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A versatile pathway to end-functionalized cellulose ethers for click chemistry applications

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1 **A versatile pathway to end-functionalized cellulose ethers for click chemistry**
2 **applications**

3

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11

12 ABSTRACT¹

13 This paper describes a versatile pathway to heterobifunctional/telechelic cellulose ethers, such as
14 tri-*O*-methyl cellulose azide and propargyl tri-*O*-methyl cellulose, having one free C-4 hydroxyl
15 group attached to the glucosyl residue at the non-reducing end for the use in Huisgen 1,3-dipolar
16 cycloaddition and copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC). The one-step
17 end-functionalization of cellulose ethers for molecular rod synthesis involves the introduction of
18 two reactive groups at both ends of the cellulose molecule, and can afford linear triblock
19 copolymers via CuAAC and further reactions. We were able to tailor the degree of polymerization
20 of end-functionalized cellulose ethers with controlled amounts of a Lewis acid, namely SnCl₄.
21 Chemical structures of the above cellulose ethers and the reaction conditions for controlling
22 molecular length are discussed.

23
24 **Keywords:** end-functionalized cellulose ether; copper(I)-catalyzed azide-alkyne cycloaddition;
25 functional molecular rod; tri-*O*-methyl cellulose azide; propargyl tri-*O*-methyl cellulose
26

27 1. Introduction

28 Methylcellulose (MC), being one of the more common cellulose ethers, has been of interest in the
29 investigation of structure-property relationships, such as thermoreversible gelation properties at
30 elevated temperature. Our research focuses on the design and synthesis of regioselectively
31 methylated cellulose derivatives via ring-opening polymerization of glucose orthopivalate
32 derivatives (Kamitakahara, Hori, & Nakatsubo, 1996; Karakawa, Mikawa, Kamitakahara, &
33 Nakatsubo, 2002; Nakatsubo, Kamitakahara, & Hori, 1996) or from natural cellulose
34 (Kamitakahara, Koschella, Mikawa, Nakatsubo, Heinze, & Klemm, 2008; Nakagawa et al., 2012)
35 and diblock methylcellulose with regioselective functionalization patterns (Nakagawa, Fenn,
36 Koschella, Heinze, & Kamitakahara, 2011a, b; Nakagawa, Steiniger, Richter, Koschella, Heinze, &
37 Kamitakahara, 2012). As a result, we found that a diblock structure composed of hydrophilic
38 cellobiosyl and hydrophobic 2,3,6-tri-*O*-methylcellulosyl segments is crucial for the
39 thermoreversible gelation of aqueous MC solutions (Nakagawa, Fenn, Koschella, Heinze,
40 Kamitakahara, 2011a). Commercial MC prepared under heterogeneous conditions is an
41 alternating block copolymer composed of densely substituted hydrophobic and less densely
42 substituted hydrophilic block sequences (Savage, 1957). The synthetic route to multiblock MC
43 derivatives composed of hydrophobic 2,3,6-tri-*O*-methylcellulosyl and hydrophilic cellobiosyl
44 segments remains open.

¹ Copper(I)-catalyzed azide-alkyne cycloaddition, CuAAC; methylcellulose, MC; cellulose triacetate, CTA; gel permeation chromatography, GPC; 2,5-dihydroxybenzoic acid, DHB; degree of polymerization, DP.

45

46 Precise control of the monosaccharide sequence to prepare multiblock derivatives is, however,
47 extremely difficult and time-consuming. We synthesized 1,2,3-triazole-linked diblock MC
48 composed of low molecular weight cellulose and 2,3,6-tri-*O*-methyl cellulose (Nakagawa,
49 Kamitakahara, & Takano, 2012) and found that a 2 wt. % aqueous solution of this MC analogue
50 exhibited thermoreversible gelation behavior, meaning that linkages between hydrophilic and
51 hydrophobic segments do not affect gelation properties. Thus, we considered utilizing linkages
52 other than the glycosidic bond to prepare multiblock MC copolymers.

53

54 To be suitable building blocks for the multiblock MC copolymers, the cellulose derivatives must
55 have functional groups at both ends of the linear molecule. Heterobifunctional/telechelic
56 derivatives are more desirable than homobifunctional/telechelic ones (Kim, Stannett, & Gilbert,
57 1973, 1976; Pohjola & Eklund, 1977; Steinmann, 1968, 1970) for the preparation of multiblock
58 copolymers. Derivatives having two different functional groups at both ends of the linear polymer
59 are therefore attractive and promising for the exploration of a new research field in cellulose
60 chemistry.

61

62 On the other hand, cellulose derivatives are known to be semi-rigid polymers (De Oliveira &
63 Glasser, 1994), which controls their physical properties. The concept of a 'molecular rod' is
64 therefore applicable to heterobifunctional/telechelic cellulose derivatives, which can be viewed as
65 bricks of a molecular Lego (Lepage, Schneider, Bodlenner, & Compain, 2015; Meldal, 2008). To
66 connect several bricks of the cellulosic Lego, two ends of the molecular rod must be separately
67 functionalized under independent activation conditions. It is then possible to covalently bind
68 several molecular bricks, adding other brick units under different reaction conditions.

