Synthesis of Peptides and Pseudopeptides Incorporating an *endo*-(2*S*,3*R*)-Norborn-5-ene Residue as a Turn Inducer

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The desymmetrization of *endo*-norborn-5-ene-2,3-dicarboxylic anhydride (**5**) by proline derivatives is used to prepare peptides and pseudopeptides incorporating an *endo*-(2*S*,3*R*)-2-amino-3-carboxynorborn-5-ene (**1**) residue. The peptides contain a single conformationally constrained β-amino acid residue, while the pseudopeptides also contain a urea linkage and two peptide chains running in parallel directions. The key step in the synthesis is a Curtius rearrangement on the amido acids **6a,b** to generate an isocyanate that is then directly reacted with suitably protected amino acids and peptides to give the peptides and pseudopeptides. The synthesis of the peptide analogue **4** is also described; in this compound, the two peptide chains run parallel to one another, and the stereochemistry of the norbornene unit within compound **4** was determined by X-ray analysis of the related peptide analogue **23**.

Introduction

β-Sheets are a widespread element of protein structure;[1] however, while a number of initiators for α-helix formation[2] and conformationally constrained analogues of the various turns[1,3] have been reported, relatively little work has been done on the synthesis of initiators for β-sheet formation. Two approaches can be adopted in the synthesis of conformationally constrained peptides; either most of the peptide backbone can be retained and constrained by the introduction of peptidomimetics[4,5] or the peptide backbone can be completely replaced by a conformationally rigid unit as exemplified by the work of Smith et al.[5] The first example of the former approach was due to Kemp,[6] who employed the epindolidione nucleus as a molecular fragment to induce β-sheet formation. The work that has been done on the design of β-sheet mimics has largely concentrated on antiparallel β-sheets, while the synthesis of constraints imposing a parallel β-sheet has by comparison been neglected.

A template for the synthesis of parallel and antiparallel β-sheets would be valuable in view of the role played by this secondary structure in the biological activity of proteins. It is well-known that proteases bind their substrates and inhibitors by generating β-sheets or β-strands, and this conformational requirement has been influential in the design of inhibitors of renin[7] and of HIV-1 protease.[8] Moreover, it has been reported that protein−DNA interactions can occur with the protein interface in a β-strand conformation.[9]

The main goal of the work described in this paper was to develop the *endo*-(2*S*,3*R*)-2-amino-3-carboxynorborn-5-ene residue (**1**) as a β-sheet inducer to allow the formation of well-defined parallel and antiparallel β-sheets. There is currently much interest in the synthesis and applications of 2-amino-3-carboxynorborn-5-ene derivatives; racemic syntheses of both the *endo*- and *exo-cis*-isomers of this β-amino acid have been reported along with methodology for their resolution.[10] In addition, a chiral auxiliary controlled Diels−Alder reaction has been

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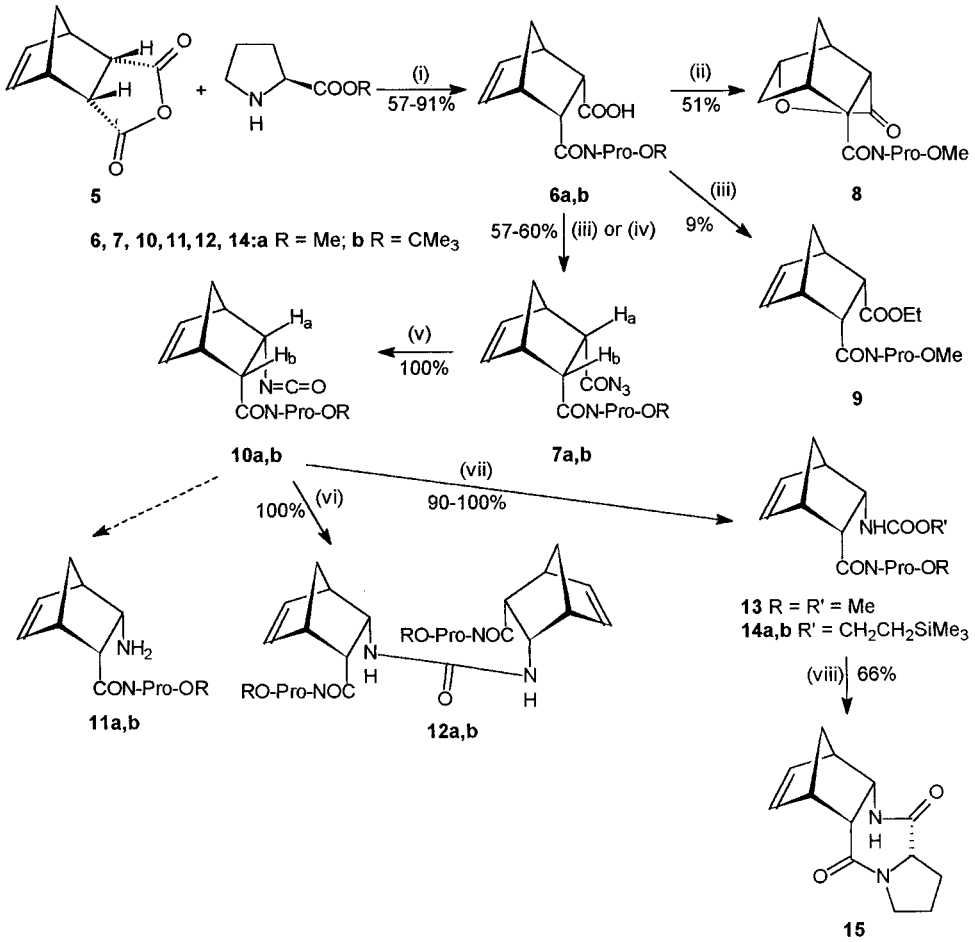
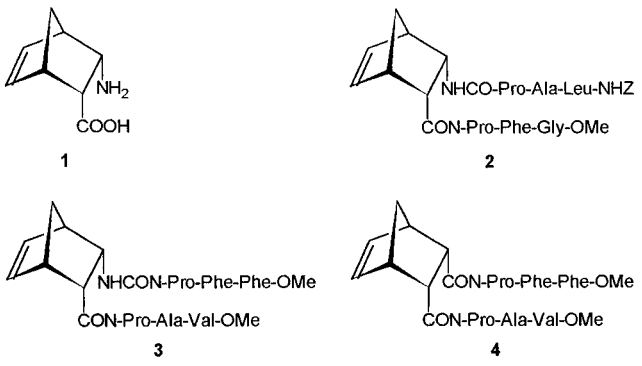
Scheme 1[a]



[a] Reagents: (i) Et_3N; (ii) H_2SO_4/NaN_3; (iii) $EtOCOCl/Et_3N/NaN_3$; (iv) $H_2C{=}CMeOCOCl/Et_3N/NaN_3$; (v) Δ/C_6H_6; (vi) THF/H_2O (1:1); (vii) R′OH; (viii) Bu_4NF/THF.

reported for the asymmetric synthesis of the *trans*-isomer.[11] Here, we describe an asymmetric synthesis of the *cis*-diastereomer of compound **1**, incorporated into peptides and pseudopeptides.[12] In recent publications, we have reported the facile desymmetrization of *meso*-anhydrides utilizing methyl prolinate[13] as a chiral reagent.[14] In this paper, we show how this methodology can be applied to the synthesis of conformationally constrained peptides **2** and pseudopeptides **3** containing an *endo*-(2*S*,3*R*)-2-amino-3-carboxynorborn-5-ene residue as well as to the synthesis of peptide analogues **4** containing an *endo*-(2*S*,3*R*)-2,3-dicarboxynorborn-5-ene residue.



Results and Discussion

Treatment of *endo*-norborn-5-ene-2,3-dicarboxylic anhydride **5** with methyl prolinate hydrochloride in the presence of triethylamine resulted in the stereoselective formation of amido acid **6a** as previously reported[14] (Scheme 1). Conversion of amido acid **6a** into the corresponding acyl azide **7a** under classical conditions proved to be problematic. In particular, treatment of **6a** with concentrated sulfuric acid and sodium azide[15] gave lactone **8**, while attempted formation via the acid chloride using thionyl chloride or oxalyl chloride[16] gave only anhydride **5**. Use of diphenyl phosphorazidate[17] was also unsuccessful, but activation of the acid functionality via a mixed anhydride[10,11,18] gave encouraging results. Reaction of acid **6a** with ethyl chloroformate and triethylamine in tetrahydrofuran at −30 °C followed by addition

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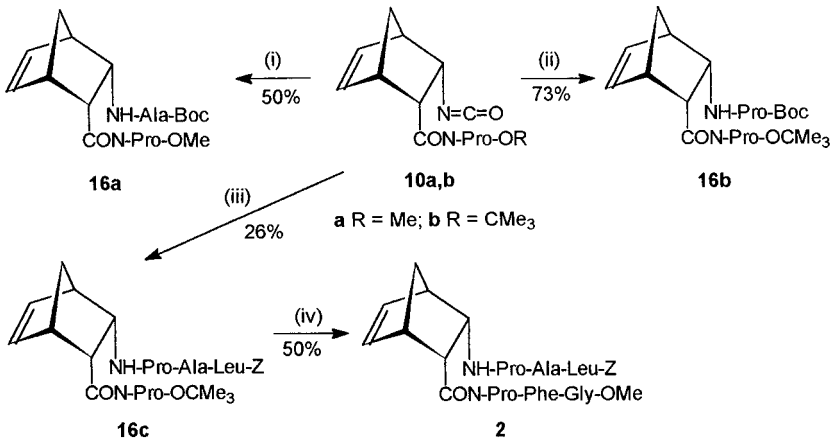
Scheme 2[a]



[a] Reagents: (i) Boc-Ala-OH/Et_3N/Δ; (ii) Boc-Pro-OH/Et_3N/Δ; (iii) **17**/Et_3N/Δ; (iv) (a) TFA, (b) H-Phe-Gly-OMe/EDC/HOBt.

