Intramolecular Aglycon Delivery on Polymer Support: Gatekeeper Monitored Glycosylation

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Received November 27, 1996[⊗]

Abstract: A novel use of polymer supported glycosyl donor for stereoselective synthesis of β-manno glycoside is described. This system features the use of polymer support in an unprecedented manner, in which the polymer sector serves as a "gatekeeper". Polymer supported thiomannoside **10** that carries a *p*-alkoxybenzyl group as a linker at *C*-2 position was synthesized. This compound was subjected to the conditions of β-mannosylation according to the procedure of *p*-methoxybenzyl assisted intramolecular aglycon delivery (IAD) to react with glycosyl acceptor **11**. Treatment with DDQ afforded the mixed acetal **12** which was followed by the activation of the anomeric C-S linkage to initiate the IAD step. This process allows the product derived from IAD to be specifically released from the polymer to give the mixture which is highly enriched with the β-manno glycoside **13**. Compatibility with the orthogonal glycosylation strategy was confirmed by the reaction with the glycosyl fluoride **11c**, and resultant disaccharide **14** was further transformed into **16** which corresponds to the core trisaccharide structure of Asn-linked oligosaccharide.

Introduction

Polymer support synthesis has been demonstrated extremely valuable for routine preparations of oligopeptides[1] and oligonucleotides,[2] and attracting renewed attention in connection with combinatorial chemistry that aims at facile preparations of small molecule libraries.[3] Application of this technology into other biomolecules, carbohydrate in particular, has become a subject of quite intense effort.[4] Potential utility of polymer support synthesis is quite obvious in the carbohydrate field, since in order to synthesize biologically relevant oligosaccharides multistep transformations (i.e., iterative protection-glycosylation-deprotection) are generally required and chromatographic purifications are necessary after each transformation. In most cases of polymer support oligosaccharide synthesis, major advantage stems from the ease of separation of the polymer bound products from excess reagents and/or coupling partners. On the other hand, Danishefsky and co-workers have reported the ingenious use of polymer supported glycals as glycosyl donors, in which the formation of interior deletion products can be precluded by their "self police" capacity.[4a]

Described herein is the use of polymer support in a manner clearly distinct from previously reported ones. In this system, the polymer sector serves as a "gatekeeper". Namely, the desired product is released into nonpolymeric phase while most of the byproducts are retrained on polymer.

Results and Discussion

Among numerous types of oligosaccharide structures found in naturally occurring glycoconjugates, β-manno (Man) glycoside, that constitutes the core structure common to all types of asparagine (Asn)-linked glycoprotein oligosaccharides, has been considered as the most difficult to synthesize stereoselectively.[5] The difficulty derives from its unique structural features: stereoelectroically disfavored equatorial glycosidic linkage with 1,2-cis stereochemistry. In this context, the utility of so called intramolecular aglycon delivery (IAD) approaches,[6−9] especially the one utilizes a *p*-methoxybenzyl (PMB) group for tethering,[8,9] has been demonstrated. The latter approach not only guarantees the exclusive formation of the correct stereoisomer but also demonstrates it is flexible enough to be applied into branched structures of Asn-linked glycan chains.[9] As depicted in Scheme 1, this transformation consists of two steps: oxidative formation of the mixed acetal from mannosyl donor **1a** and aglycon (**step 1**) and initiation of IAD (**step 2**) by an appropriate promoter, most typically $MeOSO_2CF_3$ (MeOTf).[9,10] It is to be noted that the desired product is obtained as a 2-OH derivative **2**. If this transformation is performed starting from the mannosyl donor **1b** that has a polymer linked PMB-like group at *C*-2, desired β-manno glycoside **2** is expected to be the only polymer-free product, because (1) after **step 1**, unreacted aglycon can be washed out to leave polymer-bound mixed acetal after precipitation from an ethereal solvent,[4c] and (2) all major byproducts in **step 2** arise from the failure of the IAD process, for instance,

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⊗ Abstract published in *Advance ACS Abstracts,* May 15, 1997.

