Tetrahedron 67 (2011) 144–151

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Facile synthesis of salmochelin S1, S2, MGE, DGE, and TGE

Xiaolong Yu [a,†], Yijing Dai [a,†], Tao Yang [a], Michel R. Gagné [b], Hegui Gong [a,*]

[a] Shanghai University, Department of Chemistry, Shanghai 200444, China
[b] University of North Carolina at Chapel Hill, Department of Chemistry, Chapel Hill, NC 27599, USA

ARTICLE INFO

Article history:
Received 10 August 2010
Received in revised form 31 October 2010
Accepted 2 November 2010
Available online 5 November 2010

Keywords:
Salmochelin
Total synthesis
Aryl β-*C*-glucoside

ABSTRACT

Salmochelin S1, S2, MGE, DGE, and TGE were prepared through amide bond connection of an aryl *C*-glucosyl acyl chloride (Ar^1COCl) and serine ester amines, followed by hydrogenolysis of the per-benzylated precursors. Each synthesis employed a highly diastereoselective Ni-catalyzed Negishi approach to the aryl *C*-glycoside subunit.

1. Introduction

Iron is crucial for most bacteria to grow. In mammalian cells, the iron concentration is very low (~10^{-24} M) due to the low solubility of iron under physiological conditions and the presence of strong Fe^{3+}-binding proteins.[1] To secure their iron supply, bacteria have evolved to produce small molecular siderophores to bind and transport iron from the environment.[1–6] For instance, Enterobactin (Ent), a 2,3-dihydroxybenzoyl (DHB) serine macrotrilactone (Chart 1) with a K_d for $Fe^{3+}$of ~10^{-49} M is one of the most studied siderophores.[2] The mono and di-*C*-glucosylated Ent derivatives (Chart 1), termed salmochelins, are produced from *Salmonella* species, *uropathogenic*, and *avian pathogenic Escherichia coli* strains, and certain Klebsiella strains.[3] Studies indicated that salmochelins are better Fe^{3+} siderophores than Ent in the presence of serum albumin and played a more important role for pathogenic processes in certain *E. Coli* and *Salmonella* infections.[3,4] Intensive exploration of the mechanism of how bacteria use glucosylated Ents as virulence factors has been carried out by Hantke,[3] Walsh and Liu[5] and others.[6] The enzyme-mediated in vitro syntheses of salmochelin S1, S2, SX, and the mono- (MGE), di-(DGE or salmochelin S4), and tri-*C*-glucosylated Ent (TGE) derivatives (Chart 1) have been achieved.[5b–d,6a]

An efficient chemical synthesis of the salmochelins would provide complementary access to these naturally-occurring compounds and allow for systematic structural deviations that would further bio-studies.[5,7] Our recent success in the development of a Ni-catalyzed Negishi approach to alkyl and aryl *C*-glycosides (e.g., Scheme 1)[8] has opened up opportunities to stereoselectively prepare relevant bio-active natural products containing *C*-glycoside cores that may otherwise be difficult to obtain using classical methods.[9,10] Using this method as the key step, the total synthesis of salmochelin SX, the structurally simplest derivative in the salmochelin family, has been achieved.[8a] The significance of the salmochelins as siderophores in nature prompted us to carry out and present herein a full account on the syntheses of the structurally more complex salmochelin S1, S2, and S4 (DGE) and the TGE and MGE derivatives (Chart 1).

2. Results and discussion

The structures of the salmochelins and the analogs possess characteristic amide bond connection arising from the corresponding L-serine ester amines (Chart 1) with *C*-glucosylated DHB and DHB (Chart 2). Whereas DGE, TGE, and MGE employed a cyclic tri-L-serine lactone amine, salmochelin S1 and S2 consist of linear di- and tri-L-serine ester amines, respectively (Chart 1). Hence, our general synthetic strategy for the salmochelins focused on an amide bond forming fragment assembly of a per-benzylated glucosyl acyl chloride **1** (Ar^1COCl)[8a] and benzyl-protected L-serine ester amines, capped by a one-step global hydrogenolysis/deprotection (Scheme 2).

In analogy to the synthesis of Ent,[11] the C_3-symmetric TGE was readily obtained by treatment of the trilactone triamine hydrochloride salt **2**[11a] (Chart 2) with **1**[8a], which was prepared based on a modification of our previous procedures.[12] The resulting per-benzylated TGE precursor **3** was obtained in 70% yield. Removal of the benzyl groups furnished TGE in good yield (Scheme 3).

* Corresponding author. Tel.: +86 21 6613 2410; fax: +86 21 6613 4594; e-mail address: hegui_gong@shu.edu.cn (H. Gong).
† The first two authors contributed equally to this study.

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doi:10.1016/j.tet.2010.11.007

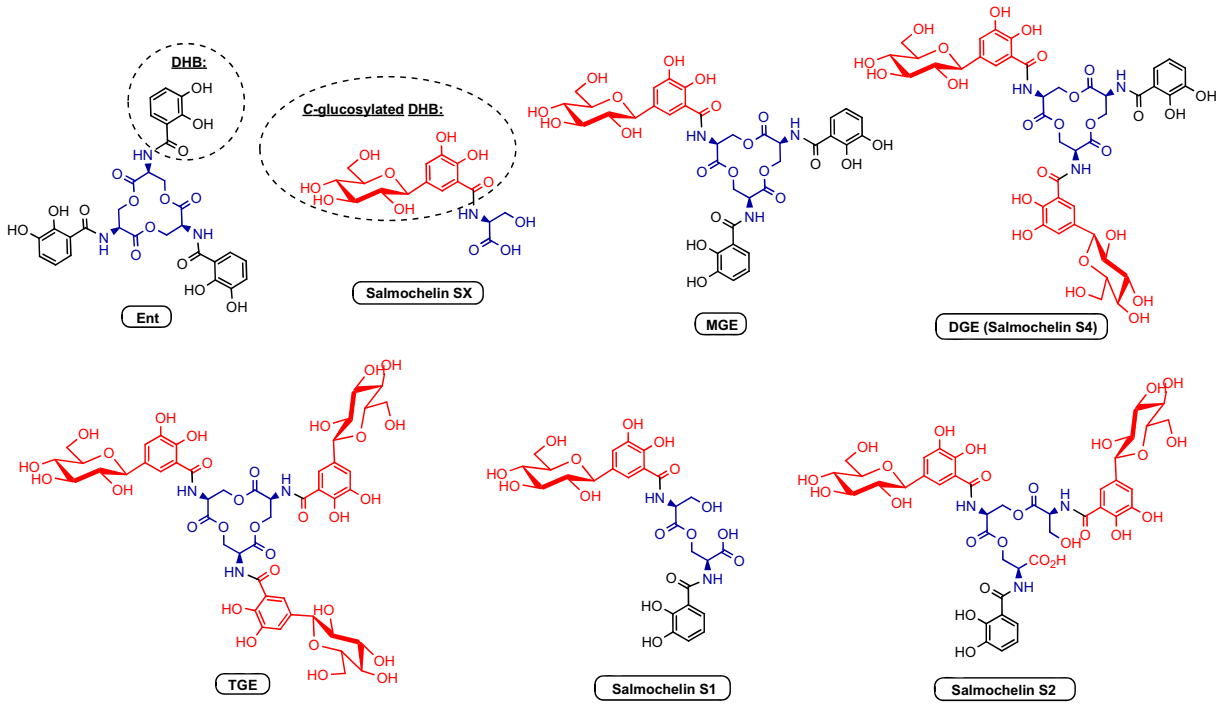
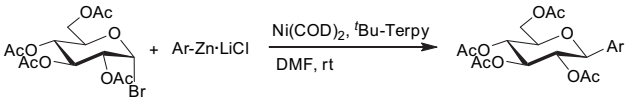


Chart 1. The structures of salmochelin derivatives.



