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STEREOSELECTIVE *C*-ALLYLATION OF 1-*C*-ALKYL-2,3,4,6-TETRA-*O*-BENZYL-D-GLUCOPYRANOSES WITH ALLYLTRIMETHYLSILANE

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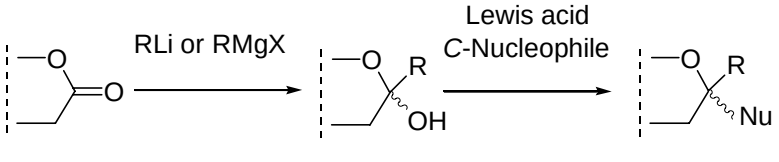
Abstract-The reaction of 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyanoses with allyltrimethylsilane in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate gave the corresponding *C*-allylated *C*-alkyl glucopyranosides in good yields. This *C*-allylation proceeded with high α-stereoselectivity.

The study of *C*-glycosides has become very significant in the fields of carbohydrate chemistry and biochemistry.[1] Much effort is currently being devoted to the formation reactions of a carbon-carbon bond at the anomeric carbon centers of the carbohydrates. Some of the reactions involved the synthesis of the *C,C*-dialkyl substituted glycosylic compounds with tertiary anomeric carbons,[2] which are of potential interest as subunits of a variety of naturally occurring products[3] and as chiral intermediates in organic chemistry.[4] The synthetic approaches for *C,C*-dialkyl glycosides reported so far are the sequential electrophilic and nucleophilic alkylation reaction to glycals,[5] the reaction of methyl keto-furanosides with allyltrimethylsilane using Lewis acid reagents,[3,6] the radical additions of acrylonitrile to nitro sugars[7] and allyltributyltin to dihalogeno sugars,[8] the Wittig reaction of ketose,[9] and the pinacol-like 1,2-migration of glycal-derived carbinols.[10] However, there have been no reports of convenient methods which can use easily available sugar derivatives as glycosyl donors and synthesize *C,C*-dialkyl glycosides having various kinds of alkyl groups at their anomeric carbon centers.

Our synthetic route for the *C,C*-dialkyl glycosides, shown in Scheme 1, makes it possible to modify their anomeric carbons with a variety of alkyl groups. It needs only two steps to introduce two alkyl groups at the anomeric carbons from the sugar lactones. The first step is the preparation of the sugar lactols (1-*C*-alkyl sugars), which have one carbon-carbon bond formation at the anomeric carbon centers, by the well-established addition of RLi or RMgX reagent to the sugar lactones.[11] The second step is the



R=alkyl

Scheme 1.

formation of another carbon-carbon bond at the anomeric carbons by the *C*-glycosylation of 1-*C*-alkyl sugars using *C*-nucleophiles. The Lewis acid catalyzed *C*-glycosylations using *C*-nuclephiles generally needed to synthesize the glycosyl donors having leaving groups or convert the anomeric hydroxyl group to other leaving groups in the reaction systems. We expected that the glycosyl cation intermediates would be stably produced from 1-*C*-alkyl sugars due to the effect of the structure-specific tertiary anomeric carbon centers, and attempted a novel approach for the second step, which can use the anomeric hydroxyl group of 1-*C*-alkyl sugars as the leaving group. Furthermore, since few reports discussed the influence of the functional groups at the anomeric position,[1,3,6] we examined the effect of the different alkyl groups at the anomeric position toward glycosylations. In this paper, as a useful method of the *C*-glycosylation in the second step, we describe the *C*-allylation of 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoses using allyltrimethylsilane as a *C*-nucleophile in detail.

