Organic Process Research & Development

Article

pubs.acs.org/OPRD

An Efficient, Commercially Viable, and Safe Process for Preparation of Losartan Potassium, an Angiotensin II Receptor Antagonist

Suri Babu Madasu,[†,‡] N. A. Vekariya,[*,†] Ch Koteswaramma,[†] Aminul Islam,[†] Paul Douglas Sanasi,[‡] and Raghu Babu Korupolu[‡]

[†]Chemical Research and Development, Aurobindo Pharma Ltd., Survey Nos.71 and 72, Indrakaran (V), Sangareddy (M), Medak District 502329, Andhra Pradesh, India

[‡]Engineering Chemistry Department, AU College of Engineering, Andhra University, Visakhapatnam-530003, Andhra Pradesh, India

ABSTRACT: An efficient, commercially viable and safe process for the preparation of losartan potassium, an antihypertensive drug substance, with an overall yield of 55.5% and ~99.9% purity (including five chemical reactions and two recrystallizations) and meeting all other regulatory requirements is described. Formation and control of all the possible impurities are also described.

INTRODUCTION

The renin−angiotensin system (RAS) is known to play an important role in cardiovascular regulation and the maintenance of blood pressure.[1] Angiotensin II is the principal active hormone of this system and acts through the stimulation of specific receptors located on various organs.[2,3] Angiotensin II antagonists are known medicaments used in the treatment of hypertension, anxiety, glaucoma, and cardiac events. One effect of angiotensin II production is vasoconstriction, resulting in an increase in systemic blood pressure. Interruption of the RAS has been shown to be an effective means of controlling hypertension as evidenced by the success of the angiotensin-converting-enzyme (ACE) inhibitors.[4,5] The actions of angiotensin II are mediated by angiotensin receptors AT_1 and AT_2. Most of the known actions of angiotensin II are mediated through the AT_1 receptors, for example vasoconstriction, aldosterone release, renal sodium reabsorption, and vasopressin secretion. The AT_2 receptor actions are blood pressure regulation and renal function. However, an alternative and possibly superior approach to controlling the RAS activity is the use of specific, nonpeptide antagonists of angiotensin II.[6,7] Among cardiovascular drugs, angiotensin II receptor antagonists such as losartan potassium (**1**) are prominently used as an active ingredient in the management of hypertension. **1** plays an effective role in patients having intolerance with ACE inhibitors.

In 1990, a group of Abbott scientists initiated an angiotensin II project using the Du Pont[8] angiotensin II antagonist as the starting point. In 1995, losartan became the first nonpeptide AT_1 receptor antagonist[9] approved by the U.S. Food and Drug Administration for clinical use. In particular, losartan is approved for the treatment of hypertension alone or in combination with other antihypertensive agents. Losartan is administered orally as its monopotassium salt. **1** is available by prescription in tablet form as a sole active ingredient (Cozaar: Merck) and as a coactive ingredient with hydrochlorothiazide (Hyzaar: Merck).

Reports are available in the literature regarding the various routes, methodologies, and processes that have been adopted for the preparation of losartan. These processes have restricted application in the industry because of less overall yield,[10,11] cumbersome workup process,[12,13] and difficult post-treatment and recovery of excessive organotin reagent.[14] To minimize the cost constraints and the number of steps, we avoided use of tributyltin azide and chose to replace tributyltin azide with sodium azide and triethylamine hydrochloride salt. A recently developed process[15] for **1** describes sodium azide and triethylamine hydrochloride salt for the construction of a tetrazole ring from the cyano group. However, this process is also encumbered by disadvantages such as treatment with hydrochloric acid which poses safety concerns as it generates hydrazoic acid from the unreacted sodium azide present in the reaction mixture. Hydrazoic acid is present ~3.45% w/w in organic solution.[16] Hydrazoic acid is toxic and extremely explosive in organic media.[17] In view of high volume requirement, huge revenues associated with this molecule, and disadvantages from the reported processes, there arises a need to develop a safe process for losartan, meeting with all regulatory aspects.

