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A High-Throughput Process for Valsartan

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Abstract:

With the redesign of three chemical steps, the throughput of the valsartan manufacturing process could be significantly increased, and with the substitution of chlorobenzene with cyclohexane in the bromination of 4′-methyl-biphenyl-2-carbonitrile (6) to 4′-bromomethyl-biphenyl-2-carbonitrile (5), halogenated solvents are no longer used in the whole valsartan production process. The alkylation of (*S*)-2-amino-3-methyl-butyric acid benzyl ester (8) with 4′-bromomethyl-biphenyl-2-carbonitrile (5), and the acylation of (*S*)-2-[(2′-cyano-biphenyl-4-ylmethyl)-amino]-3-methyl-butyric acid benzyl ester (4) to (*S*)-2-[(2′-cyano-biphenyl-4-ylmethyl)-pentanoyl-amino]-3-methyl-butyric acid benzyl ester (3) were thoroughly modified. In the acylation of 4 to 3, *N*-ethyldiisopropylamine was replaced by aqueous sodium hydroxide by using the conditions of the Schotten–Baumann reaction, leading to a better quality of intermediate 3. In the alkylation of 8 with 5, *N*-ethyldiisopropylamine was indirectly replaced by aqueous sodium hydroxide. The reaction runs under homogenous conditions with (*S*)-2-amino-3-methyl-butyric acid benzyl ester (8) acting as acceptor for hydrobromic acid; recycling of 8 is performed by extraction with aqueous sodium hydroxide.

1. Introduction

The superior efficacy, protection, tolerability and patient compliance profile of valsartan[1] have made it the leading antihypertensive therapy in the class called angiotensin II receptor blockers (ARBs). In addition, beyond hypertension, in the Valsartan Heart Failure Trial [Val-HeFT][2] and other studies involving some 50,000 patients, the cardioprotective role of valsartan in patients with heart attacks and heart failure was also demonstrated. With medical advances producing more effective treatment, more patients are surviving cardiovascular diseases, leading to increasing incidence and prevalence of chronic heart failure (CHF), which is now becoming a global problem.[3] Other predisposing conditions for CHF such as obesity and diabetes are also increasing in prevalence, with similar age-related increases. CHF is responsible for substantial morbidity and mortality.[4] Compliance is a major issue in treating hypertension because of the lack of symptoms. Even the slightest side effects may discourage patients from staying on their medication. Clinical studies have shown that ARBs have fewer side effects than calcium channel blockers or ACE inhibitors.[5] This is another reason why valsartan has done so well in a competitive market. Thus, the combination of a superior therapeutic profile and studies of unprecedented scope have made valsartan the new gold standard in cardiovascular disease.

Soon after its introduction in 1996, the demand for valsartan (**1**) rapidly increased, and it became clear that it would grow to a blockbuster compound for Novartis. In terms of production volume, an annual production rate of more than 500 tons had to be envisaged.[6] As a result, Chemical Production faced a major challenge to provide the required production capacities and logistics. In this situation, the thorough redesign of the utilized manufacturing process, which was still based on the synthesis from Research[7] and early Development,[8] was urgently needed. The main goal was not only to improve the yield of the individual chemical steps but above all to increase the throughput by making the whole process more efficient. Two main options were at hand: either to find a new, more efficient synthesis or to fully develop the potential of the current process. At the time, we decided to pursue both strategies. The target of the new synthesis was to avoid the benzyl protection group for L-valine and, if feasible, to introduce the tetrazole ring (the most cost effective chemical step) at an early stage of the synthesis. Both objectives could be met; the results of this study have been disclosed elsewhere.[9] In this paper we report how we were able to significantly improve throughput and yield by implementing relatively simple but highly effective changes to the existing manufacturing process for valsartan.

2. Original Manufacturing Process for 1

The process for the manufacture of valsartan (**1**) as it was applied in the pilot plant and to a large extent also in the early years of production is outlined in Scheme 1. It started with the bromination of commercially available[10] nitrile **6** with *N*-bromosuccinimide in chlorobenzene using 2,2′-azobisiso-

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(1) The brand name for valsartan in most countries is Diovan.

(2) (a) Cohn, J. N.; Tognoni, G.; Glazer, R. D.; Spormann, D.; Hester, A. *J. Card. Failure,* **1999**, *5*, 155–160. (b) Cohn, J. N.; Tognoni, G. *N. Engl. J. Med.* **2001**, *345*, 1667–1675.

(3) Sanderson, J. E.; Tse, T.-F. *Heart* **2003**, *89*, 585–86.

(4) Tan, L-B.; Schlosshan, D.; Williams, S. G. *J. Clin. Pract.* **2004**, *58* (2), 184–191.

(5) (a) Singh, RK.; Barker, S. *Curr. Opin. Invest. Drugs* **2005**, *6* (3), 269–274. (b) Martin, J.; Krum, H. *Pharmacol. Res.* **2002**, *46* (3), 203–212.

(6) The average daily dosage of valsartan is 160 mg.

(7) (a) Buehlmayer, P.; Furet, P.; Criscione, L.; de Gasparo, M.; Whitebread, S.; Schmidlin, T.; Lattmann, R.; Wood, J. *Bioorg. Med. Chem Lett.* **1994**, *4* (1), 29–34. (b) Buehlmayer P.; Ostermayer F.; Schmidlin T. Eur. Pat. Appl. EP443983 A1, 1991.

(8) Marterer W. Unpublished results. This work led to the process conditions for the conversions **5** → **1** (Scheme 1) used in the pilot plant and later on in production.

(9) Denni-Dischert, D.; Hirt, H.; Neville, D.; Sedelmeier G.; Schnyder, A.; Derrien, N.; Kaufmann, D. Int. Pat. Appl. PCT WO 2004/026847, 2004.

