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# Synthesis of Valsartan via Decarboxylative Biaryl Coupling

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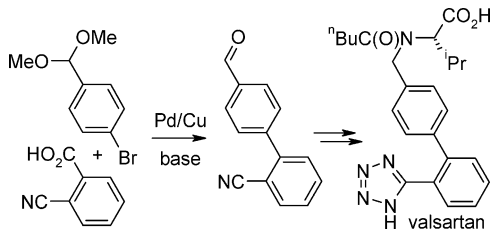
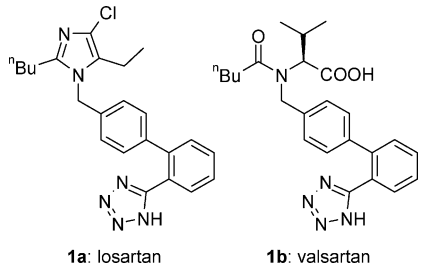
*Received June 27, 2007*




An efficient synthesis of the angiotensin II inhibitor valsartan (Diovan) is presented. Two routes were evaluated, both making use of an advanced version of our decarboxylative coupling for the construction of the biaryl moiety. Thus, in the presence of a catalyst system consisting of copper(II) oxide, 1,10-phenanthroline, and palladium(II) bromide, 2-cyanocarboxylic acid was coupled with 1-bromo(4-dimethoxymethyl)benzene in 80% yield and with 4-bromotoluene in 71% yield. The valsartan synthesis using 1-bromo(4-dimethoxymethyl)benzene was completed in four steps overall with a total yield of 39%, via a novel route that presents substantial economical and ecological advantages over the literature process, as it is more concise and stoichiometric amounts of expensive organometallic reagents are avoided.

Hypertension is one of the most prevalent diseases in developed countries with an estimated 1 billion cases worldwide,[1] conferring its treatment an enormous social and economic importance. The therapeutic standard was significantly improved in the 1980s by the introduction of losartan (**1a**; Lorzaar, Merck) (Figure 1)[2] as the first nonpeptidic angiotensin-II-receptor antagonist. An entire therapeutic class, the sartans, has since been developed, among which valsartan (**1b**; Diovan, Novartis: US $4.2 billion sales in 2006) (Figure 1) currently holds the largest market share.[3−5]




**1a**: losartan **1b**: valsartan

**FIGURE 1.** Angiotensin-II-receptor antagonists.

Their common structural element, a biphenyl unit, is essential for the binding affinity to the receptor and for the oral bioavailability. The formation of its aryl−aryl bond represents the key step in the synthesis of sartans: while for the synthesis of losartan,[2b] the uses of Negishi[6] and Ullmann[7] couplings is described in the literature, the published methods for the preparation of valsartan make use of Suzuki−Miyaura couplings.[8,9] The principal synthetic pathways leading to valsartan are depicted in Scheme 1. In route A, 2-chlorobenzonitrile (**2a**) and 4-tolylboronic acid (**3**) are coupled to give 2-cyano-4′-methylbiphenyl (**4a**), which is then brominated and reacted with L-valine methyl ester to give *N*-[(2′-cyanobiphenyl-4-yl)methyl]-L-valine methyl ester (**6**). Alternatively, **6** can be obtained via the coupling of 4-bromobenzaldehyde (**7b**) with a boronic acid derivative (e.g., **2b**), followed by reductive amination with L-valine methyl ester (route B). Route C results from a combination of both approaches, in which the sensitive formyl group in biaryl **4b** is generated by oxidation of the more robust derivative **4a**.

The main shortcoming common to these syntheses originates from the use of expensive boronic acid substrates in the cross-coupling step. We believed that we could overcome this weakness with the biaryl synthesis recently developed in our group, which instead draws on carboxylic acid salts as a stable, inexpensive, and widely available source of the aryl nucleophile.[10] In this method, these salts are decarboxylated by a copper/phenanthroline system, and the resulting aryl−copper species are coupled in situ with aryl halides by a palladium cocatalyst. Other decarboxylative couplings of the Heck type

(1) U.S. Department of Health and Human Services; National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program, NIH Publication No. 03-5233, December 2003.

