-fucopyranosyl)-α-D-galactopyranose **14**¶ (11%) were isolated together with **9** (34%) (Scheme 2).

In both cases glycals and penta- or tetra-acetyl derivatives were also isolated. The product distributions show that dimerisation of **10** competes well with its trapping by glycosyl radicals, but also that there is no dimerisation of glycosyl radicals in the presence of **10** or that it is significantly reduced.

The mechanism of these reductions is very intriguing as we could argue that not only are carbohydrate radicals involved as intermediates, but also that dimerisation is the only termination reaction, which would be very unusual. The glucopyranosyl radical **2**, for instance, has been extensively studied especially by Giese. In the absence of a radical scavenger, it mainly undergoes migration of the acetate group from position 2 to 1.[11] In the electroreduction we did not actually observe any migration at all! We extensively studied the chemical behaviour of **10**.[8] Although it acts as a good hydrogen abstractor even from MeCN, in the electroreduction we did not observe any hydrogen abstraction at all! Some coupling of **10** was observed, but only in the presence of Fe^{II}[12] and, in that particular case, the effect of Fe^{II} was interpreted using Kochi's hypothesis as being due to 'metal ion–free radical complexes of relatively longer life than a simple alkyl radical'.[13]

In conclusion, we have provided evidence for the ability of a silver cathode to generate carbohydrate radicals and perhaps to induce their dimerisation, but, for the moment, we are not able to give any satisfactory interpretation of the mechanism. Indeed, even if yields are lowered by the presence of glycals and acetate derivatives, this peculiar electroreduction affords different kinds of *C*-disaccharide-like mimics, and in this sense it could be proposed as a mild, clean, one-pot method with which to form stable interglycosidic bonds.

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Notes and References

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‡ *Selected data* for **6**: δ_H(500 MHz, C_6D_6) 1.12 (d, 3 H, H-6, $J_{5\text{-}6}$ 6.6), 4.33 (dq, 1 H, H-5, $J_{4\text{-}5}$ 3.6), 4.40 (d, 1 H, H-1, $J_{1\text{-}2}$ 3.9), 5.48 (t, 1 H, H-4, $J_{3\text{-}4}$ 3.5), 5.57 (dd, 1 H, H-2, $J_{2\text{-}3}$ 7.8), 5.78 (dd, 1 H, H-3). For **7**: δ_H(500 MHz, C_6D_6) 0.95 (d, 3 H, H-6′, $J_{5'\text{-}6'}$ 6.5), 1.19 (d, 3 H, H-6, $J_{5\text{-}6}$ 6.7), 2.85 (dq, 1 H, H-5′, $J_{4'\text{-}5'}$ 0.9), 3.60 (dd, 1 H, H-1′, $J_{1\text{-}1'}$ 4.9, $J_{1'\text{-}2'}$ 9.9), 4.12 (dq, 1 H, H-5, $J_{4\text{-}5}$ 3.8), 4.33 (dd, 1 H, H-1, $J_{1\text{-}2}$ 4.3), 5.11 (dd, 1 H, H-3′, $J_{2'\text{-}3'}$ 10.0, $J_{3'\text{-}4'}$ 3.4), 5.24 (dd, 1 H, H-4′), 5.51 (t, 1 H, H-4, $J_{3\text{-}4}$ 3.5), 5.67 (t, 1 H, H-2′), 5.80 (dd, 1 H, H-2, $J_{2\text{-}3}$ 7.1), 5.89 (dd, 1 H, H-3). For **8**: δ_H(500 MHz, C_6D_6) 1.0 (d, 3 H, H-6, $J_{5\text{-}6}$ 6.4), 2.97 (q, 1 H, H-5, $J_{4\text{-}5}$ 0), 3.37 (d, 1 H, H-1, $J_{1\text{-}2}$ 9.0), 5.22 (dd, 1 H, H-3, $J_{2\text{-}3}$ 9.0, $J_{3\text{-}4}$ 3.7), 5.22 (d, 1 H, H-4), 5.90 (t, 1 H, H-2).

