Convenient synthesis of Valsartan via a Suzuki reaction

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An efficient synthesis of the angiotensin II inhibitor Valsartan (Diovan) is presented. The formation of the aryl–aryl bond represents the key step of its synthesis, which has been done by a Suzuki coupling of aryl boronate with 2-bromophenyl oxazoline with good yield and purity. This method overcomes many of the drawbacks associated with the previously reported syntheses.

Keywords: aryl bromide, aryl boronate, Suzuki coupling, oxazoline and Valsartan

The active hormone of the rennin–angiotensin–aldosterone system (RAAS) is angiotensin II, which is formed from angiotensin I through angiotensin converting enzyme (ACE).[1] Angiotensin II binds to specific receptors located in the cell membranes of various tissues. It has a wide variety of physiological effects, including, in particular, both direct and indirect involvement in the regulation of blood pressure.[2] As a potent vasoconstrictor, angiotensin II exerts a direct pressor response. In addition, it promotes sodium retention and stimulation of aldosterone secretion.Valsartan[3] is an orally active, potent and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. The AT2 receptor subtype has not been definitely shown to be associated with cardiovascular homeostasis. The increased plasma levels of Ang II following AT1 receptor blockade with Valsartan may stimulate the unblocked AT2 receptor. This may counteract the effect of blocking the AT1 receptor. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and about a 20,000-fold greater affinity for the AT1 receptor than for the AT2 receptor. Administration of Valsartan to patients with hypertension results in reduction of blood pressure without affecting pulse rate.

The formation of the aryl–aryl bond represents the key step in the synthesis of sartans: while for the synthesis of losartan,[4] the uses of Negishi[5,6] and Ullmann[7] couplings are described in the literature and the published methods for the preparation of losartan make use of Suzuki–Miyaura couplings.[8] Among them the Suzuki reaction has proved to be very efficient as there is no need for expensive reagents and the synthesis is suitable for plant scales as well. Although preparations of several biphenyl ring systems related to Valsartan have been reported, a number of challenges and some disadvantages still exist, such as tedious reaction conditions, low yields, and multistep sequences. Therefore, developing a synthetic strategy that is efficient having a low number of steps and providing diverse access to this bioactive compound is an important goal. We now report a new, concise, and efficient approach for the synthesis of Valsartan via a Suzuki coupling.

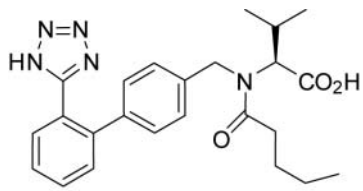
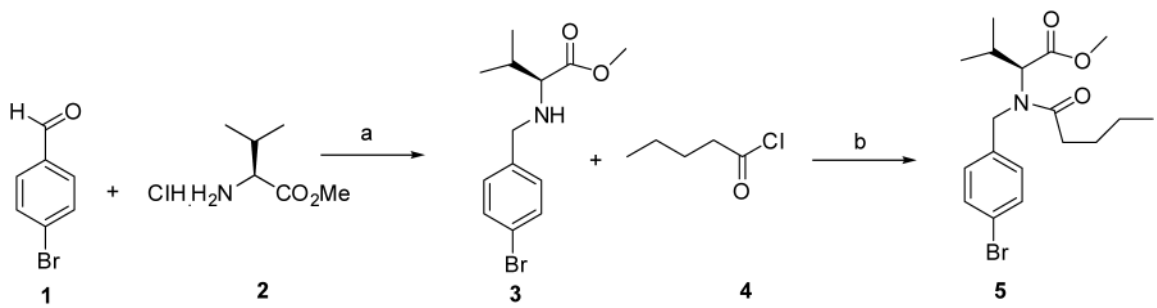


Fig. 1 **11**: Valsartan.

In our approach, in Scheme 1, inexpensive and commercially readily available 4-bromo benzaldehyde **1** was condensed with L-valine methyl ester hydrochloride **2** in the presence of triethyl amine and anhydrous magnesium sulfate, yielding the corresponding Schiff base.[9] *In situ* reduction of the imine intermediate with sodium cyanoborohydride afforded the methyl-N (4-bromobenzyl-L-valinate **3** in 90% yield. Compound **3** was N-protected with valeryl chloride **4** in the presence of triethyl amine in dichloromethane to get methyl N-(4-bromobenzyl)-N-pentanoyl-L-valinate **5** (aryl bromide) in 95% yield.

