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New and Improved Manufacturing Process for Valsartan

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Abstract:

A new and improved industrially viable manufacturing process for valsartan, an antihypertension drug, is described.

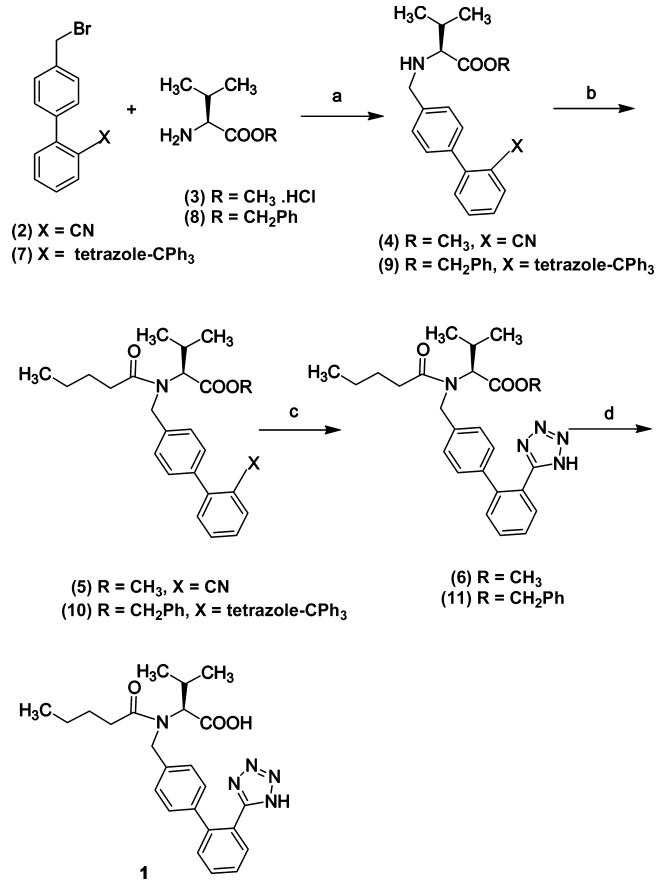
Introduction

The renin/angiotensin system (RAS) produces angiotensin II (A-II), a very potent vasoconstrictive and volume-retaining hormone, which plays a critical role in the regulation of blood pressure.[1,2] Prevention of the formation A-II, via inhibition of angiotension converting enzyme (ACE),[3] has confirmed the therapeutic benefit of inhibiting the RAS in hypertension and congestive heart failure. Valsartan **1**, commonly known as (*N*-(1-oxopentyl)-*N*-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]-methyl]-L-valine), is an orally active specific A-II receptor antagonist used as a hypotensive drug.[4] A-II receptor antagonists are safe and effective agents for the treatment of hypertension, anxiety, glaucoma, and heart failure, either alone or in conjunction with hydrochlorothiazide.[5]

Valsartan has been proposed as an alternative to the more traditional angiotensin-converting enzyme inhibitors because it selectively blocks the angiotensin type 1 (AT1) receptor.[6] Valsartan is marketed as the free acid under the name Diovan.

Several processes for the preparation of valsartan **1** have been reported in the literature.[7a−d] One of the syntheses (Scheme 1) involves reaction of 4-bromomethyl-2′-cyanobiphenyl **2** with L-valine methyl ester hydrochloride **3** to produce **4**. Compound **4** was converted into **5** by reacting with valeryl chloride in the presence of base and then cyclizing with tri-*n*-butyltinazide to form **6**. Compound **6** on hydrolysis under alkaline conditions gave **1**.

Scheme 1. **Reported route I[a] and II[b] for valsartan**



[a] Reagents and conditions: (a) *N,N*-Diisopropylethylamine, CH_2Cl_2, 72%. (b) Valeryl chloride, triethylamine, CH_2Cl_2, 92%. (c) Tributyltin azide. 62%, (d) NaOH, methanol, 50%. [b] Reagents and conditions: (a) 1,4-Dioxane, reflux, 3 h, 67%, (b) *N,N*-diisopropylethylamine, valeryl chloride, CH_2Cl_2, 25 °C, 81%. (c) 1,4-Dioxane, 1 N HCl, 60 °C, 2 h, 90%. (d) Pd/C, H_2, methanol, 24 h, 60%.

