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IMPROVEMENT OF HELIX-FORMING ABILITY OF MANNOSIDE-LINKED ETHYNYLPYRIDINE OLIGOMERS CONSTRUCTED BY CONVERGENT SYNTHESIS

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Abstract – The improvement of helix-forming ability of α-D-mannoside-linked 2,6-pyridylene ethynylene "ethynylpyridine" oligomers was made by modification of the linker between the ethynylpyridine and mannoside moieties in the oligomers. The linker involves a triazole ring because the preparation utilizes Huisgen reaction, and the proper distance between the triazole ring and the ethynylpyridine moiety was found to be important to show strong Cotton effects.

Dedicated to Professor Ei-ichi Negishi on the occasion of his 77th birthday

In the nature, helicity appears in the higher-order structures of biopolymers such as nucleic acids, peptides, and polysaccharides. The sophisticated functions of those biopolymers are based on their helical structures. Therefore in the field of biomimetic chemistry, it is one of the important issues to construct helices with synthetic materials at will.[1]

In this decade, our group has developed synthetic host compounds oligo- and poly(2,6-pyridylene ethynylene) **1**, "ethynylpyridine oligomer/polymer", in which numbers of pyridine rings are tethered with acetylene bonds at their 2- and 6-positions (Figure 1).[2,3,4] When these oligomers and polymers meet with a saccharide guest, they form helical complexes by multipoint hydrogen bonding. During the course of our study, we have designed saccharide-linked ethynylpyridine oligomers **2** that have a saccharide template at the one end. It was expected that they would form helices efficiently by intramolecular interaction between the template and the pyridine rings (Figure 2).[2] As a result, the helix formation was well achieved, showing strong circular dichroism (CD), while it remained as a problem that the synthetic scheme was sequential and laborious, and lacked generality.

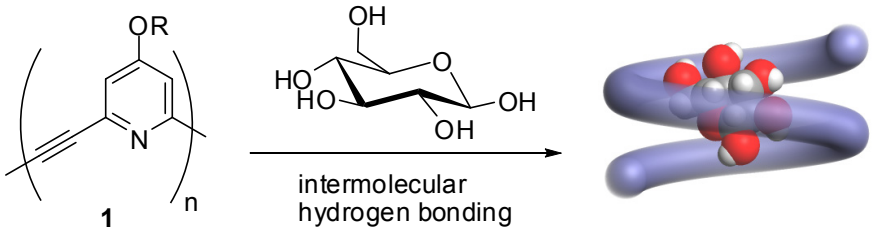


Figure 1. Basic framework of ethynylpyridine oligomers/polymers **1** and saccharide recognition to form helical structures

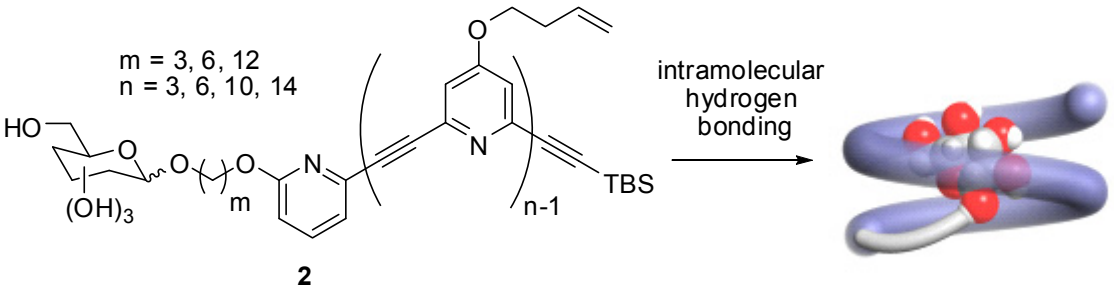


Figure 2. Saccharide-linked ethynylpyridine oligomers **2** and helix formation by intramolecular association

Therefore, we decided to develop convergent synthetic procedures to prepare a wide range of saccharide-linked ethynylpyridine oligomers more readily. Since our substrates are compatible with acetylene groups, Huisgen reaction was applied to attach saccharide azides to ethynylpyridine oligomers. In the previous report,[3] oligomer **4** was developed (Figure 3), in which an acetylene group for Huisgen reaction was attached to an ethynylpyridine moiety with a hexynylene linker to avoid steric hindrance. Although **4** could be prepared straightforwardly from **3**, the observed CD activity was rather weaker than that in the case of **2**. It was supposed that the chiral effect of the saccharide template would be discounted by the distance of the linker.

