Total Synthesis of Enterobactin *via* an Organotin Template

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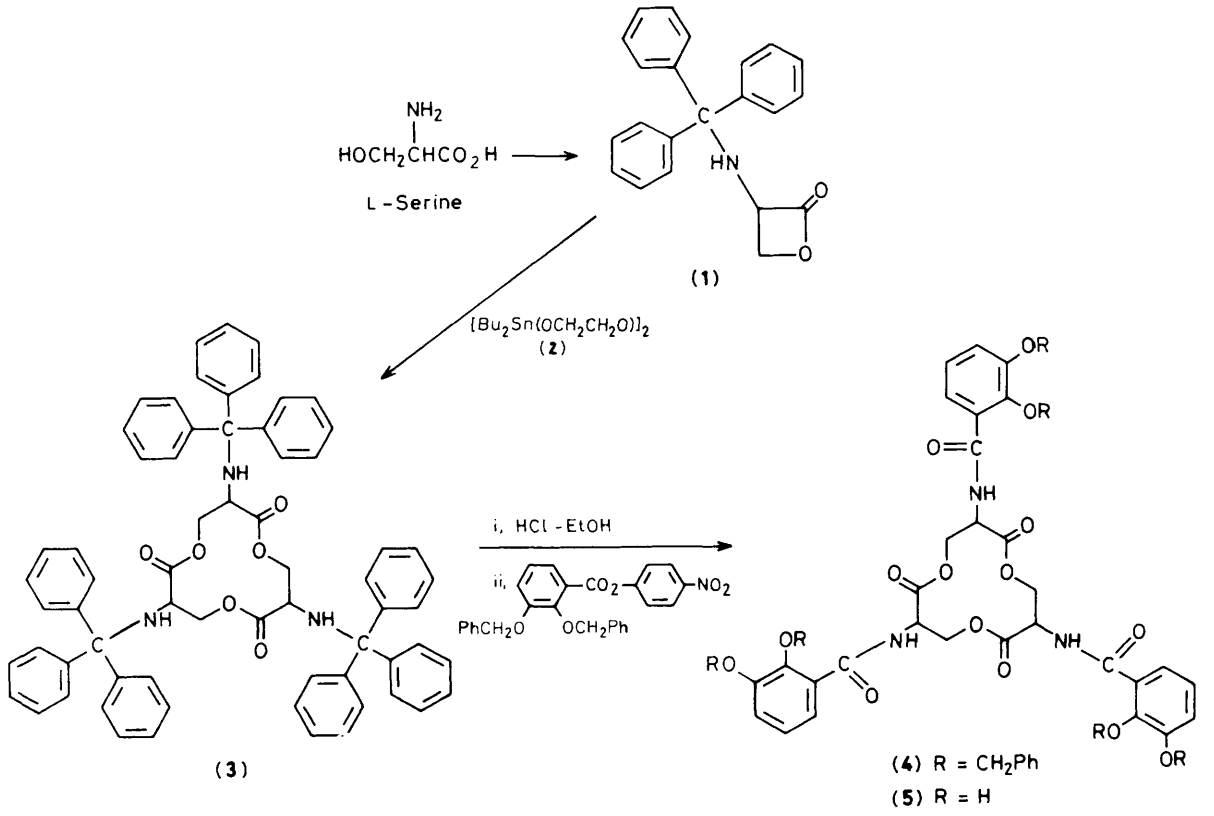
A novel synthesis of the natural iron carrier enterobactin, based on a single step conversion of the tritylated serine β-lactone (**1**) into the enterobactin skeleton (**3**) *via* the use of a cyclic organotin compound as a template, is described.

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 Corey[5] 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 cyclo-oligomerization 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 polylactones.[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] L-*N*-Tritylserine[9] (5.52 g, 0.016 mol) was dissolved in dry methylene chloride (400 ml) and treated at 0 °C with dimethylaminopyridine[10] (390 mg, 0.0032 mol) and di-isopropylcarbodi-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); $[\alpha]_D = +53.0°$ ($CHCl_3$, $c = 0.6$). The trityl group was then removed by heating (2 min) with 1 M HCl in ethanol[11] 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.

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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.

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