of aqueous sodium azide afforded the desired acyl azide **7a**, but this was always accompanied by 9% of the corresponding ethyl ester **9**. The formation of compound **9** can be explained by attack of the ethanol byproduct upon acyl azide **7a**, and this could not be eliminated even at lower temperatures. Similarly, with the more sterically hindered isobutyl chloroformate, ester formation again occurred. However, the use of isopropenyl chloroformate[19] produced the desired acyl azide **7a** as the only isolated product in 57% yield. The success of this chloroformate can be attributed to the fact that the only byproduct, acetone, is non-nucleophilic. The IR spectrum of azide **7a** showed a distinct peak at 2136 cm^{-1}, characteristic of acyl azides. Having accomplished the synthesis of **7a** in reasonable yield, the acyl azide was brought to reflux for 2 h in anhydrous benzene, affording isocyanate **10a** in quantitative yield. The coupling constants between H_a and H_b in compounds **7a** and **10a** were of comparable magnitude (9.4 Hz in **7a**; 8.8 Hz in **10a**), showing that as expected the Curtius rearrangement had occurred with complete retention of configuration at the migrating center.[16]

All attempts to directly hydrolyze isocyanate **10a** to amine **11a** were unsuccessful. Decomposition occurred under acidic or basic conditions, while neutral conditions (water/tetrahydrofuran) resulted in dimerization to give urea **12a**, as evidenced by the distinct urea carbonyl peak at 156 ppm in the ^{13}C NMR and by mass spectrometry. Isocyanate **10a** could, however, be converted into urethane **13** simply by reaction with excess methanol, and this encouraged us to investigate a two-step procedure for the hydrolysis, whereby isocyanate **10a** was trapped and subsequently deprotected. Following preliminary experiments, β-(trimethylsilyl)ethanol was chosen as a suitable urethane forming reagent in preference to other possibilities such as thiophenol and *p*-methoxybenzyl alcohol, which gave adducts that were difficult to purify. Thus, addition of β-(trimethylsilyl)ethanol to a benzene solution of isocyanate **10a** followed by heating at 80 °C gave urethane **14a** in quantitative yield. Rapid removal of the [β-(trimethylsilyl)ethoxy]carbonyl protecting group occurred upon treatment with tetrabutylammonium fluoride[20] in THF at room temperature. However, the resulting amine **11a** could not be isolated; instead, assisted by the basic reaction conditions, it cyclized onto the methyl ester to give the seven-membered ring, bislactam **15**, which was isolated after purification by flash column chromatography. The cyclization could not be prevented even at 0 °C, and at temperatures below this the deprotection failed. Cleavage of the urethane under acidic conditions was also unrewarding.

We then reasoned that a larger proline ester, such as a *tert*-butyl ester, might hinder this intramolecular cyclization. Thus, desymmetrization of anhydride **5** using *tert*-butyl prolinate[21] proceeded in 68% yield (Scheme 1), yielding amido acid **6b** as an 8:1 ratio of diastereomers that were separable by trituration with diethyl ether. Acyl azide **7b**, isocyanate **10b**, and urethane **14b** were all obtained with the same conditions developed for the methyl ester analogues, but treatment of **14b** with tetrabutylammonium fluoride again resulted in cyclization to give **15**. Similarly, all attempts to hydrolyze isocyanate **10b** led to the formation of urea **12b**.

To circumvent the inability to prepare amine **11a,b**, the direct reaction of isocyanate **10a,b** with *N*-protected amino acids was investigated.[22] Thus, reaction of isocyanate **10a** with *N*-Boc-Ala-OH and triethylamine in refluxing toluene for 2 h led directly to the desired tripeptide **16a** in 50% yield after purification by flash chromatography (Scheme 2). Urea **12a** was a byproduct of this reaction produced in 21% yield. The disappearance of the −N=C=O (2264 cm^{-1}) stretch in the IR spectrum allowed the progress of the reaction to be monitored. Tripeptide **16b** has also been prepared from isocyanate **10b** by reaction with *N*-Boc-Pro-OH, though this reaction took considerably longer (80 °C for 16 h), probably due to the effects of steric hindrance. Noticeably, **16b** exhibited a complex ^1H NMR spectrum, owing to the presence of cis and trans rotamers about the amide bonds.

Having demonstrated that peptides **16a,b** could be prepared by the reaction of isocyanates **10a,b** with simple amino acids, the reaction of the isocyanates with peptide derivatives was investigated. The amino acids used within the peptide chains were chosen purely for ease of

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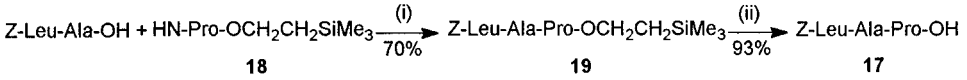
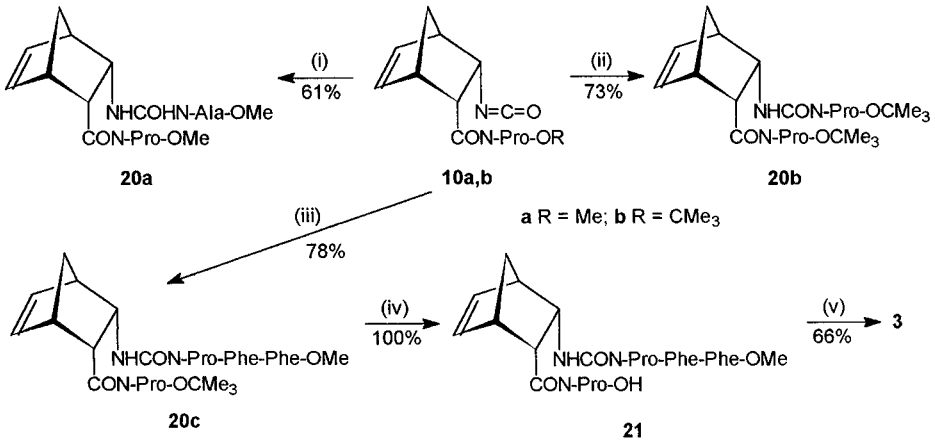
Scheme 3[a]



[a] Reagents: (i) DCC/HOBt; (ii) Bu_4NF/THF.

Scheme 4[a]



[a] Reagents: (i) H-Ala-OMe/Et_3N; (ii) H-Pro-$OCMe_3$/Et_3N; (iii) H-Pro-Phe-Phe-OMe/Et_3N; (iv) TFA; (v) H-Ala-Val-OMe/Et_3N/EDC/HOBt.

synthesis; no preference was given to amino acids known to stabilize β-sheets. The tripeptide Z-Leu-Ala-Pro-OH (**17**) was prepared from β-(trimethylsilyl)ethyl prolinate[23] (**18**) as shown in Scheme 3. Thus, condensation of compound **18** with Z-Leu-Ala-OH[24] gave the protected tripeptide **19**, which upon treatment with tetrabutylammonium fluoride gave the desired tripeptide derivative **17**. Compound **17** was synthesized in this way to avoid the use of acidolysis reactions, since preliminary experiments had shown that traces of strong acids induced the formation of urea **12b** from isocyanate **10b**. Reaction of compound **17** with isocyanate **10b** gave the desired pentapeptide **16c**. The *tert*-butyl ester could be removed from peptide **16c** by treatment with trifluoroacetic acid, and subsequent coupling to H_2N-Phe-Gly-OMe[25] gave heptapeptide **2** in 50% yield.

Isocyanates **10a,b** were also found to react with esters of amino acids and peptides as shown in Scheme 4. Thus, reaction of **10a** with alanine methyl ester gave pseudopeptide **20a**, while reaction of **10b** with proline *tert*-butyl ester and HN-Pro-Phe-Phe-OMe[26] gave pseudopeptides **20b** and **20c** respectively. In the latter case, deprotection of the *tert*-butyl ester was successfully accomplished with trifluoroacetic acid to give acid **21** in quantitative yield. Coupling of acid **18** to the dipeptide H_2N-Ala-Val-OMe[27] using water-soluble carbodiimide and HOBt gave pseudoheptapeptide **3**.

Compound **3** consists of two peptide chains running in parallel directions but slightly offset from one another by the presence of a urea linkage in one of the chains. For comparison, peptide analogue **4** consisting of a (2*S*,3*R*)-*endo*-2,3-dicarboxynorborn-5-ene residue with two peptide chains running in parallel directions but not offset from one another was also prepared. Thus, reaction of *endo*-norborn-5-ene 2,3-dicarboxylic anhydride with an *N*-terminal-proline peptide, HN-Pro-Phe-Phe-OMe,[26] resulted in ring opening to give the corresponding amido acids **22a,b** in 81% yield (Scheme 5). This reaction occurred with a complete lack of asymmetric induction, giving a 1:1 ratio of diastereomers **22a,b**. The reason for the lack of asymmetric induction in this case is not clear, but it may be that the Phe-Phe-OMe group is sufficiently large and flexible to hinder both faces of the proline ring. This would remove the factor that is thought to be responsible for the asymmetric induction when simple proline esters are used.[14] However, one of the diastereomers, **22a**, could be separated from the other by flash column chromatography in 31% overall yield. Subsequent coupling of **22a** to HN-Pro-Ala-Val-OMe[28] was accomplished *via* activation of compound **22a** as its *N*-hydroxy succinimide active ester. The isolated active ester was used without purification, and the subsequent coupling reaction with HN-Pro-Ala-Val-OMe proceeded better in dimethylformamide than in dichloromethane, giving pseudoheptapeptide **4** in 50% yield. Compound **4** exists as a mixture of two rotamers in a 10:1 ratio according to ^1H and ^{13}C NMR spectra data in $CDCl_3$. In DMSO, however, two equally populated conformations are observed, presumably due to cis and trans rotamers about one of the proline amide bonds.

