JOC*Note*

pubs.acs.org/joc

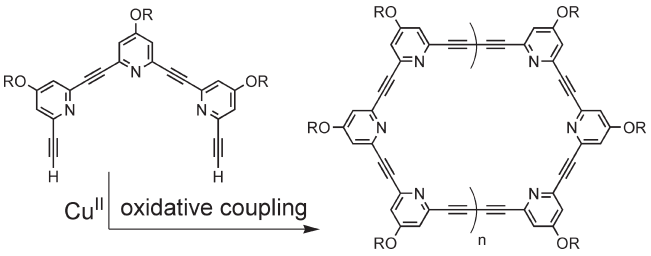
Preparation of Ethynylpyridine Macrocycles by Oxidative Coupling of an Ethynylpyridine Trimer with Terminal Acetylenes

Hajime Abe,* Hiroyuki Kurokawa, Yusuke Chida, and Masahiko Inouye*

Graduate School of Pharmaceutical Sciences, University of Toyama, Sugitani 2630, Toyama 930-0194, Japan

abeh@pha.u-toyama.ac.jp; inouye@pha.u-toyama.ac.jp

Received September 30, 2010



Macrocycles consisted of pyridine rings and acetylene bonds were prepared by Eglinton coupling from a tandem precursor bearing two terminal alkynyl groups. The composition of molecular size in the cyclized products changed by the reaction solvent. In pyridine, 9-meric and bigger macrocycles were obtained, while that of 6-mer was not. On the other hand, in pyridine/THF mixed solvent, the 6-mer was obtained as a major product.

Macrocyclic structures with multiple functionalities are efficient for constructing artificial host molecules as represented by crown ethers and calixarenes.[1] The higher symmetry of host structure and preorganization for guest molecules reduce the entropic loss upon host−guest association. During the course of our study on artificial host molecules for saccharide recognition, the tripyridinic part in **1** was found to be an effective module for monosaccharide recognition (Figure 1).[2] The pyridine rings were linked with acetylene bonds to keep rigidity and proper distances for this purpose. Incorporation of this module into the macrocyclic structure was essential to obtain the binding strength to monosaccharides.[3] We next designed macrocyclic oligomers such as **2** with increased symmetry and the number of binding sites to further improve the binding strength.[4,5] For the preparation of those macrocycles, the Sonogashira reaction was attempted to link the pyridine rings with acetylene bonds. However, acyclic polymers were obtained instead of expected macrocycles, which incidentally gave us fruitful results, in which the polymer recognizes saccharides within the helical structure.[6] To achieve macrocyclic hosts, we made an alternative plan to attempt oxidative homocoupling mediated by a copper salt[7] for the tandem acetylene **3** bearing three pyridine rings. Herein, we report the synthesis of ethynylpyridine macrocycles by oxidative homocoupling, depending on the solvents used.

The precursor for macrocyclization, tandem trimeric 2,6-pyridylene ethynylene compound **13**, was prepared as shown in Scheme 1. Aliphatic alkoxy groups at the 4-positions of the pyridine rings were introduced to improve solubility. Commercially available 2,6-dibromopyridine **4** was converted into 2,6-dibromo-4-nitropyridine **5** in three steps,[8] and it was allowed to react with metal alkoxides to give 4-alkoxypyridines **6** and **8**. The *tert*-butoxy derivative **6** was treated with CuI/NaI[9] to afford diiodide **7**. The octyloxy derivative **8** was converted into dissymmetric diyne **10** via **9** by subsequent Sonogashira couplings with 3-methylbutyn-2-ol and (*tert*-butyldimethylsilyl)-acetylene. Base-promoted liberation of acetone from **10**

(1) (a) *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Dürr, H., Eds.; VCH: Weinheim, 1991. (b) *Crown Compounds*; Cooper, S. R., Ed.; VCH: New York., 1992. (c) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, 2001.