RESULTS AND DISCUSSION

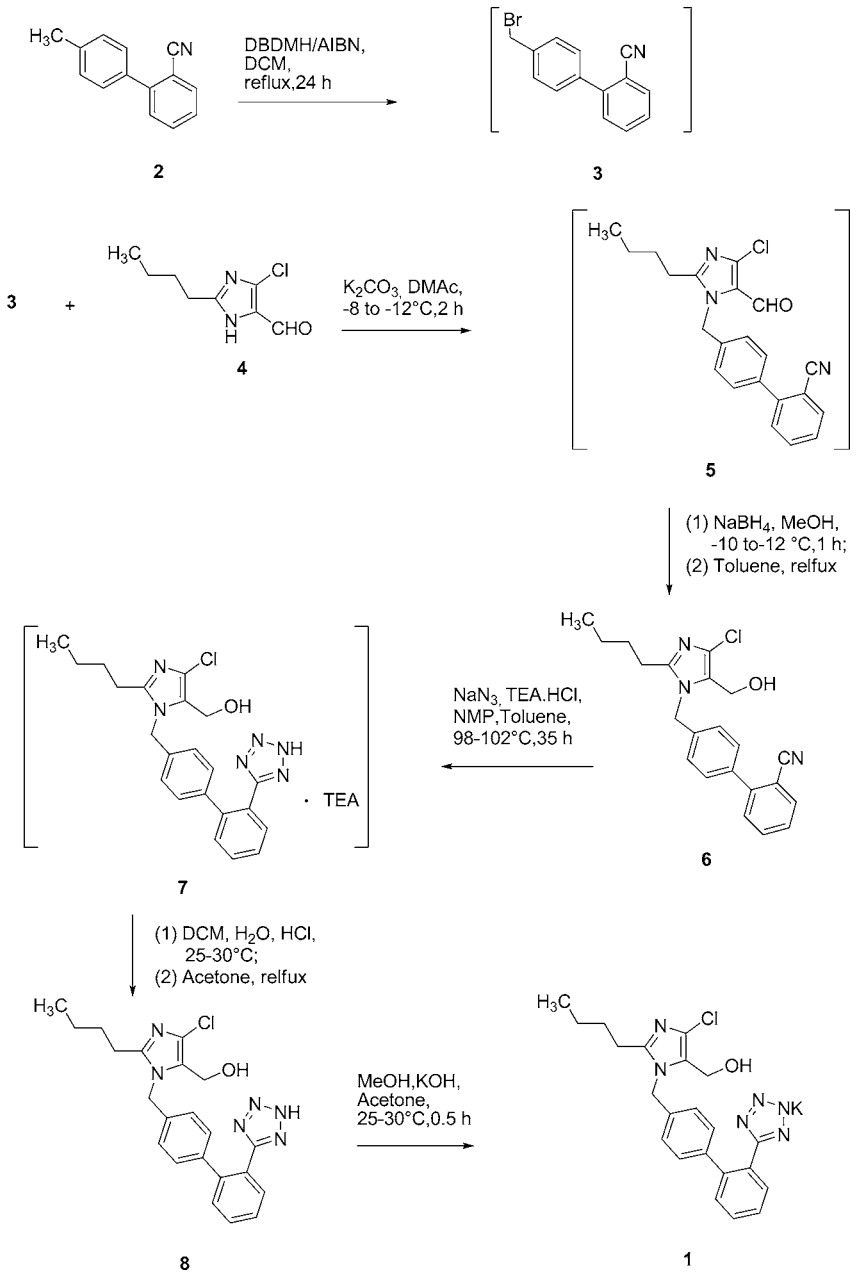
Our synthesis (Scheme 1) commenced from the commercially available *p*-tolyl benzonitrile (PTBN, **2**) and 2-*n*-butyl-4-chloro-1*H*-imidazole-5-carboxaldehyde (BCFI, **4**). Few synthetic processes for bromination of **2** with different brominating reagents are reported in the literature, such as *N*-bromosuccinamide/2,2-azobisisobutyronitrile (NBS/AIBN), NBS/benzoyl peroxide, Br_2/HOAc,[18] and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH)/AIBN. All NBS/AIBN and DBDMH/AIBN are commercially feasible and optimized in 79% and 80% isolated yield, after crystallization of the crude from methanol. Moreover, use of DBDMH/AIBN is cost-effective. The initial experiments carried out bromination of **2** in dichloromethane

Special Issue: Safety of Chemical Processes 12

Received: July 5, 2012
Published: October 15, 2012

dx.doi.org/10.1021/op300179u | *Org. Process Res. Dev.* 2012, 16, 2025−2030

Scheme 1. Synthetic route for 1



in the presence of AIBN with DBDMH at reflux for 24 h. During this reaction, bromo-PTBN **3** is formed in 85%, with 8% dibromo-PTBN **9** (formed due to over bromination, Figure 1) and a remaining 7% unreacted PTBN **2**. After achieving the unreacted PTBN limit, the dimethyl hydantoin was removed by water washing, evaporated dichloromethane, and isolation of bromo-PTBN **3** from methanol to afford pure product **3** (≥98.5%, by HPLC). The overall yield of isolated compound **3** is very low due to the solubility of the product in methanol. On the basis of experimental data, it was observed that bromo-PTBN **3** does not make any effect in the next step without isolation, and 10% yield increase realized in the isolated product. Further study regarding carry-over impact of dibromo-PTBN **9** on the product profile was conducted. During the *N*-alkylation reaction of BCFI **4** with a mixture of bromo-PTBN **3** and dibromo-PTBN **9** (30:70), it was observed that dibromo-PTBN **9** was not reacted with **4** and remained as such up to losartan cyanoalcohol **6** and was eliminated during the isolation of **6**. Thereafter, to reduce the cost of the losartan, bromination was carried out in 2 volumes dichloromethane instead of 10 without significant change in the reaction rate or handling feasibilities (Table 1) and was fixed in a mole ratio of 0.54 mol

