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Pseudoaxially Disubstituted Cyclo-β^3-tetrapeptide Scaffolds

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Abstract—An *N*,*N*-disubstituted cyclo-β^3-tetrapeptide, identified as a potential molecular scaffold, has been synthesised on a multigram scale from β-homophenylalanine by employing a nosylate-based protection strategy. C_2-Symmetric derivatives containing pseudoaxial, combinatorially addressable functionalities have been prepared from the parent cyclopeptide.

Introduction

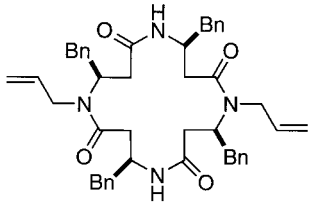
Performing reactions in a highly selective and efficient manner has been a long-term goal for organic chemists, which is nowadays being fuelled by the need to devise synthetically clean processes to give access to a vast array of complex structures.[1] This challenge has been accelerated by the development of new concepts and methods[2] and, in particular, has led to intensive research into the discovery of synthetic catalysts.[2b,3] In this context we, as part of a collaborative effort,[4] have embarked on a project to generate new families of catalysts based on a configurationally rigid, chiral scaffold with conveniently oriented functional handles for subsequent diversification through the use of combinatorial chemistry.[4–6]

We have reported recently the evaluation of a range of polyamide macrocycles derived from α-, β-, and γ-amino acids by means of molecular mechanics.[6] From this study *N*,*N*-disubstituted cyclo-(*S*,*S*,*S*,*S*)-β^3-tetrapeptides were recognised as suitable targets, possessing a rigid framework, pseudoaxially located functionality on the nitrogen atoms and a potential point of attachment to a solid support. Furthermore, such compounds might also be amenable to standard peptide methodology. These calculations were further confirmed by the synthesis and three-dimensional structure elucidation of a C_2-symmetric prototype **1** (Fig. 1) which may be seen as a tetramer of β-homophenylalanine (β^3-hPhe).[7]

Initially, cyclo-β^3-tetrapeptide **1** was prepared in sufficient amounts to elucidate its structure and physical properties. However, as we needed to obtain **1** on a larger scale in order to perform further chemistry, it became necessary to optimise the synthetic route. Herein, we report an improved synthesis that allows the preparation of **1** on a multigram scale and the functionalisation of the *N*-allyl moieties so as to facilitate direct attachment of appendages.

Results and Discussion

The previously described route leading to **1** is based on the cyclisation of a linear β^3-tetrapeptide which in turn is obtained by a Boc protection strategy from (*S*)-phenylalaninol (**2**), readily prepared from L-phenylalanine (see



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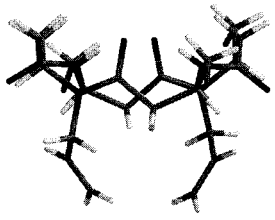

Figure 1. Drawing of compound **1** and of its X-ray crystal structure (side view, with phenyl groups omitted for clarity).

Keywords: amino acids and derivatives; aziridines; macrocycles; β^3-peptides; sulfonamides.

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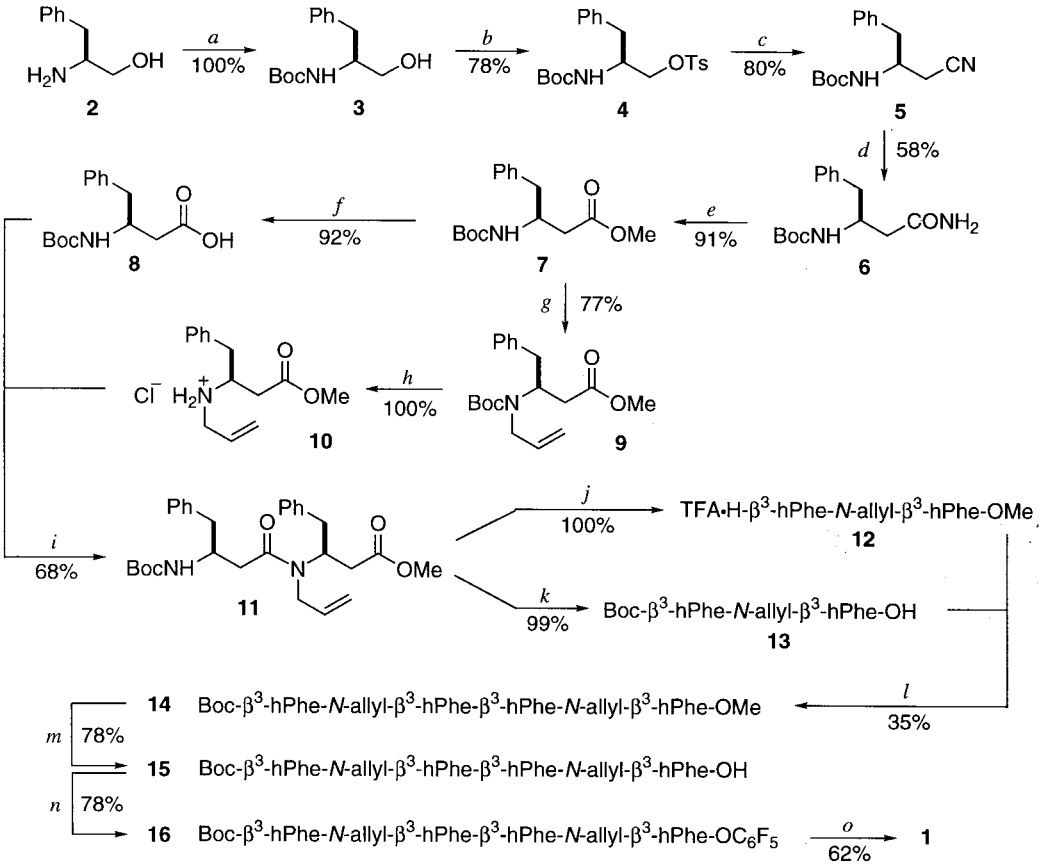
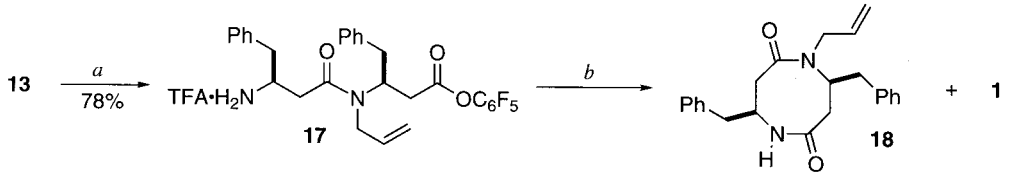


Scheme 1. (a) Boc_2O, THF, H_2O, 17 h; (b) TsCl, pyridine, $CHCl_3$, 1 h; (c) NaCN, DMF, 55°C, 22 h; (d) NaOH, H_2O_2, MeOH, H_2O, 6 h; (e) $(MeO)_2CHNMe_2$, MeOH, 7 h; (f) 1 M LiOH, dioxane, 20 h, then Amberlyst-15 resin (H^+ form); (g) KHMDS, DMF, −20°C, 5 min then allyl iodide, −20°C, 45 min; (h) TFA, CH_2Cl_2, 1 h then Amberlyst A-26 resin (Cl^- form); (i) PyBroP, HOAt, Et^iPr_2N, CH_2Cl_2, 16 h; (j) TFA, CH_2Cl_2, 2 h; (k) 1 M LiOH, dioxane, 23 h, then Amberlyst-15 resin (H^+ form); (l) PyBroP, Et^iPr_2N, CH_2Cl_2, 23 h; (m) 1 M LiOH, MeOH, 20 h, then 0.5 M citric acid; (n) C_6F_5OH, EDC·HCl, CH_2Cl_2, 15 h; (o) i: TFA, CH_2Cl_2, 3 h; ii: Et^iPr_2N, MeCN, 70°C, addition over 12 h plus further heating for 4 h.

Scheme 1).[8] Although it constitutes a highly convergent and versatile approach to tetralactam **1**, it was considered that it could be improved; with this purpose two issues were addressed.

Firstly, the possibility of shortening the synthesis by way of a one-pot dimerisation and cyclisation via the crude pentafluorophenyl ester **17** was studied. Unfortunately, the cyclic dipeptide **18** (see Scheme 2) was obtained in 74% yield (57% from **13**) instead of **1**, when the above-mentioned process was carried out under dilute conditions; at higher concentrations, without slow addition of the activated dipeptide, mixtures of **18** and **1** were formed, but the cyclo-β^3-tetrapeptide **1** was never isolated in a synthetically useful yield (see Scheme 2 and Table 1).

Secondly, evaluation of the *N*-protecting groups was addressed. The previously reported Boc-based route (see Scheme 1) proved to be problematic in two steps: (i) basic hydrolysis of the nitrile **5** directly to the acid **8** was low yielding and a longer route had to be taken via the amide **6** (49% over three steps); (ii) the allylation of the methyl ester **7** turned out to be troublesome and required very precise conditions to give acceptable yields of **9** (see Scheme 1).[9] Facing both problems, as appealing alternatives to the use of the Boc group we turned our attention to the sulfonyl-like protecting groups due to their stability to both acidic and basic media, the milder conditions required for their *N*-alkylation, and the current availability of smooth deprotection procedures.[10] Thus, phenylalaninol (**2**) was converted in a high yielding one-pot procedure to the aziridine **19** (see Scheme 3) by reaction with excess of *p*-nitrobenzenesulfonyl chloride (NsCl) and pyridine followed by a basic work up. The nosyl aziridine **19** reacted with cyanide ion with complete regioselectivity,[11] to afford the nitrile which, without purification, was hydrolysed under acidic



Scheme 2. (a) i: C_6F_5OH, EDC·HCl, CH_2Cl_2, 15 h; ii: TFA, CH_2Cl_2, 2 h; (b) Et^iPr_2N, MeCN, 70°C, 15 h.

