Solid-phase Synthesis of Oligosaccharides Using Novel Alkyne-type Linkers: Selection of Reactive Sites on the Support by Sonogashira Reaction

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Abstract: Two new alkyne-type linkers having alkynylmethyloxy moieties were elaborated for solid-phase synthesis of oligosaccharides. A propargyl glycoside-type linker between a sugar residue and a solid support was formed by the Sonogashira reaction of a propargyl glycoside with polymer-supported iodobenzene. A propargyl ester-type linker was also constructed by the same reaction of a 4-(proparygyloxycarbonyl)benzyl glycoside with the latter. Both linkers are stable against acids such as TFA but can be readily cleaved with this acid after conversion to the corresponding alkyne-cobalt complex by treatment with $Co_2(CO)_8$. The latter ester linker is generally advantageous in that mild cleavage liberates a product as its carboxybenzyl glycoside which is readily purified. The Sonogashira reaction was found to proceed only at spatially reactive sites on the solid support where the reagent accesses readily, so that the subsequent reactions including glycosylation on solid phase proceeded smoothly to result in high total yields of the desired oligosaccharides.

Key words: oligosaccharides, solid-phase synthesis, carbohydrates, glycosylations, cross-coupling

Synthesis of oligosaccharides and glycoconjugates has played important roles in investigation of their biological functions such as recognition in cellular trafficking, cell-cell adhesion, and chronic inflammation, receptors for bacterial toxin, immunostimulation, and so on. Solid-phase synthesis of oligosaccharides has been extensively investigated in order to establish practical and convenient methods for oligosaccharide synthesis.[1–11]

We have also reported solid-phase oligosaccharide synthesis by using macroporous polystyrene resin (ArgoPore™)[12] as a support.[13] Since the macroporous polystyrene resin has constant ability for the uptake of organic solvents, a wide range of solvents including protic solvents and ether can permeate easily into the pores and be used for solid-phase synthesis. α-Selective glycosylation on the macroporous polystyrene support was hence accomplished by virtue of the solvent effect of diethyl ether. A problem in macroporous polystyrene resin is the large heterogeneity in pore sizes. Dry ArgoPore™ resin has an average pore size of approximately 90 Å but also many smaller pores (<10 Å) are known to be present. Due to the space-demanding ionic reaction intermediate of glycosylation that consists of an oxocarbenium ion and a counterion, glycosylation may not proceed in small pores. Indeed, heterogeneity of resins is a common problem for solid-phase oligosaccharide synthesis. Glycosylation on solid support sometimes does not proceed quantitatively.

Selective loading on the reactive regions of a solid support (= readily accessible regions by reagents) should solve this problem. In the present study, we propose two novel alkynyl-type linkers suitable for the purpose of introducing a starting monosaccharide component to the reactive sites on the solid support by the Sonogashira reaction.

Previously, we reported propargyloxycarbonyl and propargyloxy groups are stable to neat TFA but are readily cleaved at ambient temperature by treatment with $Co_2(CO)_8$ and TFA in CH_2Cl_2 via formation of an alkyne-cobalt complex (Figure 1).[14,15] In view of its chemical behavior, the propargyloxy group was expected to formulate a useful linker for solid-phase synthesis if the alkyne terminal could be immobilized to the polymer support.

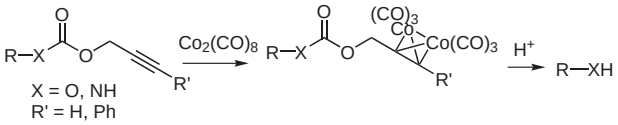

Figure 1 Cleavage of propargyloxycarbonyl group.

A propargyl glycoside-type linker was first investigated, since we already reported its use for anomeric protection.[15] Two routes were examined for introduction of propargyl glycosides to solid supports as shown in Figure 2. In route 1, Sonogashira coupling between propargyl glycosides and *p*-iodobenzoate was first carried out to afford monosaccharides with a linker moiety, which were then introduced to aminomethylated polystyrene support by amide bond formation. In route 2, propargyl glycosides were introduced by the Sonogashira reaction to polymer-support.[16] In the present study, we used ArgoPore™-NH_2 and SynPhase™ Lantern-NH_2 as supports in order to assess the general applicability of the method. SynPhase Lanterns are surface-grafted polymers optimized for solid-phase synthesis of small organic molecules and peptides.[17] A polystyrene graft, which has similar performance characteristics to conventional polystyrene resins, was used in the present study. Each SynPhase™ Lantern-NH_2 (D-series, 5 mmϕ × 12.5 mm) has 35 μmol of an amino group in the polystyrene graft.

The process of loading a monosaccharide to a polymer via route 1 is shown in Scheme 1. Propargyl 4,6-*O*-ben-

