$\times 10^4$), 253 (7.7×10^3), 305 (3.5×10^3); IR ($CHCl_3$) 2965 (s), 2930 (s), 2860 (m), 1720 (m), 1595 (s), 1580 (m), 1485 (s) cm^{-1}.

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Registry No. Flustramine A, 71239-64-0; flustramine B, 71239-65-1.

Synthesis of N^4-Acylated N^1,N^8-Bis(acyl)spermidines: An Approach to the Synthesis of Siderophores

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The synthesis of N^4-benzylspermidine and its use as a reagent in the preparation of N^1,N^8-bisacylated and N^4-acylated N^1,N^8-bis(acyl)spermidines are described. The scheme is applied to the total synthesis of N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine, a natural product isolated from *Micrococcus denitrificans*, as well as to the synthesis of several model precursors to the *Micrococcus denitrificans* siderophore, N^4-[*N*-(2-hydroxybenzoyl)threonyl]-N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine.

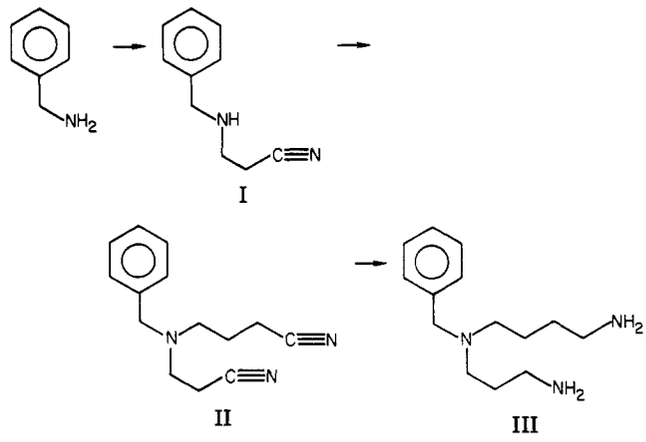
Introduction

Spermidine derivatives have long been of interest to both organic chemists and biochemists. These compounds have been shown to be potent antibiotics[1] and to have pronounced effects on both protein[2] and DNA synthesis,[3] and their physiological concentrations have been shown to change drastically with the onset of a number of different types of cancer.[4] It is generally agreed that a great deal more could be learned about the action of these spermidine compounds if they or their homologues could be synthesized. Unfortunately, their synthetic accessibility is limited.

Our interest in the total synthesis of a siderophore isolated from *Micrococcus denitrificans*, an N^1,N^8-bisacylated spermidine derivative, had led us to consider the development of an easily accessible N^4-blocked spermidine. This siderophore, N^4-[*N*-(2-hydroxybenzoyl)threonyl]-N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine (Figure 1), is a strong iron chelator and has received widespread attention because of its potential applications in the treatment of several iron-overload conditions.[5,6] Most importantly, the problems involved in the synthesis of this compound reflect many of the difficulties encountered in chemical modifications of spermidine in general.

An examination of the literature revealed that selective symmetrical acylation of the terminal N^1,N^8 amino nitrogens of spermidine proceeds poorly or not at all. For example, when cinnamoyl chloride is reacted with spermidine, the N^1,N^8-bis(cinnamoyl)amide is obtained in yields of less than 5%.[7] This is because the secondary amines react substantially faster than the terminal primary amino groups with most electrophilic reagents, which results in product mixtures consisting largely of N^1,N^4 and/or N^4,N^8-bisacylated compounds. We have shown that the above problems can be easily circumvented with the use of N^4-benzylspermidine. This N^4-protected compound can be smoothly acylated in high yield and the benzyl group removed quantitatively by hydrogenolysis. Once the benzyl protecting group has been removed, the N^4 secondary nitrogen can also be acylated, thus allowing for the selective addition of two different kinds of acyl groups to the spermidine backbone. This flexibility provides a clear-cut route to a variety of substituted spermidines including the *Micrococcus denitrificans* siderophore, N^4-[*N*-(2-hydroxybenzoyl)threonyl]-N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine, described above.[5,6]

Scheme I. Preparation of the Key Intermediate N^4-Benzylspermidine



Results and Discussion

Selective benzylation of spermidine's secondary nitrogen with benzyl bromide or similar alkylating agents is, of course, impractical, because of the product mixtures that would result. Although the secondary nitrogen is more nucleophilic than the primary terminal nitrogens, it is unreasonable to expect that such alkylating agents would

