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Stereoselective synthesis of 2-alkynyl and 2-alkenyl-1-ethoxy glucosides — new types of acetal-glycosides for use in the treatment of cancer

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ABSTRACT

Reaction of propargylaldehyde diethyl acetals **1**, **2**, **3**, and **4** and 2,3,4,6-tetra-*O*-acetyl-1-*O*-trimethylsilyl-β-D-glucopyranose **5a** in the presence of catalytic amounts of trimethylsilyl trifluoromethanesulfonate at −78°C gives the acetylated acetal-β-glucosides **6–9** in 60–90% yield with retention of configuration at C-1. Likewise 2,3,4,6-tetra-*O*-acetyl-1-*O*-trimethylsilyl-β-D-glucopyranose **5a** afforded, after in situ anomerisation to **5b** with **4**, the corresponding acetal-α-glucoside **10**. Hydrogenation and subsequent deprotection yielded the highly acid-sensitive 2-alkenyl-1-ethoxy glucosides which are of interest as selective anticancer agents.

INTRODUCTION

The treatment of cancer is badly hampered by the low selectivity of most of the known anticancer agents. Thus, the severe side effects of these drugs often cause the therapy to be terminated. In the search for new, more selective anticancer agents, we have developed a rational concept utilizing phenotypic differences of normal and cancer tissue[1]. It has been shown that there is a remarkable decrease in intracellular pH in malignant tumors as compared to normal cell tissue depending on the concentration of extracellular glucose. This difference is caused by stimulation of tumor cell glycolysis with the formation of lactic acid. Thus, under hyperglycemic conditions the mean pH of TV1A neurinoma decreased from 6.9 (normoglycemic value) to 6.1[2]. The difference in the hydronium ion concentration in malignant tumors and normal cell tissue is used in our concept to design anticancer prodrugs, which are nontoxic at pH 7.4–6.9 but can be cleaved with liberation of a toxin at pH 6.2. On the other hand, liberation of a cytotoxic compound from appropriately designed prodrugs can also be achieved selectively

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by enzymatic hydrolysis using enzymes (e.g., β-glucosidase or β-glucuronidase) having optimal activity at pH 5.0–6.2[3].

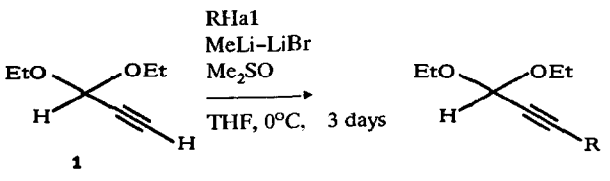
Certain highly cytotoxic aldehydes and ketones have already been employed by us[4]. Normally, cytostatic aldehydes and ketones[5] cannot be utilized in the free state since they are rapidly deactivated in the serum either by aldehyde dehydrogenases or by reaction with serum proteins and glutathione[5]. Transformation of cytotoxic aldehydes and ketones into usually nontoxic acetals or acetal-glycosides offers prodrugs, which may be cleaved by hydronium-ion catalyzed hydrolysis. It is of crucial importance that the rate of hydrolysis be high at pH 6.2. Thus, a half life ($t_{1/2}$) of 6 h at pH 6.2 would be appropriate; however, simple acetals as well as acetal-glucosides of aldehydes do not have the required properties. Therefore, considerable effort has been devoted to synthesize acetal-glycosides with appropriate acid-lability, e.g., the acetal-glycoside of aldophosphamide and 2,3-dideoxy-D-*erythro*-hex-2-enopyranoside[6] as well as of ketophosphamide and glucose[4b].

In this paper we describe the preparation of 2-alkynyl-1-ethoxy glucosides, as a new class of acetal-glycosides, which can be transformed into the highly acid-sensitive 2-alkenyl-1-ethoxy glucosides.

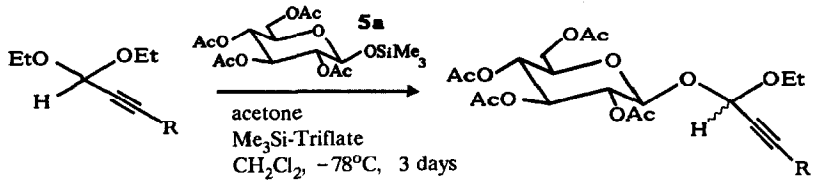
RESULTS AND DISCUSSION

For the synthesis of 2-alkynyl-1-ethoxy glucosides, 2-alkynyl acetals **1–4** were used as substrates, which are either commercially available or were prepared according to the literature[7] by reaction of 1,1-diethoxy-2-propyne (**1**) with electrophiles in the presence of a methyl lithium–lithium bromide complex and dimethylsulfoxide at 0°C (Scheme 1). The reaction time was ca. 3 h and the products **2** and **3** were obtained in 75–81% yield.

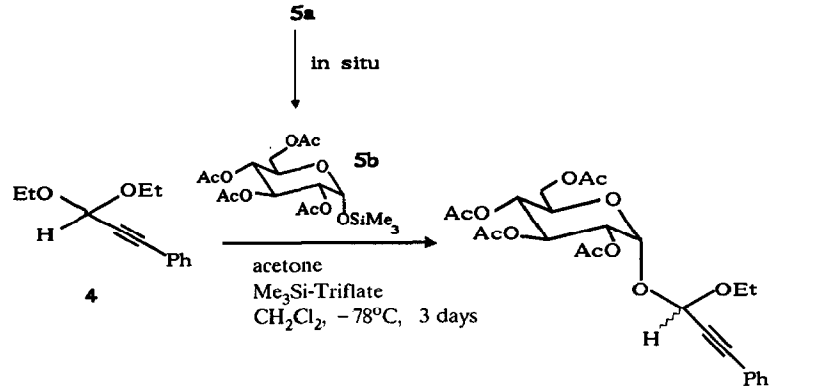
Subsequent treatment of 2,3,4,6-tetra-*O*-acetyl-1-*O*-trimethylsilyl-β-D-glucopyranose **5a** with 2-alkynyl acetals **1–4** in the presence of acetone and a catalytic amount of trimethylsilyl trifluoromethanesulfonate (Me_3Si-triflate) in CH_2Cl_2 at −78°C gave exclusively the acetal-β-glucosides **6–9** (Scheme 2)[8]. It was necessary to use at least a 3-fold excess of the acetal and a 5-fold excess of acetone in order to obtain the acetal-β-glucosides in good yields (60–90%). Acetone was added to



Scheme 1.



