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An Efficient and Telescopic Process for Valsartan, an Angiotensin II Receptor Blocker†

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ABSTRACT: An efficient, telescopic, and scalable process for an antihypertensive drug substance, valsartan with an overall yield of 58%, and ~99.9% purity is described. A simple, and safe process is developed for the recovery of tributyltin chloride from the tributyltin hydroxide, byproduct formed in the tetrazole ring construction, and reused in the synthesis of valsartan.

INTRODUCTION

The angiotensin II (AT-II) receptor blockers (ARBs) represent a newer class of antihypertensive agents. AT-II, formed in the blood by the action of angiotensin converting enzyme (ACE), is a very potent vasoconstrictive and volume-retaining hormone, which plays a critical role in the regulation of blood pressure.[1,2] ARBs are safe, and effective agents for the treatment of hypertension, anxiety, glaucoma, and heart failure, either alone or in conjunction with hydrochlorothiazide.[3] Valsartan 1 (brand name, Diovan) dilates blood vessels and reduces blood pressure by blocking the action of AT-II. Due to the superior efficacy, protection, tolerability, and patient compliance valsartan has become a leading antihypertension drug in the class of ARBs. Soon after its introduction in 1996, the demand for valsartan rapidly increased. A recent study revealed Diovan was prescribed more than 12 million times in the United States, and global sales were approximately $ 6.0 billion. A study released by the *Journal of Clinical Investigation* found some efficacy of valsartan in the treatment, and prevention of Alzheimer's disease (in a mouse model) although such use is considered to be highly experimental.[4]

Reports are available in the literature regarding the various routes, methodologies, and processes that have been adopted for the preparation of valsartan.[5] These processes have restricted application in the industry because of less overall yield, cumbersome workup process, difficult post-treatment and recovery of excessive organotin reagent. Recently, Wang et al.[6] developed an improved synthesis of valsartan, involving recovery of tributyltin chloride via tributyltin fluoride by treating with sodium fluoride. However, this process is also encumbered by some disadvantages such as (a) treatment with hydrochloric acid poses safety issues as it generates hydrazoic acid from the unreacted azide present in the reaction mixture. Hydrazoic acid is toxic, and extremely explosive in organic solutions;[7] (b) is highly corrosive on contact with a poisonous byproduct, hydrofluoric acid; (c) usage of polytetrafluoroethylene (PTFE) reactor to deal with the hydrofluoric acid; and (d) fractional distillation of tributyltin chloride, which increases the handling risk as tributyltin chloride has powerful odor, causes rashes when absorbed from the skin, and is toxic.[8] In view of high volume requirement, huge revenues associated with this molecule, and disadvantages from the reported processes, there arises a need to develop an efficient and scalable process for valsartan, meeting with all the regulatory aspects.

Construction of a tetrazole ring in the synthesis of valsartan involves the reaction of tributyltin azide and nitrile compound followed by deprotection of the tributyltin-protected tetrazole moiety. Removal of the tributyltin protection from the tetrazole ring can be achieved by treatment with sodium hydroxide,[9] wherein tributyltin hydroxide would be obtained as a byproduct. Basic hydrolysis using sodium hydroxide would generate sodium azide, if the unreacted tin azide is present in the reaction mixture. Sodium azide is not explosive and decomposes in a more controlled way upon heating, releasing nitrogen gas.[10] It was envisioned that, the thus obtained tributyltin hydroxide can be recycled as tributyltin chloride, which can be reused in the tetrazole ring construction. To the best of our knowledge such an approach has hitherto not been reported. Herein we describe an efficient, telescopic, and scalable process for valsartan from the commercially available starting materials.

