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A simple and efficient synthesis of the valsartan

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Abstract

Valsartan **1**, one of the most important agents used in antihypertensive therapy today, was synthesized starting from L-valin methyl ester hydrochloride **2** through four steps in an overall yield of 60%. The key step involves the palladium-catalyzed Suzuki coupling. This method overcomes many of the drawbacks associated with the previously reported syntheses and is more suitable for industrial production.

Keywords: Valsartan; Antihypertensive; L-Valin methyl ester hydrochloride; Synthesis; Suzuki coupling

Angiotensin II (A-II) is the principle pressor agent of the rennin angiotensin system (RAS), which plays a critical role in the regulation of blood pressure. Prevention of the formation of A-II, via inhibition of angiotensin converting enzyme (ACE) [1], 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** [2].

Although several methods had been reported for the synthesis of valsartan **1** [3], some of these methods demanded however rather severe conditions and particular reagents which were not readily available while others often required more than four steps in the synthesis and had not been amenable to large-scale synthesis. Based on our previous work about the total synthesis of valsartan **1** [4], we would like to disclose a more efficient and convergent synthetic route to valsartan **1** (Fig. 1) in three linear steps with high overall yield from L-valin methyl ester hydrochloride **6**.

The first part of the synthesis was the preparation of the key intermediate **5**, which would be used for Suzuki coupling. A solution of benzonitrile **2**, NH_4Cl, NaN_3 and LiCl in DMF was heated and stirred for 10 h at 100 °C to afford the product **3** in 90% yield [5]. The triphenylmethylation was carried out by addition of triphenylmethyl chloride to a mixture of **3** and Et_3N in CH_2Cl_2 at 0 °C and then the reaction mixture was stirred at room temperature for 3 h to produce the compound **4**. Compound **4** was treated with *n*-BuLi in THF for 1 h. Then trimethyl borate ester was added at −78 °C and the resulting mixture was stirred for 2 h at the same temperature to afford the key intermediate **5** (Scheme 1).

The second part started from L-valin methyl ester hydrochloride **6** (Scheme 2). Compound **6**, K_2CO_3 and 4-bromobenzyl bromide in DMF were allowed to heat at 80 °C for 3 h to give the alkylation product **7**. The next step was the palladium-catalyzed Suzuki coupling reaction [6], which was conducted with the boronic acid **5** and aryl bromide **7**

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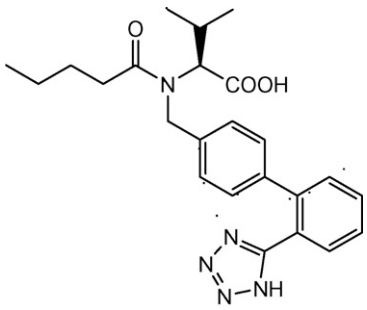
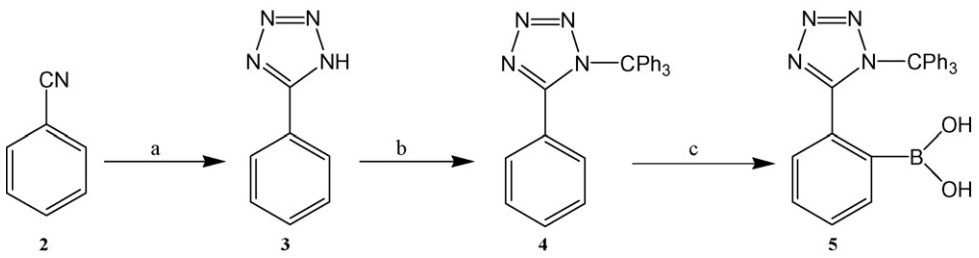
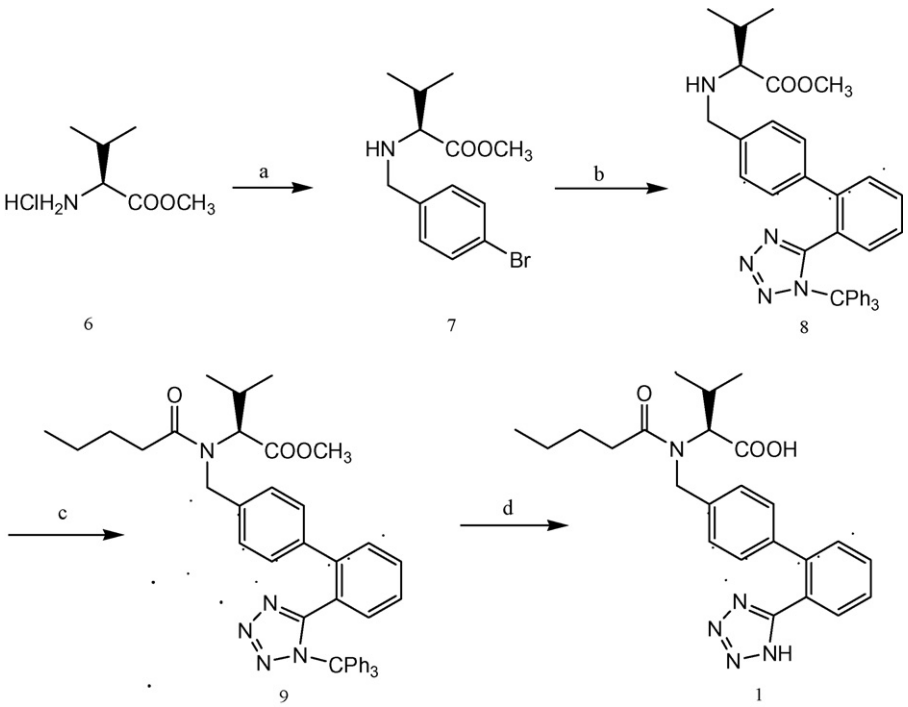


