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Total Synthesis of Cyclotheonamide C by Use of an α -Keto Cyanophosphorane Methodology for Peptide Assembly

Stéphane P. Roche,^[a] Sophie Faure,^[a] Lahssen El Blidi,^[a] and David J. Aitken^{*[a,b]}

Respectfully dedicated to Professor Jean-Claude Gramain

Keywords: Macroyclic peptide / α -Keto β -amino acids / α -Keto cyanophosphoranes / Total synthesis / Natural product synthesis

The total synthesis of cyclotheonamide C (3), a macrocyclic pentapeptide incorporating an α -keto homoarginine (k-Arg) and a vinylogous dehydrotyrosine (V- Δ Tyr) unit, has been achieved. For comparison of macrocyclisation feasibility, two linear pentapeptides bearing free ketone functions at the k-Arg units were prepared, by use of tandem oxidation/coupling reactions on α -keto cyanophosphorane precursors as the

key processes for pentapeptide elaboration. Successful activation and coupling at the pentapeptide V- Δ Tyr C terminus led to the target molecule core, and thus provided a short total synthesis of the target compound.

Introduction

The cyclotheonamides (Cts, 1–9, Figure 1) are a family of cyclic pentapeptides isolated from the marine sponges *Theonella swinhoei* and *Theonella ircinia* during the 1990s and the early 2000s.^[1] The constituent Ct amino acids are: a hydrophobic D-amino acid (D-Xaa), α -keto homoarginine (k-Arg), L-proline (Pro), L-2,3-diaminopropanoic acid (Dpr) bearing an exocyclic N^α -formyl, acetyl or substituted L-alanyl group, and a vinylogous L-tyrosine derivative (V-Tyr), bearing an extra hydroxy group in the case of CtE₅ (9) or being fully conjugated due to an extra double bond (V- Δ Tyr) in the case of CtC (3). These metabolites are potent inhibitors of serine proteases such as thrombin and trypsin, exhibiting IC₅₀ values in the 2.9–200 nM range.^[1] Central to the biological activity is the highly electrophilic k-Arg moiety, which interacts with the serine side chain of the enzymes' active site triads.^[2] This potent activity has inspired some structure–activity studies on synthetic analogues.^[3] Understandably, the challenge of Ct total synthesis has caught the attention of several research groups, in-

spiring work that has led to elegant preparations of CtA and CtB.^[4] From a strictly chemical perspective, we were attracted by the unique combination of the k-Arg and the fully conjugated V- Δ Tyr feature present in CtC (3), and we were drawn into a total synthesis venture targeting this member of the Ct family.

- 1, CtA: R¹ = Bn, R² = CHO
- 2, CtB: R¹ = Bn, R² = COCH₃
- 3, CtC: R¹ = Bn, R² = CHO, V- Δ Tyr
- 4, CtD: R¹ = *i*Pr, R² = CHO
- 5, CtE₁: R¹ = *i*Bu, R² = AlaCOBn
- 6, CtE₂: R¹ = *i*Bu, R² = AlaCOPh
- 7, CtE₃: R¹ = *i*Bu, R² = AlaCO*i*Pr
- 8, CtE₄: R¹ = *i*Bu, R² = AlaCO*i*Bu
- 9, CtE₅: R¹ = *i*Bu, R² = AlaCO*i*Bu

R³ = H, except CtE₅: R³ = OH

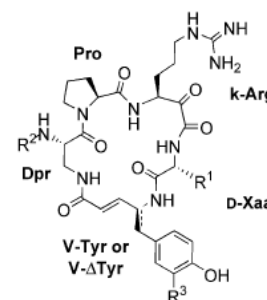


Figure 1. The cyclotheonamide (Ct) family.

At an early stage in our reflections on an appropriate synthetic approach, the elaboration of the k-Arg unit from a readily accessible α -arginine precursor, followed immediately by peptide coupling to a D-Phe fragment in a one-pot operation, seemed an attractive approach for a convergent synthesis of CtC. One means of achieving this objective was an adaptation of Nemoto's MAC methodology,^[5] and we have recently reported our results obtained by that route.^[6] An interesting alternative strategy was Wasserman's sequential oxidation/coupling sequence starting from an α -keto cyanophosphorane derivative 10; ozonolysis of this function

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generates the α -keto acyl cyanide **11**, which is trapped in situ by an amine or an alcohol to provide an α -keto amide or ester **12** in a one-pot procedure (Figure 2).^[7]

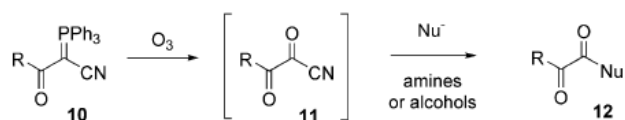


Figure 2. Wasserman's one-pot α -keto cyanophosphorane approach for the synthesis of α -keto amides and esters.

This methodology can be conveniently adapted for polymer-supported synthesis^[8] and has been variously exploited in natural product synthesis,^[9] preparation of substrates for enzymatic transformations,^[10] construction of molecular platforms^[11] and the synthesis of peptide derivatives with protease inhibitory properties.^[12] Indeed, Wasserman used this approach in his synthesis of CtE₂ and CtE₃.^[13] We decided to examine this methodology further, with the objective of expedient access to different peptide intermediates for macrocyclisation studies leading to the CtC core. In this

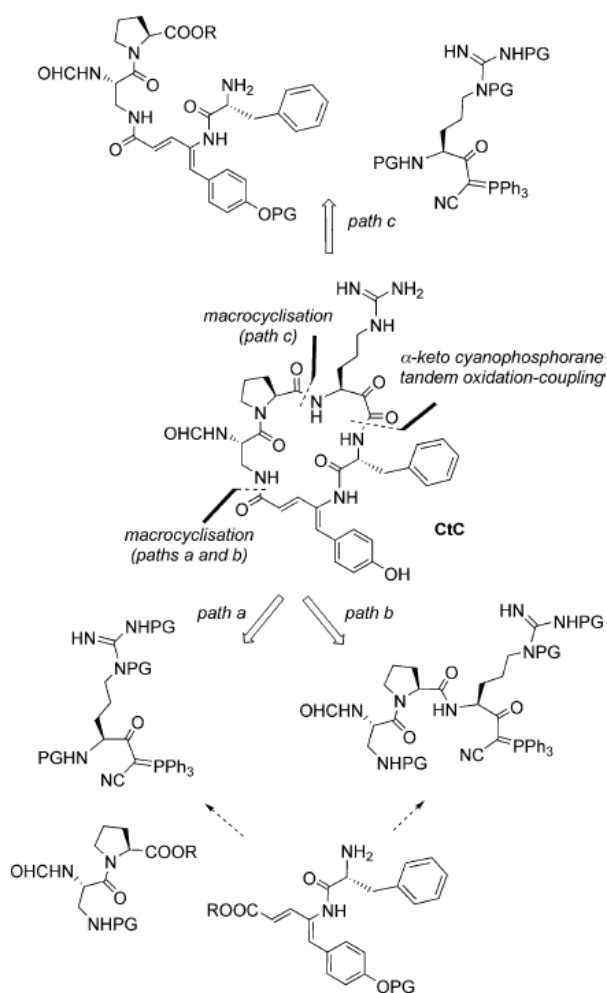
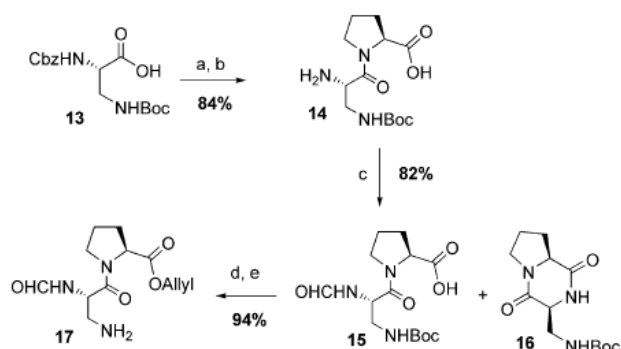


Figure 3. Retrosynthetic analysis of CtC, identifying α -keto cyanophosphorane and amine intermediates, providing three assembly combinations leading to two macrocyclisation sites.

paper we describe the total synthesis of CtC by this approach, which further delineates the scope of the tandem reaction for α -keto amide formation, providing a comparative analysis of two different macrocyclisation locations (Figure 3).

Results and Discussion

We began with the construction of two dipeptide fragments containing Pro and the nonproteinogenic Dpr amino acid (Scheme 1). General approaches to the synthesis of α,β -diamino acids were reviewed recently.^[14] The orthogonally protected derivative **13** was prepared by Izumiya's procedure^[15] and was coupled with Pro-OBn by use of EDCI/HOBt. Hydrogenation in the presence of Pd/C simultaneously cleaved the benzyl carbamate and the benzyl ester to afford the zwitterionic dipeptide **14** in 84% yield over two steps. A variety of reagents and conditions were examined for the mild *N*-formylation of this compound, the objective being to minimise the formation of the undesired diketopiperazine **16**. Optimal conditions required addition of substrate **14** to preformed acetic-formic mixed anhydride for a prolonged reaction time with cooling (below 10 °C), and these furnished *N* ^{α} -CHO-*N* ^{β} -Boc-Dpr-Pro (**15**) in 82% yield; side-product **16** was formed in only 10% yield. The dipeptide *N* ^{α} -CHO-Dpr-Pro-OAllyl (**17**), with a free *N* ^{β} amine, was easily obtained from dipeptide **15** in two steps (94% yield) by successive esterification with allyl alcohol and cleavage of the *tert*-butyl carbamate with trifluoroacetic acid (Scheme 1).

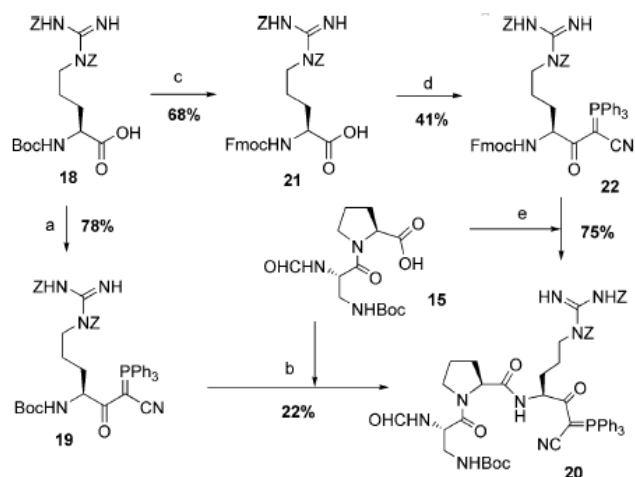


Scheme 1. Preparation of the Dpr-Pro building blocks **15** and **17**. Reagents and conditions: a) Pro-OBn, EDCI, HOBt, CH₂Cl₂, 0 °C to room temp., 12 h; b) H₂ (3.4 atm), Pd/C, MeOH, 2 h, 84% (2 steps); c) HCO₂H/Ac₂O, THF, 8–10 °C, 12 h, 82%; d) EDCI, DMAP, allyl alcohol, CH₂Cl₂, 0 °C to room temp., 5 h, then *i*Pr₂NEt, THF, 0 °C, 10 min; e) TFA/CH₂Cl₂ (1:1), 1 h at 0 °C, then workup with *i*Pr₂NEt, THF, 0 °C, 10 min, 94% (2 steps); EDCI = *N*-[3-(dimethylamino)propyl]-*N'*-ethylcarbodiimide hydrochloride, DMAP = 4-(dimethylamino)pyridine, HOBt = 1-hydroxybenzotriazole, TFA = trifluoroacetic acid.

The target α -keto cyanophosphoranes were synthesised from the protected arginine derivative *N* ^{α} -Boc-*N* ^{δ} ,*N* ^{ω} -Z₂-Arg (**18**), prepared by Ottenheim's procedure^[16] (Scheme 2). One-step preparation of α -keto cyanophos-

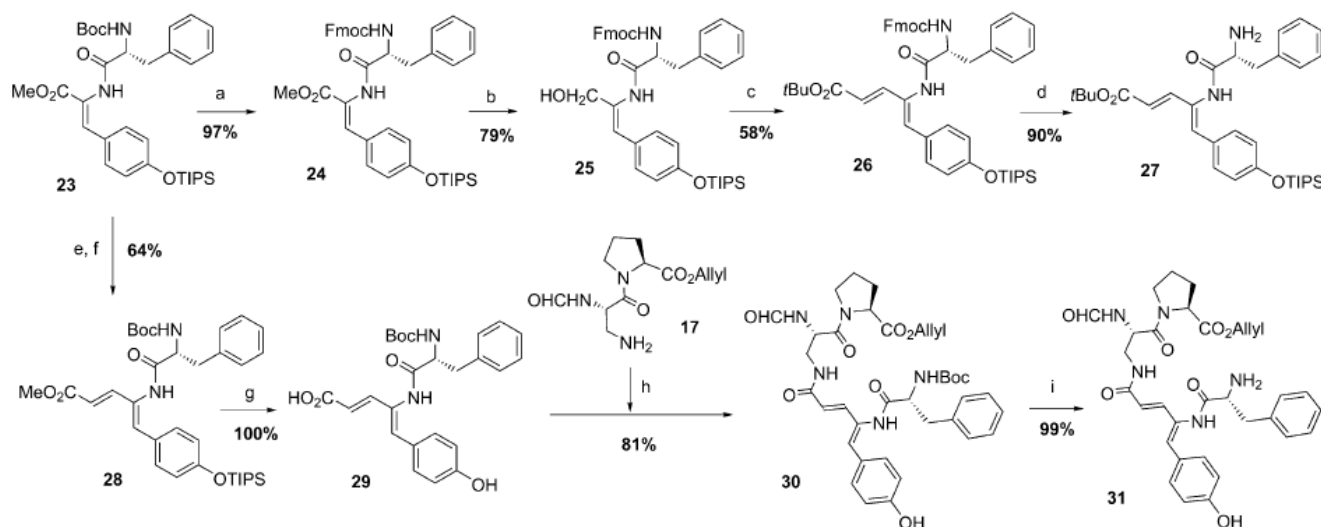
phorane **19** was achieved in 78% yield by EDCI/DMAP-mediated condensation with (triphenylphosphoranylidene)acetonitrile, under Wasserman's conditions.^[7] However, elaboration of **19** into a tripeptide α -keto cyanophosphorane proved to be more difficult. Indeed, after numerous attempts, TFA-mediated deprotection of N^α followed by EDCI/DMAP coupling of dipeptide **15** provided the desired tripeptide **20** only in a poor 22% yield (Scheme 2). We suspected that significant decomposition of the β -amino- α -keto cyanophosphorane arose during the acidic N -deprotection procedure, so we decided to change the nature of the amine protecting group. A straightforward Boc to Fmoc exchange was achieved, to provide N^α -Fmoc- N^δ , N^ω -Z₂-Arg (**21**) in 68% yield (Scheme 2). This compound was then transformed into the α -keto cyanophosphorane **22** in 41% yield. Although this yield was lower than that for **19**, the following steps were much improved: base-mediated deprotection of **22**, followed by EDCI/DMAP coupling of dipeptide **15**, proceeded smoothly to afford the target tripeptide α -keto cyanophosphorane **20** in 75% yield. These observations suggest that α -keto cyanophosphoranes derived from α -amino acids are more prone to decomposition under acidic conditions, and that, as a consequence, base-labile (or neutral) functions are a more suitable choice of N^α -protecting group.^[17]

