J = 5 Hz), 7.10 (m, 2 H, H-2′,6′), 6.80 (d, 1 H, H-5′, $J_{5'-6'}$ = 8.5 Hz). Anal. ($C_{11}H_{10}NO_2Br$) C, H, N.

1-Methyl-4-(3′,4′-dihydroxyphenyl)pyridinium Bromide (25). Compound **24** (free base, 50 mg, 0.27 mmol) was dissolved in 40 mL of methanol, 250 mg of methyl bromide was added, and the reaction mixture was kept at room temperature. The progress of the reaction was monitored by TLC. After 1 week, the reaction mixture was concentrated to dryness and the residue crystallized from ethanol to give 51 mg (68%) of fine yellow crystals: mp 244 °C dec; Thermospray LC/MS, m/e 202 (M^+). Anal. ($C_{12}H_{12}NO_2Br$) C, H, N.

1-Methyl-4-phenylpyridinium Bromide (26). To a solution of **22** (2.0 g, 12.9 mmol) in 50 mL of acetone was added 1.7 g (18 mmol) of methyl bromide and the reaction mixture was kept at room temperature overnight. The crystalline, colorless product, which came out of the solution, was filtered, washed with acetone, and dried to yield 2.50 g (78%) of **26**: mp 168–170 °C; Thermospray LC/MS, m/e 170 (M^+). Anal. ($C_{12}H_{12}NBr$) C, H, N, Br.

1-Methyl-4-phenylpyridinium Methosulfate (27). To a solution of **22** (2.0 g, 12.9 mmol) in 50 mL of acetone was added 1.4 mL (1.86 g, 14.8 mmol) of dimethyl sulfate, and the reaction mixture was kept at 50 °C for 3 h. The product came out of the solution as colorless needles, which were filtered, washed with acetone, and dried, giving 2.94 g (82%) of a crystalline product: mp 165–167 °C; Thermospray LC/MS, m/e 170 (M^+). Anal. ($C_{13}H_{15}NO_4S$) C, H, N, S.

1-Allyl-4-phenylpyridinium Bromide (28). To a solution of **22** (2.0 g, 12.9 mmol) in 50 mL of acetone was added allyl bromide (1.75 g, 14.5 mmol) and the reaction mixture was kept at room temperature overnight. The product crystallized out of solution as almost colorless needles. These were filtered, washed with acetone, and dried, giving 2.64 g (74%) of product: mp 153–156 °C; Thermospray LC/MS, m/e 196 (M^+). Anal. ($C_{14}H_{14}NBr$) C, H, N, Br.

Acknowledgment. We thank Dr. Alfred Z. Yergey, Laboratory of Theoretical and Physical Biology, NICHD, Bethesda, for performing Thermospray LC/MS spectra. We thank Richard Gilardi, Naval Research Laboratory, Washington, DC 20375-5000, for the X-ray data collection and analysis of 1-formyl-4-(3′-methoxy-4′-hydroxyphenyl)-1,2,3,6-tetrahydropyridine (**11a**).

Registry No. 1, 10338-69-9; 2, 30005-58-4; 3, 28289-54-5; 4, 5048-08-8; 4·HCl, 6653-08-3; 5, 5233-54-5; 6, 90684-18-7; 6·HBr, 94427-28-8; 6·HCl, 94427-29-9; 7, 90684-15-4; 7·HCl, 94427-30-2; 8, 90684-19-8; 8·HCl, 94427-31-3; 9, 90684-16-5; 9·HBr, 94427-32-4; 10, 94427-33-5; 11, 94427-34-6; 11a, 94427-35-7; 12, 94427-36-8; 13·HCl, 94427-37-9; 14, 94427-38-0; 15, 94427-39-1; 16, 774-52-7; 17, 94427-40-4; 18, 94427-41-5; 19, 94427-43-7; 19·HCl, 94427-42-6; 20, 94427-44-8; 20·HBr, 94427-45-9; 21, 94427-47-1; 21·HBr, 94427-46-0; 22, 939-23-1; 23, 39795-63-6; 23·HBr, 94427-48-2; 24, 79445-43-5; 24·HBr, 79445-42-4; 25, 94427-49-3; 26, 2589-31-3; 27, 39795-54-5; 28, 94427-50-6; ClC(O)OMe, 79-22-1; PhOH, 108-95-2; HC(O)OEt, 109-94-4; HCHO, 50-00-0; CH_2=$CHCH_2Br$, 106-95-6; 1-(methoxycarbonyl)-4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine, 94427-27-7; 1-methyl-4-piperidone, 1445-73-4; guaiacol, 90-05-1; 4-piperidone, 41661-47-6.

Artificial Siderophores. 1. Synthesis and Microbial Iron Transport Capabilities

Byung Hyun Lee,[†] Marvin J. Miller,*[†,§] Catherine A. Prody,[‡] and John B. Neilands*[‡]

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Several di- and trihydroxamate analogues of natural microbial iron chelators have been prepared. The syntheses involved linkage of core structural units, including pyridinedicarboxylic acid, benzenetricarboxylic acid, nitrilotriacetic acid, and tricarballylic acid, by amide bonds to 1-amino-ω-(hydroxyamino)alkanes to provide the polyhydroxamates **1–5**. The required protected (hydroxyamino)alkanes **8**, **16**, and **21** were prepared by different routes. 1-Amino-3-[(benzyloxy)amino]propane di-*p*-toluenesulfonate (**8**) was prepared from the N-protected aminopropanol **6** by oxidation to the aldehyde, formation of the substituted oxime, and reduction with $NaBH_3CN$ followed by deprotection of the Boc group. The pentyl derivatives **16** and **21** were made by direct alkylation with either benzyl acetohydroxamate or *N*-carbobenzoxy-*O*-benzylhydroxylamine. In *Escherichia coli* RW193 most of the analogues behaved nutritionally as ferrichrome. However, in *E. coli* AN193, a mutant lacking the ferrichrome receptor, capacity to use other natural siderophores was retained while response to all analogues was lost.

Iron is the most abundant transition metal and probably the most well-known metal in biological systems. Within the last 20 years several catechol and hydroxamate-containing microbial iron chelators (siderophores) have been isolated and related biochemical studies have contributed significantly to our knowledge of iron metabolism.[1-4] Siderophores are also important models of the development of drugs for the treatment of iron-overloaded patients.[5-7] Thus, the design of therapeutically useful iron chelating agents should also take into account the evolution-derived design of microbial systems. Desferal is the standard iron chelator used for the treatment of iron-storage diseases. Because Desferal must be administered by injection and large doses are needed to mobilize iron faster than it is accumulated,[8,9] the search for alternatives continues.

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[‡] University of California.
[§] Fellow of the Alfred P. Sloan Foundation (1981–1985). Recipient of a NIH Career Development Award (1983–1988).

