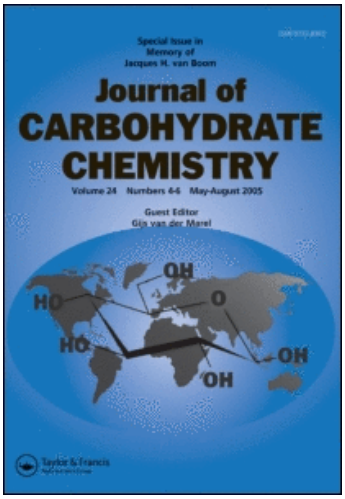

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From α-1,2-Anhydrosugars to *C*-Glycosides: The Influence of Lewis Acids and Nucleophiles on the Stereochemistry

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From α-1,2-Anhydrosugars to *C*-Glycosides: The Influence of Lewis Acids and Nucleophiles on the Stereochemistry†

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ABSTRACT

Ring opening of the epoxide function in α-1,2-anhydrosugars with alkynyl zinc and titanium compounds proceeds with retention of configuration to afford α-*C*-alkynyl-glycosides in reasonable to good yields, while the use of the corresponding alkynyltrifluoroborates results in the formation α/β mixtures. Vinyl nucleophiles predominantly afford α-products, whereas allyl and allenyl species almost exclusively yield β-*C*-glycosides.

INTRODUCTION

Carbohydrate analogs in which the anomeric oxygen is replaced by a carbon substituent have become the subject of intense studies in both synthetic organic chemistry and biochemistry over the past few decades.[1–3] The interest in these so-called *C*-glycosides is based on their occurrence as structural entities in a wide variety of biologically active compounds, ranging from the pharmacologically interesting class of *C*-nucleosides[4,5] to highly complex natural products such as palytoxin[6–8] and halichondrin B.[9,10] Apart from this, *C*-oligosaccharides have shown great promise as

†This paper is dedicated to Professor Gérard Descotes on the occasion of his 70th birthday.

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Table 1. Zn-mediated *C*-alkynyl glycosidations.

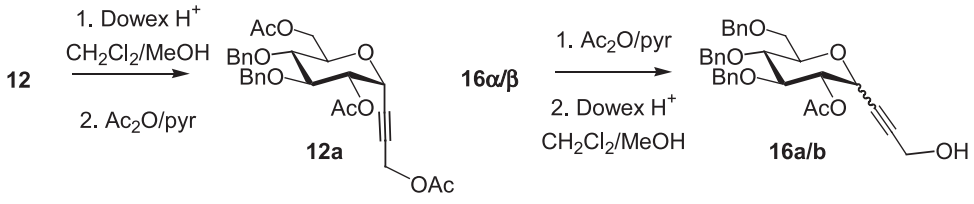
Entry	Epoxide	Alkyne	Method[a]	Product	Yield
1	**1**	**4**	A	**10**	55%
2	**2**	**5**	A	**11**	56%
3	**2**	**6**	A	**12**	76%
4	**3**	**5**	A	**13**	50%
5	**1**	**7**	A	**14**	51%
6	**1**	**7**	B	**14**	70%
7	**1**	**5**	A	**15**	59%
8	**1**	**5**	B	**15**	77%
9	**1**	**6**	B	**16**	72%
10	**1**	**8**	B	**17**	78%
11	**1**	**9**	C	**18**	84%

Note: because of the diastereoisomeric mixtures resulting from the introduction of the THP group (entries 3 and 9), the products were characterized as their acetates, obtained by the sequence of reactions shown in Scheme 1.

[a]*Method A*: 2 equiv alkyne, in THF at −50°C, 2 equiv of *n*-BuLi, 15 min. −50°C, add 1 equiv epoxide and 2 equiv $ZnCl_2$, warm up to rt, 2–3 h. *Method B*: 2 equiv alkyne, in THF at −50°C, 2 equiv of *n*-BuLi, stir 15 min. −50°C, add 2 equiv $ZnCl_2$, stir 5 min. at −50°C, add 1 equiv epoxide, warm up to rt, 2–3 h. *Method C*: sodium acetylide slurry (approx. 2 equiv) in THF at 0°C, add 2 equiv $ZnCl_2$, stir for 5 min, add 1 equiv epoxide, stir at 0°C for 1 h.

potential inhibitors of carbohydrate processing enzymes and metabolically stable models for the evaluation of recognition processes in biological systems.[11]

A particularly interesting method for the stereoselective preparation of *C*-glycosides comprises nucleophilic ring opening of 1,2-anhydrosugars.[12–17] The inherent liberation of the hydroxyl function on C-2 affords further synthetic possiblities for elaboration of the ring opened product. In this respect, we[18–20] and others[21–25] recently demonstrated the efficient conversion of 1,2-anhydrosugars into *cis*- and *trans*-fused cyclic ethers, intermediates in the synthesis of complex marine toxins. We here present our results on the ring opening of α-1,2-anhydrosugars with a range of alkynyl and alkenyl nucleophiles. The influence of the nature of the nucleophile on the stereochemical outcome of the reaction will be discussed.



Scheme 1. Removal of the THP groups and installation of acetates.

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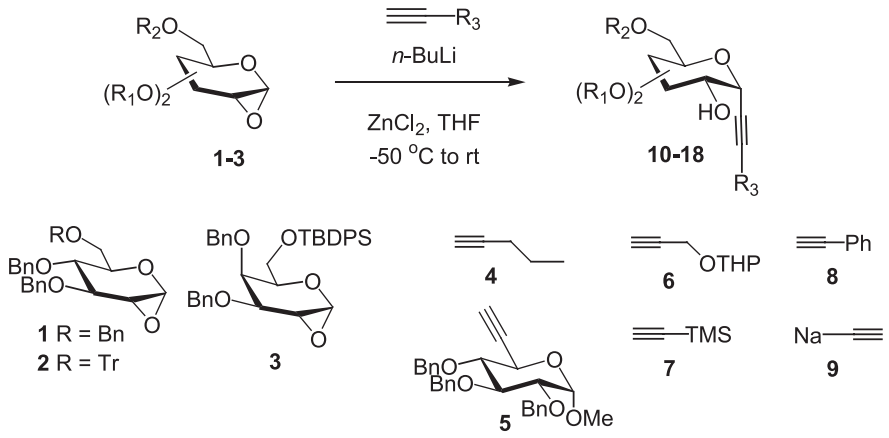


Figure 1.

