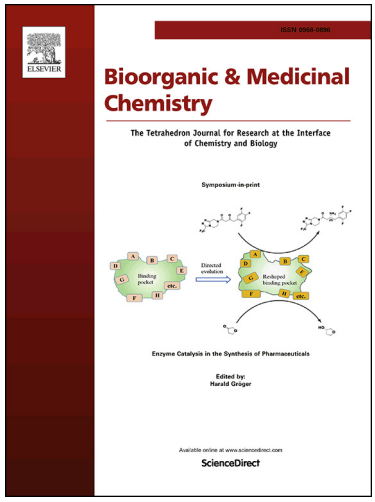
Accepted Manuscript



Development of efficient one-pot three-component assembly of trityl olmesartan medoxomil

Renata Toplak Časar, Zdenko Časar

PII: S0968-0896(18)30849-6
DOI: https://doi.org/10.1016/j.bmc.2018.06.036
Reference: BMC 14428

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 19 May 2018
Revised Date: 22 June 2018
Accepted Date: 26 June 2018

Please cite this article as: Časar, R.T., Časar, Z., Development of efficient one-pot three-component assembly of trityl olmesartan medoxomil, *Bioorganic & Medicinal Chemistry* (2018), doi: https://doi.org/10.1016/j.bmc.2018.06.036

Graphical Abstract

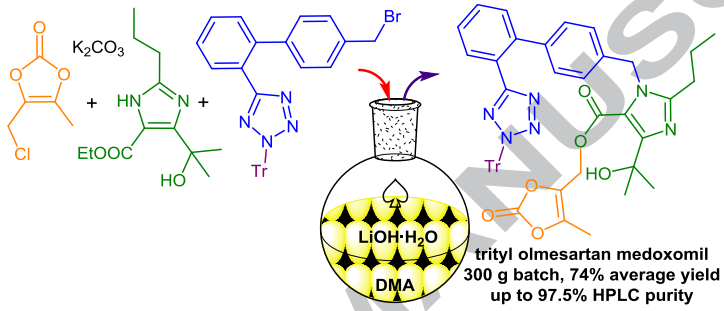
To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Development of efficient one-pot three-component assembly of trityl olmesartan medoxomil

Leave this area blank for abstract info.

Renata Toplak Časar,[a] *Zdenko Časar*[a,b,]*

[a] *Lek Pharmaceuticals, d.d., Sandoz Development Center Slovenia, Verovškova ulica 57, 1526 Ljubljana, Slovenia*
[b] *Faculty of Pharmacy, University of Ljubljana, Aškerčeva cesta 7, 1000 Ljubljana, Slovenia*



Bioorganic & Medicinal Chemistry
journal homepage: www.elsevier.com

Development of efficient one-pot three-component assembly of trityl olmesartan medoxomil

Renata Toplak Časar [a] , and Zdenko Časar [a,b,] *

[a] *Lek Pharmaceuticals, d.d., Sandoz Development Center Slovenia, Verovškova ulica 57, 1526 Ljubljana, Slovenia*
[b] *Faculty of Pharmacy, University of Ljubljana, Aškerčeva cesta 7, 1000 Ljubljana, Slovenia*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
alkylation
S_N2 reaction
ester hydrolysis
multicomponent reactions
heterocycles
olmesartan
drugs

ABSTRACT

We have elaborated a one-pot three-component assembly of trityl olmesartan medoxomil starting from commercially available ethyl 4-(2-hydroxypropan-2-yl)-2-propyl-1*H*-imidazole-5-carboxylate, 5-(4'-(bromomethyl)-[1,1'-biphenyl]-2-yl)-1-trityl-1*H*-tetrazole and 4-(chloromethyl)-5-methyl-1,3-dioxol-2-one intermediates. The developed and optimized one-pot process provides 72-75% yield of trityl olmesartan medoxomil over three steps, which represents in average ca. 90% yield per synthetic step, on a 300 g scale. The process is conducted in simple fashion and provides highly pure trityl olmesartan medoxomil (up to 97.5% by HPLC), which can be easily converted to olmesartan medoxomil that fully complies with all ICH requirements. Furthermore, the described process significantly improves the primary process to trityl olmesartan medoxomil by drastic reduction of required unit operations and application of single reaction solvent through the reaction sequence. Moreover, the amount of used organic solvents was notably reduced. The developed process has provided solid bases for industrial production of trityl olmesartan medoxomil.

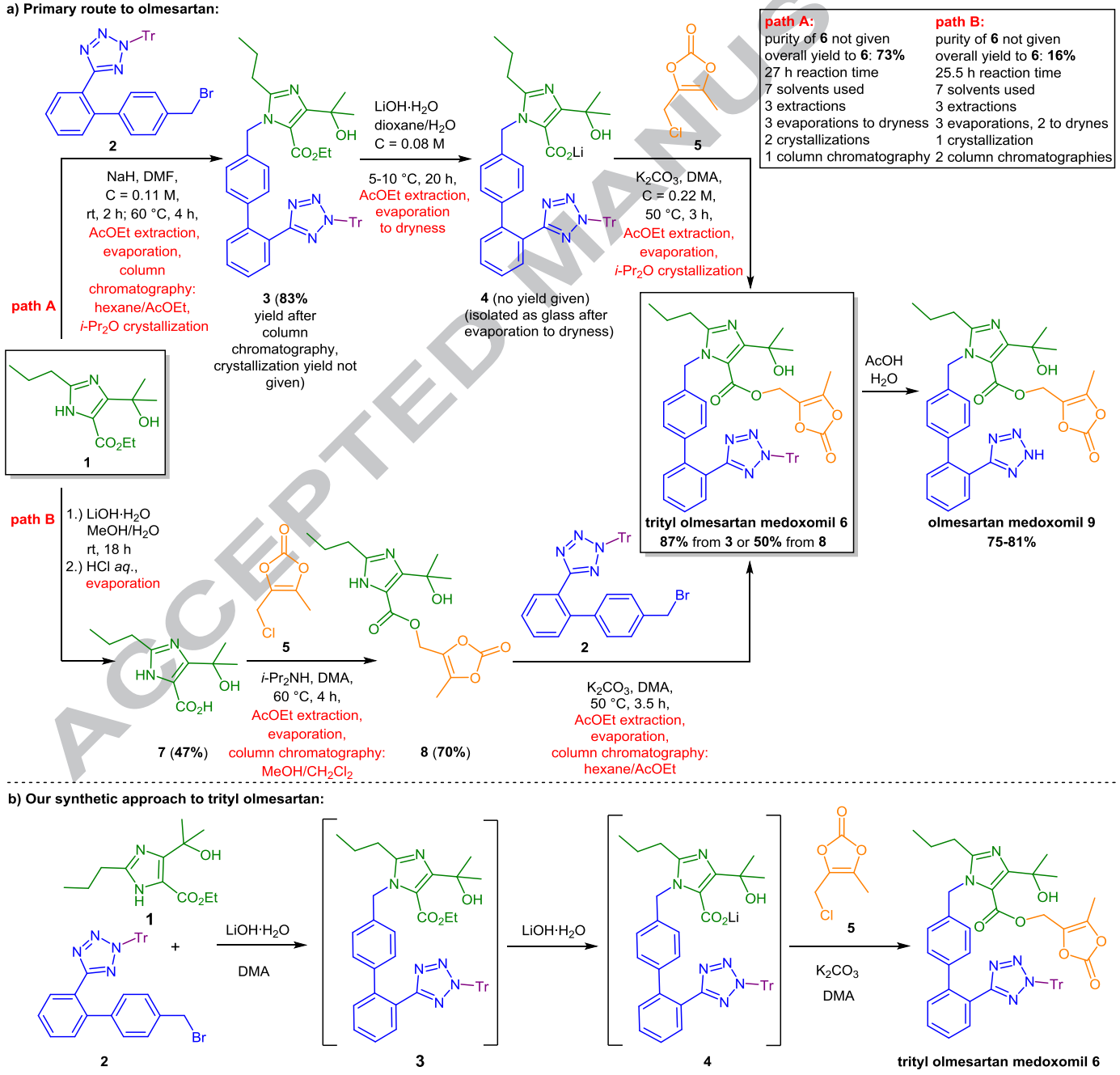
1. Introduction

Angiotensin II receptor antagonists or angiotensin II receptor blockers (ARBs) known also as sartans are important antihypertensive agents. Several molecules in this therapeutic group of compounds have been put on the market: losartan, valsartan, irbesartan, candesartan, telmisartan, eprosartan, azilsartan and olmesartan.[1] Among sartans, olmesartan medoxomil[2] displays some unique stereoelectronic features associated with hydroxyisopropyl substituent at the imidazole 4-position that might cause unique pharmacological interaction of the molecule with the AT1 receptor leading to enhanced clinical efficacy.[3] Furthermore, nowadays olmesartan medoxomil is used in many fixed dose combination drugs which increases demands on its volumetric production.[4] Moreover, recent studies indicated that olmesartan medoxomil might be more cost-effective compared to other sartans.[5] Therefore, olmesartan medoxomil represents an interesting synthetic target. Primary synthetic route to olmesartan medoxomil (Scheme 1) features long linear synthetic sequences which in the final steps involves alkylation of imidazole derivative **1** with trityl protected tetrazole biphenyl derivative **2**, ester **3** hydrolysis, alkylation of resulting carboxylate salt **4** with "medoxomil chloride" **5** and removal of trityl protection (Scheme 1, path A). Alternative assembly sequence (Scheme 1, path B) disclosed in primary patent literature proceeds through ester **3** hydrolysis, alkylation of ~~resulting~~ carboxylic acid **7** with "medoxomil chloride" **5** in the presence of a base followed by alkylation of ester **8** with tetrazole biphenyl derivative **2** to provide trityl olmesartan medoxomil **9**.[6] Interestingly, path A provides significantly higher yield of trityl olmesartan medoxomil **9** compared to path B (73% *vs.* 16%) while both have similar overall reaction time (27 h *vs.* 25.5 h) and use multiple purification steps including extractions, evaporation to dryness, column chromatographies and crystallizations (Scheme 1).[6] Although some other routes for preparation of olmesartan medoxomil[7] and its impurities[8] have been reported in the scientific literature, they either heavily relay on primary synthetic route, use minor reagent modifications compared to the primary synthetic route or apply different sequences of previously known olmesartan medoxomil assembly reactions. Therefore, the primary synthetic route[6] passing through synthetic sequence **1** → **3** → **4** → **6** (Scheme 1, path A) appears to provide a good starting point for development of an efficient and robust process for manufacture of olmesartan medoxomil in the context of selected intermediate assembly into the drug substance. Nevertheless, industrially acceptable process using this reaction sequence (Scheme 1, path A) should be developed in such a way that it would provide highly pure final intermediate **6** and preserve high overall yield of the synthetic sequence. At the same instance industrially feasible process should eliminate multiple isolation steps, which involve uneconomical as well as environmentally unacceptable separation techniques for production of high volume drugs (e.g. column chromatography)

* Corresponding author. Tel.: +386 1 5802079; fax: +386 1 5683517; e-mail: zdenko.casar@sandoz.com, zdenko.casar@ffa.uni-lj.si

and tedious as well as industrially undesirable process operations (e.g. evaporation to dryness). Moreover, large amount and number of used solvents like water, *N*,*N*-dimethylformamide (DMF), hexane, AcOEt, diisopropylether, dioxane and *N*,*N*-dimethylacetamide (DMA) should be reduced to a minimum.[6]

