Total Synthesis of the Cyclic Biphenyl Ether Peptides K-13 and OF4949-III *via* S_NAr Macrocyclization of Peptidyl Ruthenium π-Arene Complexes

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Abstract: Intramolecular nucleophilic aromatic substitution (S_NAr) of preformed ruthenium cyclopentadienyl cationic peptidyl π-complexes forms cyclic biphenyl ethers in convenient, high-yielding reactions. The utility of the method was demonstrated by the efficient convergent total synthesis of two natural products, K-13 and OF4949-III. Several analogs of K-13 and OF4949-I−IV were synthesized in high yields, and one ring system that could not be prepared by a macrolactamization method was formed in high yield by biaryl ether formation from peptidyl ruthenium complexes. Direct comparisons between these two approaches are provided. Transition metal π-complexes of either N-protected or carboxyl-protected amino acids can be used as coupling partners in peptide coupling reactions. Preformed peptidyl ruthenium complexes can be used to synthesize cyclic biphenyl ethers in a combinatorial fashion.

K-13[1] (Figure 1), a natural noncompetitive inhibitor of angiotensin converting enzyme (ACE), and OF4949-I−IV,[2] a family of competitive inhibitors of aminopeptidase B, are metallopeptidase inhibitors that contain the biaryl ether diamino diacid, isodityrosine,[3] as their basic structural subunit. Although the structures of K-13 and OF4949-III are similar (each a cyclic 17-membered biphenyl ether tripeptide), K-13 does not inhibit aminopeptidase B and OF4949-III does not inhibit ACE. Structurally, these two β-strand peptide mimetics[4] differ when viewed from the N-terminal to C-terminal direction of the peptide backbone in that K-13 has a *para−meta* substitution of the two aromatic rings while OF4949-III has *meta−para* substitutions of the biphenyl ether linkage. In either system, removal of the macrocyclic structure results in a complete loss of biological activity.[5]

The synthesis of many natural products, which are composed of cyclic biphenyl ether peptides, has been limited by the lack of general and efficient methodologies for the synthesis of biaryl ethers that contain asymmetric centers.[6] The strategy employed in most syntheses of K-13 and OF4949I−IV has been to construct the biphenyl ether moiety early in the synthesis and to form the macrocyclic peptide ring system later by cyclization through amide bond formation.[7] At the start of this work, we envisioned that a more direct approach to these molecules would be to assemble the peptide portion first and then cyclize via biaryl ether formation,[8,9] if a method that employed mild reaction conditions[10] could be developed for the construction of biaryl ethers. Pearson *et al.*, who studied the use of arene-ruthenium,[11] manganese,[12] and iron[13] π-complexes of chlorophenylalanine derivatives, reported that *p*-chlorophenylalanine ruthenium cyclopentadienyl π-complexes reacted efficiently with a variety

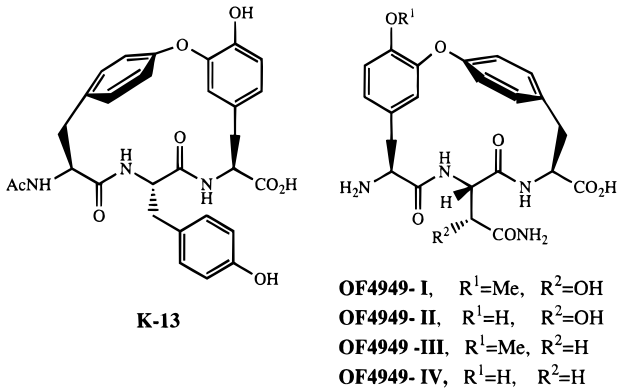

Figure 1. Structures of the naturally occurring protease inhibitors K-13 and OF4949-I−IV.

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(1) (a) Kase, H.; Kaneko, M.; Yamada, K. *J. Antibiot.* **1987**, *40*, 450−454. (b) Yasuzawa, T.; Shirahata, K.; Sano, H. *J. Antibiot.* **1987**, *40*, 455−458.

(2) (a) Sano, S.; Ikai, K.; Kuroda, H.; Nakamura, T.; Obayashi, A.; Ezure, Y.; Enomoto, H. *J. Antibiot.* **1986**, *39*, 1674−1684. (b) Sano, S.; Ikai, K.; Katayama, K.; Takesako, K.; Nakamura, T.; Obayashi, A.; Ezure, Y.; Enomoto, H. *J. Antibiot.* **1986**, *39*, 1685−1696. (c) Sano, S.; Ueno, M.; Katayama, K.; Nakamura, T.; Obayashi, A. *J. Antibiot.* **1986**, *39*, 1697−1703. (d) Sano, S.; Ikai, K.; Yoshikawa, Y.; Nakamura, T.; Obayashi, A. *J. Antibiot.* **1987**, *40*, 512−518. (e) Sano, S.; Kuroda, H.; Ueno, M.; Yoshikawa, Y.; Nakamura, T.; Obayashi, A. *J. Antibiot.* **1987**, *40*, 519−525.

(3) Frye, S. C. *Methods Enzymol.* **1984**, *107*, 388.

(4) (a) Janetka, J. W.; Satyshur, K.; Rich, D. H. *Acta Crystallogr.*, Sect. *C* **1996**, *52*, 3112−3114. (b) Janetka, J. W.; Raman, P.; Satyshur, K.; Flentke, G. R.; Rich, D. H. *J. Am. Chem. Soc.* **1997**, *119*, 441−442.

(5) Boger, D. L.; Yohannes, D. *Biomed. Chem. Lett.* **1993**, *3*, 245−250.

(6) Rao, A. V. R.; Gurjar, M. K.; Reddy, K. L.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135−2167 and references within.

(7) (a) Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063−1072. (b) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1989**, *54*, 2498−2502.

(8) Intramolecular Ullmann condensation: (a) Boger, D. L.; Yohannes, D. *J. Am. Chem. Soc.* **1991**, *113*, 1427−1429. Thalium trinitrate (TTN) mediated cyclization: (b) Inoue, T.; Sasaki, T.; Takayanagi, H.; Harigaya, Y.; Hoshino, O.; Hara, H.; Inaba, T. *J. Org. Chem.* **1996**, *61*, 3936−3937. (c) Nakamura, K.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1995**, *36*, 8621−8624.

(9) Intramolecular S_NAr Cyclization: Zhu, J. P. *Synlett* **1997**, 133 and references within.

(10) For other recent studies on novel approaches to biaryl ether formation, see: (a) Jung, M. E.; Jachiet, D.; Khan, S. I.; Kim, C. *Tetrahedron Lett.* **1995**, *36*, 361−364. (d) Jung, M. E.; Starkey, L. S. *Tetrahedron Lett.* **1995**, *36*, 7363−7366. (e) Feng, X.; Olsen, R. K. *Tetrahedron Lett.* **1991**, *32*, 5721−5724. (f) Feng, X.; Olsen, R. K. *J. Org. Chem.* **1992**, *57*, 5811−5812. (g) Moreau, P.; Guillaumet, G.; Coudert, G. *Tetrahedron* **1994**, *50*, 3407−3414. (h) Olsen, R. K.; Feng, X.; Campbell, M.; Shano, R.; Math, S. K. *J. Org. Chem.* **1995**, *60*, 6025−6031.

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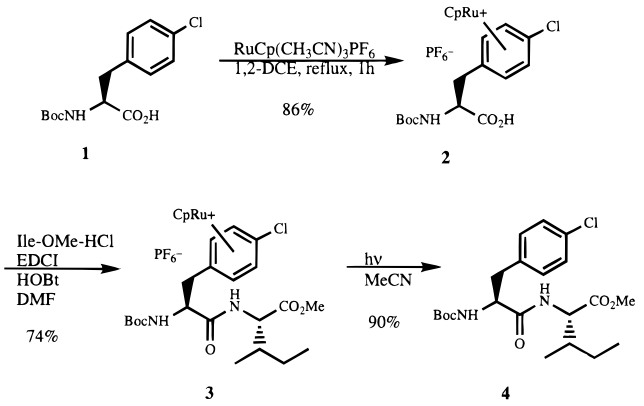
Scheme 1



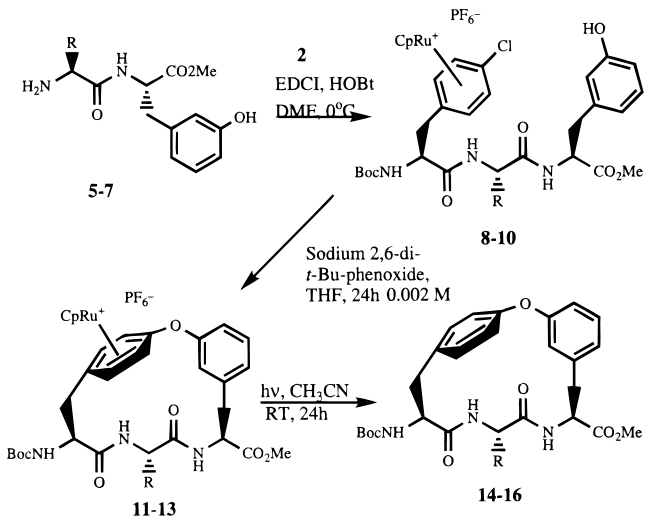
of phenols in an intermolecular fashion to form biphenyl ethers under very mild conditions and applied this to the formal total syntheses of K-13[11c] and OF4949-III.[11f]

We recently showed that Pearson's methodology could be used in an intramolecular fashion to directly cyclize peptidyl π-complexes[14] for synthesizing model cyclic 17-membered ring systems related to K-13, and soon thereafter, Pearson *et al.* used a similar strategy to synthesize a cyclic 16-membered biaryl ether peptide.[15] In order to illustrate the effectiveness of the intramolecular S_NAr reaction of peptidyl π-complexes, we report here the successful synthesis of a OF4949-III model ring system that could not be prepared by a cycloamidation approach, and the convergent total syntheses of the natural products, K-13 and OF4949-III.

