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Function-Oriented Synthesis of Simplified Caprazamycins: Discovery of Oxazolidine-Containing Uridine Derivatives as Antibacterial Agents against Drug-Resistant Bacteria

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The rational simplification of the caprazamycin (CPZ) class of nucleoside natural products was carried out to address their molecular complexity. First, analogues **6**−**8**, where the diazepanone ring of the CPZ was removed and a lipophilic side chain was attached to either the C-7′ or $N^{6'}$ atom, were used to investigate the conformation−activity relationship. On the basis of this relationship, we designed the oxazolidine-containing uridine derivatives **18**−**21** by restricting the conformation of **6**−**8**. As a result, the ^{t}Bu ester derivatives **20** were found to be the most active against a range of bacterial strains containing VRE with a potency similar to that of the parent CPZs. This study provides a novel strategy for the development of a new type of antibacterial agent effective against drug-resistant bacteria.

Introduction

Natural products can be viewed as a population of privileged structures selected by evolutional pressures to interact with a variety of biological targets and therefore are still a rich source for drug development. Roughly 60% of new drug entries between 1981 and 2006 were natural products and their derivatives.[1] However, some biologically relevant natural products possess rather large, complex, or labile chemical structures compared to synthetic drugs, which limits chemical modification in a process pursuing a structure−activity relationship (SAR). It is also true that unlike simpler synthetic compounds, natural products can be limited in supply owing to sourcing limitations or the impracticality of synthesis. There are two ways to resolve these problems: one is to develop new reactions and synthetic strategies that allow for shorter routes to a target, and the other is to design less complex targets with comparable or superior function that could be made in a practical and even synthetically novel manner. Wender et al. termed this process function-oriented synthesis (FOS[a]),[2] the central principle of which is that "the function of a biologically active lead structure can be emulated, tuned, or even improved by replacement with simpler scaffolds designed to incorporate the activity-determining structural features of the lead compounds." Although challenging, simpler scaffold designs would provide a practical synthesis of a set of analogues and synthetic innovation in current medicinal chemistry.

The caprazamycins (CPZs) (Figure 1, **1**) were isolated from a culture broth of the actinomycete strain *Streptomyces* sp. MK730-62F2 in 2003[3] and represent the newest members of a class of naturally occurring 6′-*N*-alkyl-5′-*β*-*O*-aminoribosyl-*C*-glycyluridine antibiotics including the liposidomycins[4] (LPMs, **2**). Recently, the genes for CPZ biosynthesis in *Streptomyces* sp. MK730-62F2[5] and a LPM gene cluster in *Streptomyces* sp. SN-1061M[6] have been identified. The CPZs have shown excellent antimycobacterial activity in vitro not only against drug-susceptible (MIC = 3.13 μg/mL) but also multidrug-resistant *Mycobacterium tuberculosis* strains (MIC = 3.13 μg/mL) and exhibit no significant toxicity in mice. A biological target of the 6′-*N*-alkyl-5′-*β*-*O*-aminoribosyl- *C*-glycyluridine class of antibiotics is believed to be MraY translocase,[7] and it is known that this class of antibiotics strongly inhibits MraY (IC_{50} = 0.05 μg/mL for LPMs).[4h] This integral membrane enzyme catalyzes transfer of a phosphomuramoylpentapeptide moiety onto a undecaprenyl phosphate (C_{55}-P) carrier lipid, an essential step of peptidoglycan biosynthesis.[8−10] Since MraY is an essential enzyme among bacteria,[10] it is potentially a novel target for the development of antibacterial agents to treat drug resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and vancomycin-resistant *Staphylococcus aureus* (VRSA).[11] With such excellent biological properties, the CPZs themselves are expected to become promising leads for the development of antibacterial agents with a novel mode of action. However, because of their molecular complexity, the CPZs are not suitable for use in preparing a large number of analogues for the study of a SAR in a lead optimization process. Here we describe the rational simplification of the CPZ class of nucleoside natural products to address the issue associated with their molecular complexity through FOS.

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[a]Abbreviations: CPZ, caprazamycin; FOS, function-oriented synthesis; LPM, liposidomycin; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; SAR, structure−activity relationship; VRE, vancomycin-resistant *Enterococcus*; VRSA, vancomycin-resistant *Staphylococcus aureus*.

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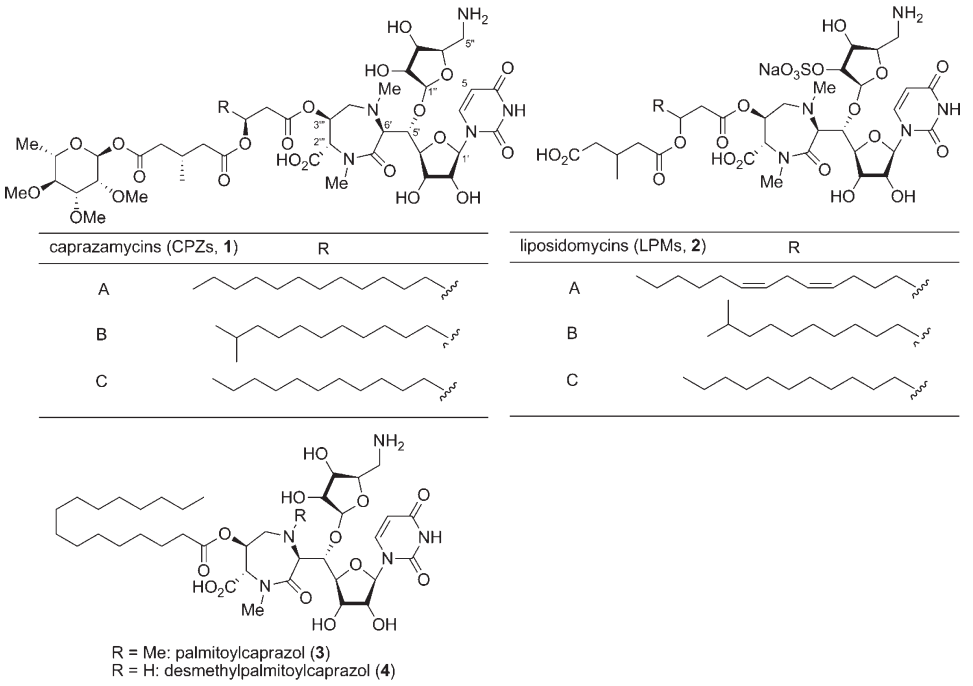


Figure 1. Structures of caprazamycins, liposidomycins, and their analogues.

Results and Discussion

Decoding the Role of the Diazepanone and Aminoribofuranose Moiety in Caprazamycins. Recently, we have revealed that palmitoylcaprazol (**3**) and its *N*-desmethyl analogue **4**, which possess a simple fatty acyl side chain at the 3‴-position of the diazepanone moiety of the CPZs, exhibited antibacterial activity with a potency similar to that of the CPZs (MIC = 6.25 μg/mL against *M. smegmatis*, 6.25−12.5 μg/mL against drug-resistant bacteria including MRSA and VRE strains).[12] Our SAR studies of several key truncated analogues of **3** have also revealed that the uridine, the aminoribose, and the fatty acyl moieties are crucial structural units of palmitoylcaprazol, and the 5′-β-*O*-aminoribosyl-*C*-glycyluridine structure is predicted to be a pharmacophore.[13] On the other hand, the diazepanone moiety was contributory to but not essential for antibacterial activity.[14] These initial SAR studies prompted us to decode the role of the diazepanone in the biological activity more precisely.

The active conformation when the CPZs bind to the target enzyme, MraY, is not yet known because the three-dimensional structure of this integral membrane protein has not been reported. Therefore, it is important to predict the interaction of CPZs with MraY by a structure−activity relationship of CPZ analogues. Although the energy-minimized conformation does not always reflect the biologically active conformation of a compound, the conformational analysis of a ligand in free form might sometimes help to understand its interaction with the target molecule. A solution structure of synthetic caprazol[15] (**5**, Figure 2), a core structure of the CPZs, was first measured by several NMR experiments in D_2O.[16] Key features of the conformation are as follows: the aminoribose moiety is oriented above the 3′-β-face of the uridine moiety, and the 3‴-hydroxyl group on the diazepanone, on which a fatty acyl side chain is installed in the CPZs, is positioned away from the 3′-β-face as shown in Figure 2b. This solution conformation, including the relative spatial orientations of the uridine, the aminoribose, and the fatty acyl side chain, was in good accordance with that observed in the X-ray crystal structure of **5**.[3d] Next, the conformations of **5** were searched by molecular mechanics to determine whether the solution and solid state structures of **5** are correlated to the global-energy minimum conformation calculated by conventional molecular mechanics. The global energy-minimized conformations of **5** were calculated by a conformational search.[18] Structural analysis of energy-minimum conformers revealed two classes of conformers (Figure 2c). In the first class, the global energy-minimized conformation was quite similar to that experimentally observed in solution and solid state in terms of the global spatial orientation of the three key moieties although the conformation of the diazepanone was distorted. In the second class, the aminoribose and the diazepanone moieties interconverted by rotation about the C4′−C5′ bond. Similar results were obtained for palmitoylcaprazol (**3**), the calculations of which were actually conducted for **3′** with a short acyl (butanoyl) group for the sake of simplification (Figure 2d). Since the diazepanone moiety is contributory to but not essential for antibacterial activity, it was predicted that the characteristic diazepanone ring system of the CPZs must play a role as a scaffold on which to hang the three key components mentioned above, thereby allowing them to be placed in the right orientation to interact with the target MraY. The diazepanone moiety is also one of the characteristic structures endowing the CPZs with molecular complexity, and thus, it might be possible to simplify the chemical structure. To obtain some insight into the rational simplification described later, a series of acyclic analogues **6**−**8**, where the diazepanone ring of the CPZs was removed and the lipophilic side chain was attached to either the C-7′ or $N^{6'}$ atom with amide or urea linkages, was used to determine the conformation−activity relationship as shown in Figure 3. First, the global energy-minimized conformations of these analogues **6**−**8** were calculated by a conformational search in a manner similar to **5**. The ionization status for **6**−**8** in H_2O

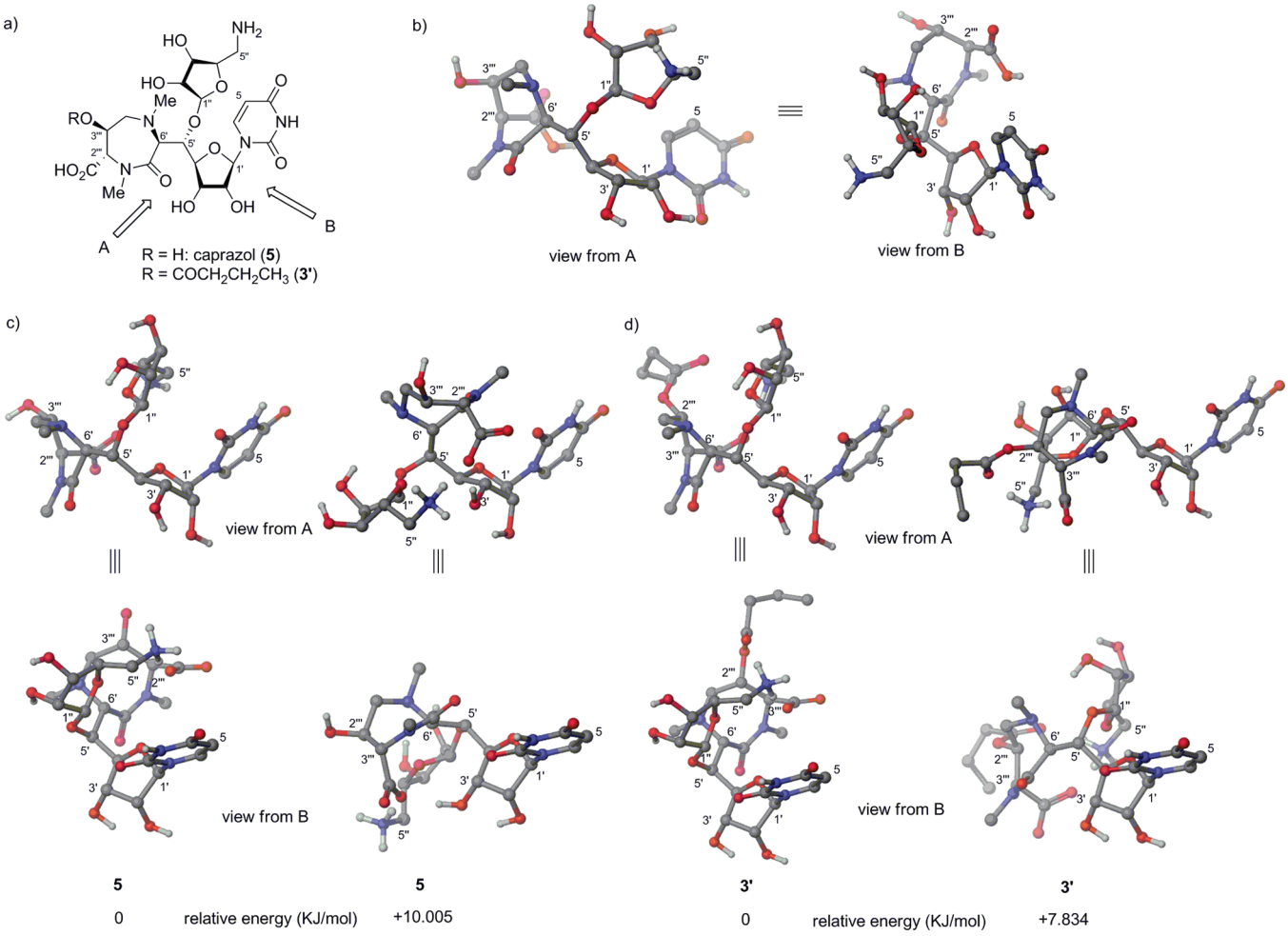


Figure 2. Structure and conformational analysis of **5** and **3′**: (a) chemical structures of caprazol (**5**) and butanoylcaprazole (**3′**); (b) solution structure of **5** in D_2O; (c) calculated two lowest energy-minimum conformers of (c) **5** and (d) **3′**. Macro-Model program, version 9.0, was used for conformational search. Conformational searching was carried out using the Monte Carlo multiple minimum (MCMM) method (100 000 steps), followed by Polak−Ribiere conjugate gradient (PRCG) minimization with the OPLS 2005 force field. Water was chosen for the solvent with the GB/SA model. The other settings were used as default.

at pH 7 ± 2 was first predicted by Epik,[24] which is an empirically based pK_a predictor and ionization state generator based upon the Hammett and Taft methodologies, generating both a protonated and free form at the $N^{6'}$-nitrogen atom for **6** and only one ionization form for **7** and **8**. These structures were used for the following conformational analysis. The lipophilic side chain of each structure was reduced to four carbon atoms to simplify the calculations. Structural analysis of energy-minimum conformers calculated for each of the **6**−**8** analogues falls into two similar classes of conformers, respectively. The classification was similar to that obtained for **3′** and **5**, and the results are summarized in Figure 4. In one class, the spatial positions of the uridine, the aminoribose, and the fatty acyl moiety are similar to those observed in the conformational analyses of **5** (class I). In the other, the aminoribose moiety and the fatty acyl side chain interconvert by rotation about the C4′−C5′ bond (class II). For example, the global energy-minimum conformer of protonated **6** at the 6″-position is in class I (Figure 4a, left), which is predicted to be 7.312 kJ/mol more stable than the corresponding class II conformer by comparing the potential energy of the lowest-energy conformer of each class. According to this analysis, the global energy-minimum conformers of the protonated and free **6** belong to class I, and compounds **7** and **8** belong to class II. From these calculations, the compounds **6** were expected to have MraY inhibitory activity.

On the basis of these predictions, analogues **6**−**8** were synthesized. As a lipophilic side chain, linear alkyl and alkyl groups containing a benzene ring were chosen. Preparation of the key intermediate **12** was previously reported by our group[12] (Scheme 1). However there was a problem in base-catalyzed hydrolysis of the methyl ester **11**, which was sensitive to the basic conditions resulting in partial decomposition. Moreover, controlling the reaction temperature was quite important and it was sometimes difficult to maintain reproducibility especially in large scale preparations. Therefore, we sought to improve this step by using LiI in refluxing AcOEt under near-neutral conditions[25] to provide the carboxylic acid **12** in 81% yield. These conditions minimized the decomposition of **11** especially through β-elimination initiated by deprotonation at the 6′-position. This improvement enabled us to prepare a sufficient quantity of the material necessary for further derivatization. As for preparation of the key intermediate **14** for the synthesis of **7** and **8**, the carboxyl group of **12** was further protected as a ^{t}Bu ester to give **13**, and hydrogenolysis of the Cbz group at the $N^{6'}$-position was catalyzed by Pd/C to give the amine **14**, which was used for the next step without further purification.

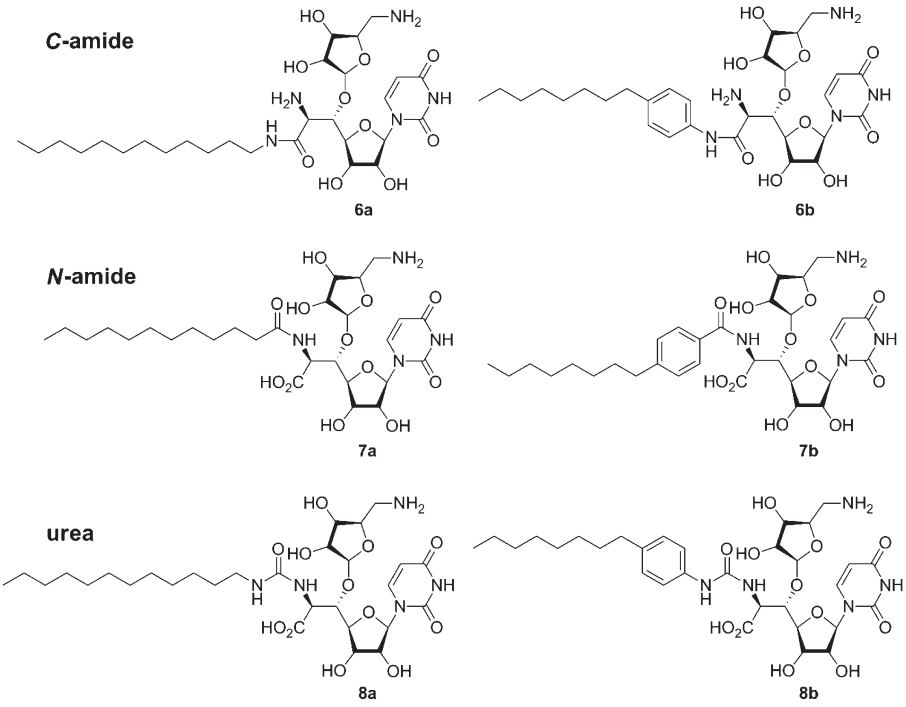


Figure 3. Structures of acyclic analogues.

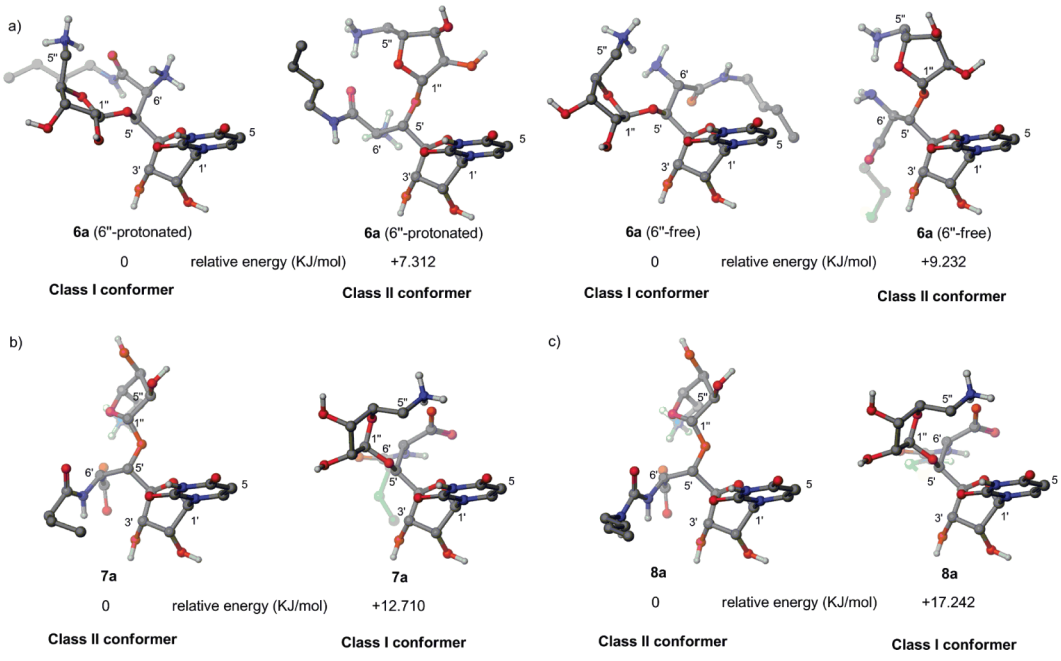
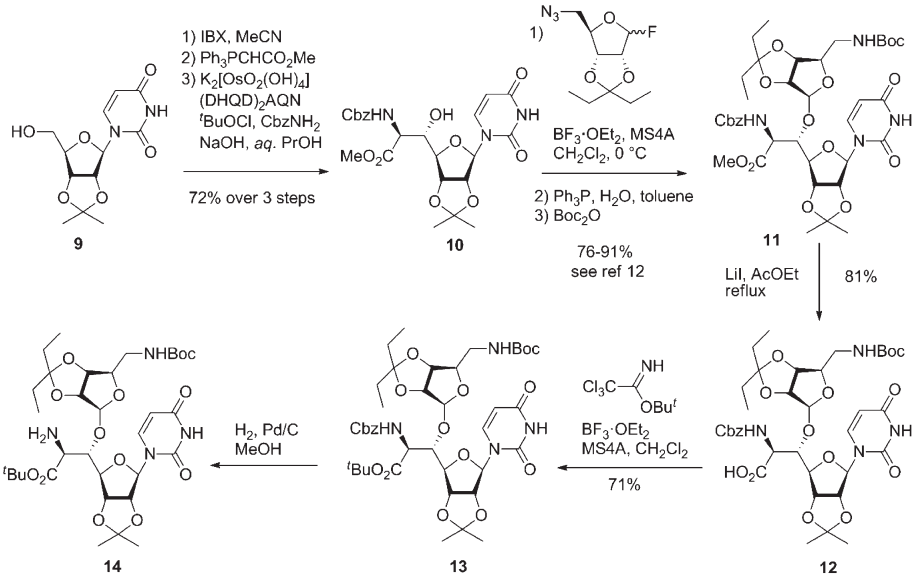


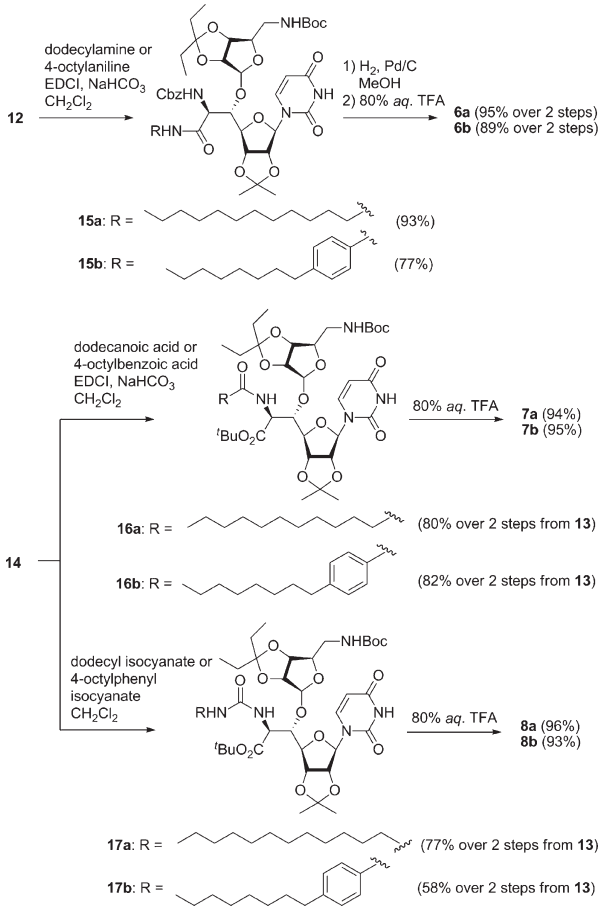
Figure 4. Two classes of energy-minimum conformation of analogues **6a**−**8a**. Macro-Model program, version 9.0, was used for conformational search. Ionization status for **6a**−**8a** in H_2O under pH 7 ± 2 was predicted by the Epik program, which generated both a protonated and free form at the $N^{6'}$-nitrogen atom for **6a**. These structures were used for the following conformational analysis. Conformational searching was carried out using the Monte Carlo multiple minimum (MCMM) method (100 000 steps), followed by Polak−Ribiere conjugate gradient (PRCG) minimization with the OPLS 2005 force field. Water was chosen for the solvent with the GB/SA model. The other settings were used as default. The lipophilic side chain of each structure was reduced to four carbon atoms to simplify the calculations. Shown are two lowest energy-minimum conformers of (a) **6a**, (b) **7a**, (c) **8a**.

