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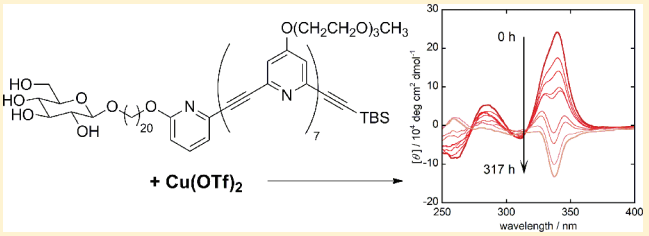
Concentration- and Time-Dependent Eccentric Changes in Circular Dichroism of Saccharide-Linked Ethynylpyridine Oligomer with Copper(II) Ions

Hajime Abe,* Yuki Ohishi, and Masahiko Inouye*

Graduate School of Pharmaceutical Sciences, University of Toyama, Toyama 930-0194, Japan

Supporting Information

ABSTRACT: We studied the preparation and circular dichroism (CD) behavior of 2,6-pyridylene ethynylene octameric oligomer linked to a β-D-glucoside moiety with a C20-alkylene chain. The addition of $Cu(OTf)_2$ salt led to a remarkable enhancement of the first CD band of the oligomer, and an unexpected concentration and time dependency were observed. For example, when 1.0×10^{-3} M of $Cu(OTf)_2$ was added to a 1,2-dichloroethane solution of the oligomer (5.0×10^{-4} M, unit concentration), the CD band appeared in the positive at first and gradually inverted into the negative with time.



A host–guest interaction plays an important role in supramolecular systems not only in the laboratory but also in nature. Recently, various supramolecular polymers have been prepared on the basis of such host–guest associations of self-assembling motifs.[1] Among such motifs, tandem heteroditopic monomers, in which a host moiety H is covalently linked with a guest moiety G as H–G, have been employed to build ··H–G···H–G·· forms of "daisy chain" supramolecular polymers by self-assembly. This type of supramolecular polymer has been represented by that having hydrogen-bonding motifs[1a,c,d] and pseudorotaxane motifs.[1a,b,2,3] In some cases, the switching of higher order structure is observed between cyclic and linear daisy chains, as well as switching among a monomeric self-complex, an oligomeric self-assembly, and a polymeric self-assembly. Sometimes, such switching can be controlled by concentration[3a,c,f,g,i,m,n] and additives.[3c,p,q] These properties enable one to control the dynamics and functions of the supramolecular polymers.

Recently, our research group has been investigating synthetic host molecules that recognize saccharide guests by hydrogen bonding. Among them, the oligomeric and polymeric "ethynylpyridine" hosts have been developed to incorporate a saccharide guest within the helical higher order structures of the hosts.[4,5] We have previously reported a new class of ethynylpyridine oligomers **1**, covalently linked with a saccharide moiety, which were found to efficiently form a helical structure by intramolecular hydrogen bonding and showed strong Cotton effects (Figure 1).[5] Subsequently, we planned to construct daisy-chain-type supramolecular polymers by using a saccharide-linked ethynylpyridine oligomer **2**, in which the host and guest moieties are linked by a much longer alkylene chain (C20) linker, as shown in Figure 2. During the course of this study, the addition of copper(II) salt was found to enhance the circular dichroism (CD) activity of the saccharide-linked

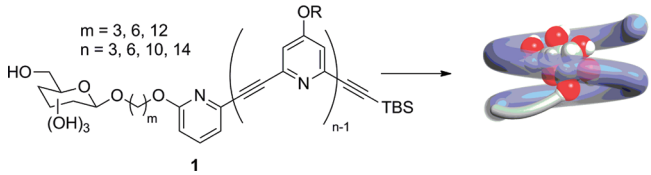


Figure 1. Tandem saccharide-linked ethynylpyridine oligomer **1** and helix formation.

oligomer. Moreover, the CD spectra of the oligomer/copper(II) complexes underwent unexpected and eccentric changes depending on time as well as the concentrations of **2** and the copper salt.

The glucoside–C20-linked ethynylpyridine oligomer **2** was synthesized as shown in Scheme 1. Condensation of 2,6-dibromo-4-nitropyridine (**3**)[6] and tetraethylene glycol monomethyl ether gave 4-pyridyl ether **4**. Then, dibromide **4** was subjected to two steps of the Sonogashira reaction with 2-methyl-3-butyn-2-ol and *tert*-butyldimethylsilylacetylene (TBSA) to give diyne **6**, which liberated acetone to yield monoprotected diethynylpyridine **7**. Similar to the two steps of the Sonogashira reaction, trimeric diiodide **8**[4f] was also derivatized to monoprotected diethynyl trimer **11**, which was further subjected to the Sonogashira reaction and treatment with excess diiodide **8** to afford a hexameric building block **12**. On the other hand, 20-bromoicosanyl glucoside tetra-*O*-acetate (**13**) was obtained from glucose penta-*O*-acetate[7] and 20-bromoicosan-1-ol[8] by Fischer synthesis. Williamson synthesis of **13** with 6-iodopyridin-2-ol[9] and the deprotection of the acetyl groups gave iodopyridine–C20-linked glucoside **15**.