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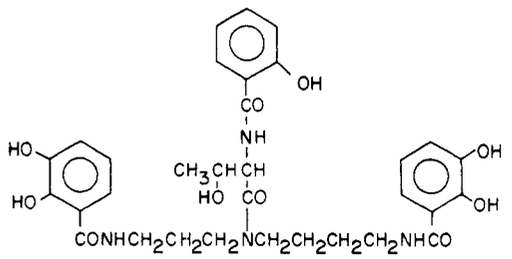


Figure 1. The siderophore N^4-[*N*-(2-hydroxybenzoyl)threonyl]-N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine from *Micrococcus denitrificans*.

attack only the secondary nitrogen without any concomitant reaction at the terminal primary nitrogens.[8] However, we have found that it is possible to construct a spermidine backbone with synthons that already have the benzyl group incorporated. The synthesis involves three steps: cyanoethylation, alkylation, and reduction, all of which proceed in high yield (Scheme I). Furthermore, all of the intermediates are stable and are easily purified by distillation.

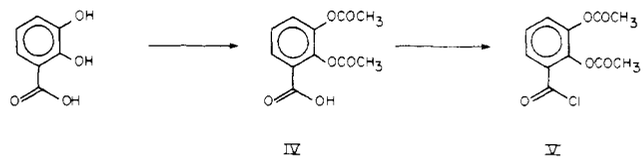
The first step, cyanoethylation of benzylamine with acrylonitrile, proceeds smoothly at room temperature.[8] Bis(cyanoethylation) of the benzylamine does not seem to present any problems. We have shown that this bis(cyanoethylation) can be effected simply with the use of excess acrylonitrile, longer reaction times, and higher temperatures. Such a symmetrical bis(nitrile) will give us access to a siderophore with one less carbon in the spermidine backbone than in the natural product, thus enabling us to determine the importance of the spermidine backbone's chain length in complexation of iron.

The resulting *N*-(2-cyanoethyl)benzylamine (I), obtained from monocyanoethylation, was alkylated with 4-chlorobutyronitrile in 1-butanol at 115 °C with potassium carbonate as the base.[9] The product, *N*-(3-cyanopropyl)-*N*-(2-cyanoethyl)benzylamine (II), was reduced with lithium aluminum hydride and aluminum chloride in diethyl ether to N^4-benzylspermidine (III). Attempted reduction of the bis(nitrile) with either lithium aluminum hydride in tetrahydrofuran or diborane in tetrahydrofuran resulted in complex product mixtures and low yields of the desired bis(amine). The N^4-benzylspermidine was found to be quite stable when kept in a dark bottle out of direct sunlight.

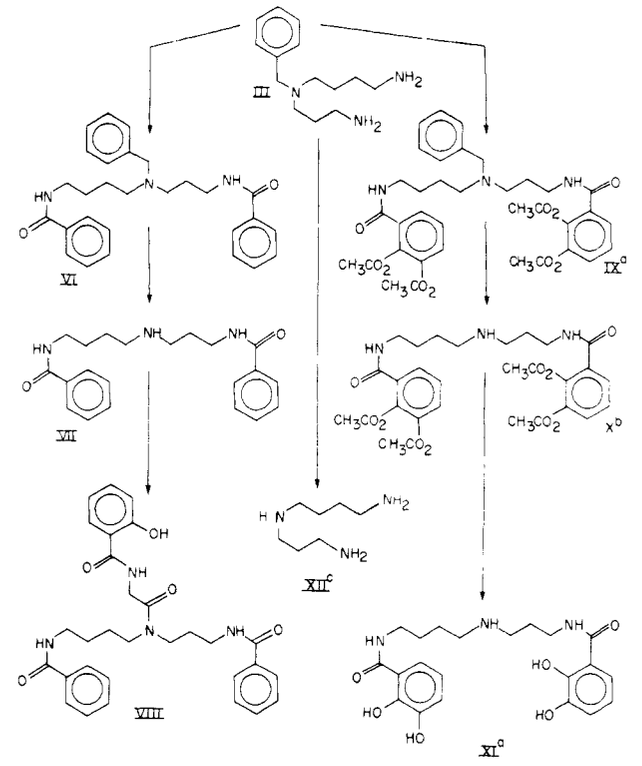
We have shown that the N^4-benzylspermidine can be hydrogenolyzed to spermidine (XII) or first N^1,N^8-bisacylated and then debenzylated (Scheme III). The debenzylation can be effected at atmospheric pressure in acetic acid over a palladium catalyst.[10] This route to spermidine and its derivatives provides us with a vehicle for the introduction of radiolabels into the spermidine backbone of compounds like the siderophore described above or, for that matter, into spermidine itself. We have acylated the benzylated spermidine with benzoyl chloride as well as with 2,3-diacetoxybenzoyl chloride in high yield.