We next turned our attention to the preparation of the nucleophilic partners (amines) for the one-pot synthesis of α -keto amides. The targets were dipeptide **27** and tetrapeptide **31**, incorporating the unique vinyllogous dehydrotyrosine (V- Δ Tyr) feature,^[18] and were constructed as follows (Scheme 3). The Z -dehydrotyrosine dipeptide **23** was available from our previous work,^[19] and a Boc to Fmoc protecting group switch (97% yield) was carried out at the N terminus to produce dipeptide **24**, which was reduced



Scheme 2. Preparation of the α -keto cyanophosphorane components **19** and **20**. Reagents and conditions: a) (triphenylphosphoranylidene)acetonitrile, EDCI, DMAP, CH_2Cl_2 , 0 °C to room temp., 12 h, 78%; b) TFA/ CH_2Cl_2 (1:1), 1 h at 0 °C, then workup with Na_2CO_3 (10%), followed by EDCI, DMAP, **15**, CH_2Cl_2 , 0 °C to room temp., 12 h, 22% (2 steps); c) TFA/ CH_2Cl_2 , 1 h at 0 °C, then FmocCl, Na_2CO_3 dioxane/water (3:2), 0 °C to room temp., 12 h, 68% (2 steps); d) EDCI, DMAP, (triphenylphosphoranylidene)acetonitrile, CH_2Cl_2 , 0 °C to room temp., 5 h, 41%; e) $\text{CH}_3\text{CN}/\text{NH}_4\text{Et}$, 0 °C to room temp., 1 h, then EDCI, DMAP, **15**, CH_2Cl_2 , 0 °C to room temp., 12 h, 75% (2 steps). EDCI = N -[3-(dimethylamino)propyl]- N' -ethylcarbodiimide hydrochloride, DMAP = 4-(dimethylamino)pyridine, TFA = trifluoroacetic acid, Fmoc = (9-fluorenyl)methyloxycarbonyl.

chemoselectively with LiAlH_4 to give the primary alcohol **25** in 79% yield. Taylor's one-pot oxidation/vinylolation protocol^[20,21] with activated manganese(IV) oxide and *tert*-butoxycarbonylmethylene triphenylphosphorane provided the requisite vinyllogous dipeptide **26** in 58% yield, with the



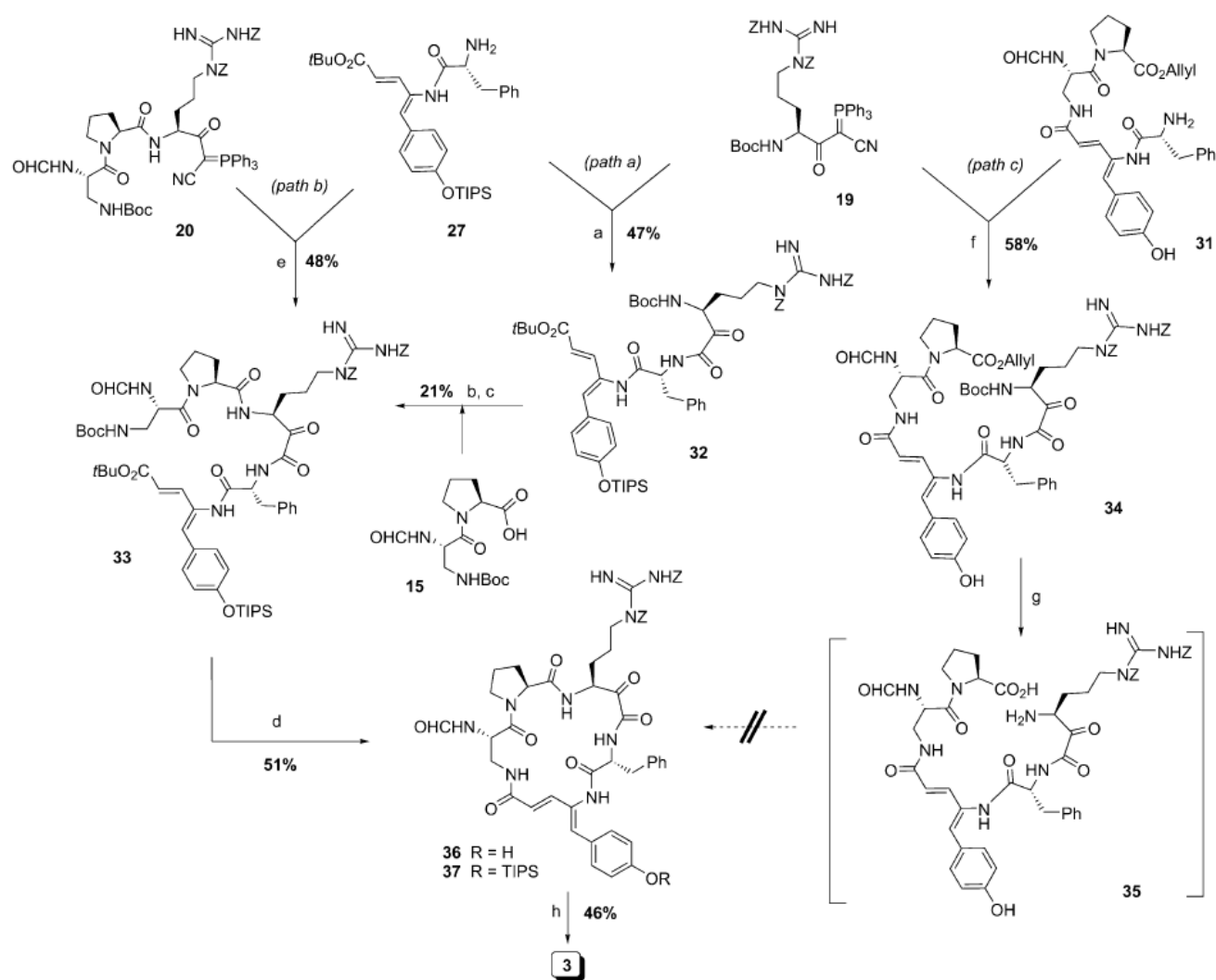
Scheme 3. Preparation of the nucleophilic components **27** and **31**. Reagents and conditions: a) TFA/ CH_2Cl_2 , 1 h at 0 °C, then FmocCl, Na_2CO_3 dioxane/water (3:2), 0 °C to room temp., 12 h, 97% (2 steps); b) LiAlH_4 , THF, 0 °C, 1 h, 79%; c) $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$, MnO_2 , CH_2Cl_2 , 40 °C, 36 h, 58%; d) $\text{Et}_2\text{NH}/\text{CH}_3\text{CN}$, 1:2, 0 °C to room temp., 1 h, 90%; e) LiAlH_4 , THF, 0 °C, 1 h, 86%; f) $\text{Ph}_3\text{P}=\text{CHCO}_2\text{tBu}$, MnO_2 , CH_2Cl_2 , 40 °C, 36 h, 74%; g) NaOH (1 M); 100%; h) DPPCl, **17**, $i\text{Pr}_2\text{NEt}$, THF, -20 °C to room temp., 12 h, 81%; i) TFA/ CH_2Cl_2 , 1 h at 0 °C, then Na_2CO_3 , 99%. DPPCl = diphenylphosphoryl chloride, TFA = trifluoroacetic acid, Fmoc = (9-fluorenyl)methyloxycarbonyl.

E configuration exclusively at the new alkene moiety. This convenient operation obviated the need for the isolation of the unstable aldehyde intermediate. Final *N*-terminal deprotection was achieved smoothly under basic conditions to provide the dipeptide amine **27** in 90% yield.

The conversion of dipeptide **23** into compound **28** by the reduction/oxidation/vinylogation sequence was reported by us previously^[19] and was reproduced in 64% yield. Hydrolysis of the *C*-terminal ester of dipeptide **28** could not be achieved without at least partial cleavage of the aryl silyl ether, an observation that highlighted the particular behaviour of the fully conjugated system of the V- Δ Tyr fragment. We decided to optimise the double transformation and obtained dipeptide **29** in quantitative yield by use of 1 M sodium hydroxide (Scheme 3).

As we had begun to expect, coupling of the *C* terminus of dipeptide **29** with dipeptide amine **17** turned out to be something of a challenge. DCC, EDCI and PyBrop all gave unsatisfactory results. After some effort, we were able to optimise the coupling conditions by using DPPCI, which furnished the new tetrapeptide **30** in a gratifying 81% yield. Liberation of the free *N*-terminal amine was achieved simply through treatment of **30** with trifluoroacetic acid, to give **31** in near quantitative yield (Scheme 3).

With all the appropriate components in hand, we began work on the oxidation/coupling sequence using different reactant combinations (Scheme 4). In the first reaction (path a), ozonolysis of the arginine α -keto cyanophosphorane **19** was carried out at -78°C for 15 min to form the electrophilic α -keto acyl cyanide intermediate, to which



Scheme 4. Tandem α -keto cyanophosphorane oxidation/coupling combinations and the synthetic end-game. Reagents and conditions: a) **19**, O_3 , CH_2Cl_2 , -78°C , 15 min, then **27**, -78°C to room temp., 1 h, 47%; b) HCO_2H , room temp., 1 h; c) EDCI, DMAP, **15**, 0°C to room temp., 12 h, 21% (2 steps); d) TFA/ CH_2Cl_2 , 1 h at 0°C , then TBTU, HOBT, $\text{DMF}/\text{CH}_2\text{Cl}_2$ (2:1, 5 mM), 0°C to room temp., 24 h, 51%; e) **20**, O_3 , CH_2Cl_2 , -78°C , 15 min, then **27** -78°C to room temp., 18 h, 48%; f) **19** (2.5 equiv.), O_3 , CH_2Cl_2 , -78°C , 15 min, then **31**, -78°C to room temp., 18 h, 58%; g) TFA/ CH_2Cl_2 , 1 h at 0°C , then $\text{Pd}(\text{PPh}_3)_4$, AcOH, room temp., 1 h; h) HF·py, anisole, room temp., 12 h, 46%. EDCI = *N*-[3-(dimethylamino)propyl]-*N'*-ethylcarbodiimide hydrochloride, DMAP = 4-(dimethylamino)pyridine, HOBT = 1-hydroxybenzotriazole, TFA = trifluoroacetic acid, TBTU = *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate.

dipeptide amine **27** was added to deliver the complex tripeptide **32**, containing the α -keto homoarginine moiety, in an encouraging 47% yield. This tripeptide was then elaborated into pentapeptide **33**, appropriate for macrocyclisation at the Dpr-V- Δ Tyr junction. Selective *N*-deprotection in the presence of the *C*-terminal *tert*-butyl ester with formic acid was moderately successful, and EDCI/DMAP coupling of dipeptide **15** afforded **33** in 21% yield over the two steps. A more direct approach (path b) brought its rewards: ozonolysis of the α -keto cyanophosphorane tripeptide **20** and subsequent addition of dipeptide amine **27** afforded the same linear pentapeptide **33** in a single step and an improved 48% yield (Scheme 4).

An alternative combination strategy (path c) led to the linear pentapeptide **34**, suited for macrocyclisation at the k-Arg-Pro junction. Ozonolysis of the arginine α -keto cyanophosphorane **19**, followed by addition of the tetrapeptide amine **31**, furnished **34** in 58% yield (Scheme 4). The relative accessibility of the arginine derivative **19** allowed us to use this component in excess (2.5 equiv.) in the reaction, which contributed to the improved yield in relation to the previous reactant combinations (paths a and b) leading to **33** (Scheme 4).

Two linear pentapeptides were thus available for the endgame of the CtC synthesis. Disappointingly, we were unable to produce the advanced macrocyclic intermediate **36** from pentapeptide **34** (Scheme 4). The sequential *C,N*-deprotection steps (trifluoroacetic acid followed by palladium-catalysed allyl ester cleavage) appeared to proceed normally, to generate the zwitterionic intermediate **35**, but this resisted macrocyclisation efforts under various sets of reaction conditions; only degraded materials were obtained. Previously, other groups working on Ct syntheses had reported successful macrocyclisation at the Pro-k-Arg junction, but in those cases the k-Arg ketone function was masked as a protected secondary alcohol.^[4a,4c] Clearly, this is a much less simple operation with the naked ketone function in place.

