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Synthesis of 4-Substituted-3-aminopiperidin-2-ones: Application to the Synthesis of a Conformationally Constrained Tetrapeptide *N*-Acetyl-Ser-Asp-Lys-Pro

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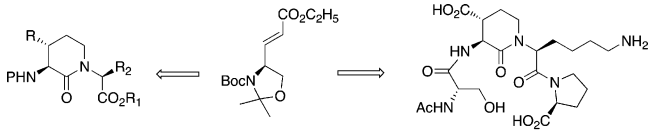

A new and practical synthetic strategy is developed for the synthesis of six-membered lactam-bridged dipeptides, 4-substituted-3-aminopiperidin-2-ones, featuring two key steps: (a) a diastereoselective addition of cuprate to (*E*)-α,*β*-unsaturated ester (**3**) and (b) racemization-free reductive amination. On the basis of this methodology, conformationally constrained tetrapeptide *N*-acetyl-Ser-Asp-Lys-Pro (AcSDKP) (**2**) has been successfully synthesized from 3-amino-4-vinylpiperidin-2-one (**22**).

Introduction

The design and synthesis of conformationally constrained peptidomimetics is an important approach in searching for the bioactive compounds with improved biological potency, selectivity, and metabolic stability relative to endogenous linear peptides.[1−3] Among the numerous strategies developed for reducing the conformational mobility, tethering the backbone side chain with the neighboring amide nitrogen into a so-called "Freidinger" lactam[4] has proven useful for the design of a variety of medicinally relevant enzyme inhibitors,[5] especially in the case of the peptidase/protease inhibitors.[6a] Therefore, synthesis of novel Freidinger lactams is currently an area of intensive research in the field of peptide and medicinal chemistry, and several types of Freidinger lactams have been synthesized.[4−7] Although 3-aminopi-

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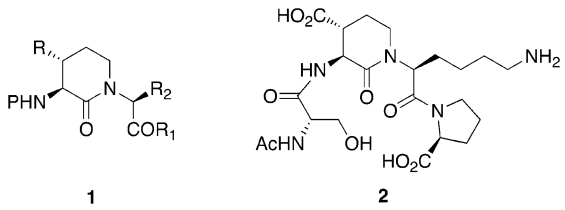
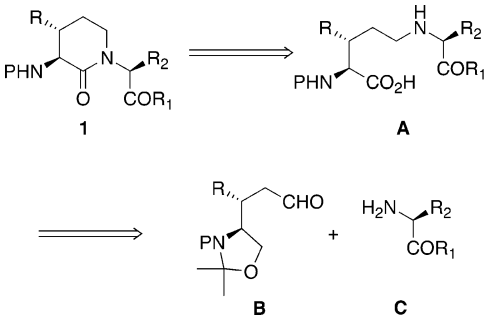


1 **2**

FIGURE 1.

SCHEME 1. Retrosynthetic Analysis for Lactam-Bridged Dipeptides



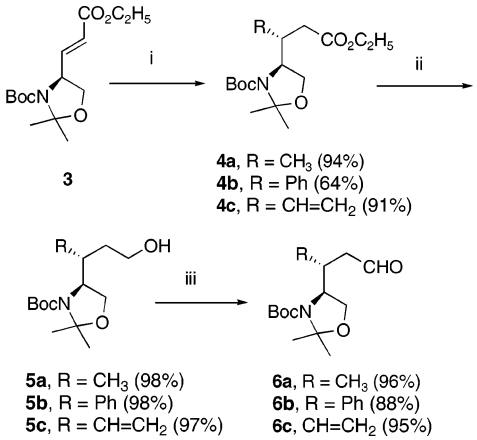
peridin-2-one is known, to the best of our knowledge a few syntheses have been reported for 1,4-disubstituted-3-aminopiperidin-2-one (**1**) (Figure 1).[6l−o,7] We have been interested in developing a short asymmetric synthesis of this type of lactam based on the following reasoning. The incorporation of a substituent at the C-4 position would not only introduce an additional point of diversity but also influence the conformation of the molecule by modulating the bulkiness of the substituent as well as the relative stereochemistry between C-3 and C-4. Because the side chains of amino acids often play important roles in bioactivities of the peptide, we deemed it important to develop a convergent synthesis that could allow us to vary systematically the substituents (R, R_1, R_2) at the periphery of the piperidin-2-one surrogate.

In this paper, we report a straightforward synthesis of enantiomerically pure (3*S*,4*R*)-3-amino-4-alkyl(aryl)-piperidin-2-ones in detail based on a strategy depicted retrosynthetically in Scheme 1. In a forward sense, lactam **1** was to be produced by a cycloamidation of amino acid **A** that in turn could be obtained by a reductive amination of amino aldehyde **B** and α-amino ester or α-amino amide **C**. Compound **B** can be traced back to Garner's aldehyde, whereas **C** is commercially available. The design and synthesis of a conformationally constrained analogue of *N*-acetyl-Ser-Asp-Lys-Pro (AcSDKP) (**2**) based on this chemistry is also to be documented (Figure 1).

Results and Discussion

Synthesis of 4-Substituted-3-aminopiperidin-2-one. Reductive amination of a suitably functionalized amino aldehyde and an amino ester is the key step in our planned synthesis of piperidin-2-one. The prerequisite amino aldehydes **6a**−**6c** were synthesized following literature procedure (Scheme 2). 1,4-Addition of lithium dimethyl or divinyl cuprates to the enoate **3** derived from serine in the presence of trimethylsilyl chloride furnished

SCHEME 2. Synthesis of Aldehydes 6a, 6b, and 6c[a]



[a] Reagents and conditions: (i) R_2CuLi (R = CH_3 for **4a**; R = $CH{=}CH_2$ for **4c**), $(CH_3)_3SiCl$, THF, −78 °C to room temperature; PhMgBr, Cu(I) for **4b**, $(CH_3)_3SiCl$, THF, −78 °C to room temperature; (ii) $LiAlH_4$, THF, room temperature, 2 h; (iii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N.

syn **4a** and **4c**, respectively,[8] in good yields and with excellent diastereofacial selectivities. Curiously, diphenyllithium cuprate failed to react with **3** under identical conditions. After much experimentation, it was found that the 1,4-Michael addition of phenylmagnesium bromide in the presence of Cu(I), according to Hruby,[9] occurred smoothly. Under these conditions, the desired syn **4b** was obtained as a single diastereomer in 64% isolated yield. Lithium aluminum hydride reduction of esters **4a**−**4c**[10] and subsequent Swern oxidation of alcohols **5a**−**5c** gave the corresponding aldehydes **6a**−**6c,** respectively.

Reductive amination of aldehyde **6a** with L-phenylalanine methyl ester **7a** (sodium triacetoxyborohydride, THF) proceeded smoothly to provide secondary amine **8a** in 90% yield (Scheme 3). After N-protection of **8a** with CbzCl, the resulting carbamate **9a** was subjected to Jones oxidation to afford directly carboxylic acid **10a**. Activation of the carboxylic acid as pentafluorophenyl ester **11a** followed by tandem N-deprotection/lactamization under catalytic hydrogenolysis conditions provided the desired piperidin-2-one (**12a**)[7] in 79% yield. Compound **12b** was prepared following the same synthetic scheme as described above for **12a**, starting from aldehyde **6b** and L-leucine methyl ester **7b** (Scheme 3). The stereochemistry of **12a** has been confirmed by X-ray analysis.