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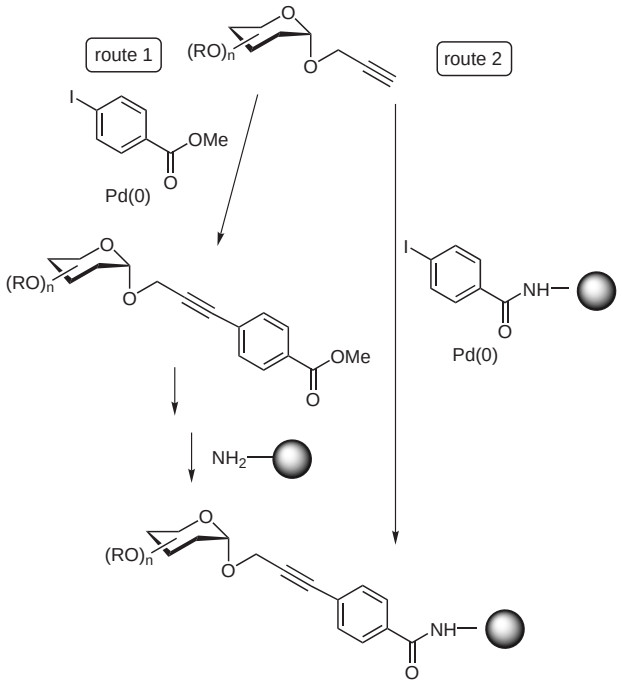
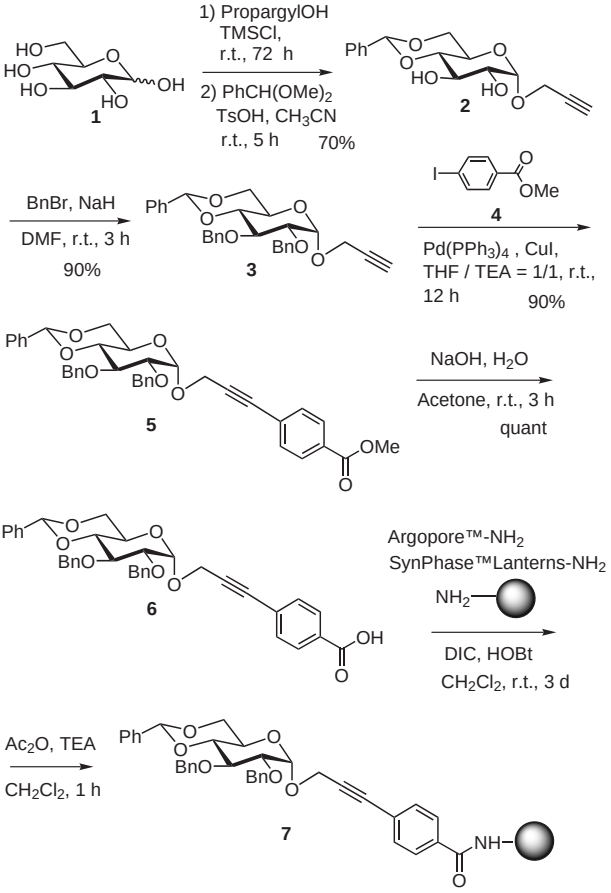


Figure 2 Methods for introduction of propargyl glycosides to the supports.



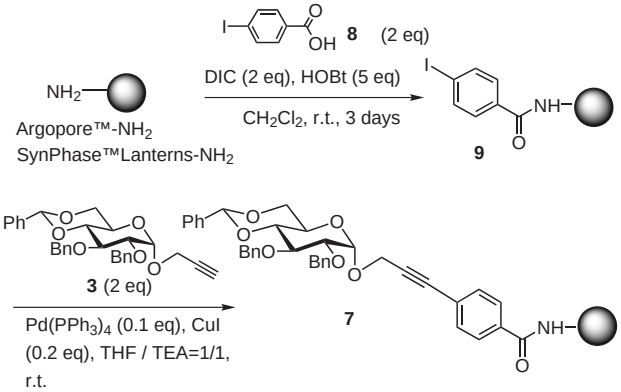
Scheme 1

zylidene glucopyranoside **2** was readily prepared by treatment of glucose **1** with propargyl alcohol and TMSCl followed by benzylidenation.[15] Benzylation of **2** gave **3**.[18] Sonogashira coupling of **3** with methyl 4-iodobenzoate (**4**) gave the coupling product **5** in a good yield.[19] After cleavage of the methyl ester of **5**, the resulting **6** was attached to a polymer support by using diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) to give the desired monosaccharide-loaded polymer **7**.[20]

The same glucose-loaded polymer **7** was also prepared via the alternative route 2 (Scheme 2).[21] Iodobenzoic acid **8** was first introduced to a polymer support. Sonogashira coupling on the solid support was carried out by the use of propargyl glycoside **3**, polymer-supported iodobenzene **9**, $Pd(PPh_3)_4$, CuI, and TEA in THF to give **7**.[22]

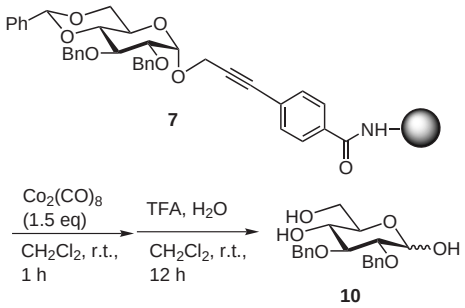
In the case of route 1, the loading yields were estimated by measuring the residual amino groups. Cleavage of the propargyl glycoside linker was then carried out (Scheme 3). The modified resin **7** was first treated with 1.5 equiv of $Co_2(CO)_8$ and then excess $Co_2(CO)_8$ was removed. Then, 10% TFA in CH_2Cl_2–H_2O (10:1) was added to the resin.[23] The liberated monosaccharide **10** was purified by silica gel TLC and weighed. The results are shown in Table 1. The yields of **10** (entries 1–3) represent cleavage yields from the resins. The loading yield on ArgoPore^{TM}-NH_2-HL (high load) was lower than that on ArgoPore^{TM}-NH_2-LL (low load; entries 1 and 2). This result indicates that a higher ratio of amino groups exist on less reactive regions on ArgoPore^{TM}-NH_2-HL. Since the cleavage of propargyl glycosides in solution proceeded quantitatively,[15] some of monosaccharide **6** was probably introduced to the region where $Co_2(CO)_8$ was unable to access.

