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Perfectly Regioselective and Sequential Protection of Glucopyranosides

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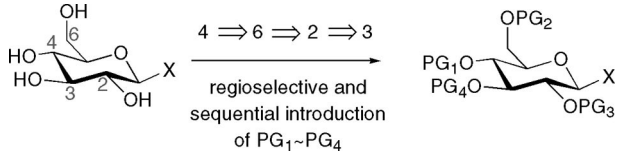
Dedicated to Professor Emeritus Kaoru Fuji on the occasion of his 70th birthday

Keywords: Regioselectivity / Protecting groups / Organocatalysis / Carbohydrates / Sequential protection

A perfectly regioselective and sequential method for the preparation of orthogonally protected glucopyranosides has been developed. An acyl group was introduced at C(4)-OH by organocatalysis with >99% regioselectivity. TBDPS, Boc, and BOM groups were sequentially introduced into the 4-*O*-acyl-glucopyranoside at C(6)-OH, C(2)-OH, and C(3)-OH, respectively, with ca. 100% regioselectivity in each step.

Introduction

Regioselective manipulation of one of the multiple hydroxy groups of carbohydrates has been a fundamental challenge in organic synthesis. We have developed an organocatalyst with functional side chains for substrate recognition, which enables the regioselective introduction of an acyl group at C(4)-OH of glycopyranosides.[1] As a further challenge, we report here a strategy for sequential introduction of protective groups into four hydroxy groups of glycopyranosides in a highly regioselective manner for each step (Scheme 1). This gives orthogonally protected glycopyranosides, which are expected to be useful intermediates for the synthesis of oligosaccharides of biological interests.[2]



Scheme 1. Preparation of an orthogonally protected glucose derivative by regioselective and sequential introduction of protective groups.

Enzymatic regioselective acylation and deacylation of carbohydrates have been extensively studied.[3] On the other hand, development of the non-enzymatic surrogates have been the focus of current organic synthesis. Regioselective acylation of a particular secondary hydroxy group among three secondary hydroxy groups of 6-*O*-protected glucose derivatives has been reported.[4] Chemoselective acylation of a secondary hydroxy group in the presence of a free primary hydroxy group is much more difficult. Kurahasi, Mizutani, and Yoshida reported a pioneering example of chemoselective acylation of a secondary hydroxy group at C(4) with 61% selectivity in the presence of a free primary hydroxy group at C(6) of octyl α-D-glucopyranoside.[5a] They also reported the regioselective acylation of octyl β-D-glucopyranoside with functionalized DMAP derivatives, which gave the 3-*O*-acetate with 49% regioselectivity.[5b] Kattnig and Albert reported the regioselective 3-*O*-acylation of octyl β-D-glucopyranoside with 57% selectivity and 60% yield by treatment with acetic anhydride in the presence of DMAP, whereas 6-*O*-acylation took place predominantly by use of acetyl chloride in place of acetic anhydride.[5c] Griswold and Miller reported an excellent approach to the selective introduction of an acetyl group at a secondary hydroxy group of octyl β-D-glucopyranoside by using peptide-based chiral catalysts. Selective 4-*O*-acylation has been achieved with 58% regioselectivity.[5d] Recently, Onomura and co-workers reported highly regioselective benzoylation of monosaccharides catalyzed by Me_2Sn-Cl_2.[5e,6]

Results and Discussion

We have reported an organocatalytic regioselective acylation of monosaccharides.[1] Acylation of the secondary hydroxy group at C(4) of octyl β-D-glucopyranoside proceeded with up to >99% selectivity in the presence of a primary hydroxy group at C(6) and two other secondary hydroxy groups at C(2) and C(3) (Scheme 2). A possible transition-state assembly for regioselective acylation of octyl β-D-glucopyranoside promoted by catalyst **1** is shown in