§ *Selected data* for **11**: δ_H(500 MHz, C_6D_6) 1.99 (ddd, 1 H, H-6a, $J_{1'\text{-}6a}$ 11.7, $J_{5\text{-}6a}$ 2.9, $J_{6a\text{-}6b}$ 14.9), 2.12 (ddd, 1 H, H-6b, $J_{1'\text{-}6b}$ 2.5, $J_{5\text{-}6b}$ 10.0), 3.86 (dd, 1 H, H-4, $J_{3\text{-}4}$ 8.0, $J_{4\text{-}5}$ 1.9), 3.93 (ddd, 1 H, H-5′, $J_{4'\text{-}5'}$ 8.0, $J_{5'\text{-}6'a}$ 4.5, $J_{5'\text{-}6'b}$ 4.3), 4.14 (ddd, 1 H, H-5), 4.15 (dd, H-2, $J_{1\text{-}2}$ 5.0, $J_{2\text{-}3}$ 2.4), 4.33 (ddd, 1 H, H-6′a, $J_{6'a\text{-}6'b}$ 11.9), 4.38 (ddd, 1 H, H- 6′b), 4.49 (dd, 1 H, H-3), 4.60 (ddd, 1 H, H-1′, $J_{1'\text{-}2'}$ 5.1), 5.24 (dd, 1 H, H-2′, $J_{2'\text{-}3'}$ 8.0), 5.26 (t, 1 H, H-4′, $J_{3'\text{-}4'}$ ≈ 7.9), 5.43 (d, 1 H, H-1), 5.53 (t, 1 H, H-3′). For **12**: δ_H(500 MHz, C_6D_6) 2.07–2.08 (dd, 2 H, H-6a, H-6b, $J_{1'\text{-}6}$ 4.6–4.8, $J_{5\text{-}6}$ 2.0), 3.22 (ddd, 1 H, H-5′, $J_{4'\text{-}5'}$ 10.0, $J_{5'\text{-}6'a}$ 2.0, $J_{5'\text{-}6'b}$ 4.9), 3.52 (dt, 1 H, H-1′, $J_{1'\text{-}2'}$ 9.2), 3.94 (dd, 1 H, H-4, $J_{3\text{-}4}$ 7.8, $J_{4\text{-}5}$ 1.6), 4.03 (dd, 1 H, H-6′a, $J_{6'a\text{-}6'b}$ 12.1), 4.16 (dd, 1 H, H-2, $J_{1\text{-}2}$ 5.2, $J_{2\text{-}3}$ 2.4), 4.26 (dd, 1 H, H-6′b), 4.26 (dt, 1 H, H-5), 4.51 (dd, 1 H, H-3), 5.23 (dd, 1 H, H-4′, $J_{3'\text{-}4'}$ 9.3), 5.30 (dd, 1 H, H-2′), 5.30 (dd, 1 H, H-3′), 5.48 (d, 1 H, H-1).

