Carbohydrate Polymers 83 (2011) 297–302

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

An efficient approach for the synthesis of oligosaccharides using ionic liquid supported glycosylation

Jian-Ying Huang*, Ang Li, Jian-Rong Li*

Department of Applied Chemistry, Zhejiang Gongshang University, Hangzhou 310035, PR China

ARTICLE INFO

Article history:
Received 8 July 2010
Received in revised form 29 July 2010
Accepted 30 July 2010
Available online 7 August 2010

Keywords:
Ionic liquid
Oligosaccharide
Glycosylation
Imidazolium
Supported

ABSTRACT

The synthesis of complex oligosaccharides has been a challenge due to their multifarious protections, deprotection processes and time-consuming chromatography. Herein, an effective strategy for the establishment of a library of oligosaccharides using imidazolium-type cation as a soluble functional support with ester and ether as linkage was demonstrated and developed. Noteworthy, IL-linkages have defined structures and molecular weights in contrast to polymer linkages, which are functionalized materials with variable loading capabilities allowing the efficient homogenous reaction conditions. All IL-tagged intermediates can be clipped off and purified by a simple phase-separation technique without further column chromatography after each glycosylation step.

1. Introduction

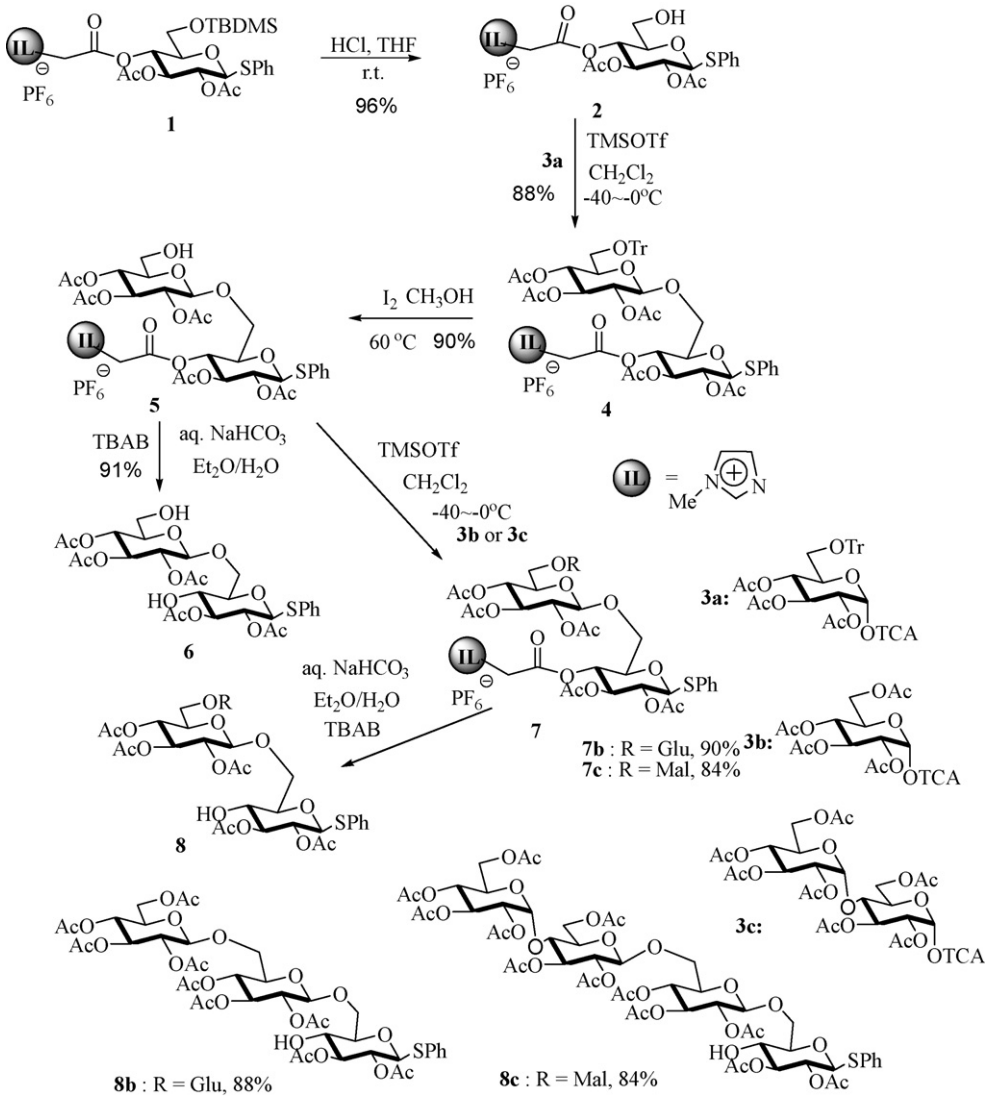
Much attention has been paid to carbohydrates in many different areas of chemistry and biology because of their molecular diversity and functionality (Sigulinsky, Bab, Victor, & Kuberan, 2010). They are more complicated than other biological macromolecules to be synthesized due to multifarious protections, deprotection processes and time-consuming chromatography (Sears & Wong, 2001; Wang, Lee, & Hung, 2007; Zhang et al., 1999). Polymer-supported oligosaccharide synthesis has been well defined for more than three decades as one of the most challenging fields in solid phase chemistry (Frechet & Schuerch, 1971), it still suffers from a series of drawback because of heterogeneous reaction conditions and stepwise characterization. So far, several protocols exploiting the ease of solution-phase reactions together with preserving the advantages of facilitated isolation procedures have been developed, which include the oligosaccharide assembly on soluble (PEG) polymers (Ando, Manabe, Nakahara, & Ito, 2001), fluorous tags (Miura, Goto, Hosaka, & Inazu, 2003), and thermoresponsive polymers (Huang, Witte, Bergbreiter, & Wong, 2001).

