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A novel asymmetric synthesis of oseltamivir phosphate (Tamiflu) from (−)-shikimic acid

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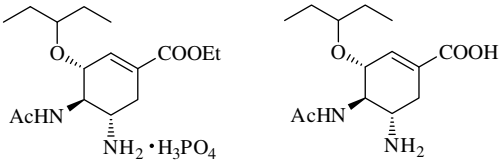
ABSTRACT

Oseltamivir phosphate **1** was synthesized starting from a readily available acetonide, that is, ethyl (3*R*,4*S*,5*R*)-3,4-*O*-isopropylidene shikimate **2**, through a new route via 11 steps and in 44% overall yield. The synthesis described in this article is characterized by two particular steps: the highly regioselective and stereoselective facile nucleophilic replacement of an OMs by an N_3 group at the C-3 position of ethyl (3*R*,4*S*,5*R*)-3,4-*O*-bismethanesulfonyl-5-*O*-benzoyl shikimate **5**, and the mild ring-opening of an aziridine with 3-pentanol at the C-1 position of ethyl (1*S*,5*R*,6*S*)-7-acetyl-5-benzoyloxy-7-azabicyclo[4,1,0]hept-2-ene-3-carboxylate **8**.

1. Introduction

Oseltamivir phosphate **1** (Tamiflu®, GS-4104-02, Ro 64-0796/002 in Fig. 1) as the prodrug of an active neuraminidase inhibitor (GS-4071, Ro 64-0802 in Fig. 1) was discovered by Kim et al. of Gilead Sciences[1], and has been licensed to Roche as an orally administered drug for the treatment and prophylaxis of human influenza A and B.[2,3] Moreover, it is also the most promising therapeutic for the treatment of the H5N1 avian flu virus.[4,5] Until now, Tamiflu has been approved in many countries worldwide, and according to WHO (World Health Organization), stockpiling of Tamiflu is currently the only way to guard against a possible pandemic that could be caused by a human influenza virus or avian flu virus.[6,7]

Due to the importance of Tamiflu for human health, the synthesis of oseltamivir phosphate has aroused much interest from synthetic chemists.[8–10] Many synthetic routes for oseltamivir phosphate have been documented in the literature. In all the reported synthetic routes, the key point should be the construction of three stereogenic chiral centers in the cyclohexanoid scaffold. Some routes are based on the derivation of these three stereogenic centers from natural starting materials, such as (−)-quinic acid,[1,2,11] (−)-shikimic acid,[2,11–14] L-serine,[15] D-xylose,[16,17] and D-glucose.[17] Some routes employed asymmetric Diels–Alder cycloadditions[18–22] as the key step followed by succeeding transformations to build up the cyclohexanoid ring and the corresponding stereogenic centers. The other miscellaneous routes started from prochiral cyclohexene derivatives[23–25] or substituted benzenes,[26–28] and used chiral organometallic catalysts or enzymes to provide an access to the required chirality.



Tamiflu™ **1**
GS-4104-02
Ro 64-0796/002

active inhibitor in *vivo*
GS-4071
Ro 64-0802

Figure 1. Oseltamivir phosphate and the active neuraminidase inhibitor.

Among all the above synthetic routes, only the route developed by Roche[11–13] can be used in the current industrial synthesis. The starting material for Roche's synthesis is (−)-shikimic acid, which can be obtained either by extraction from the Chinese star anise (1 kg of shikimic acid from 30 kg of the dried plant) or by fermentation using genetically modified *Escherichia coli*.[29,30] Herein, we report a novel practical synthesis of oseltamivir phosphate **1** also from (−)-shikimic acid, which is abundant in China.

2. Results and discussion

As depicted in Scheme 1, our synthesis started from acetonide **2**, which can be readily prepared from (−)-shikimic acid in 92% yield according to a known procedure.[12] Compound **2** was first treated with 1.3 equiv of benzoyl chloride in the presence of 2 equiv of triethylamine and a catalytic amount of DMAP in dichloromethane to produce benzoyl acetonide **3** in 98% yield. Removal of the acetonide moiety of the compound **3** gave a crystalline benzoate **4** in 94% yield by exposing **3** to concentrated hydrochloric acid in a

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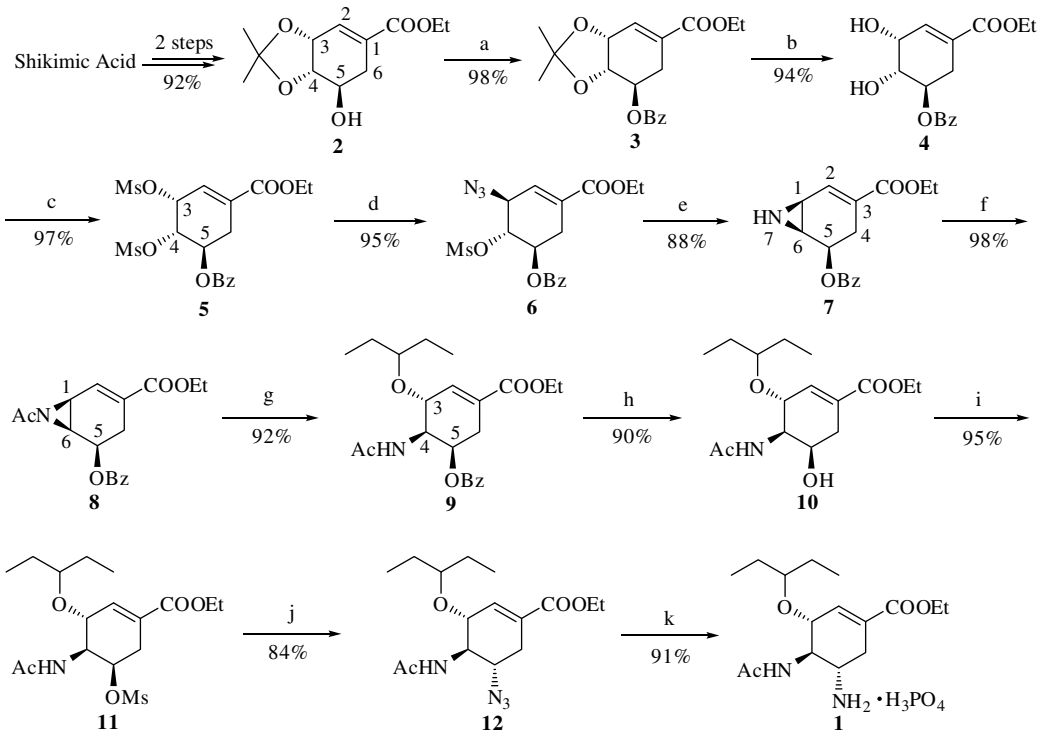