The preparation of **6**−**8** is described in Scheme 2. The carboxylic acid **12** was reacted with dodecylamine or 4-octylaniline under the conditions using EDCI and HOBt in CH_2Cl_2 to afford the corresponding amides **15a** (93%) or **15b** (77%), respectively. A two-step deprotection sequence of **15a** or **15b** with hydrogenolysis of the Cbz group and acid-catalyzed hydrolysis of the isopropylidene, 3-pentylidene, and Boc groups provided the *N*-amide derivatives **6a** (95% over two steps from **15a**) or **6b** (89% over two steps from **15b**) as TFA salts. In a similar manner, the $N^{6'}$-acyl derivatives **16a**,**b** were prepared by acylation of **14** with either dodecanoic acid or 4-octylbenzoic acid (80% over two steps for **16a**, 82% over two steps for **16b**) by using EDCI and $NaHCO_3$ in CH_2Cl_2. The urea derivatives **17a**,**b** were also prepared by

Scheme 1



Scheme 2



treatment of **14** with either dodecyl isocyanate or 4-octylphenyl isocyanate (77% over two steps for **17a**, 58% over two steps for **17b**), respectively. Global deprotection of **16** and **17** with 80% aqueous TFA successfully afforded the desired analogues **7** and **8** in good yield as shown in Scheme 2.

The inhibitory effects of a series of acyclic compounds on purified MraY activity were first evaluated,[7] and the results

Table 1. Inhibitory Activities of the Synthesized Compounds against MraY[a]

	C-amide		N-amide		urea	
	6a	**6b**	**7a**	**7b**	**8a**	**8b**
IC_{50} (μM)	18	46	63	256	36	75

[a] The activities of the compounds were tested against purified MraY from *B. subtilis*. The assay was performed in a reaction mixture of 10 mL containing, in final concentrations, 100 mM Tris-HCl, pH 7.5, 40 mM $MgCl_2$, 1.1 mM C_{55}-P, 250 mM NaCl, 0.25 mM UDP-MurNAc-[^{14}C]pentapeptide (337 Bq), and 8.4 mM *N*-lauroyl sarcosine. The mixture was incubated for 30 min at 37 °C. The radiolabeled substrate UDP-MurNAc-pentapeptide and reaction product (lipid I, product of MraY) were separated by TLC on silica gel plates.The radioactive spots were located and quantified with a radioactivity scanner. IC_{50} values were calculated with respect to a control assay without the inhibitor. Data represent the mean of independent triplicate determinations.

are shown in Table 1. The assay was performed by quantifying the incorporation of MurNAc-[^{14}C]pentapeptide by MraY from UDP-MurNAc-[^{14}C]pentapeptide into lipid I. The acyclic analogues **6**–**8** exhibited relatively moderate MraY inhibitory effects. Compounds **6**, which have the class I global energy-minimum conformation, were more active compared to **7** and **8**, compounds with the class II global energy-minimum conformation. Thus, the MraY inhibitory activity of a set of analogues was correlated to some extent to the type of conformers classified by global energy-minimum calculation by these results. It is noteworthy that the presence of a benzene ring attached to the lipophilic side chain led to a decrease in inhibitory efficiency. Antibacterial activity of the analogues was evaluated against a range of bacterial strains including MRSA and VRE, and the minimum inhibitory concentrations (MICs, μg/mL) are summarized in Table 2. The *C*-amide derivatives **6**, categorized as class I according to the global energy-minimum conformer, exhibited antibacterial activity against not only drug-susceptible but also drug-resistant *Enteroccoci* strains (VRE). On the other hand, analogues **7** and **8**, which were in the class II conformation, lost antibacterial activity, which was correlated to the MraY inhibitory activity. Although active, both MraY inhibitory and antibacterial activities of

Table 2. Antibacterial Activity of **6**−**8**

	MIC (μg/mL)[a]					
compd	*S. aureus* ATCC 29213 (MSSA)	*S. aureus* SR3637 (MRSA)	*E. faecalis* ATCC 29212	*E. faecalis* SR7914 (VRE)	*E. facium* ATCC 19434	*E. faecium* SR7917 (VRE)
6a	64	64	16	32	16	16
6b	64	64	16	64	32	32
7a	> 64	> 64	> 64	> 64	> 64	> 64
7b	> 64	> 64	64	> 64	> 64	> 64
8a	> 64	> 64	64	64	> 64	> 64
8b	> 64	> 64	64	64	> 64	> 64
vancomycin	1	1	2	> 64	1	> 64

[a] MICs were determined by a microdilution broth method as recommended by the NCCLS with cation-adjusted Mueller−Hinton broth (CA-MHB). Serial 2-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 0.1 mL. Plates were incubated at 35 °C for 20 h, and then MICs were scored

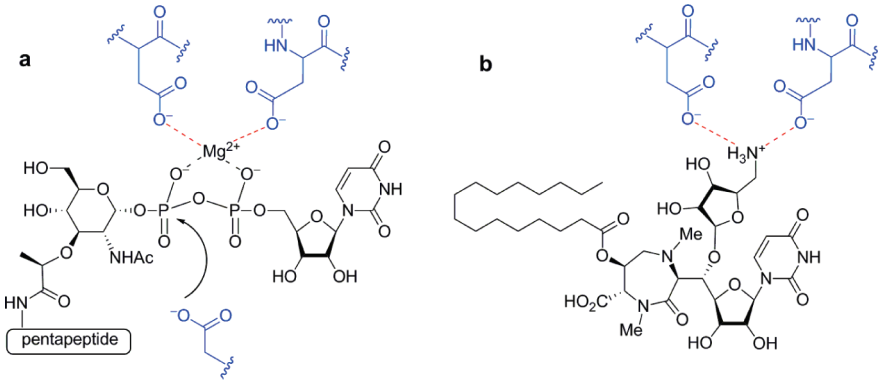


Figure 5. Proposed binding models.

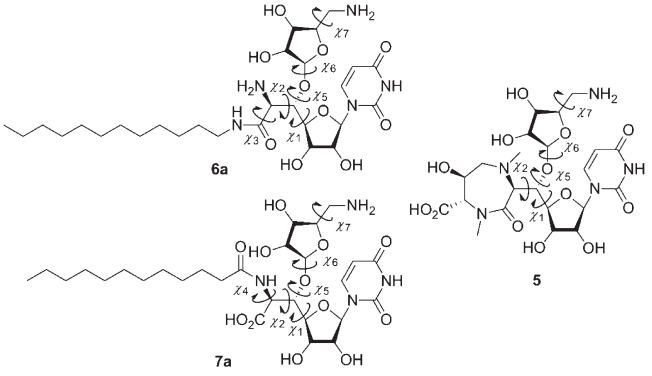


Figure 6. Structural comparison in terms of the rotatable bonds.

analogues **6**−**8** were largely reduced compared to the parent natural products, indicating that the diazepanone moiety was not essential for but contributory to antibacterial activity. Together with studies previously reported,[26] it was revealed experimentally that the characteristic diazepanone ring system of the CPZs plays a role as a scaffold on which to hang three key components, thus allowing them to be placed in the right orientation to interact with the target MraY exhibiting antibacterial activity. We further predicted the interaction of the CPZs with MraY. MraY catalyzes the first membrane step of peptidoglycan biosynthesis, where UDP-MurNAc-pentapeptide is attacked by the undecaprenyl phosphate in the bacterial cell membrane leading to the formation of lipid I. Although the three-dimensional structure is not yet available, extensive studies to elucidate the molecular basis of MraY suggested that several Asp residues are essential for the catalytic activity.[10] It was proposed that in *B. subtilis*, residues H45, D174, and D177 are involved in

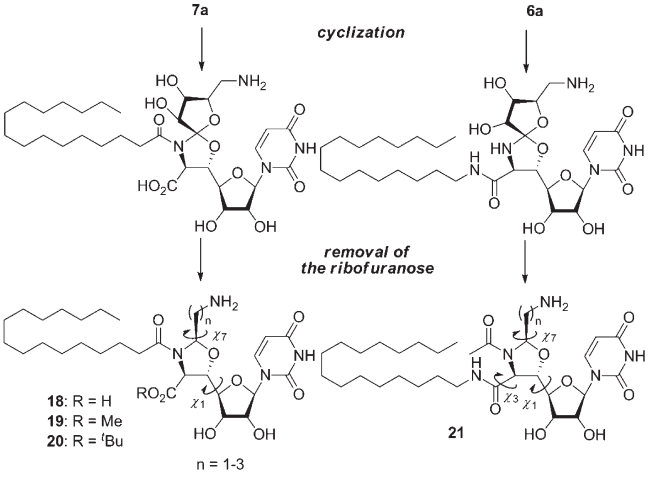
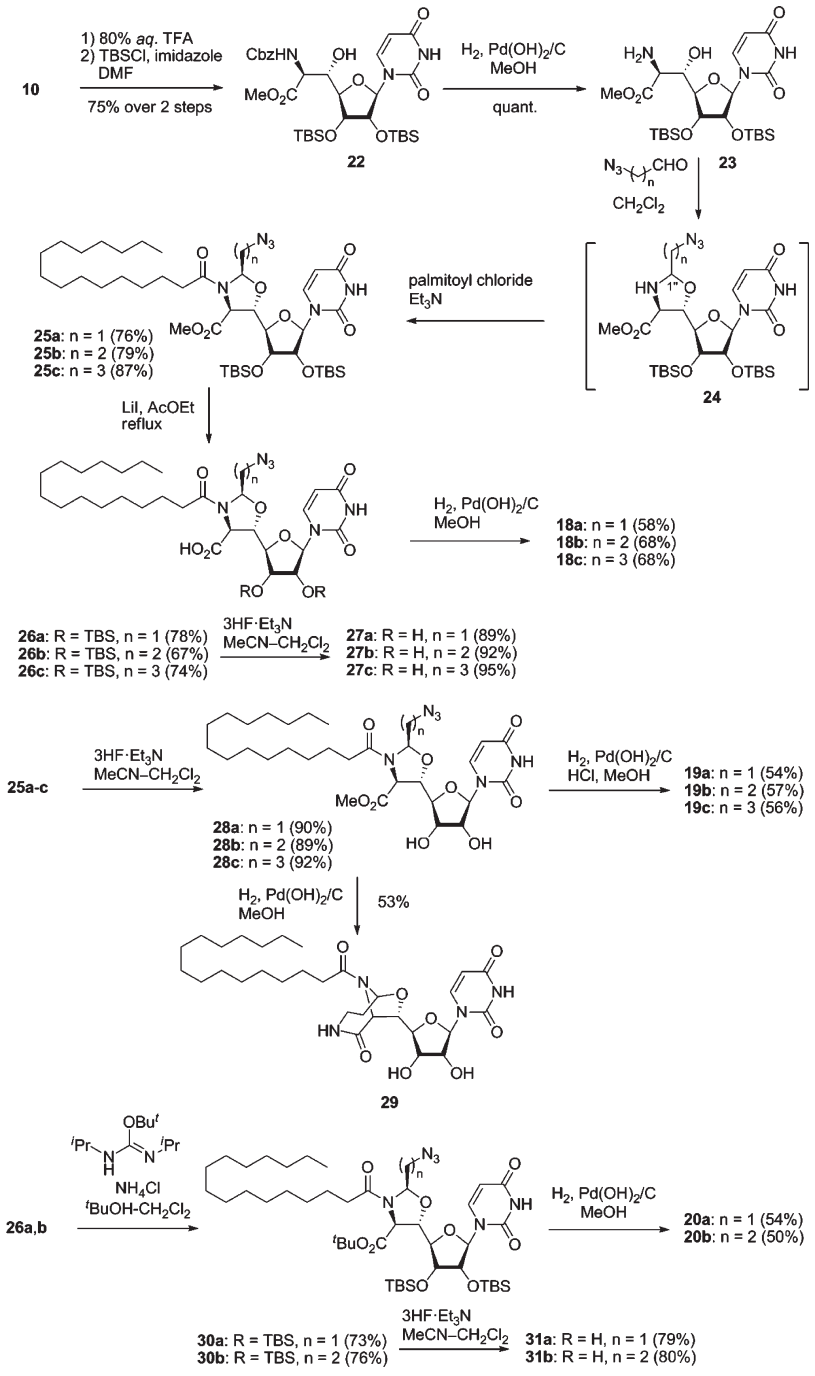


Figure 7. Structures of oxazolidine analogues.

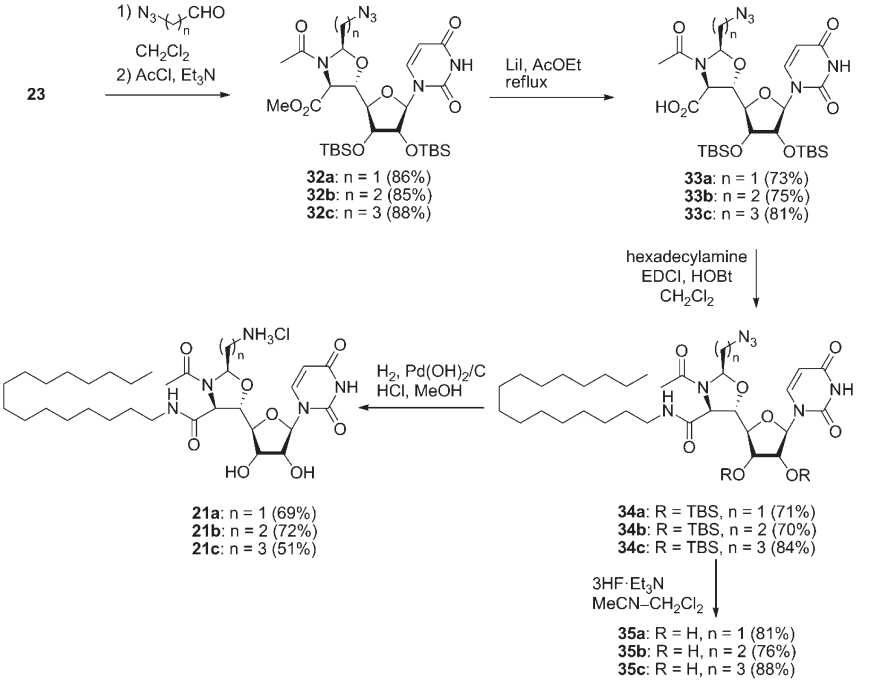
the binding with Mg^{2+}, forming a salt bridge with the diphosphate moiety of the UDP-MurNAc-pentapeptide (Figure 5a). It was also reported that the amino group at the 5″-position of 6′-*N*-alkyl-5′-*β*-*O*-aminoribosyl-*C*-glycyluridine class of antibiotics is necessary for antibacterial activity.[26c] Considering the structural similarity of the UDP-MurNAc-pentapeptide and the CPZs that share a uridine moiety, it is suggested that the ammonium group of the aminoribose moiety could form an ionic bond with the essential residues involved in the binding of the metal cation (Figure 5b). From this model, we speculated that the ribofuranose ring system might also behave as a scaffold linking the terminal ammonium group and the uridine moiety in a proper spatial position.

Scheme 3



Design, Synthesis, and Biological Evaluation of Oxazolidine-Containing Uridine Derivatives. The acyclic analogues **6**−**8** are rather flexible compounds with a number of rotatable bonds. As shown in Figure 6, the dominant determinants of the conformation of **6a** or **7a** are the dihedral angles χ_1−χ_7. Retrospectively considering the conformation of the CPZs compared to the acyclic analogues **6**−**8**, the number of the rotatable dihedral angles is reduced resulting in restriction of the conformation because the CPZs possess the diazepanone ring. This is presumably one of the reasons for the reduced biological activity of the acyclic analogues **6**−**8** with the increased number of the rotatable dihedral angles. We hypothesized that by reducing the number of the rotatable dihedral angles in the acyclic analogues **6**−**8**, we could restrict the number of possible conformers and therefore reduce the molecular complexity and retain the relative spatial orientation of the three key components of the CPZs. Incorporating sequential rotatable bonds through N-6′−C-6′−C-5′−O-5′−C-1″ into a single ring scaffold would result in simultaneous restriction of all the dihedral angles χ_2−χ_6. The oxazolidine ring was selected to be constructed by linking a nitrogen atom at the 6′-position and a carbon atom at the 1″-position of either **6a** or **7a** as shown in Figure 7. The oxazolidine ring formation might be enough to restrict the three key components, and the ribofuranose moiety and the diazepanone ring system could then be removed according to our model for the molecular basis of the activity of the CPZs. Likewise we designed the oxazolidine-containing

Scheme 4



uridine derivatives **18**−**20** from **7a** and **21** from **6a**. This design allowed us to simplify drastically the molecular architecture of the parent CPZs.

Syntheses of the oxazolidine-containing uridine derivatives **18**−**20** and **21** are summarized in Schemes 3 and 4, respectively. The isopropylidene protecting group of **10** was removed by acid-catalyzed hydrolysis, and the resulting triol was selectively protected by a TBS group to give the 2′,3′-di-*O*-TBS derivative **22** in 75% yield over two steps. Hydrogenolysis of the Cbz group at the N^6-position in **22** cleanly provided the amino alcohol **23**. An oxazolidine ring was constructed simply by mixing **23** with azidoacetaldehyde[27] to give **24** as a mixture of diastereomers at the newly formed stereogenic center (1″-position) judging by TLC and ^{1}H NMR analysis of the reaction mixture (about 2:1). Upon treatment of the crude oxazolidine **24** with palmitoyl chloride, the *N*-palmitoyloxazolidine derivative **25a** with the *R*-configuration at the aminal center was selectively obtained in 76% yield from **23**.[28] Determination of the stereochemistry of the newly formed stereogenic center (1″) was confirmed to be *R* (described later). The reaction of **23** with 3-azidopropanal[27] or 4-azidobutanal[27] also gave **25b** (79% over two steps) and **25c** (87% over two steps), respectively, after palmitoylation.

The methyl ester of **25** was converted to the carboxylic acid **26** (78% for **26a**, 67% for **26b**, 74% for **26c**) with LiI in refluxing AcOEt. Finally, deprotection of the TBS groups with 3HF·Et_3N in MeCN−CH_2Cl_2 afforded **27** (89% for **27a**, 92% for **27b**, 95% for **27c**), which was followed by reduction of the azide group to the amine by hydrogenation catalyzed by $Pd(OH)_2$/C to afford the target oxazolidine-containing uridine derivatives **18** (58% for **18a**, 68% for **18b**, 68% for **18c**). The 7′-carboxyl group was not necessary for antibacterial activity, since the *C*-amide derivatives **6a**,**b** showed antibacterial activity. Therefore, the methyl ester derivatives **19a**−**c** were also prepared in order to observe the impact of the carboxyl group attached to the oxazolidine ring on the antibacterial activity. It was also thought that a more

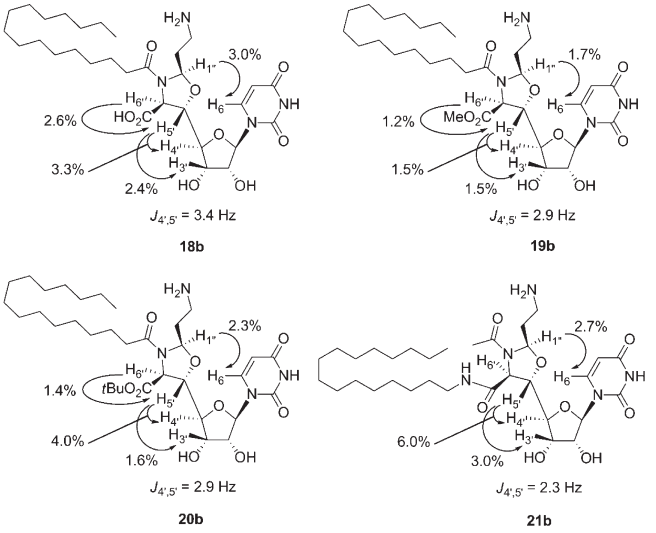


Figure 8. Key NOE correlations observed in CD_3OD.

sterically hindered ester at the 7′-position might restrict the rotation around the C4′−C5′ σ-bond linking the two rings, the ribofuranose and the oxazolidine. Thus, one of the remaining dihedral angles, χ_1, could also be modulated by the choice of a substituent at the carboxyl terminal of the oxazolidine derivatives. With this in mind, we planned to synthesize the ^{t}Bu ester analogues **20** in addition to **19**. The methyl esters **28a**−**c** were obtained simply by deprotection of the TBS groups of **25** (90% for **28a**, 89% for **28b**, 92% for 28c) followed by catalytic hydrogenation of the azide group in the presence of HCl (54% for **19a**, 57% for **19b**, 56% for 19c). In the absence of HCl, catalytic hydrogenation of **28b** gave the bicyclic lactam **29** in 53% yield, which was produced by cyclization upon generation of the free amine. This result clearly indicated that the relative configuration of the aminoalkyl group on the oxazolidine ring was cis to the methyl ester group. The formation of **29** unambiguously determined

Table 3. Antibacterial Activity of Oxazolidine Analogues

	MIC (μg/mL)[a]					
compd	*S. aureus* ATCC 29213 (MSSA)	*S. aureus* SR3637 (MRSA)	*E. faecalis* ATCC 29212	*E. faecalis* SR7914 (VRE)	*E. facium* ATCC 19434	*E. faecium* SR7917 (VRE)
I8a	> 64	> 64	> 64	> 64	> 64	> 64
18b	> 64	> 64	> 64	> 64	> 64	> 64
18c	> 64	> 64	> 64	> 64	> 64	> 64
19a	> 64	13	32	64	32	16
19b	8	8	8	16	4	8
19c	8	8	8	16	8	4
20a	8	16	4	2	4	4
20b	8	16	2	2	2	8
21a	16	32	32	16	16	16
21b	16	16	16	16	16	16
21c	16	32	16	16	16	16
28b	> 64	> 64	16	> 64	64	64
28c	> 64	> 64	32	> 64	> 64	64
4	0.5	0.5	0.5	2	1	1
vancomycin	1	1	1	> 64	> 64	> 64

[a] MICs were determined by a microdilution broth method as recommended by the NCCLS with cation-adjusted Mueller−Hinton broth (CA-MHB). Serial 2-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 0.1 mL. Plates were incubated at 35 °C for 20 h, and then MICs were scored

the stereochemistry of the aminal moiety of **18** and **19** to be the *R*-configuration. The *tert*-butyl esters **20a**,**b** were also synthesized from **26a**,**b**. Protection of the carboxylic acid **26** with *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea[29] in the presence of ammonium chloride in ^{t}BuOH−CH_2Cl_2 gave the ^{t}Bu ester 30 (73% for **30a**, 76% for **30b**). The TBS groups of **30** were removed in a similar manner to give **31** (79% for **31a**, 80% for **31b**) followed by reduction of the azide group to give **20a** (54%) and **20b** (50%), respectively. Analogues **21a**−**c**, which possess an *N*-hexadecylcarbamoyl group at the 6′-position, were synthesized as shown in Scheme 4. Oxazolidine formation of the amine **23** followed by acetylation of the resulting secondary amine selectively gave the *N*-acetyloxazolidines 32a−**c** with the *R*-configuration at the aminal center (86% for **32a**, 85% for **32b**, 88% for **32c**). The methyl esters **32a**−**c** were converted to the carboxylic acids **33a**−**c** (73% for **33a**, 75% for **33b**, 81% for **33c**), which were condensed with hexadecylamine using EDCI and HOBt to provide **34a**−**c** (71% for **34a**, 70% for **34b**, 84% for **34c**). Finally, the target analogues **21a**−**c** were obtained by deprotection of the TBS groups (81% for **35a**, 76% for **35b**, 88% for **35c**) followed by catalytic hydrogenation of the azide group (69% for **21a**, 72% for **21b**, 51% for **21c**). All the analogues were purified by C18 HPLC (80−90% aqueous MeOH, > 98% purity) and used for the evaluation of the antibacterial activity.

