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A Synthesis of RGD Model Cyclic Peptide by Palladium-Catalyzed Carbonylative Macrolactamization

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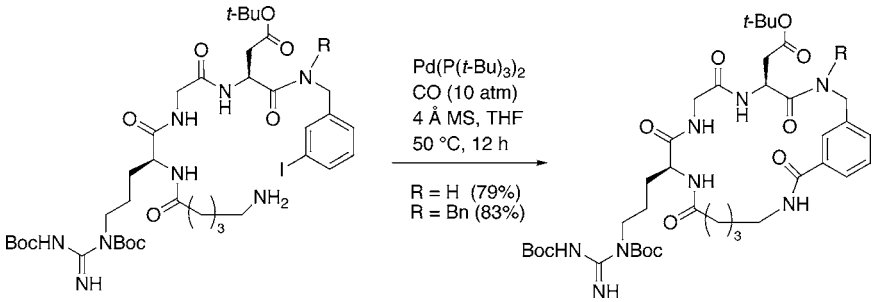
ABSTRACT



Cyclic peptidic RGD models were efficiently synthesized by Pd(P(*t*-Bu)$_3$)$_2$-catalyzed carbonylative macrolactamization in the presence of 4 Å molecular sieves under 10 atm of carbon monoxide.

Peptidomimetics are important for drug discovery, especially macrocyclic ones that are useful to find potent drug candidates by precise tuning of their conformation.[1] Several approaches to construction of the macrocyclic peptide mimetics have been reported, such as S_N2 alkylation with *S*-nucleophiles,[2,3] S_NAr macrocyclization,[3] alkene metathesis,[4] Mizoroki−Heck reaction,[5] Suzuki coupling,[6] Sonogashira coupling,[7] (3 + 2)-cycloaddition,[8] radical cyclization,[9] and ene−yne cycloisomerization.[10]

Recently, we reported palladium-catalyzed carbonylation is a powerful reaction in a combinatorial library synthesis. Both carbonylative amidation and esterification were performed on solid phase, utilizing various alkenyl iodides, alkenyl bromides, aryl iodides, and aryl triflates that are good

(1) Kahn, M. *Synlett* **1993**, 821−826.
(2) Barker, P. L.; Bullens, S.; Bunting, S.; Burdick, D. J.; Chan, K. S.; Deisher, T.; Eigenbrot, C.; Gadek, T. R.; Gantzos, R.; Lipari, M. T.; Muir, C. D.; Napier, M. A.; Pitti, R. M.; Padua, A.; Quan, C.; Stanley, M.; Struble, M.; Tom, J. Y. K.; Burnier, J. P. *J. Med. Chem.* **1992**, *35*, 2040−2048.
(3) (a) Burgess, K. *Acc. Chem. Res.* **2001**, *34*, 826−835. (b) Lee, H. B.; Pattarawarapan, M.; Roy, S.; Burgess, K. *Chem. Commun.* **2003**, 1674−1675. (c) Reyes, S. J.; Burgess, K. *Tetrahedron: Asymmetry* **2005**, *16*, 1061−1069.
(4) (a) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606−9614. (b) Clark, T. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1995**, *117*, 12364−12365. (c) Pernerstorfer, J.; Schuster, M.; Blechert, S. *Chem. Commun.* **1997**, 1949−1950. (d) Ripka, A. S.; Bohacek, R. S.; Rich, D. H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 357−360. (e) Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 4334−4344. (f) Reichwein, J. F.; Wels, B.; Kruijtzer, J. A. W.; Versluis, C.; Liskamp, R. M. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3684−3687. (g) Schafmeister, C. E.; Po, J.; Verdine, G. L. *J. Am. Chem. Soc.* **2000**, *122*, 5891−5892. (h) Rajesh, S.; Banerji, B.; Jqbal, J. *J. Org. Chem.* **2002**, *67*, 7852−7857. (i) Martin, W. H. C.; Blechert, S. *Curr. Top. Med. Chem.* **2005**, *5*, 1521−1540.
(5) (a) Akaji, K.; Teruya, K.; Akaji, M.; Aimoto, S. *Tetrahedron* **2001**, *57*, 2293−2303. (b) Reddy, P. R.; Balraju, V.; Madhavan, G. R.; Banerji, B.; Iqbal, J. *Tetrahedron Lett.* **2003**, *44*, 353−356.
(6) Li, W.; Burgess, K. *Tetrahedron Lett.* **1999**, *40*, 6527−6530.
(7) (a) Spivey, A. C.; McKendrick, J.; Srikaran, R.; Helm, B. A. *J. Org. Chem.* **2003**, *68*, 1843−1851. (b) Balraju, V.; Reddy, S.; Periasamy, M.; Iqbal, J. *J. Org. Chem.* **2005**, *70*, 9626−9628. (c) ten Brink, H. T.; Rijkers, D. T. S.; Liskamp, R. M. J. *J. Org. Chem.* **2006**, *71*, 1817−1824.
(8) (a) Angell, Y.; Burgess, K. *J. Org. Chem.* **2005**, *70*, 9595−9598. (b) Bock, V. D.; Perciaccante, R.; Jansen, P.; Hiemstra, H.; van Maarseveen, J. H. *Org. Lett.* **2006**, *8*, 919−922.