Table 1. One-pot dimerisation and cyclisation of **17**

[M]	Reaction time (h)	Yields[a] (%)	
		18	**1**
0.002[b]	15	74	–
0.1[c]	4	30	12
1[c]	19	20	21
2[c]	14	23	18

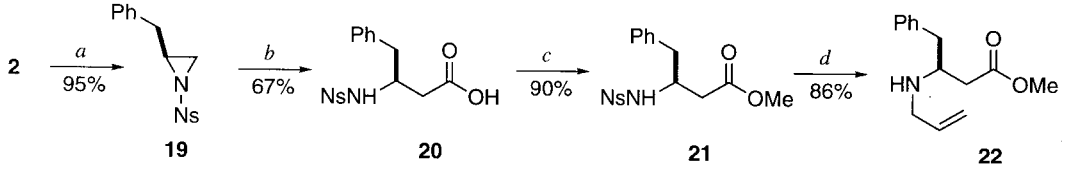
[a] Yields are given for purified products.
[b] Cyclisation performed by the slow addition over 12 h of a dilute solution of the activated ester **17** to a solution of Et^iPr_2N in MeCN at 70°C.
[c] Et^iPr_2N added dropwise to a solution of the activated ester **17** in MeCN at 70°C.

conditions to the acid **20**. It should be stressed that the β-amino acid **20** can be readily prepared in quantities up to 30 g (64% from phenylalaninol in three steps) without need for chromatographic purification or use of special equipment. The acid **20** was esterified and the resulting methyl ester **21** converted, in one pot, into the *N*-allyl amino ester **22** (86%) by treatment with allyl bromide and potassium carbonate followed by the addition of mercaptoacetic acid and DBU in order to remove the *p*-nitrobenzenesulfonyl group.[10] Thiophenol and β-mercaptoethanol proved to be equally successful regarding the cleavage of the sulfonamide, but they require the use of chromatographic purification to remove the thioether formed as coproduct that, in the former case, can be easily extracted with a dilute $NaHCO_3$ solution.[10]

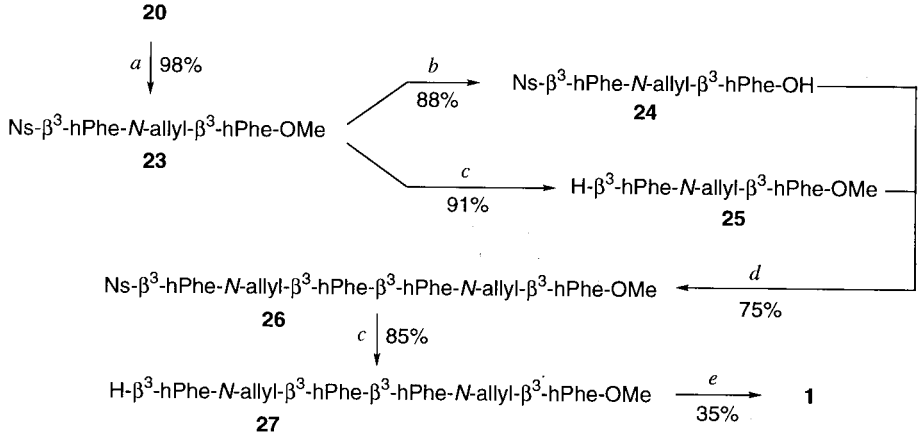
The two β^3-amino acid building blocks **20** and **22** were coupled using a thionyl chloride activation procedure to afford the dipeptide **23** in 98% yield which was subsequently split into two portions as shown in Scheme 4. The first portion was subjected to a basic hydrolysis and the second one treated with mercaptoacetic acid and DBU, to give the acid **24** (88%) and the amino ester **25** (91%) respectively.[12] Treatment of **24** with thionyl chloride followed by addition of **25** gave a complex mixture. Therefore, **24** and **25** were coupled using EDC/HOAt methodology to give the linear tetrapeptide **26** in good yield after chromatographic purification.[13] Removal of the Ns protecting group followed by hydrolysis of the ester **27** and cyclisation of the crude product under high dilution conditions (0.004 M), at 70°C in the presence of PyBroP, HOAt and Et^iPr_2N, afforded the target macrolactam **1** in 35% yield (over two steps).[14] Thus, the macrocycle **1** was prepared in 10% overall yield (12 steps from phenylalaninol) with just two chromatographic purifications required.

Having developed a route to the tetralactam **1** that enabled us to routinely access gram scale quantities, we turned our attention to the modification of the allyl substituents. We were particularly interested in the preparation of scaffold systems containing either amine or acid functionalities to which appendages might be attached through stable amide bonds. Also, a scaffold containing two independently addressable side chains was deemed highly desirable.

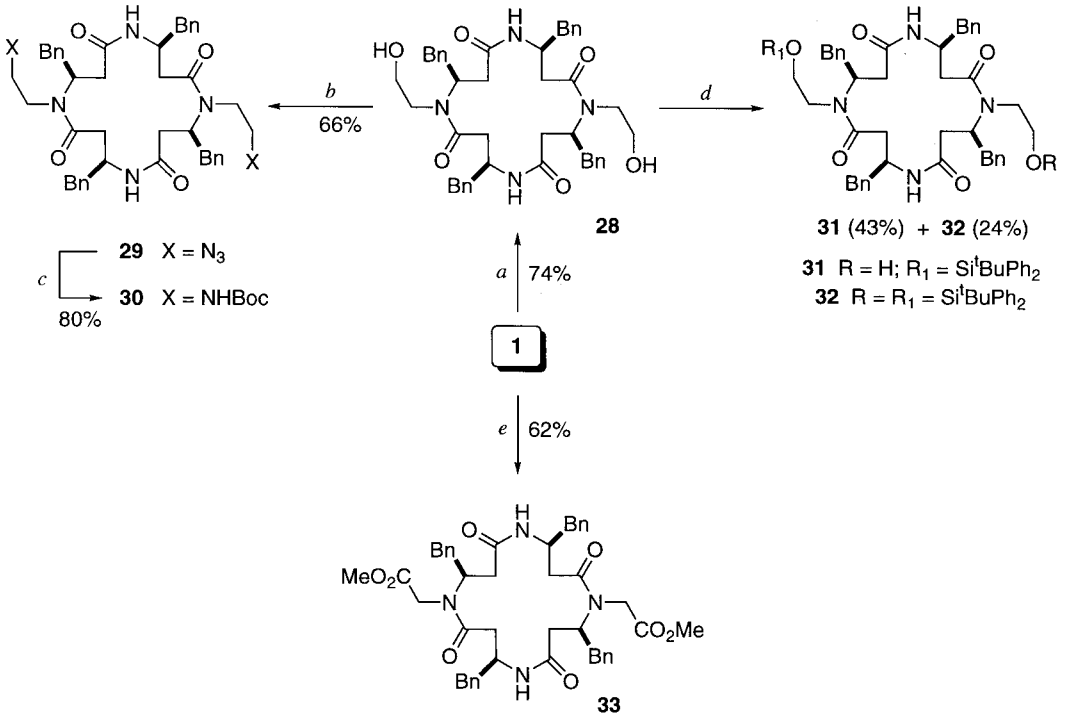
It was envisioned that amino derivatives of the tetralactam **1** might be obtained by conversion of the carbon–carbon double bonds into the corresponding hydroxy groups. Hydroboration of **1** gave no identifiable products under a variety of standard reaction conditions. However, ozonolysis followed by sodium borohydride reduction smoothly afforded the C_2-symmetric diol **28** in 74% yield (see Scheme 5). The diol **28** was converted, by a standard two step procedure, into the diazide **29** in 66% yield. The diazide **29**



Scheme 3. (a) *p*-NsCl, CH_2Cl_2, pyridine, 10 h, then 2 M KOH; (b) i: NaCN, MeCN, H_2O, 16 h. ii: 37% HCl, AcOH, reflux, 4 h; (c) PTSA, MeOH, reflux, 20 h; (d) allyl bromide, K_2CO_3, DMF, 18 h, then $HSCH_2COOH$, DBU, 3 h.



Scheme 4. (a) i: $SOCl_2$, reflux, 1 h; ii: **22**, THF, pyridine, 2 h; (b) 1 M LiOH, MeOH, 20 h then 0.5 M citric acid; (c) $HSCH_2COOH$, DBU, DMF, 16 h; (d) EDC·HCl, HOAt, CH_2Cl_2, 20 h; (e) i: 1 M LiOH, MeOH, 16 h, then 2 M HCl; ii: PyBroP, HOAt, Et^iPr_2N, MeCN, 70°C, 4 h.



Scheme 5. (a) O_3, CH_2Cl_2, −78°C, 40 min, then $NaBH_4$, MeOH, −20°C, 40 min; (b) i: MsCl, Et_3N, CH_2Cl_2, 16 h; ii: NaN_3, DMF, 22 h; (c) 1 M Me_3P, THF, −20°C, 5 min, then Boc-ON, 18 h; (d) TBDPSCl, imidazole, CH_2Cl_2, 2.5 h; (e) i: O_3, CH_2Cl_2, −78°C, 1 h, then $NH_2CONH_2{\cdot}H_2O_2$, DBU, −20°C, 16 h; ii: PTSA, MeOH, reflux, 16 h.

failed to give the desired diamine by catalytic hydrogenation (Pd/C), but the Boc-protected diamine **30**, also a C_2-symmetric compound, was readily obtained in high yield by treatment with trimethyl phosphine and Boc-ON.[15] Alternatively, **28** was desymmetrised by treatment with 1.3 equiv. of TBDPSCl in CH_2Cl_2 to afford the monosilyl ether **31** (43%) together with the disilyl ether **32** (24%) and the unreacted diol **28** (8%). Finally, ozonolysis followed by an oxidative treatment cleanly produced the corresponding diacid (83% yield), which was characterised as its dimethyl ester **33**.

In conclusion, we have synthesised the prototype of a new family of scaffolds that is readily accessible on a multigram scale employing a sulfonamide-based protection strategy. Furthermore, it may be readily derivatised to incorporate functionalities to which catalytic appendages might be directly attached. The adaptation of this methodology to the solid support and the generation of libraries of catalysts are subjects of further investigation in our laboratories.

Experimental

Melting points were taken on an Electrothermal apparatus and have not been corrected. Specific rotations were determined at 20°C on a Perkin–Elmer 241 MC polarimeter. IR spectra were recorded on either a Perkin-Elmer 681 or a Nicolet 510 FT spectrometer and only the more representative frequencies (cm^{-1}) are reported. ^1H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) spectra were recorded on a Varian Gemini 200 spectrometer; ^1H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) spectra were recorded on a Varian Unity Plus 300 spectrometer; ^1H NMR (500 MHz) spectra were recorded on a Varian Unity Inova 500 spectrometer; chemical shifts (δ) are quoted in ppm and referenced to internal TMS for ^1H NMR and $CDCl_3$ (δ 77.0), DMSO-d_6 (δ 39.7) or CD_3OD (δ 49.0) for ^{13}C NMR; data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; where appropriate, 2D techniques were also used to assist in structure elucidation. Low resolution mass spectra (LRMS) were performed by the Servei d'Espectrometria de Masses, Universitat de Barcelona. High resolution mass spectra (HRMS) were obtained from the Centro de Apoio Cientifico Tecnoloxico a Investigacion (C.A.C.T.I.), Universidad de Vigo. Elemental analyses were obtained by the Servei de Microanàlisi (CID-CSIC, Barcelona). Flash chromatography was performed on SDS silica gel (35–70 μm). Analytical thin-layer chromatography was carried out on Merck Kieselgel 60 F_{254} plates. The following solvents and reagents were purified and dried according to standard procedures: THF, CH_2Cl_2, MeOH, MeCN, Et_3N, Et^iPr_2N and pyridine. All other reagents were used as received. The following known compounds were prepared by literature procedures: (*S*)-2-*tert*-butoxycarbonylamino-3-phenyl-1-propanol (**3**),[16] (*S*)-2-*tert*-butoxycarbonylamino-3-phenyl-1-propyl *p*-toluenesulfonate (**4**),[17] and (*S*)-3-*tert*-butoxycarbonylamino-4-phenylbutanenitrile (**5**).[17]

(*S*)-3-*tert*-Butoxycarbonylamino-4-phenylbutanamide (6). A solution of NaOH (16.47 g, 410 mmol) and 33% w/v H_2O_2 (8.5 mL, 82 mmol) in H_2O (100 mL) was added to a stirred solution of **5** (10.74 g, 41 mmol) in MeOH (200 mL). After 6 h, the resulting white precipitate was filtered, washed with H_2O until neutral pH and dried in vacuo over P_4O_{10} to afford **6** (6.71 g, 58%) as a white powder: R_f=0.15 (CH_2Cl_2/MeOH 20:1); mp 125–129°C; $[\alpha]_D$=−18.96

(c=2.6 in $CHCl_3$); IR (KBr): ν 3400, 3357, 3197, 2981, 1692, 1650, 1530, 1167; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.31–7.20 (5H, m, ArH), 4.07 (1H, m, C*H*NH), 2.84 (2H, m, CH_2Ar), 2.37 (2H, m, CH_2CO), 1.38 (9H, s, $C(CH_3)_3$); ^{13}C NMR (DMSO-d_6, 50.3 MHz) δ 172.9, 155.3, 139.5, 129.8, 128.6, 126.5, 78.1, 49.9, 40.6, 40.1, 28.9; LRMS (CI, NH_3) m/z (%): $[M]^+$ 278 (100); HRMS (FAB): calcd for $[M+H]^+$ $C_{15}H_{23}N_2O_3$: 279.1709; found: 279.1708.