		C-1	1'R : 1'S
1 R = H	**6** R = H	β	1 : 4
2 R = $(CH_2)_9CH_3$	**7** R = $(CH_2)_9CH_3$	β	1 : 8
3 R = SiMe	**8** R = $SiMe_3$	β	1 : 12
4 R = Ph	**9** R = Ph	β	1 : 9



	C-1	1'R : 1'S
10	α	20 : 1

Scheme 2.

remove ethyl trimethylsilyl ether, which is formed as the second product in the reaction equilibrium. Thus, acetone and ethyl trimethylsilyl ether give acetone diethyl acetal, which is stable under the reaction conditions.

The acetal-α-glucoside **10** was synthesized in 66% yield by in situ anomerisation of 2,3,4,6-tetra-*O*-acetyl-1-*O*-trimethylsilyl-β-D-glucopyranose **5a** with catalytic amounts of Me_3Si-triflate (10 mol%) at 0°C to give 2,3,4,6-tetra-*O*-acetyl-1-*O*-trimethylsilyl-α-D-glucopyranose **5b** followed by addition of **4** at 78°C.

The synthesis of the acetal-glucosides **6–10** proceeds with complete retention of the configuration at C-1 of the employed trimethylsilyl glucoside. The amount of

the corresponding α- and β-glucoside, respectively, was below 2%. The formation of the stereogenic center C-1′ is less selective, thus the acetal-glucosides **6–10** are obtained as 1′*R* and 1′*S* epimers in a ratio of 1:4 to 1:12 for the β-glucosides **6–9** and 20:1 for the α-glucoside **10**. The observed selectivity is remarkably higher than found for the glucosidation of saturated aliphatic aldehydes with a nearly 1:1 ratio for the 1′*R* and 1′*S* epimers in the case of the β-glucosides. This is all the more surprising since the alkynyl group is quite "slim" compared to an alkyl group. Since the reaction seems to proceed under kinetic control, we assume that the selectivity in the formation of acetal-glucosides may also be governed by electronic effects. However, further investigations are necessary to explain the observed results. The ratio of the C-1′ epimers was determined by comparison of the relative intensities of the signals in the ^{1}H and ^{13}C NMR spectra of the crude reaction mixture. However, except for the acetal-β-glucoside 1′*S*-**9**, which could be obtained in a pure form by crystallisation, it was not possible to separate the C-1′ epimers.

The structures of the new compounds **6–10** were mainly determined by ^{1}H and ^{13}C NMR spectroscopy. The conformation of the glucosides is controlled by the exo and the generalised anomeric effect[9]. As described in our previous publications[4a] the determination of the configuration at C-1′ of **6–10** was accomplished by comparison of the chemical shifts of 1′-H and C-1′. Thus, for acetal-β-glucosides, $\Delta\delta$ (1′*R*) − (1′*S*) is negative for 1′-H and positive for C-1′, whereas for acetal-α-glycosides, $\Delta\delta$ (1′-*R*) − (1′*S*) is positive for 1′-H and negative for C-1′. For the β-glucosides 1′*R*-**6–9** resonances for 1′-H at δ 5.42–5.64 ppm are a doublet with *J* 2 Hz for **6** and singlets for **7–9**. To the contrary, 1′-H of 1′*S*-**6–9** resonates at δ 5.54–5.78 ppm as a doublet for compound **6** with *J* 2 Hz, a triplet for **7** with *J* 2 Hz and as singlets for **8** and **9**. For the α-glucoside **10** a singlet is found at δ 5.76 ppm for 1′-H. The chemical shift values and the coupling constants are in agreement with the proposed structures. Independently the configuration of 1′S-**9** as the major epimer in the reaction of **4** and **5a** was determined by X-ray crystallography (Fig. 1) *.

Selective hydrogenation of the triple bond of the 2-alkynyl-1-ethoxy glucosides **6–9** with nickel acetate, potassium borohydride, and diaminoethane in EtOH at room temperature under a hydrogen atmosphere gave the peracetylated 2-alkenyl-1-ethoxy glucosides **11–13** in 37–69% yield[10] (Scheme 3). These compounds are quite sensitive, especially **12**, which was obtained in only 37% yield. The hydrogenation of **8** using the described conditions yielded exclusively the nonsubstituted 2-alkenyl-1-ethoxy glucoside **11** in 57% yield with loss of the trimethylsilyl group. The configuration of the double bond in **12** and **13** was deduced from their synthesis and the coupling constants of *J* 11 Hz for the olefinic hydrogens in **13** at δ 5.70–6.40 ppm.

* Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen 2 (FRG), on quoting the depository number CSD-400292, the names of authors, and the journal citation.

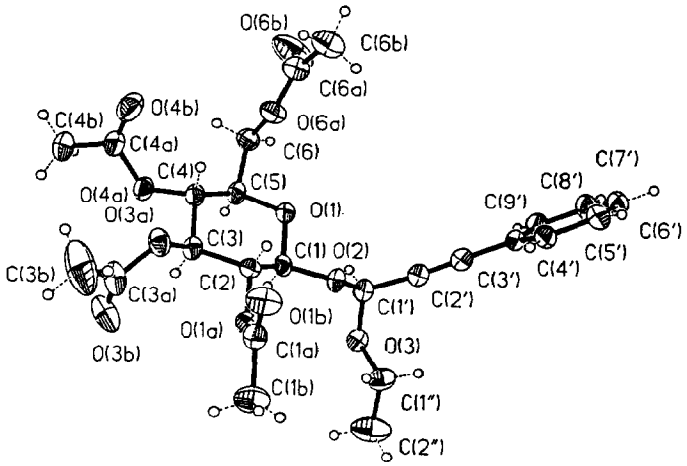
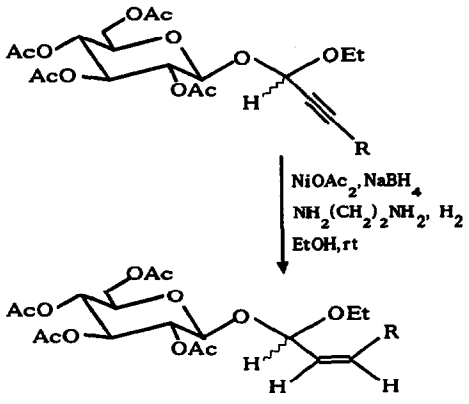


Fig. 1. X-ray structure analysis of **9**.

Deacetylation of **6**, **9**, and **13** by solvolysis using basic ion-exchange resin (Lewatit ML 500) in water-free MeOH with ultrasound afforded **14**, **15**, and **16** in 90–95% yield (Scheme 4). The acid-catalyzed hydrolysis of **15** and **16** has been studied by direct quantitative UV-spectroscopic determination of the formed α,β-unsaturated aldehydes at $\lambda_{max} = 285$ nm. The half life of **15** was 18 min at pH 2.15, clearly indicating that the hydrolysis of **15** is too slow for our concept. However, **16** has a half life of 300 min at pH 6.2 and therefore meets our requirements. This compound will be further investigated in tissue culture experiments.

