Novel Molecular Clamp Method for Anomeric Stereocontrol of Glycosylation

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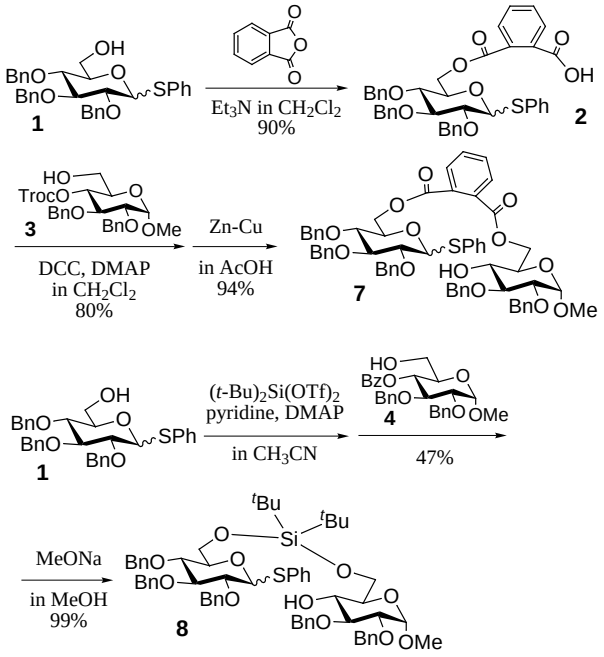
Abstract: Stereocontrolled glycosylation is described by using a molecular clamp, which binds a glycosyl donor to an acceptor and controls their spatial arrangement. An α(1→4) glycosidic linkage was formed in a good yield with high selectivity by the use of a phthaloyl bridge bound to both 6-positions of a glycosyl donor and an acceptor. β-Selective glycosylation was effected by the use of a silyl bridge attached to the same 6-positions of the same glycosyl donor and acceptor. Application of this method to the synthesis of a maltotetraose derivative is also described.

Key words: intramolecular glycosylation, stereocontrol, molecular clamp, glycosides, carbohydrate

Stereoselective glycosylation has been a major issue for efficient synthesis of oligosaccharides and glycoconjugates. Recently, various studies for anomeric stereocontrol of glycosylation have been reported by using intramolecular reaction of a glycosyl donor and a glycosyl acceptor linked together with an appropriate bridge.[1-9]

So far described methods for intramolecular glycosylation are divided into two categories. One is so-called "intramolecular aglycon delivery". In this method, the glycosyl acceptor is delivered to the donor via a linker attached on the donor moiety.[1,2] In several cases, the glycosyl acceptors were attached to the leaving groups of the donors.[2] In the other category, a stable bridge is used as a "molecular clamp" which controls the spatial arrangement of a donor and an acceptor to kinetically accelerate the glycosylation and allows a stereo- and regioselective reaction.[3-9] We reported many years ago the first application of the latter method to the synthesis of the glucosaminyl-muramic acid residue which was not formed by direct glycosylation using the oxazoline method without a molecular clamp.[3] Recently, stereoselective glycosylation reaction using this method was reported by several groups, especially by the intensive work of Ziegler et al.[4-9] More extensive studies should be addressed in order to find more convenient and practical route, since diverse sets of bridged positions and linker moieties can be used for intramolecular glycosylation.

