Total Synthesis of (+)-Polyoxin J†

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Stereoselective total synthesis of (+)-polyoxin J is described. The synthesis was achieved in a convergent manner by coupling protected thymine polyoxin C (**19**) and 5-*O*-carbamoyl polyoxamic acid **27** and subsequent removal of the protecting groups. The key steps of the synthesis of protected thymine polyoxin C involved the stereoselective electrophilic epoxidation of *E*-allyl alcohol **7** derived from isopropylidene D-ribose derivative **5**, followed by regioselective epoxide opening of **8** and conversion of resulting azido diol **9** to protected thymine polyoxin C (**19**). Protected polyoxamic acid **27** was synthesized stereoselectively by utilizing Sharpless epoxidation of tartrate-derived allylic alcohol **20** followed by a regioselective epoxide ring opening with diisopropoxytitanium diazide.

Polyoxins are an important class of peptidyl nucleosides isolated from the culture broth of *Streptomyces cacoi*.[1] The characteristic structural feature of polyoxins include a peptide linkage between the nucleoside α-amino acid and polyhydroxynorvaline. The main difference among polyoxins is the substituent in the pyrimidine bases.[2] For example, polyoxin J (**1**) is comprised of thymine polyoxin C and 5-*O*-carbamoyl polyoxamic acid. Polyoxin J and other members of the polyoxin family exhibit potent antifungal properties.[3] These biological activities of polyoxins are linked to inhibition of the enzyme chitin synthetase which catalyzes the biosynthesis of chitin, an integral constituent of the fungal cell wall.[4]

Polyoxins have exhibited high inhibitory potencies against isolated chitin synthetase from the medically important human pathogen *Candida albicans*; however, against whole cells polyoxins are inactive.[5] Either the inability of polyoxins to penetrate cells or the intracellular cleavage of polyoxins to polyoxin C may be responsible for this imparity.[6] Thus, structural modifications and biology of polyoxins became the subject of much interest over the years.[7−9] Since the first synthesis of polyoxin J by Kuzuhara and co-workers,[8f] in 1973, four other recent syntheses of polyoxin J have appeared in the literature.[8a−e] Early syntheses of amino acid nucleosides were reported by Moffatt et al. and Naka et al.[7h,i] Baltas et al. and Vogel et al. reported the synthesis of polyoxin C from noncarbohydrate precursors.[7a,c] Garner and co-workers have developed an important strategy to polyoxin C and other glycosyl α-amino acids from D-serinal.[7d] Barrett and Lebold have reported the synthesis of polyoxin C by a nitro olefin based strategy.[7e] Dondoni et al. have reported a very efficient synthesis of polyoxin C as well as polyoxamic acid by application of sugar nitrone chemistry.[8b,c,9h] For the synthesis of polyoxamic acid, Harwood and Robertson have utilized a diastereoselective cyclocondensation of chiral azomethine ylide and (*S*)-isopropylideneglyceraldehyde.[9a] Trost et al. have recently reported a novel asymmetric synthesis by deracemization of vinyl epoxide utilizing Pd-based chiral catalyst.[9b] Marshall et al. have synthesized polyoxamic acid by stereoselective allyl stannane addition to α-amino aldehyde.[9d] Saksena and co-workers have utilized Overman−Claisen rearrangement of L-tartrate-derived imi-

† In memory of Professor P. C. Rakhshit (1910−1998), an exemplary teacher, scholar, and philanthropist.

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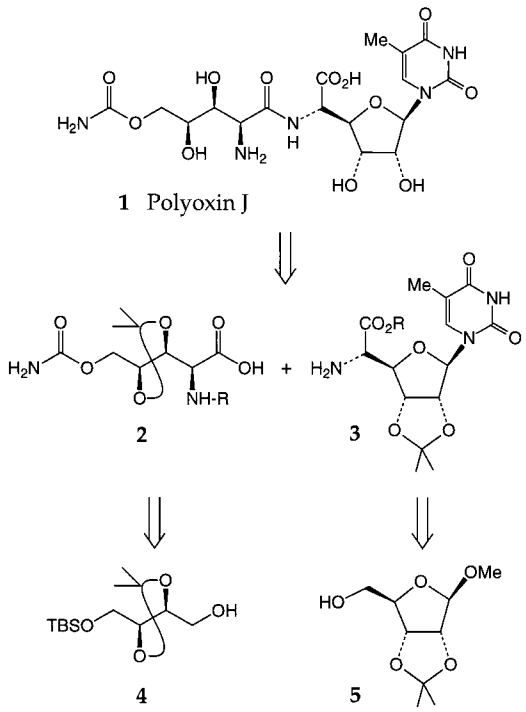


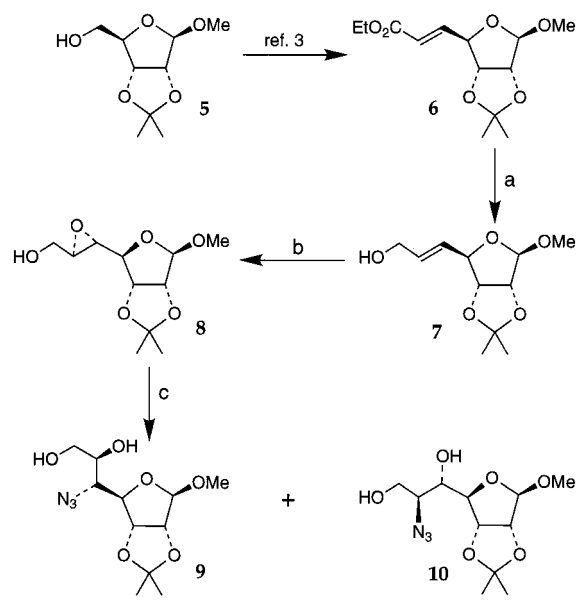
Figure 1.

date for the synthesis of polyoxamic acid.[9k] A number of other polyoxamic acid syntheses have also been reported utilizing L-tartaric acid.[9] As part of our interest in bioactive amino acid nucleosides, we recently reported a stereoselective synthesis of the antifungal nucleoside, sinefungin.[10] We have also developed highly stereoselective methodologies for the synthesis of polyoxin C by utilizing [2,3]-Wittig rearrangement reaction.[11] We now report a stereoselective and convergent total synthesis of (+)-polyoxin J. The key steps involve the stereoselective electrophilic epoxidation of ribose-derived allylic alcohol for the synthesis of thymine polyoxin C and a Sharpless epoxidation of the tartrate-derived allylic alcohol followed by a regioselective opening of epoxide ring for the synthesis of protected *O*-carbamoyl polyoxamic acid.