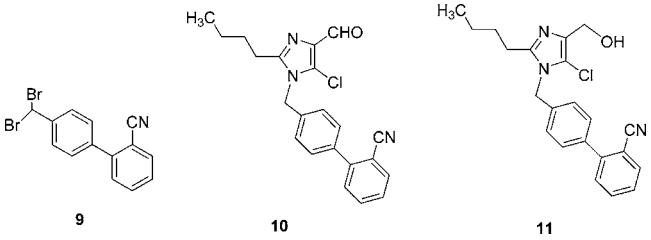


Figure 1. Structures of impurities **9**, **10**, and **11**.

dx.doi.org/10.1021/op300179u | *Org. Process Res. Dev.* 2012, 16, 2025−2030

DBDMH and 5% AIBN for reaction consistency on the basis of the experimental data.

Table 1. Screening of brominating agent, AIBN, and dichloromethane

entry	brominating reagent	mol ratio	AIBN (%)	DCM (vol)	reaction time (h)	purity by HPLC (%)[a]	yield (%)[b]
1	NBS	1.10	2	10	22	84	70.5
2	NBS	0.95	3	5	22	85	71.0
3	DBDMH	1.10	2	10	22	85	71.2
4	DBDMH	0.75	3	5	24	84	71.2
5	DBDMH	0.54	5	2	24	85	71.2
6	Br_2	1.10	2	10	18	80	68.0
7	Br_2	0.75	3	5	20	78	67.1
8	Br_2	0.54	5	2	20	75	65.5

[a]Is it reaction conversion during monitoring. [b]Isolated yields of losartan cyanoalcohol.

Reported processes[19] are available for *N*-alkylation in biphasic systems using PTC with sodium hydroxide and potassium hydroxide as bases;however, the reaction required 30 h to complete. To minimize the reaction time we evaluated the reaction in a single solvent such as dimethylacetamide, dimethylformamide, acetonitrile, or *N*-methyl-2-pyrrolidone (NMP) with potassium carbonate as base. Other than dimethyl acetamide, all other solvents furnished either lower yield or lower-purity product. Experimental results are presented in Table 2. Moreover, *N*-alkylation is completed in 2 h. Hence, the

Table 2. Screening of solvents for the *N*-alkylation

entry	solvent	temperature (°C)	time (h)	purity by HPLC (%)[a]	yield (%)[b]
1	dimethyacetamide	−8 to −12	2	80	71.2
2	dimethylformamide	−5 to −10	3	65	50.9
3	acetonitrile	−5 to −10	4	62.5	45.8
4	NMP	−5 to −10	4	69	61.0

[a]It is reaction conversion during monitoring. [b]Isolated yields of losartan cyanoalcohol.

use of dimethylacetamide would be appropriate for the reaction of **3** with **4**. After selecting dimethylacetamide as the solvent for *N*-alkylation, another key parameter, the potassium carbonate mole ratio, was studied. On the basis of the results, it was observed that a minimum of 0.86 mol is required for *N*-alkylation and more than 0.86 mol has no significant advantage (table 3).

After fixing the potassium carbonate mole ratio, it was also observed that the effect of temperature on *N*-alkylation resulted in formation of losartan cyanoaldehyde isomer **10** (Figure 1). During *N*- alkylation, the "N-1" atom of BCFI **4** will attack the

Table 3. Screening of K_2CO_3 mole ratio (m/r) for the *N*-alkylation

entry	K_2CO_3 (*m*/*r*)	purity By HPLC (%)[a]	time (h)
1	0.52	70	4
2	0.70	72	4
3	0.86	80	2
4	1.0	80	2

[a]It is reaction conversion during monitoring.

carbonium ion of bromo-PTBN **3** to form the desired product **5**. Similarly, the "N-3" atom of BCFI **4** can attack the carbonium ion of bromo-PTBN **3** to form losartan cyanoaldehyde isomer, **10**. On the basis of experimental data (Table 4), it was found that the temperature of −8 to −12 °C would be the optimum condition for *N*-alkylation to control the losartan cyanoaldehyde isomer, **10**.

Table 4. Experimental results for formation of 10

entry	temperature (°C)	time (h)	purity by HPLC (%)[a]	**10** (%)
1	−20 to −25	4	81.5	5.0
2	−8 to −12	2	81.0	4.9
3	0−5	2	78	7.0
4	25−30	1.5	72	9.5

[a]It is *N*-alkylated product conversion during monitoring.

