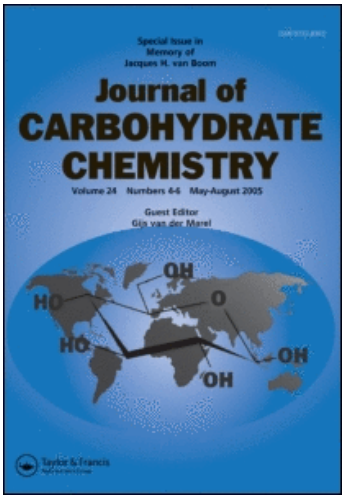

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COMMUNICATION

AN UNUSUAL SIDE REACTION IN THE PERALLYLATION OF A GLUCOSIDE BROUGHT ABOUT BY SODIUM HYDRIDE

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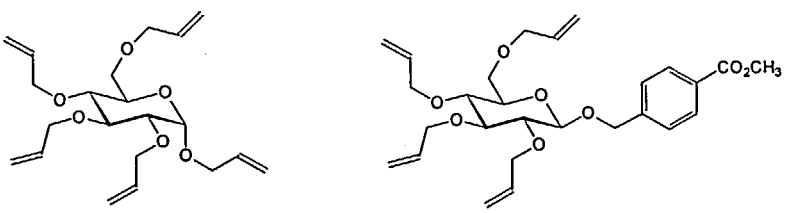
We are presently working on the combination of carbohydrate and dendrimer chemistry, both to develop the synthesis of multivalent glycomimetics and to prepare novel dendrimers with advantageous properties. In the course of this work we have used saccharides as oligofunctional core molecules for the synthesis of carbohydrate-centered dendrimers[1] and carbohydrate-centered glycoclusters.[2]



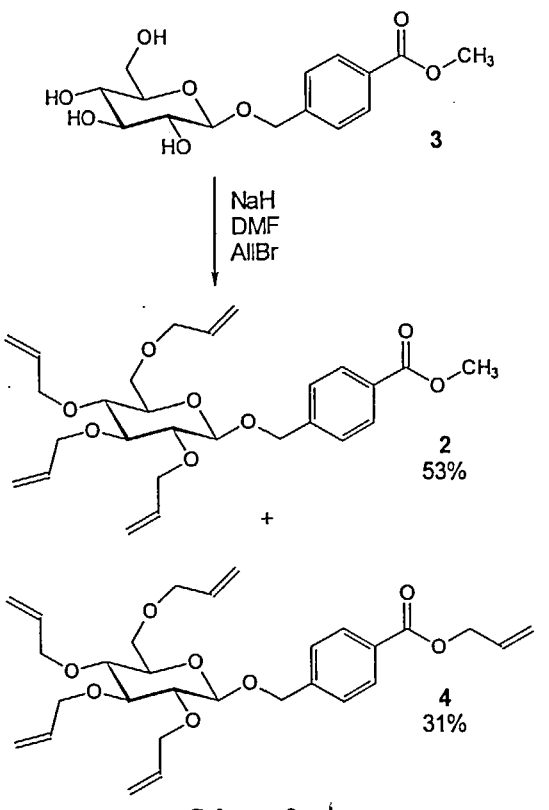
1 2

Scheme 1

The employed sugar cores, so-called octopus glycosides, were derived from fully allylated glucose (**1**, Scheme 1).[3] We are currently extending this project to the synthesis of selectively functionalized dendrimers starting from allylated glucosides such as **2**,

carrying a tether at the anomeric position. Processing of the allyl functions does not affect the aglycon moiety and will eventually lead to octopus glycosides in which the anomeric portion is discriminated from the rest of present functionalities.

