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Research Paper

An Efficient and Large Scale Synthesis of Olmesartan Medoxomil: Anti Hypertensive Drug[#]

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Abstract: An efficient and large scale synthesis of Olmesartan Medoxomil **1**, an antihypertensive drug is described.

Introduction

Lower cost and quality of the product(s) are the key to the success of the pharmaceutical products. This depends on the right route selection and robust process development in plant friendly manner to achieve best possible yields with minimum impurities. Even though, selected route is either known or found to be highly efficient, the systematic process design and study of impurity profile are always important areas to gain the competitive edge.[1]

Olmesartan Medoxomil (Benicar®, Sankyo Pharma) is currently being used as an alternative therapeutic antihypertensive agent for patients intolerant to angiotensin-converting-enzyme inhibitors.[2,3] This molecule was approved as drug by USFDA in the month of April 2002 for treatment of hypertension.[4a] One of the retro synthetic pathways suggests that the Olmesartan Medoxomil **1** can be assembled with the three structural fragments I, II & III as shown in Figure 1.

There are many other medications currently in practice to manage the hypertension.[4b] Among few precedented routes (Scheme 1),[5] the synthesis (Scheme 1, Path A) practiced in medicinal chemistry approach potentially offers a template for process development and various research groups including us focused on this synthetic sequence. Here in, we wish to report our efforts in establishing an efficient and large scale synthetic process of Olmesartan Medoxomil **1**. Grignard reaction is moisture sensitive and moderately yielding transformation. Therefore, from process standpoint, one may avoid such reactions on

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Chemistry & Biology Interface, 2013, 3, 1, 26-37

advanced intermediate therefore the Path A that involves Grignard reaction early in the process was chosen for the development.

Results and Discussion

In our endeavor, as shown in Scheme 1, the synthesis commences with the condensation of imidazole derivative **2** with bromo derivative **3** to obtain corresponding *N*-alkylated product **4**; b) Saponification of **4** to yield alkali salt **5**; c) Condensation between **5** and **6** to result in Trityl Olmesartan Medoxomil **7**; and d) acid mediated de-tritylation to yield desired compound of Olmesartan Medoxomil **1**. Eventually, we were able to telescope first three steps into a single stage process using only toluene as solvent medium which in turn helped us to develop overall two stage process for title compound **1** with high throughput. Reaction conversions were almost quantitative in each step and appropriate work-up conditions and isolation methods were established with high degree of control over impurity profile to attain final API with ICH quality.[6]

Feasibility Studies

As mentioned, synthesis of trityl olmesartan medoxomil **7** involves three different chemical conversions and the process was developed for every step. Alkali salt of *N*-biphenyl imidazole **5** was found to be unstable therefore it was treated as *in situ* intermediate during the course of synthesis. The very first reaction essentially requires equi-molar quantities of **2** and **3** to achieve total reaction conversion. The commercial lot of **3** was only ~80% pure by HPLC thus we intended to use this substrate slightly in excess quantity and it was found that the removal of left over biphenyl bromo-derivative **3** was critical. Use of ~98% pure (assay by HPLC) 3 was not the best choice to proceed for the reaction with **2** due to cost constrain as shown in Table 1. Moreover, little excess quantity of **3** was successfully removed up to acceptable level and the removal procedure is described in later stages of discussion.

Moreover, there was undue complexity involved due to the presence of impurities **8** and **9** as shown in Figure 2. The source of impurity **8** is over brominated while performing bromination of **9** to obtain **3**. Impurity **9** is none other than the left over starting material of **3**.

Additionally, ethyl analogue of hydroxyl derivative **10** which was present to the level of ~0.4% by HPLC in substrate **2** which may be due to contamination of ethyl magnesium halide in methyl magnesium halide. Methyl magnesium halide was used to prepare **2** from diester imidazole derivative. Ethyl analogue of hydroxyl ester impurity **10** was found to participate in the similar kind of chemical sequence analogous to **2** and finally resulted as ethyl analogue impurity **12** in the final API of Olmesartan Medoxomil **1** as shown in Scheme 3.

The removal of **12** was found to be very difficult in final API due to close structural proximity that caused major yield loss which in turn affected overall economy and efficiency of the process. Hence, washing strategy was employed to remove impurity **10** from substrate **2** up to the level of <0.15% prior to the synthesis.