(2) (a) Duncia, J.; Chiu, A.; Carini, D.; Georgory, G.; Johnson, A.; Price, W.; Wells, G.; Wong, P.; Calabrese, J.; Timmermans, P. *J. Med. Chem.* **1990**, *33*, 1312−1329. (b) Carini, D.; Duncia, J.; Aldrich, P.; Chiu, A.; Johnson, A.; Pierce, M.; Price, W.; Santella, J., III; Wells, G.; Wexler, R.; Wong, P.; Yoo, S. E.; Timmermans, P. *J. Med. Chem.* **1991**, *34*, 2525−2547.

(3) For sales figures, see: *Novartis Annual Report 2006*; Novartis International AG: Basel, Switzerland, 2007.

(4) For published syntheses, see: (a) Bühlmayer, P.; Ostermayer, F.; Schmidlin, T. Eur. Pat. Appl. EP443983, 1991. (b) Bühlmayer, P.; Ostermayer, F.; Schmidlin, T. U.S. Patent 5,339,578, 1995. (c) Bühlmayer, P.; Furet, P.; Criscione, L.; de Gasparo, M.; Whitebread, S.; Schmidlin, T.; Lattmann, R.; Wood, J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 29−34.

(5) For clinical trial results, see: (a) Novartis Pharma Schweiz, AG. *Health & Science* **2005**, *2*, 8−9. (b) McMurry, J.; Solomon, S.; Pieper, K.; Reed, S.; Rouleau, J.; Velazquez, E.; White, H.; Howlett, J.; Swedberg, K.; Maggioni, A.; Køber, L.; Van de Werf, F.; Califf, R.; Pfeffer, M. *J. Am. Coll. Cardiol*. **2006**, *47*, 726−733.

(6) (a) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821−1823. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442−4489.

(7) Fanta, P. E. *Chem. Rev.* **1964**, *64*, 613−632.

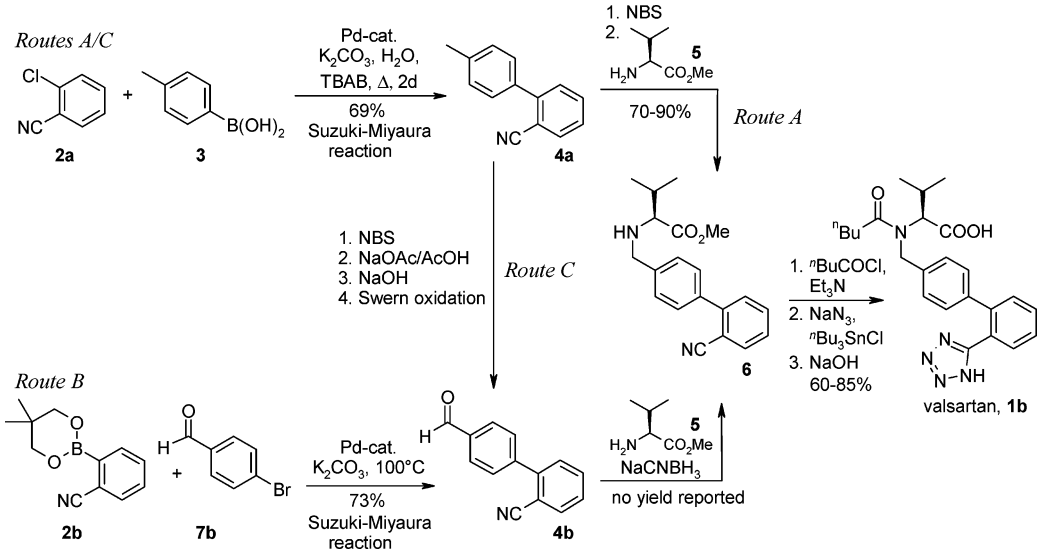
(8) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(9) For state-of-the-art Suzuki couplings, see: (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211. (b) Kristensen, J.; Lysén, M.; Vedsø, P.; Begtrup, M. *Org. Lett.* **2001**, *3*, 1435−1437.

(10) (a) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662−664. (b) Goossen, L. J.; Rodríguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *12*, 4824−4833. (c) Goossen, L. J.; Thiel, W. R.; Rodríguez, N.; Linder, C.; Melzer, B. *Adv. Synth. Catal.*, in press.