At this stage it was not clear which of the two possible diastereomers of compounds **22a**/**4** had been formed. However, reaction of the *N*-hydroxy succinimide ester of compound **22a** with alanine methyl ester gave pseudopentapeptide **23**. Compound **23** was obtained as a clear crystalline solid in 69% yield, and X-ray analysis showed the absolute configuration of **23** to be as shown in Figure 1. From this, the absolute configuration of peptide analogues **22a** and **4** could be determined. In addition to allowing the determination of the absolute configura-

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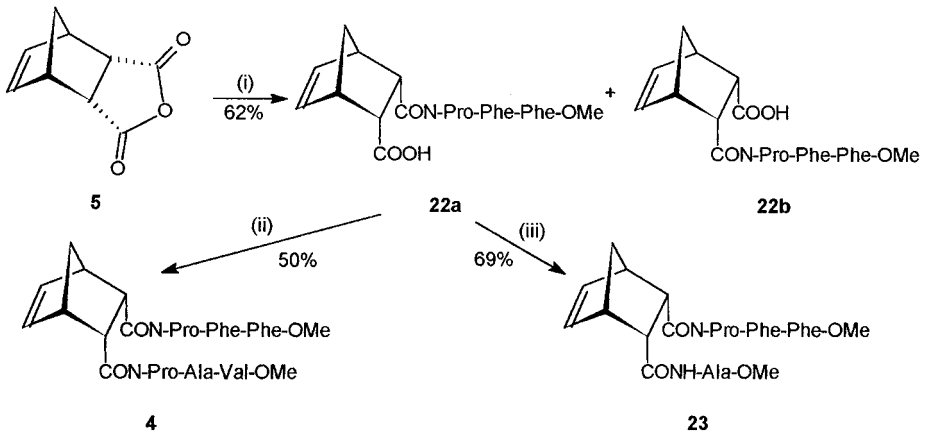
Scheme 5[a]



[a] Reagents: (i) H-Pro-Phe-Phe-OMe/Et_3N; (ii) (a) NHS/DCC, (b) HN-Pro-Ala-Val-OMe/Et_3N; (iii) (a) NHS/DCC, (b) H_2N-Ala-OMe/Et_3N.

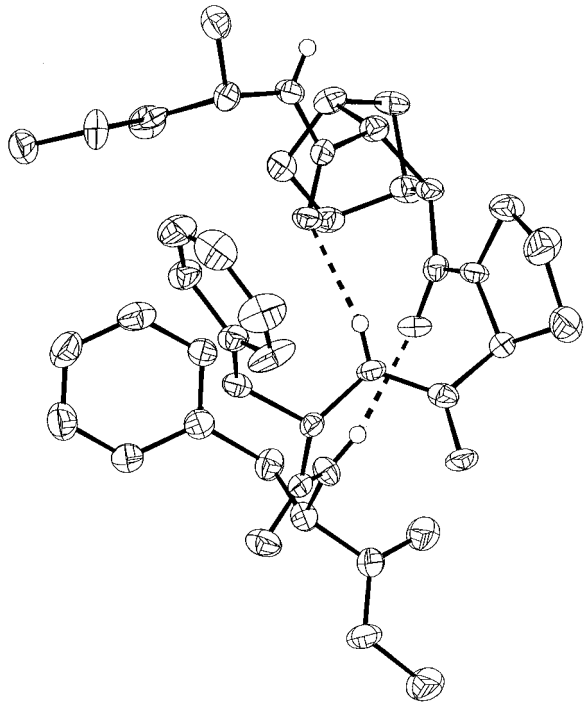


Figure 1. Solid-state structure of **23** showing the intramolecular hydrogen bonding. Thermal elipsoids are drawn at 50% probability.

tion of pseudopeptides **22**, **23**, and **4**, the X-ray structure of compound **23** also showed the presence of two intramolecular hydrogen bonds involving the amides of the Pro-Phe-Phe chain, which each form a 10-membered ring β-turn structure.[1] The conformation of compound **23** will be discussed in more detail in the following paper.

Conclusions

We have developed a short synthetic procedure for the synthesis of peptides **2** and pseudopeptides **3** incorporating the conformationally constrained β-amino acid *endo*-(2*S*,3*R*)-2-amino-3-carboxynorborn-5-ene (**1**) as a turn inducer. The key intermediates in our synthesis are isocyanates **10a,b**, and the reactions of these with nucleophiles such as amines, acids, and alcohols renders these compounds particularly attractive as synthetic building blocks for combinatorial chemistry and the creation of peptide mimics. It has also been shown that the peptides and pseudopeptides incorporating **1** are capable of undergoing further peptide chain extension under standard solution-phase peptide synthesis conditions. Heptapeptide **2** and pseudoheptapeptide **3** have the potential to form antiparallel and parallel β-sheets, respectively, with the norbornene residue acting as a β-sheet inducer. Pseudopeptide **3** differs from peptide **2** in that the urea unit slightly offsets the two peptide chains from one another, which may assist in interchain hydrogen bonding. The related peptide analogue **4** has also been prepared and has the potential to nucleate parallel β-sheet formation. The conformational analysis of compounds **2**−**4** will be discussed in the following paper.

Experimental Section

^{1}H NMR spectra were recorded at 250 MHz on a Bruker AM250 spectrometer fitted with a ^{1}H−^{13}C dual probe and were recorded at 293 K in $CDCl_3$ unless otherwise stated. Spectra were internally referenced either to TMS or to the residual solvent peak, and peaks are reported in ppm downfield of TMS. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), some combination of these, broad (br), or multiplet (m). Coupling constants are reported in hertz. ^{13}C NMR spectra were recorded at 62.5 MHz on the same spectrometer as ^{1}H NMR spectra, at 293 K and in $CDCl_3$ unless otherwise stated. Spectra were referenced to the solvent peak and are reported in ppm downfield of TMS. Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer; only characteristic absorptions are reported. Mass spectra were recorded using the FAB technique (Cs^+ ion bombardment at 25 kV) on a VG Autospec spectrometer or by chemical ionization (CI) with ammonia on either a VG model 12-253 quadrupole spectrometer or a VG Quattro II triple quadrupole spectrometer. Only significant fragment ions are reported, and only molecular ions are assigned. High-resolution mass measurements were made on a VG ZAB-E spectrometer. Optical rotations were recorded on an Optical Activity Ltd. Polar 2001 polarimeter and are reported along with the solvent and concentration in g/100 mL. Melting points are uncorrected. Elemental analyses were performed within the Chemistry department on a Carlo Erba model 1106 or model 1108 analyzer.

Flash chromatography[29] was carried out on 40−60 mm mesh silica; thin-layer chromatography was carried out on aluminum-backed silica plates (0.25 mm depth of silica containing UV254), and the plates were visualized with UV light and/or

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dodecaphosphomolybdic acid as appropriate. All yields refer to isolated, purified material, and are unoptimized. THF was dried by distillation from sodium immediately prior to use. Toluene and benzene were dried over sodium wire. Other solvents were used as supplied.

All X-ray crystallographic measurements were made at 150 K using a Delft Instruments FAST area detector diffractometer positioned at the window of a rotating anode generator using Mo Kα radiation (λ = 0.710 69 Å) by following previously described procedures.[30] Crystal data: $C_{37}H_{44}N_4O_8 \cdot 2CH_2Cl_2$ (FW 842.61); orthorhombic; space group $P2_12_12_1$; a = 11.238(2) Å, b = 18.043(2) Å and c = 20.065(2) Å; V = 4068.8(10) Å^3; Z = 4; D_c = 1.376 Mg m^{-3}; λ(Mo Kα) = 0.347 mm^{-1}; $F(000)$ = 1768. The structure was solved by direct methods (SHELXS86)[31] and refined on F^2 by full-matrix least-squares (SHELXL93)[32] using all unique data corrected for Lorentz and polarization factors but not for absorption. The structure was finally refined (499 parameters) to R [on F, $F_o > 4\sigma(F_o)$] and wR [on F^2, all 6118 data)] values of 0.11(9) and 0.1232, respectively. The Flack parameter in SHELXL93 refined to a final value of 0.11(9), confirming that the absolute structure had been determined correctly. Further details of data collection and structure refinement, atom coordinates, thermal coefficients, hydrogen atom parameters, and bond lengths and angles are available from the Cambridge Crystallographic Data Centre.[33]

Lactone 8. To a two-necked round-bottomed flask equipped with a reflux condenser and a powder funnel were added $CHCl_3$ (8 mL), amido acid **6a**[14] (0.5 g, 1.7 mmol), and concentrated H_2SO_4 (1 mL). The flask was heated to 40−50 °C, and NaN_3 (0.22 g, 3.4 mmol) was added over a period of 1.5 h, followed by heating for a further 1.5 h at 50 °C. To the cooled reaction mixture were added H_2O (30 mL) and EtOAc (40 mL). The EtOAc layer was washed with saturated aqueous K_2CO_3 (3 × 30 mL), and the solvent was dried ($MgSO_4$), filtered, and evaporated in vacuo to afford an orange oil that was subjected to flash chromatography using neat EtOAc as eluent to give (R_f = 0.18) 0.26 g (52%) of a white solid. Mp 73−76 °C. $[\alpha]^{22}_D$: −43.1 (c = 1, $CHCl_3$). IR: 1773, 1742, 1647. ^{1}H NMR: 1.6−1.8 (m, 4), 1.8−2.2 (m, 4), 2.5−2.8 (m, 3), 3.3−3.4 (m, 1), 3.6−3.8 (m, 2), 3.72 (s, 3), 4.49 (dd, 1, J = 8.6, 3.5), 4.8−4.9 (m, 1). ^{13}C NMR: 24.9, 28.9, 32.8, 37.6, 39.4, 41.2, 46.5, 47.7, 47.9, 52.2, 58.8, 80.7, 169.1, 172.9, 178.5. EI-MS m/e (relative intensity): 293 (M^+, 3), 70 (100). HRMS (EI) m/e: 293.1263 (M^+ $C_{15}H_{19}NO_5$ requires 293.1263).

Acyl Azide 7a. Isopropenyl chloroformate (0.41 mL, 3.75 mmol) was added to a mixture of amido acid **6a**[14] (1 g, 3.41 mmol) and Et_3N (1 mL) in dry THF (15 mL) at −20 °C. An aqueous solution of NaN_3 (0.55 g, 8.5 mmol) was added at −10 °C. The temperature was gradually raised to room temperature, and stirring was continued for 1 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3 × 30 mL). The organic phase was washed with aqueous Na_2CO_3 solution (30 mL), water (30 mL), and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to leave 0.57 g (53%) of a white powder. Mp: 110−113 °C. $[\alpha]^{22}_D$: −5.4 (c = 1, $CHCl_3$). IR: 2136, 1738, 1644. ^{1}H NMR: 1.35 (d, 1, J = 8.6), 1.49 (d, 1, J = 8.6), 1.9−2.4 (m, 4), 3.1−3.3 (m, 3), 3.48 (dd, 1, J = 9.4, 3.4), 3.5−3.8 (m, 2), 3.69 (s, 3), 4.49 (dd, 1, J = 8.5, 3.9), 6.25 (dd, 1, J = 5.5, 2.9), 6.35 (dd, 1, J = 5.5, 2.8). ^{13}C NMR: 24.9, 29.0, 46.2, 46.5, 46.7, 48.3, 48.4, 51.0, 52.1, 58.7, 134.1, 135.3, 170.1, 172.8, 179.6. FAB-MS m/e (relative intensity): 319 (M^+ + 1, 100), 225 (100). HRMS (FAB) m/e: 319.1403 (MH^+ $C_{15}H_{18}N_4O_4$ requires 319.1406).

