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Diazonamide studies. A direct synthesis of the indole bis-oxazole fragment from tri- and tetra-peptides using biomimetic oxidative cyclizations

Jonathan Sperry [†], Christopher J. Moody [*]

Department of Chemistry, University of Exeter, Stocker Road, Exeter, EX4 4QD, UK

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With warm congratulations to Professor Steven Ley on the award of the Tetrahedron Prize for Creativity in Organic Chemistry

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ABSTRACT

The oxidation of several readily prepared tryptophan containing tri- and tetrapeptides with DDQ results in a biomimetic cyclization and direct formation of the indole bis-oxazole fragment of diazonamide A, establishing that such a transformation is a viable route when considering the biosynthetic formation of the heterocyclic core of the natural product.

1. Introduction

The marine secondary metabolite diazonamide A, isolated from the colonial ascidian *Diazona chinensis*, was assigned as structure **1** on the basis of an X-ray crystallographic study of a derivative.[1] The compound was also reported to have potent in vitro cytotoxicity against human tumour cell lines, and this biological activity,[2] together with its unique and complex structure, ensured that diazonamide A immediately captured the imagination of synthetic organic chemists. However, when the structure finally succumbed to total synthesis in 2001, the synthetic material was found to be different from the natural product.[3,4] On the basis of a re-examination of the original X-ray data, Harran proposed the alternative structure **2** for diazonamide A (Fig. 1). Not only did this subsequently prove to be correct, but it also better fits a biosynthetic route in which the bicyclic core derives from modification of a TyrValTrpTrp tetrapeptide. Final proof that the revised structure **2** was indeed that of diazonamide A came in 2002 when Nicolaou and co-workers

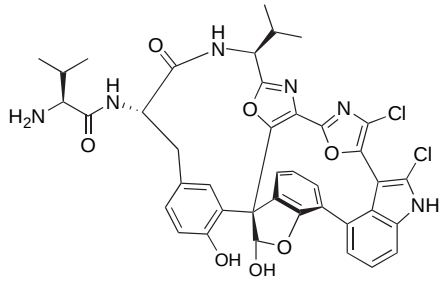

Figure 1. Originally proposed and revised structure of diazonamide A.

* Corresponding author at present address: School of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, UK; e-mail addresses: j.sperry@auckland.ac.nz (J. Sperry), c.j.moody@nottingham.ac.uk (C.J. Moody).
† Present address: Department of Chemistry, University of Auckland, 23 Symonds Street, Auckland, New Zealand.

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published the first total synthesis of the natural product.[5,6] Subsequently, the Nicolaou group reported a second route to diazonamide A,[7,8] whilst Harran and co-workers accomplished their own total synthesis of the correct structure,[9] and Magnus and co-workers completed a formal synthesis.[10] Despite the fact that these efforts have now solved the structural problem of diazonamide A, it remains of considerable interest, not only because of its reported nanomolar in vitro cytotoxicity against human tumour cell lines,[1,2,11,12] but also as a challenging target for synthetic chemists. The innovative ways in which synthetic chemists have approached this challenge are described in a recent review.[13]

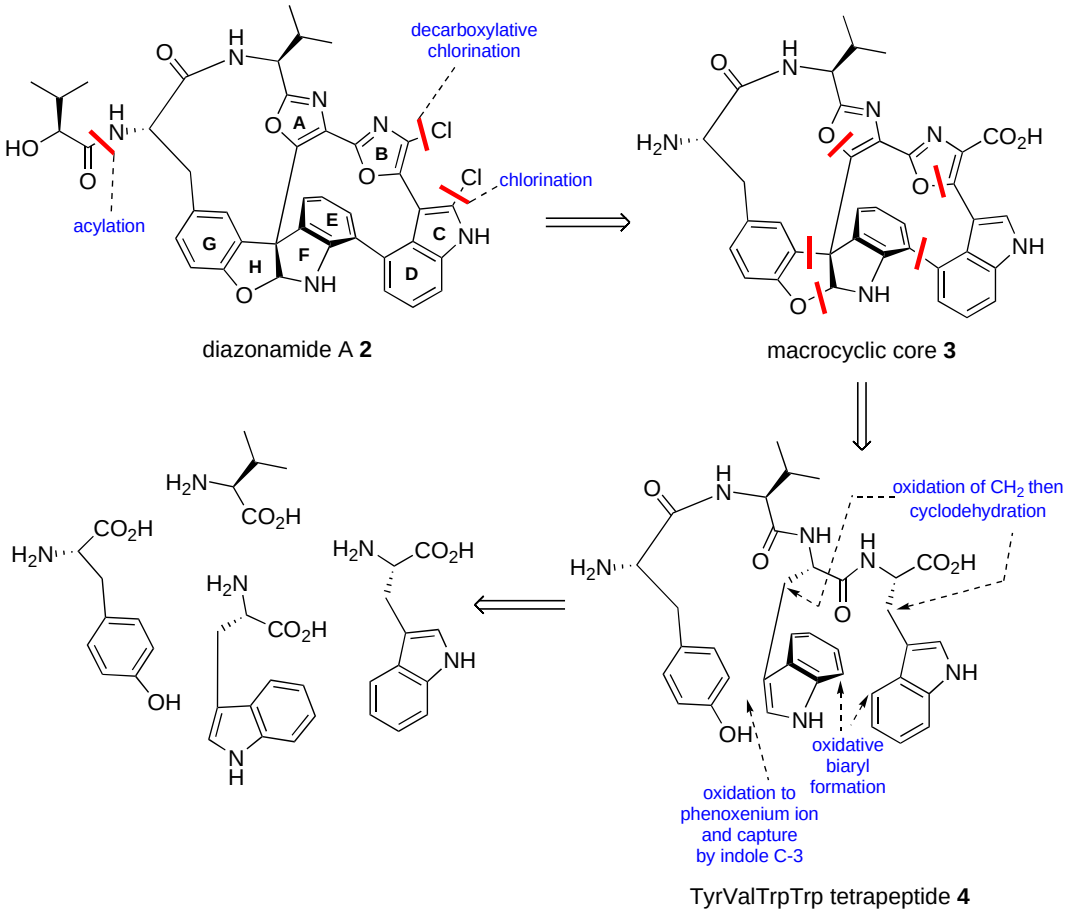
As noted previously, the correct structure of diazonamide A **2** better fits a biosynthetic route in which the bicyclic core derives from modification of a TyrValTrpTrp tetrapeptide,[4] and Harran's own synthesis of the natural product involves the formation of the G–H–F–E aminal by an oxidative cyclization of a tyrosine derivative that likely mimics the biosynthesis.[9] In continuation of our own longstanding interest in diazonamide A **2**,[14–22] which primarily involves the use of diazocarbonyl chemistry to construct strategic C–N bonds by rhodium carbene N–H insertion reactions, we were also intrigued by the possibility of a biomimetic route that involves the oxidative cyclization of the putative biosynthetic precursor, the TyrValTrpTrp tetrapeptide. We now report the full details of our endeavours in this area.[23]

2. Results and discussion

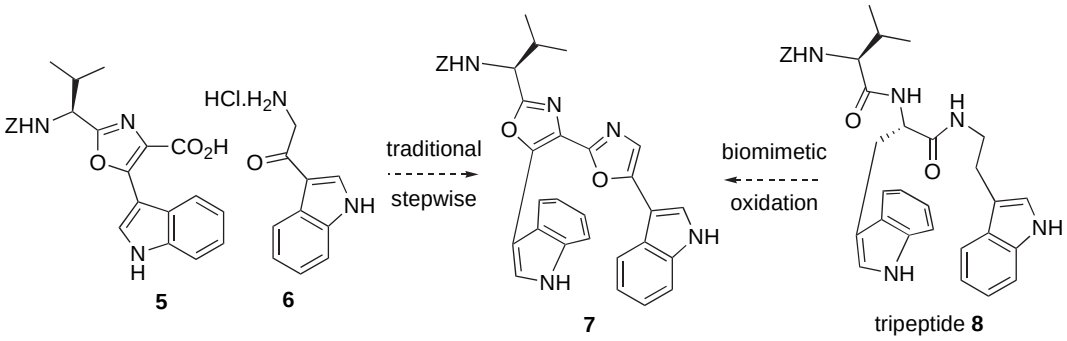
Our retrosynthetic analysis of diazonamide A **2** (Scheme 1) involves scission of the α-hydroxy isovaleric acid side chain and the two chlorine atoms. The fact that both these chlorines could be introduced by a late stage electrophilic chlorination reaction was established early in the diazonamide saga.[24,25] However, we recognized an additional possibility that the 4-chloro-oxazole might derive by a decarboxylative chlorination of the corresponding oxazole-4-carboxylic acid, as did Magnus and co-workers.[25] This reflects the putative biosynthetic precursor to diazonamide A in that C-4 of the ring-B oxazole derives from the α-carbon of tryptophan and therefore would originally bear a carboxylic acid. Hence our initial target was the macrocyclic core **3** that can be envisaged to result from a series of oxidative cyclizations of the tetrapeptide **4** as depicted in Scheme 1. Of these, 3-indolyl oxazoles are known to result from the so-called Yonemitsu oxidation of tryptamine derivatives,[26,27] and the oxidation of the tyrosine ring followed by capture by the nucleophilic indole 3-position has precedent in the aforementioned Harran synthesis.[9]

Our preliminary thoughts involved the construction of the indole bis-oxazole fragment of diazonamide A using a classical, stepwise approach that would provide an authentic sample from which to compare the outcome of any subsequent biomimetic transformations. Thus, it was envisaged that valinyloxazole-acid **5** would undergo amide coupling with aminoketone **6** followed by cyclodehydration providing the desired indole bis-oxazole **7**, the identical target that would be obtained by oxidation then cyclodehydration of tripeptide **8** if the biomimetic hypothesis were successful (Scheme 2).

Thus, the stepwise synthesis of indole bis-oxazole **7** was initiated. The HBTU/1-hydroxybenzotriazole (HOBt) mediated coupling[28] of Z-Val-OH and H-Trp-OMe hydrochloride delivered the known dipeptide **9** in excellent yield.[29] Yonemitsu oxidation of **9**



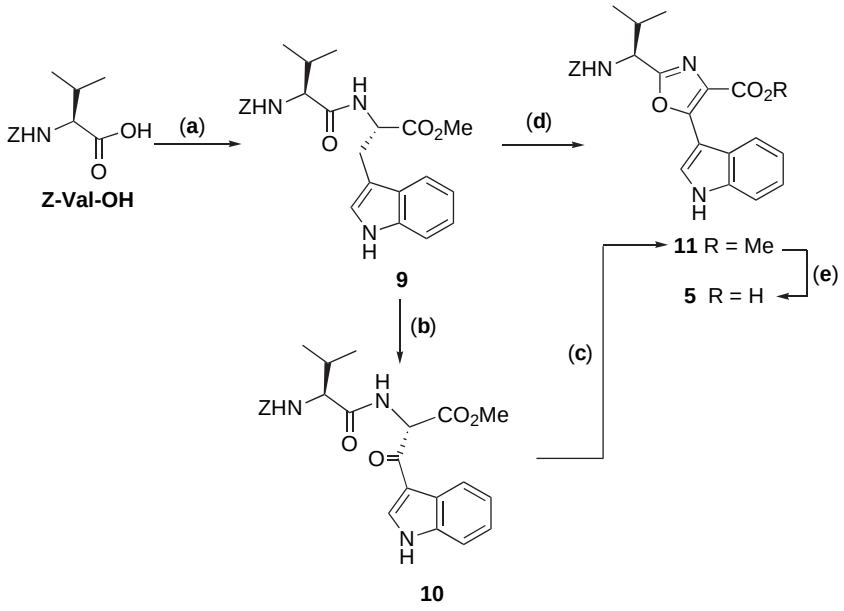
Scheme 1. Biomimetic approach to diazonamide A.



Scheme 2. Stepwise and biomimetic approaches to the indole bis-oxazole fragment of diazonamide A.

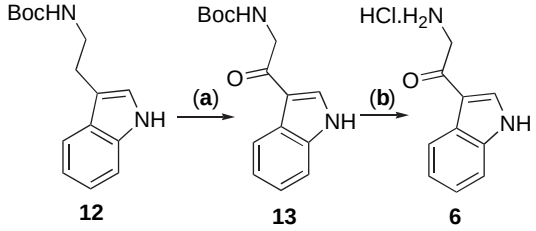
under aqueous conditions (DDQ, THF/H_2O, rt)[30] gave the 1,4-dicarbonyl compound **10** in moderate yield, which upon exposure to Wipf's cyclodehydration protocol[31] gave the desired valinyloxazole ester **11**. Gratifyingly, it was discovered that subjecting dipeptide **9** to the anhydrous variant of the Yonemitsu oxidation (DDQ, THF, reflux)[26,27] directly provided **11** in a single step and good overall yield. Straightforward saponification delivered the key carboxylic acid coupling partner **5** (Scheme 3).

Coupling of valinyloxazole-acid **5** with aminoketone **6** under the action of HBTU-HOBt gave the desired cyclodehydration precursor **14** in moderate yield. In an effort to improve the unpredictable outcome of this step, amide coupling of **5** with tryptamine gave **15**, which underwent aqueous Yonemitsu oxidation delivering **14** in excellent yield over the two steps. Unfortunately, attempting the anhydrous Yonemitsu conditions on **15** failed to give any of the desired bis-oxazole **7**. However after much



Scheme 3. Reagents and conditions: (a) H-Trp-OMe hydrochloride, HBTU, HOBt, *i*-Pr_2NEt, CH_2Cl_2, rt, 12 h, 85%; (b) DDQ, THF/H_2O (9:1), rt, 3 h, 50%; (c) PPh_3, I_2, Et_3N, CH_2Cl_2, rt, 3 h, 69%; (d) DDQ, THF, reflux, 3 h, 64%; (e) LiOH, MeOH/H_2O, rt, 16 h, 82%.

