Palladium-Mediated Macrocyclization on Solid Support and Its Applications to Combinatorial Synthesis

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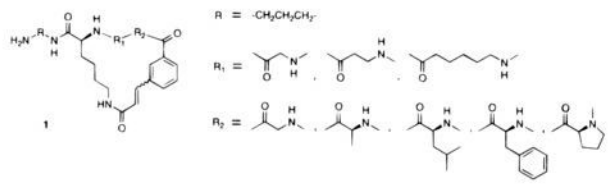
Recent revolutionary innovations in solid phase synthesis have provided access to libraries consisting of large numbers of structurally diverse organic compounds.[1] Peptide libraries,[2] derived from either chemical synthesis or molecular biological approaches, were the first to produce molecular diversity. The inherent limitations of using amino acids as building blocks in these libraries, however, have clearly restricted the scope of their applications as pharmacophores. The challenge to develop new synthetic strategies that will lead to molecularly diverse and drug-like small molecule libraries has emerged from these pioneering efforts.[3] Herein, we report a novel synthetic protocol which not only allows for the rapid and efficient generation of macrocyclic molecules **1** on solid support using modified Heck reaction conditions[4] but also has wide applicability to non-peptide combinatorial library synthesis.



A representative synthesis of **1** is outlined in Scheme 1. Treatment of Tenta Gel PHB resin[5] with carbonyldiimidazole furnished the corresponding imidazolide resin,[6] which was allowed to react with 1,3-diaminopropane to generate the amino-functionalized resin with an acid-labile carbamate linker. Orthogonally protected Fmoc-Lys(Dde)-OH was chosen as the first multifunctional building block. Utilizing well-developed Fmoc protecting group chemistry, this subunit provided ready access to differentially substituted R_1 and R_2 moieties. Palladium(0)-mediated macrocyclization employing catalytic $Pd(OAc)_2$ with Ph_3P and Bu_4NCl in a DMF/water/Et_3N solvent system proceeded smoothly at room temperature to provide **2** in 78% yield.[7] Notable features of this process are the remarkable reaction efficiency and mild reaction conditions. These qualities are evidenced by the exceptionally high purity and overall conversion of compound **2** obtained upon cleavage of the macrocycle from the resin (Figure 1). For example, only two peaks, which eluted at 4.4 and 5.4 min, were observed during HPLC-MS analysis of the crude reaction material with each displaying similar UV and identical MS properties. The two components, namely, the predominant *trans*- and minor *cis*-isomers, were unequivocally defined by ^1H NMR analysis of isolated **2**. To the best of our knowledge, this is the first demonstration of a Pd(0)-mediated carbon−carbon bond macrocyclization on a solid support.

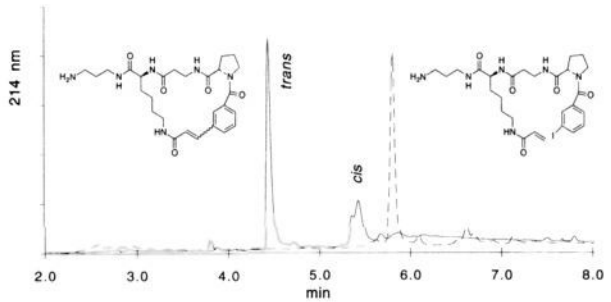
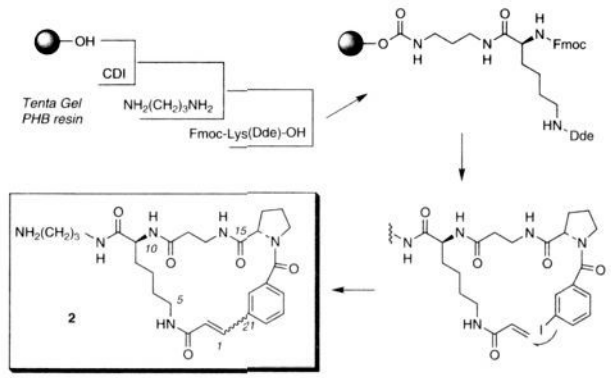


Figure 1. HPLC chromatograms of **2** prior to (dashed line) and after (solid line) cyclization.

