Framework-Reactive Siderophore Analogs as Potential Cell-Selective Drugs. Design and Syntheses of Trimelamol-Based Iron Chelators

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Currently, the role of DNA-directed alkylating agents as potential anticancer/ antimicrobial drugs is of wide interest. Most of the alkylating agents used clinically as drugs damage DNA in cells without specificity, and this can lead to undesired toxicity problems. Minimizing serum residence time by targeting the drug to select pathogens or organs might diminish the effects of nonselective reactivity. This paper describes the syntheses and preliminary studies of analogs of siderophores (microbial iron chelators) **2** and **20** that incorporate centers within the siderophore framework capable of generating potent electrophiles (iminium ions), hopefully after directed cellular recognition and uptake. Formation of *N*-aminals from trimelamol (**3**) and substituted hydroxamic acid **4** or **5** was critical for the design and synthesis of the targets. In preliminary biological testing, compound **2**, a trimelamol-based siderophore analog, was active against *Escherichia coli* X580, illustrating the therapeutic potential of this new type of siderophore-mediated drug design and delivery.

Introduction

Drugs that might be useful *in vivo* are often therapeutically ineffective because of their inability to permeate a targeted cell. One possible solution to this problem is conjugation of drugs to siderophores[1] to promote active transport of drugs into specific cells[2] (Figure 1). Siderophores are low molecular weight, organism selective, iron-sequestering agents. They tightly bind and solubilize ionic forms of iron and are recognized and actively transported into cells where, by modification, iron is released for intracellular use.[2] Microbes that recognize the iron-binding component of properly designed siderophore−drug conjugates as an iron delivery agent assimilate the conjugate and in effect commit suicide, since the attached drug is lethal to them. This alternate mode of drug delivery may lead to the development of a whole new class of microbe-selective drugs on the basis of the active transport of an essential nutrient. Siderophore conjugation also may rejuvenate known drugs which have previously relied on passive diffusion and to which resistance has now developed. Our laboratory has completed the first total synthesis of various siderophores including aerobactin,[3] arthrobactin,[4] schizokinen,[5] mycobactin,[6] and foroxymithine,[7] and all of the components of pseudobactin and several analogs.[8] The existence of albomycin,[9] salmycin[10] and related natural compounds that incorporate both a siderophore component and a toxic agent prompted attempts to prepare mimics by conjugation of siderophores directly to antimicrobial

Figure 1.

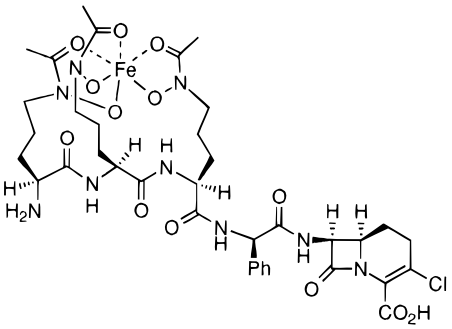

Figure 2.

agents.[10] Recently, an extensive research program has been developed in our laboratory toward the design and synthesis of siderophores attached to a variety of drugs, including, for example, carbacephalosporins, a potent class of β-lactam antibiotics.[11,12] One carbacephalosporin adduct with the siderophore component in the form of hydroxamates is shown in Figure 2. Detailed biological studies of this first generation siderophore−drug conjugate demonstrated the feasibility of microbial iron transport-mediated drug delivery.[11] Herein, we describe the design, syntheses, and preliminary studies of a potentially new class of siderophore-based antimicrobial agents that, rather than containing a separate known drug, incorporate within their framework functionality capable of generating reactive species (iminium ions in this case), hopefully after microbial recognition and assimilation. Intracellular reaction of the delivered and generated reactive agents are anticipated to be lethal to the undesired and targeted cell, thus effecting the development of new types of potential drugs.

The design of our first framework-reactive siderophore analogs (**1** and **2**) was based on trimelamol (**3**). Tri-

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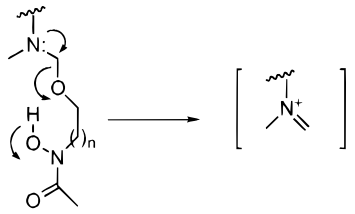


Figure 3.