With the analogues in hand, the conformation of the synthesized oxazolidine derivatives was then analyzed by NMR experiments. For the sake of the molecular structure of the oxazolidine analogues, where the tetrahydrofuran and oxazolidine rings are connected through a single σ-bond, the conformations of the analogues **18**−**21** are rather restricted and are largely governed by the rotatable dihedral angle of the σ-bond linking the two rings (χ_1). This property allowed us to predict the conformations of **18**−**20** simply by comparing the coupling constant of H-4′ and H-5′ ($J_{4',5'}$) from ^{1}H NMR and NOE experiments in D_2O (Figure 8). The overall data of **18**−**21** were similar. For example, the $J_{4',5'}$ values were relatively small ($J_{4',5'}$ = 3.4 Hz for **18b**, 2.9 Hz for **19b**, 2.9 Hz for **20b**, and 2.3 Hz for **21b**). In addition, a strong NOE correlation was observed for both H-3′and H-4′ upon irradiation at H-5′ although only for H-5′ upon irradiation at H-6′ (Figure 8). Characteristic correlation for H-6 was also observed upon irradiation at H-1″. These data indicated that the dihedral angles χ_1 were estimated to be approximately 60° (clockwise from H-4′ to H-5′) with the two endocyclic oxygen atoms of the tetrahydrofuran and oxazolidine rings in a gauche relationship. As a result, the aminoalkyl group attached to the oxazolidine ring at the 1″-position with the *R*-configuration is oriented above the 3′-β-face of the uridine moiety with the amino group vertical to the tetrahydrofuran face, and the lipophilic side chain is positioned away from the 3′-β-face. The overall conformation of the oxazolidine analogues resembles that observed and calculated for caprazol (**5**) or the class I conformers of **6**−**8**.

Table 4. Inhibitory Activities of the Oxazolidine Derivatives against MraY[a]

	18a	**18b**	**18c**	**19a**	**19b**	**19c**
IC_{50} (μM)	740	451	360	980	920	1200

[a] Experiments were conducted using the same procedure as in Table 1.

The antibacterial activity of three sets of the oxazolidine analogues was evaluated, and the data are shown in Table 3. Analogues with the carboxyl group **18a**−**c** showed no antibacterial activity with MIC up to 64 μg/mL. The corresponding ester analogues **19** and **20**, on the other hand, exhibited antibacterial activity against drug-susceptible *S. aureus*, *E. faecalis*, and *E. faecium* with MICs of 2−16 μg/mL. These analogues were also active against drug-resistant bacterial strains such as MRSA and VRE. It is noteworthy that the antibacterial activity of the *tert*-butyl ester analogues **20a**,**b** was most potent against both the drug-susceptible and drug-resistant *E. faecalis* with a potency similar to that of desmethylpalmitoylcaprazol (**4**). The large contrast between analogues with the carboxylic acid **18** and the esters **19** and **20** in terms of antibacterial activity may be attributed to the permeability of the analogues with regard to the bacterial cell membrane. The amino function at the oxazolidine moiety plays an important role in antibacterial activity by the fact that azide derivatives **28b** and **28c** showed reduced antibacterial activity to a large extent. The analogues **21a**−**c**, which possess an *N*-hexadecylcarbamoyl group at the 6′-position, also exhibited moderate activity. Although FOS of the CPZs was successfully achieved as a function of antibacterial

activity, these analogues were revealed to be weak MraY inhibitors with IC_{50} of 920−1200 μM (Table 4). There could be different target(s) of the oxazolidine analogues, such as **19** and **20**, and further studies are needed to elucidate their mode of action. In summary, a novel class of molecules with a different mode of action from the parent natural products was generated through FOS of the CPZs in this study.

Conclusions

Compared to synthetic drugs, many biologically relevant natural products possess large, complex, or labile chemical structures that may restrict chemical modifications in a structure−activity relationship study. Therefore, it is quite important to pursue FOS, a strategy for the design of less complex structured targets with comparable or superior activity that could be made in a practical manner.

Of significance in this study is a rational and drastic simplification of the CPZ's molecular architecture by decoding the role of the diazepanone and aminoribofuranose moieties in the CPZs and designing the oxazolidine scaffold assisted by conformational considerations. It is important to simplify the hydrophilic core structures of the CPZs in order to reduce the size of the molecules and to stabilize the chemically labile structure. Although this aspect of the research is likely the most difficult to accomplish, a full chemical synthetic approach based on rational drug design considering FOS led to the discovery of the oxazolidine-containing uridine derivatives as the lead compounds active against drug-resistant bacterial pathogens. Oxazolidine-containing uridine derivatives possess a simple chemical structure that can be easily prepared. The simpler scaffold design would provide a practical synthesis of a set of analogues and synthetic innovation in current medicinal chemistry. In developing novel antibacterial agents to treat drug-resistant pathogens, the target must be essential for growth, the agent different from existing drugs, and the initial "hit" scaffold amenable to structural changes that allow for optimization of the potency and efficacy to generate "lead" compounds.[30−32] This study provides a novel strategy for the development of a new type of antibacterial agent effective against drug-resistant bacteria.

Experimental Section

General Experimental Methods. NMR spectra are reported in parts per million (δ) relative to tetramethylsilane (0.00 ppm) as internal standard otherwise noted. Coupling constants (J) are reported in hertz (Hz). Abbreviations of multiplicity are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Data are 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. Purity of all the compounds tested for biological evaluation was confirmed to be >95% by HPLC and ^{1}H NMR analyses.

6-Benzyloxycarbonylamino-5-*O*-[5-*tert*-butoxycarbonylamino-5-deoxy-2,3-*O*-(3-pentylidene)-β-D-*ribo*-pentofuranosyl]-6-deoxy-2,3-*O*-isopropylidene-1-(uracil-1-yl)-β-D-*glycelo*-L-*talo*-heptofuranuronate (12). Lithium iodide (22.0 g, 163 mmol) was added to a solution of **11**[12] (8.80 g, 10.9 mmol) in AcOEt (100 mL) at room temperature, and the resulting mixture was heated under refluxed for 4 h. The reaction mixture was cooled to room temperature and diluted with AcOEt (300 mL). The solution was washed with 0.3 M aqueous HCl, brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (5 cm × 17 cm, 10% MeOH−$CHCl_3$) to afford **12** (6.97 g, 81%) as a white foam, properties of which were identical in all respects to those previously reported.[12] $[\alpha]^{21}_D$ +21.6 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.64 (br d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 7.38−7.27 (m, 5H, phenyl), 5.74 (br s, 1H, H-1′), 5.65 (br d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.22 (s, 1H, H-1″), 5.16 (d, 1H, benzyl, J = 12.5 Hz), 5.11 (m, 1H, H-2′), 5.02 (d, 1H, benzyl, J = 12.5 Hz), 4.98 (m, 1H, H-3′), 4.90 (m, 1H, H-2″), 4.65 (m, 1H, H-6′), 4.56 (d, 1H, H-3″, $J_{3'',2''}$ = 5.8 Hz), 4.50 (m, 1H, H-5′), 4.18−4.11 (m, 2H, H-4′, H-4″), 3.13 (m, 2H, H-5″a, H-5″b), 1.60 (m, 4H, CH_2CH_3 × 2), 1.49 (s, 3H, acetonide), 1.48 (s, 9H, *tert*-butyl), 1.31 (s, 3H, acetonide), 0.79 (m, 6H, CH_2CH_3 × 2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.5, 166.2, 158.5, 152.0, 138.3, 130.3, 129.7, 129.2, 128.7, 117.4, 115.6, 88.4, 87.9, 83.8, 83.4, 80.5, 57.4, 44.5, 30.5, 29.0, 28.6, 28.2, 27.8, 27.3, 25.8, 8.6, 7.9, 7.6; FABMS-HR (NBA) m/z calcd for $C_{37}H_{49}N_4O_{15}$ 789.3194, found 789.3194.

6-Benzyloxycarbonylamino-5-*O*-[5-*tert*-butoxycarbonylamino-5-deoxy-2,3-*O*-(3-pentylidene)-β-D-ribofuranosyl]-6-deoxy-*N*-dodecyl-2,3-*O*-isopropylidene-1-(uracil-1-yl)-β-D-*glycero*-L-*talo*-heptofuranuronamide (15a). A mixture of **12** (79 mg, 0.10 mmol) and dodecylamine (27.8 mg, 0.30 mmol) in CH_2Cl_2 (1 mL) was treated with EDCI (57.5 mg, 0.30 mmol) and HOBt (40 mg, 0.30 mmol) at room temperature for 12 h. The reaction mixture was partitioned between AcOEt and 0.5 N aqueous HCl, and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (2 cm × 6 cm, 60% AcOEt−hexane) to give **15a** (89 mg, 93%) as a white foam: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.68 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 7.43−7.31 (m, 5H, phenyl), 5.75 (s, 1H, H-1′), 5.69 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.21 (d, 1H, benzyl, J = 12.6 Hz), 5.19 (s, 1H, H-1″), 5.11−5.09 (m, 2H, benzyl, H-2′), 4.94 (dd, 1H, H-3′, $J_{3',2'}$ = 4.6, $J_{3',4'}$ = 9.2 Hz), 4.70 (d, 1H, H-2″, $J_{2'',3''}$ = 5.8 Hz), 4.56 (d, 1H, H-3″, $J_{3'',2''}$ = 5.8 Hz), 4.42 (m, 2H, H-5′, H-6′), 4.20 (dd, 1H, H-4′, $J_{4',3'}$ = 9.2, $J_{3',5'}$ = 4.6 Hz), 4.11 (t, 1H, H-4″, $J_{4'',5''}$ = 7.5 Hz), 3.08 (m, 1H, $CH_3(CH_2)_{10}CH_2NH$), 3.17 (m, 2H, $CH_3(CH_2)_{10}CH_2NH$, H-5″a), 3.00 (m, 1H, H-5″b), 1.57−1.32 (m, 39H, $CH_3(CH_2)_{10}CH_2NH$, *tert*-butyl, CH_2CH_3 × 2, acetonide), 0.93 (t, 3H, $CH_3(CH_2)_{10}CH_2NH$, J = 6.9 Hz), 0.85, 0.84 (each t, each 3H, CH_2CH_3, J = 7.4 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 204.6, 198.8, 191.0, 190.9, 184.5, 177.9, 170.6, 162.1, 161.8, 161.7, 149.9, 148.2, 145.2, 135.5, 128.4, 121.2, 120.2, 120.0, 118.0, 116.0, 115.3, 112.9, 112.8, 100.6, 89.7, 76.8, 73.4, 65.6, 63.4, 63.3, 63.2, 63.1, 63.0, 62.9, 62.4, 61.4, 60.6, 60.1, 58.2, 56.3, 47.0, 41.3, 40.3; ESIMS-HR m/z calcd for $C_{49}H_{79}N_5NaO_{14}$ $(M + Na)^+$ 980.5208, found 980.5222.

6-Benzyloxycarbonylamino-5-*O*-[5-*tert*-butoxycarbonylamino-5-deoxy-2,3-*O*-(3-pentylidene)-β-D-ribofuranosyl]-6-deoxy-2,3-*O*-isopropylidene-*N*-(4-octylphenyl)-1-(uracil-1-yl)-β-D-*glycero*-L-*talo*-heptofuranuronamide (15b). Compound **15b** was prepared from **12** (79 mg, 0.10 mmol) and 4-octylaniline (69 μL, 0.30 mmol) as described above for the synthesis of **15a**. Purification by silica gel column chromatography (2 cm × 6 cm, 66% AcOEt/hexane) afforded **15b** (75 mg, 77%) as a white foam: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.67 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 7.49 (d, 2H, $CH_3(CH_2)_6CH_2C_6H_4NH$, J = 8.0 Hz), 7.43−7.31 (m, 5H, phenyl), 7.49 (d, 2H, $CH_3(CH_2)_6CH_2C_6H_4NH$, J = 8.0 Hz), 5.74 (s, 1H, H-1′), 5.67 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.23 (d, 1H, benzyl, J = 12.6 Hz), 5.21 (s, 1H, H-1″), 5.14−5.09 (m, 2H, benzyl, H-2′), 5.05 (m, 1H, H-3′), 4.71 (d, 1H, H-2″, $J_{2'',3''}$ = 6.3 Hz), 4.60 (br s, 1H, H-6′), 4.56 (d, 1H, H-3″, $J_{3'',2''}$ = 6.3 Hz), 4.51 (d, 1H, H-5′, $J_{5',4'}$ = 8.6 Hz), 4.28 (m, 1H, H-4′), 4.07 (t, 1H, H-4″, $J_{4'',5''}$ = 6.9 Hz), 3.13 (dd, 1H, H-5″a, $J_{5''a,4''}$ = 6.9, $J_{5''a,5''b}$ = 13.8 Hz), 2.99 (dd, 1H, H-5″b, $J_{5''b,4''}$ = 6.9, $J_{5''b,5''a}$ = 13.8 Hz), 2.60 (t, 2H, $CH_3(CH_2)_6CH_2C_6H_4NH$, J = 6.9 Hz), 1.67−1.31 (m, 31H, $CH_3(CH_2)_6CH_2C_6H_4NH$, *tert*-butyl, CH_2CH_3 × 2, acetonide), 0.92 (t, 3H, $CH_3(CH_2)_6CH_2C_6H_4NH$, J = 6.9 Hz), 0.85, 0.84 (each t, each 3H, CH_2CH_3, J = 7.4 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 170.4, 166.2, 158.4, 158.3, 152.0, 145.6, 140.4, 138.0, 137.0, 129.7,

129.5, 129.2, 122.0, 117.4, 115.5, 112.9, 102.9, 96.5, 90.0, 87.8, 87.5, 85.5, 83.4, 82.8, 80.7, 80.3, 68.1, 57.6, 54.8, 44.2, 36.4, 33.0, 32.7, 30.6, 30.4, 30.3, 29.8, 28.8, 27.5, 25.6, 23.7, 14.5, 8.8, 7.7; ESIMS-HR m/z calcd for $C_{57}H_{71}N_5NaO_{14}$ $(M + Na)^+$ 1000.4895, found 1000.4889.

***tert*-Butyl 5-*O*-[5-*tert*-Butoxycarbonylamino-5-deoxy-2,3-*O*-(3-pentylidene)-β-D-ribofuranosyl]-6-deoxy-6-dodecanoylamino-2,3-*O*-isopropylidene-1-(uracil-1-yl)-β-D-*glycero*-L-*talo*-heptofuranuronate (16a).** A mixture of **13** (85 mg, 0.1 mmol) and 10% Pd/C (10 mg) in MeOH (3 mL) was vigorously stirred for 1 h under H_2 atmosphere. The catalyst was filtered off through a Celite pad, and the filtrate was concentrated in vacuo to give the free amine **14**. The amine **14** in CH_2Cl_2 (1 mL) was treated with EDCI (57.5 mg, 0.30 mmol) and dodecanoic acid (60 mg, 0.30 mmol) at room temperature for 30 min. The reaction mixture was diluted with AcOEt (50 mL), which was washed with 0.3 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (2 cm × 10 cm, 66% AcOEt−hexane) to give **16a** (72 mg, 80% over two steps) as a white foam: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.70 (d, 1H, H-6, $J_{6,5} = 8.0$ Hz), 5.70 (s, 1H, H-1′), 5.68 (d, 1H, H-5, $J_{5,6} = 8.0$ Hz), 5.23 (dd, 1H, H-2′, $J_{2',1'} = 1.8$, $J_{2',3'} = 6.3$ Hz), 5.08 (s, 1H, H-1″), 4.83 (dd, 1H, H-3′, $J_{3',2'} = 6.3$, $J_{3',4'} = 4.0$ Hz), 4.76 (br d, 1H, H-6′, $J_{6',5'} = 5.7$ Hz), 4.63 (d, 1H, H-2″, $J_{2'',3''} = 5.7$ Hz), 4.55 (d, 1H, H-3″, $J_{3'',2''} = 5.7$ Hz), 4.51 (d, 1H, H-5′, $J_{5',4'} = 5.7$ Hz), 4.14 (m, 2H, H-4′, H-4″), 3.26 (dd, 1H, H-5″a, $J_{5''a,4''} = 6.9$, $J_{5''a,5''b} = 14.3$ Hz), 3.05 (dd, 1H, H-5″b, $J_{5''b,4''} = 8.0$, $J_{5''b,5''a} = 14.3$ Hz), 2.36 (t, 1H, $CH_3(CH_2)_9CH_2CO$, $J = 7.5$ Hz), 2.30 (t, 1H, $CH_3(CH_2)_9CH_2CO$, $J = 7.5$ Hz), 1.67−1.32 (m, 37H, $CH_3(CH_2)_9CH_2CO$, *tert*-butyl, CH_2CH_3 × 2, acetonide), 0.93 (t, 3H, $CH_3(CH_2)_9CH_2CO$, $J = 6.9$ Hz), 0.84, 0.82 (each t, each 3H, CH_2CH_3, $J = 7.4$ Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 177.7, 176.8, 170.6, 166.4, 158.4, 152.0, 146.2, 117.2, 115.4, 114.1, 102.8, 97.6, 89.4, 87.6, 87.3, 85.9, 83.9, 83.3, 81.6, 80.2, 54.9, 44.2, 36.5, 35.0, 33.1, 30.8, 30.7, 30.6, 30.5, 30.4, 30.2, 29.8, 28.8, 28.5, 28.3, 27.5, 27.1, 26.1, 25.4, 23.7, 14.5, 8.8, 8.7, 7.6; ESIMS-HR m/z calcd for $C_{45}H_{74}N_4NaO_{14}$ $(M + H)^+$ 917.5099, found 917.5097.

***tert*-Butyl 5-*O*-[5-*tert*-Butoxycarbonylamino-5-deoxy-2,3-*O*-(3-pentylidene)-β-D-ribofuranosyl]-6-deoxy-2,3-*O*-isopropylidene-6-(4-octylbenzoylamino)-1-(uracil-1-yl)-β-D-*glycero*-L-*talo*-heptofuranuronate (16b).** Compound **16b** was prepared from **13** (85 mg, 0.10 mmol) and 4-octylbenzoic acid (70 mg, 0.30 mmol) as described above for the synthesis of **16a**. Purification by silica gel column chromatography (2 cm × 10 cm, 66% AcOEt/hexane) afforded **16b** (76 mg, 82% over two steps) as a white foam: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.75 (d, 2H, $CH_3(CH_2)_6CH_2C_6H_4CO$, $J = 8.0$ Hz), 7.71 (d, 1H, H-6, $J_{6,5} = 8.0$ Hz), 7.32 (d, 2H, $CH_3(CH_2)_6CH_2C_6H_4CO$, $J = 8.0$ Hz), 5.73 (d, 1H, H-1′, $J_{1'',2''} = 1.7$ Hz), 5.69 (d, 1H, H-5, $J_{5,6} = 8.0$ Hz), 5.22 (dd, 1H, H-2′, $J_{2',1'} = 1.7$, $J_{2',3'} = 6.3$ Hz), 5.14 (s, 1H, H-1″), 4.90 (m, 1H, H-3′), 4.83 (br s, 1H, H-6′), 4.81 (d, 1H, H-2″, $J_{2'',3''} = 5.8$ Hz), 4.61−4.59 (m, 2H, H-3″, H-5′), 4.25 (dd, 1H, H-4′, $J_{5',4'} = 9.2$, $J_{5',6'} = 4.0$ Hz), 4.13 (t, 1H, H-4″, $J_{4'',5''} = 7.4$ Hz), 3.34 (m, 1H, H-5″a), 3.11 (m, 1H, H-5″b), 2.71 (t, 2H, $CH_3(CH_2)_6CH_2C_6H_4CO$, $J = 7.5$ Hz), 1.67−1.31 (m, 31H, $CH_3(CH_2)_6CH_2C_6H_4CO$, *tert*-butyl, CH_2CH_3 × 2, acetonide), 0.92 (t, 3H, $CH_3(CH_2)_6CH_2C_6H_4CO$, $J = 6.9$ Hz), 0.84 (t, 6H, CH_2CH_3 × 2, $J = 7.4$ Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 170.7, 170.4, 166.3, 152.0, 148.6, 145.9, 132.7, 129.7, 128.6, 117.3, 115.5, 114.0, 102.9, 97.0, 89.2, 87.5, 87.4, 85.8, 84.1, 83.4, 83.1, 81.5, 80.2, 55.4, 44.3, 36.8, 33.0, 32.4, 30.6, 30.5, 30.4, 30.3, 29.8, 28.8, 28.5, 28.3, 27.4, 25.5, 23.7, 14.5, 8.8, 7.7; ESIMS-HR m/z calcd for $C_{48}H_{72}N_4NaO_{14}$ $(M + Na)^+$ 951.4943, found 951.4939.

***tert*-Butyl 5-*O*-[5-*tert*-Butoxycarbonylamino-5-deoxy-2,3-*O*-(3-pentylidene)-β-D-ribofuranosyl]-6-deoxy-6-dodecylureido-2,3-*O*-isopropylidene-1-(uracil-1-yl)-β-D-*glycero*-L-*talo*-heptofuranuronate (17a).** A mixture of **13** (85 mg, 0.1 mmol) and 10% Pd/C (10 mg) in MeOH (3 mL) was vigorously stirred for 1 h under H_2 atmosphere. The catalyst was filtered off through a Celite pad, and the filtrate was concentrated in vacuo to give the free amine **14**. The amine **14** in CH_2Cl_2 (1 mL) was treated with dodecyl isocyanate (240 mg, 1.0 mmol) at room temperature for 3 h. The reaction mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography (2 cm × 10 cm, 66% AcOEt−hexane) to give **17a** (72 mg, 77% over two steps) as a white foam: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.71 (d, 1H, H-6, $J_{6,5} = 8.0$ Hz), 5.71 (d, 1H, H-1′, $J_{1',2'} = 1.7$ Hz), 5.68 (d, 1H, H-5, $J_{5,6} = 8.0$ Hz), 5.22 (dd, 1H, H-2′, $J_{2',1'} = 1.7$, $J_{2',3'} = 6.3$ Hz), 5.08 (s, 1H, H-1″), 4.86 (dd, 1H, H-3′, $J_{3',2'} = 6.3$, $J_{3',4'} = 4.0$ Hz), 4.71 (d, 1H, H-2″, $J_{2'',3''} = 5.7$ Hz), 4.55 (d, 1H, H-3″, $J_{3'',2''} = 5.7$ Hz), 4.46 (m, 2H, H-5′, H-6′), 4.20 (dd, 1H, H-4′, $J_{4',3'} = 9.2$, $J_{4',5'} = 3.5$ Hz), 4.10 (t, 1H, H-4″, $J_{4'',5''} = 7.5$ Hz), 3.28 (dd, 1H, H-5″a, $J_{5''a,4''} = 6.9$, $J_{5''a,5''b} = 14.3$ Hz), 3.16 (m, 2H, $CH_3(CH_2)_{10}CH_2NH$), 2.99 (dd, 1H, H-5″b, $J_{5''b,4''} = 8.0$, $J_{5''b,5''a} = 14.3$ Hz), 1.59−1.32 (m, 39H, $CH_3(CH_2)_{10}CH_2NH$, *tert*-butyl, CH_2CH_3 × 2, acetonide), 0.93 (t, 3H, $CH_3(CH_2)_{10}CH_2NH$, $J = 6.9$ Hz), 0.84, 0.83 (each t, each 3H, CH_2CH_3, $J = 7.4$ Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 172.1, 166.4, 160.6, 158.5, 152.1, 146.1, 117.3, 115.4, 113.8, 102.8, 97.3, 89.0, 87.6, 87.2, 85.7, 83.6, 83.3, 82.1, 80.3, 55.2, 44.4, 40.1, 33.1, 31.3, 30.8, 30.7, 30.6, 30.5, 30.4, 29.8, 28.8, 28.5, 27.9, 27.5, 25.5, 23.7, 14.5, 8.8, 7.6; ESIMS-HR m/z calcd for $C_{44}H_{77}N_5NaO_{14}$ $(M + H)^+$ 946.5365, found 946.5343.

