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A selective ring opening reaction of 4,6-*O*-benzylidene acetals in carbohydrates using trialkylsilane derivatives

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Abstract

Reductive ring opening reactions of 4,6-*O*-benzylidene-protected carbohydrates to the corresponding benzyl ethers using trialkylsilane derivatives were examined. When Et_3SiH(or PS-DES^{TM})-TfOH was used, 6-*O*-benzyl ethers with 4-hydroxy unsubstituted were obtained, while, when Et_3SiH(or PS-DES^{TM})-$PhBCl_2$ was used, 4-*O*-benzyl ethers with 6-hydroxy unsubstituted were obtained in quantitative yield with excellent selectivity.

Recently, the protein carbohydrate recognition process was revealed to be involved in various biological responses, and has become the target of much attention.[1] We focused on the interaction between sialyl Lewis X (SLe^x, Neu5Acα2-3Galβ1-4(Fucα1-3)GlcNAc) and E-selectin which is expressed on the surface of endothelial cells during inflammation.[2] We have suggested that SLe^x-polysaccharide conjugates should be useful as homing devices for an active targeting drug delivery system (DDS) to inflammatory lesions.[3] To our knowledge, this is the first experimental evidence of SLe^x being useful as a DDS homing device.

As part of our program to develop SLe^x-polysaccharide conjugates, we conducted the selective ring opening reaction of 4,6-*O*-benzylidene acetals of Fucα1-3GlcNAc (**i**) to the corresponding 6-*O*-benzyl ether derivative, which was a useful intermediate for the synthesis of 1-4 linked oligosaccharide (**ii**) (Fig. 1).

Reductive ring opening of benzylidene acetals requires $NaBH_3CN$–HCl[4] or Et_3SiH–TFA.[5] However, $NaBH_3CN$ is a hazardous chemical that precludes its use on a large scale, and the reaction of **1** using Et_3SiH–TFA resulted in poor yield (40–50%) of the desired product. Thus, a selective method was needed to prepare 6-*O*-benzyl-4-hydroxy derivatives. Also, many 1–6-linked oligosaccharides exist in nature, and the development of an efficient method for synthesizing these compounds is important in the area of carbohydrate chemistry.[6] Here we describe the selective ring opening reaction of 4,6-*O*-benzylidene acetal in carbohydrates using Et_3SiH as a reductive reagent.

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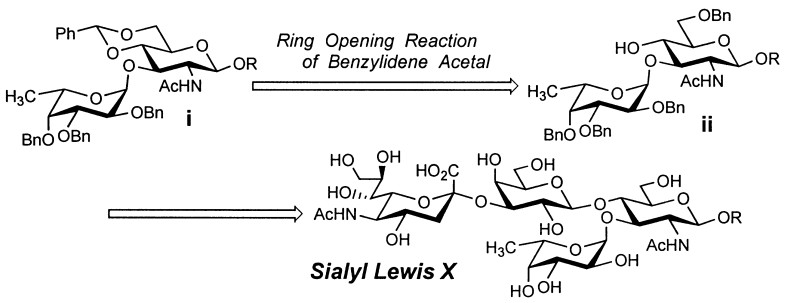
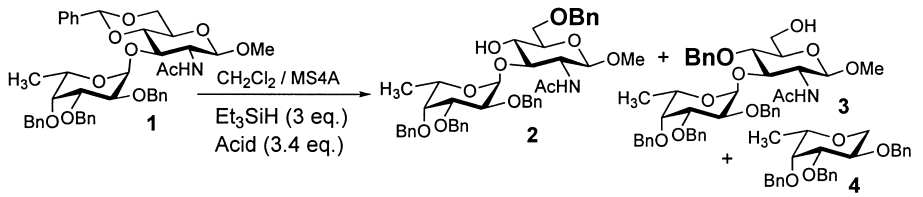


Figure 1.

