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Reinvestigation of the Synthesis of Per-benzylated Glycosylethenes: A New Result

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Abstract: Addition of vinylmagnesium bromide on the per-benzylated glucono-1,5-lactone gave, after reduction with $Et_3SiH/BF_3{\cdot}Et_2O$, a mixture of the desired *β*-*C*-vinyl glucoside **1** and the unexpected *β*-*C*-but-3-enyl glucoside **3** resulting from double addition of vinylmagnesium bromide on the lactone. Similar results have been obtained with the per-benzylated galactono-1,5-lactone. This side reaction was then been explored to prepare *β*-*C*-but-3-enyl glycosides and other *β*-*C*-glycosyl derivatives by employing different Grignard reagents. An alternative approach to the per-benzylated glycosylethenes has been studied and compared.

Glycosylethenes (e.g. (2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl)ethene, **1**) are versatile synthetic intermediates which have been used for the synthesis of *C*-glycosyl amino acids[1,2] and carbasugars.[3] During the course of studies on the synthesis of sugar amino acids, we needed to prepare the *β*-*C*-vinyl compound **1** that could be readily transformed into desired sugar amino acid derivatives.[4]

The first synthesis of this compound was reported by Kraus and Molina, by treating the per-benzylated lactone **2** with 1.5 equiv of vinylmagnesium bromide at −78 °C followed by reduction with Et_3SiH and $BF_3{\cdot}Et_2O$, in 60% yield with two steps (Scheme 1).[5] However, this reaction was found quite tricky in our hands. Our first attempt using the described procedure led to two products: the desired *β*-*C*-vinyl compound **1** together with the *β*-*C*-but-3-enyl derivative **3** in 32.6% and 17.9% isolated yield (Table 1, entry 2). The physical and spectral properties of **3** were essentially identical with those reported, since compound **3** has already been prepared by nucleophilic addition of but-3-enylmagesium bromide on the lactone **2** followed by reduction.[6,7] It is to be noticed that Dondoni and colleagues have obtained the same yield of **1** (32.5%) using similar reaction conditions.[1] Nevertheless, the formation of **3** has never been reported under these conditions.

SCHEME 1

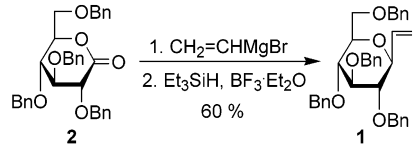
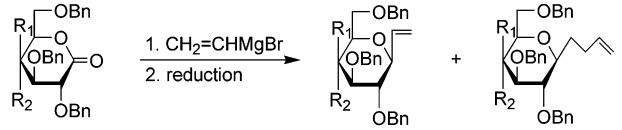


TABLE 1.



2 R_1=H, R_2=OBn
4 R_1=OBn, R_2=H

1 R_1=H, R_2=OBn
5 R_1=OBn, R_2=H

3 R_1=H, R_2=OBn
6 R_1=OBn, R_2=H

			products (yield)	
entry	lactone	CH_2=CHMgBr (equiv)	mono-adduct (**1**,**5**)	bis-adduct (**3**,**6**)
1	**2**	1.2	**1** (49.3%)	**3** (13.8%)
2	**2**	1.5	**1** (32.6%)	**3** (17.9%)
3	**2**	4		**3** (89%)
4	**4**	1.2	**5** (50%)	
5	**4**	1.5	**5** (25%)	**6** (28.4%)
6	**4**	4		**6** (47%)

To improve the yield of the desired product **1**, we tried to modify the reaction conditions. The **1**/**3** ratio was insensitive to the reaction concentration. Raising the reaction temperature led to a complex mixture. When conducted at lower temperature (−100 °C), the reaction was extremely slow, and the majority of the starting lactone was recovered. The best yield of **1** (49.3%) was obtained with 1.2 equiv of nucleophile, along with 13.8% of **3** (entry 1). A lower conversion of the starting lactone was observed when using <1.2 equiv of vinylmagnesium bromide. When the reaction was conducted with 4 equiv of vinylmagnesium bromide, compound **3** was isolated exclusively in 89% yield (entry 3).