Therefore, we considered to develop a one-pot three-component assembly of trityl olmesartan medoxomil **6** *via* synthetic sequence: **1** → [**3**] → [**4**] → **6** taking the advantage of the well-established intermediates en route to olmesartan medoxomil, while reducing number of required solvents and isolation steps in order to minimize required unit operations and generated waste.[9] Indeed, multiple bond-forming transformations (MBFTs) have attracted enormous interest in the past three decades owing to their ability to provide large number of desired compounds in time and cost-effective manner.[10] Among MBFTs, multistep sequences performed in the same reaction vessel that do not require purification of intermediates, known also as "one-pot reactions",[11] have proven to be extremely useful and therefore desirable in industrial environment including the pharmaceutical sector.[12,13] This is due to the fact that one-pot reactions are recognized to be waste and pollution reducing as they are atom,[14] time and energy efficient. Consequently, one-pot reactions are considered to be eco-friendly and sustainable.[15] Although, in parallel to our work, another one-pot three-component assembly of olmesartan medoxomil **9** appeared in the patent literature: **3** → [**4**] → [**6**] → **9**,[16] we believe that our approach is more convenient, since it provides one-pot three-component access to final intermediate **6** and not directly to the drug substance **9**. In our case the final intermediate **6** is converted to **9** *via* additional covalent bond cleavage (Tr group removal),[17] which provides additional purification possibilities, while the direct one-pot three-component access to drug substance **9** might be less favorable from regulatory point of view and reduced options to purify the drug substance. Herein, we present a facile and cost-effective method for one-pot three-component assembly of trityl olmesartan medoxomil **6**, a final intermediate in the synthesis of olmesartan medoxomil **9**.[9]



Scheme 1. a) Structure and primary synthesis of olmesartan,[6] **b)** our approach to trityl olmesartan.[9]

2. Results and discussion

2.1. Development of one-pot three-component assembly of trityl olmesartan medoxomil **6**

Since we planned to perform one-pot assembly of trityl olmesartan medoxomil **6** *via* reaction sequence **1** → [**3**] → [**4**] → **6**, we first decided to explore the most suitable solvent that could be used through the whole three-component one-pot sequence. Due to the fact that two S_N2 substitution reactions were envisioned in the overall three-component one-pot reaction sequence and inorganic bases were planned to be applied in order to facilitate the S_N2 reactions, we considered to use dipolar aprotic solvents. Namely, dipolar aprotic solvents are known to massively accelerate nucleophilic substitution reactions and are able to solubilize polar heterocyclic molecules as well as charged inorganic reagents in large amounts.[18] Already at the beginning, we have decided to eliminate hazardous sodium hydride as the base for the alkylation of imidazole **1** with **2** and decided to use $LiOH·H_2O$ as the base for the initial alkylation as well as in the ester hydrolysis step.

Therefore, the first experiment of one-pot assembly of **6** was conducted in NMP solvent (Figure 1, procedure described in the experimental part under section 4.2.1.) at room temperature. We have observed that the first alkylation step **1** → **3** proceeds relatively fast in the presence of 1.0 equiv. of $LiOH·H_2O$ and was terminated in 24 h when 2.0 area% of **1** and 3.3 area% of **2** remained in the reaction mixture along with the formed ester **3** (82.9 area%). Interestingly, after 24 hours when additional amount of $LiOH·H_2O$ (1.5 equiv.) was added, intended for the hydrolysis of ester **3**, the hydrolysis reaction proceeded very slowly (Figure 1). Indeed, after 235 h of overall reaction time 5.3 area% of ester **3** was still present in the reaction mixture together with 79.5 area% of **4** and other impurities. Nevertheless, at 236.5 h we continued our one-pot sequence with esterification of **4** with **5** (1.23 equiv.) in the presence of K_2CO_3 (1.1 equiv.) at 50 °C. The alkylation of **4** was terminated after 241 h of overall reaction time when only 2.0 area% of **5**, 5.6 area% of **3** and 6.0 area% of **4** were left in the reaction mixture. Subsequently, the product was isolated by precipitation upon water addition to the reaction mixture followed by filtration where poor filterability of the precipitate was observed. The precipitate was recrystallized twice from acetone/water mixtures to give **6**, which was contaminated with ca. 6.4 area% of ester **3**, in overall 77% yield and 91.0 area% purity.

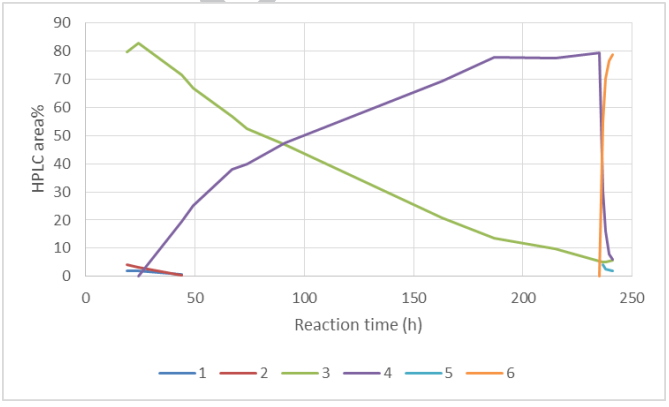


Figure 1. Progress of one-pot assembly of trityl olmesartan medoxomil **6** in NMP *via* reaction sequence **1** → [**3**] → [**4**] → **6**.

Although, this first experiment of three-component one-pot assembly of **6** was encouraging, there were several aspects of the overall process that needed significant improvement in order to assure a robust and efficient process. Among these aspects a slow and uncomplete conversion of [**3**] → [**4**] and poor filterability of precipitated **6** appeared as the most prominent challenges to be addressed. We have decided to solve firstly a slow and uncomplete conversion of [**3**] → [**4**] in the three-component one-pot process. This issue could in principle be addressed by increased temperature, modification of the applied solvent (polarity increase) or addition of water to the reaction mixture to facilitate the dissolution of LiOH. The latter approach was ruled out, since additional water in the system would facilitate the competition of hydroxide anion with carboxylate anion in the substitution reaction of [**4**] → **6** step leading to the preferential substitution of alkyl chloride moiety in **5** with OH^- instead of reacting with carboxylate **4**.

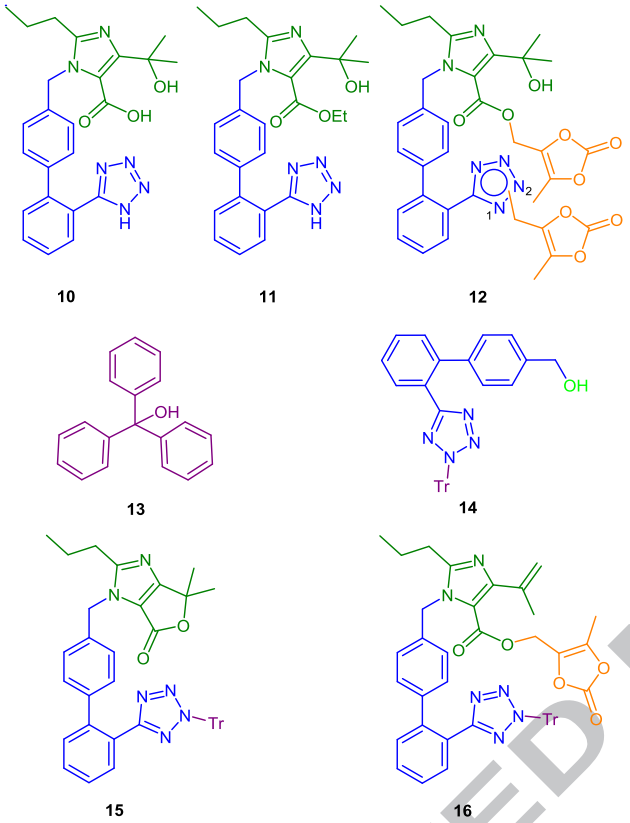
Therefore, we decided to explore several dipolar aprotic solvents such as NMP, DMA, DMSO and their mixtures at elevated temperatures. In the first set of experiments (Table 1, entries 1-6) the reaction temperature was raised to 40 °C in the sequence **1** → [**3**] → [**4**], while 50 °C was used in the [**4**] → **6** step. In the second set of experiments, higher temperature profile (50-75 °C) was kept through the whole one-pot sequence (Table 1, entries 7-10).

In the second experiment (Table 1, entry 1) we used NMP solvent at 40 °C in the sequence **1** → [**3**] → [**4**] and the last part of the sequence [**4**] → **6** was maintained at 50 °C. In this case notable shortage of overall reaction time vas observed and the whole sequence could be completed in 79 h affording product **6** in 76% yield and 94.8 area% purity after one crystallization from acetone/water mixture. The product **6** contained ca. 3 area% of ester **3** and some other impurities in the range of 0.15-0.49 area% that appeared less intriguing.

As is know from the literature related to MBFTs[13] and based on our initial experience, knowledge on formation and control of impurities in one-pot assembly of pharmaceuticals represents one of the most important tasks. Since myriad of possibilities exist for side reactions and impurities formation in multicomponent reactions, considerable attention must be paid to assure that they are closely monitored and studied. Structure of main impurities observed during the one-pot process monitoring with HPLC are highlighted in Figure 2. One of the most relevant impurities that has been detected during one-pot sequence was olmesartan **10**,[6,7b,8c,g,j] which was formed in 0.88 area% in the hydrolysis [**3**] → [**4**] step (Table 1, entry 1). Importantly, this side product was mainly converted, after addition **5**, to two regio isomers of dimedoxomil alkylated compound **12**[8e,f,g,j] as a consequence of known tautomerism in tetrazoles.[19] Impurity **11**[6,8h] (olmesartan ethyl ester) was only observed in some experiments where higher amount of LiOH, compared to that stated in Table 1, was used in hydrolysis [**3**] → [**4**] step (experiment not reported in Table 1). As a consequence of **10** and **11** formation, we have also observed thetriphenylmethanol **13** in the reaction mixture. 2'-[1-(Triphenylmethyl)-1*H*-tetrazol-5-yl][1,1'-biphenyl]-4-methanol **14** was also present in the reaction mixture as a side product of trityl protected tetrazole biphenyl derivative **2** hydrolysis, which occurred in **1** → [**3**] step despite the fact that only 1.0 equivalent of $LiOH·H_2O$ was used in order to minimize this reaction. Furthermore, we have also observed the formation of lactone **15**,[7b,8a,d] which was formed on ca. 2 area% level by the end of the [**3**] → [**4**] sequence. The lactone **15** was co-eluted with product **6** in the HPLC method for the reaction progress monitoring in [**4**] → **6** step and in the isolated product. Therefore, its levels were established with method for related substances, which showed that ca. 0.7 area% of **15** were present in isolated **6**. In addition, we have suspected that dehydro trityl olmesartan medoxomil **16**[7b,8c] was also present in the product **6**. This assumption was

based on the observation that the peak at ca. 8.9 min, where both compounds **3** and **16** co-elute in HPLC method for the reaction progress monitoring, slightly increased in [**4**] → **6** step for some experiments. The presence of **16** was later determined on kilo-lab experiments by an HPLC method for related substances.

