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ARTICLE

Synthesis of Isoxazolidine-containing Uridine Derivatives as Caprazamycin Analogues

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Simplification of caprazamycins, which are promising antibacterial nucleoside natural products, was conducted by scaffold-hopping of the structurally complex diazepanone moiety to the isoxazolidine scaffold. The designed isoxazolidine-containing uridine derivatives were synthesized by an intramolecular 1,3-dipolar cycloaddition of alkenyl nitrone as a key step. The lactone-fused isoxazolidine intermediate was easily converted to the target compounds by sequential introduction of key substituents upon ring-opening the lactone moiety by nucleophilic substitution and electrophilic capping of the resulting primary alcohol. Several analogues exhibited good activity against *H. influenza* ATCC 10211 (MIC 0.25-0.5 μg/mL) and moderate activity against vancomycin-resistant *E. faecalis* SR7914 (MIC 4-8 μg/mL).

Introduction

Peptidoglycan is a polymer that forms the bacterial cell wall, which consists of a repeated *N*-Ac muraminic acid (MurNAc) and *N*-Ac glucosamine (GluNAc) polymer cross-linked with polypeptides. In its biosynthesis, first UDP-MurNAc-peptapeptide is produced in cytoplasm. The phospho-muramoyl-pentapeptide moiety is then transferred onto a undecaprenyl-phosphate (C_{55}-P) carrier lipid in the cell membrane to form lipid I, and glycosidation of lipid I by GluNAc forms lipid II. Polymerization by glycosidation and transpeptidation of lipid II in the periplasm forms peptidoglycan. Peptidoglycan biosynthesis remains one of the best validated and studied pathways for antibacterial drug discovery, and currently used β-lactams and vancomycin inhibit the polymerization of lipid II. Extensive use of these antibiotics has led to the development of drug-resistant bacterial pathogens including methicillin-resistant *S.* aureus (MRSA), vancomycin-resistant Enterococci (VRE). Therefore, it is necessary to develop new antibiotics with a novel mode of action.[1-4] Caprazamycin B (CPZ) (Figure 1, **1**) was isolated from a culture broth of the Actinomycete strain *Streptomyces sp.* MK730-62F2 in 2003[5] and represents a member of a class of naturally occurringglycyluridine antibiotics. The CPZs have shown excellent anti-mycobacterial activity *in vitro* not only against both drug-susceptible (MIC = 3.13 μg/mL) and multidrug-resistant *Mycobacterium tuberculosis* strains (MIC = 3.13 μg/mL), and exhibit no significant toxicity in mice. A biological target of the CPZs is MraY transferase,[6] which catalyzes the formation of lipid I,[7-9] and MraY is a novel target for the development of antibacterial agents to treat drug resistant bacteria.[10] Recently our structure-activity relationship (SAR) studies of several key truncated analogues of **2**, which are effective to MRSA and VRE, have revealed that the uridine, the amine, and the fatty acyl moieties are crucial structural units (Figure 2).[11-15] We hypothesized the diazepanone moiety that serves as a scaffold to link these critical pharmacophore elements, could be replaced by a simpler scaffold. Scaffold-hopping is a medicinal chemistry method for molecular backbone replacements and is an important drug-design strategy that could be used to develop novel molecules with potent activity, altered physicochemical attributes, and better

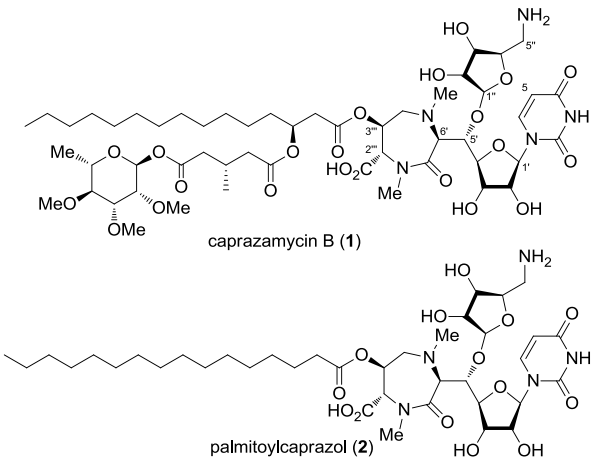


Figure 1. Structures of caprazamycin B and its analogue

ADMET properties.[16] Moreover such drug-design strategies depend on the ability to synthesize new scaffolds in short and easy steps. In our continuing efforts to develop new scaffolds useful for caprazamycin analogues, we designed an isoxazolidine as a new scaffold instead of the diazepanone and the aminoribose moieties (Figure 2). Here we describe the synthesis of uridine derivatives containing an isoxazolidine scaffold.

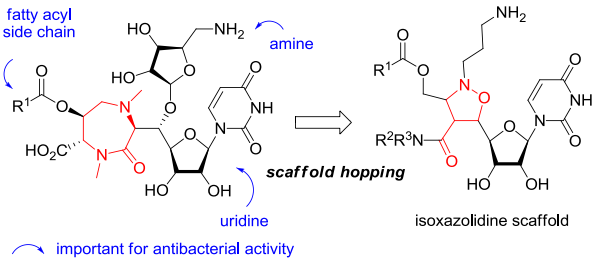
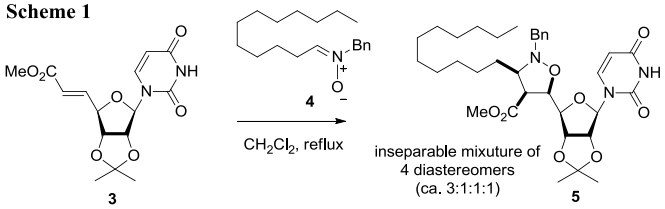


Figure 2. Design of Isoxazolidine-containing Uridine Derivatives

Results and Discussion

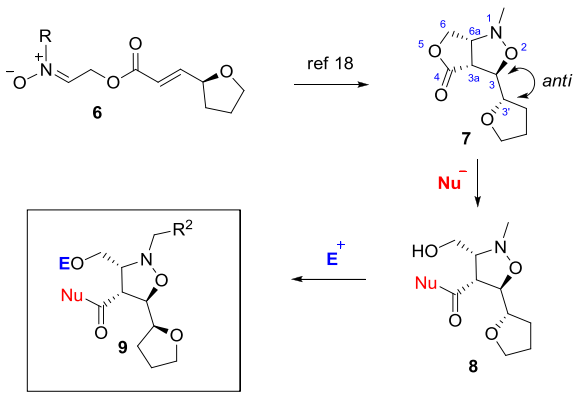
Our initial approach to the synthesis of the isoxazolidine analogues was based on the construction of the isoxazolidine ring by intermolecular 1,3-dipolar cycloaddition[17] between the α,β-unsaturated methyl ester **3** and a nitrone **4** (Scheme 1). However, the reaction did not proceed with a clean conversion and the isoxazolidine derivatives **5** were obtained as an inseparable mixture of at least four diastereomers. This result clearly indicated that the

Scheme 1



facial selectivity of the olefin, the geometry of the nitrone **4** and the *endo*/*exo* addition mode were not controlled. In order to overcome these shortcomings, we planned to investigate the intramolecular version of the 1,3-dipolar cycloaddition by using the ester-tethered alkenyl nitrone **6** to afford a lactone-fused isoxazolidine **7** (Scheme 2).[18] As was reported in the literatures, the stereochemical outcome is very reliable and the relative stereochemistry of the newly formed three contiguous stereogenic centers are predetermined by alkene geometry, while the facial selectivity was controlled by the allylic stereocenter. As a result, the reaction with the *E*-alkenyl nitrone possessing the tetrahydrofuran or 1,3-dioxorane ring at the allylic

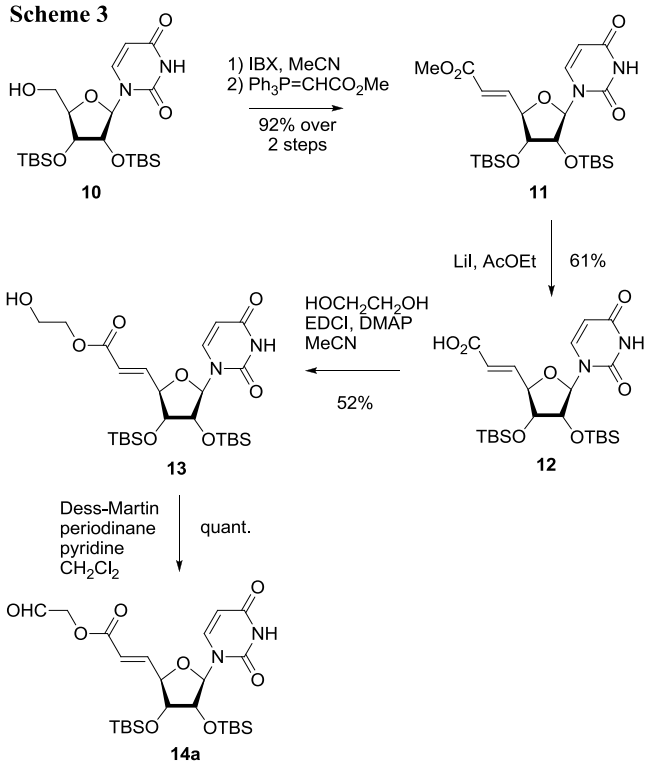
Scheme 2



position is expected to provide the lactone-fused isoxazolidine **7** with a 3,3a-*trans*-3a,6a-*cis*-3,3′-*trans* configuration highly stereoselectively. Additionally, this revised strategy allowed us to directly introduce key substituents upon ring-opening the lactone moiety in **7** by nucleophilic substitution and electrophilic capping of the resulting primary alcohol **8** to give a functionalized isoxazolidine **9**[20]. Therefore, a model study was first planned to synthesize substrates having a different protecting group at the 2′,3′-hydroxyl groups of uridine moiety in order to investigate the influence of the conformation of the ribofuranose ring on the facial selectivity of the intramolecular 1,3-dipolar cycloaddition. Compounds **14a** protected with TBS groups (Scheme 3) and **14b** protected with the isopropylidene group (Scheme 4) were prepared.