Results

Peptide Couplings of $RuCp^+$ π-Complexed Amino Acids. The $RuCp^+$ complex **2** was synthesized in 86% yield by reaction of Boc-*p*-chlorophenylalanine (**1**) with $[RuCp(MeCN)_3]PF_6$[16] (Scheme 1). The $[RuCp(MeCN)_3]PF_6$ was added to a solution of the amino acid in 1,2- dichloroethane (DCE) that was preheated and degassed with argon at 50−60 °C (in order to complex the aromatic ring of **1** selectively and prevent the unwanted complexation of the carboxylate to ruthenium). Using standard pre-activation peptide coupling conditions, the acid π-complex **2** was reacted with the methyl ester hydrochloride of isoleucine (HCl·Ile-OMe) to give the dipeptide complex **3** in 74% yield. The dipeptide complex **3** was demetalated by photolysis in acetonitrile to give a 90% yield of the dipeptide Boc-*p*-Cl-Phe-Ile-OMe (**4**), which was identical in all respects to the compound synthesized from Boc-*p*-Cl-Phe-OH (**1**) and HCl·Ile-OMe, establishing that this sequence of transformations does not epimerize chiral centers.[17]

Scheme 2[a]



[a] R = *s*-Bu (Ile); Bn (Phe);4-(O-*t*-Bu)Bn (Tyr-(O-*t*-Bu)).

Synthesis of K-13[14] and OF4949-I−IV Model Systems.[18] The *para*−*meta*-substituted tripeptide cyclization precursor **8** was synthesized in 77% yield (Scheme 2) by coupling of the Boc-*p*-Cl-Phe-OH/$RuCpPF_6$ complex **2** with isoleucyl-*m*-tyrosine methyl ester [Ile-*m*-Tyr-OMe] (**5**). The other tripeptide complexes **9** and **10** were formed in a similar fashion from the dipeptides Phe-*m*-Tyr-OMe (**6**) and Tyr-(O-*t*-Bu)-*m*-Tyr-OMe (**7**) by peptide coupling with **2** to give **9** and **10** in 62% and 59% yields, respectively.

Formation of the cyclized biphenyl ether tripeptide complex **11** was achieved in 78% yield by slow addition of tripeptide complex **8** at room temperature over a period of 5 h to a dilute solution of 2,6-di-*tert*-butylphenoxide in THF followed by additional reaction for 12 h. The complex **11** was then irradiated at 350 nm in acetonitrile for 24 h to give the cyclic biphenyl ether **14** in 83% yield. This procedure was used to cyclize the tripeptide complexes Boc-*p*-Cl-Phe[$RuCpPF_6$]-Phe-*m*-Tyr-OMe (**9**) and Boc-*p*-Cl-Phe[$RuCpPF_6$]-Tyr(O-*t*-Bu)-*m*-Tyr-OMe (**10**) in 79% and 70% yields, respectively, and after photolytic cleavage, the cyclic biaryl ether peptides **15** and **16** were obtained in 66% and 58% overall yields.

The *meta*−*para*-substituted precursors were synthesized in a related fashion. The ruthenium complex of amino ester **18** was prepared in excellent yield (92%) by reacting the methyl ester of *p*-chlorophenylalanine (**17**) with $RuCp(CH_3CN)_3PF_6$ in degassed 1,2-DCE at 60° C (Scheme 3).[11b] The free amine complex **18** was coupled to **19** to form the tripeptide complex **22** in 69% yield. Similarly, the other two tripeptide complexes Cbz-*m*-Tyr-Phe-*p*-Cl-Phe[$RuCpPF_6$]-OMe (**23**), and Cbz-*m*-Tyr-Tyr-*p*-Cl-Phe[$RuCpPF_6$]-OMe (**24**) were synthesized in 62% and 54% overall yields from dipeptides **20** and **21**, respectively. Cyclization of tripeptide complex **22** by slow addition of substrate to a dilute solution of sodium 2,6-di-*tert*-butylphenoxide in THF (final concentration 0.002 M) followed by additional reaction overnight afforded the cyclized biphenyl ether complex **25** in 78% yield. Decomplexation by irradiation at 350 nm in acetonitrile for 24 h gave cyclic biphenyl ether **28** in 70% yield. Interestingly, reaction of the tripeptide complex **22** with sodium 2,6-di-*tert*-butylphenoxide by careful addition of the base to a solution of the tripeptide at higher concentrations (0.02 M) in THF gave the cyclic biphenyl ether complex **25** in an improved 88% yield. Compound **25** was identical in all

(11) (a) Pearson, A. J.; Park, J. G.; Yang, S. H.; Chuang, Y.-H. *J. Chem. Soc., Chem. Commun.* **1989**, 1363−1364. (b) Pearson, A. J.; Park, J. G. *J. Org. Chem.* **1992**, *57*, 1744−1752. (c) Pearson, A. J.; Lee, K. *J. Org. Chem.* **1994**, *59*, 2304−2313. (d) Pearson, A. J.; Lee, K. *J. Org. Chem.* **1995**, *60*, 7153−7160. (e) Pearson, A. J.; Bignan, G. *Tetrahedron. Lett.* **1996**, *37*, 735−738. (f) Pearson, A. J.; Zhang, P.; Lee, K. *J. Org. Chem.* **1996**, *61*, 6581−6586.

(12) (a) Pearson, A. J.; Lee, K. *J. Org. Chem.* **1994**, *59*, 2314−2323. (b) Pearson, A. J.; Shin, H. *Tetrahedron* **1992**, *48*, 7527−7538. (c) Pearson, A. J.; Bruhn, P. R. *J. Org. Chem.* **1991**, *56*, 7092−7097.

(13) Pearson, A. J.; Park, J. G.; Zhu, P. Y. *J. Org. Chem.* **1992**, *57*, 3583−3589.

(14) Janetka, J. W.; Rich, D. H. *J. Am. Chem. Soc.* **1995**, *117*, 10585−10586.

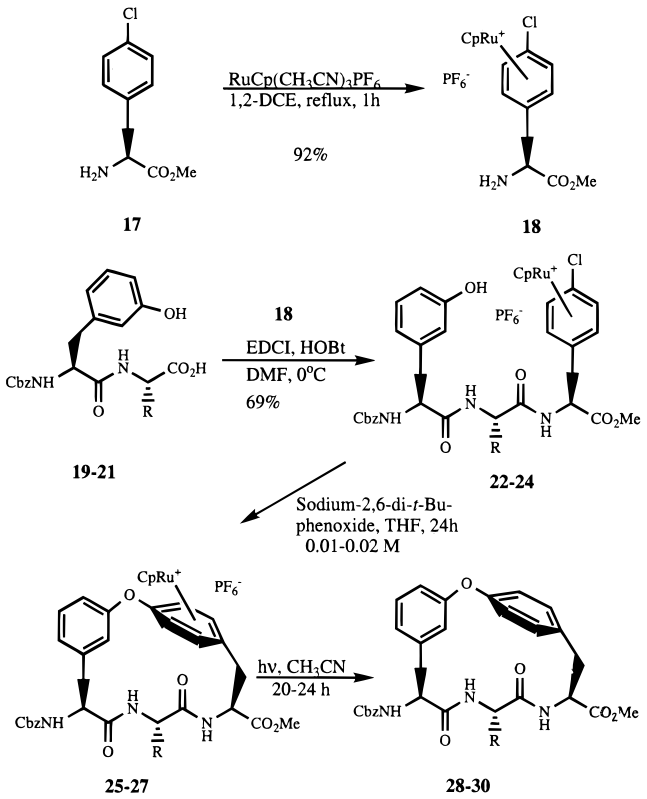
(15) Pearson, A. J.; Bignan, G.; Zhang, P.; Chelliah, M. *J. Org. Chem.* **1996**, *61*, 3940−3941.

(16) Synthesized according to Gill and Mann: Gill, T. P.; Mann, K. R. *Organometallics* **1982**, *1*, 485−488.

(17) Synthesized independently by Amy Elder, University of Wisconsin−Madison, Department of Chemistry.

(18) Details on the synthesis of dipeptide and amino acid starting materials are described in the Supplementary Information.

Scheme 3[a]



[a] R (yields for cyclization, decomplexation): = *s*-Bu (Ile), 78−88%, 70%; Bn (Phe), 86%, 75%; 4-(OH)Bn (Tyr) 81%, 73%.

respects to the complex isolated from the reaction performed under high-dilution conditions. Decomplexation of the tripeptide complex **25** afforded the desired cyclic ether **28**, which had identical physical properties as the ether isolated from the high-dilution cyclization. These reaction conditions were implemented for cyclization to the remaining cyclic biphenyl ether peptide target compounds. Macrocyclization of the tripeptide complexes **23** and **24** gave the cyclic biphenyl ether complexes **26** and **27** in 86% and 81% respective yields, which after decomplexation afforded the corresponding cyclic biphenyl ether tripeptides **29** and **30** in 73−75% yield.

Synthesis of K-13 and OF4949-III. The K-13 precursor, 3-chloro-4-methoxyphenylalanine methyl ester (**34**)**,** and the OF4949-III precursor, Boc-3-chloro-4-methoxyphenylalanine (**35**)**,** were synthesized from 3-chlorotyrosine (**31**) in simple three-step sequences and converted to the corresponding ruthenium complexes **36** and **37** (see Scheme 4 in Supporting Information).

