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The Preparation of a Fully Differentiated "Multiwarhead" Siderophore Precursor

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Abstract: A protected, fully differentiated siderophore analogue has been prepared so that "Trojan Horse"-like siderophore drug conjugates with *different* drugs can be synthesized. The key steps in the synthesis include controlled preparation of an unsymmetrical urea and its conversion to a fully differentiated isocyanurate by reaction with chloro(carbonyl) isocyanate.

Specific drug delivery for bacterial and fungal infections is of considerable interest in this time of growing resistance to modern chemotherapeutics.[1] In particular, our laboratories have been investigating the use of "Trojan Horse"-like drug delivery agents,[2] whereby known antimicrobial agents are covalently attached to actively transported, low molecular weight iron chelators, or siderophores.[2,3] The artificial siderophore **2**, a trihydroxamate-containing isocyanurate, has been previously synthesized by our research group and mimics the natural siderophore rhodotorulic acid **1** (Figure 1), but with the ability to bind iron(III) stoichiometrically.[4] Isocyanurate **2** promoted growth of various strains of *E. coli*, thus demonstrating its ability to substitute for naturally occurring siderophores. Furthermore, over the course of an iron excretion study in a rat model, isocyanurate **2** effectively treated iron overload while being completely nontoxic.[4a]

Isocyanurate siderophore **2** was thought to be an ideal candidate for "Trojan Horse" drug delivery because of its selective microbial uptake[4a] and low mammalian toxicity. By simply replacing the terminal acetyl moieties with succinyl linkers, the opportunity of conjugating up to *three* drugs exists. Toward this end, drug conjugates of 5-fluorouridine (5-FU) have been synthesized and preliminary *in vitro* testing completed.[4] The initial findings

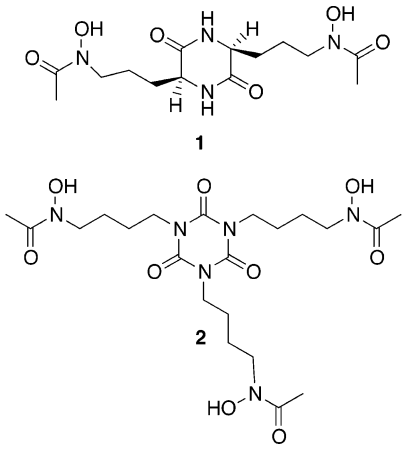

FIGURE 1. Rhodotorulic acid **1**, a natural bis-hydroxamate siderophore and synthetic trihydroxamate isocyanurate **2**.

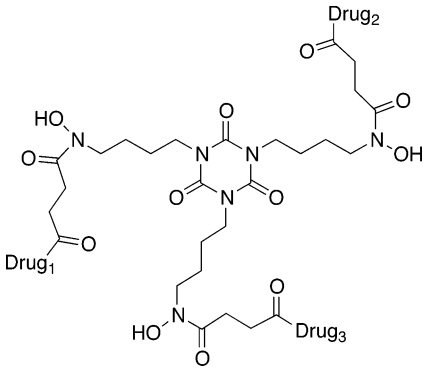

FIGURE 2. Conceptual multiwarhead siderophore−drug conjugate.

show drug conjugates containing three 5-FU molecules are more efficient than mono 5-FU drug conjugates, even at the same effective drug concentration.[4d] However, when we embarked on preparing truly "multiwarhead"-type conjugates containing two or more different drugs, the need arose to differentiate the arms of the isocyanurate scaffold (Figure 2). Previous methodologies developed in this laboratory were not compatible with such a goal, so a new synthetic scheme was required.