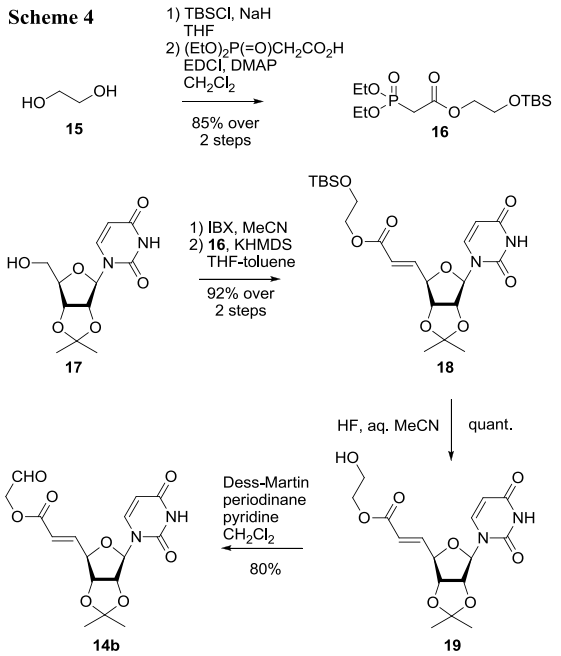
Oxidation of the 5′-hydroxyl group of 2′,3′-*O*-di-TBS uridine (**10**) with 2-iodoxybenzoic acid (IBX) followed by Wittig reaction with $Ph_3P{=}CHCO_2Me$ gave the *trans*-α,β-unsaturated ester **11** in 92% yield over two steps. Methyl ester **11** was converted to the carboxylic acid **12** by LiI in AcOEt and condensation with ethylene glycol provided the glycol ester **13** in 52% yield. The aldehyde **14a** was prepared by Dess-Martin oxidation of **13** in quantitative yield.

Scheme 3



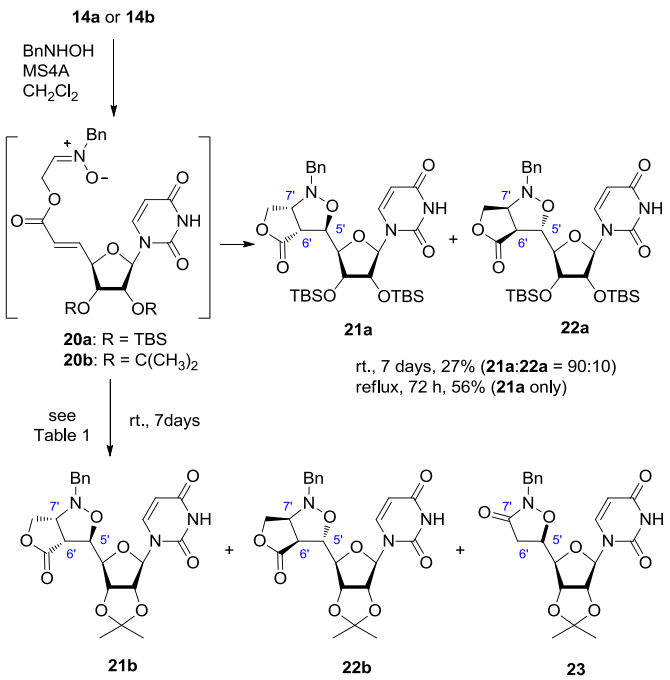
The isopropylidene-protected substrate **14b** was synthesized as shown in Scheme 4. First, the phosphonate **16** was prepared by partial protection of ethylene glycol (**15**) with a TBS group followed by acylation with diethyl phosphonoacetic acid in 85% yield over two steps. The 5′-hydroxyl group of 2′,3′-*O*-isopropylideneuridine (**17**) was oxidized by IBX, and the resulting aldehyde derivative was reacted with **16** by Horner-Wadsworth-Emmons reaction to give the α,β-unsaturated methyl ester **18** in 92% yield over two steps. After the TBS group of **18** was removed by HF to give **19**, the resulting hydroxyl group was oxidized by Dess-Martin periodinane to afford the aldehyde **14b** in 80% yield.

Scheme 4



With the substrates **14a**,**b** in hand, the model study of the key intramolecular 1,3-dipolar cycloaddition with *N*-benzylhydroxylamine was investigated (Scheme 5). The effect of several solvents on the cycloaddition was preliminarily investigated. The use of CH_2Cl_2 gave a better chemical yield of cycloadducts **21** and **22** than other solvents such as toluene or MeCN. Treatment of **14a**, which was protected with TBS groups, with *N*-benzylhydroxylamine in the presence of MS4Å in CH_2Cl_2 at room temperature resulted in clean conversion to the nitrone **20a**. Stirring an additional 7 days at room temperature provided the desired bicyclic isoxazolidines **21a** and **22a** in 27% yield as a mixture of diastereomers. The ratio of these products was determined by ^{1}H NMR (**21a**/**22a** = 90/10), and a good stereoselectivity was observed

Scheme 5



as was reported in the literatures.[18] The stereochemical outcome of these products was tentatively assigned as those in Scheme 5 according to the previous studies[18] because NOE experiments were not helpful and it was difficult to obtain crystals of **21a** and **22a** as well as their derivatives for X-ray structural analysis. The facial selectivity in the intramolecular cycloaddition of electron deficient alkenyl nitrone with the alkoxy substituent at the allylic position has been well studied and was affected by the stereochemistry of the alkoxy substituent at the allylic position.[19] Among three possible conformations (**confs A-C**, Figure 3a), the conformation with the alkoxy substituent in the inside position (**conf B**) is known to be most stable. The nitrone attacks away from the alkyl group located in

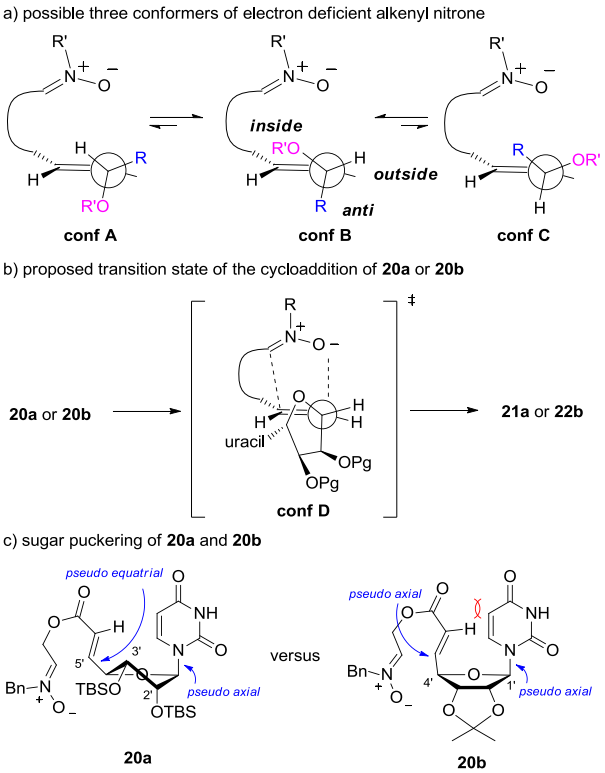


Figure 3. Conformational aspects in intramolecular cycloaddition

the *anti*-position and close to the allylic hydrogen located in the outside position in **conf B**. Cycloaddition of **20a** would also proceed through the transition state **conf D** with the oxygen atom in the ribofuranose ring in the inside position as shown in Figure 3b to afford the 4′,5′-anti-product, which corresponds to **21a**, as a major product. Previous similar system (**7** from **6** in Scheme 2) selectively gave anti-products,[18] and taking these considerations into account, chemical structures of the major and minor products were predicted to be **21a** and **22a**, respectively as in Scheme 5. Raising the reaction temperature resulted in short reaction time for completion (72 h) and increase the chemical yield and the stereoselectivity, and **21a** was obtained in 56% yield as a sole product. In order to investigate the structure-activity relationship of designed analogues, it is necessary to obtain both the diastereomers. In our efforts to reverse the stereoselectivity of the cycloaddition, several Lewis acids and metal ions were tested as additives. However, these were not effective and **21a** was obtained as a major product again. Next, the cycloaddition of **20b** with the isopropylidene group, which was prepared from **14b** and *N*-benzylhydroxylamine was investigated. Because of the decomposition of **20b** in refluxing CH_2Cl_2 in this case, the reaction was conducted at room temperature. As a result, a mixture of **21b**, **22b**, and **23** was obtained in 78% yield (Table 1, entry 1, **21b**/**22b**/**23** = 60:13:27). The ratio of the 4′,5′-*syn*-product **22b** was increased

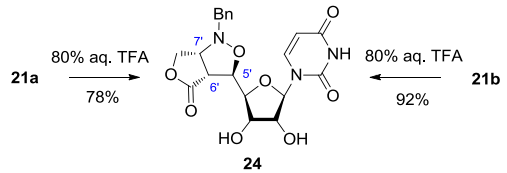
Table 1. Intramolecular 1,3-dipolar cycloaddition of nitrones 20b

entry	additive	yield (%)	ratio (**21b**:**22b**:**23**)[a]
1	-	78	60:13:27
2	$MgBr_2 \cdot OEt_2$	21	71:14:14
3	$ZnCl_2$	40	85:2:13
4	$Sc(OTf)_3$	29	24:3:72

[a]The ratio was determined by ^1H NMR.

compared that in the reaction with **20a**. The stereochemistry at the lactone-fused isoxazolidine moiety of the major product **21b** was confirmed by the fact that the diol **24**, which was obtained by deprotection of the isopropylidene group of **21b**, was completely matched to that obtained by the TBS deprotection of **21a**. Compound

Scheme 6

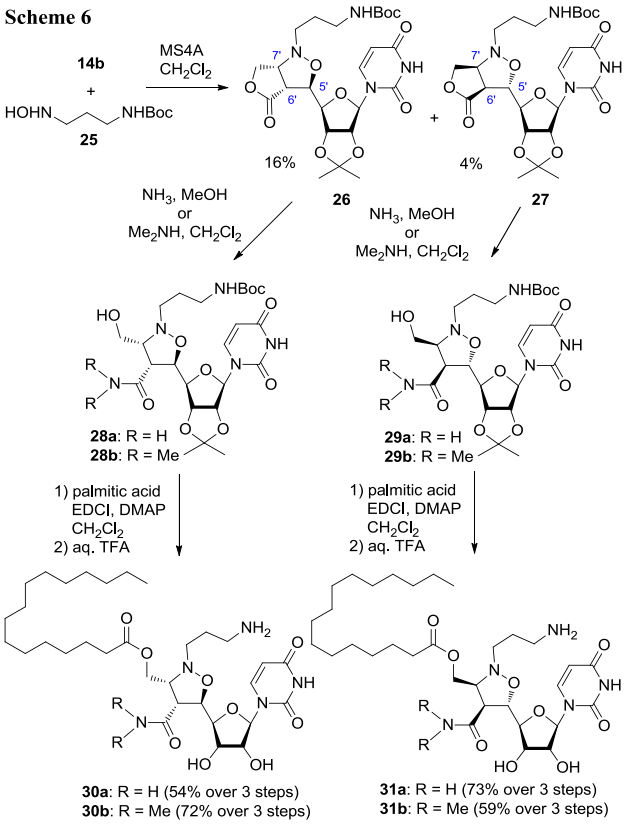


23 was obtained as a diastereomeric mixture at the 5′-position. Presumably, **23** was produced by intramolecular 1,4-addition of the oxygen of the nitrone moiety of **20a** followed by hydrolysis of the C-N double bond and the intramolecular acyl transfer to the nitrogen of the liberated *N*-benzylalkoxyamine. A small amount of this type of byproducts was also observed in the synthesis of **21a** and **22a** although the yield was not determined. Addition of Lewis acids was tested in order to increase the ratio of **22b**, however these efforts were unsuccessful (entries 2-4).