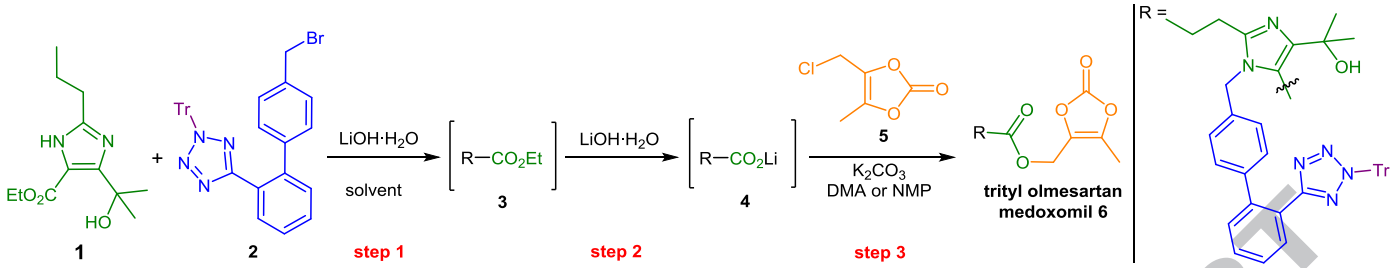
Figure 2. Impurities observed in the one-pot three-component assembly of trityl olmesartan medoxomil **6**.



Next reaction (Table 1, entry 2) was performed in dimethylacetamide (DMA) with the same temperature profile (40 °C in steps 1 to 2 and 50 °C in step 3) as in the previous example where NMP was used. Reaction was stopped after 79 h reaction time. After isolation, product **6** was obtained in 78% yield and 93.4 area% purity. Interestingly, slightly higher level of impurities **4**, **13**, **14** and **3** were present in the product compared to the reaction performed in NMP. Subsequent reaction (Table 1, entry 3) was performed in NMP/DMSO = 9:1 mixture in order to further enhance the dissolution of $LiOH \cdot H_2O$ and K_2CO_3 and facilitate desired transformations. The reaction system behaved similarly compared to one where NMP alone was used. The product **6** was obtained in 76% yield and 95.6 area% purity while levels of impurities were in general lower than in the reaction using DMA. The next two experiments (Table 1, entries 4 and 5) were performed in DMA/DMSO = 9:1 mixtures. Using DMA/DMSO = 9:1 mixture (Table 1, entry 4) resulted in nearly the same result regarding the yield and impurity profile than in the case of NMP/DMSO = 9:1 mixture. Since all performed reactions contained higher amount (11.7-15.7 area%) of unreacted **4** after 79 h reaction time (Table 1, entries 1-4), we decided to add additional portion of **5** to the reaction mixture in order to drive the reaction [**4**] → **6** to completion. Therefore, when additional 10% (0.123 equiv.) of **5** was added to the reaction mixture overall sequence was completed slightly faster (76.5 h *vs.* 79 h, Table 1, entry 5) and only 1.7 area% **4** was present in the mixture before isolation. Consequently, product **6** was isolated with higher 79% yield and 93.7 area% purity. To test the application of a greener solvent alternative,[20] the reaction sequence was also conducted in DMSO (Table 1, entry 6). Surprisingly, we have observed that in this case a significantly higher amount of **10** was formed in [**3**] → [**4**] step which reached 6 area% and was converted after addition of **5** into ca. 5.7 area% of **12**. Favourably, levels of both regioisomers **12** could be lowered to 0.25 area% after recrystallization. In addition, alcohol **14** was formed in level of 7.8 area% in [**3**] → [**4**] step and was reduced to level of 0.9 area% after crystallization from water/acetone mixture. Due to the extensive formation of **10** and **14** in [**3**] → [**4**] step we considered DMSO as a high risk solvent for the quality of **6**. In order to increase the dissolution of reagents, we have also tested DMA/DMSO = 9:1 mixture (Table 1, entry 7) using higher reaction temperature of 50 °C over the whole one-pot sequence. Also in this case the amount of formed **10** reached in [**3**] → [**4**] step was 3.57 area%, which transformed upon addition of **5** to 2.82 area% of **12** at the end of reaction sequence. Consequently, isolated product still contained 0.81 area% of **12** which appeared to be on too high level for subsequent step in order to prepare **9** of adequate quality. In the next experiment (Table 1, entry 8) we have used pure DMA with 50 °C temperature through the whole reaction sequence. The amount of **10** at the end of hydrolysis step dropped to an acceptable level of 2 area% while all other impurities formed were at the lower end of the scale compared to all performed experiments. Upon isolation, product **6** was obtained in 78% yield and 92.3 area% purity. It contained an acceptable amount of **12** (0.37 area%) while majority other impurities were also on the low levels compared to the results obtained in other experiments performed at 50 °C.

Since the price of NMP was ca. 45% higher compared to DMA, and DMSO provided significantly higher level of impurities **10** and **14** in [**3**] → [**4**] step, which might be critical for the quality of **6** and **9**, we decided to use DMA as a single solvent through the whole one-pot sequence. Since impurity profile obtained at 50 °C in DMA appeared to be manageable in the downstream chemistry (trityl protection removal), we have decided to test the one-pot sequence at higher temperatures in order to gain some reaction time. In addition, the reaction temperature had profound effect on overall reaction time as evidenced by the difference in reaction times performed at ambient temperature (ca. 241 h), 40 °C (ca. 79 h) and 50 °C (55-57 h). When the one-pot sequence was performed at 60 °C in DMA (Table 1, entry 9) we have observed significant rise in the formation of impurity **10** (> 6 area% at the end of [**3**] → [**4**] step), while other impurities maintained on similar levels compared to the 50 °C reaction. In addition, some new unidentified impurities appeared in the chromatogram of the reaction mixture at 7.4 min (0.48 area%) and 9.5 min (0.78 area%) at the end of [**3**] → [**4**] step. This gave the first indication that higher temperatures of the process might result in poor control over the impurity profile of **6**. The isolated yield of **6** dropped to 72% (95.7% purity) and the level of both impurities **12** was in the range of ca. 0.8 area%. Finally, we rose the temperature of one-pot sequence to 75 °C in DMA (Table 1, entry 10). Not surprisingly, beside already identified impurities listed in Table 1, this process provided many new unknown impurities at significant levels: at 3.0 min (1.79 area%), 7.4 min (2.40 area%) 7.9 min (2.22 area%) and 9.5 min (2.05 area%). Isolated yield of **6** dropped considerably to 47% using the same isolation process as in previous examples. Moreover, isolated product **6** had only 87.6% purity as a consequence of the presence of impurities **12**, **13**, **14**, and probably **16** at higher level than previously observed. When putting on balance overall reaction time *vs.* formation of side products, two experiments performed at 60 °C and 75 °C suggested that the optimal temperature of one-pot sequence in DMA should be set at 50 °C.

Table 1. Solvent and temperature screening in one-pot synthesis of trityl olmesartan medoxomil **6**.



Entry[†]	solvent	T [°C]	t [h]	**1** [%]	**10** [%]	**5** [%]	**9**[£] [%]	**12** [%]	**4** [%]	**13** [%]	**14** [%]	**15** [%]	**6** [%]	**3,16**[¥] [%]	**2** [%]	**9.95**[§] [%]	**yield** [%]
				1.06	0.88	0	0	0	83.61	/[#]	4.90	2.19	0	2.77	1.70	1.41	
1 [a,d]	NMP	40,50	79	0.75	0	3.75	0	0	15.76	0	3.34	/[ǂ]	69.95	2.46	0.42	1.24	76[‡]
				0	0	0	0.23	0	0.18	0.15	0.49	/[ǂ]	94.78	3.15	0.16	0.30	
				1.02	1.07	0	0	0	80.74	/[#]	4.90	2.31	0	4.25	2.01	2.01	
2 [a,d]	DMA	40,50	79	0.72	0	3.01	0.17	0.29	12.16	0.88	3.25	/[ǂ]	72.11	3.62	0.34	1.19	78[‡]
				0	0	0	0.22	0	0.35	0.23	0.72	/[ǂ]	93.38	4.09	0.06	0.47	
				1.31	1.00	0	0	0	83.26	/[#]	5.03	2.19	0	1.98	2.03	1.45	
3 [a,c]	NMP/DMSO =	40,50	79	0.82	0	2.98	0	0.61	11.96	0.69	3.17	/[ǂ]	74.31	1.83	0.38	1.16	76[‡]
	9:1			0	0	0	0.27	0	0.30	0.17	0.53	/[ǂ]	95.56	2.11	0.05	0.46	
				1.00	1.54	0	0	0	82.58	/[#]	5.32	2.25	0	1.71	2.11	1.51	
4 [a,c]	DMA/DMSO =	40,50	79	0.71	0	3.07	0.31	1.43	11.68	0.17	3.36	/[ǂ]	74.70	1.66	0.25	1.28	75[‡]
	9:1			0	0	0	0.27	0	0.37	0.18	0.56	/[ǂ]	95.62	1.93	0	0.42	
				0.89	1.19	0	0	0	80.31	/[#]	4.47	1.56	0	2.27	1.70	1.23	
5 [*,a,e]	DMA/DMSO =	40,50	76.5	0.81	0	1.51	0	0.80	1.71	0.81	3.29	/[ǂ]	84.30	3.09	0.38	1.08	79[‡]
	9:1			0	0	0	0.47	0.06	0.30	0.52	0.73	/[ǂ]	93.69	3.18	0.06	0.52	
				1.94	6.00	0	0	0	78.11	/[#]	7.77	2.47	0	1.29	0.42	1.19	
6 [*,a,e]	DMSO	40,40-50	57	1.19	0.54	0	0.28	4.74	2.19	2.14	5.42	/[ǂ]	77.59	2.05	0	1.03	74[‡]
				0	0	0	0.28	0.25	0.31	0.25	0.90	/[ǂ]	94.48	2.52	0	0.34	
				0.93	3.57	0	0	0	83.78	/[#]	4.33	2.58	0	1.46	1.62	1.12	
7 [*,b,e]	DMA/DMSO =	50	57	0.80	0	2.53	0.14	2.82	3.32	1.52	3.87	/[ǂ]	79.15	2.42	0.28	1.37	78[‡]
	9:1			0	0	0	0.70	0.81	0.50	0.79	1.78	/[ǂ]	90.07	2.83	0	1.08	
				0.86	2.00	0	0	0	83.75	/[#]	4.30	2,41	0	1.57	0.76	1.17	
8 [b,d]	DMA	50	55	0.56	0	2.58	0.20	1.40	2.16	0.99	3.63	/[ǂ]	83.95	1.82	0.11	1.17	78[‡]
				0	0	0	0.72	0.37	0.41	0.57	1.87	/[ǂ]	92.31	1.98	0	1.01	
				2.15	6.46	0	0	0	81.61	/[#]	3.19	1.13	0	1.64	0.78	1.10	
9 [d]	DMA	60	52.8	1.44	0	4.13	0.12	4.52	3.10	2.17	1.89	/[ǂ]	78.74	1.39	0.14	0.84	72[‡]
				0	0	0	0.26	0.81	0.34	0.55	0.62	/[ǂ]	95.74	1.23	0	0.25	
				1.19	3.81	0	0	0	65.40	/[#]	5.52	5.34	0	1.71	2.05	1.41	
10 [d]	DMA	75	28.5	0.74	0	2.4	0	4.35	11.55	2.47	3.67	/[ǂ]	63.96	2.68	0.25	2.34	47[‡]
				0	0	0	0.32	0.69	0.46	1.21	1.69	/[ǂ]	87.86	4.23	0	2.12	

[†] Standard reaction conditions: **1** : **2** : **5** : LiOH·H_2O : K_2CO_3 = 1.0 : 1.0 : 1.23 : (1.0 + 1.5) : 1.1 equivalents. Initially 17.5 mL of solvent defined in the table is used per gram of imidazole **1**. C (**1**) = 0.238 M. Additionally 2 mL of solvent per g of **1** used was added together with substrate **5**. Solvent used for the addition of **5** is DMA except in entries 2 and 4 where NMP was used. [a] Procedure described in the experimental part under section 4.2.2. [b] Procedure described in the experimental part under section 4.2.3. [c] 2.0 g of **1** was used. [d] 4.0 g of **1** was used. [e] 8.0 g of **1** was used. [*] Additionally 5 mL of solvent added together with second portion of LiOH·H_2O and additionally 0.123 equiv. of **5** added at the beginning of [**4**] → **6** step. Results for each compound in the reaction mixture or recrystalized product given as area% determined by HPLC analysis (see experimental section, HPLC method for reaction progress monitoring, run time = 12 min). Only peaks above reporting threshold of 0.05 area% are reported. The first row in each entry represents the composition of reaction mixture at the end of [**3**] → [**4**] step. The second row in each entry represents the composition of reaction mixture at the end of [**4**] → **6** step before isolation. The third row in each entry represents the quality of isolated product **6** after precipitation, re-digestion into a fresh solvent and one recrystallization. [§] Unknown impurity at t_R = 9.95 min. [#] In [**3**] → [**4**] step impurity **13** co-elutes under the main peak of intermediate **4** and it is not possible to monitor it in this step. [ǂ] In [**4**] → **6** step impurity **15** co-elutes under the main peak of product **6** and it is not possible to monitor it in this step and in the final product with HPLC method for reaction progress monitoring. [¥] In the HPLC method for reaction progress monitoring (run time = 12 minutes) impurities **3** and **16** co-elute and the levels of **16** were not evaluated at this stage. [£] Impurity **9** is also formed during the crystallization from acetone/water solvent as demonstrated in the discussion section. [‡] Yield of isolated product **6** after one recrystallization.