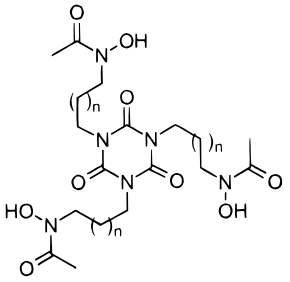
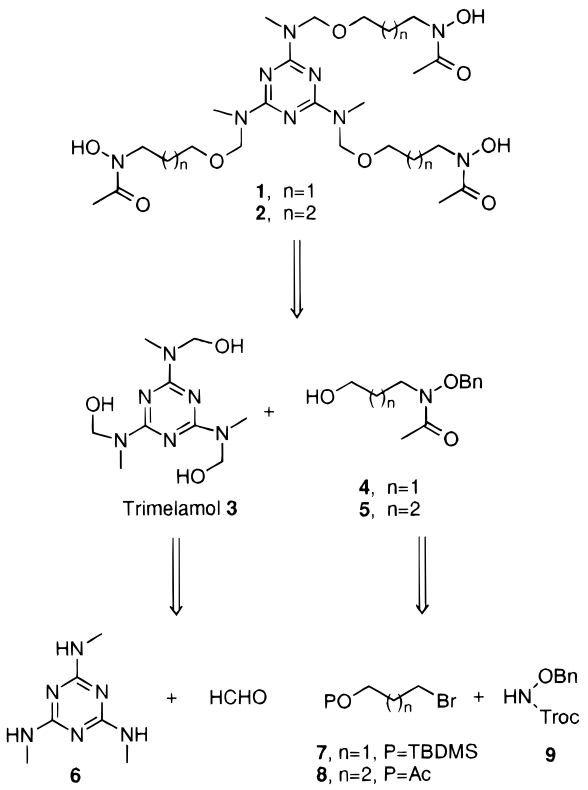


Figure 4.

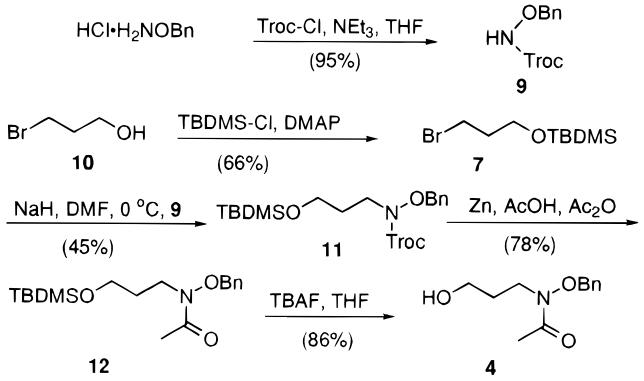
melamol is a nitrogen mustard that is used extensively in cancer chemotherapy.[13] The antitumor activity of the nitrogen mustards is similar to alkylating agents which have the ability to cross-link the two strands of DNA. Mattes *et al*. have shown that the nitrogen mustard class of alkylating agents alkylate the most negative site (the *N*7 position) of guanine.[14] As mentioned earlier, most of the alkylating agents used clinically damage DNA in cells without specificity.[15] In our case, it is expected that after rapid active-transport-facilitated assimilation, the trimelamol-like framework of the siderophore analog may generate a highly reactive iminium ion, which might react as an alkylating agent within the targeted cell and cause damage (Figure 3). Another reason for choosing trimelamol as the core structure was that it resembles cyanurates, and we have previously shown that synthetic cyanurate-based siderophore analogs (Figure 4) are remarkably effective microbial iron transport agents that are recognized and assimilated by a number of microbes.[16,17] As shown in Scheme 1, the key to the synthesis of our desired trimelamol-containing siderophore analogs (**1** and **2**) involved coupling trimelamol (**3**) to the appropriately substituted hydroxamates **4** or **5**.

Our first objective was construction of the substituted hydroxylamines **4** and **5** which were needed for attachment of trimelamol through an *N*-aminal linkage to give forms of **1** and **2**. The reaction sequence for the conversion of *N*-((trichloroethoxy)carbonyl-*O*-benzylhydroxylamine (**9**)[16] to the substituted hydroxamate **4** is represented in Scheme 2. 3-Bromopropanol (**10**) was silylated to provide **7**. The bromo group was subsequently displaced by the protected hydroxylamine **9** to afford the substituted hydroxamate **11** in 45% yield. Interestingly, attempted removal of the silyl group in the presence of tetrabutylammonium fluoride (TBAF)[18] in THF resulted in the loss of the *N*-(trichloroethoxy)carbonyl (Troc) group

Scheme 1



Scheme 2



as well. At this stage, as we eventually wanted to incorporate an *N*-acetyl group to mimic the hydroxamate portion of many natural siderophores, we tried reductive acetylation of **11** in the presence of zinc, acetic anhydride, and acetic acid and obtained the desired fully protected hydroxamate **12**.[19] Subsequent removal of the TBDMS group provided the corresponding free alcohol **4** in 86% yield.