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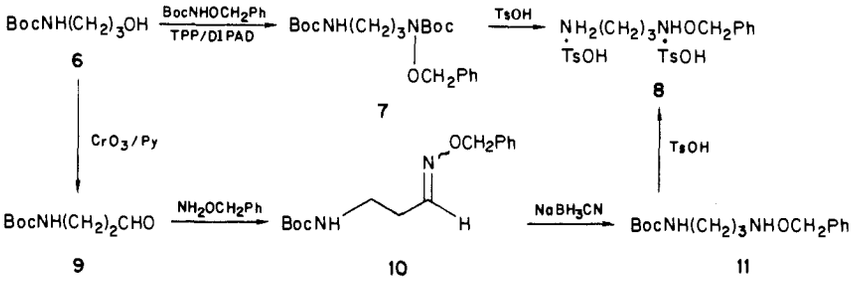
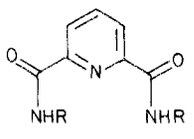
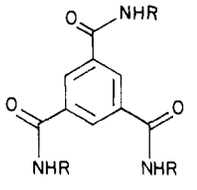
Scheme I



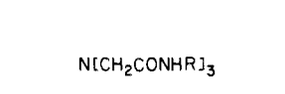
Since we completed the synthesis of the natural siderophores, schizokinen and arthrobactin,[10] our approach to the design and synthesis of new artificial siderophores has focused on dihydroxamic acid and trihydroxamic acid containing analogues. The basic concept described here is the linkage of various structural units like pyridinedicarboxylic acid, benzenetricarboxylic acid, nitrilotriacetic acid, and tricarballylic acid by amide bonds to 1-amino-ω-(hydroxyamino)alkanes to provide the corresponding polyhydroxamates. In order to further determine the affect of structural modifications on biological activity, various chain lengths of the side arms [1-amino-ω-(hydroxyamino)alkanes] were utilized and one retroanalogue of the tricarballylic acid derivatives was prepared. The response of different strains of *Escherichia coli* to these artificial siderophores was also examined.



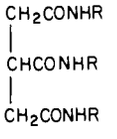
1a, R=$(CH_2)_n$N(OH)$COCH_3$; $n=3$
b, $n=5$



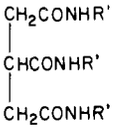
2a, R=$(CH_2)_n$N(OH)$COCH_3$; $n=3$
b, $n=5$



3, R=$(CH_2)_n$N(OH)$COCH_3$; $n=3$



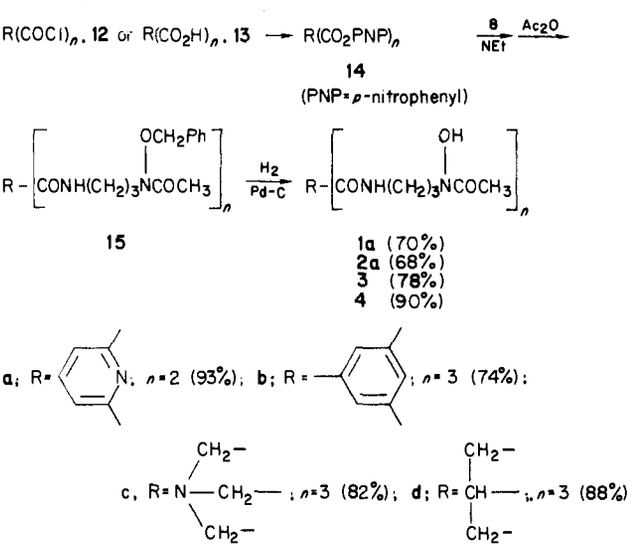
4, R=$(CH_2)_n$N(OH)$COCH_3$; $n=3$



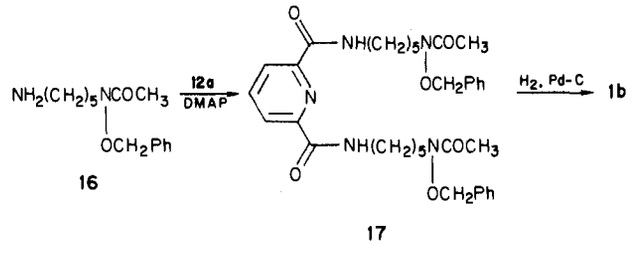
5, R'=$(CH_2)_n$CON(OH)CH_3; $n=5$;

Synthesis of Artificial Siderophores. 1-Amino-3-[(benzyloxy)amino]propane *p*-toluenesulfonate double salt (**8**) is a very important intermediate for the synthesis of artificial siderophores. Compound **8** was first prepared during the synthesis of schizokinen.[10] We report a more convenient alternative synthesis of **8** which avoids tedious chromatography. The previous preparation involved the alkylation of the protected amino alcohol **6** with *N*-(*tert*-butoxycarbonyl)-*O*-benzylhydroxylamine[10] in the presence of PPh_3/DIPAD (diisopropyl azodicarboxylate), followed by deprotection of the Boc group with *p*-toluenesulfonic acid (TsOH). In a new approach (Scheme I), the protected amino alcohol **6** was oxidized to the aldehyde **9** with CrO_3–pyridine,[11] and then the aldehyde was converted to the oxime derivative **10** by treatment with *O*-benzylhydroxylamine (OBHA) in aqueous methanol at pH 7. Compound **10** was reduced with $NaBH_3CN$[12] in acetic acid to provide **11**, which was deprotected by treatment with TsOH (2 equiv) to give **8** in 36% overall yield from **6**.

Scheme II



Scheme III



During the synthesis of schizokinen, we noted the ability to selectively acylate the amine portion of 1-amino-ω-[(benzyloxy)amino]alkanes. This selective acylation was also utilized for the syntheses of the artificial siderophores described here. First, the *p*-nitrophenyl ester derivatives **14** were prepared from the acid chloride **12** or the acid **13** (Scheme II). Compounds **14a–d** were coupled with the amine **8** in the presence of NEt_3, followed by acetylation with acetic anhydride to give the N-acylated compounds **15a–d** in 74–93% yields. Catalytic hydrogenation of **15a–d** in THF/H_2O (or 2-propanol/H_2O) gave the final products **1a**, **2a**, **3**, and **4** in 68–90% yields.

Several natural siderophores like schizokinen and arthrobactin[10] differ only in the number of methylene units in the constituent 1-amino-ω-(hydroxyamino)alkanes. Thus, analogues **1b** and **2b** which, like arthrobactin,[10] contain 1-amino-5-(hydroxyamino)pentane residues, were

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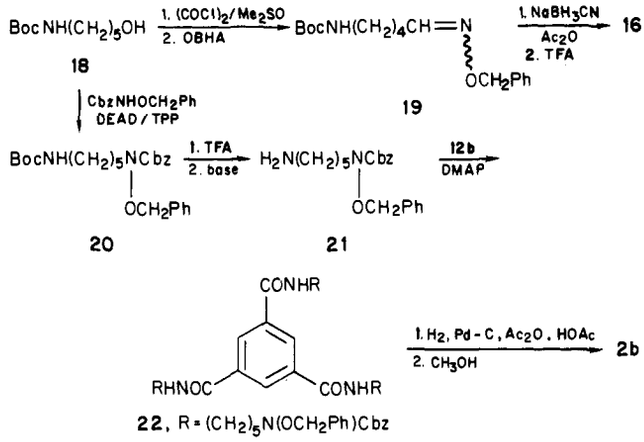
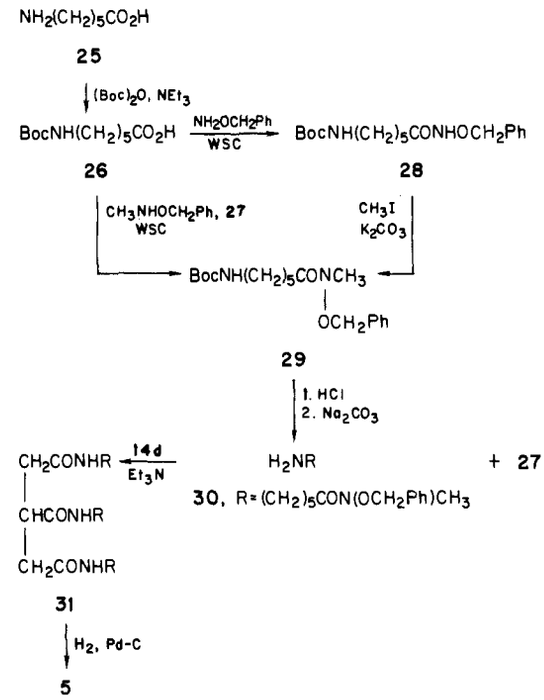
Table I. Characteristics and Sources of *E. coli* K12 Strains