First, the reductive ring opening reaction was attempted using the 4,6-*O*-benzylidene acetal of **1** which is the important intermediate in the synthesis of SLe^x-derivative. When TfOH was used at –78°C as an acid,[7] compound **1** was efficiently converted to the corresponding 6-*O*-benzyl-4-hydroxy derivative **2** in high yield with excellent selectivity (Scheme 1). However, when TfOH was used at 0°C, **2** decomposed to give fucose derivative **4**. On the other hand, using $PhBCl_2$ as an acid, the corresponding 4-*O*-benzyl-6-hydroxy derivative **3** was obtained in almost quantitative yield with excellent selectivity (Table 1, Entries 1 and 7). The five boron reagents displayed differences in regioselectivity (Table 1, Entries 3, 7, 8 and 9). Also, the use of activated molecular sieves was important in these reactions. When they were not used, for instance, the yield of **2** in the reaction of Entry 1 decreased to ca. 60%.[8] The regioselectivity may be due to the relative acidities and steric factor of O-4.[9]



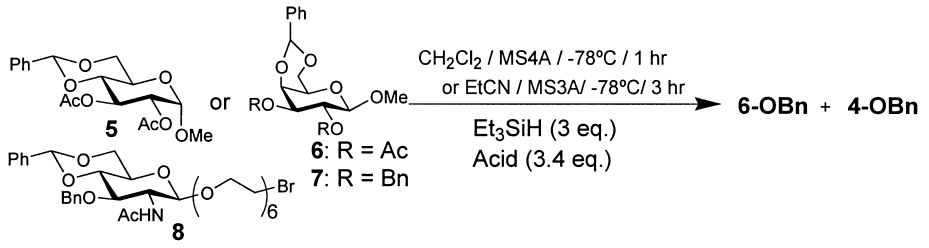
Scheme 1.

Table 1

Entry	Acid	Temp. (°C)	Time (hr)	2	3	4	SM
1	TfOH	-78	1	**87%**	N.D.	N.D.	N.D.
2	TfOH	rt	1	5%	N.D.	74%	N.D.
3	$BF_3 \cdot OEt_2$	0	12	48%	<2%[c)]	7%	20%
4	$SnCl_4$	-78	3	N.D.	15%	N.D.	81%
5	$AlCl_3$	-78	3	N.D.	68%	N.D.	27%
6	BCl_3	-78	1	N.D.	75%	N.D.	N.D.
7	$PhBCl_2$	-78	1	N.D.	**99%**	N.D.	N.D.
8	Bu_2BOTf	-78	1	25%	61%	N.D.	N.D.
9	9-BBNOTf	-78	1	<3%[c)]	84%	N.D.	N.D.

a) Yields of isolated product. b) N.D. means that the product was not detected on the thin layer chromatography and ^1H NMR spectrum of the crude product. c) The yields were estimated from the ^1H NMR spectrum of the crude product.

Other sugars were explored, with results similar to the case of fucosyl GlcNAc derivatives **1**. Using TfOH or $PhBCl_2$ as an acid led to high yield of the corresponding 6-*O*-benzyl-4-hydroxy or 4-*O*-benzyl-6-hydroxy derivative with excellent selectivity (Table 2). There was no reaction when galactose compound **6** and **7** were subjected to Et_3SiH–TFA.[5] By changing the acid from TFA to TfOH, the reaction took place smoothly to give the desired product in high yield with excellent selectivity (Table 2, Entries 2 and 3). Moreover, though BH_3–Bu_2BOTf was reported to be an efficient reagent for reductively cleaving 4,6-*O*-benzylidene-protected carbohydrates to the corresponding 4-*O*-benzyl derivatives,[10] our system using $PhBCl_2$ was found to also be widely applicable. However, when EtCN was used as the solvent (Table 2, Entry 8), the reaction almost did not take place because $PhBCl_2$ was coordinated with the nitrile group of EtCN, and thus the Lewis acidity of $PhBCl_2$ was lowered (Scheme 2).[11]



Scheme 2.

