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

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Respectfully dedicated to Professor Jean-Claude Gramain

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The total synthesis of cyclotheonamide C (**3**), a macrocyclic pentapeptide incorporating an α-keto homoarginine (k-Arg) and a vinylogous dehydrotyrosine (V-ΔTyr) 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-ΔTyr *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 CtE_5 (**9**) or being fully conjugated due to an extra double bond (V-ΔTyr) in the case of CtC (**3**). These metabolites are potent inhibitors of serine proteases such as thrombin and trypsin, exhibiting IC_{50} 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, inspiring 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-ΔTyr feature present in CtC (**3**), and we were drawn into a total synthesis venture targeting this member of the Ct family.

1, CtA : R^1 = Bn, R^2 = CHO
2, CtB : R^1 = Bn, R^2 = $COCH_3$
3, CtC : R^1 = Bn, R^2 = CHO, **V-ΔTyr**
4, CtD : R^1 = *i*Pr, R^2 = CHO
5, CtE_1 : R^1 = *i*Bu, R^2 =AlaCOBn
6, CtE_2 : R^1 = *i*Bu, R^2 = AlaCOPh
7, CtE_3 : R^1 = *i*Bu, R^2 = AlaCO*i*Pr
8, CtE_4 : R^1 = *i*Bu, R^2 = AlaCO*i*Bu
9, CtE_5 : R^1 = *i*Bu, R^2 = AlaCO*i*Bu

R^3 = H, except CtE_5: R^3 = OH

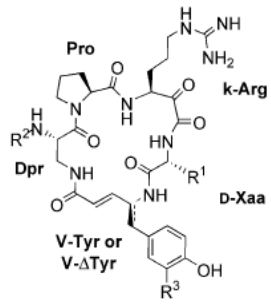

Figure 1. The cyclotheonamide (Ct) family.

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]

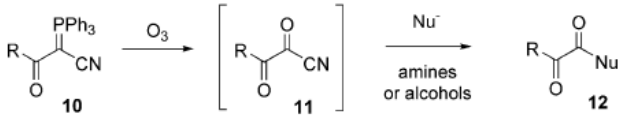


Figure 2. Wasserman's one-pot α-keto cyanophosphorane approach for the synthesis of α-keto amides and esters.

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 CtE_2 and CtE_3.[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 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).

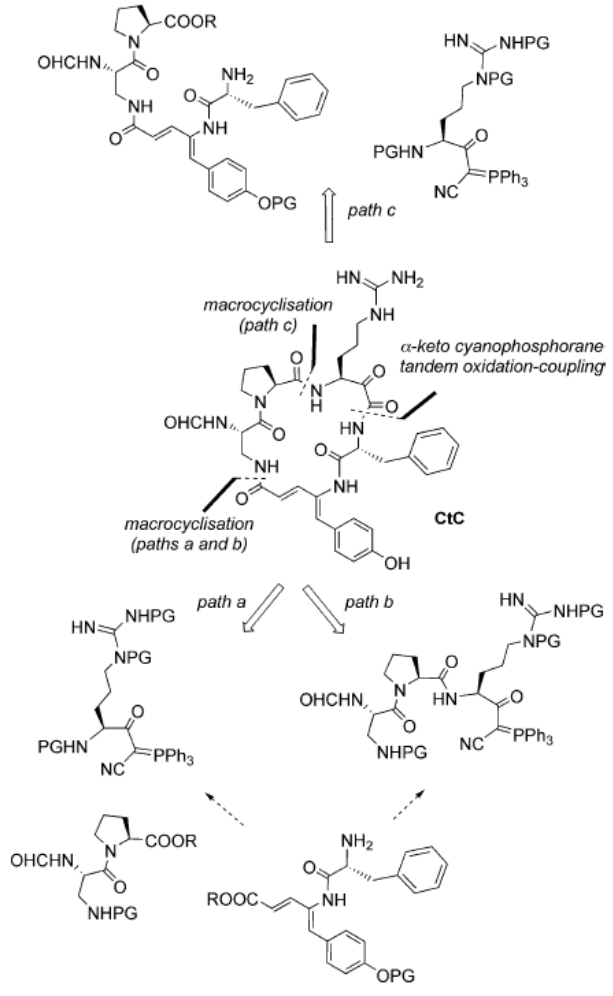
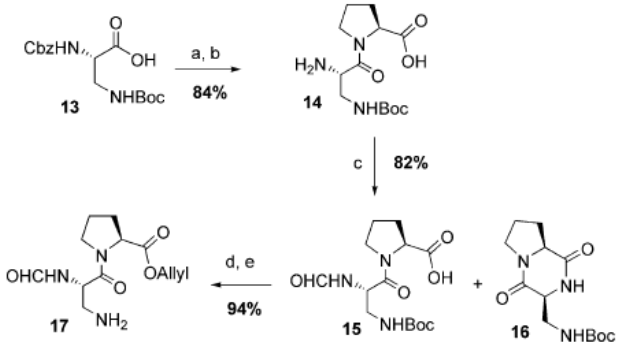


Figure 3. Retrosynthetic analysis of CtC, identifying α-keto cyanophosphorane and amine intermediates, providing three assembly combinations leading to two macrocyclisation sites.

Results and Discussion

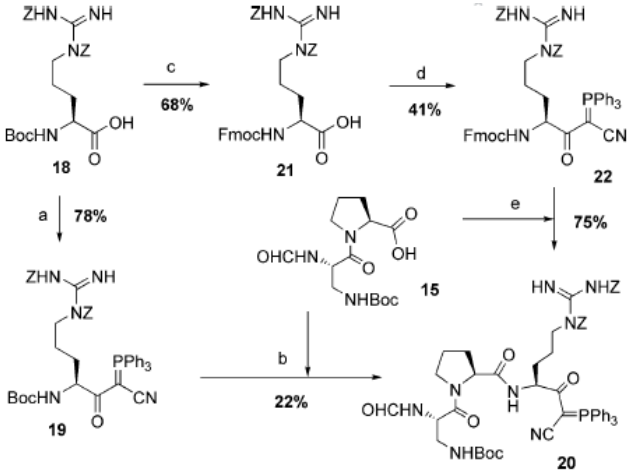
We began with the construction of two dipeptide fragments containing Pro and the nonproteinogenic Dpr amino acid (Scheme 1). General approaches to the synthesis of α,β-diamino acids were reviewed recently.[14] The orthogonally protected derivative **13** was prepared by Izumiya's procedure[15] and was 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, CH_2Cl_2, 0 °C to room temp., 12 h; b) H_2 (3.4 atm), Pd/C, MeOH, 2 h, 84% (2 steps); c) HCO_2H/Ac_2O, THF, 8–10 °C, 12 h, 82%; d) EDCI, DMAP, allyl alcohol, CH_2Cl_2, 0 °C to room temp., 5 h, then iPr$_2$NEt, THF, 0 °C, 10 min; e) TFA/CH_2Cl_2 (1:1), 1 h at 0 °C, then workup with iPr$_2$NEt, 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.

