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An asymmetric approach to 5-*O*-carbamoyl-2-*epi*-polyoxamic acid and the total synthesis of 2″-*epi*-polyoxin J

Yong-Chun Luo, Huan-Huan Zhang, Yao-Zong Liu, Rui-Ling Cheng, Peng-Fei Xu *

State Key Laboratory of Applied Organic Chemistry and College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, PR China

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ABSTRACT

A stereospecific synthetic approach to 5-*O*-carbamoyl-2-*epi*-polyoxamic acid has been developed. The asymmetric nucleophilic addition of 2-lithiofuran to a *tert*-butanesulfinyl imine was employed as the key step to construct the C-2 stereocenter and 2″-*epi*-polyoxin J has been synthesized for the first time. Significantly, the synthesis provides a facile method for the large scale and stereoselective preparation of 5-*O*-carbamoyl-2-*epi*-polyoxamic acid and some related diastereoisomers of polyoxins and its analogues because of its simple operation, excellent yield, and high stereoselectivity. This will be convenient for research of the polyoxins' structure–activity relationship and to search for more potent and effective anti-candidal agents.

1. Introduction

The polyoxins are an important group of nucleoside peptide antibiotics which have been isolated from the fermentation broth of *Streptomyces cacaoi* var. *asoensis* and are characterized by Isono et al.[1] Quite interestingly, their structure showed the presence of unique 1-(5′-amino-5′-deoxy-β-D-allofuranuronosyl)pyrimidines that constitute the common skeleton of all the members of polyoxin families. For example, polyoxin J and polyoxin L (Fig. 1) comprised of 5-*O*-carbamoyl polyoxamic acid and two different nucleoside amino acids, respectively. The unique difference between them is the substituent on the pyrimidine bases.

Polyoxins are known as antifungal agents that selectively inhibit membrane bound enzyme chitin synthase from yeast and other fungi,[2] including *Candida albicans*, a fungal pathogen which affects immunocompromised humans. In addition polyoxins are ineffective against other microorganisms, plants, or animals.[2e] Because of their biological activities, the synthesis of the polyoxins and their analogues has received considerable attention from synthetic chemists. Several groups have described total synthesis of polyoxin J.[3] Akita et al. have reported an elegant convergent approach to both polyoxins J and L.[3f,g] According to the characteristic structural features of polyoxins and the products of their hydrolytic cleavage, most of these syntheses are based on the previous construction of the 1-(5′-amino-5′-deoxy-β-D-allofuranuronosyl)pyrimidine unit. Therefore, considerable synthetic efforts have been directed toward the construction of the nucleoside skeleton.[4]

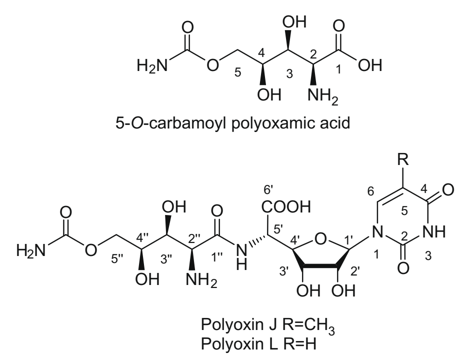

Figure 1. Structures of polyoxin J and polyoxin L.

The different biological activities against the enzyme (chitin synthase) and *C. albicans* in culture between polyoxins and the closely related nikkomycins[5] suggested that analogues of the polyoxins could be more effective as anticandidal agents. In this regard, some attention has been paid to the synthesis of structural analogues of the polyoxins,[5b,6] but there is no report concerning the preparation of diastereoisomers of the polyoxins or nikkomycins. In order to make convenient to search for more potent and safer anticandidal agents related to the polyoxins, it is necessary to develop some stereospecific synthetic methods.

In our laboratory an ongoing program aimed at using enantiomerically pure *tert*-butanesulfinamide as a chiral auxiliary for the efficient synthesis of the biologically interesting polyoxin and nikkomycin antibiotics is in progress. After we achieved the facile synthesis of polyoxin C and its analogues with different pyrimidine bases (Fig. 2),[7] we endeavored to synthesize some

* Corresponding author. Tel.: +86 931 8912281; fax: +86 931 8915557.
E-mail address: xupf@lzu.edu.cn (P.-F. Xu).

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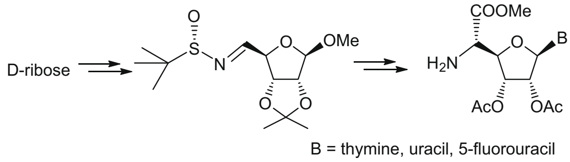
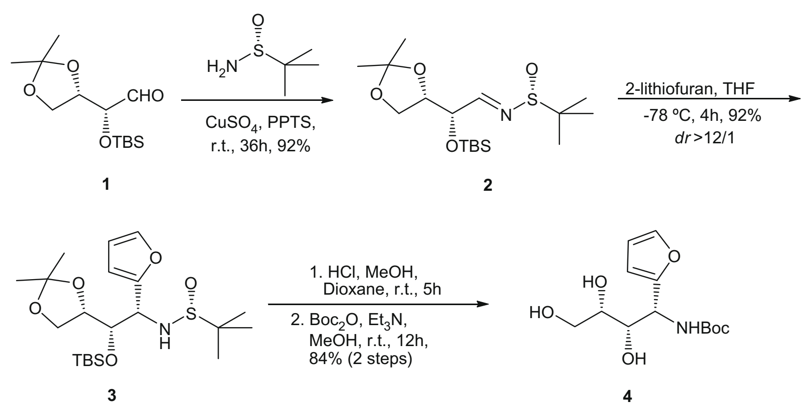


Figure 2. New approach to polyoxin Cs.