Scheme 1. Synthesis of Oseltamivir phosphate **1** starting from (−)-shikimic acid. Reagents and reaction conditions: (a) 1.3 equiv of benzoyl chloride, 2 equiv of Et_3N, cat. DMAP, 0 °C to rt for 5 h in CH_2Cl_2. (b) cat. HCl, rt for 6 h in EtOAc–H_2O (4:1). (c) 5 equiv of CH_3SO_2Cl, 4 equiv of Et_3N, cat. DMAP, 0 °C for 1 h in EtOAc. (d) 4 equiv of NaN_3, −5 °C to 0 °C for 1.5 h in DMF–H_2O (5:1). (e) 1.1 equiv of Ph_3P, rt for 2 h in THF; then 3 equiv of Et_3N, rt overnight in THF–H_2O (10:1). (f) 2 equiv of Ac_2O, 3 equiv of Et_3N, 0 °C for 0.5 h in EtOAc. (g) 1.5 equiv of $BF_3{\cdot}Et_2O$, −5 °C to 0 °C for 0.5 h in 3-pentanol. (h) 1.1 equiv of K_2CO_3, rt for 6 h in ethanol. (i) 2 equiv of CH_3SO_2Cl, 2 equiv of Et_3N, 0 °C for 1 h in CH_2Cl_2. (j) 4 equiv of NaN_3, 90 °C for 3 h in DMF–H_2O (5:1). (k) Lindlar catalyst, rt for 16 h under 1 atm. of H_2 in EtOH; then 1.2 equiv of H_3PO_4, 50 °C for 0.5 h in EtOAc–EtOH (1:1).

mixed solvent of ethyl acetate and water (4:1). Compound **4** was then treated with 5 equiv of methanesulfonyl chloride and 4 equiv of triethylamine in the presence of DMAP as a catalyst in ethyl acetate to furnish bismethanesulfonate **5** in 97% yield. It was found that the solvent ethyl acetate was obviously better than dichloromethane and chloroform here, and triethylamine worked also better than pyridine.

With bismethanesulfonate **5** in hand, we tried to replace the OMs group selectively at the C-3 position by a nitrogen nucleophile such as sodium azide or potassium azide, while keeping the OMs group at C-4 position intact. This could be done by exposing compound **5** to 4 equiv of sodium azide in aqueous *N*,*N*-dimethylformamide (DMF/H_2O = 5:1) at a lower temperature, and the monoazido compound **6** was thus obtained in 95% yield. The temperature for the reaction is crucial and should be kept in the range of −5 °C to 0 °C by a salt–ice bath. This nucleophilic substitution was quite clean, and almost no other diastereoisomer was detected by the careful HPLC analysis. The stereoselectivity and regioselectivity of the reaction are very high, and herein the *R* configuration of C-3 is inversed to the *S* configuration according to the Walden-type inversion. The highly selective attack of the azide anion (N_3^-) at C-3 position is reasonable, and can be easily understood because the C-3 position (the allylic position) is much more reactive and less hindered than the C-4 position (see also Fig. 2).

The compound **6** was successively treated with 1.1 equiv of triphenylphosphine, 3 equiv of triethylamine, and some water in tetrahydrofuran to give an aziridine **7** in 88% yield. In this transformation, reduction of the azido group and formation of the aziridine via an intramolecular nucleophilic substitution of the neighboring OMs group at C-4 position took place simultaneously, and meanwhile the (*R*)-configuration of C-4 is inversed to the (*S*)-configuration. Compound **7** was then immediately exposed to 2 equiv of acetic anhydride and to 3 equiv of triethylamine in ethyl acetate to form *N*-acetyl aziridine **8** almost quantitatively.

