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A Short and Practical Synthesis of Oseltamivir Phosphate (Tamiflu) from (−)-Shikimic Acid†

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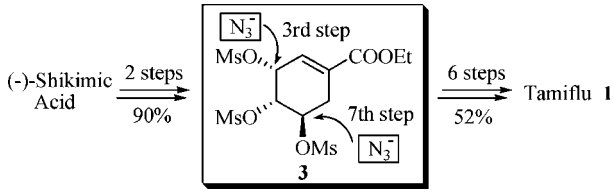

Oseltamivir phosphate (**1**) was synthesized from (−)-shikimic acid through a short and practical synthetic route via eight steps in 47% overall yield. In addition, the highly regioselective and stereoselective nucleophilic replacement of OMs by the N_3 group in the third and seventh steps has been studied in detail, and the reaction conditions were optimized.

Oseltamivir phosphate (Tamiflu, **1** in Scheme 1) has recently attracted considerable attention because it was approved as the only orally available drug for both prophylaxis and treatment of human influenza[1] and H5N1 avian flu.[2] The historic record showed that the human influenza and the H5N1 avian flu have killed numerous people in many countries,[3] and they will surely continue to threaten human health in the future. To protect people from the attack of pandemic human influenza or H5N1 avian flu, it is recommended that oseltamivir phosphate (Tamiflu, **1**) should be manufactured and stocked in every country all over the world.[4,3a]

Extensive efforts have been made by synthetic chemists[5,6] to tackle the problems in the synthesis of oseltamivir phosphate in order to develop an efficient and useful synthetic route that is anticipated to be suitable as an industrial process. The chemists at Gilead Sciences, Inc. and F. Hoffman-La Roche Ltd. have developed a practical synthesis[6a,c] that is currently used for the manufacture of oseltamivir phosphate. Among all the reported synthetic methods, La Roche's method seems to have been the best one for industrial large-scale preparation of Tamiflu until now. However, there are still some drawbacks associated with this method, for example, the long synthetic route and the relatively low total yield. Therefore, a better industrial synthetic method remains highly desirable.

Recently, we were engaged in the synthesis of oseltamivir phosphate and have just disclosed a novel 13-step synthesis starting from (−)-shikimic acid.[7] Although this synthesis has some merits such as the high overall yield, inexpensive reagents, mildness of the reaction conditions, and ease of manipulation of every step, the long synthetic route will significantly retard its use in the large-scale preparation of oseltamivir phosphate. After an extensive study, we have exploited a much short and practical synthesis of oseltamivir phosphate from (−)-shikimic acid. Herein, we would like to report the details.

As depicted in Scheme 2, our synthesis started from (−)-shikimic acid, which can be obtained by extraction from *Illicium verum* (also referred to as Chinese star anise)[8] or other natural resources,[9] or by fermentation using genetically modified *Escherichia coli*.[10] To our delight, (−)-shikimic acid is abundant

† Dedicated to Professor Li-Xin Dai (Shanghai Institute of Organic Chemistry) on the occasion of his 85th birthday.

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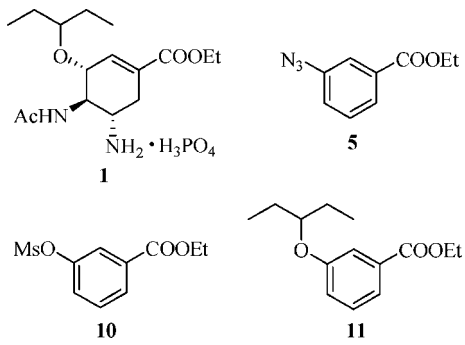
SCHEME 1



in the Chinese star anise [1.1 kg of (−)-shikimic acid from 30 kg of the dried plant] and commercially available in large quantities in China.

(−)-Shikimic acid was first converted to ethyl shikimate **2** in high yield according to a known procedure.[6c] Compound **2** was then exposed to 4.5 equiv of methanesulfonyl chloride and 5 equiv of triethylamine in ethyl acetate in the presence of a catalytic amount of DMAP, thus trimesylate **3** was obtained in 93% yield. When compound **3** was treated with 4 equiv of sodium azide in aqueous acetone (acetone/water = 5:1) at 0 °C for 4 h, a highly stereoselective nucleophilic substitution of the OMs group at the allylic C-3 position by an azido group occurred to afford azide compound **4** in 92% yield, and the (*R*)-configuration of C-3 is reversed to the (*S*)-configuration. The substitution occurred with very high regioselectivity, also, two OMs groups at C-4 and C-5 remained intact. In this step, a relatively lower temperature was crucial, otherwise compound **5** (Scheme 1) would be formed from the desired product **4** via elimination and aromatization. For example, when compound **3** was treated with 4 equiv of sodium azide in aqueous acetone at room temperature for 3 h or at 50 °C for 2 h, aromatic compound **5** was obtained in 16% and 81% yields, respectively.