K-13 was synthesized by two routes. Ac-Tyr-OH (**40**) was coupled with Tyr(OMe)-OBn-TsOH (**39**) [formed from Tyr(4-OMe) (**38**)] to give the dipeptide Ac-Tyr-Tyr(4-OMe)-OBn (**41**). Catalytic hydrogenation gave Ac-Tyr-Tyr(4-OMe)-OH (**42**) in 93% overall yield. The cyclization precursor **43** was formed in 65% yield by coupling Ac-Tyr-Tyr(4-OMe)-OH (**42**) with amine complex **36** (Scheme 5). Cyclization of tripeptide complex **43** by reaction with sodium 2, 6-di-*tert*-butyl-phenoxide in THF, produced cyclized biphenyl ether complex **44** in 76% yield, which was converted by irradiation at 350 nm to form dimethyl K-13 (**45**) in 73% yield. Demethylation[7a] of **45** with $AlBr_3$ and EtSH gave K-13 as a 7:1 mixture of isomers in 91% overall yield. Comparison of NMR data confirmed that the major isomer isolated from the reaction was the natural isomer of K-13.

K-13 also was synthesized with a carbamate protecting group on nitrogen to demonstrate stability of this protecting group to the reaction conditions**.** Reaction of Boc-Tyr-OH (**46**) with the tosylate salt of Tyr(OMe)-OBn (**39**) gave the dipeptide Boc-Tyr-Tyr(4-OMe)-OBn (**47**), which was cleaved to give Boc-Tyr-Tyr(4-OMe)-OH (**48**) in 89% overall yield. The cyclization precursor **49** (Scheme 5) was formed in 66% yield by coupling dipeptide **48** with amine complex **36**. Cyclization of tripeptide complex **49** by reaction with sodium 2,6-di-*tert*-butyl-phenoxide in THF produced cyclized biphenyl ether complex **50** in 83% yield, which was converted in 62% yield by irradiation at 350 nm to compound **51**, which has the K-13 ring system. Removal of the Boc group with 4 N HCl/dioxane followed by acetylation with Ac_2O/pyridine gave dimethyl K-13 (**45**), which was converted as before to K-13 as a 13:1 mixture of isomers in 86% overall yield. The major isomer isolated from the cyclization of the *tert*-butoxycarbonyl-protected tripeptide **49** also is the natural isomer of K-13.

Minor modifications of these procedures were needed to successfully synthesize OF4949-III. Cbz-Asn-OH (**52**) was coupled with Tyr-OMe-HCl (**53**) to form the dipeptide Cbz-Asn-Tyr-OMe (**54**), which was deprotected to afford the amine Asn-Tyr-OMe (**55**) in 57% overall yield. The cyclization tripeptide complex **56** (Scheme 6) was formed in 69% yield by coupling **55** with the acid complex **35**. When the tripeptide complex **56** was subjected to the cyclization/photolysis conditions used to prepare K-13, only a 24% overall yield of the OF4949-III ring system **57** was obtained. However, when potassium *tert*-butoxide (1.1 equiv) was used as the base in the cyclization reaction (2 h at room temperature in THF/DMF), the cyclic ether **57** was isolated in a much improved yield and converted to **58** in 56% overall yield. Saponification of ester **58**, followed by removal of the Boc group from acid **59**, afforded OF4949-III as a single isomer in 76% yield. The product isolated had identical physical properties to those of the natural product OF4949-III.

Discussion

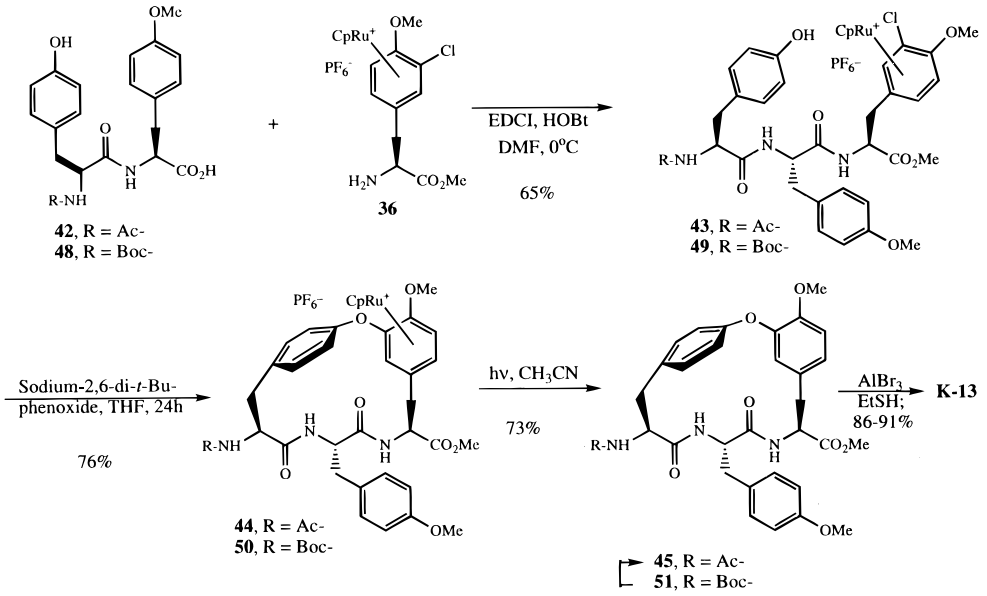
We began this work with the goal of synthesizing cyclic biphenyl ether peptides related to K-13 and OF4949-I−IV and attempted to follow a strategy similar to that developed by Pearson *et al.* for synthesizing cyclic biphenyl ethers. The intermolecular S_NAr reactions[19] of $RuCp^+$-complexed amino acids[20] gave the *acyclic* biaryl ethers in high yields under mild conditions, but the peptide cyclization step was found to be sequence dependent. Macrolactamization worked well for synthesizing the *para*−*meta* model peptides **14**−**16**, but our attempts to prepare the *meta*−*para* model peptides **28**−**29** by macrolactamization gave only dimeric or polymeric products (see Supporting Information; Schemes 7 and 8).

Therefore, we devised an alternate strategy to construct the peptide backbones of the target compounds first and to form the biphenyl ethers by an intramolecular variant of the S_NAr reaction in a later step to give the desired *cyclic* ethers. In order for this method to succeed, the chloroarene ring had to be selectively complexed over the phenolic ring of the tripeptide. Selective ring-specific complexation seemed unlikely in a preassembled tripeptide because the electron rich phenolic ring

(19) For recent reviews, see: (a) Semmelhack, M. F. Transition Metal Arene Complexes: Nucleophilic Addition. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergammon Press: New York, 1995, Vol. 12, Chapter 9.1, pp 979−1014. For recent studies, see: (b) Gill, U. S.; Moriarty, R. M.; Ku, Y. Y.; Butler, I. R. *J. Organomet. Chem.* **1991**, *417*, 313−325. (c) Lomenzo, S. A.; Nolan, S. P.; Trudell, M. L. *Organometallics* **1994**, *13*, 676−681.

(20) (a) Moriarty, R. M.; Ku, Y.-Y.; Gill, U. S. *J. Chem. Soc., Chem. Commun.* **1987**, 1837−1838. (b) Sheldrick, W. S.; Gleichmann, A. *J. Organomet. Chem.* **1994**, *470*, 183−187. (c) Gleichmann, A. J.; Wolff, J. M.; Sheldrick, W. S. *J. Chem. Soc., Dalton Trans.* **1995**, 1549−1554.

Scheme 5



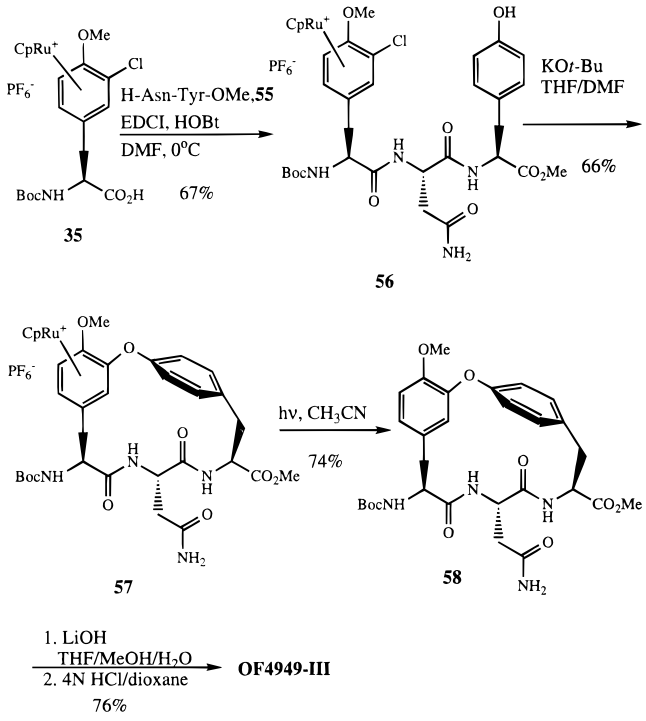
is more reactive toward complexation than the chloroarene. Therefore, the tripeptide complexes had to be assembled by peptide couplings of the corresponding amino acid ruthenium complex. The known $RuCp^+$ complex of Boc-*p*-Cl-Phe-OH (**1**)[11b] was shown to work well in peptide coupling reactions, and no epimerization or side reactions were seen.

