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Synthesis of (−)-Oseltamivir Phosphate (Tamiflu) Starting from *cis*-2,3-Bis(hydroxymethyl)aziridine

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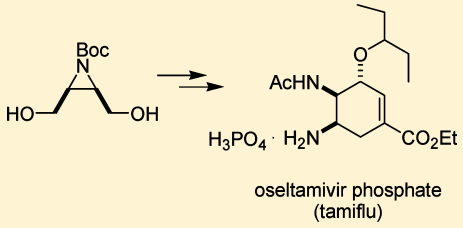
Supporting Information

ABSTRACT: Oseltamivir phosphate (Tamiflu) has been synthesized from *cis*-2,3-bis(hydroxymethyl)aziridine. After protection of the *cis*-2,3-bis-(hydroxymethyl)aziridine with a Boc group, desymmetrization provided a chiral aziridine, which was a key intermediate to install the required stereogenic center containing a nitrogen atom. Allylation and ring closing metathesis are the key reactions to obtain the cyclic product that was successfully converted to the desired oseltamivir phosphate.



Neuraminidase, responsible for cleaving sialic acid residues, is a popular target for developing anti-influenza drugs.[1] Oseltamivir (Tamiflu) and zanamivir (Relenza) were originally designed as transition state analogues according to the proposed mechanism of the action of neuraminidase. They are two of the most typical inhibitors for neuraminidase. The recent worldwide outbreak of swine flu (H1N1 human flu) and potential threat of avian flu have drawn attention to securing anti-influenza drugs in order to safeguard public health. Importantly, many countries are in need of a large stock of Tamiflu, which was first developed by Gilead Sciences, in order to prepare for a possible influenza outbreak. This recent global need for Tamiflu has led to intensive studies aimed at the development of new synthetic pathways for this neuraminidase inhibitor.[2] Thus far, many synthetic schemes utilizing readily available and inexpensive starting materials and key intermediates have been reported. Many of them already contain a cyclohexane ring or are linear materials that undergo cyclization at the later stage of the synthesis.

Aziridines are key intermediates useful for establishing stereogenic centers containing nitrogen atoms.[3] Since Tamiflu (oseltamivir) contains three stereogenic centers, two of which are attached to nitrogen atoms, this led us to examine a synthetic scheme in which an aziridine ring can be used to establish the stereogenic centers existing in Tamiflu. In fact, ring-opening of epoxide and/or aziridine intermediates has been employed for the purpose of introducing the nitrogen-containing stereogenic centers in previously reported syntheses of oseltamivir. Utilization of aziridines for the synthesis of oseltamivir was reported by Shibasaki et al. They used a synthetic pathway based on the asymmetric ring-opening of *N*-3,5-dinitrobenzoylaziridine with $TMSN_3$ in the presence of an yttrium catalyst.[4]

We were interested in the synthesis of oseltamivir utilizing an enantiomerically pure aziridine intermediate. We realized that *cis*-2,3-bis(hydroxymethyl)aziridine (**5**), which is a *meso* analogue and easily convertible to an enatiomerically pure starting material by enzymatic desymmetrization, could be used to secure the required stereogenic centers in oseltamivir phosphate.[5,6] Our retrosynthetic analysis is shown in Figure 1.

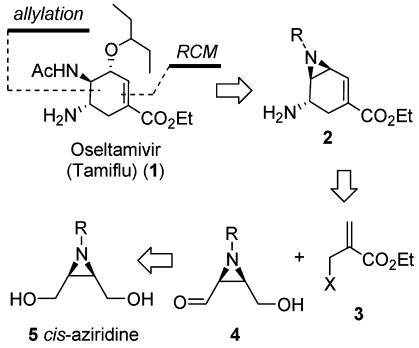


Figure 1. Retrosynthetic analysis of oseltamivir.

The target, oseltamivir (**1**), could be derived from cyclic aziridine **2**. This aziridine could, in principle, be synthesized by addition of an organometallic reagent derived from allyl halide **3** to an aldehyde **4** followed by ring-closing metathesis.[7] Aldehyde **4**, in turn, could be derived from *cis*-aziridine **5**.

Our plan for our asymmetric synthesis of oseltamivir (**1**) is based on enzymatic desymmetrization of *cis*-aziridinediol **5a**, which was prepared from protected aziridine **6**[5] through Boc-protection of nitrogen followed by deprotection of the hydroxyl groups using TBAF. Amano Lipase PS was best for our purpose[8] for the subsequent desymmetrization,[9] which successfully gave acetate **7** [$[\alpha]^{25}_{D}$ +16.8 (*c* 4.50, $CHCl_3$)]. The enatiomeric purity of **7** was determined after converting to **7a** (>99% *ee*). Protection of **7** with TBS group followed by hydrolysis provided alcohol **9**. Oxidation of alcohol **9** offered aldehyde **4a**. The next key step was allylation. Addition of the allylzinc reagent,[10] prepared by the reaction of Zn and allyl