Scheme 1. Ni-catalyzed Ar-β-*C*-glucoside formation.[8a]

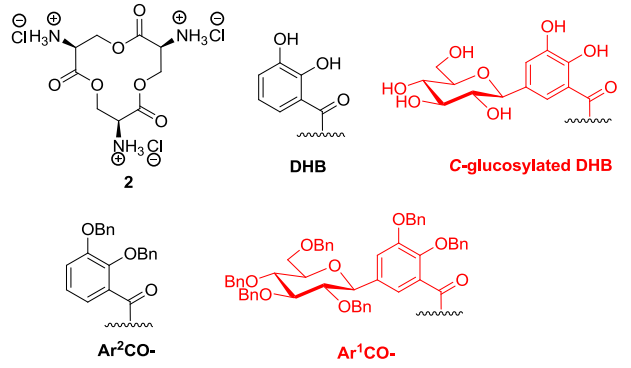
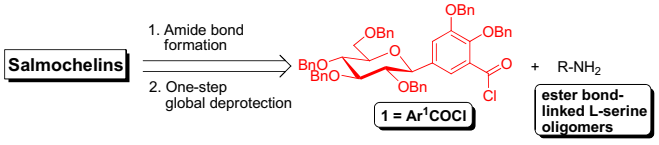
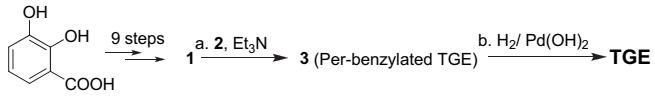


Chart 2. Structures of **2**, DHB, *C*-glucosylated DHB, Ar^2CO, and Ar^1CO.

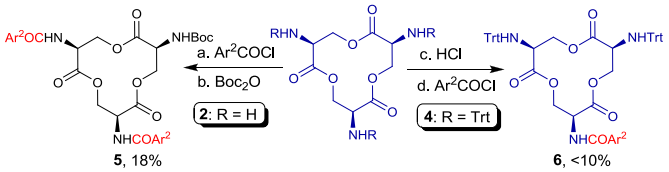


Scheme 2. A retrosynthetic scheme of salmochelin synthesis.



Scheme 3. TGE synthesis. Reaction conditions: (a) **2** (100 mol %), **1** (300 mol %), Et_3N (600 mol %), DCM (0.03 M), 0 °C, 30 min then 22 °C, 5 h, 70% over two steps. (b) H_2, $Pd(OH)_2$, MeOH/EtOAc 1:1 (0.09 M), 18 h, 92%.

The synthesis of DGE (salmochelin S4) and MGE, however requires installation of both DHB and the *C*-glucosylated DHB to the trilactone ring **2**. Initial efforts were focused on the incorporation of mono- or di-2,3-bis(benzyloxy)benzoyl (i.e., Ar^2CO, see Chart 2) into **2** and **4** with the remaining amine groups being protected (Scheme 4). Nevertheless, this strategy was unsatisfactory; the best results obtained were <18% yields for the preparation of **5** and **6** (Scheme 4). The main reason for these low yields is likely due to the instability of the trilactone ring. It was observed that **2**, **5**, and tri-Boc-protected **2** decomposed in the presence of Et_3N.

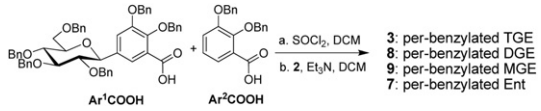


Scheme 4. mono- or di-protection of cyclic triamine.

Given the success that per-benzylated TGE **3** and per-benzylated Ent **7** were synthesized by amidation of **2** with Ar^1COCl and Ar^2COCl,[11] respectively, we reasoned that per-benzylated DGE **8** and per-benzylated MGE **9** could be prepared through amide bond formation from a mixture of the two acid chlorides and **2**. Indeed, conversion of mixtures of Ar^1COOH and Ar^2COOH to the acyl chlorides followed by treatment with **2** in the presence of Et_3N, provided mixtures of per-benzylated precursors **3**, **7**, **8**, and **9** (Table 1). The distribution of the products was dependent on the ratio of acids examined. A 1:1 mixture of the two acids appeared to result in optimal overall yields for **8** and **9** with trace of **3** and **7** (entry 1). Hydrogenolysis of **8** and **9** provided DGE and MGE in 92% and 90% yields, respectively.

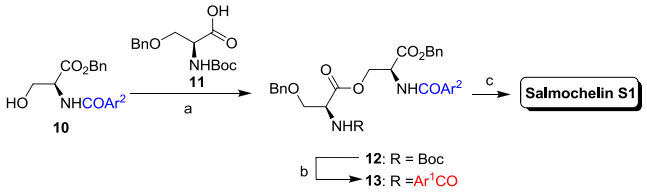
Salmochelin S1 was prepared from esterification of *N*-Ar^2CO-ser(OH)-OBn **10** with *N*-Boc-ser(OBn)-OH **11** (Scheme 5) to form Boc-protected diseryl ester **12**. Deprotection with dry HCl[13] followed by amide bond formation upon treatment with **1** (Ar^1COCl) provided per-benzylated salmochelin S1, which was converted to salmochelin S1 in high yield by hydrogenolysis (Scheme 5).

Table 1
Optimization for the formation of **8** and **9**



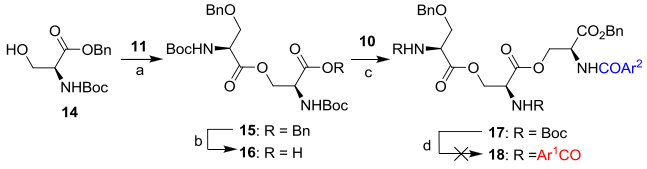
Entry[a]	Ar^1COOH: Ar^2COOH	3	8	9	7
1	1:1	Trace	27%[b]	42%	Trace
2	2:1	16%	24%	8%	Trace
3	1:2	Trace	7%	38%	14%

[a] Reaction conditions: (a) Ar^1COOH+Ar^2COOH (300 mol %), $SOCl_2$, DMF (cat.), DCM (0.2 M). (b) **2** (100 mol %), Et_3N (600 mol %), DCM (0.07 M), 20 °C, 3 h.
[b] Yields were calculated over two steps.



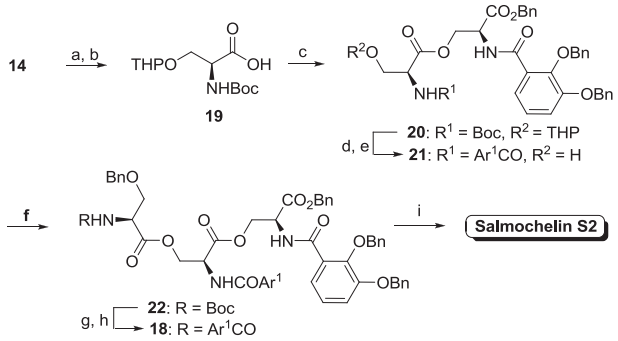
Scheme 5. Preparation of salmochelin S1. (a) **11**, EDC/HCl (130 mol %), HOBT (200 mol %), pyridine (230 mol %), CH_3CN (0.1 M), 12 h, 85%. (b) (i) HCl, MeOH/THF. (ii) Et_3N, **1**, DCM, 53%. (c) H_2, $Pd(OH)_2$, MeOH/EtOAc, 1:1, 90%.

Likewise, preparation of salmochelin S2 was first proposed beginning with coupling of **14** and **11** (Scheme 6). The resulting Boc-protected ester **15** was submitted to hydrogenolysis giving **16** in high yield. Coupling of **16** with **10**, however provided **17** in low yield, along with **12** and an aminoacrylate byproduct. This is due to E2 elimination in the acid activation step.[14a] It should be noted that *N*-benzoyl serine may undergo racemization under the EDC/HOBT coupling conditions, particularly when the carboxylic acid is not protected.[14] To our delight, no racemization occurred when **10** was utilized. Installation of Ar^1CO to **17** after removal of Boc produced trace amount of per-benzylated salmochelin S2 **18** presumably due to an rapid O→N acyl shift upon neutralization of the linear amine salt (Scheme 6).[15,16] Variation of temperature and concentration were not successful.[17]



Scheme 6. Attempt to preparation of salmochelin S2. Reaction conditions: (a) EDC/HCl (130 mol %), HOBT (180 mol %), *N*-Methylmorphorline (210 mol %), 48 h, 76%. (b) H_2, Pd/C, 21 h, 70%. (c) EDC/HCl (130 mol %), HOBT (180 mol %), *N*-Methylmorphorline (210 mol %), 24 h, 48%. (d) (i) HCl, MeOH/THF. (ii) Et_3N, **1**, DCM.

To circumvent the undesired side reactions (vide infra), a second approach to salmochelin S2 was carefully devised involving the installation of the first Ar^1CO– to a diseryl ester prior to esterificaion (Scheme 7). Coupling of the THP-protected serine **19**[14a] and **10** provided the diseryl ester **20**. Removal of THP and Boc followed by amidation with Ar^1COOH gave the diseryl alcohol **21**, which was treated with **11** to produce the triseryl ester **22**. Subsequent deprotection of Boc and acylation with **1** offered **18** in 54% yield. Finally, hydrogenolysis furnished salmochelin S2 in good yield (Scheme 7).