RESULTS AND DISCUSSION

Previous results from our group[26] showed that zinc chloride is a suitable Lewis acid for the ring opening reaction of 1,2-anhydrosugars with malonate nucleophiles. In this way, *β-C*-glycosyl malonates were obtained in good yields. As a first experiment with alkynyl anions, it was therefore decided to follow an analogous activation procedure. Thus, zinc chloride (1 M in THF) was added to a mixture of 1-pentynyllithium and α-1,2-anhydro-3,4,6-tri-*O*-benzyl-D-glucopyranose (**1**)[27] in THF at −50°C. Warming of the reaction mixture to rt, work-up and purification led to the isolation of α-pentynyl-*C*-glucoside **10** as a single isomer in 55% yield (entry 1, Table 1). Different 1,2-anhydrosugars and alkynyl anions were also subjected to the same reaction conditions (see entries 2–4). For example, by use of the carbohydrate derived alkyne **5**,[28]*C*-disaccharide precursors **13** and **15** were obtained (entries 2 and

Table 2. Ti-mediated *C*-alkynyl glycosidations.

Entry	Alkyne	Product(s)	Yield[b]
1	**5**	**15** + **19**	21% (44%)
2	**6**	**16** + **19**	48% (23%)
3	**7**	**14** + **19**	28% (16%)
4	**8**	**17**	82%
5[c]	**9**	**18**	16%

[a]Conditions: 1.25 equiv lithioalkyne in THF at −50°C, 1.25 equiv of $ClTi(OiPr)_3$ (1M in hexanes) stir for 15 min, add epoxide, slowly warm (1–2 h) to −20°C.
[b]Yield of **19** in parentheses.
[c]Sodium acetylide (18 wt% slurry in mineral oil/xylenes) was used instead of lithioalkyne.

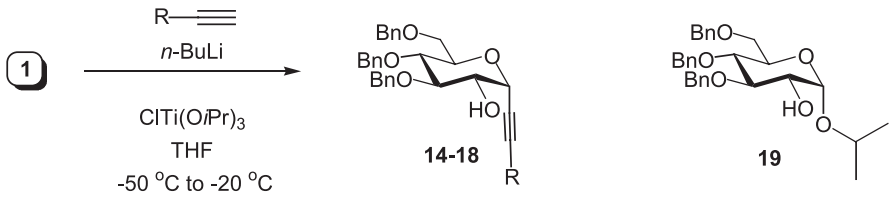
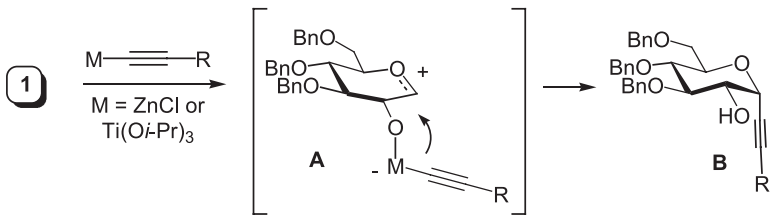


Figure 2.

4). In addition, the method proved compatible with various protective groups both on the epoxide (see compounds **2**[29] and **3**,[30] entries 2 and 4) and on the alkyne (entry 3). Unfortunately, the yields of the *C*-glycosidations remained only moderate, owing to the fact that hydrolysis of the epoxide was often substantial. Based on the assumption that the reactive species is the zinc alkyne, we reasoned that initial formation of the organozinc reagent prior to the addition of the epoxide should have a beneficial effect on the efficiency of the *C*-glycosidation. Indeed, changing the order of addition of the reagents (i.e., method B: stir the lithioalkyne with zinc chloride before adding the epoxide) consistently led to increased yields of the *C*-glycosides (see entries 6 versus 5 and entries 8 versus 7). By employing this protocol, other nucleophiles gave satisfactory yields when reacted with epoxide **1** (see entries 9 and 10). For the synthesis of α-ethynyl-*C*-glucoside **18** (entry 11), a slightly modified procedure was followed. Commercially available sodium acetylide (18 wt% slurry in xylenes/mineral oil), which is sparingly soluble in THF at −50°C, was stirred with zinc chloride at 0°C prior to the addition of epoxide **1**, to give **18** in high yield (84%) (Scheme 1, Figure 1).

As the next research objective, the influence of other Lewis acids on the outcome of the *C*-glycosidation was investigated. A report of Seebach et al.[31] demonstrated the application of the organotitanium complex arising from reaction of phenylethynyllithium with chlorotitanium triisopropoxide in reactions with aldehydes and epoxides. Accordingly, treatment of α-1,2-anhydroglucose **1** with this reactive species led to a rewarding yield of α-phenylethynyl-*C*-glycoside **17** (entry 4, Table 2). The use of other alkynyltitanium species, however, gave contrasting results. The low yield of **18** (entry 5) may be ascribed to the fact that sodium acetylide is sparingly soluble at the low temperature required to maintain the stability of the titanoalkyne. In other cases (entries 1–3), isopropoxide instead of alkynyl anion delivery by the titanium complex led to the isolation of isopropyl α-glucoside **19** as a substantial side product (Figure 2).



Scheme 2. Model for the α-selectivity of Zn- and Ti-mediated *C*-alkynyl glycosidations.

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Table 3. BF_3-mediated *C*-alkynyl glycosidations.

Entry	Alkyne	Product	Yield	α:β ratio
1	**5**	**15**	36%	1.2:1
2	**6**	**16**	65%	1:1.5
3	**7**	**14**	58%	1.7:1
4	**8**	**17**	74%	1:2.2

Conditions: 1.5 equiv lithioalkyne in THF at −78°C, add 1.4 equiv of $BF_3.OEt_2$, stir 15 min, add 1 equiv epoxide, stir at −78°C for 0.5–1 h.

The consistent α-selectivity of both the Zn- and Ti-mediated *C*-glycosidations led us to speculate on the mechanism of this reaction. It may be surmised that the metalloalkyne activates the 1,2-anhydrosugar by complexation of the Lewis acidic metal atom to the epoxide to give the ion pair **A** (Scheme 2). Next, intramolecular delivery of the nucleophile exclusively from the α-face leads to the observed products **B**. The selective formation of isopropyl α-glycoside **19** (Table 2) in the case of the titanium complex probably also takes place via the same pathway. It should be noted that this mechanism is consistent with the one postulated by Rainier et al.[15–17] for their explanation of the α-selectivity of *C*-glycosylations under the influence of organoaluminium reagents.

The putative mechanism stated above implies that a metalloalkyne complex containing a negatively charged metal centre would not (or less easily) give rise to intermediate **A**, thereby causing a drop in α-selectivity. In this respect, the relatively stable alkynyl-trifluoroborates[32] (obtained by reaction of alkynyl anions with $BF_3.OEt_2$) are the reagents of choice to provide more insight into the validity of this hypothesis. To this end, alkynyl anions also used in the Zn- and Ti-mediated reactions were treated with $BF_3.OEt_2$ (0.9 equiv) at −78°C, followed by the addition of epoxide **1** and stirring at the same temperature. As can be seen in Table 3, all the reactions gave rise to mixtures of α- and β-*C*-alkynyl glucosides in near equal amounts. Presumably, the complexation step followed by intramolecular α-directed alkynyl delivery proposed in Scheme 2 does not occur here. It would seem that in this case the lithium counterion is responsible for the activation of the epoxide, after which the oxocarbenium ion is attacked intermolecularly and non-selectively by the alkynyl nucleophile (Figure 3).