Results and Discussion

Our synthetic plan for polyoxin J is based upon coupling of protected *O*-carbamoyl polyoxamic acid **2** and polyoxin C (**3**) followed by removal of the protecting groups as outlined in Figure 1. Protected polyoxamic acid and thymine polyoxin C could be synthesized stereoselectively from the known[12] protected tartrate derivative **4** and known[13] methyl glycoside **5**, respectively. Thus, methyl glycoside **5** was readily converted to *trans*-α,*β*-unsaturated ester **6** as described previously.[10] DIBAL reduction of **6** in CH_2Cl_2 at −78 °C provided the *trans*-allylic alcohol **7** (Scheme 1). Epoxidation of **7** with *m*-CPBA in CH_2Cl_2 at 23 °C for 12 h in the presence of $NaHCO_3$ provided a single *syn* epoxide **8** in 95% yield

Scheme 1[a]



[a] Key: (a) DIBAL, CH_2Cl_2, −78 °C, 2 h (92%); (b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 23 °C, 12 h (95%); (c) $Ti(iPrO)_2(N_3)_2$, PhH, 75 °C, 15 min; (79%).

after silica gel chromatography. Stereochemical assignment of epoxide **8** was established based upon exposure of the allylic alcohol **7** to Sharpless epoxidation with (−)-diethyl D-tartrate at −22 °C for 12 h which has also provided the same *syn* epoxide **8** (77%).[14] This experiment also provided evidence that no acid-catalyzed α/*β* equilibration of the anomeric center was occurring during the *m*-CPBA epoxidation of **7**. Further evidence of this stereochemical assignment was provided after the epoxide **8** was converted to known[7e] methyl ester **16** as well as (+)-polyoxin J. To incorporate the C-5 amine functionality, epoxide **8** was subjected to regioselective epoxide opening with diisopropoxytitanium diazide in benzene at 75 °C for 15 min, as described by Sharpless and co-workers.[15] Azido diols **9** and **10** were obtained in 79% yield as a mixture (3.7:1) of isomers under the reaction conditions. These isomers were separated by silica gel chromatography.

The remarkable diastereofacial selectivity in the *m*-chloroperoxybenzoic acid (*m*-CPBA) epoxidation of allyl alcohol **7** warrants some special notes. As shown in Scheme 2, *m*-CPBA epoxidation of *cis* alcohol **11** afforded the diastereomeric mixture (55:45 mixture by 400 MHz ^{1}H NMR) of epoxides **12** with little selectivity. Furthermore, protection of the allylic alcohol **7** as *tert*-butyldimethylsilyl ether and subsequent epoxidation with *m*-CPBA resulted in epoxide **14** with little to no selectivity (53:47 mixture by 400 MHz ^{1}H NMR). These results suggest that the *trans*-allylic hydroxyl group is effectively involved in directing the *m*-CPBA epoxidation event. A highly organized transition state model **15** as depicted in Figure 2 may explain the high degree of diastereoselection associated with the current *m*-CPBA epoxidation of the allylic alcohol **7**.[16] In this model, *m*-CPBA is coordinated with the allylic hydroxyl group as well as the

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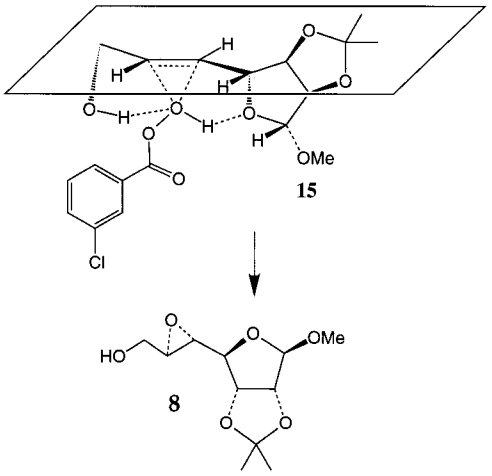
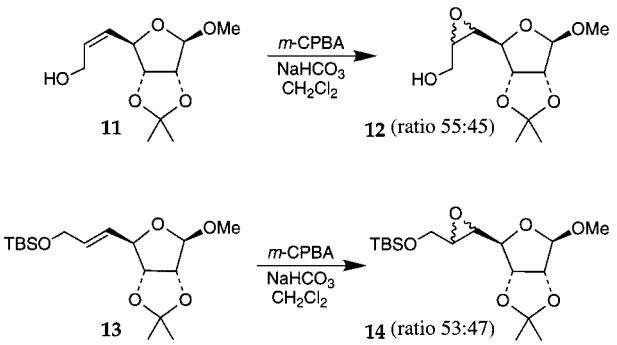


Figure 2.

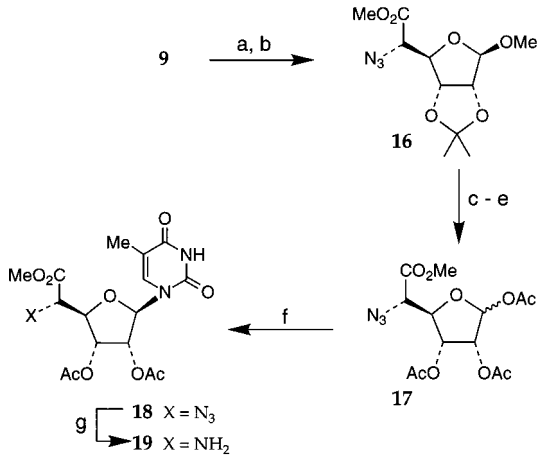
ribo furanoside ring oxygen. The *cis* alcohol **11**, on the other hand, cannot adopt such transition state geometry because of the developing nonbonded interaction between the ribo furanoside ring and the hydroxymethyl group. While the current model explains the present stereoselection, the evidence of such a model requires further experimentation which is currently in progress.

