A Practical Synthesis of (–)-Oseltamivir

Nobuhiro Satoh, Takahiro Akiba, Satoshi Yokoshima, and Tohru Fukuyama

Graduate School of Pharmaceutical Sciences, University of Tokyo,
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
Technical notes

Nuclear magnetic resonance ($^1$H NMR (400 MHz), $^{13}$C NMR (100 MHz), $^{31}$P NMR (162 MHz)) spectra were determined on a JEOL-LA400 instrument unless otherwise noted. Chemical shifts for $^1$H NMR are reported in parts per million downfield from tetramethylsilane ($\delta$) as the internal standard and coupling constants are in hertz (Hz). Chemical shifts in D$_2$O are reported in the scale relative to HOD (4.79 ppm) for $^1$H NMR. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Chemical shifts for $^{13}$C NMR were reported in ppm relative to the center line of a triplet at 77.0 ppm for deuteriochloroform. Chemical shifts in D$_2$O are reported in ppm relative to the singlet at 66.5 ppm for 1,4-dioxane.

Infrared (IR) spectra were recorded on a JASCO FT/IR-410 Fourier Transform Infrared Spectrophotometer and were reported in wavenumbers (cm$^{-1}$).

High-resolution mass spectra (HRMS) were recorded on JEOL JMS-GCmate or JEOL JMS-700 under fast atom bombardment (FAB) conditions with polyethylene glycol (PEG) as the matrix.

Melting points (mp) were determined on a Yanaco Micro Melting Point Apparatus.

Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F$_{254}$. Preparative TLC separations were made on Merck precoated analytical plates, 0.50 mm thick, silica gel 60 F$_{254}$. Compounds were eluted from the adsorbent with ethyl acetate.

Flash chromatography separations were performed on KANTO CHEMICAL Silica Gel 60 (40-100 mesh).

Reagents and solvents were of the commercial grades. All solvents were used after being dried over molecular sieves 3A or 4A. All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.
(1R,2S,3S,6R,7R)-8-benzyloxycarbonyl-2-Bromo-4-oxa-8-azatricyclo[4,3,1,0^{3,7}]decan-5-one (13)

To a stirred solution of pyridine (8) (10.0 ml, 124 mmol) in methanol (200 ml) was added sodium borohydride (5.12 g, 135 mmol) at about −40 °C. To this was added benzyl chloroformate (16.1 ml, 113 mmol) dropwise through the dropping funnel over a period of 30 minutes at such a rate that inner temperature was maintained between −47 and −35 °C. After stirring for 20 minutes, the resulting solution was gradually warmed to 0 °C. Water (200 ml) was added and the mixture was extracted three times with diethyl ether (200 ml x 2 and 100 ml x 1). The combined organic extracts were washed with 1 N HCl (200 ml), 1 N NaOH (200 ml), water (100 ml), and brine (100 ml), dried over sodium sulfate, and concentrated under reduced pressure to give the crude dihydropyridine 9 (23.5 g, 109 mmol, 96.4%) as a pale yellow oil, which was used to the next reaction without purification.

To a stirred solution of 9 (23.5 g, 109 mmol) and the MacMillan’s catalyst 10 (2.80 g, 11.0 mmol) in acetonitrile (114 ml) and water (6 ml) was added acrolein (22.0 ml, 32.9 mmol) at room temperature. After stirring for 14 hours, the reaction mixture was diluted with diethyl ether (400 ml), and washed with water (400 ml). The aqueous layer was diluted with water (100 ml) and extracted with diethyl ether (500 ml). The combined organic extracts were washed with water (300 ml), brine (300 ml), dried over sodium sulfate, and concentrated under reduced pressure to give aldehyde 11 as a pale yellow oil, which was used to the next reaction without purification.