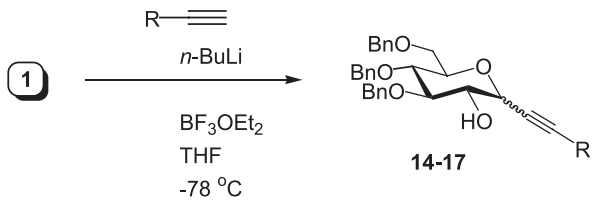


Figure 3.

Table 4. *C*-vinyl glycosidations.

Reagent	Temperature	Yield	α:β
vinylmagnesium bromide	0°C	44%	6:1
divinylmagnesium	rt	42%	6:1
divinylzinc	rt	50%	1:0

The synthetic potential of vinyl-*C*-glycosides[18] was an incentive to investigate whether these compounds could also be obtained by reaction of an appropriate organometallic reagent with a 1,2-anhydrosugar. To this end, epoxide **1** was treated with vinylmagnesium bromide and divinylmagnesium (Table 4) in THF at 0°C and rt, respectively. Notably, these reactions both led to 6:1 mixtures of isomers **20**α and **20**β in moderate yields. On the other hand, reaction of **1** with divinylzinc[33] led to the exclusive formation of the α-vinyl-*C*-glucoside **20**α in 50% yield. These results indicate that the mechanism stated for the Zn- and Ti-mediated α-*C*-alkynyl glycosidations (Scheme 2) is also valid in this case. In contrast, Rainier et al.[23] demonstrated that the reaction of **1** with vinylmagnesium bromide can be steered exclusively towards the β-product by lowering the reaction temperature to -40°C and by using CH_2Cl_2 as a solvent. Interestingly, we found that performing the reaction at -40°C, either in THF or in CH_2Cl_2, gave similar product ratios and yields as reported in Table 4 and Figure 4.

Stick[13] and Evans[14] reported that reaction of allylmagnesium bromide with epoxide **1** exclusively produces the corresponding β-*C*-allyl glucoside **21**β (Scheme 3). Moreover, β-products were also obtained by reaction of allylstannanes under the influence of a variety of Lewis acids. However, reactions of epoxide **1** with triallylborane and triallylalane[15] predominantly yield the α-product, supposedly proceeding via a similar delivery mechanism as depicted in Scheme 2. In order to gain more insight into the stereochemical outcome of the *C*-allylation, the reactions of diallylmagnesium and diallylzinc were explored. Thus, treatment of **1** with an excess of diallylmagnesium[a] in THF at rt led to the formation of the β-isomer alongside a small amount of **21**α, while in the case of diallylzinc, no trace of the α-*C*-allyl glucoside was observed and **21**β was isolated in 42% yield.

It should be noted that the only difference between the reagents presented in Table 4 and Scheme 3 is only one methylene group. The fact that this causes a complete turnaround in the stereoselectivity underlines the powerful influence of the nature of the nucleophile. A possible explanation for the β-selectivity of allyl Grignard reagents has been proposed by Rainier et al.,[22] involving chelation of the metal center to the oxygen in the sugar ring and subsequent β-directed intramolecular delivery of the nucleophile via a six-membered transition state. However, the reason for the difference in chelation mode of the allylboranes and -alanes on the one hand and the allylmagnesium and -zinc species on the other hand remains obscure.

Finally, the reactivity of the allenyl nucleophile was studied. After several attempts to react metalloallenes with epoxide **1** (i.e., allenylmagnesium bromide and allenyltributylstannane[b] with BF_3OEt_2 or TMSOTf), optimal conditions were found with

[a]Prepared according to: Ref. [34].
[b]Prepared according to: Ref. [35].

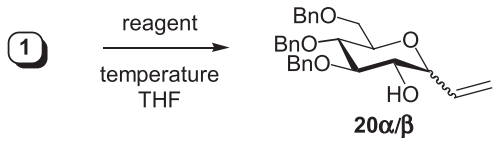


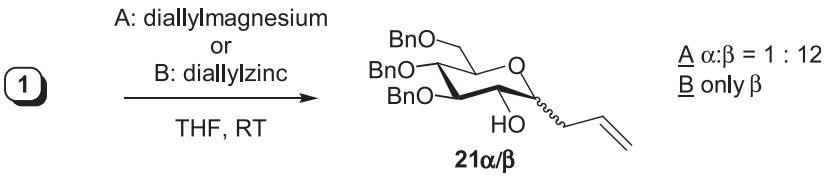
Figure 4.

the familiar organolithium/zinc chloride system (Scheme 4). Thus, a solution of allenyllithium, prepared in situ by transmetalation of allenyltributylstannane with *n*-butyllithium, was treated consecutively with zinc chloride and epoxide **1** to give *β-C*-propargyl glucoside **22** as a single stereoisomer in a yield of 79%. In contrast to the selectivity of the allyl nucleophile,[22] this cannot be explained by assuming a six membered cyclic transition state. It is of interest to note that the same compound was obtained by using propargylmagnesium chloride.[23]

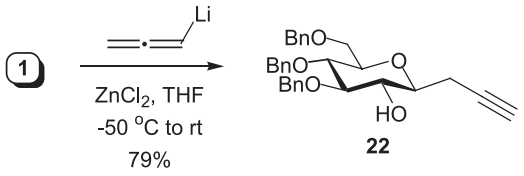
In summary, we have shown that the stereoselectivity of *C* nucleophilic attack on α 1,2 anhydrosugars is strongly dependent on the nature of both the Lewis acid promotor and the nucleophile. The chelation control mechanism, postulated earlier for alanes and boranes,[15–17] also seems to be in accordance with the results from the alkynylzinc and titanium reactions. Further evidence for this mechanism is provided by comparison of the results of the Zn and Ti-mediated *C*-glycosidations with those obtained from the BF_3-mediated reactions. Also, the outcome of the vinyl-*C*-glycosidations are in agreement with the proposed intramolecular α-delivery of the nucleophile by the metal complex, although some discrepancies remain with earlier findings.[15–17,23] In contrast, the allyl and allenyl nucleophiles described here mainly afford *β-C*-glycosides. A general rule regarding the exact factors underlying the stereoselective outcome for the concerning nucleophiles and Lewis acids is still lacking and will require further investigation.