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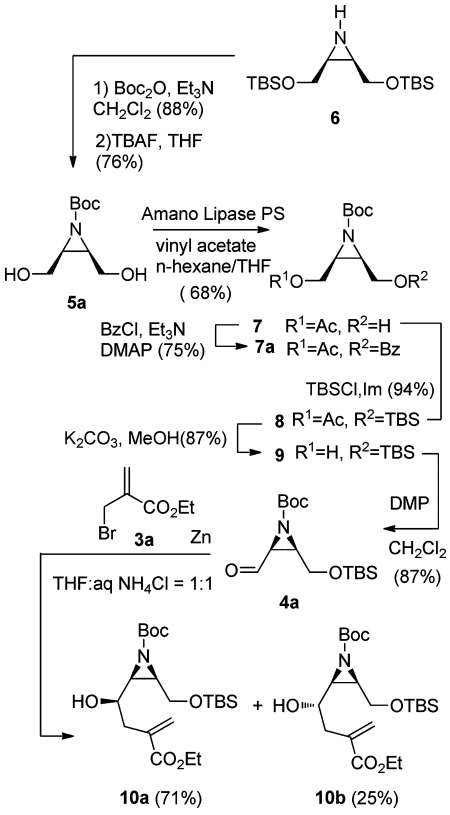
bromide **3a**, to aldehyde **4a** successfully produced homoallyl alcohols **10a** and **10b** in a ratio of ca. 3:1 (71 and 25% yield, respectively).

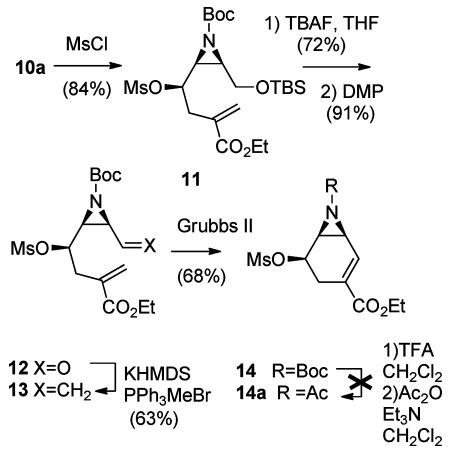
At this point, we hopefully assumed that the major isomer **10a** had the stereochemistry as shown in Scheme 1, although

Scheme 1. Synthesis of Homoallyl Alcohol 10



the stereochemistry was not confirmed until after it was converted to the final target. Nonetheless, **10a** was treated with MsCl to provide mesylate **11** (Scheme 2). The TBS group was removed to give the alcohol, which was oxidized to give aldehyde **12**. The Wittig reaction provided olefin **13**, which set the stage for the critical cyclization. Ring-closing metathesis using the second-generation Grubbs catalyst successfully provided the desired compound **14**, in 55% yield. The yield

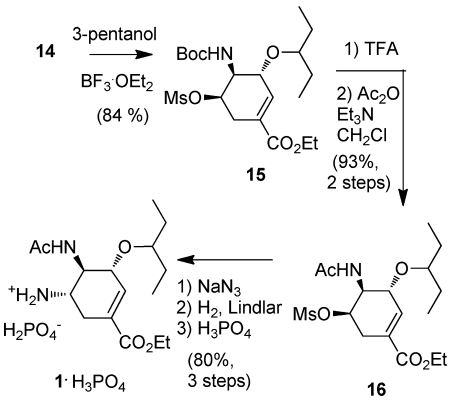
Scheme 2. Synthesis of 14



was increased to 68% after unreacted starting material was recovered and resubjected to RCM conditions. The second-generation Hoveyda–Grubbs catalyst[11] did not show improvement in the yield of this RCM reaction. An attempt to remove the Boc protection group (in order to replace it with an acetyl group) by exposure to acid (TFA, CH_2Cl_2) led to decomposition of the product, presumably resulting from a process involving opening of the aziridine ring, and this forced us to alter the synthetic route.

The aziridine ring in **14** was opened regioselectively with 3-pentanol in the presence of a Lewis acid, successfully producing **15** (Scheme 3). The Boc group was converted to an acetyl

Scheme 3. Completion of the Total Synthesis



group upon treating with TFA followed by Ac_2O. The product **16** exhibited spectral properties identical to those reported in the literature.[2b] This confirmed that **10a** obtained after allylation did in fact have the correct stereochemistry for the synthesis of oseltamivir. The total synthesis was completed according to the previously reported three-step pathway to give oseltamivir (**1**) as a phosphate salt, the spectroscopic properties of which were identical to those reported in the literature.[2h]

In conclusion, oseltamivir phosphate (Tamiflu) was successfully synthesized. The method relies on an aziridine ring, which was utilized to provide the required stereocenters, and an RCM reaction, which was employed to achieve the cyclization. The total synthesis shown here successfully opens another synthetic route for this important, biologically active compound.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR spectra were recorded on 400 or 500 MHz spectrometer at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. ^{13}C NMR spectra were recorded on 100 or 125 MHz spectrometer (with complete proton decoupling) at ambient temperature. High-resolution FAB mass spectra were recorded with a double-focusing magnetic sector mass spectrometer in positive ion mode. Flash chromatography was performed using 230–400 mesh silica gel.

