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FULL PAPER

Convergent Synthesis of Macrocyclic and Linear Desferrioxamines

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Abstract: Polyhydroxamate desferrioxamines (DFO) are nontoxic siderophores endowed with high potential for development of therapeutic chelating agents. Here we report a modular and convergent strategy for diverse synthesis of macrocyclic and linear DFOs. The strategy employed orthogonally protected *N*-hydroxy-*N*-succinylcadaverine building blocks, which allowed bidirectional extension of the DFO structure. The efficiency of the new strategy was demonstrated by the total synthesis of 44-membered macrocyclic DFO-T_1, as well as four related DFO compounds in 11–13 linear steps and 2.1%–10% overall yields. Comparison of the iron binding affinity of the DFOs revealed DFO-E as the best chelator.

Introduction

Siderophores are small molecules produced by terrestrial and marine microorganisms for the acquisition of iron nutrient.[1-7] To aid assimilation of iron, siderophores exhibit high affinity for the Fe(III) ion.[8] The high binding affinity is attributable to the dual stabilizing effects of the presence of multiple bidentate ligands embedded into a single molecular scaffold. Among hundreds of natural siderophores, several ligand classes have been identified, namely hydroxamates,[9] catecholates,[10] and *α*-hydroxyl carboxylates.[11,12] Other less prevalent ligand classses also exist such as phenolates[13] and diazeniumdiolates.[14]

Desferrioxamines (DFO-A_{1A}–DFO-X_4) and bisucarberin are polyhydroxamate siderophores composed primarily of *N*-hydroxy-*N*-succinyldiaminoalkane (HSD) residues (Figure 1a).[7] These residues are trifunctional amino-carboxylic acids, which are joined together to give the macrocyclic or linear DFO scaffolds. Due to their affinity for metal ions, DFOs and related analogues have potential application in a variaty of medicinal settings. In fact, DFO-B has been long been used as a therapeutic chelating agent for treatment of iron-overload diseases.[15-19] Furthermore, conjugates formed between DFOs and antibiotics are potential candidates for development of “Trojan horse” antibiotics.[20-22] More recently, synthetic tetrahydroxamate DFO analogues have been shown to bind the Zr(IV) ion, and these findings have inspired exploration on ^{89}Zr(IV)-based imaging agents for positron emission tomography.[23,24] To provide the structurally defined DFO samples needed for these important, on-going studies, a robust and scalable synthetic route to the DFO-type siderophores is necessary.

In previous syntheses of DFOs, in which protected 5-hydroxylamino-pentanenitrile building blocks were employed (Figure 1b).[25-28] However, the reduction of the nitrile group via hydrogenation was complicated by simultaneous N–O bond cleavage.[27,28c] Alternatively, metal-template synthesis (MTS), chemoenzymatic method, and biosynthesis have been developed for the synthesis of DFOs, though the scale and substrate scope of these methods was limited.[27],[29],[30]

Herein, we report a convergent strategy for the synthesis of cyclic bisucaberin (**1**), DFO-E (**2**), DFO-T_1 (**3**), linear DFO-G_1 (**4**), and DFO-B (**5**). Our convergent strategy hinges on divergent synthetic capabilities embodied by orthogonally protected *N*-hydroxy-*N*-succinylcadaverine (HSC) building blocks (Figure 1c). For the building block with a free carboxylic acid end, its amino terminus is masked as an azide, while, for building blocks with a free amino terminus, the carboxylic acid end is protected as an allyl ester. It was envisaged that both of the azido and the allyl protecting groups could be modified selectively for chain extension.

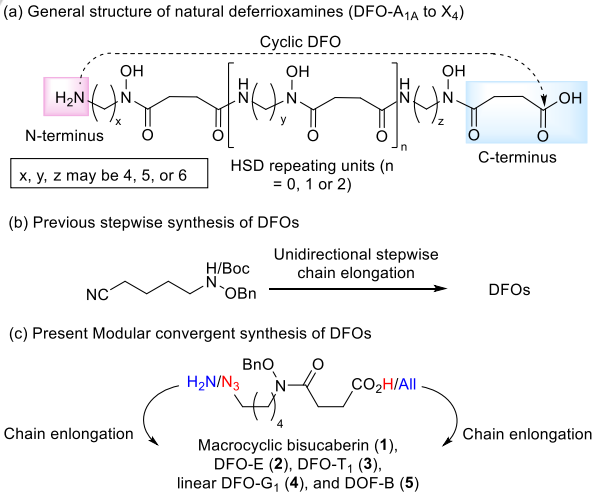

Figure 1. (a) General structure of desferrioxamines (DFO). (b) Previous stepwise synthesis of DFOs. (c) Modular convergent synthesis of bisucaberin (**1**), DFO-E (**2**), and DFO-T_1 (**3**), linear DFO-G1 (**4**) and DFO-B (**5**).

Results and Discussion

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Retrosynthetic Analysis and Building Block Preparation. The synthetic endeavour began with the synthesis of homoleptic bisucaberin (**1**) and DFOs (**2**)–(**4**); which are composed solely of HSC residues. Disconnection of the amide bonds within these targets led us to HSC carboxylic acid building block **6** and HSC amino building block **7** (Figure 2). Amino building block **7** could be derived from carboxylic acid building block **6**, and that the latter building block could be prepared from 1,5-dibromopentane **8**, known *t*-butyl-(benzyloxy)carbamate **9**,[31] and succinic anhydride (SA) via standard functional group interconversions.

Thus, substitution of dibromopentane **8** with carbamate **9** afforded *t*-butyl(5-bromopentyl)(benzyloxy)carbamate **10** along with a small amount (~10%) of disubstitution product (Scheme 1). Further substitution of carbamate **10** with sodium azide (NaN_3) then furnished *t*-butyl-(5-azidopentyl)(benzyloxy)carbamate **11**. Deprotection of the *tert*-butyloxycarbonyl (Boc) in carbamate **11** by treatment of trifluoroacetic acid (TFA) at low temperature furnished *N*-(5-azidopentyl)-*O*-benzyl-hydroxylamine **12**. Finally, aminolysis of SA with hydroxylamine **12** furnished carboxylic acid building block **6** in four linear steps (from **8**) and with an overall yield of 62%. Of note, 4.5 equiv. of SA was required to improve the conversion of the aminolysis. Having acquired HSC carboxylic acid building block **6**, amino building block **7** was prepared. Thus, alkylation of **6** with allyl bromide afforded allyl protected HSC aminocarboxylate **13**. To reduce the azide terminus of **13**, we

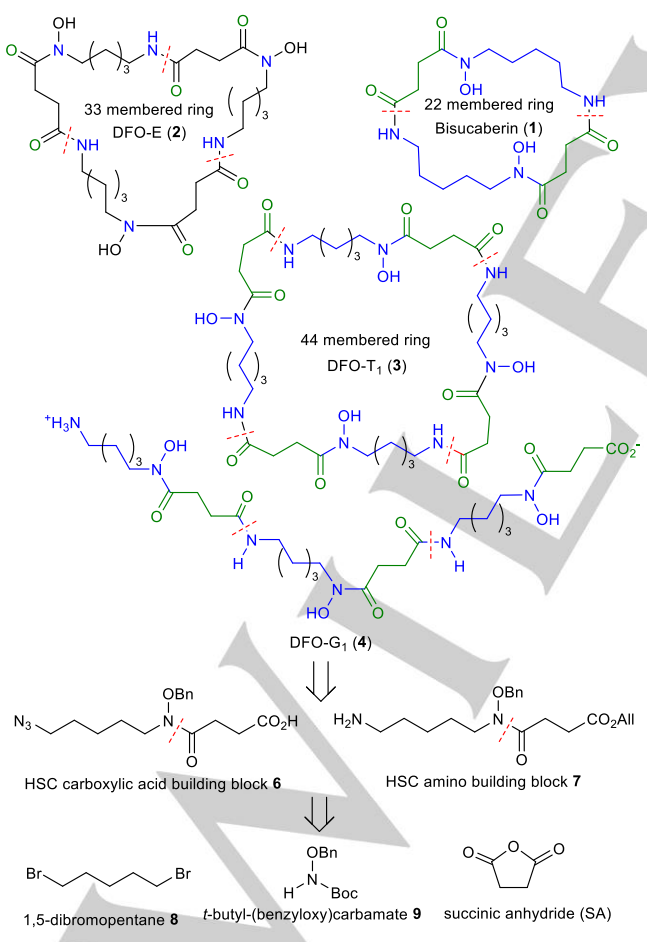
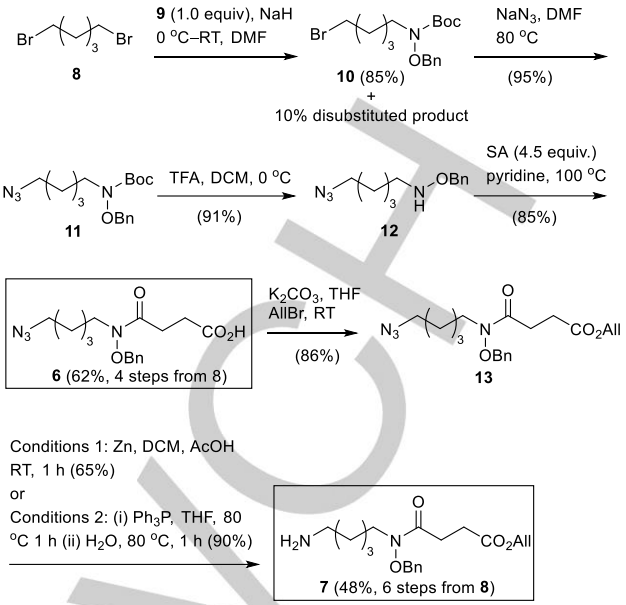


Figure 2. Retrosynthetic analysis of bisucaberin (1), and DFOs (**2**)–(**4**).



Scheme 1. Preparation of orthogonally protected HSC carboxylic acid building blocks **6** and HSC amine building block **7**.

examined the Staudinger[32] and zinc reduction procedures.[33] While both of these methods were found to be tolerant of the hydroxamic N–O bond, the yield given by the Staudinger reduction was higher.

Convergent Synthesis of Bisucaberin (1) and DFOs (2)–(4). With HSC building blocks **6** and **7** in hand, the stage was set for the synthesis of bisucaberin (**1**), DFO-E (**2**), DFO-T_1 (**3**), and DFO-G_1 (**4**) (Scheme 2). Thus, HSC carboxylic acid building block **6** was coupled with HSC amino building block **7** with the Steglich-type coupling procedure using 1-ethyl-3-(3-dimethyl-aminopropyl)-carbodiimide (EDC) and dimethylaminopyridine (DMAP) as coupling reagents.[34] The reaction proceeded smoothly to give allyl protected HSC dimer **14** in 80% yield (Scheme 2a).

