(100), 121 (26.5), 92 (11.8), 77 (11.8). Anal. Calcd for $C_{10}H_{12}SO_3$: C, 56.58; H, 5.70; S, 15.11. Found: C, 56.37; H, 5.97; S, 15.35.

2-(Methylsulfinyl)-1-(2-quinolinyl)ethanone (1f): recrystallized yield from ethyl acetate–hexane 56%; mp 131–132 °C; ^{1}H NMR (Cl_3CD) δ 2.83 (s, 3 H, CH_3), 5.12–4.53 (AB system, 2 H, δ_A 4.96, δ_B 4.72, J_{AB} = 12.0 Hz, CH_2), 8.17–7.16 (m, 3 H, Ar); ^{13}C NMR (Cl_3CD) δ 39.3 (CH_3), 60.7 (CH_2), 117.4, 127.3, 128.9, 129.4, 130.0, 137.0, 146.5, 151.2 (Ar), 193.0 (CO); IR (KBr) 3060, 3020, 3000, 2900, 1690, 1365, 1030 cm^{-1}; MS, *m/e* (rel intensity) 233 ($M^{\bullet+}$, 1.1), 218 (100), 171 (13.8), 170 (14.4), 156 (33.3), 129 (22.2), 128 (88.9). Anal. Calcd for $C_{12}H_{11}O_2NS$: C, 61.78; H, 4.75; N, 6.00; S, 13.75. Found: C, 61.45; H, 4.82; N, 6.35; S, 13.67.

2-(Methylsulfinyl)-1-(1-isoquinolinyl)ethanone (1g). The imidazolide was prepared at 50 °C. The β-keto sulfoxide was obtained as brown oil which was chromatographed on a flash silica gel column, eluting with ethyl acetate–methanol (60:40) to give a oil that was not solidified (65%); ^{1}H NMR (Cl_3CD) δ 2.80 (s, 3 H, CH_3), 5.03–4.52 (AB system, 2 H, δ_A 4.86, δ_B 4.69, J_{AB} = 14.0 Hz, CH_2), 9.23–7.60 (m, 6 H, Ar); ^{13}C NMR (Cl_3CD) δ 38.4 (CH_3), 63.3 (CH_2), 125.3, 125.4, 126.5, 129.2, 129.9, 136.3, 140.3, 149.0 (Ar), 194.5 (CO); IR (neat) 3060, 3000, 2920, 1680, 1365, 1035, 755, cm^{-1}. Anal. Calcd for $C_{12}H_{11}O_2NS$: C, 61.78; H, 4.75; N, 6.00; S, 13.75. Found: C, 61.39; H, 5.05; N, 6.25; S, 13.5.

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Registry No. **1a**, 123005-08-3; **1b**, 51840-11-0; **1c**, 2813-22-1; **1d**, 123005-09-4; **1e**, 2813-23-2; **1f**, 123005-10-7; **1g**, 123005-11-8; **2a**, 123005-04-9; **2b**, 14723-73-0; **2c**, 3708-04-1; **2d**, 123005-05-0; **2e**, 27918-36-1; **2f**, 123005-06-1; **2g**, 123005-07-2; $CH_3(CH_2)_4CO_2H$, 142-62-1; $PhCO_2H$, 65-85-0; *m*-$NO_2C_6H_4CO_2H$, 121-92-6; *p*-$MeOC_6H_4CO_2H$, 100-09-4; $CH_3(CH_2)_{14}CO_2H$, 57-10-3; Ph_3CCO_2H, 595-91-5; 1,1′-carbonyldiimidazole, 530-62-1; dimethyl sulfone, 67-71-0; dimethyl sulfoxide, 67-68-5; 3,3-dimethylbutyric acid, 1070-83-3; 2-quinolinecarboxylic acid, 93-10-7; 1-isoquinolinecarboxylic acid, 486-73-7; 1-(1-imidazolyl)-3,3-dimethylbutanone, 4122-55-8; 1-(1-imidazolyl)-1-hexanone, 60988-34-3; (1-imidazolyl)phenone, 10364-94-0; 1-imidazolyl(3-nitrophenyl)methanone, 61652-82-2; 1-imidazolyl(4-methoxyphenyl)methanone, 10364-93-9; 1-imidazolyl-2-quinolinylmethanone, 123005-03-8; imidazol-1-ylisoquinolinylmethanone, 123026-29-9; 1-imidazol-1-yl-1-hexadecanone, 26227-65-6; 1-imidazol-1-yl-2,2,2-triphenylethanone, 123005-12-9.