69

70 We have previously reported the synthesis of tri-*O*-acetyl cellulosyl azide (Kamitakahara, Enomoto,
71 Hasegawa, & Nakatsubo, 2005). This molecule is a key compound for the end-functionalization
72 of cellulose derivatives. The azide group can be easily converted into an amino group, which can
73 be used in a subsequent amidation reaction. For instance, we successfully synthesized cellulose
74 triacetate (CTA)-*block*-oligoamide-15 (Kamitakahara, Enomoto, Hasegawa, & Nakatsubo, 2005;
75 Kamitakahara & Nakatsubo, 2005), a CTA derivative carrying a single pyrene group at the reducing
76 end (Enomoto, Kamitakahara, Takano, & Nakatsubo, 2006), and a CTA derivative having a single
77 lipoic acid moiety at the reducing end (Enomoto-Rogers, Kamitakahara, Yoshinaga, & Takano,
78 2010). The high reactivity of the azide group towards alkynes is known as the click chemistry
79 approach, and is based on Huisgen 1,3-dipolar cycloaddition and copper(I)-catalyzed azide-alkyne
80 cycloaddition (CuAAC) (Kolb, Finn, & Sharpless, 2001). We have prepared comb-shaped graft

81 copolymers with CTA side chains (Enomoto-Rogers, Kamitakahara, Yoshinaga, & Takano, 2012)
82 and CTA-block-poly(γ -benzyl-L-glutamate) (Kamitakahara, Baba, Yoshinaga, Suhara, & Takano,
83 2014), knowing that the CuAAC reaction is a more powerful tool for bonding two polymeric
84 segments than amidation.

85

86 Not only cellulose esters, such as cellulose acetate, but also a representative cellulose ether,
87 methylcellulose, were also important molecular Lego bricks. Methyl tri-*O*-methyl cellulose, with
88 a single hydroxyl group at the C-4 position of the glucosyl residue at the non-reducing end was
89 prepared by methanolysis of 2,3,6-tri-*O*-methyl cellulose (Nakagawa, Fenn, Koschella, Heinze, &
90 Kamitakahara, 2011b; Nakagawa, Kamitakahara, & Takano, 2011). Propargylation of one end of
91 the cellulose ether derivative afforded a cellulose ether carrying a single alkyne group at the end of
92 the cellulosic molecular rod, methyl tri-*O*-methyl cellulose (Nakagawa, Kamitakahara, & Takano,
93 2012). Cellulose ethers are more stable than the corresponding esters in both acidic and alkaline
94 reaction conditions used to construct the cellulosic molecular architecture. Thus, we focused on
95 the synthesis of cellulosic molecular rods carrying two independent end-functional groups.

96

97 Propargylated methyl tri-*O*-methyl cellulose was synthesized from commercial methylcellulose in
98 three reaction steps: complete methylation, methanolysis, and propargylation. This molecular rod
99 has a functional group at one end (Nakagawa, Fenn, Koschella, Heinze, & Kamitakahara, 2011b),
100 which is a disadvantage. Therefore, we were motivated to synthesize cellulosic molecular rods
101 carrying two independent end-functional groups, in other words, cellulosic
102 heterobifunctional/telechelic polymers.

103

104 To introduce an azide group at the C-1 position of the glucosyl residue at the reducing end of CTA,
105 it was treated with hydrogen bromide in acetic acid to afford the α -anomer of tri-*O*-acetyl cellulose
106 bromide. The bromide was then treated with acetic acid and silver oxide to yield the β -anomer of
107 acetyl tri-*O*-acetyl cellulose, which was finally converted into the β -anomer of tri-*O*-acetyl
108 cellulose azide using trimethylsilyl azide and SnCl₄ (Kamitakahara, Enomoto, Hasegawa, &
109 Nakatsubo, 2005). We tried to produce tri-*O*-methyl cellulose azide (**2**) with a controlled
110 molecular weight from tri-*O*-methyl cellulose (**1**) in a one-step reaction. Azide and alkyne groups
111 form a pair for the 1,3-dipolar cycloaddition, and preparing propargyl tri-*O*-methyl cellulose (**3**) is,
112 therefore, of critical importance. Thus, we attempted to produce propargyl tri-*O*-methyl cellulose
113 (**3**) with a controlled molecular weight from tri-*O*-methyl cellulose (**1**) in a one-step reaction.

114

115 Moreover, the free C-4 hydroxyl of the glucosyl residue at the non-reducing end could connect with
116 other molecular bricks having epoxide, acyl, isocyanate, and other functionalities, thereby

117 extending the variety of molecular architecture motifs. Heterobifunctional/telechelic cellulose
118 derivatives, at least, provide molecules with triblock structures. The production of cellulosic
119 triblock copolymers from homobifunctional/telechelic cellulose derivatives has already been
120 reported (Kim, Stannett, & Gilbert, 1973, 1976; Pohjola & Eklund, 1977; Steinmann, 1968, 1970),
121 however, heterobifunctional/telechelic cellulose derivatives are still unknown, to the best of our
122 knowledge.