At this stage, the next step which we wanted to perform was the selective opening of aziridine **8** with the substitution of 1-ethyl propoxyl group at the allylic position (C-1 position). Compound **8** was then treated with 1.5 equiv of boron trifluoride etherate using 3-pentanol as solvent to afford a ring-opening product **9** in 92% yield. The Lewis acid-catalyzed ring-opening of aziridine **8** with 3-pentanol was achieved with regio- and stereoselectivity; the substitution of the 1-ethyl propoxyl group took place only at the C-1 position rather than at the C-6 position, and the (*S*)-configuration of C-1 in **8** was inversed to (*R*)-configuration at C-3 in **9**. The reaction temperature is also crucial here, it should be kept in the range of −5 °C to 0 °C, and the slow addition of boron trifluoride etherate was necessary because the reaction is exothermic. In this aziridine ring-opening reaction, the nucleophile (3-pentanol) approaches the face of the cyclohexene ring opposite to the benzoyl group at the C-5 position (see also Fig. 2). The high regioselectivity of this aziridine-opening reaction could be attributed to the large difference between the reactivities of both the C-1 and C-6 positions, with regards to the nucleophilic attack of 3-pentanol. The allylic position (C-1) is much more reactive than the non-allylic position (C-6), so the Lewis acid-catalyzed nucleophilic attack of 3-pentanol at allylic position was

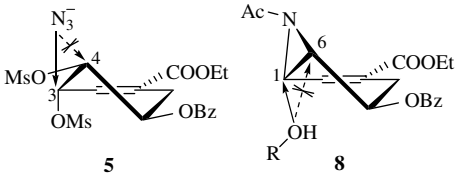

Figure 2. Regiospecific and stereospecific nucleophilic replacement of **5** and aziridine opening of **8**.

completely regiospecific. Kim et al. also observed exclusive regioselectivity in a similar aziridine-opening reaction.[1]

Alcoholysis of compound **9** in ethanol in the presence of 1.1 equiv of potassium carbonate gave compound **10** in 90% yield. Compound **10** was then treated with 2 equiv of methanesulfonyl chloride and with 2 equiv of trimethylamine in dichloromethane to produce methanesulfonate **11** in 95% yield. Compound **11** was treated with 4 equiv of sodium azide at an elevated temperature in aqueous *N*,*N*-dimethylformamide (DMF/H_2O = 5:1) to furnish an azide compound **12** in 84% yield. In this S_N2-type nucleophilic substitution, the OMs group at C-5 position of compound **11** was replaced by an azido group, and meanwhile the (*R*)-configuration of the C-5 is inversed to the (*S*)-configuration. It was found that the nucleophilic substitution did not work at all at room temperature, and it should be performed under heating conditions. In order to obtain a maximum yield, it was better to keep the reaction temperature between 85 °C and 95 °C. Actually, the large difference between the reaction temperatures of both nucleophilic substitutions of the OMs group at C-5 of compound **11** and the OMs group at C-3 of compound **5** by sodium azide is good evidence, which accounts for the exclusive regioselectivity of the nucleophilic substitution in the transformation of compound **5** to compound **6**.

Finally, azide compound **12** was reduced by hydrogenation in the presence of the Lindlar catalyst under an atmosphere of hydrogen gas to form an amine, which was directly exposed to 1.2 equiv of phosphoric acid in a mixed solvent of ethyl acetate and ethanol (1:1) to afford title compound **1** in 91% yield. Though the hydrogenation of the azido group was slow, it was quite clean. Using Raney-Ni as a catalyst also worked well here for the hydrogenation. When Pd/C was used as a catalyst, both the double bond and azido group were hydrogenated. The azido group of **12** can also be reduced by using triphenylphosphine as the reducing agent, but the yield was relatively lower.

3. Conclusion

An efficient and practical synthesis of oseltamivir phosphate **1** starting from a readily available compound **2** has been performed via 11 steps. The overall yield of the whole synthesis is 44% from compound **2** or 40% from natural material (−)-shikimic acid. The configuration of C-3 of compound **2** remains the same after double inversion, and the configurations of both C-4 and C-5 of compound **2** are inversed. The stereoselectivities are very high during these inversions. The inexpensive reagents used in all steps, ease of manipulation of every step, mildness of the reaction conditions for each step and high yields, make the synthesis attractive and potential to be developed as an industrial process in the future.

4. Experimental

4.1. General methods

Melting points are uncorrected. ^{1}H NMR spectra were acquired on Bruker AM-500. Chemical shifts were given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded on Nicolet Magna IR-550. Mass spectra were recorded on HP5989A. Column chromatography was performed on silica gel. Optical rotations of chiral compounds were measured on WZZ-1S automatic polarimeter at room temperature. All chemicals were analytically pure.

4.2. Ethyl (3*R*,4*S*,5*R*)-3,4-*O*-isopropylidene shikimate 2

Compound **2** was obtained as a colorless oil in 92% yield according to a known procedure.[12] $[\alpha]_D^{20} = -31$ (*c* 3.0, EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.30 (t, *J* = 7.1 Hz, 3H), 1.41 (s, 3H), 1.46 (s, 3H), 2.20–2.28 (m, 1H), 2.80 (dd, J_1 = 17.4 Hz; J_2 = 4.6 Hz, 1H), 3.84–3.93 (m, 1H), 4.10 (dd, J_1 = 7.1 Hz; J_2 = 6.8 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.73–4.78 (m, 1H), 6.92–6.94 (m, 1H). MS (*m*/*z*, relative intensity) 242 (M^+, 1), 227 (100), 197 (12), 167 (17), 137 (79), 121 (11), 110 (10), 95 (38), 43 (14). IR (KBr film) 3469, 2986, 2935, 1716, 1655, 1448, 1372, 1244, 1054, 860, 754 cm^{-1}.