Ester 9. When the preparation of acyl azide **7a** was carried out using ethyl chloroformate rather than isopropenyl chloroformate, in addition to acyl azide **7a** ester **9** (9%) was always obtained as a white solid. Mp: 70−74 °C. $[\alpha]^{22}_D$: −69.0 (c = 1, $CHCl_3$). IR: 1736, 1648. ^{1}H NMR: 1.19 (t, 3, J = 7.2), 1.35 (d, 1, J = 8.5), 1.49 (d, 1, J = 8.5), 1.9−2.3 (m, 4), 3.1−3.3 (m, 3), 3.40 (dd, 1, J = 9.5, 3.0), 3.71 (s, 3), 4.05 (dq, 2, J = 7.2, 2.6), 4.40 (dd, 1, J = 8.4, 4.1), 6.23 (dd, 1, J = 5.7, 3.5), 6.35 (dd, 1, J = 5.7, 3.5). ^{13}C NMR: 14.2, 24.9, 29.1, 46.4, 46.4, 46.6, 47.7, 48.4, 48.7, 52.1, 60.2, 60.2, 133.7, 135.9, 170.9, 172.3, 173.1. CI-MS m/e (relative intensity): 322 (M^+ + 1, 100). HRMS (CI, NH_3) m/e: 322.1654 (MH^+ $C_{17}H_{24}NO_5$ requires 322.1654).

Amido Acid 6b. A solution of *endo*-norborn-5-ene-2,3-dicarboxylic anhydride **5** (4.16 g, 25 mmol) and *tert*-butyl prolinate[21] (4.22 g, 28 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 18 h. The reaction mixture was subsequently washed with 0.5 M HCl (40 mL) and water (2 × 40 mL) and dried ($MgSO_4$) and the solvent evaporated in vacuo to leave a yellow oil. Trituration with Et_2O gave 4.9 g (57%) of a white crystalline solid. Mp: 108−113 °C. $[\alpha]^{22}_D$: −132.1 (c = 1, $CHCl_3$). IR: 3500−2500, 1778, 1731, 1646. ^{1}H NMR: 1.3−1.5 (m, 2), 1.48 (s, 9), 1.9−2.3 (m, 4), 3.2−3.4 (m, 4), 3.6−3.8 (m, 2), 4.37 (dd, 1, J = 8.2, 3.8), 6.23 (dd, 1, J = 5.6, 2.7), 6.28 (dd, 1, J = 5.6, 2.7). ^{13}C NMR: 24.7, 28.0, 29.0, 46.9, 47.2, 47.3, 48.4, 48.5, 50.0, 59.9, 81.3, 134.7, 135.4, 171.2, 172.4, 175.6. CI-MS m/e (relative intensity): 336 (M^+ + 1, 23), 172 (100). HRMS (CI, NH_3) m/e: 336.1811 (MH^+ $C_{18}H_{26}NO_5$ requires 336.1811). Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.70; H, 7.84; N, 3.80.

Acyl Azide 7b. Isopropenyl chloroformate (0.87 mL, 8.04 mmol) was added to a mixture of amido acid **6b** (2.45 g, 7.3 mmol) and Et_3N (2 mL) in dry THF (25 mL) at −20 °C. An aqueous solution of NaN_3 (1.19 g, 18.3 mmol) was added at −10 °C. The temperature was gradually raised to room temperature, and stirring was continued for 1 h. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (3 × 30 mL). The organic phase was washed with aqueous Na_2CO_3 solution (30 mL), water (30 mL), and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to leave 1.5 g (57%) of a white solid. Mp: 107−109 °C. $[\alpha]^{22}_D$: −19.5 (c = 1, $CHCl_3$). IR: 2138, 1729, 1647. ^{1}H NMR: 1.32 (d, 1, J = 8.6), 1.44 (s, 9), 1.47 (d, 1, J = 8.6), 1.8−2.3 (m, 4), 3.1−3.3 (m, 3), 3.43 (dd, 1, J = 9.4, 3.3), 3.5−3.8 (m, 2), 4.40 (dd, 1, J = 8.0, 3.4), 6.19 (dd, 1, J = 5.5, 2.9), 6.31 (dd, 1, J = 5.5, 2.7). ^{13}C NMR: 24.6, 28.0, 29.1, 46.2, 46.5, 46.6, 48.3, 48.3, 51.1, 59.3, 81.0, 134.0, 135.4, 169.7, 171.6, 179.5. FAB-MS m/e (relative intensity): 361 (M^+ + 1, 83), 211 (100). HRMS (FAB) m/e: 333.1816 ($MH - N_2$)$^+$ $C_{18}H_{25}N_2O_4$ requires 333.1814).

Isocyanate 10a. Acyl azide **7a** (0.55 g, 1.73 mmol) was dissolved in anhydrous benzene (10 mL) and heated at reflux for 2 h. The solvent was evaporated in vacuo to leave 0.5 g (100%) of a white solid. Mp 62−65 °C. $[\alpha]^{22}_D$: −51.6 (c = 1, $CHCl_3$). IR: 2264, 1744, 1644. ^{1}H NMR: 1.34 (d, 1, J = 9.2), 1.59 (d, 1, J = 9.2), 1.9−2.3 (m, 4), 3.1−3.2 (m, 2), 3.26 (dd, 1, J = 8.8, 2.8), 3.78 (s, 3), 3.5−3.7 (m, 2), 4.29 (dd, 1, J = 8.8, 3.7), 4.49 (dd, 1, J = 8.3, 4.0), 6.08 (dd, 1, J = 5.3, 3.0), 6.79 (dd, 1, J = 5.7, 3.6). ^{13}C NMR: 24.7, 29.0, 45.6, 46.3, 46.6, 49.1, 51.9, 52.2, 56.1, 58.7, 122.5, 129.9, 141.1, 169.3, 173.0. CI-MS m/e (relative intensity): 308 (M^+ + 18, 4), 291 (M^+ + 1, 100). HRMS (CI, NH_3) m/e: 291.1345 (MH^+ $C_{15}H_{18}N_2O_4$ requires 291.1345).

Isocyanate 10b. Acyl azide **7b** (1.5 g, 4.15 mmol) was dissolved in anhydrous benzene (15 mL), and heated at reflux for 2 h. The solvent was evaporated in vacuo to leave 1.37 g (100%) of a white solid. Mp: 61−62 °C. $[\alpha]^{22}_D$: −3.20 (c = 1, $CHCl_3$). IR: 2263, 1735, 1647. ^{1}H NMR: 1.31 (d, 1, J = 9.1), 1.47 (s, 9), 1.49 (d, 1, J = 9.1), 1.9−2.3 (m, 4), 3.1−3.2 (m, 2), 3.2−3.3 (dd, 1, J = 9.0, 2.9), 3.5−3.7 (m, 2), 4.24 (dd, 1, J = 9.1, 3.8), 4.38 (dd, 1, J = 8.9, 3.5), 6.0 (dd, 1, J = 5.6, 2.9), 6.79 (dd, 1, J = 5.6, 3.3). ^{13}C NMR: 24.5, 28.0, 29.2, 45.6, 46.3, 46.6, 49.1, 52.0, 56.1, 59.5, 81.2, 128.3, 129.8, 139.1, 169.0, 171.6. EI-MS m/e (relative intensity): 332 (M^+, 6), 70 (100). HRMS (EI) m/e: 332.1736 (M^+ $C_{18}H_{24}N_2O_4$ requires 332.1736). Anal. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 64.88; H, 7.56; N, 8.61.

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Urea 12a. Isocyanate **10a** (1 g, 3.4 mmol) was dissolved in a 1:1 solution of water/THF (10 mL). After the solution was stirred for 5 h, the solvent was evaporated in vacuo to yield a yellow oil. Purification by flash chromatography using 5% MeOH/95% EtOAc as eluent afforded (R_f = 0.11, 2% MeOH/98% EtOAc) 0.9 g (87%) of a yellow solid. Mp: 92−93 °C. $[\alpha]^{22}_D$: −50.1 (c = 1, $CHCl_3$). IR: 3375, 1742, 1638. ^{1}H NMR: 1.35 (d, 1, J = 8.8), 1.43 (d, 1, J = 8.8), 1.8−2.2 (m, 4), 2.8−3.2 (m, 2), 3.25 (dd, 1, J = 9.3, 3.1), 3.6−3.9 (m, 2), 3.75 (s, 3), 4.29 (dd, 1, J = 8.2, 5.0), 4.68 (d, 1, J = 9.8), 4.80 (dt, 1, J = 9.9, 3.6), 6.05 (dd, 1, J = 5.6, 3.0), 6.56 (dd, 1, J = 5.5, 3.1). ^{13}C NMR: 25.0, 29.2, 46.1, 46.7, 47.7, 47.8, 49.4, 52.2, 52.8, 58.7, 130.9, 140.0, 156.5, 171.1, 172.8. CI-MS m/e (relative intensity): 555 (M^+ + 1, 8). HRMS (CI, NH_3) m/e: 555.282 (MH^+ $C_{29}H_{39}N_4O_7$ requires 555.282). Anal. Calcd for $C_{29}H_{38}N_4O_7$·0.5 THF: C, 63.02; H, 7.17; N, 9.49. Found: C, 63.19; H, 7.50; N, 9.83.