Scheme 1. Outline of Synthesis of **2**



It is well-known that entropic factors are key in determining the overall yield of intramolecular cyclization processes. In solution, infinite dilution is the practical strategy to obtain reasonable reaction efficiency of the monomeric product. On solid support, the "pseudodilution" effect is attributed to some successful examples of macrocyclization by disulfide bond formation.[8] However, there is no general consensus regarding the optimum reaction conditions for solid phase macrocyclizations. These issues were addressed[9] in this system not only by using Gly, β-Ala, and ϵ-aminocaproic acid at the R_1 position to alter ring size but also by excluding proline at the R_2 position to eliminate a conformational restriction element. Surprisingly,

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(1) (a) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1232. Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385. (b) Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 10779.

(2) (a) Jung, G.; Beck-Sickinger, A. G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 367. (b) Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J. *Nature* **1991**, *354*, 82. (e) Eichler, J.; Houghten, R. A. *Nature* **1991**, *354*, 84. (d) Erb, E.; Janda, K. D.; Brenner, S. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 11422.

(3) (a) Pirrung, M. C.; Chen, J. *J. Am. Chem. Soc.* **1995**, *117*, 1240. (b) Kurth, M. J.; Randall, L. A.; Chen, C.; Melander, C.; Miller, R. B. *J. Org. Chem.* **1994**, *59*, 5862. (c) Kick, E. K.; Ellman, J. A. *J. Med. Chem.* **1995**, *38*, 1427. (d) Ohlmyer, M. H.; Swanson, R. N.; Dillard, L. W.; Reader, J. C.; Asouline, G.; Kobayshi, R.; Wigler, M.; Still, W. C. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 10922.

(4) (a) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, New York, 1991; Vol. 4, pp 833. (b) Heck, R. F. *Palladium Reagents in Organic syntheses*; Academic Press Inc.: London, 1987. (c) Jeffery, T. *Chem. Soc., Chem. Commun.* **1984**, 1287. Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667. Jeffery, T. *Tetrahedron Lett.* **1994**, *35*, 3051. (d) Yu, K.; Deshpande, M. S.; Vyas, D. M. *Tetrahedron Lett.* **1994**, *35*, 8919.

(5) Rapp, W.; *et al.* In *Proceeding of 2nd Symposium of Innovation and Perspectives in Solid Phase Synthesis*; Epton, R., Ed.; Oxford University Press: Canterbury, 1991.

(6) Hauske, J. R.; Dorff, P. *Tetrahedron Lett.* **1995**, *36*, 1589.

(7) The macrocyclization reaction was carried out in 0.01 M $Pd(OAc)_2$, 0.02 M PPh_3 and 0.02 M Bu_4NCl in DMF/H_2O/Et_3N (9/1/1 = v/v/v) at room temperature overnight. After the reaction was completed, the resin was filtered and washed extensively with DMF to remove any unbounded impurities. After drying under vacuum, the product was cleaved by a 50% TFA/47% CH_2Cl_2/3% anisole mixture at room temperature for 30 min, analyzed by HPLC-MS.

(8) Review: Andreu, D.; Albericio, F.; Sole, N. A.; Munson, M. C.; Ferrer, M.; Barany, G. *Methods Mol. Biol. (Totowa, N.J.)* **1994**, *35* (Peptide Synthesis Protocols), 91.

(9) (a) Virgilio, A. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11581. (b) Zhao, Z.; Felix, A. M. *Pept. Res.* **1994**, *7*, 218.

(10) Overall yields for the cyclized library products ranged from 75% to 85%. Full experimental procedures and total characterization of all compounds appear in the supporting information.

