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# A new solid-phase linker for Suzuki coupling with concomitant macrocyclization: synthesis of β-turn mimics

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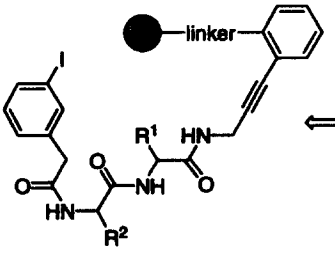
**Abstract**

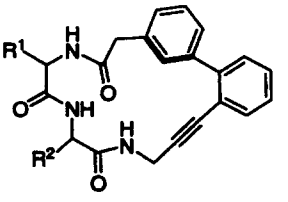
The boronic acid linker **12** was prepared and used to produce the β-turn mimics **1** via a solid-phase Suzuki coupling/macrocyclization/resin-release strategy. © 1999 Elsevier Science Ltd. All rights reserved.

*Keywords:* palladium catalysis; solid-phase syntheses; peptidomimetics; β-turns.

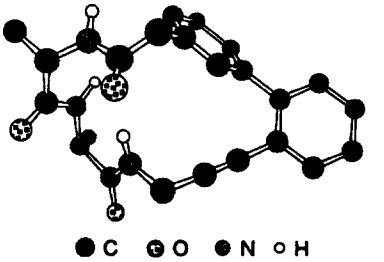
Our group is studying disruption or mimicry of protein–protein interactions using peptidomimetics wherein two amino acids are held in conformations resembling the *i*+1 and *i*+2 residues of β-turns.[1,2] Molecular modeling indicated that the biaryl structure **1** holds the two amino acid residues quite rigidly in such conformations; this is difficult to envisage from a two-dimensional line drawing, but is more easily pictured in a Chem3D representation as shown below. A solid-phase synthesis of macrocycles **1** was therefore required. This letter describes our efforts to develop a synthesis of systems **1** that involves simultaneous biaryl-coupling, macrocyclization, and resin-release.




**13**




**1a** $R^1 = R^2 = H$
**1b** $R^1 = H$; $R^2 = CH_2CONH_2$




*minimized conformation from a molecular dynamics/mechanics protocol* $R^1$ *and* $R^2$ *= Me*

A Suzuki reaction[3] was selected for formation of the key biaryl bond, consequently a novel linker system needed to be developed for this purpose. Scheme 1 shows the strategy that was used for this. A

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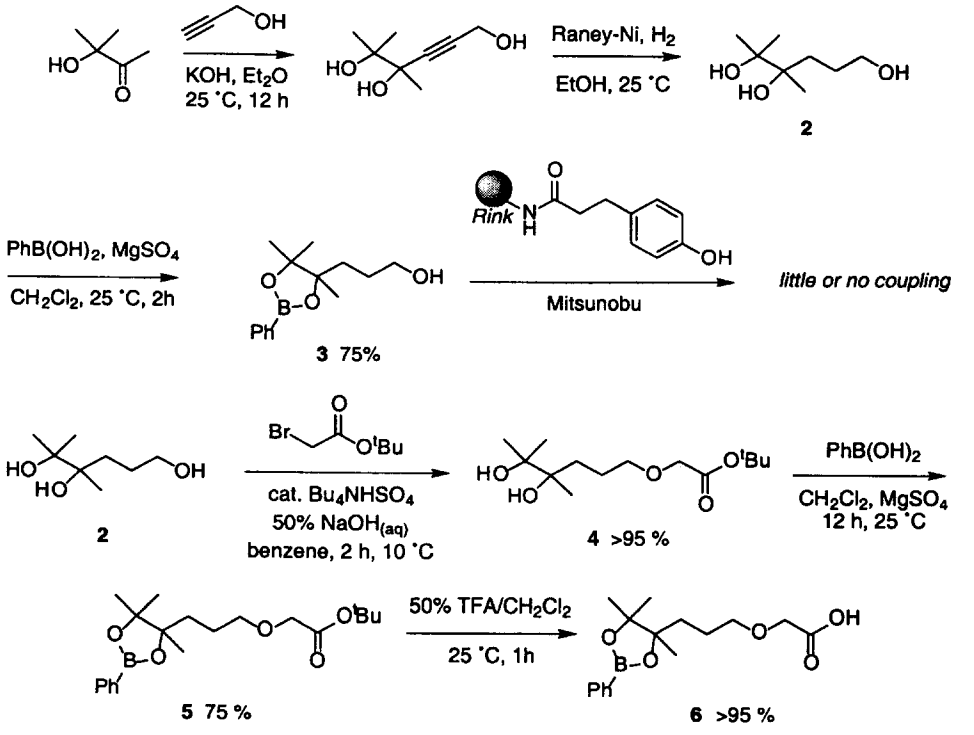
literature procedure[4] was used to transform 3-hydroxy-3-methylbutanone into the known triol **2**. This was easily converted to the model phenylboronic ester **3** under dehydrating conditions. A Mitsunobu coupling[5,6] of **3** to a resin-bound phenol was originally planned, but this reaction did not work well in practice. Consequently, a carboxylic acid group was introduced at the primary oxygen of triol **2** so that immobilization of the boronic ester on solid support could be accomplished by amide bond formation. After several attempts, it was found that an extremely efficient method for introducing the required carboxyl group was via alkylation of triol **2** with *tert*-butyl bromoacetate under phase transfer conditions. This gave the *tert*-butyl ester **4**. Addition of the model boronic acid under dehydrating conditions (as before) gave the boronic ester **5** which could then be deprotected under acidic conditions to give the desired model system **6**.

