JOC The Journal of Organic Chemistry

ARTICLE

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Assembly of Homolinear α(1→2)-Linked Nonamannoside on Ionic Liquid Support

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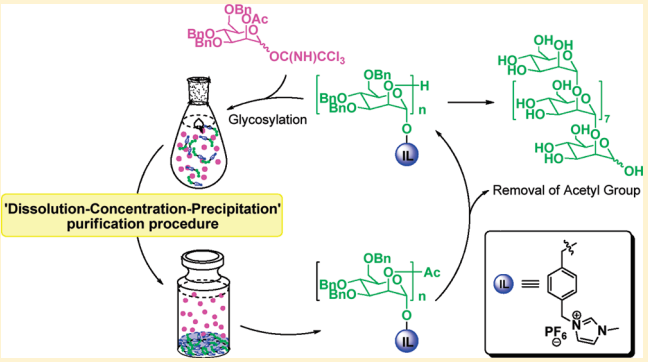
Supporting Information

ABSTRACT: An improved method for the synthesis of large and complex oligosaccharides on ionic liquid (IL) support was developed. A strategy to attach the acceptor on IL using a more stable ether linker was used to prevent undesirable decomposition and side products. A "dissolution−evaporation−precipitation" purification procedure was also developed by combining the advantages of precipitation and solid−liquid extraction to reduce mechanical loss and purification time. This approach was successfully used for the rapid assembly of ionic liquid supported homolinear α(1→2)-linked nonamannoside in 25.2% overall yield within 28.5 h.



1. INTRODUCTION

The study of carbohydrates has been widely valued in many different areas of chemistry and biology since they possess a variety of unique functionalities and structures.[1] Chemical synthesis of pure and structurally complex oligosaccharides is still a challenge because of the selective protection and deprotection of multiple hydroxyl groups. Moreover, traditional synthesis requires purification by chromatography after each glycosylation step, which is not only time-consuming but also costly.[2] Extensive efforts were made to improve the synthesis of oligosaccharides. Wong and co-workers developed a programmable one-pot oligosaccharide synthesis procedure to enhance the efficiency of synthesis by eliminating the need for protecting groups between coupling steps.[3] An iterative one-pot method for the synthesis of oligosaccharides with fewer protective group manipulations has been investigated.[4] The simplification of the purification step is also important for the improvement of the synthesis. The solid-phase approach is attractive mainly because of its simple purification process, which allows convenient product isolation and automation.[5−7] Despite its success, solid-phase synthesis has limitations because of the heterogeneous reaction conditions. An alternative polymer-supported liquid-phase strategy that maintains the homogeneous reaction conditions was developed to overcome some of the limitations of solid-phase synthesis.[8] However, several limitations of polymer-supported synthesis including low loading capacity and limited solubility of the glycosyl donors during the reaction process hamper its wider use, and there is still a need to improve the method.[9] Fluorous-assisted separations methodology using fluorous support and fluorous biphasic systems has also been recently exploited for the synthesis of oligosaccharides.[5c,10,23] In view of one-pot synthesis, this method has also developed into a strategy known as the fluorous assisted one-pot assembly of oligosaccharides.[11]

Ionic liquids have been extensively studied because of their fascinating and intriguing properties,[12] such as their use as solvents and reaction supports.[13] An attractive feature of IL supports is that their solubility can be altered readily by modifying the structure of cation or anion. This property suggests the possibility of using ionic liquids as soluble supports for organic synthesis. The compounds attached on IL are expected to retain their reactivity under homogeneous reaction conditions. Several groups have successfully demonstrated the feasibility of ionic liquid supported synthesis of peptides, nucleotides, and other types of organic molecules.[14−16]

More recently, several groups utilized ionic liquid supports as phase-separation tags in the synthesis of oligosachharides.[17,18] Although successful in the synthesis of disaccharides and trisaccharides, its application in the synthesis of more complex oligosaccharides still remains to be explored. Only recently, Pathak et al. synthesized homolinear α(1→6)-linked tetra- and octamannoside using this method via fragment coupling.[19,20] The following three key aspects of IL support may limit its application. First, the attachment strategy: whether ionic liquids should be tagged on glycosyl donors or acceptors has to be determined by the synthetic manipulation; Second, stability of linker: even trace decomposition of the unstable linker in the process may cause accumulative effects and thus limit the yield.

Received: March 24, 2011
Published: June 08, 2011

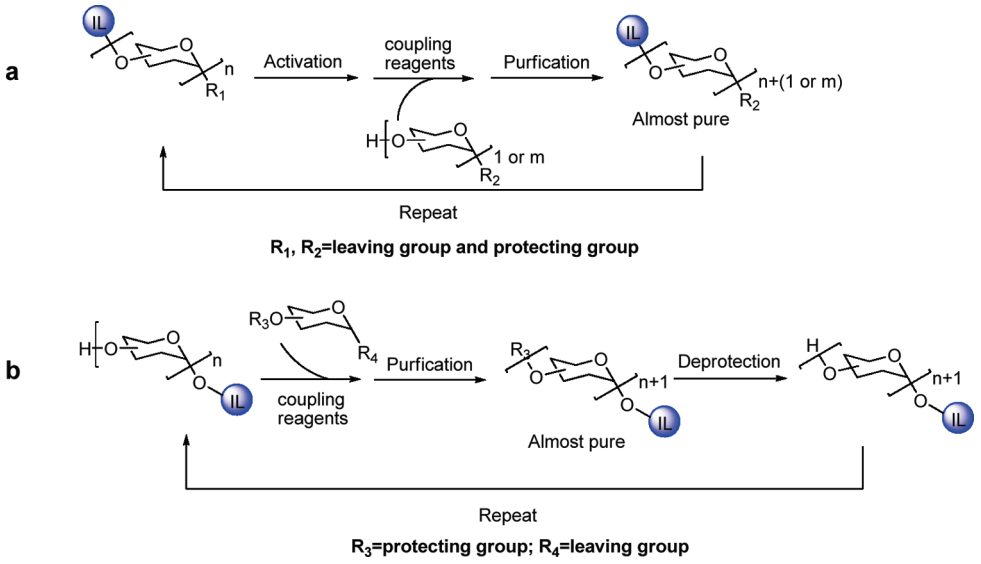


Figure 1. Oligosaccharide synthetic strategy using IL support: (a) pathway with donor attached to IL support; (b) pathway with acceptor attached to IL support.