As a kind of environmentally benign reaction media, ionic liquids (ILs) have attracted great attention from both academia and industry because of their intriguing properties (Wasserscheid & Welton, 2003). Numerous chemical reactions, including many enzymatic reactions, could be carried out in ionic liquids (Deetlefs & Seddon, 2010). They also can be used as soluble functional supports for organic synthesis, and the IL-supported substrates are expected to retain their activities as non-supported reagents, allowing the use of conventional spectroscopic analyses to monitor the reactions. After completion of the reactions and removal of the solvents, the excess reagents can be simply removed with non-polar organic solvents, such as ether and ethyl acetate, because the IL-tagged compound is insoluble. On the other hand, inorganic reagents or byproducts can be removed by precipitation with aqueous solution. Therefore, the sequence reactions can be repeated to give more complex compounds. So far, several research groups have already demonstrated the feasibility of IL-tagged organic synthesis for small molecules (Anjaiah, Chandrasekhar, & Gree, 2004; Fraga-Dubreuil & Bazureau, 2003; Legeay, Vanden Eynde, & Bazureau, 2005; Miao & Chan, 2003) and peptides (He & Chan, 2007; Miao & Chan, 2005). Recently, ionic liquid-tagged synthesis of oligonucleotides and oligosaccharide has also been successfully developed (Donga, Khaliq-Uz-Zaman, Chan, & Damha, 2006; He & Chan, 2006; Miao & Chan, 2006; Huang, Lei, & Wang, 2006; Pathak, Yerneni, Young, & Pathak, 2008; Yerneni, Pathak, & Pathak, 2009).

Although the highly successful IL-tagged oligosaccharide syntheses have been developed, it always shows singular functional linkage (ester linkage in C-4 or C-6) on donor or acceptor. Available to newer straightforward and efficient methods to prepare biologically relevant oligosaccharides is still warranted. Herein, based on the former work (Huang et al., 2006), we do further extension of

* Corresponding authors. Tel.: +86 571 8807 1024.
E-mail addresses: huangjy@mail.zjgsu.edu.cn (J.-Y. Huang), lijianrong@mail.zjgsu.edu.cn (J.-R. Li).

0144-8617/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carbpol.2010.07.068



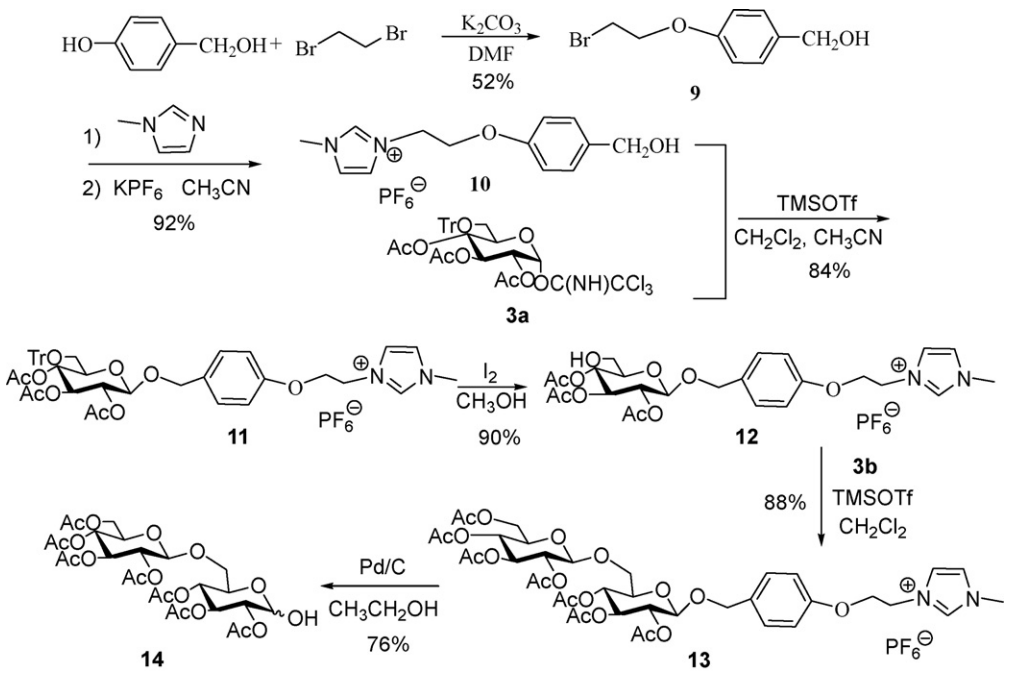
Scheme 1. Ionic liquid supported synthesis of oligosaccharides with ester as linkage.

IL-tagged synthesis of oligosaccharides using another ionic liquid linkage to demonstrate the broad scope of this novel and convenient method.