Having developed the methodology for the synthesis of lactam **12a** and **12b**, we turned our attention to the synthesis of the 3-amino-4-vinylpiperidin-2-one system. The presence of the vinyl function at the C-4 position of the piperidin-2-one ring would allow us to introduce a carboxylic acid required for the synthesis of the *N*-AcSDKP analogue (Scheme 6) and other functionalities. To further illustrate the generality of the present meth-

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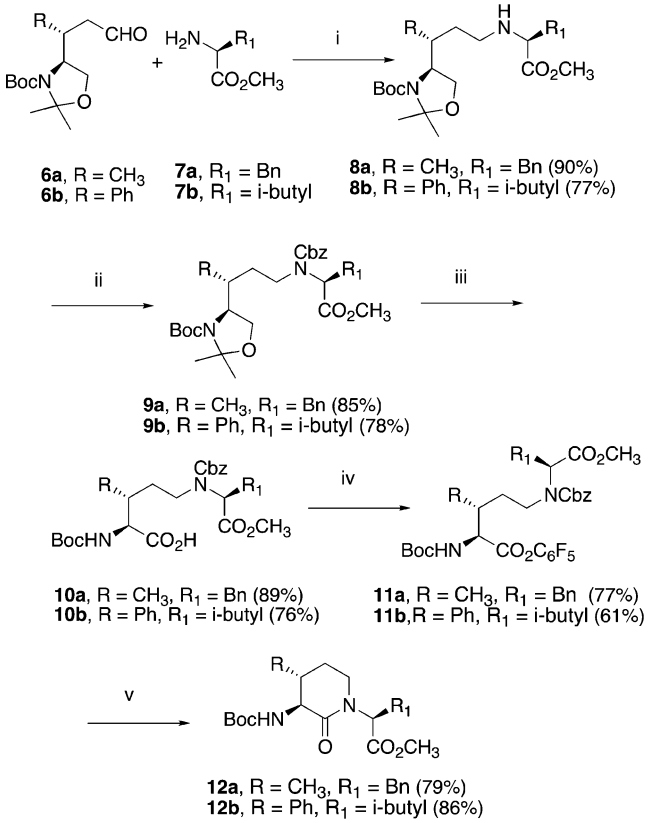
SCHEME 3. Synthesis of 4-Substituted-3-aminopiperidin-2-one 12a and 12b[a]

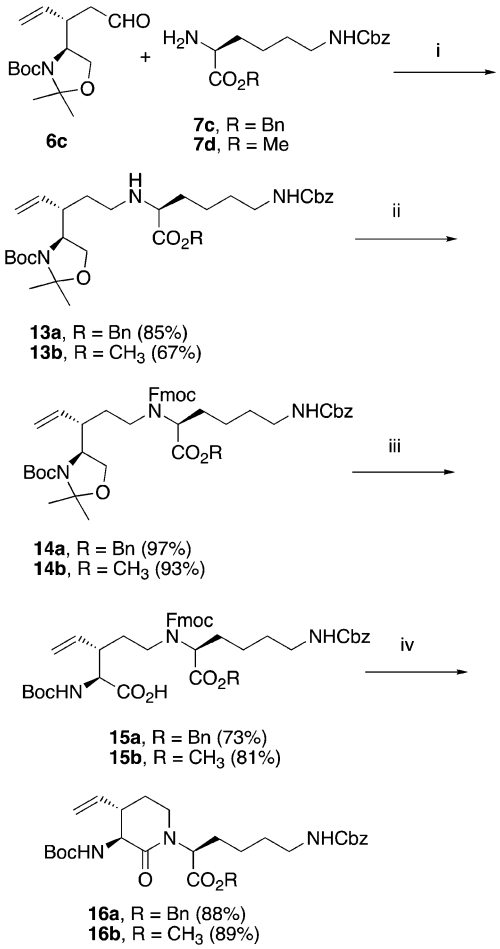


[a] Reagents and conditions: (i) $NaBH(OAc)_3$, THF, room temperature, 15 h; (ii) Cbz-Cl, Na_2CO_3, THF−H_2O (3:1), room temperature, 1 h; (iii) Jones reagent, acetone, 0 °C to room temperature, 1 h; (iv) C_6F_5OH, EDC, CH_2Cl_2, 0 °C to room temperature, 2 h; (v) H_2, 10% Pd/C, MeOH, 3 h.

odology, a side chain functionalized amino acid, L-Lys(Cbz)OBn (**7c**), was employed as a reaction partner. Thus, reductive amination of aldehyde **6c** with L-Lys(Cbz)OBn (**7c**) afforded amine **13a** in 85% yield. Protection of the secondary amine followed by Jones oxidation furnished acid **15a** in 73% yield. Removal of the Fmoc group with diethylamine and subsequent intramolecular cyclization (TBTU−HOBt−DIEA in DMF) provided lactam **16a** in 88% yield (Scheme 4). Compound **16b** was similarly prepared in good overall yield.

Synthesis of Tetrapeptide 2, Analogue of *N*-AcSDKP. The tetrapeptide *N*-acetyl-Ser-Asp-Lys-Pro (AcSDKP), isolated from bone marrow,[11] is present in various tissues and biological fluids such as plasma, urine, and circulating mononuclear cells of humans and animals.[12] It is recognized as a physiologic regulator of hematopoiesis. It inhibits the proliferation of normal hematopoietic stem cells and committed progenitors in vivo as well as in vitro[11,13] and consequently reduces the damage to the stem cell compartment resulting from treatment with chemotherapeutic agents or ionizing radiations.[14] It is well-known that AcSDKP is cleaved

SCHEME 4. Synthesis of 3-Amino-4-vinylpiperidin-2-one 16a and 16b[a]



[a] Reagents and conditions: (i) $NaBH(OAc)_3$, THF, room temperature, 15 h; (ii) Fmoc-Cl, 0.5M Na_2CO_3, THF−H_2O (3:1), room temperature, 3 h; (iii) Jones reagent, acetone, 0 °C to room temperature, 3 h; (iv) (a) $(C_2H_5)_2NH$, THF, 0 °C, 15 min, room temperature, 6 h; (b) TBTU, HOBt, DIEA, DMF, room temperature, 24 h.

from its precursor thymosin-β4, most likely by prolyl oligopeptidase,[15] and is hydrolyzed almost exclusively by angiotensin converting enzyme (ACE) between the Asp-Lys peptide bond.[16] This tetrapeptide has a 4.5-min half-life in the circulation and thus is probably released continuously in its physiological condition.[17] Another novel biological function of AcSDKP as a mediator of angiogenesis in vitro and in vivo was reported recently.[18]

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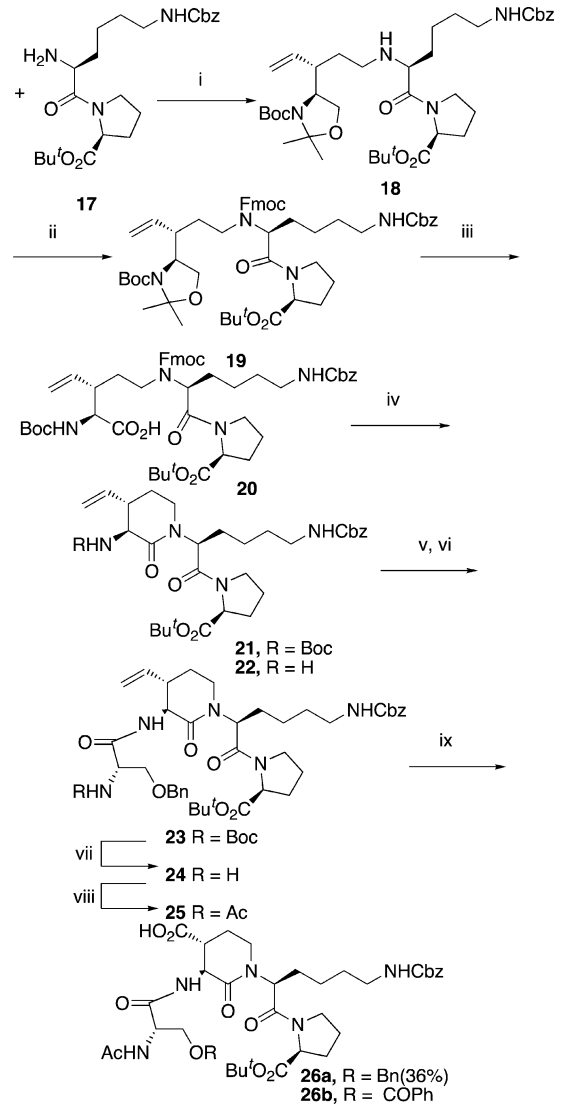
SCHEME 5. Synthesis of Tripepde 26a[a]