In the case of route 2 (entries 4–6), the yields of **10** were the sum of the two reaction steps, i.e., Sonogashira reaction and cleavage from the resins. Since cleavage yields of ArgoPore^{TM}-NH_2 and SynPhase^{TM}-NH_2 were not so different as observed in entries 2 and 3 (Table 1), the difference in the yields of **10** is attributed to the Sonogashira reaction step. When ArgoPore^{TM}-HL resin was used, the total yield of Sonogashira coupling and the cleavage steps



Scheme 2

were only 4% (entry 4). The yield of **10** (8%) was somehow improved by repeating the Sonogashira coupling step (entry 5). The yield of coupling was improved by using SynPhase™ resin (entry 6). In any case, the yields of the Sonogashira reaction on solid-supports in the present study were lower than those reported.[16] A space-demanding intermediate having many protective groups probably reacted with only the polymer-supported iodobenzene located on the reactive sites of the polymer. The low yields at this step were hence expected to be preferable for the next glycosylation step.



Scheme 3

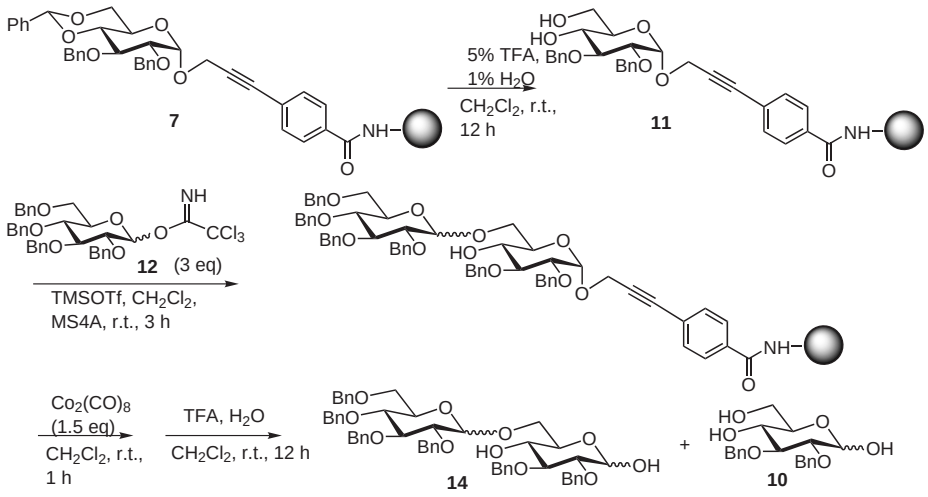
The benzylidene group on the resin **7** was cleaved to give **11**. The glycosylation reaction was then carried out by using the benzylated glycosyl trichloroacetimidate donor **12** (3 equiv to the solid supported acceptor **11**)[23] and TMSOTf (0.2 equiv to **10**) in CH_2Cl_2 (room temperature, 3 h) (Scheme 4, Table 2).[25] When **11** (ArgoPore™-HL resin) prepared via route 1 was used, the desired disaccharide **14** was obtained in 14% yield along with 30% of monosaccharide **10** after cleavage from the resin (Table 2. entry 1):[26] the latter was derived from the unreacted acceptor. The yield of **14** (51%) was improved (Table 2, entry 2), when **11** (SynPhase™ resin) was used. Thereby, only a small amount of monosaccharide **6** was observed.

Table 1 Cleavage of Alkyne Glycoside Linker with $Co_2(CO)_8$ and TFA

Entry	Resin	Loading Yield[a]	Yield of **10**
Route 1		**7**	
1	ArgoPore™-NH_2-LL (0.28 mmol/g)	83% [b]	75%[c]
2	ArgoPore™-NH_2-HL (1.16 mmol/g)	43% [b]	70%[c]
3	SynPhase™-NH_2 (35 μmol/g)	70% [b]	79%[c]
Route 2		**9**	
4	ArgoPore™-NH_2-HL (1.16 mmol/g)	93% [d]	4%[e]
5[f]	ArgoPore™-NH_2-HL (1.16 mmol/g)	93% [d]	8%[e]
6	SynPhase™-NH_2 (35 μmol/g)	quant.[d]	20%[e]

[a] Loading yield was estimated by measuring the amount of residual amino groups with the Gisin method after introduction of **6**.[24]
[b] Loading yield in **7**.
[c] Yield of **10** from **7**.
[d] Loading yield of the iodobenzoyl moiety in **9**.
[e] Yield of **10** from **9**.
[f] Sonogashira reaction was carried out twice.

By contrast, the glycosylation reaction of the acceptor **11** prepared via the Sonogashira reaction on solid-phase proceeded quantitatively on both ArgoPore™ and SynPhase™ (Table 2, entries 3 and 4). No monosaccharide **10** was observed in each case. In the case of SynPhase™, the cleavage reaction also proceeded in a good yield. These results indicated that the Sonogashira reaction of the alkyne in the protected propargyl glycoside with polymer-



Scheme 4

Table 2 Glycosylation on Solid Support Using Trichloroacetimidate as Donor

Entry	Resin	Loading Amount of **11**	Yield : **14**	Yield : **10**
Route 1				
1	ArgoPore™-NH_2-HL (1.16 mmol/g of NH_2)	31 μmol /100 mg	14%	30%
2	SynPhase™-NH_2 (35 mol/lantern of NH_2)	19 μmol /lantern	51%	trace
Route 2				
3[a]	ArgoPore™-NH_2-HL (1.16 mmol/g of NH_2)	8.6 μmol /100 mg[b]	72%	n.d.[c]
4	SynPhase™-NH_2 (35 mol/lantern of NH_2)	7.1 μmol /lantern[b]	quant	n.d.[c]