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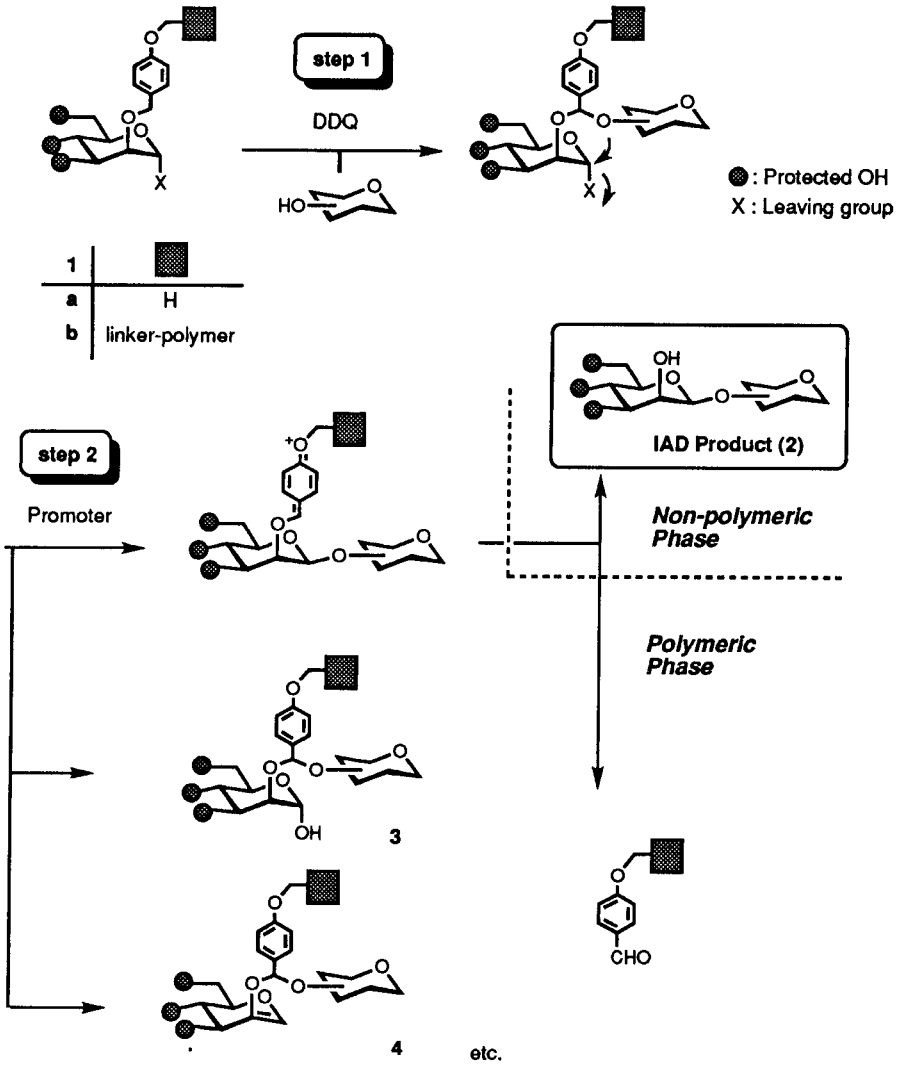
S0002-7863(96)04093-0 CCC: $14.00

Scheme 1. Reaction Pathway of β-Mannosylation



hydrolysis (i.e., **3**) or 1,2-elimination (i.e., **4**) should stay bound to the polymer. Therefore, the nonpolymeric part of the reaction should eventually become highly enriched with the desired product **2**.

This hypothesis was tested by using the polymer supported thiomannoside **10** that carries a *p*-alkoxybenzyl linker group at *C*-2 position. This material was prepared from known 4,6-*O*-benzylidene protected methylthio mannoside **6** in an analogous manner as reported for its 2-*O*-PMB counterpart,[9a] by using regioselective alkylation as a key transformation (Scheme 2). Namely, **6** was alkylated with *p*-allyloxybenzyl chloride[4h] under phase transfer conditions[11] to afford **7** as a major product. Subsequent deallylation gave **8** that was immediately alkylated into **9**. After conversion into free acid, coupling with polyethylene glycol (PEG) monomethyl ether (Aldrich, average MW 5×10^3) was performed under Mitsunobu conditions[12] to afford **10** (~80% yield[13]).

β-Mannosylation was first performed by using **11a**[14a] as a glycosyl acceptor (Scheme 3). Thus, **10** and **11a** (2.6 equiv) in CH_2Cl_2 was treated with DDQ (2.9 equiv) in the presence of molecular sieves (MS) 4Å (room temperature 3 h) to afford mixed acetal **12a**[15] [δ_H 5.58 (s, H-1), 5.46 and 4.94 (s, C*H*Ar)], which was precipitated from *tert*-butyl methyl ether (TBME), collected by filtration and washed with TBME.[16] Subsequent activation of the anomeric C-S linkage was performed by the action of MeOTf−MeSSMe (4 equiv each) in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DBMP, 4 equiv) in 1,2-dichloroethane. TLC analysis (hexane−ethyl acetate 3:1) of the reaction mixture revealed the nearly exclusive formation of the desired product,[17] except the presence of polar materials at the origin which should correspond to polymer bound byproduct(s). After aqueous workup[18] and very simple chromato-

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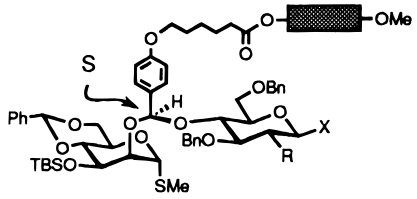
(13) The yield was calculated based on ^{1}H-NMR analysis in the presence of *p*-nitrobenzaldehyde as an internal standard. For details see Experimental Section.

(14) (a) **11a**, **11b**: Petit, J. M.; Jaquinet, J.-C.; Sinaÿ, P. *Carbohydr. Res.* **1980**, *82*, 130. (b) **11c**: Kanie, O.; Ito, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1994**, *116*, 12073. (c) **11d**: Ito, Y.; Sato, S.; Mori, M.; Ogawa, T. *J. Carbohydr. Chem.* **1988**, *7*, 359.

