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Alternative synthesis of Valsartan via Negishi coupling

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ABSTRACT

A highly efficient approach to the synthesis of valsartan is described. Directed ortho-metalation of 4,4-dimethyl-2-phenyl-4,5-dihydrooxazole provides the key organozinc intermediate for palladium catalysed biaryl coupling with methyl N-(4-bromobenzyl)-N-pentanoyl-L-valinate (aryl bromide) obtained from alkylation of methyl N–pentanoyl-L-valinate. This methodology overcomes many of drawbacks associated with previously reported syntheses.

Keywords: Valsartan, antihypertensive drug, Negishi coupling, oxazoline.

INTRODUCTION

Angiotensin II (A-II) is the principle pressor agent of the renin angiotensin system (RAS), which plays a critical role in the regulation of blood pressure.[1] Prevention of the formation of A-II, via inhibition of angiotensin converting enzyme (ACE),[2] has confirmed the therapeutic benefit of inhibiting the RAS in hypertension and congestive heart failure. This has led to the design and discovery of the nonpeptide A-II receptor antagonist valsartan **1**.[3]

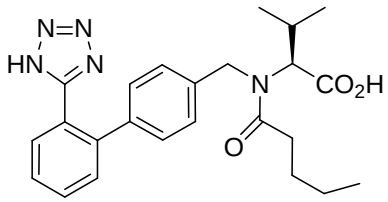

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Figure1. Valsartan

A-II antagonists have been divided into three categories, a biphenyl imidazolylmethyl such as candesartan, a monophenyl imidazolylmethyl such as eprosartan and a biphenyl without a

heterocycle at the 4-position, such as valsartan which is substituted with an *N*-(1-oxopentyl)-Lvaline and a tetrazole group at the 4-position and 2'-position respectively. The key step in the syntheses of these A-II antagonists (except the second kind) is the aryl–aryl coupling reaction to form the biphenyl moiety. Previous approaches to the synthesis of the requisite substitution pattern have employed the Ullmann coupling between 4-iodotoluene and 2-iodobenzoate, nucleophilic aromatic substitution at the *ortho*-position of a suitably activated benzoic acid derivative[4] and Ni-catalyzed coupling of (4-methylphenyl)magnesium bromide and 2-bromobenzonitrile.[5] The syntheses were then completed by the conversion of carboxy equivalent to the tetrazole and subsequent free-radical bromination of methyl group for alkylation by the heterocycle. Problems with these approaches have been (1) the nonselective and moderately yielding free-radical bromination of a late intermediate (2) the use of expensive metallic species that generate extremely dangerous metallic residues not only harmful to human health but also to the environment.

Most current methods for preparation of biaryls require either the regiospecific of desired halogen as a precursor to the organometallic reagent or require the isolation of the prerequisite organometallic after directed metalation prior to cross coupling. While these methods have had some success, especially the Suzuki boronic acid cross coupling as developed by Snieckus, we felt that a methodology which eliminates isolation and purification steps would have some useful advantages. Our approach involved the directed metalation of an appropriate carboxy protecting group followed by transmetalation with zinc chloride then transition metal catalysed cross coupling with aryl bromides. We chose the oxazoline[6] moiety as a carboxy synthon because of its excellent ortho-metalating properties, its stability in common reaction conditions, its use as a versatile synthetic intermediate and ease of converting into nitrile under mild conditions. We chose to explore Negishi cross couplings because of great tolerance of zinc-based organometallics to a wide range of sensitive functionalities.

MATERIALS AND METHODS

All solvents and reagents were purchased from the commercial 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. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ using 400 MHz, on a Varian Gemini 400 MHz FT NMR spectrometer. The chemical shifts were reported in δ ppm relative to TMS (Tetra methyl silane). The IR spectra were recorded in the solid state as KBr dispersion using Perkin Elmer FT-IR spectrophotometer. 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*-pentanoyl-L-valinate (4): To a suspension of L-valine methyl ester hydrochloride **2** (5.0 g, 29.94 mmol) in dichloromethane (50 mL) was added Et_3N (8.33 mL, 59.88 mmol) followed by valeryl chloride **3** (3.95, 32.93 mmol) at 0 ºC temperature. The mixture was stirred at 25 ºC temperature for 1 h. To the reaction mixture water (50 mL) was added and organic layer was separated and concentrated. The solid compound was triturated with heptane (50 mL) to give a colourless solid **4** (6.11 g, 95% yield), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (s, 1H),

4.12 (m, 1H), 3.59 (s, 3H), 2.48 (m, 2H), 2.13 (m, 2H), 1.95 (m, 1H), 1.45 (m, 3H), 1.25 (m, 5H), 0.86 (d, *J* = 4.4 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 173.2, 77.4, 56.8, 52.0, 36.2, 34.9, 31.2, 27.7, 22.2, 18.8; ESIMS: m/z calcd [M+]: 215; found: 216 [M+1].

