Use of *n*-Pentenyl Glycosides as Precursors to Various Spacer Functionalities

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Pent-4-enyl β-D-glucopyranoside and its peracetylated and perbenzylated derivatives are shown to be excellent substrates for preparation of a wide variety of spacer functionalities. The spacer derivatives so obtained are promising substrates for preparing agents such as *neo*-glycoconjugates, micelles, and liquid crystalline phases, which are of interest for studying various biological and physiological phenomena of carbohydrates.

Introduction

Carbohydrates are involved in a large number of biological processes, e.g., cell-recognition and regulatory processes.[1] To gain better knowledge of the biological role of carbohydrates and their interactions with other counterparts, e.g., proteins, they have been extensively studied during the past decades. For many of these biological studies it is necessary to attach the carbohydrate to a carrier such as a protein or a lipid, i.e., prepare a *neo*-glycoconjugate.[2] This is often done using a bifunctional spacer arm as a link between the carbohydrate moeity and the carrier in order to avoid shielding of parts of the oligosaccharide structure from the carrier. Since the first synthetic glycoprotein was reported in 1929[3,4] many different spacer arms and methods for coupling oligosaccharides to different carriers have been developed.[2,5,6] Micelles (liposomes) offer an alternative method for the biological studies of carbohydrates. Furthermore, amphiphilic molecules such as long chain alkyl glycosides, can form a variety of different liquid crystalline phases some of which are belived to play a vital role in biological processes such as membrane fusion and endocytosis.[7,8]

Since their implementation in 1988[9] *n*-pentenyl glycosides have proved valuable for synthesis of oligosaccharides[10,11] and enantiopure compounds[12] for mechanistic studies of glycoside hydrolysis[9,13] and electrophilic additions[14] and for determining the relative reactivities of differently protected saccharides.[15] The olefinic moeity should allow for ready transformation into spacer functionalities, as has been exemplified by Vliegenthart and co-workers.[16] Versatility would therefore be enhanced, because after having served as donor or acceptor in a saccharide synthesis, a given *n*-pentenyl glycoside could further serve for elaboration of the spacer arm. In this paper, we describe some of our exploratory work in connection with this objective.

Results and Discussion

In seeking broad application of the *n*-pentenyl group as precursor to various spacers two properties seemed important. First, mild and high-yielding conversion to different functionalities for formation of various *neo*-glycoconjugates. Second, these procedures should be compatible with the usual type of protecting groups employed in oligosaccharide synthesis, as well as being useful on free nonprotected pentenyl-glycosides. The latter property should make it possible to introduce different spacer functionalities, and hence prepare different *neo*-glycoconjugates from a common pentenyl glycoside. Such flexibility is desirable in multistep oligosaccharide synthesis.

Accordingly, *n*-pentenyl glucoside **1** and its per-acetylated and per-benzylated derivative **2** and **3,** respectively, were prepared according to standard procedures[10] and used as model compounds in this study. Several transformations of the *n*-pentenyl double bond were then examined and the results follow below.

Radical Elongations. The addition of thiols to the double bond in allyl glycosides by the use of radical chemistry has been shown to be useful on per-acetylated derivatives by Vliegenthart and co-workers.[16] When this type of chemistry was applied to derivatives **1**−**3**, the *n*-pentenyl was readily elongated into a wide variety of functionalized spacers (Scheme 1). Compounds **1**−**3** were

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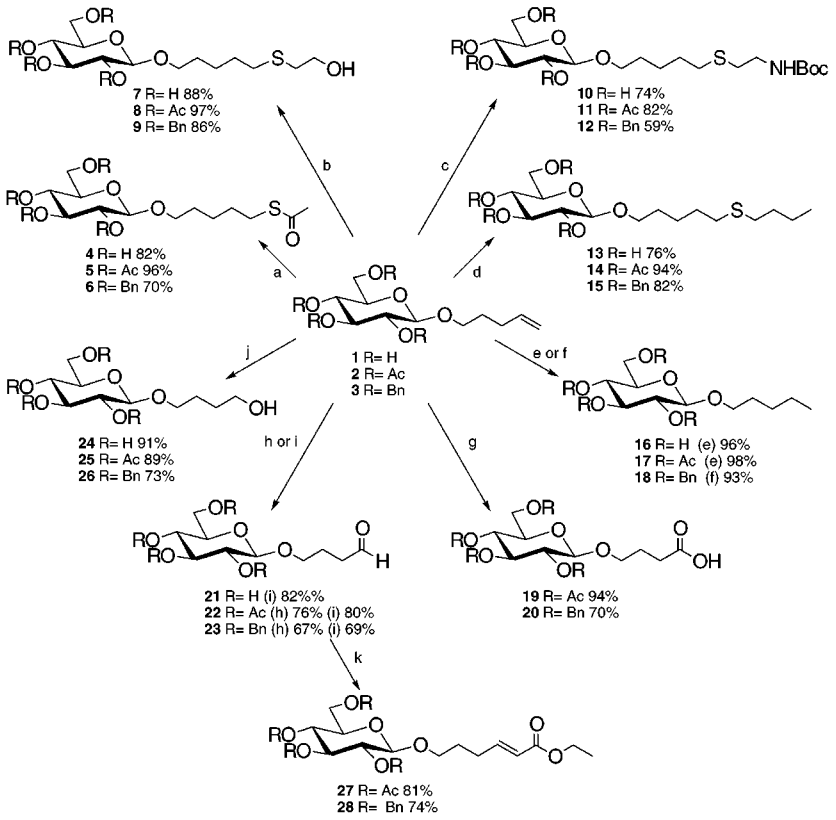
Scheme 1[a]



