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Note

Mixed-acetal glucopyranosides of 2-bromo- and 2-iodo-acetaldehyde by mild alkylation of lactol groups. Irreversible cross inhibition using a pair of glycosidases

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In 1980, mixed-acetal glycopyranosides (1-alkoxyalkyl glycopyranosides) of acetaldehyde were described for the first time [1] and used as novel substrates in optical assays for glycoside hydrolases. Since then, such compounds have been prepared by two differing reactions: proton [2] and trimethylsilyl trifluoromethanesulfonate [3] catalysed transacetalation using as substrates monosaccharide *O*-acetates with a free lactol group or the corresponding 1-*O*-trimethylsilyl derivatives. Either dimethyl or diethyl acetals of differing aldehydes can be used as donors of the aglyconic acetal group. The 2-bromo- and 2-iodo-acetaldehyde derivatives of monosaccharides have potential as prodrugs, liberating reactive, alkylating 2-halo-acetaldehydes on specific cleavage by glycosidases [4]. The substrates applied, with the exception of iodides **10** and **14**, were prepared by the above-mentioned methods [2,3,5,6]. The *O*-acetates of compounds **10** and **14**, (*R*)- and (*S*)-2-iodo-1-methoxyethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**9** and **13**), could be obtained via nucleophilic displacement from the corresponding bromides [5] using sodium iodide in dimethyl sulfoxide.

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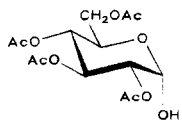

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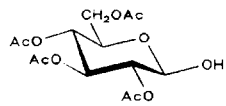

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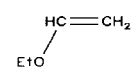

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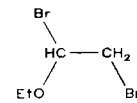

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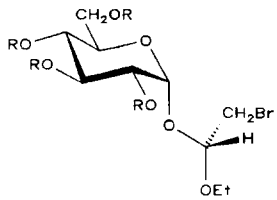
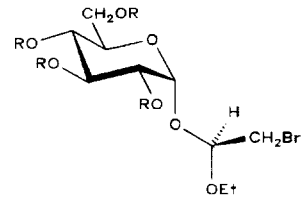


5 R=Ac

6 R=H



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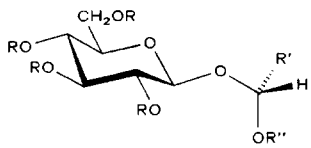
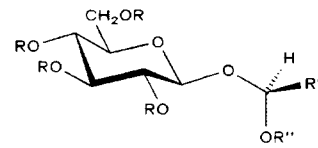
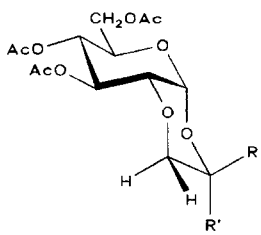
8 R=H



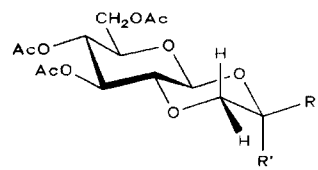
	R	R'	R''
9	Ac	CH_2I	Me
10	H	CH_2I	Me
11	Ac	CH_2Br	Et
12	H	CH_2Br	Et



	R	R'	R''
13	Ac	CH_2I	Me
14	H	CH_2I	Me
15	Ac	CH_2Br	Et
16	H	CH_2Br	Et



	R	R'
17	OEt	H
18	H	OEt



	R	R'
19	OEt	H
20	H	OEt

As a new and different access to mixed-acetal glycopyranosides, we now disclose a smooth alkylation of lactol groups by 1,2-dibromo-1-methoxyethane (**4**), which is prepared in situ through bromination of ethyl vinyl ether (**3**) [7]. The bromination of **3** and the alkylation of the anomeric hydroxyl group are carried out successively in the same reaction vessel at low temperature. The anomeric configuration of the glycopyranosides formed is the same as that of the reducing sugar used; no anomerisation of the lactol group during the reaction being observed. Using 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose (**1**), the diastereomeric mixture of (*R*)- and (*S*)-2-bromo-1-ethoxyethyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside (**5** and **7**) was obtained. Starting from crystalline 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**2**), the corresponding mixture of (*R*)- and (*S*)-2-bromo-1-ethoxyethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**11** and **15**) was formed. The products were deacetylated and the diastereomeric mixtures of the α- as well as the β-glucopyranosides were resolved by reversed phase LC. The absolute configurations of the aglyconic acetals were determined by intramolecular nucleophilic displacement of the bromide and interpretation of the ^{1}H NMR spectra of the products **17**, **18**, **19** and **20**, as described previously [2,5].