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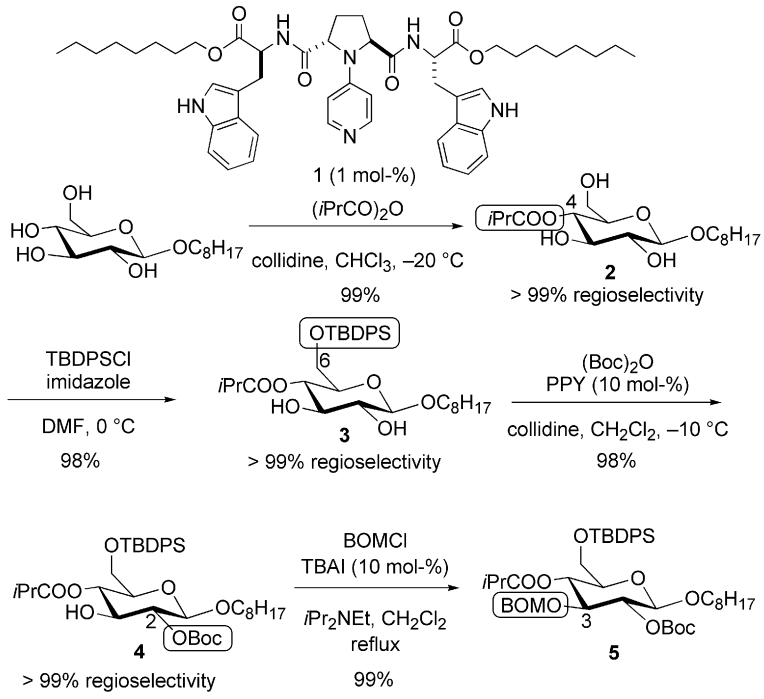


Scheme 2. Regioselective and straightforward route to orthogonally protected glucose derivative **5**.

Figure 1. Since the primary hydroxy group at C(6) is the most reactive in the substrate, it would preferentially form hydrogen bonds with an amide carbonyl group of the acylpyridinium ion generated from **1**. As the result of the H-bonding interaction, the indole NH group is located in the proximity of C(3)-OH, resulting in the formation of an additional hydrogen bond between them. The cooperative effects of two hydrogen bonds would fix the conformation of the substrate at the transition state for acylation, where the C(4)-OH group is in close proximity to the reactive carbonyl group of the acylpyridinium ion, resulting in the selective acylation at C(4)-OH. We planned to employ this catalytic regioselective acylation as a key step for the preparation of orthogonally protected glucose derivatives by a synthetic strategy shown in Scheme 2. Once the acyl group was regioselectively introduced at the intrinsically less reactive C(4)-OH group by organocatalysis, sequential introduction of the protective groups, PG_2, PG_3, and PG_4 onto C(6)-OH, C(2)-OH, and C(3)-OH, respectively, would be possible based on the intrinsic reactivity order of the C(6)-, C(2)-, and C(3)-OH groups. The orthogonally protected glucose derivative thus formed may be a potentially useful intermediate for the synthesis of oligosaccharides because each of the mono-ols with three different protective groups would be readily obtained by its deprotection.

