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Application of Negishi Cross-Coupling to the Synthesis of the Cyclic Tripeptides OF4949-III and K-13

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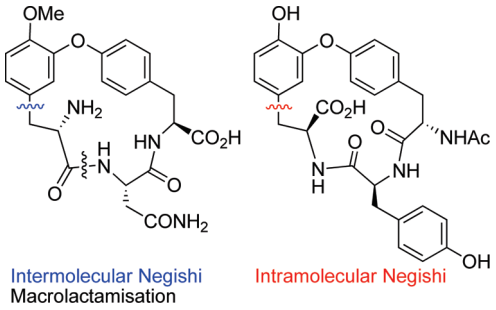

Syntheses of the cyclic tripeptides OF4949-III **1** and K-13 **2** are reported, in which the key steps are intermolecular and intramolecular Negishi cross-coupling reactions, respectively. In addition, the synthesis of a protected isomer of K-13 **25** is reported. The synthesis of K-13 features a tripeptidic organozinc reagent **11**, one of the most highly functionalized such reagents to be described. An *O*-aryltyrosine derivative **15**, prepared by S_NAr reaction between Boc-tyrosine and 2-fluorobenzaldehyde, followed by Dakin reaction, iodination, and methylation, is used as a common intermediate for all of the syntheses described. The routes to this class of cyclic tripeptide are among the shortest reported to date and demonstrate the high functional group tolerance of the carbon−zinc bond toward peptide derivatives.

Introduction

Cyclic peptides, in which the conformation of the peptide backbone is constrained,[1] are biologically significant. There are many examples of naturally occurring cyclic peptides, but among the simplest are cyclic tripeptides including the aminopeptidase inhibitor OF4949-III **1**[2] and the ACE inhibitor K-13 **2**.[3] These compounds are formally derived by oxidative cyclization of simple linear tripeptides, containing a tyrosine residue at each terminus. In the biosynthesis of OF4949-III, it is the tyrosine residue at the N-terminus that is subject to oxidation, while for K-13, it is the tyrosine residue at the C-terminus. The synthesis of cyclic tripeptides **1** and **2** has presented an opportunity to showcase methods for the stereocontrolled synthesis of the α-amino acid components, which then rely on macrolactamization procedures to complete the synthesis, and also provide motivation for the development of new cyclization methods.[4] In this paper, we describe how the Negishi cross-coupling between amino acid and peptide-derived organozinc halides, on one hand, and aryl iodides, on the other, can be employed in short syntheses of both OF4949-III and K-13. A preliminary account of a part of this work has appeared.[5]

Previous syntheses of OF4949-III, and protected derivatives, have featured the use of suitably protected isodityrosine derivatives (prepared by asymmetric hydrogenation,[6] asymmetric electrophilic amination,[7] asymmetric glycine anion chemistry,[8] or metal-mediated nucleophilic aromatic substitution[9]), which have been elaborated and then subjected to macrolactamization. An alternative approach constructs

(1) Feliu, L.; Planas, M. *Int. J. Pept. Res. Ther.* **2005**, *11*, 53–97.
(2) Sano, S.; Ikai, K.; Katayama, K.; Takesako, K.; Nakamura, T.; Obayashi, A.; Ezure, Y.; Enomoto, H. *J. Antibiot.* **1986**, *39*, 1685–1696.
(3) Yasuzawa, T.; Shirahata, K.; Sano, H. *J. Antibiot.* **1987**, *40*, 455–458.
(4) Zhu, J. *Synlett* **1997**, 133–144.
(5) Perez-Gonzalez, M.; Jackson, R. F. W. *Chem. Commun.* **2000**, 2423–2424.
(6) Schmidt, U.; Weller, D.; Holder, A.; Lieberknecht, A. *Tetrahedron Lett.* **1988**, *29*, 3227–3230.
(7) Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063–1072.
(8) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1990**, *55*, 6000–6017.
(9) Pearson, A. J.; Zhang, P. L.; Lee, K. *J. Org. Chem.* **1996**, *61*, 6581–6586.

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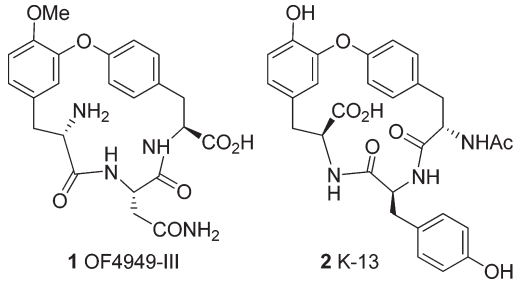
the macrocycle through formation of the biaryl ether using oxidative coupling of two (halogenated) tyrosine residues in an acyclic tripeptide precursor[10] or by intramolecular nucleophilic aromatic substitution by one tyrosine residue on the other, the latter activated by a metal carbonyl fragment.[11] Previous approaches to the synthesis of K-13 have employed similar strategies, using elaboration of suitably protected isodityrosine derivatives,[7,8,12–15] biomimetic oxidative tyrosine coupling,[16] or macrocyclic biaryl ether formation by nucleophilic aromatic substitution using halotyrosine residues activated either by metal carbonyl fragments[11] or by *ortho*-electron-withdrawing substituents.[17]

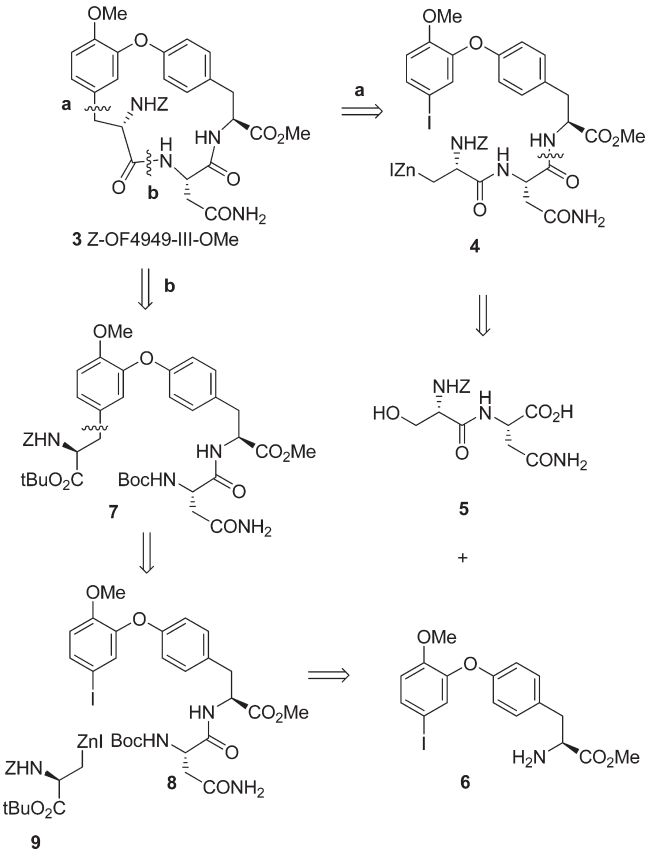


The palladium-catalyzed Negishi cross-coupling reaction between aromatic iodides and the organozinc reagent derived from protected iodoalanine to generate phenylalanine derivatives has been known for some time.[18,19] The synthesis of OF4949-III and K-13 offered an opportunity to test the effectiveness of this reaction using highly functionalized aryl iodides and also to explore whether it might be applied to peptide-derived organozinc reagents in an intramolecular manner. It is worth observing that DMF is an excellent solvent for the preparation and stabilization of organozinc reagents (possibly through promotion of partial ionization of the zinc–iodine bond, thereby reducing the tendency of the carbon–zinc bond to protonate)[20] and, of course, in peptide chemistry.

Results and Discussion

The initial strategy considered for the synthesis of OF4949-III **1** (Scheme 1) relied on formation of the protected macrocycle **3**, which had been previously synthesized by both Boger[8] and Pearson,[9] using an intramolecular Negishi reaction (step a). Initial disconnection at the more oxygenated aromatic residue has the advantage that it leads, ultimately, to the same intermediate for the synthesis of both OF4949-III and K-13 (see below). In principle, a suitable precursor to

SCHEME 1. Proposed Routes to OF4949-III

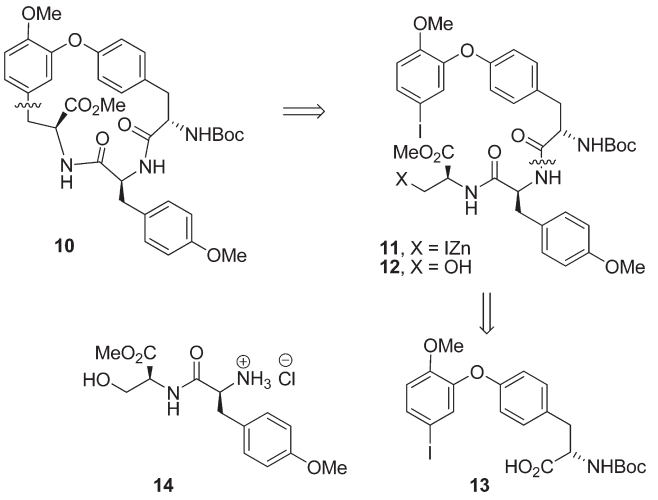


compound **4** could be prepared from the Ser-Asn derivative **5** and the tyrosine derivative **6**. However, the zinc reagent produced by this disconnection, **4**, contains a carbon–zinc bond at the N-terminus, and previous work had already established that the stability toward elimination of a carbon–zinc bond at the N-terminus of a dipeptide was substantially less than a corresponding bond at the C-terminus.[21] For this reason, the viability of reagent **4** was sufficiently uncertain that a simple reordering of steps was preferred, whereby the Negishi cross-coupling was to be carried out in an intermolecular manner between **8** and **9**, with subsequent macrolactamization of intermediate **7** (step b, Scheme 1). Compound **8** was envisaged to be easily prepared from tyrosine derivative **6**. A further issue to be determined experimentally was whether the primary amide function in **8** would be compatible with Negishi cross-coupling or indeed whether the extra polarity of this group might result in solubility problems.

In the context of the planned synthesis of K-13, the initial target was the protected derivative **10** first made by Evans[7] and then subsequently by Rich[11] and Zhu.[17] Disconnection of **10** leads to a C-terminal organozinc reagent **11**, which previous precedent had suggested might be a credible intermediate,[21] and therefore allow the viability of an intramolecular Negishi reaction to be assessed. A suitable precursor to organozinc reagent **11** could be prepared from the Ser-Tyr derivative **14** and the *O*-aryl tyrosine derivative **13** (Scheme 2).

