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Concise synthesis and antitumor activity of Bengamide E and its analogs

Wenxuan Zhang, Qingzhao Liang, Hui Li, Xiangbao Meng *, Zhongjun Li *

State Key Laboratory of Natural and Biomimetic Drugs, Department of Chemical Biology, School of Pharmaceutical Sciences, Peking University, Beijing 100191, PR China

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ABSTRACT

Bengamide E (**1a**) and C-2 epimer (**1b**), free hydroxyl analogs (**1c**) and (**1d**), and shorter chain analog (**1e**) were synthesized by utilizing (2*R*,3*S*,4*R*)-2,3,4-tris(benzyloxy)hex-5-enal (**2a**) as the chiral building block. Preliminary biological studies revealed that only compound **1c** showed slightly weaker activity than Bengamide E (**1a**) against MDA-MB-453 human breast carcinoma cells, MCF-7 human breast cancer cells and HCT-116 colon cancer cells, with the others being inactive. These results suggest that the correct stereochemistry at C-2, the alkylation on C-2 hydroxyl group, as well as the length of the carbon chain of Bengamide E are critical for structural recognition and binding to the target(s).

1. Introduction

The bengamides, first isolated by Crews and co-workers from *Jaspis* sponges in 1986,[1] display a wide range of biological activities, including antitumor, antibiotic, and anthelmintic properties.[2] These interesting biological activities have made bengamides popular targets for synthesis[3] and biological studies.[2,4] The cytotoxic mechanism of bengamides has been investigated, and it showed that they arrest cells at the G_1 and G_2/M phases of the cell cycle by binding to either methionine aminopeptidase type 1 (Met-Ap1) or type 2 (Met-Ap2).[5]

Carbohydrates have been used as chiral building blocks in asymmetric synthesis because of their known absolute stereochemistry and availability.[6] Hex-5-enals derived from carbohydrates are valuable synthons in the total synthesis of natural products and chiral compounds.[7] Herein we report a concise synthesis of Bengamide E (**1a**) and its analogs for biological evaluations. Our synthetic scheme was to utilize the polyhydroxyl carbon skeleton of D-glucose for preparation of the side chain of Bengamide E, as shown in Fig. 1.

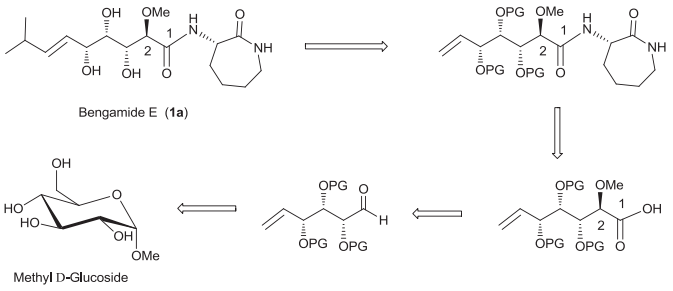

Fig. 1. The structure of Bengamide E and retrosynthetic analysis.

2. Results

(2*R*,3*S*,4*R*)-2,3,4-Tris(benzyloxy)hex-5-enal (**2a**)[8] was prepared from methyl α-D-glucoside. Initially, we attempted to prepare α-hydroxy carboxylic acid **3c** from cyanohydrin **3a** by hydrolysis (Scheme 1).[9] However, the starting material was decomposed under strong acidic conditions. Meanwhile, reduction of TBDMS protected cyanohydrin **3b** with DIBAL-H[10] failed to produce the aldehyde **3d** but resulted in an amine. Nef reaction was then tried to convert the nitro group in compound **4**[11] into an acid **3c**[12] or aldehyde **4a**.[13] Unfortunately, all tested conditions[14] could not yield the desired product.

Dondoni's group employed 2-(trimethylsily1)thiazole as a formyl anion equivalent to prepare extended carbohydrates.[15] Treatment of **2a** with 2-(trimethylsilyl)thiazole yielded a mixture of alcohols **5a** and **5b** and their TMS derivatives. Exposure of the reaction mixture to $^{n}Bu_4N^{+}F^{-}$ afforded **5a** and **5b** as a 1:1 mixture of diastereoisomers in 85% yields, which can be separated by silica gel chromatography (Scheme 2).

In our attempts to improve the stereoselective synthesis of **5a** and **5b**, a two-step oxidation/reduction procedure was planned.[16] The Swern oxidation of alcohols mixture led to ketone **5c**, which was supposed to be stereoselectively reduced to the desired

* Corresponding authors. Tel.: +86 10 82801714; fax: +86 10 82805496; e-mail addresses: xbmeng@bjmu.edu.cn (X. Meng), zjli@bjmu.edu.cn (Z. Li).

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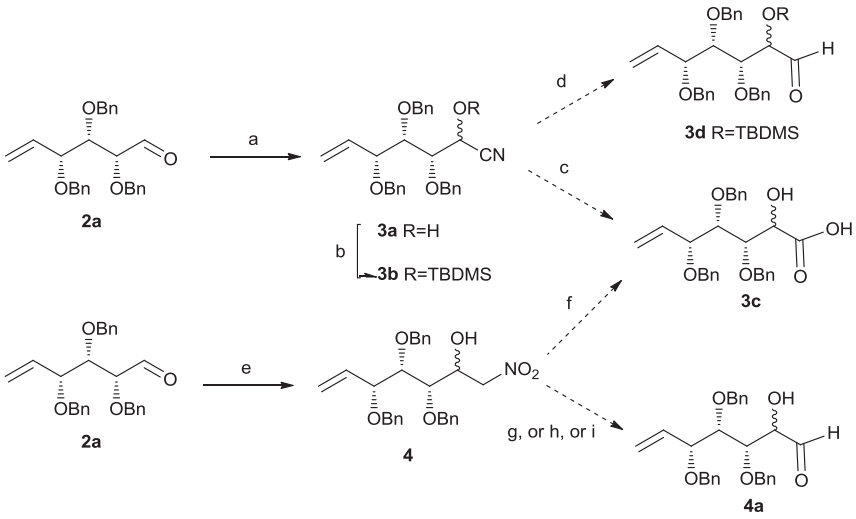
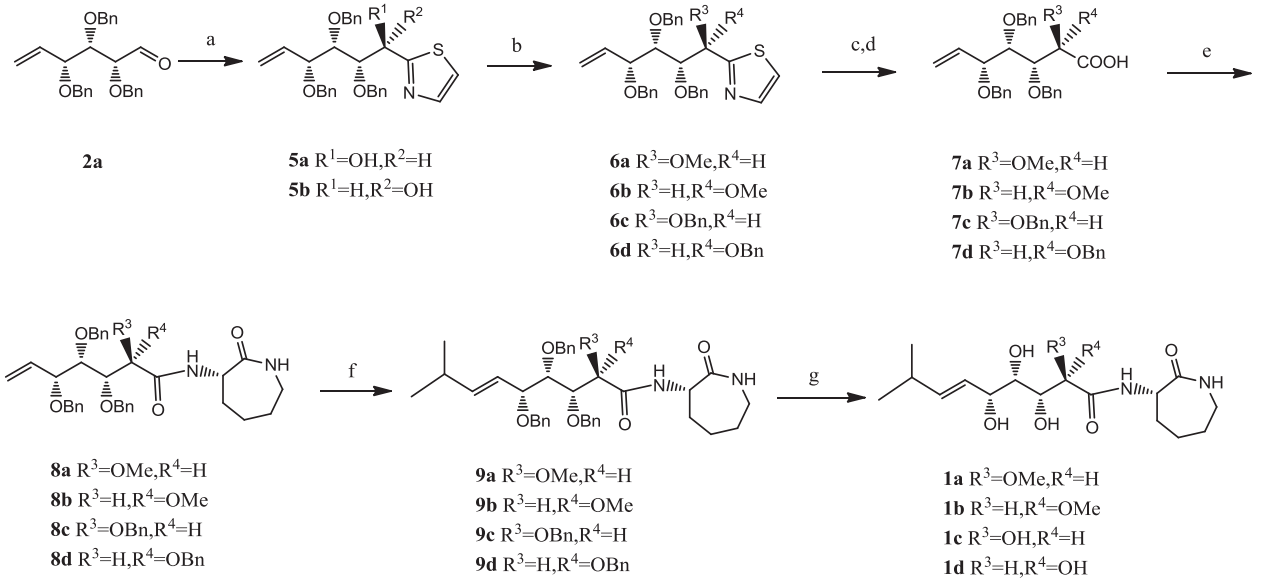


Scheme 1. Reagents and conditions: (a) (i) TMSCN, K_2CO_3, THF, 23 °C, 12 h; (ii) $^nBu_4N^+F^-$, CH_2Cl_2, 23 °C, 20 min; (b) TBDMSCl, imidazole, DMF, 12 h; (c) from **3a**: 6 N HCl (aq), CH_3OH, reflux, 24 h; (d) from **3b**; DIBAL-H, toluene, −78 °C, 1 h; (e) CH_3NO_2, ^tBuOK, ^tBuOH, THF, rt, 12 h; (f) $NaNO_2$, HOAc, DMSO, rt, 24 h; (g) $KMnO_4$, KOH/KH_2PO_4 buffer, ^tBuOH, rt, 1 h; (h) 1 N HCl (aq), ^tBuOH, rt, 12 h; (i) NaOH, H_2SO_4, CH_3OH, 30 min.