The inorganic salts were filtered after completion of *N*-alkylation and filtrate was used in situ for next reduction reaction. This reduction reaction was carried out using methanol and sodium borohydride. Addition of sodium borohydride is highly exothermic. This issue was overcome by introducing lot wise addition at lower temperature (−8 to −12 °C) over a period of 30−45 min by maintaining temperature. After complete reduction, excess sodium borohydride was decomposed with aqueous acetic acid. Losartan cyanoalcohol **6** is precipitated after decomposition of excess sodium borohydride by addition of water and with ≥96% purity, PTBN **2**, dibromo-PTBN **9** and losartan cyanoalcohol isomer **11.** All of these impurities (Figure 1) were removed from toluene by dissolving crude material at 108−110 °C followed by cooling at 23−30 °C to obtain losartan cyanoalcohol **6** pure (HPLC purity∼99.8%).

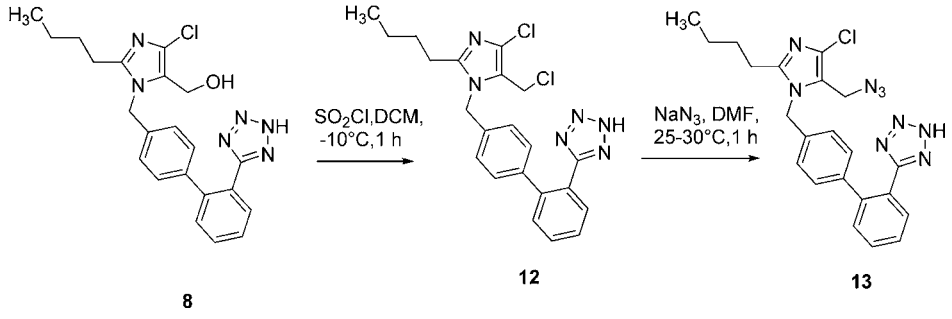
Construction of the tetrazole ring was accomplished following the widely practiced protocol by mildly refluxing the mixture of losartan cyanoalcohol **6** and hydrazoic acid triethylamine complex[20] (generated in situ from sodium azide and triethylamine hydrochloride) in toluene and NMP. During the study, it was found that the mole ratios of triethylamine hydrochloride and sodium azide have significant impact on the reaction rate and impurity profile. The tetrazole formation reaction proceeded smoothly in a shorter period (35 h) when 2.7 mol triethylamine hydrochloride and 3.0 mol sodium azide were utilized; however, at the stoichiometric ratio where one impurity due to traces of free hydrochloric acid, losartan azide **13** (Scheme 2), is formed >1%, it proved difficult to remove. Further increasing the mole ratio beyond this limit proved futile as there was no significant reduction in the reaction time. Further decreasing the mole ratio, thus taking a longer reaction time, increased the levels of the impurities. The quantities of 2.7 mol triethylamine hydrochloride and 3.0 mol sodium azide were optimal to result in intermediate **7** with not more than 0.5% losartan azide **13** impurity during reaction monitoring.

For the completion of the reaction, more than an equivalent of an amine salt to the cyano group is required. If the produced tetrazole triethylamine salt acts as a catalyst instead of triethylamine hydrochloride, a decrease in the amount of triethylamine hydrochloride should be possible; however, amine salts only react with one equivalent of the substrate[21] because the amine is stable as a tetrazole triethylamine complex and cannot be recycled in the system.

After reaction completion, workup was complicated because the reaction mass contained hydrazoic acid. Addition of

dx.doi.org/10.1021/op300179u | *Org. Process Res. Dev.* 2012, 16, 2025−2030

Scheme 2. Synthetic route for losartan azide impurity



8 12 13

Table 5. Purity data of 1

	purity by HPLC[25] (%)		[a]RS by GC (ppm)			yield (%)[b]	DSC (°C)	
entry	**1**	losartan azide	methanol	acetone	toluene		minor peak	major peak
1	99.94	0.02	[d]ND	471	[d]ND	55.52	238.18	273.63
2	99.93	0.03	[d]ND	834	[d]ND	55.59	241.32	274.06
3	99.95	0.02	[d]ND	895	[d]ND	55.55	241.63	274.12

[a]Residual solvents. [b]Overall yield. [d]Not detected.

aqueous sodium hydroxide solution followed by layer separation (three layers: organic, inorganic salts in an aqueous layer, and losartan sodium salt). Extracting losartan sodium salt into water, washing with dichloromethane, and treating with carbon was a lengthy process. Chemists on operators experienced a significant drop in blood pressure during processing, signifying a real safety concern. This tedious workup process[22] was significantly simplified as extracting losartan triethylamine salt **7** with dichloromethane. The aqueous layer contains excess HN_3·TEA, NaN_3 and inorganic salts (concentration of hydrazoic acid is ∼1.17% w/w), safely decomposed by utilizing a sodium nitrite and hydrochloric acid mixture. The absence of azide was confirmed by the following qualitative colour test.[23] To 10 mL of the mass in a test tube was added ∼1 mL of ∼2% w/v ferric chloride solution, and the absence of a blood-red coloration indicates the absence of azide.