Methyl (*S*)-3-*tert*-butoxycarbonylamino-4-phenylbutanoate (7). *N*,*N*-Dimethylformamide dimethyl acetal (10 mL, 75.4 mmol) was added dropwise to a stirred suspension of **6** (6.71 g, 24.0 mmol) in dry MeOH (60 mL). After 7 h a 0.5 M aqueous solution of citric acid (200 mL) was added and the resulting white precipitate filtered, washed with H_2O (200 mL) and dried in vacuo to afford **7** (6.39 g, 91%) as a white powder: mp 53.0–54.0°C (lit.[18] mp 54.5–55.5°C); $[\alpha]_D$=−9.58 (c=2.4 in $CHCl_3$) (lit.[18] $[\alpha]_D$=−10 (c=0.99 in $CHCl_3$)).

(*S*)-3-*tert*-Butoxycarbonylamino-4-phenylbutanoic acid [Boc-β^3-hPhe-OH] (8). A 1 M aqueous solution of LiOH (62 mL, 62 mmol) was added to a stirred solution of **7** (1.83 g, 6.3 mmol) in dioxan (160 mL). After 20 h, the resulting solution was filtered through a bed of Amberlyst-15 resin (H^+ form) and the solvent removed by vacuum distillation to afford **8** (1.60 g, 92%) as a white solid, similar in all respects to a commercially available sample (Fluka Chemie AG).

Methyl (*S*)-3-(*N*-allyl-*N*-*tert*-butoxycarbonylamino)-4-phenylbutanoate [Boc-*N*-allyl-β^3-hPhe-OMe] (9). A 0.5 M solution of KHMDS in toluene (18 mL, 9 mmol) was added dropwise to a stirred solution of **7** (2.50 g, 8.5 mmol) in dry DMF (75 mL) at −20°C under N_2. After 5 min allyl iodide (1.5 mL, 16.5 mmol) was quickly added and the resulting solution stirred for further 45 min. It was then poured into a 0.5 M aqueous solution of citric acid (150 mL) which was extracted with CH_2Cl_2 (3×100 mL). The organic portions were combined, washed with H_2O (5×100 mL) and brine (100 mL), dried ($MgSO_4$), and the solvent removed by distillation under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc 9:1) to afford **9** (2.20 g, 77%) as a colourless oil: R_f=0.16 (hexanes/EtOAc 10:1); $[\alpha]_D$=−35.71 (c=0.91 in $CHCl_3$); IR (film): ν 2977, 1740, 1694, 1366, 1171; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.31–7.19 (5H, m, ArH), 5.58 (1H, m, CH_2CH=CH_2), 5.04 (2H, m, CH_2CH=CH_2), 4.21 (1H, m, C*H*NH), 3.63 (3H, s, OCH_3), 3.62 (2H, m, CH_2CH=CH_2), 2.95 (3H, m, CH_2Ar and CH_aH_bCO), 2.56 (1H, m, CH_aH_bCO), 1.44 (9H, s, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 50.3 MHz; 1:1 rotamers ratio) δ 171.9, 171.5, 154.8, 154.5, 138.3, 134.9, 129.1, 128.2, 126.3, 116.4, 115.8, 79.9, 79.3, 56.9, 56.2, 51.4, 50.2, 49.9, 39.6, 38.7, 38.2, 37.4, 28.2; LRMS (CI, NH_3) m/z (%): $[M+NH_4]^+$ 351 (13), $[M+H]^+$ 334 (100), 278 (18); HRMS (EI): calcd for $[M]^+$ $C_{19}H_{27}NO_4$: 333.1940; found: 333.1940.

Methyl (*S*)-3-allylamino-4-phenylbutanoate hydrochloride [HCl·H-*N*-allyl-β^3-hPhe-OMe] (10). Trifluoroacetic acid (4.40 mL, 57.5 mmol) was added dropwise to a stirred solution of **9** (1.92, 5.8 mmol) in dry CH_2Cl_2 (8 mL) at 0°C under N_2. The solution was stirred at room temperature for 1 h. The volatiles were removed by distillation under reduced pressure and the residue re-dissolved in CH_2Cl_2 (20 mL). An excess of Amberlyst A-26 (Cl^- form) was added and the resulting mixture was stirred for 1 h and filtered. The solvent was removed by distillation under reduced pressure to afford **10** (1.56 g, 100%) as a colourless oil: $[\alpha]_D$=−3.55 (c=0.9 in $CHCl_3$); IR (film): ν 2958, 2900–2200, 1739, 1673, 1202; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.33–7.20 (5H, m, ArH), 6.00 (1H, m, CH_2CH=CH_2), 5.45 (2H, m, CH_2CH=CH_2), 3.71 (3H, m, C*H*NH and CH_2CH=CH_2), 3.61 (3H, s, OCH_3), 3.36 (1H, dd, J=13.8, 4.5 Hz, CH_aH_bAr), 2.90 (2H, m, CH_aH_bAr and CH_aH_bCO), 2.70 (1H, dd, J=17.7, 5.1 Hz, CH_aH_bCO); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 170.7, 135.2, 129.2, 128.9, 127.7, 127.4, 123.8, 55.0, 52.1, 48.0, 36.8, 34.4; LRMS (FAB) m/z (%): $[M-Cl]^+$ 234 (100), 160 (33), 117 (19).

Methyl *N*-*tert*-butoxycarbonyl-(*S*)-β^3-homophenylalanyl-*N*-allyl-(*S*)-β^3-homophenylalaninate [Boc-β^3-hPhe-*N*-allyl-β^3-hPhe-OMe] (11). Dry Et^iPr_2N (2.5 mL, 14.4 mmol), HOAt (328 mg, 2.4 mmol) and PyBroP (2.566 g, 5.5 mmol) were added consecutively to a stirred solution of **8** (702 mg, 2.4 mmol) and **10** (792 mg, 2.9 mmol) in dry CH_2Cl_2 (3 mL) at 0°C under N_2. The resulting mixture was stirred at room temperature for 16 h. A 0.5 M aqueous solution of citric acid (10 mL) was added and the mixture extracted with CH_2Cl_2 (3×10 mL). The organic portions were combined, dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc 7:3) to afford **11** (827 mg, 68%) as a glassy solid: R_f=0.30 (hexanes/EtOAc, 7:3); mp 87–89°C (from EtOAc/hexanes); $[\alpha]_D$=−37.89 (c=1.4 in $CHCl_3$); IR (KBr): ν 3417, 2979, 1739, 1701, 1653, 1507, 1028; ^{1}H NMR ($CDCl_3$, 200 MHz; 2:1 rotamers ratio) δ 7.40–6.88 (10H, m, ArH), 5.85 and 5.34 (1H, m, CH_2CH=CH_2, ratio 1:2), 5.61 (1H, d, J=8.0 Hz, NH), 5.15 and 4.95 (2H, m, CH_2CH=CH_2, ratio 1:2), 4.54 and 4.30 (1H, m, allylNCH, ratio 2:1), 4.17 and 3.61 (3H, m, HNC*H* and CH_2CH=CH_2), 3.41 and 3.37 (3H, s, OCH_3, ratio 2:1), 3.14–2.04 (8H, m, 2×CH_2Ar, CH_2CO_2 and CH_2CON), 1.41 and 1.37 (9H, s, $C(CH_3)_3$, ratio 2:1); ^{13}C NMR ($CDCl_3$, 50.3 MHz; asterisk denotes the minor rotamer) δ 171.9, 171.7*, 171.1*, 170.8, 155.2, 138.7*, 138.6, 138.0, 136.9*, 134.5*, 133.5, 129.3–128.3, 127.0–126.2, 117.4, 116.2*, 78.9, 78.8*, 56.5*, 55.9, 51.9*, 51.8, 50.4, 49.5, 48.9*, 44.0, 40.3, 40.0, 39.8*, 38.7, 37.3*, 36.8, 36.1, 35.6*, 28.4; LRMS (CI, NH_3) m/z (%): $[M+H]^+$ 495 (100), 297 (10), 280 (12), 279 (15); HRMS (FAB): calcd for $[M]^+$ $C_{29}H_{38}N_2O_5$: 494.2781; found: 494.2762.

TFA·H-β^3-hPhe-*N*-allyl-β^3-hPhe-OMe (12). Trifluoroacetic acid (0.60 mL, 7.8 mmol) was added dropwise to a stirred solution of **11** (395 mg, 0.78 mmol) in dry CH_2Cl_2 (1 mL) at 0°C under N_2. The solution was stirred at room temperature for 2 h. Concentration under reduced pressure afforded the crude product **12** (407 mg, 100%). An analytical sample of the free amine was prepared, as a colourless oil, by chromatographic purification (CH_2Cl_2/MeOH 9:1): IR (film): ν 3379, 3027, 2950, 1737, 1642, 1438, 1210; ^{1}H NMR ($CDCl_3$, 300 MHz; 2:1 rotamers ratio) δ 7.32–7.00 (10H, m, ArH), 5.81 and 5.47 (1H, m, CH_2CH=CH_2, ratio

1:2), 5.04 (2H, m, $CH_2CH{=}CH_2$), 4.46 (1H, m, allylNCH), 4.16 (dd, J=16.2, 7.3 Hz) and 3.75–3.33 (m) (3H, HNC*H* and $CH_2CH{=}CH_2$), 3.57 and 3.53 (3H, s, OCH_3, ratio 2:1), 3.05 (dd, J=15.4, 8.1 Hz), 2.94–2.46 (m), 2.32 (dd, J=16.2, 4.1 Hz) and 2.15 (dd, J=16.2, 8.0 Hz) (8H, 2×CH_2Ar, CH_2CO_2 and CH_2CON), 1.66 (2H, br d, J=16.0 Hz, NH_2); ^{13}C NMR ($CDCl_3$, 75.4 MHz; asterisk denotes the minor rotamer peaks) δ 172.6, 172.1*, 172.0, 171.1*, 139.0*, 138.9, 138.2, 137.0*, 134.7*, 133.9, 129.2–128.4, 126.8–126.3, 117.4, 116.6*, 56.7, 55.5, 54.5, 52.0, 51.6, 50.4, 49.8, 48.7, 43.9, 43.6, 41.4, 40.4, 39.7, 38.6, 37.4, 36.8; LRMS (ES) m/z (%): $[M]^+$ 394 (25), 377 (12), 363 (18), 303 (100); HRMS (FAB): calcd for $[M]^+$ $C_{24}H_{30}N_2O_3$: 394.2256; found: 394.2240.