2. Results and discussion

IL-tagged saccharide **1** was prepared according to the modified procedures (Huang et al., 2006; Ritter, Mong, Liu, Nakatani, & Wong, 2003; Stick & Stubbs, 2005). The selective removal of TBDMS group at C-6 in compound **1** was induced by concentrated hydrochloric acid in THF solution, which was monitored for the disappearance of the starting material **1** with TLC. After the reaction mixture was concentrated *in vacuo*, the residue was purified by simply washing with diethyl ether to afford 6-OH IL-tagged saccharide **2** in 95% yield. Anchored saccharide **2** was then glycosylated with activated glycosyl donor **3a** of which 6-OH was protected by Tr to provide IL-tagged disaccharides **4**, which was purified by washing with diethyl ether and ethyl acetate to remove the excess glycosyl donors and reagents. Here Tr group was used as a "temporary" protecting group for hydroxyl (Wahlstrom & Ronald, 1998). Selective deprotection of Tr group on **4** by I_2 in methanol afforded the IL-tagged 6′-OH disaccharide **5**. The IL-tagged 6′-OH disaccharide **5** was further treated differently. One portion was readily performed in saturated aqueous sodium bicarbonate to give the corresponding disaccharide **6** in high yield (91%) with good purity (90%). On the other hand, IL-tagged 6′-OH disaccharide **5** and glycosyl donor **3b** or **3c** were carried out in the same way to afford IL-tagged trisaccharide **7b** (90% yield) and tetrasaccharide **7c** (84% yield), respectively. After convenient cleavage of ionic liquid linkage by stirring with aqueous saturated $NaHCO_3$ in a H_2O/ether (1:1) biphasic solvent mixture in the presence of a phase transfer catalyst $Bu_4N^+Br^-$, concentration of the ether layer provided almost pure trisaccharide **8b** and tetrasaccharide **8c** in 88% and 84% yields, respectively (Scheme 1).

With our interest in developing newer and simple approaches to assembly oligosaccharides, we further investigated another ionic liquid ether linkage which is more stable than ester linkage to examine the generality of this method for the solution-phase synthesis of oligosaccharides. As shown in Scheme 2, the benzyl ether linkage ionic liquid **10** was prepared by bounding (4-(2-bromoethoxyl)phenyl) methanol to N-methylimidazole. Subsequently, glycosylation of IL-tagged compound **10** was treated with donor **3a** (3.0 equiv.) in the presence of catalyst TMSOTf



Scheme 2. Ionic liquid supported synthesis of a disaccharide with benzyl as linkage.

(0.08 equiv.) and in CH_2Cl_2/CH_3CN (2:1). The workup and simple wash with diethyl ether gave almost pure IL-tagged 6-Tr saccharide **11** in 84% yield. Specifically, due to the neighboring group participation effect, the β configuration of IL-tagged saccharide **11** was determined by ^{1}H NMR (anomeric carbon hydrogen at δ 5.54, double, J = 9.6 Hz). After removal of the protective group Tr with I_2 in methanol, IL-anchored glycosyl acceptor **12** was obtained in 90% yield. Then it was coupled with glycosyl donor **3a** to afford the IL-tagged disaccharide **13**. Finally, the compound **13** was cleaved by hydrogenation with 10% Pd/C as catalyst in ethanol. After flash chromatography disaccharide **14** was obtained of which the isomer ratio 1-OH is 3:1 (β/α) determined by ^{1}H NMR, anomeric carbon hydrogen at δ 5.50 (d, J = 9.6 Hz) is β-disaccharide, and another anomeric carbon hydrogen at δ 5.45 (d, J = 3.6 Hz) is α-disaccharide.

3. Conclusion

In summary, an effective strategy for the establishment of a library of oligosaccharides using imidazolium cation as a soluble functional support with ester and ether linkages was demonstrated and developed. All IL-tagged intermediates can be clipped off and purified by a simple phase-separation technique. Definite pure oligosaccharides can be achieved efficiently with minimal column chromatographic purification via this approach in homogeneous reaction conditions. Additionally, IL-tagged substrates were easily characterized by conventional spectroscopic techniques. Expansion of the method towards differently functionalized ionic liquid supports and the synthesis of more complex target molecules are currently being pursued.

4. Experimental

4.1. General

All solvents were distilled from the appropriate drying reagents. All reactions were performed under anhydrous conditions unless otherwise noted. Thin-layer chromatography (TLC) was performed on silica gel HSG F_{254} plates, detected with UV light (254 nm) or visualized by spraying with 20% aq. sulfuric acid and heating at 200 °C. Silica gel (H, 300–400 mesh) was used for flash chromatography. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker ADVANCE DMX-500 spectrometer or Varian Unity INOVA-400 spectrometer. Electrospray ionization mass spectra (ESI-MS) were recorded on a Bruker Esquire 3000 plus mass spectrometer (Bruker-Franzen Analytik GmbH, Bremen, Germany) equipped with an ESI interface and ion trap analyzer. High-resolution mass spectra (HRMS) were obtained on a Bruker 7-tesla FT-ICRMS equipped with an electrospray source (Billerica, MA, USA). Melting point was obtained with a WRS-1B electronic melting instrument.