As dimer **14** represented the pre-cyclized form of bisucaberin, cyclization of **14** could access the target bisucaberin (**1**). To achieve this, the allyl protecting group of **14** was first removed, exposing a free carboxylic acid end. Initially, a basic hydrolytic procedure was applied. In such conditions, the hydrolysis resulted in a deletion product; in which the succinic acid moiety was cleaved. Next, a $PdCl_2$-promoted cleavage procedure was applied, which furnished dimeric HSC carboxylic acid **15** in 75% yield.[35] Subsequent Staudinger reduction of the azido group in **15** afforded dimeric HSC amino-carboxylic acid **16**. For the cyclization of **16**, the reaction was conducted at a low concentration of **16** in DMF (8 mM); and EDC and DMAP were used as coupling reagents. After reaction at RT for 18 hours, cyclic HSC dimer **17** was obtained in a satisfying 55% yield. Hydrogenolysis of the benzyl ether groups contained within dimer **17** was subsequently achieved using standard Pd-catalyzed hydrogenation conditions to yield the target bisucaberin (**1**), which was obtained from dibromo starting material **8** over 11 linear steps and in 8.2% overall yield.

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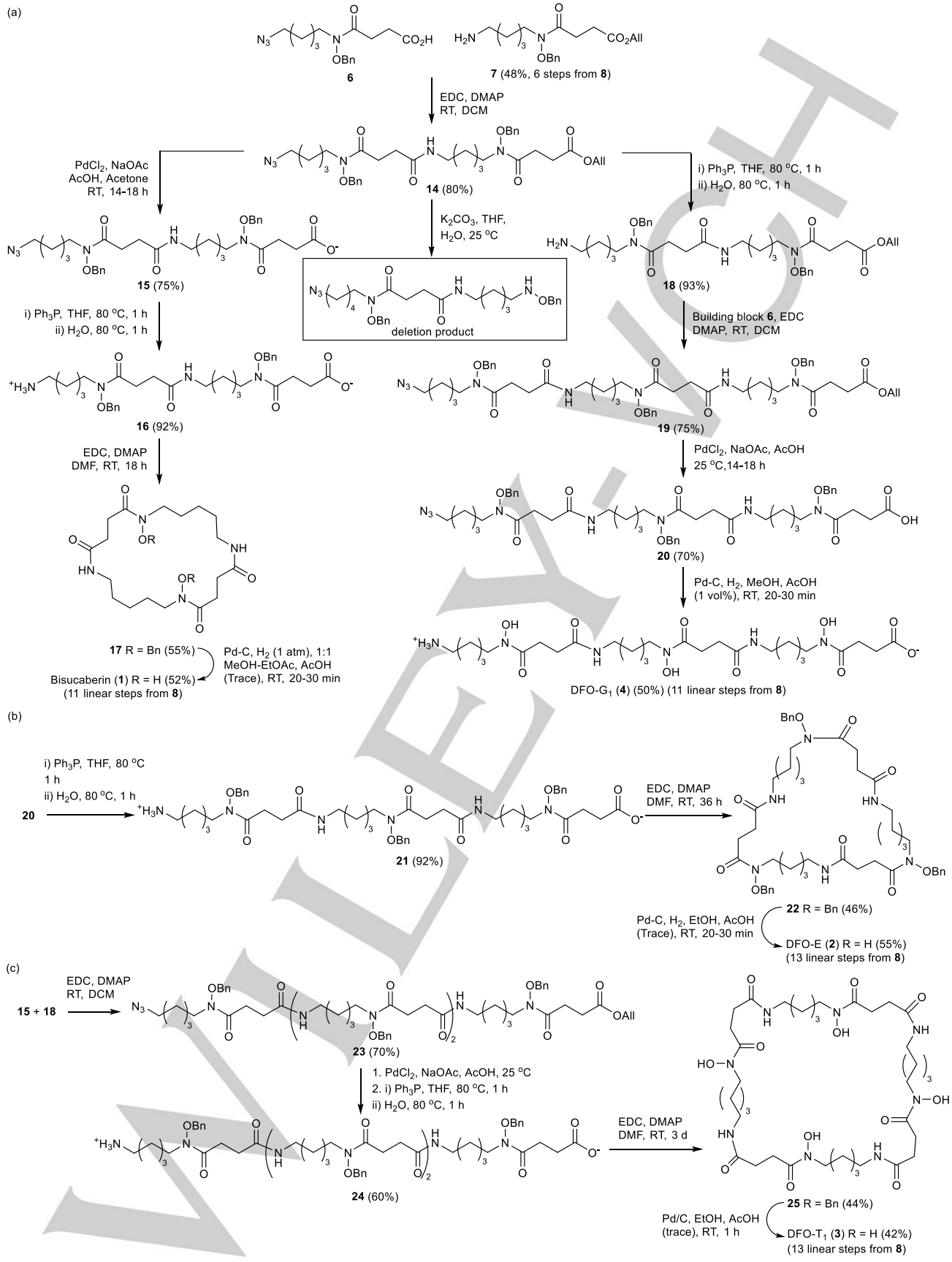

Scheme 2. (a) Synthesis of bisucaberin (**1**) and DFO-G_1 (**4**). (b) Synthesis of DFO-E (**2**) from trimeric HSC carboxylic acid **20**. (c) Synthesis of DFO-T_1 (**3**) from dimeric HSC carboxylic acid **15** and dimeric HSC amino building block **18**.

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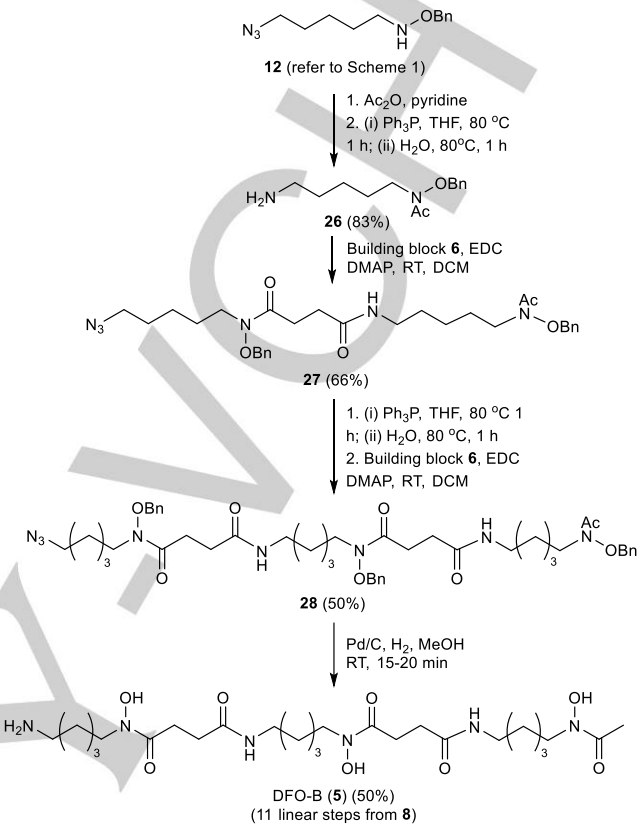
Based on the convergent strategy, we then turned to the synthesis of 33-membered macrocyclic DFO-E (**2**) and its linear counterpart DFO-G_1 (**4**). As both DFOs (**2**) and (**4**) were HSC trimers, we envisaged that they could be prepared via the simple addition of a suitable HSC unit to the dimeric compound **14**. Thus, Staudinger reduction of **14** produced dimeric amino building block **18**. Subsequent EDC coupling of this latter compound with HSC carboxylic acid building block **6** furnished allyl protected HSC trimer **19**, which represented the protected form of DFO-G_1 (**4**). Removal of the allyl ester group attached to trimer **19** via the $PdCl_2$-promoted hydrolytic procedure obtained trimeric HSC carboxylic acid **20**. Finally, one-pot azide reduction-hydrogenolysis of **20** under the Pd-catalyzed hydrogenation conditions concluded the total synthesis of DFO-G_1 (**4**). In contrast to previously reported one-pot nitrile reduction-hydrogenolysis protocol, our one-pot azido reduction-hydrogenolysis protocol was complete within 30 minutes and with no observable N–O bond cleavage.[27],[28] As such, DFO-G_1 (**4**) could be prepared from dibromo starting material **8** over 11 linear steps and in 8.1% overall yield.

For the synthesis of DFO-E (**2**), trimeric HSC carboxylic acid **20** was exploited as an advanced intermediate (Scheme 2b). Thus, Staudinger reduction of acid **20** furnished trimeric HSC aminocarboxylic acid **21**. cyclization of this compound with EDC and DMAP coupling reagents then afforded cyclic HSC trimer **22**. Global hydrogenolysis of **22** using Pd-catalyzed hydrogenation conditions finally completed the total synthesis of DFO-E (**2**), which was prepared over 13 linear steps from dibromo starting material **8** in 4.4% overall yield.

To investigate the potential of our convergent strategy, we tackled the synthesis of DFO-T_1 (**3**), the largest macrocyclic compound of the DFO family.[36] To the best of our knowledge, the total synthesis of this macrocycle has never been achieved via the stepwise elongation strategy. Our synthesis commenced with the coupling of dimeric HSC carboxylic acid building block **15** with dimeric HSC amino building block **18** using the Steglich conditions described above. The coupling proceeded to furnish allyl protected HSC tetramer **23** in 70% yield (Scheme 2c). Subsequent removal of the allyl ester followed by Staudinger reduction yielded tetrameric HSC aminocarboxylic acid **24**. Cyclization of **24** with EDC and DMAP coupling reagents furnished cyclic HSC tetramer **25** (i.e., protected DFO-T_1) in 44% yield. Due to the large ring structure embodied by DFO-T_1, a longer reaction time of 3 days was required. Final hydrogenolysis of **25** based on the Pd-catalyzed hydrogenation conditions completed the total synthesis of the target compound. By this route, DFO-T_1 (**3**) was acquired from dibromo starting material **8** over 13 linear steps and in 2.1% overall yield.

Convergent Synthesis of DFO-B (5). In addition to the homoleptic DFO compounds (**2**)–(**4**), the convergent strategy was applied to the synthesis of linear DFO-B (**5**). For this compound, the succinic acid moiety of a HSC residue is replaced with an acetyl group. Accordingly, the synthesis of DFO-B (**5**) commenced with the acetylation of *N*-(5-azidopentyl)-*O*-benzyl hydroxylamine **12** (Scheme 3). Subsequent Staudinger reduction of the azido group of this acetylated compound gave an amine intermediate **26**, which was coupled with carboxylic acid building block **6** under the Steglich conditions to furnish intermediate **27**, which comprised a complete HSC and a truncated HSC residue. Iterative Staudinger reduction the azido group in intermediate **27** followed by coupling with carboxylic acid building block **6** afforded intermediate **28**, which represented the protected form of DFO-B (**5**). Finally, one-pot azide reduction-hydrogenolysis of **28** in MeOH completed the total synthesis of the target. As before,



Scheme 3. Convergent synthesis of DFO-B (**5**).