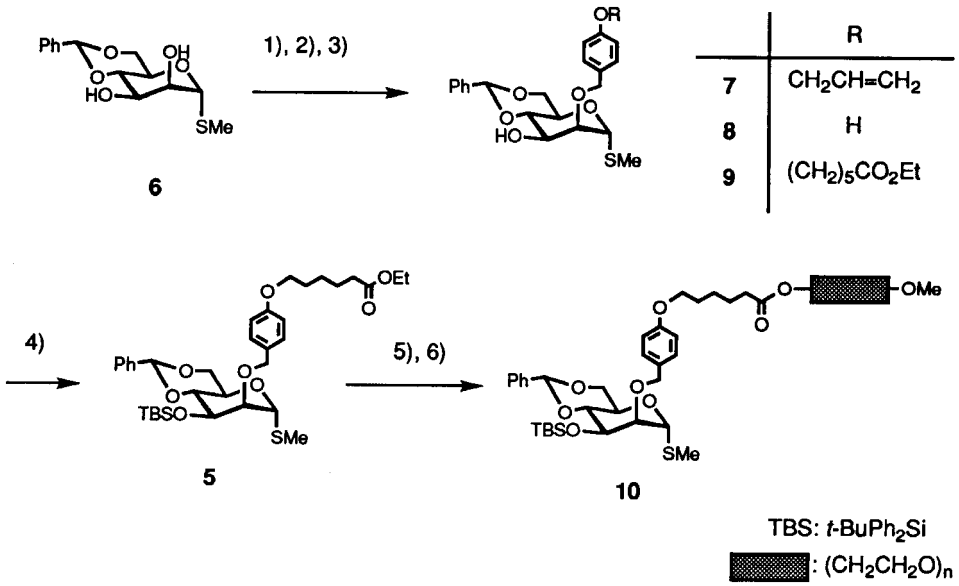
(15) ^{1}H-NMR analysis of **12a** and **12c** revealed mixed acetal formation seems to be highly stereoselective, and only a single isomer was detectable. In analogy with nonpolymeric acetals derived from PMB derivatives, the configuration of the acetalic carbon was assigned to be *S*.



12a,c

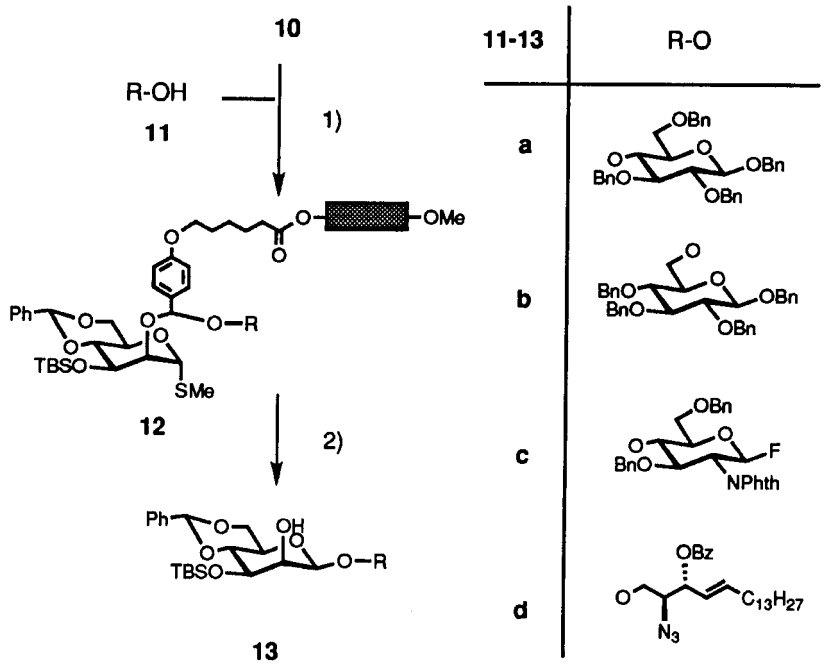
Unusually low field shifting of H-1 signal (δ 5.58 for **12a** and δ 5.63 for **12c**) is characteristic of *S* isomers (Lergenmüller, M; Nukada, T. Kuramochi, K; Dan, A.; Ito, Y.; Ogawa, T. Unpublished data). Stereochemical considerations of mixed acetal formation will be reported in due course.

Scheme 2. Synthesis of the Polymer Supported Glycosyl Donor[a]



[a] Key: (1) *p*-allyloxybenzyl chloride,[4h] aqueous NaOH, Bu_4NHSO_4/CH_2Cl_2, 43%; (2) $Pd(PPh_3)_4$, $NaBH_4$/THF; (3) $Br(CH_2)_5CO_2Et$, Cs_2CO_3/DMF, 79% (two steps); (4) TBSCl, imidazole/DMF, 81%; (5) aqueous NaOH/*t*-BuOH; (6) PEG monomethyl ether, $EtO_2CN{=}NCO_2Et$, Ph_3P/CH_2Cl_2-THF, 80%[b] (two steps). [b]Yield was estimated based on ^{1}H-NMR analysis of **10** in the presence of *p*-nitrobenzaldehyde as an internal standard.

