**Ethyl 1-(2-Methylbutyl)-2-oxocyclohexane-1-carboxylate (58).** Treatment of 0.030 g of **20** with excess of active Raney nickel in 5 mL of refluxing ethanol for 6 h followed by filtration and evaporation of the ethanol left 0.015 g of oily **58**: 63% yield; IR 1740, 1720 $cm^{-1}$; NMR $\delta$ 0.9 (t, 3), 1.1–2.5 (m, 18, 3.0–3.4 (m, 3), 4.1 (dq, 2); mass spectrum, $m/e$ 242 ($M^+$), 170, 124, 95, 81; HRMS, $m/e$ 242.188 ($C_{14}H_{26}O_3$ requires 242.188).

An authentic sample of **58** was prepared by generation of the sodium enolate of **19** by using NaH in THF and treatment with 2-methyl-1-bromobutane. This product was identical in all respects with **58**.

**2-(2-Methylbutyl)cyclohexanone (56).** A solution of 3.51 g ($2 \times 10^{-2}$ mol) of 1-pyrrolidinylcyclohexene with 3.5 g ($2 \times 10^{-2}$ mol) of 1-bromo-2-methylbutane in 20 mL of dioxane was heated at reflux for 20 h. The mixture was diluted with 10 mL of 3 N HCl and stirred for 1 h. The usual workup afforded 1.95 g of oil from which an analytical sample of **56** was obtained by preparative GC (column C): IR 1710 $cm^{-1}$; NMR $\delta$ 1.0 (d, $J \approx 8$ Hz, 3), 1.1 (d, $J \approx 8$ Hz, 3), 1.4–2.5 (m, 14); mass spectrum, $m/z$ (relative intensity) 168 ($M^+$, 5), 98 (base, 100).

A solution of 0.050 g of **5** in 5 mL of ethanol was treated with about 0.1 g of activated Raney nickel and heated at reflux for 3 h. Filtration and evaporation left 0.035 g of a mixture containing ca. 45% of **56**, identical with the **56** above by GC (columns A, C, D). None of the remaining compounds in this mixture were **57** (GC/MS).

**Acknowledgment.** Research Corp. provided support for the initial phases of this program. The Finnigan GCMS-DS was purchased with an NIH shared instrument grant. We are grateful to Professor Bruce Rickborn (UCSB) for a generous sample of **52** and to Professor Roy Olofson (Pennsylvania State University) and Mr. Thomas Arrhenius (Rice University) for helpful discussions.

**Registry No.** **1**, 70109-88-5; **2**, 39198-55-5; **3**, 108-94-1; **4**, 70234-67-2; **5**, 83720-11-0; **6**, 6651-36-1; **7**, 13482-23-0; **8**, 83720-12-1; **9**, 83720-13-2; **10**, 98-53-3; **11**, 83720-14-3; **12**, 83720-15-4; **13**, 19980-35-9; **14**, 83720-16-5; **15**, 583-60-8; **16**, 19980-33-7; **17**, 83720-17-6; **18**, 83720-18-7; **19**, 1655-07-8; **20**, 83720-19-8; **21**, 83720-21-2; **22**, 83720-22-3; **23**, 502-42-1; **24**, 70109-90-9; **25**, 83720-23-4; **26**, 502-49-8; **27**, 83720-24-5; **28**, 83720-25-6; **29**, 83720-26-7; **30**, 57044-58-3; **31**, 83780-83-0; **32**, 83720-27-8; **33**, 83720-28-9; **34**, 70109-89-6; **35**, 83780-28-3; **36**, 818-23-5; **37**, 53282-55-6; **38**, 83720-29-0; **39**, 83720-30-3; **40**, 123-19-3; **41**, 83720-31-4; **42**, 57641-21-1; **43**, 83720-32-5; **44**, 609-14-3; **45**, 83720-33-6; **46**, 83720-35-8; **47**, 83720-36-9; **48**, 83720-37-0; **49**, 83720-38-1; **50**, 83720-40-5; **51**, 83720-41-6; **52**, 33066-07-8; **53**, 1654-87-1; **55**, 3574-58-1; **56**, 20118-23-4; **58**, 83720-42-7; **59**, 78945-46-7; 1,4-dichloro-1,3-butadiene, 2984-42-1; dimethyl sulfide, 75-18-3; 1-pyrrolidinylcyclohexene, 1125-99-1; 1-bromo-2-methylbutane, 10422-35-2.

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# Natural Ferric Ionophores: Total Synthesis of Schizokinen, Schizokinen A, and Arthrobactin

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The synthesis of the microbial iron chelators schizokinen (**1**) and arthrobactin (**2**) are described. *O*-Benzyl-*N*-(carbobenzyloxy)hydroxylamine (**7**) was subjected to triphenylphosphine/diethyl azodicarboxylate mediated alkylation with alcohol amine **10** to give the N-alkylated product **13**, which was converted to the protected 1-amino-3-(acetylhydroxyamino)propane **4a** by hydrogenation in the presence of acetic anhydride. Several citric acid derivatives were prepared which were activated at both terminal carboxyl groups and protected at the internal carboxyl groups. 1-Amino-3-[(benzyloxy)amino]propane *p*-toluenesulfonic acid double salt (**19**) was coupled to citric acid derivative **28c** to give protected schizokinen **29c**, which was deprotected in two steps to yield schizokinen (**1**). The 1-amino-5-(acetylhydroxyamino)pentane derivative **4b** was deprotected and coupled with citric acid derivative **28a** to give **31**, which was deprotected in two steps to yield arthrobactin (**2**). Preliminary attempts to synthesize schizokinen resulted in formation of succinimide **26**. Reductive debenzylation of **26** provided **33** which was shown to be identical with schizokinen A.

Iron is an essential element for all life forms. Although iron is one of the most abundant elements, the extreme insolubility of ferric ion at neutral and alkaline pH places severe restrictions on its metabolism. Iron absorption from the diet is physiologically controlled, but the body has no regulatory mechanism for eliminating a toxic excess introduced by accidental overdose or by multiple transfusions. Cooley's anemia and its transfusional treatment provide an example of the difficulty of correcting deficient iron metabolism. According to the World Health Organization, the group of diseases called the thalassemias, of which Cooley's anemia is the most severe, is the largest health problem in the world for single-locus genetic diseases. Extensive iron overload induced by the multiple transfusions during treatment of Cooley's anemia causes deposition of the metal in the heart, liver, endocrine glands, and other organs. The ultimate result is organ malfunction and early death.[1]

In principle, iron overload can be treated by administration of an iron-chelating agent to promote remobilization and excretion of the deposited iron. Perhaps the best models for iron chelation are provided by microbial systems which have envolved highly specific and efficient iron-sequenstering agents.[2] These siderophores primarily utilize either hydroxamic acids[3] or catechols[4] for the che-

† Fellow of the Alfred P. Sloan Foundation, 1981–1983.

(1) Anderson, W. F. In "Inorganic Chemistry in Biology and Medicine"; Martell, A. E., Ed.; American Chemical Society: Washington, DC, 1973; Chapter 15.

(2) (a) Neilands, J. B. *Struct. Bonding (Berlin)* **1966**, *1*, 59–108. (b) Emery, T. In "Microbial Iron Metabolism"; Neilands, J. B., Ed.; Academic Press: New York, 1974; Chapter 5.

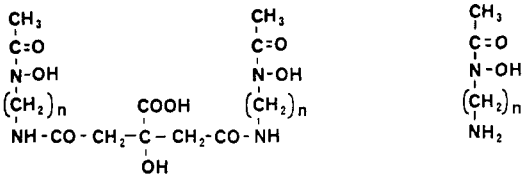
(3) (a) Maehr, H. *Pure Appl. Chem.* **1971**, *28*, 603. (b) Neilands, J. B. In "Inorganic Biochemistry"; Eichorn, G., Ed.; Elsevier: New York, 1973.

(4) Rosenberg, H.; Young, I. G. In "Microbial Iron Metabolism"; Neilands, J. B., Ed.; Academic Press: New York, 1974; Chapter 3.

0022-3263/83/1948-0024$01.50/0 

lating ligands. Most of the hydroxamate-containing siderophores, including ferrichrome,[5] rhodotorulic acid,[6] coprogen,[7] aerobactin,[8] and mycobactins,[9] contain ω-*N*-hydroxy L-amino acids. However, others, such as schizokinen (1),[10] arthrobactin (2),[11] and ferrioxamine B,[12] utilize 1-amino-ω-(hydroxyamino)alkane residues to bind ferric ion. During evolution, these residues may have resulted from decarboxylation[13] of the corresponding ω-*N*-hydroxy α-amino acids.