RESULTS AND DISCUSSION

Our synthesis (Scheme 1) commenced from the commercially available chiral pure biphenyl amino acid methyl ester **2**, and valeroyl chloride. Valeroylation of biphenyl derivative **2** using valeroyl chloride in the presence of sodium carbonate in *o*-xylene medium furnished the desired intermediate **3**. The organic layer containing the intermediate **3** as such was taken forward to the next reaction, tetrazole formation. In our studies, it was found that minor quantities of unreacted compound **2** if present in the reaction mixture would participate in the

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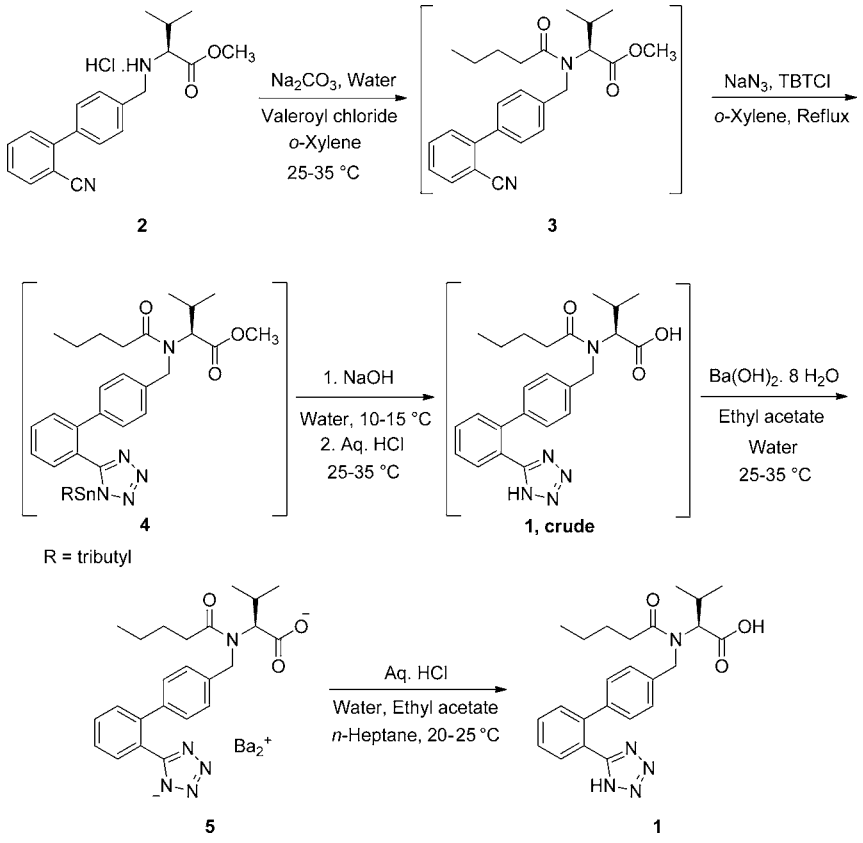
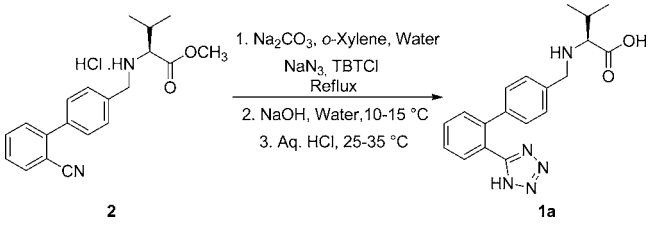
Scheme 1. Synthetic route for valsartan



subsequent reactions, and result in the desvaleroyl valsartan **1a** (Scheme 2).

Scheme 2. Synthetic route for desvaleroyl valsartan



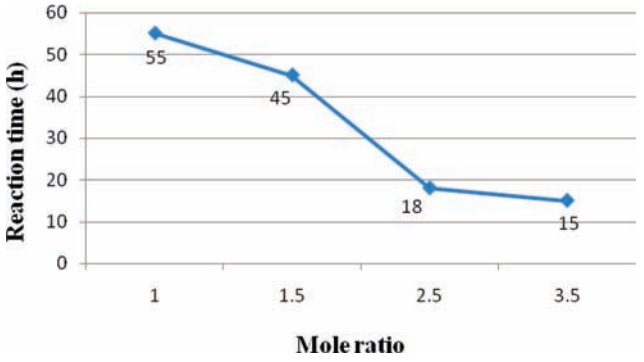


Figure 1. Effect of tributyltin chloride and sodium azide mole ratio on rate of reaction.