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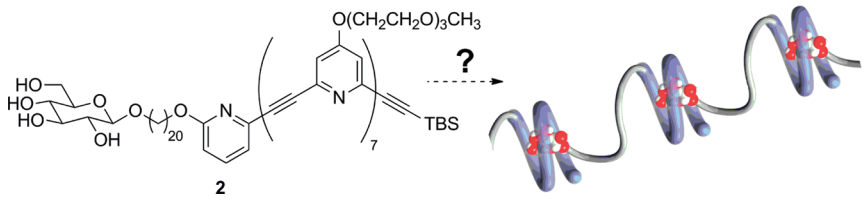
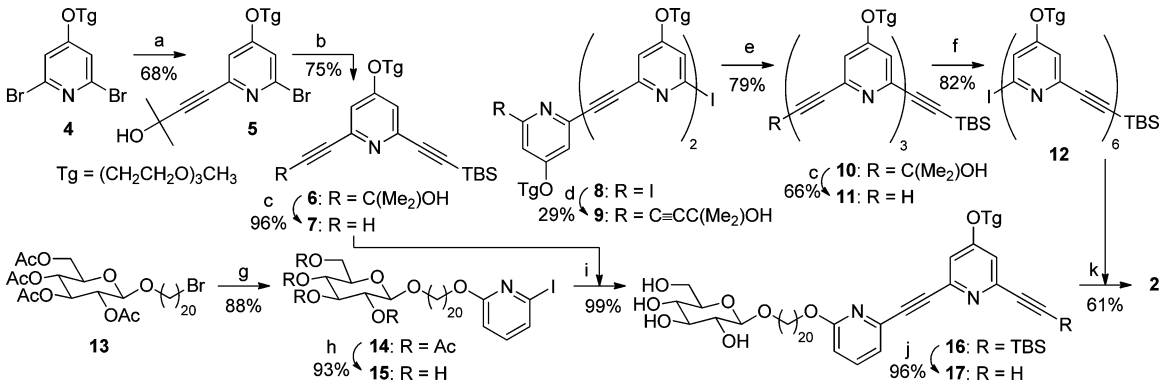


Figure 2. Supramolecular polymer formed with glucoside−C20-linked ethynylpyridine **2**.

Scheme 1. Preparation of the Glucoside−C20-Linked Ethynylpyridine Oligomer 2[a]



[a]**4**, 2-methyl-3-butyn-2-ol, $PdCl_2(PPh_3)_2$, CuI, *i*-Pr_2NH, THF; (b) *tert*-butyldimethylsilylacetylene, $PdCl_2(PPh_3)_2$, CuI, *i*-Pr_2NH, THF; (c) NaOH, toluene; (d) 2-methyl-3-butyn-2-ol, Pd(PBu-*t*$_3$)$_2$, CuI, *i*-Pr_2NH, THF; (e) *tert*-butyldimethylsilylacetylene, Pd(PBu-*t*$_3$)$_2$, CuI, *i*-Pr_2NH, THF; (f) **8**, Pd(PBu-*t*$_3$)$_2$, CuI, *i*-Pr_2NH, THF; (g) 6-iodo-2-pyridinol, K_2CO_3, acetone; (h) MeOH, Et_3N, H_2O; (i) **7**, Pd(PBu-*t*$_3$)$_2$, CuI, K_2CO_3, *i*-Pr_2NH, THF; (j) TBAF, H_2O, THF; (k) **12**, Pd(PBu-*t*$_3$)$_2$, CuI, K_2CO_3, *i*-Pr_2NH, THF.

Subsequently, one and six pyridine rings were introduced to **15** by stepwise Sonogashira reactions using **7** and **12** in order to furnish the targeted oligomer **2**.

The chiral higher order structures of **2** were studied by CD measurements. A 1,2-dichloroethane (DCE) solution of **2** (5.0×10^{-4} M, unit concentration) showed a negative CD band around 329 nm (Figure 3, orange line). This band was weak but

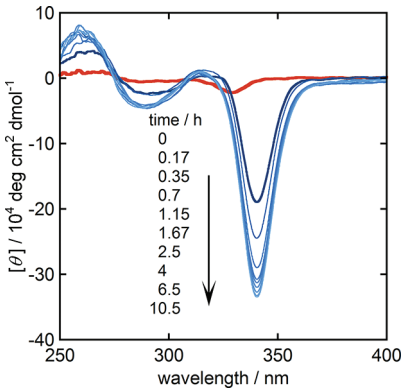


Figure 3. CD spectrum of **2** and the time-dependent CD change after the addition of Cu(II) salt: (orange) before the addition of $Cu(OTf)_2$; (deep blue to light blue) after the addition of $Cu(OTf)_2$, 0 to 10.5 h. Conditions: **2** (6.3×10^{-5} M, unit concentration = 5.0×10^{-4} M), $Cu(OTf)_2$ (2.5×10^{-4} M), DCE, 25 °C. The path length is 1 mm.

typical, indicating the formation of chiral helical higher order structure as our previous results.[4,5] The intra- and intermolecular host−guest association would be not so strong between the ethynylpyridine and glucoside moieties of **2**. Recently, our group has found that the addition of copper(II) salt sometimes improves the CD activity of ethynylpyridine oligomers.[4a,b,10] Expecting a similar effect, we treated the DCE solution of **2** with $Cu(OTf)_2$ to stabilize its helical structure. When $Cu(OTf)_2$ (2.5×10^{-4} M, 0.5 equiv to unit concentration of **2**) was added to the DCE solution of **2**, a remarkable enhancement of the first CD band was observed with red shift, as shown in Figure 3 (deep blue line). This change in the CD spectrum induced by $Cu(OTf)_2$ addition resembled the one observed in typical ethynylpyridine oligomers associated with octyl glycosides in the presence of copper(II) salt.[4a] Therefore, the stabilization of the chiral helical structure is also expected to occur in the case of **2**. On the other hand, an interesting time-dependent change in CD was observed in this mixture. Just after the addition of $Cu(OTf)_2$, the $[\theta]$ value at 340 nm was -2.4×10^4 deg cm^2 dmol^{-1}, and this negative CD band intensified with time, as shown in Figure 3 (deep blue to light blue lines). After 10 h, the CD band became steady, and the $[\theta]$ value reached approximately twice of that at the start. This time dependency could be due to the difference between the higher order structures that are kinetically and thermodynamically favored over the mixture of **2** and $Cu(OTf)_2$. It would probably take time for the mixture to achieve an equilibrium state.