The synthesis of homologous fragment **5** started with commercially available 4-bromobutyl acetate (**13**) (Scheme 3). *N*-Troc-*O*-benzylhydroxylamine (**9**) was alkylated with **13** in the presence of sodium hydride in DMF to provide the desired hydroxamino acetate **14** in 66% yield. Again, the Troc group was removed using zinc and acetic acid in the presence of acetic anhydride to afford **15** in 93% yield. Finally, the *O*-acetyl group was removed by subjecting the compound to hydrolysis in aqueous methanol and K_2CO_3 to provide alcohol **5**.

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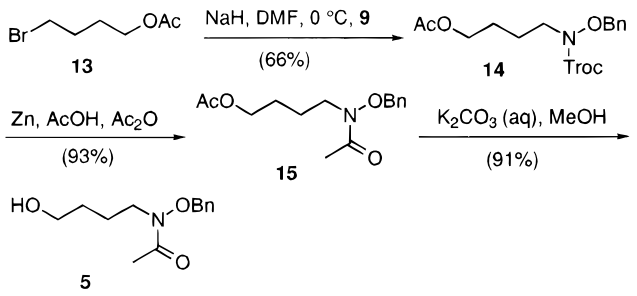
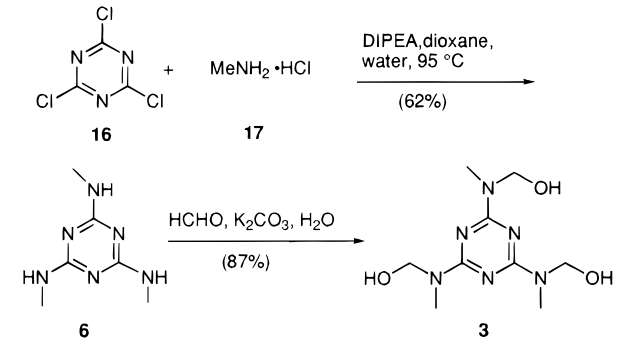
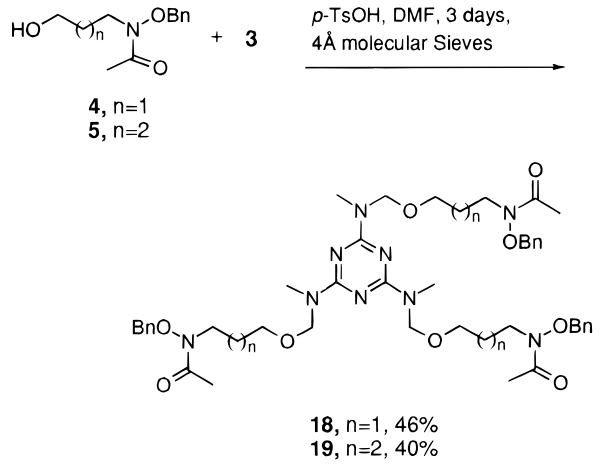
Scheme 3