Urea 12b. Isocyanate **10b** (50 mg, 0.15 mmol) was dissolved in a 1:1 solution of water/THF (1 mL). After the solution was stirred for approximately 5 h, the solvent was evaporated in vacuo to yield 52 mg (100%) of a white solid. Mp: 104−105 °C. $[\alpha]^{22}_D$: −43.4 (c = 1, $CHCl_3$). IR: 3346, 1734. ^{1}H NMR: 1.3−1.5 (m, 2), 1.46 (s, 9), 1.7−2.2 (m, 4), 2.8−3.1 (m, 2), 3.19 (dd, 1, J = 8.9, 2.9), 3.5−3.9 (m, 2), 4.21 (dd, 1, J = 8.0, 3.9), 4.7−4.9 (m, 1), 4.75 (d, 1, J = 10.3), 5.99 (dd, 1, J = 5.6, 2.8), 6.48 (dd, 1, J = 5.6, 2.9). ^{13}C NMR: 24.7, 28.0, 29.2, 46.1, 46.7, 47.6, 47.7, 48.9, 52.9, 59.5, 81.1, 131.1, 139.6, 156.6, 170.8, 171.5. CI-MS m/e (relative intensity): 639 (M^+ + 1, 40), 70 (100). HRMS (CI, NH_3) m/e: 639.3757 (MH^+ $C_{35}H_{51}N_4O_7$ requires 639.3757).

Urethane 13. Isocyanate **10a** (0.4 g, 1.37 mmol) was dissolved in MeOH (10 mL) and stirred for 5 h. The MeOH was then evaporated in vacuo to yield 0.44 g (100%) of a colorless oil. $[\alpha]^{22}_D$: −64.3 (c = 1, $CHCl_3$). IR: 3407, 3018, 1741, 1715. ^{1}H NMR: 1.35 (d, 1, J = 8.9), 1.50 (d, 1, J = 8.9), 1.8−2.3 (m, 4), 3.0−3.2 (m, 2), 3.31 (dd, 1, J = 9.3, 3.1), 3.60 (s, 3), 3.73 (s, 3), 3.5−3.8 (m, 2), 4.29 (dd, 1, J = 8.0, 4.6), 4.64 (dt, 1, J = 9.7, 3.9), 5.45 (d, 1, J = 9.9), 6.07 (dd, 1, J = 5.6, 3.0), 6.50 (dd, 1, J = 5.6, 3.0). ^{13}C NMR: 24.9, 29.1, 46.2, 46.7, 47.5, 47.6, 48.3, 51.9, 52.2, 54.0, 58.7, 131.4, 139.3, 156.6, 171.0, 172.7. CI-MS m/e (relative intensity): 323 (M^+ + 1, 100). HRMS (CI, NH_3) m/e: 323.1607 (MH^+ $C_{16}H_{23}N_2O_5$ requires 323.1607).

Urethane 14a. β-(Trimethylsilyl)ethanol (0.75 mL, 5.2 mmol) and isocyanate **10a** (1.5 g, 5.16 mmol) were heated at reflux in anhydrous benzene (20 mL) for 24 h. Solvent was subsequently removed in vacuo to afford 2.1 g (100%) of a white solid. Mp: 79−80 °C. $[\alpha]^{22}_D$: −48.3 (c = 1, $CHCl_3$). IR: 3419, 3015, 1735, 1702, 1637. ^{1}H NMR: 0.20 (s, 9), 0.8−1.0 (m, 2), 1.37 (d, 1, J = 8.9), 1.49 (d, 1, J = 8.9), 1.8−2.2 (m, 4), 3.0−3.2 (m, 2), 3.31 (dd, 1, J = 9.4, 3.0), 3.5−3.7 (m, 2), 3.74 (s, 3), 4.0−4.2 (m, 2), 4.46 (dd, 1, J = 7.9, 4.6), 4.66 (dt, 1, J = 9.9, 3.8), 5.27 (d, 1, J = 9.9), 6.07 (dd, 1, J = 5.6, 3.0), 6.54 (dd, 1, J = 5.5, 3.0). ^{13}C NMR: −1.5, 17.7, 24.9, 29.1, 46.2, 46.7, 47.5, 47.6, 48.7, 52.2, 53.8, 58.7, 62.8, 131.3, 139.6, 156.3, 171.0, 172.8. CI-MS m/z (relative intensity): 409 (M^+ + 1, 39), 291 (100). HRMS (CI, NH_3) m/e: 409.2159 (MH^+ $C_{20}H_{33}N_2O_5Si$ requires 409.2159). Anal. Calcd for $C_{20}H_{32}N_2O_5Si$·0.25 H_2O: C, 58.15; H, 7.93; N, 6.78. Found: C, 57.95; H, 7.60; N, 6.70.

Urethane 14b. β-(Trimethylsilyl)ethanol (0.65 mL, 4.5 mmol) and isocyanate **10b** (1.37 g, 4.13 mmol) were heated at reflux in anhydrous benzene (20 mL) for 24 h. Solvent was subsequently removed in vacuo to afford 1.85 g (100%) of a white solid. Mp: 64−66 °C. $[\alpha]^{22}_D$: −37.6 (c = 1, $CHCl_3$). IR: 3420, 3016, 1737, 1636. ^{1}H NMR: −0.30 (s, 9), 1.31 (d, 1, J = 9.0), 1.40 (s, 9), 1.45 (d, 1, J = 9.0), 1.7−2.2 (m, 4), 3.0−3.1 (m, 2), 3.22 (dd, 1, J = 9.4, 3.0), 3.5−3.7 (m, 2), 4.0−4.2 (m, 2), 4.22 (dd, 1, J = 7.2, 3.4), 4.51 (dt, 1, J = 9.8, 3.7), 5.39 (d, 1, J = 9.8), 6.00 (dd, 1, J = 5.6, 3.0), 6.40 (dd, 1, J = 5.6, 3.0). ^{13}C NMR: 1.6, 17.6, 24.6, 27.9, 29.1, 46.2, 46.7, 47.5, 48.2, 53.8, 59.4, 59.5, 62.6, 81.0, 131.4, 139.2, 156.3, 170.7, 171.4. CI-MS m/e (relative intensity): 451 (M^+ + 1, 100). HRMS (CI, NH_3) m/e: 451.2628 (MH^+ $C_{23}H_{39}N_2O_5Si$ requires 451.2628). Anal. Calcd for $C_{23}H_{38}N_2O_5Si$: C, 61.30; H, 8.50; N, 6.22. Found: C, 61.37; H, 8.48; N, 6.39.

Bis-lactam 15. Carbamate **14a** (0.4 g, 0.98 mmol) was stirred with 1 M aqueous tetrabutylammonium fluoride solution (4.14 mL, 14.7 mmol) in THF (5 mL) at room temperature for 24 h. Solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2 (10 mL). Water (10 mL) was added, and the layers were mixed by rapid stirring for approximately 15 min. The CH_2Cl_2 layer was extracted with saturated aqueous NH_4Cl solution (10 mL) and dried over $MgSO_4$. After filtration, solvent was evaporated in vacuo to afford a clear oil. Purification by flash chromatography using 80% EtOAc/20% MeOH as eluent yielded (R_f = 0.34) 0.15 g (66%) of a white solid. Mp: 60−61 °C. $[\alpha]^{22}_D$: +51.8 (c = 1, $CHCl_3$). IR: 3218, 3001, 1682, 1630. ^{1}H NMR: 1.42 (d, 1, J = 9.0), 1.54 (d, 1, J = 9.0), 1.8−2.5 (m, 4), 3.1−3.7 (m, 5), 4.2−4.4 (m, 2), 6.05 (dd, 1, J = 5.7, 2.9), 6.40 (s, 1), 6.51 (dd, 1, J = 5.7, 3.0). ^{13}C NMR: 23.1, 26.1, 45.7, 45.8, 45.9, 47.3, 53.3, 55.4, 56.2, 131.7, 141.2, 168.7, 173.2. CI-MS m/e (relative intensity): 233 (M^+ + 1, 100). HRMS (CI, NH_3) m/e: 233.1290 (MH^+ $C_{13}H_{17}N_2O_2$ requires 233.1290). Anal. Calcd for $C_{13}H_{16}N_2O_2$·0.2 H_2O: C, 66.19; H, 7.01; N, 11.88. Found: C, 66.15; H, 7.01; N, 11.70.

Tripeptide 16a. A solution of *N*-BOC-alanine (0.097 g, 0.51 mmol), isocyanate **10a** (0.1 g, 0.35 mmol), and Et_3N (0.072 mL, 0.51 mmol) in dry toluene (1 mL) was heated to 60 °C in an argon atmosphere for 2 h. To the cooled reaction mixture was added EtOAc (20 mL), which was subsequently washed with 0.5 M HCl (10 mL), aqueous Na_2CO_3 (10 mL), and water (10 mL). The solvent was dried ($MgSO_4$) and evaporated in vacuo to afford an orange oil that was subjected to flash chromatography using EtOAc as eluent to give (R_f = 0.3) 0.065 g (50%) of a white solid. Mp: 61−63 °C. $[\alpha]^{22}_D$: −43.6 (c = 0.5, $CHCl_3$). IR: 3313, 1745, 1712, 1644. ^{1}H NMR: 1.25 (d, 3, J = 6.0), 1.40 (d, 1, J = 8.9), 1.45 (s, 9), 1.51 (d, 1, J = 8.9), 1.8−2.3 (m, 4), 3.1−3.2 (m, 2), 3.26 (dd, 1, J = 9.3, 6.1), 3.6−3.7 (m, 2), 4.0−4.1 (m, 1), 4.40 (dd, 1, J = 8.1, 4.2), 4.82 (dt, 1, J = 8.5, 3.0), 5.05 (d, 1, J = 8.5), 6.13 (dd, 1, J = 5.4, 2.9), 6.45 (dd, 1, J = 5.4, 2.8), 7.05 (d, 1, J = 8.3). ^{13}C NMR: 19.3, 24.8, 28.3, 29.0, 46.5, 46.9, 46.9, 47.2, 47.5, 47.7, 50.1, 52.2, 58.6, 79.7, 132.1, 138.7, 155.0, 171.1, 172.1, 172.6. CI-MS m/e (relative intensity): 436 (M^+ + 1, 4), 74 (100). HRMS (CI, NH_3) m/e: 436.2448 (MH^+ $C_{22}H_{34}N_4O_6$ requires 436.2448).