Although there are a number of ways of protecting the 2,3-hydroxy groups of 2,3-dihydroxybenzoic acid (DHB), in the synthesis of the natural product N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine (XI), we found acetylation to work well.[11] This was accomplished by reacting DHB with acetic anhydride in sulfuric acid (Scheme II). The resulting 2,3-diacetoxybenzoic acid (IV), a crystalline material, when reacted in chloroform with phosphorus pentachloride, produced the corresponding acid chloride (V), again a stable crystalline compound, in 94% yield. This acid chloride as well as benzoyl chloride was condensed with N^4-benzylspermidine at 0 °C in a mixture of methylene chloride and base. The resulting amides, N^4-benzyl-N^1,N^8-bis(2,3-diacetoxybenzoyl)spermidine (IX) and N^4-benzyl-N^1,N^8-bis(benzoyl)spermidine (VI), respectively, were generated in high yield and easily purified (Scheme III).

Scheme II. Preparation of 2,3-Diacetoxybenzoyl Chloride



Scheme III. Flexibility of Synthesis Allowing for Production of Either N^1,N^8-Bis(acylated) Spermidines or N^4-Acylated N^1,N^8-Bis(acyl)spermidines



[a] Isolated as the hydrochloride salt. [b] Isolated as the acetate salt. [c] Obtained as the triacetate salt.

These bis(amides) were smoothly debenzylated at room temperature and atmospheric pressure over a palladium catalyst to produce N^1,N^8-bis(benzoyl)spermidine acetate and N^1,N^8-bis(2,3-diacetoxybenzoyl)spermidine acetate (X), a useful intermediate in the synthesis of the *Micrococcus denitrificans* siderophore. The N^1,N^8-bis(2,3-diacetoxybenzoyl)spermidine acetate was easily deacylated under nitrogen in methanolic sodium methoxide to the natural product N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine (XI). This compound is of interest in itself and has been suggested by Tait to be the biochemical precursor to the actual *Micrococcus denitrificans* siderophore.[12] The synthetic material proved to be identical with the natural

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product, thus verifying Tait's structural elucidation.

The N^1,N^8-bis(benzoyl)spermidine acetate (VII) was easily condensed with *N*-(2-hydroxybenzoyl)glycine in high yield. The condensation was effected by generating the mixed anhydride of *N*-(2-hydroxybenzoyl)glycine in situ by reacting it with trifluoroacetic anhydride. The spermidine salt reacted with this mixed anhydride in the presence of 2 equiv of 1,8-bis(dimethylamino)naphthalene. The resulting N^4-[*N*-(2-trifluoroacetoxybenzoyl)glycyl]-N^1,N^8-bis(acyl)spermidine, when treated with mild base followed by an acidic workup, provided the expected N^4-[*N*-(2-hydroxybenzoyl)glycyl]-N^1,N^8-bis(benzoyl)spermidine (VIII, Scheme III). This addition of a second acyl group to the spermidine backbone probably best exemplifies the flexibility and potential applications of the overall scheme. It offers a clear route to compounds like N^4-[*N*-(2-hydroxybenzoyl)threonyl]-N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine.

We are currently extending these methods to the total synthesis of the *Micrococcus denitrificans* siderophore and related compounds.[16]

Conclusions

N^4-Benzylspermidine is a useful vehicle for the synthesis of N^4-acyl-N^1,N^8-bis(acyl)spermidine compounds. It is stable, can be synthesized in high yield, and is easily acylated and debenzylated. With this reagent in hand, it is possible to generate N^1,N^8-bis(acyl)spermidines in yields of 80% or greater. This is far in excess of the 5–14% yields realized from the reaction of acylating agents with simple spermidine.

