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Synthesis of Cyclic Peptides Constrained with Biarylamine Linkers Using Buchwald−Hartwig C−N Coupling[#]

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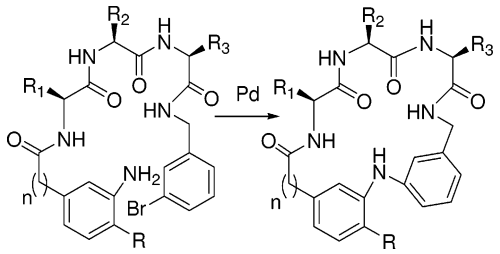

In this paper, we describe the synthesis of conformationally constrained cyclic peptides with biarylamine linkers for peptidomimetics using palladium-catalyzed intramolecular Buchwald−Hartwig C−N coupling. We have prepared a variety of di-, tri-, and tetrapeptides (16−22-membered) in good yields using this reaction.

Constraining of the linear peptides into more defined conformational structures (cyclic peptidomimetics) through cyclization is an actively pursued area of research.[1] During the past few decades, great effort has been made to develop more efficient methods for the synthesis of cyclic peptides and peptidomimetics, as potential drug leads and/or as models for conformational analysis.[2] As part of the ongoing program in our laboratory on peptidomimetics, we have developed various palladium-catalyzed C−C bond forming cyclization strategies, such as Heck, Sonogashira, and Trost-enyne cycloisomerizations.[3] In continuation to our earlier efforts, we were interested in studying carbon−nitrogen bond forming reactions, such as Buchwald−Hartwig coupling,[4] during the final cyclization step. This results in introduction of biarylamine linkers into macrocyclic peptides which may be useful as peptidomimetics.[5] The biarylamine moiety also mimics the biaryl ether moiety present in a variety of naturally occurring cyclic peptides and peptidomimetics, such as the glycopeptide antibiotics vancomycin, teicoplanin, and ristocetin A, which are highly effective and widely used clinical agents for bacterial infections (see Figure 1).[6] Here, we are describing the utility of palladium-catalyzed Buchwald−Hartwig C−N coupling reaction in cyclization of linear peptides. This is the first report of such cyclization.

Initially, we have prepared an acyclic tripeptide precursor **3** following standard solution chemistry,[7] as described in Scheme 1. The bromo compound **1** was prepared from N-Boc-Ala-OH and 3-bromobenzylamine and was transformed to tripeptide **2** by repeating the sequence of Boc deprotection followed by peptide coupling using the N-protected amino acids (N-Boc-Val-OH and N-Boc-Phe-OH). Boc deprotection on compound **2** followed by coupling with the N-Boc-3-aminobenzoic acid moiety and treatment with TFA in dichloromethane furnished the acyclic peptide precursor **3** in very good yield. Having the acyclic precursor **3** in hand, we next attempted the macrocyclization to form a cyclic peptide with a biarylamine linker under various Pd-catalyzed Buchwald−Hartwig reaction conditions

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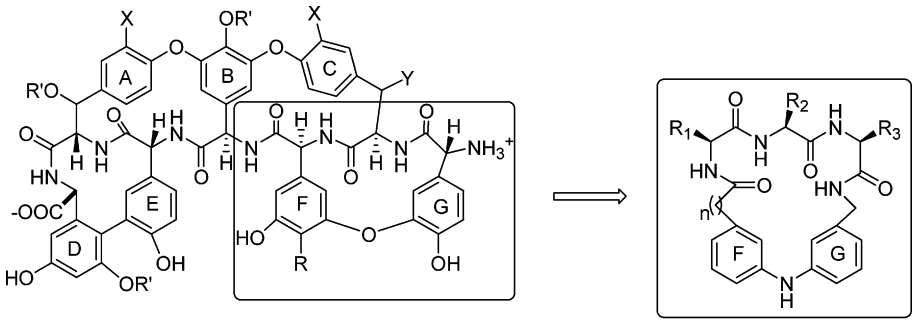
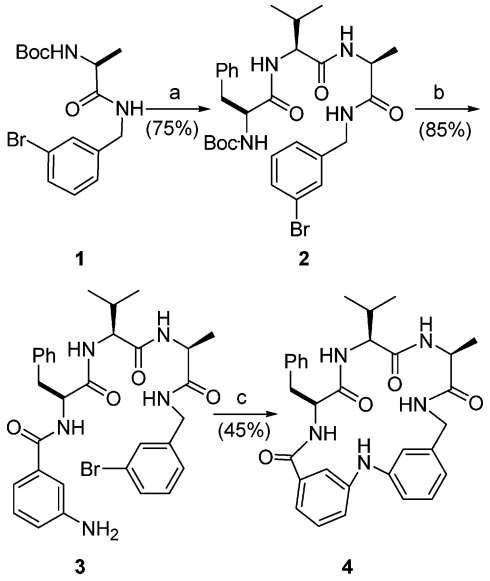


