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Sugar-induced Stereoselectivity in the Fe^{3+}-complexation of Boronic Acid-appended Trihydroxamate-type Artificial Siderophores

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Two linear- and two tripodal-trihydroxamate siderophore mimics, suspending phenylboronic acid as the sugar-binding site, have been newly prepared. These siderophore mimics strongly bind Fe^{3+} ions to give rise to the ligand-Fe^{3+} 1:1 complexes over a wide range of pH 2 to 11. Circular dichroism (CD) spectra of these complexes in the presence of a sugar, D-fructose, exhibit moderately strong bisignate Cotton effects of first negative and second positive signs in aqueous alkaline media. The sign and extent of the observed CD signals depend largely on the solution pH and the concentration and absolute configuration of the bound sugars, implying that the phenylboronate-sugar covalent interactions are capable of inducing a chirality around the metal center.

Keywords: Phenylboronic acid, hydroxamic acid, siderophore, saccharide, stereochemistry

INTRODUCTION

A variety of microorganisms secrete low molecular-weight Fe^{3+} ion transport agents called siderophores [1,2], which solubilize Fe^{3+} ions and make them available for iron-deficient cells. Meanwhile, the development of new natural and artificial siderophores has recently been received considerable attention in therapeutic treatments of iron-overload syndrome [3].

The ion uptake is one of the key processes to regulate the bacterial growth of siderophore-requiring strains [4]; namely, the microbial ion transport is accomplished by the formation of the siderophore-Fe^{3+} complex, followed by its recognition by the siderophore-receptive protein existing in the outer membrane [5]. Thus, the expressing and controlling the chirality of the siderophore-Fe^{3+} complexes are a vital event for transport of Fe^{3+} ions in microbes. The siderophores will be generally classified into two categories depending on the chemical structure of the binding site: One is the enterobactin family containing three catecholate groups and the other is the ferrichrome family containing three hydroxamate groups. They both are capable of binding a Fe^{3+} ion to give the

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octahedral complexes in either a right-handed or a left-handed propeller-like arrangement [2]. Various siderophore mimicking molecular system equipped with a covalently-bonded chiral unit, leading to highly stereospecific complexation upon Fe^{3+} binding, have been reported thus far [6]. However, there have appeared no chiral trihydroxamate-Fe^{3+} complexes provided by reversible binding of a chiral source molecule such as a sugar to the receptive center of the mimics. Therefore, in this work we have designed and synthesized two different, liner and tripodal, types of trihydroxamates as artificial siderophores, which bear one and three phenylboronate moieties, respectively, as the sugar-responsive sites. These siderophore models do not involve any chiral center in themselves. The chemical structures and abbreviations of the models synthesized in this study are shown in Figure 1 and the preparations have been achieved according to the methods as described in Scheme.

Incidentally, phenylboronic acids have been well known as a prominent sugar-recognizing tool that interacts reversibly with two hydroxyl groups of saccharides and diols in the 1,2-*cis* or 1,3-*trans* orientation [7] to form a cyclic boronate ester, in particular, in aqueous alkaline media; recently, Shinkai and coworkers have prepared several metal-chelators with a phenylboronate group and have succeeded in controlling the chirality of the metal binding site in the presence of sugars [8].

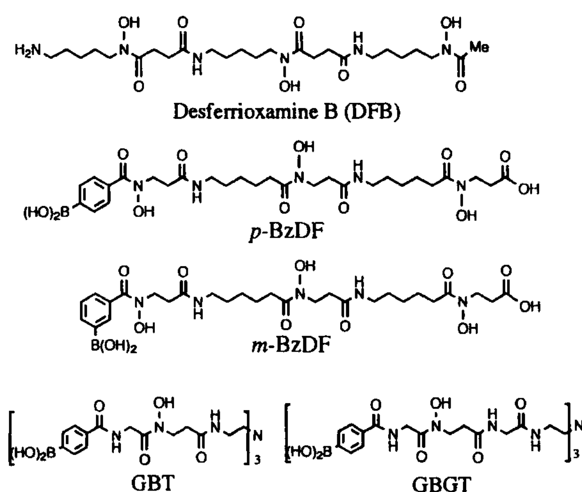

FIGURE 1 Structures of native and artificial siderophores used in this study.

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RESULTS AND DISCUSSION

Design of Ligands

The *m*- and *p*-dihydroxyboryl group-substituted benzoyl, linear tris(hydroxamate) derivatives (shown in Fig. 1; hereafter, ***m***- and ***p*-BzDFs**, respectively) have a set of three hydroxamic binders for a Fe^{3+} ion together with one terminal phenylboronic receptors for vicinal diols such as sugars. The *m*- and *p*-isomers have been synthesized to aim at evaluating the positional effect of the boryl group on the generation of the helical chirality around the Fe^{3+} center. As anticipated, the *m*- and *p*-BzDFs exhibit such characteristic sugar-dependent chirality as would be never observed for the naturally occurring, linear siderophore desferrioxamine B (**DFB**) [9]. The details will be described in the later section.

A complex of the linear tris(hydroxamate) ligands with a Fe^{3+} ion in solution will adopt five potential stereoisomers in fast equilibrium [10], *i.e.*, Δ- and Λ-enantiomeric *N-cis,cis*, *C-trans,cis*, *C-trans,trans*, *N-cis,trans*, and *N-trans,cis* [9,11]. To avoid such geometrical complexity, a symmetrically-tripodal tris(hydroxamate) ligand, **GBT**, having a nitrogen anchor assembling three peptide chains with a hydroxamate moiety and a phenylboronic acid terminus each, has been synthesized, where only Δ-*N-cis,cis* and Λ-*N-cis,cis* are allowed to exist owing to steric restrictions. It will become simple, therefore, to make qualitative evaluation of the Δ- over Λ-enantiomeric preference by circular dichroic (CD) spectroscopy. In order to examine the influence of the increased flexibility of the side chains on the complexation