Scheme 2



To convert the azido diol **9** to the protected thymine polyoxin C, treatment of **9** with periodic acid in the presence of a catalytic amount of ruthenium trichloride in a mixture of aqueous acetonitrile and carbon tetrachloride followed by reaction of the resulting acid with methyl iodide and potassium bicarbonate in DMF afforded the azido methyl ester **16** in 80% yield after silica gel chromatography.[17] It is important to note that the use of sodium periodate in place of periodic acid resulted in a 10−15% epimerization of the C-5 stereocenter. To insert the thymine at the anomeric center, **16** was converted to triacetate **17** in a three-step sequence involving (1) removal of the isopropylidene group with Dowex 50W H^+ in methanol, (2) acetylation of the resulting diol with acetic anhydride in pyridine in the presence of a catalytic amount of DMAP, and (3) acetal exchange by treatment with acetic anhydride and a

Scheme 3[a]



[a] Key: (a) $RuCl_3$ (cat.), H_5IO_6, MeCN−CCl_4−H_2O, 23 °C, 2 h; (b) MeI, $KHCO_3$, DMF, 12 h (80%); (c) Dowex 50W, MeOH, 65 °C, 12 h; (d) Ac_2O, Py, DMAP (cat.), 23 °C, 4 h; (e) Ac_2O, AcOH, CH_2Cl_2, H_2SO_4 (cat.), 0 °C to 23 °C, 2 h (79% from **16**); (f) Thymine-bis-TMS, TMSOTf, $Cl(CH_2)_2Cl$, 84 °C, 1 h (91%); (g) H_2, 10% Pd−C, MeOH, 2 h (98%).

catalytic amount of concentrated sulfuric acid in a mixture of glacial acetic acid and CH_2Cl_2 at 0 °C to 23 °C for 2 h (79% from **16**, 2:1 mixture of anomers).[11] Exposure of the triacetate **17** to Vorbrüggen reaction conditions[18] with 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine in the presence of TMSOTf in dichloroethane at 84 °C for 1 h afforded the protected β-nucleoside **18** in 91% yield after silica gel chromatography. Catalytic hydrogenation of the azide **18** over 10% Pd−C in methanol furnished the unstable amine **19** in near quantitative yield. The amine **19** was used immediately for the next reaction without further purification.

The synthesis of protected 5-*O*-carbamoyl polyoxamic acid **27** was carried out with the known allylic alcohol **20** derived from protected dimethyl L-tartrate.[19] As outlined in Scheme 4, exposure of the allylic alcohol **20** to Sharpless asymmetric epoxidation conditions with diethyl D-tartrate provided exclusively the *anti* epoxide **21** in 77% yield after silica gel chromatography.[14] It should be noted that in contrast to epoxidation of ribose derived allylic alcohol **7**, the epoxidation of **20** with *m*-CPBA at 0 °C resulted in a 65:35 mixture of *anti*/*syn* diastereomers. Epoxide **21** was then subjected to regioselective ring opening with diisopropoxytitanium diazide in benzene at 72 °C, as described by Sharpless and coworkers,[15] to afford the azido diols **22a** and **22b** as a 3:1 mixture which were inseparable by silica gel chromatography. However, catalytic hydrogenation of the mixture in the presence of BOC_2O afforded the corresponding BOC derivatives **23** and **24** which were easily separated by silica gel chromatography.[20] Attempted opening of epoxide **21** under a variety of reaction conditions did not improve the mixture ratio of the azido diols **22a** and **22b**.[21] Thus, the desired BOC derivative **23** was obtained

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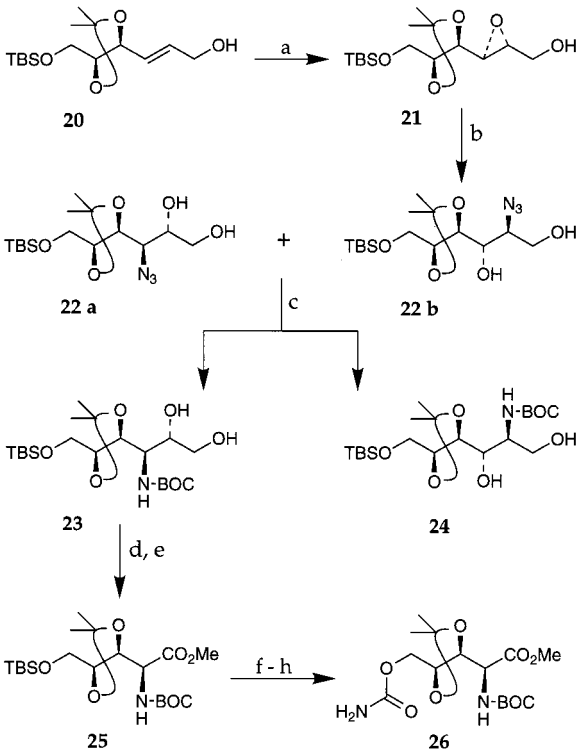
(21) Treatment of epoxide **21** with dimethoxytitanium diazide (prepared in situ) in benzene at 70 °C resulted in the azido diols **22a** and **22b** as a 1:1 mixture (yield 90%).

Scheme 4[a]



[a] Key: (a) *t*-BuOOH, (−)-DET, Ti(O*i*Pr)$_4$, −23 °C, 24 h (77%); (b) Ti(O*i*Pr)$_2$(N$_3$)$_2$, PhH, 72 °C, 15 min; (3:1 mixture, 96%); (c) H_2, 10% Pd−C, BOC_2O, EtOAc, 12 h (60% of **23** from **21**); (d) $RuCl_3$ (cat.), $NaIO_4$, acetone−H_2O (2:1), 12 h; (e) CH_2N_2, Et_2O, 0 °C (64%); (f) AcOH−THF−H_2O (3:1:1), 23 °C, 12 h; (g) *p*-NO_2-Ph-OCOCl, Py, 0 °C; (h) NH_4OH, THF, 0 °C, 30 min (85% from **25**).

in 60% yield in a two-step sequence. Subsequent conversion of **23** to methyl ester **25** was accomplished by treatment of the diol **23** with a catalytic amount of ruthenium trichloride in the presence of an excess of sodium periodate at 23 °C for 12 h followed by treatment of the resulting acid with diazomethane at 0 °C to provide the methyl ester **25** in 64% yield. The removal of the silyl group of **25** with aqueous acetic acid at 23 °C for 12 h followed by known carbamoylation furnished the BOC-protected carbamoylpolyoxamic acid ester **26** in 85% yield after chromatography.[22,8e]