Tripeptide 16b. A solution of *N*-BOC-proline (0.58 g, 2.7 mmol), isocyanate **10b** (0.60 g, 1.8 mmol), and Et_3N (0.4 mL, 2.7 mmol) in dry toluene (6 mL) was heated to 80 °C in an argon atmosphere for 24 h. To the cooled reaction mixture was added EtOAc (30 mL), which was subsequently washed with 0.5 M HCl (15 mL), aqueous Na_2CO_3 (15 mL), and water (15 mL). The solvent was dried with $MgSO_4$ and evaporated in vacuo to leave a brown/black solid that was subjected to flash chromatography using 1:1 EtOAc/petrol as eluent to give (R_f = 0.22 EtOAc) 0.40 g (46%) of a white powder. Mp: 42−44 °C. $[\alpha]^{22}_D$: −94.3 (c = 1, $CHCl_3$). IR: 3324, 3018, 1732, 1689. ^{1}H NMR (DMSO-d_6): 1.32 (s, 9), 1.41 (s, 9), 1.3−1.5 (m, 2), 1.6−2.2 (m, 8), 2.8−3.7 (m, 7), 4.0−4.1 (m, 2), 4.6−4.8 (m, 1), 5.8−6.5 (m, 2), 7.26 (d, 1, J = 9.3), 7.45 (d, 1, J = 9.1). ^{13}C NMR (DMSO-d_6) (only peaks corresponding to the major conformer are reported): 24.3, 24.6, 29.1, 29.9, 28.0, 28.0, 46.1, 46.3, 46.4, 46.7, 46.8, 47.5, 52.0, 59.4, 59.5, 79.9, 81.1, 131.3, 139.1, 156.3, 170.8, 171.6, 171.8. CI-MS m/e (relative intensity): 504 (M^+ + 1, 10), 70 (100). HRMS (CI, NH_3) m/e: 504.307 (MH^+ $C_{27}H_{42}N_3O_6$ requires 504.307). Anal. Calcd for $C_{27}H_{41}N_3O_6$·2.5H_2O: C, 59.09; H, 8.45; N, 7.66. Found: C, 58.98; H, 8.18; N, 7.29.

Tripeptide 19. To a suspension of Z-Leu-Ala-OH[24] (3.6 g, 10.7 mmol) in CH_2Cl_2 (80 mL) were added DCC (2.87 g, 13.9 mmol) and HOBt (1.90 g, 13.9 mmol), followed by HN-Pro-$CO_2CH_2CH_2SiMe_3$[23] (3.0 g, 13.9 mmol). The mixture was stirred at room temperature for 14 h before the precipitate was removed by filtration. The solution was washed with 1 M HCl (2 × 40 mL), saturated aqueous Na_2CO_3 (2 × 40 mL), and water (2 × 40 mL). The organic phase was separated, dried ($MgSO_4$), and evaporated to dryness. The crude product was purified by flash chromatography using 1:1 EtOAc/petroleum ether to give (R_f = 0.2) 4.0 g (70%) of a clear oil. $[\alpha]^{23}_D$: −43.5 (c = 1, $CHCl_3$). IR: 3293, 3013, 1731, 1643. ^{1}H

NMR: 0.42 (s, 9), 0.9−1.1 (m, 8), 1.20−1.40 (m, 10), 3.6−3.8 (m, 2), 4.1−4.8 (m, 5), 5.05−5.35 (m, 3), 6.38 (d, 1, J = 7.0), 6.97 (d, 1, J = 7.0), 7.26−7.34 (m, 5). ^{13}C NMR (only peaks corresponding to major conformer are reported): −1.6, 17.2, 17.9, 21.8, 23.0, 24.6, 24.8, 28.8, 41.9, 46.6, 46.8, 53.5, 58.9, 63.4, 66.7, 127.9, 128.4, 136.4, 156.1, 170.8, 170.9, 171.8. CI-MS m/e (relative intensity): 534 ($M^+ + 1$, 7), 90 (100). HRMS (CI, NH_3) m/e: 534.300 (MH^+ $C_{27}H_{44}N_3O_6Si$ requires 534.300). Anal. Calcd for $C_{27}H_{43}N_3O_6Si\cdot 0.33H_2O$: C, 60.08; H, 8.16; N, 7.79. Found: C, 60.13; H, 8.14; N, 7.76.

Tripeptide 17. Tripeptide **19** (3 g, 5.63 mmol) was stirred with 1 M tetra-*n*-butylammonium fluoride (16.2 mL, 56.3 mmol) in THF (60 mL) at room temperature for 24 h. Solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2 (80 mL). The CH_2Cl_2 layer was washed with 1 M HCl (2 × 40 mL) and dried over $MgSO_4$. After filtration, solvent was evaporated in vacuo to afford the crude product, which was purified by flash chromatography using EtOAc as eluent to afford (R_f = 0.17) 2.24 g (93%) of a white powder. Mp: 57−64 °C. $[\alpha]^{23}_D$: −48.6 (c = 1, $CHCl_3$). IR: 3500−2500, 3302, 3017, 1717, 1634. ^{1}H NMR: 0.92 (m, 6), 1.1−2.4 (m, 10), 3.5−3.8 (m, 2), 4.25−4.9 (m, 3), 5.1−5.2 (m, 2), 5.63 (d, 1, J = 8.4), 5.97 (d, 1, J = 8.5), 7.30−7.36 (m, 5), 8.69 (br, 1). ^{13}C NMR: 17.4, 20.3, 23.0, 24.6, 24.9, 28.9, 41.9, 46.7, 47.1, 53.4, 59.1, 66.9, 127.9, 128.5, 136.3, 156.2, 171.9, 172.4, 174.1. CI-MS m/e (relative intensity): 434 ($M^+ + 1$, 57). HRMS (CI, NH_3) m/e: 434.229 (MH^+ $C_{22}H_{32}N_3O_6$ requires 434.229). Anal. Calcd for $C_{22}H_{31}N_3O_6\cdot 0.5\ H_2O$: C, 59.70; H, 7.29; N, 9.50. Found: C, 59.80; H, 7.66; N, 9.60.

Pentapeptide 16c. A solution of tripeptide **17** (0.68 g, 1.58 mmol), isocyanate **10b** (0.35 g, 1.05 mmol), and Et_3N (0.3 mL, 2.10 mmol) in dry toluene (5 mL) was heated to 60 °C in an argon atmosphere for 16 h. To the cooled reaction mixture was added EtOAc (20 mL), which was subsequently washed with 0.5 M HCl (10 mL), saturated aqueous Na_2CO_3 (10 mL), and water (10 mL). The solvent was dried ($MgSO_4$) and evaporated in vacuo to afford an orange solid that was subjected to flash chromatography using EtOAc as eluent to give (R_f = 0.17) 0.2 g (26%) of a white powder. Mp: 83−87 °C. $[\alpha]^{23}_D$ −34.6 (c = 0.5, $CHCl_3$). IR: 3401, 3297, 3013, 1724, 1644. ^{1}H NMR: 0.95 (m, 6), 1.40 (d, 1, J = 9.1), 1.47 (s, 9), 1.47−2.2 (m, 15), 3.14−3.24 (m, 2), 3.23 (dd, 1, J = 9.2, 3.4), 3.61−3.66 (m, 4), 4.27−4.43 (m, 3), 4.65−4.80 (m, 1), 4.78 (dt, 1, J = 8.5, 3.4), 5.15 (s, 2), 5.54 (d, 1, J = 8.6), 6.08 (dd, 1, J = 5.2, 2.8), 6.4 (dd, 1, J = 5.2, 2.8), 7.0 (d, 1, J = 6.9) 7.3−7.4 (m, 6). ^{13}C NMR: 17.8, 21.6, 23.1, 24.4, 24.6, 24.7, 27.9, 29.0, 29.1, 41.8, 46.4, 46.8, 46.9, 46.9, 47.1, 47.4, 47.5, 52.5, 53.5, 59.7, 60.5, 60.8, 81.0, 127.9, 128.4, 132.0, 136.4, 138.4, 156.1, 170.6, 170.8, 171.6, 171.6, 171. CI-MS m/e (relative intensity): 722.7 ($M^+ + 1$, 100), 656.6 (65). HRMS (CI, NH_3) m/e: 722.413 (MH^+ $C_{39}H_{56}N_5O_8$ requires 722.413). Anal. Calcd for $C_{39}H_{55}N_5O_8$: C, 62.50; H, 7.86; N, 9.38. Found: C, 62.55; H, 7.81; N, 9.35.

Deprotection of 16c. Pentapeptide **16c** (0.19 g, 0.26 mmol) was dissolved in a solution of CH_2Cl_2 (2 mL) and trifluoroacetic acid (2 mL) and allowed to stir at room temperature overnight. The solvent was evaporated in vacuo to leave 0.18 g (100%) of a yellow powder. Mp: 61−65 °C. $[\alpha]^{23}_D$: −32.9 (c = 1, $CHCl_3$). IR: 3302, 3017, 1720, 1630. ^{1}H NMR: 0.95 (d, 6, J = 5.9), 1.29−1.57 (m, 16), 3.16−3.20 (m, 2), 3.28 (dd, 1, J = 9.5, 3.1), 3.50−3.85 (m, 4), 4.2−4.9 (m, 5), 5.13 (d, 2, J = 3.7), 5.50 (d, 1, J = 7.9), 6.03−6.05 (m, 1), 6.40−6.43 (m, 1) 7.20−7.45 (m, 5). ^{13}C NMR: 17.4, 21.0, 21.5, 23.0, 24.6, 24.8, 28.8, 29.0, 41.4, 46.5, 47.5, 52.7, 53.4, 59.2, 60.5, 67.0, 127.9, 128.7, 128.4, 132.1, 136.2, 138.7, 156.4, 171.5, 171.8, 172.3, 173.0, 174.6. CI-MS m/e (relative intensity): 666 ($M^+ + 1$, 70). HRMS (CI, NH_3) m/e: 666.350 (MH^+ $C_{35}H_{48}N_5O_8$ requires 666.350). Anal. Calcd for $C_{35}H_{47}N_5O_8\cdot CH_2Cl_2$: C, 57.60; H, 6.58; N, 9.33. Found: C, 57.70; H, 6.77; N, 9.13.