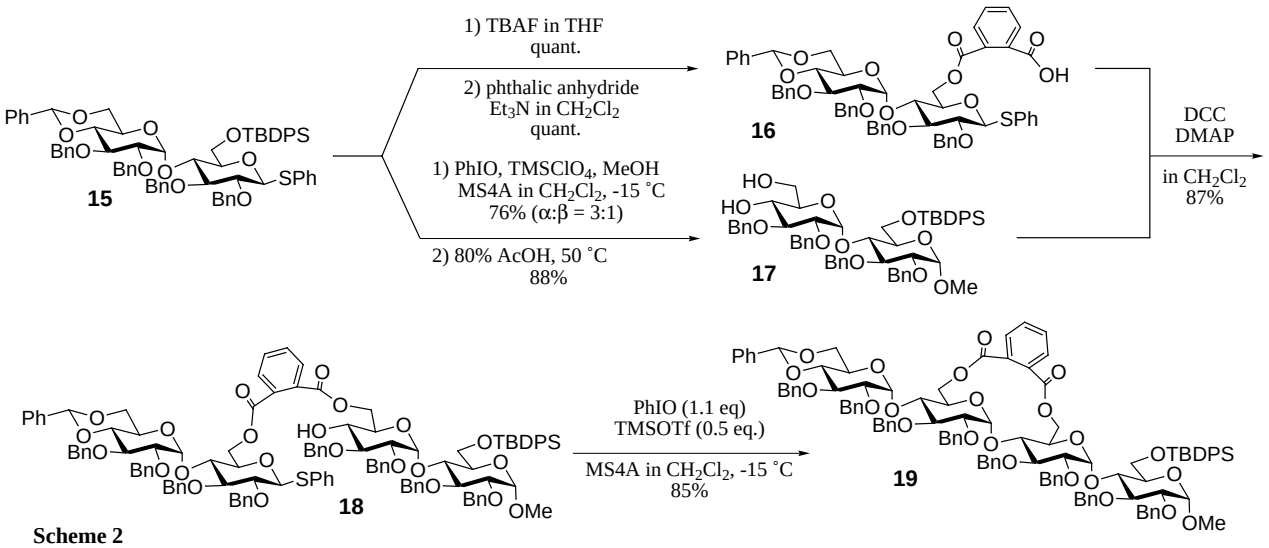
In the present study, we focused on the synthesis of (1→4) glycosidic linkage, since the 4-position of glucose is most sterically hindered and thus sometimes difficult to be glycosylated. We selected the 6-positions of a donor and an acceptor for cross-linking, since 6-positions are most reactive and thus can be readily functionalized. Either α(1→4) or β(1→4) glucoside was selectively obtained by using a phthaloyl or silyl bridge, respectively. Application of this method to the synthesis of maltotetraose is also described by segment condensation of maltose moieties.



Scheme 1

In order to investigate the effect of various linkers, a series of different bridged saccharides were prepared. Typical synthetic routes are shown in Scheme 1. Treatment of phenyl 1-thio-β-D-glucopyranoside **1** with phthalic anhydride afforded the phthaloylated derivative **2**, which was then condensed with **3** by the use of dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP). The 4-*O*-trichloroethoxycarbonyl (Troc) group of the resulting 6,6'-phthaloyl-bridged saccharide was selectively removed with Zn-Cu in AcOH to give compound **7**. The 6,6'-succinyl-bridged saccharide **6** and the 6,6'-glutaryl-bridged saccharide **5** were obtained in a similar manner. The silyl-bridged saccharide **8** was prepared by the successive reaction of $(t\text{-Bu})_2Si(OTf)_2$ with **1** and **4** followed by the removal of the benzoyl group.

Glycosylation reactions of these bridged saccharides were then examined by using 1.1 equiv of PhIO and 0.5 equiv of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as activating reagents of thioglycosides[10] under N_2 atmosphere in CH_2Cl_2.[11] Under these reaction conditions, ste-



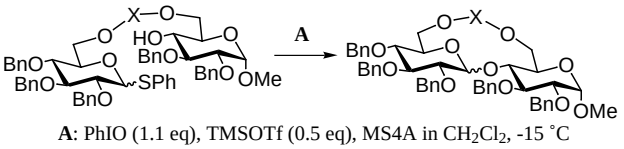
Scheme 2

reoselectivity was not observed without a molecular clamp (data not shown).

α-Selective glycosylations were achieved by the use of diester bridges. With the glutaryl linker, the desired disaccharide **9** was obtained with some α-selectivity but the yield of the glycosylation was low because of preferential hydrolysis of the thioglycoside moiety in the donor part (Table 1, Entry 1). By decreasing the chain length of the linker from glutaryl to succinyl, both the yield and α-selectivity were improved (Table 1, Entry 2). We then examined the glycosylation of **7** possessing a more rigid phthaloyl linker which is expected to suppress the free rotations around the linker. Indeed, both the yield and selectivity were dramatically improved by using a phthaloyl linker (86%, α:β = 99:1, Entry 3).