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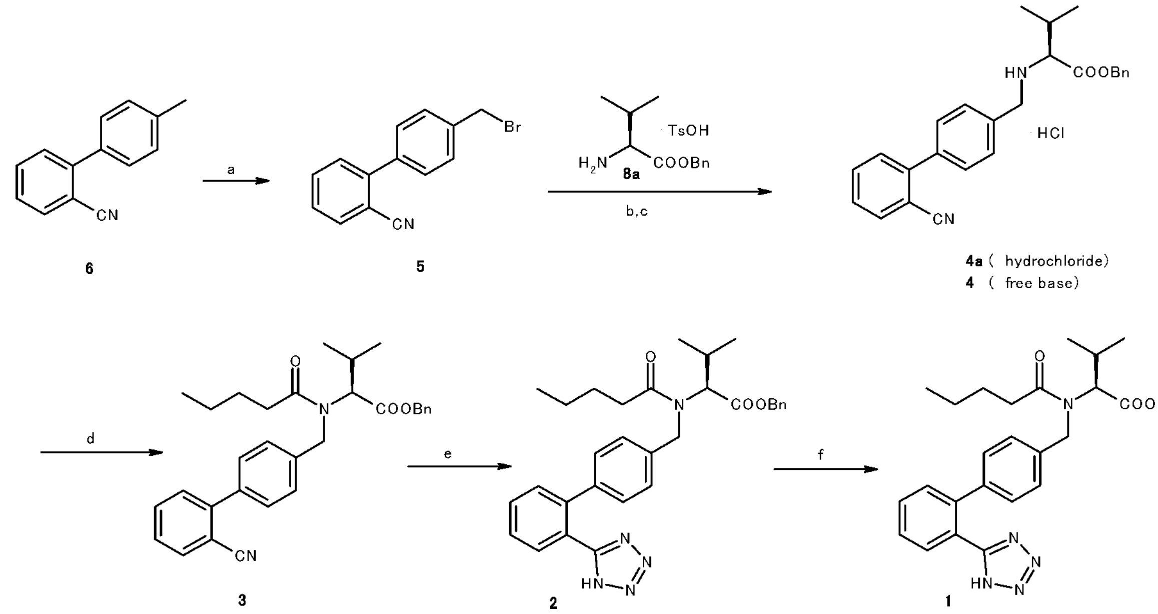
Scheme 1. **Manufacturing process of 1**[a]



[a] Reagent and conditions: (a) NBS, cat. AIBN, chlorobenzene, 4 h, 105 °C (with repetition, see section 3); (b) *N*-ethyldiisopropylamine, toluene, 5 h, 63 °C; (c) gaseous HCl, toluene, 3 h, 5°C; (d) pentanoic acid chloride, *N*-ethyldiisopropylamine, toluene, 5 h, 6–20 °C; (e) tributyltin azide, xylene, reflux; (f) catalytic hydrogenolysis, Pd–C 5%.

butyronitrile as the radical starter. In the next step, L-valine benzyl ester tosylate (**8a**) was treated with **5** and *N*-ethyldiisopropylamine in toluene, leading to **4**. The salt formation to **4a** was executed with gaseous hydrochloric acid in toluene at 0–5 °C.[11]

Hydrochloride **4a** was used as a toluene-wet filter cake in the next chemical step. The acylation **4a** → **3** was carried out in toluene in the presence of *N*-ethyldiisopropylamine, and intermediate **3** was isolated after extractive workup and solvent exchange as a 50% solution in xylene. Nitrile **3** was treated with tributyltin azide in refluxing xylene to give **2**, and removal of the benzyl protecting group leading to **1** completed the manufacturing process.

When analyzing the whole process in view of increasing throughput and yield, we saw the largest potential in the bromination **6** → **5**, in the alkylation **5** → **4a**, and in the acylation **4a** → **3**. Hence, a development program aimed at significantly improving these three chemical process steps was initiated. Moreover, since we knew from laboratory experiments that purified **3** leads in the subsequent tetrazolisation step **3** → **2** to a somewhat higher yield, we were also interested to obtain intermediates **3** and **4a** in high purity.[12] The objectives of our development activities were therefore clear: in addition to increasing the throughput for all three processes, our stringent quality requirements for the intermediates **3** and **4a** also needed to be met. The key to pure **3** was to use pure intermediate **4a** in combination with a clean process[13] for the conversion **4a** → **3**. Only such a combination would us allow to "harvest" the potential yield increase in the conversion of **3** to **2**.

3. Redesign of the Manufacturing Processes for 5

In the original process, the bromination of 4′-methylbiphenyl-2-carbonitrile (**6**) was carried out in chlorobenzene solution at 100–110 °C using the radical initiator 2,2′-azobisisobutyrontrile (AIBN). To avoid the formation of 4′-dibromomethyl-biphenyl-2-carbonitrile (**7**), the reaction had to be performed in two steps. At about 70% conversion (achieved after consumption of 0.76 equiv of NBS), the reaction mixture was cooled to 25 °C and filtered. The filter cake was washed with chlorobenzene, isopropanol,[14] and water to give after drying the first crop of bromide **5**. The mother liquor was concentrated under vacuum[15] and treated in a second reaction with an additional amount of NBS (0.30 equiv) and AIBN. By repeating the same workup procedure, a second crop of **5** was obtained, leading to a combined yield of 76%. Next to the moderate yield, this dual-bromination process led to a low throughput, and the use of a halogenated solvent was a further serious drawback. Thus, when we started our search for an improved process, the elimination of the time-consuming and labor-intensive second bromination and the substitution of chlorobenzene by a less questionable solvent were our main targets.

