Total Syntheses of Bengamides B and E

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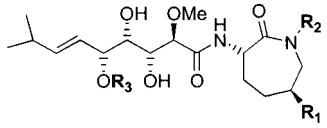
Total syntheses of the cytotoxic marine natural products bengamides B and E are described. Both bengamides are prepared via amide coupling of a protected polyhydroxylated lactone intermediate **9** with a suitably substituted aminocaprolactam intermediate. Lactone **9** is prepared in five steps from commercially available α-D-glucoheptonic γ-lactone. The key reactions are a selective deprotection of a 1,2-acetonide in the presence of a 1,3-acetonide and an (*E*)-selective olefination of an unstable aldehyde using a *gem*-dichromium reagent. The bengamide B lactam intermediate **10** is prepared in seven steps from commercially available (5*R*)-5-hydroxy-L-lysine (**12**). The desired *S*-configuration at the γ-OH lactam position is established using the Mitsunobu reaction.

Introduction

The bengamides are marine natural products first isolated by Crews et al. from Jaspidae sponges indigenous to the coral reefs that surround the Fiji islands.[1] These cyclolysine derivatives are potent antiproliferative agents against both transformed and nontransformed cells.[2] Bengamides that possess a lipophilic ester substituent on the caprolactam (e.g., bengamides A, B, M, and O) inhibit tumor cell growth at 10−100 nM (IC_{50} range) and are >100-fold more potent than their nonlactam ester-bearing counterparts (e.g., bengamides E, F, P, and Z).[3] We recently reported that bengamides B, E, and Z significantly inhibit MDA-MB-435 human breast carcinoma cells implanted as xenografts in athymic mice at well-tolerated doses.[2a] The mechanism of action of the bengamides is under investigation. To continue profiling the antitumor properties of the bengamides, additional supplies of these natural products were needed. Since a continued supply of bengamides from sponge extraction was not a practical option, we required an efficient synthesis capable of producing gram quantities of these compounds. Herein we report concise total syntheses of bengamides B and E that meet this need. Several syntheses of bengamides A, B, and E have been previously published.[4] However, all of these syntheses are long (14−15 steps for bengamide E and 30−32 steps for bengamide B) which render them impractical for preparation of grams of material.[5] The present synthesis relies on the coupling of two key intermediates: lactone **9** and aminocaprolactam **10**. Although every reported synthesis takes advantage of a similar coupling strategy, the syntheses of intermediates corresponding to **9** and **10** require a prohibitive number of protection/deprotection steps. The utilization of two commercially available natural products, α-D-glucoheptonic γ-lactone (**11**) and (5*R*)-5-hydroxy-L-lysine (**12**), makes a much shorter bengamide synthesis possible. Lactone **11** contains the same

Table 1. Representative Bengamides Isolated from Jaspidae Sponges



bengamide	R_1	R_2	R_3
A (**1**)	$O_2C(CH_2)_{12}CH_3$	H	H
B (**2**)	$O_2C(CH_2)_{12}CH_3$	Me	H
E (**3**)	H	H	H
F (**4**)	H	Me	H
M (**5**)	$O_2C(CH_2)_{11}CH(CH_3)_2$	Me	H
O (**6**)	$O_2C(CH_2)_{10}CH(CH_3)_2$	Me	H
P (**7**)	H	H	$O_2C(CH_2)_{12}CH_3$
Z (**8**)	OH	Me	H

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(5) A 10-step synthesis of bengamide E was recently reported at the 219th National ACS meeting: see Clark, T. J.; Boeckman, R. K.; Jr. *Book of Abstracts*; 219th American Chemical Society National Meeting, San Francisco, CA, Mar 26−31, 2000, Abstr ORGN-58.

