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# A new efficient synthesis of oseltamivir phosphate (Tamiflu) from (−)-shikimic acid

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ABSTRACT

New synthesis of oseltamivir phosphate was accomplished in 9 steps with a 27% overall yield from a readily available (−)-shikimic acid. Selective ring opening reaction of ketal and azide Mitsunobu reaction for facile replacement of a hydroxyl group by the N3 group at the C-3 position of (3R,4R,5R)-ethyl 4-hydroxy-5-(methoxymethoxy)-3-(pentan-3-yloxy)cyclohex-1-enecarboxylate **4** and at the C-4 position of (3R,4S,5R)-ethyl 4-acetamido-5-hydroxy-3-(pentan-3-yloxy)cyclohex-1-enecarboxylate **7** successfully served as the key steps.



Influenza A virus is one of the members of the family Orthomyxoviridae.[1] Highly virulent strains of influenza virus have caused global pandemics that killed millions of people worldwide.[1] These recurring outbreaks of influenza virus have attracted many scientists' attention toward the development of promising therapeutics.

Oseltamivir phosphate (Tamiflu) was developed for the potent neuraminidase inhibitor by Kim and coworkers of Gilead Sciences,[2] and launched to the market in 1999. Since then, it has been utilized as an orally active drug for the treatment and prophylaxis of both type A and type B human influenza.[3] Moreover, recently it has been discovered that this compound is active against the H5N1 Avian Flu virus, which causes disastrous influenza pandemic.[4] Therefore, there is an increasing demand for stocking a sufficient amount of this compound in case of possible virulent outbreaks of influenza virus. In response to the increasing demand for Tamiflu against the spreading avian flu, significant efforts to develop efficient synthetic strategies for Tamiflu have been devoted by several groups.[5]

Particularly, among all of the developed synthetic methods for oseltamivir phosphate, several synthetic approaches to oseltamivir phosphate **1** from shikimic acid have been reported. Rohloff and coworkers developed a synthesis of Tamiflu from (−)-shikimic acid in 10 steps with a 21% yield.[6] Federspiel and coworkers of Roche reported the synthetic routes to the key intermediate of Tamiflu, ethyl(3R,4S,5S)-4,5-epoxy-3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxylate, from (−)-shikimic acid (6 steps with a 63–65% overall yield),[7] and several syntheses for Tamiflu from the key intermediate were developed by the other scientists of Roche: Karpf's method (35–38% in 5 steps) and Harrington's method (61% in 7 steps).[8] Synthetic routes developed by Roche have been used for the industrial process. However, these synthetic routes contain many steps (total 11–13 steps from (−)-shikimic acid). Recently Karpf and coworkers of Roche published a new short synthetic method for Tamiflu from (−)-shikimic acid with an overall yield of 20% achieved in 8 steps.[9]

Usually, (−)-shikimic acid can be obtained by both extraction from the Chinese star anise and the fermentation process of genetically engineered *Escherichia coli*.[10] In addition to such methods, several independent synthesis routes to (−)-shikimic acid have been developed.[11] Here we report a novel efficient synthesis of oseltamivir phosphate from (−)-shikimic acid (Figs. 1–3).

Our synthesis started from pentylidene ketal **2**, which can be prepared from (−)-shikimic acid via described procedures in the literature: esterification using EtOH and benzenesulfonic acid and protection of dihydroxyl group using the reaction with 3-pentanone in the presence of triethylorthoformate.[12]

The hydroxyl group of compound **2** was readily protected with methoxymethyl ether in the presence of a catalyst of DMAP and 2 equiv of diisopropylethylamine in $CH_2Cl_2$ in a 94% yield. Ketal **3** was treated with $Et_3SiH$ and $TiCl_4$ in $CH_2Cl_2$ at −78 and −10 °C, for regioselective reductive ring opening reaction to provide hydroxyether **4** as reported by Winchienukul and coworkers.[5c] Then conversion of the hydroxyl group of compound **4** to azido