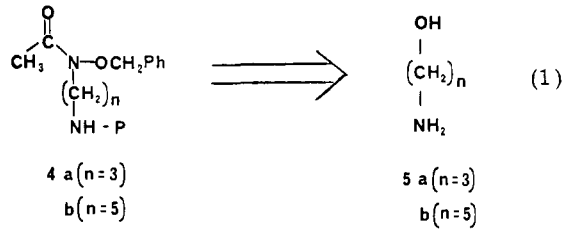
Subsequent to completion of the synthesis of aerobactin,[14] schizokinen (1) and arthrobactin (2) have been among



1 (n = 3)
2 (n = 5)

3 a (n = 3)
b (n = 5)

the targets of recent synthetic studies in our laboratory. These compounds are growth factors for *Bacillus megaterium* and *Arthrobacter pascens*, respectively. Schizokinen consists of two residues of 1-amino-3-(*N*-acetylhydroxyamino)propane (**3a**) linked to the two terminal carboxyl groups of a citric acid residue by amide bonds.[10] Similarly, arthrobactin is composed of two 1-amino-5-(*N*-acetylhydroxyamino)pentane (**3b**) residues linked to citric acid. The 1-amino-*n*-(*N*-acetylhydroxyamino)alkane fragments were initially considered to constitute the main challenge in the synthesis of **1** and **2**. Conceptually, the suitably protected forms **4a** and **4b** can be derived from the alkylation of O-protected hydroxamates with derivatives of commercially available amino alcohols **5a,b** (eq 1).



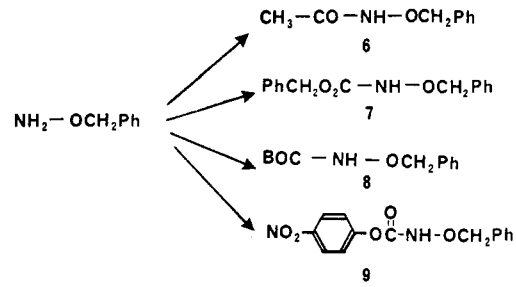
4 a (n = 3)
b (n = 5)

5 a (n = 3)
b (n = 5)

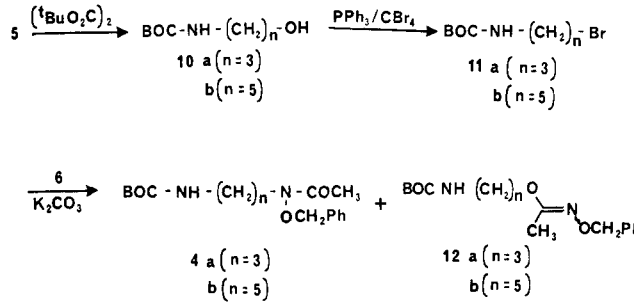
(1)

However, alkylation of O-substituted hydroxamates may occur on the carbonyl oxygen as well as on the nitrogen.[15] Thus, control over this feature was most important for our synthetic purpose, and a minimum requirement of predominant N-alkylation was essential. Consequently, studies related to the alkylation of hydroxamates were

Scheme I



Scheme II



performed by varying the leaving group on the alkylating agent, the base which generated the hydroxamate anion, and the acyl group of the hydroxamate.

In addition to the hydroxyamino fragments, a citric acid component was required which was activated at both terminal carboxyl groups and protected at the internal carboxyl and hydroxyl groups. Coupling of such a synthon with **4a** or **4b** followed by complete deprotection was expected to provide schizokinen (**1**) and arthrobactin (**2**).

## Results and Discussion

**Preparation of the Hydroxylamine Compounds.** As in the synthesis of aerobactin,[14] the benzyl group was chosen as the hydroxamate O-substituent because of its stability toward planned reactions and yet its ease of eventual removal. The required primary *O*-benzyl hydroxamates were prepared by the direct acylation of *O*-benzylhydroxylamine (OBHA, Scheme I). In this manner, O-benzyl acetohydroxamate (**6**) and *O*-benzyl-*N*-(carbobenzyloxy)hydroxylamine (**7**) have been previously prepared.[14,16] *O*-Benzyl-*N*-(*tert*-butoxycarbonyl)hydroxylamine (**8**) was prepared by the acylation of OBHA with di-*tert*-butyl dicarbonate in THF. *O*-Benzyl-*N*-[*p*-(nitrophenyl)carbobenzoxy]hydroxylamine (**9**) was prepared by acylation of OBHA with *p*-nitrobenzyl chloroformate.

Hydroxamate alkylations were performed by two methods; treatment of the corresponding hydroxamate anion with an alkyl halide and direct alkylation of hydroxamates with alcohols by using azodicarboxylates and triphenylphosphine (TPP).[14] In the first approach (Scheme II), the amino group of **5** was protected with the *tert*-butoxycarbonyl (Boc) group to provide **10**. The alcohol **10** was then converted to the bromide **11** with TPP and $CBr_4$. Treatment of **11** with O-benzyl acetohydroxamate (**6**) and $K_2CO_3$ in acetone containing a catalytic amount of KI[14] provided alkylated hydroxamates in 75–85% yield. However, a 4:1 ratio of N- to O-alkylated products (**4** and **12**) was obtained. Isomers **4b** and **12b** were easily separated by chromatography, but **4a** and **12a**

(5) (a) Neilands, J. B. *J. Am. Chem. Soc.* **1952**, *74*, 4846. (b) Rogers, S.; Neilands, J. B. *Biochemistry* **1964**, *3*, 1850.
(6) Atkins, C. L.; Neilands, J. B. *Biochemistry* **1968**, *7*, 3734.
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(9) Snow, G. A. *Bacteriol. Rev.* **1970**, *34*, 99–125.
(10) (a) Mullis, K. B.; Pollack, J. R.; Neilands, J. B. *Biochemistry* **1971**, *10*, 4894. (b) Mullis, K. B. "Schizokinen: Structure and Synthetic Works"; Ph.D. Thesis; University of California: Berkeley, 1973. (c) Nielands, J. B., personal communication.
(11) Linke, W. D.; Crueger, A.; Diekmann, H. *Arch. Microbial.* **1972**, *85*, 44. It should be noted that the $^1H$ NMR spectrum reported has the δ values mislabeled.
(12) Bickel, H.; Hall, G. E.; Keller-Schierlein, W.; Prelog, V.; Vischer, E.; Wettstein, A. *Helv. Chim. Acta* **1960**, *43*, 2129.
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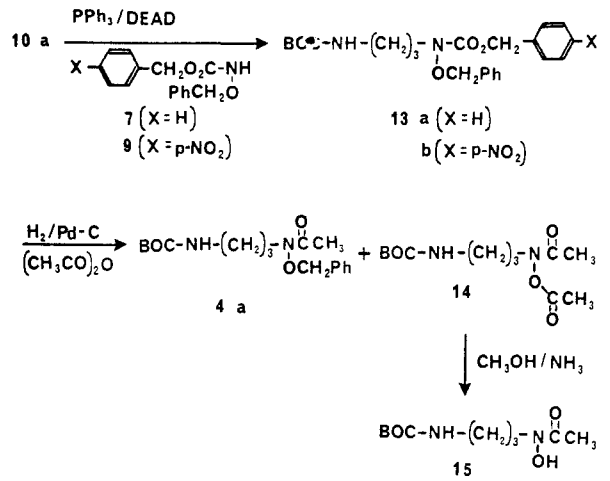
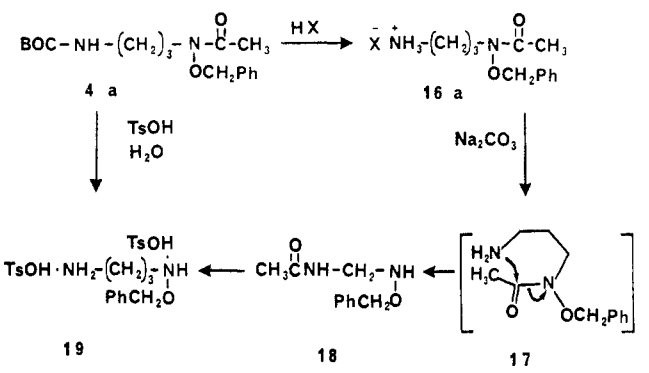
(16) Nicolaus, B. J. R.; Pagant, G.; Testa, E. *Helv. Chim. Acta* **1962**, *45*, 1381.