***tert*-Butyl 5-*O*-[5-*tert*-Butoxycarbonylamino-5-deoxy-2,3-*O*-(3-pentylidene)-β-D-ribofuranosyl]-6-deoxy-2,3-*O*-isopropylidene-6-(4-octylphenylureido)-1-(uracil-1-yl)-β-D-*glycero*-L-*talo*-heptofuranuronate (17b).** Compound **17b** was prepared from **13** (85 mg, 0.10 mmol) and 4-octylphenyl isocyanate (244 mg, 1.0 mmol) as described above for the synthesis of **17a**. Purification by silica gel column chromatography (2 cm × 10 cm, 66% AcOEt/hexane) afforded **17b** (76 mg, 58% over two steps) as a white foam: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.71 (d, 1H, H-6, $J_{6,5} = 7.9$ Hz), 7.28 (d, 2H, $CH_3(CH_2)_6CH_2C_6H_4NH$, $J = 8.0$ Hz), 7.09 (d, 2H, $CH_3(CH_2)_6CH_2C_6H_4NH$, $J = 8.0$ Hz), 5.71 (d, 1H, H-1′, $J_{1'',2''} = 1.7$ Hz), 5.67 (d, 1H, H-5, $J_{5,6} = 7.9$ Hz), 5.24 (dd, 1H, H-2′, $J_{2',1'} = 1.7$, $J_{2',3'} = 6.9$ Hz), 5.11 (s, 1H, H-1″), 4.90 (dd, 1H, H-3′, $J_{3',2'} = 6.9$, $J_{3',4'} = 4.0$ Hz), 4.73 (d, 1H, H-2″, $J_{2'',3''} = 6.3$ Hz), 4.56 (d, 1H, H-3″, $J_{3'',2''} = 6.3$ Hz), 4.53 (br s, 1H, H-6′), 4.83 (br s, 1H, H-5′), 4.23 (dd, 1H, H-4′, $J_{5',4'} = 9.2$, $J_{5',6'} = 4.5$ Hz), 4.12 (t, 1H, H-4″, $J_{4'',5''} = 7.4$ Hz), 3.30 (dd, 1H, H-5″a, $J_{5''a,4''} = 7.5$, $J_{5''a,5''b} = 13.8$ Hz), 3.01 (dd, 1H, H-5″b, $J_{5''b,4''} = 7.5$, $J_{5''b,5''a} = 13.8$ Hz), 2.57 (t, 2H, $CH_3(CH_2)_6CH_2C_6H_4NH$, $J = 8.0$ Hz), 1.61−1.31 (m, 31H, $CH_3(CH_2)_6CH_2C_6H_4NH$, *tert*-butyl, CH_2CH_3 × 2, acetonide), 0.92 (t, 3H, $CH_3(CH_2)_6CH_2C_6H_4NH$, $J = 6.9$ Hz), 0.84, 0.83 (each t, each 3H, CH_2CH_3, $J = 7.4$ Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 171.9, 166.4, 158.5, 157.8, 152.0, 146.2, 138.4, 138.1, 129.7, 120.3, 117.3, 115.5, 113.9, 102.8, 97.5, 89.2, 87.6, 87.2, 85.8, 83.9, 83.4, 83.3, 82.1, 80.4, 55.1, 44.5, 36.2, 33.0, 32.8, 30.6, 30.4, 30.3, 29.8, 28.8, 28.5, 28.4, 27.4, 25.5, 23.7, 14.5, 8.9, 7.6; ESIMS-HR m/z calcd for $C_{48}H_{73}N_5NaO_{14}$ $(M + Na)^+$ 966.5052, found 966.4919.

6-Amino-5-*O*-(5-amino-5-deoxy-β-D-ribofuranosyl)-6-deoxy-*N*-dodecyl-1-(uracil-1-yl)-β-D-*glycero*-L-*talo*-heptofuranuronamide Trifluoroacetic Salt (6a). A mixture of **15a** (50 mg, 0.060 mmol) and 10% Pd/C (10 mg) in MeOH (1 mL) was vigorously stirred for 1 h under H_2 atmosphere. The catalyst was filtered off through a Celite pad, and the filtrate was concentrated in vacuo to give the free amine. The amine was treated with 80% aqueous TFA (1 mL) at room temperature for 6 h. The reaction mixture was concentrated in vacuo, and the residue was purified by C18 reverse phase column chromatography (1.5 cm × 10 cm, 80% aqueous MeOH containing 0.5% TFA) to afford **6a** (35 mg, 95% over two steps) as a TFA salt: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.74 (d, 1H, H-6, $J_{6,5} = 8.0$ Hz), 5.86 (s, 1H, H-1′), 5.76 (d, 1H, H-5, $J_{5,6} = 8.0$ Hz), 5.15 (d, 1H, H-1″, $J_{1'',2''} = 2.3$ Hz), 4.38 (br s, 1H, H-5′), 4.30 (m, 2H, H-3′, H-3″), 4.25 (d, 1H, H-2′, $J_{2',3'} = 5.2$ Hz), 4.16−4.11 (m, 4H, H-4′, H-6′, H-2″, H-4″), 3.39 (m, 1H,

$CH_3(CH_2)_9CH_2CH_2NH$), 3.26 (br s, 2H, H-5″a, H-5″b), 3.24 (m, 1H, $CH_3(CH_2)_9CH_2CH_2NH$), 1.61 (m, 2H, $CH_3(CH_2)_9CH_2CH_2NH$), 1.35−1.32 (m, 18H, $CH_3(CH_2)_9CH_2CH_2NH$), 0.93 (t, 3H, $CH_3(CH_2)_9CH_2CH_2NH$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 168.7, 166.0, 152.1, 142.6, 112.2, 102.9, 93.2, 93.1, 85.4, 81.6, 79.4, 76.5, 74.7, 72.8, 70.3, 56.8, 43.1, 41.2, 33.0, 30.8, 30.7, 30.5, 30.4, 30.0, 28.1, 23.7, 14.4; ESIMS-HR m/z calcd for $C_{28}H_{50}N_5O_{10}$ $(M + H)^+$ 616.3479, found 616.3723.

6-Amino-5-*O*-(5-amino-5-deoxy-β-D-ribofuranosyl)-6-deoxy-1-*N*-(4-octylphenyl)(uracil-1-yl)-β-D-*glycero*-L-*talo*-heptofuranuronamide Trifluoroacetic Salt (6b). Compound **6b** was prepared from **15b** (30 mg, 0.030 mmol) as described above for the synthesis of **6a**. Purification by C18 reverse phase column chromatography (1.5 cm × 10 cm, 80% aqueous MeOH containing 0.5% TFA) afforded **6b** (17 mg, 89% over two steps) as a TFA salt: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.72 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 7.47 (d, 2H, $CH_3(CH_2)_5CH_2CH_2C_6H_4NH$, J = 8.6 Hz), 7.22 (d, 2H, $CH_3(CH_2)_5CH_2CH_2C_6H_4NH$, J = 8.6 Hz), 5.83 (d, 1H, H-1′, $J_{1',2'}$ = 2.3 Hz), 5.73 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.17 (d, 1H, H-1″, $J_{1'',2''}$ = 2.3 Hz), 4.55 (br s, 1H, H-5′), 4.43 (d, 1H, H-3″, $J_{3'',2''}$ = 6.0 Hz), 4.31 (dd, 1H, H-3′, $J_{3',2'}$ = 5.1, $J_{3',4'}$ = 8.0 Hz), 4.26 (dd, 1H, H-2′, $J_{2',1'}$ = 2.3, $J_{2',3'}$ = 5.1 Hz), 4.18 (dd, 1H, H-4′, $J_{4',3'}$ = 8.0, $J_{4',5'}$ = 5.3 Hz), 4.04 (dd, 1H, H-2″, $J_{2'',1''}$ = 2.3, $J_{2'',3''}$ = 6.0 Hz), 4.04 (t, 1H, H-6′, $J_{6',5'}$ = 5.2 Hz), 4.04 (dd, 1H, H-4″, $J_{4'',5''a}$ = 6.0, $J_{4'',5''b}$ = 6.9 Hz), 3.05 (br s, 2H, H-5″a, H-5″b), 2.60 (t, 2H, $CH_3(CH_2)_5CH_2CH_2C_6H_4NH$), 1.61 (m, 2H, $CH_3(CH_2)_5CH_2CH_2C_6H_4NH$), 1.32−1.28 (m, 10H, $CH_3(CH_2)_5CH_2CH_2C_6H_4NH$), 0.89 (t, 3H, $CH_3(CH_2)_5CH_2CH_2C_6H_4NH$, J=6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 167.0, 166.1, 152.1, 142.7, 141.8, 140.3, 136.1, 130.2, 122.1, 111.7, 102.9, 85.3, 81.1, 78.6, 76.4, 74.6, 72.8, 70.5, 57.3, 43.1, 36.4, 33.0, 32.7, 30.6, 30.4, 30.3, 23.7, 14.4; ESIMS-HR m/z calcd for $C_{30}H_{46}N_5O_{10}$ $(M + H)^+$ 636.3166, found 636.3231.

5-*O*-(5-Amino-5-deoxy-β-D-ribofuranosyl)-6-deoxy-6-dodecanoylamino-1-(uracil-1-yl)-β-D-*glycero*-L-*talo*-heptofuranuronic Acid Trifluoroacetic Salt (7a). Compound **16a** (50 mg, 0.056 mmol) was treated with 80% aqueous TFA (1 mL) at room temperature for 6 h. The reaction mixture was concentrated in vacuo, and the residue was purified by C18 reverse phase column chromatography (1.5 cm × 10 cm, 80% aqueous MeOH containing 0.5% TFA) to afford **7a** (33 mg, 94%) as a TFA salt: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.85 (d, 1H, H-6, $J_{6,5}$ = 8.1 Hz), 5.76 (s, 1H, H-1′), 5.75 (d, 1H, H-5, $J_{5,6}$=8.1 Hz), 5.20 (s, 1H, H-1″), 5.00 (d, 1H, H-6′, $J_{6',5'}$ = 2.9 Hz), 4.32 (dd, 1H, H-5′, $J_{5',4'}$ = 2.9, $J_{5',6'}$ = 4.6 Hz), 4.20 (t, 1H, H-2′, $J_{2',3'}$ = 4.0 Hz), 4.33−4.17 (m, 5H, H-3′, H-4′, H-2″, H-3″, H-4″), 4.06 (d, 1H, H-3″, $J_{3',2'}$ = 4.0 Hz), 3.30 (br d, 1H, H-5″a, $J_{5''a,5''b}$ = 12.6 Hz), 3.24 (dd, 1H, H-5″b, $J_{5''b,4''}$ = 9.2, $J_{5''b,5''a}$ = 12.6 Hz), 3.34 (t, 2H, $CH_3(CH_2)_8CH_2CH_2CO$, J=7.5 Hz), 1.64 (m, 2H, $CH_3(CH_2)_8CH_2CH_2CO$), 1.32 (br s, 16H, $CH_3(CH_2)_8CH_2CH_2CO$), 0.93 (t, 3H, $CH_3(CH_2)_8CH_2CH_2CO$, J=6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 176.6, 173.7, 166.1, 152.1, 142.9, 111.0, 102.6, 101.3, 92.2, 84.8, 79.9, 79.8, 76.3, 74.8, 73.9, 71.5, 55.0, 44.3, 36.6, 33.1, 30.8, 30.7, 30.6, 30.5, 30.4, 30.3, 26.9, 25.1, 23.7, 14.4; ESIMS-HR m/z calcd for $C_{28}H_{47}N_4O_{12}$ $(M + H)^+$ 613.3112, found 613.3177.

5-*O*-(5-Amino-5-deoxy-β-D-ribofuranosyl)-6-deoxy-1-6-(4-octylbenzolyamino)-1-(uracil-1-yl)-β-D-*glycero*-L-*talo*-heptofuranuronic Acid Trifluoroacetic Salt (7b). Compound **7b** was prepared from **16b** (50 mg, 0.056 mmol) as described above for the synthesis of **7a**. Purification by C18 reverse phase column chromatography (1.5 cm × 10 cm, 80% aqueous MeOH containing 0.5% TFA) gave **7b** (34 mg, 95%) as a TFA salt: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.86 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 7.78 (d, 2H, $CH_3(CH_2)_5CH_2CH_2C_6H_4CO$, J = 8.3 Hz), 7.32 (d, 2H, $CH_3(CH_2)_5CH_2CH_2C_6H_4CO$, J = 8.3 Hz), 5.77 (d, 1H, H-1′, $J_{1',2'}$ = 3.7 Hz), 5.76 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.25 (s, 1H, H-1″), 5.19 (d, 1H, H-6′, $J_{6',5'}$ = 3.2 Hz), 4.47 (br s, 1H, H-5′), 4.26 (dd, 1H, H-4′, $J_{4',3'}$ = 4.1, $J_{4',5'}$ = 6.0 Hz), 4.24 (dd, 1H, H-2′, $J_{2',1'}$ = 3.7, $J_{2',3'}$ = 5.5 Hz), 4.19 (dd, 1H, H-3′, $J_{3',2'}$ = 5.5, $J_{3',4'}$ = 4.1 Hz), 4.16 (m, 2H, H-2″, H-4″), 4.10 (d, 1H, H-3″, $J_{3',2'}$ = 3.7 Hz), 3.30 (br d, 1H, H-5″a, $J_{5''a,5''b}$ = 12.9 Hz), 3.23 (dd, 1H, H-5″b, $J_{5''b,4''}$ = 9.2, $J_{5''b,5''a}$ = 12.9 Hz), 2.71 (t, 2H, $CH_3(CH_2)_5CH_2CH_2C_6H_4CO$, J = 7.8 Hz), 1.67 (m, 2H, $CH_3(CH_2)_5CH_2CH_2C_6H_4CO$), 1.36−1.31 (m, 10H, $CH_3(CH_2)_5CH_2CH_2C_6H_4CO$), 0.92 (t, 3H, $CH_3(CH_2)_5CH_2CH_2C_6H_4CO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 173.7, 170.5, 166.1, 152.1, 148.8, 142.9, 132.5, 129.7, 128.7, 111.1, 102.6, 92.3, 84.8, 80.0, 79.8, 76.3, 74.7, 73.9, 71.6, 55.8, 44.3, 36.8, 33.0, 32.4, 30.5, 30.4, 30.3, 23.7, 14.4; ESIMS-HR m/z calcd for $C_{31}H_{44}N_4NaO_{12}$ $(M + Na)^+$ 687.2852, found 687.2845.

5-*O*-(5-Amino-5-deoxy-β-D-ribofuranosyl)-6-deoxy-6-dodecylureido-1-(uracil-1-yl)-β-D-*glycero*-L-*talo*-heptofuranuronic Acid Trifluoroacetic Salt (8a). Compound **8a** was prepared from **17a** (50 mg, 0.056 mmol) as described above for the synthesis of **7a**. Purification by C18 reverse phase column chromatography (1.5 cm × 10 cm, 80% aqueous MeOH containing 0.5% TFA) gave **8a** (34 mg, 96%) as a TFA salt: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.87 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.79 (d, 1H, H-1′, $J_{1',2'}$ = 4.0 Hz), 5.76 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.20 (s, 1H, H-1″), 4.80 (d, 1H, H-6′, $J_{6',5'}$ = 2.3 Hz), 4.33 (br s, 1H, H-5′), 4.20−4.17 (m, 4H, H-2′, H-3′, H-4′, H-2″), 4.13 (br d, 1H, H-4″, J = 3.6 Hz), 4.04 (d, 1H, H-3″, $J_{3',2'}$ = 4.0 Hz), 3.32 (m, 1H, H-5″a), 3.22 (m, 1H, H-5″b), 3.15 (t, 2H, $CH_3(CH_2)_9CH_2CH_2NH$, J = 6.9 Hz), 1.49 (m, 2H, $CH_3(CH_2)_9CH_2CH_2NH$), 1.32 (m, 18H, $CH_3(CH_2)_9CH_2CH_2NH$), 0.93 (t, 3H, $CH_3(CH_2)_9CH_2CH_2NH$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.4, 166.1, 160.4, 152.2, 142.8, 110.7, 102.6, 91.6, 84.8, 80.2, 79.8, 76.3, 74.7, 74.0, 71.4, 55.4, 44.4, 40.9, 33.1, 31.2, 30.8, 30.5, 28.0, 23.7, 14.4; ESIMS-HR m/z calcd for $C_{29}H_{49}N_5NaO_{12}$ $(M + Na)^+$ 682.3275, found 682.3285.

5-*O*-(5-Amino-5-deoxy-β-D-ribofuranosyl)-6-deoxy-1-6-(4-octylphenylureido)(uracil-1-yl)-β-D-*glycero*-L-*talo*-heptofuranuronic Acid Trifluoroacetic Salt (8b). Compound **8b** was prepared from **17b** (61 mg, 0.065 mmol) as described above for the synthesis of **7a**. Purification by C18 reverse phase column chromatography (1.5 cm × 10 cm, 80% aqueous MeOH containing 0.5% TFA) gave **8b** (41 mg, 93%) as a TFA salt: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.86 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 7.28 (d, 2H, $CH_3(CH_2)_5CH_2CH_2C_6H_4NH$, J = 8.1 Hz), 7.10 (d, 2H, $CH_3(CH_2)_5CH_2CH_2C_6H_4NH$, J = 8.1 Hz), 5.80 (d, 1H, H-1′, $J_{1',2'}$ = 3.7 Hz), 5.76 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.23 (s, 1H, H-1″), 4.87 (br s, 1H, H-6′), 4.42 (br s, 1H, H-5′), 4.23−4.21 (m, 3H, H-2′, H-4′, H-2″), 4.15 (br s, 1H, H-4″), 4.07 (br s, 1H, H-3″), 3.34 (m, 1H, H-5″a), 3.22 (m, 1H, H-5″b), 2.57 (t, 2H, $CH_3(CH_2)_5CH_2CH_2C_6H_4NH$, J=8.0 Hz), 1.62 (m, 2H, $CH_3(CH_2)_5CH_2CH_2CH_2C_6H_4NH$), 1.36−1.31 (m, 10H, $CH_3(CH_2)_5CH_2CH_2C_6H_4NH$), 0.93 (t, 3H, $CH_3(CH_2)_5CH_2CH_2C_6H_4NH$, J=6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 176.6, 166.1, 157.8, 152.2, 142.9, 138.6, 138.0, 129.8, 127.6, 120.4, 110.8, 102.7, 91.9, 84.8, 80.1, 79.9, 76.3, 74.7, 74.0, 71.4, 55.4, 44.3, 36.2, 33.0, 32.8, 30.6, 30.4, 30.3, 23.7, 14.4; ESIMS-HR m/z calcd for $C_{31}H_{45}N_5NaO_{12}$ $(M + Na)^+$ 702.2962, found 702.2965.

Methyl 6-Benzyloxycarbonylamino-2,3-di-*O*-(*tert*-butyldimethylsilyl)-6-deoxy-1-(uracil-1-yl)-β-D-*glycelo*-L-*talo*-heptofuranuronate (22). Compound **10** (1.50 g, 3.0 mmol) was treated with 80% aqueous TFA (30 mL) for 1 h. The solvent was removed in vacuo. The residue in DMF (30 mL) was treated with TBSCl (1.40 g, 9.0 mmol) and imidazole (1.22 g, 18.0 mmol), and the mixture was stirred for 60 h. After the reaction was quenched with H_2O (10 mL), the mixture was partitioned between AcOEt and H_2O, and the organic layers were washed H_2O, 1 N aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (5 cm × 13 cm, 33% AcOEt/hexane) to give **22** (1.56 g, 75% over two steps) as a white solid: ^{1}H NMR (CD_3OD, 500 MHz) δ 8.10 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 7.32 (m, 5H, phenyl), 5.88 (d, 1H, H-1′, $J_{1',2'}$ = 5.7 Hz), 5.70 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.15 (d, 1H, benzyl, J = 12.6 Hz), 5.01 (d, 1H, benzyl, J = 12.6 Hz), 4.51 (d, 1H, H-4′, $J_{4',3'}$ = 5.2 Hz), 4.36 (dd, 1H, H-2′, $J_{2',1'}$ = 5.7, $J_{2',3'}$ = 3.6 Hz), 4.16 (m, 1H, H-5′), 4.15 (m, 1H, H-6′), 4.12 (d, 1H, H-3′, $J_{3',4'}$ = 5.2 Hz), 3.72 (s, 3H,

−CO_2Me), 0.93, 0.88 (each s, each 9H, *tert*-butyl), 0.12, 0.12, 0.06, 0.01, (each s, each 3H, SiMe$_3$); ^{13}C NMR (CD_3OD, 125 MHz) δ 172.4, 166.1, 158.6, 152.4, 143.1, 138.1, 129.4, 129.1, 128.8, 103.1, 89.7, 87.8, 76.3, 75.2, 70.9, 67.7, 58.5, 52.9, 26.4, 18.9, 18.9, −4.2, −4.4, −4.5, −4.6; ESIMS-HR calcd for $C_{32}H_{51}N_3NaO_{10}Si_2$ $(M + Na)^+$ 716.3011, found 716.2993.

(2*R*,4*S*,5*S*)-Methyl 2-Azidomethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-di-*tert*-butyldimethylsilyloxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylate (25a). Azidoacetoaldehyde was prepared as follows. A solution of azidoethanol[33] (626 mg, 7.2 mmol) in CH_2Cl_2 (70 mL) was treated by Dess−Martin periodinane[34] (3.97 g, 9.36 mmol) at room temperature for 1 h. The insoluble was filtered off through a Celite pad, and the filtrate was concentrated in vacuo. The residue was semipurified by silica gel column chromatography (3 cm × 10 cm, 25% Et_2O−pentane) to give azidoacetoaldehyde (620 mg, quant). A solution of **22** (1.00 g, 1.45 mmol) and 10% Pd-$(OH)_2$/C (66 mg) in MeOH (15 mL) was vigorously stirred at room temperature under H_2 atmosphere for 2 h. The catalyst was filtered off through a Celite pad, and the filtrate was concentrated in vacuo to give the free amine **23**. The amine, azidoacetoaldehyde (245 mg, 2.89 mmol), and MS4A (1.0 g) in CH_2Cl_2 (15 mL) were stirred at room temperature for 3 h. After the reaction mixture was cooled to 0 °C, palmitoyl chloride (792 mg, 2.89 mmol) and Et_3N (292 mg, 2.89 mmol) were added, and the whole mixture was stirred at 0 °C for 12 h. The mixture was diluted with $CHCl_3$ (15 mL), which was washed with 0.1 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (4 cm × 15 cm, 33% AcOEt−hexane) to give **25a** (949 mg, 76%) as a yellow syrup: ^{1}H NMR (CD_3OD, 500 MHz, 3:2 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.56 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.96 (d, 1H, H-1′, $J_{1',2'}$ = 5.8 Hz), 5.85 (dd, 1H, H-1″, $J_{1'',2''a}$ = 2.3, $J_{1'',2''b}$ = 5.2 Hz), 5.75 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.94 (d, 1H, H-6′, $J_{6',5'}$ = 7.5 Hz), 4.88 (dd, 1H, H-5′, $J_{5',4'}$ = 1.2, $J_{5',6'}$ = 7.5 Hz), 4.31 (m, 3H, H-2′, H-3′, H-4′), 3.84 (s, 3H, CO_2CH_3), 3.46 (t, 2H, H-2″, $J_{2'',1''}$ = 2.3 Hz), 2.40−2.24 (m, 2H, $CH_3(CH_2)_{12}CH_2CH_2CO$), 1.61 (m, 2H, $CH_3(CH_2)_{12}CH_2CH_2CO$), 1.29 (br s, 24H, $CH_3(CH_2)_{12}CH_2CH_2CO$), 0.96, 0.90 (each s, each 9H, *tert*-butyl), 0.90 (t, 3H, $CH_3(CH_2)_{12}CH_2CH_2CO$, J = 6.9 Hz), 0.18, 0.15, 0.10, 0.07 (each s, each 3H, $SiCH_3$); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.3, 171.2, 165.6, 152.1, 141.4, 103.6, 90.8, 90.1, 84.8, 80.7, 76.1, 73.1, 60.5, 53.0, 34.8, 33.1, 30.8, 30.8, 30.6, 30.5, 30.3, 30.2, 30.1, 26.4, 26.0, 25.7, 23.8, 19.0, 18.9, 14.5, −4.1, −4.3, −4.4, −4.5; ESIMS-HR m/z calcd for $C_{42}H_{76}N_6NaO_9Si_2$ $(M + Na)^+$ 887.5110, found 887.5133.

