Total Synthesis of Parabactin, a Spermidine Siderophore †

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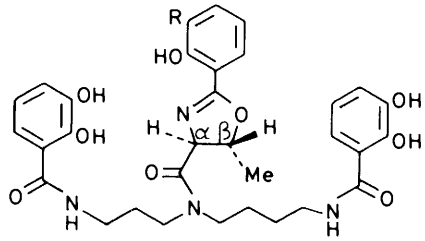
The stereoselective total synthesis of parabactin (1) has been efficiently carried out using substituted 1,3-thiazolidine-2-thione as a leaving group.

The study of naturally occurring [1] and synthetic [2] iron [Fe^{II} and Fe^{III}] chelating compounds is currently important because of their unique structure and interesting biochemical properties, *i.e.* transport of Fe(III) ion into micro-organisms [1a,c-e] and plants [1h,i,3] and cleavage of double helical DNA.[4] Some of these compounds have also been shown to be potent anticancer drugs or iron-sequestering agents [1c,5] in the treatment of acute or chronic iron poisoning. In recent years, several microbial iron-transporting compounds ('siderophores') have been discovered,[6] characterized by *X*-ray analysis,[7] and synthesized.[8] Among these siderophores, parabactin (1) [6a,c,d] and agrobactin (2),[6a-d,7d] which are of the sperimidine-containing catechol type, attracted our attention because we were interested in the synthesis and biological activities of spermidine-containing natural products and drugs.[9] We successfully attempted a total synthesis of parabactin (1) using the 'monitored aminolysis'[9,10] of 3-acyl-1,3-thiazolidine-2-thione. The full details are described here.



(1) R = H
(2) R = OH

Results and Discussion

First, we synthesized an important key intermediate, the dihydro-1,3-oxazole derivative (11) starting from methyl 2-hydroxybenzoate (3) (Scheme 1). Hydrolysis of methyl 2-benzyloxybenzoate (4), followed by treatment of the resulting carboxylic acid (5) with 1,3-thiazolidine-2-thione [10] and dicyclohexylcarbodi-imide (DCC) in the presence of catalytic 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 afforded 3-(2-benzyloxybenzoyl)-1,3-thiazolidine-2-thione (6) in excellent yield. A solution of D-threonine (36 mmol) in water–Et_3N (10 : 1; 55 ml) was added to a solution of (6) (24 mmol) in tetrahydrofuran (THF) (50 ml) to give chemoselectively the *N*-benzoyl derivative (7),[11] whose methyl ester (8) was debenzylated by the catalytic transfer hydrogenation method (Pd–C in HCO_2H–MeOH) [12] to give the phenolic ester (9) in 76% yield. This underwent smooth cyclization, with complete stereoinversion at C_β, with $SOCl_2$ to yield the α,β-*cis*-oxazoline (10) in high yield.[13] Compound (10) was epimerised at C_α with EtONa; hydrolysis of the epimer in alkaline solution followed by treatment with Amberlite IR-120 (NH_4^+) gave the *trans* epimeric carboxylic acid (11) in 92% yield. The stereochemistry was established by the ^1H n.m.r. (100 MHz) spectra [6d] of (11) and its methyl ester (12); the coupling constants of the signals for the C_α- and C_β-protons were particularly informative.

Subsequently, we prepared N^1,N^{10}-bis(benzyloxycarbonyl)-spermidine (15) in good yield by treatment of spermidine (13) with the reagent (14) (Scheme 2).[11] Attempted condensation of (11) with (15) at room temperature was not successful in spite of exhaustive efforts with various reagents, such as $(PhO)_2P(O)Cl$–pyridine, EtOC(O)Cl–pyridine, $SOCl_2$–DMF, $(COCl)_2$–Et_3N, and DCC–DMAP–1,3-thiazolidine-2-thione. This may be due to intramolecular hydrogen-bonding which would reduce the nucleophilicity of the secondary amino group of (15) (Figure 1).[9,11]

The condensation was finally achieved in the following way. Treatment of compounds (11) and (15) with phenylphosphonamide (16)–Pr^i_2NEt in MeCN under reflux for 5 h or with Ph_3P–di-2-pyridyl disulphide [14] in MeCN under the same conditions gave the desired product (17), in 55 or 41% yield respectively. Deprotection with acid and N^1,N^{10}-diacylation with 2,3-diacetoxybenzoyl chloride–Et_3N transformed (17) into parabactin tetra-acetate (18) [Fast Atom Bombardment (FAB) mass spectrum: *m/z* 789 $(M + 1)^+$] in 52% yield. Deacetylation of (18) under mild conditions afforded crude parabactin (83%), which was recrystallized from EtOAc–n-hexane to give pure parabactin (1) {m.p. 114—118 °C (lit.,[6d] 114—117 °C); $[\alpha]_D^{21}$ +99.6° (*c* 1.8, MeOH)}. The total synthesis [15] was confirmed by comparison of the R_F values (t.l.c.) and spectral data [i.r., ^1H n.m.r. (100 MHz), and FAB mass spectra] of the synthetic and natural compounds.