The key to suppress the bromination of **5** to **7** proved to be using a solvent in which **5** is only poorly soluble under the

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(10) 4′-Methyl-biphenyl-2-carbonitrile (**6**) is available in 100-g quantities from various suppliers (e.g., ABCR GmbH KH, D-76187 Karlsruhe; Waterstone Technology, Carmel, IN 45032 U.S.A.; Beta Pharma, Inc. New Haven, CT 06511 U.S.A.).

(11) If the salt formation is performed at 0–5 °C, water has to be removed prior to the addition of HCl to achieve a reasonable short filtration time. In this process, byproduct **14** (Figure 1) resulting from overalkylation is completely removed into the mother liquor.

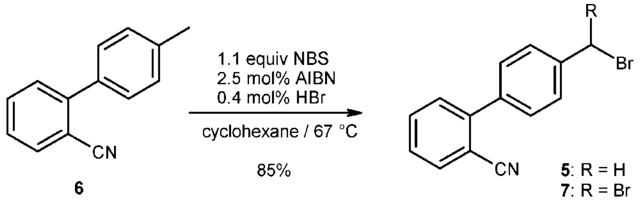
(12) When standing for weeks, crystals from the 50% xylene solution of **3** precipitated and could be collected by filtration. When using these crystals (almost 100% pure **3**) on laboratory scale to prepare **2**, an increase in yield of 3% was observed.

(13) Because **3** is not purified by crystallization, such a clean process for the conversion **4a** → **3** was indeed a condition sine qua non for the manufacture of pure **3**. In the case of process **5** → **4a**, the crystallization of hydrochloride **4a** offered, in addition to a clean alkylation process, a further opportunity to reach the required high purity for this intermediate.

(14) The wash with isopropanol was necessary to remove dibromide **7**.

(15) In this process 67% of the original amount of chlorobenzene was distilled off at 80 °C and 50 mbar.

Scheme 2. **Improved process for 5**



applied reaction conditions. When working in aliphatic solvents,[16] monobromide **5** precipitates during the reaction and is to some extent "protected" against further bromination,[17] allowing a higher conversion rate of **6** with minimal formation (<5%) of dibromide **7**. In our hands, using NBS in cyclohexane and running the reaction to 92% conversion of nitrile **6** proved to be the optimal combination. We did not consider using bromine as brominating agent.[18]

Either radical initiator AIBN (2.5 mol %) or 2,2′-azobis(2,4-dimethylvaleronitrile) (1 mol %) can be applied.[19] According to the new process, 4′-methyl-biphenyl-2-carbonitrile (**6**) and a catalytic amount of aqueous hydrobromic acid[20] are heated in cyclohexane to 67 °C. After the addition of the radical initiator, a suspension of NBS in cyclohexane is added portionwise[21] over a period of 2 h at 64–70 °C. The obtained suspension is stirred for 1 h, cooled to room temperature, and filtered. After washing with cyclohexane, isopropanol, and water, the product is discharged and dried under vacuum at 60 °C for 20 h. In contrast to the original process, the new procedure requires only one bromination step, thus increasing the throughput by at least 40%. In addition, the isolated yield could be increased by 12%. With the elimination of chlorobenzene, halogenated solvents are no longer used in the whole valsartan production process.

4. Redesign of the Manufacturing Processes for 3 and 4a

4.1. Quality Investigation. Having recognized the importance of obtaining intermediate **3** in high purity, we started this project with the reinvestigation of the analytics of this intermediate. In Figure 1, the byproducts we have been able to identify are summarized.[22] Among these, the most dominant compounds (5–8 mol % each) turned out to be (*S*)-3-methyl-2-pentanoylamino-butyric acid benzyl ester (**10**) and pentanoic acid anhydride (**11**). The compounds **12–15** were only present in small amounts (<0.5%). Compound **10** had long been underestimated[23] in the routine analysis of intermediate **3**, and anhydride **11** had not been recognized as a dominant byproduct either.

In addition to these byproducts, evidence for the presence of polymeric material in the xylene solution of **3** could also be provided.[24] Having now a clear picture about the nature and abundance of the various byproducts, the lower yield in the subsequent conversion **3** → **2** could be understood. The presence of polymeric material and identified byproducts led to losses to the mother liquor[25] in the crystallization of **2**. Moreover, since pentanoic acid anhydride is a consumer[26] of tributyltin azide, its presence also affected the conversion rate in this reaction negatively, leading to a loss in yield.[27]

To reach our manufacturing process goals of producing very pure **3**, the formation of polymers and compounds **10** and **11** had to be suppressed. Whereas compound **10** must have derived from the acylation of L-valine benzyl ester (**8**), a contaminant[28] in **4a**, anhydride **11** and the polymers had their origin in the reaction conditions of the conversion **4a** → **3**.[29] We felt that *N*-ethyldiisopropylamine was responsible both for the formation of the polymers and pentanoic acid anhydride. Apparently, this base not only acted as an acid binder for hydrochloric acid but might have also induced the formation of *n*-propyl ketene,[30] which could have reacted to produce the polymers,[31] compound **11**,[32] and ketene dimer **13**.[33] If this hypothesis were true, replacing *N*-ethyldiisopropylamine by an alternative base not capable of inducing ketene formation would solve this problem. As to the other dominant byproduct, compound **10**, its removal had to be achieved by improving the washing conditions of the filter cake of **4a**.

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(16) (a) Katsura T.; Shiratani H. Eur. Pat. Spec. EP 0709369 B1, 1999. (b) Morita A.; Kobayashi Y.; Tamura K. Jap. Pat. Appl. JP 09176103 A2, 1997.

(17) Compared to the homogenous conditions in chlorobenzene, about half of **7** is formed under the heterogeneous conditions in cyclohexane (at the same conversion rate of **6**). Dibromide **7** remains to a large extent in the mother liquor in the crystallization of bromide **5** (see Experimental Section).

