Entropically Favorable Macrolactamization. Synthesis of Isodityrosine Peptide Analogues by Tandem Erlenmeyer Condensation−Macrolactamization

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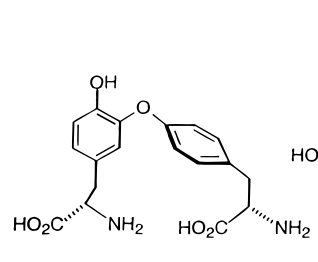
Macrolactams containing a modified isodityrosine moiety were assembled by direct addition of a bis-4-aryliden-5(4*H*)-oxazolone, derived by double Erlenmeyer condensation of diaryl ether dicarboxaldehydes and an α,ω-diamine, derived from the same precursor. Tandem acylation of diamines with the bis-Erlenmeyer oxazolone gave macrolactams in yields of up to 30%. TECM demonstrates an entropically controlled 28-membered ring closure and allows rapid access to a variety of cyclic isodityrosine peptide analogues of the biologically active natural product bastadin-5.

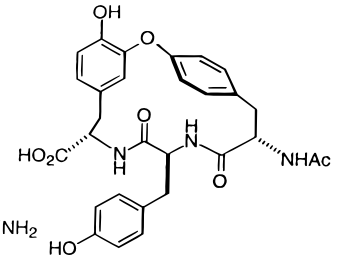
Introduction

Isodityrosine **1**, an oxidatively coupled tyrosine dimer, is a structural component of natural product cyclic peptides with unique biological properties. For example, K-13 (**2**) is a potent noncompetitive inhibitor of angiotensin converting enzyme (ACE)[1] that is produced by *Micromonospora halophytica* subsp. *exilisia K-13*.[2] OF 4949 I (**3**) and other members of the family from cultures of the fungus *Penicillium rugulosum* OF 4949 are inhibitors of aminopeptidase B.[3] The isodityrosine motif can also be seen in piperazinomycin,[4] the glycopeptide antibiotics vancomycin and ristocetin,[5] and marine sponge peptides eurypamide[6] from *Microciona eurypa*, and bastadin-5 (**4**) from *Ianthella basta* (Pallas).[7] Bastadin-5, one of a family of brominated isodityrosines peptides, mobilizes Ca^{2+} from stores within the sarcoplasmic reticulum (SR) through the Ry_1R-FKBP Ca^{2+}-receptor-channel complex (EC_{50} 2.3 μM).[8]

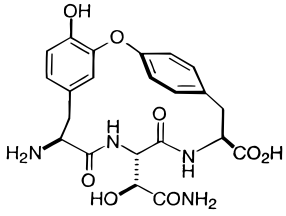
Isodityrosine plays an important role in mediating biological activity. In a seminal study by Boger et al., the essential structural elements that potentiate **1**-based inhibitors of both ACE and aminopeptidase were defined by structure−activity studies using analogues of the K-13 and OF 4949 peptide families.[9] The pharmacophore for ACE inhibitory activity includes a rigid macrocycle containing the oxidatively coupled catechol ether with a free phenolic OH. The activity of aminopeptidase inhibitors were tolerant to substitution at this position by a phenolic OMe, but more significant perturbations at this site abolished activity.[9] We have found that the phenolic diaryl ether moiety of **2** is essential for activation of the Ry_1R-FKBP Ca^{2+}-receptor-channel complex.[10] Thus, analysis of biological activity in each of the isodityrosine peptides recapitulates the primacy of the unique peptide turn-element embodied in **1**, a nonplanar phenolic diaryl ether scaffold (C−O−C−C torsional angle ∼126°).



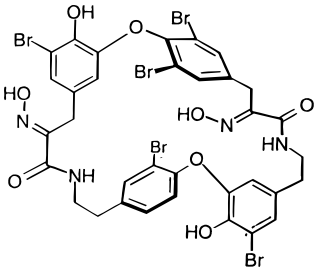
1 (*S, S*)-*Isodityrosine*



2 K-13



3 OF4949-I



4 Bastadin-5

Our investigations of the receptor binding of **4** required a method for synthesis of isodityrosine cyclic peptides while allowing flexibility for incorporation of secondary peptide elements. Strategies for ring closure of simple isodityrosine peptides (e.g., **1**−**3**) include conventional amide bond coupling,[11] closure of the diaryl ether by one-

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(1) Kase, H.; Kaneko, M.; Yamada, K. *J. Antibiot.* **1987**, *40*, 450−454.