Qualitative tests showed that the α-glucopyranosides **6** and **8** are substrates for α-D-glucosidase from bakers yeast (maltase), while the β-glucopyranosides **10**, **12**, **14** and **16** are substrates of β-D-glucosidase from sweet almonds. The compounds were completely hydrolysed by the corresponding enzyme, but no hydrolysis could be detected (TLC) when incubated overnight with enzyme having the opposite anomeric specificity. In a previous publication, we described the partial inactivation of α-D-galactosidase from green coffee beans through bromo- and iodo-acetaldehyde, liberated by the enzyme itself from the corresponding acetal glycopyranosides [4]. The focus of our interest is the action of the halogenated aldehydes on other systems than the liberating glycosidase. For this purpose, we used diastereomeric mixtures of the β-glucopyrano-

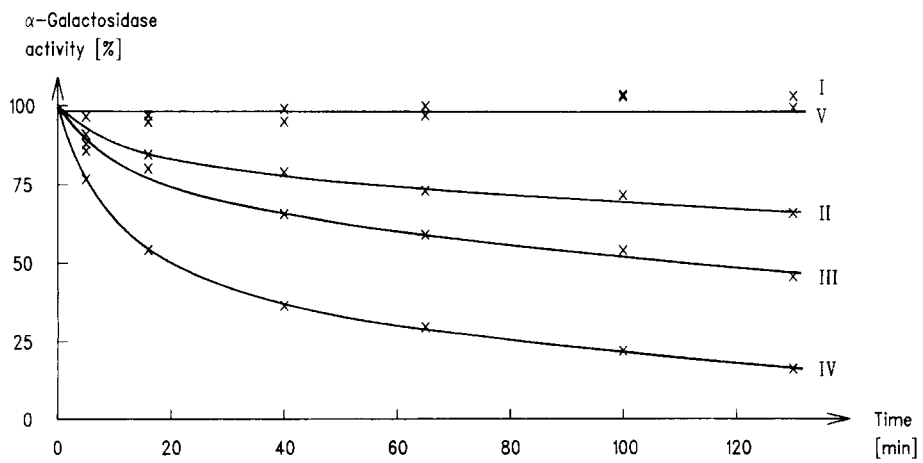


Fig. 1. Change of α-D-galactosidase activity over time in incubation mixtures containing: I, β-D-glucosidase; II, 10 mM compound **10/14**, β-D-glucosidase plus 10 mM galactose; III, 10 mM compound **12/16** plus β-D-glucosidase; IV, 10 mM compound **10/14** plus β-D-glucosidase; and V, 10 mM compound **10/14**, β-D-glucosidase plus 30 mM mercaptoethanol.

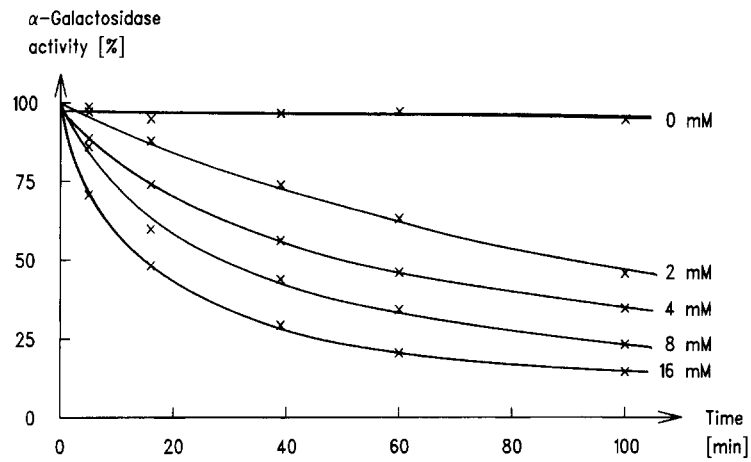


Fig. 2. Change of α-D-galactosidase activity over time in incubation mixtures containing β-D-glucosidase and given concentrations of compound **10/14**.