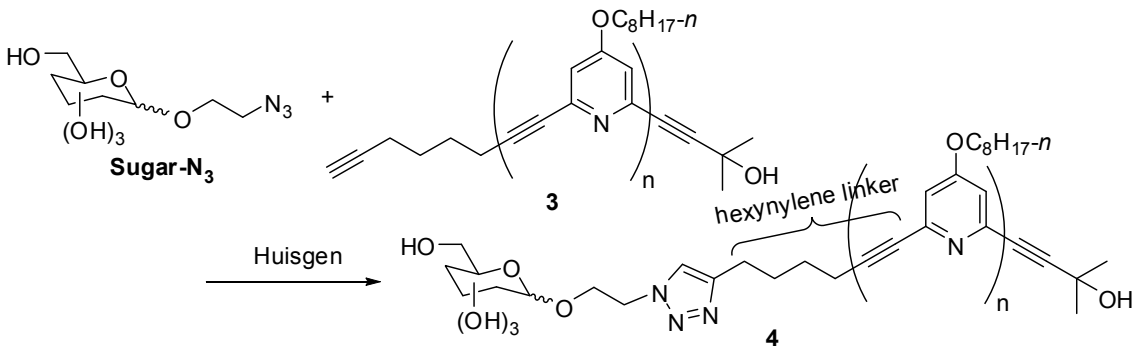


Figure 3. Saccharide-linked oligomer **4** and its preparation by Huisgen reaction from glycoside azide **Sugar-N$_3$** and acetylene **3**

Thus, we decided to develop a new type of saccharide-linked oligomers in which the oligomer and triazole moieties were directly tethered without a linker. Herein we report the helix-forming ability of saccharide-linked oligomers **6** as shown in Figure 4. The triazole ring in **6** might work as a member of supramolecular structures as reported by Hecht and coworkers.[5]