Synthesis and Analytical Characterization of a Major Desferrioxamine B Metabolite

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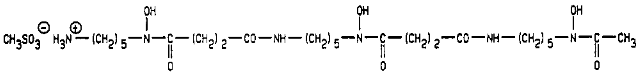
Introduction

Over the past 2 decades desferrioxamine B (**1**, Desferal, Ciba-Geigy) has been used therapeutically to treat transfusional iron overload in patients afflicted with thalassemia.[1] In addition, the drug has been used in the treatment of acute iron poisoning and as a diagnostic aid for the determination of abnormal iron stores.[2] A more recent application has been in the removal of aluminum from patients with impaired renal function undergoing chronic haemodialysis.[3,4] While desferrioxamine has been established as a very safe drug with minimal toxicity in iron-overloaded patients, there have been isolated reports of toxic side effects.[5] This dissimilarity in drug tolerability could be a direct result of differences related to the metabolism of the drug.



$$CH_3SO_3^{\ominus}\ H_3\overset{\oplus}{N}-(CH_2)_5-\overset{OH}{\overset{|}{N}}-\underset{\underset{O}{\|}}{C}-(CH_2)_2-CO-NH-(CH_2)_5-\overset{OH}{\overset{|}{N}}-\underset{\underset{O}{\|}}{C}-(CH_2)_2-CO-NH-(CH_2)_5-\overset{OH}{\overset{|}{N}}-\underset{\underset{O}{\|}}{C}-CH_3$$

1

Several early studies in desferrioxamine metabolism demonstrated the ability of plasma to degrade the iron-free compound rapidly.[6,7] This enzymatic activity was most pronounced in the plasma of the rat and mouse with lower activity observed in dog and human plasma. In contrast, the iron-bound ligand, ferrioxamine, was not metabolized to any appreciable extent.[7] The recovery of three human urinary metabolites of desferrioxamine was reported 25 years ago by Keberle.[8] The principle metabolite, known as "metabolite C" (**2**), was isolated and described as the product of an oxidative deamination reaction resulting in the corresponding carboxylic acid derivative. More recently an HPLC method has been developed that permits determination and quantitation of desferrioxamine B and metabolites as their iron(III) complexes in mammalian plasma.[9] Pharmacokinetic data from a patient who had received desferrioxamine i.m. (500 mg) revealed that the drug was rapidly converted into two main metabolites whose iron complexes exhibited spectral characteristics similar to those of ferrioxamine. It was suggested that the metabolites were N-terminal modified desferrioxamine derivatives.

It is evident that the synthesis and evaluation of desferrioxamine metabolites could prove quite useful in investigations correlating the formation of metabolites with the onset of toxic side effects. In this paper we describe the synthesis of "metabolite C" (**2**), a desferrioxamine carboxylic acid analogue, as well as the corresponding alcohol derivative (**3**), also a potential metabolite. In addition, a general procedure for the preparation of ferric and aluminum complexes of hydroxamate ligands is reported. Last, we have investigated the chromatographic behavior of these metabolites in the free and metal-bound forms in comparison to desferrioxamine B and its Fe(III) and Al(III) complexes utilizing high-performance liquid chromatography.

Results and Discussion

Bergeron and Pegram have recently described[10] an elegant total synthesis of desferrioxamine B. The synthesis is noteworthy in that the synthetic scheme is highly flexible thus providing access to various desferrioxamine analogues as well as proceeding in high overall yield. A key intermediate was the tri-*O*-benzyl-protected cyanodesferrioxamine derivative **6**. The synthesis described herein (Scheme II) is predicated on this important intermediate. The synthetic strategy was centered on the conversion of this intermediate into the fully protected deaminated

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Scheme I. Structures of the Proposed Desferrioxamine B Metabolites

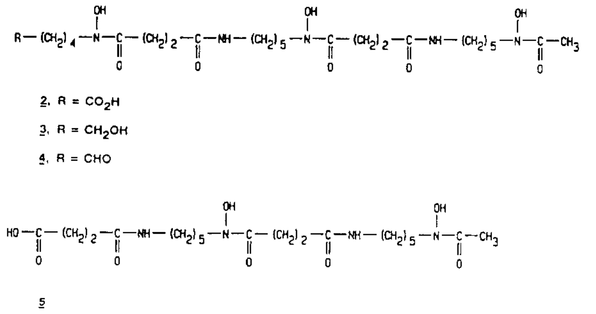


Table I. Gradient Used for the Separation of Desferrioxamine B, the Metabolites, and Their Ferric and Aluminum Complexes

	mobile phase[a]	
t, min	A, %	B, %
0	95	5
15	65	35
17	35	65
21	35	65
30	95	5

[a] Mobile phase A consisted of a 2.5 mM phosphate buffer solution (pH 3.0). Mobile phase B consisted of a mixture of mobile phase A and acetonitrile (20:80, v/v).