(10) Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett*. **1988**, *29*, 559–562.
(11) Janetka, J. W.; Rich, D. H. *J. Am. Chem. Soc*. **1997**, *119*, 6488–6495.
(12) Boger, D. L.; Yohannes, D. *J. Org. Chem*. **1989**, *54*, 2498–2502.
(13) Rao, A. V. R.; Gurjar, M. K.; Reddy, A. B.; Khare, V. B. *Tetrahedron Lett*. **1993**, *34*, 1657–1660.
(14) Beugelmans, R.; Bigot, A.; Zhu, J. P. *Tetrahedron Lett*. **1994**, *35*, 7391–7394.
(15) Pearson, A. J.; Lee, K. S. *J. Org. Chem*. **1994**, *59*, 2304–2313.
(16) Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett*. **1989**, *30*, 379–382.
(17) Bigot, A.; Bois-Choussy, M.; Zhu, J. *Tetrahedron Lett*. **2000**, *41*, 4573–4577.
(18) Jackson, R. F. W.; Moore, R. J.; Dexter, C. S.; Elliot, J.; Mowbray, C. E. *J. Org. Chem*. **1998**, *63*, 7875–7884.
(19) Rilatt, I.; Caggiano, L.; Jackson, R. F. W. *Synlett* **2005**, 2701–2719.
(20) Caggiano, L.; Jackson, R. F. W.; Meijer, A.; Pickup, B. T.; Wilkinson, K. A. *Chem.—Eur. J*. **2008**, *14*, 8798–8802.
(21) Dunn, M. J.; Jackson, R. F. W. *Tetrahedron* **1997**, *53*, 13905–13914.

SCHEME 2. Proposed Route to K-13



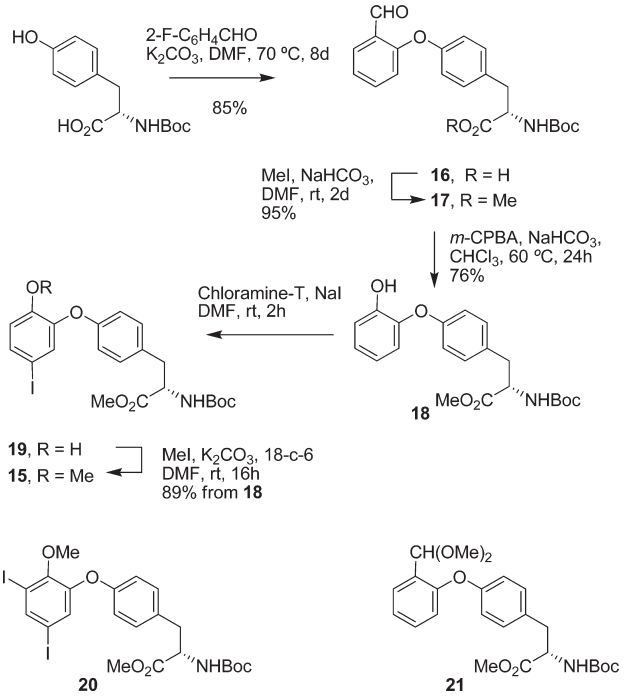
Synthesis of *O*-Aryl Tyrosine 15. The only components in the synthetic plans not commercially available were the O-arylated tyrosine derivatives **6** and **13**, both derived from a common precursor **15**. The synthesis of iodide **15** (Scheme 3) proceeded by S_NAr reaction between *N*-Boc-L-tyrosine and 2-fluorobenzaldehyde to give the biaryl ether **16** (85%), which was then converted into the methyl ester **17** (95%). Use of the free carboxylic acid of tyrosine proved essential because direct use of the corresponding methyl ester gave *rac*-**17** under the same conditions. Treatment of aldehyde **17** with *m*-CPBA gave the formate ester, which was immediately converted into the corresponding phenol **18** (76%), which had previously been made by an alternative three-step route in 30% overall yield.[22] Interestingly, use of a different batch of *m*-CPBA, which contained more water, gave the corresponding phenol directly, shortening the present route to three steps from protected tyrosine. Iodination of the phenol **18**, following Jung's conditions,[22] gave the 5-iodo derivative **19** that was directly methylated to give **15** (89% from **18** over two steps); small amounts of the corresponding 3,5-diiodo derivative **20** were also isolated in some runs. This procedure allowed the synthesis of compound **15** in five steps on a multigram scale in 55% overall yield from commercially available *N*-Boc-tyrosine and 2-fluorobenzaldehyde, with only one chromatographic purification necessary at the end of the synthesis.

Interestingly, when the methylation of **16** was scaled-up, a byproduct identified as the dimethyl acetal **21** was identified, whose formation appears to require the presence of methanol. It seems possible that methanol can be formed by decomposition of methyl bicarbonate, itself formed by reaction of sodium bicarbonate with iodomethane. The acetal **21** was found to be unstable on storage at room temperature, and after a few months, it was converted almost entirely into the aldehyde **17**.

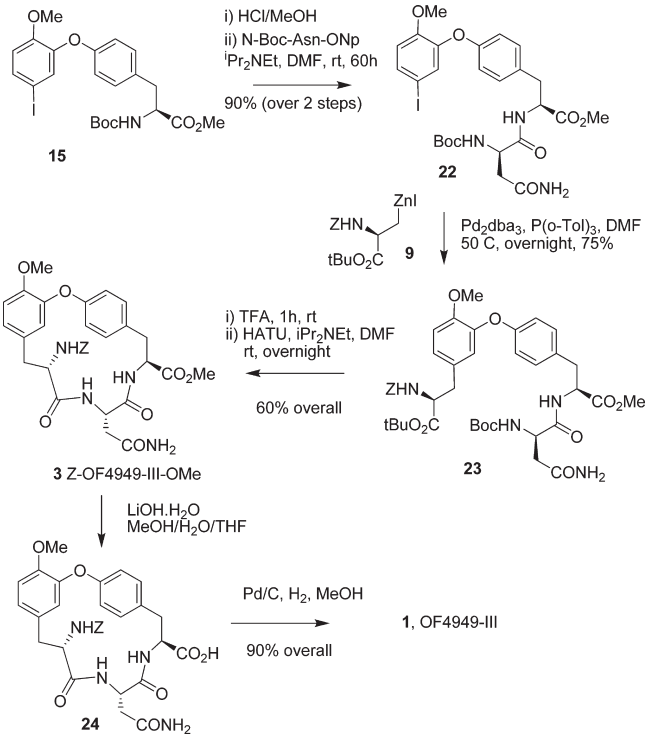
Synthesis of OF4949-III. Boc deprotection of **15** was achieved with HCl in methanol, obtained from methanol and acetyl chloride, and was followed by coupling with the active ester Boc-Asn-ONp to give the modified dipeptide **22**. Although the presence of the primary amide function in **22** might have compromised the planned Negishi cross-coupling,

(22) Jung, M. E.; Starkey, L. S. *Tetrahedron* **1997**, *53*, 8815–8824.

SCHEME 3. Preparation of *O*-Aryl Tyrosine 15



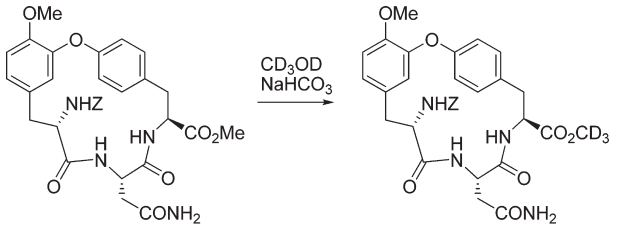
SCHEME 4. Synthesis of OF4949-III 1



reaction between the organozinc reagent **9**[23] and the aryl iodide **22** proceeded to give the cross-coupled product **23** in high yield (Scheme 4). The efficiency of this reaction further demonstrates the high functional group tolerance (especially

(23) Dumez, E.; Snaith, J. S.; Jackson, R. F. W.; McElroy, A. B.; Overington, J.; Wythes, M. J.; Withka, J. M.; McLellan, T. J. *J. Org. Chem.* **2002**, *67*, 4882–4892.

SCHEME 5. Suggested Transesterification of Protected OF4949-III 3 with CD_3OD



3 Z-OF4949-III-OMe **3a** Z-OF4949-III-OCD_3

toward acidic protons) of organozinc iodides. Recently, more examples of the tolerance of amide protons by organozinc reagents have been reported.[24] The tripeptide **23** was deprotected under acidic conditions and subjected to macrocyclization to give protected OF4949-III **3**. Using Boger's procedure,[8] the methyl ester of the macrocycle **23** was hydrolyzed to give the corresponding acid **24**, which was then subjected to hydrogenolysis[8] to give OF4949-III **1** (Scheme 4), in 12 steps and with 20% overall yield from Boc-tyrosine. The ^{1}H NMR spectrum of OF4949-III **1** matched that reported by Evans[7] (see Supporting Information), and in addition, the specific rotation $[\alpha]_D$ −30 (c = 0.5, 0.1 N HCl) was comparable, both in sign and magnitude, with all previous reports.[7,8,10]

As well as comparison of the data for OF4949-III **1** itself, comparison of the data for protected OF4949-III **3** with that already reported was made.[8,9] Although both previous groups had used CD_3OD as solvent for the NMR experiments, we found that the solubility of our sample of protected OF4949-III **3** in this solvent was poor, especially after recrystallization, although it was sufficient to allow NMR spectra to be obtained. Comparison of the ^{1}H spectrum of our sample of protected OF4949-III **3** in CD_3OD (4 mg of **3** in 1 mL of CD_3OD, to mimic Pearson's spectrum as closely as possible) showed an excellent match with that reported by Pearson[9] and a reasonable match with that reported by Boger, although Boger's description[8] of the methylene protons of the *Z*-protecting group as a singlet is at variance with what both Pearson and we have observed. It is possible that this apparent discrepancy may arise due to differences in the concentration at which the respective spectra were recorded. In order to be completely confident of our assignment of the structure of our sample of compound **3**, a comprehensive NMR investigation was carried out in both CD_3OD and $CDCl_3$, the details of which are included in the Supporting Information.

Comparison of Pearson's ^{13}C NMR spectrum of protected OF4949-III **3** in CD_3OD with ours showed two additional signals in the aliphatic carbon range of Pearson's spectrum (in addition to the three expected for compound **3** due to the methylene group in each amino acid side chain); these signals most likely arise due to minor impurities. There was one additional signal at δ 52.5 in our ^{13}C NMR spectrum which was not evident in Pearson's spectrum. A complete assignment of the ^{13}C NMR spectrum demonstrated that this signal was the methyl ester carbon, and it therefore appeared possible that, prior to Pearson's data accumulation, a transesterification reaction may have occurred with the solvent (CD_3OD) leading to the trideuteromethyl ester **3a** (Scheme 5). In order to explore this possibility, treatment of our sample with sodium bicarbonate and CD_3OD was carried out, which did indeed result in the apparent disappearance of the signal at δ 52.5 and a ^{13}C NMR spectrum which now matched Pearson's spectrum perfectly (apart from the two additional signals referred to above). Mass spectrometry of our sample, including high-resolution mass measurement, confirmed the incorporation of a CD_3 group. Of course, exchange of a CH_3 group with a CD_3 group cannot remove the signal in the ^{13}C spectrum, but the carbon atom of a CD_3 group will exhibit a 7-line splitting pattern; in addition, there would now be no enhancement of the ^{13}C signal through NOE, reducing the signal intensity further. Taken together, these effects might be expected to result in a substantial reduction in signal strength, so that the signal is rendered indistinguishable from baseline noise.