To study the effect of copper salt in detail, CD measurements were carried out for DCE solutions of **2** (5.0×10^{-4} M) treated with various equivalents (0.5, 1.5, 2.0 equiv to unit concentration of **2**) of $Cu(OTf)_2$. Contrary to the case of 0.5 equiv of $Cu(OTf)_2$ (Figure 4A, blue line, see also Figure 3), the addition of 2.0 equiv of $Cu(OTf)_2$ induced the first positive CD band at around 340 nm (Figure 4A, red line). The addition of 1.5 equiv of $Cu(OTf)_2$ induced an intermediate CD spectrum near zero (Figure 4A, purple line). It was suggested that helical complexes of the opposite sense were kinetically formed between 0.5 and 2.0 equiv of $Cu(OTf)_2$. When enough time had passed after the addition, all of the mixtures showed much stronger negative CDs at around 340 nm. Thus, we observed

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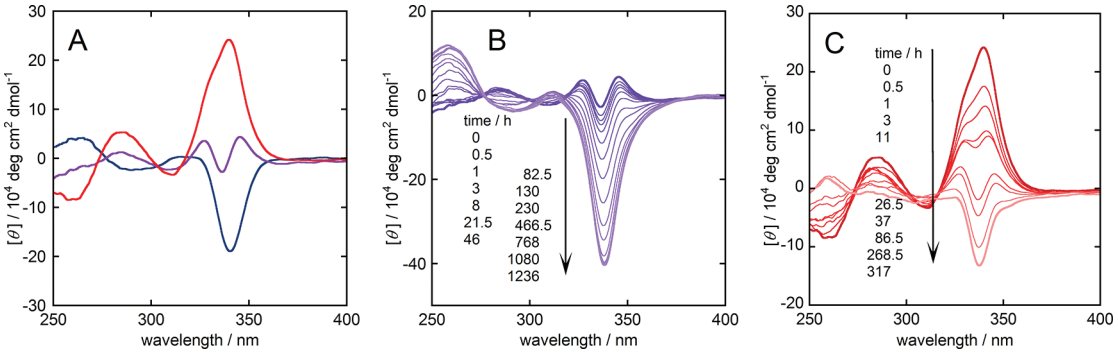

Figure 4. (A) Concentration effect of Cu $(OTf)_2$ on CD of **2**/Cu$(OTf)_2$ mixture. Conditions: **2** (6.3×10^{-5} M, unit concentration = 5.0×10^{-4} M), Cu$(OTf)_2$, DCE, 25 °C. (red) [Cu$(OTf)_2$] = 1.0×10^{-3} M; (purple) [Cu$(OTf)_2$] = 7.5×10^{-4} M; (blue) [Cu$(OTf)_2$] = 2.5×10^{-4} M. Path length =1 mm. CD spectra just after the addition of Cu$(OTf)_2$. (B) Time-dependent change in the CD spectrum of **2** (6.3×10^{-5} M, unit concentration = 5.0×10^{-4} M)/Cu$(OTf)_2$ (7.5×10^{-4} M) mixture (deep to light purple). (C) Time-dependent change in CD spectrum of **2** (6.3×10^{-5} M, unit concentration = 5.0×10^{-4} M)/Cu$(OTf)_2$ (1.0×10^{-3} M) mixture (deep to light red).

the enhancement of negative CD, the appearance of negative CD, and the reversal of CD from positive to negative, as time advanced from the addition of 0.5, 1.5, and 2.0 equiv of Cu(OTf), respectively (Figures 3 and 4B,C). The thermodynamically stable helical structures would be in the same sense in all cases.

Next, the concentration dependency of **2** was studied. To each DCE solution of **2** at 7.0×10^{-3} and 5.0×10^{-4} M (unit concentration), we added 0.5 equiv of Cu$(OTf)_2$ against the unit concentration of **2**. The first CD band was observed in the positive at around 340 nm for the 7.0×10^{-3} M solution and in the negative at around 340 nm for the 5.0×10^{-4} M solution (Figure 5).

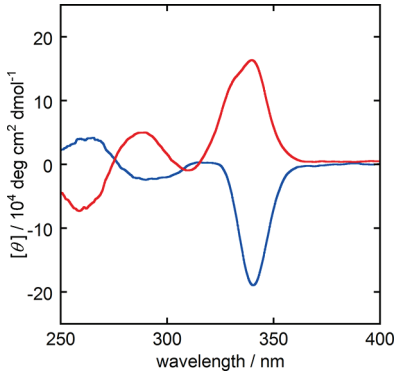

Figure 5. Concentration effect of **2** on CD of **2**/Cu$(OTf)_2$ mixture. Conditions: **2**, Cu$(OTf)_2$, DCE, 25 °C. (red) [**2**] = 8.8×10^{-4} M (unit concentration = 7.0×10^{-3} M), [Cu$(OTf)_2$] = 3.5×10^{-3} M, path length = 0.1 mm; (blue) [**2**] = 6.3×10^{-5} M (unit concentration = 5.0×10^{-4} M); [Cu$(OTf)_2$] = 2.5×10^{-4} M, path length =1 mm. CD spectra just after Cu$(OTf)_2$ addition.

When enough time had passed after the addition of Cu$(OTf)_2$, both mixtures showed much stronger negative CD activities at around 340 nm, as well as in the cases of the above-mentioned [Cu$(OTf)_2$]-varied experiments (Figure 4). Thus, the reversal of CD from positive to negative was observed in the case of 7.0×10^{-3} M of **2** with 3.5×10^{-3} M of Cu$(OTf)_2$. These findings suggested that switching of the helical sense of the kinetically formed complex occurred in a concentration-dependent manner probably from inter- to intramolecular complexation.[3a,c,f,g,i,m,n] The positive CD at around 340 nm could be caused by intermolecular complexation, which is kinetically favored in higher concentrations. Intermolecular complexation can be performed by two or more molecules of **2** with enough number of Cu(II) ions, potentially in a supramolecular polymer form. As time advanced, all mixtures fell into equilibrium states, in which the thermodynamically stable helical structures are favored, and these structures could be formed by intramolecular complexation, which is independent of concentrations. This hypothesis is summarized in Scheme 2.

