ORGANIC LETTERS

2009
Vol. 11, No. 11
2289−2292

Chiral Tetraazamacrocycles Having Four Pendant-Arms

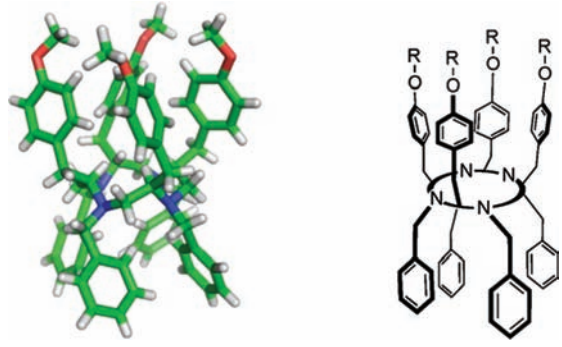
Seiji Kamioka,[†] Takashi Takahashi,[†] Susumu Kawauchi,[‡] Hiroaki Adachi,[§] Yusuke Mori,[§] Kotaro Fujii,[¶] Hidehiro Uekusa,[¶] and Takayuki Doi*[,†,§]

Department of Applied Chemistry, Tokyo Institute of Technology, 2-12-1, Ookayama, Meguro, Tokyo 152-8552, Japan, Department of Organic and Polymeric Materials, Tokyo Institute of Technology, Sosho, Inc., Department of Electrical, Electronic and Information Engineering, Osaka University, CREST JST, 2-1 Yamadaoka, Suita, Osaka, 565-0871, Japan, and Department of Chemistry and Materials Science, Tokyo Institute of Technology, Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aza-aoba, Aramaki, Aoba-ku, Sendai, 980-8578, Japan

doi_taka@mail.pharm.tohoku.ac.jp

Received March 21, 2009

ABSTRACT



A chiral tetraazamacrocycle 9 having four pendant-arms was synthesized by repeating ring opening of an Ns-aziridine with secondary amines, followed by macrocyclization. The structure of 9 has been determined by single crystal X-ray diffraction analysis and NMR studies. Sugar-hybrid molecules 12a−12f were synthesized based on the scaffold 9. NMR study showed that 12a−12f keep the similar conformation as 9 in solution.

Cyclen, 1,4,7,10-tetraazacyclododecane, has been widely studied in scientific fields as its metal complexes are utilized for sensors, imaging and therapeutic agents.[1,2] If a cyclen-like derivative has four pendant-arms that orient to the same face, it would have a vase-like three-dimensional structure as a calix[4]arene scaffold.[3,4] It could be applied to a novel sensor and/or imaging agent having a molecular recognition talent.

We designed tetraazamacrocycle **1** in which benzyl groups are on the nitrogen[5] and alkoxybenzyl groups are on the

[†] Department of Applied Chemistry, Tokyo Institute of Technology.
[‡] Department of Organic and Polymeric Materials, Tokyo Institute of Technology.
[§] Sosho, Inc., Osaka University, Tohoku University.
[¶] Department of Chemistry and Materials Science, Tokyo Institute of Technology.

(1) *Molecular and Cellular MR Imaging*; Modo, M. M., Bulte, J. W. W., Eds.; CRC Press: Boca Raton, FL, 2007.
(2) (a) Gunnlaugsson, T.; Leonard, J. P. *Chem. Commun.* **2005**, 3114–3131. (b) Bünzli, J.-C. G.; Piguet, C. *Chem. Soc. Rev.* **2005**, *34*, 1048–1077. (c) Parker, D.; Dickins, R. S.; Puschmann, H.; Crossland, C.; Howard, J. A. K. *Chem. Rev.* **2002**, *102*, 1977–2010.
(3) (a) Hamuro, Y.; Calama, M. C.; Park, H. S.; Hamilton, A. D. *Angew. Chem., Int. Ed.* **1997**, *36*, 2680–2683. (b) Park, H. S.; Lin, Q.; Hamilton, A. D. *J. Am. Chem. Soc.* **1999**, *121*, 8–13. (c) Peczuh, M. W.; Hamilton, A. D. *Chem. Rev.* **2000**, *100*, 2479–2494.
(4) Far, A. R.; Shivanyuk, A.; Rebek, J. *J. Am. Chem. Soc.* **2002**, *124*, 2854–2855.
(5) (a) Hansen, G. R.; Burg, T. E. *J. Heterocycl. Chem.* **1968**, *5*, 305. (b) Kalligeros, G. A.; Blinn, E. L. *Inorg. Chem.* **1972**, *11*, 1145–1148.