The regioselective synthesis of orthogonally protected glucose derivative **5** is shown in Scheme 2. Treatment of octyl β-D-glucopyranoside (1 g scale) with isobutyric anhydride[7,8] in the presence of 1 mol-% of catalyst **1**[9] at –20 °C in $CHCl_3$ gave 4-*O*-isobutyryl derivative **2** with >99% regioselectivity and 99% yield. No trace of regioisomers was detected. The observed regioselectivity was slightly better than that of the corresponding 0.2 mmol (58 mg) scale reaction, which gives the 4-*O*-isobutyryl- and 3-*O*-isobutyryl derivatives in a 99:1 ratio.[1] A TBDPS group was introduced selectively into the primary hydroxy group at C(6) of **2** by treatment with TBDPSCl in DMF at 0 °C to give silyl ether **3** as the sole product in 98% yield. Regioselective introduction of a protective group into the C(2)-OH group was then examined. We assumed that the C(3)-OH group is in a sterically more congested environment than the C(2)-OH group because of the neighboring C(4)-OCO*i*Pr group,[10] so that the use of bulky reagents was expected to give the corresponding 2-*O*-protected isomer preferentially. Selected examples for the optimization of the 2-*O*-selective protection are shown in Table 1. Regioselective protection of **3** was examined with triphenylmethyl chloride (TrCl), diphenylmethyl bromide (DPMBr), benzyloxymethyl chloride (BOMCl), and di-*tert*-butyl dicarbonate [$(Boc)_2O$] (Entries 1–4). The reaction took place preferentially at C(2)-OH in each case. Since the use of $(Boc)_2O$ gave the most promising results, solvent effects on the regioselectivity of the reaction with $(Boc)_2O$ were investigated (Entries 4–7).

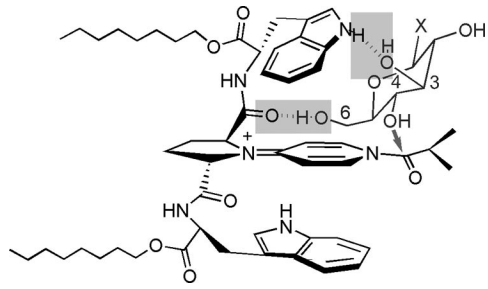
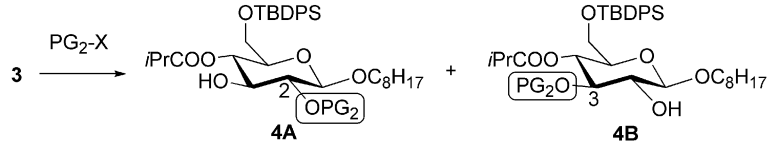


Figure 1. Possible transition-state model for the regioselective acylation of octyl β-D-glucopyranoside with catalyst **1**.

Table 1. Regioselective protection of octyl 4-*O*-isobutyryl-6-*O*-TBDPS-β-D-glucopyranoside (**3**).



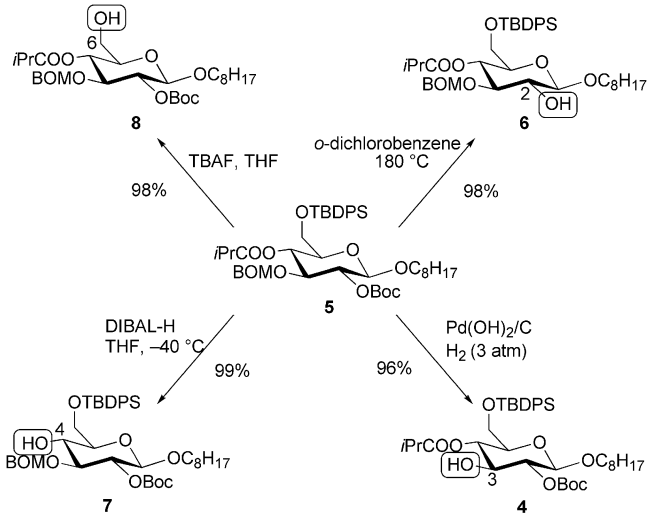
Entry	PG_2-X[a]	Solvent	Temp. [°C]/Time [h]	Yield of **4A** [%]	Yield of **4B** [%]
1[b]	TrCl	$CHCl_3$	20/168	53	ca. 0
2[b]	DPMBr	$CHCl_3$	20/168	64	ca. 0
3[c]	BOMCl	$CHCl_3$	20/24	84	12
4[d]	$(Boc)_2O$	$CHCl_3$	0/12	95	4
5[d]	$(Boc)_2O$	toluene	0/12	91	6
6[d]	$(Boc)_2O$	THF	0/12	96	2
7[d]	$(Boc)_2O$	CH_2Cl_2	0/12	98	2
8[d]	$(Boc)_2O$	CH_2Cl_2	–10/24	98	ca. 0

[a] 1.5 and 1.2 equiv. of reagents were used for Entries 1–2 and 3–8, respectively. [b] Run in the presence of 10 mol-% of PPY and 2.0 equiv. of collidine. [c] Run in the presence of 1.5 equiv. of iPr_2NEt. [d] Run in the presence of 10 mol-% of PPY and 1.5 equiv. of collidine.

