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Preparation, X-ray structure and reactivity of a stable glycosyl iodide

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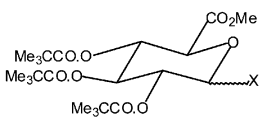
Highly selective reaction of methyl tetra-*O*-pivaloyl-β-D-glucopyranuronate 2 with iodotrimethylsilane or $(Me_3Si)_2$ and I_2 affords, in excellent yield, the 'disarmed' glycosyl iodide 1 which has good stability at 20 °C and excellent stability at 0 °C; the X-ray crystal structure of 1 is described, along with a comparison of its utility as a glycosyl donor to that of the corresponding bromide.

Although a very wide range of glycosyl donors are now available, including in particular thioglycosides,[1] anomeric trichloroacetimidates,[2] sulfoxides[3] and pentenyl glycosides,[4] anomeric halosugars are still commonly employed in glycosidation reactions. Traditionally glycosyl bromides have been used, activated by heavy metal salts (usually those of Ag and Hg, occasionally of Cd), the classical Koenigs–Knorr conditions.[5] Within the last decade it has been shown that iodine reagents are effective alternatives to the heavy metals, for both 'armed' and 'disarmed' cases, and are effective for other anomeric leaving groups.[6,7] It has been traditionally held[8] that glycosyl iodides are too difficult to prepare, and too unstable, to be useful glycosyl donors. A number of publications have appeared regarding their preparation, nevertheless, and others have cited them as reactive *in situ* intermediates.[9] In particular Gervay *et al.*[10,11] have shown that 'armed' glycosyl iodides will react with a variety of nucleophiles and have reinvestigated 'disarmed' iodosugars without isolating them.[11]

As is widely understood, substitution critically affects reactivity and stability in all carbohydrate derivatives. We now report that the pivaloate-protected glycosyl iodide **1**, derived from glucuronolactone, is formed in high yield and under mild conditions from the β-tetrapivaloate **2**[12] and moreover possesses excellent stability. We also present the X-ray structure of **1** and briefly compare its reactivity to that of the corresponding bromosugar **3**.[12]



1 X = α-I

2 X = β-O_2CCMe_3

3 X = α-Br

5 X = β-$O(CH_2)_2Ph$

Various methods for the conversion of anomeric ester **2** to glycosyl iodide **1** were studied, as summarised in Table 1. Marginally best was the hexamethyldisilane–I_2 method,[15] which generates Me_3SiI *in situ*, though the Me_3SiI procedure also afforded a 90%+ yield.[10] The chemical stability of **1** is excellent. At 0 °C it is stable for well over one year if kept dry and away from light (best stored in a Nalgene bottle); at 20 °C it remains unchanged after many months.

The glycosyl iodide **1** was readily crystallised from hexane, mp 104–105 °C and gave crystals suitable for X-ray structure determination (pale yellow prisms, orthorhombic).[17] The structure of **1** is presented in Fig. 1.

It can be seen that **1** adopts a normal 'chair' $^4C_1$ conformation: its structure differs in minor respects from that of the bromosugar **3**. The O–C(1) bond shows characteristic bond shortening (1.398 Å, identical to the O–C(1) bond in **3**: typical sp^3C–O, 1.43Å), and the C(1)–I bond characteristic lengthening (2.22 Å: typical sp^3 C–I, 2.16 Å), owing to the anomeric effect.

Table 1 Preparative methods for the anomeric iodosugar **1**

Reagents, conditions	Time/h	Yield[a] (%)
KI, $BF_3{\cdot}Et_2O$, MeCN, **2**, 80 °C[13,14]	3	67
Me_3SiI, MeCN, **2**, 50 °C[9a,10]	2.75	91
$(Me_3Si)_2$, I_2, CH_2Cl_2, **2**, 20 °C[15]	5	92
$PhSiMe_3$, I_2, MeCN, **2**, 50 °C[16]	1.7	53

[a] After chromatography and/or crystallisation.

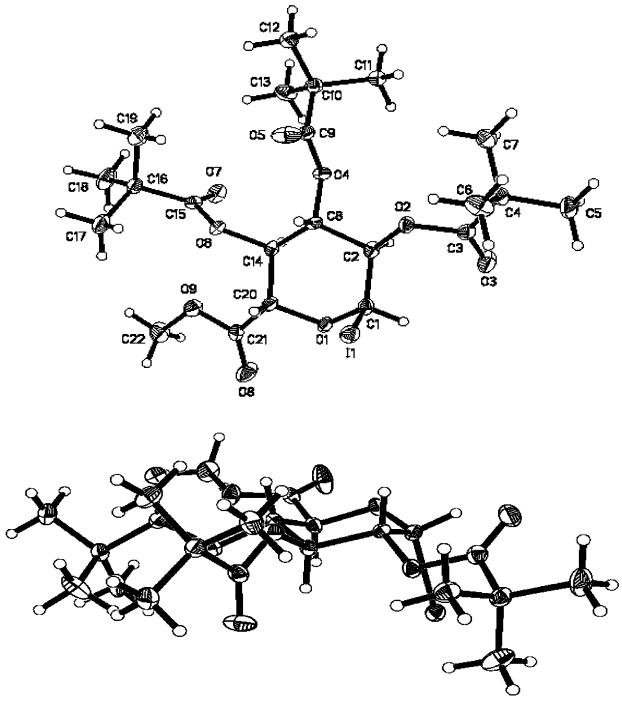


Fig. 1 X-Ray structure of iodosugar **1**, (top) in plan, (bottom) in elevation showing the 'chair'.

