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Reactions of *N*-Benzyloxycarbamate Derivatives with Stabilized Carbon Nucleophiles: A New Synthetic Approach to Polyhydroxamic Acids and Other Hydroxamate-Containing Mixed Ligand Systems†

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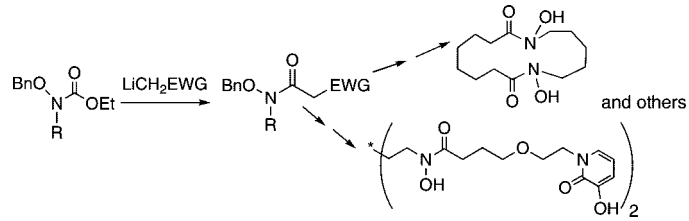

Hydroxamic acids are an important class of chelators of hard metal ions such as Fe(III), which have found applications in therapeutic, diagnostic, and separation chemistry. Hence, methods for their preparation and incorporation into various matrices are important. A new strategy for the preparation of hydroxamic acids that uses readily available *N*-benzyloxy carbamic acid ethyl ester, **1**, has been developed. *N*-Alkylation of **1** occurs readily to give *N*-alkyl-*N*-benzyloxy carbamates, **2**, which react with a variety of stabilized carbon nucleophiles to give functionalized protected hydroxamic acids, **3**, in good to excellent yields. The *O*-protected hydroxamate intermediates **3** can be further alkylated with halides to access a variety of potential metal binding hosts. The usefulness of this methodology has been demonstrated by the synthesis of a novel trihydroxamic acid **6**, mixed ligand systems **9** and **12**, and the macrocyclic dihydroxamic acid **16**.

Introduction

Hydroxamic acids are well-known chelators of hard metal ions such as Fe(III) and the actinide(IV) ions. Many bacterial and fungal siderophores rely on the hydroxamate functionality to complex and transport the ferric ion.[1] Desferrioxamine, a trihydroxamate siderophore, is used for the treatment of iron overload in patients with β-thalassemia.[2] Recently, hydroxamic acid iron chelators have been examined as potential cancer chemotherapeutic agents.[3] Another potential application of iron chelators is in the development of novel antibacterial agents.[4] In addition to their role as iron chelators, hydroxamic acids exhibit varied biological activity including antibacterial, antifungal, anti-inflammatory, and antitumor properties, which are due to their ability to inhibit a variety of enzymes.[5] There has been a recent surge in the interest of hydroxamic acids as inhibitors of histone deacetylases, resulting in the recent approval of suberoylanilide hydroxamic acid (SAHA) for the treatment of cutaneous T-cell lymphoma.[6] It is also noteworthy that many hydroxamic acid containing molecules are potent inhibitors of matrix metalloproteinases, which have been implicated in a number of pathological conditions.[7] Given the incredible pharmaceutical relevance of hydroxamic acids,[8] it is essential

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to develop new methods for their incorporation into a variety of complex structures.

As part of a program for the design and synthesis of chelators for the specific binding of ferric ion, we have been interested in developing methods for the preparation of a variety of hydroxamic acids including polyhydroxamic acids.[9] The conventional method for the preparation of hydroxamic acids usually involves coupling of acid derivatives with hydroxylamines.[10,11] Recently, there has been considerable interest in parallel methods for the synthesis of hydroxamic acids both in solution and on solid support.[12] The microwave-assisted conversion of esters into hydroxamic acids was recently reported.[13] However, the limited availability of substituted hydroxylamines places limits on the traditional coupling method, in particular in terms of the diversity of polyhydroxamates and mixed hydroxamate ligand systems that can be readily accessed.

The direct reaction of *N*-benzyloxy carbamates, such as **2**, with carbon nucleophiles is an attractive alternate approach for the synthesis of hydroxamic acids (Figure 1). There may be a couple of reasons why this strategy has not been explored. Carbamates are usually viewed as useful amine protecting groups and not as efficient electrophiles. Only recently it was reported that simple carbamates can act as electrophiles when reacted with the dianion of methyl phenyl sulfone to give amidosulfones.[14] It has also been shown that α-sulfonyl carbanions undergo intramolecular cyclization with carbamates to yield lactams.[15]

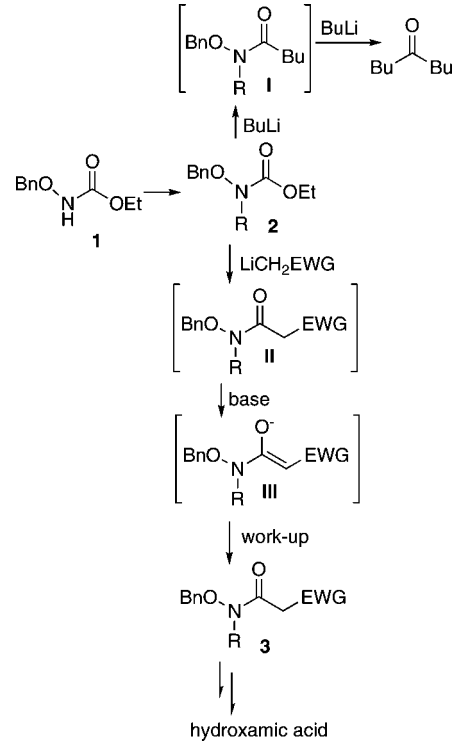

FIGURE 1. Strategy for the synthesis of hydroxamic acids.