(18) For the bromination of **6** with bromine in cyclohexane see: Haber, S. Patentschrift DE 19712339 C1, 1998.

(19) (a) Half-life for AIBN at 65 °C = 10 h. Talât-Erben, M.; Bywater, S. *J. Am. Chem. Soc.* **1955**, *77*, 3712. (b) Half-life time for 2,2′-azobis(2,4-dimethylvaleronitrile at 68 °C = 1 h. Overberger, C.G.; O'Shaughnessy, M.T.; Shalit, H. *J. Am. Chem. Soc.* **1949**, *71*, 2661.

(20) By addition of catalytic amounts of aqueous hydrobromic acid, the start of the bromination reaction can be significantly accelerated.

(21) At plant scale, the suspension of NBS was added in 8 equal portions.

(22) For this investigation compound **3** from routine production (50% solution in xylene) was used. The structures of the compounds **10** and **12–15** were derived by LC–MS, and the structure of **11** by GC–MS. In addition, compounds **10** and **13** were independently synthesized (see Experimental Section), and anhydride **11** was purchased from Fluka.

(23) At 254 nm, compound **3** has 48 times the UV absorbance of **10**.

(24) Determined in the evaporation residue of a sample of **3** (HPLC, external standard technique). We did not investigate the nature of the postulated polymeric compounds (3% relative to **3**).

(25) When in the laboratory the conversion **3** → **2** was carried out with pure **3**, less of **2** was found in the mother liquor than when using **3** from routine production.

(26) Kricheldorf, H. R.; Lepert, E. *Synthesis* **1976**, 329–330.

(27) In the manufacture of **2**, prolonged heating at reflux in xylene has to be avoided due to a decomposition tendency of **2** under these rather harsh reaction conditions. Obviously, when using a constant excess of tributyl tin azide, the presence of **11** must lead to a somewhat longer reaction time (for the same conversion rate of **3**) and therefore to a lower yield.

(28) To completely remove L-valine benzyl ester **8**, efficient washing of the filter cake of hydrochloride **4a** was required.

(29) Hydrochloride **4a** did not contain any polymeric material.

(30) Hill, C. M.; Hill, M. E.; Schofield, H. I.; Haynes, L. *J. Am. Chem. Soc.* **1952**, *73*, 166.

(31) Competitive oligomerization appeared to be a limitation in intramolecular cycloaddition reactions of ketenes. Markó, I.; Ronsmans, B.; Hesbain-Frisque, A.-M.; Dumas, St.; Ghosez, L.; Ernst, B.; Greuter, H. *J. Am. Chem. Soc.* **1985**, *107*, 2192–2194.

(32) The formation of anhydride **11** is thought to proceed via addition of pentanoic acid (formed by hydrolysis of pentanoic acid chloride) to *n*-propyl ketene or by reaction of pentanoic acid with pentanoic acid chloride. In either case, the presence of water is required. Since hydrochloride **4a** was not dried, the presence of small amounts of water could not be excluded.

(33) (a) No effort was made to determine the geometry of the double bond in **13**. However, in the preparation of structurally related ketene dimers using also *N*-ethyldiisopropylamine, exclusively the (*Z*)-isomers were obtained. Purohit, V. C.; Richardson, R. D.; Smith, J. W.; Romo, D. *J. Org. Chem* **2006**, *71* (12), 4549–4558. (b) However, in the preparation of structurally related ketene dimers using also *N*-ethyldiisopropylamine, exclusively the (*Z*)-isomers were obtained. Calter, M. A.; Orr, R. K.; Song, W. *Org. Lett.* **2003**, *5* (24), 4745–4748.