Scheme 3. β-Mannosylation on Polymer Support[a]



[a] Key: (1) DDQ, MS4Å/CH_2Cl_2, room temperature, 3 h; (2) MeOTf, DBMP, MS4Å/$ClCH_2CH_2Cl$, temperature and time described in Table 1.

graphic purification, β-Man glycoside **13a** was obtained in a practically pure form (Table 1, entry 1). Similar transformations were performed by use of **10b**−**d**[14] as aglycons to afford **13b**−**d** (entries 3−5). The most notable was the compatibility with the orthogonal glycosylation strategy.[14b,19] Namely, glycosyl fluoride **10c** was successfully used as an acceptor (entry 4), and resultant **13c** was immediately converted into acetate **14** and coupled with **15**[20] under Suzuki's conditions[21] to give trisaccharide **16** that corresponds to the common trisaccharide sequence of Asn-linked oligosaccharide (Scheme 4). Compound **16** should be a versatile intermediate for the synthesis of various types of glycoprotein related glycopeptides, since further

Table 1. Results of Polymer-Supported β-Mannosylation

entry	**11** (equiv)	T(°C)/time(h)[a]	product	yield[b] (%)
1[c,d]	**a** (2.6)	40/21	**13a**	50
2	**a** (2.0)	40/40	**13a**	48
3	**b** (1.9)	20/8	**13b**	43
4[d]	**c** (1.9)	40/120	**13c**	37[e] (48[f])
5	**d** (2.3)	40/22	**13d**	54

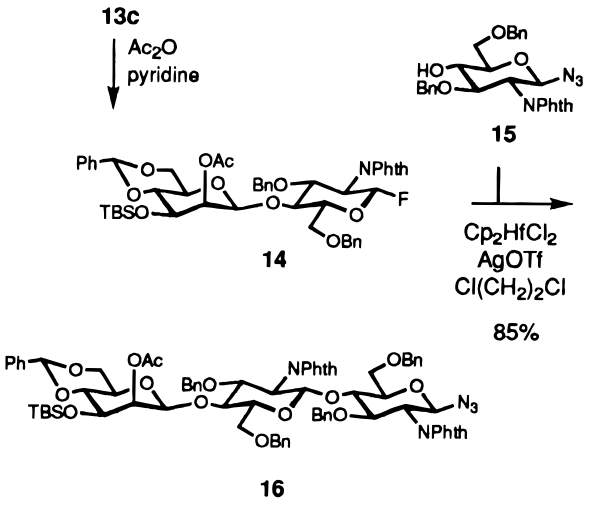
[a] Of step (2) (Scheme 3). [b] Calculated based on **10**. [c] Performed in the presence of MeSSMe (4 equiv). [d] Formation of the mixed acetal was confirmed by ^{1}H-NMR. [e] Isolated as corresponding acetate **14**. [f] Calculated based on consumed **11c**.

(16) Nearly theoretical amount of excess **10a** could be recovered from the filtrate.

(17) The reaction proceeds in a nearly identical efficiency in the absence of MeSSMe (entry 2). Careful inspection of TLC revealed the minor formation of **8a** which was isolated in ca. 5% yield. This phenomenon might be due to partial cleavage of the acetal linkage under the reaction conditions.

(18) The crude mixture proved to be substantially pure judging from ^{1}H-NMR (see Supporting Information).

Scheme 4. Synthesis of the Trisaccharide **16**



elongation of glycan chain at C-3, -4, and -6 of Man and introduction of an Asn residue at the reducing end[22] can be performed based on the well established methodologies.

In addition to the potential utility of this methodology in oligosaccharide synthesis, some similarities between the polymer supported intermediate **12** with substrates−enzyme complex of glycosyl transferase may be noticed in several contexts. Namely, glycosyl donor and acceptor are immobilized on polymer (although by covalent bonds in **12**, instead of hydrogen bonding, electrostatic and hydrophobic interactions, etc.), in an orientationally constrained manner that allows the exclusive formation of the correct stereoisomer, and the product is spontaneously dissociated from the polymer. Although the reaction efficiency in terms of yield is still lower than that the original PMB based strategy,[9] further systematic studies concerning choices of activation conditions (promoter, solvent, concentration, etc.), leaving group, protecting pattern, and the nature of polymer support and linker should allow this method to stand as a practical tool in β-Man containing oligosaccharides.

Experimental Section

General Procedures. ^{1}H- and ^{13}C-NMR spectra were taken by JEOL EX-270 as solutions in $CDCl_3$. Chemical shifts are expressed in ppm downfield from the signal for Me_4Si. Optical rotations were measured by JASCO DIP-310 as solutions in chloroform at ambient temperature. All reactions were performed under atmospheres of dry N_2 in anhydrous solvents distilled from the following desiccants: CH_2Cl_2 from P_2O_5, $(ClCH_2)_2$ and DMF from CaH_2, and THF from Na-benzophenone. Molecular Sieves 4Å were purchased from Nakarai Tesque Inc. (Kyoto) and dried at 180 °C under vacuum immediately prior to use. Unless noted otherwise, Merck silica gel (70−230 mesh) was used for column chromatography. Bio-Beads S-X4 used for size exclusion chromatography was purchased from Bio-Rad (Richmond, CA).