Third, purification technique: the existing purification technique is either through precipitation or solid−liquid extraction, which resulted in mechanical loss; optimization is likely necessary. Based on these analyses, we believe further optimization of ionic liquid supported synthesis is still necessary for its successful application in the synthesis of complex oligosaccharides.

To develop a more efficient methodology for IL supported synthesis of complex oligosaccharides, homolinear α(1→2)-linked oligomannoside was chosen as our target structure, because D-mannose oligomers are present in nature and are essential substructures in many biologically relevant glycoconjugates.[21] Moreover, oligomannan synthesis has been reported using several different methodologies,[22] including solution- and solid-phase synthesis,[8c] as well as fluorous-[23] and ionic liquid-tagged synthesis.[19,20] Specifically, the homolinear α(1→2) oligomannans were previously synthesized in the solution phase[24] and by a solid-phase approach.[25]

In the present work, we developed a glycosyl acceptor tagging strategy, employed a stable ether linker, and used a new purification technique to improve IL supported synthesis of complex oligosaccharides, which allowed the rapid assembly of a homolinear α(1→2)-linked nonamannoside without chromatographic purification.

2. RESULTS AND DISCUSSION

2.1. Development of an Acceptor Attachment Strategy. Most published methods attached the glycosyl donors to the ionic liquid supports[18−20] as illustrated in Figure 1a. Because the glycosyl donors are the reactive agents, many side products like anomer-to-anomer coupling products, donor rearrangement products, and other side products remained on the IL support and could not be removed in the purification process, which decreased the purity. Alternatively, acceptors could be attached on the ionic liquid supports to avoid the contamination by side products. Indeed, acceptors attached on the ionic liquid supports were tried in the early research,[17] but not widely used since then. Therefore, we decided to revisit this attachment strategy.

As illustrated in Figure 1b, ionic liquid supported acceptors were used for the synthesis of the α(1→2)-linked oligomannoside. An oligosaccharide attached on IL was prepared by coupling IL-supported glycosyl acceptor with glycosyl donors in an appropriate solvent such as CH_2Cl_2. Highly pure IL-tagged product was generated after washing with aqueous solution and phase separation with a solvent in which the IL-tagged oligosaccharide is not soluble (e.g., diethyl ether). The reagents as well as unreacted donor glycoside and other side products were removed during the process.

Additionally, in any support-assisted synthesis, high reaction yield is necessary because unreacted species will be carried to the next step. We could use excess donors and more reactive leaving groups to increase the reaction yield.

2.2. Synthesis of a New DOX Linker Modified Ionic Liquid Support. In previous works, ionic liquids and glycosyl donors were conjugated via an acetyl linker, which is relatively unstable under both acid and alkali conditions. Consequently, accumulation of the side products produced by the decomposition of the linker led to lower yield and purity. We designed and synthesized an IL support using α,α′-dioxyxylyl diether (DOX) as the linker.[8c] Unlike acetyl linker, it has several advantages: it is more stable under most reaction conditions and readily removable by hydrogenolysis; it can be bound via an ether or O-glycosidic linkage; and it is easily prepared from commercially available α,α′-dibromo-*p*-xylene.

The α,α′-dibromo-*p*-xylene was first treated with NaOAc to produce 4-(bromomethyl)benzyl alcohol acetate **2** (Scheme 1). Following reaction with *N*-methylimidazole and KPF_6, the acetylated IL support **3** was formed via simple phase separation. The linker-modified IL support **4** was obtained after deacetylation with NaOMe. The structure of **4** was confirmed by NMR and MS spectra.

2.3. Selection of the glycosyl Acceptor Donor and Optimization of the Coupling Condition. After the synthesis of the linker modified ionic liquid support, a glycosyl donor can be attached to it. 3,4,6-Tri-*O*-benzyl-2-*O*-acetyl-α-D-mannose trichloroacetimidate **5** was selected as the donor because it can be prepared easily from D-mannose and it has been widely used in

dx.doi.org/10.1021/jo2006126 |*J. Org. Chem.* 2011, 76, 5652–5660

Scheme 1. Synthesis of Linker-Modified IL Support

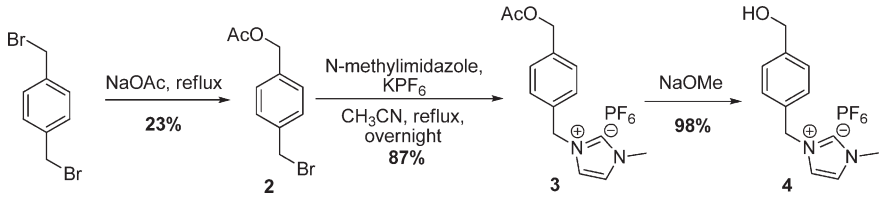
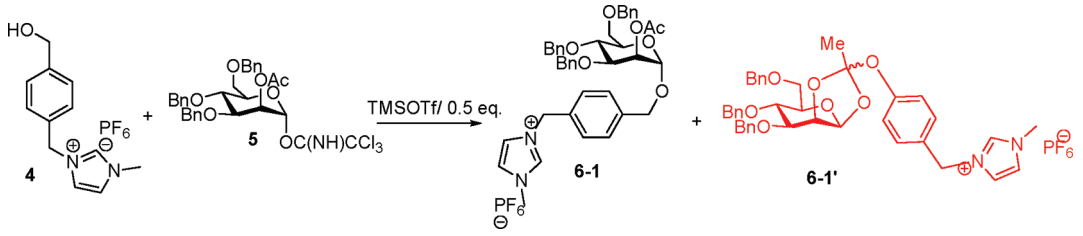


