A Novel Oxidatively Removable Linker and Its Application to α-Selective Solid-Phase Oligosaccharide Synthesis on a Macroporous Polystyrene Support

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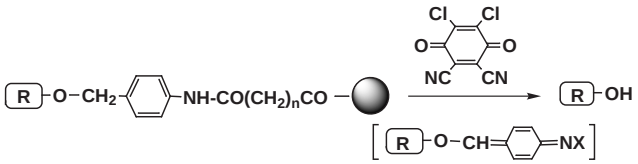
Abstract: A novel *p*-acylaminobenzyl-type linker and its application to the solid phase synthesis of oligosaccharides are described. The *p*-glutarylaminobenzyl ether of a monosaccharide was readily introduced to a polymer support by amide bond formation. The linker moiety was smoothly cleaved by DDQ oxidation. α-Selective glycosylation was accomplished by virtue of the solvent effect of diethyl ether on a solid support of a macroporous polystyrene. High α-selectivity was achieved by the use of benzylated donors possessing the bulky t-butyldiphenylsilyl group at the 6-position.

Key words: solid-phase synthesis, glycosylation, thioglycoside, macroporous polystyrene, acylaminobenzyl linker

Oligosaccharides and glycoconjugates play important roles in many biological recognition processes such as cellular trafficking, cell-cell adhesion, chronic inflammation, viral and bacterial infection, and immunostimulation by bacterial cell surface glycoconjugates. Solid-phase synthesis of oligosaccharides has been one of the most important topics in organic chemistry, because it will enable rapid and easy preparation of many oligosaccharides for biological or functional studies. Since Danishefsky's oligosaccharide synthesis on solid-phase in 1993, extensive efforts have been made and several successful studies have already been reported.[1-6] However, general and practical methods for solid-phase synthesis have not been established yet. There remain several crucial issues including i) stereoselective glycosylation on solid supports and ii) facile and selective cleavage of linkers.

In the present study, we have focused on achieving 1,2-*cis*-α-selective glycosylation on the solid support, which have not been reported. The stereoselective formation of 1,2-*cis*-glycosides such as α-glucosides is generally rather difficult since assisting effects such as neighboring-group participation are not available. The combination of diethyl ether as a solvent and perchlorates as a counteranion for oxocarbenium ion intermediates have been frequently used for α-selective glycosylation.[7] In previous solid-phase oligosaccharide synthesis, 1 or 2% cross-linked gel-type poly(styrene-co-divinylbenzene) resins have been mainly used as polymer supports. Although swelling resin in solvents is essential for solid-phase reactions, gel-type polystyrene resins show limited swelling (approx. 3.5 ml/g) in diethyl ether. In fact, glycosylation using gel-type polystyrene resins in ether did not proceed in our preliminary experiments. A mixture of CH_2Cl_2 and diethyl ether can swell a gel-type polystyrene resin, but α-selectivity of glycosylation in such a mixture was considerably reduced as compared to those in ether alone (data not shown). Such restriction of solvents has been a general problem of solid-phase organic synthesis. Recently, a new type of a polystyrene resin, ArgoPore™, was developed to overcome the solvent restrictions of gel-type polymer supports.[8] ArgoPore™ is a highly cross-linked macroporous poly(styrene-co-divinylbenzene) resin and hence has constant ability for uptake (swelling) of organic solvents. A wide range of solvents typically employed for solution-phase reactions, including protic solvents and even water, can thus permeate easily into the pores and be used for solid-phase synthesis on this resin. In addition, more rapid access of reagents to reaction sites is expected than in the case of gel-type resins, where the rate of diffusion may be low. We therefore investigated α-selective glycosylation using ether as a solvent on this macroporous polystyrene.

