JOC*Note*

A Simple, Regioselective Synthesis of 1,4-Bis(*tert*-butoxycarbonylmethyl)-tetraazacyclododecane

Cong Li and Wing-Tak Wong*

Department of Chemistry and Open Laboratory of Chemical Biology of the Institute of Molecular Technology for Drug Discovery and Synthesis, The University of Hong Kong, Pokfulam Road, Hong Kong, P. R. China

wtwong@hkucc.hku.hk

Received September 11, 2002

Abstract: A convenient synthetic route to 1,4-bis(*tert*-butoxycarbonylmethyl)tetraazacyclododecane (cyclen) (**1**) with high yield and excellent regioselectivity is described. Compound **1** reacted with a range of functionalized alkyl halides under two reaction conditions to give mono-N-alkylated 1,4-bis(*tert*-butoxycarbonylmethyl)tetraazacyclododecane (**2**−**9**) in good yield.

1,4,7,10-Tetraazacyclododecane (cyclen)-based multidentate ligands are very useful chelating agents for lanthanide(III) ions. The resulting complexes show high thermodynamic and kinetic stability in aqueous solution and have been widely used as magnetic resonance imaging (MRI) contrast agents (CAs) (Gd complexes);[1] diagnostic−therapeutic radio-pharmaceuticals carrying radionuclides such as ^{90}Y;[2] luminescence probes and labels containing Eu and Tb;[3] RNA cleavers[4] (La) and catalysts[5] (Y, La, and Yb). In these complexes, three pendant chelating moieties, especially the carboxylate at the N-substituted positions, are utilized for strong lanthanide chelation and hence give rise to neutral metal complexes. The remaining N-substituted position of cyclen can be derivatized to improve tissue selectivity,[6] enhance light-harvesting efficiency,[7] or sense pH value,[7,8] halide ions,[8] and even enzymatic activity.[9] Currently, novel systems in which two different functional groups lie on the same cyclen molecule are attracting considerable attention. Recently, Bornhop reported that a tumor-specific agent and an energy absorbing/transmitting chromophore were conjugated to one cyclen framework; the resulting lanthanide complex not only afforded ligand-specific cell targeting in vivo and in vitro, but also provided the real-time intraoperative fluorescence that correlates with anatomic imaging.[10] Although a number of methods for the mono-N-alkylation[11] and tri-N-alkylation[12] of cyclen have been developed, relatively fewer strategies for bis-alkylation are available. Selective bis-alkylations of cyclen have all been achieved via temporary diprotection by tosyl,[13] methyl,[14] and phosphoryl groups,[15] carbamates moieties,[16] silicon intermediates,[17] and oxamide groups.[18] However, nearly all these procedures only allow 1,7-bis-functionalization except refs 13b and 18, and no good direct 1,4-bis-N-alkylation of cyclen has been reported to our knowledge. In our previous reports, a direct method for the preparation of mono-N-alkylated cyclam and cyclen was described.[19] Using this procedure, a Tb complex of cyclam containing three chelated carboxylic acids and a crown ether was found to signal [Na^+] and [K^+] with luminescence lifetime as output.[20] As part of a continuous effort in this area, we report a convenient procedure for directly introducing *tert*-butoxycarbonylmethyl groups (precursor of carboxylic acid) to the two neighboring N-substituted positions of cyclen in high yield and with excellent regioselectivity.

(1) (a) Alexander, V. *Chem. Rev.* **1995**, *95*, 273. (b) Caravan, P.; Ellison, J. J.; McMurry, T. J.; Lauffer, R. B. *Chem. Rev.* **1999**, *99*, 2293. (c) Bianchi, A.; Calabi, L.; Corana, F.; Fontana, S.; Losi, P.; Maiocchi, A.; Paleari, L.; Valtancoli, B. *Coord. Chem. Rev.* **2000**, *204*, 309.

(2) (a) Anderson, C. J.; Welch, M. J. *Chem. Rev.* **1999**, *99*, 2219. (b) Volkert, W. A.; Hoffman, T. J. *Chem. Rev.* **1999**, *99*, 2269. (c) Takeunouchi, K.; Watanabe, K.; Kato, Y.; Koike, T.; Kimura, E. *J. Org. Chem.* **1993**, *58*, 1955. (d) Takenouchi, K.; Tabe, M.; Watanabe, K.; Hazato, A.; Kato, Y.; Shionoya, M.; Koike, T.; Kimura, E. *J. Org. Chem.* **1993**, *58*, 6895. (e) Brechbiel, M. W.; Pippin, C. G.; McMurry, T. J.; Milenic, D.; Roselli, M.; Colcher, D.; Gansow, O. A. *J. Chem. Soc., Chem. Commun.* **1991**, 1169. (f) Kumar, K.; Magerstädt, M.; Gansow, O. A. *J. Chem. Soc., Chem. Commun.* **1989**, 145.