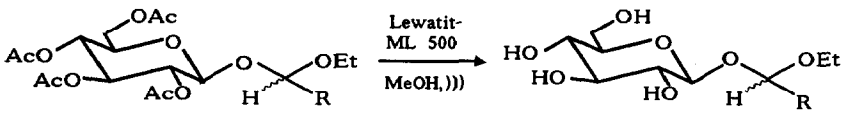
In conclusion, the glucosidation of 2-alkynyl acetals leads to acetal-glucosides of alkynals as a new class of compounds which may be hydrogenated to acetal-gluco-



6 R = H
7 R = $(CH_2)_9CH_3$
8 R = $SiMe_3$
9 R = Ph

11 R = H
12 R = $(CH_2)_9CH_3$
13 R = Ph

Scheme 3.



6 R = C ≡CH **14** R = C ≡CH

9 R = C ≡CPh **15** R = C ≡CPh

10 R = CH=CHPh **16** R = CH=CHPh

Scheme 4.

sides of alkenals. The latter compounds show a high sensitivity to acid, which makes them useful for our concept of designing more selective anticancer agents.

EXPERIMENTAL

General methods.—Melting points were determined with a Mettler FP 61 apparatus and are uncorrected. Elemental analyses were performed at the Microanalytical Laboratory, University of Göttingen. Optical Rotations were measured with a Perkin–Elmer 241 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded with a Varian XL-200 (200 MHz, internal Me_4Si) and a Varian VXR-500 S instrument (500 MHz, internal Me_4Si). The progress of all reactions was monitored by TLC on SIL G/UV_{245} (Macherey Nagel) silica gel.

Solvents used for chromatography were: *tert*-butyl methyl ether–light petroleum; *A* 1:60; *B*, 1:40; *C*, 1:20; *D*, 1:1; *E*, 1:2; *tert*-butyl methyl ether–light petroleum–MeOH; *F*, 4:1:0.5.

All reactions were carried out under Ar. in anhydrous media. It was essential to use pure materials and to maintain the stated reaction temperatures. The ratio of the 1′*R* and 1′*S* diastereomers was evaluated by the relative intensities of all ^{13}C NMR signals.

Alkylation of 1,1-diethoxy-2-propyne.—General procedure I. To a cold (0°C), stirred solution of **1** (0.56 mL, 3.90 mmol) in dry THF was added a solution of MeLi–LiBr in Et_2O (2.20 M, 1.54 mL, 3.40 mmol), and stirring was continued at this temperature for 15 min. The electrophile (3.39 mmol) was then added followed by the addition of dry Me_2SO (8.5 mL). The mixture was allowed to warm to room temperature, stirred at ambient temperature for 3 h, cooled with a cold water bath, and the reaction quenched by dropwise addition of water. Diethyl ether was added and the organic layer was washed with 20 mL of brine four times. Drying ($MgSO_4$), concentration, and flash column chromatography on silica gel (110 g, solvent *A* or *B*) yielded products **2** and **3**.

1,1-Diethoxytridec-2-yne (**2**).—*Reaction of* **1** *with 1-bromodecane according to general procedure I.* Yield 737 mg (81%); R_f 0.53 (solvent *C*); ^{1}H NMR data

($CDCl_3$): δ 0.88 (t, 3 H, *J* 7.2 Hz, 13-H_3), 1.15–1.54 (m, 22 H, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2, CH_3), 2.23 (dt, 2 H, *J* 7.6, 2 Hz, 4-H_2), 3.57, 3.74 (2 dq, 2 H, *J* 7.2, 8.8 Hz, OCH_2), 5.25 (t, 1 H, *J* 2 Hz, 1-H); ^{13}C NMR data ($CDCl_3$): δ 14.12 (C-13), 15.12 (CH_3), 18.64 (C-12), 22.70 (C-11), 28.35, 28.91, 29.12, 29.34, 29.53, 29.58, 31.92 (C-10, C-9, C-8, C-7, C-6, C-5, C-4), 60.59 (CH_2O), 75.68 (C-2), 86.60 (C-3), 91.51 (C-1); MS data: *m/z* 267 [M^+], 239 [$M - CH_2CH_3^+$], 223 [$M - OCH_2CH_3^+$]. Anal. Calcd for $C_{17}H_{32}O_2$ (268.4): C, 76.06; H, 12.02. Found: C, 76.04; H, 11.91.

1,1-Diethoxy-3-(trimethylsilyl) prop-2-yne (**3**).—*Reaction of* **1** *and trimethylsilylchloride according to general procedure I.* Yield 75%; R_f 0.34 (solvent *A*); ^1H NMR data ($CDCl_3$): δ 0.01 (s, 9 H, $SiCH_3$), 1.05 (t, 6 H, *J* 7 Hz, OCH_2CH_3), 3.39, 3.56 (2 dq, 4 H, *J* 7, 9.5 Hz, OCH_2CH_3), 5.05 (s, 1 H, 1-H); ^{13}C NMR data ($CDCl_3$): δ 0.00 (CH_3Si), 15.06 (OCH_2CH_3), 60.78 (OCH_2CH_3), 75.66 (C-2), 90.32 (C-3), 91.18 (C-1); MS data: *m/z* 199 [M^+], 155 [$M - OCH_2CH_3^+$], 127 [$M - Si(CH_3)_3^+$], 73 [$(CH_3)_3Si^+$], 45 [$OCH_2CH_3^+$]. Anal. Calcd for $C_{10}H_{20}O_2Si$ (200.4): C, 59.95; H, 10.06; Found: C, 60.00; H, 10.00.

Preparation of 2-alkynyl-1-ethoxy glucosides.—General procedure II. To a solution of 2,3,4,6-tetra-*O*-acetal-1-*O*-trimethylsilyl-β-D-glucopyranose **5a** or 2,3,4,6-tetra-*O*-acetyl-1-*O*-trimethylsilyl-α-D-glucopyranose **5b** (500 mg, 1.19 mmol; obtained from **5a** by in situ anomerisation)[11], 1,1-diethoxy-2-propyne-derivatives **1**, **2**, **3**, and **4** (3.57 mmol), and acetone (2.0 mL) in dry CH_2Cl_2 at −78°C, was added Me_3Si-triflate (0.08 mL). The reaction was stirred at −78°C for 3 days, quenched with 1:1 Et_3N–MeOH (1 mL), warmed to room temperature, and immediately filtered through silica gel (5 g, solvent *D*). The eluate was concentrated in vacuo and the residue was subjected to flash column chromatography on silica gel (80 g, solution *D*). Sometimes the yield of the glucosidation could be raised by addition of another 10 mol% of Me_3Si-triflate and stirring for 2 days at −78°C. For chromatography of all acetal-glucosides, 0.7% Et_3N was added to the solvent.