The facial selectivity in the cycloaddition of **20a** is better than that of **20b**. This could be attributed to the conformational difference of the ribofranose moiety (Figure 3c). The conformation of the ribofuranose moiety of **20a** is a 2′-*exo*-3′-*endo*, which is known as a 'North conformation'. In this conformation, the uracil base at the 1′-position is oriented in the pseudo axial position, and the substituent at the 4′-position is in the pseudo equatorial position. There is no severe steric repulsion between these substituents in **20a**, and the cycloaddition proceeds stereoselectively via **conf D**. On the other hand, the stable conformer of **20b** is different from that of **20a**, where both the substituents at the 1′- and 4′-positions are in the pseudo axial positions because of the bicycle[3.3.0] system by the 2′,3′-*O*-isopropylidene group protection. In this conformation, the uracil base and the 5′-substituent are in close proximity and the alkene hydrogen at the 6′-position could have a steric repulsion with the uracil base in the transition state of the cycloaddition via the alkoxy inside conformer **conf D**. As a result, the stereoselectivity was reduced in the case of **20b**.

With these model studies in hand, the target compounds, which possess aminoalkyl and the fatty acyl moieties at the isoxazolidine scaffold, were then synthesized starting from the isopropylidene-protected aldehyde **14b** as shown in Scheme 7. The aldehyde **14b** was treated with the hydroxylamine **25**[16] to form a nitrone, which was cyclized upon heating in CH_2Cl_2 gave **26** in 16% and **27** in 4% isolated yield, respectively, after HPLC separation. The lacton-fused isoxazolidine **26** was treated with either ammonium or dimethylamine to give the corresponding amide derivatives **28a**,**b**. Acylation of the resulting alcohol of **28a,b** by palmitic acid (EDCI, DMAP, CH_2Cl_2) followed by deprotection with TFA successfully afforded the desired isoxazolidine analogues **30a** in 54% and **30b** in 72% over three steps, respectively. In a manner similar to the synthesis of **30a,b**, analogues **31a,b** were prepared.

Scheme 6



Antibacterial activity of **30a-31b** was evaluated against a range of bacterial pathogens including *H. influenza* ATCC 10211, *S. aureus* ATCC 29213, (methicillin-sensitive), *S. aureus* SR3637 (methicillin-resistant), *E. faecalis* ATCC 29212 (vancomycin-sensitive), and *E. faecalis* SR7914 (vancomycin-resistant). The stereochemistry of the 5′-position of the analogues **30a**,**b** is expected to be opposite to that of caprazamycins. These analogues did not show any antibacterial activity except for **30b** against *H. influenza* ATCC 10211. On the other hands, the analogues **31a**,**b**, which are expected to possess the same stereochemistry to the caprazamycins at the 5′-position, exhibited good activity against *H. influenza* ATCC 10211 (MIC 0.25-0.5 μg/mL) and moderate activity against vancomycin-resistant *E. faecalis* SR7914 (MIC 4-8 μg/mL), respectively.

Table 2. Antibacterial activity of isoxazolidine analogues

	MIC (μg/mL)[a]				
	30a	**30b**	**31a**	**31b**	vancomycin
H.influenzae ATCC 10211	>32	1	0.25	0.5	1
S. aureus ATCC 29213 (MSSA)	>32	>32	>32	32	1
S. aureus SR3637 (MRSA)	>32	>32	>32	>32	1
E. faecalis ATCC 29212	>32	>32	16	16	1
E. faecalis SR7914 (VRE)	>32	>32	8	4	>64

[a]MICs were determined by a microdilution broth method as recommended by the NCCLS with cation-adjusted Mueller-Hinton broth (CA-MHB).[16] Serial two-fold dilutions of each compound were made in appropriate broth, and the plates were inoculated with 5 x 10^4 CFU of each strain in a volume of 0.1 ml. Plates were incubated at 35 °C for 20 h and then MICs were scored.

Conclusions

A simplification of caprazamycins, which are antibacterial nucleoside natural products promising as leads of novel antibiotics, was conducted by scaffold-hopping of the structurally complex diazepanone moiety to the isoxazolidine scaffold. The designed isoxazolidine-containing uridine derivatives were synthesized by an intramolecular 1,3-dipolar cycloaddition of an alkenyl nitrone as a key step. The lactone-fused isoxazolidine intermediate was easily converted to the target compounds by sequential introduction of key substituents upon ring-opening the lactone moiety by nucleophilic substitution and electrophilic capping of the resulting primary alcohol. The analogues **31a**,**b**, which are expected to possess the same stereochemistry to the caprazamycins at the 5′-position, exhibited good activity against *H. influenza* ATCC 10211 (MIC 0.25-0.5 μg/mL) and moderate activity against vancomycin-resistant *E. faecalis* SR7914 (MIC 4-8 μg/mL), respectively. Using the lactone-fused isoxazolidines **21** and **22** as common intermediates, a variety of analogues could be obtained by ring-opening of the lactone moiety by a range of nucleophiles followed by acylation of the resulting primary alcohol. Further SAR study is currently in due course in order to improve the antibacterial activity.

Experimental section

General experimental methods

NMR spectra were reported in parts per million (δ) relative to tetramethylsilane (0.00 ppm) as internal standard otherwise noted. Coupling constant (*J*) was reported in herz (Hz). Abbreviations of multiplicity were as follows; s: singlet, d; doublet, t: triplet, q: quartet, m: multiplet, br: broad. Data were presented as follows; chemical shift (multiplicity, integration, coupling constant). Assignment was based on ^{1}H–^{1}H COSY, HMBC and HMQC NMR spectra. MS data were obtained on a JEOL JMS-HX101 or JEOL JMS-700TZ.

Methyl (*E*)-2,3-Di-*O*-(*tert*-butyldimethylsilyl)-5,6-dideoxy-1-(uracil-1-yl)-β-D-*ribo*-5-ene- heptofuranuronate (11). A solution of **10** (1.66 g, 3.52 mmol) and IBX (2.00g, 7.04 mmol) in MeCN (40 mL) was stirred at 80 °C for 1 h. The reaction mixture was cooled with an ice bath, and the insolubles were filtered off through a Celite pad. The filtrate was concentrated *in vacuo* to afford the aldehyde as a colorless oil. A solution of the aldehyde in CH_2Cl_2 (15 mL) was added dropwise to a solution of $Ph_3P{=}CHCO_2Me$ (1.76 g, 5.28 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The whole reaction mixture was stirred at room temperature for 3 h. The reaction mixture was partitioned between EtOAc (300 mL) and H_2O (100 mL). The organic phase was washed with brine (100 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (7×25 cm, 50% EtOAc/hexane) to afford **11** (1.67 g, 90% over 2 steps) as a white foam. $[\alpha]^{21}_D$ +77.8° (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.2 (br s, 1H, N*H*-3), 7.32 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 6.96 (dd, 1H, H-5', $J_{5',4'}$ = 5.8, $J_{5',6'}$ = 15.5 Hz), 6.13 (dd, 1H, H-6', $J_{6',4'}$ = 1.7, $J_{6',5'}$ = 15.5 Hz), 5.77 (dd, 1H, H-5, $J_{5,NH}$ = 1.7, $J_{5,6}$ = 8.0 Hz), 5.67 (d, 1H, H-1', $J_{1',2'}$ = 2.3 Hz), 4.59 (dt, H-4', $J_{4',6'}$ = 1.8, $J_{4',3'}$ = $J_{4',5'}$ = 5.8 Hz), 4.18 (dd, 1H, H-2', $J_{2'1'}$ = 2.3, $J_{2',3'}$ = 4.1 Hz), 3.80 (dd, 1H, H-3', $J_{3',4'}$ = 3.4, $J_{3',2'}$ = 4.1 Hz), 3.75 (s, 3H, CO_2CH_3), 0.87 (s, 9H, *tert*-Bu), 0.86 (s, 9H, *tert*-Bu), 0.11 (s, 3H, C*H*$_3$), 0.06 (s, 3H, C*H*$_3$), 0.03 (s, 3H, C*H*$_3$), 0.02 (s, 3H, C*H*$_3$) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.1, 163.9, 150.3, 143.8, 139.7, 122.8, 102.5, 91.9, 81.9, 75.2, 74.9, 52.0, 25.8, 25.8, 18.1, 18.0, –4.2, –4.5, –4.7, –4.8; ESIMS-LR *m/z* 549 [(M + Na)$^+$]; ESIMS-HR calcd for $C_{24}H_{42}N_2NaO_4Si_2$ 549.2428, found 549.2425.