(3) (a) Mayer, A.; Neuenhofer, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1044. (b) Richardson, F. S. *Chem. Rev.* **1982**, *541*. (c) De Silva, A. P.; Fox, D. B.; Huxley, A. J. M.; McClenaghan, N. D.; Roiron, J. *Coord. Chem. Rev.* **1999**, *185*−*186*, 297. (d) Aoki, S.; Kawatani, H.; Goto, T.; Kimura, E.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 1123.

(4) (a) Amin, S.; Morrow, J. R.; Lake, C. H.; Churchill, M. R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 773. (b) Morrow, J. R.; Amin, S.; Lake, C. H.; Churchill, M. R. *Inorg. Chem.* **1993**, *32*, 4566. (c) Amin, S.; Voss, D. A.; Horrocks, W. D., Jr.; Lake, C. H.; Churchill, M. R.; Morrow, J. R. *Inorg. Chem.* **1994**, *33*, 3294.

(5) (a) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1237. (b) Kobayashi, S. In *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic & Professional: London, 1998; p 262.

(6) (a) Aime, S.; Botta, M.; Fasano, M.; Terreno, E. *Chem. Soc. Rev.* **1998**, *27*, 19. (b) Corsi, D. M.; Elst, L. V.; Muller, R. N.; van Bekkum, H.; Peter, J. A. *Chem. Eur. J.* **2001**, *7*, 64. (c) Aime, S.; Botta, M.; Crich, S. G.; Giovenzana, G.; Palmisano, G.; Sisti, M. *Chem. Commun.* **1999**, 1577.

(7) (a) Gunnlaugsson, T.; Parker, D. *Chem. Commun.* **1998**, 511. (b) Parker, D.; Williams, J. A. G. *Chem. Commun.* **1998**, 245. (c) Parker, D.; Senanayake, K.; Williams, J. A. G. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2129.

(8) (a) Parker, D.; Senanayake K.; Williams, J. A. G. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2129. (b) Parker, D.; Senanayake, K.; Williams, J. A. G. *Chem. Commun.* **1997**, 1777.

(9) Moats, R. A.; Fraser, S. E.; Meade, T. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 726.

(10) (a) Griffin, J. M. M.; Skwierawska, A. M.; Manning, H. C.; Marx, J. N.; Bornhop, D. J. *Tetrahedron Lett.* **2001**, *42*, 3823. (b) Manning, H. C.; Goebel, T.; Marx, J. N.; Bornhop, D. J. *Org. Lett.* **2002**, *4*, 1075.

(11) (a) Bender, J. A.; Meanwell, N. A. and Wang, T. *Tetrahedron* **2002**, *58*, 3111. (b) Bernard, H.; Yaouanc, J. J.; Clément, J. C.; des Abbayes, H.; Handel, H. *Tetrahedron Lett.* **1991**, *32*, 639. (c) Filali, A.; Yaouanc, J. J.; Handel, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 560. (d) Rohovec, J.; Gyepes, R.; Císařová, I.; Rudovský, J.; Lukeš, I. *Tetrahedron Lett.* **2000**, *41*, 1249.

(12) (a) Kimura, E.; Aoki, S.; Koike, T.; Shiro, M. *J. Am. Chem. Soc.* **1997**, *119*, 3068. (b) Dischino, D. D.; Delaney, E. J.; Emswiler, J. E.; Gaughan, G. T.; Prasad, J. S.; Srivastava, S. K.; Tweedle, M. F. *Inorg. Chem.* **1991**, *30*, 1265. (c) Boldrini, V.; Giovenzana, G. B.; Pagliarin, R.; Palmisano, G.; Sisti, M. *Tetrahedron Lett.* **2000**, *41*, 6527.

(13) (a) Dumont, A.; Jacques, V.; Xiu, P. Q.; Desreux, J. F. *Tetrahedron Lett.* **1994**, *35*, 3707. (b) Hill, J. P.; Anson, C. E.; Powell, A. K. *Tetrahedron Lett.* **2002**, *43*, 7301.

