A Stereocontrolled Access to α-*C*-(1→3)-Linked Disaccharides Containing 2-Deoxyhexopyranoses

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Abstract: A protected α-D-glucopyranosylacetaldehyde was converted by Wittig reaction with (thiazol-2-yl)carbonylmethylene-triphenyl phosphorane into the corresponding substituted 1-oxa-1,3-butadiene which by hetero-Diels–Alder reaction with ethyl vinyl ether afforded a mixture of two diastereoisomeric dihydropyran derivatives. These were separated by chromatography and the thiazol ring was transformed into an aldehyde group. Subsequent hydroboration afforded α-*C*-(1→3)-linked disaccharides containing 2-deoxyhexopyranoses of D- or L-configuration.

Key words: *C*-disaccharides, *C*-glycosides, hetero-Diels–Alder reaction, oxabutadienes, Wittig reaction

Formal replacement of the glycosidic oxygen atom by a methylene group in disaccharides leads to a group of compounds denoted trivially as *C*-disaccharides. Although this change can influence the conformational arrangement about the original C-O-C bonds,[1] it is assumed that *C*-disaccharides mimic well the structures of the natural disaccharides but – unlike them – they resist acidic as well as enzyme hydrolysis. Therefore, *C*-disaccharides are potential inhibitors of glycosidases or glycosyltransferases. Since these enzymes play a crucial role in the biosynthesis of cell-surface oligosaccharides that are important for intercellular communication, we can expect that some *C*-disaccharides could find use as compounds with therapeutic effects.[2]

For these reasons, there is an increased interest in the search for new synthetic pathways leading to *C*-disaccharides and in the study of their properties.[2–6] Because of the great structural variety of disaccharides, where e.g. one hexopyranose can be attached by an α- or β-anomeric bond to five different positions (i.e. positions 1, 2, 3, 4 or 6) of the second hexopyranose, the existing methods of preparation of *C*-disaccharides are usually multi-step syntheses, enabling the preparation of only one particular type of *C*-disaccharide. Therefore, a search for further simple syntheses of various types of *C*-disaccharides is desirable, particularly for those which could afford the final compounds in sufficient quantities for testing their properties.

In our previous studies we described a method by which a formyl group can be converted to a new dideoxyhexopyranose and using this approach, we prepared compounds in which two monosaccharides were linked either directly by a C-C bond[7] or by a -CH_2-bridge.[8] In the present communication we publish a short and simple synthesis of a new type of α-*C*-(1→3)-disaccharide using the same methodology. Some types of *C*-(1→3)-disaccharides are already known in which two monosaccharides are linked by a -CH_2-,[4] -CH(OH)-[5] or -CO-[6] bridge. Recently, the epimeric pair α-*C*-(1→3)-mannopyranoside of *N*-acetylgalactosamine and α-*C*-(1→3)-mannopyranoside of *N*-acetyltalosamine has been prepared and the former isomer showed inhibitory effects toward glycosidases and human α-1,3-fucosyltransferase.[9]

We used protected α-D-glucopyranosylacetaldehydes **1** or **2** as starting compounds. These aldehydes are accessible, even in multigram amounts, by ozonolysis of the corresponding peracetylated[10] or perbenzylated[11] propenyl derivatives. Heating a mixture of substituted acetaldehyde **1** and stabilized ylide **3**[12] in chloroform afforded *trans*-oxadiene **4**[13] which was isolated by column chromatography in 80% yield (Scheme 1). As in the previous cases,[7,8] $Eu(fod)_3$-catalyzed cycloaddition of oxadiene **4** to ethyl vinyl ether led to a mixture of two *endo*-cycloadducts **6** and **7**. Similarly to the synthesis of the branched-chain sugars,[8] we observed no chiral induction by the monosaccharide moiety in the cycloaddition reaction, both *endo*-cycloadducts **6** and **7** being formed in the ratio 1:1 (as determined by ^{1}H NMR spectroscopy and HPLC).[14] Unfortunately, the cycloadducts **6** and **7** were inseparable by preparative chromatography on silica gel. Therefore, we repeated the reaction, starting from benzyl-protected acetaldehyde **2.**

