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A novel azide-free asymmetric synthesis of oseltamivir phosphate (Tamiflu) starting from Roche's epoxide

Liang-Deng Nie, Fei-Feng Wang, Wei Ding, Xiao-Xin Shi *, Xia Lu

Department of Pharmaceutical Engineering, School of Pharmacy, East China University of Science and Technology, 130 Mei-Long Road, Shanghai 200237, PR China

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ABSTRACT

A novel azide-free asymmetric synthesis of oseltamivir phosphate **1** (Tamiflu®) starting from Roche's epoxide is described. Roche epoxide **2** was converted into *N*-acetyl aminoalcohol **3** in 95% yield via a $BF_3{\cdot}OEt_2$-catalyzed epoxide-opening with acetonitrile as a nucleophile. Compound **3** was then transformed into a methanesulfonate **4** in 98% yield. Compound **4** was converted into aziridine **5** in 91% yield. Aziridine **5** was subsequently converted into oseltamivir phosphate **1** via two paths (*a* and *b*). In the path *a*, compound **5** underwent aziridine-opening with diallylamine as a nucleophile to afford compound **7** in 93% yield; compound **7** could then be converted into oseltamivir phosphate **1** in 88% yield. In path *b*, compound **5** underwent aziridine-opening with isopropyl 2,2,2-trichloroacetimidate as a nucleophile to afford compound **8** in 94% yield, which was then converted into oseltamivir phosphate **1** in 82% yield.

1. Introduction

Recently, the synthesis of oseltamivir phosphate **1** (Tamiflu®) has attracted great interest from organic and medicinal chemists around the world, because it is an active prodrug of a potent neuraminidase inhibitor,[1,2] and has been widely used not only as a front-line therapy for H5N1 influenza[3–5] and H1N1 influenza[6] but also as a preventive agent against an unpredictable outbreak of pandemic influenza.

Due to the extreme importance of Tamiflu for human health, many synthetic routes towards oseltamivir phosphate **1** have been studied and reported up to data.[7–21] Some synthetic routes have started from natural chiral materials such as (−)-quinic acid,[1,2,8] (−)-shikimic acid,[2,8,9] L-serine,[10] D-xylose,[11] D-glucose,[12] D-mannitol,[13] L-methionine,[14] D-tartrate,[15]and D-ribose.[16] Other miscellaneous synthetic routes have started from unnatural materials such as Diels–Alder cycloaddition products,[17] Michael addition products,[18] cyclohexene derivatives,[19] benzene derivatives[20] and pyridine.[21] However, among all of the aforementioned syntheses, only Roche's synthesis starting from (−)-shikimic acid or (−)-quinic acid seems to have been developed as an industrial process for the manufacture of Tamiflu. Several synthetic routes have been disclosed by Roche.[8] Hazardous sodium azide and potentially explosive azide intermediates were involved in Roche's early synthesis.[8a] Later, Roche chemists also developed an azide-free synthesis[8c,d] of oseltamivir phosphate **1** by using allylamine[8c] or *tert*-butylamine[8d] instead of sodium azide as a nucleophile in the epoxide-opening. However, both of Roche's azide-free synthetic routes[8c,d] are quite long, and the total yields remain to be increased.

We have recently been involved in the synthesis of oseltamivir phosphate **1** in order to develop more efficient and practical synthetic processes.[9a–d] Herein we report a novel azide-free asymmetric synthesis of oseltamivir phosphate **1** (Tamiflu) starting from Roche's epoxide **2**, which could be obtained in a sequence of five steps in 63–65% yield from the naturally abundant (−)-shikimic acid[22] according to Roche's procedure.[8b,23]

2. Results and discussion

As shown in Scheme 1, Roche's epoxide **2** was first treated with 1.5 equiv of $BF_3{\cdot}OEt_2$ in acetonitrile at 0 °C to room temperature and then subjected to hydrolysis under basic conditions. This led to a highly regio- and stereoselective ring-opening process which afforded *N*-acetyl aminoalcohol **3** in 95% yield. Acetonitrile acted both as the solvent and a weak nucleophile in this $BF_3{\cdot}OEt_2$-catalyzed epoxide-opening.[24]

A possible mechanism and conformational analysis for the MeCN-mediated $BF_3{\cdot}OEt_2$-catalyzed regio- and stereoselective ring-opening of Roche's epoxide **2** is shown in Figure 1. Compound **2** most likely adopted a boat conformation, which first coordinated with $BF_3{\cdot}OEt_2$ to form chelate complex **I-1**. Intermediate **I-1** might follow path *a* or path *b* to form other chelate complexes **I-2** and **I-3** via epoxide-opening by nucleophilic attack of MeCN at C-5 or C-4. Since the fused bicyclic chelate complex **I-2** is much more stable

* Corresponding author. Tel.: +86 2164252052.
E-mail address: xxshi@ecust.edu.cn (X.-X. Shi).