Scheme 7. Reaction conditions: (a) DHP, TsOH/pyridine. (b) H_2, Pd/C. 99% over two steps. (c) **10**, EDC/HCl, HOBT, Pyridine, CH_3CN, 24 h, 83%. (d) HCl, MeOH/THF. (e) Ar^1-COOH, EDC/HCl, HOBT, pyridine, CH_3CN, 24 h. 60% over two steps. (f) **11**, EDC/HCl, HOBT, pyridine, CH_3CN, 24 h, 43%. (g) HCl. (h) EDC/HCl, Et_3N, DCM, 54% over two steps. (i) H_2, $Pd(OH)_2$, MeOH/EtOAc, 1:1, 90%.

3. Conclusion

In summary, a general and facile synthesis of salmochelin S1, S2, and S4 (DGE), MGE, and TGE was accomplished for the first time. An amide bond forming strategy by coupling of the glucosyl acid chloride with the corresponding amines, and subsequent one-step global deprotection furnished the salmochelins. Finally, the chemical synthesis of salmochelins opens up doors to structurally modified derivatives, which may ultimately become useful for biological studies.

4. Experimental section

4.1. General

For general experimental details see the Supplementary data.

4.2. General procedure a for acylation of amines with 1

To a solution of *C*-glucosyl acid Ar^1COOH (100 mol %) in dry DCM (0.05 M) were added DMF (cat.) and $SOCl_2$ (400 mol %). The reaction was stirred for 3 h at 20 °C. After the solvent and excess $SOCl_2$ were removed under reduce pressure, the acyl chloride **1** was redissovled in DCM. At 0 °C, the resulting solution was added to a solution of amine, which was prepared form a suspension of amine salt (100 mol %) in DCM upon addition of freshly distilled Et_3N (150 mol %). The reaction mixture was allowed to warm to 20 °C, and stirred for 0.5–5 h, at which point it was concentrated over silica gel. Flash column chromatography (SiO_2) gave the amide.

4.3. General procedure B for global Bn-deprotection

To a flame-dried round bottom flask equipped with a magnetic stir bar was loaded a per-benzylated salmocheline precursor, followed by the addition of MeOH/EtOAc (v/v 1:1) and $Pd(OH)_2$ (20% weight on carbon, wet). The reaction mixture was first purged with argon for 3 min, and then hydrogen for 3 min. After the reaction mixture was stirred for 18 h under hydrogen atmosphere, it was filtered (over Celite) and washed with dry MeOH. The organic solution was collected, and the solvent was removed under reduced pressure to give a white solid.

4.4. General procedure C for removing Boc group

To a solution of Boc-protected serine (0.128 mmol) in anhydrous THF (3.7 mL) at 20 °C was added a solution of anhydrous HCl in MeOH (~1 M, 2.3 mL), which was freshly prepared by the addition of acetyl chloride to MeOH. The reaction mixture was stirred till the starting

material was consumed, which was monitored by TLC, at which point the solvent and excess HCl were removed and dried in vacuo.

4.5. General conditions for preparative RP-HPLC

A solution of a crude salmochelin product in MeOH was filtered through a 0.2 μm (PTFE) Millipore syringe filter (Fisherbrand) before purification by preparative RP-HPLC using a gradient of CH_3CN in 0.1% TFA/H_2O over 40–45 min, monitored at 220 nm. The solvent was removed on a lyophilizer.

4.6. Procedures and spectral data

*4.6.1. (S)-Benzyl 2-(2,3-bis(benzyloxy)benzamido)-3-hydroxypropanoate (**10**).* To an oven-dried round bottom flask charged with H-Ser-OBzl·HCl (1.150 g, 100 mol %, 4.98 mmol), Ar^2COOH (2.000 g, 120 mol %, 5.980 mmol), and EDC·HCl (1.050 g, 110 mol %, 5.480 mmol) were added DCM (25 mL) followed by Et_3N (0.83 mL, 120 mol %, 5.98 mmol). The reaction mixture was stirred at 20 °C overnight. After removal of the solvent, the residue was dissolved in EtOAc (50 mL). The solution was washed with brine, and the organic phase was collected and dried over $MgSO_4$. Flash column chromatography (SiO_2: 20% ethyl acetate in hexanes) gave the product as a white solid (1.75 g, 3.34 mmol, 67% yield). $[\alpha]_D^{24}$ +57.11 (*c* 6.00, DCM). ^1H NMR (500 MHz, $CDCl_3$): δ 8.90 (d, *J*=7.0 Hz, 1H), 7.10 (dd, *J*=2.0, 7.5 Hz, 1H), 7.48–7.15 (m, 17H), 5.21–5.18 (m, 3H), 5.14 (s, 2H), 5.07 (d, *J*=10.5 Hz, 1H), 4.79 (quint, *J*=3.5 Hz, 1H), 3.88 (q, *J*=11.5 Hz, 2H), 2.68 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 165.7, 151.8, 147.1, 136.4, 136.3, 135.4, 129.2, 128.7, 128.6, 128.5, 128.4, 128.3, 127.9, 126.7, 124.4, 123.3, 117.5, 76.3, 71.4, 67.3, 63.3, 55.5. HRMS (MALDI): *m*/*z* $[M+Na]^+$ found 534.1888, calcd 534.1893 for $C_{31}H_{29}NO_6Na$.

*4.6.2. (S)-Benzyl3-((S)-3-(benzyloxy)-2-(tert-butoxycarbonylamino) propanoyloxy)-2-(2,3-bis(benzyloxy)benzamido)propanoate (**12**).* To a solution of **10** (0.500 g, 100 mol %, 0.940 mmol), **11** (0.310 g, 110 mol %, 1.040 mmol), and HOBT (0.250 g, 195 mol %, 1.830 mmol) in dry acetonitrile was added EDC·HCl (0.230 g, 126 mol %, 1.180 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C, then 1 h at 20 °C. Pyridine (0.175 mL, 230 mol %, 2.160 mmol,) was added, and the mixture was stirred for 48 h. After removal of the solvent in vaccuo, the residue was dissolved in EtOAc (20 mL). The solution was washed with brine, and the organic phase was collected and dried over $MgSO_4$. Flash column chromatography (SiO_2: 20% ethyl acetate in hexanes) gave the product as a white foam (0.620 g, 0.799 mmol, 85% yield). $[\alpha]_D^{24}$ −124.22 (*c* 0.90, DCM). ^1H NMR (500 MHz, $CDCl_3$): δ 8.81 (d, *J*=8.0 Hz, 1H), 7.71 (t, *J*=5.0 Hz, 1H), 7.44–7.12 (m, 20H), 5.24 (d, *J*=7.0 Hz, 1H), 5.22 (s, 2H), 5.16–5.04 (m, 6H), 4.53 (dd, *J*=10.1 and 3.5 Hz, 1H), 4.35 (dd, *J*=10.1 and 3.5 Hz, 1H), 4.25 (q, *J*=7.0 Hz, 2H), 4.09 (d, *J*=6.0 Hz, 1H), 3.31 (dd, *J*=9.5 and 3.0 Hz, 1H), 3.25 (dd, *J*=3.0 and 9.5 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 169.2, 165.2, 155.3, 151.9, 146.9, 137.5, 136.2, 135.2, 129.4, 128.7, 128.6, 128.5, 128.4, 128.3, 128.0, 127.6, 127.5, 126.6, 124.5, 123.2, 117.1, 79.9, 77.3, 77.1, 76.8, 76.2, 73.0, 71.3, 69.4, 67.7, 65.1, 53.8, 51.7. HRMS (MALDI): *m*/*z* $[M+Na]^+$ found 811.3206, calcd 811.3207 for $C_{46}H_{48}N_2O_{10}Na$.