(*E*)-2,3-Di-*O*-(*tert*-butyldimethylsilyl)-5,6-dideoxy-1-(uracil-1-yl)-β-D-*ribo*-5-ene-heptofuranuronoic acid (12). A solution of **11** (768 mg, 1.45 mmol) in EtOAc (15 mL) was treated with lithium iodide (1.95 g, 14.5 mmol) at 80 °C for 1 h. Lithium iodide (1.95 g, 14.5 mmol) was added to the reaction mixture, and the whole mixture was stirred at the same temperature for 2 h. Lithium iodide (1.95 g, 14.5 mmol) was added to the mixture, and the reaction mixture was stirred at 80 °C for 18 h. The reaction mixture was partitioned between EtOAc (50 mL) and 1 M aqueous HCl (20 mL), the organic phase was washed with H_2O (20 mL×3) and brine (20 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford **12** (453 mg, 61%) as a white amorphous solid. $[\alpha]^{21}_D$ +71.1° (*c* 0.75, CH_3OH); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.64 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 7.01 (dd, 1H, H-5', $J_{5',4'}$ = 6.3, $J_{5',6'}$ = 16.0 Hz), 6.10 (dd, 1H, H-6', $J_{6',4'}$ = 1.2, $J_{6',5'}$ = 16.0 Hz), 5.84 (d, 1H, H-1', $J_{1',2'}$ = 3.4 Hz), 5.78 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.55 (dt, H-4', $J_{4',6'}$ = 1.2, $J_{4',3'}$ = $J_{4',5'}$ = 5.2 Hz), 4.36 (t, 1H, H-2', $J_{2',1'}$ = $J_{2',3'}$ = 4.6 Hz) 4.08 (dd, 1H, H-3', $J_{3',2'}$ = 4.6, $J_{4',3'}$ = 5.2 Hz), 0.94 (s, 9H, *tert*-Bu), 0.92 (s, 9H, *tert*-Bu), 0.12 (s, 6H, C*H*$_3$), 0.11 (s, 3H, C*H*$_3$), 0.10 (s, 3H, C*H*$_3$); ^{13}C NMR (CD_3OD, 125 MHz) δ 169.0, 166.0, 152.1, 145.1, 142.5, 124.8, 103.1, 92.1, 84.2, 76.5, 75.9, 26.4, 26.3, 18.9, 18.9, –4.11, –4.40, –4.45, –4.48; ESIMS-LR *m/z* 535 [(M + Na)$^+$]; ESIMS-HR calcd for $C_{23}H_{40}N_2NaO_4Si_2$ 535.2374, found 535.2271.

2-Hydroxyethyl (*E*)-2,3-Di-*O*-(*tert*-butyldimethylsilyl)-5,6-dideoxy-1-(uracil-1-yl)-β-D-*ribo*-5-ene- heptofuranuronate (13). A solution of **12** (2.12 g, 4.14 mmol) in CH_2Cl_2 (4 mL) was added to a solution of EDCI (1.19 g, 6.21 mmol), ethylene glycol (100 mL) and DMAP (146 mg, 1.20 mmol) in CH_2Cl_2 (40 mL) at room temperature for 1 h, and the whole mixture was stirred for 20 h at the same temperature. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with 10 mM aqueous HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford **13** (1.19 g, 52%) as a colorless foam. $[\alpha]^{21}_D$ +38.7° (*c* 1.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.39 (br s, 1H, N*H*-3), 7.30 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 7.04 (dd, 1H, H-5', $J_{5',4'}$ = 5.8, $J_{5',6'}$ = 16.1 Hz), 6.20 (dd, 1H, H-6', $J_{6',4'}$ = 1.8, $J_{6',5'}$ = 16.1 Hz), 5.80 (dd, 1H, H-5, $J_{5,NH}$ = 2.3, $J_{5,6}$ = 8.0 Hz), 5.70 (d, 1H, H-1', $J_{1',2'}$ = 3.4 Hz), 4.63 (dt, H-4', $J_{4',6'}$ = 1.8, $J_{4',3'}$ = $J_{4',5'}$ = 5.8 Hz), 4.33 (m, 2H, $CO_2CH_2CH_2OH$), 4.23 (t, 1H, H-3', $J_{3',2'}$ = $J_{4',3'}$ = 3.4 Hz), 3.03 (m, 3H, $CO_2CH_2CH_2OH$, $CO_2CH_2CH_2OH$), 1.97 (br t, 1H, O*H*, *J* = 5.7 Hz), 0.91 (s, 9H, *tert*-Bu), 0.90 (s, 9H, *tert*-Bu), 0.11 (s, 3H, C*H*$_3$), 0.10 (s, 3H, C*H*$_3$), 0.08 (s, 3H, C*H*$_3$), 0.07 (s, 3H, C*H*$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.0, 163.7, 150.3, 144.2, 140.3, 122.6, 102.6, 92.3, 82.2, 75.0, 74.9, 66.5, 61.0, 25.9, 25.8, 18.1, 18.1, –4.19, –4.48, –4.64, –4.72; ESIMS-LR *m/z* 579 [(M + Na)$^+$]; ESIMS-HR calcd for $C_{25}H_{44}N_2NaO_8Si_2$ 579.2534, found 579.2536.

Formylmethyl (*E*)-2,3-Di-*O*-(*tert*-butyldimethylsilyl)-5,6-dideoxy-1-(uracil-1-yl)-β-D-*ribo*-5-ene- heptofuranuronate (14a). A solution of **13** (488 mg, 0.878 mmol) in CH_2Cl_2/pyridine (3/1, 9 mL) was treated with Dess-Martin periodinane (747 mg, 1.76 mmol) at room temperature for 1 h. Dess-Martin periodinane (1.5 g, 3.5 mmol) was added to the reaction mixture at the same temperature. After stirred for 8 h, Dess-Martin periodinane (1.40 g, 3.3 mmol) was added to the reaction mixture at the same temperature. After stirred for 30 min, the reaction mixture was added to EtOAc (300 mL), saturated aqueous $Na_2S_2O_3$ (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) at 0 °C. The biphasic layer was vigorously

stirred at the same temperature for 10 min. The organic phase was washed with H_2O (100 mL) and brine (100 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford the aldehyde **14a** (491 mg, quant.) as colorless foam. $[\alpha]^{21}_D$ +77.5° (*c* 0.15, CH_3CN); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.65 (s, 1H, C*H*O), 8.05 (br s, 1H, N*H*-3), 7.29 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 7.11 (dd, 1H, H-5', $J_{5',4'}$ = 5.2, $J_{5',6'}$ = 15.5 Hz), 6.27 (dd, 1H, H-6', $J_{6',4'}$ = 1.8, $J_{6',5'}$ = 15.5 Hz), 5.79 (dd, 1H, H-5, $J_{5,NH}$ = 2.3, $J_{5,6}$ = 8.0 Hz), 5.71 (d, 1H, H-1', $J_{1',2'}$ = 3.4 Hz), 4.81 (d, 1H, CH_2CHO-α, *J* = 16.5 Hz), 4.78 (d, 1H, CH_2CHO-β, *J* = 16.5 Hz), 4.66 (ddd, 1H, H-4', $J_{4',6'}$ = 1.8, $J_{4',5'}$ = 5.2, $J_{4',3'}$ = 6.3 Hz), 4.23 (t, 1H, H-2', $J_{2',3'}$ = $J_{2',1'}$ = 3.4 Hz), 3.89 (dd, 1H, H-3', $J_{3',2'}$ = 3.4, $J_{3',4'}$ = 6.3 Hz), 0.91 (s, 18H, *tert*-Bu), 0.15 (s, 3H, CH_3), 0.12 (s, 3H, CH_3), 0.10 (s, 3H, CH_3), 0.09 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.3, 162.4, 149.8, 145.5, 140.0, 128.6, 121.6, 102.7, 92.2, 85.4, 82.3, 77.8, 75.1, 69.0, 27.6, 25.9, 25.9, 18.2, 18.1, 17.8, –4.11, –4.46, –4.56, –4.59; APCIMS-LR *m/z* 555 [(M + H)$^+$]; APCIMS-HR calcd for $C_{25}H_{42}N_2O_8Si_2$ 555.2558, found 555.2554.

4-[(3*R*, 3a*R*, 6a*R*)-1-Aza-1-*N*-benzyl-2,5-oxa-4-oxobicyclo[3.3.0]octan-3-yl]-2,3-di-*O*-*tert*-butyldimethylsilyl-1-(uracil-1-yl)-β-D-*erythro*-furanose (21a) and 4-[(3*S*, 3a*S*, 6a*S*)-1-Aza-1-*N*-benzyl-2,5-oxa-4-oxobicyclo[3.3.0]octan-3-yl]-2,3-di-*O*-*tert*-butyl dimethylsilyl-1-(uracil-1-yl)-β-D-*erythro*-furanose (22a). A solution of **14a** (268 mg, 0.482 mmol), BnNHOH (58.1 mg, 0.472 mmol) and MS4A (5 g) in CH_2Cl_2 (50 mL) was stirred at room temperature for 7 days. The reaction mixture was filtered with a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (1×40 cm, acetone/$CHCl_3$, 0.1%) to afford the mixture of **21a** and **22a** (78.9 mg, 27%) as a colorless foam. A part of the mixture was separated by flash silica gel column chromatography (1×40 cm, acetone/$CHCl_3$, 0.3%) to afford **21a** as a colorless foam. Data for **21a**; $[\alpha]^{20}_D$ +28.3° (*c* 0.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.66 (br s, 1H, N*H*-3), 7.45 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 7.37 (m, 5H, Ph), 5.97 (d, 1H, H-1', $J_{1',2'}$ = 5.8 Hz), 5.80 (dd, 1H, H-5, $J_{5,NH}$ = 2.3, $J_{5,6}$ = 8.0 Hz), 4.29 (dd, 1H, H-3"a, $J_{3"a,3"}$ = 4.6, $J_{3"a,6"a}$ = 10.3 Hz), 4.25 (t, 1H, H-3', $J_{3',2'}$ = $J_{3',4'}$ = 5.8 Hz), 4.10 (m, 3H, H-2', H-6"), 4.03 (m, 3H, Bn, H-6"a), 3.66 (br dd, 1H, H-3", $J_{3",3"a}$ = 4.6, $J_{3",4'}$ = 7.5 Hz), 3.59 (dd, 1H, H-4', $J_{4',3'}$ = 5.8, $J_{4',3"}$ = 7.5 Hz), 0.92 (s, 9H, *tert*-Bu), 0.86 (s, 9H, *tert*-Bu), 0.22 (s, 3H, CH_3), 0.12 (s, 3H, CH_3), 0.04 (s, 3H, CH_3), 0.03 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.2, 162.9, 150.4, 140.6, 135.4, 129.0, 128.4, 103.0, 87.9, 84.5, 80.0, 74.8, 72.6, 71.1, 69.0, 68.4, 67.6, 61.7, 61.3, 51.5, 25.9, 25.9, 25.8, 18.1, 18.1, 6.60, –3.44, –4.21, –4.37, –4.46, –4.64; ESIMS-LR *m/z* 682 [(M + Na)$^+$]; ESIMS-HR calcd for $C_{32}H_{49}N_3NaO_8Si_2$ 682.2956, found 682.2957. Data for **22a** was assigned from the chart of mixture **21a** and **22a**; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.84 (br s, 1H, N*H*-3), 8.05 (d, 1H, H-6, $J_{6,5}$ = 8.2 Hz), 7.34 (m, 5H, Ph), 5.81 (d, 1H, H-1', $J_{1',2'}$ = 2.7 Hz), 5.74 (br d, 1H, H-5, $J_{5,6}$ = 8.2 Hz), 4.32 (br dd, 1H, H-3"a, $J_{3"a,3"}$ = 4.6, $J_{3"a,6"a}$ = 6.9 Hz), 4.25 (t, 1H, H-3', overlap with a peak of **21a**), 4.08 (m, 3H, Bn-α, H-2', H-6"α), 4.01 (m, 2H, Bn-β, H-6"β, overlap with a peak of **21a**), 3.93 (dd, 1H, H-6"a, $J_{6"a,6"}$ = 5.0, $J_{6"a,3"a}$ = 6.9 Hz), 3.75 (1H, H-4', overlap with a peak of **21a**), 0.90 (s, 9H, *tert*-Bu), 0.80 (s, 9H, *tert*-Bu), 0.09 (s, 3H, CH_3), 0.05 (s, 3H, CH_3), –0.04 (s, 3H, CH_3), –0.10 (s, 3H, CH_3).