(14) Ciampolini, M.; Micheloni, M.; Nardi, N.; Paoletti, P.; Dapporto P.; Zanobini, F. *J. Chem. Soc., Dalton Trans.* **1984**, 1357.

(15) Gardinier, I.; Bernard, H.; Chuburu, F.; Roignant, A.; Yaouanc J. J.; Handel, H. *Chem. Commun.* **1996**, 2157.

(16) (a) Kovacs, Z.; Sherry, A. D. *J. Chem. Soc., Chem. Commun.* **1995**, 185. (b) Kovacs, Z.; Sherry, A. D. *Synthesis* **1997**, 759.

(17) Roignant, A.; Gardinier, I.; Bernard, H.; Yaouanc, J. J.; Handel, H. *J. Chem. Soc., Chem. Commun.* **1995**, 1233.

(18) Bellouard, F.; Chuburu, F.; Kervarec, N.; Toupet, L.; Triki, S.; Le Mest, Y.; Handel, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3499.

(19) Li, C.; Wong, W. T. *Tetrahedron Lett.* **2002**, *43*, 3217.

(20) Li, C.; Wong, W. T. *Chem. Commum.* **2002**, 2034.

10.1021/jo026436+ CCC: $25.00
Published on Web 02/25/2003

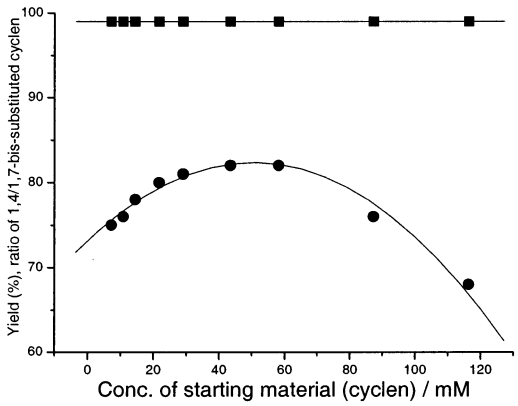
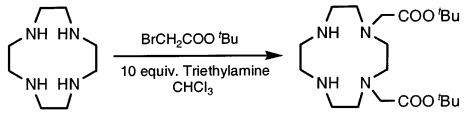


FIGURE 1. Plots of the yield (●) and the ratio (■) of 1,4/1,7-bis(*tert*-butoxycarbonylmethyl)-substituted cyclen as a function of concentrations of starting material (cyclen) in $CHCl_3$ (rt, 2.0 equiv of *tert*-butyl bromoacetate, 10 equiv of triethylamine).

SCHEME 1. Synthesis of 1,4-Bis(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (1)



Previously, Kruper found that the regioselectivity of the alkylation of polyazamacrocycles was dependent on both the steric hindrance of electrophiles and solvent systems.[21] For this reason, *tert*-butyl bromoacetate as the precursor of pendant carboxylic acid was chosen to react with cyclen in chloroform at room temperature in the presence of 10 equiv of triethylamine. 1,4-Bis(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (**1**) was isolated in good yield after flash chromatography. The 1,7-bis-substituted product was not detected (Scheme 1). Surprisingly, this excellent regioselectivity for 1,4-substituted product **1** was kept constant in the cyclen's concentration range of 10−120 mM (Figure 1). To clarify the effect of the solvent and auxiliary base on the yield of this reaction, experiments under different conditions were conducted. The following observations were summarized from the data shown in Table 1: The $CHCl_3$/triethylamine system afforded the most satisfactory result. Regioselectivity remained independent of the concentrations of the starting materials, and at the same time, the yield of bis-substituted product only has a moderate decrease when the concentration of cyclen added exceeded 60 mM. The effect of various solvents on the yield and regioselectivity was obvious, with chloroform being the solvent of choice (entries 4−6, Table 1). The use of weakly polar and aprotic solvents such as chloroform is preferable to polar, aprotic solvents such as DMF and polar, protic solvents such as methanol, which lead to substantial decreases in yield and regioselectivity by promoting proton transfer.[22] We speculated that this high regioselectivity in chloroform can be explained by the following assertion. The 12-membered cyclen ring has a strongly preferred square [3333] conformation in a less polar and aprotic solvent such as chloroform at room temperature.[23] After the first alkylation, the two 4-position N−H would be logically intraannular and H-bonded to the intraannular N lone pairs of the alkylated and the 7-position nitrogen. Thus, only the extraannular lone pairs of the two nitrogens at 4-position are available for further alkylation. To confirm the effect of base, comparative studies between the absence and the presence of various bases were performed in chloroform (entries 1−4, Table 1). Among the auxiliary bases examined, triethylamine gave the highest yield. The use of K_2CO_3 or pyridine led to a remarkable decrease in the yield of **1**, with the yield never exceeding 65%. It is also worthy of mention that the regioselectivity was kept constant regardless of the base used in the chloroform solvent system.