*4.6.3. (S)-Benzyl 3-((S)-3-(benzyloxy)-2-(2,3-bis(benzyloxy)-5-((2S, 3R,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)benzamido)propanoyloxy)-2-(2,3-bis(benzyloxy)benzamido)propanoate (**13**).* According to the general procedures C, deprotection of **12** (0.050 g, 100 mol %, 0.065 mmol) was performed using HCl (1 M in 0.88 mL MeOH) in THF (1 mL). After the solvent and excess HCl were removed, DCM (1.0 mL) and Et_3N (73 μL, 800 mol %, 0.520 mmol) were added. To the resulting solution was added a solution of **1** in DCM (1 mL) at 0 °C, which was prepared according to the general procedures A using Ar^1COOH (0.056 g, 100 mol %, 0.065 mmol) in DCM (1.6 mL), DMF (13 μL), and $SOCl_2$ (30 μL, 600 mol %, 0.174 mmol). The reaction mixture was allowed to warm to 20 °C, and stir for 0.5 h, at which point it was concentrated over silica gel. Flash column chromatography (SiO_2: 20% EtOAc in hexanes) gave the title product as a white foam (0.052 g, 0.034 mol, 53% yield). $[\alpha]_D^{24}$ −197.53 (*c* 0.90, DCM). ^1H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, *J*=2.0 Hz, 1H), 7.75 (dd, *J*=6.0 and 4.0 Hz, 1H), 7.46–6.99 (m, 55H), 5.25 (s, 2H), 5.19–5.12 (m, 5H), 5.04 (q, *J*=5.0 Hz, 2H), 5.03–4.93 (m, 4H), 4.91 (d, *J*=12.5 Hz, 1H), 4.64 (d, *J*=1.5 Hz, 2H), 4.63–4.58 (m, 3H), 4.40 (d, *J*=9.5 Hz, 1H), 4.36 (dd, *J*=7.5 and 3.5 Hz, 1H), 4.27 (d, *J*=6.5 Hz, 1H), 4.10 (s, 2H), 3.86–3.75 (m, 5H), 3.63 (dt, *J*=9.5 and 4.5 Hz, 1H), 3.51 (t, *J*=9.0 Hz, 1H), 3.29 (dd, *J*=10.0 and 3.5 Hz, 1H), 3.23 (dd, *J*=9.5 and 3.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.6, 169.3, 165.2, 164.6, 151.7, 152.0, 146.6, 147.1, 138.8, 138.4, 138.2, 137.6, 137.5, 136.2, 136.1, 129.6, 129.5, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 126.6, 126.5, 124.5, 123.2, 122.1, 117.2, 116.2, 86.9, 84.0, 81.2, 79.4, 78.4, 76.2, 76.1, 75.6, 75.1, 74.9, 73.6, 72.7, 71.2, 71.1, 69.3, 69.0, 65.2. HRMS (MALDI): *m*/*z* $[M+Na]^+$ found 1549.6177, calcd 1549.6188 for $C_{96}H_{90}N_2O_{16}Na$.

4.6.4. (S)-3-((S)-2-(2,3-Dihydroxy-5-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)benzamido)-3-hydroxypropanoyloxy)-2-(2,3-dihydroxybenzamido)propanoic acid (salmochelin S1). This compound was prepared according to the general procedure C using Per-Bn-S1 **13** (0.025 g, 100 mol %, 0.016 mmol) and Pd $(OH)_2$ (0.030 g, 20% weight on carbon). After the reaction was complete, the reaction mixture was filtered, and the organic solution was collected. The solvent was removed under reduced pressure to give the title compound as a white solid (0.009 g, 0.0145 mmol, 90%). The crude material was further purified with RP-HPLC using a gradient of 0–35% CH_3CN in 0.1% TFA/H_2O over 45 min $[\alpha]_D^{24}$ −131.81 (*c* 0.50, MeOH). ^1H NMR (500 MHz, CD_3OD): δ 7.45 (s, 1H), 7.32 (d, *J*=8.0 Hz, 1H), 7.06 (s, 1H), 6.96 (d, *J*=7.5 Hz, 1H), 6.76 (t, *J*=8.0 Hz, 1H), 5.00–4.96 (m, 1H), 4.86 (dd, *J*=10.1 and 3.0 Hz, 1H), 4.78 (dd, *J*=4.5 and 4.0 Hz, 1H), 4.56 (dd, *J*=5.0 and 10.5 Hz, 1H), 4.05 (d, *J*=9.0 Hz, 2H), 3.96 (dd, *J*=10.5 and 3.5 Hz, 1H), 3.88 (d, *J*=10.0 Hz, 1H), 3.73 (dd, *J*=12.0 and 5.0 Hz, 1H), 3.47 (quint, *J*=8.5 Hz, 2H), 3.39 (d, *J*=8.0 Hz, 2H). ^{13}C NMR (125 MHz, CD_3OD): δ 170.1, 169.5, 148.4, 148.0, 145.8, 145.5, 130.0, 118.6, 118.5, 118.2, 118.1, 117.7, 115.4, 114.9, 81.7, 80.6, 78.3, 74.9, 70.4, 64.1, 61.6, 61.4, 61.6, 55.2. HRMS (ESI): *m*/*z* $[M]^-$ found 625.1535, calcd 625.1595 for $C_{26}H_{29}N_2O_{16}$.

*4.6.5. (2S)-Benzyl 2-(2,3-bis(benzyloxy)benzamido)-3-((2S)-2-(tert-butoxycarbonylamino)-3-(tetrahydro-2H-pyran-2-yloxy)-propanoyloxy)propanoate (**20**).* To a suspension of **14** (1.000 g, 100 mol %, 3.390 mmol) and DHP (1.23 mL, 400 mol %, 13.560 mmol) in DCM (17 mL) was added pyridine *p*-toluenesulfonate (0.085 g, 10 mol %, 0.340 mmol). The mixture immediately turned homogenous, which was allowed to stir for 1 h at 20 °C. After evaporation of the solvent under reduced pressure, the residual white solid (1.144 g, 3.017 mmol, 89% yield) was dissolved in MeOH/EtOAc (6 mL, v/v 2:1), and Pd/C (0.250 g, 10% weight on carbon, wet) was added. The mixture was first purged with N_2 for 3 min, and then hydrogen for 3 min. After the reaction mixture was stirred for 12 h under hydrogen, it was filtered and washed with dry EtOAc (3×10 mL). The organic solution was collected, and the solvent was removed under reduced pressure to give **19** as colorless oil (0.864 g, 2.987 mmol, 99% yield), which was used without further purification.

To a solution of **19** (0.864 g, 100 mol %, 2.987 mmol) in dry CH_3CN (17 mL) were added **10** (1.733 g, 110 mol %, 3.286 mmol) and HOBT (0.808 g, 200 mol %, 5.974 mmol) at 0 °C, followed by EDC·HCl (0.859 g, 130 mol %, 4.481 mmol). The resulting mixture was stirred for 1 h at 0 °C, then 1 h at 20 °C. Pyridine (0.675 mL, 250 mol %, 8.364 mmol) was added, and the mixture was stirred for

48 h, at which point the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL), and the solution was washed with brine. The organic phase was separated and dried over $MgSO_4$. Flash column chromatography (SiO_2: 20% ethyl acetate in hexanes) provided a mixture of diastereomeric **20** as a white solid (1.937 g, 2.475 mmol, 83% yield). $[\alpha]_D^{24}$ −111.47 (*c* 5.20, DCM). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.84 (d, *J*=7.5 Hz, 1H), 8.80 (d, *J*=8.0 Hz, 1H), 7.72–7.70 (m, 2H), 7.49–7.16 (m, 39H), 5.43 (d, *J*=9.0 Hz, 1H), 5.29 (d, *J*=9.0 Hz, 1H), 5.28 (s, 4H), 5.23 (d, *J*=4.0 Hz, 1H), 5.19 (m, 6H), 5.17–5.07 (m, 5H), 4.56 (dd, *J*=10.1 and 4.0 Hz, 1H), 4.48–4.47 (m, 1H), 4.47–4.42 (m, 2H), 4.37 (dd, *J*=10.1 and 6.5 Hz, 1H), 4.27 (s, 1H), 4.19–4.14 (m, 2H), 3.74–3.72 (m, 2H), 3.59 (dd, *J*=10.1 and 3.5 Hz, 1H), 3.48 (td, *J*=2.0 and 7 Hz, 1H), 3.42–3.34 (m, 3H), 3.23–3.19 (m, 1H), 1.46 (s, 9H), 1.45 (s, 9H).