In Scheme 2, aryl bromide **5** was treated with potassium acetate as a base (3 equiv), $PdCl_2$ (dppf) as a catalyst (0.05 equiv) and bis(pinacolato)diboron (1.3 equiv) in 1, 2-dimethoxyethane (DME) as a solvent at 110 °C temperature for 18 h to yield aryl boronate **6** which was telescoped to the next step. This aryl boronate was coupled with 2-bromophenyl oxazoline[10] in the presence of catalytic amount of Pd $(PPh_3)_4$, 3 equiv of 1M aq. Na_2CO_3 solution in 1,2-dimethyoxyethane at 110 °C to afford methyl N-{[2′-(4, 4-dimethyl-4, 5-dihydro-1, 3-oxazol-2-yl) biphenyl-4-yl] methyl}-N-pentanoyl-L-valinate **8** in 85% yield.

In the Scheme 3, compound **8** was treated with phosphorous oxychloride at 0 °C in pyridine and then heated at 85 °C to get methyl-N-[(2′-cyanobiphenyl-4-yl)methyl]-N-pentanoyl-L-valinate **9**[11,12] in 90% yield. The compound **9**[13] was treated with



Scheme 1 (a) Anhyd. $MgSO_4$, Et_3N, CH_2Cl_2, 25 °C,12 h; then $NaBH_3CN$, AcOH, MeOH, 70 °C, 2 h , 90%; (b) Et_3N, CH_2Cl_2, 0 °C, 95%.

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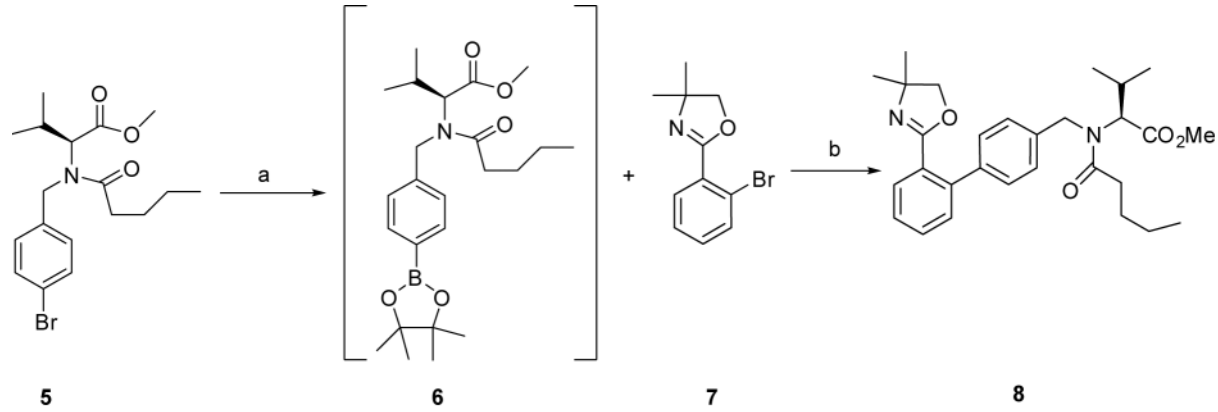
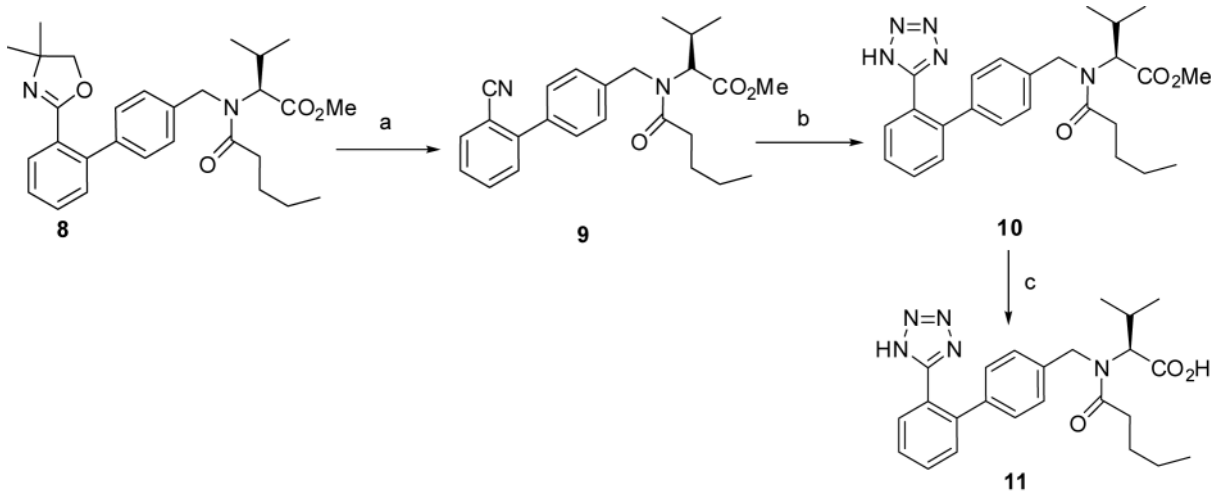


