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Synthesis of Ureidomuraymycidine Derivatives for Structure–Activity Relationship Studies of Muraymycins

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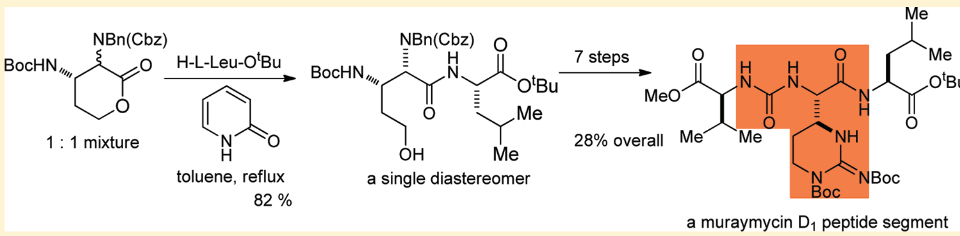
Supporting Information



ABSTRACT: One of the key constituents of the muraymycins is the 6-membered cyclic guanidine, (2*S*,3*S*)-muraymycidine (or *epi*-capreomycidine). In order to diversify the structure of the oligopeptide moiety of the muraymycins for thorough structure–activity relationship studies, we have developed a highly stereoselective synthesis of ureidomuraymycidine derivatives with the lactone **4a**.

■ INTRODUCTION

The increasing resistance among Gram-positive bacteria is concerning because they are responsible for one-third of nosocomial infections.[1] Multidrug resistance in Gram-positive cocci (i.e., staphylococci, pneumococci, and vancomycin resistance in enterococci) and mycobacteria has achieved great prominence in past 15 years.[2] Over the past decade, a few phase clinical drugs have been developed for Gram-positive bacterial infections.[3] The ultimate goal of the development of treatment of multidrug resistant strains is to find novel antibacterial agents which interfere with unexploited bacterial molecular targets.

Since peptidoglycan (PG) is an essential bacterial cell wall polymer, the machinery for PG biosynthesis provides a unique and selective target for antibiotic action. However, only a few enzymes in PG biosynthesis such as the penicillin binding proteins (PBPs) have been extensively studied.[4] Thus, the enzymes associated with the early PG biosynthesis enzymes (i.e., MurA, B, C, D, E, and F, MraY, and MurG) are still considered to be a source of unexploited drug targets.[5] Our interest in unexploited molecular targets related to PG biosynthesis is MraY,[6] which catalyzes the transformation of UDP-*N*-acylmuramyl-L-alanyl-γ-D-glutamyl-*meso*-diaminopimelyl-D-alanyl-D-alanine (Park's nucleotide) to prenylpyrophosphoryl-*N*-acylmuramyl-L-Ala-γ-D-glu-*meso*-DAP-D-Ala-D-Ala (lipid I).[7] MraY is inhibited by nucleoside-based complex natural products such as muraymycin, liposidomycin, caprazamycin, and capuramycin. Muraymycins have been isolated from *Streptmyces* spp. and possess a common core structure of capuramycin; however, their structural diversity is observed in the ester moiety (R in Figure 1) and the appended C5′-ribose unit. Promising in vivo antibactericidal activity of muraymycin A_1 (**1**) against *S. aureus* was highlighted by the Wyeth research groups.[8] Thus, it is our intent to validate the efficacy of **1** in vitro and in vivo against *M. tuberculosis*. In our effort on total synthesis of muraymycin A_1 (**1**) and D_1 (**2**), and their analogues for structure–activity relationship studies against Gram-positive bacteria including *M. tuberculosis*, it is crucial to develop an efficient synthesis of -2-amino-2-(2-iminohexahydropyrimidin-4-yl)acetic acid [-muraymycidine (**a** in Figure 1)] derivative that can readily be incorporated in the syntheses of muraymycin analogues. The 6-membered cyclic guanidine moiety seems to be essential to exhibit strong antibactericidal activities for the muraymycidins.[8b] To date, several asymmetric syntheses of (2*S*,3*R*)-capreomycidine (**b**) have been reported for the total synthesis or biosynthetic studies of the capreomycins.[9] On the other hand, very few synthetic efforts on -muraymycidine derivative **a** have been reported.[10] Recently, Tanino and co-workers reported a synthesis of the amino alcohol possessing the cyclic guanidine **c** in which they accomplished the synthesis of **c** in 11 steps from an advanced intermediate with an overall yield of 7.9%.[11] In the syntheses of the 6-membered cyclic guanidine containing α-amino acids reported to date, selectivities of the asymmetric induction to generate two consecutive chiral centers were moderate or very low, and the synthetic schemes required multiple protecting-group manipulations. Herein, we report an efficient synthesis of the ureido--muraymycidine derivatives (highlighted in Figure 1) via the optically pure diamino lactone (3*S*,4*S*)-3,4-diaminotetrahydro-2*H*-pyran-2-one derivative (**4a**).

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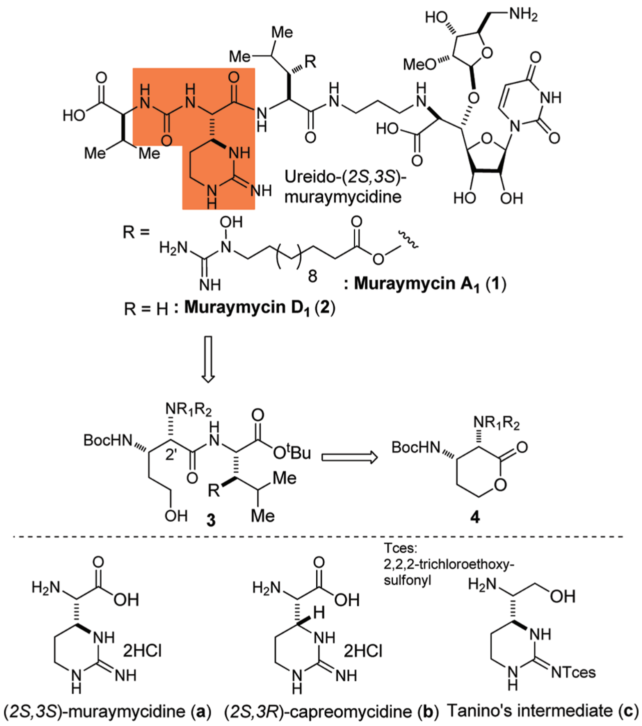


Figure 1. Retro-synthesis of muraymycins and structures of muraymycidine and capreomycidine.

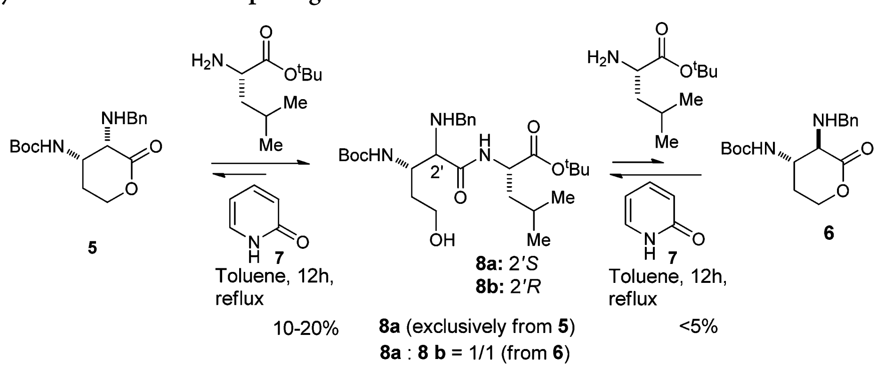
■ RESULTS AND DISCUSSION

Our synthetic strategy to efficiently synthesize ureido-(2*S*,3*S*)-muraymycidine is illustrated in Figure 1. In our preliminary studies on the synthesis of the dipeptide intermediate **3** (Figure 1), we examined the efficiency of a strategy of lactone-opening of (2*S*,3*S*)-diamino lactone **5** and (2*R*,3*S*)-diamino lactone **6** with H-L-Leu-O^{t}Bu for the synthesis of **8** (Scheme 1).[12] We observed that the lactone opening of **6** with H-L-Leu-O^{t}Bu in the presence of 2(1*H*)-pyridinone (**7**) furnished a 1:1 mixture of the dipeptides **8a** and **8b** in very poor yield (<5%). On the other hand, under the same conditions the lactone **5** yielded the desired **8a** without contamination of **8b** in 10–20% yield. These data clearly indicated that the lactone **6** was epimerized under the reaction conditions (2(1*H*)-pyridinone, toluene at reflux). Importantly, the stereochemistry of the lactone **5** was intact, and the dipeptide **8a** was not epimerized in the 2(1*H*)-pyridinone-catalyzed thermal lactone-opening reaction conditions. In addition, reactivity of the lactone **6** against H-L-Leu-O^{t}Bu was poorer than that of **5**. Low conversion of the dipeptides **8** from the lactones in Scheme 1 can be attributed to the fact that δ-hydroxypentanoic acid derivatives tend to form δ-lactones even under weak acidic conditions.[13] Indeed, the dipeptides **8a** and **8b** were relactonized to form **5** and **6**, respectively, during purification by a silica gel chromatography. In order to improve the conversion of **4** to **3** (Figure 1) and to realize epimerization of (2*R*,3*S*)-diamino lactone derivatives (e.g., **6** in Scheme 1), we explored suitable *N*-protecting groups at the C2-position of lactone **4** (R_1 and R_2 in Figure 1) in which we expected that bulky *N*-protecting groups on (2*R*,3*S*)-diamino lactone would prevent nucleophilic attack on the carbonyl group to form the undesired dipeptides possessing 2′*R*-configuration.