I. TEICOPLANIN : X = Cl; Y = H; R = H (R' = sugar unit)
II. RISTOCETIN A: X = H; Y = OH; R =Me (R' = sugar unit)

FIGURE 1. Biarylamine peptidomimetics of the glycopeptide antibiotic teicoplanin FG ring biaryl ether system.

SCHEME 1[a]



[a] Conditions: (a) (i) TFA/DCM; (ii) N-Boc-Val-OH, Et_3N, HOBt, EDC, DCM; (iii) TFA/DCM; (iv) N-Boc-Phe-OH, Et_3N, HOBt, EDC, DCM; (b) (i) TFA/DCM; (ii) 3-Boc-aminobenzoic acid, Et_3N, HOBt, EDC, DCM; (iii) TFA/DCM; (c) $Pd(OAc)_2$, BINAP, ^{t}BuOK, CH_3CN, 100 °C, 15 h.

reported in the literature. After several attempts, macrocyclization in refluxing acetonitrile with 30 mol % of $Pd(OAc)_2$, 40 mol % of *rac*-BINAP ligand, and ^{t}BuOK as base was found to be the optimized conditions to obtain biarylamine containing cyclic peptides in moderate to good yields.

Subsequently, these optimized conditions were successfully employed for the synthesis of 19−21-membered macrocyclic peptides from their corresponding acyclic peptides **3a**−**c**, and the results are summarized in Scheme 2. Acyclic peptides **3a** and **3c** cyclized smoothly to give cyclic peptides **4a** and **4c** in good yields. Surprisingly, under similar conditions ($Pd(OAc)_2$, *rac*-BINAP, ^{t}BuOK, CH_3CN), compound **3b** where $n = 1$ produced regioisomeric cyclic peptides **4b** and **5b** in the ratio of 1:3 in 54% overall yield. Formation of these regioisomeric cyclic peptides can be explained via a benzyne intermediate mechanism as reported by a Chinese group.[8] This unusual behavior observed during the cyclization of compound **3b** may be attributed to the formation of a benzyne intermediate, and probably, the size and/or conformation of the peptide are dictating the possible nucleophilic attack on either side of benzyne to give compounds **4b** and **5b**.

To minimize the formation of unwanted cyclic compound **5b**, we have replaced the ^{t}BuOK with a milder base, Cs_2CO_3, and we found that desired macrocycle **4b** is formed exclusively in good yields in the cyclization of **3b**. The scope of this Buchwald−Hartwig reaction was tested with different acyclic peptides with varying size and amino acids to give corresponding cyclic peptides (Scheme 3). We also observed that slightly better yields were obtained in the case of 20/21-membered cyclic peptides, when compared to that of 19-membered cyclic peptides.

For the synthesis of smaller-sized 16-membered cyclic peptides, acyclic peptides **6** and **8** were prepared and subjected to the above Buchwald−Hartwig reaction conditions using Cs_2CO_3 as base to furnish cyclic peptides **7** and **9**, respectively, in very good yields. We further extended our Buchwald−Hartwig cyclization method to synthesize 22-membered cyclic tetrapeptide **11** successfully in a yield of 20% (Scheme 4).