Another reason carbamates, such as **2**, have not been thought to be good synthons for the preparation of hydroxamic acids may be a perceived similarity to the well-known Weinreb amide chemistry. Reaction of **2** with a strongly basic nucleophile such as *n*-butyl lithium would be expected to give an intermediate Weinreb-like amide, **I**, that would react further to give the corresponding ketone (Figure 1). As predicted, when **2** was treated with *n*-butyllithium (2 equiv), 5-nonanone was obtained in high yield.[16]

However, we postulated that reaction of an *N*-benzyloxy carbamate, such as **2**, with stabilized carbanions should circumvent this reaction pathway and lead to the desired hydroxamate product **3** (Figure 1). Intermediate **II**, obtained by the reaction of **2** when a stabilized carbanion serves as the nucleophile, has an acidic proton and will be expected to undergo immediate deprotonation to give a stable carbanion **III**, incapable of functioning as an electrophile. Here we report a novel preparation of hydroxamic acids based on our hypothesis that allows us to access a variety of hydroxamic acids and mixed ligand chelators.

Results and Discussion

The *N*-benzyloxycarbamate **1** was prepared by the reaction of *O*-benzylhydroxylamine hydrochloride with ethyl chloroformate in pyridine at room temperature in excellent yield (Scheme 1). It is important to point out that the use of triethylamine or 4-methylmorpholine instead of pyridine in this reaction gave

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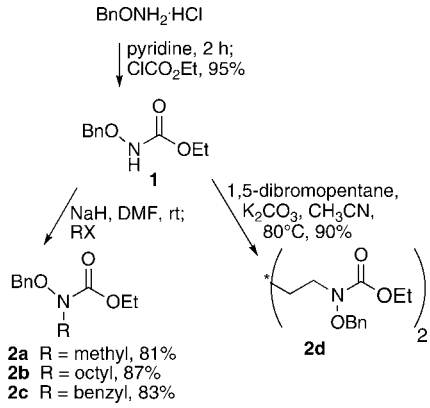
SCHEME 1



mixtures of the desired product **1** along with major quantities of the corresponding *N*,*N*-diacylated product.

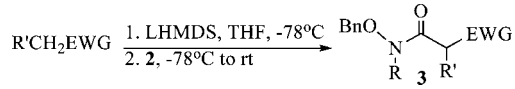
A number of *N*-alkylcarbamates were readily prepared by alkylation of **1** using one of two conditions (Scheme 1). For example, treatment of **1** with NaH in DMF followed by addition of methyl iodide (1.1 equiv) gave **2a** in 81% yield. *N*-Benzyl carbamate, **2c**, potentially a convenient synthon for the synthesis of primary hydroxamic acids, was prepared using a similar procedure. The dicarbamate **2d** could be prepared in excellent yields by alkylation of **1** with dibromopentane (0.5 equiv) in the presence of K_2CO_3 in refluxing acetonitrile.

With the *N*-benzyloxycarbamates **2** in hand, their reactions with stabilized carbon nucleophiles were then examined. The carbamate **2a** served as the model in our initial studies. Treatment of methyl phenyl sulfone (1 equiv) with LHMDS (2 equiv) in THF at −78 °C followed by addition of *N*-benzyloxycarbamate **2a** (1 equiv) gave the corresponding protected hydroxamic acid **3a** in 72% yield after workup and chromatographic purification. It was gratifying to note that our key postulate in the development of this methodology proved to be right. The presence of the electron-withdrawing sulfone group on the carbon nucleophile clearly suppresses the undesired Weinreb chemistry of the initial intermediate **II** and promotes rapid proton abstraction of the intermediate to give an enolate **III** as illustrated in Figure 1.

The coupling reaction proved to be quite general, and a variety of stabilized carbon nucleophiles could be coupled with **2a** and its analogs to give the corresponding functionalized protected hydroxamic acids, **3**, in good to excellent yield (Table 1). In most cases, efficient coupling of **2** to give **3** could be achieved by use of only 1 equiv of the carbon nucleophile and 2 equiv of LHMDS. Carbon nucleophiles carrying sulfoxide, phosphonate, sulfonamide, ester, and nitrile moieties all reacted successfully with **2** to give the corresponding product **3** in good to excellent yields. When the enolate of *tert*-butyl acetate was used in the reaction with **2** under the standard conditions, the yields were somewhat lower as a result of competing self-condensation of the ester.[17] Hence, 2 equiv of the ester enolate were initially generated with LHMDS and subsequent coupling with **2** gave good yields of the desired product. The anions of ethyl phenyl sulfone and allyl phenyl sulfone reacted cleanly with **2a** to give the desired products **3g** and **3h** in 92% and 79% yields, respectively. Further, it was possible to acylate the dicarbamate

(17) Lithium *tert*-butyl acetate was generated by slow addition of *tert*-butyl acetate to a solution of LHMDS in THF at−78°C to avoid or reduce the self-condensation of *tert*-butyl acetate.

TABLE 1. Results for the Acylation of 2a−d with Carbon Nucleophiles[a]



Carbamate	R'CH$_2$EWG	Product	Yield (%)
2a	CH_3SO_2Ph	**3a**	72 [a]
2a	CH_3SOPh	**3b**	81 [a]
2a	$CH_3P(O)(OEt)_2$	**3c**	82 [a]
2a	$CH_3SO_2N(CH_3)_2$	**3d**	90 [a]
2a	$CH_3CO_2{}^tBu$	**3e**	75 [b]
2a	CH_3CN	**3f**	55 [b]
2a	$CH_3CH_2SO_2Ph$	**3g**	92 [a]
2a	SO_2Ph	**3h**	79 [a]
2a	$CH_3CH_2CO_2{}^tBu$	NR	
2b	$CH_3CO_2{}^tBu$	**3i**	70 [b]
2c	$CH_3CO_2{}^tBu$	**3j**	52 [b] 88 [c]
2d	$CH_3CO_2{}^tBu$	**3k**	84 [c]
2d	CH_3SO_2Ph	**3l**	77 [d]
2d	SO_2Ph	**3m**	67 [d]