TABLE 1. Effect of Solvent and Base on the Yield and Regioselectivity of 1,4-Bis(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (1)

			yield[b] (%)			1,4/1,7-bis-substituted
entry	conditions[a]	base	tris	bis	mono	cyclen[c]
1	$CHCl_3$, rt	free	14	55	∼8	>99[e]
2	$CHCl_3$, rt	pyridine[f]	11	63	∼5	>99[e]
3	$CHCl_3$, rt	K_2CO_3[d]	15	57	∼6	>99[e]
4	$CHCl_3$, rt	triethylamine[f]	6	84	∼2	>99[e]
5	DMF, rt	triethylamine[f]	13	61	∼8	4.3
6	MeOH, rt	triethylamine[f]	23	46	∼7	3.2

[a] The two starting materials in all reactions were in the ratio of cyclen/*tert*-butyl bromoacetate = 1:2 and conducted at room temperature; reaction time ranged from 6 to 8 h. [b] Isolated yield of purified product after flash chromatography. [c] The ratio was determined by 400 MHz ^{1}H NMR and flash chromatography results.[24] [d] Five equivalents of K_2CO_3 was used. [e] 1,7-Bis(*tert*-butoxycarbonylmethyl)cyclen was not detected. [f] 10 equiv of triethylamine or pyridine was used.

Selective mono-N-alkylation of 1,4-bis(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (**1**) is another key step in the preparation of unsymmetrical bis-functionalized ligands, which initially requires a functional pendant group filling one of the remaining two N-substituted positions of **1**, while the other one is left for another alkylating agent. To investigate the selectivity and yields of **1** to various alkylation agents, especially those with functional groups that have been widely used in previous works,[6,9,11,21] electrophiles with pendant crown ethers, aza-crown ethers, quinaldine, carbon chain, and β-D-glucopyranoside were prepared, respectively. According to our earlier work on the preparation of mono-N-alkylated cyclam and cyclen,[19] treatment of **1** with stoichiometric electrophiles **2a**−**9a** in acetonitrile with 5.0 equiv of K_2CO_3 at 55−60 °C gave different results under these conditions, producing mono-N-alkylation products in adequate yields only with the "less active" halides **7a**−**9a** (Table 2). Using "active" alkyl halides such as allyl halide, benzyl halides, and α-halo carbonyl groups produced predominantly undesired bis-substituted com-

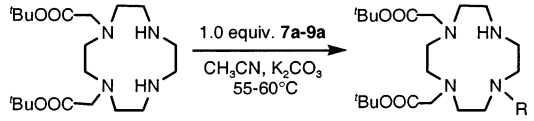
(21) Kruper, W. J., Jr.; Rudolf, P. R.; Langhoff, C. A. *J. Org. Chem.* **1993**, *58*, 3869.

(22) Reichardt, C.*Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: New York, 1988; pp 121−208.

(23) Glass, R. S. *Conformational Analysis of Medium-Sized Heterocycles*; VCH: New York, 1988; pp 122−123.

(24) The 1,4- and 1,7-bis-substituted products can be easily examined by the ^{13}C NMR spectral signal of the cyclen carbons; the 1,7-bis-substituted adduct displays two carbon signals for the 16 carbons in the macrocycle indicating a D_{2h} symmetry, whereas 1,4-bis-substituted adduct displays four carbon signals indicating C_{2v} symmetry.