EXPERIMENTAL

General methods and materials. ^1H and ^{13}C spectra were recorded on a Jeol JNM-FX-200 (200 MHz and 50 MHz, respectively). NMR shifts are reported in ppm (δ) relative to tetramethylsilane. Mass spectrometry was performed on a PE/SCIEX API 165 equipped with an electrospray interface. Solvents used for column chromatography were of technical grade and distilled before use. Dichloromethane



Scheme 3. *C*-allyl glycosidations.



Scheme 4. *β-C*-propargylation.

(Baker, p.a.), 1,2-dichloroethane (DCE, Baker, p.a.), dioxane (Baker, p.a.) and tetrahydrofuran (THF, Baker, p.a.) were stored over molecular sieves (4 Å). Toluene was refluxed with P_2O_5 for 2 h, distilled and stored over molecular sieves (4 Å). Anhydrous zinc chloride (Merck) was dissolved in anhydrous THF (1 mL/mmol) and stored over MS 4 Å. Chlorotitanium triisopropoxide (1M in hexanes, Aldrich), Dowex 50 WX 4 (H^+ form, Fluka), sodium acetylide (18 wt% slurry in xylenes/mineral oil, Aldrich), allylmagnesium chloride (2 M in THF, Fluka), vinylmagnesium bromide (1 M in THF, Aldrich), *n*-butyllithium (*n*-BuLi, 1.6 M in hexanes, Aldrich) were used as received. Column chromatography was performed on Baker silica gel (0.063–0.200 mm). TLC analysis was conducted on Merck TLC aluminium sheets silica gel 60 F_{254}, with detection by UV absorption (254 nm) and charring with 20% H_2SO_4 in ethanol. Traces of water were removed from the starting compounds by repeated coevaporation with anhydrous toluene. Drying of organic layers after work-up was effected by $MgSO_4$. Reactions were run at ambient temperature and on 0.1 to 1 mmol scale, unless stated otherwise.

General procedure for the Zn-mediated *C*-alkynyl glycosidations. *Method A*. To a cooled (−50°C) solution of the alkyne (2 equiv relative to the epoxide) in THF (5 mL/mmol) under a nitrogen atmosphere was added *n*-BuLi (2 equiv, 1.6 M in hexanes). After stirring for 20 min, a solution of the epoxide in THF (2 mL/mmol) was added, followed by $ZnCl_2$ (2 equiv, 1 M in THF). The mixture was allowed to warm up to rt and stirred until TLC analysis (50% EtOAc/light petroleum) showed no more progress (2–3 h). The reaction mixture was then poured into sat. NH_4Cl and extracted with Et_2O (2 ×). The combined organic layers were washed with sat. NH_4Cl, dried, filtered and concentrated. Silica gel chromatography (typically 15–30% EtOAc/light petroleum) then afforded the pure α-*C*-alkynyl glycoside. *Method B*. Largely the same as A, with the exception that $ZnCl_2$ was stirred for 15 min with the anion at −50°C before the epoxide was added.

1-(3,4,6-Tri-*O*-benzyl-α-D-glucopyranosyl)-1-pentyne (10). Colourless syrup obtained via method A: 0.15 g, 0.28 mmol, 55% based on 0.22 g, 0.50 mmol of **1**. ^{13}C NMR ($CDCl_3$): δ 138.4, 138.1, 138.0 (3 × C_q Bn), 128.4–127.7 (CH_{arom}), 91.0, 89.3 (2 × C≡C), 83.8, 77.7 (2 × OCH), 75.2, 75.0 (2 × CH_2 Bn), 73.5 (OCH), 73.4 (CH_2 Bn), 71.5, 68.7 (2 × OCH), 68.6 (C-6), 22.0, 20.8 (2 × CH_2 pentynyl), 13.6 (CH_3). MS/ESI: *m/z* 501.3 $[M + H]^+$. Data of the 2-OAc derivative: ^1H NMR

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($CDCl_3$): δ 7.38–7.13 (m, 15H, H_{arom}), 4.98 (dt, 1H, H-1, $J_{1,2}$ = 5.8 Hz, $J_{1,CH2}$ = 1.7 Hz), 4.87 (dd, 1H, H-2, $J_{2,3}$ = 9.7 Hz), 4.86–4.49 (m, 6H, 3 × CH_2 Bn), 4.03–3.95 (m, 2H, H-3, H-5), 3.80–3.65 (m, 3H, H-4, 2 × H-6), 2.21 (dt, 2H, $CH_2C{\equiv}$, $J_{CH2,CH2}$ = 9.2 Hz), 2.01 (s, 3H, CH_3 Ac), 1.54 (m, 2H, CH_2CH_3), 0.99 (t, 3H, CH_3 pentynyl).

(3,4,6-Tri-*O*-benzyl-α-D-glucopyranosyl)trimethylsilylethyne (14). Colourless syrup. ^{13}C NMR ($CDCl_3$): δ 138.9, 138.4, 138.2 (3 × C_q Bn), 128.7–128.0 (CH_{arom}), 100.2, 95.8 (2 × C≡C), 83.7, 77.9 (2 × OCH), 75.4 (2 × CH_2 Bn), 74.1 (OCH), 73.8 (CH_2 Bn), 71.5, 69.3 (2 × OCH), 68.8 (C-6), 0.3 (CH_3 TMS). Data of the 2-OAc derivative: ^1H NMR ($CDCl_3$): δ 7.36–7.15 (m, 15H, CH_{arom}), 4.99 (d, 1H, H-1, $J_{1,2}$ = 6.0 Hz), 4.86 (dd, 1H, H-2, $J_{2,3}$ = 9.7 Hz), 4.82–4.49 (m, 6H, 3 × CH_2 Bn), 3.99–3.92 (m, 2H, H-3, H-5), 3.78 (dd, 1H, H-6a, $J_{6a,6b}$ = 11.0 Hz, $J_{6a,5}$ = 3.6 Hz), 3.72–3.66 (m, 2H, H-4, H-6b), 1.99 (s, 3H, CH_3 Ac), 0.18 (s, 9H, 3 × CH_3 TMS). MS/ESI: *m*/*z* 531.3 $[M + H]^+$.

1-(3,4-Di-*O*-benzyl-6-*O*-trityl-α-D-glucopyranosyl)-3-(tetrahydropyran-2-yloxy)-1-propyne (12). Colourless syrup. ^{13}C NMR ($CDCl_3$): δ 143.5 (C_q Ph), 138.3, 137.5 (2 × C_q Bn), 128.5–126.6 (CH_{arom}), 96.8, 96.7 (CH THP), 86.0 (C_q Tr), 85.7 (C≡), 83.6, (OCH), 80.6 (≡C), 77.4 (OCH), 75.2, 74.8 (2 × CH_2 Bn), 73.8, 71.3, 68.3 (4 × OCH), 68.4 (C-6), 61.7, 61.5 (2 × OCH_2 THP), 54.1 ($CH_2C{\equiv}$), 29.8, 24.9, 18.6 (3 × CH_2 THP). MS/ESI: *m*/*z* 725.3 $[M + H]^+$.