Compound **4** was successively treated with 1.1 equiv of triphenylphosphine, 3 equiv of triethylamine, and a large excess of water at room temperature to afford aziridine **6** in 84% yield. It was found that the aziridine **6** was hard to separate by chromatography from the triphenylphosphine oxide, which was formed during the reaction from the oxidation of triphenylphosphine. Fortunately, compound **6** could be easily purified by first washing it into aqueous solution with an acid and then extracting it from the aqueous solution after neutralization. Sodium hydrogen sulfate was found to be the best acid for this purpose. Compound **6** was then immediately exposed to 2 equiv of acetic anhydride and 3 equiv of triethylamine in ethyl acetate to produce *N*-acetyl aziridine **7** in a nearly quantitative yield.

N-acetyl aziridine **7** was then treated with 1.5 equiv of boron trifluoride etherate in 3-pentanol to furnish a ring-opening product **8** in 86% yield. The reaction temperature should be kept below 0 °C (−8 to 0 °C) with a salt-ice bath to obtain the best yield. The stereoselectivity of this ring-opening reaction is excellent, and the (*S*)-configuration of C-1 in compound **7** is inversed to the (*R*)-configuration of C-3 in compound **8** according to the Walden-type inversion. The regioselectivity of the ring-opening reaction is also excellent because the allylic position (C-1 of compound **7**) is much more reactive than the C-6 position of compound **7**.[6a]

With the ring-opening product **8** in hand, the next step that we wanted to perform was nucleophilic replacement of OMs at the C-5 position by the N_3 group. Compound **8** was then treated with 4 equiv of sodium azide in aqueous ethanol (EtOH/H_2O = 5:1) under refluxing (around 75 °C) for 8 h to afford compound **9** in 88% yield, and the (*R*)-cofiguration of C-5 is reversed to the (*S*)-configuration.

In the sequence outlined in Scheme 2, nucleophilic replacement of OMs by the N_3 group was used twice in the third and seventh steps. To optimize the reaction conditions for the nucleophilic substitutions of methanesulfonates **3** and **8** by sodium azide, we examined the nucleophilic substitutions of compounds **3** and **8** in aqueous acetone (Me_2CO/H_2O = 5:1), aqueous *N*,*N*-dimethylformamide (DMF/ H_2O = 5:1), aqueous dimethyl sulfoxide (DMSO/H_2O = 5:1), aqueous tetrahydrofuran (THF/H_2O = 5:1), and aqueous ethanol (EtOH/H_2O = 5:1). It was found that the substitution of compound **3** by sodium azide in aqueous acetone and that for compound **8** in aqueous ethanol gave the best yield, respectively.[11,12] Notably, the reaction temperatures for the substitutions of compounds **3** and **8** differed dramatically. This is likely due to the fact that the attack of the nucleophile (N_3^-) on the allylic position of compound **3** is much easier than that on the nonallylic position of compound **8** and thus requires a much lower temperature.

Several other nitrogen-containing nucleophiles were also tested to replace the sodium azide in the nucleophilic substitutions of compounds **3** and **8**, considering hazardousness and potential explosiveness of sodium azide. The nitrogen-containing nucleophiles that have been tried include ammonia, benzylamine, allylamine, and *tert*-butylamine. Unfortunately, none of them led to the formation of the desired products, and compounds **10** and **11** (see also Scheme 1) were obtained instead.

Finally, azide **9** was transformed into the title compound **1** according to our reported procedure[7] in 91% yield. The sample of final product oseltamivir phosphate obtained from the synthesis described herein was found to be identical with the sample we obtained in the previous synthesis by comparing the analytical data.[7,6b]

In conclusion, a short and practical synthesis of the title compound **1** has been developed. As compared with our reported synthesis,[7] the total yield starting from (−)-shikimic acid increased from 40% to 47%, and the synthetic route was shortened from 13 steps to 8 steps. Higher overall yield and fewer synthetic steps, combined with other advantages such as ready crystallization of trimesylate **3** and easy purification of aziridine **6** without chromatography, make the synthesis more suitable as an industrial process. Reaction conditions for the nucleophilic replacement of OMs by the N_3 group both in the 3rd and 7th steps have been studied in detail and optimized.

