Published in final edited form as:
J Org Chem. 2012 April 20; 77(8): 3859–3867. doi:10.1021/jo300205b.

Synthesis of Ureido-Muraymycidine Derivatives for Structure Activity Relationship Studies of Muraymycins

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Abstract

One of the key constituents of the muraymycins is the 6-membered cyclic guanidine, (*2S,3S*)-muraymycidine (or *epi*-capreomycidine). In order to diversify the structure of the oligo-peptide moiety of the muraymycins for thorough structure activity relationship studies, we have developed a highly stereoselective synthesis of ureido-muraymycidine 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 last decade a few phase clinical drugs have been developed for Gram-positive bacterial infections.[3] The ultimate goal of the development of the 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 of our interest 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 analogs for structure activity relationship studies against Gram-positive bacteria including *M. tuberculosis*, it is crucial to develop an efficient synthesis of (*2S,3S*)-2-amino-2-(2-iminohexahydropyrimidin-4-yl)acetic acid [(*2S,3S*)-muraymycidine (**a** in Figure 1)] derivative that can readily be incorporated in the syntheses

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

of muraymycin analogs. 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 (*2S,3R*)-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 (*2S,3S*)-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-(*2S,3S*)-muraymycidine derivatives (highlighted in Figure 1) *via* the optically pure diamino lactone, (*3S,4S*)-3,4-diaminotetrahydro-2H-pyran-2-one derivative (**4a**).

RESULTS AND DISCUSSION

Our synthetic strategy to efficiently synthesize ureido-(*2S,3S*)-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 (*2S,3S*)-diamino-lactone **5** and (*2R,3S*)-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(1H)-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(1H)-pyridinone, toluene at reflux). Importantly, the stereochemistry of the lactone **5** was intact and the dipeptides **8a** was not epimerized in the 2(1H)-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 (*2R,3S*)-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 (*2R,3S*)-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 benzyl amine 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 Stercker reaction of the benzyl imine **9** with TMSCN could be achieved

via a convenient hydrating 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 structures of **10b** could unequivocally be determined by extensive 2D-NMR studies of **4b** that were synthesized from **10b**.[18] With a 1 : 1 mixture of **10a** and **10b** in hand, we could establish the synthesis of **4a** in 5 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* 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 (*2R,3S*)-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 3h. 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(1H)-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(1H)-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 racemization of **4b**. In all the reactions with α-amino acids summarized in Table 2, (*2R,3S*)-diaminolactone **4b** did not react with salt free α-amino acid esters. Thus, the 2(1H)-pyridinone catalyzed epimerization of **4b** to **4a** could be completed in the presence of α-amino acid esters, and only (*2S,3S*)-diaminolactone **4a** was smoothly 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(1H)-pyridinone in toluene at reflux for 5h furnished the desired **3c** exclusively in 80% yield (conditions **B**).

Under the same conditions (*2S,3S*)-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(1H)-pyridinone in toluene at refluxing temperature. Due to the fact that the *anti*-isomer **4b** exists as a pseudo-boat conformation, thus, 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 ureido-muraymycidine 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 ureido-muraymycidine 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 (*2R,3S*)-diaminolactone **4b** can readily be epimerized to the stereoelectronically favored **4a** with 2(1H)-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(1H)-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 ureido-muraymycidine moiety of the muraymycins is an important functionality to show strong antibacterial activities.[27] Thus, the ureido-(2*S*,3*S*)-muraymycidin (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. 13C NMR spectral

data were obtained using 100 and125 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 (1M in hexanes, 19.4 mmol, 19.4 mL) was added dropwise and the reaction mixture was warmed to rt. After 1h, the reaction was cooled to 0 °C and a solution of 2*S*-[(*tert*-butyloxycarbonyl)amino]-4- butyrolactone (purchased from Aldrich, 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 6h, 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 1N 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) υ_{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.