The ^1H n.m.r. (400 MHz) [$CDCl_3$–CD_3OD (4 : 1)] spectrum of synthetic parabactin (1) showed two sets of signals assignable to C_α-H [(δ 4.67784: rel. int. 17.79566%, d, *J* 6.836 Hz) and (δ 4.61433: rel. int. 6.86339%, d, *J* 6.836 Hz] and C_β–CH_3 [(δ 1.4995: rel. int. 50.97788%, d, *J* 6.592 Hz) and (δ 1.45709: rel. int. 19.507 57%, d, *J* 6.347 Hz)]; the assignments were confirmed by the decoupling experiment. Thus, it was confirmed that parabactin exists in isomeric, cisoid and transoid forms (*ca.* 2.6 : 1) with respect to the tertiary amide bond in solution, as pointed out previously in agrobactin chemistry [6d] by Neilands and his co-workers.

The protecting benzyl group of the phenolic moiety in (8) was eliminated prior to the oxazoline ring-formation, because we had recognized that compound (10) is more stable than compound (19) under the acidic conditions. The phenol (10) may be stabilized by hydrogen bonding with the *N* atom of the oxazoline ring (see Figure 2). Such a stabilizing factor is not found in (19) because of the distorted conformation between the phenyl and oxazoline ring (see Figure 3). The possibility of hydrogen-bonding between the phenolic hydroxy group and the N atom of oxazoline in compounds (10), (12), and (17) was strongly suggested by the fact that the chemical shift of the phenolic hydroxy proton occurred at particu-

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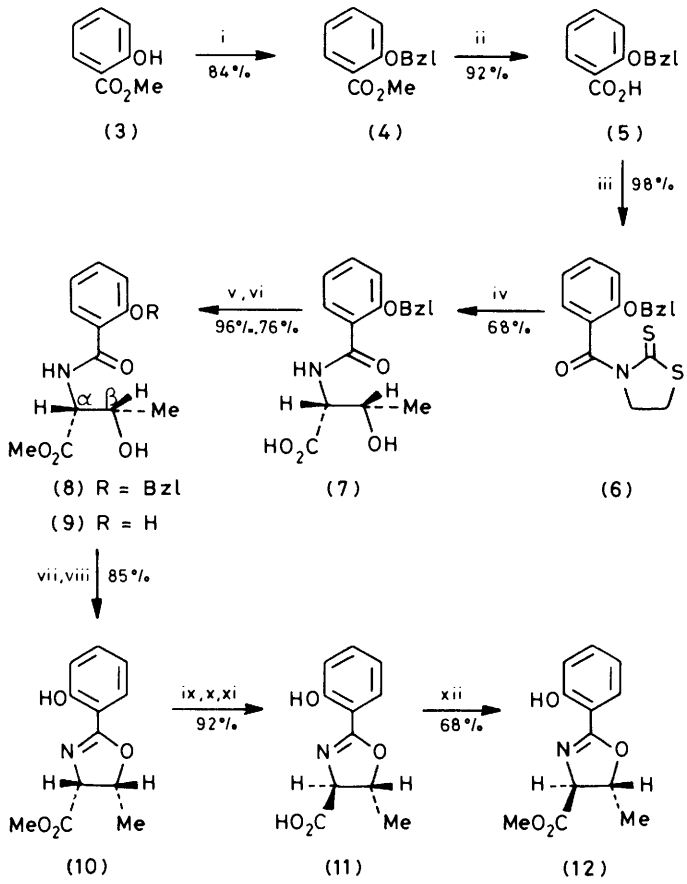
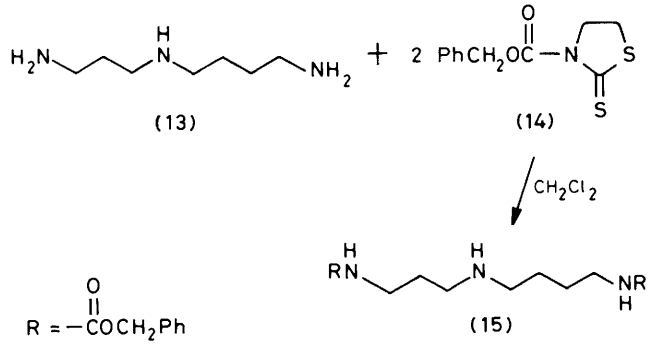


Scheme 1. *Reagents:* i, $PhCH_2Br,K_2CO_3,DMF$; ii, LiOH,aq.THF; iii, 1,3-thiazolidine-2-thione,DCC,DMAP,CH_2Cl_2; iv, D-threonine,Et_3N,water,THF; v, CH_2N_2,Et_2O; vi, Pd–C,HCO_2H, MeOH; vii, $SOCl_2$; viii, $Na_2CO_3,CHCl_3$; ix, EtONa,EtOH; x, water,reflux; xi, Amberlite IR-120 (NH_4^+); xii, CH_2N_2,Et_2O



Scheme 2.