10.1021/ol9005954 CCC: $40.75
Published on Web 05/11/2009

cyclic skeleton with (*S*)-stereochemistry as pendant-arms.[6] It is expected that all the alkoxybenzyl groups could be oriented to the same face by either $\pi-\pi$ stacking or CH$-\pi$ interaction between the benzene rings (Figure 1). We report

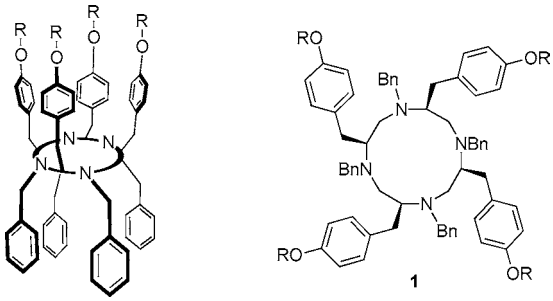
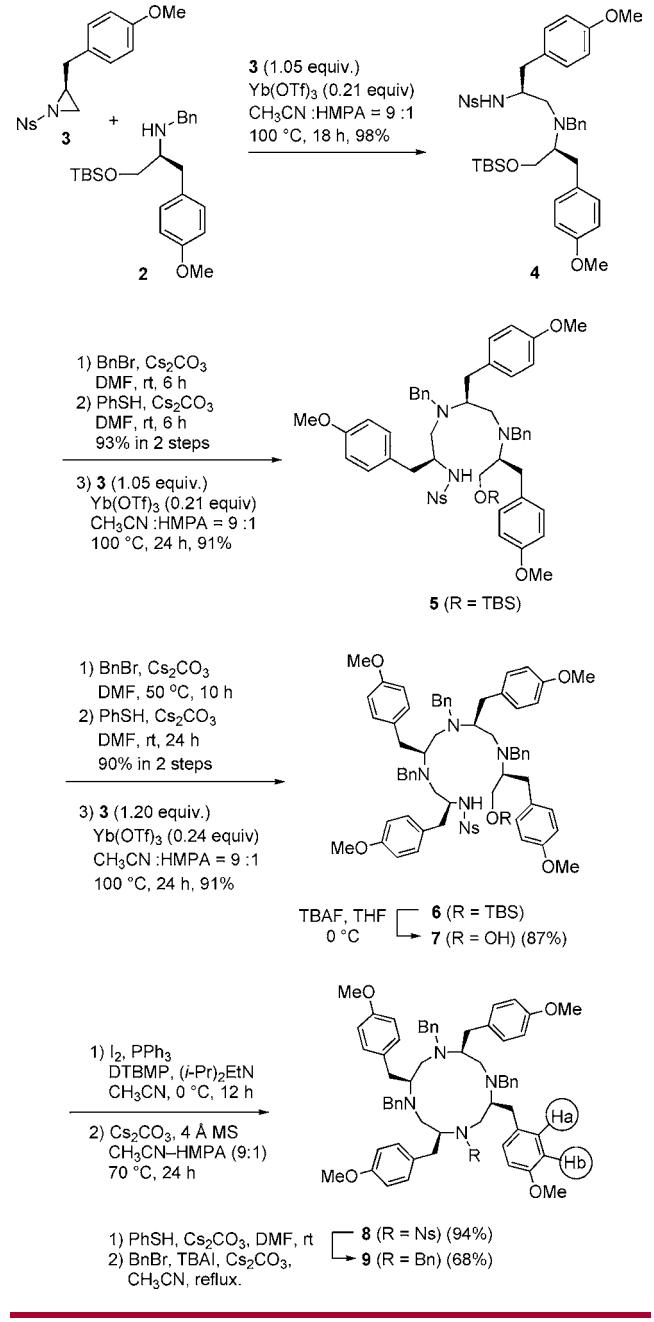