Subsequent optimizations of the one-pot process were focused on optimization of used amounts of LiOH·H_2O and K_2CO_3. First we performed four experiments in DMA at 50 °C similar to the experiment Table 1, entry 8 except that second portion of LiOH·H_2O intended for the hydrolysis [**3**] → [**4**] step was varied between 1.5-3.0 equivalents. Interestingly, we have observed that excess LiOH was competing with carboxylate anion in the S_N2 reaction on **5** in [**4**] → **6** step. Due to the lower nucleophilicity of carboxylate *vs.* hydroxide ion this led to a notably higher amount of unconsumed **4** after 77 h of overall reaction time: 3.5area% for 1.5 equiv. of LiOH used, 10.2 area% for 2.0 equiv. of LiOH used, 14.8 area% for 2.5 equiv. of LiOH used and 38.9 area% for 3.0 equiv. of LiOH used. These experiments confirmed that optimal quantity of added LiOH·H_2O in [**3**] → [**4**] step was indeed 1.5 equivalents. We have also tested, if the whole amount 2.5 equiv. (1.0 + 1.5 equiv.) of

$LiOH \cdot H_2O$ needed for the alkylation and hydrolysis step can be added at the beginning of the reaction. In this case we have observed that > 9 area% of impurity **14** was formed by the end of the ester hydrolysis step. This clearly indicated that such dosing of $LiOH \cdot H_2O$ is not appropriate for the given one-pot approach.

Next, the effect of the amount of used K_2CO_3 on the outcome of the one-pot sequence was evaluated. It is well described in the literature that the counterion effects can notably effect the outcome of S_N2 reactions.[21] For this purpose we have tested the outcome of the one-pot sequence without the use of K_2CO_3 and when 0.5, 1.0, 1.1, 1.5, 2.0 and 3.0 equiv. of K_2CO_3 were added in [**4**] → **6** step. We have observed that when [**4**] → **6** step was conducted without the presence of K_2CO_3 ca. 6 area% of **4** remained in the reaction mixture after 53 h overall reaction time. Negligible improvement was observed, when 0.5 equiv. of K_2CO_3 was used. Application of 1.0, 1.1 and 1.5 equiv. of K_2CO_3 lowered the levels of unreacted **4** after 53 h to 3.0, 2.9 and 2.9 area% respectively. Use of 2.0 and 3.0 equiv. of K_2CO_3 gave 0.9 and 0.1 area% of unreacted **4** respectively after 53 h. Higher amounts of added base also did not result in the increase of impurity **16**. Nevertheless, due to the cost issues and dissolution issues related to the use of huge amount of inorganic salt to be dissolved in organic solvent, we have decided that 1.1. equiv. of K_2CO_3 provides optimal outcome in our one-pot sequence.

After, the influence of ratio between **1** and **2** on the outcome of the reaction was probed in order to test the robustness of the one-pot sequence. For this purpose we have used 5 or 10 mol% excess of either intermediate. We have noted that 5 or 10 mol% excess of **1** *vs*. **2** had negligible influence on the outcome of the one-pot reaction as demonstrated by a slightly higher level of **1** (ca. 1.0 and 1.4 area% respectively) in the reaction mixture after completion of the overall one–pot sequence (57 h). This impurity could be easily removed from the product **6** by a single recrystallization from a water/acetone mixture. In both cases 76% yield of **6** was obtained along with 97.4-97.7 area% purity. In the next set of experiments we have also tested 5 or 10 mol% excess of trityl protected tetrazole biphenyl derivative **2** in the reaction system. In this case we have observed increased levels of impurity **14** (5.7 and 7.4 area% respectively) in the reactor mixture at the end of overall one-pot sequence (57 h). Isolated yield of product **6** was in the range 76-78% after a single crystallization from acetone/water mixture. The isolated product **6** had purity of 97.3 to 96.6 area% and contained 0.5-0.6 area% of impurity **14**. In reactions using 5 or 10 mol% excess of **1**, levels of impurity **14** were in the range of 0.4-0.5 area%. This indicated that the tested excess of **2** in the reaction mixture provided low and manageable increase of impurity **14**. These experiments also suggested that the one-pot process is relatively robust against reasonable variability of ratio between **1** and **2**.

Further set of experiments was performed where equimolar amount, 5 mol% excess and 10 mol% excess of either intermediate **1** or **2** were used in combination with a higher amount of $LiOH \cdot H_2O$ (3 equiv. instead of 1.5 equiv.) in [**3**] → [**4**] step. These experiments revealed that one-pot sequence had a tendency to slow down significantly in [**4**] → **6** step, if only usual amount of **5** (1.23 equiv.) was used as a result of competitive reaction of **5** with excess OH^-. Indeed, we have observed that 20-40 area% of unreacted **4** was present in the reaction mixture after 54 h. Additional amount of **5** (0.7 equiv.) enabled consumption of **4** in 72 h. Similarly as in the previous set of experiments, we observed that when equimolar amount of **1** and **2** or excess of **1** were used, levels of impurity **14** were low (ca. 1-2 area%) at the end of overall one-pot reaction sequence (72 h). When excess amount of **2** was applied, 3-6 area% of **14** was obtained after 72 h when one-pot sequence was finished. In all cases, impurity **14** could be removed successfully to acceptable levels (0.3-0.9 area%) after one crystallization from acetone/water mixture. Product **6** was obtained in 79-81% yield and 96.1-97.8 area% purity. These experiments suggested that the excess amount of LiOH used in [**3**] → [**4**] step did not have a direct effect on the quality of isolated product **6**, but rather on the feasibility and robustness of [**4**] → **6** step which required process adjustment by application of additional amount of **5**.

In the final stage of lab optimization we have investigated parameters that influence the filterability of precipitate after addition of reaction mixture into water and optimal procedure for recrystallization of the crude precipitate.

Performed experiments revealed that key parameters that influence the filterability of the crude precipitate are associated with: amount of unreacted intermediate **4** in the reaction mixture, quality/purity of used **5**, water temperature used for precipitation of the product **6** and time of suspension stirring after precipitation. Performed experiments have shown that, if 20-30 area% of **4** are present in the reaction mixture, which was poured into water, very poorly filterable precipitate was formed. Nevertheless, such scenario was very unlikely, due to the proven robustness of the process. We have observed that the quality of purchased **5** had high variability (74-95% GC purity). Subsequent experiments have shown, that when the GC purity of **5** was below 80 area%, highly sticky product **6** precipitate was obtained owing to the presence of several coloured impurities which sticked to the product. Therefore, **5** with purity > 80% was sourced and used and 10 vol% of acetone was added to the water used for precipitation, which assured that coloured impurities remained in the solution and did not stick to the product. These modifications of the isolation process assured constant reproducibility of filtration experiments and enabled facile and rapid filtration of the product **6**. Furthermore, performed experiments suggested that precipitate obtained from ice cooled water had worse filterability than precipitate obtained from water with ca. 20 °C. Consequently, temperature of water used in precipitation of product was raised accordingly. Finally, we have also observed that when suspension of precipitated product was stirred for a prolonged time (ca. 18 h) at ambient temperature, easily filterable precipitate was formed. All this gained knowledge was subsequently built into the kilo-lab experiments.

We have also noted that the filtered product obtained after precipitation of reaction mixture into water/acetone (v/v = 19:1) contained notable amount of DMA, which resulted in the formation of sticky product upon drying. Therefore we have introduced, before crystallization, additional re-digestion step, where drained precipitate of the product **6** was redigested into a fresh quantity of water/acetone (v/v = 19:1) and stirred at ambient temperature, and drained on the filter before entering the re-crystallization step. Product **6** obtained at this isolation stage according to the process described in Table 1, entry 8 had typically purity in the range of 86-89 area%.

Finally, we have studied the recrystallization of the crude precipitate obtained upon addition of reaction mixture to water in order to reach sufficient quality of the product **6** that could be used for the formation of **9**. We have first determined the solubility of **6** in various solvents. The first recrystallization experiments conducted in EtOH (solubility of **6** ca. 2 g/L at r.t.) were not fruitful as only ca. 30-40% yields of **6** were attained as a result of partial removal of trityl protection group with protic organic solvent. Next, we considered acetone in combination with water as a cheap and sustainable solvent option for recrystallization, albeit solubility of **6** was notably higher in acetone (solubility of **6** ca. 125 g/L at r.t.) while it is practically insoluble in water. Recrystallization was designed as cooling crystallization where suspension of **6** in acetone (0.4 to 0.6 g/mL) or acetone/water mixture in ratio 2.5:1 to 8:1 (0.09 to 0.25 g/mL) was heated to boiling point where clear solution was obtained.

The resulting solution was cooled to 0 °C while the mixture was stirred. The precipitate was collected by filtration, washed with acetone/water mixture (v/v = 1:1) and dried in a vacuum drier at 40 °C. We have observed that when recrystallization is conducted in pure acetone we were able to isolate 79-81% of **6** and chromatographic purity of **6** was notably upgraded from starting 75-82 area% to 91-92 area%. Nevertheless, very dense suspension was formed in this case, which could present some technical challenges on a larger scale. Expectedly, recrystallizations from acetone/water mixtures, gave higher yields. A 90% yield of **6** was afforded when acetone/water 2.5:1 mixture (0.09 g/L) was used and purity of the product was upgraded from 80 area% to ca. 94 area%. Applying 4:1 mixture acetone/water (0.25 g/L) gave 90-93% yield of **6** and its purity was upgraded from 88-89 area% to ca. 92 area%. When **6** was recrystallized from 8:2 mixture acetone/water (0.22 g/L) 94% yield was obtained and chromatographic purity was also improved for ca. 4 area%. This results indicated that 8:2 mixture acetone/water might be the most favourable for recrystallization of crude **6**. Since we observed that protic solvents like EtOH had unfavourable effect on recrystallization due to the degradation of **6** to **9**, we have decided to investigate the influence of the amount of water in the acetone/water on degradation of **6** during the crystallization. For this purpose we have designed a series of experiments where we compared the amount of formed **9** after 10 and 60 minutes of solution heating at reflux as well as the yield of isolated **6**. When pure acetone was used in both cases (10 and 60 min refluxing) the amount of **9** in the solution practically did not change and 89% yield of **6** was obtained in both cases. Using acetone/water 3/1 mixture proved to be a drastically different situation: level of **9** rose from starting 0.1 area% to 12.9 area% after 60 min of reflux and yield for 10 min refluxing was 91% while 60 min refluxing gave only 78% yield of **6**. Applying acetone/water 4/1 mixture in similar experiments showed a drop of yield of **6** from 93% to 87% for 10 and 60 min refluxing respectively, while the amount of **9** rose from 0.1 area% to 6.9 area% after 60 min of refluxing. Due to the proven negative effect of water on the degradation of **6** during the recrystallization, acetone/water 9/1 mixture was also tested. In this case the level of **9** rose only to 1.3 area% after 60 min refluxing and isolated yield of **6** were nearly the same (ca. 92% in average) for 10 and 60 min refluxing experiments. These experiments have shown that recrystallization of **6** should be conducted with acetone/water 9/1 mixture.