The buildup of the tetrazole ring was accomplished following the widely practiced protocol by refluxing a mixture of nitrile compound **3** and tributyltin azide (generated in situ from tributyltin chloride and sodium azide) in *o*-xylene. During the study, it was found that the mole ratio of tributyltin chloride and sodium azide have significant impact on the rate of reaction. The tetrazole formation reaction was proceeded smoothly, and in shorter period (18 h) when 2.5 mols each of tributyltin chloride, and sodium azide were utilized, further increasing the mole ratio beyond this limit, proved futile as there was no significant reduction in the reaction time (Figure 1). In addition, the levels of the impurities generated during the reaction were increased. Thus, 2.5 mols each of tributyltin chloride and sodium azide were ideal to result in intermediate **4**.

At this point, it was planned to simultaneously deprotect the tributyltin group from the tetrazole and also to hydrolyze the ester group. Ester hydrolysis is a crucial step as it may cause racemization, since the ester group is connected to the chiral center. In view of this, the hydrolysis reaction was studied carefully. We wanted to utilize the sodium hydroxide as a base for the deprotection of the tributyltin group and ester hydrolysis, as it is a cheaply available base. The quantity of base can have significant impact on the quality of hydrolyzed product. In this regard, we explored the quantity of the sodium hydroxide required to accomplish the complete deprotection of tributyltin as well as ester hydrolysis. The results obtained from the study showed that the mole ratio of the sodium hydroxide has no influence on the racemization; however, the rate of reaction was affected significantly (Table 1). It was found that 6 mol of sodium hydroxide was optimum to bring about an efficient hydrolysis of ester and deprotection of the tributyltin group (entry 3, Table 1).

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Table 1. Optimization of sodium hydroxide mole ratio (m/r) in the hydrolysis reaction

		purity by HPLC (%)			
entry	NaOH (m/r)	chemical	chiral	time (h)	yield (%)
1	4.0	94.0	96.3	30	71
2	5.0	95.0	96.8	25	82
3	6.0	97.1	96.7	12	85
4	10.0	95.3	96.9	9	85

After fixing the sodium hydroxide mole ratio, another key process parameter, reaction temperature, was studied. The hydrolysis reaction was carried out at different temperatures, and the results clearly indicated that the rate of reaction and the chemical and chiral purities were significantly influenced by the temperature. The rate of reaction was increased by increasing the temperature, whereas the chemical and chiral purities decreased. The optimum reaction temperature for the hydrolysis reaction was found to be 10−15 °C (Table 2).

Table 2. Study of temperature in the hydrolysis reaction

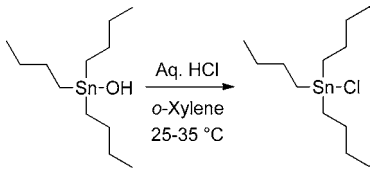
		purity by HPLC (%)			
entry	temp (°C)	chemical	chiral	time (h)	yield (%)
1	0−5	97.8	97.7	30	77
2	10−15	97.7	97.8	18	84
3	25−35	97.1	96.7	12	85
4	50−55	95.5	92.0	8	84