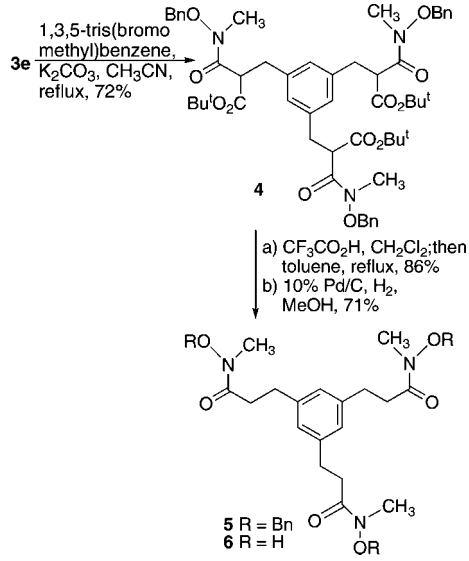
[a] Conditions: (a) Carbamate (1 equiv), RCH$_2$EWG (1−1.1 equiv), LHMDS (2 equiv), THF, −78°C to rt. (b) Carbamate (1 equiv), RCH$_2$EWG (2 equiv), LHMDS (2 equiv), THF, −78°C to rt. (c) Carbamate (1 equiv), RCH$_2$EWG (4 equiv), LHMDS (4 equiv), THF, −78°C to rt. (d) Carbamate (1 equiv), RCH$_2$EWG (2.2 equiv), LHMDS (4 equiv), THF, −78°C to rt.

2d with carbon nucleophiles of interest to give products **3k**−**3m** in good yields. One reaction that did fail was the attempted acylation of the enolate of *tert*-butyl propionate with carbamate **2a** presumably as a result of unfavorable steric factors and competing side reactions.

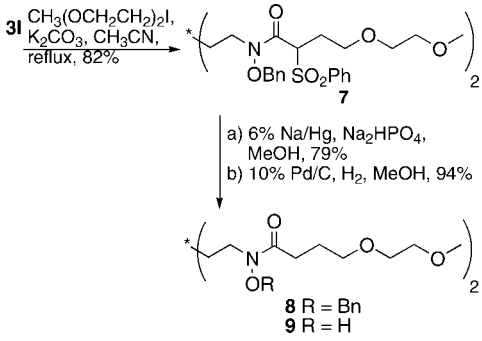
The presence of electron-withdrawing groups on the *N*-benzyloxy hydroxamates **3** allows further synthetic manipulations to obtain other polydentate chelators. The synthetic utility of these intermediates has been demonstrated by the synthesis of a number of potential metal ion binding hosts.

The first target to be synthesized was the trihydroxamic acid **6**, a potential iron chelator (Scheme 2). Treatment of 1,3,5-

SCHEME 2



SCHEME 3

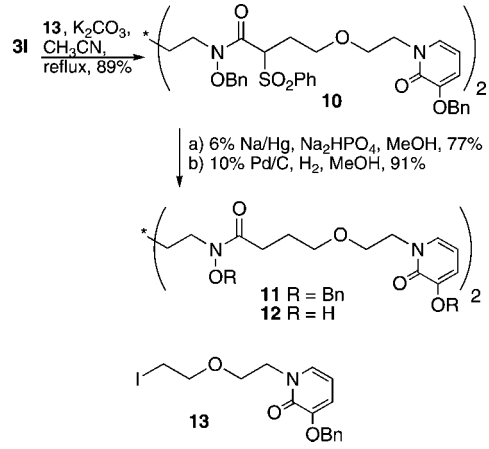


tris(bromomethyl)benzene with 3 equiv of **3e** in the presence of potassium carbonate in refluxing acetonitrile gave the desired product of trialkylation, **4**, in 72% yield after chromatographic purification. Hydrolysis of the *tert*-butyl esters by treatment with trifluoroacetic acid in dichloromethane and subsequent decarboxylation of the intermediate acid in refluxing toluene gave **5**. The benzyl protecting groups of **5** were removed using 10% Pd/ C to give the trihydroxamic acid **6** in 71% yield.[18] It is interesting to note that the trihydroxamic acid **6** is not only soluble in organic solvents but also in water.

It was felt that the dihydroxamato *tert*-butyl ester **3k** and the dihydroxamato sulfone **3l** were both good platforms that would allow the introduction of a variety of other ligands to obtain novel classes of metal ion chelators. To demonstrate this possibility, we embarked on the synthesis of dihydroxamic acid polyether **9** (Scheme 3) from the *tert*-butyl ester **3k**. When **3k** was treated with allyl bromide (6 equiv) in the presence of potassium carbonate in refluxing acetonitrile, the corresponding diallyl dihydroxamic acid could be isolated in 80% yield. Unfortunately, our attempts to introduce a polyether side chain by alkylation of **3k** with the less reactive 1-iodo-2-(2-methoxyethoxy)-ethane failed and only unreacted starting materials were recovered. This forced us to examine the use of the disulfone **3l** in this synthesis.

(18) Our preliminary binding studies show that when trihydroxamate **6** is mixed with an equimolar quantity of Fe(III) in PIPES buffer at pH 7.4, a trishydroxamato **6**−Fe(III) complex (λ_{max} = 430 nm) is formed.

SCHEME 4



Treatment of disulfone **3l** with 2.3 equiv of 1-iodo-2-(2-methoxyethoxy)ethane and potassium carbonate in refluxing acetonitrile gave the dialkylated product **7** in 82% yield after purification (Scheme 3). Subsequent desulfonylation using 6% Na/Hg amalgam followed by removal of the benzyl protecting groups by hydrogenolysis gave the desired dihydroxamic acid **9**. The presence of two hydroxamic acids as well as two polyether arms makes **9** a unique metal ion binding ligand.

