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A New Glycosylation Method Using Glycosyl Donors Substituted by Enol Ether as a Leaving Group

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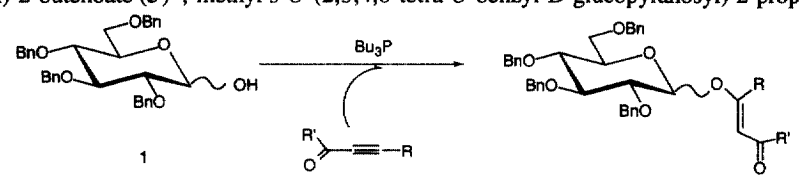
Abstract: Glycosyl donors having a leaving group of enol ether were easily prepared by the addition of the anomeric hydroxyl group of pyranose derivatives to α,β-unsaturated alkynic acid esters or -ketone. These glycosyl donors were selectively glycosidated with several glycosyl acceptors in the presence of trimethylsilyl triflate (TMSOTf). A fucosyl donor was also applied in a similar synthesis.

Key words: glycosylation; enol ether; trimethylsilyl triflate; glycosyl donors;

Selective and simple synthesis of oligosaccharides is currently an important subject in carbohydrate chemistry. In particular, glycosylation reactions play an important role in carbohydrate synthesis. We have studied a series of glycosylation reactions, and recently reported some results such as a selective glycosylation using the glycosyl donors of 1-thio-2-enosides, 3-thio-1-enoses and 1-thio-glucoside in the presence of catalytic $Pd(CH_3CN)_2Cl_2$-AgOTf.[1)]

Although Sinaÿ et al.[2)] reported isopropenyl glycosides synthesized with the Tebbe reagent, we report here a synthesis of another new type of glycosyl donors having enol ether as a leaving group and their use in glycosylation. The present glycosyl donors are characterized to be more reactive for the electrophilic reagent, because of delocalization by electron affinity of the α,β-unsaturated carbonyl group. The glycosyl donors were easily prepared by means of the tri-*n*-butylphosphine-catalyzed addition of the anomeric hydroxyl group of pyranose derivatives to α,β-unsaturated alkynic acid esters or -ketone. The reaction[3)] of tetra-*O*-benzyl-glucopyranose (**1**) with 2 equiv. of methyl 2-butynoate (**2**), methyl propiolate (**3**) or 3-butyn-2-one (**4**) in the presence of 0.3 equiv. of tri-*n*-butylphosphine as a catalyst[4)] gave methyl 3-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-2-butenoate (**5**)[5)], methyl 3-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-2-propenoate (**6**)[6)] or



Scheme 1

3-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-3-butene-2-one (**7**)[7)], respectively (Scheme 1). These products

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were characterized by ^{1}H-NMR, ^{13}C-NMR, and NOE analyses. In these syntheses, all glycosyl donors were obtained as the *E*-form,[8] because the pyranose moiety is too bulky to form the *Z*-form. These donors not only have the advantages of easy preparation and handling but also are very stable over one year even at room temperature.

The enol ether type glycosyl donors were activated with Lewis acids accompanied by electron transfer. The use of $BF_3 \cdot OEt_2$ as a Lewis acid was not effective. The yield of the disaccharide was low and most of the donor

Table 1. Results of glycosylation reactions using TMSOTf.[a]

Run[b]	D[c]	A[d]	Solvent	Temp.	Time (h)	P[e]	Yields[f] (%)	Recovery (%)[f] D[c]	A[d]	α : β[g]
1	**5**	**8**	CH_2Cl_2	r.t.	1	**11**	71	trace	27	1 : 1
2	**5**	**8**	CH_2Cl_2	−20℃	1	**11**	77	-	22	3 : 1
3	**5**	**8**	CH_2Cl_2	−50℃	0.5	**11**	82	-	-	9 : 2
4	**5**	**8**	CH_3CN	−20℃	1	**11**	68	-	47	1 : 1
5	**5**	**8**	CH_3CN	−40℃	0.5	**11**	69	-	-	2 : 9
6	**5**	**8**	C_2H_5CN	−50℃	0.5	**11**	81	-	38	2 : 7
7	**5**	**9**	C_2H_5CN	−50℃	1	**13**	55	-	37	β
8	**5**	**10**	CH_2Cl_2	−50℃	0.5	**12**	53	-	37	1 : 1.4
9	**6**	**8**	C_2H_5CN	r.t.	0.5	**11**	74	-	-	2 : 3

a) All reactions used 10 eq. of TMSOTf. b) All reactions were carried out under Ar atmosphere and Molecular Sieves 4A. c) Donor. d) Acceptor (1.5 eq.). e) Product. f) All the yields were determined from the isolated weights after silica-gel column chromatography. g) Determined by ^{1}H-NMR (300 or 400 MHz).

