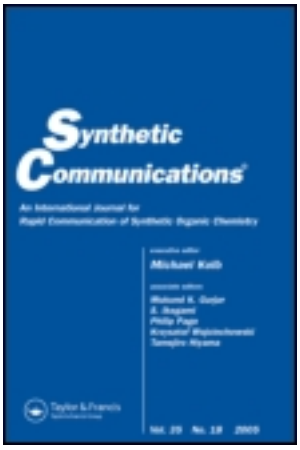

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Efficient Synthesis of Olmesartan Medoxomil, an Antihypertensive Drug

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Abstract: This document describes a simple and robust process for the synthesis of olmesartan medoxomil. This tailored process allows us to synthesize olmesartan medoxomil on a large scale with 50% overall yield. Also, our process has excellent control of the impurity profile in all the stages.

Keywords: Angiotensin receptor antagonist, anti-hypertensive, olmesartan

INTRODUCTION

Hypertension is a serious disease with a momentous impact on health and life expectancy. Controlling blood pressure and preventing complications such as coronary heart disease, renal failure, and cerebral vascular disease are the main objectives for the treatment of hypertension.[1] Olmesartan medoxomil (**1**) (Benicar®, Sankyo pharma)[2] is the latest angiotensin

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receptor antagonist approved by the U.S. Food and Drug Administration for the treatment of hypertension (Fig. 1). The drug works by inhibiting the effects of angiotensin II, a potent vasoconstrictor and one of the key contributors to cardiovascular and renal disease.[3]

Herein, we report an improved, scalable, and cost-effective route to the synthesis of olmesartan medoximil **1**.

RESULTS AND DISCUSSION

We started our approach by condensing **2** with trimethyl orthobutyrate in CH_3CN to get the dicyano imdazole derivative **3** in 96% yield and 98% high-performance liquid chromatography (HPLC) purity (Scheme 1).[4] An additional distillation of the reaction mixture in toluene using Dean–Stark reaction took care of the complete conversion of the intermediate **11** (Fig. 2) to the product **3** by expulsion of methanol. Acidic hydrolysis of **3** under reflux conditions provided **4**, which on thionyl chloride–mediated esterification in methanol at 40–50 °C afforded the diester **5** in 98% yield and 99.8 HPLC purity.

The diester **5** was then condensed with biphenyl derivative **6**[5] in the presence of potassium carbonate in refluxing acetone to provide the *N*-alkylated imidazole derivative **7** in excellent yield and purity. However, the major yield improvement in this stage was achieved during the workup procedure; out of several solvents tried, water was found to be the best. Product **7** was isolated in 98% yield and 99.9% HPLC purity. The most decisive step in our scheme (Scheme 1) was the Grignard reaction of the diester **7** because there is a possibility of getting the impurities **12** and **13** (Fig. 2). At this stage, we thought that the presence of bulky

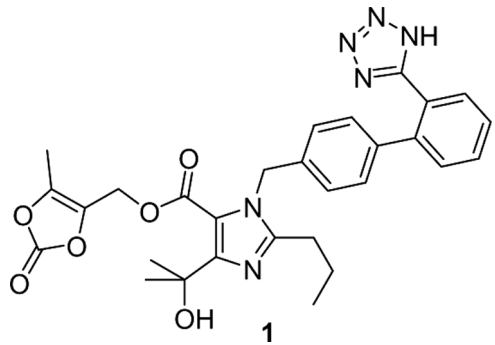

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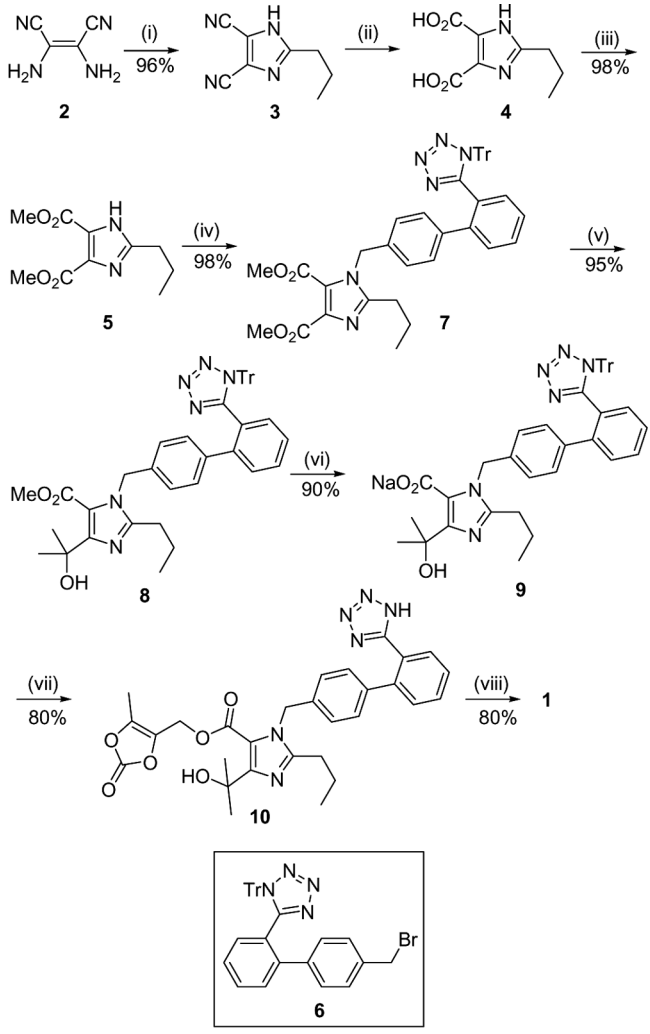
Figure 1. Structural framework of olmesartan medoximil **1**.



