

Total Synthesis of Enterobactin *via* an Organotin Template

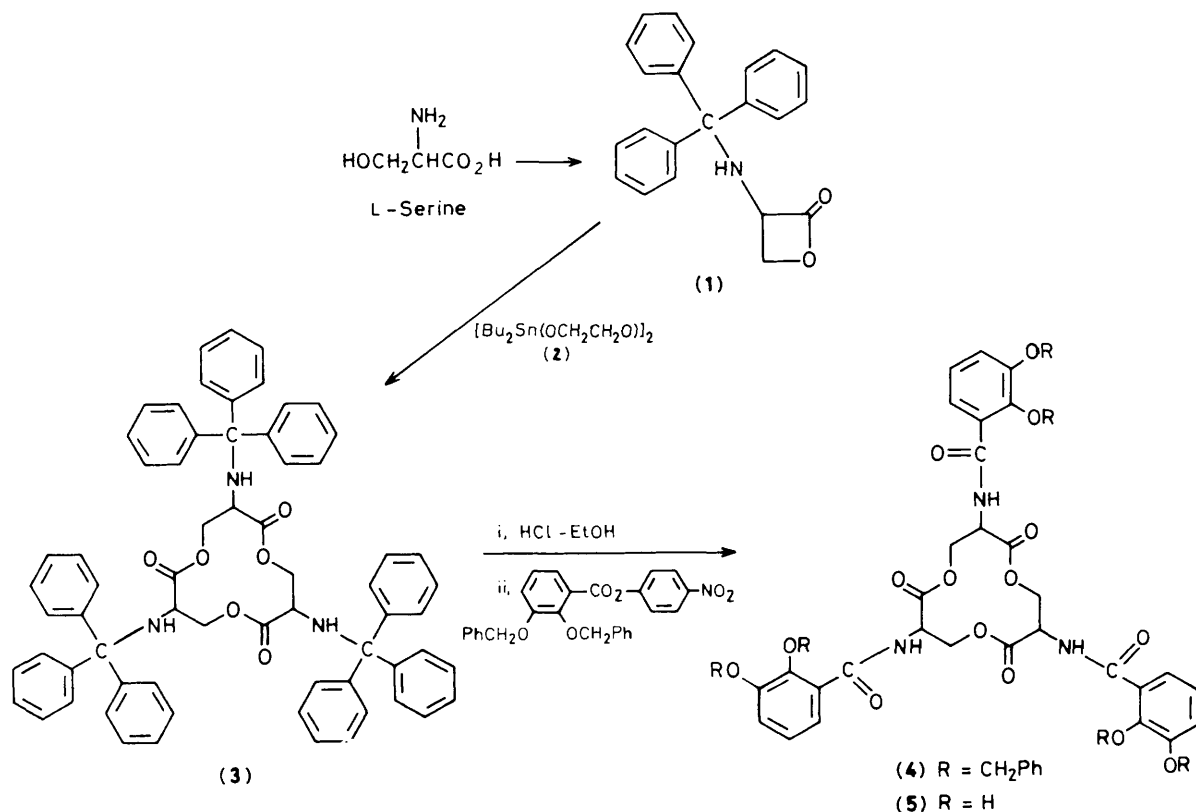
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A novel synthesis of the natural iron carrier enterobactin, based on a single step conversion of the tritylated serine β -lactone (**1**) into the enterobactin skeleton (**3**) *via* the use of a cyclic organotin compound as a template, is described.

There is increasing interest in selective and efficient iron sequestering agents for therapeutic, diagnostic, and agricultural applications.^{1,2} The most potent iron carrier known so far is the naturally occurring siderophore enterobactin.^{3,4} Enterobactin is produced in small amounts by *E. coli* and related enteric bacteria when grown in iron deficient media. Chemically, enterobactin [formula (**5**)] is composed of three serine residues which are linked to a macrocyclic trilactone substituted with three catechol residues as ligating side chains. The total synthesis of enterobactin has been achieved by Corey⁵ and Rastetter.⁶ Both methods rely on the stepwise condensation of serine derivatives to a linear trimer and its

subsequent cyclization. This cyclization is the most critical step in both procedures. In an attempt to overcome this difficulty we have developed a novel method for the cyclization of β -hydroxy-acids. The method is based on the use of cyclic tin-oxygen compounds as templates in the self condensation of β -lactones to macrocyclic poly(lactones).⁷ In this communication we describe the total synthesis of enterobactin by the tin-template method. The synthesis involves cyclization of the β -lactone derived from tritylated L-serine to the enterobactin ring skeleton in a single condensation step with 23% yield. Subsequent replacement of the trityl protecting group by catechol residues gives enterobactin.



The β -lactone of L-serine (1) was prepared by a modified Sheehan's method.⁸ *N*-Tritylserine⁹ (5.52 g, 0.016 mol) was dissolved in dry methylene chloride (400 ml) and treated at 0 °C with dimethylaminopyridine¹⁰ (390 mg, 0.0032 mol) and diisopropylcarbodi-imide (2.4 ml, 0.016 mol). The reaction mixture was stirred at room temperature for 2 days, concentrated *in vacuo*, and chromatographed on silica gel, Merck 60. Elution with benzene or toluene provided the β -lactone (1) (1.365 g, 0.0042 mol, 26%).[†] Condensation of (1) (1.0 g, 0.003 mol) to form the enterobactin skeleton (3) was achieved by treating it with the stannoxane (2) (290 mg, 0.0005 mol) in dry chloroform (25 ml) for 2.5 h under reflux. Pure (3) (230 mg, 23%) was obtained by chromatography of the crude reaction mixture on silica gel, Merck 60, and elution with toluene-ethyl acetate, 7:3,[‡] m.p. 110–112 °C; i.r. (CHCl_3), ν 1736, 1585, and 1218 cm^{-1} ; ^1H n.m.r. (CDCl_3), δ 7.48 (m, 6H), 7.22 (m, 9H), 3.85 and 3.67 (m, 1H), 3.36 (m, 2H), and 2.66 (s, 1H); $[\alpha]_D^{25} = +53.0^\circ$ (CHCl_3 , $c = 0.6$). The trityl group was then removed by heating (2 min) with 1 M HCl in ethanol¹¹ to give the ammonium salt. The latter was acylated with the nitrophenyl ester of 2,3-bis(benzyloxy)benzoic acid in dimethylformamide to provide the protected derivative (4),⁶ which was isolated by chromatography on silica gel, Merck 60, and elution with chloroform-ethanol, 95:5. Hydrogenolysis of (4) with Pd-C (5%) in dry ethanol gave enterobactin (5), quantitatively, which was found to be identical with an authentic sample.

The cyclization of the L-serine lactone (1) to the trimeric ring structure (3) with the stannoxane (2) is likely to proceed

via multiple insertions of the β -lactone (1) into the cyclic tin compound followed by expulsion of the ring product and regeneration of the tin template. This cyclization step facilitates ready access to this highly efficient iron carrier.

The authors thank Professors John C. Sheehan from M.I.T., Boston, and H. Gilon from the Hebrew University, Jerusalem, for their advice in synthesizing the β -lactone derived from tritylated serine, and Professor J. B. Neilands from the University of Berkeley, California, for providing an authentic sample of enterobactin.

Received, 24th March 1983; Com. 381

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[†] Attempts to prepare other *N*-acylated β -lactones including the *N*-[2,3-bis(benzyloxy)benzoyl] β -lactone derived from serine, which would have given the enterobactin molecule (4) directly, failed.

[‡] Small amounts of higher ring homologues such as the tetramer and pentamer were also obtained.