strain	genotype	relevant phenotype	origin/ref
RW193	F-, *proC, leu, trp, thi, lacY, rpsL, galK, ara, entA, mtl, xyl, azi, tsx, supE44*	Cannot synthesize enterobactin. Is able to transport hydroxamate and catechol type siderophores	17
AN193	as RW193, but *tonA*	Lacks the outer membrane ferrichrome receptor, and thus cannot transport ferrichrome type siderophores	I. G. Young
BN3300	as RW193, but *fhuB*	Deficient in the transport of all natural hydroxamate type siderophores	18
RWB7	as RW193, but *tonB*	Deficient in the transport of all hydroxmate and catechol type siderophores, iron citrate, and B12	lab stocks
RWV193	as RW193, but containing the ColV K30 plasmid	Able to transport aerobactin	lab stocks
BNV3040	as RWV193, but *cir*, and *iut* on the ColV K30 plasmid	Lacking the 74K outer membrane receptor for aerobactin	lab stocks

Scheme IV



Scheme V



of interest. The synthesis of these pentyl analogues **1b** and **2b** is shown in Schemes III and IV. In the first case (Scheme III), the previously prepared protected hydroxamate **16**[10] was coupled with the diacid chloride **12a** in the presence of 4-(dimethylamino)pyridine (DMAP) to give protected dihydroxamate **17** in 75% yield. Catalytic hydrogenation of **17** in methanol over Pd–C (5%) removed the benzyl protecting groups to provide pure dihydroxamic acid **1b** in 70% yield. While these steps proceed quite efficiently, the starting hydroxamate **16** is not readily available. As previously reported,[10] the direct alkylation of benzyl acetohydroxamate with appropriate halides gives mixtures of the desired N-alkylated product (i.e., **16**) and the difficult to separate O-alkylated isomers (*E* and *Z* hydroximates). A synthesis of **16** utilizing an aldehyde intermediate analogous to compound **9** (Scheme I) was not as efficient with the longer chain protected amino alcohol **18**. Specifically, attempted Collins oxidation[11] of **18** gave a multicomponent mixture. Swern oxidation [$(ClCO)_2$ + Me_2SO][13] of **18** gave a less complicated mixture including a substantial amount of aldehyde by NMR analysis. Treatment of the aldehyde with *O*-benzylhydroxylamine gave the oxime **19** in only 42% overall yield. Similar problems were recently reported by Ganem during the oxidation of analogous ω-hydroxyamino acids.[14] Consequently a modified route of our original hydroxamate alkylation procedure was used for the preparation of the trihydroxamate analogue **2b**.

The DEAD/TPP-mediated alkylation of *N*-carbobenzoxy-*O*-benzylhydroxylamine with protected amino alcohol **18** provided the desired N-alkylated material **20** with no competitive O-alkylation (Scheme IV). The treatment of **20** with trifluoroacetic acid (TFA), followed by base workup, provided the amine **21** in quantitative yield. Compound **21** was coupled with 1,3,5-benzenetricarboxylic acid chloride (**12b**) in the presence of DMAP to give the protected trihydroxamate **22** in 72% yield. Hydrogenation of compound **22** with Pd–C (5%) catalyst in acetic anhydride and acetic acid followed by methanolysis produced triacetylated compound **2b** in 62% yield.

The retroanalogue of tricarballylamide derivative **5** was synthesized from commercially available 6-aminocaproic acid (**25**, Scheme V). The amino group of **25** was protected with a Boc group to provide **26**. The protected amino acid **26** was converted to the hydroxamate derivative **28** by treating a DMF–H_2O solution of **26** at pH 4.5 with a slight excess of *O*-benzylhydroxylamine (OBHA·HCl) followed by 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (WSC) and maintaining at pH 4.5 while the mixture was stirred at room temperature for 1.5 h. The treatment of **28** with CH_3I and K_2CO_3 in acetone provide the desired N-alkylated material **29** in 60% yield. Compound **29** was also obtained by treating 6-[*tert*-butoxycarbonyl)amino]-caproic acid (**26**) with *N*-methyl-*O*-benzylhydroxylamine[15] (**27**) in the presence of WSC. Reaction of **29** with anhydrous HCl provided free amine **30** contaminated with *N*-methyl-*O*-benzylhydroxylamine (**27**) from apparent competitive hydrolysis. This mixture was coupled with

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Table II. Response of Different Strains to Artificial Siderophores[a]

strain	1a	1b	2a	2b	3	4	5	FC	RA	SK	AR	Ent
stock solution[c]	100 μM	100 μM	380 μM	130 μM	134 μM	100 μM	50 & 500 μM	50 μM	50 μM	200 μM	50 μM	20 μM
RW193	+[b]	+	–	–	+	+	+	++	+	+	±	+
AN193	–	–	–	–	–	–	–	–	+	+	±	+
BN3300	–	–	–	–	–	–	–	–	–	–	–	+
RWB7	–	–	–	–	–	–	–	–	–	–	–	–
RWV193	+	+	–	–	+	+	+	++	+	+	±	+
BNV3040	+	+	–	–	+	+	+	++	+	+	±	+

[a] FC = ferrichrome, RA = rhodotorulic Acid, SK = schizokinen, AR = arthrobactin, Ent = enterobactin. [b] ++ indicates a >25-mm halo of growth. + indicates a 10–25-mm halo. ± indicates a <10-mm halo. – indicates no growth around the disc. [c] 10 μM applied.

triester **14d** in the presence of NEt_3 to give the tris(benzyl hydroxamate) **31** cleanly after workup. The final deprotection was accomplished by hydrogenation of **31** with Pd–C (5%) catalyst to provide the retro-hydroxamate **5**.

Biological Activity. The ability of the artificial siderophores to support the growth of *E. coli* strains defective in different steps of utilization of hydroxamate type siderophores (Table I) was examined (Table II). Both the ferri and deferri forms of the natural and artificial siderophores gave the same results. Strain RW 193, which is not deficient in iron hydroxamate transport, is able to use all but compounds **2a** and **2b** as a source of iron. Surprisingly, strain AN193, which lacks the outer membrane receptor for ferrichrome, but is competent in the transport of rhodotorulic acid and schizokinen, is unable to use any of the artificial siderophores for iron. Possible polar effects of the *tonA* mutation have been noted previously.[16] Other *tonA* strains tested gave the same results. Although certain of these compounds resemble schizokinen, *E. coli* apparently can distinguish among them. As expected, strain BN3300, which is blocked in a function required for utilization of hydroxamate type siderophores, and RWB7, which is lacking an inner membrane component (*tonB*) that is required for use of both catechol and hydroxamate type siderophores, iron citrate, and vitamin B_{12}, were unable to use any of the artificial siderophores. Because some of the artificial siderophores are analogues of aerobactin, we tested these on *E. coli* strains that contain the ColV plasmid and are thus able to transport aerobactin. The colV plasmid encodes a 74K outer membrane protein that is necessary for aerobactin transport. As seen in Table II, both RWV193, which contains the ColV plasmid, and BNV3040, which contains an *iut* mutant form of pColV-K30 defective in the synthesis of the 74K receptor, were able to use all of the artificial siderophores except **2a** and **2b**. Hence none of the analogues behave like aerobactin in *E. coli*.