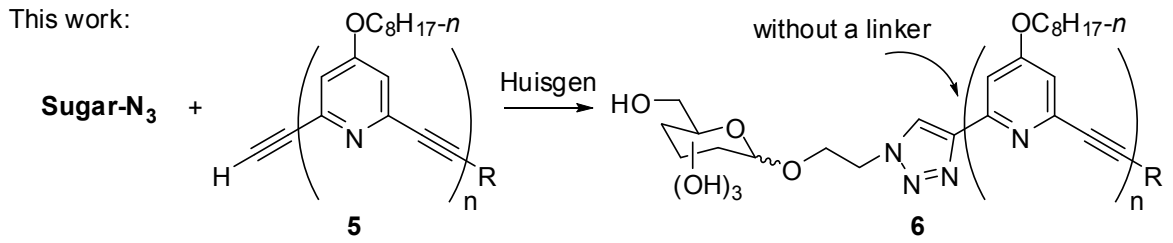
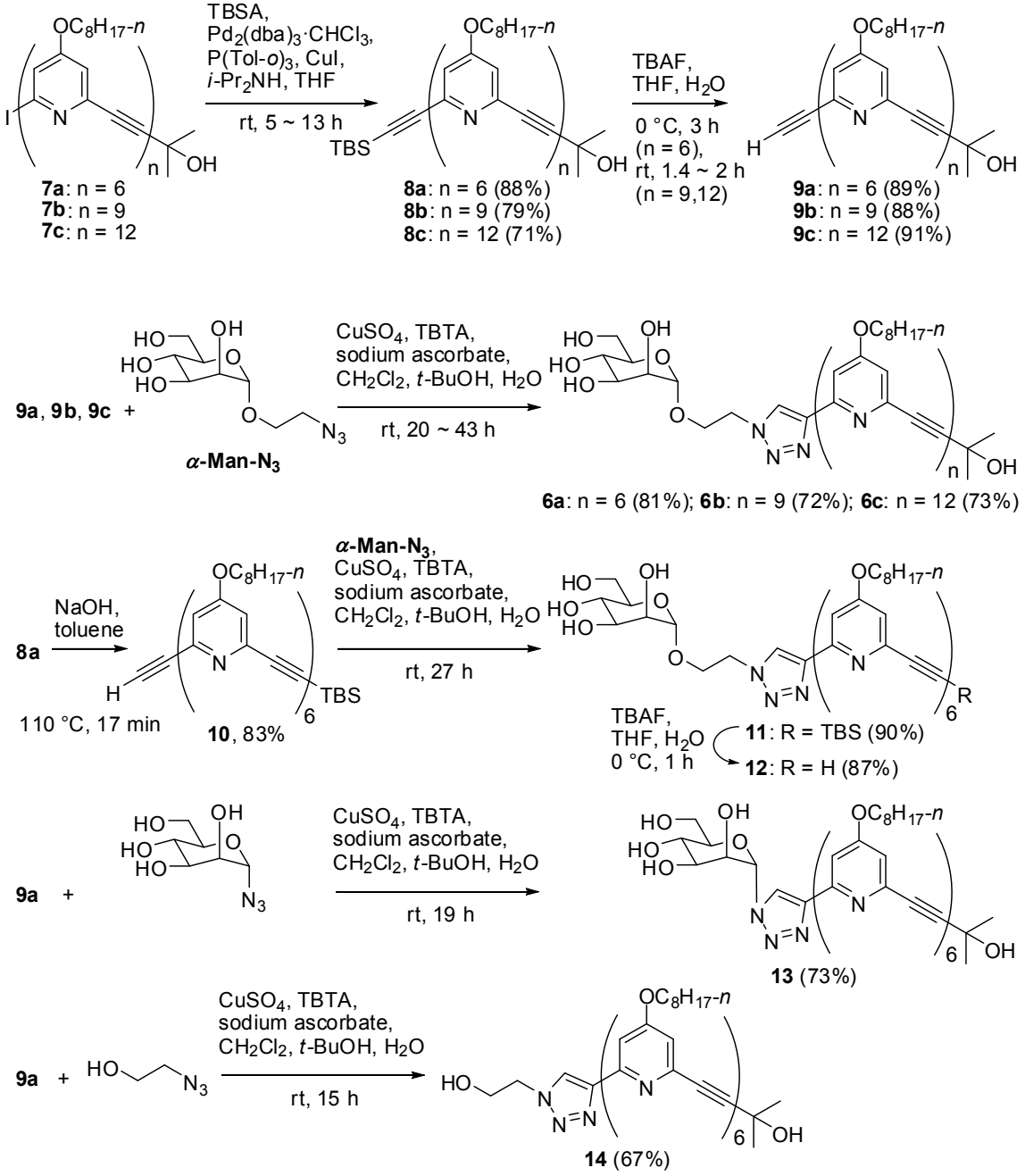


Figure 4. Saccharide-linked oligomer **6**, in which a triazole ring is attached to the ethynylpyridine moiety directly without a linker

We prepared six kinds of α-D-mannoside-linked ethynylpyridine oligomers **6a**, **6b**, **6c**, **11**, **12**, and **13** (Scheme 1), in which the triazole and the ethynylpyridine moieties are tethered directly as mentioned above (Figure 4). In **13** the α-mannosyl and the triazole moieties are also tethered directly, and in the other oligomers those two moieties via an ethylene group. The ethynylpyridine moieties of **6a**, **11**, **12**, and **13** are 6-meric, and of **6b** and **6c** are 9-meric and 12-meric, respectively. The difference among the three 6-mers **6a**, **11**, and **12** is the kind of the substituent at the opposite end to the mannoside moiety. Diol **14** was prepared as a control oligomer without an α-mannoside moiety. Transition metal-assisted synthetic protocols such as Sonogashira coupling and Huisgen reaction were inevitable throughout the synthetic route to the target compounds.

The mannoside-linked ethynylpyridine oligomers **6a**−**c** and **11** were prepared by Huisgen reaction of 2-azidoethyl α-D-mannopyranoside **α-Man-N$_3$**[6] with ethynylpyridine blocks **9a**, **9b**, **9c**, and **10** bearing two ethynyl groups at the both ends. The one end is protected with 1-hydroxy-1-methylethyl group, while the other is free, and Huisgen reaction took place with **α-Man-N$_3$** at the free end.[7] The oligomeric blocks **9a**, **9b**, and **9c** were derivatized from **7a**, **7b**, and **7c**, respectively, as shown in Scheme 1. The preparations of 6-meric oligomers **7a**, **8a**, and **9a**, and longer oligomers **7b** and **7c** were reported previously.[3] The monoiodides **7a**−**c** were coupled with (*tert*-butyldimethylsilyl)acetylene (TBSA) to give diprotected diynes **8a**−**c**. The *tert*-butyldimethylsilyl (TBS) groups of **8a**−**c** were treated with tetra-*n*-butylammonium fluoride (TBAF) to yield **9a**−**9c** by protiodesilylation. Besides, the 1-hydroxy-1-methylethyl group of **8a** was deprotected with NaOH to liberate acetone to give mono-TBS-protected diyne **10**. The Huisgen reactions of **α-Man-N$_3$** with **9a**−**c** and **10** were carried out