Impurities **8** and **9** (each ~ 8-9 % by HPLC) were eliminated to some extent (each ~ 2 % by HPLC) during the crystallization of **3** from ethyl acetate. Leftover traces of **8** and **9** did not interfere in the *N*-alkylation step and these impurities have finally been removed in the sequential crystallizations by employing acetone and acetonitrile solvents at the end of the synthesis. Crystallization by using

ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 1, 26-37

acetonitrile was specifically developed to remove the dehydration impurity **18** that was formed in the subsequent conversion of **5** to **7** in presence of chloro medoxomil **6**. The purification method by using acetonitrile was found to be highly efficient not only in removing dehydration impurity **18** but much higher level of **8** and **9** when substrate **3** was used without purification.

Optimization Studies

During optimization efforts, it was found that the alkylation reaction of **2** in presence of **3** can be achieved using potassium carbonate as a base and toluene as a solvent. Phase-transfer catalyst (PTC), tetrabutylammonium bromide (TBAB) was found to be essential to accelerate the transformation. Keeping the reaction conditions intact, we continued our efforts to find out the optimum mole equivalents of reagents (K_2CO_3 and TBAB) and toluene solvent quantity. The overall study led us to conclude that the minimum 2.2 equiv of potassium carbonate along with 0.2 equiv of TBAB were essential in order to obtain the complete reaction conversion. Solubility profile of input hydroxyl ester derivative **2** and *N*-alkylated compound **4** was taken into the consideration during optimization of solvent quantity. It was also found out that the minimum 7-8 volumes (with respect to quantity of **2**) of toluene quantity is mandatory in order to prevent precipitation of resultant **4** in the reaction mass leading to process complexity during scale up. Considering all these probable factors, the toluene quantity was specified to 10 times with respect to input hydroxyl ester derivative **2**. Surprisingly, the moisture adsorbed on potassium carbonate was found to play a dramatic role in *N*-alkylation reaction. Initially, potassium carbonate available in the laboratory was used to set the reaction conditions without checking the moisture content. Thereafter, when specific lot got exhausted and we started using new consignments, reactions did not proceed to the completion under previous defined conditions. Incidentally, it was found that the first lot of potassium carbonate picked up ~ 14% of moisture that corresponds to almost 1 equiv however new lot contains only 3%. With this understanding, the rest 11% water was judiciously added into the reaction mass to obtain similar reaction profile. On the other hand, as a control experiment, we performed reactions with potassium carbonate consignment dried under vacuum that did not proceed for completion. We envisaged that the K_2CO_3 would have been hydrolyzed to KOH and the *N*-alkylation is being occurred due to KOH instead K_2CO_3 under given reaction conditions. The same was captured as a part of the final process specification that the moisture content of potassium carbonate should be analyzed and maintained to 14% by adding additional quantity of water before starting the batch.

In the subsequent step, a first few set of experiments were carried out using isolated **4** (by using hexane) to screen the basic reaction conditions involved in subsequent steps of ester hydrolysis of **4** followed by chloro medoxmil **6** condensation. We were delighted to find that both the reaction conversions can be achieved in toluene solvent. These experimental results helped us to telescope both the steps into a single stage process. Base, potassium tertiary butoxide was found to be very effective in the ester **4** hydrolysis. Similar to previous step, water played a critical role in the ester hydrolysis as well. The water quantity essentially required to accomplish the ester hydrolysis was ~ 0.6 equiv with respect to potassium *tert*-butoxide in less than 2 h at ambient temperature. After ensuring the potassium salt **5** formation, the resulting reaction mass was directly proceeded for next step that involves the condensation with chloro medoxomil **6**. In

ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 1, 26-37

this transformation, the purity of chloro medoxomil **6** was only ~ 80% by GC. Hence, the purity of **6** reported by GC was taken into the consideration for raw material calculation. Moreover, the usage of additional quantity of different base was required to accomplish the condensation with **6**. The base chosen for this reaction was 0.6 equiv of sodium carbonate. Later on, this condensation process was found to be greatly influenced by TBAB as a phase transfer catalyst.

As mentioned before, dehydration compound **18** is one of the potential impurities formed in present base mediated esterification process. This impurity participates in the next step of detritylation reaction to yield dehydro olmesartan medoxomil **19** as an additional impurity in the final API as shown in Scheme 4.[7] Batch monitoring revealed that the dehydration happens during base mediated esterification giving rise **18** and the corresponding impurity **19** did not disproportionately increase during detritylation. The removal of dehydration impurity was also found to be very critical due to its close structural proximity with the parent compound.

In order to remove impurities, the final organic layer obtained after entire aqueous work up was subjected to distillation to yield **7** as crude substance containing 2-4 % of dehydration impurity **18** along with the several other carry over impurities. Acetone was found to be excellent choice of solvent that helped to remove all other impurities except dehydration impurity **18**. Accordingly, various crystallization methods and solvents were explored and finally concluded that the acetonitrile is the best choice of solvent to remove dehydation impurity **18** (<0.5% by HPLC). This purification also helped us to control dehydration impurity **19** content to a desired limit of <0.15% (by HPLC) and all other impurities to <0.2% (Table 1).

