Chinese Chemical Letters 25 (2014) 1525–1530

Contents lists available at ScienceDirect

Chinese Chemical Letters

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

Original article

An efficient ionic liquid supported divergent assembly of 3,6-branched glucosamine-containing pentasaccharide

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ARTICLE INFO

Article history:
Received 11 June 2014
Received in revised form 14 July 2014
Accepted 1 September 2014
Available online 28 September 2014

Keywords:
Ionic liquid
Oligosaccharide
Rapid assembling

ABSTRACT

We utilized the glycosyl acceptor tagging method with ionic liquid support for synthesis of the core segment of *Clostridium botulinum* C2 toxin ligand through a divergent synthetic strategy without chromatographic purification. The total yield was 57.1% and the reaction was completed in 10 h. The efficient ionic liquid supported glycosylation and purification procedure was applied for the synthesis of branched glucosamine-containing oligosaccharides for the first time, which expanded the scope of ionic liquid supported synthesis of biologically important oligosaccharides.

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1. Introduction

Because of the unique functionalities and structures of carbohydrates, the study of oligosaccharides has been highly valued in many areas of chemistry and biology [1]. Chemical synthesis of pure and structurally complex oligosaccharides is still a challenge due to the need of selective protection and deprotection of multiple hydroxyl groups. Moreover, traditional synthesis requires purification by chromatography after each step of glycosylation, which is not only time-consuming but also costly [2]. Solid-phase approach is one of the effective methods to improve the synthesis of oligosaccharides. It is attractive mainly because of its simple purification process, which allows convenient product isolation and automation [3–5]. In recent years, several alternative methodologies incorporating the advantages of both solid- and liquid-phase syntheses, such as polymer-supported strategy, fluorous tag method [6,7], hydrophobically assisted switching-phase (HASP) method [8–10] and ionic liquid supported oligosaccharides synthesis (ILSOS) have been developed.

Because of their fascinating and intriguing properties, ionic liquids (ILs) have been extensively studied for their use as solvents and reaction supports [11,12]. Several groups have successfully demonstrated the feasibility of ionic liquid supported synthesis of peptides, nucleotides, and other types of organic molecules [2,13]. More recently, several groups utilized ionic liquid supports as phase-separation tags in the synthesis of oligosaccharides [2,14–23].

Synthesis of amino-containing oligosaccharides is even more challenging for the traditional liquid-phase method due to the low reactivity of amino-glycosyl donors. Special reaction conditions are often required for the complete glycosylation. Recently, synthesis of some *N*-linked oligosaccharides on polymer support has been reported [24]. However, there is no report on the synthesis of branched amino-oligosaccharides with ionic liquid support in literature. Given interest in the synthesis of heteroatom-containing complex oligosaccharides, we are intrigued by the possibility of assembling amino-oligosaccharides with ionic liquid support for easy purification using low-reactive amino-glycosyl donors. To demonstrate the usefulness of ionic liquid support in the synthesis of amino-oligosaccharides is important for the maturation of this strategy as a widely applicable method for preparation of biologically active oligosaccharides.

Eckhardt and co-workers reported the structure of *C. botulinum* C2 toxin ligand in 2000 [25]. This *N*-linked oligosaccharide is a GnT-V inhibitor due to its similarity in structure compared to substrates of GnT-V [26,27]. The synthesis of segments of the *N*-linked oligosaccharide **1** (Fig. 1) would be useful in determining which parts of the molecule are essential for binding. Nishizawa and co-workers synthesized some segments of **1** with the aid of ODS adsorption method based on the affinity of long alkoxybenzyl glycoside [28].

By optimizing coupling conditions, we successfully used low-reactive amino-glycosyl donors and developed an IL supported synthesis method for the rapid assembly of 3, 6-branched

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http://dx.doi.org/10.1016/j.cclet.2014.09.016
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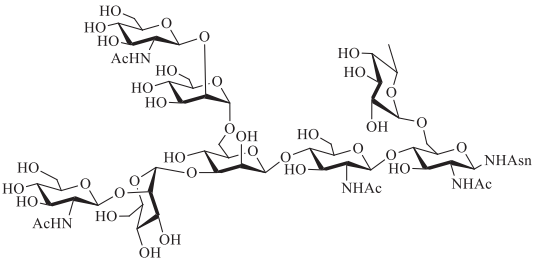

Fig. 1. The structure of *Clostridium botulinum* C2 toxin ligand **1**.

glucosamine-containing pentasaccharide, which is the core segment of *C. botulinum* C2 toxin ligand, without chromatographic purification. Furthermore, we also employed high-performance liquid chromatography (HPLC) to assess the purity of the oligosaccharide prepared by ionic liquid supported synthesis method.