Scheme 1. Preparation of mannoside-linked ethynylpyridine oligomers **6a**−**c**, **11**, **12**, and **13**, and control **14**. TBS = *tert*-butyldimethylsilyl, TBSA = (*tert*-butyldimethylsilyl)acetylene, TBAF = tetra-*n*-butylammonium fluoride, TBTA = tris((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)amine

by the use of $CuSO_4$ pre-treated with sodium ascorbate and tris((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)amine[8] (TBTA) to yield target compounds **6a**−**6c** and **11**, respectively.[7] The use of TBTA somewhat improved the yields, compared to the case without TBTA.[3] Furthermore, the TBS group of **11** was removed by TBAF to give **12**. Similarly, the substrates **13** and **14** for reference experiments were obtained by Huisgen reaction of **9a** with α-D-mannosyl azide[9] and 2-azidoethanol,[10] respectively.

The UV-vis and CD spectra of the α-D-mannoside-linked oligomers of various lengths **6a–c** and the control **14** were studied in CH_2Cl_2 solutions (Figures 5A and 5B). The unit concentration of the pyridine rings of the oligomers was set at 5.0×10^{-4} M. In CD measurements, a positive CD band was observed around 330 nm in every case. This CD band indicates the formation of a chiral helical higher-order structure for the ethynylpyridine moiety. Typically, in our studies so far, various kinds of chiral helical ethynylpyridine oligomers exhibit a CD band of a similar shape around 330 nm.[3,4] Of course, 6-mer **14** which lacks a saccharide moiety showed no meaningful CD activity. Among **6a–c**, the order of the observed CD_{max} value around 330 nm was **6a** > **6b** > **6c**. Because the pyridine unit concentrations were equal, that order reflected the order of the average CD strength of the pyridine rings in each substrate. Accordingly, that order could be explained by the distance between the mannoside template and the pyridine units, and the farther pyridine units in the longer oligomers were less affected by the template.

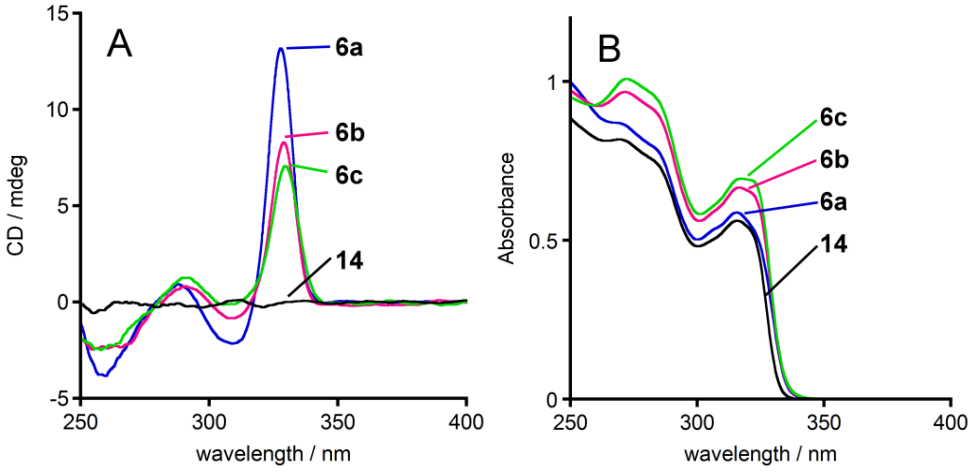


Figure 5. (A) CD and (B) UV-vis spectra of α-D-mannoside-linked ethynylpyridine oligomers (blue) **6a**, (red) **6b**, (green) **6c** and (black) control **14**. Conditions: **6a**, **6b**, **6c**, or **14** (5.0×10^{-4} M, pyridine unit conc), CH_2Cl_2, 25 °C, path length = 1 mm.