To a stirred solution of the aldehyde 11 in tert-butyl alcohol (180 ml) and water (60 ml) were added sodium dihydrogenphosphate dihydrate (25.7 g, 165 mmol), and 2-methyl-2-butene (60.0 ml, 566 mmol). To this was added sodium chlorite (29.8 g, 329 mmol) portionwise at 0 °C. After 10 minutes, the solution was warmed to room temperature and stirring was continued for an additional 1 hour. The reaction was then quenched with sodium sulfite, and the reaction mixture was partitioned between ethyl acetate (450 ml) and 3 N HCl (360 ml). The aqueous layer was thoroughly extracted with ethyl acetate (400 ml). The combined organic extracts were washed with water (350 ml), brine (350 ml), dried over sodium sulfate, and concentrated under reduced pressure. The concentrated solution was diluted with ethyl acetate and extracted four times with a saturated aqueous sodium bicarbonate solution (360 ml x 4). To a vigorously stirred mixture of the combined aqueous extracts and dichloromethane (120 ml) was added bromine until the reddish color of bromine persisted. The reaction was quenched with sodium sulfite, and the reaction mixture was extracted three times with ethyl acetate (360 ml x 3). The combined organic extracts were washed with water (300 ml), brine (300 ml), dried over sodium sulfate, and concentrated under reduced pressure. The residue was left at room temperature overnight, during which time crystallization took place. The crude product was treated with methanol to promote crystallization and then concentrated to a small volume under reduced pressure. The crystals were filtered and washed with cold methanol 3 times to afford bromolactone 13 (10.64 g, 29.1 mmol, 25.8% from pyridine, >99% ee).

The enantiomeric excess of the bromolactone 13 was determined by HPLC (DAICEL-CHIRALCEL-OD-H, hexane/i-PrOH = 70/30, flow rate = 0.8 ml/min, t_D = 22.6
min, $t_L = 27.9$ min).

$[\alpha]_D^{23} = 37.0$ (c 1.15, CHCl$_3$). mp 132.9-133.6 °C (methanol). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.38 (5H, m), 5.20 (2H, m), 5.01 ((2/3)1H, t, $J = 5.2$ Hz), 4.86 ((1/3)1H, m), 4.85 ((1/3)1H, m), 4.28 (1H, d, $J = 11.2$ Hz), 4.05 (1H, d, $J = 11.2$ Hz), 3.33 (1H, d, $J = 11.2$ Hz), 2.86 (1H, m), 2.50 ((1/3)1H, brs), 2.44 ((2/3)1H, brs), 2.26 (1H, dd, $J = 13.5, 11.2$ Hz), 2.03 (1H, d, $J = 13.5$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 175.3, 175.2, 155.4, 154.6, 136.0, 135.7, 128.6, 128.5, 128.4, 128.2, 127.9, 81.5, 81.4, 67.8, 67.6, 49.2, 48.6, 48.4, 44.8, 44.7, 36.4, 36.3, 32.6, 32.5, 26.9, 26.9. IR (neat, cm$^{-1}$): 1795, 1704, 1422, 1354, 1330, 1309, 1118, 998. Anal. Calcd for C$_{16}$H$_{16}$BrNO$_4$: C, 52.48; H, 4.40; N, 3.82; Found: C, 52.45; H, 4.35; N, 3.62.

(1$R$,2$S$,3$S$,6$R$,7$R$)-2-Bromo-8-$t$-butoxycarbonyl-4-oxa-8-azatricyclo[4,3,1,0$^6$,$^7$]decan-5-one (14)

To a stirred solution of 13 (2.52 g, 6.88 mmol) and di-$t$-butyl pyrocarbonate (1.65 g, 7.56 mmol) in ethanol (8 ml) and tetrahydrofuran (8 ml) was added 10% Pd/C (AD wet supplied by Kawaken, 1.00 g). The flask was charged with hydrogen gas (1 atm) at room temperature. The resulting suspension was vigorously stirred for 2 hours. The reaction mixture was then filtered through a Celite pad and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (dichloromethane) to give 14 (2.42 g, 91.7%) as white crystals.