In conclusion, we have demonstrated that the Buchwald−Hartwig C−N coupling reaction can be employed for the macrocyclization of di-, tri-, and tetrapeptides to produce corresponding cyclic peptides with biarylamine linkers. These cyclic peptides may prove to be useful in understanding the utility of constrained structures in the search for novel lead molecules.

Experimental Section

Typical Procedure for Intramolecular Buchwald−Hartwig C−N Coupling for 4a: *rac*-BINAP (200 mg, 0.32 mmol) was added to gradient acetonitrile and heated to 80 °C with stirring until the BINAP dissolved (∼15 min). The mixture was cooled to room temperature, and $Pd(OAc)_2$ (54 mg, 0.24 mmol) was added. The mixture was stirred at room temperature for 15 min, and then acyclic peptide **3a** (500 mg, 0.80 mmol) and base (^{t}BuOK, 180 mg, 1.6 mmol or Cs_2CO_3, 1.04 g, 3.21 mmol) were added. The mixture was heated at 100 °C (oil bath temperature) for 15−20 h. The solvent was evaporated under vacuum, and crude product was

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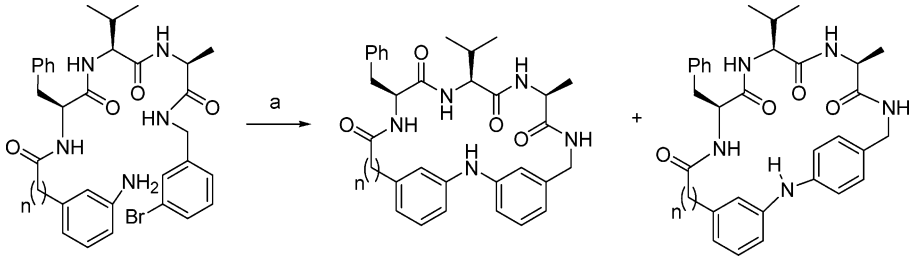
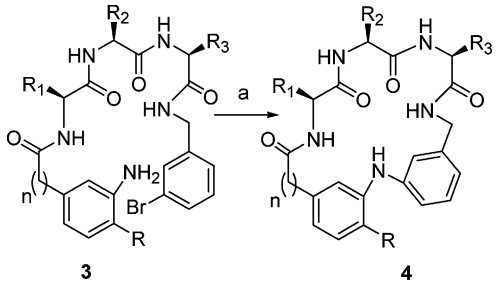
SCHEME 2 [a]



[a] Conditions: (a) $Pd(OAc)_2$, *rac*-BINAP, ^tBuOK, CH_3CN, 100 °C, 15 h.

SCHEME 3 [a]



3 **4**

3a R = H, R_1 = -CH_2Ph, R_2 = -$CH(CH_3)_2$, R_3 = -CH_3, n = 0 **4a** (42%)

3b R = H, R_1 = -CH_2Ph, R_2 = -$CH(CH_3)_2$, R_3 = -CH_3, n = 1 **4b** (50%)

3c R = H, R_1 = -CH_2Ph, R_2 = -$CH(CH_3)_2$, R_3 = -CH_3, n = 2 **4c** (53%)

3d R = H, R_1 = -CH_2Ph, R_2 = -CH_3, R_3 = -$CH_2CH(CH_3)_2$, n = 0 **4d** (44%)

3e R = H, R_1 = -CH_2Ph, n = 0, R_2 = -$CH_2CH(CH_3)_2$, R_3 = -CH_3 **4e** (41%)

3f R = H, R_1 = -CH_2Ph, n = 0, R_2 = -$CH(CH_3)CH_2CH_3$, R_3 = -CH_3 **4f** (46%)