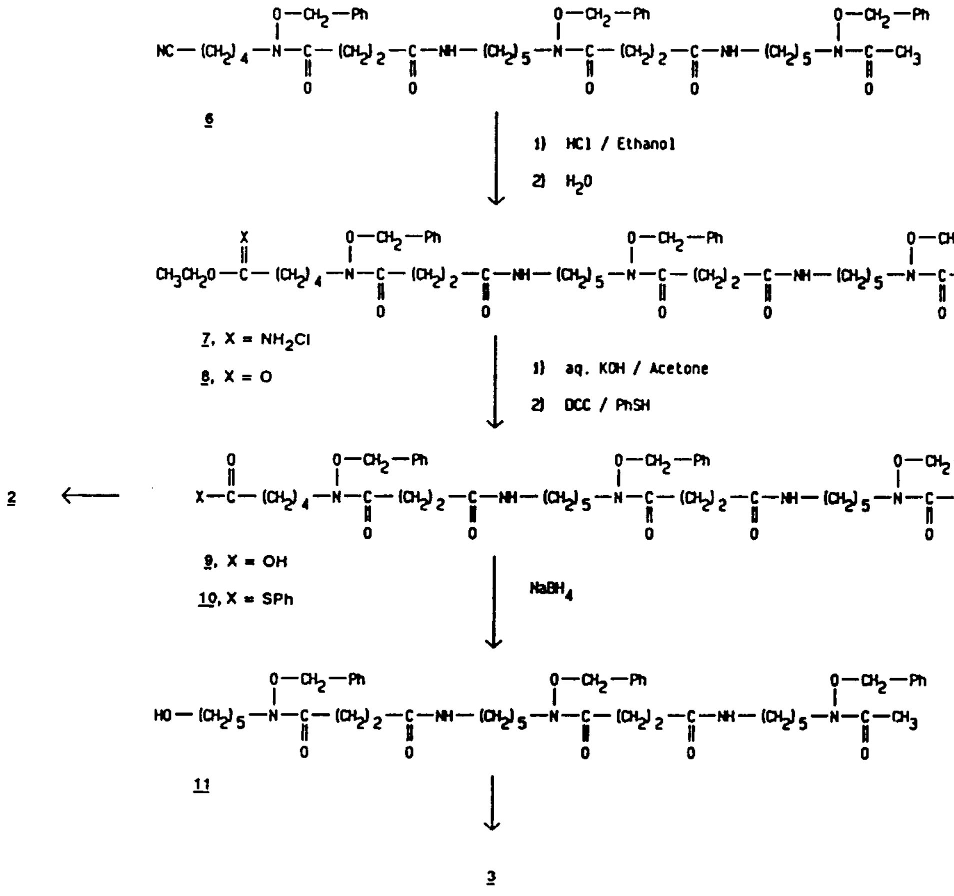
derivative through formation of an imido ester. The imidate would then be expected to hydrolyze quite readily to furnish the corresponding carboxylic ester. Saponification of this ester would then afford the desired carboxylic acid derivative. Removal of the protecting groups would then furnish "metabolite C" (**2**, Scheme I). This methodology could also be used directly to furnish the corresponding desferrioxamine alcohol derivative **3**. From a metabolic standpoint the enzymatic deamination of desferrioxamine will proceed through the imine, which will then readily hydrolyze to an unstable aldehyde. Chemical degradation of the aldehyde could then furnish the desferrioxamine carboxylic acid or alcohol derivatives.

Synthetically, one could reduce either the benzyl-protected carboxylic ester or acid directly to the desired alcohol. Catalytic hydrogenation would then afford the deprotected alcohol **3**. While the synthesis of the unstable aldehyde metabolite **4** would also be desirable, we have been unable at present to isolate the pure compound. Our investigations in this area are described briefly.

The fully protected nitrile **6** (Scheme II) was readily converted into the imido ester **7** by treatment with anhydrous ethanolic hydrochloric acid. It was critical to maintain a temperature of −20 °C during the reaction as considerable degradation occurred at higher temperatures. In the next step the imidate hydrochloride was transformed into the ester **8** by hydrolysis in 75% overall yield. Saponification of the ester **8** employing aqueous potassium hydroxide in acetone generated the corresponding carboxylic acid **9** in 55% yield. Subsequent removal of the benzyl protecting groups by catalytic hydrogenation over palladium afforded smoothly the desired product, metabolite C (**2**), in 80% yield.

A considerable effort was invested before finding appropriate conditions for synthesis of the alcohol intermediate **11**. A main concern was the stability of the benzyl-protected hydroxamate moiety to organmetallic reducing agents. It has been previously demonstrated that *N*-methoxy-*N*-methyl carboxamides are readily reduced

