Stereoselective Synthesis of Protected (2 R ,3 R ,4 S)-4,7-Diamino-2,3-dihydroxyheptanoic Acid: A Novel Amino Acid of Callipeltins A and D

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Stereoselective Synthesis of Protected (2*R*,3*R*,4*S*)-4,7-Diamino-2,3-dihydroxyheptanoic Acid: A Novel Amino Acid of Callipeltins A and D

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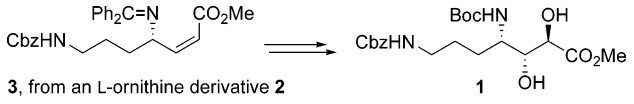

10 steps in 30% overall yield with >13:1 selectivity

An orthogonally protected derivative **1** of (2*R*,3*R*,4*S*)-4,7-diamino-2,3-dihydroxyheptanoic acid, the unusual amino acid residue of the biologically active marine peptides such as callipeltins A and D and neamphamide A, was efficiently prepared in 10 steps and 30% overall yield from a commercially available L-ornithine derivative **2**. The key step includes the *N*-diphenylmethylene-controlled diastereoselective dihydroxylation of (*Z*)-ester **3** with >13:1 selectivity for the desired isomer.

A novel cyclic depsipeptide callipeltin A was first isolated from the marine sponge *Callipelta* sp. by Minale and co-workers (Figure 1).[1] It showed some interesting biological activities such as antifungal and anti-HIV activities as well as cytotoxicity against several human carcinoma cell lines.[2] It was also shown to be a selective and powerful inhibitor of the Na^+/Ca^{2+} cardiac exchanger and a positive inotropic agent in guinea pig atria.[3] Later, callipeltin D, a truncated open-chain derivative of callipeltin A, was also isolated from *Latrunculia* sp. (Figure 1).[4]

Callipeltins A and D consist of the novel amino acid and fatty acid residues whose structures were confirmed by NMR studies, molecular mechanics calculations, and degradation studies. Recently, the syntheses of these residues have been reported in efforts toward the total synthesis of callipeltin A.[5,6] Among them, (2*R*,3*R*,4*S*)-4,7-diamino-2,3-dihydroxyheptanoic acid (DADHA) with a vicinal amino diol moiety is a key component of callipeltins A and D (Figure 1). This unusual

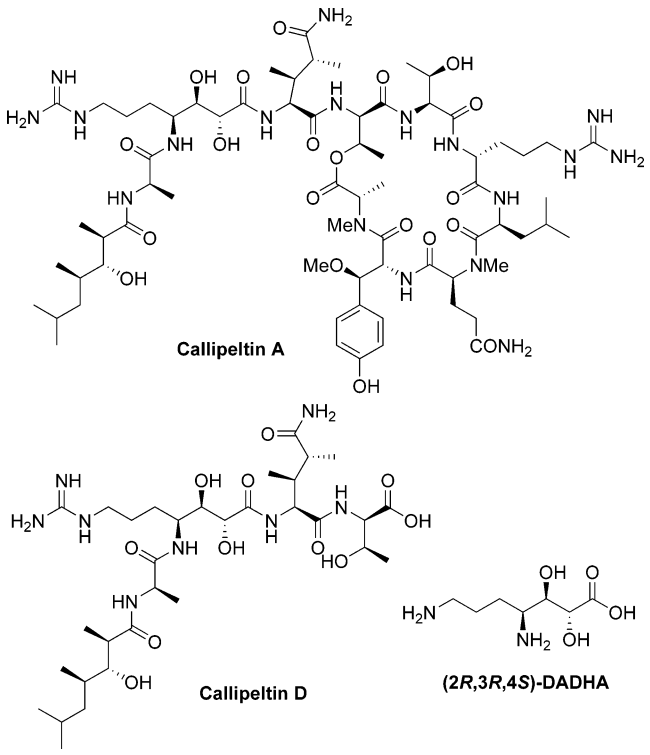

FIGURE 1. Callipeltins A and D and DADHA.