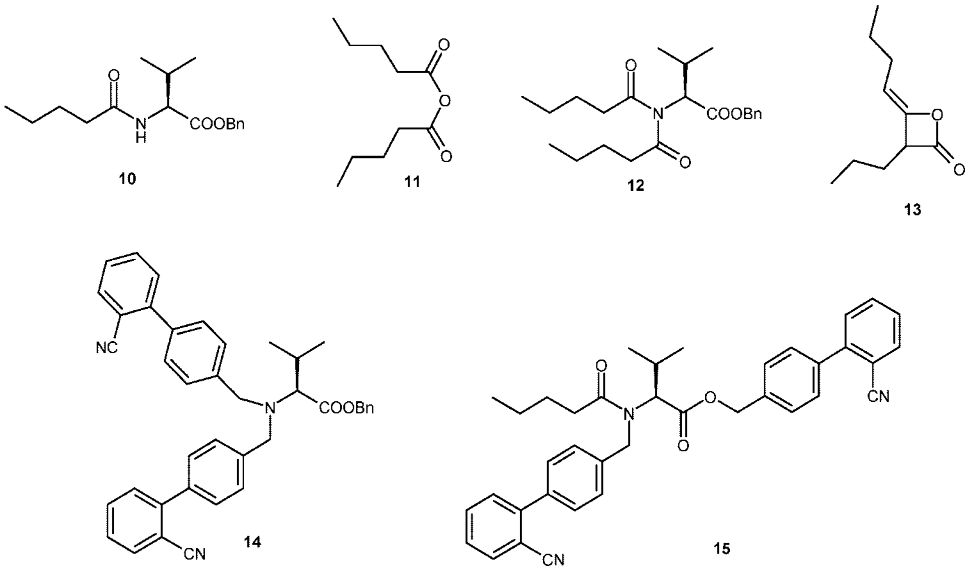

Figure 1. **Byproducts in 3**

4.2. New Process Conditions for Manufacture of 3. The consequence of the above rationale was to replace *N*-ethyldiisopropylamine by an inorganic base.[34] Thus, we were glad to prepare compound **3** in the very first screening experiment in good yield by applying Schotten–Baumann[35] conditions at 30–50 °C. As organic solvent, xylene[36] was chosen, and as inorganic bases, dissolved in the aqueous phase, potassium carbonate, sodium carbonate, sodium bicarbonate, sodium hydroxide, and potassium hydroxide were used, all leading to **3** in excellent yield. Encouraged by these promising results, we decided to develop a manufacturing process for **3** by working in xylene and using aqueous sodium hydroxide as the substitute for *N*-ethyldiisopropylamine. To realize an efficient manufacturing process using such biphasic process conditions, we had to overcome three crucial problems: (a) realizing a smooth transfer of the wet filter cake of **4a** from the nutsche,[37] (b) controlling the hydrolysis of pentanoic acid chloride, and (c) avoiding the precipitation of **4a** during acylation. In the course of our development activities, we had been able to find the suitable answers to all of these potential problems.

Since hydrochloride **4a** is only slightly soluble in water, simply dissolving this salt with water on the nutsche was not feasible.[38] To avoid large amounts of solvent, which would compromise high throughput, the transfer of **4a** from the nutsche had to be performed via the free base **4**. This was achieved by adding xylene and aqueous sodium hydroxide to the wet filter cake of **4a** at 50 °C. Under these conditions, a three-phase mixture was obtained, which could be easily transferred to the reactor of the acylation reaction.[39] The nutsche was rinsed with additional xylene, and after vigorous stirring for 1 h at 50 °C, a clear biphasic mixture was obtained. After phase separation, the colorless solution of free base **4** in xylene was now ready for the subsequent acylation. Additional aqueous sodium hydroxide was added, and to the resulting biphasic mixture was added pentanoic acid chloride within 2 h at 40 °C. After phase separation, the organic phase was filtered to remove traces of precipitated hydrochloride **4a**. To eliminate small amounts of pentanoic acid anhydride,[40] the clear filtered organic phase was washed with diluted aqueous ammonia and water. Azeotropic removal of water at 65 °C and reduced pressure led to a colorless solution of pure **3** in xylene (yield = 99.5%).

In this process, maintaining of the optimal stirrer speed turned out to be most important. If stirring was too slow, precipitation[41] of hydrochloride **4a** occurred, leading to incomplete acylation. However, to prevent rapid hydrolysis of pentanoic acid chloride, the agitating rate may not be too fast either.[42] Thus, depending on the stirrer type and reactor geometry, for each vessel the optimal range[43] for the stirring speed had to be established.

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(34) Because we wanted to avoid the implementation of a recycle process for an alternative base, we did not consider other organic bases such as pyridine or pyridine derivatives (not capable to produce ketenes) to be valuable alternatives to *N*-ethyldiisopropylamine.

(35) (a) Montanari, S.; Bertolini, G.; Casagrande, C.; Cavalleri, P.; Ferlenga, P.; Marchini, F.; Pradella, L.; Pochhhiari, F.; Santangelo, F.; Semeraro, C. *Bioorg. Med. Chem. Lett.* **1996**, *6* (22), 2795–2800. (b) For acylations with aliphatic carbonic acid chlorides running under the conditions of the Schotten–Baumann reaction, see: Georg, G. I.; Boge, T. C.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M.; Park, H.; Himes, R.H. *Bioorg. Med. Chem Lett.* **1994**, *4* (2), 335–338.

(36) Xylene was the "logical" solvent, since it was also used in the following chemical step **3** → **2**.

(37) In the original process, compound **4a** was not dried but transferred as a toluene-wet filter cake to the reactor in which the acylation reaction was performed. Thus, in the rework of this chemical step, drying of **4a** was out of the question also.

(38) Solubility of **4a** in water: at 20 °C, 2.3 g/L; at 40 °C, 3.9 g/L.

(39) Neither ester hydrolysis nor racemization was observed by applying these transfer conditions.

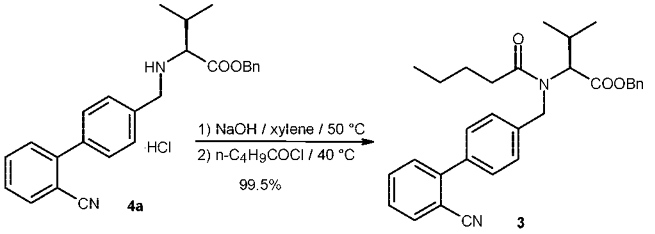
(40) Under the biphasic reaction conditions ca. 0.5 mol % of pentanoic acid anhydride is formed (original process, 5–8 mol %). Pentanoic acid chloride that we used for the acylation reaction did not contain any anhydride **11**.

(41) At low agitation rate, the transfer of hydrochloric acid from the organic to the aqueous phase seems to be somewhat retarded, allowing the buildup of a critical concentration of **4a**, leading to precipitation. Because of the low solubility of **4a** in water, once precipitated it is difficult to redissolve; additional sodium hydroxide and pentanoic acid chloride are then required to complete the reaction.

(42) A similar dependency of the conversion rate on the agitation rate has been observed in the reaction of sodium phenolate with benzoyl chloride under biphasic conditions. Lee, Y.-S.; Yeh, M.-Y.; Shih, Y.-P. *Ind. Eng. Chem. Res.* **1995**, *34*, 1572–1580.

(43) At plant scale, this reaction was performed in various reactors by using a range of stirrer types. In all cases, we did not encounter particular difficulties as to the finding of the optimal stirring speed.

Scheme 3. **Schotten–Bauman conditions to prepare 3**



When applying these new reaction conditions, virtually no new byproducts and no polymeric compounds could be detected in the 50%-xylene solution of **3**.[44] Furthermore, compared to the original process, the throughput could be trebled. Hence, our target of having a new and highly efficient manufacturing process leading to intermediate **3** of excellent quality was met.