4-[(3*R*, 3a*R*, 6a*R*)-1-Aza-1-*N*-benzyl-2,5-oxa-4-oxobicyclo[3.3.0]octan-3-yl]-2,3-di-*O*-*tert*-butyldimethylsilyl-1-(uracil-1-yl)-β-D-*erythro*-furanose (21a). A solution of **14a**, BnNHOH (205 mg, 1.67 mmol) and MS4A (17 g) in CH_2Cl_2 (170 mL) was stirred at 50 °C for 72 h. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (2×40 cm, 0.1% acetone/$CHCl_3$) to afford **21a** (168 mg, 56% over 2 steps) as a colorless foam. The characteristic data were identical to those obtained above experiment.

2-*tert*-Butyldimethylsilyloxyethyl Diethylphosphonoacetate (16). Ethylene glycol (10 mL, 179 mmol) was added dropwise to a suspension of NaH (3.87 g, 160 mmol) in THF (400 mL) at –30 °C for 1 h. The reaction mixture was stirred at 0 °C for 30 min. A solution of TBSCl (13.5 g, 89.5 mmol) in THF (100 mL) was added to the mixture at 0 °C, and the whole mixture was stirred at the same temperature for 8 h and at room temperature for 24 h. The mixture was partitioned between EtOAc (1500 mL) and H_2O (500 mL), and the organic phase was washed with H_2O (500 mL×2) and brine (500 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford 2-*tert*-butyldimethylsilyloxyethanol (14.1 g) as a colorless syrup. A solution of diethylphosphonoacetic acid (19.3 mL, 120 mmol), DMAP (488 mg, 4.00 mmol) and 2-*tert*-butyldimethylsilyloxyethanol in CH_2Cl_2 (500 mL) was treated with EDCI (23.0 g, 120 mmol) at room temperature for 13 h. The reaction mixture was partitioned between EtOAc (1500 mL) and 1 M aqueous HCl (500 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (500 mL) and brine (500 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford **16** (27.2 g, 85% over 2 steps) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.17 (m, 6H, CH_3CH_2O, $CO_2CH_2CH_2OTBS$), 3.81 (dd, 2H, $CO_2CH_2CH_2OTBS$, *J* = 5.0, *J* = 5.5 Hz), 3.00 (d, 2H, P(=O)CH_2CO_2, *J* = 21.9 Hz), 1.34 (t, 6H, CH_3CH$_2$O), 0.87 (s, 9H, *tert*-Bu), 0.06 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7, 66.7, 62.7, 62.6, 60.9, 34.9, 33.5, 25.8, 25.7, 18.3, 16.3, 16.3, –3.59, –5.38; ESIMS-LR *m/z* 377 [(M + Na)$^+$]; ESIMS-HR calcd for $C_{14}H_{31}NaO_6PSi$ 377.1525, found 377.1525.

2-*tert*-Butyldimethylsilyloxyethyl (*E*)-2,3-*O*-Isopropylidene-5,6-dideoxy-1-(uracil-1-yl)-β-D-*ribo*-5-ene-heptofuranuronate (18). A solution of 2',3'-*O*-isopropylideneuridine (**17**, 2.84 g, 10.0 mmol) and IBX (6.00g, 21.4 mmol) in MeCN (100 mL) was stirred at 70 °C for 1 h. The whole mixture was cooled with an ice bath, the insolubles were filtered off through a Celite pad. The filtrate was concentrated *in vacuo* to afford a crude aldehyde (2.95 g) as a colorless foam. A solution of KHMDS in toluene (0.5 M, 29.8 mL, 14.9 mmol) was added to a solution of the phosphonate **16** (5.31 g, 15.0 mmol) in THF (10 mL) at –78 °C, and the whole mixture was stirred at the same temperature for 30 min. A solution of the aldehyde in THF (10 mL) was added to the mixture at –78 °C for 2 h, and the whole mixture was stirred at 0 °C for 3 h. After saturated aqueous NH_4Cl (30 mL) was added, the mixture was extracted with EtOAc (500 mL×3). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (7×25 cm, Et_2O/$CHCl_3$, 25% then 7×25 cm, EtOAc/$CHCl_3$, 30%) to **18** (4.43 g, 92%) as a colorless oil. $[\alpha]^{23}_D$ +33.8° (*c* 1.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12 (br s, 1H, N*H*-3), 7.19 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 7.01 (dd, 1H, H-5', $J_{5',4'}$ = 5.6, $J_{5',6'}$ = 16.0 Hz), 6.06 (dd, 1H, H-6', $J_{6',4'}$ = 1.2, $J_{6',5'}$ = 16.0 Hz), 5.75 (dd, 1H, H-5, $J_{5,NH}$ = 2.3, $J_{5,6}$ = 8.0 Hz), 5.64 (d, 1H, H-1', $J_{1',2'}$ = 1.7 Hz), 5.05 (dd, 1H, H-2', $J_{2',1'}$ = 1.7, $J_{2',3'}$ = 6.3 Hz), 4.82 (dd, 1H, H-3', $J_{3',4'}$ = 4.6, $J_{3',2'}$ = 6.3 Hz), 4.66 (ddd, H-4', $J_{4',6'}$ = 1.2, $J_{4',3'}$ = 4.6, $J_{4',5'}$ = 5.6 Hz), 4.21 (t, 2H, $CO_2CH_2CH_2OTBS$, *J* = 5.2 Hz), 3.84 (t, 2H, $CO_2CH_2CH_2OTBS$, *J* = 5.2 Hz), 1.58 (s, 3H, acetonide), 1.57 (s, 3H, acetonide), 0.88 (s, 9H, *tert*-Bu), 0.06 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.8, 163.1, 149.9, 143.9, 142.6, 122.5, 115.0, 103.0, 95.0, 86.8, 84.6, 84.1, 66.0, 61.3, 27.3, 26.0, 25.4, 18.5, –5.14; ESIMS-LR *m/z* 505

[(M + Na)$^+$]; ESIMS-HR calcd for $C_{22}H_{34}N_2NaO_8Si$ 505.1982, found 505.1976.

2-Hydroxyethyl (*E*)-2,3-*O*-Isopropylidene-5,6-dideoxy-1-(uracil-1-yl)-β-D-*ribo*-5-ene-heptofuranuronate (19). A solution of **18** (125 mg, 0.259 mmol) in MeCN (2 mL) was treated with 48% aqueous HF (100 μL, 3 mmol) at room temperature for 10 min. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (40 mL) at 0 °C. The whole mixture was extracted with EtOAc (50 mL×3). The combined organic phase was washed with brine (20 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford **19** (104 mg, quant.) as a colorless foam. $[\alpha]^{20}_D$ +35.0° (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.04 (br s, 1H, N*H*-3), 7.20 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 7.05 (dd, 1H, H-5', $J_{5',4'}$ = 5.7, $J_{5',6'}$ = 16.1 Hz), 6.04 (dd, 1H, H-6', $J_{6',4'}$ = 1.8, $J_{6',5'}$ = 16.1 Hz), 5.77 (dd, 1H, H-5, $J_{5,NH}$ = 2.3, $J_{5,6}$ = 8.0 Hz), 5.58 (d, 1H, H-1', $J_{1',2'}$ = 1.7 Hz), 5.16 (dd, 1H, H-2', $J_{2',1'}$ = 1.7, $J_{2',3'}$ = 6.3 Hz), 4.89 (dd, 1H, H-3', $J_{3',4'}$ = 4.6, $J_{3',2'}$ = 6.3 Hz), 4.69 (ddd, H-4', $J_{4',6'}$ = 1.8, $J_{4',3'}$ = 4.6, $J_{4',5'}$ = 5.7 Hz), 4.21 (m, 2H, $CO_2CH_2CH_2OH$), 3.84 (br q, 2H, $CO_2CH_2CH_2OH$, *J* = 4.6 Hz), 2.45 (br t, 1H, O*H*, *J* = 4.6 Hz), 1.66 (s, 3H, acetonide), 1.36 (s, 3H, acetonide); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.1, 163.4, 150.3, 144.6, 123.3, 121.9, 114.7, 103.1, 96.0, 87.2, 84.4, 84.2, 67.3, 66.5, 63.2, 61.1, 27.2, 25.3, 16.4; ESIMS-LR *m/z* 391 [(M + Na)$^+$]; ESIMS-HR calcd for $C_{16}H_{20}N_2NaO_8$ 391.1117, found 391.1110.

Formylmethyl (*E*)-2,3-*O*-Isopropylidene-5,6-dideoxy-1-(uracil-1-yl)-β-D-*ribo*-5-ene-heptofuranuronate (14b). A solution of **19** (94.8 mg, 0.259 mmol) in CH_2Cl_2/pyridine (20/1, 2 mL) was treated with Dess-Martin periodinane (145 mg, 0.337 mmol) at room temperature for 1 h. After the reaction mixture was diluted with EtOAc (30 mL), saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL) were added at 0 °C, and the resulting biphasic layers were vigorously stirred at same temperature for 10 min. The mixture was partitioned between the organic phase and the aqueous phase, and the aqueous phase was extracted with EtOAc (20 mL). The combined organic phase was washed with brine (20 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford **14b** (75.5 mg, 80%) as a colorless foam, which was used for the next reaction without further purification. $[\alpha]^{21}_D$ +20.5° (*c* 1.00, CH_3CN); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.64 (s, 1H, C*H*O), 8.29 (br s, 1H, N*H*-3), 7.20 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 7.05 (dd, 1H, H-5', $J_{5',4'}$ = 5.7, $J_{5',6'}$ = 16.0 Hz), 6.04 (dd, 1H, H-6', $J_{6',4'}$ = 1.8, $J_{6',5'}$ = 16.0 Hz), 5.76 (dd, 1H, H-5, $J_{5,NH}$ = 1.7, $J_{5,6}$ = 8.0 Hz), 5.60 (d, 1H, H-1', $J_{1',2'}$ = 1.2 Hz), 5.12 (dd, 1H, H-2', $J_{2',1'}$ = 1.2, $J_{2',3'}$ = 4.0 Hz), 4.90 (dd, 1H, H-3', $J_{3',2}$ = 4.0, $J_{3',4'}$ = 6.3 Hz), 4.73 (s, 2H, CH_2CHO), 4.70 (ddd, H-4', $J_{4',6'}$ = 1.8, $J_{4',5'}$ = 5.7, $J_{4',3'}$ = 6.3 Hz), 1.65 (s, 3H, acetonide), 1.36 (s, 3H, acetonide); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214.3, 162.8, 150.0, 144.6, 143.0, 121.9, 114.8, 103.1, 95.8, 89.3, 87.1, 84.4, 84.2, 66.4, 61.2, 27.2, 25.3; APCIMS-LR *m/z* 391 [(M + Na)$^+$]; APCIMS-HR calcd for $C_{16}H_{20}N_2NaO_8$ 391.1117, found 391.1110.