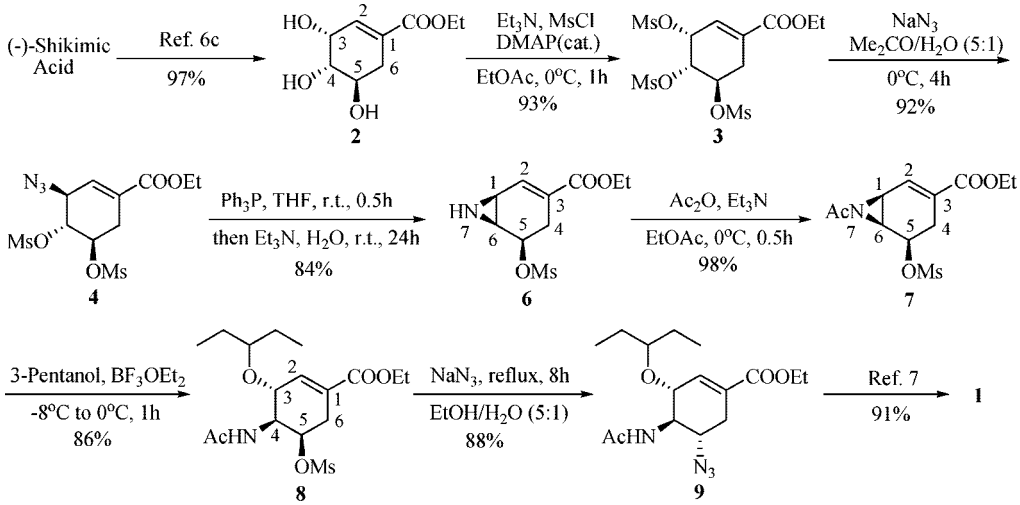
Experimental Section

Ethyl (3*R*,4*S*,5*R*)-3,4,5-*O*-Trimethanesulfonyl Shikimate (3). To a solution of (−)-ethyl shikimate **2** (11.26 g, 55.68 mmol) in ethyl acetate (150 mL) was added methanesulfonyl chloride (28.71 g, 250.63 mmol). The resulting solution was cooled to 0 °C by an ice bath, and 4-dimethylaminopyridine (2.04 g, 16.70 mmol) was added. Triethylamine (28.18 g, 278.49 mmol) was then added dropwise over 30 min, while vigorous stirring was continued. After

(11) The substitution of compound **3** with 4 equiv of sodium azide gave compound **4** in 90% yield in DMF−H_2O (0°C, 1 h), 88% yield in DMSO−H_2O (20°C, 1 h), 89% yield in THF−H_2O (0°C, 6 h), and 85% yield in EtOH−H_2O (20°C, 24 h).

(12) The substitution of compound **8** with 4 equiv of sodium azide gave compound **9** in 75% yield in Me_2CO−H_2O (59°C, 60 h), 84% yield in DMF−H_2O (90°C, 3 h), 70% yield in DMSO−H_2O (80°C, 15 h), and 64% yield in THF−H_2O (63°C, 6 d).

SCHEME 2



the addition was finished, the reaction mixture was stirred at 0 °C for another 1 h to allow the reaction to complete. The reaction was quenched by adding a dilute HCl aqueous solution (1 N, 100 mL), and the mixture was transferred into a separatory funnel. The organic phase was separated and washed with dilute potassium carbonate aqueous solution until pH 8−9. The organic solution was dried over anhydrous $MgSO_4$, and then was concentrated under vacuum to give a pale yellow oily residue that solidified on standing at room temperature. The solid was then triturated with aqueous methanol (methanol/water = 8:2) and pale yellow crystals were collected on a Buchner funnel and rinsed with aqueous methanol to give compound **3** (22.61 g, 51.80 mmol) in 93% yield, mp 97.8−99.0 °C, $[\alpha]^{25}_D$ −119.4 (*c* 1.0, EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 7.1 Hz, 3H), 2.70 (dd, J_1 = 17.5 Hz; J_2 = 5.9 Hz, 1H), 3.14 (s, 3H), 3.19 (s, 3H), 3.20 (s, 3H), 3.22 (dd, J_1 = 13.9 Hz; J_2 = 5.9 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 4.99 (dd, J_1 = 9.2 Hz; J_2 = 4.0 Hz, 1H), 5.09−5.18 (m, 1H), 5.52 (dd, $J_1 = J_2$ = 4.2 Hz, 1H), 6.80−6.86 (m, 1H). MS (*m*/*z*, rel intensity) 436 (M^+, 0.5), 390 (2), 357 (12), 341 (2), 311 (7), 267 (48), 199 (100), 155 (49), 137 (47), 109 (44), 79 (45). IR (KBr film) 3039, 2937, 1711, 1661, 1346, 1179, 889 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_{11}S_3$: C, 33.02; H, 4.62. Found: C, 33.23; H, 4.27.