Subsequent step involves acid mediated detritylation reaction to yield final API of Olmesartan Medoxomil **1** with ICH quality along with byproducts trityl alcohol **20** and trityl methyl ether **21** (Figure 4). The value of E factor of our process considering the recovery of solvent was found to be “25.3” which is much better in comparison to innovator’s process (45.7; calculated at our end).

Olmesartan Medoxomil **1** is strong acid or base sensitive molecule and conc. HCl was employed for detritylation. In this transformation, equiv of HCl was found to play a pivotal role in the formation of Olmesartan acid impurity **22**. Due to this reason, extensive optimization efforts were devoted to finalize the reaction conditions e.g.; a) mole equiv of conc. HCl: (1.2 equiv); b) methanol quantity: 5 volumes; c) reaction maintenance time: (2-3 h) and d) reaction temperature: (25-35 °C). Thereafter, the work-up procedure and isolation method were established to obtain ICH quality of final API. In work-up, the reaction mass was saturated with water, washed with hexane to remove trityl related by products (**20** and **21**) and extracted into dichloromethane after adjusting the pH of aqueous solution to 3-4 using 10% aqueous sodium bicarbonate solution. Finally, the organic layer was thoroughly washed with water and subjected to distillation at below 40 °C under vacuum to obtain **1** as crude material containing ~2% of Olmesartan acid impurity **22**. Since dichloromethane is slightly acidic in nature due to HCl contamination, longer hours (>20 h) holding (or) distillation led to formation of higher level of Olmesartan acid impurity **22**. Further, the improper distillation of final organic layer led to low yield in the next step of isolation process. In view of this, the end point of organic layer distillation was monitored by GC by capturing in-process test for dichloromethane content to less than 5%.

ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 1, 26-37

Acetone was found to be superior solvent to crystallize crude Olmesartan Medoxomil **1** that afforded material in optimal yield and desired ICH quality. Isolation method involves acetone (3 vol) which was added to the resulting crude substance **1**, heated to 50-55 °C for 20-45 min and then stirred at 25-35 °C for 1-2 h. RS/OVI specifically dichloromethane content (~ 8000 ppm instead of desired ICH limit of 600 ppm) was found to be serious cause of concern in terms of inconsistency in the polymorphic form when as is process was implemented on the concurrent pilot scale (5 Kg level). With this scale, classical distillation was followed however the process was finalized based on rotavapor distillation in the R&D lab. The nature of **1** obtained at the end of the distillation in R&D lab was found to be amorphous in nature while with the concurrent scale the material was found to be a rock solid that shows crystalline nature by pXRD analysis (Figure 5).

This observation has been validated and confirmed by distilling some portion of organic layer in the laboratory under classical mode. The following two options (I & II) were worked out to address the RS/OVI issue; **Option I:** Crude Olmesartan Medoxomil (**1**) was dissolved in 10 vol of acetone at 50-55 °C, distilled off completely under vacuum at below 55 °C and then isolated in minimum quantity of acetone (3 times) at 25-35 °C. Dichloromethane was eliminated completely but the acetone content exceeded the ICH limit (>5000 ppm) and **Option II:** The clear solution of crude **1** obtained at 50-55 °C was subjected to 80% distillation under atmospheric condition and the left over solution was cooled to 25-35 °C to obtain maximum material. The Olmesartan Medoxomil **1** obtained from the option II isolation process was free from present RS/OVI issue and qualifying all other tests against desired ICH specifications. This isolation process was well optimized, studied at the concurrent scale and implemented on the large-scale by reproducing predetermined yield and quality as shown in Table 2.

The process for the preparation of Olmesartan Medoxomil **1** and its key starting materials (**2** & **3**) have been evaluated for genotoxicity. The potential genotoxic impurities have been identified and shown to confirm to the requirements of the guideline, EMEA/CHMP/qWP/251344/2006CPMP/SWP/5199/02 on the limits of genotoxic impurities.

There was a formation of one new impurity observed to the level of 0.04-0.08% when this process was taken at a large scale. This new impurity was identified as Olmesartan methyl ester impurity **23** based on LC-MS analysis. The source for formation of impurity **23** is either due to *trans* esterification of **1** or acid catalyzed esterification of **22** with methanol under reaction conditions. However, the impurity **23** was well within the specification of desired ICH limit (<0.15%).