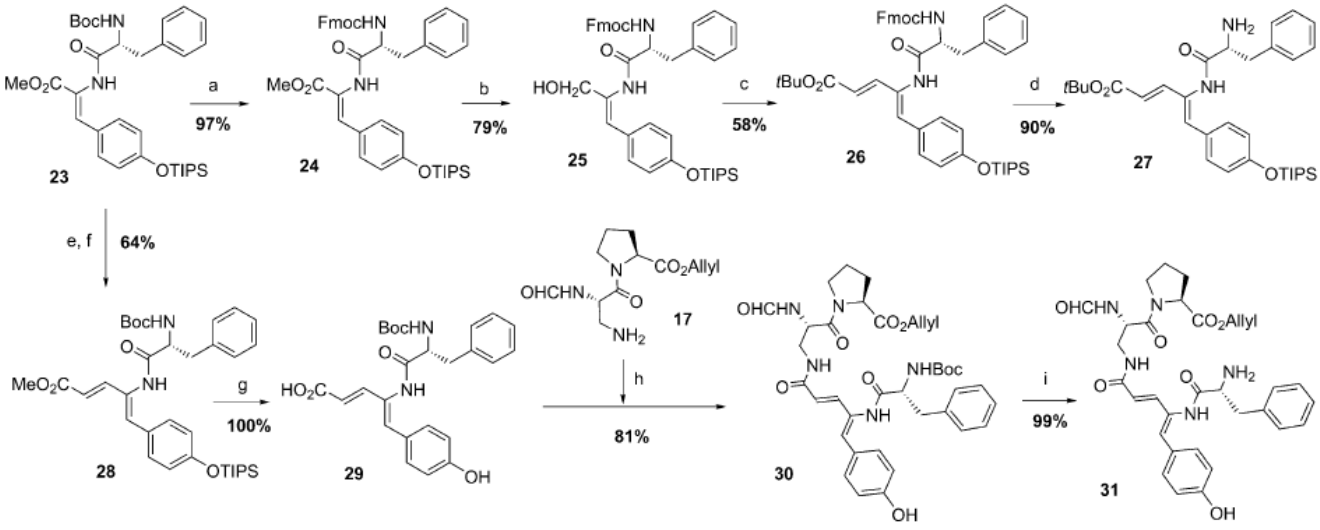
The target α-keto cyanophosphoranes were synthesised from the protected arginine derivative N^{α}-Boc-N^{δ},N^{ω}-Z_2-Arg (**18**), prepared by Ottenheijm's procedure[16] (Scheme 2). One-step preparation of α-keto cyanophos-

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}-Z_2-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]



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) CH_3CN/$NHEt_2$, 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.

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



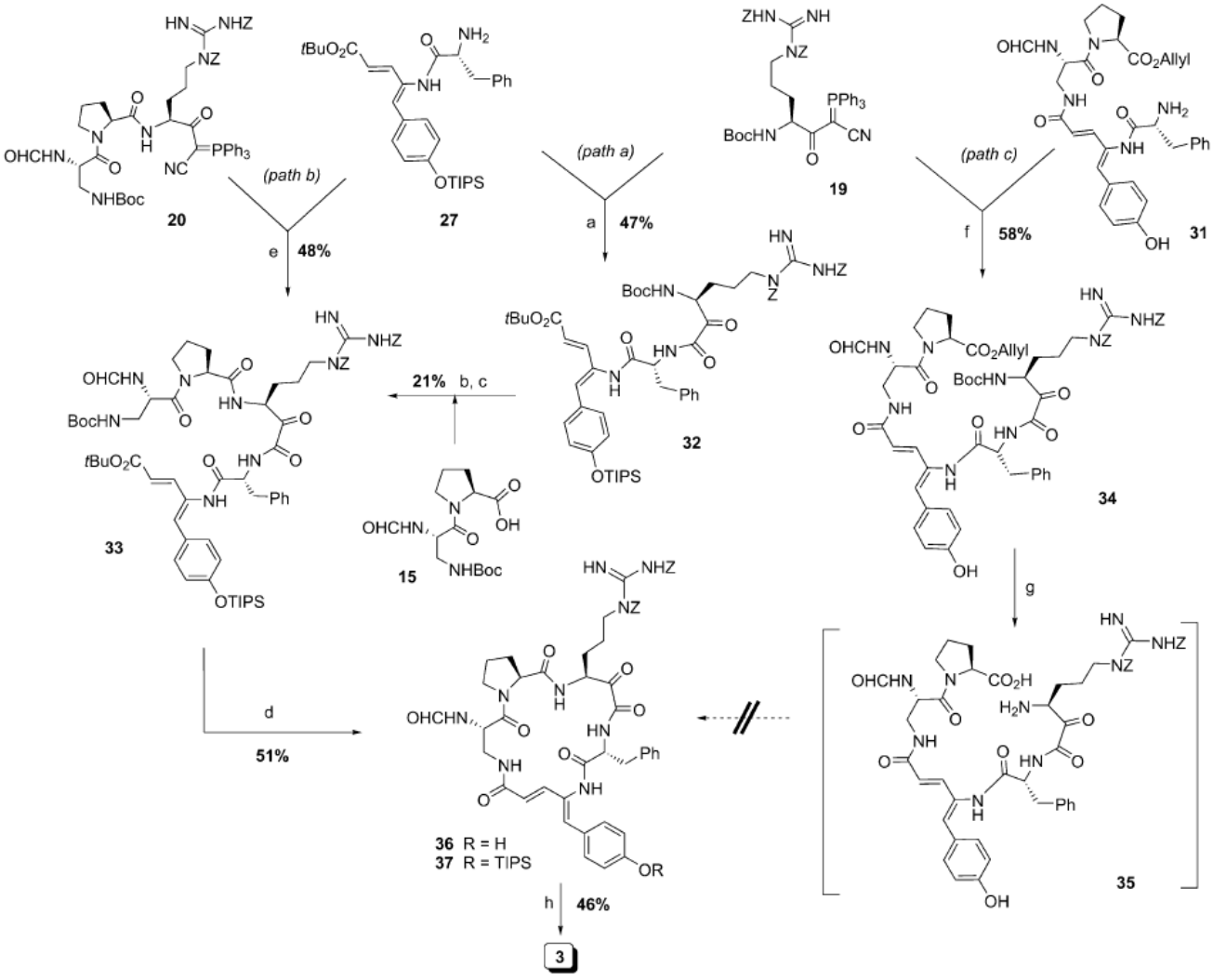
Scheme 3. Preparation of the nucleophilic components **27** and **31**. Reagents and conditions: a) TFA/CH_2Cl_2, 1 h at 0 °C, then FmocCl, Na_2CO_3 dioxane/water (3:2), 0 °C to room temp., 12 h, 97% (2 steps); b) $LiAlH_4$, THF, 0 °C, 1 h, 79%; c) $Ph_3P{=}CHCO_2Me$, MnO_2, CH_2Cl_2, 40 °C, 36 h, 58%; d) Et_2NH/CH_3CN, 1:2, 0 °C to room temp., 1 h, 90%; e) $LiAlH_4$, THF, 0 °C, 1 h, 86%; f) $Ph_3P{=}CHCO_2tBu$, MnO_2, CH_2Cl_2, 40 °C, 36 h, 74%; g) NaOH (1 M); 100%; h) DPPCl, **17**, iPr_2NEt, 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-ΔTyr 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 DPPCl, 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, DMF/CH_2Cl_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 $Pd(PPh_3)_4$, 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-ΔTyr 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-ΔTyr 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, DPPCl, 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-ΔTyr 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 μm, 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 μL, 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 × 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 H_2 (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/H_2O, 7:3); m.p. 116–118 °C. $[\alpha]_D^{20}$ = –5.0 (*c* = 1.10, NaOH 1 M). ^{1}H NMR (D_2O): 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. ^{13}C NMR (D_2O): δ = 22.0 (CH_2), 27.5 (3 × CH_3), 29.2 (CH_2), 40.0 (CH_2), 47.3 (CH_2), 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 $[M + H - H_2O]^+$, 228 $[M + H - t\text{BuO}]^+$, 184 $[M + H - H_2O - Boc]^+$.