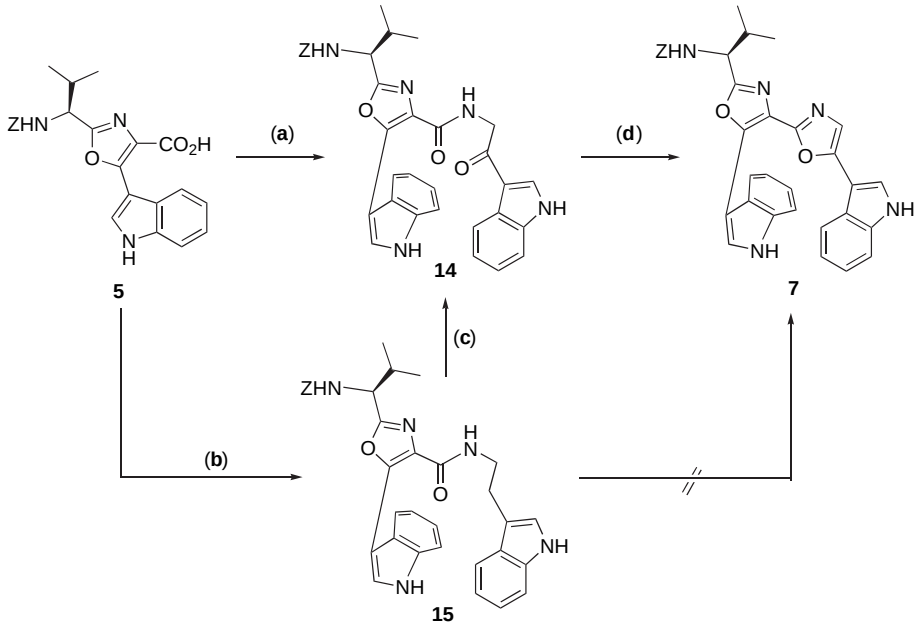
The synthesis of the aminoketone coupling partner **6** began from known Boc-tryptamine **12**,[32] which was subjected to aqueous Yonemitsu oxidation affording **13**.[6] Smooth acid mediated Boc-cleavage then provided aminoketone **6** as a stable hydrochloride salt (Scheme 4).[33]



Scheme 4. Reagents and conditions: (a) DDQ, THF/H_2O (9:1), rt, 3 h, 60%; (b) 4 M HCl in dioxane, rt, 4 h, 89%.

experimentation, successful cyclodehydration of **14** was accomplished using a modification[34] of Wipf's protocol delivering the desired indole bis-oxazole **7** (Scheme 5).

With the stepwise route to the indole bis-oxazole **7** successfully accomplished, attention turned towards the proposed biomimetic synthesis. Thus, tripeptide **8** was constructed as follows; Boc-Trp-OH was coupled with tryptamine using HBTU in the presence of HOBt affording **16** in quantitative yield. Removal of the *N*-Boc protecting group under acidic conditions gave **17**, which then underwent a second HBTU based coupling with Z-Val-OH delivering the key tripeptide **8**. The stage was now set for the key biomimetic oxidative cyclization. Subjecting tripeptide **8** to the anhydrous Yonemitsu oxidation conditions [DDQ (4.4 equiv), THF, reflux] resulted in the desired indole bis-oxazole **7**, as determined by TLC comparison to the authentic sample obtained from the stepwise route (Scheme 5), although its purification was not practical owing to the vast excess of DDQ used in the reaction. In order to allow the

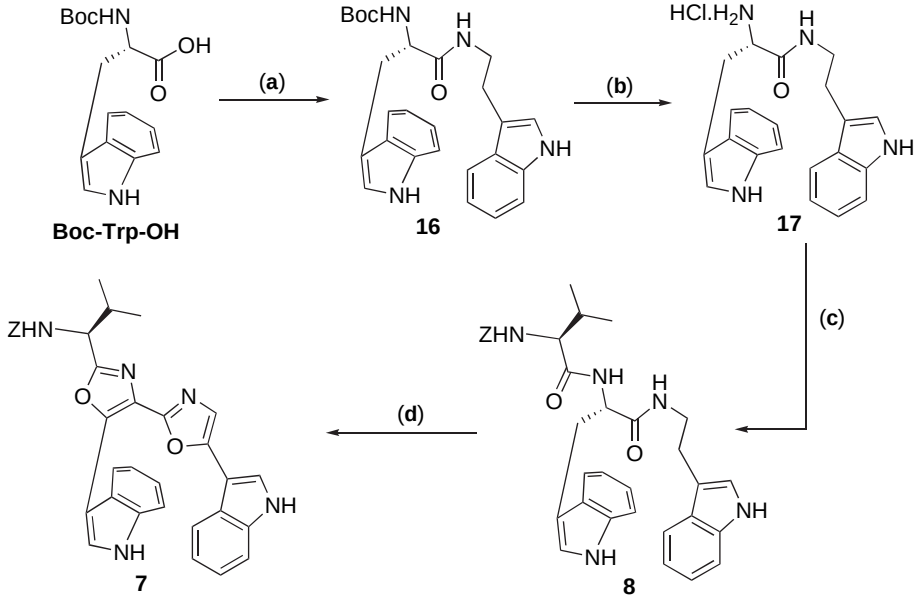


Scheme 5. Reagents and conditions: (a) aminoketone **6**, HBTU, HOBt, *i*-Pr_2NEt, CH_2Cl_2, rt, 12 h, 42%; (b) tryptamine, HBTU, HOBt, *i*-Pr_2NEt, CH_2Cl_2, rt, 12 h, 78%; (c) DDQ, THF/H_2O (9:1), rt, 3 h, 83%; (d) PPh_3, C_2Cl_6, Et_3N, THF, rt, 30 h, 48%.

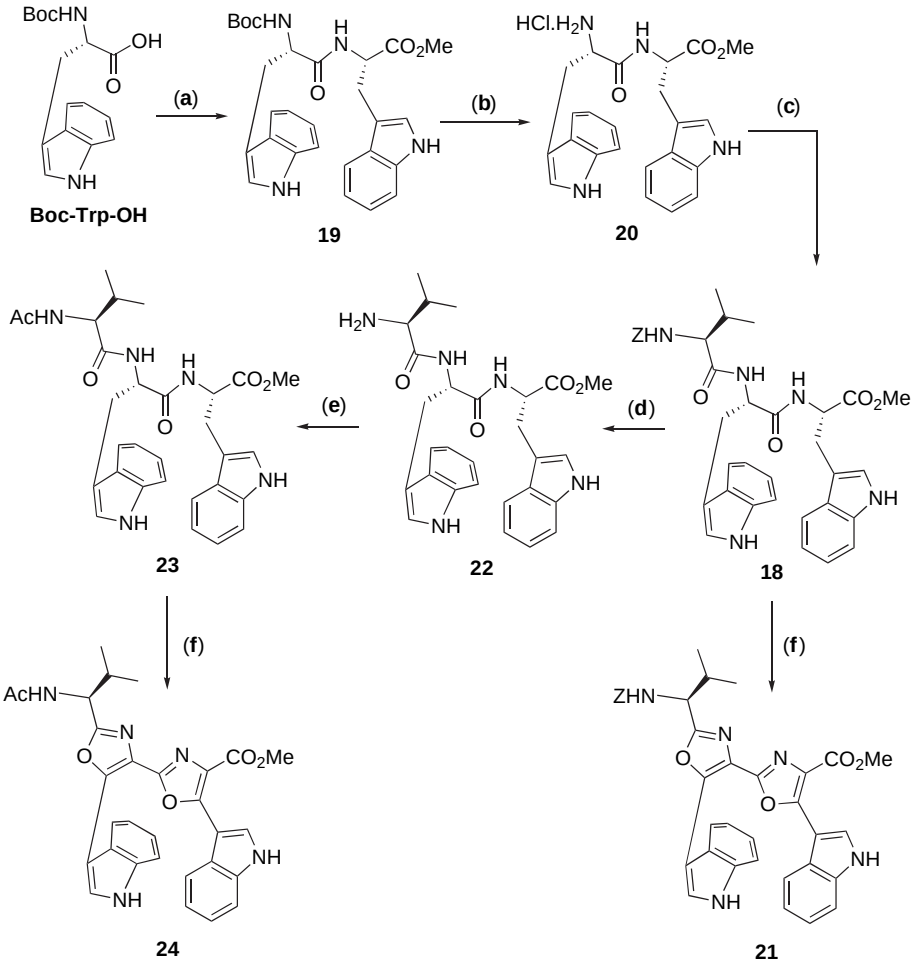
purification of **7**, only three equivalents of DDQ were used in the oxidative cyclization, gratifyingly facilitating the isolation of indole bis-oxazole **7**, albeit in poor yield. No mono-oxazole(s) were observed during the reaction and to the best of our knowledge, neither oxazole appears to differ significantly in its rate of formation. Despite the poor yield of this step, the result established that such an oxidation of the indole-3-carbinyl position in tryptophan (or tryptamine) residues, followed by cyclodehydration is a viable basis for the formation of the heterocyclic core of diazonamide A. It is also noteworthy that **7** is available in just four steps from Boc-Trp-OH (Scheme 6).

Next, we set out to investigate other tripeptide substrates in order to gauge the versatility of this approach. In an analogous route to that described for the synthesis of the tryptamine based tripeptide **8**, the synthesis of its tryptophan counterpart Z-Val-Trp-Trp-OMe **18** was therefore initiated. Boc-Trp-OH was coupled with H-Trp-OMe hydrochloride using HBTU giving the known dipeptide **19**.[35] Deprotection gave **20**, which underwent further coupling with Z-Val-OH delivering the tripeptide **18**. Gratifyingly, **18** also succumbed to the anhydrous Yonemitsu conditions, delivering the indole bis-oxazole **21** in 23% yield (Scheme 7). This improved yield (**21** vs **7**) is unsurprising and can be attributed to the presence of the electron withdrawing ester group at the C-terminus of **18**, which significantly assists the cyclization step, explaining the improved yields often observed when comparing the oxidative cyclization of tryptophan versus tryptamine derivatives.[27]

Confident that the indole bis-oxazole formation from tripeptide precursors appeared to be a general reaction, we instigated an



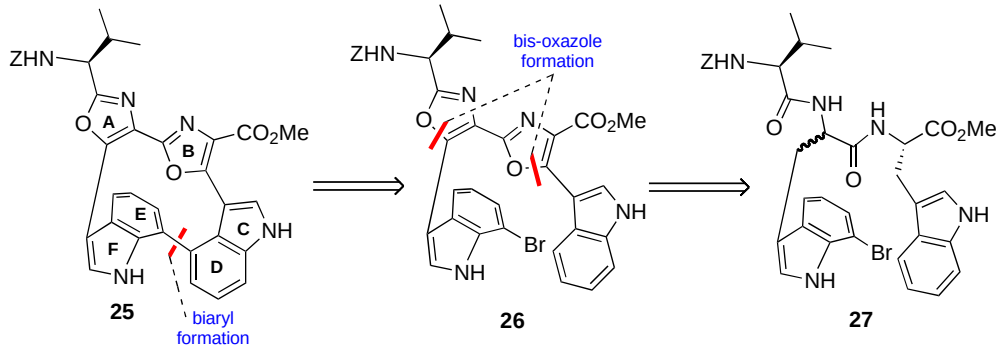
Scheme 6. Reagents and conditions: (a) tryptamine, HBTU, HOBt, *i*-Pr_2NEt, CH_2Cl_2, rt, 12 h, 100%; (b) 4 M HCl in dioxane, rt, 1 h, 92%; (c) Z-Val-OH, HBTU, HOBt, *i*-Pr_2NEt, CH_2Cl_2, rt, 12 h, 68%; (d) DDQ, THF, reflux, 3 h, 14%.



Scheme 7. Reagents and conditions: (a) H-Trp-OMe hydrochloride, HBTU, HOBt, *i*-Pr_2NEt, CH_2Cl_2, rt, 12 h, 65%; (b) 4 M HCl in dioxane, rt, 1 h, 98%; (c) Z-Val-OH, HBTU, HOBt, *i*-Pr_2NEt, CH_2Cl_2, rt, 12 h, 77%; (d) H_2, $Pd(OH)_2$ on carbon, MeOH, rt, 3 h, 91%; (e) Ac_2O, DMAP, CH_2Cl_2, rt, 16 h, 89%; (f) DDQ, THF, reflux, 3 h. 23% for **21**, 20% for **24**.

investigation to improve the yields. Previous model work in our laboratory had established that Boc-protected tripeptides were incompatible under the anhydrous Yonemitsu conditions, with extensive degradation occurring presumably due to *N*-Boc cleavage. At this stage it was unclear if the benzyloxycarbonyl (*Z*)-protecting group was hindering the yield of the bis-oxazole forming step and in order to investigate this, a tripeptide with a simple *N*-protecting group would be exposed to the cyclization conditions. To this end, hydrogenolysis of tripeptide **18** gave amine **22**, which was acetylated with acetic anhydride and DMAP, delivering the *N*-acetylated tripeptide **23**. Pleasingly, subjecting **23** to our optimized oxidative cyclization conditions led to indole bis-oxazole **24** in near identical yield to that of its Z-protected counterpart **21**, suggesting the nature of the *N*-protecting group has a negligible effect on the yield of the bis-oxazole formation (Scheme 7).

Having established an efficient route for the biomimetic synthesis of the indole bis-oxazole fragment of diazonamide A by the oxidative cyclization of various tripeptides, attention next turned towards the construction of the biaryl bond from a tripeptide precursor. Our proposed route would foresee the construction of the A–B–C–D–E–F macrocyle **25** by the Witkop-type cyclization[36–38] of the brominated indole bis-oxazole **26**, in turn available via the now established oxidative cyclization of brominated tripeptide **27**, which would itself be prepared in an analogous fashion to **18** by simply incorporating 7-bromotryptophan (Scheme 8).

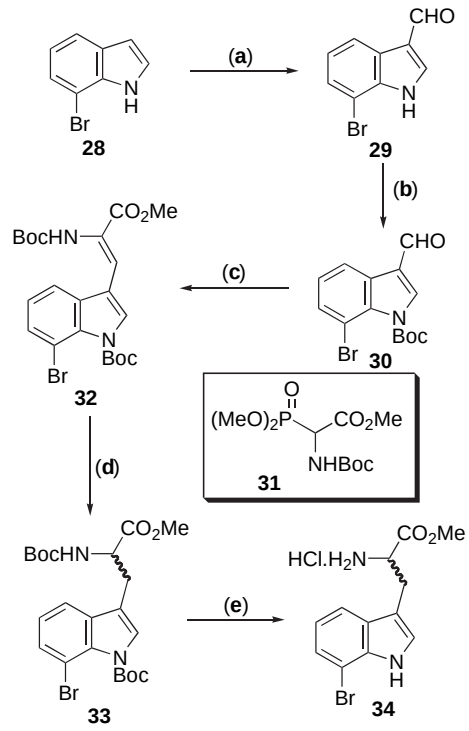


Scheme 8. Proposed macrocycle formation from tripeptide **27**.

Thus, the first consideration was the synthesis of 7-bromotryptophan. Vilsmeier formylation of 7-bromoindole **28**[39,40] gave 7-bromoindole-3-carbaldehyde **29**,[41] which underwent smooth Boc-protection delivering indole **30**. Horner–Wadsworth–Emmons olefination of **30** with our previously described phosphonoglycine **31**[17] gave alkene **32**, which underwent hydrogenation in the presence of the achiral rhodium catalyst [1,1′-bis(diisopropylphosphino)ferrocenyl]rhodium(cyclooctadiene) tetrafluoroborate] {[(DiPFc)Rh(COD)]$^{+}$BF$_4^{-}$} at 90 psi delivering the fully protected (±)-7-bromotryptophan **33**. Smooth removal of both Boc-groups with anhydrous HCl then gave the (±)-7-bromotryptophan **34**[9] as its hydrochloride salt (Scheme 9).