Conclusion

An efficient and large-scale synthesis of Olmesartan Medoxomil (**1**) was developed by understanding the root cause of impurities and incorporating the strategy to control them.

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Experimental Section

ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 1, 26-37

^{1}H NMR spectra were measured in DMSO-d_6 on Varian Gemini 2000 (400 MHz) FT NMR spectrometer; the chemical shifts were reported in δ ppm relative to TMS. The FT-IR spectra's were recorded in the solid state as a KBr dispersion using Perkin-Elmer 1650 FT-IR spectrophotometer. The mass spectrum (70 eV) was recorded on an HP-5989A LC/MS spectrometer. The solvents and reagents were used without further purification.

2-(1-Hydroxy-1-methyl-ethyl)-2-propyl-3-[2'-(1-trityl-1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3*H*-imidazole-4-carboxylic acid 5-methyl-2-oxo-[1,3] dioxol-4-ylmethyl ester 7. To a solution of 5-(1-Hydroxy-1-methyl-ethyl)-2-propyl-3*H*-imidazole-4-carboxylic acid ethyl ester (**2**, 18 Kg, 75 mol) in toluene (2 L) and water[8] (3.6 L) was added potassium carbonate (25.85 Kg, 187 mol) at 45-50 °C and then stirred at 65-70 °C for 30-40 min. 5-(4'-bromomethyl-biphenyl-2-yl)-1-trityl-1*H*-tetrazole (**3**, 48.9 Kg, 0.088 mol) and TBAB (4.82 Kg, 15 mol) were added to the resulting reaction mass and then continued stirring at 65-70 °C for 8-10 h. After reaction completion, water (180 L) was added to the reaction mass, cooled to 45-50 °C and stirred for 10-15 min. The aqueous and organic layers were separated and washed the organic layer twice with water (2 x 90 L) at 45-50 °C to ensure all the inorganic byproducts removal. The resulting final organic layer was directly taken to next step of potassium salt formation and chloromedoxomil **6** condensations.

Potassium *tert*-butoxide (12.6 Kg, 112 mol) was added to the previously obtained organic layer and stirred at 25-35 °C for 45-60 min. Water (3.17 L) was added to the resulting reaction mass and continued stirring at 25-35 °C for 1-2 h to ensure total potassium salt formation. After salt formation, sodium carbonate (3.96 Kg, 37.35 mol), TBAB (4.82 Kg, 14.96 mol) and 4-chloromethyl-5-methyl-[1,3]-dioxol-2-one (**6**, 20 Kg, 135 mol) were added at 25-35 °C and stirred at 50-55 °C for 4-5 h to facilitate chloro medoxomil condensation. After reaction completion, reaction mass was cooled to 15-20 °C, slowly quenched with water (540 L) at below 20 °C and then adjusted pH of the solution to 7-8 using 10% aq. HCl solution. Reaction mass temperature was brought to 25-35 °C and stirred for 30-45 min. The resulting bi phasic layers were separated and extracted the aqueous layer once with toluene (270 L). Both the organic layers were combined each other, washed with water (270 L) and distilled off completely at below 50 °C under vacuum to obtain thick residue of **7**. The resulting residue has been triturated in acetone (189 L) at 0-5 °C for 2-3 h. The solid obtained was filtered, washed with chilled acetone (54 L) and suck dried under vacuum for 1-2 h. The wet cake was subjected to acetonitrile (118.8 L) mediated crystallization by dissolving at 75-80 °C and stirring at 25-35°C for 20-30 min. The solid precipitated was filtered, washed with acetonitrile (39.6 L) and dried at 45-50°C under vacuum for 6-8 h to afford 36 Kg (60 %) of Trityl olmesartan medoxomil **7** as stage I intermediate. Purity by HPLC 99.6 %;^{1}H NMR (400 MHz, DMSO-d_6): δ 7.78 (d, J = 6.8 Hz, 1H), 7.63 (m, 1H), 7.54 (t, J = 6.8 Hz & J = 7.6 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.35 (m, 9H), 7.01 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 6.6 Hz, 6H), 6.77 (d, J = 8.0 Hz, 2H), 5.36 (s, 2H), 5.26 (s, 1H), 5.0 (s, 2H), 2.5 (t, J = 1.6 & 1.6 Hz, 2H), 2.02 (s, 3H), 1.53 (m, 2H), 1.5 (s, 6H), 0.75 (t, J = 7.2 & 7.6 Hz, 3H); MS (m/z) 801 (M^++H).