4-[(3*R*, 3a*R*, 6a*R*)-1-Aza-1-*N*-benzyl-2,5-oxa-4-oxobicyclo[3.3.0]octan-3-yl]-2,3-*O*-isopropylidene-1-(uracil-1-yl)-β-D-*erythro*-furanose (21b) and 4-[(3*S*, 3a*S*, 6a*S*)-1-Aza-1-*N*-benzyl-2,5-oxa-4-oxobicyclo[3.3.0]octan-3-yl]-2,3-*O*-isopropylidene-1-(uracil-1-yl)-β-D-*erythro*-furanose (22b). A solution of **14b**, BnNHOH (123 mg, 1.00 mmol) and MS4A (10 g) in MeCN (100 mL) were stirred at room temperature for 7 days. The reaction mixture was filtered off through a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (2×60 cm, EtOAc/hexane, 33%) to afford a mixture of **21b**, **22b**, **23** as a colorless foam (Table 1, entry 1, **21b**:**22b**:**23** = 60:13:27) . A part of the mixture was separated by flash silica gel column chromatography (2×60 cm, EtOAc/hexane, 20%) to obtain **21b** as a colorless foam and a mixture of isoxazolidinone compounds **23**. Data for **21b**: $[\alpha]^{21}_D$ +61.8° (*c* 12.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.85 (br s, 1H, N*H*-3), 7.35 (m, 5H, Ph), 7.23 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.61 (d, 1H, H-1', $J_{1',2'}$ = 2.3 Hz), 5.56 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.98 (dd, 1H, H-2', $J_{2',1'}$ = 2.3, $J_{2',3'}$ = 6.3 Hz), 4.94 (dd, 1H, H-3', $J_{3',4'}$ = 4.6, $J_{3',2'}$ = 6.3 Hz), 4.50 (dd, 1H, H-3", $J_{3",4'}$ = 4.6, $J_{3",3"a}$ = 5.2 Hz), 4.29 (dd, 1H, H-4', $J_{4',3"}$ = 3.4, $J_{4',3'}$ = 4.6 Hz), 4.24 (dd, 1H, H-6"α, $J_{6"\alpha,3"a}$ = 4.6, $J_{6"\alpha,6"\beta}$ = 10.8 Hz), 4.10 (d, 1H, Bn, *J* = 13.2 Hz), 3.98 (d, 1H, Bn, *J* = 13.8 Hz), 3.95 (br d, 1H, H-6"α, $J_{6"\alpha,6"\beta}$ = 10.8 Hz), 3.45 (dd, 1H, H-6"β, $J_{6"\beta,6"a}$ = 4.6, $J_{6"\beta,6"\alpha}$ = 10.8 Hz), 3.72 (dd, 1H, H-3"a, $J_{3"a,3"}$ = 5.2, $J_{3"a,6"a}$ = 8.1 Hz), 3.65 (br dd, 1H, H-6"a, $J_{6"a,6"\beta}$ = 4.6, $J_{6"a,3"a}$ = 8.1 Hz), 1.56 (s, 3H, acetonide), 1.35 (s, 3H, acetonide); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.4, 163.5, 150.3, 142.7, 135.5, 129.0, 128.9, 128.8, 115.3, 102.7, 94.7, 84.6, 83.7, 79.7, 69.1, 67.9, 61.0, 49.8, 29.8, 27.4, 25.6; ESIMS-LR *m/z* 494 [(M + Na)$^+$]; ESIMS-HR calcd for $C_{23}H_{25}N_3NaO_8$ 494.1539, found 494.1543. Data for **22b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.65 (br s, 1H, N*H*-3), 7.35 (m, 6H Ph, H-6), 5.83 (d, 1H, H-1', $J_{1',2'}$ = 2.3 Hz), 5.68 (dd, 1H, H-5, $J_{5,NH}$ = 1.7, $J_{5,6}$ = 8.0 Hz), 5.03 (dd, 1H, H-3', $J_{3',4'}$ = 4.6, $J_{3',2'}$ = 6.1 Hz), 4.86 (dd, 1H, H-2', $J_{2',1'}$ = 2.3, $J_{2',3'}$ = 6.3 Hz), 4.37 (br t, 1H, H-3", $J_{3",4'}$ = $J_{3",3"a}$ = 6.3 Hz), 4.24 (dd, 1H, H-4', $J_{4',3'}$ = 4.6, $J_{4',3"}$ = 6.3 Hz), 4.15 (dd, 1H, H-6"α, $J_{6"\alpha,3"a}$ = 4.6, $J_{6"\alpha,6"\beta}$ = 10.3 Hz), 4.10 (Bn, overlap with the peak of **21b**), 3.91 (Bn, overlap with the peak of **21b**), 3.80 (br d, 1H, H-6"α, $J_{6"\alpha,6"\beta}$ = 10.3 Hz), 3.45 (dd, 1H, H-6"β, $J_{6"\beta,6"a}$ = 5.2, $J_{6"\beta,6"\alpha}$ = 8.0 Hz) 3.65 (1H, H-6"a, overlap with the peak of **21b**), 3.55 (dd, 1H, H-3"a, $J_{3"a,3"}$ = 5.2, $J_{3"a,6"a}$ = 8.1 Hz), 1.56 (s, 3H, acetonide), 1.35 (s, 3H, acetonide); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.9, 163.5 (overlap with a peak of **21b**), 150.2, 141.7, 134.9, 128.6, 128.5, 128.4, 115.3, 102.8, 93.1, 87.1, 83.9, 80.1, 69.1(overlap with a peak of **21b**), 67.7, 61.2, 51.0, 29.8(overlap with a peak of **21b**), 27.3, 25.5. Data for the major diastereomer of **23**; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (br s, 1H, N*H*-3), 7.38 (m, 5H, Ph), 7.18 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.68 (dd, 1H, H-5, $J_{5,NH}$ = 2.3, $J_{5,6}$ = 8.0 Hz), 5.51 (d, 1H, H-1', $J_{1',2'}$ = 1.7 Hz), 4.97 (dd, 1H, H-2', $J_{2',1'}$ = 1.7, $J_{2',3'}$ = 6.3 Hz), 4.70 (dd, 1H, H-3', $J_{3',4'}$ = 4.6, $J_{3',2'}$ = 6.3 Hz), 4.27 (d, 1H, Bn, *J* = 13.7 Hz), 4.21 (d, 1H, Bn, *J* = 13.7 Hz), 4.04 (dd, H-4', $J_{4',3'}$ = 4.6, $J_{4',5'}$ = 6.3 Hz), 3.87 (m, 1H, H-5'), 2.68 (dd, H-6'α, $J_{6'\alpha,5'}$ = 4.6, $J_{6'\alpha,6'\beta}$ = 18.3 Hz), 2.65 (dd, H-6'β, $J_{6'\beta,5'}$ = 4.6, $J_{6'\beta,6'\alpha}$ = 18.3 Hz), 1.54 (s, 3H, acetonide), 1.32 (s, 3H, acetonide); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.9, 163.3, 150.0, 143.5, 134.3, 129.9, 129.3, 128.2, 115.0, 102.9, 95.9, 86.8, 84.5, 81.5, 63.1, 30.8, 27.2, 25.2. Data for the minor diastereomer of **23**; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (br s, 1H, N*H*-3), 7.34 (m, 6H, Ph, H-6), 5.76 (dd, 1H, H-5, $J_{5,NH}$ = 2.3, $J_{5,6}$ = 8.0 Hz), 5.68 (d, 1H, H-1', $J_{1',2'}$ = 2.3 Hz), 4.85 (dd, 1H, H-2', $J_{2',1'}$ = 2.3, $J_{2',3'}$ = 6.3 Hz), 4.54 (dd, 1H, H-3', $J_{3',4'}$ = 4.0, $J_{3',2'}$ = 6.3 Hz), 4.22 (s, 2H, Bn), 4.13 (dd, H-4', $J_{4',3'}$ = 4.0, $J_{4',5'}$ = 6.3 Hz), 3.75 (m, 1H, H-5'), 2.84 (dd, H-6'α, $J_{6'\alpha,5'}$ = 8.6, $J_{6'\alpha,6'\beta}$ = 17.8 Hz), 2.61 (dd, H-6'β, $J_{6'\beta,5'}$ = 8.6, $J_{6'\beta,6'\alpha}$ = 17.8 Hz), 1.54 (s, 3H, acetonide), 1.32 (s, 3H, acetonide); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.8, 163.5 (overlap with a peak of **21b**), 150.4, 142.8, 134.3, 129.8, 129.3 (overlap with a peak of **21b**), 128.3, 115.3(overlap with a peak of major product containing an isoxazolidine ring), 103.2, 94.9, 88.7, 84.4, 81.7, 63.5, 31.0, 27.4 (overlap with a peak of **21b**), 25.4.