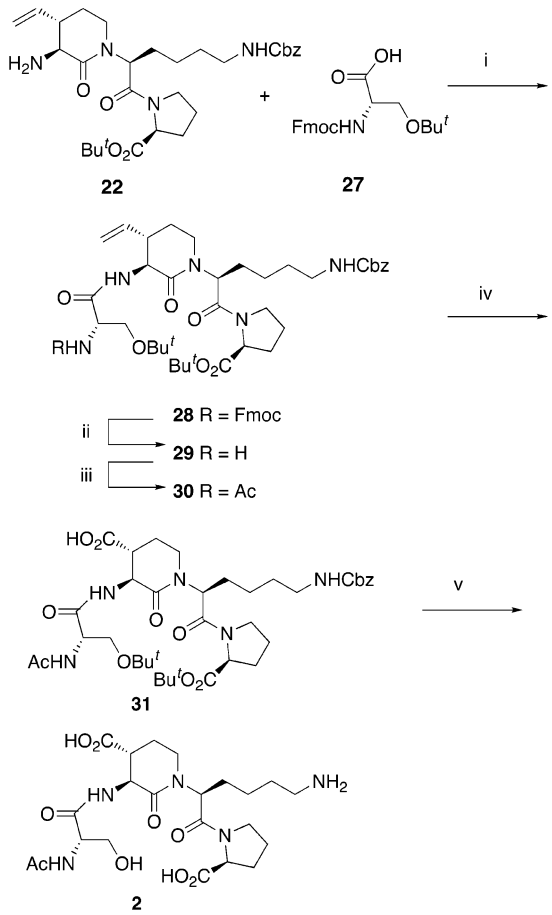


[a] Reagents and conditions: (i) $NaBH(OAc)_3$, THF, room temperature, 15 h, 74%; (ii) Fmoc-Cl, 0.5 M Na_2CO_3, THF−H_2O (3:1), room temperature, 2 h, 92%; (iii) Jones reagent, acetone, 0 °C to room temperature, 3 h, 57%; (iv) (a) $(C_2H_5)_2NH$, THF, 0 °C, 15 min, room temperature, 6 h; (b) TBTU, HOBt, DIEA, DMF, room temperature, 24 h, 71%; (v) 3 M HCl−EtOAc, −50 °C, 2 h, 0 °C, 1 h, 67%; (vi) Boc-L-Ser(OBn)OH, EDC, HOBt, CH_2Cl_2, room temperature, 24 h, 80%; (vii) 3 M HCl−EtOAc, −50 °C, 2 h, 0 °C, 1 h, 70%; (viii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, room temperature, 24 h, 51%; (ix) $NaIO_4$, $RuCl_3$, $CH_3CN-CCl_4-H_2O$ (2:2:3), room temperature, 24 h.

AcSDKP may have potential for the clinical treatment of deficient angiogenesis-related diseases.

To increase the metabolite stability of AcSDKP and to probe the bioactive conformation of AcSDKP, lactam **2** was designed wherein the β-carbon of the aspartic acid and the adjacent amide nitrogen of the lysine were connected via ethylene linkage producing a piperidin-2-one unit. It was expected that such a cyclic lactam motif should render the molecule more resistant to in vivo enzymatic degradation because the cyclic scaffold can shelter the cleavable amide bond from degradative peptidases.

SCHEME 6. Synthesis of Tetrapeptide 2, Analogue of *N*-AcSDKP[a]



[a] Reagents and conditions: (i) EDC, HOBt, CH_2Cl_2, room temperature, 24 h, 85%; (ii) Et_2NH, THF, 0 °C, then room temperature, 3 h, 96%; (iii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, room temperature, 24 h, 86%; (iv) $NaIO_4$, $RuCl_3$, $CH_3CN-CCl_4-H_2O$ (2:2:3), room temperpature, 24 h, 75%; (v) (a) CF_3COOH, room temperature, 3 h; (b) H_2, Pd/C, MeOH, room temperature, 4 h (54%).

From the viewpoint of synthesis, dipeptide **16b** is appropriately functionalized for the synthesis of a diverse set of conformationally constrained peptides by elongation at both the N- and the C-terminals. However, for the synthesis of the specifically targeted *N*-AcSDKP analogue (**2**), a more convergent synthesis is developed featuring a key reductive amination of the aldehyde **6c** with a *tert*-butyl ester of ω-*N*-Cbz-Lys-Pro (**17**) that is synthesized from ω-*N*-Cbz-*N*-Fmoc-Lys[19] and proline *tert*-butyl ester. Reductive amination between aldehyde **6c** and dipeptide amine **17** took place without event to produce compound **18** in 74% yield. Protection of the

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secondary amine (FmocCl, THF−H_2O, Na_2CO_3) followed by Jones oxidation of the *N*-Boc oxazolidine afforded acid **20**. Removal of the *N*-Fmoc function (Et_2NH, THF) followed by lactamization (TBTU, HOBt, $^iPr_2NEt$) furnished piperidin-2-one (**21**) in 71% yield. Selective removal of the *N*-Boc function without affecting the *tert*-butyl ester was realized under mild acidic conditions (3 M HCl−EtOAc at −50 °C for 2 h then at 0 °C for 1 h). Coupling of the resulting amine **22** with Boc-L-Ser(OBn)-OH afforded tetrapeptide **23** that was then converted to the *N*-Ac derivative by a sequence of selective N-deprotection and acetylation under classic conditions (51%). Oxidative cleavage of the vinyl group under Sharpless conditions[20] afforded the desired compound **26a** together with the benzoate **26b** (1:1 ratio) resulting from the concomitant oxidation of the benzyl ether group. The *O*-benzyl protected serine was selected with the hope to achieve, at the final stage of the synthesis, the simultaneous deprotection of the *O*-Bn and *N*-Cbz functions. Unfortunately, this seemingly trivial transformation was found to be more difficult than one may expect. Indeed, our attempts to cleave the *O*-benzyl ether and the *N*-Cbz protective group under various hydrogenolysis conditions varying the catalysts [Pd/C, $Pd(OH)_2$] and the solvents (MeOH, EtOAC, room temperature, 1 atm) gave a mixture of *O*-benzyl ether product and hydroxyamine. Unfortunately, when we forced the hydrogenolysis condition under pressure (60 psi) and forced transfer hydrogenolysis (cyclohexene/EtOH, $PdCl_2$, reflux and Zn/HCO_2NH_4, MeOH, rt), it resulted in complete decomposition of the starting material and failed to produce the desired tetrapeptide **2**.

To surmount this problem, the synthesis was started again using *O-tert*-butyl protected serine as the coupling partner (Scheme 6). Thus, coupling of tripeptide amine **22**, obtained by deprotection of the terminal primary amine of **21**, with *N*-Fmoc-L-Ser(O^{t}Bu) (**27**) under standard conditions (EDC, HOBt) afforded tetrapeptide **28** in 85% yield. Removal of the Fmoc protective group with diethylamine and subsequent acetylation gave acetyl tetrapeptide **30**. Oxidation of double bonds according to Sharpless proceeded smoothly in this case to provide the corresponding carboxylic acid **31** in 75% yield. Simultaneous removal of the *tert*-butyl ester and the *O-tert*-butyl ether from **31** under acidic conditions (TFA) followed by hydrogenolysis of the crude diacid afforded tetrapeptide **2** in 54% yield. Tetrapeptide **2** was thus prepared starting from α,β-unsaturated ester **3** in 13 steps with 4% overall yield. The biological studies for tetrapeptide **2** are under investigation and the results will be reported in due course.

Conclusion

In summary, we developed a concise synthesis of 4-substituted-3-aminopiperidin-2-one that can be considered as a conformationally constrained dipeptide. The synthesis is highly convergent and features a key reductive amination of the α-amino ester and the functionalized aldehyde, derived from serine. A variety of substituents can be installed adjacent to the ring nitrogen by varying both the aldehyde and the α-amino ester or the α-amino amide inputs in the reductive amination step. On the basis of this synthetic strategy, synthesis of an *N*-AcSDKP analogue is documented.

Experimental Section

General Procedure 1. Preparation of Aldehydes 6a−c. To a solution of oxalyl chloride (9.34 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added dropwise a solution of DMSO (20.33 mmol) in CH_2Cl_2 (15 mL). The resulting reaction mixture was further stirred at the same temperature for another 15 min before a solution of alcohols **5a−c** (5.49 mmol) in CH_2Cl_2 (15 mL) was added dropwise over 15 min while the temperature was kept at −78 °C. Stirring was continued for an additional 15 min followed by addition of Et_3N (38.4 mmol), and the reaction mixture was allowed to warm to room temperature. Water (50 mL) was then added, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were washed with 1 M HCl, H_2O, saturated $NaHCO_3$, and brine, successively, and then dried over Na_2SO_4. The filtered solution was concentrated under reduced pressure to give aldehydes **6a−c**, which were used directly for the next reaction without further purification.

