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Total Synthesis and Biological Evaluation of Pacidamycin D and Its 3′-Hydroxy Analogue

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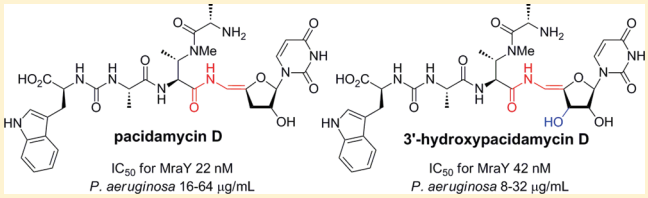
Supporting Information

ABSTRACT: Full details of the total synthesis of pacidamycin D (**4**) and its 3′-hydroxy analogue **32** are described. The chemically labile *Z*-oxyacyl enamide moiety is the most challenging chemical structure found in uridylpeptide natural products. Key elements of our approach to the synthesis of **4** include the efficient and stereocontrolled construction of the *Z*-oxyvinyl halides **6** and **7** and their copper-catalyzed cross-coupling with the tetrapeptide carboxamide **5**, a thermally unstable compound containing a number of potentially reactive functional groups. This synthetic route also allowed us to easily prepare 3′-hydroxy analogue **32**. The assemblage by cross-coupling of the *Z*-oxyvinyl halide **6** and the carboxamide **5** at a late stage of the synthesis provided ready access to a range of uridylpeptide antibiotics and their analogues, despite their inherent labile nature with potential epimerization, simply by altering the tetrapeptide moiety.



INTRODUCTION

Bacterial pathogens inevitably develop severe resistance to every new antibacterial drug launched. Multi-drug-resistant *Pseudomonas aeruginosa* is one of the most problematic bacteria because of the limited number of effective drugs in the clinic. A class of uridylpeptide antibiotics (Figure 1, **1**−**4**) has shown potent and selective antibacterial activity against strains of *P. aeruginosa*.[1,2] This class contains mureidomycins,[3−6] napsamycins,[7] pacidamycins,[8−11] and recently identified sansanmycins.[12,13] Among the class of uridylpeptide antibiotics, the mureidomycins (**1**), isolated from *Streptomyces flavidoviridens* SANK 60486, showed the most potent antibacterial activity against strains of *Pseudomonas* with minimum inhibitory concentrations (MICs) ranging from 0.1 to 3.12 μg/mL in vitro, also protecting mice against *P. aeruginosa* infection.[3−6] The pacidamycins (**4**) were isolated from the fermentation broth of the *Streptomyces coeruleorubiduns* strain and possess a Trp residue at the *C*-terminus. They also exhibit anti-*P. aeruginosa* activity with MICs ranging from 1.5 to 12.5 μg/mL.[8−11] The mode of action was well studied for **1**, and they interfere the bacterial cell wall biosynthesis in a different manner to β-lactams and vancomycin. Peptidoglycan biosynthesis consists of three stages, including the formation of uridine diphosphate *N*-acetylmuraminylpentapeptide (UDP-MurNAc-pentapeptide) in cytoplasm, the membrane-anchored synthesis of lipid I and lipid II, a precursor to the peptide glycan, and polymerization of the resulting lipid II by transpeptidation and transglycosidation (Figure 2). The second and the third stages are involved in a lipid cycle, and phospho-MurNAc-pentapeptide transferase (MraY) catalyzes the first step of the lipid-linked cycle of the reactions, where UDP-MurNAc-pentapeptide is attacked by the undecaprenol monophosphate in the bacterial cell membrane providing lipid I.[14−17] Lipid I anchored to the cell membrane is further glycosylated by *N*-acetylglucosamine to afford lipid II. Therefore, the MraY is an essential enzyme in bacteria, and **1** is a strong inhibitor of MraY (IC_{50} = 0.05 μg/mL).[18,19] Because of their structural and biological similarities, it has been suggested that **2**−**4** may share the same mode of action as **1**. Consequently, uridylpeptide antibiotics, with a novel mode of action, are expected to be good candidates as antibacterial agents against *P. aeruginosa*. Intrigued by the promising biological activity, structure−activity relationship studies have been conducted by several groups.[20−27] However, no total synthesis of **1**−**4** has yet been accomplished. Uridylpeptide antibiotics share a common structural feature. Namely, they consist of a 3′-deoxyuridine with a *Z*-enamide structure at the 4′,5′-positions, a tetrapeptide moiety containing a nonproteinogenic amino acid, and α,β-diaminobutyric acid, a urea linkage connecting two amino acids at the *C*-terminus. The α,β-diaminobutyric acid plays a pivotal role connecting the *N*-terminal amino acid, the ureadipeptide, and the 3′-deoxyuridine moieties (Figure 1). The potential difficulty in the total synthesis of this class of natural products may be the chemically labile *Z*-oxyacyl enamide moiety, which is a particularly challenging chemical structure. The analogues possessing the enamide functionality have been prepared only by a chemogenetic approach

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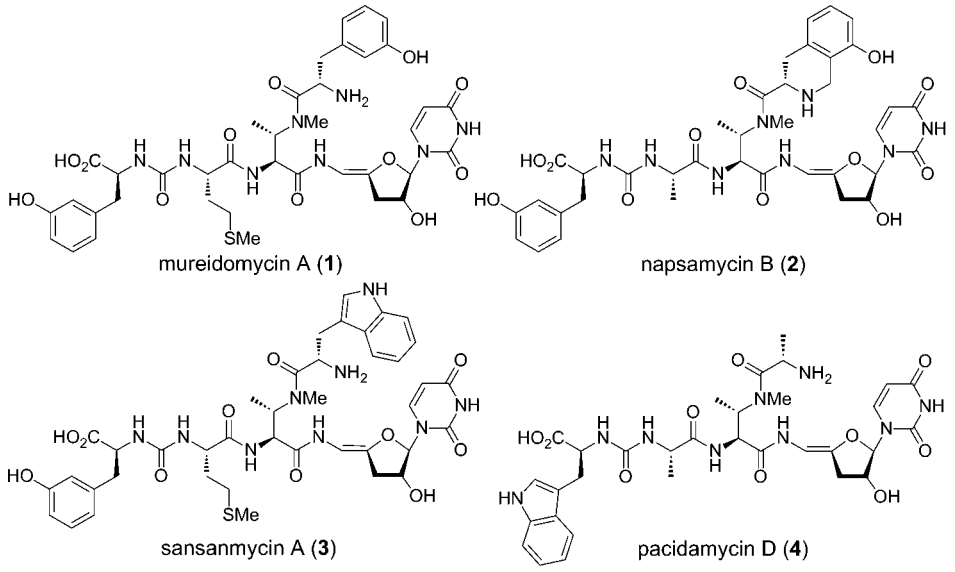

Figure 1. Structure of uridylpeptide natural products.

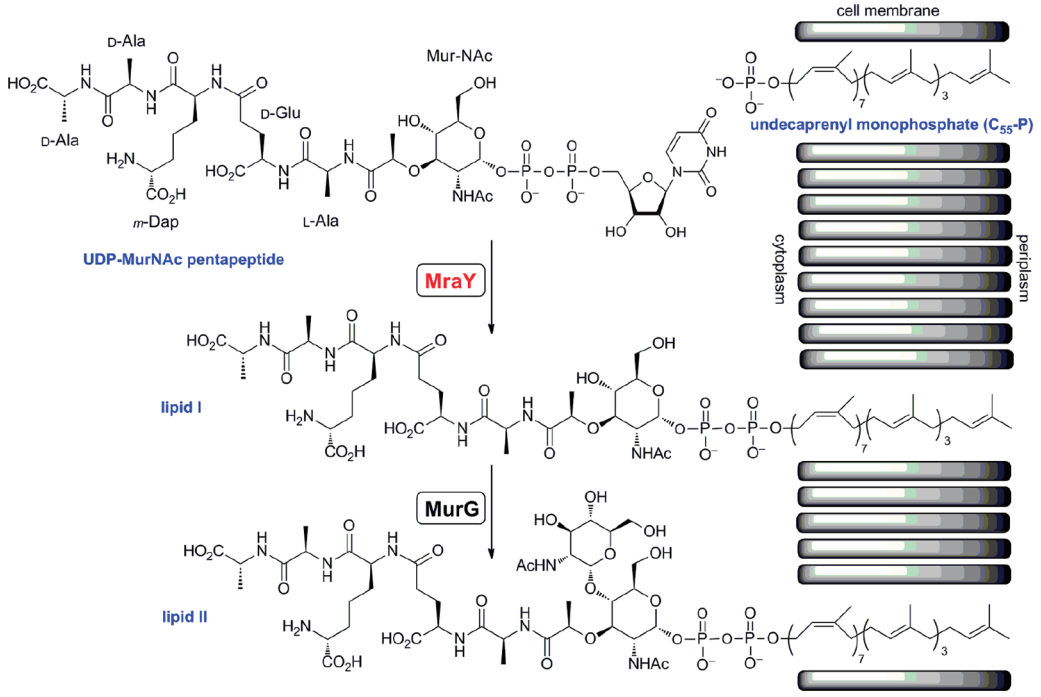

Figure 2. Biosynthesis of peptidoglycan precursor.