4-[(3*R*, 3a*R*, 6a*R*)-1-Aza-1-*N*-(3-*tert*-butoxycarbonylaminopropyl)-2,5-oxa-4-oxobicyclo[3.3.0]octan-3-yl]-2,3-*O*-isopropylidene-1-(uracil-1-yl)-β-D-*erythro*-furanose (26) and 4-[(3*S*, 3a*S*, 6a*S*)-1-Aza-1-*N*-(3-*tert*-butoxycarbonylaminopropyl)-2,5-oxa-4-oxobicyclo[3.3.0]octan-3-yl]-2,3-*O*- isopropylidene-1-(uracil-1-yl)-β-D-*erythro*-furanose (27). A suspension of **14b** (75.5 mg) and MS4A (2.1 g) in CH_2Cl_2 (21 mL) were treated with the hydroxylamine **25** (38.0 mg, 0.200

mmol) at room temperature for 7 days. The MS4A was filtered off through a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC-Pack R&D SIL 250×20 mml. D. S-5 μm 12 nm, MeOH/$CHCl_3$, 10%) to afford a mixture of diastereoisomers (34.8 mg, 25% over 3 steps) as colorless foam. The mixture of diastereo isomers was further purified by preparative HPLC (YMC-Pack R&D SIL 250×20 mm, MeOH/*i*PrOH/benzene/$CHCl_3$, 5×10^{-4}/1/5/5) to afford major products **26** (22.3 mg, 16%) as a colorless foam and minor product **27** (5.4 mg, 4%) as a colorless foam. Data for the major product **26**: $[\alpha]^{20}_D$ +44.0° (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.66 (br s, 1H, N*H*-3), 7.29 (1H, H-6, overlap with a peak of $CDCl_3$), 5.73 (br d, 1H, H-5, $J_{5,6}$ = 7.3 Hz), 5.51 (br s, 1H, H-1'), 5.08 (br d, 1H, H-2', $J_{2',3'}$ = 6.0 Hz), 5.04 (br m, 1H, H-4'), 4.84 (br m, 1H, H-3'), 4.46 (br m, 1H, H-3"), 3.37 (dd, 1H, H-6"α, $J_{6"\alpha,6"\beta}$ = 5.0, $J_{6"\alpha,6"a}$ = 10.6 Hz), 4.23 (br d, 1H, H-6"β, $J_{6"\beta,6"a}$ = 10.6 Hz), 3.71 (m, 1H, H-3"a), 3.49 (m, 1H, H-6"a), 3.28 (m, 1H, $CH_2CH_2CH_2$NHBoc-α), 3.16 (m, 1H, $CH_2CH_2CH_2$NHBoc-β), 2.87 (m, 2H, $CH_2CH_2CH_2$NHBoc), 1.78 (m, 2H, $CH_2CH_2CH_2$NHBoc), 1.58 (s, 3H, acetonide), 1.44 (s, 9H, *tert*-Bu), 1.36 (s, 3H, acetonide); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.5, 162.9, 156.2, 150.0, 143.1, 115.3, 102.8, 95.4, 85.1, 83.9, 79.9, 79.7, 68.9, 68.2, 54.3, 49.8, 38.8, 29.8, 28.6, 27.4, 25.6; ESIMS-LR *m/z* 561 [(M + Na)$^+$]; ESIMS-HR calcd for $C_{24}H_{34}N_4NaO_{10}$ 561.2173, found 561.2176; data for the minor product **27**: $[\alpha]^{20}_D$ −8.2° (*c* 0.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (br s, 1H, N*H*-3), 7.29 (1H, H-6, overlap with a peak of $CDCl_3$), 5.75 (m, 2H, H-5, H-1'), 5.05 (br m, 1H, H-2'), 4.96 (br m, 1H, H-3'), 4.87 (br m, 1H, H-4'), 4.37 (br s, 2H, H-6"α), 4.26 (br m, 1H, H-6"β), 4.18 (br m, 1H, H-3"), 3.49 (br m, 2H, H-3"a, H-6"a), 3.23 (m, 2H, $CH_2CH_2CH_2$NHBoc), 2.80 (m, 2H, $CH_2CH_2CH_2$NHBoc), 1.84 (m, 2H, $CH_2CH_2CH_2$NHBoc), 1.45 (s, 9H, *tert*-Bu), 1.36 (s, 3H, acetonide), 1.21 (s, 3H, acetonide); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.0, 162.6, 156.2, 149.7, 141.9, 115.3, 103.0, 93.4, 86.9, 84.4, 80.1, 79.8, 76.6, 68.9, 68.1, 54.4, 51.0, 38.8, 29.8, 28.6, 27.4, 25.6; ESIMS-LR *m/z* 561 [(M + Na)$^+$]; ESIMS-HR calcd for $C_{24}H_{34}N_4NaO_{10}$ 561.2173, found 561.2177.

4-[(3*R*, 4*R*, 5*R*)- 2-*N*-(3-Aminopropyl)-2-aza-4-carbamoyl-3-palmitoyloxymethyl-1-oxa-cyclopentan-5-yl]-1-(uracil-1-yl)-β-D-*erythro*-furanose (30a). Compound **26** (1.1 mg, 2.0 μmol) was treated with saturated NH_3 in methanol (2 mL) for 30 min at room temperature. The reaction mixture was concentrated *in vacuo* to afford the alcohol **28a** (1.1 mg). The alcohol **28a** in CH_2Cl_2 (1 mL) was treated with palmitic acid (0.76 mg, 2.97 μmol), DMAP (0.36 mg, 2.97 mmol) and EDCI (0.57 mg, 2.97 μmol) for 12 h at room temperature. The reaction mixture was partitioned between EtOAc (10 mL) and H_2O (3 mL), and the organic phase was washed with 1 M aqueous HCl (3 mL), saturated aqueous $NaHCO_3$ (3 mL) and brine (3 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was treated with 80% aqueous TFA for 20 min. After the reaction mixture was concentrated *in vacuo*, the residue was purified by HPLC (YMC-Pack R&D SIL 250×4.6 mml. MeOH/H_2O, 20%) to afford **30a** (0.7 mg, 54% over 3 steps) as a colorless foam. $[\alpha]^{21}_D$ +12.9° (*c* 0.07, CH_3OH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.55 (m, 2H, H-6, CON*H*$_2$-α), 7.20 (br s, 1H, CON*H*$_2$-β), 5.78 (d, 1H, H-1', $J_{1',2'}$ = 5.7 Hz), 5.63 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.58 (br m, 1H, O*H*), 5.32 (br m, 1H, O*H*), 4.38 (dd, 1H, H-5", $J_{5",4'}$ = 5.7, $J_{5",4"}$ = 8.1 Hz), 4.03-3.92 (m, 5H, H-2', H-3', H-3", CO_2CH_2), 3.86 (dd, 1H, H-4', $J_{4',3'}$ = 3.5, $J_{4',5"}$ = 5.7 Hz), 3.42 (br m, 1H, H-4"), 2.87 (m, 4H, NC*H*$_2$CH$_2$CH$_2$NH$_2$, C*H*$_2$CO$_2$), 2.27 (m, 2H, C*H*$_2$CH$_2$CO$_2$), 2.15 (t, 2H, NCH$_2$CH$_2$C*H*$_2$NH$_2$), 1.66 (m, 1H, NCH$_2$C*H*$_2$CH$_2$NH$_2$-α), 1.48 (m, 3H, C*H*$_2$CH$_2$CH$_2$CO$_2$, NCH$_2$C*H*$_2$CH$_2$NH$_2$-β), 1.22 (m, 22H, (C*H*$_2$)$_{11}$(CH$_2$)$_3$CH$_3$), 0.84 (t, 3H, (CH$_2$)$_{14}$C*H*$_3$, *J* = 6.3 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 174.2, 172.9, 169.8, 162.9, 150.7, 141.2, 102.0, 88.8, 87.1, 84.3, 82.8, 78.9, 72.2, 70.3, 37.3, 35.1, 33.3, 31.3, 29.0, 28.9, 28.9, 28.7, 28.5, 25.5, 25.0, 24.2, 22.1, 13.9; ESIMS-LR *m/z* 654 [(M + H)$^+$]; ESIMS-HR calcd for $C_{32}H_{56}N_5O_9$ 654.4000, found 654.4088.

4-[(3*R*, 4*R*, 5*R*)-2-*N*-(3-Aminopropyl)-2-aza-4-*N*,*N*-dimethylcarbamoyl-3-palmitoyloxymethyl-1-oxa-cyclopentan-5-yl]-1-(uracil-1-yl)-β-D-*erythro*-furanose (30b). A solution of **26** (2.4 mg, 4.46 μmol) in CH_2Cl_2 (0.5 mL) was treated with 40% aqueous Me_2NH (0.5 mL) for 30 min at room temperature. The reaction mixture was concentrated *in vacuo* to afford the alcohol **28b** (2.8 mg). A solution of **28b** in CH_2Cl_2 (1 mL) was treated with palmitic acid (1.7 mg, 6.69 μmol), DMAP (0.82 mg, 6.69 mmol) and EDCI (1.30 mg, 6.69 μmol) for 12 h at room temperature. The reaction mixture was partitioned between EtOAc (10 mL) and H_2O (3 mL), and the organic phase was washed with 1 M aqueous HCl (3 mL), saturated aqueous $NaHCO_3$ (3 mL) and brine (3 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was treated with 80% aqueous TFA for 20 min. After the reaction mixture was concentrated *in vacuo*, the residue was purified by HPLC (YMC-Pack R&D SIL 250×4.6 mml., MeOH/H_2O, 35%) to afford **30b** (2.2 mg, 72% over 3 steps) as a colorless foam. $[\alpha]^{23}_D$ +10.3° (*c* 0.26, CH_3OH); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.62 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.84 (d, 1H, H-1', $J_{1',2'}$ = 5.2 Hz), 5.72 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.67 (dd, 1H, H-4', $J_{4',3'}$ = 5.2, $J_{4',5"}$ = 8.6 Hz), 4.20 (t, 1H, H-2', $J_{2',1'}$ = $J_{2',3'}$ = 5.2 Hz), 4.16 (t, 1H, H-3', $J_{3',2'}$ = $J_{3',4'}$ = 5.2 Hz), 4.06 (m, 3H, , H-3", C*H*$_2$OCO), 3.98 (t, 1H, H-5", $J_{5",4'}$ = $J_{5",4"}$ = 8.6 Hz), 3.60 (br m, 1H, H-4"), 3.15 (s, 3H, NC*H*$_3$), 3.01 (m, 2H, CH$_2$CH$_2$C*H*$_2$NH$_2$), 2.94 (s, 3H, NC*H*$_3$), 2.87 (t, 2H, C*H*$_2$CH$_2$CH$_2$NH$_2$, *J* = 6.9 Hz), 2.31 (br m, 2H, CH$_3$(CH$_2$)$_{13}$C*H*$_2$CO), 2.15 (br m, 2H, CH$_3$(CH$_2$)$_{12}$C*H*$_2$CH$_2$CO), 1.84 (m, 2H, CH$_2$C*H*$_2$CH$_2$NH$_2$), 1.69 (br m, 2H, CH$_3$(CH$_2$)$_{11}$C*H*$_2$CH$_2$CH$_2$CO), 1.29 (m, 22H, CH$_3$(C*H*$_2$)$_{11}$), 0.90 (t, 3H, C*H*$_3$(CH$_2$)$_{14}$CO, *J* = 6.9 Hz); ^{13}C NMR (CD_3OD, 100 MHz) δ 183.1, 174.8, 170.5, 166.9, 153.0, 142.7, 102.9, 90.9, 85.7, 82.3, 75.0, 71.8, 66.8, 40.3, 39.3, 37.8, 36.3, 34.9, 33.1, 30.9, 30.8, 30.8, 30.7, 30.7, 30.6, 30.5, 30.4, 30.2, 29.9, 27.8, 25.9, 23.7, 14.4; ESIMS-LR *m/z* 682 [(M + H)$^+$]; ESIMS-HR calcd for $C_{34}H_{60}N_5O_9$ 682.4391, found 682.4401.