*4.6.6. (R)-Benzyl3-((S)-2-(2,3-bis(benzyloxy)-5-((2S,3S,4S,5S,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl) benzamido)-3-hydroxypropanoyloxy)-2-(2,3-bis(benzyloxy)benzamido)propanoate (**21**).* This compound was prepared according to the general procedure C by deprotection of the Boc and THP groups of **20** (0.100 g, 100 mol %, 0.128 mmol) with HCl (1 M, 2.3 mL) in THF (3.7 mL). After the solvent and excess HCl was removed, the dry residue was dissolved in THF (5 mL) at 0 °C, followed by the addition of Ar^1COOH (0.110 g, 100 mol %, 0.128 mmol), HOBT (0.170 g, 100 mol %, 0.110 mmol), and EDC·HCl (0.280 g, 110 mol %, 0.141 mmol) under nitrogen. After the reaction mixture become homogenous, 4-methyl morpholine (28 μL, 200 mol %, 0.230 mmol) was added. The resulting mixture was stirred at 0 °C for 2 h, then at 20 °C overnight. Upon evaporation of the solvent under reduced pressure, the residue was dissolved in EtOAc (5 mL). The solution was washed with brine, and the organic phase was separated and dried over $MgSO_4$. Flash column chromatography (SiO_2: 20% ethyl acetate in hexanes) gave the title product as a white foam (0.110 g, 0.077 mmol, 60% yield). $[\alpha]_D^{24}$ −342.24 (*c* 0.80, DCM). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.89 (t, *J*=7.0 Hz, 2H), 7.89 (d, *J*=2.0 Hz, 1H), 7.70 (dd, *J*=7.0 and 2.0 Hz, 1H), 7.48 (d, *J*=13.0 Hz, 2H), 7.42–7.14 (m, 45H), 6.97–6.95 (m, 2H), 5.28 (t, *J*=6.0 Hz, 2H), 5.22 (q, *J*=5.0 Hz, 3H), 5.16 (s, 3H), 5.01 (t, *J*=9.0 Hz, 2H), 4.97–4.86 (m, 5H), 4.73 (dd, *J*=4.0 and 10.5 Hz, 1H), 4.65–4.54 (m, 2H), 4.42 (d, *J*=10.5 Hz, 1H), 4.23 (d, *J*=4.5 Hz, 1H), 3.98 (q, *J*=6.5 Hz, 1H), 3.82–3.71 (m, 5H), 3.63–3.61 (m, 2H), 3.53 (dd, *J*=10.5 and 3.5 Hz, 1H), 3.48 (t, *J*=9.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 168.9, 165.8, 165.0, 151.8, 151.6, 147.0, 146.7, 138.7, 138. 3, 138.2, 137.6, 136.3, 136.2, 136.0, 135.4, 135.0, 129.5, 129.2, 128.8, 128.7, 128.7, 128.5, 128.5, 128.4, 128.3, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.6, 126.7, 126.1, 124.6, 123.3, 122.1, 117.6, 116.4, 86.8, 83.9, 81.1, 79.4, 78.3, 76.4, 76.2, 75.6, 75.2, 74.9, 73.5, 71.4, 71.2, 69.2, 67.8, 65.1, 62.4, 55.1, 51.7. HRMS (MALDI): *m*/*z* $[M+Na]^+$ found 1459.5724, calcd 1459.5719 for $C_{89}H_{84}N_2O_{16}Na$.

*4.6.7. (2R)-Benzyl 3-((3S,7S)-7-(benzyloxymethyl)-1-(2,3-bis(benzyloxy)-5-((2S,5S,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)phenyl)-11,11-dimethyl-1,6,9-trioxo-5,10-dioxa-2,8-diazadodecanecarbonyloxy)-2-(2,3-bis(benzyloxy)benzamido)propanoate (**22**).* A mixture of **21** (0.100 g, 100 mol %, 0.070 mmol), Boc-Ser (Bzl)-OH (**11**) (0.300 g, 150 mol %, 0.100 mmol), and HOBT (0.014 g, 150 mol %, 0.100 mmol) was dissolved dry acetonitrile at 0 °C, to which was added EDC·HCl (0.027 g, 200 mol %, 0.140 mmol) under N_2. The mixture was stirred for 1 h at 0 °C and an additional 1 h at 20 °C, at which point pyridine (14 μL, 250 mol %, 0.170 mmol) was added. The resulting mixture was stirred for 48 h. After removal of the solvent under reduced pressure, the residue was dissolved in EtOAc (5 mL). The solution was washed with brine, and the organic phase was collected, dried over $MgSO_4$. Flash column chromatography (SiO_2: 20% ethyl acetate in hexanes) gave the title product as a white foam (0.055 g, 0.039 mmol, 43% yield). $[\alpha]_D^{24}$ −169.12 (*c* 1.10, DCM). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.90 (d, *J*=8.0 Hz, 1H), 8.72 (d, *J*=7.5 Hz, 1H), 7.91 (s, 1H), 7.74 (dd, *J*=3.0 and 6.0 Hz, 1H), 7.50 (d, *J*=1.5 Hz, 3H), 7.45–7.15 (m, 43H), 7.09 (dd *J*=2 and 6.5 Hz, 2H), 7.00–6.98 (m, 3H), 5.29–5.07 (m, 10H), 5.02–4.89 (m, 6H), 4.73 (quint, *J*=4.0 Hz, 1H), 4.68–4.57 (m, 2H), 4.48–4.35 (m, 2H), 4.26 (t, *J*=9.0 Hz, 3H), 4.21–4.10 (m, 3H), 4.05 (dd, *J*=3.5 and 11.5 Hz, 1H), 3.89–3.74 (m, 7H), 3.64 (dd, *J*=1.5 and *J*=9.0 Hz, 1H), 3.50 (t, *J*=9.5 Hz, 1H), 3.36 (dd, *J*=3.0 and 10.0 Hz, 1H), 3.29 (dd, *J*=3.0 and 10.0 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.0, 168.9, 165.3, 164.6, 155.2, 151.9, 151.5, 147.1, 146.4, 138.7, 138.3, 138.1, 137.6, 137.5, 136.4, 136.3, 136.1, 136.0, 135.1, 129.3, 129.1, 128.7, 128.7, 128.6, 128.6, 128.5, 128.5, 128.5, 128.4, 128.3, 128.3, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 126.3, 124.5, 123.3, 122.2, 117.6, 116.0, 86.8, 83.8, 81.0, 79.8, 79.4, 78.3, 76.2, 76.1, 75.6, 75.2, 74.9, 73.5, 72.9, 71.4, 71.1, 69.3, 69.2, 67.7, 65.2, 64.4, 53.7, 51.9, 51.7. HRMS (MALDI): *m*/*z* $[M+Na]^+$ found 1736.7006, calcd 1376.7033 for $C_{104}H_{103}N_3O_{20}Na$.

*4.6.8. (S)-Benzyl 3-((S)-3-((S)-3-(benzyloxy)-2-(2,3-bis(benzyloxy)-5-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)benzamido)propanoyloxy)-2-(2,3-bis(benzyloxy)-5-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl) tetrahydro-2H-pyran-2-yl)benzamido)propanoyloxy)-2-(2,3-bis(benzyloxy)benzamido)propanoate (**18**, per-Bn-S2).* According to the general procedures C, deprotection of **22** (0.050 g, 100 mol %, 0.029 mmol) was performed using HCl (1 M in 0.7 mL MeOH) in THF (1 mL). After the solvent and excess HCl were removed, DCM (1.0 mL) and Et_3N (32 μL, 800 mol %, 0.232 mmol) were added. To the resulting solution was added a solution of **1** in DCM (1 mL) at 0 °C, which was prepared according to the general procedures A using Ar^1COOH (0.025 g, 100 mol %, 0.029 mmol). The reaction mixture was allowed to warm to 20 °C, and stir for 0.5 h, at which point it was concentrated over silica gel. Flash column chromatography (SiO_2: 20% EtOAc in hexanes) gave the product as a white foam (0.038 g, 0.016 mol, 54% yield). $[\alpha]_D^{24}$ +79.36 (*c* 0.10, DCM). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, *J*=2.0 Hz, 1H), 7.86 (d, *J*=2.0 Hz, 1H), 7.70 (dd, *J*=7.0 and 2.0 Hz, 1H), 7.42–6.91 (m, 77H), 5.21–5,17 (m, 5H), 5.13–5.11 (m, 3H), 5.10 (d, *J*=3.5 Hz, 1H), 5.04 (s, 3H), 4.98–4.87 (m, 14H), 4.74 (td, *J*=4.0 and 8.0 Hz, 1H), 4.68–4.56 (m, 8H), 4.40 (dd, *J*=10.5 and 2.0 Hz, 2H), 4.36 (dd, *J*=12.0 and 4.0 Hz, 1H), 4.20–4.15 (m, 3H), 4.11 (q, *J*=15.0 Hz, 3H), 3.85–3.74 (m, 13H), 3.64–3.60 (m, 3H), 3.52–3.46 (m, 3H), 3.34 (dd, *J*=10.0 and 3.5 Hz, 1H), 3.25 (dd, *J*=10.0 and 3.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 165.3, 151.8, 151.6, 147.0, 146.5, 146.4, 138.7, 138.3, 138.2, 137.6, 137.5, 136.4, 136.3, 136.1, 136.0, 135.9, 135.6, 135.4, 135.2, 129.5, 129.4, 129.1, 128.6, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 126.5, 126.2, 124.4, 123.2, 122.2, 122.1, 117.5, 116.2, 116.0, 86.8, 83.9, 83.8, 81.1, 81.0, 79.4, 78.3, 76.1, 76.0, 75.6, 75.2, 74.9, 73.5, 72.7, 71.3, 71.1, 69.2, 68.9, 67.7, 65.2, 64.6, 53.0, 51.9, 51.6. HRMS (MALDI): *m*/*z* $[M+Na]^+$ found 2475.0044, calcd 2475.0014 for $C_{154}H_{145}N_3O_{26}Na$.