2.2. Kilo-lab one-pot three-component assembly of trityl olmesartan medoxomil 6

After we have completed our optimization of one-pot process on the lab scale, we have decided to perform the first scale up of the process to the kilo-lab scale in order to test the process on the process equipment. A batch at kilo-lab scale experiment was planned to produce ca. 300 g of **6**. For this purpose we have performed one-pot experiments starting from 120 g of imidazole **1**. All kilo-lab reactions were conducted in a 4 L jacketed glass reactor at 50 °C in DMA and initial concentration of 0.238 M. All the substrates and reagents were added in the ratio **1** : **2** : **5** : $LiOH{\cdot}H_2O$: K_2CO_3 = 1.0 : 1.0 : 1.20-1.23 : (1.0 + 1.5) : 1.1 equivalents. We have observed in all cases that initial alkylation step **1** → [**3**] proceeded smoothly in the presence of 1 equiv. of $LiOH{\cdot}H_2O$ and already after ca. 1 h of reaction time **1** was mainly consumed (2-3 area% remaining in the mixture). In the initial scale-up experiment (not reported in Table 2, however, using the same amount of reagents and the same reaction conditions as subsequent reported experiments) we have observed that hydrolysis of ester **3** proceeds significantly slower than in lab experiments. In this experiment the whole amount of $LiOH{\cdot}H_2O$ (1.5 equiv.) intended for hydrolysis step was added in one portion as in all lab experiments. Therefore, we have added additional amount of $LiOH{\cdot}H_2O$ (0.5 equiv.) after 46.5 hours overall reaction time when 29.7 area% of **3** was still unconsumed in the reaction mixture. Nevertheless, we have found out that additional amount of $LiOH{\cdot}H_2O$ had marginal effect on the reaction rate (29.1 area% of **3** after 50 h of overall reaction time). We have also tested the influence of higher reaction temperature (60 °C between 50 h and 54 h of overall reaction time), which had a small effect on the hydrolysis rate (21.1 area% of **3** after 54 h). After testing all of the above modifications of the process to increase the hydrolysis rate in [**3**] → [**4**] step, we have turned our attention to the efficacy of stirring. The reactor used in the first kilo-lab experiment was equipped with a glass anchor stirrer. We have also observed that the whole amount of added $LiOH{\cdot}H_2O$ was not homogenously suspended in the reaction mixture, due to the partial sedimentation on the bottom of the reactor. This indicated that the key factor which had profound effect on the outcome of one-pot reaction was related to the intensity of stirring in the [**3**] → [**4**] step. Therefore, we have changed an anchor stirrer for a PTFE-coated propeller stirrer and increased the stirring speed to 500 rpm, which provided homogeneous suspension of $LiOH{\cdot}H_2O$ in the mixture. This significantly enhanced the hydrolysis rate and enabled us to reach < 1.5 area% of **3** in the mixture after 70.5 h overall reaction time. Subsequent alkylation of **4** with **5** proceeded rapidly and was terminated at 74.25 h overall reaction time. Afterwards, ca. 3 area% of **5** was present in the reaction mixture. In this experiment we were able to isolate product **6** in 64% yield and 96.5% chromatographic purity after two recrystallizations (the first provided product with only 93.6% purity) as a result of higher amount of formed impurities (e.g. **4**, **14** and **16**) which were formed due to the use of additional amount of base and increased temperature. With this knowledge in hand we conducted three consecutive one-pot experiments (Table 2) by using stepwise addition of $LiOH{\cdot}H_2O$ (1.5 equiv.; 0.5 equiv. added after 1 hour reaction overall time each hour) used in the hydrolysis step and by applying vigorous stirring using propeller stirrer at > 500 rpm.

In these experiments, we were able to reach levels of **3** below 3-4 area% in the hydrolysis step in 46.75-49.5 h. The alkylation of **4** with **5** proceeded smoothly and was finished in ca. 6-7 hours (Table 2, entries 1-2; Figure 3). When we studied a prolonged alkylation time of 20.5 h in [**4**] → **6** step (Table 2, entry 3), we have observed marginal improvement in the yield. Moreover, developed laboratory isolation processes consisting of precipitation of crude product upon addition into water/acetone, re-digestion of precipitate in water/acetone and recrystallization of wet precipitate from acetone proved to be reliable, enabling smooth filtration of crude product precipitate and recrystallized product which was usually finished in 5-10 min time. Levels of impurity **16** were in general determined to be below reporting limit (0.05 area%) by HPLC method with run time of 35 min. This method also showed that peak assigned to impurities **3** and **16** in HPLC method for reaction progress monitoring (run time = 12 min) contains in fact three compounds, since a new unknown impurity eluted just before ester **3** in HPLC with run time of 35 min. To our satisfaction, all of the performed modifications related to stepwise addition of the $LiOH{\cdot}H_2O$ base and stirring proved to be sufficient and enabled us to isolate product **6** repeatedly in 72-75% yield and 94.4-97.5% chromatographic purity after precipitation, re-digestion and a single crystallization from water/acetone mixture.

Table 2. Kilo-lab one-pot synthesis of trityl olmesartan medoxomil **6**.

Entry[†]	solvent	T [°C]	t [h]	**1** [%]	**10** [%]	**5** [%]	**9** [%]	**12** [%]	**4** [%]	**13** [%]	**14** [%]	**15** [%]	**6** [%]	**3,16**[¥] [%]	**2** [%]	**9.95**[§] [%]	**yield** [%]
				1.07	1.66	0	0	0	81.31	/[#]	5.79	3.22	0	2.97	0.82	1.39	
1	DMA	50	55.3	0.64	0	2.10	0.17	1.04	8.36	0.07	3.40	/[ǂ]	78.53	3.34	0.09	1.15	74[‡]
				0	0	0	0.15	0	0.16	0.17	0.55	/[ǂ]	97.39	1.37	0	0.16	
				1.19	1.16	0	0	0	82.87	/[#]	7.05	2.43	0	2.91	0.61	0.89	
2	DMA	50	53.3	0.87	0	2.21	0.18	0.76	6.97	0.61	4.61	/[ǂ]	78.50	3.25	0.08	0.75	72[‡]
				0	0	0	0.23	0	0.22	0.13	0.77	/[ǂ]	96.68	1.76	0	0.19	
				1.19	1.51	0	0	0	79.44	/[#]	7.17	2,82	0	4.43	0.73	0.98	
3	DMA	50	70	1.18	0	2.61	0.20	1.12	0.29	0.66	5.69	/[ǂ]	79.34	5.19	0.13	0.92	75[‡]
				0	0	0	0.15	0	0.07	0.07	0.59	/[ǂ]	95.40	3.45	0	0.16	

[†] Standard reaction conditions: **1** : **2** : **5** : LiOH·H_2O : K_2CO_3 = 1.0 : 1.0 : 1.20 : (1.0 + 1.5) : 1.1 equivalents. In entry 3 experiment 1.23 equiv. of **5** was used instead of 1.20 equiv. Initially, 17.5 mL of DMA used per gram of imidazole **1**. C (**1**) = 0.238 M. Additionally, 2 mL of DMA per gram of **1** used was added when substrate **5** was added. Results for each compound in the reaction mixture or crystalized product given as area% determined by HPLC analysis (see experimental section, HPLC method for reaction progress monitoring, run time = 12 min.). [#] In [**3**] → [**4**] step impurity **13** co-elutes under the main peak of intermediate **4** and it is not possible to monitor it in this step. [ǂ] In [**4**] → **6** step impurity **15** co-elutes under the main peak of product **6** and it is not possible to monitor it in this step and in the final product with HPLC method for reaction progress monitoring. [§]Unknown impurity at t_R = 9.95 min. [¥] In the HPLC method for reaction progress monitoring (run time = 12 minutes) impurities **3** and **16** co-elute. Levels of impurity **16** in isolated recrystallized product **6** were in general determined to be < 0.05% by HPLC method for related substances (see experimental section, run time = 35 min). The first row in each entry represents composition of reaction mixture at the end of [**3**] → [**4**] step. The second row in each entry represents composition of reaction mixture at the end of [**4**] → **6** step before isolation. The third row in each entry represents the quality of isolated product **6** after recrystallization. Purity of final isolated **6** determined with HPLC method for related substances (run time = 35 min) showed values: 97.5 area% (entry 1), 96.8 area% (entry 2) and 94.4 area% (entry 3). [‡]Yield of isolated product **6** after precipitation, re-digestion into a fresh solvent and one recrystallization.

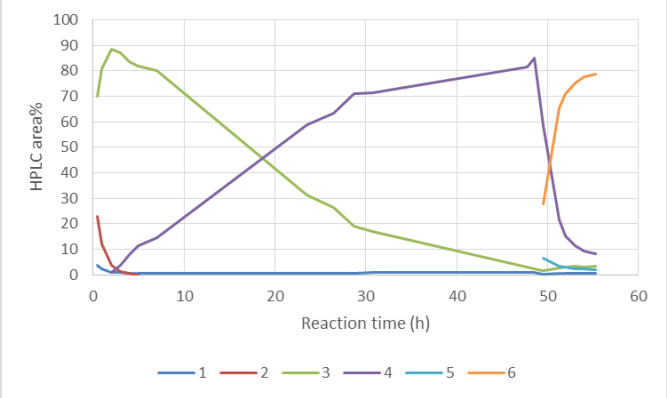


Figure 3. Progress of kilo-lab one-pot assembly of trityl olmesartan medoxomil **6** in DMA *via* reaction sequence **1** → [**3**] → [**4**] → **6** (300 g scale).

Table 3. Comparison of solvent consumption in primary and developed one-pot process.

Process step	**Primary process**[6] L of solvent/kg of **6**	**One-pot process**[9] L of solvent/kg of **6**
reaction	DMF = 16.5 H_2O = 5.4 dioxane = 11.7 DMA = 6.4	DMA = 7.9
isolation	AcOEt[a,b] H_2O[a] hexane[b] *i*-Pr_2O[c]	H_2O = 59.3 acetone = 10.9

[a] solvent used in three extraction unit operations in steps **1** → **3**, **3** → **4** and **4** → **6**, quantity of used solvent not specified; [b] solvent, used in one column chromatography purification in step **1** → **3**, quantity of used solvent not specified; [c] solvent used in two crystallization unit operations in steps **1** → **3**, and **4** → **6**, quantity of used solvent not specified.[6]

Overall, our one-pot process utilizes ca. 5 times less solvents in the reaction stage compared to the primary process (Table 3). Moreover, in our case a single reaction solvent has been used, while primary process has applied 4 different solvents. In the product isolation stage, our process has used only water and acetone, while primary process has applied water, ethyl acetate, hexane and diisopropyl ether. The comparison of used amount of solvents is not possible for isolation stage, due to lack of data for the primary process,[6] we believe that our one-pot process consumes less solvents based on the fact that primary process uses 3 extraction unit operations, one column chromatography and 2 crystallization unit operations. Therefore, we believe that we significantly reduced the amount of solvents in the overall process in our one-pot approach compared to the primary process.