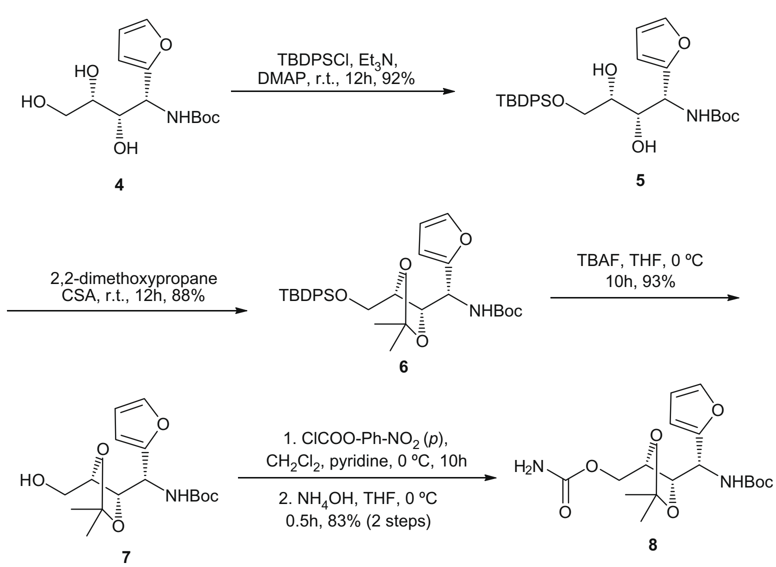
diastereoisomers of other complex members of the polyoxins. Many members of the polyoxin family and related classes of compounds feature the 5-*O*-carbamoyl polyoxamic acid as a common side chain. In view of this, we started our synthesis from the preparation of 5-*O*-carbamoyl-2-*epi*-polyoxamic acid. Although some synthetic approaches to this component have been reported,[8,3f] it was often obtained as by-product. There has been no report concerning a diastereoselective synthesis. Davis[9] has reported a stereoselective synthesis of polyoxamic acid lactone and its 2-*epi*-diastereoisomer but the total yield is low and the procedure is not suitable for preparation on a large scale. We considered that both the protected 5-*O*-carbamoyl-2-*epi*-polyoxamic acid **9** and the core structure **12** could be obtained by our own method using *tert*-butanesulfinamide as a chiral auxiliary and the furan as a masked carboxylic acid d_1-synthon. Thus, the diastereoselective nucleophilic addition of 2-lithiofuran to the *tert*-butanesulfinyl imine without any Lewis acid additive was employed to construct the C-2 stereocenter in high yield and with excellent diastereoselectivity. Followed by some classic functional group conversion, we obtained protected 5-*O*-carbamoyl-2-*epi*-polyoxamic acid **9** for coupling with the 1-(5′-amino-5′-deoxy-β-D-allofuranuronosyl)pyrimidine unit. The synthesis provides a facile method for the large-scale preparation of 5-*O*-carbamoyl-2-*epi*-polyoxamic acid because of the simple operation, excellent yield and high stereoselectivity.

2. Results and discussion

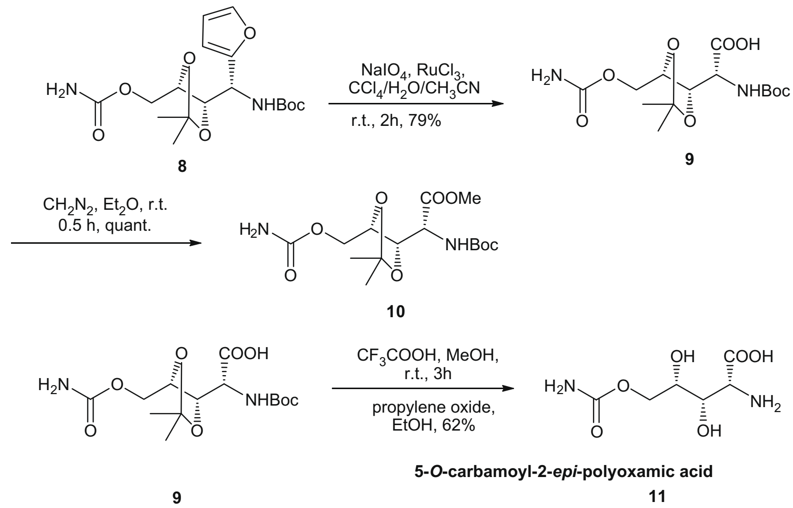
Our synthesis began with the direct condensation of (*R*)-(+)-*tert*-butanesulfinamide and aldehyde **1** (Scheme 1) derived from L-ascorbic acid.[10] In an attempt to improve the yield of the condensation, we carried out a series of reactions according to the reported methods[11] and found that the addition of 1.0 equiv of PPTS in the presence of anhydrous $CuSO_4$ could dramatically promote the reaction affording the *tert*-butanesulfinyl imine **2** in 92% yield. The aldehyde **1** was chosen as our starting material because we hoped the chirality of the aldehyde unit and the chiral *tert*-butanesulfinyl group could work as a matched combination during the nucleophilic addition. With *tert*-butanesulfinyl imine **2** in hand, the stereocontrolled installation of a potential carboxyl group was crucial to successful synthesis and it could be easily achieved by the addition of 2-lithiofuran to the *tert*-butanesulfinyl imine **2** in THF at −78 °C without any additive to give the adduct product **3** in 92% yield with excellent diastereoselectivity (dr



Scheme 1.



Scheme 2.



Scheme 3.

>12:1). Subsequently, the *tert*-butanesulfinyl group and other hydroxy protecting groups were removed simultaneously with HCl and the desired *N*-Boc derivative **4** was obtained successively in 84% yield in a two-step sequence.

When we furnished triol **4**, selective carbamoylation of the primary hydroxy (Scheme 2) was necessary. First of all, protection of the primary hydroxy with TBDPSCl selectively gave the diol **5** in high yield (92%) and the resulting diol **5** was transformed to **6** in 88% yield using 2,2-dimethoxypropane in the presence of CSA at room temperature. Then, removal of the silyl group of protected triol **6** with TBAF in THF at 0 °C for 10 h released the primary hydroxyl group in 93% yield. With the primary alcohol **7** in hand, the carbamoylation could be achieved in a two-step sequence: (1) esterification of the primary hydroxyl group with *p*-nitrophenyl chloroformate, (2) selective ammonolysis to furnish the resulting ester **8** in 83% yield over two steps after chromatography.