combining genetics and organic synthesis[28] and by biosynthesis,[29] owing to recent elucidation of biosynthetic pathway of uridylpeptide antibiotics.[30,31] The acyl enamide structure can be synthesized by addition of amides to alkynes,[32] acylation of imines,[33] Curtius rearrangement of α,β-unsaturated acyl azides,[34] condensation of carbonyl derivatives with amines,[35] oxidative amidation of alkenes,[36] oxidative decarboxylation−elimination of *N*-acyl-α-amino acids,[37] reductive amidation of ketones,[38] aza-Wittig reaction of acyl azides with aldehydes,[39] isomerization of *N*-allylamides,[40] and cross-coupling of amides with vinyl halides.[41] The methods applicable to the synthesis of uridylpeptide antibiotics **1**-**4** are quite limited among them. Recently we accomplished the first total synthesis of **4**.[42] Herein we describe the full details of the total synthesis of **4** and its 3′-hydroxy analogue **32**. Our retrosynthetic approach to **4** includes two key reactions, which are an efficient and stereocontrolled construction of the *Z*-oxyvinyl iodides **6** and **7**, and their copper-catalyzed cross-coupling with the tetrapeptide carboxamide **5** (Scheme 1). Taking the chemical lability in consideration, we planned to construct the *Z*-oxyacyl enamide moiety in the late stage of the synthesis. The tetrapeptide **5** contains a number of potentially reactive functional groups and renders selective synthetic modification difficult. The challenge of our synthetic approach is whether the *C*−*N* cross-coupling proceeds with **5**, and if so, whether the selective reaction at the *N*-unsubstituted carboxamide moiety proceeds in the presence of several potential reactive sites, including the primary amide, the carbamate, and the urea groups. The pacidamycins as well as the other congeners described in Figure 1 are 3′-deoxyuridine derivatives. Owing to the intriguing biological activity of the

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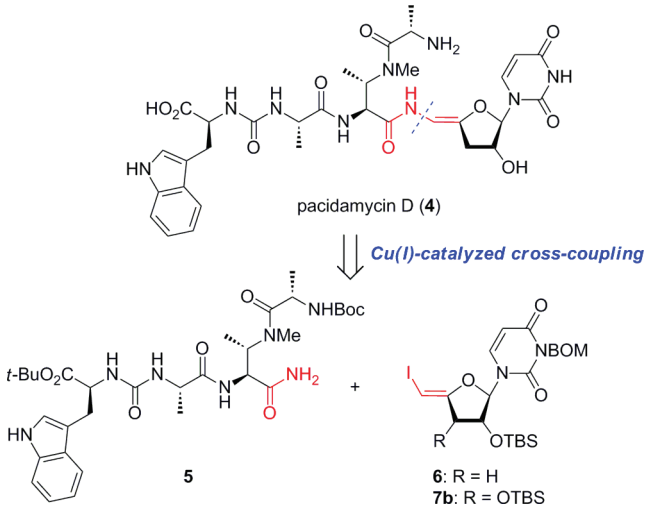
Scheme 1. Retrosynthetic Analysis of Pacidamycin D (4)

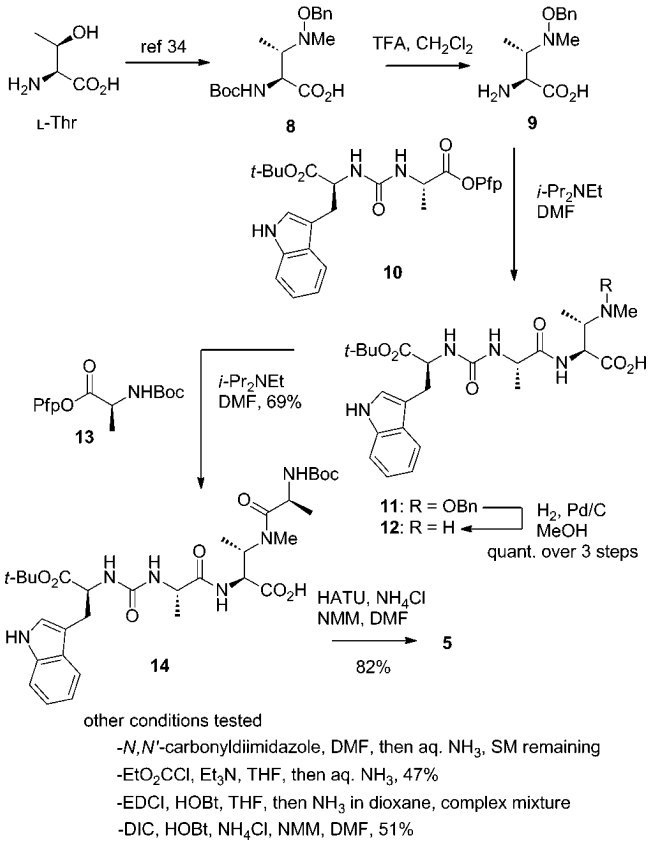


corresponding *ribo*-type, we decided to prepare an analogue such as **32** (Scheme 6) in addition to **4**. Accordingly, our first plan for the synthesis of **4** was the first construction of a *ribo*-type analogue followed by removal of the allylic 3′-hydroxyl group at the uridine moiety by Barton deoxygenation after the cross-coupling reaction.

RESULTS AND DISCUSSION

By using the known carboxylic acid **8**[29] and the pentafluorophenyl (Pfp) ester of the unsymmetrical urea **10**,[43] the tetrapeptide carboxamide **5** was prepared as shown in Scheme 2.

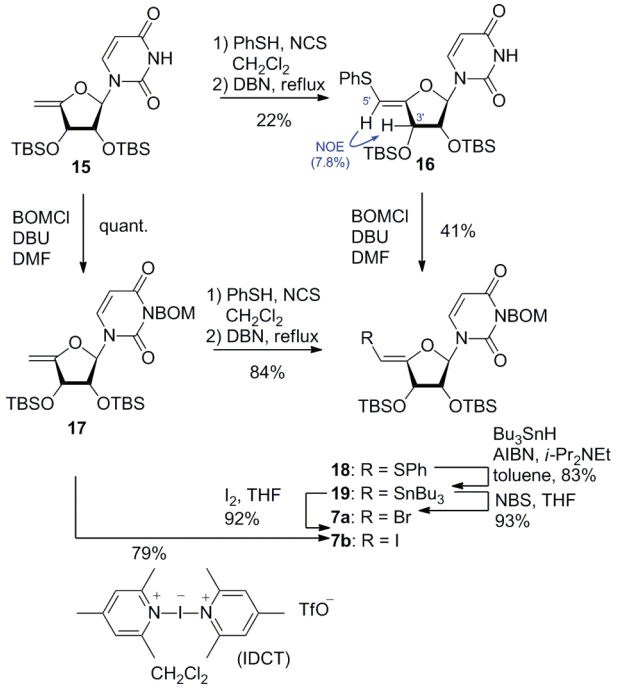
Scheme 2. Preparation of Tetrapeptide Carboxamide 5



After deprotection of the Boc group of **8**, the liberated amine **9** was condensed with **10** in the presence of *i*-Pr_2NEt in DMF to give the tripeptide **11**. *N*−*O* bond cleavage of **11** was achieved by catalytic hydrogenation to give the secondary amine **12** in quantitative yield over three steps. The amine **12** was further reacted with the Pfp ester of the *N*-Boc-L-Ala **13** to afford the tetrapeptide carboxylic acid **14**. Conversion of the carboxyl group of **14** to the carboxamide was then investigated. First, amidation of a mixed anhydride prepared from **14** by either EtO_2CCl or *N*,*N*′-carbonyldiimidazole with 28% aq ammonia was conducted. However, the desired **5** was obtained in moderate isolated yields of **5** (47−50%). The amidation was next focused on the use of peptide coupling reagents. Treatment of **14** with EDCI and HOBt in THF followed by NH_3 in dioxane at rt. gave a complex mixture of products. Optimization of the reaction conditions led us to find the conditions employing 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), NH_4Cl, *N*-methylmorpholine (NMM) in DMF to give **5** in 82% yield.

As for the uridine derivatives, the coupling partners of **5**, the synthetic study began with the preparation of oxyvinyl halides **7a** and **7b**, which are more accessible than that of the 3′-deoxyuridine derivative (Scheme 3). We first applied the method

Scheme 3. Preparation of Ribo-Type Vinyl Halides



developed by Tanaka, et al.[44] The *exo*-olefin derivative of the uridine **15**[45,46] was reacted with PhSCl generated from PhSH and NCS, and the resulting 4′-chloro-5′-phenylthio intermediate was treated with DBU to eliminate the hydrogen chloride[47,48] and provide the desired *Z*-phenylthio derivative **16**. The geometry of the olefin was confirmed by a 500 MHz NOE experiment in $CDCl_3$, where the correlation to H-3′ was observed upon irradiation at H-5′ (7.8%). The desired **16** was obtained stereoselectively; however, the yield was low (22%). Protection of the *N*-3 position of the uracil moiety improved the yield of the phenylthiolation. Namely, benzyloxymethyl (BOM) protection of **15** (BOMCl, DBU, DMF, rt, quant)

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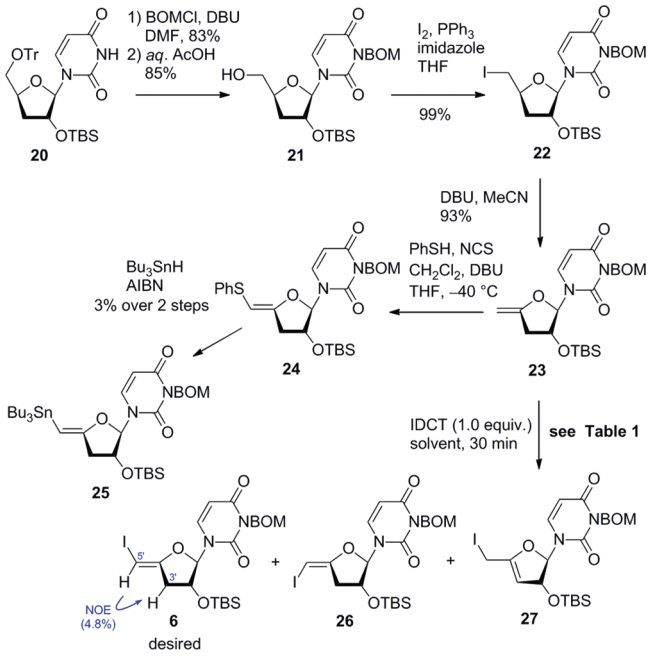
followed by the same addition−elimination sequence on **17** gave in 84% yield **18**, which was identical to that obtained from the BOM protection of the *N*-3 position of **16**. Substitution of the phenylthio group with the tributylstannyl group by a radical reaction (Bu_3SnH, AIBN, *i*-Pr_2NEt, toluene, 83%) gave the *Z*-stannyl olefin **19** selectively. The observed formation of only the *Z*-isomer **19** from **18** was based on the conformational preference of the intermediate C4′-radical as proposed in Tanaka's study.[44] Halogenation of **19** with NBS or I_2 cleanly provided the corresponding *Z*-vinyl bromide **7a** (93%) or *Z*-vinyl iodide **7b** (92%), respectively, with retention of the olefin geometry.[49]