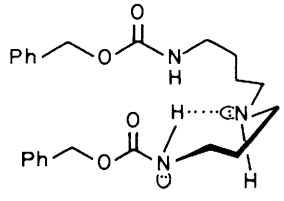


Figure 1.

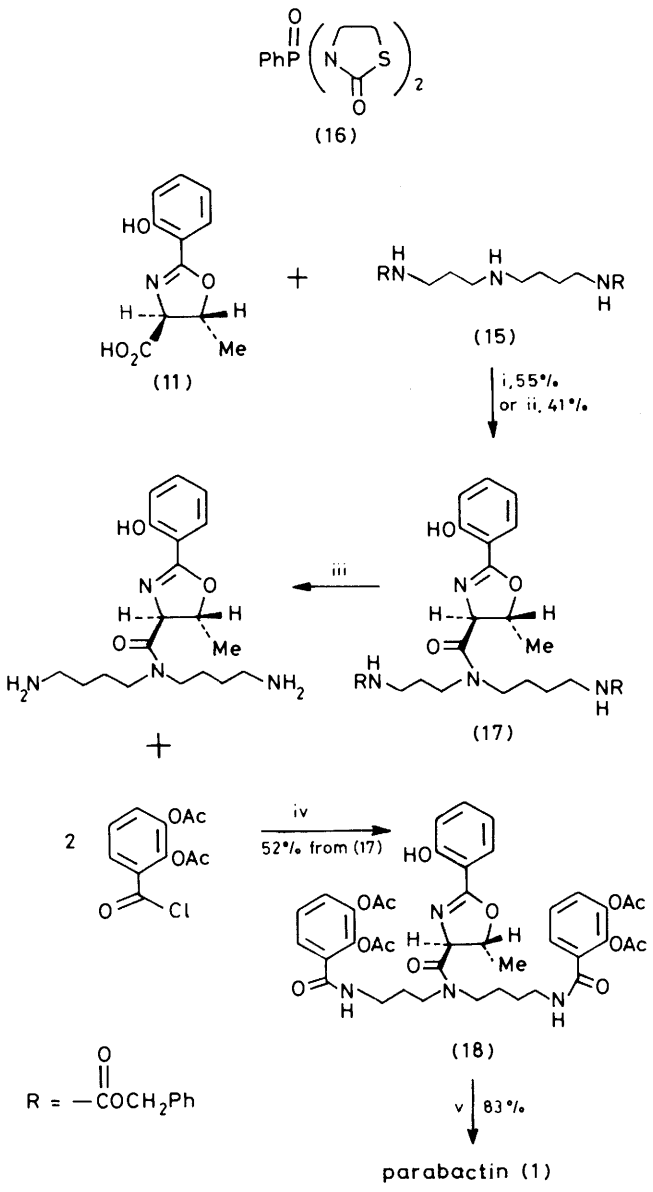
larly low field (*ca.* 11.76 p.p.m.). In the *X*-ray analysis of agrobactin (2), Eng-Wilmot and van der Helm [7d] demonstrated an analogous hydrogen-bonding.

Bergeron and Kline [16] have reported the first synthesis of parabactin, but we accomplished this work independently *via* a completely different route using our own methodology.

Experimental

General Method.—M.p.s were determined with a Yanagimoto microapparatus. I.r. spectra were recorded on a JASCO A-202 spectrophotometer and optical rotations were measured on a JASCO DIP-181 polarimeter. E.i. and FAB mass spectra were recorded on a JEOL JMS-DX300 mass spectrometer. ^1H n.m.r. spectra were determined with JEOL JNM-FX100 and -JX400 spectrometers; signals are given in p.p.m. from $SiMe_4$ as internal standard. Extracts were dried over Na_2SO_4. Merck silica gel 60H was used for flash column chromatography.

Methyl 2-Benzyloxybenzoate (4).—Anhydrous K_2CO_3 (27 g) was added to a solution of methyl salicylate (10 g) in DMF (60 ml) and benzyl bromide (8.6 ml) was added under N_2 with stirring. After being stirred at room temperature overnight, the reaction mixture was poured into cold water and extracted with a large amount of EtOAc. The extract was washed with brine, dried, and evaporated under reduced pressure to give an oily residue, which was purified by flash chromatography on a short silica gel column with $CHCl_3$ to afford *compound* (4) (13.3 g, 84%) as a colourless oil, $\nu_{max.}$ ($CHCl_3$) 1 720 cm^{-1}; δ($CDCl_3$) 3.84 (3 H, s), 5.12 (2 H, s), and 6.80—7.84



Scheme 3. *Reagents:* i, (16),Pri_2NEt,MeCN,reflux; ii, Ph_3P,di-2-pyridyl disulphide,MeCN,reflux; iii, 25% HBr–AcOH; iv, Et_3N, THF; v, K_2CO_3,MeOH

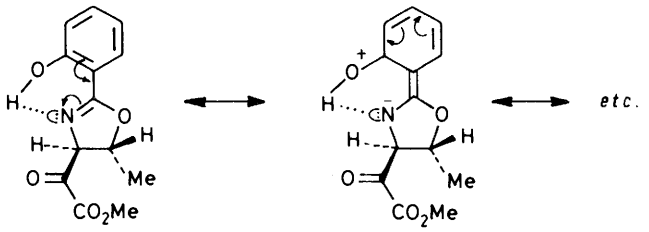


Figure 2.