TABLE 1. *Z*-OF4949-III-OMe 3 Physical Data

	Boger[8]	Pearson[9]	present work (sample after chromatography)	present work (sample recrystallized)
mp °C	178−182	181−183	245−246	259−260
$[\alpha]^{20}_D$ (MeOH)	−74, c = 0.1	−73, c = 0.35	+55, c = 0.1	+73, c = 0.1

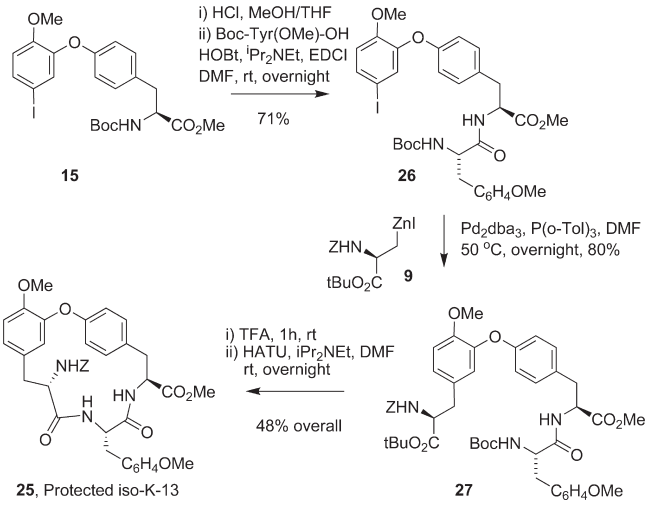
TABLE 2. Variation of Specific Rotation of Z-OF4949-III-OMe 3 with Concentration

	$[\alpha]^{20}_D$ in $CHCl_3$	$[\alpha]^{20}_D$ in CH_2Cl_2
c = 1.02	+42	+54
c = 0.41	+55	+68
c = 0.20	+59	+70
c = 0.04	+99	

Despite this excellent match of our NMR data with Pearson's data for OF4949-III-OMe **3**,[9] some discrepancies between our physical data and those already reported by Boger[8] and Pearson[9] were identified (see Table 1). A much higher melting point was recorded as was a different sign (although identical magnitude) for the optical rotation (Table 1). While the higher melting point and low solubility of our sample of *Z*-OF4949-III-OMe **3** in methanol could be due to the formation of a different polymorph, perhaps due to the fact that we were able to purify our material by recrystallization, it is very hard to rationalize the discrepancy in the sign of specific rotation, especially since we converted *Z*-OF4949-III-OMe **3** using Boger's route into OF4949-III **1**, and our physical and spectroscopic data for OF4949-III match the literature values, including Boger's,[8] in all respects. A study of the influence of concentration on specific rotation of *Z*-OF4949-III-OMe **3** in chloroform and dichloromethane (in which solvent *Z*-OF4949-III-OMe **3** was more soluble than in methanol) revealed significant variations (Table 2), perhaps pointing to aggregation. All specific rotations recorded were positive. The specific rotation of each of the amino acid building blocks used for our synthesis of *Z*-OF4949-III-OMe **3** was checked and in each case was found to be consistent with the natural *S*-isomer, ruling out the possibility that we had inadvertently made *ent*-**3**. Furthermore, no evidence for epimerization of any of

(24) Manolikakes, G.; Dong, Z. B.; Mayr, H.; Li, J. S.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 1324–1328.

SCHEME 6. Synthesis of Protected iso-K-13 25



the intermediates in our route was found, so we (and Pearson) had not inadvertently prepared a diastereoisomer of *Z*-OF4949-III-OMe **3**.

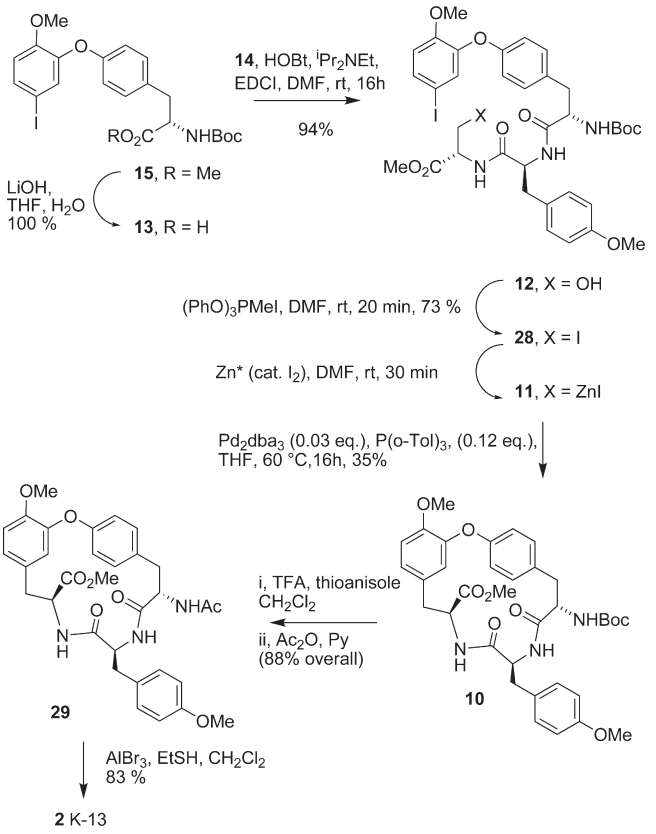
There are some similar inconsistencies in the data we observed for the free carboxylic acid **24**. For example, the specific rotation of our sample of **24** was $[\alpha]_D$ +57 ($c = 0.28$, MeOH), with Boger reporting[8] $[\alpha]_D$ −87. In the ^{1}H NMR spectrum, the methylene protons of the *Z*-protecting group appear as an AB system in our spectrum but are reported as a singlet in Boger's spectrum. Such differences may again be accounted for by the influence of concentration.

Synthesis of Protected iso-K-13. The success of this short route to OF4949-III **1** encouraged us to explore further application of the Negishi reaction in the synthesis of an isomer of K-13, protected iso-K-13 **25** (Scheme 6). This compound closely resembles OF4949-III but has a tyrosine residue in place of the asparagine residue. Deprotection of **15** and coupling with a protected tyrosine gave the dipeptide **26**, which was subjected to Negishi reaction with **9** to give the macrocyclization precursor **27**. In a similar way, the macrocyclization was achieved via peptide coupling to give the protected iso-K-13 **25**.

Synthesis of K-13. The retrosynthetic plan for K-13 made use of the intramolecular Negishi reaction that we had considered for use in the approach to OF4949-III but was rejected in this latter case due to the (relative) instability of reagents contains a carbon−zinc bond at the N-terminus of a peptide. In the event, conversion of the tyrosine derivative **15** into the required carboxylic acid **13**, followed by coupling with the dipeptide **14**, gave the modified tripeptide **12**.[21] Conversion of **12** into the iodide **28**, followed by treatment with zinc (activated by treatment with iodine), and then addition of this solution of the presumed organozinc reagent **11** to a dilute solution of a catalyst derived from $Pd_2(dba)_3$ and P(*o*-tol)$_3$ gave the desired macrocyclic peptide **10**, albeit in modest yield (35% from iodide **28**). Although it is possible that zinc could insert into the aromatic carbon−iodine bond, this process is normally slower than insertion of zinc into an aliphatic carbon−iodine bond.[25] In the event, no evidence for the formation of byproduct arising from insertion of zinc

(25) Majid, T. N.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 4413–4416.

SCHEME 7. Synthesis of K-13 2 by Intramolecular Negishi Reaction



into the aromatic carbon−iodine bond was found. Conversion of macrocyclic peptide into K-13 **2** was achieved following Evans' procedure,[7] via the intermediate **29** (Scheme 7). Our sample of synthetic K-13 exhibited physical and spectroscopic data that were in close agreement with those previously reported.[3,7,8]

In conclusion, it has been demonstrated that organozinc iodides derived from amino acids and peptides are useful intermediates in the preparation of naturally occurring cyclic tripeptides and their analogues. Further applications of this general approach to peptide modification can be envisaged.

Experimental Section

General Procedure 1: Boc Deprotection and Peptide Coupling. AcCl (5 equiv) was added slowly to a rapidly stirred solution of the Boc-protected amine (1 equiv) in MeOH/THF (3:1) at rt. The mixture was stirred overnight, and the solvent was removed under reduced pressure. Trituration with Et_2O/PE (1:1) gave a white solid, which was dissolved in dry DMF and ^{i}Pr$_2$NEt (1 equiv), HOBt (1 equiv), and the required N-protected amino acid added. EDCI (1 equiv) was added to the stirred solution in small portions over a period of 10 min at 0 °C, and the solution was then stirred at rt for 8 to 48 h. The solution was partitioned between EtOAc and water, and the aqueous layer was re-extracted with EtOAc. The combined organic phases were washed with saturated citric acid, sodium bicarbonate, water, and brine. The organic fraction was dried over $MgSO_4$ and the solvent removed under reduced pressure.

General Procedure 2: Zinc Activation and Insertion into the C−I Bond. A flame-dried flask was charged with zinc powder

(from 3 to 6 equiv) and placed under a N_2 atmosphere. Dry DMF and TMSCl were added, and the solution was stirred for 15 min at rt. Stirring was stopped, and the suspension was allowed to settle and the solution removed by syringe. The remaining solid was dried using a heating gun at reduced pressure. The activated zinc was cool to rt, and dry DMF (enough volume to obtain a 1 to 0.5 M solution of the iodoamino acid used) and the iodoalanine derivative (1.5 to 2 equiv) were added and the suspension was rapidly stirred until just a trace of starting material was detectable via TLC (80% Et_2O/PE). Zn insertion into the C−I bond is an exothermic reaction, and the excess heat was removed by an ice bath. Aryl iodide (1 equiv), $Pd_2(dba)_3$ (3 mol %), and P(*o*-Tol)$_3$ (12 mol %) were added to the suspension at rt, and the mixture was stirred overnight at 50 °C under N_2. The suspension was filtered through silica gel and the solvent removed under reduced pressure. The mixture was purified via flash chromatography.

2-(*S*)-*tert*-Butoxycarbonylamino-3-[4-(2-formylphenoxy)phenyl]propionic acid 16. 2-Fluorobenzaldehyde (18 g, 145.0 mmol) was added to a rapidly stirred solution of *N*-*tert*-butoxycarbonyl-L-tyrosine (13.57 g, 48.2 mmol) and K_2CO_3 (20 g, 145.0 mmol) in dry DMF (35 mL) at room temperature under nitrogen. The solution was stirred for 8 days at 70 °C and then cooled. The solvent was removed under reduced pressure, and aqueous NaOH (300 mL, 0.5 M) was added and the mixture extracted with Et_2O (2 × 100 mL). HCl (2 N) was added to the aqueous layer until pH ≅ 2 and was then extracted with Et_2O (3×75 mL). The organic layer was washed with water (2×100 mL) and brine (1×100 mL), dried over $MgSO_4$, and the solvent removed under reduced pressure to afford a brown foam (15.75 g, 85%), which was used directly for the next step. A sample was recrystallized to afford the acid **16** as a white solid: mp 76−77 °C ($CHCl_3$/PE); $[\alpha]^{20}_D$ +43.1 (c = 1, $CHCl_3$); ν_{max} (KBr disk) 3511 (br m, OH), 1724 (s sh, C=O), 1706 (s sh, C=O), 1672 (s sh, C=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.42 (9H, s, C(CH_3)$_3$), 3.07 (1H, dd, J = 13.5, 6.5 Hz, β), 3.21 (1H, br d, J = 13.5 Hz, β), 4.62 (1H, br d, J = 6.0 Hz, α), 5.03 (1H, d, J = 7.5 Hz, NH), 6.88 (1H, d, J = 8.0 Hz, Ar), 7.00 (2H, d, J = 8.0 Hz, Ar), 7.18 (1H, t, J = 7.5 Hz, Ar), 7.21 (2H, d, J = 8.5 Hz, Ar), 7.50 (1H, td, J = 7.5, 2.0 Hz, Ar), 7.92 (1H, dd, J = 7.5, 2.0 Hz, Ar), 10.47 (1H, s, CHO); carboxylic acid proton not observed; δ_C (100 MHz, $CDCl_3$) 28.3, 37.3, 54.3, 80.4, 118.4, 119.3, 119.5, 123.4, 126.8, 128.5, 131.1, 135.8, 155.3, 155.4, 160.0, 175.7, 189.5; m/z (EI) 385 (M^+, 18%), found M^+ 385.1529; $C_{21}H_{23}NO_6$ requires 385.1525.