The *Z*-vinyl iodide of the 3′-deoxyuridine derivative **6** was prepared as described in Scheme 4. After protecting group

Scheme 4. Preparation of 3′-Deoxyvinyl Iodide 6



manipulation of the known 3′-deoxyuridine derivative **20**[50] (BOMCl, DBU, DMF, 83%, aq AcOH, 60 °C, 85%), the primary alcohol of **21** was converted to the iodo group (I_2, PPh_3, imidazole, THF, 99%). Elimination of HI from **22** was promoted by DBU to afford the *exo*-olefin **23** in 93% yield. In a manner similar to the synthesis of **18**, the *exo*-olefin **23** was reacted with PhSCl. Although the *Z*-phenylthio derivative **24** was produced, **24** was not isolated in a pure form. The subsequent conversion of the phenylthio group of **24** to the tributylstannyl group did not proceed well, and the corresponding **25** was obtained in only 3% yield over two steps. In order to overcome these limitations, extensive efforts were investigated to obtain the desired *Z*-vinyl iodide **6**. Finally, the use of iodoniumdicollidinium triflate (IDCT)[51,52] in THF appeared to be the most promising. Thus, when the *exo*-olefin **23** was treated with 1.0 equiv of IDCT in THF for 30 min at 0 °C (Table 1, entry 1), the desired *Z*-vinyl iodide **6** was obtained in 26% yield. The undesired *E*-vinyl iodide **26** (14%) and *endo*-vinyl iodide **27** (31%) were also obtained, although these were easily separable using silica gel column chromatography. As a result, the combined isolate chemical yield of the products was 77% with the *endo*-vinyl iodide **27** being the major product albeit slightly *Z*-selective in terms of the olefin geometry

Table 1. Direct Iodination of 23

entry	solvent	temp (°C)	isolated yield (%, **6**/**26**/**27**)	ratio (**6**/**26**/**27**)
1	THF	0	26/14/31	36/13/51
2	CH_2Cl_2	rt	28/10/39	37/20/43
3	MeCN	rt	34/12/10	61/21/18
4	MeCN	0	42/10/16	62/15/23
5	MeCN	−20	53/9/25	61/10/29
6	MeCN	−40	44/9/30	53/11/36

(**6**/**26**/**27** = 36/13/51). The geometry of the desired *Z*-olefin **6** was confirmed by a 500 MHz NOE experiment in $CDCl_3$, where the correlation to H-3′ was observed upon irradiation at H-5′ (4.8%). The observed decrease of the selectivity could be attributed to the absence of a substituted hydroxyl group at the 3′-position. The effect of the solvent was then investigated to improve the selectivity. Little improvement was observed for the reaction in CH_2Cl_2 (entry 2). On the other hand, when MeCN, a polar and Lewis basic solvent, was used, the desired *Z*-vinyl iodide **6** was obtained as the major product (entries 3−6). The reaction at the lower temperature improved not only the total chemical yield (87%) but also the *Z*/*E* selectivity with a ratio of 61/10, and the desired **6** was obtained in 53% isolated yield (entry 5). Since the direct iodination of the *Z*-*exo*-olefin **23** was successful in obtaining **6**, this procedure was applied to the preparation of **7b** from **17** (Scheme 3). In this case, the iodination by IDCT afforded **7b** as the sole product in 79% yield. The observed stereochemical outcome could be rationalized as described in Scheme 5, that is the reaction of

Scheme 5. Proposed Stereoselectivity in the Direct Iodination

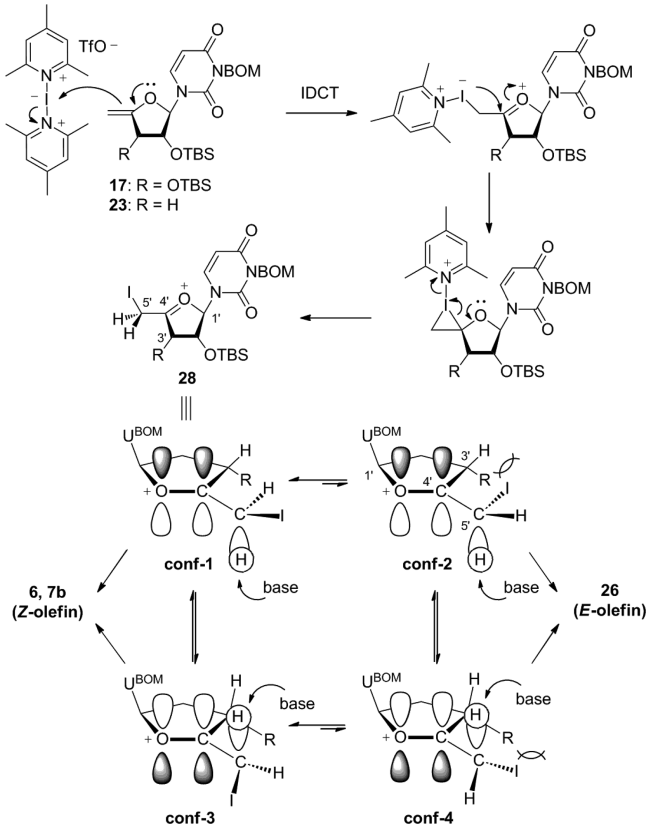


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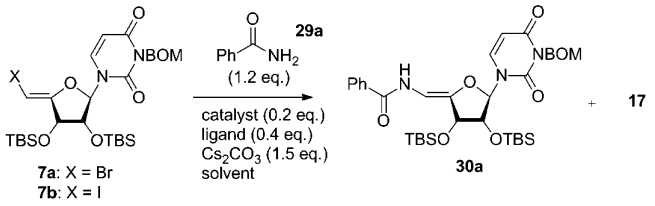
Table 2. Optimization of Cross-Coupling To Form the Enamide 30a

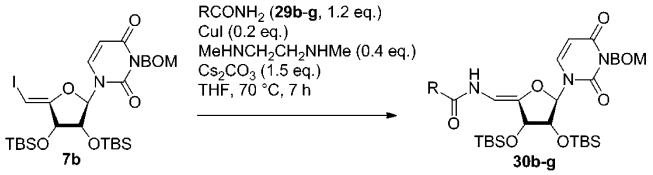


entry	X	catalyst	ligand	solvent	temperature (°C)	yield (%)
1	Br	$Pd(OAc)_2$	Xantphos	1,4-dioxane	100	**7a** recovery (38), **17** (19)
2	I	$Pd(OAc)_2$	Xantphos	1,4-dioxane	100	**7b** recovery (26), **17** (26)
3	I	$Pd(OAc)_2$	cataCXium®A	1,4-dioxane	100	**7b** recovery (51), **17** (26)
4	I	CuI	Me_2N, OH	1,4-dioxane	60	no reaction
5	I	CuI	MeHN, NHMe	THF	70	**30a** (89)
6	I	CuI	MeHN, NHMe	THF	70	**30a** (78)
7	I	CuI	N, N	THF	70	**30a** (39)

23 with IDCT presumably forms the 5′-iodo-4′-oxonium intermediate **28** and the elimination of proton provides the vinyl iodides. The elimination proceeded via a transition state where the C-5′–H-5′ σ-bond overlapped with the π-orbital of the O-4′–C-4′ double bond. This being the case, four conformers are possible in the transition state of the elimination, namely **confs-1**-**4**. Since the steric repulsion between the iodo group and the substituents at the C-3′ position (the hydrogen atom and the R group) is increased in **conf-2** and **conf-4**, it is expected that **conf-1** and **conf-3** are more energetically stable, and therefore the ensuing elimination would provide the *Z*-vinyl iodide. The difference in the conformational energies would be larger by increasing the size of the R group, resulting in high stereoselectivity as observed in the iodination of **17**. Presumably the coordination of MeCN to **28** affects the stereoselectivity of the elimination step although the precise reaction mechanism is not clear from the current study.

Once the *Z-exo*-vinyl halides **6**, **7a**, and **7b** were obtained, the key copper-catalyzed cross-coupling reaction[41] to form the oxyenamide structure was examined with **7** and benzamide (**29a**, 1.2 equiv) as a model study (Table 2). The metal catalyst was preliminarily tested with either Pd or Cu, which are widely used for *C*–*N* couplings. The reaction of both the bromide **7a** and the iodide **7b** with benzamide (**29a**) catalyzed by $Pd(OAc)_2$ in the presence of Xantphos or cataCXium and Cs_2CO_3 in 1,4-dioxane did not provide the enamide **30a** at all, and the reduced product **17** was obtained (entries 1–3).[41a,c] On the other hand, the use of a copper catalyst was promising.[41d,e] Namely, when CuI was used as the catalyst (0.2 equiv) of the coupling reaction of the iodide **7b** in the presence of *N,N*′-dimethylethylenediamine as the ligand (0.4 equiv), the *Z*-enamide **30a** was obtained in 89% yield without any isomerization of the olefin geometry (entry 5). No improvement was achieved by limited screening of the ligands briefly tested in this study (entries 6 and 7). Next, the coupling of the iodide **7b** with a variety of amide derivatives of amino acids was undertaken,[53] and the results are summarized in Table 3. Generally, all the amides **29b**–**g** reacted smoothly with the iodide **7b** under the conditions optimized in Table 2, and the corresponding

Table 3. Cu-Catalyzed Cross-Coupling with a Variety of Carboxamides



entry		R	yield (%)
1	**b**	BocHN	92
2	**c**	CbzHN	77
3[a]	**d**	H_2N	78
4	**e**	Me, BocHN	90
5	**f**	Me, BocHN	quant.
6[b]	**g**	NHCbz, O, Me, Me, N, Me, BocHN	89

[a] 2.5 equiv of Cs_2CO_3 was used. [b] 2.0 equiv of the amide, 0.5 equiv of CuI, 1.0 equiv of the ligand, and 1.5 equiv of Cs_2CO_3 were used.