Coupling of the (±)-7-bromotryptophan **34** with Z-Val-OH successfully delivered the dipeptide **35** (dr=1:1). Saponification gave acid **36**, which underwent smooth coupling with H-Trp-OMe hydrochloride delivering the brominated tripeptide **27** (dr=1:1). Gratifyingly, exposing **27** to our established anhydrous Yonemitsu oxidation conditions delivered the brominated bis-oxazole **26**, albeit in a poor 14% yield. With the key precursor **26** to hand, the biaryl bond formation was attempted. Disappointingly however, despite subjecting **26** to the Witkop-type conditions successfully applied during previous syntheses of diazonamide A,[3,6,9] no macrocycle **25** was ever observed (Scheme 10).

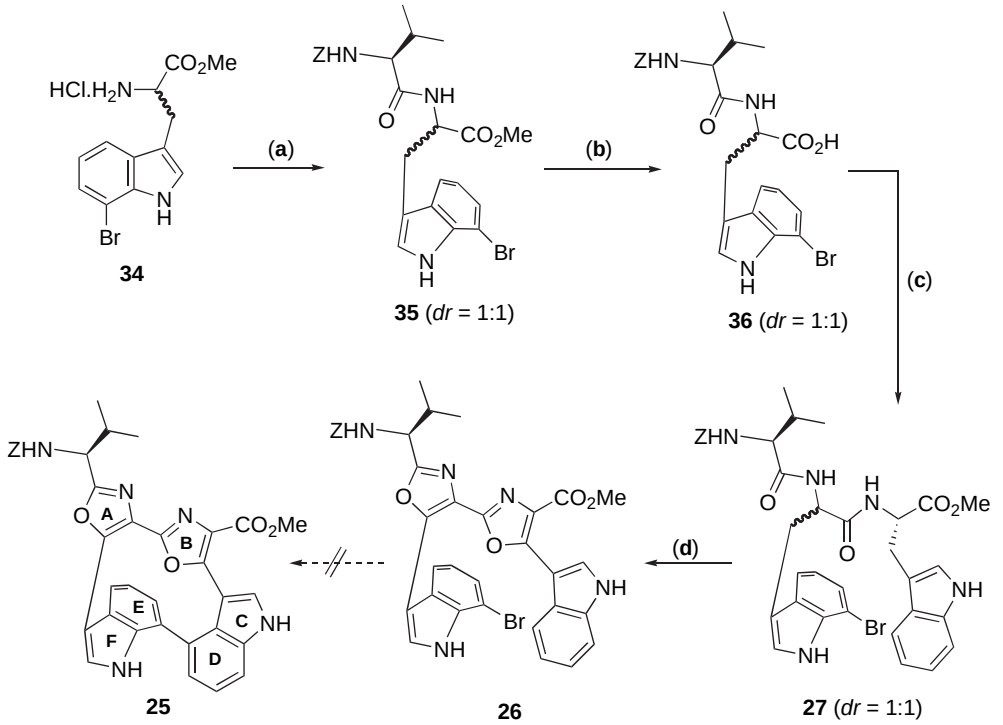
Finally, we chose to examine the more ambitious oxidative cyclization of a TyrValTrpTrp tetrapeptide, the putative precursor to diazonamide A itself. With amine **22** already to hand, its HBTU-mediated coupling to Z-Tyr-OH gave the TyrValTrpTrp tetrapeptide **37**. Gratifyingly, treatment of the tetrapeptide **37** with DDQ in anhydrous THF gave the indole bis-oxazole **38** directly, albeit in poor yield (17%). No aminal formation was observed during this reaction, suggesting DDQ is incapable of effecting the oxidative cyclization of the tyrosine side-chain as observed during the Harran synthesis of diazonamide A (Scheme 11).[9]



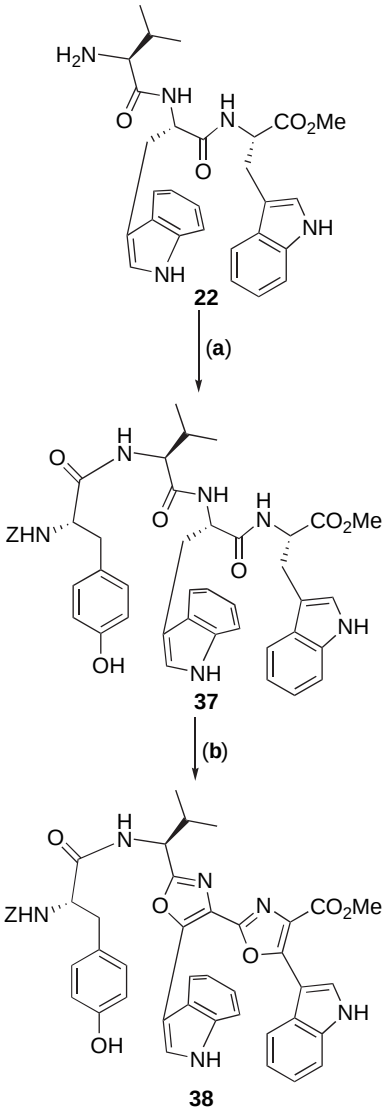
Scheme 9. Reagents and conditions: (a) $POCl_3$, DMF, 60 °C, 1 h, 63%; (b) $(Boc)_2O$, DMAP, MeCN, rt, 2 h, 87%; (c) phosphonoglycine **31**, DBU, LiCl, CH_2Cl_2, rt, 1 h, 89%; (d) H_2, 90 psi, [(DiPFc)Rh(COD)]$^{+}$BF$_4^{-}$, MeOH, rt, 48 h, 82%; (e) 4 M HCl in dioxane, 2 h, 76%.

3. Conclusions

A novel biomimetic oxidative cyclization of the tripeptide **8** provides the indole bis-oxazole core of diazonamide A concluding



Scheme 10. Reagents and conditions: (a) Z-Val-OH, HBTU, HOBt, *i*-Pr_2NEt, CH_2Cl_2, rt, 12 h, 71% (dr=1:1); (b) LiOH, MeOH/H_2O, rt, 12 h, 83% (dr=1:1); (c) H-Trp-OMe hydrochloride, HBTU, HOBt, *i*-Pr_2NEt, CH_2Cl_2, rt, 12 h, 55% (dr=1:1); (d) DDQ, THF, reflux, 3 h, 14%.



Scheme 11. Reagents and conditions: (a) Z-Tyr-OH, HBTU, HOBt, *i*-Pr_2NEt, CH_2Cl_2, rt, 12 h, 61%; (b) DDQ, THF, reflux, 3 h, 17%.

a four step synthetic sequence commencing from Boc-Trp-OH. Furthermore, this biomimetic transformation was applied to a series of tri- and tetrapeptides resulting in the direct formation of the heterocyclic core of diazonamide A. Oxidative cyclization of the brominated tripeptide **27** gave the indole bis-oxazole **26** directly, although its proposed Witkop-macrocyclization was not successful. These studies have established that oxidation of the indole-3-carbinyl position of a tryptophan (or tryptamine) precursor, followed by cyclodehydration is a viable basis for the formation of the heterocyclic core of diazonamide A.

4. Experimental

4.1. General

Commercially available reagents were used throughout without purification unless otherwise stated. Light petroleum refers to the fraction with boiling point 40–60 °C. Ether refers to diethyl ether. Reactions were routinely carried out under a nitrogen or argon atmosphere. Analytical thin layer chromatography was carried out on aluminium-backed plates coated with Merck Kieselgel 60 GF_{254}, and visualized under UV light (at 254 and/or 360 nm). Flash chromatography was carried out using Merck Kieselgel 60H silica or Matrex silica 60. Fully characterized compounds were chromatographically homogeneous.

Infrared spectra were recorded in the range 4000–600 cm^{-1} using a Nicolet Magna FT-550 spectrometer. NMR spectra were carried out on Bruker 300 and 400 MHz instruments (^1H frequencies, corresponding ^{13}C frequencies are 75 and 100 MHz). *J* values were recorded in hertz. Chemical shifts are quoted in parts per million and are referenced to TMS (as internal standard) or residual $CHCl_3$. In the ^{13}C spectra, signals corresponding to CH, CH_2 or CH_3 groups are noted; all others are C. Signal assignments were made by analysis of DEPT90/135, HMQC and HMBC experiments. In reporting NMR data for mixtures of diastereomers, signals arising from both isomers are reported separately where possible. High and low resolution mass spectra were recorded on a Micromass GCT TOF High Resolution mass spectrometer, or at the EPSRC Mass Spectrometry Service Centre (Swansea). Elemental analysis was carried out on a Perkin 2400 CHN analyzer to within ±0.5% of the theoretical values. Specific rotations were measured on an AA-1000 polarimeter and values are quoted in 10^{-1} deg cm^2 g^{-1}.

4.2. General procedure A: peptide couplings

To a solution of carboxylic acid (1 mmol), 1-hydroxybenzotriazole (2 mmol) and *N*,*N*-diisopropylethylamine (10 mmol) in dichloromethane (50 ml) was added HBTU (2 mmol) and the reaction mixture was then stirred for 30 min. Amine (1 mmol) was then added portionwise over 15 min. After stirring at room temperature for 12 h, the organic layer was washed with hydrochloric acid (2 M; 50 ml), saturated sodium hydrogen carbonate solution (50 ml) and brine (50 ml) then dried ($MgSO_4$), filtered, concentrated in vacuo and the crude product purified by flash chromatography on silica gel (ethyl acetate/light petroleum, 1:2) to give the coupled product.

4.3. General procedure B: anhydrous DDQ oxidations

A solution of the indole precursor (0.1 mmol) in THF (4 ml) was added dropwise to a stirred solution of freshly recrystallized DDQ (0.3 mmol) in THF (2 ml) and the reaction mixture was heated to reflux for 3 h. After cooling to room temperature, the solvent was concentrated in vacuo and the crude product partitioned between ethyl acetate (20 ml) and saturated sodium hydrogen carbonate solution (20 ml). The aqueous layer was removed and the organic layer washed with saturated sodium hydrogen carbonate solution (4×20 ml), water (10 ml) and brine (10 ml) then dried ($MgSO_4$), filtered, concentrated in vacuo and the crude product purified by flash chromatography on silica gel (ethyl acetate/light petroleum, 1:2) to give the bis-oxazole product.

4.4. General procedure C: aqueous DDQ oxidations

A solution of peptide (1 mmol) in THF/water (9/1, 4 ml) was added dropwise to a stirred solution of freshly recrystallized DDQ (2.2 mmol) in THF/water (9/1, 2 ml) and the reaction mixture was stirred at room temperature for 3 h. The solvent was concentrated in vacuo and the crude product partitioned between ethyl acetate (20 ml) and saturated sodium hydrogen carbonate solution (20 ml). The aqueous layer was removed and the organic layer washed with saturated sodium hydrogen carbonate solution (4×20 ml), water (10 ml) and brine (10 ml) then dried ($MgSO_4$), filtered, concentrated in vacuo and the crude product purified by flash chromatography on silica gel (ethyl acetate/light petroleum, 1:2) to give the product.

4.5. General procedure D: Boc deprotections

Hydrogen chloride in dioxane solution (4 M; 5–25 equiv) was added to the Boc-protected amine compound (1 mmol) and the reaction mixture was stirred at room temperature for 1–4 h. The solvent was concentrated in vacuo and the crude product dried (P_2O_5) at reduced pressure for 12 h to give the amine as its hydrochloride salt.

4.6. General procedure E: ester hydrolysis

Lithium hydroxide solution (1 M; 10 mmol) was added to a stirred solution of ester (0.5 mmol) in methanol (20 ml). The reaction mixture was stirred at room temperature for 12 h and the solvent was concentrated in vacuo. The resulting suspension was acidified to pH 2 with hydrochloric acid (2 M), and the whole was extracted with dichloromethane (3×10 ml). The combined organic layers were washed with hydrochloric acid (2 M; 30 ml), water (30 ml) and brine (30 ml) then dried ($MgSO_4$), filtered and concentrated in vacuo to give the carboxylic acid product.

4.6.1. (S,S)-Methyl 2-(2-benzyloxycarbonylamino-3-methylbutanoyl amino)-3-(indol-3-yl)-propanoate (Z-Val-Trp-OMe) ***9***. According to general procedure **A** the *title compound* was obtained from Z-Val-OH (250 mg, 1 mmol) and H-Trp-OMe hydrochloride (255 mg, 1 mmol) as a colourless solid (384 mg, 85%); mp 150–151 °C (from ethanol/light petroleum) (lit.[29], mp not given); $[\alpha]_D^{26}$ +6.9 (*c* 1.0, CH_2Cl_2); (Found: MH^+, 452.2176. $C_{25}H_{29}N_3O_5$+H requires 452.2185); ν_{max} (KBr)/cm^{-1} 3379, 3307, 2958, 1725, 1695, 1649, 1531, 1457, 1389, 1289, 1242, 1134, 1109, 1094, 1037, 739, 699, 630; δ_H (300 MHz; $CDCl_3$) 8.12 (1H, br s, NH), 7.26 (1H, d, *J* 7.6, ArH), 7.09–6.99 (5H, m, ArH), 6.94–6.87 (2H, m, ArH), 6.85–6.63 (2H, m, ArH), 5.32 (1H, d, *J* 9.1, NH), 4.80–4.73 (3H, m, C*H*$_2$Ph and CH of CH_2), 4.57 (1H, d, *J* 7.5, NH), 4.05 (1H, dd, *J* 5.7 and 8.9, CH of CH_2), 3.41 (3H, s, Me), 3.05–3.00 (2H, m, CH_2), 1.88–1.82 (1H, m, C*H*Me_2), 0.71 (3H, d, *J* 6.5, CH*Me*Me), 0.64 (3H, d, *J* 6.5, CHMe*Me*); δ_C (75 MHz; $CDCl_3$) 172.5, 172.0, 156.9, 136.7, 136.4, 128.9 (CH), 128.52 (CH), 128.49 (CH), 127.7, 123.7 (CH), 122.5 (CH), 120.0 (CH), 118.8 (CH), 111.8 (CH), 109.6, 67.4 (CH_2), 60.3 (CH), 53.2 (CH), 52.8 (Me), 32.0 (CH), 28.0 (CH_2), 19.5 (Me), 17.9 (Me); *m*/*z* (CI) 452 (MH^+, 34%), 451 (M^+, 10), 434 (6), 408 (38), 372 (10), 345 (9), 345 (22), 344 (100), 343 (14), 318 (8), 313 (8), 312 (28), 309 (11).