(2*S*,3*R*)-*tert*-Butyl 2-(acetoxymethyl)-3-(hydroxymethyl)-aziridine-1-carboxylate (7). To a solution of *cis*-2,3-bis(*t*-butyldimethylsilyloxymethyl)aziridine (**6**)[5] (5.3 g, 16.0 mmol) in CH_2Cl_2 (50 mL) at 0 °C were added triethylamine (4.5 mL, 32.0 mmol) and di-*tert*-butyl dicarbonate (5.2 g, 24.0 mmol). The solution was stirred for 10 min at 0 °C before it was warmed to room temperature. After additional stirring for 2 h at room temperature aqueous saturated $NaHCO_3$ (30 mL) was added to the solution. The mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc = 7:1) offered the desired Boc-protected aziridine (6.10 g, 88%) as a colorless liquid: IR (film) 2929, 2857,

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1728, 1472, 1391, 1368, 1304, 1257, 1168, 1093, 1007, 939 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.02 (s, 6H), 0.85 (s, 18H), 1.38 (s, 9H), 2.57 (m, 2H), 3.58 (ddd, J = 1.4, 4.0, 11.4 Hz, 2H), 3.74 (ddd, J = 1.8, 4.2, 11.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 80.8, 61.4, 42.3, 27.8, 25.8, 18.2, −5.4, −5.5; HRMS (FAB) calcd for $C_{21}H_{45}NO_4Si_2$ + H 432.2965, found 432.2963.

To a stirred solution of the Boc-protected aziridine (6.10 g, 14.1 mmol), prepared in the preceding procedure, in dry THF (100 mL) at room temperature was added 1.0 M in THF solution of tetrabutylammonium fluoride (TBAF) (33.9 mL, 33.9 mmol) via a syringe. After 2 h, the reaction mixture was concentrated. Purification by flash chromatography (EtOAc) offered the desired *cis*-Boc-protected aziridine diol **5a** (2.2 g, 76%) as a colorless liquid: IR (film) 3369, 2975, 1716, 1459, 1369, 1304, 1158, 1046, 838, 785 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 9H), 2.62 (m, 2H), 2.75 (m, 2H), 3.78 (m, 2H), 4.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 81.6, 59.6, 41.5, 27.5; HRMS (FAB) calcd for $C_9H_{17}NO_4$ + H 204.1236, found 204.1232.

To a solution of Boc-protected aziridinediol **5a** (1.00 g, 4.92 mmol) in *n*-hexane/THF = 10:1 (55 mL) at room temperature were added vinyl acetate (2.26 mL, 24.6 mmol) and amano lipase PS (500 mg). The mixture was stirred for 3 h at 37 °C. After TLC showed that the reaction was completed, the mixture was filtered through a pad of Celite. The Celite pad was washed with EtOAc (3 × 10 mL). After the combined filtrate was concentrated, purification by flash chromatography (hexane/EtOAc = 4:1) offered the desired chiral aziridine **7** (818 mg, 68%) as a colorless liquid: $[\alpha]^{25}_D$ +16.8 (*c* 4.50, $CHCl_3$); IR (film) 3437, 2979, 1722, 1452, 1370, 1306, 1231, 1158, 1043, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 9H), 1.99 (s, 3H), 2.64 (m, 2H), 3.19 (bs, 1H), 3.54 (m, 1H), 3.74 (dq, J = 5.4, 12.1 Hz, 1H), 4.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 161.4, 81.5, 61.6, 59.7, 41.8, 38.8, 27.5, 20.5; HRMS (FAB) calcd for $C_{11}H_{19}NO_5$ + H 246.1341, found 246.1344.

(2*S*,3*R*)-*tert*-Butyl 2-(acetoxymethyl)-3-(benzoyloxymethyl)-aziridine-1-carboxylate (7a). To a solution of *cis*-chiral aziridine **7** (8.0 mg, 0.033 mmol) in CH_2Cl_2 (3 mL) at 0 °C were added DMAP (2.1 mg, 0.017 mmol), triethylamine (7.0 μL, 0.050 mmol) and benzoyl chloride (5.0 μL, 0.043 mmol). The solution was stirred for 20 min at 0 °C before it was warmed to room temperature. After additional stirring for 2 h at room temperature aqueous saturated NH_4Cl (5 mL) was added to the solution. The mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc = 4:1) offered the desired Bz-protected aziridine (9.0 mg, 75%) as a colorless liquid. The *ee* of **7a** was determined by chiral HPLC: Chiralcel OD-H column, *n*-hexane/2-propanol = 95:5, 0.5 mL min^{-1}, 40 °C $_{isothermal}$; $\lambda_{detector}$ = 229 nm; Retention times t_R = 16.4 min (major), t_R = 19.0 min (minor) [major/minor = 99.9:0.1 → (>99% *ee*)] $[\alpha]^{30}_D$ +0.60 (*c* 0.90, $CHCl_3$); IR (film) 2977, 2928, 1727, 1602, 1452, 1369, 1271, 1158, 1113, 1039, 979 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.06 (s, 3H), 2.87 (q, J = 6.4 Hz, 1H), 2.96 (q, J = 6.4 Hz, 1H), 4.19 (dd, J = 6.2, 12.0 Hz, 1H), 4.27 (dd, J = 6.6, 12.0 Hz, 1H), 4.42 (dd, J = 2.1, 6.7 Hz, 2H), 7.45 (m, 2H), 7.58 (m, 1H), 8.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 166.2, 161.1, 133.2, 129.7, 129.7, 128.4, 81.9, 62.6, 62.1, 38.9, 38.7, 27.8, 20.7; HRMS (ESI) calcd for $C_{11}H_{23}NO_6$ + Na 372.1418, found 372.1422.