(4*S*,1′*R*)-2,2-Dimethyl-4-(1′-methyl-3′-oxopropyl)oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (6a). General procedure 1 was followed using alcohol **5a** (1.50 g, 5.49 mmol) to give 1.43 g (96%) of **6a** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (bs, 1H), 4.00−3.72 (m, 3H), 2.74−2.54 (m, 2H), 2.32−2.12 (m, 1H), 1.72−1.42 (m, 15H), 0.93 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 201.8, 153.0, 152.8, 94.3, 94.0, 80.2, 64.1, 60.9, 46.0, 45.7, 29.9, 28.3, 26.7, 26.3, 23.9, 22.4, 17.0, 16.7; MS (ESI) *m/z* 272 $[M + H]^+$, 294 $[M + Na]^+$.

General Procedure 2. Preparation of Amines 8a, 8b, 13a, 13b, and 18. To a solution of the aldehydes **6a−c** (1.0 mmol) and the amines **7a−d** and **17** (1.1−1.3 mmol) in THF (15 mL) was added sodium triacetoxyborohydride (1.1−1.4 mmol). The reaction mixture was stirred at room temperature under Ar for 15 h. The reaction was quenched by addition of aqueous saturated $NaHCO_3$, and the reaction mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine and then dried over Na_2SO_4. Purification of the crude residue by flash column chromatography provided amines **8a, 8b, 13a, 13b,** and **18**.

(4*S*,1′*R*,1″*S*)-4-[3′-(1″-Methoxycarbonyl-2″-phenylethylamino)-1′-methylpropyl]-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester (8a). General procedure 2 was followed using aldehyde (**6a**) (653 mg, 2.41 mmol) and L-PheOMe (**7a**) (518 mg, 2.89 mmol). Chromatography with heptane/ethyl acetate (2:1) gave 942 mg (90%, two rotamers) of **8a** as a yellow oil: $[\alpha]_D$ +29 (*c* 3.40, $CHCl_3$); IR (neat) ν 3328, 3027, 3020, 3012, 2979, 2953, 2878, 1732, 1686, 1495, 1476, 1455, 1435, 1392, 1366, 1255, 1172 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.12 (m, 5H), 3.89−3.76 (m, 3H), 3.63 (s, 3H), 3.51 (t, J = 7.2 Hz, 1H), 2.94 (d, J = 7.2 Hz, 2H), 2.68 (dt, J = 5.1, 10.8 Hz, 1H), 2.49−2.35 (m, 1H), 2.05−1.80 (m, 1H), 1.68−1.41 (m, 16H), 1.25 (m, 1H), 0.83 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 152.9, 152.5, 137.3, 129.1, 128.3, 126.6, 94.0, 93.6, 79.8, 79.5, 65.0, 64.5, 63.1, 61.9, 51.5, 46.4, 39.7, 33.7, 33.3, 32.0, 28.4, 26.9, 26.3, 24.3, 16.3; MS (ESI) *m/z* 435 $[M + H]^+$, 457 $[M + Na]^+$, 473 $[M + K]^+$. Anal. Calcd for $C_{24}H_{38}N_2O_5$: C, 66.33; H, 8.81; N, 6.45. Found: C, 66.09; H, 8.84; N, 6.47.

(4*S*,1′*R*,1″*S*)-4-{3′-[Benzyloxycarbonyl-(1″-methoxycarbonyl-2″-phenylethyl)amino]-1′- methylpropyl}-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester (9a). To a solution of amine (**8a**) (205 mg, 0.47 mmol) and 0.5 M Na_2CO_3 (2 mL, 1 mmol) in THF−water (6 mL, 3:1) was added dropwise benzyl chloroformate (0.08 mL, 0.52 mmol), and the resulting mixture was vigorously stirred at room temperature for 1 h. The reaction mixture was diluted with

(20) Carlsen, P. H.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

water and extracted with ethyl acetate, and the combined organic layers were washed with brine and then dried over Na_2SO_4. The crude product obtained upon concentration was purified by flash column chromatography on silica gel with heptane/ethyl acetate (6:1) and gave 226 mg (85%, two rotamers) of **9a** as an oil: $[\alpha]_D$ −57 (*c* 2.10, $CHCl_3$); IR ($CHCl_3$) ν 3028, 3013, 2980, 2879, 1741, 1686, 1476, 1455, 1393, 1377, 1367, 1257, 1174, 1085 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.04 (m, 10H), 5.21−5.06 (m, 2H), 4.36−4.15 (m, 1H), 3.84−3.52 (m, 6H), 3.38−3.02 (m, 3H), 2.87−2.72 (m, 1H), 1.45 (s, 9H), 1.85−1.35 (m, 8H), 1.17−0.95 (m, 1H), 0.83 (d, J = 6.6 Hz, 1.7H), 0.73 (d, J = 6.8 Hz, 1.3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 155.9, 155.5, 137.9, 137.8, 129.2, 128.5, 128.3, 128.2, 128.1, 128.0, 126.7, 126.6, 94.0, 93.6, 80.0, 79.6, 67.4, 67.3, 65.2, 62.3, 61.8, 61.7, 52.3, 47.2, 46.6, 36.3, 35.3, 33.9, 33.7, 31.1, 30.5, 28.5, 27.1, 26.5, 24.4, 22.9, 16.1, 15.9; MS (ESI) *m/z* 569 $[M + H]^+$, 591 $[M + Na]^+$, 607 $[M + K]^+$; HRMS calcd for $C_{32}H_{45}N_2O_7$ (M + H) 569.3226, found 569.3202.

General Procedure 3. Preparation of 10a, 10b, 15a, 15b, and 20. Jones reagent (2.67 M, 1.1 mL, 2.98 mmol) was added to a solution of **9a, 9b, 14a, 14b,** and **19** (0.99 mmol) in acetone (10 mL) at 0 °C under argon. After stirring at room temperature for 3 h, the reaction was quenched by addition of 2-propanol. The reaction mixture was further stirred for 15 min, neutralized with saturated aqueous $NaHCO_3$ to pH 4−5, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried, and evaporated under reduced pressure. Flash column chromatography on silica gel yielded acids **10a, 10b, 15a, 15b,** and **20**.

(2*S*,3*R*,1′*S*)-5-[Benzyloxycarbonyl-(1′-methoxycarbonyl-2′-phenylethyl)amino]-2-*tert*-butoxycarbonylamino-3-methyl Pentanoic Acid (10a). General procedure 3 was followed using **9a** (565 mg, 0.99 mmol). Flash column chromatography with CH_2Cl_2/ethyl acetate (5:1) gave 477 mg (89%, two rotamers) of **10a**: $[\alpha]_D$ −65 (*c* 2.50, $CHCl_3$); IR ($CHCl_3$) ν 3674, 3440, 3029, 3019, 2981, 1705, 1498, 1476, 1455, 1429, 1368, 1229, 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (bs, 1H), 7.39−7.00 (m, 10H), 5.20−5.05 (m, 3H), 4.43−4.35 (m, 0.5H), 4.27−4.04 (m, 1.5H), 3.74 (s, 1.5H), 3.55 (s, 1.5H), 3.36−3.08 (m, 3H), 3.01−2.83 (m, 0.5H), 2.70−2.62 (m, 0.5H), 2.05−1.90 (m, 1H), 1.45−0.64 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 175.9, 171.4, 171.3, 156.8, 156.2, 156.0, 155.8, 137.9, 137.6, 136.5, 136.0, 129.3, 128.5, 128.1, 126.8, 126.6, 80.0, 67.7, 67.3, 62.6, 62.4, 56.9, 56.7, 52.3, 46.9, 46.3, 36.0, 34.9, 32.9, 32.7, 31.9, 31.7, 28.3, 14.3; MS (ESI) *m/z* 543 $[M + H]^+$, 565 $[M + Na]^+$, 581 $[M + K]^+$. Anal. Calcd for $C_{29}H_{38}N_2O_8$: C, 64.19; H, 7.06; N, 5.16. Found: C, 63.92; H, 7.27; N, 4.79.