4.6.9. (S)-3-((S)-2-(2,3-Dihydroxy-5-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)benzamido)-3-((S)-2-(2,3-dihydroxy-5-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)benzamido)-3-hydroxypropanoyloxy)propanoyloxy)-2-(2,3-dihydroxybenzamido) propanoic acid (salmochelin S2). This compound was prepared according to the general procedures C using Per-Bn-S2 **18** (0.050 g, 100 mol %, 0.020 mmol) and Pd $(OH)_2$ (0.050 g, 20% weight on carbon). Filtration and removal of the solvent gave the title compound as a white solid (0.019 g, 0.018 mmol, 90% yield), which was further purified using RP-preparative HPLC using a gradient of 0–50% CH_3CN in 0.1% TFA/H_2O over 45 min $[\alpha]_D^{24}$ −70.14 (*c* 0.70, MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ 7.42 (s, 2H), 7.34 (dd, *J*=8.0 and 1.0 Hz, 1H), 7.05 (s, 2H), 6.95 (dd, *J*=8.0 and 1.5 Hz, 1H), 6.76 (t,

J=8.0 Hz, 1H), 5.10 (t, J=4.0 Hz, 1H), 5.00 (dd, J=5.5 and 4.0 Hz, 1H), 4.85–4.90 (m, 2H), 4.69 (t, J=4.0 Hz, 1H), 4.56 (td, J=10.5 and 5.0 Hz, 2H), 4.06 (d, J=7.0 Hz, 2H), 3.97 (dd, J=11.5 and 4.5 Hz, 1H), 3.88 (dt, J=13.0 and 2.0 Hz, 3H), 3.71–3.77 (m, 2H), 3.36–3.51 (m, 8H). ^{13}C NMR (125 MHz, CD_3OD): δ 170.6, 170.1, 169.8, 169.5, 169.2, 168.9, 148.5, 148.1, 145.7, 145.5, 145.4, 130.0, 118.6, 118.4, 118.2, 117.7, 117.2, 115.7, 114.9, 114.3, 81.7, 81.6, 80.6, 80.5, 78.3, 78.3, 74.9, 74.8, 70.4, 70.2, 64.2, 63.6, 61.6, 61.5, 55.1, 52.0, 51.8. HRMS (MALDI): m/z $[M+Na]^+$ found 1034.2482, calcd 1034.2502 for $C_{42}H_{49}N_3O_{26}Na$.

*4.6.10. (S)-Benzyl 3-((S)-3-(benzyloxy)-2-(tert-butoxycarbonylamino) propanoyloxy)-2-(tert-butoxycarbonylamino)propanoate (**15**).* To a solution of **14** (2.000 g, 100 mol %, 6.780 mmol) in dry acetonitrile (14 mL) was added **11** (2.200 g, 110 mol %, 7.450 mmol) and HOBT (1.870 g, 180 mol %, 12.200 mmol) at 0 °C, followed by EDC·HCl (1.690 g, 130 mol %, 8.810 mmol). The resulting mixture was stirred for 1 h at 0 °C, then 1 h at 20 °C. 4-Methyl morpholine (1.6 mL, 210 mol %, 14.240 mmol) was added, and the mixture was stirred for 48 h, at which point the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL), and the solution was washed with brine. The organic phase was separated and dried over $MgSO_4$. Flash column chromatography (SiO_2: 15% ethyl acetate in hexanes) provided the title compound as a white solid (2.950 g, 5.153 mmol, 76% yield). $[\alpha]_D^{24}$ −17.93 (c 1.90, DCM). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40–7.29 (m, 10H), 5.55 (d, J=8.5 Hz, 1H), 5.36 (d, J=7.5 Hz, 1H), 5.27–5.17 (m, 2H), 4.64–4.58 (m, 2H), 4.58 (s, 1H), 4.49 (t, J=4.0 Hz, 2H), 4.37–4.36 (m, 1H), 3.74 (dd, J=3 and 9.5 Hz, 1H), 3.60 (dd, J=2.5 and 9.5 Hz, 1H), 1.46 (s, 9H), 1.44 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 169.6, 155.4, 155.3, 137.3, 135.2, 128.6, 128.5, 128.4, 128.0, 127.8, 127.6, 80.2, 80.1, 73.26, 69.7, 67.6, 65.1, 54.0, 53.2, 28.3, 28.2.

*4.6.11. (6S,10S)-10-(Benzyloxymethyl)-2,2,14,14-tetramethyl-4,9,12-trioxo-3,8,13-trioxa-5,11-diazapentadecane-6-carboxylic acid (**16**).* To a flame-dried round bottom flask (10 mL) equipped with a magnetic stir bar was loaded **15** (1.000 g, 100 mol %, 1.750 mmol), followed by addition of MeOH/EtOAc (3 mL, v/v 2:1) and Pd/C (0.250 g, 10% weight on carbon, wet). The mixture was first purged with argon for 3 min, and then hydrogen for 3 min. After the reaction mixture was stirred for 6 h under hydrogen, it was filtered and washed with dry EtOAc (3×5 mL). The organic solution was collected, and the solvent was removed under reduced pressure to give a white solid (0.807 g, 1.663 mmol, 95% yield). The crude material was used without further purification.

*4.6.12. (S)-Benzyl 3-((6S,10S)-10-(benzyloxymethyl)-2,2,14,14-tetramethyl-4,9,12-trioxo-3,8,13-trioxa-5,11-diazapent ecanecarbonyloxy)-2-(2,3-bis(benzyloxy)benzamido)propanoate (**17**).* To a solution of crude **16** (0.100 g, 110 mol %, 0.208 mmol) in dry acetonitrile (1 mL) were added **10** (0.100 g, 100 mol %, 0.190 mmol) and HOBT (0.050 g, 195 mol %, 0.370 mmol) followed by EDC·HCl (0.046 g, 126 mol %, 0.230 mmol) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C, then 1 h at 20 °C. Pyridine (35 μL, 230 mol %, 0.440 mmol) was added and the reaction mixture was stirred for 48 h. After removal of the solvent under reduced pressure, the residue was dissolved in EtOAc (5 mL). The solution was washed with brine, and the organic phase was separated and dried over $MgSO_4$. Flash column chromatography (SiO_2: 10% ethyl acetate in hexanes) gave the product as a white solid (0.113 g, 0.091 mmol, 48% yield). $[\alpha]_D^{24}$ +124.58 (c 3.20, DCM). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (d, J=7.5 Hz, 1H), 7.72 (dd, J=7.0 and 2.5 Hz, 1H), 7.47 (d, J=6.5 Hz, 2H), 7.43–7.23 (m, 17H), 7.18–7.14 (m, 2H), 5.45 (d, J=8.5 Hz, 1H), 5.31 (d, J=8.5 Hz, 1H), 5.23 (s, 2H), 5.19–5.08 (m, 6H), 4.58 (d, J=12.5 Hz, 1H), 4.50–4.37 (m, 4H), 4.26–4.20 (m, 2H), 3.84 (d, J=10.5 Hz, 1H), 3.65 (dd, J=9.5 and 3.5 Hz, 1H), 3.49 (dd, J=5.0 and 3.0 Hz, 1H), 1.43 (s, 9H), 1.40 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 169.2, 169.0, 165.3, 155.3, 155.1, 151.9, 147.0, 146.9, 137.3, 136.3, 136.2, 135.2, 129.2, 128.7, 128.6, 128.5, 128.3, 128.0, 127.9, 127.8, 126.5, 124.5, 123.2, 117.4, 80.1, 80.0, 76.2, 73.2, 71.3, 69.6, 67.7, 65.0, 64.4, 54.0, 53.0, 52.0.