structure is also found in a recently isolated marine natural product, neamphamide A.[7]

Although it has a unique structure and is a common component in some biologically active natural products, there have been only three synthetic reports to date. The two synthetic methods using D-ribose and D-glucose as chiral templates have been published by the same group.[5c,j] Their syntheses involved a number of steps with a low yield. Lipton and co-workers reported the first synthesis of its guanide derivative via the dihydroxylation reaction of the γ-amino-α,β-unsaturated (*Z*)-ester in a respectable yield.[5h] However, the stereoselectivity of

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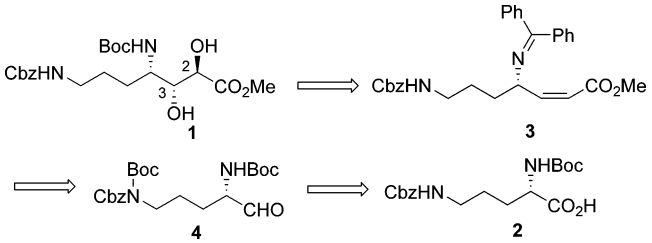
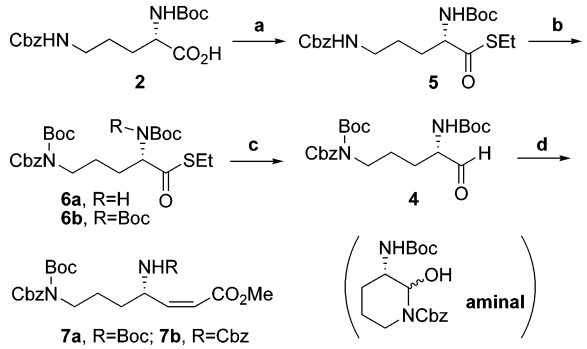
SCHEME 1. Retrosynthetic Analysis of 1



SCHEME 2. Preparation of (*Z*)-Ester 7a[a]



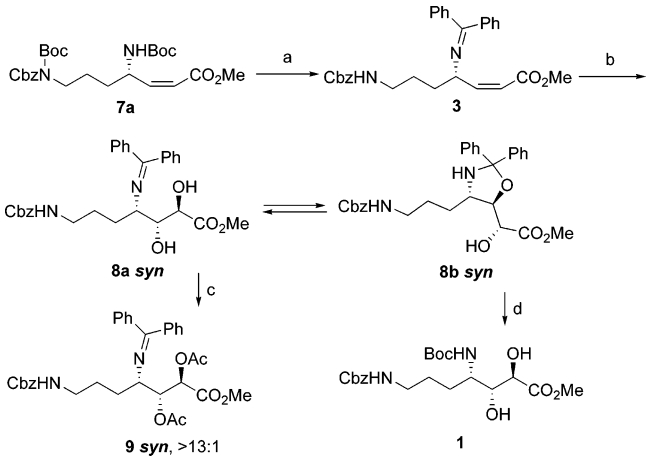
[a] Reagents and conditions: (a) (i) isobutyl chloroformate, TEA, DME, 0 °C; (ii) EtSH, TEA, 0 °C, quantitative (from **2**); (b) Boc_2O, DMAP, TEA, MeCN, rt, 68% for **6a**, 21% for **6b**; (c) 10% Pd−C, Et_3SiH, $MgSO_4$, acetone, rt; (d) KHMDS, THF, 18-crown-6, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, −78 °C, 82% for **7a** (from **6a**).

the key dihydroxylation reaction of the (*Z*)-ester was poor for the desired isomer. We wish to report here an efficient and stereoselective synthetic route for an orthogonally protected (2*R*,3*R*,4*S*)-DADHA derivative (**1**) using the syn-selective osmium-catalyzed dihydroxylation reaction of γ-amino-α,β-unsaturated (*Z*)-esters that has been recently described by us.[8]

Scheme 1 shows our retrosynthetic analysis for the target compound **1**. The 2,3-dihydroxyl functionality of **1** with the desired configuration could be established by the syn-selective OsO_4-catalyzed dihydroxylation reaction of α,β-unsaturated (*Z*)-ester **3** that would be derived in turn from the corresponding properly protected α-amino aldehyde **4**.[8] The fully protected terminal amino group of **4** seemed necessary for a successful *Z*-selective Still olefination reaction.[5h,9] We planned to obtain **4** from commercially available N^{δ}-Cbz-N^{α}-Boc-L-ornithine (**2**).