Table 1. Optimization of the Glycosylation Conditions



entry	donor (equiv)	solvent	temp (°C)	time (h)	TLC[a]	ratio of **6-1′**[b] (%)
1	2.0	CH_3CN	0	0.5	complete	21
2	2.0	CH_3CN	−40	4.0	complete	43
3	2.0	CH_3CN	50	2.0	complete	[c]
4	2.0	CH_3CN:CH_2Cl_2 (1:10)	0	0.5	complete	[c]
5	4.0	CH_3CN:CH_2Cl_2 (1:10)	0	0.5	complete	[c]
6	3.0	CH_3CN:CH_2Cl_2 (1:10)	0	0.5	complete	[c]
7	2.0	CH_3CN:CH_2Cl_2 (1:10)	0	0.5	complete	[c]
8	1.5	CH_3CN: CH_2Cl_2 (1:10)	0	0.5	incomplete	[c]

[a] Analyzed by TLC: "complete" represents no ionic liquid support remaining, "incomplete" represents IL support remaining. R_f value of ionic liquid support is 0.27 (CH^2Cl_2/CH_3OH 10:1) and Rf value of the product is 0.43 (CH_2Cl_2/CH_3OH 10:1). [b] The structure of compound **6-1′** was deduced based on ^1H NMR and ^{13}C NMR spectra of the mixture, which are included in the Supporting Information. The ratio was determined by ^1H NMR. [c] The signal of ortho ester **6-1′** was not detected by both ^1H NMR and ^{13}C NMR.

the synthesis of α(1→2)-linked mannoside.[26] Glycosyl acceptor **5** is highly reactive because of the arm-effect, and the 2-*O*-acetyl ensures α-stereospecific reaction through the neighboring group participation. Moreover, as a temporary protection group, the acetyl group can be removed easily and rapidly.

We then carried out experiments to optimize the coupling condition to ensure high reaction yield (Table 1). Generally, the IL-conjugated donor **5** and the acceptor **4** were dissolved in dry solvent, and 0.5 equiv of TMSOTf was added as a promoter of the assembling reaction. The crude product was obtained by washing with saturated aq $NaHCO_3$ and brine to remove all the water-soluble impurities. Further purification of the product was carried out by concentrating the product into syrup, which was dissolved in CH_2Cl_2 and precipitated with diethyl ether. The white precipitate was immediately separated from the solvent by centrifugation to afford the product.

Because ionic liquid **4** cannot be dissolved in CH_2Cl_2, CH_3CN was used as the solvent initially. However, an ortho ester side product such as **6-1′** was produced, which cannot be eliminated in further phase separation. As a kinetically controlled product, the formation of **6-1′** increased with the decrease of reaction temperature. Moreover, we found that when solvent was switched from CH_3CN to a mixture of CH_3CN and CH_2Cl_2 (1:10), generation of ortho ester was prevented. Fortunately, because ionic liquid modified with oligosaccharides is soluble in CH_2Cl_2, the formation of ortho ester in the assembly of oligosaccharides was avoided by selecting CH_2Cl_2 as the solvent.

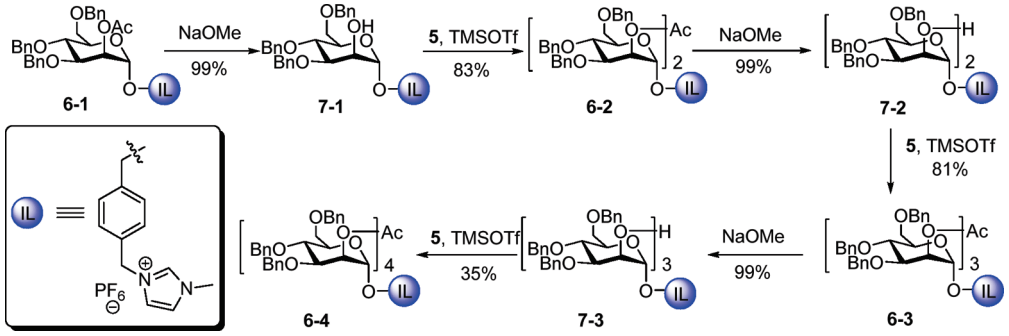
The amount of donors was also optimized to attain cost-effective and complete glycosylation. The reaction process was already highly efficient when only 2.0 equiv of donor was added according to TLC analysis.

Finally, following the optimized condition in entry 7, highly pure IL-supported monosaccharide **6-1** was prepared. The structure was confirmed by its NMR spectrum, and the NMR spectrum also showed it was highly pure. This was further supported by the MS analysis.

On the basis of careful optimization, the final glycosylation condition is as follows: 2.0 equiv of trichloroacetimidate donor with 0.5 equiv of TMSOTf as promoter in dry CH_2Cl_2 at 0 °C for 0.5 h with stirring. The same post-treatment and precipitation purification technique were used in the next steps. Because of the potential difference in nucleophilicities of the benzyl alcohol acceptor and the secondary axial alcohol acceptor, caution should be raised that the optimized reaction conditions may not be optimal for the elongation with saccharide acceptors. In our experiments, the elongation went smoothly under the optimized conditions.

dx.doi.org/10.1021/jo2006126 |*J. Org. Chem.* 2011, 76, 5652–5660

Scheme 2. Attempted Assembly of α(1→2)-Linked Mannoside Using Precipitation Purification