Scheme 4



Scheme 5

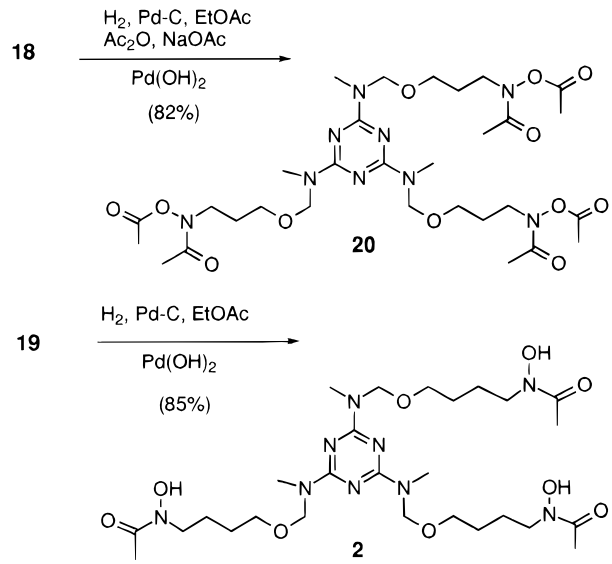


With protected hydroxamates **4** and **5** in hand, we focused our attention on the synthesis of trimelamol (**3**) (Scheme 4). The procedure described by Cumber *et al.*[13] was slightly modified. Cyanuric chloride was allowed to react with methylamine hydrochloride in an autoclave with diisopropylethylamine in a mixture of water and dioxane at 95 °C to afford **6** in 62% yield. Next, **6** was condensed with formaldehyde to provide trimelamol (**3**) in 87% yield.

After the successful synthesis of these subunits, we encountered some problems during their attempted elaboration. The condensation reaction between **3** and **4** or between **3** and **5** was complicated by the formation of not only the mixture of mono- and disubstituted trimelamol deriviatives in low yields but also unreacted starting materials. After considerable investigation, the desired trisubstituted, protected condensation products (**18** and **19**) were obtained by the simple reaction of **3** with alcohols **4** and **5**, respectively, for 3 days in DMF in the presence of catalytic *p*-toluenesulfonic acid (Scheme 5).

After preparation of the protected forms (**18** and **19**) of **1** and **2**, reductive removal of the benzyl groups from each was attempted. Treatment of **18** with 10% Pd/C in methanol under a hydrogen atmosphere resulted in rapid deprotection. However, the resulting hydroxamic acid **1** was unstable and decomposition to the corresponding alcohol and trimelamol dominated, perhaps indicating that designed hydroxamic acid assisted intramolecular cleavage of the aminal to generate an iminium ion (Figure 3) was too facile in this case. Two solutions to this problem were then considered: first, development of a prodrug analog to delay release of the free hydroxamate and, second, alteration of the chain length (n in Figure 2) between the hydroxamate and the trimelamol unit. Thus, we turned our attention to the synthesis of peracetylated prodrug **20** rather than the free hydroxamic acids. Catalytic reduction with hydrogen and 10% Pd/C in ethyl acetate containing acetic anhydride and sodium acetate provided the desired product **20** in 82% yield (Scheme 6). In contrast, we did not encounter any problem in the removal of the benzyl group from the chain-extended analog **19** during hydrogenolysis in ethyl acetate and deprotected siderophore **2** was obtained in 85% yield. Thus, the first total syntheses of trimelamol siderophore analogs were achieved.

Scheme 6



Each of the final deprotected synthetic siderophore analogs **2** and **20** has been subjected to antimicrobial activity assays with *Escherichia coli* X580 and *Candida albicans* in Luria broth cultures. Compound **2** was active, showing considerable delay in growth similar to our previous siderophore conjugates,[11] against *E. coli* X580 at a concentration of 5 μM, providing preliminary indication that its iron complex is recognized by outer membrane receptors and transported into the cell where it either exerts toxic action or reacts during the transport process by generation of electrophilic iminium ions as designed. As a result of this promising preliminary bioassay, the siderophore analogs have been submitted for detailed broad spectrum screening, which will be reported later.

Experimental Section

Instruments and general methods used have been described earlier.[20] Solvents used were dried and purified by standard

methods.[21] The term "dried" refers to the drying of an organic layer over magnesium or sodium sulfate. All reactions were performed under a nitrogen or argon atmosphere. The purity of the final compounds was confirmed by using the standard HPLC analysis.

1-((*tert*-Butyldimethylsilyl)oxy)-3-bromopropane (7). To a solution of 3-bromopropanol (**10**, 2.50 g, 17.9 mmol) in methylene chloride (100 mL) were added *tert*-butyldimethylsilyl chloride (2.90 g, 19.8 mmol), 4-(*N*,*N*- dimethylamino)-pyridine (DMAP) (1.10 g, 8.90 mmol), and triethylamine (1.90 mL, 19.8 mmol). The reaction was stirred overnight at rt and quenched with a saturated ammonium chloride solution (15 mL). The organic layer was separated, washed with brine (15 mL), sodium bicarbonate (15 mL), and water (15 mL), dried, filtered, and concentrated *in vacuo*. The crude product was subjected to column chromatography on silica gel using 2:1 hexanes/ethyl acetate (R_f = 0.8) to afford 3.00 g (66%) of substituted alkane **7** as a colorless oil: IR (neat) 2960, 2860, 1250 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (t, J = 5.5 Hz, 2H), 3.41 (t, J = 6.0 Hz, 2H), 1.9 (m, 2H), 0.79 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (80 MHz, $CDCl_3$) δ 35.4, 30.5, 30.1, 25.70, 18.1; HRMS (FAB) calcd for $C_{19}H_{31}NO_4SiCl_3$ (MH^+) 254.7032, found 254.7038.

