

# Selective cross-metathesis of cellobiose derivatives with amido-functionalized olefinic structures: A model study for synthesis of cellulosic diblock copolymers



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## ABSTRACT

This work describes a model study for synthesis of cellulose-based block copolymers, investigating selective coupling of peracetyl  $\beta$ -D-cellobiose and perethyl  $\beta$ -D-cellobiose at their reducing-ends by olefin cross-metathesis (CM). Herein we explore suitable pairs of  $\omega$ -alkenamides that permit selective, quantitative coupling by CM. Condensation reactions of hepta-O-acetyl- $\beta$ -D-cellobiosylamine or hepta-O-ethyl- $\beta$ -D-cellobiosylamine with acyl chlorides afforded the corresponding *N*-( $\beta$ -D-cellobiosyl)- $\omega$ -alkenamide derivatives with an aromatic olefin or linear olefinic structures. Among the introduced olefinic structures, CM of the undec-10-enamide (Type I olefin) and the acrylamide (Type II olefin) gave the hetero-block tetramers, *N*-(hepta-O-ethyl- $\beta$ -D-cellobiosyl)-*N*-(hepta-O-acetyl- $\beta$ -D-cellobiosyl)-alkene- $\alpha,\omega$ -diamides, with >98 % selectivity. Moreover, selectivity was not influenced by the cellobiose substituents when a Type I olefin with a long alkyl tether was used. Although the amide carbonyl group could chelate the ruthenium atom and reduce CM selectivity, the results indicated that such chelation is suppressed by sterically hindered pyranose rings or the long alkyl chain between the amido group and the double bond. Based on this model study, selective end-to-end coupling of tri-O-ethyl cellulose and acetylated cellobiose was accomplished, proving the concept that this model study with cellobiose derivatives is a useful signpost for selective synthesis of polysaccharide-based block copolymers.

## 1. Introduction

This study explores pairs of olefinic structures for selective coupling between two polysaccharide derivatives by olefin cross-metathesis (CM) reaction. Cellobiose derivatives having  $\omega$ -alkenyl groups were selected as models to develop highly selective CM between polysaccharide derivatives affording diblock polysaccharide derivatives.

Cellose, among the most abundant natural polysaccharides, is generating considerable interest in sustainable materials applications (Klemm et al., 2005). As cellulose and its derivatives have a linear backbone, they are promising candidates for block copolymer synthesis. Since the 1960s, researchers have synthesized various cellulosic block copolymers from cellulose esters (Enomoto et al., 2006; Enomoto-Rogers et al., 2011; Katsuhara et al., 2021; Mezger & Cantow, 1983a, 1984, 1983b), cellulose ethers (Ceresa, 1961; Feger & Cantow, 1980; Lu et al.,

2019; Lu, Petit, Jelonek, et al., 2020; Lu, Petit, Wang, et al., 2020), and unsubstituted cellulose (Yagi et al., 2010).

One of the synthetic methods for polysaccharide (including cellulosic) block copolymers is end-to-end coupling of two building blocks (Schatz & Lecommandoux, 2010; Volokhova et al., 2020). In the case of coupling two polysaccharides, regioselective and high-yield reactions are necessary to prevent formation of side products or the presence of residual starting polymers that would be difficult to separate from the desired copolymer product, and thus would make it difficult to obtain a pure product quantitatively. Some strategies for precise end-to-end coupling have been adopted to synthesize cellulosic block copolymers. Nakagawa et al. developed methanolysis and the glycosylation reaction to connect the reducing-end of mono- or disaccharides and the nonreducing-end of tri-O-methyl cellulose (TMC) (Nakagawa et al., 2011). This method was applied to synthesize diblock copolymers

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composed of cellulose and starch derivatives (Sommer & Zollfrank, 2022). The Copper-catalyzed Azide-Alkyne Cycloaddition (CuAAC) has been successfully applied for selective syntheses of TMC-*b*-cellulose triacetate (CTA) copolymers (Nakagawa et al., 2012), CTA-*b*-poly(γ-benzyl-L-glutamate) copolymers (Kamitakahara et al., 2014), and some TMC-*b*-disaccharides (Yamagami et al., 2018).

Besides CuAAC, olefin cross-metathesis (CM) gives opportunities to synthesize polysaccharide-based diblock copolymers with precise bond formation between two blocks. Catalyzed by metal-alkylidene complexes, CM can rapidly couple two different olefinic compounds with good yield and selectivity (Grubbs et al., 2007). CM has been applied to functionalizing saccharides, and recently cellulose derivatives (Aljarilla et al., 2010; Arrington et al., 2019; Chatterjee et al., 2003; Dong et al., 2017). Edgar et al. introduced ω-alkenyl groups (CM reactivity is high, categorized Type I by Grubbs) to cellulose esters and ethers. The olefin-containing cellulose derivatives were then selectively coupled with various α,β-unsaturated carbonyl compounds (whose CM reactivity is moderate, categorized Type II by Grubbs), to afford functionalized cellulosic compounds including TMC-*b*-polyether and TMC-*b*-polyester (Chen et al., 2020; Dong et al., 2019; Dong & Edgar, 2015; Meng et al., 2014; Meng & Edgar, 2015; Novo et al., 2022). Such copolymers synthesized by CM possess a hydrophobic and flexible alkenyl chain between two blocks, in contrast to the chemical structures that result from CuAAC (which results in connection by a heterocyclic triazole). Therefore, CM is expected to afford a new class of cellulosic block copolymers with relatively flexible linkers between blocks.

Research on selective CM has mainly focused on small molecules, teaching us that it is important to choose pairs of reactants that possess different olefinic structures, most often one highly reactive (Type I) and one moderately reactive (Type II), so as to minimize self-metathesis (Chatterjee et al., 2003). A suitable pair of olefin-bearing polysaccharides could in principle produce copolymers comprising two polysaccharide blocks by CM, potentially with high yield and purity. When linear polysaccharide block copolymers are targeted, olefin-bearing substituents must be introduced selectively at polysaccharide termini, most often at the reducing-end because of its special (aldehyde) reactivity. We hypothesized that a series of reactions affording D-cellulosylamide would work well (Fig. 1A). Kamitakahara et al. selectively introduced an azido group at the reducing end of CTA. The azido groups were then reduced to amines and condensed with 15-azido-pentadecanoyl chloride to afford the corresponding azido-pendent amides. Repeating this cycle of reduction and condensation gave a series of CTA-*b*-oligoamide-15 copolymers (Kamitakahara et al., 2005; Kamitakahara & Nakatubo, 2005). We have also synthesized CTA end-functionalized with pyrene, and related model compounds (Enomoto et al., 2006;

Enomoto-Rogers et al., 2011). This method is applicable to introduction of various olefinic structures including α,β-unsaturated carbonyl compounds, which have never been introduced at the reducing-end of cellulose derivatives.

Despite the promise of this method, not only in the field of polysaccharide chemistry but also in oligosaccharide chemistry, no research has focused on selective CM of saccharides with ω-unsaturated carboxamides. A weak point of amido-functionalized olefins as CM substrates is the possibility of formation of cyclic chelates (Fig. 1B) that decrease Ru catalytic activity and CM selectivity (Choi et al., 2001; Meng & Edgar, 2015; Yun et al., 2011, 2012). Although this reduced selectivity can be improved by modifying the chemical structure around olefins or the reaction conditions, no one to the best of our knowledge has studied CM selectivity of *N*-(glycosyl)-ω-alkenamides and pairs of olefins that enable selective CM of such compounds.

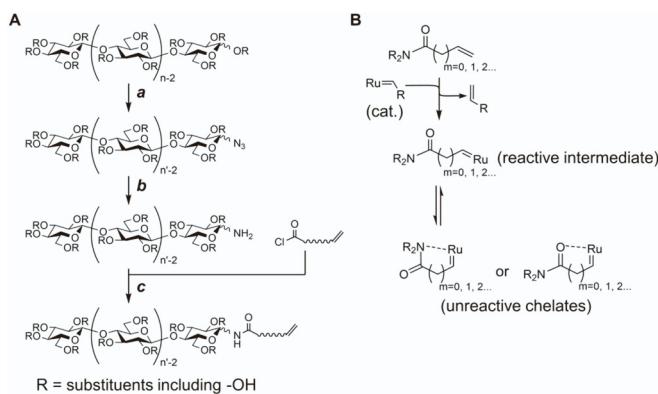
We seek to elucidate the CM selectivity of *N*-(cellulosyl)-ω-alkenamides and to design suitable pairs of olefinic structures for the selective synthesis of cellulosic diblock copolymers. To that end, we describe herein a study with cellobiose as a model. Since cellobiose, β-D-glucopyranosyl-(1 → 4)-D-glucose, has the same repeating unit and glycosidic bond as cellulose, it is reasonable to expect that CM selectivity of its derivatives may be similar to that of corresponding cellulose derivatives. On the other hand, the molecular weight of cellobiose is monodisperse and much lower than that of cellulose, meaning that its CM products can be isolated and analyzed more easily. This study therefore can provide fundamental knowledge for the combination of ω-alkenamides enabling highly selective CM to produce CM products with high yield.

We hypothesize that the undesired chelation of ω-alkenamides will be prevented by a pyranose ring near the amido group or chemical structures (such as an aromatic ring or long alkyl chain) between a double bond and an amido group. Their steric effects can prohibit an amido group from chelating to a ruthenium atom inserted into the double bond of the reaction intermediate (Fig. 1B). These structural modifications will result in highly selective CM between two different cellobiose derivatives. Based on previous research, we further hypothesize that cellobiose substituents will exert less influence on CM selectivity than will the pendent olefin (Aljarilla et al., 2010; Dong et al., 2019; Dong & Edgar, 2015; Meng & Edgar, 2015; Novo et al., 2022).

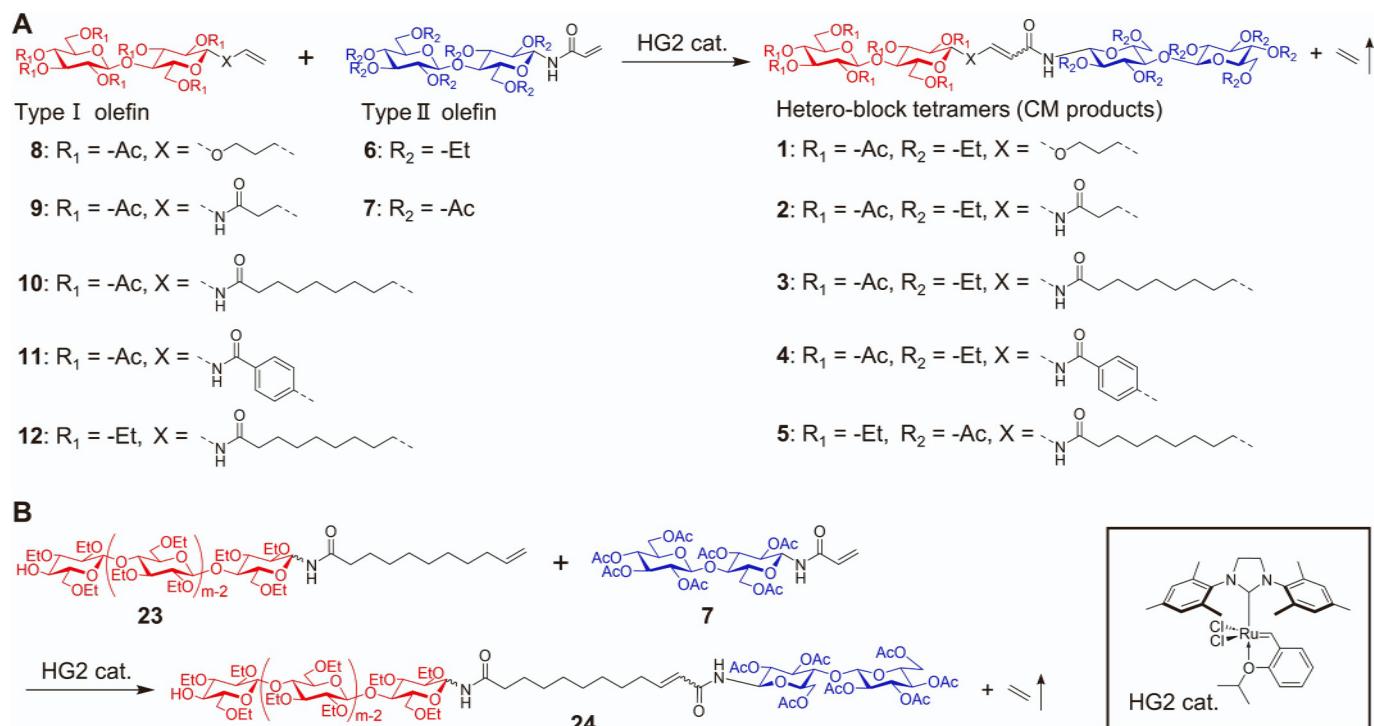
To test these hypotheses, we synthesized two *N*-(hepta-O-ethyl-β-D-cellobiosyl)-ω-alkenamides (compounds 6 and 12) and five *N*-(hepta-O-acetyl-β-D-cellobiosyl)-ω-alkenamides (compounds 7–11) as block components (Scheme 1A). Compounds 6 and 7 have acrylamide groups at their reducing-ends as the Type II olefin. The others have Type I olefins including the pent-4-enyl group (compound 8), the pent-4-enamide group (compound 9), the undec-10-enamide group (compounds 10 and 12), or the *p*-vinylbenzamido group (compound 11). We then compared CM selectivity during syntheses of five hetero-block tetramers composed of two different cellobiose components coupled in head-to-head fashion (Scheme 1A). One of the five hetero-block tetramers is the *N*-(hepta-O-ethyl-β-D-cellobiosyl)-6-((hepta-O-acetyl-β-D-cellobiosyl)oxy)-hex-2-enamide (1) and the others are *N*-(hepta-O-ethyl-β-D-cellobiosyl)-*N'*-(hepta-O-acetyl-β-D-cellobiosyl)-alkene-α,ω-diamides (compounds 2–5). Based on the model study above, we further attempted end-to-end coupling of tri-O-ethyl cellulose (TEC) and acetylated cellobiose via CM, synthesizing a diblock TEC analog (compound 24) (Scheme 1B). Using TEC as a block segment, we examined the possibility that the knowledge obtained from the model study with cellobiose can be applied to reactions involving polysaccharides.