(2*R*,4*S*,5*S*)-Methyl 2-Azidoethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-di-*tert*-butyldimethylsilyloxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylate (25b). 3-Azidopropanal was prepared as follows. A solution of 3-azido-1-propanol[35] (727 mg, 7.20 mmol) in CH_2Cl_2 (70 mL) was treated by Dess−Martin periodinane (3.97 g, 9.36 mmol) at room temperature for 1 h. The insoluble was filtered off through a Celite pad, and the filtrate was concentrated in vacuo. The residue was semipurified by silica gel column chromatography (1.5 cm×10 cm, 25% Et_2O−pentane) to give 3-azidopropanal (713 mg, quant). Compound **25b** was prepared from **22** (998 mg, 1.44 mmol) and 3-azidopropanol (285 mg, 2.88 mmol) as described above for the synthesis of **25a**. Purification by silica gel column chromatography (3 cm × 12 cm, 33% AcOEt−hexane) afforded **25b** (1.00 g, 79%) as a yellow syrup: ^{1}H NMR (CD_3OD, 500 MHz, 3:2 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.56 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.99 (d, 1H, H-1′, $J_{1',2'}$ = 5.2 Hz), 5.89 (dd, 1H, H-1″, $J_{1'',2''a}$ = 4.6, $J_{1'',2''b}$ = 8.0 Hz), 5.74 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.89 (d, 1H, H-6′, $J_{6',5'}$ = 6.0 Hz), 4.76 (dd, 1H, H-5′, $J_{5',4'}$ = 1.2, $J_{5',6'}$ = 6.0 Hz), 4.30 (m, 3H, H-2′, H-3′, H-4′), 3.84 (s, 3H, CO_2CH_3), 3.44 (t, 2H, H-3″, $J_{3'',2''}$ = 6.3 Hz), 2.40−2.25 (m, 2H, $CH_3(CH_2)_{12}CH_2CH_2CO$), 2.10−1.87 (m, 2H, H-2″), 1.60 (m, 2H, $CH_3(CH_2)_{12}CH_2CH_2CO$), 1.29 (br s, 24H, $CH_3(CH_2)_{12}CH_2CH_2CO$), 0.95, 0.91 (each s, each 9H, *tert*-butyl), 0.90 (t, 3H, $CH_3(CH_2)_{12}CH_2CH_2CO$, J = 6.9 Hz), 0.17, 0.15, 0.09, 0.06 (each s, each 3H, $SiCH_3$); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.0, 171.3, 165.6, 152.2, 141.2, 103.6, 90.3, 89.6, 85.0, 80.3, 76.3, 73.4, 60.0, 53.8, 34.9, 33.4, 33.1, 30.8, 30.7, 30.6, 30.5, 30.3, 30.2, 30.1, 26.4, 26.0, 25.7, 23.8, 19.0, 18.9, 14.5, −4.1, −4.4, −4.5, −4.6; ESIMS-HR m/z calcd for $C_{43}H_{78}N_6NaO_9Si_2$ $(M + Na)^+$ 901.5267, found 901.5249.

(2*R*,4*S*,5*S*)-Methyl 2-Azidopropyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-di-*tert*-butyldimethylsilyloxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylate (25c). 4-Azidobutanal was prepared as follows. A solution of 4-azido-1-butanol[36] (828 mg, 7.20 mmol) in CH_2Cl_2 (70 mL) was treated by Dess−Martin periodinane (3.97 g, 9.36 mmol) at room temperature for 1 h. The insoluble was filtered off through a Celite pad, and the filtrate was concentrated in vacuo. The residue was semipurified by silica gel column chromatography (1.5 cm × 10 cm, 25% Et_2O−pentane) to give 4-azidobutanal (798 mg, 98%). Compound **25c** was prepared from **22** (1.00 g, 1.44 mmol) and 4-azidopropanal (332 mg, 2.89 mmol) as described above for the synthesis of **25a**. Purification by silica gel column chromatography (3 cm×12 cm, 33% AcOEt−hexane) afforded **25c** (1.12 g, 87%) as a yellow syrup: ^{1}H NMR (CD_3OD, 500 MHz, 3:2 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.59 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.95 (d, 1H, H-1′, $J_{1',2'}$ = 5.2 Hz), 5.82 (dd, 1H, H-1″, $J_{1'',2''a}$ = 4.6, $J_{1'',2''b}$ = 6.9 Hz), 5.73 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.85 (d, 1H, H-6′, $J_{6',5'}$ = 5.7 Hz), 4.73 (dd, 1H, H-5′, $J_{5',4'}$ = 1.2, $J_{5',6'}$ = 5.7 Hz), 4.30 (m, 3H, H-2′, H-3′, H-4′), 3.84 (s, 3H, CO_2CH_3), 3.36 (t, 2H, H-4″, $J_{4'',3''}$ = 6.9 Hz), 2.44−2.20 (m, 2H, $CH_3(CH_2)_{12}CH_2CH_2CO$), 1.98−1.80 (m, 2H, H-3″), 1.80−1.68 (m, 2H, H-2″), 1.59 (m, 2H, $CH_3(CH_2)_{12}CH_2CH_2CO$), 1.29 (br s, 24H, $CH_3(CH_2)_{12}CH_2CH_2CO$), 0.95, 0.90 (each s, each 9H, *tert*-butyl), 0.90 (t, 3H, $CH_3(CH_2)_{12}CH_2CH_2CO$, J = 6.9 Hz), 0.17, 0.15, 0.09, 0.07 (each s, each 3H, $SiCH_3$); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.1, 171.8, 165.7, 152.2, 141.2, 103.4, 91.8, 89.8, 84.7, 79.9, 76.4, 73.3, 60.0, 53.7, 34.9, 33.1, 31.4, 30.8, 30.7, 30.6, 30.6, 30.5, 30.2, 30.1, 26.4, 26.1, 25.8, 25.4, 23.8, 20.9, 19.0, 14.5, −4.1, −4.4, −4.5, −4.6; ESIMS-HR m/z calcd for $C_{44}H_{80}N_6NaO_9Si_2$ $(M + Na)^+$ 915.5423, found 915.5417.

(2*R*,4*S*,5*S*)-2-Azidomethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-di-*tert*-butyldimethylsilyloxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylic Acid (26a). A mixture of **25a** (47 mg, 0.054 mmol) and LiI (87 mg, 0.65 mmol) in AcOEt (1 mL) was heated under reflux for 5 h. The mixture was cooled to room temperature and diluted with AcOEt. The mixture was washed with 0.1 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (1.5 cm×8 cm, 2% MeOH−$CHCl_3$) to give **26a** (36 mg, 78%) as a yellow syrup: ^{1}H NMR (CD_3OD, 500 MHz, 3:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.63 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 6.00 (d, 1H, H-1′, $J_{1',2'}$ = 4.6 Hz), 5.82 (dd, 1H, H-1″, $J_{1'',2''a}$ = 2.3, $J_{1'',2''b}$ = 6.9 Hz), 5.76 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.80 (d, 1H, H-5′, $J_{5',6'}$ = 6.4 Hz), 4.65 (d, 1H, H-6′, $J_{6',5'}$ = 6.4 Hz), 4.31 (m, 3H, H-2′, H-3′, H-4′), 3.43 (t, 2H, H-2″, $J_{2'',1''}$ = 4.6 Hz), 2.45−2.26 (m, 2H, $CH_3(CH_2)_{12}CH_2CH_2CO$), 1.58 (m, 2H, $CH_3(CH_2)_{12}CH_2CH_2CO$), 1.28 (br s, 24H, $CH_3(CH_2)_{12}CH_2CH_2CO$), 0.95, 0.90 (each s, each 9H, *tert*-butyl), 0.89 (t, 3H, $CH_3(CH_2)_{12}CH_2CH_2CO$, J = 6.9 Hz), 0.17, 0.14, 0.09, 0.07 (each s, each 3H, $SiCH_3$); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.4, 165.6, 152.2, 141.3, 103.5, 90.7, 89.5, 85.1, 81.9, 76.4, 73.7, 61.7, 52.7, 35.1, 33.0, 30.7, 30.7, 30.5, 30.4, 30.4, 30.2, 26.4, 26.1, 25.7, 23.6, 18.9, 18.9, 14.3, −4.1, −4.3, −4.4, −4.5; ESIMS-HR (negative mode) m/z calcd for $C_{41}H_{73}N_6O_9Si_2$ $(M - H)^-$ 849.4983, found 849.5005.

(2*R*,4*S*,5*S*)-2-Azidoethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-di-*tert*-butyldimethylsilyloxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylic Acid (26b). Compound **26b** was prepared from **25b** (53 mg, 0.06 mmol) as described above for the

synthesis of **26a**. Purification by silica gel column chromatography (1.5 cm×10 cm, 2% MeOH−$CHCl_3$) afforded **26b** (35 mg, 67%) as a yellow syrup: ^{1}H NMR (CD_3OD, 500 MHz, 3:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.65 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.98 (d, 1H, H-1′, $J_{1',2'}$ = 4.6 Hz), 5.84 (dd, 1H, H-1″, $J_{1'',2''a}$ = 4.0, $J_{1'',2''b}$ = 8.0 Hz), 5.74 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.66 (dd, 1H, H-5′, $J_{5',4'}$ = 1.2, $J_{5',6'}$ = 6.4 Hz), 4.58 (d, 1H, H-6′, $J_{6'\,5'}$ = 6.4 Hz), 4.32 (m, 3H, H-2′, H-3′, H-4′), 3.44 (t, 2H, H-3″, $J_{3'',2''}$ = 6.3 Hz), 2.44−2.22 (m, 2H, $CH_3(CH_2)_{12}CH_2$-$C\underline{H}_2CO$), 2.20−1.96 (m, 2H, H-2″), 1.60 (m, 2H, $CH_3(CH_2)_{12}$-$C\underline{H}_2CH_2CO$), 1.28 (br s, 24H, $CH_3(C\underline{H}_2)_{12}CH_2CH_2CO$), 0.95, 0.90 (each s, each 9H, *tert*-butyl), 0.89 (t, 3H, $C\underline{H}_3(CH_2)_{12}$-$CH_2CH_2CO$, J = 6.9 Hz), 0.16, 0.14, 0.09, 0.07 (each s, each 3H, $SiC\underline{H}_3$); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.0, 165.8 152.2, 141.2, 103.3, 90.0, 89.4, 85.0, 81.3, 76.6, 73.5, 61.8, 52.4, 35.1, 33.3, 33.1, 30.8, 30.8, 30.6, 30.5, 30.5, 30.2, 26.4, 26.1, 25.8, 23.8, 19.0, 18.9, 14.5, −4.1, −4.3, −4.4, −4.5; ESIMS-HR (negative mode) m/z calcd for $C_{42}H_{75}N_6O_9Si_2$ $(M - H)^-$ 863.5134, found 863.5142.

(2*R*,4*S*,5*S*)- 2-Azidopropyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-di-*tert*-butyldimethylsilyloxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylic Acid (26c). Compound **26c** was prepared from **25c** (69 mg, 0.077 mmol) as described above for the synthesis of **26a**. Purification by silica gel column chromatography (1.5 cm×10 cm, 2% MeOH−$CHCl_3$) afforded **26c** (50 mg, 74%) as a yellow syrup: ^{1}H NMR (CD_3OD, 500 MHz, 2:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.67 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.96 (d, 1H, H-1′, $J_{1',2'}$ = 4.0 Hz), 5.77 (dd, 1H, H-1″, $J_{1'',2''a}$ = 4.6, $J_{1'',2''b}$ = 8.0 Hz), 5.73 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.65 (dd, 1H, H-5′, $J_{5',4'}$ = 1.2, $J_{5',6'}$ = 5.8 Hz Hz), 4.63 (d, 1H, H-6′, $J_{6',5'}$ = 5.8 Hz), 4.32 (m, 3H, H-2′, H-3′, H-4′), 3.36 (t, 2H, H-4″, $J_{4'',3''}$ = 6.9 Hz), 2.42−2.24 (m, 2H, CH_3-$(CH_2)_{12}CH_2C\underline{H}_2CO$), 2.03−1.85 (m, 2H, H-3″), 1.84−1.70 (m, 2H, H-2″), 1.60 (m, 2H, $CH_3(CH_2)_{12}C\underline{H}_2CH_2CO$), 1.28 (br s, 24H, $CH_3(C\underline{H}_2)_{12}CH_2CH_2CO$), 0.95, 0.90 (each s, each 9H, *tert*-butyl), 0.90 (t, 3H, $C\underline{H}_3(CH_2)_{12}CH_2CH_2CO$, J = 6.9 Hz), 0.16, 0.14, 0.09, 0.09 (each s, each 3H, $SiC\underline{H}_3$); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.0, 165.8, 152.2, 141.2, 103.2, 91.8, 89.6, 84.7, 80.7, 76.6, 73.4, 60.9, 52.1, 35.1, 33.1, 31.3, 30.8, 30.8, 30.6, 30.5, 30.5, 30.2, 26.4, 26.1, 25.8, 25.5, 23.8, 18.9, 18.9, 14.5, −4.1, −4.3, −4.4, −4.5; ESIMS-HR m/z calcd for $C_{43}H_{78}N_6NaO_9Si_2$ $(M + Na)^+$ 901.5267, found 901.5282.

(2*R*,4*S*,5*S*)-2-Azidomethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylic Acid (27a). A solution of **26a** (27 mg, 0.032 mmol) in CH_3CN−CH_2Cl_2 (1:1, 1 mL) was treated with 3HF·Et_3N (51 mg, 0.32 mmol) at room temperature for 80 h. The mixture was partitioned between $CHCl_3$ and 0.1 N aqueous HCl, and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (1.5 cm × 8 cm, 10% MeOH−$CHCl_3$) to give **27a** (18 mg, 89%) as a yellow syrup: ^{1}H NMR (CD_3OD, 500 MHz, 4:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.63 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.99 (d, 1H, H-1′, $J_{1',2'}$ = 5.2 Hz), 5.73 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.69 (dd, 1H, H-1″, $J_{1'',2''a}$ = 2.3, $J_{1'',2''b}$ = 8.2 Hz), 4.66 (dd, 1H, H-5′, $J_{5',4'}$ = 1.2, $J_{5',6'}$ = 5.8 Hz), 4.43 (d, 1H, H-6′, $J_{6',5'}$ = 5.8 Hz), 4.27 (m, 2H, H-3′, H-4′), 4.23 (dd, 1H, H-2′, $J_{2',1'}$ = 5.2, $J_{2',3'}$ = 2.9 Hz), 3.39 (m, 2H, H-2″), 2.38−2.26 (m, 2H, $CH_3(CH_2)_{12}CH_2C\underline{H}_2CO$), 1.56 (m, 2H, $CH_3(CH_2)_{12}C\underline{H}_2CH_2CO$), 1.28 (br s, 24H, $CH_3(C\underline{H}_2)_{12}$-$CH_2CH_2CO$), 0.90, (t, 3H, $C\underline{H}_3(CH_2)_{12}CH_2CH_2CO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.2, 165.9, 152.4, 141.8, 103.3, 90.5, 90.1, 85.0, 82.8, 75.1, 71.8, 62.7, 52.4, 35.2, 33.1, 30.8, 30.8, 30.6, 30.5, 30.5, 30.3, 25.7, 23.8, 14.5, 9.2. ESIMS-HR (negative mode) m/z calcd for $C_{29}H_{45}N_6O_9$ $(M - H)^-$ 621.3254, found 621.3263.

(2*R*,4*S*,5*S*)-2-Azidoethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylic Acid (27b). Compound **27b** was prepared from **26b** (27 mg, 0.031 mmol) as described above for the synthesis of **27a**. Purification by silica gel column chromatography (1.5 cm×8 cm, 10% MeOH−$CHCl_3$) afforded **27b** (18 mg, 92%) as a yellow syrup: ^{1}H NMR (CD_3OD, 500 MHz, 4:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.64 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.99 (d, 1H, H-1′, $J_{1',2'}$ = 4.6 Hz), 5.72 (m, 1H, H-1″), 5.71 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.60 (dd, 1H, H-5′, $J_{5',4'}$ = 1.2, $J_{5',6'}$ = 5.7 Hz), 4.42 (d, 1H, H-6′, $J_{6',5'}$ = 5.7 Hz), 4.27 (m, 2H, H-3′, H-4′), 4.20 (dd, 1H, H-2′, $J_{2',1'}$ = 4.6, $J_{2',3'}$ = 2.9 Hz), 3.45 (t, 2H, H-3″, $J_{3'',2''}$ = 6.9 Hz), 2.34−2.22 (m, 2H, $CH_3(CH_2)_{12}$-$CH_2C\underline{H}_2CO$), 2.10 (m, 2H, H-2″), 1.56 (m, 2H, $CH_3(CH_2)_{12}$-$C\underline{H}_2CH_2CO$), 1.28 (br s, 24H, $CH_3(C\underline{H}_2)_{12}CH_2CH_2CO$), 0.90, (t, 3H, $C\underline{H}_3(CH_2)_{12}CH_2CH_2CO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 173.9, 165.9, 152.4, 141.7, 103.2, 90.0, 89.5, 85.1, 82.4, 75.3, 71.8, 62.5, 52.2, 35.3, 33.5, 33.1, 30.8, 30.8, 30.6, 30.6, 30.5, 30.3, 25.8, 23.7, 14.5, 9.2; ESIMS-HR (negative mode) m/z calcd for $C_{30}H_{47}N_6O_9$ $(M - H)^-$ 635.3405, found 635.3396.

(2*R*,4*S*,5*S*)-2-Azidopropyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylic Acid (27c). Compound **27c** was prepared from **26c** (44 mg, 0.050 mmol) as described above for the synthesis of **27a**. Purification by silica gel column chromatography (1.5 cm×8 cm, 10% MeOH−$CHCl_3$) afforded **27c** (31 mg, 95%) as a yellow syrup: ^{1}H NMR (CD_3OD, 500 MHz, 4:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.65 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.99 (d, 1H, H-1′, $J_{1',2'}$ = 5.2 Hz), 5.71 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.63 (dd, 1H, H-1″, $J_{1'',2''a}$ = 4.0, $J_{1'',2''b}$ = 8.0 Hz), 4.59 (dd, 1H, H-5′, $J_{5',4'}$ = 2.3, $J_{5',6'}$ = 5.8 Hz), 4.42 (d, 1H, H-6′, $J_{6',5'}$ = 5.8 Hz), 4.28 (dd, 1H, H-3′, $J_{3',2'}$ = 5.2, $J_{5',6'}$ = 4.6 Hz), 4.27 (dd, 1H, H-4′, $J_{5',6'}$ = 4.6, $J_{5',6'}$ = 2.3 Hz), 4.22 (t, 1H, H-2′, $J_{2',1'}$ = $J_{2',3'}$ = 5.2 Hz), 3.35 (t, 2H, H-4″, $J_{4'',3''}$ = 6.9 Hz), 2.34−2.26 (m, 2H, $CH_3(CH_2)_{12}CH_2C\underline{H}_2CO$), 1.88 (m, 2H, H-3″), 1.73 (m, 2H, H-2″), 1.57 (m, 2H, $CH_3(C\underline{H}_2)_{12}C\underline{H}_2CH_2CO$), 1.28 (br s, 24H, CH_3-$(C\underline{H}_2)_{12}CH_2CH_2CO$), 0.90 (t, 3H, $C\underline{H}_3(CH_2)_{12}CH_2CH_2CO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 173.9, 165.9, 152.4, 141.8, 103.2, 91.4, 90.0, 85.0, 82.0, 75.3, 71.9, 62.2, 52.2, 35.3, 33.1, 31.3, 30.8, 30.8, 30.6, 30.6, 30.5, 30.3, 25.8, 25.5, 23.7, 14.5, 9.2; ESIMS-HR (negative mode) m/z calcd for $C_{31}H_{49}N_6O_9$ $(M - H)^-$ 649.3567, found 649.3574.

(2*R*,4*S*,5*S*)-2-Aminomethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylic Acid (18a). A solution of **27a** (6.1 mg, 0.0098 mmol) and 10% $Pd(OH)_2$/C (1 mg) in MeOH (1 mL) was vigorously stirred at room temperature under H_2 atmosphere for 3 h. The $Pd(OH)_2$/C was filtered off through a Celite pad, and the filtrate was concentrated in vacuo. The residue was purified by C18 HPLC (80% aqueous MeOH) to give **18a** (3.4 mg, 58%) as a white foam: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.56 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.71 (d, 1H, H-1′, $J_{1',2'}$ = 4.0 Hz), 5.70 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.61 (m, 1H, H-1″), 4.61 (dd, 1H, H-5′, $J_{5',4'}$ = 4.0, $J_{5',6'}$ = 2.3 Hz), 4.53 (d, 1H, H-6′, $J_{6',5'}$ = 2.3 Hz), 4.35 (dd, 1H, H-3′, $J_{3',2'}$ = 6.3, $J_{3',4'}$ = 6.9 Hz), 4.28 (dd, 1H, H-2′, $J_{2',1'}$ = 4.0, $J_{2',3'}$ = 6.3 Hz), 3.99 (dd, 1H, H-4′, $J_{4',3'}$ = 6.9, $J_{4',5'}$ = 4.0 Hz), 3.56−3.22 (m, 2H, H-2″), 2.38−2.21 (m, 2H, $CH_3(CH_2)_{12}CH_2C\underline{H}_2CO$), 1.59 (m, 2H, $CH_3(CH_2)_{12}C\underline{H}_2CH_2CO$), 1.29 (br s, 24H, CH_3-$(C\underline{H}_2)_{12}CH_2CH_2CO$), 0.90 (t, 3H, $C\underline{H}_3(CH_2)_{12}CH_2CH_2CO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 177.3, 174.7, 166.0, 152.0, 143.6, 103.2, 93.6, 88.7, 85.4, 83.4, 74.2, 70.5, 63.0, 49.6, 40.7, 36.0, 33.1, 30.8, 30.8, 30.6, 30.5, 30.5, 30.3, 25.4, 23.8, 14.5; ESIMS-HR m/z calcd for $C_{29}H_{47}N_4O_9$ $(M - H)^-$ 595.3343, found 595.3331.

(2*R*,4*S*,5*S*)-2-Aminoethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylic Acid (18b). Compound **18b** was prepared from **27b** (8.1 mg, 0.013 mmol) as described above for the synthesis of **18a**. Purification by C18 HPLC (80% aqueous MeOH) afforded **18b** (5.3 mg, 68%) as a white foam: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.60 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.85 (d, 1H, H-1′, $J_{1',2'}$ = 4.0 Hz), 5.70 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.65 (dd, 1H, H-1″, $J_{1'',2''a}$ = 4.6, $J_{1'',2''b}$ = 5.2 Hz), 4.63 (dd, 1H, H-5′, $J_{5',4'}$ = 3.4, $J_{5',6'}$ = 4.6 Hz),

4.48 (d, 1H, H-6′, $J_{6',5'}$ = 4.6 Hz), 4.28 (t, 1H, H-3′, $J_{3',2'} = J_{3',4'}$ = 5.8 Hz), 4.23 (dd, 1H, H-2′, $J_{2',1'}$ = 4.0, $J_{2',3'}$ = 5.8 Hz), 4.13 (dd, 1H, H-4′, $J_{4',3'}$ = 5.8, $J_{4',5'}$ = 3.4 Hz), 3.07 (m, 2H, H-3″), 2.38−2.24 (m, 2H, $CH_3(CH_2)_{12}CH_2C\underline{H}_2CO$), 2.30−2.15 (m, 2H, H-2″), 1.58 (m, 2H, $CH_3(CH_2)_{12}C\underline{H}_2CH_2CO$), 1.28 (br s, 24H, $CH_3(C\underline{H}_2)_{12}CH_2CH_2CO$), 0.90 (t, 3H, $C\underline{H}_3(CH_2)_{12}CH_2$-$CH_2CO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 176.7, 175.2, 166.0, 152.2, 142.6, 103.1, 91.7, 89.5, 85.0, 82.6, 74.8, 71.2, 63.1, 49.6, 35.9, 35.6, 33.1, 31.7, 30.8, 30.8, 30.6, 30.5, 30.5, 30.3, 25.7, 23.8, 14.5; ESIMS-HR (negative mode) m/z calcd for $C_{30}H_{49}N_4O_9$ $(M - H)^-$ 609.3500, found 609.3502.

