M - $C_{15}H_{31}$), 183 (8.3, M - $C_{15}H_{31}CO$), 127 (61.8, $PO_4H_2Me_2$), 109 (22.1, PO_3Me_2). Anal. Calcd for $C_{21}H_{43}O_6P$: C, 59.69; H, 10.26; P, 7.33. Found: C, 60.02; H, 10.54; P, 7.37. ***trans*-4**: yield after TLC[8] purification (10:90 hexane-Et_2O, v/v; R_f 0.15) 73%; mp 37-38 °C; mass spectrum, *m/e* 422 (<1, M^+), 211 (100, M - $C_{15}H_{31}$), 183 (5.1, M - $C_{15}H_{31}CO$), 127 (62.0, $PO_4H_2Me_2$), 109 (25.2, PO_3Me_2). Anal. Calcd for $C_{21}H_{43}O_6P$: C, 59.69; H, 10.26; P, 7.33. Found: C, 59.90; H, 10.47; P, 7.11.

2-Pentadecyl-4-(dimethylphospho)-1,3-dioxanes (8). *cis*-8: yield after TLC[8] purification (10:90 hexane-Et_2O, v/v; R_f 0.08) 77%; mp 53-54 °C; mass spectrum, *m/e* 422 (<1, M^+), 211 (100, M - $C_{15}H_{31}$), 183 (2.9, M - $C_{15}H_{31}CO$), 127 (75.7, $PO_4H_2Me_2$), 109 (11.0, PO_3Me_2). Anal. Calcd for $C_{21}H_{43}O_6P$: C, 59.69; H, 10.26; P, 7.33. Found: C, 59.91; H, 10.55; P, 7.32. ***trans*-8**: yield after TLC[8] purification (10:90 hexane-Et_2O, v/v; R_f 0.27) 59%; mp 50.5-51.5 °C; mass spectrum, *m/e* 422 (<1, M^+), 211 (89.5, M - $C_{15}H_{31}$), 183 (3.1, M - $C_{15}H_{31}CO$), 127 (100, $PO_4H_2Me_2$), 109 (12.5, PO_3Me_2). Anal. Calcd for $C_{21}H_{43}O_6P$: C, 59.69; H, 10.26; P, 7.33. Found: C, 60.04; H, 10.46; P, 7.27.

Acknowledgment. This investigation was supported in part by Public Health Service Research Grant HL 08214 from the Program Project Branch, Extramural Programs, National Heart, Lung and Blood Institute, and by The Hormel Foundation. We also thank Thomas P. Krick for mass spectrometry service, supported by the Minnesota Agricultural Experiment Station, William J. Hansen for experimental assistance, and Dr. Ramaswamy Murari for most useful discussions.

Registry No. *cis*-1, 30889-28-2; *trans*-1, 30889-31-7; *cis*-2, 73116-77-5; *trans*-2, 73116-78-6; *cis*-3, 73116-79-7; *trans*-3, 73116-80-0; *cis*-4, 73116-81-1; *trans*-4, 73116-82-2; *cis*-5, 30889-22-6; *trans*-5, 30889-25-9; *cis*-6, 73116-83-3; *trans*-6, 73116-84-4; *cis*-7, 73116-85-5; *trans*-7, 73116-86-6; *cis*-8, 73116-87-7; *trans*-8, 73116-88-8; diphenylphosphorochloridate, 2524-64-3.

Marine Alkaloids. 2. Bromo Alkaloids from the Marine Bryozoan *Flustra foliacea*. Isolation and Structure Elucidation

Jørgen S. Carlé and Carsten Christophersen*

Marine Chemistry Section, Chemical Laboratory II, The H. C. Ørsted Institute, University of Copenhagen, DK-2100 Copenhagen, Denmark

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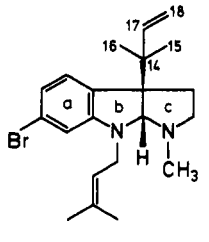
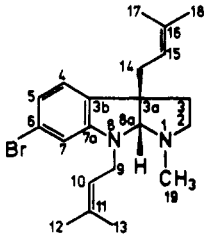
Flustramines A and B, two bromo-substituted alkaloids, were isolated from the marine bryozoan *Flustra foliacea*. The isolation procedure and detailed assignment of all ^{13}C and ^1H NMR data are reported. Nuclear Overhauser enhancement difference spectroscopy reveals the pyrrolidine rings to be cis fused, in close analogy with physostigmine.