Of the previous Ct syntheses, only Wasserman had attempted a macrocyclisation involving Dpr as the *N* terminus; the carboxylate unit was V-Tyr (activated with DCC/PFP-OH). The conjugated nature of the V- Δ Tyr partner implicated in the proposed macrocyclisation of **33** was the source of some concern; in the event, the simultaneous acidic deprotection of the *C*- and *N*-terminal functions of **33** followed by treatment with several phosphoryl-based coupling systems (DPPA, DPPCI, FDPP) led to the formation of the CtC core in yields in the 25–50% range. The best results, however, were obtained with the uronium coupling reagent TBTU together with a catalytic amount of HOBt, which provided clean access to the macrocyclic pentapeptide **37**, which was isolated in a satisfying 51% yield, with the naked k-Arg ketone intact (Scheme 4).^[22] Only one step remained for completion of the synthesis: complete deprotection of the phenol and guanidine moieties was achieved with HF-pyridine in the presence of anisole, to give CtC (**3**) in 46% yield after purification. This sample had NMR and mass spectroscopic data identical to those of the natural product.

Conclusions

In completing the second total synthesis of CtC **3** to date, we have underlined the versatility of the α -keto cyanophosphorane oxidation/coupling approach for the assembly of complex polypeptides. The construction of each of the linear pentapeptides **33** and **34** with naked ketones was achieved, allowing direct comparison between k-Arg-Pro and Dpr-V- Δ Tyr macrocyclisation sites. The latter approach provided an expedient and elegant route to the target CtC core, facilitating the convergent synthesis of CtC from three accessible starting materials: the Arg-derived cyanophosphorane **18** and the dipeptides **15** and **27**.

Experimental Section

General: Solvents were dried and purified by standard procedures. Commercial reagents were used as obtained without further purification. Thin-layer chromatography (TLC) was carried out on alumina 60 F254 (Merck) plates and flash column chromatography was carried out on 15 cm length columns of silica gel (40–63 μ m, Merck). Melting points were determined with a Reichert microscope apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 881 spectrometer. Optical rotations were measured on a Jasco DIP-370 polarimeter, in a 10 cm quartz cell. Chemical ionization mass spectra (CI-MS) with methane as ionization gas was recorded on an HP 5989B spectrometer (70 eV). Electrospray ionization mass spectra (ESI-MS) were recorded on a micro q-tof Micromass instrument (3000 V), and high-resolution mass spectra (HR-MS) were recorded on the same instrument with an internal lock mass (H_3PO_4) and an external lock mass (Leu-enkephalin). NMR spectra were recorded on a Bruker AC 400 spectrometer, operating at 400 MHz for ^1H and 100 MHz for ^{13}C . Spectra were taken at room temperature in deuterated solvents (as indicated) with use of the residual solvent signals as internal standards. Elemental analyses were performed on a Thermofinnigan FlashEA 1112 apparatus in the Microanalytical Laboratory, UMR 7565, Université Henri Poincaré, Nancy.

***N*^β-Boc-Dpr-Pro (14):** *N*^α-Z-*N*^β-Boc-Dpr (**13**,^[15] 1.82 g, 5.4 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (20 mL) under argon and cooled to 0 °C. A mixture prepared by treating commercially available Pro-OBn-HCl (1.57 g, 6.5 mmol, 1.2 equiv.) in CH_2Cl_2 (5 mL) with triethylamine (904 μ L, 6.5 mmol, 1.2 equiv.) was added to this solution at 0 °C over a period of 10 min. Next, hydroxybenzotriazole (1.09 g, 8.1 mmol, 1.5 equiv.) was added. The resulting solution was stirred for 10 min, EDCI (1.55 g, 8.1 mmol, 1.5 equiv.) was then added, and the reaction mixture was stirred and allowed to warm to room temp. over 12 h. CH_2Cl_2 (20 mL) was added, and the mixture was washed successively with citric acid solution (5%; 20 mL) and saturated NaHCO_3 solution (20 mL). The organic layer was dried with MgSO_4 and evaporated under reduced pressure to afford the crude product. Purification by flash chromatography with use of a gradient of EtOAc/cyclohexane (3:7 to 1:1) afforded the dipeptide *N*^α-Z-*N*^β-Boc-Dpr-Pro-OBn as a white solid (2.47 g, 4.7 mmol, 87%). R_f = 0.65 (EtOAc/cyclohexane, 4:6); m.p. 115–116 °C. $[\alpha]_D^{20}$ = –42.0 (c = 1.80, CHCl_3). ^1H NMR (CDCl_3): δ = 1.36 (s, 9 H), 1.75–1.82 (m, 3 H), 1.92–1.97 (m, 1 H), 3.21 (m, 1 H), 3.38 (m, 1 H), 3.66 (m, 2 H), 4.53 (m, 1 H), 4.61 (d, J = 7.0 Hz, 1 H), 5.02 (m, 2 H), 5.05 (s, 1 H), 5.14 (d, J = 12.2 Hz, 2 H), 5.61 (d, J = 8.2 Hz, 1 H), 7.19–7.29 (m, 10 H) ppm. ^{13}C NMR (CDCl_3): δ = 24.9 (CH_2), 28.4 ($3 \times \text{CH}_3$), 28.9 (CH_2), 42.7 (CH_2), 47.1 (CH_2), 52.3 (CH), 59.0 (CH), 67.0, 67.1 (2 CH_2), 79.5 (C), 128.0, 128.1,

128.2, 128.4, 128.5, 128.6 (10 × CH), 135.4, 136.3 (2 C), 156.0, 156.1 (2 C), 169.4 (C), 171.6 (C) ppm. IR (KBr): $\tilde{\nu}$ = 770, 1170, 1220, 1450, 1510, 1650, 1720, 2990, 3020, 3440 cm^{-1} . CI-MS: m/z = 951 [2M + H - Boc]⁺, 564 [M + K]⁺, 526 [M + H]⁺, 426 [M + H - Boc]⁺.

This dipeptide *N*^α-Z-*N*^β-Boc-Dpr-Pro-OBn (1.17 g, 2.23 mmol) was dissolved in methanol (58 mL), and palladium on carbon (Pd 10%, 95 mg, 0.09 mmol, 0.04 equiv.) was added. The solution was shaken under H₂ (3.4 atm) in a Parr apparatus for 2 h. The solution was filtered through a Celite pad, washed with methanol (3 × 20 mL), and evaporated under reduced pressure with a bath temperature below 30 °C to afford the crude product **14** (655 mg, 2.17 mmol, 97%) as a white solid, which was used without further purification in the next step. *R*_f = 0.50 (1-propanol/H₂O, 7:3); m.p. 116–118 °C. [α]_D²⁰ = -5.0 (*c* = 1.10, NaOH 1 M). ¹H NMR (D₂O): δ = 1.34 (d, *J* = 8.0 Hz, 9 H), 1.80–1.95 (m, 2 H), 2.07–2.24 (m, 2 H), 3.30–3.49 (m, 2 H), 3.51–3.63 (m, 2 H), 3.97 (t, *J* = 8.0 Hz, 0.5 H), 4.22 (dd, *J* = 6.0, 8.0 Hz, 0.5 H), 4.34 (br. s, 1 H) ppm. ¹³C NMR (D₂O): δ = 22.0 (CH₂), 27.5 (3 × CH₃), 29.2 (CH₂), 40.0 (CH₂), 47.3 (CH₂), 51.7 (CH), 62.1 (CH), 80.5 (C), 155.7 (C), 166.3 (C), 178.7 (C) ppm. IR (KBr): $\tilde{\nu}$ = 1170, 1278, 1369, 1650, 1710, 2977, 3341 (br) cm^{-1} . CI-MS: m/z = 324 [M + Na]⁺, 284 [M + H - H₂O]⁺, 228 [M + H - tBuO]⁺, 184 [M + H - H₂O - Boc]⁺.

N^α-CHO-*N*^β-Boc-Dpr-Pro (15): Acetic anhydride (1.1 mL, 11.8 mmol, 2.6 equiv.) was added slowly at 0 °C under argon to formic acid (0.53 mL, 14.1 mmol, 3.1 equiv.). This reaction mixture was stirred for 10 min at room temp. and was then heated at 55 °C for a further 1.5 h. The mixture was then cooled to 0 °C and diluted with dry THF (40 mL), and the dipeptide **14** (1.37 g, 4.55 mmol, 1 equiv.) was added. The reaction mixture was stirred for a further 15 h at a constant temperature of 8–10 °C. The mixture was evaporated under reduced pressure to furnish the crude product (1.37 g), which was recrystallised from EtOAc/cyclohexane (9:1) to afford the desired pure product **15** as a white solid (1.23 g, 3.73 mmol, 82%). *R*_f = 0.62 (1-propanol/H₂O, 7:3); m.p. 178–180 °C. ¹H NMR ([D₆]DMSO): δ = 1.42 (s, 9 H), 1.88–2.02 (m, 3 H), 2.15–2.27 (m, 1 H), 3.09 (m, 1 H), 3.28 (m, 1 H), 3.70 (m, 2 H), 4.32 (m, 1 H), 4.87 (m, 1 H), 6.79 (t, *J* = 5.6 Hz, 1 H), 8.07 (s, 1 H), 8.31 (d, *J* = 8.4 Hz, 1 H), 12.55 (br. s, 1 H) ppm. ¹³C NMR ([D₆]DMSO): δ = 24.3 (CH₂), 28.1 (3 × CH₃), 28.7 (CH₂), 41.6 (CH₂), 46.5 (CH₂), 48.8 (CH), 58.4 (CH), 78.0 (C), 155.6 (C), 161.0 (CH), 168.1 (C), 173.1 (C) ppm. IR (KBr): $\tilde{\nu}$ = 1170, 1253, 1530, 1648, 1707, 2976, 3260 cm^{-1} . ESI-MS: m/z = 681 [2M + Na]⁺, 367 [M + K]⁺, 352 [M + Na]⁺, 330 [M + H]⁺. C₁₄H₂₃N₃O₆ (329.35): calcd. C 51.06, H 7.04, N 12.76; found C 50.68, H 7.14, N 12.69.

Diketopiperazine Cyclo-[*N*^β-Boc-Dpr-Pro] (16): This compound was obtained by evaporation of the mother liquor from the recrystallisation described above, as a white, amorphous solid (132 mg, 0.47 mmol, 10%). *R*_f = 0.54 (EtOAc/MeOH, 9:1). ¹H NMR (CDCl₃): δ = 1.31 (s, 9 H), 1.88 (m, 1 H), 1.95 (m, 1 H), 2.04 (m, 1 H), 2.10 (m, 1 H), 3.48 (m, 3 H), 3.68 (m, 1 H), 4.02 (m, 2 H), 5.12 (br. s, 1 H), 6.84 (br. s, 1 H) ppm. ¹³C NMR (CDCl₃): δ = 22.8 (CH₂), 27.9 (CH₂), 28.3 (3 × CH₃), 39.6 (CH₂), 45.4 (CH₂), 56.8 (CH), 59.2 (CH), 80.3 (C), 157.4 (C), 165.0 (C), 170.0 (C) ppm.

General Procedure for Peptide Coupling Reaction with EDCI/DMAP: Carboxylic acid (1 mmol, 1 equiv.) was dissolved under argon in CH₂Cl₂ (5 mL), and the mixture was cooled to 0 °C. Successively, the free amine (0.77 mmol, 0.77 equiv.) or alcohol (4.0 mmol, 4.0 equiv.) and 4-(dimethylamino)pyridine (24 mg, 0.2 mmol, 0.2 equiv.) were added. This solution was stirred over 10 min, EDCI (230 mg, 1.2 mmol for amines; 307 mg, 1.6 mmol for alcohols) was then added, and the stirred reaction mixture was

allowed to warm to room temp. over a specified period. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by flash chromatography.

N^α-CHO-Dpr-Pro-OAllyl (17): *N*^α-CHO-*N*^β-Boc-Dpr-Pro-OAllyl was obtained by the General Procedure for peptide coupling with EDCI/DMAP (reaction time of 12 h), from dipeptide **15** (150 mg, 0.45 mmol, 1 equiv.) and allyl alcohol (104 mg, 122 μL, 1.8 mmol, 4 equiv.). Purification by flash chromatography with EtOAc/MeOH (9:3) afforded the desired pure product (156 mg, 0.42 mmol, 94%) as a white solid. *R*_f = 0.59 (EtOAc/cyclohexane, 9:1); m.p. 112–115 °C. [α]_D²⁰ = -56.2 (*c* = 1.01, CHCl₃). ¹H NMR (CDCl₃): δ = 1.35 (s, 9 H, 3 × CH₃), 1.91–2.00 (m, 3 H, CH₂, Pro), 2.19–2.21 (m, 1 H, CH₂, Pro), 3.23 (dd, *J* = 7.0, 14.0 Hz, 1 H, CH₂N, Dpr), 3.45 (m, 1 H, CH₂N, Dpr), 3.72 (t, *J* = 6.0 Hz, 2 H, CH₂N, Pro), 4.46 (dd, *J* = 3.8, 9.0 Hz, 1 H, CH_α, Pro), 4.55 (t, *J* = 6.0 Hz, 2 H, CH₂, Allyl), 4.95 (q, *J* = 6.5 Hz, 1 H, CH_α, Dpr), 5.18 (dd, *J* = 1.3, 10.5 Hz, 1 H, CH₂=CH, Allyl), 5.27 (dd, *J* = 1.3, 17.2 Hz, 1 H, CH₂=CH, Allyl), 5.35 (t, *J* = 6.3 Hz, 1 H, NH), 5.85 (m, 1 H, CH₂=CH, Allyl), 7.27 (d, *J* = 8.4 Hz, 1 H, NH), 8.10 (s, 1 H, NCHO) ppm. ¹³C NMR (CDCl₃): δ = 24.8 (CH₂, Pro), 28.2 (3 × CH₃, Boc), 28.8 (CH₂, Pro), 42.1 (CH₂N, Dpr), 47.1 (CH₂N, Pro), 49.4 (CH_α, Dpr), 59.0 (CH_α, Pro), 65.7 (CH₂, Allyl), 79.3 [OC(CH₃)₃], 118.7 (CH₂=), 131.5 (CH=), 156.0 (NHCOO), 161.4 (NHCHO), 169.0 (NHCO, Dpr), 171.3 (CO₂Allyl) ppm.

