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Efficient Synthesis of Oseltamivir from Readily Available Epoxide Precursor

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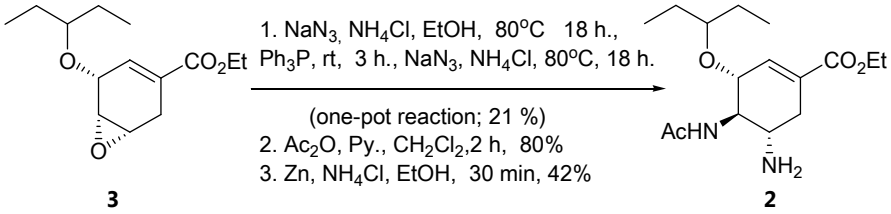
Abstract



Oseltamivir **2** was synthesized from readily available epoxide precursor **3** by one pot reaction, ring opening of the epoxide **3**, aziridine formation, ring opening of aziridine with 21% yield and acetoacetamide was completed by acetylation and followed by zinc catalytic hydrogenation was selected in the final step with an moderated yield of 42%.

Keywords: shikimic acid, epoxide ring opening, influenza, oseltamivir, oseltamivir phosphate, Tamiflu.

1. Introduction

Oseltamivir phosphate or Tamiflu® **1**, the inhibitor neuraminidase enzyme of influenza virus, is currently in use widely for acute influenza treatment which is one of a very few drugs that is currently effective against H5N1 bird flu[1]. Oseltamivir phosphate **1**(RO0640796-002) was discovered at Gilead Science with synthesize by Hoffmann-Laroche a practical 12 steps[2-7] was specifically designed on the basis of the access to the key precursor epoxide **3** (RO0640792) obtained from (-)-shikimic acid **4**[3] which is obtained either by extraction of Chinese star anise or by the fermentation of genetically engineered *E.*coli through tedious purification processes. However, more a efficient process using easily available starting material and safer reaction is still required for stockpiling the drug in preparation for a possible flu pandemic, and thus active researches have been carried out[8-15]. The starting material in the current industrial synthesis of oseltamivir is (-)-shikimic acid, with the Gilead route uses azide for ring opening and azide reduction with phosphine to reveal both amino group[3,4].

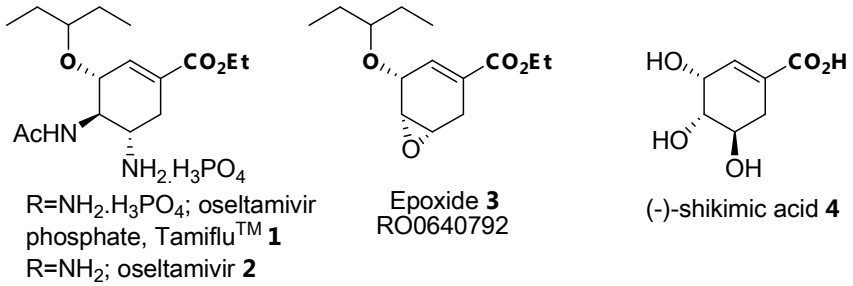
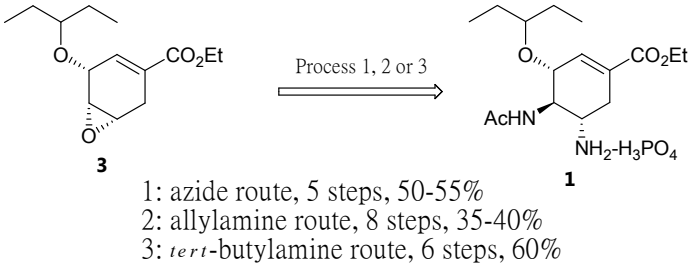


Figure 1. Oseltamivir phosphate **1**, oseltamivir **2**, epoxide **3** and (-)-shikimic acid **4**

There are three processes developed by Roche's researchers for the synthesis of **1** and **2** from proceeds through the readily available epoxide precursor intermediate **3**. The shorter and economical azide route is currently used in the industrial production[3,4] and involes potentially toxic and hazardous azide reagents, intermediates and reactions while the allylamine[5,6] and the tert-butylamine[7] routes were later reported as the alternatives to the use of hazardous azide reagents **Scheme 1**.