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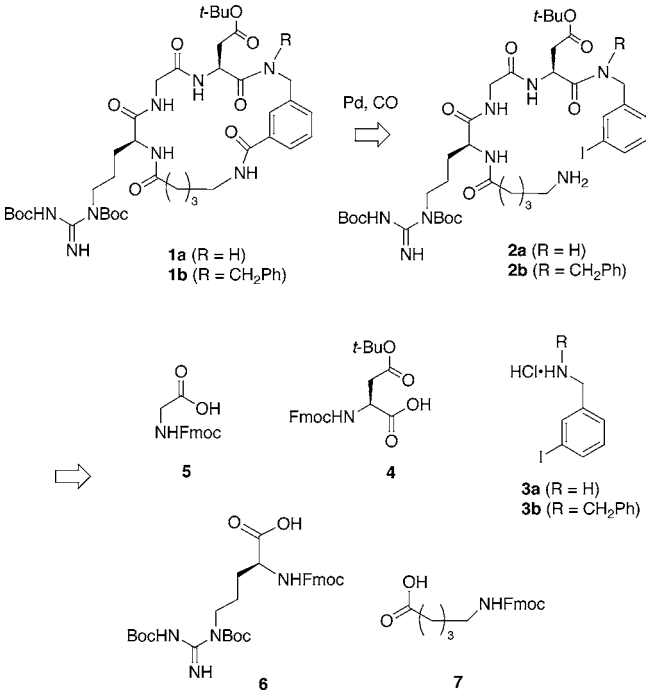
Scheme 1. Strategy for the Synthesis of Cyclic RGD Model **1**