(2) (a) Inouye, M.; Miyake, T.; Furusyo, M.; Nakazumi, H. *J. Am. Chem. Soc.* **1995**, *117*, 12416–12425. (b) Inouye, M.; Takahashi, K.; Nakazumi, H. *J. Am. Chem. Soc.* **1999**, *121*, 341–345. (c) Inouye, M.; Chiba, J.; Nakazumi, H. *J. Org. Chem.* **1999**, *64*, 8170–8176.

(3) For examples of macrocyclic host molecules for saccharide recognition, see: (a) Barwell, N. P.; Crump, M. P.; Davis, A. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7673–7676. (b) Ferrand, Y.; Klein, E.; Barwell, N. P.; Crump, M. P.; Jiménez-Barbero, J.; Vicent, C.; Boons, G.-J.; Ingale, S.; Davis, A. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1775–1779. (c) Ferrand, Y.; Crump, M. P.; Davis, A. P. *Science* **2007**, *318*, 619–622. (d) Anderson, S.; Neidlein, U.; Gramlich, V.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1596. (e) Aoyama, Y.; Tanaka, Y.; Sugahara, S. *J. Am. Chem. Soc.* **1989**, *111*, 5397–5404.

(4) For a review of acetylenic macrocyclic π-systems with host ability, see: Höger, S. In *Acetylene Chemistry*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, 2005; pp 427−452.

(5) For recent examples of syntheses of ethynylpyridine-containing macrocyclic π-systems, see: (a) Miki, K.; Fujita, M.; Inoue, Y.; Senda, Y.; Kowada, T.; Ohe, K. *J. Org. Chem.* **2010**, *75*, 3537–3540. (b) Sonoda, M.; Yamaguchi, Y.; Tahara, K.; Hirose, K.; Tobe, Y. *Tetrahedron* **2008**, *64*, 11490–11494. (c) Tobe, Y.; Nagano, A.; Kawabata, K.; Sonoda, M.; Naemura, K. *Org. Lett.* **2000**, *2*, 3265–3268. (d) Opris, D. M.; Ossenbach, A.; Lentz, D.; Schlüter, A. D. *Org. Lett.* **2008**, *10*, 2091–2093. (e) Grave, C.; Lentz, D.; Schäfer, A.; Samori, P.; Rabe, J. P.; Franke, P.; Schlüter, A. D. *J. Am. Chem. Soc.* **2003**, *125*, 6907–6918. (f) Spitler, E. L.; McClintock, S. P.; Haley, M. M. *J. Org. Chem.* **2007**, *72*, 6692–6699. (g) Baxter, P. N. W.; Dali-Youcef, R. *J. Org. Chem.* **2005**, *70*, 4935–4953. (h) Baxter, P. N. W. *Chem.—Eur. J.* **2003**, *9*, 5011–5022. (i) Campbell, K.; Kuehl, C. J.; Ferguson, M. J.; Stang, P. J.; Tykwinski, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 7266–7267. (j) Campbell, K.; McDonald, R.; Tykwinski, R. R. *J. Org. Chem.* **2002**, *67*, 1133–1140. (k) Yamaguchi, Y.; Yoshida, Z. *Chem.—Eur. J.* **2003**, *9*, 5430–5440. (l) Kobayashi, S.; Yamaguchi, Y.; Wakamiya, T.; Matsubara, Y.; Sugimoto, K.; Yoshida, Z. *Tetrahedron Lett.* **2003**, *44*, 1469–1472. (m) Jester, S.-S.; Shabelina, N.; Le Blanc, S. M.; Höger, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 6101–6105. (n) Shabelina, N.; Klyatskaya, S.; Enkelmann, V.; Höger, S. *C. R. Chim.* **2009**, *12*, 430–436.