10.1021/jo701391q CCC: $37.00 
Published on Web 08/23/2007

**SCHEME 1. Novartis Patent Literature Syntheses of Valsartan via Suzuki−Miyaura Coupling**




did not offer an alternative, as they do not allow the synthesis of nonheterocyclic biaryls.[11]

In order to incorporate this method into the synthetic pathways outlined above, a protocol had to be developed for the substrate combinations of 2-cyanobenzoic acid (**2c**) with the aryl bromides **7a**−**d,** leading to the intermediate biaryls **4a**,**b**. It soon became clear that this was not an easy task: 2-cyanobenzoic acid (**2c**) had previously been found to be particularly resistant to decarboxylation, which we rationalize with a competing coordination of cyano groups to copper. Thus, under previously optimized conditions ($PdBr_2$, $CuCO_3$/1,10-phenanthroline, $K_2CO_3$),[10] the yields barely exceeded the amount of copper employed in the reaction of **2c** with 4-bromotoluene (**7a**), even at an increased reaction temperature of 170 °C (Table 1, entry 1). In the analogous coupling of **2c** with 4-bromobenzaldehyde (**7b**), less than one Cu turnover was achieved (entry 2).

We began our search for a better catalyst system for the coupling of 2-cyanobenzoic acid (**2c**) with **7a** by varying the copper source and found copper(II) oxide to be more effective, allowing us to reduce the amount of copper to 15% (entries 3 and 4). Added phosphines had a beneficial effect, presumably by stabilizing the palladium catalyst (entries 5 and 6). Previous investigations performed in our group have shown that the protodecarboxylation of 2-cyanobenzoic acid proceeded with the same speed as the decarboxylative cross-coupling, suggesting that the copper-mediated decarboxylation step is rate-determining.[10] In an attempt to further facilitate it, we tested metal salts as additives and found that with potassium fluoride, the yield could finally be improved beyond 60% (entry 7). While this corresponds with some previous findings,[10b] we were surprised to see that palladium bromide was the most effective palladium source for this substrate combination, as bromide ions usually retard the decarboxylation step (entries 8 and 9).[10] Interestingly, copper(II) oxide continued to be the best copper source under these optimized conditions, being superior also to copper(I) oxide, although the color change during the reaction indicated a rapid reduction of the copper (entries 10 and 11). Finally, we reinvestigated the influence of the solvent system and found that, in sharp contrast to the reaction of other benzoic acids, *N*-methylpyrrolidone (NMP) alone and NMP/quinoline mixtures were both inferior to pure quinoline (entries 7, 12, and 13), with which the best yield (71%) was achieved for the synthesis of 2-cyano-4′-methylbiphenyl (**4a**).

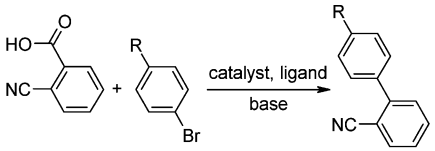
This protocol is optimal only for these specific substrate combinations; it did not lead to better results, for example, in coupling reactions of 2-nitrobenzoic acid. It gave reasonable yields in the coupling of 2-cyanobenzoic acid (**2c**) with the sensitive 4-bromobenzaldehyde (**7b**, entry 14). However, best results (≥80%) were obtained with the corresponding acetals: i.e., the dioxolane **7c** and the commercially available dimethyl acetal **7d**. During the standard acidic workup, the acetal groups were hydrolyzed quantitatively, so that without an additional step, the desired 2-cyano-4′-formylbiphenyl (**4b**) was directly isolated in an overall yield of 80% (entries 15 and 16). Thus, we decided to use the dimethyl acetal **7d** as our starting material on preparative scale for a modified route B.

Completion of the valsartan synthesis starting from 2-cyano-4′-methylbiphenyl (**4a**) via route A required bromination to give 4′-bromomethyl-2-cyanobiphenyl (**4c**) and then amination of this benzylic bromide with L-valine methyl ester (**5**), followed by acylation with valeryl chloride and tetrazole formation with sodium azide/tri-*n*-butyltin chloride. However, the bromination using *N*-bromosuccinimide (NBS) and AIBN in a cyclohexane/$CCl_4$ mixture was sluggish. Even when we deliberately aimed at incomplete conversion using 0.8 equiv of NBS, the desired product (45% isolated yield after crystallization) was formed as a mixture with the double-bromination product (17%) and unreacted starting material. In view of these discouraging results and the absence of detailed procedures for this step in the literature, we decided to abandon route A and, instead, focus on the alternative pathway involving 2-cyano-4′-formylbiphenyl (**4b**), to complete the valsartan synthesis following route B as outlined by Bühlmayer et al.[4]