We also showed[21] that a transition metal complex of an amino acid ester bearing a free amine group could be formed selectively at the aromatic ring and that transition metal complexes of monoprotected amino acid derivatives (either free acid or amine) could be reacted with other amino acids and dipeptides under standard peptide coupling conditions. The peptidyl complexes are air stable and survive aqueous workup conditions. Simultaneously, successful peptide coupling of a RuCp-complexed amino acid was reported by another group.[20c] Recently, it was also demonstrated that these complexes are compatible with the use of common protecting groups used in peptide synthesis.[19c,20c]

The deshydroxy *para*−*meta* substituted K-13 and *meta*−*para*-substituted OF4949 analogs were each synthesized in only six facile transformations from commercially available amino acid starting materials. The synthesis of the *para*−*meta* derivatives **14**−**16** by S_NAr cyclization proceeded in much higher yields than cycloamidations (about 60% overall *vs* 20−30%) and take place under nondilution reaction conditions with no evidence of dimer formation. More strikingly, the S_NAr macrocyclization also afforded the *meta*−*para*-substituted deshydroxy OF4949-III analogs **28**−**30** which we were unable to obtain by the macrolactamization approach (see Supporting Information). The *meta*−*para*-substituted compounds were formed in about 60% overall yield by S_NAr cyclization, but not at all when preformed biphenyl ethers were subjected to cyclization conditions for amide bond formation. Since both ring systems were obtained in good yield by the S_NAr macrocyclization approach, this method is preferable for these systems.

K-13 was easily synthesized by ruthenium-mediated S_NAr macrocyclization. Beginning either with an Ac-protected tyrosine tripeptide or a Boc-protected tyrosine tripeptide, K-13 was obtained as a mixture of two conformationally stable isomers isolated in ratios of 7:1 and 13:1, respectively. The major isomer obtained was shown to be natural K-13. The minor diastereomer formed by epimerization of O-methyl-tyrosine during the fragment coupling procedure could be avoided by modifying the synthetic route to eliminate the fragment coupling approach. No epimerization occurred during the stepwise approach used to synthesize the model compounds **14**−**16** and **28**−**30**. However, it should be noted that diastereomeric trisubstituted arene complexes such as found in the K-13 precursor would form atropoisomers if these were stable to interconversion, so that peptide sequences other than those investigated here might form mixtures of atropoisomers. Pearson *et al.* also obtained a 7:1 mixture of isomers in the formation of a 16-membered cyclic tripeptide biaryl ether using this methodology.[15] The major isomer was the desired product, but is was not reported whether the minor isomer was an atropoisomer or an α-center epimer.

Scheme 6



The synthesis of OF4949-III (Scheme 6) conceptually follows that used to prepare K-13, but the experimental conditions were changed to overcome experimental difficulties. DMF was added

(21) An unsuccessful attempt at selectively complexing an arene in the presence of a free amine has been described: see ref 19c.

to help solublize the intermediate asparagine tripeptide complex **56**, which tended to precipitate from THF, and potassium *tert*-butoxide was used in place of the phenoxide to obtain higher cyclization yields. Potassium *tert*-butoxide has been shown to be useful for effecting more difficult intermolecular S_NAr reactions[11e] of other RuCp chloroarene complexes. It should be noted that the other *meta*−*para* 17-membered ring systems we studied (**28**−**30**) were more difficult to synthesize by the macrolactamization approach, which may suggest a fundamental difference in the stability or ring strain of the two ring systems.

The ease of ring closure from the intramolecular S_NAr reaction in these systems probably results from a highly favorable interaction of the two aromatic rings that places the two reactive groups in close proximity. Prior to cyclization, the ring containing the leaving group is highly activated by $RuCp^+$ complexation giving rise to electron deficient rings, whereas the attacking phenoxide is electron rich. It seems plausible that interaction between the two rings could be stabilized by $\pi-\pi$ interactions[22] and/or intramolecular hydrogen bonding[23] or an attractive electrostatic interaction arising from positively and negatively charged atoms. Recently, additional examples of facile intramolecular S_NAr biaryl ether macrocyclizations of peptides constructed from *o*-nitrofluorophenylalanine have been developed by Zhu *et al.*, who have suggested that the nucleophile (phenoxide) and leaving group (fluoride) are oriented within reacting distance for macrocyclization to occur.[9] Preorganization of reacting centers has also been suggested as the rationalization for the facile macrocyclization of arylnitrenium ions to biaryl amines under nondilution conditions.[24]

Previous syntheses of K-13 and OF4949-III based on cycloamidation strategies have required more than 19 synthetic steps. In contrast, the S_NAr macrocyclization approach afforded K-13 and OF-4949-III in seven and eight steps from amino acid starting materials. These convergent total syntheses of K-13 and OF4949-III demonstrate the utility of this method for effecting the total synthesis of natural products containing cyclic biphenyl ether peptides.

The development of preformed peptidyl ruthenium complexes for synthesis represents a versatile advance in the application of organotransition metal chemistry to the synthesis of biologically relevant molecules and for creating unique molecules which could be used to probe biological systems.[25] It seems likely that many other peptidyl ruthenium π-complexes could be obtained from application of this methodology and used as precursors to synthesize other cyclic ethers. One of the most powerful applications will be to react the peptidyl ruthenium π-complex with a variety of nucleophiles in an intramolecular or intermolecular fashion to create unlimited combinatorial libraries[26] of cyclic side-chain linked peptides and substituted aromatic peptides.

(22) (a) Hunter, C. A.; Sanders, J. K. M *J. Am. Chem. Soc.* **1990**, *112*, 5525−5534. (b) Burley, S. K.; Petsko, G. A. *Science* **1985**, *229*, 23−28. (c) Morkuma, K. *Acc. Chem. Res.* **1977**, *10*, 294−300. (d) Shetty, A. S.; Zhang, J.; Moore, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 1019−1027.

(23) Newcomb, L. F.; Haque, T. S.; Gellman, S. H. *J. Am. Chem. Soc.* **1995**, *117*, 6509−6519 and references within.

(24) Abromovitch, R. A.; Shi, Q. *Heterocycles* **1994**, *38*, 2147−2151.

(25) (a) Krämer, R. *Angew. Chem., Intl. Ed. Engl.* **1996**, *35*, 1197−1199. (b) Jaouen, G.; Vessieres, A.; Butler, I. S. *Acc. Chem. Res.* **1993**, *26*, 361−369. (c) Aronson, B.; Enmon, J. L.; Izenwasser, S.; Katz, J. L.; Kelkar, S. V.; Luo, L. B.; Nolan, S. P.; Trudell, M. L. *J. Med. Chem.* **1996**, *39*, 1560−1563.

(26) (a) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385−1401. (b) Gallop, M. A.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233−1251.

Experimental Section

^{1}H NMR spectra were taken on a 300 MHz Bruker Aspect 3000 system in $CDCl_3$ unless noted otherwise. Chemical shifts were reported in ppm (δ units) downfield from tetramethylsilane. Electron impact mass spectra (EIMS) and high-resolution mass spectra (HRMS) were determined on a Kratos MS-80RFA spectrometer. LSIMS and high-resolution mass spectra (HRMS) were determined on a VG Auto Spec spectrometer.

Liquid chromatography was performed by using forced flow (flash chromatography) with the indicated solvent system. The silica gel used was 230−400 mesh Merck grade 60. Analytical thin layer chromatography (TLC) was performed on glass-backed, precoated plates (silica gel 60 F-254) of 0.25 mm thickness. For TLC staining phosphomolybdic acid in ethanol or ninhydrin with heating was used.

Dichloromethane (CH_2Cl_2), pyridine, and 2,4,6-trimethylpyridine (collidine) were distilled from calcium hydride. Tetrahydrofuran (THF), diethyl ether, and dioxane were distilled from sodium metal−benzophenone ketyl. Dimethylformamide (DMF) was supplied by Aldrich Chemical Co. in Sure-Seal bottles. Hexanes and ethyl acetate (EtOAc) were redistilled (reagent grade, EM Science). Absolute methanol and ethanol were purchased from Mallinckrodt and Quantum Chem. Corp., respectively. Triethylamine (TEA) and *N*-methylmorpholine (NMM) were purchased from Aldrich and stored over potassium hydroxide. All other solvents were used without further purification. All amino acids and protected amino acids were purchased from Bachem California, except DL-*m*-tyrosine which was purchased from Aldrich *O*-methyl-L-tyrosine from Acros Organics, and 3-chloro-L-tyrosine from Lancaster. All other reagents were purchased from Aldrich.

All reactions were carried out under an atmosphere of argon using flame-dried glassware. Photolytic cleavage of the ruthenium complex was carried out by using a Rayonet Photochemical Reactor. The compounds were dissolved in CH_3CN and irradiated with 350 nm UV light for 24 h. The solvent was concentrated to about 2 mL, and ether was added (30 mL). The regenerated $RuCp(CH_3CN)_3PF_6$ was filtered and washed with ether (2 × 10 mL). The filtrate and washings were concentrated *in vacuo*, and the crude solid was purified by column chromatography.

[*N*-(*tert*-Butoxycarbonyl)-*p*-chlorophenylalanine]cyclopentadienylruthenium Hexafluorophosphate (2).[11b] To a solution of Boc-*p*-Cl-Phe-OH (**1**) (0.250 g, 0.834 mmol) in 18 mL of degassed 1,2-DCE at 60 °C was added $RuCp(CH_3CN)_3PF_6$ (0.362 g, 0.834 mmol). The resulting solution was heated to reflux for 2 h, allowed to cool to room temperature and then filtered. The reaction mixture was concentrated in vacuo, redissolved in CH_3CN, and added to Et_2O. The light brown solid was filtered, rinsed with ether, redissolved in DCM/MeOH, concentrated in vacuo, and dried under vacuum to give the title compound as brown foam (0.437 g, 86%). ^{1}H NMR: δ 6.49−6.54 (d, 2H, J = 6.2 Hz), 6.25−6.35 (dd, 2H, J = 12.6, 5.7 Hz), 5.47 (s, 5H), 4.30−4.42 (m, 1H), 2.96−3.10 (dd, 1H, J = 14.0, 5.1 Hz), 2.70−2.81 (dd, 1H, J = 14.0, 8.0 Hz), 1.41 (s, 9H). LSIMSHRMS: calcd for $C_{19}H_{23}NO_4ClRu^+$ 466.0356 $(M)^+$, found 466.0369.