Scheme III



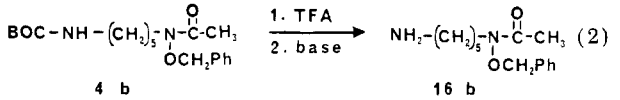
Scheme IV



were not. After the initial chromatography of **4a** and **12a**, fractions were obtained which were isographic on TLC ($R_f$ 0.24; hexanes/ethyl acetate, 65:35), but the $^1$H NMR spectrum clearly indicated the presence of both **4a** and **12a**. Repetitive chromatography eventually provided **4a** in 40–50% yield. Several different base and solvent system combinations were subsequently tried for the alkylation of **11a**, but none improved the N- to O-alkylation ratio.

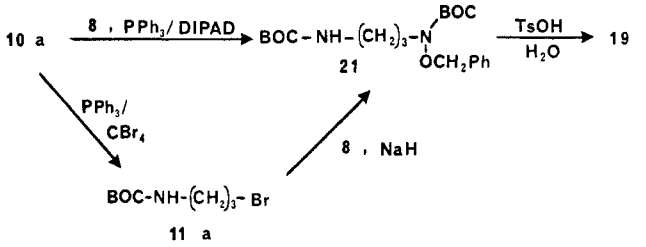
Attempted alkylation of *O*-benzyl acetohydroxamate (**6**) with **10** in the presence of DEAD/TPP gave predominant O-alkylation. However, the DEAD/TPP-mediated alkylation of the *O*-benzyl-*N*-(alkoxycarbonyl)hydroxylamines **7** and **9** with **10a** (Scheme III) gave the desired N-alkylated products **13a** and **13b** in 70–90% yields with no competitive O-alkylation. Careful catalytic hydrogenation of **13a** with 5% Pd/C selectively removed the carbobenzyloxy (Cbz) group. When the reaction was performed in the presence of acetic anhydride, the desired N-acetylated product **4a** was obtained in 65% yield. Longer hydrogenation removed both benzyl groups to provide the diacetate **14**. Methanolysis of **14** with a catalytic amount of $NH_3$ gave the hydroxamic acid **15** in quantitative yield. The same sequence was attempted by starting with the *p*-nitrobenzyl carbamate **13b**, but, surprisingly, less selective hydrogenation was observed.

Mild acid treatment was anticipated to remove the Boc protecting group from **4a** and **4b** to provide the free amines **16a** and **16b**, respectively. Indeed, treatment of **4b** with trifluoroacetic acid (TFA) gave **16b** cleanly (eq 2). How-

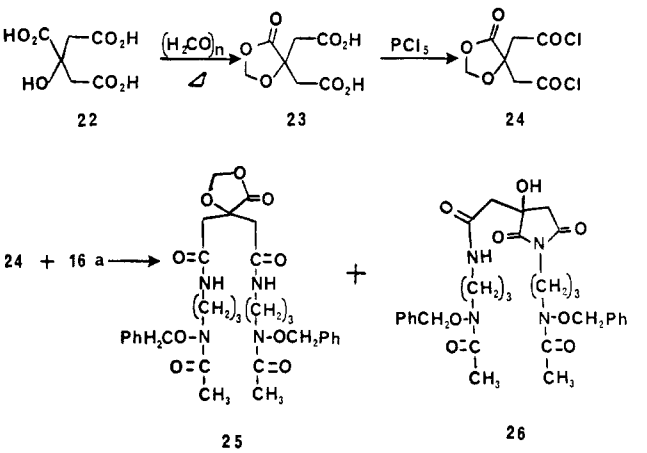


ever, the reaction of **4a** with either TFA or *p*-toluenesulfonic acid (TsOH) followed by the usual workup gave the rearranged product **18** which apparently resulted from acyl transfer (Scheme IV). Further treatment of **18** with TsOH (or TsOH·$H_2O$) gave the disalt **19**. Compound **19** could be obtained directly from **4a** or the diBoc-protected analogue **21** (Scheme V) with excess TsOH·$H_2O$. Compound **21** was obtained in 41% yield by DIPAD (diisopropyl azodicarboxylate)/TPP-mediated reaction of alcohol **10a** with the *O*-benzyl-*N*-(*tert*-butoxycarbonyl)hydroxylamine (**8**). Finally, in contrast to the reactions of **4a** with TFA or TsOH, treatment of **4a** with anhydrous HCl gave **16a** (X = Cl) in 97% yield.

Scheme V



Scheme VI



**Citric Acid Derivatives and the Coupling Reactions.** Only two of the carboxyl groups of citric acid **22** are involved in the amide linkages of schizokinen and arthrobactin. Consequently, the remaining carboxylic acid and hydroxyl groups must be protected during the synthesis. Anhydromethylenecitric acid (**23**), readily prepared from citric acid and paraformaldehyde,[18] was considered an appropriate starting material. The corresponding diacid chloride **24** was obtained by treatment of **23** with $PCl_5$[17] (Scheme VI). Reaction of **24** with the amine **16a** (200 mol %, $Et_3N$, 0 °C, 2 h) provided two major products as indicated by TLC analysis. Spectral analysis after the workup indicated that one component was the desired material **25**, and the other appeared to be the imide **26**. Presumably **26** results from intramolecular opening of the anhydromethylene unit of **25**. Facile imide formation has been observed in several similar systems.[18,19,20,22] Attempted chromatographic separation of **25** and **26** on silica

(17) Freidlander *Fortschr. Teerfarben Fabr.* **1907**, *8*, 958.
(18) Nau, C. A.; Brown, E. B.; Bailey, J. R. *J. Am. Chem. Soc.* **1925**, *47*, 2596.
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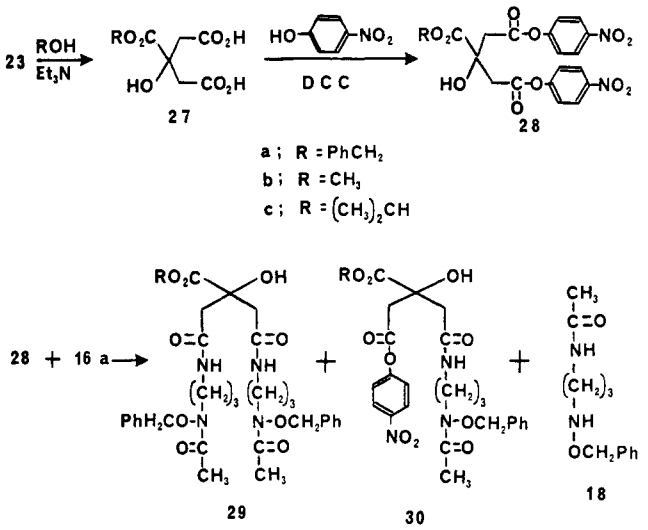
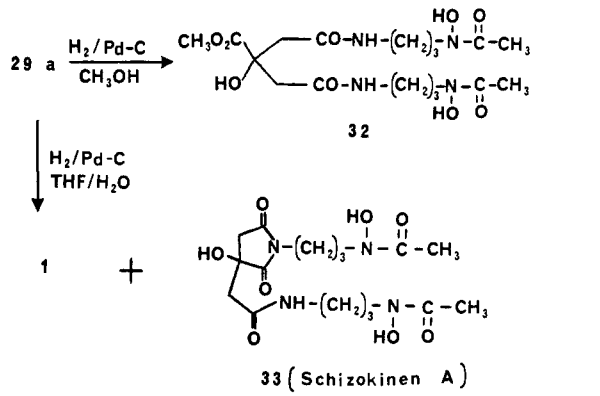
(21) Ludwig, B. J.; Dürsch, F.; Auerbach, M.; Tomeczek, K.; Berger, F. M. *J. Med. Chem.* **1967**, *10*, 556.
(22) Bickel, H.; Mertens, P.; Prelog, V.; Seibl, J.; Walser, A. *Tetrahedron, Suppl.* **1966**, *No. 8*, 171.

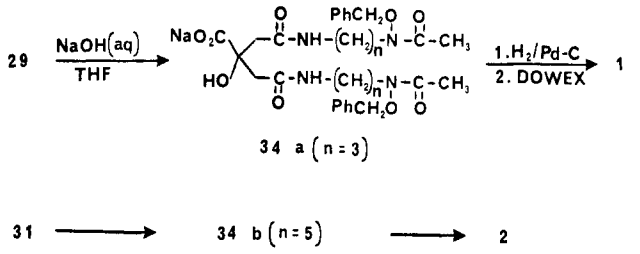
Scheme VII



Scheme VIII



Scheme IX



gel resulted in further conversion of **25** to **26**. In another control, treatment of **25** and **26** with $Et_3N$ for 1 h at room temperature resulted in complete conversion of **25** to **26**. Interestingly, during the original isolation of schizokinen, another unidentified ferric chloride positive component, schizokinen A, was obtained.[10] Schizokinen A reportedly could also be prepared from schizokinen by heating. Our observation of the ease of formation of the imide **26**, coupled with comparison of the chemical and spectral properties of **26** and those reported for schizokinen A, prompted us to suggest the imide structure (debenzylated **26**) for schizokinen A. Further comparison of the properties of debenzylated material **33** (Scheme VIII) with data provided by Professor Nielands[10b,c] confirmed **33** as the structure for schizokinen A.