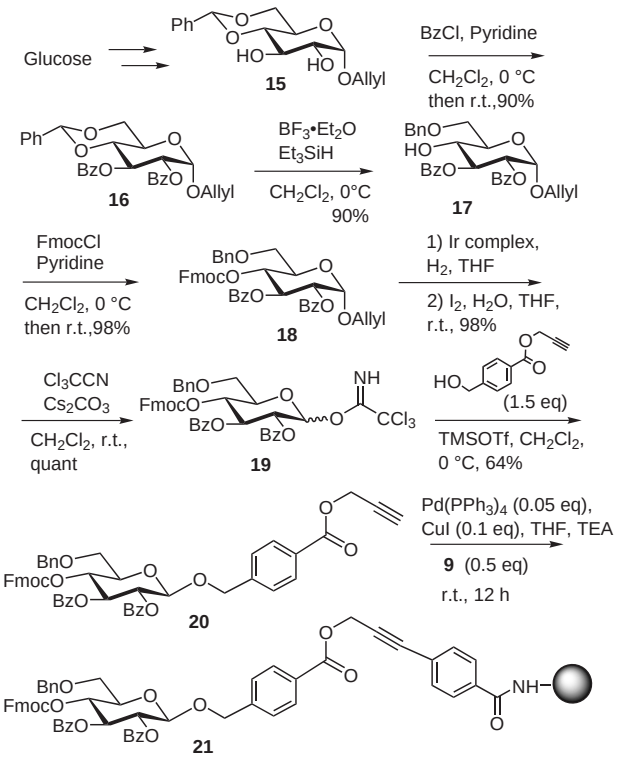
[a] Modified resin **11** prepared via route 2 (Table 1, entry 5) was used.
[b] The loading amount was calculated from the cleavage yield of **10** in Table 1.
[c] Not detected.

supported iodobenzene can select reactive regions on the polymer supports.

As described, the new alkyne-type linker can be readily cleaved by treatment with $Co_2(CO)_8$ and TFA in CH_2Cl_2 via formation of an alkyne-cobalt complex. The cleavage of the above linker affords a 1-hydroxy sugar, which can be used as a glycosyl donor for further glycosylation. Purification of the 1-hydroxy sugar is, however, sometimes difficult owing to the equilibrium between α- and β-anomers. We, therefore, investigated another alkyne-type linker consisting of an alkynyl ester and a benzyl glycoside functionality. This alkynyl ester-linker was prepared by the Sonogashira reaction of 4-(propargyloxycarbonyl)benzyl glycoside with a polymer-supported iodobenzene derivative. This linker was stable under the acidic conditions of conventional glycosylation reactions but was readily cleaved from the polymer support via conversion of the alkyne function to the corresponding alkyne-cobalt complex and then with TFA. The ester linkage can also be cleaved by conventional alkaline treatment.

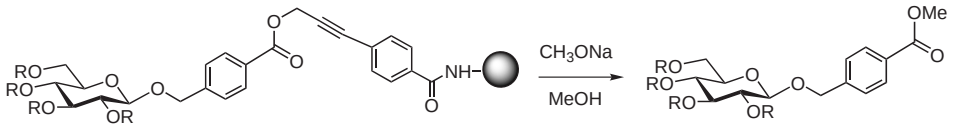
Synthesis of the monosaccharide **21** attached to the support via the alkynyl ester linker is shown in Scheme 5. The allyl 4,6-*O*-benzylidene glucopyranoside **15** was prepared from glucose according to the method given in literature.[15] Benzoylation of **15** and then reductive opening of the benzylidene ring[27] with Et_3SiH and $BF_3{\cdot}OEt_2$ gave 4-*O*-free sugar **17**.[28] The fluorenylmethyloxycarbonyl (Fmoc) group[5e] was introduced to **17** to give **18**, of which the allyl group was then removed. The resultant reducing sugar was then changed to trichloroacetimidate **19**.[29] Glycosylation of propargyl 4-(hydroxymethyl)benzoate with **19** afforded **20**.[30] Sonogashira reaction of monosaccharide **20** was then carried out with polymer-supported iodobenzene **9** (SynPhase™) in a manner similar to the preparation of **7** to give Fmoc-glucose-loaded polymer **21**. The loading yield (20%) was determined by the yield of the monosaccharide **22** that was obtained by NaOMe treatment of **21** with NaOMe (Table 3, entry 1). Other alkyne sugars were also introduced to SynPhase™ by Sonogashira coupling in ca. 20% yields as determined similarly (Table 3, entries 2–4).

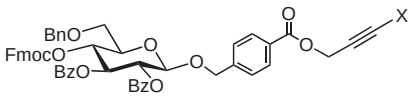
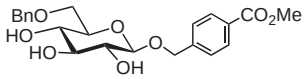
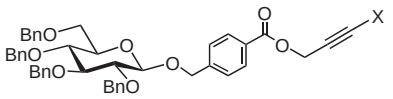
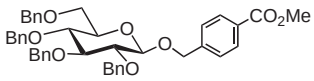
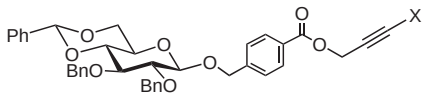
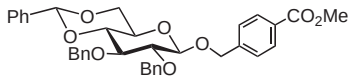
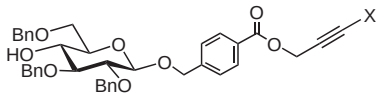
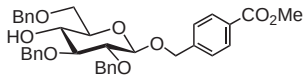
The alkynyl ester-linker was also cleaved by treatment of $Co_2(CO)_8$ and TFA. Treatment of **23** with $Co_2(CO)_8$ gave **29**, which was then reacted with TFA to afford the acid **30** in 14% from **9** (Scheme 6). The cleavage yield was lower than that by NaOMe treatment.