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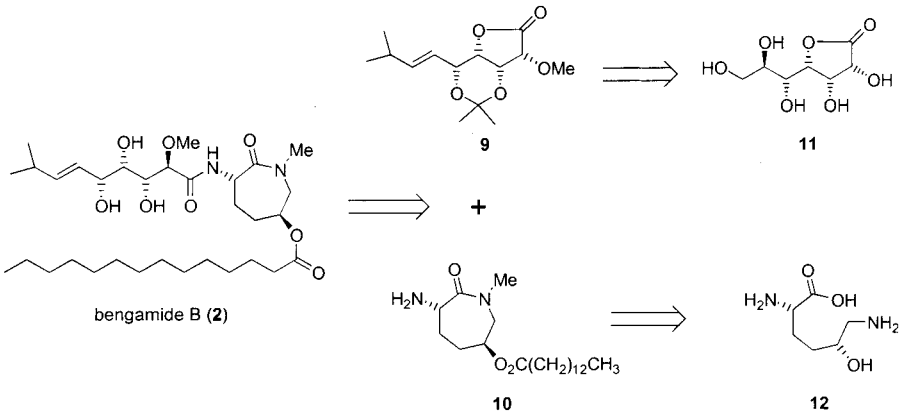
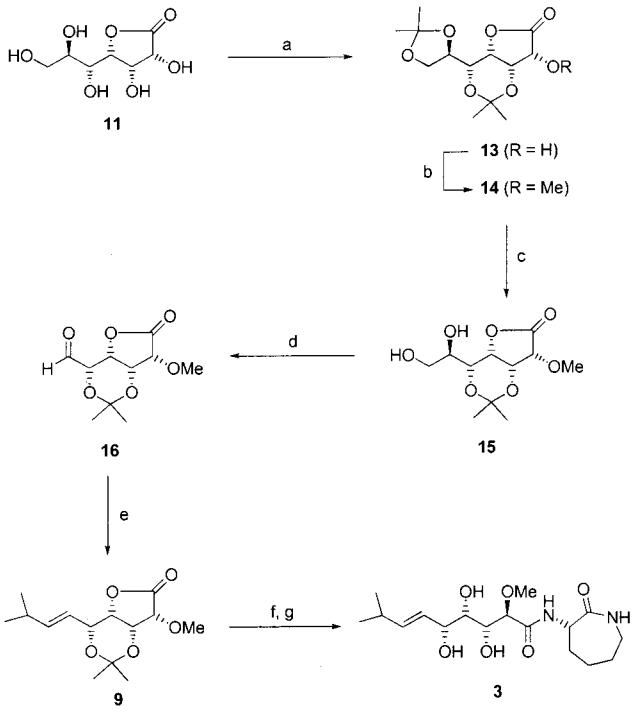


Figure 1. Retrosynthesis of bengamide B.

Scheme 1. Synthesis of Bengamide E (3)[a]



[a] Reagents: (a) acetone, cat. I_2 (86%); (b) MeI, Ag_2O (82%); (c) HOAc (68%); (d) $NaIO_4$, MeOH (85%); (e) $(CH_3)_2CHI_2$, $CrCl_2$, THF, DMF (29%); (f) L-(−)-α-amino-ϵ-caprolactam, *i*-PrOH, reflux (85%); (g) TFA, THF, H_2O (54%).

sequence of chiral hydroxy groups present on the polyhydroxylated portion common to the bengamide class. Hydroxylysine **12** contains all the functionality required to prepare bengamides that bear a caprolactam oxygen substituent. However, **12** has the opposite configuration at the γ-OH position which made an inversion reaction necessary. The retrosynthetic analysis of bengamide B in Figure 1 is representative of the present bengamide synthesis strategy.

Discussion

The synthesis of bengamide E (**3**) is outlined in Scheme 1. α-D-Glucoheptonic γ-lactone (**11**) was converted to the bis(acetonide) **13** by treatment of an acetone solution of **11** with catalytic I_2.[6] The reaction also produced approximately 10% of another bis(acetonide) that could be removed through crystallization. Methylation of the remaining unprotected hydroxyl group using Ag_2O with methyl iodide provided methyl ether **14** in 82% yield.[7] The key step in the transformation of **11** to the advanced intermediate **9** was the selective removal of the 1,2-acetonide in the presence of the 1,3-acetonide. This was accomplished by the treatment of bis(acetonide) **14** with acetic acid. The desired vicinal diol **15** was produced in 68% yield.[8] Every step up to this point did not require chromatographic purification. Oxidative cleavage of the diol with $NaIO_4$ produced aldehyde **16**. This aldehyde was prone to hydration and required repeated rotary evaporation with $CHCl_3$ or toluene to remove all traces of water. Aldehyde **16** was then olefinated with the low-valent organochromium species generated in situ from 1,1-diodoisobutane (prepared in two steps from isobutyraldehyde[9]) and $Cr(II)Cl_2$ to produce a nearly 3:1 mixture of *E* and *Z* isomers in 39% yield.[10] The desired *E* isomer, **9**, was isolated in 29% yield using preparative normal phase HPLC. None of aldehyde **16** was recoverable from the reaction mixture. Alternative olefination attempts including the Wittig reaction and the S. Julia olefination[11] produced <10% of the olefin **9**. Two steps remained in order to complete the synthesis of bengamide E. Commercially available L-(−)-α-amino-ϵ-caprolactam and lactone **9** were stirred at reflux in *i*-PrOH to give the protected bengamide E adduct in 85% yield. Finally, TFA-promoted acetonide hydrolysis produced bengamide E in 54% yield after reverse phase HPLC purification.

Once a feasible route to lactone **9** was established, the remaining challenge to produce bengamide B resided in the preparation of the substituted aminocaprolactam **10** (Scheme 2). Cyclization of (5*R*)-5-hydroxy-L-lysine (**12**) followed by *N*-Boc carbamoylation of the free amine was performed in one pot using standard peptide synthesis conditions (58% yield for two steps). The secondary alcohol was inverted using Mitsunobu conditions to give a 78% yield of *p*-NO_2-benzoate **18** in the desired *S*-configuration.[12] Selective methylation of the lactam nitrogen with MeI/NaHMDS produced lactam intermediate **19** in 83% yield. LiOH-promoted ester hydrolysis of **19** generated the corresponding alcohol **20** in 97% yield.