Two important classes of chelators for hard trivalent and tetravalent cations contain the bidentate hydroxamic acids or hydroxypyridinone ligands in their backbones. We have used the disulfone **3l** to construct a unique mixed ligand chelator **12** having both 3,2-hydroxypyridinone (HOPO) and hydroxamic acid ligands (Scheme 4). Alkylation of **3l** with 2.4 equiv of the hydroxypyridinone iodide **13**[19] using potassium carbonate in refluxing acetonitrile gave the desired product **10** in 89% yield after purification. Reductive removal of the sulfone followed by benzyl deprotection by hydrogenolysis gave the dihydroxamic acid/diHOPO ligand **12**. This interesting ligand may be well-suited to bind hard cations such as Pu(IV) and Th(IV) that have larger coordination number than Fe(III).[20]

The diene intermediate **3m** provides a pathway to access macrocyclic dihydroxamic acids by RCM exemplified by our synthesis of **16**. When the diene **3m** was treated with 5 mol % Grubbs' II catalyst in refluxing dichloromethane, the cyclic product **14** was obtained in 85% yield after purification (Scheme 5). The macrocycle **14** was obtained as a diastereomeric mixture as determined by ^{1}H NMR. The sulfone groups were removed using 6% Na/Hg amalgam. Finally, hydrogenolysis of the benzyl protecting groups with concomitant reduction of the double bond gave the desired dihydroxamic acid **16**. Macrocyclic dihydroxamic acids, such as the siderophores bisucaberin and alcaligin, have been shown to bind Fe(III) strongly. Macrocyclic hydroxamic acids have also been shown to be inhibitors of MMPs[21] and TACE.[22]

In summary, *N*-benzyloxycarbamic acid ethyl ester, **1**, is a useful starting material for the preparation of *N*-alkyl carbamates **2** that serve as synthons for the preparation of hydroxamic acids.

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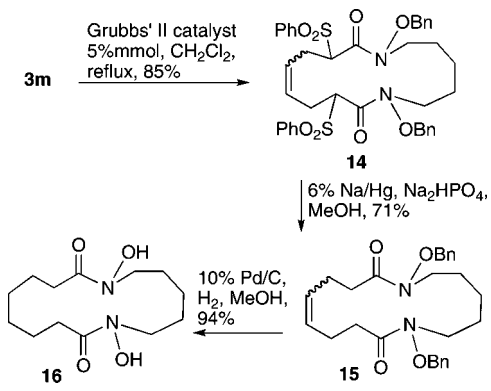
SCHEME 5



We have demonstrated that carbon nucleophiles stabilized by a variety of electron-withdrawing groups react with carbamates **2** to give functionalized protected hydroxamic acids **3**. As hypothesized, the use of stabilized carbon nucleophiles in the reaction with **2** yields the enolate of the initially formed coupled product, suppressing the Weinreb chemistry. The intermediates **3** obtained in this study can be elaborated by subsequent reactions to incorporate other desirable ligand moieties or can be easily incorporated into diverse spacer groups. Finally, we have demonstrated that this new methodology can be used to prepare a variety of polyhydroxamic acids including mixed ligand HOPO-hydroxamate ligand systems and cyclic dihydroxamic acids. We are confident that the electrophilic chemistry of *N*-benzyloxy carbamates will lead to a range of new interesting applications.

Experimental Section

***N*-Benzyloxycarbamic Acid Ethyl Ester (1).** A mixture of *O*-benzylhydroxylamine hydrochloride (1.59 g, 10 mmol) and pyridine (5 mL) was stirred at room temperature under N_2 for 2 h. The mixture was then cooled to 0 °C, ethyl chloroformate (0.96 mL, 10 mmol) was added, and the mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with EtOAc (100 mL), washed with 2 N HCl (3 × 30 mL) and saturated $NaHCO_3$ (3 × 30 mL), and dried (Na_2SO_4). The solvent was removed in vacuo. The carbamate **1** (1.84 g, 94.6%) was obtained as a colorless oil which was homogeneous by TLC and was used in the next step without purification: IR (neat) 3277, 2983, 1724 cm^{-1}; ^1H NMR (400 MHz) δ 7.91(s, 1H), 7.37−7.29(m, 5H), 4.81(s, 2H), 4.14(q, J = 7.2 Hz, 2H), 1.22(t, J = 7.2 Hz, 3H); ^{13}C NMR(100 MHz) δ 157.8, 135.6, 129.1, 128.5, 128.4, 78.5, 61.8, 14.4. Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.20; H, 6.63; N, 7.24.

***N*-Benzyloxy-*N*-methylcarbamic Acid Ethyl Ester (2a).** Sodium hydride (60% mineral oil dispersion, 0.408 g, 10.2 mmol) was added to a solution of **1** (1.80 g, 9.2 3mmol) in dry DMF (10 mL) at room temperature. After 30 min, iodomethane (0.65 mL, 10.2mmol) was added, and the mixture was stirred at room temperature for 6 h. The reaction mixture was poured into water (150 mL), and the product was extracted into hexane (3 × 50 mL). The combined organic layer was dried (Na_2SO_4) and the solvent was removed in vacuo. Purification by flash chromatography gave **2a**[23] (1.55 g, 80.6%) as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) δ 7.52−7.29(m, 5H), 4.86(s, 1H), 4.21(q, J = 7.0 Hz, 1H), 3.08(s, 3H), 1.31(t, 2H), 1.32−1.25(t, J = 7.0 Hz, 3H).