sides **10/14** and **12/16** together with β-D-glucosidase as sources for bromo- and iodo-acetaldeyde, since the free aldehydes cannot be stored and handled as such. α-D-Galactosidase from green coffee beans was used as a model for an inactivatable system. The galactosidase activity for different incubation mixtures is represented in Figs. 1 and 2. A significant loss of galactosidase activity was observed with bromo- and iodo-acetaldehyde (Fig. 1, III and IV). The iodide acts faster than the bromide due to its greater alkylating power. Galactose (10 mM), as a competitive inhibitor of α-galactosidase, protects the active site and leads to a slower rate of inactivation through iodo-acetaldehyde (Fig. 1, II). The α-galactosidase stayed perfectly active when, either no acetal glucopyranoside was added, or mercaptoethanol was present (Fig. 1, I and V). Mercaptoethanol protects as a scavenger for the alkylating aldehydes. Fig. 2 shows the inactivation of α-galactosidase with different concentrations of iodo-acetaldehyde. Increasing concentrations of the inactivator leads to faster loss of activity. However, the kinetic of inactivation is not simply first order and the data were thus not further processed.

These results suggest that halogenated acetaldehydes could also be used as cytotoxins, when liberated from acetal glycopyranosides through the corresponding glycosidases, either from the organism itself, or added. This could lead to a use of halogenated acetal glycosides pharmacologically, or for the control of microorganisms. Indeed, recently the effect of a combination of mixed-acetal glycopyranosides of 2-haloacetaldehydes and the stereochemically corresponding glycosidases on human adenocarcinoma cells was demonstrated [8].

1. Experimental

Enzyme inactivation.—α-D-Galactosidase (EC 3.2.1.22) from green coffee beans was obtained from Boehringer Mannheim. β-D-Glucosidase (EC 3.2.1.21) from sweet al-

monds was purchased from Sigma. Galactosidase activity was determined by hydrolysis of 2 mM 4-nitrophenyl α-D-galactopyranoside in 50 mM potassium phosphate buffer (pH 6.5) at 22 °C for 5 min, stopping the reaction with 200 mM borate buffer (pH 9.8) and reading the absorbance at 405 nm against blank. Bromo- and iodo-acetaldehyde solutions were prepared by complete hydrolysis (TLC) of the corresponding acetal β-D-glucopyranosides using β-D-glucosidase, 30 min before the addition of galactosidase. Galactose, mercaptoethanol, acetal glucopyranoside or glucosidase alone did not affect the activity of the galactosidase.

General methods.—Melting points are uncorrected. Reactions were monitored by TLC on Kieselgel 60 F_{254} 0.2 mm (E. Merck) using the following solvents (v/v): solvent A, 1:1 EtOAc–cyclohexane; solvent B, 17:2:1 EtOAc–MeOH–H_2O. Column chromatography was carried out with Silica 32–63, 60 Å (ICN). Optical rotations were measured with a Schmidt and Haensch Polartronic I. ^1H NMR spectra were recorded with a Bruker AC 250 (250 MHz) for solutions in $CDCl_3$ (internal Me_4Si).

(R)- And (S)-2-iodo-1-methoxyethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**9** *and* **13**).—Sodium iodide (4.0 g, 26.7 mmol) was added to a solution of (*R,S*)-2-bromo-1-methoxyethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside [5] (1.0 g, 2.06 mmol) in anhyd dimethyl sulfoxide (25 mL) and the mixture was stirred at 150 °C for 1 h. The solution was diluted with water (250 mL) and the product extracted with EtOAc (5 × 50 mL). The combined extracts were successively washed with aq 5% $Na_2S_2O_3$ (100 mL), sat. $NaHCO_3$ (100 mL) and water (100 mL), dried and concentrated. The residue was purified by column chromatography (2:3 EtOAc–cyclohexane) and the diastereomeric mixture of the products resolved by HPLC (Hypersil, 5 μm, 20 × 250 mm, 1:2 EtOAc–hexanes).