$LiAlH_4$ (1M 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 1.5h, 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, 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 2h. 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 1h 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) υ_{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-2H-pyran-4-yl)carbamate (5)

tert-Butyl ((2*S*,3*S*)-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 24h 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) υ_{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-2H-pyran-4-yl)carbamate (6)

tert-Butyl ((2*R*,3*S*)-1-amino-2-(benzylamino)-5-hydroxy-1-oxopentan-3-yl)carbamate (30 mg, 0.089 mmol) was dissolved in toluene (2 mL). The reaction mixture was stirred at reflux for 24h 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 (15mg, 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) υ_{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((*2S*)-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. sat. $NaHCO_3$ (4 mL), and CbzCl (0.23 mL, 1.58 mmol). This reaction mixture was stirred for 1h 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) υ_{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 4h. Upon completion, the reaction was cooled to rt and all volatiles were removed. Purified by silica gel column chromatography

(hexanes:EtOAc 90:10 to 50:50) to yield **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) υ_{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) υ_{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 (1M in THF, 6.93 mL, 6.93 mmol). After 1h 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) υ_{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) υ_{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*,*4S*)- and (3*S*,*4R*)-3,4-Diaminotetrahydro-2H-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 24h 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) υ_{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) υ_{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 1.5h 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 eq.) in toluene (0.4 M) were added 2(1H)-pyridinone (1-2 eq.), and α-amino acid (2-3 eq.). The reaction mixture was heated at reflux for 5h 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 eq.) in toluene (0.4 M) was added 2(1H)-pyridinone (1-2 eq.). After 3h at 130 °C, free amine (2-3 eq.) was added. The reaction mixture was heated at 130 °C for an additional 5h 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*S*,3*S*)-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%). A colorless oil: TLC (hexanes:EtOAc 50:50): R_f = 0.25; $[\alpha]^{22}_D$ +0.9 (*c* = 0.6, $CHCl_3$); IR (thin film) υ_{max} = 3330 (br), 2969, 2956, 1730, 1634, 1487, 1458, 1415, 1172, 1110, 1052, 1021, 773, 741, 692 cm^{-1}; ^1H 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.

(2*S*,3*S*)-Methyl-2-((2*S*,3*S*)-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%). A colorless oil: TLC (hexanes:EtOAc 50:50): R_f = 0.25; $[\alpha]^{22}_D$ +0.6 (*c* = 0.8, $CHCl_3$); IR (thin film) υ_{max} = 3350 (br), 3015, 2975, 2962, 1728, 1510, 1464, 1412, 1182, 1109, 1063, 1035, 769, 735, 687 cm^{-1}; ^1H 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*S*,3*S*)-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%). A clear oil: TLC (hexanes:EtOAc 50:50): R_f = 0.25; $[\alpha]^{22}_D$ +0.8 (*c* = 0.7, $CHCl_3$); IR (thin film) υ_{max} = 3340 (br), 3004, 2969, 2964, 1732, 1642, 1630, 1485, 1474, 1412, 1171, 1118, 1063, 1037, 781, 755, 691 cm^{-1};^1H 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*S*,3*S*)-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%). A colorless oil: TLC (hexanes:EtOAc 50:50): R_f = 0.25; $[\alpha]^{22}_D$ +0.8 (*c* = 0.8, $CHCl_3$); ^1H 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((2*S*,3*S*)-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%). A white foam: TLC (hexanes:EtOAc 50:50): R_f = 0.25; $[\alpha]^{22}_D$ +0.4 (*c* = 0.3, $CHCl_3$); IR (thin film) υ_{max} = 3345 (br), 3301, 2952, 2954, 1712, 1638, 1452, 1472, 1411, 1169, 1110, 1052, 1033, 774, 748, 691 cm^{-1}; ^1H 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 ((2*S*,3*S*)-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%). A 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) υ_{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.

Benzyl-benzyl((2*S*,3*S*)-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%). A white foam: TLC (hexanes:EtOAc 50:50): R_f = 0.25; $[\alpha]^{22}_D$ +0.4 (*c* = 0.6, $CHCl_3$); IR (thin film) υ_{max} = 3355 (br), 2951, 2944, 1632, 1451, 1462, 1112, 1051, 1023, 772, 751, 695 cm^{-1}; ^1H 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*S*,3*S*)-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(1H)-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 5h 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) υ_{max} = 3340 (br), 2965, 2954, 1732, 1634, 1498, 1464, 1410, 1172, 1112, 1057, 1031, 771, 745, 697 cm^{-1}; ^1H 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 6h 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) υmax = 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)