4.2. General procedure for the synthesis of compound **4**

To a stirred solution of phenyl 2,3-di-O-acetyl-4-O-[2-(3-methylimidazolium)]acetyl-1-thio-β-D-glucopy-ranoside **2** (0.25 mmol), 6-O-Tr-O-acetylated monosaccharide trichloroacetimidate donor (0.75 mmol) and 4 Å MS (1.0 g) in dried CH_2Cl_2 (20 mL), trimethylsilyl triflate (0.06 mmol) in dried CH_2Cl_2 (2 mL) was added dropwise under nitrogen condition at −40 °C. Then the reaction temperature was increased to 0 °C. After 3 h the reaction was completed. The mixture was filtered and the solvent was removed under vacuum. The residue was washed with Et_2O (5 mL), then dissolved in CH_2Cl_2 (1 mL) and washed with Et_2O (3 × 5 mL) to afford the IL-tagged disaccharides, (0.22 g, 88%).

4: ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.12 (s, 1H), 7.80–7.55 (m, 12H), 7.43–7.25 (m, 8H), 5.84–5.44 (m, 6H), 4.97–3.88 (m, 8H), 3.86–3.75 (m, 2H), 3.50–3.47 (m, 2H), 2.16–1.98 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.45, 171.43,169.9, 169.6, 169.5, 166.8, 153.4, 143.2, 134.1, 132.6, 132.5, 129.9, 129.4, 128.8, 128.6,122.5, 116.0, 104.2, 91.1, 87.1, 80.4, 77.3, 76.8, 75.8, 72.8, 71.6, 70.5, 70.0, 69.8, 66.2, 65.1, 37.4, 21.3, 21.2, 21.0, 20.9, 20.8; ESI-MS: m/z = 1009 ($[M-PF_6]^+$); ESI-HRMS: m/z calcd for $C_{53}H_{57}N_2O_{16}S$ $[M]^+$ 1009.3422, found 1009.3402.

4.3. Synthesis of compound **5**

To a solution of I_2 (20 mg, 0.079 mmol) in methanol (2 mL) was added **4** (0.20 g, 0.17 mmol). The solution was heated to 60 °C, and the reaction was monitored by TLC (CH_3OH/CH_2Cl_2, 10:1). After

completion, the solvent was removed under vacuum. The resulting residue was dissolved in CH_2Cl_2 (1 mL), washed with ether (3 × 2 mL), and dried *in vacuo* to give compound **5** (0.13 g, 84%).

5: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.10 (s, 1H), 7.74–7.63 (m, 3H), 7.44–7.33 (m, 3H), 5.33–5.30 (m, 3H), 5.15–4.77 (m, 4H), 4.25–4.20 (m, 3H), 3.92–3.68 (m, 9H), 2.00–1.77 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 171.6, 171.5, 171.45, 171.43, 166.8, 153.4, 132.6, 132.5, 129.4, 128.6,122.5, 115.0, 101.2, 87.1, 79.2, 77.3, 75.8, 74.6, 72.8, 71.6, 70.3, 70.0, 69.8, 64.2, 63.1, 37.4, 21.3, 21.2, 21.0, 20.9, 20.8. ESI-MS: *m*/*z* = 767 ([M−PF_6]$^+$); ESI-HRMS: *m*/*z* calcd for $C_{34}H_{43}N_2O_{16}S$ [M]$^+$ 767.2398, found 767.2402.

4.4. General procedure for the synthesis of compound *6*

To a solution of **5** (0.09 g, 0.10 mmol) in Et_2O/H_2O (1:1, 3.0 mL) was added saturated aqueous $NaHCO_3$ (2 mL) and TBAB (0.10 g). The mixture was stirred at room temperature for 30 min. The Et_2O phase was filtered through a short pad of silica gel. After removal of the solvent, disaccharide **6** was obtained.

6: white solid; mp: 86–90 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40–7.38 (m, 2H), 7.28–7.24 (m, 3H), 5.00–4.92 (m, 2H), 4.89–4.79 (m, 2H), 4.63 (d, *J* = 10.0 Hz, 1H), 4.57 (d, *J* = 9.9 Hz, 1H), 4.53 (d, *J* = 7.8 Hz, 1H), 4.47 (d, *J* = 7.8 Hz, 1H), 4.36 (dd, *J* = 4.1, 12.3 Hz, 1H), 4.29–4.27 (m, 1H), 4.03 (dd, *J* = 3.0, 10.3 Hz, 1H), 3.77 (dd, *J* = 5.4, 12.3 Hz, 1H), 3.63–3.42 (m, 2H), 2.98 (s, 1H, OH), 2.77 (s, 1H, OH), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 171.64, 171.62, 169.9, 169.7, 132.7, 132.5, 129.4, 128.3, 101.1, 86.2, 79.1, 77.0, 75.7, 74.5, 72.6, 71.2, 70.1, 69.9, 69.0, 62.8, 21.2, 21.1, 21.0, 20.94, 20.92; ESI-MS: *m*/*z* = 667 ([M+Na]$^+$); ESI-HRMS: *m*/*z* calcd for $C_{28}H_{37}O_{15}S$ [M+H]$^+$ 645.6422, found 645.6417.