*4.6.13. N,N′-((3S,7S,11S)-11-(2,3-Bis(benzyloxy)-5-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl) benzamido)-2,6,10-trioxo-1,5,9-trioxacyclododecane-3,7-diyl)bis(2,3-bis(benzyloxy)benzamide) (**9**, Per-Bn-MGE).* To an oven-dried round bottom flask charged with Ar^1COOH (0.116 g, 100 mol %, 0.135 mmol) and Ar^2COOH (0.090 g, 200 mol %, 0.270 mmol) in anhydrous DCM (2.0 mL) were added DMF (0.01 mL) and $SOCl_2$ (0.80 mL) at 20 °C under nitrogen. The reaction was allowed to stir for 2 h, and was removed under reduced pressure to give a yellow solid. After the solvent and excess $SOCl_2$ were removed under reduce pressure, the acyl chloride was redissovled in DCM (1 mL). At 0 °C, the acid chloride solution was added to a solution of amine, which was prepared form a suspension of trilactone triamine hydrochloride salt (0.050 g, 100 mol %, 0.135 mmol) in DCM (2.0 mL) upon addition of freshly distilled Et_3N (0.12 mL, 600 mol %, 0.809 mmol). The reaction mixture was allowed to warm to 20 °C, and stirred for 5 h, at which point it was dried over silica gel. Flash column chromatography (SiO_2: 40% EtOAc in hexanes) gave Per-Bn-MGE **9** as a white solid (0.088 g, 0.051 mmol, 38%). $[\alpha]_D^{24}$ −74.47 (c 0.30, DCM). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (t, J=8.5 Hz, 2H), 8.52 (d, J=7.15 Hz, 1H), 7.90 (s, 1H), 7.69–7.75 (m, 2H), 7.10–7.50 (m, 53H), 6.96–7.02 (m, 2H), 5.20 (dd, J=11.0 and 4.0 Hz, 3H), 5.11 (s, 4H), 5.10 (dd, J=10.5 and 3.15 Hz, 3H), 4.85–5.05 (m, 8H), 4.67 (d, J=11.5 Hz, 2H), 4.61 (d, J=12.5 Hz, 1H), 4.45 (d, J=10.5 Hz, 1H), 4.28 (d, J=9.5 Hz, 1H), 4.15–4.25 (m, 3H), 4.05–4.15 (m, 3H), 3.75–3.90 (m, 5H), 3.65 (d, J=9.5 Hz, 1H), 3.50 (t, J=9.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 165.0, 164.6, 151.7, 151.4, 147.0, 146.5, 138.7, 138.3, 138.1, 137.6, 136.3, 136.2, 136.1, 135.8, 135.6, 129.1, 129.0, 128.76, 128.72, 128.70, 128.54, 128.46, 128.43, 128.29, 128.23, 128.08, 127.82, 127.79, 127.72, 127.63, 126.44, 126.41, 126.02, 124.4, 123.3, 122.3, 117.7, 116.6, 86.7, 83.9, 80.9, 79.4, 78.3, 76.43, 76.39, 76.33, 75.6, 75.2, 74.9, 74.5, 71.3, 71.1, 69.2, 64.3, 64.2, 51.53, 51.51, 51.34. HRMS (MALDI): m/z $[M+Na]^+$ found 1754.6558, calcd 1754.6563 for $C_{106}H_{97}N_3O_{20}Na$.

*4.6.14. (R,R,S,S,R)-N,N′-((3S,7S,11S)-11-(2,3-Bis(benzyloxy)benzamido)-2,6,10-trioxo-1,5,9-trioxacyclododecane-3,7-diyl)bis(2,3-bis (benzyloxy)-5-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)benzamide) (**8**, Per-Bn-DGE).* To an oven-dried round bottom flask charged with Ar^1COOH (0.231 g, 200 mol %, 0.270 mmol) and Ar^2COOH (0.045 g, 100 mol % 0.135 mmol) were added DMF (0.01 mL) and $SOCl_2$ (0.80 mL) in anhydrous DCM (2.0 mL) at 20 °C under nitrogen. The reaction was allowed to stir for 2 h. The solvent and excess $SOCl_2$ were removed under reduced pressure to give a yellow solid, which was redissolved in DCM (1 mL). At 0 °C, the acid chloride solution was added to a solution of amine, which was prepared form a suspension of trilactone triamine hydrochloride salt (0.050 g, 100 mol %, 0.135 mmol) in DCM (2.0 mL) upon addition of freshly distilled Et_3N (0.12 mL, 600 mol %, 0.809 mmol). The reaction mixture was allowed to warm to 20 °C, and stirred for and stirred for 5 h, at which point it was dried over silica gel. Flash column chromatography (SiO_2: 40% EtOAc in hexanes) gave the Per-Bn-DGE **8** as a white solid (0.073 g, 0.032 mmol, 24%). $[\alpha]_D^{24}$ −182.93 (c 1.10, DCM). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (d, J=7.5 Hz, 1H), 8.58 (t, J=7.0 Hz, 2H), 7.93 (d, J=1.5 Hz, 2H), 7.71–7.77 (m, 1H), 7.14–7.52 (m, 70H), 6.98–7.05 (m, 4H), 5.22–5.29 (m, 3H), 5.15 (d, J=8.5 Hz, 4H), 5.14 (s, 1H), 4.90–5.10 (m, 13H), 4.70 (d, J=11.0 Hz, 4H), 4.63 (dd, J=12.0 and 1.0 Hz, 2H), 4.48 (dd, J=10.5 Hz, 2H), 4.30 (d, J=9.5 Hz, 2H), 4.10–4.28 (m, 6H), 3.77–3.90 (m, 10H), 3.68 (dt, J=6.75 and 2.55 Hz, 2H), 3.53 (td, J=9.3 and 1.45 Hz, 2H). ^{13}C NMR

(125 MHz, $CDCl_3$): δ 169.3, 169.2, 169.1, 164.9, 164.5, 151.6, 151.3, 146.9, 146.4, 146.3, 138.6, 138.2, 138.0, 137.5, 136.2, 136.1, 136.0, 135.7, 135.5, 135.4, 129.0, 128.9, 128.7, 128.65, 128.60, 128.59, 128.46, 128.43, 128.36, 128.35, 128.31, 128.17, 128.11, 127.9, 127.7, 127.69, 127.67, 127.59, 127.52, 125.9, 125.8, 124.3, 123.2, 122.1, 117.5, 116.4, 86.6, 83.8, 80.8, 79.2, 78.2, 76.31, 76.28, 76.21, 75.5, 75.0, 74.8, 73.4, 71.2, 69.0, 64.1, 63.9, 51.4, 51.2. HRMS (MALDI): *m/z* $[M+Na]^+$ found 2276.8964, calcd 2276.8969 for $C_{140}H_{131}N_3O_{25}Na$.

*4.6.15. (R,R,S,S,R,R,R,S,S,R)-N,N′,N″-((3S,7S,11S)-2,6,10-Trioxo-1,5,9-trioxacyclododecane-3,7,11-triyl)tris(2,3-bis(benzyloxy)-5-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)benzamide) (**3**, Per-Bn-TGE).* To an oven-dried round bottom flask charged with Ar^1COOH (0.070 g, 300 mol %, 0.082 mmol) were added DMF (0.01 mL) and $SOCl_2$ (0.30 mL) in anhydrous DCM (1.0 mL) at 20 °C under nitrogen. The reaction was allowed to stir for 2 h, and the solvent and excess $SOCl_2$ was removed under reduced pressure to give a yellow solid, which was redissolved in DCM (1 mL). At 0 °C, the acid chloride solution was added to a solution of amine, which was prepared form a suspension of trilactone triamine hydrochloride salt (0.010 g, 100 mol %, 0.027 mmol) in DCM (1.0 mL) up addition of Et_3N (0.023 mL, 600 mol %, 0.162 mmol). The reaction mixture was allowed to warm to 20 °C, and stirred for 5 h, at which point it was concentrated over silica gel. Flash column chromatography (SiO_2: 40% EtOAc in hexanes) gave the Per-Bn-TGE **3** as a white solid (0.052 g, 0.019 mmol, 70%). $[\alpha]_D^{24}$ −208.24 (*c* 0.50, MeOH). ^1H NMR (500 MHz, $CDCl_3$): δ 8.58 (d, *J*=7.5 Hz, 3H), 7.90 (d, *J*=2.0 Hz, 3H), 7.15–7.45 (m, 87H), 6.96–7.01 (m, 6H), 5.23 (d, *J*=11.0 Hz, 3H), 5.10 (d, *J*=11.0 Hz, 3H), 5.02–5.08 (m, 3H), 4.85–5.01 (m, 15H), 4.66 (d, *J*=11.0 Hz, 6H), 4.60 (d, *J*=12.5 Hz, 3H), 4.45 (d, *J*=10.5 Hz, 3H), 4.27 (d, *J*=9.5 Hz, 3H), 4.20 (dd, *J*=10.5 and 5.0 Hz, 3H), 4.14 (t, *J*=9.5 Hz, 3H), 3.74–3.88 (m, 15H), 3.65 (dt, *J*=9.5 and 3.0 Hz, 3H), 3.50 (t, *J*=9.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5, 164.6, 151.4, 146.5, 138.7, 138.3, 138.1, 137.6, 136.2, 135.8, 135.6, 129.1, 128.8, 128.7, 128.6, 128.5, 128.48, 128.45, 128.3, 128.2, 128.1, 127.85, 127.81, 127.7, 127.6, 126.0, 122.3, 116.6, 86.7, 84.0, 81.0, 79.4, 78.3, 76.4, 75.6, 75.2, 74.9, 73.5, 71.1, 69.1, 64.1, 51.3. HRMS (MALDI): *m/z* $[M+Na]^+$ found 2799.1370, calcd 2799.1376 for $C_{174}H_{165}N_3O_{30}Na$.