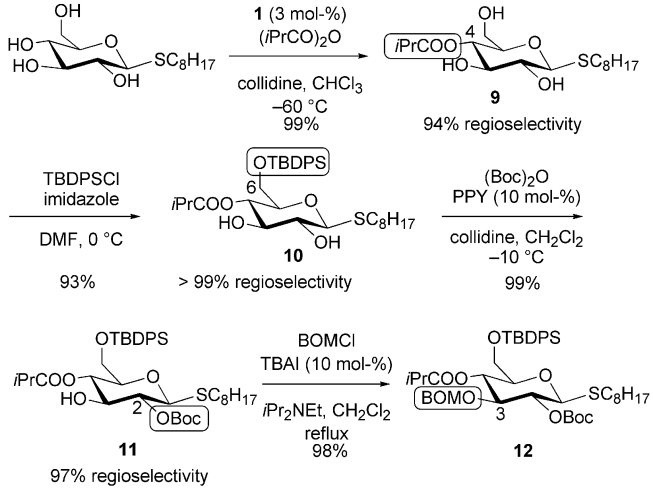
Among the solvents examined, CH_2Cl_2 gave the highest regioselectivity (98:2, Entry 7). Introduction of a Boc group was achieved exclusively at the C(2)-OH group by treatment of **3** with Boc_2O in CH_2Cl_2 at –10 °C in the presence of 4-pyrrolidinopyridine (PPY) and collidine (Entry 8 and Scheme 2). Finally, orthogonally protected glucose derivative **5** was obtained in 99% yield by treatment of **4** with BOMCl under reflux of CH_2Cl_2. Thus, a perfectly regioselective and straightforward route to **5** was developed starting from octyl β-D-glucopyranoside in 94% overall yield.

Glucose derivative **5** is expected to be a reasonable precursor for mono-ols with three different protective groups, which have been used as intermediates for oligosaccharide synthesis.[2] Preparation of the mono-ols by chemoselective deprotection of **5** was examined (Scheme 3). Thermal removal of the Boc group of **5** gave the 2-alcohol **6** in 98% yield. Hydrogenolysis, reduction with DIBAL-H, and desilylation of **5** gave the 3-, 4-, and 6-alcohols **4**, **7**, or **8**, respectively, in 96–99% yield.

The strategy for the sequential and regioselective introduction of protective groups into octyl β-D-glucopyranoside was applied to the corresponding thioglycosides because they can be used directly for glycosylation as glycosyl donors[11] (Scheme 4). Since we already know that the control of regioselectvity of acylation of octyl β-D-thioglucopyranoside in the presence of **1** is more difficult than that of octyl β-D-glucopyranoside,[1] we employed more drastic reaction conditions than those used for the acylation of octyl β-D-glucopyranoside. Acylation of octyl β-D-thioglucopyranoside with isobutyric anhydride was carried out at –60 °C with 3 mol-% of **1** to give 4-*O*-isobutyryl derivative **9** with 94% regioselectivity and 99% yield. Silylation of **9** gave 6-*O*-TBDPS derivative **10** as the sole detectable isomer in 93% yield. Introduction of a Boc group into the C(2)-OH