Next, we considered the release of the carboxylic acid function from the furan ring (Scheme 3), a crucial operation for the completion of the synthetic plan. Thus, the oxidative cleavage of the furan ring was achieved using catalytic $RuCl_3$ in the presence of an excess of $NaIO_4$ to give compound **9** in 79% yield. This conversion can also be achieved by ozonization in methanol in good yield. In order to determine the stereochemistry of C-2 generated in the nucleophilic addition, compound **9** was converted into the corresponding methyl ester **10** by treatment with a solution of CH_2N_2 in ethyl ether in quantitative yield. Comparison of the physical properties and spectroscopy of **10** with the data[8,3f] reported previously demonstrated that the stereochemistry of C-2 was the expected (*R*)-configuration required for the continuation of the synthesis of 2″-*epi*-polyoxin J and suggested the nucleophilic addition of 2-lithiofuran took place from the *Si* face of *tert*-butanesulfinyl imine **2**. Subsequently, the facile deprotection of **9** with trifluoroacetic acid in methanol furnished 5-*O*-carbamoyl-2-*epi*-polyoxamic acid **11** in moderate yield.

A highly organized transition state model as depicted in Figure 3 may explain the high degree of diastereoselection associated with the nucleophilic addition of 2-lithiofuran to *tert*-butanesulfinyl imine **2**. In this model, a six-membered cyclic transition state with lithium coordinated to the sulfinyl oxygen was formed. Obviously, the bulky *tert*-butyl group and the protected triol unit occupied the less hindered equatorial position resulting in preferential attack from the *Si* face of the *tert*-butanesulfinyl imine for this addition. Furthermore, the hindrance of the protected triol unit also favors the addition from the *Si* face. So, the excellent stereoselectivity observed during the addition should be attributed to the matched combination of the six-membered cyclic transition state and the chirality of the protected triol unit. This matched combination was also confirmed by the decreased stereoselectivity in the nucleophilic addition when (*S*)-(−)-*tert*-butanesulfinamide was used as a chiral auxiliary.

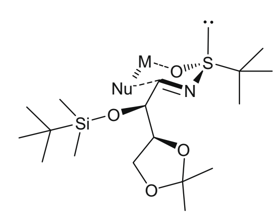
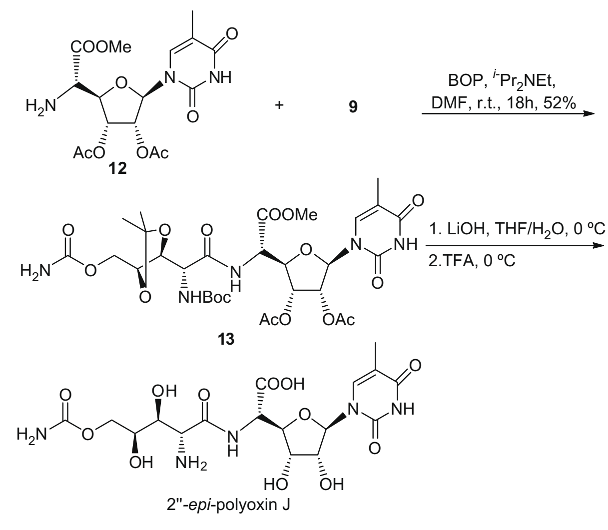


Figure 3. Proposed transition state for the nucleophilic addition.

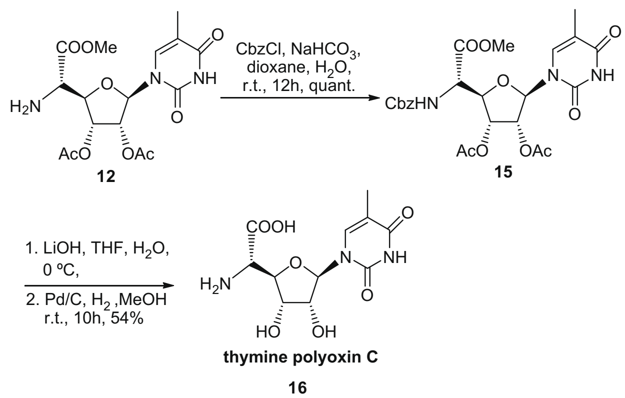
After we achieved the synthesis of **11**, we turned our attention to furnish 2″-*epi*-polyoxin J (Scheme 4). According to our previous



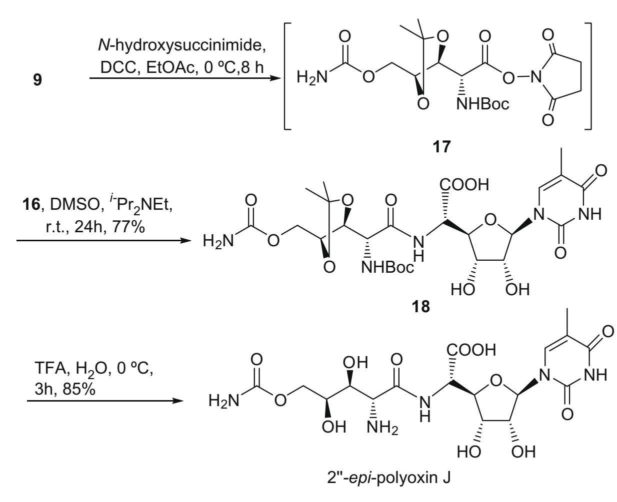
Scheme 4.

work[7] protected thymine polyoxin C **12** was easily prepared from D-ribose on a large scale. Coupling of protected 2-*epi*-polyoxamic acids **9** and **12** in the presence of BOP furnished the protected 2″-*epi*-polyoxin J **13**. Then, the deprotection procedure reported by Ghosh[3c] was employed to remove the protecting groups of **13**. However, the purification of the final product **14** was difficult.