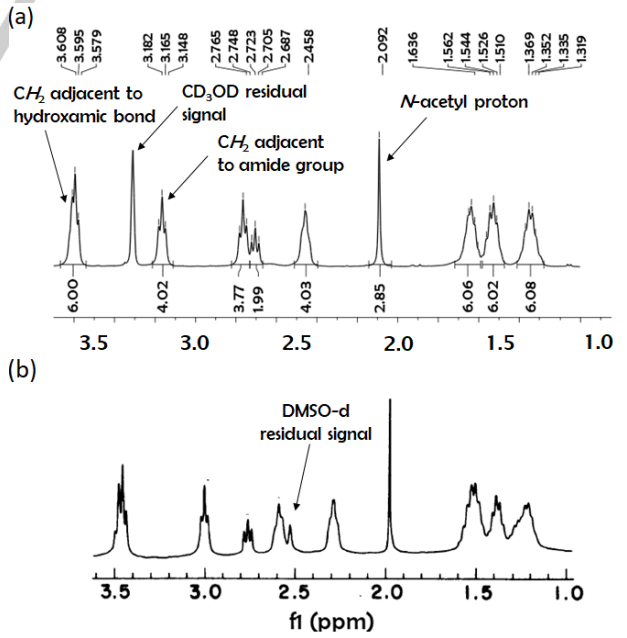


Figure 3. (a) ^{1}H-NMR spectrum of DFO-B (**5**) in CD_3OD. (b) ^{1}H-NMR spectrum of authentic sample in DMSO-d_6-D_2O (Ref 34).

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during the one-pot reaction, no trace of products resulting from N–O bond cleavage was observed. In this way, DFO-B (**5**) was obtained in 10% overall yield over 11 linear steps from starting substrate **8**.

The structures of acquired siderophore targets (**1**)–(**5**) were characterized with HRMS, ^{1}H-, and ^{13}C-NMR spectroscopy. All spectral data were in complete accordance with the assigned structures. For example, the ^{1}H-NMR spectrum of synthesized DFO-B (**5**) was in full agreement with the spectrum derived from an authentic sample (Figures 3a and 3b).[37] As shown in Figure 3a, the number of hydroxamic groups in (**5**) could be clearly inferred from the integral of the signal at 3.58–3.61 ppm, which was assigned to the methylene protons adjacent to hydroxamic N–O bonds. In addition, the signal corresponding to the *N*-acetyl methyl protons appeared as a singlet at 2.09 ppm, indicating the integrity of the hydroxamate residue at the *N*-acetyl terminal.[38]

Preliminary Fe(III) Ion Binding Studies. Once established the synthetic routes to macrocyclic bisucaberin (**1**), DFO-E (**2**), DFO-T$_1$ (**3**), linear DFO-G$_1$ (**4**), and DFO-B (**5**), we turned to the study of the binding affinity of these compounds for the Fe(III) ion. To this end, a known Chrome Azurol S (CAS) Fe(III) binding assay was performed.[39] CAS assay are commonly employed to assess the iron-binding ability of coelichelin,[9] hinduchelins,[40] and bisucaberin.[41] Briefly, a solution of Fe(III)-CAS complex with an absorbance at 630 nm (Abs630) was treated with a dilution series of siderophores (1.560 to 200 μM). Removal of the Fe(III) ion from the Fe(III)-CAS complex by the assessed siderophore decreased the absorbance at 630 nm. Figure 4 depicts the semi-logarithmic plot of Abs630 vs concentrations of siderophores.

Based on the iron de-binding curves, the concentrations of siderophores at half-titration points were determined, which are 59 μM for bisucaberin (**1**), 15 μM for DFO-E (**2**), 51 μM for DFO-T$_1$ (**3**), 49 μM for DFO-G$_1$ (**4**), and 30 μM for DFO-B (**5**). Apparently, macrocyclic DFO-E (**2**) displays a higher iron-binding affinity than linear DFO-B (**5**) and DFO-G$_1$ (**4**) (Figure 4). This result is consistent with the stability constants for the DFO-E·Fe and protonated DFO-B · Fe complexes determined by the potentiometric titration method.[42] In accordance with the literature, the higher binding affinity of DFO-E (**2**) is attributable to endocyclic pre-organization of the hydroxamate ligands that reduce the unfavorable entropy factor.[8],[43] For the macrocyclic DFOs, the binding affinity of trihydroxamic DFO-E (**2**) is higher than that of dihydroxamic bisucaberin (**1**) and tetrahydroxamic DFO-T$_1$ (**3**). bisucaberin (**1**) and tetrahydroxamic DFO-T$_1$ (**3**), the higher iron affinity of trihydroxamic DFO-E (**2**) is likely attributed to the exact number of hydroxamate groups that allows the formation of a 1:1 octahedral ligand-Fe complex.[42]

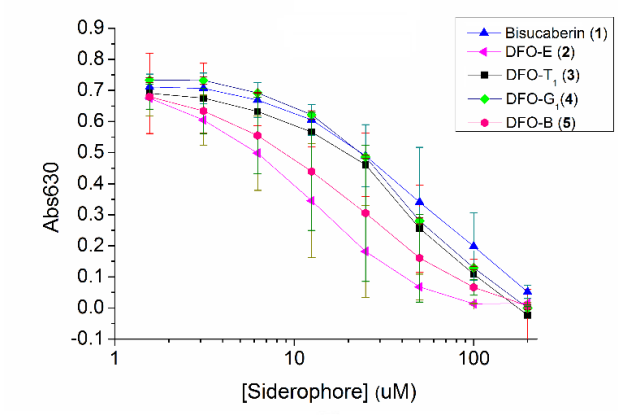

Figure 4. Fe(III) binding curves for bisucaberin (**1**) and DFOs (**3**)–(**5**).

Conclusions

In summary, a convergent strategy was developed for the synthesis of cyclic and linear desferrioxamines. The strategy relied on the use of orthogonally protected HSC amino and carboxylic acid building blocks. The protecting groups of the building blocks could be modified selectively for chain extension. This feature allowed the synthesis of cyclic bisucaberin B (**1**), DFO-E (**2**), DFO-T1 (**3**), linear DFO-G1 (**4**), and DFO-B (**5**) by the modular and convergent approach, which is necessarily more efficient than previous stepwise syntheses. We also compared the iron-chelation ability of cyclic bisucaberin B (**1**), DFO-E (**2**), DFO-T$_1$ (**3**), linear DFO-G$_1$ (**4**), and DFO-B (**5**) using the CAS binding assay. The results showed that 33-membered cyclic DFO-E (**2**) had the highest binding affinity, relative to linear DFO-G$_1$ (**4**), DFO-B (**5**), cyclic bisucaberin (**1**), and DFO-T$_1$ (**3**).

In comparison with the recent developed biosynthetic approach for synthesis of macrocycles, the convergent synthesis requires a longer scheme, but it has no pre-requisite for a large amount of molecular biology and protein chemistry to provide the necessary biological tools.[44] In addition, the chemical synthesis enjoys the flexibility of structural variation and has the capacity to prepare a compound library for structure-activity relationship studies. As an outlook of the present synthetic method, total synthesis of more challenging unsymmetrical siderophores such as DFO-X$_1$[7] avaroferrin,[45] could be possible.

Experimental Section

General Experimental: Reagent-grade chemicals and solvents were purchased from commercial vendors and used without purification. Dichloromethane (DCM) was dried with the solvent drying system (AWS-1000). Progress of the reaction was monitored by thin layer chromatography on silica gel 60 F-254 plate and visualized under UV illumination and/or by staining with acidic ceric ammonium molybdate or *p*-anisaldehyde solution. Silica gel (Geduran Si-60, 0.063–0.200 mm) for chromatography was obtained from Merck. NMR spectra were recorded at 400 or 600 MHz NMR spectrometer with the Varian console as specified. Absorbance (630 nm) in the Fe(III) binding assay was measued using Agilent 8453 UV-visible spectrophotometer G1103A.

General Staudinger reduction procedure: To a solution of **13**–**15**, **20**, **23**, or **27** (1 equiv) in dried THF (0.15 M) was added PPh_3 (2 equiv). The reaction mixture was refluxed at 80 °C for no more than an hour, then H_2O (10 equiv) was added. The mixture was stirred for additional one hour and the mixture concentrated for flash column chromatography to give amino building blocks **7**, **18**, **26**, amino derivative of **27**, amino-carboxylic acid building blocks **16**, **21**, or **24**.

General Steglich coupling procedure: To a solution of amino building block **7**, **18**, **26**, or amine derivative of **27** (1 equiv) in DCM (0.6 M), EDC (1.5 equiv), DMAP (0.2 g, 1.66 mmol 0.5 equiv) and carboxylic acid building block **6** or **15** (1 equiv) were added. The reaction mixture was stirred at RT under N_2 for 8–18 h. The reaction mixture was then diluted with DCM, which was washed by 1 N HCl (30 mL × 2), brine, dried over $MgSO_4$, filtered, and concentrated for purification with flash column chromatography to give coupling product.

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General cyclization procedure: To a solution of protected HSC amino-carboxylic acid **16**, **21** or **24** (1 equiv) in dried DMF (5–8 mM), DMAP (0.5 equiv) and EDC (1.5 equiv) were added. The reaction mixture was stirred at RT for 18 h (for **16**), 36 h (for **21**), or 96 h (for **24**), then followed by dilution with DCM (10 mL). The DCM solution was washed with 1 N HCl (10 mL × 2), brine (20 mL), dried (over $MgSO_4$), filtered, and concentrated for purification with flash column chromatography to give protected cyclized product **17**, **22**, or **25**.

General deprotection of allyl ester: To a solution of allyl ester **14**, **19** or **23** (1.0 equiv.) in acetone (0.3 M), AcOH (10 % v/v), palladium dichloride (1.0 equiv.) was added. The reaction mixture was stirred at RT for 18 h. After complete hydrolysis of the ester group, the reaction mixture was diluted with EtOAc, then washed with 1 N HCl, H_2O, brine, and dried over $MgSO_4$. The EtOAc solution was filtered and concentrated for purification with flash column chromatography to give carboxylic acid building block **15**, **20** or carboxylic acid derivative of **23**.