[*N*-(*tert*-Butoxycarbonyl)-*p*-chlorophenylalanyl-isoleucyl-*m*-tyrosine methyl ester]cyclopentadienylruthenium Hexafluorophosphate (8). To a solution of **2** (135 mg, 0.22 mmol) and HOBt (45 mg, 0.33 mmol) in 1 mL of DMF at 0 °C was added EDCI (47 mg, 0.24 mmol). The mixture was stirred for 15 min at 0 °C followed by the addition of a solution of Ile-*m*-Tyr-OMe (**5**) (68 mg, 0.22 mmol) dissolved in 1 mL of DMF and 2 h of stirring at 0 °C and then at ambient temperature for an additional 10 h. The mixture was diluted with H_2O (10 mL) and then extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were pooled, washed successively with saturated $NaHCO_3$ (2 × 10 mL), 1 N $KHSO_4$ (10 mL), and saturated NaCl (10 mL), dried over Na_2SO_4, concentrated to about 2 mL, precipitated with 50 mL of Et_2O, filtered, washed, redissolved in DCM/MeOH, and concentrated *in vacuo* to give the title compound as a brown solid (154 mg, 77%). ^{1}H NMR: δ 7.32 (d, 1H), 7.10 (t, 1H, J = 7.9 Hz), 7.00 (br s, 1H), 6.80 (br s, 1H), 6.74 (d, 1H, J = 7.5 Hz), 6.63 (d, 1H, J = 5.5 Hz), 6.45 (s, 1H, J = 5.9 Hz), 6.36 (s, 1H), 6.29 (s, 1H), 5.93 (d, 1H), 5.41 (s, 1H), 5.32 (s, 5H), 4.88 (m, 1H), 4.75 (m, 1H), 4.40 (m, 1H), 3.82 (s, 3H), 3.33 (d, 1H), 3.10 (d, 1H), 3.00 (d, 1H), 2.65 (t, 1H), 2.38 (br s, 1H), 2.00 (m, 1H), 1.50 (m, 1H), 1.28 (m, 1H), 1.35

(s, 9H), 0.75−0.95 (m, 6H). LSIMSHRMS: calcd for $C_{35}H_{45}N_3O_7ClRu^+$ 756.1986 $(M)^+$, found 756.1979.

[*N*-(*tert*-Butoxycarbonyl)-*p*-phenylalanyl-isoleucyl-*m*-tyrosyline methyl ester]cyclopentadienylruthenium Hexafluorophosphate Diphenyl Ether (11). A stock solution (1.5 mL, 0.092 mmol) was diluted with 30 mL of THF, and a solution of **8** (75 mg, 0.083 mmol) dissolved in 10 mL of THF was added via syringe pump to the above solution over 4 h and allowed to stir for an additional 20 h. The solution was concentrated *in vacuo*, dissolved in CH_3CN, and filtered. The filtrate was concentrated *in vacuo* to give **11** as a brown solid (56.0 mg, 78%) which was used in the next step without further purification.

[*N*-(*tert*-Butoxycarbonyl)-*p*-phenylalanyl-isoleucyl-*m*-tyrosine Methyl ester Diphenyl Ether (14). **11** (91.2 mg, 0.105 mmol) was dissolved in 25 mL of CH_3CN, irradiated at 350 nm for 24 h and worked up as in the general procedure. The filtrate and washings were concentrated *in vacuo*, and the crude solid was purified by column chromatography (SiO_2, 20% EtOAc/CH_2Cl_2) to give the title compound as a white solid (40 mg, 83%) (mp 225−226 °C) (R_f 0.52, 30% EtOAc/CH_2Cl_2). ^{1}H NMR: δ 7.30 (d, 1H, J = 8.9 Hz), 7.23 (t, 1H, J = 7.8 Hz), 7.03−7.14 (dq, 3H, J = 2.3, 11.0 Hz), 6.76 (dd, 1H, J = 2.5, 8.3 Hz), 6.70 (d, 1H, J = 7.7 Hz), 6.33 (d, 1H, J = 8.0), 6.24 (s, 1H), 5.88 (d, 1H, J = 6.3 Hz), 5.23 (d, 1H, J = 11.0 Hz), 4.70−4.82 (dt, 1H, J = 3.6, 7.0 Hz), 4.10−4.25 (m, 1H), 3.85−3.92 (dd, 1H, 4.7, 6.7 Hz), 3.80 (s, 3H), 3.40 (dd, 1H, J = 15.4, 3.6 Hz), 3.12 (dd, 1H, J = 5.0, 12.3 Hz), 3.01 (dd, 1H, J = 7.0, 15.3 Hz), 2.81 (t, 1H, J = 12.0 Hz), 1.90−2.08 (m, 1H), 1.47 (s, 9H), 1.56−1.45 (m, 1H), 1.05−1.20 (m, 1H), 0.91 (dd, 3H, J = 6.9, 7.4 Hz), 0.79 (d, 3H, J = 6.9 Hz). LSIMSHRMS: calcd for $C_{30}H_{39}N_3O_7$ 584.2866 $(M + H)^+$, found 554.2866.

[*p*-Chlorophenylalanine methyl ester]cyclopentadienylruthenium Hexafluorophosphate (18). To a solution of H_2N-*p*-Cl-Phe-OMe (**17**)-(0.27 g, 1.26 mmol) in 34 mL of degassed 1,2-DCE at 60 °C was added $RuCp(CH_3CN)_3PF_6$ (0.55 g, 1.26 mmol). The resulting solution was heated to reflux for 2 h, allowed to cool to room temperature and then filtered. The reaction mixture was concentrated *in vacuo*, redissolved in CH_3CN, and added to Et_2O. The light brown precipitate was filtered, rinsed with ether, redissolved in DCM/MeOH, concentrated *in vacuo*, and dried under vacuum overnight to give the title compound as a brown foam (0.61 g, 92%). ^{1}H NMR: δ 6.50−6.58 (d, 2H, J = 6.2 Hz), 6.32−6.42 (dd, 2H, J = 12.6, 5.7 Hz), 5.48 (s, 5H), 3.80 (s, 3H), 3.70−3.80 (m, 1H), 2.89−2.98 (dd, 1H, J = 13.6, 5.3 Hz), 2.70−2.81 (dd, 1H, J = 13.6, 7.7 Hz). LSIMSHRMS: calcd for $C_{15}H_{17}NO_2ClRu^+$ 379.9992 $(M)^+$, found 379.9997.

[*N*-(Carbobenzyloxy)-*m*-tyrosyl-isoleucyl-*p*-chlorophenylalanine methyl ester]cyclopentadienylruthenium Hexafluorophosphate (22). To a solution of Cbz-*m*-Tyr-Ile-OH (**19**) (0.120 g, 0.28 mmol) and HOBt (57 mg, 0.42 mmol) in 1.4 mL of DMF at 0 °C was added EDCI (59 mg, 0.31 mmol). The mixture was stirred for 15 min at 0 °C followed by the addition of a solution of **18** (0.150 g, 0.28 mmol) dissolved in 1.4 mL of DMF and 2 h of stirring at 0 °C and then at ambient temperature for an additional 10 h. The mixture was diluted with H_2O (10 mL) and then extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were pooled, washed successively with saturated $NaHCO_3$ (2 × 10 mL), 1 N $KHSO_4$ (10 mL), and saturated NaCl (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The brown oil was redissolved in CH_3CN, filtered through a plug of alumina, concentrated to about 2 mL which was added to 50 mL of Et_2O, filtered, and dried to give the title compound as a brown solid (0.180 g, 69%). ^{1}H NMR: δ 7.25−7.40 (m, 7H), 7.07−7.17 (dd, 1H, J = 7.9, 7.5 Hz), 6.72 (d, 1H, J = 7.4 Hz), 6.65 (d, 2H, J = 7.9 Hz), 6.40−6.45 (dd, 1H, J = 6.2, 1.3 Hz), 6.32−6.36 (dd, 1H, J = 6.1, 1.3 Hz), 6.28 (d, 1H, J = 6.8 Hz), 6.16 (d, 1H, J = 5.9 Hz), 6.00 (d, 1H, J = 6.8 Hz), 5.39 (s, 5H), 5.08 (s, 2H), 4.62−4.72 (dd, 1H, J = 7.0, 5.3 Hz), 4.38−4.48 (m, 1H), 4.05−4.13 (dd, 1H, J = 7.6, 7.9 Hz), 3.78 (s, 3H), 2.84−3.12 (m, 4H), 1.70−1.86 (m, 1H), 1.35−1.50 (m, 1H), 1.00−1.16 (m, 1H), 0.90 (d, 3H, J = 6.8 Hz), 0.85 (t, 3H, J = 7.3 Hz). LSIMSMS: calcd for $C_{38}H_{43}N_3O_7ClRu^+$ 790.184 $(M)^+$, found 756.1 ($C_{38}H_{44}N_3O_7Ru^+$, 756.223).