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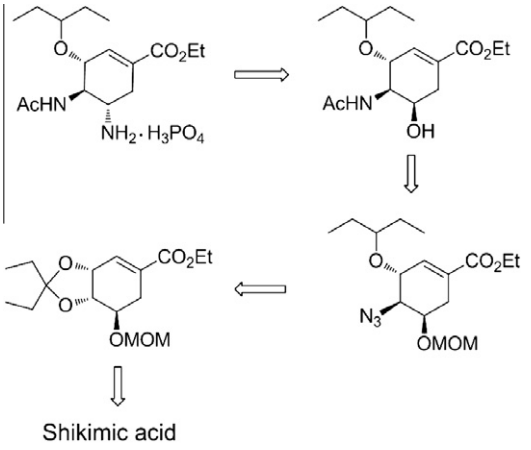


**Figure 1.** Retrosynthetic analysis of oseltamivir phosphate from (−)-shikimic acid.

group employed the azide Mitsunobu reaction using $PPh_3$, DEAD, and azidoic acid in THF to produce monoazido compound **5** in good yields.[13] In this $S_N2$ type displacement using the azide Mitsunobu reaction, the (S)-configuration of the C-5 of compound **4** was successfully inverted to the (R)-configuration.

The azide group of compound **5** was reductively acetylated by treatment with thioacetic acid and 2,6-lutidined in $CHCl_3$ at 55 °C to give compound **6** in a 76% yield.[5c] Then, deprotection of methoxymethyl group of compound **6** was performed in mild conditions, instead of strong acid conditions using trifluoroacetic acid or HCl in order to prevent deacylation of C-4. Deprotection of the MOM ether group of C-5 using 0.5 equiv of $ZrCl_4$ in dry isopropanol gave compound **7** in a 92% yield.[14]

Compound **7** was then treated with $PPh_3$, DEAD, and azidoic acid in THF to afford the azide compound **8** in an 84% yield.[14] It was found that the yield of the one-step azide Mitsunobu reaction for the azide group formation was better than the yield of the two-step reaction (80%) of primary alcohol using methanesulfonyl chloride with triethylamine for the OMs group at C-5 of compound **7**,