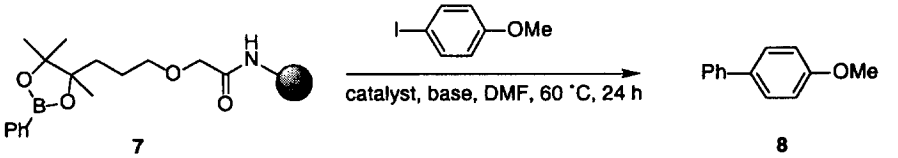



Scheme 1.

Model compound **6** facilitated a test of the efficiency of coupling boronate esters to supports and intermolecular Suzuki couplings of these. Thus, Rink's amide resin was reacted with **6** in the presence of DIC/HOBt/Et$^i$Pr$_2$N until a negative ninhydrin test was obtained. The functionalized resin **7** that was produced was then treated with 4-iodomethoxybenzene under various conditions for solid-phase Suzuki couplings,[7–9] and the resultant biaryl product **8** was assayed by GC. In each case where product was obtained, the material liberated from the resin was relatively pure (>95%, apart from unreacted 4-iodomethoxybenzene). Table 1 summarizes the conditions used, the purities observed, and the percentage yields based on the loading of the resin.

Scheme 2 outlines a synthesis of the boronic ester **12** that was required to produce the target turn mimetics **1**. 2-Bromoiodobenzene was selectively[10] coupled with a propargyl amine derivative via Sonogashira conditions.[11] The BOC-protected amine **9** was then deprotonated, metalated at the aryl bromide functionality, then quenched with tri-*iso*-propylborate.[12] Hydrolysis of the di-*iso*-propylboronate produced occurred on aqueous work-up (1 M HCl, ether extract, raise pH with NaOH, wash with Et$_2$O,