The dipeptide *N*^α-CHO-*N*^β-Boc-Dpr-Pro-OAllyl (40 mg, 0.11 mmol) was treated with a solution of CH₂Cl₂/TFA (1:1, 3 mL) at 0 °C for 1 h, and the solvents were then evaporated under reduced pressure. The residue was dissolved in and concentrated from CH₂Cl₂ (3 × 30 mL) to furnish the trifluoroacetate salt. The free dipeptide amine **17** was generated by treating a solution of this salt in THF (500 μL) with diisopropylethylamine (18 μL, 0.10 mmol, 1 equiv.) for 10 min at 0 °C. This solution was used immediately in the next step. *R*_f = 0.10 (EtOAc/MeOH, 9:1). ESI-MS: m/z = 292 [M + Na]⁺, 270 [M + H]⁺, 252 [M + H - H₂O]⁺.

General Procedure for Coupling with (Triphenylphosphoranylidene)acetonitrile: Carboxylic acid (1 mmol) was dissolved under argon in CH₂Cl₂ (25 mL), and the mixture was cooled to 0 °C in an ice bath. 4-(Dimethylamino)pyridine (0.1 mmol, 0.1 equiv.) and EDCI (1.1 mmol, 1.1 equiv.) were added successively to the reaction mixture, which was stirred for a further 5 min. (Triphenylphosphoranylidene)acetonitrile (1.2 mmol, 1.2 equiv.) was then added in one portion, and the reaction mixture was stirred and allowed to warm to room temp. over the specified period. Water (40 mL) was added, and the mixture was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic layers were dried with MgSO₄ and concentrated under reduced pressure to afford the crude residue, which was purified by flash chromatography.

N^α-Boc-*N*^β,*N*^γ-Z₂-Arg-C(PPh₃)CN (19): Product **19** was synthesised by the General Procedure for coupling with (triphenylphosphoranylidene)acetonitrile (reaction time of 12 h), from the known *N*^α-Boc-*N*^β,*N*^γ-Z₂-Arg (**18**,^[16] 700 mg, 1.29 mmol), and was obtained after purification by flash chromatography with a gradient of EtOAc/cyclohexane (3:7 to 4:6) as a white foam (832 mg, 1.01 mmol, 78%). *R*_f = 0.29 (EtOAc/cyclohexane, 4:6); m.p. 74–77 °C. ¹H NMR (CDCl₃): δ = 1.32 (s, 9 H), 1.51–1.69 (m, 3 H), 1.70–1.79 (m, 1 H), 3.86 (m, 1 H), 4.03 (m, 1 H), 5.00 (br. s, 1 H), 5.03 (s, 2 H), 5.16 (s, 2 H), 5.19 (d, *J* = 8.0 Hz, 1 H), 7.15–7.56 (m, 25 H), 9.31 (br. s, 1 H), 9.52 (br. s, 1 H) ppm. ¹³C NMR (CDCl₃): δ = 24.9 (CH₂), 28.4 (3 × CH₃), 30.4 (CH₂), 44.7 (CH₂), 47.3 (d, *J* = 130 Hz, C), 56.0 (CH), 67.1 (CH₂), 68.8 (CH₂), 79.0 (C), 120.9 (d, *J* = 15 Hz, C), 121.3 (d, *J* = 88 Hz, 3 × C), 127.6, 128.3, 128.8, 129.3, 133.2, 133.5 (25 × CH), 134.8, 137.0 (2 C), 155.6, 156.0 (2

C), 160.7 (C), 164.0 (C), 194.6 (C) ppm. IR (KBr): $\tilde{\nu}$ = 1150, 1273, 1507, 1596, 1705, 2364, 2867, 2945, 3425 cm^{-1} . $\text{C}_{47}\text{H}_{48}\text{N}_5\text{O}_7\text{P}$ (825.89): calcd. C 68.35, H 5.86, N 8.48; found C 67.28, H 6.03, N 8.42.

***N*^α-Fmoc-*N*^δ,*N*^ε-Z₂-Arg (21):** The known *N*^α-Boc-*N*^δ,*N*^ε-Z₂-Arg (18,^[16] 300 mg, 0.55 mmol, 1 equiv.) was treated at 0 °C with a solution of $\text{CH}_2\text{Cl}_2/\text{TFA}$ (1:1, 14 mL) for 1 h, and the solvents were then evaporated under reduced pressure. The residue was dissolved in and concentrated from CH_2Cl_2 (3 × 30 mL) to furnish the trifluoroacetate salt. This material was dissolved in dioxane (10 mL) at 0 °C, and a solution of Na_2CO_3 (10%; 7.0 mL, 6.7 mmol, 12 equiv.) was added. After the system had been stirred for 10 min, a white precipitate had formed. 9-Fluorenylmethyl chloroformate (157 mg, 0.61 mmol, 1.1 equiv.) was then added, and the reaction mixture was stirred and allowed to warm to room temp. over 12 h. Water (40 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with a citric acid solution (5%; 30 mL), dried with MgSO_4 and evaporated under reduced pressure to afford the crude product, which was purified by flash chromatography with a gradient of EtOAc/MeOH (from 10:0 to 9:1) to afford pure material 21 as a white solid (250 mg, 0.38 mmol, 68%). R_f = 0.50 (EtOAc/MeOH, 95:5); m.p. 36–38 °C (EtOAc/cyclohexane, 1:1). $[\alpha]_D^{20}$ = +5.4 (c = 1.25, CHCl_3). ¹H NMR (CDCl_3): δ = 1.60–1.80 (m, 3 H), 1.81–1.90 (m, 1 H), 3.95 (m, 2 H), 4.18 (br. s, 1 H), 4.41 (m, 2 H), 4.43 (br. s, 1 H), 5.10 (s, 2 H), 5.19 (s, 2 H), 6.03 (d, J = 8.5 Hz, 1 H), 7.20–7.41 (m, 18 H), 9.20–9.40 (m, 2 H) ppm. ¹³C NMR (CDCl_3): δ = 24.9 (CH_2), 28.6 (CH_2), 44.2 (CH_2), 47.2 (CH), 53.7 (CH), 67.0 (CH_2), 67.1 (CH_2), 68.9 (CH_2), 119.9 (2 × CH), 125.1 (CH), 127.0, 127.6, 127.8, 128.3, 128.7 (15 × CH), 134.7, 136.6 (2 C), 141.3, 141.4 (2 C), 143.8, 144.0 (2 C), 155.7, 156.3 (2 C), 160.5 (C), 163.7 (C), 174.7 (C) ppm. IR (KBr): $\tilde{\nu}$ = 740, 1102, 1258, 1379, 1502, 1611, 1723, 3066, 3393 cm^{-1} . ESI-MS: m/z = 687 [M + Na]⁺, 665 [M + H]⁺. $\text{C}_{37}\text{H}_{36}\text{N}_4\text{O}_8$ (664.71): calcd. C 66.86, H 5.46, N 8.43; found C 66.68, H 5.48, N 8.58.

***N*^α-Fmoc-*N*^δ,*N*^ε-Z₂-Arg-C(PPh₃)CN (22):** Product 22 was synthesised by the General Procedure for coupling with (triphenylphosphoranylidene)acetonitrile (reaction time 5 h), from 21 (2.00 g, 3.0 mmol), and obtained after purification by flash chromatography with a gradient of EtOAc/cyclohexane (1:1 to 10:0) as a white solid (1.16 g, 1.22 mmol, 41%). The desired compound 22 was crystallised from EtOAc/cyclohexane, 1:1. R_f = 0.40 (EtOAc/cyclohexane, 1:1); m.p. 105–107 °C. $[\alpha]_D^{20}$ = +28.8 (c = 1.00, CHCl_3). ¹H NMR (CDCl_3): δ = 1.75–1.85 (m, 3 H), 2.06 (br. s, 1 H), 3.77 (br. s, 1 H), 3.94 (m, 2 H), 4.07 (dd, J = 7.9, 17.8 Hz, 1 H), 4.17 (dd, J = 7.9, 17.8 Hz, 1 H), 4.83 (br. s, 1 H), 4.92 (s, 2 H), 4.98 (d, J = 6.6 Hz, 2 H), 5.61 (d, J = 7.5 Hz, 1 H), 7.00–7.60 (m, 33 H), 9.11 (br. s, 1 H), 9.39 (br. s, 1 H) ppm. ¹³C NMR (CDCl_3): δ = 24.6 (CH_2), 30.7 (CH_2), 44.7 (CH_2), 47.2 (CH), 47.6 (d, J = 125 Hz, C), 56.3 (CH), 66.8 (CH_2), 67.2 (CH_2), 68.9 (CH_2), 120.0 (4 × CH), 120.7 (d, J = 15 Hz, C), 122.5 (d, J = 93 Hz, 3 × C), 124.9 (2 × CH), 125.4, 127.1, 127.7, 128.2, 128.4, 128.8, 129.2, 133.6 (27 × CH), 134.8, 137.0 (2 C), 141.3, 144.0, 144.2 (4 C), 155.9, 156.0 (2 C), 160.7 (C), 164.0 (C), 193.8 (C) ppm. IR (KBr): $\tilde{\nu}$ = 1103, 1252, 1380, 1441, 1510, 1607, 1720, 2177 (CN), 2929, 3394 cm^{-1} . ESI-MS: m/z = 986 [M + K]⁺, 970 [M + Na]⁺, 948 [M + H]⁺, 840 [M + H – BnOH]⁺. $\text{C}_{57}\text{H}_{50}\text{N}_5\text{O}_7\text{P}$ (948.02): calcd. C 72.22, H 5.32, N 7.39; found C 72.35, H 5.47, N 7.57.

***N*^β-Boc-*N*^α-CHO-Dpr-Pro-*N*^δ,*N*^ε-Z₂-Arg-C(PPh₃)CN (20):** *N*^α-Fmoc-*N*^δ,*N*^ε-Z₂-Arg-C(PPh₃)CN (22, 90 mg, 0.095 mmol) was treated at 0 °C with $\text{CH}_3\text{CN}/\text{NHET}_2$ (2:1; 7.5 mL) for 30 min and at room temp. for a further 30 min. The solvents were then evaporated

under reduced pressure, and the residue was dissolved in and concentrated from CH_2Cl_2 (3 × 40 mL) to furnish the crude amine (90 mg, quant.), which was used without further purification.

The second step then involved the General Procedure for peptide coupling with EDCI/DMAP (reaction time of 12 h), with crude amine (0.095 mmol, 1.0 equiv.) added as the last component and dipeptide 15 (41 mg, 0.12 mmol, 1.3 equiv.). The crude reaction product was washed successively with water (5 mL) and a saturated NaCl solution (5 mL) and was then dried with MgSO_4 and evaporated under reduced pressure to furnish the crude product (125 mg). The desired tripeptide derivative 20 was obtained after purification by flash chromatography with a gradient of EtOAc/cyclohexane (10:0 to 9:1) as a white solid (74 mg, 0.071 mmol, 75%). When this procedure was reproduced on a larger scale (1–3 g) isolated product yields were lower (ca. 50%). R_f = 0.40 (EtOAc/cyclohexane, 1:1); m.p. 83–85 °C. $[\alpha]_D^{20}$ = –3.1 (c = 1.85, CHCl_3). ¹H NMR (CDCl_3): δ = 1.21 (s, 9 H, 3 × CH_3), 1.41–1.76 (m, 4 H, CH_2 , Pro, Arg), 1.79–1.98 (m, 4 H, CH_2 , Pro, Arg), 2.79 (td, J = 7.0, 13.5 Hz, 1 H, CH_2N , Dpr), 3.11 (td, J = 6.7, 13.5 Hz, 1 H, CH_2N , Dpr), 3.55 (m, 2 H, CH_2N , Pro), 3.93 (t, J = 7.1 Hz, 2 H, CH_2N , Arg), 4.30 (dd, J = 3.5, 8.3 Hz, 1 H, CH_α , Pro), 4.85 (q, J = 6.7 Hz, 1 H, CH_α , Dpr), 4.96 (s, 2 H, CH_2 , Z), 5.00 (m, 1 H, CH_α , Arg), 5.19 (s, 2 H, CH_2 , Z), 6.02 (br. s, 1 H, ^βNH, Dpr), 6.60 (d, J = 7.0 Hz, 1 H, ^αNH, Dpr), 6.79 (br. s, 1 H, NH, Arg), 7.15–7.70 (m, 25 H, CH_{ar}), 7.97 (s, 1 H, NHCHO), 9.20 (br. s, 1 H, NH), 9.38 (br. s, 1 H, NH) ppm. ¹³C NMR (CDCl_3): δ = 24.6, 24.8 (2 CH_2 , Pro, Arg), 28.3 (3 × CH_3), 29.1 (CH_2 , Pro), 30.2 (CH_2 , Arg), 42.8 (CH_2N , Dpr), 45.6 (CH_2N , Arg), 47.5 (CH_2N , Pro), 48.1 (d, J = 127 Hz, C=P), 49.0 (CH_α , Dpr), 54.6 (CH_α , Arg), 60.8 (CH_α , Pro), 67.1 (CH_2 , Z), 68.9 (CH_2 , Z), 79.2 [$\text{O}(\text{C}(\text{CH}_3)_2$)], 120.3 (d, J = 15 Hz, CN), 122.5 (d, J = 93 Hz, 3 × C_{ipso}), 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 128.6, 128.8, 129.2, 129.3, 133.4, 133.6 (25 × CH_{ar}), 134.9, 136.8 (2 C_{ipso} , Z), 156.0, 156.5 (2 NHCOO, Z), 160.6 (NHCHO), 160.7 (NHCOO, Boc), 164.1 [$\text{N}(\text{C}(\text{NH})\text{N}]$), 169.4 (NHCO, Dpr), 170.6 (NHCO, Pro), 193.6 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 1109, 1253, 1381, 1438, 1508, 1638, 1718, 2180 (CN), 3400 cm^{-1} . ESI-MS: m/z = 1037 [M + H]⁺. HR-MS: m/z calcd. for [$\text{C}_{56}\text{H}_{61}\text{N}_8\text{O}_{10}\text{P}$, H]⁺ 1037.4327; found 1037.4294 (–3.1 ppm). $\text{C}_{56}\text{H}_{61}\text{N}_8\text{O}_{10}\text{P}$ (1037.11): calcd. C 64.85, H 5.93, N 10.80; found C 64.25, H 6.05, N 10.97. Pure product 20 was analysed by reversed-phase HPLC on a C₁₈ column with a mobile phase gradient from $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1:9 to 9:1), t_R = 21.4 min: LC-MS: m/z = 1037 [M + H]⁺. After storage in the deep freezer for one week, reversed-phase HPLC analysis under the same conditions indicated the presence of two components with t_{R1} = 21.4 min and t_{R2} = 21.8 min: each showed LC-MS: m/z = 1037 [M + H]⁺.