TABLE 2. Reaction of "Less-Active" Alkylation Agents 7a−9a with 1,4-Bis(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (1)



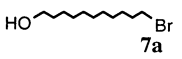
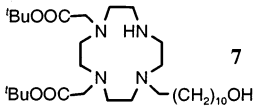
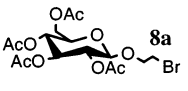
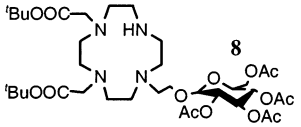
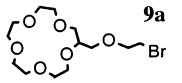
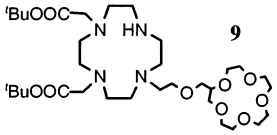
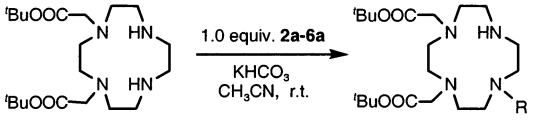
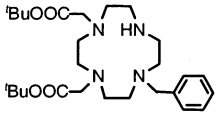
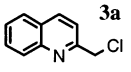
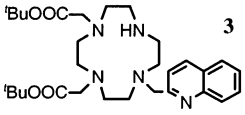
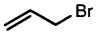
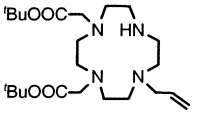
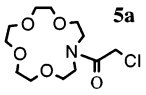
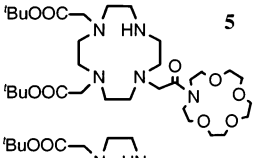
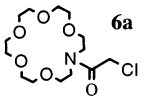
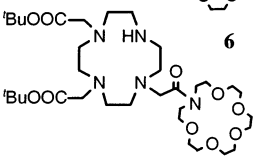
Entry	Electrophile	Time	Product	Yield (%)
1	 **7a**	10h	 **7**	91
2	 **8a**	8h	 **8**	85
3	 **9a**	8h	 **9**	81

TABLE 3. Reaction of "Active" Alkylation Agents 2a−6a with 1,4-Bis(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (1)



Entry	Electrophile	Time	Product	Yield (%)
1	**2a** 	6h	 **2**	77
2	**3a** 	6h	 **3**	85
3	**4a** 	4h	 **4**	71
4	**5a** 	8h	 **5**	83
5	**6a** 	8h	 **6**	87

pounds. Even when 1.5 equiv of **1** with these halides was used, the yields of mono-substituted products showed no obvious improvement. However, under milder reaction conditions at room temperature and the use of $KHCO_3$ instead of K_2CO_3, the reaction led to a considerable increase in the yield of monoalkylation product. A stoichiometric amount of **1** and "active" halides **2a**−**6a** provided satisfactory yields of mono-N-alkylation products **2**−**6** (77−87%) (Table 3). As can be seen in Tables 2 and 3, in addition to the reactivity, steric hindrance of eletrophiles is thought to be another important factor affecting the yield of mono-N-alkylation product **2**−**9**. For "less active" halides **7a**−**9a**, the introduction of a less sterically hindered bromide gave rise to mono-N-alkylation products in better yields. Compound **7a** with a long carbon chain gave the highest yield at 91% (entry 1, Table 2). However, the "active" halides **2a**−**6a** showed dramatically different behavior. The steric hindrance facilitated the preparation of monoalkylation products **2**−**6**, bulky electrophiles with macrocycles and quinoline such as **3a**, **5a**, and **6a** (entry 2, 4, and 5, Table 3) gave the yields all above 80%. The least sterically hindered halide **4a** with an allyl group displayed high propensity for the bis-N-substituted products; even under very mild reaction conditions the yield of bis-N-alkylation product was maintained at about 30%.

In conclusion, we developed a straightforward method for the preparation of 1,4-bis(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (**1**) in high yields and with excellent regioselectivity. Two general reaction conditions have been put forward for the synthesis of mono-N-alkylation of **1** with functionalized "active" and "less-active" halides. Furthermore, those accounts illustrate good potential since both the selective bis-alkylation and mono-alkylation of tetraazamacrocycles derivatives are in a single step without use of unnecessary protecting groups. Generally, these methods provide the introduction of different functional groups to the two remaining neighboring N-substituted positions of **1** with attractive features such as high yield, operational convenience, and cost economy. This methodology allows efficient alkylation, with a wide range of electrophiles, especially for sterically hindered macromolecules and bioactive-molecules.

Experimental Section

General Experimental Procedures. Unless otherwise stated, starting materials were obtained from commercial suppliers and used as received. Flash chromatograpy was performed using silica gel (70−230 mesh) and aluminum oxide 90 active neutral (70−230 mesh). Powdered K_2CO_3 was predried just prior to use and stored under Ar. ^1H (300 and 400 MHz) and ^{13}C (75 and 100 MHz) NMR spectra were measured in $CDCl_3$ with $SiMe_4$ (δ 0 ppm) as an internal standard. ^1H NMR data are recorded as follows: chemical shift (δ). For ^{13}C NMR spectra, the data are given as follows: chemical shift (δ). FT-IR spectra were recorded on dry KBr pellets; mass spectra (MS) were obtained at a fast atom bombardment source (FABMS) and an electron spray ionization source (ESIMS). All ESIMS spectra were carried out using MeOH as the solvent.