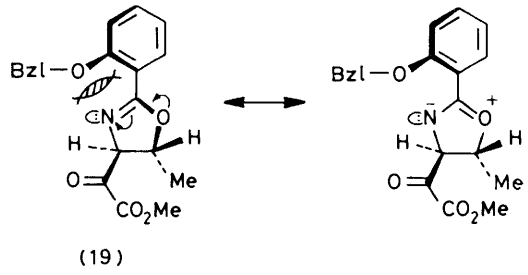


Figure 3.

(9 H, m) (Found: C, 74.5; H, 5.8%; M^+, 242. $C_{15}H_{14}O_3$ requires C, 74.36; H, 5.83%; *M*, 242).

2-*Benzyloxybenzoic Acid* (5).—A solution of $LiOH·H_2O$ (5.6 g) in water (80 ml) was added to a solution of methyl 2-benzyloxybenzoate (4) (10.4 g) in THF (80 ml). After being stirred at room temperature overnight, the reaction mixture was acidified with cold aq. 10% HCl under ice-cooling. The mixture was extracted with EtOAc and the extract was treated as usual to give the *carboxylic acid* (5) (8.7 g, 92%) as colourless prisms from EtOAc–n-hexane, m.p. 75.5—76 °C; $\nu_{max.}$ (KBr) 3 450 and 1 665 cm^{-1}; δ ($CDCl_3$) 5.36 (2 H, s), 6.96—8.08 (9 H, m), and 12.8br (1 H, s) (Found: C, 73.6; H, 5.2%; M^+, 228. $C_{14}H_{12}O_3$ requires C, 73.67; H, 5.30%; *M*, 228).

3-(2-*Benzyloxybenzoyl*)-1,3-*thiadiazolidine*-2-*thione* (6).—1,3-Thiazolidine-2-thione (3.73 g) and 2-benzyloxybenzoic acid (5) (6.5 g) were dissolved in CH_2Cl_2 (50 ml). To the solution was added DCC (6.46 g) and DMAP (100 mg) with stirring under ice-cooling. The mixture was stirred at room temperature under N_2 overnight, then the precipitate (DCC–urea) was filtered off and the filtrate was evaporated under reduced pressure to give an oily residue, which was chromatographed by the flash technique on silica gel with $CHCl_3$ to afford the *amide* (6) (9.2 g, 98%) as yellow prisms (from $CHCl_3$–Et_2O), m.p. 75.5—76.5 °C; $\nu_{max.}$ ($CHCl_3$) 1 670 cm^{-1}; δ ($CDCl_3$) 2.84 (2 H, t, *J* 7 Hz), 4.42 (2 H, t, *J* 7 Hz), 4.96 (2 H, s), and 6.76—7.32 (9 H, m) (Found: C, 62.0; H, 4.5; N, 4.3%; M^+, 329. $C_{17}H_{15}O_2NS_2$ requires C, 62.00; H, 4.59; N, 4.25%; *M*, 329).

N-(2-*Benzyloxybenzoyl*)-D-*threonine* (7).—A solution of D-threonine (4.28 g) and Et_3N (5 ml) in water (50 ml) was added to a solution of 3-(2-benzyloxybenzoyl)-1,3-thiazolidine-2-thione (6) (7.86 g) in THF (50 ml). After being stirred at room temperature for 10 days, the reaction mixture was acidified with cold aq. 10% HCl and extracted with EtOAc. The extract was washed with brine, dried, and evaporated under reduced pressure to give an oily residue, which was chromatographed on Sephadex LH-20 (Pharmacia) with MeOH to afford *compound* (7) (5.37 g, 68%) as colourless prisms from EtOAc–n-hexane, m.p. 195—196 °C; $[\alpha]_D^{23}$ −11.7° (*c* 1.0, MeOH); $\nu_{max.}$ (KBr) 3 575, 3 400, 1 725, 1 620, and 1 545 cm^{-1}; δ [$(CD_3)_2SO$] 1.08 (3 H, d, *J* 6.4 Hz), 4.20 (1 H, m), 4.42 (1 H, dd, *J* 8.3 and 3 Hz), 5.36 (2 H, s), 7.84—8.00 (9 H, m), and 8.50br (1 H, d, *J* 8.3 Hz) (Found: C, 65.85; H, 5.7; N, 4.4%; M^+, 329. $C_{18}H_{19}NO_5$ requires C, 65.64; H, 5.82; N, 4.25%; *M*, 329).