4.6.16. N,N′-((3S,7S,11S)-11-(2,3-Dihydroxy-5-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)benzamido)-2,6,10-trioxo-1,5,9-trioxacyclododecane-3,7-diyl)bis(2,3-dihydroxybenzamide) (MGE). This compound was prepared according to the general procedure B using Per-Bn-MGE **9** (0.030 g, 0.017 mmol, 100 mol %) and $Pd(OH)_2$ (0.035 g, 20% weight on carbon). The organic solution was collected, and the solvent was removed under reduced pressure to give the title compound as a white solid (0.013 g, 0.015 mmol, 90%), which was further purified using RP-HPLC using a gradient of 0–55% CH_3CN in 0.1% TFA/H_2O over 45 min $[\alpha]_D^{24}$ +166.11 (*c* 0.50, MeOH). ^1H NMR (500 MHz, CD_3OD): δ 7.41 (d, *J*=1.5 Hz, 1H), 7.27 (ddd, *J*=16.0, 8.0 and 1.0 Hz, 2H), 7.08 (d, *J*=2.0 Hz, 1H), 6.97 (dq, *J*=8.0 and 2.5 Hz, 2H), 6.75 (td, *J*=12.5 and 4.5 Hz, 2H), 5.02–5.10 (m, 3H), 4.65–4.75 (m, 3H), 4.57–4.65 (m, 3H), 4.04 (d, *J*=9.0 Hz, 1H), 3.90 (dd, *J*=12.0 and 2.0 Hz, 1H), 3.71–3.77 (m, 1H), 3.42–3.50 (m, 2H), 3.35–3.42 (m, 2H). ^{13}C NMR (125 MHz, CD_3OD): 169.5, 169.4, 169.36, 169.3, 169.2, 148.1, 148.0, 147.8, 145.8, 145.5, 130.4, 118.74, 118.72, 118.4, 118.3, 118.2, 117.8, 115.4, 115.3, 114.7, 81.7, 80.6, 78.3, 74.9, 70.4, 64.43, 64.40, 64.3, 61.6, 52.2, 52.1, 52.0. HRMS (ESI): *m/z* $[M]^-$ found 830.1898, calcd 830.1892 for $C_{36}H_{36}N_3O_{20}$.

4.6.17. (S,R,R,S,R)-N,N′-((3S,7S,11S)-11-(2,3-Dihydroxybenzamido)-2,6,10-trioxo-1,5,9-trioxacyclododecane-3,7-diyl)bis(2,3-dihydroxy-5-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)benzamide) (DGE). This compound was prepared according to the general procedure B using Per-Bn-DGE **8** (0.030 g, 0.013 mmol, 100 mol %) and $Pd(OH)_2$ (0.035 g, 20% weight on carbon). The organic solution was collected, and the solvent was removed under reduced pressure to give the tile compound as a white solid (0.012 g, 0.012 mmol, 92%), which was further purified with RP-HPLC using a gradient of 0–45% CH_3CN in 0.1% TFA/H_2O over 40 min $[\alpha]_D^{24}$ +310.68 (*c* 0.40, MeOH). ^1H NMR (500 MHz, CD_3OD): δ 7.41 (dd, *J*=2.0 and 1.0 Hz, 2H), 7.29 (d, *J*=8.0 Hz, 1H), 7.07 (d, *J*=1.5 Hz, 2H), 6.90 (dd, *J*=8.0 and 1.0 Hz, 1H), 6.76 (t, *J*=8.0 Hz, 1H), 5.07 (dd, *J*=10.0 and 5.0 Hz, 3H), 4.68–4.75 (m, 3H), 4.60 (td, *J*=12.5 and 4.5 Hz, 3H), 4.05 (dd, *J*=9.5 and 3.5 Hz, 2H), 3.89 (dd, *J*=11.5 and 1.5 Hz, 2H), 3.73 (ddd, *J*=12.0, 5.5 and 2.0 Hz, 2H), 3.50–3.35 (m, 8H). ^{13}C NMR (125 MHz, CD_3OD): δ 169.5, 169.4, 169.3, 169.2, 148.0, 147.88, 147.85, 147.7, 145.4, 130.34, 130.32, 118.74, 118.71, 118.4, 117.8, 117.7, 115.4, 114.7, 81.7, 81.6, 80.6, 80.5, 78.3, 74.9, 70.4, 64.4, 64.3, 61.6, 61.5, 52.2, 52.02, 52.0. HRMS (MALDI): *m/z* $[M+Na]^+$ found 1016.2391, calcd 1016.2396 for $C_{42}H_{47}N_3O_{25}Na$.

4.6.18. (S,R,R,S,R,S,R,R,S,R)-N,N′,N″-((3S,7S,11S)-2,6,10-Trioxo-1,5,9-trioxacyclododecane-3,7,11-triyl)tris(2,3-dihydroxy-5-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)benzamide)(TGE). This compound was prepared according to the general procedure B using Per-Bn-TGE **3** (0.050 g, 0.018 mmol, 100 mol %) and $Pd(OH)_2$, (0.040 g, 20% weight on carbon). The organic solution was collected, and the solvent was removed under reduced pressure to give the title compound as a white solid (0.019 g, 0.017 mmol, 92%), which was further purified with RP-HPLC using a gradient of 0–40% CH_3CN in 0.1% TFA/H_2O over 40 min $[\alpha]_D^{24}$ +389.57 (*c* 0.90, DCM). ^1H NMR (500 MHz, CD_3OD): δ 7.41 (s, 3H), 7.07 (s, 3H), 5.07 (dd, *J*=8.0 and 4.0 Hz, 3H), 4.72 (dd, *J*=11.0 and 7 Hz, 3H), 4.59 (dd, *J*=11.0 and 3.5 Hz, 3H), 4.04 (d, *J*=9.0 Hz, 3H), 3.88 (dd, *J*=12.0 and 2.0 Hz, 3H), 3.73 (dd, *J*=11.5 and 5.0 Hz, 3H), 3.50–3.32 (m, 12H). ^{13}C NMR (125 MHz, CD_3OD/DMSO-d_6): 170.8, 170.7, 149.2, 146.8, 131.7, 119.9, 119.2, 116.2, 83.0, 82.0, 79.7, 76.3, 71.8, 65.9, 63.0, 53.5. HRMS (ESI): *m/z* $[M]^-$ found 1154.2954, calcd 1154.2949 for $C_{48}H_{56}N_3O_{30}$.

Acknowledgements

H.G. was grateful to Professors Jianhui Fang, Jiaqiang Xu, and Qiyi Pan for their generous assistance for lab setup. Doctors Luke Nelsen and Alison Campbell were thanked for proofreading the manuscript. Andrew Blanchard and Qing Zhu were acknowledged for their contribution to the preparation of **1** and **12**, respectively. Financial support was provided by the department of chemistry, the college of Natural Sciences at Shanghai University, and Shanghai Leading Academic Discipline Project (NO. S30107).

Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2010.11.007. These data include MOL files and InChiKeys of the most important compounds described in this article.

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