Methyl-*N*-(4-bromobenzyl)-*N*-pentanoyl-L-valinate (6): Sodium hydride (60% dispersion in mineral oil (1.83 g, 46.51 mmol) was added to a solution of compound **4** (5.0 g, 23.25 mmol) and 1-bromo-4-(bromomethyl) benzene **5** (6.39 g, 25.58 mmol) in tetrahydrofuran (80 mL) and the reaction mixture was refluxed for 1h. After cooling, the mixture was diluted with ether (100 mL) and washed successively with saturated aq. NH_4Cl (50 mL) and water (100 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuum. The residue was chromatographed on silica gel and elution with a mixture of heptane and ethyl acetate (70:30) yielded the title compound **6** (6.25 g, 70 %) as a colourless oil. ^{1}H 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].

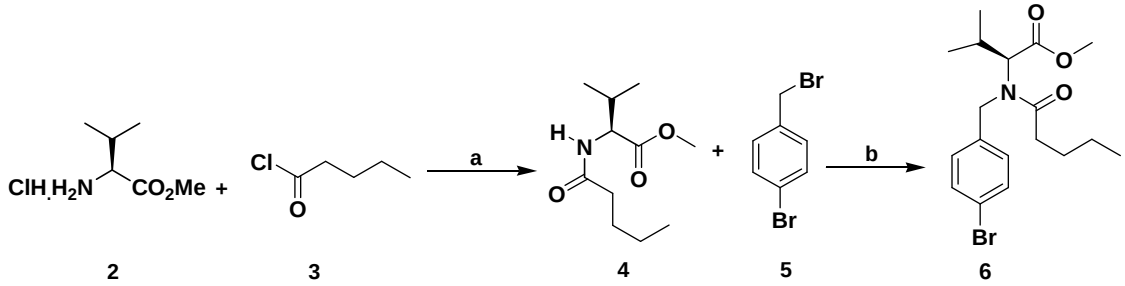
Methyl-*N*-{[2'-(4, 4-dimethyl-4,5-dihydro-1, 3-oxazol-2-yl) biphenyl-4-yl] methyl}-*N*-pentanoyl-L-valinate (8): To a stirred solution of 4,4-dimethyl-2-phenyl-4,5-dihydrooxazole **7**, (3.7 g, 0.017 mol) in THF (30 mL) at 0 ^{o}C was added 2.5M n-BuLi in hexane (12 mL, 0.02 mol). The mixture was stirred at 0 ^{o}C for 60 mints, and then 1.0M ZnCl2 in ether (41 mL, 0.03 mol) was added. The reaction mixture was brought to the ambient temperature over a period of 1 h, then tetrakis(triphenylphosphine)palladium (0) (0.2 g) and Methyl N-(4-bromobenzyl)-N-pentanoyl-L-valinate **6** (8.1g, 0.02 mol) was added. The mixture was stirred at 55 ^{o}C for 24 h, poured into saturated ammonium chloride (200 mL) and extracted with ethyl acetate (2 x 50 mL). The organic extracts were combined, washed with water (2 x 50 mL), brine (1x 50 mL), dried over $MgSO_4$ and concentrated under vacuum to give a colourless oil, (5.4 g, 55%); ^{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+].

Methyl-*N*-[(2'-cyanobiphenyl-4-yl) methyl]-*N*-pentanoyl-L-valinate (9): To a solution of 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 cooled to 25 °C, was poured onto a cold saturated solution of sodium carbonate (100 mL). After being cooled to 25 °C the mixture was quenched by addition of water (20 mL) and the resulting emulsion was extracted with ethyl acetate (50 X 2 mL). The combined organic phases were washed with water (50 mL), 10% aqueous cupric sulfate solution (80 mL) and brine (100 mL). The solution was then dried over anhydrous magnesium sulfate, filtered, concentrated under vacuum and purified by column chromatography (SiO_2, ethyl acetate /hexane 3:7), to yield methyl *N*-[(2'-cyanobiphenyl-4-yl)methyl]-*N*-pentanoyl-L-valinate **9** as a yellow oil (0.75 g, 90%), ^{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].