5-(1-Hydroxy-1-methyl-ethyl)-2-propyl-3-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3*H*-imidazole-4-carboxylic acid 5-methyl-2-oxo-[1,3] dioxol-4-ylmethylester 1. To a solution of Trityl Olmesartan Medoxmil (**7**, 23 Kg, 28.75 mol) in methanol (1 L) was slowly added Conc. HCl (1.86 L, 51 mol) and stirred at 25-35 °C for 2-3 h.

ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 1, 26-37

After reaction completion, water (207 L) was added to the resulting heterogeneous mass and washed with hexane (1 x 62 L, 2 x 31 L) at 25-35 °C to remove the liberated byproducts of trtiyl alcohol **20** and trityl methyl ether **21**. Afterwards, the compound present in aqueous layer was extracted into dichloromethane (1 x 99.2 L, 3 x 49.6 L) upon adjusting pH of the aqueous layer to 3-4 using 10% aqueous $NaHCO_3$ solution at 25-35 °C. All the organic extracts were combined each other, washed with water (104 L) at 25-35 °C and distilled off completely at below 40 °C under vacuum to obtain thick residue of **1**. Acetone (217 L) was added to the resulting thick residue and heated to 50-60 °C till the clear solution was obtained. The resulting clear solution was distilled up to 80 % under atmospheric condition, cooled to 25-35 °C and then stirred for 30-45 min to fully eject out the material. The solid obtained was filtered, washed with acetone (22 L) and dried at 45-50 °C under vacuum for 6-8 h to yield 12.5 Kg (78.12%) of final API of Olmesartan Medoxomil (**1**) with ICH quality. Purity by HPLC 99.8%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.68 (dt, 1H, J = 1.5 & 8 Hz), 7.65 (dd, 1H, J = 1.5 & 8 Hz), 7.57 (dt, 1H, J = 1.5 & 8 Hz), 7.54 (d, 1H, J = 8.0 Hz), 7.05 (d, 2H, J = 8.5 Hz), 6.87 (d, 2H, J = 8.5 Hz), 5.43 (s, 2H), 5.22 (s, 1H), 5.06 (s, 2H), 2.61 (t, 2H, J = 8 Hz), 2.08 (s, 3H), 1.58 (m, 2H), 1.48 (s, 6H), 0.88 (t, 3H, J = 7.5 Hz); ^{13}C NMR (500 MHz, DMSO-d_6): 160.7, 157.7, 155.1, 151.7, 151.1, 141.1, 140.4, 138.2, 136.6, 132.8, 130.9, 130.5, 129.0, 127.7, 125.4, 123.6, 116.2, 69.7, 54.1, 48.1, 29.6, 28.3, 20.6, 13.5, 8.7; IR (cm^{-1}): 3398, 3291, 3040, 3004, 2972, 2931, 2874, 1832, 1708, 1474, 1389, 1169, 1136, 1053, 782, 761; MS (m/z) 559 (M^++H).