(2*S*,3*R*,1′*S*)-5-[Benzyloxycarbonyl-(1′-methoxycarbonyl-2′-phenylethyl)amino]-2-*tert*-butoxycarbonylamino-pentafluorophenyl-3-methyl Pentanoate (11a). To a solution of acid **10a** (271 mg, 0.50 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added EDC (118 mg, 0.60 mmol). After stirring at that temperature for 10 min, pentafluorophenol (112 mg, 0.60 mmol) was added and stirring was continued at room temperature for 2 h. The reaction mixture was diluted with water and extracted with ethyl acetate, and the combined organic extracts were washed with brine and then dried over Na_2SO_4. The crude residue obtained upon concentration was purified by flash column chromatography on silica gel with heptane/ethyl acetate (6:1) and gave 272 mg (77%, two rotamers) of **11a** as white crystals: mp 81−82 °C; $[\alpha]_D$ −65 (*c* 1.80, $CHCl_3$); IR ($CHCl_3$) ν 3443, 3019, 2956, 1786, 1708, 1521, 1456, 1437, 1368, 1228, 1144, 998 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.04 (m, 10H), 5.29−5.08 (m, 3H), 4.63−4.48 (m, 1H), 4.09−4.01 (m, 1H), 3.77 (s, 1.5H), 3.57 (s, 1.5H), 3.47−3.24 (m, 2.5H), 3.21−3.11 (m, 0.5H), 2.78−2.56 (m, 1H), 2.26−2.03 (m, 1H), 1.47 (s, 9H), 1.53−1.40 (m, 1H), 1.35−1.02 (m, 1H), 0.96 (d, J = 6.3 Hz, 1.5H), 0.81 (d, J = 6.6 Hz, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 168.5, 168.4, 155.7, 155.5, 142.6, 141.3, 139.8, 139.5, 139.3, 138.0, 137.7, 136.5, 136.2, 129.3, 128.6, 128.4, 128.1, 126.8, 126.7, 80.4, 67.6, 67.4, 63.0, 62.3, 57.5, 57.4, 52.5, 52.3, 46.8, 46.3, 36.1, 34.9, 32.7, 32.6, 31.5, 31.3, 28.3, 14.7; MS (ESI) *m/z* 709 $[M + H]^+$, 731 $[M + Na]^+$, 747 $[M + K]^+$, 1417 $[2M + H]^+$; HRMS calcd for $C_{35}H_{37}F_5N_2O_8$-Na (M + Na) 731.2368, found 731.2378.

(2*S*,3′*S*,4′*R*)-2-(3′-*tert*-Butoxycarbonylamino-4′-methyl-2′-oxopiperidin-1′-yl)-3-phenylpropionic Acid Methyl Ester (12a). A suspension of ester **11a** (345 mg, 0.49 mmol) in MeOH (20 mL) containing a catalytic amount of 10% Pd−C (52 mg) was hydrogenated at atmospheric pressure for 3 h. The catalyst was removed by filtration through Celite. The filtrate was concentrated under reduced pressure and purification by flash column chromatography on silica gel with heptane/ethyl acetate (4:1) gave 151 mg (79%, two rotamers) of **12a** as white crystals: mp 112−113 °C; $[\alpha]_D$ −59 (*c* 2.80, $CHCl_3$); IR ($CHCl_3$) ν 3440, 3019, 2981, 2933, 2875, 1739, 1713, 1651, 1499, 1166 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.31−7.15 (m, 5H), 5.11−4.97 (m, 2H), 3.72 (s, 3H), 3.75−3.64 (m, 1H), 3.36 (dd, J = 5.6, 14.3 Hz, 1H), 3.26−2.99 (m, 3H), 1.86−1.65 (m, 2H), 1.44 (s, 9H), 1.51−1.33 (m, 1H), 1.00 (d, J = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.3, 156.4, 136.8, 128.7, 128.5, 126.7, 79.3, 58.9, 57.2, 52.2, 43.8, 34.2, 34.0, 29.3, 28.2, 18.8; MS (CI) *m/z* 391 $[M + H]^+$; HRMS calcd for $C_{21}H_{31}N_2O_5$ (M + H) 391.2232, found 391.2243.

(4*S*,1′*S*,1‴*S*)-4-{1′-[2″-(1‴-Benzyloxycarbonyl-5‴-benzyloxycarbonylaminopentylamino)ethyl]allyl}-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester (13a). General procedure 2 was followed using L-Lys(Cbz)OBn (**7c**) (1.43 g, 3.87 mmol) and aldehyde **6c** (996 mg, 3.52 mmol). Flash column chromatography with heptane/ethyl acetate (2:1) gave 1.89 g (85%, two rotamers) of **13a**: $[\alpha]_D$ +12 (*c* 1.90, $CHCl_3$); IR (neat) ν 3691, 3452, 3069, 3020, 3015, 2981, 2939, 2881, 1723,1687, 1515, 1455, 1393, 1378, 1367, 1238, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.30 (m, 10H), 5.69−5.48 (m, 1H), 5.19−4.95 (m, 6H), 4.94−4.81 (m, 1H), 3.94−3.70 (m, 3H), 3.20 (t, J = 6.4 Hz, 1H), 3.12 (q, J = 6.2 Hz, 2H), 2.68−2.58 (m, 1H), 2.56−2.44 (m, 1H), 2.38−2.26 (m, 1H), 1.46 (s, 9H), 1.65−1.24 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 156.4, 152.9, 152.8, 139.3, 136.7, 135.9, 128.6, 128.5, 128.4, 128.1, 117.3, 116.8, 94.2, 93.7, 80.0, 79.7, 66.6, 66.4, 65.4, 61.6, 60.9, 46.5, 45.7, 40.9, 33.1, 30.7, 30.4, 29.7, 28.5, 27.1, 26.4, 24.5, 23.0, 22.7, 22.9; MS (ESI) *m/z* 638 $[M + H]^+$, 660 $[M + Na]^+$. Anal. Calcd for $C_{36}H_{51}N_3O_7$: C, 67.79; H, 8.06; N, 6.59. Found: C, 67.59; H, 8.31; N, 6.43.

General Procedure 4. Preparation of 14a, 14b, and 19. To a cooled (0 °C) solution of amines **13a, 13b,** and **18** (0.5 mmol) and 0.5 M Na_2CO_3 (2 mL, 1 mmol) in THF−water (20 mL, 3:1) was added 9-fluorenylmethyl chloroformate (0.55 mmol) in one portion, and the resulting mixture was vigorously stirred at room temperature for 3 h. The reaction mixture was diluted with water, extracted with ethyl acetate, and the combined organic layers were washed with brine and then dried over Na_2SO_4. The residue obtained upon concentration was purified by flash column chromatography on silica gel to give **14a, 14b,** and **19**.

(4*S*,1′*S*,1‴*S*)-4-(1′-{2″-[(1‴-Benzyloxycarbonyl-5‴-benzyloxycarbonylaminopentyl)-(9*H*-fluoren-9-ylmethoxycarbonyl)amino]ethyl}allyl)-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester (14a). General procedure 4 was followed using **13a** (231 mg, 0.36 mmol). Flash column chromatography with heptane/ethyl acetate (4:1) gave 294 mg (97%, two rotamers) of **14a**: $[\alpha]_D$ −2 (*c* 1.70, $CHCl_3$); IR ($CHCl_3$) ν 3452, 3069, 3020, 2983, 2940, 2876, 1689, 1515, 1477, 1453, 1393, 1378, 1367 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7,79−7,70 (m, 2H), 7.58−7.46 (m, 2H), 7.44−7.19 (m, 14H), 5.69−5.32 (m, 1H), 5.18−4.85 (m, 7H), 4.64−4.28 (m, 3H), 4.22−3.93 (m, 1H), 3.85−3.55 (m, 3H), 3.22−2.93 (m, 4H), 2.33−2.12 (m, 1H), 2.08−1.91 (m, 1H), 1.85−1.62 (m, 1H), 1.44−1.41 (2s, 9H), 1.58−1.22 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 170.7, 156.3, 155.7, 152.7, 152.0, 143.8, 141.3, 138.5, 138.4, 136.6, 135.5, 128.5, 128.4, 128.2, 128.0, 127.6, 127.0, 126.9, 125.0, 124.8, 119.9, 117.3, 116.8, 94.0, 93.5, 79.9, 79.7, 67.1, 66.7, 66.4, 65.4, 65.3, 60.5, 60.1, 59.8, 47.3, 47.2, 46.2, 46.1, 45.5, 40.7, 29.6, 29.4, 29.3, 28.9, 28.3, 27.1, 26.4, 24.3,

23.5, 22.6; MS (ESI) *m/z* 860 $[M + H]^+$, 882 $[M + Na]^+$. Anal. Calcd for $C_{51}H_{61}N_3O_9$: C, 71.22; H, 7.15; N, 4.89. Found: C, 71.07; H, 7.22; N, 4.75.