Experimental Section

Materials. All reagents were purchased from Aldrich. Unless specified otherwise, Na_2SO_4 was used as a drying agent. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Boiling points are also uncorrected. Samples for ^1H NMR were prepared in $DCCl_3$ with chemical shifts given in parts per million relative to an internal Me_4Si standard unless stated otherwise. The spectra were recorded on Varian T-60 and XL-100 spectrometers. The infrared spectra were recorded on a Perkin-Elmer 257 grating spectrometer; liquid samples were run neat while solids were prepared in KBr. High-pressure liquid chromatography was carried out on a Waters 100 Å μStyragel column. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Preparative thin layer chromatography was done on 20 × 20 cm silica gel plates obtained from Analtech.

***N*-(2-Cyanoethyl)benzylamine (I).** A mixture of benzylamine (100 g, 0.993 mol) and acrylonitrile (45.0 g, 0.848 mol) was stirred for 40 h. Upon fractional distillation of the reaction mixture, 120 g (88%) of the desired product was obtained from the 101–115 °C (0.15 mm) fraction [lit.[8] bp 184–185 °C (23 mm)]; NMR δ 1.49 (s, 1 H), 2.38 (t, 2 H, J = 2.8 Hz), 2.79 (t, 2 H, J = 2.8 Hz), 3.72 (s, 2 H), 7.23 (s, 5 H); IR 3335 (m), 3010 (m), 2910 (m), 2840 (s), 2240 (s) cm^{-1}.

Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55. Found: C, 74.88; H, 7.52.

***N*-(2-Cyanoethyl)-*N*-(3-cyanopropyl)benzylamine (II).** A solution of 4-chlorobutyronitrile (11.0 g, 0.110 mol) in 40 mL of anhydrous 1-butanol was added over a 4-h period to a mixture of *N*-(2-cyanoethyl)benzylamine (25.0 g, 0.156 mol), anhydrous sodium carbonate (18.8 g, 0.180 mol), and potassium iodide (3.0 g, 0.02 mol) at 115 °C. The reaction mixture was allowed to stir an additional 17 h at 115 °C. After cooling to room temperature, the mixture was filtered and the solid washed with Et_2O. The combined filtrate and washings were extracted with 3 N HCl (3 × 50 mL), and the resulting acid solution was washed with Et_2O (2 × 50 mL), made basic with K_2CO_3, and extracted with ether (3 × 100 mL). The final ether extracts were dried over K_2CO_3 and filtered, and the ether was evaporated to leave 28.1 g of crude oil. Subsequent distillation provided 15.9 g (66%) of the desired product: bp 176 °C (0.05 mm); NMR δ 1.74 (m, 2 H), 2.50 (m, 8 H), 3.58 (s, 2 H), 7.32 (s, 5 H); IR 2940 (s), 2820 (s), 2240 (s) cm^{-1}.

Anal. Calcd for $C_{14}H_{17}N_3$: C, 73.98; H, 7.54. Found: C, 73.95; H, 7.58.

N^4-Benzylspermidine (III). A solution of $AlCl_3$ (13.5 g, 0.101 mol) in 125 mL of anhydrous Et_2O was rapidly added to a suspension of $LiAlH_4$ (3.85 g, 0.101 mol) in 200 mL of anhydrous Et_2O. After vigorous stirring of the resulting mixture under N_2, a solution of *N*-(2-cyanoethyl)-*N*-(3-cyanopropyl)benzylamine (10.0 g, 0.004 mol) in 125 mL of anhydrous Et_2O was added over a 2-h period.[13] After being stirred for an additional 16 h, the reaction mixture was cooled to 0 °C and quenched with 200 mL of aqueous 30% KOH (w/v), and the ether was layer decanted. The remaining emulsion was extracted exhaustively with ether, the extracts and decant having a combined volume of 2.5 L. The ethereal solution was then back-extracted with 2 × 100 mL of cold saturated aqueous NaCl and the ether evaporated. The resulting oil was taken up in 500 mL of $HCCl_3$, dried, filtered, and reduced in vacuo to give 10.2 g of crude product which upon fractional distillation gave 6.41 g (63%) of the desired compound: bp 130–132 °C (0.2 mm); NMR δ 1.12 (s, 4 H), 1.50 (m, 6 H), 2.55 (m, 8 H), 3.54 (s, 2 H), 7.30 (s, 5 H); IR 3365 (m), 3285 (m), 2930 (s) cm^{-1}.

Anal. Calcd for $C_{14}H_{25}N_3$: C, 71.44; H, 10.71. Found: C, 71.63; H, 10.64.

