Total Synthesis of the Siderophore Vibrioferrin

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Total synthesis of vibrioferrin (1), a siderophore, was achieved *via* chiral dibenzyl citrate separated by optical resolution. It was elucidated that the configuration of the citrate moiety of vibrioferrin was *R*.

Key words vibrioferrin; siderophore; total synthesis; optical resolution

Vibrioferrin (**1**), which was isolated from *Vibrio parahaemolyticus* is a siderophore, one of the iron-chelating compounds produced by bacteria. Yamamoto *et al*. proposed the structure of **1** shown Fig. 1 based on partial chemical degradation data and spectral analyses.[1] They confirmed that **1** was a mixture of reversible epimeric isomers at the 2‴ position on the pyrrolidinone ring and that the 2″ methine carbon bound to the pyrrolidinone ring was the *S* form. However, the configuration of the center carbon at the 2 position in the citrate moiety could not be determined. For the purpose of complete elucidation of the structure of **1**, we attempted a total synthesis of **1** and its derivatives.

Dibenzyl citrate (**2**)[2] was prepared from citric acid (**3**) *via* 4,4-(5-oxo-1,3-dioxolane)diacetic acid[3] (**4**) and its anhydride[4] (**5**). The optical resolution of **2** proceeded by recrystallization of the salt of **2** and quinine in 27% yield to afford *R*-**2** with an enantiomeric excess of 99%. Fortunately, recrystallization four times of the salt of **2** and cinchonidine gave *S*-**2** with an enantiomeric excess of 99% in 24% yield. The configuration of the chiral citrates (*R*-**2** and *S*-**2**) were determined by the transformation of *R*-**2** to a known chiral compound, chiral dimethyl citrate (**7**)[5] (Chart 1).

Vibrioferrin (**1**)[6] was successfully synthesized from *S*-**2** (Chart 2). Esterification of *S*-**2** with alcohol (**9**), which was prepared from *N*-Boc-alanine (**8**) and ethanolamine, afforded **10**. Condensation of the amine afforded by debutoxycarbonylation of **10** with 1-benzyl α-ketoglutarate[7] gave **11**, which had a pyrrolidinone ring, and subsequent debenzylation gave vibrioferrin (**1**).

References and Notes

1) Yamamoto S., Okujo N., Yoshida T., Matsuura S., Shinoda S., *J. Biochem*., **115**, 868—874 (1994).
2) Dibenzoate (**2**): A mixture of **6** (10.0 g, 34.0 mmol), benzyl alcohol (36.0 ml, 348 mmol), Et_3N (31.0 ml, 222 mol), and $CHCl_3$ (200 ml) was refluxed for 1 week. After removal of the solvent, the mixture was

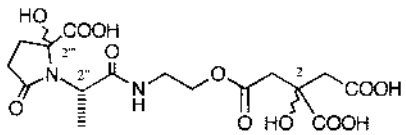
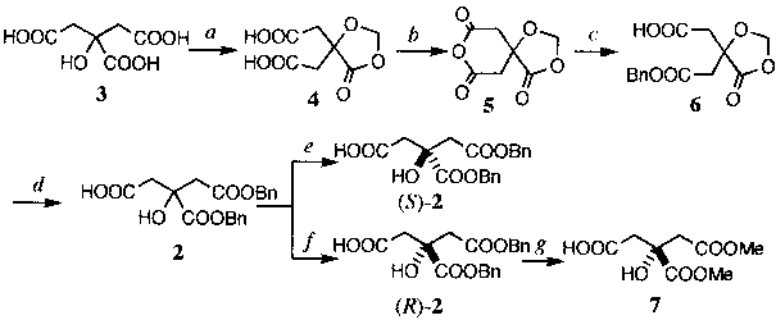
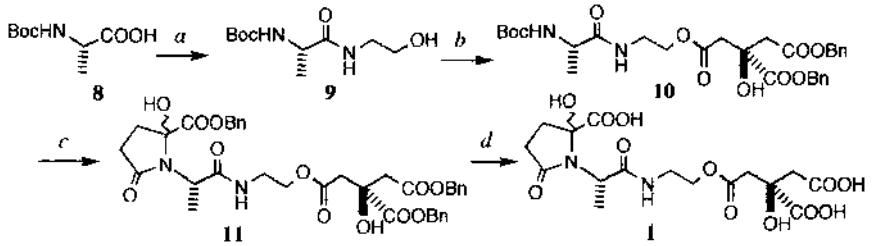


Fig. 1. Proposed Structure of Vibrioferrin (**1**)



a) $(CH_2O)_n$, 160 °C, 0.5 h, 46%; *b*) $PhNMe_2$, $POCl_3$, dry $CHCl_3$, r.t., 0.5 h, 63%; *c*) dry pyridine, BnOH, dry $CHCl_3$, reflux, 1 d, 77%; *d*) dry Et_3N, BnOH, dry $CHCl_3$, reflux, 1 week, 49%; *e*) i) (−)-cinchonidine; ii) recrystallization four times from AcOEt; iii) HCl, 24%, 99% ee from chiral HPLC, ($[\alpha]_D$ −6.80°); *f*) i) (−)-quinine; ii) recrystallization three times from AcOEt; iii) HCl, 27%, 99% ee from chiral HPLC ($[\alpha]_D$ +6.49°); *g*) NaH, abs. MeOH, 0 °C, 4 h, 44% ($[\alpha]_D$ +3.78° [lit.[4] $[\alpha]_D$ +4.0°]).