***N*-Fmoc-D-Phe-ΔTyr(OTIPS)-OMe (24):** The known dipeptide ester *N*-Boc-D-Phe-ΔTyr(OTIPS)-OMe (23,^[19] 3.59 g, 6.02 mmol, 1 equiv.) was treated at 0 °C with a solution of $\text{CH}_2\text{Cl}_2/\text{TFA}$ (1:1; 20 mL) for 1 h, and the solvents were then evaporated under reduced pressure. The residue was dissolved in and concentrated from CH_2Cl_2 (3 × 30 mL) to furnish the trifluoroacetate salt. This material was dissolved in dioxane (60 mL) at 0 °C, and a solution of Na_2CO_3 (10%; 40 mL) was added. After the system had been stirred for 10 min, a white precipitate had formed. 9-Fluorenylmethyl chloroformate (1.71 g, 6.61 mmol, 1.1 equiv.) was then added, and the reaction mixture was stirred and allowed to warm to room temp. over 18 h. Water (100 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (5 × 30 mL). The combined organic phases were washed with a citric acid solution (5%; 30 mL), dried with MgSO_4 and evaporated under reduced pressure to afford the crude product, which was purified by flash chromatography with EtOAc/cyclohexane (20:80) as eluent. Prod-

uct **24** was isolated as a white foam (4.18 g, 5.81 mmol, 97%). $R_f = 0.22$ (EtOAc/cyclohexane, 2:8); m.p. 70–73 °C. $[\alpha]_D^{20} = +21.2$ ($c = 1.00$, CHCl₃). ¹H NMR (CDCl₃): $\delta = 1.11$ (d, $J = 7.2$ Hz, 18 H), 1.25 (hept, $J = 7.2$ Hz, 3 H), 3.17 (m, 1 H), 3.31 (m, 1 H), 3.77 (s, 3 H), 4.17 (t, $J = 6.0$ Hz, 1 H), 4.29 (m, 1 H), 4.49 (m, 1 H), 4.78 (br. s, 1 H), 5.71 (d, $J = 6.0$ Hz, 1 H), 6.81 (d, $J = 8.0$ Hz, 2 H), 7.22–7.38 (m, 9 H), 7.41 (t, $J = 7.0$ Hz, 3 H), 7.51 (dd, $J = 7.5$, 13.0 Hz, 2 H), 7.76 (d, $J = 7.5$ Hz, 2 H), 7.90 (br. s, 1 H) ppm. ¹³C NMR (CDCl₃): $\delta = 12.7$ (3 × CH), 17.9 (6 × CH₃), 37.8 (CH₂), 47.0 (CH), 52.5 (CH₃), 56.2 (CH), 67.2 (CH₂), 120.0, 120.1 (6 × CH), 121.6 (C), 125.1 (CH), 126.1 (C), 127.0, 127.7, 128.7, 129.5, 131.9 (10 × CH), 134.2 (CH), 136.5 (C), 141.2, 141.4 (4 × C), 143.7 (C), 157.6 (C), 165.6 (C), 170.5 (C) ppm. IR (KBr): $\tilde{\nu} = 765$, 1230, 1535, 1660, 1700, 2400, 2910 cm⁻¹. ESI-MS: $m/z = 741$ [M + Na]⁺. HR-MS: m/z calcd. for [C₄₃H₅₀N₂O₆Si + H]⁺ 719.3516; found 719.3497 ($\delta = -2.7$ ppm). C₄₃H₅₀N₂O₆Si (718.96): calcd. C 71.84, H 7.01, N 3.90; found C 72.39, H 7.02, N 3.92.

General Procedure for Reduction of Esters to Corresponding Alcohols: Lithium aluminium hydride (2.3 mmol, 2.3 equiv.) was suspended at 0 °C under argon in THF (30 mL). A solution of ester (1 mmol) in THF (6 mL) was added dropwise over 5 min, and the reaction mixture was then stirred for a specified time and, when stated, allowed to warm to room temp. After this time, the reaction was cautiously quenched at 0 °C successively with water (4 mL) and HCl solution (1 M, 4 mL). After the system had been stirred for 10 min, MgSO₄ was added in excess and the mixture was stirred for a further 30 min. After filtration, solids were washed with EtOAc (3 × 20 mL), and the combined filtrates were evaporated under reduced pressure to furnish the crude product, which was purified by flash chromatography to afford the desired pure product.

General Procedure for One-Pot Oxidation/Vinylogation of Alcohol with Activated MnO₂ and Phosphorane: Allylic alcohol (0.35 mmol, 1 equiv.) was dissolved under argon in CH₂Cl₂ (10 mL). Activated manganese(IV) oxide (305 mg, 3.5 mmol, 10 equiv.) and a stabilised phosphorane (0.52 mmol, 1.5 equiv.) were added in succession. The reaction mixture was heated at 40–55 °C. After 24 h, a further portion of activated manganese(IV) oxide (305 mg, 3.5 mmol, 10 equiv.) was added, and the mixture was stirred at reflux for a further 12 h. Solids were removed by filtration through Celite and washed with CH₂Cl₂ (3 × 40 mL). The combined organic filtrates were evaporated under reduced pressure to furnish the crude product as a brown oil, which was purified by flash chromatography to afford the desired vinylogated product.

N-Fmoc-D-Phe-ΔTyr(OTIPS)-CH₂OH (25): Product **25** was synthesised by the General Procedure for reduction, with a reaction time of 1 h at 0 °C, from the dipeptide ester **24** (498 mg, 0.69 mmol, 1 equiv.). Purification by flash chromatography with a gradient of EtOAc/cyclohexane (2:8 to 1:1) afforded product **25** as a white foam (379 mg, 0.55 mmol, 79%). $R_f = 0.60$ (EtOAc/cyclohexane, 1:1); m.p. 48–51 °C. $[\alpha]_D^{20} = +32.6$ ($c = 1.40$, CHCl₃). ¹H NMR (CDCl₃): $\delta = 1.10$ (d, $J = 7.2$ Hz, 18 H), 1.25 (hept, $J = 7.2$ Hz, 3 H), 1.81 (br. s, 1 H), 3.13 (m, 2 H), 4.19 (t, $J = 6.7$ Hz, 1 H), 4.31 (br. s, 2 H), 4.48 (dd, $J = 7.0$, 10.4 Hz, 1 H), 4.49–4.56 (m, 1 H), 5.41 (br. s, 1 H), 5.98 (s, 1 H), 6.77 (d, $J = 8.5$ Hz, 2 H), 6.84 (m, 2 H), 7.22 (m, 2 H), 7.26–7.38 (m, 6 H), 7.42 (t, $J = 7.4$ Hz, 2 H), 7.52 (dd, $J = 7.5$, 11.0 Hz, 2 H), 7.77 (br. s, 3 H) ppm. ¹³C NMR (CDCl₃): $\delta = 12.6$ (3 × CH), 17.9 (6 × CH₃), 38.5 (CH₂), 47.1 (CH), 57.1 (CH), 64.3 (CH₂), 67.2 (CH₂), 117.4 (CH), 120.0, 120.4 (6 × CH), 124.9 (CH), 126.7 (C), 127.4, 128.9, 129.3, 129.5, 130.1 (10 × CH), 133.8, 135.8 (2 C), 141.3, 143.6 (4 C), 155.5 (C), 155.8 (C), 169.9 (C) ppm. IR (KBr): $\tilde{\nu} = 740$, 913, 1267, 1504, 1604, 1667, 2887, 2945, 3300, 3410 (br) cm⁻¹. ESI-MS: $m/z = 713$ [M + Na]⁺,

673 [M + H - H₂O]⁺. HR-MS: m/z calcd. for [C₄₂H₅₀N₂O₅Si + H]⁺ 691.3567; found 691.3570 (+1.3 ppm). C₄₂H₅₀N₂O₅Si (690.95): calcd. C 73.01, H 7.29, N 4.05; found C 73.01, H 7.34, N 4.11.

N-Fmoc-D-Phe-V-ΔTyr(OTIPS)-OrBu (26): The general procedure for oxidation/vinylogation was followed, with heating at 40 °C, with the dipeptide alcohol **25** (4.39 g, 6.35 mmol). After purification by flash chromatography with a gradient of EtOAc/cyclohexane (1:9 to 2:8), the product **26** was obtained as a yellow foam (2.92 g, 3.71 mmol, 58%). $R_f = 0.28$ (EtOAc/cyclohexane, 2:8); m.p. 86–89 °C. $[\alpha]_D^{20} = +20.2$ ($c = 1.20$, CHCl₃). ¹H NMR ([D₆]acetone): $\delta = 1.10$ (d, $J = 6.8$ Hz, 18 H, 6 × CH₃), 1.22 (hept, $J = 6.8$ Hz, 3 H, 3 × SiCH), 1.51 (s, 9 H, 3 × CH₃), 3.14 (m, 1 H, CH₂Ph), 3.39 (m, 1 H, CH₂Ph), 4.22 (m, 2 H, CH₂, Fmoc), 4.41 (t, $J = 8.0$ Hz, 1 H, CH, Fmoc), 4.91 (br. s, 1 H, CH_α), 5.93 (d, $J = 15.0$ Hz, 1 H, CH_α=CH V-ΔTyr), 6.81 (s, 1 H, CH_β=C V-ΔTyr), 6.88 (d, $J = 8.0$ Hz, 2 H, CH_{ar}), 7.19–7.44 (m, 11 H, 9 × CH_{ar} + NH + CH_β=CH V-ΔTyr), 7.57–7.66 (m, 4 H, CH_{ar}), 7.84 (d, $J = 8.0$ Hz, 2 H, CH_{ar}), 8.87 (br. s, 1 H, NH) ppm. ¹³C NMR (CDCl₃): $\delta = 12.7$ (3 × SiCH), 17.9 (6 × CH₃), 28.1 [OC(CH₃)₃], 37.7 (CH₂Ph), 47.1 (CH), 56.4 (CH_α), 67.0 (CH₂), 80.3 [OC(CH₃)₃], 119.2 (CH_α=CH, V-ΔTyr), 119.9, 120.1 (6 × CH_{ar}), 125.0 (CH_{ar}), 127.2, 127.8 (4 × CH_{ar}), 128.6 (2 × C_{ipso}), 128.9, 129.4 (4 × CH_{ar}), 131.1 (2 × CH_{ar}), 134.2 (CH_β=C, V-ΔTyr), 136.3 (C_{ipso}), 141.3 (2 × C_{ipso}, Fmoc), 142.7 (CH_β=CH, V-ΔTyr), 143.6 (2 × C_{ipso}, Fmoc), 156.3 (CH=C_γ, V-ΔTyr), 156.9 (NHCOO), 166.2 (NHCO), 169.9 (CO₂ *t*Bu) ppm. IR (KBr): $\tilde{\nu} = 740$, 913, 1150, 1273, 1507, 1596, 1704, 2867, 2945, 3427 cm⁻¹. HR-MS: m/z calcd. for [C₄₈H₅₈N₂O₆Si + Na]⁺ 809.3962; found 809.3978 (+2.0 ppm). C₄₈H₅₈N₂O₆Si (787.07): calcd. C 73.25, H 7.43, N 3.56; found C 73.55, H 7.34, N 3.54.

D-Phe-V-ΔTyr(OTIPS)-OrBu (27): Protected vinylogous dipeptide **26** (50 mg, 0.063 mmol, 1 equiv.) was treated at 0 °C with CH₃CN/NHEt₂ (2:1; 4.5 mL) for 30 min and at room temp. for a further 30 min. The solvents were then evaporated under reduced pressure, and the residue was dissolved in and concentrated from CH₂Cl₂ (3 × 40 mL) to furnish the crude dipeptide amine **27**, which was generally used without further purification for the next step. On one occasion, the product was purified by flash chromatography with use of a gradient of EtOAc/cyclohexane (2:8 to 3:7) to afford the pure free amine **27** (32 mg, 0.057 mmol, 90%) as a yellow solid. $R_f = 0.50$ (EtOAc/cyclohexane, 4:6). $[\alpha]_D^{20} = -1.8$ ($c = 1.01$, CHCl₃). ¹H NMR (CDCl₃): $\delta = 1.01$ (d, $J = 7.2$ Hz, 18 H, 6 × CH₃), 1.17 (hept, $J = 7.2$, Hz, 3 H, 3 × CHSi), 1.43 (s, 9 H, 3 × CH₃), 1.49 (br. s, 2 H, NH₂), 2.85 (dd, $J = 8.8$, 13.7 Hz, 1 H, CH₂Ph), 3.23 (dd, $J = 4.0$, 13.7 Hz, 1 H, CH₂Ph), 3.71 (dd, $J = 4.0$, 8.8 Hz, 1 H, CH_α), 5.65 (d, $J = 15.4$ Hz, 1 H, CH_α=CH V-ΔTyr), 6.57 (s, 1 H, CH_β=C V-ΔTyr), 6.71 (s, $J = 8.6$ Hz, 2 H, CH_{ar}), 7.17–7.32 (m, 8 H, 7 × CH_{ar} + CH_β=CH V-ΔTyr), 8.78 (br. s, 1 H, NH) ppm. ¹³C NMR (CDCl₃): $\delta = 12.7$ (3 × SiCH), 18.0 (6 × CH₃), 28.3 (3 × CH₃), 40.4 (CH₂Ph), 56.6 (CH_α), 80.4 [OC(CH₃)₃], 119.4 (CH_α=CH, V-ΔTyr), 120.1 (2 × CH_{ar}), 127.1 (CH_{ar}), 127.6 (C_{ipso}), 129.0, 129.6 (4 × CH_{ar}), 129.7 (C_{ipso}), 130.9 (2 × CH_{ar}), 133.2 (CH_β=C, V-ΔTyr), 137.5 (C_{ipso}), 142.8 (CH_β=CH, V-ΔTyr), 156.8 (CH=C_γ, V-ΔTyr), 166.2 (NHCO), 172.8 (CO₂ *t*Bu) ppm. ESI-MS: $m/z = 565$ [M + H]⁺, 509 [M + H - C₄H₈]⁺. (-)ESI-MS: $m/z = 563$ [M - H]⁻. HR-MS: m/z calcd. for [C₃₃H₄₈N₂O₄Si + Na]⁺ 587.3281; found 587.3300 (+3.2 ppm).