Boc-β^3-hPhe-*N*-allyl-β^3-hPhe-OH (13). A 1 M aqueous solution of LiOH (6.0 mL, 6 mmol) was added to a stirred solution of **11** (302 mg, 0.6 mmol) in dioxane (30 mL). After 23 h the resulting solution was filtered through a bed of Amberlyst-15 resin (H^+ form) and the solvent removed by vacuum distillation to afford **13** (291 mg, 99%) as a colourless oil: R_f=0.55 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D$=−41.21 (c=0.1 in $CHCl_3$); IR (film): ν 3333, 2977, 2621, 1707, 1636, 1595, 1169; ^{1}H NMR ($CDCl_3$, 500 MHz; 1:1 rotamers ratio) δ 7.33–6.85 (10H, m, ArH), 5.86, 5.50 and 5.36 (2H, m, $CH_2CH{=}CH_2$ and NH), 5.15 and 4.95 (2H, m, $CH_2CH{=}CH_2$), 4.50 and 4.24 (1H, m, allylNCH), 4.14, 3.72, 3.62 and 3.49 (3H, m, HNC*H* and $CH_2CH{=}CH_2$), 3.07–1.92 (8H, m, 2×CH_2Ar, CH_2CO_2 and CH_2CON), 1.39 and 1.30 (9H, s, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 175.4, 174.4, 172.5, 171.7, 156.4, 155.8, 138.5, 138.1, 137.2, 134.6, 133.3, 129.4–128.4, 127.0–126.3, 117.6, 116.8, 80.5, 79.3, 56.9, 56.3, 50.6, 49.7, 49.3, 44.2, 41.0, 40.5, 40.0, 38.6, 37.5, 36.9, 36.2, 36.1, 28.4; LRMS (ES) m/z (%): $[M]^+$ 480 (25), 407 (14), 389 (63), 289 (100); HRMS (FAB): calcd for $[M]^+$ $C_{28}H_{36}N_2O_5$: 480.2624; found: 480.2613.

Boc-β^3-hPhe-*N*-allyl-β^3-hPhe-β^3-hPhe-*N*-allyl-β^3-hPhe-OMe (14). Dry Et^{i}Pr$_2$N (0.30 mL, 1.73 mmol) was added to a stirred solution of **13** (283 mg, 0.57 mmol), **12** (354 mg, 0.58 mmol) and PyBroP (408 mg, 0.87 mmol) in dry CH_2Cl_2 (2 mL) at 0°C under N_2. The resulting mixture was stirred at room temperature for 24 h and the solvent was removed by distillation under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 20:1) to afford **14** (161 mg, 35%) as a colourless oil: R_f=0.13 (CH_2Cl_2/MeOH 20:1); $[\alpha]_D$=−39.69 (c=1.6 in $CHCl_3$); IR (film): ν 3245, 2970, 2869, 1710, 1646, 1454, 1177, 1084; ^{1}H NMR ($CDCl_3$, 300 MHz; mixture of rotamers) δ 7.35–7.08 (18H, m, ArH), 7.03–6.88 (2H, m, ArH), 5.84 and 5.48–4.83 (6H, m, 2×$CH_2CH{=}CH_2$ and 2×$CH_2CH{=}CH_2$), 4.70–3.93 and 3.80–3.32 (11H, m, 2×allylNCH, 2×HNC*H*, 2×$CH_2CH{=}CH_2$ and OCH_3), 3.17–2.04 (16H, 4×CH_2Ar, CH_2CO_2 and 3×CH_2CON), 1.40, 1.37 and 1.33 (9H, s, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 172.1–170.9, 169.8, 168.5, 156.5, 138.8–137.5, 137.1, 136.8, 135.0, 134.1, 137.0, 130.0–128.2, 126.8–125.6, 117.5–115.8, 79.7–78.3, 56.5–55.4, 51.8, 51.7, 50.0, 49.4, 48.5, 47.6, 47.0, 43.8, 40.5–35.0, 28.3; LRMS (MALDI-TOF) m/z: $[M+K]^+$ 895.7, $[M+Na]^+$ 879.7; HRMS (FAB): calcd for $[M+H]^+$ $C_{52}H_{65}N_4O_7$: 857.4853; found: 857.4827. HPLC (250×4 mm Nucleosil C18; H_2O (+0.045% TFA): MeCN (+0.036% TFA); 10–100% of MeCN in 330 min; 1 mL/min): t_r=26.2 min.

Boc-β^3-hPhe-*N*-allyl-β^3-hPhe-β^3-hPhe-*N*-allyl-β^3-hPhe-OH (15). A 1 M aqueous solution of LiOH (1.4 mL, 1.4 mmol) was added to a stirred solution of **14** (123 mg, 0.14 mmol) in MeOH (3 mL). After 20 h the resulting solution was diluted with EtOAc (20 mL), washed with a 0.5 M aqueous solution of citric acid (2×20 mL) and H_2O (20 mL), dried ($MgSO_4$) and the solvent removed by vacuum distillation to afford **15** (95 mg, 78%) as a colourless oil which was used without further purification: R_f=0.11 (CH_2Cl_2/MeOH 20:1); $[\alpha]_D$=−42.47 (c=2.0 in $CHCl_3$); IR (film): ν 3318, 2971, 2864, 1711, 1642, 1455, 1171, 1088; ^{1}H NMR ($CDCl_3$, 500 MHz; mixture of rotamers) δ 7.32–7.05 (18H, m, ArH), 6.96–6.81 (3H, m, ArH and NH), 5.93–5.71 and 5.54–4.84 (7H, m, 2×$CH_2CH{=}CH_2$ and 2×$CH_2CH{=}CH_2$ and NH), 4.64–3.44 (8H, m, 2×allylNCH, 2×HNC*H* and 2×$CH_2CH{=}CH_2$), 3.24–1.89 (16H, 4×CH_2Ar, CH_2CO_2 and 3×CH_2CON), 1.40–1.29 (9H, m, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 174.3–169.1, 156.7–154.8, 138.6–137.1, 135.0–133.3, 129.9–128.4, 127.9–126.1, 118.1–116.4, 80.2–78.5, 57.2–56.5, 51.9–47.1, 44.3, 44.1, 40.9–35.0, 28.3; LRMS (ES) m/z (%): $[M+H]^+$ 844 (10), 795 (100); HRMS (FAB): calcd for $[M+H]^+$ $C_{51}H_{63}N_4O_7$: 843.4697; found: 843.4698.

Boc-β^3-hPhe-*N*-allyl-β^3-hPhe-β^3-hPhe-*N*-allyl-β^3-hPhe-OC$_6$F$_5$ (16). A solution of pentafluorophenol (12 mg, 65 μmol) and EDC·HCl (15 mg, 78 μmol) in dry CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of **15** (41 mg, 47 μmol) in dry CH_2Cl_2 (2 mL) at 0°C under N_2. The mixture was stirred at room temperature for 15 h, washed with a 0.5 M aqueous solution of citric acid (5 mL) and brine (5 mL) and dried ($MgSO_4$). The solvent was removed by distillation under reduced pressure to afford **16** (38 mg, 78%) as a colourless oil which was used without further purification: R_f=0.56 (CH_2Cl_2/MeOH 20:1); IR (film): ν 3247, 2971, 2869, 1788, 1709, 1645, 1522, 1454, 1175, 1086; ^{1}H NMR ($CDCl_3$, 200 MHz; mixture of rotamers) δ 7.60–6.80 (20H, m, ArH), 5.96–4.80 (6H, m, 2×$CH_2CH{=}CH_2$ and 2×$CH_2CH{=}CH_2$), 4.54–3.92 (4H, m, 2×allylNCH and 2×HNC*H*), 3.80–1.80 (20H, 2×$CH_2CH{=}CH_2$, 4×CH_2Ar, CH_2CO_2 and 3×CH_2CON), 1.39–1.29 (9H, m, $C(CH_3)_3$); LRMS (ES) m/z (%): $[M+H]^+$ 1009 (75), 905 (100), 743 (20), 547 (17); HRMS (FAB): calcd for $[M+H]^+$ $C_{57}H_{62}F_5N_4O_7$: 1009.4539; found: 1009.4547.

Cyclo-(*N*-allyl-β^3-hPhe-β^3-hPhe-*N*-allyl-β^3-hPhe-β^3-hPhe) (1). Trifluoroacetic acid (30 μL, 0.39 mmol) was added dropwise to a stirred solution of **16** (38 mg, 37 μmol) in dry CH_2Cl_2 (1 mL) at 0°C under N_2. The resulting mixture was stirred at room temperature for 3 h. The solvent was removed by distillation under reduced pressure and the residue was added in dry MeCN (4 mL) over a period of 12 h to a stirred solution of dry Et^{i}Pr$_2$N (10 μL, 58 μmol) in dry MeCN (20 mL) at 70°C under N_2. After stirring for further 4 h the solvent was removed by distillation under reduced pressure. The residue was dissolved in EtOAc (10 mL), washed with a 0.5 M aqueous solution of citric acid (2×5 mL), a 0.1 M aqueous solution of NaOH

(2×5 mL) and H_2O (5 mL), dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 50:1) to afford the tetralactam **1** (17 mg, 62%) as a colourless foam: R_f=0.24 (CH_2Cl_2/MeOH 50:1); mp 162–163°C (from CH_2Cl_2/pentane); $[\alpha]_D$=−54.56 (c=1.0 in $CHCl_3$); IR (KBr): ν 3404, 3064, 2957, 1653, 1505, 1382, 1214; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (1H, d, J=10.0 Hz, NH), 7.30–7.16 (10H, m, ArH), 5.14 (1H, m, CH_2CH=CH_2), 4.88 (2H, m, CH_2CH=CH_2), 4.45 (1H, m, HNC*H*), 3.70 (1H, m, allylNCH), 3.33 (4H, m, CH_2CH=CH_2, allylNCHCH_aH_bAr, CH_aH_bCONH), 3.11 (1H, dd, J=13.5, 7.5 Hz, allylNCHCH_aH_bAr), 3.03 (2H, m, HNCHCH_2Ar), 2.33 (1H, dd, J=13.0, 5.0 Hz, CH_aH_bCONH), 2.30 (1H, dd, J=17.0, 2.5 Hz, CH_aH_bCON-allyl), 2.03 (1H, dd, J=17.0, 4.0 Hz, CH_aH_bCONallyl); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 171.9, 170.1, 138.6, 138.5, 132.4, 129.3, 129.2, 128.6, 128.5, 126.7, 126.5, 118.2, 63.9, 55.7, 46.7, 40.1, 39.8, 38.7, 35.6; HRMS (FAB): calcd for $[M+H]^+$ $C_{46}H_{53}N_4O_4$: 725.4067; found: 725.4079.