Experimental Section

General Methods. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 727B spectrometer. Proton NMR spectra were obtained on Varian A-60A, XL-100, or EM-390 spectrometers. Chemical shifts are reported in ppm relative to tetramethylsilane (δ units). Elemental analyses were performed by Midwest Microlabs, Indianapolis, IN. Mass spectra were recorded on an AEI Scientific Apparatus MS 902 or a Du Pont 102 spectrometer. Field-desorption mass spectra were obtained by Dr. John L. Occolwitz (Eli Lilly and Co). Experiments performed at constant pH utilized a Metrohm CD3 combititrator–pH stat.

3-[(*tert*-Butoxycarbonyl)amino]propanal (9). Chromium(VI) oxide (2 g, 20 mmol) was added to a stirred solution of pyridine (3.5 g) in dry methylene chloride (25 mL). The deep red solution was stirred for 15 min at room temperature. Then, a solution of amino alcohol **6** (0.9 g, 5 mmol) in CH_2Cl_2 (5 mL) was added in one portion. The reaction mixture was allowed to stir at room temperature for 25 min. The solution was decanted from the residue and the residue was washed with CH_2Cl_2 (20 mL). The combined organic phase was washed with aqueous 5% NaOH (3 × 25 mL), 0.5 M citric acid (50 mL), aqueous 5% $NaHCO_3$ (25 mL), and brine. After the mixture was dried (Na_2SO_4) and the solvent evaporated, the product was obtained as an oil: 0.67 g (75%); ^1H NMR ($CDCl_3$) δ 1.44 (s, 9 H), 2.67 (t, 2 H), 3.42 (q, 2 H), 5.3 (br, 1 H), 9.88 (s, 1 H); IR (neat) 1700–1720 cm^{-1}.

Oxime Derivative 10 from Aldehyde 9. *O*-Benzylhydroxylamine hydrochloride (0.94 g, 1.5 equiv) was dissolved in H_2O at pH 6–7 with use of 1 N NaOH. To this solution, the aldehyde **9** (0.56 g) in methanol (20 mL) was added at once. The reaction mixture was allowed to stir at room temperature for 1 h. Volatile components were evaporated, and the residue was taken up in ethyl acetate. The organic layer was washed twice with 0.5 M citric acid and once with H_2O and brine. After the mixture was dried (Na_2SO_4) and solvent evaporated, the residue was chromatographed on a silica plate (2 mm, Chromatotron), eluting with ethyl acetate/hexane (20:80). The product was obtained as a colorless oil (*E* and *Z* isomers were not separated, *E*/*Z* ratio of 5:4): 0.8 g (58% yield from **6**); ^1H NMR ($CDCl_3$) δ 1.42 (s, 9 H), 2.3 and 2.5 (q, 2 H), 3.0–3.4 (m, 2 H), 4.97 (br s, 1 H), 5.02 and 5.10 (s, 2 H), 7.35 (s, 5 H), 6.72 and 7.42 (t, 1 H); IR (neat) 1710, 1510, 1360 cm^{-1}. Anal. ($C_{15}H_{22}N_2O_3$) C, H, N.

5-[(*tert*-Butoxycarbonyl)amino]pentanal *O*-Benzyloxime (19). A solution of oxalyl chloride (0.7 mL, 8 mmol) in CH_2Cl_2 (20 mL) was cooled to −70 °C and a solution of Me_2SO (1 mL, 15 mmol) in CH_2Cl_2 (10 mL) was added. The mixture was stirred for 5 min and a solution of alcohol **18** (3.5 mmol, 711 mg) in CH_2Cl_2 (20 mL) was added. The mixture was stirred for 25 min at −70 °C and NEt_3 (10 mL, 70 mmol) was added. After the mixture was stirred for 20 min, the cooling bath was removed and stirring was continued for 15 min. The mixture was poured into H_2O (500 mL) and extracted with ether. The ether extract was dried ($MgSO_4$) and concentrated to afford crude aldehyde. The crude aldehyde was treated with *O*-benzylhydroxylamine (430 mg, 3.5 mmol) in MeOH–H_2O (7:13, 2/ mL) at pH 7. After 30 min, the mixture was taken up in ethyl acetate and washed with 0.5 M citric acid and brine. After the solvent was dried ($MgSO_4$) and evaporated, the residue was chromatographed on a silica plate (2 mm, chromatotron, eluting with ethyl acetate/hexane (1:4), to afford the desired oxime **19** (450 mg; 42%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.3–1.8 (m, 13 H), 2.23 and 2.4 (q, 2 H), 3.13 (q, 2 H), 4.8 (br, 1 H), 5.03 and 5.12 (s, 2 H), 7.35 (s, 5 H), 6.68 and 7.48 (t, 1 H); IR (neat) 1705, 1510, 1360 cm^{-1}.

Hydroxamate 16. The oxime (211 mg, 0.60 mmol) and acetic anhydride (140 μL, 1.38 mmol) were dissolved in acetic acid (2 mL) and treated with $NaBH_3CN$ (45 mg, 0.69 mmol). The mixture was allowed to stir at room temperature for 1.5 h and taken up in ethyl acetate (80 mL). The mixture was washed twice with 10% Na_2CO_3 and brine. After the solvent was dried (Na_2SO_4) and evaporated, the desired known[10] N-acetylated material was isolated as a colorless oil (222 mg, 92%) which can be deprotected by treatment with TFA to provide **16**.[10].

1-[(*tert*-Butoxycarbonyl)amino]-3-[(benzyloxy)amino]propane (11). Compound **10** (0.67 g, 2.4 mmol) was dissolved in acetic acid (4 mL) and treated with $NaBH_3CN$ (0.151 g, 2.4 mmol). After the mixture was stirred at room temperature for 2 h, it was taken into ethyl acetate. The solution was washed twice with saturated Na_2CO_3 and once with H_2O and brine. After the

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solution was dried (Na_2SO_4) and the solvent evaporated, the residue was an oil: 0.51 g (75%); ^1H NMR ($CDCl_3$) δ 1.43 (s, 9 H), 1.5–1.8 (m, 2 H), 2.97 (t, 2 H), 3.19 (q, 2 H), 4.70 (s, 2 H), 4.8 (br s, 1 H, NH), 7.40 (s, 5 H).

1-Amino-3-[(benzyloxy)amino]propane Di-*p*-toluenesulfonate (8) from 11. Compound 11 (0.28 g, 1 mmol) was dissolved in dioxane (10 mL) and TsOH (0.38 g, 2.2 mmol) was dissolved in dioxane separately. Both solutions were combined and H_2O (1.5 equiv) was added. The reaction mixture was allowed to stand for 3 days. Ether was added to the reaction mixture and compound 8 crystallized out in 78% yield (0.416 g). This product had the same ^1H NMR and melting point when compared with those for the previous preparation of 8.[10] Anal. ($C_{24}H_{32}N_2O_7S_2 \cdot 0.5H_2O$) C, H, N.