(2*S*,3*R*)-*tert*-Butyl 2-(acetoxymethyl)-3-((*tert*-butyldimethylsilyloxy)methyl)aziridine-1-carboxylate (8). To a stirred solution of the chiral aziridine **7** (810 mg, 3.30 mmol) in CH_2Cl_2 (10 mL) were added imidazole (337 mg, 4.95 mmol) and TBSCl (597 mg, 3.96 mmol) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C before it was warmed to room temperature. After additional stirring for 1 h at room temperature aqueous saturated NaCl (10 mL) was added to the solution. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc = 7:1) offered the desired TBS-protected aziridine **8** (1.01 g, 94%) as a colorless oil: $[\alpha]^{22}_D$ +18.0 (*c* 1.30, $CHCl_3$); IR (film) 2929, 2856, 1727, 1465, 1369, 1304, 1230, 1159, 1097, 1038, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 1.42 (s, 9H), 2.07 (s, 3H), 2.66 (m, 1H), 2.74 (m, 1H), 3.56 (dd, J = 6.5, 11.4 Hz, 1H), 3.86 (dd, J = 5.5, 11.4 Hz, 1H), 4.06 (dd, J = 7.2, 11.9 Hz, 1H), 4.18 (dd, J = 5.3, 11.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 161.5, 81.3, 62.2, 61.1, 42.0, 38.8, 27.7, 25.7, 20.7, 18.1, −5.4, −5.5; HRMS (FAB) calcd for $C_{17}H_{33}NO_5Si$ + H 360.2206, found 360.2202.

(2*R*,3*S*)-*tert*-Butyl 2-((*tert*-butyldimethylsilyloxy)methyl)-3-(hydroxymethyl)aziridine-1-carboxylate (9). To a solution of TBS-protected aziridine **8** (1.36 g, 3.78 mmol) in methanol (15 mL) was added potassium carbonate (K_2CO_3) (627 mg, 4.54 mmol) at room temperature, and the solution was stirred for 2 h at room temperature. After reaction was completed, aqueous saturated NH_4Cl solution (15 mL) was added. The mixture was extracted with ether (3 × 10 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc = 7:1) offered the alcohol **9** (1.04 g, 87%) as a colorless oil: $[\alpha]^{21}_D$ +22.7 (*c* 1.52, $CHCl_3$); IR (film) 3435, 2936, 1727, 1467, 1368, 1303, 1161, 1094, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 3H), 010 (s, 3H), 0.89 (s, 9H), 1.44 (s, 9H), 2.50 (m, 1H), 2.74 (m, 2H), 3.51 (dd, J = 8.1, 11.5 Hz, 1H), 3.56 (ddd, J = 4.4, 7.2 12.0 Hz, 1H), 3.89 (ddd, J = 5.5, 9.0, 12.0 Hz, 1H), 4.09 (dd, J = 5.3, 11.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 81.6, 61.6, 60.8, 41.6, 41.2, 27.8, 18.2, −5.4, −5.5; HRMS (FAB) calcd for $C_{15}H_{31}NO_4Si$ + H 318.2101, found 318.2103.

(2*R*,3*S*)-1-*tert*-Butyl 2-((*tert*-butyldimethylsilyloxy)methyl)-3-formylaziridine-1-carboxylate (4a). The alcohol **9** (1.62 g, 5.10 mmol) was dissolved in CH_2Cl_2 (50 mL). To this solution was added Dess−Martin periodinane (DMP) (4.30 g, 10.2 mmol). The resulting solution was stirred for 2 h at room temperature. After the reaction was completed, aqueous saturated $NaHCO_3$ (30 mL) and aqueous saturated $Na_2S_2O_3$ (15 mL) were added. The mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc = 7:1) offered the desired aldehyde **4a** (1.40 g, 87%) as a colorless oil: $[\alpha]^{22}_D$ −70.8 (*c* 1.32, $CHCl_3$); IR (film) 2931, 2857, 1729, 1472, 1392, 1368, 1293, 1256, 1159, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.83 (s, 9H), 1.41 (s, 9H), 2.90 (m, 1H), 2.98 (dd, J = 4.8, 6.9 Hz, 1H), 3.79 (dd, J = 4.4, 11.7 Hz, 1H), 3.91 (dd, J = 4.3, 11.7 Hz, 1H), 9.33 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 160.3, 82.3, 60.1, 45.8, 45.0, 27.7, 25.7, 18.2, −5.6; HRMS (FAB) calcd for $C_{15}H_{29}NO_4Si$ + H 316.1944, found 316.1945.