Ethyl (3*S*,4*R*,5*R*)-3-Azido-4,5-dimethanesulfonyloxycyclohex-1-ene-1-carboxylate (4). Compound **3** (10.00 g, 22.91 mmol) was dissolved in acetone (80 mL), and the solution was cooled to 0 °C by an ice bath. A freshly prepared solution of sodium azide (5.96 g, 91.68 mmol) in water (16 mL) was then added in 10 min. The mixture was stirred at 0 °C for 4 h, and the reaction was traced by TLC. Toluene (200 mL) and water (50 mL) were added upon the disappearance of **3**, then the organic phase was separated and washed successively with water (50 mL) and brine (25 mL). The organic solution was dried over anhydrous $MgSO_4$, and the solvents were removed by distillation under vacuum. The crude product was then purified by chromatography to furnish azide compound **4** (8.08 g, 21.07 mmol) in 92% yield. $[\alpha]^{25}_D$ +45.1 (*c* 1.9, EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 7.1 Hz, 3H), 2.64−2.72 (m, 1H), 3.16 (s, 3H), 3.21 (dd, J_1 = 15.1 Hz; J_2 = 5.7 Hz, 1H), 3.23 (s, 3H), 4.25 (q, J = 7.1 Hz, 2H), 4.31−4.38 (m, 1H), 4.77 (dd, J_1 = 9.9 Hz; J_2 = 8.1 Hz, 1H), 4.86−4.94 (m, 1H), 6.74−6.79 (m, 1H). HRMS *m*/*z* calcd for $(C_{11}H_{17}N_3O_8S_2 + Na)^+$ 406.0355, found 406.0354. IR (KBr film) 2979, 2938, 2112, 1716, 1358, 1258, 1178, 1016, 820, 521 cm^{-1}.

Ethyl (1*S*,5*R*,6*S*)-5-Methanesulfonyloxy-7-azabicyclo[4.1.0]hept-2-ene-3-carboxylate (6). To a solution of compound **4** (8.08 g, 21.07 mmol) in tetrahydrofuran (250 mL) was added triphenylphosphine (6.08 g, 23.18 mmol) in portions. After the solution was stirred at room temperature for half an hour, triethylamine (6.40 g, 63.25 mmol) and water (40 mL) were added, then the resulting mixture was stirred at room temperature for 24 h. Toluene (100 mL) was added, and the reaction mixture was transferred into a separatory funnel. The organic phase was then washed three times with aqueous sodium hydrogen sulfate (5% w/v, 3 × 80 mL). The aqueous solutions were combined and neutralized to pH 9−10 by adding potassium carbonate (16.65 g, 120.47 mmol) powder. The basic aqueous solution was extracted twice with ethyl acetate (2 × 100 mL). The organic extracts were combined and dried over anhydrous Na_2SO_4, and evaporation of the solvent under vacuum gave a crude oil that was seeded to afford compound **6** (4.62 g, 17.68 mmol) as pale yellow crystals in 84% yield. $[\alpha]^{20}_D$ −116.5 (*c* 1.0, EtOAc). ^{1}H NMR (acetone-d_6) δ 1.24 (t, J = 7.1 Hz, 3H), 1.87−2.02 (m, 1H), 2.21−2.35 (m, 1H), 2.64−3.02 (m, 3H), 3.20 (s, 3H), 4.14 (q, J = 7.1 Hz, 2H), 4.86−5.08 (m, 1H), 7.09−7.16 (m, 1H). MS (*m*/*z*, rel intensity) 262 (M^+ + 1, 1), 259 (3), 243 (3), 184 (57), 166 (4), 155 (5), 138 (12), 111 (8), 105 (100), 77 (13). HRMS *m*/*z* calcd for $(C_{10}H_{15}NO_5S)^+$ + 1 262.0749, found 262.0752. IR (KBr film) 3249, 2991, 1704, 1363, 1355, 1265, 1187, 1173, 1121, 955, 723, 540 cm^{-1}. Anal. Calcd for $C_{10}H_{15}NO_5S$: C, 45.97; H, 5.79; N,5.36. Found: C, 45.97; H, 5.60; N, 5.14.