Analogously to **1**, the Wittig reaction of **2** afforded oxadiene **5** and subsequent cycloaddition under the same conditions as in the preceding case gave 1:1 mixture of two cycloadducts **8** and **9**.[15] We confirmed the structural identity of the pair of products **6** and **7** and the pair **8** and **9** by deacetylation of the mixture of cycloadducts **6** and **7** and subsequent benzylation which gave a mixture of cycloadducts **8** and **9**. Contrary to the pair **6** and **7**, the mixture of **8** and **9** was well separable on silica gel and pure com-

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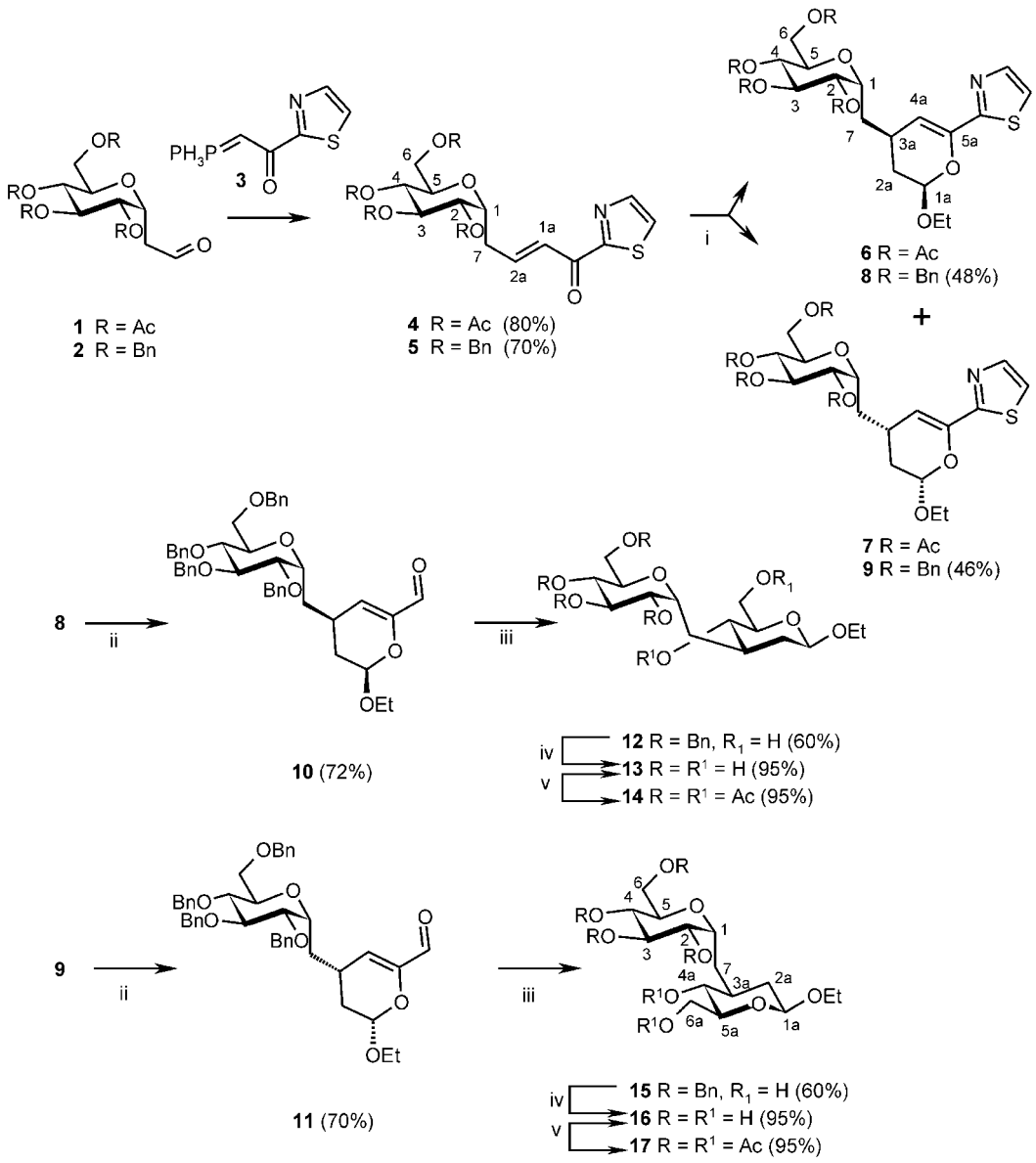