Table 1
Intermolecular Suzuki couplings of resin **7**

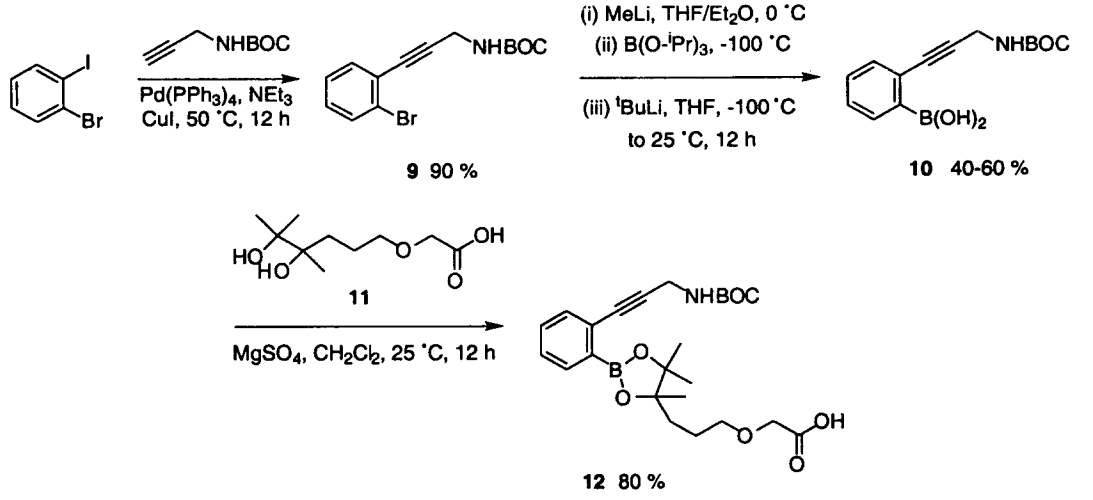



**7** **8**

| Entry | Catalyst | Mol % | equiv. 4-MeOC$_6$H$_4$I | Base[a] | Purity[c] | Yield[d] (%) |
|---|---|---|---|---|---|---|
| 1 | $PdCl_2$dppf | 5 | 2 | $NEt_3$ | - | 0 |
| 2 | $PdCl_2$dppf | 20 | 2 | $NEt_3$[b] | >95 | 13 |
| 3 | $PdCl_2$dppf | 5 | 2 | 2 M $K_3PO_4$ | >95 | 58 |
| 4 | $Pd(PPh_3)_4$ | 5 | 2 | 2 M $K_3PO_4$ | >95 | 47 |
| 5 | $PdCl_2$binap | 5 | 2 | 2 M $K_3PO_4$ | >95 | 64 |
| 6 | $PdCl_2$binap | 5 | 5 | 2 M $K_3PO_4$ | >95 | 85 |

[a] Three equivalents of base were used unless otherwise indicated. [b] Five equivalents of base were used. [c] As measured by GC. [d] As measured by GC versus benzophenone internal standard relative to the loading level of the resin before coupling of **6**; the mixtures were passed through silica plugs to remove excess ligand/metal before the analysis.

lower pH using 3 M HCl, $Et_2O$ extract). Unfortunately, in common with many boronic acids, the product **10** tended to cyclotrimerize to the corresponding boroxin on standing; consequently, it was best used immediately in the next step of the sequence. Dehydrative coupling of **10** to the diol **11** gave the desired product **12** that was relatively stable and could be purified by flash chromatography.




Scheme 2.

Macrocyclizations to give the desired products **1** were performed as follows. Compound **12** was attached to an amino functionalized resin (MBHA or TentaGel; DIC, HOBt, Et$^i$Pr$_2$N, DMF, same coupling conditions used throughout). Unfortunately, successive couplings of amino acids to **12** on a solid phase were not viable, possibly due to interaction of the N-terminus with the boron center after the first coupling. Consequently, derivatives of the type ArCH$_2$CO-AA$^1$-AA$^2$-OH (where Ar=3-iodophenyl) were prepared via solution phase methods, then coupled to solid supported **12** to give the linear derivatives **13**. Cyclizations leading to compounds **1** (**1a**, R$^1$=R$^2$=H; and **1b**, R$^1$=L-CH$_2$CONH$_2$,