N-Boc-D-Phe-V-ΔTyr(OTIPS)-OMe (28): Product **28** was synthesised in two steps. The first step followed the General Procedure for reduction with the known dipeptide ester *N*-Boc-D-Phe-ΔTyr(OTIPS)-OMe (**23**,¹⁹¹ 2.00 g, 3.35 mmol, 1 equiv.), with a reaction time of 2.5 h at room temp. The allylic alcohol dipeptide *N*-Boc-D-

Phe- Δ Tyr(OTIPS)-CH₂OH was obtained after purification by flash chromatography with EtOAc/cyclohexane (2:8) as a white foam (1.64 g, 2.88 mmol, 86%). R_f = 0.16 (EtOAc/cyclohexane, 2:8); m.p. 36–38 °C. $[\alpha]_D^{20}$ = +20.5 (c = 1.40, CHCl₃). ¹H NMR (CDCl₃): δ = 1.01 (d, J = 7.5 Hz, 18 H), 1.18 (hept, J = 8.0 Hz, 3 H), 1.29 (s, 9 H), 3.02 (d, J = 10.8 Hz, 2 H), 4.21 (t, J = 7.2 Hz, 2 H), 4.31 (br. s, 1 H), 4.49 (t, J = 7.2 Hz, 1 H), 4.88 (br. s, 1 H), 5.76 (s, 1 H), 6.68 (d, J = 8.0 Hz, 2 H), 6.75 (d, J = 8.0 Hz, 2 H), 7.09–7.20 (m, 5 H), 7.79 (br. s, 1 H) ppm. ¹³C NMR (CDCl₃): δ = 12.6 (3 \times CH), 17.9 (6 \times CH₃), 28.2 (3 \times CH₃), 38.3 (CH₂), 56.6 (C), 64.2 (CH₂), 80.6 (C), 116.8 (CH), 119.2 (2 \times CH), 126.8 (C), 127.2 (CH), 128.9, 129.3, 129.4 (6 \times CH), 133.9 (C), 136.1 (C), 155.2 (C), 155.4 (C), 170.3 (C) ppm. IR (CHCl₃): $\tilde{\nu}$ = 760, 1260, 1500, 1510, 1680, 1720, 2820, 2850, 3420 (br) cm⁻¹.

The second step followed the General Procedure for oxidation/vinylogation, with heating at 50 °C and use of the allylic alcohol dipeptide *N*-Boc-D-Phe- Δ Tyr(OTIPS)-CH₂OH (200 mg, 0.35 mmol), to afford the desired product **28** after purification by flash chromatography with EtOAc/cyclohexane (1:9), as a pale yellow foam (162 mg, 0.26 mmol, 74%). R_f = 0.42 (EtOAc/cyclohexane, 3:7); m.p. 71–73 °C. $[\alpha]_D^{20}$ = +68.0 (c = 1.60, CHCl₃). ¹H NMR (CDCl₃): δ = 1.02 (d, J = 7.2 Hz, 18 H, 6 \times CH₃), 1.16 (hept, J = 7.2 Hz, 3 H, 3 \times SiCH), 1.34 (s, 9 H, 3 \times CH₃), 3.00 (dd, J = 7.1, 13.8 Hz, 1 H, CH₂Ph), 3.13 (dd, J = 7.1, 13.8 Hz, 1 H, CH₂Ph), 3.64 (s, 3 H, OCH₃), 4.51 (q, J = 7.1 Hz, 1 H, CH₂), 5.08 (d, J = 8.4 Hz, 1 H, NH), 5.59 (d, J = 15.4 Hz, 1 H, CH₂=CH V- Δ Tyr), 6.53 (s, 1 H, CH₈=C V- Δ Tyr), 6.67 (d, J = 8.6 Hz, 2 H, CH_{ar}), 7.13 (d, J = 8.6 Hz, 2 H, CH_{ar}), 7.15–7.26 (m, 6 H, 5 \times CH_{ar} + CH_β=CH V- Δ Tyr), 7.47 (s, 1 H, NH) ppm. ¹³C NMR (CDCl₃): δ = 12.6 (3 \times SiCH), 17.9 (6 \times CH₃), 28.3 (3 \times CH₃), 37.5 (CH₂Ph), 51.4 (OCH₃), 56.0 (CH₂), 80.6 [OC(CH₃)₃], 116.8 (CH₂=CH, V- Δ Tyr), 120.1 (2 \times CH_{ar}), 127.0 (CH_{ar}), 127.1 (C_{ipso}), 128.6 (C_{ipso}), 128.8, 129.4, 131.2 (6 \times CH_{ar}), 135.0 (CH₈=C, V- Δ Tyr), 136.5 (C_{ipso}), 144.0 (CH_β=CH, V- Δ Tyr), 155.9 (CH=C_γ, V- Δ Tyr), 157.0 (NHCOO), 167.3 (NHCO), 170.4 (CO₂Me) ppm. IR (CHCl₃): $\tilde{\nu}$ = 760, 1235, 1506, 1532, 1590, 1675, 1700, 2880, 2950, 3300 cm⁻¹. HR-MS: m/z calcd. for [C₃₅H₅₀N₂O₆Si + Na]⁺ 645.3336; found 645.3343 (+1.2 ppm). C₃₅H₅₀N₂O₆Si (622.87): calcd. C 67.49, H 8.09, N 4.50; found C 67.52, H 8.09, N 4.59.

N-Boc-D-Phe-V- Δ Tyr-OH (**29**): The protected vinylogous dipeptide **28** (156 mg, 0.25 mmol, 1 equiv.) was dissolved in EtOH (95%; 6 mL), and the solution was cooled to 0 °C over 10 min. A sodium hydroxide solution (1 M; 3.8 mL, 3.8 mmol, 15 equiv.) was added slowly to the reaction mixture, which was stirred for a further 6 h at 0 °C. The yellow solution was concentrated under reduced pressure to remove the ethanol, taken to pH 1 with a HCl solution (1 M, 3 mL) and extracted with EtOAc (3 \times 20 mL). Combined organic extracts were evaporated under reduced pressure to afford the carboxylic acid **29** as a yellow solid (113 mg, 0.25 mmol, 100%). This product was used without further purification. R_f = 0.00 (EtOAc/MeOH, 9:1). ¹H NMR ([D₆]acetone): δ = 1.24 (s, 9 H), 2.90 (dd, J = 7.1, 13.0 Hz, 1 H), 3.19 (dd, J = 7.1, 13.0 Hz, 1 H), 4.49 (m, 1 H), 5.75 (d, J = 15 Hz, 1 H), 6.25 (d, J = 8.0 Hz, 1 H), 6.69 (d, J = 8.0 Hz, 2 H), 6.70 (s, 1 H), 7.10–7.25 (m, 5 H), 7.25 (s, 1 H), 7.37 (d, J = 8.0 Hz, 2 H), 8.45 (br. s, 1 H), 8.57 (br. s, 1 H), 10.0–11.0 (br. s, 1 H) ppm. ¹³C NMR ([D₆]acetone): δ = 28.7 (3 \times CH₃), 38.3 (CH₂), 57.9 (CH), 79.8 (C), 116.4 (CH), 117.6 (2 \times CH), 127.3 (C), 127.4 (CH), 129.0 (2 \times CH), 129.3 (C), 129.6 (2 \times CH), 132.1 (2 \times CH), 136.4 (CH), 138.5 (C), 146.3 (CH), 156.8 (C), 159.2 (C), 168.8 (C), 172.2 (C) ppm.

N-Boc-D-Phe-V- Δ Tyr-N^ω-CHO-Dpr-Pro-Oallyl (**30**): A solution of carboxylic acid **29** (280 mg, 0.62 mmol, 1 equiv.) in THF (3 \times mL)

was cooled to –20 °C under argon, and diisopropylethylamine (119 μ L, 0.68 mmol, 1.1 equiv.) was added slowly. The reaction mixture was stirred briskly for a further 20 min, and a solution of diphenylphosphoryl chloride (154 mg, 0.65 mmol, 1.05 equiv.) in THF (1 mL) and a solution of dipeptide **17** (217 mg, 0.81 mmol, 1.3 equiv.) in THF (2 \times mL) were then successively added dropwise. The reaction mixture was stirred for a further 1 h at –20 °C and was then allowed to warm to room temp. over 24 h. The solvent was evaporated under reduced pressure, and the residue was taken up with EtOAc (40 mL). This solution was washed with a saturated NaHCO₃ solution (5 \times 15 mL) until the aqueous phase was transparent. The organic phase was dried with MgSO₄ and evaporated to furnish the crude product, which was purified by flash chromatography with a gradient of CH₂Cl₂/MeOH (98:2 to 95:5) to afford the pure desired protected tetrapeptide **30** as a yellow foam (353 mg, 0.50 mmol, 81%). R_f = 0.50 (CH₂Cl₂/MeOH, 9:1); m.p. 110–112 °C. $[\alpha]_D^{20}$ = –66.4 (c = 2.00, CHCl₃). ¹H NMR ([D₆]acetone): δ = 1.36 (s, 9 H, 3 \times CH₃), 1.90–1.96 (m, 3 H, CH₂, Pro), 2.25 (m, 1 H, CH₂, Pro), 3.00 (t, J = 13.2 Hz, 1 H, CH₂, Phe), 3.27 (m, 2 H, CH₂, Phe + OH), 3.33 (dd, J = 4.0, 13.8 Hz, 1 H, CH₂N, Dpr), 3.48 (m, 1 H, CH₂N, Dpr), 3.77 (m, 1 H, CH₂N, Pro), 3.90 (m, 1 H, CH₂N, Pro), 4.53 (br. s, 1 H, CH₂, Pro), 4.59 (m, 2 H, CH₂, Allyl), 4.72 (m, 1 H, CH₂, Phe), 5.00–5.09 (m, 1 H, CH₂, Dpr), 5.20 (m, 1 H, CH₂=CH Allyl), 5.32 (m, 1 H, CH₂=CH Allyl), 5.91 (m, 1 H, CH₂=CH Allyl), 6.02 (d, J = 15.3 Hz, 1 H, CH₂=CH V- Δ Tyr), 6.44 (d, J = 8.6 Hz, 1 H, NH), 6.74 (s, 1 H, CH₈=C V- Δ Tyr), 6.83 (d, J = 8.6 Hz, 2 H, CH_{ar}), 7.25–7.52 (m, 8 H, 7 \times CH_{ar} + CH_β=CH V- Δ Tyr), 7.98 (d, J = 8.6 Hz, 1 H, NH), 8.17 (s, 1 H, NCHO), 8.89 (br. s, 1 H, NH), 8.97 (d, J = 8.7 Hz, 1 H, NH) ppm. ¹³C NMR ([D₆]acetone): δ = 25.6 (CH₂, Pro), 28.7 (3 \times CH₃, Boc), 31.7 (CH₂, Pro), 38.5 (CH₂, Phe), 42.0 (CH₂N, Dpr), 47.8 (CH₂N, Pro), 50.4 (CH₂, Dpr), 57.4 (CH₂, Phe), 59.8 (CH₂, Pro), 66.0 (CH₂, Allyl), 79.5 [OC(CH₃)₃], 116.4 (2 \times CH_{ar}), 118.3 (CH₂=CH, Allyl), 120.4 (CH₂=CH, V- Δ Tyr), 127.3 (CH_{ar}), 127.5 (C_{ipso}), 129.2 (2 \times CH_{ar}), 130.4 (C_{ipso}), 130.5, 132.6 (4 \times CH_{ar}), 133.4 (CH=CH₂, Allyl), 135.1 (CH₈=C, V- Δ Tyr), 139.1 (C_{ipso}), 141.2 (CH_β=CH, V- Δ Tyr), 156.8 (CH=C_γ, V- Δ Tyr), 158.9 (NHCOO), 162.2 (NHCHO), 167.3 (NHCO, Phe), 169.6 (NHCO, V- Δ Tyr), 169.9 (NHCO, Dpr), 172.7 (CO₂Allyl) ppm. IR (KBr): $\tilde{\nu}$ = 760, 1235, 1506, 1532, 1590, 1675, 1700, 2880, 2950, 3300 cm⁻¹. ESI-MS: m/z = 726 [M + Na]⁺, 704 [M + H]⁺, 604 [M + H – Boc]⁺. HR-MS: m/z calcd. for [C₃₇H₄₅N₅O₉ + Na]⁺ 726.3115; found 726.3108 (δ = –1.0 ppm). C₃₇H₄₅N₅O₉·H₂O (721.80): calcd. C 61.57, H 6.56, N 9.70; found C 61.33, H 6.48, N 9.74.