(2) Yasuzawa, Y.; Shirata, K.; Sano, H. *J. Antibiot.* **1987**, *40*, 455−458

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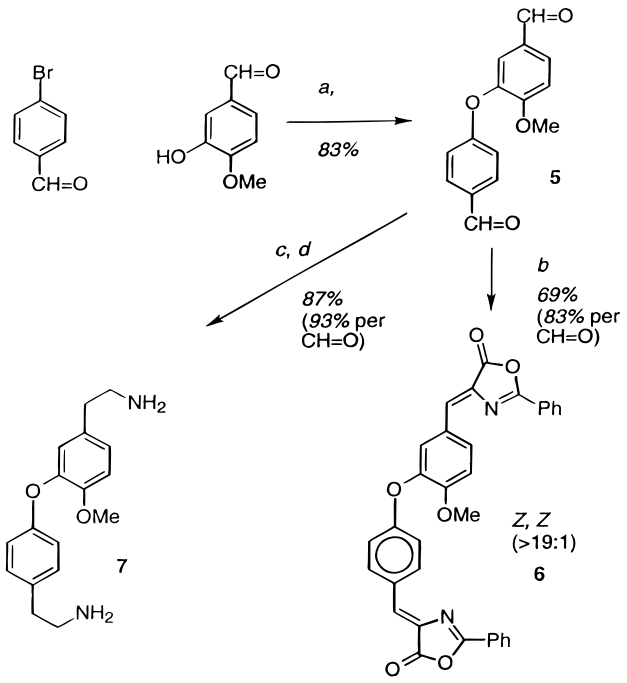
electron oxidative coupling,[12] modified Ullmann coupling,[13] and S_NAr nucleophilic displacement of activated aryl fluorides.[14] The drawback in each method is the requirement of multistep preparation of suitably functionalized intermediates. With two exceptions,[11a,12d−g] each method was deployed for synthesis of smaller ring cyclic peptides (~14-membered), and it was not obvious they would be practicable for larger ring macrolactams. We present here a convergent strategy that allows rapid assembly of analogues of **4** in less than four steps from simple aryl aldehydes by exploiting a tandem Erlenmeyer condensation[15]−macrolactamization (TECM). Tight entropic control of macrocyclization is afforded in TECM by use of a relatively rigid Erlenmeyer bis-"azlactone" (bis-4-aryliden-5(4*H*)-oxazolone) as an acylating agent in stepwise tandem amide bond formation with similarly constrained α,ω-diamines. The product is a cyclic peptide analogue bearing two planar α,β-dehydroamino residues that can be transformed with ease to relatively unconstrained isodityrosine peptidomimetics. Although Erlenmeyer oxazolones have been used to make peptide bonds previously,[16] the present work appears to be their first application to macrolactamization and the synthesis of cyclic peptide analogues.[17] Macrolactamization by TECM complements oxidative coupling and S_NAr coupling strategies by allowing rapid access to analogues of **4** with variable diamine components.

Results and Discussion

Dialdehyde **5** (Scheme 1),[18] conveniently prepared by Ullmann coupling of commercially available 3-hydroxy-4-methoxybenzaldehyde with 4-bromobenzaldehyde (CuO, K_2CO_3, pyridine, 83%), was treated with *N*-benzoylglycine (hippuric acid) under the conditions described by Finar and Libman (Ac_2O, $Pb(OAc)_2$, reflux 24 h)[19] followed by workup and trituration of the crude product with EtOAc to obtain **6** as a bright yellow solid (mp 279−281 °C, 69%; average of 83% yield per CH=O group). Under these conditions, the *Z*,*Z*-geometrical isomer **6** is obtained with >19:1 selectivity.[20] Diamine **7** was readily prepared from **5** by double Henry condensation−elimination (CH_3NO_2, 16 equiv, Ac_2O, NH_4OAc, HOAc, reflux, 3 h) followed by reduction of the resultant bis-β-nitrostyrene ($LiAlH_4$, THF, reflux, 11 h; 87% for two steps, 93% per CH=O).

Scheme 1[a]



[a] (a) CuO, K_2CO_3, py, 140 °C, 15 h; (b) Ac_2O, *N*-Bz-Gly, $Pb(OAc)_2$, 110 °C, 24 h; (c) CH_3NO_2, 16 equiv, AcOH, NH_4OAc, reflux, 3 h; (d) $LiAlH_4$, THF, reflux, 12 h.