4.3. Ethyl (3*R*,4*S*,5*R*)-5-*O*-benzoyl-3,4-*O*-isopropylidene shikimate 3

Compound **2** (6.40 g, 26.42 mmol), triethylamine (5.35 g, 52.87 mmol), and DMAP (161 mg, 1.32 mmol) were dissolved in dichloromethane (70 mL), and the solution was cooled to 0 °C by an ice bath. Benzoyl chloride (4.83 g, 34.36 mmol) was added dropwise in 10 min. The ice bath was removed, and mixture was then stirred and traced by TLC. After stirring was continued around 5 h, the reaction was complete. The solution was transferred into a separatory funnel and washed successively with dilute hydrochloric aqueous solution, potassium carbonate aqueous solution, and brine. Solvent was evaporated to give a crude oil, which was purified by chromatography to produce compound **3** (8.97 g, 25.90 mmol) in 98% yield. $[\alpha]_D^{25} = -55$ (*c* 3.4, EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.31 (t, *J* = 7.1 Hz, 3H), 1.41 (s, 3H), 1.44 (s, 3H), 2.51 (dd, J_1 = 17.9 Hz; J_2 = 6.3 Hz, 1H), 2.90 (dd, J_1 = 17.8 Hz; J_2 = 3.5 Hz, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 4.39 (dd, $J_1 = J_2$ = 6.2 Hz, 1H), 4.77–4.85 (m, 1H), 5.46 (dd, J_1 = 11.3 Hz; J_2 = 5.8 Hz, 1H), 6.93–6.99 (m, 1H), 7.43 (dd, $J_1 = J_2$ = 7.5 Hz, 2H), 7.52–7.59 (m, 1H), 8.02 (d, *J* = 8.2 Hz, 2H). HRMS (EI) calcd for $C_{19}H_{23}O_6$ (M+1): 347.1495. Found: 347.1483. IR (KBr film) 3042, 2979, 1722, 1633, 1600, 1450, 1260, 1112, 1058, 1032, 858, 716 cm^{-1}.

4.4. Ethyl (3*R*,4*R*,5*R*)-5-*O*-benzoyl shikimate 4

To a solution of compound **3** (8.97 g, 25.90 mmol) in ethyl acetate (20 mL) and water (5 mL) was added concentrated hydrochloric acid (3 mL). The mixture was stirred at room temperature and analyzed by TLC. After stirring was continued around 6 h, the reaction was complete. Ethyl acetate (80 mL) and water (50 mL) were added and stirred. The organic phase was separated and washed with potassium carbonate aqueous solution. Organic solution was dried over anhydrous $MgSO_4$, and then concentrated to dryness to give crude product as a pale yellow solid, which was collected on a Buchner funnel and rinsed with hexane. Recrystallization of the pale yellow solid in the mixed solvent of ethyl acetate and hexane (1:2) afforded compound **4** (7.46 g, 24.35 mmol) as white crystals in 94% yield, mp 128.8–129.2 °C, $[\alpha]_D^{25} = -122$ (*c* 2.7, EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.29 (t, *J* = 7.1 Hz, 3H), 2.50 (dd, J_1 = 17.2 Hz; J_2 = 6.0 Hz, 1H), 2.98 (dd, J_1 = 17.1 Hz; J_2 = 6.3 Hz, 1H), 3.22 (br s, 1H), 3.34 (br s, 1H), 4.04 (dd, $J_1 = J_2$ = 3.6 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.48–4.52 (m, 1H), 5.46–5.49 (m, 1H), 6.90–6.94 (m, 1H), 7.42 (dd, $J_1 = J_2$ = 7.9 Hz, 2H), 7.52–7.58 (m, 1H), 7.95–8.02 (m, 1H). MS (*m*/*z*, relative intensity) 306 (M^+, 1), 288 (2), 259 (3), 243 (3), 184 (57), 166 (4), 155 (5), 138 (12), 111 (8), 105 (100), 77 (13). IR (KBr film) 3302, 2950, 1725, 1709, 1600, 1450, 1279, 1253, 1132, 1100, 710 cm^{-1}. Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.74; H, 5.68.

4.5. Ethyl (3*R*,4*S*,5*R*)-5-*O*-benzoyl-3,4-*O*-bismethanesulfonyl shikimate 5

Compound **4** (7.80 g, 25.46 mmol) was dissolved in ethyl acetate (150 mL), and the solution was cooled to 0 °C by an ice bath. Methanesulfonyl chloride (14.57 g, 127.30 mmol) and DMAP (156 mg, 1.28 mmol) were added, and then triethylamine (10.31 g, 101.89 mmol) was added dropwise within 10 min. After addition,

the stirring was continued for 1 h, TLC showed that the reaction was complete. Water (100 mL) was added, and the mixture was then transferred to a separatory funnel. The organic phase was separated and washed with potassium carbonate aqueous solution to pH 8. The organic solution was dried over anhydrous $MgSO_4$ and concentrated to dryness to give a crude oil, which was purified by chromatography to produce compound **5** (11.42 g, 24.69 mmol) in 97% yield. $[\alpha]_D^{25} = -135$ (*c* 1.9, EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J = 7.1 Hz, 3H), 2.60 (dd, J_1 = 19.0 Hz; J_2 = 6.6 Hz, 1H), 3.09 (s, 3H), 3.18 (s, 3H), 3.22 (dd, J_1 = 19.1 Hz; J_2 = 6.7 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 5.16 (dd, J_1 = 8.9 Hz; J_2 = 4.0 Hz, 1H), 5.52–5.72 (m, 2H), 6.83–6.98 (m, 1H), 7.47 (dd, $J_1 = J_2$ = 7.7 Hz, 2H), 7.58–7.63 (m, 1H), 8.03 (d, J = 7.5 Hz, 2H). MS (EI) calcd for $C_{18}H_{22}O_{10}S_2$: 462.0654. Found: 462.0654. IR (KBr film) 3031, 2979, 2944, 1722, 1658, 1600, 1453, 1180, 1110, 1032, 1174, 910, 716, 530 cm^{-1}.