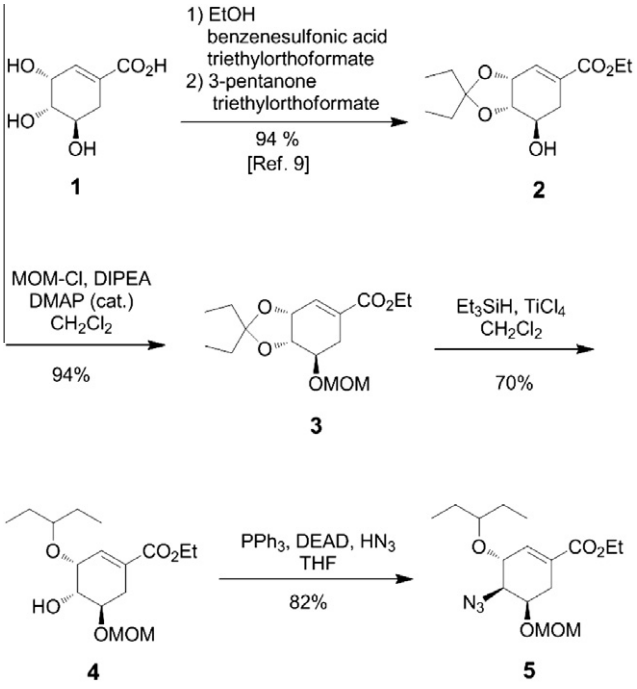


**Figure 2.** Synthesis of ketal azide **5**.

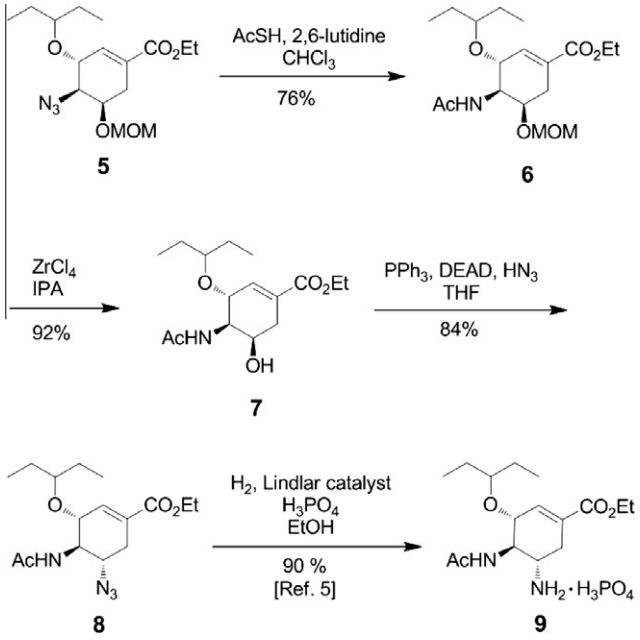


**Figure 3.** Completion of the synthesis of Tamiflu.

followed by the $S_N2$ type nucleophilic substitution with sodium azide.

Next, in order to produce the primary amine of C-5, hydrogenation reduction of the azide functionality of compound **8** by hydrogen gas was performed in the presence of Lindlar catalyst because of the possibility of hydrogenation on the double bond if Pd/C was used instead. Finally, treatment with 1.2 equiv of phosphoric acid in EtOH at 50 °C afforded oseltamivir phosphate **1** to be prepared in a 90% yield via previously reported method.[5f]

In conclusion, a new efficient method for the synthesis of oseltamivir phosphate **1** from an easily available material **2**, which is readily prepared from (−)-shikimic acid, has been accomplished via 7 steps and achieved a 29% overall yield (from (−)-shikimic acid, 9 steps and a 27% overall yield). The key steps of this synthetic approach are the selective ring opening reaction of ketal and the employment of the azide Mitsunobu reaction contributing to the concision of the synthesis. Moreover, the reagents used in all steps are inexpensive, and each step is easy to carry out. Therefore, the efficient synthetic route for the synthesis of Tamiflu will be a potential and promising candidate applicable for industrial processes.

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14. Procedures and selected data.

(a) Synthesis of compound **3**. Diisopropylethylamine (4.30 g, 33.29 mmol) and DMAP (406 mg, 3.33 mmol) were added to compound **2** (4.5 g, 16.66 mmol) in $CH_2Cl_2$ (50 mL). The mixture was cooled to 0 °C. Methoxymethyl chloride (2.01 g, 25.00 mmol) was added dropwise to the mixture. After the reaction mixture was stirred at 0 °C for 10 min, heated to 40 °C, and stirred for 5 h, the mixture was extracted with $Et_2O$ (2 × 50 mL) and washed with brine (50 mL). The organic phase was concentrated under reduced pressure, and the crude residue was purified by silica gel flash chromatography using 1:1 hexane/EtOAc as eluent to give compound **3** (4.95 g, 94%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.83–6.92 (m, 1H), 4.64–4.81 (m, 3H), 4.37–4.42 (dd, *J* = 6.2, 6.2 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.36 (m, 1H), 3.23 (s, 3 H), 2.73 (dd, *J* = 16.4, 4.9 Hz, 1H), 2.24 (dd, *J* = 17.8, 6.5 Hz, 1H), 1.53–1.64 (m, 4H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.4, 134.7, 130.1, 114.1, 96.8, 76.8, 72.8, 68.7, 61.3, 55.5, 30.1, 29.4, 28.7, 14.2, 8.8, 8.2; HRMS (ESI) *m*/*z* (M+H)$^+$ calcd for $C_{16}H_{26}O_6$ = 314.3563, found 314.3574.

