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Synthesis of cyclic peptides using a palladium-catalyzed enyne cycloisomerization☆

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Abstract—In this letter, we report a palladium-catalyzed enyne cycloisomerization of linear peptides to generate small cyclic peptides embedded with a conjugated 1,3-diene. The utility of these resulting macrocyclic dienes is demonstrated by carrying out [4+2] cycloadditions with dienophiles to generate constrained cyclic peptides with cyclic linkers.

Palladium-catalyzed coupling reactions are very efficient and reliable methods for the introduction of new carbon–carbon bonds.[1] Palladium-catalyzed Heck, Suzuki, Stille and Sonogashira reactions have already made significant impact in organic synthesis, whereas enyne cycloisomerization as developed by Trost is beginning to attract the attention of organic chemists for the synthesis of cyclic dienes[2,3] (Fig. 1). As part of an ongoing program in our laboratory on peptidomimetics,[4] we became interested in applying the palladium-catalyzed enyne cycloisomerization to incorporate a diene moiety into a macrocyclic structure, a functionality having significant synthetic application. The palladium-catalyzed enyne cycloisomerization generally results in a conjugated diene having two exocyclic double bonds (Fig. 1, path a). However, the studies demonstrated here show that cyclization of peptides results in a conjugated diene having exocyclic and endocyclic double bonds[5] (Fig. 1, path b) and our preliminary results on this useful isomerization are disclosed in this letter.

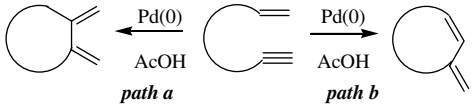
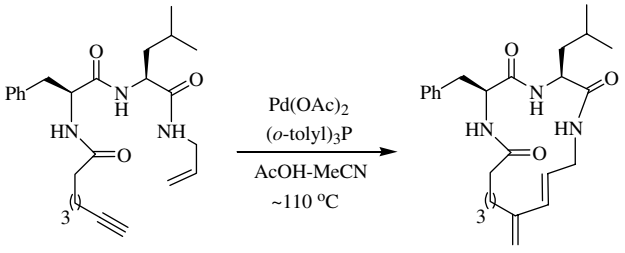


Figure 1. Pd-catalyzed enyne cycloisomerization.

We have synthesized an acyclic Phe-Leu dipetide **1** having an alkyne at the C-terminus and an alkene moiety at the N-terminus. The dipeptide **1** was subjected to palladium-catalyzed cycloisomerization conditions ($Pd(OAc)_2$, (o-tolyl)$_3$P, AcOH–MeCN) as reported by Trost et al.[5] To our delight, the macrocyclization was successful and the cyclic product was obtained in 28% yield (Scheme 1). However, the spectral data revealed that this reaction resulted in macrocyclic diene **2**. The *E*-stereochemistry of the endocyclic double bond and *s*-transoid form of the 1,3-diene were established using NMR data (1-D and 2-D), which is in accordance with the literature.[6,7] To our knowledge the palladium-catalyzed enyne cycloisomerization to form macrocycles/cyclic peptides has not been reported, previously.



1 **2** (28%)

Scheme 1.

Keywords: Peptidomimetics; Enyne cycloisomerization; Cyclic peptide; Diels–Alder reaction.

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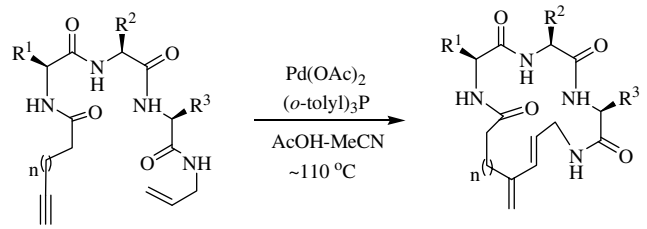


3a. $R^1 = -CH_2Ph$, $R^2 = -CH_2CH(CH_3)_2$, $R^3 = -CH_3$, n = 1 — **4a** (33%)

3b. $R^1 = -CH_2Ph$, $R^2 = -CH_2CH(CH_3)_2$, $R^3 = -CH_3$, n = 2 — **4b** (45%)

3c. $R^1 = -CH_2Ph$, $R^2 = -CH_2CH(CH_3)_2$, $R^3 = -CH_3$, n = 3 — **4c** (54%)

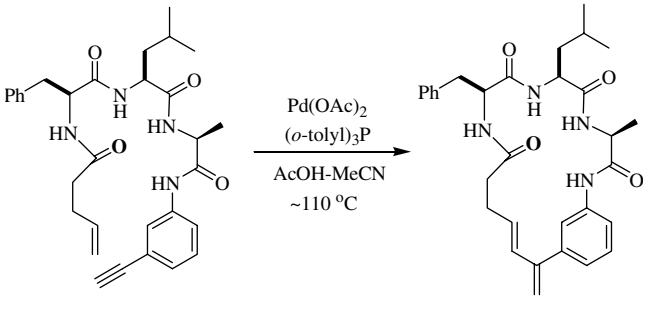
3d. $R^1 = -CH_2Ph$, $R^2 = -CH(CH_3)_2$, $R^3 = -CH_3$, n = 1 — **4d** (40%)

3e. $R^1 = -CH(CH_3)CH_2CH_3$, $R^2 = -CH(CH_3)_2$, $R^3 = -CH_2Ph$, n = 1 — **4e** (46%)

Scheme 2.