Scheme 1 *Reagents and conditions*: i. ethyl vinyl ether, $Eu(fod)_3$ (7.5 mol%), CH_2Cl_2, r.t., 6 h; ii. a) MeOTf, MeCN, r.t., 15 min, b) $NaBH_4$, MeOH, r.t., 15 min, c) $AgNO_3$, $MeCN/H_2O$, r.t., 20 min; iii. a) $Me_2S{\cdot}BH_3$, THF, r.t., 18 h, b) NaOH, H_2O_2, r.t., 40 min; iv. H_2/Pd-C, MeOH, r.t., 16 h v. Ac_2O, pyridine, DMAP, r.t., 4 h.

pounds were obtained by flash chromatography. Mass and NMR spectra confirmed that compounds **8** and **9** represent a pair of diastereoisomers differing only in configuration on the dihydropyran ring.[15] Moreover, the presence of NOE between the protons H-1a and H-3a in the individual diastereoisomers **8** and **9** confirmed the *cis*-configuration of substituents on the dihydropyran ring in both compounds.

In the two subsequent steps, both the individual cycloadducts **8** and **9** were converted into compounds **12** and **15**. In the first step, the thiazole substituent was in the known way[16] transformed to a formyl group, giving rise to little stable aldehydes **10** and **11**. Their hydroboration with an excess of $(CH_3)_2S{\cdot}BH_3$, with simultaneous reduction of the formyl group, proceeded stereoselectively from the less hindered side of the dihydropyran double bond and afforded benzylated products **12** and **15**.[17] Removal of the benzyl protecting groups by hydrogenation gave ethyl glycosides of α-*C*-(1→3)-disaccharides **13** and **16**, which were characterized as peracetyl derivatives **14** and **17**.[18] Whereas ethyl glycoside of C-disaccharide **17** with L-configuration in the new deoxyhexopyranose was obtained as a crystalline compound of mp 145–147 °C, its diastereoisomer **14** was contaminated with minor impurities (up to 20%), even after chromatography on silica gel. As shown by NMR spectra, in both the new deoxypyranoses **14** and **17** all substituents are equatorial[18] (for **14**: J = H-1a/H-$2a_{ax}$ = 9.4 Hz; J = H-3a/H-4a = 9.0 Hz; J = H-4a/H-5a = 10.0 Hz; for **17**: J = H-1a/H-$2a_{ax}$ = 8.1 Hz; J = H-3a/H-4a = J = H-4a/H-5a = 9.9 Hz).

The L-configuration of the new deoxyhexopyranose in the crystalline ethyl glycoside **17** has been unequivocally confirmed by X-ray crystallographic analysis (see Figure 1),[19] which leaves the D-configuration for the new deoxyhexopyranose in ethyl glycoside **14**.

In summary, we have shown that the described method represent a direct and rapid approach to two diastereoisomeric α-*C*-(1→3)-disaccharides **13** and **16** in which D-glucose is linked by methylene bridge with 2-deoxyhexopyranose in the D- and in the L-configuration, respectively. Now, we are trying to use as starting compounds other aldehydes derived from monosaccharides (e.g. of *galacto* or *manno* configuration) in order to obtain a broader series of α-*C*-(1→3)-disaccharides for biological activity screening.