1,4-Bis(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (1). 1,4,7,10-Tetraazacyclododecane (cyclen) (400 mg, 2.3 mmol) was dissolved in 20 mL of anhydrous $CHCl_3$, and 10.0 equiv of triethylamine (2.3 g, 23.2 mmol) was added to the solution. *tert*-Butyl bromoacetate (2 equiv, 904.8 mg, 4.6 mmol) dissolved in 10 mL of $CHCl_3$ was added dropwise to the vigorously stirred solution. The addition lasted for about 1 h, and the solution continued to react for another 6 h at room temperature. $CHCl_3$ was evaporated, the transparent oil was dissolved in 10 mL of water, and the pH was adjusted to 11−12 by addition of 40% (w/v) NaOH solution. The mixture was extracted with $CHCl_3$ (4 × 15 mL), and the $CHCl_3$ extracts were combined and dried over Na_2SO_4. The combined extracts were

dried in vacuo, and the residue was loaded onto an aluminum oxide (neutral, 70−230 mesh) column. The column was eluted with a mixture of CH_2Cl_2/MeOH = 100:3 (v/v) (R_f = 0.35), the product was collected, and solvent was removed to give **1** as a white powder solid: yield 778 mg (84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32, 2.98−2.96, 2.89−2.87, 1.41; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 81.6, 53.4, 51.1, 49.9, 46.5, 46.1, 28.2; IR (KBr, cm^{-1}) 2976, 1732, 1715, 1636, 1559, 1457, 1167; ESIMS *m*/*z* 401.3 (M + H)$^+$; HRFABMS *m*/*z* 401.3130 (M + H)$^+$ [calcd for $C_{20}H_{41}N_4O_4$ (M +H)$^+$ 401.3128].

General Method for the Preparation of 2−6. To the appropriate electrophiles **2a**−**6a** (0.30 mmol) dissolved in 10.0 mL of acetonitrile was added dropwise a mixture of 1.0 equiv of 1,4-bis(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane **1** (120.0 mg, 0.30 mmol) and 5.0 equiv of $KHCO_3$ (208.5 mg, 1.5 mmol) in 40 mL of anhydrous acetonitrile under a N_2 atmosphere for ∼30 min. The mixture was stirred at room temperature for ∼4−8 h, and the solution was filtered under reduced pressure and dried in vacuo to give the crude products **2**−**6**.

7-Benzyl-1,4-bis(*tert*-butoxycarbonylmethyl)-1,4,8,11-tetraazacyclotetradecane (2). The reaction was carried out as described in the general procedure. The crude product was purified by flash chromatography on aluminum oxide (EtOAc/MeOH = 100:8, R_f = 0.20) to give **2** as a colorless oil: yield 122.2 mg (83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.23, 3.69, 3.36, 3.12, 3.05−2.54, 1.44, 1.36; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.7, 138.4, 129.6, 128.6, 127.8, 81.6, 81.5, 62.9, 58.9, 51.8, 51.5, 50.4, 50.1, 49.9, 49.6, 48.5, 48.0, 47.6, 28.3, 28.2; IR (KBr, cm^{-1}) 2980, 1726, 1452, 1362, 1254, 1215, 1151, 731, 700; ESIMS *m*/*z* 491.4 (M + H)$^+$; HRFABMS *m*/*z* 491.3597 (M + H)$^+$ [calcd for $C_{27}H_{47}N_4O_4$ (M + H)$^+$, 491.3597].