4.6.2. (S,S)-Methyl 2-(2-benzyloxycarbonylamino-3-methylbutanoyl amino)-3-(indol-3-yl)-3-oxopropanoate ***10***. According to general procedure **C** the *title compound* was obtained from **9** (451 mg, 1 mmol) as a colourless solid (233 mg, 50%), mp 85–87 °C (from dichloromethane/light petroleum); $[\alpha]_D^{26}$ +4.9 (*c* 1.1, $CHCl_3$); (Found: C, 64.2; H, 6.0; N, 8.7. $C_{25}H_{27}N_3O_6$ requires C, 64.5; H, 5.9; N, 9.0%); (Found: M^+, 465.1916. $C_{25}H_{27}N_3O_6$ requires 465.1900); ν_{max} (KBr)/cm^{-1} 3377, 2962, 1715, 1646, 1519, 1435, 1244, 1026, 749, 697; δ_H (400 MHz; DMSO-d_6) 12.24 (1H, br s, NH), 8.76 (1H, d, *J* 7.4, NH), 8.45 (1H, d, *J* 3.3, ArH), 8.13 (1H, dd, *J* 2.0 and 6.5, ArH), 7.50 (9H, m, 8 ArH and NH), 5.95 (1H, d, *J* 7.4, CH), 5.00 (2H, m, CH_2), 4.03 (1H, m, CH), 3.62 (3H, s, Me), 1.97 (1H, m, C*H*Me_2), 0.88–0.78 (6H, m, CH*Me*$_2$); δ_C (100 MHz; DMSO-d_6) 185.9, 171.9, 168.8, 156.5, 137.4, 137.0, 136.8 (CH), 128.8 (CH), 128.2 (CH), 128.1 (CH), 125.9, 123.8 (CH), 122.8 (CH), 121.5 (CH), 114.2, 112.9 (CH), 65.8 (CH_2), 60.1 (CH), 59.1 (CH), 52.8 (Me), 30.9 (CH), 19.5 (Me), 18.4 (Me); *m*/*z* (EI); 465 (M^+, 3%), 236 (16), 234 (14), 233 (14), 216 (16), 201 (11), 173 (11), 162 (23), 158 (12), 146 (27), 143 (10), 132 (14), 130 (26), 117 (25), 116 (35), 108 (28), 107 (22), 91 (100), 90 (16), 89 (28), 88 (17), 79 (30), 77 (23), 72 (21), 65 (16), 55 (12).

4.6.3. (S)-Methyl 2-(1-benzyloxycarbonylamino-2-methylpropyl)-5-(indol-3-yl)-oxazole-4-carboxylate ***11***.

4.6.3.1. Method 1. Triethylamine (610 μl, 4.4 mmol) was added dropwise to a stirred solution of iodine (559 mg, 2.2 mmol) and triphenylphosphine (576 mg, 2.2 mmol) in dichloromethane (3 ml). After stirring for 15 min, a solution of **10** (465 mg, 1 mmol) in dichloromethane (3 ml) was added dropwise over 10 min. The mixture was stirred at room temperature for 3 h, concentrated in vacuo and purified by flash chromatography on silica gel (ethyl acetate/light petroleum, 1:2) to give the *title compound* as an orange solid (308 mg, 69%), mp 99–101 °C (from chloroform/light petroleum); $[\alpha]_D^{26}$ +20.3 (*c* 0.8, THF); (Found: C, 67.4; H, 5.7; N, 9.5. $C_{25}H_{25}N_3O_5$ requires C, 67.1; H, 5.6; N, 9.4%); (Found: M^+, 447.1792. $C_{25}H_{25}N_3O_5$ requires 447.1794); ν_{max} (KBr)/cm^{-1} 3341, 2958, 1927, 1683, 1596, 1568, 1532, 1497, 1458, 1429, 1373, 1331, 1280, 1246, 1215, 1160, 1143, 1130, 1100, 1091, 1038, 928, 816, 784, 736, 696, 664, 598; δ_H (300 MHz; $CDCl_3$) 8.66 (1H, br s, NH), 8.60 (1H, d, *J* 3.0, ArH), 7.92 (1H, d, *J* 9.0, ArH), 7.26 (1H, dd, *J* 3.0 and 6.0, ArH), 7.21–7.04 (7H, m, ArH), 5.42 (1H, d, *J* 9.0, NH), 5.01–4.91 (2H, m, CH_2), 4.81 (1H, dd, *J* 6.0 and 9.0, CH), 3.77 (3H, s, Me), 2.18 (1H, m, C*H*Me_2), 0.75 (6H, d, *J* 6.0, CH*Me*$_2$); δ_C (100 MHz; $CDCl_3$) 163.1, 159.7, 156.3, 155.0, 136.1, 135.8, 128.7 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 125.0, 123.2 (CH), 122.7, 121.6 (CH), 121.1 (CH), 111.8 (CH), 103.7, 67.3 (CH_2), 55.0 (CH), 52.0 (Me), 32.8 (CH), 19.0 (Me), 18.2 (Me); *m*/*z* (EI); 447 (M^+, 9%), 340 (12), 339 (53), 297 (25), 296 (93), 241 (27), 211 (14), 183 (9), 155 (23), 154 (11), 116 (22), 114 (14), 92 (11), 91 (100), 90 (11), 83 (12), 81 (10), 78 (11), 65 (18), 57 (20), 55 (26).

4.6.3.2. Method 2. According to general procedure **B** but using 2.2 equiv DDQ, the *title compound* was obtained from **9** (45 mg, 0.1 mmol) as an orange solid (29 mg, 64%), spectroscopic data as above.

4.6.4. (S)-2-(1-Benzyloxycarbonylamino-2-methylpropyl)-5-(indol-3-yl)oxazole-4-carboxylic acid ***5***. According to general procedure **E** the *title compound* was obtained from **11** (224 mg, 0.5 mmol) as an orange solid (182 mg, 82%), mp 207–208 °C (from chloroform/hexanes); $[\alpha]_D^{31}$ +10.6 (*c* 0.9, THF); (Found: C, 66.5; H, 5.7; N, 9.6. $C_{24}H_{23}N_3O_5$ requires C, 66.5; H, 5.4; N, 9.3%); (Found: M^+, 433.1625. $C_{24}H_{23}N_3O_5$ requires 433.1638); ν_{max} (KBr)/cm^{-1} 3409, 1702, 1597, 1525, 1457, 1411, 1339, 1244, 1129, 1027, 744, 697; δ_H (400 MHz; DMSO-d_6) 12.71 (1H, br s, CO_2H), 11.85 (1H, br s, NH), 8.64 (1H, d, *J* 2.9, ArH), 8.18 (1H, d, *J* 8.6, NH), 8.11 (1H, d, *J* 8.0, ArH), 7.50 (1H, d, *J* 8.0, ArH), 7.36–7.14 (7H, m, ArH), 5.07 (2H, m, CH_2), 4.58 (1H, m, CH), 2.27 (1H, m, C*H*Me_2), 1.00 (3H, d, *J* 6.7, CH*Me*Me), 0.87 (3H, d, *J* 6.7, CHMe*Me*); δ_C (100 MHz; DMSO-d_6) 164.2, 159.9, 156.7, 154.1, 137.4, 136.4, 130.4 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH), 125.2, 123.2, 123.0 (CH), 121.34 (CH), 121.28 (CH), 112.7 (CH), 102.9, 66.1 (CH_2), 55.5 (CH), 31.4 (CH), 19.6 (Me), 19.2 (Me); *m*/*z* (EI); 433 (M^+, 4%), 325 (10), 238 (24), 210 (10), 156 (23), 155 (24), 144 (33), 142 (11), 130 (22), 128 (12), 117 (18), 116 (16), 114 (11), 108 (42), 107 (33), 100 (38), 98 (11), 90 (11), 89 (21), 79 (54), 78 (12), 77 (40), 65 (14), 63 (11), 56 (11), 51 (18).

4.6.5. N-tert-Boc-3-aminoacetylindole ***13***. According to general procedure **C** the *title compound* was obtained from *N*-Boc tryptamine[32] **12** (260 mg, 1 mmol) as a colourless solid (156 mg, 60%), mp 215–220 °C (from ethanol/light petroleum); (lit.[6], mp not given); (Found: M^+, 274.1326. $C_{15}H_{18}N_2O_3$ requires 274.1317); ν_{max} (KBr)/cm^{-1} 3331, 3262, 3120, 2981, 2917, 1690, 1648, 1536, 1518, 1369, 1294, 1169, 923, 746, 641, 618; δ_H (300 MHz; DMSO-d_6) 12.01 (1H, br s, NH), 8.42 (1H, d, *J* 3.0, ArH), 8.17 (1H, d, *J* 6.6, ArH), 7.48 (1H, dd, *J* 1.8 and 5.6, ArH), 7.25–7.17 (2H, m, ArH), 7.02 (1H, t, *J* 5.8, NH), 4.30 (2H, d, *J* 5.8, CH_2), 1.42 (9H, s, CMe_3); δ_C (75 MHz; DMSO-d_6) 191.1, 156.3, 136.7, 133.7 (CH), 125.7, 123.2 (CH), 122.2 (CH), 121.5 (CH), 114.3, 112.5 (CH), 78.2, 47.2 (CH_2), 28.6 (Me); *m*/*z* (CI) 274 (M^+, 3%), 200 (10), 144 (100), 116 (23), 89 (17), 57 (9).

4.6.6. N-3-Aminoacetylindole hydrochloride ***6***. According to general procedure **D** the *title compound* was obtained from **13** (275 mg, 1 mmol) and HCl in dioxane solution (4 M; 2.5 ml, 10 mmol, 4 h) as a pink solid (188 mg, 89%), mp >260 °C (from water/THF/light

petroleum) (lit.[33], mp >250 °C, solvent not stated) (Found: MH^+ (free amine), 175.0878. $C_{10}H_{10}N_2O$+H requires 175.0871); ν_{max} (KBr)/cm^{-1} 3414, 3110, 2925, 1664, 1523, 1477, 1459, 1437, 1391, 1347, 1314, 1243, 1165, 1107, 924, 897, 754; δ_H (300 MHz; DMSO-d_6) 12.38 (1H, br s, NH), 8.45 (1H, d, *J* 2.8, ArH), 8.27 (3H, br s, $-NH_3$), 8.11 (1H, d, *J* 4.9, ArH), 7.47 (1H, m, ArH), 7.22–7.18 (2H, m, ArH), 4.30 (2H, d, *J* 5.2, CH_2); δ_C (75 MHz; DMSO-d_6) 187.1, 135.5 (CH), 125.4, 123.6 (CH), 122.7 (CH), 121.2 (CH), 113.4, 112.8 (CH), 44.2 (CH_2), 1×C not observed; *m*/*z* (CI) 175 (MH^+, 100%), 160 (14), 158 (27), 157 (46), 144 (26), 118 (61).

4.6.7. (S)-2-(1-Benzyloxycarbonylamino-2-methylpropyl)-5-(indol-3-yl)-N-[2-(indol-3-yl)-2-oxo-ethyl]oxazole-4-carbamide ***14***

4.6.7.1. Method 1. According to general procedure **A** the *title compound* was obtained from acid **5** (433 mg, 1 mmol) and amine **6** (210 mg, 1 mmol) as colourless solid (247 mg, 42%); mp 79–81 °C (from ethyl acetate/light petroleum); $[\alpha]_D^{31}$ −9.7 (*c* 0.7, THF); (Found: M+NH_4^+, 607.2668. $C_{34}H_{31}N_5O_5$+NH_4^+ requires 607.2663); ν_{max} (KBr)/cm^{-1} 3421, 1710, 1637, 1508, 1430, 1384, 1245, 1119, 1070, 940, 847, 744, 558; δ_H (300 MHz; DMSO-d_6); 12.08 (1H, br s, NH), 11.81 (1H, br s, NH), 8.89 (1H, s, ArH), 8.51 (1H, s, ArH), 8.26 (1H, br m, NH), 8.24 (1H, br m, NH), 8.18–8.16 (2H, m, ArH), 7.48 (2H, d, *J* 7.4, ArH), 7.37–7.35 (2H, m, ArH), 7.30–7.28 (2H, m, ArH), 7.22–7.14 (5H, m, ArH), 5.08 (2H, s, CH_2), 4.70 (2H, d, *J* 4.7, CH_2), 4.67–4.63 (1H, m, CH), 2.37–2.32 (1H, m, C*H*Me_2), 1.05 (3H, d, *J* 6.3, CH*Me*Me), 0.93 (3H, d, *J* 6.3, CHMe*Me*); δ_C (100 MHz; DMSO-d_6) 190.3, 165.0, 162.0, 159.5, 156.7, 151.3, 137.3, 136.9, 136.5, 134.1 (CH), 130.3 (CH), 128.8 (CH), 128.3 (CH), 125.9, 125.2 (CH), 125.1, 123.4 (CH), 122.8 (CH), 122.4 (CH), 121.6 (CH), 121.3 (CH), 121.1 (CH), 114.4, 112.7 (CH), 103.1 (CH), 66.1 (CH_2), 55.7 (CH), 46.3 (CH_2), 31.4 (CH), 19.7 (Me), 19.3 (Me), 1×C not observed; *m*/*z* (ES^+) 607 (M^+, 4%), 590 (33), 484 (27), 483 (100), 462 (25), 461 (72), 445 (18), 430 (52), 413 (88), 400 (15), 72 (99).

4.6.8. (S)-2-(1-Benzyloxycarbonylamino-2-methylpropyl)-5-(indol-3-yl)-N-[2-(indol-3-yl)-ethyl]oxazole-4-carboxamide ***15***. According to general procedure **A** the *title compound* was obtained from acid **5** (433 mg, 1 mmol) and tryptamine (192 mg, 1.2 mmol) as a colourless solid (449 mg, 78%); mp 192–193 °C (from chloroform); $[\alpha]_D^{32}$ −45.0 (*c* 0.2, THF); (Found: C, 70.7; H, 5.8; N, 12.1. $C_{34}H_{33}N_5O_4$ requires C, 70.9; H, 5.8; N, 12.2%), (Found: M^+, 575.2548. $C_{34}H_{33}N_5O_4$ requires 575.2533); ν_{max} (KBr)/cm^{-1} 3407, 2925, 2854, 1696, 1641, 1594, 1540, 1458, 1384, 1243, 1126, 1026, 944, 744, 697, 586; δ_H (400 MHz; DMSO-d_6); 11.78 (1H, br s, NH), 10.81 (1H, br s, NH), 8.93 (1H, d, *J* 2.8, ArH), 8.20 (1H, d, *J* 8.4, NH), 8.15 (2H, m, ArH), 7.61 (1H, d, *J* 7.9, ArH), 7.48 (1H, d, *J* 7.9, ArH), 7.35–7.27 (6H, m, 5 ArH and NH), 7.20–7.12 (3H, m, ArH), 7.05 (1H, t, *J* 7.1, ArH), 6.98 (1H, t, *J* 7.4, ArH), 5.09–5.03 (2H, d, *J* 12.7, CH_2), 4.58 (1H, m, CH), 3.55 (2H, br m, CH_2), 2.94 (2H, t, *J* 7.5, CH_2), 2.32–2.27 (1H, m, C*H*Me_2), 1.02 (3H, d, *J* 6.6, CH*Me*Me), 0.88 (3H, d, *J* 6.6, CHMe*Me*); δ_C (100 MHz; DMSO-d_6) 161.8, 159.2, 156.6, 151.0, 137.3, 136.7, 136.5, 130.3 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH) 127.7, 125.5, 125.1, 123.0 (CH), 122.7 (CH), 121.4 (CH), 121.3 (CH), 121.1 (CH), 118.9 (CH), 118.7 (CH), 112.6 (CH), 112.3, 111.8 (CH), 103.2, 66.1 (CH_2), 55.6 (CH), 40.8 (CH_2), 31.4 (CH), 26.0 (CH_2), 19.6 (Me), 19.3 (Me); *m*/*z* (FI) 575 (M^+, 2%), 468 (29), 467 (100), 426 (28), 424 (22), 410 (10), 186 (26), 108 (59).