4.5. General procedure for the synthesis of compounds *7*

To a solution of IL-tagged saccharide **5** (0.18 g, 0.2 mmol), O-acetylated monosaccharide trichloroacetimidate donor (**3b** or **3c**, respectively) (0.30 mmol) and 4 Å MS (1.0 g) in dried CH_2Cl_2 (20 mL) was dropwise added trimethylsilyl triflate (0.04 mmol) in dried CH_2Cl_2 (2 mL) under nitrogen at −40 °C. Then the reaction temperature was allowed to increase to 0 °C. After 3 h the reaction was completed. The mixture was filtered and the solvent was removed under vacuum. The residue was washed with Et_2O (5 mL), and then dissolved in CH_2Cl_2 (1 mL) and washed with Et_2O (3 × 5 mL) to afford IL-tagged disaccharides **7b** and **7c**, respectively.**7b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.03 (s, 1H), 7.40–7.30 (m, 2H), 7.27–7.22 (m, 3H), 5.75–5.48 (m, 2H), 5.38–5.30 (m, 2H), 5.21–5.15 (m, 3H), 5.03–4.97 (m, 3H), 4.96–4.66 (m, 5H), 4.27–4.17 (m, 2H), 4.06–4.03 (m, 2H), 3.72–3.69 (m, 1H), 3.67–3.60 (m, 5H), 2.02–1.96 (m, 21H), 1.95 (s, 3H), 1.93 (s, 3H), 1.91 (s, 3H); ESI-MS: *m*/*z* = 1097 ([M−PF_6]$^+$); ESI-HRMS: *m*/*z* calcd for $C_{48}H_{61}N_2O_{25}S$ [M]$^+$ 1097.3317, found 1097.3412.**7c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.11 (s, 1 H), 7.44–7.42 (m, 2H), 7.35–7.22 (m, 3H), 5.75 (d, *J* = 17.7 Hz, 1H), 5.54 (d, *J* = 17.7 Hz, 1H), 5.40–5.18 (m, 5H), 5.09–4.79 (m, 7H), 4.72–4.66 (m, 2H), 4.54–4.48 (m, 2H), 4.31–4.14 (m, 9H), 3.79 (d, *J* = 9.6 Hz, 1H), 3.72–3.53 (m, 4H), 2.14 (s, 3H), 2.09–2.07 (m, 12H), 2.06 (s, 3H), 2.03–2.01 (m, 12H), 2.00 (s, 3H), 1.99 (m, 6H). ESI-MS: *m*/*z* = 1385 ([M−PF_6]$^+$); ESI-HRMS: *m*/*z* calcd for $C_{60}H_{77}N_2O_{33}S$ [M]$^+$ 1385.4135, found 1385.4127.

4.6. General procedure for the synthesis of compounds *8*

To a solution of **7** (0.10 mmol) in Et_2O/H_2O (1:1, 3.0 mL) was added saturated aqueous $NaHCO_3$ (2 mL) and TBAB (0.10 g). The mixture was stirred at room temperature for 30 min. The Et_2O phase was filtered through a short pad of silica gel. After removal of the solvent, free trisaccharide **8b** or tetrasaccharide **8c** were afforded as a white solid.

8b: white solid; mp: 105–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.29 (m, 2H), 7.27–7.19 (m, 3H), 5.16–5.07 (m, 2H), 5.03–4.97 (m, 3H), 4.96–4.91 (m, 2H), 4.89–4.80 (m, 2H), 4.68–4.66 (m, 1H), 4.47 (d, *J* = 8.0 Hz, 1H), 4.27–4.17 (m, 2H), 4.06–4.03 (m, 2H), 3.72–3.69 (m, 1H), 3.67–3.60 (m, 5H), 3.42 (s, 1H), 2.02 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.98 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H), 1.93 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 170.9, 170.8, 170.6, 170.1, 170.0, 169.9, 169.7, 169.6, 132.7, 131.5, 129.6, 127.8, 100.8, 100.7, 86.0, 78.8, 76.9, 76.3, 74.4, 72.8, 72.7, 72.0, 71.2, 71.1, 69.9, 69.4, 69.0, 68.2, 67.7, 61.8, 21.04, 21.01 20.8, 20.75, 20.70, 20.66, 20.59, 20.55, 20.52; ESI-MS: *m*/*z* = 997 ([M+Na]$^+$); ESI-HRMS: *m*/*z* calcd for $C_{42}H_{55}O_{24}S$ [M+H]$^+$ 975.2718, found 975.2727.

8c: white solid; mp: 113–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.42 (m, 2H), 7.35–7.24 (m, 3H), 5.40–5.30 (m, 3H), 5.20–5.14 (m, 1H), 5.09–4.97 (m, 3H), 4.92–4.79 (m, 4H), 4.72 (d, *J* = 9.6 Hz, 1H), 4.66 (d, *J* = 8.4 Hz, 1H), 4.54 (d, *J* = 8.0 Hz, 1H), 4.48 (dd, *J* = 2.4, 12.4 Hz, 1H), 4.31–4.20 (m, 4H), 4.14–3.90 (m, 5H), 3.79 (d, *J* = 9.6 Hz, 1H), 3.72–3.62 (m, 3H), 3.53 (d, *J* = 4.8 Hz, 1H), 2.14 (s, 3H), 2.09 (s, 3H), 2.07 (s, 6H), 2.06 (s, 3H), 2.03 (s, 3H), 2.02 (s, 6H), 2.01 (s, 3H), 2.00 (s, 3H), 1.99 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 170.7, 170.5, 170.4, 170.1, 169.9, 169.8, 169.7, 169.5, 169.44, 169.42, 169.40, 132.8, 131.7, 129.1, 127.8, 100.7, 100.3, 95.5, 85.8, 78.9, 77.2, 75.1, 73.8, 72.8, 72.3, 71.9, 71.1, 70.2, 70.02, 69.99, 69.6, 69.3, 69.2, 69.0, 68.5, 68.0, 67.9, 67.7, 65.5, 65.3, 62.7, 61.5, 61.4, 20.94, 20.90, 20.87, 20.77, 20.72, 20.69, 20.64, 20.59, 20.50, 20.45, 20.36, 19.1; ESI-MS: *m*/*z* = 1285 ([M+Na]$^+$); ESI-HRMS: *m*/*z* calcd for $C_{54}H_{71}O_{32}S$ [M+H]$^+$ 1263.3631, found 1263.3695.