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/H_2O, 7:3); m.p. 178–180 °C. ^{1}H NMR ([D_6]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. ^{13}C NMR ([D_6]DMSO): δ = 24.3 (CH_2), 28.1 (3 × CH_3), 28.7 (CH_2), 41.6 (CH_2), 46.5 (CH_2), 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 $[M + H]^+$. $C_{14}H_{23}N_3O_6$ (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). ^{1}H NMR ($CDCl_3$): 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. ^{13}C NMR ($CDCl_3$): δ = 22.8 (CH_2), 27.9 (CH_2), 28.3 (3 × CH_3), 39.6 (CH_2), 45.4 (CH_2), 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 CH_2Cl_2 (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 (97:3) 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. $[\alpha]_D^{20}$ = –56.2 (*c* = 1.01, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.35 (s, 9 H, 3 × CH_3), 1.91–2.00 (m, 3 H, CH_2, Pro), 2.19–2.21 (m, 1 H, CH_2, Pro), 3.23 (dd, *J* = 7.0, 14.0 Hz, 1 H, CH_2N, Dpr), 3.45 (m, 1 H, CH_2N, Dpr), 3.72 (t, *J* = 6.0 Hz, 2 H, CH_2N, Pro), 4.46 (dd, *J* = 3.8, 9.0 Hz, 1 H, CH_α, Pro), 4.55 (t, *J* = 6.0 Hz, 2 H, CH_2, Allyl), 4.95 (q, *J* = 6.5 Hz, 1 H, CH_α, Dpr), 5.18 (dd, *J* = 1.3, 10.5 Hz, 1 H, C*H*$_2$=CH, Allyl), 5.27 (dd, *J* = 1.3, 17.2 Hz, 1 H, C*H*$_2$=CH, Allyl), 5.35 (t, *J* = 6.3 Hz, 1 H, NH), 5.85 (m, 1 H, CH$_2$=C*H*, Allyl), 7.27 (d, *J* = 8.4 Hz, 1 H, NH), 8.10 (s, 1 H, NCHO) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.8 (CH_2, Pro), 28.2 (3 × CH_3, Boc), 28.8 (CH_2, Pro), 42.1 (CH_2N, Dpr), 47.1 (CH_2N, Pro), 49.4 (CH_α, Dpr), 59.0 (CH_α, Pro), 65.7 (CH_2, Allyl), 79.3 [*O*C(CH$_3$)$_3$], 118.7 (CH_2=), 131.5 (CH=), 156.0 (NHCOO), 161.4 (NHCHO), 169.0 (NHCO, Dpr), 171.3 (CO_2Allyl) ppm.

The dipeptide N^{α}-CHO-N^{β}-Boc-Dpr-Pro-OAllyl (40 mg, 0.11 mmol) was treated with a solution of CH_2Cl_2/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 CH_2Cl_2 (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 $[M + H - H_2O]^+$.

General Procedure for Coupling with (Triphenylphosphoranylidene)-acetonitrile: Carboxylic acid (1 mmol) was dissolved under argon in CH_2Cl_2 (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 CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure to afford the crude residue, which was purified by flash chromatography.