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, 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; ^{1}H 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 18h. 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) was added AcOH (20 μL) and $Pd(OH)_2$/C (25 wt% 10 mg) under N_2. H_2 gas was introduced via double-folded balloon and the reaction mixture was stirred for 6h under H_2. Upon completion, the solution was filtered through Celite. The crude mixture was dissolved in EtOAc, and washed with aq. sat. $NaHCO_3$. 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 eq) in CH_3CN (0.5 mL) at rt. After 12h, the reaction mixture was diluted with EtOAc, and washed with $NaHCO_3$ (aq.), 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) υ_{max} = 3356, 2983, 1741, 1684, 1631, 1572, 1275, 1260, 764 cm^{-1}; ^{1}H 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'*-di-*tert*-butoxycarbonyl-*S*-methyl isothiourea (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 14h. 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) υ_{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-((*4R,8S,11S*)-11-isobutyl-4-isopropyl-14,14-dimethyl-3,6,9,12-tetraoxo-2,13-dioxa-5,7,10-triazapentadecan-8-yl)tetrahydropyrimidine-1(2H)-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 12h at rt, all volatiles were evaporated *in vacuo*. The crude product was passed through 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) υ_{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 18h. 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) υ_{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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The National Institutes of Health is greatly acknowledged for financial support of this work (AI084411-02). We also thank University of Tennessee for generous financial support. NMR data were obtained on instruments supported by the NIH Shared Instrumentation Grant.

REFERENCES AND NOTES

1. Grenet K, Guillemot D, Jarlier V, Moreau B, Dubourdieu S, Ruimy R, Armand-Lefevre L, Brau P, Andremont A. Emerg Infect Dis. 2004; 10:1150. [PubMed: 15207074]
2. Gaynes R, Edwards JR. Clin Infect Dis. 2005; 41:848. [PubMed: 16107985]
3. Sekigichi J, Fujino T, Saruto K, Kawano F, Takami J, Miyazaki H, Kuratsuji T, Yoshikura H, Kirikae T. Jpn J Infect Dis. 2003; 56:133. [PubMed: 12944686]
4. Wright GD. Science. 2007; 315:1373. [PubMed: 17347430]
5. (a) Cudic P, Behenna DC, Yu MK, Kruger RG, Szwczuk LM, McCafferty DG. Bioorg Med Chem Lett. 2001; 11:3107. [PubMed: 11720853] (b) Helm JS, Hu Y, Chen L, Gross B, Walker S. J Am Chem Soc. 2003; 125:11168. [PubMed: 16220917] (c) Bachelier A, Mayer R, Klein CD. Bioorg Med Chem Lett. 2006; 16:5605. [PubMed: 16945528] (d) Antane S, Caufield CE, Hu W, Keeney D, Labthavikul P, Morris K, Naughton SM, Petersen PJ, Rasmussenm BA, Singh G, Yang Y. Bioorg Med Chem. 2006; 16:176.(e) Taha MO, Atallah N, Al-Bakri AG, Pradis-Bleau C, Zalloum H, Yonis KS, Levesque PC. Bioorg Med Chem. 2008; 16:1218. [PubMed: 17988876] (f) Bryskier A, Dini AC. Antimicr Agents: Antibacter Antifung. 2005:377.(g) Kotnik M, Humljan J, Contreras-Martel C, Oblak M, Kristan K, Hervé M, Blanot D, Urleb U, Gobec S, Dessen A, Solmajer T. J Mol Biol. 2007; 370:107. [PubMed: 17507028] (h) Perdih A, Kovac A, Wolber G, Blanot D, Gobec S, Solmajer T. Bioorg Med Chem Lett. 2009; 19:2668. [PubMed: 19369074] (i) Humljan J, Kotnik M, Contreras-Martel C, Blanot D, Urleb U, Dessen A, Solmajer T, Gobec S. J Med Chem. 2008; 51:7486. [PubMed: 19007109]
6. Bugg TDH, Timothy DH, Lloyd AJ, Roper DI. Infect Disorders: Drug Targets. 2006; 6:85.
7. (a) Kurosu M, Mahapatra S, Narayanasamy P, Crick DC. Tetrahedron Lett. 2007; 48:799.(b) Kurosu M, Narayanasamy P, Crick DC. Heterocycles. 2007; 72:339.(c) Kurosu M, Li K. J Org Chem. 2008; 73:9767. [PubMed: 18783274] (d) Kurosu M, Li K, Crick DC. Org Lett. 2009; 11:2393. [PubMed: 19405507]
8. (a) McDonald LA, Barbieri LR, Carter GT, Lenoy E, Lotvin J, Petersen PJ, Siegel MM, Singh G, Williamson RT. J Am Chem Soc. 2002; 124:10260. [PubMed: 12197711] (b) Lin YI, Li Z, Francisco GD, McDonald LA, Davis RA, Singh G, Yang Y, Mansour TS. Bioorg Med Chem Lett. 2002; 12:2341. [PubMed: 12161129]
9. (a) Johnson AW, Bycroft BW, Cameron D. J Chem Soc C. 1971:3040.(b) Wakamiya T, Mizuno K, Ukita T, Teshima T, Shiba T. Bull Chem Soc Jpn. 1978; 51:850.(c) Shiba T, Ukita T, Mizuno K, Teshima T, Wakamiya T. Tetrahedron Lett. 1977; 18:2681.(d) Jackson MD, Gould SJ, Zabriskie TM. J Org Chem. 2002; 67:2934. [PubMed: 11975549] (e) DeMong DE, Williams RM. J Am Chem Soc. 2003; 125:8561. [PubMed: 12848564]
10. Sarabia F, Martín-Ortiz L. Tetrahedron. 2005; 61:11850.
11. (a) Tanino T, Ichikawa S, Shiro M, Matsuda A. J Org Chem. 2010; 75:1366. [PubMed: 20143822] (b) Tanino T, Ichikawa S, Matsuda A. Org Lett. 2011; 13:4028. [PubMed: 21736287]
12. The optically pure lactones **5** and **6** were synthesized via the synthetic procedures summarized in Scheme 2 with a minor modification.
13. Barrett AGM, Bezuidenhoudt BCB, Dhanak D, Gasiecki AF, Howell AR, Lee AC, Russell MA. J Org Chem. 1989; 54:3321.