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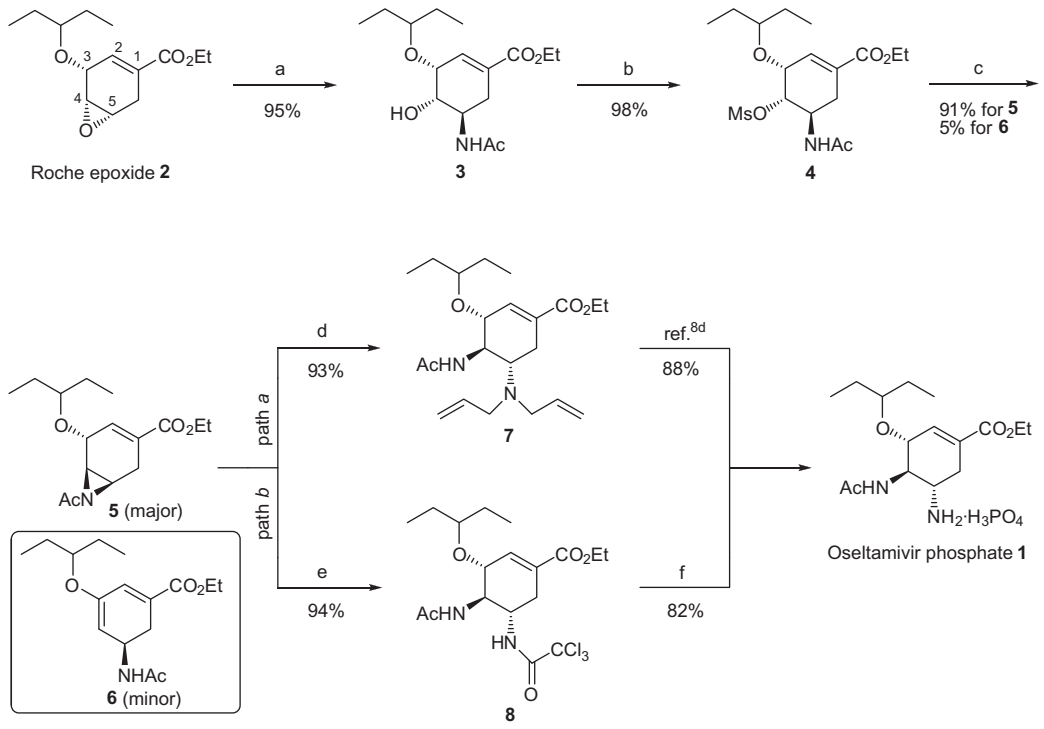

Scheme 1. A novel azide-free asymmetric synthesis of oseltamivir phosphate **1** starting from Roche's epoxide **2**. Reagents and conditions: (a) 1.5 equiv of $BF_3{\cdot}OEt_2$, 0 °C in CH_3CN for 1 h; then water at rt in aqueous acetonitrile (CH_3CN/H_2O = 10:1) for 4 h, and then 8.0 equiv of powdered K_2CO_3 at rt for 36 h; (b) 1.5 equiv of MsCl, 1.5 equiv of Et_3N, 0.1 equiv of DMAP, 0 °C in CH_2Cl_2 for 1 h; (c) 2.0 equiv of NaH, rt in CH_2Cl_2/DMSO (30:1) for 8 h; (d) $(allyl)_2NH$, reflux (112 °C) for 6 h; (e) 1.5 equiv of isopropyl 2,2,2-trichloroacetimidate, 2.0 equiv of $BF_3{\cdot}OEt_2$, −15 °C in CH_2Cl_2 for 20 min; (f) 2.5 equiv of Cs_2CO_3, 80 °C in DMSO for 15 min, then AcOH/H_2O (1:1), 80 °C in DMSO for 20 min; 1.1 equiv of H_3PO_4, 50 °C in EtOAc/EtOH (1:1) for 2 h.