Therefore, deprotection of the tributyltin group and the ester hydrolysis with sodium hydroxide furnished the crude valsartan as the sodium salt, which solubilized in the aqueous layer, and the byproduct, tributyltin hydroxide (TBTOH), was a suspension in the *o*-xylene layer. It was observed that tributyltin hydroxide was sparingly soluble in the aqueous layer containing the valsartan sodium salt. To make the aqueous layer completely free from this inorganic impurity, the pH of the aqueous layer was adjusted to 6.5−7.0 using dilute hydrochloric acid, and the aqueous layer was then washed with dichloromethane. Subsequently, the aqueous layer pH was adjusted to 3−4, and the resulting valsartan free acid was extracted into the ethyl acetate. The chemical and chiral purities of the valsartan free acid were found to be 97.7% and 97.8%, respectively. In order to enhance the purity, the ethyl acetate layer containing the valsartan crude was treated with barium hydroxide octahydrate in the water medium to furnish the valsartan barium salt **5**. The valsartan barium salt that precipitated from the reaction mixture was isolated and displayed an enhancement in chemical purity to 99.6% and in chiral purity to 99.8% with an overall yield of 75% (after four chemical reactions, conversion of **2** → **5**).

The release of the valsartan free acid **1** from the highly pure valsartan barium salt **5** was achieved by adjusting the pH of the mixture containing **5**, water, and ethyl acetate with dilute hydrochloric acid to 2.5−3.5. Initially, the valsartan free acid was isolated from the ethyl acetate layer by cooling to 0−5 °C; however, this process resulted in 55% yield. Optimization of the solid isolation temperature, and time increased the yield slightly (60%). Therefore, the further yield improvement study was carried out by using a solvent/antisolvent technique; *n*-heptane as an antisolvent provided an optimum yield of 77% with 99.9% chemical purity, and 99.98% chiral purity at 20−25 °C. Complete analysis of the final product showed the barium content to be less than 5 ppm and the tin content to be less than 1 ppm (Table 3). This process was demonstrated successfully on a commercial scale of 150 kg of **2**.

After achieving the valsartan with high quality and yield, our focus was shifted to the toxic tin waste, tributyltin hydroxide, generated in the tetrazole ring construction. In recent studies, we found that the byproduct tributyltin hydroxide, formed during the tetrazole ring construction, could be converted into tributyltin chloride which can then be reused for the same reaction. The *o*-xylene layer containing the byproduct, tributyltin hydroxide, was treated with dilute hydrochloric acid to regenerate the active tributyltin chloride (Scheme 3).

Scheme 3. Conversion of tributyltin hydroxide into tributyltin chloride



The *o*-xylene layer containing the recovered tributyltin chloride as such was efficiently reused in the construction of tetrazole ring. Adopting this methodology, the recovery and reuse of tributyltin chloride was demonstrated at a scale of 150 kg of **2**.

CONCLUSION

An efficient, telescopic, and scalable process has been developed for synthesis of valsartan with an overall yield of 58%. The drug substance, valsartan synthesized through this protocol complied with all the regulatory requirements. The byproduct, tributyltin hydroxide, formed during the tetrazole ring construction was recycled as tributyltin chloride and reused in the same reaction, which enabled us to develop an environmentally friendly process. The process described in this article has certain advantages over the reported processes.

EXPERIMENTAL SECTION

A liquid chromatograph equipped with variable wavelength UV detector and integrator was used in recording HPLC

Table 3. Quality data of valsartan

	purity by HPLC (%)			RS[a] by GC (%)				
entry	chemical	chiral	**1a**	*n*-heptane	EA[c]	Sn (ppm)	Ba (ppm)	yield (%)[b]
1	99.91	99.95	ND	3245	ND[d]	<1.0	<5.0	57.7
2	99.92	99.98	ND	2243	ND	<1.0	<5.0	58.3
3	99.89	99.99	ND	1938	ND	<1.0	<5.0	58.1

[a]RS = Residual solvents. [b]Overall yield. [c]EA = ethyl acetate. [d]ND = not detected.