Heating **6** with (1*R*,2*R*)-1,2-diphenyl-1,2-diaminoethane in pyridine (50 °C, 5 mM in each component) gave a chiral macrolactam **8** (CD, λ 252 nm, Δε −8.9) in low yield (~6%) accompanied by polymeric material. Macrolactamization under the same conditions with the conformationally flexible 3-oxapentane-1,5-diamine (interatomic N−N distance in extended conformation, 7.2 Å) gave **9** in 6% yield while 1,7-heptanediamine ($CHCl_3$, 50 °C, N−N 7.5 Å) gave macrolactam **10** in 7% yield. In marked contrast, condensation of **6** with the diamine **7** (N−N ~ 9 Å) resulted *in a 4- to 5-fold increase in yield* to a give the regioisomeric 28-membered macrocycles **11a,b** as a 1:1 mixture in 30% combined yield after chromatography.[21] No Michael addition of amine to oxazolone was observed under the conditions of macrolactamization.[22] When reaction was carried out at higher temperatures

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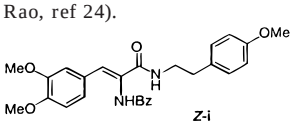
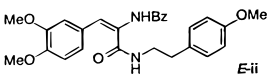
(18) All new compounds were characterized (>95% pure) by ^1H NMR (300 or 600 MHz), ^{13}C NMR, IR, FAB, or MALDI MS and gave satisfactory HRMS (Δmmu ≤ 5 mmu).

(19) Finar, I. L.; Libman, D. D. *J. Chem. Soc.* **1949**, 2726−2728.

(20) Assignment of *Z*,*Z*-**6** configuration is based on NMR chemical shift of vinyl protons, δ 7.19 (s, 1H), 7.27 (s, 1H), which are relatively upfield shift of those for *E*-isomers. For example, vinyl signals for *Z*-**i** and *E*-**ii** occur at δ 7.14 and δ 7.48 ppm, respectively (see review by Rao, ref 24).



Z-**i**



E-**ii**

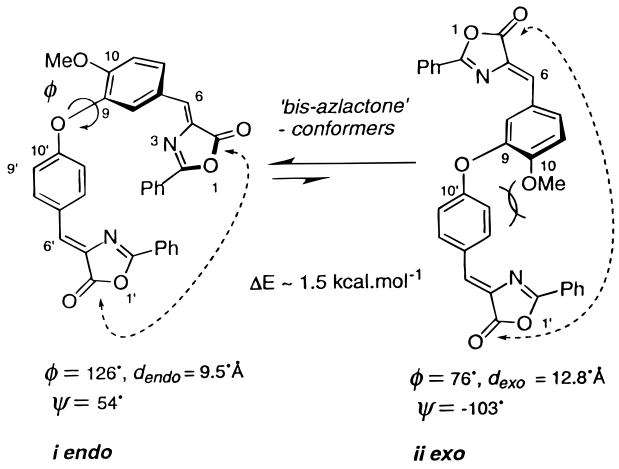
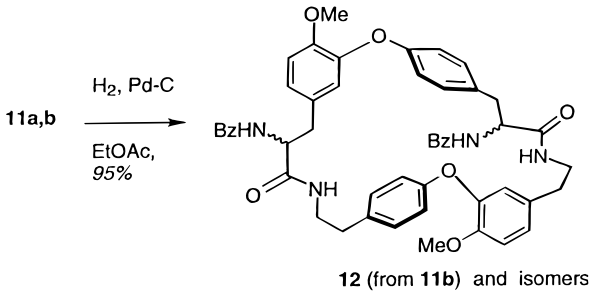


Figure 1. Ground state conformations of **6** (PM3) obtained by molecular mechanics. Torsional angle φ is defined as C10−C9−O−C10′ while angle ψ is defined as C9−O−C10′−C9′ and d is the intercarbonyl distance.

(toluene, 110 °C) macrolactamization was faster but was also accompanied by elimination of H_2O and formation of imidazolones (UV). Hydrogenation of the mixture **11a,b** (1 atm H_2, Pd−C, MeOH) provided the isodityrosine cyclic peptide **12** (95%) as a mixture of isomers.