*(1RS) 1-Ethoxy-prop-2-ynyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside* (**6**).—*Reaction of* **1** *and* **5a** *according to general procedure II.* Yield 72%; R_f 0.28 (solvent *D*); ^1H NMR data ($CDCl_3$): δ 1.18–1.32 (m, 3 H, OCH_2CH_3), 2.02, 2.04, 2.05, 2.09 (4 s, 12 H, CH_3CO), 2.60 (dd, 1 H, *J* 0.8, 2 Hz, 3′-H), 3.59 (dq, 1 H, *J* 7, 10 Hz, OCH_2CH_3), 3.70–3.82 (m, 1 H, 5-H), 3.89 (dq, 1 H, *J* 7, 9 Hz, CH_2O), 4.15 (dd, 1 H, *J* 3, 12 Hz, 6-H_a), 4.24 (dd, 1 H, *J* 4.5, 12 Hz, 6-H_b), 4.95 (d, 1 H, *J* 8 Hz, 1-H), 5.06 (t, 1 H, *J* 9 Hz, 4-H), 5.10 (dd, 1 H, *J* 9.5, 10.5 Hz, 2-H), 5.26 (t, 1 H, *J* 9 Hz, 3-H), 5.42 (d, 0.2 H, *J* 2 Hz, 1′-H, *R* epimer), 5.58 (d, 0.8 H, *J* 2 Hz, 0.8 Hz, 1′-H, *S* epimer); ^{13}C NMR data ($CDCl_3$): δ 14.82 (CH_3CH_2, *R* epimer), 14.86 (CH_3CH_2, *S* epimer), 20.62, 20.74 (CH_3CO), 61.04 (CH_3CH_2O, *S* epimer), 61.95 (C-6), 62.72 (CH_3CH_2O, *R* epimer), 68.22 (C-4), 70.98 (C-2), 71.05 (C-3′, *S* epimer), 72.02 (C-3′, *R* epimer), 72.10 (C-5), 72.93 (C-3), 74.74 (C-2′, *S* epimer), 77.77 (C-2′, *R* epimer), 89.25 (C-1, *S* epimer), 91.11 (C-1, *R* epimer), 95.18 (C-1′, *S* epimer), 96.68 (C-1′, *R* epimer), 169.2, 169.4, 170.3, 170.6 (C=O); MS data: *m/z* 430 [M^+], 331 [$M - O -$ aglucon$^+$], 73 [aglucon$^+$], 43 [CH_3CO^+]; MS data (DCI): *m/z* 448

$[M + NH_4^+]$. Anal. Calcd for: $C_{19}H_{26}O_{14}$ (430.4); C, 53.02; H, 6.09; Found: C, 53.20; H, 6.22.

(1RS) 1-Ethoxy-tridec-2-ynyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**7**).—*Reaction of* **2** *and* **5a** *according to general procedure II.* Yield 69%; R_f 0.46 (solvent *D*); ^{1}H NMR data: ($CDCl_3$): δ 0.86 (t, 3 H, *J* 7 Hz, 13′-H_3), 1.08–1.42 (m, 17 H, 12′-H_2, 11′-H_2, 10′-H_2, 9′-H_2, 8′-H_2, 7′-H_2, 6′-H_2, OCH_2CH_3), 1.50 (q, 2 H, *J* 7 Hz, 5′-H_2), 1.98, 2.02, 2.03, 2.06 (4 s, 12 H, CH_3CO), 2.22 (dt, 2 H, *J* 2, 7.5 Hz, 4′-H_2), 3.54 (dq, 1 H, *J* 7, 9 Hz, OCH_2CH_3), 3.65–3.77 (m, 1 H, 5-H), 3.84 (dq, 1 H, *J* 7, 9 Hz, OCH_2CH_3), 4.11 (dd, 1 H, *J* 3, 13 Hz, 6-H_a), 4.22 (dd, 1 H, *J* 5, 12 Hz, 6-H_b), 4.93 (d, 1 H, *J* 8 Hz, 1-H), 5.04 (t, 1 H, *J* 9 Hz, 4-H), 5.07 (dd, 1 H, *J* 8.5, 9 Hz, 2-H), 5.24 (t, 1 H, *J* 9 Hz, 3-H), 5.54 (s, 0.1 H, 1′-H, *R* epimer), 5.54 (t, 0.9 H, *J* 2 Hz, 1′-H, *S* epimer). ^{13}C NMR data ($CDCl_3$): δ 14.12 (C-13′), 14.21 (OCH_2CH_3, *R* epimer), 14.93 (OCH_2CH_3, *S* epimer), 20.64 (CH_3CO), 20.74 (C-12′), 22.69 (C-11′), 28.22 (C-10′), 28.95 (C-9′), 29.10 (C-8′), 29.33 (C-7′), 29.51 (C-6′), 29.58 (C-5′), 31.90 (C-4′), 60.50 (OCH_2CH_3, *S* epimer), 62.01 (C-6), 62.33 (OCH_2CH_3, *R* epimer), 68.31 (C-4), 71.08 (C-2), 72.02 (C-5), 73.08 (C-3), 74.28 (C-2′, *R* epimer), 74.37 (C-2′, *S* epimer), 87.92 (C-3′), 89.93 (C-1, *S* epimer), 91.85 (C-1, *R* epimer), 95.15 (C-1′, *S* epimer), 96.62 (C-1′, *R* epimer), 169.2, 169.4, 170.3, 170.6, 170.7 (C=O). MS data (DCI): *m/z* 588 $[M + NH_4^+]$, 223 $[M - C_{14}H_{19}O_{10}^+]$. Anal. Calcd for $C_{29}H_{46}O_{11}$ (570.7); Ber. C, 61.04; H, 8.13; Found: C, 61.15; H, 8.10.