The synthetic steps for suitably protected γ-amino-α,β-unsaturated (*Z*)-ester **7a** are shown in Scheme 2. The required aldehyde precursor **4** for **7a** was made efficiently from **2** according to the Fukuyama's protocol.[10] However, the terminal amino group of thioester **5** that was obtained in a quantitative yield from the commercially available L-ornithine derivative **2** should be further protected with a Boc group to prevent formation of the aminal (Scheme 2) that has been known to be unreactive toward certain nucleophiles such as an enolate[9] or an ylide.[5h] In this process, a significant amount of the diBoc-protected derivative at the internal amino group (**6b**) was also produced. The best result for **6a** was obtained with 1.5 equiv

SCHEME 3. Stereoselective Dihydroxylation toward the Target Compound 1[a]



[a] Reagents and conditions: (a) (i) AcCl, MeOH, 0 °C to rt, (ii) benzophenone imine, DCM, rt, 92%; (b) cat. OsO_4, NMO, THF−H_2O, rt; 90%; (c) Ac_2O, TEA, DMAP, DCM, rt, 94%; (d) (i) TFA, aq THF, rt, (ii) Boc_2O, $NaHCO_3$, THF−H_2O, 65%.

of Boc_2O, 0.1 equiv of DMAP, and 2 equiv of Et_3N. Compound **6b** was very slow under the Fukuyama conditions, but it can be recycled to thioester **5** after separation from **6a**. Compound **6a** was then subjected to the Fukuyama conditions to give aldehyde **4** as a crude product. The use of 2.0 equiv of $MgSO_4$ and more than 0.5 M of the thioester in acetone was the optimal condition.[10b] The crude aldehyde **4** was used without purification for the next step to minimize the possible racemization of the unstable α-amino aldehyde.[11] The *Z*-selective olefination under the Still conditions resulted in the desired γ-amino-α,β-unsaturated (*Z*)-ester **7a** as a major product in a ratio of more than 16:1.[12]

The *N*-diphenylmethylene group that is necessary for the syn-selective dihydroxylation reaction of **3** could be easily introduced by a transimination reaction between benzophenone imine and the HCl salt of the *N*-deprotected product of **7a** (Scheme 3).[13] In the hydrolysis step, the two Boc groups of **7a** were selectively removed with HCl in MeOH at 0 °C in the presence of both the ester and the Cbz groups. Then, the dihydroxylation of **3** produced diol **8** in 90% yield under the typical OsO_4-catalyzed reaction conditions. It was difficult to determine the correct diastereomeric ratio of **8** because of the facile isomerism between ketimine diol **8a** and oxazolidine **8b**.[14] Thus, the two hydroxyl groups of **8a** were acetylated in excellent yield to afford diacetate **9** of which diastereomeric ratio was determined to be >13:1 by ^1H NMR for the desired syn isomer (see below). It indicates that the *N*-diphenylmethylene-controlled dihydroxylation reaction of **3** has resulted in the desired configuration of **8a** with a similar selectivity. For comparison, the same dihydroxylation reaction of N^{α}-Cbz-protected (*Z*)-ester **7b** (Scheme 2) resulted in an ~1:1 mixture of the diastereomeric diols.[15] Compound **7b** was prepared from commercially avail-