(6) (a) Inouye, M.; Waki, M.; Abe, H. *J. Am. Chem. Soc.* **2004**, *126*, 2022–2027. (b) Abe, H.; Masuda, N.; Waki, M.; Inouye, M. *J. Am. Chem. Soc.* **2005**, *127*, 16189–16196. (c) Waki, M.; Abe, H.; Inouye, M. *Chem.—Eur. J.* **2006**, *12*, 7839–7847. (d) Waki, M.; Abe, H.; Inouye, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3059–3061. (e) Abe, H.; Machiguchi, H.; Matsumoto, S.; Inouye, M. *J. Org. Chem.* **2008**, *73*, 4650–4661. (f) Abe, H.; Murayama, D.; Kayamori, F.; Inouye, M. *Macromolecules* **2008**, *41*, 6903–6909. (g) Abe, H.; Takashima, S.; Yamamoto, T.; Inouye, M. *Chem. Commun.* **2009**, 2121–2123.

(7) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632–2657.

(8) Rodriguez-Ubis, J. C.; Sedano, R.; Barroso, G.; Juanes, O.; Brunet, E. *Helv. Chim. Acta* **1997**, *80*, 86–96. See also: Nettekoven, M.; Jenny, C. *Org. Process Res. Dev.* **2003**, *7*, 38–43.

(9) Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844–14845.

DOI: 10.1021/jo101921e Published on Web 12/08/2010

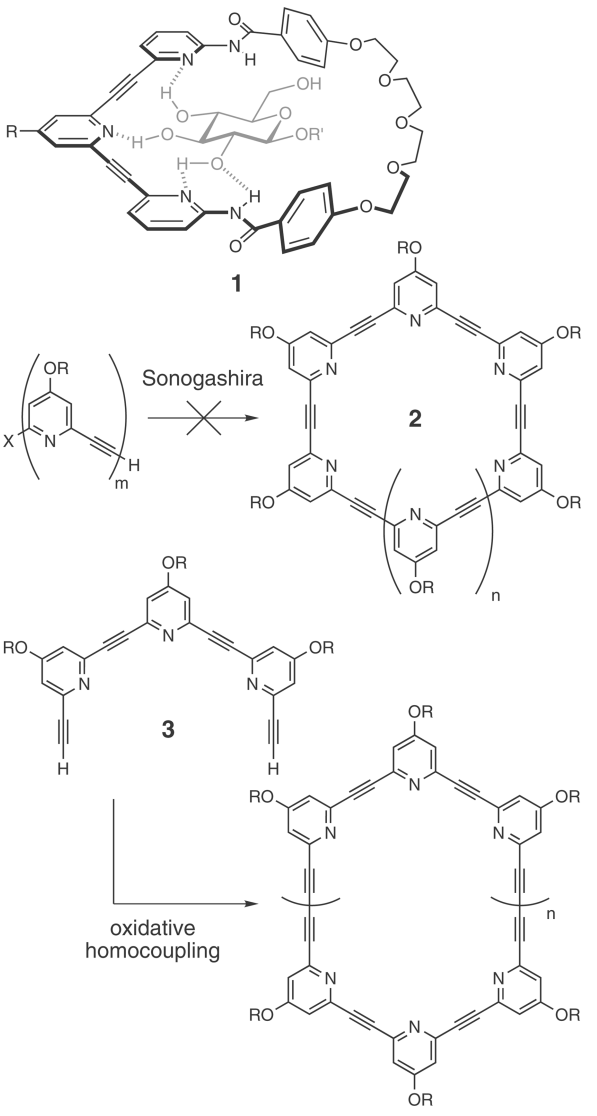


FIGURE 1. Ethynylpyridine macrocycles. **1**: macrocyclic host molecule previously reported. **2**: highly symmetrical macrocycles, which could not be obtained by Sonogashira coupling. Bottom: diyne-including macrocycles by oxidative homocoupling of **3**.

gave **11**. The diiodide **7** was assembled with 2 equiv of **11** by Sonogashira reaction to yield **12**, whose two silyl groups were finally deprotected to obtain the tandem precursor **13**.