N-(2-*Benzyloxybenzoyl*)-D-*threonine Methyl Ester* (8).—Usual methylation of (7) (20 g) with CH_2N_2 gave the *methyl ester* (8) (20.2 g, 96%) as a colourless oil, $[\alpha]_D^{26}$ −18.1° (*c* 1.0, $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 3 630, 3 300, 1 735, and 1 642 cm^{-1}; δ ($CDCl_3$) 1.06 (3 H, d, *J* 6.6 Hz), 1.82 (1 H, s), 3.68 (3 H, s), 4.22 (1 H, m), 4.75 (1 H, dd, *J* 8.5 and 2.9 Hz), 5.20 (2 H, s), 6.88—8.26 (9 H, m), and 8.50 (1 H, d, *J* 8.5 Hz) (Found: C, 63.3; H, 5.9; N, 3.8; M^+, 343. $C_{19}H_{21}O_5N·H_2O$ requires C, 63.14; H, 6.42; N, 3.88%; *M*, 343).

N-(2-*Hydroxybenzoyl*)-D-*threonine Methyl Ester* (9).—10%

Pd–C (10 g) was slowly added to a solution of (8) (15 g) in 90% HCO_2H–MeOH (1 : 9; 600 ml) with stirring under N_2. The mixture was stirred under N_2 for 30 min and Pd–C was filtered off. The filtrate was evaporated under reduced pressure to give an oily residue, which was purified by the usual flash column chromatography on silica gel with acetone–$CHCl_3$ (1 : 4) to afford *compound* (9) (8.7 g, 76%) as a colourless oil, $[\alpha]_D^{26}$ −7.8° (*c* 1.0, $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 3 600sh, 3 450, 3 020, 1 738, 1 640, 1 600, and 1 525 cm^{-1}; δ ($CDCl_3$) 1.28 (3 H, d, *J* 6.3 Hz), 2.66br (1 H, s), 3.78 (3 H, s), 4.46 (1 H, m), 4.78 (1 H, dd, *J* 8.3 and 2.5 Hz), 6.60—7.60 (5 H, m), and 11.96br (1 H, s) (Found: C, 53.5, H, 5.8; N, 5.3%; M^+, 253. $C_{12}H_{15}O_5N\cdot H_2O$ requires C, 53.13; H, 6.32; N, 5.16%; *M*, 253).

(4R,5R)-2-(2-*Hydroxyphenyl*)-4-*methoxycarbonyl*-5-*methyl*-4,5-*dihydro-oxazole* (10).—*N*-(2-Hydroxybenzoyl)-D-threonine methyl ester (9) (6.65 g) was dissolved in cold thionyl chloride (20 ml) under N_2. The mixture was stirred at room temperature for 2 h and the excess of thionyl chloride was evaporated under reduced pressure to give an oily residue, which was dissolved in $CHCl_3$ (200 ml). To the $CHCl_3$ solution under ice-cooling was added anhydrous Na_2CO_3 (15 g). The mixture was stirred at room temperature for 1 h and the solid Na_2CO_3 was filtered off. The filtrate was washed with brine, dried, and evaporated under reduced pressure to give an oily residue, which was purified by flash column chromatography ($CHCl_3$) to afford *compound* (10) (5.25 g, 85%) as a colourless oil, $[\alpha]_D^{28}$ −36.3° (*c* 1.0, $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 2 950, 1 737, and 1 640 cm^{-1}; δ($CDCl_3$) 1.40 (3 H, m), 3.75 (3 H, s), 4.98 (2 H, m), 6.60—7.72 (4 H, m), and 11.76br (1 H, s) (Found: C, 61.0; H, 5.5; N, 5.8%; M^+, 235. $C_{12}H_{13}O_4N$ requires C, 61.27; H, 5.57; N, 5.96%; *M*, 235).

(4S,5R)-2-(2-*Hydroxyphenyl*)-5-*methyl*-4,5-*dihydro-oxazole*-4-*carboxylic Acid* (11) *and Its Methyl Ester* (12).—(4*R*,5*R*)-2-(2-Hydroxyphenyl)-4-methoxycarbonyl-5-methyl-4,5-dihydro-oxazole (10) (5 g) was dissolved in dry EtOH (100 ml), to which was added dropwise with stirring a solution of Na (1 g) in dry EtOH (50 ml). After being stirred at room temperature for 10 min, water (4 ml) was added and the mixture was refluxed for 15 min. The solvent was evaporated under reduced pressure to give an oily residue, which was placed on the top of a column prepared from Amberlite IR-120 (NH_4^+) and water and eluted with water. The aqueous solution was evaporated under reduced pressure to give the *carboxylic acid* (11) (4.1 g, 92%) as a pale yellow solid, $\nu_{max.}$ (KBr) 3 350, 1 680, and 1 610 cm^{-1}; δ ($CDCl_3$–CD_3OD) 1.52 (3 H, d, *J* 6.4 Hz), 4.33 (1 H, d, *J* 6.8 Hz), 4.90 (1 H, quintet-like, *J* 6.8 and 6.4 Hz), and 6.60—7.72 (4 H, m) (Found: M^+, 221.069. $C_{11}H_{11}NO_4$ requires *M*, 221.069).