***N*-Benzyloxy-[5-(benzyloxyethoxycarbonylamino)pentyl]carbamic Acid Ethyl Ester (2d).** Potassium carbonate (0.863 g, 6.25 mmol) was added to a solution of **1** (0.229 g, 1.25 mmol) and 1,5-dibromopentane (0.07 mL, 0.5 mmol) in dry acetonitrile (5 mL) at room temperature, and the mixture was heated at reflux for 2 days. The reaction mixture was cooled, poured into water (50 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product was purified by radial chromatography (EtOAc/hexanes) followed by a second purification by radial chromatography (CH_2Cl_2) to give **2c** (0.265 g, 89.5%) as a colorless oil: IR (neat) 2981, 2938, 1704 cm^{-1}; ^1H NMR (200 MHz) δ 7.48−7.28(m, 10H), 4.83(s, 4H), 4.20(q, J = 7.0 Hz, 4H), 3.41(t, J = 7.0 Hz, 4H), 1.71−1.48(m, 4H), 1.38−1.22(m, 2H), 1.30(t, J = 7.0 Hz, 6H); ^{13}C NMR (50 MHz) δ 157.4, 135.6, 129.3, 128.5, 128.4, 77.1, 62.0, 49.6, 26.8, 23.9, 14.6. Anal. Calcd for $C_{25}H_{34}N_2O_6$: C, 65.48; H, 7.47; N, 6.11. Found: C, 65.29; H, 7.63; N, 5.87.

Representative Procedure for the Intermolecular Acylation of 2a−c. Synthesis of 2-Benzenesulfonyl-*N*-benzyloxy-*N*-methyl Acetamide (3a). A solution of LHMDS (1.24 mL, 1.24 mmol) was added to a solution of methyl phenyl sulfone (0.097 g, 0.62 mmol) in anhydrous THF (2.5 mL) at −78 °C under N_2, and the mixture was stirred at −78 °C for 30 min. A solution of **2a** (0.130 g, 0.62 mmol) in anhydrous THF (2.5 mL) was added, and the reaction mixture was stirred at −78 °C for 30 min and then at room temperature for 16 h. The reaction was quenched with 10% aqueous AcOH solution (5 mL), and the solvent was removed in vacuo. The residue was diluted with EtOAc (50 mL), washed with saturated $NaHCO_3$ (2 × 10 mL) and brine (10 mL), and dried (Na_2SO_4). The solvent was removed in vacuo. The crude product was purified by radial chromatography to give **3a** (0.144 g, 72.7%) as a colorless oil: IR (neat) 3065, 3032, 2929, 1668 cm^{-1}; ^1H NMR (200 MHz) δ 8.04−7.85(m, 2H), 7.75−7.48(m, 3H), 7.48−7.30(m, 5H), 4.94(s, 2H), 4.22(s, 2H), 3.19(s, 3H); ^{13}C NMR (100 MHz) δ 162.9, 139.3, 134.0, 133.8, 129.6, 129.3, 129.0, 128.9, 128.6, 76.8, 58.1, 33.6. Anal. Calcd for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.37; N, 4.39. Found: C, 60.37; H, 5.39; N, 4.43.

***N*-Benzyloxy-*N*-methylmalonamic Acid *tert*-Butyl Ester (3e).** A solution of *tert*-butyl acetate (0.216 g, 1.86 mmol) in anhydrous THF (2 mL) was added to a solution of LHMDS (1.86 mL, 1.86 mmol) in anhydrous THF (2 mL) at −78 °C under nitrogen, and the solution was stirred at −78 °C for 30 min. A solution of **2a** (0.195 g, 0.93 mmol) in anhydrous THF (2 mL) was then added, and the reaction mixture was stirred at −78 °C for 4 h and then at room temperature for 16 h. The reaction workup followed the representative procedure. The product **3e** (0.195 g, 75.3%) was obtained as a colorless oil. IR (neat) 2934, 2979, 1732, 1668 cm^{-1}; ^1H NMR (200 MHz) δ 7.49−7.30(m, 5H), 4.86(s, 2H), 3.35(s, 2H), 3.23(s, 3H), 1.43 (s, 9H); ^{13}C NMR (50 MHz) δ 168.6, 166.4, 134.3, 129.3, 129.0, 128.7, 81.6, 76.4, 41.8, 33.7, 27.9. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.63; H, 7.50; N, 4.63.

2-Benzenesulfonyl-*N*-[5-(benzenesulfonylacetylbenzyloxyamino]-pentyl-*N*-benzyloxy Acetamide (3l). Following the representative procedure using **2d** (0.229 g, 0.5 mmol), methyl phenylsulfone (0.172 g, 1.1 mmol), and LHMDS (2.0 mL, 2.0 mmol), the product **3l** (0.262 g, 77.3%) was obtained as a white solid. Mp 197.0−198.0 °C; IR (KBr) 3009, 2930, 2877, 1659 cm^{-1}; ^1H NMR (200 MHz) δ 7.92−7.90(m, 4H), 7.64−7.51(m, 6H), 7.39(s, 10H), 4.90(s, 4H), 4.19(s, 4H), 3.60(t, J = 7.0 Hz, 4H), 1.60−1.52(m, 4H), 1.26−1.22 (m, 2H); ^{13}C NMR (50 MHz) δ 162.6, 139.6, 133.9, 129.5, 129.3, 129.0, 128.9, 128.6, 76.8, 58.3, 45.3, 26.2, 23.6. Anal. Calcd for $C_{35}H_{38}N_2O_8S_2$: C, 61.93; H, 5.64; N, 4.13. Found: C, 61.58; H, 5.39; N, 3.87.