First eluted compound **9** (392 mg, 36%), which was crystallised from Et_2O–petroleum ether 30/50; mp 92–93 °C; $[\alpha]_D^{20}$ −27.9° (*c* 1.1, $CHCl_3$); R_f 0.41 (solvent A); ^1H NMR: δ 5.23 (t, 1 H, $J_{2,3}$ 9.5, $J_{3,4}$ 9.3 Hz, H-3), 5.06 (dd, 1 H, $J_{4,5}$ 10.0 Hz, H-4), 5.05 (dd, 1 H, $J_{1,2}$ 7.8 Hz, H-2), 4.79 (d, 1 H, H-1), 4.75 (t, 1 H, $J_{1',2'}$ 5.6 Hz, H-1'), 4.20 (dd, 1 H, $J_{5,6a}$ 5.3, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.15 (dd, 1 H, $J_{5,6b}$ 3.2 Hz, H-6b), 3.73 (ddd, 1 H, H-5), 3.43 (s, 3 H, Me), 3.25 (d, 2 H, H-2'), 2.08, 2.07, 2.04 and 2.01 (4 s, 12 H, Ac). Anal. Calcd for $C_{17}H_{25}IO_{11}$: C, 38.36; H, 4.73. Found: C, 38.42; H, 4.83.Second eluted compound **13** (383 mg, 35%), which was crystallised from Et_2O–petroleum ether 30/50; mp 128–129 °C; $[\alpha]_D^{20}$ −26.4° (*c* 1.1, $CHCl_3$); R_f 0.36 (solvent A); ^1H NMR: δ 5.24 (t, 1 H, $J_{2,3} = J_{3,4}$ 9.3 Hz, H-3), 5.09 (t, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 5.05 (dd, 1 H, $J_{1,2}$ 8.0 Hz, H-2), 4.82 (t, 1 H, $J_{1',2'}$ 5.3 Hz, H-1'), 4.81 (d, 1 H, H-1), 4.25 (dd, 1 H, $J_{5,6a}$ 5.1, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.16 (dd, 1 H, $J_{5,6b}$ 2.6 Hz, H-6b), 3.74 (ddd, 1 H, H-5), 3.39 (s, 3 H, Me), 3.27 (d, 2 H, H-2'), 2.12, 2.08, 2.05 and 2.03 (4 s, 12 H, Ac). Anal. Calcd for $C_{17}H_{25}IO_{11}$: C, 38.36; H, 4.73. Found: C, 38.32; H, 4.80.

(R)- And (S)-2-iodo-1-methoxyethyl β-D-glucopyranoside (**10** *and* **14**).—Sodium methoxide was added to suspensions of compounds **9** (360 mg, 0.676 mmol) and **13** (300 mg, 0.564 mmol) in anhyd MeOH (20 mL each) until basic. After complete deacetylation, the solutions formed were filtered through silica gel (2.5 × 3 cm, MeOH) and the filtrates concentrated. The residues were purified by column chromatography (22:2:1 EtOAc–MeOH–H_2O) and crystallised from MeOH–Et_2O.

Compound **10** (196 mg, 95%); mp 151–151.5 °C; $[\alpha]_D^{20}$ −30.3° (*c* 1.1, EtOH); R_f

0.33 (solvent B). Anal. Calcd for $C_9H_{17}IO_7$: C, 29.69; H, 4.71. Found: C, 30.06; H, 4.86. Compound **14** (240 mg, 97%); mp 125–126 °C; $[\alpha]_D^{20}$ −27.0° (*c* 1.1, EtOH); R_f 0.32 (solvent B). Anal. Calcd for $C_9H_{17}IO_7$: C, 29.69; H, 4.71. Found: C, 29.84; H, 4.77.