2-(*S*)-*tert*-Butoxycarbonylamino-3-[4-(2-formylphenoxy)phenyl]propionic acid methyl ester 17. MeI (12.14 mL, 195 mmol) was added dropwise to a rapidly stirred solution of the carboxylic acid **16** (15 g, 39 mmol) and $NaHCO_3$ (5.8 g, 69 mmol) in dry DMF (130 mL), and the solution was stirred at rt for 2 days. The solution was removed under reduced pressure, diluted with aqueous KOH (250 mL, 0.5 N), and extracted with EtOAc (3× 150 mL). The organic layer was washed with water (2×200 mL) and brine (1 × 150 mL), dried over $MgSO_4$, and the solvent removed under reduced pressure to afford the methyl ester **17** (15.23 g, 95%) that was used directly for the Perkin reaction. A small amount of the mixture was purified by chromatography (isocratic CH_2Cl_2) to afford methyl ester **17** as a colorless oil: $[\alpha]^{20}_D$ +43.1 (c = 1, $CHCl_3$); found C 66.33%, H 6.33%, N 3.38%; $C_{22}H_{25}NO_6$ requires C 66.15%, H 6.31%, N 3.51%; ν_{max} (KBr disk) 3358 (s sh, NH), 2990 (m sh, Ar−H), 2872 (m sh, Ar−H), 1739 (s sh, C=O), 1691 (s br, C=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.43 (9H, s, C(CH_3)$_3$), 3.03 (1H, dd, J = 13.5, 6.5 Hz, β), 3.15 (1H, dd, J = 13.5, 5.5 Hz, β), 3.74 (3H, s, OMe), 4.56−4.64 (1H, m, α), 5.12 (1H, br d, J = 8.5 Hz, NH), 6.88 (1H, d, J = 8.5 Hz, Ar), 7.00 (2H, d, J = 8.5 Hz, Ar), 7.14−7.21 (3H, m, Ar), 7.51 (1H, dt, J = 1.5, 8.0 Hz, Ar), 7.93 (1H, dd, J = 7.5, 2.0 Hz, Ar), 10.50 (1H, s, CHO); δ_C (125 MHz, $CDCl_3$) 28.3, 37.8, 52.3, 54.5, 79.9, 118.4, 119.4, 123.3, 126.8, 128.4, 131.0, 132.3, 135.8, 155.0, 155.4, 160.0, 172.2, 189.3; m/z (EI) 399 (M^+, 0.2%), found M^+ 399.1673; $C_{22}H_{25}NO_6$ requires 399.1682.

2-(*S*)-*tert*-Butoxycarbonylamino-3-[4-(2-dimethoxymethylphenoxy)phenyl]propionic acid methyl ester 21. When the methylation to prepare the methyl ester **17** was scaled-up, the formation of an unexpected byproduct was observed (25% yield, by NMR) that was identified as the dimethyl acetal **21**. The product is not stable, and after long storage on the bench, it decomposes to the aldehyde **17**. The acetal **21** was purified by chromatography (isocratic 16% EtOAc/PE) and obtained as a pale yellow viscous oil, as a mixture with the aldehyde **17** (20%): $[\alpha]^{20}_D$ +37.0 (c = 1.3, $CHCl_3$); ν_{max} (reflex) 2975 (br w, Ar−H), 1713 (s br, C=O), 1693 (s br, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.30 (9H, s, C(CH_3)$_3$), 2.88 (1H, dd, J = 14.0, 6.5 Hz, β), 2.97 (1H, dd, J = 14.0, 5.5 Hz, β), 3.23 (6H, br s, OMe), 3.60 (3H, s, OMe), 4.41−4.48 (1H, m, α), 4.90 (1H, d, J = 8.0 Hz, NH), 5.50 (1H, s, CH-acetal), 6.74−6.79 (3H, m, Ar), 6.95 (2H, d, J = 8.5 Hz Ar), 7.01−7.06 (1H, m, Ar), 7.13−7.19 (1H, m, Ar), 7.51 (1H, dd, J = 7.5, 2.0 Hz, Ar); δ_C (100 MHz; $CDCl_3$) 27.9, 37.2, 51.8, 53.5, 79.5, 98.9, 117.9 (x 2), 118.8, 123.2, 127.3, 129.1, 129.4, 130.1 (x 2), 153.9, 154.7, 156.4, 171.9 (this is a partial peak listing); m/z (ES) 468 (MNa^+, 95%), found MNa^+ 468.2005; $C_{24}H_{31}NO_7Na$ requires 468.1998.

2-(*S*)-*tert*-Butoxycarbonylamino-3-[4-(2-hydroxyphenoxy)phenyl]propionic acid methyl ester 18. *m*CPBA (70%, 6.16 g, 25 mmol) was added in small portions to a rapidly stirred suspension of the aldehyde **17** (5.34 g, 13.4 mmol) and $NaHCO_3$ (3.15 g, 37.5 mmol) in $CHCl_3$ (60 mL). The solution was stirred at 60 °C for 24 h. Solid Na_2SO_3 (3.15 g, 25 mmol) was added, and the mixture was stirred for 1 h. The solvent was removed under reduced pressure to afford a brown foam, and water (150 mL) was added and the mixture extracted with EtOAc (3 × 75 mL). The organic layer was washed with saturated solution of $NaHCO_3$ (2×100 mL) and brine (1×100 mL), dried over $MgSO_4$, and solvent removed under reduced pressure. Purification was carried out by flash chromatography (gradient: 20% EtOAc/PE−50% EtOAc/PE) to afford the phenol **18** as a white solid (3.95 g, 76%) was obtained. A small sample was crystallized from $CHCl_3$ giving the phenol **18** as a white solid: mp 63−64 °C ($CHCl_3$); $[\alpha]^{20}_D$ +47.0 (c = 1, $CHCl_3$), lit.[22] $[\alpha]^{20}_D$ +39.9 (c = 1, $CHCl_3$); δ_C (100 MHz, $CDCl_3$) 28.3, 37.6, 52.3, 54.4, 80.0, 116.3, 117.9, 119.1, 120.6, 124.8, 130.7, 131.2, 143.3, 147.6, 155.0, 155.9, 172.3. Other spectroscopic data were consistent with that reported by Jung.[22]

2-(*S*)-*tert*-Butoxycarbonylamino-3-[4-(5-iodo-2-methoxyphenoxy)phenyl]propionic acid methyl ester 15.[22] Chloramine T hydrate (1.70 g, 7.47 mmol) was slowly added over 10 min to a rapidly stirred solution of NaI (1.12 g, 7.47 mmol) and phenol **18** (3 g, 7.74 mmol) in DMF (30 mL) at rt and left to stir for 2 h. Water (40 mL) was added to the solution and then 2 N HCl until pH ≅ 3. Water (225 mL) was added, and the solution was extracted with EtOAc (3×90 mL). The organic layer was washed with aqueous $Na_2S_2O_3$ (100 mL, 10%), water (100 mL), and brine (100 mL), dried over $MgSO_4$, and the solvent removed under reduced pressure to give the crude iodophenol **19** (4.42 g), contaminated with 4-methylbenzenesulfonamide as Jung noted,[22] and which was used directly in the next step. MeI (5.3 g, 37.35 mmol) was added to a rapidly stirred solution of the crude iodophenol **19** (3.94 g), used without purification from the previous step, 18-crown-6 (98 mg, 0.38 mmol), and K_2CO_3 (2.06 g, 14.9 mmol) in DMF (9.4 mL) at rt and was left to stir for 48 h at rt. Aqueous NH_4OH (1.5 mL, 28%) was added and the solution stirred for a further 20 min. Water (140 mL) was added and the solution extracted with EtOAc (3 × 70 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude material was purified by column chromatography (gradient 15−17% EtOAc/PE) and gave the product **15** (3.24 g, 89% from phenol **18**, based on the proportion

of crude iodophenol used) as a white solid: mp 91−92 °C (EtOAc/PE); $[\alpha]^{20}_D$ +35.8 (c = 1, $CHCl_3$); found C 50.16%, H 4.81%, N 2.58%; $C_{22}H_{26}INO_6$ requires C 50.11%, H 4.97%, N 2.66%; ν_{max} (KBr disk) 3355 (m sh, NH), 2931 (w sh, Ar−H), 1737 (s sh, C═O), 1689 (s sh, C═O) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.42 (9H, s, $C(CH_3)_3$), 3.02 (1H, dd, J = 13.5, 6.0 Hz, β), 3.08 (1H, dd, J = 13.5, 6.0 Hz, β), 3.71 (3H, s, OMe), 3.81 (3H, s, OMe), 4.53−4.60 (1H, m, α), 4.99 (1H, d, J = 8.0 Hz, NH), 6.75 (1H, d, J = 8.5 Hz, Ar), 6.87 (2H, d, J = 8.5 Hz, Ar), 7.07 (2H, d, J = 8.5 Hz, Ar), 7.21 (1H, d, J = 2.0 Hz, Ar), 7.41 (1H, dd, J = 8.5, 2.0 Hz, Ar); δ_C (125 MHz, $CDCl_3$) 28.3, 37.7, 52.2, 54.4, 56.1, 80.0, 81.9, 114.7, 117.5, 129.3, 130.5, 130.7, 133.5, 146.1, 151.5, 155.0, 156.3, 172.3; m/z (EI) 527 (M^+, 4%), found M^+ 527.0795; $C_{22}H_{26}INO_6$ requires 527.0805.

2-(*S*)-*tert*-Butoxycarbonylamino-3-[4-(3,5-diiodo-2-methoxyphenoxy)phenyl]propionic acid methyl ester 20. In some runs, purification of compound **15** also allowed the isolation of the diiodo product **20** as a white solid: mp 64−65 °C (Et_2O/PE); $[\alpha]^{20}_D$ +25.0 (c = 1, $CHCl_3$); ν_{max} (KBr disk) 3554 (s sh, NH), 2970 (w sh, ArH), 1734 (s sh, C═O), 1688 (s sh, C═O) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.42 (9H, s, $C(CH_3)_3$), 3.02 (1H, dd, J = 14.0, 6.0 Hz, β), 3.12 (1H, dd, J = 14.0, 6.0 Hz, β), 3.72 (3H, s, OMe), 3.84 (3H, s, OMe), 4.54−4.65 (1H, m, α), 5.01 (1H, d, J = 8.0 Hz, NH), 6.89 (2H, d, J = 8.5 Hz, Ar), 7.11 (2H, d, J = 8.5 Hz, Ar), 7.18 (1H, d, J = 2.0 Hz, Ar), 7.85 (1H, d, J = 2.0 Hz, Ar); δ_C (125 MHz, $CDCl_3$) 28.3, 37.7, 52.3, 54.5, 60.9, 80.0, 87.3, 94.0, 118.0, 130.0, 130.8, 131.6, 141.6, 149.6, 151.5, 155.1, 155.6, 172.3; m/z (FAB+) 654 (MH^+ 7%), found MH^+ 653.9834; $C_{22}H_{26}I_2NO_6$ requires 653.9850.