To complete the synthesis of polyoxin J, methyl ester **26** was first selectively hydrolyzed with aqueous lithium hydroxide at 0 °C for 2 h (Scheme 5). The resulting carbamoylpolyoxamic acid **27** was then coupled with the protected thymine polyoxin C (**19**) in the presence of BOP reagent[23] and diisopropylethylamine to furnish the peptide derivative **28** in 63% yield. Selective ester hydrolysis with aqueous lithium hydroxide followed by removal of the BOC and isopropylidene groups by treatment with trifluoroacetic acid at 0 °C for 2 h afforded the synthetic (+)-polyoxin J (**1**) ([α]$^{23}_D$ +29, *c* 0.14, H_2O; lit.[8b] [α]$^{23}_D$ +30, *c* 0.10, H_2O) in 53% yield after silica gel chromatography. The spectroscopic data (^{1}H and ^{13}C NMR) of the synthetic (+)-polyoxin J (**1**) is in full agreement with the spectra of both natural and synthetic (+)-polyoxin J kindly provided by Professor Alessandro Dondoni.

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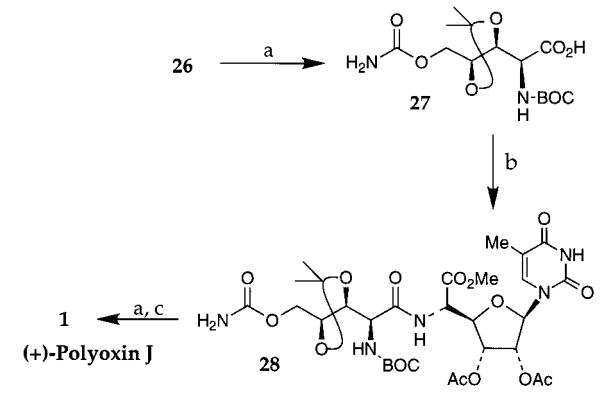
Scheme 5[a]



[a] Key: (a) LiOH, THF−H_2O, 0 °C, 2 h (b) **19**, BOP, *i*Pr$_2$NEt, DMF, 23 °C, 12 h (63%); (c) CF_3CO_2H, 0 °C, 2 h (53%).

Conclusion

A stereoselective total synthesis of (+)-polyoxin J has been accomplished. The key components of the synthesis were protected thymine polyoxin C (**19**) and 5-*O*-carbamoyl polyoxamic acid **27** which were synthesized from D-ribose and dimethyl L-tartrate, respectively. The key steps of the synthesis of protected thymine polyoxin C involved the diastereoselective electrophilic epoxidation of *E*-allyl alcohol **7** derived from isopropylidene D-ribose derivative **5** with *m*-CPBA, followed by regioselective epoxide opening of **8** with diisopropoxytitanium diazide. The protected 5-*O*-carbamoyl polyoxamic acid **27** was stereoselectively synthesized by Sharpless epoxidation of L-tartrate derived allylic alcohol followed by a regioselective epoxide ring opening with diisopropoxytitanium diazide. While the regiochemical control of epoxide opening was somewhat less satisfactory, the synthesis was accomplished with complete control of stereochemistry. The current synthesis is flexible and therefore provides a convenient access to the synthesis of various (+)-polyoxin J analogues for biological evaluation.

Experimental Section

All melting points were recorded and uncorrected. Anhydrous solvents were obtained as follows: dichloromethane was refluxed over P_2O_5 for 2 h, followed by distillation; 1,2-dichloroethane, distillation from P_2O_5; trimethylchlorosilane, pyridine and benzene, distillation from CaH_2. All other solvents were HPLC grade. Column chromatography was performed with Whatman 240−400 mesh silica gel under low pressure of 5−10 psi. Thin-layer chromatography (TLC) was carried out with E. Merck silica gel 60 F-254 plates.

Methyl (*E*)-5,6-Dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hept-5-enofuranoside (7). To a stirred solution of ester **6** (1.7 g, 6.24 mmol) in CH_2Cl_2 (10 mL) was added diisobutyl aluminum hydride (1 M in hexane, 19 mL, 19 mmol) at −78 °C. The resulting mixture was stirred for 2 h at −78 °C and then carefully quenched with water (3 mL). The mixture was allowed to warm to 23 °C. The mixture was filtered through a glass wool plug, and the solid residue was rinsed several times with CH_2Cl_2 and water. The filtrate was transferred into a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue which was purified on a silica gel column (50% ethyl acetate/hexane) to afford **7** as a colorless oil (1.33 g, 92%): [α]$^{23}_D$ −42.2 (*c* 0.83, $CHCl_3$); IR ($CHCl_3$) 3423, 2950, 2930, 1630, 1374, 1088 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (m, 2H), 4.98 (s, 1H), 4.66 (d, 1H, *J* = 8.2 Hz), 4.61 (s, 2H), 4.15 (t, 1H, *J* = 5.4 Hz),

3.34 (s, 3H), 1.49 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.4, 130.4, 112.3, 109.3, 87.4, 85.4, 84.5, 62.6, 54.7, 26.4, 24.9; MS (CI) *m*/*z* 230 (M^+), 215, 198, 155, 141, 112, 93. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.34; H, 7.92.