2. Experimental

2.1. Standard procedure A: glycosylation using trichloro-acetimidates and TMSOTf

Acceptor and trichloroacetimidate donor were co-evaporated three times with toluene (3 × 5 mL) and dried under vacuum. After crushed 4 Å molecular sieves were added, the mixture was dissolved in dry CH_2Cl_2 or CH_2Cl_2:CH_3CN (10:1, only for IL-supported monosaccharide synthesis), and the solution was maintained at the desired reaction temperature. After stirring for 10 min, a solution of TMSOTf in dry CH_2Cl_2 was added.

2.2. Standard procedure B: purification by the ionic liquid tag method

After filtration and concentration of the reaction mixture, the residue was dissolved in CH_2Cl_2 and then quickly washed with saturated aq. $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. After evaporation in vacuo, the residue was dissolved in CH_2Cl_2 (2 mL/g), and 5 equiv. volume of isopropyl ether was added. The solvent was removed partially by rotary evaporation in vacuo until the residual solution was about 2 equiv. volume of the initially added CH_2Cl_2. The precipitate was immediately collected by centrifugation (4000 r/min, 10 min).

2.3. Standard procedure C: removal of acetate protecting groups

To a solution of protected glycoside in methanol (1 g/10 mL), saturated sodium methoxide solution in methanol was added. After stirring at room temperature for 45 min, when TLC showed complete consumption of substance, 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.

4-[(1-Methylimdazoliumhexafluorophospho)methyl]benzyl 3,6-di-*O*-acetyl-2,4-di-*O*-benzyl-*α*-D-mannopyranoside (**4**): Acceptor **2** (152 mg, 0.436 mmol), donor **3** (510 mg, 0.875 mmol), and promoter TMSOTf (40 μL, 0.29 mmol) were used to synthesize IL supported monosaccharide **4** (281 mg, 82.7%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1H, ArH), 7.22–7.07 (m, 36H, ArH), 5.16 (s, 2H, Ar-CH_2-N), 5.11 (dd, 1H, H-3), 4.82 (d, 1H, H-1), 4.58–4.35 (m, 6H, ArCH_2), 4.16 (m, 2H, H-6), 3.85 (t, 1H, H-4), 3.77 (t, 1H, H-2), 3.68 (s, 3H, N-CH_3), 3.54 (m, 1H, H-5), 1.95 (s, 3H, Ac), 1.86 (s, 3H, Ac). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.81, 170.21, 138.47, 137.80, 137.70, 136.18, 132.59, 128.98, 128.83, 128.49, 128.39, 127.88, 127.77, 123.78, 121.97, 97.22, 75.70, 74.89, 73.77, 73.28, 72.90, 70.06, 68.77, 68.31, 63.17, 52.85, 36.18, 22.88, 21.06, 20.88. HR-ESI-MS: *m*/*z* calcd. for $C_{36}H_{41}N_2O_8$ 629.28574 $[M\text{-}PF_6]^+$, found: 629.28469.

4-[(1-Methylimdazoliumhexafluorophospho)methyl]benzyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-*α*-D-mannopyranosyl-(1→6)-[2-*O*-acetyl-3,4,6-tri-*O*-benzyl-*α*-D-mannopyranosyl-(1→3)]-2,4-di-*O*-benzyl-*α*-D-mannopyranoside (**7**): Acceptor **5** (80 mg, 0.116 mmol), donor **6** (440 mg, 0.690 mmol), and promoter TMSOTf (21 μL, 0.116 mmol) were used to prepare IL supported trisaccharide **7** (142 mg, 80.7%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.09 (s, 1H, ArH), 7.34–7.19 (m, 46H, ArH), 5.55 (s, 1H, H-2′), 5.52 (s, 1H, H-2″), 5.27 (s, 2H, Ar-CH_2-N), 5.23 (s, 1H, H-1), 5.00 (s, 1H, H-1′), 4.94 (s, 1H, H-1″), 4.91 (t, 2H, ArCH_2), 4.80 (d, 1H, ArCH_2), 4.71–4.61 (m, 7H, ArCH_2), 4.54–4.41 (m, 8H, ArCH_2), 4.21 (d, 1H, H-6), 4.08 (dd, 1H, H-6), 4.03–3.65 (m, 19H), 2.19 (s, 3H, Ac), 2.12 (s, 3H, Ac). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.36, 170.15, 138.93, 138.60, 138.55, 138.30, 138.26, 138.01, 137.89, 137.85, 136.57, 129.05, 128.85, 128.50, 128.46, 128.42, 128.37, 128.35, 128.25, 128.09, 127.99, 127.80, 127.73, 127.69, 127.57, 123.69, 121.75, 99.81, 98.13, 96.47, 78.09, 75.24, 74.96, 74.90, 74.47, 74.30, 73.40, 72.36, 72.28, 71.90, 71.59, 71.37, 69.22, 68.92, 68.84, 68.48, 68.38, 66.45, 53.57, 53.11, 36.33, 21.20, 21.05. HR-ESI-MS: *m*/*z* calcd. for $C_{90}H_{97}N_2O_{18}$ 1493.67309 $[M\text{-}PF_6]^+$, found: 1493.67758.