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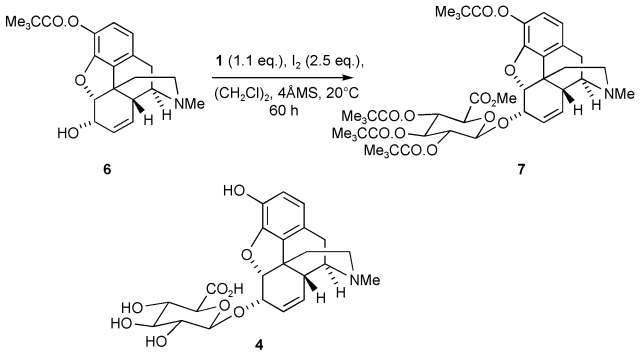

Scheme 1

The conformations of the C(2) and C(5)/C(6) substituents, however, differ between **1** and **3**, probably owing to the relative sizes of the Br/I atoms and packing effects. The ^{1}H NMR spectra of the two halosugars also show some differences. Both the H(2)–H(3) axial–axial and H(1)–H(2) axial–equatorial coupling constants in **1**, respectively 9.8 and 4.4 Hz,[17] fall within the typical pyranose range, but very interestingly the chemical shift of the 2-H is significantly lower in **1** than in **3**, whereas the chemical shift of the 1-H is higher in **1** than in **3**. A similar trend has been noted before in anomeric iodosugars of the galactose series:[15] moreover the difference in chemical shifts of the anomeric protons of **1** and **3**, at 0.36 ppm, is comparable to that between the anomeric protons of the parent 2-bromo- and 2-iodo-tetrahydropyrans (0.46 ppm) as given by Anderson and Sepp.[18]

Because of the continuing interest in morphine-6-glucuronide **4** as an analgesic more potent and better tolerated than morphine itself,[13,19] the glycosyl donor ability of **1** was studied in this context (Scheme 1). In a model experiment, **1** (1 eq.) proved to be a suitable donor for glycosidation of 2-phenylethanol (1.5 eq.) using $ZnCl_2$ (1.1 eq.) as catalyst in 1,2-dichloroethane (20 h, 20 °C); glucuronate ester **5**[20] was isolated in 56% yield (unoptimised). Reaction of 3-*O*-pivaloyl morphine **6**[19c] with **1** (1.1 eq.) mediated by I_2 (2.5 eq.) *with no other catalyst* afforded glucuronate ester **7** (55% after chromatography) after 60 h.[13,21] The yield compares well to that obtained using the trichloroacetimidate method[22] and the product was identical to **7** prepared in that way; moreover only a 10% excess of **1** is required. By contrast, reaction of **6** with the bromosugar **3** (which afforded typically 80–85% yields in glycosidation of primary alcohol acceptors)[20] under comparable conditions gave only a 20% yield of **7**. Finally, base-catalysed hydrolysis of **7** led cleanly to morphine-6-glucuronide **4**[19c] in 85% yield.

In summary, we have characterised a highly stable 'disarmed' glycosyl iodide, namely **1**, and shown it to possess a typical chair structure by X-ray diffraction. This represents the first crystal structure for this class of molecule. Furthermore, we have shown glycosyl iodide **1** to be an effective glycosyl donor in reactions with both a primary and a secondary alcohol acceptor.

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17 Full characterisation was obtained for **1**. ^{1}H NMR of **1**: δ_H (400 MHz, $CDCl_3$) 1.13, 1.18 and 1.20 (27 H, 3 s, 3 × Me_3C), 3.74 (3 H, s, CH_3O), 4.27 (1 H, dd, J = 9.8 and 4.4 Hz, 2-H), 4.37 (1 H, d, J = 10.3 Hz, 5-H), 5.31 (1 H, t, 3-H), 5.61 (1 H, t, 4-H) and 7.01 (1 H, d, J = 4.4 Hz, 1-H). ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 27.42, 27.51, 38.95, 39.12, 39.17, 53.34, 68.31, 70.37, 70.94, 71.70, 75.49, 167.04, 176.99 and 177.30. Found: C, 46.4; H, 6.25; MNa^+, 593.1230. $C_{22}H_{35}IO_9$ requires C, 46.3; H, 6.20%; $C_{22}H_{35}IO_9Na$ requires *m/z*, 593.1224. *Crystal data*: $C_{22}H_{35}IO_9$, M_w = 570.40, orthorhombic, space group $P2_12_12_1$, a = 9.6982(16), b = 11.4712(19), c = 22.658(4) Å, T = 100 K, U = 2520.7(7) Å^3, Z = 4, μ(Mo-Kα) = 1.317 mm^{-1}, 4595 reflections collected, 3911 unique.[23] R_{int} = 0.0413, final $wR(F^2)$ = 0.0525 (all data). Absolute structure *Flack*[24] = 0.006(16). CCDC reference number 205813. See http://www.rsc.org/suppdata/cc/b3/b302629a/ for crystallographic data in CIF or other electronic format.

^{1}H NMR of **3**: δ_H (400 MHz, $CDCl_3$) 1.14, 1.17 and 1.19 (27 H, 3 s, 3 × Me_3C), 3.74 (3 H, s, CH_3O), 4.59 (1 H, d, J = 10.3 Hz, 5-H), 4.85 (1 H, dd, J = 9.9 and 4.1 Hz, 2-H), 5.28 (1 H, t, 3-H), 5.69 (1 H, t, 4-H) and 6.66 (1 H, d, J = 4.1 Hz, 1-H)..

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