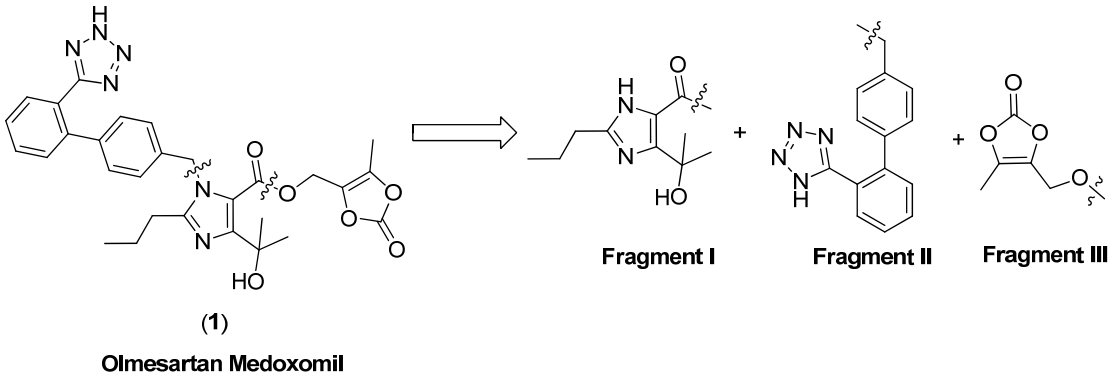
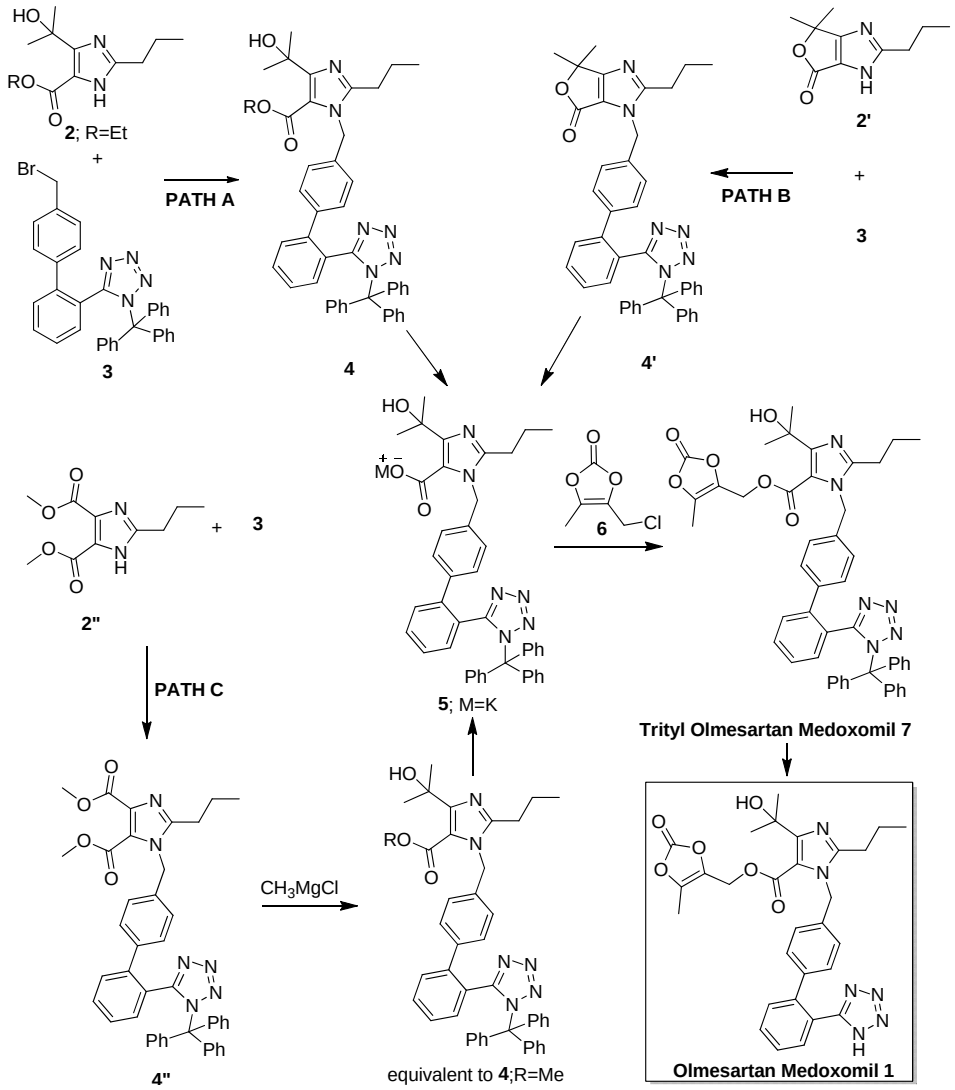


Figure 1. Retro synthetic analysis of Olmesartan Medoxomil (**1**)

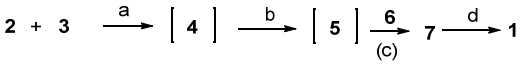
ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 1, 26-37

Scheme 1. Precedented Routes for Olmesartan Medoxomil



Scheme 2. Synthesis of Olmesartan Medoxomil[a]



[a]***Reagents and conditions***: a) K_2CO_3, TBAB, Toluene-H_2O, 65-70 °C, 8-10 h; b) KO^{t}Bu-H_2O, 25-35 °C, 1-2 h; c) Na_2CO_3, TBAB, H_2O, 10% Aq. HCl solution, acetone and acetonitrile; d) MeOH, Conc. HCl, 25-35 °C, 2-3 h, H_2O, Hexane, CH_2Cl_2, 10% aq. $NaHCO_3$ solution, acetone

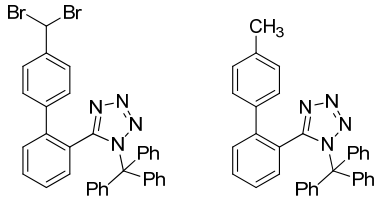
ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 1, 26-37

Table 1. Cost comparison between impure and pure form of 3

Available forms of **3**	Cost/ Kg ($)	Assay (%) of **3**[a]	**8**[a] (%)	**9**[a] (%)
Impure **3**	~34/Kg	80	10	7.5
Pure **3**	~70/Kg	98	0.15	0.15

