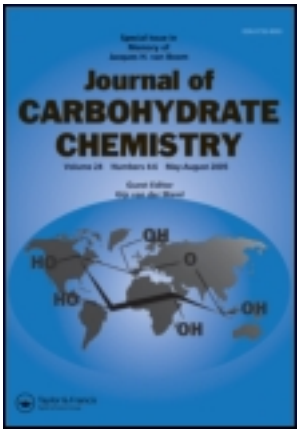

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Microwave-Assisted Regioselective Benzylation: An Access to Glycal Derivatives with a Free Hydroxyl Group at C4

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D-glucal, D-galactal, and their 6-O-TBDMS derivatives were benzylated in a two-step procedure under microwave conditions. In the first step glycals were converted into dibutylstannylene acetal or tributyltin ether intermediates, which were next alkylated with benzyl bromide in the presence of Bu_4NBr. In all cases the 4-OH group stayed unsubstituted. Microwave-assisted benzylation contributes to a significant reduction of the reaction time in comparison with the classical synthesis, which requires several hours of heating. *Supplemental materials are available for this article. Go to the publisher's online edition of* Journal of Carbohydrate Chemistry *to view the free supplemental file.*

Keywords Glycals; Regioselective benzylation; Microwave irradiation

INTRODUCTION

Glycals are versatile synthetic intermediates for the preparation of 2-deoxyglycosides and 2,3-unsaturated glycosides that can be easily functionalized at the C-2 and C-3 positions.[1–4] The utilization of glycals as the building blocks for the total synthesis of various natural products is of great interest in bioorganic and medicinal chemistry. Perbenzylated glycals are readily

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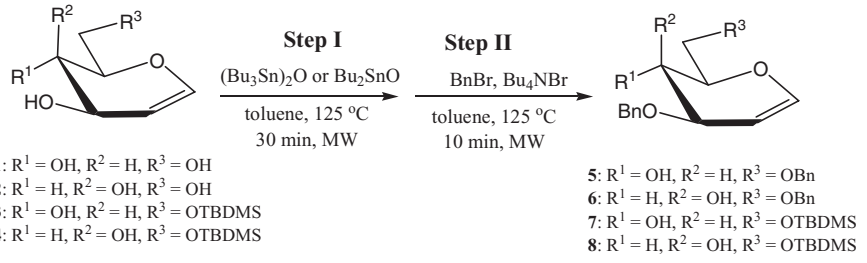
available substrates[5] that can be employed as glycosyl donors. More complex is the regioselective functionalization of the hydroxyl groups in glycals affording valuable glycosyl acceptors. Among them, the derivatives of D-glucal and D-galactal possessing a free hydroxyl group at C-4 are important substrates. The synthesis of di-O-benzylated D-glucal and D-galactal derivatives in a direct benzylation with BnBr in DMF/NaH leads preferentially to 4,6-di-O-benzyl products and per-O-benzylated glycals. For example, the yield of 3,6-di-O-benzyl-D-galactal as a minor product is in the range 8%–20%.[6] The synthesis of 3,6-di-O-benzyl-D-glucal has recently been accomplished via 4,6-O-p-methoxybenzylidene acetal in 61% yield in four steps.[7] In order to eliminate the multistep synthesis and improve the yield of 3,6-substituted glycals, a selective enhancement of the nucleophilicity of the 3-OH over the 4-OH group is necessary. It is possible to differentiate the reactivity of hydroxyl groups via organotin derivatives: dibutylstannylene acetals[8] and tributyltin ethers.[9] Both strategies have had several successful applications in carbohydrate chemistry. Many examples of regioselective benzylation of hexopyranoses and hexopyranosides after prior conversion to dibutylstannylene acetal[10] and tributyltin ether[11] intermediates have been reported. Among many successful regioselective benzylations, a preparative utilization of stannyl ethers and dibutylstannylene acetals of D-glucal[12–14] and D-galactal[15] derivatives and their subsequent benzylation have been reported. Both steps—the regioselective O-stannylation and benzylation—require several hours of heating in reflux to afford mono- or disubstituted D-glucal derivatives as major products. The purpose of the present work is to compare the classical reaction conditions with the microwave irradiation, which has become an emerging technique in organic chemistry and has recently been frequently used in the field of carbohydrate chemistry for protecting group manipulations and glycosidations.[16] Although the microwave-assisted one-pot protocol for the preparation of 3-O-alkylated galactosides using stannylene acetal chemistry has been described,[17] no report on microwave-assisted alkylation of glycals is available.