In order to avoid formation of imide **26**, we considered other protected citric acid derivatives. Thus, reaction of anhydromethylenecitric acid (**23**) with a variety of alcohols in the presence of excess $Et_3N$ produced the monoesters **27** (Scheme VII). The bis(*p*-nitrophenyl) esters **28** were then prepared by reaction of **27** with dicyclohexylcarbodiimide (DCC) and *p*-nitrophenol. The reaction of **28a** and the amine **16a** in the presence of a number of tertiary bases gave three products and recovered ester **28**. The desired product **29** and the monoamide **30** were obtained in only ~10% yield. The major product was **18** which again appeared to result from intramolecular acyl transfer of **16a**. However, no imides were obtained nor were products observed which would result from attack of the hydroxylamine portion of **18** on the mono- or bis(*p*-nitrophenyl) esters **30** and **28**, respectively.

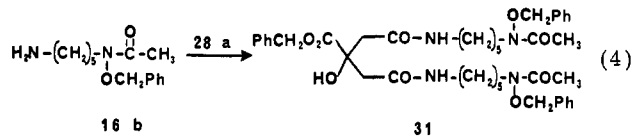
This latter observation prompted us to attempt the coupling of **28** with the previously prepared 1-amino-3-[(benzyloxy)amino]propane **19**. Indeed, the reaction of **28a** with **19a** followed by acetylation with acetic anhydride did provide the desired bis amide **29a** (eq 3). Spectral analysis

$$28 + 29 \rightarrow \xrightarrow{(CH_3CO)_2O} 26 + 29 \qquad (3)$$

of the crude reaction mixture also indicated the succinimide **26**. Attempted chromatographic purification of **29** again resulted in its conversion of **26**. In fact, just dissolving the mixture in polar protic solvents like 2-propanol promoted imide formation. Similar results were obtained upon attempting the coupling reaction with the methyl ester **28b**.

In order to minimize the imide formation, we decided to attempt the coupling reaction of **19** with **28c**, the bis(*p*-nitrophenyl) ester containing the more hindered isopropyl group to protect the internal carboxyl group of the citric acid. The reaction was performed as before with subsequent addition of acetic anhydride to acetylate the hydroxylamine groups before the workup. In this case the desired product **29c** was obtained in 75.6% yield with no contamination by the imide **26**.

In contrast to the problems associated with the coupling of **28a** and **19**, the reaction of **28a** with **16b** [1-amino-5-[(benzyloxy)acetylamino]pentane] provided the desired protected arthrobactin **31** cleanly (eq 4). In this case the



(4)

free amine of **16b** could be used directly since it is not susceptible to the intramolecular acyl-transfer reaction observed with **16a**. Thus, the absence of added base to liberate the free amine appears to help avoid undesired imide formation. The longer hydrocarbon chain, or branching in the chain as in our aerobactin synthesis,[14] also seems to diminish competitive imide formation.

All that remained for the synthesis of schizokinen (**1**) and arthrobacin (**2**) was respective deprotection of **29** and **31**. Initial attempts at the catalytic hydrogenation of **29a** indicated that polar solvents were required to avoid precipitation of the product on the catalyst. However, when **29a** was hydrogenolyzed in methanol, the monomethyl ester **32** was obtained (Scheme VIII). This again indicated the lability of the internal protected carboxyl group. A change of the solvent to THF–$H_2O$ resulted in cyclization and eventual production of the imide **33** (schizokinen A) as the major product and very little of the desired schizokinen (**1**). Similarly direct hydrogenation of **31** did not produce arthrobactin (**2**) cleanly. Alternatively, **29c** and **31** were separately saponified with aqueous NaOH in THF. The resulting sodium carboxylates **34a** and **34b** were debenzylated with $H_2$ and Pd/C to provide schizokinen (**1**) and arthrobactin (**2**) cleanly (Scheme IX). Thus, the

carboxylate anions of **34a** and **34b** effectively prohibits the undesired imide formation.

In conclusion, the alkylation of O-substituted hydroxamates offers an attractive route to the constituents of the natural hydroxamate siderophores. The versatility of the resulting intermediates has been demonstrated by the total synthesis of the natural microbial iron chelators schizokinen and arthrobactin. The chemistry involved has also led to the determination of the structore of schizokinen A. Further studies are being directed toward the synthesis of analogues of the microbial iron chelators which may be clinically useful for teatment of iron overload.

## Experimental Section

**General Methods.** Melting points were taken on a Thomas-Hoover capilary melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 727B spectrophotometer. Proton NMR spectra were obtained on a Varian A60, EM-390 or XL-100 spectrometer in deuteriochloroform (unless otherwise stated) and are reported in parts per million downfield of internal tetramethylsilane ($\delta$ units).

Mass spectra were recorded on an AEI Scientific Apparatus MS902 or Du Pont DP 102 spectrometer. Elemental analyses were performed by Midwest Microlabs. Field desorption mass spectra were obtained by Mr. John L. Occolwitz (Eli Lilly and Co.).

***O*-Benzyl Acetohydroxamate (6).** This was prepared by the method of Nicolaus et al.[16] except that the product was purified by acid/base extraction rather than by vacuum distillation.

***O*-Benzyl-*N*-(carbobenzyloxy)hydroxylamine (7).** *O*-Benzylhydroxylamine hydrochloride (3.19 g, 0.02 mol) was suspended in dry acetonitrile (40 mL) and treated with pyridine (3.23 mL, 0.04 mol). After the mixture was cooled to 0 °C, benzyl chloroformate (2.85 mL, 0.02 mol) was added dropwise with stirring. The mixture was allowed to warm to room temperature and vigorously stirred for 24 h. Volatile components were evaporated, and the residue was taken up in ethyl acetate. This was washed twice with 0.6 N HCl, once with $H_2O$, once with 0.6 M $NaHCO_3$, and once again with $H_2O$. After the mixture was dried ($MgSO_4$) and the solvent evaporated, the residue was crystallized from ethyl acetate/hexane to yield **7**: 3.09 g (60%); colorless crystals; mp 66–67 °C (lit.[21] mp 65–68 °C); $^1H$ NMR ($CDCl_3$) $\delta$ 4.8 (s, 2 H), 5.12 (s, 2 H), 7.32 (s, 10 H), 7.63 (s, 1 H, NH).

***O*-Benzyl-*N*-(*tert*-butoxycarbonyl)hydroxylamine (8).** *O*-Benzylhydroxylamine hydrochloride (6.38 g, 0.04 mol) was suspended in THF/$H_2O$ (1:1, 80 mL) and treated with $NEt_3$ (triethylamine; 5.49 mL, 0.04 mol). Di-*tert*-butyl dicarbonate (8.72 g, 0.04 mol) dissolved in THF (20 mL) was added dropwise with stirring for 30 min at room temperature. After the addition was completed, the reaction mixture was allowed to stir 1.5 h more at room temperature. Volatile components were evaporated, and the residue was taken up in ethyl acetate. This was washed twice with 0.5 M citric acid and once with $H_2O$. After the mixture was dried ($MgSO_4$) and the solvent evaporated, the residue was crystallized from hexane to yield **8**: 8.20 g (92%); colorless crystals; mp 45–47 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.45 (s, 9 H), 4.84 (s, 2 H), 7.38 (s, 5 H), 7.75 (s, 1 H, NH). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.64; H, 7.70; N, 6.25.

***O*-Benzyl-*N*-(*p*-nitrobenzyloxycarbonyl)hydroxylamine (9).** *O*-Benzylhydroxylamine hydrochloride (3.19 g, 0.02 mol) was suspended in dry acetonitrile (40 mL) and treated with pyridine (3.23 mL, 0.04 mol). *p*-Nitrobenzyl chloroformate (4.31 g, 0.02 mol) dissolved in acetonitrile (20 mL) was added dropwise with stirring for 30 min at room temperature. After the addition was completed, the reaction mixture was allowed to stir for 24 h. Volatile components were evaporated, and the residue was taken into ethyl acetate. This was washed twice with 0.6 N HCl once with $H_2O$, once with 0.6 M $NaHCO_3$, and once again with $H_2O$. After the mixture was dried and the solvent evaporated, the residue was crystallized from ethyl acetate/hexane to yield **9**: 3.42 g (57%); light yellow crystals; mp 96–97 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 4.87 (s, 2 H), 5.23 (s, 2 H), 7.40 (s, 5 H), 7.67 (d, 2 H), 8.20 (d, 2 H).