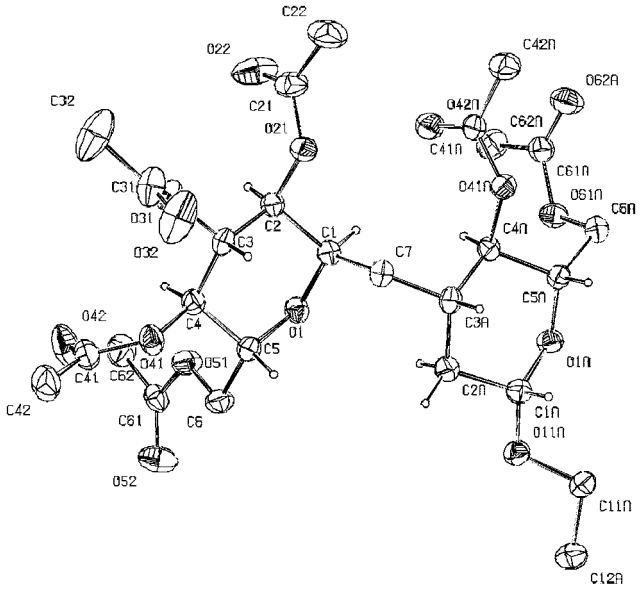

Figure 1

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(13) Selected data of compound **4**: pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.02 (d, 1 H, *J* = 2.9 Hz, CH-thiazole); 7.70 (d, 1 H, *J* = 2.9 Hz, CH-thiazole); 7.41 (d, 1 H, *J* = 15.7 Hz, H-1a); 7.25 (ddd, 1 H, *J* = 15.7 Hz, *J* = 7.1 Hz, *J* = 3.0 Hz, H-2a); 5.34 (dd, 1 H, *J* = 9.2 Hz, *J* = 8.9 Hz, H-3); 5.13 (dd, 1 H, *J* = 8.9 Hz, *J* = 5.5 Hz, H-2); 4.96 (dd, 1 H, *J* = 8.87 Hz, *J* = 8.80 Hz, H-4); 4.42 (ddd, 1 H, *J* = 4.9 Hz, *J* = 4.8 Hz, *J* = 5.5 Hz, H-1); 4.25 (dd, 1 H, *J* = 12.2 Hz, *J* = 6.0, H-6′); 4.04 (dd, 1 H, *J* = 12.2 Hz, *J* = 2.1 Hz, H-6); 3.92 (m, H-5); 2.85 (m, 1 H, H-7), 2.63 (m, 1 H, H-7′); 2.06, 2.05, 2.04, 2.00 (s, 4 × 3H, Ac). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) : 180.85 (*C*O-C=C); 170.55, 196.88, 169.5, 169.41, 169.37 (4 × O=*C*-CH_3); 167.65 (thiazole C-2); 144.68 and 126.46 (2 × CH-thiazole); 144.62 and 126.46 (2 × -CH=); 71.16 (C-1); 69.87 (C-3); 69.73 (C-2); 69.17 (C-5); 68.40

(C-4); 61.90 (C-6); 29.74(C-7); 20.49, 20.47, 20.44, 20.38 (4 × O=*C*-CH_3). ESI MS: 676.4 (M + H).

(14) The NOE experiments with the obtained mixture of cycloadducts proved the *cis* relative configurations on dihydropyran ring in both componds **6** and **7**. The NMR spectra did not reveal any *endo*-cycloadducts in the reaction mixture.