Now homocoupling macrocyclization of the precursor **13** was investigated. Common procedures known as Glaser and Hay coupling in the presence of catalytic amount of copper salt under air gave only a tarry complex mixture.[10] It was found that Eglinton procedure yields macrocyclic products by mixing **13** with an excess amount of copper(II) acetate in a pyridine solution under an argon atmosphere (Table 1, entry 1).[7] Interestingly, the macrocyclic products mainly consisted of 9-mer **15** and 12-mer **16**, while the smallest 6-mer **14** was not detected. In ESI-MS analyses, trace signals of 15-meric product were also observed. On the other hand, when **13** was treated with copper(II) acetate in pyridine/THF mixed solvent, the 6-mer **14** was obtained as a major product in a moderate yield (entry 4). The use of copper(II) triflate instead of copper(II) acetate gave no cyclized products (entry 5).

Because of electric dipole moment on pyridine rings, the pyridine−acetylene−pyridine structure prefers transoid conformation to cisoid one in order to avoid electrostatic replusion.[6a,b] Actually, DFT calculations for a model trimer **17** indicated that cisoid conformer **17-cis** is less stable than transoid conformer **17-trans** (Figure 2). The ring size of 9-mer **15** and bigger macrocycles allows transoid conformation by forming a zigzag crown structure (Figure S1, Supporting Information). However, 6-mer **14** is too small to form a zigzag structure and is expected to form a virtually plain structure consisting of only the cisoid conformation, in which all of the pyridinic nitrogen atoms direct to the inside of the macrocycle. The reason for the solvent effect in the oxidative macrocyclization is still obscured. The solubility of copper salts would be different in pyridine vs pyridine/THF. Copper(II) ion turns into copper(I) at the oxidative dimerization. If the copper(I) species disturbed the aimed reaction, its precipitation may be favorable.

Among the macrocyclic products, the bigger product showed the bigger R_f value in normal-phase TLC, possibly due to hydrophobicity caused by alkyl groups. Only **14** is solid, and it showed lower solubility to MeOH and chloroform, probably because of good packing of the plain molecules. In ^{1}H NMR analyses, aromatic signals for bigger macrocycles appeared downfield (Table 2). This finding would be due to the contribution of the transoid conformation as supported by DFT calculation for models **17-trans** and **cis** (Figure S2, Supporting Information). For the precursor **13**, the chemical shifts were close to those of the 12-mer **16**, suggesting that **13** is predominantly in transoid conformation in a $CDCl_3$ solution.

SCHEME 1. Preparation of Tandem Precursor 13

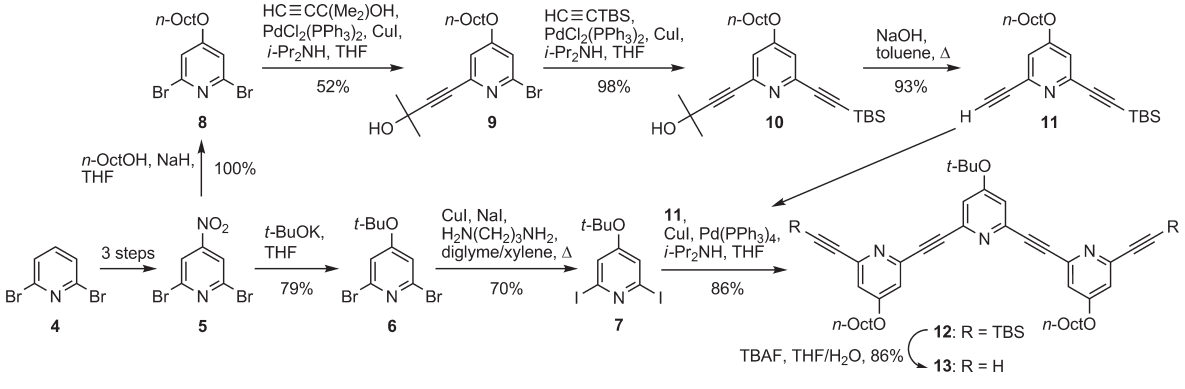
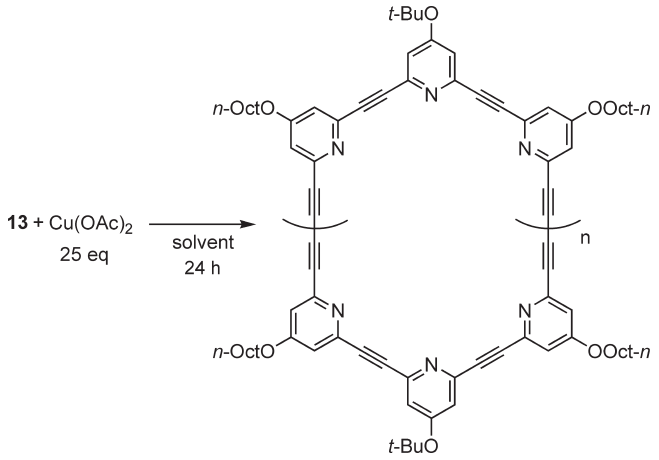