Formation of the *p*-Nitrophenyl Esters. Method A. *p*-Nitrophenol (2 or 3 equiv) was dissolved in acetonitrile (0.05–0.1 M solution) and treated with NEt_3 (4 or 6 equiv). The corresponding acid chloride in acetonitrile (0.05–0.1 M) was added dropwise with stirring for 10–30 min at room temperature. After the addition was completed, the reaction mixture was stirred for 1–3 h at room temperature. The desired ester precipitated from the solution along with $NEt_3 \cdot HCl$. The precipitate was filtered and washed with H_2O, EtOH, and ether.

2,6-Pyridinedicarboxylic acid bis(*p*-nitrophenyl ester) (14a) was prepared by method A. After the washing, pure **14a** was obtained as a solid (1.2 g, 63%): mp 236–238 °C; ^1H NMR (Me_2SO-d_6) δ 7.75 (d, 4 H), 8.3–8.7 (m, 7 H).

Benztricarboxylic acid tris(*p*-nitrophenyl ester) (14b) was prepared by method A. The product was obtained as a solid (1.24 g, 65%): mp 285 °C dec.

Method B. The corresponding acid and *p*-nitrophenol were suspended in ethyl acetate or DMF/CH_3CN. DCC in ethyl acetate was added at 0 °C. The mixture was stirred for 30 min at 0 °C, then warmed to room temperature, and stirred an additional 5 min. After dicyclohexylurea was filtered off, the residue was chromatographed on silical gel, eluting with CH_2Cl_2. The solution containing product was washed several times with saturated $NaHCO_3$ and H_2O and brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, the residue was recrystallized.

Nitrilotriacetic acid tris(*p*-nitrophenyl ester) (14c) was prepared from nitrilotriacetic acid and *p*-nitrophenol by method B. The product was recrystallized from ethyl acetate/hexane (0.54 g, 10%): mp 161–162 °C; ^1H NMR ($CDCl_3$) δ 4.13 (s, 6 H), 7.37 (d, 6 H), 8.34 (d, 6 H).

Tricarballylic acid tris(*p*-nitrophenyl ester) (14d) was prepared from tricarballylic acid and *p*-nitrophenol by method B. The product was recrystallized from ethyl acetate/hexane (1.0 g, 18.6%): mp 144–146 °C; ^1H NMR ($CDCl_3$) δ 3.0–3.5 (m, 4 H), 3.5–3.9 (m, 1 H), 7.32 (d, 6 H), 8.30 (d, 6 H).

General Procedure of Formation of Acetylhydroxamates from *p*-Nitrophenyl Esters. A solution containing 1-amino-3-[(benzyloxy)amino]propane di-*p*-toluensulfonate (8) in acetonitrile (0.05–0.1 M) was treated with NEt_3. the corresponding *p*-nitrophenyl ester was added all at once as a solid. The suspension (or solution) was stirred for 2 h at room temperature. Volatile components were evaporated, and the residue was taken up in ethyl acetate. The solution was washed several times with 10% Na_2CO_3 and once with H_2O and brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, the residue was redissolved in CH_3CN (0.1 M). The solution was treated with acetic anhydride. The mixture was allowed to stir at room temperature for 2 h. After the solvent was evaporated, the residue was vacuum desiccated overnight to yield the pure product.

***N*,*N*′-Bis[3-[acetyl(benzyloxy)amino]propyl]-2,6-pyridinedicarbamide (15a)** was prepared from **14a** and **8** by the general procedure. Compound **15a** was obtained as a colorless oil (0.236 g, 93%): ^1H NMR ($CDCl_3$) δ 1.8–2.0 (m, 4 H), 2.13 (s, 6 H), 3.50 (q, 4 H), 3.80 (t, 4 H), 4.87 (s, 4 H), 7.43 (s, 10 H), 7.9–8.4 (m, 3 H), 9.28 (t, 2 H, NH); IR (neat) 3390, 1640–1680 cm^{-1}. Anal. ($C_{31}H_{39}N_5O_6 \cdot 0.5H_2O$) C, H, N.

Tris[3-[acetyl(benzyloxy)amino]propyl]-1,3,5-benztricarbamide (15b) was prepared from **14b** and **8** by the general procedure. Compound **15b** was isolated as a colorless oil: 55 mg (74%); ^1H NMR ($CDCl_3$) δ 1.6–1.95 (m, 6 H), 2.1 (s, 9 H), 3.43 (q, 6 H), 3.79 (t, 6 H), 4.83 (s, 6 H), 7.42 (s, 15 H), 7.6 (br, 3 H, NH), 8.5 (s, 3 H). Anal. ($C_{69}H_{78}N_6O_{12} \cdot H_2O$) C, H, N.

***N*,*N*′,*N*″-Tris[3-[acetyl(benzyloxy)amino]propyl]nitrilotriacetamide (15c)** was prepared from **14c** and **8** by the general procedure. Compound **15c** was obtained as a colorless oil: 25 mg (82%); ^1H NMR ($CDCl_3$) δ 1.5–1.9 (m, 6 H), 2.07 (s, 9 H), 3.27 (q, 6 H), 3.46 (s, 6 H), 3.70 (t, 6 H), 4.79 (s, 6 H), 7.45 (s, 15 H), 7.93 (br t, NH, 3 H).

***N*,*N*′,*N*″-Tris[3-[acetyl(benzyloxy)amino]propyl]tricarballylamide (15d)** was prepared from **14d** and **8** by the general procedure. Compound **15d** was obtained as a powder: 0.69 g (88%); mp 127–129 °C; ^1H NMR ($CDCl_3$) δ 1.65–1.69 (m, 6 H), 2.05 (s, 9 H), 2.35–2.85 (m, 5 H), 3.20 (q, 6 H), 3.70 (t, 6 H), 4.83 (s, 6 H), 7.20 (t, 3 H, NH), 7.42 (s, 15 H); IR ($CHCl_3$) 1640, 1660 cm^{-1}. Anal. ($C_{42}H_{56}N_6O_9$) C, H, N.

Formation of the Polyhydroxamates from 15 by Hydrogenation. The corresponding benzyl hydroxamates **15a–d** were dissolved in a solvent such as MeOH, THF/H_2O, 2-PrOH/H_2O and treated with 5% Pd on carbon (100 wt %) under 1 atm of H_2 for 3–5 h at room temperature. The reaction mixture was filtered and evaporated. The desired compounds were obtained in pure form.

***N*,*N*′-Bis[3-(acetylhydroxyamino)propyl]-2,6-pyridinedicarbamide (1a)** was obtained in 72.5% (0.1 g) yield as a powder: ^1H NMR (D_2O) δ 1.6–2.0 (m, 4 H), 2.0 (s, 6 H), 3.27 (t, 4 H), 3.60 (t, 4 H), 8.18 (s, 3 H); mass spectrum (FD), *m/e* 395 (M^+), 396 (M + 1); R_f 0.86 for reverse phase (RP-2) in 2-PrOH/H_2O (70:30); R_f 0.39 for reverse phase (RP-2) in 2-PrOH/H_2O (30:70).