2,3-Diacetoxybenzoic Acid (IV). A suspension of 2,3-dihydroxybenzoic acid (10.0 g, 0.065 mol) in acetic anhydride (14.6 g, 0.143 mol) was stirred under N_2 and 2–3 drops of concentrated sulfuric acid added. Within 5 min a thick white precipitate developed and 70 mL of anhydrous Et_2O was added. After stirring under N_2 for an additional 12 h, the slurry was poured over 200 g of ice and the mixture extracted with CH_2Cl_2 (7 × 100 mL). The organic phase was then back-extracted with ice water (1 × 75, 2 × 50 mL), dried, filtered, and reduced in vacuo to give 15.22 g (98%) of the desired compound, a white solid: mp 157–158 °C (benzene/$HCCl_3$) (lit.[14] 157–158 °C); NMR δ 2.24 (s, 6 H), 7.34–7.60 (m, 2 H), 7.72–8.05 (m, 1 H), 8.55–9.55 (br s, 1 H); IR 2900 (m), 2700 (m), 2560 (m), 1775 (s), 1685 (s) cm^{-1}.

Anal. Calcd for $C_{11}H_{10}O_6$: C, 55.47; H, 4.23. Found: C, 55.33; H, 4.13.

2,3-Diacetoxybenzoyl Chloride (V). A solution of the 2,3-diacetoxybenzoic acid (16.41 g, 0.069 mol) in 600 mL of anhydrous EtOH-free chloroform was cooled to 0 °C under N_2 and phosphorus pentachloride (20.14 g, 0.097 mol) added. The reaction mixture was allowed to warm slowly to room temperature and the reaction continued for 24 h. The solvent was then evaporated and the crude product taken up in 900 mL of benzene and washed with aqueous 5% $NaHCO_3$ (w/v) (3 × 50 mL). The benzene solution was dried, filtered, and reduced in vacuo to give 16.70 g (94%) of the product: mp 76–77 °C (CCl_4); NMR (acetone-d_6) δ 2.29 (s, 3 H), 2.32 (s, 3 H), 7.67 (m, 3 H); IR 1750 (s), 1450 (m), 1370 (m), 1200 (s) cm^{-1}.

Anal. Calcd for $C_{11}H_9O_5Cl$: C, 51.48; H, 3.54. Found: C, 51.49; H, 3.47.

N^4-Benzyl-N^1,N^8-bis(benzoyl)spermidine (VI). A flask was charged with a solution of N^4-benzylspermidine (2.50 g, 0.10 mol) in 50 mL of dry, degassed pyridine under N_2. The flask was protected from light and cooled to −78 °C, and the benzoyl chloride (3.00 g, 0.021 mol) in 32 mL of dry, degassed methylene chloride was added over a period of 1.5 h. The reaction mixture was stirred under N_2 for an additional 30 h and allowed to warm slowly to room temperature. It was then poured into 125 mL of H_2O and extracted with benzene (1 × 15, 1 × 25 mL). The combined benzene extracts were washed with aqueous 15% Na_2CO_3 (w/v) (3 × 15 mL) and H_2O (5 × 25 mL), dried, filtered, and reduced in vacuo to yield 3.37 g of the desired compound. An additional 0.78 g of product was isolated by adjusting the pH of the original aqueous solution to 11.0 with KOH, extracting with $HCCl_3$ (2 × 20 mL) and combining, drying, and evaporating the organic extracts as before, for a total yield of 4.15 g (95%) of the desired compound: mp 100.5–102.5 °C (EtOAc/petroleum ether); NMR δ 1.63 (m, 6 H), 2.47 (m, 4 H), 3.47 (m, 6 H), 6.43 (br s, 2 H),

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(14) Pollack, J. R. A., Stevens, R., Eds. "Dictionary of Organic Compounds"; Oxford University Press: New York, 1965; Vol. 2, p 1055.

6.93–7.83 (m, 15 H); IR 3340 (s), 1630 (s), 1525 (s), 690 (s) cm^{-1}.

Anal. Calcd for $C_{28}H_{33}N_3O_2$: C, 75.81; H, 7.50; N, 9.47. Found: C, 75.73; H, 7.46; N, 9.37.