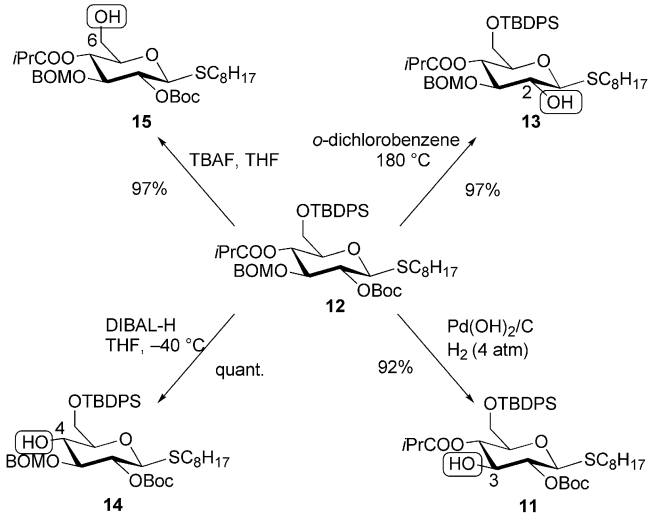
Scheme 3. Preparation of protected mono-ols **4** and **6**–**8** from **5**.



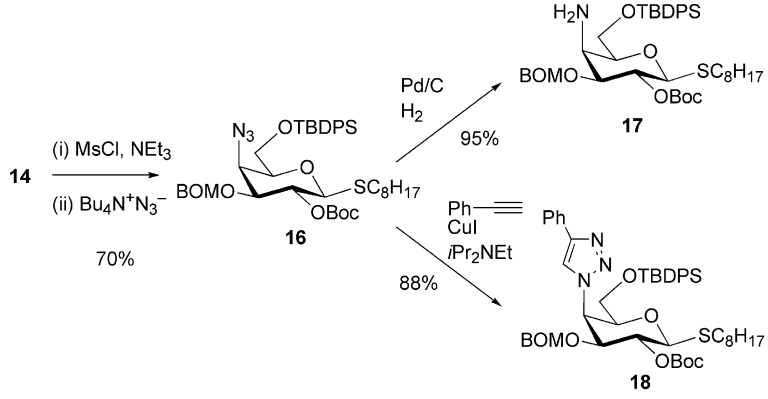
Scheme 4. Regioselective and straightforward route to orthogonally protected thioglycosides **12**.

group of **10** was achieved with 97% regioselectivity and 99% yield. Finally, a BOM group was introduced at the C(3)-OH group of **11** to give **12** in 98% yield.

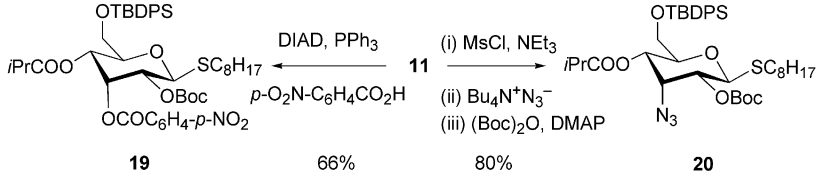
Octyl β-D-thioglucopyranoside mono-ols with three different protective groups, **11** and **13**–**15**, were readily obtained from **12** (Scheme 5) according to similar methods employed for the transformation of **5** to **4** and **6**–**8**. Preparations of the 2-, 4-, and 6-alcohols, **13**, **14**, and **15** were accomplished in high yields according to the same procedures for **6**, **7**, and **8**, respectively. Removal of the BOM group at the C(2)-OH group of **12** required slightly harsher conditions [4 atm of hydrogen, 30 wt.-% of $Pd(OH)_2/C$] to give **11** in 92% yield. Protected mono-ols **11** and **13**–**15** appear to be potentially useful intermediates for oligosaccharide synthesis. Additionally, they are useful for the modification of natural glycosides. For example, the hydroxy group at C(4) of **14** was transformed to an azide group by mesylation followed by azide substitution to give azidoglycoside **16** in 70% yield with inversion of configuration (Scheme 6). Azidoglycosides are useful precursors for aminoglycosides[12] and triazole-linked glycosides.[13,14] Azidoglycoside **16** was readily converted to 4-amino-4-deoxyglucoside **17** and triazole-linked glycoside **18** in 95% and 88% yield, respectively. Protected glucose derivative **11** was readily converted to fully protected allose derivative **19** in 66% yield by inversion of the configuration at the C(3)-OH group under Mitsunobu conditions, and also to protected azidoglycoside **20** under conditions similar to those for **16** (Scheme 7). Similarly, azidoglycoside **21** was readily prepared from **15** in