## 2. Abbreviations

AC-X-Y refers to peracetyl cellobiose with terminally ω-unsaturated substituents at the reducing-end, where “X” denotes the linkage between cellobiose and ω-unsaturated substituents and “Y” denotes the terminally unsaturated functional group. Regarding X, “O” refers to the ether linkage, while “NHCO” refers to the amido linkage. If ω-unsaturated



**Fig. 1.** A) Synthetic approach to introduce olefin structures into reducing-ends of cellulose derivatives. B) Chelates of the reaction intermediate in cross-metathesis. a: introduction of azido group at reducing-end of cellobiose derivatives, b: reduction of azido to amine, c: condensation of amine and ω-alkenyl chloride.



**Scheme 1.** (A) Synthesis of hetero-block tetramers 1–5 composed of two different cellobiose derivatives coupled in head-to-head fashion. (B) End-to-end coupling of TEC derivative 23 and acetylated cellobiose 7.

substituent is a linear olefinic chain, “Y” is written as “C<sub>n</sub>” (n: chain length). The *p*-vinylbenzoyl group was indicated as “C<sub>v</sub>.” For example, AC-O-C5 refers to pent-4-enyl hepta-O-acetyl- $\beta$ -D-cellobioside (8), while AC-NHCO-C<sub>v</sub> refers to *N*-(hepta-O-acetyl- $\beta$ -D-cellobiosyl)-*p*-vinylbenzamide (11). EC-C<sub>n</sub> refers to perethyl cellobiose with terminally  $\omega$ -unsaturated carboxamides at the reducing-end, where “n” denotes the length of the terminally unsaturated chain. For example, EC-C3 refers to *N*-(hepta-O-ethyl- $\beta$ -D-cellobiosyl)-prop-2-enamide (6).

TEC-Z refers to end-functionalized TEC, where “Z” denotes the chemical structure at the reducing-end. Regarding Z, “N<sub>3</sub>”, “NH<sub>2</sub>”, and “C11” are assigned to azido, amino, and undec-10-enamide group, respectively. For example, TEC-C11 refers to *N*-(2,3,6-tri-O-ethyl-D-cellosyl)-undec-10-enamide (23).

Cross-metathesis and self-metathesis products are abbreviated like [AC-X-Y]-*b*-[EC-C<sub>n</sub>]. For example, [AC-O-C5]-*b*-[EC-C3] refers to the hetero-block tetramer of compounds 8 and 6 (compound 1). The CM product 24 from TEC-C11 and AC-NHCO-C3 is abbreviated as TEC-*b*-AC.

### 3. Experimental

#### 3.1. Materials

Cellobiose was purchased from Nacalai Tesque, Inc. Tin(IV) chloride (1.0 M in CH<sub>2</sub>Cl<sub>2</sub>) and Hoveyda-Grubbs catalyst 2nd generation (HG2, Umicore, M720) were purchased from Sigma-Aldrich. Ethyl cellulose (nominal viscosity, 90–110 cps for 5 % solution in 80:20 toluene/ethanol at 25 °C; DS(ethyl) = 2.51, determined by <sup>1</sup>H NMR; number-average molecular weight ( $M_n$ ) = 6.61 × 10<sup>4</sup>, molecular-weight dispersity ( $D$ ) = 2.13, determined by GPC), pent-4-en-1-ol, pent-4-en-1-enoic acid, *p*-vinylbenzoic acid, undec-10-enoic acid, trimethylsilyl azide (TMS-N<sub>3</sub>), sodium hydride (60 % dispersion in mineral oil), and trimethylsilyl trifluoromethanesulfonate (TMSOTf) were purchased from Tokyo Chemical Industry Co., Ltd. The other reagents were purchased from Nacalai Tesque, Inc. or FUJIFILM Wako Pure Chemical Corporation. All reagents were used as received.

Anhydrous dichloromethane (DCM, Super<sup>2</sup>) was purchased from

Kanto Chemical Co., Inc. The other solvents were purchased from either Nacalai Tesque, Inc. or FUJIFILM Wako Pure Chemical Corporation. Anhydrous DCM, anhydrous chloroform, anhydrous tetrahydrofuran (THF), and anhydrous dimethyl formamide (DMF) were used after column purification (Nikko Hansen & Co., Ltd., Glass Contour or Glass Contour mini). Dimethyl sulfoxide (DMSO) was dried over activated molecular sieves 3A (Nacalai Tesque, Inc.) before usage.

#### 3.2. Measurements

<sup>1</sup>H, <sup>13</sup>C, and 2D NMR spectra were recorded on a Varian 500 FT-NMR (500 MHz) or Varian INOVA300 FT-NMR (300 MHz) spectrometer in chloroform-*d* (CDCl<sub>3</sub>) with tetramethylsilane (TMS) as an internal standard, using pulse sequences for one- or two-dimensional spectra. Chemical shifts ( $\delta$ ) and coupling constants ( $J$ ) were given in ppm and Hz, respectively.

Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) spectra were recorded on a Bruker Autoflex III mass spectrometer in the positive ion. Reflector mode was used for cellobiose derivatives, and reflector or linear mode was used for cellulose derivatives. Peptide and protein standards (Bruker Corp.) were used as calibrations. 2,5-Dihydroxybenzoic acid (DHB) was used as a matrix.

Apparent values of molecular weight were obtained from gel permeation chromatography (GPC) in THF (KANTO Chemical Co., Inc.) with LC-10A system (Shimadzu Corp.), calibrated with polystyrene standards (TSK standard, Tosoh Corp.). GPC measurements were carried out at 40 °C and 0.2 mL/min flow rate on connected TSKgel SuperHZ3000, 2000, and 1000 (Tosoh Corp.) columns with refractive index detector Shodex RI-504 (Resonac Co., Ltd.).

#### 3.3. Synthesis and CM coupling of cellobiose and cellulose derivatives having olefinic structures at the reducing-end

Information about experimental details and assignments of NMR and MS resonances not mentioned in the body are shown in Section S1 of the

## Supporting information (SI).

3.3.1. (2,3,4,6-Tetra-O-acetyl- $\beta$ -D-glucopyranosyl)-(1  $\rightarrow$  4)-2,3,6-tri-O-acetyl- $\beta$ -D-glucopyranosylazide (14)

Compound **14** was synthesized according to the method in (Kamitakahara & Nakatsubo, 2005) with slight modifications. To a solution of acetyl (2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyl)-(1  $\rightarrow$  4)-2,3,6-tri-O-acetyl-D-glucopyranose (**13**) (Kamitakahara et al., 2006) (1.00 g, 1.47 mmol, 1.0 equiv.) in anhydrous CHCl<sub>3</sub> (5 mL), TMS-N<sub>3</sub> (0.289 mL, 2.21 mmol, 1.5 equiv.) and SnCl<sub>4</sub> (0.737 mL, 0.737 mmol, 0.5 equiv.) were added under N<sub>2</sub> atmosphere at 0 °C. The mixture was then stirred at ambient temperature ( $\approx$ 23 °C). After 19 h, TMS-N<sub>3</sub> (0.290 mL, 2.21 mmol, 1.5 equiv.) was added to the reaction mixture. After 30 h from the second addition of TMS-N<sub>3</sub>, the reaction mixture was extracted with CHCl<sub>3</sub>, washed with distilled water (DSW), saturated aq. NaHCO<sub>3</sub>, and brine, then dried with Na<sub>2</sub>SO<sub>4</sub>. Na<sub>2</sub>SO<sub>4</sub> was removed through filtration and the filtrate was concentrated, then dried in vacuo at room temperature (RT). The obtained crude crystals (0.900 g) were recrystallized from ethanol to give peracetyl  $\beta$ -D-cellobiosylazide **14** (colorless solid, 0.869 g, 1.31 mmol, 89.1 mol%).

3.3.2.  $\beta$ -D-Glucopyranosyl-(1  $\rightarrow$  4)- $\beta$ -D-glucopyranosylazide (15)

(Yamagami et al., 2018)

To a solution of peracetyl  $\beta$ -D-cellobiosylazide **14** (1.95 g, 2.94 mmol, 1.0 equiv.) in anhydrous THF (20 mL) and methanol (20 mL), 28 % NaOCH<sub>3</sub> (0.568 g, 2.94 mmol, 1.0 equiv.) was added, and the solution was stirred for 6.0 h under N<sub>2</sub> atmosphere at an ambient temperature. The reaction mixture was neutralized with AMBERLYST® 15DRY (ORGANO Corp.), filtered, and washed with THF. All organic phases were concentrated to dryness, dried in vacuo at 40 °C to give  $\beta$ -D-cellobiosylazide **15** (colorless solid, 1.07 g, 98.8 mol% yield). The product was directly used for the next reaction without further purification.

3.3.3. (2,3,4,6-Tetra-O-ethyl- $\beta$ -D-glucopyranosyl)-(1  $\rightarrow$  4)-2,3,6-tri-O-ethyl- $\beta$ -D-glucopyranosylazide (16)

To a solution of  $\beta$ -D-cellobiosylazide **15** (1.07 g, 2.90 mmol, 1.0 equiv.) in anhydrous DMF (30 mL), NaH (1.63 g, 40.7 mmol, 14 equiv.) was added, and the solution was stirred for at least 10 min under N<sub>2</sub> atmosphere at RT. C<sub>2</sub>H<sub>5</sub>I (3.29 mL, 40.7 mmol, 14 equiv.) was then added slowly, and the solution was stirred for 72 h at 30 °C. Excess NaH was quenched with methanol, and the reaction mixture was extracted with DCM. The organic layer was washed with DSW, saturated aq. NaHCO<sub>3</sub>, and brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Then, Na<sub>2</sub>SO<sub>4</sub> was filtered off, and the filtrate and washings were concentrated to dryness. The obtained crude product (yellow syrup, 2.11 g) was purified by column chromatography (eluent: *n*-hexane (*n*-Hex)/ethyl acetate (EtOAc) = 1/0  $\rightarrow$  3/1 (v/v)), to give perethyl  $\beta$ -D-cellobiosylazide **16** (yellow solid, 1.20 g, 2.13 mmol, 73.3 mol% yield).