Methyl (5*S*,6*S*)-5,6-Epoxy-2,3-*O*-isopropylidene-β-D-*ribo*-heptanofuranoside (8). To a stirred solution of alcohol **7** (1.29 g, 5.61 mmol) in CH_2Cl_2 (10 mL) were added *m*-CPBA (1.21 g, 8.41 mmol) and $NaHCO_3$ (700 mg, 8.33 mmol). The resulting mixture was stirred at 23 °C for 12 h. After this period, the solvent was removed under reduced pressure, and the residue was diluted with ethyl acetate (20 mL) and water (10 mL). The layers were separated, and the organic layer was washed with aqueous $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvents gave a residue which was chromatographed over silica gel (40% ethyl acetate/hexane) to furnish the epoxide **8** as a colorless oil (1.31 g, 95%): $[\alpha]^{23}_D$ −30.5 (*c* 1.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (s, 1H), 4.67 (d, 1H, *J* = 5.9 Hz), 4.58 (d, 1H, *J* = 5.9 Hz), 4.04 (d, 1H, *J* = 7.1 Hz), 3.91 (dd, 1H, *J* = 2.4, 12.7 Hz), 3.64 (dd, 1H, *J* = 4.2, 12.7 Hz), 3.39 (s, 3H), 3.11 (dd, 1H, *J* = 2.2, 7.1 Hz), 3.03 (ddd, 1H, *J* = 2.2, 2.4, 4.2 Hz), 1.46 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.6, 109.3, 87.0, 85.1, 81.2, 60.8, 56.1, 55.7, 54.9, 26.3, 24.8; MS (CI) *m*/*z* 247 (M^+ + H), 231, 215. Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.60; H, 7.37. Found: C, 53.21; H, 7.63.

Methyl (5*R*,6*R*)-5-Azido-5-deoxy-2,3-*O*-isopropylidene-β-D-*ribo*-heptanofuranoside (9). To a stirred solution of Ti(O*i*Pr)$_4$ (0.37 mL, 1.23 mmol) in benzene (5 mL) was added $TMSN_3$ (0.33 mL, 2.46 mmol), and the resulting mixture was heated at 75 °C for 5 h. After this period, a solution of **8** (202 mg, 0.82 mmol) in benzene (2 mL) was added at 75 °C. The resulting mixture was stirred for 15 min, and then the mixture was cooled to 23 °C. Benzene was removed under reduced pressure, the residue was diluted with THF (10 mL), and 5% aqueous citric acid (10 mL) was added. The resulting mixture was stirred for 2 h, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue which was chromatographed over silica gel (40% ethyl acetate/hexane) to furnish the azido diols **9** (155 mg, 63%) and **10** (39 mg, 16%) as colorless oils. Major azido diol **9**: $[\alpha]^{23}_D$ −28.8 (*c* 0.57, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (s, 1H), 4.83 (dd, 1H, *J* = 1.4, 5.9 Hz), 4.61 (d, 1H, *J* = 5.9 Hz), 4.18 (dd, 1H, *J* = 1.4, 8.3 Hz), 3.92 (m, 1H), 3.75−3.85 (m, 2H), 3.61 (dd, 1H, *J* = 5.9, 8.3 Hz), 3.42 (s, 3H), 1.48 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.9, 110.3, 86.6, 84.7, 81.9, 72.2, 64.7, 62.7, 56.2, 26.4, 24.8. Anal. Calcd for $C_{11}H_{19}N_3O_6$: C, 45.67; H, 6.62. Found C, 45.61; H, 6.36. Minor azido diol **10**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.02 (s, 1H), 4.84 (d, 1H, *J* = 6.0 Hz), 4.70 (s, 1H), 4.58 (d, 1H, *J* = 6.0 Hz), 3.80−4.05 (m, 4H), 3.48 (s, 3H), 1.50 (s, 3H), 1.32 (s, 3H).

Methyl (Methyl 5-azido-5-deoxy-2,3-*O*-isopropylidene-β-D-allofuranosid)uronate (16). To a stirred solution of the azido diol **9** (448 mg, 1.55 mmol) in a mixture (2:2:3) of MeCN−CCl_4−H_2O (7 mL) were added H_5IO_6 (1.41 g, 6.2 mmol) and $RuCl_3$ (5 mg). The resulting suspension was stirred for 2 h at 23 °C. After this period, CH_2Cl_2 (10 mL) followed by water (10 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvents gave the crude acid which was dissolved in DMF (2 mL), and methyl iodide (0.2 mL, 3.1 mmol) followed by $KHCO_3$ (310 mg, 3.1 mmol) was added. The reaction mixture was stirred at 23 °C for 12 h. The reaction mixture was then diluted with ethyl acetate (100 mL), and the organic layer was washed with saturated aqueous ammonium chloride and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvents gave a residue which was chromatographed over silica gel (10% ethyl acetate/hexane) to afford the ester **16** as a colorless oil (356 mg, 80%): $[\alpha]^{23}_D$ −52.2 (*c* 1.62, $CHCl_3$); lit.[7d] $[\alpha]^{23}_D$ −55.3 (*c* 0.89, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (s, 1H), 4.86 (dd, 1H, *J* = 0.8, 5.9 Hz), 4.59 (d, 1H, *J* = 5.9 Hz), 4.44 (dd, 1H, *J* = 0.8, 8.8 Hz), 3.83 (s, 3H), 3.81 (d, 1H, *J* = 8.8 Hz), 3.33 (s, 3H), 1.48 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 112.8, 110.2, 86.2, 85.0, 81.6, 63.3, 55.7, 52.7, 26.4, 24.9.

Methyl (5-Azido-5-deoxy-1,2,3-tri-*O*-acetyl-D-allofuranosid)uronate (17). To a stirred solution of the azide **16** (206 mg, 0.72 mmol) in MeOH (8 mL) was added Dowex 50 W H^+ resin (1 g). The resulting mixture was heated at reflux at 65 °C for 12 h. The resin was filtered off, and the filter cake was washed with MeOH. The filtrate was evaporated to give a residue which was dissolved in CH_2Cl_2 (3 mL), and pyridine (1 mL), DMAP (5 mg), and Ac_2O (0.25 mL) were added. The resulting mixture was stirred at 23 °C for for 4 h. After this period, the mixture was diluted with CH_2Cl_2 (10 mL) and washed with 1 M aqueous $NaHSO_4$ solution and brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and to a stirred solution of the residue in CH_2Cl_2 (1 mL) at 0 °C were added AcOH (1 mL), Ac_2O (0.5 mL), and 1 drop of concentrated H_2SO_4. The resulting mixture was stirred at 0 °C for 1 h and then at 23 °C for an additional 1 h. The mixture was poured onto ice and allowed to stir for 30 min. The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layer was washed with water and saturated aqueous $NaHCO_3$ and dried over anhydrous Na_2SO_4. Evaporation of the solvent furnished a residue which was chromatographed over silica gel (33% ethyl acetate/hexane) to afford the triacetate **17** (205 mg, 79%) as an oil (α/β = 1/2, by 400 MHz ^{1}H NMR): β anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (s, 1H), 5.53 (dd, 1H, *J* = 4.8, 7.2 Hz), 5.36 (d, 1H, *J* = 4.8 Hz), 4.60 (dd, 1H, *J* = 4.4, 7.2 Hz), 4.33 (d, 1H, *J* = 4.4 Hz), 3.80 (s, 3H), 2.12 (s, 6H), 2.08 (s, 3H); α anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (d, 1H, *J* = 4.4 Hz), 5.33 (dd, 1H, *J* = 4.8, 7.2 Hz), 5.22 (dd, 1H, *J* = 4.8, 6.8 Hz), 4.62 (t, 1H, *J* = 2.8 Hz), 4.40 (d, 1H, *J* = 3 Hz), 3.83 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H).