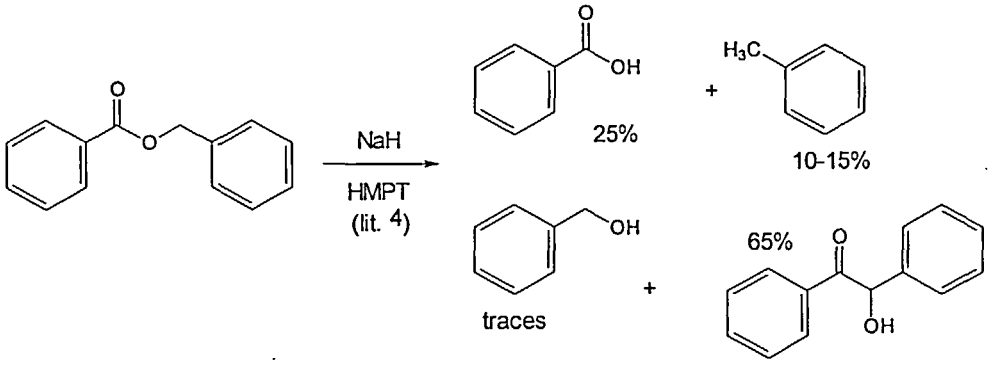
The synthesis of the desired compound **2** started from the unprotected glucoside **3**, which was obtained by glucosylation of methyl 4-(hydroxymethyl)benzoate, followed by deprotection of the glycon part. However, in course of the Williamson perallylation of the functionalized glucoside **3**, carried out with sodium hydride and allyl bromide in dry DMF under argon atmosphere at room temperature over a short period (2 h), an unexpected product was formed in substantial amount, besides the expected tetra-allylated glucoside **2**. The unknown was identified as the allyl ester **4**, in which the methyl carboxylate is replaced by an allyl ester moiety (Scheme 2).



Scheme 2

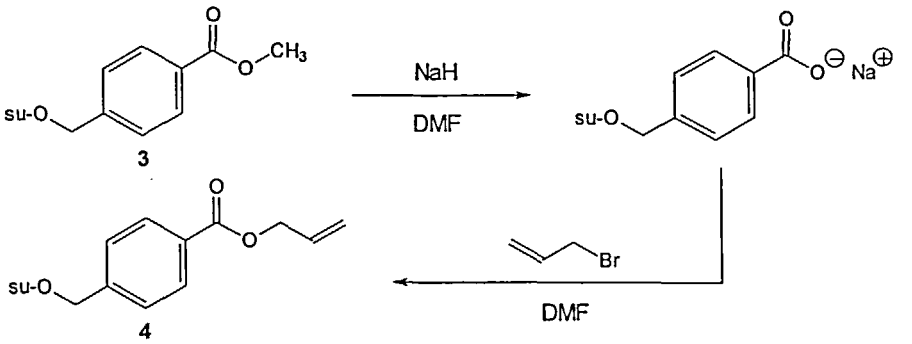
This result can not be explained by a transesterification reaction because of the absence of free allylic alcohol and the strictly anhydrous conditions applied. These conditions also preclude a saponification by hydroxide and subsequent nucleophilic substitution of the resulting carboxylate. Searching the literature in trying to explain the surprising result, we found some related work dealing with the nucleophilic properties of sodium hydride in dipolar aprotic solvents such as HMPTA and its reactions with some nonenolizable esters.[4] Cleavage of the starting esters was frequently observed, such as in the case of benzyl benzoate, where the free carboxylate was obtained, besides benzoin and traces of benzylic alcohol (Scheme 3). Toluene, isolated from the reaction mixture, apparently stems from the starting ester. Ester cleavage is thus obviously brought about by nucleo-

philic attack of a hydride ion at the benzylic carbon atom, leading to a formal nucleophilic substitution reaction, in which benzoate is replaced by hydride. Ethyl benzoate was cleaved also to afford benzoic acid in 60% yield under the same reaction conditions.



Scheme 3

In analogy to these results, the observed side reaction during the allylation of **3** can be explained as follows: after cleavage of the ester bond induced by sodium hydride in the dipolar aprotic solvent DMF, the resulting carboxylate is intercepted by allyl bromide giving rise to the unexpected product **4** (Scheme 4). The alcoholic component of ester **3** could have escaped as methane, formed during the nucleophilic attack of hydride on the methyl group.