**3-[(*tert*-Butoxycarbonyl)amino]-1-propanol (10a).** 3-Amino-1-propanol (7.5 g, 0.1 mol; Aldrich) was dissolved in THF/$H_2O$ (1:1, 150 mL). Di-*tert*-butyl dicarbonate (21.8 g, 0.1 mol; Sigma) dissolved in THF (50 mL) was added dropwise with stirring for 30 min at room temperature. After the addition was completed, the reaction mixture was allowed to stir 2 h more at room temperature. Volatile components were evaporated, and the residue was taken up in ethyl acetate. This was washed twice with 0.5 M citric acid and once with $H_2O$. After the mixture was dried ($MgSO_4$) and the solvent evaporated, the residue was an oil: 12.6 g (72%); $^1H$ NMR ($CDCl_3$) $\delta$ 1.43 (s, 9 H), 1.5–1.9 (m, 2 H), 3.23 (q, 2 H), 3.63 (t, 2 H), 4.17 (s, 1 H, OH), 5.70 (s, 1 H, NH).

**5-[(*tert*-Butoxycarbonyl)amino]-1-pentanol (10b).** 5-Amino-1-pentanol (10.31 g, 0.1 mol; Aldrich) was dissolved in acetonitrile (200 mL). Di-*tert*-butyl dicarbonate (21.8 g, 0.1 mol) dissolved in acetonitrile (50 mL) was added dropwise with stirring for 30 min and the mixture allowed to stir 24 h at room temperature. Volatile components were evaporated, and the residue was taken up in ethyl acetate. This was washed twice with 0.5 M citric acid and once with $H_2O$. After the mixture was dried ($MgSO_4$) and the solvent evaporated, the residue was vacuum desiccated overnight to yield an oil: 18.70 g (92%); $^1H$ NMR ($CDCl_3$) $\delta$ 1.2–1.7 (m, 15 H), 3.08 (q, 2 H), 3.58 (t, 2 H), 3.97 (s, 1 H, OH), 5.42 (s, 1 H, NH).

**3-[(*tert*-Butoxycarbonyl)amino]-1-propyl Bromide (11a).** 3-[(*tert*-Butoxycarbonyl)amino]-1-propanol (**10a**; 6.4 g, 0.0365 mol) and $PPh_3$ (12.45 g, 0.0485 mol) were dissolved in dry THF (150 mL) and treated dropwise with $CBr_4$ (15.75 g, 0.0475 mol) in acetonitrile (60 mL) such that the temperature did not rise much above ambient. After the mixture was stirred at room temperature for 6 h, the solvent was evaporated, and the residue was chromatographed on silica gel (4 × 60 cm), eluting with ethyl acetate/hexane (20:80). **11a** was crystallized from hexane: 6.52 g (75%); mp 38–39 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.43 (s, 9 H), 1.8–2.2 (m, 2 H), 3.1–3.4 (m, 4 H), 5.10 (s, 1 H, NH). Anal. Calcd for $C_8H_{16}NO_2Br$: C, 40.35; H, 6.77; N, 5.88. Found: C, 40.17; H, 7.01; N, 5.89.

**5-[(*tert*-Butoxycarbonyl)amino]-1-pentyl Bromide (11b).** 5-[(*tert*-Butoxycarbonyl)amino]-1-pentanol (**10b**; 2.03 g, 10 mmol) and $PPh_3$ (3 g, 11.5 mmol) were dissolved in dry THF (50 mL). $CBr_4$ (3.8 g, 11.5 mmol) in THF (15 mL) was added dropwise over 2 h at room temperature. The reaction was allowed to stir overnight. The solvent was evaporated, and the residue was chromatographed on silica gel (2 × 60 cm), eluting with ethyl acetate/hexanes (20:80). Compound **11b** was crystallized from hexane: 2.08 g (78%); mp 26–28 °C; $^1H$ NMR $\delta$ 1.2–1.7 (m, 13 H), 1.7–2.0 (m, 2 H), 3.15 (q, 2 H), 3.40 (t, 2 H), 4.80 (br s, 1 H, NH); mass spectrum (CI with Ar), *m/e* 210 (M − 55, for $HO_2C$–$NH_2^+$–$(CH_2)_5$–Br).

**1-[(*tert*-Butoxycarbonyl)amino]-3-[acetyl(benzyloxy)amino]propane (4a).** 3-[(*tert*-Butoxycarbonyl)amino]-1-propyl bromide (**11a**; 1.79 g, 7.5 mmol) *O*-benzyl acetohydroxamate (**6**; 2.5 g, 15 mmol), KI (0.2 g, 1.2 mmol), and anhydrous $K_2CO_3$ (5.52 g, 50 mmol) were placed in dry acetone (30 mL) and refluxed for 24 h. After filtration and evaporation, the residue was taken up in ether. This was washed twice with 0.5 N NaOH and once with $H_2O$. After the mixture was dried and the solvent evaporated, the residue was chromatographed on silica gel (2 × 50 cm), eluting with $CH_2Cl_2$/*i*-PrOH (98:2) *several times*. The product was obtained as a colorless oil: 1.09 g (45%); $^1H$ NMR ($CDCl_3$) $\delta$ 1.43 (s, 9 H), 1.6–1.9 (m, 2 H), 2.00 (s, 2 H), 3.12 (q, 2 H), 3.71 (t, 2 H), 4.82 (s, 2 H), 5.12 (s, 1 H, NH), 7.45 (s, 5 H); mass spectrum (CI with Ar), *m/e* 323 (M + 1). In addition, a small amount of the hydroximate **12a** was obtained from the earlier column fraction (about 11%). Compound **12a** was crystallized from chloroform/hexane: mp 86.5–88.5 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.43 (s, 9 H), 1.92 (s, 3 H), 1.7–2.0 (m, 2 H), 3.30 (q, 2 H), 4.10 (t, 2 H), 4.98 (s, 2 H), 5.40 (s, 1 H, NH), 7.40 (s, 5 H).

**1-[(*tert*-Butoxycarbonyl)amino]-5-[acetyl(benzyloxy)amino]pentane (4b).** 5-[(*tert*-Butoxycarbonyl)amino]-1-pentyl bromide (**11b**; 1.33 g, 5 mmol), *O*-benzyl acetohydroxamate (**6**; 1.65 g, 10 mmol), KI (0.17 g, 1 mmol), and anhydrous $K_2CO_3$ (3.68 g, 40 mmol) were placed in dry acetone (25 mL) and refluxed for 24 h. The reaction mixture was filtered, evaporated, dissolved in ether, and washed with 0.5 N NaOH to remove excess **6**. After

the mixture was dried and the solvent evaporated, the residue was chromatographed on silica gel (2 × 50 cm), eluting with ethyl acetate/hexane (35:65) to yield the product **4b**: colorless oil; 1.08 g (62%); $^1$H NMR ($CDCl_3$) δ 1.1–1.8 (m, 15 H), 2.07 (s, 3 H), 3.08 (q, 2 H), 3.72 (t, 2 H) 4.80 (s, 2 H), 4.90 (s, 1 H, NH), 7.41 (s, 5 H). Anal. Calcd for $C_{19}H_{30}N_2O_4$: C, 65.11; H, 8.63; N, 7.99. Found: C, 64.99; H, 8.85; N, 7.96.

**General Procedure for Alkylation of Hydroxamates 7–9 with Alcohol 10a Mediated by $PPh_3$/DEAD or Diisopropyl Azodicarboxylate (DIPAD).** The alcohol **10a** as an approximately 0.1 M solution in dry THF was treated with the hydroxamate (**7**, **8**, or **9**, 1.2 equiv) and $PPh_3$ (1.3 equiv). To this solution was added DEAD or DIPAD (1.3 equiv in a small amount of dry THF) dropwise over about 0.5 h with stirring at room temperature. The reactions were generally complete within an additional hour at room temperature, but if TLC indicated the presence of the starting alcohol, the reaction was left overnight. Products were characterized after isolation by spectral and elemental analysis when possible. Chromatography on silica gel was the standard method of isolation when **7** was alkylated with **10a** by the general procedure. **13a** was isolated in 78% yield by chromatography, eluting with ethyl acetate/hexane (20:80). The product was a colorless oil: $^1$H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 1.6–1.9 (m, 2 H), 2.01 (s, 3 H), 3.11 (q, 2 H), 3.53 (t, 2 H), 4.86 (s, 3 H, including NH), 5.23 (s, 2 H), 7.42 (2 s, 10 H). Anal. Calcd for $C_{20}H_{30}N_2O_5$: C, 66.65; H, 7.30; N, 6.76. Found: C, 66.34; H, 7.37; N, 6.64.