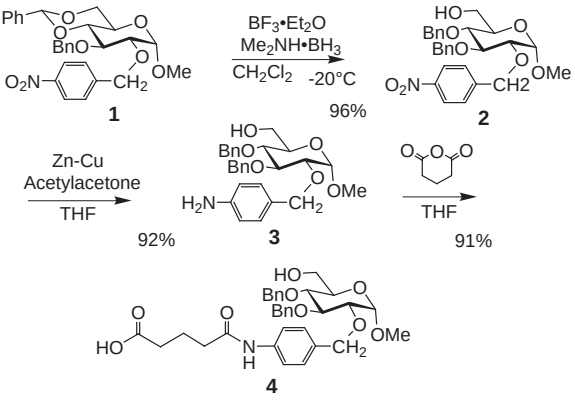
Clear-cut linking/liberation procedures to/from polymer supports are indispensable for successful solid-phase synthesis. Acid-stable linkers are of particular importance for oligosaccharides and glycoconjugates synthesis by the solid-phase strategy since glycosylation reactions are normally carried out under acidic conditions. Wang-type linkers having *p*-alkoxybenzyl ether linkages labile to Lewis acids are not suitable in this. In addition, selective cleavage of linkers, leaving other protecting groups intact, followed by purification and final deprotection is a rational strategy for oligosaccharide synthesis. This is an obvious difference from the solid-phase synthesis of peptides where all the side chain protections and linkers may be removed simultaneously. In the case of oligosaccharides purification in protected forms is generally more effective, whereas completely deprotected peptides have been successfully purified by HPLC. We recently reported several new acid-stable benzyl-type protecting groups e.g., *p*-nitrobenzyl, *p*-acylaminobenzyl, and *p*-azidobenzyl groups and their application to the synthesis of complex glycoconjugates.[10] *p*-Acylaminobenzyl ethers among them, i.e., *p*-acetamidobenzyl and *p*-pivaloylaminobenzyl ether, are much more stable under acidic conditions than *p*-methoxybenzyl (MPM) ether, though the former can be readily cleaved by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation at a rate comparable to the cleavage of the latter MPM ether. This fact suggests that the *p*-acylaminobenzyl group should be used as a versatile acid-stable linker by using appropriate spacers.



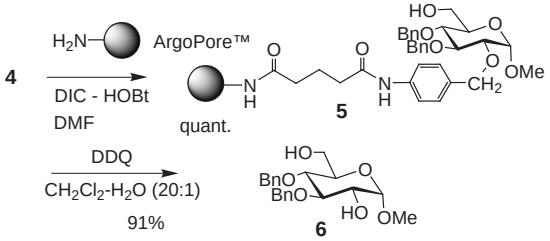
Scheme 1

The *p*-acylaminobenzyl ether linker can be easily obtained from the corresponding *p*-nitrobenzyl ether by reduction of the nitro group and subsequent acylation with bifunctional carboxylic acids, e.g., glutaric acid. Introduction of the linker at glycosidic position should be avoided, since its cleavage usually gives an equilibrium mixture of the anomeric hydroxy group and thus renders purification of the product difficult. A synthesis of monosaccharides possessing 2-*O*-bound *p*-acylaminobenzyl ether linker is shown in **Scheme 2** as an example. The 2-*O*-glutarylaminobenzylated monosaccharide **4**[11] was prepared from 2-*O*-*p*-nitrobenzyl glucose derivative **1**[12] via regioselective ring opening with $BH_3.Me_2NH$ and $BF_3.OEt_2$ in CH_2Cl_2,[13] reduction of the nitro function by Zn-Cu and acetylacetone[14,15], and final *N*-glutarylation (**Scheme 2**).