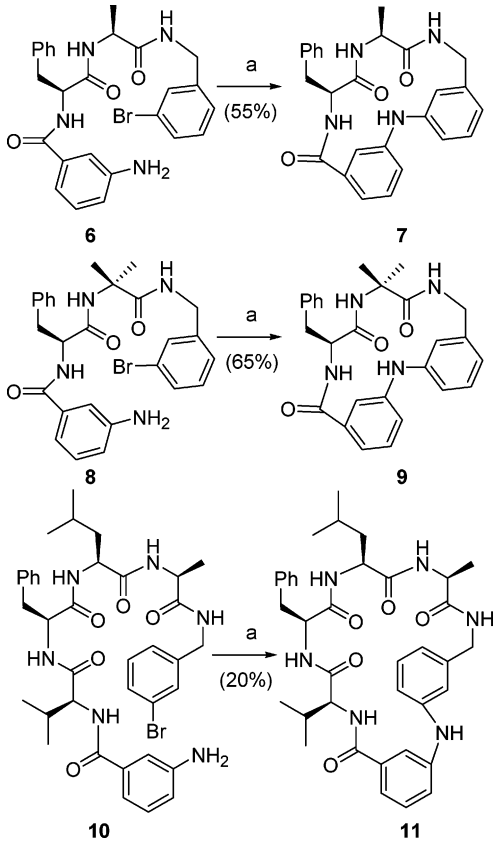
3g R = H, R_1 = -$CH(CH_3)_2$, n = 0, R_2 = -$CH_2CH(CH_3)_2$, R_3 = -CH_3 **4g** (36%)

3h R = CH_3, R_1 = -CH_2Ph, n = 0, R_2 = -$CH(CH_3)_2$, R_3 = -CH_3 **4h** (29%)

[a] Conditions: (a) $Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3, CH_3CN, 100 °C, 15 h.

subjected to column chromatography on 230−400 mesh silica gel using $CHCl_3/CH_3OH$ (98:2) to isolate the desired cyclic peptide **4a** as a solid (yield 42%): mp 177−179 °C; $[\alpha]^{20}_D$ −50.8° (*c* 0.25, DMSO); IR (KBr) ν 3310, 2962, 1654, 1590, 1525 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.70 (d, J = 6.45 Hz, 1H), 8.33 (s, 1H), 8.27−8.20 (m, 1H), 7.54 (d, J = 8.06 Hz, 1H), 7.69 (s, 1H), 7.40−7.12 (m, 10H), 7.02 (dd, J_1 = 1.34 Hz, J_2 = 2.41 Hz, 1H), 6.77 (dd, J_1 = 2.14 Hz, J_2 = 8.06 Hz, 1H), 6.70 (d, J = 6.71 Hz, 1H), 4.75 (q, J = 6.71 Hz, 1H), 4.26−4.11 (m, 3H), 3.98 (dd, J_1 = 6.17 Hz, J_2 = 15.23 Hz, 1H), 3.09 (dd, J_1 = 7.79 Hz, J_2 = 13.43 Hz, 1H), 2.96 (dd, J_1 = 7.79 Hz, J_2 = 13.43 Hz, 1H), 2.24−2.20 (m, 1H), 1.25 (d, J = 7.25 Hz, 3H), 0.67 (d, J = 6.72 Hz, 3H), 0.58

SCHEME 4 [a]



6 **7** **8** **9** **10** **11**

[a] Conditions: (a) $Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3, CH_3CN, 100 °C, 15 h.

(d, J = 6.98 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 172.3, 171.4, 170.5, 167.9, 143.1, 142.9, 141.1, 137.6, 134.7, 129.4 (2C), 129.0, 128.8, 128.1 (2C), 126.3, 126.1, 121.1, 119.6, 118.3, 117.1, 113.6, 57.5, 55.9, 48.0, 42.5, 36.4, 28.0, 19.1, 18.4, 16.7; ES-MS *m*/*z* calcd for $C_{31}H_{35}N_5O_4$ 541, found 542 ($M^{+\bullet}$ + 1, 100).

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Supporting Information Available: Experimental details of compounds, characterization data, and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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