Scheme II. Synthesis of the Benzyl-Protected Desferrioxamine B Carboxylic Acid and Alcohol Derivatives



by lithium aluminum hydride.[11] The reaction proceeds through a stable lithium-chelated intermediate which upon hydrolysis furnishes the aldehyde. This methodology has been employed successfully in the preparation of N-protected α-amino aldehydes.[12] Attempted selective reduction of the ester functionality in **8** was unsuccessful under a variety of reaction conditions, including activated sodium borohydride[13] and the diisobutylaluminum hydride–butyllithium complex,[14] as well as lithium borohydride.[15] In all cases there occurred significant degradation of the starting ester **8** with the formation of several products as determined by HPLC analysis. In the reaction with lithium borohydride a major product was separated and analyzed spectroscopically. The compound was established to be a low molecular weight alcohol [(M + H) = 337] formed by cleavage of the central hydroxamate moiety. As a result of these findings, we decided to concentrate our efforts on the reduction of the triprotected carboxylic acid **9**. While an initial ethyl chloroformate activation[16] failed, success was finally achieved via formation of the intermediate thioester and subsequent reduction with sodium borohydride.[17] Formation of the thioester **10** was achieved by initial dicyclohexylcarbodiimide activation in the presence of thiophenol and (dimethylamino)pyridine in methylene chloride. This coumpound was smoothly reduced at room temperature in absolute ethanol following addition of sodium borohydride to afford the benzyl-protected alcohol **11** in 85% yield. Last, the benzyl groups were removed by catalytic hydrogenation over palladium to furnish the desired product **3** (Scheme I) in 79% yield.

At this point our attention was focused on generating the aldehyde **4** (Scheme I). Alcohol **11** was oxidized to the corresponding benzyl-protected aldehyde by employing the catalytic oxidant tetrapropylammonium perruthenate[18] in the presence of 4-methylmorpholine *N*-oxide in 70% yield. Attempts at catalytic hydrogenation employing various hydrogen donors and solvents were unsuccessful in generating aldehyde **4**. In most cases a mixture of products was obtained that could not be separated. We next protected the aldehyde as its dioxolane derivative. Catalytic hydrogenation over palladium furnished the debenzylated product in high yield while the aldehyde protecting group remained intact. Attempted hydrolysis of the dioxolane functionality with aqueous acetone containing catalytic p-TsOH resulted in the unexpected cleavage of the hydroxamate group to afford the carboxylic acid **5**. This degradation product was spectroscopically identical with an authentic sample.

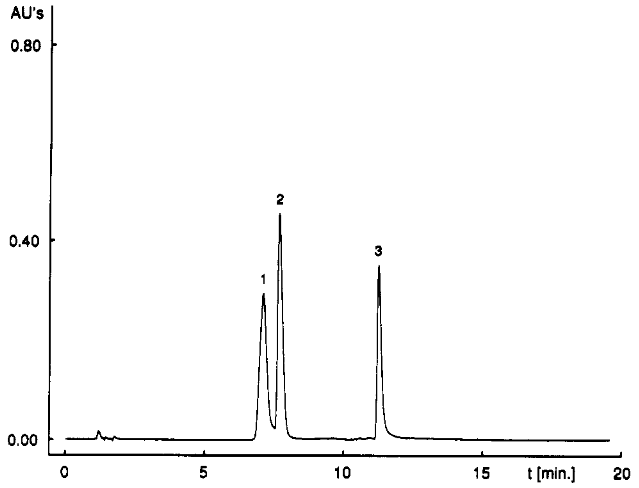


Figure 1. Chromatogram of a mixture of desferrioxamine B and its ferric and aluminum complexes.

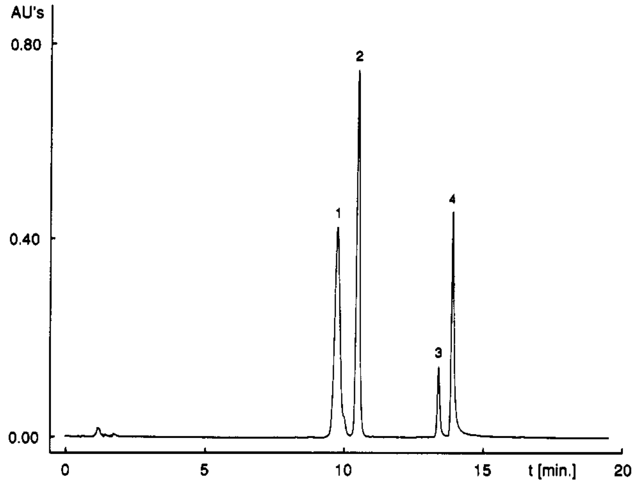


Figure 2. Chromatogram of a mixture of metabolite C and its ferric and aluminum complexes.

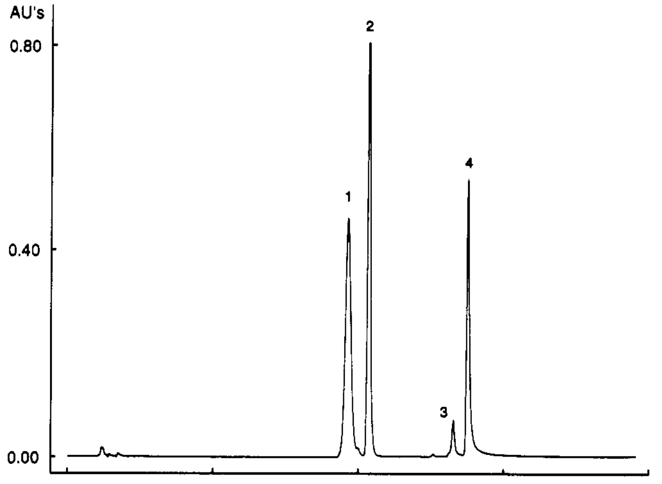


Figure 3. Chromatogram of a mixture of the desferrioxamine alcohol derivative and its ferric and aluminum complexes.