Crude losartan **8** was isolated from a dichloromethane and water mixture by neutralizing with hydrochloric acid at pH 4.0−4.3 with an isolated solid purity ≥99.3% that consisted of unreacted losartan cyanoalcohol **6**, losartan azide **13**, degradent-1, and degradent-2.[24] All of these impurities were removed by recrystallizing the crude material from acetone to obtain losartan **8** pure (HPLC purity 99.8%).

Finally, the redesigned process furnished losartan potassium (**1**) with an overall yield of 55.5% from PTBN after five steps at around 99.9% purity and meeting other quality parameters (Table 5). We have also determined that the potassium content in **1** was found to be 8.47% w/w (by IC) which is equal to 1.0 mol (8.46% w/w; theoretically) of potassium in losartan potassium drug substance. It is concluded that losartan and potassium exist as 1:1 salt.

CONCLUSION

An efficient, commercially viable, and safe process has been developed for the synthesis of **1** with an overall yield of 55.5% and ∼99.9% purity. The drug substance, **1**, synthesized through this protocol, complied with all the regulatory requirements. The process described in this article has certain advantages over the reported processes; the major workup procedure during a cyano-to-tetrazole reaction is simplified to overcome the safety issue of hydrazoic acid.

EXPERIMENTAL SECTION

^{1}H NMR, ^{13}C NMR, and DEPT spectral data were obtained in dimethyl sulfoxide (DMSO-d_6) at 500 and 300 MHz spectrometers. The chemical shift values were reported on the δ scale in parts per million (ppm), downfield from tetramethyl silane (TMS, δ = 0.0) as an internal standard. Spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), and m (multiplet) as well as brs (broad). Coupling constants (J) are given in hertz. IR spectra were recorded in the solid state as KBr dispersion using a Perkin-Elmer Spectrum One Fourier transform (FT)-IR spectrophotometer. Mass spectrum was recorded using a Perkin-Elmer PE SCIEX-API 2000, equipped with sn ESI source used online with an HPLC system after the ultraviolet (UV) detector. HPLC chromatographic purity was determined by using an area normalization method. The thermal analysis was carried out on DSC Q 1000 TA. The thermogram was recorded from 40 to 320 °C. The solvents and reagents were used without purification.

2-*n*-Butyl-4-chloro-5-hydroxymethyl-1-[[(2^1-cyano)-[1,1^1-biphenyl]-4-yl]-methyl]-1*H*-imidazole (Losartan Cyano Alcohol) 6. To a solution of PTBN **2** (150 kg, 0.777 kmol) in dichloromethane (300 L) was added AIBN (7.5 kg, 5% w/w) and 1,3-dibromo-5,5-dimethylhydantoin (120 kg, 0.419 kmol) at room temperature. Resultant mixture was heated to reflux for 24 h at 40−42 °C. After completion of reaction removed the dimethyl hydantoin by washing with water (2 × 225 L), followed by washing with 5% aqueous SMBS solution (300 L) and finally washing with water. Evaporated the dichloromethane completely under reduced pressure at 30−45 °C to get solid bromo-PTBN **3** (∼230 kg, having HPLC purity ∼85%; PTBN ∼7%; dibromo-PTBN ∼8%). To solid bromo-PTBN (**3**) was charged *N*,*N*-dimethylacetamide (450 L) and BCFI **4** (124.8 kg, 0.669 kmol) at room temperature. The resulting mixture was cooled to −8 to −12 °C under nitrogen. Potassium carbonate (92.1 kg, 0.667 kmol; anhydrous powder) was added, and the mixture