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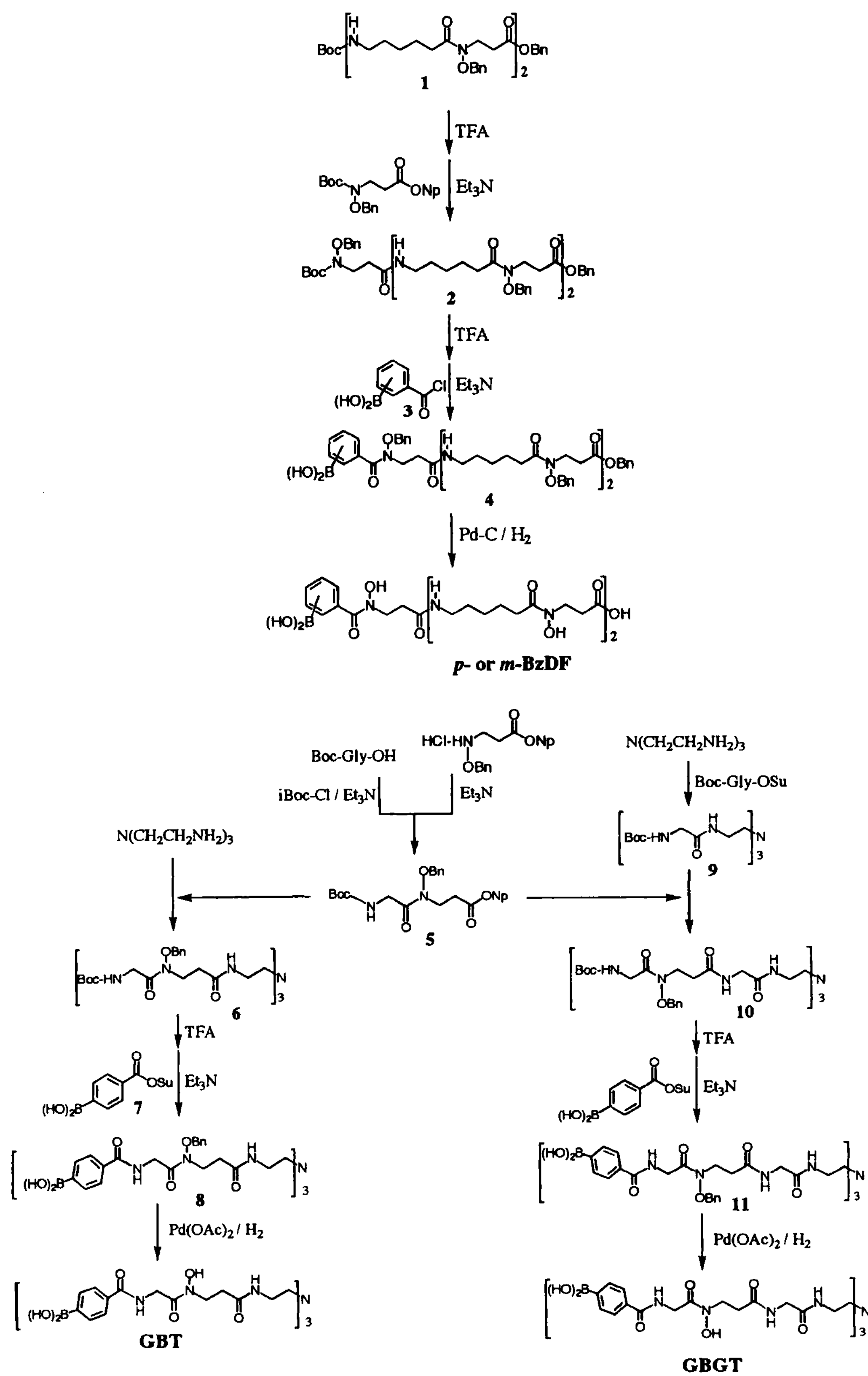

SCHEME Synthetic scheme for the siderophore analogs.

phenomena, the **GBGT** molecule has also been synthesized, in which a glycyl residue is employed as a spacer between the hydroxamate group and the nitrogen anchor of **GBT**.

Relative Stability of the Fe^{3+}-complexes of *m*- and *p*-BzDFs in the Absence or Presence of Sugars

An aqueous solution of equimolar mixtures of **BzDFs** and $Fe(NO_3)_3$ afforded a UV-vis spectrum involving a maximum absorption band at 425 nm due to the ligand-to-metal charge transfer (LMCT) band. The change in absorbance with changing molar concentrations of Fe^{3+} at a constant concentration of, for example, ***m*-BzDF** is shown in Figure 2 and the inset of Figure 2 displays a titration plot of the absorbance at 425 nm *versus* Fe^{3+} concentration, which has a sharp end point for ***m*-BzDF**:Fe^{3+}=1:1 in agreement with the formation of the ***p*-BzDF**-Fe^{3+} complex.

The stability constants for the Fe^{3+}-complexes of *m*- and ***p*-BzDF** and desferrioxamine B (**DFB**), for comparison, in the absence or presence of a constant concentration of D-fructose at pH 11 were determined by using competing reaction with EDTA [3, 12] and were monitored by following the decrease in absorbance at 425 nm. Table I summarizes the results thus obtained. Without the sugar, both stability constants of the ***m*-BzDF** and ***p*-BzDF**-Fe^{3+} complexes are smaller than that of the **DFB**-Fe^{3+}complex, indicating that the decrease in the stability is attributed to the bulkiness of the phenyl group. The ligand ***p*-BzDF** exhibited the same stoichiometric behavior as did ***m*-BzDF** to form a 1 : 1 complex, which was 160-fold more stable toward removal of Fe^{3+} by EDTA than the corresponding ***m*-BzDF** complex probably because of less electrostatic repulsion between the carboxylate and boronate anions in the *p*- *vs*. *m*-complexes.

Meanwhile, the addition of D-fructose results in 40-fold enhanced stability for the ***m*-BzDF**-Fe^{3+} complex, but only 1.5-fold for the *p*-complex. Inspection of CPK molecular models reveals that increased intramolecular hydro gen-bondings between the bound-sugar hydroxyl and the side-chain carboxylate groups contribute to the remarkable stabilization of the *m*-complex.

Figure 3 shows plots of the absorbances against increasing pH values from 1.0 through 12.5 for the *m*- and ***p*-BzDF**-Fe^{3+} complexes and, for comparison, the **DFB**-Fe^{3+} complex with or without a sugar, D-fructose. All the complexes possess pronounced stability in almost the whole pH ranges examined, although a sudden drop in absorbance was observed below pH 1.5 and above pH 12.0; the former drop being due probably to difficult deprotonation of the hydroxamate moieties in the strongly acidic region and the latter drop due to facile precipitation

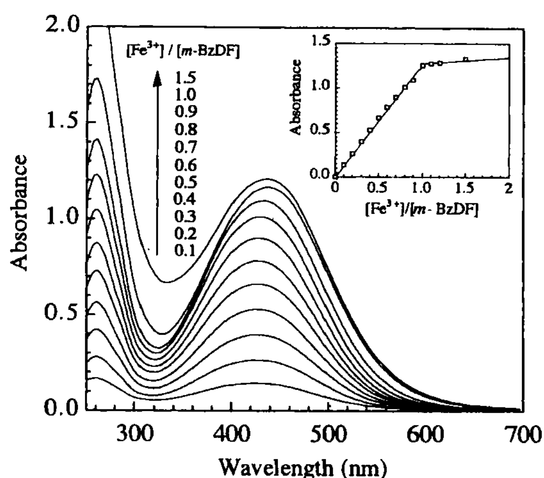

FIGURE 2 UV titration plots for the ***m*-BzDF**-Fe^{3+} complexation; [***m*-BzDF**] = 4.0 × 10^{-4} M; pH 5.0 (0.05 M acetate buffer).

TABLE I Stability constants of ferric complexes in the presence or absence of D-fructose

Ligand	Sugar	Log *K*
DFB	–	30.6
p-BzDF	–	28.8
p-BzDF	D-Fructose	29.0
m-BzDF	–	26.6
m-BzDF	D-Fructose	28.2

[Ligand] = [Fe^{3+}] = [EDTA] = 3.9 × 10^{-4} M, [D-fructose] = 0.05 M, pH 11.0 buffered with 0.05 M carbonate.