(b) Synthesis of compound **4**. $Et_3SiH$ (1.94 g, 16.67 mmol) was added to compound **3** (4.05 g, 12.82 mmol) in $CH_2Cl_2$ (50 mL) at −78 °C. $TiCl_4$ (2.92 g, 15.38 mmol) in $CH_2Cl_2$ (20 mL) was added dropwise to the mixture. After the temperature of the reaction mixture was raised to −10 °C, the mixture was stirred at −10 °C for 6 h, $TiCl_4$ (0.73 mg, 3.85 mmol) was added dropwise, and the mixture was stirred for 1 h. 10% $NH_4OH$ (10 mL) was added and the suspension was filtered. The mixture was extracted with $CH_2Cl_2$ (3 × 50 mL) and washed with water (50 mL) and brine (50 mL). The organic phase was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure, and then the crude residue was purified by silica gel flash chromatography using 9:1 $CH_2Cl_2$/MeOH as eluent to give compound **4** (2.81 g, 70%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.77–6.83 (m, 1H), 4.61–4.93 (m, 3H), 4.29–4.38 (m,1H), 4.12 (q, *J* = 7.2 Hz, 2H), 4.08–4.13 (m, 1H), 3.35–3.75 (m, 1H), 3.23 (s, 3 H), 2.81–2.88 (m, 2H), 2.71–2.74 (m, 1H), 1.56–1.67 (m, 4H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.5, 135.9, 130.0, 128.3, 96.7, 86.1, 74.2, 69.7, 61.6, 55.6, 29.1, 28.3, 27.8, 14.2, 9.7, 9.2; HRMS (ESI) *m*/*z* (M+H)$^+$ calcd for $C_{16}H_{28}O_6$ = 316.3899, found 316.3952.

(c) Synthesis of compound **5**. Azidoic acid (4.45 mL, 1.8 M, 8.01 mmol) in benzene was added dropwise to DEAD (1.39 g, 7.97 mmol) and PPh3 (2.09 g, 7.97 mmol) in THF (30 mL) at 10 °C. Then, compound **4** (2.1 g, 6.64 mmol) in THF (20 mL) was added to the mixture at 10 °C. After the reaction mixture was stirred at 10 °C, the mixture was stirred at room temperature for 8 h. The mixture was extracted with ethyl ether (2 × 50 mL) and washed with water (50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, and then the crude residue was purified by silica gel flash chromatography using 1:3 hexane/EtOAc as eluent to give compound **5** (1.85 g, 82%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.78–6.85 (m, 1H), 4.51–4.78 (m, 3H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.01–4.07 (m, 1H), 3.63 (dd, *J* = 8.2, 11.0 Hz, 1H), 3.41–3.48 (m, 1H), 3.35 (s, 3 H), 3.03–3.10 (m, 1H), 1.51–1.62 (m, 4H), 1.30 (t, *J* = 7.4 Hz, 3H), 0.95 (t, *J* = 7.2 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz $CDCl_3$) $\delta$ 166.3, 136.8, 129.7, 96.6, 82.7, 76.4, 66.1, 61.3, 55.4, 31.7, 27.2, 25.7, 14.1, 9.6, 9.5; HRMS (ESI) *m*/*z* (M+H)$^+$ calcd for $C_{16}H_{27}N_3O_5$ = 341.4027, found 341.3987.