Methyl 2-*O*-*p*-Allyloxybenzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (7). Compound **6** (1.11 g, 3.72 mmol) was dissolved in CH_2Cl_2 (50 mL) containing *p*-allyloxybenzyl chloride (3.05 mmol in cyclohexane, 2.5 mL, 7.6 mmol) and tetra-*n*-butylammonium hydrogen sulfate (0.25 g, 0.74 mmol). NaOH (1.25 N, 6 mL, 7.5 mmol) was then added, and the two-phase mixture was heated under reflux with vigorous stirring for 40 h. The resulting mixture was washed with water and brine, successively, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (toluene−AcOEt 10:1) to afford 712 mg (43%) of compound **7** together with the corresponding regioisomer (376 mg, contaminated with *p*-allyloxybenzyl alcohol). Compound **7**: ^{1}H-NMR δ 7−7.6 (m, 7H, Ar), 6.90 (2H, d, J 8.9 Hz, Ar), 5.9−6.3 (1H, m, C*H*═CH_2), 5.53 (1H, s, C*H*Ph), 5.24 (1H, s, H-1), 4.67 (1H, d, J = 11.6 Hz, CH_2Ar), 4.5−4.6 (3H, m, CH_2Ar and CH_2CH═), 3.7−4.3 (6H, m, H-2, 3, 4, 5, 6), 2.10 (3H, s, SMe); ^{13}C-NMR δ 158.5, 137.2, 133.1, 129.6, 129.3, 129.0, 128.9, 128.3, 128.2, 126.3, 126.0, 125.2, 117.6, 114.8, 114.5, 102.0 (*C*HPh), 83.8 (C-1), 79.6, 79.4, 72.7, 68.8, 68.7, 68.5, 63.8, 13.7 (SMe).

Corresponding regioisomer: ^{1}H-NMR δ 5.59 (1H, s, C*H*Ph), 5.21 (1H, s, H-1), 2.11 (3H, s, SMe); ^{13}C-NMR δ 101.8 (*C*HPh), 85.9 (C-1), 13.7 (SMe).

Methyl 4,6-*O*-Benzylidene-2-*O*-*p*-(5-ethoxycarbonyl)pentoxybenzyl-1-thio-α-D-mannopyranoside (9). To a solution of compound **7** (671 mg, 1.51 mmol) in THF (10 mL) were added $Pd(Ph_3P)_4$ (35 mg, 0.03 mmol) and $NaBH_4$ (120 mg, 3.2 mmol). After being stirred at room temperature for 24 h, the mixture was diluted with AcOEt−ice water, quenched with 2 N HCl (ca. 3 mL), and washed with water and brine, successively. The organic layer was dried over $MgSO_4$, evaporated *in vacuo*, and exposed to high vacuum for 1 h to afford crude **8**. The residue was dissolved in DMF (5 mL) containing ethyl 6-bromohexanoate (0.40 mL, 2.2 mmol), and Cs_2CO_3 (740 mg, 2.27 mmol) was added to the solution. After being stirred for 4 h, the mixture was diluted with ether, washed with ice-cold water (× 2) and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography (hexane−AcOEt 3:1) to afford 652 mg (79%) of compound **9**: $[\alpha]_D$ +53.1° (*c* 1.8, $CHCl_3$); ^{1}H-NMR δ 5.56 (1H, s, C*H*Ph), 5.26 (1H, s, H-1), 4.69 and 4.53 (each 1H, ABq, J = 11.5 Hz, CH_2Ar), 3.8−4.3 (10H, m, H-2, 3, 4, 5, 6, OCH_2CH$_2$−, COOCH_2CH$_3$), 2.41 (1H, d, J = 8.3 Hz, OH), 2.33 (2H, t, J = 7.4 Hz, CH_2COO), 1.4−1.9 (6H, m, $(CH_2)_3$), 1.26 (3H, t, J = 7.1 Hz, CH_2CH_3); δ_c 173.6, 159.0, 137.3, 129.7, 129.2, 129.1, 128.2, 126.4, 114.5, 102.1 (*C*HPh), 83.8 (C-1), 79.7, 79.4, 77.2, 72.7, 68.9, 68.6, 67.6, 63.8, 60.2, 34.2, 28.9, 25.6, 24.7, 14.2, 13.7 (SMe).

Anal. Calcd for $C_{29}H_{38}O_8S$: C, 63.72; H, 7.01. Found: C, 63.50; H, 6.97.

Methyl 4,6-*O*-benzylidene-3-*O*-*tert*-butyldiphenylsilyl-2-*O*-*p*-(5-ethoxycarbonyl)pentoxybenzyl-1-thio-α-D-mannopyranoside (5). To a solution of compound **9** (605 mg, 1.11 mmol) and imidazole (150 mg, 2.20 mmol) in DMF (5 mL) was added *tert*-butyldiphenylsilyl chloride (0.44 mL, 1.7 mmol). The mixture was stirred at 50°C for 18 h, cooled to room temperature, diluted with ether, and washed with water. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane−AcOEt 6:1−3:1) to afford 702 mg (81%) of compound **5**: $[\alpha]_D$ +54.4° (*c* 1.2, $CHCl_3$); ^{1}H-NMR δ 5.43 (1H, s, C*H*Ph), 4.95 (1H, d, J <1 Hz, H-1), 4.56 and 4.40 (each 1H, ABq J 11.2 Hz, CH_2Ph), 3.80 (1H, t, J = 9.9 Hz, H-4), 3.41 (1H, dd, J = 3 and <1 Hz, H-2), 2.33 (2H, t, J = 7 Hz), 1.95 (3H, s, SMe), 1.4−1.9 (6H, m, $(CH_2)_3$), 1.25 (3H, t, J = 7 Hz, CH_2CH_3), 1.05 (9H, s, *t*-Bu); ^{13}C-NMR δ 173.5, 58.7, 137.5, 136.0, 135.9, 135.8, 133.9, 133.5, 130.0, 129.6, 129.4, 129.3, 128.6, 127.9, 127.6, 127.3, 126.2, 114.2, 101.7 (*C*HPh), 84.6 (C-1), 80.0, 78.9, 73.0, 71.0, 68.5, 67.6, 64.5, 60.2, 34.2, 28.9, 26.9, 25.6 (Me_3C), 24.7, 19.3, 14.2, 13.6.