Figure 1. Designed tetraazamacrocyclic molecules **1**.

the asymmetric synthesis of tetraazamacrocycle **1** and its spectroscopic analysis as well as X-ray single crystal structural analysis. We initially developed the regioselective ring-opening of aziridine **3** with secondary benzylamine **2**, both of which are readily prepared from *O*-methyl-L-tyrosine in optically pure form.[7] Yb(OTf)$_3$-catalyzed[8] ring-opening of aziridine **3** was successfully achieved when an aziridine unit was protected with a nosyl (2-nitrobenzenesulfonyl, Ns) group (Scheme 1).[9,10] The desired **4** was provided in 98% yield as a single regioisomer. After N-benzylation of Ns-amide **4** (BnBr/Cs_2CO_3), the Ns group was removed (PhSH/Cs_2CO_3). The resulting secondary benzylamine was used for the next ring-opening reaction of Ns-aziridine **3**. The reaction was performed using 0.21 equiv of Yb(OTf)$_3$ as previously mentioned to afford the desired 1,4,7-triazanonane **5** in 91% yield. This three-step process, N-benzylation, removal of the Ns group, and the ring-opening of aziridine **3**, was repeatedly performed to provide 1,4,7,10-tetraazadodecane **6**. It should be noted that the ring-opening of Ns-aziridine **3** with various secondary benzylamines proceeded in good yields with complete regioselectivity. Removal of the TBS groups in **6** (TBAF/THF) provided the cyclization precursor **7**. Alcohol **7** was converted to the corresponding iodide (I_2/PPh_3/ 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP)/(*i*-Pr)$_2$EtN), which was immediately subjected to macrocyclization using Cs_2CO_3

Scheme 1. Synthesis of Tetraazamacrocycle **9**



as base.[11,12] The intramolecular alkylation smoothly proceeded at 70 °C in acetonitrile−HMPA (9:1) in the presence of 4 Å molecular sieves leading to 12-membered tetraazamacrocycle **8** in 94% yield from **7**. The reaction was reproducible in a 10 g-scale. Removal of the Ns group in **8** and benzylation of the resulting secondary amine furnished the desired tetraazamacrocycle **9** in 68% yield from **8**.

The ^{13}C NMR spectrum of **9** exhibited 13 carbon signals corresponding to the simple unit of 2-(benzylamino)-1-

(6) Synthesis, conformational analysis, and metal complexes of chiral tetra-C-ethylcyclens have been reported. (a) Tsuboyama, S.; Tsuboyama, K.; Higashi, I.; Yanagita, M. *Tetrahedron Lett.* **1970**, *45*, 1367–1370. (b) Tsuboyama, K.; Tsuboyama, S.; Uzawa, J.; Kobayashi, K.; Sakurai, T. *Tetrahedron Lett.* **1977**, *52*, 4603–4606. (c) Kobayashi, K.; Takahashi, H.; Nishio, M.; Umezawa, Y.; Tsuboyama, K.; Tsuboyama, S. *Anal. Sci.* **2000**, *16*, 1103–1104.

(7) Experimental details are described in Supporting Information.

(8) (a) Meguro, M.; Asao, N.; Yamamoto, Y. *Tetrahedron Lett.* **1994**, *35*, 7395–7398. (b) Meguro, M.; Yamamoto, Y. *Heterocycles* **1996**, *43*, 2473–2482.

(9) (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373–6374. (b) Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831–5834.

(10) Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 5253–5256.

(11) (a) Kurosawa, W.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **1993**, *125*, 8112–8113.