N^{α}-Boc-N^{δ},N^{ε}-Z_2-Arg-C(PPh$_3$)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^{δ},N^{ε}-Z_2-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. ^{1}H NMR ($CDCl_3$): 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. ^{13}C NMR ($CDCl_3$): δ = 24.9 (CH_2), 28.4 (3 × CH_3), 30.4 (CH_2), 44.7 (CH_2), 47.3 (d, *J* = 130 Hz, C), 56.0 (CH), 67.1 (CH_2), 68.8 (CH_2), 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}. $C_{47}H_{48}N_5O_7P$ (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}-Z_2-Arg (21): The known N^{α}-Boc-N^{δ},N^{ε}-Z_2-Arg (**18**,[16] 300 mg, 0.55 mmol, 1 equiv.) was treated at 0 °C with a solution of CH_2Cl_2/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, $CHCl_3$). ^{1}H 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. ^{13}C 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 $[M + H]^+$. $C_{37}H_{36}N_4O_8$ (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}-Z_2-Arg-C(PPh$_3$)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, $CHCl_3$). ^{1}H 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. ^{13}C 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 $[M + H - BnOH]^+$. $C_{57}H_{50}N_5O_7P$ (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}-Z_2-Arg-C(PPh$_3$)CN (20): N^{α}-Fmoc-N^{δ},N^{ε}-Z_2-Arg-C(PPh$_3$)CN (**22**, 90 mg, 0.095 mmol) was treated at 0 °C with $CH_3CN/NHEt_2$ (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, $CHCl_3$). ^{1}H 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, $^{\beta}$NH, Dpr), 6.60 (d, J = 7.0 Hz, 1 H, $^{\alpha}$NH, 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. ^{13}C 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 [O*C*(CH_3)$_3$], 120.3 (d, J = 15 Hz, CN), 122.5 (d, J = 93 Hz, 3 × C_{ipso}-P), 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 [NC(=NH)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 $[C_{56}H_{61}N_8O_{10}P, H]^+$ 1037.4327; found 1037.4294 (–3.1 ppm). $C_{56}H_{61}N_8O_{10}P$ (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 C_{18} column with a mobile phase gradient from CH_3CN/H_2O (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 CH_2Cl_2/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, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 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. ^{13}C NMR ($CDCl_3$): δ = 12.7 (3 × CH), 17.9 (6 × CH_3), 37.8 (CH_2), 47.0 (CH), 52.5 (CH_3), 56.2 (CH), 67.2 (CH_2), 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 $[C_{43}H_{50}N_2O_6Si + H]^+$ 719.3516; found 719.3497 (δ = –2.7 ppm). $C_{43}H_{50}N_2O_6Si$ (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, $MgSO_4$ 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 MnO_2 and Phosphorane: Allylic alcohol (0.35 mmol, 1 equiv.) was dissolved under argon in CH_2Cl_2 (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 CH_2Cl_2 (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)-CH_2OH (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, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 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. ^{13}C NMR ($CDCl_3$): δ = 12.6 (3 × CH), 17.9 (6 × CH_3), 38.5 (CH_2), 47.1 (CH), 57.1 (CH), 64.3 (CH_2), 67.2 (CH_2), 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 $[M + H - H_2O]^+$. HR-MS: *m*/*z* calcd. for $[C_{42}H_{50}N_2O_5Si + H]^+$ 691.3567; found 691.3570 (+1.3 ppm). $C_{42}H_{50}N_2O_5Si$ (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)-O*t*Bu (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, $CHCl_3$). ^{1}H NMR ([D$_6$]acetone): δ = 1.10 (d, *J* = 6.8 Hz, 18 H, 6 × CH_3), 1.22 (hept, *J* = 6.8 Hz, 3 H, 3 × SiCH), 1.51 (s, 9 H, 3 × CH_3), 3.14 (m, 1 H, CH_2Ph), 3.39 (m, 1 H, CH_2Ph), 4.22 (m, 2 H, CH_2, 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_δ=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. ^{13}C NMR ($CDCl_3$): δ = 12.7 (3 × SiCH), 17.9 (6 × CH_3), 28.1 [OC(CH_3)$_3$], 37.7 (CH_2Ph), 47.1 (CH), 56.4 (CH_α), 67.0 (CH_2), 80.3 [O*C*(CH_3)$_3$], 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_δ=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 (CO_2 *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 $[C_{48}H_{58}N_2O_6Si + Na]^+$ 809.3962; found 809.3978 (+2.0 ppm). $C_{48}H_{58}N_2O_6Si$ (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)-O*t*Bu (27): Protected vinylogous dipeptide **26** (50 mg, 0.063 mmol, 1 equiv.) was treated at 0 °C with CH_3CN/$NHEt_2$ (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 CH_2Cl_2 (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, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.01 (d, *J* = 7.2 Hz, 18 H, 6 × CH_3), 1.17 (hept, *J* = 7.2, Hz, 3 H, 3 × CHSi), 1.43 (s, 9 H, 3 × CH_3), 1.49 (br. s, 2 H, NH_2), 2.85 (dd, *J* = 8.8, 13.7 Hz, 1 H, CH_2Ph), 3.23 (dd, *J* = 4.0, 13.7 Hz, 1 H, CH_2Ph), 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_δ=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. ^{13}C NMR ($CDCl_3$): δ = 12.7 (3 × SiCH), 18.0 (6 × CH_3), 28.3 (3 × CH_3), 40.4 (CH_2Ph), 56.6 (CH_α), 80.4 [O*C*(CH_3)$_3$], 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_δ=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 (CO_2*t*Bu) ppm. ESI-MS: *m*/*z* = 565 $[M + H]^+$, 509 $[M + H - C_4H_8]^+$. (–)ESI-MS: *m*/*z* = 563 $[M - H]^-$. HR-MS: *m*/*z* calcd. for $[C_{33}H_{48}N_2O_4Si + Na]^+$ 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**,[19] 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-ΔTyr(OTIPS)-CH_2OH 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, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 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. ^{13}C NMR ($CDCl_3$): δ = 12.6 (3 × CH), 17.9 (6 × CH_3), 28.2 (3 × CH_3), 38.3 (CH_2), 56.6 (C), 64.2 (CH_2), 80.6 (C), 116.8 (CH), 119.2 (2 × CH), 126.8 (C), 127.2 (CH), 128.9, 129.3, 129.4 (6 × CH), 133.9 (C), 136.1 (C), 155.2 (C), 155.4 (C), 170.3 (C) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 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-ΔTyr(OTIPS)-CH_2OH (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, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.02 (d, J = 7.2 Hz, 18 H, 6 × CH_3), 1.16 (hept, J = 7.2, Hz, 3 H, 3 × SiCH), 1.34 (s, 9 H, 3 × CH_3), 3.00 (dd, J = 7.1, 13.8 Hz, 1 H, CH_2Ph), 3.13 (dd, J = 7.1, 13.8 Hz, 1 H, CH_2Ph), 3.64 (s, 3 H, OCH_3), 4.51 (q, J = 7.1 Hz, 1 H, CH_α), 5.08 (d, J = 8.4 Hz, 1 H, NH), 5.59 (d, J = 15.4 Hz, 1 H, CH_α=CH V-ΔTyr), 6.53 (s, 1 H, CH_δ=C V-ΔTyr), 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 × CH_{ar} + CH_β=CH V-ΔTyr), 7.47 (s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.6 (3 × SiCH), 17.9 (6 × CH_3), 28.3 (3 × CH_3), 37.5 (CH_2Ph), 51.4 (OCH_3), 56.0 (CH_α), 80.6 [$OC(CH_3)_3$], 116.8 (CH_α=CH, V-ΔTyr), 120.1 (2 × CH_{ar}), 127.0 (CH_{ar}), 127.1 (C_{ipso}), 128.6 (C_{ipso}), 128.8, 129.4, 131.2 (6 × CH_{ar}), 135.0 (CH_δ=C, V-ΔTyr), 136.5 (C_{ipso}), 144.0 (CH_β=CH, V-ΔTyr), 155.9 (CH=C_γ, V-ΔTyr), 157.0 (NHCOO), 167.3 (NHCO), 170.4 (CO_2Me) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 760, 1235, 1506, 1532, 1590, 1675, 1700, 2880, 2950, 3300 cm^{-1}. HR-MS: *m/z* calcd. for $[C_{35}H_{50}N_2O_6Si + Na]^+$ 645.3336; found 645.3343 (+1.2 ppm). $C_{35}H_{50}N_2O_6Si$ (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-ΔTyr-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 × 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). ^{1}H NMR ([D$_6$]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. ^{13}C NMR ([D$_6$]acetone): δ = 28.7 (3 × CH_3), 38.3 (CH_2), 57.9 (CH), 79.8 (C), 116.4 (CH), 117.6 (2 × CH), 127.3 (C), 127.4 (CH), 129.0 (2 × CH), 129.3 (C), 129.6 (2 × CH), 132.1 (2 × 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-ΔTyr-N^α-CHO-Dpr-Pro-OAllyl (30):** A solution of carboxylic acid **29** (280 mg, 0.62 mmol, 1 equiv.) in THF (3 × mL) was cooled to –20 °C under argon, and diisopropylethylamine (119 µL, 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 × 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 $NaHCO_3$ solution (5 × 15 mL) until the aqueous phase was transparent. The organic phase was dried with $MgSO_4$ and evaporated to furnish the crude product, which was purified by flash chromatography with a gradient of CH_2Cl_2/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 (CH_2Cl_2/MeOH, 9:1); m.p. 110–112 °C. $[\alpha]_D^{20}$ = –66.4 (c = 2.00, $CHCl_3$). ^{1}H NMR ([D$_6$]-acetone): δ = 1.36 (s, 9 H, 3 × CH_3), 1.90–1.96 (m, 3 H, CH_2, Pro), 2.25 (m, 1 H, CH_2, Pro), 3.00 (t, J = 13.2 Hz, 1 H, CH_2, Phe), 3.27 (m, 2 H, CH_2, Phe + OH), 3.33 (dd, J = 4.0, 13.8 Hz, 1 H, CH_2N, Dpr), 3.48 (m, 1 H, CH_2N, Dpr), 3.77 (m, 1 H, CH_2N, Pro), 3.90 (m, 1 H, CH_2N, Pro), 4.53 (br. s, 1 H, CH_α, Pro), 4.59 (m, 2 H, CH_2, Allyl), 4.72 (m, 1 H, CH_α, Phe), 5.00–5.09 (m, 1 H, CH_α, Dpr), 5.20 (m, 1 H, CH_2=CH Allyl), 5.32 (m, 1 H, CH_2=CH Allyl), 5.91 (m, 1 H, CH_2=CH Allyl), 6.02 (d, J = 15.3 Hz, 1 H, CH_α=CH V-ΔTyr), 6.44 (d, J = 8.6 Hz, 1 H, NH), 6.74 (s, 1 H, CH_δ=C V-ΔTyr), 6.83 (d, J = 8.6 Hz, 2 H, CH_{ar}), 7.25–7.52 (m, 8 H, 7 × CH_{ar} + CH_β=CH V-ΔTyr), 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. ^{13}C NMR ([D$_6$]acetone): δ = 25.6 (CH_2, Pro), 28.7 (3 × CH_3, Boc), 31.7 (CH_2, Pro), 38.5 (CH_2, Phe), 42.0 (CH_2N, Dpr), 47.8 (CH_2N, Pro), 50.4 (CH_α, Dpr), 57.4 (CH_α, Phe), 59.8 (CH_α, Pro), 66.0 (CH_2, Allyl), 79.5 [$OC(CH_3)_3$], 116.4 (2 × CH_{ar}), 118.3 (CH_2=CH, Allyl), 120.4 (CH_α=CH, V-ΔTyr), 127.3 (CH_{ar}), 127.5 (C_{ipso}), 129.2 (2 × CH_{ar}), 130.4 (C_{ipso}), 130.5, 132.6 (4 × CH_{ar}), 133.4 (CH=CH_2, Allyl), 135.1 (CH_δ=C, V-ΔTyr), 139.1 (C_{ipso}), 141.2 (CH_β=CH, V-ΔTyr), 156.8 (CH=C_γ, V-ΔTyr), 158.9 (NHCOO), 162.2 (NHCHO), 167.3 (NHCO, Phe), 169.6 (NHCO, V-ΔTyr), 169.9 (NHCO, Dpr), 172.7 (CO_2Allyl) 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 $[C_{37}H_{45}N_5O_9 + Na]^+$ 726.3115; found 726.3108 (δ = –1.0 ppm). $C_{37}H_{45}N_5O_9 \cdot H_2O$ (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-ΔTyr-N^α-CHO-Dpr-Pro-OAllyl (31): Protected tetrapeptide **30** (353 mg, 0.50 mmol) was treated at 0 °C with a solution of CH_2Cl_2/TFA (1:1; 14 mL) for 1 h, and 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, 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 $NaHCO_3$ solution. The resulting aqueous phase was extracted with EtOAc (3 × 20 mL), dried with $MgSO_4$ 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 (CH_2Cl_2/MeOH, 9:1). ^{1}H NMR ([D$_6$]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.