The monosaccharide **4** was readily introduced to aminomethylated macroporous polystyrene resin ArgoPore™ amine by the use of **4** (1.2 equiv.), *N*,*N*'-diisopropylcarbodiimide (DIC), and 1-hydroxybenzotriazole (HOBt) in CH_2Cl_2 quantitatively (**Scheme 3**).[16] The linker of **5** was smoothly cleaved by DDQ oxidation in CH_2Cl_2-H_2O (20:1) to give **6** in a good yield.[17]

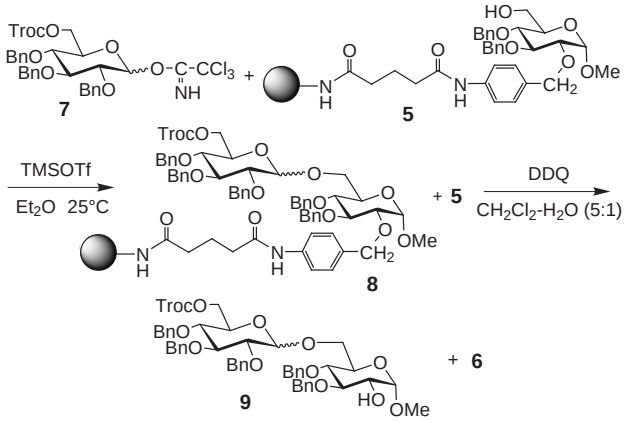


Scheme 2



Scheme 3

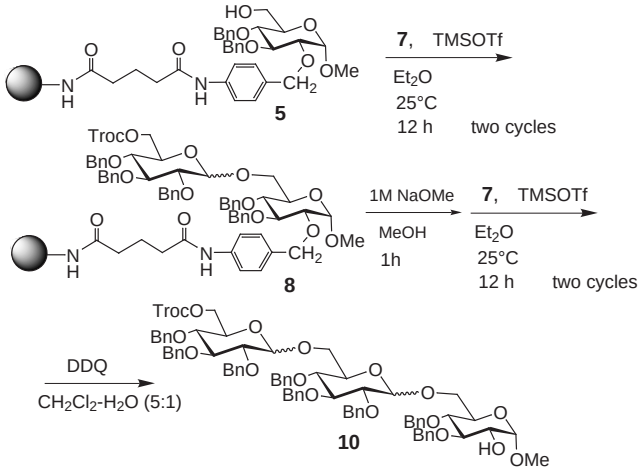
Glycosylation on solid support was then investigated by the use of a benzylated glycosyl trichloroacetimidate donor with a 6-*O*-trichloroethoxycarbonyl (Troc) **7**,[18] since we previously found α-selectivity was enhanced by the influence of the 6-*O*-Troc function.[7,14] The glycosylation was carried out using 3 equiv. of donor **7** to solid supported acceptor **5** and TMSOTf (0.2 equiv. relative to **7**) in ether (25 °C, 12 h) (**Scheme 4**).



Scheme 4

The glycosylation proceeded to give the desired disaccharide **9** in 48% yield along with 25% of monosaccharide **6** derived from unreacted acceptor after cleavage from the resin.[19] α-Preferential glycosylation by virtue of the solvent effect of ether was thus achieved though the selectivity was not satisfactory (α:β = 2:1). The chemical yield of **9** (47%) was not improved and unreacted monosaccharide **6** was recovered in 21% yield, even when the glycosylation reaction step was repeated twice. These results indicated the existence of reactive and non-reactive monosaccharide residues on the pore surface of the support (Table 1). Dry ArgoPore™ resin has an average pore size of approximately 90 Å. Since the intermediates of acylation reaction are non-ionic, they may readily reach the amino groups even in smaller pores and thus acylation reaction proceeds quantitatively. On the other hand, the ionic reaction intermediates derived from the glycosyl donor consists of oxocarbenium ions and a potentially large counterions. Glycosylation therefore may not proceed in small pores owing to steric hindrance of the resin itself but may proceed efficiently in larger pores. This assumption was confirmed by the following trisaccharide synthesis (**Scheme 5**).