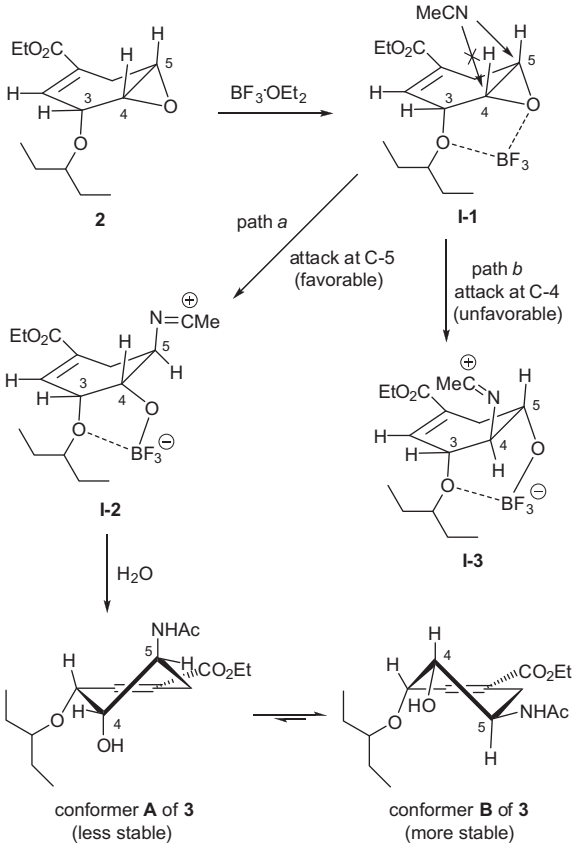

Figure 1. Mechanism and conformational analysis of the $BF_3{\cdot}OEt_2$-catalyzed highly regioselective epoxide-opening of Roche's epoxide **2** with MeCN as a nucleophile.

than the bridged bicyclic chelate complex **I-3**, the nucleophilic attack of MeCN at C-5 (path *a*) is favorable, whereas the nucleophilic attack of MeCN at C-4 (path *b*) is unfavorable. Intermediate **I-2** then underwent hydrolysis to afford a twist chair conformer **A** of compound **3**, and this less stable conformer rapidly flipped to become a more stable twist chair conformer **B** of compound **3**, where both the NHAc and OH groups were located on equatorial positions. Furthermore, during the above $BF_3{\cdot}OEt_2$-catalyzed epoxide-opening, the nucleophile MeCN would attack C-5 on the opposite side of the epoxide moiety, and thus the (*S*) absolute configuration of C-5 was inverted to (*R*).

Compound **3** was treated with 1.5 equiv of methanesulfonyl chloride in the presence of 1.5 equiv of triethylamine and 0.1 equiv of 4-*N*,*N*-dimethylaminopyridine (DMAP) to afford mesylate **4** in 98% yield. When compound **4** was treated with a base, the desired aziridine **5** was obtained via intramolecular S_N2-type nucleophilic substitution, while the undesired 1,3-diene **6** was also formed as a by-product via β-elimination. In order to obtain the best yield of the desired product **5**, optimization of the reaction conditions for conversion of compound **4** to aziridine **5** was carried out. Various bases such as sodium bicarbonate, sodium carbonate, potassium carbonate, potassium *tert*-butoxide, sodium ethoxide and sodium hydride were tested for the reaction. Various solvents such as ethanol, acetonitrile, tetrahydrofuran, ethyl acetate, toluene, dichloromethane, chloroform, 1,2-dimethoxyethane, *N*,*N*-dimethylformamide and dimethyl sulfoxide were also tested. We found that when the reaction was performed in a mixed solvent of dichloromethane and dimethyl sulfoxide (CH_2Cl_2/DMSO = 30:1) at room temperature with 2.0 equiv of sodium hydride as the base, the desired aziridine **5** was obtained in 91% yield, and only a small amount of the undesired β-elimination by-product **6** was formed.