The formation of **3** resulted from two additions of vinylmagnesium bromide on the lactone **2** (Figure 1): the first addition led to the deprotonated hemiketal **A**, which is in equilibrium with the enone **B**; the second underwent either a Michael fashion or a S_N 2′ mechanism and furnished the hydroxy enone or the hemiketal **7** after hydrolysis.

To check this hypothesis, we then tried to trap the postulated intermediates with other nucleophiles. Lactone **2** was first treated with 1.2 equiv of vinylmagnesium bromide over 2.5 h at −78 °C, followed by addition of 4 equiv of phenylmagnesium bromide (2.5 h at −78 °C). Reduction of the obtained hemiketal with TMSOTf/Et_3-SiH afforded the desired compound **8** in 70% yield (Scheme 2). However, all attempts to react the protonated hemiketal **A** (compound **11**, Scheme 3) with vinylmagnesium bromide failed (use of excess of nucleophile, activation with *n*BuLi or Na, etc.). This might be due to the difference of the lactol stereocenter of the deprotonated hemiketal **A**, formed probably by an α-attack of the nucleophile on the lactone, with the protonated (and also equilibrated) form **11** where the hydroxy group prefers the α position. Although the formation of enone

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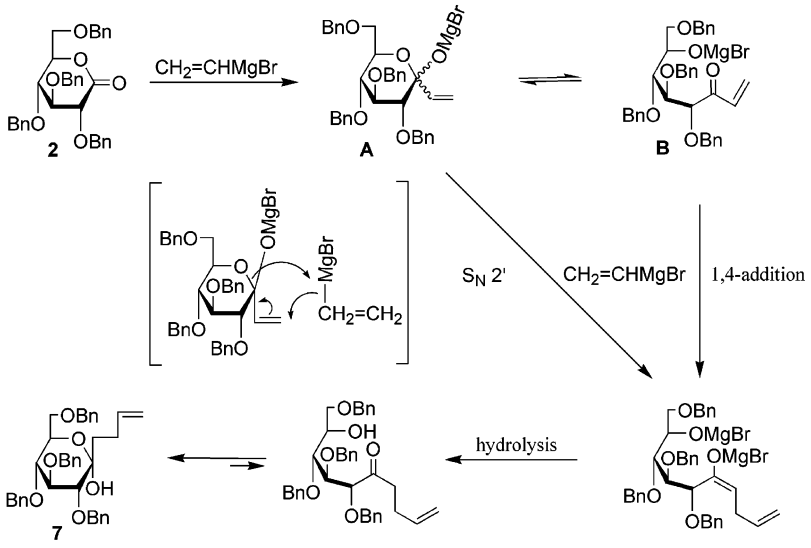
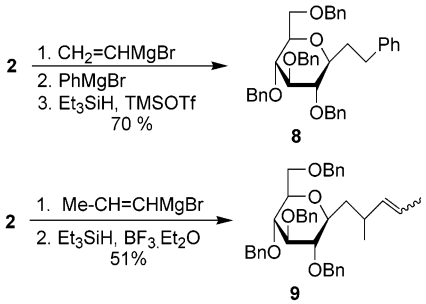
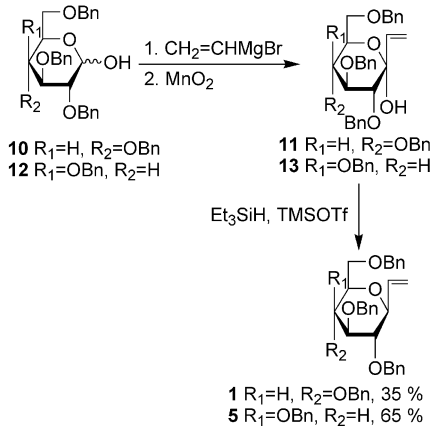


FIGURE 1. Proposed mechanism for the formation of the hemiketal **7**.