4.7. Synthesis of (4-(2-bromoethoxyl)phenyl)methanol *9*

A mixture of 4-(hydroxymethyl)phenol (2.48 g, 20 mmol) and K_2CO_3 (8.28 g, 60 mmol) in 1,2-dibromoethane (20 mL) and DMF (10 mL), was stirred in 45 °C for 6 h. After the reaction mixture was filtered, the filtrate was concentrated under vacuum. The residue was then dissolved in 20 mL H_2O, extraction by EtOAc (3 × 20 mL), the organic solvent was washed with brine, dried with anhydrous Na_2SO_4, concentrated under vacuum. The resulting residue was subjected to flash chromatography on a silica gel column with hexane/EtOAc as the eluent to give compound **9** (2.4 g, 52%).**9**: white solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.2 Hz, 2H, Ph), 6.91 (d, *J* = 8.2 Hz, 2H, Ph), 4.63 (s, 2H), 4.30 (t, *J* = 6.3 Hz, 2H), 364 (t, *J* = 6.3 Hz, 2H); ESI-MS: *m*/*z* = 253 ([M+Na]$^+$).

4.8. Synthesis of compound *10*

A solution of **9** (2.3 g, 10 mmol) and N-methylimidazole (0.82 g, 10 mmol) in dried CH_3CN (15 mL) was stirred at 80 °C for 12 h. KPF_6 (1.8 g, 10 mmol) was added and the mixture was stirred for further 24 h. After it was filtered and evaporated *in vacuo*, the residue was washed with Et_2O (3 × 5 mL) and EtOAc (3 × 5 mL) to give **10** (3.47 g, 92%), which was directly used in the next step.**10**: white solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.18 (s, 1H, NH), 7.81 (s, 1H), 7.71 (s, 1H), 7.23 (d, *J* = 8.2 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 2H), 4.58 (t, *J* = 4.4 Hz, 2H), 4.41 (d, *J* = 5.3 Hz, 2H), 4.33 (t, *J* = 4.4 Hz, 2H,), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.1, 137.5, 135.9, 128.4, 124.0, 123.3, 114.8, 66.3, 62.9, 49.0, 36.3; ESI-MS: m/z = 233 ([M−PF_6]$^+$); ESI-HRMS: *m*/*z* calcd for $C_{13}H_{17}N_2O_2$ [M]$^+$ 233.1318, found 233.1327.

4.9. Synthesis of compound *11*

To a solution of IL-bounded compound **10** (0.08 g, 0.2 mmol), 6-O-Tr-O-acetylated monosaccharide trichloroacetimidate donor (0.43 g, 0.6 mmol) and 4 Å MS (1.0 g) in dried CH_2Cl_2 (10 mL) and CH_3CN (5 mL) was dropwise added trimethylsilyl triflate

(0.04 mmol) in dried CH_2Cl_2 (2 mL) under nitrogen at −40 °C, and then the reaction temperature was allowed to increase to 0 °C. After 3 h the reaction was completed. The mixture was filtered and the solvent was removed under vacuum. The residue was washed with Et_2O (5 mL), and then dissolved in CH_2Cl_2 (1 mL) and washed with Et_2O (3 × 5 mL) to afford the ionic liquid supported monosaccharide **11** (0.52 g, 84%).

11: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.16 (s, 1H, NH), 7.65–6.92 (m, 21H), 5.54 (d, *J* = 9.6 Hz, 1H), 5.40–4.50 (m, 7H), 4.26–3.46 (m, 8H), 2.09 (s, 3H), 2.05 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 170.1, 169.9, 156.7, 143.9, 137.0, 132.2, 132.1, 129.4, 128.3, 126.1, 123.0, 122.8, 120.2, 104.7, 76.8, 76.2, 72.9, 69.1, 68.4, 68.2, 67.9, 56.6, 37.9, 21.2, 21.15, 21.10; ESI-MS: *m*/*z* = 763 ($[M-PF_6]^+$); ESI-HRMS: *m*/*z* calcd for $C_{44}H_{47}N_2O_{10}$ $[M]^+$ 763.3213, found 763.3222.

4.10. Synthesis of compound **12**

To a solution of I_2 (20 mg, 0.079 mmol) in methanol (2 mL) was dissolved **11** (0.16 g, 0.17 mmol). The solution was heated to 60 °C, and the reaction was monitored by TLC (CH_3OH/CH_2Cl_2, 10:1). After completion, the solvent was removed under vacuum. The resulting residue was dissolved in CH_2Cl_2 (1 mL), washed with ether (3 × 2 mL), and dried *in vacuo* to give compound **12** (0.10 g, 90%).**12**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.18 (s, 1H, NH), 7.45–7.02 (m, 6H), 5.51 (d, *J* = 9.6 Hz, 1H), 5.38–4.53 (m, 7H), 4.26–3.49 (m, 8H), 2.08 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 170.7, 170.2, 155.7, 137.1, 130.9, 128.3, 122.4, 123.4, 122.8, 104.6, 75.8, 75.4, 72.9, 69.1, 68.4, 68.2, 67.9, 56.6, 37.0, 21.1, 21.0, 19.99; ESI-MS: *m*/*z* = 521 ($[M-PF_6]^+$); ESI-HRMS: *m*/*z* calcd for $C_{25}H_{33}N_2O_{10}$ $[M]^+$ 521.2129, found 521.2138.