Scheme 2. Hypothetical Mechanism of Concentration- and Time-Dependent CD Inversion

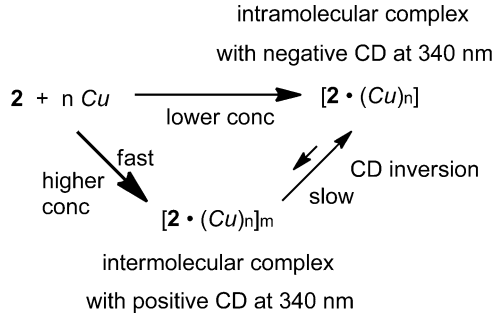

Figure 6 summarizes the types of time-dependent transformation of the first CD band in the experiments as a function of the concentrations of **2** and Cu$(OTf)_2$. Blue, purple, and red dots indicate negative-to-negative, zero-to-negative, and positive-to-negative transformations, respectively. The concentration dependency can be observed in the higher concentrations of **2** and Cu$(OTf)_2$, which exhibit the first positive CD band kinetically, as mentioned above.

We performed additional experiments to understand how **2** and Cu$(OTf)_2$ aggregate, but unfortunately, little positive data could be obtained. In dynamic light-scattering (DLS) analyses, the observed scattering light was too weak to determine the size of the aggregate, suggesting that it was not that big. ESI-MS measurements indicated the existence of up to trimeric aggregate involving copper ions (Figure S4 in the Supporting Information), though time dependency could not be established. NMR experiments were carried out under various conditions; however, no definite results were obtained because of the strong broadening (Figure S5 in Supporting

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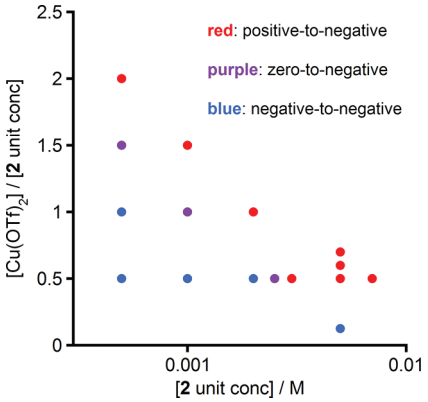

Figure 6. Graphical summary of the time dependencies of the CD changes plotted as a function of the unit concentration of **2** and the molar ratio of $Cu(OTf)_2$ to the unit of **2**: (red) positive-to-negative, (purple) zero-to-negative, (blue) negative-to-negative CD changes. Conditions: DCE, 25 °C. For typical CD changes, see Figures 3 and 4B,C.

Information), probably caused by the coordination with copper(II) ion at the nitrogen atoms as our previous report.[4a]

In summary, saccharide-linked ethynylpyridine oligomer **2**, which consists of β-D-glucopyranoside and octameric ethynylpyridine moieties linked with a C20−alkylene linker, was prepared. The CD of oligomer **2** was enhanced by the addition of $Cu(OTf)_2$, and the shape of the CD spectrum changed depending on time and concentration. During the measurements, which depended on the concentrations of **2** and $Cu(OTf)_2$, we observed an unexpected positive-to-negative inversion of the CD band at around 340 nm with time in mixtures with high concentrations of **2** and $Cu(OTf)_2$. In contrast, negative-to-negative CD enhancement was observed in the case of low concentrations. We assumed that the positive CD was due to the complex that was kinetically produced and turned into a thermodynamically stable product with time.

EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded using tetramethylsilane (TMS) as an internal reference. Melting points were not corrected. THF was freshly distilled from sodium benzophenone ketyl before use. 1,2-Dicholoroethane of anhydrous grade was used for the spectroscopic analyses. 2,6-Dibromo-4-nitropyridine[6] (**3**), triethylene glycol-derived diiodo trimer[4f] **8**, penta-*O*-acetyl-β-D-glucopyranose,[7] 20-bromoicosan-1-ol,[8] and 6-iodo-2-pyridinol[9] were prepared according to the procedures in the literature.

Triethylene Glycol-Derived 2,6-Dibromopyridine 4. This compound was prepared in a similar way to the case of diiodo analogue.[4f] To a suspension of NaH (5.1 g, 0.13 mmol; commercial 60% dispersion was washed thoroughly with hexane prior to use) in THF (330 mL) was slowly added triethylene glycol monomethyl ether (17.4 g, 0.106 mol) at 0 °C, and subsequently 2,6-dibromo-4-nitropyridine (**3**, 30 g, 0.11 mmol) was added to the mixture in one portion at the same temperature. The reaction mixture was stirred for 1 h at 0 °C and additionally for 4 h at room temperature. The resulting mixture was quenched with a saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (300 mL × 3). The combined organic layer was dried over $MgSO_4$ and concentrated by a rotary evaporator. The resulting syrup was subjected to silica gel column chromatography (eluent; hexane/AcOEt = 1:1) to yield **4** (39 g, 92%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.02 (s, 2H), 4.20 (t, *J* = 4.2 Hz, 2H), 3.86 (t, *J* = 4.5 Hz, 2H), 3.71−3.63 (m, 6H), 3.56−3.53 (m, 2H), 3.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.4, 140.5, 113.5, 71.5, 70.6, 70.24, 70.21, 68.7, 68.2; IR (neat) ν_{max} 2877, 1574, 1536 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{12}H_{17}Br_2NNaO_4$ (M + Na$^+$) 421.9402, found 421.9386.