In order to resolve this problem, we thought that the protecting groups of **12** should be removed before coupling. Thus, **12** was converted into the corresponding *N*-Cbz derivative **15** in quantitative yield. Subsequently, compound **15** was transformed into thymine polyoxin C **16** by the standard deprotection sequence (Scheme 5). Having obtained compound **16**, we saw that what remained to complete the synthesis of 2″-*epi*-polyoxin J was the coupling of **9** and **16** via an amide bond as follows (Scheme 6). Treatment of **9** with *N*,*N*-dicyclohexylcarbodiimide-*N*-hydroxysuccinimide gave the active ester **17** which was then condensed with thymine polyoxin C to afford the dipeptide **18** in 77% yield. Removal of the *N*-Boc and *O*-isopropylidene protecting groups upon acid hydrolysis provided 2″-*epi*-polyoxin J **14** in 85% yield.



Scheme 5.



Scheme 6.

3. Conclusions

In conclusion, a stereospecific synthesis of 5-*O*-carbamoyl-2-*epi*-polyoxamic acid has been developed in high yield and with excellent stereoselectivity. During the preparation of enantiomerically pure *tert*-butanesulfinyl imine, we found that PPTS could promote the condensation of *tert*-butanesulfinamide and the aliphatic aldehyde with large substituent. This discovery simplified the preparation of the *tert*-butanesulfinyl imine. As our previous work, the nucleophilic addition of 2-lithiofuran to a *tert*-butanesulfinyl imine was employed as a key step to construct the stereochemistry at C-2 of an α-amino acid successfully. Combined with our previous work on the synthesis of polyoxin C, 2″-*epi*-polyoxin J was synthesized by a convergent strategy for the first time.

4. Experimental

Unless noted otherwise, reagents available commercially were used without further purification. Solvents were dried by heating at reflux for at least 12 h over P_2O_5 (dichloromethane) or sodium/benzophenone (toluene, THF, and *n*-hexane), and were freshly distilled prior to use. Flash chromatography was carried out utilizing silica gel 200–300 mesh. ^{1}H NMR spectra were recorded on a Bruker AM-400 (400 MHz) spectrometer, and are reported in ppm using a solvent as an internal standard ($CDCl_3$ at 7.26 ppm). *J* values are recorded in hertz and abbreviations used are s—singlet, d—doublet, m—multiplet, br—broad. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker AM-400 (100 MHz) spectrometer, and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Optical rotations were measured on the Perkin Elmer 341 polarimeter. Melting points were determined on an XT-4 melting point apparatus, and are uncorrected. HRMS were performed on Bruker Apex II mass instrument (ESI). For chiral diastereomeric products, the diastereomeric ratios were determined by integration of suitable sets of peaks on the ^{1}H NMR (Bruker-400 MHz). ^{1}H NMR, and ^{13}C NMR data are those of the major diastereomer unless otherwise noted.

4.1. (S_R,2*S*,3*S*)-(−)-*N*-(2-*tert*-Butyldimethylsilyloxy-3,4-isopropylidenedioxy)butylidine-*tert*-butanesulfinamide (2)

To a 0.5 M solution of *R*-(+)-*tert*-butanesulfinamide (484 mg, 4.0 mmol) in dry dichloromethane were added anhydrous $CuSO_4$ (1.4 g, 8.8 mmol) and PPTS (1.0 g, 4.0 mmol) followed by the aldehyde **1** (1.2 g, 4.4 mmol). The mixture was stirred at room temperature for 36 h. The reaction mixture was filtered through a pad of Celite, and the filter cake was washed well with dichloromethane. The organic phase was combined and washed with brine, dried over Na_2SO_4. Evaporation of the solvent gave a residue which was chromatographed over silica gel to afford the *tert*-butanesulfinyl imine **2** (1.39 g, 92%) as a colorless oil. $[\alpha]_D^{20} = -129$ (*c* 1.37, $CHCl_3$); IR (KBr): 2965, 2932, 2892, 2858, 1626, 1469, 1368, 1254, 1152, 1089 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.99 (d, *J* = 3.6 Hz, 1H), 4.48 (dd, *J* = 3.6 Hz, 5.6 Hz, 1H), 4.25 (dd, *J* = 5.6 Hz, 12.4 Hz, 1H), 3.99 (dd, *J* = 6.8 Hz, 8.4 Hz, 1H), 3.86 (dd, *J* = 5.6 Hz, 8.8 Hz, 1H), 1.37 (s, 3H), 1.28 (s, 3H), 1.17 (s, 9H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.4, 109.9, 75.0, 65.2, 57.0, 26.1, 25.7, 25.0, 22.5, 18.2, −4.6, −5.0; HRMS (calcd for $C_{17}H_{35}NO_4SSiNa$) 400.1948, found 400.1944 (M+Na$^+$).

4.2. (S_R,1*R*,2*S*,3*S*)-(+)-*N*-(2-*tert*-Butyldimethylsilyloxy-1-(2-furyl)-3,4-isopropylidenedioxy)butyl-*tert*-butanesulfin-amide 3

To a solution of *n*-BuLi (2.164 M in hexane, 3.0 mmol) at −78 °C was added furan (245 mg, 3.6 mmol) in THF (5 mL), which was stirred at room temperature for 3 h. The mixture was then cooled to −78 °C, to which was added 0.5 M solution of *tert*-butanesulfinyl imine **2** (754 mg, 2.0 mmol) in anhydrous THF via syringe over 10 min. The mixture was stirred at −78 °C for 3 h and quenched with a saturated NH_4Cl solution (2 mL). The solvent was evaporated under reduced pressure and the residue was dissolved in water (10 mL), then extracted with EtOAc, dried with Na_2SO_4 and concentrated. Flash chromatography (petroleum ether/ethyl acetate, 6:1), afforded compound **3** (820 mg, 92%) as an oil. $[\alpha]_D^{20} = +11$ (*c* 1.13, $CHCl_3$); IR (KBr): 3337, 3221, 2982, 2955, 2931, 2897, 2858, 1469, 1371, 1253, 1218, 1148, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31 (d, *J* = 0.8 Hz, 1H), 6.45 (d, *J* = 3.2 Hz, 1H), 6.34 (dd, *J* = 2.0 Hz, 3.2 Hz, 1H), 4.44 (d, *J* = 9.6 Hz, 1H), 4.39 (dd, *J* = 3.2 Hz, 5.6 Hz, 1H), 4.03 (dd, *J* = 4.8 Hz, 8.4 Hz, 1H), 3.91–3.99 (m, 2H), 3.69 (t, *J* = 6.8 Hz, 1H), 1.40 (s, 3H), 1.30 (s, 3H), 1.22 (s, 9H), 0.91 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 152.9, 141.9, 110.6, 109.3, 108.9, 76.7, 74.7, 65.6, 58.5, 58.1, 26.4, 25.9, 25.5, 22.6, 18.3, −4.4, −4.5; HRMS (calcd for $C_{21}H_{40}NO_5SSi$) 446.2391, found 446.2382 ($M+H^+$).