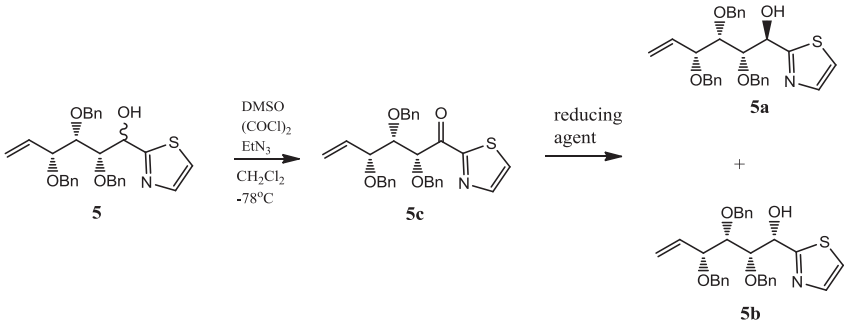
Scheme 2. Reagents and conditions: (a) (i) 2-(trimethylsilyl)thiazole (2-TST), CH_2Cl_2, 23 °C, 6 h, (ii) $^nBu_4N^+F^-$, CH_2Cl_2, 23 °C, 20 min, 43% yield for **5a** and 43% yield for **5b**;(b) NaH, MeI, THF, rt, 12 h, 95% yield for **6a** and 96% yield for **6b**; NaH, BnBr, THF, rt, 12 h, 92% yield for **6c** and 95% yield for **6d**; (c) (i) MeI, 4 Å MS, MeCN, reflux, 12 h, (ii) $NaBH_4$, MeOH, 0 °C, 30 min, (iii) $AgNO_3$, MeCN/H_2O (4:1), 23 °C, 10 min; (d)$NaClO_2$, $NaH_2PO_4·H_2O$, H_2O_2, MeCN/^{t}BuOH/H_2O (2:2:1), rt, 3 h, 80% yield for **7a**, 78% yield for **7b**, 76% yield for **7c**, 73% yield for **7d**; (e) L-(−)-α-amino-δ-caprolactam, EDCI, HOBt, Et_3N, DMF, rt, 12 h, 85% yield for **8a**, 78% yield for **8b**, 72% yield for **8c**, 78% yield for **8d**; (f) Hoveyda–Grubbs catalysts second generation, 3-methyl-1-butene, CH_2Cl_2, reflux, 24 h, 93% yield for **9a**, 88% yield for **9b**, 89% yield for **9c**, 90% yield for **9d**; (g) Na, NH_3, THF, −78 °C, 1 h, 58% yield for **1a**, 71% yield for **1b**, 43% yield for **1c**, 50% yield for **1d**.

anti-alcohol **5a** or *syn*-alcohol **5b** with a satisfactory yield. Although it was highly efficient to afford the *syn*-diastereomer **5b** when treated with DIBAL-H, $ZnBH_4$, or DIBAL/$ZnCl_2$, no stereoselection in favor of the *anti*-diastereomer **5a** was observed in the presence of $NaBH_4$, $LiBH_4$, L-selecrtide, as well as $LiAlH_4$ (Table 1). The *syn*-diastereoselectivity observed could be explained that borohydride attacked the less hindered face of the carbonyl of **5c** in the conformation B, according to the Cram chelate model (Fig. 2).[16] In the nonchelated conformation A (Felkin–Ahn–Houk model), *si*-face and *re*-face could be attacked by borohydride at the same time. Mitsunobu reaction was then tried to invert secondary hydroxyl group at C-2 of **5b**, but no reaction was observed when PPh_3/DIAD/*p*-NO_2BzOH condition was employed.

Methylation of alcohol **5a** with methyl iodide in the presence of sodium hydride formed methyl ether **6a** in 95% yield. The next step required the conversion of the thiazole moiety into an aldehyde. This procedure was carried out in a one-pot, three-step sequence developed by Dondoni.[15] Hence, **6a** was first N-methylated by treatment with methyl iodide in the presence of molecular sieves in acetonitrile for 12 h at 82 °C. Subsequent reduction of the thiazolinium with sodium borohydride in MeOH at 0 °C for 30 min afforded thiazolidine. Initially, mercury(II) chloride was used to convert the thiazolidine to α-methyloxyaldehyde, but the yield was disappointing. Silver nitriate[17] was then tried and a better yield was obtained. Oxidation of the aldehyde by sodium chlorite and sodium dihydrogen phosphate in the presence of hydrogen peroxide afforded acid **7a** in 80% overall yield.

Coupling of acid **7a** with commercially available L-(+)-α-amino-δ-caprolactam[18] was achieved by using EDCI/HOBt, and the amide **8a** was thereby obtained in 85% yield. In order to introduce the terminal

Table 1
Reduction of ketone **5c**



Entry	Reducing agent	**5b**/**5a**[g]	Yield[h] (%)
1	DIBAL-H[a,d]	>95:5	94%
2	DIBAL-H/$ZnCl_2$[a,b]	>95:5	93%
3	$Zn(BH_4)_2$[a,f]	>95:5	96%
4	$NaBH_4$[d,e]	50:50	93%
5	$LiBH_4$[b,c]	50:50	94%
6	L-Selecrtide[b,c]	50:50	97%
7	$LiAlH_4$[a,b]	50:50	96%

[a] Et_2O used as solvent.
[b] Reaction was at −78 °C.
[c] THF used as solvent.
[d] Reaction was at 0 °C.
[e] MeOH used as solvent.
[f] Reaction was at −20 °C.
[g] Diastereomer ratio determined by ^1H NMR analysis on crude mixture of both diastereomers.
[h] Yield refers to the column purified product.

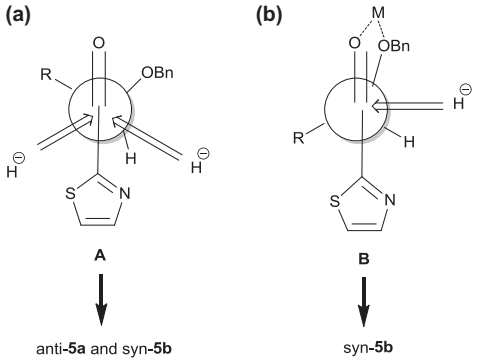


Fig. 2. Nonchelated (A) and chelated (B) model in the reduction of ketone **5c**.

isopropyl group of Bengamide E, olefin cross metathesis was tried.[3d,g] Treating **8a** and 3-methyl-1-butene with second-generation Hoveyda–Grubbs catalyst afforded compound **9a** in 93% yield with an excellent selectivity (>19:5 mixture of *E*:*Z* isomers, as determined by ^1H NMR spectroscopy). Removal of benzyl groups in **9a** with Na/NH_3[19] afforded Bengamide E (**1a**) in 58% yield after purification over silica gel. The ^1H NMR and ^{13}C NMR data were in good agreement with those reported for natural Bengamide E.[3] The optical rotation of our synthetic sample ($[\alpha]_D^{29}$ +36.0 (*c* 1.33, MeOH)) was comparable to that reported by Crews ($[\alpha]_D^{29}$ +37.0 (*c* 0.043, MeOH)).[1]

Bengamide E analogs with modifications at the C-2 position were prepared using the synthetic route outlined in Scheme 2. (2*S*)-Bengamide E (**1b**) was synthesized from *S*-methoxylthiazoles (**6b**), using the similar synthetic route as Bengamide E (**1a**). For free hydroxyl analogs, benzyl ether was employed to protect the C-2 hydroxyl group of alcohol **5a** or **5b** temporarily. Treatment of **5a** or **5b** with benzyl bromide and sodium hydride afforded **6c** or **6d** in 92% and 95% yield. Compounds **7c**–**9c** and **7d**–**9d** were prepared in a similar way to **7a**–**9a**. Finally, 2-*OH*-Bengamide E (**1c**) and (**1d**) were prepared via deprotection of *per*-benzyl ether of **9c** and **d**.

Bengamide E analogs without C-2 were also prepared. Compound **2a**, (2*S*,3*S*,4*R*)-2,3,4-tris(benzyloxy) hex-5-ena (**2b**)[8] or (2*R*,3*S*,4*S*)-2,3,4-tris(benzyloxy)hex-5-ena (**2c**),[8] was oxidized to acid **10a**–**c** by the Pinnick oxidation in a satisfied yield (83–88%). Coupling of acid **10a**–**c** with L-(+)-α-amino-δ-caprolactam afforded **11a**–**c** in 72–81% yield. Olefin cross metathesis of **11a**–**c** and 3-methyl-1-butene with second-generation Hoveyda–Grubbs catalyst afforded compound **12a**–**c** in 75–88% yield. Birch reduction (Na/NH_3) of **12a**–**c** afforded **1e**–**g** in 40–42% yield (Scheme 3).

All these compounds were tested with MDA-MB-453 human breast carcinoma cells, MCF-7 human breast cancer cells and HCT-116 colon cancer cells for their antitumor activities (Table 2).[2a] Compound **1c** showed almost two fold less activity than Bengamide E (**1a**). No growth inhibitions were observed for other compounds at concentrations up to 100 μM.