^{13}C NMR ([D$_6$]acetone): δ = 27.2 (CH_2), 31.7 (CH_2), 37.3 (CH_2), 41.8 (CH_2), 48.1 (CH_2), 50.2 (CH), 50.3 (CH), 59.8 (CH), 66.2 (CH_2), 116.5 (2 × CH), 118.5 (CH_2), 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 CH_2Cl_2 (30–60 mL) was purged at –78 °C with O_2 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 CH_2Cl_2 (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}-Z$_2$-k-Arg-D-Phe-V-ΔTyr(OTIPS)-O*t*Bu (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. $[\alpha]_D^{20}$ = –3.6 (c = 1.50, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.01 (d, J = 7.2 Hz, 18 H, 6 × CH_3), 1.18 (m, 3 H, SiCH), 1.35 (s, 9 H, 3 × CH_3), 1.41 (s, 9 H, 3 × CH_3), 1.48–1.58 (m, 3 H, CH_2, k-Arg), 1.72–1.78 (m, 1 H, CH_2, k-Arg), 2.99–3.18 (m, 2 H, CH_2, Phe), 3.87 (m, 2 H, CH_2N, k-Arg), 4.02 (br. s, CH_α, Phe), 4.69 (m, 1 H, CH_α, k-Arg), 5.03 (m, 2 H, CH_2, Z), 5.07 (m, 2 H, CH_2, 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. ^{13}C NMR ([D$_6$]acetone): δ = 12.3 (3 × SiCH), 18.3 (6 × CH_3), 24.6 (CH_2, k-Arg), 25.6 (CH_2, k-Arg), 28.2 (3 × CH_3, Boc or CO_2tBu), 28.4 (3 × CH_3, Boc or CO_2tBu), 37.7 (CH_2, Phe), 44.7 (CH_2N, k-Arg), 56.0 (CH_α), 58.1 (CH_α), 67.3 (CH_2, Z), 69.3 (CH_2, Z), 80.4 [O*C*(CH$_3$)$_3$], 80.9 [O-C-(CH$_3$)$_3$], 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 (CO_2Me), 197.8 (CO, k-Arg) ppm. IR (KBr): $\tilde{\nu}$ = 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 [$C_{61}H_{80}N_6O_{12}Si$ + H]$^+$ 1117.5682; found 1117.5703 (+1.9 ppm).