3-[((Trichloroethoxy)carbonyl)(benzyloxy)amino]-1-((*tert*-butyldimethylsilyl)oxy)propane (11). Sodium hydride (250 mg, 60% dispersion in mineral oil, 5.9 mmol) was washed with dry hexanes (2 × 2 mL) and suspended in DMF (5 mL). A solution of *N*-((trichloroethoxy)carbonyl)-*O*-benzylhydroxylamine (**9**,[16] 1.30 g, 4.50 mmol) in DMF (5 mL) was added to the mixture at 0 °C, and the solution was stirred for 45 min at rt. 1-((*tert*-Butyldimethylsilyl)oxy)-3-bromopropane (**7**, 1.50 g, 5.90 mmol) in DMF (5 mL) was added to the reaction mixture at 0 °C, and the solution was stirred overnight at rt. Cold water was added to the mixture, and the resulting solution was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with water, dried, filtered, and evaporated. Column chromatography of the crude residue on silica gel using 6:1 hexanes/ether (R_f = 0.7 in 2:1 hexanes/ether) afforded 0.964 g (45%) of TBDMS-protected hydroxamate **11** as a clear oil: IR (neat) 2940, 2860, 1720, 1250, 1100 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.35 (m, 5H), 4.90 (s, 2H), 4.84 (s, 2H), 3.67 (t, J = 6.0 Hz, 2H), 3.64 (t, J = 7.0 Hz, 2H), 1.87 (quintet, J = 7.5 Hz, 2H), 0.91 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 134.8, 129.43, 128.7, 128.4, 95.0, 74.9, 60.2, 47.1, 30.1, 25.78, 18.2; HRMS (FAB) calcd for $C_{19}H_{31}NO_4SiCl_3$ (MH^+) 470.2016, found 470.2018.

3-[Acetyl(benzyloxy)amino]-1-((*t*-butyldimethylsilyl)-oxy)propane (12). To a solution of **11** (0.195 g, 0.414 mmol) in THF (2 mL) and acetic acid (2 mL) were added zinc dust (0.405 g, 6.2 mmol) and acetic anhydride (0.585 mL, 6.2 mmol). The mixture was stirred for 2 h at rt and diluted with THF (10 mL). The reaction mixture was filtered, and the excess volatiles were removed *in vacuo*. The mixture was taken up in ethyl acetate (20 mL), washed with a saturated sodium bicarbonate solution (3 × 10 mL), water (5 mL), and brine (5 mL), dried, filtered, evaporated, and purified by chromatography on silica gel with 4:1 hexanes/ethyl acetate (R_f = 0.5 in 2:1 hexanes/ethyl acetate) to provide hydroxamate **12** as an oil: IR (neat) 2970, 1660, 1100 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.29 (m, 5H), 4.81 (s, 2H), 3.73−3.70 (t, J = 6.0 Hz, 2H), 2.07 (s, 3H), 1.84−1.80 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 133.1, 129.4, 128.9, 128.7, 76.7, 58.1, 47.0, 40.9, 29.5, 29.3, 19.8, 18.0; MS (CI) m/z 290 (MH^+). Anal. Calcd for $C_{18}H_{34}O_3NSi$: C, 63.48; H, 10.06; N, 4.11. Found: C, 63.29; H, 9.88; N, 4.11.

3-[Acetyl(benzyloxy)amino]-1-propanol (4). 3-[Acetyl-(benzyloxy)amino]-1-((*t*-butyldimethylsilyl)oxy)propane (**12**, 0.139 g, 0.414 mmol) was dissolved in THF (5 mL). Tetrabutylammonium fluoride (TBAF) in THF (1.24 mL of 1 M solution, 1.24 mmol) was added to the mixture, and the solution was stirred overnight at rt. The excess volatiles were removed *in vacuo*. Purification by chromatography on silica gel using ethyl acetate (R_f = 0.3) provided 0.80 g of substituted alcohol **4** (86%) as a clear oil: IR (neat) 3400, 2960, 1650, 1400, 1100 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 5H), 4.82 (s, 2H), 3.77−3.73 (t, J = 6.3 Hz, 2H), 3.54−3.49, (t, J = 6.0 Hz, 2H), 3.00 (br s, 1H), 2.00 (s, 3H), 1.82−1.74 (quintet, J = 6.0 Hz , 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 133.9, 128.9, 128.7, 128.4, 76.0, 58.3, 41.6, 29.5, 19.9; HRMS (FAB) calcd for $C_{12}H_{17}NO_3$ (MH^+) 224.1287, found 224.1290. Anal. Calcd for $C_{12}H_{18}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.35; H, 7.5; N, 6.23.