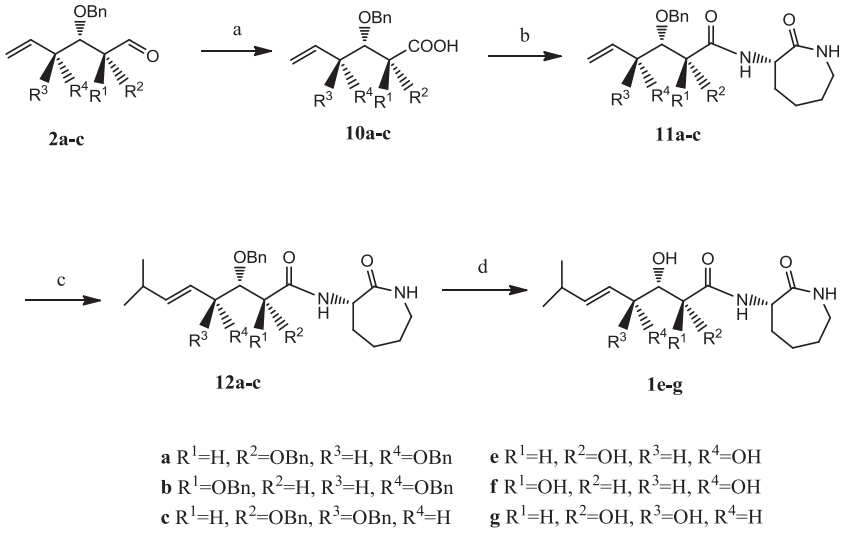
3. Conclusion

In conclusion, we have achieved a concise synthesis of Bengamide E and its analogs with modifications at C-2 position. The side chain was constructed by utilizing (2*R*,3*S*,4*R*)-2,3,4-tris(benzyloxy) hex-5-enal (**2a**) as the chiral building block, with a Dondoni reaction and *E*-olefination by olefin cross metathesis. Compared with natural Bengamide E (**1a**), only compound **1c** showed slightly weaker cytotoxic activity, with the rest being inactive. These reveal the significance of the stereochemistry at C-2 position, alkylation on C-2 hydroxyl group and the length of carbon chain of Bengamide E for structural recognition and binding to the target(s).[2b,3g]

4. Experimental

4.1. Synthesis

^1H and ^{13}C NMR spectra were recorded on a Bruker 400 instrument using TMS as the internal standard. Mass spectra were obtained on an IBIMDS Sciex QStar mass spectrometer. Optical



a R^1=H, R^2=OBn, R^3=H, R^4=OBn
b R^1=OBn, R^2=H, R^3=H, R^4=OBn
c R^1=H, R^2=OBn, R^3=OBn, R^4=H
e R^1=H, R^2=OH, R^3=H, R^4=OH
f R^1=OH, R^2=H, R^3=H, R^4=OH
g R^1=H, R^2=OH, R^3=OH, R^4=H

Scheme 3. Reagents and conditions: (a) $NaClO_2$, $NaH_2PO_4 \cdot H_2O$, H_2O_2, MeCN/^{t}BuOH/H_2O (2:2:1), rt, 3 h, 88% yield for **10a**, 83% yield for **10b**, 84% yield for **10c**; (b) L-(−)-α-amino-δ-caprolactam, EDCI, HOBt, Et_3N, DMF, rt, 12 h, 81% yield for **11a**, 79% yield for **11b**, 72% yield for **11c**; (c) Hoveyda–Grubbs catalysts second generation, 3-methyl-1-butene, CH_2Cl_2, reflux, 24 h, 88% yield for **12a**, 88% yield for **12b**, 75% yield for **12c**; (d)Na, NH_3, THF, −78 °C, 1 h, 48% yield for **1e**, 42% yield for **1f**, 40% yield for **1g**.

Table 2
Antitumor activities of **1a**–**g** against three cancer cell lines (IC_{50} in μM)

Entry	HCT-116	MDA-MB-453	MCF-7
1a	9.02	6.71	3.36
1b	>100	>100	>100
1c	25.49	11.36	8.35
1d	>100	>100	>100
1e	>100	>100	>100
1f	>100	>100	>100
1g	>100	>100	>100

rotations were measured at 25 °C using an Optical Activity AA10R automatic polarimeter. TLC was performed on glass plates coated with Silica Gel GF_{254} (Merck). Column chromatography was performed on Silica Gel H60 (Haiyang Chemical Factory, Qingdao, Shandong, China). Solvents were purified by standard procedures.

4.2. General procedure for the synthesis of 5a, 5b

A solution of the aldehyde **2a** (2.1 g, 5.05 mmol) and 2-(trimethylsilyl) thiazole (1.6 mL, 10.1 mmol) in dry dichloromethane (25 mL) was stirred for 6 h at 23 °C. The solvent was treated with tetra-*n*-butylammonium fluoride (10.1 mmol). After 20 min of stirring, the solution was extracted with dichloromethane, dried with Na_2SO_4 and the solvent was removed in vacuo. The residue was chromatographed on silica gel (10:1 PE/ethyl acetate) to give the *anti*-isomer **5a** (1.09 g, 43%) as a colorless syrup and *syn*-isomer **5b** (1.07 g, 43%) as a colorless syrup.

*4.2.1. (1R,2S,3S,4R)-2,3,4-Tris(benzyloxy)-1-(2-thiazolyl)hex-5-en-1-ol (**5a**).* $[\alpha]_D^{25}$ −3.8 (*c* 2.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J*=3.2 Hz, 1H), 7.22–7.49 (m, 15H), 5.73–5.85 (m, 1H), 5.28–5.44 (m, 3H), 4.91 (t, *J*=10.2 Hz, 2H), 4.73 (d, *J*=11.4 Hz, 1H), 4.61 (d, *J*=11.4 Hz, 1H), 4.55 (d, *J*=11.4 Hz, 1H), 4.33–4.50 (m, 3H), 4.21 (dd, *J*=4.4, 2.9 Hz, 1H), 3.72 (dd, *J*=7.1, 2.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 143.0, 138.1, 137.9, 134.8, 128.4, 128.4, 128.4, 128.0, 127.9, 127.8, 127.6, 119.8, 119.0, 82.4, 82.0, 79.8, 74.9, 72.3, 71.8, 70.8. HRMS (ESI) *m*/*z* calcd for $C_{30}H_{32}NO_4S$ (M+H) 502.20462, found 502.20466.

*4.2.2. (1S,2S,3S,4R)-2,3,4-Tris(benzyloxy)-1-(2-thiazolyl)hex-5-en-1-ol (**5b**).* $[\alpha]_D^{25}$ −18.5 (*c* 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J*=3.2 Hz, 1H), 7.24–7.36 (m, 16H), 7.04–7.06 (m, 2H), 6.02 (ddd, *J*=17.6, 10.7, 7.3 Hz, 1H), 5.41 (s, 1H), 5.37 (d, *J*=9.5 Hz, 1H), 5.16 (d, *J*=3.5 Hz, 1H), 4.76 (d, *J*=2.2 Hz, 2H), 4.66–4.72 (m, 5H), 4.41–4.50 (m, 3H), 4.18–4.21 (m, 3H), 3.90 (dd, *J*=6.3, 4.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 142.5, 138.1, 137.7, 134.8, 128.5, 128.4, 128.3, 128.2 (2), 128.0, 127.8 (2), 127.6, 119.4, 119.1, 82.4, 81.6, 80.0, 75.0, 74.9, 72.0, 70.8. HRMS (ESI) *m*/*z* calcd for $C_{30}H_{32}NO_4S$ (M+H) 502.20462, found 502.20466.

4.3. General procedure for the synthesis of 6a,b

To a solution of compound **5a**,**b** (1 equiv) in dry THF (2 mL) was added portionwise NaH 60% (3 equiv) at room temperature. The reaction mixture was stirred for 20 min and then methyl iodide (2 equiv) was added sequentially. The solution was stirred at room temperature overnight until MeOH was added. The solvent was concentrated at reduced pressure, saturated aqueous $NaHCO_3$ was then added, and the mixture was extracted with dichloromethane. After drying (anhydrous Na_2SO_4), the solvent was removed under vacuum and the residue was chromatographed on silica gel (10:1 PE/ethyl acetate) to give the *O*-methyl derivative **6a**,**b**.

*4.3.1. 2-((1R,2R,3S,4R)-2,3,4-Tris(benzyloxy)-1-methoxyhex-5-en-1-yl)thiazole (**6a**).* Yield: 95%, colorless syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J*=3.2 Hz, 1H), 7.14–7.52 (m, 16H), 5.90–5.93 (m, 1H), 5.34 (d, *J*=1.5 Hz, 1H), 5.31 (d, *J*=9.0, Hz, 1H), 4.71–4.80 (m, 1H), 4.69 (dd, *J*=11.6, 4.3 Hz, 1H), 4.55 (d, *J*=11.1 Hz, 1H), 4.44 (dd, *J*=11.5, 3.4 Hz 2H), 4.24 (t, *J*=6.6 Hz, 1H), 4.17 (t, *J*=5.3 Hz, 1H), 3.74 (t, *J*=5.4 Hz, 1H), 3.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 142.2, 138.9, 138.6, 138.5, 135.6, 128.4, 128.2, 128.2, 128.1, 128.1, 127.8, 127.5, 127.4, 127.3, 120.3, 119.2, 81.6, 81.3, 81.1, 80.7, 75.3, 74.3, 70.5, 57.2. HRMS (ESI) *m*/*z* calcd for $C_{31}H_{34}NO_4S$ (M+H) 516.22031, found 516.22007.

*4.3.2. 2-((1S,2R,3S,4R)-2,3,4-Tris(benzyloxy)-1-methoxyhex-5-en-1-yl)thiazole (**6b**).* Yield: 96%, colorless syrup; $[\alpha]_D^{25}$ −25.3 (*c* 1.58, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J*=3.2 Hz, 1H), 7.13–7.46 (m, 15H), 5.95–6.04 (m, 1H), 5.40 (s, 1H), 5.36 (d, *J*=7.5 Hz, 1H), 4.63–4.77 (m, 3H), 4.45 (d, *J*=11.9 Hz, 1H), 4.29 (d, *J*=10.9 Hz, 1H), 4.09 (dd, *J*=6.8, 3.9 Hz, 1H), 4.04 (dd, *J*=7.0, 4.5 Hz, 1H), 3.83 (dd, *J*=6.8, 4.4 Hz, 1H), 3.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 138.0, 137.8, 137.4, 134.8, 128.7, 128.4, 128.3, 128.1 (2), 127.7 (2),

119.6, 82.1, 81.3, 80.8, 80.3, 75.4, 74.5, 70.6, 58.5. HRMS (ESI) *m/z* calcd for $C_{31}H_{34}NO_4S$ (M+H) 516.22031, found 516.22007.

4.4. General procedure for the synthesis of 6c,d

To a solution of compound **5c**,**d** (1 equiv) in dry THF (2 mL) was added portionwise NaH 60% (3 equiv) at room temperature. The reaction mixture was stirred for 20 min and then benzyl bromide (2 equiv) was added sequentially. The solution was stirred at room temperature overnight until MeOH was added. The solvent was concentrated at reduced pressure, saturated $NaHCO_3$ was added, and the mixture was extracted with dichloromethane. After drying (anhydrous Na_2SO_4), the solvent was removed under vacuum and the residue was chromatographed on silica gel (10:1 PE/ethyl acetate) to give the *O*-benzyl derivative **6c**,**d**.