*(R)- And (S)-2-bromo-1-ethoxyethyl 2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranoside* (**5** *and* **7**).—Bromine (0.5 mL, 9.8 mmol) was added dropwise to a stirred solution of freshly distilled ethyl vinyl ether (1 mL, 10.4 mmol) in anhyd CH_2Cl_2 (20 mL) at −78 °C. A solution of compound **1** [9] (590 mg, 1.69 mmol) in anhyd CH_2Cl_2 (3 mL) was added, followed by DBU (1.35 mL, 9 mmol). After 20 min the solution was diluted with water (250 mL) and the products extracted with CH_2Cl_2 (5 × 20 mL). The combined extracts were washed with 5% $NaHCO_3$ (100 mL), water (100 mL), dried and concentrated. The residue was purified by column chromatography (1:2 EtOAc–cyclohexane) and gave a slowly crystallising syrup (745 mg, 88%). The mixture of isomers was deacetylated, resolved (see below) and samples conventionally reacetylated to obtain the analytical data of **5** and **7**.

Compound **5**: mp 107.5 °C from EtOAc-Et_2O–petroleum ether 60/70; $[\alpha]_D^{21}$ +109.2° (*c* 1.1, EtOAc); R_f 0.46 (solvent A); ^{1}H NMR: δ 5.50 (dd, 1 H, $J_{2,3}$ 10.5, $J_{3,4}$ 9.3 Hz, H-3), 5.36 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.07 (t, 1 H, $J_{4,5}$ 9.3 Hz, H-4), 4.92 (dd, 1 H, H-2), 4.87 (dd, 1 H, $J_{1',2'a}$ 5.8, $J_{1',2'b}$ 5.0 Hz, H-1′), 4.20–4.32 (m, 2 H, H-5, 6a), 4.08–4.16 (m, 1 H, H-6b), 3.68 and 3.59 (2 dq, 2 H, J_{gem} 9.2, J_{vic} 7.1 Hz, CH_2–CH_3), 3.48 (dd, 1 H, $J_{2'a,2'b}$ 11.0 Hz, H-2′a), 3.42 (dd, 1 H, H-2′b), 2.10, 2.06, 2.05 and 2.02 (4 s, 12 H, Ac), 1.22 (t, 3 H, CH_2–CH_3). Anal. Calcd for $C_{18}H_{27}BrO_{11}$: C, 43.30; H, 5.45. Found: C, 43.54; H, 5.48.Compound **7**: mp 74 °C from EtOAc-Et_2O–petroleum ether 60/70; $[\alpha]_D^{21}$ +129.9° (*c* 0.5, EtOAc); R_f 0.49 (solvent A); ^{1}H NMR: δ 5.52 (dd, 1 H, $J_{2,3}$ 10.3, $J_{3,4}$ 9.5 Hz, H-3), 5.43 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.09 (t, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 4.92 (dd, 1 H, H-2), 4.85 (t, 1 H, $J_{1',2'a}$ 5.9, $J_{1',2'b}$ 5.7 Hz, H-1′), 4.22–4.33 (m, 2 H, H-5, 6a), 4.05–4.14 (m, 1 H, H-6b), 3.80 and 3.58 (2 dq, 2 H, J_{gem} 9.1, J_{vic} 7.2 Hz, CH_2–CH_3), 3.45 (dd, 1 H, $J_{2'a,2'b}$ 11.3 Hz, H-2′a), 3.40 (dd, 1 H, H-2′b), 2.10, 2.06, 2.04 and 202 (4 s, 12 H, Ac), 1.21 (t, 3 H, CH_2–CH_3). Anal. Calcd for $C_{18}H_{27}BrO_{11}$: C, 43.30; H, 5.45. Found: C, 43.52; H, 5.48.

*(R)- And (S)-2-bromo-1-ethoxyethyl α-*D*-glucopyranoside* (**6** *and* **8**).—The diastereomeric mixture of **5**/**7** (745 mg, 1.49 mmol) was deacetylated in anhyd MeOH (30 mL) using sodium methoxide as described for the synthesis of compound **10**. The solution was then passed through silica gel (2.5 × 4 cm, MeOH), the filtrate concentrated, and the residue purified by column chromatography (22:2:1 EtOAc–MeOH–H_2O). The isomers were then separated by HPLC (Hypersil ODS, 5 μm, 20 × 250 mm, 1:5 MeOH–H_2O) and crystallised from MeOH–Et_2O.