The 5-fold increase in yield of macrolactams **11a**,**b** with diamine **7** contrasts with the lower yielding cyclizations of simple diamines and lends support to our proposal that TECM coupling of **6** and **7** is channeled to form the macrolactam **11a,b**. Diamines are acylated by stepwise addition to an oxazolone group to give putative monoacylated amines which may undergo intermolecular addition, leading to polymer, or macrolactamization by intramolecular addition. Because the distance from the primary NH_2 group to oxazolone C═O in this intermediate will be similar to d, the C═O to C═O distance in **6** (Figure 1), the efficiency of macrolactamization is partly governed by a close match of d to the corresponding N−N distance in the diamine as shown from the following analysis. Molecular mechanics calculations (PM3 level, MacSpartan Plus) show that **6** exists in two significantly populated ground-state configurations *i* and *ii* (see Figure 1).[23] Both forms have planar conjugated arylidene oxazolones with limited degrees of rotational freedom. This is confirmed by the UV spectrum of the bis-oxazolone **6** (MeOH, λ_{max} 408 nm, ϵ 24000) which shows the typical extended chromophore reported for closely related planar benzylidene mono-oxazolones.[24] Fortuitously, the torsional angle (C10−C9−O−C10′, φ = 126°) in *i* is very close to that seen in **4** in both solid-state X-ray[7a] and calculated solution conformations (MM2, φ = 125.8°).[10] While the geometry of the *exo* conformer *ii* precludes ring formation and will likely lead to polymer, the *endo* conformer *i* required for cyclization (intercarbonyl distance d = 9.5 Å) is lower in energy and easily accessible due to a relatively low barrier for interconversion of *i* and *ii* by geared rotation about the diaryl ether "hinge". A similar analysis suggests that the diaryl ether moiety of diamine **7** is also conformationally constrained, although the aminoethyl side-chains are somewhat more flexible. The interatomic distance between amine groups in the extended conformation (N−N d = ∼9.0 Å) closely matches the intercarbonyl distance in **6** which allows for facile macrolactamization. This suggests the optimal contact N−N distance for macrolactamization is ∼ 9 Å. The other two diamines (Scheme 2) lack the optimal N−N distance (d = 5.9−7.3 Å) to achieve an enthalpically favorable transitional state due to torsional strain, or, as in the case of 1,7-heptanediamine (N−N, d = 9.8 Å), are too conformationally mobile for efficient ring closure (entropic barrier).

Conclusion

The convergent TECM strategy is well-suited to preparation of isodityrosine−isodityramine cyclic analogues of bastadin-5 (**4**). Twenty-eight-membered ring macrocycles were obtained in four steps and in good overall yield (∼20−26%) from a common precursor **5**. TECM provides for considerable variation of the isodityrosine theme that is not readily duplicated with existing ring closures based on oxidative coupling or S_NAr nucleophilic substitution. We will report the TECM synthesis of compounds related to **4** and biological activity in due course.

Experimental Section

General. Simple α,ω-diamines were purchased from Aldrich and used as supplied except for 1,7-heptanediamine which was distilled from KOH at reduced pressure. TLC was carried out on plastic plates coated with silica (0.2 mm) containing a fluorescent indicator and visualized under a UV lamp and then exposed to I_2 vapor or sprayed with a solution of vanillin in ethanolic−H_2SO_4 or ninhydrin in ethanol followed by heating. Purity of each compound was established as >95% by ^{1}H NMR and TLC or HPLC. Pyridine, dichloromethane, and THF were distilled from glass over CaH_2. MALDI MS was measured on a custom-built FTMS instrument in the laboratory of Professor Carlito Lebrilla in the Department of Chemistry, UC Davis (Carroll, J. A.; Penn, S. G.; Fannin, S. T.; Wu, J. Y.; Cancilla, M. T.; Green, M. K.; Lebrilla, C. B. *Anal. Chem.* **1996**, *68*, 1798−1804) using dihydroxybenzoic acid (DHB) as matrix. FABMS and EIMS were provided by the UC Riverside MS Facility.

Dialdehyde (5). *p*-Bromobenzaldehyde (5.0 g, 27.0 mmol) was added to a solution of 3-hydroxy-4-methoxybenzaldehyde (Aldrich, 6.16 g, 40.05 mmol) in pyridine (60 mL). Oven-dried potassium carbonate K_2CO_3 (7.5 g, 54.4 mmol) and CuO (4.3 g, 54.04 mmol) were added to the mixture which was subsequently heated to 115 °C under an atmosphere of N_2 for 12 h. The mixture was cooled, filtered over a bed of Celite, and

