Synthesis of Peptidyl Ruthenium π-Arene Complexes: Application to the Synthesis of Cyclic Biphenyl Ether Peptides

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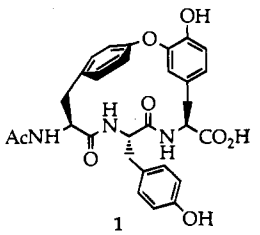
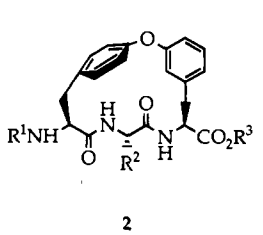
Cyclic biphenyl ethers are structural components of many biologically active peptide-derived compounds (e.g., piperanomycin, bouvardin, RA I−XIV, and the vancomycin family of antibiotics),[1] the kistamicins,[2] the chloropeptins,[3] and the protease inhibitors K-13 (**1**) and OF4949 I−IV.[4] Pearson has synthesized ruthenium π-complexes of amino acids and used these to prepare *acyclic* diphenyl ethers by S_NAr reaction with the appropriate phenol.[5] *Acyclic* peptidyl diphenyl ethers can be converted into macrocyclic diphenyl ethers by an intramolecular amide bond forming reaction. A more direct and versatile approach to these cyclic structures would be to form the peptide backbone first and the diphenyl ether later in the synthesis. Herein, we demonstrate that ruthenium π-complexes of *peptides* can be synthesized and utilized to prepare cyclic peptidyl biphenyl ethers **2** *via* a macrocyclization that constructs the biphenyl ether in the last synthetic step. Other peptides that contain diverse aromatic side chains are also attainable by application of this chemistry.



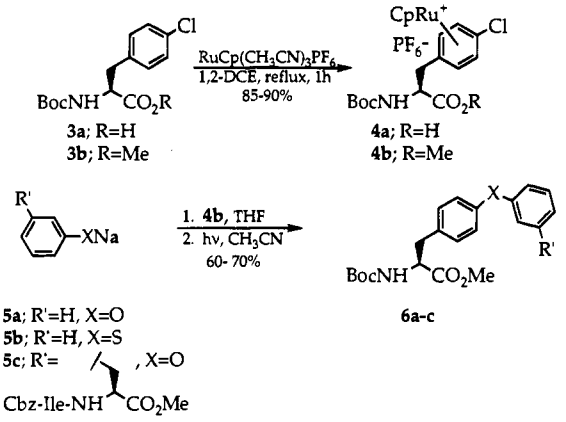
1



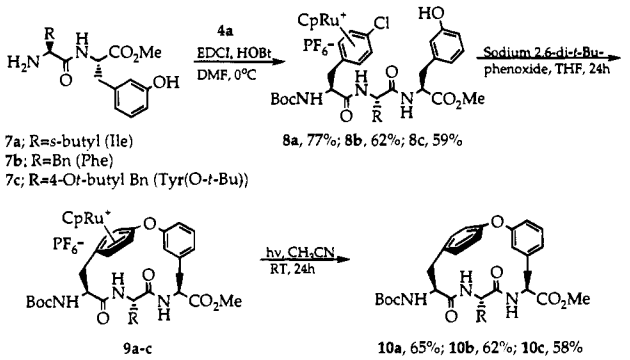
2

Ruthenium π-complexes of protected aromatic amino acids[6] **4a,b** are formed in 85−90% yield (Scheme 1) by the reaction of $RuCp(CH_3CN)_3PF_6$[7] with Boc-*p*-Cl-Phe-OH (**3a**) and Boc-*p*-Cl-Phe-OMe (**3b**).[5b] In analogy to the work described by Pearson,[5] the ester **4b** readily reacts with different nucleophiles **5**. Reaction of complex **4b** with NaOPh followed by photolytic decomplexation in CH_3CN at 350 nm gave biphenyl ether **6a** in 70% overall yield. Similarly, reaction of complex **4b** with NaSPh produced biphenyl thioether **6b**. Other phenols, including the tyrosine-containing peptide **5c**, can be utilized as nucleophiles to give a variety of acyclic biphenyl ethers such as **6c** in good yields.

