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Regioselectivity in the reductive ring-opening reaction of 1,2-*O*-benzylidene sugars

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Abstract—Regioselectivity in the ring-opening reaction of 1,2-*O*-benzylidene sugars was studied. In the reductive ring-opening reaction of 1,2-*O*-benzylidene derivatives, only a C–*O*1 bond was cleaved in the case of *manno*-type, but both the C–*O*1 and C–*O*2 bonds were cleaved in the case of *gluco*-type.

The reductive ring-opening reaction of benzylidene acetal has been used frequently for regioselective protection and/or transformation of the diol function. Generally, one of the two C–*O* bonds in benzylidene acetal can be selectively cleaved, and the direction of cleavage is dependent on steric and electronic factors as well as on the nature of the cleavage reagent.[1] A number of methods for the reduction of benzylidene acetal have been developed and the 4,6-*O*-benzylidene acetal of hexopyranosides has been useful precursors of the carbohydrate chemistry.[2–11] However, lack of an efficient method for the synthesis of 1,2-*O*-benzylidene derivatives in sufficient amount to use for reaction had caused a delay of the development of the ring-opening reaction. To aid research around the 1,2-*O*-benzylidene sugars, we recently reported an improved and practical synthesis of 1,2-*O*-benzylidene and 1,2-*O*-*p*-methoxybenzylidene hexopyranoses that most aldoses can apply.[12] We thought that 1,2-*O*-benzylidene sugars, synthesized easily from the corresponding 2-benzoyloxy glycosyl halides by the reductive cyclization, are attractive as the stable derivative protecting and/or activating the anomeric position selectively. But, the general nature of the 1,2-*O*-benzylidene derivatives had not yet been known well.

We now report the first attempt to open the ring of 1,2-*O*-benzylidene sugars under the reductive condition. In this communication, regioselectivity in the reaction of two types of 1,2-*O*-benzylidene sugars, *manno*- and *gluco*-type, was studied.

Two types of 1,2-*O*-benzylidene derivatives **1**–**4**,[13] *manno*- and *gluco*-type, were used as substrates for three reductive ring-opening conditions, Et_3SiH–TFA in the CH_2Cl_2 system[7] and BH_3·THF–TMSOTf in the THF system[5,6] and $NaBH_3CN$–TMSCl in the CH_3CN system.[10] Results of the reductive ring-opening reaction was summarized in Table 1.

Treatment of benzylidene **1** with Et_3SiH in the presence of TFA gave a 2-*O*-benzylated derivative **5**[14] exclusively (entry 1). Although contamination of H_2O was removed with AW-300 (acid washed molecular sieves, 4A), in the use of *p*-methoxybenzylidene **2** in place of benzylidene **1** as a substrate only a 1,2-OH derivative **6** was obtained and the *p*-methoxybenzylated compound has not yet been obtained (entry 2). This result suggests that the *p*-methoxybenzyl group on the reduced product may be unstable in this reaction and/or the handling step. On the other hand, BH_3·THF–TMSOTf in the THF system was successful and gave 2-*O*-benzyl ether **5** or *p*-methoxybenzyl ether **7** by the reductive ring-opening reaction of benzylidene **1** or *p*-methoxybenzylidene **2** (entries 3, 4). The use of $NaBH_3CN$–TMSCl in the CH_3CN system was also effective for the ring-opening reaction of benzylidene **1** or *p*-methoxybenzylidene **2** (entries 5, 6). The cleavage of the C–*O*2 bond was not observed at all under these conditions. These results means that the sterically less hindered anomeric oxygen, which is pointed to the equatorial at *manno*-type 1,2-*O*-benzylidene derivatives **1** or **2** having the *C1* conformation, reacts with a proton or Lewis acid to give the 2-*O*-benzyl ether.

Keywords: benzylidene; reduction; ring-opening reaction; protecting group.

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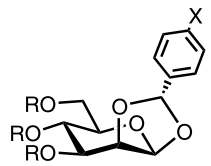
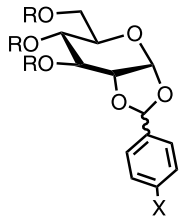
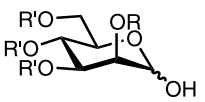
Table 1. Reductive ring-opening reaction of 1,2-*O*-benzylidene derivatives



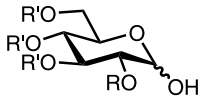
1 : R = Bz, X = H
2 : R = *p*-MBz, X = OMe



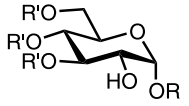
3 : R = Bz, X = H
4 : R = *p*-MBz, X = OMe