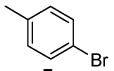
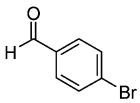
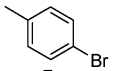
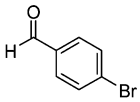
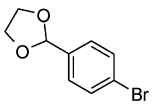
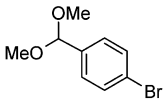
Hence, reductive amination of **4b** with L-valine methyl ester in the presence of sodium cyanoborohydride gave the amine **6** in 90% yield (Scheme 2), and the subsequent acylation with valeryl chloride/pyridine in dichloromethane furnished inter-

(11) (a) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323−10333. (b) Peschko, C.; Winklhofer, C.; Steglich, W. *Chem. Eur. J.* **2000**, *6*, 1147−1152. (c) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350−11351.

**TABLE 1. Optimization of the Catalyst System and Conditions for the Key Coupling Step**[a]



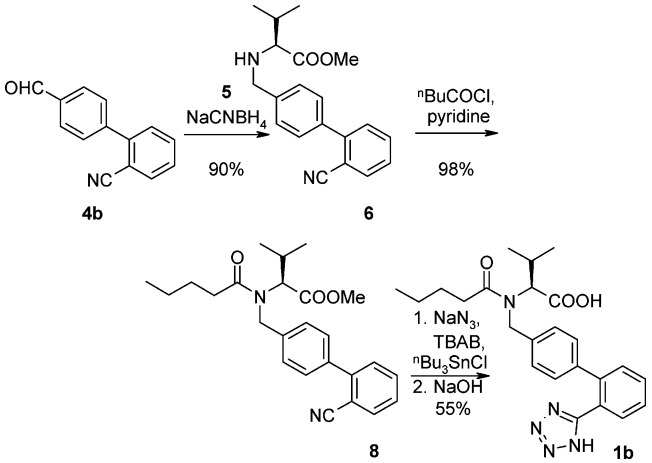

**2c** **7a** R= $CH_3$ **4a** R= $CH_3$
**7b** R=CHO **4b** R= CHO
**7c** R= 1,3-dioxolane
**7d** R= $CH(OMe)_2$

| Entry | Aryl halide | Catalyst | Additive | Solvent | Product, Yield/% |
|---|---|---|---|---|---|
| 1 |  **7a** | 2 % $PdBr_2$, 30 % $CuCO_3$ | - | NMP/quin. | **4a**, 36 |
| 2 |  **7b** | " | - | " | **4b**, 20 |
| 3 |  **7a** | 2 % $PdBr_2$, 30 % CuO | - | " | **4a**, 47 |
| 4 | " | 2 % $PdBr_2$, 15 % CuO | - | " | **4a**, 42 |
| 5[b] | " | " | $PPh_3$ | " | **4a**, 54 |
| 6[b] | " | " | $P(^iPr)Ph_2$ | " | **4a**, 58 |
| 7[c] | " | 2 % $PdBr_2$, 15 % CuO | KF / $PPh_3$ | " | **4a**, 65 |
| 8[c] | " | 2 % $Pd(acac)_2$, 15 % CuO | " | " | **4a**, 61 |
| 9[c] | " | 2 % Pd(OAc), 15 % CuO | " | " | **4a**, 50 |
| 10[c] | " | 2 % $PdBr_2$,15 % $Cu_2O$ | " | " | **4a**, 45 |
| 11[c] | " | 2 % $PdBr_2$, 15 % Cu(OAc) | " | " | **4a**, 34 |
| 12[d] | " | 2 % $PdBr_2$, 15 % CuO | " | NMP | **4a**, 21 |
| 13[d] | " | " | " | quin. | **4a**,70(71) |
| 14[d] |  **7b** | 2 % $PdBr_2$, 15 % CuO | " | quin. | **4b**, 51 |
| 15[e] |  **7c** | 2 % $PdBr_2$, 15 % CuO | " | quin. | **4b**,78(81) |
| 16[e] |  **7d** | 2 % $PdBr_2$, 15 % CuO | " | quin. | **4b**,77(80) |