Scheme 2 (a) Bis (pinacolato) diboron, KOAc, $PdCl_2$ (dppf), DME, 110 °C, 18 h. (b) Pd $(PPh_3)_4$, Na_2CO_3, H_2O, 6h, 85%.



Scheme 3 (a) $POCl_3$, pyridine, 85 °C, 14 h, 90% ; (b) NaN_3, Bu_3SnCl, TBAB, toluene,110 °C, 60%; (c) NaOH, MeOH, water, 25 °C, 95%.

sodium azide and tributyl tin chloride to get compound **10** in 60% yields. Finally the anticipated product **11**, Valsartan was synthesised from compound **10** by treating with 1N sodium hydroxide aqueous solution in methanol in 95% yield.

In summary, a highly efficient approach to the biphenyltetrazole structure of the A-II antagonists has been developed by employing a Suzuki reaction of aryl boronate with 2-bromophenyl oxazoline. Application of this approach provided an industrial viable procedure to the synthesis of Valsartan, which is a potent, orally active, nonpeptide antagonist of the angiotensin II AT1-receptor subtype.

Experimental

All solvents and reagents were purchased from the suppliers and used without further purification. All non-aqueous reactions were performed in dry glassware under an atmosphere of dry nitrogen. Organic solutions were concentrated under reduced pressure. Thin layer chromatography was performed on Merck precoated Silica-gel $60F_{254}$ plates. ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 using 400 MHz, on a Varian Gemini 400 MHz FT NMR spectrometer. The chemical shifts were reported in δ ppm relative to TMS. The mass spectra were recorded on Shimadzu LCMS-QP 800 LC-MS and AB-4000 Q-trap LC-MS/MS. Melting points were obtained by using the open capillary method and are uncorrected.

Methyl-N (4-bromobenzyl-L-valinate **(3)**: A mixture of 4-bromobenzaldehyde (3.0 g, 16.21 mmol), L-valine methyl ester hydrochloride (5.41 g, 32.43 mmol), triethyl amine (4.51 mL, 32.43 mmol) and magnesium sulfate (10.0 g) was stirred in dichloromethane (30 mL) at 25 °C for 12 h. All solids were filtered off, volatile components were removed under reduced pressure, and the residue was dissolved in methanol (30 mL) and glacial acetic acid (0.2 mL). This solution was kept below 10 °C while portions of sodium cyanoborohydride (2.0 g, 32.43 mmol) were added. The reaction mixture was heated at 70 °C for 2 h. under N_2 atmosphere. The reaction was monitored by TLC and no starting material was left. The reaction mixture was cooled down to 25 °C and quenched with water (50 mL) and extracted with ethyl acetate (2 × 100 mL). The organic layer was concentrated under vacuum to get crude residue. The crude was purified by column chromatography (SiO_2, ethyl acetate/hexane 3:7), yielding compound methyl-N (4-bromobenzyl-L-valinate **3** as an oil (4.3 g, 90% yield), R_f = 0.3 (7:3; heptanes/EtOAc), ^1H NMR (400 MHz, DMSO-d_6) δ 7.48 (d, J = 7.6 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 5.25 (m, 2H), 4.43 (s, 3H), 2.78 (m, 1H), 1.85 (m, 1H), 0.87 (d, J = 6.8, 3H), 0.82 (d, J = 6.8, 3H), ^{13}C NMR (DMSO-d_6) δ 178.7.3, 138.9, 131.2, 130.3, 121.5, 68.2, 50.9, 51.4, 32.6, 19.4,18.9; ESIMS: *m/z* Calcd [M+]: 300. Found: 301 [M+H+]; HRMS (ESI): *m/z* Calcd [M+]: 300.1915. Found: 300.1923 [M +].