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chromatogram. Mass spectra were recorded using 4000-Q-trap LC−MS/MS mass spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 at 500 MHz on a Varian Unity INOVA 500 and 400 MHz on a Mercury Plus Varian 400 MHz FT NMR spectrometer; the chemical shifts are reported in δ (ppm) relative to TMS (δ 0.00 ppm), and DMSO-d_6 (δ 39.50 ppm). IR spectra were recorded on a Perkin-Elmer FT IR instrument (KBr pellet method). The thermal analysis was carried out on DSC Q1000 TA. The thermogram was recorded from 40 to 160 °C under the nitrogen flow of 50 mL/min at a heating rate of 10 °C/min. The tin content was analyzed by an inductively coupled plasma optical emission spectrometry (ICP-OES) method.

***N*-(1-Oxopentyl)-*N*-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl-L-valine Barium (5).** A suspension of **2** (150 kg, 0.418 kmol) in *o*-xylene (450 L) was treated with a solution of sodium carbonate (44.4 kg, 0.419 kmol) in water (450 L) at room temperature, and layers were separated. Sodium carbonate (44.4 kg, 0.419 kmol) was charged into the organic layer followed by valeryl chloride (90 kg, 0.747 kmol) was added in three equivalent lots with 1 h maintenance at room temperature between each lot. The reaction mixture was stirred for 2 h at room temperature, water (150 L) was charged, and the organic layer was separated followed by washing with a solution of aqueous HCl (assay 33%, 38 L, 0.343 kmol) in water (338 L). To the organic layer were charged *o*-xylene (450 L), tributyltin chloride (340 kg, 1.044 kmol), and sodium azide (67.8 kg, 1.043 kmol) at room temperature. The reaction mixture was heated to 145 °C, stirred for 18 h, and then cooled to room temperature, and the unwanted solid (sodium chloride) filtered . The filtrate was charged into a solution of sodium hydroxide (100.5 kg, 2.512 kmol) in water (780 L) at 10−15 °C and stirred for 18 h. The layers were separated at 25−35 °C, and the aqueous layer was washed with *o*-xylene (2 × 225 L). Dichloromethane (600 L) was charged into the aqueous layer, pH was adjusted to 6.5−7.0 with a solution of aqueous HCl (assay 33%, 150 L, 1.356 kmol) in water (150 L), and the layers were separated. The aqueous layer was washed with dichloromethane (2 × 400 L) and treated with charcoal (7.5 kg) for 60 min. Ethyl acetate (450 L) was charged into the aqueous layer, and the pH was adjusted to 3−4 with a solution of aqueous HCl (assay 33%, 120 L, 1.085 kmol) in water (120 L). The aqueous and the organic layers were separated, and product was extracted from the aqueous layer with ethyl acetate (450 L). Total organic layers were combined and washed with water (150 L) followed by a solution of sodium chloride (22.5 g) in water (150 L). Water (900 L) was charged to the ethyl acetate layer and stirred for 15 min, and barium hydroxide octahydrate (165 kg, 0.523 kmol) was charged. The resultant reaction mixture was stirred for 2−3 h at room temperature and the precipitated solid filtered. The wet solid was washed with ethyl acetate (150 L) and dried under vacuum at 75−80 °C to furnish 180 kg (75%) of the title compound. Purity by HPLC: chemical 99.6%, chiral 99.8%. IR (KBr, cm^{-1}): 2958, 2929, 2870, 1628, 1570, 1460, 1409, 1355, 1104, 1008. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.73 (d, J = 6.8, Hz, 3H), 0.89 (t, J = 7.6 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H), 1.12−1.60 (m, 4H), 1.97−2.18 (m, 2H), 2.39−2.45 (m, 1H), 3.75, 4.47 (d, J = 10.4, 10.4 Hz, 1H), 4.52, 4.75 (d, J = 17.2, 17.2 Hz, 2H), 6.94 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 1H), 7.28−7.38 (m, 3H), 7.52−7.58 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.8, 14.0, 19.4, 20.5, 20.8, 21.9, 22.1, 27.1, 27.3, 28.0, 33.0, 45.9, 48.2, 70.2, 125.7, 126.6, 127.5, 128.4, 128.9, 130.0, 130.5, 132.2, 137.2, 138.0, 139.4, 140.6, 160.8, 173.5, 173.7, 176.6, 176.9. Mass: 436.4 (M + H)$^+$, 458.6 (M + Na)$^+$.