4.6.9. (S)-2-(1-Benzyloxycarbonylamino-2-methylpropyl)-5-(indol-3-yl)-N-[2-(indol-3-yl)-2-oxo-ethyl]oxazole-4-carbamide ***14***

4.6.9.1. Method 2. According to general procedure **C** the *title compound* was obtained from **15** (575 mg, 1 mmol) as a colourless solid (489 mg, 83%); data as above.

4.6.10. (S)-2-(1-Benzyloxycarbonylamino-2-methylpropyl)-5-(indol-3-yl)-N-[2-(indol-3-yl)-[2,4]bis-oxazoyl-2-yl ***7***

4.6.10.1. Method 1. Triethylamine (900 μl, 6.4 mmol) was added dropwise to a stirred solution of hexachloroethane (752 mg, 3.2 mmol) and triphenylphosphine (832 mg, 3.2 mmol) in THF (3 ml). After stirring for 15 min, a solution of **14** (850 mg, 1.44 mmol) in THF (6 ml) was added dropwise. The reaction mixture was stirred at room temperature for 30 h, concentrated in vacuo and purified by flash chromatography on silica gel (ethyl acetate/light petroleum, 1:3) to give the *title compound* as an orange solid (395 mg, 48%); mp 124–125 °C (from dichloromethane); $[\alpha]_D^{33}$ −25.0 (*c* 0.2, THF); (Found: MH^+, 572.2288. $C_{34}H_{29}N_5O_4$+H requires 572.2292); ν_{max} (KBr)/cm^{-1} 3403, 1705, 1631, 1509, 1457, 1425, 1338, 1242, 1118, 1042, 1013, 962, 914, 742, 697; δ_H (400 MHz; DMSO-d_6) 11.84 (1H, br d, *J* 2.9, NH), 11.64 (1H, br d, *J* 2.5, NH), 9.13 (1H, d, *J* 2.9, ArH), 8.27 (1H, br d, *J* 8.6, NH), 8.15 (1H, d, *J* 8.0, ArH), 7.90 (1H, d, *J* 7.8, ArH), 7.83 (1H, d, *J* 2.5, ArH), 7.71 (1H, s, ArH), 7.53 (1H, d, *J* 8.0, ArH), 7.47 (1H, d, *J* 8.0, ArH), 7.35 (2H, m, ArH), 7.29–7.15 (7H, m, ArH), 5.08 (2H, m, CH_2), 4.68 (1H, m, CH), 2.35 (1H, m, C*H*Me_2), 1.05 (3H, d, *J* 6.6, CH*Me*Me), 0.94 (3H, d, *J* 6.6, CHMe*Me*); δ_C (100 MHz; DMSO-d_6) 161.1, 156.7, 154.0, 148.1, 147.7, 137.4, 136.9, 136.5, 128.80 (CH), 128.76 (CH), 128.3 (CH), 128.2 (CH), 125.0, 124.1 (CH), 124.0, 123.0 (CH), 122.7 (CH), 121.2 (CH), 121.1 (CH), 120.7 (CH), 120.6, 120.0 (CH), 112.6 (CH), 103.9, 103.4, 66.1 (CH_2), 55.7 (CH), 31.5 (CH), 19.7 (Me), 19.3 (Me), 2×CH not observed; *m*/*z* (ES^+) 572 (MH^+, 100%), 119 (21), 91 (59), 72 (38).

4.6.11. (S)-Nα-tert-Butoxycarbonyl-N-(3-indolyl)ethyl tryptophanamide (Boc-Trp-Tryptamine) ***16***. According to general procedure **A** the *title compound* was obtained from Boc-Trp-OH (305 mg, 1 mmol) and tryptamine (161 mg, 1 mmol) as a colourless solid (446 mg, 100%), mp 92–93 °C (from ethanol/light petroleum); $[\alpha]_D^{32}$ +6.8 (*c* 1.0, EtOH); (Found: C, 69.6; H, 6.9; N, 12.3. $C_{26}H_{30}N_4O_3$ requires C, 69.9; H, 6.8; N, 12.6%); (Found: MH^+, 447.2411. $C_{26}H_{30}N_4O_3$+H requires 447.2396); ν_{max} (KBr)/cm^{-1} 3411, 3319, 2970, 2919, 1705, 1655, 1521, 1511, 1460, 1367, 1250, 1163, 733; δ_H (300 MHz; DMSO-d_6) 10.87 (2H, br s, 2 NH), 8.05 (1H, br m, NH), 7.63 (1H, d, *J* 7.8, ArH), 7.58 (1H, d, *J* 7.8, ArH), 7.38 (2H, d, *J* 7.9, ArH), 7.18–7.00 (6H, m, ArH), 6.81 (1H, d, *J* 8.2, NH), 4.21 (1H, dd, *J* 8.4 and 13.7, CH), 3.40 (2H, m, CH_2), 3.10 (1H, dd, *J* 4.7 and 13.7, CH), 2.98–2.79 (3H, m, CH and CH_2), 1.37 (9H, s, CMe_3); δ_C (75 MHz; DMSO-d_6) 172.2, 155.5, 136.6, 136.4, 127.7, 127.5, 123.9 (CH), 123.0 (CH), 121.3 (CH), 121.2 (CH), 118.9 (CH), 118.61 (CH), 118.57 (CH), 118.49 (CH), 112.1, 111.7 (CH), 111.6 (CH), 110.7, 78.3, 55.5 (CH), 39.9 (CH_2), 28.5 (Me), 28.3 (CH_2), 25.4 (CH_2); *m*/*z* (CI) 447 (MH^+, 2%), 375 (10), 373 (31), 348 (19), 347 (85), 244 (42), 201 (22), 171 (25), 159 (20), 158 (23), 155 (21), 144 (58), 130 (100), 125 (18), 91 (16).

4.6.12. (S)-N-(3-indolyl)ethyl tryptophanamide hydrochloride (H-Trp-Tryptamine) ***17***. According to general procedure **D** the *title compound* was obtained from **16** (447 mg, 1 mmol) and HCl in dioxane solution (4 M; 1.3 ml, 5 mmol, 1 h) as a colourless solid (352 mg, 92%), mp 135–138 °C (decomp.); $[\alpha]_D^{32}$ +44.5 (*c* 1.0, EtOH); (Found: M^+ (free amine), 346.1812. $C_{21}H_{22}N_4O$ requires 346.1794); ν_{max} (KBr)/cm^{-1} 3407, 1669, 1546, 1490, 1457, 1340, 1229, 1096, 743; δ_H (300 MHz; DMSO-d_6) 10.87 (1H, br s, NH), 10.70 (1H, br s, NH), 8.54 (1H, br t, *J* 5.0, NH), 8.06 (3H, br s, $-NH_3$), 7.45 (1H, d, *J* 7.8, ArH), 7.38 (1H, d, *J* 8.1, ArH), 7.14 (2H, m, ArH), 7.01 (1H, s, ArH), 6.91–6.74 (5H, m, ArH), 3.74 (1H, m, CH), 3.19–3.10 (2H, m, CH_2), 2.92 (2H, t, *J* 7.2, CH_2), 2.53 (2H, t, *J* 7.2, CH_2); δ_C (75 MHz; DMSO-d_6) 168.6, 136.6, 127.5, 127.4, 125.2, 123.2, 121.4 (CH), 121.3 (CH), 118.9 (CH), 118.7 (CH), 118.6 (CH), 118.5 (CH), 111.8 (CH), 111.7, 107.4, 53.2 (CH), 40.0 (CH_2), 27.6 (CH_2), 25.2 (CH_2), 1×C and 1×CH not observed; *m*/*z* (EI) 346 (M^+, 8%), 371 (11), 329 (16), 217 (10), 171 (13), 159 (17), 130 (100), 115 (14), 103 (12), 77 (13).

4.6.13. (S,S)-Benzyl-(1,2{-(indol-3-yl)-1-[2-(indol-3-yl)-ethylcarbamoyl]ethylcarbamoyl}-2-methylpropyl)carbamate (Z-Val-Trp-Tryptamine) ***8***. According to general procedure **A** the *title compound* was

obtained from Z-Val-OH (303 mg, 1.2 mmol) and amine **17** (383 mg, 1 mmol) as a colourless solid (394 mg, 68%), mp 198–200 °C (from chloroform/light petroleum); $[\alpha]_D^{26}$ −10.0 (*c* 1.1, EtOH); (Found: C, 70.2; H, 6.4; N, 11.9. $C_{34}H_{37}N_5O_4$ requires C, 70.5; H, 6.4; N, 12.1%); (Found: M^+, 579.2843. $C_{34}H_{37}N_5O_4$ requires 579.2840); ν_{max} (KBr)/cm^{-1} 3413, 3286, 3057, 2960, 2927, 1695, 1642, 1533, 1457, 1292, 1244, 1227, 1091, 1042, 852, 740, 695; δ_H (400 MHz; DMSO-d_6) 10.76 (1H. br s, NH), 10.74 (1H, br s, NH), 7.93 (1H, br t, *J* 5.2, NH), 7.91 (1H, br m, NH), 7.54 (1H, d, *J* 7.7, ArH), 7.47 (1H, d, *J* 7.7, ArH), 7.34–7.30 (8H, m, 7×ArH and NH), 7.12 (1H, d, *J* 1.4, ArH), 7.07–7.03 (3H, m, ArH), 6.94 (2H, m, ArH), 5.03 (2H, d, *J* 12.7, CH_2), 4.52 (1H, m, CH), 3.86 (1H, dd, *J* 6.9 and 8.6, CH), 3.28 (2H, br m, CH_2), 3.05 (1H, dd, *J* 8.6 and 14.5, CH of CH_2), 2.96 (1H, dd, *J* 7.6 and 14.5, CH of CH_2), 2.69 (2H, t, *J* 6.2, CH_2), 1.92 (1H, m, C*H*Me_2), 0.75 (6H, d, *J* 6.8, CH*Me*$_2$); δ_C (100 MHz; DMSO-d_6) 171.5, 171.2, 156.6, 137.5, 136.7, 136.5, 128.8 (CH), 128.2 (CH), 128.1 (CH), 127.8, 127.6, 124.0 (CH), 123.0 (CH), 121.33 (CH), 121.25 (CH), 118.9 (CH), 118.7 (CH), 112.1, 111.8 (CH), 111.6 (CH), 110.4, 65.9 (CH_2), 60.8 (CH), 53.8 (CH), 39.8 (CH_2), 30.8 (CH), 28.5 (CH_2), 25.4 (CH_2), 19.6 (Me), 18.5 (Me), 2×CH not observed; *m*/*z* (EI) 579 (M^+, 2%), 471 (10), 384 (8) 372 (12), 330 (23), 329 (100), 310 (31), 285 (49), 284 (90), 143 (26), 130 (70), 129 (30), 102 (21), 77 (20), 63 (10).

4.6.14. (S)-2-(1-Benzyloxycarbonylamino-2-methylpropyl)-5-(indol-3-yl)-N-[2-(indol-3-yl)-[2,4]bis-oxazoyl-2-yl ***7***

4.6.14.1. Method 2. According to general procedure **B** the *title compound* was obtained from tripeptide **8** (58 mg, 0.1 mmol) as an orange solid (8 mg, 14%); data as described previously.

4.6.15. (S,S)-Methyl 2-[2-tert-butoxycarbonylamino-3-(indol-3-yl)-propionylamino]-3-(indol-3-yl)propanoate (Boc-Trp-Trp-OMe) ***19****.* According to general procedure **A** the *title compound* was obtained from Boc-Trp-OH (305 mg, 1 mmol) and H-Trp-OMe hydrochloride (255 mg, 1 mmol) as a colourless solid (328 mg, 65%), mp 73–75 °C (from dichloromethane/light petroleum) (lit.[35], mp not given); $[\alpha]_D^{32}$ −17.8 (*c* 1.02, MeOH); (lit.[35], $[\alpha]_D^{25}$ −15.0 (*c* 0.9, MeOH)); ν_{max} (KBr)/cm^{-1} 3401, 3329, 3047, 2996, 2924, 1726, 1700, 1649, 1516, 1449, 1383, 1352, 1326, 1245, 1194, 1157, 728; δ_H (400 MHz; DMSO-d_6) 10.88 (1H, br s, NH), 10.79 (1H, br s, NH), 8.28 (1H, d, *J* 7.3, NH), 7.57 (1H, d, *J* 7.8, ArH), 7.46 (1H, d, *J* 7.8, ArH), 7.33–7.31 (2H, m, ArH), 7.16 (1H, s, ArH), 7.07–7.02 (3H, m, ArH), 6.99–6.93 (2H, m, ArH), 6.72 (1H, d, *J* 8.4, NH), 4.58–4.55 (1H, dd, *J* 7.0 and 13.8, CH), 4.24–4.21 (1H, m, CH), 3.54 (3H, s, Me), 3.18–3.07 (2H, m, CH_2), 3.01 (1H, dd, *J* 4.8 and 15.3, CH), 2.88–2.83 (1H, m, CH), 1.28 (9H, s, CMe_3); δ_C (100 MHz; DMSO-d_6) 172.7, 172.6, 155.6, 136.51, 136.47, 127.8, 127.5, 124.2 (CH), 124.1 (CH), 121.4 (CH), 121.3 (CH), 119.0 (CH), 118.9 (CH), 118.6 (CH), 118.4 (CH), 111.9 (CH), 111.7 (CH), 110.6, 109.6, 78.5, 55.4 (CH), 53.5 (CH), 52.3 (Me), 28.6 (Me), 28.1 (CH_2), 27.6 (CH_2).