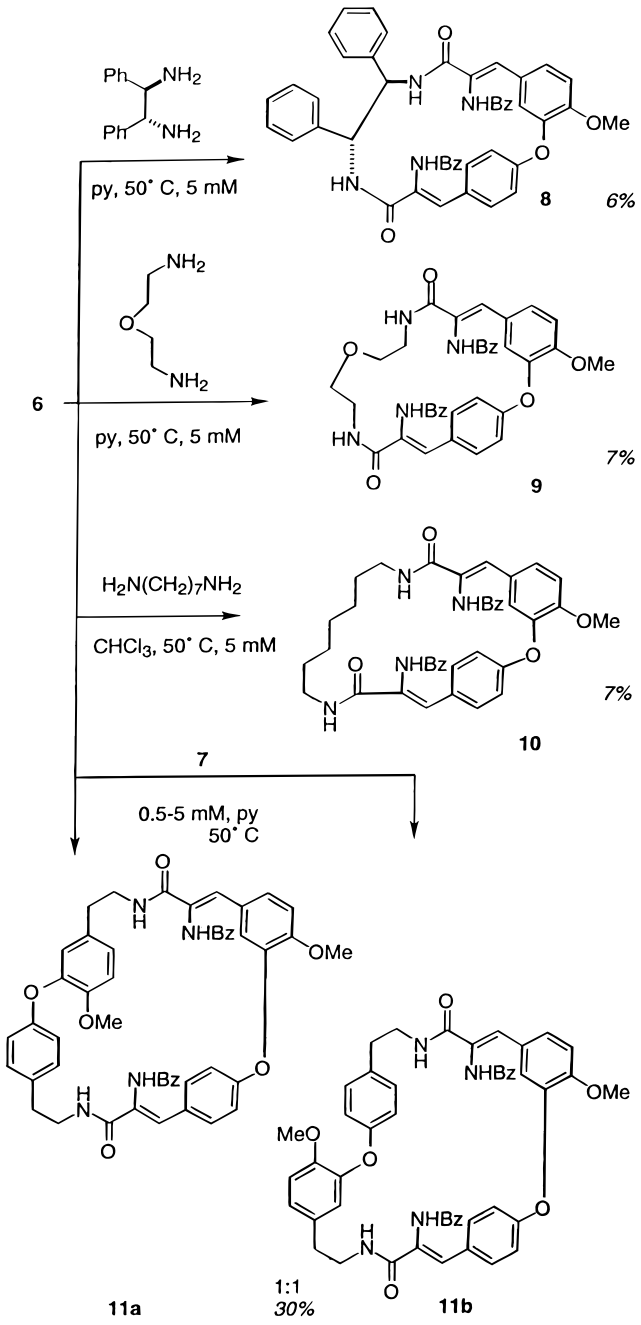
(21) Two isomers arise, in the present case, because the coupling partners are nonsymmetrical and "head-to-head" or "head-to-tail" condensations are equally probable. The isomers **11a**,**b** could be separated by HPLC (reversed phase, C_{18}, Dynamax, 1:1 MeOH/H_2O), but the head−tail orientations were not assigned.

(22) The balance of the recovered mass was insoluble polymer.

(23) A conformation almost identical in energy (ΔE < 0.2 kcal mol^{-1}) can be achieved by 180° rotation of the C6−C7 bond; however, this does not change the distance d_{endo} appreciably.

(24) Rao, Y. S.; Filler, R. *Synthesis* **1975**, 749−764.

Scheme 2. Macrolactamization Reactions of Bis-oxazolone 6



concentrated to a brown glass. The residue was purified by chromatography (silica, 1:4 *n*-hexane/$CHCl_3$) and recrystallized from EtOAc/*n*-hexane to give colorless crystals of **5** (5.7 g, 83%). mp 83−85 °C; IR (NaCl, neat) ν 1710 (CH═O), 1605 (C═C) cm^{-1}; UV ($CHCl_3$) λ_{max} 273 nm (ϵ 16600); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3H), 7.00 (d, 2H, J = 8.7 Hz), 7.18 (d, 1H, J = 8.4 Hz), 7.79 (d, 1H, J = 8.4 Hz), 7.83 (d, 2H, J = 8.7 Hz), 9.87 (s, 1H), 9.90 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 56.0 (CH_3), 112.5 (CH), 116.4 (CH), 122.0 (CH), 129.4 (CH), 130.2 (C), 131.2 (C), 131.7 (CH), 143.55 (C), 156.6 (C), 162.5 (C), 189.7 (CH), 190.4 (CH); HREIMS found m/z 256.0742 (M^+), $C_{15}H_{12}O_4$ requires 256.0736. Anal. Calcd for $C_{15}H_{12}O_4$: C, 70.30; H, 4.71. Found: C, 69.97; H, 4.69.