dx.doi.org/10.1021/op300179u | Org. Process Res. Dev. 2012, 16, 2025−2030

was stirred for 2 h at −8 to −12 °C under nitrogen; thereafter, the contents were maintained at room temperature for 2 h. The inorganic salts were filtered and washed with *N*,*N*-dimethylacetamide (75 L). The filtrate contains losartan cyanoaldehyde **5** (having HPLC purity ∼80%; losartan cyanoaldehyde isomer ∼5%; PTBN ∼7%; dibromo-PTBN ∼8%). The filtrate was cooled to −8 to −12 °C under nitrogen. Methanol (150 L) was added followed by slow, lotwise addition of sodium borohydride (7.5 kg, 0.198 kmol) in 30−45 min, maintaining temperature at −8 to −12 °C under nitrogen. After addition, the contents stirred at room temperature for 1 h. Aqueous acetic acid (50% w/w, 24 kg, 0.199 kmol) was added in 15−20 min to quench the excess sodium borohydride; this mixture was stirred for 1 h, water (345 L) was added, and the resultant reaction mixture was stirred for 2−3 h at 5−10 °C. The precipitated solid was filtered, washed with water (2 × 190 L), and then with toluene (2 × 150 L) to obtain crude losartan cyanoalcohol (**6**) (∼ 300 kg). The crude **6** was dissolved in toluene (1800 L) at reflux and then cooled to room temperature. The resultant reaction mixture was stirred for 2 h, and the crystallized solid was filtered, washed with toluene (300 L), and dried under vacuum at 50−60 °C to furnish 210 kg (71.2%) of the title compound **6**. Purity by HPLC:[25] 99.8%; MR: 159−160 °C; IR (KBr, cm^{-1}): 3273.54, 2962.98, 2940.70, 2872.71, 2222.89, 1593.91, 1575.05, 1481.13, 1465.20, 1424.29, 1251.40, 1011.63, 999.23, 821.70, 777.44, 767.96; ^{1}H NMR (DMSO, 500 MHz, δ): 0.79 (t, 3H), 1.20 and 1.27 (m, 2H), 1.46 (q, 2H), 2.53 (t, 2H), 4.40 (d, 2H), 5.30 (t, 1H), 5.36 (s, 2H), 7.25 (d, 2H), 7.56 and 7.77 (m, 4H), 7.77 and 7.94 (m, 1H), 7.95 (d, 1H); ^{13}C NMR and DEPT (DMSO, 500 MHz, δ): 13.54 (CH_3), 21.59 (CH_2), 25.79 (CH_2), 29.07 (CH_2), 46.43 (CH_2), 51.39 (CH_2), 110.15 (C), 118.42 (C), 125.33 (C), 125.68 (C), 126.62 (CH, CH), 128.21 (CH), 129.0 (CH, CH), 130.01 (CH), 133.47 (CH), 133.81 (CH), 136.91 (C), 137.66 (C), 143.98 (C), 147.34 (C); MS $m/_Z$ (ESI): 380.15 $[(MH)^+]$.

2-*n*-Butyl-4-chloro-5-hydroxymethyl-1-[[(2^1-(1*H*-tetrazol-5-yl)[1,1^1-biphenyl]-4-yl]-methyl]-1*H*-imidazole (Losartan) 8. To a solution of losartan cyanoalcohol (**6**) (100 kg, 0.263 kmol) in a mixture of toluene (200 L) and NMP (58 kg, 0.586 kmol) at 70−75 °C was added sodium azide (51.4 kg, 0.790 kmol) and triethylamine hydrochloride (98.6 kg, 0.717 kmol). The resultant mixture was heated to 98−102 °C for 35 h. and cooled to room temperature. Water (800 L) was charged, and losartan was extracted as triethylamine salt **7** with dichloromethane (1 × 700 L; 1 × 300 L). The aqueous layer containing sodium azide was safely decomposed by adding sodium nitrite (35.8 kg, 0.519 kmol) and hydrochloric acid (∼71.6 kg, 0.685 kmol) at 4−10 °C in 1 h (maintaining pH at ∼2.5), and the aqueous layer was drained. The dichloromethane layer was treated with carbon and washed with dichloromethane (100 L). Water (1200 L) was charged into the organic layer, and the pH was adjusted to 4.0−4.3 with a solution of hydrochloric acid (assay 35%, 21.6 kg, 0.205 kmol). The resultant reaction mixture was stirred at room temperature for 2 h and then for 2 h at 2−5 °C; the precipitated solid was filtered, washed with dichloromethane (2 × 50 L; 2−5 °C), and then washed with water (2 × 50 L; 2−5 °C) to obtain losartan **8**, crude (∼220 kg). The crude was dissolved in acetone (500 L) at room temperature, then heated to reflux for 1 h, and thereafter cooled to room temperature. The resultant reaction mixture was stirred at room temperature for 2 h and then 2 h at 2−5 °C; the crystallized solid was filtered, washed with acetone (100 L; 2−5 °C), and dried under vacuum at 50−60 °C to furnish 91 kg (81.7%) of the title compound **8**. Purity by HPLC:[25] 99.8%; MR: 184.3−186 °C; IR (KBr, cm^{-1}): 3374.23,2952.47, 2926.14, 2867.82, 1973.78, 1579.25, 1468.81, 1436.75, 1411.42, 1358.06, 1322.74, 1263.54, 1230.22, 1191.20, 1087.22, 1034.89, 1008.04, 996.08, 763.45; ^{1}H NMR (DMSO, 500 MHz, δ): 0.80 (t, 3H), 1.21 and 1.26 (m, 2H), 1.42 and 1.48 (m, 2H), 2.45 and 2.48 (m, 2H), 4.34 (s, 2H), 5.25 (s, 2H), 7.03 and 7.10 (m, 4H), 7.52 and 7.59 (m, 2H), 7.66 and 7.69 (m, 2H); ^{13}C NMR and DEPT (DMSO, 500 MHz, δ): 13.59 (CH_3), 21.60 (CH_2), 25.78 (CH_2), 28.99 (CH_2), 46.41 (CH_2), 51.34 (CH_2), 123.59 (C), 125.25 (C), 125.64 (C, C), 126.25 (CH, CH), 127.80 (CH), 129.11 (CH, CH), 130.54 (CH), 130.57 (CH), 131.00 (CH), 136.17 (C), 138.44 (C), 141.01 (C), 147.38 (C); MS $m/_Z$ (ESI): 423.17 $[(MH)^+]$.