Our previous syntheses[4a−d] of isocyanurate siderophore drug conjugates did not allow facile differentiation of the three side chains of the symmetrical isocyanurate. A typical procedure involved attempted sequential removal of the identical 2,2,2-trichloroethoxycarbonyl (Troc) groups on the side chains of the scaffold. Unfortunately, this method yielded only small quantities of mono-deprotected material (~10−15% yields, 75% based on recovered starting material) and required careful chromatographic isolation. To circumvent these problems, we designed a new synthesis of the isocyanurate ring with each side chain having a different protecting group. The key step in this construction is the cyclization of chloro(carbonyl) isocyanate with an appropriate unsymmetrical urea as shown retrosynthetically in Scheme 1.[5]

As shown in Schemes 2 and 3, the synthesis began with the appropriately protected *O*-benzyl hydroxylamine

(1) (a) Koshland, D. E., Jr. *Science* **1994**, *254*, 327 (Editorial). (b) Travis, J. *Science* **1994**, *254*, 360. (c) Davies, J. *Science* **1994**, *254*, 375. (d) Nikaido, H. *Science* **1994**, *254*, 382. (e) Spratt, B. G. *Science* **1994**, *254*, 388. (f) Review: Chu, D. T. W.; Plattner, J. J.; Katz, L. *J. Med. Chem.* **1996**, *39*, 3853.

(2) For relevant reviews and "Trojan-Horse" delivery concepts, see: (a) Roosenberg, J. M.; Lin, Y.-M.; Lu, Y.; Miller, M. J. *Curr. Med. Chem.* **2000**, *7*, 159. (b) Malouin, F.; Miller, M. J. *Acc. Chem. Res.* **1993**, *26*, 241. (c) Miller, M. J.; Malouin, F. *The Development of Iron Chelators for Clinical Use*; Bergeron, R. J., Brittenham, G. M., Eds.; CRC: Ann Arbor, 1994; p 275. (d) Roosenberg, J. M.; Miller, M. J. *J. Org. Chem.* **2000**, *65*, 4833.

(3) Neilands, J. B. Methodology of Siderophores. *Structure and Bonding*; Springer-Verlag: Berlin, 1984.

(4) (a) Lee, B. H.; Prody, C. A.; Neilands, J. B.; Miller, M. J. *J. Med. Chem.* **1985**, *28*, 323. (b) Ghosh, M.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 1020. (c) Ghosh, M.; Miller, M. J. *Bioorg. Med. Chem.* **1995**, *3*, 1519. (d) Miller, M. J.; Lu, Y. *Bioorg. Med. Chem.* **1999**, *7*, 3035.

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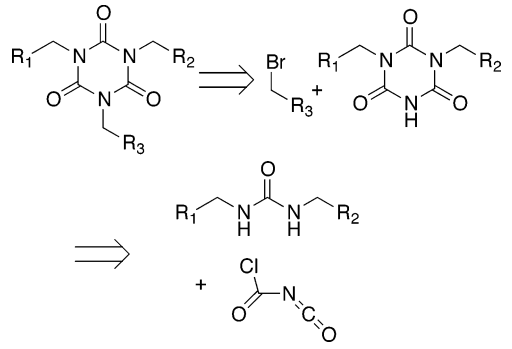
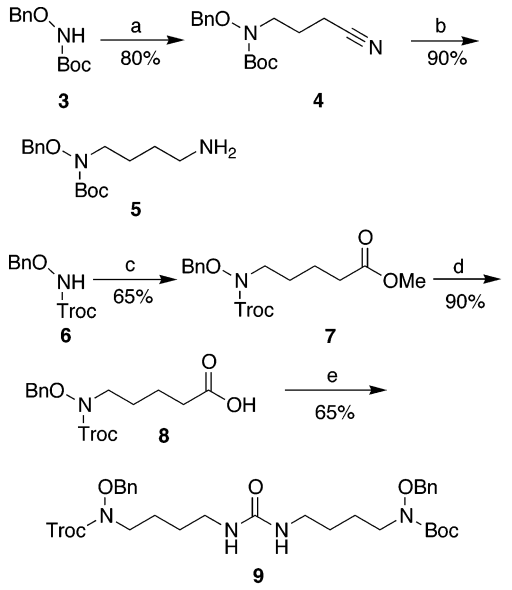
SCHEME 1