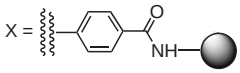


Scheme 5

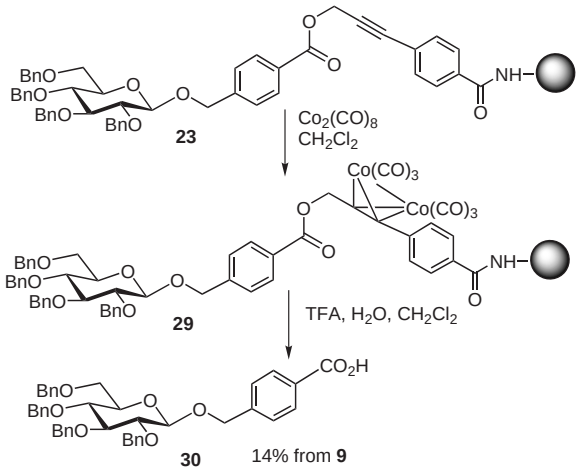
Table 3 Introduction of Alkyne Sugars on Solid Support by Sonogashira Coupling



Entry	Compound[a]	Product	Yield[b]
1	 **21**	 **22**	20%
2	 **23**	 **24**	21%
3	 **25**	 **26**	17%
4	 **27**	 **28**	19%

[a] 

[b] The yields are based on the isolated products. The values denoted the sum of the two-step conversions: coupling to the resin and cleavage.

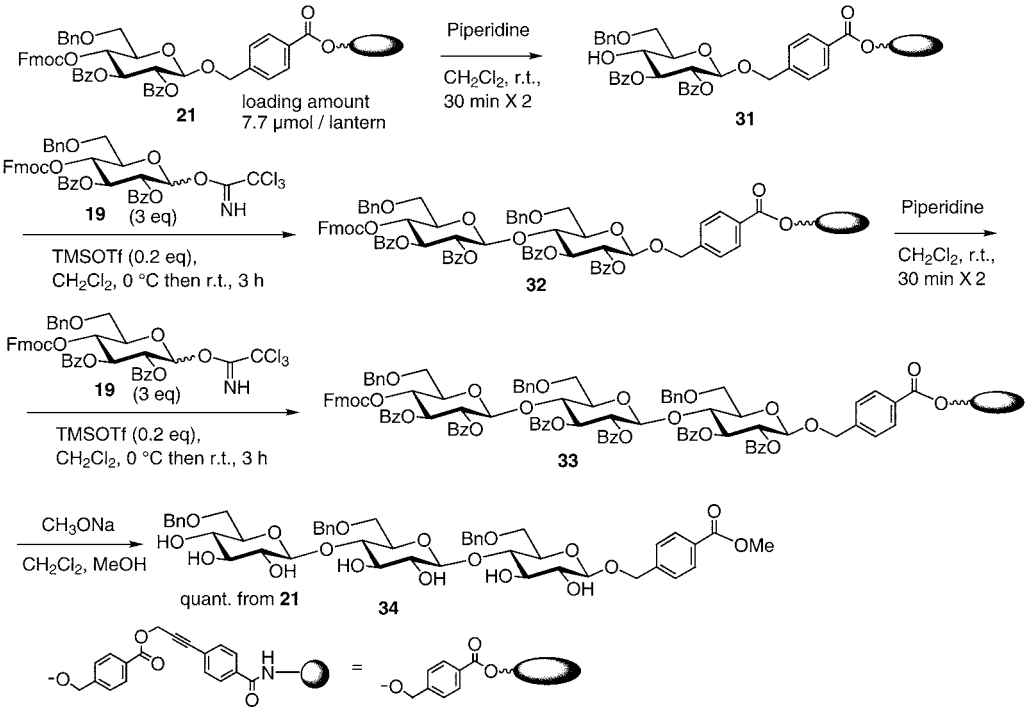


Scheme 6

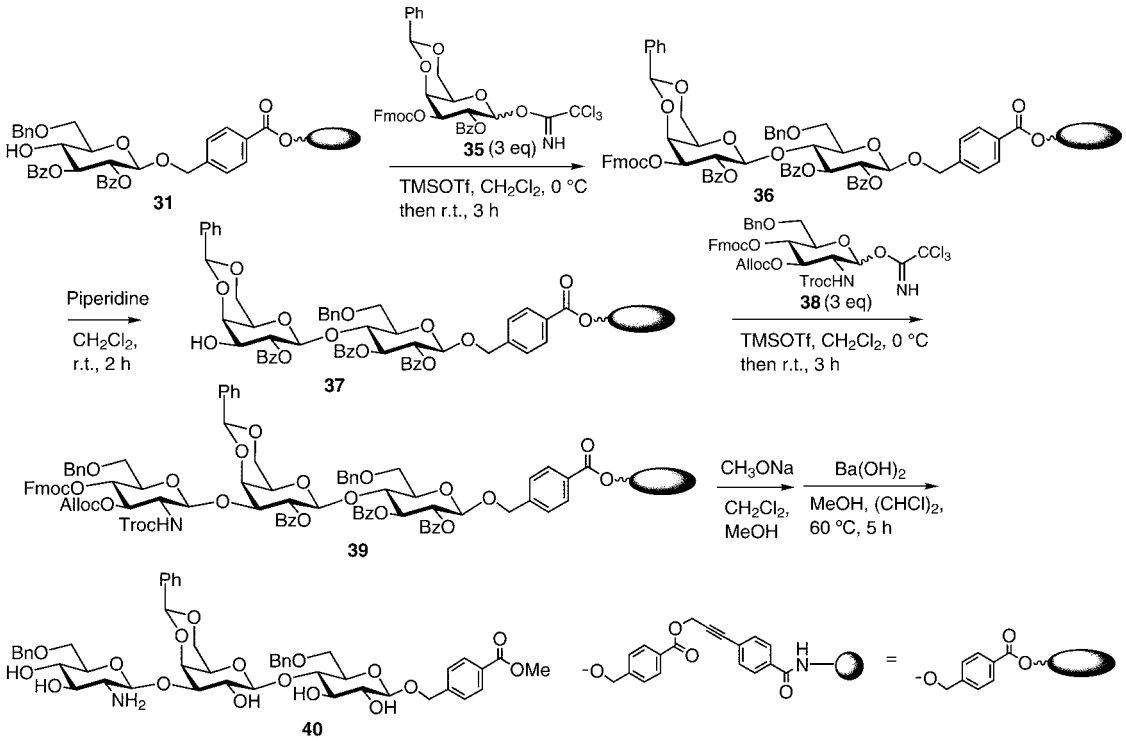
Solid-phase oligosaccharide synthesis was then investigated by the use of the alkynyl-ester linker. After removal of the Fmoc group, glycosylation of **31** was carried out using 3 equiv of trichloroacetimidate donor **19** and TMSOTf (0.2 equiv to **31**) in CH_2Cl_2 (room temperature, 3 h) to give **32** (Scheme 7). The Fmoc group of **32** was removed, and the second glycosylation was then carried out to give the trisaccharide **33**. The desired trisaccharide **34** was obtained quantitatively after cleavage from the resin.[31]