We first investigated chemical properties of *N*-benzyl-*N*-Cbz-protected lactones **4a** and **4b**. The syntheses of **4a** and **4b** are illustrated in Scheme 2. The (2*S*)-aminobutanal derivative **9** was readily synthesized from (2*S*)-2-amino γ-butyrolactone according to the reported procedures.[14] The aldehyde **9** was subjected to the Strecker reaction with benzylamine and TMSCN to form a mixture of 2,3-diaminonitriles **10a** and **10b**.[15] In our extensive reaction screening (**9**→**10**), the Strecker reaction conditions that provided **10** with greater than 80% yield are summarized in Table 1.

The Strecker reactions with Lewis acids (e.g., ZnI_2, $Cu(OTf)_2$, $Sn(OTf)_2$, $La(OTf)_3$)[16] provided the undesired product **10b** as a major product with low yields (<30%) due probably to instability of the aldehyde **9** under strong Lewis acidic conditions. The reaction with the thiourea catalyst provided a 1:3.5 mixture of **10a** and **10b** in 88% yield (conditions **A**). A Ti-mediated Strecker reaction resulted in a 1:1.5 mixture of **10a** and **10b** (conditions **B**). It was found that the Strecker reaction of the benzyl imine **9** with TMSCN could be achieved via a convenient dehydrating reagent, $MgSO_4$, to furnish a 1:1 mixture of **10a** and **10b** in 88% yield (conditions **C**). The same Strecker reactions with the known chiral catalysts such as thioureas and salene–transition-metal complexes resulted in the formation of a mixture of **10a** and **10b** in very poor yield (<30%) with low **10a**/**10b** selectivity.[17] The structure of **10b** could unequivocally be determined by extensive 2D-NMR studies of **4b** that was synthesized from **10b**.[18] With a 1:1 mixture of **10a** and **10b** in hand, we could establish the synthesis of **4a** in five steps including epimerization of the C2-center (Scheme 2). Cbz protection of a mixture of the Strecker products was accomplished under buffered conditions in CH_2Cl_2 to afford **11a** and **11b** in 96% yield. Hydration of a mixture of the nitriles **11a** and **11b** was achieved by using $InCl_3$ in the presence of acetaldoxime at 70 °C to afford a mixture of *N*-benzyl-*N*-Cbz-protected *primary*

Scheme 1. Preliminary Studies of Lactone-Opening Reactions



Scheme 2. Syntheses of Lactones 4a and 4b and Lactone-Opening Reactions

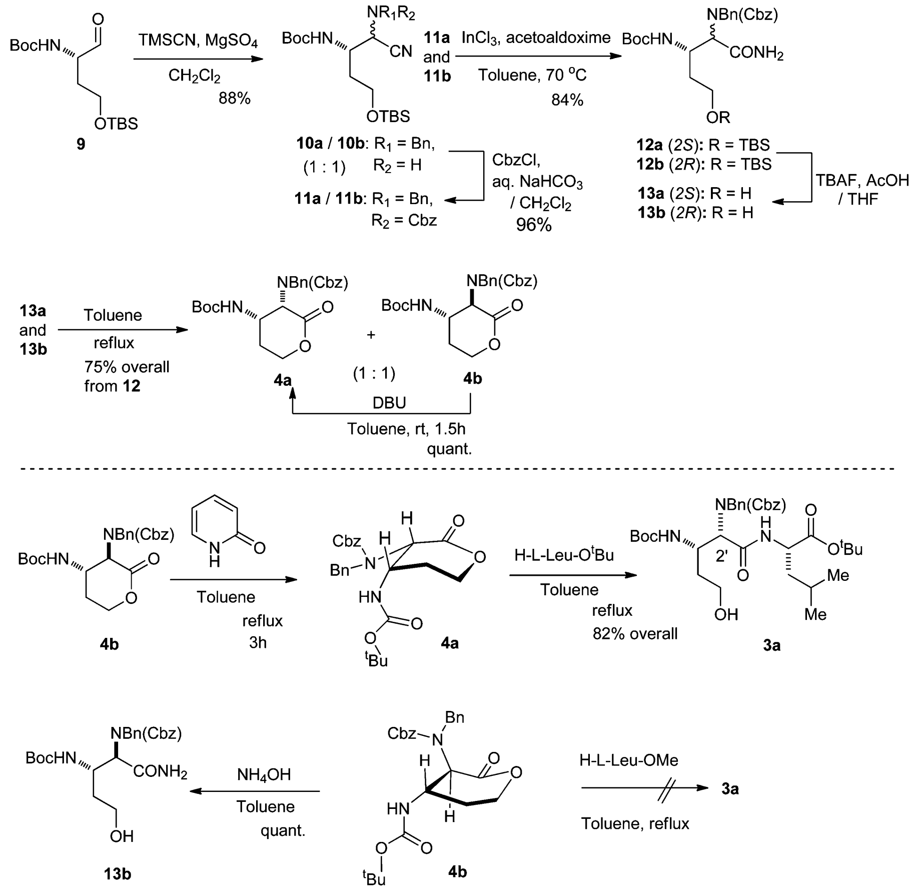
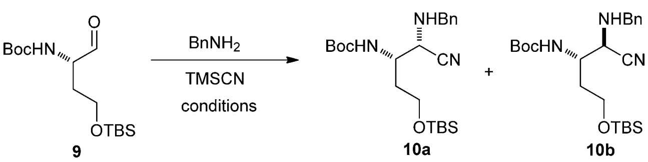
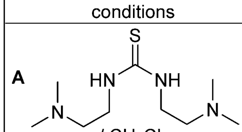


Table 1. Strecker Reactions of the α-Amino Aldedyde 9

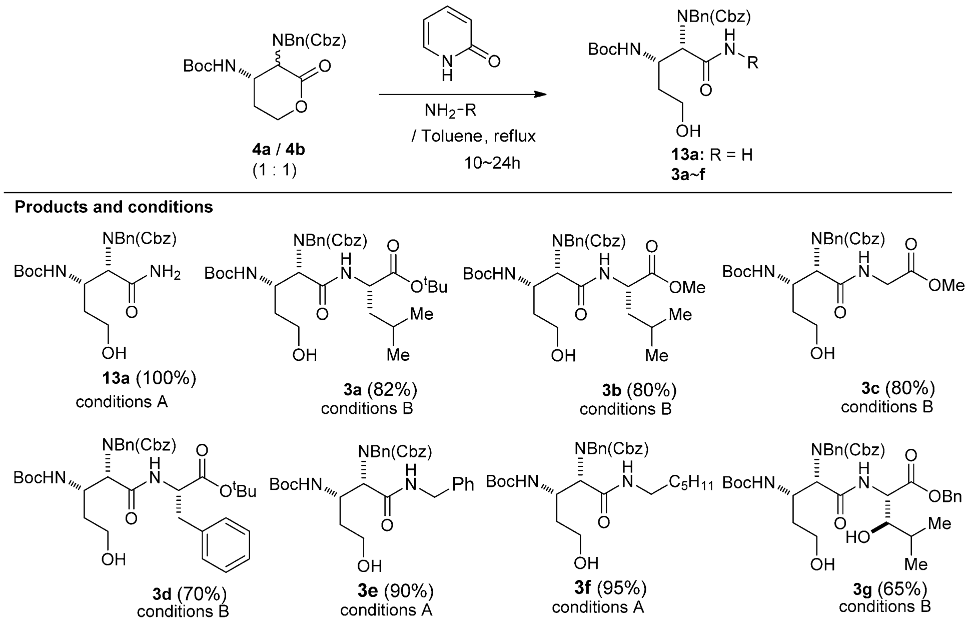


	conditions	yield (%)	selectivity (10a : 10b)
A	 / CH_2Cl_2	88	1 : 3.5
B	$Ti(OiPr)_4$, HCO_2H, H_2O / CH_2Cl_2	85	1 : 1.5
C	$MgSO_4$ / CH_2Cl_2	88	1 : 1

amide **12a** and **12b** in 86% yield.[19] Desilylation of **12** followed by a thermal lactonization of the resulting mixture of **13a** and **13b** in toluene at refluxing temperature provided **4a** and **4b** in 75% overall yield. The structure of (2*R*,3*S*)-diaminolactone **4b** was established via extensive 2D-NMR techniques (vide supra). Gratifyingly, the undesired lactone **4b** could be epimerized to the desired lactone **4a** with DBU in quantitative yield. Epimerization of **4b** to **4a** was also observed under the conditions (2(1H)-pyridinone, toluene at reflux) used for opening of the lactone with H-L-Leu-O^{t}Bu (**5**→**8a** in Scheme 1). Under these conditions, epimerization of **4b** to **4a** was completed in 3 h. The synthesis of the desired dipeptide **3a** could be accomplished via a one-pot operation in which H-L-Leu-O^{t}Bu was added into a solution of the completely epimerized lactone. We realized that the undesired lactone **4b** could not be opened with H-L-Leu-O^{t}Bu even after prolonged reaction times. Among amine nucleophiles tested, only NH_3 could react with **4b** at room temperature in the absence of 2(1*H*)-pyridinone to furnish **13b** in quantitative yield. Therefore, the dipeptide **3a** can be synthesized without contamination of the epimer of **3a** from a 1:1 mixture of **4a** and **4b** through epimerization.