$[\alpha]_D^{23} = -35.6$ (c 1.11, CHCl$_3$). mp 132.8-133.7 °C (methanol). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.95 ((2/3)1H, t, $J = 5.3$ Hz), 4.89 ((2/3)1H, d, $J = 5.3$ Hz), 4.86 ((1/3)1H, d, $J = 5.1$ Hz), 4.76 ((1/3)1H, t, $J = 5.1$ Hz), 4.26 (1H, d, $J = 3.6$ Hz), 3.94 (1H, d, $J = 11.2$ Hz), 3.25 (1H, m), 2.84 (1H, d, $J = 14.4$, 10.8 Hz), 2.01 (1H, d, $J = 14.4$ Hz), 1.50 (9H, s). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 175.7, 175.6, 154.7, 154.0, 81.7, 81.5, 81.3, 81.0, 49.5, 48.7, 48.3, 48.0, 45.0, 44.3, 36.6, 36.4, 32.8, 32.7, 27.0, 27.0. IR (neat, cm$^{-1}$): 2978, 1798, 1697, 1412, 1364, 1334, 1313, 1173, 1152, 1123, 999. Anal. Calcd for C$_{16}$H$_{18}$BrNO$_4$: C, 47.00; H, 5.46; N, 4.22; Found: C, 46.87; H, 5.41; N, 3.92.

(1$R$,2$S$,3$S$,6$R$,7$R$)-2-Bromo-8-$t$-butoxycarbonyl-4-oxa-8-azatricyclo[4,3,1,0$^6$,$^7$]decan-5,9-dione (15)

To a solution of 14 (4.50 g, 13.6 mmol) and ruthenium dioxide n-hydrate (0.335 g, 1.35 mmol) in dichloroethane (63 ml) were added water (32 ml) and sodium periodate (8.69 g,
40.6 mmol). The resulting solution was stirred at 80 °C for 3 hours. Additional sodium periodate (1.45 g, 0.678 mmol) was added to the reaction mixture, which was stirred at 80 °C for another 30 minutes before quenching with isopropyl alcohol (1 ml). After addition of water (30 ml), the reaction mixture was filtered through filter paper to recover ruthenium dioxide n-hydrate. The filtrate was then partitioned between water and dichloromethane. The aqueous phase was extracted once with dichloromethane. The combined organic extracts were washed with aqueous sodium sulfate solution, brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give 15 (4.00 g, 11.6 mmol, 85.3%) as white crystals.

The combined aqueous layer containing black precipitate was filtered through filter paper again, and the combined black precipitate was dried in vacuo to give ruthenium dioxide n-hydrate (0.313 g, 93.4%), which was reused without further purification to convert 14 (4.20 g, 12.6 mmol) into 15 (3.75 g, 10.8 mmol, 85.6%).

\[ \alpha_d^{23} = -41.8 \text{ (c 1.14, CHCl}_3) \text{.} \] mp 160.1-161.4 °C (ethyl acetate). 1H NMR (400 MHz, CDCl3): \( \delta \) 5.51 (1H, dd, \( J = 5.3, 5.0 \text{ Hz} \)), 5.05 (1H, dd, \( J = 5.3, 0.9 \text{ Hz} \)), 4.26 (1H, dd, \( J = 3.9, 0.9 \text{ Hz} \)), 3.19 (1H, m), 2.88 (1H, ddd, \( J = 10.6, 5.0, 0.7 \text{ Hz} \)), 2.42 (1H, ddd, \( J = 15.4, 10.6, 2.3 \text{ Hz} \)), 2.25 (1H, ddd, \( J = 15.4, 2.7, 0.7 \text{ Hz} \)), 1.58 (9H, s). 13C NMR (100 MHz, CDCl3): \( \delta \) 174.1, 166.9, 150.1, 85.3, 79.9, 53.6, 47.5, 43.4, 34.8, 27.9, 26.2. IR (neat, cm\(^{-1}\)): 1799, 1784, 1750, 1722, 1398, 1297, 1285, 1249, 1150, 974. Anal. Calcd for C\(_{13}\)H\(_{16}\)BrN\(_2\)O\(_5\): C, 45.10; H, 4.66; N, 4.05; Found: C, 45.34; H, 4.64; N, 3.79.