***N*-(1-Oxopentyl)-*N*-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl-L-valine (1).** To a solution of **5** (35 kg, 0.061 kmol) in ethyl acetate (140 L) and water (175 L) was added a solution of aqueous HCl (assay 33%, 14 L, 0.126 kmol) in water (14 L), and the pH was adjusted to 2.5−3.5 at room temperature. The organic layer was separated, and product was extracted from the aqueous layer with ethyl acetate (35 L). Total organic layers were combined, and the solvent was distilled completely below 45 °C under vacuum. The residue was cooled to room temperature and dissolved in ethyl acetate (175 L). The resulted solution was cooled to 20−25 °C, *n*-heptane (525 L) was slowly added and stirred for 2−2.5 h. The solid was filtered and washed with *n*-heptane (4 L). The wet solid was dried in FBD at 35 °C for 3−4 h, followed by 4 h at 65−70 °C to obtain 20.6 kg (77%) of the title compound. Purity by HPLC: chemical 99.91%, chiral 99.95%. Barium content: <5 ppm. Tin content: <1.0 ppm. Ethyl acetate: 0 ppm, *n*-heptane: 3245 ppm. DSC: 99.4 °C. $[\alpha]^{20}_{D}$ = (−) 65.6 (c = 1% w/v in methanol). IR (KBr, cm^{-1}): 3418, 2953, 2923, 2854, 1730, 1599, 1459, 1377. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (d, J = 6.0 Hz, 6H), 0.99 (t, J = 6.8 Hz, 3H), 1.38−1.48 (m, 2H), 1.71−1.79 (m, 2H), 2.61 (t, J = 7.6 Hz, 2H), 2.68−2.75 (m, 1H), 3.40 (d, J = 11.2 Hz, 1H), 4.22, 4.98 (d, J = 14.8, 14.8 Hz, 2H), 7.20 (m, 4H), 7.47 (d, J = 8.0 Hz, 1H), 7.53 (t, J = 7.6 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.7, 13.8, 18.4, 18.8, 19.4, 20.1, 21.6, 21.8, 26.8, 27.0, 27.5, 32.4, 45.4, 48.7, 62.9, 65.7, 123.5, 126.3, 126.9, 127.5, 128.3, 128.8, 130.5, 130.6, 131.0, 137.1, 137.8, 138.2, 141.2, 141.3, 154.9, 171.6, 171.9, 173.4, 173.5. Mass: 436.2 (M + H)$^+$, 458.4 (M + Na)$^+$. Anal. Calcd for $C_{24}H_{29}N_5O_3$ (435.52): C, 66.19, H, 6.71, N, 16.08. Found: C, 66.09, H, 6.71, N, 15.76.

Tributyltin Chloride Recovery. The *o*-xylene layer containing tributyltin hydroxide (1300 L, 1.044 kmol, equivalent to 340 kg of tributyltin chloride) from the 150 kg batch of **2** was charged into a reactor, and around 650 L of *o*-xylene was distilled below 90 °C under reduced pressure. The resultant reaction mixture was cooled to room temperature, and water (500 L) was charged and stirred for 30 min. A solution of aqueous HCl (33% assay, 124 L, 1.121 kmol) and water (124 L) was charged into the reaction mixture and stirred for 3 h at room temperature. The organic layer was separated, and the aqueous layer was washed with *o*-xylene (100 L). Total organic layers were combined (695 kg, tributyltin chloride assay 43%) to furnish 299 kg (88%) of recovered tributyltin chloride. IR (KBr, cm^{-1}): 2957, 2925, 2872, 2855, 1463, 1377, 1075, 876. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87−0.97 (m, 9H), 1.27−1.39 (m, 12H), 1.61−1.68 (m, 6H).

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Notes

The authors declare no competing financial interest.

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