After the second glucose residue was introduced as described above, the 6-*O*-Troc group of the disaccharide **8** was removed by NaOMe in MeOH.[20] Glycosylation with the trichloroacetimidate **7** and TMSOTf was then repeated at two times. The desired trisaccharide **10** was obtained in 42% yield after cleavage from the resin and the disaccharide **9** was formed in only a tiny amount as indicated by thin layer chromatography (TLC) analysis. This result shows that ca. 90% of disaccharide acceptor on the sup-



Scheme 5

port was glycosylated by the second glycosylation step to give the trisaccharide whereas the monosaccharide acceptor on unreactive site was not glycosylated by the second cycle of the reaction.

The above experiments indicate that the presence of unreactive sites on the macroporous polystyrene resin therefore is not expected to cause serious problems in the total process of oligosaccharide synthesis.

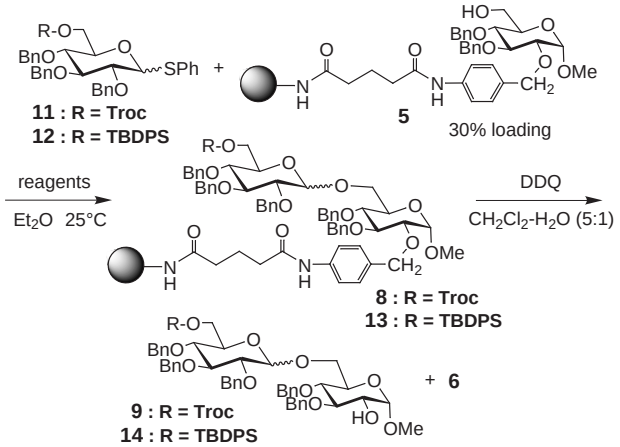
Nevertheless, we tried to use only those amino functions on the surface of large pores in order to improve the yield of glycosylation at the first step. Selective loading of the monosaccharide **4** on the reactive sites, i.e., the surface of large pores was accomplished by decreasing the loading levels (**Table 1**). Monosaccharide resins were prepared in which 30 or 50% of the total amino groups were acylated with the monosaccharide **4**.[15] The unreacted amino group on the resin was blocked by acetylation. The glycosylation was carried out on the solid support in ether by using 3 equiv. of the imidate **7** and 0.2 equiv. of TMSOTf at 25 °C and the results are shown in **Table 1**.[18] The yields of the disaccharide increased as the loading ratio decreased as expected. By using the 30% loading resin, the disaccharide **9** was obtained in 82% yield with trace amounts of monosaccharide **6**. Subsequent glycosylation also proceeded smoothly using 30% loaded resin to give the trisaccharide **10** in 70% yield from **5** (total 4 steps, average yield 92%).

Table 1 Glycosylation on ArgoPore™ using trichloroacetimidate **7** in ether as the function of the loading level of the monosaccharide

entry	loading level (%)	time	yield (%) **9**	**6**	α : β
1	100	12 h x 2	47	21	65 : 35
2	50	12 h x 2	55	21	66 : 34
3	30	12 h x 2	82	trace	65 : 35

By the use of a macroporous polystyrene, we succeeded in glycosylation on solid support in ether in good yields though the α-selectivity was not satisfactory.

α-Glycosylation on solid support was next investigated by using thioglycosides as glycosyl donors on the basis of our recent methodologies,[7] since it is difficult to obtain high α-selectivity by using glycosyl trichloroacetimidates.[21] The results using 6-*O*-Troc thioglycoside **11** as a donor are summarized in **Table 2**. All the reactions were carried out by using 3 equiv. of the thioglycoside relative to the acceptor. PhSeNPhth-$Mg(ClO_4)_2$ which effectively promotes glycosylation with thioglycosides under mild conditions[7a] in solution also promoted the reaction on solid-support, but a considerable portion of the acceptor on the solid-support was not glycosylated even though the 30% loaded resin was employed (entry 1). The α-selectivity was, however, improved to α:β = 84:16. This result shows some of acceptor **5** was still loaded on less reactive sites of the polymer, which may be accessible by other strong activating reagents. Hypervalent iodine reagents prepared from PhIO and strong Lewis acids were previously shown very high reactivity, where the α-selectivity can be controlled by selecting Lewis acids.[7b] The glycosylation with thioglycoside **11** was effected by the use of either PhI*O*-$TMSClO_4$ (entry 2) or PhIO-$SnCl_4$-$AgClO_4$ (entry 3) to give the disaccharide **9** in ca. 60% yields with trace amounts of monosaccharide **6** after cleavage from the resin, with moderate α selectivity (α:β = 3:1).