Problems associated with this synthetic process have been (a) the use of highly toxic tri-*n*-butyltinazide in the conversion of compound **5** to compound **6**[8,9] at the penultimate stage of valsartan synthesis, (b) contamination of final product with traces of toxic tin metal, (c) racemisation of valsartan up to 15% during hydrolysis under basic conditions,[10] and (d) low purity and low yield of valsartan. To achieve acceptable purity, chiral purity and acceptable limit of tin as per ICH guidelines to meet the pharmaceutical compositions, a series of purifications are being demanded, resulting in low yield.

Another process for preparation of valsartan by the same authors has been described in Scheme 1. Compound **7** was

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(1) Duncia, J. V.; Chiu, A. T.; Carini, D. J.; Gregory, G. B.; Johnson, A. L.; Price, W. A.; Wells, G. J.; Wong, P. C.; Calabrese, J. C.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1990**, *33*, 1312.

(2) Sealey, J. E.; Laragh, J. H.; *Hypertension: Pathophysiology, Diagnosis and Management*; Laragh, J. H., Brenner, B. M., Eds.; Raven: New York, 1990, 1287.

(3) Wyvratt, M. J.; Patchett, A. A. *Med. Res. Rev.* **1985**, *5*, 483.

(4) Buhlmayer, P.; Furet, P.; Criscione, L.; De Gasparo, M.; Whitebread, S.; Schmidlin, T.; Lattmann, R.; Wood, J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 29.

(5) Cocolas, G. H., Delgado, J. N.; Remers, W. A., Eds. *Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 10th ed.; Lippincott-Raven: Philadelphia, New York, 1998; p 603.

(6) Wexler, W. A.; Greenlee, W. J.; Irvin, J. D.; Goldberg, M. R.; Prendergast, K.; Smith, R. D.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1996**, *39*, 625.

(7) (a) Buhlmayer, P.; Ostermayer, F.; Schmidlin, T. U.S. Patent 5,399,578, 1995. (b) Rukhman, I.; Dolitzky, B. Z.; Flyaks, E. U.S. Patent 7,199,144, 2007. (c) Radi, S.; Stach, J.; Dedinova, E. EP 1,622,882,2004. (d) Cosme Gomez, A.; Paloma Nicolau, F. E. PCT WO 2008/138871, 2008.

(8) Wittenberger, S. J.; Donner, B. G. *J. Org. Chem.* **1993**, *58*, 4139.

(9) Chen, Z.; Guojun, Z.; Lijing, F.; Li, Y. *Synlett* **2006**, 477.

(10) Boojamra, C. G.; Burow, K. M.; Thompson, L. A.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 1240.

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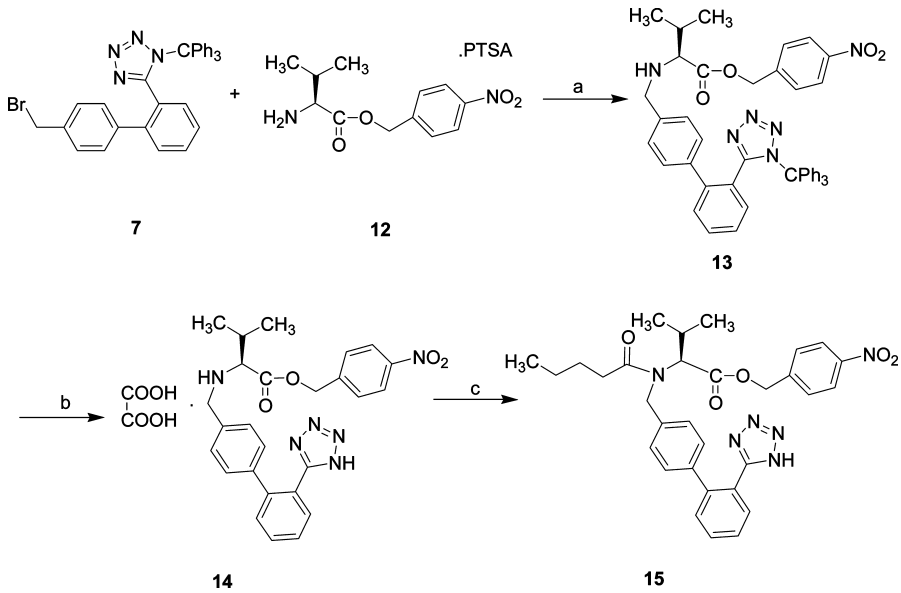
Scheme 2[a]