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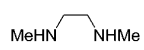
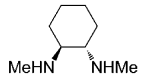
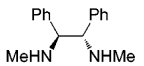
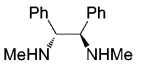
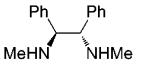
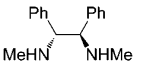
Z-enamide derivatives **30b–g** were obtained in good yield (77% quant). No epimerization at the α-position of the carboxamide moiety under these conditions (entries 4–6), an important characteristic for the final coupling with the tetrapeptide **5**, which contains four α-protons to the carbonyls.

Then, the coupling of **7b** with the tetrapeptide **5** was investigated (Scheme 6 and Table 4). The iodide **7b** was

Table 4. Optimization of Cross-Coupling of 5 and 7b

entry	CuI (eq.)	ligand (eq.)	reaction time (h)	yield of **31** (%)
1	0.2	**A**  (0.4)	7	trace
2	0.2	**B**  (0.4)	7	16
3	0.2	**C**  (0.4)	7	30
4	0.2	**D**  (0.4)	7	32
5	0.8	**C**  (0.4)	9	70
6	0.8	**D**  (0.4)	10	86

reacted with the tetrapeptide **5** under the optimized conditions (0.2 equiv of CuI, 0.4 equiv of $MeNHCH_2CH_2NHMe$, Cs_2CO_3, THF, 70 °C, entry 1). However, a large amount of the iodide remained unreacted, and only a trace amount of the desired **31a** was obtained. Although not fully confirmed, cyclic products such as **34** and **35**, the structures of which are shown in Figure 3, were obtained from the reaction mixture as indicated

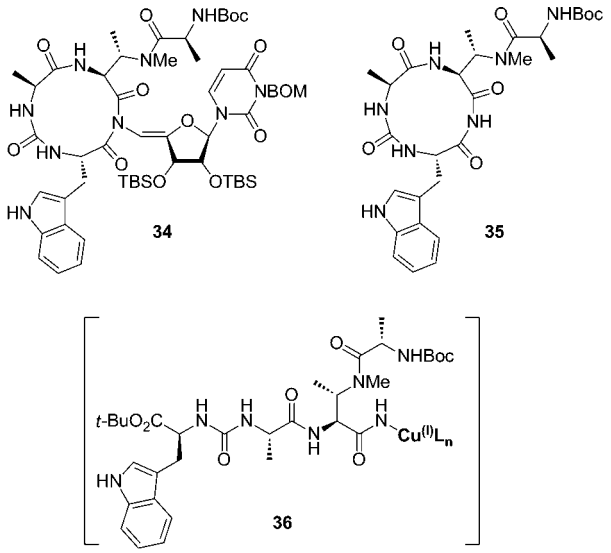
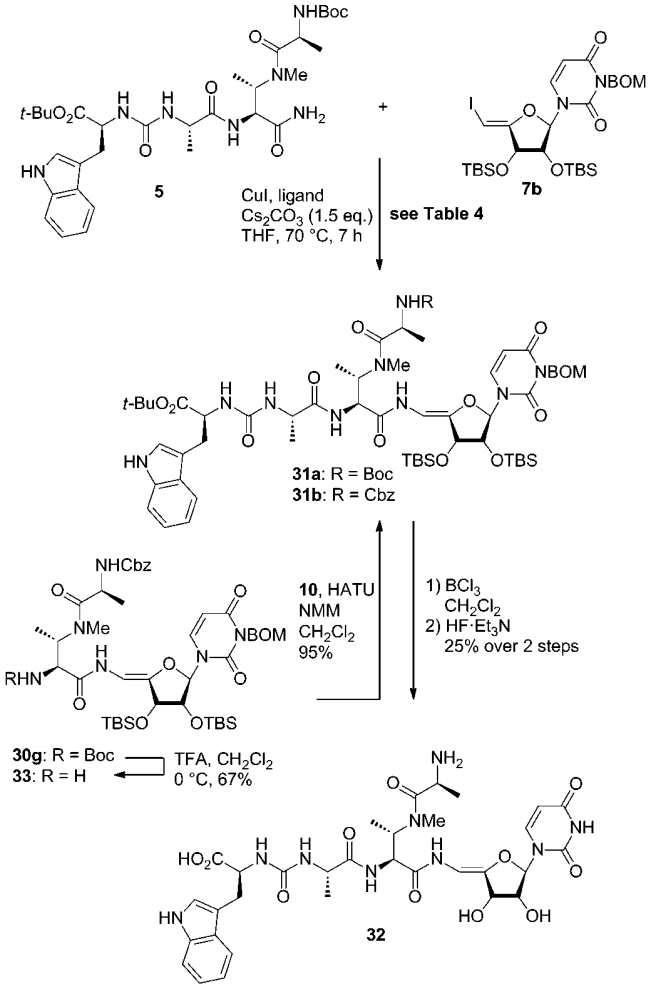


Figure 3. Structure of byproduct in cross-coupling of **5** and **7b**.

by MS analysis. In general, the copper-mediated *C–N* cross-coupling proceeds through initial formation of the nitrogen–copper complex followed by an oxidative insertion into the halide and reductive elimination.[41f] It is presumed that if the oxidative insertion was slow, the nitrogen atom activated by formation of the carboxamide–copper(I) complex **36** would react with the *t*-Bu ester at the *C*-terminus to form cyclic compounds **34** and **35**. In order to prevent the approach of the nitrogen atom to the *t*-Bu ester, the size of the ligand coordinating to the copper atom was increased, namely by choosing specific ligands **B**-**D** (Table 4). Consistent with this hypothesis, the use of the ligands **B**-**D** resulted in increased yields (entries 2–4, 16–32%). Their stereochemistry did not influence the chemical yield (entry 3 vs 4). The improved 86% yield of **31** can be attributed to increased catalyst loading (0.8 equiv), which indicates that the catalyst coordinates to the highly functionalized tetrapeptide carboxamide **5**, thereby resulting in reduced catalytic activity. However, the copper-catalyzed cross-coupling is still effective in forming the *Z*-oxyacyl enamide moiety, which is chemically labile and the most challenging chemical structure in the molecule to construct, using the tetrapeptide carboxamide **5**. Of note is the highly selective reaction at the *N*-unsubstituted carboxamide moiety despite the presence of several potential reactive sites, including the primary amide, the carbamate, and the urea groups. An alternative approach to prepare **31** from the intermediate **30g** would be by sequential coupling (Scheme 6). Deprotection of

Scheme 6. Synthesis of the 3′-Hydroxypacidamycin D (32)



the Boc group of **30g** was achieved by TFA in CH_2Cl_2 at 0 °C, and the liberated amine **33** was coupled with the urea–dipeptide **10** (HATU and NMM in CH_2Cl_2, 95%) to give **31b**. Deprotection of the protecting groups in **31a** (BCl_3,[55]

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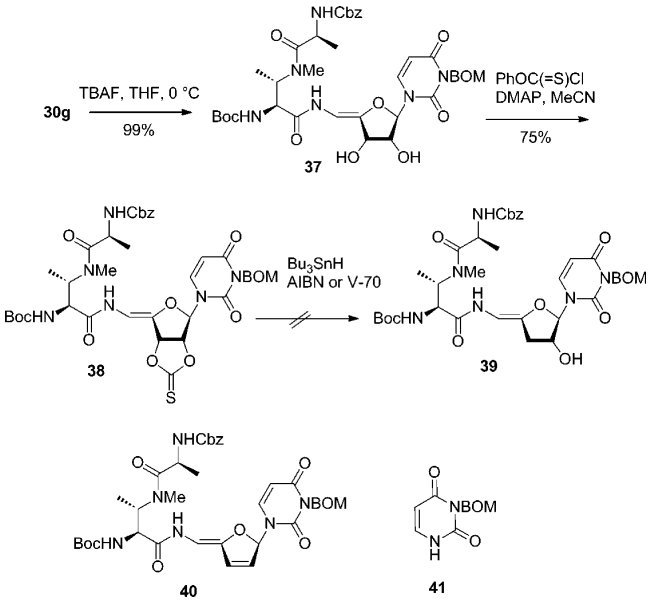
CH_2Cl_2, −78 °C, then 3HF·NEt_3, 25% over two steps) provided 3′-hydroxyl pacidamycin D (**32**), a ribonucleoside analogue.

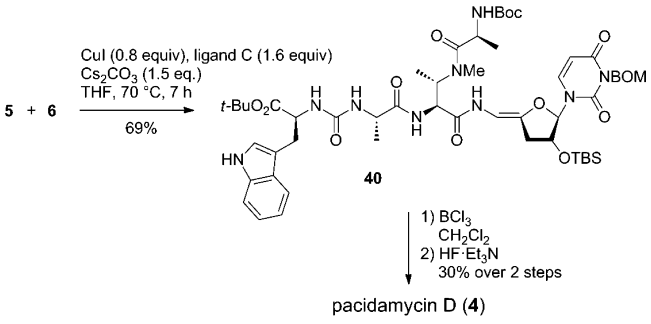
Although unsuccessful, preliminary model studies toward the total synthesis of **4** were first conducted using a selective deoxygenation of the allylic 3′-hydroxyl group on the cyclic thiocarbonate **38** (Scheme 7). Thus, the TBS groups of **30g**

Scheme 7. Attempt of Deoxygenation of 38



were removed (TBAF, THF, 99%), and the resulting diol **37** was reacted with *O*-phenyl chlorothionoformate in MeCN[56] to afford the cyclic thiocarbonate **38** in 75% yield. However, exposure of **38** to either Bu_3SnH and AIBN[57] in toluene at reflux or Bu_3SnH and V-70[58] in CH_2Cl_2 at room temperature led to a complex mixture of products such as **40** and **41**, and the desired deoxygenated compound **39** was not isolated. Ultimately, the total synthesis of **4** was pursued with the 3′-deoxyvinyl iodide **6** (Scheme 8). The iodide **6** and the