When compound **9** was alkylated with **10a** by the general procedure, **13b** was isolated in 89% yield by chromatography, eluting with $CH_2Cl_2$. The product was a colorless oil: $^1$H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 1.6–1.9 (m, 2 H), 3.13 (q, 2 H), 3.57 (t, 2 H), 4.75 (s, 1 H, NH), 4.90 (s, 2 H), 5.30 (s, 2 H), 7.43 (s, 5 H), 7.55 (d, 2 H), 8.30 (d, 2 H).

When compound **8** was alkylated with **10a** by the general procedure, **21** was isolated in 41% yield by chromatography, eluting with ethyl acetate/hexane (20:80). The product was a colorless oil: $^1$H NMR ($CDCl_3$) δ 1.43 (s, 9 H), 1.50 (s, 9 H), 1.60–1.80 (m, 2 H), 3.10 (q, 2 H), 3.47 (t, 2 H), 4.83 (s, 3 H, including NH), 7.40 (s, 5 H). Anal. Calcd for $C_{20}H_{32}N_2O_5$: C, 63.13; H, 8.48; N, 7.36. Found: C, 62.99; H, 8.59; N, 7.16.

Compound **21** can be prepared from **11a** (1 equiv) and **8** (1.1 equiv) by treatment with NaH (1.3 equiv) in DMF at 100 °C for 3 h. The reaction mixture was taken into ethyl acetate and washed with $H_2O$ five times and once with brine. After the mixture was dried and the solvent evaporated, the residue was chromatographed on silica gel, eluting with ethyl acetate/hexane (20:80). The product **21** was isolated in 70% yield.

**General Procedure for Exchange of the Cbz Group with an Acetyl Group.** Compound **13**, as an approximately 0.1 M solution in ethyl acetate, was treated with $Ac_2O$ (2.5 equiv) and 5% Pd on carbon (15–20% of the weight of **13**) and stirred under 1 atm of $H_2$ at 0 °C for 3 h. The reaction mixture was filtered and evaporated, and the residue was taken up in ether. This was washed twice with 0.5 M NaOH and once with $H_2O$ and brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, the crude product was chromatographed on silica gel, eluting with ethyl acetate/hexane (35:65). When **13a** was converted to **4a** by the general procedure, **4a** was isolated in 65% yield (optimum). When **13b** was converted to **4a** by the general procedure, **4a** was isolated in 55% yield (optimum). This product had identical spectral and TLC properties when compared with those for the previous preparation of **4a**. Compound **14** can be prepared under the same conditions with a longer reaction time (5 h). If the reaction mixture was subsequently treated with $CH_3OH$ and a catalytic amount of $NH_3$ for an additional 5 h, compound **15** was isolated as an oil in quantitative yield: $^1$H NMR (acetone-$d_6$) δ 1.40 (s, 9 H), 1.6–1.9 (m, 2 H), 2.04 (s, 3 H), 3.08 (q, 2 H), 3.63 (t, 2 H), 6.0 (s, 1 H, OH).

**1-Amino-5-[acetyl(benzyloxy)amino]pentane (16b).** 1-[(*tert*-Butoxycarbonyl)amino]-5-[acetyl(benzyloxy)amino]pentane (**4b**; 0.526 g, 1.5 mmol) was stirred with $CF_3CO_2H$ (2.0 mL) for 15 min at room temperature. Excess $CF_3CO_2H$ was removed by rotary evaporation. The residue was partitioned between $CHCl_3$ (30 mL) and 10% $Na_2CO_3$. The chloroform layer containing free amine **16b** was dried ($K_2CO_3$) and concentrated to give 0.345 g (92%) of **16b** as an oil: $^1$H NMR ($CDCl_3$) δ 1.1–1.8 (m, 6 H), 2.07 (s, 3 H), 2.63 (t, 2 H), 3.63 (t, 2 H), 4.80 (s, 1 H), 7.42 (s, 5 H).

**1-Amino-3-[acetyl(benzyloxy)amino]propane Hydrochloride Salt (16a).** 1-[(*tert*-Butoxycarbonyl)amino]-3-[acetyl(benzyloxy)amino] propane (**4a**; 1.8 g, 5.58 mmol) was dissolved in anhydrous ether (30 mL) at 0 °C. A stream of HCl gas was passed through this solution for 15–30 min. The solvent was evaporated to provide **16a** in 97% yield as a white solid (very hygroscopic): mp 69–72 °C; $^1$H NMR ($D_2O$) δ 1.7–2.1 (m, 2 H), 2.0 (s, 3 H), 2.92 (t, 2 H), 3.73 (t, 2 H), 4.83 (s, 2 H), 7.43 (s, 5 H). Anal. Calcd for $C_{12}H_{19}N_2O_2Cl$: C, 55.70; H, 7.40; N, 10.83; Cl, 13.70. Found: C, 55.24; H, 7.19; N, 10.53; Cl, 13.89.

**1-(Acetylamino)-3-[(benzyloxy)amino]propane (18).** Compound **4a** (0.322 g, 1 mmol) was stirred with $CF_3CO_2H$ (2 mL) for 15 min at room temperature. Excess $CF_3CO_2H$ was removed by rotary evaporation. The residue was partitioned between $CHCl_3$ (30 mL) and 10% $Na_2CO_3$. After the mixture was dried ($MgSO_4$) and the solvent evaporated, the residue contained more than two products. It was chromatographed on silical gel, eluting with $CH_2Cl_2$/*i*-PrOH (90:10). Compound **18** was isolated in 52% yield as a colorless oil: $^1$H NMR ($CDCl_3$) δ 1.5–1.8 (m, 2 H), δ 1.89 (s, 3 H), 2.92 (t, 2 H), 3.25 (q, 2 H), 4.70 (s, 2 H), 5.4 (s, 1 H, OH), 6.37 (s, 1 H, NH). Compound **18** was also isolated from the coupling reaction (see Scheme VII) and had the same spectral and TLC properties.

**1-Amino-3-[(benzyloxy)amino]propane *p*-Toluenesulfonic Acid Double Salt (19). (a) Preparation from 4a.** Compound **4a** (0.322 g, 1 mmol) was dissolved in dioxane (10 mL), and TsOH (0.379 g, 2.2 mmol) was dissolved in dioxane (10 mL) separately. Both solutions were combined, and $H_2O$ (1.5 equiv) was added. The reaction mixture was allowed to stand for 3 days. Ether was added to the reaction mixture, and **19** crystallized out: 72% yield (0.384 g); mp 150–152 °C; $^1$H NMR ($D_2O$) δ 1.9–2.3 (m, 2 H), 2.40 (s, 6 H), 3.15 (t, 2 H), 3.50 (t, 2 H), 5.21 (s, 2 H), 7.57 (d, 4 H), 7.71 (s, 5 H), 7.95 (d, 4 H). Anal. Calcd for $C_{24}H_{32}N_2O_7S_2 \cdot 0.5H_2O$: C, 54.02; H, 6.23, N, 5.25. Found: C, 53.93; H, 6.09; N, 5.34.

**(b) Preparation from 18.** Compound **18** (0.11 g, 0.5 mmol) and TsOH (0.189 g, 1.1 mmol) were dissolved in dioxane/$H_2O$ (7:3, 10 mL). The reaction mixture was allowed to stand for 7 days. After evaporation of the solvent, the residue was recrystallized from methanol/ether to provide **19** in 75% yield (0.20 g).

**(c) Preparation from 21.** Compound **21** (1.18 g, 3.1 mmol) and TsOH (1.17 g, 6.82 mmol) were dissolved in dioxane/$H_2O$ (7:3, 50 mL). The solvent was evaporated with rotary evaporater at 50 °C. After removal of solvent, a white precipitate was formed which was recrystallized from methanol/ether to yield 1.35 g (81.7%) of **19**. All three preparations provided **19** with the same melting point and $^1$H NMR spectrum.

**Coupling Reaction of Anhydromethylenecitryl Chloride 24 with Amine Hydrochloride 16a.** Amine hydrochloride **16a** (0.382 g, 1.47 mmol) and anhydromethylenecitryl chloride **24**[17,18] (0.177 g, 0.73 mmol) were dissolved in $CHCl_3$ (50 mL). $Et_3N$ (0.297 g, 2.94 mmol) in $CHCl_3$ (25 mL) was added dropwise with stirring at 0 °C. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred an additional 1 h. Then the solution was washed once with 0.5 M citric acid (aqueous), once with $H_2O$, 0.5 M $NaHCO_3$, and finally with brine. Then it was dried ($MgSO_4$) and evaporated to give a yellow oil which was contaminated by other side products ($^1$H NMR showed at least 90% desired product **25**). The oil was chromatographed on silica gel (2 × 50 cm), eluting with $CH_2Cl_2$/*i*-PrOH (90:10). The separation was not successful due to the decomposition of **25**.