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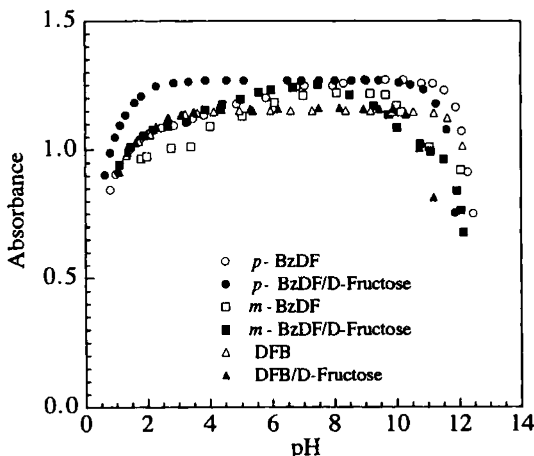

FIGURE 3 Plots of absorbance *vs.* pH for the Fe^{3+} complexation in the presence or absence of 0.1 M D-fructose; 25°C; pH adjusted with HCl and NaOH.

of Fe^{3+} ions as oxyhydroxide polymers in the strongly alkaline region. The added sugar exerted virtually no significant influence on both the absorbance and wavelength in the region from pH 7.0 to 10.0. In further alkaline region, however, the absorbance due to the 1:1 Fe^{3+} complexes decrease more in the presence *vs.* absence of the sugar. This decrease is due to the ligand exchange of the hydroxamate by deprotonated sugar molecules. On the other hands, the addition of a sugar resulted in a substantial increase in absorption in the pH region less than 7.0 for both ***m***- and ***p*-BzDF**-Fe^{3+} complexes. This observation suggests that the added sugar can covalently interact well enough with the dihydroxyboryl acid moiety even in acidic media, thereby to increase the solubility of the Fe^{3+} complexes in water; the complexes without sugars are inherently non-ionic and less hydrophilic, since both the carboxy and boryl groups are fully protonated in acidic media.

Effect of Added Saccharides on the Stereoselectivity

The configurations of siderophore-Fe^{3+} complexes can be determined by CD spectrophotometry. In general, Λ-isomers will exhibit a positive Cotton effect at the LMCT band, but Δ-isomers a negative Cotton effect [13]. Without addition of sugars, the complexes of Fe^{3+} with the ligands employed here (***p*-BzDF**, ***m*-BzDF**, **GBT**, and **GBGT**) were all CD-silent. Moreover, the ferric complex with DFB was CD-silent even in the presence of sugars. On the other hand, with addition of any sugars tested, all the complexes show an exciton coupling-type Cotton effect. In order to discover the possible relationship between the configuration of added saccharides and the sign of circular dichroism (CD) spectra, CD spectra have been taken in the presence of various monosaccharides. The spectra of ***p*-BzDF**-Fe^{3+} are displayed in Figure 4 and the relationship thus obtained is summarized in Table II. It is obvious that the signal signs are closely related to the configuration of the sugars used; namely, D-fructose, D-arabinose and D-mannose exhibit a negative Cotton effect, *i.e.*, negative at 420 nm and positive at 360 nm, with an isodichroic point at approximately 380 nm. The observation clearly indicates that the complex prefers to adopt a Δ-chirality. On the other hand, D-galactose and D-glucose exhibit a positive Cotton effect indicative of these

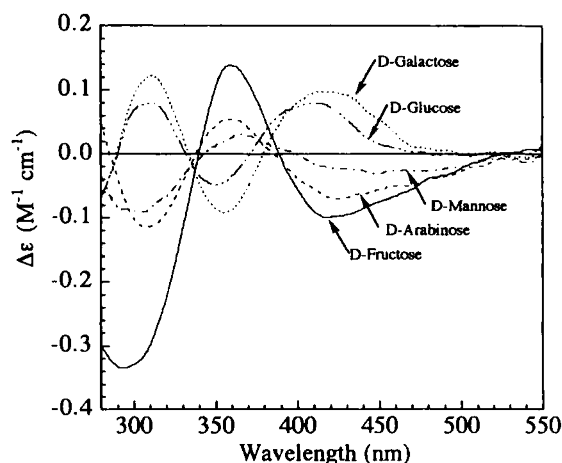

FIGURE 4 CD spectra of the ***p*-BzDF**-Fe^{3+} complex in the presence of saccharides; [***p*-BzDF**] = [Fe^{3+}] = 3.9×10^{-4} M; [Saccharide] = 0.1 M; pH 11.0 (0.05 M carbonate buffer).

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TABLE II Relationship between metal chirality and sugar configuration

Saccharide	λ/nm (Δε × 10^2)	Chirality	Configuration of 2-OH
D-Fructose	418,360 (−9.95, +13.8)	Δ	up [a]
D-Arabinose	424,360 (−7.05, +5.38)	Δ	up
D-Mannose	449,367 (−3.08, +3.02)	Δ	up
D-Galactose	416,356 (+9.69, −9.21)	Λ	down
D-Glucose	411,351 (+7.89, −4.86)	Λ	down

[a] See the text for definition.

complexes commonly having the same handedness (Λ) as that of the naturally occurring ferrichrome. As expected, the CD spectral curves with L-fructose are a mirror image of that with D-fructose (Fig. 5), reconfirming that Δ- and Λ-isomers are selectively produced in the presence of D- and L-fructose, respectively. As Table II shows, saccharides are designated as either "up" or "down" depending upon the configuration of the hydroxyl group next to the carbonyl group; that is to say, when the hydroxyl group in question possesses the same configuration as that of the asymmetric carbon atom at the lowest position in the vertical Fisher formula, the saccharides are designated as "down", while the opposite configuration "up". Thus, the "up" and "down" are well correlated with a negative and a positive Cotton effects, respectively, as shown in Table II. This correlation between the chirality of metal-complexes and the configuration of the hydroxyl group at the C-2 position of sugar is general in all complexes with respect to D-arabinose, D-mannose, D-galactose, and D-glucose.

Figure 6 shows plots of CD amplitudes at 425 nm *vs.* D-fructose concentrations at pH 11 at constant concentrations of ligands and Fe^{3+} ion with *m*- and *p*-**BzDFs**. The saturation of the intensity occurred at a fructose concentration of 0.02 M (Fig. 6). The neighboring sugar unit can approach the metal center more closely in the *m*-complex than in the *p*-complex, because the *m*-complex exhibits the CD intensity stronger than the *p*-complex. The geometrical situations are depicted in Figure 9.

Figure 7 shows plots of CD intensities *vs.* medium pH values under the same conditions described above; with *p*-**BzDF** the CD intensity starts to increase from pH 7.0 and then saturates at pH 10. On the other hand, the CD intensity increasing for the *m*-**BzDF** occurs at pH 8.5 – 11.0

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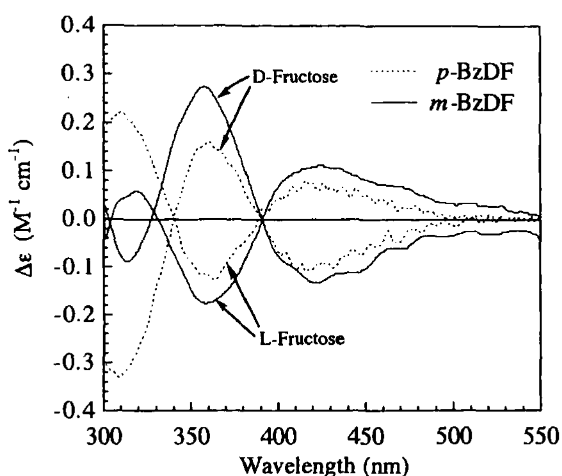

FIGURE 5 CD spectra of the *p*-(- - -) and *m*-( ) **BzDF**-Fe^{3+} complexes in the presence of 0.05 M D- or L-fructose at pH 11.