***t*-Butyl(benzyloxy)(5-bromopentyl)carbamate 10**: To a mixture of 1,5-dibromopantane (1 g, 4.37 mmol) and *N*-Boc-*O*-benzyl-hydroxylamine (2.24 mmol) in DMF (0.3 M), 60% NaH (suspended in oil droplets) (0.11 g, 2.7 mmol) was added at 0 °C under N_2. The mixture was stirred at 25 °C until completion of the alkylation. The reaction mixture was diluted with DCM (25 mL), followed by washing with satd. NH_4Cl (20 mL) and brine (40 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated for purification by flash column chromatography to give carbamate **10** as a colorless oily liquid. (1.37 g, 85%). For **10**, R_f = 0.3 (Et_2O/hexanes, 1/9); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.35 (m, 5H), 4.83 (s, 2H, PhC$\underline{H_2}$), 3.41 (t, J = 6.8 Hz, 2H, N(OBn)C$\underline{H_2}$), 3.38 (t, J = 6.4 Hz, 2H, BrC$\underline{H_2}$), 1.85 (quintet, J = 7.6 Hz, 2H), 1.61 (quintet, J = 7.6 Hz, 2H, C$\underline{H_2}$), 1.51 (s, 9 H, *tert*-butyl), 1.43 (quintet, J = 7.2 Hz, 2H, C$\underline{H_2}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 135.9, 129.6, 128.7, 128.6, 81.5, 77.1, 49.5, 33.8, 32.6, 28.6, 26.4, 25.6. HRMS (ESI) calcd. for $C_{17}H_{26}BrNO_3$ [M + Na]$^+$, 394.0988; found: 394.0989.

***t*-Butyl(5-azidopentyl)(benzyloxy)carbamate 11 and *N*-(5-azidopentyl)-*O*-benzylhydroxylamine 12**: To a solution of carbamate **10** (6 g, 16.2 mmol) in dried DMF (50 mL), sodium azide (4.2 g, 64.8 mmol) was added. The reaction mixture was stirred at 80 °C for 3 h. After completion of the reaction, the mixture was diluted with EtOAc (75 mL), washed with H_2O (100 mL × 2), brine (100 mL), dried over $MgSO_4$, filtered, and concentrated for flash column chromatography to give azido containing carbamate **11** as a colorless oily liquid (5.08 g, 94%). For **11**, R_f = 0.15 (DCM/hexanes, 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.34 (m, 5H), 4.82 (s, 2H, PhC$\underline{H_2}$), 3.41 (t, J = 7.2 Hz, 2H, N(OBn)C$\underline{H_2}$), 3.25 (t, J = 7.2 Hz, 2H, N_3C$\underline{H_2}$), 1.63-1.56 (m, 4H, C$\underline{H_2}$ × 2), 1.51 (s, 9 H, *tert*-butyl), 1.36 (quintet, J = 7.2 Hz, 2H, C$\underline{H_2}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 135.9, 129.6, 128.7, 128.66, 81.5, 77.2, 51.5, 49.6, 28.8, 28.6, 26.8, 24.1. HRMS (ESI) calcd. for $C_{17}H_{26}N_4O_3$ [M + Na]$^+$, 357.1897; found: 357.1902.

To a solution of **11** (4 g, 12.0 mmol) in DCM (20 mL), trifluoroacetic acid (10 mL) was added slowly at 0 °C. The reaction mixture was stirred at RT for 20 min. After complete deprotection of the Boc group, the reaction mixture was diluted with DCM (30 mL), which was washed with satd. $NaHCO_3$ (50 mL × 2), brine (50 mL), dried over $MgSO_4$, filtered, and concentrated for flash column chromatography to give compound **12** as a colorless oily liquid (2.55 g, 91%). For **12**, R_f = 0.1 (EtOAc/hexanes, 1/9); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 5.54 (br, 1H, N(OBn)$\underline{H}$), 4.70 (s, 2H, PhC$\underline{H_2}$), 3.26 (t, J = 6.8 Hz, 2H, NH(OBn)C$\underline{H_2}$), 2.93 (t, J = 6.8 Hz, 2H, C$\underline{H_2}$$N_3$), 1.60 (quintet, J = 7.2 Hz, 2H, C$\underline{H_2}$), 1.54 (quintet, J = 7.2 Hz, 2H, C$\underline{H_2}$), 1.40 (quintet, J = 6.8 Hz, 2H, C$\underline{H_2}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 128.6, 128.0, 76.5, 52.1, 51.5, 29.0, 27.2, 24.6. HRMS (ESI) calcd. for $C_{12}H_{18}N_4O$ [M + H]$^+$, 235.1553; found: 235.1557.

HSC carboxylic acid building block 6: To a solution of *N*-(5-azidopentyl)-*O*-benzylhydroxylamine **12** (8.63 g, 36.9 mmol) in pyridine (125 mL), SA (17.4 mL, 184.0 mmol) was added. The reaction mixture was stirred at 100 °C for ~1 h. After completion of the reaction, the solvent was removed by the rotary evaporator and the residue was absorbed in EtOAc (100 mL). The EtOAc solution was washed by 1 N HCl (70 mL × 2), brine, dried over $MgSO_4$, filtered, and concentrated for flash column chromatography to give building block **6** (10.5 g, 85%). For **6**, R_f = 0.2 (MeOH/DCM, 1/19); H^1 NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 5H), 4.85 (s, 2H, PhC$\underline{H_2}$), 3.66 (t, J = 5.6 Hz, 2H, C(=O)N(OBn)C$\underline{H_2}$), 3.25 (t, J = 6.4 Hz, 2H, C$\underline{H_2}$$N_3$), 2.72 (t, J = 5.4 Hz, 2H, succinyl C$\underline{H_2}$), 2.64 (t, J = 5.4 Hz, 2H, succinyl C$\underline{H_2}$), 1.66 (quintet, J = 7.6 Hz, 2H, C$\underline{H_2}$), 1.60 (quintet, J = 6.8 Hz, 2H, C$\underline{H_2}$), 1.36 (quintet, J = 6.8 Hz, 2H, C$\underline{H_2}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 134.4, 129.44, 129.37, 129.0, 76.6, 51.5, 45.6, 29.0, 28.7, 27.5, 26.6, 24.1. HRMS (ESI) calcd. for $C_{16}H_{22}N_4O_4^+$ [M + H]$^+$, 335.1714; found: 335.1718.

Allyl 4-((5-azidopentyl)(benzyloxy)amino)-4-oxobutanoate (protected HSC amino-carboxylate) 13: To a solution of HSC carboxylic acid building block **6** (4 g, 11.96 mmol) in THF (10 mL), 3-bromoprop-1-ene (4.14 g, 47.85 mmol), K_2CO_3 (4.96 g, 35.89 mmol), and Bu_4NI (4.42 g, 11.96 mmol) were added. The reaction mixture was stirred at RT for 2.5 h. The reaction mixture was then diluted with DCM (120 mL), which was washed by 1 N HCl (130 mL × 2), H_2O, brine, dried over $MgSO_4$, filtered, and concentrated for purification with flash column chromatography to give protected HSC amino-carboxylate **13** (3.84 g, 10.26 mmol). For **13**, R_f = 0.2 (EtOAc /hexanes 1/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.37 (m, 5H), 5.91 (ddd, J = 5.6, 10.8, 22.6 Hz , 1H, $OCH_2C\underline{H}$=CH_2), 5.32 (dq, J = 1.6, 17.2 Hz,1H, OCH_2CH=C$\underline{H_2}$), 5.23 (dq, J = 1.6, 10.4 Hz, 1H, OCH_2CH=C$\underline{H_2}$) , 4.86 (s, 2H, PhC$\underline{H_2}$), 4.61 (t, J =1.4 Hz, 1H, C(=O)OC$\underline{H_2}$), 4.59 (t, J =1.4 Hz, 1H, C(=O)OC$\underline{H_2}$), 3.64 (t, J = 6.8 Hz, 2H, N(OBn)C$\underline{H_2}$), 3.25 (t, J = 7 Hz, 2H, C$\underline{H_2}$$N_3$), 2.77 - 2.74 (m, 2H, succinyl C$\underline{H_2}$), 2.67- 2.64 (m, J = 6.4 Hz, 2H, succinyl C$\underline{H_2}$), 1.69 - 1.60 (m, 4H, C$\underline{H_2}$), 1.40 - 1.32 (m, 2H, C$\underline{H_2}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 132.4, 129.4, 129.2, 129.0, 118.4, 77.6, 77.3, 77.0, 76.7, 65.5, 51.5, 45.6, 28.9, 28.7, 27.6, 26.6, 24.1. HRMS (ESI) calcd. for $C_{19}H_{26}N_4O_4$ [M + H]$^+$, 375.2027; found: 375.2019.

HSC amino building block 7: Protected HSC amino-carboxylate **13** (0.3 g, 0.8 mmol) was subjected to the general Staudinger reduction procedure to give HSC amino building block **7** (0.27 g, 90%) as a colorless amorphous solid. Analytical data for **7**, R_f = 0.2 (28% $NH_{3(aq)}$/isopropanol 1/19); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 5H), 5.92 (ddt, J = 16.4, 10.8, 6 Hz, 1H, $OCH_2C\underline{H}$=CH_2), 5.32 (dq, J = 17.2, 1.2 Hz, 1H, OCH_2CH=C$\underline{H_2}$), 5.23 (dq, J = 10.4, 1.2 Hz, 1H, OCH_2CH=C$\underline{H_2}$) , 4.86 (s, 2H, PhC$\underline{H_2}$), 4.60 (dt, J = 6, 1.2 Hz, 2H, C(=O)OC$\underline{H_2}$), 3.64 (t, J = 7.2 Hz, 2H, N(OBn)C$\underline{H_2}$), 2.75 (t, J = 6.4 Hz, 2H, succinyl C$\underline{H_2}$), 2.69-2.64 (m, 4H, succinyl C$\underline{H_2}$, C$\underline{H_2}$$NH_2$), 1.65 (quintet, J = 7.6 Hz, 2H, C$\underline{H_2}$), 1.45-1.41 (m, 2H, C$\underline{H_2}$), 1.35-1.26 (m, 2H, C$\underline{H_2}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 132.2, 129.1, 128.9, 128.7, 118.1, 76.4, 65.3, 45.5, 42.1, 33.4, 28.7, 27.4, 26.7, 24.0. Without the HRMS characterization, HSC amino building block **7** was employed for preparation of HSC dimer **14**.