123

124 Consequently, the aim of this research was to find the appropriate reaction conditions affording
125 end-functionalized cellulose ethers, such as tri-*O*-methyl cellulose azide (**2**) and propargyl
126 tri-*O*-methyl cellulose (**3**), for click chemistry and further conversion using the remaining
127 functionalized end of the ethers. This paper describes well-controlled synthetic methods for
128 preparing cellulosic precursors for CuAAC, namely tri-*O*-methyl cellulose azide (**2**) and propargyl
129 tri-*O*-methyl cellulose (**3**). The reaction conditions used to introduce azide and propargyl groups
130 onto the tri-*O*-methyl cellulose (**1**) scaffold and the structures of reaction products are also
131 discussed.

132

133 2. MATERIALS AND METHODS

134 2.1. Materials

135 All reagents and solvents were obtained from Nacalai Tesque, Wako Chemical, and Sasaki
136 Chemical, Japan, and were used as received.

137

138 2.2. Analytical measurements

139 ¹H and ¹³C NMR spectra were acquired in CDCl₃ on a Varian 500 NMR spectrometer at room
140 temperature. The molecular weights of the products were measured by gel permeation
141 chromatography (GPC) in chloroform on a Shimadzu SEC system (CBM-20A, SPD-10A_{VP},
142 SIL-10A, LC-10AT_{VP}, FCV-10AL_{VP}, CTO-10A_{VP}, RID-10A, and FRC-10A, Shimadzu, Japan).
143 Sample solutions were passed through a syringe filter (Sartorius Stedim, Minisart RC 4 or RC 15;
144 pore size 0.45 μm) before GPC analysis. Shodex columns (K802, K802.5, and K805) with a
145 guard column (Shodex, K-G) were used. Number- and weight-averaged molecular weights (*M_n*
146 and *M_w*) and polydispersity indices (*M_w/M_n*) were estimated using polystyrene standards (Shodex).
147 Matrix-assisted laser desorption/ionization time-of-flight mass spectra (MALDI-TOF MS) were
148 recorded on a Bruker Autoflex III machine in the positive ion linear mode. 2,5-Dihydroxybenzoic
149 acid (DHB) was used as a matrix for these measurements.

150

151 2.3. Synthetic methods

152 2.3.1. 2,3,6-Tri-*O*-methyl cellulose (**1**)

Complete methylation of SM-400 (Shin-Etsu Chemical, Japan) to afford 2,3,6-tri-*O*-methyl cellulose (**1**) was carried out as previously described (Nakagawa, Kamitakahara, & Takano, 2011). MALDI-TOF MS (positive linear mode; DHB matrix):
DP (degree of polymerization) = 5: C₄₇H₈₆O₂₆ Calcd. [M]⁺ 1066.54; Found [M+Na]⁺ = 1089.637
DP = 6: C₅₆H₁₀₂O₃₁ Calcd. [M]⁺ 1270.64; Found [M+Na]⁺ = 1293.733
DP = 7: C₆₅H₁₁₈O₃₆ Calcd. [M]⁺ 1474.74; Found [M+Na]⁺ = 1497.964
DP = 8: C₇₄H₁₃₄O₄₁ Calcd. [M]⁺ 1678.84; Found [M+Na]⁺ = 1701.954
DP = 9: C₈₃H₁₅₀O₄₆ Calcd. [M]⁺ 1882.94; Found [M+Na]⁺ = 1905.979
DP = 10: C₉₂H₁₆₆O₅₁ Calcd. [M]⁺ 2087.04; Found [M+Na]⁺ = 2109.946
DP = 11: C₁₀₁H₁₈₂O₅₆ Calcd. [M]⁺ 2291.14; Found [M+Na]⁺ = 2313.76
DP = 12: C₁₁₀H₁₉₈O₆₁ Calcd. [M]⁺ 2495.24; Found [M+Na]⁺ = 2517.776
DP = 13: C₁₁₉H₂₁₄O₆₆ Calcd. [M]⁺ 2699.34; Found [M+Na]⁺ = 2721.576
DP = 14: C₁₂₈H₂₃₀O₇₁ Calcd. [M]⁺ 2903.44; Found [M+Na]⁺ = 2926.146
DP = 15: C₁₃₇H₂₄₆O₇₆ Calcd. [M]⁺ 3107.54; Found [M+Na]⁺ = 3129.431
DP = 16: C₁₄₆H₂₆₂O₈₁ Calcd. [M]⁺ 3311.64; Found [M+Na]⁺ = 3332.968
DP = 17: C₁₅₅H₂₇₈O₈₆ Calcd. [M]⁺ 3515.74; Found [M+Na]⁺ = 3536.968
DP = 18: C₁₆₄H₂₉₄O₉₁ Calcd. [M]⁺ 3717.84; Found [M+Na]⁺ = 3740.437
DP = 19: C₁₇₃H₃₁₀O₉₆ Calcd. [M]⁺ 3923.94; Found [M+Na]⁺ = 3944.958