TABLE 1. Macrocyclic Products and Solvent Effect of Eglinton Coupling of 13



		product/%[a]		
entry	solvent	**14**, 6-mer (n = 1)	**15**, 9-mer (n = 2)	**16**, 12-mer (n = 3)
1	pyridine	nd	9	8
2	pyridine/THF(1:1)	13	nd	nd
3	pyridine/THF(1:2)	24	nd	nd
4	pyridine/THF(2:5)	39	6	4
5	pyridine/THF(2:5)[b]	nd	nd	nd

[a]Isolated yield. nd = not detected. [b]$Cu(OTf)_2$ was used instead of $Cu(OAc)_2$. Reaction time was 48 h, and 51% of **13** was recovered.

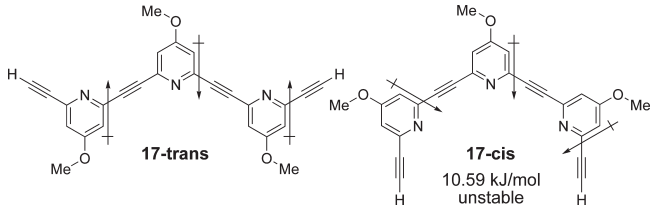


FIGURE 2. DFT-predicted relative stability of cisoid and transoid conformers of trimeric precursor model **17**. Conditions: geometry optimization at the B3LYP/6-31 level; single-point energies at the B3LYP/6-311+G(2d,p) level. Arrows indicate local dipole moments on pyridine rings.

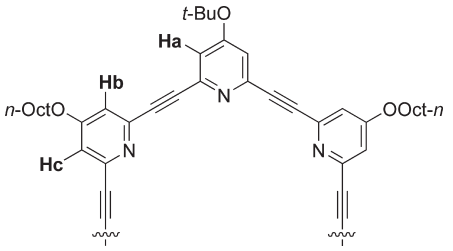
The pyridine-containing macrocycles obtained here have potential as a host molecule to accommodate polar guest molecules such as saccharides by multiple hydrogen bonds. In particular, the macrocyclic structures may suit to the size recognition. *tert*-Butyl groups can be removed by acid cleavage and subsequently brought to further functionalization to confer additional properties. We are now investigating their host abilities and improvement of the macrocycles.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, using tetramethylsilane (TMS) as an internal reference. Melting points were not corrected. THF was freshly distilled from sodium benzophenone ketyl before use. Pyridine was also distilled from CaH_2 before use. The tandem precursor **13** was prepared by the procedure following our previous study[2] (see the Supporting Information).

(10) For examples of the attempted reagents, $Cu(OAc)_2$/TMEDA/THF/air; CuI/2,2-bipyridyl/I_2/K_2CO_3/benzene.

TABLE 2. ^1H NMR Chemical Shifts for Aromatic Protons of Macrocycles 14−16 and Substrate 13[a]



	δ (ppm)		
compd	Ha	Hb	Hc
13, precursor	7.19	7.14	6.99
14, 6-mer	7.08	7.02	6.98
15, 9-mer	7.14	7.06	7.00
16, 12-mer	7.20	7.11	7.02

[a]Conditions: 500 MHz, $CDCl_3$, 23 °C.