*4.4.1. 2-((1R,2R,3S,4R)-1,2,3,4-Tetra(benzyloxy)hex-5-en-1-yl)thiazole (**6c**).* Yield: 92%, colorless syrup; $[\alpha]_D^{25}$ −6.6 (*c* 1.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J*=3.2 Hz, 1H), 7.18–7.31 (m, 20H), 5.83–5.92 (m, 1H), 5.26 (s, 1H), 5.23 (d, *J*=6.3 Hz, 1H), 4.98 (d, *J*=5.3 Hz, 1H), 4.48–4.70 (m, 5H), 4.41 (d, *J*=11.5 Hz, 1H), 4.31 (d, *J*=11.8 Hz, 1H), 4.21–4.24 (m, 2H), 3.69 (t, *J*=5.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 142.1, 138.8, 138.6, 138.4, 137.6, 135.5, 128.4, 128.2, 128.1, 128.1, 128.0, 127.9, 127.7, 127.7, 127.6, 127.4, 120.5, 119.2, 81.8, 81.4, 81.1, 79.0, 75.3, 74.5, 71.3, 70.5. HRMS (ESI) *m/z* calcd for $C_{37}H_{38}NO_4S$ (M+H) 592.25161, found 592.25250.

*4.4.2. 2-((1S,2R,3S,4R)-1,2,3,4-Tetra(benzyloxy)hex-5-en-1-yl) thiazole (**6d**).* Yield: 95%, colorless syrup; $[\alpha]_D^{25}$ −40.9 (*c* 4.70, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.89–7.90 (m, 1H), 7.30–7.43 (m, 20H), 7.23–7.24 (m, 2H), 5.88–5.94 (m, 1H), 5.33 (d, *J*=10.4 Hz, 1H), 5.18 (d, *J*=17.4 Hz, 1H), 5.07 (dd, *J*=3.8, 2.5 Hz, 1H), 4.63–4.84 (m, 5H), 4.45 (dd, *J*=10.9, 2.0 Hz, 1H), 4.31 (dd, *J*=11.8, 1.6 Hz, 1H), 4.23–4.26 (m, 2H), 3.82 (d, *J*=1.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 142.7, 138.8, 138.5, 138.1, 137.3, 135.5, 128.7, 128.6, 128.5, 128.4, 128.2, 128.2, 128.0, 127.8, 127.5, 127.4, 120.0, 119.1, 82.3, 82.0, 80.0, 78.9, 75.6, 75.4, 72.1, 70.3. HRMS (ESI) *m/z* calcd for $C_{37}H_{38}NO_4S$ (M+H) 592.25161, found 592.25196.

4.5. General procedure for the synthesis of 7a–d

A mixture of the thiazole derivative **6a**–**d**, methyl iodide (5 equiv) and activated 4 Å powdered molecular sieves in CH_3CN (5 mL) was refluxed for 12 h. The suspension was filtered and then concentrated. The residue was dissolved in CH_3OH (2 mL), cooled (ice bath), and treated with $NaBH_4$ (2 equiv). The resulting mixture was stirred at 0 °C for 30 min, diluted with acetone (1 mL), filtered through Celite, and concentrated. To a solution of the residue in 4:1 CH_3CN/H_2O (2 mL) was added $AgNO_3$ (1 equiv). The mixture was stirred at 23 °C for 10 min and then filtered through Celite and concentrated to give the crude aldehyde (90% pure by ^1H NMR) as clear yellow syrup. The syrup was dissolved in $MeCN/^tBuOH/H_2O$ (2:2:1), treated with $NaClO_2$ (3 equiv), $NaH_2PO_4 \cdot H_2O$ (3 equiv) and 35% H_2O_2 (10 equiv). The mixture was stirred at room temperature for 3 h, Na_2SO_3 and 1 N HCl (aq) were added, and the solution was extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The crude was purified by flash chromatography on silica gel (50:1 dichloromethane/methanol) to give **7a**–**d**.

*4.5.1. (2S,3R,4S,5R)-3,4,5-Tris(benzyloxy)-2-methoxyhept-6-enoic acid (**7a**).* Yield: 80%, colorless syrup; $[\alpha]_D^{25}$ −16.0 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.14–7.44 (m, 16H), 5.85 (m, 1H), 5.20–5.47 (m, 2H), 4.68–4.83 (m, 3H), 4.61 (d, *J*=11.7 Hz, 1H), 4.54 (d, *J*=11.1 Hz, 1H), 4.37 (d, *J*=11.7 Hz, 1H), 4.18 (t, *J*=4.0 Hz, 1H), 3.99 (dd, *J*=5.6, 2.5 Hz, 1H), 3.79 (t, *J*=5.6 Hz, 1H), 3.74 (d, *J*=2.4 Hz, 1H), 3.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 138.0, 137.8, 137.4, 134.8, 128.7, 128.4, 128.3, 128.1, 128.1, 127.7 (2), 119.6, 82.1, 81.3, 80.3 (2), 75.4, 74.5, 70.6, 58.5. HRMS (ESI) *m/z* calcd for $C_{29}H_{32}NaO_6$ (M+Na) 499.20911, found 499.21042.

*4.5.2. (2R,3R,4S,5R)-3,4,5-Tris(benzyloxy)-2-methoxyhept-6-enoic acid (**7b**).* Yield: 78%, colorless syrup; $[\alpha]_D^{25}$ −27.7 (*c* 1.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.17–7.34 (m, 15H), 5.92–6.00 (m, 1H), 5.36 (s, 1H), 5.32 (d, *J*=6.7 Hz, 1H), 4.55–4.75 (m, 5H), 4.37 (d, *J*=12.0 Hz, 1H), 4.17 (dd, *J*=7.2, 3.1 Hz, 1H), 3.82–3.84 (m, 2H), 3.62 (d, *J*=3.1 Hz, 1H), 3.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 138.2, 137.9, 137.5, 135.0, 128.7, 128.4, 128.2, 128.1 (2), 127.9, 127.5 (2), 118.9, 81.5, 80.1, 79.9, 78.8, 75.5, 75.3, 70.1, 58.7. HRMS (ESI) *m/z* calcd for $C_{29}H_{32}NaO_6$ (M+Na) 499.20911, found 499.21001.

*4.5.3. (2S,3R,4S,5R)-2,3,4,5-Tetra(benzyloxy)hept-6-enoic acid (**7c**).* Yield: 76%, colorless syrup; $[\alpha]_D^{25}$ −22.9 (*c* 0.35, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.07–7.22 (m, 21H), 5.76 (ddd, *J*=17.7, 10.3, 7.6 Hz, 1H), 5.16 (d, *J*=11.0 Hz, 1H), 5.01 (d, *J*=17.4 Hz, 1H), 4.46–4.67 (m, 6H), 4.16 (dd, *J*=7.5, 3.4 Hz, 1H), 4.04 (d, *J*=12.0 Hz, 1H), 3.91 (d, *J*=11.7 Hz, 1H), 3.77 (d, *J*=3.3 Hz, 1H), 3.72 (dd, *J*=7.5, 3.5 Hz, 1H), 3.49 (dd, *J*=7.5, 3.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 138.2, 138.0, 137.7, 136.9, 135.2, 128.7, 128.5, 128.5, 128.3, 128.3, 128.1, 127.9, 127.7, 127.6, 127.0, 119.1, 81.6, 80.0, 78.9, 77.5, 75.6, 75.5, 73.1, 70.0. HRMS (ESI) *m/z* calcd for $C_{35}H_{36}NaO_6$ (M+Na) 575.24041, found 575.24121.

*4.5.4. (2R,3R,4S,5R)-2,3,4,5-Tetra(benzyloxy)hept-6-enoic acid (**7d**).* Yield: 73%, colorless syrup; $[\alpha]_D^{25}$ −8.2 (*c* 0.49, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.34 (m, 22H), 5.83–5.92 (m, 1H), 5.37 (s, 1H), 5.33 (d, *J*=3.8 Hz, 1H), 4.61–4.86 (m, 6H), 4.39 (d, *J*=11.7 Hz, 1H), 4.32 (d, *J*=11.5 Hz, 1H), 4.22 (t, *J*=5.8 Hz, 1H), 4.12 (d, *J*=5.8 Hz, 2H), 3.83 (t, *J*=5.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 138.0, 137.9, 137.0, 134.8, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0 (3), 127.9, 127.2 (2), 119.5, 81.4, 81.0, 80.7, 79.6, 75.4, 74.6, 72.6, 70.6. HRMS (ESI) *m/z* calcd for $C_{35}H_{36}NaO_6$ (M+Na) 575.24041, found 575.24097.

4.6. General procedure for the synthesis of 8a–d

To a solution of the acid **7a**–**d** in dry DMF were added EDCI (2 equiv), HOBt (2 equiv), and Et_3N (3 equiv). After 30 min, L-(−)-α-amino-δ-caprolactam (1.5 equiv) was added and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated, dissolved in dichloromethane and 1 N HCl was added. The resultant solution was then partitioned between dichloromethane and water. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The crude was purified by flash chromatography on silica gel (5:1 PE/ethyl acetate) to give **8a**–**d**.