Triethylene Glycol-Derived 2-Bromo-6-(3-hydroxy-3-methyl-1-butynyl)pyridine 5. To a mixture of **4** (15.0 g, 37.6 mmol), $PdCl_2(PPh_3)_2$ (1.05 g, 1.50 mmol), and 2-methyl-3-butyn-2-ol (3.16 g, 37.6 mmol) in *i*-Pr_2NH (150 mL) and THF (150 mL) was added CuI (0.14 g, 0.75 mmol) at 0 °C. The mixture was stirred for 3 h at room temperature, and the resulting mixture was diluted with ether (200 mL) and filtered. The filtrate was concentrated by a rotary evaporator, and the resulting residue was purified by silica gel column chromatography (eluent: AcOEt/hexane = 2:1) to yield **5** (8.9 g, 68%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.98 (d, *J* = 2.1 Hz, 1H), 6.93 (d, *J* = 2.1 Hz, 1H), 4.17 (t, *J* = 4.5 Hz, 2H), 3.86 (t, *J* = 4.2 Hz, 2H), 3.71−3.64 (m, 6H), 3.57−3.54 (m, 2H), 3.38 (s, 3H), 2.61 (s, 1H), 1.61 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.6, 143.5, 142.0, 113.7, 113.4, 94.7, 80.2, 71.7, 70.8, 70.49, 70.45, 69.0, 68.0, 65.2, 58.9, 31.0; IR (neat) ν_{max} 3407, 2980, 2879, 2233, 1582, 1540 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{24}BrNNaO_5$ (M + Na$^+$) 424.0736, found 424.0747.

Triethylene Glycol-Derived 2-(*tert*-Butyldimethylsilylethynyl)-6-(3-hydroxy-3-methyl-1-butynyl)pyridine 6. To a mixture of **5** (8.84 g, 25.4 mmol), $PdCl_2(PPh_3)_2$ (0.89 g, 1.3 mmol), and *tert*-butyldimethylsilylacetylene (10.7 g, 76.3 mmol) in *i*-Pr_2NH (50 mL) and THF (50 mL) was added CuI (97 mg, 0.51 mmol) at 0 °C. The mixture was stirred for 11 h at room temperature, the resulting mixture was diluted with ether (100 mL) and filtered. The filtrate was concentrated by a rotary evaporator, and the resulting residue was purified by silica gel column chromatography (eluent: AcOEt/hexane = 3:2) to yield **6** (8.7 g, 75%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.94 (d, *J* = 2.1 Hz, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 4.17 (t, *J* = 4.2 Hz, 2H), 3.85 (t, *J* = 4.5 Hz, 2H), 3.72−3.63 (m, 6H), 3.56−3.53 (m, 2H), 3.38 (s, 3H), 2.58 (s, 1H), 1.61 (s, 6H), 0.99 (s, 9H), 0.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.6, 144.13, 144.10, 113.8, 113.1, 103.8, 93.6, 93.3, 81.1, 71.8, 70.9, 70.6, 70.5, 69.1, 67.7, 65.2, 59.0, 31.1, 26.2, 16.7, −4.7; IR (neat) ν_{max} 3410, 2929, 2226, 2162, 1580, 1553 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{25}H_{39}NNaO_5Si$ (M + Na$^+$) 484.2495, found 484.2471.

Triethylene Glycol-Derived 2-(*tert*-Butyldimethylsilylethynyl)-6-ethynylpyridine 7. To a suspension of pulverized NaOH (92 mg, 2.3 mmol) in toluene (43 mL) was added **6** (0.985 g, 2.13 mmol) at room temperature. The mixture was refluxed for 30 min and successively filtered and evaporated. The evaporated residue was purified by silica gel column chromatography (eluent: AcOEt/hexane = 1:1) to yield **7** (0.829 g, 96%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.97 (s, 2H), 4.18 (t, *J* = 4.5 Hz, 2H), 3.86 (t, *J* = 4.8 Hz, 2H), 3.72−3.63 (m, 6H), 3.55−3.53 (m, 2H), 3.38 (s, 3H), 3.09 (s, 1H), 0.99 (s, 9H), 0.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.7, 144.4, 143.4, 114.0, 113.8, 103.7, 93.5, 93.3, 82.3, 77.1, 71.9, 71.0, 70.7, 70.6, 69.2, 67.8, 59.1, 26.2, 16.8, −4.7; IR (neat) ν_{max} 3235, 2951, 2928, 2885, 2858, 2165, 2109, 1580, 1554 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{22}H_{33}NNaO_4Si$ (M + Na$^+$) 426.2077, found 426.2090.

Triethylene Glycol-Derived 2-Bromo-6-(3-hydroxy-3-methyl-1-butynyl)pyridine Trimer 9. To a mixture of glycol-derived diiodo trimer **8** (1.05 g, 1.03 mmol), $Pd(PPh_3)_4$ (0.48 g, 0.0041 mmol), and 2-methyl-3-butyn-2-ol (0.26 g, 3.1 mmol) in *i*-Pr_2NH (12 mL) and THF (12 mL) was added CuI (7.8 mg, 0.0041 mmol) at room temperature. The mixture stirred for 6 h at room temperature. The resulting mixture was diluted with ether (20 mL) and filtered. The filtrate was concentrated by a rotary evaporator, and the resulting residue was purified by silica gel column chromatography (eluent: AcOEt/MeOH = 50:1) to yield **9** (0.29 g, 29%) as a brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (d, *J* = 2.4 Hz, 2H), 7.16 (s, 2H), 7.14 (d, *J* = 2.1 Hz, 2H), 7.11 (d, *J* = 2.7 Hz, 2H), 4.22−4.16 (m, 6H), 3.91−3.85 (m, 6H), 3.76−3.64 (m, 18H), 3.58−3.54 (m, 6H), 3.38 (s, 9H), 2.68 (s, 1H), 1.63 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.9, 164.8, 164.5, 144.2, 143.7, 143.5, 143.4, 121.4, 117.5, 114.52, 114.46, 113.9, 113.8, 93.9, 88.0, 87.3, 87.0, 86.5, 80.9, 71.8, 70.9, 70.5, 69.1, 69.0, 68.0, 67.8, 65.2, 59.0, 31.1; IR (neat) ν_{max} 3410, 2878, 2227, 1581, 1551, 1532 cm^{-1}; HRMS (ESI−TOF) calcd for $C_{45}H_{58}IN_3NaO_{13}$ (M + Na$^+$) 998.2912, found 998.2894.