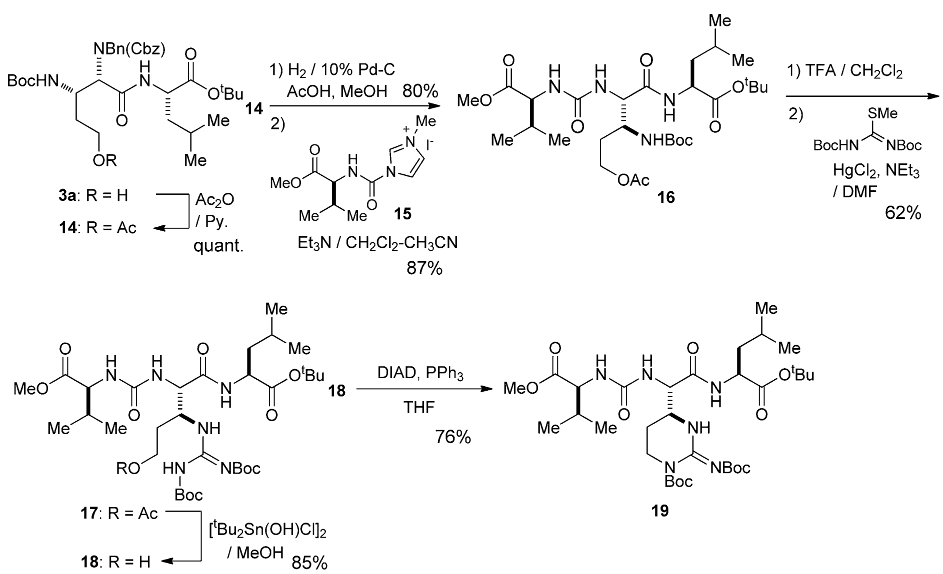
In order to obtain more insight into epimerization followed by opening of the lactone **4b**, we examined the lactone-opening reactions with a wide range of *primary* amines and α-amino acids (e.g., H-L-Leu-O^{t}Bu, H-L-Leu-OMe, Gly-OMe, H-L-Phe-O^{t}Bu, and others). Table 2 summarizes the selected examples of 2(1*H*)-pyridinone-catalyzed lactone-opening reactions of a mixture of **4a** and **4b** (1:1). The lactone-opening reactions with the reactive amines (e.g., NH_3, $PhCH_2NH_2$, $C_6H_{13}NH_2$) were successfully achieved by addition of the amine nucleophiles after completion of epimerization (**4b**→**4a**) to afford the corresponding *primary* or *secondary* amides with 90–100% yield (conditions **A**). On the other hand, lactone-opening reactions with the α-amino acids did not require adding the nucleophiles after completion of the epimerization of **4b**. In all of the reactions with α-amino acids summarized in Table 2, (2*R*,3*S*)-diamino lactone **4b** did not react with salt-free α-amino acid esters. Thus, the 2(1*H*)-pyridinone catalyzed epimerization of **4b** to **4a** could be completed in the presence of α-amino acid esters, and only (2*S*,3*S*)-diaminolactone **4a** was smoothly

Table 2. Lactone-Opening Reactions with Amines and α-Amino Acid Esters



Conditions A: 2(1H)-pyridinone in toluene, reflux for 3h followed by NH_2-R.
Conditions B: 2(1H)-pyridinone, NH_2-R in toluene, reflux

Scheme 3. Synthesis of Ureidomuraymycidine Tripeptide 19



reacted with α-amino acid esters. Lactone-opening reaction of a 1: 1 mixture of **4a** and **4b** with H-L-Gly-OMe and 2(1*H*)-pyridinone in toluene at reflux for 5 h furnished the desired **3c** exclusively in 80% yield (conditions **B**).

Under the same conditions, (2*S*,3*S*)-benzyl-2-amino-3-hydroxy-4-methylpentanoate was reacted with a mixture of the lactones to furnish **3g** in 65% yield (90% yield based on recovering **4a**) without formation of the other diastereomers. The dipeptide **3g** is a valuable intermediate for a total synthesis of muraymycin A_1 (**1**). The dipeptides **3a–g** in Table 2 were stable under weak acidic and basic conditions (pH 4.0–9.0) at room temperature; relactonizations of **3a–g** to **4a** were not observed. The plausible lowest-energy conformers of **4a** and **4b** are illustrated in Scheme 2. Those conformers were obtained via MM2 calculations[20] and supported by the NOESY correlations.[21] The *syn*-isomer **4a** is significantly lower in energy than the *anti*-isomer **4b**; the calculated free energy difference was 6.86 kcal/mol. Thus, we concluded that epimerization of **4b** could readily be achieved by using 2(1*H*)-pyridinone in toluene at refluxing temperature. Because the *anti*-isomer **4b** exists as a pseudoboat conformation, the amino groups at the C2- and C3-positions hinder the nucleophilic additions of α-amino acids to the lactone carbonyl from both *re*- and *si*-faces.

Synthesis of the ureido tripeptide **19** was achieved from the dipeptide **3a** (Scheme 3). The *primary* alcohol of **3a** was first protected as its acetate to afford **14** in quantitative yield. The *N*-Bn and *N*-Cbz groups of **14** were removed by hydrogenation to generate free amine which was subjected to the urea-forming reaction with the imidazolium salt **15** to furnish **16** in 70%

overall yield.[22] The Boc group of **16** was removed by using 50% TFA at 0 °C and the generated salt free amine was coupled with *N,N′*-di-*tert*-butoxycarbonyl-*S*-methyl isothiourea in the presence of Et_3N and $HgCl_2$ to afford **17** in 62% yield.[23] $[{}^tBu_2Sn(OH)Cl]_2$-catalyzed deacetylation[24] of **17** followed by an intramolecular Mitsunobu reaction with DIAD and PPh_3 completed the synthesis of the fully protected ureidomuraymycidine tripeptide **19** in 65% overall yield. The segment **19** possesses ideal protecting groups for a total synthesis of muraymycin D_1 (**2**).

■ CONCLUSIONS

In summary, we present a highly stereoselctive synthesis of ureidomuraymycidine tripeptide **19** from a 1:1 mixture of the lactones **4a** and **4b**. δ-Lactones have not been widely utilized for functionalization of alcohols and amines due mainly to undesired reversible reactions.[25] We realized that (2*R*,3*S*)-diamino lactone **4b** can readily be epimerized to the stereoelectronically favored **4a** with 2(1*H*)-pyridinone. In addition, the lactone **4b** was not susceptible to lactone-opening reactions with α-amino acid derivatives. Thus, epimerization followed by selective lactone-opening reactions of a mixture of **4a** and **4b** with α-amino acids can be achieved in the presence of 2(1*H*)-pyridinone to furnish the corresponding dipeptides as a single diastereomer. Relactonizations of the δ-hydroxy dipeptides synthesized in this program were not observed under mild acidic and basic conditions; thus, high-yield dipeptide formations from the lactones **4a** and **4b** were achieved.[26] The ureidomuraymycidine moiety of the muraymycins is an important functionality to show strong antibacterial activities.[27] Thus, the ureidomuraymycidin (highlighted in Figure 1) should be retained as the intact stereochemistry for SAR studies of the muraymycins. As illustrated in Table 2, we will diversify the structure of muraymycin A_1 and D_1 for a thorough SAR study via the lactone-opening reactions of a 1:1 mixture of **4a** and **4b**, which could be synthesized from the known aldehyde **9** in over 50% overall yield. Total synthesis of muraymycins A_1 and D_1, and preliminary SAR of the muraymycins will be reported elsewhere.

■ EXPERIMENTAL SECTION

All reagents and solvents were of commercial grade and were used as received without further purification unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl under an argon atmosphere prior to use. Methylene chloride (CH_2Cl_2), acetonitrile (CH_3CN), benzene, toluene, and triethylamine (Et_3N) were distilled from calcium hydride under an argon atmosphere. Flash chromatography was performed with Whatman silica gel (Purasil 60 Å, 230−400 Mesh). Analytical thin-layer chromatography was performed with 0.25 mm coated commercial silica gel plates (EMD, silica gel $60F_{254}$) visualizing at 254 nm or developed with ceric ammonium molybdate or anisaldehyde solutions by heating on a hot plate. ^1H NMR spectral data were obtained using 300, 400, and 500 MHz instruments. ^{13}C NMR spectral data were obtained using 100 and 125 MHz instruments. For all NMR spectra, δ values are given in ppm and *J* values in Hz.