Compound **5** could be converted to oseltamivir phosphate **1** via both path *a* and path *b*. In path *a*, a solution of compound **5** in

diallylamine was allowed to reflux for 6 h; the aziridine-opening took place smoothly to afford compound **7** in 93% yield. Compound **7** was then converted into oseltamivir phosphate **1** in 88% yield after palladium-catalyzed deallylation and ammonium salt formation was carried out according to the literature.[8d] In path *b*, compound **5** was first treated with 1.5 equiv of isopropyl 2,2,2-trichloroacetimidate and 2.0 equiv of $BF_3{\cdot}OEt_2$ in dichloromethane at −15 °C. The aziridine-opening took place very rapidly to afford the desired product **8** in 94% yield. Compound **8** was then treated with 2.5 equiv of cesium carbonate at 80 °C in DMSO;[25] removal of the trichloroacetyl group occurred rapidly to give the base of oseltamivir, which was used as such to react with 1.1 equiv of phosphoric acid in a mixed solvent of ethyl acetate and ethanol (EtOAc/EtOH = 1:1) to furnish oseltamivir phosphate **1** in 82% yield. The conversion of aziridine **5** into oseltamivir phosphate **1** via path *a* gave a better yield over 2 steps, but the conversion via path *b* avoided the use of a poisonous transition metal palladium catalyst,[8d] which might be significant in drug synthesis.

It should be noted that because of the bulkiness of the 3-pentoxy group at the C-3 position, both nitrogen-nucleophiles (diallylamine and isopropyl 2,2,2-trichloroacetimidate) would favorably attack the much less-hindered C-5 position of aziridine **5** in an opposite direction with high regio- and stereoselectivities; the (*R*)-absolute configuration of C-5 was inverted to an (*S*)-configuration during the above aziridine-opening.

3. Conclusion

In conclusion, a novel azide-free asymmetric synthesis of oseltamivir phosphate **1** starting from Roche's epoxide **2** is described. Roche's epoxide **2** was converted into the key intermediate aziridine **5** in 85% yield over 3 steps. Aziridine **5** was then converted into compound **1** in 82% yield over 2 steps via path *a*, or in 77% yield over 2 steps via path *b*. The key step of the above azide-free synthesis is the $BF_3{\cdot}OEt_2$-catalyzed highly regio- and stereoselective epoxide-opening of Roche epoxide **2** with CH_3CN as the nucleophile. Compared with the two previous Roche azide-free syntheses,[8c,d] the present synthesis of oseltamivir phosphate **1** from Roche's epoxide **2** has been shortened from 8 steps[8d] (or 9 steps[8c]) to 6 steps, and the overall yield from Roche's epoxide **2** to oseltamivir phosphate **1** has been increased from 35–38%[8c] or 61%[8d] to 69% (path *a*) or 65% (path *b*).

4. Experimental

4.1. General

^1H NMR and ^{13}C NMR spectra were obtained on a Bruker AM-500 spectrometer at 300 K, and chemical shifts are given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. Infrared (IR) spectra were recorded on a Nicolet 6700 instrument. MS spectra were recorded on a Shimadzu GC–MS 2010 or a LC/MSD TOF HR-MS equipment. Melting points were determined on a Mel-TEMP II apparatus. Optical rotations of chiral compounds were measured on WZZ-1S automatic polarimeter at room temperature. Column chromatography was performed on silica gel. All chemicals were analytically pure. Epoxide **2** was prepared in five steps according to the Roche report.[8b,23]

4.2. (3*R*,4*S*,5*R*)-Ethyl 5-acetylamido-4-hydroxy-3-(pentan-3-yloxy)cyclohex-1-ene carboxylate 3