[a] Reagents and conditions: (a) *N*,*N*-Diisopropylethylamine, DMF, 45 °C. (b) Methanol, IPA-HCl, oxalic acid, 25 °C, 3 h. (c) Na_2CO_3, valeryl chloride, *N*,*N*-diisopropylethylamine, toluene, 10 °C, 5 h.

reacted with L-valine benzyl ester, **8**, to produce **9**, which was further treated with valeryl chloride to yield **10**. Compound **10** was treated with acid for detritylation to yield **11**, which on catalytic Pd/C hydrogenation yielded valsartan, **1**.

Some of the drawbacks of the approach are (a) isolation of intermediates as an oily mass with low quality,[11] (b) debenzylation of **11** with a large amount of Pd/C (~35% w/w) at high pressure H_2 gas, (c) purification of crude valsartan. The product synthesized by this approach required multiple purifications to meet the regulatory requirement, resulting in a significant drop in yield.[12,13] To overcome the drawbacks, there is a need to develop an industrially viable and safe manufacturing process for the preparation of valsartan, **1**.

Results and Discussion

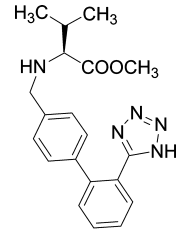
Initially, we attempted to produce valsartan through Scheme 2 involving new intermediate **14**. Valine *p*-nitrobenzyl ester **12** was prepared according to the method described in the literature.[14] Compound **12** was N-alkylated in the presence of base to produce compound **13** which was subsequently detritylated by treating with acid, and **14** was isolated as a white solid with purity greater than 95% by HPLC.

N-Acylation of the amine function in the valine moiety of compound **14** in the presence of base resulted in compound **15** with purity about 75% by HPLC. As expected, N-acylation occurred at both NH functions of valine and tetrazole in compound **14** that led to low purity of **15**. Further conversion of impure **15** to valsartan on commercial scale is not worthwhile. This synthetic approach was unsuccessful due to the lack of single acylation at the NH function of the valine moiety.

Alternatively, compound **13** (Scheme 3) was treated with oxalic acid, and the corresponding oxalate salt **16** was isolated. The NH function of the valine moiety of **16** was acylated with valeryl chloride in the presence of *N*,*N*-diisopropylethylamine, and compound **17** was isolated with purity greater than 95%. Compound **17** was detritylated in mild acidic conditions to yield **15**, which was debenzylated with Pd/C to afforded crude valsartan. Although hydrogenation of **15** was successful with a commercially viable quantity of Pd/C (10% Pd/C, 50% wet), the crude product was contaminated with byproduct *p*-toluidine. Several attempts made to remove *p*-toluidine from crude valsartan, however, were unsuccessful to achieve required quality consistently.

As the elimination of byproduct *p*-toluidine from **1** was unsuccessful, an alternative commercially viable process was developed (Scheme 4) for **1** involving an inventive hydrolysis of **6** using barium hydroxide to achieve purity greater than 99.8% with enantiomeric purity greater than 99.8% and high yield.