4.6. Ethyl (3*S*,4*R*,5*R*)-3-azido-5-benzoyloxy-4-methanesulfonyloxy-cyclohex-1-ene-1-carboxylate 6

Compound **5** (11.50 g, 24.86 mmol) was dissolved in DMF (35 mL), and the solution was cooled to −5 °C by a salt–ice bath. A freshly prepared solution of sodium azide (6.60 g, 101.51 mmol) in a mixed solvent of DMF (40 mL) and water (15 mL) was added dropwise within 15 min. After the addition was finished, stirring was continued at −5 °C to 0 °C for 1.5 h. TLC showed that the reaction was complete. The reaction solution was then diluted with toluene (120 mL) and water (200 mL). The organic phase was separated, and then washed with water (30 mL) and brine (20 mL). The organic solution was dried over anhydrous Na_2SO_4. The solvent was then removed off by distillation under vacuum to give a crude oil, which gradually solidified as pale yellow crystals. The crystals were collected on a Buchner funnel and rinsed with aqueous methanol (methanol/water = 4/1) and hexane to afford compound **6** (9.67 g, 23.62 mmol) in 95% yield with 99.5% purity (HPLC analysis: 20RBAX-C18 column, 4.6 × 250 mm; mobile phase: acetonitrile/water = 45/55), mp 90.3–90.7 °C, $[\alpha]_D^{25} = -27$ (*c* 2.8, EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.1 Hz, 3H), 2.48–2.61 (m, 1H), 3.07 (s, 3H), 3.21 (dd, J_1 = 18.0 Hz; J_2 = 6.0 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 4.36–4.46 (m, 1H), 4.97 (dd, J_1 = 10.0 Hz; J_2 = 8.1 Hz, 1H), 5.34–5.48 (m, 1H), 6.76–6.81 (m, 1H), 7.46 (dd, $J_1 = J_2$ = 7.8 Hz, 2H), 7.54–7.62 (m, 1H), 8.11 (d, J = 8.3 Hz, 2H). MS (*m*/*z*, relative intensity) 367 ($M^+ - N_3$, 5), 336 (1), 308 (1), 285 (1), 257 (1), 245 (2), 217 (2), 199 (2), 180 (6), 163 (4), 152 (14), 124 (5), 105 (100), 77 (15). IR (KBr film) 2979, 2940, 2133, 1720, 1658, 1600, 1450, 1342, 1263, 1168, 1119, 1011, 969, 711, 513 cm^{-1}. Anal. Calcd for $C_{17}H_{19}N_3O_7S$: C, 49.87; H, 4.68; N, 10.26. Found: C, 50.21; H, 4.38; N, 9.98.

4.7. Ethyl (1*S*,5*R*,6*S*)-5-benzoyloxy-7-aza-bicyclo[4,1,0]hept-2-ene-3-carboxylate 7

To a solution of compound **6** (2.00 g, 4.88 mmol) in THF (50 mL) was added triphenylphosphine (1.41 g, 5.38 mmol). Stirring was continued at room temperature for 2 h, and then triethylamine (1.48 g, 14.63 mmol) and water (5 mL) were added. The resulting mixture was stirred at room temperature overnight. The reaction solution was concentrated under vacuum to remove THF, and the residue was partitioned between ethyl acetate (60 mL) and water (30 mL). The organic phase was separated and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by chromatography to give compound **7** (1.236 g, 4.30 mmol) as a pale yellow oil in 88% yield. $[\alpha]_D^{25} = -63$ (*c* 0.8, EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.17 (br s, NH, 1H), 1.29 (t, J = 7.1 Hz, 3H), 2.40–2.49 (m,1H), 2.69–2.79 (m, 1H), 2.83–3.12 (m, 2H), 4.20 (q, J = 7.1 Hz, 2H), 5.29–5.38 (m, 1H), 7.15–7.24 (m, 1H), 7.46 (dd, $J_1 = J_2$ = 7.8 Hz, 2H), 7.58 (dd, $J_1 = J_2$ = 7.4 Hz, 1H), 8.11 (d, J = 7.6 Hz, 2H). HRMS (EI) calcd for $C_{16}H_{17}NO_4$: 287.1158. Found: 287.1165. IR (KBr film) 3302, 2979, 1710, 1650, 1600, 1450, 1326, 1268, 1678, 1110, 1023, 987, 711, 684 cm^{-1}.