4.11. Synthesis of compound **13**

To a solution of IL-bounded compound **12** (0.10 g, 0.15 mmol), O-acetylated monosaccharide trichloroacetimidate donor (0.15 g, 0.30 mmol) and 4 Å MS (1.0 g) in dried CH_2Cl_2 (20 mL) was dropwise added trimethylsilyl triflate (0.03 mmol) in dried CH_2Cl_2 (2 mL) under nitrogen at −40 °C. Then the reaction temperature was allowed to increase to 0 °C. After 3 h the reaction was completed. The mixture was filtered and the solvent was removed under vacuum. The residue was washed with Et_2O (5 mL), and then dissolved in CH_2Cl_2 (1 mL) and washed with Et_2O (3 × 5 mL) to afford the ionic liquid supported disaccharide **13** (0.13 g, 88%).**13**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.16 (s, 1H, NH), 7.42–6.91 (m, 6H), 4.58–4.41 (m, 11H), 4.33–4.03 (m, 6H), 3.86–3.58 (m, 5H), 3.49 (s, 1H, OH), 2.09–2.06 (m, 9H), 2.05 (s, 3H), 2.03 (s, 3H), 1.98 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 171.65, 171.64, 170.6, 170.3, 169.9, 169.7, 156.4, 136.0, 130.9, 128.3, 124.1, 123.8, 122.4, 105.2, 101.7, 75.8, 75.4, 72.9, 69.1, 69.0, 68.4, 68.35, 68.31, 68.2, 67.9, 63.3, 61.1, 56.6, 37.9, 21.2, 21.1, 21.0, 20.94, 20.92, 19.99; ESI-MS: *m*/*z* = 851 ($[M-PF_6]^+$); ESI-HRMS: *m*/*z* calcd for $C_{39}H_{51}N_2O_{19}$ $[M]^+$ 851.3143, found 851.3202.

4.12. Synthesis of compound **14**

A solution of IL-bound disaccharide **13** (0.13 g, 0.13 mmol) in ethanol (15 mL) was hydrogenated at atmospheric pressure over 10% Pd/C black (15 mg) for 48 h. After the reaction was completed, the catalyst was filtered off. Ethanol was evaporated under vacuum, and the residue was purified by flash chromatography on silica gel using hexane/EtOAc as the eluent to afford **14**(α) (16 mg, 19%) and **14**(β) (49 mg, 57%).**14**(β): white solid; mp: 100–102 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.50 (d, *J* = 9.6 Hz, 1H), 5.42–5.40 (m, 1H), 5.36–5.10 (m, 2H), 4.98–4.89 (m, 2H), 4.59–4.50 (m, 2H), 4.26–4.03 (m, 3H), 3.86–3.84 (d, *J* = 11.1 Hz, 1H), 3.76–3.70 (m, 2H), 3.68–3.58 (m, 1H), 3.46 (s, 1H, OH), 2.09 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 170.4, 170.3, 170.0, 169.6, 169.5, 169.2, 104.9, 89.8, 76.9, 72.9, 72.4, 71.8, 71.7, 71.1, 69.8, 69.1, 68.1, 61.8, 21.1, 21.08, 21.07, 21.03, 21.0, 20.91, 20.8; ESI-HRMS: *m*/*z* calcd for $C_{26}H_{37}O_{18}$ $[M+H]^+$ 637.1942, found 637.1983.**14**(α): white solid; mp: 95–98 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.45 (d, *J* = 3.6 Hz, 1H), 5.37–5.10 (m, 3H), 4.72–4.58 (m, 2H), 4.45–4.30 (m, 2H), 3.95–3.89 (m, 3H), 3.82–3.78 (m, 1H), 3.76–3.70 (m, 2H), 3.55–3.42 (m, 1H), 2.95 (s, 1H, OH), 2.09 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.95 (s, 3H), 1.94 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 170.3, 170.2, 170.1, 169.7, 169.4, 168.9, 100.5, 89.9, 77.2, 73.0, 72.5, 71.7, 71.5, 70.0, 69.2, 68.5, 68.2, 62.7, 21.13, 21.10, 21.07, 21.05, 21.0, 20.9, 20.5;; ESI-MS: *m*/*z* = 659 ($[M+Na]^+$); ESI-HRMS: *m*/*z* calcd for $C_{26}H_{37}O_{18}$ $[M+H]^+$ 637.1942, found 637.1983.

Acknowledgments

This work was supported by the Education of Zhejiang Province (No. Y200906515) and Zhejiang Gongshang University (No. X-106).

References

Ando, H., Manabe, S., Nakahara, Y., & Ito, Y. (2001). Tag-reporter strategy for facile oligosaccharide synthesis on polymer support. *Journal of the American Chemical Society*, *123*, 3848–3849.