Scheme 4

Although cleavage of esters has been observed in halide-mediated processes,[5] it is rather unlikely that sodium bromide, formed in the allylation reaction with **3**, causes the observed conversion of the ester group, because the herein applied reaction conditions are

different from the reported ones. Moreover, the reported cleavage of benzyl benzoate and ethyl benzoate, respectively, proceeded in the absence of halide ions. [4]

It can therefore, be concluded that the commonly used deprotonating agent sodium hydride showed to have substantial nucleophilic properties in dipolar aprotic solvents and this might be considered and even utilized in the preparation of carbohydrate core molecules.

EXPERIMENTAL

General methods. Dry DMF was purchased from Fluka AG. TLC was performed on silica gel plates (GF_{254}, Merck). Detection was effected by UV irradiation and subsequent charring with 10% sulphuric acid in ethanol followed by heat treatment. Flash chromatography was performed on silica gel 60 (230-400 mesh, particle size 0.040-0.063 mm, Merck). Optical rotations were measured on a Perkin-Elmer 241 polarimeter (sodium-D-line: 589 nm, length of cell 1 dm) in chloroform. Melting points were measured with an Apotec apparatus and are uncorrected. NMR spectra were recorded on Bruker AMX 400 (400.13 MHz for ^1H, 100.61 MHz for ^{13}C) and DRX 500 (500.13 MHz for ^1H, 125.76 MHz for ^{13}C). The spectra were calibrated on the solvent peak ($CDCl_3$, 7.24 ppm for ^1H and 77.0 ppm for ^{13}C). Assignment of the peaks was achieved with the aid of 2D-NMR techniques (^1H-^1H-COSY and HMQC). In the reported data the abbreviation "su" denotes a sugar moiety. MALDI-TOF-mass spectra were recorded on a Bruker Biflex III with 19 kV acceleration voltage and DHB (2,4-dihydroxybenzoic acid) as matrix (*c* 10 μg/μL in 40% acetonitrile/water). Ionisation was effected with a nitrogen laser at 337 nm.

Perallylation reaction of methyl ester 3. Glucoside **3** (1.045 g, 3.18 mmol) was dissolved in dry DMF (40 mL) under an argon atmosphere. After cooling to 0 °C, sodium hydride (610 mg of a 55-65% suspension in paraffin oil corresponding to approximately 366 mg, 15.26 mmol (4.8 eq) pure sodium hydride) were added. After evolution of hydrogen had stopped, the solution was allowed to warm to rt. 3-Bromo-1-propene (1.3 mL, 15.90 mmol, 5.0 eq) was added and the mixture was stirred at rt until the starting material **3** was consumed completely (TLC, petroleum ether/ethyl acetate 2:1). Then water (25 mL) and dichloromethane (55 mL) were added, the phases were separated, the aqueous phase was extracted three times with dichloromethane (20 mL) and the combined organic phases were three times washed with water (30 mL) and then dried over magne-

sium sulphate. Filtration followed by evaporation of the solvents yielded the crude mixture of compounds **2** and **4** which was separated by flash chromatography (silica gel, petroleum ether/ethyl acetate 4:1).