A solution of Roche's epoxide **2** (10.00 g, 39.32 mmol) in CH_3CN (150 mL) was cooled to 0 °C with an ice bath. Next, $BF_3{\cdot}OEt_2$ (8.360 g, 58.90 mmol) was added dropwise over 10 min to the above solution, after which the reaction solution was stirred for 1 h at 0 °C. Water (15 mL) was then added, the ice bath was removed, and the mixture was stirred for 4 h. Powdered potassium carbonate (43.48 g, 314.6 mmol) was then added in portions, and the suspension was stirred at room temperature for approximately 36 h. The suspension was filtered by suction, and the cake was washed twice with acetonitrile (2 × 50 mL). The filtrates were combined, and acetonitrile was removed by vacuum distillation. The residue was then partitioned between ethyl acetate (200 mL) and water (50 mL). The two phases were separated, and the aqueous phase was extracted twice with ethyl acetate (2 × 40 mL). The extracts were combined, washed with brine (50 mL), and dried over anhydrous $MgSO_4$. The organic solvents were removed by vacuum distillation to give an oily residue, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:4) to afford compound **3** (11.71 g, 37.36 mmol) in 95% yield. Mp 98.1–98.6 °C. $[\alpha]_D^{20} = -171$ (*c* 2.00, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.4 Hz, 3H, CH_3 in 3-pentoxyl), 0.92 (t, J = 7.4 Hz, 3H, CH_3 in 3-pentoxyl), 1.26 (t, J = 7.1 Hz, 3H, CH_3 in COOEt), 1.43–1.60 (m, 4H, both CH_2 in 3-pentoxyl), 2.00 (s, 3H, CH_3 in Ac), 2.04 (dd, J_1 = 18.0 Hz; J_2 = 9.4 Hz, 1H, H-6), 2.73 (br s, 1H, OH), 3.01 (dd, J_1 = 18.0 Hz; J_2 = 5.4 Hz, 1H, H-6′), 3.43–3.48 (m, 1H, OCH in 3-pentoxyl), 3.58–3.64 (m, 1H, H-5), 4.04 (dd, J_1 = 4.4 Hz, J_2 = 4.6 Hz, 1H, H-4), 4.14–4.26 (m, 3H, H-3 and OCH_2 in COOEt), 5.91 (d, J = 6.4 Hz, 1H, H-2), 6.86 (br s, 1H, NHAc). ^{13}C NMR ($CDCl_3$) δ 171.26, 166.19, 135.18, 131.10, 82.16, 71.30, 71.07, 60.93, 47.41, 30.21, 26.54, 26.15, 23.27, 14.15, 9.72, 9.42. HRMS (EI) calcd for $(C_{16}H_{27}NO_5)^+$: 313.1889; found: 313.1884. IR (KBr film) 3448, 3285, 2961, 1718, 1621, 1546, 1369, 1251, 1094 cm^{-1}.

4.3. (3*R*,4*S*,5*R*)-Ethyl 5-acetylamido-4-methanesulfonyloxy-3-(pentan-3-yloxy)cyclohex-1-ene carboxylate 4

A solution of compound **3** (5.000 g, 15.95 mmol), Et_3N (2.420 g, 23.92 mmol) and DMAP (190.0 mg, 1.555 mmol) in ethyl acetate (100 mL) was cooled to 0 °C with an ice bath. Methanesulfonyl chloride (2.740 g, 23.92 mmol) was added dropwise, and the resulting solution was then stirred at 0 °C for 1 h. An aqueous solution of HCl (1 mol L^{-1}, 50 mL) was added, and the mixture was stirred vigorously for 5 min. The two phases were separated, and the aqueous solution was extracted twice with ethyl acetate (2 × 50 mL). The extracts were combined, washed with an aqueous solution of ammonia (10% w/w, 30 mL), and dried over anhydrous $MgSO_4$. The solvent was removed by vacuum distillation to give the crude product as a pale yellow oil, which could be used as such for the next step or was purified by flash chromatography (eluent: EtOAc/hexane = 1:3) to afford compound **4** (6.118 g, 15.63 mmol) in 98% yield. $[\alpha]_D^{20} = -118$ (*c* 1.30, $CHCl_3$). ^1H NMR (acetone-d_6) δ 0.90 (t, J = 7.4 Hz, 3H, CH_3 in 3-pentoxyl), 0.94 (t, J = 7.4 Hz, 3H, CH_3 in 3-pentoxyl), 1.27 (t, J = 7.1 Hz, 3H, CH_3 in COOEt), 1.54–1.62 (m, 4H, both CH_2 in 3-pentoxyl), 1.91 (s, 3H, CH_3 in Ac), 2.42 (dd, J_1 = 18.0 Hz, J_2 = 6.9 Hz, 1H, H-6), 2.79 (dd, J_1 = 18.0 Hz, J_2 = 5.9 Hz, 1H, H-6′), 3.16 (s, 3H, CH_3 in Ms), 3.51–3.58 (m, 1H, OCH in 3-pentoxyl), 4.19 (q, J = 7.1 Hz, 2H, OCH_2 in COOEt), 4.39–4.44 (m, 1H, H-5), 4.48–4.56 (m, 1H, H-4), 4.93 (dd, J_1 = 7.6 Hz; J_2 = 4.7 Hz, 1H, H-3), 6.82 (br s, 1H, NHAc), 7.24 (d, J = 7.6 Hz, 1H, H-2). ^{13}C NMR (acetone-d_6) δ 169.73, 165.49, 134.95, 130.21, 82.09, 78.81, 70.44, 60.53, 44.78, 37.69, 29.21, 25.97, 25.88, 22.33, 13.65, 9.16, 8.73. HRMS (ESI) calcd for $(C_{17}H_{29}NO_7S+Na)^+$: 414.1562; found: 414.1562. IR (neat) 3274, 2968, 2936, 1716, 1656, 1550, 1463, 1359, 1246, 1176, 1058, 966, 862, 528 cm^{-1}.