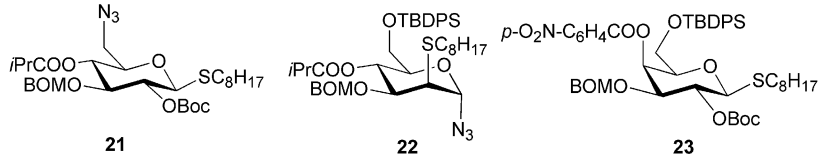
Scheme 5. Preparation of protected mono-ols **11** and **13**–**15** from **12**.



Scheme 6. Preparation of aminoglycoside **17** and triazole-linked glycoside **18** from protected glucose mono-ol **14**.



Scheme 7. Preparation of fully protected allose derivative **19** and azidoglycoside **20** from protected glucose mono-ol **11**.



83% yield. On the other hand, attempted azide substitution of the hydroxy group at C(2) of **13** gave 1-azido-2-octylthio derivative **22** by rearrangement of the octylthio group in 64% yield.[15] Glycosyl azide **22** is expected to be a versatile intermediate for the synthesis of oligosaccharides containing an *N*-glycosyltriazole linkage and also to be a protected glycosyl donor under enzyme-catalyzed glycosidation.[16] Fully protected galactose derivative **23** was also obtained from **14** under Mitsunobu conditions in 62% yield, which may be a potentially useful intermediate for the synthesis of galactose-containing oligosaccharides.

Conclusions

We have developed a method for highly regioselective and sequential introduction of four different protective groups onto four hydroxy groups of glycopyranosides. Each of the protective groups of the orthogonally protected glucopyranosides was readily removed to give the corresponding mono-ols with three different protective groups, which are possible intermediates for the synthesis of natural and modified oligosaccharides with structural diversity. This method provides a new way for regioselective manipulation of carbohydrates.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data for all new compounds.

Acknowledgments

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[1] a) T. Kawabata, W. Muramatsu, T. Nishio, T. Shibata, H. Schedel, *J. Am. Chem. Soc.* **2007**, *129*, 12890–12895; b) T. Kawabata, T. Furuta, *Chem. Lett.* **2009**, *38*, 640–647.

[2] a) C.-H. Wong, X.-S. Ye, Z. Zhang, *J. Am. Chem. Soc.* **1998**, *120*, 7137–7138; b) C.-C. Wang, J.-C. Lee, S.-Y. Luo, S. S. Kulkarni, Y.-W. Huang, C.-C. Lee, K.-L. Chang, S.-C. Hung, *Nature* **2007**, *446*, 896–899; c) A. Français, D. Urban, J.-M. Beau, *Angew. Chem. Int. Ed.* **2007**, *46*, 8662–8665.

[3] For an excellent review, see: U. T. Bornscheuer, R. J. Kazlauskas, *Hydrolases in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**, pp. 141–159.

[4] a) G. Hu, A. Vesella, *Helv. Chim. Acta* **2003**, *86*, 4369–4391; b) N. Moitessier, Y. Chapleur, *Tetrahedron Lett.* **2003**, *44*, 1731–1735; c) N. Moitessier, P. Englebienne, Y. Chapleur, *Tetrahedron* **2005**, *61*, 6839–6853; d) W. Muramatsu, T. Kawabata, *Tetrahedron Lett.* **2007**, *48*, 5031–5033.