The trisaccharide Glc*N*β(1→3)Galβ(1→4)Glc (**40**) was prepared from **31** as shown in Scheme 8. The 3-*O*-Fmoc galactosyl donor **35** was prepared according to Schmidt's method.[5e] The *N*-Troc glucosaminyl donor **38** was prepared from the intermediate for the synthesis of lipid A.[32] The reactions proceeded quantitatively at all the reaction steps, i.e., two glycosylation steps, Fmoc deprotection step, and cleavage steps to give trisaccharide **40** in a quantitative yield.

As described above, two alkyne-type linkers were developed for solid-phase oligosaccharide synthesis. Monosaccharide components having an alkyne moiety were introduced to polymer supports by the Sonogashira coupling reaction. Since the alkynyl copper intermediate of the Sonogashira reaction, which has many protective groups, is polarized and space-demanding, it may reach only reactive sites on the polymer supports. The subsequent reactions including glycosylation proceeded smoothly, resulting in high total yields of the synthesis. The present concept, selection of reactive sites on polymer supports by a particular reaction, is expected to be generally applicable to solid-phase organic synthesis.



Scheme 7



Scheme 8

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(18) **3**: Mp: 98 °C; $[\alpha]_D^{22}$ = +13 (c 1.10, $CHCl_3$); ESI-Mass (positive) *m/z* 509.3 [$(M + Na)^+$]; ^{1}H NMR ($CDCl_3$) δ = 7.48–7.24 (15 H, m, PhCH × 3), 5.54 (1 H, s, PhCH), 5.05 (1 H, d, *J* = 3.0 Hz, H-1), 4.93–4.73 (4 H, m, $PhCH_2$ × 2), 4.51 (1 H, t, *J* = 9.0 Hz, H-3), 4.30 (2 H, d, *J* = 3.0 Hz, OCH_2-CCH), 4.26 (1 H, dd, *J* = 10.4, 5.2 Hz, H-6a), 3.88–3.86 (1 H, m, H-5), 3.75–3.72 (2 H, m, H-2 and H-4), 3.62 (1 H, d, *J* = 5.2 Hz, H-6b), 2.47 (1 H, t, *J* = 3.0 Hz, OCH_2-CCH). Found: C, 73.79; H, 6.11%. Calcd for $C_{30}H_{30}O_6$: C, 74.06; H, 6.21%.

(19) **5**: Mp: 162 °C; $[\alpha]_D^{22}$ = +37 (c 1.00, $CHCl_3$); ESI-Mass (positive) *m/z* 629.3 [$(M + Na)^+$]; ^{1}H NMR ($CDCl_3$) δ = 8.00 (2 H, m, $CC_6H_4CO_2Me$), 7.50–7.21 (17 H, m, PhCH × 3 + $CC_6H_4CO_2Me$), 5.56 (1 H, s, PhCH), 5.10 (1 H, d, *J* = 3.6 Hz, H-1), 4.93–4.73 (4 H, m, $PhCH_2$ × 2), 4.54 (2 , d, *J* = 3.0 Hz, OCH_2-CCH), 4.26 (1 H, dd, *J* = 10.3, 4.9 Hz, H-6a), 4.09 (1 H, t, *J* = 9.1 Hz, H-3), 3.95–3.92 (1 H, m, H-5), 3.92 (3 H, s, $CC_6H_4CO_2Me$), 3.71 (1 H, d, *J* = 10.3 Hz, H-6b), 3.65–3.61 (2 H, m, H-2 and H-4). Found: C, 72.92; H, 5.75%. Calcd for $C_{38}H_{36}O_8 \cdot 1/2H_2O$: C, 72.48; H, 5.92%.