14. (a) Shimizu T, Osako K, Nakata T. Tetrahedron Lett. 1997; 38:2685.(b) Ragains JR, Winkler JD. Org Lett. 2006; 8:4437. [PubMed: 16986919]
15. Herranz R, Suarez-Gea ML, Vinuesa S, Garcia-Lopez MT. J Org Chem. 1993; 58:5186.
16. Merino P, Marqués-López E, Tejero T, Herrera RP. Tetrahedron. 2009; 65:1219.
17. Zuend SJ, Coughlin MP, Lalonde MP, Jacobsen EN. Nature. 2009; 461:968. [PubMed: 19829379] Vachal P, Jacobsen EN. Org Lett. 2000; 2:867. [PubMed: 10754690] Martens J. Chem Cat Chem. 2010; 2:379. and references cited therein.
18. The NOESY correlations of one of most lower-energy conformers of **4b** are illustrated in Supporting Information
19. Kim ES, Lee HS, Kim SH, Kim JN. Tetrahedron Lett. 2010; 51:1589.
20. MM2 calculations were performed using SPARTAN on a Silicon Graphics O2 work station.
21. See Supporting Information.
22. (a) Batey RA, Santhakumar V, Yoshina-Ishii C, Taylor SD. Tetrahedron Lett. 1998; 39:6267.(b) Maresca KP, Hillier SM, Femia FJ, Keith D, Barone C, Joyal JL, Zimmerman CN, Kozikowski AP, Barrett JA, Eckelman WC, Babich JW. J Med Chem. 2009; 52:347. [PubMed: 19111054]
23. Kim KS, Qian L. Tetrahedron Lett. 1993; 34:7677.
24. Orita A, Hamada Y, Nakano T, Toyoshima S, Otera J. Chem Eur J. 2001; 7:3321. [PubMed: 11531118]
25. A limited number of examples have been found in the literature: for example, see. Fernández MM, Diez A, Rubiralta M, Montenegro E, Casamitjana N. J Org Chem. 2002; 67:7587. [PubMed: 12398477]
26. Openshaw HC, Whittaker N. J Chem Soc. 1969:89.
27. Yamashita A, Norton E, Petersen PJ, Rasmussen BA, Singh G, Yang Y, Mansour TS, Ho DM. Bioorg Med Chem Lett. 2003; 13:3345. [PubMed: 12951123]