[5] a) T. Kurahashi, T. Mizutani, J. Yoshida, *J. Chem. Soc. Perkin Trans. 1* **1999**, 465–473; b) T. Kurahashi, T. Mizutani, J. Yoshida, *Tetrahedron* **2002**, *58*, 8669–8677; c) E. Kattnig, M. Albert, *Org. Lett.* **2004**, *6*, 945–948; d) K. S. Griswold, S. J. Miller, *Tetrahedron* **2003**, *59*, 8869–8875; e) Y. Demizu, Y. Kubo, H. Miyoshi, T. Maki, Y. Matsumura, N. Moriyama, O. Onomura, *Org. Lett.* **2008**, *10*, 5075–5077.

[6] For pioneering examples of regioselective manipulation of polyols, see: a) C. A. Lewis, S. J. Miller, *Angew. Chem. Int. Ed.* **2006**, *45*, 5616–5619; b) K. W. Fiori, A. L. A. Puchlopek, S. J. Miller, *Nature Chem.* **2009**, *1*, 630–634.

[7] Among the various anhydrides examined, isobutyric anhydride gave the best selectivity in our previous studies on the kinetic resolution of racemic alcohols and regioselective acylation of carbohydrates, see: a) T. Kawabata, M. Nagato, K. Takasu, K. Fuji, *J. Am. Chem. Soc.* **1997**, *119*, 3169–3170; b) T. Kawabata, K. Yamamoto, Y. Momose, Y. Nagaoka, H. Yoshida, K. Fuji, *Chem. Commun.* **2001**, 2700–2701; c) T. Kawabata, R. Stragies, T. Fukaya, K. Fuji, *Chirality* **2003**, *15*, 71–76; d) T. Kawabata, R. Stragies, T. Fukaya, Y. Nagaoka, H. Schedel, K. Fuji, *Tetrahedron Lett.* **2003**, *44*, 1545–1548; e) T. Kawabata, W. Muramatsu, T. Nishio, T. Shibata, Y. Uruno, R. Stragies, *Synthesis* **2008**, 747–753; f) ref.[1]

[8] The reasons why isobutyric anhydride usually gives better results in selective acylation are not clear. We assume that it may be due to its steric effects as well as its high k_{cat}/k_{uncat} ratio, see: C. B. Fischer, S. Xu, H. Zipse, *Chem. Eur. J.* **2006**, *12*, 5779–5784.

[9] For an excellent review on chiral PPY and DMAP analogues in asymmetric synthesis, see: R. P. Wurz, *Chem. Rev.* **2007**, *107*, 5570–5595.

[10] The C(4)-OCO*i*Pr group is assumed to be located closer to the C(3)-OH group due to the buttressing effect of the neighboring bulky TBDPS group at C(6).

[11] For an example, see: K. C. Nicolaou, S. P. Seitz, D. P. Papahatjis, *J. Am. Chem. Soc.* **1983**, *105*, 2430–2434.

[12] a) C. L. Stevens, P. Blumbergs, D. H. Otterbach, J. L. Strominger, M. Matsuhashi, D. X. Dietzler, *J. Am. Chem. Soc.* **1964**, *86*, 2937–2938; b) R. J. Ferrier, *Carbohydr. Chem.* **2003**, *34*, 118–135.

[13] S. Dedola, S. A. Nepogodiev, R. A. Field, *Org. Biomol. Chem.* **2007**, *5*, 1006–1017.

[14] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021.

[15] The rearrangement of the octylthio group of thioglucopyranosides has been reported, see: K. C. Nicolaou, T. Ladduwahetty, J. L. Randall, A. Chucholowski, *J. Am. Chem. Soc.* **1986**, *108*, 2466–2467.

[16] P. Fialová, A. T. Carmona, I. Robina, R. Ettrich, P. Sedmera, V. Prikrylová, L. Petrásková-Husáková, V. Kren, *Tetrahedron Lett.* **2005**, *46*, 8715–8718.

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