4.3. *tert*-Butyl (1*R*,2*S*,3*S*)-1-(2-furyl)-2,3,4-trihydroxybutylcarbamate 4

The product **3** (445 mg, 1.0 mmol) was dissolved in methanol (10 mL), to which was added 4 M HCl (5 mL) in 1,4-dioxane (20 mmol). The mixture was stirred for 5 h at room temperature and then concentrated. The residue was dissolved in methanol (5 mL) and then Boc_2O (262 mg, 1.2 mmol) and Et_3N (0.3 mL, 2.5 mmol) were added into the solution successively. The mixture was stirred for 12 h at room temperature and concentrated. Flash chromatography (petroleum ether/ethyl acetate, 1.5:1), afforded compound **4** (241 mg, 84% from **3**) as a white solid. Mp: 118–120 °C; $[\alpha]_D^{20} = +63$ (*c* 0.82, MeOH); IR (KBr): 3530, 3400, 3352, 3006, 2976, 2924, 1677, 1521, 1276, 1233, 1166, 1004 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.39 (d, *J* = 0.8 Hz, 1H), 6.37 (d, *J* = 3.2 Hz, 1H), 6.35 (d, *J* = 6.0 Hz, 1H), 5.33 (d, *J* = 7.6 Hz, 1H), 4.82 (t, *J* = 8.0 Hz, 1H), 3.73–3.84 (m, 5H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.6, 151.5, 142.4, 110.5, 108.2, 80.9, 73.1, 69.9, 64.3, 51.3, 28.3; HRMS (calcd for $C_{13}H_{22}NO_6$) 288.1442, found 288.1443 ($M+H^+$).

4.4. *tert*-Butyl (1*R*,2*S*,3*S*)-4-*tert*-butyldiphenylsilyloxy-1-(2-furyl)-2,3-dihydroxybutylcarbamate 5

To a solution of *N*-Boc-aminotriol **4** (574 mg, 2.0 mmol) in CH_2Cl_2 (20 mL) were added *tert*-butyldiphenylsilyl chloride (0.57 mL, 2.2 mmol), freshly distilled Et_3N (0.31 mL, 2.0 mmol) and DMAP (10 mg, 0.06 mmol). The mixture was stirred at room temperature for 20 h. The mixture was then concentrated and water (20 mL) was added. The aqueous phase was extracted thrice with CH_2Cl_2 and twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 4:1) to give the monosilylated compound **5** (920 mg, 88%) as a colorless oil. $[\alpha]_D^{20} = +20$ (*c* 1.31, $CHCl_3$); IR (KBr): 3410, 2958, 2933, 2858, 2250, 1694, 1590, 1501, 1367, 1249, 1167, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.67 (dd, *J* = 1.6 Hz, 5.6 Hz, 4H), 7.37–7.47 (m, 7H), 6.35 (dd, *J* = 2.0 Hz, 3.2 Hz, 1H), 6.28 (d, *J* = 2.8 Hz, 1H), 5.47 (d, *J* = 6.4 Hz, 1H), 4.88 (t, *J* = 8.0 Hz, 1H), 3.95 (d, *J* = 6.8 Hz, 1H), 3.78 (br s, 3H), 1.46 (s, 9H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 142.1, 135.6, 135.5, 133.1, 133.0, 129.8, 127.8, 110.4, 107.6, 80.3, 71.7, 70.2, 65.1, 51.7, 28.3, 26.8, 19.2; HRMS (calcd for $C_{29}H_{40}NO_6Si$) 526.2619, found 526.2621 ($M+H^+$).

4.5. *tert*-Butyl (1*R*,2*S*,3*S*)-4-*tert*-butyldiphenylsilyloxy-1-(2-furyl)-2,3-isopropylidenedioxybutylcarbamate (6)

Under an inert atmosphere, to a solution of the monosilylated compound **5** (525 mg, 1.0 mmol) in freshly distilled 2,2-dimethoxypropane (13 mL/mmol) was added camphor sulfonic acid (2.5 g, 1.05 mmol). The solution was stirred at room temperature for 24 h and then hydrolyzed with a saturated aqueous solution of $NaHCO_3$. The mixture was concentrated and water (20 mL) was added. The aqueous phase was extracted with EtOAc thrice. The combined organic layers were successively washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 8:1) to give compound **6** (560 mg, 98%). $[\alpha]_D^{20} = -3$ (*c* 0.76, $CHCl_3$); IR (KBr): 3448, 3342, 3071, 2980, 2932, 2859, 1715, 1496, 1368, 1246, 1167, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.70 (dd, *J* = 7.2 Hz, 13.6 Hz, 4H), 7.35–7.47 (m, 7H), 6.34 (dd, *J* = 2.0 Hz, 3.2 Hz, 1H), 6.26 (d, *J* = 3.2 Hz, 1H), 5.05 (d, *J* = 9.2 Hz, 1H), 4.97 (br, 1H), 4.32 (t, *J* = 6.0 Hz, 1H), 4.04 (s, 1H), 3.78 (dd, *J* = 3.6 Hz, 10.8 Hz, 1H), 3.68 (dd, *J* = 4.0 Hz, 10.8 Hz, 1H), 1.42 (s, 9H), 1.40 (s, 3H), 1.30 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.0, 141.9, 135.7, 133.2, 129.8, 129.7, 127.7, 127.6, 110.3, 109.8, 107.7, 63.9, 28.3, 27.3, 27.0, 26.9, 19.2; HRMS (calcd for $C_{32}H_{44}NO_6Si$) 566.2932, found 566.2936 ($M+H^+$).