Methyl 2,3-Di-*O*-acetyl-5-azido-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-β-D-allofuranuronate (18). To a stirred suspension of thymine (190 mg, 1.5 mmol) in hexamethyldisilazane (4.5 mL) at 23 °C was added trimethylchlorosilane (0.3 mL) and the resulting mixture was heated at 120 °C for 2 h under nitrogen atmosphere. The reaction mixture was cooled to 23 °C, and the solvent was removed under reduced pressure to give the crude bis-silylated thymine. To the above residue, dry dichloroethane (4 mL) followed by a solution of triacetate **17** (205 mg, 0.57 mmol) in 2 mL dichloroethane was added. TMSOTf (0.31 mL, 1.71 mmol) was then added, and the resulting mixture was heated at 84 °C for 1 h. After this period, the reaction mixture was cooled to 23 °C and quenched with saturated aqueous $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated to a residue. Silica gel chromatography (2% MeOH/CH_2Cl_2) of the residue furnished **18** as a pale brown foam (221 mg, 91%): $[\alpha]^{23}_D$ −52.3 (*c* 0.82, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.30 (s, 1H), 6.19 (d, 1H, *J* = 7.3 Hz), 5.38 (dd, 1H, *J* = 2.9, 6.3 Hz), 5.30 (t, 1H, *J* = 6.9 Hz), 4.51 (d, 1H, *J* = 3.3 Hz), 4.45 (t, 1H, *J* = 2.9 Hz), 3.87 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 169.3, 167.1, 163.5, 150.7, 134.7, 112.2, 85.4, 81.5, 71.0, 69.8, 62.8, 53.2, 20.3, 20.2, 12.7; MS (CI) *m*/*z* 426 (M^+ + H), 300, 212, 127. Anal. Calcd for $C_{16}H_{19}N_5O_9$: C, 45.18; H, 4.50. Found: C, 45.31; H, 4.69.

(2*R*,3*R*,4*R*,5*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-4,5-(isopropylidenedioxy)hexan-1-ol (21). To a suspension of powdered 4 Å molecular sieves (500 mg) in CH_2Cl_2 (8 mL) at −23 °C were sequentially added Ti(O*i*Pr)$_4$ (72 μL, 0.24 mmol) and diethyl D-tartrate (50 μL, 0.29 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 15 min at −23 °C, and then a solution of alcohol **20** (715 mg, 2.32 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The mixture was stirred for 15 min, and *tert*-butyl hydroperoxide (1.5 mL, 5 M in *n*-decane) was added dropwise. The resulting mixture was stirred at −23 °C for 0.5 h and was put into a freezer of −23 °C for 24 h. After this period, aqueous NaOH solution (4 N) buffered with saturated aqueous NaCl (5 mL) was added,

and the mixture was stirred at 0 °C for 1 h. The mixture was filtered through a Celite pad, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 and evaporated to give a residue. Silica gel chromatography (25% ethyl acetate/hexane) furnished epoxide **21** as a colorless oil (574 mg, 77%): $[\alpha]^{23}_D$ +21 (*c* 0.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92−3.98 (m, 3H), 3.75 (m, 2H), 3.68 (m, 1H), 3.18 (m, 2H), 1.89 (br s, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.8, 78.9, 76.8, 63.3, 60.9, 56.0, 55.1, 26.8, 26.6, 25.8, 8.2, −5.5, −5.6; MS (CI) *m*/*z* 319 (M^+ + H), 303, 261, 243. Anal. Calcd for $C_{15}H_{30}O_5Si$: C, 56.57; H, 9.50. Found: C, 56.47; H, 9.83.

(2*R*,3*R*,4*S*,5*S*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-6-[(*tert*-butyldimethylsilyl)oxy]-4,5-(isopropylidenedioxy)-1,2-hexanediol (23). To a stirred solution of Ti(O*i*Pr)$_4$ (0.13 mL, 0.43 mmol) in dry benzene (3 mL) was added $TMSN_3$ (0.11 mL, 0.85 mmol) under nitrogen atmosphere. The resulting mixture was refluxed at 80 °C for 5 h. A solution of epoxide **21** (63.9 mg, 0.201 mmol) in benzene (2 mL) was added to the above refluxing mixture. The resulting mixture was continued to reflux at 80 °C for an additional 15 min. The reaction mixture was cooled to 23 °C, and benzene was removed under reduced pressure. The residue was dissolved in THF (3 mL), and saturated Roche's salt solution (3 mL) was added. The resulting mixture was stirred at 23 °C for 12 h. After this period, the reaction mixture was diluted with ethyl acetate (5 mL) and filtered through a pad of Celite, and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated. Silica gel chromatography (25% ethyl acetate/hexane) of the residue furnished an inseparable mixture (3:1, by 400 MHz ^{1}H NMR) of azides **22a** and **22b** as colorless oil (70 mg, 96%). Azide **22a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.28−4.16 (m, 2H), 3.91−3.85 (m, 3H), 3.74−3.61 (m, 2H), 3.53 (br s, 1H), 3.37 (dd, 1H, *J* = 7.7, 2.8 Hz), 2.72 (br s, 1H), 1.44 (s, 3H), 1.38 (s, 3H), 0.87 (s, 9H), 0.06 (s, 6H); azide **22b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.20−4.18 (m, 2H), 3.95−3.92 (m, 3H), 3.82−3.72 (m, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 0.88 (s, 9H), 0.08 (s, 6H).