Heptapeptide 2. Et_3N (0.10 mL, 0.76 mmol) was added to a cooled (0 °C) suspension of the acid prepared above (0.17 g, 0.32 mmol), EDC (0.063 g, 0.33 mmol), HOBt (0.045 g, 0.33 mmol), and $CF_3CO_2\cdot H_3N$-Phe-Gly-OMe[25] (0.18 g, 0.51 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 24 h, washed with 0.5 M HCl (5 mL), saturated aqueous Na_2CO_3 (5 mL), and H_2O (5 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue subjected to flash chromatography using 5% MeOH/95% EtOAc as eluent to afford (R_f = 0.12) 0.15 g (66%) of a white powder. Mp: 68−71 °C. $[\alpha]^{23}_D$: −65.4 (c = 1, $CHCl_3$). IR: 3411, 3326, 1708, 1657, 1631. ^{1}H NMR data are given in the following paper in this issue. ^{13}C NMR (150 MHz): 17.6, 21.4, 23.1, 24.7, 24.9, 25.0, 28.8, 28.9, 36.8, 41.0, 41.4, 46.4, 47.0, 47.3, 47.5, 48.0, 49.8, 51.5, 52.2, 52.9, 54.0, 60.5, 61.3, 66.7, 127.0, 127.9, 128.4, 128.6, 129.5, 130.2, 136.4, 136.5, 140.4, 156.3, 170.0, 170.2, 171.2, 171.9, 172.1, 172.2. FAB-MS m/e (relative intensity): 906 ($M^+ + 23$, 55), 884 ($M^+ + 1$, 50), 107 (100). HRMS (FAB) m/e: 884.4517 (MH^+ $C_{47}H_{62}N_7O_{10}$ requires 884.4558). Anal. Calcd for $C_{47}H_{61}N_7O_{10}\cdot 3\ CH_3OH$: C, 61.25; H, 7.51; N, 10.01. Found: C, 61.04; H, 7.43; N, 9.89.

Pseudotripeptide 20a. Et_3N (0.5 mL) was added to a cooled (0 °C) suspension of isocyanate **10a** (0.5 g, 1.72 mmol) and alanine methyl ester hydrochloride (0.36 g, 2.58 mmol) in CH_2Cl_2 (8 mL). The reaction mixture was stirred at room temperature for 18 h and subsequently washed with 0.5 M HCl (5 mL), aqueous Na_2CO_3 (5 mL), and H_2O (5 mL) and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue subjected to flash chromatography using EtOAc as eluent to give (R_f = 0.33) 0.4 g (61%) of a white solid. Mp: 54−55 °C. $[\alpha]^{22}_D$: −53.1 (c = 1, $CHCl_3$). IR: 3420, 3018, 1742, 1672, 1632. ^{1}H NMR: 1.32 (d, 3, J = 7.2), 1.35 (d, 1, J = 8.8), 1.48 (d, 1, J = 8.8), 1.9−2.2 (m, 4), 3.0−3.2 (m, 2), 3.28 (dd, 1, J = 9.1, 3.1), 3.5−3.8 (m, 2), 3.70 (s, 6), 4.35 (dd, 1, J = 8.2, 4.9), 4.39 (pent, 1, J = 7.3), 4.74 (d, 1, J = 7.1), 4.81 (dt, 1, J = 9.5, 3.8), 5.28 (d, 1, J = 9.5), 6.10 (dd, 1, J = 5.4, 3.0), 6.49 (dd, 1, J = 5.5, 3.0). ^{13}C NMR: 18.8, 24.9, 29.2, 46.1, 46.7, 47.6, 47.7, 48.6, 48.9, 52.2, 52.3, 52.9, 58.7, 131.7, 139.2, 156.7, 171.5, 172.8, 174.4. CI-MS m/e (relative intensity): 394 ($M^+ + 1$, 100). HRMS (CI, NH_3) m/e: 394.1978 (MH^+ $C_{19}H_{28}N_3O_6$ requires 394.1978).

Pseudotripeptide 20b. A solution of isocyanate **10b** (0.5 g, 15 mmol) and *tert*-butyl prolinate[21] (0.28 g, 16.5 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 18 h. The reaction mixture was subsequently washed with 0.5 M HCl (10 mL), saturated aqueous Na_2CO_3 (10 mL), and H_2O (10 mL) and dried ($MgSO_4$) and the solvent evaporated in vacuo to leave 0.68 g of a yellow oil. Purification by flash chromatography using EtOAc as eluent yielded (R_f = 0.28) 0.55 g (73%) of a white solid. Mp: 42−44 °C. $[\alpha]^{23}_D$: −57.5 (c = 1, $CHCl_3$). IR: 3347, 1735, 1636. ^{1}H NMR: 1.40 (s, 18), 1.3−1.6 (m, 2), 1.75−2.2 (m, 8), 3.0−3.5 (m, 4), 3.21 (dd, 1, J = 9.0, 2.8), 3.4−3.7 (m, 2), 4.1−4.3 (m, 2), 4.78 (dt, 1, J = 9.5, 3.6), 5.15 (d, 1, J = 9.5), 6.05 (dd, 1, J = 5.3, 3.1), 6.41 (dd, 1, J = 5.3, 3.5). ^{13}C NMR: 22.3, 24.2, 27.9, 28.0, 29.1, 29.7, 45.4, 46.3, 47.2, 47.4, 47.6, 48.4, 53.2, 59.5, 59.5, 80.8, 81.0, 131.8, 139.6, 155.8, 171.1, 171.3, 172.31. CI-MS m/e (relative intensity): 504 ($M^+ + 1$,100). HRMS (CI, NH_3) m/e: 504.3074 (MH^+ $C_{27}H_{42}N_3O_6$ requires 504.3073). Anal. Calcd for $C_{27}H_{41}N_3O_6\cdot 1.25\ H_2O$: C, 61.62; H, 8.34; N, 7.99. Found: C, 61.62; H, 8.03; N, 8.18.

Pseudopentapetide 20c. Et_3N (1 mL) was added to a cooled (0 °C) suspension of isocyanate **10b** (1.15 g, 3.5 mmol) and $CF_3CO_2H\cdot$HN-Pro-Phe-Phe-OMe[26] (2.41 g, 4.5 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 18 h, subsequently washed with 0.5 M HCl (5 mL), saturated aqueous Na_2CO_3 (5 mL), and H_2O (5 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo to leave a yellow solid. Trituration with EtOAc yielded 2.05 g (78%) of a white solid. Mp: 60−61 °C. $[\alpha]^{23}_D$: −95.1 (c = 1, $CHCl_3$). IR: 3407, 3313, 3016, 1734, 1636. ^{1}H NMR: 1.3−1.5 (m, 2), 1.46 (s, 9), 1.6−2.2 (m, 8), 2.9−3.2 (m, 8), 3.25 (dd, 1, J = 9.0, 3.0), 3.67 (s, 3), 3.6−3.7 (m, 2), 4.2−4.3 (m, 2), 4.6−4.9 (m, 3), 5.97 (d, 1, J = 7.3), 6.10 (dd, 1, J = 5.8, 3.3), 6.37 (dd, 1, J = 5.8, 2.5), 7.0−7.4 (m, 12). ^{13}C NMR: 24.6, 24.6, 27.8, 28.0, 28.1, 37.1, 37.7, 45.9, 46.6, 46.6, 47.0, 47.6, 47.8, 52.2, 53.4, 53.6, 53.7, 59.5, 60.4, 81.2, 126.7, 126.8, 128.4, 128.4, 129.2, 132.4, 138.2, 136.4, 136.9, 157.3, 170.8, 171.2, 171.4, 171.6, 172.3. CI-MS m/e (relative intensity): 756 ($M^+ + 1$, 12), 424 (100). HRMS (CI, NH_3) m/e: 756.397 (MH^+

$C_{42}H_{54}N_5O_8$ requires 756.397). Anal. Calcd for $C_{42}H_{53}N_5O_8 \cdot 1.5\ H_2O$: C, 64.43; H, 7.21; N, 8.95. Found: C, 64.75; H, 7.23; N, 8.67.

Acid 21. Pseudopentapeptide **20c** (1.90 g, 2.5 mmol) was dissolved in a solution of CH_2Cl_2 (10 mL) and trifluoroacetic acid (3 mL) and allowed to stir at room temperature overnight. The solvent was evaporated in vacuo to leave 1.76 g (100%) of a yellow powder. Mp: 42−44 °C. $[\alpha]^{23}_D$: −62.0 ($c = 1$, $CHCl_3$). IR: 3286, 1716, 1633. ^{1}H NMR: 1.40 (d, 1, $J = 8.4$), 1.55 (d, 1, $J = 8.4$), 1.6−2.3 (m, 8), 2.9−3.2 (m, 8), 3.25 (dd, 1, $J = 9.1$, 5.0), 3.6−3.70 (m, 2), 3.69 (s, 3), 4.2−4.4 (m, 1), 4.4−4.5 (m, 1), 4.5−4.8 (m, 3), 6.10 (dd, 1, $J = 5.7$, 3.3), 6.28 (dd, 1, $J = 5.7$, 3.1), 6.88 (d, 1, $J = 7.7$), 7.0−7.3 (m, 12), 8.05 (br, 1). ^{13}C NMR: 24.2, 24.7, 28.5, 29.2, 37.3, 37.6, 45.8, 46.1, 46.8, 47.5, 47.6, 47.9, 52.4, 53.7, 54.2, 54.3, 59.2, 60.5, 127.1, 128.6, 129.2, 133.1, 137.6, 135.8, 136.1, 157.5, 171.2, 171.3, 173.0, 173.1, 174.9. CI-MS *m/e* (relative intensity): 700 ($M^+ + 1$, 13), 550 (100). HRMS (CI, NH_3) *m/e*: 700.335 (MH^+ $C_{38}H_{46}N_5O_8$ requires 700.335). Anal. Calcd for $C_{38}H_{45}N_5O_8 \cdot 1.5\ H_2O$: C, 57.35; H, 5.85; N, 8.47. Found: C, 57.35; H, 5.62; N, 8.19.