4.6.16. (S,S)-Methyl 2-[2-amino-3-(indol-3-yl)propionylamino]-3-(indol-3-yl)propanoate hydrochloride (H-Trp-Trp-OMe) ***20****.* According to general procedure **D** the *title compound* was obtained from **19** (506 mg, 1 mmol) and HCl in dioxane (4 M; 1.8 ml, 7 mmol, 1 h) as a beige solid (433 mg, 98%), mp 152–154 °C; $[\alpha]_D^{32}$ +9.1 (*c* 0.9, EtOH); (Found: MH^+ (free amine), 405.1926. $C_{23}H_{24}N_4O_3$+H requires 405.1926); ν_{max} (KBr)/cm^{-1} 3375, 3325, 2929, 2842, 1731, 1675, 1536, 1454, 1429, 1367, 1203, 1116, 733; δ_H (400 MHz; DMSO-d_6) 11.09 (1H, br s, NH), 11.02 (1H, br s, NH), 9.24 (1H, d, *J* 7.2, NH), 8.22 (3H, br s, –NH_3), 7.72 (1H, d, *J* 7.8, ArH), 7.48 (1H, d, *J* 7.8, ArH), 7.34 (2H, dd, *J* 3.0 and 8.0, ArH), 7.23 (2H, m, ArH), 7.05 (2H, m, ArH), 6.96 (2H, m, ArH), 4.58 (1H, dd, *J* 6.9 and 14.0, CH), 4.05 (1H, m, CH), 3.54 (3H, s, Me), 3.36 (1H, dd, *J* 7.0 and 14.7, CH), 3.27 (1H, dd, *J* 5.4 and 14.7, CH), 3.15 (2H, m, CH_2); δ_C (100 MHz; DMSO-d_6) 172.1, 169.2, 136.7, 136.6, 127.6, 127.4, 125.5 (CH), 124.6 (CH), 121.5, 121.4, 119.1 (CH), 118.9 (CH), 118.8, 118.3 (CH), 112.0 (CH), 111.9 (CH), 109.3, 107.2, 53.9 (CH), 52.9 (CH), 52.5 (Me), 27.7 (CH_2), 27.6 (CH_2); *m*/*z* (CI) 405 (MH^+, 27%), 388 (13), 387 (15), 288 (11), 259 (13), 256 (16), 244 (38), 130 (100).

4.6.17. (S,S,S)-Benzyl-1,2{-(indol-3-yl)-1-[2-(indol-3-yl)-3-methylbutanoylamino]-3-(indol-3-yl)-propionylamino}-3-(indol-3-yl)propanoate (Z-Val-Trp-Trp-OMe) ***18****.* According to general procedure **A** the *title compound* was obtained from Z-Val-OH (303 mg, 1.2 mmol) and amine **20** (441 mg, 1 mmol) as a colourless solid (490 mg, 77%), mp 181–182 °C (from dichloromethane/light petroleum); $[\alpha]_D^{31}$ +12.4 (*c* 0.9, THF); (Found: C, 67.5; H, 6.2; N, 11.0. $C_{36}H_{39}N_5O_6$ requires C, 67.8; H, 6.2; N, 11.0%); (Found: MH^+, 638.2975. $C_{36}H_{39}N_5O_6$+H requires 638.2973); ν_{max} (KBr)/cm^{-1} 3404, 3316, 3058, 2961, 1705, 1651, 1521, 1457, 1437, 1342, 1230, 1097, 1026, 1010, 841, 743, 698; δ_H (400 MHz; DMSO-d_6) 10.84 (1H, br s, NH), 10.82 (1H, br s, NH), 8.36 (1H, d, *J* 7.3, NH), 7.83 (1H, d, *J* 8.1, NH), 7.56 (1H, d, *J* 7.6, ArH), 7.41 (1H, d, *J* 7.9, ArH), 7.40–7.21 (8H, m, 7×ArH and NH), 7.12 (2H, m, ArH), 7.03 (2H, m, ArH), 6.97–6.92 (2H, m, ArH), 5.02 (1H, d, *J* 12.5, CH of CH_2), 4.98 (1H, d, *J* 12.5, CH of CH_2), 4.63 (1H, dd, *J* 8.0 and 14.0, CH), 4.52 (1H, dd, *J* 6.8 and 14.0, CH), 3.83 (1H, dd, *J* 7.0 and 8.7, CH), 3.49 (3H, s, Me), 3.08 (3H, m, CH and CH_2), 2.93 (1H, m, CH), 1.85 (1H, m, C*H*Me_2), 0.70 (6H, m, CH*Me*$_2$); δ_C (100 MHz; DMSO-d_6); 172.0, 171.5, 170.7, 156.1, 137.0, 136.1, 136.0, 128.3 (CH), 127.8 (CH), 127.7 (CH), 127.3, 127.1, 123.7 (CH), 123.6 (CH), 121.0 (CH), 120.8 (CH), 118.4 (CH), 118.2 (CH), 117.9 (CH), 111.4 (CH), 111.2 (CH), 109.8, 109.1, 65.4 (CH_2), 60.1 (CH), 53.1 (CH), 52.9 (Me), 51.7 (CH), 30.4 (CH), 27.8 (CH_2), 27.0 (CH_2), 19.1 (Me), 18.0 (Me), 1×CH not observed; *m*/*z* (ES^+) 638 (MH^+, 6%), 530 (20), 529 (24), 388 (27), 387 (100), 329 (67), 312 (50), 201 (9), 131 (16), 130 (99), 100 (31), 79 (33), 63 (12), 51 (19), 44 (42).

4.6.18. (S)-Methyl-2-(1-benzyloxycarbonylamino-2-methylpropyl)-5,5′-bis(indol-3-yl)-[2,4′]bis-oxazoyl-4-carboxylate ***21****.* According to general procedure **B** the *title compound* was obtained from **18** (64 mg, 0.1 mmol) as an orange solid (15 mg, 23%), mp 145–147 °C (from dichloromethane); $[\alpha]_D^{34}$ −29.2 (*c* 0.7, THF); (Found: MH^+, 630.2347. $C_{36}H_{31}N_5O_6$+H requires 630.2347); ν_{max} (KBr)/cm^{-1} 3410, 2925, 1702, 1621, 1588, 1508, 1458, 1375, 1330, 1281, 1222, 1089, 743; δ_H (400 MHz; DMSO-d_6) 12.03 (2H, br s, 2 NH), 9.21 (1H, d, *J* 2.5, ArH), 8.75 (1H, d, *J* 3.0, ArH), 8.30 (1H, d, *J* 8.4, NH), 8.18 (1H, d, *J* 7.8, ArH), 8.13 (1H, d, *J* 8.0, ArH), 7.54 (2H, dd, *J* 5.3 and 7.8, ArH), 7.39 (2H, d, *J* 6.3, ArH), 7.31–7.24 (5H, m, ArH), 7.21–7.15 (2H, m, ArH), 5.11 (2H, s, CH_2), 4.76 (1H, m, CH), 3.96 (3H, s, Me), 2.45–2.37 (1H, m, C*H*Me_2), 1.10 (3H, d, *J* 6.4, CH*Me*Me), 1.01 (3H, d, *J* 6.4, CHMe*Me*); δ_C (100 MHz; DMSO-d_6) 163.1, 161.2, 156.8, 153.9, 152.7, 149.1, 137.4, 136.6, 136.5, 130.7 (CH), 129.2 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH) 125.2, 125.0, 123.4, 123.2 (CH), 123.1 (CH), 121.5 (CH), 121.24 (CH), 121.18 (CH), 119.8, 112.9 (CH), 112.7 (CH), 103.2, 102.7, 66.2 (CH_2), 55.6 (CH), 52.3 (Me), 31.5 (CH), 19.6 (Me), 19.2 (Me), 1×CH not observed; *m*/*z* (ES^+) 630 (MH^+, 2%), 530 (21), 529 (31), 388 (25), 387 (100), 355 (18), 329 (68), 312 (50), 186 (11), 131 (14), 130 (99), 100 (32), 79 (33), 63 (12), 51 (18), 44 (42).

4.6.19. (S,S,S)-Ethyl 2-[(2-amino-3-methylbutanoylamino)-3-(indol-3-yl)-propionylamino]-3-(indol-3-yl)propanoate (H-Val-Trp-Trp-OMe) ***22****.* Pearlman's catalyst (50 mg) was added to a stirred solution of **18** (640 mg, 1 mmol) in anhydrous methanol (10 ml) and the reaction mixture was evacuated and purged with nitrogen (×5), hydrogen (×5), and then applied with hydrogen gas (1 atm). The reaction mixture was stirred at room temperature for 3 h, filtered through a pad of Celite® and the solid residue washed with methanol. The filtrate was concentrated in vacuo to give the *title compound* as a colourless solid (458 mg, 91%), mp 81–83 °C (from ether); $[\alpha]_D^{32}$ +9.2 (*c* 1.0, THF); (Found: MH^+, 504.2605. $C_{28}H_{33}N_5O_4$+H requires 504.2607); ν_{max} (KBr)/cm^{-1} 3406, 3321, 3057, 2957, 2927, 1741, 1654, 1515, 1458, 1437, 1342, 1212, 1100, 1010, 909, 742; δ_H (400 MHz; DMSO-d_6) 10.87 (1H, br d, *J* 1.7, NH), 10.80 (1H, br d, *J* 1.8, NH), 8.44 (1H, br d, *J* 7.4, NH), 7.98 (1H, br d, *J* 8.5, NH), 7.56 (1H, d, *J* 7.9, ArH), 7.45 (1H, d, *J* 7.8, ArH), 7.33–7.28 (2H, dd, *J* 8.0 and 10.0 ArH),

7.13–6.99 (2H, dd, *J* 2.1 and 14.4, ArH), 7.04 (2H, m, ArH), 6.95 (2H, m, ArH), 4.65 (1H, dd, *J* 8.1 and 13.3, CH), 4.52 (1H, dd, *J* 7.4 and 13.9, CH), 3.53 (3H, s, Me), 3.15–3.02 (3H, m, CH and CH_2), 2.94–2.88 (2H, m, CH_2), 1.84–1.81 (3H, m, C*H*Me_2 and NH_2), 0.73 (3H, d, *J* 6.8, CH*Me*Me), 0.54 (3H, d, *J* 6.8, CHMe*Me*); δ_C (100 MHz; DMSO-d_6) 174.4, 172.6, 172.1, 136.51, 136.49, 127.9, 127.5, 124.2 (CH), 124.1, 121.4 (CH), 121.3 (CH), 118.90 (CH), 118.87 (CH), 118.6 (CH), 118.4 (CH) 111.9 (CH), 111.7 (CH), 110.2 (CH), 109.7, 69.5 (CH), 53.5 (CH), 52.9 (CH), 52.3 (Me), 31.4 (CH), 28.6 (CH_2), 27.5 (CH_2), 19.9 (Me), 16.9 (Me); *m*/*z* (ES^+) 504 (MH^+, 11%), 503 (24), 432 (22), 387 (30), 303 (26), 302 (17), 286 (24), 272 (16), 259 (29), 258 (100), 257 (32), 244 (12), 231 (33), 201 (17), 186 (18), 170 (11), 131 (12), 130 (100), 72 (37), 55 (11), 44 (19).

4.6.20. (S,S,S)-Methyl 2-[(2-acetyl-3-methylbutanoylamino)-3-(indol-3-yl)-propionylamino]-3-(indol-3-yl)propanoate (Ac-Val-Trp-Trp-OMe) ***23***. Acetic anhydride (472 μl, 5 mmol) in dichloromethane (2 ml) was added dropwise to a stirred solution of **22** (500 mg, 0.99 mmol) and DMAP (14 mg, 0.12 mmol) in dichloromethane (5 ml). The reaction mixture was stirred at room temperature for 12 h and the solvent removed in vacuo. Purification by flash chromatography on silica gel (ethyl acetate) gave the *title compound* as a colourless solid (480 mg, 89%), mp 234–235 °C (from dichloromethane/light petroleum); $[\alpha]_D^{23}$ +9.1 (*c* 0.1, THF); (Found: M^+, 545.2557. $C_{30}H_{35}N_5O_5$ requires 545.2638); ν_{max} (KBr)/cm^{-1} 3409, 3292, 3058, 2960, 2921, 1735, 1639, 1542, 1457, 1437, 1354, 1231, 1094, 1010, 741; δ_H (400 MHz; DMSO-d_6) 10.86 (2H, br s, 2 NH), 8.25 (1H, d, *J* 8.1, NH), 8.01 (1H, d, *J* 7.9, NH), 7.73 (1H, d, *J* 8.8, NH), 7.56 (1H, d, *J* 7.9, ArH), 7.43 (1H, d, *J* 7.6, ArH), 7.14–7.11 (2H, m, ArH), 7.09–6.94 (6H, m, ArH), 4.63–4.49 (2H, m, 2×CH), 4.15–4.10 (1H, m, CH), 3.52 (3H, s, Me), 3.10–3.05 (3H, m, CH of CH_2 and CH_2), 2.96–2.90 (1H, dd, *J* 7.1 and 8.5, CH of CH_2), 1.91–1.78 (4H, m, Me and C*H*Me_2), 0.73 (6H, d, *J* 6.4, CH*Me*$_2$); δ_C (100 MHz; DMSO-d_6) 172.4, 171.9, 171.4, 169.8, 136.54, 136.46, 127.8, 127.5, 124.1 (CH), 124.0 (CH), 121.4 (CH), 121.3 (CH), 119.9 (CH), 118.8 (CH), 118.6 (CH), 118.4 (CH), 111.9 (CH), 111.7 (CH), 110.3, 109.6, 58.2 (CH), 53.5 (CH), 53.4 (CH), 52.2 (Me), 30.8 (CH), 28.0 (CH_2), 27.5 (CH_2), 22.9 (Me), 19.6 (Me), 18.5 (Me); *m*/*z* (FI) 545 (M^+, 3%), 431 (32), 430 (100), 372 (17), 222 (15), 218 (12), 215 (43), 168 (13), 158 (10), 131 (19), 130 (18), 129 (42), 117 (53).

4.6.21. (S)-Methyl 2-(1-acetylamino-2-methylpropyl)-5,5′-bis(indol-3-yl)-[2,4′]bis-oxazoyl-4-carboxylate ***24***. According to general procedure **B** the *title compound* was obtained from **23** (55 mg, 0.1 mmol) as an orange solid (11 mg, 20%), mp >270 °C (from ethyl acetate/light petroleum); $[\alpha]_D^{30}$ −12.6 (*c* 0.6, THF); (Found: MH^+, 538.2089. $C_{30}H_{27}N_5O_5$+H requires 538.2085); ν_{max} (KBr)/cm^{-1} 3427, 2959, 2925, 2856, 1694, 1657, 1627, 1591, 1458, 1432, 1379, 1281, 1229, 1129, 1093, 1045, 740; δ_H (400 MHz; DMSO-d_6); 12.00 (2H, br s, NH), 9.15 (1H, d, *J* 2.8, ArH), 8.72 (1H, d, *J* 2.9, ArH), 8.62 (1H, d, *J* 8.6, NH), 8.11–8.08 (2H, m, ArH), 7.54–7.51 (2H, m, ArH), 7.33–7.13 (4H, m, ArH), 5.00 (1H, m, CH), 3.93 (3H, s, Me), 2.56 (1H, m, C*H*Me_2), 1.96 (3H, s, Me), 1.07 (3H, d, *J* 6.8, CH*Me*Me), 1.00 (3H, d, *J* 6.8, CHMe*Me*); δ_C (100 MHz; DMSO-d_6) 170.1, 163.1, 161.3, 153.9, 152.7, 148.9, 136.6, 136.5, 130.7 (CH), 129.1 (CH), 128.8 (CH), 125.2, 125.1, 123.5, 123.2 (CH), 123.1 (CH), 121.5 (CH), 121.3 (CH), 121.2 (CH), 119.8, 112.9 (CH), 112.7 (CH), 103.2, 102.7, 53.0 (CH), 52.3 (Me), 31.5 (CH), 22.8 (Me), 19.6 (Me), 19.1 (Me); *m*/*z* (ES^+) 538 (MH^+, 100%), 132 (32), 118 (45), 114 (19), 100 (13), 77 (51).