First eluted **6** (168 mg, 34%); mp 124 °C; $[\alpha]_D^{20}$ +106.7° (*c* 0.7, MeOH); R_f 0.34 (solvent B). Anal. Calcd for $C_{10}H_{19}BrO_7$: C, 36.27; H, 5.78. Found: C, 36.53; H, 5.92.

Second eluted **8** (183 mg, 37%); mp 114–115 °C; $[\alpha]_D^{20}$ +126.3° (*c* 1.0, MeOH); R_f 0.35 (solvent B). Anal. Calcd for $C_{10}H_{19}BrO_7$: C, 36.27; H, 5.78. Found: C, 36.35; H, 5.88.

*(R)- And (S)-2-bromo-1-ethoxyethyl 2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranoside* (**11** *and* **15**).—A solution of compound **2** [10] (1.0 g, 2.87 mmol) in anhyd CH_2Cl_2 (4 mL) was alkylated as described for the synthesis of compound **5**/**7** using **4**, freshly prepared

from **3** (1.6 mL, 16.6 mmol) and bromine (0.75 mL, 14.6 mmol) in anhyd CH_2Cl_2 (25 mL) and DBU (2.1 mL, 14.1 mmol). The residue was purified by column chromatography (1:2 EtOAc–cyclohexane) and gave a slowly crystallising syrup (1.3 g, 91%). The mixture of isomers was deacetylated, resolved (see below) and samples conventionally reacetylated to obtain the analytical data of **11** and **15**.

Compound **11**: mp 83 °C from EtOAc-Et_2O–petroleum ether 60/70; $[\alpha]_D^{21}$ −34.0° (*c* 0.8, EtOAc); R_f 0.46 (solvent A); ^{1}H NMR: δ 5.23 (t, 1 H, $J_{2,3} = J_{3,4}$ 9.3 Hz, H-3), 5.05 (dd, 1 H, $J_{1,2}$ 8.3 Hz, H-2), 5.05 (t, 1 H, $J_{4,5}$ 9.3 Hz, H-4), 4.87 (dd, 1 H, $J_{1',2'a}$ 5.0, $J_{1',2'b}$ 6.2 Hz, H-1'), 4.83 (d, 1 H, H-1), 4.19 (dd, 1 H, $J_{5,6a}$ 5.0, $J_{6a,6b}$ 12.3 Hz, H-6a), 4.15 (dd, 1 H, $J_{5,6b}$ 3.3 Hz, H-6b), 3.73 (ddd, 1 H, H-5), 3.81 and 3.56 (2 dq, 2 H, J_{gem} 9.3, J_{vic} 7.2 Hz, CH_2–CH_3), 3.42 (dd, 1 H, $J_{2'a,2'b}$ 11.3 Hz, H-2'a), 3.38 (dd, 1 H, H-2'b), 2.08, 2.05, 2.04 and 2.01 (4 s, 12 H, Ac), 1.24 (t, 3 H, CH_2–CH_3). Anal. Calcd for $C_{18}H_{27}BrO_{11}$: C, 43.30; H, 5.45. Found: C, 43.21; H, 5.58.