Pseudoheptapeptide 3. Et_3N (0.4 mL, 2.8 mmol) was added to a cooled (0 °C) suspension of acid **21** (0.4 g, 0.57 mmol), water-soluble carbodiimide (0.143 g, 0.75 mmol), HOBt (0.1 g, 0.75 mmol), and $CF_3CO_2H \cdot H_2N$-Ala-Val-OMe[27] (0.24 g, 0.75 mmol) in CH_2Cl_2 (8 mL). The reaction mixture was stirred at room temperature for 24 h, subsequently washed with 0.5 M HCl (5 mL), saturated aqueous Na_2CO_3 (5 mL), and H_2O (5 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue subjected to flash chromatography using 4% MeOH/96% EtOAc as eluent to give (R_f = 0.23) 0.34 g (66%) of a white foam. Mp: 68−72 °C. $[\alpha]^{23}_D$: −109.6 ($c = 1$, $CHCl_3$). IR: 3419, 3302, 3048, 1743, 1643. ^{1}H NMR: 0.89 (d, 3, $J = 6.8$), 0.91 (d, 3, $J = 6.8$), 1.39 (d, 3, J = 7.0), 1.3−2.5 (m, 11), 2.8−3.2 (m, 8), 3.2 (dd, 1, $J = 9.1$, 3.3), 3.6−3.75 (m, 2), 3.66 (s, 3), 3.73 (s, 3), 4.2−4.9 (m, 7), 5.81 (d, 1, $J = 8.9$), 6.15 (dd, 1, $J = 5.8$, 3.0), 6.33 (dd, 1, $J = 6.0$, 3.0), 6.60 (d, 1, $J = 8.5$), 7.0 (d, 1, $J = 7.9$), 7.1−7.3 (m, 12). ^{13}C NMR (150 MHz): 17.5, 17.6, 18.9, 24.5, 24.9, 27.6, 28.1, 31.0, 37.1, 37.7, 45.8, 46.9, 47.0, 47.4, 47.7, 47.8, 49.0, 52.1, 52.1, 53.4, 53.7, 53.7, 57.0, 59.9, 60.3, 126.7, 126.8, 128.3, 128.4, 129.1, 129.1, 132.6, 136.2, 136.8, 138.0, 157.1, 170.6, 171.1, 171.5, 171.8, 172.0, 172.1, 173.1. FAB-MS *m/e* (relative intensity): 907 ($M^+ + 23$, 100), 885 ($M^+ + 1$, 56), 461 (43). HRMS (FAB) *m/e*: 884.4627 (MH^+ $C_{47}H_{62}N_7O_{10}$ requires 884.4558).

Amido Acid 22a. Et_3N (4.24 mL, 30 mmol) was added to a cooled (0 °C) suspension of *endo*-norborn-5-ene-2,3-dicarboxylic anhydride **5** (0.99 g, 6.0 mmol) and $CF_3CO_2H \cdot$HN-Pro-Phe-Phe-OMe[26] (3.6 g, 6.7 mmol) in CH_2Cl_2 (40 mL). The reaction mixture was stirred at room temperature for 24 h, subsequently washed with 0.5 M HCl (20 mL) and water (20 mL), and dried ($MgSO_4$) and the solvent evaporated in vacuo to leave a yellow solid. Purification by flash chromatography using EtOAc as eluent gave (R_f = 0.34, 10% MeOH/90% EtOAc) 1.02 g (31%) of a white solid. Mp: 96−98 °C. $[\alpha]^{22}_D$: −93.3 ($c = 1$, $CHCl_3$). IR: 3500−2500, 3328, 3011, 1732, 1634. ^{1}H NMR: 1.30 (d, 1, $J = 8.6$), 1.42 (d, 1, $J = 8.6$), 1.6−2.0 (m, 4), 2.8−3.1 (m, 4), 3.0−3.5 (m, 6), 3.58 (s, 3), 4.35 (dd, 1, J = 8.5, 3.9), 4.5−4.8 (m, 2), 6.10 (dd, 1, $J = 5.3$, 2.9), 6.35 (dd, 1, $J = 5.5$, 2.9), 7.0−7.3 (m, 11), 7.40 (d, 1, $J = 9.1$). ^{13}C NMR: 23.9, 29.1, 36.3, 37.9, 46.8, 46.8, 47.4, 47.8, 48.7, 49.2, 52.1, 54.3, 54.4, 61.2, 126.4, 126.8, 128.2, 128.4, 129.1, 129.3, 132.8, 137.6, 137.6, 137.9, 171.5, 171.9, 172.0, 173.0, 174.9. CI-MS *m/e* (relative intensity): 588 ($M^+ + 1$, 10), 424 (100). HRMS (CI, NH_3) *m/e*: 588.271 (MH^+ $C_{33}H_{38}N_3O_7$ requires 588.271). Anal. Calcd for $C_{33}H_{37}N_3O_7 \cdot$EtOAc: C, 65.76; H, 6.71; N, 6.22. Found C, 65.41; H, 6.88; N, 6.29.

Pseudoheptapeptide 4. To a suspension of amido acid **22a** (0.56 g, 0.95 mmol) and DCC (0.3 g, 1.43 mmol) in CH_2Cl_2 (15 mL) was added NHS (0.16 g, 1.43 mmol) over a period of 5 min at 0 °C. After the mixture was stirred for 16 h, the byproduct was removed by filtration. The filtrate was washed with water (3 × 10 mL) and the organic layer dried ($MgSO_4$) and evaporated to dryness in vacuo yielding 0.6 g of *N*-hydroxysuccinimide ester. The crude ester was then redissolved in CH_2Cl_2 (10 mL), and $CF_3CO_2H \cdot$HN-Pro-Ala-Val-OMe[28] (1.15 g, 2.87 mmol) and Et_3N (0.4 mL, 2.87 mmol) were added at 0 °C. The solution was stirred at room temperature for 9 h and then washed sequentially with 1 M HCl (5 mL), saturated aqueous Na_2CO_3 (5 mL), and H_2O (5 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated to dryness in vacuo, affording a white foamy solid. Flash chromatography using 2% MeOH/98% EtOAc as eluent gave (R_f = 0.11) 0.41 g (50%) of a white powder. Mp: 96−99 °C. $[\alpha]^{22}_D$: −87.6 ($c = 1$, $CHCl_3$). IR: 3420, 3293, 1738, 1659, 1642, 1632. ^{1}H NMR data are given in the following paper in this issue. ^{13}C NMR (150 MHz): 17.3, 17.7, 18.8, 24.2, 24.9, 28.6, 28.6, 31.1, 36.2, 37.9, 46.3, 46.7, 46.8, 47.0, 47.6, 47.7, 48.3, 49.4, 50.0, 51.9, 52.0, 54.2, 56.9, 59.5, 60.8, 126.5, 126.9, 128.2, 128.5, 128.9, 129.3, 131.2, 136.6, 137.7, 138.2, 171.5, 171.6, 172.0, 172.1, 172.1, 172.3, 172.5, 172.7. FAB-MS *m/e* (relative intensity): 891 ($M^+ + 23$, 100), 869 ($M^+ + 1$, 20). HRMS (FAB) *m/e*: 869.4976 (MH^+ $C_{47}H_{61}N_6O_{10}$ requires 869.4449). Anal. Calcd for $C_{47}H_{60}N_6O_{10} \cdot H_2O$: C, 63.64; H, 7.05; N, 9.47. Found: C, 63.71; H, 7.23; N, 9.55.

Pseudopentapeptide 23. To a suspension of amido acid **22a** (0.5 g, 0.85 mmol) and DCC (0.21 g, 1.02 mmol) in CH_2Cl_2 (20 mL) was added NHS (0.11 g, 1.02 mmol) over a period of 5 min at 0 °C. After being stirred for 16 h, the byproduct was removed by filtration. The filtrate was washed with water (3 × 10 mL) and the organic layer dried ($MgSO_4$), filtered, and evaporated to dryness in vacuo, yielding 0.52 g of crude *N*-hydroxysuccinimide ester. The ester was then redissolved in CH_2Cl_2 (10 mL), and $HCl \cdot H_2N$-Ala-OMe (0.58 g, 4.1 mmol) and Et_3N (0.57 mL) were added at 0 °C. The solution was stirred at room temperature for 9 h, and then washed sequentially with 1 M HCl (5 mL), saturated aqueous Na_2CO_3 (5 mL), and H_2O (5 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated to dryness in vacuo, affording a white foamy solid. Flash chromatography using 2% MeOH/98% EtOAc as eluent afforded (R_f = 0.17) 0.36 g (69%) of a white powder. Mp: 209−213 °C. $[\alpha]^{23}_D$: −97.4 ($c = 1$, $CHCl_3$). IR: 3420, 3316, 3054, 1744, 1664. ^{1}H NMR: 1.37 (d, 3, $J = 7.2$), 1.39 (d, 1, $J = 8.6$), 1.53 (d, 1, $J = 8.6$), 1.7−2.1 (m, 4), 3.28−3.55 (m, 10), 3.59 (s, 3), 3.73 (s, 3), 4.38 (dd, 1, J = 6.0, 2.1), 4.42 (pent., 1, $J = 7.2$), 4.60 (q, 1, $J = 7.9$), 4.73 (ddd, 1, J = 12.5, 9.3, 3.5), 6.05 (dd, 1, $J = 5.5$, 2.8), 6.41 (d, 1, $J = 7.3$), 6.66 (dd, 1, $J = 5.5$, 3.0), 7.10−7.30 (m, 10), 7.53 (d, 1, $J = 7.7$), 8.14 (d, 1, $J = 9.3$). ^{13}C NMR: 18.1, 24.2, 29.3, 36.3, 38.3, 46.8, 47.0, 47.8, 48.2, 48.2, 48.6, 49.8, 51.9, 52.5, 54.3, 54.4, 61.5, 126.3, 126.5, 128.2, 128.2, 128.7, 129.3, 130.8, 137.2, 138.7, 139.4, 171.5, 171.6, 171.94, 172.2, 173.0, 173.2. CI-MS *m/e* (relative intensity): 691 ($M^+ + 18$, 2), 673 ($M^+ +$ 1, 13), 250 (100). HRMS (CI, NH_3) *m/e*: 673.3237 (MH^+ $C_{37}H_{45}N_4O_8$ requires 673.3237). Anal. Calcd for $C_{37}H_{44}N_4O_8 \cdot 0.2$ EtOAc: C, 65.75; H, 6.66; N, 8.12. Found: C, 66.09; H, 7.03; N, 8.00.

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Supporting Information Available: Tables of crystal data, atomic coordinates, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates and isotropic displacement parameters, and possible hydrogen bonds and short contacts for $C_{37}H_{44}N_4O_8 \cdot 2(CH_2Cl_2)$ (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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