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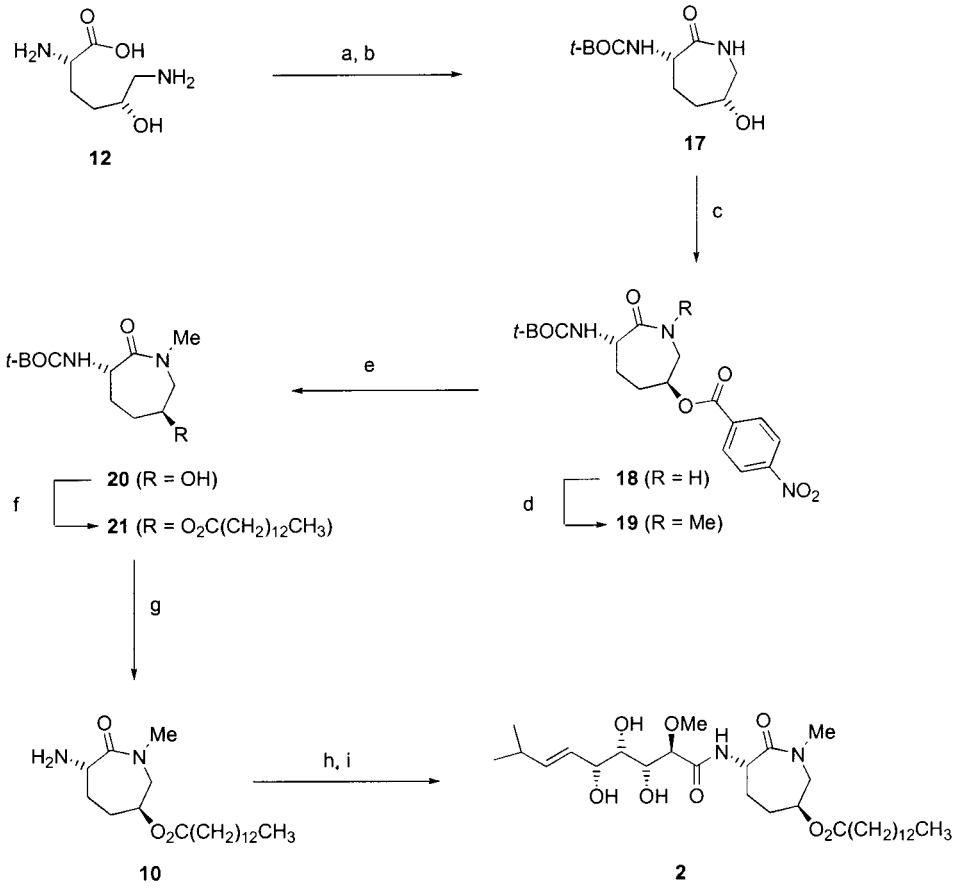
Scheme 2. Synthesis of Bengamide B (2)[a]



[a] Reagents: (a) EDCI, HOBT, DMF; (b) $(Boc)_2O$ (58% for two steps); (c) DEAD, PPh_3, *p*-nitrobenzoic acid (78%); (d) MeI, NaHMDS (83%); (e) LiOH (97%); (f) EDCI, DMAP, myristic acid (94%); (g) TFA, (99%); (h) **9**, *i*-PrOH, 80 °C; (i) TFA, THF, H_2O (61% for two steps).

Esterification of **20** with myristic acid in the presence of EDCI and DMAP produced the bengamide B lactam intermediate **21** in 94% yield. Treatment of **21** with TFA removed the BOC protecting group. Neutralization (NH_4-OH) of the crude TFA salt and chromatographic purification gave the amine **10** in 99% yield. Condensation of lactone **9** with aminocaprolactam **10** in refluxing *i*-PrOH provided the corresponding amide without competing amine attack on the acyclic ester moiety. Subsequent acetonide hydrolysis with TFA generated bengamide B (**2**) in 61% yield (two steps).

In conclusion, a synthetic route has been established that is capable of providing gram amounts of two members of the bengamide natural product class starting from two commercially available natural products. The benefits of the present synthesis are 2-fold: 1) multigram quantities of these relatively scarce natural products facilitate further biological testing in animal models, and 2) several series of bengamide analogues can be prepared through modification of both the lactone and aminocaprolactam intermediates.[13]

Experimental Section

General Methods. All chemicals were obtained from commercial suppliers and used without further purification. Flash column chromatography was performed with silica (Merck EM9385, 230−400 mesh). ^1H and ^{13}C NMR spectra were recorded at 500 or 300 and at 125 and 75 MHz, respectively, in $CDCl_3$ unless otherwise mentioned. Proton and carbon chemical shifts are expressed in ppm relative to internal tetramethylsilane, coupling constants (*J*) are expressed in hertz.