(2*S*,3*S*,1″*S*)-3-{2′-[(1″-Benzyloxycarbonyl-5″-benzyloxycarbonylaminopentyl)-(9*H*-fluoren-9-ylmethoxycarbonyl)-amino]ethyl}-2-*tert*-butoxycarbonylaminopent-4-enoic Acid (15a). General procedure 3 was followed using **14a** (322 mg, 0.38 mmol). Flash column chromatography with heptane/ethyl acetate (2:1) gave 227 mg (73%, two rotamers) of **15a**: $[\alpha]_D$ −4 (*c* 1.10, $CHCl_3$); IR ($CHCl_3$) *ν* 3445, 3069, 3021, 2957, 2871, 1706, 1500, 1477, 1453, 1420, 1369, 1224, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 7.79−7.66 (m, 2H), 7.57−7.43 (m, 2H), 7.41−7.16 (m, 14H), 5.66−5.30 (m, 1H), 5.23−4.84 (m, 8H), 4.63−3.92 (m, 5H), 3.27−2.88 (m, 4H), 2.64−2.22 (m, 1H), 2.07−1.02 (m, 17H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 174.2, 171.2, 170.7, 156.8, 156.4, 156.2, 155.7, 143.9, 143.7, 141.3, 138.5, 135.6, 135.5, 128.8, 128.5, 128.2, 128.1, 127.6, 127.0, 124.8, 124.5, 120.0, 119.0, 118.7, 79.9, 66.8, 66.7, 60.3, 59.9, 56.7, 47.3, 47.2, 45.2, 45.1, 44.3, 44.2, 40.9, 40.8, 30.3, 30.2, 29.8, 28.3, 23.6, 23.5; MS (ESI) *m/z* 834 $[M + H]^+$, 856 $[M + Na]^+$, 872 $[M + K]^+$. Anal. Calcd for $C_{48}H_{55}N_3O_{10}$: C, 69.13; H, 6.65; N, 5.04. Found: C, 69.17; H, 6.64; N, 5.18.

General Procedure 5. Preparation of 16a, 16b, and 21. To a solution of acids **15a, 15b,** and **20** (0.24 mmol) in dry THF (2 mL) at 0 °C was added dropwise diethylamine (10 mL) under argon during 15 min, and the reaction mixture was stirred at room temperature for 6 h. The solvent was evaporated to dryness. To a solution of the oil obtained above in dry DMF (25 mL) were added TBTU (0.72 mmol), HOBt (0.72 mmol), and DIEA (0.96 mmol), and the reaction mixture was stirred at room temperature for 24 h. The reaction was quenched by addition of water, and the reaction mixture was extracted with ethyl acetate. The organic layers were washed with 1 N $KHSO_4$, H_2O, saturated $NaHCO_3$, and brine and then dried over Na_2SO_4 and evaporated. Flash column chromatography on silica gel gave **16a, 16b,** and **21**.

(2*S*,3′*S*,4′*S*)-6-Benzyloxycarbonylamino-2-(3′-*tert*-butoxycarbonylamino-2′-oxo-4′-vinylpiperidin-1′-yl)-hexanoic Acid Benzyl Ester (16a). General procedure 5 was followed using **15a** (200 mg, 0.24 mmol). Flash column chromatography with heptane/ethyl acetate (3:1) gave 125 mg (88%, two rotamers) of **16a**: $[\alpha]_D$ −21 (*c* 0.70, $CHCl_3$); IR ($CHCl_3$) *ν* 3449, 3020, 2983, 2937, 2868, 1714, 1655, 1507, 1455, 1438, 1368, 1326, 1265, 1167 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 7.38−7.30 (m, 10H), 5.76 (ddd, *J* = 8.0, 10.3, 16.9 Hz, 1H), 5.19−4.94 (m, 8H), 4.88 (bs, 1H), 4.05 (m, 1H), 3.28−3.12 (m, 4H), 2.40−2.27 (m, 1H), 2.06−1.92 (m, 2H), 1.82−1.60 (m, 2H), 1.43 (s, 9H), 1.58−1.21 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.8, 170.6, 156.5, 156.2, 138.6, 136.7, 135.4, 128.6, 128.4, 128.2, 128.0, 116.0, 79.5, 66.9, 66.4, 56.4, 55.2, 43.6, 41.6, 40.5, 29.2, 28.3, 27.8, 27.5, 23.2; MS (ESI) *m/z* 594 $[M + H]^+$, 616 $[M + Na]^+$, 632 $[M + K]^+$. Anal. Calcd for $C_{33}H_{43}N_3O_7$: C, 66.76; H, 7.30; N, 7.08. Found: C, 66.48; H, 7.61: N, 6.99.

(2*S*,2′*S*)-1-(2′-Amino-6′-benzyloxycarbonylamino-hexanoyl)-pyrrolidine-2-carboxylic Acid *tert*-Butyl Ester (17). To a solution of L-Pro-OBu^t (1.83 g, 10.70 mmol) and Fmoc-L-Lys(Cbz)OH (4.50 g, 8.90 mmol) in CH_2Cl_2 (25 mL) was added EDC (2.00 g, 10.70 mmol) and HOBt (1.44 g, 10.70 mmol), and the reaction mixture was stirred at room temperature under Ar for 24 h. Water was added, and the reaction mixture was extracted with CH_2Cl_2. The organic extracts were washed with 1 N $KHSO_4$, H_2O, saturated $NaHCO_3$, and brine, successively, and then dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue obtained was purified by flash column chromatography with heptane/ethyl acetate (4:1 then 2:1) to give 5.25 g (89%) of Fmoc-l-Lys(Cbz)-Pro-OBu^t: $[\alpha]_D$ −36 (*c* 1.60, $CHCl_3$); IR (neat) *ν* 3296, 2941, 1713, 1637, 1524, 1446, 1366, 1241, 1149, 1092, 1030, 914, 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 7.73 (d, *J* = 7.4 Hz, 2H), 7.57 (d, *J* = 7.3 Hz, 2H), 7.43−7.19 (m, 9H), 5.88 (d, *J* = 8.1 Hz, 1H), 5.44 (bs, 1H), 5.06 (s, 2H), 4.59−4.04 (m, 5H), 3.74−3.42 (m, 2H), 3.32−3.03 (m, 2H), 2.26−1.32 (m, 10H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 171.1, 170.4, 156.6, 156.1, 143.9, 143.8, 141.2, 136.8, 128.4, 128.1, 127.9, 127.7, 127.0, 125.1, 119.9, 81.5, 66.9, 66.4, 59.6, 52.1, 47.1, 47.0, 40.4, 31.9, 29.1, 28.9, 27.9, 24.9, 21.5; MS (ESI) *m/z* 678 $[M + Na]^+$; HRMS calcd for $C_{38}H_{45}N_3O_7Na$ (M + Na) 678.3155, found 678.3149.

To a solution of Fmoc-L-Lys(Cbz)-ProOBu^t (5.20 g, 7.94 mmol) in dry THF (50 mL) at 0 °C was added dropwise diethylamine (20 mL) under Ar during 15 min and the reaction mixture was stirred at room temperature for 3 h. Solvent was removed by evaporation under reduced pressure, and purification by flash column chromatography on silica gel with heptane/ethyl acetate (1:1) and then CH_2Cl_2/MeOH (20:1) gave 3.00 g (87%) of **17** as an oil: $[\alpha]_D$ −37 (*c* 2.10, $CHCl_3$); IR (neat) *ν* 3300, 2932, 2873, 1713, 1633,1530, 1445, 1366, 1245, 1150, 1092, 1025, 981, 847 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 7.42−7.18 (m, 5H), 5.81 (m, 1H), 5.06 (s, 2H), 4.41−4.26 (m, 1H), 3.68−3.38 (m, 3H), 3.27−3.06 (m, 2H), 2.28−1.30 (m, 12H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 174.0, 171.3, 156.6, 136.9, 128.4, 128.0, 127.9, 81.2, 66.3, 59.6, 52.5, 46.6, 40.5, 34.5, 29.8, 29.5, 27.9, 24.9, 22.2; MS (ESI) *m/z* 434 $[M + H]^+$, 456 $[M + Na]^+$; HRMS calcd for $C_{23}H_{35}N_3O_5Na$ (M + Na) 456.2474, found 456.2458.