[a] Key: (a) CH_3COSH, AlBN, dioxane, N_2, 75 °C; (b) $HOCH_2CH_2SH$, AlBN, dioxane, N_2, 75 °C; (c) $HSCH_2CH_2NHBoc$, AlBN, dioxane, N_2, 75 °C; (d) $CH_3(CH_2)_2CH_2SH$, AlBN, dioxane, N_2, 75 °C; (e) H_2, Pd−C, EtOAc or MeOH, 2 h; (f) H_2, Wilkinson's catalyst, EtOAc, 2 h; (g) $RuCl_3/NaIO_4$, CH_2Cl_2−MeCN−H_2O 2:2:3; (h) $OsO_4/NaIO_4$, dioxane−H_2O 4:1; (i) O_3, CH_2Cl_2, −78 °C then DMS; (j) O_3, CH_2Cl_2, −78 °C then BH_3−DMS or $NaBH_4$; NaH, $(EtO)_3P(O)CH_2COOEt$, THF, 0 °C.

treated with different thiols (thiolacetic acid, mercaptoethanol, 2-[(*tert*-butoxycarbonyl)amino]-1-ethanethiol,[17] or butanethiol) in the presence of AIBN at 75 °C to give the sulfide spacer glycosides in good yields (97−59%) (Scheme 1). The use of thioacetic acid gave compounds **4**, **5**, and **6** in 82, 96, and 70% yield, respectively. The thioacetoxy group of these compounds can be cleaved using NaOMe in MeOH to yield the corresponding thiol spacers. Reaction of the model compounds with mercaptoethanol in the presence of AIBN in dioxane at 75 °C gave **7**, **8**, and **9** in 88, 97, and 86% yield, respectively. The hydroxyl group of these 5-(2-hydroxyethylthio)pentyl spacers can be used for further conversions into other functional groups, e.g,. by introduction of a leaving group and subsequent displacement or oxidation.

Cysteamine has been coupled to allyl glycosides in various ways[18] and the amino group used in different elongations and subsequent formation of conjugates.[19] The use of cysteamine hydrochloride directly in the radical reaction was explored, but was found to give sluggish, low yielding reactions. Therefore attention was turned to the N-protected compound 2-[(*tert*-butoxycarbonyl)amino]-1-ethanethiol.[17] Radical elongations with this thiol proceeded cleanly and gave high yields. Thus, compounds **10**, **11**, and **12** were isolated in 74, 82, and 59% yield, respectively.

An easy way of preparing long chain alkyl glycosides for the study of micelles and the use of liposomes would be via thiol addition to a terminal double bond. The length of the sulfide spacer can then easily be varied by the use of different nonbranched alkanethiols. Such variations allow control over the critical micelle concentration.[20] Reaction of *n*-pentenyl glucosides **1**, **2**, and **3** with butanethiol in the presence of AIBN to give the sulfide spacer derivatives **13**, **14**, and **15** in 76, 94, and 82% yield, respectively.

Reduction. The *n*-pentenyl of compounds **1**, **2**, and **3** was reduced to the pentanyl derivatives **16**, **17**, and **18** by catalytic hydrogenation.

Oxidations. Oxidative cleavage of an olefin can be achieved by various procedures[21] leading to either the aldehyde or the carboxylic acid. A convenient route to the carboxylic acid is by use of a catalytic amount of ruthenium tetraoxide with sodium periodate as the stoichiometric oxidant.[22,23] *n*-Pentenyl glucosides **2** and **3** were treated with these oxidants in CH_2Cl_2-MeCN−H_2O 2:2:3[22] to give the corresponding carboxylic acid derivatives **19** and **20** in 94 and 70%, respectively. However on prolonged reaction, the benzylated derivative

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started to decompose as indicated by TLC. The decomposition most probably resulted from the oxidation of the benzylic carbons.

The aldehydes **22** and **23** were prepared in good yields (76% and 67%) using osmium tetraoxide and sodium periodate in dioxane−H_2O 4:1.[24]

Ozonolysis. Reductive ozonolysis[25,26] has been used to transform allyl glycosides into formylmethyl glycosides[27] that can be used for further elongations or conjugations. Here reductive ozonolysis of **2** and **3** in CH_2Cl_2 at −78 °C using dimethyl sulfide[28] as the reducing agent produced aldehydes **22** (80%) and **23** (69%). The yields were comparable to those obtained in the earlier described osmium tetraoxide oxidation. Changing the reducing agent in the ozonolysis to borane dimethyl sulfide complex[29] gave the hydroxypropyl derivatives **25** and **26** (89 and 73%, respectively). By using reductive ozonolysis in methanol at −78 °C with dimethyl sulfide as reagent it was also possible to obtain the unprotected formylpropyl compound **21** (82%). The hydroxypropyl derivative **24** (91%) was here obtained by adding sodium borohydride[30] as reducing reagent.

Further Elongations. As mentioned above, several of these functional groups can be used for further functional group transformations and spacer elongations. The aldehyde derivatives could for example be used in Wittig-type reactions.[31] Thus, aldehyde derivatives **22** and **23** were reacted with sodium hydride and triethyl phosphonoacetate to give the ester derivatives **27** and **28** in 81 and 74% yield, respectively. Also, a Wittig reaction using an alkyl phosphonium ylide in order to synthesize long chain alkyl glycosides would be an alternative to radical elongations.

The pentenyl glycoside double bond gives rise to a variety of functionalized spacers (hydroxyl group, alkyl chain, masked amine or thiol, aldehyde and carboxylic acid) all of which are useful for preparation of *neo*-glycoconjugates, or suitable for direct use in biological experiments. The transformations proceeded in good to high yields (59−97%), independently of the presence or absence of protecting groups such as acetyl or benzyl.