Scheme 6

Table 2 Glycosylation with 6-*O*-Ttov thioglycoside **11** on ArgoPore™ in ether

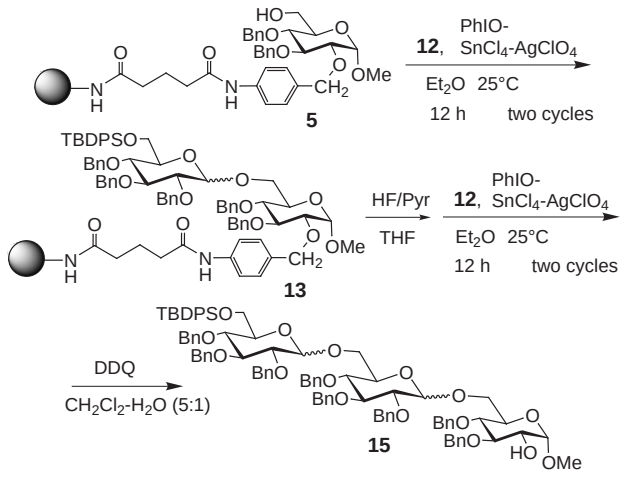
entry	reagents (equiv. to donor)	temp.	yield (%) **9**	**6**	α : β
1	PhSeNPhth-$Mg(ClO_4)_2$ (1.2-0.5)	35°C	43	30	84 : 16
2	PhIO-$TMSClO_4$ (1.0-0.5)	25°C	61	trace	76 : 24
3	PhIO-$SnCl_4$-$AgClO_4$ (1.0-0.5-0.5)	25°C	62	trace	75 : 25

We recently found a strong α-orienting effect of bulky trityl (Trt) and t-butyldimethylsilyl (TBDMS) groups at the 6-position of glycosyl donors[7a,22]. Since Trt group is readily cleaved by acids, 6-*O*-TBDPS thioglycoside **12** was examined and the results are shown in **Table 3**. α-Selectivity was dramatically improved by the use of 6-*O*-TBDPS donor **12** as expected. Activation by PhSeNPhth-$Mg(ClO_4)_2$ or NBS-$LiNO_3$[7c] gave disaccharide **14** with high α-selectivity, though some of the monosaccharide **6** was recovered (entry 1, 2). Combination of PhIO with $SnCl_4$-$AgClO_4$ completed the reaction to give the disaccharide **14** in 62% yield with substantially high α-selectivity (α:β = 9:1) (entry 3).[23] This was the most practical result in terms of both yield and α-selectivity.

Table 3. Glycosylation with 6-*O*-TBDPS thioglycoside **12** on ArgoPore™ in ether.

entry	reagents (equiv. to donor)	temp.	yield (%) **14**	yield (%) **6**	α : β
1	PhSeNPhth-$Mg(ClO_4)_2$ (1.2-0.5)	35°C	48	22	100 : 0
2	NBS-$LiNO_3$ (1.2-0.5)	25°C	41	20	97 : 3
3	PhIO-$SnCl_4$-$AgClO_4$ (1.0-0.5-0.5)	25°C	62	trace	90 : 10

The synthesis of trisaccharide **15** was investigated by use of 6-*O*-TBDPS thioglycoside **12** as a donor and PhIO-$SnCl_4$-$AgClO_4$ as promoter (**Scheme 7**). After the first glycosylation step, the 6-*O*-TBDPS group was removed by HF/Pyr in THF.[24] The second glycosylation step was then carried out in the same manner as the first one. At each step, the glycosylation reaction was repeated two times each with 3 equiv. of the donor. Finally, cleavage from the resin by DDQ oxidation afforded the trisaccharide **15** in 50% yield (total 4 steps, average yield 84%). The α:β selectivity was 9:1 for each anomeric position as judged by ^{1}H NMR analysis.