(2*S*,2′*S*,3″*S*,4″*S*)-1-[2′-(3″-Amino-2″-oxo-4″-vinyl-piperidin-1″-yl)-6′-benzyloxycarbonylamino-hexanoyl]-pyrrolidine-2-carboxylic Acid *tert*-Butyl Ester (22). To a solution of **21** (399 mg, 0.60 mmol) in ethyl acetate (9 mL) was added concentrated HCl (3 mL) at −50 °C, and the reaction mixture was stirred at that temperature for 2 h and then stirred at 0 °C for 1 h. The reaction mixture was neutralized with a saturated solution of $NaHCO_3$ and then extracted with ethyl acetate. The organic layers were combined and washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. Flash column chromatography with CH_2Cl_2 and then CH_2Cl_2/MeOH (20:1) gave 260 mg (67%) of **22** as an oil: $[\alpha]_D$ −91 (*c* 1.10, $CHCl_3$); IR (neat) *ν* 3329, 2977, 2935, 2874, 1720, 1643, 1532, 1487, 1440, 1393, 1367, 1248, 1153, 1094, 1025, 919, 845, 753, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 7.37−7.25 (m, 5H), 5.81−5.58 (m, 1H), 5.51−5.41 (m, 1H), 5.40−5.26 (m, 1H), 5.24−4.99 (m, 4H), 4.37−4.26 (m, 1H), 3.78−3.55 (m, 2H), 3.43−3.30 (m, 2H), 3.28−3.11 (m, 3H), 2.83−2.58 (bs, 2H), 2.43−2.24 (m, 1H), 2.21−1.23 (m, 12H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 171.3, 171.2, 168.7, 156.5, 139.2, 136.8, 128.4, 128.0, 128.0, 116.7, 81.3, 66.4, 59.8, 55.9, 53.6, 47.2, 44.6, 41.7, 40.6, 29.3, 29.1, 28.2, 27.9, 27.5, 24.8, 22.6; MS (ESI) *m/z* 557 $[M + H]^+$, 579 $[M + Na]^+$; HRMS calcd for $C_{50}H_{44}N_4O_6Na$ (M + Na) 579.3159, found 579.3167.

(2*S*,2′*S*,3″*S*,4″*S*,2‴*S*)-1-{2′-[3″-(3‴-Benzyloxy-2‴-*tert*-butoxycarbonylamino-propionylamino)-2″-oxo-4″-vinyl-piperidin-1″-yl]-6′-benzyloxycarbonylamino-hexanoyl}-pyrrolidine-2-carboxylic Acid *tert*-Butyl Ester (23). To a solution of **22** (250 mg, 0.45 mmol) and Boc-L-Ser(OBn)OH (145 mg, 0.49 mmol) in CH_2Cl_2 (25 mL) was added EDC (103 mg, 0.54 mmol) and HOBt (72 mg, 0.54 mmol), and the reaction mixture was stirred at room temperature under Ar for 24 h. Water was added, and the reaction mixture was extracted with CH_2Cl_2. The organic extracts were washed with 1 N $KHSO_4$, H_2O, saturated $NaHCO_3$, and brine, successively, and then dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue obtained was purified by flash column chromatography with heptane/ethyl acetate (4:1 then 2:1) to give 303 mg (80%) of **23** as white crystals: mp 55−56 °C; $[\alpha]_D$ −59 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) *ν* 3445, 3015, 2983, 2934, 2871, 1714, 1681, 1644, 1515, 1487, 1455, 1393, 1368, 1236, 1156, 1100, 1025, 923, 844 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 7.38−7.22 (m, 10H), 7.19−7.06 (m, 1H), 5.76−5.58 (m, 1H), 5.52−5.35 (m, 1H), 5.33−5.19 (m, 2H), 5.15−4.89 (m, 4H), 4.61−4.43 (m, 2H), 4.39−4.23 (m, 2H), 4.14−3.98 (m, 1H), 3.93−3.72 (m, 2H), 3.70−3.27 (m, 4H), 3.25−3.07 (m, 2H), 2.64−2.41 (m, 1H), 2.66−1.12 (m, 12H), 1.44 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 171.2, 170.7, 169.0, 168.8, 156.5,

155.4, 138.4, 137.6, 136.9, 128.4, 128.1, 128.0, 127.8, 116.2, 81.3, 80.0, 73.3, 70.0, 66.4, 59.8, 54.8, 53.9, 47.1, 42.7, 41.3, 40.6, 29.3, 29.1, 28.3, 27.9, 24.8, 22.8; MS (ESI) *m/z* 856 $[M + Na]^+$; HRMS calcd for $C_{45}H_{63}N_5O_{10}Na$ (M + Na) 856.4473, found 856.4487.

(2*S*,2′*S*,3″*S*,4″*S*,2‴*S*)-1-{2′-[3″-(2‴-Amino-3‴-benzyloxy-propionylamino)-2″-oxo-4″-vinyl-piperidin-1″-yl]-6′-benzyloxycarbonylamino-hexanoyl}-pyrrolidine-2-carboxylic Acid *tert*-Butyl Ester (24). This compound was prepared following the same procedure as described for **22** starting from **23** (380 mg, 0.46 mmol). Flash column chromatography with CH_2Cl_2 and then CH_2Cl_2/MeOH (20:1) gave 234 mg (70%, two rotamers): $[\alpha]_D$ −81 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) ν 3452, 3377, 3022, 3016, 2948, 2868, 1716, 1643, 1517, 1454, 1393, 1368, 1228, 1205, 1154, 1095, 1027, 990, 923, 843 cm^{-1}; H NMR (300 MHz, $CDCl_3$) δ 7.95−7.82 (m, 1H), 7.40−7.22 (m, 10H), 5.76−5.58 (m, 1H), 5.50−4.91 (m, 6H), 4.56−4.14 (m, 4H), 3.90−3.08 (m, 9H), 2.58−1.19 (m, 16H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 171.2, 169.4, 169.3, 156.5, 138.6, 137.8, 136.8, 128.4, 128.1, 128.0, 127.7, 116.1, 81.3, 73.1, 72.2, 66.4, 59.7, 55.0, 53.9, 47.1, 43.2, 41.2, 40.6, 29.3, 29.1, 28.4, 28.0, 24.8, 22.8; MS (ESI) *m/z* 756 $[M + Na]^+$, 734 $[M + H]^+$; HRMS calcd for $C_{40}H_{57}N_5O_8$ (M + H) 734.4129, found 734.4103.

(2*S*,2′*S*,3″*S*,4″*S*,2‴*S*)-1-{2′-[3″-(2‴-Acetylamino-3‴-benzyloxy-propionylamino)-2″-oxo-4″-vinyl-piperidin-1″-yl]-6′-benzyloxycarbonylamino-hexanoyl}-pyrrolidine-2-carboxylic Acid *tert*-Butyl Ester (25). To a stirred solution of amine **24** (1.25 g, 1.71 mmol) in dry CH_2Cl_2 were added triethylamine (0.31 mL, 2.22 mmol), a catalytic amount of DMAP (5 mg), and acetic anhydride (0.21 mL, 2.22 mmol). The reaction mixture was stirred at room temperature overnight under an argon atmosphere. The reaction was quenched by the addition of several drops of MeOH. The reaction mixture was extracted with dichloromethane and the combined organic extracts were washed with 1 N $KHSO_4$, a saturated solution of $NaHCO_3$, and brine and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by HPLC (CH_3CN:H_2O, 45:55, Colonne Symmetry, 250 × 4.6 mm, C 18) to give 675 mg (51%) of **25** as white crystals: mp 61−62 °C; $[\alpha]_D$ −60 (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) ν 3301, 2931, 1718, 1631, 1522, 1437, 1366, 1244, 1150, 915, 843 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.23 (m, 11H), 6.59−6.67 (m, 1H), 5.75−5.56 (m, 1H), 5.42−5.33 (m, 1H), 5.31−5.22 (m, 1H), 5.11−4.92 (m, 4H), 4.68−4.57 (m, 1H), 4.55−4.50 (s, 2H), 4.36−4.27 (m, 1H), 4.15−3.08 (m, 9H), 2.64−2.45 (m, 1H), 2.23−1.20 (m, 12H), 1.97 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 170.4, 170.2, 168.9, 168.7, 156.5, 138.4, 137.5, 136.8, 128.4, 128.0, 127.9, 127.9, 116.2, 81.3, 73.4, 69.5, 66.4, 59.7, 54.7, 53.9, 52.2, 47.1, 42.7, 41.3, 40.6, 29.3, 29.1, 28.4, 28.1, 27.9, 24.8, 23.2, 22.8; MS (ESI) *m/z* 798 $[M + Na]^+$; HRMS calcd for $C_{42}H_{57}N_5O_9Na$ (M + Na) 798.4054, found 798.4049. Anal. Calcd $C_{42}H_{57}N_5O_9$: C, 65.01; H, 7.40; N, 9.03. Found: C, 64.58; H, 7.25; N, 8.66.