4.3. New Process Conditions for Manufacture of 4a. To completely eliminate *N*-ethyldiisopropylamine from our production plants, our next target was to substitute this base also in the alkylation process **5** → **4a**.[45] To simply adapt the conditions of the Schotten–Baumann reaction we used for the acylation process **4a** → **3** proved not to be feasible. The susceptibility of L-valine benzyl ester toward hydrolysis was too pronounced to allow the presence of an aqueous base under the conditions of the alkylation reaction. Apparently, in contrast to the above described acylation process, homogenous and water-free reaction conditions were required.[46] Since we had no intention to replace *N*-ethyldiisopropylamine by another tertiary amine base, we envisaged a process in which the substrate itself, L-valine benzyl ester (**8**), should act also as the base for hydrogen bromide. To prevent hydrolysis, recycling of salt **8b** was expected to be performed by extraction with sodium hydroxide under controlled pH and temperature condition. According to this concept, we would have succeeded in replacing *N*-ethyldiisopropylamine by an inorganic base, not directly as in the acylation **4a** → **3**, but at least indirectly. If feasible, *N*-ethyldiisopropylamine and its laborious recycling by extraction and distillation would have been definitively eliminated from our production plants.

Two imminent problems were envisioned: the double alkylation (leading to byproduct **14**) and ester hydrolysis of **8**, **8a**, and/or **8b** under the applied reaction conditions. By running the alkylation reaction with 2.4 equiv of L-valine benzyl ester, the issue with the double alkylation could be brought under control.[47] By working at pH 8–9 and at 20 °C, ester hydrolysis in the conversion of tosylate **8a** to the free base **8** could be suppressed to a large extent. Similarly, optimal results for the recycling of free base **8** were achieved when working at pH 9 and 20 °C. The redesigned process, which can be performed in a multi-hundred-ton scale, is summarized in Scheme 4. It starts with the preparation of a solution of L-valine benzyl ester (**8**) in xylene by treating the corresponding tosylate **8a** with aqueous sodium hydroxide. After phase separation and washing, the organic phase containing the free base **8** is transferred to the alkylation reactor and treated with **5** for 2 h at 60 °C. Water is added to dissolve a large part of the salts of **8**. After phase separation, water and concentrated hydrochloric acid are added until pH 3 is reached. Under these conditions, only small amounts of **8** remain in the organic phase.

To the xylene phase containing the free base **4** is added aqueous hydrochloric acid with vigorous stirring at 70 °C and reduced pressure under simultaneous azeotropic water removal.[48] The resulting hot suspension[49] is filtered and washed with xylene, leading to highly pure intermediate **4a**, which can be directly used as a xylene-wet filter cake in the subsequent acylation reaction. The recycle of L-valine benzyl ester (**8**) is performed by adding xylene and aqueous sodium hydroxide to the combined aqueous phases containing the salts of **8**. Since its introduction into production, this recycling process of **8** has been repeated several hundred times.[50]

4.4. Success Factors for High Throughput in New Processes for 3 and 4a. Considering the relatively small and straightforward changes that have been implemented in the new processes for intermediates **3** and **4a**, the extent of how they have contributed to increase the throughput[51] (3-fold in both processes) is somewhat astonishing. In order to increase the throughput of a given process, two options are at hand: (a) to run the process in higher concentrations or (b) to shorten the cycle time. Of course, the combination of both of these two possibilities would lead to the largest benefit. Fortunately, in our case, we were able to realize such a combination in both processes.

In the acylation **4a** → **3**, the direct transfer of the xylene-wet filter cake of **4a** from the nutsche to the vessel of the acylation reaction proved to be especially fruitful. By using a mixture of xylene and aqueous sodium hydroxide, the volume involved in this transfer could be kept to an absolute minimum, and by separating the aqueous phase prior to the addition of pentanoic acid chloride, the small volume could be maintained. Compared to the original process, with this procedure the concentration could be doubled. As to the cycle time, omitting the time-consuming solvent exchange from toluene to xylene showed the largest benefit (10 h). In addition, the shorter

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(44) Unreacted **4a** was the main byproduct in the 50% xylene solution of **3** (see Experimental Section).

(45) With the elimination of *N*-ethyldiisopropylamine in both steps, the plant equipment for the recycling of this base could be used for other purposes.

(46) In the meantime, a process using heterogeneous reaction conditions for the conversion **5** → **4a** has been reported. Kumar, A.; Nimbalkar, M. M.; Barve, S. G.; Metil, D. S.; Shimpukade, B. D., Kushwaha, L.; Kelkar, R. S. Eur. Pat. Appl. EP 1714963 A1, 2006. The process runs in water/toluene at 50–55 °C for 25 h in the presence of potassium carbonate, potassium iodide, and tetrabutyl ammonium bromide.

(47) With this molar excess of **8**, 1% of compound **14** was formed. Byproduct **14** was completely removed during filtration and washing of **4a**.

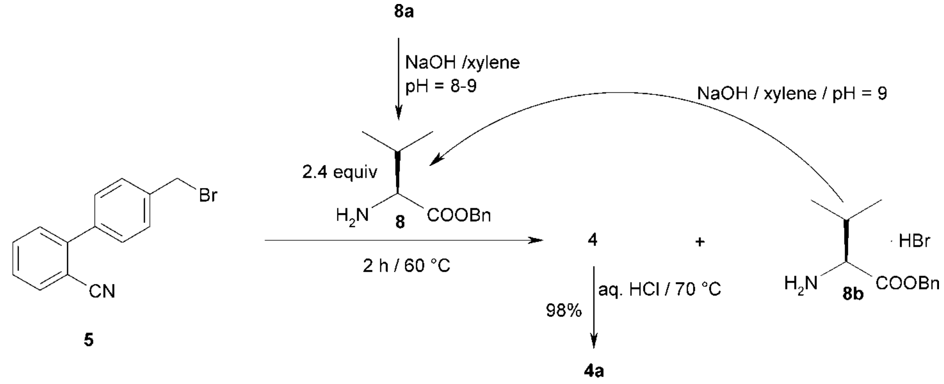
(48) The removal of water leads to more robust process conditions (no formation of oily material, reliable high conversion rate), and in addition, the absence of water leads also to a better filtration behavior of hydrochloride **4a**.