The *methyl ester* (12) was a pale yellow oil, $[\alpha]_D^{26}$ +41.1° (*c* 1.0, $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 3 020, 1 735, and 1 640 cm^{-1}; δ ($CDCl_3$) 1.52 (3 H, d, *J* 6.4 Hz), 3.76 (3 H, s), 4.46 (1 H, d, *J* 6.8 Hz), 5.02 (1 H, quintet-like, *J* 6.8 and 6.4 Hz), 6.60—7.72 (4 H, m), and 11.76br (1 H, s) (Found: C, 61.4; H, 5.6; N, 6.35%; M^+, 235. $C_{12}H_{13}O_4N$ requires C, 61.27; H, 5.57; N, 5.96%; *M*, 235).

N^1,N^{10}-*Bis*(*benzyloxycarbonyl*)*spermidine* (15).—A solution of spermidine (13) (6 g) in CH_2Cl_2 (200 ml) was added to a yellow solution of 3-benzyloxycarbonyl-1,3-thiazolidine-2-thione (14) (20 mg) in CH_2Cl_2 (500 ml). After being stirred at room temperature under N_2 for 3 h, the colourless reaction mixture was washed with aqueous 2% NaOH solution to remove 1,3-thiazolidine-2-thione. Usual work-up gave the *diamide* (15) (11.2 g, 69%) as colourless crystals, m.p. 104.5—105 °C (from benzene–Et_2O); $\nu_{max.}$ (KBr) 3 380, 2 685, and 1 540 cm^{-1}; δ ($CDCl_3$) 1.08—1.80 (7 H, m), 2.40—2.80 (4 H, m), 3.00—3.40 (4 H, m), 5.06 (4 H, s), 5.26br (1 H, s), 5.54br (1 H, s), and 7.04— 7.60 (10 H, m) (Found: C, 66.7; H, 7.7; N, 10.25%; M^+, 413. $C_{23}H_{31}O_4N_3$ requires C, 66.80; H, 7.56; N, 10.16%; *M*, 413).

(4S,5R)N-[3-(*Benzyloxycarbonylamino*)*propyl*]-N-[4-(*benzyloxycarbonylamino*)*butyl*]-2-(2-*hydroxyphenyl*)-5-*methyl*-4,5-*dihydro-oxazole*-4-*carboxamide* (17).—(*a*) *Method* 1. *N*,*N*-Di-isopropylethylamine (0.52 ml) was added to a suspension of the carboxylic acid (11) (442 mg), N^1,N^{10}-bis-(benzyloxycarbonyl)spermidine (15) (1.24 g), and phenylbis-(2-thioxo-1,3-thiazolidin-3-yl)phosphine oxide (16) (1.032 g) in MeCN (80 ml). The mixture was refluxed under N_2 for 5 h and the solvent was evaporated under reduced pressure to give an oily residue. The residue was purified by column chromatography on Sephadex LH-20 with MeOH and by flash column chromatography with Et_2O–CH_2Cl_2 (1 : 1) to give the *amide* (17) (676 mg, 55%) as a pale yellow oil, $[\alpha]_D^{26}$ +67.6° (*c* 0.5, $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 3 460, 2 950, 1 710, 1 635, and 1 520 cm^{-1}; δ ($CDCl_3$) 1.20—2.04 (9 H, m), 2.80—3.76 (8 H, m), 4.56 (1 H, m), 5.12 (4 H, s), 5.24br (2 H, s), 5.44 (1 H, m), 6.72—7.80 (14 H, m), and 11.75br (1 H, s) (Found: C, 64.2; H, 6.3; N, 8.9%; M^+, 616. $C_{34}H_{40}O_7N_4\cdot H_2O$ requires C, 64.33; H, 6.67; N, 8.83%; *M*, 616).

(*b*) *Method* 2. A suspension of triphenylphosphine (786 mg), carboxylic acid (11) (442 mg), N^1,N^{10}-bis(benzyloxycarbonyl)-spermidine (15) (1.24 g), and di-2-pyridyl disulphide (660 mg) in MeCN (80 ml) was refluxed under N_2 for 5 h.[14] The reaction mixture was subjected to the usual work-up to give the amide (17) (499 mg, 41%).

(*c*) *Method* 3. A solution of diphenylphosphoryl azide [17] (3.3 g) in DMF (10 ml) was added to a solution of the carboxylic acid (11) (1.77 g) and compound (15) (4.96 g) in DMF (50 ml) under ice-cooling with stirring. After addition of Et_3N (1.7 ml) and DMAP (100 mg) under the same conditions, the mixture was stirred at room temperature under N_2 for 3 days and treated as usual to give the amide (17) (295 mg, 6%).