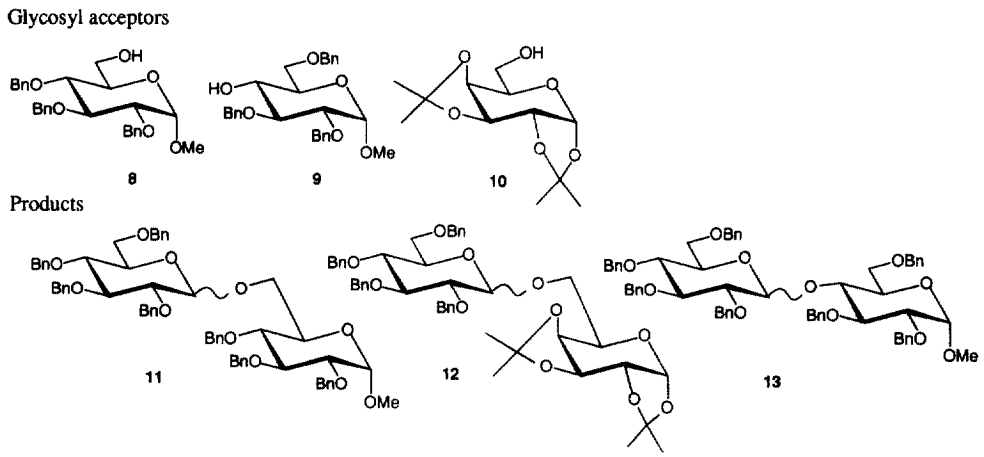


Fig.1

(**5**) and the acceptors employed were recovered. On the other hand, the glycosylation became feasible using excess amount of TMSOTf. The reactions were actually carried out with 9-12 equiv. of TMSOTf and 1.2-2.0 equiv. of acceptors (**8**-**10**) for 1 equiv. of donors (**5**-**7**) under Ar atmosphere in the presence of Molecular Sieves 4A. The results are summarized in Table 1.[9]

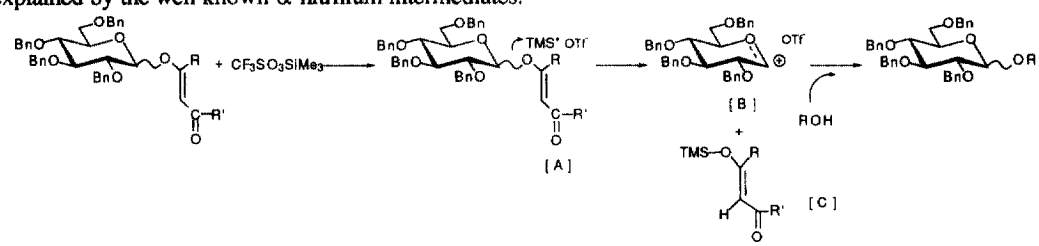
The highest yield was 82-81% (Runs 3 and 6) for the reaction of **5** with **8**. The yield and anomeric configuration were influenced by the reaction conditions such as the ratio of reagents, the solvent and temperature. When 1.0 equiv. of TMSOTf was used to carry out the reaction overnight at room temperature, the yield of disaccharide (**11**) was 19%, and excess amounts of **5** and **8** were recovered (not shown in the Table). On the contrary, the use of 10 equiv. of TMSOTf and 1.5 equiv. of acceptor (**8**) to donor (**5**) afforded **11** in 71% yield for 1 h at room temperature (Run 1). The addition of larger (12 eq.) or smaller (9 eq.) amounts of

TMSOTf to 1.2 or 2.0 equiv. of **8** afforded **11** in lower yields. The reaction temperature significantly affected the yield of the disaccharide. The yields of the products tend to increase at lower temperature, resulting in 82% yield of **11** at -50 ℃ (Run 3). The type of solvent, such as dichloromethane, acetonitrile and propionitrile, scarcely affected the reaction yield but significantly affected the α- or β-selectivity of the product. For instance, α-disaccharide was preferentially produced in dichloromethane at lower temperature. In Run 3, the ratio of α:β was 9:2. In acetonitrile at -40 ℃, the disaccharide was obtained in 69% yield with high β-selectivity (α:β=2:9, Run 5) and the selectivity was better than that at -20 ℃ (α:β=1:1, Run 4). In propionitrile at -50 ℃, the yield of **11** was 81% and the α:β ratio was 2:7 as expected (Run 6).

Glycosylation of 4-OH of the acceptor (**9**) instead of 6-OH (**8**) at -50 ℃ in propionitrile gave (1 → 4) disaccharide **13** in 55% yield with complete β-selectivity (Run 7).