Trityl olmesartan medoxomil **6** prepared according to three-component one-pot process was successfully integrated into our in-house process for the removal of trityl protection using hydrohalic acid in the final step of olmesartan medoxomil **9** synthesis.[17] Produced olmesartan medoxomil **9** had purity over 99.5% and fully complied with all regulatory requirements for active pharmaceutical ingredients. The developed one-pot process was further scaled-up to pilot plant where registration batches of **6**[9] and **9**[17] were produced and the process was successfully registered at European health authorities.

3. Conclusion

We have developed a one-pot three-component assembly of trityl olmesartan medoxomil **6** in overall 72-75% yield and up to 97.5% HPLC purity on 300 g scale. Although overall yield of our process is probably slightly higher compared to the primary synthetic route, where 73% overall yield of **6** with unknown quality over three steps was reported (without taking into account the first step crystallization process yield), we are convinced that our process provides notable benefits. Key feature of our method is exceptional operational simplicity and efficiency. Albeit our process proceeds in twice the overall reaction time compared to the primary synthetic route (ca. 55 h *vs.* ca. 27 h), numerous advantages of our process marginalize this aspect in terms of overall process efficiency. Indeed, we have significantly reduced the number of unit operations compared to the best primary synthetic route (Scheme 1, path A): from 3 evaporations to dryness, 3 extractions, 1 column chromatography, 2 crystallizations and 2 product dryings to 1 precipitation, 1 re-

digestion of product in fresh solvent mixture, 1 crystallization and 1 product drying. At the same time we have reduced the number of used solvents from 7 solvents (DMF, hexane, AcOEt, *i*-Pr_2O, dioxane, H_2O, DMA) in primary synthetic route to 3 solvents (DMA, acetone, H_2O) in our process. Moreover, our process operates at higher concentrations 0.213-0.238 M *vs*. 0.108 M (step 1), 0.083 M (step 2) in primary synthetic route, which significantly reduces the amount of used solvents. Therefore, we believe that our one-pot process demonstrates notable process intensification aspects and provides economically and environmentally viable alternative to other processes used for the preparation of trityl olmesartan medoxomil **6**.

4. Experimental section

4.1. General

Imidazole **1** was obtained from Changzhou EST Chemical Co., Ltd. China (97-98% HPLC purity), trityl protected tetrazole biphenyl **2** was sourced from Zhejiang Tianyu Pharmaceutical Co., Ltd. China (≥97% HPLC purity) and medoxomil chloride **5** was obtained from Dezhou Xinda Chemical Co., Ltd. China (GC purity 90-91%). Reagents and solvents were acquired from commercial sources and were used without further purification. Reactions were monitored by using analytical TLC plates (Merck; silica gel 60 F254, 0.25 mm), and compounds were visualized with UV radiation. Silica gel grade 60 (70–230 mesh, Merck) was used for column chromatography. Standards of identified impurities were either purchased from commercial sources (**13** and **14**) or were prepared according to procedures similar to those published in the literature (**10**,[6,7b,8c,g,j] **11**,[6,8h] **12**,[8e,f,g,j] **15**,[7b,8a,d] and **16**[7b,8c]). Identification of each impurity in the chromatogram was determined by comparison with retention time of an authentic sample of each impurity, which has been characterized by NMR spectroscopy and/or mass spectrometry. Compound **6** was characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy and MS spectrometry. IR spectra were obtained on Thermo Nicolet Nexus FT IR spectrophotometer instrument. NMR spectra were recorded on the Varian VNMRS 400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Chemical shifts are reported in δ ppm referenced to TMS as an internal standard. Mass spectra were recorded on Micromass QTOF Ultima Global apparatus.

The progress of one-pot reactions were analyzed by a rapid HPLC method using an XBridge Shield RP18 column (3.5 µm, 50 × 4.60 mm). Solvent: MeCN. Mobile phase A: phosphate buffer (25 mM KH_2PO_4, pH = 2.5). Mobile phase B: acetonitrile. Temperature of column 30 °C. Flow rate 1.0 mL/min. Wavelength 225 nm. Injection volume 20 µL. Gradient: m.p. A : m.p. B; 0 min (90:10), 6.7 min (20:80), 10.0 min (20:80), 10.1 min (90:10), 12.0 min (90:10). t_R (**1**) = 2.5 min, t_R (**10**) = 3.3 min, t_R (**5**) = 3.4 min, t_R (**11**) = 4.4 min, t_R (**9**) = 4.5 min, t_R (**12** two regioisomers) = 5.3 and 5.8 min, t_R (**4**) = 6.8 min, t_R (**13**) = 6.9 min, t_R (**14**) = 7.7 min, t_R (**15**) = 8.2 min, t_R (**6**) = 8.6 min, t_R (**3**) = 8.9 min, t_R (**16**) = 8.9 min, t_R (**2**) =9.7 min.

The purity of isolated product **6** obtained on kilo-lab scale was also analyzed by an HPLC method using an XBridge C18 column (3.5 µm, 150 × 4.60 mm). Solvent: MeCN. Mobile phase A: phosphate buffer (25 mM KH_2PO_4, pH = 2.5). Mobile phase B: acetonitrile. Temperature of column 30 °C. Flow rate 1.0 mL/min. Wavelength 225 nm. Injection volume 20 µL. Gradient: m.p. A : m.p. B; 0 min (80:20), 10 min (35:65), 25 min (20:80), 30 min (20:80), 30.1 min (80:20), 35 min (80:20). t_R (**1**) = 2.4 min, t_R (**9**) = 11.2 min, t_R (**4**) = 13.2 min, t_R (**13**) = 13.6 min, t_R (**14**) = 16.8 min, t_R (**15**) = 21.4 min, t_R (**6**) = 22.1 min, t_R (unknown imp.) = 23.7 min, t_R (**3**) = 23.9 min, t_R (**16**) = 24.7 min, t_R (**2**) = 26.9 min.

4.2. Synthetic procedures

*4.2.1. One-pot three-component assembly of trityl olmesartan medoxomil **6** in NMP (Figure 1).*

Imidazole **1** (4.0 g, 16.65 mmol), trityl protected tetrazole biphenyl **2** (9.29 g, 16.66 mmol) and LiOH·H_2O (0.70 g, 16.66 mmol) were charged in a 250 mL triple neck flask. Afterwards, 70 mL of *N*-methyl-2-pyrrolidone (NMP) was added and flask was flushed with nitrogen. The reaction mixture was stirred at room temperature for 24 h, then LiOH·H_2O (1.05 g, 0.25 mmol) was added and reaction mixture was stirred at room temperature for 212.5 h (ca. 9 days). After 9 days K_2CO_3 (2.53 g, 18.31 mmol) was added to the reaction mixture followed by a dropwise addition of medoxomil chloride **5** (3.20 g 20.5 mmol, ~ 95%) in 8 mL of DMA. The reaction mixture was heated to 50 °C and stirred for another 4.5 h. Then, it was poured during the stirring in a mixture of ice (102 g) and water (311 mL) and stirred for 18 h at room temperature. The product was filtered off and was re-slurred three times in 150 mL of water. A poorly filterable precipitate was formed which contained sticky particles. A wet product was recrystallized from acetone: to the wet precipitate (22.7 g) acetone (20 mL) was added and mixture was heated to reflux where the solution was clarified, cooled to room temperature, stirred for 1 h and then for 1 h at 0 °C. The resulting precipitate was filtered off, washed with 20 mL of acetone/water = 1/1 (v/v) mixture. The product was dried in vacuum at 40 ° C for 24 h to give 11.85 g (89% yield) of the product **6**. The obtained product **6** (11.5 g) was additionally recrystallized: 52 mL of acetone/water = 4/1 (v/v) mixture was added, mixture was heated to reflux where the solution clarified. The solution was cooled to room temperature, stirred for 1 h and then for 2 h at 0 °C. The resulting precipitate was filtered off, washed with 11.5 mL of acetone/water (v/v = 1/1). Drying in vacuum at 40 °C for 24 h gave 10.01 g (87% yield) of the product **6** which had 91% HPLC purity (overall yield 77%) and contained 6 area% of ester **3**.

*4.2.2. Solvent optimization experiments in one-pot three-component assembly of trityl olmesartan medoxomil **6**: procedure A (Table 1, entries 1-6).*

Imidazole **1** (2.0-8.0 g, 8.3-33.3 mmol), trityl protected tetrazole biphenyl **2** (1.0 equivalent) and LiOH·H_2O (1.0 equivalent) were stirred at ambient temperature in solvent-1 (17.5 mL/g of **1**). The course of the reaction was monitored by HPLC. At partial conversion to the ester **3** (when ca. 10% of the **2** was present in the reaction mixture), the temperature was raised to 40 °C. When quantitative conversion to ester **3** was reached LiOH·H_2O (1.5 equivalent) was added at 40 °C to the reaction mixture and stirred at this temperature until the sufficient conversion to **4** was obtained. The reaction mixtures in entry 1-4 experiments were cooled to ambient temperature, in entry 5-6 experiments the temperature was maintained and reaction mixture stirred at 40 °C until the reaction mixture contained less than 3% of **3**. Then K_2CO_3 (1.1 equivalent) was added followed by dropwise addition of **5** (1.23 equivalent) solution in solvent-2 (2 mL/g of **1**). The temperature of the reaction was raised to 50 °C and mixture was stirred until quantitative conversion to **6** was obtained (if necessary, a smaller proportion of **5** was added). The reaction mixture was cooled and poured onto a mixture of ice and water, stirred for at least 0.5 h, the precipitate was filtered and then re-slurred twice in water. The crude wet product was recrystallized from acetone and obtained precipitate was washed with a mixture of acetone/water (v/v = 1/1).

*4.2.3. Solvent optimization experiments in one-pot three-component assembly of trityl olmesartan medoxomil **6**: procedure B (Table 1, entries 7-8).*

Imidazole **1** (4.0-8.0 g, 16.7-33.3 mmol), trityl protected tetrazole biphenyl **2** (1.0 equivalent) and LiOH·H_2O (1.0 equivalent) were stirred at 50 °C in solvent-1 (17.5 mL/g of **1**). The course of the reaction was monitored by HPLC. When quantitative conversion to ester **3** was reached LiOH·H_2O (1.5 equivalent) was added at 50 °C to the reaction mixture and stirred at this temperature until the complete conversion to **4** was obtained. Then, K_2CO_3 (1.1 equivalent) was added to the reaction mixture followed by dropwise addition of **5** (1.23 equivalent) solution in solvent-2 (2 mL/g of **1**). The mixture was stirred at 50 °C until quantitative conversion to **6** was reached (if necessary, a smaller proportion of **5** was added).The reaction mixture was cooled and poured onto a mixture of ice and water, stirred for at least 0.5 h, the precipitate was filtered and then re-slurred twice in water. The crude wet product was recrystallized from acetone and obtained precipitate was washed with a mixture of acetone/water (v/v = 1/1).