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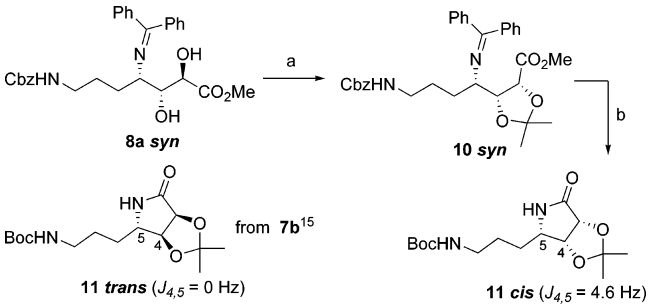
SCHEME 4. Assignment of the Relative Stereochemistry of 8a[a]



[a] Reagents and conditions: (a) 2,2-DMP, PPTS, PhH, reflux, 75%; (b) (i) Boc_2O, DMAP, MeCN, rt, (ii) 10% Pd−C, HCO_2NH_4, MeOH, reflux, 89% of **11** ***cis*** (from **8a** ***syn***).

able N^{α},N^{δ}-di-Cbz-L-ornithine using a synthetic sequence similar to that with **2**. The poor selectivity with the similar compound has been reported.[5h] Even the Sharpless asymmetric dihydroxylation reactions could not override the inherent selectivity of the *Z*-ester. It is quite remarkable that the simple achiral *N*-diphenylmethylene group on the γ-amino group shown here can enhance the syn-diastereofacial selectivity to a great extent.[8]

The relative configuration of the diol in **8a** was confirmed by comparing the coupling constants of the γ-lactams (Scheme 4). After protection of the diol of **8a** into acetonide **10**, the terminal amine of **10** was protected with a Boc group and then the catalytic hydrogenation removed both the benzophenone and the Cbz protecting groups, resulting in lactam **11** ***cis*** as the only isomer after purification.[8,16] A significant amount of the isomeric lactam **11** ***trans*** was obtained separately using a similar reaction sequence from the diastereomeric diol that was in turn derived from the OsO_4-catalyzed dihydroxylation of **7b** (see above).[15] The coupling constant between H-4 and H-5 of the major isomer (**11** ***cis***) was 4.6 Hz, and that of the minor isomer (**11** ***trans***) was 0 Hz. It has been reported that the value of $J_{4,5}$ of the cis γ-lactam is larger than that of the trans γ-lactam in a similar system.[7b,8,17] Therefore, the relative configuration of the diol in the major isomer **8a** should be syn to the amino group, which is the same configuration as that in the target compound **1**.

Finally, the dihydroxylation product **8a** was converted into the target compound **1**, the orthogonally protected derivative of DADHA (Scheme 3). Among several acids such as aq HCl, *p*-TsOH, PPTS, and TFA, TFA in aqueous THF was the best for selective removal of the *N*-diphenylmethylene group of **8a** in the presence of the Cbz group to give the ammonium salt.

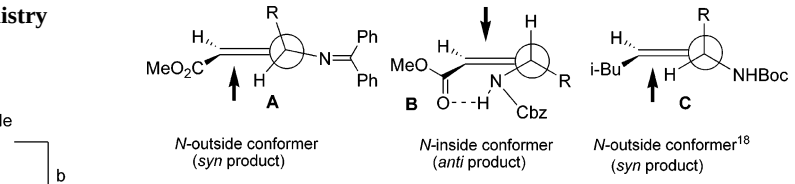


FIGURE 2. Probable transition-state models.

Then, the protection of the α-amino group with a Boc group gave the desired product **1** in a combined yield of 65% after purification.

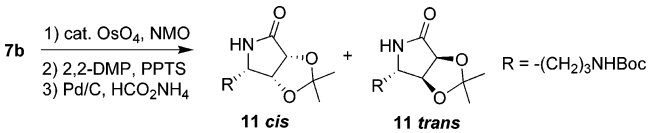
The enhanced stereoselectivity shown by the *N*-diphenylmethylene group could be rationalized by the favorable *N*-outside conformation caused by the steric hindrance from the methoxycarbonyl group as described in the literature (model A, Figure 2).[8] The *N*-inside conformation of the *N*-Cbz or *N*-Boc derivative would compete with its *N*-outside conformation because of the intramolecular hydrogen bonding between the methoxycarbonyl group and the N-H proton (model B), resulting in the poor syn or no selectivity.[5h] The preference of the *N*-outside conformation of the *N*-Boc group in the alkyl-substituted *Z*-olefin was proposed to explain the syn dihydroxylation selectivity by Krysan and co-workers (model C).[18]