3.3.4. 2,3,6-Tri-O-ethyl cellulose (TEC) (**26**) ( $M_n = 3.12 \times 10^4$ ,  $DP_n = 126.2$ ,  $D = 2.96$ )

Complete ethylation of commercial ethyl cellulose to afford compound **26** (71.7 wt%) was conducted through Williamson etherification with NaH and C<sub>2</sub>H<sub>5</sub>I carried out twice in succession, by a method analogous to that previously reported for the synthesis of TMC (Nakagawa et al., 2011) (Kamitakahara et al., 2016). See S1.20 in SI for a detailed procedure, assignments of <sup>1</sup>H, <sup>13</sup>C NMR resonances, and MALDI-TOF MS peaks.

3.3.5. 2,3,6-Tri-O-ethyl cellosylazide (TEC-N<sub>3</sub>) (**27**)

Azido end-functionalized TEC was synthesized by a method analogous to that previously used for end-functionalizing TMC (Kamitakahara et al., 2016). To a solution of TEC **26** (100 mg, 0.406 mmol of AGU) in anhydrous CHCl<sub>3</sub> (2.04 mL), TMS-N<sub>3</sub> (48.0  $\mu$ L, 0.362 mmol, 0.890 equiv./AGU) was added, then stirred for 30 min at 25 °C. SnCl<sub>4</sub> (54.0  $\mu$ L, 0.0540 mmol, 0.133 equiv./AGU) was then added to the solution

dropwise and stirred 4.0 h at 25 °C. After SnCl<sub>4</sub> was quenched with triethylamine (TEA), the reaction mixture was extracted with EtOAc. The organic layer was then washed with DSW, saturated aq. NaHCO<sub>3</sub>, and brine, then dried over Na<sub>2</sub>SO<sub>4</sub>. After Na<sub>2</sub>SO<sub>4</sub> was filtered off, the filtrate and washings were concentrated and dried in vacuo at RT, to give TEC-N<sub>3</sub> **27** (100 mg, quant. yield,  $M_n = 2.44 \times 10^3$ ,  $DP_n = 9.9$ ,  $D = 1.61$ ).

3.3.6. General procedure for synthesizing D-cellobiosylamine and D-cellosylamine derivatives (compounds **17**, **18**, and **28**), illustrated with (2,3,4,6-tetra-O-ethyl- $\beta$ -D-glucopyranosyl)-(1  $\rightarrow$  4)-2,3,6-tri-O-ethyl- $\beta$ -D-glucopyranosylamine (17)

Perethyl  $\beta$ -D-cellobiosylazide **16** (0.100 g, 0.178 mmol, 1.0 equiv.) was dissolved in a mixture of anhydrous THF (1.6 mL) and ethanol (0.4 mL). Then 10 % Pd/C (0.100 g) was added to the solution. The reaction mixture was stirred for 3.6 h under H<sub>2</sub> atmosphere at ambient temperature. The solution was filtered through Celite® and washed with excess DCM. The filtrate and washings were concentrated and dried in vacuo at 23–30 °C, to give perethyl  $\beta$ -D-cellobiosylamine **17** (colorless solid, 0.0912 g, 0.170 mmol, 95.5 mol% yield). Peracetyl  $\beta$ -D-cellobiosylamine **18** and TEC-NH<sub>2</sub> **28** were synthesized by equivalent procedures (S1.5. and S1.22. in the SI).

3.3.7. General procedure for introducing  $\omega$ -unsaturated structures at the reducing-ends of cellobiose and cellulose derivatives, illustrated with EC-C3 6

To a solution of perethyl  $\beta$ -D-cellobiosylamine **17** (0.126 g, 0.235 mmol, 1.0 equiv.) in anhydrous DCM (5.0 mL), TEA (65.5  $\mu$ L, 0.470 mmol, 2.0 equiv.) was added and stirred for 18 min at 0 °C (ice bath). Acryloyl chloride (29.0  $\mu$ L, 0.357 mmol, 1.5 equiv.) was then added slowly, and the solution was stirred under N<sub>2</sub> for 10 min at 0 °C and for 3.3 h at RT. The reaction mixture was extracted with DCM, washed with DSW and brine, then dried over Na<sub>2</sub>SO<sub>4</sub>. Na<sub>2</sub>SO<sub>4</sub> was filtered off and the filtrate and washings were concentrated to dryness, then dried in vacuo. The obtained crude product (0.139 g) was purified by Pure C-815 Flash chromatography system (Büchi, silica, eluent: *n*-Hex and EtOAc, gradient) to give EC-C3 **6** (0.081 mg, 0.235 mmol, 58.3 mol% yield). Similar procedures were employed for preparing AC-NHCO-C3 **7**, AC-NHCO-C5 **9**, AC-NHCO-C11 **10**, AC-NHCO-Cv **11**, and EC-C11 **12** (S1.6.–S1.10. in SI). *N*-(2,3,6-Tri-O-ethyl-cellulosyl)-undec-10-enamide (**23**) (TEC-C11) was also synthesized using similar procedures but was purified by gel filtration chromatography (Sephadex™ LH-20, eluent: 20 vol% methanol in DCM) (S1.23. in SI).

*N*-(2,3,6-Tri-O-ethyl-4-O-(2,3,4,6-tetra-O-ethyl- $\beta$ -D-glucopyranosyl)- $\beta$ -D-glucopyranosyl)-prop-2-enamide (**6**) (EC-C3)

TLC:  $R_f = 0.53$  (eluent: *n*-Hex/EtOAc = 1/2 (v/v));

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 6.31 (dd,  $J = 17.0$ ,  $J = 1.1$ , 1H, NHCOCHCH<sub>2</sub> (trans)), 6.08 (dd,  $J = 17.0$ ,  $J = 10.3$ , 1H, NHCOCHCH<sub>2</sub>), 6.00 (d,  $J_{NH,1} = 9.6$ , 1H, NHCOCHCH<sub>2</sub>), 5.70 (dd,  $J = 10.3$ ,  $J = 1.1$ , 1H, NHCOCHCH<sub>2</sub> (cis)), 5.14 (t,  $J = J_{1,2} = 9.3$ , 1H, H1), 4.29 (d,  $J_{1',2'} = 7.8$ , 1H, H1'), 4.00 (dt,  $J = 15.8$ , 7.1, 1H, CH<sub>2</sub>CH<sub>3</sub>), 3.90–3.41 (m, 20H, H4, H3, H5, H6a, H6b, H6a', H6b', CH<sub>2</sub>CH<sub>3</sub>), 3.33 (t,  $J_{3',2'} = J_{3',4'} = 9.3$ , 1H, H3'), 3.20 (ddd,  $J_{5',4'} = 7.8$ ,  $J_{5',6a'} = 3.6$ ,  $J_{5',6b'} = 1.8$ , 1H, H5'), 3.16 (t,  $J = J = 8.9$ , 1H, H4'), 3.12 (t,  $J = J_{2,3} = 8.8$ , 1H, H2), 3.00 (t,  $J = J = 8.5$ , 1H, H2'), 1.24–1.12 (m, 21H, CH<sub>2</sub>CH<sub>3</sub>);

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 165.4 (NHCOCHCH<sub>2</sub>), 130.8 (NHCOCHCH<sub>2</sub>), 127.7 (NHCOCHCH<sub>2</sub>), 103.2 (C1'), 85.2 (C4'), 83.6 (C3), 82.4 (C2), 80.9 (C2), 79.2 (C1), 77.8 (C3'), 77.4 (C5), 77.0 (C4), 75.1 (C5'), 69.3, 68.9, 68.6, 68.4, 68.3, 68.0, 67.8, 66.9, 66.6 (C6, C6', CH<sub>2</sub>CH<sub>3</sub>), 16.0, 15.9, 15.8, 15.7, 15.3 (CH<sub>2</sub>CH<sub>3</sub>);

MALDI-TOF MS: calcd. for C<sub>29</sub>H<sub>53</sub>NO<sub>11</sub>, 591.362; found, [M + Na]<sup>+</sup> = 615.763.

**3.3.8. Pent-4-enyl 2,3,6-tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyl)- $\beta$ -D-glucopyranoside (8) (AC-O-C5) (Kamitakahara et al., 2012; Kamitakahara et al., 2007)**

(2,3,4,6-Tetra-O-acetyl- $\beta$ -D-glucopyranosyl)-(1 → 4)-2,3,6-tri-O-acetyl- $\alpha$ -D-glucopyranosyl-2,2,2-trichloroacetimidate (20) (Kamitakahara et al., 2012; Tietze et al., 2009) (88.5 mg, 0.114 mmol, 1.0 equiv.) was dried in vacuo overnight. Activated molecular sieves 4A (0.406 g) and anhydrous DCM (4.0 mL) were added to a flask under N<sub>2</sub> and cooled to 0 °C. Pent-4-en-1-ol (0.227 mL, 2.27 mmol, 20 equiv.) was added to the solution and stirred for 1.4 h at 0 °C. TMSOTf (5.1  $\mu$ L, 0.0282 mmol, 0.25 equiv.) was then added dropwise, and stirred for 25.4 h at 0 °C. The reaction mixture was filtered through Celite®, which was washed with excess EtOAc. The filtrate and washings were washed with saturated aq. NaHCO<sub>3</sub>, DSW, and brine, then dried over Na<sub>2</sub>SO<sub>4</sub>. Then Na<sub>2</sub>SO<sub>4</sub> was filtered off, and the filtrate and washings were concentrated to dryness, then dried in vacuo at 50–55 °C. The obtained crude product (0.0958 g) was purified by four repetitions of preparative thin layer chromatography (PTLC) (1st: eluent: *n*-Hex/EtOAc = 1/1 (v/v), 2nd–4th: eluent: *n*-Hex/EtOAc = 3/1 (v/v)), to give AC-O-C5 8 (0.0284 g, 0.0403 mmol, 35.5 mol%).

**3.3.9. Typical procedure for cross-metathesis (CM) of two cellobiose derivatives producing hetero-block tetramers, illustrated with [AC-NHCO-C5]-b-[EC-C3] 2**

All instruments and materials used below were dried overnight in vacuo at RT. AC-NHCO-C5 9 (10.0 mg, 0.014 mmol, 1.0 equiv.) and BHT (1.3 mg, 10 wt% of total olefins) were dissolved in anhydrous DCM (0.2 mL) and heated to 30 °C under N<sub>2</sub>. Solutions of EC-C3 6 (11.5 mg, 0.020 mmol, 1.4 equiv.) and HG2 (1.3 mg, 0.0021 mmol, 0.15 equiv.) in dry DCM (0.2 mL) were separately prepared, having been sonicated for a few tens of seconds. To the solution of Type I olefin 9 and BHT, the solution of Type II olefin 6 was added, and the solution stirred 10 min under N<sub>2</sub> at 30 °C. The solution of HG2 was then added slowly, and the reaction mixture was stirred for 9.0 h at 35 °C. The reaction was terminated by adding excess ethyl vinyl ether. The reaction mixture was concentrated to dryness, then dried in vacuo at RT. The obtained crude product was purified by Pure C-815 Flash chromatography system (silica, eluent: *n*-Hex and 20 vol% ethanol in EtOAc, gradient), to give mixture of CM product 2 and self-metathesis (SM) by-product 22 (total mass: 0.0117 g, CM: 58.0 mol% yield, CM/SM = 89/11 (mol/mol) from <sup>1</sup>H NMR). Similar procedures were employed for preparing [AC-O-C5]-b-[EC-C3] (compound 1), [AC-NHCO-C11]-b-[EC-C3] (compound 3), [AC-NHCO-Cv]-b-[EC-C3] (compound 4), and [AC-NHCO-C3]-b-[EC-C11] (compound 5) (S1.14.–S1.17. in SI).