Bis-oxazolone (6). Dialdehyde **5** (512 mg, 2.0 mmol) in Ac_2O (10 mL) under atmospheric N_2 was added to a 50 mL RBF. In a separate 25 mL flask, a mixture of $Pb(OAc)_2$ (650 mg, 2.0 mmol) and hippuric acid (2.15 g, 12.0 mmol) in Ac_2O (5 mL) was heated with stirring until a clear orange solution was obtained. The resultant solution was cannulated into the solution containing the aldehyde, followed by an additional wash with Ac_2O (5 mL). The reaction refluxed (138 °C) under atmospheric N_2 for 24 h. The reaction mixture was cooled in an ice bath, forming a heavy yellow precipitate which was filtered and washed with cold Ac_2O. The yellow amorphous solid was dissolved in $CHCl_3$ (750 mL), washed with water (3 × 200 mL), dried over Na_2SO_4, and concentrated to a yellow paste which was triturated with EtOAc to yield **6** (746 mg, 69%). mp 279−281 °C; IR (NaCl, neat) ν 1792, 1766 (CO) cm^{-1}; UV ($CHCl_3$) λ_{max} 408 nm (ϵ 24000), 388 (26800); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.10 (d, 1H, J = 8.3 Hz), 7.13 (d, 2H, J = 8.7 Hz), 7.19 (s, 1H), 7.27 (s, 1H), 7.44−7.60 (m, 6H), 7.87 (dd, 1H, J = 8.3, 1.8 Hz), 8.03 (bd, 2H, J = 8.6 Hz), 8.16 (bd, 2H, J = 7.6 Hz), 8.25 (d, 2H, J = 8.7 Hz), 8.27 (d, 1H, J = 1.8 Hz); ^{13}C NMR (150.2 MHz, pyridine-d_5) δ 56.6, 114.2, 117.9, 118.0, 126.1,126.5, 126.6, 128.3, 128.9, 129.3, 129.7, 129.9, 131.1, 131.3, 131.5, 131.7, 132.6, 133.0, 133.9, 134.1, 135.5, 144.6, 155.1, 161.4, 163.8; HREIMS found m/z 543.1548 (MH^+), $C_{33}H_{23}N_2O_6$ requires 543.1556. Anal. Calcd for $C_{33}H_{23}N_2O_6$: C, 73.06; H, 4.09; N, 5.16. Found: C, 73.03; H, 5.16.

Diamine (7). A solution of aldehyde **5** (1.5 g, 5.9 mmol) in CH_3NO_2 (5.9 g, 96.0 mmol) and glacial acetic acid (3.4 mL) was treated with NH_4OAc (367 mg, 4.72 mmol). The mixture was heated at reflux for 3 h and concentrated to give a yellow solid. The solid was applied to a column of silica and eluted with 2:3 EtOAc/hexane. Evaporation of the solvent gave the bis-nitrostyrene as yellow foam (1.8 g, 89%) which was used immediately in the next reaction. mp 130−132 °C; IR (NaCl, neat) ν 1631, 1608, 1571, 1543, 1502 cm^{-1}; UV ($CHCl_3$) λ_{max} 351 nm (ϵ 19300); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H), 6.95 (d, 1H, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 2.1 Hz, 1H), 7.46 (dd, J = 8.7 Hz, 2.1 Hz, 1H), 7.46 (s, 1H), 7.51 (m, 2H), 7.55 (d, J = 7.2 Hz, 2H), 7.92 (d, J = 13.5 Hz, 2H), 7.97 (d, J = 13.5 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 56.1 (CH_3), 113.2 (CH), 117.0 (2 CH), 121.9 (CH), 123.3 (C), 124.4 (C), 128.5 (CH), 131.0 (2 CH), 135.8 (CH), 135.8 (CH), 137.9 (CH), 138.4 (CH), 143.7 (C), 154.8 (C), 160.8 (C); HRCIMS found m/z 360.1210 ($M + NH_4^+$), $C_{17}H_{18}N_3O_6$ requires 360.1196.