(2*S*)-*tert*-Butyl (4-((*tert*-Butyldimethylsilyl)oxy)-1-oxobutan-2-yl)carbamate (9). MeNHOMe·HCl (1.89 g, 19.4 mmol) was suspended in CH_2Cl_2 (97 mL) and cooled to 0 °C. Me_2AlCl (1 M in hexanes, 19.4 mmol, 19.4 mL) was added dropwise, and the reaction mixture was warmed to rt. After 1 h, the reaction was cooled to 0 °C, and a solution of 2*S*-[(*tert*-butyloxycarbonyl)amino]-4-butyrolactone (1.95 g, 9.69 mmol) in CH_2Cl_2 (49 mL) was added via syringe pump over 15 min. The reaction mixture was stirred for 6 h and quenched with pH 8 phosphate buffer solution. The heterogeneous mixture was filtered, and the filtrate was extracted with CH_2Cl_2. The generated Weinreb amide was used in the next step without purification. A stirred solution of the Weinreb amide (3.60 g, 13.70 mmol) and 2,6-lutidine (0.92 mL, 27.40 mmol) in CH_2Cl_2 (55 mL) was cooled to 0 °C. TBSOTf (3.46 mL, 15.10 mmol) was added, and the reaction mixture was stirred for 30 min. The reaction was quenched with water and extracted with EtOAc. The extract was washed with 1 N HCl, brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel column chromatography gave (2*S*)-*tert*-butyl (3,9,9,10,10-pentamethyl-4-oxo-2,8-dioxa-3-aza-9-silaundecan-5-yl)carbamate (4.71 g, 12.50 mmol, 91%) as an amorphous solid: TLC (hexanes/EtOAc 25:75) R_f = 0.7; $[\alpha]^{22}_D$ +0.4 (*c* = 0.9, $CHCl_3$); IR (thin film) ν_{max} = 3323 (br), 2930, 2858, 1716, 1669, 1500, 1390, 1366, 1253, 1173, 1101, 941, 836, 778 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.45 (d, *J* = 7.7 Hz, 1H), 4.74 (br s, 1H), 3.20 (s, 3H), 1.96 (dd, *J* = 4.7, 9.0 Hz, 1H), 1.79−1.61 (m, 1H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.7, 79.4, 61.7, 59.9, 48.9, 34.9, 32.3, 28.5, 26.0, 18.3, −5.4; HRMS (ESI$^+$) *m*/*z* calcd for $C_{17}H_{37}N_2O_5Si$ [M + H] 377.2472, found 377.2472.

$LiAlH_4$ (1 M in THF, 15.90 mmol, 15.90 mL) was slowly added to a THF solution (40 mL) of (2*S*)-*tert*-butyl (3,9,9,10,10-pentamethyl-4-oxo-2,8-dioxa-3-aza-9-silaundecan-5-yl)carbamate (3.00 g, 7.97 mmol) at 0 °C. After 1.5 h, the reaction mixture was diluted with Et_2O, and quenched with brine. The precipitates were filtered. The combined organic solution was dried over $MgSO_4$, and evaporated. This was used for the next reaction without purification.

General Procedure of Strecker Reaction: Synthesis of a Mixture of 10a and 10b. A CH_2Cl_2 (72 mL) solution of aldehyde **9** (2.30 g, 7.24 mmol), benzylamine (0.87 mL, 7.97 mmol), and an excess of $MgSO_4$ were stirred at room temparature for 2 h. The solids were then filtered off, and the mixture was concentrated in vacuo to give an intermediate imine. The imine was dissolved in CH_2Cl_2 (72 mL), and TMSCN (1.93 mL, 14.50 mmol) was then added. The reaction was stirred for 1 h then poured into saturated $NaHCO_3$ (aq.). The aqueous layer was extracted with CH_2Cl_2 (3×), and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 80:20) gave a mixture of **10a** and **10b** (2.77 g, 6.38 mmol, 88%) as an oil: IR (thin film) ν_{max} = 3332 (br), 3065, 3031, 2932, 2228, 1714, 1505, 1367, 1255, 1172, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.51−7.17 (m, 5H), 5.42 (d, *J* = 6.6 Hz, 0.5H), 5.21 (d, *J* = 8.4 Hz, 0.5H), 2.12−1.70 (m, 3H), 1.46 (s, 9H), 0.93−0.90 (m, 9H), 0.10−0.05 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.7, 138.2, 128.6, 128.4, 128.4, 127.6, 119.0, 118.6, 80.0, 60.1, 59.8, 54.3, 52.1, 51.5, 51.3, 50.9, 34.1, 32.3, 28.5, 28.4, 26.1, 25.9, 25.9, 18.2, 18.2, −5.5; HRMS (ESI$^+$) *m*/*z* calcd for $C_{23}H_{40}N_3O_3Si$ [M + H] 434.2839, found 434.2839.

***tert*-Butyl ((3*S*,4*S*)-3-(Benzylamino)-2-oxotetrahydro-2*H*-pyran-4-yl)carbamate (5).** *tert*-Butyl (1-amino-2-(benzylamino)-5-hydroxy-1-oxopentan-3-yl)carbamate (40 mg, 0.12 mmol) was dissolved in toluene (2 mL). The reaction mixture was stirred at reflux for 24 h and cooled to rt. All volatiles were evaporated in vacuo. Purification by silica gel column chromatography (hexanes/EtOAc 90:10 to 50:50) yielded product **5** as an amorphous white solid (25 mg, 0.08 mmol, 63%). Data for **5**: TLC (hexanes/EtOAc 50:50) R_f = 0.4, $[\alpha]^{22}_D$ +36 (*c* = 0.85, $CHCl_3$); IR (thin film) ν_{max} = 3351 (br), 2979, 2929, 1693, 1524, 1459, 1418, 1364, 1259, 1170, 1075, 994, 873, 773, 739, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.39−7.28 (m, 5H), 5.45 (s, 1H), 4.94 (s, 1H), 4.42 (m, 1H), 4.28 (m, 1H), 4.02 (d, *J* = 12.5 Hz, 1H), 3.91−3.77 (ddd, *J* = 13.5, 12.5, 14.0 Hz, 1H), 3.66 (m, 1H), 3.46−3.38 (dd, *J* = 7.5, 10.5 Hz, 1H), 2.51−2.49 (m, 1H), 1.98−1.94 (m, 2H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9, 171.4, 156.2, 155.7, 139.5, 138.7, 128.7, 128.5, 128.1, 127.4, 79.9, 65.8, 65.5, 60.6, 57.9, 51.8, 50.5, 49.6, 45.0, 30.4, 28.4; HRMS (ESI$^+$) *m*/*z* calcd for $C_{17}H_{24}N_2O_4Na$ [M + Na] 343.1634, found 343.1637.

***tert*-Butyl ((3*R*,4*S*)-3-(Benzylamino)-2-oxotetrahydro-2*H*-pyran-4-yl)carbamate (6).** *tert*-Butyl (2*R*,3*S*)-1-amino-2-(benzylamino)-5-hydroxy-1-oxopentan-3-ylcarbamate (30 mg, 0.089 mmol) was dissolved in toluene (2 mL). The reaction mixture was stirred at reflux for 24 h and cooled to rt. All volatiles were evaporated in vacuo. Purification by silica gel column chromatography (hexanes/EtOAc 90:10 to 50:50) yielded product **6** as an amorphous white solid (15 mg, 0.048 mmol, 53%). Data for **6**: TLC (hexanes/EtOAc 50:50) R_f = 0.4, $[\alpha]^{22}_{D}$ −0.6 (c = 0.75, $CHCl_3$); IR (thin film) ν_{max} = 3351 (br), 2979, 2929, 1693, 1524, 1459, 1418, 1364, 1259, 1170, 1075, 994, 873, 773, 739, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.29−7.19 (m, 5H), 5.36 (s, 1H), 4.83 (s, 1H), 4.39−4.32 (m, 1H), 4.23−4.18 (m, 1H), 3.92 (d, J = 12.0 Hz, 1H), 3.82−3.65 (ddd, J = 14.0, 12.5, 13.5 Hz, 1H), 3.55 (m, 1H), 3.37−3.28 (dd, J = 5.0, 10.5 Hz, 1H), 2.43−2.34 (m, 1H), 2.07−2.02 (m, 1H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9, 171.4, 156.2, 155.7, 139.6, 138.8, 128.7, 128.5, 128.1, 127.5, 79.9, 65.5, 60.6, 57.9, 51.8, 50.5, 49.6, 45.0, 30.36, 28.4, 27.5; HRMS (ESI$^+$) m/z calcd for $C_{17}H_{24}N_2O_4Na$ [M + Na] 343.1634, found 343.1636.

Benzyl (Benzyl)((2*S*)-2-((*tert*-butoxycarbonyl)amino)-4-((*tert*-butyldimethylsilyl)oxy)-1-cyanobutyl)carbamate (12). To a stirred solution of a 1:1 mixture of **10a** and **10b** (342 mg, 0.79 mmol) in CH_2Cl_2 (4 mL) were added aq satd $NaHCO_3$ (4 mL) and CbzCl (0.23 mL, 1.58 mmol). This reaction mixture was stirred for 1 h at rt. Upon completion, the aqueous layer was extracted with CH_2Cl_2 (3×), and the combined organic extract was dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography (hexanes/EtOAc 90:10 to 80:20) to yield a 1:1 mixture of the Cbz-protected products **11a** and **11b** (430 mg, 0.76 mmol, 96%) as an oil: TLC (hexanes/EtOAc 75:25) R_f = 0.65; IR (thin film) ν_{max} = 3362 (br), 3034, 2956, 2858, 2247, 1716, 1498, 1471, 1367, 1254, 1171, 1102, 1003, 837, 777, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.46−7.14 (m, 10H), 5.31 (br s, 1H), 5.17 (br s, 2H), 4.87−4.69 (m, 2H), 4.23−4.15 (m, 1H), 4.20 (d, J = 3.9 Hz, 1H), 3.83−3.54 (m, 2H), 1.74 (br s, 1H), 1.57 (br s, 1H), 1.45 (s, 9H), 0.92−0.89 (m, 9H), 0.10−0.03 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.3, 137.0, 135.6, 128.8, 128.6, 128.4, 128.2, 127.7, 127.7, 127.1, 116.4, 80.1, 77.2, 68.6, 65.4, 59.7, 53.1, 50.3, 32.9, 28.6, 28.5, 28.5, 28.4, 28.4, 26.1, 26.1, 26.0, 26.0, 25.9, 18.2, −5.3, −5.4, −5.5; HRMS (ESI$^+$) m/z calcd for $C_{31}H_{45}N_3O_5SiNa$ [M + Na] 590.3026, found 590.3017.