2-Benzenesulfonylpent-4-enoic Acid {5-[(2-Benzenesulfonylpent-4-enoyl)benzyloxyamino]pentyl}benzyloxy Amide (3m). Following

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(23) Inglesi, M.; Nicola, M.; Magnetti, S. *Farmaco* **1990**, *45* (12), 1327–1340.

the representative procedure using **2d** (0.345 g, 0.75 mmol), (but-3-enylsulfonyl)benzene (0.323 g, 1.65 mmol), and LHMDS (3.3 mL, 3.3 mmol) in THF (10 mL), the product **3m** (0.380 g, 66.8%) was obtained as a pale yellow oil. IR (neat) 3066, 3033, 2945, 2871, 1661, 1652 cm^{-1}; ^1H NMR (400 MHz) δ 7.87−7.84(m, 4H), 7.66−7.62(m, 6H), 7.49−7.38(m, 10H), 5.56−5.48(m, 2H), 5.07−4.98(m,6H),4.87−4.76(m,4H),3.74−3.67(m,2H),3.51−3.45(m, 2H), 2.70−2.66(m, 2H), 2.57−2.49(m, 2H), 1.53−1.47(m, 4H), 1.27−1.20(m, 2H); ^{13}C NMR (100 MHz) δ 165.4, 136.8, 134.1, 133.9, 131.8, 129.9, 129.3, 129.1, 128.8, 128.7, 119.0, 77.4, 64.7, 45.5, 32.4, 26.0, 23.6. Anal. Calcd for $C_{41}H_{46}N_2O_8S_2$: C, 64.88; H, 6.11; N, 3.69. Found: C, 64.66; H, 6.19; N, 3.68.

***N*-Benzyloxy-2-{3,5-bis[2-benzyloxymethylcarbamoyl)-2-*tert*-butoxycarbonylethyl]benzyl}-*N*-methylmalonamic Acid *tert*-Butyl Ester (4).** Potassium carbonate (0.690 g, 5.0 mmol) was added to a solution of **3e** (0.279 g, 1.01 mmol) and 1,3,5-tris(bromomethyl)-benzene (0.120 g, 0.34mmol) in dry acetonitrile (10 mL) at room temperature, and the mixture was heated at reflux for 2 days. After cooling, the reaction mixture was poured into water (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product was purified by radial chromatography to give **4** (0.232 g, 71.8%) as a colorless oil: IR (neat) 2979, 2933, 1732, 1668 cm^{-1}; ^1H NMR (200 MHz) δ 7.45−7.15(m, 15H), 6.88(d, J = 2.9 Hz, 3H), 4.67−4.58(m, 6H), 3.93−3.70(m, 3H), 3.11−3.00(m, 15H), 1.34(s, 27H); ^{13}C NMR (50 MHz) δ 170.8, 168.4, 139.0, 134.5, 129.2, 128.8, 128.6, 127.9, 81.5, 76.5, 51.4, 34.5, 34.3, 27.9. Anal. Calcd for $C_{54}H_{69}N_3O_{12}\cdot 3H_2O$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.23; H, 7.17; N, 4.12.

***N*-Benzyloxy-3-{3,5-bis[2-benzyloxymethylcarbamoyl)ethyl]phenyl}-*N*-methyl Propionamide (5).** Trifluoroacetic acid (0.08 mL, 0.92 mmol) was added to a solution of **4** (0.146 g, 0.15 mmol) in CH_2Cl_2 (1 mL) at 0 °C, and the mixture was stirred at room temperature for 2 h. Solvent and the excess trifluoroacetic acid were removed in vacuo. The crude tricarboxylic acid was dissolved in toluene (5 mL), and the solution was heated at reflux for 2 d. The solvent was removed in vacuo. The crude product was purified by radial chromatography to give **5** (0.084 g, 85.7%) as a colorless oil: IR (neat) 3031, 2931, 1661 cm^{-1}; ^1H NMR (200 MHz) δ 7.38−7.26(m, 15H), 6.81(s, 3H), 4.73(s, 6H), 3.18(s, 9H), 2.96−2.73(m, 6H), 2.73−2.51(m, 6H); ^{13}C NMR (50 MHz) δ 174.3, 141.6, 134.6, 129.2, 129.0, 128.7, 126.3, 76.3, 34.1, 33.8, 30.6. Anal. Calcd for $C_{39}H_{45}N_3O_6$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.82; H, 7.09; N, 6.55.

3-{3,5-Bis[2-hydroxymethylcarbamoyl)ethyl]phenyl}-*N*-hydroxyl-*N*-methyl Propionamide (6). Palladium on carbon (10%, 16 mg) was added to a solution of **5** (0.083 g, 0.127 mmol) in MeOH (4 mL), and the mixture was stirred at room temperature under H_2 atmosphere for 6 h. The catalyst was removed by centrifugation followed by filtration. After drying under high vacuum, the trihydroxamic acid **6** (0.034 g, 70.8%) was obtained as a pale yellow oil: IR (neat) 3412, 2930, 1605 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 6.92(s, 3H), 3.19(s, 9H), 2.84−2.73(m, 12H); ^{13}C NMR (50 MHz, CD_3OD) δ 173.6, 141.5, 125.8, 36.6, 32.7, 29.2. Anal. Calcd for $C_{18}H_{27}N_3O_6\cdot H_2O$: C, 54.12; H, 7.32; N, 10.52. Found: C, 54.36; H, 7.27; N, 10.43.