(20) **6**: ESI-Mass (negative) *m/z* 605.2 [$(M - H)^-$]; ^{1}H NMR ($CDCl_3$) δ = 8.00 (2 H, m, $CC_6H_4CO_2H$), 7.50–7.21 (17 H, m, PhCH × 3 + $CC_6H_4CO_2H$), 5.56 (1 H, s, PhCH), 5.10 (1 H, d, *J* = 3.6 Hz, H-1), 4.93–4.73 (4 H, m, $PhCH_2$ × 2), 4.54 (2 H, d, *J* = 3.0 Hz, OCH_2-CCH), 4.26 (1 H, dd, *J* = 10.3, 4.9 Hz, H-6a), 4.09 (1 H, t, *J* = 9.1 Hz, H-3), 3.95–3.92 (1 H, m, H-5), 3.71 (1 H, d, *J* = 10.3 Hz, H-6b), 3.65–3.61 (2 H, m, H-2 and H-4). Found: C, 72.24; H, 5.78%. Calcd for $C_{37}H_{34}O_8 \cdot 1/2H_2O$: C, 72.18; H, 5.73%. A typical procedure for introduction of a monosaccharide **6** on solid support. ArgoPore resin (NH_2-LL: 0.28 mmol/g) (100mg, 28.0 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 **6** (38.9 mg, 56.0 μmol), HOBt (18.9 mg, 140 μmol), CH_2Cl_2 (3.0 mL), and DIC (8.8 μL, 56.0 μmol) were added to the tube, successively. The reaction mixture was shaken for 3 d with Rotator RT-50 (Taitech) and filtered. The resin was washed with CH_2Cl_2 and the residual amino groups on the resin were then capped with acetic anhydride (1.0 mL) and triethylamine (1.0 mL) in CH_2Cl_2 (2.0 mL) by shaking for 30 min. The resin was washed successively with DMF, MeOH, and CH_2Cl_2.

(21) A typical procedure for introduction of 4-iodobenzoic acid **8** on solid support. SynPhase™ resin (NH_2-HL: 35.0 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 **8** (17.4 mg, 70.0 μmol), HOBt (23.6 mg, 175 μmol), CH_2Cl_2 (3.0 mL), and DIC (11.0 μL,

70.0 μmol) were added to the tube, successively. The reaction mixture was shaken for 3 d with Rotator RT-50 (Taitech) and filtered. The resin was washed with CH_2Cl_2 and the residual amino groups on the resin were then capped with acetic anhydride (1.0 mL) and triethylamine (1.0 mL) in CH_2Cl_2 (2.0 mL) by shaking for 30 min. The resin was washed successively with DMF, MeOH, and CH_2Cl_2.

(22) A typical procedure for Sonogashira coupling of monosaccharide **3** on solid support. SynPhase™ resin **9** (NH_2: 35.0 μmol) was placed in a polypropylene tube (Varian) fitted with a filter, and washed with THF. CuI (2.6 mg, 14.0 μmol), $Pd(PPh_3)_4$ (8.1 mg, 7.0 μmol), THF (2.5 mL), TEA (2.5 mL) and **3** (34.1 mg, 70.0 μmol) were added to the tube, successively. The reaction mixture was shaken for 24 h with Rotator RT-50 (Taitech) and filtered. The resin was washed with DMF, MeOH and CH_2Cl_2 to give **7**.

(23) A typical cleavage reaction of alkynylmethyloxy linker: The ArgoPore™ resin **7** (100 mg of ArgoPore™ resin) was shaken with a mixture of $Co_2(CO)_8$ (14.4 mg, 42.0 μmol) in CH_2Cl_2 (3.0 mL) at room temperature for 1 h. After the reaction mixture was filtered, the resin was washed with DMF and CH_2Cl_2 (3.0 mL). The resin was shaken with TFA (0.5 mL) in CH_2Cl_2 (4.0 mL) and water (0.5 mL) at room temperature for 12 h and then filtered. The resin was then washed with ethyl acetate. 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 ($CHCl_3$–MeOH = 5:1) to give colorless solid **10**. Yield 5.1 mg (75%). ESI-Mass (positive) *m/z* 383.1 [(M + Na)$^+$]; ^{1}H NMR ($CDCl_3$) δ = 7.35–7.24 (10 H, m, PhCH × 2), 5.24 (1 H, d, *J* = 3.63 Hz, H-1), 4.93–4.63 (4 H, m, $PhCH_2$ × 2), 4.26 (1 H, dd, *J* = 10.4, 5.2 Hz, H-6a), 3.84–3.73 (2 H, m, H-6b), 3.71–3.62 (1 H, m, H-5), 3.57–3.52 (2 H, m, H-2 and H-4), 2.19 (2 H, d, *J* = 8.3 Hz, OH × 2).

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(25) The typical procedure for glycosylation on solid-support: The monosaccharide resin **11** (62% loading) (100 mg of ArgoPore™ resin) was washed with dry CH_2Cl_2 (3 mL). To the resin were added Molecular Sieves 4A beads, 8–12 mesh (200 mg), a solution of a glycosyl trichloroacetimidate **12** (38.9 mg, 56.0 μmol) in dry CH_2Cl_2 (3.0 mL), and TMSOTf (8.8 μL, 56.0 μmol), successively. The reaction mixture was shaken with Rotator RT-50 (Taitech) at room temperature for 3 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 with DMF and CH_2Cl_2.

(26) **14**: ESI-Mass (positive) *m/z* 905.4 [(M + Na)$^+$]; ^{1}H NMR ($CDCl_3$) δ = 7.34–7.21 (30 H, m, PhCH × 6), 5.01 (1/2 H, d, *J* = 3.2 Hz, H-1α), 4.93–4.43 (14 H, m, $PhCH_2$ × 6, H-1′α, H-1′β, H-1β), 3.84–3.73 (4 H, m, H-2, H-3, H-3′, and H-4′), 3.76–3.62 (4 H, m, H-4, H-5, H-2′, and H-5′), 3.57–3.37 (4 H, m, H-6, and H-6′), 2.50 (2 H, s, OH × 2).