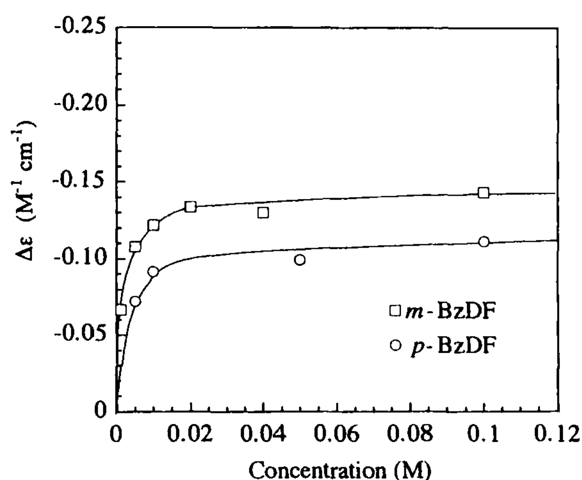

FIGURE 6 Plots of Δε at λmax 425 nm *vs.* D-fructose concentration; [*p*-**BzDF**] = [*m*-**BzDF**] = [Fe^{3+}] = 4.0 × 10^{-4} M; pH 11.0 (0.05 M carbonate buffer).

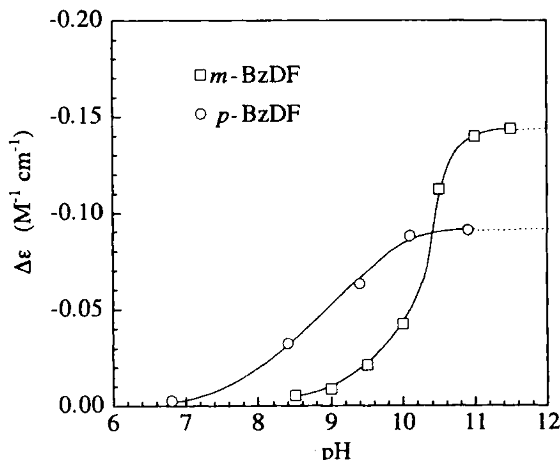

FIGURE 7 Plots of $\Delta\varepsilon$ at λmax 425 nm *vs.* pH in 0.02 M D-fructose aqueous solution.

higher than the increasing for the ***p*-BzDF**. This can be accounted for by the electron-withdrawing nature of the hydroxamate group; the boron atom at the *p*-position to the carbonyl carbon is relatively electron-deficient as compared to that at the *m*-position. Thus, the boron atom at the *p*-position is more susceptible to acceptance of an OH^- anion than at the *m*-position. In general, it is well known that an OH^- anion adds to the sp^2 hybrid orbital of a boron atom around pH 9.0 to give rise to the sp^3 boron orbital favorable for sugar binding as shown in Figure 8 [14]. Thus, the increases in the CD amplitudes with increasing pHs are indicative of OH^- addition to the boron atom, which alters the boron orbitals from a planar sp^2 to tetrahedral sp^3 to force the bound sugar to approach the metal center, as depicted in Figure 9. It is concluded, therefore, that the close proximity of the bound chiral source sugar and the metal center is crucial for stereoselective complexation.

The CD spectra of the complexes of the tripodal type (**GBT** and **GBGT**) in the presence of D-fructose, as shown in Figure 10, are particularly interesting when comparing its performance with those of the linear type ligands. Both of the tripodal complexes provide a more intense Cotton effect (1.5-fold) with a negative exciton coupling than does the corresponding linear ***p*-BzDF** complex; when the proportion of the bound sugar reaches a saturation level, a second and a third sugar molecules of the three bound-sugar molecules are also capable of cooperatively contributing to the stereoselectivity in case of the tripodal ligands, although only one sugar in the case of the linear ligands. However, the second and third sugar molecules attached to the boron would be less effective in inducing chirality due to steric and electrostatic repulsion between them. In fact, linear trihydroxamate derivatives (***p*-BzDF** and ***m*-BzDF**) showed the saturation of CD intensity around the concentration of 0.02 M D-fructose, while tripodal models required still higher concentration for the complete saturation.

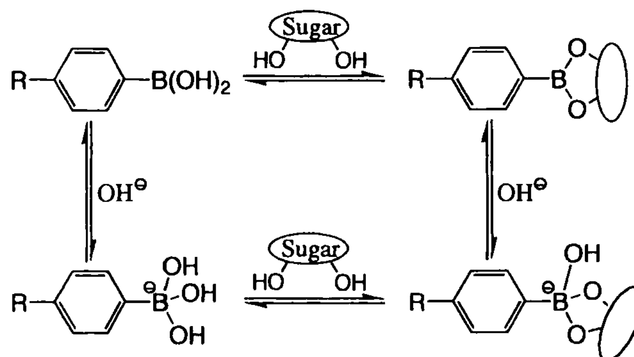

FIGURE 8 Saccharide binding to phenylboronic acid.

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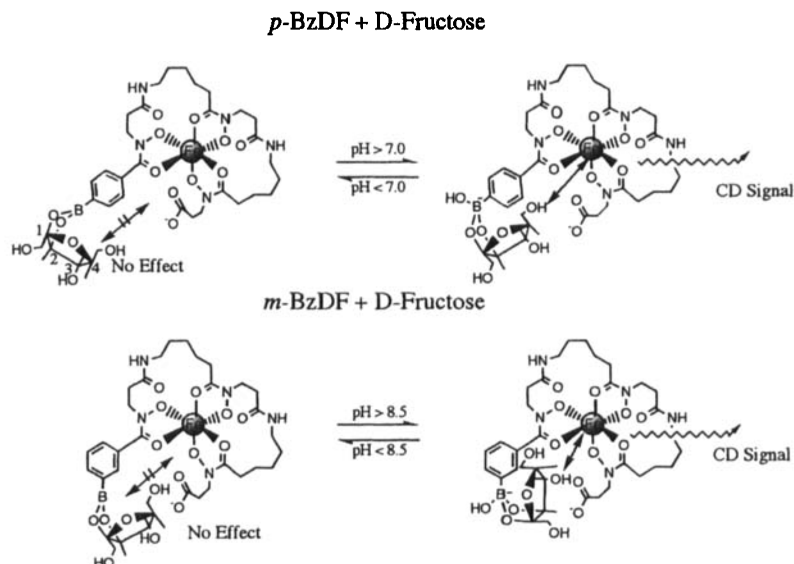

FIGURE 9 The closest proximity between the bound sugar and the metal center in each complexation.