*4.2.4. One-pot three-component assembly of trityl olmesartan medoxomil **6** on 300 g scale (Table 2, entries 1-3).*

Imidazole **1** (120.15 g, 500 mmol), trityl protected tetrazole biphenyl **2** (278.75 g, 500 mmol) and LiOH·H_2O (20.98 g, 500 mmol) were charged in a 4 L reactor. Afterwards, DMA (2100 mL) was added to the reactor. The mixture was heated within 20-25 min to 50 °C ($T_{reaction\ mixture}$ = 50±1 °C, T_{jacket} = 52±1 °C).

After 1 hour from the beginning of heating, LiOH·H_2O (10.0 g) was added at 50 °C to the reaction mixture, followed by LiOH·H_2O (10.0 g, 238 mmol) after 2 hours and LiOH·H_2O (11.5 g, 274 mmol) after 3 hours of reaction time. During the addition of each portion of LiOH·H_2O, reaction mixture was stirred vigorously. The reaction kinetics was monitored by HPLC. The reaction mixture was sampled at 1 hour intervals until the end of addition of LiOH·H_2O, afterwards at 2 to 3 hours intervals.

At the residual 2-3 area% of ester **3** in the reaction mixture (48-51 h from the beginning of the reaction), K_2CO_3 (76.02 g, 550 mmol) was added into the reaction mixture and then slowly within 10 minutes the medoxomil chloride **5** (95.68 g-105.0 g, 600-615 mmol, 89-92% GC purity) solution in 240 mL DMA was added. The reaction mixture is stirred at 50 °C to a quantitative conversion into trityl olmesartan medoxomil **6**. Reaction kinetics was monitored with HPLC at 1 hour intervals. Conversion from lithium salt **4** to trityl olmesartan medoxomil **6** takes 6 to 7 h from the addition of **5** solution.

The reaction mixture was cooled to 35-40 °C and pumped in 5-10 min to a 20 L reactor containing mixture of 11.6 L of water and 0.3 L of acetone. The reactor was washed with additional 0.3 L of acetone and the solution was added to the mixture of water/acetone. The resulting suspension was stirred for 18 hours at ambient temperature (20-25 °C). Then the precipitate was filtered. The suspension was transferred in 15 minutes to the filter, and the obtained precipitate cake on the filter was drained for 45-60 minutes after filtration was finished.

The obtained wet cake was transferred back to the reactor with a mixture of 5.7 L of water and 0.3 L of acetone. The product was digested for about 1 hour at ambient temperature (24 °C) during the stirring. The precipitate was filtered off (filtering was performed in 15 minutes, draining of the product on the filter was done in 45 min).

The wet product was charged into a 5 L reactor with an outlet, and 1.4 L to 2.1 L of acetone was added (depending on the water content in the wet cake, loss on drying IPC was taken to determine the amount of dry matter in the cake; per 1 g of dry crude **6** 4.5 mL of acetone/water = 4:1 mixture was used). The mixture was heated to 60 °C in 25-35 min, then heated to boiling point T = 62-66 °C for up to 15 min. Afterwards, the reaction mixture was cooled to 25 °C in 30-45 min. The product **6** precipitates from the mixture at T ~ 40 °C. The reactor was maintained for 1 hour at 25 °C, then cooled to -5 °C in 0.5 hours and then the temperature in the reactor was maintained at -5 °C for 1 hour. Afterwards, product **6** was filtered off, filtering was carried out in 5 minutes. The reactor and the product were washed with 450 mL of acetone:water = 1:1 (v/v) mixture. The product was drained on the filter for 15 minutes and dried at 60-70 °C. The quality of **6** was determined by HPLC analysis (method run time = 35 minutes; see data in Table 2 footnote). Three consecutive batches of the process were performed giving trityl olmesartan medoxomil **6** as a white solid 295 g (74% yield and 97.5% HPLC purity; Table 2, entry 1), 290 g (72% yield and 96.8% HPLC purity; Table 2, entry 2) and 301 g (75% yield and 94.4% HPLC purity; Table 2, entry 3)..

IR (ATR): 2977, 1818, 1805, 1736, 1673, 1473, 1449, 1426, 1393, 1223, 1170, 1141, 957, 752 cm^{-1};

^{1}H NMR (DMSO-d_6) δ = 0.73 (3H, t, *J* = 7.4 Hz), 1.48 (6H, s), 1.46-1.56 (2H, m), 2.01 (3H, s), 2.41 (2H, t, *J* = 7.4 Hz), 4.99 (2H, s), 5.24 (1H, s), 5.34 (2H, s), 6.75 (2H, d, *J* = 8.2 Hz), 6.82-6.89 (6H, m), 7.0 (2H, d, *J* = 8.2 Hz), 7.27-7.40 (9H, m), 7.43-7.48 (1H, m), 7.50-7.56 (1H, m), 7.59-7.65 (1H, m), 7.75-7.79 (1H, m) ppm;

^{13}C NMR (DMSO-d_6) δ = 8.9, 13.7, 20.5, 28.4, 29.9, 48.2, 54.3, 69.8, 82.4, 116.4, 125.2, 125.9, 128.0, 128.0, 128.5, 129.2, 129.7, 130.7, 130.7, 133.0, 136.2, 139.1, 140.5, 141.0, 141.3, 151.1, 151.8, 157.9, 160.8, 163.6 ppm;

Mass peak (ESI+): 801 m/z (corresponds to $[M+H]^+$), 859 m/z (corresponds to $[M+NH_4+MeCN]^+$).

Trityl olmesartan medoxomil **6** is a known compound and has been previously characterized in the literature.[7a,b,e,8j] The characterization data of this compound were consistent with those previously reported.

Acknowledgments

Authors gratefully acknowledge Mrs. Darja Jereb for technical assistance in all synthetic experiments leading to the results presented in this manuscript. We thank Mrs. Lidija Kolenc for HPLC analyses; Matjaž Uštar (MSc) for the HPLC method development; Dr. Maja Harej for NMR analysis; Dr. Andrej Kocijan for mass spectrometry analysis; Mrs. Marjeta Hočevar (BSc) and Dr. Petra Novak for technical support; Mrs. Nina Žigart (MPharm) for critical reading of the manuscript and Lek d.d. for the support of this project.

A. Supplementary data

Supplementary data that contains copies of the HPLC charts and MS spectra associated with this article can be found, in the online version, at http://dx.doi.org/

References and notes

1. For reviews on structure, pharmacology, synthesis and analytics of sartans, see:
a) Timmermans PB. Angiotensin II receptor antagonists: an emerging new class of cardiovascular therapeutics. *Hypertens Res*. 1999;22:147–53;

b) Mimran A, Ribstein J, Ducailar G. Angiotensin II receptor antagonists and hypertension. *Clin Exp Hypertens*. 1999;21:847–858;
c) Petrella R, Michailidis P. Retrospective analysis of real-world efficacy of angiotensin receptor blockers versus other classes of antihypertensive agents in blood pressure management. *Clin Ther*. 2011;33:1190–1203;
d) Michel MC, Foster C, Brunner HR, Liu L. A systematic comparison of the properties of clinically used angiotensin ii type 1 receptor antagonists. *Pharmacol Rev*. 2013;65:809–848;
e) Mavromoustakos T, Agelis G, Durdagi S. AT1 antagonists: a patent review (2008 – 2012). *Expert Opin Ther. Patents* 2013;23:1483–1494;
f) Muszalska I, Sobczak A, Dołhań A, Jelińska A. Analysis of sartans: a review. *J Pharm Sci*. 2014;103:2–28;
g) Swann S, Bigi S. Angiotensin II receptor antagonists with carboxylic functionalities in cardiovascular disease. In: Lamberth C, Dinges J, eds. *Bioactive carboxylic compound classes: pharmaceuticals and agrochemicals*. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co. KGaA; 2016:87–101.

2. For reviews on structure, pharmacology, synthesis and analytics of olmesartan, see:
a) Neutel JM, Elliott WJ, Izzo Jr. JL, Chen CL, Masonson HNJ. Antihypertensive efficacy of olmesartan medoxomil, a new angiotensin ii receptor antagonist, as assessed by ambulatory blood pressure measurements. *Clin Hypertens*. 2002;4:325–331;
b) Chilman-Blair K, Rabasseda X. Olmesartan, an AT1-selective antihypertensive agent. *Drugs Today* 2003;39:745–761;
c) Stumpe, KO. Olmesartan compared with other angiotensin II receptor antagonists: head-to-head trials. *Clin. Ther*. 2004;26:a33–a37;
d) Krzesinski JM, Scheen AJ. Le medicament du mois: olmesartan medoxomil (belsar ou olmetec). *Rev Med Liege* 2004;59:607-611;
e) Chrysant SG, Dimas B, Shiraz M. Treatment of hypertension with olmesartan medoxomil, alone and in combination with a diuretic: an update. *J Hum Hypertens*. 2007;21:699–708;
f) Fabia MJ, Abdilla N, Oltra R, Fernandez C, Redon J. Antihypertensive activity of angiotensin II AT1 receptor antagonists: a systematic review of studies with 24 h ambulatory blood pressure monitoring. *J Hypertens*. 2007;25:1327–1336;
g) Saito I, Kushiro T, Ishikawa M, Matsushita Y, Sagawa K, Hiramatsu K, Komiya M. Early antihypertensive efficacy of olmesartan medoxomil. *J Clin Hypertens*. 2008;10:930–935;
h) Yanagisawa H, Koike H, Miura SI. Olmesartan medoxomil: an angiotensin ii receptor blocker. In: Huang X, Aslanian RG, eds. *Case studies in modern drug discovery and development*. Hoboken, NJ: John Wiley & Sons, Inc; 2012:45–66;
i) Volpe M, Tocci G. Olmesartan in the treatment of hypertension in elderly patients: a review of the primary evidence. *Drugs Aging* 2013;30:987–998;
j) Al-Majed AA, Bakheit AHH, Aziz HAA, Al-Jallal AAM. Olmesartan. *Profiles Drug Subst, Excipients, Relat Methodol*. 2017;42:241–286.

3. Mire DE, Silfani TN, Pugsley MK. A review of the structural and functional features of olmesartan medoxomil,anangiotensin receptor blocker. *J Cardiovasc Pharmacol*. 2005;46:585–593.

4. For fixed dose combinations of olmesartan medoxomil, see:
a) de la Sierraa A, Volpe M. Olmesartan-based therapies: an effective way to improve blood pressure control and cardiovascular protection. *J Hypertens*. 2013;31:S13–S17;
b) Chrysant SG. Triple-drug, fixed-dose combinations for the treatment of hypertension: focus on olmesartan/amlodipine/hydrochlorothiazide combination. *Drugs Today* 2011;47:197–206.

5. For clinical and economic value of olmesartan medoxomil in treatment of hypertension, see:
a) Kourlaba G, Gialama F, Tsioufis K, Maniadakis N. A literature review to evaluate the clinical and economic value of olmesartan for the treatment of hypertensive patients. *Int J Cardiol*. 2016;221:60–74;
b) Costa FV. Improving adherence to treatment and reducing economic costs of hypertension: the role of olmesartan-based treatment. *High Blood Press Cardiovasc Prev*. 2017;24:265–274;
c) Mazza A, Sacco AP, Townsend DM, Bregola G, Contatto E, Cappello I, Schiavon L, Ramazzina E, Rubelloh D. Cost-benefit effectiveness of angiotensin-II receptor blockers in patients with uncomplicated hypertension: a comparative analysis. *Biomed Pharmacother*. 2017;90:665–669.

6. Yanagisawa H, Shimoji Y, Fujimoto K, Kanazaki T, Anemiya Y, Koike H, Sada T. 1-Biphenylimidazole derivatives, their preparation and their therapeutic use. Eur. Patent EP 503785 B1.