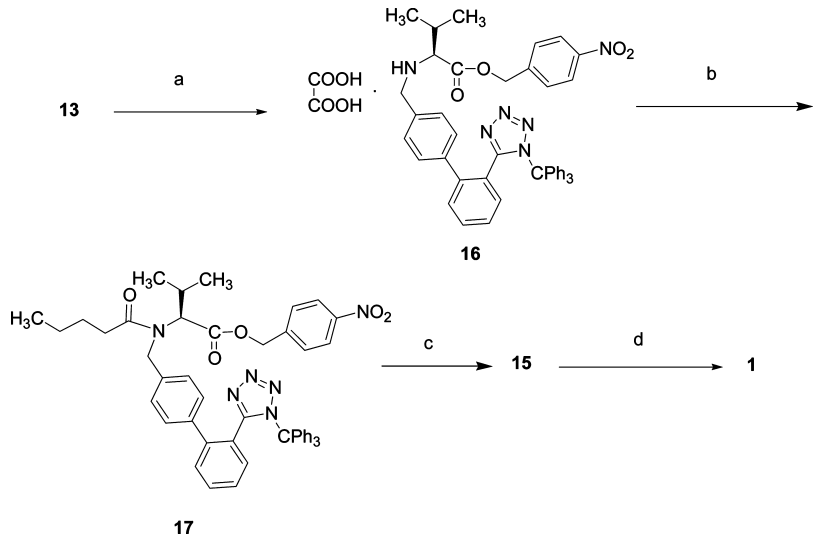
Process for *N*-[[2′-(1-Triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methyl]-L-valine Methyl Ester Oxalate (18a). Compound **7** was reacted with compound **3** (Scheme 4) in the presence of *N*,*N*-diisopropylethylamine in DMF at ambient temperature. The product **18** was extracted with ethyl acetate and treated with oxalic acid to form the corresponding salt as **18a**. Compound **18a** was isolated with purity greater than 98% by HPLC and used in the subsequent acylation reaction. The major impurity **21** was eliminated into the mother liquor during isolation of **18a**.



21

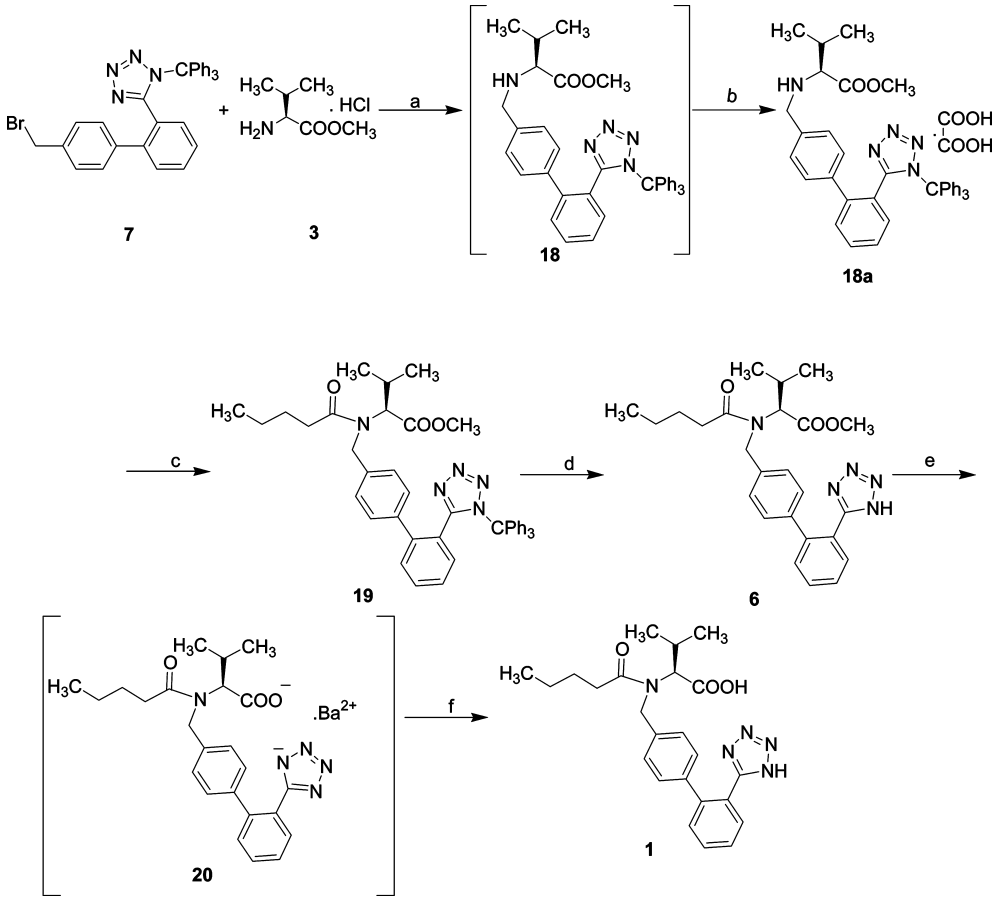
Process for *N*-(1-Oxopentyl)-*N*-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-L-valine Methyl Ester (6). Compound **18a** was acylated with valeryl chloride in the presence of *N*,*N*-diisopropylethylamine and detritylated with IPA-HCl in anhy-