171

172 2.3.2. Tri-*O*-methyl cellulosyl azide (**2**)

To a solution of tri-*O*-methyl cellulose (**1**) (51.1 mg, $M_n = 2.58 \times 10^{-4}$, $DP_n = 126$) in anhydrous chloroform (0.633 mL) were added 0.32 mL of trimethylsilyl azide (0.2 mL) in anhydrous chloroform (9.8 mL) (TMS-N₃: 4.87×10^{-2} mmol, 0.195 equiv./anhydro glucose unit (AGU)) and 0.047 mL of tin(IV) tetrachloride (0.1 mL) in anhydrous chloroform (4.9 mL) (SnCl₄: 8.16×10^{-3} mmol, 0.034 equiv./AGU). The reaction mixture was stirred at room temperature (r.t.) for 4 h and was subsequently neutralized with 0.113 mL of triethylamine (0.2 mL) in chloroform (9.8 mL) (Et₃N: 2 equiv. with respect to SnCl₄). The reaction mixture was extracted with ethyl acetate, washed with water and brine, dried over Na₂SO₄, and concentrated *in vacuo* to give tri-*O*-methyl cellulosyl azide (**2**) (42.6 mg).

¹H-NMR (500 MHz, CDCl₃): δ 2.96 (t, $J = 9.0$ Hz, H2), 3.22 (t, $J = 9.0$ Hz, H3), 3.29 (broad d, $J = 9.0$ Hz, H5), 3.39 (OCH₃), 3.54 (OCH₃), 3.58 (OCH₃), 3.62–3.84 (H4, H6), 4.28 (d, $J = 8.0$, H1), 4.34 (d, $J = 8.0$, internal H1), 4.47 (d, $J = 8.5$ Hz, H1-β at reducing end), 5.45 (d, $J = 3.5$ Hz, H1-α at reducing end).

¹³C-NMR (125 MHz, CDCl₃): δ 59.0, 59.1, 59.1 (C6-OCH₃), 59.2, 59.4, 60.1, 60.3 (C3-OCH₃), 60.4, 60.5 (C2-OCH₃), 60.6, 60.7, 60.8, 61.3, 69.8, 69.9, 70.2 (C6 internal), 70.5, 71.0, 72.3, 74.8 (C5 internal), 74.9, 75.7, 76.9, 77.2, 77.4 (C4 internal), 77.5, 80.8, 81.1, 81.2, 82.8, 83.1, 83.4, 83.5

189 (C2 internal), 84.6, 84.9, 85.0 (C3 internal), 85.1, 87.0 (C1 α at reducing end), 87.3, 89.9 (C1 β at
190 reducing end), 103.1 (C1 internal), 103.3, 103.4.
191 MALDI-TOF MS (positive linear mode; DHB matrix):
192 DP = 5: C₄₅H₈₁N₃O₂₅ Calcd. [M]⁺ 1063.52; Found [M+Na]⁺ = 1086.441
193 DP = 6: C₅₄H₉₇N₃O₃₀ Calcd. [M]⁺ 1267.62; Found [M+Na]⁺ = 1290.637
194 DP = 7: C₆₃H₁₁₃N₃O₃₅ Calcd. [M]⁺ 1471.72; Found [M+Na]⁺ = 1494.81
195 DP = 8: C₇₂H₁₂₉N₃O₄₀ Calcd. [M]⁺ 1675.82; Found [M+Na]⁺ = 1698.909
196 DP = 9: C₈₁H₁₄₅N₃O₄₅ Calcd. [M]⁺ 1879.92; Found [M+Na]⁺ = 1902.891
197 DP = 10: C₉₀H₁₆₁N₃O₅₀ Calcd. [M]⁺ 2084.01; Found [M–N₂+Na]⁺ = 2078.970, [M–N₂+K]⁺ =
198 2094.96, [M+Na]⁺ = 2106.909, [M+K]⁺ = 2122.97
199 DP = 11: C₉₉H₁₇₇N₃O₅₅ Calcd. [M]⁺ 2288.11; Found [M+Na]⁺ = 2310.949
200 DP = 12: C₁₀₈H₁₉₃N₃O₆₀ Calcd. [M]⁺ 2492.21; Found [M+Na]⁺ = 2515.075
201 DP = 13: C₁₁₇H₂₀₉N₃O₆₅ Calcd. [M]⁺ 2696.31; Found [M+Na]⁺ = 2718.929
202 DP = 14: C₁₂₆H₂₂₅N₃O₇₀ Calcd. [M]⁺ 2900.41; Found [M+Na]⁺ = 2922.819
203 DP = 15: C₁₃₅H₂₄₁N₃O₇₅ Calcd. [M]⁺ 3104.51; Found [M+Na]⁺ = 3126.248
204 DP = 16: C₁₄₄H₂₅₇N₃O₈₀ Calcd. [M]⁺ 3308.61; Found [M+Na]⁺ = 3331.014
205 DP = 17: C₁₅₃H₂₇₃N₃O₈₅ Calcd. [M]⁺ 3512.71; Found [M+Na]⁺ = 3534.132
206 DP = 18: C₁₆₂H₂₈₉N₃O₉₀ Calcd. [M]⁺ 3716.81; Found [M+Na]⁺ = 3738.273
207 DP = 19: C₁₇₁H₃₀₅N₃O₉₅ Calcd. [M]⁺ 3920.91; Found [M+Na]⁺ = 3942.31.