The benzylated derivative gave in most cases lower yields, not only in the radical elongations, but also in the oxidations. The radical reactions were more sluggish, and in the oxidations, the benzylated compound was prone to give byproducts. These byproducts most probably resulted from radical reactions or the oxidation of the benzylic carbon. The benzylated derivatives also require more demanding deprotection strategies.[32] The acetylated derivative **2**, on the other hand, was high yielding in all reaction types, and deprotections are straightforward and tolerant of the functionalities introduced. The nonprotected derivative **1** gave only slightly lower yields in the various reactions, but the advantage is that it is possible to introduce any desirable functional group at a late stage in a multistep synthesis.

Experimental Section

General procedures. THF and CH_2Cl_2 were distilled over CaH_2 before use. AIBN was recrystallized from methanol before use. Thin-layer chromatography was performed using silica gel 60 F-254 (Merck) plates with detection by UV, charring with 8% H_2SO_4, ninhydrin, or AMC (ammonium molybdate−cerium(IV) sulfate−10% sulfuric acid 100 g:2 g:2 L). Organic solutions were dried over $MgSO_4$ before concentrations, which were performed under reduced pressure at 40 °C (waterbath). Column chromatography was performed on silica gel (Matrix Silica Si 60A, 35−70 μm, Amicon). NMR spectra were recorded in $CDCl_3$ at 25 °C (internal standard Me_4Si, δ = 0.00) unless otherwise stated, using a 270 MHz or a 300 MHz instrument. High-resolution fast atom bombardment mass spectrometry (HRMS) was performed using 3-nitrobenzyl alcohol as a matrix. Compounds **1**,[10] **2**,[10] **3**,[10] and 2-[(*tert*-Butoxycarbonyl)amino]-1-ethanethiol[16] were prepared as reported in the literature.

General Method for Radical Elongations. A solution of a pent-4-enyl glycoside (0.5 mmol), AIBN (0.1−0.25 mmol) and thioacetic acid, 2-mercaptoethanol, butanethiol, or 2-[(*tert*-butoxycarbonyl)amino]-1-ethanethiol (7.5 mmol) in 1,4-dioxane (4 mL) was thoroughly degassed (N_2) before reacted at 75 °C (preheated oilbath). After stirring for 1−4 h, the reaction was quenched with cyclohexene (0.3 mL), concentrated and coconcentrated twice with toluene. The residue was then subjected to flash chromatography to yield the sulfide spacer derivative.

5-Thioacetoxypentyl β-D-Glucopyranoside (4). This compound was prepared according to the general procedure from pent-4-enyl β-D-glucopyranoside (**1**) (87 mg, 0.35 mmol) and thioacetic acid followed by flash chromatography ($CHCl_3$−MeOH 7:1) to give **4** (93 mg, 0.29 mmol, 82%): $[\alpha]_D$ −20.3° (*c* 0.3, MeOH); ^{1}H NMR ($CDCl_3$, selected data) δ 1.47−1.61 (m, 6H), 2.30 (s, 3H), 2.87 (t, 2H), 3.17 (m, 1H), 4.25 (d, 1H, J = 7.69 Hz); ^{13}C NMR (CD_3OD) δ 26.2, 29.7, 30.1, 30.5, 62.7, 70.5, 71.5, 75.0, 77.8, 78.0, 104.2, 197.7.

Anal. Calcd for $C_{13}H_{24}O_7S$: C, 48.13; H, 7.46. Found: C, 47.96; H, 7.41.

5-Thioacetoxypentyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (5). According to the general method, per-O-acetylated pent-4-enyl glucoside **2** (150 mg, 0.36 mmol) was treated with thioacetic acid and AIBN (0.07 mmol) to give, after flash chromatography (light petroleum−EtOAc 6:1), sulfide **5** (170 mg, 0.35 mmol, 96%): $[\alpha]_D$ −16.2° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.26−1.63 (dd, 6H), 2.00, 2.02, 2.05, 2.08 (s, 3H each), 2.32 (s, 3H), 2.85 (t, 2H), 3.47 (m, 1H), 3.68 (m, 1H), 4.15, 4.28 (dd, 1H each), 4.50 (d, 1H, J = 7.69 Hz), 4.98, 5.08, 5.21 (dd, 1H each);^{13}C NMR ($CDCl_3$): δ 20.6 (2 signals), 20.7 (2 signals), 25.0, 28.8, 28.9, 29.1, 30.6, 61.9, 68.4, 69.7, 71.3, 71.7, 72.8, 100.7, 169.3, 169.4, 170.3, 170.7, 195.8.

Anal. Calcd for $C_{21}H_{32}O_{11}S$: C, 51.21; H, 6.55; S, 6.51. Found: C, 51.35; H, 6.40; S, 6.63.

5-Thioacethoxypentyl 2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranoside (6). Per-O-benzylated pent-4-enyl glucoside **3** (500 mg, 0.82 mmol) was reacted with thioacetic acid and AIBN (0.16 mmol) according to the general procedure to give, after flash chromatography (light petroleum−EtOAc 6:1) compound **6** (390 mg, 0.57 mmol, 70%): $[\alpha]_D$ +32.1° (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, selected data) δ 1.19−1.70 (m, 6H), 2.27 (s, 3H), 2.85 (t, 2H), 3.41 (m, 1H), 3.54−3.80 (m, 6H), 3.98 (t, 1H); ^{13}C NMR ($CDCl_3$) δ 25.1, 25.4, 29.0, 29.3, 30.6, 67.9, 68.5, 70.2, 73.1, 73.5, 75.1, 75.6, 77.7, 80.1, 82.1, 97.0, 125.7−138.9, 195.8; HRMS calcd for $C_{41}H_{49}O_7S$ $[M + H]^+$ 685.3199, found 685.3104.