Compound **15**: mp 90 °C from EtOAc-Et_2O–petroleum ether 60/70; $[\alpha]_D^{21}$ −13.5° (*c* 0.6, EtOAc); R_f 0.44 (solvent A); ^{1}H NMR: δ 5.23 (t, 1 H, $J_{2,3} = J_{3,4}$ 9.3 Hz, H-3), 5.08 (t, 1 H, $J_{4,5}$ 9.3 Hz, H-4), 5.03 (dd, 1 H, $J_{1,2}$ 7.8 Hz, H-2), 4.95 (dd, 1 H, $J_{1',2'a}$ 4.2, $J_{1',2'b}$ 6.9 Hz, H-1'), 4.80 (d, 1 H, H-1), 4.24 (dd, 1 H, $J_{5,6a}$ 5.3, $J_{6a,6b}$ 12.5 Hz, H-6a), 4.14 (dd, 1 H, $J_{5,6b}$ 2.6 Hz, H-6b), 3.72 (ddd, 1 H, H-5), 3.74 and 3.58 (2 dq, 2 H, J_{gem} 9.2, J_{vic} 7.2 Hz, CH_2–CH_3), 3.42 (dd, 1 H, $J_{2'a,2'b}$ 11.1 Hz, H-2'a), 3.36 (dd, 1 H, H-2'b), 2.10, 2.05, 2.04 and 2.01 (4 s, 12 H, Ac), 1.25 (t, 3 H, CH_2–CH_3). Anal. Calcd for $C_{18}H_{27}BrO_{11}$: C, 43.30; H, 5.45. Found: C, 43.54; H, 5.50.

*(R)- And (S)-2-bromo-1-ethoxyethyl β-*D*-glucopyranoside* (**12** *and* **16**).—The diastereomeric mixture of **11**/**15** (550 mg, 1.10 mmol) was deacetylated in anhyd MeOH (20 mL) using sodium methoxide as described for the synthesis of compound **10**. The solution was then passed through silica gel (2.5 × 4 cm, MeOH), the filtrate concentrated and the residue purified by column chromatography (22:2:1 EtOAc–MeOH–H_2O). The isomers were then separated by HPLC (Hypersil ODS, 5 μm, 20 × 250 mm, 1:5 MeOH–H_2O) and crystallised from MeOH–Et_2O.

First eluted **16** (104 mg, 28.5%); mp 123–124 °C; $[\alpha]_D^{20}$ −20.9° (*c* 1.0, MeOH); R_f 0.38 (solvent B). Anal. Calcd for $C_{10}H_{19}BrO_7$: C, 36.27; H, 5.78. Found: C, 36.51; H, 6.03.

Second eluted **12** (221 mg, 60.7%); mp 147.5 °C; $[\alpha]_D^{20}$ −48.7° (*c* 1.0, MeOH); R_f 0.39 (solvent B). Anal. Calcd for $C_{10}H_{19}BrO_7$: C, 36.27; H, 5.78. Found: C, 36.23; H, 5.95.

*(6R)- And (6S)-ethoxy-(3,4,6-tri-*O*-acetyl-α-*D*-glucopyrano)[1,2-b]-1,4-dioxane* (**17** *and* **18**).—Potassium *tert*-butoxide (20 mg each) was added to solutions of **5** (28 mg, 85 μmol) and **7** (31 mg, 94 μmol) in *tert*-butanol (4 mL each) and the mixtures were stirred at 40 °C overnight. The solutions were then filtered through silica gel (2 × 4 cm, MeOH), the filtrates concentrated and the residues acetylated using 2:3 Ac_2O–pyridine (4 mL). After 1 h the solutions were concentrated, the residues purified by column chromatography (1:2 EtOAc–cyclohexane) and the products analysed by ^{1}H NMR.

Compound **17** (30 mg, 93%); R_f 0.45 (solvent A); ^{1}H NMR: δ 5.71 (t, 1 H, $J_{2,3} = J_{3,4}$ 9.6 Hz, H-3), 5.41 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.05 (t, 1 H, $J_{4,5}$ 10.0 Hz, H-4), 4.88 (d, 1 H, $J_{1',2'b}$ 2.4 Hz, H-1'), 4.27 (dd, 1 H, $J_{5,6a}$ 4.1, $J_{6a,6b}$ 12.5 Hz, H-6a), 4.11 (ddd, 1 H, $J_{5,6b}$ 2.3 Hz, H-5), 4.06 (dd, 1 H, H-6b), 3.93 (dd, 1 H, $J_{2'a,2'b}$ 12.5 Hz,

H-2′a), 3.77 (dd, 1 H, H-2), 3.83 and 3.53 (2 dq, 2 H, J_{gem} 9.9, J_{vic} 7.1 Hz, CH_2CH$_3$), 3.45 (d, 1 H, H-2′b), 2.06, 2.05 and 2.01 (3 s, 9 H, Ac), 1.22 (t, 3 H, CH$_2$CH_3).