7-(2-Methylquinoline)-1,4-bis(*tert*-butoxycarbonylmethyl)-1,4,8,11-tetraazacyclotetradecane (3). The reaction was carried out as described in the general procedure. The crude product was purified by flash chromatography on aluminum oxide (EtOAc/MeOH = 100:10, R_f = 0.25) to give **3** as a colorless oil: yield 138.1 mg (85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11, 8.00, 7.76, 7.66, 7.53, 7.50, 4.03, 3.36, 3.16, 3.07−3.03, 2.90−2.79, 1.44, 1.25; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.5, 158.7, 147.6, 136.6, 129.7, 129.1, 127.6, 127.2, 126.5, 121.6, 81.5, 81.4, 64.1, 58.6, 51.5, 50.7, 50.4, 49.9, 49.6, 48.1, 48.0, 47.7, 28.1, 28.0; IR (KBr, cm^{-1}) 2965, 2847, 1717, 1559, 1457, 1259, 1151, 813, 752; ESIMS *m*/*z* 542.3 (M + H)$^+$; HRFABMS *m*/*z* 542.3728 (M + H)$^+$ [calcd for $C_{30}H_{48}N_5O_4$ (M + H)$^+$, 542.3706].

7-Allyl-1,4-bis(*tert*-butoxycarbonylmethyl)-1,4,8,11-tetraazacyclotetradecane (4). The reaction was carried out as described in the general procedure. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 100:19, R_f = 0.30) to give **4** as a colorless oil: yield 101.7 mg (77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88−5.84, 5.19−5.16, 3.35, 3.27, 3.20, 3.10−2.60, 1.44, 1.43; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.7, 134.6, 119.0, 81.7, 60.7, 58.6, 51.5, 50.6, 50.2, 49.4, 48.9, 48.6, 48.1, 47.9, 28.3, 28.2; IR (KBr, cm^{-1}) 3094, 2971, 1732, 1715, 1653, 1457, 1369, 1254, 1156; ESIMS *m*/*z* 441.3 (M + H)$^+$; HRFABMS *m*/*z* 441.3439 (M + H)$^+$ [calcd for $C_{23}H_{45}N_4O_4$ (M + H)$^+$, 441.3441].

7-(*N*-Acetylaza-15-crown-5)-1,4-bis(*tert*-butoxycarbonylmethyl)-1,4,8,11-tetraazacyclotetradecane (5). The reaction was carried out as described in the general procedure. The crude product was purified by flash chromatography on aluminum oxide (CH_2Cl_2/MeOH = 100:2.5, R_f = 0.25) to give **5** as a colorless oil: yield 164.3 mg (83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74, 3.63−3.54, 3.51, 3.42, 3.33, 3.24, 3.03−3.01, 2.91−2.75, 1.40, 1.39; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.6, 169.9, 81.7, 81.6, 71.6, 70.5, 70.3, 70.1, 69.9, 69.4, 57.9, 56.9, 51.8, 51.6, 51.3, 49.8, 49.7, 49.6, 49.2, 49.1, 47.3, 28.3, 28.2; IR (KBr, cm^{-1}) 2977, 1732, 1715, 1657, 1637, 1506, 1458, 1362, 1242, 1154, 1108; ESIMS *m*/*z* 660.4 (M + H)$^+$; HRFABMS *m*/*z* 660.4547 (M + H)$^+$ [calcd for $C_{32}H_{62}N_5O_9$ (M + H)$^+$, 660.4548].

7-(*N*-Acetylaza-18-crown-6)-1,4-bis(*tert*-butoxycarbonylmethyl)-1,4,8,11-tetraazacyclotetradecane (6). The reaction was carried out as described in the general procedure. The crude product was purified by flash chromatography on aluminum oxide (CH_2Cl_2/MeOH = 100:2.5, R_f = 0.25) to give **6** as a colorless oil: yield 183.7 mg (87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77−3.49, 3.35, 3.27, 3.18−2.72, 1.42, 1.40; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.6, 169.9, 81.6, 71.2, 70.8, 70.7, 70.6, 70.4, 70.2, 69.9, 69.6, 57.9, 56.7, 51.9, 51.8, 51.2, 49.7, 49.6, 49.5, 49.2, 48.4, 47.3, 46.7, 28.3, 28.2; IR (KBr, cm^{-1}) 2976, 1732, 1717, 1651, 1636, 1506, 1458, 1362, 1242, 1151, 1109; ESIMS *m*/*z* 704.5 (M + H)$^+$; HRFABMS *m*/*z* 704.4802 (M + H)$^+$ [calcd for $C_{34}H_{66}N_5O_{10}$ (M + H)$^+$, 704.4810].

General Method for the Preparation of 7−9. To the appropriate electrophiles **7a**−**9a** (0.30 mmol) dissolved in 10.0 mL of acetonitrile was added dropwise a mixture of 1.0 equiv of 1,4-bis(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane **1** (120.0 mg, 0.30 mmol) and 5.0 equiv of K_2CO_3 (207.0 mg, 1.5 mmol) in 40 mL of anhydrous acetonitrile under a N_2 atmosphere for ∼30 min. The mixture was stirred at 55−60 °C for ∼8−10 h, the solution was filtered under reduced pressure, and the extract was dried in vacuo to give the crude products **7**−**9**.