2-(*S*)-(2-(*S*)-*tert*-Butoxycarbonylamino-3-carbamoylpropionylamino)-3-[4-(5-iodo-2-methoxyphenoxy)phenyl]propionic acid methyl ester 22. Compound **22** was synthesized following General Procedure 1. Deprotection of compound **15** (2.8 g, 5.31 mmol) was achieved with AcCl (2.08 g, 26.5 mmol) in MeOH/THF (20 mL) and triturated with Et_2O/PE (3×12 mL). Peptide coupling was achieved with Boc-Asn-ONp (1.87 g, 5.31 mmol and $^iPr_2NEt$ (0.69 g, 5.31 mmol) in dry DMF (8 mL). The solution was stirred for 60 h at rt, and then the solvent was removed under reduced pressure. The crude material was triturated with Et_2O (3×10 mL) and dried under vacuum to afford the product **22** (3.05 g, 90%) as a white solid: mp 208−210 °C (EtOAc/PE); $[\alpha]^{20}_D$ +9.0 (c = 1.2, $CHCl_3$); ν_{max} (film) 3433 (m sh, NH), 3329 (br m, NH), 2978 (w sh, ArH), 1741 (s sh, C═O), 1687 (s sh, C═O), 1662 (s sh, C═O), 1645 (s sh, C═O) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.44 (9H, s, $C(CH_3)_3$), 2.54 (1H, dd, J = 16.0, 6.0 Hz, β_1), 2.92 (1H, br d, J = 16.0 Hz, β_1), 3.01 (1H, dd, J = 14.0, 6.5 Hz, β_2), 3.10 (1H, dd, J = 13.5, 5.5 Hz, β_2), 3.69 (3H, s, OMe), 3.81 (3H, s, OMe), 4.43−4.50 (1H, m, α_1), 4.77 (1H, q, J = 7.0 Hz, α_2), 5.45 (1H, br s, NH_2), 5.81 (1H, br s, NH_2), 6.04 (1H, br d, J = 7.0 Hz, NH-α_1), 6.75 (1H, d, J = 8.5 Hz, Ar), 6.86 (2H, d, J = 8.5 Hz, Ar), 7.10 (2H, d, J = 8.0 Hz, Ar), 7.22 (1H, d, J = 2.0 Hz, Ar), 7.34 (1H, br d, J = 5.5 Hz, NH-α_2), 7.41 (1H, dd, J = 9.0, 2.0 Hz, Ar); δ_C (125 MHz, $CDCl_3$) 28.3, 36.7, 37.3, 51.0, 52.3, 53.7, 56.1, 80.4, 82.0, 114.7, 117.4, 129.5, 130.5, 130.6, 133.6, 146.0, 151.5, 155.7, 156.4, 170.8, 171.4, 173.3; m/z (EI) 567 ($M^+ - {}^t$BuOH, 0.8%), found $M^+ - {}^t$BuOH 567.0498; $C_{22}H_{22}IN_3O_7$ requires 567.0503.

3-{4-[5-(2-(*S*)-Benzyloxycarbonylamino-2-*tert*-butoxycarbonylethyl)-2-methoxyphenoxy]phenyl}-2-(*S*)-(2-(*S*)-*tert*-butoxycarbonylamino-3-carbamoylpropionylamino)propionic acid methyl ester 23. Compound **23** was synthesized following General Procedure 2. Zinc activation and insertion were achieved using Zn (620 mg, 9.48 mmol) and TMSCl (200 μL) in dry DMF (1 + 3 mL) and *Z*-I-Ala-O^{t}Bu (1.54 g, 3.8 mmol) to give zinc reagent **9**. Coupling was performed with the aryl iodide **22** (2.03 g, 3.16 mmol) with $Pd_2(dba)_3$ (87 mg, 95 μmol) and P(*o*-Tol)$_3$ (115 mg, 380 μmol) in DMF (3 mL). The crude product was purified by flash chromatography (100% CH_2Cl_2−5% MeOH/CH_2Cl_2) and gave the product **23** (1.88 g, 75%) as a yellow amorphous solid: mp 105−108 °C (THF/PE); $[\alpha]^{20}_D$ +79.0 (c = 0.5, $CHCl_3$); ν_{max} (reflex) 3307 (m sh, NH), 1729 (br s, C═O), 1683 (s sh, C═O), 1665 (br s, C═O), 1638 (br s, C═O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.36 (9H, s, $C(CH_3)_3$), 1.42 (9H, s, $C(CH_3)_3$), 2.49 (1H, dd, J = 15.5, 6.0 Hz, β), 2.85−3.03 (4H, m, β), 3.07 (1H, dd, J = 14.0, 5.0 Hz, β), 3.67 (3H, s, OMe), 3.79 (3H, s, OMe), 4.38−4.49 (2H, m, α), 4.70−4.78 (1H, m, α), 5.06 (2H, s, CH_2-(*Z*)), 5.39 (1H, br d, J = 8.0 Hz, NH), 5.64 (1H, br s, NH_2), 5.87 (1H, br s, NH_2), 6.05 (1H, br d, J = 6.5 Hz, NH), 6.76 (1H, br s, Ar), 6.81 (2H, d, J = 8.5 Hz, Ar), 6.87−6.89 (2H, m, Ar), 7.03 (2H, d, J = 8.5 Hz, Ar), 7.26−7.36 (6H, m, Ar + NH); δ_C (100 MHz, $CDCl_3$) 27.9, 28.3, 36.7, 37.2, 37.5, 50.9, 52.3, 53.6, 55.3, 56.0, 66.8, 80.4, 82.4, 112.7, 117.2, 122.1, 125.6, 128.0, 128.1, 128.5, 129.1, 129.9, 130.4, 136.4, 144.6, 150.3, 155.6, 156.8, 170.7, 170.9, 171.5; two carbon signals are obscured; m/z (ES) 793 (MH^+, 30%), found MH^+ 793.3674; $C_{41}H_{53}N_4O_{12}$ requires 793.3660.

9-(*S*)-Benzyloxycarbonylamino-12-(*S*)-carbamoylmethyl-4-methoxy-10,13-dioxo-2-oxa-11,14-diazatricyclo[15.2.2.1^{3,7}]docosa-1-(20),3,5,7(22),17(21),18-hexaene-15-(*S*)-carboxylic acid methyl ester 3. Peptide **23** (845 mg, 1.07 mmol) was dissolved in TFA/CH_2Cl_2 (1:1, 30 mL) and stirred for 30 min at rt. The solvent was removed under reduced pressure, the solid triturated with Et_2O (2 × 5 mL), and the solvent decanted, leaving a tan solid. The sample was dried under vacuum then dissolved in dry DMF (130 mL). $^iPr_2NEt$ (1.38 g, 10.7 mmol) was added to the solution and stirred for 10 min. The solution was poured into a dropping funnel and slowly added to a stirred solution of HATU (1.63 g, 4.28 mmol) in dry DMF (200 mL) at 0 °C, over a period of 2 h. The solution was stirred overnight at rt then poured into water (500 mL) and extracted with EtOAc (3 × 200 mL). The organic layer was washed with water (2×150 mL) and brine (2×150 mL), dried over $MgSO_4$, and the solvent removed under reduced pressure to afford the crude compound. Flash chromatography (CH_2Cl_2−4% MeOH/CH_2Cl_2) gave *Z*-OF4949-III-OMe **3** (393 mg, 60%) as a tan solid. Crystallization of a sample from MeOH yielded the product **3** as a white solid: mp 257−260 °C (MeOH); $[\alpha]^{20}_D$ +42.1 (c = 1.02, $CHCl_3$); ν_{max} (reflex) 3436 (w sh, NH), 3327 (w sh, NH), 3287 (w sh, NH), 1763 (m sh, C═O), 1650 (s sh, C═O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.35−2.60 (3H, m, β_b, β_b, β_{aR}), 2.78 (1H, br d, J = 13.5 Hz, β_{cR}), 2.96 (1H, dd, J = 13.5, 4.0 Hz, β_{cS}), 3.27 (1H, dd, J = 13.0, 3.0 Hz, β_{aS}), 3.76 (3H, s, OMe), 3.88 (3H, s, OMe), 4.50−4.60 (2H, m, α_b, α_c), 4.79−4.90 (1H, m, α_a), 5.02 (1H, d, J = 12.5 Hz, CH_2−(*Z*)), 5.12 (1H, d, J = 12.5 Hz, CH_2−(*Z*)), 5.68 (1H, d, J = 7.0 Hz, NH), 5.82 (1H, d, J = 2.0 Hz, H_{sh}), 5.95 (1H, br s, NH), 6.42 (1H, br s, NH), 6.50 (1H, d, J = 8.0 Hz, H_d), 6.72 (1H, d, J = 8.0 Hz, H_e), 6.82 (1H, d, J = 8.0 Hz, H_f), 7.00 (1H, dd, J = 8.0, 2.0 Hz, H_g), 7.08 (1H, d, J = 8.0 Hz, H_h), 7.24 (1H, d, J = 8.0 Hz, H_i), 7.26−7.36 (6H, m, *Z* + NH), 8.21 (1H, br d, J = 8.5 Hz, NH); δ_C (100 MHz, $CDCl_3$) 37.3 (β_c), 38.6 (β_a), 39.2 (β_b), 48.3 (α_b), 52.5 (q), 53.5 (α_a), 53.6 (α_c), 55.8 (p), 66.7 (u), 111.4 (e), 115.6 (sh), 121.8 (f), 122.7 (g), 123.5 (d), 127.1 (m), 127.8 (×2, v), 128.0 (w), 128.4 (×2, z), 130.3 (i), 132.1 (h), 133.2 (o), 136.3 (y), 147.6 (j), 149.1 (k), 153.7 (n), 155.8 (s), 169.4 (C═O), 169.7 (C═O), 171.7 (r), 173.1 (x); m/z (ES) 619 (MH^+, 100%), found MH^+ 619.2400; $C_{32}H_{35}N_4O_9$ requires 619.2404. Details of the assignment are included in the Supporting Information, together with the NMR data in CD_3OD, and the NMR spectra in CD_3OD resulting from treatment with $NaHCO_3$. The ESI-MS of the NMR sample showed a single mass ion at 644, corresponding to the Na^+ adduct of the trideuteromethyl ester **3a**; found MNa^+ 644.2391; $C_{32}H_{31}D_3N_4O_9Na$ requires 644.2409.