Scheme 3[a]



[a] Reagents and conditions: (a) Oxalic acid, ethyl acetate, 15−20 °C. (b) Aqueous Na_2CO_3, valeryl chloride, *N*,*N*-diisopropylethylamine, toluene. (c) IPA-HCl, methanol. (d) Pd/C, H_2, ethyl acetate.

Scheme 4. **Improved route for valsartan**[a]



[a] Reagents and conditions: (a) *N*,*N*-diisopropylethylamine, DMF, 45−50 °C. (b) Oxalic acid, ethyl acetate, 10−15 °C, 76%. (c) Na_2CO_3, valeryl chloride, *N*,*N*-diisopropylethylamine, toluene, 5−10 °C, 95%. (d) Methanol, IPA-HCl, 20−30 °C, 72%. (e) Aqueous barium hydroxide, 20−30 °C. (f) Aqueous HCl, ethyl acetate, 65%.

drous conditions to yield compound **6**. A robust purification method has been developed to remove process impurities, and compound **6** was isolated with purity greater than 97% by HPLC.

Process for *N*-(1-Oxopentyl)-*N*-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-L-valine(1). Compound **6** can be hydrolysed with alkaline and alkaline earth metal hydroxides. However, hydrolysis with bases such as lithium hydroxide,

Table 1. **Optimization of base in the hydrolysis of compound 6**

entry	base	reaction time (h)	ee[a] **1** (%)
1	NaOH	9	88.00
2	LiOH	8	91.00
3	KOH	8	86.90
4	$Ba(OH)_2$	10	99.95
5	$Ca(OH)_2$	9	91.20

[a] Isolated product purity.

sodium hydroxide, potassium hydroxide, etc., resulted in racemisation up to 15% (Table 1).

It was found in our hands that hydrolysis of compound **6** with barium hydroxide, however, resulted in compound **1** with less than 3% of racemisation. Further, compound **20** was crystallized from the reaction mixture with enantiomeric purity greater than 99.7% by HPLC. Barium hydroxide is a suitable base to hydrolyse the compound **6** efficiently and to produce compound **1** with minimum racemisation, which on single crystallization resulted in compound **1** with higher purity and enantiomeric purity and with less than 20 ppm of barium content. This process was performed on a commercial scale of 250 kg of **7** to **1** successfully. Purity, enantiomeric purity (ee), and overall yield of **1** are presented in Table 2.

Conclusion

We have provided an improved, industrially viable and safe manufacturing process for valsartan that is substantially free from tin and meets the regulatory norms in terms of quality with high yield.

Experimental Section

Materials and Instruments. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 300 spectrometer at 300 and 75 MHz, respectively, and the chemical shifts were reported as δ values in parts per million relative to TMS as an internal standard. Infrared spectra were recorded in the solid state as KBr dispersion using a Perkin-Elmer spectrophotometer. Mass spectra were recorded on API 2000 Perkin-Elmer PE-SCIEX mass spectrometer. The melting points were recorded on open capillaries and are uncorrected.