During the last decade, the biology of the phylum Bryozoa (syn. Polyzoa, Ectoprocta, or moss animals) has received a great deal of attention,[1] and much data have accumulated about the chemistry of marine natural products.[2] However, despite these facts, chemical investigations of Bryozoa seem to be virtually nonexistent. This is the more curious since the phylum is represented by species abundantly available in fresh water as well as in the marine environment, where they greatly add to the problem of "fouling".[1,3]

A study of the chemical ecology of the marine bryozoan *Flustra foliacea* (L.) revealed this species to contain an allelochemical mixture of monoterpenes,[4] as well as a mixture of brominated alkaloids.[5] The literature on marine alkaloids is very scarce; moreover, the few bromo-substituted members of this class seem to bear no resemblance to patterns established from terrestrial sources. In this paper we wish to report the detailed isolation procedure and structural assignments of flustramines A (1) and B (2),[6] two brominated alkaloids refer-



1. FLUSTRAMINE A



2. FLUSTRAMINE B

rable to the basic physostigmine skeleton known from the minor group of alkaloids from Calabar bean (*Physostigma venenosum* Balf. of family Leguminosae).

Results and Discussion

Isolation. Repeated column chromatography (silica gel) of a petroleum ether extract of freeze-dried bryozoans left 25 mg of each alkaloid as colorless oils. High-resolution mass spectrometry revealed the compounds to be isomers with the elemental composition $C_{21}H_{29}BrN_2$. As discussed below, spectral analysis made it apparent that the species differ only in the structure of one of the side chains.

Mass Spectra. Fragment ions at *m/e* 210/208 appearing in the spectra of flustramines A and B were found to have the elemental composition C_9H_7NBr. We attribute

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Table I. NMR Data of Flustramines A and B

position	flustramine A C[a]	flustramine B C[a]	flustramine A H[b]	flustramine A $J_{H/H}$, Hz	flustramine B H[b]	flustramine B $J_{H/H}$, Hz
2	53.2	52.8	2.7 (1 H, m)		2.7 (1 H, m)	
3	34.5°	38.9°	2.2 (1 H, m)		2.0 (1 H, m)	
3a	63.4	56.7				
3b	132.5⁺	133.9⁺				
4	125.8	124.0	6.87 (1 H, d)	$^3J_{H(C-4)/H(C-5)} = 8.3$	6.79 (1 H, d)	$^3J_{H(C-4)/H(C-5)} = 7.2$
5	119.1‡	120.6‡	6.67 (1 H, dd)	$^3J_{H(C-5)/H(C-4)} = 8.3$	6.73 (1 H, dd)	$^3J_{H(C-5)/H(C-4)} = 7.2$
6	121.7	121.3		$^4J_{H(C-5)/H(C-7)} = 1.5$		$^4J_{H(C-5)/H(C-7)} = 1.5$
7	109.9	109.3	6.47 (1 H, d)	$^4J_{H(C-7)/H(C-5)} = 1.5$	6.51 (1 H, d)	$^4J_{H(C-7)/H(C-5)} = 1.5$
7a	153.6	151.1				
8a	89.3	91.6	4.37 (1 H, s)		4.31 (1 H, s)	
9	45.9	46.2	3.84 (2 H, d)	$^3J_{H(C-9)/H(C-10)} = 6.3$	3.82 (2 H, m)	
10	120.9‡	120.3‡	5.18 (1 H, t)	$^3J_{H(C-10)/H(C-9)} = 6.3$	5.11 (1 H, t)	
11	134.6⁺	134.7⁺				
12	25.6*	25.7*	1.73 (3 H, s)*		1.71 (3 H, s)*	
13	18.1	18.1	1.72 (3 H, s)*		1.72 (3 H, s)*	
14	43.3	38.2			2.39 (2 H, d)	$^3J_{H(C-14)/H(C-15)} = 7.2$
15	23.5*	119.9‡	1.01 (3 H, s)‡		4.92 (1 H, t)	$^3J_{H(C-15)/H(C-14)} = 7.2$
16	22.5*	134.7	0.95 (3 H, s)‡			
17	144.9	25.9*	5.9 (1 H, m)		1.65 (3 H, s)‡	
18	113.1	18.1	5.0 (2 H, m)		1.57 (3 H, s)‡	
19	37.8°	38.1°	2.43 (3 H, s)		2.47 (3 H, s)	