2-Benzenesulfonyl-*N*-[5-({2-benzenesulfonyl-4-[2-(3-benzyloxy-2-oxo-2*H*-pyridin-1-yl)ethoxy]butyryl}benzyloxyamino)pentyl]-*N*-benzyloxy-4-[2-(3-benzyloxy-2-oxo-2*H*-pyridin-1-yl)-ethoxy] Butyramide (10). To a solution of **3l** (123 mg, 0.18 mmol) in dry acetonitrile (5 mL) at room temperature were added K_2CO_3 (248 mg, 1.8 mmol) and 3-(benzyloxy)-1-(2-(2-iodoethoxy)ethyl)pyridin-2(1*H*)-one, **13**[19] (176 mg, 0.44 mmol), and the mixture was heated at reflux for 2 d. After cooling, the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo. Purification by radial chromatography gave **10** (0.195 g, 88.6%) as a viscous yellow oil. IR (neat) 3065, 3031, 2871, 2931, 1660, 1652, 1606 cm^{-1}; ^1H NMR (400 MHz) δ 7.94−7.78(m, 4H), 7.70−7.45(m, 6H), 7.45−7.27(m, 20H), 6.69−6.53(m, 4H), 5.86−5.77(m,2H),5.12−4.97(m,4H),4.97−4.80(m,4H),4.25−4.12(m, 2H), 4.07−3.92(m, 2H), 3.84−3.70(m, 2H), 3.68−3.48(m, 8H), 3.44−3.29(m, 2H), 3.24−3.11(m, 2H), 2.27−1.18(m, 10H); ^{13}C NMR (100 MHz) δ 165.7, 158.0, 148.7, 137.1, 136.4, 134.0, 130.2, 129.8, 129.6, 129.3, 128.9, 128.7, 128.5, 127.9, 127.3, 115.8, 104.0, 77.2, 70.7, 68.5, 67.3, 62.8, 49.5, 45.8, 45.0, 28.5, 26.3, 23.8.

***N*-Benzyloxy-*N*-[5-(benzyloxy-4-[2-(3-benzyloxy-2-oxo-2*H*-pyridin-1-yl)ethoxy]butyryl}benzyloxyamino)pentyl]-4-[2-(3-benzyloxy-2-oxo-2*H*-pyridin-1-yl)-ethoxy] Butyramide (11).** To a solution of **10** (0.122 g, 0.1 mmol) in MeOH (2 mL) at 0 °C were added Na_2HPO_4 (0.114 g, 0.8 mmol) and 10% Na/Hg amalgam (0.56 g, 2.4 mmol). The mixture was stirred at 0 °C for 5 h and then at room temperature for 16 h. The reaction mixture was vacuum filtered through a short silica gel column and rinsed with MeOH (50 mL). The solvent was removed in vacuo. The residue was diluted with EtOAc (50 mL), washed with saturated $NaHCO_3$ (3 × 10 mL), and dried (Na_2SO_4). The solvent was removed in vacuo. Purification by radial chromatography gave the protected hydroxamic acid **11** (0.072 g, 76.6%) as a colorless oil. IR (neat) 3064, 3033, 3937, 2868, 1652, 1602 cm^{-1}; ^1H NMR (400 MHz) δ 7.45−7.27(m, 20H), 6.94(dd, J = 6.8, 1.6 Hz, 2H), 6.59(dd, J = 7.4, 1.6 Hz, 2H), 5.89(t, J = 7.2 Hz, 2H), 5.07(s, 4H), 4.75(s, 4H), 4.11(t, J = 4.9 Hz, 4H), 3.70(t, J = 5.1 Hz, 4H), 3.64−3.55(m, 4H), 3.39(t, J = 6.2 Hz, 4H), 2.41(t, J = 7.2 Hz, 4H), 1.81(quintet, J = 6.4 Hz, 4H), 1.62(quin, J = 7.6 Hz, 4H), 1.31−1.21(m, 2H); ^{13}C NMR (100 MHz) δ 174.0, 158.1, 148.7, 136.4, 134.6, 130.5, 129.0, 128.9, 128.7, 128.5, 127.9, 127.3, 115.7, 103.9, 76.3, 70.7, 70.4, 68.5, 49.7, 45.4, 28.9, 26.6, 24.6, 24.0. Anal. Calcd for $C_{55}H_{64}N_4O_{10}$: C, 70.19; H, 6.85; N, 5.95. Found: C, 70.33; H, 6.55; N, 6.12.

***N*-Hydroxy-*N*-[5-(hydroxy-4-[2-(3-hydroxy-2-oxo-2*H*-pyridin-1-yl)ethoxy]butyryl}benzyloxyamino)pentyl]-4-[2-(3-hydroxy-2-oxo-2*H*-pyridin-1-yl)ethoxy] Butyramide (12).** Palladium on carbon (10%, 10 mg) was added to a solution of **11** (54 mg, 0.057 mmol) in MeOH (2 mL), and the mixture was stirred at room temperature under H_2 atmosphere for 16 h. The catalyst was removed by centrifugation followed by filtration. The solvent was removed in vacuo. The dihydroxamic acid/dihydroxypyridinone **12** (30 mg, 90.9%) was obtained as a reddish oil. IR (neat) 3207(br), 2931, 2869, 1652, 1601 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.10(d, J = 6.7 Hz, 2H), 6.82(d, J = 7.4 Hz, 2H), 6.20(t, J = 7.2 Hz, 2H), 4.17(t, J = 5.0 Hz, 4H), 3.70(t, J = 5.1 Hz, 4H), 3.72(t, J = 4.7 Hz, 4H), 3.56(t, J = 6.8 Hz, 4H), 3.45(t, J = 6.2 Hz, 4H), 2.48(t, J = 7.3 Hz, 4H), 1.79(quintet, J = 6.2 Hz, 4H), 1.64(quintet, J = 6.5 Hz, 4H), 1.29(t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.6, 160.0, 148.1, 130.4, 117.1, 107.6, 71.5, 69.4, 50.8, 48.7, 34.7, 30.0, 27.3, 26.0, 24.6. Anal. Calcd for $C_{27}H_{40}N_4O_{10}\cdot H_2O$: C, 54.17; H, 7.07; N, 9.36. Found: C, 53.95; H, 6.98; N, 9.04.