To a stirred solution of the above mixture of azides in ethyl acetate (2 mL) was sequentially added di-*tert*-butyl dicarbonate (53 mg, 0.24 mmol) and 10% Pd−C (10 mg). The resulting suspension was stirred under a hydrogen-filled balloon for 12 h. After this period, the mixture was filtered through a Celite pad, and the Celite pad was washed with ethyl acetate. Evaporation of the filtrate gave a residue which was chromatographed on silica gel (30% ethyl acetate/hexane) to furnish the BOC derivatives **23** (52 mg, 60% from **21**) and **24** (17 mg, 20% from **21**) as colorless oils. BOC derivative **23**: $[\alpha]^{23}_D$ −3.4 (*c* 3.59, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (d, 1H, *J* = 8.9 Hz), 4.46 (d, 1H, *J* = 7.8 Hz), 3.82−3.78 (m, 2H), 3.73−3.66 (m, 2H), 3.63−3.57 (m, 3H), 3.49 (t, 1H, *J* = 9.3 Hz), 2.69 (d, 1H, *J* = 9.3 Hz), 1.44 (s, 9H), 1.42 (s, 3H), 1.37 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 109.0, 80.5, 77.2, 71.8, 63.4, 62.6, 50.7, 28.2, 27.0, 26.6, 25.8, 18.2, −5.6; MS (CI) *m*/*z* 436 (M^+ + H), 336, 322. Anal. Calcd for $C_{20}H_{41}O_7SiN$: C, 55.14; H, 9.48; N, 3.22; found: C, 54.87; H, 9.15; N, 2.98. BOC derivative **24**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53 (d, 1H, *J* = 7.6 Hz), 4.41 (s, 1H), 3.96−3.90 (m, 3H), 3.82−3.69 (m, 3H), 3.27 (d, 1H, *J* = 7.6 Hz), 1.44 (s, 9H), 1.38 (s, 3H), 1.37 (s, 3H), 0.89 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.5, 81.0, 79.7, 78.6, 76.0, 63.8, 62.4, 53.3, 28.3, 26.8, 26.7, 25.7, 18.2, −5.6.

Methyl 2-[(*N*-*tert*-Butoxycarbonyl)amino]-5-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-3,4-*O*-isopropylidene-L-xylonate (25). To a stirred solution of **23** (50 mg, 0.11 mmol) in 2 mL acetone were added an aqueous solution (1 mL) of $NaIO_4$ (150 mg, 0.702 mmol) and $RuCl_3$ (2 mg). The resulting mixture was stirred at 23 °C for 12 h. The reaction was quenched with 2-propanol (1 mL). Ethyl acetate (5 mL) and saturated aqueous ammonium chloride (5 mL) were added, and the reaction mixture was filtered through a Celite pad. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The pale yellow residue was dissolved in THF (2 mL), and an ethereal solution of CH_2N_2 was added at 0 °C. The mixture was stirred at 0 °C for 30 min until TLC showed the disappearance of the acid (R_f = 0.2, 50% ethyl acetate/hexane). Excess CH_2N_2 was destroyed by addition of glacial AcOH (0.2 mL), and the reaction mixture was concentrated under reduced pressure. The residue was chromatographed on a silica gel column (10% ethyl acetate/hexane) to furnish the ester **25** as a colorless oil (32.5 mg, 64%): $[\alpha]^{23}_D$ +0.3 (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (d, 1H, *J* = 9.6 Hz), 4.44 (dd, 1H, *J* = 1.5, 9.6 Hz), 4.40 (dd, 1H, *J* = 8.1, 1.5 Hz), 3.89 (m, 1H), 3.82−3.76 (m, 2H), 3.77 (s, 3H), 1.44 (s, 9H), 1.40 (s, 3H), 1.36 (s, 3H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 155.7, 109.5, 80.0, 77.7, 77.2, 62.6, 53.2, 52.5, 28.2, 26.8, 25.8, 18.2, −5.5; MS (CI) *m*/*z* 434 (M^+ + H), 378, 362.

Methyl 5-*O*-(Aminocarbonyl)-2-[(*N*-*tert*-butoxycarbonyl)amino]-2-deoxy-3,4-*O*-isopropylidene-L-xylonate (26). Methyl ester **25** (17 mg, 0.039 mmol) was dissolved in a mixture (3:1:1) of AcOH−THF−H_2O (1 mL), and the resulting solution was stirred at 23 °C for 12 h. After this period, the solvents were removed under reduced pressure, and the residue was dissolved in ethyl acetate (5 mL). The mixture was washed with saturated aqueous sodium bicarbonate and brine and dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 mL), and pyridine (0.1 mL) followed by *p*-nitrophenyl chloroformate (28.6 mg, 0.142 mmol) was added at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. After this period, the mixture was diluted with CH_2Cl_2 (5 mL) and washed with aqueous saturated sodium bicarbonate and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a pale yellow solid which was dissolved in THF (2 mL). The resulting solution was cooled to 0 °C, and aqueous ammonia (0.1 mL) was added. After stirring for 30 min at 0 °C, the mixture was diluted with ethyl acetate (10 mL), washed with saturated aqueous sodium bicarbonate and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure furnished a residue which was purified on a silica gel column (40% ethyl acetate/hexane) to afford the carbamate **26** (12 mg, 85%) as an oil: $[\alpha]^{23}_D$ −2.8 (*c* 0.84, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.29 (d, 1H, *J* = 9.7 Hz), 5.17 (br s, 2H), 4.45 (dd, 1H, *J* = 1.4, 9.5 Hz), 4.26 (dd, 1H, *J* = 1.4, 8.4 Hz), 4.19 (d, 2H, *J* = 5.3 Hz), 3.98 (m, 1H), 3.73 (s, 3H), 1.39 (s, 9H), 1.36 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.5, 156.2, 155.8, 110.0, 80.3, 78.1, 74.8, 63.9, 53.0, 52.6, 28.1, 26.7, 26.6. Anal. Calcd for $C_{15}H_{26}N_2O_8$: C, 49.61; H, 7.49; N, 7.72. Found: C, 49.56; H 7.22; N, 7.69.