208

209 2.3.3. Propargyl tri-*O*-methyl cellulose (**3**)

210 To a solution of tri-*O*-methyl cellulose (**1**) (50 mg, $M_n = 2.58 \times 10^4$, $DP_n = 126$) in anhydrous
211 dichloromethane (1 mL) were added 2-propyne-1-ol (4.2 μ L, 7.1×10^{-2} mmol, 0.3 equiv./AGU) and
212 SnCl₄ (2.4 μ L, 0.021 mmol, 0.085 equiv./AGU). The reaction mixture was stirred at r.t. for 4 h
213 and was subsequently extracted with chloroform, washed with water and brine, dried over Na₂SO₄,
214 and concentrated *in vacuo* to give propargyl tri-*O*-methyl cellulose (**3**) (42 mg).
215 ¹H-NMR (500 MHz, CDCl₃): δ 2.43 (CH₂CCH), 2.95 (t, $J = 9.0$ Hz, H₂), 3.20 (t, $J = 9.0$ Hz, H₃)
216 3.28 (broad d, $J = 9.0$ Hz, H₅), 3.37(OCH₃), 3.53(OCH₃), 3.57 (OCH₃), 3.62–3.66 (H₆), 3.72–3.81
217 (H₆), 3.69 (t, $J = 9.0$ Hz, H₄), 4.28–4.29 (CH₂CCH), 4.34 (d, 1H, $J = 8.0$, internal H₁), 4.38–4.39
218 (CH₂CCH), 4.49 (d, $J = 8.0$ Hz, H₁- β at reducing end), 5.20 (d, $J = 4.0$ Hz, H₁- α at reducing end).
219 ¹³C-NMR (125 MHz, CDCl₃): δ 54.4 (CH₂CCH (C1- α)), 55.6 (CH₂CCH (C1- β)), 58.4, 59.0, 59.1
220 (C6-OCH₃), 59.2, 59.3, 59.6, 60.1, 60.3 (C3-OCH₃), 60.3, 60.4, 60.5 (C2-OCH₃), 60.7, 60.8, 70.0,
221 70.2 (C6 (internal)), 70.4, 72.0, 73.1, 73.3, 74.6, 74.7, 74.8 (C5 internal), 74.9, 77.1, 77.2, 77.4 (C4
222 internal), 77.5, 77.6, 77.9, 78.7, 78.9, 79.3, 80.7, 81.0, 82.8 (C2 at reducing end (C1- β)), 83.3, 83.5
223 (C2 internal), 83.7, 84.4 (C3 at reducing end (C1- β)), 84.9, 85.0 (C3 internal), 86.1, 94.5 (C1- α at
224 reducing end), 100.7 (C1- β at reducing end), 101.2, 103.1 (C1 internal), 103.2, 103.3.

225 MALDI-TOF MS (positive linear mode; DHB as matrix):
226 DP = 4: C₃₉H₆₈O₂₁ Calcd. [M]⁺ 872.43; Found [M+Na]⁺ = 895.164
227 DP = 5: C₄₈H₈₄O₂₆ Calcd. [M]⁺ 1076.53; Found [M+Na]⁺ = 1099.249
228 DP = 6: C₅₇H₁₀₀O₃₁ Calcd. [M]⁺ 1280.62; Found [M+Na]⁺ = 1303.425
229 DP = 7: C₆₆H₁₁₆O₃₆ Calcd. [M]⁺ 1484.72; Found [M+Na]⁺ = 1507.497
230 DP = 8: C₇₅H₁₃₂O₄₁ Calcd. [M]⁺ 1688.82; Found [M+Na]⁺ = 1711.584
231 DP = 9: C₈₄H₁₄₈O₄₆ Calcd. [M]⁺ 1892.92; Found [M+Na]⁺ = 1915.701
232 DP = 10: C₉₃H₁₆₄O₅₁ Calcd. [M]⁺ 2097.02; Found [M+Na]⁺ = 2119.702
233 DP = 11: C₁₀₂H₁₈₀O₅₆ Calcd. [M]⁺ 2301.12; Found [M+Na]⁺ = 2323.797
234 DP = 12: C₁₁₁H₁₉₆O₆₁ Calcd. [M]⁺ 2505.22; Found [M+Na]⁺ = 2527.612
235 DP = 13: C₁₂₀H₂₁₂O₆₆ Calcd. [M]⁺ 2709.32; Found [M+Na]⁺ = 2731.001
236 DP = 14: C₁₂₉H₂₂₈O₇₁ Calcd. [M]⁺ 2913.42; Found [M+Na]⁺ = 2936.027
237 DP = 15: C₁₃₈H₂₄₄O₇₆ Calcd. [M]⁺ 3117.52; Found [M+Na]⁺ = 3139.696
238 DP = 16: C₁₄₇H₂₆₀O₈₁ Calcd. [M]⁺ 3321.62; Found [M+Na]⁺ = 3343.723
239 DP = 17: C₁₅₆H₂₇₆O₈₆ Calcd. [M]⁺ 3525.72; Found [M+Na]⁺ = 3547.69
240 DP = 18: C₁₆₅H₂₉₂O₉₁ Calcd. [M]⁺ 3729.82; Found [M+Na]⁺ = 3752.824
241 DP = 19: C₁₇₄H₃₀₈O₉₆ Calcd. [M]⁺ 3933.92; Found [M+Na]⁺ = 3956.686.