Bengamide B (2). A solution consisting of **9** (1.0 g, 3.7 mmol), **10** (1.2 g, 3.4 mmol), and *i*-PrOH (5 mL) was stirred at 80 °C for 16 h. The *i*-PrOH was removed on a rotary evaporator, and the crude product was chromatographed (2% $MeOH/CH_2Cl_2$) to yield 1.82 g (83%) of acetonide which was used directly in the next step. To the acetonide (precooled in a 0 °C bath) was added a solution of 6 mL of TFA, 6 mL of THF, and 4 mL of H_2O precooled to ca. 0 °C. The reaction was stirred at 0 °C for 20 min. The solvents were removed using a rotary evaporator under high vacuum (<5 Torr) at 0 °C. The residue was dissolved in 20 mL of MeOH and neutralized with the dropwise addition of concentrated NH_4OH at 0 °C. The solution was evaporated to dryness and chromatographed (2% $MeOH/CH_2Cl_2$). The product was further purified by preparative reverse phase HPLC (C_{18} column, isocratic 20% CH_3CN/H_2O) to yield 1.25 g (73%) of waxy white solid: α^{20}_D +63.6° (*c* 2.9, $CHCl_3$) (lit.[1a] α^{20}_D +34.6 ° (*c* 0.075, MeOH)); ^1H NMR δ 8.11 (d, J = 6.2; 1H), 5.79 (ddd, J = 15.5, 6.5, 0.9, 1H), 5.46 (ddd, J = 15.6, 7.3, 1.3, 1H), 4.65 (m, 2H), 4.28 (s, 1H), 4.22 (t, J = 6.3, 1H), 3.80 (m, 2H), 3.67 (dd, J = 14.6, 10.1, 1H), 3.60 (s, 1H), 3.55 (s, 3H), 3.22 (m, 2H), 3.11 (s, 3H), 3.07 (s, 1H), 2.31 (t, J = 7.4, 2H), 2.15 (m, 2H), 1.97 (m, 1H), 1.63 (m, 4H), 1.26 (m, 20H), 1.00 (dd, J = 6.8, 2.7, 6H), 0.88 (t, J = 6.8, 3H); ^{13}C NMR 173.02, 172.15, 171.78, 141.48, 125.40, 80.83, 74.32, 72.86, 72.33, 69.17, 60.06, 53.36, 51.33, 36.40, 34.35, 32.68, 31.92, 30.80, 29.68, 29.65, 29.60, 29.45, 29.35, 29.24, 29.10, 29.00, 24.78, 22.69, 22.22, 22.11, 14.12. Anal. Calcd for

(12) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) The Mitsunobu reaction was not attempted with myristic acid. *p*-NO_2-benzoate ester **18** was a convenient intermediate for the synthesis of bengamide B analogues.

(13) The synthesis and antitumor activity of bengamide analogues will be published elsewhere.

$C_{32}H_{58}N_2O_8$: C, 64.19; H, 9.76; N, 4.68. Found: C, 63.91; H, 9.87; N, 4.50.

Bengamide E (3). A solution of **9** (98 mg, 0.37 mmol), L-(−)-α-amino-ϵ-caprolactam (142 mg, 1.11 mmol), and *i*-PrOH (2 mL) was stirred at reflux for 18 h. The *i*-PrOH was removed on a rotary evaporator, and the crude product was chromatographed (3% MeOH/CH_2Cl_2) to yield 123.8 mg (85%) of acetonide. To 150 mg of this acetonide (precooled to 0 °C) was added a solution of TFA (3 mL), THF (3 mL), and H_2O (2 mL) precooled to 0 °C. The reaction was stirred at 0 °C for 20 min. The solvents were removed using a rotary evaporator under high vacuum (<5 Torr) at 0 °C. The residue was dissolved in MeOH (10 mL) and neutralized with concentrated NH_4OH at 0 °C. The solvents were removed using a rotary evaporator and chromatographed (3% MeOH/CH_2Cl_2). The product was further purified by preparative reverse phase HPLC (C_{18} column, isocratic 30% CH_3CN/H_2O) to yield 73 mg (54%) of **3** as a white solid: α^{20}_D +57.9° (*c* 0.75, CH_2Cl_2) (lit.[1b] α^{20}_D +36.9 ° (*c* 0.043, MeOH)); ^{1}H NMR δ 7.91 (d, J = 6.5; 1H), 6.17 (t, J = 5.7; 1H), 5.72 (ddd, J = 15.5, 6.5, and 0.8, 1H), 5.39 (ddd, J = 15.6, 7.3, and 1.4, 1H), 4.48 (ddd, J = 11.2, 6.5, and 1.3, 1H), 4.16 (t, J = 6.2, 1H), 3.76 (dd, J = 6.9 and 1.3, 1H), 3.72 (d, J = 6.9, 1H), 3.54 (d, J = 4.6, 1H), 3.47 (s, 3H), 3.22 (m, 2H), 2.25 (m, 1H), 1.99 (m, 2H), 1.78 (m, 2H), 1.51 (m, 1H), 1.36 (m, 1H), 0.94 (d, J = 2.5, 3H), 0.93 (d, J = 2.7, 3H); ^{13}C NMR δ 172.18, 169.47, 139.22, 122.79, 78.42, 71.64, 70.14, 69.82, 57.31, 49.41, 39.50, 28.42, 28.20, 26.23, 25.34, 19.52. Anal. Calcd for $C_{17}H_{30}N_2O_6$: C, 56.97; H, 8.44; N, 7.82. Found: C, 56.61; H, 8.09; N, 7.59.