**Note:** NMR resonances derived from protons or carbons of four pyranose rings are distinguished as follows. Protons and carbons of the reducing-end or the non-reducing-end pyranose ring of Type I olefin-containing cellobiose derivatives are described with no symbol (e.g., H1), or with the single prime (e.g., H1'). Regarding Type II olefin-bearing cellobiose segments, protons and carbons of the reducing-end or the non-reducing-end pyranose ring are described with the double prime (e.g., H1'') or the triple prime (e.g., H1''').

(*E*)-*N*<sup>1</sup>-(2,3,4,6-Tetra-O-ethyl- $\beta$ -D-glucopyranosyl)-(1 → 4)-2,3,6-tri-O-ethyl- $\beta$ -D-glucopyranosyl)-*N*<sup>6</sup>-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyl)-(1 → 4)-2,3,6-tri-O-acetyl- $\beta$ -D-glucopyranosyl)-hex-2-ene-1,6-diamide ([AC-NHCO-C5]-b-[EC-C3]) (2)

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  = 6.81 (dt, *J* = 15.2, 6.6, 1H, NHCOCH<sub>2</sub>CH<sub>2</sub>CHCHCONH), 6.21–6.17 (m, 2H, NHCOCH<sub>2</sub>CH<sub>2</sub>CHCHCONH, NHCOCH<sub>2</sub>CH<sub>2</sub>CHCHCONH), 5.76 (d, *J* = 15.4, 1H, NHCOCH<sub>2</sub>CH<sub>2</sub>CHCHCONH), 5.31–5.04 (m, 5H, H3, H1, H1'', H3', H4'), 4.93 (m, 1H, H2'), 4.81 (t, *J*<sub>2,1</sub> = *J*<sub>2,3</sub> = 9.6, 1H, H2), 4.55–4.45 (m, 2H, H1', H6), 4.38 (dd, *J*<sub>6,6'</sub> = 12, *J*<sub>6,5'</sub> = 4.2, 1H, H6'), 4.29 (d, *J*<sub>1'',2''</sub> = 7.9, 1H, H1''), 4.15–3.93 (m, 3H, H6, H6', 1/2 CH<sub>2</sub>CH<sub>3</sub>), 3.87–3.29 (m, 24H, 13/2 CH<sub>2</sub>CH<sub>3</sub>, 2 H6'', 2 H6'', H4'', H4, H5, H5', H5'', H3'', H3'''), 3.21–3.09 (m, 3H, H5'', H4'', H2''), 2.99 (t, *J*<sub>2'',1''</sub> = *J*<sub>2'',3''</sub> = 8.5, 1H, H2''), 2.48 (t, *J* = 6.7 Hz, 1H, NHCOCH<sub>2</sub>CH<sub>2</sub>CHCHCONH), 2.37–2.24 (m, 2H,

NHCOCH<sub>2</sub>CH<sub>2</sub>CHCHCONH), 2.20–1.93 (m, 21H, COCH<sub>3</sub>), 1.28–1.05 (m, 21H, 7CH<sub>2</sub>CH<sub>3</sub>);

**<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):**  $\delta$  = 171.7 (NHCOCH<sub>2</sub>CH<sub>2</sub>CHCHCONH), 170.6, 170.5, 170.4, 169.4, 169.1 (COCH<sub>3</sub>), 165.5 (NHCOCH<sub>2</sub>CH<sub>2</sub>CHCHCONH), 143.5 (NHCOCH<sub>2</sub>CH<sub>2</sub>CHCHCONH), 124.6 (NHCOCH<sub>2</sub>CH<sub>2</sub>CHCHCONH), 103.1 (C1''), 100.8 (C1'), 85.1 (C4''), 83.8 (C3''), 82.4 (C2''), 80.9 (C2''), 79.2 (C1''), 78.3 (C1), 77.8 (C3''), 77.0 (C5''), 76.3 (C4 or C5), 75.0 (C5''), 74.7 (C5 or C4), 73.0 (C3'), 72.1 (C3 and C5'), 71.7 (C2'), 71.1 (C2), 69.3, 68.9, 68.7, 68.4, 68.3, 68.1, 67.9, 66.9, 66.5 (7-CH<sub>2</sub>CH<sub>3</sub>, C6'', C6'', C4'), 61.7 (C6 and C6'), 34.7 (NHCOCH<sub>2</sub>CH<sub>2</sub>CHCHCONH), 27.0 (NHCOCH<sub>2</sub>CH<sub>2</sub>CHCHCONH), 21.0, 20.8, 20.7 (COCH<sub>3</sub>), 16.0, 15.8, 15.7, 15.3 (CH<sub>2</sub>CH<sub>3</sub>);

**MALDI-TOF MS:** calcd. for C<sub>58</sub>H<sub>92</sub>N<sub>2</sub>O<sub>29</sub>, 1280.579; found, [M + Na]<sup>+</sup> = 1303.584, [M + K]<sup>+</sup> = 1319.527.

**3.3.10. CM between TEC-C11 23 and AC-NHCO-C3 7 affording (E)-*N*<sup>1</sup>-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyl)-(1 → 4)-2,3,6-tri-O-acetyl- $\beta$ -D-glucopyranosyl)-*N*<sup>12</sup>-(2,3,6-tri-O-ethyl-cellulosyl)-dodec-2-ene-1,12-diamide (24)**

All instruments and materials used below were dried overnight in vacuo at RT. AC-NHCO-C3 7 (18.1 mg, 0.0262 mmol, 7.0 equiv.), TEC-C11 23 ( $M_n$  = 2.45 × 10<sup>3</sup>, *D* = 1.77, 9.3 mg, 3.8  $\mu$ mol, 1.0 equiv.), and BHT (2.7 mg, 10 wt% of total olefins) were dissolved in anhydrous DCM (0.4 mL), sonicated for 10 s, and heated to 35 °C for 10 min under N<sub>2</sub>. A solution of HG2 in anhydrous DCM (5.54 mM) was separately prepared and sonicated for 10 s. To the solution of saccharides and BHT, the solution of HG2 (0.2 mL, 0.7 mg of HG2, 1.1  $\mu$ mol, 0.28 equiv.) was added slowly, and the reaction mixture was stirred for 24 h at 35 °C. The reaction was terminated by adding excess ethyl vinyl ether. The reaction mixture was concentrated to dryness, then dried in vacuo at RT. The obtained crude product was purified by gel filtration chromatography (Sephadex<sup>TM</sup> LH-60, eluent: 20 vol% MeOH in DCM), to give TEC-b-AC 24 ( $M_n$  = 6.51 × 10<sup>3</sup>, *D* = 1.37, 3.0 mg).

**Note:** <sup>1</sup>H and <sup>13</sup>C NMR resonances derived from TEC derivatives were assigned like “H1[X]” or “C1[X],” where X indicates the position of AGU units having the proton or carbon. Regarding [X], the AGU units at the non-reducing-end, internal AGU units, and the AGU unit at the reducing-end were denoted as [A], [B], and [C], respectively. For TEC-b-AC, NMR resonances derived from the AGU units at the reducing-end and non-reducing-end of the acetylated cellobiose segment were described with symbols [D] and [E], respectively. Refer to Fig. 5C and D for the chemical structures.

**<sup>1</sup>H NMR (500 MHz)**  $\delta$  = 6.91–6.80 (dt, *J* = 15.2, 6.9, NHCO(CH<sub>2</sub>)<sub>8</sub>CHCHCONH), 6.14 (d, *J*<sub>NH-1</sub> = 9.3, NH-C1[D]), 5.85 (d, *J*<sub>NH-1</sub> = 9.6, NH-C1[C]), 5.69 (*J* = 14.9, d, NHCO(CH<sub>2</sub>)<sub>8</sub>CHCHCONH), 5.25–5.32 (m, H1[D], H3[D]), 5.13 (t, *J*<sub>3,4</sub> = *J*<sub>2,3</sub> = 9.3, H3[E]), 5.11–5.01 (m, H4 [E], H1[C]), 4.93 (dd, *J*<sub>1,2</sub> = 8.0, H2[E]), 4.86 (t, *J*<sub>2,3</sub> = 9.6, H2[D]), 4.50 (d, H1[E]), 4.46 (d, *J*<sub>6,6</sub> = 11.6, H6[D]), 4.42 (d, *J*<sub>1,2</sub> = 7.9, H1 [A]), 4.36–4.39 (H6[E]), 4.34 (d, *J*<sub>1,2</sub> = 7.8, H1[B]), 4.14 (dd, *J*<sub>6,5</sub> = 4.0, *J*<sub>6,6</sub> = 12.1, H6[D]), 4.05 (dd, *J*<sub>6,5</sub> = 2.2, *J*<sub>6,5</sub> = 12.4, H6[E]), 3.42–4.01 (m, CH<sub>2</sub>CH<sub>3</sub>, H4[A–D], H5[D & E], H6[A–C]), 3.38 (t, *J*<sub>2,3</sub> = 8.9, H3[C]), 3.31–3.34 (m, H5[A]), 3.14–3.22 (m, H3[A & B], H5[B]), 2.96–3.07 (m, H2[A–C]), 1.98–2.12 (m, COCH<sub>3</sub>, NHCOCH<sub>2</sub>(CH<sub>2</sub>)<sub>6</sub>CH<sub>2</sub>CHCHCONH), 1.38–1.43 (m, NHCO(CH<sub>2</sub>)<sub>6</sub>CH<sub>2</sub>CH<sub>2</sub>CHCHCONH), 1.12–1.27 (m, NHCO(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>4</sub>(CH<sub>2</sub>)<sub>2</sub>C<sub>2</sub>H<sub>4</sub>CONH, CH<sub>2</sub>CH<sub>3</sub>);

**<sup>13</sup>C NMR (125 MHz)**  $\delta$  = 103.0 (C1[A & B]), 100.8 (C1[E]), 83.7 (C3 [B]), 82.1 (C2[B]), 78.5 (C1[D]), 75.4 (C5[B]), 68.5 and 68.4 (CH<sub>2</sub>CH<sub>3</sub>), 68.1 (C4[E]), 66.6 (C6[A–C]), 61.8 (C6[E]), 62.2 (C6[D]), 29.3 (NHCO(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>4</sub>(CH<sub>2</sub>)<sub>2</sub>C<sub>2</sub>H<sub>4</sub>CONH), 20.9, 20.8, and 20.7 (COCH<sub>3</sub>), 15.8, and 15.4 (CH<sub>2</sub>CH<sub>3</sub>);

**MALDI-TOF MS (positive linear mode; DHB as matrix):**

calcd. for C<sub>110</sub>H<sub>188</sub>N<sub>2</sub>O<sub>49</sub> (DP = 8, 6 + 2), 2322.679; found [M + Na]<sup>+</sup> = 2347.483,

C<sub>122</sub>H<sub>210</sub>N<sub>2</sub>O<sub>54</sub> (DP = 9, 7 + 2), 2568.982; found [M + Na]<sup>+</sup> = 2593.858,

$C_{134}H_{232}N_2O_{59}$  (DP = 10, 8 + 2), 2815.285; found  $[M + Na]^+ = 2840.224$ ,

$C_{146}H_{254}N_2O_{64}$  (DP = 11, 9 + 2), 3061.588; found  $[M + Na]^+ = 3086.547$ ,

$C_{158}H_{276}N_2O_{69}$  (DP = 12, 10 + 2), 3307.891; found  $[M + Na]^+ = 3332.868$ ,

$C_{170}H_{298}N_2O_{74}$  (DP = 13, 11 + 2), 3554.194; found  $[M + Na]^+ = 3579.130$ ,

$C_{182}H_{320}N_2O_{79}$  (DP = 14, 12 + 2), 3800.497; found  $[M + Na]^+ = 3825.403$ ,

$C_{194}H_{342}N_2O_{84}$  (DP = 15, 13 + 2), 4046.800; found  $[M + Na]^+ = 4071.622$ ,

$C_{206}H_{364}N_2O_{89}$  (DP = 16, 14 + 2), 4293.103; found  $[M + Na]^+ = 4317.870$ ,

$C_{218}H_{386}N_2O_{94}$  (DP = 17, 15 + 2), 4539.406; found  $[M + Na]^+ = 4564.058$ ,

$C_{230}H_{408}N_2O_{99}$  (DP = 18, 16 + 2), 4785.709; found  $[M + Na]^+ = 4810.288$ ,