*4.6.1. (2R,3R,4S,5R)-3,4,5-Tris(benzyloxy)-2-methoxy-N-((S)-2-oxoazepan-3-yl)hept-6-enamide (**8a**).* Yield: 85%, colorless syrup; $[\alpha]_D^{25}$ +15.5 (*c* 2.33, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J*=6.0 Hz, 1H), 7.21–7.37 (m, 15H), 6.61 (t, *J*=6.2 Hz, 1H), 6.02 (m, 1H), 5.41 (d, *J*=17.3 Hz, 1H), 5.35 (d, *J*=10.4 Hz, 1H), 4.83 (d, *J*=11.1 Hz, 1H), 4.75 (d, *J*=11.0 Hz, 1H), 4.63–4.69 (m, 3H), 4.54 (dd, *J*=10.0, 6.0 Hz, 1H), 4.37 (d, *J*=11.9 Hz, 1H), 4.25 (dd, *J*=7.5, 3.8 Hz, 1H), 4.16 (dd, *J*=7.2, 2.8 Hz, 1H), 3.90 (dd, *J*=7.2, 3.9 Hz 1H), 3.76 (d, *J*=2.8 Hz, 1H), 3.25 (s, 3H), 3.17–3.20 (m, 2H), 2.10 (d, *J*=6.0 Hz, 1H), 1.97–2.00 (m, 1H), 1.46–1.55 (m, 1H), 1.32–1.42 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 169.4, 138.9, 138.4, 135.8, 128.3, 128.2, 128.0, 127.5, 127.3, 127.2, 118.9, 82.3, 82.1, 80.9, 80.7, 75.6, 74.9, 70.3,

58.0, 51.8, 42.0, 31.5, 28.9, 27.9. HRMS (ESI) *m*/*z* calcd for $C_{35}H_{43}N_2O_6$ (M+H) 587.31156, found 587.31177.

*4.6.2. (2S,3R,4S,5R)-3,4,5-Tris(benzyloxy)-2-methoxy-N-((S)-2-oxoazepan-3-yl)hept-6-enamide (**8b**).* Yield: 78%, colorless syrup; 78% $[\alpha]_D^{25}$ −27.4 (*c* 2.63, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J*=7.0 Hz, 1H), 7.21–7.39 (m, 15H), 6.30 (t, *J*=6.2 Hz, 1H), 5.98–6.07 (m, 1H), 5.38 (d, *J*=2.1 Hz, 1H), 5.35 (d, *J*=9.5 Hz, 1H), 4.68–4.81 (m, 3H), 4.53–4.63 (m, 3H), 4.39 (d, *J*=12.0 Hz, 1H), 4.22 (dd, *J*=7.8, 2.3 Hz, 1H), 3.84–3.86 (m, 2H), 3.60 (d, *J*=2.4 Hz, 1H), 3.20–3.28 (m, 5H), 1.77–1.88 (m, 4H), 1.27–1.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 169.6, 138.6, 138.5, 137.6, 135.3, 128.8, 128.4, 128.2 (2), 128.0, 127.9, 127.7, 127.5, 118.7, 82.2, 82.0, 80.8, 78.9, 75.7, 75.4, 70.2, 59.1, 51.7, 42.1, 31.3, 30.9, 28.9, 28.0. HRMS (ESI) *m*/*z* calcd for $C_{35}H_{43}N_2O_6$ (M+H) 587.31156, found 587.31262.

*4.6.3. (2R,3R,4S,5R)-2,3,4,5-Tetra(benzyloxy)-N-((S)-2-oxoazepan-3-yl)hept-6-enamide (**8c**).* Yield: 72%, colorless syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J*=7.0 Hz, 1H), 7.25–7.41 (m, 21H), 7.13 (t, *J*=5.8 Hz, 1H), 5.89–5.98 (m, 1H), 5.31 (d, *J*=11.0 Hz, 1H), 5.14 (d, *J*=17.4 Hz, 1H), 4.85 (d, *J*=11.2 Hz, 1H), 4.78 (d, *J*=11.0 Hz, 1H), 4.58–4.68 (m, 5H), 4.34 (dd, *J*=8.2, 2.5 Hz, 1H), 4.26 (d, *J*=12.0 Hz, 1H), 3.97 (d, *J*=11.1 Hz, 1H), 3.81–3.85 (m, 2H), 3.58 (dd, *J*=7.3, 2.6 Hz, 1H), 3.13–3.28 (m, 2H), 1.73–1.91 (m, 4H), 1.32–1.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 169.6, 138.7, 138.5, 137.7, 136.8, 135.5, 129.0, 128.9, 128.5, 128.5, 128.3, 128.2, 128.2, 128.1, 127.9, 127.7, 127.5, 127.3, 119.0, 82.3, 80.7, 79.9, 78.6, 77.6, 77.4, 77.2, 76.9, 75.8, 75.6, 73.4, 70.0, 51.8, 42.0, 31.3, 28.8, 28.1.

*4.6.4. (2S,3R,4S,5R)-2,3,4,5-Tetra(benzyloxy)-N-((S)-2-oxoazepa-3-yl)hept-6-enamide (**8d**).* Yield: 78%, colorless syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J*=5.9 Hz, 1H), 7.23–7.39 (m, 21H), 7.07 (t, *J*=6.0 Hz, 1H), 6.05 (ddd, *J*=17.7, 10.3, 7.7 Hz, 1H), 5.43 (d, *J*=17.4 Hz, 1H), 5.37 (d, *J*=10.6 Hz, 1H), 4.89 (d, *J*=11.1 Hz, 1H), 4.66–4.78 (m, 4H), 4.57 (dd, *J*=10.3, 5.8 Hz, 1H), 4.49 (d, *J*=11.8 Hz, 1H), 4.41 (d, *J*=11.8 Hz, 1H), 4.36 (d, *J*=12.0 Hz, 1H), 4.27–4.31 (m, 2H), 4.09 (d, *J*=2.7 Hz, 1H), 3.96 (dd, *J*=7.0, 3.9 Hz, 1H), 3.10–3.22 (m, 2H), 2.09 (d, *J*=13.1 Hz, 1H), 2.00 (d, *J*=14.2 Hz, 1H), 1.78–1.89 (m, 2H), 1.50 (dd, *J*=8.0, 16.0 Hz, 1H), 1.37 (dd, *J*=21.9, 11.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 169.5, 138.9, 138.8, 138.4, 137.5, 135.7, 128.5, 128.4, 128.2 (2), 128.1, 127.8, 127.6, 127.5, 127.4 (2), 119.1, 82.1, 81.5, 80.9, 80.4, 75.7, 75.1, 72.3, 70.3, 51.9, 41.9, 31.4, 28.9, 28.0.

4.7. General procedure for the synthesis of 9a–d

Compound **8a–d** was dissolved in a 1:2 CH_2Cl_2/3-methyl-1-butene mixture (3 mL), and Hoveyda–Grubbs catalysts second generation (0.3 equiv) was added. The flask was then capped and the mixture was refluxed for 24 h, after which the crude mixture was concentrated and purified by flash column chromatography on silica gel (5:1 PE/acetone) to yield **9a–9d**.

*4.7.1. (2R,3R,4S,5R,E)-3,4,5-Tris(benzyloxy)-2-methoxy-8-methyl-N-((S)-2-oxoazepan-3-yl)non-6-enamide (**9a**).* Yield: 93%, brown foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J*=5.8 Hz, 1H), 7.22–7.34 (m, 15H), 6.09 (s, 1H), 5.78 (dd, *J*=15.7, 6.4 Hz, 1H), 5.58 (dd, *J*=15.7, 8.0 Hz, 1H), 4.81 (d, *J*=11.2 Hz, 1H), 4.74 (d, *J*=11.0 Hz, 1H), 4.61–4.68 (m, 3H), 4.54 (dd, *J*=10.2, 6.1 Hz, 1H), 4.33 (d, *J*=12.0 Hz, 1H), 4.14–4.20 (m, 2H), 3.84 (dd, *J*=3.8, 7.2 Hz, 1H), 3.72 (d, *J*=2.6 Hz, 1H), 3.22 (s, 4H), 2.34 (dd, *J*=13.2, 6.5 Hz, 1H), 2.08 (d, *J*=13.7 Hz, 1H), 1.99 (d, *J*=15.5 Hz, 1H), 1.82–1.88 (m, 2H), 1.39–1.51 (m, 3H), 1.35 (s, 3H), 1.28 (s, 2H), 1.02 (t, *J*=6.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 169.5, 143.0, 139.0, 138.6, 128.3, 128.3, 128.3, 128.3, 128.1, 128.0, 127.5, 127.4, 127.2, 124.4, 82.7, 82.3, 81.2, 80.5, 77.5, 77.4, 77.2, 76.9, 75.8, 75.1, 69.7, 57.9, 51.9, 41.9, 31.5, 31.0, 28.9, 28.0, 22.4. HRMS (ESI) *m*/*z* calcd for $C_{38}H_{49}N_2O_6$ (M+H) 629.36014, found 629.35851.

*4.7.2. (2S,3R,4S,5R,E)-3,4,5-Tris(benzyloxy)-2-methoxy-8-methyl-N-((S)-2-oxoazepan-3-yl)non-6-enamide (**9b**).* Yield: 88%, brown foam; $[\alpha]_D^{25}$ −58.9 (*c* 1.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J*=6.9 Hz, 1H), 7.22–7.40 (m, 15H), 6.59 (s, 1H), 5.70 (dd, *J*=15.7, 6.4 Hz, 1H), 5.60 (dd, *J*=7.6, 1.1 Hz, 1H), 4.79 (dd, *J*=20.7, 11.2 Hz, 2H), 4.54–4.70 (m, 4H), 4.38 (d, *J*=12.1 Hz, 1H), 4.25 (dd, *J*=8.1, 2.6 Hz, 1H), 3.75–3.82 (m, 2H), 3.57 (d, *J*=2.6 Hz, 1H), 3.19–3.30 (m, 5H), 2.32–2.43 (m, 1H), 1.72–1.89 (m, 4H), 1.27–1.38 (m, 2H), 1.06 (dd, *J*=11.2, 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 169.6, 142.8, 138.6, 138.7, 137.8, 128.9, 128.4, 128.2 (2), 127.8, 127.6, 127.5, 127.2, 123.9, 82.9, 82.2, 81.0, 78.4, 75.7, 75.5, 69.6, 59.1, 51.7, 42.0, 31.4, 31.0, 28.9, 28.0, 22.4. HRMS (ESI) *m*/*z* calcd for $C_{38}H_{49}N_2O_6$ (M+H) 629.36014, found 629.35851.