When the CD spectrum of **6a** (Figure 6, blue line) was compared with that of the previous mannoside-linked ethynylpyridine 6-mer **4** (sugar = α-D-mannoside, n = 6, black line) composed by Huisgen reaction with a longer linker,[3] the strength of the CD band of **6a** were found to be much enhanced as expected. On contrary, 6-mer **13** (green line), in which the mannoside and ethynylpyridine moieties are tethered with merely one triazole ring, showed much weaker CD than **6a**. For **13**, flexibility of conformation would extremely be limited, so the interaction between ethynylpyridine and mannoside moieties would not work well. It was also found that the strength of the CD band around 330 nm for **6a–c** was comparable to that for **2** (sugar = α-D-mannoside, m = 3, n = 6, orange line) having a flexible alkylene linker without a triazole ring.

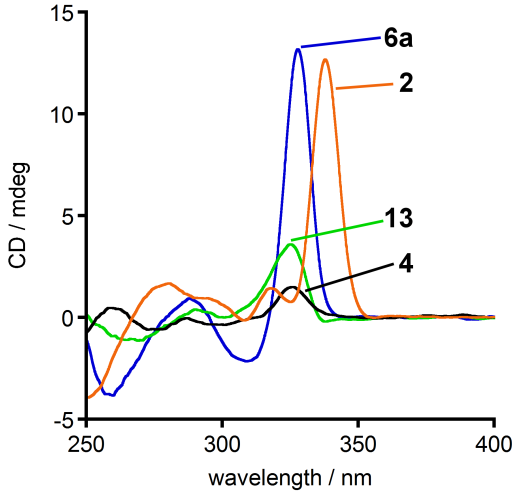


Figure 6. Comparison of CD spectra of α-D-mannoside-linked ethynylpyridine 6-mers (blue) **6a**, (green) **13**, (orange) **2**[2] (sugar = α-D-mannoside, m = 3, n = 6), and (black) **4**[3] (sugar = α-D-mannoside, n = 6), of which the structures differ about the linker. Conditions: **6a**, **13**, **4** (5.0×10^{-4} M, pyridine unit conc), or **2** (6.0×10^{-4} M, pyridine unit conc), CH_2Cl_2, 25 °C, path length = 1 mm. The spectrum of **2** was normalized in such a way that pyridine unit conc becomes 5.0×10^{-4} M.

The effect of substituent at the other end of the oligomer was studied by using **6a**, **11**, and **12**. The CD and UV-vis spectra were shown in Figure 7, and the order of the strength of the first Cotton effect was **6a** > **12** > **11**, that is, the helix stabilization effect of the substituents was in the order of 1-hydroxy-1-methylethyl > H > TBS. The 1-hydroxy-1-methylethyl group in **6a** would form a hydrogen bond with a pyridine nitrogen atom or a saccharide oxygen atom to stabilize the helix. Such a stabilization effect is supported by the molecular models obtained by Monte-Carlo analyses using a methoxy analogue of **6a** (Figure 8).

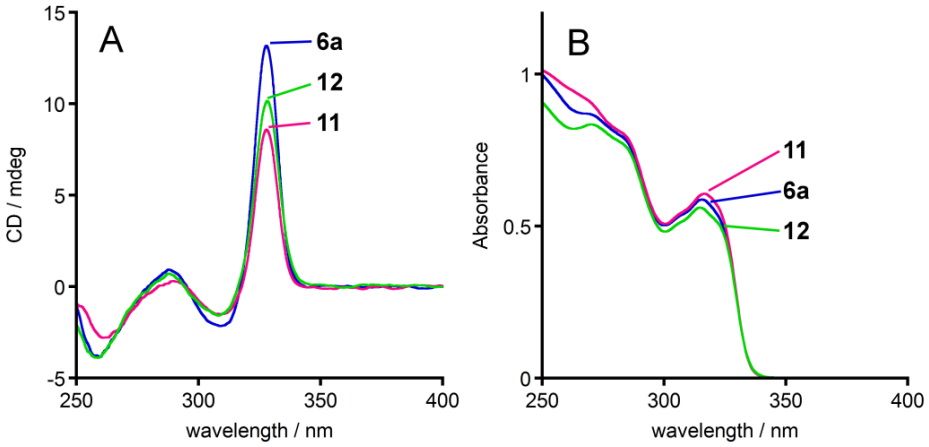


Figure 7. (A) CD and (B) UV-vis spectra of α-D-mannoside-linked ethynylpyridine 6-mers (blue) **6a**, (red) **11**, and (green) **12**, of which the structures differ about the terminal group. Conditions: **6a**, **11**, or **12** (5.0×10^{-4} M, pyridine unit conc), CH_2Cl_2, 25 °C, path length = 1 mm.