To a stirred solution of **11a** and **11b** (a 1:1 mixture, 2.34 g, 4.12 mmol) in toluene (27 mL) were added $InCl_3$ (137.0 mg, 0.62 mmol) and acetaldoxime (1.26 mL, 20.6 mmol). The reaction mixture was heated at 70 °C for 4 h. Upon completion, the reaction was cooled to rt, and all volatiles were removed. Purification by silica gel column chromatography (hexanes/EtOAc 90:10 to 50:50) to yielded **12a** and **12b** (2.03 g, 3.47 mmol, 84%) as an amorphous white solid. Data for **12a**: TLC (hexanes/EtOAc 50:50) R_f = 0.5; $[\alpha]^{22}_{D}$ −0.4 (c = 3.1, $CHCl_3$); IR (thin film) ν_{max} = 3350 (br), 2956, 2930, 2857, 2556, 2490, 2406, 1682, 1454, 1412, 1366, 1255, 1169, 1094, 1030, 991, 837, 775, 735, 697 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 7.47−7.02 (m, 10H), 6.37 (br s, 1 H), 5.07 (br s, 2H), 4.69 (d, J = 16.0 Hz, 1H), 4.65−4.39 (m, 2H), 4.21 (br s, 1H), 3.55 (br s, 2H), 1.64 (br s, 1H), 1.49 (br s, 1H), 1.39 (s, 9H), 0.86 (s, 9H), 0.00 (br s, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ173.6, 158.3, 157.7, 157.6, 139.7, 137.5, 129.4, 129.3, 129.1, 128.4, 128.0, 80.2, 68.9, 63.4, 61.1, 36.0, 28.8, 26.5, 19.1, −5.2, −5.2; HRMS (ESI$^+$) m/z calcd for $C_{31}H_{47}N_3O_6SiNa$ [M + Na] 608.3132, found 608.3128. Data for **12b**: TLC (hexanes/EtOAc 50:50) R_f = 0.55; $[\alpha]^{22}_{D}$ +0.6 (c = 1.3, $CHCl_3$); IR (thin film) ν_{max} = 3339 (br), 2956, 2930, 2857, 2541, 2474, 2406, 1683, 1499, 1463, 1407, 1366, 1254, 1172, 1098, 1030, 837, 776, 735, 697, 665 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 7.50−6.90 (m, 9H), 6.28 (d, J = 9.8 Hz, 1H), 5.18 (br s, 1H), 5.13−4.94 (m, 2H), 4.75−4.56 (m, 2H), 4.50(d, J = 16.0 Hz, 1H), 4.34−4.17 (m, 1H), 3.73 (d, J = 6.3 Hz, 2H), 1.77 (br s, 1H), 1.60 (br s, 1H), 1.40 (s, 9H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ 178.1, 173.3, 157.7, 129.3, 129.2, 128.9, 128.9, 127.8, 127.6, 80.1, 68.8, 63.6, 61.3, 35.9, 28.8, 26.5, 19.1, −5.3; HRMS (ESI$^+$) m/z calcd for $C_{31}H_{48}N_3O_6Si$ [M + H] 586.3312, found 586.3306. A mixture of **12a** and **12b** was used for the next reaction.

Benzyl ((3*S*)-1-Amino-3-((*tert*-butoxycarbonyl)amino)-5-hydroxy-1-oxopentan-2-yl)(benzyl)carbamate (13). To a stirred solution of **12a** and **12b** (1:1, 2.03 g, 3.47 mmol) and HOAc (0.01 mL, 1.74 mmol) in THF (18 mL) was added TBAF (1 M in THF, 6.93 mL, 6.93 mmol). After 1 h at rt, all volatiles were concentrated in vacuo. Purification by silica gel column chromatography (hexanes/EtOAc 50:50 to 0:100) gave a mixture of **13a** and **13b** (1.48 g, 3.13 mmol, 90%). Data for **13a**: TLC (hexanes/EtOAc 25:75) R_f = 0.15; $[\alpha]^{22}_{D}$ −0.3 (c 2.1, $CHCl_3$); IR (thin film) ν_{max} = 3340 (br), 3200 (br), 2963, 2932, 1683, 1498, 1454, 1406, 1367, 1255, 1169, 1123, 1054, 1028, 1005, 771, 739, 698 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.48−7.14 (m, 10H), 7.00 (br s, 1H), 6.62−6.47 (m, 1H), 5.03 (br s, 2H), 4.64 (br s, 2H), 4.48 (d, J = 16.0 Hz, 1H), 4.30 (br s, 1H), 3.98 (br s, 1H), 3.32 (br s, 2H), 1.57−1.43 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 171.8, 170.5, 155.3, 128.7, 128.1, 128.0, 127.7, 127.6, 127.1, 126.4, 77.9, 66.6, 60.6, 57.8, 47.6, 35.0, 31.2, 28.4, 28.2, 22.1, 13.9; HRMS (ESI$^+$) m/z calcd for $C_{25}H_{33}N_3O_6Na$ [M + Na] 494.2267, found 494.2268. Data for **13b**: TLC (hexanes/EtOAc 25:75) R_f = 0.05; $[\alpha]^{22}_{D}$ +0.2 (c = 1.1, $CHCl_3$); IR (thin film) ν_{max} = 3346 (br), 3201 (br), 2976, 2933, 1684, 1513, 1499, 1453, 1404, 1366, 1345, 1258, 1170, 1052, 1029, 768, 737, 698 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.82 (br s, 1H), 7.48−7.04 (m, 10H), 6.90 (d, J = 5.5 Hz, 1H), 6.53 (d, J = 9.8 Hz, 1H), 5.05−4.95 (m, 1H), 4.91 (br s, 1H), 4.63 (d, J = 16.8 Hz, 1H), 4.54 (d, J = 10.2 Hz, 1H), 4.44−4.30 (m, 2H), 4.07−3.89 (m,1 H), 3.54−3.35 (m, 2H), 1.54 (br s, 2H), 1.34 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 175.4, 170.6, 155.4, 128.0, 127.8, 127.4, 127.0, 126.2, 126.0, 77.5, 66.4, 61.5, 58.1, 46.9, 34.2, 31.2, 28.3, 28.2, 22.1, 13.9; HRMS (ESI$^+$) m/z calcd for $C_{25}H_{33}N_3O_6Na$ [M + Na] 494.2267, found 494.2263. A mixture of these alcohols was used for the next reaction.

(3*S*,4*S*)- and (3*S*,4*R*)-3,4-Diaminotetrahydro-2*H*-pyran-2-one (4a and 4b). A mixture of benzyl (1-amino-3-(*tert*-butoxycarbonyl)-amino)-5-hydroxy-1-oxopentan-2-yl)(benzyl)carbamates (117 mg, 0.248 mmol) was dissolved in toluene (5 mL). The reaction mixture was stirred at reflux for 24 h and cooled to rt. All volatiles were evaporated in vacuo. Purification by silica gel column chromatography (hexanes/EtOAc 90:10 to 50:50) yielded **4a** and **4b** as an amorphous white solid (94 mg, 0.21 mmol, 83%). Data for **4a**: TLC (hexanes/EtOAc 50:50) R_f = 0.4, (benzene/acetone 80:20) R_f = 0.75; $[\alpha]^{22}_{D}$ +46 (c = 0.75, $CHCl_3$); IR (thin film) ν_{max} = 3353 (br), 2978, 2932, 1699, 1519, 1454, 1420, 1366, 1261, 1171, 1075, 993, 871, 771, 737, 700 cm^{-1}; ^1H NMR (benzene-d_6, 400 MHz) δ 7.37−7.21 (m, 2H), 7.21−7.08 (m, 3H), 7.04 (br s, 5H), 6.62 (d, J = 7.7 Hz, 1H), 5.08−5.05 (d, J = 12.4 Hz, 1H), 4.94−4.91 (d, J = 12.4 Hz, 1H), 4.49−4.45 (d, J = 16.0 Hz, 1H), 4.39−4.35 (d, J = 15.6 Hz, 1H), 4.11 (br s, 1H), 4.02−3.97 (dd, J = 10.5 Hz, 1H), 3.42−3.39 (d, J = 11.2 Hz, 1H), 3.33−3.31(d, J = 6.8 Hz, 1H), 1.57−1.54 (d, J = 12.0 Hz, 1H), 1.38 (s, 9H), 1.02−0.97 (dd, J = 11.2, 13.8 Hz, 1H); ^{13}C NMR (benzene-d_6, 100 MHz) δ 165.6, 157.7, 155.1, 136.7, 136.1, 128.3, 128.1, 127.8, 127.5, 127.3, 127.2, 126.7, 126.5, 78.6, 67.7, 63.8, 59.2, 52.7, 47.9, 27.9, 27.7; HRMS (ESI$^+$) m/z calcd for $C_{25}H_{30}N_2O_6Na$ [M + Na] 477.2002, found 477.1999. Data for **4b**: TLC (hexanes/EtOAc 50:50) R_f = 0.4 (benzene/acetone 80:20) R_f = 0.8; $[\alpha]^{22}_{D}$ −0.8 (c 2.5, $CHCl_3$); IR (thin film) ν_{max} = 3368 (br), 2977, 2361, 1745, 1712, 1500, 1474, 1455, 1426, 1392, 1366, 1250, 1169, 1079, 992, 911, 865, 737, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40−7.18 (m, 10H), 5.12 (d, J = 14.5 Hz, 2H), 4.54 (d, J = 16.0 Hz, 2H), 4.31−4.10 (m, 2H), 4.01 (br s, 1H), 3.71−3.47 (m, 1H), 2.23−1.92 (m, 1H), 1.92−1.61 (m, 1H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0, 154.9, 136.0, 135.3, 129.0, 128.8, 128.7, 128.7, 128.5, 128.3, 128.1, 127.8, 127.7, 79.9, 77.2, 68.7, 67.9, 66.5, 66.2, 62.1, 61.4, 54.0, 53.1, 49.7, 49.0, 30.2, 28.4; HRMS (ESI$^+$) m/z calcd for $C_{25}H_{30}N_2O_6Na$ [M + Na] 477.2002, found 477.1999.