(6*E*)-6,7,8,9-Tetradeoxy-8-methyl-2-*O*-methyl-3,5-*O*-(1-methylethylidene)-gulonon-6-enonic Acid Lactone (9). 15 (100 g, 0.382 mol) was dissolved into a 1:1 mixture of methanol/H_2O (2 L). The stirred mixture was cooled in an ice−water bath to about 8 °C. Solid $NaIO_4$ (98 g, 0.458 mol) was added portionwise. The reaction was complete within 40 min as indicated by TLC (silica gel, 5% MeOH/15% EtOAc/CH_2Cl_2). Solid NaCl was added into the reaction mixture to saturate the methanolic solution. The solid was filtered and washed with 2 L CH_2Cl_2. The filtrate was extracted with 3 × 200 mL CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and conentrated to a syrup, which formed a precipitate upon addition of hexane. The solid was filtered and rinsed with Et_2O. The crude product was chromatographed (3%MeOH/CH_2Cl_2) to give 75 g (85%) **16** as a white solid. This solid readily hydrated on standing. Prior to use in the next step, **16** was dissolved in $CHCl_3$ then concentrated in vacuo several times. Mp 125−127 °C; ^{1}H NMR δ 9.62 (s, 1H), 4.78 (t, J = 6, 1H), 4.46 (s, 2H), 4.15 (d, J = 6, 1H), 3.67 (s, 3H), 1.59 (s, 3H), 1.57 (s, 3H); ^{13}C NMR δ 198.8, 171.9, 99.0, 78.4, 74.4, 72.9, 68.4, 67.4, 59.2, 28.7, 19.0. To a 1 L round-bottom flask, under N_2, was added anhydrous THF (300 mL) and anhydrous DMF (13 mL). Anhydrous $CrCl_2$ (20 g, 0.16 mol) was added and stirred for 1 h. A solution of **16** (4.6 g 20 mmol) and 1,1-diiodo-2-methylpropane (12.4 g 40 mmol) in THF (200 mL) and DMF (4 mL) was added over 5 min. The resulting slurry was stirred for 1.5 h then quenched with a 100 mL solution of saturated aq NH_4Cl containing 2 g $Na_2S_2O_3$ and 10 g NH_4HCO_3 followed by solid NH_4HCO_3 (30 g). The resulting slurry was filtered through a bed of Na_2SO_4 and silica gel and evaporated to give an oil. The oil was chromatographed on silica gel (25% EtOAc/CH_2Cl_2) to give 2.1 g (39%) of a mixture of **9** and the corresponding *Z* isomer. The mixture was purified by preparative normal phase HPLC (silica column, isocratic 50% EtOAc/hexane) to give 1.54 g (28.5%) of **9** as a white solid: $[\alpha]^{25}_D$ −132.7 ° (*c* 1.036 $CHCl_3$); ^{1}H NMR δ 5.85 (dd, J = 15.6 and 6.2, 1H), 5.64 (ddd, J = 15.6, 7.5, and 1.3, 1H), 4.74 (dd, J = 3.8 and 2.1, 1H), 4.48 (dd, J = 7.5 and 1.8, 1H), 4.12 (d, J = 3.9, 1H), 4.02 (t, J = 2.0, 1H), 3.68 (s, 3H), 2.36 (m, 1H), 1.56 (s, 3H), 1.51 (s, 3H), 1.04 (d, J = 1.9, 3H), 1.03 (d, J = 1.9, 3H); ^{13}C NMR δ 172.8, 143.2, 122.0, 98.7, 79.0, 71.7, 70.0, 67.6, 59.2, 30.7, 29.2, 21.9, 21.8, 19.2. HRMS calcd for $C_{14}H_{22}O_5Na$ (M+Na)$^+$ 293.1365, found 293.1355.

(3*S*,6*S*)-3-Aminohexahydro-6-(tridecylcarbonyl)oxy-2*H*-azepin-2-one (10). A solution of **20** (3.6 g, 7.7 mmol), TFA (5 mL), and CH_2Cl_2 (10 mL) was stirred at 25 °C for 2 h. The reaction mixture was concentrated in vacuo. The residue was dissolved in 100 mL of CH_3CN and neutralized with NH_4OH. The solution was conentrated using a rotary evaporator and chromatographed (2.5% MeOH/CH_2Cl_2) to yield 2.8 g (99%) of **10** as a white solid. ^{1}H NMR δ 5.69 (s, 2H), 4.61 (t, J = 9.4,-1H), 4.13 (d, J = 10.9, 1H), 3.64 (dd, J = 10.2 and 14.7, 1H), 3.20 (d, J = 14.7, 1H), 3.06 (s, 3H), 2.30 (t, J = 7.5, 2H), 2.14 (m, 2H), 1.83 (m, 2H), 1.61 (t, J = 6.8, 2H), 1.26 (m, 20H), 0.88 (t, J = 6.8, 3H); ^{13}C NMR 179.87, 179.52, 76.06, 60.03, 59.68, 43.32, 41.26, 39.27, 38.85, 36.57, 36.37, 35.39, 31.77, 29.61, 21.06. HRMS calc. for $C_{21}H_{40}N_2O_3Na$ (M + Na)$^+$ 391.2936, found 391.2926.