Methyl N-(4-bromobenzyl)-N-pentanoyl -L- valinate **(5):** To a solution of methyl-N (4-bromobenzyl-L-valinate **3** (2.0 g, 6.66 mmol) in dichloromethane (20 mL) was added Et_3N (1.11 mL, 8.0 mmol) followed by valeryl chloride **4** (0.96 g, 8.0 mmol) at 0 °C temperature. The mixture was stirred at 25 °C temperature for 1 h. To the reaction mixture water (50 mL) was added and organic layer was separated and concentrated. The crude was purified by column chromatography (SiO_2, ethyl acetate/hexane 3:7), yielding compound methyl N-(4-bromobenzyl)-N-pentanoyl -L- valinate **5** as a pale yellow oil (2.43 g, 95% yield), R_f = 0.5 (7:3 ; heptanes/EtOAc), ^1H NMR (400 MHz, DMSO-d_6): δ 7.54 (d, J = 6.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 5.01 (s, 2H), 4.13 (m, 1H) 3.31 (s, 5H), 2.32 (t, J = 14.8 Hz, 2H) 1.50 (m, 2H), 1.93 (m, 1H), 1.24 (m, 3H), 1.22 (m, 3H), 0.83 (d, J = 7.6 Hz, 3H)); ^{13}C NMR (400 MHz, DMSO-d_6): δ 173.9, 136.5, 133.1, 131.3, 121.1, 68.3, 52.5, 49.9, 34.2, 29.5, 27.2, 24.1, 23.2, 22.1, 19.2; ESIMS:

m/z Calcd [M+]: 384. Found: 385 [M+1]. HRMS (ESI): *m/z* Calcd [M+]: 384.3079. Found: 384.3085 [M +].

Methyl N-{[2′-(4, 4-dimethyl-4, 5-dihydro-1, 3-oxazol-2-yl) biphenyl-4-yl] methyl}-N-pentanoyl-L-valinate **(8):** Aryl bromide **5** (2 g, 5.20 mmol), bis (pinacolato) diboron (1.71 g, 6.77 mmol), KOAc (1.53 g, 15.62 mmol) and $PdCl_2$ (dppf) (0.190 g, 0.260 mmol) were suspended in dry 1,2-dimethoxyethane (20 mL, degassed by sparging with N_2), and heated to 110 ºC for 18 h. The reaction was monitored by TLC and no starting material was present. So aryl boronate synthesis is ready and now to the reaction mixture itself Pd $(PPh_3)_4$ (0.3 g, 0.260 mmol) was added followed by 2-brmophenyl oxazoline **7** (1.6 g, 6.23 mmol) and 1M sodium carbonate solution (15.5 mL). The heating was continued for another 6 h and progress of reaction was monitored by TLC, and maximum consumption of starting material (aryl boronate) was observed. After cooling to 25 °C, the solution was diluted with ethyl acetate (100 mL) washed with H_2O (2 × 50 mL) and brine (2 × 30 mL), dried over anhyd. $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel, and elution with a mixture of heptanes and ethyl acetate (70:30) yielded the title compound **8** (6.97 g, 85%) as a colourless oil, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.09–7.59 (m, 8H), 4.52–4.74 (m, 2H), 4.18–4.20 (d, 1H) 3.71–3.77 (q, 2H); 3.31–3.36 (d, 3H), 2.25–2.33 (m, 2H), 1.90–2.20 (m, 2H), 1.55–1.6 (m, 1H), 1.40–1.45 (2H, m), 1.00–1.20 (6H, m), 0.88–0.91 (3H, t), 0.76–0.80 (6H, m) ^{13}C NMR (DMSO-d_6) δ 14.14, 18.63, 19.69, 22.20, 27.35, 27.67, 28.12, 32.76, 48.52, 51.81, 62.25, 67.91, 78.91, 126.18, 127.58, 128.17, 128.68, 130.28, 130.47, 130.97, 137.23, 139.59, 141.05, 162.37, 170.96, 173.81; ESIMS: *m/z* Calcd [M+]: 478. Found: 479 [M+H+]; HRMS (ESI): *m/z* Calcd [M+]: 478.2832. Found: 478.2930 [M+].