1-(2,6-Di-*O*-acetyl-3,4-di-*O*-benzyl-α-D-glucopyranosyl)-3-acetoxy-1-propyne (12a). THP ether **11** (0.74 g, 1.0 mmol) was dissolved in CH_2Cl_2/MeOH (1/5 mL) and Dowex H^+ (300 mg) was added. The mixture was stirred overnight, after which the resin was filtered off and the filtrate concentrated. This was dissolved in Ac_2O/pyridine (1/2 mL) and stirred for 1 h, and after evaporation of the solvents by repeated coevaporation with toluene, followed by column chromatography (20–40% EtOAc/light petroleum) triacetate **11a** (0.34 g, 0.65 mmol, 65%) was obtained as a colourless syrup. ^1H NMR ($CDCl_3$): δ 7.37–7.25 (m, 10H, H_{arom}), 4.98 (dt, 1H, H-1, $J_{1,2}$ = 5.9 Hz, $J_{1,CH2}$ = 1.7 Hz), 4.89 (dd, 1H, H-2, $J_{2,3}$ = 9.8 Hz), 4.87–4.79 (m, 3H, CH_2 Bn, CH*H* Bn), 4.74 (d, 2H, $CH_2C{\equiv}$), 4.57 (d, 1H, C*H*H Bn), 4.35 (dd, 1H, H-6a, $J_{6a,6b}$ = 12.2 Hz, $J_{6a,5}$ = 2.4 Hz), 4.28 (dd, 1H, H-6b, $J_{6b,5}$ = 4.0 Hz), 4.03–3.95 (m, 2H, H-3, H-5), 3.56 (dd, 1H, H-4). ^{13}C NMR ($CDCl_3$): δ 169.9, 169.4, 169.2 (3 × C = O), 137.9, 137.1 (2 × C_q Bn), 128.0–127.1 (CH_{arom}), 83.6 (C≡), 80.7 (OCH), 79.8 (≡C), 76.6 (OCH), 74.9, 74.6 (2 × CH_2 Bn), 71.9, 71.5, 65.0 (3 × OCH), 62.3 (C-6), 51.4 ($CH_2C{\equiv}$), 20.2, 20.0 (3 × CH_3 Ac). MS/ESI: *m*/*z* 525.2 $[M + H]^+$.

Methyl 7-deoxy-2,3,4-tri-*O*-benzyl-7-(3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl)-α-D-gluco-hept-6-ynopyranoside (15). ^{13}C NMR ($CDCl_3$): δ 138.3–137.5 (C_q Bn), 128.1–127.3 (CH_{arom}), 98.0 (C-1), 86.8 (C≡), 83.3, 81.8, 80.5 (3 × OCH), 79.8 (≡C), 78.9, 77.1 (2 × OCH), 75.5, 75.0, 74.7, 74.6 (4 × CH_2 Bn), 73.7 (OCH), 73.1 (2 × CH_2 Bn), 71.0, 68.2 (2 × OCH), 68.0 (C-6′), 61.4 (C-5′), 55.5 (OMe). MS/ESI: *m*/*z* 891.4 $[M + H]^+$. Data of the 2′-OAc derivative: ^1H NMR ($CDCl_3$): δ 7.36–7.10 (m, 30H, H_{arom}), 5.07 (dd, 1H, H-1′, $J_{1',2'}$ = 6.0 Hz, $J_{1',5}$ = 1.6 Hz), 5.00–4.44 (m, 12H,

6 × CH_2 Bn), 4.92 (dd, 1H, H-2′, $J_{2',3'}$ = 9.9 Hz), 4.54 (d, 1H, H-1, $J_{1,2}$ = 3.0 Hz), 4.43 (dd, 1H, H-5, $J_{5,4}$ = 9.8 Hz), 3.98 (ddd, 1H, H-5′, $J_{5',4'}$ = 9.9 Hz, $J_{5',6a'}$ = 3.2 Hz, $J_{5',6b'}$ = 1.2 Hz), 3.90 (t, 1H, H-3′, $J_{3',4'} = J_{3',2'}$ = 9.4 Hz), 3.89 (t, 1H, H-3, $J_{3,4} = J_{3,2}$ = 9.3 Hz), 3.76–3.61 (m, 3H, 2 × H-6′, H-4′), 3.55–3.48 (m, 2H, H-2, H-4), 3.42 (s, 3H, OMe), 1.91 (s, 3H, CH_3 Ac).

Methyl 7-deoxy-2,3,4-tri-*O*-benzyl-7-(3,4-di-*O*-benzyl-6-*O*-trityl-α-D-glucopyranosyl)-α-D-*gluco*-hept-6-ynopyranoside (11). ^{13}C NMR ($CDCl_3$): δ 143.5 (C_q Ph), 138.3, 138.2, 137.8, 137.6, 137.5 (5 × C_q Bn), 128.5–126.6 (CH_{arom}), 98.0 (C-1), 86.6, 85.9 (C_q Tr, C≡), 83.5, 81.9, 80.5 (3 × OCH), 80.3 (≡C), 78.9, 77.3 (2 × OCH), 75.5, 75.0, 74.5 (4 × CH_2 Bn), 73.9 (OCH), 73.1 (CH_2 Bn), 70.9, 68.3 (2 × OCH), 61.8 (C-6′), 61.5 (OCH), 55.4 (OMe). MS/ESI: *m/z* 1043.5 $[M + H]^+$. Data of the 2′-OAc derivative: ^{1}H NMR ($CDCl_3$): δ 7.48–7.12 (m, 40H, CH_{arom}), 5.17 (dd, 1H, H-1′, $J_{1',2'}$ = 6.0 Hz, $J_{1',5}$ = 1.7 Hz), 5.04 (dd, 1H, H-2′, $J_{2',3'}$ = 9.4 Hz), 4.98–4.46 (m, 9H, 4 × CH_2 Bn, CH*H* Bn), 4.52 (d, 1H, H-1, 3.5 Hz), 4.39 (dd, 1H, H-5, $J_{5,4}$ = 9.9 Hz), 4.31 (d, 1H, C*H*H Bn), 3.95–3.84 (m, 4H, H-3, H-3′, H-4′, H-5′), 3.59–3.47 (m, 3H, H-2, H-4, H-6a′), 3.40 (s, 3H, OMe), 3.21 (dd, 1H, H-6b′, $J_{6b',6a'}$ = 10.2 Hz, $J_{6b',5'}$ = 2.4 Hz), 1.95 (s, 3H, CH_3 Ac).