$C_{242}H_{430}N_2O_{104}$  (DP = 19, 17 + 2), 5032.012; found  $[M + Na]^+ = 5056.471$ ,

$C_{254}H_{452}N_2O_{109}$  (DP = 20, 18 + 2), 5278.315; found  $[M + Na]^+ = 5302.715$ ,

$C_{266}H_{474}N_2O_{114}$  (DP = 21, 19 + 2), 5524.618; found  $[M + Na]^+ = 5548.866$ ,

$C_{278}H_{496}N_2O_{119}$  (DP = 22, 20 + 2), 5770.921; found  $[M + Na]^+ = 5795.069$ ,

$C_{290}H_{518}N_2O_{124}$  (DP = 23, 21 + 2), 6017.224; found  $[M + Na]^+ = 6041.165$ ,

$C_{302}H_{540}N_2O_{129}$  (DP = 24, 22 + 2), 6263.527; found  $[M + Na]^+ = 6287.380$ ,

$C_{314}H_{562}N_2O_{134}$  (DP = 25, 23 + 2), 6509.830; found  $[M + Na]^+ = 6533.526$ ,

$C_{326}H_{584}N_2O_{139}$  (DP = 26, 24 + 2), 6756.133; found  $[M + Na]^+ = 6779.646$ ,

$C_{338}H_{606}N_2O_{144}$  (DP = 27, 25 + 2), 7002.436; found  $[M + Na]^+ = 7025.519$ ,

$C_{350}H_{628}N_2O_{149}$  (DP = 28, 26 + 2), 7248.739; found  $[M + Na]^+ = 7271.569$ ,

$C_{362}H_{650}N_2O_{154}$  (DP = 29, 27 + 2), 7495.042; found  $[M + Na]^+ = 7517.849$ ,

$C_{374}H_{672}N_2O_{159}$  (DP = 30, 28 + 2), 7741.345; found  $[M + Na]^+ = 7763.615$ .

$C_{386}H_{694}N_2O_{164}$  (DP = 31, 29 + 2), 7982.603; found  $[M + Na]^+ = 8010.305$ ,

$C_{398}H_{716}N_2O_{169}$  (DP = 32, 30 + 2), 8233.951; found  $[M + Na]^+ = 8255.251$ ,

$C_{410}H_{738}N_2O_{174}$  (DP = 33, 31 + 2), 8480.254; found  $[M + Na]^+ = 8502.472$ ,

$C_{422}H_{760}N_2O_{179}$  (DP = 34, 32 + 2), 8726.557; found  $[M + Na]^+ = 8748.441$ ,

$C_{434}H_{782}N_2O_{184}$  (DP = 35, 33 + 2), 8972.860; found  $[M + Na]^+ = 8994.704$ ,

$C_{446}H_{804}N_2O_{189}$  (DP = 36, 34 + 2), 9219.163; found  $[M + Na]^+ = 9241.426$ ,

$C_{458}H_{826}N_2O_{194}$  (DP = 37, 35 + 2), 9465.466; found  $[M + Na]^+ = 9485.179$ ,

$C_{470}H_{848}N_2O_{199}$  (DP = 38, 36 + 2), 9711.769; found  $[M + Na]^+ = 9730.591$ ,

$C_{482}H_{870}N_2O_{204}$  (DP = 39, 37 + 2), 9958.572; found  $[M + Na]^+ = 9976.060$ ,

$C_{494}H_{892}N_2O_{209}$  (DP = 40, 38 + 2), 10,204.375; found  $[M + Na]^+ = 10,224.284$ .

## 4. Results and discussion

### 4.1. Selection of olefinic structures and substituents for investigation of CM selectivity

To the best of our knowledge, there has been no report describing the investigation of CM selectivity of *N*-(glycosyl)- $\omega$ -alkenamides or the structural factors that impact such selectivity. As shown in **Scheme 2A–C**, we selected four Type I olefin structures (pent-4-enyl, pent-4-enamide, undec-10-enamide, and *p*-vinylbenzamido), and one acrylamide (prop-2-enamide) group as Type II. Regarding substituents of cellobiose derivatives, acetyl and ethyl groups were selected in this study. We sought thereby to elucidate the structural effects of olefins and substituents of cellobiose on CM selectivity.

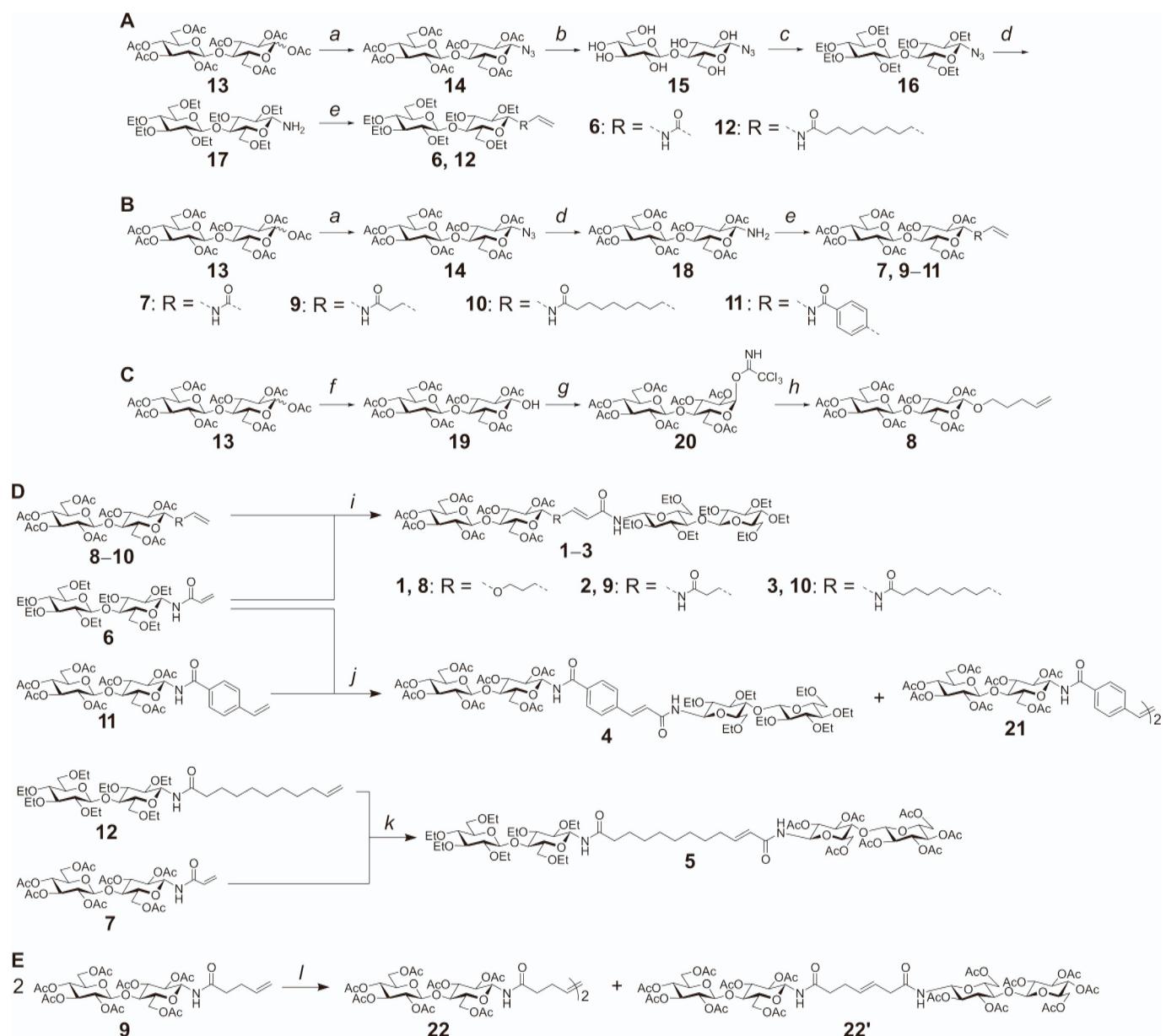
The Type II acrylamide was used to synthesize compounds **6** and **7**.  $\alpha,\beta$ -Unsaturated acrylamide has been shown to selectively couple with Type I olefins attached to the end or side of some polymers (Dong et al., 2017). The pent-4-enyl and pent-4-enamide groups were selected to compare CM selectivity of the cellobiosylamide (AC-NHCO-C5 **9**) with that of the corresponding cellobioside (AC-O-C5 **8**). They have the same  $\omega$ -alkenyl structures, differing only in the linking groups between the olefin and the pyranose ring reducing-end (**8**: ether, **9**: amide). Since pent-4-enyl groups at the end or side of cellulose derivatives selectively couple some  $\alpha,\beta$ -unsaturated carbonyl compounds (Chen et al., 2020; Dong & Edgar, 2015), compound **8** should have high CM selectivity. Therefore, we can discuss the influence of cellobiosylamide on CM selectivity by comparing the syntheses of CM products **1** and **2**. Because of the potential for chelation between carboxamide and ruthenium atom, CM selectivity of compound **9** may be lower than that of compound **8**.

Besides compound **9**, we synthesized AC-NHCO-C11 **10** to evaluate the influence of the length of the linear Type I olefin on the CM selectivity of the cellobiosylamide. When a double bond is distant from an amido group, the ruthenium atom of the reaction intermediate cannot approach the amide carbonyl closely enough to be coordinated (Fig. 1B). The rate of chelation thus may decrease and CM selectivity of compound **10** may be higher than that of compound **9**. AC-NHCO-Cv **11** was also selected to investigate the effect of rigidity between a double bond and an amide carbonyl group on CM selectivity. The rigid aromatic ring of the *p*-vinylbenzamido group may prohibit Ru chelation by the amide carbonyl, resulting in high CM selectivity.

We also evaluated the reactivity of cellobiosylamides with the acrylamide group (compounds **6**, **7**) or the undec-10-enamide group (compounds **10**, **12**), containing either electron-withdrawing acetyl ester substituents (compounds **7**, **10**) or electron-donating ethyl ethers (compounds **6**, **12**). These substituents are prominent in industrially important cellulose acetate and ethyl cellulose, but they differently affect the outcome of glycosylation reactions. In glycosylation with 4-pentenyl glycosides, Fraser-Reid et al. reported that glycosyl donors having an ether-protecting group at the C2 position showed higher reactivity than those having an ester-protecting group at the same position (Fraser-Reid & Lopez, 2010, 2011; Mootoo et al., 1988). It was also reported that  $\beta$ -selectivity of a glycosylation reaction was reduced by electron-withdrawing substituents when the glycosyl acceptor had weak nucleophilicity (van der Vorm et al., 2019). Therefore, we can predict the impact of cellulose electron-withdrawing vs. -donating substituents upon the outcome of CM reactions by comparing synthesis of [AC-NHCO-C11]-*b*-[EC-C3] **3** with that of [AC-NHCO-C3]-*b*-[EC-C11] **5**.