9-(*S*)-Benzyloxycarbonylamino-12-(*S*)-carbamoylmethyl-4-methoxy-10,13-dioxo-2-oxa-11,14-diazatricyclo[15.2.2.1^{3,7}]docosa-1-(20),3,5,7(22),17(21),18-hexaene-15-(*S*)-carboxylic acid 24. Following the procedure of Boger,[8] *Z*-OF4949-III-OMe **3** (40 mg, 0.065 mmol) and LiOH monohydrate (8 mg, 0.195 mmol) were dissolved in THF/MeOH/H_2O 3:1:1 (2 mL) and stirred at rt for 4 h. HCl (1 M, 2 mL) was added and then water (3 mL), and the aqueous solution was extracted with $CHCl_3$/^{i}PrOH 5:1 (5 × 2 mL). The organic fractions were collected, dried over

$MgSO_4$, evaporated under reduced pressure, and triturated with Et_2O (2×2 mL) to afford the acid **24** (37 mg, 95%) as a white flaky solid: mp 142−145 °C (MeOH); $[\alpha]^{20}_D$ +57.1 (c = 0.28, CH_3OH) and $[\alpha]^{20}_D$ +31.2 (c = 0.56, CH_3OH), lit.[8] $[\alpha]^{22}_D$ −87 (c = 0.27, CH_3OH); ν_{max} (reflex) 3292 (br w, OH and NH), 2931 (br w, Ar−H), 1651 (br s, C=O) cm^{-1}; δ_H (400 MHz, CD_3OD) 2.53 (1H, dd, J = 15.5, 8.5 Hz, β), 2.59−2.70 (2H, m, β), 2.82 (1H, dd, J = 14.0, 1.0 Hz, β), 2.99 (1H, dd, J = 14.0, 6.0 Hz, β), 3.38 (1H, dd, J = 13.0, 3.5 Hz, β), 3.84 (3H, s, OMe), 4.43 (1H, dd, J = 6.0, 1.5 Hz, α), 4.70 (1H, dd, J = 12.5, 3.5 Hz, α), 4.79 (1H, dd, J = 8.5, 5.0 Hz, α), 5.02 (1H, d, J = 12.5 Hz, CH_2−(Z)), 5.14 (1H, d, J = 12.5 Hz, CH_2−(Z)), 5.87 (1H, d, J = 2.0 Hz, H_{sh}), 6.46 (1H, dd, J = 8.0, 2.0 Hz, Ar), 6.78 (1H, d, J = 8.0 Hz, Ar), 6.84 (1H, dd, J = 8.0, 2.5 Hz, Ar), 6.97 (1H, dd, J = 8.0, 2.5 Hz, Ar), 7.18 (1H, dd, J = 8.0, 2.0 Hz, Ar), 7.28−7.40 (6H, m, Ar); 6 exchangeable protons; δ_C (125 MHz, CD_3OD) 38.3, 39.6, 40.2, 50.0, 54.9, 55.1, 56.6, 67.6, 113.0, 117.2, 122.9, 123.4, 124.9, 129.1, 129.5, 131.0, 131.6, 133.2, 133.8, 135.5, 138.2, 149.2, 150.5, 155.2, 157.3, 171.2, 171.9, 174.2, 174.5; m/z (ES) 627 (MNa^+ 100%), found MNa^+ 627.2039; $C_{31}H_{32}N_4O_9Na$ requires 627.2067.

OF4949-III, 1. Following the procedure described by Boger,[8] Z-OF4949-III-OH **24** (37 mg, 61.2 mmol) was dissolved in MeOH (10 mL) and Pd/C 10% (10 mg) was added to the stirred solution. The flask was evacuated and filled with H_2 three times and then stirred overnight under hydrogen (1 atm.). The reaction was not complete by TLC analysis, so the suspension was filtered through Celite/glass wool and the solvent removed under reduced pressure. The crude material was redissolved in MeOH (10 mL), and Pd/C 10% (10 mg) was added. The flask was evacuated and filled with hydrogen (×3) and stirred under hydrogen overnight. The suspension was filtered through Celite/glass wool and the solvent removed under reduced pressure to give OF4949-III **1** (27 mg, 95%) as a white solid: mp 218−224 °C (dec.) (lit. mp 219−225 °C dec., natural: 217−225 °C dec.);[7] δ_H (500 MHz, D_2O) 2.48 (1H, dd, J = 15.5, 10.0 Hz, β_b), 2.55 (1H, t, J = 13.0 Hz, β_a), 2.76 (1H, dd, J = 15.5, 4.0 Hz, β_b), 2.97 (1H, dd, J = 15.5, 6.0 Hz, β_c), 3.05 (1H, dd, J = 15.0, 2.0 Hz, β_c), 3.29 (1H, dd, J = 13.0, 3.5 Hz, β_a), 3.82 (3H, s, OMe), 4.14 (1H, dd, J = 6.0, 2.0 Hz, α_c), 4.36 (1H, dd, J = 12.5, 3.5 Hz, α_a), 4.73 (1H, dd, J = 10.0, 4.0 Hz, α_b), 5.77 (1H, d, J = 2.0 Hz, H_{sh}), 6.75 (1H, dd, J = 8.0, 2.0 Hz, H_d), 6.82 (1H, dd, J = 8.0, 2.5 Hz, H_f), 6.96 (1H, d, J = 8.5 Hz, H_e), 6.97 (1H, dd, J = 8.0, 2.5 Hz, H_g), 7.14 (1H, dd, J = 8.5, 2.0 Hz, H_h), 7.37 (1H, dd, J = 8.5, 2.0 Hz, H_i); δ_C (125 MHz, D_2O) 35.2 (β_c), 38.7 (β_b), 38.8 (β_a), 49.1 (α_b), 52.4 (α_c), 55.8 (OCH_3), 56.8 (α_a), 112.3 (e), 115.1 (sh), 115.8, 121.4 (f), 122.2 (g), 124.3 (d), 124.6, 130.7 (i), 131.9 (h), 135.8, 147.8, 148.8, 152.2, 167.4, 170.0, 174.2.

The sample was dissolved in 0.1 N aqueous HCl, and optical rotation, NMR, and accurate mass of the hydrochloride salt were recorded: $[\alpha]^{20}_D$ −26.5 (c = 1.1, 0.1 N HCl) and $[\alpha]^{20}_D$ −30.0 (c = 0.5, 0.1 N HCl), lit. $[\alpha]^{30}_D$ −35 (c = 1.4, 1 N HCl),[7] $[\alpha]^{30}_D$ −34 (c = 1.0, 0.1 N HCl),[8] $[\alpha]^{27}_D$ −38.2 (c = 1.06, 0.1 N HCl).[10] OF4949-III·HCl: δ_H (500 MHz, D_2O) 2.45−2.56 (1H, m, β), 2.57−2.75 (2H, m, β), 2.94−3.11 (2H, m, β), 3.35 (1H, br d, J = 11.0 Hz, β), 3.81 (3H, s, OMe), 4.14 (1H, br d, J = 3.5 Hz, α), 5.74 (1H, br s, H_{sh}), 6.75 (1H, br d, J = 7.5 Hz, Ar), 6.83 (1H, br d, J = 8.0 Hz, Ar), 6.96 (2H, br d, J = 8.0 Hz, Ar), 7.13 (1H, br d, J = 7.0 Hz, Ar), 7.36 (1H, br d, J = 7.0 Hz, Ar), two α protons not observed, presumably located under the HOD peak 4.66−4.76, together with 7 exchangeable protons; δ_C (125 MHz, D_2O) 35.1, 37.6, 38.5, 49.0, 52.4, 54.2, 55.8, 112.3, 115.0, 121.5, 122.3, 124.3, 124.5, 130.7, 132.0, 134.7, 147.8, 148.7, 152.4, 167.4, 170.4, 173.9, 174.4; m/z (ES) 471 (MH^+, 75%), found MH^+ 471.1882; $C_{23}H_{27}N_4O_7$ requires 471.1880.

2-(*S*)-[2-(*S*)-*tert*-Butoxycarbonylamino-3-(4-methoxyphenyl)-propionylamino]-3-[4-(5-iodo-2-methoxyphenoxy)phenyl]propionic acid methyl ester 26. Compound **26** was synthesized following General Procedure 1. Deprotection of compound **15** (341 mg, 0.65 mmol) was achieved with AcCl (254 mg, 3.24 mmol) in MeOH/THF (2.5 mL) and triturated with Et_2O/PE (2×2 mL). Peptide coupling with Boc-Tyr(OMe)-OH (191 mg, 0.65 mmol) was achieved with $^iPr_2NEt$ (84 mg, 0.65 mmol), HOBt (87 mg, 0.65 mmol), and EDCI (124 mg, 0.65 mmol) in dry DMF (1.7 mL). The solution was stirred overnight at rt and partitioned between EtOAc (10 mL × 3) and water. The combined organic phases were washed with saturated citric acid, bicarbonate, water, and brine. The solution was dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude material was purified via flash chromatography (gradient: 70% Et_2O/PE−100% Et_2O−100% EtOAc) to afford the dipeptide **26** (323 mg, 71%) as a white solid: mp 135−136 °C (CH_2Cl_2/PE); $[\alpha]^{20}_D$ +25.0 (c = 1.1, $CHCl_3$); ν_{max} (reflex) 3327 (br w, NH), 2949 (br w, Ar−H), 1735 (m sh, C=O), 1685 (m sh, C=O), 1654 (m sh, C=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.39 (9H, s, $C(CH_3)_3$), 2.91−3.06 (4H, m, β), 3.64 (3H, s, OMe), 3.75 (3H, s, OMe), 3.79 (3H, s, OMe), 4.22−4.33 (1H, br m, α), 4.73 (1H, dd, J = 13.0, 6.0 Hz, α), 4.89−4.99 (1H, br m, NH), 6.31 (1H, d, J = 7.5 Hz, NH), 6.73 (1H, d, J = 8.5 Hz, Ar), 6.78−6.82 (4H, m, Ar), 6.92 (2H, d, J = 8.5 Hz, Ar), 7.09 (2H, d, J = 8.5 Hz, Ar), 7.18 (1H, d, J = 2.0 Hz, Ar), 7.40 (1H, dd, J = 8.5, 2.0 Hz, Ar); δ_C (125 MHz, $CDCl_3$) 28.2, 37.3 (2 carbons), 52.2, 53.3, 55.2, 55.8, 56.0, 80.2, 81.9, 114.0, 114.6, 117.4, 128.3, 129.2, 130.3, 130.5, 133.5, 140.0, 146.0, 151.4, 155.3, 156.3, 158.6, 170.8, 171.3; m/z (ES) 705 (MH^+, 50%), found MH^+ 705.1688; $C_{32}H_{38}N_2O_8I$ requires 705.1673.