N^{β}-Boc-N^{α}-CHO-Dpr-Pro-N^{δ},N^{ε}-Z$_2$-k-Arg-D-Phe-V-ΔTyr(OTIPS)-O*t*Bu (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 CH_2Cl_2/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 (CH_2Cl_2/MeOH, 95:5); m.p. 132–135 °C. $[\alpha]_D^{20}$ = –47.8 (c = 1.90, $CHCl_3$). ^{1}H NMR ([D$_6$]acetone): δ = 1.01 (d, J = 7.2 Hz, 18 H, 6 × CH_3), 1.25 (m, 3 H, 3 × SiCH), 1.40 (s, 9 H, 3 × CH_3), 1.49 (s, 9 H, 3 × CH_3), 1.60–1.92 (m, 8 H, CH_2, Pro + k-Arg), 3.23 (m, 1 H, CH_2, Phe), 3.37 (m, 3 H, CH_2, Phe + CH_2N Dpr), 3.66 (m, 2 H, CH_2N, Pro), 3.90–3.99 (m, 1 H, CH_2N, k-Arg), 4.02–4.11 (m, 1 H, CH_2N, 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 + CH_2 Z), 5.31 (m, 2 H, CH_2, 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. ^{13}C NMR ([D$_6$]acetone): δ = 14.7 (3 × SiCH), 18.4 (6 × CH_3), 25.6 (CH_2, Pro), 26.0 (CH_2, k-Arg), 27.9 (CH_2, Pro), 28.6 (3 × CH_3, Boc or CO_2tBu), 28.8 (3 × CH_3, Boc or CO_2tBu), 30.7 (CH_2, k-Arg), 37.7 (CH_2, Phe), 43.4 (CH_2N, Dpr), 45.2 (CH_2N, k-Arg), 48.2 (CH_2N, Pro), 50.6 (CH_α, Dpr), 55.4 (CH_α, k-Arg), 55.9 (CH_α, Phe), 60.9 (CH_α, Pro), 67.4 (CH_2, Z), 69.5 (CH_2, Z), 79.4 [O*C*(CH$_3$)$_3$], 80.5 [O*C*(CH$_3$)$_3$], 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 (CO_2tBu), 196.2 (CO, k-Arg) ppm. IR (KBr): $\tilde{\nu}$ = 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 [$C_{70}H_{93}N_9O_{15}Si$ + H]$^+$ 1328.6639; found 1328.6586 (δ = –4.0 ppm). $C_{70}H_{93}N_9O_{15}Si$ (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}-Z$_2$-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 CH_2Cl_2/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 (CH_2Cl_2/MeOH, 95:5); m.p. 96–98 °C. $[\alpha]_D^{20}$ = –12.7 (c = 1.00, $CHCl_3$). ^{1}H NMR ([D$_6$]acetone): δ = 1.24 (s, 9 H, 3 × CH_3), 1.50–1.72 (m, 6 H, CH_2, Pro + k-Arg), 1.75–1.89 (m, 2 H, CH_2, Pro + k-Arg), 2.70–3.00 (br. s, 2 H, CH_2, Phe + OH), 3.08 (m, 1 H, CH_2, Phe), 3.26 (m, 2 H, CH_2N, Dpr), 3.65 (m, 2 H, CH_2N, Pro), 3.85 (m, 2 H, CH_2N, k-Arg), 4.33 (m, 1 H, CH_α, Pro), 4.46 (m, 2 H, CH_2, 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 + CH_2, Z), 5.06 (m, 1 H, CH_2=CH, Allyl), 5.13–5.22 (m, 3 H, CH_2=CH, Allyl + CH_2, Z), 5.78 (m, 1 H, CH_2=C*H*, 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. ^{13}C NMR ([D$_6$]acetone): δ = 25.5 (2 × CH_2, Pro + k-Arg), 26.2 (CH_2, Pro or k-Arg), 26.3 (CH_2, Pro or k-Arg), 28.6 (3 × CH_3, Boc), 38.0 (CH_2, Phe), 42.0 (CH_2N, Dpr), 45.1 (CH_2N, k-Arg), 47.9 (CH_2N, Pro), 50.4 (CH_α, Dpr), 56.1 (CH_α, Phe), 59.8 (2 × CH_α, Pro + k-Arg), 66.0 (CH_2, Allyl), 67.3 (CH_2, Z), 69.4 (CH_2, Z), 79.5 [O*C*(CH$_3$)$_3$], 116.4 (2 × CH_{ar}), 118.3 (CH_2=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 (*C*H=CH_2, Allyl), 135.3 (CH_δ=C, V-ΔTyr), 136.4 (2 × C_{ipso}, Phe + Z), 138.4