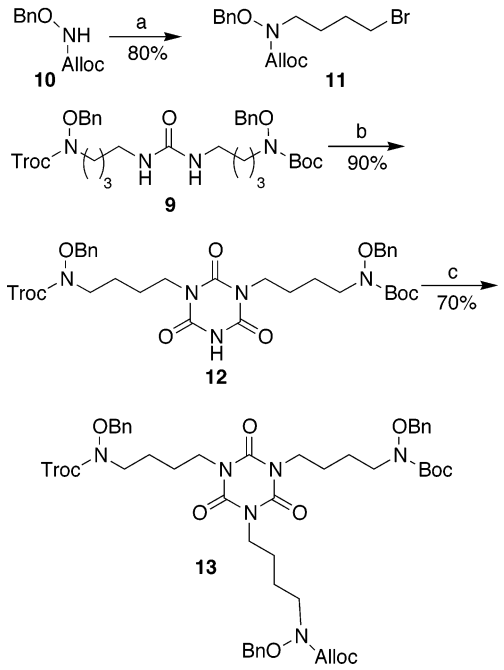
SCHEME 2[a]



[a] Reagents: (a) NaH, NaI, 4-chlorobutyronitrile, DMF, 70 °C, 5 h; (b) Raney Ni, ammonium hydroxide, H_2 (45 psi), MeOH; (c) 5-hydroxypentanoic acid methyl ester, triphenylphosphine, diisopropylazodicarboxylate, THF, 8 h; (d) 2 M HCl, dioxane, reflux, 12 h; (e) (i) diphenylphophoryl azide, NEt_3, toluene, 4 h, (ii) reflux, 2 h, (iii) **5**, NMM, 8 h.

(OBHA) derivatives **3**, **6**, and **10**.[6−8] Alkylation of **3** with 4-chlorobutyronitrile provided nitrile **4**, which was reduced with Raney nickel under a pressurized (45 psi) H_2 atmosphere to afford amine **5**.[9] Reaction of **6** with 5-hydroxypentanoic acid methyl ester under Mitsunobu[10] conditions followed by acid hydrolysis of product **7** afforded acid **8** in 59% yield for two steps. Acid **8** was directly treated with diphenylphosphoryl azide (DPPA) for 4 h and heated at reflux for 2 h to induce a Curtius

SCHEME 3[a]



[a] Reagents: (a) NaH, 1,4-dibromobutane, DMF, 16 h; (b) Chloro(carbonyl) isocyanate, 2,6-lutidine, CH_2Cl_2, 1 h; (c) NaH, NaI, **11**, DMF, 24 h.

rearrangement to generate the corresponding isocyanate. Upon cooling, the reaction mixture was exposed to amine **5**, providing the desired unsymmetrical urea **9**.

Gratifyingly, cyclization of urea **9** with chloro(carbonyl) isocyanate in the presence of 2,6-lutidine or 2,4,6-collidine provided dialkyl isocyanurate **12** in 90% yield. The use of more basic amines, such as triethylamine, gave poorer yields. Alkylation of **12** by treatment with NaH followed by exposure to excess bromide **11** reproducibly afforded the desired differentially protected isocyanurate **13** in multigram quantities.

In conclusion, we have developed methodology for scalable syntheses of a differentially protected trialkyl isocyanurates which are anticipated to be useful for the preparation of siderophore analogue conjugates that contain up to three different drugs. To this end, we are specifically interested in siderophore drug conjugates that contain drugs with different targets within microbial cells. Libraries of "multiwarhead" siderophores can be envisioned as tools for discovery of new antimicrobial agents and will be reported in due course.

Experimental Section

General Methods. ^{1}H NMR and ^{13}C NMR spectra were obtained on 300, 500, or 600 MHz spectrometers and were referenced to TMS or residual $CDCl_3$. Analytical TLC was carried out using Merck aluminum-backed 0.2 mm silica gel 60 F-254 plates. Column chromatography was conducted using Merck silica gel 60 (230−400 mesh). All reactions were periodically monitored by TLC and worked up after the complete consumption of starting materials unless specified otherwise. The term "dried" refers to treatment with $MgSO_4$. Solvents were removed under aspirator pressure on a rotary evaporator. Water was deionized (DI) prior to use. Anhydrous tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone. Dimethylformamide (DMF) was distilled under reduced pressure

(5) Gorbatenko, V. I. *Tetrahedron* **1993**, *49*, 3227. After submission of this manuscript, a synthesis on solid-support of 1,3,5-trisubstituted isocyanurates was reported by Houghten and co-workers: Yu, Y. P.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem*. **2002**, *4*, 484.