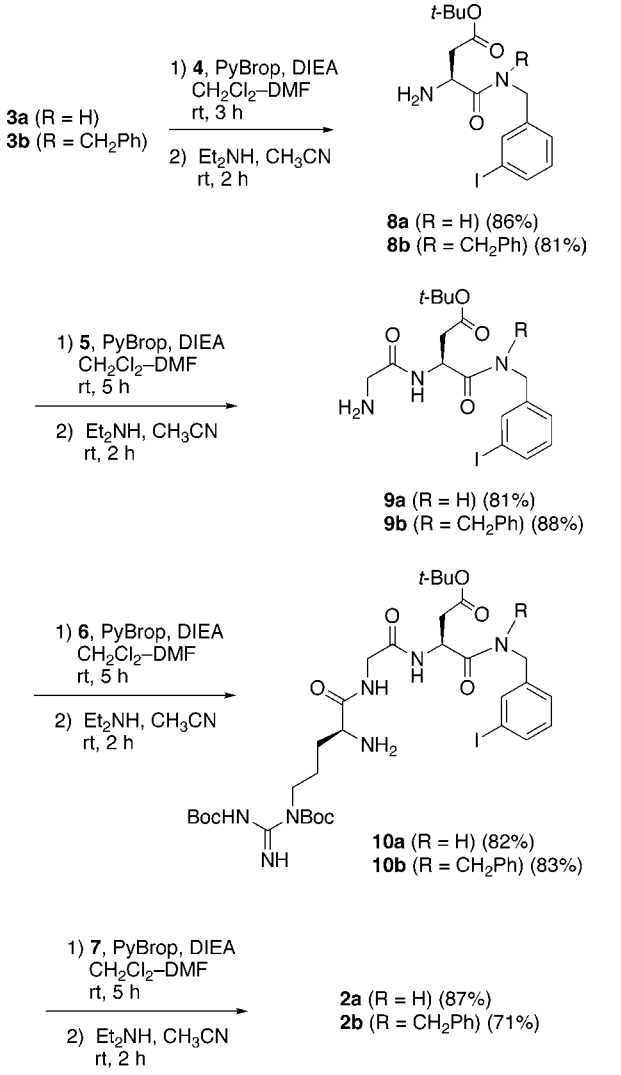


precursors as masked activated esters.[11] It was also applied to the construction of macrocyclic lactones.[12,13] For example, we reported a combinatorial synthesis of a 128-member macrosphelide library, utilizing palladium-catalyzed carbonylative macrolactonization on solid-phase.[11d] We report an efficient synthesis of cyclic peptidic RGD models utilizing palladium-catalyzed carbonylative macrolactamization.

Cyclic RGD models have been studied as a selective integrin receptor antagonist.[2,3,14] We designed RGD peptidomimetics **1** that contain a RGD sequence, an (aminomethyl)benzoic acid, and an ω-amino acid. Assembly of (aminomethyl)benzoic acids substituted at the ortho, meta, and para positions and ω-amino acids with different numbers of the methylene unit would lead to a variety of cyclic RGD models. As a part of the synthesis of a combinatorial library of cyclic RGD models, we initially planned the syntheses of **1a** (R = H) and **1b** (R = CH_2Ph), containing *m*-(aminomethyl)benzoic acids[14d,15] and ω-aminovaleric acid. Synthetic strategy for **1** is illustrated in Scheme 1. The cyclic peptide **1** can be synthesized by palladium-catalyzed carbonylative macrolactamization of **2**. It would be of interest to know the effect of the R-substituent in **2** in this cyclization. The cyclization precursor **2** would be prepared by sequential amidation of *m*-iodobenzylamines **3**, Fmoc-Asp(O*t*-Bu)-OH (**4**), Fmoc-Gly-OH (**5**), Fmoc-Arg(Boc)$_2$-OH (**6**), and *N*-Fmoc-ω-aminovaleric acid (**7**).

The cyclization precursors **2** were prepared as shown in Scheme 2. Coupling of amine **3a** and Fmoc-Asp(O*t*-Bu)-OH (**4**) was performed using PyBrop-diisopropylethylamine (DIEA) in CH_2Cl_2−DMF (9:1) at ambient temperature.[16] Removal of the Fmoc group using diethylamine in acetoni-

Scheme 2. Synthesis of Cyclization Precursors **2**



(9) Balraju, V.; Reddy, S.; Periasamy, M.; Iqbal, J. *Tetrahedron Lett.* **2005**, *46*, 5207−5210.

(10) Balraju, V.; Dev, R. V.; Reddy, D. S.; Iqbal, J. *Tetrahedron Lett.* **2006**, *47*, 3569−3571.

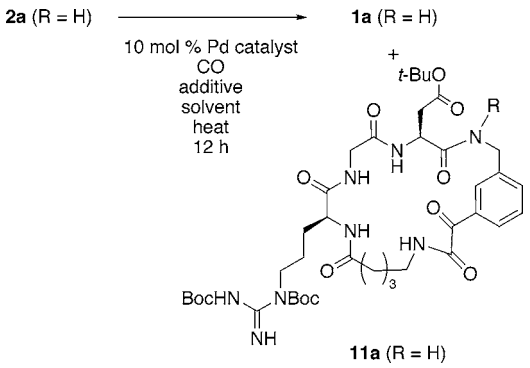
(11) (a) Takahashi, T.; Inoue, H.; Tomida, S.; Doi, T.; Bray, A. *Tetrahedron Lett.* **1999**, *40*, 7843−7846. (b) Takahashi, T.; Inoue, H.; Yamamura, Y.; Doi, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 3230−3233. (c) Hashimoto, M.; Mori, A.; Inoue, H.; Nagamiya, H.; Doi, T.; Takahashi, T. *Tetrahedron Lett.* **2003**, *44*, 1251−1254. (d) Takahashi, T.; Kusaka, S.; Doi, T.; Sunazuka, T.; Omura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5230−5234. (e) Doi, T.; Inoue, H.; Tokita, M.; Watanabe, J.; Takahashi, T. *J. Comb. Chem.* **2008**, *10*, 135−141.

(12) (a) Takahashi, T.; Nagashima, T.; Tsuji, J. *Chem. Lett.* **1980**, 369−372. (b) Takahashi, T.; Ikeda, H.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3885−3888.

