The reaction of **1b** was examined in CTABr, using excess substrate so that there was a rapid evolution of *p*-nitrophenol followed by a slow reaction as the acylated intermediate was hydrolyzed to regenerate the catalyst (Scheme I). The kinetic analysis under burst conditions shows that the catalytic efficiency of **1b** mainly depends on acylation process at pH 7.30 (Table II).

Figure 1 shows the pH–rate profiles for the reactions of **3a** with **1b** and **2** in the presence of CTABr. The log k_c–pH profiles in Figure 1 indicate that the catalytic action of **1b** involves both of the imidazole and hydroxamic acid groups over the pH range studied. It is noteworthy that the stereoselective behavior of **1b** corresponds to a bell-shaped curve with the maximum at near pH 6.2. This behavior is quite different from that of **2** (the stereoselectivity does not depend on pH). The above observation indicates that at lower pH (<7) the stereoselectivity of **1b** is determined by the reactivity of the imidazole group rather than that of the hydroxamic acid group. However, at higher pH (>7), the reaction occurs mostly at the hydroxamic acid site as mentioned above.

The present study demonstrates an interesting kinetic property of the optically active bifunctional catalyst toward the enantiomeric amino acid ester derivatives in the presence of CTABr, and a mechanism is suggested for the stereselective behavior involving acylation of the optically active imidazole and hydroxamic acid functions because the stereoselectivity depends on pH. A detailed study of the mechanisms involving the deacylation process is a future problem.

Registry No. **1a**, 55258-10-1; **1b**, 75232-98-3; **2**, 73048-81-4; L-**3a**, 2578-84-9; D-**3a**, 2578-85-0; DL-**3a**, 2578-86-1; L-**3b**, 1168-87-2; D-**3b**, 30960-00-0; DL-**3b**, 4108-17-2; L-**3c**, 1456-03-7; D-**3c**, 1243-60-3; DL-**3c**, 70148-11-7; CTABr, 57-09-0.

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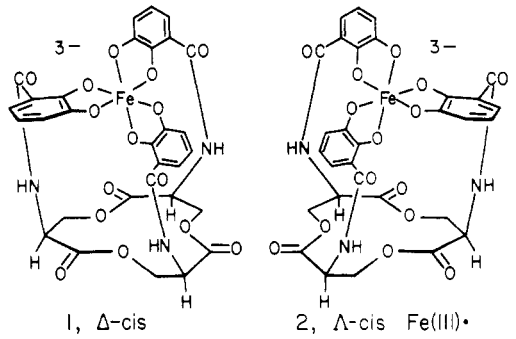
Syntheses of Enterobactin and Enantioenterobactin

Summary: Enterobactin, the siderophore (iron-binding ionophore) of the enteric bacteria has been synthesized from L-serine; the antipode of the natural product, enantioenterobactin, synthesized from D-serine, displays the unnatural Λ-cis configuration of the metal center in its Fe(III) complex.

Sir: Microbes have evolved specialized ligands or siderophores[1] for the acquisition and transport of insoluble Fe(III) [$K_{sp}(Fe(OH)_3) \simeq 10^{-38}$][2] into the cell. Three distinct mechanisms for siderophore-mediated iron transport, differing in the details of entry and release of iron, have been recognized.[1]

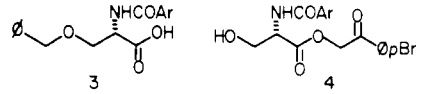
Enterobactin,[3] the cyclic trimer of *N*-(2,3-dihydroxybenzoyl)-L-serine (see antipode **15**), is a siderophore which is overproduced by *E. coli* and related enteric bacteria under low iron stress. The catechol-based siderophore forms a ferric complex, **1**, of exceptional stability (K_f = 10^{52}).[4] The transport of **1**, mediated by a membrane receptor protein,[5] is followed by hydrolysis of the 12-membered, serine-derived trilactone and release of iron.[1]



1, Δ-cis Fe(III)•enterobactin — **2**, Λ-cis Fe(III)•enantioenterobactin

Fe(III)–enterobactin exists predominantly as the Δ-cis complex **1**,[6] the configuration of the L-seryl ester platform favoring the Δ helicity of the iron–catecholate center. It has been assumed that the chirality of **1** may play a key role in the recognition, binding, and transport of the complex into the bacterial cell. Herein we report the syntheses of enantioenterobactin (D-serylenterobactin) **15** (Scheme I; cf. Λ-cis complex **2**) and of the naturally occuring antipode, enterobactin (see Δ-cis complex **1**). Details of membrane receptor binding and transport studies in *E. coli* with synthetic enterobactin and its antipode (**15**) will appear elsewhere.[7]