(15) Ethyl vinyl ether (1.5mL, 15 mmol) and $Eu(fod)_3$ (460 mg, 0.4 mmol) were added to a solution of **5** (4 g, 6.2 mmol) in dichloromethane (10.7 mL) and the reaction mixture was sonicated for 6 h at room temperature. The solvent and the excess ethyl vinyl ether were evaporated. Chromatography of the residue (light petroleum–EtOAc, 8:1) afforded 2.05 g (48%) of compound **8** (R_f = 0.29) and 1.94 g (46%) of compound **9** (R_f = 0.42).
Selected data of compound **8**: ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.83 (d, 1 H, *J* = 3.3 Hz, CH-thiazole); 7.17–7.32 (m, 21 H, 4 × C_6H_5, CH-thiazole); 6.08 (d, 1 H, *J* = 3.4 Hz, H-4a); 5.20 (dd, 1 H, *J* = 2.1 Hz, *J* = 6.8 Hz, H-1a); 4.96–4.48 (m, 8 H, 4 × C_6H_5-C*H*$_2$); 4.30 (m, 1 H, H-1); 4.02 (dq, 1 H, *J* = 9.6 Hz, *J* = 7.0, -O-C*H*$_2$-CH_3); 3.82–3.62 (m, 8 H, H-2, H-3, H-4, H-5, H-6, H-6′, -O-C*H*$_2$-CH_3); 2.62 (m, 1 H, H-3a); 2.17 (ddd, 1 H,, *J* = 2.1 Hz, *J* = 4.6 Hz, *J* = 11.5, H-2a_{eq}); 1.98 (m, 2 H, H-7, H-7′); 1.88 (ddd, 1 H, *J* = 6.8 Hz, *J* = 11.5 Hz, *J* = 11.5, H-2a_{ax}); 1.30 (t, 3 H, *J* = 7.0, -O-CH_2-C*H*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 164.62 (thiazole C-2); 143.73 (C-5a); 143.28 (CH-thiazole); 138.36, 138.27, 138.22, 138.12 (4 × *ipso* C_6H_5-CH_2), 128.36-127.57 (20 × C_6H_5-CH_2); 118.48 (CH-thiazole); 104.24 (C-4a); 99.61 (C-1a); 82.36, 80.13, 78.07, 72.31, 71.48 (C-1, C-2, C-3, C-4, C-5); 75.42, 74.96, 73.53, 73.14 (4 × C_6H_5-CH_2); 69.1 (C-6); 64.65 (O-*C*H$_2$-CH_3); 33.76 (C-2a); 30.22 (C-7); 27.67 (C-3a); 15.27 (O-CH_2-*C*H$_3$). ESI MS: 748.2 (M + H).
Selected data of compound **9:** ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.82 (d, 1 H, *J* = 3.3 Hz, CH-thiazole); 7.15–7.38 (m, 21 H, 4 × C_6H_5, CH-thiazole); 5.97 (d, 1 H, *J* = 3.2 Hz, H-4a); 5.20 (dd, 1 H, *J* = 1.7 Hz, *J* = 6.7 Hz, H-1a); 4.97–4.50 (m, 8 H, 4 × C_6H_5-C*H*$_2$); 4.25 (m, 1 H, H-1); 4.05 (dq, 1 H, *J* = 9.6 Hz, *J* = 7.0 Hz, O-C*H*$_2$-CH_3); 4.08–3.59 (m, 8 H, H-2, H-3, H-4, H-5, H-6, H-6′, O-C*H*$_2$-CH_3); 2.67 (m, 1 H, H-3a), 2.22 (ddd, 1 H, *J* = 1.7 Hz, *J* = 2.6 Hz, *J* = 13.3 Hz, H-2a_{eq}); 2.09 (m, 1 H, H-7); 1.87 (m, 1 H, H-7′); 1.75 (ddd, 1 H, *J* = 6.7 Hz, *J* = 13.3 Hz, *J* = 13.3 Hz, H-2a_{ax}); 1.30 (t, 3 H, *J* = 7.0 Hz, O-CH_2-C*H*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 164.40 (thiazole C-2); 143.86 (C-5a); 143.29 (CH-thiazole); 138.68, 138.22, 138.04 (4 × *ipso* C_6H_5-CH_2); 128.49-127.57 (20 × C_6H_5-CH_2); 118.40 (CH-thiazole); 105.65 (C-4a); 99.85 (C-1a); 82.53, 79.95, 77.99, 71.45, 71.32 (C-1, C-2, C-3, C-4, C-5); 77.56, 76.36, 73.47, 72.83 (4 × C_6H_5-*C*H$_2$); 68.89 (C-6); 64.74 (O-*C*H$_2$-CH_3); 32.36 (C-2a); 30.16 (C-7); 27.15 (C-3a); 15.28 (O-CH_2-*C*H$_3$). ESI MS: 748.2 (M + H).

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(17) A solution of aldehyde **10** (230 mg, 0.33 mmol) in tetrahydrofuran (3.4 mL) was cooled to 0 °C and then treated with 1 M solution of $(CH_3)_2S{\cdot}BH_3$ in tetrahydrofuran (0.69 mL, 0.69 mmol). The reaction mixture was stirred for 20 min at 0 °C and for 18 h at room temperature. Then, 0.37 mL of 30% NaOH and 0.37 mL of 30% H_2O_2 were added at 0 °C, and the solution was stirred at room temperature for 40 min. After dilution with brine (10 mL), the solution was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried (Mg_2SO_4). Evaporation of the solvent under reduced pressure and chromatography of the residue (light petroleum–ethyl acetate 1:1) afforded 143 mg (60%) of **12** (R_f = 0.5) as a colorless oil.