(6) (a) For the preparation of Boc OBHA, see: Lee, B. H.; Miller, M. J. *J. Org. Chem*. **1983**, *48*, 24. (b) For an excellent review of related chemistry relating to protected hydroxylamines, see: Romine, J. L. *Org. Prep. Proced. Int*. **1996**, *28*, 249.

(7) For the preparation of Troc OBHA, see; Lee, B. H.; Gerfen, G. J.; Miller, M. J. *J. Org. Chem*. **1984**, *49*, 2418.

(8) For the preparation of Alloc OBHA, see: Dolence, E. K.; Miller, M. J. *J. Org. Chem*. **1991**, *56*, 492.

(9) Bergeron, R. J.; McManis, J. S. *Tetrahedron* **1989**, *45*, 4939.

(10) Mitsunobu, O. *Synthesis* **1981**, 1.

over CaH_2 and stored over 4 Å sieves and under argon. Methylene chloride (CH_2Cl_2) was distilled over CaH_2 and used directly. All other purchased reagents were of reagent grade quality and were used without further purification.

4-[*N*-(*tert*-Butyloxycarbonyl)benzyloxyamino]butyronitrile (4). To a solution of **3**[6] (5.58 g, 25.0 mmol) in DMF (50 mL) under argon was added NaH (1.04 g, 60% oil dispersion (*Caution: flammable/pyrophoric*), 26.1 mmol) at 0 °C (ice bath). After H_2 evolution ceased, 4-chlorobutyronitrile (2.35 mL, 26.3 mmol) and NaI (370 mg, 2.5 mmol) were added. The solution turned to pale yellow and was heated in an oil bath (60−70 °C external bath temperature). After 5 h, the reaction mixture was cooled to room temperature and diluted with EtOAc (150 mL) and water (200 mL). The organic layer was separated, and the aqueous layer was washed with EtOAc (2 × 100 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to yield a crude reaction product which was purified by flash chromatography over silica gel (4:1 hexanes/EtOAc) yielding nitrile **4** as a colorless oil: 5.80 g, 80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.35 (m, 5H), 4.84 (s, 2H), 3.52 (t, J = 6.5 Hz, 2H), 2.32 (t, J = 7.3 Hz, 2H), 1.88 (m, 2H), 1.52 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.31, 135.30, 129.53, 128.74, 128.54, 119.18, 81.96, 76.90, 48.12, 28.28, 23.49, 14.86; IR (neat) 2978, 2247, 1701 cm^{-1}; HRMS (FAB) for $C_{16}H_{22}N_2O_3$ (M + H) calcd 291.171, found 291.169.

4-[*N*-(*tert*-Butyloxycarbonyl)benzyloxyamino]-1-butylamine (5). Nitrile **4** (1.89 g, 6.50 mmol) was added to a Parr bottle containing methanol (16 mL), ammonium hydroxide (5 mL), and Raney nickel (1 mL, Raney 2800 nickel 50% slurry in H_2O). The heterogeneous mixture was cooled in an ice bath, and gaseous ammonia was bubbled into the mixture for 20 min. The Parr bottle was placed on the Parr apparatus under a H_2 atmosphere (45 psi) for 5 h. The mixture was purged with argon and filtered (*Caution*: Ra Ni is pyrophoric when dry and exposed to air). The biphasic mixture was washed with diethyl ether (100 mL) and 1 M NaOH (50 mL). The aqueous layer was separated, and the organic layer was washed with brine (50 mL), dried, filtered, and evaporated. Amine **5** was isolated as a colorless oil with greater than 95% purity based on ^{1}H NMR and was used without further purification: 1.72 g, 90%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.33 (m, 5H), 4.81 (s, 2H), 3.41 (t, J = 7.35 Hz, 2H), 2.67 (t, J = 7.05 Hz, 2H), 1.61 (m, 2H), 1.49 (s, 9H), 1.41 (m, 2H), 1.30 (bs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.59, 135.65, 129.37, 128.48, 128.41, 81.24, 76.90, 49.42, 41.59, 30.79, 28.32, 24.42; IR (neat) 3375, 3066, 2927, 2934, 1702, 1588 cm^{-1}; HRMS (FAB) for $C_{16}H_{26}N_2O_3$ (M + H) calcd 295.202, found 295.201.