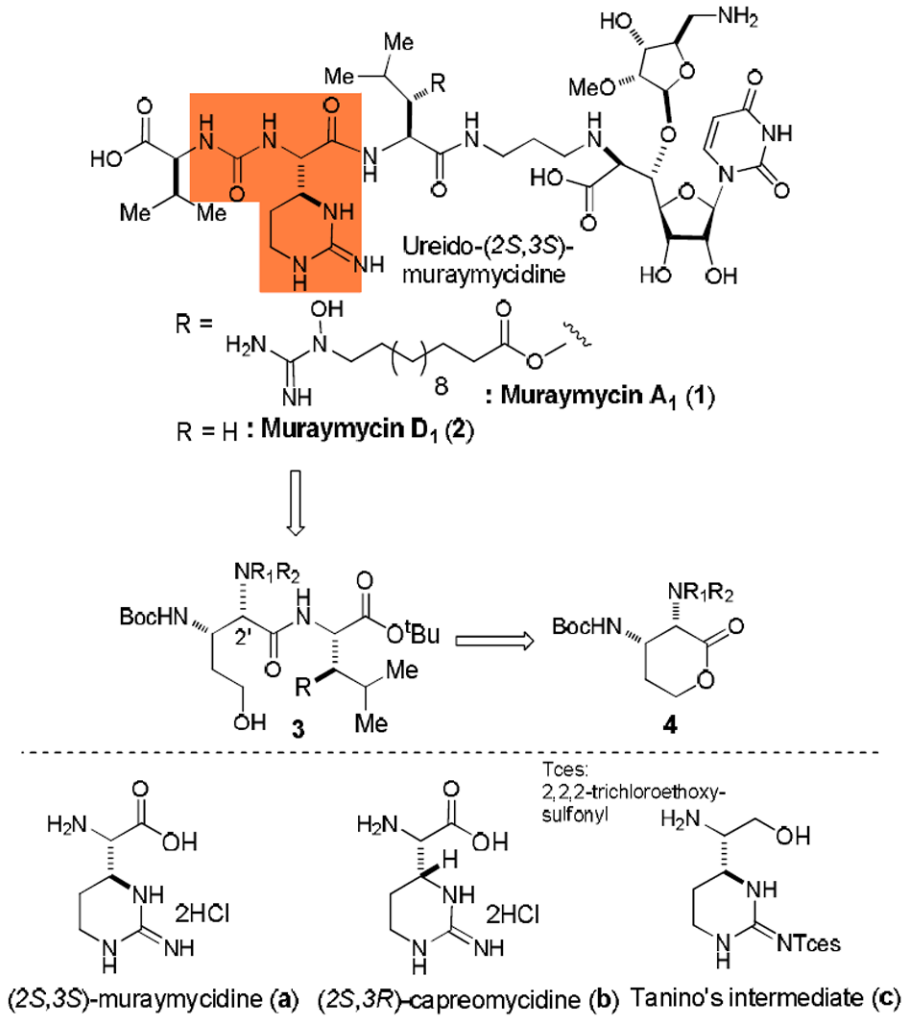
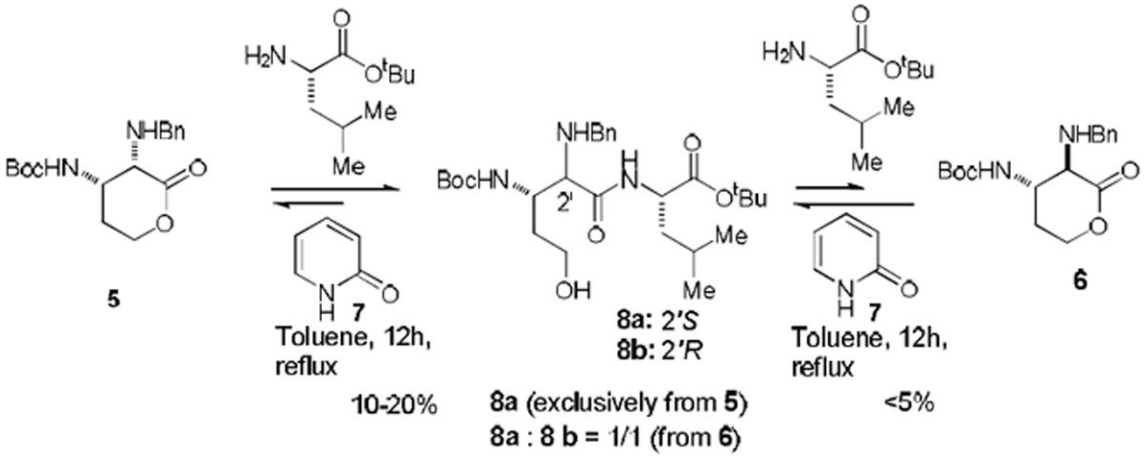