4-[((Trichloroethoxy)carbonyl)(benzyloxy)amino]-1-acetoxybutane (14). Sodium hydride (0.240 g, 60% dispersion in mineral oil, 5.8 mmol) was washed with dry hexanes (2 × 2 mL) and suspended in DMF (5 mL). A solution of *N*-((trichloroethoxy)carbonyl)-*O*-benzylhydroxylamine (**9**, 1.30 g, 4.50 mmol) in DMF (5 mL) was added to the mixture at 0 °C, and the solution was stirred for 45 min at rt. 4-Bromobutyl acetate (**13**, 1.10g, 5.80 mmol) in DMF (5 mL) was added to the reaction mixture at 0 °C, and the solution was stirred overnight at rt. Cold water was added to the mixture, and the solution was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with brine (5 mL) and water (5 mL), dried, filtered, and evaporated. Column chromatography of the crude residue on silica gel using 6:1 hexanes/ether (R_f = 0.55 in 4:1 hexanes/ether) afforded 1.20 g (67%) of substituted hydroxamate **14** as a clear oil: IR (neat) 2980, 1740, 1240 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.30 (m, 5H), 4.90 (s, 2H), 4.80 (s, 2H), 4.06−4.01 (t, J = 6.0 Hz, 2H), 3.54−3.50 (t, J = 6.9 Hz, 2H), 2.02 (s, 3H), 1.73−1.60 (m, 4H); ^{13}C NMR (80 MHz, $CDCl_3$) δ 171.0, 155.1, 134.8, 129.4, 128.8, 128.5, 95.2, 76.8, 75.1, 63.8, 49.3, 25.7, 23.5, 20.9; HRMS (FAB) calcd for $C_{16}H_{21}NO_5NCl_3$ (MH^+) 412.0485, found 412.0506. Anal. Calcd for $C_{16}H_{20}NO_5Cl_3$: C, 46.57; H, 4.88; N, 3.39. Found: C, 46.39; H, 4.99; N, 3.3.

4-[Acetyl(benzyloxy)amino]-1-acetoxybutane (15). To a solution of **14** (1.20 g, 2.90 mmol) in THF (15 mL) and acetic acid (10 mL) were added zinc dust (2.80 g, 43.6 mmol) and acetic anhydride (4.1 mL, 43.6 mmol). The mixture was stirred for 2 h at rt and diluted with THF (40 mL). The reaction mixture was filtered, and the excess volatiles were removed *in vacuo*. The mixture was taken up in ethyl acetate (50 mL), washed with a saturated sodium bicarbonate solution (3 × 10 mL), brine (15 mL), and water (15 mL), dried, filtered, evaporated, and purified by column chromatography on silica gel with 2:1 hexanes/ethyl acetate (R_f = 0.2) to provide 0.750 g (93%) of protected hydroxamate **15** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.30 (m, 5H), 4.80 (s, 2H), 4.07−4.03 (t, J = 6.3 Hz, 2H), 3.68−3.64 (t, J = 6.6 Hz, 3H), 2.10 (s, 3H), 2.02 (s, 3H), 1.70−1.61(m, 4H); ^{13}C NMR (80 MHz, $CDCl_3$) δ 172.2, 170.9, 134.3, 128.9, 128.6, 76.1, 63.7, 44.8, 25.7, 23.3, 20.7, 20.3; MS (CI) m/z 280 (MH^+). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.36; H, 7.39; N, 4.99.