Scheme 7

In summary, we have successfully accomplished solid-phase synthesis of oligosaccharides by applying solution phase synthesis methodologies. α-Selective glycosylation on solid support was achieved by using a macroporous polystyrene support, ArgoPore™, which permits the use of diethyl ether as the solvent. We also demonstrated the versatility of an acylaminobenzyl linker which can be selectively cleaved by DDQ oxidation. The strong α-orienting effect of the 6-*O*-TBDPS function is applicable to α-selective glycosylation in general.

Acknowledgement

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(11) **4**:^{1}H NMR (500 MHz, $CDCl_3$) δ:7.69 (s, 1H, CONHPh), 7.47 (d, 2H, J = 8.24 Hz, *o* protons of $CONHPhCH_2O$), 7.36-7.27 (m, 12H, Ph x 2, *m* protons of $CONHPhCH_2O$), 4.95, (d, 2H, Jgem = 10.99 Hz, CH_2Ph), 4.83 (d, 2H, Jgem = 10.99 Hz,

CH_2Ph), 4.86 (d, 2H, Jgem = 10.99 Hz, CH_2Ph), 4.63 (d, 2H, Jgem = 10.99 Hz, CH_2Ph), 4.73 (d, 2H, Jgem = 12.36 Hz, CH_2Ph), 4.60 (d, 2H, Jgem = 12.36 Hz, CH_2Ph), 4.53 (d, 1H, $J_{1,2}$ = 3.43 Hz, H-1), 3.99 (dd, 1H, $J_{2,3}$ = 9.16 Hz, $J_{3,4}$ = 9.16 Hz, H-3), 3.77 (dd, 1H, $J_{6,5}$ = 2.52 Hz, $J_{6,6'}$ = 11.90 Hz, H-6), 3.69 (dd, 1H, $J_{6',5}$ = 3.89 Hz, $J_{6',6}$ = 11.90 Hz, H-6'), 3.65-3.62 (m, 1H, H-5), 3.52 (dd, 1H, $J_{3,4}$ = 9.16 Hz, $J_{4,5}$ = 9.62 Hz, H-4), 3.45 (dd, 1H, $J_{1,2}$ = 3.43 Hz, $J_{2,3}$ = 9.16 Hz H-2), 3.34 (s, 3H, OMe), 2.46-2.39 (m, 4H, $HOCOCH_2CH_2CH_2CONHPh$), 2.06-2.00 (m, 2H, $HOCOCH_2CH_2CH_2CONHPh$); FAB-MS (positive) m/z 616.2 [$(M+Na)^+$].

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(15) Reduction with $NaBH_4$-$NiCl_2$·$6H_2O$ in MeOH also gave **3** in good yields.

(16) A typical procedure for introduction of a monosaccharide on solid support. ArgoPore resin (NH_2:0.60 mmol/g) (1.41 g, 845 μmol) was placed in a polypropylene tube (Varian) fitted with a filter, and washed with 5% diisopropylamine in CH_2Cl_2 and then CH_2Cl_2. Compound **4** (251 mg, 423 μmol), HOBt (286 mg, 4.22 mmol), CH_2Cl_2, and DIC (132 μl, 1.69 μmol) were added to the tube, successively. The reaction mixture was shaken for 3 d and filtered. The resin was washed with CH_2Cl_2 and stained with Bromophenol Blue in order to check the progress of *N*-acylation. The residual amino groups on the resin were then capped with acetic anhydride (1.0 ml) and triethylamine (500 μl) in CH_2Cl_2 (2.0 ml) by shaking for 10 min. The capping reaction was repeated until the color of the resin turned from blue green to pale yellow. The resin was then shaken with 1M NaOMe (15 ml) for 1 h and then washed successively with MeOH, CH_2Cl_2, and diethyl ether. Yield of the resin 1.68 g (Theoretical yield of the resin is 1.68 g.).