**2-Hydroxy-1,2,3-propanetricarboxylic Acid 2-Benzyl Ester (27a).** Anhydromethylenecitric acid **23**[18] (2.04 g, 0.10 mmol) and $Et_3N$ (3.06 mL, 22 mmol) were dissolved in $CHCl_3$ (30 mL). Benzyl alcohol (3.24 g, 30 mmol) was added, and the reaction mixture was refluxed for 3 days. The reaction mixture was added to ethyl acetate (100 mL) and extracted twice with 0.5 M $NaHCO_3$ (100 mL). The aqueous layer was adjusted to pH 2 with concentrated HCl, and then it was reextracted with ethyl acetate (200 mL) three times. After the mixture was dried ($MgSO_4$) and the solvent evaporated the residue was recrystallized from ethyl acetate (or ethyl acetate/hexane) to yield **27a**: 1.61 g (57%); colorless crystals; mp 128–129 °C; $^1$H NMR ($CDCl_3$) δ 2.88 (d, 4 H), 5.20 (s, 2 H), 7.40 (s, 5 H), 7.87 (br s, 3 H, $CO_2H$ and OH).

**2-Hydroxy-1,2,3-propanetricarboxylic Acid 2-Methyl Ester (27b).** Anhydromethylene citric acid **23** (0.51 g, 2.5 mmol) and $Et_3N$ (0.8 mL, 5.5 mmol) were dissolved in methanol (20 mL) and refluxed for 12 h. The reaction mixture was passed through a column of Dowex 50-X8 ($H^+$); 50-mL bed) and washed through with a further 60 mL of $H_2O$. The solution was evaporated at reduced pressure. The residue was recrystallized from methanol/ether to yield **27b**: 0.38 g (74%); mp 166–168 °C (lit.[23] mp 167 °C); $^1H$ NMR (acetone-$d_6$) $\delta$ 2.87 (d, 4 H), 3.75 (s, 3 H).

**2-Hydroxy-1,2,3-Propanetricarboxylic Acid 2-Isopropyl Ester (27c).** Anhydromethylene citric acid **23** (0.51 g, 2.5 mmol) and $Et_3N$ (0.8 mL, 5.5 mmol) were dissolved in *i*-PrOH (15 mL) and refluxed for 21 h. The reaction mixture was passed through a column of Dowex 50-X8 ($H^+$; 50-mL bed) and washed through with a further 60 mL of $H_2O$. The solution was evaporated at reduced pressure. The residue was recrystallized from acetone/hexane to yield **27c**: 0.44 g (75%); colorless crystals; mp 126–128 °C; $^1H$ NMR (acetone-$d_6$) $\delta$ 1.27 (d, 6 H), 2.88 (d, 4 H), 4.9–5.2 (m, 1 H).

**General Procedure for the Preparation of Citric Acid Triester Derivatives 28.** The diacid **27** and *p*-nitrophenol (1.3 equiv) were dissolved in dry acetonitrile to give a 0.1 M solution. The solution was cooled in an ice bath, and DCC (1.3 equiv in a small amount of dry acetonitrile) was added all at once. The solution was stirred 0.5 h at 0 °C, warmed to room temperature, and stirred an additional 5 h. After the dicyclohexyl urea was filtered off, the residue was chromatographed on silica gel eluting with $CH_2Cl_2$. The solution containing product was washed five times with saturated $NaHCO_3$ and brine and dried ($MgSO_4$). The solvent was evaporated, and the residue was recrystallized from ethyl acetate/hexane to give **28**. **28a**: 41% yield; mp 142.5–143.5 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 3.32 (d, 4 H), 5.28 (s, 2 H), 7.32 (d, 4 H), 7.40 (s, 5 H), 8.32 (d, 4 H). **28b**: 40% yield; mp 124–126 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 3.22 (s, 4 H), 3.90 (s, 3 H), 4.10 (s, 1 H), 7.32 (d, 4 H), 8.32 (d, 4 H). **28c**: 42% yield; mp 138–140 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.30 (d, 6 H), 3.21 (s, 4 H), 4.13 (s, 1 H, OH), 5.0–5.3 (m, 1 H), 7.30 (d, 4 H), 8.30 (d, 4 H).

***Coupling Reaction of Amine Hydrochloride* 16a with Activated Ester 28a.** Activated ester **28a** (100 mg, 0.194 mmol) and amine hydrochloride **16a** (110 mg, 0.444 mmol) were suspended in acetonitrile (20 mL), and $Et_3N$ (0.116 mL, 0.832 mmol) in acetonitrile (5 mL) was added dropwise. The resulting solution was allowed to stir for 3.5 h at room temperature. After the solvent was evaporated, preparative TLC (silica, 90% ethyl acetate–10% *i*-PrOH) was performed. Most of the product obtained was the acyl-transfer product **18**. Very small amounts (<10%) of **29** and **30** were isolated. **29a**: $^1H$ NMR ($CDCl_3$) $\delta$ 1.6–1.9 (m, 4 H) 2.07 (s, 6 H), 2.72 (s, 4 H), 3.20 (q, 4 H), 3.68 (t, 4 H), 4.82 (s, 4 H), 5.20 (s, 2 H), 7.10 (t, 2 H, NH), 7.36 (s, 5 H), 7.43 (s, 10 H). **30a**: $^1H$ NMR ($CDCl_3$) $\delta$ 1.6–1.9 (m, 2 H), 2.11 (s, 2 H), 2.74 (d, 2 H), 3.0–3.3 (m, 4 H), 3.70 (t, 2 H), 4.83 (s, 2 H), 5.24 (s, 2 H), 7.17 (d, 2 H), 7.38 (d, 10 H), 8.25 (d, 2 H).

**Coupling Reaction of Amine *p*-Toluenesulfonic Acid Double Salt 19 with Activated Ester 28.** Activated ester **28** and **19** (2.4 equiv) were suspended in acetonitrile (~0.1 M solution). $Et_3N$ (6.8 equiv) in acetonitrile was added dropwise. The solution was allowed to stir 1 h at room temperature. It was then taken into ethyl acetate and washed with 10% $Na_2CO_3$ several times and once with $H_2O$ and brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, the residue was dissolved in acetonitrile, and acetic anhydride (3 equiv) was added. This solution was allowed to stir 2–3 h at room temperature. After evaporation the residue was chromatographed on silica gel, eluting with ethyl acetate/*i*-PrOH (90:10). When **19** was coupled with **28a**, two main products **26** and **29a**, were observed (85% yield, **26**/**29a** ratio of 5:7) **26**: oil; $^1H$ NMR ($CDCl_3$) $\delta$ 1.6–1.9 (m, 4 H), 2.05 (d, 6 H), 2.70 (s, 2 H), 2.82 (s, 2 H), 3.20 (t, 2 H), 3.35–3.75 (m, 6 H), 4.80 (d, 4 H), 7.13 (t, 1 H, NH), 7.42 (s, 10 H). When **19** was coupled with **28b**, two products, **26** and **29b**, were obtained (82% yield, **26**/**29b** ratio of 3:2 by $^1H$ NMR). When **19** was coupled with **28c** only one product, **29c**, was obtained in 75% yield without chromatography as a colorless oil. **29c**: $^1H$ NMR ($CDCl_3$) $\delta$ 1.24 (d, 6 H), 1.5–1.85 (m, 4 H), 2.07 (s, 6 H), 2.67 (s, 4 H), 3.20 (q, 4 H) 3.70 (t, 4 H), 4.81 (s, 4 H), 4.97–5.25 (m, 1 H), 7.0 (t, 2 H, NH), 7.42 (s, 10 H); IR (neat) 1730, 1640 $cm^{-1}$.

**Tribenzylarthrobactin 31.** Activated ester **28a** (0.27 g, 0.46 mmole) was dissolved in acetonitrile (30 mL). Amine **16b** (0.27 g, 1.07 mmol) in acetonitrile was added, followed by addition of $Et_3N$ (0.128 mL, 0.92 mmol). The reaction mixture was allowed to stir 2.5 h at room temperature. The reaction mixture was taken up in ethyl acetate (70 mL) and washed with phosphate buffer (pH 8.5, 1 M) several times and then once with water and brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, 0.329 g (95.6%) of pure **31** was isolated as an oil: $^1H$ NMR ($CDCl_3$) $\delta$ 1.2–1.8 (m, 12 H), 2.07 (s, 6 H), 2.67 (d, 4 H), 3.15 (q, 4 H), 3.63 (t, 4 H), 4.72 (s, 4 H), 5.18 (s, 2 H), 7.0 (t, 2 H, NH), 7.36 (s, 5 H), 7.44 (s, 10 H); IR (neat) 1730, 1640 $cm^{-1}$.