### 4.2. Introduction of olefinic structures into the reducing-end of cellobiose derivatives

*N*-(Hepta-O-acetyl- $\beta$ -D-cellobiosyl)- $\omega$ -alkenamides (compounds **7**, **9–11**) and *N*-(hepta-O-ethyl- $\beta$ -D-cellobiosyl)- $\omega$ -alkenamides (compounds **6** and **12**) were synthesized according to the routes shown in **Scheme 2A** and **B**, respectively. NMR analyses revealed successful



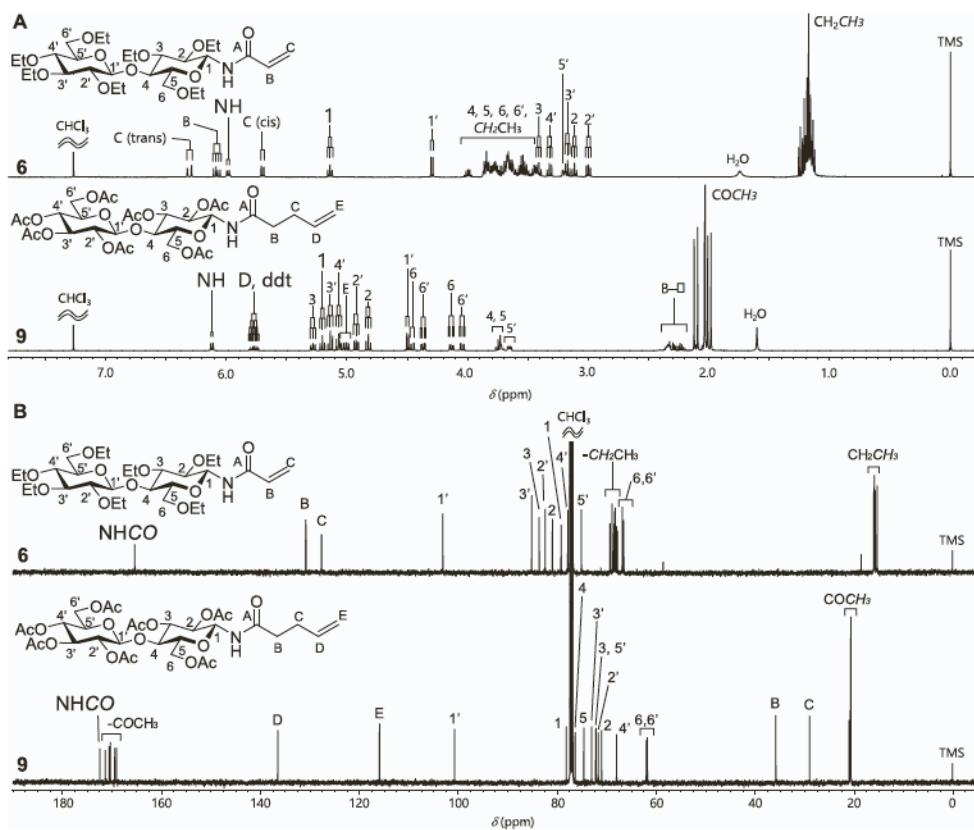
**Scheme 2.** Synthetic routes for hetero-block tetramers 1–5. (A–C): Introduction of olefinic structures at the reducing-end of ethylated cellobiosylamide 6 and 12 (A), acetylated cellobiosylamide 7 and 9–11 (B), and acetylated cellobioside 8 (C). (D): Cross-metathesis reactions for compounds 1–5. (E): Self-metathesis reaction of compound 9.

Reagents and conditions: a) TMS-N<sub>3</sub>/SnCl<sub>4</sub>/dry CHCl<sub>3</sub>/RT/24 h/89.1 mol%; b) NaOCH<sub>3</sub>/dry THF/CH<sub>3</sub>OH/RT/6.0 h/98.8 mol%; c) C<sub>2</sub>H<sub>5</sub>I/NaH/dry DMF/30 °C/72 h/73.0 mol%; d) 10 % Pd on C/H<sub>2</sub> gas/dry THF/C<sub>2</sub>H<sub>5</sub>OH/RT/4.4 h/quantitative yield; e) acyl chlorides/TEA/dry CH<sub>2</sub>Cl<sub>2</sub>/10 °C-RT/1.7–118 h/34.8–75.3 mol%; f) N<sub>2</sub>H<sub>4</sub>·HOAc/dry THF/RT/9.0 h/99.0 mol%; g) CCl<sub>3</sub>CN/DBU/dry CH<sub>2</sub>Cl<sub>2</sub>/0 °C/3.5 h/quantitative yield; h) pent-4-en-1-ol/TMSOTf/MS 4 Å/dry CH<sub>2</sub>Cl<sub>2</sub>/0 °C/25 h/36.0 mol%; i) Hoveyda-Grubbs cat. 2nd generation (HG2)/BHT/dry CH<sub>2</sub>Cl<sub>2</sub>/35 °C/8.9 h, 54.2 mol% (compound 1), 9.0 h, 58.0 mol% (compound 2), or 24 h, 72.4 mol% (compound 3); j) HG2/BHT/dry CH<sub>2</sub>Cl<sub>2</sub>/35 °C/24 h/38.5 mol% (compound 4) and 41.0 mol% (compound 21); k) HG2/BHT/dry CH<sub>2</sub>Cl<sub>2</sub>/35 °C/24 h/68.5 mol%; l) HG2/BHT/dry CH<sub>2</sub>Cl<sub>2</sub>/35 °C/7 h/61.1 wt% (mixture of 22 and 22').

synthesis of compounds 6, 7, and 9–12, with varied olefinic structure at the reducing-end. Fig. 2 representatively shows the <sup>1</sup>H and <sup>13</sup>C NMR spectra of EC-C3 6 and AC-NHCO-C5 9. Proton and carbon resonances were assigned by 2D NMR analyses (Fig. S2). Carboxamide protons (NH in Fig. 2A) appear as a broad doublet between 5.8 and 7.0 ppm. COSY experiments (Fig. S2A–G) showed that the amido proton correlates only with the proton at the reducing-end of D-cellobiose (denoted as “1” in Fig. 2A, between 5.1 and 5.3 ppm). In addition, HMBC analyses (Fig. S2O–U) revealed that the carbon resonance derived from each amide carbonyl group (NHCO, Fig. 2B) correlated only with the C-1 proton at the reducing-end of D-cellobiose. These results proved selective

introduction of olefinic structures including acrylamide group at the reducing-end of D-cellobiose derivatives.

Schmidt glycosylation was adopted to synthesize AC-O-C5 8 (Scheme 2C, Figs. S1 and S2). Four PTLC purifications were required to obtain the pure target product due to a by-product having a similar *R*<sub>f</sub> value to compound 8 (cf. 3.3.8.) likely because of an orthoester leading to deacetylation at the C2 position during glycosylation (Fig. S3) (Kettelhout & Werz, 2016). Thus, glycosylation is less selective for the installation of olefinic structures into end groups of saccharides than amidation when they contain acetyl substituents.



**Fig. 2.** <sup>1</sup>H and <sup>13</sup>C NMR spectra ( $\text{CDCl}_3$ ) of EC-C3 **6** and AC-NHCO-C5 **9**. A: <sup>1</sup>H NMR spectra. B: <sup>13</sup>C NMR spectra. 1D NMR spectra for the other cellobiose derivatives are shown in Fig. S1.

#### 4.3. NMR analyses of CM products

Five hetero-block tetramers **1–5** were synthesized by CM reaction of cellobiose derivatives having Type I (compounds **8–12**) or Type II olefins (compounds **6, 7**, Scheme 2D). Tetramers have spacers with an internal olefin, connected at both ends to cellobiose derivative reducing-ends, thereby coupling two cellobiose derivatives in head-to-head fashion.

For hetero-block tetramers **1–5**, proton and carbon resonances were assigned by 2D NMR (Fig. S4–6). In <sup>1</sup>H and <sup>13</sup>C NMR spectra of CM product **2** (Fig. 3), resonances derived from both coupled segments (compounds **6** and **9**) are observed (cf. Fig. 2). Resonances derived from olefin protons and carbons (e.g., denoted as “D” in Figs. 2A, 3A') shift predictably after CM (Table S1). The number of olefinic protons is also observed to decrease by one after CM (Figs. 2A, 3A', Table S1). NMR results prove that the terminal olefins of compounds **6–12** were converted to the expected asymmetric internal olefins and, thus, prove successful CM (Chen et al., 2020; Dong et al., 2019; Dong & Edgar, 2015; Meng & Edgar, 2015). Coupling constants between internal olefin protons are 15.5 Hz (Fig. 3A'), indicating that *E*-isomers of CM products **1–5** dominate.

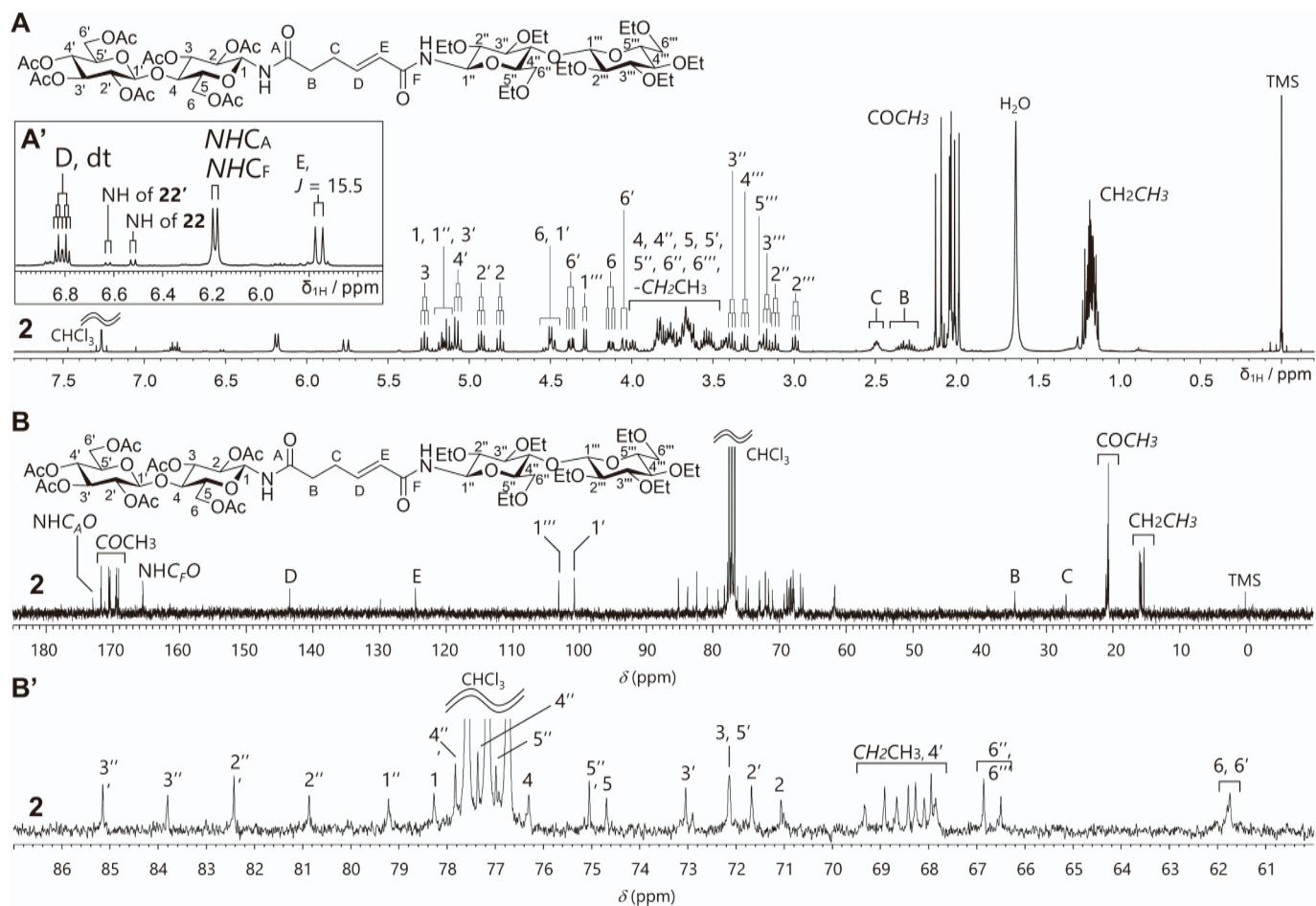
As shown in Fig. 3A', two small doublets appear at 6.54 and 6.57 ppm. A self-metathesis (SM) experiment using AC-NHCO-C5 **9** (Scheme 2E, S1.18, in SI) revealed that these are derived from the carboxamides of [AC-NHCO-C5]-*b*-[AC-NHCO-C5] **22** (6.54 ppm) and [AC-NHCO-C5]-*b*-[AC-NHCO-C4] **22'** (6.57 ppm), respectively (Fig. S7). Homo-block tetramers of Type I olefins can be formed by competing SM during CM reactions but should be consumed rapidly if CM reactivity is high (Chatterjee et al., 2003). Thus, the remaining SM product **22** strongly suggests that the pair of AC-NHCO-C5 **9** and EC-C3 **6** has low CM reactivity. Regarding the hetero-block tetramer **22'**, the isomerization of terminal olefins to internal olefins during olefin metathesis was reported

previously (Formentín et al., 2005; Hong et al., 2005; Schmidt, 2004). The mechanism remains unclear, but there has been a suggestion that a dinuclear Ru complex from the metathesis catalyst is responsible for the isomerization process (Hong et al., 2004). The homo-block tetramer **21** also appeared after 24 h of CM, indicating that CM of AC-NHCO-Cv **11** and EC-C3 **6** is not highly selective (S1.16., Fig. S8).