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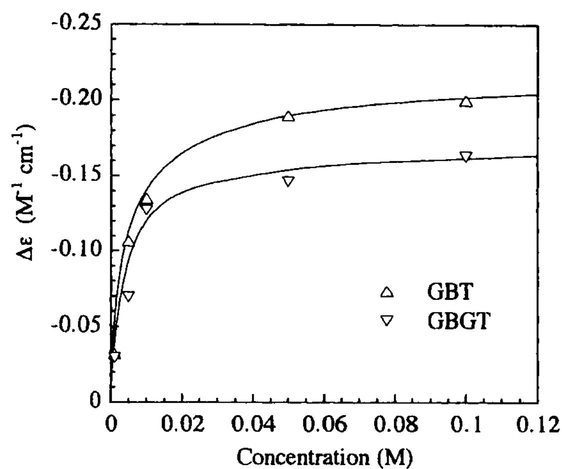

FIGURE 10 Plots of at Δε at λmax 425 nm *vs.* D-fructose concentration; [**GBT**] = [**GBGT**] = [Fe^{3+}] = 4.0 × 10^{-4} M; pH 11.0 (0.05 M carbonate buffer).

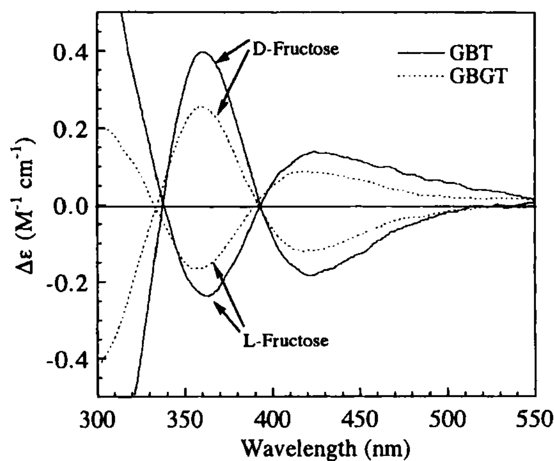

FIGURE 11 CD spectra of the **GBT**(–) and **GBGT**(- - -)-Fe^{3+} complexes in the presence of 0.05 M D- or L-fructose at pH 11.

Meanwhile, the extent of the right handedness (Δ) for the **GBGT** complex is lower than for the **GBT** complex due probably to the former bearing relatively longer spacers with higher flexibility at the periphery of the coordination site than the later. Thus, **GBGT** with glycyl spacers reduces the stereoselectivity as compared to **GBT**. Of course, the sign of the exciton coupling was perfectly reversed, when L-fructose was substituted for D-fructose (Fig. 11).

CONCLUSIONS

This work demonstrated that the chirality of the sugar covalently bound to the molecular terminus of the artificial siderophores is transmitted

to the metal center, and the chiral stereoselectivity can be controlled by adding sugars to the system. Unfortunately, we have not examined the iron uptaking ability of microorganisms in the presence of the sugar-suspending siderophore mimics, since the present system can function only in the alkaline region. We are now preparing sugar-responsive artificial siderophores acting in the neutral region, accordingly. The results will appear elsewhere in the near future.

EXPERIMENTAL SECTIONS

Instruments

^{1}H-NMR and infrared spectra were recorded on a Jeol JNM-A400 FT NMR and a Simadzu FTIR-8200A spectrophotometers, respectively. UV-Vis and CD spectra were measured on a Shimadzu UV-2500PC spectrophotometer and a Jasco J-720 circular dichroism spectrophotometers. The solution pH was measured with a Toa HM-30V digital pH meter. HPLC purification was performed by JAI LC-908 recycling preparative HPLC using a column packed with a JAIGEL-ODS, S-343-15.

Materials

$Fe(NO_3)_3 \cdot 9H_2O$ was purchased from Tokyo Kasei Co. (Tokyo, Japan) and used as received. Protected amino acids were of special grade and purchased from Peptide Institute Inc. and used without further purification. *N*-(tert-Butoxycarbonyl)-6-aminohexanoyl-*N*-benzyloxy-β-alanyl-6-aminohexanoyl-*N*-benzyloxy-β-alanine benzyl ester (**1**) [15], *m*- and *p*-dihydroxyborylbenzoyl chloride (**3-*m*** and **3-*p***) were prepared according to literature procedures [16]. Solvents were distilled after drying. A "standard work-up" consists of filtration, rotary-evaporation of the solvent, extracting into ethyl acetate, washings successively with three 50 mL portions of 5% citric acid, three 50 mL portions of 5% Na_2CO_3, and 50 mL brine, separation of the organic layer, drying over $MgSO_4$, condensation, and purification by chromatography on silica gel.

The following abbreviations have been used: Ac, acetyl; Bn, benzyl; Boc, tert-butyloxycarbonyl; DMF, *N,N*-dimethylformamide; DMSO, dimethylsulfoxide; iBoc, iso-butyloxycarbonyl; Su, succinimide; TFA, trifluoroacetic acid; WSC, water soluble carbodiimide.

Measurements of UV-vis and CD Spectra

A typical procedure: UV-vis spectral measurements were performed in a thermostated cell holder maintained at 25°C throughout and the following protocol was typically employed: A buffered solution (3.00 mL) of 1.91×10^{-4} M trihydroxamate ligands of various pHs was placed in the cell unless otherwise noted. The concentrations of $Fe(NO_3)_3 \cdot 9H_2O$ were changed over the range of 0 to 3.00×10^{-4} M. In the presence of sugars, a given amount of, for example, D-fructose (5.40 mg, 0.10 M) as a solid was added to the mixed solution. In addition to carbonate and acetate buffers, 0.05–1.00 M HCl and NaOH solutions were employed to adjust the solution pH in highly acidic and alkaline regions. After UV-vis measurements, the same samples were also employed for the CD measurements.

Iron Exchange Reaction

The iron complex solution of ligands was prepared by mixing a stock solution of the ligands (3.00 mL, 4.00×10^{-4} M, in pH 11.0 carbonate buffer) with $Fe(NO_3)_3 \cdot 9H_2O$ (50.0 µL, 2.41×10^{-2} M in MeOH). An EDTA stock solution was prepared by dissolving EDTA $\cdot$ 2Na $\cdot$ $2H_2O$ in pH 11.0 carbonate buffer solution to give a concentration of 1.86×10^{-2} M. Ligands exchange reactions were initiated by

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mixing 3.00 mL of the iron complex solution with 50.0 µL of the EDTA solution at 25°C. The kinetics of iron exchange was monitored spectrophotometrically at 425 nm. After the iron exchange had been equilibrated, 5.40 mg of D-fructose was added to the solution, and the reaction was monitored by following the decreasing absorbance at 425 nm.