(12) (a) Kan, T.; Fujiawara, A.; Kobayashi, H.; Fukuyama, T. *Tetrahedron* **2002**, *58*, 6267–6276. (b) An, H.; Cummins, L. L.; Griffey, R. H.; Bharadwaj, R.; Haly, B. D.; Fraser, A. S.; Wilson-Lingardo, L.; Risen, L. M.; Wyatt, J. R.; Cook, P. D. *J. Am. Chem. Soc.* **1997**, *119*, 3696–3708.

(4-methoxyphenyl)propyl. The structure of tetraazamacrocycle **9** was unambiguously determined by single crystal X-ray diffraction analysis shown in Figure 2.[13] It was found

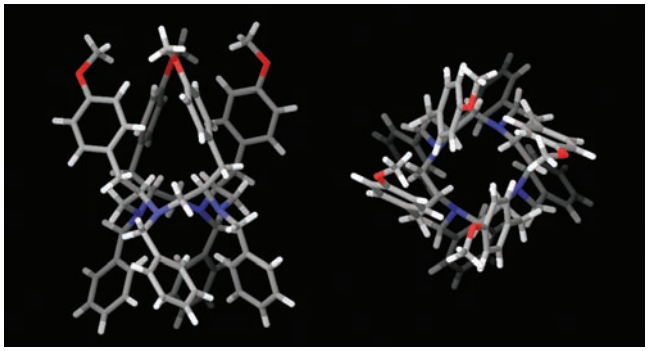


Figure 2. X-ray single crystal structure of **9**.

that four methoxyphenyl groups are oriented to the top face of the macrocyclic ring and four N-benzyl groups are oriented to the bottom face of the macrocycle. Additionally, four 4-methoxyphenyl groups are in a direction perpendicular to each other. The calculated distance of 3.402 Å between Ha at the 2-position of the 4-methoxyphenyl groups shown in Scheme 1 and the adjacent phenyl ring of the 4-methoxyphenyl groups suggests CH$-\pi$ interactions. On the basis of the X-ray crystal structure of **9**, the NMR chemical shifts of Ha and Hb in **9** and H-3 and H-2 in 4-methylanisole were calculated by the differences in the values from tetramethylsilane with a GIAO method at the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d,p) level using Gaussian 03.[14] It was suggested that large high-field shift (-0.92 ppm) for Ha compared with H-3 in 4-methylanisole would be expected by magnetic anisotropic effects derived from CH$-\pi$ interaction whereas no significant effect would be observed for Hb ($+0.02$ ppm) (Table 1). ^{1}H NMR analysis of **9** using various

Table 1. Calculation of the Chemical Shifts of Ha and Hb in **9**

entry	**9**[a] (ppm)		4-methylanisole[a] (ppm)		Δ (ppm)
1	Ha	6.41	H-3	7.33	−0.92
2	Hb	6.96	H-2	6.94	0.02

[a] Chemical shift was predicted based on DFT calculation [B3LYP/6-311G(2d,p)/B3LYP/6-31G(d,p)].

deuterated solvents exhibited large high-field shifts for Ha (-0.58 ppm in $CDCl_3$, -0.50 ppm in CD_2Cl_2 and -0.46 ppm in benzene-d_6) and small shifts for Hb [-0.07 ppm in $CDCl_3$, -0.04 ppm in CD_2Cl_2 and $+0.16$ ppm in benzene-d_6] comparing with the chemical shifts of 4-methylanisole in the corresponding solvents (Table 2). The tendency of

Table 2. ^{1}H NMR analysis of **9**

entry	$CDCl_3$[a] (Δ[b]) (ppm)	CD_2Cl_2[a] (Δ[b]) (ppm)	benzene-d_6[a] (Δ[b]) (ppm)
Ha	6.57 (−0.58)	6.62 (−0.50)	6.53 (−0.46)
Hb	6.80 (−0.07)	6.79 (−0.04)	6.97 (0.16)

[a] ^{1}H NMR was measured at 25 °C. [b] Differences of the chemical shifts of Ha and Hb in **9** compared with those of the corresponding H-3 and H-2 in 4-methylanisole measured in the respective solvents.

large high-field shift of Ha and small shift for Hb is in good accordance with the results from the theoretical calculation described above. Therefore, it is suggested that the conformation of **9** shown in Figure 2 is also dominant in solution as well as in the single crystal.