¶ *Selected data* for **13**: δ_H(500 MHz, $CDCl_3$) 1.12 (d, 3 H, H-6′, $J_{5'\text{-}6'}$ 6.4), 1.84 (ddd, 1 H, H-6a, $J_{1'\text{-}6a}$ 4.2, $J_{5\text{-}6a}$ 8.2, $J_{6a\text{-}6b}$ 14.5), 2.00–2.05 (m, 1 H, H-6b), 3.85 (ddd, 1 H, H-5, $J_{4\text{-}5}$ 1.9, $J_{5\text{-}6b}$ 5.7), 4.05 (dq, 1 H, H-5′, $J_{4'\text{-}5'}$ 1.9), 4.17 (dd, 1 H, H-4, $J_{3\text{-}4}$ 7.9), 4.27 (dd, 1 H, H-2, $J_{1\text{-}2}$ 5.2, $J_{2\text{-}3}$ 2.4), 4.35 (ddd, 1 H, H-1′, $J_{1'\text{-}2'}$ 5.6, $J_{1'\text{-}6b}$ 11.6), 4.57 (dd, 1 H, H-3, $J_{2\text{-}3}$ 2.4), 5.20 (dd, 1 H, H-3′, $J_{2'\text{-}3'}$ 10.0, $J_{3'\text{-}4'}$ 3.0), 5.25 (dd, 1 H, H-4′), 5.28 (dd, 1 H, H-2′), 5.47 (d, 1 H, H-1). For **14**: δ_H(500 MHz, $CDCl_3$) 1.12 (d, 3 H, H-6′, $J_{5'\text{-}6'}$ 6.4), 1.55 (ddd, 1 H, H-6a, $J_{1'\text{-}6a}$ 11.0, $J_{5\text{-}6a}$ 2.0, $J_{6a\text{-}6b}$ 14.7), 1.86 (ddd, 1 H, H-6b, $J_{1'\text{-}6b}$ 1.9, $J_{5\text{-}6b}$ 10.6), 3.63 (dt, 1 H, H- 1′, $J_{1'\text{-}2'}$ 9.6), 3.79 (q, 1 H, H-5′), 4.02 (dd, 1 H, H-4, $J_{3\text{-}4}$ 7.9, $J_{4\text{-}5}$ 1.9), 4.07 (dd, 1 H, H-5), 4.25 (dd, 1 H, H-2, $J_{1\text{-}2}$ 4.9, $J_{2\text{-}3}$ 2.4), 4.54 (dd, 1 H, H-3), 4.98 (dd, 1 H, H-3′, J3′-4′ 3.4, $J_{2'\text{-}3'}$ 10.1), 5.05 (t, 1 H, H-2′), 5.25 (d, 1 H, H-4′), 5.47 (d, 1 H, H-1).

1 For a comprehensive description of *C*-glycosides, see D. E. Levy and C. Tang, *The Chemistry of* C-*glycosides*, Tetrahedron Organic Chemistry Series, Pergamon Press, 1995, vol. 13.
2 P. Sinaÿ, *Pure Appl. Chem.*, 1997, **69**, 459; Y. Wang, P. G. Goekjian, D. M. Ryckman, W. H. Miller, S. A. Babirad and Y. Kishi, *J. Org. Chem.*, 1992, **57**, 482; J.-F. Espinoza, F. J. Cañada, J. L. Asensio, M. Martin-Lomas, R. R. Schmidt and J. Jiménes-Barbero, *J. Am. Chem. Soc.*, 1996, **118**, 10 862; G. Rubinstenn, P. Sinaÿ and P. Berthault, *J. Phys. Chem., A*, 1997, **101**, 2536.
3 M. Benedetto, G. Miglierini, P. Mussini, F. Pelizzoni, S. Rondinini and G. Sello, *Carbohydr. Lett.*, 1995, **1**, 321.
4 S. Rondinini, P. Mussini, G. Sello and E. Vismara, *J. Electrochem. Soc.*, 1998, **145**, 1108.
5 A. Alberti, M. Della Bona, D. Macciantelli, F. Pelizzoni, G. Sello, G. Torri and E. Vismara, *Tetrahedron*, 1996, **52**, 10 241.
6 F. Maran, E. Vianello, G. Catellani and F. D'Angeli, *Electrochim. Acta*, 1989, **34**, 587.
7 H. Shah and O. P. Bahl, *Carbohydr. Res.*, 1974, **32**, 15.
8 E. Vismara, A. Donna, F. Minisci, A. Naggi, N. Pastori and G. Torri, *J. Org. Chem.*, 1993, **58**, 959.
9 E. I. Stout , W. M. Doane and V. C. Trinkus, *Carbohydr. Res.*, 1976, **50**, 282.
10 A. Bravo, H.-R. Bjørsvig, F. Fontana, L. Liguori and F. Minisci, *J. Org. Chem.*, 1997, **62**, 3849 and references cited therein.
11 B. Giese, B. Rückert, K. S. Gröningen, R. Muhn and H. J. Lindner, *Liebigs Ann. Chem.*, 1988, 997.
12 E. Vismara, N. Pastori, M. Guerrini, L. Liguori, A. Naggi and G. Torri, Abstracts XVIIth International Carbohydrate Symposium, Ottawa, Canada, 1994, 338.
13 J. Kochi and F. F. Rust, *J. Am. Chem. Soc.*, 1961, **83**, 2017.

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