4.6. *tert*-Butyl (1*R*,2*S*,3*S*)-1-(2-furyl)-2,3-isopropylidenedioxy-4-hydroxybutylcarbamate 7

To a solution of **6** (735 mg, 1.3 mmol) in THF (5 mL) was added a 1 M solution of TBAF in THF (2.6 mL, 2.6 mmol, 2 equiv). The resulting solution was stirred for 10 h at 0 °C, quenched with saturated NH_4Cl (2 mL) and diluted with water (10 mL), extracted with Et_2O. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 5:1) to give **7** (396 mg, 93%) as a colorless oil. $[\alpha]_D^{20} = +12$ (*c* 1.14, $CHCl_3$); IR (KBr): 3449, 3334, 2982, 2934, 2250, 1701, 1504, 1370, 1248, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37 (dd, *J* = 0.8 Hz, 1.6 Hz, 1H), 6.34 (dd, *J* = 2.0 Hz, 3.2 Hz, 1H), 6.29 (d, *J* = 3.2 Hz, 1H), 5.23 (d, *J* = 8.0 Hz, 1H), 4.96 (br s, 1H), 4.19 (dd, *J* = 6.0 Hz, 8.0 Hz, 1H), 4.05 (t, *J* = 3.6 Hz, 1H), 3.77 (d, *J* = 12 Hz, 1H), 3.61 (dd, *J* = 5.6 Hz, 11.6 Hz, 1H), 2.31 (s, 1H), 1.43 (s, 9H), 1.40 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.1, 151.5, 142.0, 110.4, 109.7, 107.8, 80.2, 78.6, 78.2, 62.3, 50.5, 28.3, 28.0, 27.3, 26.7; HRMS (calcd for $C_{16}H_{25}NO_6Na$) 350.1574, found 350.1574 ($M+Na^+$).

4.7. (1*R*)-4-*O*-(Aminocarbonyl)-1-((*tert*-butoxycarbonyl)amino)-1-deoxy-1-(2-furyl)-2,3-*O*-isopropylidene-D-threitol 8

Compound **7** (196 mg, 0.6 mmol) was dissolved in CH_2C1_2 (3 mL). Pyridine (0.5 mL) followed by *p*-nitrophenylchloroformate (305 mg, 1.51 mmol) was added at 0 °C. The resulting mixture was stirred at 0 °C for 10 h. The reaction mixture was diluted with CH_2C1_2 and washed with saturated aqueous $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a pale yellow solid which was dissolved in THF (3 mL). The resulting mixture was cooled to 0 °C, and aqueous ammonia (0.5 mL) was added. After stirring for 30 min at 0 °C, the mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (petroleum ether/EtOAc, 5:1) to give pure **8** (184 mg, 83%) as an oil. $[\alpha]_D^{20} = +5$ (*c* 1.13, $CHCl_3$); IR (KBr): 3447, 3352, 2983, 2934, 2252, 1713, 1602, 1503, 1370, 1333, 1250, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37 (dd, *J* = 0.4 Hz, 1.6 Hz, 1H), 6.34 (dd, *J* = 2.0 Hz, 3.2 Hz, 1H), 6.29 (d, *J* = 3.2 Hz, 1H), 5.23 (d, *J* = 11.2 Hz, 1H), 4.99 (br, 3H), 4.09–4.21 (m, 4H), 1.44 (s, 9H), 1.40 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 256.5, 155.1, 151.3, 142.1, 110.4, 110.3, 107.8, 80.2, 79.3, 76.3, 65.2, 50.5, 29.6, 28.3, 28.2, 27.0, 26.7; HRMS (calcd for $C_{17}H_{27}N_2O_7$) 371.1813, found 371.1810 (M+H$^+$).

4.8. (3*S*,4*S*)-5-((Aminocarbonyl)oxy)-*N*-((1,1-dimethylethoxy) carbonyl)-3,4-((1-methylethylidene)dioxy)-norvaline 9 and methyl ester 10

To a well-stirred solution of $NaIO_4$ (0.351 g, 1.65 mmol) in H_2O–CCl_4–CH_3CN (3:2:3, 7.4 mL) was added $RuCl_3$ (2.8 mg, 0.013 mmol). After stirring for 15 min, the 2-furyl derivative **8** (0.1 g, 0.27 mmol) in CH_3CN (0.5 mL) was added. The color of the solution turned instantaneously from yellowish to black. Then enough $NaIO_4$ was added to restore the yellowish color. After 5 min, the mixture was diluted with water (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed successively with 20% aqueous $NaHSO_3$ until colorless and brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. This residue was taken up with saturated aqueous K_2CO_3 (10 mL), the solution was stirred for 10 min and then washed with EtOAc (2 × 15 mL). Acidification (pH 2) of the aqueous layer by addition of 2 M HCl, extracted with CH_2Cl_2 (3 × 20 mL), dried over magnesium sulfate, and evaporation of the solvent under reduced pressure gave pure **9** (82 mg, 87%) as an oil. $[\alpha]_D^{20} = -23$ (*c* 0.64, acetone); IR (KBr): 3382, 3205, 3060, 2957, 1747, 1700, 1458, 1377, 1242, 1095, 1053 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.49 (d, *J* = 8.4 Hz, 1H), 5.35–5.48 (br s, 3H), 4.67 (d, *J* = 4.4 Hz, 1H), 4.35 (s, 1H), 4.23 (d, *J* = 4.8 Hz, 2H), 4.14 (dd, *J* = 4.4 Hz, 12.4 Hz, 1H), 1.46 (s, 9H), 1.42 (s, 6H); ^{1}H NMR (400 MHz, DMSO) δ (ppm) 12.90 (br s, 1H), 7.34 (d, *J* = 9.2 Hz, 1H), 6.45–6.67 (br d, 2H), 3.98–4.22 (m, 4H), 3.79 (dd, *J* = 7.2 Hz, 11.6 Hz, 1H), 1.34 (s, 9H), 1.31 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ (ppm) 171.8, 156.4, 155.4, 109.2, 78.5, 76.4, 76.3, 64.3, 55.4, 28.1, 27.2, 26.9; HRMS (calcd for $C_{14}H_{24}N_2O_8$-Na) 371.1425, found 371.1429 (M+Na$^+$).