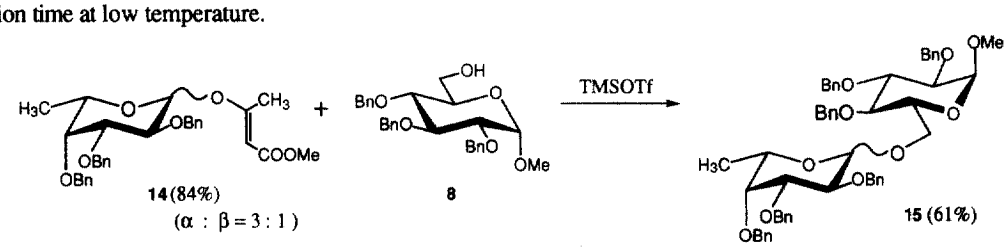
The reaction of **6** with **8** in propionitrile gave **11** in 74% yield (Run 9). The α:β ratio of **11** was 2:3. When the same glycosylation reactions were carried out in dichloromethane, the yield of **11** was lower. The yield in the reaction of **7**, a donor having α,β-unsaturated ketone, with **8** was not better than those of **5** or **6** with **8**.

In these reactions, excess amount of TMSOTf gave disaccharides in ca. 80% yield. When an α-glycosyl donor (**5**α) or an α,β-anomeric mixture (**5**) was reacted with a glycosyl acceptor, the ratio of α- and β- disaccharide was the same. This fact suggests that the donors having the enol ether as a leaving group are activated with Lewis acid to give the same oxycarbenium ion intermediate [B] which reacts with the glycosyl acceptor to form the final product disaccharide. The plausible reaction mechanism is shown in Scheme 2. In a weakly polar solvent such as dichloromethane, α-selectivity was enhanced due to the anomeric effect and thermodynamic control *via* intermediate [B]. On the other hand, β-selectivity in a strong polar solvent such as propionitrile or acetonitrile can be explained by the well known α-nitrilium intermediates.[10]



Scheme 2

Our method using enol ether donor (**5**) seems to be superior to the previous method[2] in terms of chemical yield and α,β-selectivity. These donors would be useful to the glycosylation of unstable compounds due to the short reaction time at low temperature.



Scheme 3

A stable fucosyl donor (**14**) was easily prepared from L-fucose in a similar way in 84% yield (α:β=3:1, *E*-form). The fucosyl donor can be applied to the synthesis for disaccharide (**15**). Treatment of 1.5 equiv. of acceptor (**8**) and donor (**14**) at -50 ℃ in dichloromethane for 1 h gave disaccharide (**15**) in 61% (α:β=2:3). Therefore, it is expected that the fucosyl donor (**14**) would be used for the synthesis of Le^x antigen or other

important oligosaccharides.

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References and notes

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[3] A general procedure: To a solution of 1-OH **1** (270 mg, 0.5 mmol) in dichloromethane (1.0 ml) was added **3** (83.2 μl, 1.0 mmol) and *n*-Bu_3P (36.9 μ l, 0.15 mmol) under Ar atmosphere at r.t. The mixture was stirred at r.t. overnight and then evaporated. The residue was purified by silica-gel column chromatography (hexane:AcOEt=1:1) to give an α,β-mixture **6** as a syrup (Yield 269 mg, 86%). The glycosyl donor **7** was prepared with 0.7 eq. of *n*-Bu_3P at 50 ℃ overnight.

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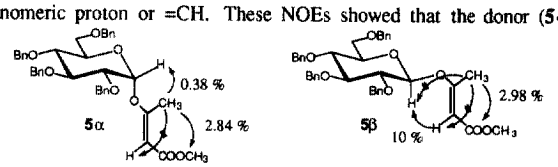
[5]$[\alpha]_D^{22}$ +61.2° (*c* 0.98, $CHCl_3$); MS[FAB] m/z : 637 $(M-H)^+$, 661 $(M+Na)^+$; Anal. Calcd for $C_{39}H_{42}O_8$: C,73.33; H, 6.63. Found: C, 72.94; H, 6.54 ; α-anomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (3H, s, CH_3), 3.66 (1H, dd, H-2), 3.68 (3H, s, OCH_3), 3.76 (1H, dd, H-4), 4.05 (1H, dd, H-3), 5.34 (1H, d, H-1), 5.42 (1H, s, C=CH); $J_{1,2}$ = 3.5, $J_{2,3}$ = 10, $J_{3,4}$ = 9, $J_{4,5}$ = 10 Hz; ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2 (CH_3), 50.9 (OCH_3), 77 (C-4), 79.3 (C-2), 81.7 (C-3), 94.1 (C-1), 95.3 (C=CHCOOCH$_3$), 168.2 (CH_3C=CHCOOCH$_3$), 169.6 (C=O); β-anomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (3H, s, CH_3), 3.67 (3H, s, OCH_3), 4.93 (1H, d, H-1), 5.35 (1H, s, C=CH); $J_{1,2}$ = 7; ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2 (CH_3), 99 (C-1).