In contrast, no SM product resonances were evident in <sup>1</sup>H and <sup>13</sup>C NMR spectra of hetero-block tetramers **1**, **3**, or **5** (Fig. S4). This indicates that each pair of compounds **6** and **8** (AC-O-C5), **6** and **10** (AC-NHCO-C11), and **7** (AC-NHCO-C3) and **12** (EC-C11) affords CM products with high selectivity. Thus, it is likely that the chemical structures of  $\omega$ -alkenyl “handles” can affect CM selectivity of olefin-bearing cellobiose derivatives. In the next Section 4.4, we will discuss the influence of the  $\omega$ -alkenyl structures and substituents of olefin-bearing cellobiose derivatives on their CM selectivity.

#### 4.4. Influence of chemical structures of cellobiose-based block components on CM selectivity

To evaluate CM selectivity of these Type I and Type II cellobiose derivatives, the proportion of the CM product (CM ratio) was calculated by <sup>1</sup>H NMR spectrum integration (S1.19. in SI), allowing us to evaluate the influence of some structural factors on CM selectivity. The structural factors include ether vs. amido linkage connecting  $\omega$ -alkenyl group with the pyranose ring, length of linker to  $\omega$ -alkene (pent-4-enamide vs. undec-10-enamide), rigidity (linear vs. aromatic olefin), and cellobiose substituents. As described in the Introduction, the previously established method for  $\alpha$ -cellulosylamide derivatives can be adopted to introduce olefinic structures at the reducing-end of polysaccharides (Kamitakahara et al., 2005; Kamitakahara & Nakatsubo, 2005). However, there is a risk that the amide carbonyl group may chelate ruthenium to an extent dependent on chemical structure and reaction conditions, resulting in



**Fig. 3.** 1D NMR spectra of [AC-NHCO-C5]-b-[EC-C3] (compound 2). A and A': Full spectrum (A) and enlarged spectrum around 5.5–7.0 ppm (A') of <sup>1</sup>H NMR. B and B': Full (B) and enlarged <sup>13</sup>C NMR spectra around 60–87 ppm (B'). NMR spectra of the other hetero-block tetramers are shown in Figs. S4 and S5.

lower CM selectivity (Choi et al., 2001; Meng & Edgar, 2015; Yun et al., 2011, 2012).

#### 4.4.1. Influence of pyranose ring on CM selectivity (Table 1 entry 1)

Choi et al. reported that CM selectivity of an  $\alpha,\beta$ -unsaturated amide is

improved by attaching sterically hindered structures (e.g., cyclohexyl) to the amide nitrogen (Choi et al., 2001), suggesting that formation of 4-membered chelate intermediates (compounds A, A' in Fig. 4A) is thereby suppressed. We therefore hypothesized that acrylamide-containing cellobiose **6** and **7** would similarly exhibit high CM selectivity because

**Table 1**  
Summary of reaction conditions, CM ratio, and yield in syntheses of hetero-block tetramers **1–5**<sup>a,b</sup>.

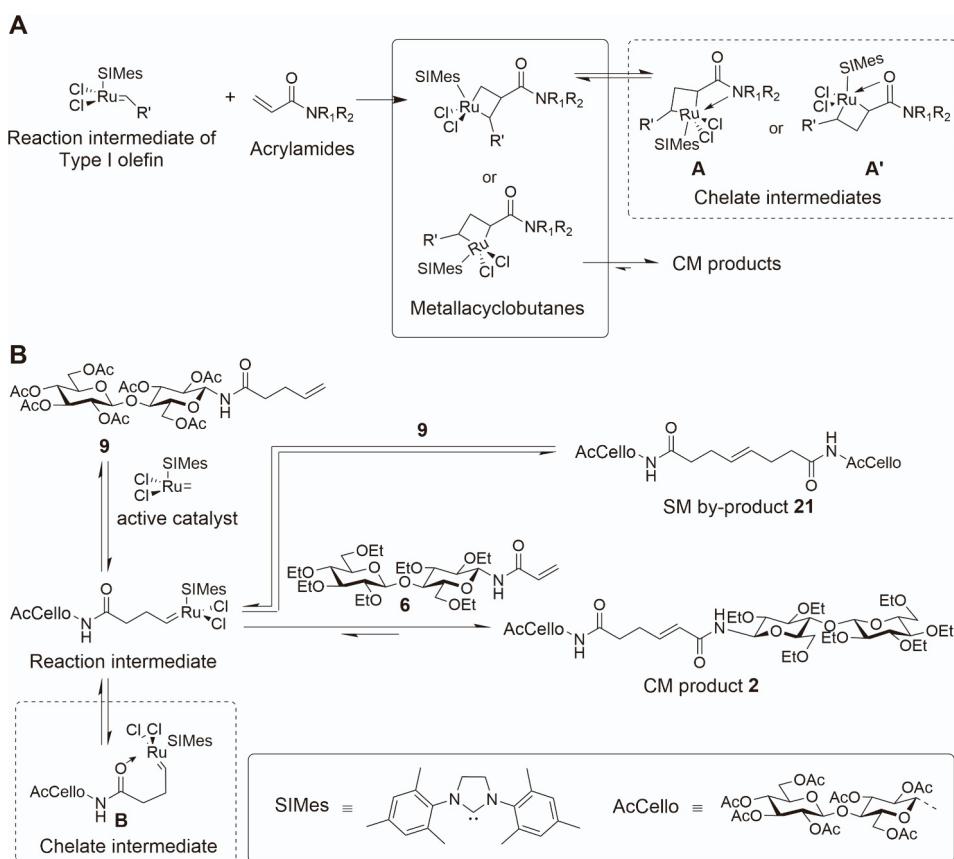
Entry	Type I olefin		Type II olefin		Time (h)	CM products	CM ratio <sup>d</sup> (%)	Yield <sup>d</sup> (mol%)		
	SG <sup>c</sup>	$\omega$ -Alkenyl groups	(equiv./Type I)	SG <sup>c</sup>						
1	8	Ac	~O-CH=CH <sub>2</sub>	6 (1.4)	Et		5.1	1	Quantitative	54
2	9	Ac	~NH-C(=O)-CH=CH <sub>2</sub>	6 (1.4)	Et		9.0	2	89	58
3	10	Ac	~NH-C(=O)-CH <sub>2</sub> -CH <sub>2</sub> -CH=CH <sub>2</sub>	6 (1.7)	Et		24	3	98	72
4	12	Et	~NH-C(=O)-CH <sub>2</sub> -CH <sub>2</sub> -CH=CH <sub>2</sub>	7 (1.7)	Ac		24	5	98	69
5	11	Ac	~NH-C(=O)-C <sub>6</sub> H <sub>4</sub> -CH=CH <sub>2</sub>	6 (1.4)	Et		24	4	64	37

<sup>a</sup> 0.15 equiv. of Hoveyda-Grubbs 2nd generation catalyst (HG2) was used in each reaction.

<sup>b</sup> Reactions were conducted with dichloromethane as the solvent and at 35 °C.

<sup>c</sup> Substituents of cellobiose derivatives. Ac: acetyl group, Et: ethyl group.

<sup>d</sup> Determined by <sup>1</sup>H NMR.



**Fig. 4.** (A) Illustration of proposed acrylamide chelation mechanism. Reaction intermediate of Type I olefin and acrylamide can form two different metallacyclobutanes. One turns into the CM product, the other can form 4-membered chelate intermediates A and A'. (B) Illustration of proposed chelation during CM reaction between compounds 9 and 6. Ru catalyst and AC-NHCO-C5 9 form the reaction intermediate. In addition to CM or SM, the formation of 6-membered chelate B can occur. B is inactive to CM and decreases catalyst turnover, reducing the rate of metathesis reaction.

of the bulky pyranose ring. To examine this hypothesis, we conducted CM between AC-O-C5 **8** and EC-C3 **6**. The pent-4-enyl group of compound **8** was used for selective CM with some  $\alpha$ , $\beta$ -unsaturated carbonyl compounds in previous research regarding end- or side-functionalization of cellulose derivatives (Chen et al., 2020; Dong & Edgar, 2015). Entry 1 in Table 1 shows that CM of compounds **8** and **6** afforded the hetero-block tetramer **1** with complete selectivity, consistent with our hypothesis.

#### 4.4.2. Influence of the linking group between $\omega$ -alkenyl groups and cellobiose derivatives on CM selectivity for the synthesis of hetero-block tetramers (Table 1 entry 2)

CM of AC-NHCO-C5 **9** and EC-C3 **6** afforded lower CM selectivity (89 %) than that of compounds **8** and **6** (Table 1, entries 1, 2). Since AC-O-C5 **8** and AC-NHCO-C5 **9** differ only in the linkage between  $\omega$ -alkenyl substituent and cellobiose derivative (**8**: ether, **9**: amido), this clearly indicates that the amido group reduces CM selectivity. This reduced CM selectivity is likely because of the 6-membered chelate intermediate of compound **9** (Fig. 4B).

#### 4.4.3. Influence of length and rigidity of $\omega$ -alkenamides on CM selectivity (Table 1, entries 3, 5)

To address our hypothesis that CM selectivity of  $\omega$ -alkenamides can be improved by structures that sterically prohibit chelation of Ru by the amide, we selected the undec-10-enamide, whose alkyl chain is more than twice as long as that of pent-4-enamide, as well as the rigid *p*-vinylbenzamido group.

Reaction of AC-NHCO-C11 **10** with EC-C3 **6** afforded a CM ratio of 98 % (entry 3, Table 1), supporting the concept that a longer amido-

olefin spacer would discourage chelation and thereby enhance CM. In contrast, reaction of AC-NHCO-Cv **11** with **6** afforded a CM ratio of 64 % in 36 % yield, both of which were the lowest among these model compounds (entry 5, Table 1). This result indicates that CM selectivity of compound **11** is low in spite of the *p*-vinylbenzamido rigidity. Presumably, this low CM selectivity can be attributed to the aromatic ring itself, possibly due to its steric demand. Regarding the effect of Ru-aromatic coordination on CM reaction, there are ample examples indicating that the HG2 catalyst is compatible with metathesis reactions including CM in aromatic systems (Van Otterlo & De Koning, 2009).

#### 4.4.4. Influence of cellobiose substituents on CM selectivity (Table 1, entries 3, 4)

Reaction of EC-C11 **12** with AC-NHCO-C3 **7** affords the same CM ratio (98 %) with similar yield (68 %) as CM of compounds **6** and **10** (CM ratio 98 %, 72 % yield). Thus, selective CM of cellobiose derivatives containing undec-10-enamide and acrylamides occurs even if their substituents are swapped for each other, clearly illustrating that selectivity and yield of CM reactions with these groups do not depend on the nature (electron-donating vs. -withdrawing) of cellobiose substituents.

The contrast to substituent influence observed on glycosylation reactions, noted in Section 4.1, is likely due to the fact that the pyranose rings are rather distant from the reacting olefin, thus their electron density does not strongly influence CM.

#### 4.5. End-to-end coupling of TEC and acetylated cellobiose via CM based on the model study

To examine the applicability of knowledge from the model study

toward end-to-end coupling involving polysaccharides, we conducted CM between cellulose and cellobiose derivatives. Completely ethylated cellulose (TEC) was chosen as a polysaccharide segment because it allows us to test the CM selectivity with MALDI-TOF MS analysis.

The undec-10-enamide group was introduced at TEC reducing-end by previously reported methods for end-functionalizing cellulose derivatives including azido end-functionalization of cellulose ethers (Kamitakahara et al., 2016) (Kamitakahara et al., 2005) (Scheme 3A). TEC-C11 23 was then coupled with AC-NHCO-C3 7 via CM, giving TEC-*b*-AC 24 (Scheme 3B). Dichloromethane was used as a solvent since it afforded the best selectivity and yield among those examined in CM with the cellobiose models (See S8 in SI).