5-[*N*-(Trichloroethoxycarbonyl)benzyloxyamino]pentanoic Acid Methyl Ester (7). To a solution of **6**[7] (3.24 g, 10.9 mmol), triphenylphosphine (3.12 g, 11.9 mmol), and 5-hydroxypentanoic acid methyl ester[11] (1.57 g, 11.9 mmol) in anhydrous THF (40 mL) was added a solution of diisopropylazodicarboxylate (DIAD, 2.34 mL, 11.9 mmol) in THF (10 mL) dropwise over 10 min. The solution was stirred for 8 h before being diluted with EtOAc (150 mL) and water (200 mL). The organic layer was removed, and the aqueous layer was washed with EtOAc (2 × 100 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to yield a yellow oil. The crude product was purified by flash chromatography over silica gel (4:1 hexanes/EtOAc) after most of the triphenylphosphine oxide was removed by crystallization from 1:1 Et_2O/hexanes. Methyl ester **7** was isolated as a colorless oil: 3.37 g, 75%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43−7.32 (m, 5H), 4.91 (s, 2H),4.81 (s, 2H),3.62 (s, 3H), 3.50 (t, J = 6.3 Hz, 2H), 2.29 (t, J = 6.75 Hz, 2H), 1.64 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.54, 155.00, 134.79, 129.17, 128.64, 128.41, 95.20, 77.12, 75.02, 51.42, 49.23, 33.38, 26.28, 21.84; IR (neat) 3033, 2951,1740, 1720 cm^{-1}; HRMS (FAB) for $C_{16}H_{20}Cl_3NO_5$ (M + H) calcd 412.0485, found 412.0471.

5-[*N*-(Trichloroethoxycarbonyl)benzyloxyamino]pentanoic Acid (8). Methyl ester **7** (3.37 g, 8.18 mmol) was heated to reflux (oil bath temperature 120 °C) in dioxane (15 mL) and 2 M HCl (15 mL) for 16 h and then cooled to room temperature. The mixture was extracted with EtOAc (4 × 25 mL). The organic layers were combined, washed with brine, dried, filtered, and evaporated. The crude acid was isolated by extraction and used directly in the next reaction. Thus, the residue was dissolved in Et_2O (75 mL) and washed with aqueous 10% Na_2CO_3 (4 × 50 mL). The organic layer was removed, and the aqueous layers were combined, acidified with 2 M HCl, and extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to yield acid **8** as a colorless oil: 2.94 g, 90%. Although used directly, characterization data includes: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.36 (m, 5H), 4.93 (s, 2H), 4.83 (s, 2H), 3.52 (m, 2H), 2.36 (m, 2H), 1.67 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.22, 155.17, 134.84, 129.53, 128.87, 128.57, 95.24, 77.30, 75.15, 49.33, 33.43, 26.30, 21.67; IR (neat) 3435, 2942, 1711 cm^{-1}; HRMS (FAB) for $C_{15}H_{18}Cl_3NO_5$ (M + H) calcd 398.0329, found 398.0349.