***N*-[[2′-(1-Triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methyl]-L-valine-4-nitrobenzyl Ester (13).** L-Valine *p*-nitrobenzyl ester **12** (19.2 g, 0.044 mol) was added to a mixture of 1-triphenylmethyl-5-[4′-(bromomethyl)biphenyl-2-yl]tetrazole **7** (25 g, 0.044 mol) and *N*,*N*-dimethylformamide (75 mL) at 25−30 °C and stirred for 10 min. *N*,*N*-Diisopropylethylamine (14.2 g, 0.11 mol) was added to the reaction mass and heated to 45 °C. The resulting reaction mixture was maintained until completion of reaction at 45 °C and cooled to 20−30 °C. The reaction mass was dissolved in methylene chloride (125 mL) and washed successively with water (3 × 100 mL). The organic layer was separated and concentrated completely under reduced pressure to dryness to yield **13.** Yield 85% (27.8 g). ^{1}H NMR (DMSO-d_6) δ: 0.86−0.91 (m, 6H), 1.87−1.92 (m, 1H), 3.01−3.03 (m, 1H), 3.51−3.75 (dd, 2H), 5.30 (s, 2H), 6.82−8.25 (m, 27H).

***N*-[[2′-(1H-Tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-L-valine-4-nitrobenzyl Ester Oxalate (14).** Compound **13** (20 g, 0.027 mol) was added to a mixture of methanol (100 L) and 20% w/w isopropyl alcohol hydrogen chloride (0.79 g; 0.0054 mol) at 25 °C and stirred for 3 h. The reaction mass was cooled, filtered off the solid byproduct, trityl methyl ether, and the filtrate was concentrated. The resulting concentrated mass was dissolved in ethyl acetate (100 mL) and treated with oxalic acid dihydrate (3.7 g, 0.0297 mol) at 20−30 °C. The reaction mixture was cooled to 0−5 °C, and the solid product was filtered, washed with ethyl acetate (20 mL), and dried at 45−50 °C to yield **14**. Yield 90% (14.04 g). mp 137−140 °C. ^{1}H NMR (DMSO-d_6) δ: 0.86−0.95 (m, 6H), 2.01−2.08 (m, 1H), 3.27−3.29 (m, 1H), 3.67−3.90 (dd, 2H), 5.31 (s, 2H), 7.05−8.27 (m, 12H). Mass: 487.1 $[M + H]^+$.

***N*-[[2′-(1-Triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methyl]-L-valine Methyl Ester Oxalate (18a).** L-Valine methyl ester hydrochloride **3** (132.2 g, 0.789 mol) was added to a mixture of 1-triphenylmethyl-5-[4′-(bromomethyl)biphenyl-2-yl]tetrazole **7** (400 g, 0.717 mol) and *N*,*N*-dimethylformamide (400 mL) at 25−30 °C and stirred for 10 min. *N*,*N*-Diisopropylethylamine (231.7 g, 1.79 mol) was added to the reaction mass and heated to 45−50 °C. The resulting reaction mixture was maintained until completion of reaction at 45−50 °C. The reaction mass was cooled to 10−15 °C and quenched by pouring into a mixture of ethyl acetate (2 L) and water (400 mL). The organic layer was separated and washed successively with water (400 mL) followed by 10% w/w aqueous sodium chloride solution (200 mL). The ethyl acetate layer was separated and treated with oxalic acid dihydrate (99.5 g, 0.789 mol) at 10−15 °C. The reaction mixture was cooled to 0−5 °C, and the solid product was filtered, washed with ethyl acetate (400 mL), and dried at 45−50 °C to yield **18a**. Yield 76% (420 g). HPLC purity 98.14%. mp 172−176 °C. $[\alpha]^{20}_D = +5.3$ (*c* 0.5% w/v in methanol). IR (cm^{-1}): 3443 (N−H), 3186 (O−H), 1759 (C═O), 1644 (C═O). ^{1}H NMR (DMSO-d_6) δ: 0.86−0.97 (m, 6H), 1.96−2.03 (m, 1H), 3.26−3.27 (m, 1H), 3.7 (s, 3H), 3.82−3.90 (m, 2H), 6.85−7.79 (m, 23H). ^{13}C NMR (DMSO-d_6) δ: 19.1, 19.9, 30.9, 51.4, 52.7, 66.2, 83.2, 126.6, 128.7, 129.2, 129.5, 129.7, 130.4, 131.2, 131.4, 136.4,140.4, 141.7, 142.1, 163.7, 164.4, 173.0. Anal. Calcd for $C_{41}H_{39}N_5O_6$: C, 70.57; H, 5.59; N, 10.03. Found: C, 71.40; H, 5.55; N, 10.00.