HSC dimer 14: HSC amino building block **7** (1.16 g, 3.33 mmol) in DCM (5 mL) was coupled with HSC carboxylic acid building block **6** (1.11 g, 3.33 mmol) in accordance with general Steglich coupling procedure. The reaction mixture was stirred at RT for 3 h. The reaction mixture was then diluted with DCM (30 mL), which was washed by 1 N HCl (30 mL × 2), brine, dried over $MgSO_4$, filtered, and concentrated for purification with flash column chromatography to give HSC dimer **14** (1.76 g, 80%). Analytical data for **14**, R_f = 0.1 (1% isopropanol in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 10H), 6.03 (t, J = 5.2 Hz, 1H, C(=O)N$\underline{H}$), 5.93 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H, $OCH_2C\underline{H}$=CH_2), 5.32 (dq, J = 17.4, 1.6 Hz, 1H, OCH_2CH=C$\underline{H_2}$), 5.23 (dq, J = 10.4, 1.2 Hz, 1H, OCH_2CH=C$\underline{H_2}$) , 4.85 (s, 4H, PhC$\underline{H_2}$ × 2), 4.59 (dt, J = 5.6, 1.2 Hz, 2H, C(=O)OC$\underline{H_2}$), 3.64 (t, J = 7.2 Hz, 2H, N(OBn)C$\underline{H_2}$), 3.62 (t, J = 7.2 Hz, 2H, N(OBn)C$\underline{H_2}$), 3.28-3.18 (m, 4H, C$\underline{H_2}$$N_3$, C(=O)NHC$\underline{H_2}$), 2.80-2.73 (m, 4H, succinyl C$\underline{H_2}$ × 2), 2.67-2.64 (m, 2H, succinyl C$\underline{H_2}$), 2.46 (t, J = 6.8 Hz, 2H, succinyl C$\underline{H_2}$), 1.64 (quintet, J = 6.8 Hz, 6H, C$\underline{H_2}$ × 3), 1.49 (quintet, J = 6.8Hz, 2H, C$\underline{H_2}$), 1.39 - 1.28 (m, 4H, C$\underline{H_2}$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.8, 173.2, 172.7, 172.1, 134.5, 132.2, 129.2, 129.0, 128.7, 118.1, 76.5, 76.3, 65.3, 51.2, 45.3, 45.2, 39.4, 30.8, 29.7, 29.0, 28.6, 28.5, 28.2, 27.3, 26.5, 26.4, 23.91, 23.88. HRMS (ESI) calcd. for $C_{35}H_{48}N_6O_7$ [M + H]$^+$, 665.3657; found: 665.3657.

Dimeric HSC carboxylic acid 15: Deprotection of the allyl ester group in HSC dimer **14** (0.225 g, 0.34 mmol) followed the general deallylation

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procedure. Carboxylic acid building block **15** was obtained as a yellowish oily substance (0.16 g, 75%) through flash chromatography purification (Elution: isopropanol/DCM, 1/19). Analytical data for **15**, R_f = 0.5 (isopropanol/DCM, 1/9). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.34 (m, 10H), 6.75 (br, 1H, C(=O)N*H*), 4.86 (s, 2H, PhC*H*$_2$), 4.83 (s, 2H, PhC*H*$_2$), 3.73 (t, *J* = 5.2 Hz, 2H, C(=O)N(OBn)C*H*$_2$), 3.62 (t, *J* = 6.4 Hz, 2H, C(=O)N(OBn)C*H*$_2$), 3.25-3.20 (m, 4H, C(=O)NHC*H*$_2$, N_3C*H*$_2$), 2.83 (t, *J* = 6.4 Hz, 2H, succinyl C*H*$_2$), 2.67 (s, 4H, succinyl C*H*$_2$ × 2), 2.53 (t, *J* = 6.8 Hz, 2H, succinyl C*H*$_2$), 1.67-1.55 (m, 6H, C*H*$_2$ × 3), 1.49-1.45 (m, 2H, C*H*$_2$), 1.37-1.30 (m, 4H, C*H*$_2$ × 2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 174.3, 173.8, 172.5, 134.6, 134.3, 129.3, 129.1, 128.8, 76.6, 76.3, 51.3, 45.4, 44.6, 39.5, 30.7, 28.5, 28.5, 28.2, 27.0, 26.6, 26.4, 23.9, 23.7. Of note, signals at 64.3 and 25.3 ppm are residual signals from a trace of isopropanol. HRMS (ESI) calcd. for $C_{32}H_{44}N_6O_7$ [M + H]$^+$, 625.3344; found: 625.3347.

Dimeric HSC amino-carboxylic acid 16: Reduction of dimeric carboxylic acid building **15** (0.9 g, 1.44 mmol) followed the general Staudinger reduction procedure. After the workup procedure, the reaction mixture was purified with flash column chromatography (Elution: 28% $NH_{3(aq)}$/isopropanol, 1/9) to give dimeric aminocarboxylic acid **16** (0.8 g, 92%) as an orange oily liquid. Analytical data for **16**, R_f = 0.3 (28% $NH_{3(aq)}$/isopropanol, 1/19). ^{1}H NMR (400 MHz, CD_3OD) δ 7.45-7.38 (m, 10H), 4.92 (s, 2H, PhC*H*$_2$), 4.91 (s, 2H, PhC*H*$_2$), 3.72-3.64 (m, 4H, C(=O)N(OBn)C*H*$_2$ × 2), 3.13 (t, *J* = 6.8 Hz 2H, C(=O)NHC*H*$_2$), 2.89 (t, *J* = 7.2 Hz, 2H, NH_2C*H*$_2$), 2.73 (br, 4H, succinyl C*H*$_2$ × 2), 2.51 (t, *J* = 6.8 Hz, 2H, succinyl C*H*$_2$), 2.45 (t, *J* = 6.4 Hz, 2H, succinyl C*H*$_2$), 1.70-1.59 (m, 6H, C*H*$_2$ × 3), 1.49 (quintet, *J* = 7.6 Hz, 2H, C*H*$_2$), 1.33 (quintet, *J* = 7.2 Hz, 4H, C*H*$_2$ × 2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 175.2, 174.2, 172.5, 134.8, 134.4, 129.3, 129.1, 128.9, 128.8, 128.71, 128.66, 76.3, 76.2, 45.0, 44.7, 39.5, 39.2, 32.0, 30.6, 28.7, 28.1, 27.3, 26.4, 26.3, 23.6, 23.4. Of note, signals at 64.0 and 25.4 ppm are residual signals of isopropanol. HRMS (ESI) calcd. for $C_{32}H_{46}N_4O_7$ [M + H]$^+$, 599.3439; found: 599.3451.

Cyclized HSC dimer 17: Cyclization of dimeric HSC amino-carboxylic acid **16** (170 mg, 0.28 mmol) followed the general cyclization procedure. After the workup, the crude product was purified with flash column chromatography (Elution: EtOH/DCM, 1/19) to give cyclized HSC dimer **17** (90 mg, 55%) as an orange oily liquid. Analytical data for **17**, R_f = 0.3 (EtOH/DCM, 1/19). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (br, 10H), 6.65 (br, 2H, C(=O)N*H* × 2), 4.86 (s, 4H, PhC*H*$_2$ × 2), 3.72 (t, *J* = 5.2 Hz, 4H, C(=O)N(OBn)C*H*$_2$ × 2), 3.20 3.18 (m, 4H, C(=O)NHC*H*$_2$ × 2), 2.88 (t, *J* = 7.2 Hz, 4H, succinyl C*H*$_2$ × 2), 2.59 (t, *J* = 7.2 Hz, 4H, succinyl C*H*$_2$ × 2), 1.63 (quintet, *J* = 4.8 Hz, 4H, C*H*$_2$ × 2), 1.55 (m, 4H, C*H*$_2$ × 2), 1.26 (m, 4H, C*H*$_2$ × 2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 172.5, 134.4, 129.4, 129.2, 129.0, 76.5, 43.1, 39.7, 30.9, 28.5, 26.7, 26.2, 22.6. HRMS (ESI) calcd. for $C_{32}H_{44}N_4O_6$ [M + H]$^+$, 581.3334; found: 581.3337.

Bisucaberin (1): To a solution of protected cyclized HSC dimer **17** (66 mg) in 1:1 MeOH-EtOAc (14 mL), acetic acid (70 µL) and 10% Pd-C (33 mg) were added. The reaction mixture was stirred at RT for 30 min, then Pd-C was removed by filtration (over celite). The filtrate was concentrated for column chromatography (Elution: EtOH/DCM, 1/9) to afford **1** as a white glassy solid (24 mg, 52%). Analytical data for **1**: R_f = 0.25 (EtOH/DCM, 1/9); ^{1}H NMR (400 MHz, CD_3OD) δ 3.63 (t, *J* = 6.8 Hz, 4H, C(=O)N(OH)C*H*$_2$ × 2), 3.17 (t, *J* = 5.6 Hz, 4H, C(=O)NHC*H*$_2$ × 2), 2.78 (t, *J* = 7.2 Hz, 4H, succinyl C*H*$_2$ × 2), 2.48 (t, *J* = 6.8 Hz, 4 H, succinyl C*H*$_2$ × 2), 1.63 (m, 4H, C*H*$_2$ × 2), 1.52 (m, 4H, C*H*$_2$ × 2), 1.30 (m, 4H, C*H*$_2$ × 2). ^{13}C NMR (100 MHz, CD_3OD) δ 175.1, 174.4, 48.1, 39.9, 32.1, 29.3, 29.2, 26.9, 23.9. HRMS (ESI) calcd. for $C_{18}H_{32}N_4O_6$ [M + H]$^+$, 401.2395; found: 401.2390.

Dimeric HSC amino building block 18: Reduction of protected HSC dimer **14** (0.28 g, 0.42 mmol) followed the general Staudinger reduction procedure. The crude reduction product was purified by flash column chromatography (Elution: 28% $NH_{3(aq)}$/isoprapanol, 1/19) to give **18** (0.25 g, 93%) as a yellow oily liquid. Analytical data for **18**, R_f = 0.2 (28% $NH_{3(aq)}$/isopropanol, 1/19); ^{1}H NMR (400 MHz, CDCl3) δ 7.38 (s, 10H), 6.10 (t, *J* = 5.2 Hz, 1H, CON*H*), 5.91 (ddt, *J* = 17.6, 10.4, 5.6 Hz , 1H, OCH_2C*H*=CH_2), 5.32 (dq, *J* = 17.2, 1.6 Hz,1H, OCH_2CH=C*H*$_2$), 5.22 (dq, *J* = 10.4, 1.2 Hz, 1H, OCH_2CH=C*H*$_2$), 4.85 (s, 4H, PhC*H*$_2$ × 2), 4.59 (dt, *J* = 5.6, 1.2 Hz, 2H, C(=O)OC*H*$_2$), 3.63 (d, *J* = 5.2 Hz, 4H, N(OBn)C*H*$_2$ × 2) , 3.23 (d, *J* = 6.8 Hz, 2H, NHC*H*$_2$), 2.79-2.73 (m, 4H, succinyl C*H*$_2$ × 2), 2.68-2.64 (m, 4H, succinyl C*H*$_2$, C*H*$_2$$NH_2$), 2.50-2.44 (m, 2H, succinyl C*H*$_2$), 1.68-1.59 (m, 4H, C*H*$_2$ × 2), 1.52-1.40 (m, 4H, C*H*$_2$ × 2), 1.34-1.26 (m, 4H, C*H*$_2$ × 2). ^{13}C NMR (100 MHz, CDCl3) δ 173.2, 172.7, 172.20, 172.15, 134.5, 132.2, 129.19, 129.15, 129.0, 128.9, 128.74, 128.71, 118.1, 76.4, 76.3, 65.3, 45.4, 45.3, 42.0, 39.3, 33.2, 30.8, 30.6, 29.0, 28.6, 28.2, 28.0, 27.4, 26.7, 26.5, 24.0, 23.9. As dimeric HSC amino building block **18** was directly taken to the coupling reaction, no HRMS data was obtained.