4.6.22. 7-Bromoindole-3-carbaldehyde ***29***. Phosphorus oxychloride (4.2 ml, 45 mmol) was added dropwise to a cooled solution of DMF (30 ml) at 0 °C. After stirring at room temperature for 15 min, a cooled solution of 7-bromoindole[39,40] **28** (6.3 g, 32.4 mmol) in DMF (60 ml) was added dropwise at 0 °C. The reaction mixture was stirred at 60 °C for 1 h, and poured onto sodium hydroxide solution (1 M; 100 ml) and crushed ice (~150 g). The aqueous layer was extracted with dichloromethane (2×100 ml). The combined organic extracts were washed with water (100 ml) and brine (100 ml) then dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography on silica gel (ethyl acetate/light petroleum, 1:3) gave the *title compound* as a yellow solid (4.5 g, 63%), mp 171–172 °C (from ethyl acetate), (lit.[41], mp 165–167 °C (solvent not stated)); (Found: M^+, 222.9626. $C_9H_6{}^{79}BrNO$ requires 222.9633); ν_{max} (KBr)/cm^{-1} 3195, 1639, 1522, 1448, 1389, 1271, 1243, 1204, 1126, 1098, 879, 831, 777, 740, 652; δ_H (300 MHz; Acetone-d_6) 11.37 (1H, br s, NH), 10.08 (1H, s, CHO), 8.31 (1H, s, 2-H), 8.24 (1H, dd, *J* 0.8 and 7.9, ArH), 7.51 (1H, dd, *J* 0.8 and 7.7), 7.21 (1H, t, *J* 7.7, ArH); δ_C (75 MHz; Acetone-d_6) 186.1 (CHO), 139.0 (CH), 137.1, 127.6 (CH), 127.4, 125.0 (CH), 122.1 (CH), 121.2, 106.0; *m*/*z* (EI) 225 (MH^+, 4%), 224 (M^+, 57), 222 (M^+, 63), 221 (100), 193 (13), 143 (11), 115 (27), 114 (15), 89 (13), 88 (14), 87 (9), 63 (10).

4.6.23. 7-Bromo-1-tert-butoxycarbonylindole-3-carboxaldehyde ***30***. A solution of **29** (1.7 g, 7.8 mmol) and di-*tert*-butyl dicarbonate (2.2 g, 10 mmol) in acetonitrile (25 ml) was added DMAP (95 mg, 0.78 mmol). The reaction mixture was stirred at room temperature for 2 h then concentrated in vacuo. Purification by flash chromatography on silica gel (ethyl acetate/light petroleum, 1:4) gave the *title compound* as an orange solid (2.2 g, 87%), mp 90–91 °C (from ether/light petroleum); (Found: C, 52.3; H, 4.3; N, 4.0. $C_{14}H_{14}BrNO_3$ requires C, 51.9; H, 4.4; N, 4.3%); (Found: M^+, 323.0147. $C_{14}H_{14}{}^{79}BrNO_3$ requires 323.0157); ν_{max} (KBr)/cm^{-1} 3445, 1751, 1678, 1476, 1418, 1372, 1320, 1245, 1147, 1112, 782, 771, 735; δ_H (300 MHz; $CDCl_3$) 10.10 (1H, s, CHO), 8.33 (1H, d, *J* 6.0, ArH), 8.16 (1H, s, 2-H), 7.65 (1H, dd, *J* 3.0 and 6.0, ArH), 7.27 (1H, m, ArH), 1.72 (9H, s, CMe_3); δ_C (75 MHz; $CDCl_3$) 185.6 (CHO), 148.0, 139.9, 134.8, 131.9 (CH), 129.8, 126.4 (CH), 121.7 (CH), 121.2 (CH), 107.8, 86.9, 28.3 (Me); *m*/*z* (EI) 325 (M^+, 7%), 323 (M^+, 6), 251 (11), 249 (11), 223 (79), 195 (23), 193 (24), 143 (11), 116 (14), 114 (30), 89 (14), 88 (21), 87 (13), 63 (11), 58 (11), 57 (100), 56 (21).

4.6.24. (Z)-Methyl 3-(7-bromo-1-tert-butoxycarbonylindol-3-yl)-2-(N-tert-butoxycarbonylamino)propenoate ***32***. To a solution of phosphonoglycine **31**[17] (1.00 g, 3.4 mmol) in dichloromethane (1 ml) was added DBU (0.48 ml, 3.2 mmol) and lithium chloride (0.14 g, 3.2 mmol) and the reaction mixture was stirred for 10 min. A solution of **30** (0.94 g, 2.9 mmol) in dichloromethane (2 ml) was added dropwise and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane (20 ml) and washed with potassium hydrogen sulfate (1 M; 20 ml). The aqueous layer was removed and the organic layer washed with further potassium hydrogen sulfate (1 M; 20 ml) and brine (2×20 ml). The combined aqueous layers were extracted with dichloromethane (20 ml) and the combined organic layers dried ($MgSO_4$), filtered and the solvent removed in vacuo. Purification by flash chromatography on silica gel (ethyl acetate/light petroleum, 1:3) gave the *title compound* as a colourless solid (1.28 g, 89%), mp 45–46 °C (from ether); (Found: C, 53.2; H, 5.4; N, 5.4. $C_{22}H_{27}BrN_2O_6$ requires C, 53.3; H, 5.5; N, 5.7%); (Found: M^+, 494.1047. $C_{22}H_{27}{}^{79}BrN_2O_6$ requires 494.1052); ν_{max} (KBr)/cm^{-1} 3420, 2980, 1718, 1640, 1591, 1488, 1370, 1331, 1253, 1144, 1098, 1016, 837, 781; δ_H (300 MHz; $CDCl_3$) 7.73 (1H, s, 2-H), 7.57 (1H, dd, *J* 3.0 and 6.0, ArH), 7.45 (2H, m, ArH and =CH), 7.06 (1H, t, *J* 6.0, ArH), 6.09 (1H, br s, NH), 3.77 (3H, s, Me), 1.55 (9H, s, CMe_3), 1.17 (9H, s, CMe_3); δ_C (75 MHz; $CDCl_3$) 166.2, 153.1, 148.6, 133.8, 133.4, 131.11 (CH), 130.85 (CH), 124.8 (CH), 122.2 (CH), 118.6 (CH), 114.1, 108.4, 85.8, 81.2, 53.0 (Me), 28.6 (Me), 28.3 (Me), 1×C not observed; *m*/*z* (CI) 495 (MH^+, 14%), 494 (M^+, 11), 441 (20), 439 (22), 397 (27), 395 (32), 394 (22), 383 (12), 382 (88), 369 (10), 366 (25), 364 (14),

340 (81), 322 (49), 321 (11), 320 (42), 308 (16), 306 (16), 296 (90), 295 (36), 294 (100), 293 (32), 264 (23), 262 (24), 242 (18), 217 (10), 57 (10).

*4.6.25. (±)-Methyl 3-(7-bromo-1-tert-butoxycarbonylindol-3-yl)-2-(N-tert-butoxycarbonylamino)propanoate **33**.* Alkene **32** (950 mg, 1.91 mmol) and $[(DiPFc)Rh(COD)]^+BF_4^-$ (34 mg) were placed in the reaction vessel and the system was purged with nitrogen (×5). The vessel was then charged with methanol (10 ml), evacuated and purged with nitrogen (×5), hydrogen (×5), pressurized with hydrogen to 90 psi and stirred for 48 h at this pressure. The reaction mixture was concentrated in vacuo and purified by flash chromatography on silica gel (ethyl acetate/light petroleum, 1:9) to give the *title compound* as a colourless solid (0.78 g, 82%), mp 33–35 °C (from ether); (Found: M^+, 496.1205. $C_{22}H_{29}{}^{79}BrN_2O_6$ requires 496.1209); ν_{max} (CH_2Cl_2)/cm^{-1} 3432, 2983, 2951, 2934, 1747, 1714, 1605, 1500, 1476, 1456, 1439, 1415, 1394, 1370, 1352, 1326, 1234, 1156, 1101, 1063, 1018, 856, 837, 806, 611; δ_H (300 MHz; $CDCl_3$) 7.45 (1H, d, *J* 6.0, ArH), 7.38 (1H, d, *J* 9.0, ArH), 7.25 (1H, s, 2-H), 7.02 (1H, t, *J* 6.0, ArH), 5.04 (1H, d, *J* 9.0, NH), 4.56 (1H, m, CH), 3.61 (3H, s, Me), 3.15–3.00 (2H, m, CH_2), 1.62 (9H, s, CMe_3), 1.29 (9H, s, CMe_3); δ_C (75 MHz; $CDCl_3$) 172.6, 155.5, 148.8, 134.5, 130.5 (CH), 128.0 (CH), 124.3 (CH), 118.5 (CH), 115.0, 108.5, 84.8, 80.5, 54.0 (CH), 52.8 (Me), 28.7 (Me), 28.4 (Me), 28.1 (CH_2), 1×C not observed; *m*/*z* (CI) 496 (M^+, 5%), 399 (9), 343 (54), 341 (55), 323 (10), 307 (31), 299 (34), 297 (36), 296 (13), 295 (100), 291 (10), 281 (8), 263 (69), 219 (19).

*4.6.26. (±)-7-Bromotryptophan methyl ester hydrochloride **34**.* According to general procedure **D** the *title compound* was obtained from **33** (500 mg, 1 mmol) and HCl in dioxane solution (4 M; 6.3 ml, 25 mmol, 2 h) as an orange solid (253 mg, 76%), mp 190–192 °C (from THF/water/light petroleum) (lit.[9], mp not given); (Found: MH^+ (free amine), 297.0241. $C_{12}H_{13}{}^{79}BrN_2O_2$+H requires 297.0239); ν_{max} (KBr)/cm^{-1} 3420, 3267, 2923, 2857, 1744, 1588, 1562, 1508, 1438, 1340, 1290, 1239, 1218, 1200, 1088, 774, 736; δ_H (300 MHz; DMSO-d_6) 11.33 (1H, br s, NH), 8.63 (3H, br s, $-NH_3$), 7.50 (1H, d, *J* 5.9, ArH), 7.35–7.24 (2H, m, ArH), 6.99 (1H, t, *J* 6.0, ArH), 4.33 (1H, m, CH), 3.68 (3H, s, Me), 3.31–3.29 (2H, m, CH_2); δ_C (75 MHz; DMSO-d_6) 170.0, 134.8, 129.1, 126.9 (CH), 124.1 (CH), 120.5 (CH), 118.0 (CH), 108.2, 104.7, 53.1, 52.8, 26.3 (CH_2); *m*/*z* (FAB^+) 297 (MH^+, 100%), 296 (16), 289 (13), 282 (30), 280 (30), 240 (10), 239 (14), 238 (11), 237 (14), 233 (19), 231 (7), 219 (18), 217 (8), 210 (26), 208 (24), 168 (8), 156 (11), 155 (37).

*4.6.27. (S,RS)-Methyl 2-(2-benzyloxycarbonylamino-3-methylbutanoylamino)-3-(7-bromoindol-3-yl)propanoate **35**.* According to general procedure **A** the *title compound* was obtained from Z-Val-OH (300 mg, 1.2 mmol) and amine **34** (334 mg, 1 mmol) as a colourless solid (376 mg, 71%), a mixture of diastereomers (1:1), mp 53–55 °C (from ether) (lit.[9], mp not given); $[\alpha]_D^{24}$ +20.1 (*c* 0.9, CH_2Cl_2); (Found: MH^+, 530.1288. $C_{25}H_{28}{}^{79}BrN_3O_5$+H requires 530.1285); ν_{max} (KBr)/cm^{-1} 3417, 2961, 2930, 1742, 1710, 1657, 1521, 1437, 1337, 1217, 1104, 1026, 848, 777, 736, 697; δ_H (300 MHz; $CDCl_3$) 8.46+8.32 (1H, br s, NH), 7.79–7.18 (6H, m, ArH), 7.02–6.95 (2H, m, ArH), 6.67+6.53 (1H, d, *J* 7.0, ArH), 5.42+5.26 (1H, d, *J* 8.5, NH), 5.13–5.04 (3H, m, CH and CH_2), 4.96–4.93 (1H, m, NH), 4.13–4.09+4.06–4.04 (1H, m, CH), 3.68+3.65 (3H, s, Me), 3.28 (2H, m, CH_2), 2.18–2.16+2.10–2.06 (1H, m, C*H*Me$_2$), 0.95–0.80 (6H, m, CH*Me*$_2$); δ_C (75 MHz; $CDCl_3$) 172.4+172.3 (C, diast.), 171.4, 156.8, 135.1, 129.1 (CH), 129.0, 128.8 (CH), 128.7, 128.5 (CH), 125.0 (CH), 124.3+124.0 (CH, diast.), 121.3 (CH), 118.2 (CH), 111.2, 105.3, 67.6 (CH_2), 60.7 (CH), 53.0+52.7 (Me, diast.), 52.9 (CH), 31.6+31.1 (CH, diast.), 28.2 (CH_2), 19.7+19.5 (Me, diast.), 18.1+17.4 (Me, diast.); *m*/*z* (EI) 532 (MH^+, 24%), 531 (M^+, 100), 529 (M^+, 98), 500 (8), 499 (10), 497 (10), 486 (11), 473 (7), 452 (26), 451 (89), 449 (27), 438 (12), 425 (11), 424 (22), 423 (70), 421 (77), 419 (17), 408 (32), 362 (8), 297 (8), 282 (7), 279 (22), 238 (7), 211 (9), 210 (47), 207 (47), 201 (50), 201 (18), 169 (5), 162 (5), 130 (48), 129 (19), 106 (11), 91 (100), 77 (16), 72 (15), 43 (16).