242

243 3. Results and Discussion

244

245 **Scheme 1.** Synthesis of tri-*O*-methyl cellulose azide (**2**) and propargyl tri-*O*-methyl cellulose (**3**)
246 from tri-*O*-methyl cellulose (**1**).

247

248 3.1. Tri-*O*-methyl cellulose (**1**)

249 The MALDI-TOF MS spectrum of tri-*O*-methyl cellulose (**1**) (Figure 1A) indicates that the base
250 peak (among peaks with the same DP) corresponds to the pseudo molecular ion [M+Na]⁺ of the
251 fully methylated methylcellulose with methyl groups at both ends of the molecule, meaning that
252 both the C-1 hydroxyl of the glucosyl residue at the reducing end and the C-4 hydroxyl of the
253 glucosyl residue at the non-reducing end are methylated. The spectrum, however, also showed
254 peaks with lower intensities. For instance, sodium adduct ion peaks were found, corresponding to

255 tri-*O*-methyl cellulose (**1**) with a few non-methylated hydroxyl groups on the cellulosic backbone.
256 Pseudo molecular ion $[M+Na]^+$ peaks with $m/z = 2313.760$ and 2299.870 were attributed to
257 completely methylated methylcellulose (DP = 11) and to methylcellulose (DP = 11) with one
258 hydroxyl group, respectively.

259
260 **Figure 1.** MALDI-TOF MS spectra of (A) tri-*O*-methyl cellulose (**1**) ($DP_n = 322$), (B) tri-*O*-methyl
261 cellosyl azide (**2**) ($DP_n = 27.5$), and (C) propargyl tri-*O*-methyl celloside (**3**) ($DP_n = 13.2$).
262

263 3.2. Synthesis of tri-*O*-methyl cellosyl azide (**2**)

264 We tried to prepare the tri-*O*-methyl cellosyl azide (**2**) using the synthetic strategy used for
265 tri-*O*-acetyl- β -cellosyl azide (Kamitakahara, Enomoto, Hasegawa, & Nakatsubo, 2005). We
266 have already found that the α -anomer of acetyl tri-*O*-acetyl cellulose is relatively stable under
267 azidation conditions using trimethylsilyl azide and $SnCl_4$. To replace the anomeric acetyl group
268 with azide, a mixture of acetate α - and β -anomers was first converted to the β -anomer of acetyl
269 tri-*O*-acetyl cellulose via an S_N2 reaction of tri-*O*-acetyl cellosyl α -bromide. The β -anomer of
270 acetyl tri-*O*-acetyl cellulose was converted to tri-*O*-methyl β -cellosyl azide. Hydrogen bromide,
271 however, led to intensive degradation of tri-*O*-methyl cellulose (**1**), which was more reactive than
272 tri-*O*-acetyl cellulose.

273
274 Due to the higher reactivity of tri-*O*-methyl cellulose (**1**) compared to tri-*O*-acetyl cellulose, we
275 subsequently tried to prepare a mixture of α - and β -anomers of tri-*O*-methyl cellosyl azide (**2**)
276 from α - and β -anomers of methyl tri-*O*-methyl cellulose (**1**) in a one-step reaction. After the

277 optimization of reaction conditions, the above synthesis was successfully accomplished.

278

279 The MALDI-TOF MS spectrum of tri-*O*-methyl cellulose azide (**2**) (Figure 1B) shows that it has
280 one free hydroxyl group at the non-reducing end, specifically at the C-4 position of the glucosyl
281 residue. The reaction mechanism to synthesis tri-*O*-methyl cellulose azide (**2**) having one free
282 C-4 hydroxyl group attached to the glucosyl residue at the non-reducing end from tri-*O*-methyl
283 cellulose (**1**) is illustrated in Scheme S1. Repetitive signals consisting of two major peaks are
284 shown. For instance, pseudo molecular ion peaks with $m/z = 2310.949$ ($[M+Na]^+$) and $m/z =$
285 2282.861 ($[M-N_2+Na]^+$) are attributed to tri-*O*-methyl cellulose azide (**2**) with $DP = 11$ and one
286 free hydroxyl group attached to the C-4 carbon of the glucosyl residue at the non-reducing end.