(49) In the original process, the salt formation was performed at 0–5 °C. The crystallization at 70 °C leads to faster filtration and higher purity (99.5%). To reach the same purity with the original procedure, an additional crystallization from isopropanol would have been required.

(50) Needless to say that such a recycling process would make great demands on the production plant logistics. Hence, the advantages of the new process leading to **4a** are most likely to be harvested in the combination with a large production volume. For smaller production amounts (e.g., <100 tons per year), the conditions of the original process might appear to be somewhat more attractive.

(51) A 3-fold increase in throughput means that in the same production equipment and time the production rate could be increased by a factor of 3. Increasing the production capacity by investing in more equipment is not considered here as an increase in throughput.

Scheme 4. **New production process for 4a**



reaction time (5 vs 2 h) contributed also to the reduction of the cycle time. As a result of the phase separation prior to the addition of bromo compound **5**, the concentration in the alkylation process **5** → **4a** could be increased by 50%. As to the cycle time, notable shortening (2 h) was achieved by using a higher temperature for filtration and washing.

5. Summary

In the conversion of 4′-methyl-biphenyl-2-carbonitrile (**6**) to 4′-bromomethyl-biphenyl-2-carbonitrile (**5**), chlorobenzene was replaced by cyclohexane, which allows the reaction to be run in a single bromination step, leading to higher throughput and yield. The alkylation of (*S*)-2-amino-3-methyl-butyric acid benzyl ester (**8**) with 4′-bromomethyl-biphenyl-2-carbonitrile (**5**) and the acylation process of (*S*)-2-[(2′-cyano-biphenyl-4-ylmethyl)-amino]-3-methyl-butyric acid benzyl ester (**4**) to (*S*)-2-[(2′-cyano-biphenyl-4-ylmethyl)-pentanoyl-amino]-3-methyl-butyric acid benzyl ester (**3**) were thoroughly redesigned. In both processes, *N*-ethyldiisopropylamine was replaced by aqueous sodium hydroxide. The acylation of intermediate **4** to **3** is running under the conditions of the Schotten–Baumann reaction, leading to a better quality of intermediate **3**, which in turn gives a higher yield in the subsequent conversion of **3** to (*S*)-3-methyl-2-{pentanoyl-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amino}-butyric acid benzyl ester (**2**). The alkylation of L-valine benzyl ester (**8**) with 4′-bromomethyl-biphenyl-2-carbonitrile (**5**) is performed under homogenous conditions with **8** acting as the acceptor for hydrobromic acid. Recycling of **8** is performed by extraction with aqueous sodium hydroxide. With all of these improvements, the throughput and yield of the manufacturing process of valsartan (**1**) could be significantly increased. With the elimination of chlorobenzene in the bromination of **6**, halogenated solvents are no longer used in the whole valsartan production process.

6. Experimental Section

4′-Bromomethyl-biphenyl-2-carbonitrile (5). A suitable reactor was charged with 4′-methyl-biphenyl-2-carbonitrile **6** (200 g, 1.03 mol, GC assay 100%), 48% aqueous hydrobromic acid (0.7 g), and cyclohexane (500 mL), and the mixture was heated to 67 °C. To the obtained clear solution was added 2,2′-azobisisobutyronitrile (4.2 g, 0.025 mol). A small portion of suspension containing *N*-bromosuccinimide (202.8 g, 1.12 mol) in cyclohexane (500 mL) was added. The reaction mixture turned orange, and a temperature increase of 1–2 °C was observed, indicating the start of the reaction. The remaining NBS suspension in cyclohexane was now added in portions within 2 h at 65–68 °C. The addition funnel was rinsed with cyclohexane (100 mL), and the reaction mixture was stirred for 1 h at 67 °C and then cooled within 4 h to 20 °C. The mixture was filtered, and the filter cake was washed with cyclohexane (300 mL), isopropanol (150 mL), and 65 °C warm water (400 mL). Drying at 60 °C for 20 h gave 244 g of bromo compound **5** (yield = 85%). Assay (HPLC) = 98%, with 1–2% nitrile **6** and <1% of dibromide **7**.

(*S*)-2-[(2′-Cyano-biphenyl-4-ylmethyl)-amino]-3-methyl-butyric Acid Benzyl Ester Hydro Chloride (4a). *Step 1. Preparation of Base 8.* A suitable reactor was charged with xylene (719 mL) and water (1890 mL). Under stirring, L-valine benzyl ester tosylate (**8a**) (1145 g, 93%, 2.81 mol) and 30% aqueous sodium hydroxide (369 g, 2.77 mol) were added alternatively in portions at 20 °C such as to maintain the pH <8.5. To set the pH at 9.0, additional 30% aqueous sodium hydroxide (43 g, 0.32 mol) was added. Phase separation led to a colorless xylene phase (1187 g) containing 545 g of 8 (yield = 94%).

Step 2. Alkylation. In a suitable reactor was placed bromide **5** (299 g 97%, 1.07 mol). The above described xylene solution (1187 g) containing **8** (545 g, 2.63 mol) was added at room temperature. Within 45 min the mixture was heated to 60 °C and stirred at this temperature for 2 h. Water (300 mL) was added. After phase separation (water phase = recycle stream A), the organic phase was treated at 60 °C with water (540 mL) and 32% aqueous hydrochloric acid (35 g, 0.31 mol) to give a pH of 3.0. Phase separation (water phase = recycle stream B) at 60 °C afforded a xylene phase containing free base **4**.