*4.7.3. (2R,3R,4S,5R,E)-2,3,4,5-Tetra(benzyloxy)-8-methyl-N-((S)-2-oxoazepan-3-yl)non-6-enamide (**9c**).* Yield: 89%, brown foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J*=7.0 Hz, 1H), 7.23–7.41 (m, 21H), 7.02 (s, 1H), 5.49 (dd, *J*=15.7, 7.6 Hz, 1H), 5.41 (dd, *J*=15.7, 6.0 Hz, 1H), 4.85 (d, *J*=11.3 Hz, 1H), 4.78 (d, *J*=11.1 Hz, 1H), 4.58–4.67 (m, 5H), 4.34 (dd, *J*=8.1, 2.6 Hz, 1H), 4.26 (d, *J*=12.1 Hz, 1H), 3.92 (d, *J*=11.1 Hz, 1H), 3.76–3.82 (m, 2H), 3.50 (dd, *J*=7.6, 2.8 Hz, 1H), 3.18–3.28 (m, 2H), 2.28–2.36 (m, 1H), 1.73–1.90 (m, 4H), 1.27–1.38 (m, 3H), 1.04 (dd, *J*=13.1, 6.7 Hz, 6H), 0.88–0.95 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 169.6, 138.8, 138.6, 137.9, 136.9, 129.0 (2), 128.5, 128.4, 128.2, 128.1 (2), 127.8, 127.7, 127.5, 127.2, 123.9, 82.7, 80.9, 80.1, 78.0, 75.8, 75.7, 73.5, 69.3, 51.8, 42.0, 31.4, 30.9, 28.8, 28.1, 22.4, 22.3. HRMS (ESI) *m*/*z* calcd for $C_{44}H_{53}N_2O_6$ (M+H) 705.38981, found 705.39074.

*4.7.4. (2S,3R,4S,5R,E)-2,3,4,5-Tetra(benzyloxy)-8-methyl-N-((S)-2-oxoazepan-3-yl)non-6-enamide (**9d**).* Yield: 90%, brown foam; $[\alpha]_D^{25}$ −7.9 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J*=4.8 Hz, 1H), 7.22–7.35 (m, 20H), 7.01–7.07 (m, 1H), 5.82 (dd, *J*=15.7, 6.4 Hz, 1H), 5.62 (dd, *J*=15.7, 8.2 Hz, 1H), 4.89 (d, *J*=11.1 Hz, 1H), 4.63–4.77 (m, 4H), 4.56 (dd, *J*=26.4, 11.8 Hz, 2H), 4.47 (d, *J*=11.8 Hz, 1H), 4.41 (d, *J*=11.8 Hz, 1H), 4.24–4.34 (m, 3H), 4.06 (s, 1H), 3.90–3.93 (m, 1H), 3.15–3.21 (m, 2H), 2.33–2.42 (m, 1H), 1.97–2.10 (m, 2H), 1.78–1.89 (m, 1H), 1.49 (dd, *J*=24.0, 11.3 Hz, 1H), 1.36 (dd, *J*=23.3, 11.9 Hz, 2H), 1.05 (td, *J*=6.6, 1.3 Hz, 6H), 0.93 (dd, *J*=15.8, 9.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 169.5, 143.0, 139.0, 138.9, 138.7, 137.6, 128.4, 128.3 (2), 128.1, 128.1, 127.7, 127.5, 127.4, 127.3, 124.4, 82.8, 81.7, 80.7, 80.6, 75.8, 75.2, 72.2, 69.8, 51.9, 41.9, 31.4, 31.0, 28.9, 28.0, 22.4. HRMS (ESI) *m*/*z* calcd for $C_{44}H_{53}N_2O_6$ (M+H) 705.38981, found 705.39093.

4.8. General procedure for the synthesis of 1a–d

To a solution of **9a–d** in a mixture of THF (3 mL) and liquid ammonia (15 mL) at −78 °C was added sodium metal until the blue color persisted. After 1 h, the reaction finished and the NH_3 (g) was evaporated. The residue was then partitioned between dichloromethane and water. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The crude was purified by flash chromatography on silica gel (5:1 ethyl acetate/methanol) to give **1a–d**.

*4.8.1. Bengamide E (**1a**).* Yield: 58%, white foam; $[\alpha]_D^{29}$ +36.0 (*c* 1.33, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J*=6.9 Hz, 1H), 6.17 (t, *J*=6.0 Hz, 1H), 5.81 (dd, *J*=15.6, 6.5 Hz, 1H), 5.44 (ddd, *J*=15.5, 7.1, 1.2 Hz, 1H), 4.58 (dd, *J*=10.1, 7.0 Hz, 1H), 4.25 (t, *J*=6.3 Hz, 1H), 4.03 (d, *J*=6.6 Hz, 1H), 3.96 (t, *J*=5.3 Hz, 1H), 3.83 (d, *J*=5.5 Hz, 1H), 3.60 (s, 1H), 3.53 (s, 3H), 3.41–3.21 (m, 2H), 3.18–2.99 (m, 2H), 2.32 (dq, *J*=12.7, 6.4 Hz, 1H), 2.05 (dd, *J*=25.1, 9.8 Hz, 2H), 1.95–1.64 (m, 5H),

1.64–1.49 (m, 1H), 1.49–1.35 (m, 1H), 1.01 (dd, *J*=6.8, 1.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 171.6, 141.7, 125.5, 81.5, 74.0, 72.6, 59.6, 51.9, 42.0, 41.9, 31.0, 30.8, 28.7, 27.9, 22.2, 22.1. HRMS (ESI) *m*/*z* calcd for $C_{17}H_{31}N_2O_6$ (M+H) 359.21766, found 359.21771.

*4.8.2. (2S,3R,4S,5R,E)-3,4,5-Trihydroxy-2-methoxy-8-methyl-N-((S)-2-oxoazepan-3-yl)non-6-enamide (**1b**).* Yield: 71%, white foam; $[\alpha]_D^{25}$ −24.4 (*c* 1.97, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J*=6.9 Hz, 1H), 6.17 (t, *J*=6.0 Hz, 1H), 5.81 (dd, *J*=15.6, 6.5 Hz, 1H), 5.44 (ddd, *J*=15.5, 7.1, 1.2 Hz, 1H), 4.58 (dd, *J*=10.1, 7.0 Hz, 1H), 4.25 (t, *J*=6.3 Hz, 1H), 4.03 (d, *J*=6.6 Hz, 1H), 3.96 (t, *J*=5.3 Hz, 1H), 3.83 (d, *J*=5.5 Hz, 1H), 3.60 (s, 1H), 3.53 (s, 3H), 3.24–3.37 (m, 2H), 3.08 (d, *J*=4.7 Hz, 1H), 3.03 (s, 1H), 2.28–2.36 (m, 1H), 2.01–2.10 (m, 2H), 1.50–1.59 (m, 1H), 1.38–1.48 (m, 1H), 1.01 (dd, *J*=6.8, 1.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 170.1, 141.8, 125.4, 82.1, 73.9, 73.0, 71.9, 59.2, 51.7, 42.1, 31.1, 30.7, 28.8, 27.9, 22.2, 22.1. HRMS (ESI) *m*/*z* calcd for $C_{17}H_{30}N_2NaO_6$ (M+Na) 381.20046, found 381.20046.

*4.8.3. (2R,3R,4S,5R,E)-2,3,4,5-Tetrahydroxy-8-methyl-N-((S)-2-oxoazepan-3-yl)non-6-enamide (**1c**).* Yield: 43%, colorless syrup; $[\alpha]_D^{25}$ +34.7 (*c* 1.5, CH_3OH); ^{1}H NMR (400 MHz, D_2O) δ 5.86 (dd, *J*=15.5, 6.4 Hz, 1H), 5.39 (dd, *J*=15.6, 8.1 Hz, 1H), 4.64 (d, *J*=10.4 Hz, 1H), 4.28 (d, *J*=6.5 Hz, 1H), 4.15 (t, *J*=8.1 Hz, 1H), 3.85 (d, *J*=5.5 Hz, 1H), 3.70 (d, *J*=8.0 Hz, 1H), 3.27–3.39 (m, 2H), 2.28–2.36 (m, 1H), 2.02 (d, *J*=12.4 Hz, 1H), 1.66–1.93 (m, 4H), 1.40 (dd, *J*=25.0, 11.8 Hz, 1H), 0.99 (d, *J*=6.8 Hz, 6H). ^{13}C NMR (100 MHz, D_2O) δ 177.0, 173.3, 143.7, 124.3, 73.7, 72.9, 72.7, 70.8, 52.1, 41.4, 30.3, 30.0, 27.6, 27.4, 21.3. HRMS (ESI) *m*/*z* calcd for $C_{16}H_{28}N_2NaO_6$ (M+Na) 367.18396, found 367.18445.

*4.8.4. (2S,3R,4S,5R,E)-2,3,4,5-Tetrahydroxy-8-methyl-N-((S)-2-oxoazepan-3-yl)non-6-enamide (**1d**).* Yield: 50%, colorless syrup; $[\alpha]_D^{25}$ −24.0 (*c* 0.5, CH_3OH); ^{1}H NMR (400 MHz, D_2O) δ 5.82 (dd, *J*=15.5, 6.5 Hz, 1H), 5.45 (ddd, *J*=15.6, 7.7, 1.2 Hz, 1H), 4.62 (dd, *J*=11.2, 1.5 Hz, 1H), 4.31 (d, *J*=3.5 Hz, 1H), 4.16 (t, *J*=7.8 Hz, 1H), 3.94 (t, *J*=3.8 Hz, 1H), 3.66 (dd, *J*=6.0, 4.4 Hz, 1H), 3.23–3.36 (m, 2H), 2.26–2.34 (m, 1H), 1.97–2.02 (m, 1H), 1.63–1.89 (m, 4H), 1.31–1.41 (m, 1H), 0.96 (d, *J*=6.8 Hz, 6H). ^{13}C NMR (100 MHz, D_2O) δ 177.0, 173.3, 143.0, 124.5, 74.4, 73.0, 72.7, 71.1, 51.9, 41.3, 30.2, 30.0, 27.5, 27.3, 21.3, 21.2. HRMS (ESI) *m*/*z* calcd for $C_{16}H_{28}N_2NaO_6$ (M+Na) 367.18396, found 367.18439.