(2*R*,4*S*,5*S*)-2-Aminopropyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylic Acid (18c). Compound **18c** was prepared from **27c** (8.4 mg, 0.013 mmol) as described above for the synthesis of **18a**. Purification by C18 HPLC (80% aqueous MeOH) afforded **18c** (5.5 mg, 68%) as a white foam: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.61 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.94 (d, 1H, H-1′, $J_{1',2'}$ = 4.6 Hz), 5.69 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.66 (dd, 1H, H-1″, $J_{1'',2''a}$ = 5.2, $J_{1'',2''b}$ = 5.7 Hz), 4.60 (dd, 1H, H-5′, $J_{5',4'}$ = 2.3, $J_{5',6'}$ = 5.7 Hz), 4.46 (d, 1H, H-6′, $J_{6',5'}$ = 5.7 Hz), 4.22 (dd, 1H, H-3′, $J_{3',2'}$ = 5.2, $J_{3',4'}$ = 5.8 Hz), 4.21 (dd, 1H, H-4′, $J_{4',3'}$ = 5.8, $J_{4',5'}$ = 2.3 Hz), 4.19 (dd, 1H, H-2′, $J_{2',1'}$ = 4.6, $J_{2',3'}$ = 5.2 Hz), 2.99−2.93 (m, 2H, H-4″), 2.36−2.24 (m, 2H, $CH_3(CH_2)_{12}CH_2C\underline{H}_2CO$), 1.93−1.80 (m, 2H, H-3″), 1.79 (m, 2H, H-2″), 1.59 (m, 2H, $CH_3(CH_2)_{12}$-$C\underline{H}_2CH_2CO$), 1.28 (br s, 24H, $CH_3(C\underline{H}_2)_{12}CH_2CH_2CO$), 0.90 (t, 3H, $C\underline{H}_3(CH_2)_{12}CH_2CH_2CO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 176.4, 174.3, 166.1, 152.4, 141.9, 103.2, 90.9, 90.4, 85.1, 82.2, 75.2, 71.8, 62.6, 49.8, 40.4, 35.4, 33.1, 31.2, 30.8, 30.8, 30.6, 30.6, 30.5, 30.3, 25.8, 24.2, 23.7, 14.5; ESIMS-HR (negative mode) m/z calcd for $C_{31}H_{51}N_4O_9$ $(M - H)^-$ 623.3656, found 623.3664.

(2*R*,4*S*,5*S*)-Methyl 2-Azidomethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylate (28a). Compound **28a** was prepared from **25a** (70 mg, 0.080 mmol) as described above for the synthesis of **27a**. Purification by silica gel column chromatography (2 cm × 8 cm, 5% MeOH−$CHCl_3$) afforded **28a** (46 mg, 90%) as a colorless syrup: ^{1}H NMR (CD_3OD, 500 MHz, 2:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.54 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.89 (d, 1H, H-1′, $J_{1',2'}$ = 4.6 Hz), 5.76 (dd, 1H, H-1″, $J_{1'',2''a}$ = 5.2, $J_{1'',2''b}$ = 6.4 Hz), 5.73 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.95 (d, 1H, H-6′, $J_{6',5'}$ = 6.9 Hz), 4.94 (dd, 1H, H-5′, $J_{5',4'}$ = 2.3, $J_{5',6'}$ = 6.9 Hz), 4.31 (t, 1H, H-3′, $J_{3',2'} = J_{3',4'}$ = 5.8 Hz), 4.24 (dd, 1H, H-2′, $J_{2',1'}$ = 4.6, $J_{2',3'}$ = 5.8 Hz), 4.13 (dd, 1H, H-4′, $J_{4',3'}$ = 5.8, $J_{4',5'}$ = 2.3 Hz), 3.84 (s, 3H, $CO_2C\underline{H}_3$), 3.48 (br s, 2H, H-2″), 2.40−2.27 (m, 2H, $CH_3(CH_2)_{12}CH_2C\underline{H}_2CO$), 1.58 (m, 2H, $CH_3(CH_2)_{12}C\underline{H}_2CH_2CO$), 1.28 (br s, 24H, $CH_3(C\underline{H}_2)_{12}$-$CH_2CH_2CO$), 0.90 (t, 3H, $C\underline{H}_3(CH_2)_{12}CH_2CH_2CO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.5, 171.5, 165.9, 152.2, 142.2, 103.4, 91.2, 90.8, 84.8, 81.0, 74.6, 71.1, 60.1, 53.4, 35.0, 33.1, 30.8, 30.8, 30.6, 30.5, 30.2, 30.1, 25.9, 25.6, 23.8, 14.5; ESIMS-HR m/z calcd for $C_{30}H_{48}N_6NaO_9$ $(M + Na)^+$ 659.3375, found 659.3371.

(2*R*,4*S*,5*S*)-Methyl 2-Azidoethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylate (28b). Compound **28b** was prepared from **25b** (87 mg, 0.10 mmol) as described above for the synthesis of **27a**. Purification by silica gel column chromatography (2 cm × 8 cm, 5% MeOH−$CHCl_3$) afforded **28b** (57 mg, 89%) as a colorless syrup: ^{1}H NMR (CD_3OD, 500 MHz, 3:2 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.55 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.92 (d, 1H, H-1′, $J_{1',2'}$ = 4.6 Hz), 5.75 (dd, 1H, H-1″, $J_{1'',2''a}$ = 3.4, $J_{1'',2''b}$ = 9.2 Hz), 5.71 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.87 (d, 1H, H-6′, $J_{6',5'}$ = 4.6 Hz), 4.77 (dd, 1H, H-5′, $J_{5',4'}$ = 2.3, $J_{5',6'}$ = 4.6 Hz), 4.28 (dd, 1H, H-3′, $J_{3',2'}$ = 5.2, $J_{3',4'}$ = 4.0 Hz), 4.21 (dd, 1H, H-2′, $J_{2',1'}$ = 4.6, $J_{2',3'}$ = 5.2 Hz), 4.16 (dd, 1H, H-4′, $J_{4',3'}$ = 4.0, $J_{4',5'}$ = 2.3 Hz), 3.84 (s, 3H, $CO_2C\underline{H}_3$), 3.42 (t, 2H, H-3″, $J_{3'',2''}$ = 6.9 Hz), 2.40−2.24 (m, 2H, -CH_3-$(CH_2)_{12}CH_2C\underline{H}_2CO$), 2.12−1.88 (m, 2H, H-2″), 1.58 (m, 2H, $CH_3(CH_2)_{12}C\underline{H}_2CH_2CO$), 1.29 (br s, 24H, $CH_3(C\underline{H}_2)_{12}$-$CH_2CH_2CO$), 0.90 (t, 3H, $C\underline{H}_3(CH_2)_{12}CH_2CH_2CO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.1, 171.9, 165.9, 152.3, 142.0, 103.4, 90.9, 90.0, 84.5, 80.8, 74.8, 71.3, 60.2, 53.8, 35.1, 33.8, 33.1, 30.8, 30.8, 30.6, 30.5, 30.2, 30.1, 26.0, 25.7, 23.7, 14.5; ESIMS-HR m/z calcd for $C_{31}H_{50}N_6NaO_9$ $(M + Na)^+$ 673.3532, found 673.3531.

(2*R*,4*S*,5*S*)-Methyl 2-Azidopropyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylate (28c). Compound **28c** was prepared from **25c** (93 mg, 0.10 mmol) as described above for the synthesis of **27a**. Purification by silica gel column chromatography (2 cm × 8 cm, 5% MeOH−$CHCl_3$) afforded **28c** (64 mg, 92%) as a colorless syrup: ^{1}H NMR (CD_3OD, 500 MHz, 3:2 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.56 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.92 (d, 1H, H-1′, $J_{1',2'}$ = 4.6 Hz), 5.69 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.67 (dd, 1H, H-1″, $J_{1'',2''a}$ = 4.0, $J_{1'',2''b}$ = 6.9 Hz), 4.86 (d, 1H, H-6′, $J_{6',5'}$ = 6.9 Hz), 4.75 (dd, 1H, H-5′, $J_{5',4'}$ = 2.3, $J_{5',6'}$ = 6.9 Hz), 4.27 (dd, 1H, H-3′, $J_{3',2'}$ = 5.2, $J_{3',4'}$ = 4.6 Hz), 4.21 (dd, 1H, H-2′, $J_{2',1'}$ = 4.6, $J_{2',3'}$ = 5.2 Hz), 4.16 (dd, 1H, H-4′, $J_{4',3'}$ = 4.6, $J_{4',5'}$ = 2.3 Hz), 3.84 (s, 3H, $CO_2C\underline{H}_3$), 3.34 (t, 2H, H-4″, $J_{4'',3''}$ = 6.9 Hz), 2.38−2.18 (m, 2H, $C\underline{H}_3$-$(CH_2)_{12}CH_2C\underline{H}_2CO$), 1.97−1.85 (m, 2H, H-3″), 1.80−1.68 (m, 2H, H-2″), 1.58 (m, 2H, $CH_3(CH_2)_{12}C\underline{H}_2CH_2CO$), 1.28 (br s, 24H, $CH_3(C\underline{H}_2)_{12}CH_2CH_2CO$), 0.90 (t, 3H, $C\underline{H}_3(CH_2)_{12}$-$CH_2CH_2CO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.1, 171.9, 165.9, 152.3, 142.1, 103.3, 91.7, 90.8, 84.5, 80.6, 74.9, 71.4, 60.2, 53.7, 35.1, 33.1, 31.7, 30.8, 30.8, 30.6, 30.5, 30.2, 30.1, 26.0, 25.7, 25.3, 23.8, 14.4; ESIMS-HR m/z calcd for $C_{32}H_{52}N_6NaO_9$ $(M + Na)^+$ 687.3688, found 687.3692.

(2*R*,4*S*,5*S*)-Methyl 2-Aminomethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylate HCl Salt (19a). Compound **19a** was prepared from **28a** (7.8 mg, 0.012 mmol) in the presence of 1 N aqueous HCl (0.5 mL) as described above for the synthesis of **18a**. Purification by C18 HPLC (85% aqueous MeOH containing 0.5% HCl) afforded **19a** (4.2 mg, 54%) as a white foam: ^{1}H NMR (CD_3OD, 500 MHz, 9:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.53 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.70 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.69 (d, 1H, H-1′ $J_{1',2'}$ = 3.4 Hz), 5.68 (m, 1H, H-1″), 5.05 (d, 1H, H-6′, $J_{6',5'}$ = 2.4 Hz), 4.81 (dd, 1H, H-5′, $J_{5',4'}$ = 3.4, $J_{5',6'}$ = 2.4 Hz), 4.36 (dd, 1H, H-3′, $J_{3',2'}$ = 6.4, $J_{3',4'}$ = 6.9 Hz), 4.31 (dd, 1H, H-2′, $J_{2',1'}$ = 3.4, $J_{2',3'}$ = 6.4 Hz), 4.03 (dd, 1H, H-4′, $J_{4',3'}$ = 6.9, $J_{4',5'}$ = 3.4 Hz), 3.87 (s, 3H, $CO_2C\underline{H}_3$), 3.35 (m, 2H, H-2″), 2.38−2.24 (m, 2H, CH_3-$(CH_2)_{12}CH_2C\underline{H}_2CO$), 1.59 (m, 2H, $CH_3(CH_2)_{12}C\underline{H}_2CH_2CO$), 1.28 (br s, 24H, $CH_3(C\underline{H}_2)_{12}CH_2CH_2CO$), 0.90 (t, 3H, $C\underline{H}_3$-$(CH_2)_{12}CH_2CH_2CO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 175.1, 172.7, 165.9, 152.0, 143.6, 103.3, 94.0, 88.6, 84.7, 81.7, 74.0, 70.5, 60.6, 54.0, 35.4, 33.1, 30.8, 30.8, 30.6, 30.5, 30.5, 30.1, 25.3, 23.7, 14.4; ESIMS-HR m/z calcd for $C_{30}H_{51}N_4O_9$ $(M + H)^+$ 611.3651, found 611.3651.

(2*R*,4*S*,5*S*)-Methyl 2-Aminoethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylate HCl Salt (19b). Compound **19b** was prepared from **28b** (8.2 mg, 0.013 mmol) in the presence of 1 N aqueous HCl (0.5 mL) as described above for the synthesis of **18a**. Purification by C18 HPLC (85% aqueous MeOH containing 0.5% HCl) afforded **19b** (4.9 mg, 57%) as a white foam: ^{1}H NMR (CD_3OD, 500 MHz, 9:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.55 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.77 (d, 1H, H-1′, $J_{1',2'}$ = 4.0 Hz), 5.70 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.68 (dd, 1H, H-1″, $J_{1'',2''a}$ = 5.2, $J_{1'',2''b}$ = 6.3 Hz), 4.99 (d, 1H, H-6′, $J_{6',5'}$ = 3.5 Hz), 4.79 (dd, 1H, H-5′, $J_{5',4'}$ = 2.9, $J_{5',6'}$ = 3.5 Hz), 4.32 (dd, 1H, H-3′, $J_{3',2'}$ = 5.8, $J_{3',4'}$ = 6.3 Hz), 4.27 (dd, 1H, H-2′, $J_{2',1'}$ = 4.0, $J_{2',3'}$ = 5.8 Hz), 4.08 (dd, 1H, H-4′, $J_{4',3'}$ = 6.3, $J_{4',5'}$ = 2.9 Hz), 3.85 (s, 3H, $CO_2C\underline{H}_3$), 3.07 (m, 2H, H-3″), 2.35−2.25 (m, 2H, $CH_3(CH_2)_{12}CH_2C\underline{H}_2CO$), 2.17−2.08 (m, 2H, H-2″), 1.56 (m, 2H, $CH_3(CH_2)_{12}C\underline{H}_2CH_2CO$), 1.29 (br s, 24H, CH_3-$(C\underline{H}_2)_{12}CH_2CH_2CO$), 0.90 (t, 3H, $C\underline{H}_3(CH_2)_{12}CH_2CH_2CO$,

J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.8, 172.0, 165.9, 152.2, 143.0, 103.2, 90.1, 89.9, 84.5, 81.1, 74.4, 70.9, 60.4, 53.8, 36.9, 35.2, 33.1, 30.8, 30.8, 30.6, 30.5, 30.5, 30.1, 25.6, 23.7, 14.4; ESIMS-HR m/z calcd for $C_{31}H_{53}N_4O_9$ $(M + H)^+$ 625.3807, found 625.3803.

(2*R*,4*S*,5*S*)-Methyl 2-Aminopropyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylate HCl Salt (19c). Compound **19c** was prepared from **28c** (8.7 mg, 0.013 mmol) in the presence of 1 N aqueous HCl (0.5 mL) as described above for the synthesis of **18a**. Purification by C18 HPLC (85% aqueous MeOH containing 0.5% HCl) afforded **19c** (4.9 mg, 56%) as a white foam: ^{1}H NMR (CD_3OD, 500 MHz, 9:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.55 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.84 (d, 1H, H-1′, $J_{1',2'}$ = 4.0 Hz), 5.69 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.63 (dd, 1H, H-1″, $J_{1'',2''a}$ = 4.6, $J_{1'',2''b}$ = 5.2 Hz), 4.93 (d, 1H, H-6′, $J_{6',5'}$ = 4.0 Hz), 4.76 (dd, 1H, H-5′, $J_{5',4'}$ = 2.9, $J_{5',6'}$ = 4.0 Hz), 4.28 (dd, 1H, H-3′, $J_{3',2'}$ = 5.7, $J_{3',4'}$ = 5.2 Hz), 4.24 (dd, 1H, H-2′, $J_{2',1'}$ = 4.0, $J_{2',3'}$ = 5.7 Hz), 4.12 (dd, 1H, H-4′, $J_{4',3'}$ = 5.2, $J_{4',5'}$ = 2.9 Hz), 3.84 (s, 3H, CO_2CH_3), 2.96 (m, 2H, H-4″), 2.36−2.21 (m, 2H, $CH_3(CH_2)_{12}CH_2C\underline{H}_2CO$), 1.89−1.76 (m, 2H, H-2″), 1.74 (m, 2H, H-3″), 1.58 (m, 2H, $CH_3(CH_2)_{12}C\underline{H}_2CH_2CO$), 1.28 (br s, 24H, $CH_3(C\underline{H}_2)_{12}CH_2CH_2CO$), 0.90 (t, 3H, $C\underline{H}_3(CH_2)_{12}$-$CH_2CH_2CO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.4, 171.9, 165.9, 152.2, 142.5, 103.2, 91.4, 91.3, 84.5, 80.7, 74.7, 71.4, 60.3, 53.7, 35.2, 33.1, 31.6, 30.8, 30.8, 30.6, 30.6, 30.5, 30.2, 25.7, 24.0, 23.8, 14.5; ESIMS-HR m/z calcd for $C_{32}H_{55}N_4O_9$ $(M + H)^+$ 639.3964, found 639.3964.

Bicyclic Lactam (29). A solution of **28b** (7.9 mg, 0.012 mmol) and 10% $Pd(OH)_2$/C (1.0 mg) in MeOH (1 mL) was vigorously stirred at room temperature under H_2 atmosphere for 4 h. The catalyst was filtered off through a Celite pad, and the filtrate was concentrated in vacuo. The residue was purified by C18 HPLC (80% aqueous MeOH) to give **29** (3.9 mg, 53%) as a white foam: ^{1}H NMR (500 MHz, CD_3OD, 5:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.42 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 6.24 (dd, 1H, H-1″, $J_{1'',2''a}$ = 1.7, $J_{1'',2''b}$ = 4.0 Hz), 5.93 (d, 1H, H-1′, $J_{1',2'}$ = 5.2 Hz), 5.71 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.91 (t, 1H, H-5′, $J_{5',4'} = J_{5',6'}$ = 2.3 Hz), 4.72 (d, 1H, H-5′, $J_{6',5'}$ = 2.3 Hz), 4.25 (t, 1H, H-3′, $J_{3',2'} = J_{3',4'}$ = 5.2 Hz), 4.15 (t, 1H, H-2′, $J_{2',1'} = J_{2',3'}$ = 5.2 Hz), 4.10 (dd, 1H, H-3′, $J_{4',3'}$ = 5.2, $J_{4',5'}$ = 2.3 Hz), 3.59−3.18 (m, 2H, H-3″), 2.40−2.29 (m, 2H, $CH_3(CH_2)_{12}CH_2C\underline{H}_2CO$), 2.05−1.93 (m, 2H, H-2″), 1.55 (br s, 2H, $CH_3(C\underline{H}_2)_{12}$-$CH_2C\underline{H}_2CO$), 1.29 (br s, 24H, $CH_3(C\underline{H}_2)_{12}CH_2CH_2CO$), 0.90 (t, 3H, $C\underline{H}_3(CH_2)_{12}CH_2CH_2CO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 172.0, 165.9, 141.5, 103.4, 89.9, 88.6, 86.5, 80.8, 74.8, 71.2, 63.6, 52.1, 37.7, 34.9, 34.8, 33.1, 30.8, 30.8, 30.8, 30.6, 30.6, 30.5, 30.4, 30.2, 25.6, 23.8, 14.5; ESIMS-HR m/z calcd for $C_{30}H_{48}N_4NaO_8$ $(M + Na)^+$ 615.3364, found 615.3372.

(2*R*,4*S*,5*S*)-*tert*-Butyl 2-Azidomethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-di-*tert*-butyldimethylsilyloxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylate (30a). A solution of **26a** (212 mg, 0.25 mmol) in ^{t}BuOH−CH_2Cl_2 (1:1, 4 mL) was treated with *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea (251 mg, 1.25 mmol) and NH_4Cl (41 mg, 1.25 mmol) at 0 °C for 20 h. The mixture was diluted with $CHCl_3$ (200 mL), which was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (2 cm×10 cm, 33% AcOEt−hexane) to give **30a** (165 mg, 73%) as a white foam: ^{1}H NMR (CD_3OD, 500 MHz, 3:2 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.63 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.91 (d, 1H, H-1′, $J_{1',2'}$ = 4.0 Hz), 5.83 (dd, 1H, H-1″, $J_{1'',2''a}$ = 2.9, $J_{1'',2''b}$ = 5.2 Hz), 5.75 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.84 (dd, 1H, H-5′, $J_{5',4'}$ = 1.2, $J_{5',6'}$ = 6.3 Hz), 4.78 (d, 1H, H-6′, $J_{6',5'}$ = 6.3 Hz), 4.30 (dd, 1H, H-3′, $J_{3',2'}$ = 4.0, $J_{3',4'}$ = 4.6 Hz), 4.28 (t, 1H, H-2′, $J_{2',1'} = J_{2',3'}$ = 4.0 Hz), 4.24 (dd, 1H, H-4′, $J_{4',3'}$ = 4.6, $J_{4',5'}$ = 1.2 Hz), 3.53 (m, 2H, H-2″), 2.44−2.18 (m, 2H, $CH_3(CH_2)_{12}CH_2C\underline{H}_2CO$), 1.60 (m, 2H, $CH_3(CH_2)_{12}C\underline{H}_2CH_2CO$), 1.53 (s, 9H, *tert*-butyl), 1.28 (br s, 24H, $CH_3(C\underline{H}_2)_{12}CH_2CH_2CO$), 0.94, 0.91 (each s, each 9H, *tert*-butyl), 0.90 (t, 3H, $C\underline{H}_3(CH_2)_{12}CH_2CH_2CO$, J = 6.9 Hz), 0.15, 0.14, 0.10, 0.09 (each s, each 3H, $SiC\underline{H}_3$); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.4, 169.7, 165.9, 152.1, 141.5, 103.3, 93.9, 90.3, 84.8, 81.0, 76.3, 72.8, 60.9, 53.4, 34.9, 33.1, 30.8, 30.7, 30.5, 30.5, 30.4, 30.3, 30.1, 30.1, 28.2, 26.4, 26.4, 26.0, 25.6, 23.7, 18.9, 18.9, 14.5, −4.1, −4.4, −4.4, −4.5; ESIMS-HR m/z calcd for $C_{45}H_{82}N_6NaO_9Si_2$ $(M + Na)^+$ 929.5574, found 929.5583.

(2*R*,4*S*,5*S*)-*tert*-Butyl 2-Azidoethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-di-*tert*-butyldimethylsilyloxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylate (30b). Compound **30b** was prepared from **26b** (171 mg, 0.20 mmol) as described above for the synthesis of **30a**. Purification by silica gel column chromatography (2 cm×10 cm, 33% AcOEt−hexane) afforded **30b** (138 mg, 76%) as a yellow syrup: ^{1}H NMR (CD_3OD, 500 MHz, 2:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.63 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.95 (d, 1H, H-1′, $J_{1',2'}$ = 4.6 Hz), 5.89 (dd, 1H, H-1″, $J_{1'',2''a}$ = 4.6, $J_{1'',2''b}$ = 8.0 Hz), 5.74 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.72 (d, 1H, H-6′, $J_{6',5'}$ = 6.3 Hz), 4.63 (dd, 1H, H-5′, $J_{5',4'}$ = 1.2, $J_{5',6'}$ = 6.3 Hz), 4.29 (t, 1H, H-3′, $J_{3',2'} = J_{3',4'}$ = 4.0 Hz), 4.28 (dd, 1H, H-2′, $J_{2',1'}$ = 4.6, $J_{2',3'}$ = 4.0 Hz), 4.26 (dd, 1H, H-4′, $J_{4',3'}$ = 4.0, $J_{4',5'}$ = 1.2 Hz), 3.46 (t, 2H, H-3″, $J_{3'',2''}$ = 6.9 Hz), 2.42−2.15 (m, 2H, $CH_3(CH_2)_{12}CH_2$-$C\underline{H}_2CO$), 2.10−1.89 (m, 2H, H-2″), 1.62 (m, 2H, $CH_3(CH_2)_{12}$-$C\underline{H}_2CH_2CO$), 1.53 (s, 9H, *tert*-butyl), 1.28 (br s, 24H, CH_3-$(C\underline{H}_2)_{12}CH_2CH_2CO$), 0.95, 0.91 (each s, each 9H, *tert*-butyl), 0.88 (t, 3H, $C\underline{H}_3(CH_2)_{12}CH_2CH_2CO$, J = 6.9 Hz), 0.17, 0.15, 0.10, 0.09 (each s, each 3H, $SiC\underline{H}_3$); ^{13}C NMR (CD_3OD, 125 MHz) δ 173.9, 170.4, 165.9, 152.2, 141.2, 103.3, 93.9, 89.8, 84.9, 80.5, 76.3, 73.1, 60.6, 35.0, 33.4, 33.1, 30.8, 30.8, 30.7, 30.5, 30.5, 30.4, 30.2, 30.1, 28.2, 26.4, 26.4, 26.1, 25.7, 23.7, 19.0, 18.9, 14.5, −4.1, −4.4, −4.4, −4.5; ESIMS-HR m/z calcd for $C_{46}H_{84}N_6NaO_9Si_2$ $(M + Na)^+$ 943.5731, found 943.5734.