[*N*-(Carbobenzyloxy)-*m*-tyrosyl-isoleucyl-*p*-phenylalanine methyl ester]cyclopentadienylruthenium Hexafluorophosphate Diphenyl Ether (25). Method A (Slow Addition). A stock solution (1.6 mL, 0.098 mmol) was diluted with 30 mL of THF, and a solution of **22** (83 mg, 0.089 mmol) dissolved in 10 mL of THF was added *via* syringe pump to the above solution over 4 h and allowed to stir for an additional 20 h. The solution was filtered through a plug of neutral alumina and concentrated *in vacuo* to give the title compound as a brown solid (65 mg, 78%). LSIMSHRMS: calcd for $C_{38}H_{42}N_3O_7Ru^+$ 754.2077 $(M)^+$, found 754.2093.

Method B (Nondilution). A stock solution (1.6 mL, 0.098 mmol) was added slowly to a solution of **22** (83 mg, 0.089 mmol) dissolved in 4 mL of THF, and the resultant mixture was stirred for 20−24 h. The solution was filtered through a plug of neutral alumina and concentrated *in vacuo* to give the title compound as a brown solid (73 mg, 88%). ^{1}H NMR: δ 7.32−7.40 (m, 6H), 7.18−7.25 (dd, 1H, J = 7.8, 8.2 Hz), 6.92−7.00 (dd, 1H, J = 8.2, 1.9 Hz), 6.72−6.80 (d, 1H, J = 7.6 Hz), 6.23−6.30 (d, 1H, J = 6.2 Hz), 6.13−6.19 (dd, 1H, J = 6.2, 1.0 Hz), 6.05−6.14 (m, 5H), 5.41 (s, 5H), 5.17 (d, 1H, J = 12.2 Hz), 5.07 (d, 1H, J = 12.2 Hz), 4.80−4.90 (dd, 1H, J = 12.3, 3.0 Hz), 4.49−4.56 (dd, 1H, J = 6.8, 1.5 Hz), 4.33−4.40 (d, 1H, J = 5.0 Hz), 3.82 (s, 3H), 3.15−3.26 (m, 2H), 2.90−3.00 (d, 1H, J = 12.8 Hz), 2.57−2.70 (t, 1H, J = 12.7 Hz), 1.77−1.92 (m, 1H), 1.30−1.45 (m, 1H), 1.05−1.20 (m, 1H), 0.92 (d, 3H, J = 6.8 Hz), 0.88 (t, 3H, J = 7.4 Hz). LSIMSHRMS: calcd for $C_{38}H_{42}N_3O_7Ru^+$ 754.2077 $(M)^+$, found 754.2088.

***N*-(Carbobenzyloxy)-*m*-tyrosyl-isoleucyl-*p*-phenylalanine Methyl Ester Diphenyl Ether (28).** Ruthenium complex **25** (66 mg, 0.073 mmol) was dissolved in 30 mL of CH_3CN, irradiated at 350 nm for 24 h, and worked up according to the general procedure. The filtrate and washings were concentrated *in vacuo*, and the crude solid was purified by column chromatography (SiO_2, 20% EtOAc/CH_2Cl_2) to give the title compound as a white solid (30 mg, 70%) (R_f 0.29, 20% EtOAc/CH_2Cl_2). ^{1}H NMR: δ 7.30−7.40 (s, 5H), 7.08−7.18 (t, 1H, J = 7.8 Hz), 6.93−7.06 (m, 2H), 6.82−6.92 (dd, 1H, J = 8.1, 2.4 Hz), 6.50−6.59 (d, 1H, J = 7.4 Hz), 6.42−6.48 (d, 1H, J = 8.8 Hz), 6.04−6.13 (d, 1H, J = 9.9 Hz), 5.84 (s, 1H), 5.42 (d, 1H, J = 7.0 Hz), 5.03−5.22 (dd, 2H, J = 40 Hz, 9.9 Hz), 4.85−4.98 (m, 1H), 4.47−4.54 (m, 1H), 4.30−4.36 (m, 1H), 3.85 (s, 3H), 3.38−3.46 (dd, 1H, J = 3.9, 13.4 Hz), 3.18−3.26 (dd, 1H, J = 6.8, 14.1 Hz), 2.72−2.80 (d, 1H, J = 12.9 Hz), 2.49−2.61 (t, 1H, J = 12.9 Hz), 1.61−1.75 (br s, 1H), 1.23−1.40 (br s, 1H), 0.94−1.11 (br s, 1H), 0.89 (d, 3H, J = 7.1 Hz), 0.85 (t, 3H, J = 6.9 Hz). LSIMSHRMS: calcd for $C_{33}H_{37}N_3O_7$ 588.2710 $(M + H)^+$, found 588.2706.

[3-Chloro-4-*O*-methyltyrosine methyl ester]cyclopentadienylruthenium Hexafluorophosphate (36). To a solution of H_2N-Tyr-(3-Cl)(OMe)-OMe (**34**) (80.0 mg, 0.33 mmol) in 1,2-DCE (10 mL) at 60 °C was added $RuCp(CH_3CN)_3PF_6$ (173 mg, 0.40 mmol). The resulting solution was heated to reflux for 2 h, allowed to cool to room temperature and then filtered through a plug of alumina. The reaction mixture was concentrated *in vacuo*, redissolved in CH_3CN, and added to Et_2O. The light brown precipitate was filtered, redissolved in DCM/MeOH, concentrated *in vacuo*, and dried under vacuum overnight to give the title compound as a foam (183 mg, 89%). ^{1}H NMR: δ 6.58−6.62 (d, 2H, J = 13.7 Hz), 6.39−6.46 (d, 1H, J = 7.7 Hz), 6.07−6.18 (dd, 1H, J = 13.7, 7.7 Hz), 5.39 (s, 5H), 3.95 (s, 3H), 3.78 (s, 3H), 3.70−3.83 (m, 1H), 2.84−2.95 (dd, 1H, J = 16.3, 6.9 Hz), 2.70−2.81 (dd, 1H, J = 16.3, 8.6 Hz). LSIMSHRMS: calcd for $C_{16}H_{19}NO_3ClRu^+$ 410.0098 $(M)^+$, found 410.0101.

[*N*-(*tert*-Butoxycarbonyl)-3-chlorotyrosine methyl ester]cyclopentadienylruthenium Hexafluorophosphate (37). To a solution of Boc-Tyr-(3-Cl)(OMe)-OH (**35**) (158 mg, 0.46 mmol) in 1,2-DCE (12 mL) at 60 °C was added $RuCp(CH_3CN)_3PF_6$ (200 mg, 0.46 mmol). The resulting solution was heated to reflux for 2 h, allowed to cool to room temperature and then filtered through a plug of neutral alumina. The reaction mixture was concentrated *in vacuo*, redissolved in CH_3CN, and added to Et_2O. The light brown precipitate was filtered, washed, redissolved in DCM/MeOH, concentrated *in vacuo*, and dried under vacuum overnight to give the title compound (236 mg, 80%). ^{1}H NMR: δ 6.40−6.60 (m, 3H), 6.08−6.13 (t, 2H, J = 7.7 Hz), 5.39 (s, 5H), 4.31−4.43 (m, 1H), 3.97 (s, 3H), 2.92−3.12 (m, 1H), 2.71−2.82 (m, 1H), 1.42 (s, 9H). LSIMSHRMS: calcd for $C_{20}H_{25}NO_5ClRu^+$ 496.0467 $(M)^+$, found 496.0464.

***N*-Acetyltyrosyl-4-*O*-methyltyrosine-OBn (41).** To a solution of Ac-Tyr-OH (**40**) (0.31 g, 1.4 mmol) and HOBt (0.29 g, 2.1 mmol) in 10 mL of DMF at 0 °C were added Tyr(4-OMe)-OBn-TsOH (**39**) (0.60 g, 1.3 mmol) and EDCI (0.32 g, 1.6 mmol), followed by NMM (0.14

mL, 1.3 mmol). The solution was stirred for 2−4 h at 0 °C and then overnight at ambient temperature. The reaction mixture was diluted with EtOAc (200 mL) and then washed successively with H_2O (1 × 30 mL), saturated $NaHCO_3$ (2 × 30 mL), 1 N $KHSO_4$ (1 × 30 mL), and saturated NaCl (1 × 40 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2) using 5% MeOH/CH_2Cl_2 as the eluant to afford 0.62 g (97%) of the title compound as a white crystalline solid. ^{1}H NMR: δ 7.35 (dd, 3H, J = 1.5, 5.3 Hz), 7.28 (d, 1H, J = 4.0 Hz), 7.25 (d, 1H, J = 2.2 Hz), 6.97 (d, 2H, J = 8.5 Hz), 6.85 (d, 2H, J = 8.6 Hz), 6.68 (dd, 4H, J = 6.4, 8.3 Hz), 6.43 (d, 1H, J = 6.5 Hz), 6.35 (d, 1H, J = 7.9 Hz), 5.10 (s, 2H), 4.67−4.83 (dd, 1H, J = 6.1, 13.7 Hz), 4.20−4.35 (dd, 1H, J = 6.9, 13.5 Hz), 3.72 (s, 3H), 3.00 (dd, 1H, J = 5.7, 13.6 Hz), 2.90 (d, 3H, J = 9.4 Hz), 1.92 (s, 3H). EIHRMS: calcd for $C_{28}H_{30}N_2O_6$ 490.2104, found 490.2080.