2-*n*-Butyl-4-chloro-5-hydroxymethyl-1-[[(2^1-(1*H*-tetrazol-5-yl)[1,1^1-biphenyl]-4-yl]-methyl]-1*H*-imidazole, Potassium Salt (1) 1. Losartan **8** (70 kg, 0.165 kmol) was dissolved in preheated methanol (834 L) at 40−45 °C and cooled to room temperature, treated with carbon (10%), and washed with methanol (70 L). To this filtrate was added a solution of potassium hydroxide (assay 85%, 10.58 kg, 0.161 kmol) in methanol (175 L) at room temperature; the mixture was stirred for 30 min and filtered through 0.22 μm. The methanol was evaporated completely under vacuum at 35−45 °C to form a residue which was stripped out with acetone (2 × 140 L) to remove the last traces of methanol. Acetone (210 L) was added, and this mixture was heated to 58−60 °C for 15−20 min. The resultant reaction mixture was stirred at room temperature for 2 h and then 2 h at 2−5 °C,; the solid was filtered, washed with acetone (117 L; 2−5 °C), and dried under vacuum at 50−60 °C to furnish 72.8 kg (95.3%) of the title compound **1**. Purity by HPLC:[25] 99.9%; Potassium content: 8.47% w/w (by IC); IR (KBr, cm^{-1}): 3374.23, 2957.18, 2930.14, 2871.51, 1982.46, 1579.66, 1471.86, 1459.70, 1358.05, 1260.03, 1188.45, 1094.05, 1008.31, 996.87, 764.02; ^{1}H NMR (DMSO, 300 MHz, δ): 0.81 (t, 3H), 1.22 and 1.29 (m, 2H), 1.43 and 1.53 (m, 2H), 2.47 and 2.52 (m, 2H), 4.32 (d, 2H), 5.21 (s, 2H), 5.30 (t, 1H), 6.90 (d, 2H), 7.10 (d, 2H), 7.26 and 7.36 (m, 3H), 7.54 (m, 1H); ^{13}C NMR and DEPT (DMSO, 300 MHz, δ): 13.7 (CH_3), 21.7 (CH_2), 25.8 (CH_2), 29.1 (CH_2), 46.5 (CH_2), 51.3 (CH_2), 125.3 (C), 125.3 (CH, CH), 125.6 (C), 126.7 (CH), 127.3 (CH), 129.4 (CH, CH), 130.1 (CH), 130.5 (CH), 132.5 (C), 134.6 (C), 139.9 (C), 141.1 (C), 147.3 (C), 160.7 (C); MS $m/_Z$ (ESI): 423.17 $[(MH)^+]$, 461.1 $[(MH)^+K]$.

AUTHOR INFORMATION

Corresponding Author

*navekariya1@rediffmail.com

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to colleagues in the Analytical Research Department of APL Research Centre, a division of Aurobindo Pharma Limited, Hyderabad, for their valuable contribution to this work. We also thank the management for giving us permission to publish this work.

REFERENCES

(1) Sealy, J. E.; Laraugh, J. H. In *Hypertension: Pathaophysiology, Diagnosis and Management*; Laraugh, J. H., Brenner, B. M., Eds.; Raven: New York, 1990; p 1287.

(2) Valloton, M. B. *Trends Pharmacol. Sci.* **1987**, *8*, 69.

(3) Marsden, P. A.; Brnner, B. M.; Ballermann, B. J. In *Hypertension: Pathaophysiology, Diagnosis and Management*; Laraugh, J. H., Brenner, B. M., Eds.; Raven: New York, 1990; p 1247.

(4) Ondetti, M. A.; Rubin, B.; Cushman, D. W. *Science* **1977**, *196*, 441.