5 : R = Bn, R' = Bz
6 : R = H, R' = *p*-MBz
7 : R = *p*-MBn, R' = *p*-MBz



8 : R = Bn, R' = Bz
10 : R = H, R' = *p*-MBz
11 : R = *p*-MBn, R' = *p*-MBz



9 : R = Bn, R' = Bz
12 : R = *p*-MBn, R' = *p*-MBz

Entry	Substrate	Condition[a]	Temperature	Product (yield %)
1	**1**	A	rt	**5** (84%)
2	**2**	A	rt	**6** (quant.)
3	**1**	B	0°C–rt	**5** (87%)
4	**2**	B	0°C–rt	**7** (90%)
5	**1**	C	Reflux	**5** (92%)
6	**2**	C	rt	**7** (68%)
7	**3**	A	rt	**8** (23%), **9** (70%)
8	**4**	A	rt	**10** (quant.)
9	**3**	B	0°C–rt	**8** (43%), **9** (49%)
10	**4**	B	0°C	**11** (20%), **12** (59%)
11	**3**	C	Reflux	**8** (48%), **9** (43%)
12	**4**	C	rt	**12** (79%)

[a] A: Et_3SiH, TFA, AW-300/CH_2Cl_2; B: BH_3THF, TMSOTf, AW-300/THF; C: $NaBH_3CN$, TMSCl, AW-300/CH_3CN.

In the case of *gluco*-type 1,2-*O*-benzylidene derivative **3** or *p*-methoxybenzylidene derivative **4**, the regioselectivity of the ring-opening reaction was changed from that of the *manno*-type. Under the reductive ring-opening reaction of 1,2-*O*-benzylidene derivatives, only the C–*O*1 bond was cleaved in the case of *manno*-type **1** or **2**, but both the C–*O*1 and C–*O*2 bonds were cleaved in the case of *gluco*-type **3** or **4**. Reaction of benzylidene **3** with Et_3SiH in the presence of TFA gave 2-*O*-benzyl ether **8**[14] with 1-*O*-benzyl ether **9**[14] in the ratio of 23% to 70% (entry 7). The 1,2-OH derivative **10** was obtained in the use of the *p*-methoxybenzylidene **4** under this condition similarly to *manno*-type *p*-methoxybenzylidene **2** (entry 8). Mixtures of 2-*O*-benzyl ether **8** and 1-*O*-benzyl ether **9** or 2-*O*-*p*-methoxybenzyl ether **11** and 1-*O*-*p*-methoxybenzyl ether **12** were obtained under the reaction using BH_3·THF–TMSOTf in the THF system (entries 9, 10). The $NaBH_3CN$–TMSCl in the CH_3CN system also converted benzylidene **3** into a mixture of 2-*O*-benzyl ether **8** and 1-*O*-benzyl ether **9** (entry 11). Interestingly, 1,2-*O*-*p*-methoxybenzylidene derivative **4** gave 1-*O*-*p*-methoxybenzyl ether **12** without 2-*O*-*p*-methoxybenzyl ether **11** (entry 12).

In the *gluco*-type 1,2-*O*-benzylidene derivatives **3** or **4** having the strain conformation,[12,15] the situation around the anomeric or 2-*O* position is different from the *manno*-type, and is the cause of the change in regioselectivity. Whereas it is difficult to estimate the differences of stereoelectronic effect between *manno*- and *gluco*-types, the regioselectivity in the reductive ring-opening reaction of 1,2-*O*-benzylidene or 1,2-*O*-*p*-methoxybenzylidene derivatives appears to be relevant to the steric effect around the anomeric or the 2-*O* position. By detailed studies related to the stereochemistry of the benzylidene position and the solvent effect, more suitable conditions for the regioselective ring-opening reaction of 1,2-*O*-benzylidene derivatives may be developed in the near future.

Thus, the reductive ring-opening reaction of the 1,2-*O*-benzylidene sugars was demonstrated. The ring-opening products, having a benzyl or *p*-methoxybenzyl ether at the anomeric or C-2 position, are promising precursors for the carbohydrate chemistry.