4.8. Ethyl (1*S*,5*R*,6*S*)-7-acetyl-5-benzoyloxy-7-aza-bicyclo[4,1,0]-hept-2-ene-3-carboxylate 8

Compound **7** (1.39 g, 4.84 mmol) and triethylamine (1.47 g, 14.53 mmol) were dissolved in ethyl acetate (60 mL), and the solution was cooled to 0 °C by an ice bath. Acetic anhydride (0.99 g, 9.70 mmol) was added, and stirring was continued at 0 °C for 30 min. TLC showed that the reaction was complete. Potassium carbonate aqueous solution was added to adjust the pH 9–10. The organic phase was separated and washed with brine. After the organic solution was dried over anhydrous $MgSO_4$, the solvent was evaporated under vacuum to give a crude oil, which was purified by chromatography to afford compound **8** (1.57 g, 4.77 mmol) in 98% yield. $[\alpha]_D^{25} = -41$ (*c* 1.6, EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.1Hz, 3H), 2.17 (s, 3H), 2.32–2.47 (m, 1H), 3.04–3.18 (m, 1H), 3.29 (dd, J_1 = 10.7 Hz; J_1 = 5.9 Hz, 1H), 3.36 (dd, J_1 = 6.1 Hz; J_2 = 4.1 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 5.29–5.40 (m, 1H), 7.15 (dd, $J_1 = J_2$ = 3.9 Hz, 1H), 7.49 (dd, $J_1 = J_2$ = 7.8 Hz, 2H), 7.61 (dd, $J_1 = J_2$ = 7.4 Hz, 1H), 8.11 (d, J = 7.3 Hz, 2H). HRMS (EI) calcd for $C_{18}H_{20}NO_5$ (M+1): 330.1341. Found: 330.1327. IR (KBr film) 2981, 1721, 1648, 1600, 1452, 1374, 1258, 1202, 1100, 910, 833, 712 cm^{-1}.

4.9. Ethyl (3*R*,4*R*,5*R*)-4-acetamido-5-benzoyloxy-3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxylate 9

A solution of compound **8** (1.60 g, 4.86 mmol) in 3-pentanol (10 mL) was cooled to −5 °C by a salt–ice bath. A freshly prepared solution of $BF_3{\cdot}OEt_2$ (1.04 g, 7.33 mmol) in 3-pentanol (5 mL) was added dropwise within 10 min, and stirring was further continued at −5 °C to 0 °C for around 0.5 h. The reaction mixture was diluted with ethyl acetate (50 mL), and potassium carbonate aqueous solution was added to adjust pH 9–10. The organic phase was separated and washed with brine. The aqueous solution was extracted once more with ethyl acetate (20 mL). The extracts were combined and dried over anhydrous $MgSO_4$. The organic solution was evaporated under vacuum to give the crude product, which was purified by chromatography to furnish compound **9** (1.87 g, 4.48 mmol) in 92% yield. $[\alpha]_D^{25} = -113$ (*c* 1.6, EtOAc). ^{1}H NMR ($CDCl_3$) δ 0.86–0.97 (m, 6H), 1.30 (t, J = 7.1 Hz, 3H), 1.48–1.64 (m, 4H), 2.00 (s, 3H), 2.58 (dd, J_1 = 19.0 Hz; J_2 = 5.8 Hz, 1H), 2.85–2.98 (m, 1H), 3.41–3.52 (m, 1H), 4.12–4.19 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.43–4.51 (m, 1H), 5.54–5.67 (m, 2H), 6.90–6.98 (m, 1H), 7.46 (dd, $J_1 = J_2$ = .9 Hz, 2H), 7.58 (dd, $J_1 = J_2$ = 7.4 Hz, 1H), 7.98 (d, J = 7.1 Hz, 2H). HRMS (EI) calcd for $C_{23}H_{31}NO_6$: 417.2151. Found: 417.2150. IR (KBr film) 3292, 2973, 1721, 1653, 1600, 1550, 1453, 1368, 1268, 1099, 712 cm^{-1}.

4.10. Ethyl (3*R*,4*R*,5*R*)-4-acetamido-3-(1-ethyl-propoxy)-5-hydroxy-cyclohex-1-ene-1-carboxylate 10

To a solution of compound **9** (1.70 g, 4.07 mmol) in absolute ethanol (30 mL) was added the powder of potassium carbonate (0.66 g, 4.78 mmol). The mixture was then well stirred at room temperature for around 6 h. After TLC showed that the reaction was complete, ethanol was removed by distillation under vacuum. The residue was then partitioned between ethyl acetate (50 mL) and water (30 mL). The organic phase was separated and washed was brine. The organic solution was dried over anhydrous $MgSO_4$. Removal of the solvent by rotavaporator gave the crude product as off-white crystals, which was collected on a Buchner funnel and rinsed with the mixed solvent of ethyl acetate and hexane (4:1) to furnish compound **10** (1.15 g, 3.67 mmol) in 90% yield, mp 131.9–132.2 °C, $[\alpha]_D^{25} = -104$ (*c* 3.0, EtOAc). ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.4 Hz, 6H), 1.29 (t, J = 7.1 Hz, 3H), 1.42–1.62 (m, 4H),

2.02 (s, 3H), 2.43 (dd, J_1 = 18.6 Hz; J_2 = 5.1 Hz, 1H), 2.53–2.71 (m, 1H), 3.33–3.45 (m, 1H), 3.90–3.98 (m, 1H), 4.06 (br s, NH, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.23–4.30 (m, 1H), 6.19–6.21 (m, 1H), 6.38 (s, 1H). MS (*m/z*, relative intensity) 314 (M^++1, 7), 313 (M^+, 2), 267 (11), 242 (13), 226 (21), 212 (55), 208 (39), 197 (19), 155 (46), 142 (100), 138 (47), 96 (77), 59 (12). IR (KBr film) 3490, 3335, 2969, 2917, 1703, 1642, 1544, 1465, 1374, 1309, 1250, 1105, 950 cm^{-1}. Anal. Calcd for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.47. Found: C, 61.31; H, 8.70; N, 4.37.