First, we used 2,3,4,6-tetra-*O*-benzyl-1-*C*-methyl-D-glucopyranose (**1**), which was prepared by the reaction of methyllithium with 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was then used as the Lewis acid reagent of **1** to synthesize the *C*, *C*-dialkyl glucopyranosides by the reaction between **1** and allyltrimethylsilane. The desired *C*-allylated *C*-alkyl glucopyranoside (**2**) was obtained in 49 % yield by the reaction of **1** with 2 equiv. of allyltrimethylsilane using 10 mol % TMSOTf in CH_2Cl_2 at –10 ºC in the presence of Drierite ($CaSO_4$). However, benzyl 2,3,4,6-tetra-*O*-benzyl-1-*C*- methyl-α-D-glucopyranoside (**3**) was produced in 30% yield as a by-product. It was suggested that compound (**1**) was decomposed under this reaction condition and afforded benzyl alcohol, which worked as the glycosyl acceptor of **1** to afford the *O*-glycoside (**3**). Li *et*

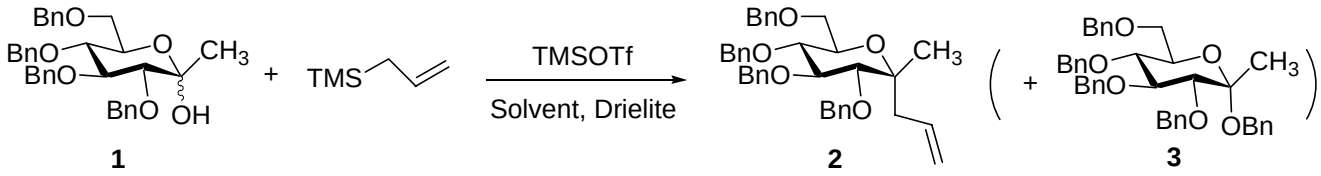


Table 1. The reaction of **1** with allyltrimethylsilane using TMSOTf.

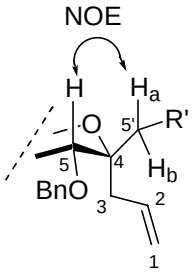
Entry[a]	Solvent	Mol% of TMSOTf	Temp. (ºC)	Yield (%) of **2**	Yield (%) of **3**
1	CH_2Cl_2	10	-10	49	30
2	$(C_2H_5)_2O$	10	-10	trace	25
3	CH_3CN	10	-10	67	15
4	CH_3CN	20	-10	76	9
5	CH_3CN	5	-10	63	9
6	CH_3CN	20	0	69	14
7	CH_3CN	20	-20	79	7
8	CH_3CN	20	-40	84	3
9[b]	CH_3CN	20	-40	40	7
10[c]	CH_3CN	20	-40	88	trace

[a] Molar ratio; **1**:allyltrimethylsilane=1:2. Reaction time; 3 h. [b] The use of 1.5 equiv. of allyltrimethylsilane.
[c] The use of 3 equiv. of allyltrimethylsilane.

al. also found that the by–product (**3**) was produced during the *O*-glycosidation using the derivatives of **1**.[12]

In order to improve the yield of **2**, we examined the solvents, catalytic amounts of TMSOTf, temperatures, and molar ratios in this reaction. As the solvent, Et_2O was totally ineffective, however, the reaction using CH_3CN increased the yield of **2** up to 67% and reduced the production of **3** to 15% yield. It was postulated that CH_3CN influenced the Lewis acidity of TMSOTf and accelerated the formation of the oxonium ion due to the association of the solvent.[13] During the investigation of the catalytic amounts of TMSOTf, the use of 20 mol% TMSOTf improved the yield of **2** up to 76%, while the reaction using only 5 mol% TMSOTf gave **2** in 63% yield. The temperature had an important effect upon the production of **2** and the by-product (**3**). The reaction conditions at –40 ºC gave **2** in 84% yield. The amount of allyltrimethylsilane influenced the yield of **2**. The use of 1.5 equiv. of allyltrimethylsilane gave **2** in low yield, while the use of 3 equiv. of allyltrimethylsilane slightly increased the yield to 88% in comparison with the reaction using 2 equiv. of allyltrimethylsilane. These results are summarized in Table 1.