3-{4-[5-(2-(*S*)-Benzyloxycarbonylamino-2-*tert*-butoxycarbonylethyl)-2-methoxyphenoxy]phenyl}-2-(*S*)-[2-(*S*)-*tert*-butoxycarbonylamino-3-(4-methoxyphenyl)propionylamino]propionic acid methyl ester 27. Compound **27** was synthesized following General Procedure 2. Zinc activation and insertion were achieved using Zn (42 mg, 0.64 mmol) and TMSCl (10 μL) in dry DMF (100 + 200 μL) and Z-I-Ala-O^{t}Bu (104 mg, 0.25 mmol) to give zinc reagent **9**. Coupling was performed with the aryl iodide **26** (150 mg, 0.21 mmol) with $Pd_2(dba)_3$ (6 mg, 6.4 μmol) and P(o-Tol)$_3$ (8 mg, 26 μmol). The crude material was purified via flash chromatography (gradient: 40−70% EtOAc/^{i}hexane) to afford the product **27** (146 mg, 80%) as a white solid: mp 70−74 °C (Et_2O); $[\alpha]^{20}_D$ +32.2 (c = 1.0, $CHCl_3$); ν_{max} (solution 0.8 g/mL $CHCl_3$) 3022 (s sh, NH), 1716 (br s, C=O), 1678 (br m, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.36 (9H, s, $C(CH_3)_3$), 1.38 (9H, s, $C(CH_3)_3$), 2.91−3.02 (6H, m, β), 3.63 (3H, s, OMe), 3.74 (3H, s, OMe), 3.77 (3H, s, OMe), 4.23−4.33 (1H, br m, α), 4.41−4.46 (1H, m, α), 4.67−4.78 (1H, br m, α), 5.01 (1H, br d, NH), 5.05 (2H, s, CH_2−(Z)), 5.25 (1H, br d, NH), 6.33 (1H, d, J = 7.5 Hz, NH), 6.75−6.82 (5H, m, Ar), 6.84−6.90 (4H, m, Ar), 7.04−7.10 (2H, m, Ar), 7.25−7.35 (5H, m, Ar); δ_C (100 MHz, $CDCl_3$) 27.9, 28.2, 37.2, 37.3, 37.4, 52.2, 53.4, 55.12, 55.15, 55.8, 55.9, 66.8, 80.1, 82.3, 112.6, 114.0, 117.0, 122.3, 125.4, 128.0, 128.1, 128.3, 128.5, 128.9, 129.5, 130.2, 130.3, 131.0, 136.3, 144.5, 150.4, 155.5, 157.0, 158.6, 170.5, 170.8, 171.4; m/z (ES) 856 (MH^+, 100%), found MH^+ 856.4041; $C_{47}H_{58}N_3O_{12}$ requires 856.4021.

9-(*S*)-Benzyloxycarbonylamino-4-methoxy-12-(*S*)-(4-methoxybenzyl)-10,13-dioxo-2-oxa-11,14-diazatricyclo[15.2.2.1^{3,7}]docosa-1(20),3,5,7(22),17(21),18-hexaene-15-(*S*)-carboxylic acid methyl ester 25. Compound **27** (135 mg, 0.16 mmol) was dissolved in TFA (2.5 mL) and stirred for 1 h at rt. The solvent was removed under reduced pressure, and the residual solid was triturated with Et_2O (2×2 mL) and dried under vacuum. The solid was dissolved in dry DMF (12 mL), and $^iPr_2NEt$ (205 mg, 1.59 mmol) was added under nitrogen. The solution was stirred for 10 min then poured into a dropping funnel and slowly added to a stirred solution of HATU (240 mg, 0.63 mmol) in dry DMF (19 mL) at 0 °C. The mixture was stirred overnight at rt under nitrogen. The solution was poured into water (50 mL) and extracted with Et_2O (2×20 mL) and EtOAc (20 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure.

The crude solid was purified via flash chromatography (gradient: 5−10% acetone/CH_2Cl_2) to afford protected iso-K-13 **25** (52 mg, 48%) as a white solid: mp 132−133 °C (MeOH); $[\alpha]^{20}_D$ +35.4 (c = 0.8, $CHCl_3$); ν_{max} (solution 0.8 g/mL $CHCl_3$) 3422 (m sh, NH), 3018 (s sh, NH), 2957 (w sh, Ar−H), 1740, 1715, and 1673 (br m, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.41 (1H, t, J = 13.0 Hz, β_a), 2.70 (1H, dd, J = 14.0, 2.0 Hz, β_c), 2.77 (1H, dd, J = 14.0, 7.5 Hz, β_b), 2.91 (1H, dd, J = 14.0, 4.5 Hz, β_b), 3.11 (1H, dd, J = 14.5, 6.0 Hz, β_c), 3.31 (1H, dd, J = 13.5, 4.0 Hz, β_a), 3.75 (3H, s, OMe), 3.82 (3H, s, OMe), 3.88 (3H, s, OMe), 4.42−4.48 (2H, m, α_b, α_c), 4.85−4.91 (1H, m, α_a), 5.09 (1H, d, J = 12.5 Hz, CH_2−(Z)), 5.18 (1H, d, J = 12.5 Hz, CH_2−(Z)), 5.52 (1H, d, J = 7.5 Hz, NH), 5.84 (1H, d, J = 2.0 Hz, H_{sh}), 5.86 (1H, d, J = 10.0 Hz, NH), 6.44 (1H, d, J = 8.0 Hz, NH), 6.51 (1H, dd, J = 8.0, 2.0 Hz, H_d), 6.73 (1H, d, J = 8.5 Hz, H_e), 6.79 (2H, br d, J = 8.5 Hz, Ar), 6.87 (2H, br s, Ar), 7.05 (1H, d, J = 8.5 Hz, Ar), 7.08 (2H, d, J = 9.0 Hz, Ar), 7.27 (1H, d, J = 8.5 Hz, Ar), 7.35−7.39 (5H, m, Ar); δ_C (100 MHz, $CDCl_3$) 37.2, 38.4, 39.1, 52.7, 53.1 (2 carbons), 54.1, 55.2, 55.9, 66.7, 111.5, 114.2, 115.6, 121.7, 123.1, 123.8, 127.2, 127.4, 128.0, 128.1, 128.5, 130.4, 130.5, 131.8, 132.5, 136.5, 147.8, 149.1, 154.2, 155.6, 158.8, 168.6, 169.2, 171.5; m/z (ES) 704 (MNa^+, 100%), found MNa^+ 704.2584; $C_{38}H_{39}N_3O_9Na$ requires 704.2584.

2-(*S*)-*tert*-Butoxycarbonylamino-3-[4-(5-iodo-2-methoxyphenoxy)phenyl]propionic acid 13. Lithium hydroxide monohydrate (312 mg, 7.43 mmol) was added in one portion to a rapidly stirred solution of the methyl ester **15** (1.8 g, 3.41 mmol) in a mixture of THF (20 mL) and water (5 mL) at rt. The reaction was stirred overnight, and the solvents were removed under reduced pressure. The resulting white solid was dissolved in water (40 mL) and acidified with citric acid (10% aqueous solution) until a white precipitate appeared. Et_2O (20 mL) was added, and the phases were separated. The aqueous layer was extracted with Et_2O (2 × 20 mL), and the combined organic fractions were washed with saturated brine (20 mL), dried over Na_2SO_4, and filtered. The solvent was removed under reduced pressure to give the acid **13** (1.75 g, 99%) as a white solid: mp 61−64 °C; $[\alpha]^{20}_D$ +30.8 (c = 1.0, $CHCl_3$); ν_{max} (KBr disk) 3322 (CO_2H), 1717 (C=O), 1576, 1506, 1491 (Ar), 1223 (C−N), 1166 (C−O) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.33 (1 H, br s, CO_2H), 1.43 (9 H, s, $C(CH_3)_3$), 3.04 (1 H, dd, J = 14.0, 6.5 Hz, β), 3.17 (1 H, dd, J = 14.0, 5.0 Hz, β), 3.80 (3 H, s, OMe), 4.53−4.63 (1 H, br m, α), 4.96 (1 H, br d, J = 8.0 Hz, NH), 6.74 (1 H, d, J = 9.0 Hz, Ar), 6.87 (2 H, br d, J = 8.5 Hz, Ar), 7.12 (2 H, br d, J = 8.0 Hz, Ar), 7.23 (1 H, br s, Ar), 7.41 (1 H, dd, J = 8.5, 2.0 Hz, Ar); δ_C (125 MHz, $CDCl_3$) 28.3, 37.0, 54.3, 56.1, 80.4, 81.9, 114.7, 117.5, 129.5, 130.4, 130.6, 133.6, 146.0, 151.5, 155.5, 156.5, 176.2; m/z (EI+) 513 (3%, M^+), 457 (3, $M^+ - C_4H_8$), 396 (9, $M^+ - C_4H_8 - CO_2 - NH_3$), 339 (100, $ArCH_2^+$), found M^+ 513.0666; $C_{21}H_{24}N_1O_6I$ requires 513.0648.

2-(*S*)-[2-(*S*)-{2-(*S*)-*tert*-Butoxycarbonylamino-3-[4-(5-iodo-2-methoxyphenoxy)phenyl]propionylamino}-3-(4-methoxyphenyl)-propionylamino]-3-hydroxypropionic acid methyl ester 12. HOBt (555 mg, 4.11 mmol), $^iPr_2NEt$ (650 μL, 3.72 mmol), and EDCI hydrochloride (695 mg, 3.63 mmol) were added to a rapidly stirred solution of the acid **13** (1.70 g, 3.31 mmol) and H-Tyr(OMe)-Ser-OMe·HCl **14** (1.18 g, 3.55 mmol) in DMF (16 mL) at rt under nitrogen. The reaction was stirred overnight and then poured into water (200 mL). The resulting white precipitate was filtered and washed with water (200 mL), dried under vacuum, and gave, without the need for further purification, the tripeptide **12** (2.46 g, 94%) as a white solid (a sample was recrystallized): mp 192−193 °C ($CHCl_3$); $[\alpha]^{20}_D$ −14.0 (c = 1.0, acetone); found C 52.93%; H 5.31%; N 5.28%; $C_{35}H_{42}N_3O_{10}I$ requires C 53.10%; H 5.35%; N 5.31%; ν_{max} (KBr disk) 3314 (OH), 1743, 1730, 1675, 1645 (C=O), 1512, 1493 (Ar), 1250, 1224 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.34 (9 H, s, $C(CH_3)_3$), 2.85−3.10 (4 H, m, β), 3.42 (1 H, br s, OH), 3.74 (3 H, s, OMe), 3.75 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.80−3.86 (1 H, m, β-OH), 3.87−3.91 (1 H, m, β-OH), 4.23−4.30 (1 H, m, α), 4.56 (1 H, dt, J = 7.5, 3.5 Hz, α), 4.68 (1 H, q, J = 7.0 Hz, α), 4.96 (1 H, br d, J = 6.5 Hz, NH), 6.54 (1 H, br d, J = 7.5 Hz, NH), 6.75 (1 H, d, J = 9.0 Hz, Ar), 6.79 (2 H, br d, J = 8.5 Hz, Ar), 6.87 (2 H, br d, J = 8.5 Hz, Ar), 7.02 (2 H, br d, J = 8.5 Hz, Ar), 7.11 (3 H, br d, J = 8.5 Hz, Ar and NH), 7.22 (1 H, d, J = 2.0 Hz, Ar), 7.42 (1 H, dd, J = 8.5, 2.0 Hz, Ar); δ_C (125 MHz, $CDCl_3$) 28.2, 36.8, 37.0, 52.6, 54.1, 55.0, 55.2, 56.0, 62.7, 80.9, 81.9, 114.1, 114.7, 117.6, 127.9, 129.5, 130.4, 130.5, 130.7, 133.7, 145.8, 151.5, 155.6, 156.5, 158.7, 170.4, 170.7, 171.4, one carbon signal obscured; m/z (EI+) 775 (2%, $M^+ - CH_3 - H$), 339 (100, $ArCH_2^+$), found $M^+ - CH_3 - H$, 775.1572; $C_{34}H_{38}N_3O_{10}I$ requires 775.1602.