4.11. Ethyl (3*R*,4*S*,5*R*)-4-acetamido-3-(1-ethyl-propoxy)-5-methanesulfonyloxy -cyclohex-1-ene-1-carboxylate 11

Compound **10** (0.98 g, 3.13 mmol) and triethylamine (0.64 g, 6.32 mmol) were dissolved in dichloromethane (15 mL), and the solution was cooled to 0 °C by an ice bath. Methanesulfonyl chloride (0.72 g, 6.29 mmol) was added, and then the resulting solution was stirred at 0 °C for 1 h. After TLC showed that the reaction was complete, more dichloromethane (20 mL) and dilute potassium carbonate aqueous solution (2 M, 35 mL) were added. The organic phase was washed with brine and then dried over anhydrous $MgSO_4$. After the solvent was removed by a rotavaporator, the crude product was purified by chromatography to give compound **11** (1.17 g, 2.99 mmol) in 95% yield, mp 139.4–139.9 °C, $[\alpha]_D^{25} = -85$ (*c* 0.7, ethyl acetate). ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.5 Hz, 6H), 1.31 (t, J = 7.1 Hz, 3H), 1.43–1.58 (m, 4H), 2.02 (s, 3H), 2.73 (dd, J_1 = 19.1 Hz; J_2 = 4.4 Hz, 1H), 2.80–2.91 (m, 1H), 3.06 (s, 3H), 3.34–3.44 (m, 1H), 4.08 (d, J = 6.8 Hz, 1H), 4.23 (q, J = 7.1 Hz, 1H), 4.27–4.35 (m, 1H), 5.21 (dd, J_1 = 6.8 Hz; J_2 = 4.3 Hz, 1H), 6.03 (d, J = 8.0 Hz, 1H), 6.88 (s, 1H). MS (*m/z*, relative intensity) 392 (M^++1, 6), 345 (9), 320 (8), 304 (23), 222 (89), 212 (43), 208 (38), 166 (24), 152 (46), 142 (100), 136 (31), 110 (24), 96 (49). HRMS (EI) calcd for $C_{17}H_{30}NO_7S$ (M+1): 392.1743. Found: 392.1743. IR (KBr, film) 3306, 2969, 2940, 2875, 1720, 1653, 1541, 1343, 1255, 1178, 1199, 910, 530 cm^{-1}.

4.12. Ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-azido-3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxylate 12

To a solution of compound **11** (1.20 g, 3.06 mmol) in a mixed solvent of DMF (15 mL) and water (3 mL) was added sodium azide (0.80 g, 12.30 mmol). The mixture was heated to 90 °C and stirred at this temperature for 3 h, and TLC showed that the reaction was complete. After the reaction solution was cooled down to room temperature, toluene (50 mL) and water (45 mL) were added. The organic phase was separated and washed with water (20 mL) once more. The organic solution was dried over anhydrous Na_2SO_4, and then concentrated under vacuum to produce a crude oil, which was purified by chromatography to give compound **12** (0.87 g, 2.57 mmol) in 84% yield, mp 135.9–136.8 °C (lit.[11] 137–138 °C), $[\alpha]_D^{20} = -44$ (*c* 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.83–0.95 (m, 6H), 1.30 (t, J = 7.1 Hz, 3H), 1.42–1.58 (m, 4H), 2.04 (s, 3H), 2.23 (dd, J_1 = 17.5 Hz; J_2 = 10.5 Hz, 1H), 2.85 (dd, J_1 = 17.6 Hz; J_2 = 5.4 Hz, 1H), 3.27–3.40 (m, 1H), 3.46 (dd, J_1 = 18.6 Hz; J_2 = 8.4 Hz, 1 H), 4.08–4.27 (m, 3H), 4.50 (d, J = 8.3 Hz, 1H), 6.38 (d, J = 7.6 Hz, 1H), 6.78 (s, 1H). MS (*m/z*, relative intensity) 339 (M^++1, 5), 310 (3), 267 (45), 251 (48), 223 (50), 212 (80), 181 (69), 167 (49), 152 (44), 142 (100), 135 (37), 96 (61), 80 (20). IR (KBr, film) 3217, 2975, 2106, 1717, 1659, 1563, 1378, 1332, 1254, 1079 cm^{-1}.

4.13. Oseltamivir phosphate 1

To a three-necked flask which was equipped with an inlet and an outlet were added compound **12** (0.51 g, 1.51 mmol), ethanol (20 mL), and Lindlar catalyst (0.30 g). After the flask was purged with hydrogen gas several times, the mixture was well stirred at room temperature under an atmosphere of hydrogen gas for 16 h. TLC showed that the reaction was complete. The mixture was then filtered through a thin layer of Celite to remove the Lindlar catalyst. The solvent was concentrated to dryness, and a mixed solvent of ethyl acetate (5 mL) and ethanol (4 mL) was added. The solution was well stirred and warmed to 50 °C, and a freshly prepared solution of phosphoric acid (0.36 g, 85%, 1.80 mmol) in ethanol (1 mL) was added dropwise. After stirring was continued at 50 °C for 0.5 h, white crystals formed, and the suspension was cooled to room temperature. Filtration and rinsing with cooled acetone afforded compound **1** (0.57 g, 1.39 mmol) in 91% yield, mp 203.3–204.1 °C (lit.[11] 203–204 °C), $[\alpha]_D^{20} = -39$ (*c* 1, H_2O) {lit.[11] $[\alpha]_D^{20} = -40$ (*c* 1, H_2O)}. ^{1}H NMR (D_2O) δ 0.84 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.40–1.63 (m, 4H), 2.09 (s, 3H), 2.52 (dd, J_1 = 15.5 Hz; J_2 = 12.2 Hz, 1H), 2.97 (dd, J_1 = 17.1 Hz; J_2 = 4.7 Hz, 1H), 3.48–3.66 (m, 2H), 4.06 (dd, $J_1 = J_2$ = 10.1 Hz, 1H), 4.25 (dd, J_1 = 13.7 Hz; J_2 = 6.7 Hz, 1H), 4.34 (d, J = 8.3 Hz, 1H), 6.86 (s, 1H). MS (*m/z*, relative intensity) 314 (M+1+H^+, 7), 295 (1), 267 (11), 254 (11), 242 (13), 226 (21), 212 (55), 197 (19), 184 (19), 166 (10), 155 (46), 142 (100), 110 (20), 96 (77). HRMS (EI) calcd for $C_{16}H_{29}N_2O_4$ (M+H^+): 313.2127. Found: 313.2131. IR (KBr, film) 3354, 3249, 2969, 2938, 2875, 1621, 1558, 1547, 1374, 1130, 1067, 942 cm^{-1}. Anal. Calcd for $C_{16}H_{31}N_2O_8P$: C, 46.83; H, 7.61; N, 6.83. Found: C, 46.42; H, 7.68; N, 6.63.