4-[Acetyl(benzyloxy)amino]-1-butanol (5). 4-[Acetyl-(benzyloxy)amino]-1-acetoxybutane (**15**, 0.600 g, 2.15 mmol) was dissolved in a mixture of methanol (7 mL) and water (1 mL). A potassium carbonate solution (1 N, 4 mL, 4.30 mmol) was added, and the solution was stirred overnight at rt. The methanol was removed. The resulting aqueous solution was acidified to pH = 2 with 1 N HCl and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried, and evaporated to afford 0.462 g (92%) (R_f = 0.2 in ethyl acetate) of substituted alcohol **5** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 5H), 4.70 (s, 2H), 3.59 (br s, 1H), 3.55−3.50 (t, J = 6.6 Hz, 4H), 1.99 (s, 3H), 1.70−1.60 (quintet, J = 6.9 Hz, 2H), 1.51−1.42 (quintet, J = 6.6 Hz, 2H); ^{13}C NMR (80 MHz, $CDCl_3$) δ 172.3, 134.3, 129.1, 128.3, 128.2, 76.15, 61.7, 45.0, 29.6, 23.4, 20.3; HRMS (FAB) calcd for $C_{13}H_{20}NO_3$ (MH^+) 238.1443, found 238.1440. Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C,65.96; H, 7.94; N, 6.04.

***N*^{2},*N*^{4},*N*^{6}-Trimethylmelamine (6).** To a mixture of cyanuric chloride (**16**, 2.00 g, 10.8 mmol) and methylamine hydrochloride (**17**, 5.90 g, 86.7 mmol) in a mixture of dioxane

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(100 mL) and water (10 mL) was added diisopropylethylamine (24.0 mL, 130 mmol). The mixture was heated at 95 °C in a ZipperClave autoclave for 8 h and stirred overnight at rt. Excess volatiles were removed *in vacuo*, and the residue was diluted with ethyl acetate (200 mL). The mixture was washed with brine (50 mL) and water (50 mL). The separated organic layer was dried and concentrated *in vacuo*. Column chromatography of the crude on silica gel with 2:1 hexanes/ethyl acetate provided 1.12 g of **6**[16] (62%) as a pale yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40−6.00 (br s, 3H), 2.84 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 28.0; HRMS (EI) m/z calcd for $C_6H_{12}N_6$: 168.1123, found 168.1119.

Trimelamol [*N*^{2},*N*^{4},*N*^{6}-Trimethyl-*N*^{2},*N*^{4},*N*^{6}-trimethylolmelamine] (3). To a suspension of **6** (2.00 g, 11.8 mmol) in potassium carbonate solution (0.200 g in 7 mL of water) was added aqueous formaldehyde (33%, 3.2 mL). The mixture was heated slightly for 5 min and was left stirring overnight at rt. The resulting precipitate was collected by filtration, washed with cold water, and dried to give 2.02 g of trimelamol (**3**) (72%) as white crystals: mp 128−131 °C (lit.[16] mp 128−131 °C); ^{1}H NMR (500 MHz, CD_3OD) δ 5.11 (s, 6H), 3.15 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD) δ 167.1, 72.8, 33.7; HRMS (FAB) calcd for $C_9H_{19}N_6O_3$ (MH^+) 259.1519, found 259.1511.

Tris(*N*-((((*N*′-acetyl-*O*-benzylhydroxamino)propyl)oxy)methyl)-*N*-methylamino) Cyanurate (18). To a solution of trimelamol (**3**, 0.040 g, 0.149 mmol) in DMF (2 mL) were added **4** (0.100 g, 0.448 mmol) *p*-toluenesulfonic acid (0.024 g, 0.149 mmol), and 4 Å molecular sieves (0.100 g), and the reaction was stirred for 48 h at rt. The mixture was diluted with ethyl acetate (20 mL), filtered, washed with a sodium bicarbonate solution (10%, 15 mL), water (10 mL), and brine (10 mL), and dried. The volatiles were removed *in vacuo*. The crude product was purified on silica gel by column chromatography with 5:2.5:1 methylene chloride/ethyl acetate/ethanol (R_f = 0.6) to provide 0.060 g of protected siderophore **18** (46%) as a clear oil: IR (neat) 2965, 2870, 1670, 1540, 1200 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.25 (s, 15H), 5.15−5.00 (br s, 6H), 3.72−3.52 (br s, 6H), 3.55−3.40 (br s, 6H), 3.15−2.90 (br s, 9H), 2.05 (s, 9H), 1.88−1.82 (br s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 166.0, 134.4, 129.1, 128.8, 128.6, 77.8, 76.1, 65.0, 42.8, 32.9, 27.2, 20.5; HRMS (FAB) calcd for $C_{45}H_{64}N_9O_9$ (MH^+) 874.4827, found 874.4832.