The solvent effect was then investigated on the glycosylation of **7**. Glycoside **11** was obtained also with high α-selectivity in Et_2O, which generally promotes α-selective glycosylation[12a,b] (Entry 4). The yield was, however, decreased owing to hydrolysis of the donor moiety. In CH_3CN, the β-glycoside was obtained preferentially via the known α-nitrilium kinetic intermediates[12] (Entry 5). Without the molecular clamp, β(1→4)-glycoside was also obtained preferentially (α:β = 12:88) under the same reaction conditions.[10] In this case, the solvent effect of CH_3CN dominated over the effect of the molecular clamp, though the α-oriented effect of the phthaloyl bridge was observed to some extent.

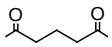
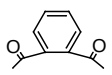
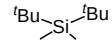
β-Selective glycosylation was effected by the use of the silyl linker. The glycosylation of **8** proceeded smoothly to give the β-glucoside **12** preferentially even in CH_2Cl_2, a solvent in which stereoselective glycosylation is seldom observed, in a good yield (82%, α:β = 15:85, Entry 6). Interestingly, Et_2O promoted β-glycosylation in this case to afford β-glucoside with a higher selectivity (Entry 7). This peculiar result suggests that Et_2O first kinetically attached to the oxocarbenium ion intermediate from the α-face and then the proximal acceptor immediately attacked the intermediate from the β-face before the α-orientated Et_2O complex changed into the thermodynamically more stable β-orientated one. This assumption is supported by the very fast reaction rate of this particular glycosylation as compared to the normal α-preferential reaction in ether (e.g. Entry 4). β-Selective glycosylation was also effected with a similarly high selectivity by the use of the known solvent effect of CH_3CN (Entry 8).



A: PhIO (1.1 eq), TMSOTf (0.5 eq), MS4A in CH_2Cl_2, -15 ˚C

5, X = glutaryl
6, X = succinyl
7, X = phthaloyl
8, X = silyl
9, X = glutaryl
10, X = succinyl
11, X = phthaloyl
12, X = silyl

Table 1. Intramolecular Glycosylation

Entry	X (linker)	Solvent	Time	Yield (%)	α : β[a]
1		CH_2Cl_2	10 min	37	89 : 11
2		CH_2Cl_2	10 min	67	93 : 7
3		CH_2Cl_2	10 min	86	99 : 1
4		Et_2O	15 h	46	99 : 1
5		CH_3CN	30 min	83	28 : 72
6		CH_2Cl_2	20 min	82	15 : 85
7		Et_2O	30 min	70	2 : 98
8		CH_3CN	30 min	77	3 : 97

[a] The ratio of α:β was determined by ^{1}H-NMR.

The present "molecular clamp" method was next applied to the synthesis of maltotetraose [= α(1→4) linked tetraglucose] by a segment condensation of two maltose units as shown in Scheme 2. The disaccharide thioglycoside **15**[13] was prepared from maltose as a common synthetic intermediate for both glycosyl donor and acceptor. After *t*-butyldiphenylsilyl (TBDPS) group of **15** was removed with tetrabutylammonium fluoride (TBAF), the resulting 6-OH free disaccharide was reacted with phthalic anhydride to give the donor part **16**.[14] The acceptor part **17**[15] was obtained by glycosylation of **15** with MeOH followed by debenzylidenation. Compounds **16** and **17** were coupled with DCC and DMAP to afford the bridged tetrasaccharide **18**.[16] Intramolecular glycosylation of compound **18** was carried out under N_2 atmosphere in CH_2Cl_2 by using 1.1 equiv of PhIO and 0.5 equiv of TMSOTf to afford the desired tetrasaccharide **19**[17] in a good yield with perfect α-selectivity.