Scheme 8. Total Synthesis of Pacidamycin D (4)



tetrapeptide **5** were coupled using the optimized conditions (0.8 equiv of CuI, 1.6 equiv of ligand C, Cs_2CO_3, THF, 70 °C, 69%) to afford the fully protected pacidamycin D (**42**). Finally, deprotection of the BOM, Cbz and *t*-Bu groups (BCl_3, CH_2Cl_2, −78 °C) and the TBS group (5HF·NEt_3, 30% over two steps) successfully afforded **4** as the TFA salts. The analytical data for the synthetic compound were in good agreement with those reported for the natural material.[11]

The MraY inhibitory[59,60] and antibacterial activity[61] of **4** and **32** was evaluated. Synthetic pacidamycin D (**4**) potently inhibited MraY using cell-free biochemical assay with an IC_{50} value of 22 nM. 3′-Hydroxypacidamycin D (**32**) also exhibited good MraY inhibitory activity (IC_{50} = 42 nM). The antibacterial activity of **4** and **32** was then evaluated against a range of *P. aeruginosa* strains (Table 5). Pacidamycin D (**4**) exhibited

Table 5. Antibacterial Activity of 4 and 32

	MIC (μg/mL)	
strain	**4**	**32**
P. *aeruginosa* PAO1	64	32
P. *aeruginosa* ATCC 25619	16	16
P. *aeruginosa* SR 27156	16	16
P. *aeruginosa* YY165(ΔmexB)	16	8

antibacterial activity with an MIC value of 64 μg/mL for *P. aeruginosa* PAO1, 16 μg/mL for *P. aeruginosa* ATCC 25619, 16 μg/mL for *P. aeruginosa* SR 27156, and 16 μg/mL for *P. aeruginosa* YY165(ΔmexB), respectively. Slightly better antibacterial activity was observed for **32** with an MIC value of 32 μg/mL for *P. aeruginosa* PAO1, 16 μg/mL for *P. aeruginosa* ATCC 25619, 16 μg/mL for *P. aeruginosa* SR 27156, and 8 μg/mL for *P. aeruginosa* YY165(ΔmexB), respectively. These data suggest that introducing the hydroxyl group at the 3′-position of the uridine moiety is tolerated for both MraY inhibition and antibacterial activity.

CONCLUSION

In summary, the details of total synthesis of pacidamycin D has been described. The assemblage by $Cu^{(I)}$-catalyzed cross-coupling of the *Z*-oxyvinyl halide **6** and the tetrapeptide **5** at a late stage of the synthesis allowed ready access to a range of uridylpeptide antibiotics and their analogues, despite their inherent labile nature with potential epimerization, simply by altering the tetrapeptide moiety, which could be obtained by conventional solid-phase parallel synthesis. Both **4** and **32** exhibit potent MraY inhibitory and antibacterial activity against *P. aeruginosa*. Moreover, introducing the hydroxyl group at the 3′-position of the uridine moiety was tolerated in both the MraY biochemical inhibition and whole-cell antibacterial activity, which is advantageous from a medicinal chemical point of view because the 3′-hydroxyl analogue is synthetically more accessible.

EXPERIMENTAL SECTION

Experimental procedure and characterization data for compounds **4**–**6**, **7b**, **12**, **14**, **17**, **21**–**23**, **31a**, and **42** are described in ref 42.

3-(Benzyloxymethyl)-1-[(*Z*)-2,3-di-*O*-(*tert*-butyldimethylsilyl)-4,5-dehydro-5-phenylthio-β-D-*ribo*-pentofuranosyl]uracil (18). A solution of NCS (457 mg, 3.43 mmol) in CH_2Cl_2 (20 mL) was treated with benzenethiol (309 μL, 3.01 mmol) at 0 °C under N_2 for 30 min. Compound **17** (788 mg, 1.37 mmol) was added to the mixture, which was stirred at 0 °C for further 30 min. 1,5-Diazabicyclo[4.3.0]non-5-ene (337 μL, 2.74 mmol) was added to the mixture, which was refluxed for 2 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by silica gel column chromatography (10 × 2.6 cm, 10–12% EtOAc/hexane) to give **18** (788 mg, 84%) as a pale yellow oil: $[\alpha]^{23}_D$ +35.0 (*c* 1.01, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.17 (m, 10H), 7.06 (d, 1H, *J* = 8.1 Hz), 6.21 (d, 1H, *J* = 5.6 Hz), 5.80 (d, 1H, *J* = 8.1 Hz), 5.50 (d, 1H, *J* = 9.8 Hz), 5.46

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(d, 1H, J = 9.8 Hz), 5.44 (d, 1H, J = 0.5 Hz), 4.68 (s, 2H), 4.46 (d, 1H, J = 4.2 Hz), 4.28 (dd, 1H, J = 4.2, 5.6 Hz), 0.94 (s, 9H), 0.87 (s, 9H), 0.14 (s, 3H), 0.14 (s, 3H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.4, 157.2, 150.9, 138.1, 137.9, 136.3, 129.2, 128.4, 128.4, 127.8, 126.7, 126.3, 103.1, 94.9, 91.1, 75.3, 72.3, 72.3, 70.5, 25.9, 25.8, 18.3, 18.1, 4.2, 4.3, 4.5, 4.8 (C27); ESIMS-LR m/z 683 [(M + H)$^+$]; ESIMS-HR calcd for $C_{35}H_{51}N_2O_6SSi_2$ 683.3001, found 683.2999; IR (ATR) ν_{max} 2956, 2932, 2888, 2859, 1725, 1681, 1585, 1454, 1409, 1353, 1315, 1255, 1220, 1167, 1093, 1026, 948, 910, 861, 837, 810, 779, 739, 694 cm^{-1}.

3-(Benzyloxymethyl)-1-[(*Z*)-2,3-di-*O*-(*tert*-butyldimethylsilyl)-4,5-dehydro-5-tributylstannyl-β-D-*ribo*-pentofuranosyl]-uracil (19). A solution of **18** (390 mg, 0.57 mmol) in toluene (8 mL) was added by n-Bu_3SnH (457 μL, 1.71 mmol), AIBN (47 mg, 0.29 mmol), and Hunig's base (299 μL, 1.71 mmol) at room temperature under N_2. The mixture was refluxed for 6 h. The solvent was removed, and the residue was purified by silica gel column chromatography (2.6 × 15 cm, 5−20% EtOAc/hexane) to give **19** (409 mg, 83%) as a colorless oil: $[\alpha]^{23}_D$ +31.8 (c 0.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39−7.25 (m, 5H), 7.09 (d, 1H, J = 8.1 Hz), 6.10 (d, 1H, J = 4.9 Hz), 5.79 (d, 1H, J = 8.1 Hz), 5.51 (d, 1H, J = 9.7 Hz), 5.47 (d, 1H, J = 9.7 Hz), 4.79 (d, 1H, J = 0.7 Hz), 4.70 (s, 2H), 4.28 (d, 1H, J = 4.0 Hz), 4.07 (dd, 1H, J = 4.0, 4.9 Hz), 1.53−1.43 (m, 6H), 1.34−1.24 (m, 6H), 0.94−0.88 (m, 6H), 0.92 (s, 9H), 0.87 (t, 9H, J = 7.3 Hz), 0.86 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.9, 162.4, 150.8, 137.8, 137.4, 128.3, 127.7, 102.4, 94.9, 89.4, 75.7, 72.5, 72.2, 70.3, 29.1, 27.2, 25.8, 25.6, 18.3, 18.0, 13.7, 10.1, −4.4, −4.5, −4.7, −4.9; ESIMS-LR m/z 865 [(M + H)$^+$]; ESIMS-HR calcd for $C_{41}H_{73}N_2O_6Si_2Sn$ 865.4024, found 865.4022; IR (ATR) ν_{max} 2955, 2928, 2857, 1722, 1681, 1453, 1352, 1253, 1168, 1073, 1057, 957, 898, 869, 837, 806, 778, 734, 696, 648 cm^{-1}.

3-(Benzyloxymethyl)-1-[(*Z*)-2,3-di-*O*-(*tert*-butyldimethylsilyl)-4,5-dehydro-5-bromo-β-D-*ribo*-pentofuranosyl]uracil (7a). A solution of **19** (70 mg, 0.081 mmol) in THF (2 mL) was treated with NBS (22 mg, 0.122 mmol) at room temperature under N_2 for 2 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by silica gel column chromatography (2 × 7.5 cm, 10−20% EtOAc/hexane) to give **7a** (49 mg, 93%) as a pale yellow oil: $[\alpha]^{23}_D$ +0.7 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.25 (m, 5H), 7.11 (d, 1H, J = 8.3 Hz), 6.27 (d, 1H, J = 6.4 Hz), 5.85 (d, 1H, J = 8.3 Hz), 5.50 (d, 1H, J = 9.8 Hz), 5.47 (d, 1H, J = 9.8 Hz), 5.36 (s, 1H), 4.69 (s, 2H), 4.43 (d, 1H, J = 4.2 Hz), 4.28 (dd, 1H, J = 4.2, 6.4 Hz), 0.92 (s, 9H), 0.84 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.04 (s, 3H), −0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.3, 156.4, 150.9, 138.1, 137.9, 128.4, 127.8, 127.8, 103.3, 90.8, 80.3, 75.5, 72.3, 72.2, 70.5, 25.8, 25.7, 18.3, 18.1, −4.4, −4.5, −4.9; ESIMS-LR m/z 653 [(M + H)$^+$]; ESIMS-HR calcd for $C_{29}H_{46}BrN_2O_6Si_2$ 653.2072, found 653.2074; IR (ATR) ν_{max} 2954, 2930, 2887, 2858, 1723, 1679, 1639, 1452, 1408, 1351, 1310, 1254, 1218, 1167, 1098, 1028, 945, 908, 836, 810, 777, 735, 698, 674 cm^{-1}.