[6] $[\alpha]_D^{25}$+65.8° (*c* 0.9, $CHCl_3$); MS[FAB] m/z : 647 $(M+Na)^+$; Anal. Calcd for $C_{38}H_{40}O_8$: C,73.06; H, 6.45. Found: C, 72.94; H, 6.54 ; α-anomer; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (1H, dd, H-2), 3.74 (3H, s, OCH_3), 3.72 - 3.75 (2H, m, H-4, 5), 4.05 (1H, dd, H-3), 5.15 (1H, d, H-1), 5.58 (1H, d, CH=CHCOOCH$_3$), 7.56 (1H, d, CH=CHCOOCH$_3$); $J_{1,2}$ = 3, $J_{2,3}$ = 9, $J_{3,4}$ = 8, $J_{CH=CH}$ = 12 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.1 (OCH_3), 76.8 (C-4), 78.9 (C-2), 81.6 (C-3), 98.4 (C-1), 100.8 (CH=CHCOOCH$_3$), 159.1 (CH=CHCOOCH$_3$), 167.6 (C=O); β-anomer; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 - 3.80 (4H, m, H-2,3,6a,4), 3.75 (3H, s,OCH_3), 4.79 (1H, d, H-1), 5.54 (1H, d, CH=CHCOOCH$_3$), 7.65 (1H, d, CH=CHCOOCH$_3$) $J_{1,2}$ = 11, $J_{CH=CH}$ = 12 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.1 (OCH_3), 77.1 (C-4), 81.3 (C-2), 84.2 (C-3), 100.8 (CH=CHCOOCH$_3$), 100.8(C-1), 159.7 (CH=CH-COOCH$_3$), 167.5 (C=O).

[7] $[\alpha]_D^{25}$+85.5° (*c* 0.51, $CHCl_3$); MS[FAB] m/z : 632 $(M+Na)^+$; Anal. Calcd for $C_{38}H_{40}O_7$: C,74.98; H, 6.62. Found: C, 74.69; H, 6.49 ; α-anomer; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (3H, s, CH_3), 3.65 (1H, dd, H-2), 3.78 (1H, dd, H-4), 4.01 (1H, dd, H-3), 5.11 (1H, d, H-1), 5.88 (1H, d, CH=CHCOCH$_3$), 7.42 (1H, d, CH=CHCOCH$_3$); $J_{1,2}$ = 3, $J_{2,3}$ = 9, $J_{3,4}$ = 9, $J_{CH=CH}$ = 12.5 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2 (CH_3), 76.9 (C-4), 79.1 (C-2), 81.6 (C-3), 98.7 (C-1), 111 (CH=CHCOCH$_3$), 158.9 (CH=CH-COCH$_3$), 197.2 (C=O); β-anomer; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (3H, s, CH_3), 3.55 - 3.73 (5H, m, H-3,4,5,6a,6b), 3.62 (1H, dd, H-2), 4.79 (1H, d, H-1), 5.84 (1H, d, CH=CHCOCH$_3$), 7.51 (1H, d, CH=CHCOCH$_3$) $J_{1,2}$ = 7.5, $J_{CH=CH}$ = 12.5 Hz.

[8] All donors (**5**,**6**,**7** and **14**) were confirmed as *E*-form with NOE (300 or 400 MHz NMR). For example, 0.38% NOE was observed between the anomeric proton and methyl group in compound (**5**α), and 2.84% NOE existed in the methyl and $COOCH_3$ groups. On the other hand, no NOE between the methyl group and =CH was observed. For the compound (**5**β) NOE between the methyl group and $COOCH_3$ was observed in 2.98%, and 10% NOE was observed for the anomeric proton and =CH. No NOE was observed between the methyl group and the anomeric proton or =CH. These NOEs showed that the donor (**5**α, **5**β) was in *E*-form. The other donors gave similar results.



[9] A typical glycosylation procedure: To a solution of enol ether glycosyl donor **5** (35.0 mg, 54.8 μ mol) in dichloromethane (1.0 ml) was added MS 4A (powder, 200 mg), a solution of 6-OH compound **8** (38.0 mg, 82.2 μ mol) in dichloromethane (1.0 ml) and TMSOTf (106 μ l, 548 μ mol) under Ar atmosphere at -50 ℃ and the mixture was stirred for 0.5 h. The mixture was filtered by celite for removing MS 4A. The organic layer was washed with 10% $NaHCO_3$, H_2O, dried (Na_2SO_4), and then, evaporated. The residue was purified by silica-gel column chromatography (hexane:AcOEt=5:2) to give an α,β-mixture of the product as a syrup (Yield 44.2 mg, 82%).

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