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References

1. Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681.
2. Kim, C. U.; Lew, W.; Williams, M. A.; Wu, H.; Zhang, L.; Chen, X.; Escarpe, P. A.; Mendel, D. B.; Laver, W. G.; Stevens, R. C. *J. Med. Chem.* **1998**, *41*, 2451.
3. Schmidt, A. C. *Drugs* **2004**, *64*, 2031.
4. Moscona, A. *New Engl. J. Med.* **2005**, *353*, 1363.
5. Russell, R. J.; Haire, L. F.; Stevens, D. J.; Collins, P. J.; Lin, Y. P.; Blackburn, G. M.; Hay, A. J.; Gamblin, S. J.; Skehel, J. J. *Nature* **2006**, *443*, 45.
6. Farina, V.; Brown, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7330.
7. Laver, G.; Garman, E. *Science* **2001**, *293*, 1776.
8. Shibasaki, M.; Kanai, M. *Eur. J. Org. Chem.* **2008**, 1839.
9. Abrecht, S.; Harrington, P.; Iding, H.; Karpf, M.; Trussardi, R.; Wirz, B.; Zutter, U. *Chimia* **2004**, *58*, 621.
10. Abrecht, S.; Federspiel, M. C.; Estermann, H.; Fisher, R.; Karpf, M.; Mair, H.-J.; Oberhauser, T.; Rimmler, G.; Trussardi, R.; Zutter, U. *Chimia* **2007**, *61*, 93.
11. Rohloff, J. C.; Kent, K. M.; Postich, M. J.; Becker, M. W.; Chapman, H. H.; Kelly, D. E.; Lew, W.; Louie, M. S.; McGee, L. R.; Prisbe, E. J.; Schultze, L. M.; Yu, R. H.; Zhang, L. *J. Org. Chem.* **1998**, *63*, 4545.
12. Federspiel, M.; Fisher, R.; Henning, M.; Mair, H. J.; Oberhauser, T.; Rimmler, G.; Albiez, T.; Bruhin, J.; Estermann, H.; Gandert, C.; Gockel, V.; Gotzo, S.; Hoffmann, U.; Huber, G.; Janatsch, G.; Lauper, S.; Rockel-Stabler, O.; Trussardi, R.; Zwahlen, A. G. *Org. Process Res. Dev.* **1999**, *3*, 266.
13. Karpf, M.; Trussardi, R. *J. Org. Chem.* **2001**, *66*, 2044.
14. Harrington, P. J.; Brown, J. D.; Foderaro, T.; Hughes, R. C. *Org. Process Res. Dev.* **2004**, *8*, 86.
15. Cong, X.; Yao, Z.-J. *J. Org. Chem.* **2006**, *71*, 5365.
16. Shie, J.-J.; Fang, J.-M.; Wang, S.-Y.; Tasi, K.-C.; Cheng, Y.-S. E.; Yang, A.-S.; Hsiao, S.-C.; Su, C.-Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 11892.
17. Radatus, B. K.; Murthy, K. S. K.; Weeratunga, G.; Horne, S. E.; Kothakonda, K. K.; Wolf, E. C. G.; Wang, Z. *United States Patent* 2008/0009639.
18. Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310.
19. Kipassa, N. T.; Okamura, H.; Kina, K.; Hamada, T.; Iwagawa, T. *Org. Lett.* **2008**, *10*, 815.
20. Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5734.
21. Yamatsugu, K.; Kamijo, S.; Suto, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2007**, *48*, 1403.
22. Abrecht, S.; Karpf, M.; Trussardi, R.; Wirz, B. *United States Patent* 6,403,824.
23. Mita, T.; Fukuda, N.; Roca, F. X.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 259.
24. Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312.

25. Bromfield, K. M.; Graden, H.; Hagberg, D. P.; Olsson, T.; Kann, N. *Chem. Commun.* **2007**, 3183.
26. Zutter, U.; Iding, H.; Spurr, P.; Wirz, B. *J. Org. Chem.* **2008**, *73*, 4895.
27. Shie, J.-J.; Fang, J.-M.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5788.
28. Iding, H.; Wirz, B.; Zutter, U. *United States Patent* 6,518,048.
29. Draths, K. M.; Knop, D. R.; Frost, J. W. *J. Am. Chem. Soc.* **1999**, *121*, 1603.
30. Pittard, A. J. In *Escherichia coli and Salmonella: Cellular and Molecular Biology*; Neidhardt, F. C., Ed.; ASM Press: Washington, DC, 1996. Chapter 28.