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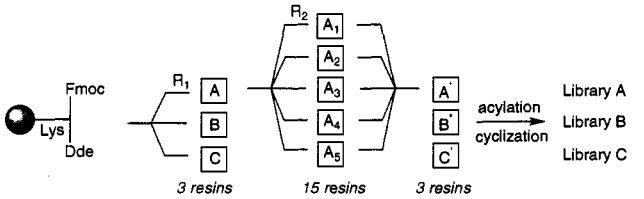
Scheme 2. Combinatorial Synthesis of Macrocyclized Libraries



these variations led to no observable difference in reaction yields. For example, all 15 compounds depicted in **1** were obtained in comparable yield and in high purity.[10] These observations support that the Pd(0)-mediated intramolecular macrocyclization reactions on solid support described in this report uniquely provide access to structurally diverse molecules generated from a wide variety of substrates.

The remarkable versatility of this Pd(0)-mediated cyclization protocol encouraged us to incorporate combinatorial steps into our synthesis. The array of diversity elements we can readily introduce into our synthesis, as well as the structural features of macrocyclic molecules, clearly provides an entry into a new source of structural variants suitable for random drug screening. For example, Scheme 2 illustrates the combinatorial protocol to generate **1** in three libraries. The Fmoc-L-Lys(Dde) resin was split into three pools for incorporation of the R_1 element, giving resin pools A, B, and C. Each of these pools was further partitioned into five portions for coupling at the R_2 position. The resulting five resins from pool A, *i.e.*, A_{1-5}, were combined to give pool A′, and subsequent steps provided library A consisting of equimolar amounts of five R_2 substituents. Libraries B and C were similarly produced using resin pools B and C. With this protocol, diversity was established at the R_2 position. Despite the structural intricacy of the library mixture, we were able to unambiguously confirm each component prior to and after cyclization. Representative HPLC chromatograms, together with the mass spectral data, are shown in Figure 2. Once again, we found that all generalities described in the previous section held for the combinatorial synthesis. In all three libraries, the cyclized compounds were obtained as mixtures of predominant *trans*- plus minor *cis*-isomers and exhibited the identical high purity and efficiency of the Pd(0)-mediated macrocyclization conducted on a single substrate.[10]

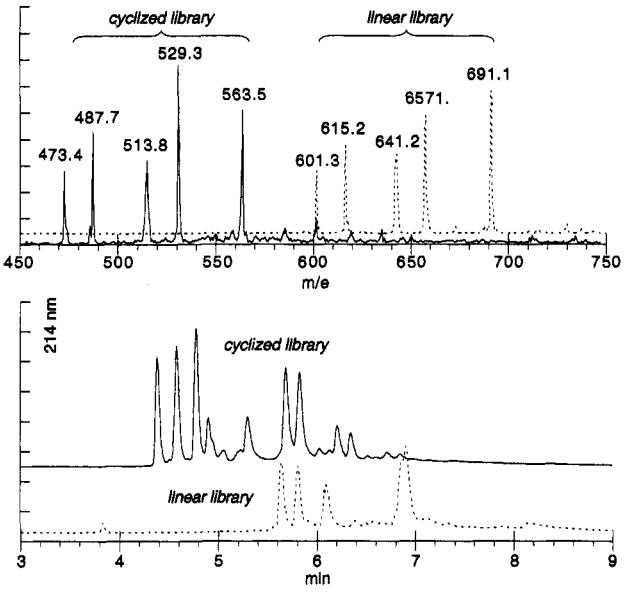


Figure 2. Mass spectra and HPLC chromatograms of linear and cyclized libraries.

In summary, we have developed a unique and versatile reaction system which allows the synthesis of macrocyclized targets containing 20−24 members effectively on solid support using a modified Heck reaction protocol. The mild reaction conditions and high yields allowed the direct application of this protocol to the efficient construction of a non-peptide combinatorial library.

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Supporting Information Available: Text description of experimental procedures, spectral data, and HPLC-MS of all cyclic molecules (24 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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