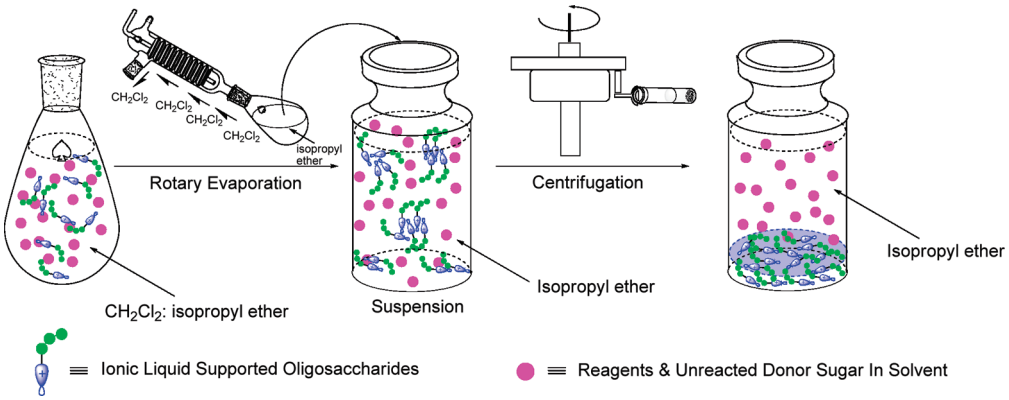


Figure 2. Novel purification technique for IL-supported oligosaccharide synthesis.

2.4. Attempted Assembly of α(1→2)-Linked Oligomannoside Using Precipitation Purification. After the attachment of a sugar to the IL support, the IL-supported monosaccharide **6-1** was deacetylated by treatment with NaOMe. The mixture was concentrated in vacuo, dissolved in CH_2Cl_2, and filtered. The acceptor **7-1** was obtained after evaporating solvent, which was sufficiently pure for further reactions.

Glycosyl trichloroacetimidates served as donors in two consecutive glycosylation reactions to furnish α(1→2)-linked trimannoside (Scheme 2), whose structure was confirmed by NMR spectrum and MS analysis. However, when this approach was employed to assemble the tetrasaccharide, even though the coupling was still highly efficient according to spectroscopic analysis, only 35% of the product was recovered.

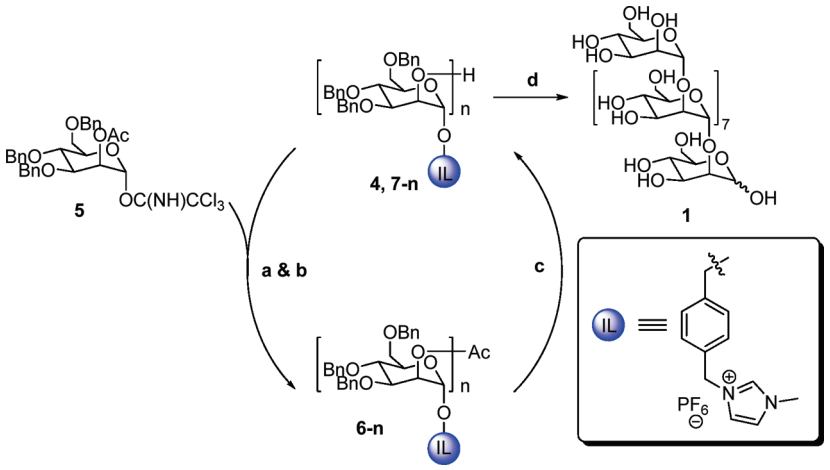
2.5. Development of a New Purification Procedure. The low recovery in the synthesis of tetrasaccharide motivated us to develop a new purification procedure. The existing purification procedure for IL-supported synthesis includes either precipitation or solid−liquid extraction. In the precipitation method, the low recovery is probably attributed to the less role played by the IL moiety when larger oligosaccharides are attached to it, thus increasing the solubility of the IL−oligosacchride conjugate.[12b] The decreased influence of IL on the solubility of the IL−oligosacchride causes greater loss of product in synthesis of larger oligosaccharides due to the gradually increased solubility. To avoid the increased solubility of ionic liquid tagged oligosaccharides in solvents like CH_2Cl_2, we tried solid−liquid extraction. The crude products were washed with diethyl ether directly without polar solvent. However, because of the extremely high viscosity of ionic liquid species and thus poor impurity dissolution kinetics, products were still not pure after stirring for 48 h at room temperature in a large volume of diethyl ether.

To improve the purification process of ionic liquid tagged oligosaccharides, we designed a novel purification procedure that consisted of mixed-solvent dissolution, evaporation, precipitation, and centrifugation steps (Figure 2). In this strategy, the reaction mixture was first dissolved in a mixed solvent of dichloromethane and isopropyl ether. Subsequently, the solvent was removed partially by rotary evaporation in vacuo. Dichloromethane was evaporated before isopropyl ether because its boiling point is lower. With the evaporation of polar solvent dichloromethane, ionic liquid tagged oligosaccharides precipitated gradually. After the complete removal of CH_2Cl_2, the white precipitates in isopropyl ether were collected by centrifugation to yield the product. This "dissolution−evaporation−precipitation" purification procedure is equivalent to the precipitation procedure in nonpolar solvent, but the new evaporation−precipitation procedure showed higher recovery than the traditional precipitation procedure. Compared with the solid−liquid extraction method, this method avoided slow impurity dissolution kinetics; it was shown to be quite efficient.

We used the optimized coupling conditions, and this new purification technique to synthesize homolinear α(1→2)-linked nonamannoside. The reaction was conducted under the optimized coupling conditions: 2.0 equiv of trichloroacetimidate donor with 0.5 equiv TMSOTf as promoter in dry CH_2Cl_2

dx.doi.org/10.1021/jo2006126 |J. Org. Chem. 2011, 76, 5652–5660

Scheme 3. IL-Supported Assembly of Homolinear α(1→2)-Linked Nonamannoside[a]



[a] Key: (a) Glycosylation: TMSOTf (0.5 equiv), CH_2Cl_2, molecular sieves (4 Å), 0 °C, Ar, 30 min. (b) Purification. (c) Removal of acetyl group: NaOMe, MeOH, 1 h. (d) Hydrogenation: H_2 (4 atm), $Pb(OH)_2$, MeOH/EtOAc, 4 d.

stirred at 0 °C for 0.5 h. After the glycosylation was complete, the solution was concentrated in vacuo to a syrup, dissolved in CH_2Cl_2, and washed with satd aq $NaHCO_3$ and brine. For further purification, the crude product was concentrated into a syrup, dissolved in CH_2Cl_2, and added with isopropyl ether. Thereafter, solvent was removed partially by rotary evaporation in vacuo, until the remaining solution was about double the original CH_2Cl_2 volume; a white precipitate appeared, and it was immediately collected by centrifugation (Figure 2). The purification procedure produced highly pure IL-supported species.