We have evaluated two fundamentally different approaches to enterobactin and its antipode (**15**). The first entails the coupling of differentially protected *N*-[2,3-bis(benzyloxy)benzoyl]serine monomers, e.g., **3**[8] and **4**.[8]



3 **4**

Ar = 2,3-bis(benzyloxy)phenyl

The second utilizes urethane protection for the monomer amino groups (e.g., see Scheme I) and introduces the *N*-benzoyl ligands only after cyclization of the seryl ester platform. Inherent to the second approach is urethane deprotection and subsequent N-acylation of three amino groups in the cyclic triester of L- or D-serine (cf. **13** in Scheme I). The propensity for *O*- to *N*-acyl shifts in *O*-acylserine derivatives,[9] e.g., **13**, poses a potential risk late in the synthetic sequence for the urethane approach. Consequently, we initially weighed the risk inherent to any *N*-benzoyl monomer approach, viz., racemization of an activated ester (e.g., from **3**) during coupling.

A survey of coupling methods revealed dicyclohexylcarbodiimide/*N*-hydroxybenzotriazole (DCC/HOBt)[10] to be the most satisfactory for the coupling of monomers **3**

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(2) Linke, W. F. "Solubilities. Inorganic and Metal-Organic Compounds", 4th ed.; Van Nostrand: Princeton, NJ, 1958; Vol. 1, p 1039.
(3) (a) Pollock, J. R.; Neilands, J. B. *Biochem. Biophys. Res. Commun.* **1970**, *38*, 989. (b) O'Brien, I. G.; Gibson, F. *Biochim. Biophys. Acta* **1970**, *215*, 393.
(4) Harris, W. R.; Carrano, C. J.; Cooper, S. R.; Sofen, S. R.; Avdeef, A. E.; McArdle, J. V.; Raymond, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 6097.
(5) Hollifield, W. C., Jr.; Neilands, J. B. *Biochemistry* **1978**, *17*, 1922.
(6) (a) McArdle, J. V.; Sofen, S. R.; Cooper, S. R.; Raymond, K. N. *Inorg. Chem.* **1978**, *17*, 3075. (b) Isied, S. S.; Kuo, G.; Raymond, K. N. *J. Am. Chem. Soc.* **1976**, *98*, 1763.
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(8) Satisfactory spectral data (^{1}H NMR, IR, and mass spectra) were obtained for this compound.
(9) Schröder, E.; Lübke, K. "The Peptides"; Academic Press: New York, 1965; Vol. 1, pp 213–214.
(10) (a) König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788. (b) Klausner, Y.; Chorev, M. *J. Chem. Soc., Chem. Commun.* **1975**, 973. (c) Chorev, M.; Knobler, Y.; Klausner, Y. *J. Chem. Res. (S)* **1977**, 202. (d) Weber, U. *Z. Naturforsch., B.* **1976**, *31*, 1157. (e) Young, G. T. "Proceedings of the 12th European Peptide Symposium"; Hanson, H., Jakubke, H., Eds.; North-Holland Publishing Co.: Amsterdam, 1973; p 132.

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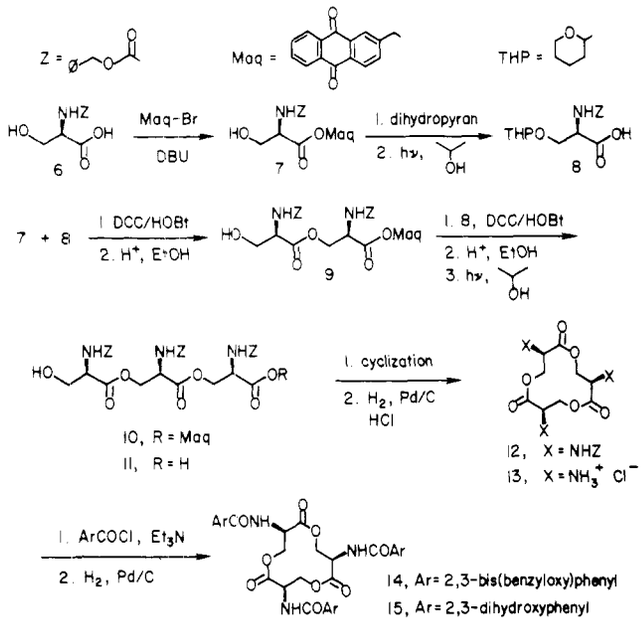
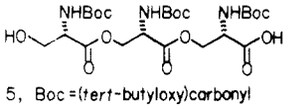
Scheme I



and 4. Nonetheless, the DCC/HOBt-mediated coupling yields an approximately 1:1 mixture of diastereomeric dimers (66%).[11] Despite the success achieved with DCC/HOBt for the coupling of *N*-benzoyl amino acids,[10e] no satisfactory solution could be found to limit racemization of protected *N*-(2,3-dihydroxybenzoyl)serine monomers.