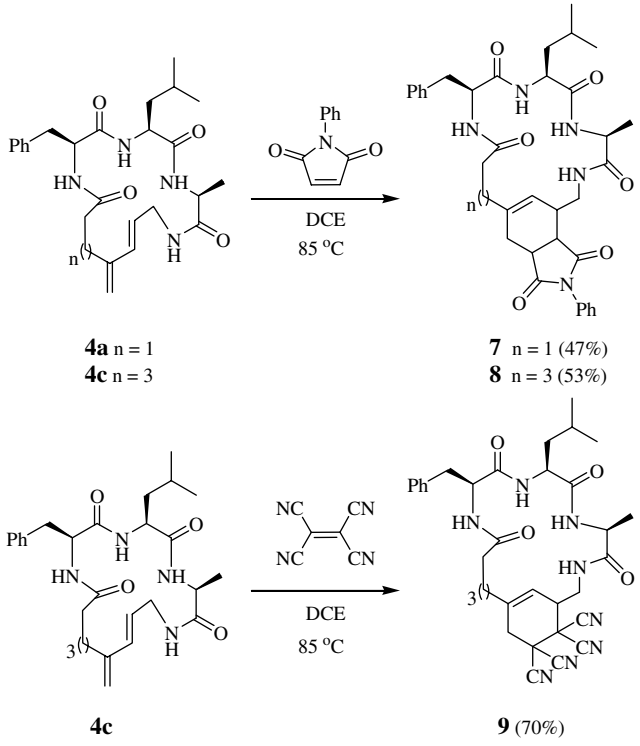
Next, we synthesized acyclic tripeptides **3a**–**e** by varying the chain length and the amino acids. All the linear peptides were synthesized using standard solution-phase peptide coupling procedures.[8] The tripeptides **3a**–**e** underwent cycloisomerization smoothly to furnish the desired macrocycles **4a**–**e** in fair yields.[9] We anticipated that the linker length might play a role in the *E*,*Z*-selectivity of the endocyclic double bond, but only *E*-isomers were observed in all cases. The change in amino acids had little or no effect on the reaction (Scheme 2). The acyclic tripeptide **5** was synthesized by switching the alkyne to the N-terminus and alkene moiety to the C-terminus. The cycloisomerization of **5** produced cyclic peptide **6** in good yield.[10] It is noteworthy that the rigid aryl acetylene linker had no effect on the cycloisomerization or the geometry of the endocyclic double bond of the resulting cyclic peptide (Scheme 3).

The cyclic peptides formed during the cycloisomerization possess a conjugated 1,3-diene moiety, a functional group with several potential synthetic applications.[11]



5 **6** (49%)

Scheme 3.



4a n = 1
4c n = 3

7 n = 1 (47%)
8 n = 3 (53%)

4c

9 (70%)

Scheme 4.

We attempted the Diels–Alder reaction on these compounds to demonstrate the synthetic utility of the conjugated diene present in these cyclic peptides. The reactive dienophile *N*-phenylmaleimide was refluxed with macrocyclic diene **4a** in dicholoroethane (DCE) to give compound **7** in a 1:1 diastereomeric ratio.[12] Similarly, macrocyclic diene **4c** reacted with *N*-phenylmaleimide and tetracyanoethylene to produce the corresponding adducts **8** and **9**, respectively, in moderate to good yields[13] (Scheme 4).

In conclusion, we have demonstrated the utility of palladium-catalyzed enyne cycloisomerization during the macrocyclization of linear peptides to furnish constrained small cyclic peptides with novel linkers. The resulting macrocycles having a 1,3-diene moiety can be used for further functionalization to generate a variety of linkers leading to useful peptidomimetics. We also demonstrated the Diels–Alder reaction of these cyclic dienes in several cases by reacting with dienophiles.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.053.

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9. Typical procedure for cycloisomerization: 40 mol % of $Pd(OAc)_2$, and 80 mol % of $(o\text{-tolyl})_3P$ were added to warm HPLC grade acetonitrile (1.5×10^{-3} M) and the solution refluxed at 110 °C for 30 min. Then, glacial acetic acid (10 equiv) was added to the refluxing solution. After 10 min the acylic peptide (500 mg) was added in a single portion and the reaction continued for 15 h at the same temperature. The reaction mixture was filtered through a pad of Celite and washed with hot acetonitrile (100 ml). The filtrate was concentrated and the product was isolated by flash column chromatography on silica gel using CH_2Cl_2/MeOH (98/2) as eluent.
10. All new compounds were characterized from spectral data. See, Supporting information for details.
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12. The Diels–Alder adduct **9** was isolated as a diastereomeric mixture.
13. The diastereomers (1:1) formed in these reaction were cleanly separated using column chromatography. The stereochemistry of the substituents on the newly formed cyclohexene ring were not assigned.