**Methylschizokinen 32.** Compound **29a** (18 mg, 0.026 mmol) was dissolved in methanol (15 mL) and treated with 5% Pd on carbon (7 mg). The mixture was stirred at room temperature under 1 atm of $H_2$ for 7 h, filtered, and evaporated to give **32** as a hydroscopic, slightly off-white powder: 9.6 mg (85%); $^1H$ NMR ($D_2O$) $\delta$ 1.7–1.9 (m, 4 H), 2.02 (s, 6 H), 2.64 (s, 4 H), 3.17 (t, 4 H), 3.45–3.75 (m, 7 H); IR ($CHCl_3$) 1730, 1630 $cm^{-1}$.

**Schizokinen A (33).** Compound **26** (90 mg, 0.154 mmol) was dissolved in THF/water (7:3, 15 mL) and treated with 5% Pd on carbon (90 mg). The reaction mixture was stirred at room temperature under 1 atm of $H_2$ for 3 h and then filtered and evaporated to give pure **33** (48 mg, 77%) as white hydroscopic powder: $^1H$ NMR ($D_2O$) $\delta$ 1.5–1.9 (m, 4 H), 2.03 (s, 6 H), 2.6–3.2 (m, 6 H), 3.4–3.8 (m, 6 H); IR ($CHCl_3$) 1780 (weak), 1710, 1625 $cm^{-1}$; paper chromatography $R_f$ 0.73 [butanol/water/acetic acid, 60:25:15 v/v (lit.[10] $R_f$ 0.74)]; mass spectrum (FD), *m/e* 402 ($M^+$), 403 (M + 1), 359 [M – ($CH_3C{\equiv}O^+$)], 445 [M + ($CH_3C{\equiv}O^+$)].

**Schizokinen (1).** Compound **29c** (55 mg, 0.086 mmol) was dissolved in THF (5 mL) and treated with NaOH (0.525 N, 175 $\mu$L). The reaction mixture was stirred for 2 h (reaction was followed by TLC). Without isolation and characterization of **34a**, the reaction mixture was treated with 5% Pd on carbon (50 mg) under 1 atm of $H_2$ for 3 h at room temperature. The reaction mixture was filtered and passed through a column of Dowex 50-X8 ($H^+$; 20-mL bed). After a further 30 mL of $H_2O$ was eluted, the solution was evaporated to give 31 mg (85%) of **1** as a powder. The 90-MHz $^1H$ NMR ($D_2O$)[10] and the IR spectra[24] were identical with those depicted in the literature for natural schizokinen. Paper chromatography (butanol/$H_2O$/acetic acid, 60:25:15, and *i*-PrOH/$H_2O$, 7:3) gave the same $R_f$ values (0.61, 0.66) as reported for the natural substance (0.60, 0.64):[10] mass spectrum (FD), *m/e* 402 (M - $H_2O$), 403 (M + 1 - $H_2O$), 445 [M - $H_2O$ + ($CH_3C{\equiv}O^+$)].

**Arthrobactin (2).** Compound **31** (120 mg, 0.161 mmol) was dissolved in THF (7 mL) and treated with 1 M NaOH (20 $\mu$L). The reaction mixture was stirred at room temperature for 2 h. Without isolation of **34b** the reaction mixture was treated with 5% Pd on carbon (120 mg) under 1 atm of $H_2$ for 3 h at room temperature. The reaction mixture was filtered and passed through a column of Dowex 50-X8 ($H^+$; 30-mL bed). After elution with 30 mL more of $H_2O$, the solution was evaporated at reduced pressure to give **2** as a hygroscopic, slightly off-white powder: 52.5 mg (68.6%). The 90-MHz $^1H$ NMR ($D_2O$) and IR spectra were in good agreement with those reported for the natural material.[11] In butanol/$H_2O$/acetic acid (60:25:15) and in *i*-PrOH/$H_2O$ (7:3) they gave $R_f$ values of 0.81 and 0.81, respectively: mass spectrum (FD), *m/e* 459 (M + 1 - $H_2O$), 458 (M - $H_2O$).

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**Registry No.** **1**, 35418-52-1; **2**, 39007-57-3; **4a**, 83948-50-9; **4b**, 83948-51-0; **5a**, 156-87-6; **5b**, 2508-29-4; **6**, 4797-81-3; **7**, 15255-86-4; **8**, 79722-21-7; **9**, 83948-52-1; **10a**, 58885-58-8; **10b**, 75178-90-4; **11a**, 83948-53-2; **11b**, 83948-54-3; **12a**, 83948-55-4; **12b**, 83948-56-5; **13a**,

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# New Construction of a Steroidal Ring System. Stereoselective Synthesis of (±)-Androstane-2,17-dione

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Intramolecular Diels–Alder reaction of the triene **3** afforded the tricyclic olefin **4** which, after deprotection of the ketal groups, was treated with ethylaluminum dichloride to give (±)-androstane-2,17-dione (**6**) stereoselectively.

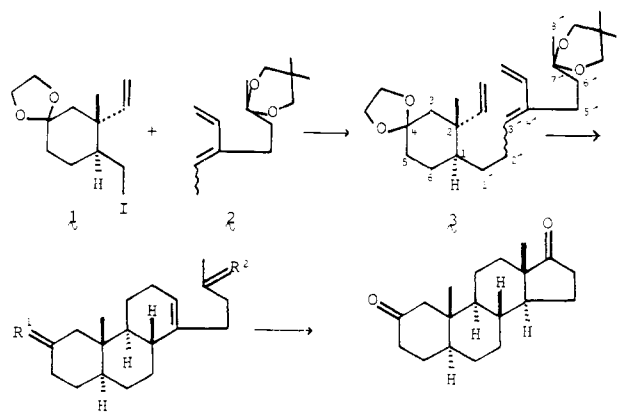
In a recent development toward the synthesis of steroids, the intramolecular cycloaddition reaction has played an important role because of its effective regio- and stereoselectivity. Among the numerous reports using it as a key step, much attention has been focused on the synthesis of A-aromatic steroids[1,2] such as estrone and estradiol and on the stereocontrolled construction of *trans*-hydrindan ring systems.[3] We now report a novel stereoselective synthesis of a nonaromatic steroid employing an intramolecular Diels–Alder reaction and a subsequent Lewis acid catalyzed ring-closure reaction as key steps.

## Results and Discussion

For the purpose of accomplishment of our synthetic strategy, illustrated in Scheme I, the dienophile **1** was prepared from Hagemann's ester according to the method reported by us,[4] whereas the diene **2** was synthesized as follows (Scheme II).

Ethyl 2,5,5-trimethyl-1,3-dioxane-2-acetate (**7**),[5] on treatment with lithium aluminum hydride (3 equiv) in tetrahydrofuran at ambient temperature afforded the alcohol **8**, which was then converted to the iodide **10** via the tosylate **9** by tosylation of **8** with *p*-toluenesulfonyl chloride (1.5 equiv) and pyridine (2 equiv) in methylene chloride

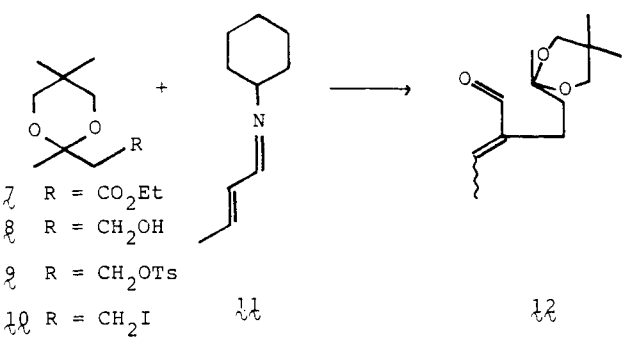
Scheme I



**4** $R^1 = O(CH_2)_2O$, $R^2 = OCH_2C(CH_3)_2CH_2O$

**5** $R^1 = R^2 = O$

Scheme II



**7** R = $CO_2Et$

**8** R = $CH_2OH$

**9** R = $CH_2OTs$

**10** R = $CH_2I$

and subsequent treatment of **9** with sodium iodide (5 equiv) in acetone (65% yield from **7**). Regioselective alkylation of crotonaldehyde with the iodide **10** has been carried out by using the Schiff base **11** and lithium diisopropylamide (1.1 equiv) under the conditions reported by Schlessinger[6] to afford the $\alpha$-alkylated product **12** in 45% yield. Wittig methylenation[7] of **12** with triphenylmethylphosphonium bromide (2.5 equiv) and *n*-butyl-

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