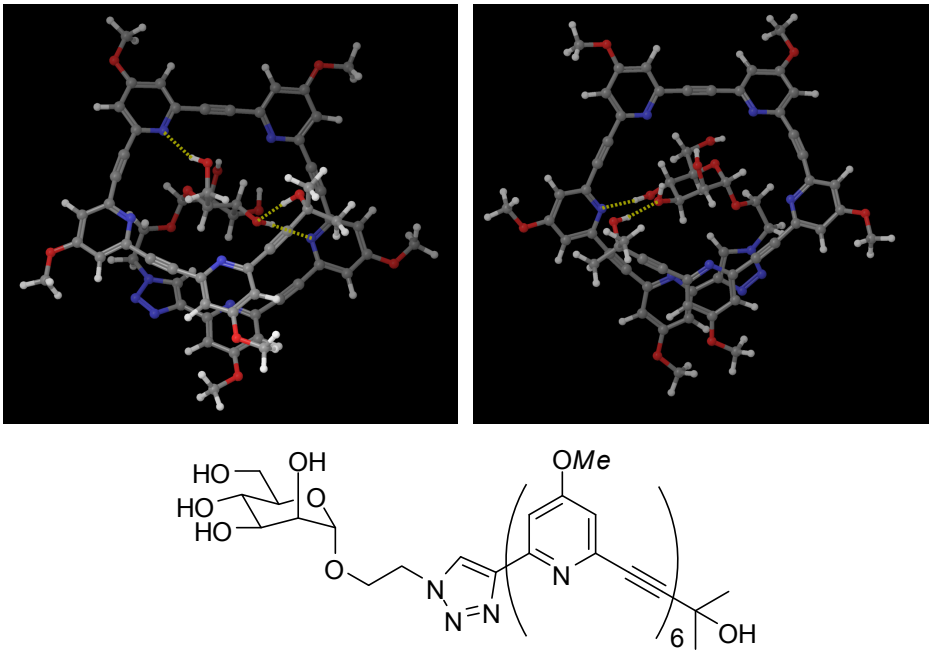


Figure 8. Molecular models for α-D-mannoside-linked ethynylpyridine 6-mer obtained by Monte-Carlo analyses. The model compound is an analogue of **6a**, in which the six octyloxy groups of **6a** were simplified to methoxy groups as shown. Hydrogen bonds are represented as broken lines. The helical senses of the oligomer are: (left) *P*-helix, (right) *M*-helix. *P*-Helix was predicted to be slightly stable by ca. 3 kJ/mol at the local minima. Procedure: Monte-Carlo analyses, energies were evaluated by MM calculation based on an OPLS 2005 force field by using MacroModel. Solvent: $CHCl_3$.

The additive effect of MeOH was studied to estimate the contribution of hydrogen bonding for the helix formation. CD and UV-vis spectra of **6a** were measured in a mixed solvent CH_2Cl_2/MeOH = 3:1 and compared to those measured in CH_2Cl_2. As shown in Figure 9 (blue solid and broken lines), the addition of MeOH suppressed the Cotton effect because MeOH disturbed the helix formation by the inhibition of the intramolecular hydrogen bonding.