Scheme 1. Synthetic scheme of olmesartan medoxomil **1**. Reagents and conditions: (i) CH_3CN, reflux, PhMe; (ii) 6N aq. HCI; (iii) methanol/$SOCI_2$; (iv) **6** K_2CO_3, acetone; (v) CH_3MgCI, toluene; (vi) $NaOH/H_2O$/acetone; (vii) Na_2CO_3/DMF; and (viii) acetic acid/acetone.

biphenyl tetrazole moiety in **7** would help in getting the right regioselectivity during the Grignard reaction.

As we expected, the Grignard reaction of **7** with 3 equivalents of MeMgCl in anhydrous toluene proceeded smoothly, and the required tertiary hydroxyl derivative **8** was obtained in 95% yield and 95% HPLC

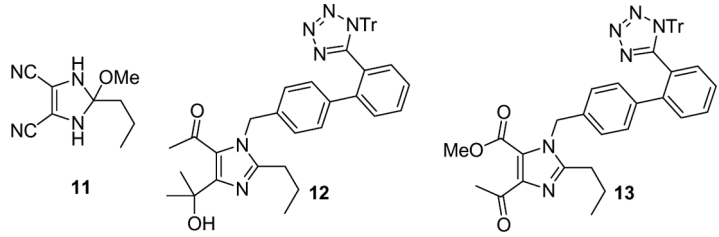


Figure 2. Olmesartan impurities.

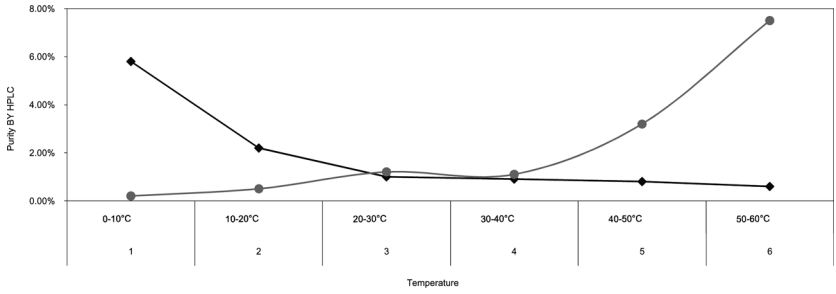


Figure 3. Effect of temperature on Grignard reaction. ●, 5-Acetyl impurity and ◆, 4-acetyl impurity.

purity. Although we observed the formation of impurities **12** and **13** in small quantities, we could able to optimize the reaction conditions to minimize the impurity level to less than 2%. Reaction temperature played a major role in controlling the regioisomeric impurities. At higher temperature (more than 40 °C), the formation of **12** was more (up to 7.5%), and **13** was formed in trace amounts (0.6%). At lower temperature (less than 20 °C), **13** was observed at a higher level (5.8%) and **12** was detected in trace quantities (0.2%). Based on the experiments, the optimum temperature of this reaction was found to be 20–40 °C. The effect of temperature on Grignard reaction is represented in Fig. 3. Saponification of teritiary hydroxyl ester **8** with aqueous NaOH afforded the sodium salt **9**, which on alkylation with 4-chloromethyl-5-methyl-1,3-dioxolen-2-one provided **10** in 80% yield. Deprotection of trityl group in **10** with acetic acid in acetone provided olmesartan medoximil **1** in 80% yield and 99.7% HPLC purity after crystallization (Scheme 1).

CONCLUSION

An efficient method for the synthesis of olmesartan medoxomil was achieved and realized on a plant scale.