4.4. (3*R*,4*R*,5*R*)-Ethyl 4,5-acetylimino-3-(pentan-3-yloxy)-cyclohex-1-ene carboxylate 5

To a solution of compound **4** (2.000 g, 5.109 mmol) in a mixed solvent of dichloromethane and dimethyl sulfoxide (60 mL, CH_2Cl_2/DMSO = 30:1), was added NaH (490.0 mg, 50% in mineral oil, 10.21 mmol) in portions. The suspension was then stirred at room temperature for 8 h, and the reaction was monitored by TLC. The mixture was cooled to 0 °C, and water (30 mL) was slowly added to quench the reaction. The two phases were separated, and the aqueous solution was extracted twice with dichloromethane (2 × 30 mL). The extracts were combined and dried over anhydrous $MgSO_4$. The organic solution was concentrated by vacuum distillation to give the crude product as a pale yellow oil, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:4) to afford compound **5** (1.375 g, 4.655 mmol) in 91% yield as well as compound **6** (75.0 mg, 0.254 mmol) in 5% yield.

Characterization data for compound **5**: $[\alpha]_D^{20} = -46$ (*c* 0.60, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.91 (t, *J* = 7.4 Hz, 3H, CH_3 in 3-pentoxyl), 0.96 (t, *J* = 7.4 Hz, 3H, CH_3 in 3-pentoxyl), 1.29 (t, *J* = 7.1 Hz, 3H, CH_3 in COOEt), 1.48–1.62 (m, 4H, both CH_2 in 3-pentoxyl), 2.14 (s, 3H, CH_3 in Ac), 2.65 (dd, J_1 = 18.0 Hz, J_2 = 4.8 Hz, 1H, H-6), 2.87–3.01 (m, 3H, H-4, H-5 and H-6′), 3.41–3.49 (m, 1H, OCH in 3-pentoxyl), 4.21 (q, *J* = 7.1 Hz, 2H, OCH_2 in COOEt), 4.36–4.41 (m, 1H, H-3), 6.83 (d, *J* = 4.2 Hz, 1H, H-2). ^{13}C NMR ($CDCl_3$) δ 182.55, 166.46, 133.04, 127.72, 82.41, 68.50, 60.87, 37.11, 34.76, 26.62, 26.56, 23.78, 23.44, 14.15, 9.89, 9.44. HRMS (EI) calcd for $(C_{16}H_{25}NO_4)^+$: 295.1784; found: 295.1786. IR (neat) 2969, 2875, 1710, 1426, 1368, 1248, 1063, 743 cm^{-1}.

Characterization data for (5*R*)-ethyl 5-acetylamido-3-(pentan-3-yloxy)cyclohexa-1,3-diene carboxylate **6**: Mp 108.5–109.1 °C. $[\alpha]_D^{20} = +118$ (*c* 1.10, $CHCl_3$). ^{1}H NMR (acetone-d_6) δ 0.90 (t, *J* = 7.4 Hz, 3H, CH_3 in 3-pentoxyl), 0.92 (t, *J* = 7.4 Hz, 3H, CH_3 in 3-pentoxyl), 1.29 (t, *J* = 7.1 Hz, 3H, CH_3 in COOEt), 1.56–1.66 (m, 4H, both CH_2 in 3-pentoxyl), 1.83 (s, 3H, CH_3 in Ac), 2.55 (dd, J_1 = 18.0 Hz; J_2 = 8.0 Hz, 1H, H-6), 2.68 (dd, J_1 = 18.0 Hz; J_2 = 4.9 Hz, 1H, H-6′), 3.94–4.00 (m, 1H, OCH in 3-pentoxyl), 4.20 (q, *J* = 7.1 Hz, 2H, OCH_2 in COOEt), 4.70–4.76 (m, 1H, H-5), 5.08 (d, *J* = 5. 6 Hz, 1H, H-4), 6.79 (s, 1H, H-2), 7.32 (br s, 1H, NHAc). ^{13}C NMR (acetone-d_6) δ 168.22, 165.74, 152.27, 131.89, 129.32, 99.54, 78.46, 60.25, 42.37, 29.03, 25.23, 25.12, 22.05, 13.65, 8.88, 8.85. HRMS (EI) calcd for $(C_{16}H_{25}NO_4)^+$: 295.1784; found: 295.1785. IR (KBr film) 3350, 2969, 1674, 1650, 1596, 1522, 1278, 1270, 1212, 1200, 1067, 985, 835, 585 cm^{-1}.