Methyl-N-[(2′-cyanobiphenyl-4-yl) methyl]-N-pentanoyl-L-valinate **(9)**: To a solution of compound, methyl N-{[2′-(4, 4-dimethyl-4, 5-dihydro-1, 3-oxazol-2-yl) biphenyl-4-yl] methyl}-N-pentanoyl-L-valinate **8** (1 g, 2.09 mmol) in dry pyridine (5 mL), phosphorus oxychloride (0.64 g, 4.18 mmol) was added dropwise at 0 °C. The resulting solution was stirred at 85 °C (bath temperature under nitrogen for 14 h and, after being cooled to room temperature, was poured into a cold saturated solution of sodium carbonate (100 mL). After being cooled to room temperature the mixture was quenched by addition of water, and the resulting emulsion was extracted with ethyl acetate. The combined organic phases were washed with water, 10% aqueous cupric sulfate solution, and brine. The solution then was dried over anhydrous magnesium sulfate, filtered, concentrated under vacuum, and purified by column chromatography (SiO_2, ethyl acetate/hexane 3:7), yielding compound methyl-N-[(2′-cyanobiphenyl-4-yl) methyl]-N-pentanoyl-L-valinate **9** as a yellow oil (0.75 g, 90% yield), ^{1}H NMR (400 MHz,DMSO-d_6) δ 7.17–7.86 (m, 8H), 4.53–4.87 (m, 2H), 4.13–4.18 (m, 1H), 3.25–3.33 (d, 3H), 2.24–2.35 (m, 2H), 2.00–2.13 (m, 1H), 1.41–1.53 (2H, m), 1.10–1.31 (2H, m), 0.86–1.08 (3H, m), 0.68–0.79 (6H, m) ^{13}C NMR (DMSO-d_6) δ 14.16, 18.45, 19.59, 22.21, 27.56, 32,76, 48.39, 52.07, 62.17, 65.09, 110.46, 119.03, 126.72, 127.54, 128.51, 128.63, 130.66, 134.22, 136.86, 139.19, 144.72, 170.59, 174.13; ESIMS: *m/z* Calcd [M+]: 406. Found: 407 [M+H+], 429 [M+ +Na]; HRMS (ESI): *m/z* Calcd [M+]: 406.5173. Found: 406.5092 [M +].

N-Pentanoyl-N-{[2′-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}-L-valine **(11)**: To a solution of compound 10 (0.4 g, 0.89 mmol) in methanol (5 mL) was added 1 N NaOH (1 mL) aq. solution and stirred the reaction mixture at 25 °C for 12 h. The progress of reaction is monitored by TLC and no starting material was observed. The reaction mixture was diluted with methyl tertiary butyl ether (20 mL) and water (30 mL). The organic phase was separated and the aqueous layer was acidified with aqueous HCl solution (2N) until a pH of 3 was reached. Extraction was carried out with methyl tertiary butyl ether (2 × 30 mL) followed by drying and evaporating to dryness, to furnish the desired product as a white solid (0.36 g, 95%). and the anticipated product, Valsartan **11**, m.p. 114–118 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.6 (brs, 1H), 7.72 (m, 4H), 7.24 (m, 1H), 7.15 (m, 2H), 6.94 (m, 1H), 4.58 (m, 1H), 4.40 (m, 1H), 3.33 (m, 1H), 2.25 (m, 1H), 1.52 (m, 6H), 0.9 (m, 3H), 0.84 (m, 3H), 0.74 (m, 3H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 174.0, 172.4, 171.8, 141.7, 138.2, 131.54, 131.1, 131.0, 129.3,128.8, 128.2, 127.4, 126.7, 70.3, 63.4, 49.9, 32.9, 28.05, 27.3, 22.2, 20.6, 14.2; ESIMS: *m/z* Calcd [M+]: 435. Found: 436 [M+H+]; HRMS (ESI): *m/z* Calcd [M+]: 435.5187. Found: 435.5125 [M +].

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