\( (1S,4R,5S,6S,7S)\)-5-Bromo-6-hydroxy-2-\( \text{-} \)butoxycarbonyl-2-azabicyclo[2,2,2]octan-3-one-7-carboxamide (16)

\[ \begin{array}{c}
\text{15} \quad \text{NH}_3 \\
\text{t-BuOH-THF} \\
0 \text{°C} \\
\text{16}
\end{array} \]

Ammonia gas was passed through an ice-cold solution of lactone 15 (4.30 g, 12.4 mmol) in tetrahydrofuran (80 ml) and \( \text{t} \)-butyl alcohol (80 ml) over a period of 2.5 hours. After concentration of the reaction mixture under reduced pressure, the crude product was purified by silica gel column chromatography (methanol/dichloromethane = 1/9) to give 16 (4.29 g, 95.1%) as white crystals.

\[ \alpha_d^{23} = 8.70 \text{ (c 1.21, DMF)} \text{.} \] mp 137.7-138.7 °C (Methanol). 1H NMR (400 MHz, CDCl3): \( \delta \) 6.10-5.85 (1H, brs), 5.85-5.60 (1H, brs), 4.91 (1H, m), 4.84 (1H, dd, \( J = 3.2, 2.8 \text{ Hz} \)), 4.39 (1H, m), 4.08 (1H, t, \( J = 3.2 \text{ Hz} \)), 3.02 (1H, m), 2.92 (1H, ddd, \( J = 14.2, 6.9, 2.0 \text{ Hz} \)), 1.56 (9H, s). 13C NMR (100 MHz, CDCl3): \( \delta \) 175.6, 168.5, 149.8, 84.8, 79.0, 55.6, 50.6, 48.5, 41.8, 28.0, 27.5. IR (neat, cm\(^{-1}\)): 1772, 1732, 1716, 1668, 1370, 1291, 1255, 1150. Anal. Calcd for C\(_{13}\)H\(_{16}\)BrN\(_2\)O\(_5\): C, 42.99; H, 5.27; N, 7.71; Found: C, 42.69; H, 5.33; N, 7.53.
(1S,4R,5S,6S,7S)-5-Bromo-6-methanesulfonyloxy-2-t-butoxycarbonyl-2-azabicyclo[2,2,2]octan-3-one-7-carboxamide (17)

![Chemical Structure]

To a solution of alcohol 16 (1.95 g, 5.37 mmol) and triethylamine (2.25 ml, 16.11 mmol) in dichloromethane (50 ml) was added methanesulfonyl chloride (499 µl, 6.45 mmol) slowly at room temperature. After stirring for 15 minutes, additional methanesulfonyl chloride (120 µl, 1.55 mmol) was added. The reaction mixture was stirred for an additional 25 minutes before quenching with aqueous saturated sodium bicarbonate. After the aqueous phase was saturated with sodium chloride, the organic phase was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (methanol/dichloromethane = 1/19 to 1/9) to give 17 (2.15 g, 4.87 mmol, 90.7%) as a white solid.

\[\alpha_D^{23} = -4.4 \text{ (c 0.91, DMF).} \]

mp 161.9-162.7 °C (methanol). \(^1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta 5.80-5.50\) (1H, brs), \(\delta 5.75-5.45\) (1H, brs), \(\delta 5.21\) (1H, dd, \(J = 3.7, 2.8\) Hz), \(\delta 5.14\) (1H, dd, \(J = 3.6, 3.6\) Hz), \(\delta 4.25\) (1H, dd, \(J = 3.6, 2.8\) Hz), \(\delta 3.13\) (3H, s), \(\delta 3.04\) (1H, m), \(\delta 2.95\) (1H, m), \(\delta 2.76\) (1H, ddd, \(J = 14.7, 6.4, 2.8\) Hz), \(\delta 2.17\) (1H, ddd, \(J = 14.7, 11.0, 3.7\) Hz), \(\delta 1.61\) (9H, s). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 170.3, 167.6, 149.8, 85.4, 83.0, 55.4, 48.1, 45.1, 39.5, 38.3, 28.0, 24.7\). IR (neat, cm\(^{-1}\)):