(13) Lu, S.-M.; Apler, H. *Chem. Eur. J.* **2007**, *13*, 5908−5916.

(14) (a) Aumailley, M.; Gurrath, M.; Müller, G.; Calvete, J.; Timpl, R.; Kessler, H. *FEBS Lett.* **1991**, *291*, 50−54. (b) Lender, A.; Yao, W. Q.; Sprengeler, P. A.; Spanevello, R. A.; Furst, G. T.; Hirschmann, R.; Smith, A. B., III. *Int. J. Peptide Protein Res.* **1993**, *42*, 509−517. (c) Cheng, S.; Craig, W. S.; Mullen, D.; Tschopp, J. F.; Dixon, D.; Pierschbacher, M. D. *J. Med. Chem.* **1994**, *37*, 1−8. (d) Jackson, S.; DeGrado, W.; Dwivedi, A.; Parthasarathy, A.; Higley, A.; Krywko, J.; Rockwell, A.; Markwalder, J.; Wells, G.; Wexler, R.; Mousa, S.; Harlow, R. *J. Am. Chem. Soc.* **1994**, *116*, 3220−3230. (e) Haubner, R.; Gratias, R.; Diefenbach, B.; Goodman, S. L.; Jonczyk, A.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 7461−7472. (f) Dechantsreiter, M. A.; Planker, E.; Mathä, B.; Lohof, E.; Hölzemann, G.; Jonczyk, A.; Goodman, S. L.; Kessler, H. *J. Med. Chem.* **1999**, *42*, 3033−3049. (g) Oishi, S.; Kamano, T.; Niida, A.; Odagaki, Y.; Hamanaka, N.; Yamamoto, M.; Ajito K.; Tamamura, H.; Otaka, A.; Fujii, N. *J. Org. Chem.* **2002**, *67*, 6162−6173.

Scheme 3. Palladium-Catalyzed Carbonylative Macrocyclization of **2a**



trile afforded **8a** (R = H) in 86% yield.[17] Sequential peptide elongation with Fmoc-Gly-OH (**5**), Fmoc-Arg(Boc)$_2$-OH (**6**), and *N*-Fmoc-ω-aminovaleric acid (**7**) under the same reaction conditions described above provided **2a** in good yield. *N*-Benzyl derivative **2b** was also prepared from *N*-benzyl-*m*-iodobenzylamine (**3b**) in a similar manner.

Palladium-catalyzed carbonylative macrolactamization of **2a** was investigated (Table 1). We initially compared the

Table 1. Optimization of Palladium-Catalyzed Carbonylative Macrocyclization of **2a**

entry	Pd catalyst	additives	CO (atm)	solvent	temp (°C)	yield (%) **1a** (**11a**)
1	Pd(P(*t*-Bu)$_3$)$_2$	NEt$_3$-DMAP	10	DMF	50	41
2	POPd	NEt$_3$-DMAP	10	DMF	50	12
3	Pd(PPh$_3$)$_4$	NEt$_3$-DMAP	10	DMF	50	9
4	Pd(P(*t*-Bu)$_3$)$_2$	3 Å MS	10	DMF	50	49
5	Pd(P(*t*-Bu)$_3$)$_2$	4 Å MS	10	DMF	50	64(7)
6	Pd(P(*t*-Bu)$_3$)$_2$	Ag$_2$CO$_3$	10	DMF	50	51
7	Pd(P(*t*-Bu)$_3$)$_2$	TMEDA	10	DMF	50	21
8	Pd(P(*t*-Bu)$_3$)$_2$	4 Å MS	5	DMF	50	43(trace)
9	Pd(P(*t*-Bu)$_3$)$_2$	4 Å MS	20	DMF	50	61(9)
10	Pd(P(*t*-Bu)$_3$)$_2$	4 Å MS	30	DMF	50	63(7)
11	Pd(P(*t*-Bu)$_3$)$_2$	4 Å MS	10	THF	50	79(9)
12	Pd(P(*t*-Bu)$_3$)$_2$	4 Å MS	10	NMP	50	32
13	Pd(P(*t*-Bu)$_3$)$_2$	4 Å MS	10	DMPU	50	41
14	Pd(P(*t*-Bu)$_3$)$_2$	4 Å MS	10	1,4-dioxane	50	trace
15	Pd(P(*t*-Bu)$_3$)$_2$	4 Å MS	10	THF	40	49
16	Pd(P(*t*-Bu)$_3$)$_2$	4 Å MS	10	THF	65	21