Cyclo-(*N*-allyl-β^3-hPhe-β^3-hPhe) (18). A solution of pentafluorophenol (146 mg, 0.79 mmol) and EDC·HCl (169 mg, 0.92 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of **13** (291 mg, 0.59 mmol) in dry CH_2Cl_2 (10 mL) at 0°C under N_2. The mixture was stirred at room temperature for 15 h, washed with a 0.5 M aqueous solution of citric acid (15 mL) and H_2O (15 mL) and dried ($MgSO_4$). The solvent was removed by distillation under reduced pressure and the residue dissolved in dry CH_2Cl_2 (2 mL). Trifluoroacetic acid (0.35 mL, 4.57 mmol) was added dropwise to the stirred solution at 0°C under N_2 and the resulting mixture was stirred at room temperature for 2 h. The solvent was removed by distillation under reduced pressure, the residue dissolved in dry MeCN (20 mL) and added, over a period of 12 h, to a stirred solution of dry Et^{i}Pr$_2$N (0.20 mL, 1.16 mmol) in dry MeCN (180 mL) at 70°C under N_2. After stirring for 3 h the solvent was removed by distillation under reduced pressure. The residue was dissolved in EtOAc (100 mL), washed with a 0.5 M aqueous solution of citric acid (2×50 mL), a 0.1 M aqueous solution of NaOH (2×50 mL) and H_2O (50 mL), dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 20:1) to afford **18** (122 mg, 57%) as a white solid: R_f=0.20 (CH_2Cl_2/MeOH 20:1); mp 185–186°C (from CH_2Cl_2/hexane); $[\alpha]_D$=−26.93 (c=1.0 in $CHCl_3$); IR (KBr): ν 3215, 3020, 2910, 1665, 1635, 1400, 1355; ^{1}H NMR ($CDCl_3$, 300 MHz, δ 7.35–7.24 (6H, m, ArH), 7.13–7.07 (4H, m, ArH), 5.91 (1H, br s, NH), 5.67 (1H, br s, CH_2CH=CH_2), 5.16 (2H, m, CH_2CH=CH_2), 4.39 (1H, m, CH_aH_bCH=CH_2), 3.88 (1H, m, allylNCH), 3.82 (1H, m, HNC*H*), 3.28 (1H, m, CH_aH_bCH=CH_2), 2.96–2.85 (4H, m, 2×CH_2Ar), 2.65 (1H, t, J=13.8 Hz, CH_aH_bCONallyl), 2.46 (2H, m, CH_aH_bCONallyl and CH_aH_bCONH), 2.36 (1H, m, CH_aH_bCONH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 171.6, 170.0, 136.2 (×2), 133.0, 129.3, 129.1, 128.8, 127.2, 127.1, 118.2, 56.7, 52.1, 50.9, 42.8, 41.0, 40.3; LRMS (FAB) m/z (%): $[M+Na]^+$ 385 (10), $[M+H]^+$ 363 (100), 289 (10), 271 (47), 244 (42); HRMS (FAB): calcd for $[M+H]^+$ $C_{23}H_{27}N_2O_2$: 363.2073; found: 363.2056.

(*S*)-*N*-*p*-Nitrobenzenesulfonyl-2-benzylaziridine (19). *p*-Nitrobenzenesulfonyl chloride (4.44 g, 20.0 mmol) was added in one portion to a stirred suspension of **2** (1.01 g, 6.7 mmol) in dry CH_2Cl_2 (5 mL) and dry pyridine (2.2 mL) at 0°C. The resulting mixture was stirred at room temperature for 10 h, diluted with CH_2Cl_2 (100 mL) and washed with 2 M HCl (2×100 mL), which was subsequently extracted with CH_2Cl_2 (20 mL). The organic portions were combined and shaken with a 2 M aqueous solution of KOH (3×100 mL), which was subsequently extracted with CH_2Cl_2 (20 mL). The organic portions were combined, washed with H_2O (100 mL), dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure to afford **19** (2.02 g, 95%) as a brown crystalline solid that was used without further purification: R_f=0.54 (CH_2Cl_2); mp 130–133°C (from acetone/hexanes); $[\alpha]_D$=−0.56 (c=6.8 in $CHCl_3$); IR (KBr): ν 3107, 2925, 1530, 1345, 1165; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16 (2H, AA′BB′, J_{AB}=8.7 Hz, ArH), 7.88 (2H, AA′BB′, J_{AB}=8.7 Hz, ArH), 7.13–7.06 (3H, m, ArH), 6.99–6.96 (2H, m, ArH), 3.07–2.94 (2H, m, NCH_aH_b and CH_aH_bAr), 2.89 (1H, d, J=6.6 Hz, CH_aH_bAr), 2.48 (1H, dd, J=13.8, 7.8 Hz, NCH), 2.31 (1H, d, J=4.2 Hz, NCH_aH_b); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 150.4, 143.5, 136.9, 129.0, 128.7, 128.5, 126.7, 124.0, 42.8, 37.65, 33.4; LRMS (FAB) m/z (%): $[M+H]^+$ 319 (100), 246 (24), 215 (47). Anal. Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.80; S, 10.07. Found: C, 56.41; H, 4.43; N, 8.80; S, 9.88.

(*S*)-3-(*p*-Nitrobenzenesulfonyl)amino-4-phenylbutanoic acid (20). NaCN (25.50 g, 0.52 mol) was added in one portion to a suspension of **19** (53.83 g, 169 mmol) in MeCN (750 mL) and H_2O (200 mL) and the resulting mixture stirred vigorously at room temperature for 16 h. The final solution was diluted with EtOAc (400 mL), washed successively with a saturated aqueous solution of NH_4Cl (3×400 mL) and H_2O (400 mL), dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure to afford the crude nitrile as a dark brown viscous oil. Then, 37% HCl (1000 mL) and glacial AcOH (250 mL) were consecutively added to the crude nitrile and the resulting mixture heated at reflux for 4 h. After cooling, the solution was extracted with CH_2Cl_2 (4×400 mL), dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure. The residual solid was powdered and washed with hexanes (500 mL) to afford **20** (40.98 g, 67%) as a cream coloured solid: R_f=0.16 (CH_2Cl_2/MeOH 20:1); mp 164–168°C (from CH_2Cl_2/hexanes); $[\alpha]_D$=−41.3 (c=1.0 in EtOH); IR (KBr): ν 3233, 3150–2400, 1767, 1533, 1150; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.19 (2H, d, J=8.7 Hz, ArH), 7.77 (2H, d, J=8.4 Hz, ArH), 7.14–7.00 (5H, m, ArH), 3.68 (1H, m, NCH), 2.69 (1H, dd, J=13.5, 5.4 Hz, CH_aH_bAr), 2.60 (1H, dd, J=13.5, 7.8 Hz, CH_aH_bAr), 2.33 (2H, d, J=6.3 Hz, CH_2CO); ^{13}C NMR (DMSO-d_6, 75.4 MHz) δ 171.9, 149.2, 147.0, 137.8, 129.3, 128.3, 127.8, 126.3, 124.4, 52.9, 41.0, 40.3; LRMS (FAB) m/z (%): $[M+H]^+$ 365 (100). Anal. Calcd for $C_{16}H_{16}N_2O_6S$: C, 52.70; H, 4.43; N, 7.69; S, 8.69. Found: C, 52.74; H, 4.41; N, 7.69; S, 8.69.

Methyl (*S*)-3-(*p*-Nitrobenzenesulfonyl)amino-4-phenylbutanoate (21). *p*-Toluenesulfonic acid (19.77 g, 104 mmol) was added in one portion to a stirred solution

of **20** (25.26 g, 69 mmol) in dry MeOH (200 mL). The resulting solution was heated at reflux under N_2 (allowing the condensing methanol to pass through a bed of 3 Å molecular sieves) for 20 h, cooled and quenched with H_2O (100 mL) to afford a white precipitate. The solvent was removed by filtration and the residue thoroughly washed with H_2O (4×100 mL) and dissolved in CH_2Cl_2 from which the remaining H_2O was extracted. The solution was dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure to afford **21** (23.50 g, 90%) as a creamy solid: R_f=0.15 (CH_2Cl_2); mp 95–96°C (from CH_2Cl_2/hexanes); $[\alpha]_D$=−46.94 (c=1.0 in $CHCl_3$); IR (KBr): ν 3271, 1723, 1524, 1333, 1160; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15 (2H, AA′BB′, J_{AB}=9.0 Hz, ArH), 7.76 (2H, AA′BB′, J_{AB}=9.0 Hz, ArH), 7.17–7.10 (3H, m, ArH), 7.00–6.96 (2H, m, ArH), 5.49 (1H, br d, J=9.0 Hz, NH), 3.81 (1H, m, NCH), 3.68 (3H, s, OCH_3), 2.85 (1H, dd, J=13.8, 6.3 Hz, CH_aH$_b$Ar), 2.76 (1H, dd, J=13.8, 8.4 Hz, CH$_a$$H_b$Ar), 2.66 (1H, dd, J=16.5, 5.4 Hz, CH_aH$_b$CO), 2.60 (1H, dd, J=16.5, 5.1 Hz, CH$_a$$H_b$CO); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 171.6, 150.0, 146.0, 136.6, 129.1, 128.7, 128.0, 127.0, 124.1, 52.8, 51.9, 40.8, 38.8; LRMS (FAB) m/z (%): [M+Na]$^+$ 401 (12), [M+H]$^+$ 379 (100), 305 (81); HRMS (FAB): calcd for [M+H]$^+$ $C_{17}H_{19}N_2O_6S$: 379.0964; found: 379.0975.

Methyl (*S*)-3-allylamino-4-phenylbutanoate (22). Anhydrous K_2CO_3 (3.33 g, 24.0 mmol) was added in one portion to a stirred solution of **21** (4.07 g, 10.8 mmol) and allyl bromide (1.10 mL, 12.7 mmol) in moist DMF (100 mL) at room temperature. After 18 h, mercaptoacetic acid (1.65 mL, 23.7 mmol) was added followed by DBU (16.0 mL, 107.1 mmol) and the mixture stirred for further 3 h. The resulting suspension was diluted with EtOAc (200 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (3×150 mL) which was subsequently extracted with EtOAc (200 mL). The organic portions were combined, dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure to afford **22** (2.15 g, 86%) as an orange oil: R_f=0.53 (CH_2Cl_2/MeOH, 20:1); $[\alpha]_D$=−8.34 (c=0.9 in $CHCl_3$); IR (film): ν 3334, 2952, 1739, 1438, 1200; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.29–7.10 (5H, m, ArH), 5.83 (1H, m, CH_2CH=CH_2), 5.14 (2H, m, CH_2CH=CH_2), 3.65 (3H, s, OCH_3), 3.29 (3H, m, NCH and CH_2CH=CH_2), 2.85 (1H, dd, J=13.4, 6.0 Hz, CH_aH$_b$Ar), 2.70 (1H, dd, J=13.4, 7.2 Hz, CH$_a$$H_b$Ar), 2.40 (2H, d, J=6.4 Hz, CH_2CO); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 172.5, 138.3, 136.5, 129.2, 128.3, 126.2, 115.8, 55.2, 51.4, 49.5, 40.4, 38.4; LRMS (CI, NH_3) m/z (%): [M+H]$^+$ 234 (100); HRMS (FAB): calcd for [M+H]$^+$ $C_{14}H_{20}NO_2$: 234.1494; found: 234.1496.