2.6. Rapid Assembly of Nonamannoside Using the New Purification Procedure. Following the pathway illustrated in Scheme 3, α(1→2)-linked nonamannoside **7**−**9** was synthesized with glycosyl trichloroacetimidates **5** as donors in consecutive glycosylation reactions. The structure of **7**−**9** was supported by ^{1}H and ^{13}C NMR spectra and further confirmed by MALDI-TOF-MS analysis, which showed a m/z at 4132.1 $[M - PF_6]^+$. Details of each step are listed in Table 2. Nonamer **7**−**9** was prepared in average yields of 80−90% per step. The short reaction times, about 3 h per monomer addition, allowed for the synthesis of **7**−**9** in 25.2% overall yield within 28.5 h. Comparing with the manual solid supported synthesis of a structurally similar heptamannoside in 14 days and 9% overall,[25] our method is faster and higher yielding. Our method is similar to the automated solid-phase synthesis method for oligosaccharides in terms of reaction time and yield.[6a] Moreover, the 2 equiv excess of glycosyl donors used in our method is much less than that in automated solid-phase synthesis, which used a 10−20 equiv excess of donors.

The target nonamannoside **1** was eventually achieved following catalytic hydrogenation and simple purification. The final structure confirmation of nonamannoside **1** was obtained by its ^{1}H and ^{13}C NMR spectra, as well as MALDI-TOF-MS analysis, which showed a molecular ion m/z peak at 1498.4 $[M + Na]^+$.

In summary, we have developed an acceptor-tagged supporting strategy mainly to eliminate undesirable side products. A more stable ether linker was employed to decrease the accumulative decomposition, and we designed a new purification technique to minimize the loss of product. With this method, we achieved the efficient synthesis of a nanosacharide on IL support without chromatographic purification. Our method for the efficient synthesis of large oligosaccharides on IL support could be a very useful technique to produce oligosaccharides on a large scale. Currently, other complex oligosaccharides are being synthesized using this technique in our laboratory.

3. EXPERIMENTAL SECTION

Synthesis of 4-(Bromomethyl)benzyl Alcohol Acetate (2). A mixture of α,α′-dibromo-*p*-xylene (10.0 g, 37.9 mmol) and AcONa (6.21 g, 75.8 mmol) in dried MeCN (300 mL) was stirred at reflux for 16 h. The residue obtained by evaporation was dissolved in Et_2O, washed with saturated aq NaCl solution, and dried ($MgSO_4$). After concentration, column chromatographic purification yielded **2** (2.12 g, 23.0%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 4H), 5.10 (s, 2H), 4.49 (s, 2H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 137.9, 136.2, 129.2, 128.6, 65.6, 32.8, 20.8.

Synthesis of 3-[4-(Acetoxymethyl)benzyl]-1-methylimidazolium Hexafluorophosphate (3). Compound **2** (2.0 g, 8.2 mmol) was dissolved in dry CH_3CN (30 mL) under argon, and to it were added *N*-methylimidazole (1.31 mL, 16.4 mmol) and KPF_6 (1.5 g, 8.2 mmol). The reaction was refluxed overnight at 80 °C with stirring, and TLC showed complete conversion. The reaction mixture was cooled to room temperature, filtered, and concentrated under vacuum. The residue was dissolved in CH_3CN (1 mL) and precipitated with diethyl ether (10 mL) to obtain acetylated IL support **3** (2.82 g, 87.0%) as a colorless oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (s, 1H), 7.78 (s, 1H), 7.71 (s, 1H), 7.42 (m, 4H), 5.41 (s, 2H), 5.08 (s, 2H), 3.85 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.7, 137.3, 137.1, 135.0, 129.0, 128.9, 124.5, 122.8, 65.4, 52.0, 36.3, 21.1; ESI-MS m/z calcd 245.1 $[M - PF_6]^+$, found 245.1 $[M - PF_6]^+$; HRMS m/z calcd 245.12845 $[M - PF_6]^+$ for $C_{14}H_{17}N_2O_2$, found 245.12805.

Synthesis of 3-[4-(Hydroxymethyl)benzyl]-1-methylimidazolium Hexafluorophosphate (4). The acetylated IL support **3** (1.5 g, 3.8 mmol) was dissolved in MeOH (20 mL), a solution of NaOMe (0.1 M in MeOH) was added, and the mixture was stirred for 1 h. The mixture was concentrated in vacuo, dissolved in CH_3CN, and filtered. After concentration, the IL support **4** (1.32 g, 98.7%) was obtained as a colorless oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 7.68 (s, 1H), 7.62 (s, 1H), 7.29 (d, 4H), 5.31 (s, 2H), 4.43 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.7, 137.0, 133.5, 128.6, 127.4, 124.4, 122.7, 62.9, 52.2, 36.3.

dx.doi.org/10.1021/jo2006126 |*J. Org. Chem.* 2011, 76, 5652–5660

Table 2. IL Supported Assembly of Homolinear α(1→2)-Linked Nonamannoside

n	operation[b]	product	time[a] (min)	recovery (%)
1	A and B	**6-1**	60 + 30 + 40	85.6
	C	**7-1**	60	>99
2	A and B	**6-2**	60 + 30 + 40	86.8
	C	**7-2**	60	>99
3	A and B	**6-3**	60 + 30 + 40	88.1
	C	**7-3**	60	>99
4	A and B	**6-4**	60 + 30 + 40	81.7
	C	**7-4**	60	>99
5	A and B	**6-5**	60 + 30 + 40	89.6
	C	**7-5**	60	>99
6	A and B	**6-6**	60 + 30 + 40	88.5
	C	**7-6**	60	>99
7	A and B	**6-7**	60 + 30 + 40	92.0
	C	**7-7**	60	>99
8	A and B	**6-8**	60 + 30 + 40	85.0
	C	**7-8**	60	>99
9	A and B	**6-9**	60 + 30 + 40	80.1
	C	**7-9**	60	>99
total			1710	25.2

[a] The time includes the preparation time before glycosylation (60 min), the time of glycosylation (30 min), and the time of purification (40 min). The time for removal of acetyl protecting groups is about 1 h. [b] A: glycosylation. B: purification. C: removal of acetyl group.