3,5:6,7-Bis-*O*-(1-methylethylidene)-α-D-glucoheptonic γ-Lactone (13). α-D-Glucoheptonic γ-lactone (**11**) (500 g, 2.4 mol) was added into 9 L of acetone in a 5 gal plastic drum. The mixture was agitated mechanically until most of the solid dissolved (15−20 min). Iodine (60 g, 0.236 mol) was added portionwise to the lactone solution over 5−10 min. The resulting mixture was stirred overnight. A saturated solution of $Na_2S_2O_3$ (1.3 L) was added to the iodine solution to quench the reaction. The resulting solution was conentrated to about half of its original volume in vacuo, and brine solution (5 L) was added. The resulting mixture was extracted with 3 × 1.2 L EtOAc. All organic layers were combined and evaporated to dryness. The solid was slurried with a mixture of ether and hexane (3:7), and filtered. The filter cake was washed with Et_2O (50 mL) and air-dried to produce 599 g of the desired compound as a white powder (86.5%): mp 150−152 °C (lit.[14] mp 153−154 °C), ^{1}H NMR δ 4.62 (m, 1H), 4.50 (m, 1H), 4.35 (m, 2H), 4.07 (m, 1H), 3.93 (m, 1H), 3.82 (dd, J = 4.0 and 8.9, 1H), 3.08 (dd, J = 2.0 and 8.5, 1H), 1.51 (s, 3H), 1.44 (s, 3H), 1.39 (s, 3H), 1.35 (s, 3H); ^{13}C NMR δ 174.4, 109.4, 98.6, 72.8, 71.4, 69.3, 68.4, 67.8, 66.7, 28.6, 26.7, 24.6, 19.3.

2-*O*-Methyl-3,5:6,7-bis-*O*-(1-methylethylidene)-α-D-glucoheptonic γ-Lactone (14). 13 (719 g, 2.49 mol) was added into 4.5 L of CH_2Cl_2 in a 5 gal plastic drum. The mixture was stirred under N_2. Iodomethane (2500 g, 17.6 mol) was added immediately followed by addition of silver(I) oxide (1750 g, 7.58 mol). H_2O (30 mL) was added to the reaction mixture. An ice bath was used to maintain the reaction temperature at 15−30 °C. The reaction was stirred in the absence of light for 18 h. After diluting the reaction mixture with 1.5 L of CH_2Cl_2, the solid was filtered and washed with an additional 2.2 L of CH_2Cl_2. The undesired solid was discarded, and the filtrate was evaporated to dryness. The residue was slurried in Et_2O (1.5 L), filtered, and dried to give 618 g of product (82%): mp 139−141 °C; ^{1}H NMR δ 4.70 (dd, J = 5 and 6, 1H), 4.35 (m, 1H); 4.27 (s, 1H) 1.35 (s, 3H), 4.13 (d, J = 5, 1H), 4.10 (d, J = 6, 1 H), 3.92 (dd, J = 4.5 and 9, 1H), 3.82 (dd, J = 2 and 9, 1H), 3.65 (s, 3H), 1.48 (s, 3H), 1.42 (s,6 H); ^{13}C NMR δ 172.5, 109.6, 98.5, 79.0, 73.1, 69.5, 68.6, 67.5, 66.9, 59.1, 28.9, 26.9, 24.9, 19.4. HRMS calcd for $C_{14}H_{22}O_7Na$ (M + Na)$^+$ 325.1258, found 325.1264.

2-*O*-Methyl-3,5-*O*-(1-methylethylidene)-α-D-glucoheptonic γ-Lactone (15). 14 (618 g, 2.05 mol) was dissolved in 8 L of a mixture of HOAc and H_2O (1:1) over 30 min. The solution was stirred at ambient temperature overnight. The solution was evaporated to dryness in vacuo. The solid was slurried in 3−5 L of hot acetone and filtered. After oven drying at 20−30 °C, 363 g of the desired compound was obtained (67.6%): mp 177−178 °C; ^{1}H NMR δ 4.92 (bt, 1H), 4.80 (dd, J = 2 and 4, 1H), 4.50 (d, J = 5.5, 1H), 4.42 (bd, 1H), 4.38 (s, 1H), 3.95 (dd, J = 2 and 9, 1H), 3.55 (bdd, J = 2 and 9, 2H), 3.42 (s, 3H), 3.38 (m, 1H), 1.42 (s, 3H), 1.22 (s, 3H); ^{13}C NMR δ 173.3, 97.5, 78.3, 68.8, 68.5, 67.2, 67.1, 62.2, 57.4, 28.9, 19.2. Anal. Calcd for $C_{11}H_{18}O_7$: C, 50.38; H, 6.92. Found: C, 50.14; H, 6.91.