EXPERIMENTAL

General Methods and Materials

^{1}H NMR spectra were recorded in $CDCl_3$ and dimethyl sulfoxide (DMSO-d_6), using a Varian Gemini 200-MHz FT NMR spectrometer; the chemical shifts are reported in δ ppm relative to tetramethyl silane (TMS). FT-IR spectra were recorded on a Perkin-Elmer 1650 FT-IR spectrophotometer. The mass spectra (70 eV) were recorded on HP-5989A liquid chromatography-mass spectra (LC-MS) spectrometer. The melting points were determined using the capillary method on a Polmon (model MP-96) melting-point apparatus and are uncorrected. The solvents and reagents were used without further purification.

2-Propylimidazole-4,5-dicarbonitrile (3)[2a]

A mixture of diaminomaleonitrile **2** (100.0 kg, 926 mol) and trimethyl ortho butyrate (165.0 kg, 114.8 mol) in CH_3CN (300.0 L) was refluxed for 5 h. After the solvent was removed in vacuo, the residue was diluted with toluene (300.0 L) and refluxed in a Dean–Stark reaction setup for 7–8 h. After cooling to 60 °C, cyclohexane (200.0 L) was added, and the mixture was stirred at room temperature for 30–60 min. The precipitated product **3** was collected by filtration and washed with cyclohexane (50.0 L). Yield 145.0 kg (98%); mp 142–144 °C (literature mp 141–144 °C).[2a] Purity by HPLC: 99.0%.

2-Propylimidazole-4,5-dicarboxylic Acid (4)[2a]

A solution of **3** (100.0 kg, 625 mol) in 6*N* aq. HCl (1000.0 L) was refluxed for 4 h. After cooling to room temperature, water (1000.0 L) was added, and the precipitated solid was filtered and charged in to a beaker containing water (1000.0 L). The pH of the solution was maintained between 9 and 10 using 10% sodium hydroxide solution (100.0 L), and it was subjected to carbon treatment. Then the pH of the solution was adjusted between 1 and 2 using aqueous hydrochloric acid (12.0 L) and stirred for 1 h. The precipitated product **4** was collected by filtration. Yield 117.5 kg (95%); mp 262–264 °C (literature mp 261–263 °C).[2a] FT-IR (KBr) 3454, 1744 cm^{-1}, Purity by HPLC: 99.8%.

Dimethyl 2-Propylimidazole-4,5-dicarboxylate (5)

Thionyl chloride (92.0 L, 2500 mol) was added slowly to a solution of **4** (100.0 kg, 505 mol) in methanol (300 L) at 40–45 °C for about 1 h and

stirred for 8–10 h. It was cooled to 0–5 °C and then poured slowly to chilled water (300.0 L). It was neutralized by the addition of 700 L of 10% sodium hydroxide solution. The precipitated product **5** was filtered, washed with water (200.0 L), and dried at 60–70 °C. Yield 109.5 g (96%); mp 152–155 °C; FT IR (KBr) 3443, 1734 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 0.90 (t, $J = 7.5$ Hz, 3H), 1.60–1.79 (m, 2H), 2.60 (t, $J = 7.4$ Hz, 2H), 3.78 (s, 3H), 3.8 (s, 3H), 13.10 (bs, 1H). Purity by HPLC: 99.8%; $M^+ + 1 = 227.1$.

Dimethyl-2-propyl-1-[4-(2-trityltetrazol-5-yl)phenyl]-phenyl Methyl Imadazole-4,5-carboxylate (7)

Dimethyl-2-propylimidazole-4,5-dicarboxylate **5** (31.5 kg, 139.3 mol) was dissolved in acetone (160.0 L). *N,N*-Dimethyl acetamide (32.0 L) was added to this solution followed by **6** (81.5 kg, 146 mol) and potassium carbonate (38.5kg, 278 mol). The reaction mixture was heated to reflux for 4–5 h. Acetone was distilled off partially (50–60% of initial volume), and the reaction mixture was cooled to room temperature. Water (315.0 L) was then added, and the stirring continued for another hour. The precipitated solid was filtered and washed with water (160 L) and dried at 70–80 °C for 8–10 h to get the title compound **7**. Yield 97.0 kg (99%); Mp 162–164 °C; FT IR (KBr) 1740 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, $J = 7.6$ Hz, 3H), 1.59–1.80 (m, 2H), 2.55 (t, $J = 7.6$ Hz, 2H), 3.70 (s, 3H), 3.93 (s, 3H), 5.30 (s, 2H), 6.70–7.95 (m, 23H). Purity by HPLC: 98.0%; $M^+ + 1 = 703.6$ (m/e).

Methyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[4-(2-trityltetrazol-5-yl)phenyl]-phenyl Methyl Imadazole-5-carboxylate (8)

To a solution of **7** (55.0 kg, 78.3 mol) in toluene (165.0 L), a solution of methyl magnesium chloride in tetrahydrofuran (25.5%, 69.0 L, 234 mol) was added at room temperature. After completion (1 h), the reaction mass was quenched with 10% acetic acid (50 L) and extracted with toluene (55.0 L). Solvent was distilled off under reduced pressure to obtain the title compound **8** as a residue. Yield 55.0 kg (99%); FT IR (KBr) 3421 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, $J = 7.6$ Hz, 3H), 1.59–1.80 (m, 2H), 1.71 (s, 6H,), 2.40–2.59 (m, 2H), 3.62 (s, 3H), 5.30 (s, 2H), 6.68–7.90 (m, 23H). Purity by HPLC: 95.0%; $M^+ + 1 = 703.6$ (m/e).

4-(1-Hydroxy-1-methylethyl)-2-propyl-1-[4-(2-trityltetrazol-5-yl)phenyl]-phenyl Methyl Imadazole-5-carboxylic Acid Sodium Salt (9)

To a solution of **8** (55.0 kg, 78.3 mol) in 385.0 L of acetone, a solution of sodium hydroxide (3.10 kg, 78 mol) in water (275.0L) was added, and the reaction mixture was stirred at 25–30 °C for 4–5 h. After completion of the reaction, it was diluted with 25% aqueous sodium chloride solution and extracted with ethyl acetate (300.0 L). Solvent was distilled off under reduced pressure, and the crude product was codistilled with toluene (165.0 L) and finally stirred with heptane (165.0 L) for 2–3 h. Removal of the solvent gave the crude product **9**, which was dried under vacuum. This product was directly used in the next step. Crude yield 55.0 kg (99%). Purity by HPLC: 90%; FT-IR (KBr) 3404 cm^{-1}.

(5-Methy2-oxo-1,3-dioxolen-4-yl)-methyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[4-(2-trityltetrazol-5-yl)phenyl]-phenyl Methyl Imadazole-5-carboxylate (10)[2a]

To a solution of **9** (55.0 kg, 77.46 mol) in of *N,N*-dimethyl acetamide (162.0 L), sodium carbonate (12.6 kg, 118 mol) and 4-chloromethyl-5-methyl-1,3-dioxolen-2-one (14.7 kg, 100 mol) were added, and the mixture was heated to 45–50 °C for 4–5 h. Aqueous sodium chloride solution (10%, 540.0 L) and toluene (270.0 L) were added to the reaction mixture, and the pH was adjusted to 7–8 with 10% aqueous hydrochloric acid. The aqueous layer was separated and extracted with toluene (108.0 L). The combined organic layers were washed with 10% sodium chloride solution (2×108.0 L). The solvent was evaporated under reduced pressure, and the residue was recrystallized from acetonitrile to get the title compound **10**. Yield 49.6 kg (80%); Mp 103–104 °C (literature mp 102–104 °C).[2a] FT-IR (KBr) 3404, 1819 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (t, $J = 7.2$ Hz, 3H), 1.41–1.60 (m, 2H), 1.56 (s, 6H), 2.0 (s, 3H), 2.30–2.60 (m, 2H), 5.02 (s, 2H), 5.22 (s, 1H), 5.31 (s, 2H), 6.75 (d, $J = 8.2$ Hz, 2H), 6.82 (d, $J = 8.2$ Hz, 4H), 6.98 (d, $J = 8.2$ Hz, 2H), 7.23–7.82 (m, 15H). Purity by HPLC: 99%; $M^+ + 1 = 801.6$ (m/e).

Olmesartan Medoximil (1)[2a]

A solution of **10** (25.0 kg, 31.25 mol) in 40% aqueous acetic acid (750.0 L, 60 mol) was heated at 55–60 °C for 2–3 h. It was cooled to room temperature and diluted with water (375.0 L). The precipitated solids were filtered

off, and the filtrate was extracted with CH_2Cl_2 (625.0 L). The organic layer was washed with a mixture of 5% aqueous sodium bicarbonate solution (150.0 L) and 5% sodium chloride solution (780.0 L). Removal of the solvent followed by recrystallization in acetone gave the pure product **1** as a white solid. Yield 14.0 kg (80%); mp 180–182 °C (literature Mp 180–182 °C).[2a] FT-IR (KBr) 1832, 1740, 1707 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 0.87 (t, $J = 7.2$ Hz, 3H), 1.41–1.60 (m, 2H), 1.45 (s, 6H), 2.05 (s, 3H), 2.41–2.78 (m, 2H), 5.02 (s, 2H), 5.20 (s, 1H), 5.40 (s, 2H), 6.85 (d, $J = 8.0$ Hz, 2H), 7.04 (d, $J = 8.0$ Hz, 2H), 7.52–7.78 (m, 4H), 15.8 (bs, 1H). Purity by HPLC: 99.9%; $M^+ + 1 = 559.3$ (m/e).

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