5-(Hydroxythioethyl)pentyl βDGlucopyranoside (7). Pent-4-enyl glucoside **1** was treated with AIBN (61 mg, 0.37 mmol) and mercaptoethanol (0.97 mL, 13.8 mmol) as described

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(32) Compound **14** was debenzylated using hydrogenation (Pd/C 10%, 120 psi).

in the general procedure. Flash chromatography ($CHCl_3$−MeOH 5:1) yielded **7** (0.266 g, 0.82 mmol) in 88%: $[\alpha]_D$ −22.8° (*c* 1.2, MeOH); ^{1}H NMR (CD_3OD, selected data) δ 1.45−1.66 (m, 6H), 2.56 (t, 2H), 2.63 (t, 2H), 4.25 (d, 1H, J = 7.69 Hz); ^{13}C NMR (CD_3OD) δ 26.2, 30.3, 30.6, 32.9, 35.1, 62.4, 62.6, 70.5, 71.5, 74.9, 77.7, 77.9, 104.1. Anal. Calcd for $C_{13}H_{26}O_7S$: C, 47.84; H, 8.03; S, 9.82. Found: C, 47.71; H, 7.88; S, 9.78.

5-(2-Hydroxythioethyl)pentyl 2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranoside (8). Pent-4-enyl glucoside **2** (104 mg, 0.249 mmol) was reacted with AIBN (8 mg, 0.05 mmol) and mercaptoethanol (262 μL, 3.73 mmol) according to the general procedure. Purification of the crude product by flash chromatography (CH_2Cl_2−acetone 9:1) gave **8** (120 mg, 0.24 mmol, 97%): $[\alpha]_D$ −17.7° (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, selected data) δ 1.19−1.62 (m, 6H), 2.00, 2.03, 2.05, 2.09 (s, 3H each), 2.52 (t, 2H), 2.72 (t, 2H), 3.48 (m, 1H), 3.82−3.89 (m, 1H), 4.49 (d, 1H, J = 7.69 Hz); ^{13}C NMR ($CDCl_3$) δ 20.6 (2 signals), 20.7, 20.8, 25.1, 29.0, 29.3, 31.6, 35.3, 60.4, 62.0, 68.5, 69.9, 71.4, 71.8, 72.9, 100.3, 169.4, 170.3, 170.7. Anal. Calcd for $C_{21}H_{34}O_{11}S$: C, 51.00; H, 6.93; S, 6.48. Found: C, 50.96; H, 6.96; S, 6.37.

5-(Hydroxythioethyl)pentyl 2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranoside (9). This compound was prepared according to the general procedure starting from benzylated pent-4-enyl glucoside **3** (269 mg, 0.44 mmol), AIBN (29 mg, 0.18 mmol), and mercaptoethanol (465 μL, 6.63 mmol). Flash chromatography (toluene−EtOAc 6:1) of the crude product gave **9** (260 mg, 0.42 mmol, 86%) as a white solid: $[\alpha]_D$ +3.7° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, selected data) δ 1.33−1.54 (m, 6H), 2.32 (t, 2H), 5.52 (t, 2H), 3.80 (m, 1H), 4.24 (d, 1H, J = 7.97); ^{13}C NMR ($CDCl_3$) δ 25.4, 29.4, 29.5, 31.5, 32.2, 60.2, 68.9, 73.4, 74.7, 74.9, 75.6, 77.8, 82.2, 84.6, 103.5, 127.4, 127.5, 127.6, 127.6, 127.7, 127.8 (2C), 128.2, 137.9, 138.0, 138.3, 138.4; HRMS calcd for $C_{41}H_{51}O_7S$ $[M + H]^+$ 687.3356, found 687.3336.

5-[2-[(*tert*-Butoxycarbonyl)amino]-1-thioethyl]pentyl *β*-D-Glucopyranoside (10). According to the general procedure, **1** (234 mg, 0.94 mmol) was treated with AIBN (77 mg, 0.47 mmol) and 2-[(*tert*-butoxycarbonyl)amino]-1-ethanethiol (2,52 g, 14.16 mmol) to give, after flash chromatography ($CHCl_3$−MeOH 8:1), **10** (297 mg, 0.70 mmol, 74%): $[\alpha]_D$ −18.5° (*c* 1.1, MeOH); ^{1}H NMR (CD_3OD, selected data) δ 1.43−1.67 (s, 9H, m, 6H), 2.53−2.60 (2t, 2H each), 4.25 (d, 1H, J = 7.69 Hz); ^{13}C NMR (CD_3OD): δ 26.2, 28.7, 30.3, 30.5, 32.5, 32.6, 41.3, 62.6, 70.5, 71.5, 74.9, 77.7, 77.9, 104.1, 156.4. Anal. Calcd for $C_{18}H_{35}O_8NS$: C, 50.81; H, 8.29; S, 7.54. Found: C, 50.67; H, 8.17; S, 7.52.