***N*,*N*′,*N*″-Tris[3-(acetylhydroxyamino)propyl]-1,3,5-benztricarbamide (2a)** was obtained as a colorless oil in 68% (19 mg) yield: ^1H NMR (D_2O) δ 1.6–2.0 (m, 6 H), 2.07 (s, 9 H), 3.43 (q, 6 H), 3.75 (t, 6 H), 8.42 (s, 3 H); R_f 0.67 for reverse phase (RP-2) in 2-PrOH/H_2O (70:30); R_f 0.86 for paper chromatography in butanol/acetic acid/H_2O (60:15:25).

***N*,*N*′,*N*″-Tris[3-(acetylhydroxyamino)propyl]nitrilotriacetamide (3)** was obtained as a powder in 90% yield; ^1H NMR (D_2O) δ 1.6–1.9 (m, 6 H), 2.07 (s, 9 H), 3.2–3.5 (m, 12 H), 3.67 (t, 6 H); R_f 0.76 for paper chromatography in butanol/acetic acid/H_2O (60:15:25); R_f 0.83 for reverse phase (RP-2) in 2-PrOH/H_2O (70:30); mass spectrum (FD), *m/e* 533 (M^+).

***N*,*N*′,*N*″-Tris[3-(acetylhydroxyamino)propyl]tricarballylamide (4)** was obtained as an oil in 90% yield (168 mg); ^1H NMR (D_2O) δ 1.5–1.9 (m, 6 H), 2.03 (s, 9 H), 2.2–2.65 (m, 5 H), 3.15 (t, 6 H), 3.60 (t, 6 H); R_f 0.75 for paper chromatography in butanol/acetic acid/H_2O (60:15:25); R_f 0.81 for reverse phase (RP-2) in 2-PrOH/H_2O (70:30); mass spectrum (FD), *m/e* 519 (M + 1).

***N*,*N*′-Bis[5-[acetyl(benzyloxy)amino]pentyl]-2,6-pyridinedicarbamide (17) from 16.** 4-(Dimethylamino)pyridine (0.5 g, 4 mmol) was dissolved in acetonitrile (30 mL). Diacid chloride **12** (0.4 g, 2 mmol) in acetonitrile (10 mL) was added dropwise with stirring for 10 min at room temperature. After the addition was complete, the mixture was allowed to stir at room temperature for 20 min, and then compound **16** (1.4 g, 5 mmol) was added. The reaction mixture was allowed to stir at room temperature for 24 h. After the solvent was evaporated the residue was taken into ethyl acetate and washed with 0.5 M citric acid, H_2O, 10% $NaHCO_3$, H_2O, and brine. After the reaction mixture was dried ($MgSO_4$) and the solvent evaporated, the residue was chromatographed on silica gel, eluting with ethyl acetate. The oily **17** was isolated in 75% yield (1.11 g): ^1H NMR ($CDCl_3$) δ 1.2–1.8 (m, 12 H), 2.02 (s, 6 H), 3.2–3.8 (m, 8 H) [or 3.65 (t, 4 H), 3.40 (q, 4 H)], 4.82 (s, 4 H), 7.38 (s, 10 H), 7.9–8.5 (m, 3 H), 8.78 (t, 2 H, NH).

***N*,*N*′-Bis[5-(acetylhydroxyamino)pentyl]-2,6-pyridinedicarbamide (1b).** Compound **17** (0.316 g, 0.5 mmol) was dissolved in methanol (50 mL) and treated with 5% Pd on carbon (0.15 g) under 1 atm of H_2 for 4 h at room temperature. The reaction mixture was filtered and evaporated. The desired compound **1** was obtained in 58% (0.13 g) yield: ^1H NMR (D_2O) δ 1.1–1.8 (m, 12 H), 2.07 (s, 6 H), 3.3–4.1 (m, 8 H), 8.34 (s, 3 H); R_f 0.14 for 10% *i*-PrOH/90% CH_2Cl_2; R_f 0.21 for 30% *i*-PrOH/70% CH_2Cl_2; reverse phase (RP-2), R_f 0.72 for 70% *i*-PrOH/30% H_2O.

1-[(*tert*-Butoxycarbonyl)amino]-5-[(benzyloxycarbonyl)(benzyloxy)amino]pentane (20). The protected amino alcohol **18** (2.03 g, 10 mmol), TPP (3 g, 11.5 mmol), and

$CbzNHOCH_2Ph$ (3 g, 11.5 mmol) were dissolved in THF (30 mL). DEAD (2 mL, 11.5 mmol) in THF (10 mL) was added dropwise for 20 min at room temperature with stirring. The solution was allowed to stir for 24 h at room temperature. After the solvent was evaporated, the residue was chromatographed on silica gel (2 × 50 cm), eluting with ethyl acetate/hexane (16.7:83.3). The product was obtained as a colorless oil: 3.1 g (70%); ^1H NMR ($CDCl_3$) δ 1.2–1.8 (m, 15 H), 3.05 (q, 2 H), 3.47 (t, 2 H), 4.7 (br s, 1 H, NH), 4.83 (s, 2 H), 5.20 (s, 2 H), 7.31 (2 s, 10 H); IR (neat) 1650, 1710 cm^{-1}. Anal. ($C_{25}H_{34}N_2O_5$) C, H, N.

1-Amino-5-[(benzyloxycarbonyl)(benzyloxy)amino]pentane (21). 1-[(*tert*-Butoxycarbonyl)amino]-5-[(benzyloxycarbonyl)(benzyloxy)amino]pentane (**20**; 2.12 g, 5 mmol) was stirred with CF_3CO_2H (2.5 mL) for 15 min at room temperature. Excess CF_3CO_2H was removed by rotary evaporation. The residue was partitioned between ethyl acetate (40 mL) and 10% Na_2CO_3. the ethyl acetate layer containing free amine **21** was dried (K_2CO_3) and concentrated to give 1.69 g (100%) of **21** as an oil: ^1H NMR ($CDCl_3$) δ 1.1–1.8 (m, 6 H), 2.68 (t, 2 H), 3.47 (t, 2 H), 4.75 (br s, 2 H), 4.84 (s, 2 H), 5.20 (s, 2 H), 7.33 (2 s, 10 H).

Compound 22 from 21. 4-(Dimethylamino)pyridine (0.733 g, 6 mmol) was dissolved in acetonitrile (30 mL). Benzenetricarboxylic acid chloride (**12b**; 0.53 g, 2 mmol) in acetonitrile (10 mL) was added dropwise with stirring for 10 min at room temperature. After the addition was complete, the mixture was allowed to stir at room temperature for 24 h. After the solvent was evaporated, the residue was taken into ethyl acetate and washed once with 10% Na_2CO_3, once again with H_2O. After the reaction mixture was dried ($MgSO_4$) and the solvent evaporated, the residue was chromatographed on silica gel (2 × 50 cm), eluting with ethyl acetate to yield the product **22** as a colorless oil: 2.27 g (72%); ^1H NMR ($CDCl_3$) δ 1.0–1.8 (m, 18 H), 2.0 (s, 9 H), 3.15–3.70 (m, 12 H), 4.83 (s, 6 H), 5.20 (s, 6 H), 7.33 (2 s, 30 H), 8.47 (s, 3 H). Anal. ($C_{45}H_{54}N_6O_9 \cdot 2H_2O$) H, N; C: calcd, 62.92; found 62.43.