Preparation of the Ferric Metabolite C Complex. The ferric complex of metabolite C was prepared by utilizing a new method. Previously, hydroxamate and catecholamide ferric complexes were obtained by treatment of the free ligands with simple ferric salts. This can lead to problems especially when initial basic solutions are required for chelator solubility. In our hands, formation of hydroxamate iron(III) chelates employing such methods has led to unsatisfactory results. Invariably, the overall yields were low, and chromatographic separation of precipitated ferric salts was necessary. We now wish to report that reaction of hydroxamate ligands with commercially available metal acetylacetonate complexes in a two-phase system furnishes in high yield the corresponding metal siderophore chelates. Thus, treatment of an aqueous suspension of metabolite C with 1 equiv of ferric acetyl-

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acetonate dissolved in ethyl acetate results in rapid formation of the water-soluble 1:1 ferric–metabolite C complex (**2a**). The workup involved simply washing of the aqueous layer with organic solvent followed by lyophilization. Ferric hydroxamate complexes produced and isolated in this manner typically do not require additional purification.

HPLC Separation. We next determined the chromatographic behavior of the three ligands (desferrioxamine B, metabolite C, and the desferrioxamine alcohol derivative) in mixtures with their iron(III) and aluminum(III) metal complexes. The chromatograms, shown in Figures 1–3, were generated by utilizing a phosphate buffer/acetonitrile gradient system (Table I) in which each component is at a concentration of 100 mg/L. With use of a modification of the HPLC method described earlier,[19] the free ligands and their two corresponding complexes could be resolved easily. Employing a mobile phase without the addition of EDTA permitted the use of silca-based reversed-phase supports in place of the polymeric material that had been used previously. Peaks 1 and 2 correspond to the ferric and aluminum complexes, respectively, whereas peak 3 (Figure 1) and peak 4 (Figures 2 and 3) represent the free ligand. The minor component (peak 3 in Figures 2 and 3) develops only when a mixture of the three compounds is chromatographed and is not present in the individual chromatograms. As has been advanced previously,[20] the ferric complexes, owing to their more compact molecular structure, elute faster than the corresponding free ligands on silica-based supports. Replacement of the terminal amino group of desferrioxamine B by the carboxylic acid or alcohol functionality resulted in an expected increase in the retention time at the applied low pH.

Conclusion. The synthetic utility of the fully *O*-benzyl-protected cyanodesferrioxamine derivative **6** has been demonstrated by the synthesis of a major metabolite of desferrioxamine B. The analytical and spectral characterization of metabolite C and the desferrioxamine alcohol derivative will facilitate further pharmacokinetic studies in desferrioxamine metabolism. Additionally, the novel procedure described for the preparation of the ferric metabolite C complex employing ferric acetylacetonate in a two-phase system will find use in the siderophore field. This procedure should be applicable to a wide range of siderophore chelators, including the catecholamine-containing ligands. Further, it may be possible to broaden the scope of this method by making use of the various metal acetylacetonate complexes available.

Experimental Section

^{1}H NMR spectra were obtained at 360 or 400 MHz. FAB mass spectra were determined on a VG ZAB-HF spectrometer (VG Analytical, Manchester, UK). Melting points are uncorrected. Standard samples of desferrioxamine B and ferrioxamine were obtained from the Pharmaceutical Division of Ciba-Geigy. Reaction progress and purification were monitored by analytical reversed-phase HPLC, and the purity of all title compounds determined to be ≥94% by HPLC and ^{1}H NMR analysis unless otherwise indicated.

Instrumentation and Chromatographic Conditions. The gradient HPLC system used consisted of an LKB 2150 double-piston pump, a low-pressure gradient mixer LKB 2152 (Uppsala, Sweden), a three-way mixing valve LEE (Westbrook, USA), and a Kratos 773 UV detector (Ramsey, USA) set to a detection wavelength of 220 nm. Samples were injected by using a Gilson 231 autosampler (Villiers-Le-Bel, France), equipped with a Rheodyne Model 7010 injection valve (Cotati, USA) and data processed with integration software Nelson Model 2600, revision 5 (Cupertino, USA), running on an IBM-AT03 personal computer. The gradient system used is shown in Table I. The flow rate of the mobile phase was 1 mL/min. The sample volume injected was 50 μL throughout all experiments.

Stationary Phase. HIBAR columns (Merk, Darmstadt, FRG; 4.0 mm × 125 mm) were filled with spherical reversed-phase silicagel of 5-μm diameter, a pore size of 100 Å, and C18 coating (Macherey-Nagel, Dueren, FRG). The column endings were equipped with stainless steel frits.