SCHEME 2



SCHEME 3



by double addition of vinylmagnesium bromide to esters has already been reported,[8] to the best of our knowledge, this is the first report of formation of this kind of product in the case of sugar lactone. We have therefore explored the scope of this reaction. Treatment of **2** with 4 equiv of prop-1-enylmagnesium bromide under the same condition also furnished the product of double addition: compound **9** was isolated in 51% yield as a mixture of four diastereoisomers (Scheme 2). Similar results were obtained with the galactonolactone **4**. As shown in Table 1, treatment of lactone **4** with 1.5 equiv of vinylmagnesium bromide gave, after reduction, 25% of **5** (product of single addition) and 28.4% of **6** (product of double addition) (entry 5). Use of 1.2 equiv of nucleophile led to the *β*-*C*-vinyl galactoside **5** in 50% yields (entry 4). The known compound **6**, already prepared by addition of but-3-enylmagesium bromide on lactone **4**,[9,10] has been obtained in 47% yield by using 4 equiv of vinylmagnesium bromide (entry 6).

To avoid the formation of bis-adduct, we decided to follow a different synthetic approach. In fact, Nakai and colleagues have recently reported the synthesis of the hemiketal **11** from the per-benzylated D-glucose **10** in 97% yield (Scheme 3).[11] Their strategy implied the addition of vinylmagnesium bromide on **10**, followed by oxidation of the so-formed allylic alcohol with MnO_2. Following this procedure, we have observed that the oxidation step is very slow (more than one week's reaction) and a large excess of oxidant (three times in weight) is needed. Reduction of the crude hemiketal **11** with $Et_3SiH/BF_3{\cdot}Et_2O$ (or TMSOTf) afforded compound **1** contaminated by an unidentified byproduct with similar polarity. This has made the purification of **1** extremely difficult. Compound **1** was isolated only in 35% total yield. In the case of the *galacto* derivative, this reaction sequence worked better: compound **5** was isolated in 65% overall yield, without any difficulty of purification.

In summary, we have demonstrated that nucleophilic addition of vinylmagnesium bromide on the per-benzylated glycono-1,5-lactones led to the formation of double conjugated addition product, along with the desired single addition product. The reaction conditions have then been

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optimized to prepare the per-benzylated glycosylethenes **1** and **5**. The second method explored, through an alternative approach to the intermediate hemiketals **11** and **13**, afforded a better result only for compound **5** (65% total yield instead of 50%). The observed side reaction with vinylmagnesium bromide has been successfully explored to prepare the *β*-*C*-but-3-enyl glycosides and other *β*-*C*-glycosides.

Experimental Section

General Comments. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution. All assignments were confirmed by ^{1}H/^{1}H, ^{1}H/^{13}C correlations, and Dept 135. Column chromatography was performed on E. Merck Silica Gel 60 (230−400 mesh). Analytical thin-layer chromatography was performed on E. Merck aluminum percolated plates of Silica Gel 60F-254 with detection by UV and by spraying with 6 N H_2SO_4 and heating about 2 min at 300 °C. Dichloromethane was distilled over CaH_2. THF was distilled over sodium and benzophenone prior to use.

General Procedure for the Preparation of *β*-*C*-Alkenyl Glycosides (1, 3, 5, 6, and 9) by Addition of Organomagnesium Reagent on the Lactone. To a cold (−78 °C) solution of lactone **2** or **4** (0.25 mmol) in THF (2.5 mL) under an argon atmosphere was added dropwise the corresponding commercially available organomagnesium reagent. After 2.5 h of stirring at −78 °C, the reaction mixture was quenched with saturated NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give the corresponding hemiketal. To a cooled (−40 °C) solution of the hemiketal in anhydrous acetonitrile (or dichloromethane when TMSOTf was used) (1 mL) were added triethylsilane (3 equiv) and boron trifluoride−diethyl ether (1 equiv) or TMSOTf (0.2 equiv). The solution was stirred 10 to 30 min at −40 °C (monitoring by TLC), then quenched with saturated K_2CO_3 and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by preparative thin-layer chromatography (1:4 Et_2O/cyclohexane) afforded the corresponding *β*-*C*-glycoside.