(5) Patchett, A. A.; Harris, E.; Tristram, E. W.; Wyvratt, M. J.; Wu, M. T.; Taub, D.; Greenlee, W. J.; Lohr, N. S.; Hoffsommer, R. D.; Joshua, H.; Ruyle, W. V.; Rothrock, J. W.; Aster, S. D.; Maycock, A. L.; Robinson, F. M.; Hirschmann, R.; Sweet, C. S.; Ulm, E. H.; Gross, D. M.; Vassil, T. C.; Stone, C. A. *Nature* **1980**, *288*, 280.

(6) Soffer, R. L.; Sen, I. *J. Cardiovasc. Pharmacol.* **1985**, *7*, 63.

(7) Xei, M. H.; Liu, F. Y.; Wong, P. C.; Timmermans, P. B. M. W. M.; Cogan, M. G. *Kidney Intl.* **1990**, *38*, 473.

(8) Duncia, J. V.; Carini, D. J.; Chiu, A. T.; Johnson, A. L.; Prince, W. A.; Wong, P. C.; Wexler, R. R.; Timmermans, P. B. M. W. M. *Med. Res. Rev.* **1992**, *12*, 149.

(9) Karl, F. H.; Johannes, F. E. M. *J. Am. Soc. Nephrol.* **2002**, *13*, 1100.

(10) Veerka, M.; Putala, M.; Brath, H.; Zupancic, S. A Process for the Preparation of Sartan Derivates and Intermediates Useful in Such Process. EP 1,764,365 A, 2007.

(11) Robert, D. L.; Anthony, O. K.; Cheng, Y. C.; Edward, G. C.; Bruces, S. F.; Edward, F. R.; Chunhua, Y.; David, R. L.; Robert, A. R.; David, M. T.; Thomas, R. V.; Paul, J. R. *J. Org. Chem.* **1994**, *59*, 6391.

(12) George, B. S.; George, C. D.; David, C. H.; Anthony, O. K.; Thomas, R. V. *J. Org. Chem.* **1994**, *59*, 8151.

(13) Zachary, P. D.; Barry, K. S. *J. Org. Chem.* **2001**, *66*, 7945.

(14) Carini, D. J.; Duncia, J. V.; Paul, E.; Aldrich.; Chiu, A. T.; Johnson, A. L.; Michael, E. Pieru.; Prince, W. A.; Joseph, B. S, III; Gregory, J. Wells.; Wexler, R. R.; Wong, P. C.; Sung-Eun, Yoo.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1991**, *34*, 2525.

(15) Jang, S. Y.; Kim, S. B.; Yun, S.; Kim, H. K.; Suh, K. H. Method for preparing Losartan. WO/2007/133040, 2007.

(16) Ramakrishnan, A.; Bhushhan, V. D.; Dinesh, D. B.; Kundan, S. S. An Improved Process for the Manufacture of Losartan Potassium. WO/2007/119246, 2007.

(17) Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379.

(18) David, J. C.; John, V. D.; Pancras, C. B. W. U.S. Patent, 5,138,069, 1992.

(19) Veera, R. A.; Udaya, B. R. S.; Rajendiran, C.; Jasti, V. An Improved Process for the Preparation of Losartan. WO/2007/020654, 2007.

(20) Joo, Y.-H.; Gao, H.; Zhang, Y.; Shreeve, J. M. *Inorg. Chem.* **2010**, *49*, 3282.

(21) Kiyato, K.; Toshikazu, O.; Sunao, M.; Ryozo, O. *Synthesis* **1998**, *6*, 910.

(22) Deo, K.; Desai, S.; Rathod, D.; Parikh, C.; Mokal, R. An Improved Process for Preparing Losartan Potassium. WO/2010/029457 A2, 2010.

(23) Charles, E. R.; Calvin, M. A. *Anal. Chem.* **1957**, *29*, 854.

(24) Zhongxi, Z. Z.; Qingxi, W.; Erie, W. T.; Xue-Zhi, Q.; Dominic, I. *J. Pharm. Biomed. Anal.* **1999**, *20*, 129.

(25) HPLC Method: Hypersil BDS C_{18}, 250 mm × 4.6 mm, 5 μm; flow: 1.5 mL/min: eluent A: Buffer, preparation: Dissolve 2.03 g of sodium dihydrogen orthophosphate dehydrate in 1000 mL of water. Adjust pH to 2.45 ± 0.05 using orthophosphoric acid. Filter through 0.45 μ; eluent B: water and acetonitrile in the ratio of 20:80 (v/v); Gradient: 0 min: 67% A, 33% B; 6 min: 67% A, 33% B; 40 min: 20% A, 80% B; 50 min: 20% A, 80% B; 55 min: 67% A, 33% B; 65 min: 67% A, 33% B. UV detection at 230 nm.