The Corey synthesis of enterobactin[12] via the enantiomer of D-serine cyclic trimer **13** (Scheme I) showed the viability of the urethane approach. Our application of the DCC/HOBt coupling method to urethane-protected monomers revealed the lack of racemization during coupling. However, (*tert*-butyloxy)carbonyl-protected trimer hydroxy acid **5**[8,13] produced by sequential DCC/HOBt couplings failed to cleanly cyclize under a variety of conditions, including those used by Corey et al.[12] for cyclization of the corresponding *N*-[(benzyloxy)carbonyl]-protected trimer hydroxy acid (see enantiomer **11**, Scheme I). Crude cyclization mixtures derived from **5** could not be purified nor deprotected to give a cyclic triammonium salt (see enantiomer **13**, Scheme I).



5, Boc = (*tert*-butyloxy)carbonyl

Our successful approach to enantioenterobactin (and enterobactin) is outlined in Scheme I. *N*-[(Benzyloxy)carbonyl]-D-serine[14] (**6**) was alkylated with 2-(bromomethyl)anthraquinone[15] (MaqBr), giving acid-protected monomer **7**[8,13] (92%). Hydroxyl-protected monomer **8**[8,12] was derived from **7** by reaction with dihydropyran followed by photoreductive deprotection[15] of the Maq ester (82% overall). Coupling of **7** and **8** and removal of the THP protecting group yielded crystalline dimer alcohol **9**[8,13] (88% overall). Further coupling of **9** with **8** and THP removal yielded crystalline trimer alcohol **10**[8,13] (95% overall). Removal of the Maq ester generated the enantiomer (**11**[8]) of Corey's linear trimer enterobactin precursor[12] (67–82%).

Trimer **11** could be cyclized in low yield by DCC/HOBt coupling by Masamune's *tert*-butyl thioester/cuprous triflate method[16] or, preferably, by Corey's imidazolyl disulfide procedure.[12] Hydrogenolysis of crystalline **12**[8,13] in the presence of HCl proceeded smoothly to trihydrochloride salt **13** which was acylated without isolation to give hexabenzylenantioenterobactin (**14**,[8,13] 61–69% overall). Further hydrogenolysis yielded enantioenterobactin (**15**,[13] 56–89%) which was indistinguishable from natural enterobactin by ^{1}H NMR, IR, TLC, UV, field-desorption mass spectrometry (M^+, m/e 669), and melting point. Ferric enantioenterobactin (**2**) displays a CD spectrum which in intensity and sign of rotation is exactly the mirror image of that measured[17] for the natural ferric complex (**1**).

Scheme I applied to *N*-[(benzyloxy)carbonyl]-L-serine[14] yielded enterobactin indistinguishable in all respects (vide supra) from natural material.

Synthetic L-serylenterobactin is fully active in iron transport in *E. coli*, whereas D-serylenterobactin (enantioenterobactin, **15**) is completely inactive.[7]

Acknowledgment is made to Professor J. B. Neilands (Berkeley) for his continued collaboration and encouragement. We thank Dr. C. Costello for field-desorption and exact mass spectra and the National Institutes of Health (Grant AM 20452) and Firmenich and Co. for generous financial support.

Registry No. **1**, 61481-53-6; **2**, 75363-12-1; **6**, 6081-61-4; **7**, 75299-15-9; **8**, 75299-16-0; **9**, 75299-17-1; **10**, 75299-18-2; **11**, 75299-19-3; **12**, 75363-09-6; **13**, 75363-10-9; **14**, 75299-20-6; **15**, 75363-11-0; 2-(bromoethyl)anthraquinone, 7598-10-9.

(11) Separated by LC.
(12) Corey, E. J.; Bhattacharyya, S. *Tetrahedron Lett.* **1977**, 3919.
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(18) Firmenich Assistant Professor of Natural Products Chemistry, Alfred P. Sloan Fellow, 1980–1982.

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Selective Catalysis of Diels–Alder Reactions of 2-Methoxy-5-methyl-1,4-benzoquinone

Summary: The poor regioselectivity of Diels–Alder reactions of 2-methoxy-5-methylbenzoquinone with alkyl-substituted dienes can be directed to favor either isomeric adduct by using stannic chloride or boron trifluoride catalysts.

Sir: Diels–Alder reactions of *p*-benzoquinones have been used to advantage in many well-known syntheses (e.g., steroids,[1] reserpine,[2] and gibberellic acid[3]). Indeed,

(1) (a) Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. *J. Am. Chem. Soc.* **1952**, *74*, 4223. (b) Cohen, N.; Banner, B.; Eichel, W.; Valenta, Z.; Dickenson, R. *Synth. Commun.* **1978**, *8*, 427. (c) Das, J.; Kubela, R.; MacAlpine, G.; Stojanac, Z.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3308.

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