(1RS) 1-Ethoxy-3-(trimethylsilyl) prop-2-ynyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**8**).—*Reaction of* **3** *and* **5a** *according to general procedures II.* Yield 60%; R_f 0.41 (solvent *E*); ^{1}H NMR data ($CDCl_3$): δ 0.20 (s, 9 H, CH_3Si), 1.23 (t, 3 H, *J* 7 Hz, OCH_2CH_3), 2.01, 2.03, 2.04, 2.08 (4 s, 12 H, CH_3CO), 3.56 (dq, 1 H, *J* 7, 9.5 Hz, OCH_2CH_3), 3.66–3.80 (m, 1 H, 5-H), 3.85 (dq, 2 H, *J* 7, 9.5 Hz, OCH_2CH_3), 4.13 (dd, 1 H, *J* 3, 12 Hz, 6-H_a), 4.23 (dd, 1 H, *J* 4.5, 12 Hz, 6-H_b), 4.94 (d, 1 H, *J* 8 Hz, 1-H), 5.06 (t, 1 H, *J* 9 Hz, 4-H), 5.09 (dd, 1 H, *J* 9, 10 Hz, 2-H), 5.22 (t, 1 H, *J* 9 Hz, 3-H), 5.54 (s, 1 H, 1′-H, *S* epimer); ^{13}C NMR data ($CDCl_3$): δ −0.37 (CH_3Si), 14.89 (OCH_2CH_3) 20.61, 20.68, 20.72 (CH_3CO), 60.76 (OCH_2CH_3, *S* epimer), 61.98 (C-6), 62.26 (OCH_2CH_3, *R* epimer), 68.29 (C-4), 71.04 (C-2), 72.06 (C-5), 73.09 (C-3), 89.57 (C-1, *S* epimer), 90.34 (C-3′, *R* epimer), 91.51 (C-1, *R* epimer), 91.98 (C-3′, *S* epimer), 95.23 (C-1′, *S* epimer), 95.61 (C-1′, *R* epimer), 98.47 (C-2′, *S* epimer), 99.71 (C-2′, *R* epimer), 169.2, 169.4, 170.3, 170.6 (C=O); MS data DCI): *m/z* 520 $[M + NH_4^+]$, 364 [M − aglucon + NH_3]. Anal. Calcd for: $C_{22}H_{34}O_{11}Si$ (502.6); C, 52.58; H, 6.82; Found: C, 52.67; H, 6.90.

(1RS) 1-Ethoxy-3-(phenyl) prop-2-ynyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**9**).—*Reaction of* **4** *and* **5a** *according to general procedure II.* Yield 90%; R_f 0.27 (solvent *E*); ^{1}H NMR data ($CDCl_3$): δ 1.27 (t, 3 H, *J* 7 Hz, OCH_2CH_3), 2.01, 2.02, 2.04, 2.09 (4 s, 12 H, CH_3CO), 3.65 (dq, 1 H, *J* 7, 9.5 Hz, OCH_2CH_3), 3.70–3.82 (m, 1 H, 5-H), 3.95 (dq, 1 H, *J* 7, 9.5 Hz, OCH_2CH_3), 4.15 (dd, 1 H, *J* 3, 12.5 Hz, 6-H_a), 4.25 (dd, 1 H, *J* 4.5, 12.5 Hz, 6-H_b), 5.03 (d, 1 H, *J* 8 Hz, 1-H), 5.02–5.32

(m, 3 H, 2-H, 3-H, 4-H), 5.64 (s, 0.1 H, 1'-H, *R* epimer), 5.78 (s, 0.9 H, 1'-H, *S* epimer), 7.27–7.52 (2 m, 5 H, phenyl-H); ^{13}C NMR data ($CDCl_3$): δ 14.95 (OCH_2CH_3), 20.64, 20.75 (CH_3CO), 61.06 (OCH_2CH_3, *S* epimer), 62.00 (C-6), 62.87 (OCH_2CH_3, *R* epimer), 68.27 (C-4, *S* epimer, 68.38 (C-4, *R* epimer), 71.07 (C-2, *S* epimer), 71.14 (C-2, *R* epimer), 72.11 (C-5, *S* epimer), 72.78 (C-5, *R* epimer), 73.05 (C-3), 82.99, 86.30 (C-2', C-3'), 90.26 (C-1, *S* epimer), 92.01 (C-1, *R* epimer), 95.26 (C-1', *S* epimer), 96.55 (C-1', *R* epimer), 121.4 (*i*-C-phenyl), 128.2, 128.4, 128.4, 129.2, 131.9 (*o*-, *m*-, *p*-C-phenyl), 169.3, 169.4, 170.3, 170.7 (C=O); MS data (FAB, matrix 3-NBA): *m/z* 507 [M^+], 331 [glucoside$^+$]. Anal. Calcd for: $C_{25}H_{30}O_{11}$ (506.5); C, 59.28; H, 5.97; Found: C, 59.33; H, 6.12.

X-ray structure analysis of **9** $C_{25}H_{30}O_{11}$ (506.49): monoclinic; space group $P2_1$; $a = 1011.6(2)$, $b = 725.90(10)$, $c = 1836.9(4)$ pm, $\beta = 98.98(3)°$, $V = 1.3323(4)$ nm^3; $Z = 2$; $d_x = 1.263$ Mg/m^3; $\mu = 0.100$ mm^{-1}; Siemens-Stoe AED2 diffractometer; MoKα ($\lambda = 71.073$ pm); $T = 293(2)$ K; scan 3.55–22.45°; reciprocal lattice segment, index range: $-10 < h < 9$, $0 < k < 7$, $0 < l < 19$; 1853 independent reflexions collected. Direct methods were used for solution (SHELXTL) and full-matrix least squares (SHELXL-92) for refinement on F^2; *R1* = 0.0400; *wR2* = 0.1074.

*Synthesis of (1*RS*) 1-ethoxy-3-(phenyl) prop-2-ynyl 2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranoside* (**10**).—To a solution of **5a** (500 mg, 1.19 mmol) in dry CH_2Cl_2 (10–15 mL:) was added at 0°C Me_3Si-triflate (10 mol%, 21 μL). The mixture was stirred at 0°C until anomerization to give **5b** was completed (TLC, silica gel, solvent *D*). After cooling to −78°C, 1,1-diethoxy-3-phenyl-2-propyne (740 mg, 3.57 mmol), acetone (2 mL) and further Me_3Si-triflate (20 mol%, 64 μL) was added dropwise. The reaction and the workup were carried out according to general procedure II. Yield 66%; R_f 0.21 (solvent *E*); ^1H NMR data (C_6D_6): δ 1.09 (t, 3 H, *J* 7 Hz, CH_3), 1.61, 1.67, 1.70, 1.73 (4 s, 12 H, CH_3CO), 3.48–3.63 (m, 1 H, OCH_2CH_3), 3.72–3.90 (m, 1 H, OCH_2CH_3), 4.01–4.33 (m, 3 H, 6-H_2, 5-H), 5.15 (dd, 1 H, *J* 4, 10 Hz, 2-H), 5.36 (t, 1 H, *J* 9.5 Hz, 4-H), 5.76 (s, 1 H, 1'-H), 5.79 (d, 1 H, *J* 4 Hz, 1-H), 5.97 (dt, 1 H, *J* 9.5, 10 Hz, 3-H), 6.82–6.98 (m, 3 H, phenyl-H), 7.28–7.44 (m, 2 H, phenyl-H); ^{13}C NMR data (C_6D_6): δ 15.07 (OCH_2CH_3), 20.13, 20.19, 20.25, 20.36 (CH_3CO), 61.12 (OCH_2CH_3), 61.91 (C-6), 68.87 (C-4), 68.92 (C-2), 70.61, 70.72 (C-5), 71.02 (C-3), 84.26 (C-3'), 86.51 (C-2'), 90.38 (C-1), 92.23 (C-1'), 121.9 (*i*-C-phenyl), 129.2, 132.1, 132.2 (*o*-, *m*-, *p*-C-phenyl), 169.2, 169.5, 169.6, 169.9 (C=O); MS data (200 eV, DCI): *m/z* 524 [$M + NH_4^+$]. Anal. Calcd for: $C_{25}H_{30}O_{11}$ (506.5); C, 59.28; H, 5.97; Found: C, 59.37; H, 6.04.