Epimerization of the Lactone 4b to 4a. To a stirred solution of the lactone **4b** (20 mg, 0.044 mmol) in toluene (2 mL) was added DBU (14 mg, 0.088 mmol). After 1.5 h at rt, all volatiles were evaporated in vacuo. Purification by silica gel column chromatography (hexanes/EtOAc 90:10 to 50:50) gave the lactone **4a** as a single diastereomer.

General Procedure for Lactone-Opening Reaction. To a stirred solution of a 1:1 mixture of the lactones **4a** and **4b** (1 equiv) in toluene (0.4 M) were added 2(1*H*)-pyridinone (1−2 equiv) and α-amino acid (2−3 equiv). The reaction mixture was heated at reflux for

5 h and cooled to rt. All volatiles were evaporated in vacuo. Purification by silica gel column chromatography (hexanes/EtOAc 65:35 to 50:50) yielded the desired product (procedure A). To a stirred solution of a 1:1 mixture of the lactone **4a** and **4b** (1 equiv) in toluene (0.4 M) was added 2(1*H*)-pyridinone (1−2 equiv). After 3 h at 130 °C, free amine (2−3 equiv) was added. The reaction mixture was heated at 130 °C for an additional 5 h and cooled to rt. All volatiles were evaporated in vacuo. Purification by silica gel column chromatography (hexanes/EtOAc 65:35 to 50:50) yielded the desired product (procedure B).

(*S*)-Methyl 2-(-2-(benzyl((benzyloxy)carbonyl)amino)-3-((*tert*-butoxycarbonyl)amino)-5-hydroxypentanamido)-4-methylpentanoate (3b). The dipeptide **3b** was synthesized using general procedure A, **3b** (22 mg, 0.036 mmol, 80%): colorless oil; TLC (hexanes/EtOAc 50:50) R_f = 0.25; $[\alpha]^{22}{}_D$ +0.9 (c = 0.6, $CHCl_3$); IR (thin film) ν_{max} = 3330 (br), 2969, 2956, 1730, 1634, 1487, 1458, 1415, 1172, 1110, 1052, 1021, 773, 741, 692 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.15−8.92 (m, 1H), 7.61−7.05 (m, 8H), 6.90 (d, J = 6.7 Hz, 2H), 6.75−6.52 (m, 1H), 5.03 (br s, 1H), 4.95 (br s, 1H), 4.73 (d, J = 5.9 Hz, 2H), 4.49−4.37 (m, 2H), 4.37−4.24 (m, 1H), 4.12−3.99 (m, 1H), 3.69−3.59 (s, 3H), 3.46 (d, J = 7.4 Hz, 2H), 1.73−1.47 (m, 5H), 1.41 (s, 9H), 0.92 (d, J = 5.9 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 185.6, 172.6, 168.6, 156.4, 155.4, 139.9, 136.5, 127.9, 127.7, 127.2, 127.0, 126.8, 126.2, 125.9, 77.7, 66.5, 61.6, 57.9, 51.9, 47.6, 47.2, 33.7, 28.1, 24.2, 22.9, 21.0; HRMS (ESI$^+$) m/z calcd for $C_{32}H_{46}N_3O_8$ [M + H] 600.3285, found 600.3288.

-Methyl 2-(2-(Benzyl((benzyloxy)carbonyl)amino)-3-((*tert*-butoxycarbonyl)amino)-5-hydroxypentanamido)-3-hydroxy-4-methylpentanoate (3g). The dipeptide **3g** was synthesized using general procedure A, **3g** (20 mg, 0.029 mmol, 65%): colorless oil; TLC (hexanes/EtOAc 50:50) R_f = 0.25; $[\alpha]^{22}{}_D$ +0.6 (c = 0.8, $CHCl_3$); IR (thin film) ν_{max} = 3350 (br), 3015, 2975, 2962, 1728, 1510, 1464, 1412, 1182, 1109, 1063, 1035, 769, 735, 687 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.42−7.28 (m, 6H), 7.28−6.86 (m, 9H), 5.17−4.85 (m, 5H), 4.76−4.53 (m, 2H), 4.44−4.26 (m, 2H), 4.01 (d, J = 5.9 Hz, 1H), 3.36 (m, 2H), 1.54 (br s, 2H), 1.34 (s, 9H), 1.24, (br s, 1H), 0.94−0.71 (m, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.3, 135.8, 128.5, 128.2, 127.9, 127.8, 127.7, 127.2, 127.1, 126.9, 125.9, 66.5, 66.4, 65.9, 58.0, 54.9, 31.3, 28.2, 28.1, 22.2, 13.9 ; HRMS (ESI$^+$) m/z calcd for $C_{38}H_{50}N_3O_9$ [M + H] 692.3547, found 692.3543.

(*S*)-*tert*-Butyl 2-(2-(Benzyl((benzyloxy)carbonyl)amino)-3-((*tert*-butoxycarbonyl)amino)-5-hydroxypentanamido)-3-phenylpropanoate (3d). The dipeptide **3d** was synthesized using general procedure A, **3d** (21 mg, 0.031 mmol, 70%): clear oil; TLC (hexanes/EtOAc 50:50) R_f = 0.25; $[\alpha]^{22}{}_D$ +0.8 (c = 0.7, $CHCl_3$); IR (thin film) ν_{max} = 3340 (br), 3004, 2969, 2964, 1732, 1642, 1630, 1485, 1474, 1412, 1171, 1118, 1063, 1037, 781, 755, 691 cm^{-1};^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.92−8.83 (m, 1H), 7.17 (dd, J = 7.0, 15.7 Hz, 13H), 6.94−6.79 (m, 2H), 6.54−6.43 (m, 1H), 5.11−4.82 (m, 3H), 4.71−4.55 (m, 2H), 4.42−4.20 (m, 3H), 4.04−3.87 (m, 2H), 3.46−3.37 (m, 1H), 3.30−3.25 (m, 1H), 3.03−2.92 (m, 1H), 2.87−2.80 (m, 1H), 1.60−1.50 (m, 1H), 1.43−1.18 (m, 18H), 1.13−1.02 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 185.6, 170.4, 170.3, 170.1, 168.3, 156.4, 155.4, 155.3, 137.1, 136.1, 127.9, 127.7, 127.4, 127.1, 126.9, 126.5, 126.2, 125.8, 80.9, 80.8, 77.6, 66.4, 61.6, 57.6, 47.7, 46.9, 37.1, 31.3, 27.6, 22.1, 13.9; HRMS (ESI$^+$) m/z calcd for $C_{38}H_{50}N_3O_8$ [M + H] 676.3598, found 676.3597.

Methyl 2-(2-(Benzyl((benzyloxy)carbonyl)amino)-3-((*tert*-butoxycarbonyl)amino)-5-hydroxypentanamido)acetate (3c). The dipeptide **3c** was synthesized using general procedure A, **3c** (20 mg, 0.036 mmol, 80%): colorless oil; TLC (hexanes/EtOAc 50:50) R_f = 0.25; $[\alpha]^{22}{}_D$ +0.8 (c = 0.8, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.55−8.38 (m, 1H), 7.45−7.01 (m, 10H), 6.52 (m, 1H), 5.05 (br s, 2H), 4.78−4.65 (m, 2H), 4.51−4.48 (m, 1H), 4.34 (s, 1H), 3.99 (d, J = 8.5 Hz, 1H), 3.70−3.66 (m, 2H), 3.61 (s, 3H), 3.36−3.25 (m, 2H), 1.48 (m, 2H), 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.6, 156.9, 137.7, 135.9, 128.6, 128.3, 127.3, 79.9, 68.3, 60.6, 58.4, 52.4, 48.7, 40.9, 36.5, 28.4; HRMS (ESI$^+$) m/z calcd for $C_{28}H_{38}N_3O_8$ [M + H] 544.2659, found 544.2657.

Benzyl (Benzyl)(1-(benzylamino)-3-((*tert*-butoxycarbonyl)-amino)-5-hydroxy-1-oxopentan-2-yl)carbamate (3e). The amide **3e** was synthesized using general procedure B, **3e** (23 mg, 0.04 mmol, 90%): white foam; TLC (hexanes/EtOAc 50:50) R_f = 0.25; $[\alpha]^{22}{}_D$ +0.4 (c = 0.3, $CHCl_3$); IR (thin film) ν_{max} = 3345 (br), 3301, 2952, 2954, 1712, 1638, 1452, 1472, 1411, 1169, 1110, 1052, 1033, 774, 748, 691 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.97 (br s, 1H), 7.48−6.81 (m, 15H), 6.62−6.52 (m, 1H), 4.98 (m, 1H), 4.91 (m, 1H), 4.68−4.62 (m, 1H), 4.58−4.51 (m, 1H), 4.47−4.34 (m, 2H), 4.20−3.97 (m, 3H), 3.49−3.34 (m, 2H), 1.61−1.46 (m, 2H), 1.34 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 185.6, 168.4, 156.3, 155.4, 139.6, 138.8, 136.4, 128.2, 128.0, 127.8, 127.5, 127.4, 127.0, 126.8, 126.1, 126.0, 77.5, 66.4, 61.7, 58.0, 47.4, 46.9, 42.1, 34.0, 31.2, 28.3, 28.2, 22.1; HRMS (ESI$^+$) m/z calcd for $C_{32}H_{40}N_3O_6$ [M + H] 562.2917, found 562.2917.