In this study, we used microwave irradiation in the tin-mediated two-step synthesis of mono- and dibenzylated glycals (Sch. 1). In our initial microwave-assisted experiments D-glucal (**1**) was transformed into



Scheme 1: Microwave-assisted regioselective benzylation of glycals **1**–**4**.

Table 1: Microwave-assisted regioselective dibenzylation of D-glucal (**1**) upon activation with $(Bu_3Sn)_2O$

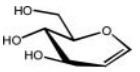
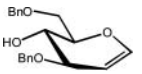
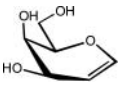
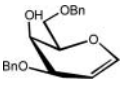
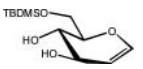
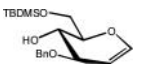
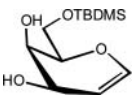
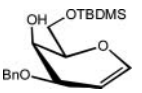
	Step I				Step II				
Entry	Temp. (°C)	Power (W)	Time* (min)	Program type	Temp. (°C)	Power (W)	Time* (min)	Program type	Yield (%)
1	125	17	30	Conventional	125	1–2	20	Conventional	0
2	125	100	60	Power cycling	125	60	30	Power cycling	38
3	125	150	30	Power cycling	80	100	15	Power cycling	41
4	125	150	30	Power cycling	125	100	10	Power cycling	51**
5	80	150	30	Power cycling	125	100	10	Power cycling	10
6	125	150	15	Power cycling	125	100	10	Power cycling	27

*Effective time of specified microwave energy.
**59% in the classical synthesis.[13a]

3,6-di-O-benzyl-D-glucal (**5**) (Table 1). Thus, stannylation of D-glucal **1** with 1.05 equiv. of bis(tributyltin)oxide and subsequent treatment of the stannylated intermediate with 3.4 equiv. of benzyl bromide in the presence of Bu_4NBr gave dibenzyl ether **5** as a main product. Reactions were carried out with controlled microwave irradiation under sealed vessel conditions by using the CEM Discover microwave synthesizer in 10 mL glass vessels with stirring in toluene as solvent. The preferred concentration of glycal substrate was 0.5–1.0 mmol/2 mL of toluene. It was found that the microwave-assisted benzylation cannot be carried out in a solvent-free manner or in more concentrated solutions. In both cases 2-(1′-hydroxy-2′-benzyloxyethyl)furan was formed as a major product (^{1}H NMR[18a,b] and ^{13}C NMR[18b] spectral data matched those reported).

Based on the results presented in Table 1, it can be concluded that the yield of the reaction depends both on the power level and the reaction time. The typical conventional program based on the reaction temperature was initially applied and the temperature was set to 125°C (Table 1, entry 1). The microwave power levels—17 W in step I and 2 W in step II—were automatically adjusted to maintain the reaction temperature of 125°C. The set values of 150 W in step I and 100 W in step II were never reached. Under these conditions no product was observed. In the following experiments, in order to ensure the required level of microwave power, instead of a conventional program, another power cycling control program was used (Table 1, entries 2–6). It was observed that the repeating cycles of strong microwave could enhance the reaction yields. This observation suggests that microwave is not just a simple heating source and that the power level is the most important parameter. The described increase of the reaction yield with the microwave power level under a controlled temperature indicates a possibility of the existence of a nonthermal microwave effect, which is in accordance with published reports.[19] The reaction time depended on the applied microwave power and temperature, and in the optimal

Table 2: Microwave-assisted regioselective benzylation of glycal derivatives **1**–**4**

Entry	Substrate	Product	Organotin compound	Yield (%)
1			$(Bu_3Sn)_2O$	51
2	**1**	**5**	Bu_2SnO	44
3			$(Bu_3Sn)_2O$	59
4	**2**	**6**	Bu_2SnO	52
5			$(Bu_3Sn)_2O$	54
6	**3**	**7**	Bu_2SnO	50
7			$(Bu_3Sn)_2O$	71
8	**4**	**8**	Bu_2SnO	61

case was set to 30 min in the O-stannylation step (150 W, 125°C) and 10 min in the benzylation step (100 W, 125°C). The yield of 3,6-di-O-benzyl-D-glucal (**5**) was comparable to the classical method[13a] (Table 1, entry 4) and was chosen for further experiments on regioselective benzylation of glycals **2**–**4**. The overall yields obtained are presented in Table 2.