Methyl *N*-(*p*-nitrobenzenesulfonyl)-(*S*)-β^3-homophenylalanyl-*N*-allyl-(*S*)-β^3-homophenylalaninate [Ns-β^3-hPhe-*N*-allyl-β^3-hPhe-OMe] (23). A stirred suspension of **20** (2.72 g, 7.5 mmol) (predried by co-evaporation with dry toluene) in thionyl chloride (11.0 mL, 150.8 mmol) was heated at reflux under N_2. After 1 h the excess of thionyl chloride was removed by distillation under reduced pressure to afford the crude acid chloride as a light brown oil. The acid chloride was dissolved in dry THF (15 mL) and added dropwise to a stirred solution of **22** (1.92 g, 9.2 mmol) (predried by co-evaporation with dry toluene) in dry pyridine (6.0 mL, 73.4 mmol) at 0°C. The resulting solution was stirred at room temperature for 2 h. The mixture was diluted with EtOAc (50 mL), washed with an aqueous solution of citric acid (2×50 mL) and brine (50 mL) and dried ($MgSO_4$). The solvent was removed by distillation under reduced pressure to afford **23** (4.26 g, 98%) as an orange oil. An analytical sample was prepared by chromatographic purification (hexanes/EtOAc 7:3) to afford a yellow oil: R_f=0.18 (hexanes/EtOAc, 7:3); $[\alpha]_D$=−48.92 (c=1.2 in $CHCl_3$); IR (film): ν 3317, 3029, 1737, 1629, 1530, 1163; ^{1}H NMR ($CDCl_3$, 500 MHz; 1:1 rotamers ratio) δ 8.11 and 8.08 (2H, AA′BB′, J_{AB}=9.0 Hz, ArH), 7.74 and 7.68 (2H, AA′BB′, J_{AB}=9.0 Hz, ArH), 7.30–6.91 (10H, m, ArH), 6.25 and 6.00 (1H, d, J=9.0 Hz, NH), 5.78 and 5.38 (1H, m, CH_2CH=CH_2), 5.11 and 5.00 (2H, m, CH_2CH=CH_2), 4.56 and 4.24 (1H, m, allylNCH), 4.13 (dd, J=16.0, 5.0 Hz) and 3.76–3.52 (m) (3H, HNCH and CH_2CH=CH_2), 3.65 and 3.62 (3H, s, OCH_3), 3.04 (dd, J=13.5, 8.5 Hz), 2.92 (dd, J=13.5, 7.5 Hz), 2.84 (dd, J=16.5, 9.0 Hz), 2.78 (d, J=7.5 Hz), 2.73–2.58 (m), 2.47 (dd, J=17.0, 5.0 Hz), 2.43 (d, J=4.5 Hz), 2.34 (dd, J=14.0, 6.0 Hz), 2.08 (dd, J=16.5, 3.5 Hz) (8H, 2×CH_2Ar, CH_2CO_2 and CH_2CON); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 172.1, 171.8, 171.1, 170.9, 149.7, 149.6, 146.7, 146.6, 138.1, 138.0, 137.1, 134.3, 133.2, 129.6–126.8, 124.1, 124.0, 117.6, 116.7, 56.1, 53.7, 53.4, 52.1, 51.9, 42.2, 41.0, 40.6, 39.7, 38.7, 37.5, 37.3, 36.8, 36.5; HRMS (FAB): calcd for [M+H]$^+$ $C_{30}H_{34}N_3O_7S$: 580.2117; found: 580.2107.

Ns-β^3-hPhe-*N*-allyl-β^3-hPhe-OH (24). A 1 M aqueous solution of LiOH (250 mL, 250 mmol) was added to a stirred solution of **23** (13.53 g, 23 mmol) in MeOH (300 mL). After 20 h the solution was diluted with EtOAc (600 mL) and washed with a 0.5 M aqueous solution of citric acid (2×100 mL) which was subsequently extracted with EtOAc (300 mL). The organic portions were combined, washed with brine (300 mL), dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure to afford **24** (12.07 g, 91%) as a light brown foam. An analytical sample was prepared by chromatographic purification (CH_2Cl_2/MeOH 10:1) to afford a yellow oil: R_f=0.22 (CH_2Cl_2/MeOH 20:1); $[\alpha]_D$=−58.25 (c=1.4 in $CHCl_3$); IR (film): ν 3220, 3029, 1713, 1609, 1530, 1351, 1164; ^{1}H NMR ($CDCl_3$, 500 MHz; 1:1 rotamers ratio) δ 8.10 and 8.03 (2H, AA′BB′, J_{AB}=9.0 Hz, ArH), 7.73 and 7.62 (2H, AA′BB′, J_{AB}=8.5 Hz, ArH), 7.28–7.16 (4H, m, ArH), 7.09–7.03 (3H, m, ArH), 6.99 (1H, m, ArH), 6.91–6.87 (2H, m, ArH), 6.26 and 6.14 (1H, d, J=9.0 Hz, NH), 5.81 and 5.39 (1H, m, CH_2CH=CH_2), 5.15 and 4.99 (2H, m, CH_2CH=CH_2), 4.59 and 4.28 (1H, m, allylNCH), 4.12 (dd, J=16.0, 5.0 Hz) and 3.76–3.53 (m) (3H, HNCH and CH_2CH=CH_2), 3.02 (dd, J=14.0, 8.5 Hz), 2.93 (dd, J=14.0, 7.5 Hz), 2.86 (dd, J=16.0, 8.5 Hz), 2.75 (d, J=7.5 Hz), 2.73–2.61 (m), 2.51 (dd, J=17.0, 4.5 Hz), 2.44 (d, J=5.0 Hz), 2.29 (dd, J=13.5, 5.5 Hz), 2.04 (dd, J=17.0, 4.0 Hz) (8H, 2×CH_2Ar, CH_2CO_2 and CH_2CON); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 175.7, 174.6, 171.5, 171.1, 149.2, 149.1, 146.3, 146.2, 137.7, 137.5, 137.3, 136.8, 133.8, 133.0, 128.9–126.2, 123.8, 123.7, 117.6, 116.8, 55.9, 53.4, 53.2, 49.6, 44.1, 40.3, 39.2, 38.4, 37.9, 37.3, 36.5; LRMS (FAB) m/z (%): [M+H]$^+$ 566 (100), 548 (65); HRMS (FAB): calcd for [M+H]$^+$ $C_{29}H_{32}N_3O_7S$: 566.1961; found: 566.1950.

H-β³-hPhe-*N*-allyl-β³-hPhe-OMe (25). DBU (6.30 mL, 42.2 mmol) was added to a stirred solution of **23** (2.46 g, 4.2 mmol) and mercaptoacetic acid (0.70 mL, 10.1 mmol) in DMF (50 mL). After 16 h the solution was diluted with EtOAc (200 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (3×100 mL) which was subsequently extracted with EtOAc (100 mL). The organic portions were combined, dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure to afford **25** (1.46 g, 88%) as an orange oil. The physical and spectroscopic data are identical to that of the free amine of **12**.

Ns-β³-hPhe-*N*-allyl-β³-hPhe-β³-hPhe-*N*-allyl-β³-hPhe-OMe (26). HOAt (0.879 g, 6.46 mmol) and EDC·HCl (0.915 g, 4.77 mmol) were added consecutively, as solids, to a stirred solution of **24** (1.806 g, 3.20 mmol) and **25** (1.434 g, 3.65 mmol) in dry CH_2Cl_2 (25 mL) at 0°C under N_2. The mixture was stirred at room temperature for 20 h, diluted with CH_2Cl_2 (100 mL) and washed with a 0.5 M aqueous solution of citric acid (2×100 mL), which was subsequently extracted with CH_2Cl_2 (50 mL). The organic portions were combined, dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 10:1) to afford **26** (2.264 g, 75%) as an orange oil: R_f=0.15 (CH_2Cl_2/MeOH 10:1); $[\alpha]_D$=−33.81 (c=1.1 in $CHCl_3$); IR (film): ν 3303, 3029, 2927, 1737, 1644, 1530, 1349, 1163; ^{1}H NMR ($CDCl_3$, 500 MHz; mixture of rotamers) δ 8.15–8.03 (2H, m, ArH), 7.82–7.63 (2H, m, ArH), 7.29–6.88 (20H, m, ArH), 6.43 (m), 6.35 (d, J=7.5 Hz), 6.26 (d, J=8.0 Hz), 6.15 (d, J=9.0 Hz), 6.08 (d, J=9.0 Hz), 5.80 (m), 5.37 (m), 5.28 (m) and 5.20–4.90 (m) (8H, 2×NH, 2×CH_2CH=CH_2 and 2×CH_2CH=CH_2), 4.60 (m), 4.38 (m), 4.30 (m), 4.19–3.98 (m) and 3.75–3.52 (m) (11H, 2×allylNCH, 2×HNCH, 2×CH_2CH=CH_2 and OCH_3), 3.08–2.24 (m), 2.18–2.07 (m), 2.01 (dd, J=16.5, 4.0 Hz) and 1.95 (dd, J=16.5, 4.0 Hz) (16H, 4×CH_2Ar, CH_2CO_2 and 3×CH_2CON); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 172.2–168.1, 149.6–149.3, 147.0–146.9, 138.9–136.9, 134.8–133.3, 129.2–127.8, 126.7–126.4, 124.0–123.8, 118.0–116.4, 56.5–55.5, 53.7–53.1, 52.1–51.5, 50.9–49.2, 48.1–46.4, 44.5–43.4, 40.8–34.4; LRMS (FAB) m/z (%): $[M+Na]^+$ 965 (48), $[M+H]^+$ 943 (100), 742 (27), 549 (65); HRMS (FAB): calcd for $[M+H]^+$ $C_{53}H_{60}N_5O_9S$: 942.4112; found: 942.4145.