Tris(*N*-((((*N*′,*O*-diacetylhydroxamino)propyl)oxy)methyl)-*N*-methylamino) Cyanurate (20). To a solution of **18** (0.020 g, 0.11 mmol) in ethyl acetate (2 mL) were added acetic anhydride (0.5 mL), sodium acetate (0.250 g), and 10% Pd/C (0.002 g, 0.016 mmol). The reaction mixture was stirred at rt and atmospheric pressure under hydrogen for 4 h. The catalyst was removed by filtration through a pad of Celite, and the solvent was evaporated to afford 0.012 g of siderophore analog **20** (95%) as a colorless oil. The reaction also was reproducible on larger scale (0.250 g). For **20**: HPLC t_R 7.4 min (15% 2-propanol in methylene chloride); IR (neat) 3500, 2970, 2870, 1670, 1540, 1400; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.15−5.00 (br s, 6H), 3.72−3.52 (br s, 6H), 3.55−3.40 (br s, 6H), 3.15−2.90 (br s, 9H), 2.10 (s, 9H), 2.05 (br s, 9H), 1.88−1.82 (br s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 168.4, 166.0, 77.9, 65.4, 45.4, 33.1, 27.3, 20.2, 18.4; HRMS (FAB) calcd for $C_{30}H_{51}N_9O_{12}Na$ (M + Na) 752.3555, Found 752.3585.

Tris(*N*-((((*N*′-acetyl-*O*-benzylhydroxamino)butyl)oxy)methyl-*N*-methylamino) Cyanurate (19). To a solution of trimelamol (**3**, 0.040 g, 0.149 mmol) in DMF (2 mL) were added **5** (0.100 g, 0.448 mmol), *p*-toluenesulfonic acid (0.024 g, 0.149 mmol), and 4 Å molecular sieves (0.100 g), and the reaction was stirred for 48 h at rt. The mixture was diluted with ethyl acetate (20 mL), filtered, washed with sodium bicarbonate solution (10%, 15 mL), water (10 mL), and brine (10 mL), and dried. The volatiles were removed *in vacuo*, and the residue was chromatographed on silica gel with 5:2.5:1 methylene chloride/ethyl acetate/ethanol (R_f = 0.5) to provide 0.055 g of **19** (40%) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (s, 15H), 5.15−5.00 (br s, 6H), 4.80 (s, 6H), 3.72−3.52 (br s, 6H), 3.55−3.40 (br s, 6H), 3.15−2.90 (br s, 9H), 2.05 (s, 9H), 1.88−1.82 (br s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 165.8, 134.2, 129.2, 128.8, 128.6, 75.9, 66.9, 44.9, 32.6, 23.6, 20.2; HRMS (FAB) calcd for $C_{48}H_{70}N_9O_9$ (MH^+) 916.5297, found 916.5295.

Tris(*N*-((((*N*′-acetylhydroxamino)butyl)oxy)methyl)-*N*-methylamino) Cyanurate (2). To a solution of tris(*N*-((((*N*′-acetyl-*O*-benzylhydroxamino)butyl)oxy)methyl-*N*-methylamino) cyanurate (**19**, 0.018 g, 0.12 mmol) in ethyl acetate (2 mL) were added powderd sodium acetate (0.075 g) and Pd/C and $Pd(OH)_2$ (0.002 g, 0.008 mmol) . The reaction was stirred overnight at rt under an atmosphere of hydrogen (1 atm). The reaction mixture was filtered through a pad of Celite, and the volatiles were removed *in vacuo* to provide 0.008 g of **2** (85%) as a clean oil. The reaction was reproducible on larger scale (0.250 g). For **2**: HPLC t_R 7.5 min (15% 2-propanol in methylene chloride); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.20−5.15 (br s, 6H), 3.72−3.52 (br s, 6H), 3.55−3.40 (br s, 6H), 3.15−2.90 (br s, 9H), 2.05 (br s, 9H), 1.88−1.82 (br s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 166.0, 77.9, 67.3, 47.3, 33.1, 27.3, 20.2, 18.4; MS (FAB) m/z 664 (M + H_2O).

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Supporting Information Available: HPLC traces of **2** and **20** and ^{1}H and ^{13}C NMR spectra of **2**, **7**, **11**, **18**, **19**, and 20 (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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