The above bis-nitrostyrene (1.3 g, 3.8 mmol) in THF (10 mL) was added over 10 min to a solution of $LiAlH_4$ (2.9 g, 77.0 mmol) in THF (40 mL) at reflux under an atmosphere of N_2, and heating was continued for 11 h. The mixture was cooled to 0 °C and quenched with excess 6 M NaOH (aq, 400 mL) and stirred for 40 min to produce a clear solution. The alkaline solution was extracted with EtOAc (3 × 200 mL), and the organic extracts were washed with brine and dried over Na_2SO_4. The volatiles were removed to afford the air-sensitive, hygroscopic diamine **7** as a yellow oil (1.1 g, 98%). IR (NaCl, neat) ν 1505 cm^{-1} (NH_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56 (bs), 2.64 (t, J = 6.6 Hz, 2H), 2.71 (t, J = 6.6 Hz, 2H), 2.89 (t, J = 7.2 Hz, 2H), 2.95 (t, J = 6.9 Hz, 2H), 3.83 (s, 3H), 6.80 (s, 1H), 6.87 (d, J = 6.6 Hz, 2H), 6.93 (s, 2H), 7.11 (d, J = 6.6 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 39.0 (CH_2), 39.1 (CH_2), 43.4 (2 × CH_2), 56.2 (CH_3), 113.3 (CH), 117.1 (CH), 121.2 (CH), 121.3 (CH), 124.6 (CH), 129.7 (CH), 132.9 (C), 133.7 (C), 144.1 (C), 149.9 (C). ESI found (MH^+) m/z 287, $C_{17}H_{23}N_2O_2$ requires 287.1760.

Macrolactam (8). Bis-oxazolone **6** (50.0 mg, 0.09 mmol) was stirred in pyridine (18 mL, 5 mM) at 60 °C for 15 min. A solution of (1*R*,2*R*)-(+)-1,2-diphenylethylene-1,2-diamine dihydrochloride in pyridine (2.0 mL) was added and stirring continued for 20 h. The reaction mixture was concentrated to a yellow solid, dissolved in $CHCl_3$ and washed with brine, dried over Na_2SO_4, and concentrated to a yellow glass which was purified by flash chromatography (SiO_2, 3:97 MeOH/$CHCl_3$) followed by HPLC (silica, Dynamax, 2:98 MeOH/CH_2Cl_2, 4 mL/min) to afford chiral macrolactam **8** (3.8 mg, 6%). $[\alpha]^{24}_D$ +1.43° (*c* 0.14, MeOH); UV (MeOH) λ_{max} 306 (ϵ 24000); CD (MeOH): λ 252 nm ($\Delta\epsilon$ −8.9), 278 (+0.9), 316 (+4.8), 327 (+5.1), IR (NaCl, neat) ν 1655 (CO), 1505 (C═C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (bs, 3H), 5.33 (bs, 1H), 5.50 (bs, 1H), 6.59 (d, J = 7.5 Hz, 2H), 6.80 (d, J = 7.5 Hz, 2H), 7.17 (m, 10H), 7.35 (m, 2H), 7.56 (m, 2H), 7.83 (m, 2H), 8.05 (bs, 1H), 8.23

(bs, 1H); ^{13}C NMR (150.8 MHz, $CDCl_3$) 53.4 (CH_2), 55.9 (CH_2), 59.8 (CH_3), 112.7, 116.2, 122.3, 127.5, 127.7, 127.6, 128.6, 128.9, 131.1, 132.3, 133.1, 138.4, 143.2, 152.5, 158.7, 166.8; MALDI MS, found *m*/*z* 737.2786 ($MH^+ - H_2O$), $C_{47}H_{38}N_4O_6$ requires 754.2791.

Macrolactam (9). Bis-oxazolone **6** (25.0 mg, 0.05 mmol) was stirred in pyridine (98 mL, 0.5 mM) at 50 °C for 15 min. To the solution was added 3-oxapentane-1,5-diamine dihydrochloride **2** (9.7 mg, 0.06 mmol) in pyridine (2 mL). The reaction was cooled and concentrated after 3 days. The subsequent yellow residue was taken up in $CHCl_3$, washed with 0.1 N HCl and brine, dried over Na_2SO_4, and concentrated to a pale yellow glass. HPLC (silica, Dynamax, 2:98 MeOH/CH_2Cl_2) afforded unreacted **6** (5 mg) and macrolactam **9** (2.3 mg, 7%); IR (NaCl, neat) 1648 (CO), 1506 (C═C) cm^{-1}; UV λ_{max} 305 (ϵ 27000); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (bs, 4H), 3.88 (s, 3H), 6.80 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 8.4 Hz, 2H), 7.19 (s 1H), 7.22 (s, 1H), 7.30 (bs,1H), 7.34 (s, 1H), 7.45 (m, 10H), 7.65 (bs, 1H), 7.73 (d, J = 7.8 Hz, 2H), 7.86 (d, J = 8.1 Hz, 2H); ^{13}C NMR (150.2 MHz, $CDCl_3$) 52.7 (CH_2), 53.4 (CH_2), 55.9 (CH_3), 111.5, 112.38, 117.46, 122.2, 122.7, 127.3, 127.4, 127.6, 128.3, 128.7, 128.8, 128.9, 131.5, 132.2, 132.3, 132.4, 132.5, 133.7, 152.2, 158.3, 163.6, 165.9; MALDI MS found *m*/*z* 629.1865 ($MH^+ - H_2O$), $C_{37}H_{34}N_4O_7$ requires 646.2427.