Syntheses

N-(tert-Butoxycarbonyl)-N-benzyloxy-β-alanyl-6-aminohexanoyl-N-benzyloxy-β-alanyl-6-aminohexanoyl-N-benzyloxy-β-alanine Benzyl Ester (2)

Compound 1 (2.20 g, 2.83 mmol) was treated with TFA (15 mL) in anhydrous CH_2Cl_2 (15 mL) for 1 hour at room temperature under N_2. After excess TFA was rotary-evaporated at reduced pressure, the residue was dissolved in dry THF (30 mL) and 2.10 mL of Et_3N (15.1 mmol) was added. To the stirred solution was added dropwise *N*-(tert-butoxycarbonyl)-*N*-benzyloxy-β-alanine *p*-nitrophenyl ester (1.20 g, 1.0 eq) in dry THF (20 mL). The mixture was stirred overnight at room temperature, and subjected to the standard work-up using AcOEt/*n*-hexane (2:3) and $CHCl_3$/MeOH (10:1) as eluents to yield the desired product as a colorless oil: yield: 2.60 g (95%); IR (neat) 1732 (—CO_2—), 1699 (—OCON—), 1651 (—CON—), 748 and 700 (—Ph) cm^{-1};. ^1H-NMR ($CDCl_3$): δ 1.26 (m, 4H, γ-CH_2 of hexanoic acid), 1.42–1.60 (m, 17H, β- and δ-CH_2 of hexanoic acid and CH_3 of Boc), 2.32 (m, 4H, α-CH_2 of hexanoic acid), 2.45 (m, 4H, α-CH_2 of β-alanine), 2.62 (t, $J = 6.6$ Hz, 2H, —CH_2 CO_2Bn), 3.18 (m, 4H, ε-CH_2 of hexanoic acid), 3.75–3.96 (m, 6H, β-CH_2 of β-alanine), 4.76, 4.81 and 4.83 (s × 3, 6H, CH_2 of -$NOCH_2$Ph), 5.05 (s, 2H, CH_2 of —CO_2CH_2Ph), 5.98 and 6.22 (s, br, 2H, CONH), 7.29–7.37 (m, 20H, —Ph); Elemental Anal. Calcd. for $C_{54}H_{71}N_5O_{11}$: C, 67.13; H, 7.41; N, 7.25%. Found: C, 67.31; H, 7.49; N, 7.20%.

N-(p-Dihydroxyborylbenzoyl)-N-benzyloxy-β-alanyl-6-aminohexanoyl-N-benzyloxy-β-alanyl-6-aminohexanoyl-N-benzyloxy-β-alanine Benzyl Ester (4-p)

Compound **2** (2.60 g, 2.69 mmol) was treated with TFA (15.0 mL, 20 eq) in anhydrous CH_2Cl_2 (20 mL) for 1 hour at room temperature under N_2. Excess TFA was removed by rotary evaporation. The residue was dissolved in dry THF (30 mL), Et_3N (4.90 mL, 35.2 mmol) was added, and then compound **3-*p*** (1.2 eq) in dry THF (30 mL) was added dropwise. The mixture was allowed to stir overnight at room temperature, and it was subjected to the standard work-up using $CHCl_3$/MeOH (10:1) to yield the product as a colorless oil: 2.05 g (70%); IR (neat) 1742, (—CO_2—), 1680–1640, (—CON—), 750 and 705 (—Ph) cm^{-1}; ^1H-NMR ($CDCl_3$): δ 1.23 (m, 4H, γ-CH_2 of hexanoic acid), 1.30–1.52 (m, 8H, β- and δ-CH_2 of hexanoic acid), 2.25 (m, 4H, α-CH_2 of hexanoic acid), 2.40 (m, 4H, α-CH_2 of β-alanine), 2.60 (t, $J = 6.6$ Hz, 2H, CH_2 of —CH_2CO_2Bn), 3.18 (m, 4H, ε-CH_2 of hexanoic acid), 3.75–4.01 (m, 6H, β-CH_2 of β-alanine), 4.85 (s, 6H, CH_2 of — $NOCH_2$Ph), 5.09 (s, 2H, CH_2 of —CO_2CH_2Ph), 6.30 and 6.49 (s, br, 2H, CONH), 7.30 (m, 20H, —Ph), 7.70 (d, $J = 8.0$ Hz, 2H, *m*-ArH to —$B(OH)_2$), 7.91 (d, $J = 8.0$ Hz, 2H, *o*-ArH to —$B(OH)_2$), 8.00 (s, br, 2H, —$B(OH)_2$).

N-(m-Dihydroxyborylbenzoyl)-N-benzyloxy-β-alanyl-6-aminohexanoyl-N-benzyloxy-β-alanyl-6-aminohexanoyl-N-benzyloxy-β-alanine Benzyl Ester (4-m)

4-*m* was prepared analogous to a procedure for preparation of **4-*p*** from **2** and **3-*m***, and obtained as a colorless oil: yield, 200 mg (76%); IR (neat); 1737, (—CO_2—), 1688–1637, (—CON—), 750 and 700 (—Ph) cm^{-1}; ^1H-NMR ($CDCl_3$): δ 1.25 (m, 4H, γ-CH_2 of hexanoic acid), 1.40–1.60 (m, 8H, β-and δ-CH_2 of hexanoic acid), 2.30 (m, 4H, α-CH_2 of hexanoic acid), 2.48 (m, 4H, α-CH_2 of β-alanine), 2.62 (t, $J = 6.4$ Hz, 2H, CH_2 of

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—CH_2CO_2Bn), 3.12 and 3.22 (s, 4H, ε-CH_2 of hexanoic acid), 3.95–3.97 (m, 6H, β-CH_2 of β-alanine), 4.76–4.79 (s, 6H, CH_2 of —$NOCH_2Ph$), 5.05 (s, 2H, CH_2 of —CO_2CH_2Ph), 6.60–6.80 (s, br, 2H, CONH), 7.17 (s, 1H, *o*-ArH to —$B(OH)_2$), 7.26–7.36 (m, 20H, —Ph), 7.65 (m, 1H, *m*-ArH to —$B(OH)_2$), 7.97 (d, *J* = 8.0 Hz, 2H, *o*- and *p*-ArH to —$B(OH)_2$).

N-(p-Dihydroxyborylbenzoyl)-N-hydroxy-β-alanyl-6-aminohexanoyl-N-hydoxy-β-alanyl-6-aminohexanoyl-N-hydroxy-β-alanine (p-BzDF)

Compound **4-*p*** (2.00 g, 1.84 mmol) in MeOH (20 ml) was debenzylated with $Pd(OAc)_2$ (200 mg) under H_2 for 12 h at ambient temperature. After the completion of reaction having been confirmed by ^{1}H-NMR, the catalyst was filtered off. The evaporation of the solvent under reduced pressure gave the residue, which was purified by HPLC using MeOH as eluent to afford ***p*-BzDF** as a colorless amorphous solid: yield, 920 mg (73%); IR (KBr) 3600–2700 (OH), 1685–1640 (—CON—) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.30 (m, 4H, γ-CH_2 of hexanoic acid), 1.43 (m, 4H, δ-CH_2 of hexanoic acid), 1.52 (m, 4H, β-CH_2 of hexanoic acid), 2.36 (m, 8H, α-CH_2 of hexanoic acid and α-CH_2 of β-alanine), 2.54 (m, 2H, —CH_2COO—), 3.04 (m, 4H, ε-CH_2 of hexanoic acid), 3.72 (m, 4H, β-CH_2 of β-alanine), 3.83 (m, 2H, β-CH_2 of β-alanine), 7.41 and 7.59 (s, br, 2H, CONH), 7.52 (d, *J* = 8.0 Hz, 4H, *m*-ArH to —$B(OH)_2$), 7.79 (d, *J* = 8.0 Hz, 2H, *o*-ArH to —$B(OH)_2$); MS (SIMS$^-$): m/z 653.2 (M-H$^+$)$^-$; Elemental Anal. Calcd. for $C_{28}H_{44}BN_5O_{12} \cdot CH_3OH$: C, 50.81; H, 7.06; N, 10.22%. Found: C, 50.63; H, 6.99; N, 9.96%.