Step 3. Salt Formation. To this solution was added additional xylene (954 mL), and the mixture was heated to 72 °C. Under vigorous stirring, 32% aqueous hydrochloric acid (177 g, 1.55 mol) was added at reduced pressure within 2 h while water was continuously removed by Dean–Stark distillation. After addition of ca. 10 g of 32% aqueous hydrochloric acid, the product started to crystallize. The hot suspension was filtered, and the filter cake was washed with xylene (483 mL) and water (403 mL = recycle stream C). The wet filter cake (583 g) was used as the starting material for the subsequent acylation reaction. Drying led to 446 g of **4a** (yield = 98%). Assay (HPLC) = 99.5%. Main impurities: hydrochloride of **8** and bromide **5**.

*Step 4. Recycling of Base **8**.* To the combined aqueous recycle streams A, B, and C were added xylene (629 mL), water (206 mL), 30% aqueous sodium hydroxide (67 g, 0.50 mol), and tosylate **8a** (487 g, 93%, 1.19 mol). To the white suspension was added 30% aqueous sodium hydroxide (205 g, 2.29 mol) such as to reach a pH of 9.0. Phase separation gave a colorless xylene phase (1132 g) containing 550 g of **8**, ready for use in the next alkylation reaction

(*S*)-2-[(2′-Cyano-biphenyl-4-ylmethyl)-pentanoyl-amino]-3-methyl-butyric Acid Benzyl Ester (3). A 1-L glass reactor equipped with an anchor stirrer was charged with xylene-wet **4a** from the nutsche (180,1 g = 156.4 dry, 0.360 mol), xylene (150 mL), water (100 mL), and 30% aqueous sodium hydroxide (52.8 g, 0.40 mol). The mixture was stirred at 50 °C for 30 min. After that time, a well-transferable three-phasic mixture was formed. Additional xylene (126 mL) was added, and the stirring speed was increased to 240 rpm. After 1 h, a biphasic mixture was obtained containing practically no more crystals. The aqueous phase was separated, and to the organic phase were added water (215 mL) and 30% aqueous sodium hydroxide (87.2 g, 0.654 mol). Under further vigorous stirring (240 rpm), pentanoic acid chloride (60.7 g, 0.504 mol) was added below the surface within 2 h at 40 °C. The aqueous phase was separated, and the organic phase was filtered to remove small amounts (<0.1 g) of precipitated **4a**. To the clear, colorless organic phase was added a mixture of 25% ammonia (5.4 g) and water (39 g), and the mixture was stirred for 30 min at 40 °C. After phase separation, the organic phase was washed with water (90 mL) and concentrated at 65 °C and reduced pressure until the water content in the organic phase met the requirements. At the end of the distillation 286 g of a colorless solution containing 173.7 g of **3** was obtained (yield = 99.5%). Assay (HPLC) of solvent free sample >99%. Main impurity: hydrochloride **4a** (≤0.5%).

3-Methyl-2-pentanoylamino-butyric Acid Benzyl Ester (10). A 1.5-L glass reactor was charged with L-valine benzyl ester tosylate, **8a** (100 g, 0.263 mol), and dichloromethane (350 mL). To the fine suspension was added *N*-ethyldiisopropylamine (69.5 g, 0.537 mol) under stirring. The resulting clear solution was cooled to 5 °C, and pentanoic acid chloride (32.3 g, 0.268 mol) was added within 45 min at 5–10 °C. The mixture was then stirred for 1 h at 0–5 °C. The reaction mixture was treated with 1% aqueous hydrochloric acid (500 mL) at room temperature. After phase separation, the organic phase was washed with 1% aqueous hydrochloric acid (2 × 250 mL), 5% aqueous sodium bicarbonate (250 mL), and water (500 mL). The organic phase was concentrated under vacuum (25 mbar) and 40 °C to give 74.4 g of a yellowish oil (HPLC purity = 98.9%, yield = 96 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.77–0.97 (m, 9H), 1.2–1.35 (m, 2H), 1.4–1.56 (m, 2H), 1.99–2.1 (m, 1H), 2.1–2.25 (m, 2H), 4.15–4.3 (m, 1H), 5.08–5.2 (m, 2H), 7.3–7.45 (m, 5H), 8.05–8.17 (br d, 1H); EI-MS *m/z* 291 (M$^+$).

4-Butylidene-3-propyl-oxetan-2-one (13). A 1-L glass reactor was charged with pentanoic acid chloride (99.5 g, 0.809 mol) and heptane-fraction (500 mL). Under stirring, triethylamine (87.4 g, 0.83 mol) was added within 1 h. At the end of the addition, the temperature was 50 °C. The reaction mixture was stirred for 72 h at room temperature, and the resulting suspension was filtered. The filter cake was washed with heptane-fraction (5 × 100 mL). The combined organic phase was concentrated under vacuum at 45 °C, and the evaporation residue was distilled at 1.5 mbar (bp = 125 °C) to give 33.9 g of a slightly yellowish oil (GC purity = 96%, yield = 48.9%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.85 (t, J = 7.35 Hz, 3 H) 0.89 (t, J = 7.35 Hz, 3 H) 1.26–1.52 (m, 4 H) 1.62–1.76 (m, 2 H) 1.96–2.09 (m, 2 H) 3.88 (td, J = 7.20, 1.03 Hz, 1 H) 4.63 (td, J = 7.64, 1.32 Hz, 1 H); EI-MS *m/z* 168 (M$^+$).

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