Anal. Calcd for $C_{45}H_{56}O_8SSi$: C, 68.85; H, 7.19; S, 4.08. Found: C, 68.89; H, 7.17; S, 4.34.

Polymer-Supported Glycosyl Donor 10. To compound **5** (662 mg, 0.843 mmol) in *tert*-butyl alcohol (15 mL) was added 1.25 N NaOH (2.5 mL, 3.1 mmol), and the mixture was stirred at 50 °C for 20 h. Resulting mixture was diluted with AcOEt−ice water and acidified with 2 N HCl (ca. 2.5 mL). Layers were separated, and the organic layer was washed with brine (×3), dried over $MgSO_4$, and evaporated *in vacuo*. The residue was exposed to high vacuum for 3 h to afford free acid (655 mg).

To a stirred mixture of triphenylphosphine (550 mg, 2.1 mmol) in THF (5 mL) was added diethyl azodicarboxylate (0.33 mL, 2.1 mmol) at 0 °C. Then, a solution of the aforesaid carboxylic acid and polyethylene glycol monomethyl ether (Aldrich, average MW 5×10^3; 5.05 g, ca. 1.0 mmol) in THF−CH_2Cl_2 (3:2, 25 mL in total) was added dropwise. The mixture was stirred at 0 °C for 0.5 h and at room temperature for 2 h, quenched with acetic acid (0.5 mL), and stirred for additional 0.5 h. Then, acetic anhydride (2 mL) and pyridine (2 mL) were added, and the mixture was stirred for 3 h and evaporated *in*

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vacuo. The residue was treated with *tert*-butyl methyl ether (ca. 100 mL). Solid materials were collected by filtration, washed with cold *tert*-butyl methyl ether, and dried under high vacuum to afford 5.537 g (97%) of **10**: ^{1}H-NMR δ 5.42 (1H, s, C*H*Ph), 4.95 (1H, s, H-1), 3.38 (3H, s, OMe), 2.38 (2H, t, J 7 Hz, CH_2CO), 1.96 (3H, s, SMe), 1.05 (9H, s, *t*-Bu).

One gram of this material was estimated to contain ca. 0.116 mmol of mannose residue based on ^{1}H-NMR as follows. To be brief, 92.7 mg of **10** was mixed with 10.2 mg (0.067 mmol) of *p*-nitrobenzaldehyde in $CDCl_3$ and subjected to ^{1}H-NMR measurement. Relative intensities of aldehyde (δ 10.15), benzylidene (δ 5.42) and *tert*-butyl (δ 1.05) peaks were 6.02:1:8.83. Thus, carbohydrate content of **10** should be either 0.067/6.02/0.0927 = 0.120 mmol/g or 0.067 × 8.83/9/6.02/0.0927 = 0.111 mmol/g and estimated to be (0.120 + 0.111)/2 = 0.116 mmol/g.

Representative Experimental Procedure of Stereoselective *β*-Mannosylation on Polymer Support. Benzyl *O*-(4,6-*O*-Benzylidene-3-*O*-*tert*-butyldiphenylsilyl-*β*-D-mannopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-*β*-D-glucopyranoside (13a). Under ice-water cooling, DDQ (25 mg, 0.11 mmol) was added to a stirred mixture of **10** (330 mg, 0.0383 mmol), **11a** (54 mg, 0.10 mmol), and molecular sieves 4Å (0.3 g) in CH_2Cl_2 (2 mL) with positive flush of N_2. The mixture was stirred at room temperature for 3 h, quenched with aqueous solution of ascorbic acid (0.7%)−citric acid (1.3%)−NaOH (0.9%) (3 mL), stirred for 5 min, diluted with CH_2Cl_2−brine, and filtered through Celite. The filtrate was extracted with CH_2Cl_2 (×5), and combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo*. The residue was triturated with *tert*-butyl methyl ether−hexane (3:1, 20 mL). Solid materials were collected by filtration, washed with cold *tert*-butyl methyl ether, and dried under vacuum to afford the mixed acetal **12a** (334 mg): ^{1}H-NMR δ 5.58 (1H, s, C-1), 5.46 and 4.94 (each 1H, s, C*H*Ar), 2.36 (2H, t, J = 7 Hz, CH_2COO), 1.92 (3H, s, SMe), 0.87 (s, *t*-Bu). The mother liquor was evaporated *in vacuo*, and the residue was purified by preparative TLC to afford recovered **11a** (32.5 mg, 0.060 mmol).