5-[2-[(*tert*-Butoxycarbonyl)amino]-1-thioethyl]pentyl 2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranoside (11). Pent-4-enyl glucoside **2** (200 mg, 0.479 mmol) was reacted with AIBN (24 mg, 0.14 mmol) and 2-[(*tert*-butoxycarbonyl)amino]-1-ethanethiol (1.28 g, 7.18 mmol) as described in the general procedure. Flash chromatography (toluene−EtOAc 3:1) of the crude product gave **11** (234 mg, 0.39 mmol, 82%): $[\alpha]_D$ −14.4° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, selected data) δ 1.45−1.61 (s, 9H, m, 6H), 2.52 (t, 2H), 2.63 (t, 2H), 3.30 (m, 2H), 3.48 (m, 1H), 3.87 (m, 1H), 4.50 (d, 1H, J = 7.97 Hz); ^{13}C NMR ($CDCl_3$) δ 20.6 (2 signals), 20.7 (2 signals), 25.0, 28.4, 29.0, 29.2, 31.6, 32.2, 39.9, 61.9, 68.3, 69.7, 71.2, 71.6, 72.7, 100.6, 155.5, 169.0, 169.1, 170.0, 170.3; HRMS calcd for $C_{26}H_{44}O_{12}NS$ $[M + H]^+$ 594.2540, found 594.2590.

5-[2-[(*tert*-Butoxycarbonyl)amino]-1-thioethyl]pentyl 2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranoside (12). This compound was prepared according to the general procedure starting from pent-4-enyl glucoside **3** (210 mg, 0.34 mmol), AIBN (28 mg, 0.17 mmol), and 2-[(*tert*-butoxycarbonyl)amino]-1-ethanethiol (0.921 g, 5.17 mmol). The crude product was subjected to flash chromatography (toluene−EtOAc 8:1) to give **12** (160 mg, 0.20 mmol, 59%): $[\alpha]_D$ +4.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, selected data): δ 1.43−1.68 (s, 9H, m, 6H), 2.47 (t, 2H), 2.59 (t, 2H), 3.27 (m, 2H), 4.37 (d, 1H, J = 7.69 Hz); ^{13}C NMR ($CDCl_3$) δ 25.0, 25.4, 28.1, 28.4, 29.3, 29.4, 31.6, 32.2, 39.8, 68.9, 69.6, 73.4, 74.7, 74.9, 75.6, 76.5, 77.8, 82.1, 84.6, 103.5, 127.4, 127.5, 127.7, 127.8, 127.9, 128.1, 129.5, 137.9, 138.0, 138.3, 138.4, 155.5; HRMS calcd for $C_{46}H_{59}O_8NS$ $[M + H]^+$ 786.4040, found 786.4014.

5-(Thiobutyl)pentyl *β*-D-Glucopyranoside (13). This compound was prepared according to the general procedure starting from **1** (239 mg, 0.96 mmol), AIBN (63 mg, 0.37 mmol), and butanethiol (1.55 mL, 14.46 mmol). Flash chromatography $CHCl_3$−MeOH 8:1) of the crude product yielded **13** (247 mg, 0.73 mmol) in 76%: $[\alpha]_D$ −12.7° (*c* 0.9, MeOH); ^{1}H NMR (CD_3OD, selected data) δ 0.92 (t, 3H), 1.37−1.66 (m, 10H), 2.51 (t + t, 2H each), 4.25 (d, 1H, J = 7.97 Hz); ^{13}C NMR (CD_3OD) δ 14.0, 22.9, 26.3, 30.3, 30.5, 32.5, 32.7, 32.9, 62.6, 70.5, 71.5, 74.9, 77.7, 77.9, 104.1. Anal. Calcd for $C_{15}H_{30}O_{16}S$: C, 53.23; H, 8.93; S, 9.47. Found: C, 53.11; H, 8.90; S, 9.57.

5-(Thiobutyl)pentyl 2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranoside (14). This compound was prepared according to the general procedure starting from **2** (111 mg, 0.27 mmol), AIBN (9 mg, 0.05 mmol), and butanethiol (427 μL, 3.99 mmol). Purification by flash chromatography gave **14** (126 mg, 0.25 mmol, 94%): $[\alpha]_D$ −15.7° (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, selected data): δ 0.91 (t, 3H), 1.36−1.61 (m, 10H), 2.50 (t, 4H), 3.48 (m, 1H), 4.85 (m, 1H), 4.49 (d, 1H, J = 7.69 Hz); ^{13}C NMR ($CDCl_3$) δ 13.6, 20.5, 20.6, 20.7, 22.0, 25.1, 29.0, 29.3, 31.7, 31.8, 32.0, 61.9, 68.4, 69.8, 71.3, 72.8, 100.8, 169.2, 169.3, 170.2, 170.6. Anal. Calcd for $C_{23}H_{38}O_{10}S$: C, 54.53; H, 7.56; S, 6.33. Found: C, 54.65; H, 7.69; S, 6.37.

5-(Thiobutyl)pentyl 2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranoside (15). Pent-4-enyl glucoside **3** (254 mg, 0.42 mmol) was reacted with AIBN (27 mg, 0.17 mmol) and butanethiol according to the general procedure. The crude product was subjected to flash chromatography to give **15** (240 mg, 0.34 mmol, 82%): $[\alpha]_D$ +4.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, selected data) δ 0.87 (t, 3H), 1.34−1.1.68 (m, 10H), 2.45 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.0, 25.5, 29.4, 29.5, 31.8, 31.9, 32.0, 68.9, 69.7, 73.3, 74.6, 74.7, 74.8, 75.5, 77.8, 82.1, 84.6, 103.4, 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.1, 137.8, 137.9, 138.3, 138.4; HRMS calcd for $C_{43}H_{55}O_6S$ $[M + H]^+$ 699.3719, found 699.3693.