(4S,5R)-N-[3-(2,3-*Diacetoxybenzamido*)*propyl*]-N-[4-(2,3-*diacetoxybenzamido*)*butyl*]-2-(2-*hydroxyphenyl*)-5-*methyl*-4,5-*dihydro-oxazole*-4-*carboxamide* (18).—Compound (17) (164 mg) and anisole (0.2 ml) were dissolved in 5 ml of 25% HBr in acetic acid at 0 °C under N_2 with stirring. After being stirred at room temperature for 3 h, the mixture was evaporated under reduced pressure to give a viscous oily residue. The residue was washed with Et_2O by a decantation technique and suspended in dry THF (60 ml). To the suspension was added Et_3N (0.2 ml), followed by a solution of 2,3-diacetoxybenzoyl chloride (164 mg) in dry THF (20 ml) slowly with stirring under ice-cooling. After being stirred at room temperature under N_2 overnight, the precipitate (Et_3N·HCl) was filtered off and the filtrate was evaporated under reduced pressure to give an oily residue. Purification of the residue by flash column chromatography (20% acetone in $CHCl_3$) gave *compound* (18) [110 mg, 52% from (17)] as a pale yellow oil, $[\alpha]_D^{25}$ +50.2° (*c* 0.9, $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 3 450, 2 950, 1 770, 1 640, and 1 520 cm^{-1}; δ ($CDCl_3$) 1.40—2.00 (9 H, m), 2.26 (12 H, s), 3.00—3.76 (8 H, m), 4.60 (1 H, m), 5.37 (1 H, m), and 6.20—7.92 (12 H, m) [Found: C, 56.4; H, 5.2; N, 6.3; FAB MS, $(M + H)^+$, 789. $C_{40}H_{44}O_{13}N_4\cdot 2/3CHCl_3$ requires C, 56.25; H, 5.18; N, 6.45%; *M*, 788].

Parabactin (1).—Potassium carbonate (30 mg) was added to a solution of compound (18) (80 mg) in MeOH–water (10 : 1; 16.5 ml). After being stirred at room temperature for 30 min, the reaction mixture was concentrated under reduced pressure to give an oily residue, to which was added water and the mixture was extracted with EtOAc. The extract was washed

with brine, dried, and evaporated under reduced pressure to give crude parabactin (1) (52 mg, 83%), which was recrystallised from EtOAc–n-hexane to afford pure parabactin (1) (42 mg) as colourless crystals, m.p. 114—118 °C (lit.,[6d] 114—117 °C); $[\alpha]_D^{21}$ +99.6° (*c* 1.8, MeOH); $\nu_{max.}$ (KBr) 3 350br, 1 630, 1 595sh, 1 540, 1 485sh, 1 450, 1 365sh, 1 320, 1 255, and 735 cm^{-1}; δ ($CDCl_3$–CD_3OD; 4 : 1) 1.40—2.20 (6 H, m), 1.46 (3 H, m), 3.00—3.92 (m), 4.62 (1 H, m), 5.38 (1 H, m), and 6.40—7.72 (10 H, m); $\lambda_{max.}$ (EtOH) 309 (ε 11 200) and 250 nm (27 300) [Found: C, 61.5; H, 5.8; N, 9.1; FAB MS, $(M + H)^+$, 621. Calc. for $C_{32}H_{36}N_4O_9$: C, 61.92; H, 5.85; N, 9.03; *M*, 620].

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References

1 (*a*) 'Microbial Iron Metabolism,' ed. J. B. Neilands, Academic Press, New York, 1974; (*b*) 'The Porphyrins,' ed. D. Dolphin, Academic Press, New York, 1979, vol. 6; (*c*) T. Emery and J. B. Neilands, *J. Am. Chem. Soc.*, 1960, **82**, 3658; (*d*) J. R. Pollack and J. B. Neilands, *Biochem. Biophys. Res. Commun.*, 1970, **38**, 989; (*e*) I. G. O'Brien and F. Gibson, *Biochim. Biophys. Acta*, 1970, **215**, 393; (*f*) T. Takita Y. Muraoka, T. Nakatani, A. Fujii, Y. Umezawa, H. Nakagawa, and H. Umezawa, *J. Antibiot. (Tokyo)*, 1978, **31**, 801; (*g*) T. Takita, *Kagaku No Ryoiki* 1979. **33**, 695 and references cited therein; (*h*) T. Takemoto, K. Nomoto. S. Fushiya, R. Ouchi, G. Kusano, H. Hikino, S. Takagi, Y. Matsuura, and M. Kakudo, *Proc. Jpn. Acad.*, 1978, **54***B*, 469; (*i*) K. Nomoto and Y. Ohfue, *J. Synth. Org. Chem. Jpn.*, 1982, **40**, 401 and references cited therein.