[a] Spectra measured at 22.63 MHz in $CDCl_3$ (50 mg mL^{-1}). Chemical shifts are given in parts per million relative to internal Me_4Si. [b] Spectra measured at 270 MHz in $CDCl_3$ (50 mg mL^{-1}). Chemical shifts are given in parts per million relative to internal Me_4Si. Assignments for values marked with the same symbols may be interchanged.

these ions to the brominated analogue of the indole fragment ion known to be highly indicative of indole, oxindole, or indoline subunits.[7] The choice of the indoline configuration in this case rests on the observed +,− sign sequence of the magnetic circular dicroism curves exhibited by both alkaloids.[5,8]

The base peaks at *m/e* 253/251 imply the physostigmine-like nature of the skeleton. These ions are believed to give rise to the bromoindole fragment ions at *m/e* 210/208 by a cyclic collapse of ring c.[9] The bromine atom must then be placed in the indoline part of the molecule and the *N*-methyl group at N-1. Loss of 69 (C_5H_9) and 68 (C_5H_8) mass units, consecutively, from the molecular ion corresponds to the loss of two isoprene units.

^{1}H NMR spectral data (270-MHz) (see Table I) on comparison with data reported for analogous systems[9] lend further support to the above assignments. A key signal originated from the single proton at C-8a. The coupling pattern in the aromatic region indicated that the bromine atom was situated at either C-5 or C-6.

The ^{1}H NMR spectra revealed the position of the isoprene units. As no exchangeable protons were observed in these spectra and absorption bands corresponding to a N–H stretching vibration were lacking in the IR spectra, both compounds must carry an isoprene unit at N-8. The position of the other isoprene unit was established from the sharp singlet proton resonances at δ 4.37 and 4.31 in **1** and **2**, respectively. As these signals originate from the 8a hydrogen atom, C-3a must be quaternary, in casu, substituted with an isoprene unit.

The structures of the side chains could be unraveled from 270-MHz spectra, where all the relevant signals were separated. In the case of flustramine A, the C-3a substituent revealed itself as an inverted γ,γ-dimethylallyl (2-methyl-3-buten-2-yl) structure based on the C-15 and C-16 methyl signals and the ABX pattern of the three vinylic protons by comparison with data for, e.g., roquefortine[9] and oxaline.[10] Data obtained for the C-3a substituent in **2** were in good agreement with values reported for the γ,γ-dimethylallyl system.[11]

The N-8 substituents in both **1** and **2** were γ,γ-dimethylallyl groups as confirmed by comparison of the pertinent ^{1}H NMR results with those reported for fumitremorgin B[12] (lanosulin).[13] The full assignments of the ^{1}H NMR spectra of flustramines A and B together with the ^{13}C NMR signals are shown in Table I. Whenever possible the origins of the ^{1}H NMR resonances were verified by extensive decoupling experiments.

The ^{13}C NMR chemical shifts of the skeleton carbons in flustramines A and B were assigned by comparison with the shifts of physostigmine[14] and roquefortine.[9] Evidence for the location of the bromine atom at C-6 was obtained by comparing the calculated shifts for C-5 and C-6 substituted isomers with those observed. The calculated shifts were based on data from ref 14 and 9 by using substituent effects tabulated in ref 15. Identification of the isoprene substituents was based partially on roquefortine and calculated shifts, respectively, using the parameters in ref 16. Substitution of an inverted γ,γ-dimethylallyl group in **1** with a γ,γ-dimethylallyl group in **2** was consistent with the replacement of the signals at δ 144.9 (C-17) and 113.1 (C-18) observed for **1**, appearing at the expected values of δ 120.9 and 134.6, respectively, in the spectrum of **2**.

Nuclear Overhauser enhancement (NOE) difference spectroscopy proved highly informative. This method has

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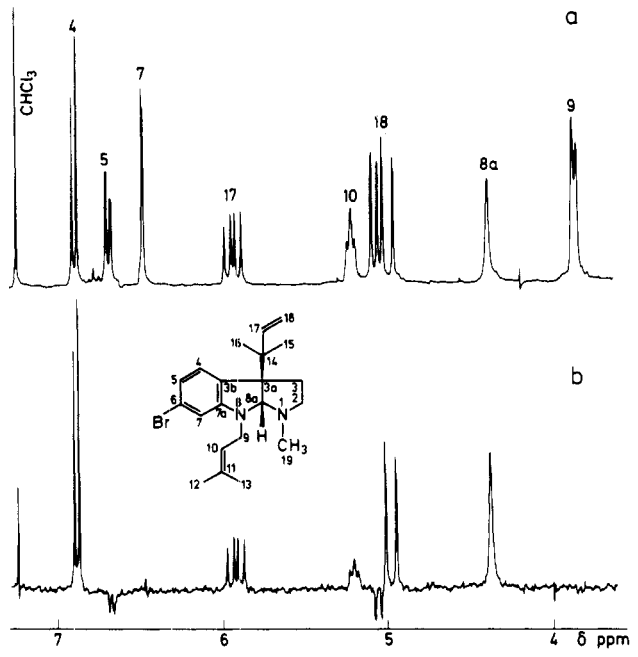