(2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranosyl)ethene (1): mp 72−73 °C, $[\alpha]_D$ +33 (*c* 1, CH_2Cl_2) [lit.[1] mp 68−69 °C, $[\alpha]_D$ +28 (*c* 0.2, $CHCl_3$)].

1-(2′,3′,4′,6′-Tetra-*O*-benzyl-*β*-D-glucopyranosyl)-3-butene (3): mp 83−84 °C, $[\alpha]_D$ +6.2 (*c* 1, CH_2Cl_2) [lit.[7] mp 83−84 °C, $[\alpha]_D$ +3 (*c* 1.2, $CHCl_3$)].

(2,3,4,6-Tetra-*O*-benzyl-*β*-D-galactopyranosyl)ethene (5): oil, $[\alpha]_D$ +19.2 (*c* 1.3, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) *δ* 3.52−3.64 (m, 3 H), 3.70−3.74 (m, 2 H), 3.96 (d, 1 H, *J* = 2.8 Hz), 4.41 (dd, 2 H, *J* = 11.8, 15.5 Hz), 4.60−4.96 (m, 6 H), 5.25 (dd, 1 H, *J* = 1.5, 10.5 Hz), 5.40 (dd, 1 H, *J* = 1.5, 17.3 Hz), 5.89−5.95 (m, 1 H), 7.21−7.36 (m, 20 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) *δ* 67.0, 72.6, 73.6, 74.0, 74.6, 75.4, 76.9, 79.0, 80.8, 84.4, 118.4, 127.6, 127.7, 127.8, 128.3, 128.4, 128.5, 135.5, 138.0, 138.4, 138.6, 138.9. Anal. Calcd for $C_{36}H_{38}O_5$: C, 78.51; H, 6.97. Found: C, 78.42; H, 7.06.

1-(2′,3′,4′,6′-Tetra-*O*-benzyl-*β*-D-galactopyranosyl)-3-butene (6): mp 54−56 °C, $[\alpha]_D$ +2.2 (*c* 1, $CHCl_3$) [lit.[10] $[\alpha]_D$ −2.0 (*c* 1, $CHCl_3$)]; ^{1}H NMR (250 MHz, $CDCl_3$) *δ* 1.43−1.57 (m, 1 H), 1.78−1.91 (m, 1 H), 1.92−2.27 (m, 2 H), 3.14 (td, 1 H, *J* = 2.5, 9.3 Hz), 3.39−3.63 (m, 5 H), 3.89 (d, 1 H, *J* = 2.5 Hz), 4.33 and 4.40 (2d, 2 H, *J* = 11.8 Hz), 4.53−4.69 (m, 4 H), 4.83−4.94 (m, 4 H), 5.65−5.82 (m, 1 H), 7.14−7.31 (m, 20 H). ^{13}C NMR (62.9 MHz, $CDCl_3$) *δ* 29.9, 31.1, 69.2, 72.3, 73.6; 73.8, 74.5, 75.6, 77.2, 79.1, 79.3, 85.0, 114.7, 127.7, 127.8, 128.0, 128.2, 128.3, 128.5, 138.1, 138.5, 138.6, 138.9.