Scheme 1. Three Synthetic Routes of oseltamivir phosphate **1** from epoxide **2**

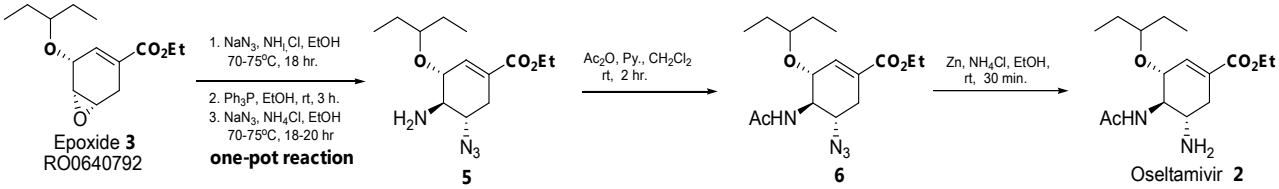
Although the use of azide chemistry on an industrial scale is well documented the potential hazards[18-20] related to its application promped us to evaluate an azide-free synthesis in order to establish an independent, safe, and efficient alternative route amenable to a risk-free large scale industrial production of **1** and **2**[4,6].

2. Materials and methods

The following analytical methods were employed unless otherwise indicated. Melting points were determined on a Stuart Scientific Melting Point apparatus (Bibby Sterlin Ltd., UK) and are uncorrected. FT-IR spectra were recorded on a Perkin-Elmer FT-IR Spectrum RXI spectrometer (Perkin Elmer Instruments LLC., USA). Solutions of samples in dichloromethane or ethyl acetate were dropped onto a potassium bromide crystal cell. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Mercury NMR spectrometer operated at 400.00 MHz for ^{1}H and 100.00 MHz for ^{13}C (Varian Company, USA) using samples dissolved in $CDCl_3$ or D_2O. Mass spectra were recorded on a Waters Micromass Quatto micro API ESCi (Waters, USA).

3. Results and discussions

As part of program to use readily available epoxide precursor **3** and herein report our sucess in the development of a concise and efficeint synthesis of oseltamivir **2** as shown in **Scheme 2**



Scheme 2 Synthesis of oseltamivir **2**

Azidoamine **5** was prepared by one pot reaction from readily available epoxide precursor **3**[16,17], by heating with sodium azide and ammonium chloride in ethanol and reductive cyclization of the azido alcohol intermediat with triphenyl phosphine at room temperature for 3 hours and followed by ring opening of intermediate with sodium azide, ammonium chloride at 80°C for 18-20 hours provided the azidoamine **5** in moderated yield, 21%.

Azidoamine **5** was directly acylated with acetic anhydride and pyridine to afforded azidoacetamide **6** in 80% yield, which was reduced using catalytic hydrogenation with Zn in the present of ammonium chloride in aqeous ethanol to provide oseltamivir **2** in 42% yield.

The spectroscopic data of all compounds obtained by this synthetic route are consistent with those reported in the literature[3].

4. Conclusion

In conclusion, we have synthesized oseltamivir **2** moderated yield from readily available epoxide precursor **3** by using one pot reaction as key steps and believe that our synthetic route to **2** is highly practical for a number of reasons: First, inexpensive and commenly used reagents are employed. Furethermore, although the overall yield of Azidoamine **5** from readily available epoxide precursor **3** is rather moderated yield, Azidoamine **5** can be obtained an a large scale without tedious purification procedure.

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Experimental Section

General Procedure for the Synthesis

Synthesis of ethyl (3*R*,4*R*,5*S*)-4-amino-5-azido-3-(1-ethyl-propoxy)-1-cyclohexene-1-carboxylate 5