[(4-Allyloxycarbonylphenyl)methyl] 2,3,4,6-tetra-*O*-allyl-β-D-glucopyranoside (4). First fraction, 50 mg (0.97 mmol, 31%), colourless waxlike solid; $[\alpha]_D^{20}$ -27.0° (*c* 0.60, $CHCl_3$); mp 31.4-31.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (2H, ddd ≈ d, 2 arom H), 7.41 (2H, ddd ≈ d, 2 arom H), 5.83-6.07 (5H, m, 4 CH_2=**CH**-CH_2-Osu, CH_2=CH_a-CH_2-OOC), 5.39 (1H, ddt ≈ dq, CH_bH_c=CH-CH_2-OOC), 5.11-5.30 (9H, m, 4 CH_2=CH-CH_2-Osu, CH_b**H**$_c$=CH-CH_2-OOC), 4.96 (1H, d, suO-CH_AH_B), 4.80 (2H, ddd ≈ dt, CH_2=CH-CH_d**H**$_e$-OOC), 4.66 (1H, d, suO-CH_AH_B), 3.96-4.39 (9H, m, H-1, 4 CH_2=CH-CH_2-Osu), 3.69 (1H, dd, H-6'), 3.60 (1H, dd, H-6), 3.31-3.39 (3H, m, H-3, H-4, H-5), 3.26 (1H, dd, H-2) ppm; $^3J_{1,2}$ = 7.6, $^3J_{2,3}$ = 9.2, $^3J_{5,6}$ = 4.1, $^3J_{5,6'}$ = 1.5, $^2J_{6,6'}$ = 10.7, $^2J_{A,B}$ = 13.2, $^3J_{a,b}$ = 17.3, $^4J_{a,d}$ = $^4J_{a,e}$ = 1.5 Hz; ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 166.1 (C, COO), 143.0 (C, arom C), 135.2, 135.0, 134.8, 134.7, (CH, 4 CH_2=**CH**-CH_2-Osu), 132.4 (CH, CH_2=**CH**-CH_2-OOC), 129.7, 127.2 (CH, 4 arom C), 129.4 (C, arom C), 118.2 (CH_2, CH_2=CH-CH_2-OOC), 117.0, 116.9, 116.7 (CH_2, 4 CH_2=CH-CH_2-Osu), 102.7 (CH, C-1), 84.2, 77.5, 74.9 (CH, C-3, -4, -5), 81.6 (CH, C-2), 74.4, 73.8, 73.7, 72.5 (CH_2, 4 CH_2=CH-**C**H_2-Osu), 70.3 (CH_2, suO-CH_2), 68.9 (CH_2, C-6), 65.5 (CH_2, CH_2=CH-**C**H_2-OOC) ppm; MALDI-TOF-MS: *m/z* 537.3 ((M + Na)$^+$, calcd 537.2), 553.3 ((M + K)$^+$, calcd 553.2).

Anal. Calcd for $C_{29}H_{38}O_8$ (514.6): C, 67.69; H, 7.44. Found: C, 67.17; H, 7.45.

[(4-Methoxycarbonylphenyl)methyl] 2,3,4,6-tetra-*O*-allyl-β-D-glucopyranoside (2). Second fraction, 830 mg (1.70 mmol, 53%), colourless solid; $[\alpha]_D^{20}$ -14.0 (*c* 0.70, $CHCl_3$); mp 64.0-64.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (2H, ddd ≈ d, 2 arom H), 7.41 (2H, ddd ≈ d, 2 arom H), 5.82-5.99 (4H, m, 4 CH_2=**CH**-CH_2), 5.10-5.29 (8H, m, 4 **C**H_2=CH-CH_2), 4.95 (1H, d, suO-CH_AH_B), 4.66 (1H, d, suO-CH_AH_B), 3.96-4.38 (9H, m, H-1, 4 CH_2=CH-CH_2), 3.89 (3H, s, O-CH_3), 3.69 (1H, dd, H-6'), 3.60 (1H, dd, H-6), 3.30-3.39 (3H, m, H-3, H-4, H-5), 3.26 (1H, dd, H-2) ppm; $^3J_{1,2}$ = 7.6, $^3J_{2,3}$ = 9.2, $^3J_{5,6}$ = 4.1, $^3J_{5,6'}$ = 1.5, $^2J_{6,6'}$ = 10.7, $^2J_{A,B}$ = 13.2 Hz; ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 167.0 (C, COO), 142.9 (C, arom C), 135.2, 135.0, 134.8, 134.7, (CH, 4 CH_2=**CH**-CH_2), 129.7, 127.2 (CH, 4 arom C), 129.4 (C, arom C), 117.1, 117.0, 116.9, 116.7 (CH_2, 4 **C**H_2=CH-CH_2), 102.7 (CH, C-1), 84.2, 77.5, 74.9 (CH, C-3, -4, -5), 81.6 (CH, C-2), 74.4,

73.8, 73.7, 72.5 (CH_2, 4 CH_2=CH-CH_2), 70.4 (CH_2, suO-CH_2), 68.9 (CH_2, C-6), 52.1 (CH_3, OCH_3) ppm; MALDI-TOF-MS: *m/z* 511.3 $((M + Na)^+$, calcd 511.2), 527.3 $(M + K)^+$, calcd 527.2.

Anal. Calcd for $C_{27}H_{36}O_8$ (488.6): C, 66.38; H, 7.43. Found: C, C 65.707; H, 7.40.

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