Mobile Phase. Mobile phase A (pH = 3.0) was made by mixing 10 mL of a buffer stock solution with 990 mL of deionized water. Mobile phase B was prepared by mixing 80% (v/v) HPLC-grade acetonitrile with 20% (v/v) of phase A. The stock buffer solution was prepared by dissolving 60.0 g of potassium dihydrogen phosphate in 950 mL of deionized water and adding orthophosphoric acid to reach a pH value of 2.5 (about 6.75 g of orthophosphoric acid, 85%, is used). Water was then added to reach 1 L of total volume.

***N′*-[5-[[4-[[5-[Acetyl(phenylmethoxy)amino]pentyl]amino]-1,4-dioxobutyl](phenylmethoxy)amino]pentyl]-*N*-(4-cyanobutyl)-*N*-(phenylmethoxy)butanediamide (6)** was prepared according to a published procedure.[10]

***N′*-[5-[[4-[[5-[Acetyl(phenylmethoxy)amino]pentyl]amino]-1,4-dioxobutyl](phenylmethoxy)amino]pentyl]-*N*-(5-ethoxy-5-iminopentyl)-*N*-(phenylmethoxy)butanediamide Hydrochloride (7).** Dry HCl gas was bubbled into absolute ethanol (30 mL) under ice cooling and stirring for 1 h. The solution was then charged with the nitrile **6** (1.55 g, 1.87 mmol), and the suspension allowed to stand at −20 °C for 20 h. The resulting solution was concentrated under reduced pressure to afford **7** as a viscous oil which solidified under high vacuum. The crude material was used directly without further purification (HPLC = ~83%); ^{1}H NMR (CH_3OD) δ 1.25–1.37 (m, 4 H), 1.42 (t, *J* = 7, 3 H), 1.43–1.56 (m, 4 H), 1.57–1.76 (m, 8 H), 2.06 (s, 3 H), 2.38–2.50 (m, 4 H), 2.62 (m, 2 H) 2.68–2.79 (m, 4 H), 3.09–3.18 (m, 4 H), 3.60–3.75 (m, 6 H), 4.31–4.40 (q, *J* = 7, 2 H), 4.85–4.93 (m, 6 H), 7.34–7.47 (m, 15 H); IR (CH_2Cl_2) 3680, 3440, 3260, 3030, 2940, 2860, 1660, 1530, 1495, 1450, 1410 cm^{-1}.

***N′*-[5-[[4-[[5-[Acetyl(phenylmethoxy)amino]pentyl]amino]-1,4-dioxobutyl](phenylmethoxy)amino]pentyl]-*N*-(4-(ethoxycarbonyl)butyl)-*N*-(phenylmethoxy)butanediamide (8).** To a flask containing the crude imidate hydrochloride **7** (1.70 g) was added 50 mL of ice water. The resulting mixture was allowed to stand for 6 h, and then the product was extracted into methylene chloride (4 × 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution, water, and brine; dried over anhydrous sodium sulfate; and evaporated to dryness under reduced pressure. The residue was chromatographed on silica (4% CH_3OH/CH_2Cl_2) to afford **8** (1.22 g, 75%) as a waxlike solid: ^{1}H NMR (CH_3OD) δ 1.21 (t, *J* = 8, 3 H), 1.28–1.37 (m, 4 H), 1.43–1.53 (m, 4 H), 1.56–1.68 (m, 8 H), 2.05 (s, 3 H), 2.30 (t, *J* = 7, 2 H), 2.43 (t, *J* = 7, 4 H), 2.68–2.78 (m, 4 H), 3.09–3.18 (m, 4 H), 3.62–3.71 (m, 6 H), 4.08 (q, *J* = 7, 2 H) 4.87 (m, 6 H), 7.34–7.46 (m, 15 H), 7.84–7.89 (m, 2 H); IR (CH_2Cl_2) 3680, 3440, 3340, 3040, 2940, 2860, 1730, 1660, 1520, 1450, 1410 cm^{-1}; FABMS calcd for $C_{48}H_{67}N_5O_{10}$ 874.10, found 874 (M + H)$^+$).

***N′*-[5-[[4-[[5-[Acetyl(phenylmethoxy)amino]pentyl]amino]-1,4-dioxobutyl](phenylmethoxy)amino]pentyl]-*N*-(4-carboxybutyl)-*N*-(phenylmethoxy)butanediamide (9).** To a stirred solution of the ester **8** (1.15 g, 1.31 mmol) in acetone (70 mL) was added dropwise with ice cooling 25 mL of aqueous KOH solution (0.073 g, 1.31 mmol). After the addition was complete, the ice bath was removed and the solution was stirred at room temperature overnight. After the removal of solvent in vacuo, the residue was diluted with 30 mL of ice water and acidified by the dropwise addition of an aqueous 0.1 M HCl solution. Following extraction with ethyl acetate, the combined organic layers were washed with brine and dried (Na_2SO_4). Evaporation of the solvent followed by chromatography on silica (4% CH_3OH/CH_2Cl_2) furnished **9** (0.61 g, 55%) as a clear oil: ^{1}H NMR (CH_3OD) δ 1.26–1.37 (m, 4 H), 1.43–1.55 (m, 4 H), 1.56–1.69 (m, 8 H), 2.05 (s, 3 H), 2.29–2.35 (t, *J* = 7, 2 H), 2.38–2.48 (t, *J* = 7, 4 H), 2.68–2.78 (m, 4 H), 3.09–3.18 (t, *J* = 8, 4 H), 3.62–3.71 (m,