To a mixture of 17 (2.259 g, 5.118 mmol), allyl alcohol (17.4 ml, 256 mmol), and molecular sieves 4 Å (2.56 g) in 1,2-dichloroethane (33.8 ml) was added diacetoxyiodobenzene (3.297 g, 10.24 mmol). After stirring for 15 minutes at room temperature, the reaction mixture was heated at 60 °C for 10.5 hours. After quenching with saturated aqueous sodium bicarbonate and saturated aqueous sodium thiosulfate, the resulting mixture was filtered through a Celite pad, and washed with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1/1) to give 18 (2.233 g, 4.490 mmol, 87.7%) as a white amorphous solid.

\[\alpha_D^{23} = -2.7 \text{ (c 1.04, CHCl}_3\). \]

To a mixture of 17 (2.259 g, 5.118 mmol), allyl alcohol (17.4 ml, 256 mmol), and molecular sieves 4 Å (2.56 g) in 1,2-dichloroethane (33.8 ml) was added diacetoxyiodobenzene (3.297 g, 10.24 mmol). After stirring for 15 minutes at room temperature, the reaction mixture was heated at 60 °C for 10.5 hours. After quenching with saturated aqueous sodium bicarbonate and saturated aqueous sodium thiosulfate, the resulting mixture was filtered through a Celite pad, and washed with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1/1) to give 18 (2.233 g, 4.490 mmol, 87.7%) as a white amorphous solid.

\[\alpha_D^{23} = -2.7 \text{ (c 1.04, CHCl}_3\). \]

\(^1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta 5.91\) (1H, m), \(\delta 5.32\)
(1H, dd, J = 17.4, 1.4 Hz), 5.29-5.22 (1H, brs), 5.24 (1H, d, J = 10.8 Hz), 4.97 (1H, s), 4.59 (2H, d, J = 5.7 Hz), 4.25 (1H, m), 4.22 (1H, dd, J = 2.8, 1.4 Hz), 3.19 (3H, s), 3.00 (1H, m), 2.76 (1H, m), 1.64 (1H, m), 1.56 (9H, s) 13C NMR (100 MHz, CDCl3): δ 167.0, 155.3, 148.8, 132.4, 118.2, 85.2, 84.0, 66.1, 54.7, 47.9, 46.5, 45.9, 38.5, 31.3, 27.9. IR (neat, cm−1): 1781, 1747, 1731, 1710, 1521, 1370, 1294, 1237, 1177, 1148. Anal. Calcd for C17H25BrN2O8S: 497.0593 (M+H+); Found: 497.0592.

(1S,5S,6R)-5-allyloxycarbonylamino-7-t-butoxycarbonyl-3-ethoxycarbonyl-7-azabicyclo[4,1,0]heptan-2-ene (19)

To a stirred solution of 18 (2.233 g, 4.490 mmol) in ethanol (8.98 ml) was added portionwise a 1.0 M solution of sodium ethoxide in ethanol (9.05 ml, 9.05 mmol) at 0 °C until TLC (ethyl acetate/hexane = 1/2) indicated complete reaction. The resulting solution was diluted with dichloromethane, quenched with acetic acid, and neutralized with aqueous saturated sodium bicarbonate. After the reaction mixture was filtered through a Celite pad, aqueous saturated sodium bicarbonate was added. The aqueous phase was saturated with sodium chloride and extracted with dichloromethane three times. The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1/2) to give 19 (1.438 g, 3.924 mmol, 87.4%) as an off-white amorphous solid. [α]D23 = −68.7 (c 1.81, CHCl3). 1H NMR (400 MHz, CDCl3): δ 7.21 (1H, dd, J = 4.6, 3.2 Hz), 5.90 (1H, m), 5.30 (1H, d, J = 17.4 Hz), 5.22 (1H, d, J = 10.5 Hz), 4.70-4.50 (1H, brs), 4.61 (2H, s), 4.56 (1H, brd, J = 4.8 Hz), 4.20 (2H, q, J = 7.3 Hz), 3.12 (1H, d, J = 5.6 Hz), 2.99 (1H, dd, J = 5.6, 4.8 Hz), 2.73 (1H, d, J = 17.1 Hz), 2.39 (1H, d, J = 17.1 Hz), 1.45 (9H, s), 1.29 (1H, t, J = 7.3 Hz). 13C NMR (100 MHz, CDCl3): δ 165.8, 160.5, 155.4, 134.0, 132.5, 130.2, 118.0, 82.2, 65.7, 61.0, 42.4, 41.8, 32.4, 27.8, 26.8, 14.1. IR (neat, cm−1): 3330, 2980, 1715, 1530, 1369, 1259, 1156, 1096, 1058. HRMS Calcd for C18H26N2O6: 366.1791; Found: 366.1788.