***N,N',N''*-Tris[5-(acetylhydroxyamino)pentyl]-1,3,5-benzenetricarboxamide (2b).** Compound **22** (0.568 g, 0.5 mmol) was dissolved in acetic acid (20 mL) and treated with acetic anhydride (0.4 mL, 4 mmol). This mixture was treated with 5% Pd on carbon (200 mg) under 1 atm of H_2 for 5 h. After the removal of acetic acid and acetic anhydride by freeze-drying, methanol was added and evaporated three times. The residue was redissolved in methanol (20 mL). After the mixture was filtered, it was allowed to stir for 10 h at room temperature. After the solvent was evaporated, compound **2b** was isolated as an oil: 0.2 g (62%); ^1H NMR ($CDCl_3$) δ 1.0–1.8 (m, 18 H), 2.03 (s, 9 H), 3.15–3.80 (m, 12 H), 6.73 (s, 6 H, OH and NH), 8.47 (s, 3 H); R_f 0.82, reverse phase (RP-2), in *i*-PrOH/H_2O (70:30); R_f 0.42, reverse phase (RP-2) in 2-PrOH/H_2O (30:70).

6-[(*tert*-Butoxycarbonyl)amino]caproic Acid (26). 6-Aminocaproic acid (**25**; 3.305 g, 25.2 mmol) was dissolved in H_2O (30 mL) and treated with di-*tert*-butyl pyrocarbonate (5 g, 22.9 mmol) in THF (30 mL). The reaction mixture was allowed to stir for 24 h at room temperature. The mixture was taken into ethyl acetate (150 mL) and washed twice with 0.5 M citric acid and once with H_2O. 10% Na_2CO_3 (100 mL) was added to the organic layer. The desired product went into the basic aqueous layer, which was then acidified with 3 N HCl to pH 2.5. The acidic aqueous layer was reextracted with ethyl acetate. After the extract was dried ($MgSO_4$) and the solvent evaporated, **26** was isolated as a colorless oil: 2.6 g (49%); ^1H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 1.2–1.9 (m, 6 H), 2.33 (t, 2 H), 3.13 (t, 2 H), 5.10 (s, 1 H, NH), 11.1 (s, CO_2H, 1 H); IR (neat) 1705 cm^{-1}.

Benzyl 6-[(*tert*-Butoxycarbonyl)amino]caprohydroxamate (28) from 26. Compound **26** (2.31 g, 10 mmol) and *O*-benzylhydroxylamine hydrochloride (1.76 g, 11 mmol) were dissolved in H_2O/DMF (1:1, 30 mL), and the pH was adjusted to 4.5 with 2 N NaOH. 1-Ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (WSC; 2.73 g, 15 mmol) was slowly added over 5 min. The pH was maintained at 4.5 with 1 N HCl while the solution was stirred at room temperature for 1 h. The mixture was extracted with two portions of ethyl acetate and washed: once with 5% $NaHCO_3$, once with H_2O, once with 0.5 M citric acid, and once with saturated NaCl. The solvent was dried ($MgSO_4$) and evaporated, the desired compound **28** was obtained as a colorless oil: 3.10 g (90%); ^1H NMR ($CDCl_3$) δ 1.15–1.8 (m, 15 H), 1.9–2.3 (m, 2 H), 3.07 (q, 2 H), 4.87 (s, 3 H, including NH), 7.38 (s, 5 H); IR (neat) 1680, 1650, 1700 (sh) cm^{-1}; mass spectrum (EI), *m/e* 279 (M – 57).

Benzyl *N*-Methyl-6-[(*tert*-butoxycarbonyl)amino]caprohydroxamate (29) from 28. Compound **28** (0.672 g, 2 mmol), methyl iodide (0.247 mL, 2 mmol), and K_2CO_3 (1.38 g, 10 mmol) were suspended in acetone (30 mL). The reaction mixture was allowed to stire for 24 h at room temperature. It was taken into ether and washed: twice with H_2O, twice with 0.5 M NaOH, and once with H_2O and brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, the product was obtained as a colorless oil: 0.42 g (60%); ^1H NMR ($CDCl_3$) δ 1.1–1.8 (m, 15 H), 2.35 (t, 2 H), 3.10 (q, 4 H), 3.21 (s, 3 H), 4.80 (s, 3 H, including NH), 7.43 (s, 5 H); IR (neat) 1655, 1705 cm^{-1}; mass spectrum (EI), *m/e* 293 (M – 57), 251 [M – 99; (NH_3^+)-$(CH_2)_5CON(OCH_2Ph)Me$]. Anal. ($C_{19}H_{30}N_2O_4 \cdot 0.5H_2O$) C, H, N.

Compound 29 from 26. Compound **26** (0.231 g, 1.9 mmol) and *N*-methyl-*O*-benzylhydroxylamine hydrochloride (**27**; 0.35 g, 2.02 mmol) were dissolved in H_2O/DMF (1:1, 20 mL), and the pH was adjusted to 4.5 with 2 N NaOH. WSC (0.575 g, 3 mmol) was slowly added over 5 min. the pH was maintained at 4.5 with 1 N HCl while the solution was stirred at room temperature for 1.5 h. the mixture was extracted with two portions of ethyl acetate and washed: once with 5% $NaHCO_3$, once with H_2O, once with 0.5 M citric acid, and once with saturated NaCl. The solvent was dried ($MgSO_4$) and evaporated. The desired product **29** was obtained as a colorless oil: 0.48 g (72%) and was identical with that prepared from **28**.

Deprotection of 29 with HCl. Compound **29** (0.70 g, 2 mmol) was dissolved in anhydrous ether (30 mL). Anhydrous HCl gas was passed through the solution at 0 °C for 45 min. An additional 100 mL of ether was added and the solution was extracted with 0.5 N HCl. The acidic solution containing the desired product was carefully neutralized to pH 10 with Na_2CO_3 (solid). This mixture was reextracted with three portions of $CHCl_3$. After the mixture was dried (K_2CO_3) and evaporated, the mixture of **30** and **27** was obtained (**30**/**27** = 2:1 by ^1H NMR) in 70% yield. **30**: ^1H NMR ($CDCl_3$) δ 1.1–1.8 (m, 6 H), 2.37 (t, 2 H), 2.67 (t, 2 H), 3.20 (s, 3 H), 4.2 (br s, NH_2, 2 H), 4.83 (s, 2 H), 7.43 (s, 5 H).

***N,N',N''*-Tris[5-[(benzyloxy)methylcarbamoyl]pentyl]-tricarballylamide (31).** The mixture of **30** and **27** (0.32 g) and triester **14d** (0.14 g, 0.21 mmol) were dissolved in acetonitrile (40 mL) and treated with NEt_3 (0.11 mL). The mixture was allowed to stire for 3 h at room temperature. It was taken into ethyl acetate and washed: twice with 0.5 M citric acid, once with H_2O, twice with 10% Na_2CO_3, and once with H_2O and brine. After the mixture was dried ($MgSO_4$) and evaporated, the desired product **31** was obtained as an oil: 0.21 g (93%); ^1H NMR ($CDCl_3$) δ 1.1–1.8 (m, 18 H), 3.0–3.4 (m, 15 H), 4.83 (s, 6 H), 6.80 (t, 3 H, NH), 7.43 (s, 15 H), 2.20–2.80 (m, 11 H). Anal. ($C_{48}H_{68}N_6O_9 \cdot 0.5H_2O$) C, H, N.