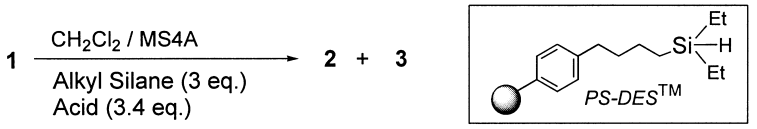
Table 2

Entry	Substrate	Acid	Solvent	6-OBn	4-OBn	SM
1	**5**	TfOH	CH_2Cl_2	90%	N.D.	N.D.
2	**6**	TfOH	CH_2Cl_2	98%	N.D.	N.D.
3	**7**	TfOH	CH_2Cl_2	85%	N.D.	N.D.
4	**8**	TfOH	CH_2Cl_2	87%	N.D.	N.D.
5	**5**	$PhBCl_2$	CH_2Cl_2	N.D.	91%	N.D.
6	**6**	$PhBCl_2$	CH_2Cl_2	N.D.	85%	N.D.
7	**8**	$PhBCl_2$	CH_2Cl_2	N.D.	92%	N.D.
8	**5**	$PhBCl_2$	EtCN	N.D.	2%	95%

a) All yields were isolated yield. b) N.D. means that the product was not detected on the thin layer chromatography and ^1H NMR spectrum of the crude product.

Recently, rapid progress has been made in solid-phase organic synthesis,[12] and in the area of combinatorial chemistry, the utility of the polymer-supported reagent is well-recognized because of the ease of the workup and separation of products and reagent. To expand application of solid phase organic synthesis, the ring opening reaction using PS-DES™ was examined (Scheme 3).[13]

As shown in Table 3, the reaction using PS-DES™ was equivalent to the case of Et_3SiH. On the other hand, using $i Pr_3SiH$, a bulky alkylsilane derivative, resulted in an extremely reduced conversion yield (Table 3, Entry 6).[14] These results showed that the polymer-supported trialkylsilane derivative was effective for this reduction, and the choice of silane reagent was also important.



Scheme 3.

Table 3

Entry	Silane	Acid	Time	2	3	SM
1	Et_3SiH	TfOH	1	87%	N.D.	N.D.
2	Et_3SiH	$PhBCl_2$	1	N.D.	99%	N.D.
3	PS-DES™	TfOH	1	94%	N.D.	N.D.
4	PS-DES™	$PhBCl_2$	1	N.D.	93%	N.D.
5	iPr_3SiH	TfOH	1	93%	N.D.	N.D.
6	iPr_3SiH	$PhBCl_2$	3	N.D.	15%	80%

1) All yields were isolated yield. 2) N.D. means that the product was not detected on the thin layer chromatography and ^1H NMR spectrum of the crude product.

In summary, when a suitable Lewis acid is used in the presence of trialkylsilane derivative, 4,6-*O*-benzylidene-protected carbohydrates can be converted to the desired corresponding *O*-benzyl ethers in high yield with excellent selectivity. These methods should be useful for synthesizing various oligosaccharides.[14]

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14. The general procedure is as follows: Molecular sieves 4A (1.5 g) were placed in a 20-mL flask and dried at 140 °C over 4 h with vacuation (ca. 0.1 mmHg). After cooling to room temperature, **1** (300 mg, 0.425 mmol), and CH_2Cl_2 (5 ml) were added to the flask. After stirring for 1 h at room temperature, the mixture was cooled to –78°C, and then to the stirred solution, Et_3SiH (220 μl, 1.38 mmol) and TfOH (94 μl, 1.22 mmol) were added successively. After being stirred for 1 h at –78°C, Et_3N (1 ml) and MeOH (1 ml) were added successively, and the mixture was diluted with $CHCl_3$ and washed with aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column (25 g, $CHCl_3$:MeOH = 100:1) giving **2** (262 mg, 87%).