The acid **9** was dissolved in diethyl ether and treated with an ethereal solution of diazomethane to give the ester **10** (78 mg, 100%) as an oil. $[\alpha]_D^{20} = -28$ (*c* 0.8, CH_2Cl_2); IR (KBr): 3438, 3369, 2987, 1750, 1690, 1615, 1527, 1429, 1375 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.43 (d, *J* = 7.2 Hz, 1H), 4.95 (br s, 2H), 4.61 (d, *J* = 5.6 Hz, 1H), 4.35 (d, *J* = 6.0 Hz, 1H), 4.24–4.28 (m, 1H), 4.16 (dd, *J* = 5.2 Hz, 11.2 Hz, 1H), 4.03 (dd, *J* = 4.0 Hz, 8.0 Hz, 1H), 3.79 (s, 3H), 1.45 (s, 9H), 1.40 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.0, 156.2, 155.1, 110.5, 80.4, 79.8, 75.7, 64.9, 55.1, 52.5, 28.3, 27.0, 26.8; HRMS (calcd for $C_{15}H_{26}N_2O_8$-Na) 385.1581, found 385.1582 (M+Na$^+$).

4.9. 5-*O*-Carbamoyl-2-*epi*-polyoxamic acid 11

Compound **9** (150 mg, 0.43 mmol) was dissolved in 3 mL of cold MeOH–trifluoroacetic acid (v/v, 1:10) and the solution was stirred for 1.5 h at room temperature. Then the solvent was evaporated under reduced pressure below 30 °C. The residue was dissolved in 1 mL of EtOH and propylene oxide (5 mL) was added slowly. The white solid started to precipitate, which was collected by filtration to give **11** in the yield of 62%. Mp: 78–82 °C; $[\alpha]_D^{20} = +0.7$ (*c* 0.64, H_2O); ^{1}H NMR (400 MHz, D_2O) δ (ppm) 4.13 (s, 1H), 4.06–4.08 (m, 2H), 3.95–3.99 (m, 2H); ^{1}H NMR (400 MHz, DMSO) δ (ppm) 7.49 (br s, 2H), 6.48 (br s, 2H), 3.89 (d, *J* = 6.0 Hz, 1H), 3.74–3.78 (m, 1H), 3.42 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ (ppm) 157.2, 69.6, 69.2, 65.3, 56.9; HRMS (calcd for $C_6H_{13}N_2O_6$) 209.0768, found 209.0733 (M+H$^+$).

4.10. Peptide derivative 13

To a stirred solution of **9** (90 mg, 0.26 mmol) and **12** (100 mg, 0.25 mmol) in DMF (3 mL) were sequentially added BOP reagent (200 mg, 0.48 mmol) and diisopropylethylamine (0.13 mL, 0.75 mmol). The resulting mixture was stirred at 23 °C for 18 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (chloroform/methanol, 30:1) to furnish the coupling product **13** (115 mg, 63%) as a white foam. Mp: 124–125 °C; $[\alpha]_D^{20} = +7$ (*c* 0.84, $CHCl_3$); IR (KBr): 3301, 2983, 1748, 1697, 1373, 1243, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.38 (br s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.13 (s, 1H), 5.84 (d, *J* = 7.2 Hz, 1H), 5.58 (d, *J* = 7.6 Hz, 1H), 5.48 (s, 1H), 5.30 (d, *J* = 5.2 Hz, 1H), 5.12 (br s, 3H), 4.40–4.47 (m, 2H), 4.34 (br s, 1H), 4.30 (d, *J* = 12 Hz, 1H), 4.08–4.13 (m, 1H), 4.03 (t, *J* = 7.2 Hz, 1H), 3.78 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 1.91 (s, 3H), 1.43 (s, 12H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.1, 169.7, 169.6, 168.8, 163.6, 156.7, 155.8, 150.4, 136.1, 111.8, 110.3, 88.0, 81.5, 80.7, 72.4, 69.2, 64.5, 60.4, 56.2, 53.1, 52.9, 28.2, 26.8, 26.7, 21.0, 20.4, 14.2, 12.4; HRMS (calcd for $C_{30}H_{44}N_5O_{16}$) 730.2778, found: 730.2789 (M+H$^+$).

4.11. Methyl 5-((Benzyloxycarbonyl)amino)-5-deoxy-1,2,3-tri-*O*-acetyl-D-*allo*-hexofuranuronate 15

The crude amine **12** (400 mg, 1.0 mmol) was dissolved in dioxane (10 mL) and the solution was treated with 7% aqueous $NaHCO_3$ (5 mL). After stirring for 20 min at 0 °C, the reaction mixture was treated with benzyl chloroformate (0.16 mL, 1.1 mmol) and was stirred for 12 h at ambient temperature. Then water (15 mL) was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over magnesium sulfate, and the solvent was removed in vacuo. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 1:2.5) to give pure **15** (530 mg, quantitative) as colorless oil. $[\alpha]_D^{20} = +16$ (*c* 0.85, CH_2Cl_2); IR (KBr): 3299, 3065, 1750, 1696, 1239 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.14 (br s, 1H), 7.27–7.37 (m, 5H), 7.03 (s, 1H), 5.92 (d, *J* = 5.6 Hz, 2H), 5.51 (t, *J* = 5.6 Hz, 1H), 5.26 (t, *J* = 6.0 Hz, 1H), 5.10 (s, 2H), 4.82 (d, *J* = 3.9 Hz, 1H), 4.38 (t, *J* = 4.4 Hz, 1H), 3.78 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.6, 169.5, 169.3, 163.3, 156.0, 135.8, 135.5, 128.5, 128.3, 128.1, 112.0, 87.5, 81.9, 77.2, 72.3, 69.7, 67.4, 60.3, 55.1, 52.9, 20.3, 12.4; HRMS (calcd for $C_{24}H_{31}N_4O_{11}$) 551.1989, found 551.1984 (M+NH_4^+).