MALDI-TOF MS and NMR analyses revealed that the designed CM strategy enables highly selective end-to-end coupling of TEC and acetylated cellobiose. In MALDI-TOF MS spectra of compounds 23 and 24 (Fig. 5A and B), observed molecular weights were in good agreement with the calculated ones of sodium additives of TEC-C11 (peak *b*), TEC-*b*-AC (peak *d*), and the TEC derivatives with one unsubstituted hydroxy group (peaks *a* and *c*). This indicates installation of one undec-10-enamide group into each TEC molecule and successful connection with AC-NHCO-C3.

In each <sup>1</sup>H NMR spectrum of compounds 23 and 24 (Fig. 5C and D), a resonance derived from the C-1 proton of the reducing-end AGU (denoted as “1[C]”) appears as a triplet around 5.0 ppm, indicating that the undec-10-enamide group was regioselectively installed at the reducing-end of TEC. After CM, proton resonances of acetylated cellobiose appeared, and resonances derived from olefin protons (“J” and “K”) shifted and changed their splitting patterns in the same manner as models (Fig. 5D, cf. Fig. 3 and Table S1). The result indicates that the terminally unsaturated structure was end-selectively introduced into TEC and coupled with AC-NHCO-C3, thus proving the selective synthesis of TEC-*b*-AC diblock cellulose analog via CM.

## 5. Conclusions

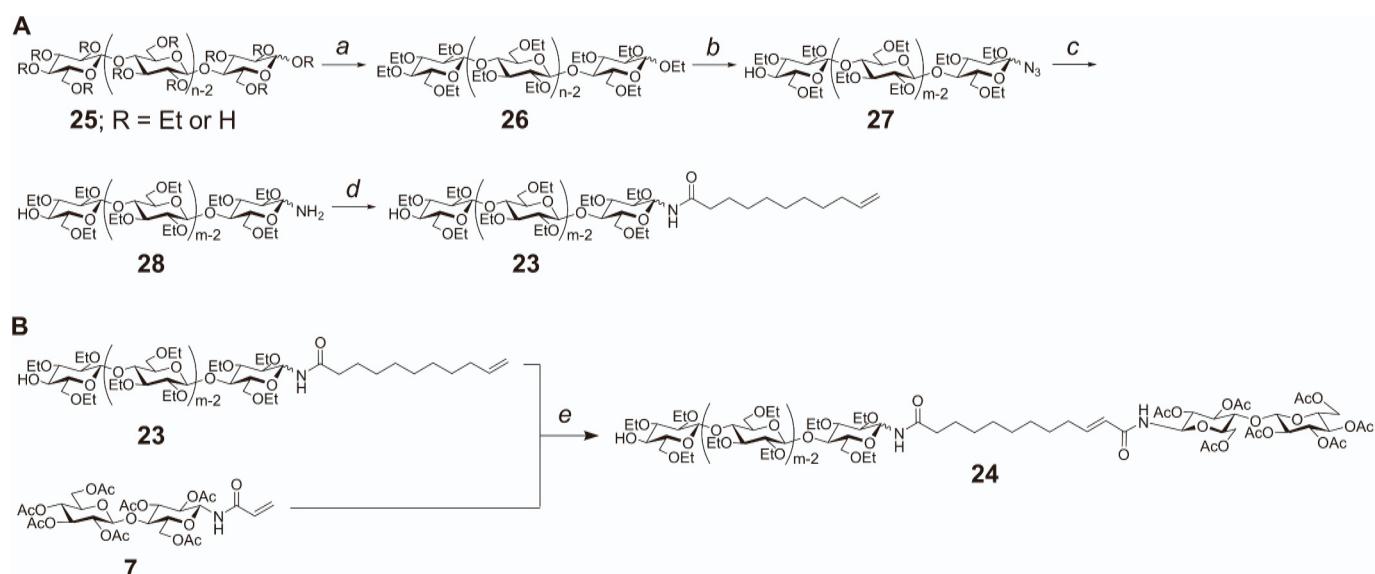
We explored CM coupling of intentionally designed peracetyl and perethyl cellobiose derivatives to prepare hetero-block tetramers 1–5 as a model study for our target polysaccharide block copolymers, to help design a CM strategy that can afford polysaccharide-based block copolymers including polysaccharide-polysaccharide hetero-block

copolymers with high yield and purity.

We gained considerable insight into CM structure-property-reactivity relationships from this model study. We were able to confirm our hypothesis that a pyranose ring near the amido group or long alkyl spacers between the amido group and double bond would prevent undesired chelation of the amide carbonyl group to the Ru atom that impairs CM reaction rate and selectivity, while a rigid aromatic spacer did not accomplish the same thing, causing low yields and poor CM selectivity, refuting that part of the hypothesis. We were also able to show that, for reactants bearing undec-10-enamide and acrylamide groups, high CM selectivity could be achieved independently of whether the cellobiose moiety bore electron-withdrawing or donating substituents. The results confirmed our second hypothesis that CM selectivity is less influenced by the substituents of cellobiose derivatives than by the olefinic structures.

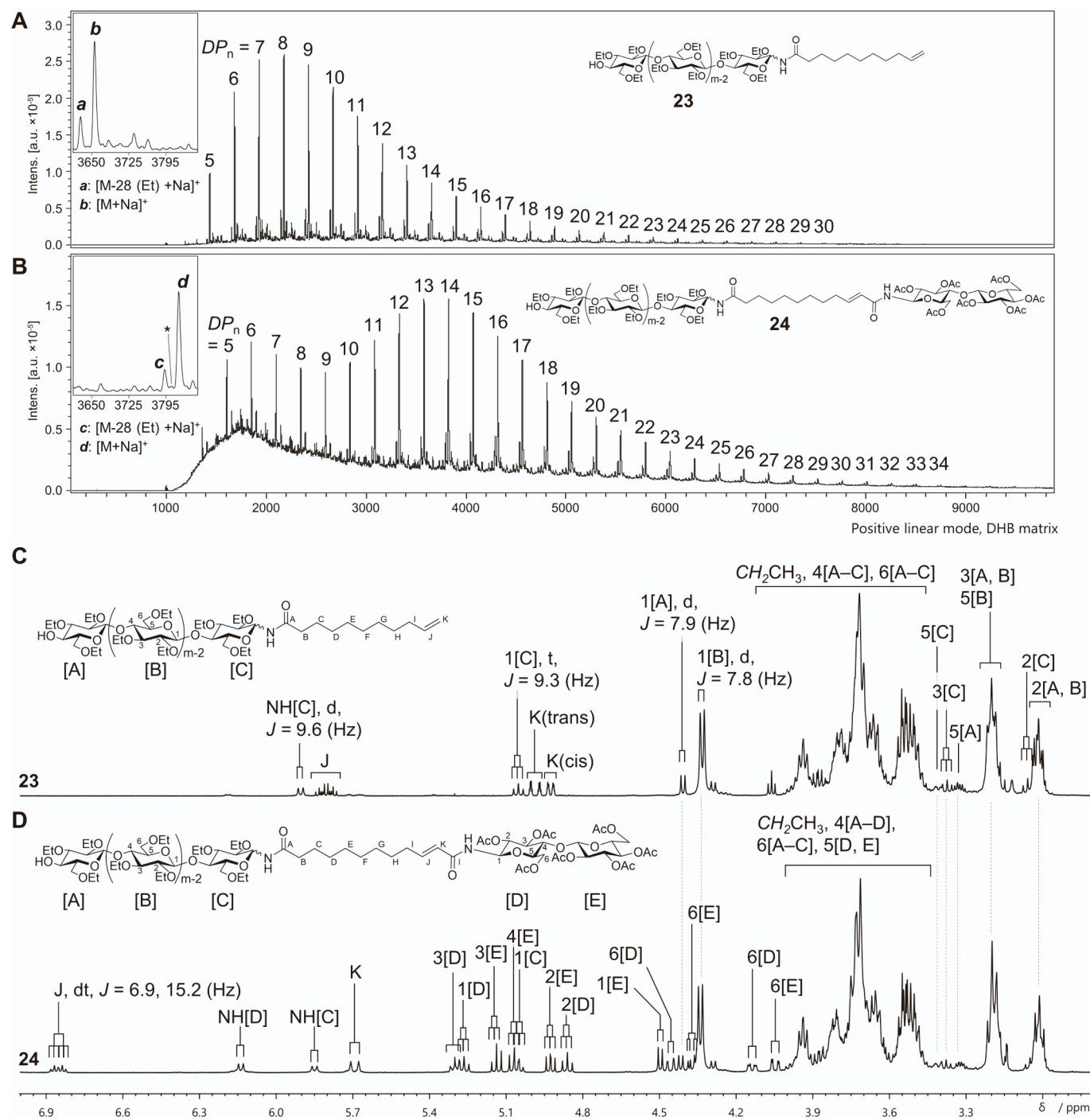
Moreover, the undec-10-enamide group was regioselectively introduced at TEC reducing end, then coupled with the acrylamide of AC-NHCO-C3 with complete selectivity, affording diblock TEC analog 24. This proved the principle that pairs of olefin “handles” showing high CM selectivity in the model study could be applied to selective end-to-end coupling involving polysaccharides.

We achieved herein CM coupling reactions between cellobiose derivatives by synthesizing hetero-block tetramers 1–5 composed of peracetyl  $\alpha$ -cellobiose and perethyl  $\alpha$ -cellobiose, in the process identifying useful solvents and conditions, and developing methods to quantify selectivity. We fully expect that this model study will contribute to the development of a CM strategy that can broadly afford polysaccharide-based block copolymers, not only from cellulose but from potentially any other polysaccharides. The results of this study enable us to predict that these polysaccharide-polysaccharide hetero-block copolymers can be prepared in high yield, with high selectivity and purity, and without having to resort to a large excess of either CM partner. This becomes especially important upon graduating to polymer-polymer CM coupling since contamination of the desired product by SM by-products and/or residual starting polymers would require a potentially difficult polymer-polymer separation in order to provide pure CM products. We look forward to sharing the results of these polymer-polymer CM coupling reactions in future reports.



**Scheme 3.** (A): Synthesis of TEC-C11 23. (B) CM between compounds 23 and 7 affording TEC-*b*-AC 24.

Reagents and conditions: a) NaH/C<sub>2</sub>H<sub>5</sub>I/dry DMSO/50 °C/3 days, then NaH/C<sub>2</sub>H<sub>5</sub>I/dry DMSO/dry THF/50 °C/3 days, 72.2 wt%; b) TMS-N<sub>3</sub>/SnCl<sub>4</sub>/dry CHCl<sub>3</sub>/25 °C/4.0 h/quantitative yield; c) 10 % Pd on C/dry THF/C<sub>2</sub>H<sub>5</sub>OH/H<sub>2</sub> gas/RT/7.1 h/quantitative yield, d) undec-10-enoyl chloride/TEA/dry CH<sub>2</sub>Cl<sub>2</sub>/15 °C/30.3 h/50.91 mol%; e) HG2/BHT/dry CH<sub>2</sub>Cl<sub>2</sub>/24 h/35 °C/12.1 mol%.



**Fig. 5.** MALDI-TOF MS (A and B) and  $^1\text{H}$  NMR (C and D, 2.8–7.0 ppm) spectra of TEC-C11 **23** and TEC-*b*-AC **24**. In the MALDI-TOF MS spectra,  $m/z$  values of sodium adduct ions,  $[\text{M} + \text{Na}]^+$  of compounds were observed.  $DP_n$  values of compound **24** are the total  $DP$  ( $DP_n = m + 2$ ). Inset enlarged spectra corresponding to the mass range  $m/z = 3615$ – $3860$ . NMR spectra were taken in  $\text{CDCl}_3$ .  $^{13}\text{C}$  and 2D NMR spectra are shown in S9 in SI.

#### CRediT authorship contribution statement

**Yuuki Sato:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Kazuki Sugimura:** Writing – review & editing. **Kevin J. Edgar:** Writing – review & editing, Visualization. **Hiroshi Kamitakahara:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Data availability

The data that has been used is confidential.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.carbpol.2024.122274>.

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