H-β³-hPhe-*N*-allyl-β³-hPhe-β³-hPhe-*N*-allyl-β³-hPhe-OMe (27). Neat DBU (0.80 mL, 5.35 mmol) was added to a stirred solution of **26** (510 mg, 0.54 mmol) and mercaptoacetic acid (80 μL, 1.15 mmol) in dry DMF (10 mL) under N_2. After 23 h the solution was diluted with EtOAc (50 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (3×50 mL) which was subsequently extracted with EtOAc (50 mL). The organic portions were combined, dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure to afford **27** (348 mg, 85%) as an orange oil: R_f=0.22 (CH_2Cl_2/MeOH 10:1); IR (film): ν 3305, 3029, 2927, 1737, 1642, 1495; ^{1}H NMR ($CDCl_3$, 300 MHz; mixture of rotamers) δ 7.30–6.93 (20H, m, ArH), 5.82, 5.37 and 5.18–4.93 (6H, m, 2×CH_2CH=CH_2 and 2×CH_2CH=CH_2), 4.54, 4.39, 4.29, 4.13, 3.68–3.50 and 3.41 (11H, 2×allylNCH, 2×HNCH, 2×CH_2CH=CH_2 and OCH_3), 3.09–2.11 (16H, m, 4×CH_2Ar, CH_2CO_2 and 3×CH_2CON); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 171.9–168.0, 138.0–136.0, 134.5–132.9, 128.6–127.5, 125.7–125.5, 117.7–114.8, 55.3, 50.9, 49.6–48.7, 48.5, 47.2, 46.4, 43.5–42.0, 39.9–34.9; LRMS (FAB) m/z (%): $[M+Na]^+$ 780 (10), $[M+H]^+$ 758 (100), 597 (12), 557 (10); HRMS (FAB): calcd for $[M+H]^+$ $C_{47}H_{57}N_4O_5$: 757.4329; found: 757.4356.

Cyclo-(*N*-allyl-β³-hPhe-β³-hPhe-*N*-allyl-β³-hPhe-β³-hPhe) (1). A 1 M aqueous solution of LiOH (21 mL, 21 mmol) was added to a stirred solution of the tetrapeptide **27** (1.589 g, 2.1 mmol) in MeOH (42 mL). After 16 h the solution was quenched with 2 M HCl (20 mL) and extracted with CH_2Cl_2 (2×100 mL). The organic fractions were combined, dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure to afford a light yellow oil, which was filtered through a plug of silica gel (CH_2Cl_2/MeOH 10:1) to afford an oil (1.310 g). A portion of this crude material (632 mg) was co-evaporated with dry toluene, dissolved in dry MeCN (2.4 L) and stirred at 0°C under N_2. Dry Et^iPr_2N (1.45 mL, 8.3 mmol), HOAt (226 mg, 1.7 mmol) and a solution of PyBroP (0.792 g, 1.7 mmol) in dry MeCN (100 mL) were added and the resulting mixture was heated at 70°C; after 2 h an additional solution of PyBroP (0.785 g, 1.7 mmol) in dry MeCN (100 mL) was added dropwise and the solution stirred for further 2 h. The solvent was removed by distillation under reduced pressure and the residue was purified by flash chromatography (CH_2Cl_2/MeOH 10:1) to afford pure tetralactam **1** (254 mg, 35% overall yield). The physical and spectroscopic data are identical to that given previously.

Cyclo-(*N*-(2-hydroxyethyl)-β³-hPhe-β³-hPhe-*N*-(2-hydroxyethyl)-β³-hPhe-β³-hPhe) (28). Ozone was bubbled through a stirred solution of **1** (93 mg, 0.128 mmol) in dry CH_2Cl_2 (10 mL) at −78°C. After 40 min the solution was warmed to −20°C and $NaBH_4$ (149 mg, 4.0 mmol) and dry MeOH (10 mL) added consecutively. After a further 40 min, the solvent was removed by distillation under reduced pressure and the residue diluted with EtOAc (20 mL), washed with H_2O (2×20 mL), dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure to afford **28** (70 mg, 74%) as a glassy solid: R_f=0.18 (CH_2Cl_2/MeOH 10:1); $[\alpha]_D$=−77.28 (c=1.1 in $CHCl_3$); IR (film): ν 3392, 2929, 1646, 1517, 1455, 1379; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.00 (1H, d, J=10.0 Hz, NH), 7.40–7.00 (10H, m, ArH), 4.47 (1H, m, HNCH), 3.79 (1H, m, alkylNCH), 3.48 (2H, m, CH_aH$_b$OH and CH_aH$_b$CONH), 3.40 (1H, dd, J=13.5, 9.5 Hz, alkylNCHCH_aH$_b$Ar), 3.15 (1H, m, CH$_a$$H_b$OH), 3.06 (1H, dd, J=13.5, 7.0 Hz, HNCHCH_aH$_b$Ar), 2.97 (3H, m, alkylNCHCH$_a$$H_b$Ar, HNCHCH$_a$$H_b$Ar and C$H_aH_bCH_2$OH), 2.44 (3H, m, CH$_a$$H_b$CONH, C$H_aH_b$CONalkyl and CH$_a$$H_bCH_2$OH), 2.11 (1H, dd, J=18.0, 4.5 Hz, CH$_a$$H_b$CONalkyl); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 173.2, 171.2, 138.5, 138.4, 129.3, 129.1, 128.7, 128.6, 126.9, 126.6, 61.8, 60.5, 53.6, 47.0, 41.0, 40.2, 38.1, 35.3; LRMS (FAB) m/z (%): $[M+Na]^+$ 755 (18), $[M+H]^+$ 733 (100), 715 (40); HRMS (FAB): calcd $[M+H]^+$ for $C_{44}H_{53}N_4O_6$: 733.3965; found: 733.3932.

Cyclo-(*N*-(2-azidoethyl)-β³-hPhe-β³-hPhe-*N*-(2-azidoethyl)-β³-hPhe-β³-hPhe) (29). Methanesulfonyl chloride

(90 μL, 1.16 mmol) was added to a stirred solution of **28** (207 mg, 0.28 mmol) in dry CH_2Cl_2 (25 mL) and dry Et_3N (0.20 mL, 1.44 mmol) under N_2. After 16 h the mixture was diluted with CH_2Cl_2 (50 mL) and washed with H_2O (2×50 mL) which was subsequently extracted with CH_2Cl_2 (25 mL). The organic portions were combined, dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure. NaN_3 (118 mg, 1.82 mmol) was added to a stirred solution of the residue dissolved in DMF (10 mL) at room temperature under N_2. After 22 h the solvent was removed by distillation under reduced pressure and the residue diluted with EtOAc (50 mL) and washed with brine (2×50 mL) which was subsequently extracted with EtOAc (25 mL). The organic portions were combined, dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure to afford **29** (147 mg, 66%) as an off-white foam: R_f=0.70 (EtOAc); $[\alpha]_D$=−93.62 (c=1.1 in $CHCl_3$); IR (film): ν 3402, 3027, 2927, 2101, 1659, 1503, 1377, 1263; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66 (1H, d, J=10.0 Hz, NH), 7.30–7.18 (10H, m, ArH), 4.50 (1H, m, HNC*H*), 3.54 (1H, m, alkylNCH), 3.40 (2H, m, alkylNCHCH_aH$_b$Ar and CH_aH$_b$CONH), 3.22 (1H, m, CH_aH$_b$N$_3$), 3.06–2.84 (5H, m, HNCHCH_2Ar, alkylNCHCH$_a$$H_bAr, CH_a$$H_bN_3$ and CH_aH$_b$CH$_2$N$_3$), 2.44 (1H, dd, J=10.5, 4.5 Hz, CH$_a$$H_bCH_2N_3$), 2.39 (1H, dd, J=17.5, 2.5 Hz, CH_aH$_b$CONalkyl), 2.34 (1H, dd, J=13.0, 4.5 Hz, CH$_a$$H_b$CONH), 2.28 (1H, dd, J=17.5, 4.5 Hz, CH$_a$$H_b$CONalkyl); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 172.8, 169.5, 138.6, 138.5, 129.2, 129.1, 128.6, 128.4, 126.8, 126.5, 63.1, 50.2, 49.0, 46.7, 40.6, 40.2, 38.2, 35.1; LRMS (FAB) *m/z* (%): [M+H]$^+$ 784 (100), 691 (16), 460 (30); HRMS (FAB): calcd for [M+H]$^+$ $C_{44}H_{51}N_{10}O_4$: 783.4095; found: 783.4120.

Cyclo-[*N*-2-(*tert*-butoxycarbonyl)aminoethyl-β^3-hPhe-β^3-hPhe-*N*-2-(*tert*-butoxycarbonyl)aminoethyl-β^3-hPhe-β^3-hPhe] (30). A 1 M solution of Me_3P in dry THF (53 μL, 53 μmol) was added to a stirred solution of **29** (19 mg, 24 μmol) in dry THF (0.5 mL) at −20°C under N_2. After 5 min Boc-ON (13 mg, 53 μmol) was added and the resulting solution was stirred for further 15 min at −20°C and at room temperature for 18 h. The final solution was diluted with CH_2Cl_2 (10 mL) and washed with H_2O (2×10 mL) which was subsequently extracted with CH_2Cl_2 (5 mL). The organic fractions were combined and washed with a 2 M aqueous solution of KOH (2×10 mL) which was subsequently extracted with CH_2Cl_2 (5 mL). The organic fractions were combined, washed with brine (10 mL), dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:1) to afford **30** (20 mg, 80%) as a glassy solid: R_f=0.48 (hexanes/EtOAc, 1:1); $[\alpha]_D$=−46.60 (c=1.5 in $CHCl_3$); IR (film): ν 3400, 3342, 2996, 2950, 1817, 1715, 1663, 1510, 1263; ^{1}H NMR ($CDCl_3$, 500 MHz; mixture of rotamers) δ 8.03 (m), 7.95 (d, J=10.0 Hz) and 7.79 (m) (1H, NH), 7.32–6.97 (10H, m, ArH), 4.58–4.30 (2H, m, ^{t}BuOCONH and HNC*H*), 3.63 (1H, m, alkylNCH), 3.40, 3.11–2.36, 2.18 and 2.06 (12H, m, 2×CH$_2$Ar, 2×CH$_2$CON, CH_2CH$_2$NH and CH$_2$CH_2NH), 1.42–1.20 (9H, m, C(CH$_3$)$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 173.0, 169.9, 155.6, 138.5, 138.4, 129.3, 129.1, 128.8, 128.5, 127.0, 126.6, 79.2, 61.4, 52.2, 47.0, 40.7, 40.3, 38.7, 38.3, 35.9, 28.4; LRMS (FAB) *m/z* (%): [M+Na]$^+$ 954 (41), [M+H]$^+$ 931 (28), 831 (100), 731 (34), 714 (27); HRMS (FAB): calcd for [M+H]$^+$ $C_{54}H_{71}N_6O_8$: 931.5333; found: 931.5291.