Benzyl (1-Amino-3-((*tert*-butoxycarbonyl)amino)-5-hydroxy-1-oxopentan-2-yl)(benzyl)carbamate (13a). The amide **13a** was synthesized using general procedure B, **13a** (21 mg, 0.044 mmol, 100%): white foam. Data for **13a**: TLC (hexanes/EtOAc 25:75) R_f = 0.15; $[\alpha]^{22}{}_D$ −0.3 (c 2.1, $CHCl_3$); IR (thin film) ν_{max} = 3340 (br), 3200 (br), 2963, 2932, 1683, 1498, 1454, 1406, 1367, 1255, 1169, 1123, 1054, 1028, 1005, 771, 739, 698 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.48−7.14 (m, 10H), 7.00 (br s, 1H), 6.62−6.47 (m, 1H), 5.03 (br s, 2H), 4.64 (br s, 2H), 4.48 (d, J = 16.0 Hz, 1H), 4.30 (br s, 1H), 3.98 (br s, 1H), 3.32 (br s, 2H), 1.57−1.43 (m, 2H), 1.37 (s, 9H) ; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 171.8, 170.5, 155.3, 128.7, 128.1, 128.0, 127.7, 127.6, 127.1, 126.4, 77.9, 66.6, 60.6, 57.8, 47.6, 35.0, 31.2, 28.4, 28.2, 22.1, 13.9; HRMS (ESI$^+$) m/z calcd for $C_{25}H_{33}N_3O_6Na$ [M + Na] 494.2267, found 494.2268.

Benzyl Benzyl(3-((*tert*-butoxycarbonyl)amino)-5-hydroxy-1-(octylamino)-1-oxopentan-2-yl)carbamate (3f). The amide **3f** was synthesized using general procedure B, **3f** (24 mg, 0.042 mmol, 95%): white foam; TLC (hexanes/EtOAc 50:50) R_f = 0.25; $[\alpha]^{22}{}_D$ +0.4 (c = 0.6, $CHCl_3$); IR (thin film) ν_{max} = 3355 (br), 2951, 2944, 1632, 1451, 1462, 1112, 1051, 1023, 772, 751, 695 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.45−8.34 (m, 1H), 7.53−7.28 (m, 2H), 7.19 (d, J = 7.0 Hz, 5H), 7.06 (d, J = 6.7 Hz, 2H), 6.92 (br s, 1H), 6.56−6.45 (m, 1H), 4.99 (br s, 1H), 4.93−4.85 (m, 1H), 4.66−4.57 (m, 1H), 4.51 (br s, 1H), 4.39 (d, J = 17.6 Hz, 2H), 4.07−3.95 (m, 1H), 3.39 (d, J = 5.9 Hz, 2H), 2.86 (br s, 2H), 1.56−1.42 (m, 2H), 1.34 (s, 9H), 1.30−1.16 (m, 12H), 0.88−0.83 (m, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 185.7, 168.1, 156.3, 155.4, 139.8, 136.5, 128.1, 127.7, 127.5, 127.2, 127.1, 126.9, 126.4, 126.1, 125.9, 77.6, 66.4, 61.8, 58.1, 47.3, 46.9, 31.3, 28.5, 26.4, 22.1, 13.9; HRMS (ESI$^+$) m/z calcd for $C_{33}H_{50}N_3O_6$ [M + H] 584.3700, found 584.3701.

(*S*)-*tert*-Butyl 2-(2-(Benzyl((benzyloxy)carbonyl)amino)-3-((*tert*-butoxycarbonyl)amino)-5-hydroxypentanamido)-4-methylpentanoate (3a). To a stirred solution of a 1:1 mixture of **4a** and **4b** (37.0 mg, 0.081 mmol) and 2(1*H*)-pyridinone (15.4 mg, 0.16 mmol) in toluene (0.4 mL) was added H-L-Leu-O^{t}Bu (60.0 mg, 0.413 mmol). The reaction mixture was stirred at 130 °C for 5 h and cooled to rt. Purification by silica gel column chromatography (hexanes/EtOAc 65:35 to 50:50) provided **3a** (43 mg, 0.067 mmol, 82%) as a colorless oil: TLC (hexanes/EtOAc 50:50) R_f = 0.25; $[\alpha]^{22}{}_D$ +0.8 (c = 0.5, $CHCl_3$); IR (thin film) ν_{max} = 3340 (br), 2965, 2954, 1732, 1634, 1498, 1464, 1410, 1172, 1112, 1057, 1031, 771, 745, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27−7.33 (m, 10H), 6.67 (s, 1H), 5.32 (s, 1H), 5.19 (m, 2H), 4.48−4.56 (m, 3H), 4.28 (m, 2H), 3.64 (br s, 2H), 1.75 (br s, 2H), 1.45 (s, 9H), 1.29 (m, 3H), 0.89 (br s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.5, 157.5, 156.3, 137.4, 135.9, 128.8, 128.6, 128.2, 127.9, 81.9, 79.8, 68.1, 64.7, 58.8, 51.5, 47.1, 41.4, 35.3, 28.4, 27.9, 24.9, 22.7, 22.1; HRMS (ESI$^+$) m/z calcd for $C_{35}H_{52}N_3O_8$ [M + H] 642.3754, found 642.3756.

(*S*)-*tert*-Butyl 2-((2*S*,3*S*)-5-Acetoxy-2-(benzyl((benzyloxy)-carbonyl)amino)-3-((*tert*-butoxycarbonyl)amino)-pentanamido)-4-methylpentanoate (14). To a stirred solution of the dipeptide **3a** (43 mg, 0.067 mmol) in pyridine (0.1 mL) was added acetic anhydride (0.1 mL). The reaction mixture was stirred for 6 h at rt, and all volatiles were evaporated in vacuo. Purification by silica gel column chromatography (hexanes/EtOAc 80:20 to 50:50) gave **14** (44 mg, 0.064 mmol, 95%) as a white foam: TLC (hexanes/EtOAc

50:50) R_f = 0.7; $[\alpha]^{22}_D$ +0.8 (c = 0.75, $CHCl_3$); IR (thin film) ν_{max} = 3336, 2974, 1739, 1718, 1677, 1516, 1453, 1367, 1246, 1152, 1043, 751, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.21−7.30 (m, 10H), 6.72 (s, 1H), 5.18 (s, 2H), 4.61 (d, J = 16.5 Hz, 1H), 4.48 (s, 1H), 4.42 (d, J = 11.0 Hz, 1H), 4.31(m, 1H), 4.19 (m, 2H), 4.12 (m, 2H), 2.05(s, 3H), 1.98 (m, 2H), 1.81 (m, 2H), 1.46 (m, 1H), 1.44 (s, 9H), 1.39 (s, 9H), 0.95 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.4, 171.1, 168.1, 157.5, 155.5, 137.8, 135.9, 128.5, 128.1, 127.9, 127.7, 127.3, 81.8, 79.5, 67.9, 64.3, 63.8, 61.4, 51.7, 51.4, 51.3, 50.4, 47.4, 42.1, 41.5, 30.8, 29.8, 28.4, 27.9, 24.9, 24.8, 22.8, 22.4, 22.2, 20.9; HRMS (ESI$^+$) m/z calcd for $C_{37}H_{54}N_3O_9$ [M + H] 684.3860, found 684.3863.

(*S*)-1-((1-Methoxy-3-methyl-1-oxobutan-2-yl)carbamoyl)-3-methyl-1*H*-imidazol-3-ium Iodide (15). To a stirred suspension of the HCl·H-L-Val-OH (500 mg, 2.99 mmol) in CH_2Cl_2 (0.3M) were added Et_3N (0.92 mL, 6.58 mmol) and DMAP (37 mg, 0.3 mmol), and *N,N*-carbonyldiimidazole (534 mg, 3.29 mmol) was added at 0 °C. The reaction mixture was warmed to rt and stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2, and the combined organic phase was washed with H_2O and brine and dried over Na_2SO_4. The crude material was purified by basic alumina column chromatography to give (*S*)-methyl 2-(1*H*-imidazole-1-carboxamido)-3-methylbutanoate as colorless oil (587 mg, 2.61 mmol, 87%): TLC ($CHCl_3$/MeOH 90:10) R_f = 0.25; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.19 (s, 1H), 7.43 (s 1H), 6.75 (d, J = 8.0 Hz, 1H), 4.59 (m, 1H), 3−81 (s, 3H), 2.28 (m, 1H), 1.01 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.1, 148.9, 136.1, 130.7, 115.9, 58.8, 52.6, 31.4, 18.9, 17.9; HRMS (ESI$^+$) m/z calcd for $C_{10}H_{15}N_3O_3$ 225.1113, found 225.1115.

To a stirred solution of (*S*)-methyl 2-(1*H*-imidazole-1-carboxamido)-3-methylbutanoate (587 mg, 2.61 mmol) in dry CH_3CN (13 mL) were added Et_3N (0.40 mL, 2.88 mmol) and MeI (0.18 mL, 2.88 mmol). The reaction mixture was stirred at rt for 18 h. All volatiles were evaporated in vacuo. The resulting light yellow solid **15** (959 mg) was used in the following reactions without further purification.