Figure 1. (a) The low-field part of the 270-MHz FT ^1H NMR spectrum of flustramine A ($CDCl_3$, δ, relative to Me_4Si). The number above the peaks refers to the carbon atom to which the resonating protons are attached. (b) ^1H–[^1H] nuclear Overhauser enhancement difference spectrum of the same part of the molecule. The spectrum was built up by simultaneous presaturation of the upfield-shifted resonances of the two methyl groups at C-15 and C-16 (1.01 and 0.95 ppm, respectively).

previously been used only in a limited number of cases, especially for the assignment of ^1H NMR spectra of biological macromolecules, but we here report the application of the ^1H–[^1H] NOE difference technique on relatively small molecules as a useful aid in the structure elucidation of natural products. NOE difference ^1H NMR spectra are obtained as the difference between a spectrum recorded with and a spectrum recorded without nuclear Overhauser enhancement caused by presaturation of individual resonances (i.e., the resulting free-induction decay is that corresponding to the difference spectrum between the irradiated and nonirradiated spectra). Furthermore, using a cyclic sequence[17,18] it is possible to eliminate effectively spurious effects due to long-term drift in sensitivity, resolution, and field-frequency ratio of the spectrometer. By this technique one may obtain reliable values even in cases where only minor Overhauser effects are present.

Figure 1a shows the low-field part of the ^1H NMR spectrum of flustramine A. The number above the peaks refers to the carbon atom to which the resonating protons are attached. Signals 4, 5, and 7 are due to the aromatic protons, reflecting the ortho (J = 8.3 Hz) and meta (J = 1.5 Hz) couplings. The protons at 17 and 18 show the ABX pattern of the inverse isoprene unit, and the signals at 10 and 9 show the AB_2 pattern (J = 6.3 Hz) in the γ,γ-dimethylallyl unit at N-8. The remaining singlet is due to the C-8a proton.

Figure 1b shows the low-field part of the ^1H–[^1H] nuclear Overhauser enhancement difference spectrum of flustramine A. The resonances here are due to the enhancements only, in this case built up by simultaneous presaturation of the six methyl protons at C-15 and C-16 (not shown in the figure) resonating at δ 1.01 and 0.95, respectively. The absolute enhancements (expressed in %) are obtained by considering the integrals of a resonance relative to the resonances of the presaturated protons.

The observed enhancements are 3.6% for the proton attached to C-4, 2.1% for that at C-17, 3.1% for that at C-18, 3.1% for that at C-8a, and a small but significant enhancement of the proton situated at C-10. In the aromatic region, observation of an enhancement for the ortho-coupled (J = 8.3 Hz) resonance *and* absence of enhancements at the other two protons unequivocally place the bromine atom at C-6 instead of C-5 (see above).

The enhancement of the C-8a proton shows a close proximity of this proton to the two presaturated methyl groups, thereby confirming the expected[19,20] cis configuration around the C-3a/C-8a bond in flustramine A.

Comparison of the two spectra (a and b) shows that only one of the C-18 protons gives rise to an enhancement (3.1%). This proton must therefore be situated closest to the two methyl groups, i.e., the proton which is trans to the C-17 proton.

In a series of ^1H NOE difference measurements in flustramine B, the C-6 position of the bromine atom and the cis configuration around the C-3a/C-8a bond were demonstrated.

Experimental Section

Mass spectra were recorded at 70 eV on a VG MM 7070F instrument; precise mass measurements were obtained by the peak matching method. UV spectra were recorded on a Unicam SP 18 instrument, and IR spectra on a Perkin-Elmer 580 spectrometer. ^{13}C NMR spectra were recorded at 22.63 MHz on a Bruker WH90, while ^1H NMR were recorded at 270 MHz on a Bruker HX 270 FT instrument. In the case of the NOE difference measurements, the method described in ref 6 was used on argon-flushed and dust-free samples. All NMR spectra were recorded in $CDCl_3$ and chemical shifts are reported in parts per million downfield from internal Me_4Si.