In summary, the molecular clamp method allows facile and stereocontrolled glycosylations. In previous studies of the molecular clamp method, anomeric selectivity has been controlled by the selection of both bridged positions and linker moieties.[3-9] We demonstrated here phthaloyl and silyl bridges attached to the same 6-positions of the donor and the acceptor afforded α- and β-anomers, respectively, with high selectivity. Our results indicate anomeric selectivity can be also controlled by the length, rigidity, and structural feature of linkers, even if the attached positions to the donor and an acceptor are fixed. This method is expected to be useful particularly for oligosaccharide synthesis via segment condensation as described above.

Acknowledgement

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(11) A typical procedure for glycosylation by molecular clamp method: To a suspension of **7** (22 mg, 21 μmol), PhIO (4.4 mg, 23 μmol), and Molecular Sieves 4A (MS4A) (50 mg) in 2 ml of CH_2Cl_2 was added TMSOTf (2 μl, 10 μmol) at -15 °C under N_2 atmosphere. After the mixture was stirred at -15 °C for 15 min, ethyl acetate (AcOEt) and saturated aqueous $NaHCO_3$ solution were added. After MS4A were removed by filtration, the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by preparative silica-gel thin layer chromatography (TLC) (toluene : AcOEt = 5:1) to give **11**: Yield 17 mg (86%, α : β = 99:1). **11**: ^{1}H NMR (500 MHz, $CDCl_3$), α-anomer: δ = 5.94 (d, 1H, $J_{1',2'}$ = 4.12 Hz, H-1'), 4.54 (d, 1H, $J_{1,2}$ = 3.43 Hz, H-1), 3.40 (s, 3H, OMe); β-anomer: δ = 3.36 (s, 3H, OMe); ESI-MS m/z 925.385 [(M+Na)$^+$]. **9**: ^{1}H NMR (500 MHz, $CDCl_3$), α-anomer: δ = 5.84 (d, 1H, $J_{1',2'}$ = 3.89 Hz, H-1'), 4.62 (d, 1H, $J_{1,2}$ = 3.43 Hz, H-1), 3.39 (s, 3H, OMe); β-anomer: δ = 3.38 (s, 3H, OMe); ESI-MS m/z 959.409 [(M+Na)$^+$]. **10**: ^{1}H NMR (500 MHz, $CDCl_3$), α-anomer: δ = 5.94 (d, 1H, $J_{1',2'}$ = 4.12 Hz, H-1'), 4.60 (d, 1H, $J_{1,2}$ = 3.43 Hz, H-1), 3.39 (s, 3H, OMe); β-anomer: δ = 3.40 (s, 3H, OMe); ESI-MS m/z 911.360 [(M+Na)$^+$]. **12**: β-anomer: δ = 4.87 (d, 1H, $J_{1',2'}$ = 6.64 Hz, H-1'), 4.61 (d, 1H, $J_{1,2}$ = 3.66 Hz, H-1), 3.42 (s, 3H, OMe); α-anomer: δ = 3.38 (s, 3H, OMe); ESI-MS m/z 969.455 [(M+Na)$^+$].

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(13) The maltose unit **15** was prepared as follows. To a solution of maltose octaacetate (85.3 g, 126 mmol) in $(CH_2Cl)_2$ (1.3 l) were added phenylthio trimethylsilane (TMSSPh, 26.3 ml, 139 mmol) and ZnI_2 (65.0 g 252 mmol) at room temperature. After being stirred overnight, the mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in AcOEt and the solution was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (toluene : AcOEt = 2:1) to give the phenyl thiomaltoside as an oily product (75.8 g, 83%). To the solution of the resulting thioglycoside (16.8 g, 23.1 mmol) in MeOH (1 l) was added 1M NaOMe in MeOH (10 ml) at room temperature. After being stirred for 4 h, the reaction mixture was neutralized with Dowex 50W-X8 (H^+). The resin was removed by filtration and the filtrate was concentrated in vacuo. To the solution of the residue in DMF (200 ml) were added $PhCH(OMe)_2$ (5.2 ml, 34.7 mmol) and $TsOH•H_2O$ (1.0 g) at room temperature. The reaction mixture was warmed to 60 °C under reduced pressure (15 mmHg) and then stirred for 3 h. After the reaction mixture