Methyl 7-deoxy-2,3,4-tri-*O*-benzyl-7-(3,4-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-galacto-pyranosyl)-α-D-*gluco*-hept-6-ynopyranoside (13). ^{13}C NMR ($CDCl_3$): δ 138.8–138.1 (C_q Bn), 135.6–127.5 (CH_{arom}), 133.2 (C_q Ph), 98.5 (C-1), 86.0 (C≡), 82.3, 81.2, 81.0 (3 × OCH), 80.7 (≡C), 79.2 (OCH), 75.9, 75.4, 74.8 (3 × CH_2 Bn), 74.3 (OCH), 73.6 (CH_2 Bn), 73.5 (OCH), 72.1 (CH_2 Bn), 68.7, 67.5 (2 × OCH), 62.2 (C-6′), 61.8 (OCH), 55.9 (OMe), 27.0 (CH_3*t*-Bu), 19.3 (C_q*t*-Bu). MS/ESI: *m/z* 1039.5 $[M + H]^+$. Data for the 2′-OAc derivative: ^{1}H NMR ($CDCl_3$): δ 7.65–7.18 (m, 30H, CH_{arom}), 5.31 (dd, 1H, H-2′, $J_{2',1'}$ = 6.0 Hz, $J_{2',3'}$ = 10.2 Hz), 5.07 (dd, 1H, H-1′, $J_{1',5}$ = 1.5 Hz), 4.95–4.65 (m, 7H, 3 × CH_2, CH*H* Bn), 4.57 (d, 1H, H-1, $J_{1,2}$ = 3.5 Hz), 4.54 (d, 1H, C*H*H Bn), 4.45 (dd, 1H, H-5, $J_{5,4}$ = 9.9 Hz), 4.38 (AB, 2H, CH_2 Bn), 4.02–3.96 (m, 2H, H-4′, H-5′), 3.92 (t, 1H, H-3, $J_{3,2} = J_{3,4}$ = 9.3 Hz), 3.85–3.72 (m, 3H, H-3′, 2 × H-6′), 3.56–3.47 (m, 2H, H-2, H-4), 3.48 (OMe), 1.06 (s, 9H, *t*-Bu). MS: *m/z* 1099 $[M + NH_4]^+$, 1104 $[M + Na]^+$, 1120 $[M + K]^+$.

(3,4,6-Tri-*O*-benzyl-α-D-glucopyranosyl)phenylethyne (17). Colourless syrup. ^{13}C NMR ($CDCl_3$): δ 138.4, 137.9, 137.7 (3 × C_q Bn), 131.9 (CH Ph), 128.7–127.6 (CH Bn), 121.8 (C_q Ph), 89.9 (C≡), 83.5 (OCH), 83.3 (≡C), 77.6 (OCH), 75.2, 75.0 (2 × CH_2 Bn), 73.9 (OCH), 73.4 (CH_2 Bn), 71.4, 68.9 (2 × OCH), 68.4 (C-6). ^{1}H NMR ($CDCl_3$): δ 7.46–7.14 (m, 20H, H_{arom}), 5.04 (d, 1H, H-1, $J_{1,2}$ = 5.1 Hz), 4.97–4.49 (m, 6H, 3 × CH_2 Bn), 4.07 (m, 1H, H-5), 3.85–3.65 (m, 5H, H-2, H-3, H-4, H-6). ESI-MS: *m/z* 557 $[M + Na]^+$, 573 $[M + K]^+$.

(3,4,6-Tri-*O*-benzyl-α-D-glucopyranosyl)ethyne (18). A cooled (0°C) suspension of sodium acetylide (16.6 mmol, 5.2 mL 18 wt% slurry in xylenes/mineral oil) in THF (15 mL) was treated with a solution of anhydrous $ZnCl_2$ (16.6 mL, 1 M in THF). Almost immediately, the inhomogeneous mixture became more transparent and stirring was continued for 15 min. Epoxide **1** (8.3 mmol, 3.6 g) was added in THF (15 mL) and

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the mixture was warmed up to rt and stirred for 1 h, after which TLC analysis showed complete conversion of the starting compound. Work-up and column chromatography in the usual manner gave **18** (3.18 g, 6.9 mmol, 84%) as a colourless oil. ^{13}C NMR ($CDCl_3$): δ 138.0, 137.5, 137.4 (C_q Bn), 127.8–127.2 (CH_{arom}), 83.1 (OCH), 77.6 (C≡C), 77.0 (OCH), 74.8, 74.4 (CH_2 Bn), 73.5 (OCH), 73.0 (CH_2 Bn), 70.6 (OCH), 68.0 (C-6), 67.7 (OCH). MS/ESI: *m/z* 459.2 $[M + H]^+$. Data of the 2-OAc derivative: ^{1}H NMR ($CDCl_3$): δ 7.36–7.13 (m, 15H, H_{arom}), 4.98 (dd, 1H, H-1, $J_{1,2}$ = 5.7 Hz, $J_{1\equiv CH}$ = 2.2 Hz), 4.92 (dd, 1H, H-2, $J_{2,3}$ = 9.6 Hz), 4.87–4.48 (m, 6H, 3 × CH_2 Bn), 4.05–3.96 (m, 2H, H-3, H-5), 3.81–3.65 (m, 3H, H-4, 2 × H-6), 2.53 (d, 1H, ≡CH), 2.01 (s, 3H, CH_3 Ac).

1-(3,4,6-Tri-*O*-benzyl-α-D-glucopyranosyl)-3-(tetrahydropyran-2-yloxy)-1-propyne (16). ^{13}C NMR ($CDCl_3$): δ 138.6, 138.0, 137.8 (C_q Bn), 128.5–127.7 (CH_{arom}), 97.4, 97.1 (2 × CH THP), 86.5 (C≡), 83.9 (OCH), 80.4 (≡C), 77.5 (OCH), 75.3, 75.0 (2 × CH_2 Bn), 73.8 (OCH), 73.5 (CH_2 Bn), 71.4, 68.6 (2 × OCH), 68.5 (C-6), 62.2, 62.0 (2 × OCH_2 THP), 54.5, 54.4 (2 × O*C*H_2C≡), 30.3, 25.3, 19.1, 19.0 (4 × CH_2 THP). MS/ESI: *m/z* 573.3 $[M + H]^+$.