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6 H), 4.87 (m, 6 H), 7.34–7.46 (m, 15 H); IR (KBr) 3320, 3030, 2940, 2860, 2600, 1728, 1655, 1550, 1455, 1410 cm^{-1}; FABMS calcd for $C_{46}H_{63}N_5O_{10}$ 846.04, found 846.5 ((M + H)$^+$).

***N'*-[5-[[4-[[5-[Acetyl(phenylmethoxy)amino]pentyl]amino]-1,4-dioxobutyl](phenylmethoxy)amino]pentyl]-*N*-(4-((phenylthio)carbonyl)butyl)-*N*-(phenylmethoxy)butanediamide (10).** The acid **9** (2.09 g, 2.47 mmol) and thiophenol (0.299 g, 2.72 mmol) were dissolved with stirring in methylene chloride (50 mL). To the ice-cooled solution was added dropwise dicyclohexylcarbodiimide (0.637 g, 3.09 mmol) in 15 mL of methylene chloride followed by (dimethylamino)pyridine (0.059 g, 0.48 mmol) in 10 mL of methylene chloride. After the addition was complete, the ice bath was removed and the reaction mixture stirred overnight. The cloudy solution was filtered, and the white solid washed with additional solvent. The organic solution was washed with an aqueous 0.5 M HCl solution and a saturated $NaHCO_3$ solution, then dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The crude oil **10** (1.89 g) was used directly without further purification (HPLC = ~87%): ^{1}H NMR (CH_3OD) δ 1.27–1.36 (m, 4 H), 1.42–1.56 (m, 4 H), 1.57–1.70 (m, 8 H), 2.05 (s, 3 H), 2.37–2.46 (m, 4 H), 2.65–2.77 (m, 6 H), 3.10–3.17 (t, *J* = 8, 4 H), 3.60–3.71 (m, 6 H), 4.86–4.93 (m, 6 H), 7.34–7.46 (m, 20 H); IR (CH_2Cl_2) 3680, 3440, 3340, 3040, 2940, 2860, 1700, 1660, 1520, 1450, 1410 cm^{-1}; FABMS calcd for $C_{52}H_{67}N_5O_9S$ 938.21, found 938 ((M + H)$^+$).

***N'*-[5-[[4-[[5-[Acetyl(phenylmethoxy)amino]pentyl]amino]-1,4-dioxobutyl](phenylmethoxy)amino]pentyl]-*N*-(5-hydroxypentyl)-*N*-(phenylmethoxy)butanediamide (11).** Under a blanket of argon sodium borohydride (0.20 g, 5.28 mmol) was added to a solution of the thioester **10** (1.10 g, 1.17 mmol) in absolute ethanol (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The solution was cooled, and then saturated aqueous ammonium chloride (30 mL) was added. The resulting mixture was poured into ice-cold aqueous 1 N HCl (50 mL) and extracted with methylene chloride (3 × 75 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification was effected by chromatography on silica eluting with 4% CH_3OH/CH_2Cl_2 to afford 11 (0.83 g, 85%): ^{1}H NMR ($CDCl_3$) δ 1.23–1.37 (m, 6 H), 1.45–1.55 (m, 6 H), 1.58–1.66 (m, 6 H), 2.09 (s, 3 H), 2.45–2.51 (m, 4 H), 2.75–2.84 (m, 4 H), 3.15–3.21 (m, 4 H), 3.57 (t, *J* = 7, 2 H), 3.58–3.67 (m, 6 H), 4.80 (s, 2 H), 4.85 (d, *J* = 4, 4 H), 6.38–6.50 (m, 2 H), 7.37 (s, 15 H); IR (CH_2Cl_2) 3680, 3610, 3440, 3340, 3040, 2940, 2860, 1660, 1520, 1450, 1410 cm^{-1}; FABMS calcd for $C_{46}H_{65}N_5O_9$ 832.06, found 832 (M + H)$^+$.