Next, we investigated a method for the modification of the RO groups in **1** using the new scaffold, tetraazamacrocycle **9**. Since it is well-known that cluster glycosides exhibit affinity enhancement,[15] we planned the synthesis of the sugar-hybrid molecules **12** having various glycosides utilizing copper-catalyzed 1,3-dipolar cycloaddition (Scheme 2).[16,17] Removal of all the methyl ethers with BBr_3, followed by O-alkylation of the resulting phenols with propargyl bromide provided the alkyne-containing tetraazamacrocycle **10** in 51% overall yield. The 1,3-dipolar cycloaddition of tetrayne **10** to azido-containing glycosides **11** proceeded at room temperature in the presence of CuI in THF and (i-Pr)$_2$EtN except for a lactoside at 50 °C. The products were obtained as a mixture of its Cu(II) complexes, which were treated with cyclen in refluxing THF to remove the Cu(II) ion and all acetyl groups in the glycosides. As depicted in Table 3,

(13) The single crystal was obtained from a 1 mL solution of benzene and hexane (65:35) containing 1 mg of **9**. We investigated 44 combinations of mixed solvents (CH_2Cl_2, $CHCl_3$, CCl_4, PhH) and (C_5H_{12}, C_6H_{14}, Et_2O, EtOAc, THF, 1,4-dioxane, toluene, MeOH, EtOH, i-PrOH, t-BuOH) for crystallization. The single crystal X-ray diffraction data were collected on a Rigaku R-AXIS RAPID imaging plate diffractometer with Mo$K\alpha$ radiation ($\lambda = 0.71075$ Å). Crystal data for **9**: C_{68} H_{76} N_4 O_4, C_6 H_6, M_r =1091.44, Crystal System = *Triclinic*, Space group = *P*1 (no. 1), Lattice Parameters $a = 10.4685(19)$ Å, $b = 14.642(3)$ Å, $c = 20.231(5)$ Å, $\alpha = 79.047(9)°$, $\beta = 89.633(9)°$, $\gamma = 81.328(7)°$, $V = 3009.0(10)$ Å^3, $Z = 2$, $T = 93$ K, $R_1 = 0.0444[\ I > 2\sigma\ (I)$; 11424 refs.], $wR = 0.1160$(all data; 13580 refs.), Gof = 1.063. CCDC 706437 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

(14) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Jr. Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision D.02; Gaussian, Inc.: Wallingford, CT, 2004.

(15) Lee, Y. C.; Lee, R. T. *Acc. Chem. Res.* **1995**, *28*, 321–327.

(16) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599.

(17) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.

Scheme 2. Synthesis of Sugar-Hybrid Molecules **12**

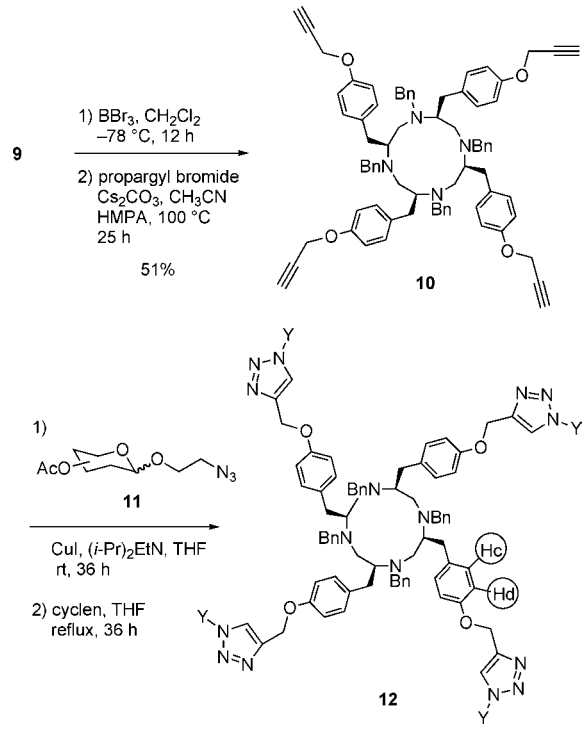
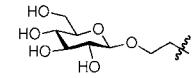
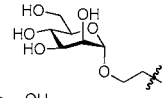
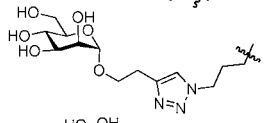
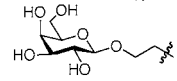
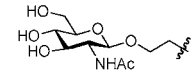
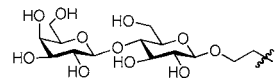