1-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl)-1-propyn-3-ol (16a). THP-ether **16**α (90 mg, 0.13 mmol) was dissolved in Ac_2O/pyridine (0.5/1 mL) and stirred for 1 h. After removal of the solvents by repeated coevaporation with toluene, the crude acteylated product was redissolved in CH_2Cl_2/MeOH (0.2/1.5 mL), treated with Dowex H^+ (50 mg) stirred overnight. The resin was then filtered off and the filtrate concentrated. Column chromatography (50–60% EtOAc/light petroleum) yielded **16a** (47 mg, 0.075 mmol, 57%) as a colourless syrup. ^{1}H NMR ($CDCl_3$): δ 7.37–7.13 (m, 15H, H_{arom}), 5.01 (dt, 1H, H-1, $J_{1,2}$ = 5.9 Hz, $J_{1,CH2C\equiv}$ = 1.8 Hz), 4.90 (dd, 1H, H-2, $J_{2,3}$ = 9.8 Hz), 4.86–4.50 (m, 6H, 3 × CH_2 Bn), 4.31 (d, 2H, $CH_2C\equiv$), 4.00–3.93 (m, 2H, H-3, H-5), 3.78–3.66 (m, 3H, H-4, 2 × H-6), 2.03 (s, 3H, CH_3 Ac). MS/ESI: *m/z* 530.2 $[M + H]^+$.

General procedure for the Ti-mediated *C*-alkynyl glycosidations. To a cooled (−50°C) solution of the lithioalkyne (prepared as described in the previous section, 1.25 equiv relative to the epoxide) was added $ClTi(O\text{-}iPr)_3$ (1.25 equiv, 1 M in hexanes). The yellow mixture was stirred at −50°C for 15 min, after which a solution of the epoxide in THF (2 mL/mmol) was added. The solution was allowed to slowly warm to −20°C (1–2 h). The reaction mixture was poured into aq HCl (1 M) and extracted with Et_2O (2 ×). The combined organic layers were washed with sat. $NaHCO_3$, dried, filtered and concentrated in vacuo. Column chromatography described above gave the α-*C*-alkynyl glycoside and, in some cases, isopropyl glycoside **19**.

Isopropyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (19). ^{13}C NMR ($CDCl_3$): δ 138.4, 137.7, 137.5 (C_q Bn), 127.8–127.0 (CH_{arom}), 96.5 (C-1), 83.1, 77.4 (2 × OCH), 74.8, 74.5, 72.9 (3 × CH_2 Bn), 72.4, 70.0, 69.6 (2 × OCH, CH *i*-Pr), 68.0 (C-6), 22.8, 21.1 (2 × CH_3*i*-Pr). MS/ESI: *m/z* 493.3 $[M + H]^+$, 515.3 $[M + Na]^+$. Data for the 2-OAc derivative: ^{1}H NMR ($CDCl_3$): δ 7.38–7.12 (m, 15H, H_{arom}), 5.15 (d, 1H, H-1, $J_{1,2}$ = 3.8 Hz), 4.85–4.47 (m, 7H, 3 × CH_2 Bn, H-2), 4.02 (t, 1H, *J* = 9.4 Hz, H-3/4),

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3.95–3.62 (m, 5H, H-3/4, H-5, 2 × H-6, C*Hi*-Pr), 2.03 (s, 3H, CH_3 Ac), 1.20 (d, 3H, CH_3*i*-Pr, J = 6.2 Hz), 1.10 (d, 3H, CH_3*i*-Pr).

General procedure for the BF_3-mediated *C*-alkynyl glycosidations. To a cooled (−78°C) solution of the lithioalkyne (prepared as described in the previous section, 1.5 equiv relative to the epoxide) was added $BF_3.OEt_2$ (1.4 equiv). The mixture was stirred at −78°C for 15 min, after which a solution of the epoxide in THF (2 mL/mmol) was added. The solution was stirred at −78°C for 0.5–1 h. The reaction mixture was poured into sat. $NaHCO_3$ and extracted with Et_2O (2 ×). The combined organic layers were washed with sat. $NaHCO_3$, dried, filtered and concentrated in vacuo. Column chromatography was effected as described above to give the α- and *β-C*-alkynyl glycosides.

(3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl)trimethylsilylethyne (14β). Data of the 2-OAc derivative: ^{1}H NMR ($CDCl_3$): δ 7.33–7.12 (m, 15H, H_{arom}), 5.15 (t, 1H, H-2, $J_{2,1} = J_{2,3}$ = 9.4 Hz), 4.82–4.48 (m, 6H, 3 × CH_2 Bn), 4.03 (d, 1H, H-1), 3.77–3.56 (m, 4H, H-3, H-4, 2 × H-6), 3.43 (m, 1H, H-5). MS/ESI: *m/z* 573.3 $[M + H]^+$.

Methyl 7-deoxy-2,3,4-tri-*O*-benzyl-7-(3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-α-D-*gluco*-hept-6-ynopyranoside (15β). Analytical data of 2′-OAc derivative of **15***β*: ^{1}H NMR ($CDCl_3$): δ 7.38–7.13 (m, 30H, H_{arom}), 5.14 (dd, 1H, H-2′, $J_{2',1'}$ = 9.7 Hz, $J_{2',3'}$ = 9.3 Hz), 4.93–4.45 (m, 12H, 6 × CH_2 Bn), 4.51 (d, 1H, H-1, $J_{1,2}$ = 3.5 Hz), 4.36 (bd, 1H, H-5, $J_{5,4}$ = 9.9 Hz), 4.10 (dd, 1H, H-1′, $J_{1',5}$ = 1.4 Hz, $J_{1',2'}$ = 10.0 Hz), 3.85 (t, 1H, H-3, $J_{3,4} = J_{3,2}$ = 9.3 Hz), 3.73–3.65 (m, 3H, H-4′, H-5′, H-6a′), 3.60 (t, 1H, H-3′), 3.50–3.43 (m, 3H, H-2, H-4, H-6b′), 3.37 (s, 3H, OMe), 1.88 (s, 3H, CH_3 Ac). MS/ESI: *m/z* 933.4 $[M + H]^+$.

(3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl)phenylethyne (19β). Spectroscopic data were identical to those described earlier.[19]

1-(2-*O*-acetyl-3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl)-1-propyn-3-ol (16b). ^{1}H NMR ($CDCl_3$): δ 7.32–7.11 (m, 15H, H_{arom}), 5.14 (t, 1H, H-2, $J_{2,1} = J_{2,3}$ = 9.5 Hz), 4.83–4.46 (m, 6H, 3 × CH_2 Bn), 4.22 (bs, 2H, $CH_2C{\equiv}$), 4.07 (dt, 1H, H-1, $J_{1,CH2C{\equiv}}$ = 1.5 Hz), 3.75–3.58 (m, 4H, H-3, H-4, 2 × H-6), 3.50–3.44 (m, 1H, H-5). MS/ESI: *m/z* 530.2 $[M + H]^+$.