(3*S*,6*R*)-3-(*tert*-Butoxycarbonyl)aminohexahydro-6-hydroxy-2*H*-azepin-2-one (17). (5*R*)-5-Hydroxy-L-lysine (**12**) (10 g, 0.040 mol), 1-hydroxybenzotriazole hydrate (8.2 g, 0.060 mol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide·HCl (EDCI) (11.6 g, 0.060 mol) were added sequentially to 500 mL of DMF with stirring. After 0.5 h, Et_3N (16.8 mL, 0.120

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mol) was added. The reaction was stirred at 25 °C for 48 h. Di-*tert*-butyl dicarbonate (17.6 g, 0.080 mol) and Et_3N (16.8 mL, 0.120 mol) were then sequentially added. Stirring was continued for 16 h. The reaction mixture was filtered to remove Et_3N-HCl, and the solvent was removed by rotary evaporation under high vacuum to give a thick oil. The oil was dissolved in 150 mL of CH_2Cl_2 and applied to a silica gel column (150 g, 40 × 250 mm). The column was eluted with 3% MeOH/CH_2Cl_2 to give the crude product as a solid. The crude solid was dissolved in 120 mL of CH_2Cl_2 with heating and then cooled to −20 °C for 1 h. The resulting solid was filtered and washed with 50 mL of CH_2Cl_2. The combined filtrates were evaporated to dryness. CH_2Cl_2 (40 mL) was added to this residue, and the resulting slurry was stirred for 0.5 h at 25 °C. The slurry was filtered and the solid washed with 25 mL of CH_2Cl_2. The solids were combined to give 5.57 g (58%) of **17**: ^{1}H NMR (d_6-DMSO) δ 7.42 (t, J = 5.1, 1H), 6.38 (d, J = 6.6, 1H), 4.60 (d, J = 4.2, 1H), 4.07 (m, 1H), 3.74 (m, 1H), 3.32 (m, 1H), 3.03 (m, 1H), 1.8−1.5 (m, 4H), 1.39 (s, 9H); ^{13}C NMR (d_6-DMSO) δ 173.8, 154.5, 77.9, 63.7, 52.4, 45.1, 34.2, 28.1, 24.9. Anal. Calcd for $C_{11}H_{20}N_2O_4$: C, 54.08; H, 8.25; N, 11.47. Found: C, 54.06; H, 8.11; N, 11.41.

(3*S*,6*S*)-3-(*tert*-Butoxycarbonyl)aminohexahydro-6-(4-nitrophenylcarbonyl)oxy-2*H*-azepin-2-one (18). To a 500 mL flask were added **17** (6 g, 0.025 mol), 4-nitrobenzoic acid (8.25 g, 0.05 mol), and triphenylphosphine (12.9 g, 0.05 mol). The flask was purged with N_2, and 200 mL of freshly distilled THF (Na metal) was added. The mixture was cooled in a −20 °C bath, and diethyl azodicarboxylate (7.8 mL, 0.05 mol) was added at a rate to maintain ≤10 °C. The reaction was allowed to warm to room temperature (~2 h) and stirred for 14 h. The solvent was evaporated, and the residue dissolved in 200 mL of EtOAc. This was washed with 5% $NaHCO_3$ (3 × 150 mL) and brine (1 × 150 mL) and then dried with Na_2SO_4 and evaporated to give an oil. To this oil was added 100 mL of ether. The resulting solid was filtered and washed with ether (3 × 50 mL), acetone (2 × 50 mL), and MeOH (2 × 50 mL) to give 6.2 g of **18**. The combined filtrate and washes were evaporated, and the residue was chromatographed on a silica gel column with CH_2Cl_2:hexane (1:1) and then ether to give 1.34 g of **18** for a combined yield of 7.54 g (78%): ^{1}H NMR δ 8.29 (d, J = 8.4, 1H), 8.18 (d, J = 8.4, 2H), 6.44 (m, 1H), 5.90 (d, J = 5.7, 1H), 4.91 (m, 1H), 4.42 (m, 1H), 3.58−3.41 (m, 2H), 2.36−2.25 (m, 2H), 2.16−2.03 (m, 1H), 1.82−1.65 (m, 1H), 1.45 (s, 9H); ^{13}C NMR δ 174.9, 163.6, 155.2, 150.8, 134.9, 130.8, 123.6, 79.8, 72.8, 52.8, 45.0, 33.0, 29.8, 28.4. Anal. Calcd for $C_{18}H_{23}N_3O_7$: C, 54.96; H, 5.86; N, 10.68. Found: 54.97; H, 5.88; N, 10.60.