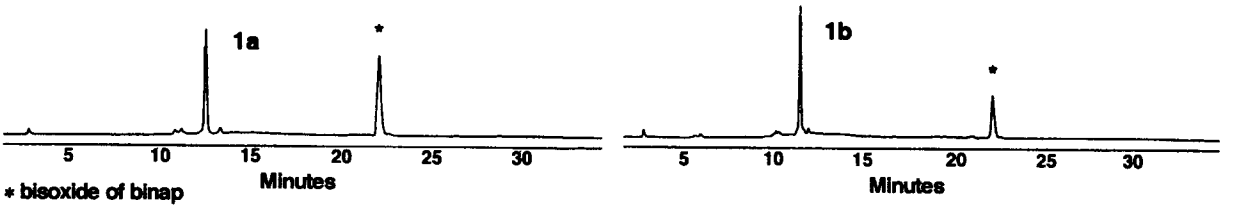



Figure 1. HPLC traces for compounds **1a** and **1b**

$R^2$=H) were examined under the conditions developed in Table 1, entries 5 and 6. In both cases, HPLC of the crude material isolated from the resin indicated formation of the desired product contaminated only with the bisphosphine oxide of BINAP (Fig. 1). The yield of material isolated was in the order of 30% in both cases; both products **1a** and **1b** were characterized by $^1H/^{13}C$ NMR, and MALDI MS.[13] For compound **1b**, temperature coefficients were measured for the N*H* protons in DMSO. This parameter was a low value for the propargylic N*H*, as expected for this solvent shielded and/or H-bonded proton in the anticipated turn conformation of these compounds.

In conclusion, this work provides proof of the concept for a Suzuki-coupling/macrocyclization/resin-release strategy leading to relatively rigid β-turn mimics.

## Acknowledgements

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## References

1. Feng, Y.; Wang, Z.; Jin, S.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 10768.
2. Feng, Y.; Pattarawarapan, M.; Wang, Z.; Burgess, K. *Organic Lett.* **1999**, *1*, 121.
3. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
4. Colonge, J.; Clerc, G. *Mém. Prés. a la Soc. Chim.* **1954**, 1454.
5. Mitsunobu, O. *Synthesis* **1981**, 1.
6. Hughes, D. L. The Mitsunobu Reaction, In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley and Sons: New York, 1992; p. 335.
7. Guiles, J. W.; Johnson, S. G.; Murray, W. V. *J. Org. Chem.* **1996**, *61*, 5169.
8. Piettre, S. R.; Baltzer, S. *Tetrahedron Lett.* **1997**, *38*, 1197.
9. Pavia, M. R.; Cohen, M. P.; Dilley, G. J.; Dubuc, G. R.; Durgin, T. L.; Forman, F. W.; Hediger, M. E.; Milot, G.; Powers, T. S.; Sucholeiki, I.; Zhou, S.; Hangauer, D. G. *Bioorg. Med. Chem.* **1996**, *4*, 659.
10. Goldfinger, M. B.; Crawford, K. B.; Swager, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 4578.
11. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.
12. Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316.
13. **1a**: $^1H$ NMR (300 MHz, $CD_3OD$) 8.85 (1H, b), 8.54 (1H, b), 7.94 (1H, b), 7.62–7.19 (8H, m), 4.22 (2H, d, *J*=6.3 Hz), 3.89 (2H, d, *J*=6.6 Hz), 3.77 (4H, m). $^{13}C$ NMR (75 MHz, $CD_3OD$) 29.68, 42.25, 43.48, 45.71, 82.65, 88.55, 122.39, 128.14, 128.29, 129.59, 129.63, 129.91, 130.69, 132.53, 134.43, 135.28, 142.21, 145.53, 171.29, 172.68, 176.16. MS (MALDI$^+$) calcd: 362, found: 362. **1b**: $^1H$ NMR (300 MHz, DMSO-$d_6$) 8.93 (1H, t), 8.36 (1H, d, *J*=5.1), 7.90 (1H), 7.61–6.91 (10H, m), 4.50 (1H, m), 4.15 (2H, m), 3.68 (2H, s), 3.56 (2H, m), 2.55 (2H, dd). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) 28.65, 35.81, 40.66, 44.23, 49.61, 80.74, 88.87, 120.33, 126.76, 127.29, 128.38, 128.83, 128.91, 129.69, 131.04, 133.41, 134.61, 139.59, 143.25, 169.00, 170.50, 171.95, 172.81, 172.89. MS (MALDI+Na) calcd: 441, found: 441.