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(28) **17**: ESI-Mass (positive) *m/z* 541.1 [(M + Na)$^+$]; ^{1}H NMR ($CDCl_3$) δ = 7.48–7.24 (15 H, m, PhCO × 2 and $PhCH_2$), 5.94–5.88 (1 H, m, $OCH_2CH{=}CH_2$), 5.75 (1 H, d, *J* = 9.6 Hz, H-2), 5.37–5.26 (2 H, m, $OCH_2CH{=}CH_2$), 5.24 (1 H, t, *J* = 9.6 Hz, H-3), 5.05 (1 H, d, *J* = 3.6 Hz, H-1), 4.93–4.73 (4 H, m, $PhCH_2$ and $OCH_2CH{=}CH_2$), 4.26 (1 H, dd, *J* = 10.4, 5.2 Hz, H-6a), 3.88–3.86 (1 H, m, H-5), 3.75–3.72 (1 H, m, H-4), 3.62 (1 H, d, *J* = 5.2 Hz, H-6b).

(29) **18**: ESI-Mass (positive) *m/z* 763.2 [(M + Na)$^+$]; ^{1}H NMR ($CDCl_3$) δ = 8.00–7.24 [24 H, m, PhCO × 2, $PhCH_2$, and $C_{13}H_9$-CH_2-OCO(Fmoc)], 5.94–5.88 (1 H, m, $OCH_2CH{=}CH_2$), 5.75 (1 H, d, *J* = 9.6 Hz, H-2), 5.56 (1 H, dd, *J* = 9.6, 7.9 Hz, H-4), 5.37–5.26 (2 H, m, $OCH_2CH{=}CH_2$), 5.24 (1 H, t, *J* = 9.6 Hz, H-3), 5.05 (1 H, d, *J* = 3.6 Hz, H-1), 4.93–4.73 (4 H, m, $PhCH_2$ and $OCH_2CH{=}CH_2$), 4.26 (1 H, dd, *J* = 10.4, 5.2 Hz, H-6a), 3.94 [1 H, d, *J* = 10.3 Hz, $C_{13}H_9$-CH_2-OCO(Fmoc)], 3.88–3.86 (1 H, m, H-5), 3.75–3.72 (1 H, m, H-4), 3.62 (1 H, d, *J* = 5.2 Hz, H-6b).

(30) **20**: Mp: 144 °C; $[\alpha]_D^{24}$ = +134 (c 1.00, $CHCl_3$); ESI-Mass (positive) m/z 895.2 [(M + Na)$^+$]; ^{1}H NMR ($CDCl_3$) δ = 8.01 (2 H, m, $OCH_2C_6H_4CO_2CH_2$-CCH), 7.48–7.25 (17 H, m, $PhCH_2$ × 3, and $OCH_2C_6H_4CO_2CH_2$-CCH), 4.71 (1 H, d, *J* = 8.6 Hz, H-1), 4.88–4.45 (8 H, m, $PhCH_2$ × 3 and $OCH_2C_6H_4CO_2H$), 4.51 (1 H, t, *J* = 9.1 Hz, H-3), 4.26 (1 H, dd, *J* = 10.4, 5.2 Hz, H-6a), 3.91 (2 H, d, *J* = 3.0 Hz, $OCH_2C_6H_4CO_2CH_2$-CCH), 3.88–3.86 (1 H, m, H-5), 3.72 (1 H, d, *J* = 10.3 Hz, H-6b), 3.65–3.57 (2 H, m, H-2 and H-4), 2.47 (1 H, t, *J* = 3.0 Hz, $OCH_2C_6H_4CO_2CH_2$-CCH).

(31) A typical procedure for solid-phase glycosylation using a glycosyl trichloroacetimidate: The 4-*O*-Fmoc resin **21** (21% loading) (SynPhase™-NH_2; 7.7 μmol) was washed with CH_2Cl_2 (3.0 mL). To the resin was added 25% piperidine in CH_2Cl_2 (3.0 mL). The reaction mixture was shaken with Rotator RT-50 (Taitech) at room temperature for 30 min. The solution was removed by filtration and the resin was washed with CH_2Cl_2, DMF and MeOH. The resin was then washed with 5% TMSOTf in dry CH_2Cl_2 and then dry CH_2Cl_2 (3 mL). Trichloroacetimidate **19** (19.5 mg, 23.1 μmol), dry CH_2Cl_2 (3.0 mL), and TMSOTf (0.3 μL, 1.5 μmol) were added. The reaction mixture was shaken with Rotator RT-50 (Taitech) at room temperature for 30 min to give resin-linked disaccharide **32**.
Typical procedure of cleavage from solid support by alkali. SynPhase resin linked with disaccharide via alkynyl ester linker was shaken with a mixture of 28% CH_3ONa in MeOH (1.0 mL), MeOH (1.0 mL) and CH_2Cl_2 (2.0 mL) at room temperature for 12 h. After the reaction mixture was filtered, EtOAc and 0.1 N aqueous HCl were added to the filtrate. 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 ($CHCl_3$–MeOH = 5:1) to give the desired compound.
34: Yield 7.2 mg (quant.). ESI-Mass (positive) *m/z* 945.5 [(M + Na)$^+$]; ^{1}H NMR ($CDCl_3$) δ = 7.84–7.21 (19 H, m, $PhCH_2$ × 3 and $OCH_2C_6H_4CO_2Me$), 4.83–4.43 (10 H, m, $PhCH_2$ × 3, $OCH_2C_6H_4CO_2Me$, H-1β, H-1′β, and H-1′′β), 3.93 (3 H, s, $OCH_2C_6H_4CO_2Me$), 3.84–3.60 (12H, m, H-2, H-3, H-4, H-5, H-2′, H-3′, H-4′, H-5′, H-2′′, H-3′′, H-4′′ and H-5′), 3.57–3.37 (4 H, m, H-6, H-6′, and H-6′′), 2.50 (4 H, s, OH × 7).

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