(d) Synthesis of compound **6**. Thioacetic acid (1.79 g, 23.50 mmol) was added dropwise to compound **5** (1.15 g, 3.36 mmol) and 2.6-lutidine (2.52 g, 23.50 mmol) in $CHCl_3$ (30 mL) at room temperature. After the reaction mixture was stirred at 55 °C for 6 h, the mixture was concentrated under reduced pressure, and then the crude residue was purified by silica gel flash chromatography using 1:2 hexane/EtOAc as eluent to give compound **6** (0.91 g, 76%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.77 (m, 1H), 4.71 (d, *J* = 7.0 Hz, 1H), 4.64 (d, *J* = 7.0 Hz, 1H), 4.36–4.42 (m, 1H), 4.21–4.13 (m, 3H), 3.89 (t, *J* = 6.7 Hz, 1H), 3.61 (s, 1H), 3.43 (s, 3 H), 3.30 (q, *J* = 6.7 Hz, 1H), 2.71 (d, *J* = 17.3 Hz, 1H) 2.46 (dd, *J* = 18.1, 4.8 Hz, 1H), 2.01 (s, 3H), 1.47–1.62 (m, 4H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.8, 166.4, 136.3, 129.4, 96.7, 82.4,72.9, 67.1, 61.3, 55.7, 55.2, 31.8, 26.9, 26.0, 23.7, 14.3, 9.7, 9.6.; HRMS (ESI) *m*/*z* (M+H)$^+$ calcd for $C_{18}H_{31}NO_6$ = 357.4418, found 357.4392.

(e) Synthesis of compound **7**. $ZrCl_4$ (0.24 g, 1.02 mmol) in isopropanol (10 mL) was added to compound **6** (0.72 g, 2.04 mmol) in isopropanol (20 mL). After the reaction mixture was stirred at 50 °C for 4 h, the mixture was extracted with ethyl acetate (2 × 30 mL) and washed with water (30 mL) and brine (30 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, and then the crude residue was purified by silica gel flash chromatography using 1:4 hexane/EtOAc as eluent to give compound **5** (0.59 g, 92%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.78 (s, 1H), 5.73 (d, *J* = 6.3 Hz, 1H), 4.36 (m, 1H), 4.28–4.14 (m, 3H), 3.90 (t, *J* = 6.7 Hz, 1H), 3.61 (s, 1H), 3.32 (q, *J* = 6.7 Hz, 1H), 2.70 (d, *J* = 17.3 Hz, 1H) 2.47 (dd, *J* = 18.2, 5.1 Hz, 1H), 2.04 (s, 3H), 1.43–1.62 (m, 4H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.9, 166.8, 136.4, 129.4, 82.3,72.9, 67.4, 61.1, 55.2, 31.9, 26.7, 26.1, 23.8, 14.3, 9.8, 9.7.; HRMS (ESI) *m*/*z* (M+H)$^+$ calcd for $C_{16}H_{27}NO_5$ = 313.1889, found 313.1871.

(f) Synthesis of compound **8**. Azidoic acid (1.48 mL, 1.8 M, 8.01 mmol) in benzene was added dropwise to DEAD (0.47 g, 2.68 mmol) and $PPh_3$ (0.71 g, 2.68 mmol) in THF (20 mL) at 10 °C. Then, compound **6** (0.70 g, 2.24 mmol) in THF was added to the mixture at 10 °C. After the reaction mixture was stirred at 10 °C, the mixture was stirred at room temperature for 8 h. The mixture was extracted with ethyl ether (2 × 30 mL) and washed with water (30 mL) and brine (30 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, and then the crude residue was purified by silica gel flash chromatography using 1:2 hexane/EtOAc as eluent to give compound **7** (0.64 g, 84%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.78 (s, 1 H), 5.93 (d, *J* = 7.4 Hz, 1 H), 4.55 (d, *J* = 7.2 Hz, 1H), 4.16–4.48 (m, 3 H), 3.25−3.37 (m, 2 H), 2.85 (dd, *J* = 17.6, 5.6 Hz, 1H), 2.18−2.31 (m, 1 H), 2.04 (s, 3 H), 1.46−1.51 (m, 4 H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.82−0.95 (m, 6 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.2, 165.9, 137.9, 128.2, 82.1, 73.4, 61.2, 58.4, 57.2, 30.6, 26.3, 25.7, 23.6, 14.2, 9.6, 9.4; HRMS (ESI) *m*/*z* (M+H)$^+$ calcd for $C_{16}H_{27}N_4O_4$ = 339.2032, found 339.2041.