[a] General conditions: 1.20 mmol of 2-cyanobenzoic acid, 1.00 mmol of aryl halide, 1.20 mmol of $K_2CO_3$, 250 mg of molecular sieves, 0.15 mmol of phenanthroline, 1.0 mL of NMP, 0.5 mL of quinoline, 24 h, 170 °C. Yields were determined by GC analysis using *n*-tetradecane as the internal standard; yields given in parentheses are isolated yields. [b] Modifications: 0.02 mmol of phosphine ligand. [c] Modifications: 0.02 mmol of phosphine ligand, 1.00 mmol of $K_2CO_3$, 0.50 mmol of KF. [d] Modifications: 0.02 mmol of phosphine ligand, 1.00 mmol of base, 0.50 mmol of KF, and 1.5 mL of solvent. [e] Modifications:1.00 mmol of 2-cyanobenzoic acid, 1.50 mmol of aryl halide.

mediate **7** almost quantitatively. The use of pyridine as the base, rather than triethylamine as previously employed,[4] significantly increased the yield and at the same time reduced the reaction time. Conversion of the nitrile function of intermediate **8** to the tetrazole remained troublesome, and despite all efforts in optimizing this step, we could not improve the yield beyond a threshold of 55%. This was only obtained after we figured out that adding tetra-*n*-butylammonium bromide facilitates the

**SCHEME 2. Completion of the Valsartan Synthesis**




reaction of **8** with tri-*n*-butyltin chloride and sodium azide. The product was liberated after the subsequent methyl ester hydrolysis.

Overall, in this application to the synthesis of the antihypertensive valsartan, we were able to significantly improve the decarboxylative biaryl coupling of 2-cyanobenzoic acid and demonstrate for the first time the advantages of this concept in the synthesis of complex, biologically active molecules. Thus, valsartan was synthesized in four isolated steps and an overall yield of 39%, which compares favorably to the literature routes, especially as the use of organometallic reagents such as boronic acids can be avoided altogether.

## Experimental Section

**Synthesis of 2-Cyano-4′-methylbiphenyl (4a): General Method for Biaryl Synthesis.** An oven-dried 20 mL crimp-top vial was charged with copper(II) oxide (11.9 mg, 0.15 mmol), potassium carbonate (138.2 mg, 1.00 mmol), potassium fluoride (29.1 mg, 0.50 mmol), 1,10-phenanthroline (27.0 mg, 0.15 mmol), 2-cyanobenzoic acid (**2c**; 162.0 mg, 1.10 mmol), palladium(II) bromide (5.3 mg, 0.02 mmol), triphenylphosphine (5.2 mg, 0.02 mmol), and ground 3 Å molecular sieves (250 mg). The reaction vessel was closed with a septum cap and evacuated and flushed with nitrogen three times. Subsequently, a solution of 4-bromotoluene (**7a**; 171.0 mg, 1.00 mmol) and the internal standard *n*-tetradecane (50 $\mu$L) in quinoline (1.5 mL) was added via syringe. The resulting solution was stirred for 24 h at 170 °C and then poured into aqueous HCl (1 N, 20 mL). The resulting mixture was extracted repeatedly with ethyl acetate (20 mL portions). The combined organic layers were washed with water and brine, dried over $MgSO_4$, and filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography ($SiO_2$, ethyl acetate/hexane 1/5), yielding **4a** as a yellow solid (138 mg, 71%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-cyano-4′-methylbiphenyl [CAS: 114772-53-1].

**Synthesis of 2-Cyano-4′-formylbiphenyl (4b).** Compound **4b** was prepared by following the general method from 2-cyanobenzoic acid (**2c**; 147 mg, 1.00 mmol) and 1-bromo(4-dimethoxymethyl)-benzene (**7d**; 346.6 mg, 1.50 mmol), yielding **4b** as a light yellow solid (166 mg, 80%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-cyano-4′-formylbiphenyl [CAS: 135689-93-9].

**Acknowledgment.** We thank Saltigo GmbH for financial support and Umicore AG for the donation of metal catalysts.

**Supporting Information Available:** Text and figures giving complete experimental procedures and analytical data ($^1$H NMR/$^{13}$C NMR, MS, elemental analyses) for compounds **1b**, **2c**, **4a**−**d,** **6**, **7c**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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