(2*R*,4*S*,5*S*)-*tert*-Butyl 2-Azidomethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylate (31a). Compound **31a** was prepared from **30a** (150 mg, 0.17 mmol) as described above for the synthesis of **37a**. Purification by silica gel column chromatography (1.5 cm× 8 cm, 75% AcOEt−hexane) afforded **31a** (89 mg, 79%) as a colorless syrup: ^{1}H NMR (CD_3OD, 500 MHz, 2:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.54 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.89 (d, 1H, H-1′, $J_{1',2'}$ = 4.6 Hz), 5.70 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.69 (dd, 1H, H-1″, $J_{1'',2''a}$ = 4.6, $J_{1'',2''b}$ = 6.9 Hz), 4.87 (dd, 1H, H-5′, $J_{5',4'}$ = 2.3, $J_{5',6'}$ = 4.6 Hz), 4.80 (d, 1H, H-6′, $J_{6',5'}$ = 4.6 Hz), 4.31 (t, 1H, H-3′, $J_{3',2'} = J_{3',4'}$ = 5.2 Hz), 4.23 (dd, 1H, H-2′, $J_{2',1'}$ = 4.6, $J_{2',3'}$ = 5.2 Hz), 4.10 (m, 1H, H-4′, $J_{4',3'}$ = 5.2, $J_{4',5'}$ = 2.3 Hz), 3.49 (t, 2H, H-2″, $J_{2'',1''}$ = 3.5 Hz), 2.40−2.25 (m, 2H, $CH_3(CH_2)_{12}CH_2C\underline{H}_2CO$), 1.59 (m, 2H, $CH_3(CH_2)_{12}C\underline{H}_2CH_2CO$), 1.54 (s, 9H, *tert*-butyl), 1.29 (br s, 24H, $CH_3(C\underline{H}_2)_{12}CH_2CH_2CO$), 0.90 (t, 3H, $C\underline{H}_3(CH_2)_{12}$-$CH_2CH_2CO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.4, 169.9, 165.9, 152.3, 142.2, 103.4, 91.1, 90.8, 84.8, 81.3, 74.6, 71.2, 61.3, 53.4, 35.1, 33.1, 30.8, 30.8, 30.7, 30.6, 30.5, 30.4, 30.2, 30.2, 28.1, 26.0, 25.6, 23.7, 14.5; ESIMS-HR m/z calcd for $C_{33}H_{54}N_6NaO_9$ $(M + Na)^+$ 701.3845, found 701.3859.

(2*R*,4*S*,5*S*)-*tert*-Butyl 2-Azidoethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylate (31b). Compound **31b** was prepared from **30b** (121 mg, 0.13 mmol) as described above for the synthesis of **27a**. Purification by silica gel column chromatography (1.5 cm× 8 cm, 75% AcOEt−hexane) afforded **31b** (73 mg, 80%) as a colorless syrup: ^{1}H NMR (CD_3OD, 500 MHz, 2:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.57 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.93 (d, 1H, H-1′, $J_{1',2'}$ = 5.2 Hz), 5.74 (dd, 1H, H-1″, $J_{1'',2''a}$ = 4.0, $J_{1'',2''b}$ = 7.5 Hz), 5.71 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.73 (d, 1H, H-6′, $J_{6',5'}$ = 5.2 Hz), 4.69 (dd, 1H, H-5′, $J_{5',4'}$ = 2.3, $J_{5',6'}$ = 5.2 Hz), 4.28 (dd, 1H, H-3′, $J_{3',2'}$ = 4.6, $J_{3',4'}$ = 5.2 Hz), 4.21 (dd, 1H, H-2′, $J_{2',1'}$ = 5.2, $J_{2',3'}$ = 4.6 Hz), 4.14 (dd, 1H, H-4′, $J_{4',3'}$ = 5.2, $J_{4',5'}$ = 2.3 Hz), 3.43 (t, 2H, H-3″,

$J_{3'',2''}$ = 6.4 Hz), 2.40−2.18 (m, 2H, $CH_3(CH_2)_{12}CH_2CH_2CO$), 2.12−1.88 (m, 2H, H-2″), 1.61 (m, 2H, $CH_3(CH_2)_{12}CH_2$-CH_2CO), 1.53 (s, 9H, *tert*-butyl), 1.29 (br s, 24H, CH_3-$(CH_2)_{12}CH_2CH_2CO$), 0.90 (t, 3H, $CH_3(CH_2)_{12}CH_2CH_2CO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.0, 170.5, 165.9, 152.3, 142.0, 103.3, 90.8, 89.9, 84.6, 81.1, 74.9, 71.4, 60.9, 35.2, 33.9, 33.1, 30.8, 30.7, 30.6, 30.6, 30.5, 30.4, 30.2, 30.2, 28.2, 26.1, 25.7, 23.8, 14.5; ESIMS-HR m/z calcd for $C_{34}H_{56}N_6NaO_9$ $(M + Na)^+$ 715.4001, found 715.4009.

(2*R*,4*S*,5*S*)-*tert*-Butyl 2-Aminomethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylate (20a). Compound **20a** was prepared from **31a** (11 mg, 0.016 mmol) as described above for the synthesis of **18a**. Purification by C18 HPLC (90% aqueous MeOH) afforded **20a** (5.6 mg, 54%) as a white foam: ^{1}H NMR (500 MHz, CD_3OD, 2:1 mixture of rotamers at 20 °C, data for the major diastereomer) δ 7.54 (d, 1H, H-6, $J_{6,5}$ = 8.2 Hz), 5.70 (d, 1H, H-5, $J_{5,6}$ = 8.2 Hz), 5.67 (m, 1H, H-1″), 5.66 (d, 1H, H-1′, $J_{1',2'}$ = 3.2 Hz), 4.93 (d, 1H, H-6′, $J_{6',5'}$ = 2.8 Hz), 4.72 (dd, 1H, H-5′, $J_{5',4'}$ = 3.2, $J_{5',6'}$ = 2.8 Hz), 4.37 (dd, 1H, H-3′, $J_{3',2'}$ = 6.9, $J_{3',4'}$ = 6.9 Hz), 4.32 (dd, 1H, H-2′, $J_{2',1'}$ = 3.2, $J_{2',3'}$ = 6.9 Hz), 4.02 (dd, 1H, H-4′, $J_{4',3'}$ = 6.9, $J_{4',5'}$ = 3.2 Hz), 3.32 (m, 2H, H-2″), 2.41−2.16 (m, 2H, $CH_3(CH_2)_{12}CH_2CH_2CO$), 1.59 (m, 2H, $CH_3(CH_2)_{12}$-CH_2CH_2CO), 1.56 (s, 9H, *tert*-butyl), 1.29 (br s, 24H, CH_3-$(CH_2)_{12}CH_2CH_2CO$), 0.90 (t, 3H, $CH_3(CH_2)_{12}CH_2CH_2CO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.8, 171.7, 165.9, 152.0, 143.7, 103.2, 94.3, 88.6, 84.7, 82.1, 74.1, 70.6, 60.8, 42.1, 35.5, 33.0, 30.8, 30.8, 30.6, 30.5, 30.4, 30.3, 30.2, 30.2, 28.1, 25.3, 23.8, 14.5; ESIMS-HR calcd for $C_{33}H_{57}N_4O_9$ $(M + H)^+$ 653.4120, found 653.4140.

(2*R*,4*S*,5*S*)-*tert*-Butyl 2-Aminoethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-3-palmitoyl-(1,3)-oxazolidine-4-carboxylate (20b). Compound **20b** was prepared from **31b** (7.9 mg, 0.011 mmol) as described above for the synthesis of **18a**. Purification by C18 HPLC (90% aqueous MeOH) afforded **20b** (3.8 mg, 50%) as a white foam: ^{1}H NMR (500 MHz, CD_3OD, 3:2 mixture of rotamers at 20 °C, data for the major diastereomer) δ 7.56 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.77 (d, 1H, H-1′, $J_{1',2'}$ = 4.0 Hz), 5.69 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.67 (t, 1H, H-1″, $J_{1'',2''}$ = 5.2 Hz), 4.82 (d, 1H, H-6′, $J_{6',5'}$ = 4.0 Hz), 4.71 (d, 1H, H-5′, $J_{5',4'}$ = 2.9, $J_{5',6'}$ = 4.0 Hz), 4.32 (t, 1H, H-3′, $J_{3',2'}$ = $J_{3',4'}$ = 5.7 Hz), 4.27 (dd, 1H, H-2′, $J_{2',1'}$ = 4.0, $J_{2',3'}$ = 5.7 Hz), 4.07 (dd, 1H, H-4′, $J_{4',3'}$ = 5.7, $J_{4',5'}$ = 2.9 Hz), 3.16−3.04 (m, 2H, H-3″), 2.32 (m, 2H, $CH_3(CH_2)_{12}CH_2CH_2CO$), 2.27−2.14 (m, 2H, H-2″), 1.57 (m, 2H, $CH_3(CH_2)_{12}CH_2CH_2CO$), 1.54 (s, 9H, *tert*-butyl), 1.28 (br s, 24H, $CH_3(CH_2)_{12}CH_2CH_2CO$), 0.90 (t, 3H, $CH_3(CH_2)_{12}CH_2CH_2CO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.6, 170.4, 165.9, 152.2, 142.9, 103.2, 90.8, 89.9, 84.5, 81.3, 74.5, 71.1, 61.0, 39.0, 37.1, 35.3, 33.1, 30.8, 30.8, 30.8, 30.6, 30.6, 30.5, 30.4, 30.2, 28.2, 25.9, 23.7, 14.4; ESIMS-HR calcd for $C_{34}H_{59}N_4O_9$ $(M + H)^+$ 667.4277, found 667.4284.

(2*R*,4*S*,5*S*)-Methyl 3-Acetyl-2-azidomethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-di-*tert*-butyldimethylsilyloxy-4-(uracil-1-yl)]tetrahydrofuryl-(1,3)-oxazolidine-4-carboxylate (32a). Compound **32a** was prepared from **22** (500 mg, 0.72 mmol), azidoacetoaldehyde (123 mg, 1.4 mmol), and acetyl chloride (110 mg, 1.4 mmol) as described above for the synthesis of **25a**. Purification by silica gel column chromatography (2 cm×8 cm, 33% AcOEt−hexane) afforded **32a** (414 mg, 86%) as a yellow foam: ^{1}H NMR (CD_3OD, 500 MHz, 3:2 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.60 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.96 (d, 1H, H-1′, $J_{1',2'}$ = 5.7 Hz), 5.82 (dd, 1H, H-1″, $J_{1'',2''a}$ = 4.6, $J_{1'',2''b}$ = 7.5 Hz), 5.76 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.93 (br s, 1H, H-6′), 4.71 (d, 1H, H-5′, $J_{5',4'}$ = 1.2 Hz), 4.32 (dd, 1H, H-2′, $J_{2',1'}$ = 5.7, $J_{2',3'}$ = 4.6 Hz), 4.29 (dd, 1H, H-3′, $J_{3',2'}$ = 4.6, $J_{3',4'}$ = 3.5 Hz), 4.25 (dd, 1H, H-4′, $J_{4',3'}$ = 3.5, $J_{4',5'}$ = 1.2 Hz), 3.85 (s, 3H, CO_2CH_3), 3.46 (t, 2H, H-2″), 2.07 (s, 3H, acetyl), 0.95, 0.91 (each s, each 9H, *tert*-butyl), 0.18, 0.15, 0.10, 0.07 (each s, each 3H, $SiCH_3$); ^{13}C NMR (CD_3OD, 125 MHz) δ 172.1, 171.1, 170.5, 165.7, 152.2, 141.5, 103.5, 90.8, 90.4, 84.6, 80.6, 76.1, 73.1, 61.0, 53.8, 53.1, 26.4, 22.2, 18.9, 18.9, −4.1, −4.3, −4.4, −4.5; ESIMS-HR m/z calcd for $C_{28}H_{48}N_6NaO_9Si_2$ $(M + Na)^+$ 691.2914, found 691.2909.

(2*R*,4*S*,5*S*)-Methyl 3-Acetyl-2-azidoethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-di-*tert*-butyldimethylsilyloxy-4-(uracil-1-yl)]tetrahydrofuryl-(1,3)-oxazolidine-4-carboxylate (32b). Compound **32b** was prepared from **22** (500 mg, 0.72 mmol), 3-azidopropanal (143 mg, 1.4 mmol), and acetyl chloride (113 mg, 1.4 mmol) as described above for the synthesis of **25a**. Purification by silica gel column chromatography (2 cm×10 cm, 33% AcOEt−hexane) afforded **32b** (417 mg, 85%) as a yellow foam: ^{1}H NMR (CD_3OD, 500 MHz, 3:2 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.59 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.98 (d, 1H, H-1′, $J_{1',2'}$ = 5.2 Hz), 5.85 (dd, 1H, H-1″, $J_{1'',2''a}$ = 4.0, $J_{1'',2''b}$ = 8.0 Hz), 5.74 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.86 (d, 1H, H-6′, $J_{6',5'}$ = 5.8 Hz), 4.74 (dd, 1H, H-5′, $J_{5',4'}$ = 1.2, $J_{5',6'}$ = 5.8 Hz), 4.31 (dd, 1H, H-2′, $J_{2',1'}$ = 5.2, $J_{2',3'}$ = 4.6 Hz), 4.30 (dd, 1H, H-3′, $J_{3',2'}$ = 4.6, $J_{3',4'}$ = 4.0 Hz), 4.27 (dd, 1H, H-4′, $J_{4',3'}$ = 4.0, $J_{4',5'}$ = 1.2 Hz), 3.85 (s, 3H, CO_2CH_3), 3.44 (t, 2H, H-3″, $J_{3'',2''}$ = 6.3 Hz), 2.16−2.01 (m, 2H, H-2″), 2.03 (s, 3H, acetyl), 0.95, 0.90 (each s, each 9H, *tert*-butyl), 0.16, 0.15, 0.09, 0.07 (each s, each 3H, $SiCH_3$); ^{13}C NMR (CD_3OD, 125 MHz) δ 171.5, 171.2, 170.0, 165.5, 152.1, 141.2, 103.4, 90.2, 89.8, 84.5, 80.2, 76.2, 73.2, 60.5, 53.8, 33.3, 26.4, 22.3, 18.9, 18.9, −4.2, −4.3, −4.3, −4.6; ESIMS-HR m/z calcd for $C_{29}H_{50}N_6NaO_9Si_2$ $(M + Na)^+$ 705.3070, found 705.3077.

(2*R*,4*S*,5*S*)-Methyl 3-Acetyl-2-azidopropyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-di-*tert*-butyldimethylsilyloxy-4-(uracil-1-yl)]tetrahydrofuryl-(1,3)-oxazolidine-4-carboxylate (32c). Compound **32c** was prepared from **22** (300 mg, 0.43 mmol), 4-azidobutanal (98 mg, 0.87 mmol), and acetyl chloride (68 mg, 0.87 mmol) as described above for the synthesis of **25a**. Purification by silica gel column chromatography (2 cm×8 cm, 33% AcOEt−hexane) afforded **32c** (265 mg, 88%) as a yellow foam: ^{1}H NMR (CD_3OD, 500 MHz, 3:2 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.65 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.95 (d, 1H, H-1′, $J_{1',2'}$ = 5.2 Hz), 5.80 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.79 (m, 1H, H-1″), 4.85 (d, 1H, H-6′, $J_{6',5'}$ = 5.7 Hz), 4.70 (dd, 1H, H-5′, $J_{5',4'}$ = 1.2, $J_{5',6'}$ = 5.7 Hz), 4.31 (dd, 1H, H-3′, $J_{3',2'}$ = 5.2, $J_{3',4'}$ = 4.0 Hz), 4.29 (dd, 1H, H-2′, $J_{2',1'}$ = 1.2, $J_{2',3'}$ = 5.2 Hz), 4.24 (dd, 1H, H-4′, $J_{4',3'}$ = 4.0, $J_{4',5'}$ = 1.2 Hz), 3.85 (s, 3H, CO_2CH_3), 3.36 (t, 2H, H-4″, $J_{4'',3''}$ = 6.9 Hz), 2.04 (s, 3H, acetyl), 1.95−1.70 (m, 4H, H-2′, H-3″), 0.95, 0.91 (each s, each 9H, *tert*-butyl), 0.16, 0.15, 0.11, 0.09 (each s, each 3H, $SiCH_3$); ^{13}C NMR (CD_3OD, 125 MHz) δ 171.5, 171.1, 165.5, 152.2, 141.1, 103.2, 91.8, 89.9, 84.1, 79.8, 76.3, 73.1, 60.4, 53.7, 51.9, 31.3, 26.4, 25.4, 22.3, 18.9, 18.9, −4.1, −4.3, −4.4, −4.5; ESIMS-HR m/z calcd for $C_{30}H_{52}N_6NaO_9Si_2$ $(M + Na)^+$ 719.3227, found 719.3223.

(2*R*,4*S*,5*S*)-3-Acetyl-2-azidomethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-di-*tert*-butyldimethylsilyloxy-4-(uracil-1-yl)]tetrahydrofuryl-(1,3)-oxazolidine-4-carboxylic Acid (33a). Compound **33a** was prepared from **32a** (101 mg, 0.15 mmol) as described above for the synthesis of **26a**. Purification by silica gel column chromatography (2 cm×10 cm, 5% MeOH−$CHCl_3$) afforded **33a** (72 mg, 73%) as a yellow syrup: ^{1}H NMR (CD_3OD, 500 MHz, 3:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.69 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 6.01 (d, 1H, H-1′, $J_{1',2'}$ = 4.6 Hz), 5.77 (dd, 1H, H-1″, $J_{1''\ 2''a}$ = 4.0, $J_{1''\ 2''b}$ = 8.2 Hz), 5.76, (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.68 (dd, 1H, H-5′, $J_{5',4'}$ = 1.2, $J_{5',6'}$ = 6.9 Hz), 4.44 (d, 1H, H-6′, $J_{6',5'}$ = 6.9 Hz), 4.37 (dd, 1H, H-4′, $J_{4',3'}$ = 4.0, $J_{4',5'}$ = 1.2 Hz), 4.31 (dd, 1H, H-2′, $J_{2',1'}$ = 4.6, $J_{2',3'}$ = 4.0 Hz), 4.30 (t, 1H, H-3′, $J_{3',2'}$ = $J_{3',4'}$ = 4.0 Hz), 3.67−3.40 (m, 2H, H-4″), 2.04 (s, 3H, acetyl), 1.90 (m, 2H, H-2″), 1.79 (m, 2H, H-3″), 0.94, 0.90 (each s, each 9H, *tert*-butyl), 0.16, 0.13, 0.09, 0.09 (each s, each 3H, $SiCH_3$); ^{13}C NMR (CD_3OD, 125 MHz) δ 176.2, 171.9, 165.8, 152.2, 141.4, 103.4, 90.5, 89.3, 84.6, 82.0, 76.4, 73.7, 62.8, 52.0, 26.4, 22.4, 18.9, 18.9, −4.2, −4.4, −4.4, −4.5; ESIMS-HR (negative mode) m/z calcd for $C_{27}H_{45}N_6O_9Si_2$ $(M - H)^-$ 653.2792, found 653.2798.

(2*R*,4*S*,5*S*)-3-Acetyl-2-azidoethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-di-*tert*-butyldimethylsilyloxy-4-(uracil-1-yl)]tetrahydrofuryl-(1,3)-oxazolidine-4-carboxylic Acid (33b). Compound **33b** was prepared from **32b** (120 mg, 0.18 mmol) as described above for the

synthesis of **26a**. Purification by silica gel column chromatography (2 cm×10 cm, 5% MeOH−$CHCl_3$) afforded **33b** (88 mg, 75%) as a yellow syrup: ^{1}H NMR (CD_3OD, 500 MHz, 3:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.71 (d, 1H, H-6, $J_{6,5}$ = 8.2 Hz), 5.97 (d, 1H, H-1′, $J_{1',2'}$ = 3.6 Hz), 5.80 (dd, 1H, H-1″, $J_{1'',2''a}$ = 3.7, $J_{1'',2''b}$ = 4.4 Hz), 5.74 (d, 1H, H-5, $J_{5,6}$ = 8.2 Hz), 4.61 (dd, 1H, H-5′, $J_{5',4'}$ = 1.4, $J_{5',6'}$ = 6.4 H), 4.45 (d, 1H, H-6′, $J_{6',5'}$ = 6.4 Hz), 4.37 (d, 1H, H-4′, $J_{4',5'}$ = 1.4 Hz), 4.31 (m, 2H, H-2′, H-3′), 3.47 (m, 2H, H-3″), 2.20−1.98 (m, 2H, H-2″), 2.04 (s, 3H, acetyl), 0.94, 0.91 (each s, each 9H, *tert*-butyl), 0.15, 0.14, 0.09, 0.08 (each s, each 3H, $SiCH_3$); ^{13}C NMR (CD_3OD, 125 MHz) δ 176.5, 171.6, 165.9, 152.2, 141.3, 103.2, 89.8, 89.5, 84.7, 81.6, 76.6, 73.5, 62.7, 33.2, 26.4, 22.4, 19.0, 18.9, −4.1, −4.3, −4.4, −4.5; ESIMS-HR (negative mode) *m*/*z* calcd for $C_{28}H_{47}N_6O_9Si_2$ $(M - H)^-$ 667.2949, found 667.2956.

(2*R*,4*S*,5*S*)-3-Acetyl-2-azidopropyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-di-*tert*-butyldimethylsilyloxy-4-(uracil-1-yl)]tetrahydrofuryl-(1,3)-oxazolidine-4-carboxylic Acid (33c). Compound **33c** was prepared from **32c** (115 mg, 0.18 mmol) as described above for the synthesis of **26a**. Purification by silica gel column chromatography (2 cm×10 cm, 5% MeOH−$CHCl_3$) afforded **33c** (91 mg, 81%) as a yellow syrup: ^{1}H NMR (CD_3OD, 500 MHz, 2:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.75 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.94 (d, 1H, H-1′, $J_{1',2'}$ = 4.0 Hz), 5.74 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.70, (dd, 1H, H-1″, $J_{1'',2''a}$ = 4.0, $J_{1'',2''b}$ = 7.5 Hz), 4.60 (dd, 1H, H-5′, $J_{5',4'}$ = 1.7, $J_{5',6'}$ = 6.9 Hz), 4.45 (d, 1H, H-6′, $J_{6',5'}$ = 6.9 Hz), 4.33 (dd, 1H, H-4′, $J_{4',3'}$ = 4.0, $J_{4',5'}$ = 1.7 Hz), 4.29 (dd, 1H, H-2′, $J_{2',1'}$ = 4.0, $J_{2',3'}$ = 5.2 Hz), 4.28 (dd, 1H, H-3′, $J_{3',2'}$ = 5.2, $J_{3',4'}$ = 4.0 Hz), 3.36 (m, 2H, H-4″), 2.05 (s, 3H, acetyl), 1.93−1.71 (m, 2H, H-2″), 1.79 (m, 2H, H-3″), 0.94, 0.90 (each s, each 9H, *tert*-butyl), 0.15, 0.14, 0.09, 0.08 (each s, each 3H, $SiCH_3$); ^{13}C NMR (CD_3OD, 125 MHz) δ 176.7, 171.5, 165.9, 152.1, 141.3, 103.0, 91.5, 89.6, 84.3, 81.0, 76.7, 73.3, 62.5, 52.1, 31.1, 26.4, 25.6, 22.5, 18.9, 18.9, −4.1, −4.3, −4.4, −4.5; ESIMS-HR (negative mode) *m*/*z* calcd for $C_{29}H_{49}N_6O_9Si_2$ $(M - H)^-$ 681.3105, found 681.3114.