N-(m-Dihydroxyborylbenzoyl)-N-hydroxy-β-alanyl-6-aminohexanoyl-N-hydoxy-β-alanyl-6-aminohexanoyl-N-hydroxy-β-alanine (m-BzDF)

The hydrogenolysis of compound **4-*m*** (1.80 g, 1.7 mmol) with H_2-$Pd(OAc)_2$ was achieved according to a procedure for preparation of ***p*-BzDF**, affording the crude ***m*-BzDF**. The crude product was purified by HPLC using a linear MeOH/H_2O gradient from 70/30 to 80/20 at 20 min. The lyophilization afforded a white powder: 130 mg (12%); mp 245–250°C (decomp.); IR (KBr) 3600–2700 (—OH), 1740 (—CO_2—), 1634 (—CON—) cm^{-1}; ^{1}H-NMR (D_2O) δ 1.70 (m, 4H, γ-CH_2 of hexanoic acid), 1.88 (m, 8H, β-and δ-CH_2 of hexanoic acid), 2.79 (m, 4H, α-CH_2 of hexanoic acid), 2.84–3.01 (m, 6H, α-CH_2 of β-alanine), 3.52 (t, *J* = 7.0 Hz, 4H, ε-CH_2 of hexanoic acid), 4.16–4.24 (m, 6H, β-CH_2 of β-alanine), 7.63 (d, *J* = 7.6 Hz, 1H, *p*-ArH to carbonyl), 7.72 (t, *J* = 7.6 Hz, 1H, *m*-ArH to carbonyl), 7.96 (s, 1H, *o*-ArH to carbonyl), 8.01 (d, *J* = 7.6 Hz, 1H, *o*-ArH to carbonyl); MS (FAB): m/z 708.4 (M+Glycerol-2(H_2O)-H$^+$)$^-$; Elemental Anal. Calcd. for $C_{28}H_{44}BN_5O_{12} \cdot CH_3OH \cdot H_2O$: C, 49.51; H, 7.16; N, 9.95%. Found: C, 49.39; H, 7.01; N, 9.58%.

N-(tert-Butoxycarbonyl)-glycyl-N-benzyloxy-β-alanine p-Nitrophenyl Ester (5)

N-Benzyloxy-β-alanine *p*-nitrophenyl ester hydrochloride (7.00 g, 1.1 eq) was sonicated in dry THF (40 mL) containing Et_3N (2.80 mL, 1.1 eq) for 30 min. The supernatant was filtered. Meanwhile, Et_3N (2.80 mL, 1.1 eq) was added to the stirred solution of *N*-Boc-glycine (3.16 g, 18.0 mmol) in dry THF (100 mL) and cooled to −17°C and then a solution of isobutyl chloroformate (2.60 mL, 1.1 eq) in dry THF (30 mL) was added dropwise slowly at −17°C under N_2 and stirred for 10 hours. To this solution the supernatant solution prepared above was added dropwise at −17°C under N_2. After being stirred at −17°C for 12 h, the mixture was subjected to the standard work-up using AcOEt/*n*-hexane (2 : 3) as eluent to yield the desired product as a pale yellow oil: 6.21 g (72%); IR (neat) 1772 (—CO_2—), 1720 (—OCON—), 1680 (—CON—) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.50 (s, 9H, CH_3 of Boc), 2.83 (t, *J* = 6.4 Hz, 2H,

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α-CH_2 of β-alanine), 4.09–4.15 (br, 4H, β-CH_2 of β-alanine and CH_2 of glycine), 4.88 (s, 2H, —$NOCH_2Ph$), 5.23 (s, br, 1H, CONH), 7.08 (d, $J = 8.8$ Hz, 2H, *m*-ArH to —NO_2), 7.27–7.41 (br, 5H, —Ph), 8.16 (d, $J = 8.8$ Hz, 2H, *o*-ArH to —NO_2); Elemental Anal. Calcd. for $C_{23}H_{27}N_3O_8$: C, 58.35; H, 5.75; N, 8.87%. Found: C, 58.60; H, 5.86; N, 8.80%.

Tris [2-[3-[2-[N-(tert-butoxycarbonyl) amino]ethan-N-benzyloxyamido] propanamido]ethyl]amine (6)

A solution of compound **5** (5.50 g, 3.3 eq) in dry THF (20 mL) was added dropwise to a solution of tris(2-aminoethyl)amine (0.44 g, 3.01 mmol) in dry THF (20 mL) at 36°C under an atmosphere of nitrogen. After being stirred overnight, the mixture was subjected to the standard work-up using AcOEt/*n*-hexane (2 : 3) and $CHCl_3$/MeOH (10 : 1) to yield the desired product as a colorless amorphous solid: 3.20 g (91%); IR (KBr) 1655 (—CON—) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.42 (s, 27H, CH_3 of Boc), 2.37–2.47 (m, 12H, —NCH_2CH_2N—), 3.13 (s, br, 6H, α-CH_2 of β-alanine), 3.96–4.01 (m, 12H, β-CH_2 of β-alanine and CH_2 of glycine), 4.83 (s, 6H, CH_2 of —$NOCH_2Ph$), 5.43–6.88 (s, br, 6H, CONH), 7.32–7.38 (m, 15H, —Ph).

p-Dihydroxyborylbenzoic Acid N-hydroxysuccinimide Ester (7)

4-Carboxyphenylboronic acid (6.00 g, 36.16 mmol) and *N*-hydroxysuccinimide (8.32 g, 2.0 eq) was dissolved in anhydrous DMF (100 mL) and cooled to −10°C under N_2. To the solution was added WSC·HCl (13.86 g, 2.0 eq) in anhydrous CH_2Cl_2 (150 mL). The reaction mixture was stirred overnight. After evaporation of the solvent in vacuo, the resi due was taken up in ethyl acetate (400 ml) and washed with three 50 ml portions of water and with brine. The organic layer was dried over $MgSO_4$, and concentrated to yield the desired product as a white solid: 8.35 g (96%); mp 173–176°C; IR (KBr) 1740 (—CO_2—) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.91 (s, 4H, —CH_2CH_2—), 8.04 (dd, $J = 7.7$ Hz, 4H, ArH), 8.47 (s, 2H, —$B(OH)_2$).

Tris[2-[3-[2-[N-(p-dihydroxyborylbenzoyl) amino]ethan-N-benzyloxyamido]propanamido] ethyl]amine (8)

Compound **6** (1.00 g, 0.84 mmol) was stirred with TFA (7.68 mL, 80 eq) in anhydrous CH_2Cl_2 (20 mL) for 1 hour at room temperature under N_2. Excess TFA and the solvent were removed by evaporation under reduced pressure. The residue was dissolved in dry DMSO (40 mL) and Et_3N (1.49 mL, 10.6 mmol) was added. Compound **7** (0.70 g, 3.6 eq) in dry THF (20 mL) was added dropwise to deprotected **6**. After the reaction was stirred for 3 days, the solvent was rotary-evaporated. The crude product was purified by HPLC using MeOH/H_2O (3:1) to give **8** as a white amorphous powder: yield, 323 mg (32%); ^{1}H-NMR (DMSO-d_6) δ 2.50 (s, 12H, —NCH_2CH_2N—), 3.15 (s, 6H, β-CH_2 of β-alanine), 3.89 (s, 6H, CH_2 of glycine), 4.20 (s, 6H, α-CH_2 of β-alanine), 4.97 (s, 6H, CH_2 of —$NOCH_2Ph$), 7.20–7.46 (m, 15H, ArH of benzyl), 7.77–7.89 (m, 12H, ArH of phenylboronic acid).