Preparation of 2-alkenyl-1-ethoxy glucosides.—General procedure III. To a stirred solution of nickel acetate (4.40 mg, 0.02 mmol) in dry EtOH was added under an H_2 atmosphere at room temperature KBH_4 in EtOH (1.0 M, 0.02 ml) and 3 drops of 1,2-diaminoethane. To the resulting black mixture the acetal-glucosides **6–9** (0.37 mmol) were added and the solution stirred under an H_2 atmosphere until the reduction of the triple bond was completed (TLC, silica gel, solvent *D*). In the presence of any traces of water the reduction fails and the solution becomes clear. The reaction was quenched by addition of active coal and the mixture filtered

TABLE I

Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($pm^2 \times 10^{-1}$) of **9**, U_{eq} is defined as 1/3 of the trace of orthogonalized U_{ij} tensor

Atom	x	y	z	U_{eq}
O-1	6815(2)	−11(4)	2534(1)	29(1)
C-1	8104(3)	−752(5)	2784(2)	27(1)
C-2	8235(3)	−2524(5)	2373(2)	27(1)
O-1A	9528(2)	−3301(4)	2627(1)	30(1)
C-1A	9587(4)	−5140(6)	2776(2)	33(1)
O-1B	8632(3)	−6116(4)	2686(2)	49(1)
C-1B	10984(4)	−5721(7)	3046(3)	53(1)
C-3	8140(4)	−2082(5)	1558(2)	29(1)
O-3A	8069(3)	−3772(4)	1153(1)	38(1)
C-3A	9133(5)	−4274(7)	835(2)	47(1)
C-3B	8896(8)	−6037(10)	443(4)	100(2)
O-3B	10125(3)	−3380(5)	885(2)	63(1)
C-4	6874(4)	−1002(6)	1281(2)	32(1)
O-4A	7076(2)	−217(4)	587(1)	36(1)
C-4A	6116(4)	−475(6)	−12(2)	38(1)
O-4B	5098(4)	−1278(6)	14(2)	57(1)
C-4B	6532(4)	414(7)	−672(2)	49(1)
C-5	6642(4)	594(6)	1784(2)	32(1)
C-6	5231(4)	1343(6)	1624(2)	38(1)
O-6A	4350(3)	−86(5)	1800(2)	43(1)
C-6A	3107(5)	400(8)	1863(3)	52(1)
C-6B	2340(5)	−1129(10)	2130(3)	71(2)
O-6B	2685(4)	1902(8)	1715(3)	97(2)
O-2	8121(2)	−1161(4)	3530(1)	29(1)
C-1′	8337(4)	428(5)	3989(2)	29(1)
C-2′	7564(4)	142(5)	4600(2)	31(1)
C-3′	6872(4)	0(6)	5068(2)	31(1)
C-4′	6044(3)	−137(6)	5635(2)	31(1)
C-5′	5713(4)	−1847(6)	5882(2)	35(1)
C-6′	4910(4)	−1970(7)	6429(2)	41(1)
C-7′	4458(4)	−418(7)	6721(2)	46(1)
C-8′	4784(5)	1298(7)	6479(2)	48(1)
C-9′	5583(4)	1446(7)	5940(2)	40(1)
O-3	9687(2)	770(4)	4210(1)	31(1)
C-1″	10378(4)	−618(6)	4680(2)	40(1)
C-2″	11804(4)	−36(8)	4863(3)	65(1)
O-1	6815(2)	−11(4)	2534(1)	29(1)
C-1	8104(3)	−752(5)	2784(2)	27(1)
C-2	8235(3)	−2524(5)	2373(2)	27(1)
O-1A	9528(2)	−3301(4)	2627(1)	30(1)
C-1A	9587(4)	−5140(6)	2776(2)	33(1)
O-1B	8632(3)	−6116(4)	2686(2)	49(1)
C-1B	10984(4)	−5721(7)	3046(3)	53(1)
C-3	8140(4)	−2082(5)	1558(2)	29(1)
O-3A	8069(3)	−3772(4)	1153(1)	38(1)
C-3A	9133(5)	−4274(7)	835(2)	47(1)
C-3B	8896(8)	−6037(10)	443(4)	100(2)
O-3B	10125(3)	−3380(5)	885(2)	63(1)

TABLE I (continued)

Atom	x	y	z	U_{eq}
C-4	6874(4)	−1002(6)	1281(2)	32(1)
O-4A	7076(2)	−217(4)	587(1)	36(1)
C-4A	6116(4)	−475(6)	−12(2)	38(1)
O-4B	5098(4)	−1278(6)	14(2)	57(1)
C-4B	6532(4)	414(7)	−672(2)	49(1)
C-5	6642(4)	594(6)	1784(2)	32(1)
C-6	5231(4)	1343(6)	1624(2)	38(1)
O-6A	4350(3)	−86(5)	1800(2)	43(1)
C-6A	3107(5)	400(8)	1863(3)	52(1)
C-6B	2340(5)	−1129(10)	2130(3)	71(2)
O-6B	2685(4)	1902(8)	1715(3)	97(2)
O-2	8121(2)	−1161(4)	3530(1)	29(1)
C-1′	8337(4)	428(5)	3989(2)	29(1)
C-2′	7564(4)	142(5)	4600(2)	31(1)
C-3′	6872(4)	0(6)	5068(2)	31(1)
C-4′	6044(3)	−137(6)	5635(2)	31(1)
C-5′	5713(4)	−1847(6)	5882(2)	35(1)
C-6′	4910(4)	−1970(7)	6429(2)	41(1)
C-7′	4458(4)	−418(7)	6721(2)	46(1)
C-8′	4784(5)	1298(7)	6479(2)	48(1)
C-9′	5583(4)	1446(7)	5940(2)	40(1)
O-3	9687(2)	770(4)	4210(1)	31(1)
C-1″	10378(4)	−618(6)	4680(2)	40(1)
C-2″	11804(4)	−36(8)	4863(3)	65(1)

through Celite (solvent *D*). Concentration of the filtrates in vacuo and flash chromatography on silica gel (solvent *D*) afforded the products **11–13**. For chromatography of all products, 0.7% Et_3N was added to the solvent.