(2*R*,3*S*)-*tert*-Butyl 2-((*tert*-butyldimethylsilyloxy)methyl)-3-((*R*)-3-(ethoxycarbonyl)-1-hydroxybut-3-en-1-yl)aziridine-1-carboxylate (10a) and (2*R*,3*S*)-*tert*-Buyl 2-((*tert*-butyldimethylsilyloxy)methyl)-3-[(*S*)-3-(ethoxycarbonyl)-1-hydroxybut-3-en-1-yl]aziridine-1-carboxylate (10b). To a solution of aldehyde **4a** (1.40 g, 4.44 mmol) in a mixture of THF (30 mL) and aqueous saturated NH_4Cl (30 mL) were added zinc dust (844 mg, 13.3 mmol) and ethyl 3-bromomethylacrylate (**3a**) (2.57 g, 13.3 mmol) at 0 °C. The mixture was stirred for 4 h at 0 °C and then diluted with ether (30 mL) and water (30 mL). The mixture was extracted with ether (3 × 30 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc = 4:1) offered the desired alcohol **10a** (1.35 g, 71%) and alcohol **10b** (480 mg, 25%) as a colorless oil. **10a**: $[\alpha]^{21}_D$ +13.1 (*c* 1.73, $CHCl_3$); IR (film) 3460, 2937, 2364, 1719, 1629, 1467, 1368, 1302, 1264, 1161, 950, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ - 0.04 (s, 3H), - 0.03 (s, 3H), 0.77 (s, 9H), 1.14 (t, J = 7.1 Hz, 3H), 1.31 (s, 9H), 2.38 (dd, J = 6.5, 8.6 Hz, 1H), 2.48 (dd, J = 8.4, 14.6 Hz, 1H), 2.57 (q, J = 6.2 Hz, 1H), 2.73 (dd, J = 3.6, 14.7 Hz, 1H), 3.14 (d, J = 2.0 Hz, 1H), 3.50 (m, 2H), 3.91 (dd, J = 6.0, 11.4 Hz, 1H), 4.07 (dq, J = 1.3, 7.1 Hz, 2H), 5.66 (d, J = 1.0 Hz, 1H), 6.14 (d, J = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 161.2, 136.5, 127.1, 80.9, 68.7, 61.7, 60.4, 44.7, 41.3, 37.2, 27.5, 25.5, 17.9, 13.8, −5.7, −5.8; HRMS (FAB) calcd for $C_{21}H_{39}NO_6Si$ + H 430.2625, found 430.2622. **10b**: $[\alpha]^{21}_D$ +0.44 (*c* 1.66, $CHCl_3$); IR (film) 3451, 2930, 2857, 1720, 1631, 1472, 1392, 1368, 1302, 1255, 1159, 1082, 942 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.05 (s, 3H), −0.03 (s, 3H), 0.78 (s, 9H), 1.17 (t, J = 7.1 Hz, 3H), 1.33 (s, 9H), 2.43 (m, 2H), 2.56 (m, 2H), 2.70 (bs, 1H), 3.58 (m, 2H), 3.70 (dd, J = 6.2, 11.4 Hz, 1H), 4.08 (q, J = 7.1 Hz, 2H), 5.62

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(d, J = 1.1 Hz, 1H), 6.15 (d, J = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 161.6, 136.3, 127.4, 81.0, 67.7, 61.1, 60.4, 45.8, 42.8, 37.5, 27.6, 25.6, 17.9, 13.9, −5.6, −5.7; HRMS (FAB) calcd for $C_{21}H_{39}NO_6Si$ + H 430.2625, found 430.2621.

(2*R*,3*S*)-1-*tert*-Butyl 2-((*tert*-butyldimethylsilyloxy)methyl)-3-((*R*)-3-(ethoxycarbonyl)-1-(methanesulfonyloxy)but-3-en-1-yl)-aziridine-1-carboxylate (11). To a stirred solution of the alcohol **10a** (1.35 g, 3.14 mmol) in CH_2Cl_2 (50 mL) were added triethylamine (1.53 mL, 11.0 mmol) and methanesulfinyl chloride (0.73 mL, 9.42 mmol) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C before it was warmed to room temperature. After additional stirring for 2 h at room temperature water (50 mL) was added to the solution. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc = 4:1) offered the desired Ms-protected aziridine **11** (1.33 g, 84%) as a colorless oil: $[\alpha]^{22}_D$ −1.55 (c 1.33, $CHCl_3$); IR (film) 2937, 1713, 1630, 1518, 1337, 1186, 1044, 964, 915 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.89 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H), 1.44 (s, 9H), 2.71 (m, 3H), 3.00 (s, 3H), 3.02 (m, 1H), 3.82 (m, 2H), 4.21 (dq, J = 2.5, 7.2 Hz, 2H), 4.73 (ddd, J = 3.6, 7.4, 9.4 Hz, 1H), 5.78 (s, 1H), 6.32 (d, J = 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 161.2, 134.9, 129.0, 81.6, 77.0, 61.0, 60.8, 43.4, 42.7, 38.6, 36.8, 27.7, 25.8, 18.2, 14.0, −5.4, −5.5; HRMS (FAB) calcd for $C_{22}H_{41}NO_8SSi$ + H 508.2400, found 508.2402.