(C_{ipso}, Z), 141.9 (CH_β=CH, V-ΔTyr), 156.6 (2 × NHCOO, Z), 157.0 (CH=C_γ, V-ΔTyr), 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-ΔTyr), 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 cm^{-1}. ESI-MS: *m/z* = 1188 $[M + Na]^+$, 1156 $[M + H]^+$. HR-MS: *m/z* calcd. for $[C_{60}H_{69}N_9O_{15} + H]^+$ 1156.4991; found 1156.5043 (+4.5 ppm). $C_{60}H_{69}N_9O_{15}$ (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-ΔTyr(OTIPS)] (37): Protected pentapeptide **33** (160 mg, 0.12 mmol, 1 equiv.) was treated at 0 °C with a solution of CH_2Cl_2/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 × 30 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 CH_2Cl_2/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 CH_2Cl_2/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 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_D^{22}$ = +44.0 (*c* = 0.80, $CHCl_3$). ^{1}H NMR ([D$_6$]acetone): δ = 1.10 (d, *J* = 7.3 Hz, 18 H, 6 × CH_3), 1.29 (m, 3 H, 3 × 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 Hz, 1 H, CH_2, Phe), 3.28 (dd, *J* = 5.8, 13.9 Hz, 1 H, CH_2, Phe), 3.39 (dd, *J* = 6.5, 16.5 Hz, 1 H, CH_2N, Pro), 3.56 (dd, *J* = 7.0, 16.5 Hz, 1 H, CH_2N, Pro), 4.00 (m, 2 H, CH_2N, k-Arg), 4.23 (t, *J* = 6.9 Hz, 1 H, CH_2N, Dpr), 4.55 (dd, *J* = 4.9, 8.4 Hz, 1 H, CH_α, Pro), 4.78 (dd, *J* = 6.5, 10.3 Hz, 1 H, CH_α, Dpr), 4.84 (dd, *J* = 5.9, 9.7 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 Hz, 1 H, CH_α=CH V-ΔTyr), 6.84 (s, 1 H, CH_δ=C V-ΔTyr), 6.86 (d, *J* = 8.8 Hz, 2 H, 2 × CH_{ar}), 7.14–7.52 (m, 19 H, 17 × CH_{ar} + CH_β=CH V-ΔTyr + 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 ([D$_6$]acetone): δ = 13.4 (3 × SiCH), 18.3 (6 × 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 (CH_α=CH, V-ΔTyr + 2 × CH_{ar}), 127.5, 128.5, 128.8, 129.0, 129.2, 129.6, 130.1 (13 × CH_{ar}), 130.6 (2 × C_{ipso}), 131.6 (CH_{ar}), 132.0 (2 × CH_{ar}), 133.4 (CH_{ar}), 135.4 (CH_δ=C, V-ΔTyr), 136.3 (C_{ipso}, Phe), 138.0 (C_{ipso}, Z), 138.5 (C_{ipso}, Z), 142.0 (CH_β=CH, V-ΔTyr), 156.6 (NHCOO, Z), 157.3 (NHCOO, Z), 160.0 (CH=C_γ, V-ΔTyr), 161.1 (NHCHO), 161.5 [NC(=NH)N], 164.4 (NHCO, Phe), 166.1 (NHCO, Dpr), 169.5 (NHCO, V-ΔTyr), 170.1 (NHCO, Pro), 174.5 (NHCO, k-Arg), 196.1 (CO, k-Arg) ppm. ESI-MS: *m/z* = 1186 $[M + H + MeOH]^+$, 1154 $[M + H]^+$. HR-MS: *m/z* calcd. for $[C_{61}H_{75}N_9O_{12}Si + H]^+$ 1154.5383; found 1154.5377 (δ = –0.5 ppm).

Cyclo[N^α-CHO-Dpr-Pro-k-Arg-D-Phe-V-ΔTyr], 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 × 150 mm, CH_3CN/H_2O + 0.1% 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%). ^{1}H NMR (CD_3OD): δ = 1.45–1.78 (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 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 Hz, 1 H, V-ΔTyr α), 6.75 and 6.82 (d, *J* = 8.6 Hz, 2 H, V-ΔTyr), 6.91 (s, 1 H, V-ΔTyr δ), 7.13–7.38 (m, 6 H), 7.41 and 7.45 (d, *J* = 8.7 Hz, 2 H, V-ΔTyr), 8.06 and 8.07 (s, 1 H, CHO) ppm. ^{13}C NMR (CD_3OD): δ = 23.5 (CH_2), 25.6 (CH_2), 25.7 (CH_2), 30.5 (CH_2), 40.8 (2 × 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 × CH), 121.8 (CH), 126.5 (C), 127.4 (CH), 129.1 (2 × CH), 129.9 (C), 130.6 (2 × CH), 130.7 (2 × 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 $[M + H]^+$, 748 $[M + H + H_2O]^+$. HR-MS: *m/z* calcd. for $[C_{36}H_{44}N_9O_8 + H_2O]^+$ 748.3418; found 748.3435 (+2.2 ppm).

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

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[1] a) N. Fusetani, S. Matsunaga, *J. Am. Chem. Soc.* **1990**, *112*, 7053–7054; b) Y. Nakao, S. Matsunaga, N. Fusetani, *Bioorg. Med. Chem.* **1995**, *3*, 1115–1122; c) Y. Nakao, N. Oku, S. Matsunaga, N. Fusetani, *J. Nat. Prod.* **1998**, *61*, 667–670; d) Y. Murakami, M. Takei, K. Shindo, C. Kitazume, J. Tanaka, T. Higa, H. Fukamachi, *J. Nat. Prod.* **2002**, *65*, 259–261.

[2] a) B. E. Maryanoff, X. Qiu, K. P. Padmanabhan, A. Tulinsky, H. R. Almond, P. Andrade-Gordon, M. N. Greco, J. A. Kauffman, K. C. Nicolaou, A. Liu, P. H. Brungs, N. Fusetani, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 8048–8052; b) S. D. Lewis, A. S. Ng, J. J. Baldwin, N. Fusetani, A. M. Naylor, J. A. Shafer, *Thrombosis Res.* **1993**, *70*, 173–190; c) A. Y. Lee, M. Hagihara, R. Karmacharya, M. W. Albers, S. L. Schreiber, J. Clardy, *J. Am. Chem. Soc.* **1993**, *115*, 12619–12620; d) V. Ganesh, A. Y. Lee, J. Clardy, A. Tulinsky, *Protein Sci.* **1996**, *5*, 825–835.

[3] a) B. E. Maryanoff, H.-C. Zhang, M. N. Greco, K. A. Glover, J. A. Kauffman, P. Andrade-Gordon, *Bioorg. Med. Chem.* **1995**, *3*, 1025–1038; b) M. N. Greco, B. E. Maryanoff, in: *Advances in Amino Acid Mimetics and Peptidomimetics*, Vol. 1 (Ed.: A. Abel), JAI Press, Greenwich, **1997**; pp. 41–76.