(2*S*,2′*S*,3″*S*,4″*R*,2‴*S*)-3-(2′-Acetylamino-3′-benzyloxy-propionylamino)-1-[5″-benzyloxycarbonylamino-1″-(2‴-*tert*-butoxycarbonyl-pyrrolidine-1‴-carbonyl)-pentyl]-2-oxo-piperidine-4-carboxylic Acid (26a). Acetyl lactam **25** (150 mg, 0.19 mmol) was dissolved in carbon tetrachloride (2 mL), acetonitrile (2 mL), and distilled water (3 mL). To this biphasic solution were added sodium metaperiodate (213 mg, 0.76 mmol) and a catalytic amount of ruthenium trichloride hydrate (1 mg, 2.2 mol %), and the reaction mixture was stirred vigorously at room temperature under an argon atmosphere for 24 h. Then, 10 mL of CH_2Cl_2 was added, and the phases were separated. The upper aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and then concentrated. Purification by reversed phase HPLC (Colonne Hypercarb debit 1 mL/min, eluted with CH_3CN/CH_2Cl_2/2% CH_3COOH) gave 55 mg (36%) of **26a** as white solid: mp 88−89 °C; $[\alpha]_D$ −88 (*c* 1.00, $CHCl_3$); IR (neat) ν 3304, 2926, 1713, 1632, 1530, 1443, 1366, 1247, 1150, 1095, 1026, 982, 915, 842, 733, 696 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.28−7.12 (m, 10H), 5.19 (t, *J* = 7.6 Hz, 1H), 4.95 (s, 2H), 4.82−4.68 (m, 4H), 4.53 (t, *J* = 5.2 Hz, 1H), 4.42 (s, 2H), 4.25−4.15 (m, 1H), 3.71−3.62 (m, 1H), 3.59 (d, *J* = 5.3 Hz, 2H), 3.49−3.16 (m, 4H), 3.07−2.93 (m, 2H), 2.18−1.14 (m, 13H), 1.88 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.8, 173.2, 173.0, 172.0, 170.4, 169.9, 158.9, 139.3, 138.5, 129.5, 129.4, 128.9, 128.8, 128.7, 82.7, 74.2, 71.0, 67.3, 61.6, 55.8, 54.5, 53.8, 48.4, 44.7, 43.0, 41.5, 30.5, 30.2, 29.1, 28.3, 26.9, 25.8, 24.0, 22.6; MS (ESI) *m/z* 816 $[M + Na]^+$; HRMS calcd for $C_{41}H_{55}N_5O_{11}Na$ (M + Na) 816.3796, found 816.3770.

(2*S*,2′*S*,3″*S*,4″*S*,2‴*S*)-1-{2′-[3″-(2‴-Amino-3‴-*tert*-butoxy-propionylamino)-2″-oxo-4″-vinyl-piperidin-1″-yl]-6′-benzyloxycarbonylamino-hexanoyl}-pyrrolidine-2-carboxylic Acid *tert*-Butyl Ester (29). This compound was prepared according to the procedure described for **17** starting from **28** (278 mg, 0.40 mmol). Flash column chromatography with CH_2Cl_2/ethyl acetate (1:1) and then CH_2Cl_2/MeOH (20:1) gave 203 mg (96%) of **29** as white crystals: mp 53−55 °C; $[\alpha]_D$ −84 (*c* 0.50, $CHCl_3$); IR (neat) ν 3319, 2972, 2932, 2871, 1716, 1632, 1518, 1435, 1391, 1364, 1245, 1194, 1150, 1082, 1020, 914, 845 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.3 Hz, 1H), 7.37−7.23 (m, 5H), 5.78−5.61 (m, 1H), 5.38−5.27 (m, 1H), 5.24 (t, *J* = 7.6 Hz, 1H), 5.11−4.96 (m, 4H), 4.33 (dd, *J* = 4.2, 9.0 Hz, 1H), 4.20 (t, *J* = 9.7 Hz, 1H), 3.91−3.71 (m, 1H), 3.65−3.48 (m, 4H), 3.43−3.30 (m, 2H), 3.26−3.05 (m, 2H), 2.22−2.08 (m, 1H), 2.05−1.80 (m, 5H), 1.77−1.61 (m, 2H), 1.57−1.47 (m, 2H), 1.41 (s, 9H), 1.37−1.24 (m, 2H), 1.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 171.2, 169.4, 169.2, 156.5, 138.7, 136.8, 128.4, 128.1, 128.0, 116.0, 81.3, 73.3, 66.4, 63.8, 59.7, 55.4, 53.9, 53.9, 47.2, 47.1, 43.2, 41.2, 40.6, 29.3, 29.1, 28.4, 27.9, 27.5, 24.8, 22.8; MS (ESI) *m/z* 700 $[M + H]^+$, 722 $[M + Na]^+$; HRMS calcd for $C_{37}H_{57}N_5O_8Na$ (M + Na) 722.4105, found 722.4133.

(3*S*,4*R*,2′*S*,1″*S*,2‴*S*)-3-(2′-Acetylamino-3′-hydroxy-propionylamino)-1-[5″-amino-1″-(2‴-carboxy-pyrrolidine-1‴-carbonyl)-pentyl]-2-oxo-piperidine-4-carboxylic Acid (2). Acid **31** (80 mg, 0.11 mmol) was treated with trifluoroacetic acid (5 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 3 h. The volatile was evaporated under reduced pressure to dryness. A suspension of crude diacid in MeOH (10 mL) containing a catalytic amount of 10% Pd−C (18 mg) was hydrogenated at atmospheric pressure for 3 h. The catalyst was removed by filtration through Celite. The filtrate was concentrated under reduced pressure, and the crude residue obtained was purified by reversed phase HPLC (Colonne Hypercarb debit 1 mL/min, eluted with CH_3CN/0.5% CF_3COOH (85%) and H_2O/0.5% CF_3COOH (15%)) to give 27 mg (54%) of tetrapeptide **2** as white solid: mp 94−96 °C; $[\alpha]_D$ −93 (*c* 0.25, H_2O); IR (neat) ν 2951, 1631, 1435, 1180, 1129, 838, 798, 721 cm^{-1}; ^1H NMR (300 MHz, D_2O diaoxane as reference) δ 5.19 (t, *J* = 6.9 Hz, 1H), 4.46−4.30 (m, 3H), 3.77 (dd, *J* = 4.7, 11.5 Hz, 2H), 3.57 (t, *J* = 6.4 Hz, 2H), 3.41 (dt, *J* = 3.9, 12.5 Hz, 1H), 3.32−3.20 (m, 1H), 3.06 (dt, *J* = 3.8, 11.2 Hz, 1H), 2.93 (t, *J* = 7.5 Hz, 2H), 2.33−2.12 (m, 2H), 2.06−1.89 (m, 6H), 1.86−1.54 (m, 4H), 1.42−1.14 (m, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 176.0, 174.4, 171.6, 169.8, 169.2, 163.0 (q, *J* = 35 Hz), 116.0 (q, *J* = 291 Hz), 61.2, 59.8, 55.6, 55.2, 52.1, 47.6, 43.0, 42.2, 39.3, 28.9, 27.1, 26.4, 24.9, 24.5, 22.0, 21.8; MS (ESI) *m/z* 514 $[M + H]^+$; HRMS calcd for $C_{22}H_{36}N_5O_9Na$ (M + H) 514.2513, found 514.2546.

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Supporting Information Available: General information and all spectroscopic data for compounds **6b**, **6c**, **8b**, **9b**, **10b**, **11b**, **12b**, **13b**, **14b**, **15b**, **16b**, **18**, **19**, **20**, **21**, **28**, **30,** and **31**; X-ray crystallographic data (CIF) and ORTEP drawing for compound **12a**; copies of ^1H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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