1-[4-[*N*-(Trichloroethoxycarbonyl)benzyloxyamino]butyl]-3-[4-[*N*-(*tert*-butyloxycarbonyl)benzyloxyamino]butyl]urea (9). To a solution of triethylamine (0.790 mL, 5.64 mmol) and acid **8** (2.25 g, 5.64 mmol) in toluene (20 mL) was added diphenylphosphoryl azide (1.28 mL, 5.92 mmol). The solution was stirred at room temperature for 4 h followed by heating to reflux (125 °C oil bath temperature) for 2 h. The reaction mixture was cooled to room temperature, amine **5** (1.66 g, 5.64 mmol) was added in one portion, and the resulting solution stirred for 8 h. The volatiles were evaporated, and the residue was taken up in EtOAc (100 mL) and water (100 mL). The aqueous layer was removed and extracted with EtOAc (2 × 80 mL). The organic layers were combined and washed with 1 M HCl (100 mL), water (100 mL), saturated $NaHCO_3$ (100 mL), and brine (100 mL). The organic layer was separated, dried, filtered, and evaporated. The crude material was purified by flash chromatography over silica gel (1:1−1:3 hexanes/EtOAc) to yield **9** as a colorless oil: 2.5360 g, 65%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44−7.32 (m, 10H), 4.91 (s, 2H),4.82 (s, 2H), 4.80 (s, 2H), 4.47 (t, 1H, J = 6 Hz), 4.45 (t, 1H, J = 6 Hz), 3.52 (t, 2H, J = 6.9 Hz), 3.42 (t, 2H, J = 6.6 Hz), 3.12 (m, 4H), 1.62 (m, 4H), 1.49 (s, 9H), 1.45 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.18, 156.64, 155.14, 135.54, 134.84, 129.54, 129.42, 128.87, 128.58, 128.48, 95.32, 81.39, 77.24, 76.89, 75.16, 49.30, 48.99, 40.16, 39.99, 28.36, 27.31, 27.20, 24.55, 24.40; IR (neat) 3032, 2938, 1717, 1634, 1571 cm^{-1}; HRMS (FAB) for $C_{31}H_{43}Cl_3N_4O_7$ (M + H) calcd 689.2276, found 689.2243.

4-[*N*-(Allyloxycarbonyl)benzyloxyamino]-1-bromobutane (11). To a solution of **10**[8] (1.95 g, 9.41 mmol) in DMF (30 mL) under argon was added NaH (0.450 g, 11.3 mmol) at 0 °C. After H_2 evolution ceased, 1,4-dibromobutane (2.60 mL, 21.8 mmol) was added, and the resulting solution stirred for 18 h. The reaction mixture was diluted with EtOAc (100 mL) and water (200 mL). The organic layer was separated, and the aqueous layer was washed with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to yield a crude reaction product which was purified by flash chromatography over silica gel (10:1 hexanes/EtOAc). Compound **11** was isolated as a colorless oil: 2.58 g, 80%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40−7.35 (m, 5H), 5.97(m, 1H, J = 17.1, 10.2, and 5.7 Hz), 5.36 (d, 1H, J = 17.1 Hz), 5.27 (d, 1H, J = 10.2 Hz), 4.88 (s, 2H), 4.67 (d, 2H, J = 5.7 Hz), 3.48 (t, 2H, J = 6.9 Hz) 3.38 (t, 2H, J = 6.3 Hz), 1.86 (m, 2H), 1.75 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.88, 135.24, 132.19, 129.19, 128.47, 128.32, 118.00, 76.99, 66.43, 48.65, 32.98, 29.63, 25.53; IR (neat) 3065, 3032, 2942, 1705, 1648, 1497, 1454, 1398, 1342, 1293, 1242, 1160, 1092, 995, 934, 750, 699 cm^{-1}; HRMS (FAB) for $C_{15}H_{18}$ Cl_3NO_5 (M + H) calcd 342.0705, found 342.0714.