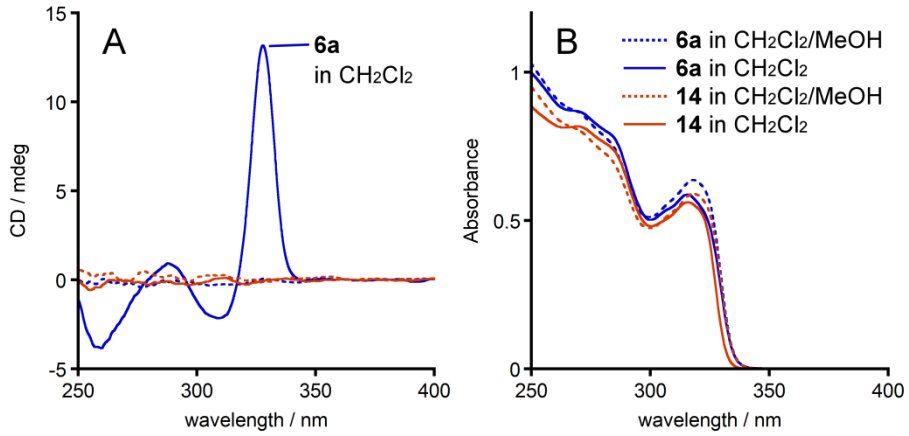


Figure 9. The additive effect of MeOH. (A) CD and (B) UV-vis spectra of (blue) **6a** and (red) **14** in (solid lines) CH_2Cl_2 and (broken lines) CH_2Cl_2/MeOH. Conditions: **6a** or **14** (5.0×10^{-4} M, pyridine unit conc), CH_2Cl_2 or CH_2Cl_2/MeOH (3:1), 25 °C, path length = 1 mm.

Among UV-vis spectra shown in Figures 5B, 7B, and 9B, the differences were small. When the unit concentration of pyridine rings were set same, spectrum of **6a** appeared to become weaker than those of **6b** and **6c** (Figure 5B). That is, absorption per one pyridine unit is weaker for **6a**, probably because of hypochromism caused by π-interaction in the helix, corresponding to the stronger CD.

In summary, new α-D-mannoside-linked ethynylpyridine oligomers have been investigated to improve their chiral helical higher-order structure. Convergent syntheses involving Huisgen reaction yielded a variety of ethynylpyridine oligomers, with changing the lengths of oligomer and linker, and the kind of substituent at the end of the oligomer. As a result, the 6-mer **6a**, of which ethynylpyridine and triazole moieties are tethered directly and the opposite end is protected by 1-hydroxy-1-methylethyl group showed an intense CD band around 330 nm. The CD intensity was much improved compared to our previous mannoside-linked oligomer which has a longer linker.

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7. Preparation of **6a**; A typical procedure for Huisgen reaction. To a mixture of **9a** (30.4 mg, 20.8 μmol), 2-azidoethyl α-D-mannopyranoside (**α-Man-N_3**, 11.2 mg, 44.9 μmol), sodium ascorbate (2.7 mg, 13.5 μmol), TBTA (2.4 mg, 4.5 μmol), CH_2Cl_2, (1 mL), and *t*-BuOH (1 mL) was added a water (1 mL) solution of $CuSO_4$ (0.71 mg, 4.5 μmol). After the mixture was stirred for 22.5 h at room temperature, additional **α-Man-N_3** (11.2 mg, 44.9 μmol) was added to the mixture. The reaction mixture was stirred additionally for 5.5 h, and then a water (0.3 mL) solution of $CuSO_4$ (0.71 mg, 4.5 μmol), sodium ascorbate (2.7 mg, 13.5 μmol), and TBTA (2.4 mg, 4.5 μmol) was added to the mixture. The resulting reaction mixture was stirred for 15 h and concentrated by a rotary evaporator, and the resulting residue was subjected to silica gel column chromatography (eluent: $CHCl_3$ to $CHCl_3$/MeOH = 20:1) to afford **6a** (28.9 mg, 81% based on **9a**) as a pale brown solid. mp 90−95 °C; ν_{max} (KBr) 3353, 2925, 2855, 2354, 1584, 1548 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1 H), 7.60 (d, J = 2.4 Hz, 1 H), 7.16−6.91 (m, 11 H), 4.96 (s, 1 H), 4.83 (br s, 1 H), 4.72−4.46 (br m, 3 H), 4.14−3.90 (m, 14 H), 3.88−3.71 (br m, 3 H), 3.60−3.48 (br, 2 H), 1.90−1.70 (m, 12 H), 1.61 (s, 6 H), 1.52−1.12 (m, 60 H), 0.96−0.80 (m, 18 H); δ_C (75 MHz, $CDCl_3$) 165.44, 165.27, 143.80, 143.64, 114.41, 114.45, 87.60, 87.43, 87.09, 77.24, 68.88, 65.33, 31.89, 31.23, 29.30, 28.98, 28.85, 25.95, 22.78, 14.24; HRMS (ESI) Calcd for $C_{103}H_{137}N_9O_{13}$ ($M + Na^+$): 1732.0266; Found: 1732.0260.
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