Retroanalogue of Carballylic Acid Derivative 5. Compound **31** (0.2 g, 2.29 mmol) was dissolved in THF/H_2O (2:1, 15 mL) and treated with 5% Pd on carbon (200 mg) under 1 atm of H_2 for 3 h at room temperature. The reaction mixture was filtered and evaporated to yield **5** as an oil: 110 mg (80%); ^1H NMR (D_2O) δ 1.2–1.8 (m, 18 H), 2.2–2.8 (m, 11 H), 3.0–3.5 (m, 15 H); paper chromatography, R_f 0.80 in butanol/acetic acid/H_2O (60:15:25); R_f 0.65 for reverse phase (RP-2) in 2-PrOH/H_2O (30:70).

Biological Activity. The ability of artificial siderophores to support growth of *Escherichia coli* K12 strains was examined by placing filter paper discs on nutrient agar plates seeded with an overlay of the strain in soft nutrient agar containing 0.1 mM deferriferrichrome A. Because *E. coli* is unable to use ferrichrome A, addition of this chelator makes the nutrient plate iron deficient. Each disc was them impregnated with 10 μL of 50–500 μM siderophore solution. The siderophores were dissolved in water, and the hydroxamic acid functionality was measured by the ferric perchlorate reagent with a_{mm} = 1.0 at 480 nm. The diameter of the growth response zone was scored after 12 and 24 h of incubation at 37 °C. Growth response assays were done with both the ferri and deferri forms of the artificial siderophores.

Acknowledgment. We gratefully acknowledge support of this research at Notre Dame by NIH Grant GM 25845 and at Berkeley by NIH Grant AI 04156. Dr. John L.

Occolwitz (Eli Lilly and Co.) kindly provided the mass spectral data.

Registry No. 1a, 94136-68-2; 1b, 94136-69-3; 2a, 94136-70-6; 2b, 94136-71-7; 3, 94136-53-5; 4, 94136-54-6; 5, 94136-55-7; 6, 58885-58-8; 8, 94136-56-8; 9, 58885-60-2; 10, 94136-57-9; 11, 94136-58-0; 12a, 3739-94-4; 12b, 4422-95-1; 14a, 56173-26-3; 14b, 56173-27-4; 14c, 94136-72-8; 14d, 94136-73-9; 15a, 94136-74-0; 15b, 94136-75-1; 15c, 94136-76-2; 15d, 94136-77-3; 16, 83966-23-8; 17, 94136-59-1; 18, 75178-90-4; 19, 94136-60-4; 20, 94136-61-5; 21, 94136-62-6; 22, 94136-63-7; 25, 60-32-2; 26, 6404-29-1; 27, 71925-14-9; 28, 94136-64-8; 29, 94136-65-9; 30, 94136-66-0; 31, 94136-67-1; $CbzNHOCH_2Ph$, 15255-86-4; Fe, 7439-89-6; *O*-benzylhydroxylamine hydrochloride, 2687-43-6; 5-[(*tert*-butoxycarbonyl)amino]pentanal, 94136-78-4; di-*tert*-butyl pyrocarbonate, 24424-99-5.

Artificial Siderophores. 2. Syntheses of Trihydroxamate Analogues of Rhodotorulic Acid and Their Biological Iron Transport Capabilities in *Escherichia coli*

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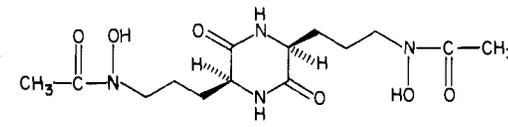
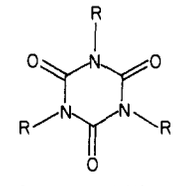
Tris[(acetylhydroxyamino)alkyl] isocyanurates **2a–c** were synthesized from α,ω-dibromoalkanes **5** in four steps. The alkylation of the bromides **5a–c** with *O*-benzyl-*N*-[(trichloroethoxy)carbonyl]hydroxylamine in the presence of DBU gave N-alkylation products **7a–c**. The (trichloroethoxy)cabronyl protecting group of **7a–c** was easily removed by Zn dust in acetic acid. When the reaction was performed with acetic anhydride, the desired N-acetylated materials **10a–c** were obtained. The alkylation of cyanuric acid with **12** in the presence of base provided the N-alkylated materials **13**, which were hydrogenated to provide **2a–c**. In order to determine the affect of structural modifications on biological activity, various chain lengths of the side arms were utilized and the retroanalogue **3** was prepared. Most of the compounds examined acted as ferrichrome in supporting the iron nutrition of *Escherichia coli*. However, tris[(acetylhydroxyamino)butyl] isocyanurate **2b**, and to some extent its pentyl analogue, **2c**, displayed the unique and remarkable property of supporting growth of *fhuB* mutants, the latter unresponsive to the other analogues and to all natural siderophores tested.

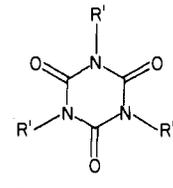
Microbial iron chelators (siderophores) are useful substrates for the study of iron metabolism[1-3] and the development of drugs for the treatment of iron-overloaded patients.[4-6] We reported the syntheses and biological activities of several analogues of schizokinen and arthrobactin in the earlier paper.[7] Most of the analogues prepared behaved nutritionally like ferrichrome in iron transport in *Escherichia coli*. In this paper, we report syntheses and biological activities of isocyanuric acid derivatives with structures similar to rhodotorulic acid[8] (**1**). Rhodotorulic acid is more effective than the currently used drug Desferal in promoting urinary and fecal iron excretion in the rat screen. But the painful local reaction to this compound administered im or sc curtailed its use.[9] These side effects may be due to the insolubility of rhodotorulic acid in water. In addition, rhodotorulic acid has only two binding sites per molecule (quadradentate); therefore the rhodotorulate–iron complex must have a minimum of a 3:2 stoichiometry.[10] To improve the iron binding efficiency, molecules designed to mimic the siderophore should be reasonably soluble, coordinate iron stoichiometrically (have hexadentate coordination with Fe^{3+}), and perhaps maintain a core similar to the diketopriperazine ring of rhodotorulic acid. Thus, isocyanuric acid derivatives **2–4** were chosen as target molecules.



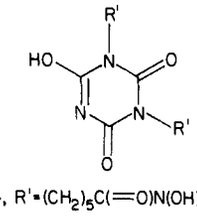
rhodotorulic acid (1)



2a, $R=(CH_2)_nN(OH)C(=O)CH_3$; $n=3$
b, $n=4$
c, $n=5$



3, $R=(CH_2)_5C(=O)N(OH)CH_3$



4, $R'=(CH_2)_5C(=O)N(OH)CH_3$

Synthesis of Artificial Siderophores. Since tri-N-alkylation of cyanuric acid (**12**) is precedented,[11] the key to the synthesis of the designated targets **2–4** was the preparation of the appropriate *N*-(ω-haloalkyl) hydroxamate side chains. Thus, as shown in Scheme I, treatment of the dihalide **5b** with *O*-benzylacetohydroxamate **8** and K_2CO_3 in acetone provided a 1:3 ratio of the O- and N-alkylated products **9** and **10** in 55% yield. The isomeric hydroximates [(*E*)- and (*Z*)-**9**] and the desired N-alkylated hydroxamate **10** were difficult to separate chromato-

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