12a (334 mg) was mixed with 2,6-di-*tert*-butyl-4-methylpyridine (41 mg, 0.20 mmol) and molecular sieves 4Å (0.3 g) in $(ClCH_2)_2$ (3.5 mL) and stirred at room temperature. Then, a solution of MeOTf in $(ClCH_2)_2$ (1M, 0.20 mL, 0.20 mmol) was added followed by MeSSMe (18 μL, 0.10 mmol). The mixture was stirred at 40°C for 21 h, quenched with Et_3N (40 μL), diluted with ether−aqueous $NaHCO_3$, and filtered through Celite. The filtrate was washed with water (×3) and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue (54 mg) was purified by a column of Bio-Beads S-X4 (toluene) to afford **13a** (19.9 mg, 50%), together with 1.1 mg of **11a**.

13a: $[\alpha]_D$ +15.2° (*c* 1.1, $CHCl_3$); ^{1}H-NMR δ 5.35 (1H, s, C*H*Ph), 4.46 (1H, d, J = 7.6 Hz, H-1^1), 4.42 (1H, s, H-1^2), 1.03 (9H, s, *t*-Bu); ^{13}C-NMR δ 102.7 (C-1^1), 101.8 (*C*HPh), 100.2 (C-1^2), 82.8, 81.8, 78.3, 77.3, 77.2, 75.5, 75.1, 74.4, 73.4, 72.6, 71.4, 71.2, 68.5, 68.4, 66.6, 26.9, 19.3.

Anal. Calcd for $C_{63}H_{68}O_{11}Si$•0.5 H_2O: C, 72.88; H, 6.70. Found: C, 72.70; H, 6.66.

The same reaction was also performed in the absence of MeSSMe to give **13a** in a nearly identical efficiency. Thus, 445 mg (0.052 mmol) of **10** was reacted with 60 mg (0.11 mmol) of **11a** to afford the mixed acetal **12a** that was treated with MeOTf (0.27 mmol) and DBMP (55 mg, 0.27 mmol) at 40 °C for 40 h. Subsequent workup and purification by a short column of silica gel (hexane−AcOEt 3:1) afforded 25.4 mg (48%) of **13a**.

Benzyl *O*-(4,6-*O*-benzylidene-3-*O*-*tert*-butyldiphenylsilyl-*β*-D-mannopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-*β*-D-glucopyranoside (13b). Synthesized from 415 mg (0.048 mmol) of **10** and 50 mg (0.092 mmol) of **11b** [(1) 22 mg (0.097 mmol) of DDQ (room temperature 3 h); (2) MeOTf (0.27 mmol)−DBMP (0.27 mmol) (room temperature 8 h)]. Yield 21.3 mg (43%): $[\alpha]_D$ −3.6° (*c* 1.0); ^{1}H-NMR δ 5.41 (1H, s, C*H*Ph), 4.47 (1H, d, J = 7.6 Hz, H-1^1), 4.26 (1H, s, H-1^2), 3.12 (ddd, J = 9.7, 9.7 and 5.0 Hz, H-5^2), 1.03 (9H, s, *t*-Bu); ^{13}C-NMR δ 102.4 (C-1^1), 101.8 (*C*HPh), 100.9 (C-1^2), 84.8, 82.2, 78.4, 78.0, 77.2, 75.7, 74.9, 74.6, 72.7, 71.6, 71.2, 68.5, 68.7, 26.9, 19.4.

Anal. Calcd for $C_{63}H_{68}O_{11}Si$•0.5 H_2O: C, 72.88; H, 6.70. Found: C, 72.60; H, 6.73.

***O*-(2-*O*-Acetyl-4,6-*O*-benzylidene-3-*O*-*tert*-butyldiphenylsilyl-*β*-D-mannopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl Fluoride (14).** **10** (702 mg, 0.081 mmol) and 80 mg (0.15 mmol) of **11c** were reacted [(1) 36 mg (0.16 mmol) of DDQ (room temperature 3 h)] to afford 719 mg of **12c**; ^{1}H-NMR δ 5.87 (1H, dd, J = 54 and 7 Hz, H-1^1), 5.63 (1H, d, J <1 Hz, H-1^2), 5.35 and 4.80 (each 1H, s, C*H*Ar), 1.96 (3H, s, SMe), 0.89 (9H, s, *t*-Bu), together with recovered **11c** (46.1 mg). **12c** was subsequently treated with MeOTf (0.41 mmol)−DBMP (0.41 mmol) (40 °C, 5d). The reaction mixture was worked up as described for **13a**, and the crude material was subjected to acetylation (Ac_2O−DMAP/pyridine, room temperature 18 h) . The mixture was evaporated *in vacuo* and purified by silica gel column chromatography (hexane−AcOEt 3:1) to afford 30.5 mg (37%, 48% based on consumed **11c**) of **14**: $[\alpha]_D$ +48.8° (*c* 0.4); ^{1}H-NMR δ 5.80 (1H, dd, J = 53.6 and 7.4 Hz, H-1^1), 5.21 (1H, s, C*H*Ph), 5.14 (1H, dd, J = 2.3 and <1 Hz, H-2^2), 4.47 (1H, d, J <1 Hz, H-1^2), 2.20 (3H, s, Ac), 0.98 (9H, s, *t*-Bu); ^{13}C- NMR δ 104.69 ($^1J_{C-F}$ 214.8 Hz, C-1^1), 101.7 (*C*HPh), 99.0 (C-1^2), 78.6, 78.0, 75.8, 75.7, 74.6, 74.4, 74.3, 73.5, 71.8, 71.1, 68.3, 67.7, 66.5, 55.5 ($^2J_{C-F}$ 18.0 Hz, C-2^2), 26.6, 21.6 (Ac), 19.1.