4.5. (3*R*,4*R*,5*S*)-Ethyl 4-acetylamido-5-diallylamino-3-(pentan-3-yloxy)cyclohex-1-ene carboxylate 7

Aziridine **5** (2.000 g, 6.771 mmol) was dissolved in diallylamine (10 mL), and the solution was then heated at reflux (112 °C) for approximately 6 h under an argon atmosphere. When TLC showed the reaction was complete, diallylamine was removed by vacuum distillation to give a crude oil, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:5) to afford compound **7** (2.472 g, 6.298 mmol) in 93% yield. $[\alpha]_D^{20} = -30$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, *J* = 7.4 Hz, 3H, CH_3 in 3-pentoxyl), 0.90 (t, *J* = 7.4 Hz, 3H, CH_3 in 3-pentoxyl), 1.30 (t, *J* = 7.1 Hz, 3H, CH_3 in COOEt), 1.46–1.55 (m, 4H, both CH_2 in 3-pentoxyl), 2.00 (s, 3H, CH_3 in Ac), 2.19 (dd, J_1 = 17.6 Hz; J_2 = 7.6 Hz, 1H, H-6), 2.58 (dd, J_1 = 17.6 Hz; J_2 = 4.1 Hz, 1H, H-6′), 2.92 (dd, J_1 = 14.2 Hz; J_2 = 7.8 Hz, 2H, two sp^3-H in allyl), 3.00–3.09 (m, 1H, H-5), 3.24–3.37 (m, 3H, the other two sp^3-H in allyl, and OCH in pentoxyl), 3.89–3.98 (m, 1H, H-4), 4.06 (dd, J_1 = 8.2 Hz, J_2 = 7.3 Hz, 1H, H-3), 4.21 (q, *J* = 7.1 Hz, 2H, CH_2 in COOEt), 5.08 (d, *J* = 10.1 Hz, 2H, two terminal sp^2-H in allyl), 5.16 (d, *J* = 17.1 Hz, 2H, the other two terminal sp^2-H in allyl), 5.61 (d, *J* = 8.2 Hz, H-2), 5.65–5.78 (m, 2H, two inner sp^2-H in allyl), 6.73 (br s, 1H, NHAc). ^{13}C NMR ($CDCl_3$) δ 170.43, 170.01, 138.52, 137.31, 129.93, 116.92, 82.38, 77.72, 61.10, 56.50, 53.52, 52.49, 26.31, 25.82, 23.92, 23.69, 14.50, 9.84, 9.52. HRMS (ESI) calcd for $(C_{22}H_{36}N_2O_4+H)^+$: 393.2753; found: 393.2752. IR (KBr film) 3269, 2962, 1710, 1652, 1563, 1369, 1237, 1122, 912 cm^{-1}.

4.6. Isopropyl 2,2,2-trichloroacetimidate

A solution of 1,8-diazabicyclo[5,4,0]undec-7-ene (1.523 g, 10.00 mmol) and isopropanol (3.000 g, 49.92 mmol) in dichloromethane (30 mL) was cooled to 0 °C with an ice bath. Trichloroacetonitrile (1.160 g, 8.034 mmol) was then added dropwise. After the addition was complete, the mixture was stirred at 0 °C for 1 h. The ice bath was then removed, and stirring was continued at room temperature for 4 h. The reaction solution was concentrated under vacuum to give a brown oily residue, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:8) to furnish isopropyl 2,2,2-trichloroacetimidate (1.183 g, 5.785 mmol) as a colorless oil in 72% yield. ^{1}H NMR ($CDCl_3$) δ 1.37 (d, *J* = 6.2 Hz, 6H, two CH_3 in iospropyl), 5.10–5.18 (m, 1H, OCH in isopropyl), 8.23 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 162.16, 91.98, 72.88, 21.08. HRMS (EI) calcd for $(C_5H_8Cl_3NO)^+$: 202.9671; found: 202.9674. IR (neat) 3347, 2983, 1661, 1359, 1294, 1112, 1081, 976, 859, 797, 650 cm^{-1}.