(3,4,6-Tri-*O*-benzyl-α/β-D-glucopyranosyl)ethene (20α/β). *Method A:* To a chilled (0°C) solution of epoxide **1** (0.29 g, 0.67 mmol) in THF (5 mL) under a nitrogen atmosphere was added vinylmagnesium bromide (1.0 mmol, 1.0 mL, 1 M in THF). After 15 min, the reaction mixture was poured into sat. NH_4Cl and extracted with Et_2O (2 ×). The combined organic layers were washed with water, dried, concentrated and the residue purified by column chromatography (0–5% acetone/toluene) to afford **20**α (117 mg, 0.25 mmol, 37%) and **20***β* (20 mg, 0.043 mmol, 7%). Spectroscopic data for known acetylated derivatives of compounds **20**α[15–17] and **20***β*[23] were in accordance with those reported. *Method B:* A divinylmagnesium solution was prepared according to the known procedure for diallylmagnesium.[34] Thus, vinylmagnesium bromide (4 mL, 1 M in THF) was treated with dioxane (0.34

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mL). The resulting suspension was stirred for 2 h, after which it was centrifuged for 15 min at 1500 rpm. Part of the supernatant (1.0 mL) was added to a solution of epoxide **1** (0.22 g, 0.50 mmol) in THF (2 mL). After stirring for 2 h, the mixture was worked-up and the product purified in the same manner as described above, giving a 6:1 mixture of **20**α/β (97 mg, 0.21 mmol, 42%). *Method C:* Divinylzinc was prepared analogous to a known procedure[33] by treatment of vinylmagnesium bromide (2 mL, 1M in THF) with $ZnCl_2$ (1 mL, 1M in THF) and stirring for 1 day. Then, dioxane (0.17 mL) was added and stirring was continued for 0.5 h, after which the suspension was centrifuged for 15 min at 1500 rpm. Of the supernatant, 1.5 mL was added to a solution of epoxide **1** (0.22 g, 0.50 mmol) in THF (2 mL). After usual work-up and purification, **20**α (0.11 g, 0.25 mmol, 50%) was obtained as a single isomer.

3-(3,4,6-Tri-*O*-benzyl-α/β-D-glucopyranosyl)-1-propene (21α/β). *Method A:* Diallylmagnesium was prepared according to the literature procedure.[34] A solution of allylmagnesium chloride (2 mL, 2M in THF) was treated with dioxane (0.34 mL) and the heterogeneous mixture was stirred for 2 h. After centrifugation, 0.5 mL of the supernatant was added to a solution of epoxide **1** (0.50 mmol) in THF (2 mL). Work-up and purification proceeded as mentioned for **20**, to give **21**α (17 mg, 0.036 mmol, 7%) and **21**β (0.18 g, 0.38 mmol, 76%) as colourless syrups. Data of **21**β were in full accord with those reported.[13,14] Data for **21**α: ^{13}C NMR ($CDCl_3$): δ 138.1, 137.8, 137.6 (3 × C_q Bn), 134.1 (= CH), 128.6–127.5 (CH_{arom}), 117.3 (= CH_2), 79.0, 74.8 (2 × OCH), 74.2 (CH_2 Bn), 74.1 (OCH), 73.3 (CH_2 Bn), 72.9 (OCH), 72.1 (CH_2 Bn), 68.9 (C-6), 68.3 (OCH), 34.2 (CH_2CH =). MS/ESI: *m/z* 475.2 [M + H]. Data for the 2-OAc derivative of **21**α: ^{1}H NMR ($CDCl_3$): δ 7.33–7.15 (m, 15H, H_{arom}), 5.85–5.71 (m, 1H, = CH), 5.30 (bs, = CH*H*), 5.11–5.03 (m, 2H, = C*H*H, H-2), 4.85–4.46 (m, 6H, 3 × CH_2 Bn), 4.05 (ddd, 1H, H-1, $J_{1,2}$ = 7.7 Hz, $J_{1,CH2a}$ = 8.7 Hz, $J_{1,CH2b}$ = 1.9 Hz), 3.87–3.62 (m, 5H, H-3, H-4, H-5, 2 × H-6), 2.55–2.23 (m, 2H, CH_2C =), 2.14 (s, 3H, CH_3 Ac). MS/ESI: *m/z* 517.3 $[M + H]^+$. *Method B:* By analogy with the preparation of divinylzinc,[33] diallylzinc was prepared by adding $ZnCl_2$ (1 mL, 1 M in THF) to allylmagnesium chloride (1 mL, 2 M in THF). Subsequent further manipulations and reaction with **1** (0.22 mmol, 0.50 mmol) were executed as described above for divinylzinc, to give **21**β (0.10 g, 0.21 mmol, 42%).

3-(3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl)-1-propyne (22). To a cooled (−78°C) solution of allenyltributylstannane[35] (1.85 mL, 6.0 mmol) in THF (12 mL) was added *n*-BuLi (6.0 mmol, 3.75 mL 1.6 M in hexanes). After stirring for 10 min, a solution of $ZnCl_2$ (6.0 mL 1 M in THF) was added and the mixture was warmed up to −40°C over a period of 15 min. After the addition of epoxide **1** (1.30 g, 3.0 mmol), dissolved in THF (6 mL), the reaction mixture was warmed up to rt and stirred for 45 min. The mixture was poured into sat. NH_4Cl and extracted with Et_2O (2 ×). The combined organic layers were washed with sat. NH_4Cl, dried and concentrated. Column chromatography (20–40% EtOAc/light petroleum) yielded **22** (1.12 g, 2.38 mmol, 79%) as a colourless oil. ^{13}C NMR ($CDCl_3$): δ 138.1, 137.8, 137.6 (3 × C_q Bn), 128.1–127.1 (CH_{arom}), 86.0, (OCH), 80.1 (C≡), 78.8, 77.7, 76.6 (3 × OCH), 74.7, 74.3, 72.9 (3 × CH_2 Bn), 72.4 (OCH), 69.8 (≡CH), 68.3 (C-6), 21.5 (*C*H_2C≡). MS: *m/z* 495.2 $[M + Na]^+$. Data for the 2-OAc derivative of **22**: ^{1}H NMR ($CDCl_3$): δ 7.33–7.15 (m, 15H, H_{arom}), 4.99 (t, 1H, H-2, $J_{2,1}$ = $J_{2,3}$ = 9.3 Hz), 4.85–4.52 (m, 6H,

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3 × CH_2 Bn), 3.80–3.62 (m, 4H), 3.53–3.42 (m, 2H), 2.49–2.45 (m, 2H, $CH_2C\equiv$), 1.99 (t, 1H, $\equiv CH$, J = 2.4 Hz), 1.95 (s, 3H, CH_3). MS/ESI: m/z 515.2 $[M + H]^+$.

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