Pentyl *β*-D-Glucopyranoside (16). Pd/C (10%, 35 mg) was added to a solution of **1** (124 mg, 0.50 mmol) in MeOH (5 mL). The mixture was hydrogenated (120 psi) for 2 h, filtered through Celite, and evaporated. Purification of the residue on a Sephadex LH-20 gel column eluated with MeOH gave **16** (114 mg, 0.46 mmol, 96%): $[\alpha]_D$ −16.4° (*c* 1.7, MeOH); ^{1}H NMR (CD_3OD, selected data) δ 0.92 (t, 3H), 1.33−1.34 (m, 4H), 1.60−1.65 (m, 2H), 3.49−3.57 (m, 1H), 3.83−3.93 (m, 2H), 4.24 (d, 1H, J = 7.69 Hz); ^{13}C NMR (CD_3OD) δ 14.4, 23.6, 29.3, 30.5, 62.7, 70.8, 71.6, 75.0, 77.8, 78.0, 104.2.

Anal. Calcd for $C_{11}H_{22}O_6$: C, 52.79; H, 8.86. Found: C, 52.70; H, 8.72.

Pentyl 2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranoside (17). **2** (124 mg, 0.30 mmol) was dissolved in EtOAc (4 mL), and Pd/C (10%, 25 mg) was added. The mixture was hydrogenated (120 psi) for 2 h, filtered through Celite, and evaporated. Flash chromatography (toluene−EtOAc 3:1) of the residue gave **17** (122 mg, 0.29 mmol, 98%): $[\alpha]_D$ −17.5° (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, selected data) δ 0.89 (t, 3H), 1.24−1.34 (m, 4H), 1.55−1.1.59 (m, 2H), 3.47 (m, 1H), 3.87 (m, 1H), 4.50 (d, 1H, J = 7.97 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.6, 20.7, 22.3, 28.0, 29.1, 62.0, 68.5, 70.2, 71.4, 71.7, 72.9, 100.9, 169.3, 169.4, 170.3, 170.7.

Anal. Calcd for $C_{19}H_{30}O_{10}$: C, 54.54; H, 7.23. Found: C, 54.53; H, 7.29.

Pentyl 2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranoside (18). To a solution of **3** (250 mg, 0.41 mmol) in EtOAc (6 mL) was added tris(triphenylphosphine)rhodium(I) chloride (25 mg), and the mixture was hydrogenated in a Parr apparatus (120 psi). After 2 h, the mixture was concentrated and purified by flash chromatography (toluene−EtOAc 4:1) to give **18** (234 mg, 0.38 mmol, 93%): $[\alpha]_D$ +5.8° (*c* 1.0, $CHCl_3$): ^{1}H NMR ($CDCl_3$, selected data) δ 0.82 (t, 3H), 1.28−1.33 (m, 4H), 1.57−1.96 (m, 2H), 3.90 (m, 1H), 4.32 (d, 1H, J = 7.97 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 28.4, 29.5, 69.0, 70.1, 73.4, 74.8, 74.8, 74.9, 75.6, 77.9, 82.2, 84.7, 103.6, 127.4, 127.5, 127.6, 127.7, 127.8, 128.0, 128.2, 138.0, 138.1, 138.5. HRMS calcd for $C_{39}H_{47}O_6$ $[M + H]^+$-611.3373, found 611.3276.

3-Carboxypropyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (19). $NaIO_4$ (210 mg, 0.99 mmol) and $RuCl_3 \cdot H_2O$ (1.2 mg, 0.005 mmol) were added to a vigorously stirred solution of **2** (100 mg, 0.24 mmol) in $CH_2Cl_2-MeCN-H_2O$ 2:2:3 (1.2 mL). After 2 h, an additional amount of $NaIO_4$ (210 mg, 0.99 mmol) was added, and the stirring was continued for 2 h. The mixture was then diluted with H_2O and extracted with CH_2Cl_2. The combined organic phases were dried, filtered, and evaporated. The residue was subjected to flash chromatography (toluene−EtOAc 2:3) to give **19** (98 mg, 0.22 mmol, 94%): $[\alpha]_D$ −16.6° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, selected data) δ 1.84 (m, 2H), 2.37 (t, 2H), 3.49 (m, 1H), 3.86 (m, 1H), 4.42 (d, 1H, J = 7.97 Hz); ^{13}C NMR ($CDCl_3$) δ 20.7, 20.8, 24.6, 30.1, 61.9, 68.4, 68.5, 71.2, 71.8, 72.8, 100.7, 169.2, 169.4, 170.1, 170.6, 178.1.

Anal. Calcd for $C_{18}H_{26}O_{12}$: C, 49.77; H, 6.03. Found: C, 49.86; H, 5.91.

3-Carboxypropyl 2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranoside (20). Pent-4-enyl glucoside **3** (248 mg, 0.41 mmol) dissolved in $CH_2Cl_2-MeCN-H_2O$ 2:2:3 (5.6 mL) was treated with $NaIO_4$ (358 mg, 1.67 mmol) and $RuCl_3 \cdot H_2O$ (2 mg, 0.009 mmol) as described for compound **19**. After 3 h, TLC indicated formation of byproducts, and therefore, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried, filtered, and evaporated. Flash chromatography (toluene−EtOAc 3:2) of the residue gave **20** (179 mg, 0.28 mmol, 70%): $[\alpha]_D$ +6.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, selected data): δ 1.98 (m, 2H), 2.48 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 25.0, 30.7, 68.6, 68.9, 73.5, 74.6, 74.9, 75.0, 75.6, 77.8, 82.2, 84.6, 103.4, 127.4, 127.5, 127.6, 127.7, 127.8, 128.0, 128.2, 138.0, 138.1, 138.5, 178.8. HRMS calcd for $C_{38}H_{41}O_8$ $[M - H]^-$ 625.2801, found 625.2770.