General Procedure a: Coupling Reaction Using Trichloroacetimidates and TMSOTf. IL support **4** and trichloroacetimidate **5** were coevaporated three times with toluene (3 × 5 mL) and dried under vacuum. After crushed 4 Å molecular sieves (0.5 g) were added, the mixture was dissolved in dry CH_2Cl_2 or 10:1 CH_2Cl_2/CH_3CN (only for IL-supported monosaccharide synthesis), and then the solution was cooled to 0 °C. After the mixture was stirred for 10 min, a solution of 0.5 equiv of TMSOTf in dry CH_2Cl_2 was added, and after 30 min, when TLC showed complete consumption of acceptor, the reaction was quenched at the same temperature by the addition of Et_3N.

General Procedure B: Purification by Precipitation. After filtration and concentration of the reaction mixture, the residue was dissolved in CH_2Cl_2, quickly washed with saturated aqueous $NaHCO_3$ solution and saturated aq NaCl solution, and dried over anhydrous Na_2SO_4. After evaporation in vacuo to a syrup, the residue was diluted in CH_2Cl_2 (1 mL/g), and 10 equiv volume of diethyl ether was added. Each oligomer was precipitated out of solution as a white precipitate. After centrifugation (3000 r/min, 10 min), the precipitate was collected and became sticky oil.

General Procedure C: Purification by the Novel Technique. After filtration and concentration of the reaction mixture, the residue was dissolved in CH_2Cl_2, quickly washed saturated aqueous $NaHCO_3$ solution and saturated aq NaCl solution, and dried over anhydrous Na_2SO_4. After evaporation in vacuo, the residue was dissolved in CH_2Cl_2 (5 mL/g), and then 4 equiv volume of isopropyl ether was added. The solvent was removed partially by rotary evaporation in vacuo until the residual solution was about two equivalent volume of the initially added CH_2Cl_2. Each oligomer was precipitated out of solution as a white precipitate. After centrifugation (3000 r/min, 10 min), the precipitate was collected and became a sticky oil.

For compound **6-3** and **6-7**, some additional signals at around δ 92 ppm were detected in their ^{13}C NMR spectra, which were potentially derived from residual donors. These additional signals were removed easily by a second round of evaporation−precipitation separation following the purification protocol, and the products were nearly quantitatively recovered after the second purification. Both the ^{13}C NMR spectra before and after the second purification were attached in the Supporting Information for each compound.

General Procedure D: Removal of Acetate Protecting Groups. To a solution of **6-n** in methanol (1 g/100 mL) was added saturated sodium methoxide solution in methanol (1 mL). After the solution was stirred at room temperature for 45 min, when TLC showed complete consumption of the compound **6-n**, the solution was neutralized with concentrated HCl and evaporated in vacuo. The residue was dissolved in CH_2Cl_2 and filtered. The filtrate solution was concentrated to give the target compound **7-n**.

*4-[(1-Methylimdazoliumhexafluorophospho)methyl]benzyl 2-O-acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranoside (**6-1**).* Acceptor **4** (150 mg, 0.431 mmol), donor **5** (550 mg, 0.862 mmol), and promoter TMSOTf (39 μL, 0.22 mmol) were used to synthesize IL-supported monosaccharide **6-1** (305 mg, 85.6%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.72 (s, 1H), 7.64 (s, 1H), 7.35−7.12 (m, 21H), 5.35 (s, 2H), 5.23 (s, 1H), 4.87 (s, 1H), 4.70−4.43 (m, 8H), 3.79 (s, 4H), 3.63 (m, 4H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 138.8, 138.3, 137.1, 134.8, 128.7, 128.1, 127.9, 122.8, 96.9, 72.8, 71.7, 71.2, 69.2, 68.5, 68.3, 52.1, 36.3, 21.3; ESI-MS *m/z* calcd 677.3 $[M - PF_6]^+$, found 677.3 $[M - PF_6]^+$; HRMS *m/z* calcd 677.32213 $[M - PF_6]^+$ for $C_{41}H_{45}N_2O_7$, found 677.32075.

*4-[(1-Methylimdazoliumhexafluorophospho)methyl]benzyl 2-O-acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranoside (**6-2**).* Acceptor **7-1** (200 mg, 0.256 mmol), donor **5** (330 mg, 0.512 mmol), and promoter TMSOTf (23 μL, 0.13 mmol) were used to prepare IL-supported disaccharide **6−2** (280 mg, 86.8%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.30−7.06 (m, 36H), 5.30 (s, 2H), 5.26 (s, 1H), 5.08 (s, 1H), 4.99 (s, 1H), 4.86 (dd, 2H), 4.70−4.30 (m, 12H), 4.04 (s, 1H), 3.98−3.71 (m, 12H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 138.2, 136.6, 129.1, 128.4, 128.3, 128.0, 127.8, 127.5, 121.7, 99.6, 98.3, 78.1, 75.1, 73.4, 71.9, 68.7, 53.5, 53.2, 36.3, 21.1; ESI-MS *m/z* calcd 1109.5 $[M - PF_6]^+$, found 1109.3 $[M - PF_6]^+$; HRMS *m/z* calcd 1109.51580 $[M - PF_6]^+$ for $C_{68}H_{73}N_2O_{12}$, found 1109.51611.