Allyl protected HSC trimer 19: Coupling of HSC dimeric amino building block **18** (0.47 g, 0.74 mmol) with HSC carboxylic acid building block **6** (0.22 g, 0.74 mmol) followed the general intermolecular Steglich coupling procedure. After the workup, the crude mixture was then diluted with DCM (20 mL), then washed with 1 N HCl (20 mL × 2), brine, dried over $MgSO_4$, filtered, and concentrated for purification with flash chromatography (Elution: isoprapanol/DCM, 1/19) to give HSC trimer **19** (0.53 g, 75%). Analytical data for **19**, R_f = 0.3 (5% isopropanol in DCM); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (br, 15H), 6.29 (br, 2H, C(=O)N*H* × 2), 6.31 (s, 1H, C(=O)N*H*), 5.92 (ddt, *J* = 17.4, 10.8, 5.4 Hz, 1H, OCH_2C*H*=CH_2), 5.31 (dq, *J* = 17.4, 1.2 Hz, 1H, OCH_2CH=C*H*$_2$), 5.22 (dq, *J* = 10.8, 1.2 Hz, 1H, OCH_2CH=C*H*$_2$) , 4.853 (s, 2H, PhC*H*$_2$), 4.848 (s, 2H, PhC*H*$_2$ × 2), 4.59 (dt, *J* = 6.0, 1.2 Hz, 2H, C(=O)OC*H*$_2$), 3.63 (br, 6H, N(OBn)C*H*$_2$ × 3), 3.23 (t, *J* = 7.2 Hz, 2H, C*H*$_2$$N_3$), 3.20 (m, 4H, C(=O)NHC*H*$_2$ × 2), 2.80 (br, 4H, succinyl C*H*$_2$ × 2), 2.74 (t, *J* = 6.6 Hz, 2H, succinyl C*H*$_2$), 2.65 (t, *J* = 7.2 Hz, 2H, succinyl C*H*$_2$), 2.50-2.46 (m, 4H, succinyl C*H*$_2$ × 2), 1.66-1.60 (m, 6H, C*H*$_2$ × 3), 1.57 (quintet, *J* = 7.2 Hz, 2H, C*H*$_2$), 1.52-1.46 (m, 4H, C*H*$_2$ × 2), 1.34 (quintet, *J* = 7.2 Hz, 2H, C*H*$_2$), 1.30 (quintet, *J* = 7.2 Hz, 4H, C*H*$_2$ × 2). ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.0, 172.7, 172.1, 134.4, 132.2, 129.2, 129.1, 128.94, 128.92, 128.7, 118.1, 76.5, 76.3, 65.3, 51.2, 45.3, 44.8, 39.4, 30.7, 30.6, 29.1, 28.62, 28.55, 28.5, 28.2, 28.1, 28.0, 27.4, 26.5, 26.4, 24.0, 23.9, 23.7. HRMS (ESI) calcd. for $C_{51}H_{70}N_8O_{10}$ [M + H]$^+$, 955.5288; found: 955.5289.

Trimeric HSC carboxylic acid 20: Deprotection of the allyl ester at HSC trimer **19** (6.97 g, 5.6 mmol) followed the general deallylation procedure and trimeric amino building block **20** (3.84 g, 4.2 mmol) was obtained as a glassy yellowish solid after flash chromatography purification (Elution: isopropanol/DCM, 1/19). Analytical data for **20**, R_f = 0.5 (isopropanol/DCM, 1/19). ^{1}H NMR (600 MHz, CD_3OD) δ 7.44 (m, 15H), 4.90 (s, 6H, PhC*H*$_2$ × 3), 3.65 (br, 6H, C(=O)N(OBn)C*H*$_2$ × 3), 3.25 (t, *J* = 7.2 Hz, 2H, N_3C*H*$_2$), 3.14 (t, *J* = 7.2 Hz, 4H, C(=O)NHC*H*$_2$ × 2), 2.74 (br, 6H, succinyl C*H*$_2$ × 3), 2.54 (br, 2H, succinyl C*H*$_2$), 2.43 (t, *J* = 6.6 Hz, 4H, succinyl C*H*$_2$ × 2), 1.63 (quintet, *J* = 7.2 Hz, 6H, C*H*$_2$ × 3), 1.56 (quintet, *J* = 7.2 Hz, 2H, C*H*$_2$), 1.49 (quintet, *J* = 7.2 Hz, 4H, C*H*$_2$ × 2), 1.37-1.31 (m, 6H, C*H*$_2$ × 3). ^{13}C NMR (150 MHz, CD_3OD) δ 176.9, 175.4, 174.7, 174.6, 136.2, 130.6, 129.9, 129.7, 77.2, 52.3, 46.1, 40.3, 40.2, 31.2, 29.9, 29.8, 29.5, 28.9, 28.6, 27.5, 27.3, 25.0, 24.9, 24.8. HRMS (ESI) calcd. for $C_{48}H_{66}N_8O_{10}$ [M + H]$^+$, 915.4975; found: 915.4989.

DFO G_1 (4): To a solution of trimeric HSC carboxylic acid **20** (95 mg, 0.1 mmol) in MeOH (5 mL) and acetic acid additive (0.05 mL) was added 10% Pd-C (60 mg). The reaction mixture was stirred under a H_2 balloon at RT for 20 min. Upon complete azido reduction and hydrogenolysis, the Pd-C was filtered off through celite and filtrate was concentrated for flash chromatography purification (Elution: 28% $NH_{3(aq)}$/isopropanol, 1/9) to obtain (**4**) (27 mg, 0.05 mmol, 50%). Analytical data for (**4**), R_f = 0.1 (28% $NH_{3(aq)}$/isopropanol, 1/9). ^{1}H NMR (400 MHz, D_2O) δ 3.66 (quintet, *J* = 6.4 Hz, 6H, C(=O)N(OBn)C*H*$_2$ × 3), 3.19 (t, *J* = 6.4 Hz, 4H, C(=O)NHC*H*$_2$ × 2), 3.01 (t, *J* = 7.6 Hz, 2H, C*H*$_2$$NH_2$), 2.82 (t, *J* = 7.2 Hz, 2H, succinamic C*H*$_2$ × 1), 2.76 (t, *J* = 7.2 Hz, 2H, succinamic C*H*$_2$ × 1), 2.54-2.49 (m, 8H, succinyl C*H*$_2$ × 4), 1.72-1.63 (m, 8H, C*H*$_2$ × 4), 1.54 (quintet, *J* = 7.2 Hz, 4H, C*H*$_2$ × 2), 1.42-1.30 (m, 6H, C*H*$_2$ × 3). ^{13}C NMR (100 MHz, D_2O internal standard $CDCl_3$) δ 175.1, 174.2, 170.0, 167.3, 107.8, 48.2, 48.1, 48.0, 47.7, 39.6, 39.5, 32.14, 32.05, 30.8, 30.7, 28.22, 28.20, 28.0, 27.9, 26.61, 26.55,

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25.8, 25.6, 23.3, 23.0, 22.9. HRMS (ESI) calcd. for $C_{27}H_{50}N_6O_{10}$ [M + H]$^+$, 619.3661; found: 619.3664.

Trimeric HSC amino-carboxylic acid 21: Reduction of HSC trimeric carboxylic acid **20** (700 mg, 0.76 mmol) to trimeric HSC amino-carboxylic acid **21** followed by the general Staudinger reduction procedure. The amino-carboxylic acid **21** (614 mg, 0.7 mmol) as a yellow oily liquid via flash chromatography purification (Elution: 28% $NH_{3(aq)}$/isopropanol, 1/9). Analytical data for **21**, R_f = 0.2 (28% $NH_{3(aq)}$/isopropanol, 1/9). ^{1}H NMR (600 MHz, CD_3OD) δ 7.45-7.34 (m, 15H), 4.91 (s, 2H, PhC$\underline{H_2}$), 4.89 (s, 4H, PhC$\underline{H_2}$ × 2), 3.68 (t, J = 8.4 Hz, 2H, C(=O)N(OBn)C$\underline{H_2}$), 3.64 (t, J = 6.6 Hz, 4H, C(=O)N(OBn)C$\underline{H_2}$ × 2), 3.14-3.12 (m, 4H, C(=O)NHC$\underline{H_2}$ × 2), 2.86 (t, J = 7.2 Hz, 2H, $NH_2C\underline{H_2}$), 2.73 (br, 6H, succinyl C$\underline{H_2}$ × 3), 2.43 (t, J = 6.6 Hz, 6H, succinyl C$\underline{H_2}$ × 3), 1.66-1.59 (m, 8H, C$\underline{H_2}$ x 4), 1.48 (quintet, J = 7.2 Hz, 4H, C$\underline{H_2}$ × 2), 1.36-1.28 (m, 6H, C$\underline{H_2}$ × 3). ^{13}C NMR (150 MHz, CD_3OD) δ 180.8, 176.4, 175.5, 175.4, 174.5, 136.4, 136.1, 134.7, 134.6, 131.3, 131.2, 130.62, 130.60, 130.55, 130.0, 129.9, 129.8, 129.7, 129.6, 77.2, 40.7, 40.24, 40.21, 33.2, 31.2, 31.0, 30.2, 29.90, 29.86, 28.9, 28.7, 28.2, 27.5, 27.4, 27.2, 25.0, 24.9, 24.4. HRMS (ESI) calcd. for $C_{48}H_{68}N_6O_{10}$ [M + H]$^+$, 889.5070; found: 889.5092.