287

288 Figure 2 shows 1H -NMR spectra of tri-*O*-methyl cellulose (**1**), tri-*O*-methyl cellulose azide (**2**),
289 and propargyl tri-*O*-methyl celloside (**3**). All proton resonances of tri-*O*-methyl cellulose (**1**)
290 were assigned based on previous studies (Karakawa, Mikawa, Kamitakahara, & Nakatsubo, 2002;
291 Nakagawa, Fenn, Koschella, Heinze, & Kamitakahara, 2011b). Resonances with low intensities at
292 5.45 and 4.47 ppm were attributed to α - and β -anomeric protons of the glucosyl residue at the
293 reducing end of tri-*O*-methyl cellulose azide (**2**), respectively, as shown in Figure 2B.

294

295 **Figure 2.** 1H -NMR spectra of (A) tri-*O*-methyl cellulose (**1**) ($DP_n = 322$), (B) tri-*O*-methyl
296 cellosyl azide (**2**) ($DP_n = 27.5$), and (C) propargyl tri-*O*-methyl celloside (**3**) ($DP_n = 71.2$).

297

298 All carbon resonances of tri-*O*-methyl cellulose (**1**) were also assigned, as shown in Figure 3. In
299 Figure 3B, resonances with low intensities at 87.0 and 89.9 ppm were assigned to α - and
300 β -anomeric carbons of the glucosyl residue at the reducing end of tri-*O*-methyl cellosyl azide (**2**),
301 respectively.

302

303

304 **Figure 3.** ^{13}C -NMR spectra of (A) tri-*O*-methyl cellulose (**1**) ($DP_n = 322$), (B) tri-*O*-methyl
305 cellosyl azide (**2**) ($DP_n = 27.5$), and (C) propargyl tri-*O*-methyl celloside (**3**) ($DP_n = 71.2$).

306

307 3.3. Synthesis of propargyl tri-*O*-methyl celloside (**3**)

308 It was subsequently planned to prepare propargyl tri-*O*-methyl celloside (**3**) from tri-*O*-methyl
309 cellulose (**1**) via in a one-step reaction. Propargyl alcohol was coupled at the C-1 position of the
310 glucosyl residue at the reducing end of tri-*O*-methyl cellulose (**1**).

311 The MALDI-TOF MS spectrum of propargyl tri-*O*-methyl celloside (**3**) (Figure 1C) indicates that
312 it has one free C-4 hydroxyl group attached to the glucosyl residue at the non-reducing end ($DP_n =$
313 13.2, obtained from tri-*O*-methyl cellulose having $DP_n=65.4$), as exemplified by the detection of a
314 pseudo molecular ion peak ($[\text{M}+\text{Na}]^+$) with $m/z = 2323.797$. The expanded MALDI-TOF MS
315 spectra are shown in Figure S1. The reaction mechanism to synthesis propargyl tri-*O*-methyl
316 celloside (**3**) having one free C-4 hydroxyl group attached to the glucosyl residue at the
317 non-reducing end from tri-*O*-methyl cellulose (**1**) is illustrated in Scheme S1.

318

319 As shown in Figure 2C, the ^1H -NMR spectrum of propargyl tri-*O*-methyl celloside (**3**) showed
320 signals of alkyne and methylene protons of the propargyl group at 2.43 and 4.28–4.39 ppm,

respectively. In the corresponding ^{13}C -NMR spectrum (Figure 3C), the methylene carbons of the propargyl group appeared at 54.4 (CH_2CCH (C1- α)) and 55.6 ppm (CH_2CCH (C1- β)). Anomeric protons of the glucosyl residue at the reducing end of propargyl tri-*O*-methyl cellulose (**3**) appeared at 4.49 (H1- β) and 5.20 ppm (H1- α), as shown in Figure 2C. In addition, anomeric carbons of the glucosyl residue at the reducing end of propargyl tri-*O*-methyl cellulose (**3**) appeared at 94.5 (C1- α) and 100.7 ppm (C1- β), as shown in Figure 3C.

3.4. Control of molecular weight of cellulose ethers carrying two independent end-functional groups

The molecular weight of end-functionalized cellulose ethers influences the physical properties of block copolymers when they are used as one of the molecular Lego bricks. For instance, a well-defined diblock copolymer exhibits microphase separation (Kamitakahara, Baba, Yoshinaga, Suhara, & Takano, 2014), which has received considerable attention. Molecular lengths of the two segments usually affect microphase separation patterns of diblock copolymers, motivating us to explore reaction conditions for obtaining end-functionalized cellulose ethers with tailored molecular weights.

End-azidation of tri-*O*-methyl cellulose (**1**) was carried out with trimethylsilyl azide and SnCl_4 in anhydrous chloroform, with reaction conditions summarized in Table 1. The degree of polymerization of tri-*O*-methyl cellulose azide (**2**) decreased with increasing amounts of SnCl_4 . This result means that we are able to control the DP of tri-*O*-methyl cellulose azide (**2**). Actually, tri-*O*-methyl cellulose azide (**2**) having one free C-4 hydroxyl group attached to the glucosyl residue at the non-reducing end with DP from 20 to 81 was produced.