In conclusion, we have developed an efficient and stereoselective synthetic route for the orthogonally protected derivative **1** of (2*R*,3*R*,4*S*)-4,7-diamino-2,3-dihydroxyheptanoic acid (DADHA) in 10 steps and 30% overall yield from commercially available N^{δ}-Cbz-N^{α}-Boc-L-ornithine (**2**). DADHA is an unusual amino acid residue of some biologically active marine peptides such as callipeltins A and D and neamphamide A and has a unique structure with a γ-amino-α,β-dihydroxycarboxylic acid unit. The key intermediate, suitably protected γ-amino-α,β-unsaturated (*Z*)-ester **7a**, was efficiently obtained using the Fukuyama's protocol from **2**. The *N*-diphenylmethylene-controlled OsO_4-catalyzed dihydroxylation of the Z-ester **3** successfully introduced the dihydroxyl functionality of the desired configuration in the target compound with high selectivity. The orthogonally protected derivative **1** of DADHA would be useful for further transformation such as guanylation at the terminal amine to provide a protected derivative of (2*R*,3*R*,4*S*)-4-amino-7-guanidino-2,3-dihydroxyheptanoic acid (AGDHE). The higher yield and shorter synthetic steps presented here would also be valuable for a total synthesis of the natural marine peptides such as callipeltins A and D and neamphamide A.

Experimental Section

Methyl (2*Z*,4*S*)-7-(*N*-Benzyloxycarbonyl-*N*-*tert*-butoxycarbonyl)amino-4-(*tert*-butoxycarbonyl)aminohept-2-enoate (7a). To a suspension of thioester **6a** (0.291 g, 0.570 mmol), 10% Pd/C (0.062 g, 0.057 mmol), and $MgSO_4$ (0.137 g, 1.14 mmol) in dry acetone (0.8 mL) was added triethylsilane (0.14 mL, 0.855 mmol). The mixture was stirred for 1 h at room temperature and then filtered through a Celite pad that was rinsed with Et_2O (10 mL × 2). The filtrate was washed with water (15 mL), and the water layer was extracted with Et_2O (15 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give crude aldehyde **4**. To a solution of bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (0.191 g, 0.602 mmol) and 18-crown-6 (0.665 g, 2.51 mmol) in dry THF (10 mL) at −78 °C was slowly added KHMDS (0.5 M in toluene, 1.2 mL,

(15) A ca. 1:1 mixture of the diastereomeric diols obtained from the same dihydroxylation reaction of **7b** was protected to give the acetonide derivative that was treated under the catalytic hydrogenation conditions to produce a mixture of the γ-lactams (**11** ***cis*** and **11** ***trans***). Each isomer was separated by SiO_2 column chromatography. One of the lactams with a smaller *J* value (0 Hz) was attributed to **11** ***trans*** and the other showed the same spectroscopic data as those of **11** ***cis***.