9,14-Bis-benzenesulfonyl-1,7-bis-benzyloxy-1,7-diazacyclopentadec-11-ene-8,15-dione (14). To a solution of Grubbs' catalyst (second generation, 15 mg, 5% mmol) in CH_2Cl_2 (30 mL) at room temperature under N_2 was added a solution of **3m** (0.268 g, 0.35 mmol), and the mixture was heated at reflux for 20 h. The solvent was removed in vacuo. The crude product was purified by radial chromatography (EtOAc/hexane = 1:4−1:1) to give **14** as yellowish oil (0.217 g, 84.7%, mixture of diastereomers) Anal. Calcd for $C_{39}H_{42}N_2O_8S_2$: C, 64.09; H, 5.79; N, 3.83. Found: C, 64.06; H, 5.61; N, 3.52. In order to characterize and simplify the NMR spectra, **14** was purified by a second careful chromatography to give less polar isomer and more polar isomer. **Less polar isomer**: IR (neat) 3065, 2944, 1661, 1652 cm^{-1}; ^1H NMR (200 MHz) δ 7.89−7.74(m,4H),7.72−7.59(m,2H),7.59−7.44(m,4H),7.44−7.29(m, 10H), 5.14(t, J = 3.0 Hz, 2H), 5.09(d, J = 10.3 Hz, 2H), 4.89(d, J = 10.2 Hz, 2H), 4.70(dd, J = 11.8, 1.4 Hz, 2H), 4.19(ddd, J = 14.6, 11.0, 3.6 Hz, 2H), 3.22(dt, J = 14.6, 3.6 Hz, 2H), 2.59(d, J = 13.2 Hz, 2H), 2.42−2.33(m, 2H), 1.81−1.74(m, 2H), 1.46−1.39(m, 2H), 1.14(quin, J = 7.4 Hz, 2H); ^{13}C NMR (50 MHz) δ 165.2, 136.9, 134.2, 134.0, 130.1, 129.0, 128.9, 128.8, 128.7, 127.8, 76.6,

64.9, 45.5, 31.2, 26.5, 23.6. **More polar isomer**: IR (neat) 3065, 2945, 1668 cm^{-1}; ^1H NMR (200 MHz) δ 7.91−7.74(m, 4H), 7.73−7.59(m, 2H), 7.58−7.44(m, 4H), 7.44−7.29(m, 10H), 5.19(d, J = 5.9 Hz, 2H), 4.91(d, J = 11.0 Hz, 2H), 4.88(d, J = 10.2 Hz, 2H), 4.72(dd, J = 9.5, 3.7 Hz, 2H), 4.16(ddd, J = 14.6, 11.7, 2.2 Hz, 2H), 3.14(dt, J = 14.6, 3.7 Hz, 2H), 2.52−2.41(m, 4H), 1.65−1.54(m, 2H), 1.34−1.25(m, 2H), 1.12−1.03(m, 2H); ^{13}C NMR (50 MHz) δ 165.3, 136.8, 134.0, 133.9, 130.1, 129.2, 129.1, 128.9, 128.7, 127.5, 76.6, 65.6, 44.5, 27.6, 27.1, 24.6.

1,7-Bis-benzyloxy-1,7-diazacyclopentadec-11-ene-8,15-dione (15). To a solution of **14** (0.539 g, 0.74 mmol) in MeOH (15 mL) at 0 °C were added Na_2HPO_4 (0.838 g, 5.9 mmol) and 10% Na/Hg amalgam (4.15 g, 17.7 mmol), and the mixture was stirred at 0 °C for 4 h and at room temperature overnight. The reaction mixture was vacuum filtered through a short silica gel column rinsing with MeOH (50 mL). The solvent was removed in vacuo. The residue was diluted with EtOAc (50 mL), washed with saturated $NaHCO_3$ (3 × 10 mL), and dried (Na_2SO_4). The solvent was removed in vacuo. Purification by radial chromatography gave **15** (0.235 g, 70.8%) as a yellowish oil. IR (neat) 3064, 3032, 2932, 2860, 1661, 1652 cm^{-1}; ^1H NMR (200 MHz) δ 7.49−7.21(m, 10H), 5.61−5.35(m, 2H), 4.88−4.63(m, 4H), 3.89−3.52(m, 4H), 2.63−2.17(m, 8H), 1.75−1.42(m, 4H), 1.39−1.08(m, 2H); ^{13}C NMR (50 MHz) δ 173.5, 134.9, 129.5, 129.0, 128.9, 128.6, 75.9, 75.8, 44.1, 32.4, 30.9, 26.9, 26.2, 23.6, 23.5. Anal. Calcd for $C_{27}H_{34}N_2O_4$: C, 71.97; H, 7.61; N, 6.22. Found: C, 71.88; H, 7.72; N, 6.19.

1,7-Dihydroxy-1,7-diazacyclopentadecane-8,15-dione (16). Palladium on carbon (10%, 26 mg) was added to a solution of **15** (0.139 g, 0.31 mmol) in MeOH (6 mL), and the mixture was stirred at room temperature under H_2 atmosphere for 18 h. The catalyst was removed by centrifugation followed by filtration. The solvent was removed in vacuo. The macrocyclic dihydroxamic acid **16** (0.081 g, 96.4%) was obtained as a light pink solid, which was homogeneous on the basis of ^1H NMR and TLC. Mp 195.0−196.0 °C; IR (KBr) 3195(br), 2941, 2864, 1587 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 3.87−3.44(m, 4H), 2.72−2.16(m, 4H), 1.91−1.46(m, 8H), 1.46−1.02(m, 6H); ^{13}C NMR (50 MHz, CD_3OD) δ 176.3, 47.9, 31.9, 29.1, 26.8, 25.2, 23.7. Anal. Calcd for $C_{13}H_{24}N_2O_4 \cdot 0.25H_2O$: C, 56.40; H, 8.92; N, 10.12. Found: C, 56.14; H, 9.05; N, 10.13.

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Supporting Information Available: Synthetic details for all compounds and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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