Benzylated glycals **5**–**8** were purified by column chromatography and their structures were elucidated with the aid of ^1H and ^{13}C NMR spectroscopy data (including two-dimensional HSQC, HMBC experiments, and simulation analysis) and mass spectrometry analysis (for details see the experimental section). In all cases 4-OH groups stayed unsubstituted, which was confirmed by the acetylation of glycals **5**–**8** and the comparison of chemical shifts of H-4 protons. The H-4 protons of 4-O-acetylated products resonated at lower fields than the H-4 protons in glycals with free 4-OH groups. ^1H NMR spectral data for 4-O-acetyl-3,6-di-O-benzyl-D-glucal[20] and 4-O-acetyl-3,6-di-O-benzyl-D-galactal[21] matched those reported.

EXPERIMENTAL

General Methods

NMR spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Varian spectrometer at a frequency of 600 MHz. NMR simulation analysis

was performed using MestReNova software.[22] Optical rotations were measured with a P-2000 Jasco polarimeter using a sodium lamp (589 nm) at rt. Mass spectra were recorded in the positive mode on a Mariner (Perseptive Biosystem) detector using the electrospray-ionization (ESI) technique. The experiments were performed in 10 mL vessels in a CEM Discover microwave synthesizer interfaced with a personal computer. The synthesizer was connected to an air compressor system (1.5 atm) that automatically provided cooling and assisted the microwave power tuning in order to not significantly overcome the maximum set temperature. TLC was performed on precoated plates of silica gel G (Merck); components were detected by charring with 10% sulfuric acid in ethanol. Column chromatography was performed on silica gel 60 (70–230 mesh, E. Merck) developed with hexane/EtOAc solvent systems. All evaporations were performed under diminished pressure at 50°C.

General Procedure for Microwave-Assisted Benzylation

General Procedure for Dibenzylation

Glycal **1** or **2** (0.68 mmol) was suspended in toluene (2 mL) and Bu_2SnO or $(Bu_3Sn)_2O$ was added (1.05 equiv). The mixture was exposed to microwave irradiation at 125°C and 30 min (power cycling, 150 W, 60 cycles) was required to obtain a homogenous light yellow solution (Table 1, Step I, entry 4). Then benzyl bromide (3.4 equiv.) and Bu_4NBr (2 equiv.) were added and the mixture was irradiated again at 125°C and 10 min (power cycling, 100 W, 30 cycles) (Table 1, Step II, entry 4). The reaction mixture was diluted with toluene (50 mL), washed with water (3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated to give crude products. Crude products were purified by column chromatography on silica gel with the hexane/ethyl acetate system 10:1 → 6:1 and yielded **5** or **6** as colorless oils in the amounts presented in Table 2.

General Procedure for Monobenzylation

Glycal **3** or **4** (0.68 mmol) was suspended in toluene (2 mL) and Bu_2SnO or $(Bu_3Sn)_2O$ was added (1.05 equiv). The mixture was exposed to microwave irradiation at 125°C and 30 min (power cycling, 150 W, 60 cycles) was required to obtain a homogenous light yellow solution (Table 1, Step I, entry 4). Then benzyl bromide (1.7 equiv.) and Bu_4NBr (1 equiv.) were added and the mixture was irradiated again at 125°C and 10 min (power cycling, 100 W, 30 cycles) (Table 1, Step II, entry 4). The reaction mixture was diluted with toluene (50 mL), washed with water (3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated to give crude products. Crude products were purified by column chromatography on silica gel with the hexane/ethyl acetate

system 20:1 → 10:1 and yielded **7** or **8** as colorless oils in yields presented in Table 2.