(1RS) 1-Ethoxy-prop-2-enyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**11**).—*Reduction of* **6** *according to general procedure III.* Yield 52%; R_f 0.34 (solvent *D*); ^1H NMR data ($CDCl_3$): δ 1.21 (2 t, 3 H, *J* 7 Hz, OCH_2CH_3), 1.98–2.10 (m, 12 H, CH_3CO), 3.38–3.80 (m, 3 H, 5-H, OCH_2CH_3), 4.13 (dd, 1 H, *J* 3, 12.5 Hz, 6-H_a), 4.25 (dd, 1 H, *J* 5, 12.5 Hz, 6-H_b), 4.70–5.28 (m, 5 H, 1-H, 2-H, 3-H, 4-H, 1′-H), 5.33 (dt, 1 H, *J* 1.5, 12 Hz, 3′-H_a), 5.46 (dt, 1 H, *J* 1.5, 18 Hz, 3′-H_b), 5.81 (ddd, 1 H, *J* 5, 10, 17 Hz, 2′-H); ^{13}C NMR data (acetone-d_6): δ 15.45 (OCH_2CH_3, *S* epimer), 15.52 (OCH_2CH_3, *R* epimer), 20.54, 20.60 (CH_3CO), 61.48 (OCH_2CH_3, *S* epimer), 62.18 (OCH_2CH_3, *R* epimer), 62.83 (C-6, *S* epimer), 63.35 (C-6, *R* epimer), 69.43 (C-4), 72.10 (C-2), 72.45 (C-5), 73.53 (C-3), 96.83 (C-1, *S* epimer), 97.18 (C-1, *R* epimer), 100.5 (C-1′, *S* epimer), 103.1 (C-1′, *R* epimer), 117.8 (C-3′, *R* epimer), 118.6 (C-3′, *S* epimer), 136.1 (C-2′, *S* epimer), 136.3 (C-2′, *R* epimer), 169.6, 170.0, 170.3, 170.7 (C=O); MS data (DCI): *m/z* 450 [$M + NH_4^+$], 365 [$M - aglucon + NH_4^+$], 331 [$M - O - aglucon^+$]. Anal. Calcd for $C_{19}H_{28}O_{11}$ (423.4): C, 52.77; H, 6.53; Found: C, 52.87; H, 6.53.

(1RS) 1-Ethoxy-tridec-2-enyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**12**).—*Reduction of* **7** *according to general procedure III.* Yield 37%; R_f 0.50 (solvent *D*);

^{1}H NMR data ($CDCl_3$): δ 0.88 (t, 3 H, J 7 Hz, 13′-H_3), 1.14–1.48 (m, 19 H, 12′-H_2, 11′-H_2, 10′-H_2, 9′-H_2, 8′-H_2, 7′-H_2, 6′-H_2, 5′-H_2, CH_3), 2.00, 2.02, 2.03, 2.07, 2.10 (5 s, 14 H, CH_3CO, 4′-H_2), 3.42–3.80 (m, 3 H, OCH_2CH_3, 5-H), 4.06–4.32 (m, 2 H, 6-H_2), 4.68–5.32 (m, 6 H, 1-H, 2-H, 3-H, 4-H, 1′-H, 3′-H), 5.45–5.70 (m, 1 H, 2′-H); ^{13}C NMR data ($CDCl_3$): δ 14.11 (C-13), 15.23 (OCH_2CH_3), 20.61, 20.63, 20.72 (CH_3CO), 22.69 (C-12), 27.87, 28.07, 28.87, 29.11, 29.26, 29.29, 29.35, 29.50, 29.61, 31.92, 32.10, 32.75 (C-11, C-10, C-9, C-8, C-7, C-6, C-5, C-4), 59.48, 60.90 (OCH_2CH_3), 61.97, 62.13 (C-6), 68.46, 69.49 (C-4), 71.32, 71.95, 72.15, 72.18 (C-2, C-5), 73.15, 73.32 (C-3), 95.34, 95.64, 95.85 (C-1, C-1′), 125.7, 127.3 (C-3′), 136.0 (C-2′), 169.1, 169.4, 170.3, 170.6, 170.9 (C=O); MS data (DCI): m/z 591 [$M + NH_4^+$], 590 [$M + NH_3^+$], 3.66 [M – aglucon + NH_4^+], 225 [aglucon$^+$]. Anal. Calcd for $C_{29}H_{48}O_{11}$ (572.7): C, 60.82; H, 8.45; Found: C, 60.81; H, 8.50.

(1RS) 1-Ethoxy-3-(phenyl)prop-2-enyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**13**).—*Reduction of* **9** *according to general procedure III.* Yield 69%; R_f 0.42 (solvent *D*); ^{1}H NMR data (C_6D_6): δ 1.06 (t, 3 H, J 7 Hz, OCH_2CH_3), 1.59, 1.60, 1.62, 1.64 (4 s, 12 H, CH_3CO), 3.09 (ddd, 1 H, J 2.5, 4.5, 10 Hz, 5-H), 3.34 (dq, 1 H, J 7, 9 Hz, OCH_2CH_3), 3.64 (dq, 1 H, J 7, 9 Hz, OCH_2CH_3), 3.89 (dd, 1 H, J 2, 12 Hz, 6-H_a), 4.11 (dd, 1 H, J 4.5, 12 Hz, 6-H_b), 4.85–4.88 (m, 1 H, 1-H), 5.20–5.25 (m, 1 H, 2-H), 5.36–5.39 (m, 2 H, 3-H*, 4-H*), 5.74 (dd, 1 H, J 1, 7.5 Hz, 1′-H), 5.79 (dd, 1 H, J 7.5, 11 Hz, 2′-H), 6.40 (d, 1 H, J 11 Hz, 3′-H), 6.97–7.16 (m, 3 H, phenyl-H), 7.38 (d, 2 H, J 7 Hz, phenyl-H); ^{13}C NMR data (acetone-d_6): δ 15.57 (OCH_2CH_3), 20.50, 20.56 (CH_3CO), 60.90 (OCH_2CH_3), 62.87 (C-6), 69.41 (C-4), 72.11 (C-2), 72.44 (C-5), 73.58 (C-3) 96.28 (C-1), 97.14 (C-1′), 128.6 (*p*-C-phenyl), 128.8 (C-2′), 129.2, 129.9 (*o*-, *m*-C-phenyl), 133.5 (C-3′), 136.8 (*i*-C-phenyl), 169.6, 170.0, 170.3, 170.6 (C=O); MS data (DCI): m/z 526 [$M + NH_4^+$], 331 [glucoside – O^+], 102 [C=CHPh$^+$]. Anal. Calcd for $C_{25}H_{32}O_{11}$ (508.5): C, 59.05; H, 6.34; Found: C, 59.11; H, 6.55.