3-(Benzyloxymethyl)-1-[(*Z*)-2,3-di-*O*-(*tert*-butyldimethylsilyl)-4,5-dehydro-5-iodo-β-D-*ribo*-pentofuranosyl]uracil (7b). A solution of **19** (1.09 g, 1.26 mmol) in THF (20 mL) was treated with I_2 (480 mg, 1.89 mmol) at room temperature under N_2 for 1 h. The reaction mixture was diluted with 10% aqueous $Na_2S_2O_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by silica gel column chromatography (4.6 × 13 cm, 5−20% EtOAc/hexane) to give **7b** (810 mg, 92%) as a pale yellow oil. Characterization data may be found in ref 42.

(2*S*,3*S*)-3-[(*S*)-2-(Benzyloxycarbonylamino)-*N*-methylpropanamido]-2-(*tert*-butoxycarbonylamino)butanoic Acid. A solution of (2*S*,3*S*)-3-amino-2-(*tert*-butoxycarbonylamino)butanoic acid (458 mg, 1.97 mmol), *Z*-L-Ala-OSu (821 mg, 2.56 mmol), and Hunig's base (517 μL, 2.96 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with 0.5 N aqueous HCl and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo to give the crude title compound as a white foam. This compound was used to the next reaction without further purification.

(2*S*,3*S*)-3-[(*S*)-2-(Benzyloxycarbonylamino)-*N*-methylpropanamido]-2-(*tert*-butoxycarbonylamino)butanamide (29g). A solution of crude **42** (1.97 mmol), NH_4Cl (1.05 g, 19.7 mmol), and HATU (1.50 g, 3.94 mmol) in DMF (10 mL) was added by N-methylmorpholine (3.03 mL, 27.6 mmol) at 0 °C under N_2, and the mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with 0.2 N aqueous HCl and brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by silica gel column chromatography (2.6 × 15 cm, 0−5% MeOH/$CHCl_3$) to give **29g** (673 mg, 78% for two steps) as a white solid: $[\alpha]^{23}_D$ −2.8 (c 0.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.39−7.29 (m, 5H), 6.67 (br s, 1H), 5.70 (d, 1H, J = 8.0 Hz), 5.56 (d, 1H, J = 7.1 Hz), 5.43 (br s, 1H), 5.11 (d, 1H, J = 12.2 Hz), 5.08 (d, 1H, J = 12.2 Hz), 4.67−4.61 (m, 1H), 4.56−4.48 (m, 1H), 4.46−4.39 (m, 1H), 2.97 (s, 3H), 1.43 (s, 9H), 1.39 (d, 3H, J = 6.6 Hz), 1.19 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 173.8, 172.3, 155.8, 155.6, 136.6, 128.6, 128.3, 128.2, 80.1, 66.9, 57.1, 53.6, 47.7, 31.0, 28.4, 18.3, 12.3 (C17); FABMS-LR m/z 437.873 [(M + H)$^+$]; FABMS-HR calcd for $C_{21}H_{33}N_4O_6$ 437.2400, found 437.2394; IR (ATR) ν_{max} 2954, 2931, 2887, 2859, 2126, 1725, 1679, 1452, 1408, 1351, 1256, 1221, 1189, 1166, 1096, 1023, 944, 910, 837, 810, 778, 737, 698 cm^{-1}.

Typical Procedure for the Cu-Catalyzed Cross-Coupling Compound 30a (Table 2, Entry 5). Vinyl iodide **7b** (70 mg, 0.1 mmol), benzamide (14.5 mg, 0.120 mmol), copper(I) iodide (3.81 mg, 0.020 mmol), and cesium carbonate (48.9 mg, 0.150 mmol) were added to a dried test tube under N_2. Tetrahydrofuran (1 mL) and *N*,*N*′-dimethylethane-1,2-diamine (3.53 mg, 0.040 mmol) were added to the mixture. The mixture was evacuated and backfilled with N_2 three times and stirred at 70 °C for 7 h. The reaction mixture was cooled to room temperature and diluted with EtOAc. The precipitates were filtered off through Celite pad, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (2 × 7.5 cm, 15−35% EtOAc/hexane) to give **30a** (61.7 m g, 89%) as a white solid: $[\alpha]^{23}_D$ −19.0 (c 0.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84−7.78 (m, 2H), 7.62 (d, 1H, J = 10.0 Hz), 7.55−7.24 (m, 7H), 7.14 (d, 1H, J = 8.1 Hz), 6.60 (d, 1H, J = 10.3 Hz), 6.31 (d, 1H, J = 7.1 Hz), 5.86 (d, 1H, J = 8.1 Hz), 5.51 (d, 1H, J = 9.7 Hz), 5.47 (d, 1H, J = 9.7 Hz), 4.69 (s, 2H), 4.50 (d, 1H, J = 4.2 Hz), 4.31 (dd, 1H, J = 7.1, 4.2 Hz), 0.93 (s, 9H), 0.85 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), 0.05 (s, 3H), −0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.9, 162.3, 151.2, 141.8, 138.4, 137.8, 133.3, 132.3, 128.9, 128.5, 127.9, 127.8, 127.3, 103.4, 101.7, 90.1, 75.3, 72.3, 71.2, 70.5, 25.9, 25.7, 18.3, 18.1, −4.0, −4.3, −4.4, −4.9 (C28); ESIMS-LR m/z 694 [(M + H)$^+$]; ESIMS-HR calcd for $C_{36}H_{52}N_3O_7Si_2$ 694.3338, found 694.3342; IR (ATR) ν_{max} 3322, 2930, 2887, 2858, 1721, 1674, 1581, 1517, 1486, 1454, 1409, 1357, 1253, 1180, 1155, 1092, 1042, 948, 833, 810, 777, 695 cm^{-1}.

Data for 30b: colorless oil; $[\alpha]^{23}_D$ −19.8 (c 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93 (d, 1H, J = 7.6 Hz), 7.43−7.22 (m, 5H), 7.10 (d, 1H, J = 8.1 Hz), 6.32 (d, 1H, J = 10.2 Hz), 6.27 (d, 1H, J = 7.1 Hz), 5.82 (d, 1H, J = 8.1 Hz), 5.51 (d, 1H, J = 9.6 Hz), 5.44 (d, 1H, J = 9.6 Hz), 5.21 (br s, 1H), 4.68 (s, 2H), 4.40 (d, 1H, J = 4.0 Hz), 4.24−4.11 (m, 1H), 3.86 (d, 1H, J = 4.5 Hz), 3.84 (d, 1H, J = 4.5 Hz), 1.40 (s, 1H), 0.90 (s, 1H), 0.83 (s, 1H), 0.11 (s, 1H), 0.09 (s, 1H), 0.02 (s, 1H), −0.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.6, 162.2, 156.2, 151.2, 141.5, 138.4, 137.7, 128.4, 127.9, 127.8, 103.3, 100.6, 89.6, 80.5, 75.4, 72.2, 71.1, 70.4, 44.3, 28.3, 25.8, 25.7, 18.2, 18.0, −4.1, −4.4, −4.4, −5.0 (C28); ESIMS-LR m/z 747 [(M + H)$^+$]; ESIMS-HR calcd for $C_{36}H_{59}N_4O_9Si_2$ 747.3815, found 747.3815; IR (ATR) ν_{max} 3321, 2932, 2860, 1670, 1527, 1456, 1365, 1255, 1216, 1165, 1099, 1075, 1047, 948, 901, 836, 778, 734, 700 cm^{-1}.

Data for 30c: colorless oil; $[\alpha]^{23}_D$ −15.3 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84 (d, 1H, J = 8.2 Hz), 7.45−7.08 (m, 10H), 7.02 (d, 1H, J = 8.1 Hz), 6.32 (d, 1H, J = 10.4 Hz), 6.22 (d, 1H, J = 6.7 Hz), 5.78 (d, 1H, J = 8.1 Hz), 5.47 (d, 1H, J = 9.4 Hz), 5.39 (d, 1H, J = 9.4 Hz), 5.09 (s, 2H), 4.64 (s, 2H), 4.38 (d, 1H, J = 3.7 Hz), 4.13 (dd, 1H, J = 3.7, 6.7 Hz), 4.00 (dd, 1H, J = 5.9, 16.8 Hz), 3.89

(dd, 1H, J = 5.2, 16.8 Hz), 0.89 (s, 9H), 0.81 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H), 0.01 (s, 3H), −0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.1, 162.1, 156.7, 151.1, 141.6, 138.4, 137.7, 136.1, 128.7, 128.5, 128.4, 128.1, 127.9, 127.8, 103.3, 100.6, 89.9, 75.4, 72.2, 71.1, 70.4, 67.4, 44.5, 25.8, 25.7, 18.2, 18.0, −4.1, −4.4, −4.4, −5.0 (C31); ESIMS-LR m/z 781 [(M + H)$^+$]; ESIMS-HR calcd for $C_{39}H_{57}N_4O_9Si_2$ 781.3659, found 781.3658; IR (ATR) ν_{max} 3318, 2932, 2859, 1721, 1670, 1524, 1456, 1358, 1255, 1215, 1173, 1098, 1074, 1045, 948, 900, 836, 779, 737, 699 cm^{-1}.

Data for 30d: colorless oil; $[\alpha]^{23}_D$ −27.0 (c 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.86 (d, 1H, J = 10.8 Hz), 7.38−7.26 (m, 5H), 7.12 (d, 1H, J = 8.1 Hz), 6.35 (d, 1H, J = 10.8 Hz), 6.28 (d, 1H, J = 6.9 Hz), 5.84 (d, 1H, J = 8.1 Hz), 5.51 (d, 1H, J = 9.6 Hz), 5.47 (d, 1H, J = 9.6 Hz), 4.69 (s, 2H), 4.43 (d, 1H, J = 4.2 Hz), 4.26 (dd, 1H, J = 4.2, 6.9 Hz), 3.44 (d, 1H, J = 17.8 Hz), 3.39 (d, 1H, J = 17.8 Hz), 0.91 (s, 9H), 0.84 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.04 (s, 3H), −0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 162.2, 151.0, 141.4, 138.3, 137.8, 128.3, 127.7, 127.6, 103.1, 100.5, 89.9, 75.4, 72.1, 71.1, 70.4, 44.5, 25.8, 25.6, 18.1, 17.9, −4.2, −4.5, −4.5, −5.1 (C25); ESIMS-LR m/z 647 [(M + H)$^+$]; ESIMS-HR calcd for $C_{31}H_{51}N_4O_7Si_2$ 647.3291, found 647.3281; IR (ATR) ν_{max} 3322, 2931, 2858, 1721, 1670, 1512, 1454, 1409, 1354, 1253, 1181, 1095, 1042, 944, 898, 832, 776, 738, 698 cm^{-1}.