(2*S*,3*R*)-*tert*-Butyl 2-((*R*)-3-(ethoxycarbonyl)-1-(methanesulfonyloxy)but-3-en-1-yl)-3-formylaziridine-1-carboxylate (12). To a stirred solution of Ms-protected aziridine **11** (1.33 g, 2.62 mmol) in dry THF (50 mL) at 0 °C was added tetrabutylammonium fluoride (TBAF) [5.24 mL (1.0 M in THF), 5.24 mmol] via a syringe. After 2 h, the reaction mixture was concentrated. Purification by flash chromatography (hexane/EtOAc = 2:1) offered the desired alcohol (744 mg, 72%) as a colorless oil: $[\alpha]^{22}_D$ +1.78 (c 1.23, $CHCl_3$); IR (film) 3400, 2979, 1718, 1511, 1369, 1258, 1172, 1090, 1061, 944, 859 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, J = 7.1 Hz, 3H), 1.35 (s, 9H), 2.62−2.73 (m, 3H), 2.86 (bs, 1H), 2.93 (s, 3H), 2.98 (m, 1H), 3.54 (m, 1H), 3.81 (m, 1H), 4.13 (m, 2H) 4.65 (ddd, J = 3.5, 9.2, 9.2 Hz, 1H), 5.72 (s, 1H), 6.24 (d, J = 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 160.9, 134.8, 128.9, 81.7, 76.2, 60.7, 59.3, 43.1, 43.0, 38.1, 36.6, 27.5, 13.9; HRMS (FAB) calcd for $C_{16}H_{27}NO_8S$ + Na 416.1355, found 416.1352.

The alcohol (744 mg, 1.89 mmol), prepared in the preceding procedure, was dissolved in CH_2Cl_2 (40 mL). To this solution was added Dess−Martin periodinane (DMP) (1.60 g, 3.78 mmol). The resulting solution was stirred for 2 h at room temperature. After the reaction was completed, aqueous saturated $NaHCO_3$ (20 mL) and aqueous saturated $Na_2S_2O_3$ (10 mL) were added. The mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc = 2:1) offered the desired aldehyde **12** (670 mg, 91%) as a colorless oil: $[\alpha]^{20}_D$ +48.6 (c 1.54, $CHCl_3$); IR (film) 2982, 1727, 1633, 1368, 1293, 1156, 919, 848 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3H), 1.38 (s, 9H), 2.67 (dd, J = 9.1, 14.5 Hz, 1H), 2.87 (s, 3H), 2.94 (t, J = 7.1 Hz, 1H), 2.98 (m, 1H), 3.16 (dd, J = 4.1, 6.4 Hz, 1H), 4.17 (m, 2H), 4.72 (ddd, J = 3.9, 7.3, 9.1 Hz, 1H), 5.74 (d, J = 0.5 Hz, 1H), 6.28 (d, J = 0.9 Hz, 1H), 9.37 (d, J = 4.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.3, 166.0, 159.1, 134.2, 129.5, 83.0, 75.7, 60.9, 45.2, 45.0, 38.1, 36.3, 27.5, 13.9; HRMS (FAB) calcd for $C_{16}H_{25}NO_8S$ + H 392.1379, found 392.1382.

(2*S*,3*S*)-*tert*-Butyl 2-((*R*)-3-(ethoxycarbonyl)-1-(methanesulfonyloxy)but-3-en-1-yl)-3-vinylaziridine-1-carboxylate (13). To a solution of methyltriphenylphosphonium bromide (1.83 g, 5.13 mmol) in THF (15 mL) was added potassium bis(trimethylsilyl)amide (KHMDS) (10.26 mL (0.5 M in toluene), 5.13 mmol), and the mixture was stirred for 30 min at −20 °C. After dropwise addition of a solution of aldehyde **12** (670 mg, 1.71 mmol) in THF (3 mL) to the above solution via cannula, the reaction mixture was stirred for 3 h at −20 °C. After the reaction was completed, aqueous saturated NH_4Cl (20 mL) was added. The mixture was extracted with ether (3 × 20 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc = 4:1) offered the desired vinylaziridine **13** (420 mg, 63%) as a colorless oil: $[\alpha]^{20}_D$ +25.1 (c 1.33, $CHCl_3$); IR (film) 2979, 2932, 1717, 1629, 1502, 1338, 1246, 1175, 1094, 957 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3H), 1.41 (s, 9H), 2.71 (m, 2H), 2.89 (s, 3H), 2.99 (dd, J = 3.3, 14.6 Hz, 1H), 3.10 (t, J = 6.0 Hz, 1H), 4.17 (m, 2H), 4.60 (ddd, J = 3.6, 8.2, 9.4 Hz, 1H), 5.35 (d, J = 11.0 Hz, 1H), 5.44 (d, J = 17.0 Hz, 1H), 5.74 (s, 1H), 5.80 (ddd, J = 5.9, 10.4, 16.8 Hz, 1H), 6.28 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 161.1, 134.9, 131.0, 128.9, 120.1, 81.7, 76.4, 60.8, 44.5, 43.4, 38.5, 36.6, 27.7, 14.0; HRMS (FAB) calcd for $C_{17}H_{27}NO_7S$ + Na 412.1406, found 412.1402.