7-(1-Undecanol)-1,4-bis(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclotetradecane (7). The reaction was carried out as described in the general procedure. The crude product was purified by flash chromatography on aluminum oxide (EtOAc/MeOH = 100:8, R_f = 0.25) to give **7** as a colorless oil: yield 155.6 mg (91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56, 3.31, 3.23, 3.05−2.94, 2.93−2.70, 2.51−2.46, 1.51, 1.40 (s, 20H), 1.22; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 169.7, 81.5, 81.4, 62.7, 58.4, 58.0, 51.3, 51.1, 50.6, 50.3, 49.3, 48.7, 48.0, 47.8, 32.7, 29.5, 29.4, 29.3, 28.2, 28.1, 27.3, 27.0, 25.7; IR (KBr, cm^{-1}) 2973, 2857, 1735, 1457, 1376, 1160; ESIMS *m*/*z* 571.5 (M + H)$^+$; HRFABMS *m*/*z* 571.4792 (M + H)$^+$ [calcd for $C_{31}H_{63}N_4O_5$ (M + H)$^+$ 571.4798].

7-(2,3,4,6-Tetraacetyl-1-(2-ethoxyl)-D-glucopyranoside)-1,4-bis(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclotetradecane (8). The reaction was carried out as described in the general procedure. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 100:7, R_f = 0.25) to give **8** as a colorless oil: yield 197.6 mg (85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20, 4.96, 4.83, 4.44, 4.22−4.17, 4.04−3.98, 3.90−3.83, 3.64−3.60, 3.57−3.50, 3.32, 3.28, 2.97, 2.90−2.57, 1.98, 1.93, 1.91, 1.88, 1.38, 1.37; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.4, 170.1, 169.9, 169.4, 169.2, 100.9, 81.7, 81.6, 72.8, 72.0, 71.3, 68.4, 67.8, 61.9, 58.1, 56.6, 51.7, 51.3, 50.9, 50.8, 49.5, 49.1, 48.5, 48.1, 47.5, 28.2, 28.0, 20.8, 20.5; IR (KBr, cm^{-1}) 2971, 1753, 1732, 1636, 1559, 1457, 1365, 1227, 1158, 1038; ESIMS *m*/*z* 775.4 (M + H)$^+$; HRFABMS *m*/*z* 775.4344 (M + H)$^+$ [calcd for $C_{36}H_{63}N_4O_{14}$ (M + H)$^+$ 775.4341].

7-(2-(Ethoxymethyl)-15-crown-5)-1,4-bis(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclotetradecane (9). The reaction was carried out as described in the general procedure. The crude product was purified by flash chromatography on aluminum oxide (CH_2Cl_2/MeOH = 100:2.5, R_f = 0.20) to give **9** as a colorless oil: yield 168.5 mg (83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71−3.42, 3.34, 3.26, 3.07−2.54, 1.41, 1.39; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.7, 81.6, 81.5, 78.2, 71.1, 70.6, 70.5, 70.4, 70.3, 70.2, 70.1, 69.9, 69.5, 68.5, 58.4, 56.5, 51.5, 51.2, 50.8, 49.5, 49.1, 48.1, 48.0, 47.5, 28.3, 28.2; IR (KBr, cm^{-1}) 2971, 2922, 2868, 1732, 1716, 1653, 1557, 1457, 1260, 1157, 1115; ESIMS *m*/*z* 677.5 (M + H)$^+$; HRFABMS *m*/*z* 677.4702 (M + H)$^+$ [calcd for $C_{33}H_{65}N_4O_{10}$ *m*/*z* (M + H)$^+$ 677.4701.

Acknowledgment. We gratefully acknowledge financial support from the Hong Kong Research Grants Council and the University of Hong Kong. This work is also supported by an Area of Excellence Scheme of the University Grants Committee (Hong Kong). C.L. acknowledges the receipt of a postgraduate studentship administered by the University of Hong Kong.

Supporting Information Available: Experimental details and characterization data of halides **3a**, **5a**, **6a**, **8a**, and **9a**; ^{1}H NMR, ^{13}C NMR, and ESI-MS spectra of compounds **2**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026436+