Data for 30e: white foam; $[\alpha]^{23}_D$ −14.6 (c 0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.92−7.65 (m, 1H), 7.41−7.24 (m, 5H), 7.12 (d, 1H, J = 8.2 Hz), 6.31 (d, 1H, J = 10.2 Hz), 6.28 (d, 1H, J = 6.4 Hz), 5.85 (d, 1H, J = 8.2 Hz), 5.51 (d, 1H, J = 9.7 Hz), 5.47 (d, 1H, J = 9.7 Hz), 4.94−4.77 (m, 1H), 4.69 (s, 2H), 4.42 (d, 1H, J = 4.1 Hz), 4.29−4.09 (m, 2H), 1.39 (s, 9H), 1.38 (d, 3H, J = 6.4 Hz), 0.91 (s, 9H), 0.84 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H), 0.03 (s, 3H), −0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.4, 162.2, 155.7, 151.0, 141.6, 138.0, 137.7, 128.3, 127.7, 127.7, 103.2, 100.7, 89.7, 80.7, 75.5, 72.1, 71.0, 70.4, 50.0, 28.2, 25.7, 25.6, 18.1, 17.9, 17.6, −4.3, −4.5, −4.5, −5.1 (C29); ESIMS-LR m/z 761 [(M + H)$^+$]; ESIMS-HR calcd for $C_{37}H_{61}N_4O_9Si_2$ 761.3972, found 761.3969; IR (ATR) ν_{max} 3323, 2933, 2859, 2289, 2051, 1721, 1673, 1498, 1454, 1356, 1253, 1162, 1095, 1048, 945, 892, 835, 777, 698 cm^{-1}.

Data for 30f: white foam; $[\alpha]^{23}_D$ −24.5 (c 0.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.25 (m, 5H), 7.08 (d, 1H, J = 8.1 Hz), 6.30 (d, 1H, J = 10.3 Hz), 6.28 (d, 1H, J = 6.4 Hz), 5.83 (d, 1H, J = 8.1 Hz), 5.52 (d, 1H, J = 9.6 Hz), 5.47 (d, 1H, J = 9.6 Hz), 4.69 (s, 2H), 4.40 (d, 1H, J = 4.2 Hz), 4.31−4.09 (m, 2H), 1.40 (s, 9H), 1.37 (d, 3H, J = 7.1 Hz), 0.90 (s, 9H), 0.83 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.03 (s, 3H), −0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.6, 162.1, 155.6, 151.0, 141.3, 138.1, 137.7, 128.3, 127.7, 127.7, 103.2, 100.7, 89.5, 80.4, 75.5, 72.1, 71.0, 70.3, 49.9, 28.3, 25.7, 25.6, 18.1, 17.9, 14.2, −4.2, −4.5, −4.6, −5.1 (C29); ESIMS-LR m/z 761 [(M + H)$^+$]; ESIMS-HR calcd for $C_{37}H_{61}N_4O_9Si_2$ 761.3972, found 761.3968; IR (ATR) ν_{max} 3318, 2932, 2859, 2288, 2051, 1717, 1670, 1497, 1454, 1360, 1253, 1162, 1096, 1047, 947, 891, 834, 777, 698 cm^{-1}.

Data for 30g: white solid; $[\alpha]^{23}_D$ +1.2 (c 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12 (br s, 1H), 7.41−7.23 (m, 10H), 7.13 (d, 1H, J = 8.0 Hz), 6.27 (d, 1H, J = 10.0 Hz), 6.21 (d, 1H, J = 6.1 Hz), 5.81 (d, 1H, J = 8.0 Hz), 5.77 (d, 1H, J = 7.1 Hz), 5.63 (d, 1H, J = 8.1 Hz), 5.48 (d, 1H, J = 9.8 Hz), 5.43 (d, 1H, J = 9.8 Hz), 5.12 (d, 1H, J = 12.2 Hz), 5.04 (d, 1H, J = 12.2 Hz), 4.67 (s, 2H), 4.64−4.51 (m, 2H), 4.40 (d, 1H, J = 4.2 Hz), 4.34−4.29 (m, 1H), 4.28−4.23 (m, 1H), 2.90 (s, 3H), 1.39 (s, 9H), 1.33 (d, 3H, J = 6.6 Hz), 1.24 (d, 3H, J = 7.6 Hz), 0.90 (s, 9H), 0.83 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.03 (s, 3H), −0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.0, 173.0, 167.0, 162.3, 155.6, 155.5, 151.0, 142.1, 138.4, 137.9, 136.6, 128.6, 128.4, 128.2, 127.8, 103.1, 100.3, 90.6 80.3, 75.4, 72.2, 71.1, 70.4, 66.9, 58.5, 53.1, 47.6, 30.7, 28.3, 25.8, 25.7, 18.6, 18.2, 18.0, 13.3, −4.2, −4.4, −4.5, −5.0 (C40); ESIMS-LR m/z 1009 [(M + H)$^+$]; ESIMS-HR calcd for $C_{50}H_{77}N_6O_{12}Si_2$ 1009.5133, found 1009.5130; IR (ATR) ν_{max} 3696, 3664, 3308, 2933, 2859, 2288, 2051, 1981, 1720, 1678, 1498, 1453, 1411, 1354, 1253, 1163, 1095, 1049, 1033, 946, 902, 836, 778, 737, 697 cm^{-1}.

Compound 33. A solution of **30g** (74.3 mg, 0.074 mmol) in CH_2Cl_2 (2.4 mL) was treated with TFA (0.3 mL, 3.89 mmol) at 0 °C. The mixture was stirred at 0 °C for 6 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo to give crude **33** (45 mg, 0.074 mmol) as a brown oil. This compound was used to the next reaction without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.86 (d, 1H, J = 11.0 Hz), 7.37−7.25 (m, 10H), 7.10 (d, 1H, J = 8.2 Hz), 6.27 (d, 1H, J = 10.8 Hz), 6.18 (d, 1H, J = 6.8 Hz), 5.82 (d, 1H, J = 8.2 Hz), 5.68 (d, 1H, J = 7.6 Hz), 5.52 (d, 1H, J = 15.6 Hz), 5.47 (d, 1H, J = 15.6 Hz), 5.10−5.07 (m, 4H), 4.70−4.66 (m, 2H), 4.68 (s, 2H), 4.62−4.57 (m, 1H), 4.41 (d, 1H, J = 4.2 Hz), 4.33−4.23 (m, 2H), 3.54 (d, 1H, J = 4.9 Hz), 2.92 (s, 3H), 1.34 (d, 3H, J = 7.3 Hz), 1.31 (d, 3H, J = 6.6 Hz), 0.91 (s, 9H), 0.83 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.03 (s, 3H), −0.03 (s, 3H).

Compound 31b. A solution of **33** (45 mg, 0.074 mmol) and **10** (21.8 mg, 0.058 mmol) in CH_2Cl_2 (1 mL) was added to HATU (27.6 mg, 0.073 mmol) and *N*-methylmorpholine (16 μL, 0.145 mmol) at room temperature under N_2 for 3 h. The reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by silica gel column chromatography (2 × 7.5 cm, 0−5% MeOH/$CHCl_3$) to give **31b** (58 mg, 64% over 2 steps) as a white solid: $[\alpha]^{23}_D$ −2.8 (c 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57−7.40 (m, 1H), 7.40−7.18 (m, 11H), 7.07 (d, 1H, J = 8.3 Hz), 7.06 (t, 1H, J = 7.6 Hz), 6.99 (t, 1H, J = 7.5 Hz), 6.95 (s, 1H), 6.18 (d, 1H, J = 9.3 Hz), 6.10 (d, 1H, J = 5.6 Hz), 5.76 (d, 1H, J = 8.3 Hz), 5.45 (d, 1H, J = 9.4 Hz), 5.40 (d, 1H, J = 9.4 Hz), 5.09 (d, 1H, J = 14.4 Hz), 5.05 (d, 1H, J = 14.4 Hz), 4.73−4.59 (m, 3H), 4.65 (s, 2H), 4.59−4.45 (m, 2H), 4.36 (d, 1H, J = 3.9 Hz), 4.32−4.23 (m, 1H), 3.27−2.73 (m, 2H), 2.62 (s, 3H), 1.39−1.15 (m, 18H), 0.87 (s, 9H), 0.82 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H), −0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.0, 174.8, 173.3, 172.6, 166.4, 162.4, 157.2, 155.9, 150.8, 142.6, 139.2, 137.8, 137.7, 136.5, 135.9, 128.6, 128.4, 128.2, 127.9, 127.8, 124.0, 121.8, 119.0, 118.7, 111.5, 109.2, 102.8, 100.4, 91.4, 82.3, 75.1, 72.2, 71.3, 70.3, 66.9, 57.9, 53.8, 51.2, 49.5, 47.6, 30.2, 29.8, 28.0, 25.8, 25.7, 19.0, 18.5, 18.2, 18.0, 13.9, −4.2, −4.4, −4.5, −5.0 (C54); ESIMS-LR m/z 1266 [(M + H)$^+$]; ESIMS-HR calcd for $C_{64}H_{92}N_9O_{14}Si_2$ 1266.6297, found 1266.6290; IR (ATR) ν_{max} 3347, 2932, 2857, 2165, 2051, 1981, 1722, 1675, 1531, 1454, 1411, 1355, 1253, 1157, 1095, 1028, 948, 902, 838, 779, 740, 697 cm^{-1}.