Ethyl (1*S*,5*R*,6*S*)-7-(*tert*-butoxycarbonyl)-5-(methanesulfonyloxy)-7-azabicyclo[4.1.0]hept-2-ene-3-carboxylate (14). To a stirred solution of vinylaziridine **13** (44 mg, 0.12 mmol) in dry CH_2Cl_2 (10 mL) at at room temperature was added Grubbs catalyst (second generation) (10 mg, 0.012 mmol), producing a light brown solution, which was stirred for 18 h at 40 °C. The mixture was then concentrated. Purification by flash chromatography (hexane/EtOAc = 4:1) offered the desired aziridine **14** (24 mg, 55%) as a brown oil: $[\alpha]^{22}_D$ −8.29 (c 1.62, $CHCl_3$); IR (film) 2980, 2940, 1711, 1360, 1291, 1256, 1175, 1078, 951 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 1.44 (s, 9H), 2.37 (ddd, J = 3.4, 10.2, 13.6 Hz, 1H), 3.03 (ddd, J = 1.8, 6.7, 8.5 Hz, 1H), 3.10 (dd, J = 4.7, 6.3 Hz, 1H), 3.17 (s, 3H), 3.35 (td, J = 2.0, 6.4 Hz, 1H), 4.19 (dq, J = 1.4, 7.2 Hz, 2H), 4.98 (ddd, J = 2.3, 6.7, 9.0 Hz, 1H), 7.09 (dd, J = 3.5, 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 160.4, 132.6, 131.2, 82.5, 75.1, 61.1, 40.7, 39.3, 36.0, 27.7, 26.5, 14.1; HRMS (FAB) calcd for $C_{15}H_{23}NO_7S$ + Na 384.1093, found 384.1095.

Ethyl (3*R*,4*S*,5*R*)-4-(*tert*-butoxycarbonylamino)-3-(1-ethylpropoxy)-5-(methanesulfonyloxy)cyclohex-1-ene-1-carboxylate (15). To a stirred solution of aziridine **14** (60 mg, 0.17 mmol) in 3-pentanol (5 mL) at −8 °C was added BF_3·OEt_2 (31 μL, 0.25 mmol) in 3-pentanol (2 mL) via a syringe. The reaction mixture was stirred for 1 h at −8 °C. The mixture was diluted with EtOAc (10 mL) and an aqueous solution of potassium carbonate (15% w/v, 10 mL). The organic phase was separated and washed with water (5 mL) and brine (5 mL). The organic layer was dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc = 4:1) offered the compound **15** (62 mg, 84%) as a white solid: mp 157−158.5 °C; $[\alpha]^{19}_D$ −75.4 (c 1.52, $CHCl_3$); IR (film) 3363, 2968, 2929, 1720, 1681, 1523, 1459, 1344, 1259, 1173, 1066, 984 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89−0.94 (m, 6H), 1.29 (t, J = 7.1 Hz, 3H), 1.43 (s, 9H), 1.49−1.55 (m, 4H), 2.76 (m, 2H), 3.04 (s, 3H), 3.39 (m, 1H), 3.99 (m, 2H), 4.21 (q, J = 7.1 Hz, 2H), 4.77 (bd, J = 4.1 Hz, 1H), 5.22 (bs, 1H), 6.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 155.4, 136.5, 127.8, 82.4, 80.2, 77.6, 72.8, 61.1, 52.8, 38.8, 29.6, 29.3, 28.3, 26.3, 26.0, 14.1, 9.6, 9.3; HRMS (FAB) calcd for $C_{20}H_{35}NO_8S$ + Na 472.1981, found 472.1981.