(17) A typical cleavage reaction of acylaminobenzyl linker: ArgoPore resin linked with monosaccharide via acylaminobenzyl linker (174 mg, 57.6 μmol of a monosaccharide) was shaken with a mixture of DDQ (15. 7 mg, 69.1 μmol) in CH_2Cl_2 (2.5 ml) and water (125 μl) at room temperature for 4 h. After the reaction mixture was filtered, saturated ascorbic acid solution (10 ml) was added to the filtrate to quench excess DDQ. The resin was shaken again with DDQ (7.9 mg, 34.5 μmol) in CH_2Cl_2 (2.5 ml) and water (125 μl) at room temperature for 4 h and worked up as the same manner. The organic layer was combined, washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified with preparative silica-gel TLC (toluene-EtOAc = 1:1) to give colorless solid. Yield 19.6 mg (91%).

(18) The general procedure for solid-phase glycosylation using a glycosyl trichloroacetimidate: The monosaccharide resin (30% loading) (155 mg, 30.0 μmol) was washed with dry ether (3 ml) three times. To the resin were added Molecular Sieves 4A beads, 8-12 mesh (200 mg), a solution of a glycosyl trichloroacetimidate (69.3 mg, 90.0 μmol) in dry ether (3.0ml), and TMSOTf (3.5 μl, 18.0 μmol), successively. The reaction mixture was shaken with Rotator RT-50 (Taitech) at room temperature for 12 h. The solution was removed by filtration and the resin was washed with CH_2Cl_2 and ether. After Molecular Sieves 4Å beads were removed by picking with forceps, the resins were washed twice with ether and dried under vacuum. After this procedure was repeated, the resins were subjected to cleavage reaction by DDQ or deprotection of the Troc group.

(19) All the yields were obtained after cleavage from the resin followed by purification by silica-gel column chromatography or preparative silica-gel TLC.

(20) Typical procedure for the removal of the Troc group: To the disaccharide resin **8** (180 mg) was added a solution of MeONa in MeOH (1 M, 3 ml). After the reaction mixture was shaken for 1 h, the solution was removed by filtration and the resin was washed with MeOH and CH_2Cl_2.

(21) α-Selectivity was improved to α:β = 4:1 by virtue of α-orienting effect of the 6-*O*-TBDPS group by using 0.2 equiv. of $TBSClO_4$ as a catalyst.

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(23) The general procedure for solid-phase glycosylation using a thioglycoside: The monosaccharide resin (30% loading) (129 mg, 25 μmol) was washed with dry ether (3 ml) three times. To the resin (30% loading) were added Molecular Sieves 4Å beads, 8-12 mesh (200 mg), a solution of a thioglycoside (75 μmol) in dry ether (3.0 ml), PhIO (16.5 mg, 54 μmol), $SnCl_4$ (4.4 μl, 38 μmol), and $AgClO_4$ (8 mg, 39 μmol), successively. The reaction mixture was shaken with Rotator RT-50 (Taitech) (or Nautilus™ 2400, Argonaut Technologies[8]) at room temperature for 12 h. The solution was removed by filtration and the resin was washed successively with ether and CH_2Cl_2. After Molecular Sieves 4Å beads were removed by picking with forceps, the resins were washed twice with ether and the resins were dried under vacuum. After this procedure was repeated two times, the resins were subjected to cleavage reaction by DDQ or deprotection of the Troc or TBDPS group.

(24) The general procedure for cleavage of TBDPS group: To a disaccharide resin[23] was added a solution of hydrogen fluoride-pyridine (Aldrich) (1ml) in THF (2 ml). The reaction mixture was shaken at room temperature for 18 h. The solution was removed by filtration and the resin was washed successively with THF and CH_2Cl_2.

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