(3*S*,6*S*)-1-Methyl-3-(*tert*-Butoxycarbonyl)aminohexahydro-6-(4-nitrophenylcarbonyl)oxy-2*H*-azepin-2-one (19). To a solution of **17** (5.0 g, 12.7 mmol) and THF (50 mL) at −7 °C was added KHMDS (15.3 mL, 15.3 mmol, 1 M solution in THF) within 5 min. After the mixture was stirred at −78 °C for 30 min, MeI (3.6 g, 25 mmol) was added dropwise to the reaction mixture. The reaction was stirred at 25 °C for 18 h. The reaction was quenched with 50 mL of H_2O. The mixture was extracted with 2 × 100 mL of EtOAc. The organic layers were dried over Na_2SO_4, conentrated, and chromatographed (40% EtOAc/hexane) to yield 4.3 g (83.0%) of **19** as a white solid: ^{1}H NMR δ 8.31 (d, J = 9.1, 2H), 8.20 (d, J = 8.7, 2H), 6.00 (d, J = 5.7, 1H), 4.88 (t, J = 10.6, 1H), 4.50 (dd, J = 6.0 and 10.2, 1H), 3.82 (dd, J = 9.8 and 17.7, 1H), 3.38 (d, J = 14.7, 1H), 3.15 (s, 3H), 2.21 (m, 3H), 1.68 (m, 1H), 1.46 (s, 9H); ^{13}C NMR δ 172.94, 164.16, 155.59, 151.18, 135.37, 131.19, 124.05, 80.06, 71.59, 53.66, 52.99, 36.76, 33.15, 30.38, 28.78. HRMS calcd for $C_{19}H_{25}N_3O_7Na$ $(M + Na)^+$ 430.1585, found 430.1597.

(3*S*,6*S*)-1-Methyl-3-(*tert*-butoxycarbonyl)aminohexahydro-6-hydroxy-2*H*-azepin-2-one (20). To a solution of **19** (4.1 g, 9.8 mmol), MeOH (40 mL), and H_2O (10 mL) was added LiOH/H_2O (0.83 g, 20 mmol) at 25 °C. After being stirred at this temperature for 1h, the reaction was quenched with dry ice (CO_2) and evaporated to dryness. To the residue was added a solution consisting of CH_2Cl_2 (45 mL) and MeOH (5 mL). The solution was filtered through Celite. The filtrate was evaporated to dryness and chromatographed (10% EtOAc/CH_2Cl_2) to yield 2.52 g (97.0%) of **20** as a white solid: ^{1}H NMR δ 6.00 (d, J = 5.6, 1H), 4.38 (dd, J = 6.4 and 10.2, 1H), 3.61 (m, 2H), 3.21 (dd, J = 1.9 and 12.4, 1H), 3.06 (s, 3H), 2.66 (d, J = 4.5, 1H), 2.21 (d, J = 12.4, 1H), 2.08 (d, J = 14.3, 1H), 1.82 (m, 1H), 1.60 (td, J = 2.3 and 13.9,1H), 1.44(s, 9H); ^{13}C NMR δ 174.53, 157.04, 81.46, 69.80, 58.37, 54.63, 38.78, 38 41, 32.14, 30.21. HRMS calcd for $C_{12}H_{22}N_2O_4Na$ $(M+Na)^+$ 281.1472, found 281.1475.

(3*S*,6*S*)-1-Methyl-3-(*tert*-butoxycarbonyl)aminohexahydro-6-(tridecylcarbonyl)oxy-2*H*-azepin-2-one (21). To a solution of myristic acid (2.97 g, 13.0 mmol) and CH_2Cl_2 (50 mL) were added EDCI (2.62 g, 13.65 mmol) and DMAP (1.67 g, 13.65 mmol) at 25 °C. After being stirred at 25 °C for 30 min, a solution of **19** (2.4 g, 9.3 mmol) and CH_2Cl_2 (50 mL) was added portionwise. The reaction was stirred for 16 h at 25 °C. After being stirred, the reaction was quenched with 50 mL of H_2O. The mixture was extracted with EtOAc (2 × 100 mL). The organic layers were dried (Na_2SO_4), conentrated, and chromatographed (2.5% EtOAc/CH_2Cl_2) to yield 4.1 g (94.2%) of **21** as a white solid: ^{1}H NMR δ 5.97 (d, J = 5.6, 1H), 4.60 (tt, J = 3.4 and 10.6, 1H), 4.43 (dd, J = 6.0 and 10.6, 1H), 3.63 (dd, J = 10.2 and 14.7, 1H), 3.20 (d, J = 14.7, 1H), 3.24 (s, 3H), 2.30 (t, J = 7.5, 2H), 2.13 (d, J = 10.6, 2H), 1.92 (m, 1H), 1.61 (m, 3H), 1.45 (s, 9H), 0.93 (m, 20H), 0.88 (t, J = 6.4, 3H); ^{13}C NMR ($CDCl_3$) δ 173.42, 172.98, 155.58, 79.94, 69.75, 53.79, 53.00, 36.68, 34.73, 33.23, 32.30, 30.49, 30.02, 29.98, 29.83, 29.73, 29.62, 29.47, 28.78, 25.25, 23.07,14.50. HRMS calcd for $C_{26}H_{48}N_2O_5Na$ $(M + Na)^+$ 491.3455, found 491.3470.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of **9**, **14**, **19**, **20**, and **21** are available free of charge via the Internet at http://pubs.acs.org.

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