Fig. 1. The structure of valsartan 1.



Scheme 1. Reagents and conditions: (a) NH_4Cl, NaN_3, LiCl, DMF, 100 °C, 12 h, 96%; (b) Ph_3CCl, Et_3N, CH_2Cl_2, 94%; (c) *n*-BuLi, $B(OMe)_3$, THF, 94%.



Scheme 2. Reagents and conditions: (a) K_2CO_3, 4-bromobenzyl bromide, DMF, 80 °C, 88%; (b) compound 5, Na_2CO_3, $Pd(PPh_3)_4$, toluene, H_2O, 80 °C, 77%; (c) valeroyl chloride, pyridine, CH_2Cl_2, 0 °C, 90%; (d) (1) 1 mol/L NaOH (or *p*-TsOH), MeOH, reflux; (2) 3 mol/L NaOH, MeOH, reflux, 98%.

in the presence of K_2CO_3 and $Pd(PPh_3)_4$ at 80 °C for 10 h to afford the coupling product **8** in 75% yield. Acylation of **8** with valeroyl chloride was realized in the presence of pyridine in CH_2Cl_2 at 0 °C to produce the compound **9**. Deprotection of triphenylmethyl group and hydrolysis of the methyl ester could be carried out with NaOH in one-pot manner without isolation of the intermediate to achieve the anticipated product, valsartan **1** [6,7] in almost 100% yield.

In summary, a simple and efficient approach had been described. The overall yield of this approach was nearly 60%. The approach we had developed for the preparation of valsartan **1** had several advantages over the previously published methods. All of the starting materials were readily available and were relatively inexpensive. The reactions could be performed on large scale with minimal inconvenience and the desired products were obtained in reasonable yields. Application of this approach provided a practical procedure to the synthesis of valsartan **1**.

Acknowledgments

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[7] Spectral data of synthetic compound (1): m.p. 116–117 °C; $[\alpha]_D^{24}$ −63 (c 3, MeOH); 1H NMR (400 MHz, CD_3OD (δ ppm): 0.77–0.90 (m, 3H), 0.92–0.99 (m, 3H), 1.00–1.12 (m, 3H), 1.21–1.33 (m, 1H), 1.35–1.43 (m, 1H), 1.44–1.59 (m, 1H), 1.63–1.67 (m, 1H), 2.14–2.37 (m, 1H), 2.49–2.55 (m, 1H), 2.60–2.68 (m, 1H), 3.30–3.34 (m, 1H), 4.11–4.13 (m, 1H), 4.57–4.79 (m, 1H), 7.00–7.24 (m, 4H), 7.50–7.62 (m, 2H), 7.63–7.65 (m, 2H). 13C NMR (100 MHz, CD_3OD (ppm): 14.17, 19.29, 19.43, 20.03, 20.59, 23.28, 23.35, 28.40, 28.51, 29.13, 34.35, 34.44, 47.35, 50.59, 64.95, 67.88, 124.09, 124.26, 127.75, 128.63, 128.81, 128.94, 129.77, 130.29, 131.58, 131.76, 132.45, 138.66, 138.85, 139.41, 139.61, 143.01, 143.14, 156.56, 156.68, 172.88, 173.51, 176.91, 177.12. MS (FAB): M^+ = 435, found: 436 (M^++1), 458 (M^++Na). IR (film): 3430, 3116, 2963, 2933, 2873, 2745, 2615, 1733, 1602, 1472, 1410, 1274, 1205, 1163, 1106, 1054, 998, 938, 853, 814, 759, 683, 623, 561, 519 cm^{-1}.