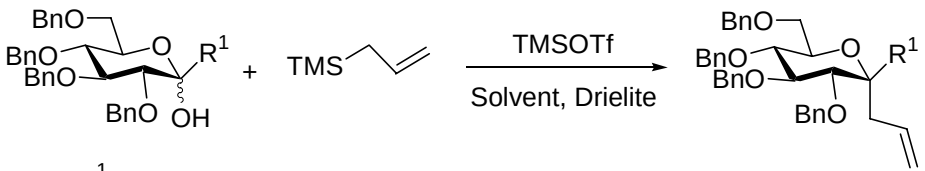
The measurement of NMR spectrum of **2** indicated that **2** was obtained only with a single isomer in these reactions and an NOE interaction between H-5' and H-5 was observed as shown in Figure 1. The nucleophilic attack of allyltrimethylsilane stereoselectively took place from the axial direction.[14] It was reported that the *C*-allylations of the 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose derivatives with allyltrimethylsilane using Lewis acids predominantly gave the *C*-allyl α–glucopyranoside.[13,14] Moreover, we found that the 1-*C*-methyl groups of **1** played an important role in the appearance of the higher α-stereoselectivity.



2: R'= -H
8: R'=-CH_3
11: R'=-Ph

Figure 1.

Next, we used 2,3,4,6-tetra-*O*-benzyl-1-*C*-ethyl-D-glucopyranose (**4**), 2,3,4,6-tetra-*O*-benzyl-1-*C*-butyl-D-glucopyranose (**5**), 1-*C*-allyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**6**), and 1-*C*-benzyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**7**) as the 1-*C*-alkyl sugars, which were prepared by the reaction of suitable organometallic reagents with glucono-1,5-lactone. We examined the *C*-allylation of **4**-**7** using allyltrimethylsliane in the presence of 20 mol% TMSOTf in CH_3CN at –40 ºC. The *C*-allylated *C*-alkyl glucopyranosides (**8**) and (**9**) were obtained from **4** and **5** in 88 and 88% yields, respectively.



1: R^1= -CH_3
4: R^1= -CH_2CH_3
5: R^1= -$CH_2CH_2CH_2CH_3$
6: R^1= -$CH_2CH{=}CH_2$
7: R^1= -CH_2Ph

2: R^1= -CH_3
8: R^1= -CH_2CH_3
9: R^1= -$CH_2CH_2CH_2CH_3$
10: R^1= -$CH_2CH{=}CH_2$
11: R^1= -CH_2Ph

Table 2. The reaction of 1-*C*-alkyl-D-glucopyranose (**1**, **4**-**7**) with allyltrimethylsilane using TMSOTf.

Entry[a]	1-*C*-alkyl-D-glucopyranose	Solvent	Temp. (°C)	Time (h)	Product	Yield (%)
1	**1**	CH_3CN	-40	3	**2**	88
2	**4**	CH_3CN	-40	3	**8**	88
3	**5**	CH_3CN	-40	2.5	**9**	88
4	**6**	CH_3CN	-40	3	**10**	31
5[b]	**6**	CH_3CN	-40	3	**10**	46
6[b]	**6**	CH_3CN/CH_2Cl_2 (v/v=1/1)	-78	3	**10**	53
7	**7**	CH_3CN	-40	4	**11**	18
8[c]	**7**	CH_3CN	-40	4	**11**	60
9[c]	**7**	CH_3CN/CH_2Cl_2 (v/v=1/1)	-78	6	**11**	61
10[b,c]	**7**	CH_3CN/CH_2Cl_2 (v/v=1/1)	-78	6	**11**	78

[a] Molar ratio; 1-*C*-alkyl-D-glucopyranose: allyltrimethylsilane: TMSOTf=1:3:0.2. [b] The use of 6 equiv. of allyltrimethylsilane. [c] The use of 40 mol% TMSOTf.