O-Deacetylation of **6**, **9**, *and* **13**.—*General procedure IV.* To a solution of the acetal glucosides **6**, **9**, and **13**, respectively (200 mg, 0.46 mmol) in dry MeOH, Lewatit ML 500 (OH^-) resin (2.5 g, type I) was added and the mixture stirred with ultrasound for 3 h at a temperature < 40°C with monitoring by TLC (solvent *F*). The mixture was filtered and the eluate was concentrated in vacuo to afford the products. Purification is possible, but in most cases not necessary, by flash chromatography on silica gel (solvent *F* and 0.7% Et_3N).

(1RS) 1-Ethoxy-prop-2-ynyl β-D-glucopyranoside (**14**).—*O-Deacetylation of* **6** *according to general procedure IV.* R_f 0.22 (solvent *F*); ^{1}H NMR data (C_5D_5N): δ 1.22 (t, 3 H, J 7 Hz, CH_3), 3.70–4.56 (m, 9 H, CH_2, 6-H_2, 2-H, 3-H, 4-H, 5-H, 3′-H), 5.03 (s, 4 H, OH), 5.29, 5.30 (2 d, 1 H, J 8 Hz, 1-H), 6.07 (s, 0.2 H, 1′-H, *R* epimer), 6.25 (s, 0.8 H, 1′-H, *S* epimer); ^{13}C NMR data (CD_3OD): δ 15.29 (OCH_2CH_3), 60.49, 62.76 (OCH_2CH_3, *S* epimer, C-6), 63.07 (OCH_2CH_3, *R* epimer), 71.48 (C-4, *R* epimer), 71.58 (C-4, *S* epimer), 74.79 (C-2, *S* epimer), 74.92 (C-2, *R* epimer), 78.07 (C-5, *S* epimer), 78.12 (C-5, *R* epimer), 78.28 (C-3), 89.32

(C-1, *S* epimer), 92.42 (C-1, *R* epimer), 99.06 (C-1', *S* epimer), 101.1 (C-1', *R* epimer); MS data (FAB): *m/z* 285 [M + Na^+]. Anal. Calcd for $C_{11}H_{18}O_7$ (262.3): C, 50.38; H, 6.92; Found: C, 50.30; H, 7.01.

(1RS) 1-Ethoxy-3-(phenyl) prop-2-ynyl β-D-glucopyranoside (**15**).—*O-Deacetylation of* **9** *according to general procedure IV.* Yield 95%; R_f 0.46 (solvent *F*); ^1H NMR data (C_5D_5N): δ 1.25 (t, 3 H, *J* 7 Hz, OCH_2CH_3), 3.97–4.02 (m, 1 H, 5-H), 4.10 (dq, 2 H, *J* 7, 9 Hz, OCH_2CH_3), 4.26 (dq, 1 H, *J* 7, 9 Hz, OCH_2CH_3), 4.12–4.19, 4.30–4.36, 4.39–4.46, 4.52–4.58 (5 m, 4 H, 2-H, 3-H, 4-H, 6-H), 5.04 (s, 4 H, OH), 5.38 (d, 1 H, *J* 7.5 Hz, 1-H), 6.28 (s, 0.1 H, 1'-H), 6.46 (s, 0.9 H, 1'-H), 7.32–7.61 (m, 5 H, phenyl-H); ^{13}C NMR data (C_5D_5N): δ 15.36 (OCH_2CH_3), 59.54 (OCH_2CH_3), 62.58 (C-6), 71.46 (C-4), 74.88 (C-2), 78.52 (C-5), 78.87 (C-3), 85.70, 85.91 (C-2', C-3'), 89.20 (C-1), 99.29 (C-1'), 122.32 (*i*-C-phenyl), 128.8, 129.0 (*m*-phenyl), 129.5 (*p*-phenyl), 132.2, 132.2 (*o*-phenyl). MS data (DCI): *m/z* 356 [M + NH_4^+], 159 [aglucon$^+$]. Anal. Calcd for $C_{17}H_{22}O_7$ (338.4): C, 60.35; H, 6.55; Found: C, 60.17; H, 6.56.

(1RS) 1-Ethoxy-3-(phenyl) prop-2-enyl β-D-glucopyranoside (**16**).—*O-Deacetylation of* **13** *according to general procedure IV.* Yield 95%; R_f 0.26 (solvent *F*); ^1H NMR data (C_5D_5N): δ 1.17 (t, 3 H, *J* 7 Hz, OCH_2CH_3), 3.80–4.55 (m, 12 H, 2-H, 3-H, 4-H, 5-H, 6-H_2, OCH_2CH_3, 4OH), 5.37 (d, 1 H, *J* 7.5 Hz, 1-H), 6.13 (dd, 1 H, *J* 7.5, 11.5 Hz, 2'-H), 6.20–6.36 (m, 1 H, 1'-H), 6.69 (d, 1 H, *J* 11.5 Hz, 3'-H), 7.20–7.40 (m, 5 H, phenyl-H); ^{13}C NMR data (pyridine-d_5): δ 15.64 (OCH_2CH_3), 59.80 (OCH_2CH_3), 62.52 (C-6), 71.44 (C-4), 75.14 (C-2), 78.51 (C-5), 78.61 (C-3), 96.33 (C-1), 100.3 (C-1'), 128.0 (C-2' or C-3'), 128.8, 129.4 (*o*- or *m*-C-phenyl), 129.4, 129.8 (*o*- or *m*-C-phenyl), 132.2 (*p*-C-phenyl), 132.6 (C-2' or C-3'), 136.6 (*i*-C-phenyl); MS data (DCI): *m/z* 358 [M + NH^+], 296 [M − $OCH_2CH_3^+$], 143 [$C_6H_7O_4$ + NH_4^+]. Anal. Calcd for $C_{17}H_{22}O_7$ (340.4); C, 59.99; H, 7.12 Found: C, 59.93; H, 7.06.

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