Table 1. Azido end-functionalization of tri-*O*-methyl cellulose (**1**).

entry	TMS- N_3 (equiv/AGU)	SnCl_4 (equiv./AGU)	$M_n/10^4$	M_w/M_n	DP_n
1	0.195	0.034	1.7	2.0	81
2	0.390	0.067	1.1	1.9	54
3	0.585	0.100	0.41	2.9	20

Moreover, end-propargylation of tri-*O*-methyl cellulose (**1**) was carried out with 2-propyne-1-ol and SnCl_4 in anhydrous dichloromethane, with reaction conditions summarized in Table 2. The DP of propargyl tri-*O*-methyl cellulose (**3**) decreased with increasing amounts of SnCl_4 . This result means that we are also able to control the DP of propargyl tri-*O*-methyl cellulose (**3**) having one free C-4 hydroxyl group attached to the glucosyl residue at the non-reducing end, producing the above compound with DP from 29 to 45.

Table 2. Propargyl end-functionalization of tri-*O*-methyl cellulose (**1**).

entry	2-propyn-1-ol (equiv./AGU)	SnCl ₄ (equiv./AGU)	$M_n/10^3$	M_w/M_n	DP_n
1	0.3	0.070	9.2	1.9	45
2	0.3	0.085	7.7	2.2	38
3	0.3	0.100	6.0	2.0	29

4. Conclusion

MALDI-TOF MS, ¹H- and ¹³C-NMR spectra confirm that the end-functionalization of fully methylated cellulose proceeded to afford cellulosic molecular rods carrying two independent end groups at the both ends of the molecules. Controlled degradation of the fully protected cellulose ethers by Lewis acid in presence of trimethylsilyl azide or propargyl alcohol produced tri-*O*-methyl cellulosyl azide (**2**) and propargyl tri-*O*-methyl cellulose (**3**) with tailored DP, respectively, having a free hydroxyl group at the C-4 position of the non-reducing glucopyranosyl residue. These methods furnished end-functionalized cellulose ethers as semi-rigid linear hydrophobic molecular Lego bricks with tunable degrees of polymerization. The free C-4 hydroxyl of the glucosyl residue at the non-reducing end could connect with other molecular bricks, thereby extending the variety of molecular architecture motifs. The developed chemistry will enable us to initiate a new era of precise block architecture of polysaccharide derivatives.

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Supporting Information

Reaction mechanisms of the tri-*O*-methyl cellulosyl azide (**2**) and propargyl tri-*O*-methyl cellulose (**3**) syntheses from tri-*O*-methyl cellulose (**1**) are illustrated in Scheme S1. MALDI-TOF MS spectra of tri-*O*-methyl cellulose (**1**), tri-*O*-methyl cellulosyl azide (**2**), and propargyl tri-*O*-methyl cellulose (**3**) in the region of $DP = 11$ are shown in Figure S1. MALDI-TOF MS spectra of tri-*O*-methyl cellulose (**1**) with a DP_n of 322, obtained using positive ion linear mode, are shown in Figure S2. Expanded ¹H- and ¹³C-NMR spectra of tri-*O*-methyl cellulose (**1**) ($DP_n = 322$), tri-*O*-methyl cellulosyl azide (**2**) ($DP_n = 27.5$), and propargyl tri-*O*-methyl cellulose (**3**) ($DP_n = 71.2$) in the anomeric proton region are shown in Figures S3 and S4, respectively.

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457

458

459 **Figure Captions**

460 **Scheme 1.** Synthesis of tri-*O*-methyl cellulose azide (**2**) and propargyl tri-*O*-methyl cellulose (**3**)
461 from tri-*O*-methyl cellulose (**1**).

462 **Figure 1.** MALDI-TOF MS spectra of (A) tri-*O*-methyl cellulose (**1**) ($DP_n = 322$), (B) tri-*O*-methyl
463 cellulose azide (**2**) ($DP_n = 27.5$), and (C) propargyl tri-*O*-methyl cellulose (**3**) ($DP_n = 13.2$).

464 **Figure 2.** ^1H -NMR spectra of (A) tri-*O*-methyl cellulose (**1**) ($DP_n = 322$), (B) tri-*O*-methyl
465 cellulose azide (**2**) ($DP_n = 27.5$), and (C) propargyl tri-*O*-methyl cellulose (**3**) ($DP_n = 71.2$).

466 **Figure 3.** ^{13}C -NMR spectra of (A) tri-*O*-methyl cellulose (**1**) ($DP_n = 322$), (B)
467 tri-*O*-methylcellulose azide (**2**) ($DP_n = 27.5$), and (C) propargyl tri-*O*-methyl cellulose (**3**) (DP_n
468 $= 71.2$).

469

470 **Table 1.** Azido end-functionalization of tri-*O*-methyl cellulose (**1**).

471 **Table 2.** Propargyl end-functionalization of tri-*O*-methyl cellulose (**1**).