(2*R*,6*S*,7*S*)-Methyl 7-(2-Acetoxyethyl)-6-(((*S*)-1-*tert*-butoxy-4-methyl-1-oxopentan-2-yl)carbamoyl)-2-isopropyl-11,11-dimethyl-4,9-dioxo-10-oxa-3,5,8-triazadodecan-1-oate (16). To a stirred solution of **14** (100.0 mg, 0.15 mmol) in MeOH (30 mL) were added AcOH (20 μL) and $Pd(OH)_2$/C (25 wt % 10 mg) under N_2. H_2 gas was introduced via a double-folded balloon, and the reaction mixture was stirred for 6 h under H_2. Upon completion, the solution was filtered through Celite. The crude mixture was dissolved in EtOAc and washed with aq satd $NaHCO_3$. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to yield the desired *primary* amine. To a stirred solution of the *primary* amine in CH_2Cl_2 (0.5 mL) was added a solution of imidazolium salt **15** (2.5 equiv) in CH_3CN (0.5 mL) at rt. After 12 h, the reaction mixture was diluted with EtOAc, washed with $NaHCO_3$ (aq) and brine, and dried over Na_2SO_4. The crude material was purified by silica gel column chromatography to give **16** as white foam (79.0 mg, 0.13 mmol, 87%): TLC (hexanes/EtOAc 50:50) R_f = 0.25; $[\alpha]^{22}_D$ −2.5 (c = 0.5, $CHCl_3$); IR (thin film) ν_{max} = 3356, 2983, 1741, 1684, 1631, 1572, 1275, 1260, 764 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.82 (d, J = 8.0 Hz, 1H), 6.36 (s, 1H), 5.13 (d, J = 7.6 Hz, 1H), 5.01 (d, J = 8.0 Hz, 1H), 4.51 (m, 1H), 4.42 (m, 1H), 4.38 (m, 1H), 4.38 (m, 1H), 4.29 (m, 1H), 3.74 (s, 3H), 2.09 (m, 1H), 2.06 (s, 3H), 1.93 (d, J = 5.5 Hz, 1H), (m, 2H), 1.56−1.58 (m, 2H), 1.46 (s, 9H), 1.42 (s, 9H), 0.94 (m, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.3, 171.8, 171.5, 170.2, 157.7, 81.8, 80.1, 61.5, 58.4, 57.3, 52.1, 51.5, 50.1, 41.6, 41.2, 31.4, 28.3, 28.2, 27.9, 24.9, 24.8, 22.8, 22.7, 22.1, 21.1, 19.1, 17.9; HRMS (ESI$^+$) m/z calcd for $C_{29}H_{52}N_4O_{10}$ 616.3683, found 616.3686.

(8*S*,9*S*,13*R*)-Methyl 8-(2-Acetoxyethyl)-9-(((*S*)-1-*tert*-butoxy-4-methyl-1-oxopentan-2-yl)carbamoyl)-6-((*tert*-butoxycarbonyl)amino)-13-isopropyl-2,2-dimethyl-4,11-dioxo-3-oxa-5,7,10,12-tetraazatetradec-5-en-14-oate (17). To a stirred solution of **16** (20.0 mg, 0.033 mmol) was added cooled TFA (50% in CH_2Cl_2, 1 mL). The reaction mixture was stirred at 0 °C for 30 min, warmed to rt, diluted with CH_2Cl_2 (10 mL), and poured into $NaHCO_3$ solution. The aqueous layer was extracted with $CHCl_3$ (3×). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to provide the free amine as an oil: TLC (CH_2Cl_2/MeOH 90:10) R_f = 0.25. To a stirred solution of the free amine (15.0 mg, 0.028 mmol) in DMF (0.3 mL) were added *N,N'*-bis-*tert*-butoxycarbonyl-*S*-methylisothiourea (12.2 mg, 0.042 mmol), Et_3N (8.5 mg, 0.084 mmol), and $HgCl_2$ (11.4 mg, 0.042 mmol). The reaction mixture was stirred at rt for 14 h. Upon completion, the reaction mixture was diluted with EtOAc and filtered through Celite. The combined organic phase was washed with brine (2×), dried over Na_2SO_4, and concentrated in vacuo. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 50:50) to give **17** (13.0 mg, 0.018 mmol, 62%): TLC (hexanes/EtOAc 50:50) R_f = 0.25; $[\alpha]^{22}_D$ −3.16 (c = 0.3, $CHCl_3$); IR (thin film) ν_{max} = 3284, 2978, 1792, 1726, 1639, 1614, 1540, 1369, 1264, 1100, 1058, 737 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 11.34 (s, 1H,), 8.65 (d, J = 7.5 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 5.03 (d, J = 9.0 Hz, 1H), 4.61 (t, J = 7.0 Hz, 1H), 4.42 (m, 3H), 4.16 (m, 1H), 4.12 (m, 1H), 3.73 (s, 3H), 2.18 (s, 1H), 2.08 (m, 2H), 2.07 (s, 3H), 2.05 (m, 2H), 1.98 (m, 2H), 1.43−1.53 (m, 27H), 0.91 (m, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.3, 171.5, 171.2, 170.1, 157.9, 156.7, 152.7, 83.6, 81.4, 79.9, 61.3, 60.4, 58.1, 57.8, 51.9, 51.5, 51.4, 41.4, 31.6, 29.1, 28.4, 28.1, 27.9, 24.9, 22.9, 21.9, 20.9, 19.2, 17.9; HRMS (ESI$^+$) m/z calcd for $C_{35}H_{62}N_6O_{12}$ 758.4426, found 758.4428.

(*S*)-*tert*-Butyl 2-((*tert*-Butoxycarbonyl)imino)-4-((4*R*,8*S*,11*S*)-11-isobutyl-4-isopropyl-14,14-dimethyl-3,6,9,12-tetraoxo-2,13-dioxa-5,7,10-triazapentadecan-8-yl)-tetrahydropyrimidine-1(2*H*)-carboxylate (19). To a stirred solution of **17** (12.5 mg, 0.016 mmol) in MeOH (0.5 mL) was added $[^tBu_2Sn(OH)Cl]_2$ (0.0008 mmol). After 12 h at rt, all volatiles were evaporated in vacuo. The crude product was passed through a silica gel pad (hexanes/EtOAc 50:50) to provide the free alcohol **18** (10.0 mg, 0.014 mmol, 85%) as a white foam: TLC (hexanes/EtOAc 50:50) R_f = 0.20; $[\alpha]^{22}_D$ −2.13 (c = 0.5, $CHCl_3$); IR (thin film) ν_{max} = 3273 (br), 2929, 2927, 1732, 1645, 1556, 1430, 1369, 1264, 1210, 1155, 1050, 1075, 1020, 764, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 11.39 (s, 1H), 8.82 (d, J = 9.0 Hz, 1H), 6.56 (d, J = 9.0 Hz, 1H), 6.25 (s, 1H), 5.14 (d, J = 9.0 Hz, 1H), 4.62 (m, 1H), 4.59 (m, 1H), 4.59 (m, 2H), 4.39 (m, 1H), 3.73 (s, 3H), 3.68 (m, 1H), 3.55 (t, 1H), 2.16 (m, 1H), 1.95 (m, 1H), 1.74 (s, 9H), 1.51 (s, 9H), 1.47 (s, 9H), 0.96 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4, 172.0, 170.1, 162.6, 157.5, 156.6, 152.6, 83.6, 82.0, 79.6, 58.4, 57.9, 56.4, 52.1, 51.3, 51.1, 41.6, 34.9, 31.3, 29.7, 28.2, 28.1, 27.9, 24.8, 23.0, 21.6, 19.1, 17.9; HRMS (ESI$^+$) m/z calcd for $C_{33}H_{61}N_6O_{11}$ [M + H] 717.4398, found 717.4399. The alcohol **18** (10.0 mg, 0.014 mmol) was dissolved in THF (0.3 mL), and PPh_3 (36.7 mg, 0.14 mmol) and DIAD (28.3 mg, 0.14 mmol) were added. The reaction mixture was stirred at rt for 18 h. Upon completion, the crude mixture was concentrated in vacuo, and the crude product was purified by silica gel chromatography (hexanes/EtOAc 60:40) to yield **19** (7.0 mg, 0.011 mmol, 76%) as a colorless oil: TLC (hexanes/EtOAc 50:50) R_f = 0.30; $[\alpha]^{22}_D$ −2.15 (c = 0.1, $CHCl_3$); IR (thin film) ν_{max} = 3276, 2933, 1728, 1637, 1617, 1544, 1372, 1276, 1105, 1063, 739 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 4.63 (m, 1H), 4.55 (m, 2H), 4.33 (m, 1H), 4.21 (d, J = 5.0 Hz, 1H), 3.72 (s, 3H), 3.63 (m, 1H), 3.59 (m, 1H), 2.13 (m, 1H), 1.91 (m, 1H), 1.62 (m, 2H), 1.59 (m, 1H), 1.56 (s, 9H), 1.46 (s, 18H), 1.31 (m, 2H), 0.87−0.98 (m, 12H); ^{13}C NMR (CD_3OD, 100 MHz) δ 174.7, 173.2, 172.1, 164.1, 160.1, 158.3, 153.9, 84.8, 82.8, 80.6, 59.8, 58.9, 57.3, 52.9, 52.5, 41.5, 36.4, 32.2, 28.6, 28.3, 28.2, 25.9; HRMS (ESI$^+$) m/z calcd for $C_{33}H_{58}N_6O_{10}$ [M + H] 699.4293, found 699.4291.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes

The authors declare no competing financial interest.

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