4-[(3*S*, 4*S*, 5*S*)- 2-*N*-(3-Aminopropyl)-2-aza-4-carbamoyl-3-palmitoyloxymethyl-1-oxa-cyclopentan-5-yl]-1-(uracil-1-yl)-β-D-*erythro*-furanose (31a). In a manner similar to the synthesis of **30a**, **31a** (0.9 mg, 73%) was obtained as a colorless foam after HPLC purification (YMC-Pack R&D SIL 250×4.6 mm, MeOH/H_2O, 20%). $[\alpha]^{19}_D$ +15.3° (*c* 0.09, CH_3OH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.4 (br s, N*H*-3), 7.66 (m, 4H, H-6, CH$_2$CH$_2$CH$_2$N*H*$_2$, CON*H*$_2$-α), 7.23 (br s, 1H, CON*H*$_2$-β), 5.77 (d, 1H, H-1', $J_{1',2'}$ = 5.2 Hz), 5.72 (dd, 1H, H-5, $J_{5,NH-3}$ = 1.7, $J_{5,6}$ = 8.0 Hz), 5.58 (br d, 1H, O*H*, *J* = 5.7 Hz), 5.32 (br d, 1H, O*H*, *J* = 5.7 Hz), 4.35 (dd, 1H, H-5", $J_{5",4'}$ = 3.5, $J_{5",4"}$ = 8.6 Hz), 4.07 (dd, 1H, CO$_2$C*H*$_2$-α, $J_{CO2CH2-\alpha,3"}$ = 5.2, $J_{CO2CH2-\alpha,CO2CH2-\beta}$ = 11.5 Hz), 3.99 (m, 3H, H-2', H-3', CO$_2$C*H*$_2$-β), 3.91 (br dd, 1H, H-3", $J_{3",CO2CH2-\alpha}$ = 3.5, $J_{3",4"}$ = 8.2 Hz), 3.78 (br t, 1H, H-4', $J_{4',3'}$ = $J_{4',5"}$ = 5.2 Hz), 3.42 (br m, 1H, H-4"), 2.82 (m, 4H, NC*H*$_2$CH$_2$CH$_2$NH$_2$, C*H*$_2$CO$_2$), 2.28 (t, 2H, C*H*$_2$CH$_2$CO$_2$, *J* = 7.4 Hz), 2.17 (t, 2H, NCH$_2$CH$_2$C*H*$_2$NH$_2$, *J* = 7.3 Hz), 1.77 (m, 2H, NCH$_2$C*H*$_2$CH$_2$NH$_2$), 1.46 (m, 3H, (C*H*$_2$)$_2$CH$_2$CH$_2$CO$_2$), 1.22 (m, 20H, (C*H*$_2$)$_{10}$(CH$_2$)$_4$CH$_3$), 0.84 (t, 3H, (CH$_2$)$_{14}$C*H*$_3$, *J* = 6.3 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 174.5, 172.7, 169.8, 163.0, 150.6, 140.4, 101.9, 94.1, 87.9, 82.2, 79.2, 72.5, 70.1, 40.1, 40.0, 39.9, 39.9, 37.5, 33.7, 33.3, 31.3, 29.1, 28.9, 28.7, 28.6, 28.5, 24.5, 24.3, 22.1, 14.0; ESIMS-LR *m/z* 654 [(M + H)$^+$]; ESIMS-HR calcd for $C_{32}H_{56}N_5O_9$ 654.4000, found 654.4088.

4-[(3*S*, 4*S*, 5*S*)- 2-*N*-(3-Aminopropyl)-2-aza-4-*N*,*N*-dimethylcarbamoyl-3-palmitoyloxymethyl-1-oxa-cyclopentan-5-yl]-1-(uracil-1-yl)-β-D-*erythro*-furanose (31b). In a manner similar to the synthesis of **30b**, **31b** (1.2 mg, 59% over 3 steps) was obtained as a colorless foam after HPLC purification (YMC-Pack R&D SIL 250×4.6 mml., MeOH/H_2O, 35%). $[\alpha]^{23}_D$ +10.7° (*c* 0.15, CH_3OH); ^{1}H NMR (CD_3OD, 400 MHz) δ 7.73 (d, 1H, H-6, $J_{6,5}$ = 8.2 Hz), 5.83 (d, 1H, H-1', $J_{1',2'}$ = 3.2 Hz), 5.72 (d, 1H, H-5, $J_{5,6}$ = 8.2 Hz), 4.61 (br dd, 1H, H-4', $J_{4',3'}$ = 5.0, $J_{4',5''}$ = 8.7 Hz), 4.10 (m, 3H, H-2', H-3', CH_2OCO-α), 3.93 (m, 2H, H-5", CH_2OCO-β), 3.73 (br m, 1H, H-3"), 3.51 (br m, 1H, H-4"), 3.16 (s, 3H, NCH_3), 3.02 (m, 4H, CH_2CH$_2$CH$_2$NH$_2$, CH$_2$CH$_2$CH_2NH$_2$), 2.98 (s, 3H, NCH_3), 2.32 (br m, 1H, CH$_3$(CH$_2$)$_{13}$CH_2CO-α), 2.15 (br m, 3H, CH$_3$(CH$_2$)$_{13}$CH_2CO-β, CH$_3$(CH$_2$)$_{12}$CH_2CH$_2$CO), 1.87 (m, 2H, CH$_2$CH_2CH$_2$NH$_2$), 1.59 (br m, 4H, CH$_3$(CH$_2$)$_{10}$CH_2CH_2(CH$_2$)$_2$CO), 1.29 (m, 20H, CH$_3$(CH_2)$_{10}$), 0.90 (t, 3H, CH_3(CH$_2$)$_{14}$CO, *J* = 6.9 Hz); ^{13}C NMR (CD_3OD, 100 MHz) δ 182.9, 174.8, 170.1, 166.2, 142.4, 102.8, 91.9, 83.6, 82.2, 75.1, 71.8, 67.2, 63.3, 40.2, 39.2, 37.8, 36.2, 34.8, 33.1, 30.9, 30.8, 30.7, 30.5, 30.2, 27.8, 25.9, 23.7, 14.4; ESIMS-LR *m/z* 682 [(M + H)$^+$]; ESIMS-HR calcd for $C_{34}H_{60}N_5O_9$ 682.4391, found 682.4401.

(3''*R*, 3''a*R*, 6''a*R*) 5'-(1''-*N*-Benzyl-1''-aza-2'',5''-oxa-4''-oxobicyclo[3,3,0]octan-3''-yl)- 1'-(uracil-1-yl)-β-D-*erythro*-furanose (24) from 21a. Compound **21a** (0.8 mg, 1.21 μmol) was treated with 80% aqueous TFA (1 mL) for 1 h at room temperature. The reaction mixture was concentrated *in vacuo* to afford **24** (0.4 mg, 78%). $[\alpha]^{22}_D$ +22.5° (*c* 0.10, CH_3OH); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.43-7.32 (m, 6H, H-6, Ph), 5.89 (d, 1H, H-1', $J_{1',2'}$ = 5.2 Hz), 5.26 (d, 1H, H-5, $J_{5,6}$ = 8.2 Hz), 4.42 (dd, 1H, H-3", $J_{3",4'}$ = 4.6, $J_{3",3"a}$ = 10.9 Hz), 4.32 (dd, 1H, H-4', $J_{4',3'}$ = 3.4, $J_{4',3"}$ = 4.6 Hz), 4.23 (m, 3H, Bn, H-6"α), 4.18 (dd, H-3', $J_{3',4'}$ = 3.4, $J_{3',2'}$ = 5.2 Hz), 3.94 (d, 1H, H-6"β, $J_{6"β,6"α}$ = 4.6 Hz), 3.75 (m, 2H, H-3"a, H-6"a); ^{13}C NMR (CD_3OD, 100 MHz) δ 177.3, 164.4, 151.1, 141.0, 136.9, 129.0, 128.5, 128.2, 127.4, 101.6, 89.0, 84.0, 79.8, 74.0, 69.7, 50.6, 29.4; ESIMS-LR *m/z* 454 [(M + Na)$^+$]; ESIMS-HR calcd for $C_{20}H_{21}N_3NaO_8$ 454.1226, found 454.1224.

(3''*R*, 3''a*R*, 6''a*R*) 5'-(1''-*N*-Benzyl-1''-aza-2'',5''-oxa-4''-oxobicyclo[3,3,0]octan-3''-yl)-1'-(uracil-1-yl)-β-D-*erythro*-furanose (24) from 21b. Compound **21b** (1.3 mg, 2.76 μmol) was treated with 80% aqueous TFA (1 mL) for 1 h at room temperature. The reaction mixture was concentrated *in vacuo* to afford **24** (1.1 mg, 92%). The characteristic data were identical to those obtained from **21a**.

Antibacterial Activity Evaluation

Vancomycin-resistant *Enterococcus faecalis* SR7914 (VanA) and *Entercoccus faecium* SR7917 (VanA), and methicillin-resistant *Staphylococcus aureus* SR3637 were clinical isolates collected from hospitals of Japan and kindly provided by Shionogi & Co., Ltd. (Osaka, Japan).[37] MICs were determined by a microdilution broth method as recommended by the NCCLS (National Committee for Clinical Laboratory Standards, **2000**, National Committee for Clinical Laboratory Standards, Wayne, Pa.) with cation-adjusted Mueller-Hinton broth (CA-MHB) (Becton Dickinson, Sparks, Md.). Serial two-fold dilutions of each compound were made in appropriate broth, and the plates were inoculated with 5×10^4 CFU of each strain in a volume of 0.1mL Plates were incubated at 35 °C for 20 h and then MICs were scored.

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