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0.60 mmol). After 15 min at −78 °C, the crude aldehyde **4** in dry THF (10 mL) was added dropwise to the reaction mixture, and the resulting mixture was stirred for another 30 min. The reaction was quenched with a saturated aqueous NH_4Cl solution (5 mL), and the aqueous layer was extracted with EtOAc (15 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude alkene. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 8:1) to give **7a** (0.235 g, 82%) as colorless oil over the two steps [(*Z*)/(*E*) = 16.4:1]: $[\alpha]^{21}_D$ +18.9 (*c* 1.10, $CHCl_3$); IR (film on a silicon wafer) 3386, 1750, 1723, 1717, 1696, 1648 cm^{-1}; ^1H NMR δ 1.42 (s, 9H), 1.47 (s, 9H), 1.51−1.68 (m, 4H), 3.66 (dt, *J* = 7.1, 2.6, 2H), 3.70 (s, 3H), 4.80 (br s, 1H), 5.02−5.13 (m, 1H), 5.22 (s, 2H), 5.78 (dd, *J* = 11.6, 1.0, 1H), 6.05 (br s, 1H), 7.27−7.41 (m, 5H); ^{13}C NMR δ 25.3, 28.0, 28.4, 31.6, 46.2, 49.0, 51.4, 68.3, 79.5, 82.8, 119.6, 128.28, 128.33, 128.56, 135.8, 150.2, 152.1, 153.9, 155.3, 166.0; HRMS (CI) calcd for $C_{26}H_{39}N_2O_8$ (M^+ + 1) 507.2707, found 507.2707. Anal. Calcd: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.40; H, 7.79; N, 5.65.

Methyl (2*Z*,4*S*)-7-(Benzyloxycarbonyl)amino-4-(diphenylmethylene)aminohept-2-enoate (3). To a solution of ester **7a** (0.400 g, 0.790 mmol) in dry MeOH (15 mL) at 0 °C was added dropwise AcCl (2 mL, 28.03 mmol). The solution was stirred for 2 h at 0 °C, and then the solvent was evaporated under reduced pressure. To the crude ammonium salt was added dry DCM (15 mL), and benzophenonone imine (0.150 g, 0.830 mmol) was added to the resulting suspension mixture at room temperature. After 12 h, the reaction was quenched with a satd aq $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with DCM (20 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 8:1) to give compound **3** as pale yellow oil (0.343 g, 92%) [(*Z*)/(*E*) = 16.4:1]: $[\alpha]^{21}_D$ +64.3 (*c* 0.41, $CHCl_3$); IR (film on a silicon wafer) 3354, 1722, 1708, 1648, 1618 cm^{-1}; ^1H NMR δ 1.32−1.72 (m, 3H), 1.70−1.75 (m, 1H), 2.96−3.08 (m, 1H), 3.12−3.24 (m, 1H), 3.51 (s, 3H), 4.91−5.06 (m, 2H), 5.07 (s, 2H), 5.72 (d, *J* = 11.5, 1H), 6.37 (dd, *J* = 11.5, 8.8, 1H), 7.07 (br s, 2H), 7.29−7.41 (m, 11H), 7.59−7.61 (m, 2H); ^{13}C NMR δ 26.0, 33.2, 40.4, 51.1, 60.0, 66.4, 117.9, 127.6, 127.98, 128.02, 128.1, 128.3, 128.4, 128.46, 128.50, 128.57, 128.59, 130.2, 136.8, 137.0, 139.7, 150.2, 156.3, 166.1, 169.5; HRMS (CI) calcd for $C_{29}H_{31}N_2O_4$ (M^+ + 1) 471.2285, found 471.2284.