1-[4-[*N*-(Trichloroethoxycarbonyl)benzyloxyamino]butyl]-3-[4-[*N*-(*tert*-butyloxycarbonyl)benzyloxyamino]butyl][1.3.5]triazinane-2,4,6-trione (12). To a stirring solution of urea **9** (2.54 g, 3.67 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C was added 2,6-lutidine (0.43 mL, 3.7 mmol) followed by chloro(carbonyl) isocyanate (technical grade, 0.30 mL, 3.7 mmol). The solution turned deep yellow and was allowed to warm to room

(11) Huckstep, M.; Taylor, R. J. K.; Caton, M. P. L. *Synthesis* **1982**, 881.

temperature. After 1 h, the solvent was evaporated, and the crude yellow oil was directly purified by flash chromatography over silica gel (2:1 hexanes/EtOAc) to yield **12** as a viscous, colorless oil: 2.37 g, 90%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.44−7.33 (m, 10H), 4.92 (s, 2H), 4.83 (s, 2H), 4.82 (s, 2H), 3.83 (broad t, 4H), 3.54 (bt, 2H), 3.44 (bt, 2H), 1.64 (m, 8H), 1.50 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.55, 155.12, 149.49, 148.09, 148.03, 135.61, 134.87, 129.55, 129.42, 128.87, 128.58, 128.54, 128.47, 95.32, 81.41, 77.30, 76.90, 75.18, 49.21, 49.06, 42.17, 42.00, 28.36, 25.08, 24.94, 24.28, 24.15; IR (neat) 3224, 3109, 2952, 1720, 1687, 1457, 1409, 1369, 1288, 1156, 1111, 1049 cm^{-1}; HRMS (FAB) for $C_{33}H_{42}Cl_3N_5O_9$ (M + H) calcd 758.2126, found 758.2142.

1-[4-[*N*-(Trichloroethoxycarbonyl)benzyloxyamino]-butyl]-3-[4-[*N*-(*tert*-butyloxycarbonyl)benzyloxyamino]-butyl]-5-[4-[*N*-(allyloxycarbonyl)benzyloxyamino]butyl]-[1.3.5]triazinane-2,4,6-trione, 13. To a stirring solution of compound **12** (2.37 g, 3.12 mmol) in DMF (3.5 mL) under argon at 0 °C was added NaH (60% dispersion in mineral oil, 0.143 g, 3.43 mmol). Upon complete addition of NaH, the solution turned brown and NaI (90 mg, 0.60 mmol) was added followed by bromide **11** (1.58 g, 4.61 mmol) in DMF (1.5 mL). The solution was stirred for 24 h. The disappearance of compound **12** was monitored by TLC (2:1 hexanes/EtOAc, $R_f = 0.15$). The reaction was quenched with water (80 mL), and the mixture was extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed with brine (50 mL), dried, filtered, and evaporated. The crude product was purified by flash chromatography (7:3 hexanes/EtOAc) to yield **13** as a colorless oil: 2.20 g, 70%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.33 (m, 15H), 5.97-(m, 1H, J = 17.1, 10.2, and 5.7 Hz), 5.36 (d, 1H, J = 17.1 Hz), 5.27 (d, 1H, J = 10.2 Hz), 4.92 (s, 2H), 4.85 (s, 2H), 4.83 (s, 2H), 4.81(s, 2H), 4.67 (d, 2H, J = 5.7 Hz), 3.83 (m, 6H), 3.53 (broad t, 2H), 3.47 (bt, 2H), 3.43 (bt,2H), 1.66−1.59 (m, 12 H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.03, 156.54, 155.08, 148.88, 135.61, 135.39, 134.87, 129.53, 129.41, 129.36, 128.85, 128.63, 128.56, 128.50, 128.45, 118.16, 95.33, 81.33, 77.28, 77.19, 76.9, 75.16, 66.63, 60.37, 49.26, 49.12, 42.65, 42.59, 42.49, 28.36, 25.12, 25.04, 24.97, 24.35, 24.26, 24.22, 21.04; IR (neat) 3032, 2948, 2875, 1689, 1464, 1360, 1286, 1233, 1159, 1113 cm^{-1}; HRMS (FAB) for $C_{48}H_{61}Cl_3N_6O_{12}$ MS FAB (M + H) found 1021.30.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **4**, **5**, **7**, **9**, and **11**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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