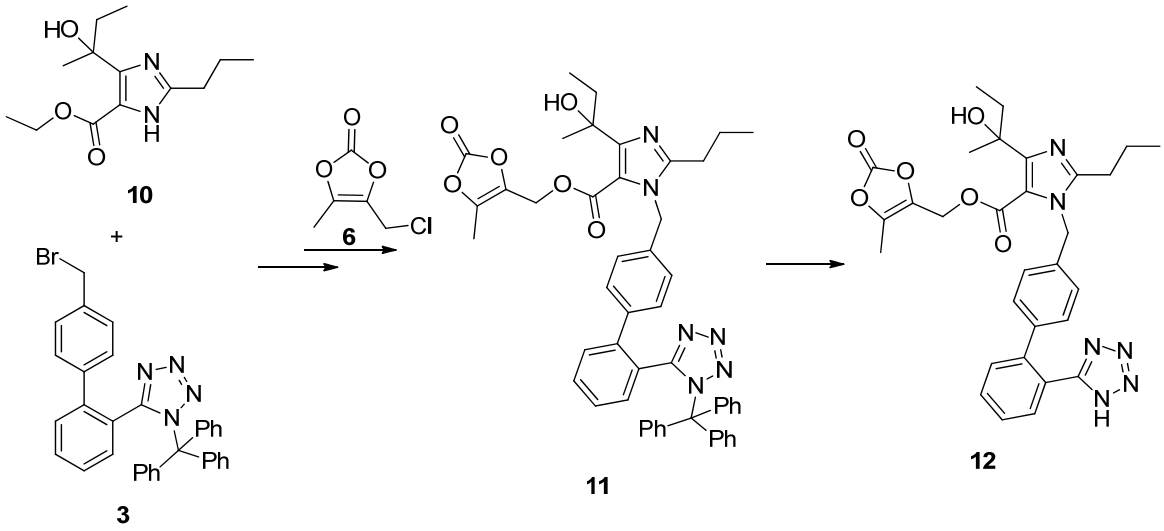
[a]*assay by HPLC (%)*



8 **9**

Figure 2. Impurities of Biphenylbromo analogue **3**

Scheme 3. **Formation of Ethyl Analogue of Olmesartan Medoxomil (12)**



ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 1, 26-37

Table 2. **Solvent screening for *N*-alkylation of imidazole derivative 2**

Entry	Solvent	Volume	Yield of **11** %	Crude purity by HPLC (%)
1	Acetone	20	66.0	93.3
2	DMAC	8	49.6	75.5
3	Toluene DMAC	6 2	60.8	89.0
4	Toluene Water	8 2	46.5	57.6
5	Toluene	10	98.9	86.6
6	Toluene	10	97.9	83.5

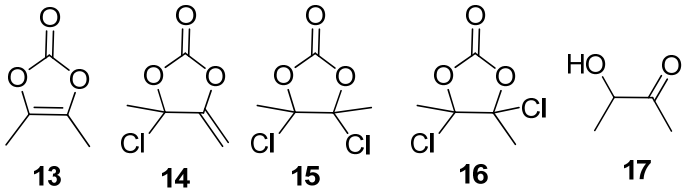


Figure 3. Impurities of Chloro Medoxomil (**6**)

Scheme 4. Formation of Dehydro Olmesartan Medoxomil Impurity (19)

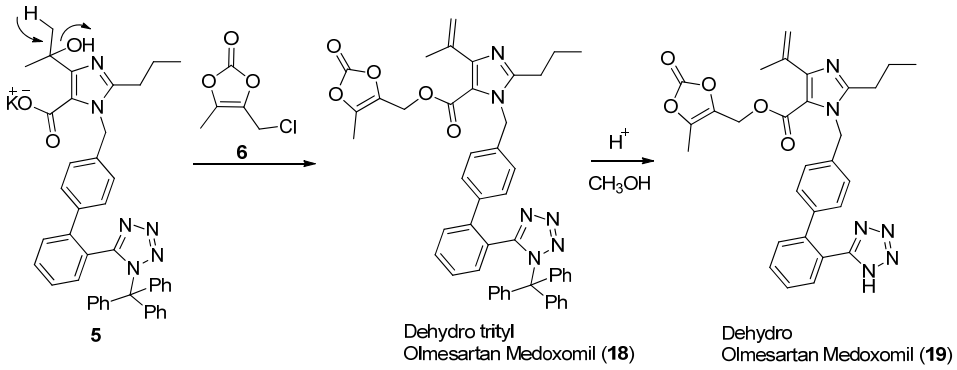
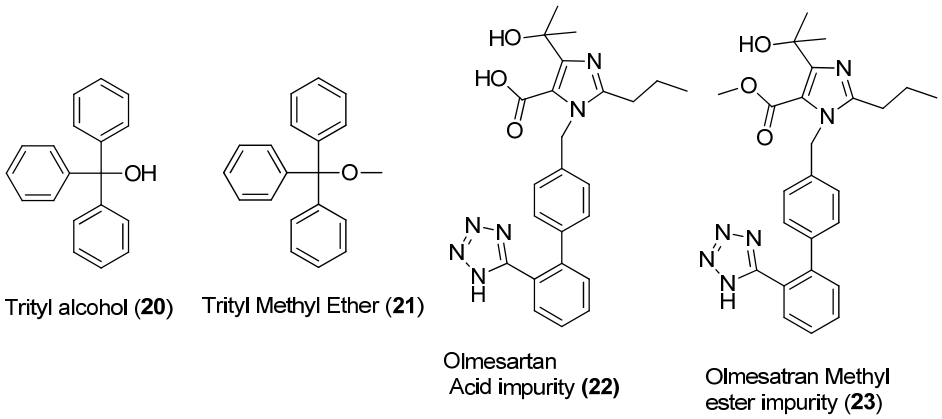