*4-[(1-Methylimdazoliumhexafluorophospho)methyl]benzyl 2-O-Acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranoside (**6-3**).* Acceptor **7−2** (200 mg, 0.165 mmol), donor **5** (210 mg, 0.330 mmol), and promoter TMSOTf (15 μL, 0.082 mmol) were used to prepare IL-supported trisaccharide **6-3** (245 mg, 88.1%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.32−6.98 (m, 51H), 5.53 (d, 1H), 5.18 (d, 2H), 5.04 (s, 1H), 5.01 (s, 1H), 4.98 (s, 1H), 4.82 (m, 2H), 4.67−4.24 (m, 18H), 4.09−3.71 (m, 20H), 2.11 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 139.2, 138.9, 138.8, 138.5, 138.4, 138.3, 138.2, 138.0, 137.8, 137.7, 137.4, 131.9, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.2, 123.3, 121.7, 121.6, 121.5, 100.7, 99.4, 98.4, 80.2, 79.9, 79.5, 79.3, 77.4, 77.2, 77.0, 76.7, 75.6, 75.2, 75.1, 75.0, 74.8, 74.4, 74.3, 73.3, 73.1, 72.6, 72.2, 72.1, 71.9, 71.8, 71.5, 71.1, 69.8, 69.7, 69.3, 69.1, 68.9, 68.7, 68.4, 68.3, 53.2, 36.4, 29.7, 22.9, 21.1; ESI-MS *m/z* calcd 1541.7 $[M - PF_6]^+$, found 1541.9 $[M - PF_6]^+$; HRMS *m/z* calcd 1541.70948 $[M - PF_6]^+$ for $C_{95}H_{101}N_2O_{17}$, found 1541.70776.

*4-[(1-Methylimdazoliumhexafluorophospho)methyl]benzyl 2-O-Acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranoside (**6-4**).* Acceptor **7-3** (200 mg, 0.122 mmol), donor **5** (155 mg, 0.243 mmol), and promoter TMSOTf (11 μL, 0.061 mmol) were used to prepare IL-supported tetrasaccharide **6-4** (210 mg, 81.7%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 9.16

dx.doi.org/10.1021/jo2006126 |J. Org. Chem. 2011, 76, 5652–5660

(s, 1H), 7.60−7.00 (m, 70H), 5.63 (d, 1H), 5.28 (m, 2H), 5.39−4.10 (m, 30H), 4.09−3.54 (m, 26H), 2.18 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 138.5, 129.1, 128.5, 128.2, 127.9, 127.7, 127.5, 121.7, 101.3, 100.7, 99.5, 98.5, 75.2, 74.4, 72.2, 71.3, 68.4, 53.5, 53.1, 36.3, 21.2; ESI-MS m/z calcd 1974.9 $[M - PF_6]^+$, found 1974.2 $[M - PF_6]^+$; HRMS m/z 1974.90705 $[M - PF_6]^+$ calcd for $C_{122}H_{129}N_2O_{22}$, found 1974.90449.

*4-[(1-Methylimdazoliumhexafluorophospho)methyl]benzyl 2-O-Acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranoside (**6**-**5**).* Acceptor **7**-**4** (180 mg, 0.0870 mmol), donor **5** (110 mg, 0.173 mmol), and promoter TMSOTf (8.0 μL, 0.043 mmol) were used to prepare IL-supported pentasaccharide **6**−**5** (198 mg, 89.6%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 7.70−6.98 (m, 81H), 5.75 (m, 1H), 5.50−3.55 (m, 72H), 2.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 138.5, 138.4, 138.3, 136.5, 128.0, 127.6, 121.8, 101.5, 100.9, 99.5, 98.6, 97.2, 80.2, 74.7, 73.4, 72.2, 69.9, 68.4, 53.6, 53.1, 36.3, 23.1; MALDI-TOF-MS m/z calcd 2406.1 $[M - PF_6]^+$, found 2405.1 $[M - PF_6]^+$; HRMS m/z calcd 2406.09682 $[M - PF_6]^+$ for $C_{149}H_{157}N_2O_{27}$, found 2406.09692.

*4-[(1-Methylimdazoliumhexafluorophospho)methyl]benzyl 2-O-Acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranoside (**6**-**6**).* Acceptor **7**-**5** (180 mg, 0.0720 mmol), donor **5** (91.0 mg, 0.143 mmol), and promoter TMSOTf (7.0 μL, 0.036 mmol) were used to prepare IL-supported hexasaccharide **6**-**6** (190 mg, 88.5%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.57−6.88 (m, 98H), 5.72 (m, 1H,), 5.30−3.19 (m, 84H), 2.20 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 138.6, 129.1, 128.6, 128.3, 128.1, 127.8, 127.4, 121.7, 101.6, 101.5, 100.9, 99.5, 98.5, 74.6, 73.4, 72.0, 69.4, 68.3, 53.1, 36.3, 23.0, 21.2; MALDI-TOF-MS m/z calcd 2838.3 $[M - PF_6]^+$, found 2838.2 $[M - PF_6]^+$; HRMS m/z calcd 2838.29050 $[M - PF_6]^+$ for $C_{176}H_{185}N_2O_{32}$, found 2838.28284.