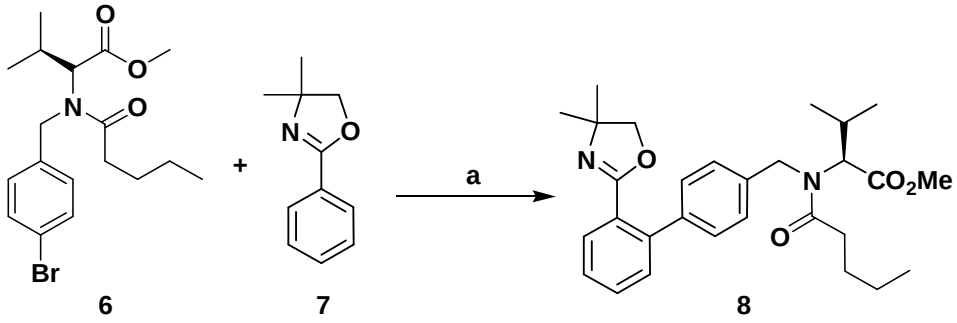
RESULTS AND DISCUSSION

In the present approach (**scheme 1**) inexpensive and commercially available valeryl chloride **3** was coupled with L-valine methyl ester hydrochloride **2** in the presence of triethyl amine in dichloromethane at 0 °C to get methyl *N*–pentanoyl-L-valinate **4** (95 % yield). Compound **4** was *N*-protected with 1-bromo-4-(bromomethyl)benzene **5** with sodium hydride in tetrahydrofuran to get methyl *N*-(4-bromobenzyl)-N-pentanoyl-L- valinate **6** (70 % yield).



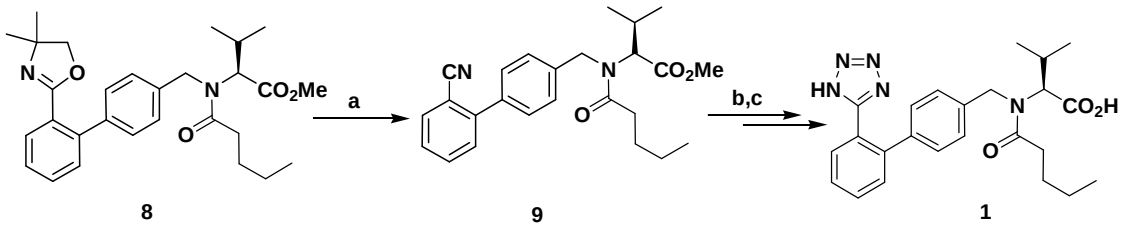
Scheme 1: (a) Et_3N, CH_2Cl_2, 0 °C, 95%; (b) NaH, THF, 70%.

The 4,4-dimethyl-2-phenyl-4,5-dihydrooxazole **7** was metalated with 2.5M n-BuLi at 0 ^oC for 60 mints and transmetalated with $ZnCl_2$ in THF solvent. The methyl *N*-(4-bromobenzyl)-*N*-pentanoyl-L-valinate (aryl bromide) **6** was then added with tetrakis(triphenylphosphine)palladium (0) and the mixture was stirred for 24 h at 55 ^oC to afford the methyl *N*-{[2'-(4, 4-dimethyl-4, 5-dihydro-1, 3-oxazol-2-yl)biphenyl-4-yl] methyl}-*N*-pentanoyl-L-valinate[7] **8** (55 % yield) (**Scheme 2**).



Scheme 2: (a) n-BuLi, $ZnCl_2$, $Pd(PPh_3)_4$, THF, 24 h, 55 %.

The compound **8** (Scheme3) in pyridine was treated with phosphorous oxychloride at 0 °C and heated at 85 °C any time to get methyl-*N*-[(2'-cyanobiphenyl-4-yl)methyl]-*N*-pentanoyl-L-valinate[7] **9** in 90% yield. The conversion of compound **9** to compound **1** has already been reported in the literature.[7]



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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 % yield).

CONCLUSION

In summary, an extremely efficient approach to the biphenyl oxazoline structure of the Valsartan has been developed by employing a combination of the directed ortho metalation and Negishi coupling methodologies.

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