[4] a) M. Hagihara, S. L. Schreiber, *J. Am. Chem. Soc.* **1992**, *114*, 6570–6571; b) P. Wipf, H. Kim, *J. Org. Chem.* **1993**, *58*, 5592–5594; c) J. Deng, Y. Hamada, T. Shioiri, S. Matsunaga, N. Fusetani, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1729–1731; d) B. E. Maryanoff, M. N. Greco, H. C. Zhang, P. Andrade-Gordon, J. A. Kauffman, K. C. Nicolaou, A. Liu, P. H. Brungs, *J. Am. Chem. Soc.* **1995**, *117*, 1225–1239; e) H. M. M. Bastiaans,

J. L. Van der Baan, H. C. J. Ottenheijm, *J. Org. Chem.* **1997**, *62*, 3880–3889.
[5] a) H. Nemoto, Y. Kubota, Y. Yamamoto, *J. Org. Chem.* **1990**, *55*, 4515–4516; b) H. Nemoto, R. Ma, I. Suzuki, M. Shibuya, *Org. Lett.* **2000**, *2*, 4245–4247.
[6] S. Roche, S. Faure, D. J. Aitken, *Angew. Chem. Int. Ed.* **2008**, *47*, 6840–6842.
[7] H. H. Wasserman, W.-B. Ho, *J. Org. Chem.* **1994**, *59*, 4364–4366.
[8] S. Weik, J. Rademann, *Angew. Chem. Int. Ed.* **2003**, *42*, 2491–2494.
[9] a) D. Sellanes, E. Manta, G. Serra, *Tetrahedron Lett.* **2007**, *48*, 1827–1830; b) J. A. R. Rodrigues, P. J. S. Moran, C. D. F. Milagre, C. V. Ursini, *Tetrahedron Lett.* **2004**, *45*, 3579–3582; c) H. H. Wasserman, J.-H. Chen, M. Xia, *J. Am. Chem. Soc.* **1999**, *121*, 1401–1402; d) H. H. Wasserman, J. Wang, *J. Org. Chem.* **1998**, *63*, 5581–5586; e) H. H. Wasserman, A. K. Petersen, *Tetrahedron Lett.* **1997**, *38*, 953–956; f) H. H. Wasserman, A. K. Petersen, *J. Org. Chem.* **1997**, *62*, 8972–8973.
[10] a) S. Faure, A. A. Jensen, V. Maurat, X. Gu, E. Sagot, D. J. Aitken, J. Bolte, T. Gefflaut, L. Bunch, *J. Med. Chem.* **2006**, *49*, 6532–6538; b) X. Gu, M. Xian, S. Roy-Faure, J. Bolte, D. J. Aitken, T. Gefflaut, *Tetrahedron Lett.* **2006**, *47*, 193–196; c) S. R. Crosby, M. J. Hatelel, C. L. Willis, *Tetrahedron Lett.* **2000**, *41*, 397–401; d) M. D. Fletcher, J. R. Harding, R. A. Hughes, N. M. Kelly, H. Schmalz, A. Sutherland, C. L. Willis, *J. Chem. Soc. Perkin Trans. 1* **2000**, 43–52.
[11] G. Haberhauer, *Synlett* **2004**, 1003–1006.
[12] a) D. G. Barrett, V. M. Boncek, J. G. Catalano, D. N. Deaton, A. M. Hassell, C. H. Jurgensen, S. T. Long, R. B. McFadyen, A. B. Miller, L. R. Miller, J. A. Payne, J. A. Ray, V. Samano, L. M. Shewchuk, F. X. Tavares, K. J. Wells-Knecht, D. H. Willard Jr., L. L. Wright, H.-Q. Q. Zhou, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3540–3546; b) Y. Choe, L. S. Brinen, M. S. Price, J. C. Engel, M. Lange, C. Grisostomi, S. G. Weston, P. V. Pallai, H. Cheng, L. W. Hardy, D. S. Hartsough, M. McMakin, R. F. Tilton, C. M. Baldino, C. S. Craik, *Bioorg. Med. Chem.* **2005**, *13*, 2141–2156; c) W. Han, Z. Hu, X. Jiang, Z. R. Wasserman, C. P. Decicco, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1111–1114.
[13] a) H. H. Wasserman, R. Zhang, *Tetrahedron* **2002**, *58*, 6277–6283; b) H. H. Wasserman, R. Zhang, *Tetrahedron Lett.* **2002**, *43*, 3743–3746.
[14] A. Viso, R. Fernández de la Pradilla, A. García, A. Flores, *Chem. Rev.* **2005**, *105*, 3167–3196.
[15] a) M. Waki, Y. Kitajima, N. Izumiya, *Synthesis* **1981**, 266–268; b) Z. Zhang, A. Van Aerschot, C. Hendrix, R. Busson, F. David, P. Sandra, P. Herdewijn, *Tetrahedron* **2000**, *56*, 2513–2522.
[16] M. Jetten, C. A. M. Peters, J. W. F. M. van Nispen, H. C. J. Ottenheijm, *Tetrahedron Lett.* **1991**, *32*, 6025–6028.
[17] As a further indication of their fragility, we noticed that α-keto cyanophosphorane building blocks undergo some transformation (possibly an epimerisation) upon storage for a week in a deep freezer. For more details, see the experimental part.
[18] Interestingly, a vinylogous dehydrovaline derivative was obtained from flash vacuum pyrolysis of an appropriate α-keto alkoxycarbonylphosphorane, albeit in low yield; see: R. A. Aitken, N. Karodia, T. Massil, R. J. Young, *J. Chem. Soc. Perkin Trans. 1* **2002**, 533–541.
[19] D. J. Aitken, S. Faure, S. Roche, *Tetrahedron Lett.* **2003**, *44*, 8827–8830.
[20] X. Wei, R. J. K. Taylor, *J. Org. Chem.* **2000**, *65*, 616–620.
[21] For a recent review of this methodology, see: R. J. K. Taylor, M. Reid, J. Foot, S. A. Raw, *Acc. Chem. Res.* **2005**, *38*, 851–869.
[22] In a recent total synthesis of cryptophycin 3, TBTU/HOBt was the preferred coupling system for a macrocyclisation step requiring activation of a β-substituted acrylic *C* terminus; see: P. Danner, M. Bauer, P. Phukan, M. E. Maier, *Eur. J. Org. Chem.* **2005**, 317–325.