2-(*S*)-[2-(*S*)-{2-(*S*)-*tert*-Butoxycarbonylamino-3-[4-(5-iodo-2-methoxyphenoxy)phenyl]propionylamino}-3-(4-methoxyphenyl)-propionylamino]-3-iodopropionic acid methyl ester 28. $(PhO)_3$-PMeI (11.14 g, 24.6 mmol) was added to a stirred solution of the alcohol **12** (9.75 g, 12.3 mmol) in DMF (40 mL) at rt under nitrogen. After 1 h, the reaction was quenched by the slow addition of MeOH (2 mL) and was stirred for a further 30 min. The reaction was diluted with water (200 mL) resulting in a precipitate. CH_2Cl_2 (200 mL) was added, and the aqueous layer was separated and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic fractions were washed with aqueous sodium sulfite (10% in H_2O, 100 mL), water (100 mL), and brine (100 mL), dried over Na_2SO_4, and filtered. The solvent was removed under reduced pressure to give a crude solid which was purified by recrystallization from cold Et_2O (100 mL, 0 °C). The precipitate was filtered, washed with cold Et_2O, and dried to give the diiodide **28** (8.1 g, 73%) as a white solid: mp 162 °C (dec.) (EtOAc); $[\alpha]^{20}_D$ +10.0 (c = 0.6, $CHCl_3$); found C 46.57%; H 4.40%; N 4.53%; $C_{35}H_{41}N_3O_9I_2$ requires C 46.63%; H 4.58%; N 4.66%; ν_{max} (KBr disk) 1730, 1690, 1648, (C=O), 1530, 1512, 1492 (Ar), 1248, 1223 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.38 (9 H, s, $C(CH_3)_3$, 2.93 (1 H, dd, J = 14.0, 7.0 Hz, β), 2.99−3.07 (3 H, m, β), 3.49 (1 H, dd, J = 10.5, 4.5 Hz, β), 3.53 (1 H, dd, J = 10.5, 4.5 Hz, β), 3.77 (6 H, s, OMe), 3.79 (3 H, s, OMe), 4.31 (1 H, br d, J = 6.0 Hz, α), 4.60 (1 H, q, J = 7.0 Hz, α), 4.67 (1 H, dt, J = 7.5, 4.5 Hz, α), 4.91 (1 H, br s, NH), 6.40 (1 H, br d, J = 6.0 Hz, NH), 6.64 (1 H, br s, NH), 6.74 (1 H, d, J = 8.5 Hz, Ar), 6.81 (2 H, br d, J = 8.5 Hz, Ar), 6.88 (2 H, br d, J = 8.0 Hz, Ar), 7.02 (2 H, br d, J = 8.0 Hz, Ar), 7.14 (2 H, br d, J = 8.0 Hz, Ar), 7.24 (1 H, br d, J = 2.0 Hz, Ar), 7.42 (1 H, dd, J = 8.5, 2.0 Hz, Ar); δ_C (125 MHz, $CDCl_3$) 7.0, 28.4, 37.8, 38.0, 53.0, 53.2, 54.5, 55.3, 56.1, 80.7, 82.0, 114.4, 114.8, 117.7, 127.9, 129.6, 130.4, 130.7, 131.0, 133.8, 147.4, 152.9, 155.0, 157.6, 159.6, 169.3, 170.5, 171.2, one carbon signal obscured; m/z (EI+) 773 (2%, $M^+ - HI$), 339 (10, $ArCH_2^+$), 128 (100, HI), found $M^+ - HI$, 773.1787; $C_{35}H_{40}N_3O_9I$ requires 773.1809.

15-(*S*)-*tert*-Butoxycarbonylamino-4-methoxy-12-(*S*)-(4-methoxybenzyl)-11,14-dioxo-2-oxa-10,13-diazatricyclo[15.2.2.1^{3,7}]-docosa-1(20),3,5,7(22),17(21),18-hexaene-9-(*S*)-carboxylic acid methyl ester 10. Iodine (4 mg, 0.016 mmol) was added to a rapidly stirred suspension of zinc (24 mg, 0.38 mmol) in DMF (0.5 mL) at rt under nitrogen. After 30 min, a solution of the diiodide **28** (300 mg, 0.33 mmol) in DMF (0.5 mL) was added, and the reaction was stirred for a further 30 min. The solution of the organozinc iodide **11** was then added dropwise to a stirred solution of Pd_2dba_3 (9.2 mg, 3 mol %, 0.01 mmol) and P(*o*-Tol)$_3$ (12.2 mg, 12 mol %, 0.04 mmol) in THF (140 mL), and the reaction was heated at 60 °C and stirred for 16 h. The solvent was removed under reduced pressure to give a crude oil which was dissolved in EtOAc (25 mL), washed with water (2×10 mL) and saturated brine (10 mL), dried over Na_2SO_4, and filtered. The solvent was removed under reduced pressure to give a crude solid which was purified by column chromatography [silica, CH_2Cl_2−acetone, 10:1] to give the macrocyclic peptide **10** (75 mg, 35%): mp 247−248 °C (lit. mp 245−246 °C);[7] R_f[CH_2Cl_2−acetone,

10:1] 0.3; $[\alpha]^{20}_D$ +41.3 (c = 0.9, CH_2Cl_2); found C 64.85%; H 6.19%; N 6.46%; $C_{35}H_{41}N_3O_9$ requires C 64.90%; H 6.38%; N 6.49%; δ_H (500 MHz, $CDCl_3$) 1.42 (9 H, s, $C(CH_3)_3$), 2.64 (1 H, dd, J = 13.0, 10.0 Hz, β), 2.74 (1 H, t, J = 12.0 Hz, β), 2.80 (1 H, dd, J = 14.5, 4.5 Hz, β), 3.07 (1 H, dd, J = 12.0, 5.0 Hz, β), 3.17 (1 H, br dd, J = 13.5, 3.5 Hz, β), 3.21 (1 H, dd, J = 15.0, 4.5 Hz, β), 3.62 (3 H, s, OMe), 3.67 (3 H, s, OMe), 3.81 (3 H, s, OMe), 3.81−3.87 (1 H, br m, α), 4.07−4.16 (1 H, br m, α), 4.26−4.31 (1 H, m, α), 5.24 (1 H, br d, J = 7.5 Hz, NH), 5.41 (1 H, d, J = 4.5 Hz, NH), 6.00 (1 H, br s, Ar), 6.14 (1 H, br d, J = 5.5 Hz, NH), 6.44 (1 H, dd, J = 8.5, 2.0 Hz, Ar), 6.68 (2 H, br d, J = 8.5 Hz, Ar), 6.71 (2 H, br dd, J = 8.0, 2.5 Hz, Ar), 6.96 (2 H, d, J = 8.5 Hz, Ar), 7.04 (2 H, br dt, J = 8.0, 2.5 Hz, Ar), 7.22 (1 H, br s, Ar); δ_C (125 MHz, $CDCl_3$) 28.4, 29.3, 35.2, 38.6, 39.5, 52.5, 53.7, 55.1, 56.0, 56.4, 57.4, 79.8, 112.1, 113.9, 118.0, 121.2, 122.5, 122.7, 127.9, 128.3, 129.8, 130.1, 131.4, 132.5, 148.5, 148.8, 155.0, 155.3, 158.6, 169.9, 170.6; m/z (EI+) 647 (2%, M^+), 575 (5, $MH^+ - {}^tBuO$), 547 (30, $M^+ - C_4H_8 - CO_2$), 298 (100, $ArCH_2^+$), found M^+, 647.2831; $C_{35}H_{41}N_3O_9$ requires 647.2843.

K-13, 2. Following the literature procedure described by Evans,[7] the Boc-protected derivative **10** (155 mg, 0.24 mmol), thioanisole (850 μL), and TFA (6 mL) in CH_2Cl_2 (17.5 mL), followed by Ac_2O (2.1 mL) in a solvent mixture of CH_2Cl_2/pyridine (5:1, 21 mL), gave after purification by column chromatography [silica, CH_2Cl_2−MeOH, 98:2 to 95:5] the acetyl derivative **29** (124 mg, 88%). Again following the literature procedure described by Evans,[7] the methyl-protected derivative **29** (60 mg, 0.1 mmol), $AlBr_3$ (1.0 M solution in dibromoethane, 2.97 mL, 2.97 mmol), and EtSH (4 mL) in CH_2Cl_2 (11 mL) gave after purification by column chromatography [silica, EtOAc−CH_3CO_2H, 93:7] K-13 **2** (46 mg, 83%) as a pale yellow solid: mp 265−270 °C (dec.) (MeOH/Et_2O), lit.[2] 260−270 °C (dec.); $[\alpha]^{20}_D$−6.6 (c = 1.4, MeOH), lit.[7] $[\alpha]^{20}_D$−6.5 (c = 0.46, MeOH), natural[3] $[\alpha]^{20}_D$ −3.4 (c = 0.6, MeOH); δ_H (500 MHz, CD_3OD) 2.03 (3 H, s, OAc), 2.77 (1 H, t, J = 12.0 Hz, β_a), 2.85 (1 H, dd, J = 13.5, 5.0 Hz, β_b), 2.91 (1 H, dd, J = 15.5, 9.0 Hz, β_c), 2.95 (1 H, dd, J = 13.0, 6.0 Hz, β_b), 3.01 (1 H, dd, J = 12.5, 5.5 Hz, β_a), 3.17 (1 H, dd, J = 15.5, 2.0 Hz, β_c), 4.17 (1 H, t, J = 5.5 Hz, α_b), 4.40−4.48 (2 H, m, α), 6.38 (1 H, d, J = 2.0 Hz, Ar), 6.57−6.62 (2 H, m, Ar), 6.66 (1 H, dd, J = 8.0, 2.5 Hz, Ar), 6.73 (1 H, dd, J = 8.0, 2.0 Hz, Ar), 6.80 (1 H, d, J = 8.0 Hz, Ar), 6.93−6.99 (3 H, m, Ar), 7.04 (1 H, dd, J = 8.5, 2.5 Hz, Ar), 7.29 (1 H, dd, J = 8.0, 2.0 Hz, Ar); δ_C (125.7 MHz, CD_3OD) 22.4, 36.6, 38.7, 39.1, 54.3, 55.9, 57.3, 115.8, 117.5, 118.8, 120.8, 122.1, 125.4, 128.2, 130.7, 131.2, 132.0 (2 carbons, assigned from $^1H-^{13}C$ correlation), 132.8, 147.5, 147.8, 157.0, 158.2, 171.5, 172.2, 172.9, 175.5. The NMR data are closely comparable with that reported by Evans. In the ^1H spectrum, we observe close overlap of two α-proton signals, where Evans reports resolved signals.[7] In the ^{13}C spectrum, we note two clearly resolvable signals at 147.5 and 147.9 and a slightly different chemical shift for one of the α-carbon signals at 54.3 (this rather broad signal is assigned through $^1H-^{13}C$ correlation). In addition, the shift for the carboxylic acid carbon, which we note at 175.5, was reported by Evans at 177.8.[7] These minor differences are most likely accounted for by chemical shift concentration dependence.

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Supporting Information Available: Data comparison for *Z*-OF4949-III-OMe **3** and NMR structure assignment of *Z*-OF4949-III-OMe **3**; data comparison and NMR structure assignment for OF4949-III **1**; supporting NMR spectra for structural assignments; ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.