*4-[(1-Methylimdazoliumhexafluorophospho)methyl]benzyl 2-O-Acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranoside (**6**-**7**).* Acceptor **7**-**6** (180 mg, 0.0610 mmol), donor **5** (80.0 mg, 0.122 mmol), and promoter TMSOTf (6.0 μL, 0.031 mmol) were used to prepare IL-supported heptasaccharide **6**−**7** (192 mg, 92.0%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.47−6.85 (m, 116H), 5.61 (m, 1H,), 5.33−3.49 (m, 99H), 2.11 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 139.3, 139.2, 139.0, 138.6, 138.4, 138.2, 137.0, 132.0, 129.0, 128.9, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.5, 127.4, 126.4, 126.1, 123.5, 121.6, 101.5, 101.4, 101.0, 100.8, 99.5, 98.5, 80.1, 79.2, 77.4, 77.2, 77.1, 76.9, 76.8, 76.3, 75.2, 75.1, 74.8, 73.3, 72.4, 72.2, 72.0, 71.9, 69.8, 69.4, 68.8, 68.4, 53.1, 36.4, 22.9, 21.2; MALDI-TOF-MS m/z calcd 3270.5 $[M - PF_6]^+$, found 3270.7 $[M - PF_6]^+$; HRMS m/z calcd 3270.48417 $[M - PF_6]^+$ for $C_{203}H_{213}N_2O_{37}$, found 3272.45480.

*4-[(1-Methylimdazoliumhexafluorophospho)methyl]benzyl 2-O-Acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranoside (**6**-**8**).* Acceptor **7**-**7** (167 mg, 0.0490 mmol), donor **5** (64 mg, 0.098 mmol), and promoter TMSOTf (5.0 μL, 0.025 mmol) were used to prepare IL-supported octasaccharide **6**-**8** (162 mg, 85.0%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.53−6.84 (m, 124H), 5.66 (m, 1H), 5.41−3.33 (m, 108H), 2.13 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 139.3, 139.0, 138.6, 138.2, 137.1, 132.0, 129.0, 128.9, 128.7, 128.6, 128.3, 128.0, 127.9, 127.8, 127.5, 127.4, 126.0, 123.4, 121.6, 101.6, 101.4, 101.3, 100.8, 100.8, 99.4, 98.5, 80.1, 79.1, 77.1, 76.8, 76.7, 75.6, 75.2, 75.1, 74.8, 73.3, 72.4, 72.2, 72.0, 71.9, 71.7, 69.9, 69.4, 68.8, 68.4, 53.2, 36.4, 22.9, 21.2; MALDI-TOF-MS m/z calcd 3702.7 $[M - PF_6]^+$, found 3702.8 $[M - PF_6]^+$; HRMS m/z calcd 3702.67785 $[M - PF_6]^+$ for $C_{230}H_{241}N_2O_{42}$, found 3704.69963.

*4-[(1-Methylimdazoliumhexafluorophospho)methyl]benzyl 2-O-Acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranoside (**6**-**9**).* Acceptor **7**-**8** (151 mg, 0.0400 mmol), donor **5** (51 mg, 0.080 mmol), and promoter TMSOTf (4.0 μL, 0.020 mmol) were used to prepare IL-supported monosaccharide **6**−**9** (136 mg, 80.1%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.46−6.82 (m, 147H), 5.60 (m, 1H,), 5.27−3.25 (m, 128H), 2.17 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 139.3, 139.1, 139.0, 138.7, 138.5, 138.4, 138.2, 137.2, 131.9, 129.0, 128.9, 128.7, 128.6, 128.5, 128.3, 128.1, 127.9, 127.8, 127.6, 127.5, 127.3, 126.0, 123.3, 121.5, 101.7, 101.4, 101.0, 100.9, 99.5, 98.5, 97.2, 80.1, 79.1, 77.4, 77.3, 77.1, 76.8, 75.2, 74.8, 73.3, 72.3, 72.2, 71.9, 71.5, 69.9, 69.4, 68.7, 68.3, 53.2, 36.4, 29.7, 29.4, 22.9, 21.2; MALDI-TOF-MS m/z calcd 4134.9 $[M - PF_6]^+$, found 4132.1 $[M - PF_6]^+$; HRMS m/z calcd 4134.87152 $[M - PF_6]^+$ for $C_{257}H_{269}N_2O_{47}$, found 4134.71675.

*α-D-Mannopyranosyl-(1→2)-α-D-mannopyranosyl-(1→2)-α-D-mannopyranosyl-(1→2)-α-D-mannopyranosyl-(1→2)-α-D-mannopyranosyl-(1→2)-α-D-mannopyranosyl-(1→2)-α-D-mannopyranosyl-(1→2)-α/β-D-mannopyranoside (**1**).* The protected nonamannoside **7**-**9** (135 mg, 0.0318 mmol) was dissolved in 10% EtOAc/MeOH (10 mL). In the presence of $Pb(OH)_2$ the solution was stirred under 4 atm of H_2 for 4 d at room temperature. The heterogeneous mixture was filtered over Celite, and the solid mass was washed with a large amount of MeOH. Following concentration of the mixture in vacuo, the residue was redissolved in H_2O, and CH_3CN was added to produce a white precipitate. The nonamannoside **1** (42.0 mg, 89.4%) was obtained as a colorless syrup after removal of the supernatant by centrifugation: ^{1}H NMR (400 MHz, D_2O) δ 5.41 (s, 1H), 5.26 (s, 1H), 5.17 (s, 4H), 5.04 (d, 1H), 4.93 (s, 1H), 4.68 (s, 70H), 4.13 (s, 1H), 3.95 (m, 6H), 3.85−3.65 (m, 19H), 3.65−3.45 (m, 27H), 3.42 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 105.4, 102.1, 100.5, 99.2, 92.4, 78.5, 76.3, 73.2, 72.4, 70.3, 69.7, 66.7, 61.0, 60.9; ESI-MS m/z calcd 1494.5 $[M + Na]^+$, found 1494.4 $[M + Na]^+$; MALDI-TOF-MS m/z calcd 1498.5 $[M + Na]^+$, found 1498.4 $[M + Na]^+$.

■ ASSOCIATED CONTENT

Supporting Information. General procedures and characterization data (^{1}H and ^{13}C NMR spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

This work was financially supported by the National Natural Science Foundation of China (No. 20732001) and the State New

Drug Innovation (the Ministry of Science and Technology of China, No. 2009ZX09501-011).

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