(18) Selected data of compound **14:** ^{1}H NMR ($CDCl_3$) : δ (ppm) 5.25 (dd, 1 H, *J* = 9.4 Hz, *J* = 9.4 Hz, H-3); 4.98 (dd, 1 H, *J* = 9.4 Hz, *J* = 5.7 Hz, H-2); 4.93 (dd, 1 H, *J* = 9.4 Hz, *J* = 9.2 Hz, H-4); 4.75 (dd, 1 H, *J* = 9.0 Hz, *J* = 10.0 Hz, H-4a); 4.52 (dd, 1 H, *J* = 1.0 Hz, *J* = 9.4 Hz, H-1a); 4.31–4.20 (m, 4 H, H-1, H-6a, H-6, H-6′); 4.12 (dd, 1 H *J* = 2.2 Hz, *J* = 12.1 Hz, H-6a′); 3.95 (m, 1 H, O-CH_2-C*H*$_3$); 3.85 (m, 1 H, H-5); 3.59–3.51 (m, 2 H, H-5a, -O-CH_2-C*H*$_3$); 2.20 (m, 1 H, H-2$a_{eq.}$); 2.14–2.04 (m, 19 H, 6 × Ac, H-7); 1.65 (m, 2 H, H-3a, H-7′); 1.54 (m, 1 H, H-2$a_{ax.}$); 1.23 (t, 1 H, *J* = 7.0 Hz, O-CH_2-C*H*$_3$). ^{13}C NMR (125 MHz $CDCl_3$) δ (ppm): 100.74 (C-1a); 74.50 (C-5a); 72.58 (C-1); 71.70 (C-4a); 70.05 (C-2); 69.56 (C-3); 68.77 (C-5); 68.66 (C-4); 64.67 (O-*C*H$_2$-CH_3); 62.63 (C-6); 62.38 (C-6a); 37.16 (C-2a); 36.00 (C-7); 27.50 (C-3a); 20.50 (Ac); 15.00 (O-CH_2-*C*H$_3$). ESI MS: 627.3 (M + Na).
Selected data of compound **17:** ^{1}H NMR ($CDCl_3$) : δ (ppm) 5.25 (dd, 1 H, *J* = 8.9 Hz, *J* = 8.9 Hz, H-3); 5.09 (dd, 1 H, *J* = 9.2 Hz, *J* = 5.7 Hz, H-2); 4.94 (dd, 1 H, *J* = 8.9 Hz, *J* = 8.9 Hz, H-4); 4.74 (dd, 1 H, *J* = 9.9 Hz, *J* = 9.9 Hz H-4a); 4.53 (d, 1 H, *J* = 8.1 Hz, H-1a); 4.33–4.18 (m, 4 H, H-1, H-6a, H-6, H-6′); 4.08 (dd, 1 H, *J* = 2.3 Hz, *J* = 12.1 Hz, H-6a′); 3.96 (dq, 1 H, *J* = 9.2 Hz, *J* = 7.1 Hz, O-C*H*$_2$-CH_3); 3.82 (m, 1 H, H-5); 3.59–3.51 (m, 2 H, H-5a, O-C*H*$_2$-CH_3); 2.17–2.02 (m, 19 H, 6 × Ac, H-2$a_{eq.}$); 1.99–1.87 (m, 2 H, H-7, H-3a); 1.41 (ddd, 1 H,, *J* = 8.1 Hz, *J* = 9.7 Hz, *J* = 12.7 Hz, H-2$a_{ax.}$); 1.3–1.18 (m, 1 H, H-7′); 1.24 (t, 3 H, *J* = 7.1 Hz, -O-CH_2-C*H*$_3$). ^{13}C NMR (125 MHz $CDCl_3$) δ (ppm) : 101.22 (C-1a); 74.51 (C-5a); 70.44 (C-4a); 69.99 (C-3); 69.90 (C-2); 69.11 (C-4); 68.60 (C-5); 68.45 (C-1); 64.66 (O-*C*H$_2$-CH_3); 62.80 (C-6a); 62.1(C-6); 35.04 (C-2a); 34.41 (C-3a); 26.57 (C-7); 20.62 (Ac), 14.94 (O-CH_2-*C*H$_3$). ESI MS: 627.3 (M + Na).

(19) Crystallographic data for the structure **17** have been deposited with the Cambridge Crystallographic Data Centre; reference number CCDC 203383. Copies of the data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (E-mail: deposit@ccdc.cam.ac.u).