Ethyl (1*S*,5*R*,6*S*)-7-Acetyl-5-methanesulfonyloxy-7-azabicyclo[4.1.0]hept-2 -ene-3-carboxylate (7). Compound **6** (4.44 g, 16.99 mmol) and triethylamine (5.16 g, 50.99 mmol) were dissolved in ethyl acetate (65 mL). The solution was then cooled to 0 °C with an ice bath, and acetic anhydride (3.47 g, 33.99 mmol) was added dropwise over 15 min. After the addition was finished, the reaction mixture was further stirred for half an hour. The reaction was quenched by adding an aqueous solution of potassium carbonate (15% w/v, 35 mL), then the organic phase was separated and washed successively with water (20 mL) and brine (15 mL). After the organic phase was dried over anhydrous Na_2SO_4, evaporation of the solvent under vacuum gave a pale yellow oily product that could be directly used for the next step or purified by flash chromatography to furnish compound **7** (5.06 g, 16.68 mmol) in 98% yield. $[\alpha]^{20}_D$ −22.2 (*c* 1.1, EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.1 Hz, 3H), 2.21 (s, 3H), 2.32−2.46 (m, 1H), 3.04−3.14 (m, 1H), 3.18 (s, 3H), 3.24 (dd, J_1 = 5.9 Hz; J_2 = 4.7 Hz, 1H), 3.35−3.41 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.96−5.06 (m, 1H), 7.10 (dd, J_1 = 4.5 Hz; J_2 = 3.5 Hz, 1H). HRMS *m*/*z* calcd for $C_{12}H_{17}NO_6S$ 303.0777, found 303.0765. IR (KBr film) 2979, 2937, 1710, 1421, 1358, 1259, 1174, 947, 831, 545 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO_6S$: C, 47.52; H, 5.65; N, 4.62. Found: C, 47.77; H, 5.70; N, 4.60.

Ethyl (3*R*,4*S*,5*R*)-4-Acetamido-3-(1-ethylpropoxy)-5-methanesulfonyloxycyclohex-1-ene-1-carboxylate (8). Compound **7** (5.00 g, 16.48 mmol) was dissolved in 3-pentanol (20 mL), and the solution was cooled to −8 °C by a salt-ice bath. To this cooled solution was gradually added a freshly prepared solution of boron

trifluoride−diethyl etherate (3.15 mL, 24.86 mmol) in 3-pentanol (15 mL) within a period of 15 min. After addition was finished, the reaction mixture was further stirred for 1 h. The mixture was diluted with ethyl acetate (100 mL) and an aqueous solution of potassium carbonate (15% w/v, 30 mL). The organic phase was separated and washed successively with water (20 mL) and brine (20 mL). The organic solution was dried over anhydrous $MgSO_4$, and evaporation of the solvents under vacuum gave a crude oil that was purified by chromatography to furnish compound **8** (5.56 g, 14.20 mmol) in 86% yield. The analytical data showed that compound **8** obtained herein was identical with the sample obtained in the previous article.[7]

Ethyl (3*R*,4*R*,5*S*)-4-Acetamido-5-azido-3-(1-ethylpropoxy)cyclohex-1-ene-1-carboxylate (9). Compound **8** (2.50 g, 6.39 mmol) was placed in a round-bottomed flask with a stir bar. Ethanol (25 mL) and water (5 mL) were added. The mixture was stirred, and a white powder of sodium azide (1.66 g, 25.54 mmol) was added. The reaction mixture was heated to reflux, and stirring was continued at reflux for 8 h. The reaction was monitored by TLC. When TLC showed that the reaction was complete, ethanol was distilled off under a reduced pressure. The residue was cooled to room temperature and ethyl acetate (80 mL) and water (30 mL) were added. The organic phase was separated and washed with brine (20 mL). The organic solution was dried over anhydrous $MgSO_4$, and evaporation of the solvent under vacuum produced a crude oil that was purified by chromatography to afford compound **9** (1.91 g, 5.64 mmol) in 88% yield. The analytical data showed that compound **9** obtained herein was identical with the sample obtained in the previous article.[7]

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Supporting Information Available: Characterization data for compounds **1**, **5**, and **8**−**11**, and copies of ^{1}H NMR of compounds **1** and **3**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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