Ethyl (3*R*,4*S*,5*R*)-4-(acetamido)-3-(1-ethylpropoxy)-5-(methanesulfonyloxy)cyclohex-1-ene-1-carboxylate (16). The compound **15** (51 mg, 011 mmol) was dissolved in CH_2Cl_2 (10 mL) at 0 °C. To this solution was added TFA (168 μL, 2.26 mmol). The resulting solution was stirred for 1 h at 0 °C, before it was warmed to room temperature. After additional stirring for 18 h at room temperature, the solution was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) at 0 °C. To this solution were added triethylamine (78 μL, 0.57 mmol) and acetic anhydride (16 μL, 0.17 mmol). The solution was stirred for 10 min at 0 °C before it was warmed to room temperature. After additional stirring for 3 h at room temperature, the reaction mixture was concentrated. Purification by flash chromatography (hexane/EtOAc = 4:1) offered the desired acetyl-protected **16** (41 mg, 93%) as a white solid: mp 137−138.5 °C; $[\alpha]^{24}_D$ −82.6 (c 1.20, EtOAc); IR (film) 3298, 2967, 2932, 1716, 1650, 1543, 1344, 1260, 1175, 1098, 1042, 906 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, J = 7.4 Hz, 6H), 1.31 (t, J = 7.1 Hz, 3H), 1.49−1.59 (m, 4H), 2.03 (s, 3H), 2.70 (m, 1H), 2.86 (m, 1H), 3.05 (s, 3H), 3.39 (m, 1H), 4.07 (m, 1H), 4.24 (q, J = 7.1 Hz, 2H), 4.32 (ddd, J = 2.4, 8.0, 10.4 Hz, 1H), 5.25 (ddd, J = 2.5, 4.4, 6.9, 1H), 5.72 (d, J = 8.0, 1H), 6.88 (s, 1H); ^{13}C NMR (125

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MHz, $CDCl_3$) δ 170.5, 165.7, 136.9, 127.6, 82.3, 77.9, 72.5, 61.2, 51.6, 38.7, 29.7, 26.3, 25.9, 23.3, 14.2, 9.5, 9.4; HRMS (FAB) calcd for $C_{17}H_{30}NO_7S$ + H 392.1743, found 392.1745.

Oseltamivir Phosphate (1). To a solution of compound **16** (40 mg, 0.10 mmol) in a mixture of DMF (5 mL) and water (1 mL) was added sodium azide (26 mg, 0.40 mmol). The mixture was heated to 90 °C and stirred at this temperature for 18 h. After the reaction solution was cooled down to room temperature, toluene (15 mL) and water (15 mL) were added. The organic phase was separated and washed with water (5 mL). The organic layer was dried (Na_2SO_4) and concentrated. Purification by flash chromatography (hexane/EtOAc = 4:1) offered the desired azide (32 mg, 94%) as a white solid: mp 138−139 °C; $[\alpha]^{21}_D$ −44.7 (*c* 0.83, $CHCl_3$); IR (film) 3726, 2969, 2100, 1718, 1659, 1554, 1455, 1315, 1312, 1254, 1084 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.4 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.46−1.54 (m, 4H), 2.03 (s, 3H), 2.22 (m, 1H), 2.85 (dd, *J* = 5.3, 17.3 Hz, 1H), 3.33 (m, 2H), 4.20 (m, 2H), 4.25 (ddd, *J* = 5.8, 10.6, 16.6 Hz, 1H), 4.55 (m, 1H), 6.03 (bs, 1H), 6.77 (t, *J* = 2.3, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 165.8, 137.9, 128.1, 82.0, 73.4, 61.0, 58.0, 57.2, 30.5, 26.2, 25.6, 23.5, 14.1, 9.5, 9.3; HRMS (FAB) calcd for $C_{16}H_{26}N_4O_4$ + H 339.2032, found 339.2035.

To a solution of azide (12 mg, 0.035 mmol) prepared in the previous procedure in ethanol (5 mL) was treated with Lindlar's catalyst (12 mg) under an atmosphere of hydrogen for 18 h at room temperature. After filtration through a pad of Celite with ethanol (3 × 5 mL), the solution was concentrated. The residue was dissolved in ethanol (1 mL) and added slowly in portions to a solution of phosphoric acid (85%, 4.0 mg, 0.042 mmol) in ethanol (1 mL). The mixture was heated to 55 °C and stirred at this temperature for 30 min. White solids formed, and the suspension was cooled to room temperature. Filtration and rinsing with cooled acetone afforded oseltamivir phosphate **1** (12 mg, 86%) as a white solid: mp 202−203 °C; $[\alpha]^{29}_D$ −30.8 (*c* 0.70, H_2O); ^1H NMR (500 MHz, D_2O) δ 0.73 (d, *J* = 7.4 Hz, 3H), 0.77 (d, *J* = 7.4 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.33−1.48 (m, 4H), 1.97 (s, 3H), 2.41 (m, 1H), 2.85 (dd, *J* = 5.1, 17.2 Hz, 1H), 3.48 (m, 2H), 3.95 (t, *J* = 11.1 Hz, 1H), 4.14 (m, 2H), 4.22 (d, *J* = 8.7, 1H), 6.74 (s, 1H); ^{13}C NMR (125 MHz, D_2O) δ 175.2, 167.4, 137.8, 127.6, 84.3, 75.0, 62.3, 52.6, 49.1, 28.1, 25.4, 25.0, 22.3, 13.2, 8.5, 8.4; HRMS (FAB) calcd for $C_{16}H_{31}N_2O_8P$ + Na 433.1716, found 433.1719.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra (^1H and ^{13}C) for **5a**, **4a**, **7**, **7a**, **8**−**16**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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