4.12. Thymine polyoxin C 16

To a solution of **15** (88.7 mg, 0.166 mmol) in THF (8 mL) and H_2O (1.5 mL) at 0 °C was added solid LiOH·H_2O (24 mg, 0.57 mmol). The resulting yellow solution was stirred at 0 °C until the TLC (5:4:1 $CHC1_3$/MeOH/H_2O) showed the starting material disappeared. The mixture was diluted with H_2O (10 mL) and extracted with CH_2C1_2 (3 × 20 mL) to remove any nonacidic material, and the resulting basic solution was cooled to 0 °C and acidified to pH 2–3 with 1 N HC1. This mixture was extracted with EtOAc (6 × 20 mL), and all organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow solid. The solid was dissolved in MeOH (4.5 mL) and 5% Pd/C (33 mg) was added to the solution. The black suspension was stirred under H_2 atm for 4 h when the TLC (5:4:1 $CHC1_3$/MeOH/H_2O) showed complete consume of starting material (R_f, 0.51). The reaction mixture was filtered through a pad of Celite bed eluting with hot H_2O (3 × 10 mL), and the filtrate was concentrated in vacuo to give **16** as a yellow solid (20.8 mg, 54% yield). Mp: 184–186 °C; $[\alpha]_D^{20} = +9$ (*c* 0.47, H_2O); IR (KBr): 3579, 3419, 3336, 1712, 1681, 1674, 1609 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ (ppm) 7.43 (s, 1H), 5.77 (d, *J* = 5.2 Hz, 1H), 4.55 (t, *J* = 5.6 Hz, 1H), 4.26–4.31 (m, 2H), 4.05 (dd, *J* = 2.4 Hz, 5.6 Hz, 1H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, D_2O) δ (ppm) 168.5, 156.0, 150.2, 137.0, 110.7, 88.5, 80.6, 71.8, 68.0, 54.3, 11.5.

4.13. Peptide derivative 18

To a cooled (0 °C) solution of **9** (20.7 mg, 0.059 mmol) in EtOAc (7 mL) were added DCC (11.7 mg, 0.059 mmol) and *N*-hydroxysuccinimide (6.85 mg, 0.059 mmol). The mixture was stirred at 0 °C for 8 h and then the solvent was evaporated under reduced pressure. The crude **17** was dissolved in DMSO (3 mL), and the solution was treated with **16** (18 mg, 0.06 mmol) and diisopropylethylamine (0.01 mL, 0.06 mmol). The reaction mixture was stirred at ambient temperature for 24 h. The mixture was directly chromatographed on silica gel ($CHCl_3$/MeOH/H_2O, 5:2:0.5) to give the product **18** (21 mg, 58%) as a white solid.

Mp: 195–200 °C; $[\alpha]_D^{20} = -0.6$ (*c* 0.71, MeOH); IR (KBr): 3437, 1700, 1523 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ (ppm) 7.47 (d, *J* = 0.8 Hz, 1H), 5.85 (d, *J* = 6.4 Hz, 1H), 4.57 (d, *J* = 3.2 Hz, 1H), 4.43 (br s, 1H), 4.25–4.33 (m, 4H), 4.15–4.19 (m, 2H), 4.06 (d, *J* = 12.4 Hz, 1H), 1.88 (s, 3H), 1.39 (s, 3H), 1.38 (s, 9H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, D_2O) δ (ppm) 173.4, 170.4, 166.3, 158.7, 157.0, 151.9, 137.4, 111.5, 110.8, 87.2, 85.1, 81.8, 76.9, 75.9, 73.1, 69.4, 63.9, 62.5, 56.1, 48.8, 27.4, 25.9, 25.7, 11.7; HRMS (calcd for $C_{25}H_{38}N_5O_{14}$) 632.2410, found: 632.2403 ($M+H^+$).

4.14. 2″-*Epi*-polyoxin J 14

A solution of **18** (13 mg, 0.022 mmol) in 2:1 trifluoroacetic acid–water (3 mL) was stirred at 0 °C for 2 h. The solvent was evaporated under reduced pressure below 40 °C. The brownish solid residue was purified by column chromatography ($CHCl_3$/MeOH/H_2O, 5:4:1) to give pure 2″-*epi*-polyoxin J **14** (8 mg, 80%) as a white solid.

Mp: 165–170 °C; $[\alpha]_D^{20} = +1.1$ (*c* 0.61, H_2O); IR (KBr): 3431, 2990, 1710 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ (ppm) 7.51 (d, *J* = 0.8 Hz, 1H), 5.82 (d, *J* = 5.6 Hz, 1H), 4.55 (d, *J* = 3.6 Hz, 1H), 4.47 (t, *J* = 5.2 Hz, 1H), 4.31 (d, *J* = 5.6 Hz, 1H), 4.21–4.26 (m, 2H), 4.15 (dd, *J* = 2.0 Hz, 5.6 Hz, 1H), 4.05–4.09 (m, 2H), 3.92–3.96 (m, 1H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, D_2O) δ (ppm) 166.5, 166.3, 158.8, 151.8, 137.5, 111.7, 88.5, 83.6, 72.8, 70.9, 68.5, 67.5, 65.2, 62.5, 56.3, 48.8, 11.5; HRMS (calcd for $C_{17}H_{26}N_5O_{12}$) 492.1572, found: 492.1576 ($M+H^+$).

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