Table 3. Copper-Catalyzed 1,3-Dipolar Cycloaddition of **10** and **11** and the ^{1}H NMR Chemical Shifts of the Hc and Hd in **12**

Product	Y	Isolated Yield (%)	Hc (Δ^a) (ppm)	Hd (Δ^a) (ppm)
12a[b]		83	6.79 (–0.30)	6.94 (0.02)
12b[b]		79	6.78 (–0.31)	6.93 (0.01)
12c[b]		87	6.74 (–0.35)	6.92 (0.00)
12d[c]		88	6.81 (–0.27)	6.93 (0.02)
12e[c]		85	6.83 (–0.25)	6.93 (0.02)
12f[b]		80[d]	6.78 (–0.31)	6.93 (0.02)

[a] Differences of the chemical shifts of Hc and Hd in **12** compared with those of the 4-methylanisole-containing sugar unit. [b] ^{1}H NMR spectra were measured at 80 °C in DMSO-d_6. [c] ^{1}H NMR spectra were measured at 100 °C in DMSO-d_6. [d] Reaction was performed at 50 °C.

sugar-hybrid molecules **12** were exclusively obtained in high yields (79−88% in 2 steps). The conformation of sugar-hybrid molecules **12** was elucidated by the ^{1}H NMR analysis. If sugar-hybrid molecules **12** have kept the same conformation as **9** like four 4-alkoxyphenyl groups are at right angles to each other, high-field shift for Hc will be observed by magnetic anisotropic effects derived from CH−π interaction and chemical shift for Hd will not be affected comparing to the 4-methoxyphenol-containing sugar unit. Indeed, ^{1}H NMR analysis using deuterated DMSO exhibited high-field shifts (−0.25 to −0.35 ppm) for Hc and no significant shift (up to +0.02 ppm) for Hd (Table 3). These results suggested that all sugar-hybrid molecules **12** have the similar conformation that four methoxyphenyl groups face on one side of the macrocyclic ring without relying on the species of sugars, the stereochemistry of anomeric positions and the number of sugars.

In summary, we have demonstrated the efficient synthesis of tetraazamacrocycle **9** utilizing ring-opening of an Ns-aziridine with secondary benzylamines and intramolecular alkylation with the Ns-amides as key steps. The structure of tetraazamacrocycle **9** was unambiguously determined by single crystal X-ray diffraction analysis. Comparing the high-field shift of Ha in ^{1}H NMR spectrum of **9** with the expected shift by theoretical calculation of magnetic anisotropic effects based on the X-ray structure, it is suggested that the solid-state conformation is dominant in solution. Hybridization of **9** with various glycosides was performed using regioselective copper-catalyzed 1,3-dipolar cycloaddition. The ^{1}H NMR study suggests that the sugar-hybrid tetraazamacrocycles **12** have kept the similar conformation as **9** in solution. Therefore, it is expected that various molecular recognition sites could be introduced to **1** utilizing this method. Further study for metal chelation and introduction of cyclic peptides to **1** is in progress.

Acknowledgment. We thank Prof. Shigeki Kuwata (Tokyotech) and Prof. Hajime Iwamoto (Niigata Univ.) for helpful discussion for structure elucidation. This work was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan (No. 16350051).

Supporting Information Available: Experimental details and NMR spectra of **2**−**10** and **12a**−**12f**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9005954