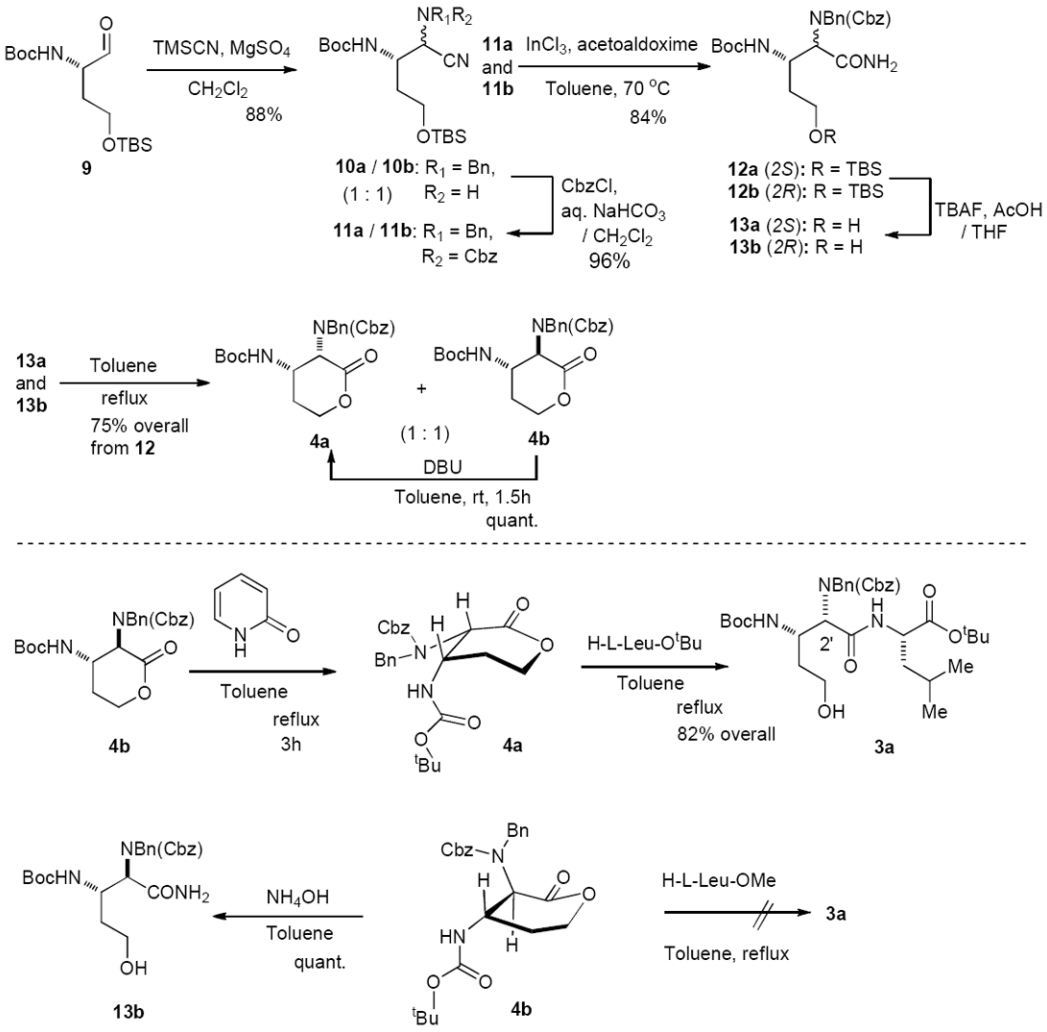