***N*-[[2′-(1-Triphenylmethyltetrazol-5yl]biphenyl-4-yl]-methyl]-*N*-valeryl-L-valine Methyl Ester (19).** Compound **18a** (150 g, 0.215 mol) was added to a mixture of toluene (450 mL) and water (300 mL) and basified with 10% w/w aqueous sodium carbonate solution (450 mL) at 20−30 °C. The organic layer was separated and washed with water (150 mL) followed by 10% w/w aqueous sodium chloride solution. The organic

(11) Ashok, K.; Manmohan, M. N.; Sanjay, G. B.; Dattatray, S. M.; Rahul, S. K.; Bharat, D. S.; Larkesh, D. K. U.S. Patent Appl. Publ. U.S. 2006/0281801, 2006.
(12) Cepanec, I.; Litvic, M.; Koretic, S.; Bartolinlic, A.; Druskovic, V.; Sporec, A. PCT Int. Appl. WO 2005/049586, 2005.
(13) Soni, R. R.; Vasoya, S. L.; Gotikar, R. C.; Pandey A. K.; Shah, H. R. PCT Int. Appl. WO 2007/032019, 2007.
(14) Tagami, Y.; Katsura, T.; Itaya, N. EP 985,658, 2004.
(15) Erwin, E. M. U.S. Patent 6,869,970, 2005.

Table 2. **Purity, enantiomeric purity, and overall yield of commercial batches**

			by HPLC (%)		residual solvent (by GC, ppm)				
entry	cmpd[a] **7** (kg)	cmpd[a] **1** (kg)	purity	ee	ethyl acetate	methanol	barium (ppm)	DSC (°C)	overall yield (%)
1	250	64.80	99.86	99.92	3984	180	7	90.41	33.2
2	250	64.05	99.82	99.90	3556	219	7	89.42	32.8
3	250	66.20	99.85	99.95	2871	164	8	88.75	33.9

[a] cmpd = compound.

layer was separated, dried over anhydrous sodium sulfate, and reacted with valeryl chloride (33.7 g, 0.23 mol) in the presence of *N*,*N*-diisopropylethylamine (55.6 g, 0.43 mol) at 0−5 °C. The reaction mixture was stirred at 5−10 °C for 3 h and quenched into water (150 mL). The organic layer was separated and washed with 10% w/w sodium carbonate solution (68 mL) followed by 10% w/w aqueous oxalic acid solution (40 mL). The organic phase was separated and concentrated completely under reduced pressure to dryness to yield **19** as an oily mass. Yield 95% (141.3 g). HPLC purity 97.21%. IR (cm^{-1}): 1743 (C═O), 1656 (C═O). ^{1}H NMR (DMSO-d_6) δ: 0.68−0.78 (m, 5H), 0.84−0.90 (m, 4H), 1.06−1.52 (m, 4H), 2.17−2.3 (m, 3H), 3.3 (s, 3H), 4.18−4.73 (m, 3H), 6.9−7.7 (m, 23H).