(2*R*,4*S*,5*S*)-3-Acetyl-2-azidomethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-di-*tert*-butyldimethylsilyloxy-4-(uracil-1-yl)]tetrahydrofuryl-*N*-hexadecyl-(1,3)-oxazolidine-4-carboxylamide (34a). A mixture of **33a** (40 mg, 0.061 mmol), hexadecylamine (44 mg, 0.18 mmol), and HOBt (25 mg, 0.18 mmol) in CH_2Cl_2 (1 mL) was treated with EDCI (35 mg, 0.18 mmol) at room teperature for 12 h. The mixture was diluted with AcOEt (50 mL), which was washed with 0.1 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (1.5 cm×8 cm, 50% AcOEt−hexane) to give **34a** (38 mg, 71%) as a yellow syrup: ^{1}H NMR (CD_3OD, 500 MHz, 1:1 mixture of rotamers at 20 °C, data for one rotamer) δ 7.75 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.98 (d, 1H, H-1′, $J_{1',2'}$ = 4.6 Hz), 5.92 (dd, 1H, H-1″, $J_{1'',2''a}$ = 4.6, $J_{1'',2''b}$ = 7.5 Hz), 5.82 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.59 (d, 1H, H-6′, $J_{6',5'}$ = 6.9 Hz), 4.54 (d, 1H, H-5′, $J_{5',4'}$ = 1.2, $J_{5',6'}$ = 8.0 Hz), 4.33 (dd, 1H, H-2′, $J_{2',1'}$ = 4.6, $J_{2',3'}$ = 4.0 Hz), 4.30 (dd, 1H, H-3′, $J_{3',2'}$ = 4.0, $J_{3',4'}$ = 4.6 Hz), 4.21 (dd, 1H, H-4′, $J_{4',3'}$ = 4.6, $J_{4',5'}$ = 1.2 Hz), 3.85−3.71 (m, 2H, H-2″), 3.36−3.25 (m, 2H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$), 2.07 (s, 3H, acetyl), 1.52 (m, 2H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$), 1.29 (br s, 26H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$), 0.94, 0.89 (each s, each 9H, *tert*-butyl), 0.89 (t, 3H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$, J = 6.9 Hz), 0.16, 0.14, 0.09, 0.07 (each s, each 3H, $SiCH_3$); ^{13}C NMR (CD_3OD, 125 MHz) δ 171.9, 170.9, 170.6, 165.9, 152.2, 141.6, 103.4, 91.1, 90.3, 83.5, 81.9, 76.1, 73.2, 62.4, 52.8, 40.7, 33.1, 30.8, 30.7, 30.5, 28.0, 26.5, 23.8, 22.3, 22.2, 19.0, 19.0, −4.2, −4.4, −4.4, −4.5; ESIMS-HR *m*/*z* calcd for $C_{43}H_{79}N_7NaO_8Si_2$ $(M + Na)^+$ 900.5421, found 900.5428.

(2*R*,4*S*,5*S*)-3-Acetyl-2-azidoethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-di-*tert*-butyldimethylsilyloxy-4-(uracil-1-yl)]tetrahydrofuryl-*N*-hexadecyl-(1,3)-oxazolidine-4-carboxylamide (34b). Compound **34b** was prepared from **33b** (29 mg, 0.044 mmol) as described above for the synthesis of **34a**. Purification by silica gel column chromatography (1.5 cm × 8 cm, 50% AcOEt−hexane) afforded **34b** (27 mg, 70%) as a yellow syrup: ^{1}H NMR (CD_3OD, 500 MHz, 1:1 mixture of rotamers at 20 °C, data for one rotamer) δ 7.78 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.95 (d, 1H, H-1′, $J_{1',2'}$ = 4.6 Hz), 5.83 (m, 1H, H-1″), 5.80 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 4.52 (d, 1H, H-6′, $J_{6',5'}$ = 7.5 Hz), 4.50 (dd, 1H, H-5′, $J_{5',4'}$ = 1.2, $J_{5',6'}$ = 7.5 Hz), 4.30 (t, 1H, H-2′, $J_{2',1'} = J_{2',3'}$ = 4.6 Hz), 4.29 (dd, 1H, H-3′, $J_{3',2'}$ = 4.6, $J_{3',4'}$ = 4.0 Hz), 4.22 (dd, 1H, H-4′, $J_{4',3'}$ = 4.0, $J_{4',5'}$ = 1.2 Hz), 3.54 (t, 2H, H-3″, $J_{3'',2''}$ = 5.2 Hz), 3.36−3.24 (m, 2H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$), 2.28−2.05 (m, 2H, H-2″), 2.14 (s, 3H, acetyl), 1.51 (m, 2H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$), 1.29 (br s, 26H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$), 0.94, 0.91 (each s, each 9H, *tert*-butyl), 0.89 (t, 3H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$, J = 6.9 Hz), 0.14, 0.14, 0.10, 0.09 (each s, each 3H, $SiCH_3$); ^{13}C NMR (CD_3OD, 125 MHz) δ 171.5, 171.1, 170.9, 166.0, 152.3, 141.4, 103.2, 90.6, 90.5, 83.5, 81.5, 76.4, 73.2, 62.3, 52.8, 40.8, 33.6, 33.1, 30.8, 30.7, 30.5, 28.0, 26.4, 23.8, 22.3, 22.1, 19.0, 19.0, 14.5, −4.0, −4.0, −4.4, −4.5; MS-HR *m*/*z* calcd for $C_{44}H_{81}N_7NaO_8Si_2$ $(M + Na)^+$ 914.5577, found 914.5580.

(2*R*,4*S*,5*S*)-3-Acetyl-2-azidopropyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-di-*tert*-butyldimethylsilyloxy-4-(uracil-1-yl)]tetrahydrofuryl-*N*-hexadecyl-(1,3)-oxazolidine-4-carboxylamide (34c). Compound **34c** was prepared from **33c** (40 mg, 0.059 mmol) as described above for the synthesis of **34a**. Purification by silica gel column chromatography (1.5 cm × 20 cm, 50% AcOEt−hexane) afforded **34c** (45 mg, 84%) as a yellow syrup: ^{1}H NMR (CD_3OD, 500 MHz, 1:1 mixture of rotamers at 20 °C, data for one rotamer) δ 7.82 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.92 (d, 1H, H-1′, $J_{1',2'}$ = 4.0 Hz), 5.79 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.78 (m, 1H, H-1″), 4.52 (d, 1H, H-6′, $J_{6',5'}$ = 7.5 Hz), 4.50 (dd, 1H, H-5′, $J_{5',4'}$ = 1.2, $J_{5',6'}$ = 7.5 Hz), 4.31 (dd, 1H, H-2′, $J_{2',1'}$ = 4.0, $J_{2',3'}$ = 5.7 Hz), 4.27 (dd, 1H, H-3′, $J_{3',2'}$ = 5.7, $J_{3',4'}$ = 4.6 Hz), 4.24 (dd, 1H, H-4′, $J_{4',3'}$ = 4.6, $J_{4',5'}$ = 1.2 Hz), 3.38 (t, 2H, H-4″, $J_{4'',3''}$ = 6.9 Hz), 3.36−3.24 (m, 2H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$), 2.14 (s, 3H, acetyl), 1.91 (m, 2H, H-2″), 1.80 (m, 2H, H-3″), 1.52 (m, 2H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$), 1.29 (br s, 26H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$), 0.94, 0.91 (each s, each 9H, *tert*-butyl), 0.90 (t, 3H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$, J = 6.9 Hz), 0.15, 0.14, 0.11, 0.11 (each s, each 3H, $SiCH_3$); ^{13}C NMR (CD_3OD, 125 MHz) δ 171.5, 171.1, 170.6, 165.9, 152.2, 141.4, 103.0, 92.3, 90.5, 83.4, 80.1, 76.5, 73.0, 60.8, 52.1, 40.7, 32.3, 31.6, 30.8, 30.7, 30.5, 28.0, 26.5, 25.7, 25.6, 23.8, 22.4, 22.1, 19.0, 19.0, 14.5, −4.0, −4.0, −4.4, −4.5; ESIMS-HR *m*/*z* calcd for $C_{45}H_{83}N_7NaO_8Si_2$ $(M + Na)^+$ 928.5734, found 928.5735.

(2*R*,4*S*,5*S*)-3-Acetyl-2-azidomethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-*N*-hexadecyl-(1,3)-oxazolidine-4-carboxylamide (35a). Compound **35a** was prepared from **34a** (26 mg, 0.030 mmol) as described above for the synthesis of **27a**. Purification by silica gel column chromatography (1.5 cm×8 cm, 2% MeOH−$CHCl_3$) afforded **35a** (16 mg, 81%) as a yellow syrup: ^{1}H NMR (CD_3OD, 500 MHz, 3:2 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.63 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.90 (d, 1H, H-1′, $J_{1',2'}$ = 4.0 Hz), 5.73 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.67 (dd, 1H, H-1″, $J_{1'',2''a}$ = 2.3, $J_{1'',2''b}$ = 6.3 Hz), 4.66 (dd, 1H, H-5′, $J_{5',4'}$ = 2.3, $J_{5',6'}$ = 7.5 Hz), 4.61 (d, 1H, H-6′, $J_{6',5'}$ = 7.5 Hz), 4.31 (dd, 1H, H-3′, $J_{3',2'}$ = 5.2, $J_{3',4'}$ = 5.7 Hz), 4.25 (dd, 1H, H-2′, $J_{2',1'}$ = 4.0, $J_{2',3'}$ = 5.2 Hz), 4.12 (dd, 1H, H-4′, $J_{4',3'}$ = 5.7, $J_{4',5'}$ = 2.3 Hz), 3.65 (m, 2H, H-2″), 3.36−3.14 (m, 2H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$), 2.01 (s, 3H, acetyl), 1.53 (m, 2H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$), 1.29 (br s, 26H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$), 0.90 (t, 3H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 172.3, 171.1, 170.9, 165.9, 152.3, 142.3, 103.3, 91.3, 91.1, 84.0, 82.2, 74.7, 71.3, 62.6, 52.7, 40.9, 33.1, 30.8, 30.7, 30.7, 30.5, 30.4, 30.4, 30.3, 28.0, 23.8, 22.2, 14.5; ESIMS-HR *m*/*z* calcd for $C_{31}H_{51}N_7NaO_8$ $(M + Na)^+$ 672.3691, found 672.3697.

(2*R*,4*S*,5*S*)-3-Acetyl-2-azidoethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-*N*-hexadecyl-(1,3)-oxazolidine-4-carboxylamide (35b). Compound **35b** was prepared from **34b** (25 mg, 0.028 mmol) as described above for the synthesis of **27a**. Purification by silica gel column chromatography (1.5 cm×8 cm, 2% MeOH−$CHCl_3$) afforded **35b** (14 mg, 76%) as a yellow syrup: ^{1}H NMR (CD_3OD, 500 MHz, 1:1 mixture of rotamers at 20 °C, data for one rotamer) δ 7.70 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.93 (d, 1H, H-1′, $J_{1',2'}$ = 4.6 Hz), 5.76 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.75 (m, 1H, H-1″), 4.57 (d, 1H, H-6′, $J_{6',5'}$ = 6.9 Hz), 4.56 (dd, 1H, H-5′, $J_{5',4'}$ = 1.7, $J_{5',6'}$ = 6.9 Hz), 4.27 (dd, 1H, H-3′, $J_{3',2'}$ = 5.7, $J_{3',4'}$ = 5.2 Hz), 4.22 (dd, 1H, H-2′, $J_{2',1'}$ = 4.6, $J_{2',3'}$ = 5.7 Hz), 4.13 (dd, 1H, H-4′, $J_{4',3'}$ = 5.2, $J_{4',5'}$ = 1.7 Hz), 3.53 (t, 2H, H-3″, $J_{3'',2''}$ = 6.9 Hz), 3.36−3.22 (m, 2H, $CH_3(CH_2)_{13}CH_2C\underline{H}_2NHCO$), 2.12 (s, 3H, acetyl), 2.05 (m, 2H, H-2″), 1.54 (m, 2H, $CH_3(CH_2)_{13}C\underline{H}_2CH_2NHCO$, 1.29 (br s, 26H, $CH_3(C\underline{H}_2)_{13}CH_2CH_2NHCO$), 0.90 (t, 3H, $C\underline{H}_3(CH_2)_{13}CH_2CH_2NHCO$), J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 171.9, 171.1, 170.8, 165.9, 152.3, 142.1, 103.3, 91.0, 90.3, 83.9, 81.7, 74.9, 71.4, 62.5, 40.8, 33.9, 33.1, 30.8, 30.7, 30.7, 30.5, 30.4, 30.4, 30.3, 28.0, 23.8, 22.1, 14.5; ESIMS-HR m/z calcd for $C_{32}H_{53}N_7NaO_8$ (M + Na)$^+$ 686.3848, found 686.3851.

(2*R*,4*S*,5*S*)-3-Acetyl-2-azidopropyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-*N*-hexadecyl-(1,3)-oxazolidine-4-carboxylamide (35c). Compound **35c** was prepared from **34c** (39 mg, 0.043 mmol) as described above for the synthesis of **27a**. Purification by silica gel column chromatography (1.5 cm× 8 cm, 2% MeOH−$CHCl_3$) afforded **35c** (26 mg, 88%) as a yellow syrup: ^{1}H NMR (CD_3OD, 500 MHz, 1:1 mixture of rotamers at 20 °C, data for one rotamer) δ 7.71 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.92 (d, 1H, H-1′, $J_{1',2'}$ = 4.6 Hz), 5.75 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.64 (m, 1H, H-1″), 4.57 (d, 1H, H-6′, $J_{6',5'}$ = 6.9 Hz), 4.56 (dd, 1H, H-5′, $J_{5',4'}$ = 1.7, $J_{5',6'}$ = 6.9 Hz), 4.26 (t, 1H, H-3′, $J_{3',2'}$ = $J_{3',4'}$ = 5.7 Hz), 4.22 (dd, 1H, H-2′, $J_{2',1'}$ = 4.6, $J_{2',3'}$ = 5.7 Hz), 4.13 (dd, 1H, H-4′, $J_{4',3'}$ = 5.7, $J_{4',5'}$ = 1.7 Hz), 3.42 (t, 2H, H-4″, $J_{4'',3''}$ = 6.9 Hz), 3.35−3.24 (m, 2H, $CH_3(CH_2)_{13}CH_2C\underline{H}_2NHCO$), 2.11 (s, 3H, acetyl), 1.92 (m, 2H, H-2″), 1.76 (m, 2H, H-3″), 1.53 (m, 2H, $CH_3(CH_2)_{13}C\underline{H}_2CH_2NHCO$), 1.29 (br s, 26H, $CH_3(C\underline{H}_2)_{13}CH_2CH_2NHCO$), 0.90 (t, 3H, $C\underline{H}_3(CH_2)_{13}CH_2CH_2NHCO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 171.9, 171.1, 170.9, 165.9, 152.3, 142.2, 103.2, 92.2, 90.8, 83.8, 81.5, 74.9, 71.4, 62.5, 52.2, 40.8, 33.1, 31.9, 30.8, 30.8, 30.7, 30.5, 30.4, 30.4, 30.4, 28.0, 25.5, 23.8, 22.1, 14.5; ESIMS-HR m/z calcd for $C_{33}H_{55}N_7NaO_8$ (M + Na)$^+$ 700.4004, found 700.4006.

(2*R*,4*S*,5*S*)-3-Acetyl-2-aminomethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-*N*-hexadecyl-(1,3)-oxazolidine-4-carboxylamide HCl Salt (21a). Compound **21a** was prepared from **35a** (9.7 mg, 0.015 mmol) as described above for the synthesis of **18a**. Purification by C18 HPLC (85% aqueous MeOH containing 0.5% HCl) afforded **21a** (6.4 mg, 69%) as a white foam: ^{1}H NMR (CD_3OD, 500 MHz, 9:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.57 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.71 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.67 (d, 1H, H-1′, $J_{1',2'}$ = 3.5 Hz), 5.62 (dd, 1H, H-1″, $J_{1'',2''a}$ = 2.3, $J_{1'',2''b}$ = 2.9 Hz), 4.69 (d, 1H, H-6′, $J_{6',5'}$ = 2.3 Hz), 4.61 (t, 1H, H-5′, $J_{5',4'}$ = $J_{5',6'}$ = 2.3 Hz), 4.41 (dd, 1H, H-3′, $J_{3',2'}$ = 6.3, $J_{3',4'}$ = 6.9 Hz), 4.32 (dd, 1H, H-2′, $J_{2',1'}$ = 3.5, $J_{2',3'}$ = 6.3 Hz), 4.04 (dd, 1H, H-4′, $J_{4',3'}$ = 6.9, $J_{4',5'}$ = 2.3 Hz), 3.51 (m, 2H, H-2″), 3.36−3.18 (m, 2H, $CH_3(CH_2)_{13}CH_2C\underline{H}_2NHCO$), 2.03 (s, 3H, acetyl), 1.57 (br s, 2H, $CH_3(CH_2)_{13}C\underline{H}_2CH_2NHCO$), 1.29 (br s, 26H, $CH_3(C\underline{H}_2)_{13}CH_2CH_2NHCO$), 0.90 (t, 3H, $C\underline{H}_3(CH_2)_{13}CH_2CH_2NHCO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 172.6, 172.2, 165.9, 152.1, 143.8, 103.4, 93.9, 89.2, 85.1, 82.6, 73.9, 70.3, 61.9, 41.0, 33.1, 30.8, 30.7, 30.7, 30.4, 30.4, 30.2, 28.0, 23.7, 23.0, 14.4; ESIMS-HR m/z calcd for $C_{31}H_{54}N_5O_8$ (M + H)$^+$ 624.3967, found 624.3964.

(2*R*,4*S*,5*S*)-3-Acetyl-2-aminoethyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-*N*-hexadecyl-(1,3)-oxazolidine-4-carboxylamide HCl Salt (21b). Compound **21b** was prepared from **35b** (9.2 mg, 0.014 mmol) as described above for the synthesis of **18a**. Purification by C18 HPLC (85% aqueous MeOH containing 0.5% HCl) afforded **21b** (6.4 mg, 72%) as a white foam: ^{1}H NMR (CD_3OD, 500 MHz, 5:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.63 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.80 (d, 1H, H-1′, $J_{1',2'}$ = 3.5 Hz), 5.71 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.65 (t, 1H, H-1″, $J_{1'',2''}$ = 5.2 Hz), 4.62 (d, 1H, H-6′, $J_{6',5'}$ = 5.2 Hz), 4.57 (dd, 1H, H-5′, $J_{5',4'}$ = 2.3, $J_{5',6'}$ = 5.2 Hz), 4.32 (dd, 1H, H-3′, $J_{3',2'}$ = 5.8, $J_{3',4'}$ = 6.3 Hz), 4.28 (dd, 1H, H-2′, $J_{2',1'}$ = 3.5, $J_{2',3'}$ = 5.8 Hz), 4.08 (dd, 1H, H-4′, $J_{4',3'}$ = 6.3, $J_{4',5'}$ = 2.3 Hz), 3.34−3.18 (m, 2H, $CH_3(CH_2)_{13}CH_2C\underline{H}_2NHCO$), 3.11 (t, 2H, H-3″, $J_{3'',2''}$ = 6.3 Hz), 2.26 (br s, 2H, H-2″), 2.02 (s, 3H, acetyl), 1.56 (br s, 2H, $CH_3(CH_2)_{13}C\underline{H}_2CH_2NHCO$), 1.29 (br s, 26H, $CH_3(C\underline{H}_2)_{13}CH_2CH_2NHCO$), 0.90 (t, 3H, $C\underline{H}_3(CH_2)_{13}CH_2CH_2NHCO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 172.2, 171.3, 165.9, 152.2, 142.9, 103.2, 92.7, 90.4, 83.9, 82.0, 74.5, 70.9, 62.5, 41.0, 33.1, 32.2, 30.8, 30.8, 30.7, 30.5, 30.4, 30.3, 28.1, 23.7, 22.6, 14.5; ESIMS-HR m/z calcd for $C_{32}H_{56}N_5O_8$ (M + H)$^+$ 638.4123, found 638.4123.

(2*R*,4*S*,5*S*)-3-Acetyl-2-aminopropyl-5-[(1*R*,2*R*,3*R*,4*R*)-2,3-dihydroxy-4-(uracil-1-yl)]tetrahydrofuryl-*N*-hexadecyl-(1,3)-oxazolidine-4-carboxylamide HCl Salt (21c). Compound **21c** was prepared from **35c** (9.7 mg, 0.014 mmol) as described above for the synthesis of **18a**. Purification by C18 HPLC (85% aqueous MeOH containing 0.5% HCl) afforded **21c** (4.8 mg, 51%) as a white foam: ^{1}H NMR (CD_3OD, 500 MHz, 2:1 mixture of rotamers at 20 °C, data for the major rotamer) δ 7.65 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.87 (d, 1H, H-1′, $J_{1',2'}$ = 3.5 Hz), 5.71 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.60 (dd, 1H, H-1″, $J_{1'',2''a}$ = 3.4, $J_{1'',2''b}$ = 6.3 Hz), 4.58 (d, 1H, H-6′, $J_{6',5'}$ = 5.8 Hz), 4.55 (dd, 1H, H-5′, $J_{5',4'}$ = 1.7, $J_{5',6'}$ = 5.8 Hz), 4.27 (dd, 1H, H-3′, $J_{3',2'}$ = 5.2, $J_{3',4'}$ = 5.8 Hz), 4.23 (dd, 1H, H-2′, $J_{2',1'}$ = 3.5, $J_{2',3'}$ = 5.2 Hz), 4.11 (dd, 1H, H-4′, $J_{4',3'}$ = 5.8, $J_{4',5'}$ = 1.7 Hz), 3.33−3.15 (m, 2H, $CH_3(CH_2)_{13}CH_2C\underline{H}_2NHCO$), 2.99 (t, 2H, H-4″, $J_{4'',3''}$ = 6.9 Hz), 2.00 (s, 3H, acetyl), 1.84 (m, 4H, H-2″, H-3″), 1.54 (m, 2H, $CH_3(CH_2)_{13}C\underline{H}_2CH_2NHCO$), 1.29 (br s, 26H, $CH_3(C\underline{H}_2)_{13}CH_2CH_2NHCO$), 0.90 (t, 3H, $C\underline{H}_3(CH_2)_{13}CH_2CH_2NHCO$, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 171.8, 171.0, 166.0, 152.2, 142.5, 103.1, 91.8, 91.8, 83.5, 81.7, 74.9, 71.3, 62.5, 40.4, 33.1, 31.5, 30.8, 30.7, 30.5, 30.4, 30.3, 28.0, 24.2, 23.8, 22.6, 14.5; ESIMS-HR m/z calcd for $C_{33}H_{58}N_5O_8$ (M + H)$^+$ 652.4280, found 652.4281.

Enzymatic Evaluation. The activities of the compounds were tested against purified MraY from *B. subtilis*.[7] The assay was performed in a reaction mixture (10 μL) containing, in final concentrations, 100 mM Tris-HCl, pH 7.5, 40 mM $MgCl_2$, 1.1 mM C_{55}-P, 250 mM NaCl, 0.25 mM UDP-MurNAc-[^{14}C]pentapeptide (337 Bq), and 8.4 mM *N*-lauroyl sarcosine. The reaction was initiated by the addition of MraY enzyme, and the mixture was incubated for 30 min at 37 °C under shaking with a thermomixer (Eppendorf). The reaction was stopped by heating at 100 °C for 1 min. The radiolabeled substrate UDP-MurNAc-pentapeptide and reaction product (lipid I, product of MraY) were separated by TLC on silica gel plates LK6D (Whatman) using 2-propanol/concentrated ammonium hydroxide/water (6:3:1, v/v/v) as a mobile phase. The radioactive spots were located and quantified with a radioactivity scanner (model Multi-Tracemaster LB285; EG&G Wallac/Berthold). IC_{50} values were calculated with respect to a control assay without the inhibitor. Data represent the mean of independent triplicate determinations.

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 2-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 0.1 mL. Plates were incubated at 35 °C for 20 h, and then MICs were scored.

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Supporting Information Available: HPLC purity data and NOE data. This material is available free of charge via the Internet at http://pubs.acs.org.

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