Table 3. Batch results for the preparation of **7**

Batch size (kg)	Yield (%)	Purity by HPLC											
		Crude after toluene distillation				After acetone isolation				After acetonitrile isolation			
		7	**18**	**8**	**9**	**7**	**18**	**8**	**9**	**7**	**18**	**8**	**9**
5	62	76.5	3.5	1.48	8.6	96.1	2.0	0.2	0.36	99	0.3	ND	0.08
5	62.5	76.8	3.4	1.38	8.9	95.8	1.8	0.2	0.3	98.8	0.29	0.03	0.1

ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 1, 26-37



Trityl alcohol (**20**) Trityl Methyl Ether (**21**) Olmesartan Acid impurity (**22**) Olmesatran Methyl ester impurity (**23**)

Figure 4. Structures of Byproducts (**20** & **21**) and process related impurities (**22** & **23**) of stage II

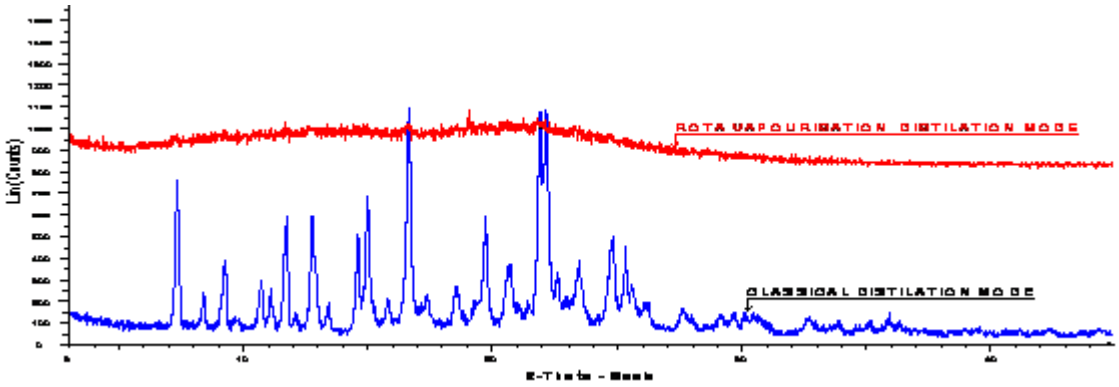


Figure 5. pXRD of Crude **1** obtained from Rota vapor and classical mode of distillation process

Table 4. Batch results for detritylation of **7**

S. No	Batch size (Kg)	Purity by HPLC							RS/OVI	
		22	**23**	**12**	**19**	**7**	**SMUI***	**1**	**Acetone**	**DCM**
1	23	0.09	0.08	0.03	0.01	ND	0.03	99.7	789	ND
2	23	0.11	0.06	0.03	0.02	0.03	0.03	99.6	1401	ND
3	23	0.10	0.07	0.03	0.03	ND	0.04	99.6	985	ND
4	23	0.01	0.06	0.03	0.02	ND	0.03	99.8	436	ND

**SMUI: Single maximum unknown impurity; ND: not detected*

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Chemistry & Biology Interface, 2013, 3, 1, 26-37

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[8] Water quantity required for the present reaction is 15% with respect to input K_2CO_3. The moisture content of K_2CO_3 will be analyzed part of in-process analysis before every batch start-up to calculate how much extra amount of water is additionally needed.