***N*-Acetyltyrosyl-tyrosine(4-OMe)-OH (42).** To a stirred solution of Ac-Tyr-Tyr(4-OMe)-OBn (**41**) (0.32 g, 0.65 mmol) in 5 mL of MeOH was added 30 mg of 10% Pd/C. The flask was fitted with a balloon of H_2, and the resulting slurry was stirred for 2 h at room temperature, filtered through an acrodisc, and concentrated *in vacuo* to give 0.25 g (96%) of the free acid **42** as a white solid (254.7 mg, 96%). ^{1}H NMR: δ 7.20 (d, 1H, J = 7.9 Hz), 7.05 (d, 2H, J = 8.5 Hz), 6.95 (d, 2H, J = 8.6 Hz), 6.90 (d, 1H, J = 8.0 Hz), 6.75 (d, 2H, J = 8.3 Hz), 6.65 (d, 2H, J = 8.3 Hz), 4.60−4.70 (t, 1H, J = 6.0 Hz), 4.50−4.60 (t, 1H, J = 7.0 Hz), 3.73 (s, 3H), 3.07 (dd, 1H, J = 5.7, 15.4 Hz), 2.80−3.00 (m, 2H), 2.80 (dd, 1H, J = 7.7, 15.4 Hz), 1.89 (s, 3H). LSIMSHRMS: calcd for $C_{21}H_{24}N_2O_6$ 401.1713 $(M + H)^+$, found 401.1716.

***[N*-Acetyltyrosyl-tyrosyl(4-OMe)-3-chlorotyrosine methyl ester]-cyclopentadienylruthenium Hexafluorophosphate (43).** To a solution of *N*-Ac-Tyr-Tyr(4-OMe)-OH (**42**) (120 mg, 0.30 mmol) and HOBt (60.8 mg, 0.45 mmol) in 2 mL of DMF at 0 °C was added EDCI (63.3 mg, 0.30 mmol). The mixture was stirred for 15 min at 0 °C followed by the addition of a solution of **36** (166 mg, 0.30 mmol) dissolved in 1 mL of DMF and 2 h of stiring at 0 °C and then at ambient temperature for an additional 10 h. The mixture was diluted with H_2O (10 mL) and then extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were pooled, washed successively with saturated $NaHCO_3$ (2 × 10 mL) and saturated NaCl (10 mL), dried over Na_2SO_4, concentrated to about 2 mL, precipitated with 50 mL of Et_2O, filtered, redissolved in DCM/MeOH, concentrated *in vacuo*, and dried to give the title compound as a brown solid (182.0 mg, 65%). ^{1}H NMR: δ 7.00−7.10 (dd, 2H), 6.90−7.00 (d, 2H), 6.78 (d, 2H), 6.70 (t, 2H), 6.40−6.55 (m, 1H), 6.30−6.40 (m, 1H), 5.90−6.05 (m, 1H), 5.33 (s, 5H), 4.50−4.70 (m, 1H), 4.40−4.50 (m, 1H), 4.35−4.45 (m, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 2.70−3.10 (m, 6H), 1.93 (s, 3H). LSIMSHRMS: calcd for $C_{37}H_{41}N_3O_8ClRu^+$ 792.1633 $(M)^+$, found 792.1629.

***[N*-Acetyltyrosyl-tyrosyl(4-OMe)-3-tyrosine(4-OMe)methylester]-cyclopentadienylruthenium Hexafluorophosphate Diphenyl Ether (44).** A stock solution of sodium 2,6-di-*tert*-butylphenoxide was prepared at ambient temperature from 60% NaH (0.62 mmol) and 2,6-di-*tert*-butylphenol (0.62 mmol) in 10 mL of THF. A stock solution (3.0 mL, 0.186 mmol) was added to a solution of **43** (158 mg, 0.169 mmol) in THF (9 mL) and DMF (3.0 mL) and allowed to stir for 20−24 h. The solution was filtered, concentrated to 2 mL, and added to Et_2O (50 mL). The precipitate was filtered, redissolved in DCM/MeOH, concentrated *in vacuo*, and dried under vacuum overnight to give the title compound as a brown foam (115.0 mg, 76%). ^{1}H NMR: δ 7.40−7.34 (dd, 1H), 7.00−7.10 (m, 2H), 6.94−7.05 (dd, 4H), 6.80−6.85 (d, 1H), 6.65−6.80 (dd, 3H), 6.40 (d, 1H), 6.30 (d, 1H), 5.80−5.90 (m, 1H), 5.37 (s, 5H), 4.47−4.65 (m, 1H), 4.35−4.43 (m, 1H), 4.20−4.30 (m, 1H), 3.94 (s, 3H), 3.80 (s, 3H), 3.71 (s, 3H), 2.70−3.20 (m, 6H), 2.03 (s, 3H). LSIMSHRMS: calcd for $C_{37}H_{40}N_3O_8Ru^+$ 756.1870 $(M)^+$, found 756.1868.

***N*-Acetyltyrosyl-tyrosyl(4-OMe)-3-tyrosine(4-OMe) methyl Ester Diphenyl Ether (Trimethyl K-13) (45). (a) From Acyl Dipeptide.** Complex **44** (100 mg, 0.111 mmol) was dissolved in 30 mL of CH_3-CN and irradiated at 350 nm for 24 h. The solvent was concentrated *in vacuo*, and the crude solid was purified by column chromatography (SiO_2, 5% MeOH/CH_2Cl_2, R_f = 0.40) followed by rechromatography (20% EtOAc/CH_2Cl_2) to give **45** as a white solid. (47.6 mg, 73%) (R_f 0.35, 5% MeOH/CH_2Cl_2).

(b) From Carbamate-Protected Dipeptide. Cyclic ether **51** (8.3 mg, 0.013 mmol) was dissolved in 4N HCl/dioxane (5 mL) and stirred for 1 h at room temperature. The solution was concentrated *in vacuo* and dissolved in CH_2Cl_2/pyridine (2.5 mL/0.5 mL). Ac_2O (0.12 mL, 1.06 mmol) was added, and the resultant solution was stirred for 3 h at room temperature. The reaction mixture was concentrated *in vacuo*, and the yellowish oil was purified by column chromatography (SiO_2, 5% MeOH/CH_2Cl_2; R_f 0.35) to give the title compound as a white solid 7.2 mg, 95%). ^{1}H NMR: δ 7.27−7.33 (dd, 1H, 8.3, 2.2 Hz), 7.08−7.13 (dd, 1H, J = 8.3 Hz, 2.2 Hz), 7.05−7.09 (dd, 1H, J = 8.2, 2.2 Hz), 6.98−7.04 (d, 2H, J = 8.6 Hz), 6.50−6.58 (dd, 2H, J = 8.3, 5.0 Hz), 6.71−6.76 (d, 2H, J = 8.6 Hz), 6.49−6.55 (dd, 2H, J = 8.3, 2.2 Hz), 6.42−6.48 (d, 1H, J = 8.4 Hz), 6.07−6.11 (d, 1H, J = 2.1 Hz), 5.66−5.71 (d, 1H, J = 5.3 Hz), 4.58−4.69 (m, 1H), 4.32−4.38 (dd, 1H, J = 9.4, 4.4 Hz), 3.99−4.09 (dt, 1H, J = 9.2, 5.0 Hz), 3.87 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 3.20−3.29 (dd, 2H, J = 14.0, 4.4 Hz), 3.12−3.20 (dd, 1H, J = 12.3, 5.5 Hz), 2.77−2.90 (m, 2H), 2.66−2.76 (dd, 1H, J = 13.0, 9.5 Hz), 2.03 (s, 3H). LSIMSHRMS: calcd for $C_{32}H_{35}N_3O_8$ 590.2502 $(M + H)^+$, found 590.2502.

K-13. Following the procedure of Evans,[7a] **45** (7.0 mg, 0.012 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and added to a solution of 1.0 M $AlBr_3$ (0.4 mL, 0.36 mmol) in freshly distilled EtSH (0.5 mL). The resultant orange slurry was stirred for 15 h at room temperature and the solvent removed *in vacuo*. The crude orange oil was purified by column chromatography (SiO_2, 85:7:5 CH_2Cl_2/MeOH/AcOH). The resultant solid was rechromatographed (93% EtOAc/AcOH), to give K-13 as a white solid (6.6 mg, 91%). R_f 0.27 (80:15:5 CH_2Cl_2/MeOH/AcOH). ^{1}H NMR (500 MHz, methanol-d_4): δ 7.08−7.12 (d, 1H, 7.5 Hz), 6.84−6.88 (dd, 1H, J = 8.5 Hz, 2.2 Hz), 6.78−6.82 (d, 1H, J = 8.5 Hz), 6.71−6.78 (d, 2H, J = 7.5 Hz), 6.50−6.58 (q, 2H, J = 8.0 Hz), 6.44−6.50 (dd, 1H, J = 8.5, 2.5 Hz), 6.36−6.42 (d, 2H, J = 8.0 Hz), 6.14 (s, 1H), 4.18−4.25 (dd, 1H, J = 12.0, 5.0 Hz), 3.99−4.09 (s, 1H), 3.89−3.95 (t, 1H, J = 5.0 Hz), 2.93−3.01 (d, 1H, J = 13.5) 2.77−2.85 (dd, 1H, J = 5.0, 12.5 Hz), 2.64−2.76 (m, 3H), 2.56−2.64 (t, 1H, J = 12.0 Hz), 1.83 (s, 3H). LSIMSMS: calcd for $C_{29}H_{29}N_3O_8$ 548.5713 $(M + H)^+$, found 548, 570 $(M + Na)^+$, found 570.