1,5-Anhydro-3,6-di-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enopyranose (3,6-di-*O*-benzyl-D-glucal) (5)

$[\alpha]_D^{22}$ −22.7 (*c* 1.0, $CHCl_3$), lit.[13a] $[\alpha]_D^{23}$ −25.0 (*c* 5.7, $CHCl_3$), lit.[12a] $[\alpha]_D$ −32.2 (*c* 2.5, $CHCl_3$). ^{1}H NMR and ^{13}C NMR ($CDCl_3$) spectral data matched those reported.[12a,13a]

1,5-Anhydro-3,6-di-*O*-benzyl-2-deoxy-D-*lyxo*-hex-1-enopyranose (3,6-di-*O*-benzyl-D-galactal) (6)

$[\alpha]_D^{22}$ −14.9 (*c* 1.3, $CHCl_3$), lit.[15] $[\alpha]_D^{23}$ −21.5 (*c* 2.6, $CHCl_3$). ^{1}H NMR and ^{13}C NMR ($CDCl_3$) spectral data matched those reported.[15]

1,5-Anhydro-3-*O*-benzyl-6-*O*-*tert*-butyldimetylsilyl-2-deoxy-D-*arabino*-hex-1-enopyranose (3-*O*-benzyl-6-*O*-*tert*-butyldimetylsilyl-D-glucal) (7)

$[\alpha]_D^{25}$ −9.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 7.374 (ddd, 2H, J = 7.5, 1.7, 1.7 Hz, CH_2Ph, H_{orto}), 7.342 (ddd, 2H, J = 7.5, 7.2, 1.7 Hz, CH_2Ph, H_{meta}), 7.279 (dddd, J = 7.2, 7.2, 1.7, 1.7 Hz, 1H, CH_2Ph, H_{para}), 6.339 (dd, J = 6.1, 1.6 Hz, 1H, H-1), 4.805 (dd, J = 6.1, 2.2 Hz, 1H, H-2), 4.701, 4.661 (ABq, J = 11.8 Hz, 2H, CH_2Ph), 4.106 (ddd, J = 6.9, 2.2, 1.6 Hz, 1H, H-3), 3.983 (ddd, J = 9.4, 6.9, 2.8 Hz, 1H, H-4), 3.973 (dd, J = 11.1, 4.5 Hz, 1H, H-6a), 3.900 (dd, J = 11.1, 4.7 Hz, 1H, H-6b), 3.802 (ddd, J = 9.4, 4.7, 4.5 Hz, 1H, H-5), 2.855 (d, 1H, J = 2.8 Hz, 4-OH), 0.905 (s, 9H, Si[C(CH_3)$_3$(CH_3)$_2$]), 0.089 (s, 6H, Si[C(CH_3)$_3$(CH_3)$_2$]). ^{13}C NMR: δ 144.524 (C-1), 138.516 (CH_2Ph_q), 128.441, 127.792, 127.669 (5C, CH_2Ph), 100.151 (C-2), 77.323 (C-5), 76.402 (C-3), 71.014 (*C*H$_2$Ph), 69.839 (C-4), 63.373 (C-6), 25.891 (3C, Si[C(*C*H$_3$)$_3$(CH_3)$_2$]), 18.338 (Si[*C*(CH_3)$_3$(CH_3)$_2$]), −5.373, −5.427 (2C, Si[C(CH_3)$_3$(*C*H$_3$)$_2$]). ESI-HRMS: Calcd for $C_{19}H_{30}O_4SiNa$ ([M+Na]$^+$): m/z 373.1811, found: m/z 373.1802.

Acetylation of **7** (0.2 mmol) with acetic anhydride (40 μL) in pyridine (0.5 mL) for 18 h at rt gave the 4-O-acetyl derivative as an oil. ^{1}H NMR: δ 7.400–7.270 (m, 5H, CH_2Ph), 6.440 (dd, J = 6.3, 1.2 Hz, 1H, H-1), 5.307 (ddd, J = 5.2, 4.2, 1.0 Hz, 1H, H-4), 4.863 (ddd, J = 6.3, 3.9, 1.0 Hz, 1H, H-2), 4.620, 4.600 (ABq, J = 11.8 Hz, 2H, CH_2Ph), 4.126 (dddd, J = 6.3, 5.2, 4.9, 1.3 Hz, 1H, H-5), 3.916 (dddd, J = 4.2, 3.9, 1.3, 1.2 Hz, 1H, H-3), 3.861 (dd, J = 11.2, 6.35 Hz, 1H, H-6b), 3.832 (dd, J = 11.2, 4.9 Hz, 1H, H-6a), 2.061 (s, 3H, CH_3CO), 0.890 (s, 9H, Si[C(CH_3)$_3$(CH_3)$_2$]), 0.052, 0.043 (2 s, 6H, Si[C(CH_3)$_3$(CH_3)$_2$]).