*4.6.28. (S,RS)-2-(2-Benzyloxycarbonylamino-3-methylbutanoylamino)-3-(7-bromoindol-3-yl)carboxylic acid **36**.* According to general procedure **E** the *title compound* was obtained from ester **35** (265 mg, 0.5 mmol) as a colourless solid (214 mg, 83%), a mixture of diastereomers (1:1), mp 214–217 °C (from ethyl acetate/light petroleum); $[\alpha]_D^{24}$ −9.1 (*c* 0.1, CH_2Cl_2); (Found: MH^+, 516.1124. $C_{24}H_{26}{}^{79}BrN_3O_5$+H requires 516.1129); ν_{max} (KBr)/cm^{-1} 3411, 3392, 3365, 2963, 1742, 1713, 1648, 1535, 1435, 1405, 1338, 1294, 1245, 1179, 1100, 1041, 777, 738, 698; δ_H (300 MHz; DMSO-d_6) 12.40 (1H, br s, CO_2H), 10.89 (1H, br d, *J* 4.1, NH), 7.98 (1H, br m, NH), 7.32 (1H, d, *J* 7.4, ArH), 7.13–6.83 (8H, m, 7×ArH and NH), 6.71 (1H, t, *J* 6.7 ArH), 4.81–4.75 (2H, m, CH_2), 4.27 (1H, m, CH), 3.69–3.62 (1H, m, CH), 2.91–2.75 (2H, m, CH_2), 1.62–1.56 (1H, m, C*H*Me$_2$), 0.68–0.36 (6H, m, CH*Me*$_2$); δ_C (75 MHz; DMSO-d_6) 198.2, 173.6+173.5 (C, diast.), 156.5, 137.4, 134.7, 133.1+130.0 (CH, diast.), 129.4, 129.3, 128.9+128.7 (CH, diast.), 128.4+128.1 (CH, diast.), 125.6+125.5 (CH, diast.), 120.2 (CH), 118.2 (CH), 111.6 (CH), 104.5, 65.8 (CH_2), 60.1 (CH), 53.1+52.9 (CH, diast.), 30.9 (CH), 27.8+27.5 (CH, diast.), 19.5 (Me), 18.4 (Me); *m*/*z* (EI) 516 (MH^+, 99%), 515 (4), 500 (9), 498 (8), 474 (16), 472 (21), 440 (9), 438 (82), 425 (59), 410 (52), 408 (54), 384 (32), 382 (36), 347 (9), 330 (8), 304 (10), 286 (9), 251 (10), 212 (11), 209 (13), 169 (11), 160 (11), 133 (14), 132 (62), 108 (65), 106 (37), 91 (19), 72 (100).

*4.6.29. Monobrominated tripeptide **27**.* According to general procedure **A** the *title compound* was obtained from acid **36** (515 mg, 1 mmol) and H-Trp-OMe hydrochloride (305 mg, 1.2 mmol) as a colourless solid (393 mg, 55%), a mixture of diastereomers (1:1), mp 185–187 °C (from dichloromethane); $[\alpha]_D^{29}$ +18.3 (*c* 0.7, THF); (Found: MH^+, 716.2064. $C_{36}H_{38}{}^{79}BrN_5O_6$+H requires 716.2064); ν_{max} (KBr)/cm^{-1} 3407, 3292, 3061, 2960, 1734, 1693, 1641, 1533, 1456, 1436, 1338, 1291, 1243, 1097, 1027, 845, 771, 740, 698; δ_H (300 MHz; DMSO-d_6) 10.85+10.77 (1H, br s, NH), 10.64 (1H, br s, NH), 8.29+8.21 (1H, br d, *J* 7.5, NH), 7.95+7.76 (1H, br d, *J* 7.9, NH), 7.39–7.31 (1H, m, ArH), 7.27 (1H, d, *J* 7.7, ArH), 7.20 (1H, d, *J* 7.7, ArH), 7.10–6.58 (12H, m, 11×ArH and NH), 4.83–4.60 (2H, m, CH_2), 4.43–4.33 (1H, m, CH), 4.31–4.27 (1H, m, CH), 3.60–3.51 (1H, m, CH), 3.35+3.27 (3H, s, Me), 3.02–2.70 (3H, m, CH of CH_2 and CH_2), 2.58–2.50 (1H, m, CH of CH_2), 1.65–1.59+1.47–1.34 (1H, m, C*H*Me$_2$), 0.47 (3H, d, *J* 6.2, CH*Me*Me), 0.26 (3H, d, *J* 6.2, CHMe*Me*); δ_C (75 MHz; DMSO-d_6) 172.7+172.3 (C, diast.), 171.8+171.7 (C, diast.), 171.4, 171.3, 156.6+156.4 (C, diast.), 137.4+137.3 (C, diast.), 136.4, 134.7+134.6 (C, diast.), 129.5, 129.2, 128.70 (CH), 128.66 (CH), 128.14 (CH), 128.08 (CH), 127.42, 127.37, 125.9+125.5 (CH, diast.), 124.2+124.1 (CH, diast.), 123.8+123.7 (CH, diast.), 121.3 (CH), 120.0+119.9 (CH, diast.) 118.8+118.5 (CH, diast.), 118.3 (CH), 111.8 (CH), 109.7+109.5 (C, diast.), 104.4+104.3 (C, diast.), 65.8+65.3 (CH_2, diast.), 60.4 (CH), 53.5+53.1 (CH, diast.), 52.3 (Me), 52.1 (CH), 27.6+27.4 (CH_2, diast.), 19.4+19.3 (Me, diast.), 18.3+18.0 (Me, diast.); *m*/*z* 718 (MH^+, 27%), 717 (M^+, 23), 716 (MH^+, 27), 715 (M^+, 14), 330 (3), 329 (11), 328 (2), 309 (4), 308 (6), 307 (21), 306 (1), 292 (6), 291 (4), 290 (4), 289 (12), 288 (1), 266 (11), 264 (11), 239 (12), 237 (14), 220 (9), 219 (24), 218 (3), 217 (6), 216 (3), 210 (19), 208 (20), 202 (18), 201 (47), 170 (8), 169 (5), 168 (4), 167 (6), 166 (7), 165 (7), 162 (5), 159 (20), 158 (8), 157 (5), 156 (12), 155 (41), 154 (100), 153 (10), 152 (12), 151 (4), 150 (6), 146 (7).

*4.6.30. Monobrominated bis-oxazole **26**.* According to general procedure **B** the *title compound* was obtained from **27** (72 mg, 0.1 mmol) as an orange solid (10 mg, 14%), mp 98–100 °C (from ether); $[\alpha]_D^{29}$ +7.3 (*c* 0.1, THF); (Found: MH^+, 708.1453. $C_{36}H_{30}{}^{79}BrN_5O_6$+H requires 708.1458); ν_{max} (KBr)/cm^{-1} 3343,

3064, 2960, 2926, 2873, 2855, 1707, 1621, 1597, 1572, 1525, 1458, 1431, 1374, 1335, 1282, 1244, 1213, 1128, 1084, 1027, 977, 929, 745; δ_H (300 MHz; DMSO-d_6) 11.26 (2H, br s, 2 NH), 8.67 (1H, s, ArH), 8.20 (1H, d, *J* 8.5, NH), 8.13 (1H, d, *J* 8.0, ArH), 7.53 (1H, d, *J* 7.9, ArH), 7.35–7.17 (11H, m, ArH), 5.11–5.07 (2H, m, CH_2), 4.65–4.60 (1H, m, CH), 3.85 (3H, s, Me), 2.08–1.93 (1H, m, C*H*Me$_2$), 1.01 (3H, d, *J* 6.3, CH*Me*Me), 0.91 (3H, d, *J* 6.3, CHMe*Me*); δ_C (75 MHz; DMSO-d_6) 163.0, 160.1, 156.9, 156.6, 154.5, 139.2, 137.2, 136.3, 130.3 (CH), 129.3 (CH), 128.7 (CH), 128.6 (CH), 128.2 (CH), 128.l (CH), 125.7 (CH), 125.0, 123.0 (CH), 122.1, 121.4 (CH), 121.1 (CH), 112.9, 112.7 (CH), 102.6, 66.0 (CH_2), 55.4 (CH), 51.8 (Me), 31.3 (CH), 19.5 (Me), 19.1 (Me), 1×CH and 4×C not observed; *m*/*z* (FAB$^+$) 710 (MH^+, 2%), 708 (MH^+, 1), 472 (1), 470 (3), 450 (4), 449 (11), 448 (33), 447 (16), 331 (1), 329 (2), 314 (1), 312 (5), 309 (2), 308 (7), 307 (28), 291 (3), 290 (5), 289 (14), 274 (2), 273 (3), 272 (2), 271 (1), 219 (7), 216 (4), 178 (2), 176 (6), 165 (6), 164 (2), 156 (7), 155 (27), 154 (100), 153 (7), 152 (9), 151 (3), 150 (4), 144 (6).

4.6.31. (S,S,S,S)-Methyl [2-{2-[2-benzyloxycarbonyamino-(2-methylpropyl)-4-hydroxyphenyl-propionylamino]-3-methylbutanoylamino]-3-(indol-3-yl)-propionylamino]-3-(indol-3-yl)propanoate (Z-Tyr-Val-Trp-Trp-OMe) ***37***. According to general proce dure **A** the *title compound* was obtained from Z-Tyr-OH (378 mg, 1.2 mmol) and amine **22** (503 mg, 1 mmol) as a colourless solid (489 mg, 61%), mp 111–113 °C (from ethyl acetate); $[\alpha]_D^{30}$ +11.3 (*c* 0.8, THF); (Found: C, 67.2; H, 6.1; N, 10.0. $C_{45}H_{48}N_6O_8$ requires C, 67.5; H, 6.0; N, 10.3%); (Found: MH^+, 801.3603. $C_{45}H_{48}N_6O_8$+H requires 801.3606); ν_{max} (KBr)/cm^{-1} 3418, 3061, 2980, 1700, 1638, 1532, 1516, 1457, 1440, 1365, 1344, 1257, 1218, 1139, 1104, 1080, 1050, 817, 742, 698; δ_H (400 MHz; DMSO-d_6); 10.87 (1H, br s, NH), 10.83 (1H, br s, NH), 9.19 (1H, s, OH), 8.33 (1H, d, *J* 7.1, NH), 8.09 (1H, d, *J* 7.9, NH), 7.83 (1H, d, *J* 8.8, NH), 7.57 (1H, d, *J* 8.0, ArH), 7.47–7.42 (1H, m, ArH), 7.34–7.22 (8H, m, 7×ArH and NH), 7.13–7.04 (6H, m, ArH), 6.97 (2H, m, ArH), 6.64 (2H, m, ArH), 4.95 (2H, s, CH_2), 4.63 (1H, m, CH), 4.54–4.50 (1H, m, CH), 4.26–4.19 (2H, m, 2×CH), 3.51 (3H, s, Me), 3.12–3.05 (3H, m, CH of CH_2 and CH_2), 3.01–2.91 (2H, m, CH_2), 2.62–2.56 (1H, m, CH of CH_2), 1.95–1.90 (1H, m, C*H*Me$_2$), 0.77 (6H, d, *J* 5.8, CH*Me*$_2$); δ_C (100 MHz; DMSO-d_6) 172.4, 172.0, 171.9, 171.8, 171.1, 156.3, 156.2, 137.5, 136.5, 136.4, 130.7 (CH), 130.6, 128.8 (CH), 128.7, 128.3 (CH), 128.1 (CH), 127.9, 127.8 (CH), 127.5, 124.0 (CH), 121.4 (CH), 118.8 (CH), 118.7 (CH), 118.3 (CH), 115.2 (CH), 111.9 (CH), 111.7 (CH), 110.2 (CH), 109.6 (CH), 65.6 (CH_2), 57.9 (CH), 56.8 (Me), 53.5 (CH), 53.4 (CH), 52.2 (CH), 36.9 (CH_2), 30.9 (CH), 28.2 (CH_2), 27.6 (CH_2), 19.6 (Me), 18.4 (Me); *m*/*z* (ES$^+$) 801 (MH^+, 90%), 583 (10), 405 (14), 366 (21), 365 (49), 247 (72), 225 (100), 159 (23), 143 (33), 100 (99), 83 (22), 72 (41), 61 (64), 43 (28).

4.6.32. (S,S)-Methyl 2-{1-[2-benzyloxycarbonylamino-3-(4-hydroxyphenyl)propionylamino]-2-methyl-propyl}-2,4′]bis-oxazoyl-4-carboxylate ***38***. According to general procedure **B** the title compound was obtained from **37** (80 mg, 0.1 mmol) as an orange solid, (14 mg, 17%), mp 146–148 °C (from ethyl acetate); $[\alpha]_D^{25}$ +40.0 (*c* 0.1, THF); (Found: MH^+, 793.2985. $C_{45}H_{40}N_6O_8$+H requires 793.2980); ν_{max} (KBr)/cm^{-1} 3411, 2960, 2915, 1704, 1668, 1617, 1589, 1516, 1457, 1375, 1337, 1244, 1218, 1130, 1086, 1052, 745; δ_H (400 MHz; DMSO-d_6); 12.00 (2H, br s, 2 NH), 9.21 (1H, d, *J* 2.9, ArH), 9.11 (1H, s, OH), 8.82 (1H, d, *J* 8.7, NH), 8.72 (1H, d, *J* 2.9, ArH), 8.18 (1H, d, *J* 7.8, ArH), 8.13 (1H, d, *J* 7.7, ArH), 7.40–7.38 (2H, m, ArH), 7.73–7.05 (12H, m, 11 ArH and NH), 6.58–6.56 (2H, m, ArH), 5.08–5.01 (1H, m, CH), 4.93 (2H, s, CH_2), 4.39 (1H, m, CH), 3.91 (3H, s, Me), 2.95 (1H, m, CH of CH_2), 2.70 (1H, m, CH of CH_2), 2.46 (1H, m, C*H*Me$_2$), 1.11 (3H, d, *J* 6.6, CH*Me*Me), 1.03 (3H, d, *J* 6.6, CHMe*Me*); δ_C (100 MHz; DMSO-d_6) 172.6, 163.1, 160.9, 156.4, 156.2, 153.9, 152.7, 149.1, 137.5, 136.6, 136.5, 130.7 (CH), 129.2 (CH), 128.8 (CH), 128.7 (CH), 128.5, 128.14 (CH), 128.09 (CH), 128.0 (CH), 127.9 (CH), 125.2, 125.0, 123.4, 123.1 (CH), 121.6 (CH), 121.4 (CH), 119.8, 115.5 (CH), 115.2 (CH), 112.8 (CH), 112.7 (CH), 103.2, 102.7, 65.6 (CH_2), 56.8 (Me), 53.0 (CH), 52.3 (CH), 31.7 (CH), 19.6 (Me), 19.1 (Me), 1×CH_2 not observed; *m*/*z* (ES$^+$) 793 (3%, MH^+), 698 (3), 687 (12), 685 (39), 684 (95), 669 (11), 651 (10), 641 (10), 638 (17), 637 (31), 579 (9), 494 (9), 420 (11), 394 (10), 365 (9), 337 (9), 310 (9), 309 (10), 280 (19), 266 (23), 239 (21), 223 (29), 219 (52), 205 (50), 170 (53), 169 (80), 168 (100), 144 (20), 117 (15), 108 (58), 107 (63), 91 (30), 79 (99), 77 (98), 53 (28), 52 (81), 46 (70).

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