D-Phe-V- Δ Tyr-N^ω-CHO-Dpr-Pro-Oallyl (**31**): Protected tetrapeptide **30** (353 mg, 0.50 mmol) was treated at 0 °C with a solution of CH₂Cl₂/TFA (1:1; 14 mL) for 1 h, and solvents were then evaporated under reduced pressure. The residue was dissolved in and concentrated from CH₂Cl₂ (3 \times 30 mL) to furnish the trifluoroacetate salt, which was taken up with water (40 mL) to give a solution at pH 2.0, and the solution was adjusted to pH 7.0 with a saturated NaHCO₃ solution. The resulting aqueous phase was extracted with EtOAc (3 \times 20 mL), dried with MgSO₄ and evaporated under reduced pressure to afford the pure tetrapeptide amine **31** (299 mg, 0.49 mmol, 99%) as a yellow solid, which was used for the next step without further purification. R_f = 0.00 (CH₂Cl₂/MeOH, 9:1). ¹H NMR ([D₆]acetone): δ = 1.64–1.78 (m, 3 H), 2.01 (m, 1 H), 2.80 (m, 1 H), 3.00 (m, 1 H), 3.21 (m, 2 H), 3.39 (m, 2 H), 3.55 (m, 2 H), 3.71–3.85 (m, 1 H), 4.26 (m, 1 H), 4.36 (m, 2 H), 4.77 (m, 1 H), 4.94 (t, J = 8.5 Hz, 1 H), 5.07 (m, 1 H), 5.66 (m, 1 H), 5.77 (m, 1 H), 6.51 (d, J = 8.1 Hz, 2 H), 6.61 (d, J = 8.3 Hz, 1 H), 6.68 (d, J = 7.8 Hz, 1 H), 6.88 (s, 1 H), 6.98 (d, J = 8.2 Hz, 2 H), 7.00–7.22 (m, 7 H), 7.47 (d, J = 8.2 Hz, 1 H), 7.92 (s, 1 H) ppm.

¹³C NMR ([D₆]acetone): δ = 27.2 (CH₂), 31.7 (CH₂), 37.3 (CH₂), 41.8 (CH₂), 48.1 (CH₂), 50.2 (CH), 50.3 (CH), 59.8 (CH), 66.2 (CH₂), 116.5 (2 × CH), 118.5 (CH₂), 122.1 (CH), 127.1 (C), 127.3 (CH), 129.2, 130.4 (4 × CH), 130.6 (C), 132.1 (2 × CH), 133.2 (CH), 135.2 (CH), 140.0 (C), 141.3 (CH), 159.4 (C), 162.4 (CH), 167.2 (C), 169.5 (C), 172.4 (C), 175.3 (C) ppm.

General Procedure for Tandem Oxidation/Coupling Reactions: A solution of α-keto cyanophosphorane (1.1 to 2.1 mmol, 1.1 to 2.1 equiv.) in CH₂Cl₂ (30–60 mL) was purged at –78 °C with O₂ for 5 min and then ozonised (Ozone generator 502, Fischer technology) for 20 min until the solution turned deep yellow-green. The solution containing the α-keto acyl cyanide intermediate was purged with argon for 15 min until it became light yellow. A solution of free peptide amine (1.0 mmol, 1.0 equiv.) in CH₂Cl₂ (3–6 mL) was then added to the reaction mixture, and the resulting solution was stirred at –78 °C for a further 1 h and warmed slowly to room temp. over a specified time. The solvent was evaporated under reduced pressure to afford the crude residue, which was immediately purified by flash chromatography.

N^α-Boc-N^δ,N^ε-Z₂-k-Arg-D-Phe-V-ΔTyr(OTIPS)-OrBu (32): Product 32 was synthesised by the General Procedure for tandem oxidation/coupling (reaction time 1 h), from α-keto cyanophosphorane 19 (56 mg, 0.068 mmol, 1.2 equiv.) and amine 27 (32 mg, 0.057 mmol, 1 equiv.). The crude product (120 mg) was purified immediately by flash chromatography with EtOAc/cyclohexane (1:9) to provide the desired tripeptide 32 as a yellow foam (30 mg, 0.027 mmol, 47%). *R*_f = 0.12 (EtOAc/cyclohexane, 2:8); m.p. 102–104 °C. [α]_D²⁰ = –3.6 (*c* = 1.50, CHCl₃). ¹H NMR (CDCl₃): δ = 1.01 (d, *J* = 7.2 Hz, 18 H, 6 × CH₃), 1.18 (m, 3 H, SiCH), 1.35 (s, 9 H, 3 × CH₃), 1.41 (s, 9 H, 3 × CH₃), 1.48–1.58 (m, 3 H, CH₂, k-Arg), 1.72–1.78 (m, 1 H, CH₂, k-Arg), 2.99–3.18 (m, 2 H, CH₂, Phe), 3.87 (m, 2 H, CH₂N, k-Arg), 4.02 (br. s, CH_α, Phe), 4.69 (m, 1 H, CH_α, k-Arg), 5.03 (m, 2 H, CH₂, Z), 5.07 (m, 2 H, CH₂, Z), 5.52 (d, *J* = 15.6 Hz, 1 H, CH_α=CH V-ΔTyr), 5.70 (m, 1 H, NH), 6.56 (s, 1 H, CH_δ=C V-ΔTyr, V-ΔTyr), 6.71 (d, *J* = 8.8 Hz, 2 H, CH_{ar}), 7.10–7.38 (m, 19 H, 17 × CH_{ar} + CH_β=CH V-ΔTyr + NH), 7.57 (m, 1 H, NH), 9.10–9.30 (m, 2 H, NH) ppm. ¹³C NMR ([D₆]acetone): δ = 12.3 (3 × SiCH), 18.3 (6 × CH₃), 24.6 (CH₂, k-Arg), 25.6 (CH₂, k-Arg), 28.2 (3 × CH₃, Boc or CO₂tBu), 28.4 (3 × CH₃, Boc or CO₂tBu), 37.7 (CH₂, Phe), 44.7 (CH₂N, k-Arg), 56.0 (CH_α), 58.1 (CH_α), 67.3 (CH₂, Z), 69.3 (CH₂, Z), 80.4 [OC(CH₃)₃], 80.9 [O-C(CH₃)₃], 120.1 (CH_α=CH, V-ΔTyr), 120.9 (2 × CH_{ar}), 127.4, 127.7, 128.4, 128.8, 129.3 (8 × CH_{ar}), 130.4 (C_{ipso}), 129.5, 130.2, 130.4 (5 × CH_{ar}), 130.4 (C_{ipso}, V-ΔTyr), 131.9, 132.4 (4 × CH_{ar}), 135.2 (CH_δ=C, V-ΔTyr), 136.4 (C_{ipso}), 137.9 (2 × C_{ipso}, Z), 144.3 (CH_β=CH, V-ΔTyr), 156.4 (NHCOO, Z), 157.6 (NHCOO, Z), 158.6 (CH=C_γ, V-ΔTyr), 161.4 (NHCOO, Boc), 163.1 [NC(=NH)N], 166.6 (NHCO, Phe), 166.9 (NHCO, k-Arg), 170.3 (CO₂Me), 197.8 (CO, k-Arg) ppm. IR (KBr): ν̄ = 1098, 1253, 1450, 1378, 1446, 1508, 1608, 1654, 1720, 2976, 3393 cm⁻¹. ESI-MS: *m/z* = 1140 [M + H + MeOH]⁺, 1118 [M + H]⁺. HR-MS: *m/z* calcd. for [C₆₁H₈₀N₆O₁₂Si + H]⁺ 1117.5682; found 1117.5703 (+1.9 ppm).

N^α-Boc-N^δ-CHO-Dpr-Pro-N^δ,N^ε-Z₂-k-Arg-D-Phe-V-ΔTyr(OTIPS)-OrBu (33): Product 33 was synthesised by the General Procedure for tandem oxidation/coupling (reaction time 18 h), from the tripeptide α-keto cyanophosphorane 20 (74 mg, 0.071 mmol, 1.1 equiv.) and amine 27 (36 mg, 0.064 mmol, 1 equiv.). The crude product (110 mg) was purified immediately by flash chromatography with a gradient of CH₂Cl₂/MeOH (100:0 to 98:2) to provide the desired linear pentapeptide 33 as a yellow-orange foam (41 mg, 0.031 mmol, 48%). *R*_f = 0.30 (CH₂Cl₂/MeOH, 95:5); m.p. 132–135 °C. [α]_D²⁰ = –47.8 (*c* = 1.90, CHCl₃). ¹H NMR ([D₆]acetone): δ

= 1.01 (d, *J* = 7.2 Hz, 18 H, 6 × CH₃), 1.25 (m, 3 H, 3 × SiCH), 1.40 (s, 9 H, 3 × CH₃), 1.49 (s, 9 H, 3 × CH₃), 1.60–1.92 (m, 8 H, CH₂, Pro + k-Arg), 3.23 (m, 1 H, CH₂, Phe), 3.37 (m, 3 H, CH₂, Phe + CH₂N Dpr), 3.66 (m, 2 H, CH₂N, Pro), 3.90–3.99 (m, 1 H, CH₂N, k-Arg), 4.02–4.11 (m, 1 H, CH₂N, k-Arg), 4.48 (m, 1 H, CH_α, Pro), 4.92 (m, 1 H, CH_α, Dpr), 5.02 (dd, *J* = 8.2, 14.0 Hz, 1 H, CH_α, Phe), 5.13 (m, 3 H, CH_α k-Arg + CH₂ Z), 5.31 (m, 2 H, CH₂, Z), 5.80 (d, *J* = 15.3 Hz, 1 H, CH_α=CH V-ΔTyr), 6.39 (br. s, 1 H, NH), 6.81 (s, 1 H, CH_δ=C V-ΔTyr), 6.88 (d, *J* = 8.4 Hz, 2 H, 2 × CH_{ar}), 7.10–7.35 (m, 19 H, 17 × CH_{ar} + CH_β=CH V-ΔTyr + NH), 7.89 (d, *J* = 7.2 Hz, 1 H, NH), 8.13 (s, 1 H, NCHO), 8.17 (d, *J* = 8.4 Hz, 1 H, NH), 9.12 (s, 1 H, NH), 9.32 (br. s, 1 H, NH), 9.51 (br. s, 1 H, NH) ppm. ¹³C NMR ([D₆]acetone): δ = 14.7 (3 × SiCH), 18.4 (6 × CH₃), 25.6 (CH₂, Pro), 26.0 (CH₂, k-Arg), 27.9 (CH₂, Pro), 28.6 (3 × CH₃, Boc or CO₂tBu), 28.8 (3 × CH₃, Boc or CO₂tBu), 30.7 (CH₂, k-Arg), 37.7 (CH₂, Phe), 43.4 (CH₂N, Dpr), 45.2 (CH₂N, k-Arg), 48.2 (CH₂N, Pro), 50.6 (CH_α, Dpr), 55.4 (CH_α, k-Arg), 55.9 (CH_α, Phe), 60.9 (CH_α, Pro), 67.4 (CH₂, Z), 69.5 (CH₂, Z), 79.4 [OC(CH₃)₃], 80.5 [OC(CH₃)₃], 120.1 (CH_α=CH, V-ΔTyr), 120.9 (2 × CH_{ar}), 127.5, 128.6, 128.8, 129.1, 129.4, 130.6 (15 × CH_{ar}), 130.8 (2 × C_{ipso}), 132.4 (2 × CH_{ar}), 135.4 (CH_δ=C, V-ΔTyr), 136.4 (C_{ipso}, Phe), 138.1 (C_{ipso}, Z), 138.4 (C_{ipso}, Z), 144.3 (CH_β=CH, V-ΔTyr), 156.6 (NHCOO, Z), 157.2 (CH=C_γ, V-ΔTyr), 157.5 (NHCOO, Z), 161.5 (NHCOO, Boc), 161.9 (NHCHO), 164.6 [NC(=NH)N], 166.7 (2 × NHCO, Phe + Dpr), 169.9 (NHCO, k-Arg), 170.0 (NHCO, Pro), 172.6 (CO₂tBu), 196.2 (CO, k-Arg) ppm. IR (KBr): ν̄ = 689, 914, 1172, 1268, 1368, 1508, 1600, 1721, 2869, 2947, 3291 cm⁻¹. ESI-MS: *m/z* = 1367 [M + K]⁺, 1351 [M + Na]⁺, 1329 [M + H]⁺. HR-MS: *m/z* calcd. for [C₇₀H₉₃N₉O₁₅Si + H]⁺ 1328.6639; found 1328.6586 (δ = –4.0 ppm). C₇₀H₉₃N₉O₁₅Si (1328.63): calcd. C 63.28, H 7.06, N 9.49; found C 63.21, H 7.15, N 9.44.