Compound **18** (18 mg, 51%); R_f 0.46 (solvent A); ^{1}H NMR: δ 5.71 (t, 1 H, $J_{2,3}$ 9.6, $J_{3,4}$ 9.4 Hz, H-3), 5.10 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.05 (t, 1 H, $J_{4,5}$ 9.4 Hz, H-4), 4.75 (dd, 1 H, $J_{1',2'a}$ 8.4, $J_{1',2'b}$ 3.1 Hz, H-1′), 4.24–4.32 (m, 1 H, H-6a), 4.20–4.27 (m, 1 H, H-5), 4.03–4.12 (m, 1 H, H-6b), 3.67 (dd, 1 H, H-2), 3.59 (dd, 1 H, $J_{2'a,2'b}$ 12.3 Hz, H-2′a), 3.96 and 3.55 (2 dq, 2 H, J_{gem} 9.4, J_{vic} 7.0 Hz, CH_2CH$_3$), 3.48 (dd, 1 H, H-2′b), 2.07, 2.04 and 2.01 (3 s, 9 H, Ac), 1.21 (t, 3 H, CH$_2$CH_3).

*(6R)- And (6S)-ethoxy-(3,4,6-tri-*O*-acetyl-β-*D*-glucopyrano)[1,2-b]-1,4-dioxane* (**19** *and* **20**).—Compounds **12** (26 mg, 78.5 μmol) and **16** (20 mg, 60.4 μmol) were treated as described for the synthesis of **17** and **18**.

Compound **19** (23 mg, 78%); R_f 0.41 (solvent A); ^{1}H NMR: δ 5.15 (t, 1 H, $J_{2,3} = J_{3,4}$ 9.7 Hz, H-3), 5.07 (t, 1 H, $J_{4,5}$ 9.7 Hz, H-4), 4.81 (dd, 1 H, $J_{1',2'a}$ 2.8, $J_{1',2'b}$ 9.1 Hz, H-1′), 4.51 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 4.21 (dd, 1 H, $J_{5,6a}$ 4.3, $J_{6a,6b}$ 12.7 Hz, H-6a), 4.15 (dd, 1 H, $J_{5,6b}$ 2.5 Hz, H-6b), 3.82 (dd, 1 H, $J_{2'a,2'b}$ 11.8 Hz, H-2′a), 3.80 (ddd, 1 H, H-5), 3.99 and 3.57 (2 dq, 2 H, J_{gem} 9.7, J_{vic} 7.2 Hz, CH_2CH$_3$), 3.29 (dd, 1 H, H-2′b), 3.20 (dd, 1 H, H-2), 2.05, 2.04 and 2.00 (3 s, 9 H, Ac), 1.19 (t, 3 H, CH$_2$CH_3).

Compound **20** (21 mg, 92%); R_f 0.36 (solvent A); ^{1}H NMR: δ 5.22 (t, 1 H, $J_{2,3}$ 10.0, $J_{3,4}$ 9.4 Hz, H-3), 5.05 (t, 1 H, $J_{4,5}$ 9.9 Hz, H-4), 4.83 (d, 1 H, $J_{1',2'b}$ 2.4, H-1′), 4.82 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1), 4.22 (dd, 1 H, $J_{5,6a}$ 4.7, $J_{6a,6b}$ 12.7 Hz, H-6a), 4.13 (dd, 1 H, $J_{5,6b}$ 2.5 Hz, H-6b), 3.82 (d, 1 H, $J_{2'a,2'b}$ 12.2 Hz, H-2′a), 3.81 (ddd, 1 H, H-5), 3.67 (dd, 1 H, H-2′b), 3.88 and 3.54 (2 dq, 2 H, J_{gem} 10.0, J_{vic} 7.1 Hz, CH_2CH$_3$), 3.29 (dd, 1 H, H-2), 2.05, 2.02 and 2.00 (3 s, 9 H, Ac), 1.23 (t, 3 H, CH$_2$CH_3).

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