3-Formylpropyl β-D-Glucopyranoside (21). A solution of compound **1** (159 mg, 0.641 mmol) in dry MeOH (8 mL) was ozonized (3% ozone in oxygen) at −78 °C until the pale blue color of unreacted ozone appeared (∼15 min). Excess ozone was removed by passing a stream of dry N_2 through the solution, which then was treated with DMS (735 μL, 10.0 mmol) and allowed to attain room temperature. After being stirred for 3 days, the mixture was concentrated and purified by flash chromatography ($CHCl_3$−MeOH 3:1) to give **21** (131 mg, 0.524 mmol, 82%): $[\alpha]_D$ −25.1° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD, selected data) δ 1.18 (m, 2H), 1.67−1.71 (m, 2H), 4.13 (d, 1H, J = 7.97 Hz); ^{13}C NMR (CD_3OD) δ 26.0, 34.3, 62.6, 70.4, 71.5, 75.0, 77.7, 77.9, 104.1, 204.1. HRMS calcd for $C_{10}H_{17}O_7$ $[M - H]^-$ 249.0975, found 249.0995.

3-Formylpropyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (22). OsO_4/$NaIO_4$ Oxidation. To a solution of pent-4-enyl glucoside **2** (250 mg, 0.60 mmol) in dioxane−H_2O 4:1 (6 mL) was added OsO_4 (51 μL, 2.5 wt % solution in 2-methyl-2-propanol, 0.004 mmol). The solution was stirred vigorously for 10 min. The solution turned dark brown, which indicated formation of the osmate ester. $NaIO_4$ (187 mg, 0.87 mmol) was added during 30 min. After being stirred for an additional 1.5 h, the solution was diluted with CH_2Cl_2 and washed with H_2O twice. The organic phase was dried, filtered, and evaporated. Flash chromatography (toluene−EtOAc 2:1) of the residue gave the aldehyde **22** (190 mg, 0.45 mmol) in 76%.

Ozonolysis. A solution of **2** (200 mg, 0.48 mmol) in dry CH_2Cl_2 (10 mL) was ozonized at −78 °C as described for **21**. Excess ozone was removed, and the solution was then treated with DMS (551 μL, 7.52 mmol) and allowed to attain room temperature. After being stirred for an additional 25 h, the reaction mixture was evaporated and the residue was subjected to flash chromatography (toluene−EtOAc 2:1) to give **22** (161 mg, 0.38 mmol, 80%): $[\alpha]_D$ −14.3° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, selected data) δ 1.94 (m, 2H), 2.55 (t, 2H), 3.54−3.62 (m, 1H), 3.90−3.98 (m, 1H), 5.51 (d, 1H, J = 8.06 Hz); ^{13}C NMR ($CDCl_3$) δ 20.5, 20.6, 20.7, 22.1, 40.3, 61.8, 68.3, 68.7, 71.1, 71.7, 72.7, 100.6, 169.2, 169.3, 170.1, 170.5, 201.7.

Anal. Calcd for $C_{18}H_{26}O_{11}$: C, 51.67; H, 6.26. Found: C, 51.81; H, 6.35.

3-Formylpropyl 2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranoside (23). OsO_4/$NaIO_4$ Oxidation. Benzylated pent-4-enyl glucoside **3** (185 mg, 0.30 mmol) was dissolved in dioxane−H_2O 4:1 (4 mL) and treated with OsO_4 (40 μL, 0.003 mmol) and $NaIO_4$ (148 mg, 0.69 mmol) as described for compound **21**. After being stirred for 2 h at ambient temperature, the mixture was diluted with CH_2Cl_2, washed with H_2O (2×), dried, filtered, and evaporated. The residue was subjected to flash chromatography (light petroleum−EtOAc 4:1) to give **23** (124 mg, 0.20 mmol, 67%).

Ozonolysis. Compound **3** (260 mg, 0.43 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and ozonized at −78 °C as described for **21**. After removal of excess ozone, DMS (491 μL, 6.68 mmol) was added and the reaction was allowed to reach room temperature. Stirring was continued for an additional 3 days, where after the reaction mixture was evaporated. Flash chromatography (toluene−EtOAc 7:1) of the crude product yielded **23** (180 mg, 0.30 mmol) in 69%: $[\alpha]_D$ +5.5° (*c* 0.6, $CHCl_3$); ^{1}H NMR (CDCl3, selected data) δ 1.84−1.91 (m, 2H), 2.43−2.48 (m, 2H), 3.83−3.91 (m, 1H), 4.28 (d, 1H, J = 7.69 Hz); ^{13}C NMR ($CDCl_3$) δ 22.1, 40.2, 68.3, 68.4, 73.0, 74.4, 74.4, 74.5, 75.2, 77.4, 81.8, 84.2, 103.0, 127.0, 127.1, 127.2, 127.3, 127.4, 127.6, 127.8, 129.1, 129.2, 137.5, 137.9, 138.0, 201.2.

This aldehyde was prone to oxidize to the corresponding carboxylic acid derivative. HRMS data was in agreement to those obtained for the carboxylic acid compound **20**.

4-Hydroxybutyl β-D-Glucopyranoside (24). A solution of **1** (93 mg, 0.38 mmol) in dry MeOH (5 mL) was treated with ozone at −78 °C as described for **21**. To the colorless solution was then added a solution of $NaBH_4$ (380 mg, 10.1 mmol) in MeOH (3 mL), and the mixture was allowed to reach room temperature. After the mixture was stirred overnight, aqueous 5% HCl was added (pH 2) and stirring was continued for 1 h. The mixture was then concentrated, and the residue was purified using a Sephadex LH-20 gel column (MeOH) to give **24** (86 mg, 0.34 mmol, 91%): $[\alpha]_D$ −32.8° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD, selected data) δ 1.49−1.60 (m, 4H), 3.43−3.58 (m, 4H), 3.73−3.83 (m, 2H), 4.15 (d, 1H, J = 7.97 Hz); ^{13}C NMR (CD_3OD) δ 27.1, 30.0, 62.5, 62.6, 70.4, 71.4, 74.9, 77.6, 77.8, 104.1; HRMS calcd for $C_{10}H_{19}O_7$ $[M - H]^-$ 251.1131, found 251.1153.