A solution of epoxide **3** (0.50 g, 1.97 mmol) in EtOH (3 mL) was added dropwise to the mixture of sodium azide (0.256 g, 3.94 mmol), ammonium chloride (0.211 g, 3.94 mmol), and EtOH (10 mL). The reaction mixture was heated at 70 ^{0}C for 18 hours. And the triphenylphosphin (1.03 g. 3.94 mmol) was add to the reaction at the room temperature for 3 hours. The mixture was heated at reflux for 16.0 hours after sodium azide (0.256 g, 3.94 mmol) and ammonium chloride (0.211 g, 3.94 mmol) were added. The residue was extracted with EtOAc (20 mL), washed with sodium bicarbonate (10 mL), water (2x10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The resulting brown oil was purified by column chromatography on silica gel, eluting with 10% ethyl acetate–hexane to provide the ethyl 4-amino-5-azido-3-pentylidene ketal compound **5** (0.12 g, 21 %), R_f on TLC chromatogram = 0.45 (50% ethyl acetate:hexane). ^{1}H NMR ($CDCl_3$) (δ, ppm): 0.91 (t, *J*=7.4 Hz, 6H, (-C($CH_2C\underline{H}_3$)$_2$), 1.28 (t, *J*=7.2 Hz, 3H, (-$CH_2C\underline{H}_3$)), 1.54 (m, 4H, (-C($C\underline{H}_2CH_3$)$_2$), 1.69 (br, 2H, (-NH_2), 2.21-2.37 (m, 1H, -$C\underline{H}_2$-), 2.82-2.89 (m, 2H, -$C\underline{H}_2$- and –$C\underline{H}NH_2$), 3.37 (quint, *J*=5.8 Hz, 1H, (-$C\underline{H}$(CH_2CH_3)$_2$)), 3.40-3.52 (m, 1H, -$C\underline{H}$-N_3), 3.90 (m, 1H, -$C\underline{H}$-O-), 4.20 (q, *J*=7.2 Hz, 2H, (-$C\underline{H}_2CH_3$)), 6.82 (m, 1H, (-$C\underline{H}$=C-)); ^{13}C NMR ($CDCl_3$) (δ, ppm): 9.4 (-C($CH_2\underline{C}H_3$)$_2$), 9.7 (-C($CH_2\underline{C}H_3$)$_2$), 14.2 (-$CH_2\underline{C}H_3$), 25.6 (-C($\underline{C}H_2CH_3$)$_2$), 26.4 (-C($\underline{C}H_2CH_3$)$_2$), 29.7 (-$\underline{C}H_2$-), 56.1 (-$\underline{C}H$-N_3), 61.0 (-$\underline{C}H_2CH_3$), 61.6 (-$\underline{C}H$-NH_2), 78.1 (-$\underline{C}H$-O-), 81.2 (-$\underline{C}H$(CH_2CH_3)$_2$)), 128.1 (-CH=$\underline{C}$-), 137.5 (-$\underline{C}$H=C-), 165.9 (-$\underline{C}$=O), FTIR, cm^{-1}: 3382 (-NH_2), 2967 (C=C-H), 2102 (-N_3), 1715 (C=O), 1247, 1102, 1071 (C-O).

Synthesis of ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-azido-3-(1-ethyl-propoxy)-1-cyclohexene-1-carboxylate 6

A solution of ethyl 4-amino-5-azido-3-pentylidene ketal compound **5** (0.70 g. 2.36 mmol), acetic anhydride (2 mL) and pyridine (1 mL) in CH_2Cl_2 (5 mL) were added to the reaction and then refluxed for 3.0 hours. The reaction mixture was extracted with CH_2Cl_2 (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to provide the acetamido azide compound **6** (0.611 g, 80%), R_f on TLC chromatogram = 0.50 (50% ethyl acetate:hexane). ^{1}H NMR ($CDCl_3$) (δ, ppm): 0.92 (t, *J*=7.3 Hz, 3H, (-C($CH_2C\underline{H}_3$)$_2$), 0.93 (t, *J*=7.3 Hz, 3H, (-C($CH_2C\underline{H}_3$)$_2$), 1.32 (t, *J*=7.1 Hz, 3H, (-$CH_2C\underline{H}_3$)), 1.47-1.59 (m, 4H, (-C($C\underline{H}_2CH_3$)$_2$), 2.06 (s, 3H, (-C(O)$C\underline{H}_3$)), 2.10-2.31 (m, 1H, (-$C\underline{H}_2$-)), 2.88 (dd, J_1=5.7 Hz, J_2=17.1 Hz, 1H, (-$C\underline{H}_2$-)), 3.35 (m, 2H, (-$C\underline{H}$(CH_2CH_3)$_2$, (-$C\underline{H}$-O-)), 4.23 (q, *J*=7.1 Hz, 2H, (-$C\underline{H}_2CH_3$)), 4.27-4.34 (m, 1H, (-$C\underline{H}$-N_3)), 4.57-4.60 (m, 1H, (-$C\underline{H}$-NHAc)), 6.01 (d, *J*=7.4 Hz, 1H, (-$N\underline{H}$-(C=O)-CH_3)), 6.81 (dd, J_1=2.2 Hz, J_2=2.3 Hz, 1H, (-$C\underline{H}$=C-); ^{13}C NMR ($CDCl_3$) (δ, ppm): 9.3 (-C($CH_2\underline{C}H_3$)$_2$), 9.6 (-C($CH_2\underline{C}H_3$)$_2$), 14.2 (-$CH_2\underline{C}H_3$), 25.6 (-C($\underline{C}H_2CH_3$)$_2$), 26.3 (-C($\underline{C}H_2CH_3$)$_2$), 30.6 (-$\underline{C}H_2$-), 57.1 (-$\underline{C}H$-N_3), 58.2 (-$\underline{C}H_2CH_3$), 61.1 (-$\underline{C}H$-NH_2), 73.31 (-$\underline{C}H$NHAc), 78.1 (-$\underline{C}H$-O-), 82.0 (-$\underline{C}H$(CH_2CH_3)$_2$)), 128.2 (-CH=$\underline{C}$-), 137.9 (-$\underline{C}$H=C-), 165.8 (-$\underline{C}$=O), 171.1 (-NH($\underline{C}$O)CH_3), FTIR, cm^{-1} : 3269 (-NH), 2929 (C=C-H), 2104 (-N_3), 1716 (C=O), 1253, 1183, 1080 (C-O) .