was cooled to room temperature, pyridine (100 ml), DMAP (282 mg, 2.31 mmol), and TDBPSCl (12.7 ml, 46.2 mmol) were added. After being stirred overnight, the mixture was concentrated in vacuo. The residue was dissolved in AcOEt and the solution was washed with 1 M HCl and brine, dried over $MgSO_4$, and concentrated in vacuo. After the residue (crude product 23.7 g) was dissolved in DMF (300 ml), NaH (5.56 g, 139 mmol) and BnBr (14.2 ml, 116 mmol) was added at 0 °C. The mixture was stirred at room temperature overnight. After usual work-up, purification by flash silica-gel column chromatography (toluene : AcOEt = 30:1) gave **15** (20.2 g, 78%).

(14) To a solution of **15** (532 mg, 474 μmol) in THF (2.5 ml) was added 1 M TBAF in THF (2.5 ml, 2.5 mmol). The mixture was stirred at room temperature for 2.5 h. After usual work-up, the residue was purified by flash silica-gel column chromatography (toluene : AcOEt = 10:1) to give the 6-OH free disaccharide as a syrup, quantitatively. To the solution of the disaccharide (436 mg, 494 μmol) in CH_2Cl_2 were added phthalic anhydride (113 mg, 763 μmol) and Et_3N (138 μl, 988 μmol) at room temperature and the mixture was stirred at the same temperature overnight. After usual work-up, purification by flash silica-gel column chromatography ($CHCl_3$: acetone = 3:1) gave **16** as a syrup, quantitatively.

(15) To a suspension of **15** (200 mg, 178 μmol), MeOH (14.4 μl, 356 μl), PhIO (59 mg, 267 μmol), $AgClO_4$ (4.6 mg, 67 μmol), and MS4A (50 mg) in 2 ml of CH_2Cl_2 was added TMSCl (4.5 μl, 53 μmol) at -15 °C under N_2 atmosphere. The mixture was stirred at -15 °C for 1 h. After usual work-up, purification by preparative silica-gel TLC (toluene : AcOEt = 30:1) gave the methyl glycosides (α-anomer:107 mg, 59%; β-anomer:36 mg, 36%). The solution of the the α-glycoside (107 mg, 102 μmol) in 80% AcOH (5 ml) was stirred at 50 °C for 4 h and the mixture was then concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (toluene : AcOEt = 5:1) to give **17** as a syrup (85 mg, 88%).

(16) To a solution of compound **16** (159 mg, 155 μmol) and **17** (114 mg, 119 μmol) in CH_2Cl_2 (2 ml) were added DCC (49 mg, 239 μmol) and DMAP (1.5 mg, 12 μmol) at 0 °C. The mixture was then stirred at room temperature overnight. The insoluble materials were filtered off and the filtrate concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (toluene : AcOEt = 10:1) to give **18** as a syrup (204 mg, 87%).

(17) To a suspension of **18** (42 mg, 21 μmol), PhIO (6.9 mg, 32 μmol), and MS4A (50 mg) in 2 ml of CH_2Cl_2 was added TMSOTf (0.39 μl, 2 μmol) at -15 °C under N_2 atmosphere. After the mixture was stirred at -15 °C for 30 min, AcOEt and saturated aqueous $NaHCO_3$ solution were added. After usual work-up, purification by preparative silica-gel TLC (toluene : AcOEt = 7:1) gave **19** as a syrup: Yield 33 mg (85%, α-anomer only). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.72 (d, 1H, $J_{1',2'}$ = 3.89 Hz, H-1'), 5.57 (d, 1H, $J_{1'',2''}$ = 4.12 Hz, H-1''), 5.44 (d, 1H, $J_{1''',2'''}$ = 3.66 Hz, H-1'''), 4.60 (d, 1H, $J_{1,2}$ = 3.43 Hz, H-1), 3.40 (s, 3H, OMe); ESI-MS m/z 1879.71 [$(M+Na)^+$].

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