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13. The *gluco*-type compounds **3** and **4** are the (*R*):(*S*)=7:3 diastereomeric mixture on the benzylidene position.
14. Selected spectral data for ring-opening product **5**: ^{1}H NMR ($CDCl_3$) δ 6.12 (dd, 0.85H, $J_{3,4}=J_{4,5}=9.9$ Hz, H-4α), 6.01 (dd, 0.15H, $J_{3,4}=J_{4,5}=9.9$ Hz, H-4β), 5.78 (dd, 0.85H, $J_{2,3}=2.9$ Hz, H-3α), 5.48 (dd, 0.15H, $J_{2,3}=2.9$ Hz, H-3β), 5.41 (br s, 0.85H, H-1α), 5.04 (br d, 0.15H, $J_{1,2}=11.0$ Hz, H-1β), 4.93 (d, 0.15H, $J=11.0$ Hz, benzylβ); **7**: ^{1}H NMR ($CDCl_3$) δ 6.03 (dd, 0.8H, $J_{3,4}=J_{4,5}=9.9$ Hz, H-4α), 5.93 (dd, 0.2H, $J_{3,4}=J_{4,5}=9.9$ Hz, H-4β), 5.71 (dd, 0.8H, $J_{2,3}=2.9$ Hz, H-3α), 5.40 (dd, 0.2H, $J_{2,3}=2.9$ Hz, H-3β), 5.38 (br s, 0.8H, H-1α), 5.01 (br s, 0.2H, H-1β), 4.85 (d, 0.2H, $J=11.0$ Hz, benzylβ); **8**: ^{1}H NMR ($CDCl_3$) δ 5.98 (dd, 0.7H, $J_{2,3}=J_{3,4}=9.9$ Hz, H-3α), 5.71 (dd, 0.3H, $J_{2,3}=J_{3,4}=9.9$ Hz, H-3β), 5.53 (dd, 0.7H, $J_{4,5}=9.9$ Hz, H-4α), 5.52 (dd, 0.3H, $J_{4,5}=9.9$ Hz, H-4β), 5.39 (br s, 0.7H, H-1α), 5.01 (dd, 0.3H, $J_{1,2}=7.5$, $J_{1,OH}=5.0$ Hz, H-1β), 4.85 and 4.70 (each d, 0.6H, $J=11.7$ Hz, benzylβ), 4.05 (ddd, 0.3H, $J_{5,6a}=3.3$, $J_{5,6b}=5.1$ Hz, H-5β), 4.01 (d, 0.3H, O*H*β), 3.81 (dd, 0.7H, $J_{1,2}=3.7$ Hz, H-2α), 3.63 (dd, 0.3H, H-2β), 3.61 (br s, 0.7H, O*H*α); **9**: ^{1}H NMR ($CDCl_3$) δ 5.75 (dd, 1H, $J_{2,3}=J_{3,4}=9.9$ Hz, H-3), 5.59 (dd, 1H, $J_{4,5}=9.9$ Hz, H-4), 5.15 (d, 1H, $J_{1,2}=4.0$ Hz, H-1), 4.86 and 4.66 (each d, 2H, $J=11.7$ Hz, benzyl), 4.54 (dd, 1H, $J_{5,6a}=2.6$, $J_{6a,6b}=11.7$ Hz, H-6a), 4.43 (dd, 1H, $J_{5,6b}=5.1$ Hz, H-6b), 4.37 (ddd, 1H, H-5), 3.94 (br s, 1H, H-2), 2.43 (br s, 1H, O*H*); ^{13}C NMR ($CDCl_3$) δ 97.64 (C-1), 73.96 (C-3), 71.42 (C-2), 70.28 (benzyl), 68.99 (C-4), 68.26 (C-5), 63.00 (C-6); **11**: ^{1}H NMR ($CDCl_3$) δ 5.88 (dd, 0.7H, $J_{2,3}=J_{3,4}=9.9$ Hz, H-3α), 5.62 (dd, 0.3H, $J_{2,3}=J_{3,4}=9.9$ Hz, H-3β), 5.45 (dd, 0.7H, $J_{4,5}=9.9$ Hz, H-4α), 5.43 (dd, 0.3H, $J_{4,5}=9.9$ Hz, H-4β), 5.32 (br s, 0.7H, H-1α), 4.98 (dd, 0.3H, $J_{1,2}=7.7$, $J_{1,OH}=5.1$ Hz, H-1β), 4.75 and 4.63 (each d, 0.6H, $J=11.7$ Hz, benzylβ), 3.57 (dd, 0.3H, H-2β), 3.50 (br s, 0.7H, O*H*α); **12**: ^{1}H NMR ($CDCl_3$) δ 5.67 (dd, 1H, $J_{2,3}9=J_{3,4}=9.9$ Hz, H-3), 5.52 (dd, 1H, $J_{4,5}=9.9$ Hz, H-4), 5.10 (d, 1H, $J_{1,2}=4.0$ Hz, H-1), 4.78 and 4.57 (each d, 2H, $J=11.4$ Hz, benzyl), 4.53 (dd, 1H, $J_{5,6a}=2.9$, $J_{6a,6b}=12.1$ Hz, H-6a), 4.39 (dd, 1H, $J_{5,6b}=5.5$ Hz, H-6b), 4.33 (ddd, 1H, H-5), 3.89 (ddd, 1H, $J_{2,OH}=11.0$ Hz, H-2), 2.48 (d, 1H, O*H*); ^{13}C NMR ($CDCl_3$) δ 97.29 (C-1), 73.74 (C-3), 71.43 (C-2), 69.78 (benzyl), 68.82 (C-4), 68.25 (C-5), 62.92 (C-6).
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