4.9. General procedure for the synthesis of 10a–c

The aldehyde **2a–c** was dissolved in MeCN/^{t}BuOH/H_2O (2:2:1), and treated with $NaClO_2$ (3 equiv), $NaH_2PO_4 \cdot H_2O$ (3 equiv) and 35% H_2O_2 (10 equiv). The mixture was stirred at room temperature for 3 h, Na_2SO_3 and 1 N HCl (aq) were added, and the mixture was extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The crude was purified by flash chromatography on silica gel (50:1 dichloromethane/methanol) to give **10a–c**.

*4.9.1. (2R,3S,4R)-2,3,4-Tris(benzyloxy)hex-5-enoic acid (**10a**).* Yield: 88%, colorless syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.29 (m, 15H), 5.64–5.74 (m, 1H), 5.16–5.23 (m, 2H), 4.78 (d, *J*=11.2 Hz, 1H), 4.66 (d, *J*=11.3 Hz, 1H), 4.52–4.59 (m, 2H), 4.29–4.37 (m, 2H), 4.15 (t, *J*=7.5 Hz, 1H), 4.08 (d, *J*=2.9 Hz, 1H), 3.88 (dd, *J*=7.2, 3.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 138.1, 137.8, 136.7, 134.5, 128.5, 128.4, 128.4, 128.3, 128.2, 127.9, 127.8, 127.6, 119.9, 81.7, 81.3, 78.2, 75.3, 73.5, 71.7. HRMS (ESI) *m*/*z* calcd for $C_{27}H_{28}NaO_5$ (M+Na) 455.18290, found 455.18360.

*4.9.2. (2S,3S,4R)-2,3,4-Tris(benzyloxy)hex-5-enoic acid (**10b**).* Yield: 83%, colorless syrup; $[\alpha]_D^{25}$ +13.6 (*c* 0.88, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.43 (m, 15H), 5.91–6.00 (m, 1H), 5.49–5.56 (m, 2H), 4.80 (d, *J*=11.4 Hz, 1H), 4.60–4.70 (m, 5H), 4.51 (d, *J*=2.0 Hz, 1H), 4.44 (d, *J*=11.4 Hz, 1H), 4.18–4.24 (m, 2H), 4.05 (d, *J*=8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 140.7, 138.1, 137.6, 137.1, 135.9, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 127.1, 120.4, 81.9, 79.2, 77.9, 77.6, 77.3, 76.9, 74.7, 73.7, 70.3, 65.0. HRMS (ESI) *m*/*z* calcd for $C_{27}H_{28}NaO_5$ (M+Na) 455.18290, found 455.18367.

*4.9.3. (2R,3S,4S)-2,3,4-Tris(benzyloxy)hex-5-enoic acid (**10c**).* Yield: 84%, colorless syrup; $[\alpha]_D^{25}$ −15.5 (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.41 (m, 15H), 5.92–6.10 (m, 1H), 5.48 (d, *J*=17.2 Hz, 1H), 5.40 (d, *J*=10.4 Hz, 1H), 4.70–4.86 (m, 4H), 4.45–4.50 (m, 2H), 4.34 (s, 1H), 4.25 (s, 1H), 4.01 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 138.2, 138.1, 137.2, 135.0, 132.4, 132.3, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1 (2), 127.8, 82.7, 80.9, 78.8, 74.9, 72.8, 70.9. HRMS (ESI) *m*/*z* calcd for $C_{27}H_{28}NaO_5$ (M+Na) 455.18290, found 455.18337.

4.10. General procedure for the synthesis of 11a–c

To the solution of the acid **10a–c** in dry DMF were added EDCI (2 equiv), HOBt (2 equiv), and Et_3N (3 equiv). After 30 min, L-(−)-α-amino-δ-caprolactam (1.5 equiv) was added and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated, dissolved in dichloromethane and 1N HCl was added. The resultant solution was then partitioned between dichloromethane and water. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The crude was purified by flash chromatography on silica gel (5:1 PE/acetone) to give **11a–c**.

*4.10.1. (2R,3S,4R)-2,3,4-Tris(benzyloxy)-N-((S)-2-oxoazepan-3-yl) hex-5-enamide (**11a**).* Yield: 81%, white solid; $[\alpha]_D^{25}$ +37.1 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J*=5.2 Hz, 1H), 7.19–7.32 (m, 15H), 6.31 (t, *J*=6.1 Hz, 1H), 5.73–5.82 (m, 1H), 5.29 (dd, *J*=10.3, 1.3 Hz, 1H), 5.24 (d, *J*=17.2 Hz, 1H), 4.84 (d, *J*=11.6 Hz, 1H), 4.54–4.62 (m, 3H), 4.41–4.44 (m, 2H), 4.23 (dd, *J*=10.7, 5.3 Hz, 1H), 4.17 (t, *J*=7.9 Hz, 1H), 4.03 (d, *J*=2.4 Hz, 1H), 3.95 (dd, *J*=7.8, 2.4 Hz, 1H), 3.17–3.21 (m, 2H), 1.95–2.01 (m, 2H), 1.76–1.83 (m, 2H), 1.37 (dd, *J*=23.6, 11.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 170.1, 138.8, 138.6, 136.8, 135.1, 128.9, 128.5, 128.3, 128.2, 128.0, 127.8, 127.4, 127.3, 119.7, 82.8, 82.5, 80.3, 77.5, 77.1, 76.8, 75.8, 73.9, 71.1, 52.1, 41.9, 31.3, 28.9, 27.9. HRMS (ESI) *m*/*z* calcd for $C_{33}H_{39}N_2O_5$ (M+H) 543.28535, found 543.28524.

*4.10.2. (2S,3S,4R)-2,3,4-Tris(benzyloxy)-N-((S)-2-oxoazepan-3-yl) hex-5-enamide (**11b**).* Yield: 79%, white solid; $[\alpha]_D^{25}$ +23.9 (*c* 0.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J*=5.4 Hz, 1H), 7.42–7.11 (m, 17H), 5.79–6.01 (m, 1H), 5.49 (d, *J*=17.2 Hz, 1H), 5.43 (d, *J*=10.3 Hz, 1H), 4.67–4.41 (m, 5H), 4.37 (s, 1H), 4.28 (dd, *J*=10.6, 5.6 Hz, 1H), 4.21 (d, *J*=11.6 Hz, 1H), 4.13 (t, *J*=8.1 Hz, 1H), 3.98 (d, *J*=8.2 Hz, 1H), 3.08–3.16 (m, 1H), 1.94 (d, *J*=11.3 Hz, 2H), 1.71–1.77 (m, 2H), 1.35 (dd, *J*=25.2, 13.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 170.8, 138.3, 138.1, 137.0, 136.2, 128.8, 128.5, 128.4, 128.2, 128.1, 128.0, 127.7, 127.5, 127.5, 120.2, 82.5, 79.6, 79.3, 75.4, 74.3, 70.0, 51.9, 41.9, 31.2, 28.8, 27.9. HRMS (ESI) *m*/*z* calcd for $C_{33}H_{39}N_2O_5$ (M+H) 543.28535, found 543.28543.

*4.10.3. (2R,3S,4S)-2,3,4-Tris(benzyloxy)-N-((S)-2-oxoazepan-3-yl) hex-5-enamide (**11c**).* Yield: 72%, white solid; $[\alpha]_D^{25}$ −9.2 (*c* 0.87, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J*=6.6 Hz, 1H), 7.27–7.41 (m, 15H), 5.88 (ddd, *J*=17.6, 10.3, 7.7 Hz, 1H), 5.48 (d, *J*=17.2 Hz, 1H), 5.33 (d, *J*=11.3 Hz, 1H), 4.83 (dd, *J*=28.2, 11.5 Hz, 2H), 4.46–4.72 (m, 4H), 4.47 (d, *J*=11.7 Hz, 1H), 4.32 (t, *J*=7.4 Hz, 1H), 4.20 (d, *J*=2.9 Hz, 1H), 3.99 (dd, *J*=7.2, 2.9 Hz, 1H), 3.16–3.20 (m, 2H), 2.05 (d, *J*=13.4 Hz, 1H), 1.95 (d, *J*=14.2 Hz, 1H), 1.76–1.81 (m, 2H), 1.29–1.44 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 169.1,

138.8, 138.7, 137.3, 135.2, 132.2, 132.1, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.4, 127.4, 119.7, 83.4, 81.6, 80.0, 77.6, 74.7, 72.9, 70.9, 51.9, 41.9, 31.22, 28.9, 28.1. HRMS (ESI) *m*/*z* calcd for $C_{33}H_{39}N_2O_5$ (M+H) 543.28535, found 543.28547.

4.11. General procedure for the synthesis of 12a–c

Compound **11a–c** was dissolved in a 1:2 CH_2Cl_2/3-methyl-1-butene mixture (3 mL), and Hoveyda–Grubbs catalysts second generation (0.3 equiv) was added. The flask was then capped and the mixture was refluxed for 24 h, after which the crude mixture was concentrated and purified by flash column chromatography (silica gel, 5:1 PE/acetone) to yield **12a–c**.