Macrolactam (10). Macrolactam **10** was prepared as for **9**, but $CHCl_3$ was used as solvent instead of pyridine. Workup and HPLC as before gave macrolactam in 7% yield. IR 1638 (C═O), 1508 (C═C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (m, 2H), 1.34 (m, 4H), 1.55 (m, 2H), 1.62 (m, 2H), 3.27 (m, 2H), 3.47 (m, 2H), 3.96 (s, 3H), 6.03 (s, 1H), 6.22 (m, 2H), 6.54 (m, 2H), 6.62 (s, 1H), 6.94 (s, 1H), 7.60 (m, 15H), 8.00 (d, 2H, J = 7.8 Hz,), 8.85 (bs, 1H); MALDI found *m*/*z* 695.2843 ($M + Na^+$), $C_{40}H_{40}N_4O_6$ requires 672.2948.

Macrolactams (11a,b). A solution of diamine **2** (29.0 mg, 0.10 mmol) and bis-oxazolone **6** (50.0 mg, 0.09 mmol) in pyridine (200.0 mL, 0.5 mM) was stirred at 50 °C. Reaction was complete after 4 days as visualized by TLC. The pale yellow solution was cooled and concentrated under vacuum to afford a yellow amorphous solid. The residue was purified by flash chromatography (silica, 3:97 MeOH/CH_2Cl_2), followed by HPLC with the same solvent (silica, Dynamax 25 × 300 mm, 4.0 mL/min) to obtain **11a,b** eluting as a single peak (rt 14 min, 22.0 mg, 30%). Three late-eluting peaks (rt, 16−30 min) were shown to be higher MW oligomeric products (MALDI MS) and were not investigated further. **11a,b**, mp 213−217 °C; IR (NaCl, neat) ν 1652−1634 cm^{-1}; UV ($CHCl_3$) λ_{max} 287 (ϵ 35000); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54 (m, 4H), 2.89 (m, 4H), 3.47 (m, 4H), 3.59 (s, 3H), 3.63 (s, 3H), 3.72 (m, 4H), 3.92 (s, 6H), 6.31 (bs), 6.42 (bs), 6.54 (m, 6H), 6.65 (m, 8 H), 6.72 (m, 4H), 6.92 (m, 12H), 7.12 (m, 6H), 7.20 (s, 1H), 7.30 (m, 3H), 7.43 (m, 4H), 7.54 (m, 4H), 7.93 (m, 8H), 8.28 (bs), 8.63 (bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.8, 34.0, 34.4, 40.1, 40.3, 40.4, 41.0, 52.7, 55.7, 55.9, 56.0, 111.8, 111.9, 112.2, 113.5, 114.3, 114.6, 116.0, 117.4, 122.0, 122.0, 122.5, 124.5, 124.9, 125.6, 125.7, 126.2, 127.4, 127.7, 127.9, 128.4, 128.5, 128.7, 128.8, 129.7, 130.1, 130.2, 130.5, 130.9, 131.3, 131.8, 132.1, 132.2, 132.3, 132.4, 132.6, 133.3, 143.6, 145.0, 149.4, 149.7, 149.9, 150.2, 154.7, 154.8, 156.2, 157.0, 164.7, 165.2, 165.9, 166.3, 166.8, 167.1; MALDI, *m*/*z* 851 ($M + Na^+$, 100%), 829 ($M + H^+$, 8); HRFABMS found *m*/*z* 829.3219 (MH^+), $C_{50}H_{45}N_4O_8$ requires 829.3237.

Isodityrosine Peptides (12). A sample of **11a**,**b** (4 mg) was hydrogenated in MeOH over H_2 (1 atm) and 10% Pd−C for 16 h. The mixture was filtered through Celite and evaporated to give the peptide **12** as a mixture of isomers (∼95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70 (m), {3.38 (m), 3.81 (s), 3.84 (s), 3.86 (s) = 4 × OMe}, 4.63 (m), 5.10 (m), 5.84 (m), 6.89 (m), 7.00 (m), 7.44 (m), 7.68 (m); MALDI FTMS found *m*/*z* 855.3324 ($M + Na^+$, $C_{50}H_{48}N_4O_8Na$ requires 855.3370.

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Supporting Information Available: Copies of ^{1}H NMR and MS of **5**−**12** and ^{13}C NMR of **5**−**7** and **11a,b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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