2-Methyl-1-(2′,3′,4′,6′-tetra-*O*-benzyl-*β*-D-glucopyranosyl)-3-pentene (9): 51% of a mixture of four diastereoisomers. Further purification by preparative thin-layer chromatography (3:2 CH_2Cl_2/cyclohexane) allowed the separation into two major isomers **9a** and **9b**. **9a**: R_f 0.32 (3:2 CH_2Cl_2/cyclohexane), mp 78−80 °C; ^{1}H NMR (250 MHz, $CDCl_3$) *δ* 0.91 (d, 3 H, *J* = 6.8 Hz), 1.35−1.61 (m, 2 H), 1.51 (dd, 3 H, *J* = 1.8, 6.8 Hz), 2.80−2.90 (m, 1 H), 3.13−3.28 (m, 3 H), 3.58−3.66 (m, 4 H), 4.45−5.06 (m, 8 H), 4.97−5.06 (m, 1 H), 5.34−5.41 (m, 1 H), 7.21−7.29 (m, 20 H). ^{13}C NMR (62.9 MHz, $CDCl_3$) *δ* 13.0, 21.9, 27.5, 39.3, 69.0, 73.6, 75.0, 75.3, 75.7, 78.7, 78.9, 82.8, 87.5, 123.7, 127.8, 128.0, 128.1, 128.6, 136.1, 138.4, 138.8, 159.4. **9b**: R_f 0.27 (3:2 CH_2Cl_2/cyclohexane), mp 58−60 °C; ^{1}H NMR (250 MHz, $CDCl_3$) *δ* 0.94 (d, 3 H, *J* = 6.5 Hz), 1.33−1.70 (m, 2 H), 1.56 (dd, 3 H, *J* = 1.0, 6.3 Hz), 2.72−2.88 (m, 1 H), 3.20−3.40 (m, 3 H), 3.58−3.68 (m, 4 H), 4.53−4.62 (m, 4 H), 4.77−4.85 (m, 4 H), 5.13−5.38 (m, 2 H), 7.21−7.31 (m, 20 H). ^{13}C NMR (62.9 MHz, $CDCl_3$) *δ* 13.1, 20.1, 27.6, 39.3, 69.2, 73.6, 75.1, 75.4, 75.7, 77.3, 78.8, 79.2, 83.0, 87.6, 122.1, 127.8, 127.9, 128.1, 128.6, 137.4, 138.4, 138.8, 159.2. Anal. Calcd for $C_{40}H_{46}O_5$: C, 77.18; H, 7.64. Found: C, 77.36; H, 7.55.

1-(2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranosyl)-2-phenylethane (8). To a cold (−78 °C) solution of lactone **2** (135 mg, 0.25 mmol) in THF (2.5 mL) under an argon atmosphere was added dropwise vinylmagnesium bromide (1 M solution in THF, 300 *μ*L, 0.3 mmol). After 2.5 h of stirring at −78 °C, phenylmagnesium bromide (1 M solution in THF, 1 mL, 1 mmol) was added and the reaction was continued over 2.5 h at −78 °C. The reaction mixture was then quenched with saturated NH_4Cl and treated as described in the general procedure. The corresponding hemiketal was reduced with 3 equiv of Et_3SiH and 0.6 equiv of TMSOTf as described in the general procedure to afford, after purification by preparative thin-layer chromatography (1:4 Et_2O/cyclohexane), 110 mg of a white solid: 70%, mp 90−91 °C, $[\alpha]_D$ −8.3 (*c* 0.7, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) *δ* 1.83−1.93 (m, 1 H), 2.16−2.26 (m, 1 H), 2.72−2.85 (m, 1 H), 2.91−3.00 (m, 1 H), 3.28−3.50 (m, 3 H), 3.69−3.88 (m, 4 H), 4.64−4.78 (m, 4 H), 4.90−4.97 (m, 4 H), 7.22−7.45 (m, 25 H). ^{13}C NMR (62.9 MHz, $CDCl_3$) *δ* 31.8, 33.5, 69.2, 73.6, 75.1, 75.4, 75.7, 78.4, 78.8, 79.0, 82.6, 87.4, 125.9, 127.7, 127.9, 128.0, 128.1, 128.5, 128.6, 128.7, 138.2, 138.3, 138.7, 142.2. Anal. Calcd for $C_{42}H_{44}O_5$: C, 80.23; H, 7.05. Found: C, 80.08; H, 7.19.

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