Cyclic HSC trimer 22 and DFO-E (2): Cyclization of trimeric HSC amino-carboxylic acid **21** (0.55 g, 0.62 mmol) followed the general intramolecular Steglich coupling procedure (Elution: EtOH/DCM, 1/19) to give cyclic HSC trimer **22** (0.25 g, 45%). Analytical data for **22**, R_f = 0.1 (EtOH/DCM, 1/19). ^{1}H NMR (400 MHz, CD_3OD) δ 7.43-7.37 (m, 15H), 4.88 (s, 6H, PhC$\underline{H_2}$ × 3), 3.66 (t, J = 6.8 Hz, 6H, C(=O)N(OBn)C$\underline{H_2}$ × 3), 3.14 (t, J = 6.8 Hz, 6H, C(=O)NHC$\underline{H_2}$ × 3), 2.72 (t, J = 6.8 Hz, 6H, succinyl C$\underline{H_2}$ × 3), 2.43 (t, J = 6.8 Hz, 6H, succinyl C$\underline{H_2}$ × 3), 1.61 (quintet, J = 7.2 Hz, 6H, C$\underline{H_2}$ × 3), 1.47 (quintet, J = 7.2 Hz, 6H, C$\underline{H_2}$ × 3), 1.29 (quintet, J = 7.2 Hz, 6H, C$\underline{H_2}$ × 3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 174.6, 130.6, 129.9, 129.7, 77.1, 45.8, 40.3, 40.1, 31.3, 29.8, 29.0, 27.4, 24.7. HRMS (ESI) calcd. for $C_{48}H_{66}N_6O_9$ [M + H]$^+$, 871.4964; found: 871.4992.

To a solution of cyclic HSC trimer **22** (60 mg, 0.07 mmol) in EtOH (14 mL), acetic acid additive (0.14 mL) and 10% Pd-C (30 mg) were added. The reaction was stirred at RT under a H_2 balloon for 30 min. Then the Pd-C was filtered off over celite and the filtrate was concentrated for flash chromatography (Elution: MeOH/DCM, 1/9) to afford DFO-E (**2**) (23 mg, 55%) as a white glassy solid. Analytical data for (**2**), R_f = 0.25 (MeOH/DCM, 1/9). ^{1}H NMR (600 MHz, CD_3OD) δ 3.61 (t, J = 6.6 Hz, 6H, C(=O)N(OH)C$\underline{H_2}$ × 3), 3.17 (t, J = 6.6 Hz, 6H, C(=O)NHC$\underline{H_2}$ × 3), 2.78 (t, J = 6.6 Hz, 6H, succinyl C$\underline{H_2}$ × 3), 2.47 (t, J = 6.6 Hz, 6 H, succinyl C$\underline{H_2}$ × 3), 1.63 (quintet, J = 7.2 Hz, 6H, C$\underline{H_2}$ × 3), 1.52 (quintet, J = 7.2 Hz, 6H, C$\underline{H_2}$ × 3), 1.32 (quintet, J = 7.2 Hz, 6H, C$\underline{H_2}$ × 3). ^{13}C NMR ((150 MHz, CD_3OD) δ 175.0, 174.4, 48.7, 40.1, 31.7, 29.8, 28.9, 27.2, 24.6. HRMS (ESI) calcd. for $C_{27}H_{48}N_6O_9$ [M + H]$^+$, 601.3556; found: 601.3562.

Protected HSC tetramer 23: Coupling of dimeric HSC carboxylic acid building block **15** (0.2 g, 0.32 mmol) with dimeric HSC amino building block **18** (0.24 g, 0.37 mmol) followed the general Steglich coupling procedure to give HSC tetramer **23** (0.30 g, 75%). After workup procedure, the crude mixture was purified by flash column chromatography (Elution: MeOH/DCM, 1/19) to give protected HSC tetramer **23** as a glassy white solid (0.30 g, 75%). Analytical data for **23**, R_f = 0.3 (MeOH/DCM 5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 20H), 6.49 (s, 1H, C(=O)N$\underline{H}$), 6.38 (s, 2H, C(=O)N$\underline{H}$ × 2), 5.92 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H, $OCH_2C\underline{H}$=CH_2), 5.31 (dd, J = 17, 1.4 Hz, 1H, OCH_2CH=C$\underline{H_2}$), 5.22 (dd, J = 10.6, 1.0 Hz, 1H, OCH_2CH=C$\underline{H_2}$) , 4.85 (s, 2H, PhC$\underline{H_2}$), 4.85 (s, 6H, PhC$\underline{H_2}$ × 3), 4.58 (d, J = 5.6 Hz, 2H, C(=O)OC$\underline{H_2}$), 3.63 (br, 8H, N(OBn)C$\underline{H_2}$× 4), 3.24-3.16 (m, 8H, C$\underline{H_2}$N$_3$, NHC$\underline{H_2}$ × 3), 2.79-2.72 (m, 8H, succinyl C$\underline{H_2}$ × 4), 2.64 (t, 2H, succinyl C$\underline{H_2}$), 2.48 (quartet, 6H, succinyl C$\underline{H_2}$ × 3), 1.66 - 1.55 (m, 10H, C$\underline{H_2}$ × 5), 1.48 (quintet, 6H, C$\underline{H_2}$ × 3), 1.37-1.26 (m, 8H, C$\underline{H_2}$ × 4). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 174.0, 173.1, 172.7, 172.14, 172.11, 134.4, 132.2, 129.17, 129.15, 129.14, 128.9, 128.7, 118.1, 76.4, 76.3, 65.3, 51.2, 45.3, 44.9, 39.4, 35.1, 30.6, 29.1, 28.7, 28.6, 28.5, 28.0, 27.4, 26.50, 26.45, 24.0, 23.9, 23.7. HRMS (ESI) calcd. for $C_{67}H_{92}N_{10}O_{13}$ [M + H]$^+$, 1245.6918; found: 1245.6951.

Tetrameric HSC amino-carboxylic acid 24: Removal of the allyl group and azido reduction of HSC tetramer **23** (180 mg, 0.15 mmol) followed general deallylation and Staudinger reduction method to obtain tetrameric HSC aminocarboxylic acid **24** (110 mg, 60% over two steps), (Elution: 28% $NH_{3(aq)}$/isopropanol, 1/9). Analytical data for **24**, R_f = 0.2 (10% $NH_{3(aq)}$/isopropanol, 1/9). ^{1}H NMR (400 MHz, CD_3OD) δ 7.44-7.37 (m, 20H), 4.91 (s, 2H, PhC$\underline{H_2}$), 4.90 (s, 6H, PhC$\underline{H_2}$ × 3), 3.69-3.65 (m, 8H, C(=O)N(OBn)C$\underline{H_2}$ × 4), 3.15-3.11 (m, 6H, C(=O)NHC$\underline{H_2}$ × 3), 2.86 (t, J = 7.2 Hz, 2H, $NH_2C\underline{H_2}$), 2.73 (br, 8H, succinyl C$\underline{H_2}$ × 4), 2.46-2.42 (m, 8H, succinyl C$\underline{H_2}$ × 4), 1.63 (quintet, J = 6.4 Hz, 8H, C$\underline{H_2}$ × 4), 1.48 (quintet, J = 7.2 Hz, 8H, C$\underline{H_2}$ × 4), 1.35-1.26 (m, 8H, C$\underline{H_2}$ × 4). ^{13}C NMR (150 MHz, CD_3OD) δ 175.3, 174.6, 136.4, 136.2, 134.7, 134.6, 133.8, 133.1, 133.0, 131.3, 131.2, 130.63, 130.60, 130.6, 130.0, 129.9, 129.86, 129.69, 129.65, 77.2, 46.1, 40.7, 40.2, 32.7, 31.2, 31.0, 29.9, 28.9, 28.7, 28.1, 27.5, 27.2, 25.0, 24.96, 24.4. HRMS (ESI) calcd. for $C_{64}H_{90}N_8O_{13}$ [M + H]$^+$, 1179.6700; found: 1179.6726.

Protected cyclic HSC tetramer 25 and DFO-T_1 (3): Cyclization of tetrameric HSC amino-carboxylic acid **24** (0.11 g, 0.09 mmol) followed the general cyclization procedure. After flash chromatography purification (Elution: MeOH/DCM, 1/12), cyclized HSC tetramer **25** (46 mg, 44%) was obtained as a white amorphous substance. Analytical data for **25**, R_f = 0.25 (MeOH/DCM, 1/9). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.38 (m, 20H), 7.01 (br, 3H, C(=O)NH), 4.87-4.84 (m, 8H, PhC$\underline{H_2}$ × 4), 3.64 (t, J = 7.2 Hz, 8H, C(=O)N(OBn)C$\underline{H_2}$ × 4), 3.19 (quartet, J = 6. Hz, 8H, C(=O)NHC$\underline{H_2}$ × 4), 2.88-2.80 (m, 8H, succinyl C$\underline{H_2}$ × 4), 2.57-2.48 (m, 8H, succinyl C$\underline{H_2}$ × 8), 1.62 (quintet, J = 6.8 Hz, 8H, C$\underline{H_2}$ × 4), 1.50 (quintet, J = 6.8 Hz, 8H, C$\underline{H_2}$ × 4), 1.28 (quintet, J = 7.6 Hz, 8H, C$\underline{H_2}$ × 4). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 172.1, 134.3, 132.1, 132.0, 131.95, 131.9, 129.2, 129.0, 128.7, 128.6, 128.4, 77.2, 76.4, 70.6, 44.7, 39.4, 30.5, 28.1, 28.0, 26.5, 23.5. HRMS (ESI) calcd. for $C_{64}H_{88}N_8O_{12}$ [M + H]$^+$, 1161.6594; found: 1161.6621.

To a solution of cyclic HSC tetramer **25** (36 mg, 0.031 mmol) in EtOH (6 mL) were added 2 drops of acetic acid and 10% Pd-C (36 mg) under N_2. The reaction was stirred at RT under H_2 (1 atm) for 1 h. The Pd-C was filtered over celite and the filtrate was concentrated for purification with column chromatography ($CHCl_3$/MeOH/H_2O, 60/25/4) to afford DFO-T_1 (**3**) (10.5 mg, 0.013 mmol, 42%) as a white glassy solid. For (**3**), R_f = 0.2 ($CHCl_3$/MeOH/H_2O, 60/25/4). ^{1}H NMR (400 MHz, CD_3OD) δ 3.61 (m, 8H, C(=O)N(OH)C$\underline{H_2}$ × 4), 3.17 (t, J = 6.4 Hz, 8H, C(=O)NHC$\underline{H_2}$ × 4), 2.78 (t, J = 6.0 Hz, 8H, succinyl C$\underline{H_2}$ × 4), 2.48 (t, J = 6.4 Hz, 8 H, succinyl C$\underline{H_2}$ × 4), 1.64 (quintet, J = 6.8 Hz, 6H, C$\underline{H_2}$ × 3), 1.52 (quintet, J = 7.2 Hz, 8H, C$\underline{H_2}$ × 4), 1.33 (m, 8H, C$\underline{H_2}$ × 4). ^{13}C NMR ((150 MHz, CD_3OD) δ 181.4, 174.5, 48.3, 48.2, 48.0, 40.3, 31.5, 29.9, 29.0, 27.3, 24.7. HRMS (ESI) calcd. for $C_{36}H_{64}N_8O_{12}$ [M + H]$^+$, 801.4716; found: 801.4734.