Scheme 1



Scheme 2



Peptidyl ruthenium complexes were synthesized and used to prepare the cyclic biphenyl ethers **10a−c**. Tripeptide cyclization precursors **8a−c** were prepared by activation of ruthenium complex **4a** with HOBt and EDCI in DMF at 0 °C followed by the addition of various dipeptides[8] **7a−c** (Scheme 2). Coupling of complex **4a** with dipeptide **7a** at 0 °C for 2 h and at ambient temperature for 10 h gave tripeptide π-complex **8a** in 77% yield. Macrocyclization was achieved by slow addition of **8a** over 4 h to a solution of sodium 2,6-di-*tert*-butylphenoxide in THF (final concentration, 0.002 M) and stirring for an additional 20 h, to give cyclic complex **9a**, which after photolysis in CH_3CN at 350 nm for 24 h furnished the cyclic biphenyl ether tripeptide **10a** in 65% overall yield. Good yields of the biphenyl ethers **10b** and **10c** also were obtained when the dipeptides Phe-*m*-Tyr-OMe (**7b**) and Tyr(O-*t*-Bu)-*m*-Tyr-OMe (**7c**) were used.[10]

Our results show that cyclic biphenyl ether tripeptides can be formed easily through an intramolecular S_NAr reaction of $RuCp^+$ π-complexes of tripeptides. In most syntheses of macrocyclic biphenyl ether containing natural products[1,5,11,12]

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(4) Boger, D. L.; Yohannes, D. *Biomed. Chem. Lett.* **1993**, *3*, 245−250 and references within.

(5) (a) Pearson, A. J.; Lee, K. *J. Org. Chem.* **1994**, *59*, 2304−2313. (b) Pearson, A. J.; Park, J. G. *J. Org. Chem.* **1992**, *57*, 1744−1752. (c) Pearson, A. J.; Park, J. G.; Yang, S. H.; Chuang, Y.-H. *J. Chem. Soc., Chem. Commun.* **1989**, 1363−1364

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(8) Synthesized from coupling of L-*m*-Tyr-OMe (obtained from the resolution of D,L-*m*-Tyr-OMe with α-chymotrypsin,[9] followed by esterification with HCl/MeOH) to Z-Ile, Z-Phe, and Z-Tyr (O-*t*-Bu), respectively using EDCI, HOBt, and NMM in DMF, followed by catalytic hydrogenation with 10% Pd/C in MeOH.

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(10) All products were characterized by ^1H NMR and HR-FAB-MS.

(11) (a) Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063−1072. (b) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1990**, *55*, 600−6017. (c) Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 379−382 and references within.

(12) Other methods: (a) Pearson, A. J.; Lee, K. *J. Org. Chem.* **1994**, *59*, 2314−2323. (b) Feng, X.; Olsen, R. K. *J. Org. Chem.* **1992**, *57*, 5811−5812. (c) Nishiyama, S.; Kim, M. H.; Yamamura, S. *Tetrahedron Lett.* **1994**, *35*, 8397−8400. (d) Rao, A. V. R.; Reddy, K. L.; Rao, A. S. *Tetrahedron Lett.* **1994**, *35*, 8465−8468. (e) Boger, D. L.; Patane, M. A.; Zhou, J. *J. Am. Chem. Soc.* **1994**, *116*, 8544−8556. (f) Boger, D. L.; Borzilleri, R. M. *Biomed. Chem. Lett.* **1995**, *5*, 1187−1190. (g) Bois-Choussy, M.; Beugelmans, R.; Bouillon, J.-P.; Zhu, J. *Tetrahedron Lett.* **1995**, *36*, 4781−4784 and references within.

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the ring system has been closed *via* a cycloamidation reaction in the final step. The yields of the 17-membered tripeptide ring system products **10a–c** obtained from the S_NAr reaction are surprisingly good and much better than the low yields of cyclic products we obtained *via* amide bond formation.[11ab,12f,13] Interestingly, another intramolecular biphenyl ether S_NAr macrocyclization on a closely related system proceeds readily,[12f,g] which has been attributed to preorientation of the electron-poor π-complexed ring and the electron-rich phenol ring in a conformation that places the nucleophile and leaving group within bond-forming distance.[12g,14]

The successful use of amino acid ruthenium π-complexes in peptide coupling results from preferential reaction of the α-amino group in **7a–c** with the activated carboxyl group in **4a** rather than with the arene complex, although under different reaction conditions amines will react in an S_NAr fashion.[15] It also should be noted that the versatility of the chemistry described here facilitates construction of numerous cyclic biphenyl ether analogs of **2** by variation of the N-terminal substituent (R^1), the central amino acid (R^2), and the C-terminal substituent (R^3) of **2** in a combinatorial[16] fashion during the synthesis. Similar variation of the nucleophile **5** would lead to diverse libraries of substituted aromatic peptides.

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Supporting Information Available: Experimental details of peptide coupling, cyclization, and decomplexation (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(13) Polymers are common side products from the cyclization of medium-membered peptide ring systems. The outcome is sequence specific, sensitive to cyclization method used,[11b] and difficult to predict. See also: Pastuszak, J.; Gardner, J. H.; Singh, J.; Rich, D. H. *J. Org. Chem.* **1982**, *47*, 2982–2987.

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