***N*-(1-Oxopentyl)-*N*-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-L-valine Methyl Ester (6).** Compound **19** (100 g, 0.1445 mol) was added to a mixture of methanol (1 L) and 20% w/w isopropyl alcohol hydrogen chloride (2.756 g; 0.0143 mol) at 20−30 °C and stirred for 5 h. The reaction mass was cooled, filtered off the solid byproduct, trityl methyl ether, and the filtrate was concentrated. The resulting concentrated mass was dissolved in ethyl acetate (300 mL) and treated with 2% w/w aqueous sodium carbonate solution (700 mL). The aqueous layer was separated, the pH was adjusted to 7−8 with 10% w/w aqueous acetic acid, and the solution was washed with ethyl acetate (100 mL). The aqueous layer was separated and acidified with 10% w/w aqueous acetic acid to pH 4.0 to precipitate product. The solid product was filtered, washed with water, and dried to yield **6**. Yield 72.3% (47 g). HPLC purity 97.21%. mp 70−71 °C [lit. 70.9−73.3 °C]. ^{1}H NMR (DMSO-d_6) δ: 0.76−0.93 (m, 9H), 1.18−1.46 (m, 4H), 2.29−2.51 (m, 3H), 3.30 (s, 3H), 4.47−4.74 (m, 3H), 6.98−7.07 (m, 4H), 7.47−7.63 (m, 4H). Mass: 450.3 $(M + H)^+$.

***N*-(1-Oxopentyl)-*N*-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-L-valine (1).** Compound **6** (45 g, 0.1 mol) was hydrolyzed with 15% w/v aqueous barium hydroxide solution (528 mL) at 20−30 °C for 10 h. The precipitated solid was filtered, treated with 10% w/v dilute hydrochloric acid to pH 0.5−1.5 in water, and crude valsartan was isolated. The crude valsartan was dissolved in 2.5% w/v aqueous sodium carbonate solution (460 mL) at 20−30 °C, acidified to pH 5.0 with 10% w/v hydrochloric acid, and then washed with methylene chloride (90 mL). The aqueous layer was further acidified to pH 1.0 with 10% w/v hydrochloric acid, and the product was extracted with ethyl acetate (495 mL). The organic layer was separated and distilled completely under reduced pressure at 50−60 °C. The resulting solid mass was recrystallized from ethyl acetate (225 mL), filtered at −15 to −20 °C, and dried at 45−50 °C to yield **1**. Yield 65% (28.5 g). HPLC purity 99.82%, ee = 99.95%. DSC: 90.4 °C [lit. 80−95 °C]. $[\alpha]^{20}_D = (-)$ 67.9 (*c* 1% w/v in methanol). IR (cm^{-1}): 3441 (N−H), 2964 (O−H), 1732 (C═O), 1603 (C═O). ^{1}H NMR (DMSO-d_6) δ: 0.69−0.94 (m, 9H), 1.08−1.21 (m, 1H), 1.27−1.56 (m, 3H), 1.97−2.11 (m, 1H), 2.16−2.50 (m, 2H), 4.06−4.62 (m, 3H), 6.99−7.21 (m, 4H), 7.52−7.71 (m, 4H), 12.67 (br, 1H), 16.20 (br, 1H). Mass: 436.3 $(M + H)^+$. Anal. Calcd for $C_{24}H_{29}N_5O_3$ (435.52): C, 66.19; H, 6.71; N, 16.08. Found: C, 66.50; H, 6.85; N, 15.80. ^{13}C NMR (DMSO-d_6) δ: 41.6, 14.7, 19.3, 19.7, 20.3, 21.0, 22.5, 27.7, 27.9, 28.4, 33.3, 41.2, 46.3, 63.8, 66.6, 124.3, 127.1, 127.8, 128.4, 128.6, 129.2, 129.7, 131.4, 131.5, 131.9, 138.0, 138.6, 139.1, 142.1, 142.2, 155.2, 172.5, 172.8, 174.3. Barium content: 8 ppm. Ethyl acetate: 2759 ppm. Methanol: 125 ppm.

HPLC Conditions for Enantiomer Purity.

Column:	Chiralcel OD-H, 5 μ (250 mm × 4.6 mm)
Detection:	UV, 220 nm
Flow:	0.8 mL/min
Injection volume:	10 μL
Data acquisition time:	30 min
Pump mode:	isocratic
Mobile phase:	prepare a mixture of *n*-hexane and isopropyl alcohol in the ratio of 850:150. To the mixture, add 1 mL of trifluoroacetic acid and degas
Retention time of valsartan:	∼13 min
Retention time of enantiomer:	∼8.2 min

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