7. For synthesis of olmesartan medoxomil, see:
a) Babu KS, Reddy MS, Tagore AR, Reddy GS, Sebastian S, Varma MS, Venkateswarlu G, Bhattacharya A, Reddy PP, Anand RV. Efficient synthesis of olmesartan medoxomil, an antihypertensive drug. *Synth Commun*. 2009;39:291–298;
b) Raju MN, Kolla N, Mukkanti K, Bandichhor R. An efficient and large scale synthesis of olmesartan medoxomil: anti hypertensive drug. *Chem Biol Interface* 2013;3:26-37;
c) Dams I, Ostaszewska A, Szczepek W. The development of a process for the preparation of olmesartan medoxomil with pharmaceutical-grade purity. *J Przem Chem*. 2015;94:1326–1332;
d) Seki M. 2,4-Dimethoxybenzyl Group for the Protection of Tetrazole: An Efficient Synthesis of Olmesartan Medoxomil through C–H Arylation. *Synthesis* 2015;47:2985–2990;
e) Hanumantha Rao B, Subramanyeswara Rao IV, Ravi Kanth V, Prasada Rao KVV, Balamurali Krishna K, Syama Sundar B. A competent and commercially viable process for the synthesis of the anti-hypertensive drug olmesartan medoxomil. *Sci Pharm*. 2015;83:465–478.

8. For synthesis of olmesartan medoxomil impurities, see:
a) Zhang F. Wu T. Preparation of olmesartan medoxomil. PCT Int. Appl. WO 2004085428 A1;
b)Pati HN, Lahiri S, Sabbam RK, Vangala VB, Ramalingam B, Hiriyanna SG, Bose P. A convenient and practical synthesis of olmesartan medoxomil methyl ether. *J Heterocyclic Chem*. 2008;45:917–920;
c) Babu KS, Tagore AR, Reddy GS, Venkateswarlu G, Reddy PP, Anand RV. Synthesis of related substances of olmesartan medoxomil, anti-hypertensive drug. *Arkivoc* 2010;ii:292–302;
d) Park JH, Chang JS, El-Gamal MI, Choi WK, Lee WS, Chung HJ, Kim HI, Cho YJ, Lee BS, Jeon HR, Lee YS, Choi YW, Lee J, Oh CH. Novel amides and esters prodrugs of olmesartan: synthesis, bioconversion, and pharmacokinetic evaluation. *Bioorg Med Chem Lett*. 2010;20:5895–5899;
e) Mswang Dj, Song M, Hang Tj, Sun Dz. Identification of related substances in olmesartan medoxomil by LC-MS/MS. *Chin J Pharm Anal*. 2012;32:82–87;
f) Rao CK, Kumar KK, VijayaLaxmi M, Srinivasulu P, Madhusudhan G, Mukkanti K, Srinivas KSV. Development and validation of stability indicating lc method for olmesartan medoxomil. *Am J Anal Chem*. 2012;3:153-160;
g) Venkanna G, Madhusudhan G, Mukkanti K, Sankar A, Sampath Kumar Y, Venakata Narayana G. Synthesis and characterization of process-related impurities of antihypertensive drug olmesartan medoxomil. *J Chem*. 2013;Article ID 516459:8 pages;
h) Seki M. Novel and efficient debenzylation of *N*-benzyltetrazole derivatives with the rosenmund catalyst. *Synthesis* 2014;46:3249–3255;
i) Rao BH, Rao IVS, Kanth VR, Prasadarao KVV, Krishna KB, Sundar BS. Process related impurities in the preparation of olmesartan medoxomil: an-antihypertensive drug. *Indo Am J Pharm Res*. 2015;5:2744–2751;
j) Dams I, Ostaszewska A, Puchalska M, Chmiel J, Cmoch P, Bujak I, Białońska A, Szczepek WJ. Synthesis and physicochemical characterization of the process-related impurities of olmesartan medoxomil. Do 5-(biphenyl-2-yl)-1-triphenylmethyltetrazole intermediates in sartan syntheses exist? *Molecules* 2015;20:21346–21363.

9. The work presented herein is based on our European patent: Toplak Časar R. A process for the preparation of olmesartan medoxomil. Eur. Patent EP 2173741 B1.

10. For reviews and book chapters on multiple bond-forming reactions, see:
a) Posner GH. Multicomponent one-pot annulations forming three to six bonds. *Chem Rev*. 1986;86:831–844;
b) Dömling A. Recent developments in isocyanide based multicomponent reactions in applied chemistry. *Chem Rev*. 2006;106:17–89;
c) Touré BB, Hall DG. Natural product synthesis using multicomponent reaction strategies. *Chem Rev*. 2009;109:4439–4486;
d) Coquerel Y, Boddaert T, Presset M, Mailhol D, Rodriguez J. Multiple bond-forming transformations: the key concept toward eco-compatible synthetic organic chemistry. In: Pignataro B, ed. *Ideas in Chemistry and Molecular Sciences: Advances in Synthetic*

Chemistry. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co. KGaA; 2010:187–202;
e) Volla CMR, Atodiresei I, Rueping M. Catalytic C−C bond-forming multi-component cascade or domino reactions: pushing the boundaries of complexity in asymmetric organocatalysis. *Chem Rev*. 2014;114: 2390–2431;
f) Alegre-Requena JV, Marqués-López E, Herrera RP. Introduction. In: Herrera RP, Marqués-López E, eds. *Multicomponent Reactions: Concepts and Applications for Design and Synthesis*. Hoboken, NJ: John Wiley & Sons, Inc; 2015: 1–15;
g) Das D. Multicomponent reactions in organic synthesis using copper-based nanocatalysts. *ChemistrySelect* 2016;1:1959–1980;
h) Faisca Phillips AM, Pombeiro AJL, Kopylovich MN. Recent advances in cascade reactions initiated by alcohol oxidation. *ChemCatChem* 2017;9:217–246.

11. For reviews and book chapters on one-pot reactions, see:
a) Albrecht Ł, Jiang H, Jørgensen KA. Simple recipe for sophisticated cocktails: organocatalytic one-pot reactions—concept, nomenclature, and future perspectives. *Angew Chem Int Ed*. 2011;50:8492–8509;
b) Hayashi Y. Pot economy and one-pot synthesis. *Chem Sci*. 2016;7:866–880;
c) Yi W, Zeng X, Gao S. Pot Economy Synthesis. In: Zhang W, Cue BW, eds. *Green Techniques for Organic Synthesis and Medicinal Chemistry*, Second Edition. Chichester, UK: John Wiley & Sons, Ltd; 2018:407–439;
d) Corma A, Navas J, Sabater MJ. Advances in one-pot synthesis through borrowing hydrogen catalysis. *Chem Rev*. 2018;118:1410–1459.
12. For reviews on application of one-pot processes in pharmaceutical industry, see:
a) Cue BW, Zhang J. Green process chemistry in the pharmaceutical industry. *Green Chem Lett Rev*. 2009;2:193–211;
b) Vaxelaire C, Winter P, Christmann M. One-pot reactions accelerate the synthesis of active pharmaceutical ingredients. *Angew Chem Int Ed*. 2011;50:3605–3607;
c) Banik BK. One-pot reactions: expeditious synthesis of diverse organic compounds of current interests. *Mod Chem Appl*. 2017;5:229.
13. For articles on application of one-pot processes in pharmaceutical industry, see:
a) Goswami A, Kotoky R, Rastogi RC, Ghosh AC. One-pot efficient process for 16-dehydropregnenolone acetate. *Org Process Res Dev*. 2003;7:306–308;
b) Aalla S, Gilla G, Bojja Y, Anumula RR, Vummenthala PR, Padi PR. An efficient and telescopic process for valsartan, an angiotensin ii receptor blocker. *Org Process Res Dev*. 2012;16:682–686;
c) Vedantham R, Vetukuri VNKVPR, Boini A, Khagga M, Bandichhor R. Improved one-pot synthesis of citalopram diol and its conversion to citalopram. *Org Process Res Dev*. 2013;17:798–805;
d) Srinivas G, Reddy AVR, Prabahar KJ, Rao KvvP, Sanasi PD, Korupolu R. Improved one-pot synthesis of N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenyl propanamide; a key intermediate for the preparation of racemic tolterodine. *Sustain Chem Process* 2014;2:2;
e) Gu SX, Du JW, Ju XL, Chen QP. A scalable one-pot process for the synthesis of florfenicol phosphodiester. *Org Process Res Dev*. 2014;18:552–554;
f) Mali AC, Deshmukh DG, Joshi DR, Lad HD, Patel PI, Medhane VJ, Mathad VT. Facile approach for the synthesis of rivaroxaban using alternate synthon: reaction, crystallization and isolation in single pot to achieve desired yield, quality and crystal form. *Sustain Chem Process* 2015;3:11;
g) Hayashi Y, Ogasawara S. Time economical total synthesis of (−)-oseltamivir. *Org Lett*. 2016;18:3426–3429;
h) Ball M, Jones MF, Kenley F, Pittam JD. An improved convergent synthesis of AZD7762: a one-pot construction of a highly substituted thiophene at the multikilogram scale. *Org Process Res Dev*. 2017;21:310–316;
i) Hayashi Y, Koshino S, Ojima K, Kwon E. Pot economy in the total synthesis of estradiol methyl ether by using an organocatalyst. *Angew Chem Int Ed*. 2017;56:11812–11815.
14. a) Trost BM. The atom economy—a search for synthetic efficiency. *Science* 1991;254:1471–1477;
b) Newhouse T, Baran PS, Hoffmann RW. The economies of synthesis. *Chem Soc Rev*. 2009;38:3010–3021.
15. a) Sydnes MO. One-pot reactions: a step towards greener chemistry. *Curr Green Chem*. 2014;1:216–226;
b) Sheldon RA. The E factor 25 years on: the rise of green chemistry and sustainability. *Green Chem*. 2017;19:18–43.
16. Zupančič S, Pečavar A, Vrbinc M, Osolnik R. Process for the preparation of olmesartan medoxomil. Eur. Patent EP 1910343 B1.
17. Pirc S, Selič L. A process for the preparation or purification of olmesartan medoxomil or olmesartan medoxomil hydrohalide salt. Eur. Patent EP 2176253 B1.
18. Ashcroft CP, Dunn PJ, Hayler JD, Wells AS. Survey of solvent usage in papers published in Organic Process Research & Development 1997−2012. *Org Process Res Dev*. 2015;19:740−747
19. a) Koldobskii GI. Ostrovskii VA, Gidaspov BV. Tautomerism and acid-base properties of tetrazoles. *Chem Heterocycl Compd*. 1980;16:665–674;
b) Wong MW, Leung-Toung R, Wentrup C. Tautomeric equilibrium and hydrogen shifts of tetrazole in the gas phase and in solution. *J Am Chem Soc*. 1993;115:2465–2472;
c) Kiselev VG, Cheblakov PB, Gritsan NP. Tautomerism and thermal decomposition of tetrazole: high-level ab initio study. *J Phys Chem. A* 2011;115:1743–1753.
20. Alder CM, Hayler JD, Henderson RK, Redman AM, Shukla L, Shuster LE, Sneddon HF. Updating and further expanding GSK's solvent sustainability guide. *Green Chem*. 2016;18:3879–3890.
21. Valentín EM, Montes I, Adam W. Counterion effects in the nucleophilic substitution reaction of the acetate ion with alkyl bromides in the synthesis of esters. *J Chem Educ*. 2009;86:1315–1318.