Cyclo-[*N*-2-hydroxyethyl-β^3-hPhe-β^3-hPhe-*N*-2-(*tert*-butyldiphenylsilyloxy)ethyl-β^3-hPhe-β^3-hPhe] (31) and cyclo-[*N*-2-(*tert*-butyldiphenylsilyloxy)ethyl-β^3-hPhe-β^3-hPhe-*N*-2-(*tert*-butyldiphenylsilyloxy)ethyl-β^3-hPhe-β^3-hPhe] (32). Imidazole (30 mg, 0.44 mmol) and *tert*-butyldiphenylsilyl chloride (48 μL, 0.18 mmol) were added consecutively to a stirred solution of **28** (103 mg, 0.14 mmol) in dry CH_2Cl_2 at 0°C under N_2 and the resulting mixture was stirred at room temperature for 2.5 h. The solution was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (2×10 mL), which was subsequently extracted with CH_2Cl_2 (10 mL). The organic portions were combined, dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc 3:1) to afford the disilyl ether **32** (41 mg, 24%) as a colourless oil: R_f=0.16 (hexanes/EtOAc, 3:1); $[\alpha]_D$=−16.43 (c=1.4 in $CHCl_3$); IR (film): ν 3396, 2930, 1648, 1513, 1111; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46–7.00 (21H, m, ArH and NH), 4.15 (1H, m, C*H*NH), 3.51 (1H, m, alkylNCH), 3.20 (1H, dd, J=13.5, 8.5 Hz, CH_aH$_b$CONH), 3.16 (1H, dd, J=13.0, 12.0 Hz, alkylNCHCH_aH$_b$Ar), 2.99–2.83 (6H, m, HNCHCH_2Ar, CH$_2$OSi and CH_2CH$_2$OSi), 2.80 (1H, dd, J=13.0, 9.0 Hz, alkylNCHCH$_a$$H_b$Ar), 2.24 (1H, dd, J=13.5, 5.0 Hz, CH$_a$$H_b$CONH), 1.83 (1H, dd, J=17.5, 2.5 Hz, CH_aH$_b$CONalkyl), 1.50 (1H, dd, J=17.5, 4.5 Hz, CH$_a$$H_b$CONalkyl), 0.93 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 171.9, 169.4, 138.6, 138.5, 135.6, 135.5, 133.1, 132.9, 129.9, 129.8, 129.3, 129.2, 128.6, 128.4, 127.8, 127.7, 126.7, 126.5, 64.0, 60.0, 53.3, 46.6, 40.0, 39.7, 38.7, 35.1, 26.8, 19.0; LRMS (FAB) *m/z* (%): [M+H]$^+$ 1210 (48), 1152 (17), 1132 (11), 954 (100), 862 (12); HRMS (FAB): calcd for [M+H]$^+$ $C_{76}H_{89}N_4O_6Si_2$: 1209.6321; found: 1209.6281. Later fractions, eluting with hexanes/EtOAc (1:1) afforded the monosilyl ether **31** (59 mg, 43%), as a colourless oil: R_f=0.31 (hexanes/EtOAc, 1:1); $[\alpha]_D$=−58.21 (c=1.18 in $CHCl_3$); IR (film): ν 3398, 2933, 1646, 1510, 1079; ^{1}H NMR ($CDCl_3$, 500 MHz; asterisk denotes signals associated with the *N*-(2-hydroxyethyl)-β^3-hPhe-β^3-hPhe portion of the molecule) δ 7.79 (1H, d, J=10.0 Hz, NH), 7.61 (1H, d, J=10.0 Hz, NH*), 7.46–6.95 (30H, m, ArH), 4.33 (1H, m, C*H*NH), 4.14 (1H, m, C*H*NH*), 3.78 (1H, m, alkylNCH*), 3.57–3.41 (2H, m, alkylNCH and CH_aH$_b$O*), 3.40–3.31 (2H, m, alkylNCHCH_aH$_b$Ar* and CH_aH$_b$CONH*), 3.28–3.20 (2H, m, alkylNCHCH_aH$_b$Ar and CH_aH$_b$CONH), 3.11 (1H, m, CH$_a$$H_b$O*), 3.03–2.76 (11H, m, CH$_2$O, CH$_2$N, CH_aH$_b$N*, HNCHCH_2Ar, HNCHCH_2Ar*, alkylNCHCH$_a$$H_b$Ar and alkylNCHCH$_a$$H_b$Ar*), 2.40–2.25 (4H, m, CH$_a$$H_b$CONH*, CH$_a$$H_b$CONH, C$H_aH_b$CONalkyl and CH$_a$$H_b$N*), 1.76 (1H, dd, J=17.5, 4.5 Hz, CH$_a$$H_b$CONalkyl), 1.65 (1H, dd, J=17.5, 3.0 Hz, CH_aH$_b$CONalkyl*), 1.52 (1H, dd, J=17.5, 4.0 Hz, CH$_a$$H_b$CONalkyl*), 0.89 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 173.2, 172.0, 171.1, 169.6, 138.7, 138.5, 138.4, 135.6, 135.5, 132.9, 132.8, 129.8, 129.3, 129.1, 128.7, 128.6, 128.5, 128.4, 127.7, 127.6 (×2), 126.9, 126.7, 126.6, 64.2, 61.8, 60.8, 59.8, 53.8, 53.1, 46.9, 46.8, 40.9, 40.3 (×2), 39.6, 38.7, 38.0, 34.8, 34.7, 26.7, 18.8; LRMS (FAB) *m/z* (%): [M+Na]$^+$ 994 (15), [M+H]$^+$ 972 (77), 716 (59), 664

(70), 648 (100); HRMS (FAB): calcd for $[M+H]^+$ $C_{60}H_{71}N_4O_6Si$: 971.5143; found: 971.5096. Further elution using CH_2Cl_2/MeOH (20:1) afforded recovered diol **28** (8 mg, 8%) as a glassy solid. The physical and spectroscopic data are identical to that given previously.

Cyclo-[*N*-(methoxycarbonylmethyl)-β^3-hPhe-β^3-hPhe-*N*-(methoxycarbonylmethyl)-β^3-hPhe-β^3-hPhe] (33). Ozone was bubbled through a stirred solution of the tetralactam **1** (0.15 g, 0.21 mmol) in dry CH_2Cl_2 (15 mL) at −78°C. After 1 h the solution was warmed to −20°C, DBU (0.12 mL, 0.80 mmol) and urea-hydrogen peroxide addition compound (80 mg, 0.86 mmol) added consecutively and the resulting mixture was stirred at room temperature for 16 h. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with 2 M HCl (2×25 mL) which was subsequently extracted with CH_2Cl_2 (25 mL). The organic portions were combined, dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure to afford the crude diacid (130 mg, 83%) as a white solid. *p*-Toluenesulfonic acid (100 mg, 0.54 mmol) was added to the solid dissolved in dry MeOH (10 mL) and the resulting solution heated at reflux for 16 h, cooled and the solvent removed by distillation under reduced pressure. The residue was diluted with CH_2Cl_2 (40 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (2×20 mL) which was subsequently extracted with CH_2Cl_2 (20 mL). The organic portions were combined, dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure to afford **33** (100 mg, 62%) as a white solid. An analytical sample was prepared by chromatographic purification (CH_2Cl_2/MeOH 40:1) to afford a white solid: R_f=0.33 (CH_2Cl_2/MeOH 40:1); $[\alpha]_D$=−74.14 (c=1.3 in CH_2Cl_2); IR (film): ν 3409, 3333, 2927, 1750, 1650, 1513, 1204; ^{1}H NMR ($CDCl_3$, 500 MHz; 2:1 rotamers ratio, asterisk denotes minor rotamer peaks) δ 7.39 (1H, d, J=10.0 Hz, NH), 7.29–6.92 (20H, m, ArH), 6.69 (1H, d, J=9.0 Hz, NH*), 4.39 (1H, s, HNC*H*), 4.25 (2H, m, HNC*H** and alkylNCH*), 4.18 (1H, d, J=17.0 Hz, CH_aH$_b$CO$_2$CH$_3^*$), 3.81 (3H, s, CO$_2$CH_3^*), 3.74 (1H, d, J=17.0 Hz, CH$_a$$H_bCO_2CH_3^*$), 3.63 (2H, m, alkylNCH and CH_aH$_b$CO$_2$CH$_3$), 3.57 (3H, s, CO$_2$CH$_3$), 3.51 (1H, d, J=18.5 Hz, CH$_a$$H_bCO_2CH_3$), 3.44 (1H, dd, J=13.5, 7.0 Hz, alkylNCHCH_aH$_b$Ar), 3.31 (1H, dd, J=13.5, 11.5 Hz, CH_aH$_b$CONH), 3.19 (1H, dd, J=13.5, 7.5 Hz, alkylNCHCH$_a$$H_b$Ar), 3.06–2.89 (5H, m, C$H_aH_b$CONH*, HNCHC$H_2$Ar, HNCHC$H_aH_b$Ar* and alkylNCHC$H_aH_b$Ar*), 2.78 (1H, dd, J=13.0, 9.5 Hz, HNCHCH$_a$$H_b$Ar*), 2.61–2.51 (3H, m, CH_aH$_b$CONalkyl, CH_aH$_b$CONalkyl* and alkylNCHCH$_a$$H_b$Ar*), 2.29 (1H, dd, J=13.5, 4.5 Hz, CH$_a$$H_b$CONH), 2.18–2.10 (3H, m, CH$_a$$H_b$CONalkyl, CH$_a$$H_b$CONalkyl* and CH$_a$$H_b$CONH*); ^{1}H NMR ($CD_3OD$, 500 MHz) δ 7.36–6.97 (10H, m, ArH), 4.41 (1H, d, J=17.5 Hz, CH_aH$_b$CO$_2$), 4.23 (1H, m, alkylNCH), 4.05 (1H, m, HNC*H*), 3.88 (1H, d, J=17.5 Hz, CH$_a$$H_bCO_2$), 3.83 (3H, s, OCH$_3$), 3.02 (1H, d, J=13.5, 5.0 Hz, alkylNCHCH_aH$_b$Ar), 2.95 (2H, m, HNCHCH_aH$_b$Ar and CH_aH$_b$CONH), 2.77 (1H, dd, J=16.5, 5.0 Hz, CH_aH$_b$CONalkyl), 2.64 (1H, dd, J=13.5, 9.5 Hz, alkylNCHCH$_a$$H_b$Ar), 2.45 (1H, dd, J=14.0, 11.0 Hz, CH$_a$$H_b$CONH), 2.18 (1H, dd, J=16.5, 3.5 Hz, CH$_a$$H_b$CONalkyl), 2.05 (1H, dd, J=14.0, 3.5 Hz, HNCHCH$_a$$H_b$Ar); ^{13}C NMR ($CDCl_3$, 75.4 MHz; asterisk denotes minor rotamer peaks) δ 172.9, 171.3*, 170.1*, 169.7, 169.4, 169.0, 138.8, 138.8, 138.3*, 136.9*, 129.3–128.5, 126.9–126.4, 65.7*, 57.5, 54.0, 52.4*, 52.3, 47.7*, 46.6, 43.3*, 40.5*, 39.8, 39.7, 39.2*, 39.1*, 38.5, 35.0, 32.7*; ^{13}C NMR (CD_3OD, 75.4 MHz) δ 172.2, 172.1, 172.0, 139.8, 138.9, 130.5, 130.3, 129.7, 127.7, 127.6, 59.1, 52.5, 50.0, 44.3, 41.1, 39.3, 38.9, 33.5; LRMS (FAB) m/z: $[M+Na]^+$ 811 (100), $[M+H]^+$ 789 (90), 757 (16), 729 (14), 697 (20), 663 (33), 647 (33); HRMS (FAB): calcd $[M+H]^+$ for $C_{46}H_{53}N_4O_8$: 789.3863; found: 789.3829.

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