1,5-Anhydro-3-*O*-benzyl-6-*O*-*tert*-butyldimetylsilyl-2-deoxy-D-*lyxo*-hex-1-enopyranose (3-*O*-benzyl-6-*O*-*tert*-butyldimetylsilyl-D-galactal) (8)

$[\alpha]_D^{25}$ −10.3 (*c* 2.0, $CHCl_3$). ^1H NMR: δ 7.380–7.288 (m, 5H, CH_2Ph), 6.396 (dd, J = 6.3, 1.8 Hz, 1H, H-1), 4.701 (ddd, J = 6.3, 2.0, 2.0 Hz, 1H, H-2), 4.664, 4.622 (ABq, J = 11.81 Hz, 2H, CH_2Ph), 4.209 (dddd, J = 4.4, 2.0, 1.8, 0.4 Hz, 1H, H-3), 4.128 (dddd, J = 4.4, 3.5, 3.0, 2.0 Hz, 1H, H-4), 3.950 (dddd, J = 6.6, 6.4, 3.5, 0.4 Hz, 1H, H-5), 3.851 (dd, J = 11.0, 6.4 Hz, 1H, H-6a), 3.828 (dd, J = 11.0, 6.6 Hz, 1H, H-6b), 2.538 (d, 1H, J = 3.0 Hz , 4-OH), 0.907 (s, 9H, Si[C(CH_3)$_3$(CH_3)$_2$]), 0.095, 0.090 (2 s, 6H, Si[C(CH_3)$_3$(CH_3)$_2$]). ^{13}C NMR: δ 145.004 (C-1), 137.792 (CH_2Ph_q), 128.531, 127.931, 127.807, (5C, CH_2Ph), 99.558 (C-2), 76.643, 71.057, 70,477, 62,447, 62,111 (5C, C-3, C-4, C-5, C-6, CH_2Ph), 25.919 (3C, Si[C(CH_3)$_3$(CH_3)$_2$]), 18.377 (Si[C(CH_3)$_3$(CH_3)$_2$]), −5.371, −5.397 (2C, Si[C(CH_3)$_3$(CH_3)$_2$]). ESI-HRMS: Calcd for $C_{19}H_{30}O_4SiNa$ ($[M+Na]^+$): m/z 373.1811, found: m/z 373.1780.

Acetylation of **8** (0.2 mmol) with acetic anhydride (40 μL) in pyridine (0.5 mL) for 18 h at rt gave the 4-O-acetyl derivative as an oil. ^1H NMR: δ 7.345–7.250 (m, 5H, CH_2Ph), 6.375 (dd, J = 6.3, 2.0 Hz, 1H, H-1), 5.606 (ddd, J = 4.2, 1.7, 1.3 Hz, 1H, H-4), 4.696, 4.502 (ABq, J = 11.8 Hz, 2H, CH_2Ph), 4.737 (ddd, J = 6.3, 1.9, 1.7 Hz, 1H, H-2), 4.253 (ddd, J = 4.2, 2.0, 1.9 Hz, 1H, H-3), 4.033 (dddd, J = 7.1, 6.2, 1.3, 0.9 Hz, 1H, H-5), 3.766 (dd, J = 10.2, 6.2 Hz, 1H, H-6a), 3.684 (dd, J = 10.2, 7.1, 1H, H-6b), 2.134 (s, 3H, CH_3CO), 0.901 (s, 9H, Si[C(CH_3)$_3$(CH_3)$_2$]), 0.066, 0.062 (2 s, 6H, Si[C(CH_3)$_3$(CH_3)$_2$]).

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