4-Hydroxybutyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (25). Compound **2** (93 mg, 0.22 mmol) in dry CH_2Cl_2 (4 mL) was treated with ozone at −78 °C as described for **21**. After removal of excess ozone, the solution was allowed to reach room temperature before it was treated with $BH_3 \cdot$DMS (63 μL, 0.67 mmol). After the mixture was stirred at ambient temperature for 3 days, aqueous 1 M HCl (1 mL) was added. The mixture was stirred vigorously for 1 h, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and H_2O, dried, and concentrated. The residue was subjected to flash chromatography (toluene−EtOAc 1:1) to give **25** (80 mg, 0.19 mmol, 89%): $[\alpha]_D$ −17.2° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, selected data) δ 1.45−1.59 (m, 4H), 3.38−3.45 (m, 1H), 3.51 (t, 2H), 3.76−3.82 (m, 1H), 4.40 (d, 1H, J = 7.97 Hz); ^{13}C NMR ($CDCl_3$) δ 20.5, 20.6, 25.7, 29.1, 61.8, 62.1, 68.4, 69.9, 71.2, 71.6, 72.7, 100.6, 169.3, 169.4, 170.2, 170.7.

Anal. Calcd for $C_{18}H_{28}O_{11}$: C, 51.43; H, 6.71. Found: C, 51.56; H, 6.73.

4-Hydroxybutyl 2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranoside (26). A solution of **2** (260 mg, 0.427 mmol) in dry CH_2Cl_2 (8 mL) was ozonized at −78 °C as described for **21** and then treated with $BH_3 \cdot$DMS (122 μL, 1.28 mmol) and worked up as described for **25**. This gave, after flash chromatography (toluene−EtOAc 3:1), compound **26** (191 mg, 0.31 mmol, 73%): $[\alpha]_D$ +7° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, selected data) δ 1.56−1.68 (m, 4H), 3.87−3.92 (m, 1H); 4.32 (d, 1H, J = 7.88 Hz); ^{13}C NMR ($CDCl_3$) δ 26.3, 29.6, 62.5, 68.9, 69.9, 73.4, 74.8, 74.9, 75.6, 77.8, 82.2, 84.7, 103.5, 127.4, 127.5, 127.6, 127.7, 127.8, 128.0, 128.2, 137.9, 137.9, 138.3, 138.4; HRMS calcd for $C_{38}H_{44}O_7Na$ $[M + Na]^+$ 635.2985, found 635.3002.

5-(Carboxyethyl)pent-4-enyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (27). To a stirred mixture of NaH (95%, 8.1 mg, 0.32 mmol) in THF (1 mL) under argon atmosphere was added triethyl phosphonoacetate (64 μL, 0.32 mmol). Stirring was continued at ambient temperature until the evolution of gas ceased. The mixture was then cooled to 0 °C, and a solution of **22** (104 mg, 0.25 mmol) in THF (3 mL) was

added dropwise. After stirring at room temperature for 3 h TLC indicated complete reaction and H_2O (1 mL) was added. The mixture was diluted with CH_2Cl_2, washed with H_2O, dried and concentrated. Flash chromatography (toluene−EtOAc 3:1) gave **27** (98 mg, 0.20 mmol, 81%): $[\alpha]_D$ −14.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, selected data): δ 1.29 (t, 3H), 1.75 (m, 2H), 2.26 (m, 2H), 3.50 (m, 1H), 3.89 (m, 1H), 4.11−4.30 (m, 4H), 4.48 (d, 1H, J = 8.0 Hz), 5.82 (d, 1H), 6.87−6.98 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 20.6, 27.8, 28.3, 60.2, 61.9, 68.4, 68.8, 71.3, 71.8, 72.8, 100.8, 122.0, 147.9, 166.5, 169.2, 169.4, 170.3, 170.6; HRMS calcd for $C_{22}H_{33}O_{12}$ $[M + H]^+$ 489.1972, found 489.2026.

5-(Carboxyethyl)pent-4-enyl 2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranoside (28). A solution of compound **23** (80 mg, 0.13 mmol) in THF (2 mL) was added dropwise at 0 °C to a stirred solution of the Wittig reagent, prepared from NaH (95% 5 mg, 0.20 mmol) and triethyl phosphonoacetate (39 μL, 0.20 mmol) as described for **27**. After 3 h, TLC indicated complete reaction, and the mixture was worked up as described for **27**. Purification by flash chromatography (light petroleum−EtOAc 3:1) yielded **28** (66 mg, 0.10 mmol) in 74%: $[\alpha]_D$ +3.5° (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, selected data) δ 1.25 (m, 3H), 1.78 (m, 2H), 2.23 (m, 2H), 5.83 (d, 1H), 6.83−6.98 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 27.8, 28.8, 62.5, 67.2, 68.5, 70.3, 73.3, 73.5, 75.1, 75.7, 77.7, 80.1, 82,1, 103.5, 121.8, 127.6, 127.7, 127.9, 128.0, 128.4, 137.9, 138.2, 138.3, 138.9, 148.2, 166.6; HRMS calcd for $C_{42}H_{49}O_8$ $[M + H]^+$ 681.3427, found 681.3414.

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Supporting Information Available: ^{1}H NMR spectra for compounds **6**, **9**, **11**, **12**, **15**, **18**, **20**, **21**, **23**, **24**, and **26**−**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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