Anal. Calcd for $C_{59}H_{60}NO_{12}FSi$: C, 69.33; H, 5.92; N, 1.37. Found: C, 69.15; H, 6.03; N, 1.43.

2-Azido-3-(benzoyloxy)-4-*E*-D-*erythro*-octadec-4-ene-1-yl 4,6-*O*-Benzylidene-3-*O*-*tert*-butyldiphenylsilyl-*β*-D-mannopyranoside (13d). Prepared from 360 mg (0.042 mmol) of **10** and 42 mg (0.097 mmol) of **11d** [(1) 22 mg (0.097 mmol) of DDQ (room temperature 3 h); (2) MeOTf (0.21 mmol)−DBMP (0.21 mmol) (40 °C, 22 h)]. Yield 21.0 mg (54%)**:** $[\alpha]_D$ −17.3° (*c* 0.8); ^{1}H-NMR δ 5.89 (1H, ddd, J = 15, 7 and 7 Hz, H-5′), 5.45−5.65 (2H, m, H-3′ and −4′), 5.38 (1H, s, C*H*Ph), 4.33 (1H, s, H-1), 3.17 (ddd, J = 9.7, 9.7, and 5.0 Hz, H-5), 2.05 (1H, q, J = 7 Hz, H-6′), 1.23 (22H, bs, $C_{11}H_{22}CH_3$), 1.04 (9H, s, *t*-Bu), 0.88 (3H, t, J 7 Hz, CH_3); ^{13}C-NMR δ 101.8 (*C*HPh), 100.2 (C-1), 78.2, 77.2, 77.2, 74.6, 72.7, 71.4, 68.4, 68.3, 66.9, 63.5, 32.4, 31.9, 29.63, 29.58, 29.40, 29.35, 29.1, 28.7, 26.9, 22.7, 19.3, 14.1.

Anal. Calcd for $C_{54}H_{71}O_8N_3Si$: C, 70.63; H, 7.79; N, 4.58. Found: C, 70.13; H, 7.82; N, 4.63.

***O*-(4,6-*O*-Benzylidene-3-*O*-*tert*-butyldiphenylsilyl-*β*-D-mannopyranosyl)-(1→4)-*O*-(3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl Azide (16).** A mixture of Cp_2HfCl_2 (23 mg, 0.061 mmol), AgOTf (31 mg, 0.12 mmol), and molecular sieves 4Å (0.15 g) in 1,2-dichloroethane (0.5 mL) was stirred at room temperature for 10 min and then cooled down to −15 °C. A solution of compounds **14** (30.5 mg, 0.030 mmol) and **15** (22.6 mg, 0.044 mmol) in 1,2-dichloroethane (2 mL in total) was added dropwise. The mixture was stirred for 1.5 h while gradually warmed up to room temperature, quenched with ice−$NaHCO_3$, and diluted with AcOEt. The suspension was stirred for 10 min and filtered through Celite. The filtrate was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by a column of Bio-Beads S-X4 (toluene) and then by preparative TLC (hexane−AcOEt 2:1) to afford 38.3 mg (85%) of **16**: $[\alpha]_D$ +10.9° (*c* 1.5); ^{1}H-NMR δ 5.22 (1H, d, J = 8 Hz, H-1^2), 5.20 (1H, s, C*H*Ph), 5.15 (1H, d, J = 2 Hz, H-2^3), 5.14 (1H, d, J = 8.9 Hz, H-1^1), 4.51 (1H, s, H-1^3), 2.21 (3H, s, Ac), 0.98 (9H, s, *t*-Bu); ^{13}C-NMR δ 101.7 (*C*HPh), 98.9 ($^1J_{C-H}$ 157 Hz, C-1^3), 96.8 ($^1J_{C-H}$ 165 Hz, C-1^2), 85.5 ($^1J_{C-H}$ 162 Hz, C-1^1), 78.7, 78.4, 77.7, 77.2, 76.7, 76.4, 75.1, 74.5, 74.3, 73.0, 72.9, 71.9. 71.2, 68.3, 67.7, 67.5, 66.6, 56.4 and 55.1 (C-2^1 and −2^2), 26.7, 21.1 (Ac), 19.1.

Anal. Calcd for $C_{79}H_{85}N_5O_{18}Si$: C, 68.90; H, 5.65; N, 4.62. Found: C, 68.83; H, 5.65; N, 4.43.

Acknowledgment. This paper is dedicated to Prof. Hans Paulsen on the occasion of his 75th birthday. A part of this work was financially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture and also by the Special Coordination Funds of the Science and Technology Agency of the Japanese Government. We thank Ms. M. Yoshida and her staff for elemental analyses and Ms. A. Takahashi for technical assistance.

Supporting Information Available: Copies of ^{1}H- NMR of **10**, **12a**, **12c** and ^{1}H- and ^{13}C-NMR of **13a**, **13b**, **13d** and **14** and TLC profiles of *β*-manosylations that gave **13a** and **13c** (13 pages). See any current masthead page for ordering and Internet access instructions.

JA964093P