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Triethylene Glycol-Derived 2-(*tert*-Butyldimethylsilylethynyl)-6-(3-hydroxy-3-methyl-1-butynyl)pyridine Trimer 10. To a mixture of **9** (3.02 g, 3.09 mmol), Pd(PBu-t_3)$_2$ (79 mg, 0.16 mmol), and *tert*-butyldimethylsilylacetylene (1.30 g, 9.28 mmol) in *i*-Pr$_2$NH (47 mL) and THF (47 mL) was added CuI (29 mg, 0.16 mmol) at room temperature, and the mixture was stirred for 10 h at room temperature. The resulting mixture was filtered, the filtrate was concentrated by a rotary evaporator, and the resulting residue was purified by silica gel column chromatography (eluent: AcOEt/MeOH = 200:1) to yield **10** (2.4 g, 79%) as a brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18 (s, 2H), 7.14 (d, J = 2.1 Hz, 2H), 7.01 (d, J = 2.4 Hz, 2H), 6.98 (d, J = 2.4 Hz, 2H), 4.24−4.18 (m, 6H), 3.91−3.86 (m, 6H), 3.75−3.62(m, 18H), 3.58−3.54 (m, 6H), 3.38 (s, 9H), 1.63 (s, 6H), 1.00 (s, 9H), 0.20 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.9, 164.8, 164.7, 144.3, 144.2, 143.7, 143.6, 143.4, 143.3, 114.6, 114.5, 114.4, 114.3, 113.9, 113.8, 113.7, 103.6, 94.0, 93.6, 87.5, 87.3, 87.1, 87.0, 80.9, 71.8, 70.9, 70.53, 70.50, 69.1, 68.0, 67.9, 67.8, 65.2, 59.0, 31.1, 26.1, 16.7, −4.7; IR (neat) ν_{max} 3394, 3009, 2929, 2885, 2228, 1583, 1551 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{53}H_{73}N_3NaO_{13}Si$ (M + Na$^+$) 1010.4810, found 1010.4796.

Triethylene Glycol-Derived 2-(*tert*-Butyldimethylsilylethynyl)-6-ethynylpyridine Trimer 11. To a suspension of pulverized NaOH (92 mg, 2.3 mmol) in toluene (80 mL) was added **10** (2.67 g, 2.70 mmol) at room temperature. The mixture was refluxed for 30 min, and the resulting mixture was filtered. The filtrate was concentrated by a rotary evaporator, and the resulting residue was purified by silica gel column chromatography (eluent: AcOEt/MeOH = 200:1) to yield **11** (1.66 g, 66%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.16−7.11 (m, 4H), 7.04 (d, J = 2.4 Hz, 2H), 7.01 (d, J = 2.4 Hz, 2H), 4.21−4.18 (m, 6H), 3.91−3.86 (m, 6H), 3.75−3.64 (m, 18H), 3.58−3.54 (m, 6H), 3.39−3.38 (m, 9H), 3.12 (s, 1H), 1.00 (s, 9H), 0.20 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.9, 164.8, 144.5, 143.8, 143.6, 143.5, 121.4, 117.5, 114.6, 114.0, 113.8, 93.9, 88.0, 87.4, 87.0, 86.5, 80.9, 71.9, 71.0, 70.6, 69.2, 68.0, 67.9, 67.8, 59.1, 26.2, 16.8, −4.6; IR (neat) ν_{max} 3236, 2927, 2885, 2859, 2163, 2111, 1582, 1551 cm^{-1}; HRMS (ESI−TOF) calcd for $C_{50}H_{67}N_3NaO_{12}Si$ (M + Na$^+$) 952.4392, found 952.4432.

Triethylene Glycol-Derived 2-Bromo-6-(3-hydroxy-3-methyl-1-butynyl) Hexamer 12. To a mixture of **8** (5.05 g, 4.95 mmol), **11** (0.767 g, 8.25 mmol), and Pd(PBu-t_3)$_2$ (21.1 mg, 0.00413 mmol) in *i*-Pr$_2$NH (30 mL) and THF (30 mL) was added CuI (7.9 mg, 0.0041 mmol) at room temperature. The mixture stirred for 11 h at room temperature, and the resulting mixture was filtered. The filtrate was concentrated by a rotary evaporator, and the resulting residue was purified by silica gel column chromatography (eluent: AcOEt/MeOH = 25:1) to yield **12** (1.20 g, 82%) as a brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (d, J = 2.4 Hz, 2H) 7.28 (s, 1H), 7.18−7.17 (m, 7H), 7.15 (d, J = 2.4 Hz, 2H), 7.13 (d, J = 2.7 Hz, 2H), 7.01 (d, J = 2.4 Hz, 2H), 4.21−4.15 (m, 14H), 3.91−3.85 (m, 14H), 3.76−3.64 (m, 36H), 3.58−3.54 (m, 14H), 3.39 (s, 18H), 1.00 (s, 9H), 0.20 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.9, 164.7, 164.5, 144.4, 143.7, 143.6, 121.5, 117.5, 114.6, 113.8, 103.7, 93.6, 88.1, 87.3, 87.2, 87.0, 86.5, 71.9, 70.9, 70.6, 69.1, 68.0, 67.8, 59.0, 26.2, 16.7, −4.7; IR (neat) ν_{max} 3009, 2928, 2883, 2226, 2163, 1582, 1550 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{90}H_{117}IN_6NaO_{24}Si$ (M + Na$^+$) 1844.6862, found 1844.6882.