5-*O*-(Aminocarbonyl)-2-[(*N*-*tert*-butoxycarbonyl)amino]-2-deoxy-3,4-*O*-isopropylidene-L-xylonic Acid (27). To a stirred solution of ester **26** (338 mg, 0.93 mmol) in a mixture (1:5) of THF−H_2O (3 mL) at 0 °C was added LiOH·H_2O (118 mg, 2.81 mmol). The resulting reaction mixture was stirred at 0 °C for 2 h. The mixture was carefully acidified with 1 N aqueous HCl solution to pH 4. The mixture was diluted with ethyl acetate (20 mL) and brine (10 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to furnish the acid **27** (290 mg, 90%) as a white foam: $[\alpha]^{23}_D$ +0.4 (*c* 2.2, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (d, 1H, *J* = 9.6 Hz), 5.29 (br s, 2H), 4.51 (d, 1H, *J* = 9.6 Hz), 4.36 (d, 1H, *J* = 7.4 Hz), 4.28 (m, 2H), 4.03 (m, 1H), 1.45 (s, 9H), 1.39 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.9, 157.0, 156.0, 110.1, 80.6, 78.0, 74.9, 64.0, 52.9, 28.3, 26.8, 26.7; MS (FAB) *m*/*z* 349 (M^+ + H), 293, 249. HRMS (FAB) Calcd for $C_{14}H_{25}N_2O_8$ (M^++H) 349.1611. Found: 349.1615.

Peptide Derivative 28. To a stirred solution of azide **18** (192 mg, 0.45 mmol) in MeOH (5 mL) was suspended 10% Pd−C (20 mg). The resulting mixture was stirred under a hydrogen-filled balloon for 2 h. After this period, the mixture was filtered through a Celite pad, and the filter cake was washed thoroughly with methanol. The filtrate was evaporated

under reduced pressure to give the crude amine **19** (177 mg) as a white foam which was used for the next step immediately without further purification. An analytical sample was obtained after chromatography over silica gel (5% MeOH/CH_2Cl_2): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.04 (s, 1H), 6.56 (d, 1H, J = 7.6 Hz), 5.82 (d, 1H, J = 5.4 Hz), 5.55 (t, 1H, J = 6.0 Hz), 5.31 (t, 1H, J = 6.0 Hz), 5.00 (dd, 1H, J = 3.9, 7.6 Hz), 4.38 (t, 1H, J = 5.1 Hz), 3.81 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 1.94 (s, 3H).

To a stirred solution of the above amine and acid **27** (143 mg, 0.41 mmol) in DMF (5 mL) was sequentially added BOP reagent (363 mg, 0.82 mmol) and diisopropylethylamine (0.22 mL, 1.26 mmol). The resulting mixture was stirred at 23 °C for 12 h. The solvent was removed under reduced pressure, and the residue was chromatographed over silica gel (90% ethyl acetate/hexane) to furnish the coupling product **28** (190 mg, 63% from **27**) as a white foam: $[\alpha]^{23}_D$ +12.6 (*c* 1.44, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 7.60 (d, 1H, J = 6.3 Hz), 7.00 (s, 1H), 5.63 (t, 1H, J = 6.6 Hz), 5.58 (d, 1H, J = 1.9 Hz), 5.50 (d, 1H, J = 9.3 Hz), 5.38 (m, 1H), 5.15 (br s, 2H), 4.95 (m, 1H), 4.47 (dd, 2H, J = 3.5, 6.6 Hz), 4.39 (m, 2H), 4.28 (d, 1H, J = 8.6 Hz), 3.98 (dd, 1H, J = 4.2, 8.4 Hz), 3.80 (s, 3H), 2.17 (s, 3H), 2.16 (s, 3H),1.92 (s, 3H), 1.43 (s, 9H), 1.41 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.3, 171.5, 171.3, 170.2, 166.1, 159.4, 157.7, 152.3, 139.3, 112.1, 111.2, 91.2, 82.5, 81.4, 78.8, 77.2, 73.9, 71.3, 61.2, 55.9, 54.9, 53.3, 28.6, 27.1, 20.4, 20.3, 12.4; MS (CI) *m*/*z* 730 (M^+ + H), 630, 444, 196, 154, 127. HRMS (FAB) Calcd for $C_{30}H_{44}N_5O_{16}$ (M^+ + H) 730.2783. Found: 730.2784.

Polyoxin J (1). To a stirred solution of protected polyoxin J (**28**) (19 mg, 0.026 mmol) in a mixture (1:5) of THF and water (1.5 mL) at 0 °C was added $LiOH\cdot H_2O$ (10 mg, 0.24 mmol). The resulting reaction mixture was stirred at 0 °C for 2 h. After this period, trifluoroacetic acid (3 mL) was added, and the mixture was continued to stir at 0 °C for an additional 2 h. The solvent was removed under vacuum at 23 °C, and the residue was chromatographed over silica gel using a mixture (5:4:1) of $CHCl_3-MeOH-H_2O$ as the eluent to furnish polyoxin J (**1**) (6.7 mg, 53%) as a pale yellow solid: mp 195−200 °C; $[\alpha]^{23}_D$ +29.0 (*c* 0.14, H_2O), lit.[8b] $[\alpha]^{23}_D$ +30 (*c* 0.10, H_2O); ^{1}H NMR (200 MHz, D_2O) δ 7.43 (s, 1H), 5.73 (d, 1H, J = 5.6 Hz), 4.47 (d, 1H, J = 3.9 Hz), 4.39 (t, 1H, J = 5.7 Hz), 4.23 (t, 1H, J = 5.7 Hz), 4.16 (m, 2H), 4.10 (dd, 1H, J = 5.0, 1.3 Hz), 3.99−4.03 (m, 4H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, D_2O) δ 174.7, 168.7, 167.4, 160.1, 152.9, 138.8, 112.7, 89.8, 85.2, 73.7, 71.1, 70.7, 69.6, 66.3, 57.4, 57.1, 12.6; MS (FAB) *m*/*z* 492 (M^+ + H), 207. HRMS [FAB] Calcd for $C_{17}H_{26}N_5O_{12}$ (M^+ + H) 492.1578. Found: 492.1583.

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Supporting Information Available: ^{1}H NMR or ^{13}C NMR spectra for compounds **1**, **10**, **12**, **14**, **16**, **17**, **19**, **22**, **24**, **25**, and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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