2 J. J. Christensen, D. J. Eatough, and R. M. Izatt, *Chem. Rev.*, 1974, **74**, 351 and references cited therein; F. Vögtle and E. Weber, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 753 and references cited therein; F. L. Weitl and K. N. Raymond, *J. Am. Chem. Soc.*, 1979, **101**, 2728; R. J. Bergeron, P. S. Burton, K. A. McGovern, E. J. St. Onge, and R. R. Streiff, *J. Med. Chem.*, 1980, **23**, 1130; F. L. Weitl and K. N. Raymond, *J. Org. Chem.*, 1981, **46**, 5234; M. I. Dawson, R. L.-S. Chan, I. S. Cloudsdale, and W. R. Harris, *Tetrahedron Lett.*, 1981, **22**, 2739; M. Otsuka, M. Yoshida, S. Kobayashi, M. Ohno, Y. Sugiura, T. Takita, and H. Umezawa, *J. Am. Chem. Soc.*, 1981, **103**, 6986; E. Kimura, *Kagaku No Ryoiki*, 1981, **35**, 865 and references cited therein; R. J. Bergeron, S. J. Kline, N. J. Stolowich, K. A. McGovern, and P. S. Burton, *J. Org. Chem.*, 1981, **46**, 4524.

3 Y. Sugiura, H. Tanaka, Y. Mino, T. Ishida, N. Ota, M. Inoue, K. Nomoto, H. Yoshioka, and T. Takemoto, *J. Am. Chem. Soc.*, 1981, **103**, 6979; Y. Mino, T. Ishida, N. Ota, M. Inoue, K. Nomoto, H. Yoshioka, T. Takemoto, Y. Sugiura, and H. Tanaka, *Inorg. Chem.*, 1981, **20**, 3440.

4 Y. Sugiura, *J. Am. Chem. Soc.*, 1980, **102**, 5208; R. P. Hertzberg and P. B. Dervan, *J. Am. Chem. Soc.*, 1982, **104**, 313; J. W. Lown and A. V. Joshua, *J. Chem. Soc., Chem. Commun.*, 1982, 1298; P. G. Schultz, J. S. Taylor, and P. B. Dervan, *J. Am. Chem. Soc.*, 1982, **104**, 6861.

5 J. B. Neilands, *Adv. Chem. Ser.*, 1973, No. 162, 3—32.

6 (*a*) G. H. Tait, *Biochem. J.*, 1975, **146**, 191; (*b*) S. A. Ong, T. Peterson, and J. B. Neilands, *J. Biol. Chem.*, 1979, **254**, 1860; (*c*) T. Peterson and J. B. Neilands, *Tetrahedron Lett.*, 1979, 4805; (*d*) T. Peterson, K.-E. Falk, S. A. Leong, M. P. Klein, and J. B. Neilands, *J. Am. Chem. Soc.*, 1980, **102**, 7715; (*e*) R. D. Perry and C. L. San Clemente, *J. Bacteriol.*, 1979, **140**, 1129.

7 (*a*) E. Hough and E. Rogers, *Biochem. Biophys. Res. Commun.*, 1974, **57**, 73; (*b*) R. C. Hider, J. Silver, J. B. Neilands, I. E. G. Morrison, and L. V. C. Rees, *FEBS Lett.*, 1979, **102**, 326; (*c*) D. van der Helm, J. R. Baker, D. L. Eng-Wilmot, M. B. Hossain, and R. A. Loghry, *J. Am. Chem. Soc.*, 1980, **102**, 4224; (*d*) D. L. Eng-Wilmot and D. van der Helm, *J. Am. Chem. Soc.*, 1980, **102**, 7719.

8 Y. Isowa, M. Ohmori, and H. Kurita, *Bull. Chem. Soc. Jpn.*, 1974, **47**, 215; E. J. Corey and S. Bhattacharyya, *Tetrahedron Lett.*, 1977, 3919; P. J. Maurer and M. J. Miller, *J. Am. Chem. Soc.*, 1983, **105**, 240.

9 E. Fujita, *Pure Appl. Chem.*, 1981, **53**, 1141; Y. Nagao, *Yakugaku Zasshi*, 1981, **102**, 401; Y. Nagao and E. Fujita, *Heterocycles*, 1982, **17**, 537.

10 Y. Nagao, K. Seno, K. Kawabata, T. Miyasaka, S. Takao, and E. Fujita, *Tetrahedron Lett.*, 1980, **21**, 841; Y. Nagao, T. Ikeda, M. Yagi, E. Fujita, and M. Shiro, *J. Am. Chem. Soc.*, 1982, **104**, 2079.

11 Y. Nagao, T. Miyasaka, K. Seno, M. Yagi, and E. Fujita, *Chem. Lett.*, 1981, 463.

12 B. ElAmin, G. M. Anantharamaiah, G. P. Royer, and G. E. Means, *J. Org. Chem.*, 1979, **44**, 3442.

13 D. F. Elliott, *J. Chem. Soc.*, 1950, 62.

14 S. Kobayashi, T. Iimori, T. Izawa, and M. Ohno, *J. Am. Chem. Soc.*, 1981, **103**, 2406.

15 Orally reported at the '41st Symposium on Synthetic Organic Chemistry,' Tokyo, Japan, June 4, 1981.

16 R. J. Bergeron and S. J. Kline, *J. Am. Chem. Soc.*, 1982, **104**, 4489.

17 T. Shioiri, K. Ninomiya, and S. Yamada, *J. Am. Chem. Soc.*, 1972, **94**, 6203.

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