20-Bromoicosanyl 2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranoside (13). To a solution of penta-*O*-acetyl-*β*-D-glucopyranose (7.11 g, 18.2 mmol) and 20-bromoicosan-1-ol (5.5 g, 15 mmol) in CH_2Cl_2 (65 mL) was added BF_3·Et_2O (11.5 mL, 91.1 mmol) dropwise during 90 min at 0 °C. The reaction mixture was stirred for 32 h at 0 °C, and the resulting mixture was poured into a mixture of ice and aqueous $NaHCO_3$ with being stirred. The organic layer was separated and washed successively with additional water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and concentrated by a rotary evaporator. The resulting residue was purified by silica gel column chromatography (eluent: AcOEt/hexane = 1:4) to yield **13** (2.23 g, 22%) as a colorless solid: mp 84−86 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.24−5.17 (m, 1H), 5.12−5.05 (m, 1H), 5.01−4.95 (m, 1H), 4.49 (d, J = 7.8 Hz, 1H), 4.28−4.24 (m, 1H), 4.15−4.11 (m, 1H), 3.88−3.85 (m, 1H), 3.72−3.64 (m, 1H), 3.50−3.45 (m, 1H), 3.41 (t, J = 6.6 Hz, 2H), 2.09 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.90−1.81 (m, 2H), 1.44−1.40 (m, 2H), 1.36−1.18 (m, 32H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 170.2, 169.2, 169.1, 100.8, 72.9, 71.7, 71.4, 70.3, 68.5, 62.0, 34.2, 32.9, 29.8, 29.7, 29.6, 29.5, 28.9, 28.3, 25.9, 20.9, 20.8; IR (KBr) ν_{max} 2921, 2851, 1763, 1741, 1473 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{34}H_{59}BrNaO_{10}$ (M + Na$^+$) 729.3189, found 729.3216.

2-Iodo-6-(20-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)-icosanyl)pyridine 14. To a suspension of K_2CO_3 (1.96 g, 14.2 mmol) in acetone (20 mL) were added **13** (1.67 g, 2.36 mmol) and 6-iodo-2-pyridinol (0.63 g, 2.8 mmol) subsequently at room temperature. The reaction mixture was refluxed for 7 h, and the resulting mixture was filtered. The filtrate was concentrated by a rotary evaporator, and the resulting residue was purified by silica gel column chromatography (eluent: AcOEt/hexane = 2:1) to yield **14** (1.72 g, 22%) as a colorless solid: mp 72−73 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29−7.26 (m, 1H), 7.19−7.14 (m, 1H), 6.68−6.65 (m, 1H), 5.24−5.17 (m, 2H), 5.12−5.06 (m, 1H), 5.01−4.96 (m, 1H), 5.48 (d, J = 7.8 Hz, 1H), 4.30−4.22 (m, 3H), 4.16−4.11 (m, 1H), 3.91−3.83 (m, 1H), 3.66−3.50 (m, 1H), 3.50−3.43 (m, 1H), 2.09 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.78−1.69 (m, 2H), 1.59−1.20 (m, 34H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 170.2, 169.2, 169.1, 163.2, 139.4, 127.1, 113.6, 109.8, 100.8, 72.9, 71.7, 71.3, 70.3, 68.5, 66.9, 62.0, 29.8, 29.7, 29.6, 29.5, 29.4, 28.9, 26.1, 25.9, 20.9, 20.74, 20.71; IR (KBr) ν_{max} 2918, 2850, 1755, 1581, 1551 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{39}H_{62}INNaO_{11}$ (M + Na$^+$) 870.3265, found 870.3303.

2-(20-(*β*-D-Glucopyranosyloxy)icosanyl)-6-iodopyridine (15). To a mixed solution of MeOH (30 mL), Et_3N (6 mL), and water (6 mL) was added **14** (1.67 g, 2.01 mmol) at room temperature. The reaction mixture was refluxed for 2 h. The resulting mixture was concentrated by a rotary evaporator, and the resulting residue was purified by silica gel column chromatography (eluent: CH_2Cl_2/MeOH = 10:1) to yield **15** (1.27 g, 93%) as a colorless solid: mp 96−98 °C; ^{1}H NMR ($CDCl_3$/CD_3OD = 1:1, 300 MHz) δ 7.32−7.30 (m, 1H), 7.25−7.20 (m, 1H), 6.72−6.69 (m, 1H), 4.28 (d, J = 7.5 Hz, 1H), 4.26−4.22 (m, 2H), 3.94−3.85 (m, 2H), 3.77−3.71 (m, 1H), 3.59−3.51 (m, 1H), 3.42−3.21 (m, 4H), 1.80−1.71 (m, 2H), 1.68−1.59 (m, 2H), 1.48−1.20 (m, 32H); ^{13}C NMR ($CDCl_3$/CD_3OD = 1:1, 75 MHz) δ 162.8, 139.2, 126.8, 112.9, 109.0, 102.4, 76.1, 75.6, 73.1, 69.8, 69.7, 66.4, 61.2, 29.22, 29.17, 29.11, 29.08, 28.9, 25.52, 25.49; IR (KBr) ν_{max} 3357, 2920, 2850, 1583, 1549 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{31}H_{54}INNaO_7$ (M + Na$^+$) 702.2843, found 702.2828.