***N*-(5-Aminopentyl)-*N*-(benzyloxy)acetamide 26**: To a solution of *N*-(5-azidopentyl)-*O*-benzylhydroxylamine **12** (2.44 g, 10.42 mmol) in DCM (10 mL), DMAP (0.64 g, 5.21 mmol) and Ac_2O (2 mL, 20.8 mmol) were added at 0 ºC. The reaction mixture was then stirred at RT for 15 min. After completion of the acetylation, the reaction mixture was diluted with DCM (30 mL) followed by washing 1 N HCl (30 mL × 2), brine (40 mL), and dried over $MgSO_4$. After filtration, the DCM solution was concentrated and the crude acetylation product was directly taken to the Staudinger reduction. A solution of the acetamide intermediate in dried THF (10 mL) was subjected to the general Staudinger reduction procedure and amine product **26** (2.16 g, 83%) was obtained as an oily liquid after the flash column chromatography purification (28% $NH_{3(aq)}$/isopropanol, 1/19). Analytical data for **26**, R_f = 0.25 (28% $NH_{3\,(aq)}$/isopropanol, 1/19). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.36 (m, 5H), 4.81 (s, 2H, PhC$\underline{H_2}$), 3.64 (t, J = 6.8 Hz, 2H, N(OBn)C$\underline{H_2}$), 2.67 (t, J = 6.8 Hz, 2H, C$\underline{H_2}$NH$_2$), 2.09 (s, 3H, C(=O)C$\underline{H_3}$), 1.65 (quintet, J = 7.6 Hz, 2H, C$\underline{H_2}$), 1.46 (quintet, J = 7.2 Hz, 2H, C$\underline{H_2}$), 1.36-1.28 (m, 2H, C$\underline{H_2}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 134.6, 129.2, 129.0, 128.8, 76.4, 45.3, 42.0, 33.3, 26.8, 24.1, 20.6. HRMS (ESI) calcd. for $C_{14}H_{22}N_2O_2$ [M + H]$^+$, 251.1754; found: 251.1760.

One half HSC unit 27: Coupling of HSC carboxylic acid building block **6** (106 mg, 0.32 mmol) with *N*-(5-aminopentyl)-*N*-(benzyloxy)acetamide **26** (80 mg, 0.32 mmol) followed by the general Steglich coupling procedure

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(Elution: isopropanol/DCM, 1/19) to obtain intermediate **27** (128 mg, 70%). Analytical data for **27**, R_f = 0.3 (isopropanol/DCM, 1/19). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 10H), 5.98 (br, 1H, C(=O)NH), 4.85 (s, 2H, PhC$\underline{H_2}$), 4.81 (s, 2H, PhC$\underline{H_2}$), 3.63 (br, 4H, N(OBn)C$\underline{H_2}$ × 2), 3.25-3.20 (m, 4H, C$\underline{H_2}$N$_3$, C(=O)NHC$\underline{H_2}$), 2.79 (t, J = 6.4 Hz, 2H, succinyl C$\underline{H_2}$), 2.46 (t, J = 6.4 Hz, 2H, succinyl C$\underline{H_2}$) 2.10 (s, 3H, C(=O)C$\underline{H_3}$), 1.67-1.57 (m, 6H, C$\underline{H_2}$ × 3), 1.51 (quintet, J = 7.6 Hz, 2H, C$\underline{H_2}$), 1.39-1.27 (m, 4H, C$\underline{H_2}$ × 2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 129.37, 129.36, 129.2, 128.95, 128.94, 76.7, 76.5, 51.5, 45.6, 39.6, 31.0, 29.2, 28.7, 28.4, 26.7, 26.6, 24.1, 20.8. HRMS (ESI) calcd. for $C_{30}H_{42}N_6O_5$ [M + H]$^+$, 567.3289; found: 567.3296.

Protected DFO-B 28 and DFO-B (5): To a solution of one-half HSC unit **27** (0.55 g, 0.97 mmol) in dried THF (3 mL) was added PPh_3 (0.3 g, 1.2 mmol). The reaction mixture was stirred at 80 °C for an hour then followed by addition of H_2O (0.17 mL, 9.7 mmol). The mixture was stirred for additional one hour then was concentrated for flash column chromatography to give an amine intermediate (0.42 g, 0.78 mmol). Without characterization, the amine intermediate (0.77 g, 1.42 mmol) was coupled with HSC carboxylic acid building block **6** (0.5 g, 1.5 mmol) in dried DCM (3 mL) based on the general Steglich coupling procedure. After the workup and flash chromatography purification (Elution: isopropanol/toluene, 1/9), protected DFO-B **28** was obtained as an oily substance (0.90 g, 60% over two steps). Analytical data for **28**, R_f = 0.2 (isopropanol/toluene, 1/9). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 15H), 6.34-6.30 (br, 2H, C(=O)N$\underline{H}$ × 2), 4.85 (s, 4H, PhC$\underline{H_2}$ × 2), 4.80 (s, 2H, PhC$\underline{H_2}$), 3.63 (br, 6H, N(OBn)C$\underline{H_2}$ × 3), 3.26-3.17 (m, 6H, C(=O)NHC$\underline{H_2}$ × 2, C$\underline{H_2}$N$_3$), 2.82-2.80 (m, 4H, succinyl C$\underline{H_2}$ × 2), 2.51-2.46 (quintet, J = 6.8 Hz, 4H, succinyl C$\underline{H_2}$ × 2), 2.09 (s, 3H, C(=O)C$\underline{H_3}$), 1.63-1.56 (m, 6H, C$\underline{H_2}$ × 3), 1.50 (quintet, J = 7.2 Hz, 4H, C$\underline{H_2}$ × 2), 1.37-1.26 (m, 8H, C$\underline{H_2}$ × 4). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 168.9, 134.4, 129.3, 129.17, 129.15, 129.0, 128.8, 128.7, 76.4, 76.3, 51.2, 45.3, 45.0, 44.8, 39.4, 30.69, 30.65, 29.0, 28.5, 28.12, 28.05, 27.2, 26.4, 25.6, 23.93, 23.88, 23.8, 23.6, 20.5. HRMS (ESI) calcd. for $C_{46}H_{64}N_8O_8$ [M + H]$^+$, 857.4920; found: 857.4903.

A solution of **28** (92 mg, 0.11 mmol) in MeOH (10 mL) was briefly purged with N_2. Then, 10% Pd/C (50 mg) were added. The reaction mixture was stirred at RT under a H_2 balloon for about 20 min. Then, the Pd/C was removed by filtration (over celite) and the filtrate was concentrated for purification with flash chromatography (Elution: 28% $NH_{3(aq)}$/isopropanol, 1/4) to obtain DFO-B (**5**) (30 mg, 50%). Analytical data for (**5**), R_f = 0.15 (28% $NH_{3(aq)}$/isopropanol, 1/4). ^{1}H NMR (400 MHz, CD_3OD) δ 3.60 (t, J = 6.4 Hz, 6H, N(OH)C$\underline{H_2}$ × 3), 3.17 (t, J = 6.8 Hz, 4H, C(=O)NHC$\underline{H_2}$ × 2), 2.77 (t, J = 6.8 Hz, 4H, succinyl C$\underline{H_2}$ × 2), 2.71 (t, J = 7.2 Hz, 2H, C$\underline{H_2}$NH$_2$), 2.46 (m, 4H, succinyl C$\underline{H_2}$ × 2), 2.09 (s, 3H, C(=O)C$\underline{H_3}$), 1.64 (quintet, J = 6.4 Hz, 6H, C$\underline{H_2}$ × 3), 1.53 (quintet, J = 6.4 Hz, 6H, C$\underline{H_2}$ × 3), 1.35 (quintet, J = 6.4 Hz, 6H, C$\underline{H_2}$ × 3). ^{13}C NMR (150 MHz, CD_3OD) δ 174.9, 174.3, 173.4, 41.8, 40.3, 31.51, 31.45, 29.98, 29.95, 28.9, 28.8, 27.4, 27.3, 24.92, 24.89, 24.7, 20.2. HRMS (ESI) calcd. for $C_{25}H_{48}N_6O_8$ [M + H]$^+$, 561.3606; found: 561.3612.

CAS competitive Fe(III) binding assay: The competitive Fe(III) binding assay was performed in accordance with the literature procedure.[39] Preparation of CAS-Fe(III) assay solution: 1.5 mL of 1.00 mM $FeCl_3$ solution and 7.5 mL of 2.0 mM of CAS were mixed; then poured into to a 100 mL volumetric flask. To the CAS-Fe(III) mixture were added the 2.0 mM CTAB and 1 M MES buffer solutions. The resulting solution was made up to 100 mL with DI water. As such, the CAS-Fe(III) assay solution was prepared (preparation of the 2.0 mM CAS dye solution, 1 mM $FeCl_3$ solution, 2.42 mM CTAB solution, and 1 M MES buffer (pH 5.6) were given in SI). A series of siderophore solutions with concentrations 1.563, 3.125, 6.250, 12.50, 25.0, 50.0, 100.0, and 200.0 μM were prepared by serial dilution from a 400 μM stock solution.

In the assay, 0.5 mL of a siderophore solution was added to 0.5 mL of above CAS-Fe(III) assay solution in a 1.5 mL eppendorf at RT. After mixing by inversion (× 5), the mixture was left at RT in dark for 3 h. Then, the solution was poured into a quartz cuvette and its absorbance (Abs630) was measured.

Conflicts of interest

There are no conflicts to declare.

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Keywords: siderophores • desferrioxamines • hydroxamate • convergent synthesis • iron binding

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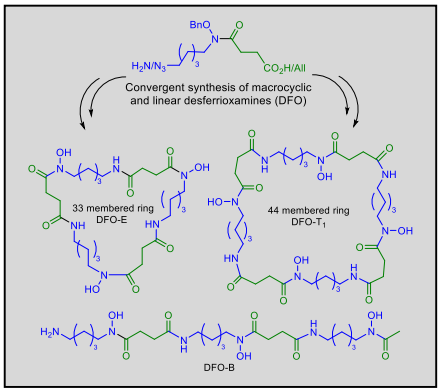
Metal Binders



A novel convergent synthetic strategy has been developed for total synthesis of linear and macrocyclic deferroxamines (DFO), which include 22-membered macrocyclic bisucaberin, 33-membered macrocyclic DFO-E, 44-membered macrocyclic DFO-T_1, linear DFO-G_1, and DFO-B. In the Chrome Azurol S competitive iron(III) binding assay, DFO-E was found to be the best Fe(III) ion binder.

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