4.7. (3*R*,4*R*,5*S*)-Ethyl 4-acetylamido-3-(pentan-3-yloxy)-5-(2,2,2-trichloro-acetimido)cyclohex-1-ene carboxylate 8

A solution of aziridine **5** (590.0 mg, 1.997 mmol) and isopropyl 2,2,2-trichloroacetimidate (610.0 mg, 2.983 mmol) in dichloromethane (15 mL) was cooled to −15 °C with a salt-ice bath. Next, $BF_3{\cdot}OEt_2$ (570.0 mg, 4.012 mmol) was dropwise added over 2 min. After the addition was complete, the mixture was stirred at −15 °C for 20 min. The reaction was immediately quenched by adding water (10 mL). After the mixture was vigorously stirred for 10 min, the two phases were separated, and the aqueous phase was extracted twice with dichloromethane (2 × 15 mL). The organic extracts were combined and dried over anhydrous $MgSO_4$. Evaporation of the solvent under vacuum gave a solid residue, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:5) to afford compound **8** (860.0 mg, 1.879 mmol) as off-white crystals in 94% yield. Mp 193.9–195.2 °C, $[\alpha]_D^{20} = -45$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J* = 7.4 Hz, 6H, both CH_3 in 3-pentoxyl), 1.31 (t, *J* = 7.1 Hz, 3H, CH_3 in COOEt), 1.46–1.58 (m, 4H, two CH_2 in 3-pentoxyl), 2.00 (s, 3H, CH_3 in Ac), 2.51 (dd, J_1 = 18.1 Hz; J_2 = 8.3 Hz, 1H, H-6), 2.83 (dd, J_1 = 18.1 Hz; J_2 = 5.1 Hz, 1H, H-6′), 3.36–3.44 (m, 1H, OCH in 3-pentoxyl), 4.03–4.16 (m, 2H, H-4 and H-5), 4.19–4.30 (m, 3H, H-3 and OCH_2 in COOEt), 5.98 (d, *J* = 8.0 Hz, 1H, H-2), 6.85 (br s, 1H, NHAc), 8.07 (br s, 1H, $NHCOCl_3$). ^{13}C NMR ($CDCl_3$) δ 171.43, 165.86, 162.69, 137.11, 128.83, 92.46, 82.43, 74.87, 61.07, 52.97, 50.61, 29.34, 26.22, 25.72, 23.22, 14.17, 9.55, 9.23. HRMS (EI) calcd for $(C_{18}H_{27}Cl_3N_2O_5)^+$: 456.0986; found: 456.0989. IR (KBr film) 3345, 3181, 2972, 1714, 1666, 1546, 1245, 1059, 831, 669 cm^{-1}.

4.8. Oseltamivir phosphate 1

A solution of compound **8** (460.0 mg, 1.005 mmol) in DMSO (8 mL) was heated to 80 °C. Fine powdered Cs_2CO_3 (815.0 mg, 2.501 mmol) was added quickly, and the mixture was stirred at 80 °C for 15 min. An aqueous solution of acetic acid (50% w/w, 3 mL) was added, and stirring was continued at 80 °C for 20 min. After the mixture was cooled down to room temperature, ethyl acetate (30 mL) and an aqueous solution of K_2CO_3 (20% w/w, 15 mL) were added. After the mixture was vigorously stirred for

10 min, the two phases were separated, and the aqueous phase was extracted twice with ethyl acetate (2 × 20 mL). The organic extracts were combined and dried over anhydrous $MgSO_4$. Evaporation of the solvent under vacuum gave a pale yellow oily residue, which was dissolved in a mixed solvent of ethyl acetate (4 mL) and ethanol (4 mL). Phosphoric acid (85%, 130.0 mg, 1.128 mmol) was then added, and the resulting suspension was heated and stirred at 50 °C for 2 h. The suspension was cooled down to room temperature, and then allowed to stand overnight. White crystals were collected on a Buchner funnel by suction and washed twice with ethyl acetate (2 × 1 mL). After being dried overnight in warm air, oseltamivir phosphate **1** (0.340 g, 0.828 mmol) was obtained in 82% yield. The characterization data of compound **1** were identical with those of the sample obtained in our previous report.[9a–d]

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