***β*-D-Glucoside-Linked TBS-Protected Dimer 16.** To a mixture of **7** (0.465 g, 1.15 mmol), **15** (0.623 g, 0.917 mmol), Pd(PBu-t_3)$_2$ (23 mg, 0.0046 mmol), *i*-Pr$_2$NH (16 mL), and THF (16 mL) was added CuI (8.9 mg, 0.0046 mmol) at room temperature. The mixture was stirred for 5 h at room temperature, and then to the mixture was added 3-aminopropyl-functionalized silica gel (11.1 mg). After 1 h, the mixture was filtered to remove the insoluble materials. The filtrate was concentrated by a rotary evaporator and the resulting residue was purified by a silica gel column chromatography (eluent: AcOEt/MeOH = 20:1) to yield **15** (0.66 g, 99%) as a brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55−7.50 (m, 1H), 7.19−7.17 (m, 1H), 7.01 (d, J = 2.4 Hz, 1H), 6.99 (d, J = 2.4 Hz, 1H), 6.73−6.70 (m, 1H), 4.32−4.28 (m, 3H), 4.21−4.18 (m, 2H), 3.88−3.80 (m, 5H), 3.74−3.50 (m, 11H), 3.44−3.28 (m, 5H), 1.80−1.70 (m, 2H), 1.68−1.54 (m, 2H), 1.48−1.20 (m, 32H), 1.00 (s, 9H), 0.19 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.7, 163.6, 144.4, 144.0, 139.1, 138.3, 122.2, 114.1, 113.6, 111.9, 103.8, 102.7, 93.5, 88.1, 86.7, 76.3, 75.4, 73.3, 72.0, 70.9, 70.63, 70.58, 69.4, 69.2, 67.8, 66.4, 61.5, 59.0, 29.84, 29.80, 29.76, 29.7, 29.6, 29.1, 26.2, 25.9, 16.8, −4.7; IR (neat) ν_{max} 3396, 3013, 2926, 2855, 1579, 1553 cm^{-1}; HRMS (ESI−TOF) calcd for $C_{53}H_{86}N_2NaO_{11}Si$ (M + Na$^+$) 977.5899, found 977.5922.

***β*-D-Glucoside-Linked Dimer 17.** To a THF (28 mL) solution of **16** (0.585 g, 0.612 mmol) were added tetrabutylammonium fluoride (TBAF, 1.0 M solution in THF, 0.92 mL, 0.92 mmol) and a few drops of water. The reaction mixture was stirred for 30 min at room temperature, and the resulting mixture was concentrated by a rotary evaporator and the resulting residue was purified by silica gel column chromatography (eluent: AcOEt/MeOH = 20:1) to yield **17** (0.49 g,

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96%) as a brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57−7.51 (m, 1H), 7.20−7.17 (m, 1H), 7.13 (d, J = 1.8 Hz, 1H), 7.02 (d, J = 1.8 Hz, 1H), 6.74−6.71 (m, 1H), 4.32−4.28 (m, 3H), 4.22−4.19 (m, 2H), 3.88−3.80 (m, 5H), 3.74−3.50 (m, 11H), 3.44−3.28 (m, 5H), 3.15 (s, 1H), 1.81−1.71 (m, 2H), 1.68−1.54 (m, 2H), 1.48−1.20 (m, 32H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.9, 164.0, 163.7, 144.1, 143.5, 139.1, 138.3, 121.2, 114.1, 113.9, 112.0, 102.7, 88.3, 86.5, 82.2, 75.4, 73.5, 71.9, 71.0, 70.64 70.59, 69.7, 69.2, 67.9, 66.4, 59.1, 29.8, 29.6, 29.5, 29.1, 26.0; IR (neat) ν_{max} 3393, 3305, 3019, 2926, 2854, 1582, 1555 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{47}H_{72}N_2NaO_{11}$ (M + Na$^+$) 863.5034, found 863.4995.

β-D-Glucoside-Linked Octamer 2. To a mixture of **12** (1.14 g, 0.641 mmol), **17** (0.43 g, 0.51 mmol), and Pd(PBu-t_3)$_2$ (13 mg, 0.0026 mmol) in i-Pr$_2$NH (60 mL) and THF (60 mL) was added CuI (4.9 mg, 0.0026 mmol) at room temperature. The mixture was stirred for 9 h at room temperature, and the resulting mixture was filtered off to remove the insoluble materials. The filtrate was concentrated by a rotary evaporator and the resulting residue was purified by silica gel column chromatography (eluent: AcOEt/MeOH = 9:1) to yield **2** (0.79 g, 61%) as a brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58−7.52 (m, 1H), 7.22−7.16 (m, 13H), 7.13 (d, J = 2.1 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 6.75−6.72 (m, 1H), 4.34−4.30 (m, 3H), 4.26−4.18 (m, 14H), 3.94−3.86 (m, 17H), 3.76−3.55 (m, 59H), 3.49−3.31 (m, 23H), 1.82−1.73 (m, 2H), 1.50−1.19 (m, 34H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.0, 164.8, 163.6, 144.4, 144.1, 143.8, 143.7, 143.6, 139.0, 138.3, 121.2, 114.6, 114.2, 113.8, 112.0, 103.7, 102.8, 93.6, 88.4, 87.50, 87.45, 87.32, 87.27, 87.1, 86.5, 86.4, 75.5, 74.4, 73.8, 71.9, 70.9, 70.6, 69.1, 68.0, 67.8, 66.4, 59.1, 29.6, 29.4, 29.0, 26.2, 26.1, 26.0; IR (neat) ν_{max} 3422, 3012, 2927, 2857, 1584, 1551 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{137}H_{188}N_8NaO_{35}Si$ (M + Na$^+$) 2556.2876, found 2556.2936

CD Experiments for Studying the Additive Effects of Cu(OTf)$_2$ and Time-Dependency. To prepare sample solution, Cu(OTf)$_2$ was added as DMSO solution (0.125 M) just before the final dilution of a DCE solution of **2**, and the resulting solution was shaken for 1 min and then subjected to CD measurements. The sample solution was kept in a cuvette with screw cap, and during the intervals between the measurements, it was preserved in the dark at 25 °C.

■ ASSOCIATED CONTENT

Supporting Information

UV−vis spectra of **2** and **2**/Cu(OTf)$_2$ mixtures, time-course CD changes corresponding to Figure 5, ^{1}H NMR and ESI-MS spectra of **2**/Cu(OTf)$_2$ mixture, and ^{1}H and ^{13}C NMR spectra for compounds **2**, **4**−**7**, and **9**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: abeh@pha.u-toyama.ac.jp, inouye@pha.u-toyama.ac.jp.

Notes

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