[*N*-(*tert*-Butoxycarbonyl)-3-chlorotyrosyl(4-OMe)-asparagyl-tyrosine methyl ester]cyclopentadienylruthenium Hexafluorophosphate (56). To a solution of complex **37** (205 mg, 0.32 mmol) and HOBt (65.0 mg, 0.48 mmol) in 2 mL of DMF at 0 °C was added EDCI (68.0 mg, 0.35 mmol). The mixture was stirred for 15 min at 0 °C followed by the addition of a solution of H_2N-Asn-Tyr-OMe (**55**) (98 mg, 0.32 mmol) dissolved in 1 mL of DMF and 2 h of stirring at 0 °C and then at ambient temperature for an additional 10 h. The mixture was diluted with H_2O (10 mL) and then extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were pooled, washed successively with saturated $NaHCO_3$ (2 × 10 mL) and saturated NaCl (10 mL), dried over Na_2SO_4, concentrated to about 2 mL, precipitated with 50 mL of Et_2O, filtered, and dried to give the title compound as a brown solid (201 mg, 67%). ^{1}H NMR: δ 6.85−6.95 (t, 2H, J = 6.1 Hz), 6.60−6.75 (t, 2H, J = 9.3 Hz), 6.41−6.55 (d, 1H), 6.25−6.35 (d, 1H, J = 6.1 Hz), 6.00−6.20 (dd, 1H), 5.21 (s, 5H), 4.55−4.68 (m, 1H), 4.45−4.57 (m, 1H), 4.16−4.36 (m, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 2.32−3.07 (m, 6H), 1.30 (s, 9H). LSIMSHRMS: calcd for $C_{34}H_{42}N_4O_9ClRu^+$ 787.1690 $(M)^+$, found 787.1687.

[*N*-(*tert*-Butoxycarbonyl)-3-tyrosyl(4-OMe)-asparagyl-tyrosine methyl ester]cyclopentadienylruthenium Hexafluorophosphate Biphenyl Ether (57). Method A. A stock solution of sodium 2,6-di-*tert*-butylphenoxide was prepared at ambient temperature from 60% NaH (0.62 mmol) and 2,6-di-*tert*-butylphenol (0.62 mmol) in 10 mL of THF. A stock solution (1.7 mL, 0.10 mmol) was added to a solution of **56** (40.0 mg, 0.042 mmol) in 6 mL of THF/DMF (2:1) and allowed to stir for 20−24 h. The solution was filtered, concentrated to 2 mL, and added to Et_2O (100 mL). The precipitate was filtered, redissolved in DCM/MeOH, concentrated *in vacuo*, and dried under vacuum overnight to give the title compound (14.6 mg, 39%) as a brown solid.

Method B. To a solution of KO-*t*-Bu[11e] [2.4 mg (0.023 mmol) in THF (1 mL)] at −78 °C was added a solution of **56** (20.0 mg, 0.021 mmol) dissolved in 3 mL of THF/DMF (2:1). The mixture was allowed to warm to room temperature, stirred for 2 h, filtered, concentrated to 2 mL, and added to Et_2O (50 mL). The precipitate was filtered, redissolved in DCM/MeOH, concentrated *in vacuo*, and dried to give

the title compound as a brown solid (12.4 mg, 66%). ^{1}H NMR: δ 7.10−7.45 (m, 1H), 6.77−7.05 (m, 2H), 6.54−6.74 (m, 1H), 5.70−6.40 (m, 3H), 5.25 (s, 5H), 4.50−4.75 (m, 2H), 4.16−4.36 (m, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 2.25−3.50 (m, 6H), 1.35 (s, 9H). LSIMSHRMS: calcd for $C_{34}H_{41}N_4O_9Ru^+$ 751.1927 $(M)^+$, found 751.1961.

[N-(*tert*-Butoxycarbonyl)-3-tyrosyl(4-OMe)-asparagyl-tyrosine Methyl Ester Diphenyl Ether (58). Complex **57** (10.0 mg, 0.012 mmol) was dissolved in 25 mL of CH_3CN and irradiated at 350 nm for 24 h. The solvent was concentrated *in vacuo* and the residue purified by column chromatography (SiO_2, 10% MeOH/CH_2Cl_2; R_f 0.61) to give the title compound as a white solid (4.8 mg, 74%). ^{1}H NMR: δ 8.30−8.38 (d, 1H), 7.30−7.38 (dd, 1H, J = 8.2, 2.4 Hz), 7.10−7.20 (dd, 1H, J = 2.4, 8.1 Hz), 7.05−7.11 (dd, 1H, J = 5.1, 2.4 Hz), 6.82−6.98 (m, 3H), 6.60−6.70 (dd, 1H, J = 8.2, 2.4 Hz), 6.00−6.10 (br s, 1H), 5.87−5.90 (d, 1H, J = 1.8 Hz), 5.59−5.66 (br s, 1H), 5.17−5.26 (d, 1H, J = 8.4 Hz), 4.83−4.95 (m, 1H), 4.37−4.4.53 (m, 2H), 3.93 (s, 3H), 3.81 (s, 3H), 3.33−3.42 (dd, 1H, J = 4.0, 13.0 Hz), 3.04−3.15 (dd, 1H, J = 5.4, 14.1 Hz), 2.72−2.82 (d, 1H, J = 14.1 Hz), 2.58−2.68 (t, 1H, J = 12.9 Hz), 2.50−2.62 (d, 2H, J = 5.7 Hz), 1.41−1.46 (s, 9H). LSIMSHRMS: calcd for $C_{29}H_{36}N_4O_9$ 585.2561 $(M + H)^+$, found 585.2573.

Boc-OF4949-III (59). LiOH (3.7 mg, 0.03 mmol) was added as a solid to a solution of **58** (7.1 mg, 0.012 mmol) in THF/MeOH/H_2O (0.6 mL/0.2 mL/0.2 mL) cooled to 0 °C. The resultant mixture was stirred for 1 h and the solution brought to pH of 2−3 by addition of 1 N HCl. The solution was diluted with 1.0 mL of H_2O and concentrated and the aqueous solution extracted with 1:2 2-propanol/dichloromethane (6 × 3 mL). The organic fractions were pooled, dried over $MgSO_4$, and concentrated *in vacuo* to give the free acid **59** as a white solid (6.6 mg, 95%). R_f: 0.26 (80:15:5 CH_2Cl_2/MeOH/AcOH). ^{1}H NMR (300 MHz, methanol-d_4): δ 7.35−7.42 (dd, 1H, J = 8.3, 1.4 Hz), 7.17−7.24 (dd, 1H, J = 8.4, 1.4 Hz), 6.96−7.04 (dd, 1H, J = 1.5, 8.3 Hz), 6.90−6.95 (d, 1H, J = 8.1 Hz), 6.84−6.90 (dd, 1H, J = 1.6, 8.2 Hz), 6.58−6.64 (d, 1H, J = 8.1 Hz), 5.89 (s, 1H), 4.90−4.29 (m, 3H), 3.89 (s, 3H), 3.36−3.45 (dd, 1H, J = 12.9, 3.7 Hz), 2.92−3.05 (m, 1H), 2.80−2.90 (d, 1H, J = 14.0 Hz), 2.63−2.73 (dd, 1H, J = 14.2, 4.6 Hz), 2.61−2.68 (d, 2H, J = 14.0 Hz), 2.49−2.60 (dd, 1H, J = 15.5, 8.3 Hz), 1.44 (s, 9H). LSIMSMS: calcd for $C_{28}H_{34}N_4O_9$ 571 $(M + H)^+$, found 571 $(M + Na)^+$, found 593.

OF4949-III. Boc-OF4949-III (**59**) was dissolved in 4 N HCl in dioxane and stirred for 1 h at room temperature and filtered. The filtrate was concentrated *in vacuo* to give an oily solid which was dissolved in H_2O, filtered, and lyophilized to give OF4949-III as a white solid (4.7 mg, 80%). ^{1}H NMR (D_2O): δ 7.44−7.51 (dd, 1H, J = 8.4, 2.1 Hz), 7.23−7.31 (dd, 1H, J = 8.3, 1.6 Hz), 7.03−7.13 (dd, 1H, J = 2.6, 8.4 Hz), 7.02−7.11 (d, 1H, J = 8.1 Hz), 6.87−6.94 (dd, 1H, J = 2.4, 8.2 Hz), 6.82−6.88 (dd, 1H, J = 8.3, 1.6 Hz), 5.82−5.85 (d, 1H, J = 1.7 Hz), 4.41−4.49 (dd, 3H, J = 3.4, 12.3 Hz), 3.95 (s, 3H), 3.35−3.45 (dd, 2H, J = 11.9, 2.2 Hz), 3.52−3.60 (dd, 1H, J = 11.8, 3.3 Hz), 3.36−3.45 (dd, 1H, J = 12.9, 3.7 Hz), 2.91−3.05 (dt, 1H, J = 12.0, 3.2 Hz), 2.78−2.91 (dd, 1H, J = 15.4 Hz, 4.1 Hz), 2.60−2.73 (t, 1H, J = 12.6) 2.52−2.63 (dd, 1H, J = 15.2, 10.0 Hz). LSIMSMS: calcd for $C_{23}H_{26}N_4O_7$ 470.4810 $(M + H)^+$, $(M + Na)^+$, found 493.

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Supporting Information Available: Procedures for the syntheses of compounds, **3, 4, 9**−**10**, **12**−**13**, **15**−**16**, **17**, **23**−**24**, **26**−**27**, **29**−**30**, and **31**−**35** (Scheme IV), **39**, **47**−**51**, **54**−**55**, **60**−**62**, and **63**−**65** (Scheme VII), and **66**−**70** (Scheme VIII) and ^{1}H NMR spectra of compounds **8**−**10**, **14**−**16**, **22**−**30**, **45**, **51**, and **58** (39 pages). See any current masthead page for ordering and Internet access instructions.

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