4-[(1-Methylimdazoliumhexafluorophospho)methyl]benzyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (**14**): Acceptor **2** (48 mg, 0.128 mmol), donor **13** (148 mg, 0.255 mmol) and promoter TMSOTf (20 μL, 0.109 mmol) were used to give **14** (94 mg, 90%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1H, ArH), 7.78 (s, 4H, ArH), 7.27–7.10 (m, 6H), 5.75 (dd, 1H), 5.19 (s, 2H, Ar-CH_2-N), 4.82–4.54 (m, 2H, Ar-CH_2), 4.33 (m, 2H), 4.20 (dd, 1H), 3.89 (m, 1H), 3.87 (s, 3H, N-CH_3), 2.12 (s, 3H, Ac), 2.02 (s, 3H, Ac), 1.85(s, 3H, Ac). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.84, 170.22, 169.61, 138.41, 136.30, 134.86, 132.16, 131.19, 129.33, 129.18, 123.74, 122.14, 96.91, 71.99, 70.60, 70.50, 69.07, 62.06, 54.61, 53.55, 53.12, 36.38, 20.89, 20.72, 20.54. HR-ESI-MS: *m*/*z* calcd. for $C_{32}H_{34}N_3O_{10}$ 620.22387 $[M\text{-}PF_6]^+$, found: 620.22354.

4-[(1-Methylimdazoliumhexafluorophospho)methyl]benzyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucosyl-(1→2)-3,4,6-tri-*O*-benzyl-*α*-D-mannopyranosyl-(1→6)-[3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucosyl-(1→2)-3,4,6-tri-*O*-benzyl-*α*-D-mannopyranosyl-(1→3)]-2,4-di-*O*-benzyl-*α*-D-mannopyranoside (**15**): Acceptor **11** (51 mg, 0.0328 mmol), donor **13** (133 mg, 0.229 mmol) and promoter TMSOTf (6 μL, 0.0328 mmol) were used to prepare IL supported pentasaccharide **15** (64 mg, 87.3%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.42 (s, 1H, ArH), 7.90–6.99 (m, 54H, ArH), 5.81–3.22 (m, 55H), 2.89–1.81 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.61, 170.46, 170.26, 170.09, 170.00, 169.76, 169.55, 169.42, 169.25, 167.64, 138.63, 138.60, 138.54, 138.36, 138.27, 138.13, 138.03, 137.92, 137.77, 137.50, 137.31, 137.18, 134.48, 134.33, 134.23, 134.17, 134.13, 132.30, 132.22, 132.10, 131.94, 131.82, 131.70, 131.48, 131.39, 131.25, 131.18, 131.03, 130.86, 130.37, 129.91, 129.25, 129.16, 129.09, 128.98, 128.53, 128.33, 128.20, 128.08, 128.02, 127.91, 127.81, 127.70, 127.63, 127.59, 127.53, 127.42, 127.37, 127.30, 127.19, 126.99, 126.66, 126.45, 126.34, 126.29, 126.10, 124.19, 124.06, 123.95, 123.78, 123.55, 123.50, 123.39, 123.30, 121.64, 121.59, 121.49, 121.42, 120.63, 99.57, 99.04, 97.18, 96.63, 96.03, 75.13, 74.57, 74.25, 73.37, 72.84, 72.60, 71.92, 71.03, 70.55, 70.53, 70.49, 70.45, 70.11, 69.63, 69.06, 68.74, 68.50, 67.04, 65.73, 62.23, 62.05, 61.80, 61.68, 61.56, 61.11, 60.98, 54.99, 54.65, 54.38, 54.36, 54.30, 54.11, 53.50, 53.13, 36.47, 36.41, 36.34, 36.29, 35.70, 29.76, 29.48, 29.33. HR-ESI-MS: *m*/*z* calcd. for $C_{126}H_{131}N_4O_{34}$ 2243.86392 $[M\text{-}PF_6]^+$, found: 2243.86281.

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