Chart 1



a) $NH_2CH_2CH_2OH$, EDC, dry CH_2Cl_2, r.t.., 12 h, 59%; *b*) (*S*)-**2**, EDC, dry CH_2Cl_2, 0°C, 3 h, 64%; *c*) i) CF_3COOH, 0 °C, 3 h; ii) $HOCOCH_2CH_2COCOOBn$, EDC, dry CH_2Cl_2, r.t.., 24 h, 40%; *d*) $Pd(OH)_2$–C/H_2, AcOEt, r.t., 6 h, 98% ($[\alpha]_D$ +6.52°,[8] [lit.[1] $[\alpha]_D$ +13.3°]).

Chart 2

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poured into 1 N HCl aq. (500 ml), then extracted with Et_2O (100 ml×3), and the solvent was removed. The residue was dissolved in aqueous saturated $NaHCO_3$ solution (400 ml) and washed with Et_2O (100 ml×3). The aqueous layer was made acidic with aqueous 10% HCl solution and extracted with Et_2O (200 ml×3). The ethereal layer was washed with brine, dried over anhydrous $MgSO_4$, and the solvent was removed. The layer in which the residue was dissolved in hot hexane was separated and the solvent was removed. Crystallization of the residue from Et_2O (10 ml) and recrystallization from Et_2O gave pure **2** (6.16 g, 49%) as colorless needles, mp 80—83 °C. *Anal.* Calcd for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41. Found: C, 64.32; H, 5.44. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.82, 2.84, 2.91, 2.93 (each 1H, each d), 5.06, 5.14 (each s, each 2H), 7.27—7.34 (10H, m). FAB-MS (positive ion mode) *m*/*z*: 373 $(M+1)^+$.

3) Gastaldi C., *Chemiches Zentralblatt*, **1923**, 152.
4) Nau C. A., Brown E. B., Bailey J. R., *J. Am. Chem. Soc*., **47**, 2596—2606 (1925).
5) Bergeron R. J., Xin M., Smith R. E., Wollenweber M., McManis J. S., Ludin C., Abboud K. A., *Tetrahedron*, **53**, 427—434 (1997).

6) $[\alpha]_D^{24}$ +6.52° (*c*=1.38, MeOH) ($[\alpha]_D^{20}$ +13.3° (*c*=1.4, MeOH)). ^{1}H-NMR (500 MHz, acetone-d_6) (Values in parentheses are reported ones[1]) δ: 1.47 (1.5H, d) (1.45), 1.50 (1.5H, d) (1.48), 2.15—2.26 (1H, m) (2.17—2.26), 2.40—2.61 (3H, m) (2.36—2.58), 2.83 (1H, d) (2.81), 2.84 (1H, d) (2.84), 2.97 (2H, d) (2.95, 2.96), 3.32—3.48 (2H, m) (3.32—3.52), 4.00 (0.5H, q) (4.00), 4.04—4.16 (2H, m) (4.07—4.16), 4.33 (0.5H, q) (4.30). ^{13}C-NMR (125 MHz, acetone-d_6) (Values in parentheses are reported ones[1]) δ: 14.4 (14.3), 14.7 (14.7), 33.2 (33.0), 34.5 (34.3), 39.2, 39.3 (39.0), 43.5 (43.4), 43.6 (43.4), 44.4 (44.2), 44.5 (44.3), 52.7 (52.5), 52.7 (52.7), 63.9 (63.9), 64.0 (64.0), 73.8 (73.6), 90.8 (90.7), 90.9 (90.9), 169.9 (170.0), 171.5 (171.6), 171.6 (171.7), 172.1 (171.9), 172.7 (172.6), 173.1 (173.0), 174.4 (174.2), 175.5 (175.4), 175.5 (175.5), 175.7 (175.6, 175.9). FAB-HRMS (positive ion mode) *m*/*z*: 435.1264 (Calcd. for $C_{16}H_{23}N_2O_{12}$: 435.1251). A diastereomer of **1** was prepared from (*R*)-**2** by the same synthetic method as **1**; $[\alpha]_D^{24}$ −12.4° (*c*=1.19, MeOH). ^{13}C-NMR (125 MHz, acetone-d_6) δ: 14.4, 14.8, 33.0, 34.5, 39.1, 39.3, 43.5, 43.7, 44.5, 44.7, 52.6, 52.8, 63.9, 64.3, 73.8, 90.9, 91.0, 169.7, 169.8, 171.5, 171.6, 171.9, 172.8, 173.1, 174.4, 175.7, 175.7, 175.9.

7) Natsugari H., Kawano Y., Morimoto A., Yoshioka K., Ochiai M., *J. Chem. Soc., Chem. Commun.*, **1987**, 62—63.

8) The value of the optical rotation of synthetic vibrioferrin was about half that of the reported one. We did not recieve an authentic sample of natural product. However, we think that our synthetic compound is almost optically pure, because the ratio of the mixture of epimers due to the 2‴ position of synthetic compound is the same as reported one. In the next paper, we will include additional details including the siderophore activity of the synthetic and natural compounds.