***N'*-[5-[[4-[[5-(Acetylhydroxyamino)pentyl]amino]-1,4-dioxobutyl]hydroxyamino]pentyl]-*N*-(4-carboxybutyl)-*N*-hydroxybutanediamide (2).** The acid **9** (0.52 g, 0.61 mmol) was dissolved in 50 mL of absolute ethanol. To the cloudy solution was added palladium on carbon (0.26 g) under a blanket of argon. The argon atmosphere was replaced with hydrogen, and the mixture stirred vigorously overnight under ambient conditions. Hydrogen was removed at reduced pressure and replaced with argon. The suspension was heated to 80 °C and then filtered over Celite, followed by washing with hot ethanol. Solvent removal followed by recrystallization from water afforded **2** (0.28 g, 80%) as a white solid: mp 140–141 °C ^{1}H NMR (CD_3OD) δ 1.28–1.39 (m, 4 H), 1.47–1.56 (m, 4 H), 1.57–1.69 (m, 8 H), 2.09 (s, 3 H), 2.29–2.35 (t, *J* = 7, 2 H), 2.42–2.49 (t, *J* = 7, 4 H), 2.72–2.80 (t, *J* = 7, 4 H), 3.12–3.20 (t, *J* = 7, 4 H), 3.55–3.65 (m, 6 H); IR (KBr) 3420, 3300, 3140, 2930, 2860, 1720, 1620, 1565, 1460, 1395 cm^{-1}; FABMS ((M + H)$^+$) = 576. Anal. Calcd for $C_{25}H_{45}N_5O_{10}$: C, 52.16; H, 7.88; N, 12.17. Found: C, 51.92; H, 7.83; N, 12.10.

General Procedure for Preparation of Complexes. *N'*-[5-[[4-[[5-(Acetylhydroxyamino)pentyl]amino]-1,4-dioxobutyl]hydroxyamino]pentyl]-*N*-(4-carboxybutyl)-*N*-hydroxybutanediamide Ferric Complex (2a). To a suspension of the acid **2** (23 mg, 0.04 mmol) in water (5 mL) was added ferric acetylacetonate (13 mg) dissolved in ethyl acetate (5 mL). The two-phase system was stirred vigorously for 2 h at room temperature, and then the layers were separated. The aqueous solution was washed with ethyl acetate and then lyophilized to afford the product **2a** (24 mg, 96%) as a red solid: FABMS calcd for $C_{25}H_{42}FeN_5O_{10}$ 628.49, found 629 ((M + H)$^+$).

***N'*-[5-[[4-[[5-(Acetylhydroxyamino)pentyl]amino]-1,4-dioxobutyl]hydroxyamino]pentyl]-*N*-(5-hydroxypentyl)-*N*-hydroxybutanediamide (3).** To a solution of the alcohol **11** (0.472 g, 0.567 mmol) in absolute ethanol (50 mL) was introduced 10% palladium on carbon (0.23 g). The suspension was stirred under a hydrogen atmosphere overnight. After being heated to 80 °C, the mixture was filtered over Celite. Removal of solvent in vacuo followed by recrystallization from water furnished **3** (0.25 g, 79%) as a white solid (mp 135–136 °C): ^{1}H NMR (CH_3OD) δ 1.28–1.42 (m, 6 H), 1.47–1.58 (m, 6 H), 1.58–1.68 (m, 6 H), 2.09 (s, 3 H), 2.45 (t, *J* = 7, 4 H), 2.76 (t, *J* = 7, 4 H), 3.15 (t, *J* = 7, 4 H), 3.54 (t, *J* = 7, 2 H), 3.60 (t, *J* = 7, 6 H); IR (KBr) 3420, 3300, 3140, 2930, 2860, 1620, 1565, 1460, 1395 cm^{-1}; FABMS ((M + H)$^+$) = 562. Anal. Calcd for $C_{25}H_{47}N_5O_9 \cdot H_2O$: C, 51.80; H, 8.52; N, 12.08. Found: C, 51.87; H, 8.36; N, 12.17.

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Registry No. 1 (free base), 70-51-9; 1 (free base aluminum complex), 97633-18-6; 1 (free base iron complex), 14836-73-8; **2**, 123152-37-4; **2** (aluminum complex), 123169-11-9; **2a**, 123169-09-5; **3**, 123152-38-5; **3** (aluminum complex), 123169-12-0; **3** (iron complex), 123169-10-8; **4** benzylated dioxolane derivative, 123152-45-4; **4** dioxolane derivative, 123152-46-5; **5**, 84211-46-1; **6**, 112139-65-8; **7**, 123152-39-6; **8**, 123152-40-9; **9**, 123152-41-0; **9** (X = H), 123152-44-3; **10**, 123152-42-1; **11**, 123152-43-2.

Supplementary Material Available: ^{1}H NMR spectra for compounds **2**, **3**, and **7–11** (7 pages). Ordering information is given on any current masthead page.

Simple Titration Method Using Diphenyl Ditelluride as a Colored Indicator for the Determination of Organolithium and Organomagnesium Reagents[1]

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Rapid and accurate determination of the concentration of organolithium and organomagnesium reagents has become increasingly important with the wide use of these reagents in organic synthesis.[2] Recently developed colorimetric single-titration methods[3-11] are significantly

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