Anjaiah, S., Chandrasekhar, S., & Gree, R. (2004). Synthesis and preliminary use of novel acrylic ester-derived task-specific ionic liquids. *Tetrahedron Letters*, *45*, 569–571.

Deetlefs, M., & Seddon, K. R. (2010). Assessing the greenness of some typical laboratory ionic liquid preparations. *Green Chemistry*, *12*, 17–30.

Donga, R. A., Khaliq-Uz-Zaman, S. M., Chan, T.-H., & Damha, M. J. (2006). A novel approach to oligonucleotide synthesis using an imidazolium ion tag as a soluble support. *Journal of Organic Chemistry*, *71*, 7907–7910.

Fraga-Dubreuil, J., & Bazureau, J. P. (2003). Efficient combination of task-specific ionic liquid and microwave dielectric heating applied to a one-pot three component synthesis of a small library of 4-thiazolidinones. *Tetrahedron*, *59*, 6121–6130.

Frechet, J. M., & Schuerch, J. C. (1971). Solid-phase synthesis of oligosaccharides. I. Preparation of the solid support: poly(p(1-propen-3-ol-l-yl) styrene). *Journal of the American Chemical Society*, *93*, 492–496.

He, X., & Chan, T.-H. (2006). Ionic-tag-assisted oligosaccharide synthesis. *Synthesis*, *10*, 1645–1651.

He, X., & Chan, T.-H. (2007). Structurally defined imidazolium-type ionic oligomers as soluble/solid support for peptide synthesis. *Organic Letters*, *9*, 2681–2684.

Huang, J.-Y., Lei, M., & Wang, Y.-G. (2006). A novel and efficient ionic liquid supported synthesis of oligosaccharides. *Tetrahedron Letters*, *47*, 3047–3050.

Huang, X., Witte, K. L., Bergbreiter, D. E., & Wong, C. H. (2001). Homogenous enzymatic synthesis using a thermo-responsive water-soluble polymer support. *Advanced Synthesis & Catalysis*, *343*, 675–681.

Legeay, J.-C., Vanden Eynde, J. J., & Bazureau, J. P. (2005). Ionic liquid phase technology supported the three component synthesis of Hantzsch 1,4-dihydropyridines and Biginelli 3,4-dihydropyrimidin-2(1H)-ones under microwave dielectric heating. *Tetrahedron*, *61*, 12386–12397.

Miao, W., & Chan, T.-H. (2003). Exploration of ionic liquids as soluble supports for organic synthesis demonstration with a Suzuki coupling reaction. *Organic Letters*, *5*, 5003–5005.

Miao, W., & Chan, T.-H. (2005). Ionic-liquid-supported peptide synthesis demonstrated by the synthesis of Leu5-enkephalin. *Journal of Organic Chemistry*, *70*, 3251–3255.

Miao, W., & Chan, T.-H. (2006). Ionic-liquid-supported synthesis: A novel liquid-phase strategy for organic synthesis. *Accounts of Chemical Research*, *39*, 897–908.

Miura, T., Goto, K., Hosaka, D., & Inazu, T. (2003). Oligosaccharide synthesis on a fluorous support. *Angewandte Chemie International Edition*, *42*, 2047–2051.

Pathak, A. K., Yerneni, C. K., Young, Z., & Pathak, V. (2008). Oligomannan synthesis using ionic liquid supported glycosylation. *Organic Letters*, *10*, 145–148.

Ritter, T. K., Mong, K. T., Liu, H. T., Nakatani, T., & Wong, C.-H. (2003). A programmable one-pot oligosaccharide synthesis for diversifying the sugar domains of natural products: A case study of vancomycin. *Angewandte Chemie International Edition*, *42*, 4657–4660.

Sears, P., & Wong, C. H. (2001). Toward automated synthesis of oligosaccharides and glycoproteins. *Science*, *91*, 2344–2350.

Sigulinsky, C., Bab, P., Victor, X. V., & Kuberan, B. (2010). Preparation and characterization of (15)N-enriched, size-defined heparan sulfate precursor oligosaccharides. *Carbohydrate Research*, *345*, 250–256.

Stick, R. V., & Stubbs, K. A. (2005). From glycoside hydrolases to thioglycoligases: the synthesis of thioglycosides. *Tetrahedron: Asymmetry*, *16*, 321–335.

Wahlstrom, J. L., & Ronald, R. C. (1998). Detritylation of ethers using iodine–alcohol reagents: An acid-catalyzed reaction. *Journal of Organic Chemistry*, *63*, 6021–6022.

Wang, C. C., Lee, K. L., & Hung, S. C. (2007). Regioselective one-pot protection of carbohydrates. *Nature*, *446*, 896–899.

Wasserscheid, P., & Welton, T. (2003). *Ionic Liquids in Synthesis*. Weinheim, Germany: Wiley-VCH.

Yerneni, C. K., Pathak, V., & Pathak, A. K. (2009). Imidazolium cation supported solution-phase assembly of homolinear ((1 → 6)-linked octamannoside: An efficient alternate approach for oligosaccharide synthesis. *Journal of Organic Chemistry*, *74*, 6307–6310.

Zhang, Z. Y., Ollmann, I. R., Ye, X. S., Wischant, R., Baasov, T., & Wong, C. H. (1999). Programmable one-pot oligosaccharide synthesis. *Journal of the American Chemical Society*, *121*, 734–753.