effect of palladium-catalysts [Pd(P(*t*-Bu)$_3$)$_2$,[18] POPd,[19] Pd(PPh$_3$)$_4$]. The reaction was carried out in the presence of 10 mol % of the Pd-catalyst with NEt$_3$−DMAP in DMF at 50 °C for 12 h under CO (10 atm). The starting material was completely consumed when Pd(P(*t*-Bu)$_3$)$_2$ was used as a catalyst. The desired product **1a** was obtained in 41% yield (entry 1). POPd and Pd(PPh$_3$)$_4$ are less effective (12%, 9% yield, entries 2 and 3). Probably, P(*t*-Bu)$_3$ ligand electronically and sterically accelerates both the oxidative addition of **2a** to palladium(0) and final reductive elimination in the formation of amide **1a**.

Because the Boc group was partially removed under the above reaction conditions, we examined the effect of various additives in place of NEt$_3$−DMAP (3 Å MS, 4 Å MS, Ag$_2$CO$_3$, TMEDA). Actually, the yield was dramatically affected by the base, and the use of 4 Å MS increased the yield up to 64% (entry 5), and the Boc group was sustained.[20] A small amount of double carbonylated product **11a** was detected by LC−MS (7%).[21] Then, the effect of CO pressure was investigated. When the reaction was carried out under 5 atm of CO, the reaction was not complete, but only a trace amount of **11a** was observed (entry 8). On the other hand, no effect of the higher pressure of CO under 20 and 30 atm was observed (entries 9 and 10 vs entry 5).

The solvent effect was found to be crucial. It was found that THF is an effective solvent in this reaction. The yield of **1a** increased to 79%, and double carbonylative product **11a** was also observed in 9% yield (entry 11 vs entries 5, 12, 13, and 14). Interestingly, the desired reaction did not proceed in 1,4-dioxane (entry 14). The reaction temperature is also important to control the reaction. The reaction was not complete at 40 °C (entry 15), whereas removal of the Boc group was observed at 65 °C (entry 16).

Using the optimized reaction conditions, we performed cyclization of *N*-benzyl derivative **2b**. The palladium-catalyzed carbonylative macrolactamization efficiently proceeded [Pd(P(*t*-Bu)$_3$)$_2$ (10 mol %)/CO (10 atm)/4 Å MS/THF/50 °C/12 h] to furnish the desired **1b** in 83% yield. Since the double carbonylation product was not detected, it was found that the *N*-benzyl substituent in **2b** suppresses the double carbonylation.

In conclusion, we have demonstrated the palladium-catalyzed carbonylative macrolactamization of **2a** and **2b** in the synthesis of RGD cyclic peptide mimetics **1a** and **1b**. The reaction of *N*-benzyl group **2b** provided **1b** in better yield than in **2a**. It was suggested that the *N*-benzyl group can be effectively utilized as a linker on solid-phase toward a combinatorial library synthesis of various RGD cyclic models.

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Supporting Information Available: Experimental details, NMR spectra of **8a**−**10a**, **8b**−**10b**, **2a**, **2b**, **1a**, and **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Smythe, M. L.; von Itzstein, M. *J. Am. Chem. Soc.* **1994**, *116*, 2725−2733.

(16) PyBroP = bromo-tris-pyrrolidino-phosphonium hexafluorophosphate. (a) Coste, J.; Dufour, M.-N.; Pantaloni, A.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 669−672. (b) Coste, J.; Frérot, E.; Jouin, P.; Castro, B. *Tetrahedron Lett.* **1991**, *32*, 1967−1970.

(17) (a) Carpino, L. A.; Han, G. Y. *J. Org. Chem.* **1972**, *37*, 3404−3409. (b) Carpino, L. A. *Acc. Chem. Res.* **1987**, *20*, 401−407.

(18) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343−6348.

(19) POPd = PdCl$_2$[P(OH)(*t*-Bu)$_2$]$_2$ Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513−1516.

(20) Urata, H.; Hu, N.-X.; Maekawa, H.; Fuchikami, T. *Tetrahedron Lett.* **1991**, *32*, 4733−4736.

(21) Ozawa, F.; Soyama, H.; Yanagihara, H.; Aoyama, I.; Takino, H.; Izawa, K.; Yamamoto, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1985**, *107*, 3235−3245.