*4.11.1. (2R,3S,4R,E)-2,3,4-Tris(benzyloxy)-7-methyl-N-((S)-2-oxoazepan-3-yl)oct-5-enamide (**12a**).* Yield: 88%, brown foam; $[\alpha]_D^{25}$ +31.1 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J*=5.3 Hz, 1H), 7.13–7.41 (m, 16H), 5.69 (dd, *J*=15.6, 6.6 Hz, 1H), 5.37 (ddd, *J*=15.5, 8.6, 0.8 Hz, 1H), 4.91 (d, *J*=11.6 Hz, 1H), 4.58 (t, *J*=10.8 Hz, 3H), 4.44 (dd, *J*=11.3, 2.8 Hz, 2H), 4.25 (dd, *J*=10.6, 5.3 Hz, 1H), 4.19 (t, *J*=8.4 Hz, 1H), 4.04 (d, *J*=2.2 Hz, 1H), 3.98 (dd, *J*=8.3, 2.2 Hz, 1H), 3.10–3.23 (m, 2H), 2.31–2.39 (m, 1H), 1.99 (t, *J*=15.0 Hz, 3H), 1.74–1.83 (m, 2H), 1.34–1.43 (m, 2H), 1.04 (dd, *J*=6.8, 3.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 175.2, 149.0, 143.9, 143.8, 141.9, 133.7, 133.5, 133.3, 133.1, 133.0, 133.0, 132.8, 132.3, 132.1, 128.9, 88.2, 87.5, 85.7, 82.4, 82.1, 81.8, 81.0, 79.0, 75.7, 57.0, 46.9, 36.2, 36.0, 33.9, 32.9, 27.4, 27.3. HRMS (ESI) *m*/*z* calcd for $C_{36}H_{45}N_2O_5$ (M+H) 585.33230, found 585.33372.

*4.11.2. (2S,3S,4R,E)-2,3,4-Tris(benzyloxy)-7-methyl-N-((S)-2-oxoazepan-3-yl)oct-5-enamide (**12b**).* Yield: 88%, brown foam; $[\alpha]_D^{25}$ +15.2 (*c* 0.79, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J*=5.1 Hz, 1H), 7.21–7.33 (m, 17H), 6.74 (s, 1H), 5.85 (dd, *J*=15.5, 6.5 Hz, 1H), 5.40 (dd, *J*=15.2, 8.2 Hz, 1H), 4.36–4.60 (m, 6H), 4.26 (dd, *J*=10.3, 5.4 Hz, 1H), 4.18 (d, *J*=11.6 Hz, 1H), 4.06 (t, *J*=8.5 Hz, 1H), 3.95 (dd, *J*=8.5, 1.6 Hz, 1H), 3.07–3.25 (m, 2H), 2.34–2.42 (m, 1H), 1.69–1.96 (m, 5H), 1.28–1.47 (m, 2H), 1.03 (dd, *J*=6.6, 2.3 Hz, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 180.1, 175.8, 149.3, 143.6, 142.1, 133.8, 133.4, 133.3, 133.0, 132.6, 132.4, 129.9, 87.7, 84.6, 84.1, 82.4, 82.1, 81.8, 80.3, 79.3, 74.5, 56.9, 47.0, 36.3, 36.1, 33.9, 32.9, 27.4, 27.1. HRMS (ESI) *m*/*z* calcd for $C_{36}H_{45}N_2O_5$ (M+H) 585.33230, found 585.33364.

*4.11.3. (2R,3S,4S,E)-2,3,4-Tris(benzyloxy)-7-methyl-N-((S)-2-oxoazepan-3-yl)oct-5-enamide (**12c**).* Yield: 75%, brown foam; $[\alpha]_D^{25}$ −10.8 (*c* 1.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J*=6.6 Hz, 1H), 7.25–7.40 (m, 15H), 7.06 (s, 1H), 5.83 (dd, *J*=15.6, 6.6 Hz, 1H), 5.36 (dd, *J*=15.6, 8.2 Hz, 1H), 4.82 (q, *J*=11.6 Hz, 2H), 4.69 (d, *J*=11.7 Hz, 1H), 4.57 (dt, *J*=19.0, 11.7 Hz, 3H), 4.44 (d, *J*=11.7 Hz, 1H), 4.27 (t, *J*=7.7 Hz, 1H), 4.14 (d, *J*=2.9 Hz, 1H), 3.89 (dd, *J*=7.2, 2.9 Hz, 1H), 3.17–3.27 (m, 2H), 2.26–2.34 (m, 1H), 2.04 (d, *J*=13.8 Hz, 1H), 1.95 (dd, *J*=11.3, 3.0 Hz, 1H), 1.80 (d, *J*=13.1 Hz, 2H), 1.31–1.47 (m, 2H), 0.99 (t, *J*=6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 169.2, 143.5, 139.0, 137.3, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.3, 123.9, 83.6, 81.3, 79.9, 77.5, 77.2, 76.9, 74.8, 72.5, 70.5, 51.8, 42.0, 31.5, 30.9, 28.9, 28.1, 22.3. HRMS (ESI) *m*/*z* calcd for $C_{36}H_{45}N_2O_5$ (M+H) 585.33230, found 585.33372.

4.12. General procedure for the synthesis of 1e–g

To a solution of **12a–c** in a mixture of THF (3 mL) and liquid ammonia (15 mL) at −78 °C was added sodium metal until the blue color persisted. After 1 h, the reaction finished and the NH_3 (g) was evaporated. The residue was then partitioned between dichloromethane and water. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The crude was purified by flash chromatography on silica gel (5:1 ethyl acetate/methanol) to give **1e–g**.

*4.12.1. (2R,3S,4R,E)-2,3,4-Trihydroxy-7-methyl-N-((S)-2-oxoazepan-3-yl)oct-5-enamide (**1e**).* Yield: 48%, colorless syrup; $[\alpha]_D^{25}$ +21.4 (*c* 0.56, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J*=6.9 Hz, 1H), 6.63 (s, 1H), 5.81 (dd, *J*=15.5, 6.5 Hz, 1H), 5.52 (dd, *J*=15.5, 7.1 Hz, 1H), 4.60 (dd, *J*=10.7, 7.3 Hz, 1H), 4.44 (s, 1H), 4.42–4.28 (m, 3H), 3.96 (d, *J*=5.0 Hz, 1H), 3.24–3.37 (m, 3H), 2.28–2.37 (m, 1H), 1.79–2.06 (m, 5H), 1.61 (dd, *J*=23.8, 12.3 Hz, 1H), 1.43 (dd, *J*=22.7, 12.5 Hz, 1H), 1.01 (dd, *J*=6.7, 1.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 172.2, 142.3, 125.4, 74.2, 74.1, 73.4, 52.1, 42.0, 30.8, 30.6, 28.6, 28.0, 22.1, 22.1. HRMS (ESI) *m*/*z* calcd for $C_{15}H_{26}N_2NaO_5$ (M+Na) 337.17339, found 337.17384.

*4.12.2. (2S,3S,4R,E)-2,3,4-Trihydroxy-7-methyl-N-((S)-2-oxoazepan-3-yl)oct-5-enamide (**1f**).* Yield: 42%, colorless syrup; $[\alpha]_D^{25}$ −12.3 (*c* 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J*=6.6 Hz, 1H), 6.60 (s, 1H), 5.77 (dd, *J*=15.5, 6.2 Hz, 1H), 5.58 (dd, *J*=15.7, 6.3 Hz, 1H), 4.57 (dd, *J*=10.8, 6.9 Hz, 1H), 4.39 (d, *J*=6.0 Hz, 1H), 4.15 (d, *J*=7.5 Hz, 1H), 3.67 (d, *J*=7.5 Hz, 1H), 3.18–3.35 (s, 2H), 2.27–2.35 (m, 1H), 2.00–2.04 (m, 2H), 1.76–1.87 (m, 3H), 1.57 (dd, *J*=23.4, 12.0 Hz, 1H), 1.40 (dd, *J*=21.7, 11.0 Hz, 1H), 0.99 (d, *J*=6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 172.9, 140.7, 126.0, 74.8, 71.8, 71.2, 70.5, 52.2, 42.1, 31.3, 30.8, 28.8, 28.0, 22.2, 22.2. HRMS (ESI) *m*/*z* calcd for $C_{15}H_{26}N_2NaO_5$ (M+Na) 337.17339, found 337.17398.

*4.12.3. (2R,3S,4S,E)-2,3,4-Trihydroxy-7-methyl-N-((S)-2-oxoazepan-3-yl)oct-5-enamide (**1g**).* Yield: 40%, colorless syrup; $[\alpha]_D^{25}$ −32.4 (*c* 0.37, CH_3OH); ^{1}H NMR (400 MHz, D_2O) δ 5.75 (dd, *J*=15.5, 6.2 Hz, 1H), 5.32 (dd, *J*=16.9, 7.7 Hz, 1H), 4.45 (d, *J*=11.1 Hz, 1H), 4.20 (d, *J*=4.0 Hz, 1H), 4.13 (t, *J*=6.9 Hz, 1H), 3.71 (dd, *J*=6.3, 4.0 Hz, 1H), 3.18–3.24 (m, 2H), 2.13–2.21 (m, 1H), 1.86–1.96 (m, 1H), 154–1.80 (m, 5H), 1.28 (ddd, *J*=14.0, 11.6, 3.1 Hz, 1H), 0.87 (dd, *J*=6.8, 1.4 Hz, 6H). ^{13}C NMR (100 MHz, D_2O) δ 177.0, 173.0, 143.0, 124.2, 75.1, 72.8, 72.1, 52.1, 41.3, 30.1, 29.7, 27.5, 27.4, 21.3, 21.0. HRMS (ESI) *m*/*z* calcd for $C_{15}H_{26}N_2NaO_5$ (M+Na) 337.17339, found 337.17409.

4.13. Methods for bioactivity assays

Each test solution for in vitro assay was prepared by diluting with DMSO. All cells used in the research were prepared at 3.5×10^4 cells/mL concentration and each 100 μL cells suspension was seeded in 96-well cell microplate for 24 h (37 °C, 5% CO_2). Then each solution was added and incubated for another 72 h. For the control group, equivalent concentration of DMSO (final concentration 0.5%) was added. MTT (3-[4,5-dimethylthiazol-2yl]-diphenyl tetrazolium bromide) method was employed to measure the number of surviving cells and recorded the OD value at 492/620 nm. The IC_{50} values were calculated using Prism Graph pad software of the triplicate experiment.

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Supplementary data

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