Synthesis of ethyl (3*R*,4*R*,5*S*)-4-*N*-acetamido-5-amino-3-(1-ethyl-propoxy)-1-cyclohexene-1-carboxylate; oseltamivir 2

Zinc dust 1.0 g was added to the solution of azido compound **6** (0.10 g. 0.31 mmol) and ammonium chloride (0.162 g, 3.10 mmol) in EtOH (5 mL). After the reaction mixture was stirred at the room temperature for 30 mins, the reaction mixture was quench with ammoniumhydroxide solution and then added EtOAc (10 mL). The mixture was washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford oseltamivir **2** (0.039 g, 42%), R_f on TLC chromatogram = 0.15 (9:1 ethyl acetate:MeOH).). ^{1}H NMR ($CDCl_3$) (δ, ppm): 0.88 (t, *J*=7.8 Hz, 3H, (-C(CH_2C$\underline{H}_3$)$_2$), 0.89 (t, *J*=7.0 Hz, 3H, (-C(CH_2C$\underline{H}_3$)$_2$), 1.28 (t, *J*=7.0 Hz, 3H, (-CH_2C$\underline{H}_3$)), 1.46-1.54 (m, 4H, (-C(C$\underline{H}_2$$CH_3$)$_2$)), 2.03 (s, 3H, (-NH-C(O)C$\underline{H}_3$)), 2.11-2.18 (m, 1H, (-C$\underline{H}_2$-)), 2.74 (dd, J_1=5.5 Hz, J_2=17.6 Hz, 1H, (-C$\underline{H}_2$-)), 3.22 (m, 1H, (-C$\underline{H}$-NH_2)), 3.33 (quint, *J*=5.5 Hz, 1H, (-C$\underline{H}$(CH_2CH_3)$_2$), 3.53 (q, *J*=9.36 Hz, 1H, (-C$\underline{H}$-NHAc)), 4.19 (q, *J*=7.0 Hz, 2H, (-C$\underline{H}_2CH_3$)), 5.78 (d, *J*=7.8 Hz, 1H, (-N$\underline{H}$-(C=O)-CH_3)), 6.77 (s, 1H, (-C$\underline{H}$=C-)); ^{13}C NMR ($CDCl_3$) (δ, ppm): 9.3 (-C(CH_2C$\underline{H}_3$)$_2$), 9.6 (-C(CH_2C$\underline{H}_3$)$_2$), 14.2 (-CH_2C$\underline{H}_3$), 23.5 (-NH(CO)C$\underline{H}_3$), 25.6 (-C(C$\underline{H}_2$$CH_3$)$_2$), 26.3 (-C(C$\underline{H}_2$$CH_3$)$_2$), 30.6 (-C$\underline{H}_2$-), 57.1 (-C$\underline{H}$-$NH_2$), 58.2 (-C$\underline{H}$-NH-), 61.1 (-C$\underline{H}$-O-), 82.0 (-C$\underline{H}$($CH_2CH_3$)$_2$), 128.2 (-CH=C$\underline{}$-), 137.9 (-C$\underline{H}$=C-), 165.8 (-C$\underline{}$=O), 171.1 (-NH(C$\underline{}$O)$CH_3$), FTIR, cm^{-1}: 3282 (-NH_2), 2954 (C=C-H), 1716 (C=O), 1259, 1095 (C-O).

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