N^1,N^8-Bis(benzoyl)spermidine (VII). A solution of N^4-benzyl-N^1,N^8-bis(benzoyl)spermidine (0.277 g, 0.62 mmol) in 2.5 mL of glacial acetic acid was added to a suspension of PdO (0.043 g, 0.3 mmol) in 1.25 mL of glacial acetic acid. The hydrogenolysis was allowed to proceed until no more hydrogen was taken up. The reaction mixture was then filtered, the acetic acid evaporated, and the residue taken up in 10 mL of anhydrous methanol. The resulting alcoholic solution was adjusted to pH 11 with NaOMe and reduced in vacuo. The crude product was taken up in 10 mL of $HCCl_3$ and washed with cold H_2O (3 × 5 mL). The organic phase was then dried, filtered, and evaporated to give 0.209 g (95%) of the desired white crystalline product: mp 130.5–133.0 °C; NMR δ 1.16 (m, 7 H), 2.63 (m, 4 H), 3.43 (m, 4 H), 6.53 (br s, 2 H), 7.13–7.73 (m, 10 H); IR 3310 (s), 2920 (m), 2860 (m), 2800 (m), 1615 (s), 1515 (s) cm^{-1}.

Anal. Calcd for $C_{21}H_{27}N_3O_2$: C, 71.36; H, 7.70; N, 11.89. Found: C, 71.18; H, 7.60; N, 11.73.

N^4-[N-(2-Hydroxybenzoyl)glycyl]-N^1,N^8-bis(benzoyl)spermidine (VIII). Trifluoroacetic anhydride (0.446 g, 2.1 mmol) was added with stirring to a suspension of N-(2-hydroxybenzoyl)glycine[15] (0.165 g, 0.85 mmol) in 20 mL of CH_2Cl_2. The resulting mixture was refluxed at 50 °C for 2 h. The solution was evaporated to dryness under high vacuum, and the N-(2-trifluoroacetoxybenzoyl)glycyl trifluoroacetic anhydride residue was redissolved in 15 mL of CH_2Cl_2. After the solution was cooled to −78 °C and 1,8-bis(dimethylamino)naphthalene (0.398 g, 1.86 mmol) in 5 mL of CH_2Cl_2 was added, the N^1,N^8-bis(benzoyl)spermidine acetate (0.257 g, 0.62 mmol) in 10 mL of CH_2Cl_2 was added dropwise. The reaction mixture was allowed to warm to room temperature with continued stirring under N_2. After 30 h, the solution was washed with cold 1.1% aqueous HCl (w/v) and ice water (3 × 5 mL), dried, filtered, and evaporated. The residue was dissolved in 25 mL of degassed methanol, and NaOMe was added to a pH of approximately 9. After the solution was stirred under N_2 for 30 min, the pH was adjusted to approximately 2 by addition of HCl gas dissolved in methanol. The solution was evaporated and the residue was dissolved in 50 mL of CH_2Cl_2, filtered, and evaporated to yield 294 mg (89% crude yield) of the product.

An analytical sample was purified on silica gel by eluting with 5% MeOH in EtOAc: NMR δ 1.17–2.33 (br m, 6 H), 3.33 (br m, 8 H), 4.13 (br s, 2 H), 6.50–8.00 (br m, 17 H), 12.07 (s, 1 H); IR 3260 (m), 2915 (m), 1628 (s), 1525 (m), 1299 (m) cm^{-1}.

Anal. Calcd for $C_{30}H_{34}N_4O_5$: C, 67.91; H, 6.46; N, 10.56. Found: C, 67.72; H, 6.55; N, 10.44.

N^4-Benzyl-N^1,N^8-bis(2,3-diacetoxybenzoyl)spermidine Hydrochloride (IX). A solution of N^4-benzylspermidine (2.80 g, 11.9 mmol) and 1,8-bis(dimethylamino)naphthalene (5.00 g, 23.3 mmol) in 400 mL of CH_2Cl_2 was cooled to 0 °C under N_2. The 2,3-diacetoxybenzoyl chloride (6.00 g, 23.4 mmol) in 250 mL of CH_2Cl_2 was added over a 4-h period. After addition was completed, the reaction vessel was allowed to warm slowly to room temperature with continued stirring under N_2. After 20 h, the reaction mixture was again cooled to 0 °C, washed with ice-cold 1.1% aqueous HCl (w/v) (3 × 30 mL) and ice water (3 × 30 mL), dried, filtered, and evaporated to give 5.62 g (66% crude yield) of the desired product, a white, semicrystalline solid. Yields as high as 80% were obtained when a 20% excess of the acid chloride was used.