3′-Hydroxypacidamycin D (32). *From **31a**.* A solution of **31a** (30 mg, 0.024 mmol) in CH_2Cl_2 (2 mL) was treated with 1 M BCl_3 in CH_2Cl_2 (243 μL, 0.243 mmol) at −78 °C for 1 h and then, −40 °C for 1 h under N_2. After MeOH and saturated aqueous $NaHCO_3$ were added at −78 °C, the resulting mixture was stirred at 0 °C for further 5 min. The mixture was extracted with $CHCl_3$, and the combined organic layers were dried over Na_2SO_4, and filtrated. Ethane-1,2-dithiol (10.2 μL, 0.122 mmol) was added to the filtrate, and the mixture was concentrated *in vacuo*. A solution of the resulting residue in CH_2Cl_2/MeCN (1:1, 4 mL) was treated with triethylamine trihydrofluoride (119 μL, 0.730 mmol) at room temperature under N_2 for 96 h. The volatiles were removed *in vacuo*, and the residue was purified by ODS column chromatography (1.1 × 30 cm, 0−40% MeCN/H_2O containing 0.1% TFA) to give **32** as a TFA salt (5.1 mg, 25% over 2 steps) after lyophilization as a white foam.

*From **31b**.* A solution of **31b** (26 mg, 0.021 mmol) in CH_2Cl_2 (2 mL) was treated with 1 M BCl_3 in CH_2Cl_2 (411 μL, 0.411 mmol) at −78 to −40 °C for 2 h and then, at 0 °C for 2 h under N_2. After MeOH and saturated aqueous $NaHCO_3$ were added at −78 °C, the resulting mixture was stirred at 0 °C for further 5 min. The mixture was extracted with $CHCl_3$, and the combined organic layers were dried over Na_2SO_4, and filtrated. Ethane-1,2-dithiol (8.6 μL, 0.103 mmol) was added to the filtrate, and the mixture was concentrated in vacuo. A solution of the resulting residue in CH_2Cl_2/MeCN (1:1, 4 mL) was treated with triethylamine trihydrofluoride (0.10 mL, 0.616 mmol) at room temperature under N_2 for 96 h. The volatiles were removed in vacuo, and the residue was purified by ODS column chromatography (1.1 × 30 cm, 0−30% MeCN/H_2O containing 0.1% TFA) to give **32** (4.5 mg, 26% over two steps) after lyophilization as a white foam:

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$[\alpha]^{23}_{D}$ −13.6 (*c* 0.11, H_2O); ^{1}H NMR (D_2O, 500 MHz) δ 7.69 (d, 1H, *J* = 7.8 Hz), 7.54 (dd, 1H, *J* = 3.4, 8.1 Hz), 7.52 (d, 1H, *J* = 8.1 Hz), 7.28 (s, 1H), 7.26 (dd, 1H, *J* = 7.8, 8.1 Hz), 7.18 (t, 1H, *J* = 7.8 Hz), 6.19 (s, 1H), 6.11 (d, 1H, *J* = 5.4 Hz), 5.88 (d, 1H, *J* = 8.1 Hz), 4.89 (dq, 1H, *J* = 5.9, 7.6 Hz), 4.74 (d, 1H, *J* = 5.9 Hz), 4.59−4.50 (m, 3H), 4.29 (q, 1H, *J* = 6.9 Hz), 4.13 (q, 1H, *J* = 7.2 Hz), 3.33 (dd, 1H, *J* = 4.9, 14.7 Hz), 3.23 (ddd, 1H, *J* = 3.4, 7.5, 14.7 Hz), 2.87 (d, 3H, *J* = 2.7 Hz), 1.33 (d, 2H, *J* = 7.2 Hz), 1.25 (d, 3H, *J* = 7.6 Hz), 1.17 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (D_2O, 100 MHz) δ 183.2, 179.3, 173.6, 170.8, 168.8, 161.5, 154.3, 147.1, 144.7, 139.0, 130.1, 127.1, 124.6, 122.0, 121.7, 114.6, 113.3, 105.7, 102.1, 93.7, 75.3, 71.3, 59.5, 58.3, 53.5, 52.7, 50.2, 32.3, 31.1, 19.6, 18.2, 15.6; ESIMS-LR *m*/*z* 728 [(M + H)$^+$]; ESIMS-HR calcd for $C_{32}H_{42}N_9O_{11}$ 728.2998, found 728.2996; IR (ATR) ν_{max} 3294, 1655, 1546, 1459, 1388, 1261, 1186, 1134, 801, 747, 722 cm^{-1}.

Compound 37. A solution of **30g** (281 mg, 0.278 mmol) in THF (3 mL) was treated with 1 M TBAF solution in THF (835 μL, 0.835 mmol) at 0 °C under N_2 for 30 min. The volatiles were removed in vacuo, and the residue was purified by silica gel column chromatography (2.6 × 10 cm, 0−10% MeOH/$CHCl_3$) to give **37** (217 mg, 99%) as a white solid: $[\alpha]^{23}_{D}$ −1.8 (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.67 (d, 1H, *J* = 9.3 Hz), 7.42−7.18 (m, 10H), 6.92−6.92 (m, 1H), 6.34 (d, 1H, *J* = 9.8 Hz), 6.23 (br s, 1H), 5.99 (br s, 1H), 5.75 (br s, 1H), 5.64 (d, 1H, *J* = 7.3 Hz), 5.50 (d, 1H, *J* = 9.7 Hz), 5.45 (d, 1H, *J* = 9.7 Hz), 5.08 (d, 1H, *J* = 12.2 Hz), 5.03 (d, 1H, *J* = 12.2 Hz), 4.70 (d, 1H, *J* = 12.0 Hz), 4.66 (d, 1H, *J* = 12.0 Hz), 4.60−4.51 (m, 1H), 4.51−4.31 (m, 3H), 3.87−3.87 (m, 1H), 2.98 (s, 3H), 1.39 (s, 9H), 1.20 (d, 3H, *J* = 4.6 Hz), 1.16 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.4, 167.5, 161.9, 155.8, 155.6, 151.4, 141.9, 137.6, 137.5, 136.4, 128.5, 128.4, 128.1, 128.1, 127.9, 127.8, 103.6, 103.1, 100.3, 80.5, 74.2, 72.4, 70.4, 68.9, 66.8, 57.8, 51.4, 47.3, 30.5, 28.3, 18.1, 14.0 (C32); ESIMS-LR *m*/*z* 781 [(M + H)$^+$]; ESIMS-HR calcd for $C_{38}H_{49}N_6O_{12}$ 781.3403, found 781.3406; IR (ATR) ν_{max} 3297, 2981, 1716, 1659, 1525, 1454, 1414, 1363, 1230, 1164, 1051, 809, 774, 738, 698 cm^{-1}.

Compound 38. A solution of **37** (60 mg, 0.077 mmol) and DMAP (23.5 mg, 0.192 mmol) in MeCN (1 mL) was treated with *O*-phenyl chlorothionocarbonate (19.9 mg, 0.115 mmol) at 0 °C under N_2. The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by silica gel column chromatography (2 × 7.5 cm, 50−100% EtOAc/Hexane) to give **38** (48 mg, 75%) as a white solid: $[\alpha]^{23}_{D}$ +191.1 (*c* 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.51 (d, 1H, *J* = 7.6 Hz), 7.40−7.19 (m, 11H), 6.24 (d, 1H, *J* = 9.6 Hz), 5.84 (s, 1H), 5.76 (d, 1H, *J* = 8.1 Hz), 5.48 (d, 1H, *J* = 7.6 Hz), 5.43 (d, 1H, *J* = 10.1 Hz), 5.33 (d, 1H, *J* = 10.1 Hz), 5.33 (d, 1H, *J* = 7.6 Hz), 5.10 (d, 1H, *J* = 12.2 Hz), 5.02 (d, 1H, *J* = 12.2 Hz), 4.73−4.50 (m, 3H), 4.65 (s, 2H), 4.54−4.36 (m, 2H), 2.89 (s, 3H), 1.36 (s, 9H), 1.30 (d, 3H, *J* = 6.6 Hz), 1.10 (d, 3H, *J* = 6.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.7, 170.1, 167.1, 162.0, 155.6, 150.8, 142.8, 141.8, 137.6, 136.3, 128.6, 128.4, 128.3, 128.2, 127.9, 127.6, 103.1, 100.2, 97.1, 83.6, 80.3, 72.6, 70.4, 66.9, 57.4, 52.5, 48.7, 47.4, 30.4, 28.3, 18.3, 12.7; ESIMS-LR *m*/*z* 823 [(M + H)$^+$]; ESIMS-HR calcd for $C_{39}H_{47}N_6O_{12}S$ 823.2967, found 823.2969; IR (ATR) ν_{max} 3300, 2981, 1718, 1666, 1499, 1453, 1412, 1362, 1229, 1163, 1060, 807, 738, 697 cm^{-1}.

Fluorescence-Based MraY Assay.[53,54] Reactions were carried out in 384-well microplate. Reaction mixtures contained, in a final volume of 20 μL, 50 mM Tris-HCl (pH 7.6), 50 mM KCl, 25 mM $MgCl_2$, 0.2% Triton X-100, 8% glycerol, 100 μM C_{55}-P and 100 μM UDP-MurNAc-dansylpentapeptide. The reaction was initiated by the addition of *Staphylococcus aureus* MraY enzyme (11 ng/5 μL/well). After 3−4 h incubation at room temperature, the formation of dansylated lipid I was monitored by fluorescence enhancement (excitation at 355 nm, emission at 535 nm) by using the EnVision 2103 Multilabel Plate Reader. The inhibitory effects of the each compound were determined in the MraY assays described above. The mixtures contained 2% dimethyl sulfoxide in order to increase the solubility of the compounds.

Antibacterial Activity Evaluation. *P. aeruginosa* PAO1, *P. aeruginosa* ATCC 25619, *P. aeruginosa* SR 27156, and *P. aeruginosa* YY165(ΔmexB) were clinical isolates collected from hospitals of Japan and kindly provided by Shionogi & Co., Ltd. (Osaka, Japan). 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). 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.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR data for ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The version of this paper published on the web on January 18, 2012 contained errors in Table 5, the Conclusion, and the characterization of compounds **7b**, **32**, and **37** in the Experimental Section. The corrected version was reposted on January 23, 2012.