Figure 1.

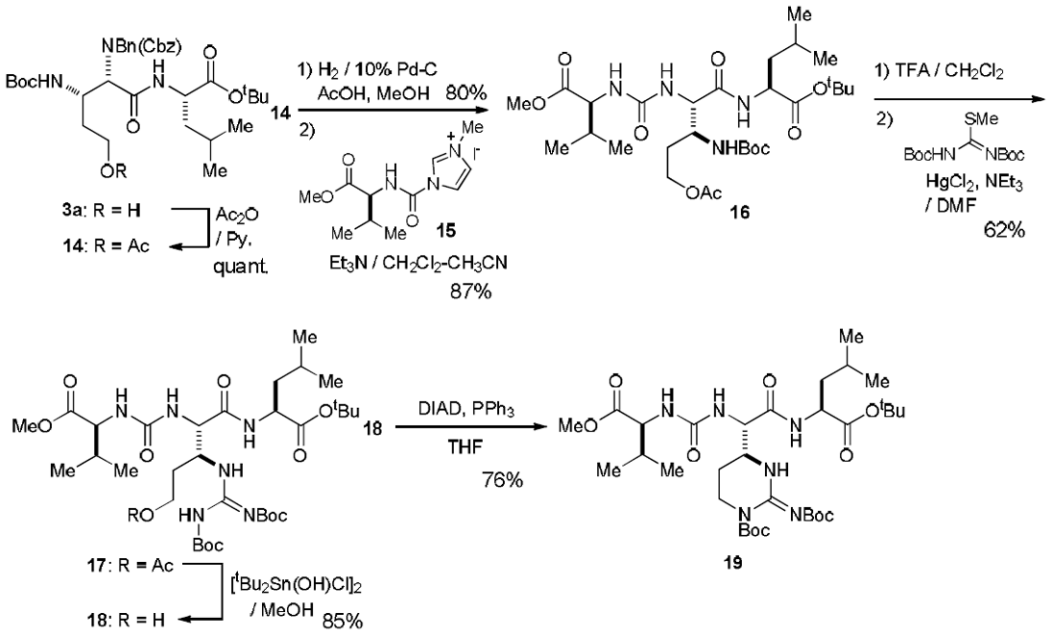


Scheme 1.
Preliminary Studies of Lactone-Opening Reactions.



Scheme 2.

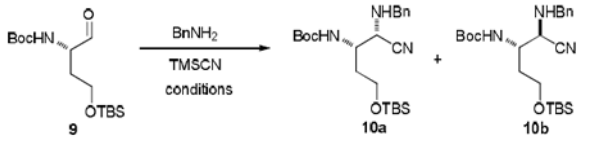
Syntheses of Lactones 4a and 4b, and Lactone-opening Reactions.



Scheme 3.
Synthesis of Ureido-Muraymycidine Tripeptide 19.

Table 1

Strecker Reactions of the α-Amino-Aldedyde 9.



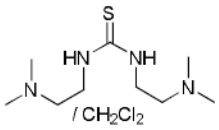
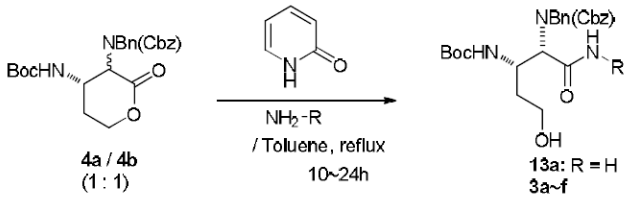
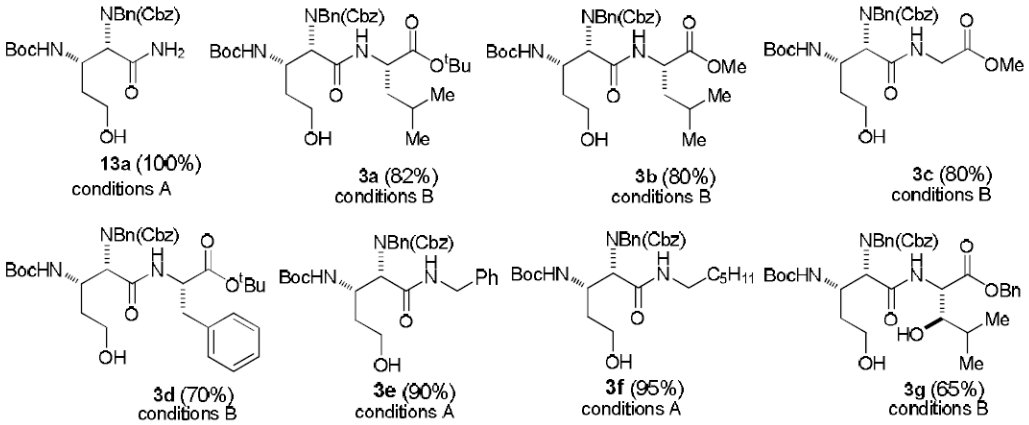
	conditions	yield(%)	selectivity (10a : 10b)
A		88	1 : 3.5
B	$Ti(OiPr)_4$, HCO_2H, H_2O / CH_2Cl_2	85	1 : 1.5
C	$MgSO_4$ / CH_2Cl_2	88	1 : 1

Table 2

Lactone-opening Reactions with Amines and α-Amino acid Esters.



Products and conditions



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