Isolation of Flustramines A and B. Freeze-dried (71 g) *Flustra foliacea* (L.) (1 kg wet weight) were extracted with petroleum ether. After evaporation this gave 1.33 g of black oil which contained 5.5% bromine. On the basis of UV absorption (254 and 280 nm) this oil was separated into three fractions by column chromatography (silica gel, A60 Lobar, Merck; MeOH–CH_2Cl_2 5:95). A simple Beilstein test indicated that the bromo compounds were contained in the most polar fraction. Repeated column chromatography of this fraction (silica gel, A60 Lobar, Merck) in ethyl acetate gave three fractions. A Beilstein test indicated that only the two most polar fractions contained halogens. These two fractions were each rechromatographed in ethyl acetate and gave equal amounts of analytically pure flustramine A (25 mg, 0.035% on dry weight) and flustramine B as colorless oils.

Flustramine A ($C_{21}H_{29}N_2Br$): mass spectrum (100 °C), m/e 390/388 (6), 321/319 (51), 290/288 (6), 278/276 (9), 253/251 (80), 210/208 (16), 172(13), 171(10), 129(6), 69(100); high-resolution mass spectrum, m/e 388.150 (calcd for $C_{21}H_{29}N_2Br$ 388.151), 319.081 (calcd for $C_{16}H_{20}N_2Br$ 319.081), 251.016 (calcd for $C_{11}H_{12}N_2Br$ 251.018), 207.9762 (calcd for C_9H_7NBr 207.9762), 69.0704 (calcd for C_5H_9 69.0704); UV λ_{max} (nm, EtOH) 218 (ϵ 2.0 × 10^4), 263 (8.6 × 10^3), 319 (3.4 × 10^3); in 0.5 M ethanolic HCl 218 (ϵ 2.1 × 10^4), 255 (7.5 × 10^3), 307 (3.5 × 10^3); IR ($CHCl_3$) 2970 (s), 2935 (s), 2860 (m), 1670 (m), 1635 (m), 1591 (s), 1580 (m), 1488 (s) cm^{-1}.

Flustramine B ($C_{21}H_{29}N_2Br$): mass spectrum (100 °C), m/e 390/388 (6), 321/319 (28), 290/288 (8), 278/276 (16), 253/251 (19), 210/208 (12), 172 (9), 171 (9), 129 (9), 69 (100); high-resolution mass spectrum, m/e 388.150 (calcd for $C_{21}H_{29}N_2Br$ 388.151), 319.081 (calcd for $C_{16}H_{20}N_2Br$ 319.081), 251.016 (calcd for $C_{11}H_{12}N_2Br$ 251.018), 207.9765 (calcd for C_9H_7NBr 207.9762), 69.0704 (calcd for C_5H_9 69.0704); UV λ_{max} (nm, EtOH) 218 (ϵ 2.0 × 10^4), 262 (9.2 × 10^3), 317 (3.5 × 10^3); in 0.5 M ethanolic HCl 219 (ϵ 2.1

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$\times 10^4$), 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

R. J. Bergeron,* K. A. McGovern, M. A. Channing, and P. S. Burton

Department of Medicinal Chemistry, J. Hillis Miller Health Center, University of Florida, Gainesville, Florida 32610

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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.

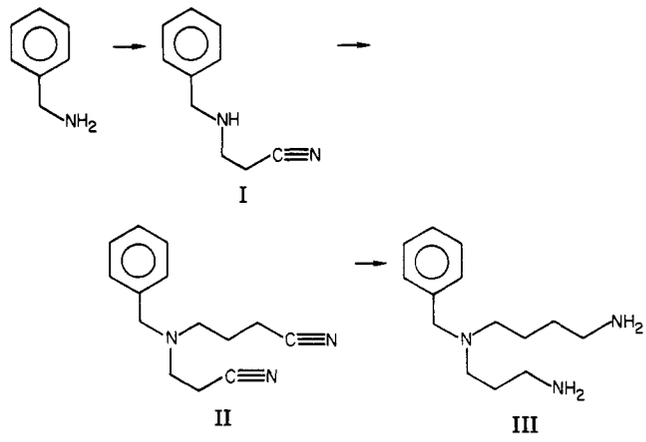
Introduction

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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