N^α-Boc-N^δ,N^ε-Z₂-k-Arg-D-Phe-V-ΔTyr-N^α-CHO-Dpr-Pro-OAllyl (34): Product 34 was synthesised by the General Procedure for tandem oxidation/coupling (reaction time 18 h) from the α-keto cyanophosphorane 19 (191 mg, 0.23 mmol, 2.1 equiv.) and amine 31 (65 mg, 0.107 mmol, 1 equiv.). The crude product (231 mg) was purified immediately by flash chromatography with a gradient of CH₂Cl₂/MeOH (100:0 to 98:2) to provide the pure linear pentapeptide 34 as a yellow-orange foam (72 mg, 0.062 mmol, 58%). *R*_f = 0.20 (CH₂Cl₂/MeOH, 95:5); m.p. 96–98 °C. [α]_D²⁰ = –12.7 (*c* = 1.00, CHCl₃). ¹H NMR ([D₆]acetone): δ = 1.24 (s, 9 H, 3 × CH₃), 1.50–1.72 (m, 6 H, CH₂, Pro + k-Arg), 1.75–1.89 (m, 2 H, CH₂, Pro + k-Arg), 2.70–3.00 (br. s, 2 H, CH₂, Phe + OH), 3.08 (m, 1 H, CH₂, Phe), 3.26 (m, 2 H, CH₂N, Dpr), 3.65 (m, 2 H, CH₂N, Pro), 3.85 (m, 2 H, CH₂N, k-Arg), 4.33 (m, 1 H, CH_α, Pro), 4.46 (m, 2 H, CH₂, Allyl), 4.81 (m, 1 H, CH_α, Phe), 4.90 (m, 1 H, CH_α, k-Arg), 4.95–5.02 (m, 3 H, CH_α, Dpr + CH₂, Z), 5.06 (m, 1 H, CH₂=CH, Allyl), 5.13–5.22 (m, 3 H, CH₂=CH, Allyl + CH₂, Z), 5.78 (m, 1 H, CH₂=CH, Allyl), 5.91 (d, *J* = 15.2 Hz, 1 H, CH_α=CH V-ΔTyr), 6.22 (br. s, 1 H, NH), 6.60 (s, 1 H, CH_δ=C V-ΔTyr), 6.67 (d, *J* = 8.8 Hz, 2 H, 2 × CH_{ar}), 6.72 (br. s, 1 H, NH), 7.10–7.35 (m, 19 H, 17 × CH_{ar} + CH_β=CH V-ΔTyr + NH), 7.98 (br. s, 1 H, NH), 8.03 (s, 1 H, NCHO), 8.64 (br. s, 1 H, NH), 9.05–9.40 (m, 2 H, 2 × NH) ppm. ¹³C NMR ([D₆]acetone): δ = 25.5 (2 × CH₂, Pro + k-Arg), 26.2 (CH₂, Pro or k-Arg), 26.3 (CH₂, Pro or k-Arg), 28.6 (3 × CH₃, Boc), 38.0 (CH₂, Phe), 42.0 (CH₂N, Dpr), 45.1 (CH₂N, k-Arg), 47.9 (CH₂N, Pro), 50.4 (CH_α, Dpr), 56.1 (CH_α, Phe), 59.8 (2 × CH_α, Pro + k-Arg), 66.0 (CH₂, Allyl), 67.3 (CH₂, Z), 69.4 (CH₂, Z), 79.5 [OC(CH₃)₃], 116.4 (2 × CH_{ar}), 118.3 (CH₂=CH, Allyl), 121.6 (CH_α=CH, V-ΔTyr), 127.4 (C_{ipso}), 127.7, 128.5, 128.8, 129.2, 129.8, 130.0 (17 × CH_{ar}), 130.3 (C_{ipso}), 131.8 (CH=CH₂, Allyl), 135.3 (CH_δ=C, V-ΔTyr), 136.4 (2 × C_{ipso}, Phe + Z), 138.4

(C_{ipso} , Z), 141.9 ($CH_{\beta}=\text{CH}$, V- Δ Tyr), 156.6 ($2 \times \text{NHCOO}$, Z), 157.0 ($\text{CH}=\text{C}_{\gamma}$, V- Δ Tyr), 158.9 (NHCOO, Boc), 162.4 (NHCHO), 164.5 [NC(=NH)N], 167.5 (NHCO, Phe), 167.6 (NHCO, k-Arg), 169.5 (NHCO, V- Δ Tyr), 170.2 (NHCO, Dpr), 172.3 (CO_2Allyl), 197.2 (CO, k-Arg) ppm. IR (KBr): $\tilde{\nu} = 1097, 1175, 1447, 1512, 1610, 1652, 1720, 2928, 3390 \text{ cm}^{-1}$. ESI-MS: $m/z = 1188$ [$\text{M} + \text{Na}$] $^{+}$, 1156 [$\text{M} + \text{H}$] $^{+}$. HR-MS: m/z calcd. for [$\text{C}_{60}\text{H}_{69}\text{N}_9\text{O}_{15} + \text{H}$] $^{+}$ 1156.4991; found 1156.5043 (+4.5 ppm). $\text{C}_{60}\text{H}_{69}\text{N}_9\text{O}_{15}$ (1156.25): calcd. C 62.33, H 6.01, N 10.90; found C 61.70, H 6.25, N 10.67.

Cyclo[N^{α} -CHO-Dpr-Pro- N^{δ} , N^{ϵ} -Z $_2$ -k-Arg-D-Phe-V- Δ Tyr(OTIPS)] (37): Protected pentapeptide 33 (160 mg, 0.12 mmol, 1 equiv.) was treated at 0 °C with a solution of $\text{CH}_2\text{Cl}_2/\text{TFA}$ (1:1; 6 mL) for 1 h, and the solvents were then evaporated under reduced pressure. The residue was dissolved in and concentrated from CH_2Cl_2 ($3 \times 30 \text{ mL}$) to furnish the crude trifluoroacetate salt. This residue was dissolved in CH_2Cl_2 (20 mL) and washed with a solution of NaHCO_3 (pH 8; 5 mL) and then with water (5 mL). The organic phase was dried with MgSO_4 and concentrated under reduced pressure to afford the crude N,C -deprotected pentapeptide (142 mg, 0.12 mmol, quant.). This material was engaged in macrocyclisation reactions without further purification. A sample of crude deprotected pentapeptide (40 mg, 0.034 mmol, 1 equiv.) was dissolved in a mixture of $\text{CH}_2\text{Cl}_2/\text{DMF}$ (2:1; 6 mL; 0.005 M) at 0 °C under argon. TBTU (22 mg, 0.068 mmol, 2 equiv.) and HOBt (1 mg, 0.007 mmol, 0.2 equiv.) were added successively, and the solution was stirred briskly and allowed to warm to room temp. over 24 h. The solvent was evaporated under reduced pressure to afford a crude residue (53 mg), which was purified by flash chromatography with a gradient of $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (100:0 to 9:1) to provide the pure macrocycle 37 as a pale yellow foam (20 mg, 0.017 mmol, 51%). $R_f = 0.27$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 95:5). $[\alpha]_D^{25} = +44.0$ ($c = 0.80$, CHCl_3). ^1H NMR ($[\text{D}_6]$ acetone): $\delta = 1.10$ (d, $J = 7.3 \text{ Hz}$, 18 H, $6 \times \text{CH}_3$), 1.29 (m, 3 H, $3 \times \text{SiCH}$), 1.55–2.15 (m, 8 H, CH_2 , Pro + k-Arg), 2.73 (m, 1 H, CH_2N , Dpr), 3.11 (dd, $J = 9.5, 13.9 \text{ Hz}$, 1 H, CH_2 , Phe), 3.28 (dd, $J = 5.8, 13.9 \text{ Hz}$, 1 H, CH_2 , Phe), 3.39 (dd, $J = 6.5, 16.5 \text{ Hz}$, 1 H, CH_2N , Pro), 3.56 (dd, $J = 7.0, 16.5 \text{ Hz}$, 1 H, CH_2N , Pro), 4.00 (m, 2 H, CH_2N , k-Arg), 4.23 (t, $J = 6.9 \text{ Hz}$, 1 H, CH_2N , Dpr), 4.55 (dd, $J = 4.9, 8.4 \text{ Hz}$, 1 H, CH_{α} , Pro), 4.78 (dd, $J = 6.5, 10.3 \text{ Hz}$, 1 H, CH_{α} , Dpr), 4.84 (dd, $J = 5.9, 9.7 \text{ Hz}$, 1 H, CH_{α} , Phe), 5.12 (m, 3 H, CH_{α} , k-Arg + CH_2 , Z), 5.32 (m, 3 H, CH_2 , Z + NH), 5.95 (d, $J = 15.0 \text{ Hz}$, 1 H, $\text{CH}_{\alpha}=\text{CH}$ V- Δ Tyr), 6.84 (s, 1 H, $\text{CH}_2=\text{C}$ V- Δ Tyr), 6.86 (d, $J = 8.8 \text{ Hz}$, 2 H, $2 \times \text{CH}_{\text{ar}}$), 7.14–7.52 (m, 19 H, $17 \times \text{CH}_{\text{ar}}$ + $\text{CH}_{\beta}=\text{CH}$ V- Δ Tyr + NH), 7.86 (br. s, 1 H, NH), 8.04 (br. s, 1 H, NH), 8.10 (s, 1 H, NCHO), 8.68 (s, 1 H, NH), 9.30 (br. s, 1 H, NH), 9.49 (br. s, 1 H, NH) ppm. ^{13}C NMR ($[\text{D}_6]$ acetone): $\delta = 13.4$ ($3 \times \text{SiCH}$), 18.3 ($6 \times \text{CH}_3$), 25.5 (CH_2 , Pro), 26.0 (CH_2 , k-Arg), 28.5 (CH_2 , Pro), 32.6 (CH_2 , k-Arg), 38.7 (CH_2 , Phe), 41.6 (CH_2N , Dpr), 44.7 (CH_2N , k-Arg), 48.6 (CH_2N , Pro), 49.1 (CH_{α} , Dpr), 56.1 (CH_{α} , Phe), 59.7 (CH_{α} , k-Arg), 60.0 (CH_{α} , Pro), 67.2 (CH_2 , Z), 69.6 (CH_2 , Z), 120.7 ($\text{CH}_{\alpha}=\text{CH}$, V- Δ Tyr + $2 \times \text{CH}_{\text{ar}}$), 127.5, 128.5, 128.8, 129.0, 129.2, 129.6, 130.1 ($13 \times \text{CH}_{\text{ar}}$), 130.6 ($2 \times \text{C}_{ipso}$), 131.6 (CH_{ar}), 132.0 ($2 \times \text{CH}_{\text{ar}}$), 133.4 (CH_{ar}), 135.4 ($\text{CH}_{\delta}=\text{C}$, V- Δ Tyr), 136.3 (C_{ipso} , Phe), 138.0 (C_{ipso} , Z), 138.5 (C_{ipso} , Z), 142.0 ($\text{CH}_{\beta}=\text{CH}$, V- Δ Tyr), 156.6 (NHCOO, Z), 157.3 (NHCOO, Z), 160.0 ($\text{CH}=\text{C}_{\gamma}$, V- Δ Tyr), 161.1 (NHCHO), 161.5 [NC(=NH)N], 164.4 (NHCO, Phe), 166.1 (NHCO, Dpr), 169.5 (NHCO, V- Δ Tyr), 170.1 (NHCO, Pro), 174.5 (NHCO, k-Arg), 196.1 (CO, k-Arg) ppm. ESI-MS: $m/z = 1186$ [$\text{M} + \text{H} + \text{MeOH}$] $^{+}$, 1154 [$\text{M} + \text{H}$] $^{+}$. HR-MS: m/z calcd. for [$\text{C}_{61}\text{H}_{75}\text{N}_9\text{O}_{12}\text{Si} + \text{H}$] $^{+}$ 1154.5383; found 1154.5377 ($\delta = -0.5 \text{ ppm}$).

Cyclo[N^{α} -CHO-Dpr-Pro-k-Arg-D-Phe-V- Δ Tyr], Cyclotheonamide C (3): The α -keto amide macrocycle 37 (29 mg, 0.025 mmol) was transferred to a Teflon[®] vessel and treated with HF-pyridine

(1.5 mL) and anisole (0.22 mL). The reaction mixture was stirred at room temp. for 12 h, and argon was then bubbled through the mixture for 3 h. Water (10 mL) was added, and the solution was concentrated under reduced pressure. Preparative HPLC purification (XTerra prep MS C_{18} , 10 μm , $10 \times 150 \text{ mm}$, $\text{CH}_3\text{CN}/\text{H}_2\text{O} + 0.1\% \text{ TFA}$, 25:75, flow 1 mL min^{-1}), followed by lyophilisation and filtration through a SPE cartridge (Waters OASIS HLB 3cc) with MeOH as eluent, afforded 3 as yellow foam (8.4 mg, 0.012 mmol, 46%). ^1H NMR (CD_3OD): $\delta = 1.45\text{--}1.78$ (m, 3 H), 1.86–2.10 (m, 3 H), 2.14–2.35 (m, 2 H), 2.84 (m, 1 H, Dpr β), 3.04 (dd, $J = 9.1, 13.0 \text{ Hz}$, 1 H, Phe β), 3.08–3.20 (m, 2 H, k-Arg ϵ), 3.23–3.42 (m, 1 H, Phe β), 3.56 (m, 1 H, Pro δ), 3.78 (m, 1 H, Pro δ), 4.15 (m, 1 H, k-Arg β), 4.29 (m, 1 H, Dpr β), 4.53 (m, 1 H, Pro α), 4.75 (m, 1 H, Dpr α), 5.03 (m, 1 H, Phe α), 6.21 and 6.15 (d, $J = 15.8 \text{ Hz}$, 1 H, V- Δ Tyr α), 6.75 and 6.82 (d, $J = 8.6 \text{ Hz}$, 2 H, V- Δ Tyr), 6.91 (s, 1 H, V- Δ Tyr δ), 7.13–7.38 (m, 6 H), 7.41 and 7.45 (d, $J = 8.7 \text{ Hz}$, 2 H, V- Δ Tyr), 8.06 and 8.07 (s, 1 H, CHO) ppm. ^{13}C NMR (CD_3OD): $\delta = 23.5$ (CH_2), 25.6 (CH_2), 25.7 (CH_2), 30.5 (CH_2), 40.8 ($2 \times \text{CH}_2$), 41.8 (CH_2), 49.5 (CH_2), 49.8 (CH), 54.4 (CH), 55.5 (CH), 61.6 (CH), 116.2 ($2 \times \text{CH}$), 121.8 (CH), 126.5 (C), 127.4 (CH), 129.1 ($2 \times \text{CH}$), 129.9 (C), 130.6 ($2 \times \text{CH}$), 130.7 ($2 \times \text{CH}$), 136.9 (CH), 137.0 (C), 140.5 (CH), 158.2 (C), 159.4 (C), 162.9 (CH), 168.4 (C), 171.2 (C), 171.6 (C), 171.9 (C), 176.1 (C) ppm. (^{13}C chemical shifts were determined from HMQC and HMBC experiments). ESI-MS: $m/z = 730$ [$\text{M} + \text{H}$] $^{+}$, 748 [$\text{M} + \text{H} + \text{H}_2\text{O}$] $^{+}$. HR-MS: m/z calcd. for [$\text{C}_{36}\text{H}_{44}\text{N}_9\text{O}_8 + \text{H}_2\text{O}$] $^{+}$ 748.3418; found 748.3435 (+2.2 ppm).

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra for all significant new compounds; ^1H NMR and HR-MS spectra for compound 3.

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