Tris[2-[3-[2-[N-(p-dihydroxyborylbenzoyl) amino]ethan-N-hydroxyamido]propanamido] ethyl]amine (GBT)

The hydrogenolysis of compound **8** (500 mg, 0.40 mmol) afforded the crude **GBT** using a procedure for the preparation of ***p*-BzDF**. The crude product was purified by HPLC using MeOH/H_2O (3 : 1) to yield **GBT** as a white amorphous powder: yield, 70 mg (18%); IR (KBr) 3300 (—OH), 1650 (—CON—) cm^{-1}; ^{1}H-NMR (D_2O) δ 2.46–2.56 (s, 12H, —NCH_2CH_2N—), 3.15 (s, 6H, α-CH_2 of β-alanine), 3.72 (s, 6H, CH_2 of glycine), 4.19 (s, 6H, β-CH_2 of β-alanine), 7.56 (m, 12H, ArH); Elemental Anal. Calcd. for

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$C_{48}H_{66}B_3N_{13}O_{21} \cdot 3(H_2O)$: C, 46.86; H, 5.90; N, 13.01%. Found: C, 46.53; H, 6.02; N, 12.74%.

Tris[2-[2-[N-(tert-botoxycarbonyl)amino] ethanamido] ethyl]amine (9)

A solution of *N*-Boc-glycine *N*-hydroxysuccinimide ester (2.10 g, 3.2 eq) in dry THF (20 mL) was added dropwise to a solution of tris(2-aminoethyl)amine (0.34 g, 2.30 mmol) in dry THF (20 mL) at 35°C under N_2. After being stirred overnight, the reaction mixture was subjected to the standard work-up using $CHCl_3$/MeOH (10:1) as eluents, affording the desired product as a colorless amorphous solid: yield, 1.15 g (75%) IR (KBr) 3308 (—NH), 1701 (—OCON—), 1659 (—CON—) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.44 (s, 27H, CH_3 of Boc), 2.55 (t, $J = 5.2$ Hz, 6H, —$NHCH_2CH_2N$—), 3.27 (dt, $J = 5.2$ Hz, 6H, —$NHCH_2CH_2CO$—), 3.82 (d, $J = 5.6$ Hz, 6H, CH_2 of glycine), 5.81 (s, 3H, OCONH), 7.19 (s, 3H, CONH).

Tris[2-[2-[3-[2-[N-(tert- butoxycarbonyl) amino]ethan-N- benzyloxyamido] propanamido] ethanamido]ethyl]amine (10)

Compound **9** (1.13 g, 1.71 mmol) was treated with TFA (10.5 mL, 80 eq) in anhydrous CH_2Cl_2 (20 mL) for 3 hour at room temperature under N_2. Excess TFA and the solvent were removed under reduced pressure. The remaining product was dissolved in dry THF (30 mL) and Et_3N (1.67 mL, 12.0 mmol) was added. A solution of compound **5** (2.67 g, 3.3 eq) in dry THF (20 mL) was added dropwise to deprotected **9** (0.44 g, 3.01 mmol) at 36°C under N_2 atmosphere. After being stirred overnight, the mixture was subjected to the standard work-up using AcOEt/*n*-hexane (2:3) and $CHCl_3$/MeOH (10:1) as eluents to afford the desired product as a colorless amorphous solid: 1.43 g (90%); IR (KBr) 3315 (—NH), 1705 (—OCON—), 1657 (—CON—), 754 and 700 (—Ph) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.43 (s, 27H, CH_3 of Boc), 2.45–2.53 (m, 12H, —NCH_2CH_2N—), 3.12 (s, 6H, α-CH_2 of β-alanine), 3.85 (s, 6H, CH_2 of glycine), 3.97–4.04 (s, 12H, β-CH_2 of β-alanine and CH_2 of glycine), 4.84 (s, 6H, CH_2 of $NOCH_2Ph$), 5.41 (s, 3H, OCONH), 7.10 (s, 6H, CONH), 7.10–7.38 (m, 21H, —Ph and CONH).

Tris[2-[2-[3-[2-[N-(p-dihydroxyborylbenzoyl) amino]ethan-N-benzyloxyamido] propanamido] ethanamido]ethyl]amine (11)

Compound **10** (1.43 g, 1.05 mmol) was treated with TFA (6.50 mL, 80 eq) in anhydrous CH_2Cl_2 (20 mL) for 3 hour at room temperature under N_2. Excess TFA and the solvent were rotary-evaporated. The residue was dissolved in dry THF (30 mL) and Et_3N (1.40 mL, 10.1 mmol) was added. Compound **7** (0.70 g, 3.6 eq) in dry THF (20 mL) was added dropwise to deprotected **10**. The reaction mixture was stirred overnight. After evaporation of the solvent, the residue was purified by HPLC using with MeOH/H_2O (3:1) to give the product as a white amorphous powder: yield, 330 mg (24%); IR (KBr) 3000–3760 (—NH and —OH), 1649 (—CON—), 702 and 754 (—Ph) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.53 (m, 12H of —NCH_2CH_2N—), 3.13 (dt, $J = 6.0$ Hz, 6H, α-CH_2 of β-alanine), 3.69 (d, $J = 5.6$ Hz, 6H, CH_2 of glycine), 3.89 (t, $J = 7.0$ Hz, 6H, CH_2 of glycine), 4.18 (d, $J = 6.0$ Hz, 6H, β-CH_2 of β-alanine), 4.96 (s, 6H, CH_2 of $NOCH_2Ph$), 7.26 (t, br, 6H, —$B(OH)_2$), 7.36–7.45 (m, 15H, —Ph), 7.53, 7.66 and 8.00 (s, br, 9H, CONH), 7.77 and 7.83 (dd, $J = 8.4$ Hz, 12H, ArH of phenylboronic acid).

Tris[2-[2-[3-[2-[N-(p-dihydroxyborylbenzoyl) amino]ethan-N-hydroxyamido]propanamido] ethanamido]ethyl]amine (GBGT)

The hydrogenolysis of compound **11** (330 mg, 0.28 mmol) afforded the crude **GBGT** according to the procedure for preparation of ***p*-BzDF**. The crude product was purified by HPLC using MeOH/H_2O (3:1), affording the product as a white amorphous powder: yield, 50 mg (19%); ^{1}H-NMR (D_2O) δ 2.59–2.68 (m, 12H,

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—NCH_2CH_2N—), 2.83 (m, 6H, α-CH_2 of β-alanine), 3.38 (m, 6H, CH_2 of glycine), 3.67 (m, 6H, CH_2 of glycine), 3.85 (m, 6H, β-CH_2 of β-alanine), 7.71 and 7.73 (dd, $J = 8.4$ Hz, 12H, ArH); Elemental Anal. Calcd. for $C_{48}H_{66}B_3N_{13}O_{21} \cdot CH_3OH \cdot H_2O$: C, 47.33; H, 5.84; N, 14.64%. Found: C, 47.08; H, 5.98; N, 14.40%.

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