Oxidative Coupling of 13 in Pyridine/THF. Preparation of 6-mer 14. A mixture of $Cu(OAc)_2$ (1.1 g, 6.25 mmol), pyridine (120 mL), and THF (200 mL) was bubbled with argon for 1 h, and then acetylene precursor **13** (160 mg, 0.25 mmol) was added to the resulting suspension. After being stirred for 12 h at room temperature, the resulting mixture was diluted with H_2O (200 mL) and AcOEt (200 mL) and extracted with ether repeatedly. The combined ether layer was washed with 5% hydrochloric acid, water, aqueous $NaHCO_3$, and brine subsequently and concentrated with a rotary evaporator. The resulting residue was subjected to silica gel column chromatography (eluent: $CHCl_3$/MeOH = 50:1 to 10:1) to yield 6-mer **14** (64 mg, 39%) as a pale brown solid. 9-Mer **15** (11 mg, 6%) and 12-mer **16** (6 mg, 4%) were also isolated as pale brown oils. **14**: mp 240 °C dec; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, J = 7.0 Hz, 12 H), 1.25−1.38 (m, 32 H), 1.42−1.45 (m, 8 H), 1.51 (s, 18 H), 1.77−1.81 (m, 8 H), 4.01 (t, J = 6.5 Hz, 8 H), 6.98 (s, 4 H), 7.02 (s, 4 H), 7.08 (s, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 22.6, 25.8, 28.8, 29.17, 29.22, 31.8, 68.5, 72.8, 80.4, 87.0, 87.4, 114.0, 114.2, 119.5, 143.3, 143.9, 144.2, 165.1; IR (KBr) 2928, 2856, 2227, 2153, 1576, 1545 cm^{-1}; ESI-HRMS m/z calcd for $C_{86}H_{98}N_6NaO_6$ ($M + Na^+$) 1333.7446, found 1333.7373. **15**: ^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, J = 7.3 Hz, 18 H), 1.25−1.38 (m, 48 H), 1.42−1.45 (m, 12 H), 1.49 (s, 27 H), 1.77−1.81 (m, 12 H), 4.01 (t, J = 6.8 Hz, 12 H), 7.00 (d, J = 2.5 Hz, 6 H), 7.06 (d, J = 2.5 Hz, 6 H), 7.14 (s, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 22.6, 25.8, 28.7, 29.1, 29.2, 31.7, 68.7, 73.0, 80.7, 81.1, 87.1, 87.5, 114.0, 114.7, 119.6, 143.1, 143.7, 144.2, 163.2, 165.3; IR (neat) 2925, 2855, 2227, 2154, 1579, 1544 cm^{-1}; ESI-HRMS m/z calcd for $C_{129}H_{146}DN_9NaO_9$ ($M + H^+$) 1990.1252, found 1990.1255. **16**: ^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, J = 7.0 Hz, 24 H), 1.25−1.38 (m, 64 H), 1.42−1.45 (m, 16 H), 1.50 (s, 36 H), 1.78−1.82 (m, 16 H), 4.02 (t, J = 6.5 Hz, 16 H), 7.02 (d, J = 2.3 Hz, 8 H), 7.11 (d, J = 2.3 Hz, 8 H), 7.20 (s, 8 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 22.6, 25.8, 28.7, 29.16, 29.20, 31.8, 68.7, 73.0, 81.2, 87.1, 87.5, 115.0, 120.0, 143.1, 143.6, 144.2, 163.3, 165.3; IR (neat) 2925, 2855, 2224, 2153, 1579, 1544 cm^{-1}; ESI-HRMS m/z calcd for $C_{172}H_{194}D_2N_{12}NaO_{12}$ ($M + H^+$) 2646.5058, found 2646.5071.

Acknowledgment. This study was supported by Mitsubishi Chemical Corporation Fund.

Supporting Information Available: Experimental procedures, Figures S1 and S2, details of theoretical analyses, and copies of NMR spectra for compounds **6**, **7**, and **9**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.