Compounds (**4**) and (**5**) indicated almost similar reactivity to **1**, however the *C*-allylation of **6** and **7** proceeded in low yields under this reaction condition. The reactivities of **6** and **7** having unsaturated alkyl groups were different from those of **1**, **4** and **5**, and in the reaction using **6** and **7**, several by-products were produced. Moreover, we examined several different reaction conditions using **6** and **7**, and consequently found the reaction using 6 equiv. of allyltrimethylsilane in CH_2Cl_2-CH_3CN (v/v=1/1) at –78 °C afforded the desired allylated compounds (**10**) and (**11**) in the satisfactory yields of 53 and 78% yields, respectively. Compound (**10**) is a good precursor to synthesize a spiro sugar.[8] These results are shown in Table 2. It was ascertained that compounds (**8**-**11**) were also produced with single isomers based on the NMR spectra and the NOE interactions between H-5 and H_a-5' of **8** and **11** shown in Figure 1, which indicated the α orientation of the allylic substituent.

In summary, as a new synthetic approach to *C*,*C*-dialkyl substituted glycosylic compounds, we have demonstrated the *C*-allylation of 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoses using allyltrimethylsilane and found that the catalytic amount of TMSOTf stereoselectively promoted this *C*-allylation to produce the *C*-allylated *C*-alkyl glycosides in good yields. This *C*-allylation was achieved without introducing any leaving groups to the anomeric hydroxyl group and the differences in the glycosidation reactivity were observed among the various alkyl groups.

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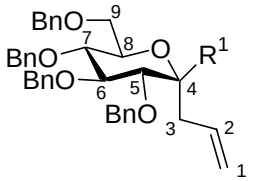
15. A typical experimental procedure is as follows: TMSOTf (7.2 μL, 0.0.4 mmol) was added to a solution of **1** (110 mg, 0.2 mmol) and allyltrimethylsilane (94.7 μL, 0.6 mmol) in CH_3CN (3 mL) at –40 ºC in the presence of $CaSO_4$ (*ca*. 100 mg). The resulting mixture was stirred for 3 h. The reaction was then quenched by the addition of a sat. $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with $CHCl_3$, and the organic layer was washed with water and a sat. NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative silica gel TLC (ethyl acetate/hexane=1/4) to give **2** as a white oil (101 mg, 88%).
16. Compound (**2**): $[\alpha]_D^{22}$=+49.6º (c=2.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (3H, s, H-5'), 2.34 (1H, dd, *J*=7.8, 15.1 Hz, H_a-3), 2.66 (1H, dd, *J*=6.3, 15.1 Hz, H_b-3), 3.37 (1H, d, J=9.3 Hz, H-5), 3.62-3.71 (4H, m, H-7, 8, 9), 3.88 (1H, t, *J*=9.3 Hz, H-6), 4.52-4.93 (8H, m, CH_2Ph), 5.08-5.12 (2H, m, H-1), 5.83 (1H, m, H-2): ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.04 (C-5'), 34.13 (C-3), 69.22 (C-9), 72.25 (C-8), 79.11 (C-7), 77.03 (C-4), 84.01 (C-6), 86.17 (C-5), 117. 84 (C-1), 132.63 (C-2).



2: R^1= -CH_3 (5')

8: R^1= 5' 6'

9: R^1= 5' 7' 6' 8'

10: R^1= 5' 7' 6'

11: R^1= 5' Ph

Compound (**8**): $[\alpha]_D^{22}$=+47.3º (c=4.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, t, *J*=7.4 Hz, H-6'), 1.57 (1H, m, H_a-5'), 1.80 (1H, m, H_b-5'), 2.38 (1H, dd, *J*=7.8, 15.4 Hz, H_a-3), 2.69 (1H, dd, *J*=6.3, 15.4 Hz, H_b-3), 3.60 (1H, t, *J*=9.5 Hz, H-7), 3.64-3.67 (1H, m, H-8), 3.68-3.69 (1H, m, H_a-9), 3.75 (1H, dd, J=4.2, 11.2 Hz, H_b-9), 3.59 (1H, d, *J*=9.5 Hz, H-5), 3.93 (1H, t, *J*=9.5 Hz, H-6), 4.53-4.93 (8H, m, CH_2Ph), 5.08-5.12 (2H, m, H-1), 5.85 (1H, m, H-2): ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.20 (C-6'), 28.49 (C-5'), 34.75 (C-3), 69.37 (C-9), 72.44 (C-8), 79.19 (C-7), 78.13 (C-4), 80.71 (C-5), 84.43 (C-6), 117.69 (C-1), 132.95 (C-2). Compound (**9**): $[\alpha]_D^{22}$=+32.1º (c=5.2, $CHCl_3$); ^{1}H

NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, *J*=6.9 Hz, H-8'), 1.17-1.29 (3H, m, H-7'and H_a-6'), 1.50-1.57 (2H, m, H_b-6' and H_a-5'), 1.67-1.72 (1H, m, H_b-5'), 2.37 (1H, dd, *J*=7.8, 15.4 Hz, H_a-3), 2.68 (1H, dd, *J*=6.3, 15.4 Hz, H_b-3), 3.59 (1H, t, *J*=9.3 Hz, H-7), 3.60 (1H, d, *J*=9.3 Hz, H-5), 3.63-3.65 (1H, m, H-8), 3.65-3.68 (1H, m, H_a-9), 3.74 (1H, dd, *J*=4.1, 11.1 Hz, H_b-9), 3.92 (1H, t, *J*=9.0 Hz, H-6), 4.53-4.92 (8H, m, CH_2Ph), 5.08-5.12 (2H, m, H-1), 5.85 (1H, m, H-2): ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.26 (C-8'), 23.19 (C-7'), 24.92 (C-6'), 34.80 (C-3), 35.77 (C-5'), 69.34 (C-9), 72.41 (C-8), 78.18 (C-4), 79.18 (C-7), 81.26 (C-5), 84.47 (C-6), 117.67 (C-1), 132.96 (C-2). Compound (**10**): $[\alpha]_D^{22}$=+72.6º (c=1.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (1H, dd, *J*=9.4, 14.8 Hz, H_a-5'), 2.31 (1H, dd, *J*=8.1, 15.4 Hz, H_a-3'), 2.51 (1H, dd, *J*=4.6, 14.6 Hz, H_b-5'), 2.63 (1H, dd, *J*=6.1, 15.4 Hz, H_b-3'), 3.50 (1H, t, *J*=9.5 Hz, H-7), 3.53 (1H, d, *J*=9.5 Hz, H-5), 3.57-3.61 (1H, m, H-8), 3.62-3.69 (2H, m, H-9), 3.83 (1H, t, *J*=9.3 Hz, H-6), 4.47-4.84 (8H, m, CH_2Ph), 4.94-5.06 (4H, m, H-1, 7'), 5.74-5.94 (2H, m, H-2, 6'): ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.34 (C-3), 40.69 (C-5'), 69.30 (C-9), 72.57 (C-8), 78.68 (C-4), 79.09 (C-7), 81.31 (C-5), 84.41 (C-6), 117.93 (C-1), 118.14 (C-7'), 132.54 (C-2), 134.35 (C-6'). Compound (**11**): $[\alpha]_D^{22}$=+27.4º (c=3.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.53 (1H, dd, *J*=8.0, 15.3 Hz, H_a-3), 2.79 (1H, d, *J*=14.4 Hz, H_a-5'), 2.81 (1H, dd, *J*=7.8, 14.8 Hz, H_b-3), 3.19 (1H, d, *J*=14.4 Hz, H_b-5'), 3.35 (1H, d, *J*=9.5 Hz, H-5), 3.49 (1H, t, *J*=9.5 Hz, H-7), 3.68-3.74 (1H, m, H-8), 3.75-3.82 (2H, m, H-9), 3.92 (1H, t, *J*=9.2 Hz, H-6), 4.22-4.90 (8H, m, CH_2Ph), 5.15-5.19 (2H, m, H-1), 5.95 (1H, m, H-2): ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.13 (C-3), 42.30 (C-5'), 69.53 (C-9), 72.47 (C-8), 79.04 (C-7), 79.46 (C-4), 80.29 (C-5), 84.74 (C-6), 118.11 (C-1), 132.74 (C-2).