Methyl (2*R*,3*R*,4*S*)-7-(Benzyloxycarbonyl)amino-2,3-diacetoxy-4-(diphenylmethylene)aminoheptanoate (9). To a mixture of ester **3** (97 mg, 0.206 mmol) and NMO (53 mg, 0.453 mmol) in THF (2 mL) and H_2O (2 mL) was added OsO_4 (5.2 mg, 0.021 mmol). The mixture was stirred for 48 h at room temperature. The reaction was quenched with a satd aq Na_2SO_3 solution (5 mL), and the resulting mixture was stirred further for 30 min. The aqueous layer was extracted by Et_2O (10 mL × 4). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give crude diol **8** (110 mg, 0.218 mmol). The crude diol could be purified by silica gel column chromatography (hexane/EtOAc = 1:1) to give diol **8** (93 mg, 90%) as colorless oil. The crude diol product was dissolved in dry DCM (10 mL) and treated with Ac_2O (0.10 mL, 1.03 mmol), TEA (0.14 mL, 1.03 mmol), and DMAP (3 mg, 0.021 mmol). The reaction mixture was stirred for 24 h at room temperature. The reaction was quenched with a satd aq $NaHCO_3$ solution (5 mL), and the aqueous layer was extracted with DCM (10 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (hexane/EtOAc = 8:1) to give compound **9** as pale yellow oil (103 mg, 85%): IR (film on a silicon wafer) 3403, 3031, 1751, 1724, 1624 cm^{-1}; ^1H NMR δ 1.30−1.55 (m, 2H), 1.60−1.80 (m, 2H), 2.00 (s, 3H), 2.05 (s, 3H), 3.09 (q, *J* = 6.6, 2H), 3.53 (s, 3H), 3.73−3.83 (m, 1H), 4.75 (br s, 1H), 5.08 (s, 2H), 5.24 (d, *J* = 4.0, 1H), 5.48 (dd, *J* = 7.0, 4.0, 1H), 7.11−7.14 (m, 2H), 7.29−7.45 (m, 11H), 7.55−7.58 (m, 2H); ^{13}C NMR δ 20.5, 20.8, 26.4, 28.9, 40.7, 52.3 60.6, 66.5, 71.2, 73.1, 127.9, 128.0, 128.15, 128.21, 128.4, 128.5, 128.9, 130.0, 132.4, 136.5, 156.3, 167.4, 169.6, 169.8; HRMS (CI) calcd for $C_{33}H_{37}N_2O_8$ (M^+ + 1) 589.2551, found 589.2557.

Methyl (2*R*,3*R*,4*S*)-7-(Benzyloxycarbonyl)amino-4-(*tert*-butoxycarbonyl)amino-2,3-dihydroxyheptanoate (1). To a solution of purified diol **8** (187 mg, 0.371 mmol) in THF (5 mL) were slowly added TFA (0.4 mL, 5.39 mmol) and H_2O (0.2 mL), and the resulting mixture was stirred for 3.5 h at room temperature. The solvent was then evaporated under reduced pressure, and the remaining TFA was removed by addition of toluene and the following evaporation in vacuo. To the crude ammonium salt were added H_2O (3 mL) and THF (3 mL) followed by addition of Boc_2O (121 mg, 0.557 mmol) and $NaHCO_3$ (93 mg, 1.11 mmol). The reaction mixture was stirred for 24 h at room temperature. The reaction was quenched with a satd aq NH_4Cl solution (5 mL). Then, the aqueous layer was extracted with EtOAc (5 mL × 4), and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to give compound **1** as colorless oil (106 mg, 65%): $[\alpha]^{18}_D$ −9.01 (*c* 0.24, $CHCl_3$); IR (film on a silicon wafer) 3649, 3627, 3386, 3355, 1716, 1702, 1696 cm^{-1}; ^1H NMR (measured at 328 K) δ 1.44 (s, 9H), 1.53−1.67 (m, 4H), 3.18−3.25 (m, 2H), 3.27 (br s, 1H), 3.70 (br d, *J* = 8.4, 1H), 3.81−3.91 (m, 1H), 3.82 (s, 3H), 3.97 (dd, *J* = 8.5, 5.6, 1H), 4.45 (br s, 1H), 4.80 (br d, *J* = 8.8, 2H), 5.10 (s, 2H), 7.29−7.36 (m, 5H); ^{13}C NMR δ 26.9, 28.3, 28.8, 40.7, 50.5, 52.7, 66.7, 71.3, 73.7, 80.6, 128.1, 128.3, 136.5, 156.5, 157.7, 174.1; HRMS (CI) calcd for $C_{21}H_{33}N_2O_8$ (M^+ + 1) 441.2238, found 441.2235.

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Supporting Information Available: Experimental procedures for **5**, **6a**, **10**, **11** ***cis***, and **11** ***trans***. ^1H and ^{13}C NMR spectra for **1**, **3**, **5**, **6a**, **7a**, **9**, **10**, **11** ***cis*** [**11** ***cis*** with D_2O], and **11** ***trans***. This material is available free of charge via the Internet at http://pubs.acs.org.

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