An analytical sample was purified by high-pressure liquid chromatography on a 100-Å μStyragel column eluting with THF. This purification demonstrated that the crude product was in excess of 95% pure: mp 121–123 °C; NMR δ 1.50 (m, 6 H), 2.23 (s, 12 H), 2.93 (m, 4 H), 3.27 (m, 4 H), 3.83 (s, 2 H), 7.27 (m, 14 H); IR 3220 (m), 1765 (s), 1563 (m), 1374 (m), 1201 (s) cm^{-1}.

Anal. Calcd for $C_{36}H_{42}O_{10}N_3Cl$: C, 60.71; H, 5.94; N, 5.90; Cl, 4.98. Found: C, 60.59; H, 5.95; N, 5.71; Cl, 4.80.

N^1,N^8-Bis(2,3-dihydroxybenzoyl)spermidine Hydrochloride (XI). The PdO catalyst (0.12 g, 0.98 mmol) was suspended in 3 mL of glacial acetic acid and a solution of N^4-benzyl-N^1,N^8-bis(2,3-diacetoxybenzoyl)spermidine hydrochloride (1.20 g, 1.68 mmol) in 9 mL of glacial acetic acid was introduced. The mixture was stirred until no more hydrogen was taken up and filtered, and the solvent was evaporated. The crude product was taken up in 75 mL of absolute methanol and, after thorough deoxygenation of the resulting solution with N_2, NaOMe (0.37 g, 6.72 mmol) was added and the mixture stirred 2.25 h under N_2. The methanol was removed in vacuo, the residue taken up in 250 mL of distilled deoxygenated H_2O, and the pH adjusted to 2 with concentrated HCl. After 1 h of sonication, the acidic solution was washed with acid-free EtOAc (5 × 100 mL) and reduced in vacuo. The crude product was then taken up in 50 mL of anhydrous deoxygenated EtOH, filtered through a Teflon millipore, and reduced in vacuo to afford 647 mg (85%) of the desired compound. Both the UV and NMR spectra of the product were identical with those of an authentic sample: NMR (trifluoroacetic acid; chemical shifts calculated relative to internal CH_2Cl_2, 5.28 ppm) δ 2.13 (br m, 6 H), 3.50, 3.86 (2 br overlapping m, 8 H), 7.30 (br m, 8 H).

Spermidine Triacetate (XII). A solution of N^4-benzylspermidine (0.500 g, 2.12 mmol) in 10 mL of glacial acetic acid was added to a suspension of PdO (0.142 g, 2.31 mmol) in 4 mL of glacial acetic acid. The hydrogenolysis was allowed to proceed until no more hydrogen was taken up. The reaction mixture was then filtered and reduced in vacuo to yield 1.17 g of crude oil. The proportion of pure product was determined by NMR assay in deuteriotrifluoroacetic acid. Upon comparison with an authentic sample using anhydrous sodium formate as an internal standard, the oil was calculated to contain 0.652 g (94%) of the desired salt.

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Registry No. I, 706-03-6; II, 1216-04-2; III, 73038-05-8; IV, 486-79-3; V, 65055-19-8; VI, 73038-06-9; VII, 73038-07-0; VIII, 73038-08-1; IX, 73038-09-2; XI, 73038-10-5; XII, 73038-11-6; benzylamine, 100-46-9; acrylonitrile, 107-13-1; 4-chlorobutyronitrile, 628-20-6; 2,3-dihydroxybenzoic acid, 303-38-8; benzoyl chloride, 98-88-4; N-(2-hydroxybenzoyl)glycine, 487-54-7; N^1,N^8-bis(benzoyl)spermidine acetate, 73038-12-7.

(15) This reagent may be obtained from BaChem, Torrance, CA.

(16) Using these procedures, we have synthesized N^4-(salicyloylglycyl)-N^1,N^8-bis(2,3-dihydrobenzoyl)spermidine. This was accomplished either by first forming the copper chelate of compound XI followed by condensation at N^4, with N-[2-(trifluoroacetoxy)benzoyl]glycyltrifluoracetic anhydride, or by condensing the anhydride with N^1,N^8-bis[2,3-(methylenedioxy)benzoyl]spermidine followed by BCl_3 removal of the protecting group. See: Bergeron, R. J.; Burton, P. S.; Kline, S. J.; McGovern, K. A. Abstracts from the ACS 1980 meetings in minature, Tampa, FL.