(3S,4S,5S)-5-allyloxycarbonylamino-4-t-butoxycarbonylamino-1-ethoxycarbonyl-3-(3-pentyloxy)-cyclohex-2-ene (20)

Aziridine 19 (442.1 mg, 1.207 mmol) was dissolved in hot 3-pentanol (6.0 ml) and then cooled to −20 °C. To the stirred suspension was added 0.50 M solution of boron trifluoride diethyl ether complex in 3-pentanol (2.88 mL, 1.44 mmol) at −20 °C over 20
minutes. After stirring for an additional 30 minutes, the reaction mixture was warmed to 0 °C and quenched with aqueous saturated sodium bicarbonate. The mixture was extracted twice with toluene, and the combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (dichloromethane/hexane = 1/3) to give 20 (341.0 mg, 0.750 mmol, 62.2%) as a white amorphous solid.

\[ [\alpha]_D^{23} = -37.7 \text{ (c 1.27, CHCl}_3). \]

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 6.80 (1H, s), 5.89 (1H, m), 5.63 (1H, d, \( J = 8.7 \text{ Hz} \)), 5.28 (1H, brd, \( J = 17.2 \text{ Hz} \)), 5.19 (1H, d, \( J = 10.3 \text{ Hz} \)), 4.65-4.45 (1H, m), 4.54 (2H, brs), 4.20 (2H, q, \( J = 7.1 \text{ Hz} \)), 3.94 (1H, m), 3.87 (1H, m), 3.77 (1H, m), 3.41 (1H, quintet, \( J = 5.5 \text{ Hz} \)), 2.75 (1H, dd, \( J = 18.3, 8.3 \text{ Hz} \)), 2.34 (1H, dd, \( J = 18.3, 8.3 \text{ Hz} \)), 1.55 (4H, dq, \( J = 7.3, 5.5 \text{ Hz} \)), 1.42 (9H, s), 1.28 (3H, t, \( J = 7.3 \text{ Hz} \)), 0.91 (6H, t, \( J = 7.3 \text{ Hz} \)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 166.0, 156.3, 137.2, 132.8, 129.3, 117.2, 82.5, 79.5, 75.5, 60.8, 54.9, 50.0, 30.6, 28.2, 26.2, 25.9, 14.1, 9.3. IR (neat, cm\(^{-1}\)): 3335, 2978, 1716, 1685, 1541, 1243, 1173, 1058. Anal. Calcd for C\(_{23}\)H\(_{38}\)N\(_2\)O\(_7\): C, 60.77; H, 8.43; N, 6.16; Found: C, 60.49; H, 8.41; N, 6.09.

(3S,4S,5S)-5-allyloxy carbonylamino-4-amo no-1-ethoxycarbonyl-3-(3-pentyloxy)cyclohex-2-ene (23)

To a stirred solution of 20 (341.0 mg, 0.750 mmol) in dichloromethane (5.0 ml) was added trifluoroacetic acid (1.11 ml, 15.0 mmol) at 0 °C, and the resulting solution was allowed to warm to room temperature. After stirring for 3 hours, the reaction mixture was cooled to 0 °C, quenched with saturated aqueous sodium bicarbonate, and warmed to room temperature. The aqueous phase was saturated with sodium chloride and extracted with dichloromethane 3 times. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give crude amine 23 (257.5 mg) as a pale yellow amorphous solid, which was used for the next acetylation without further purification.

(3S,4S,5S)-4-acetamido-5-allyloxy carbonylamino-1-ethoxycarbonyl-3-(3-pentyloxy)cyclohex-2-ene (21)

To a stirred solution of 23 (257.5 mg, 0.727 mmol) in pyridine (2.6 ml) was added acetic anhydride (1.3 ml) at room temperature. After stirring for an hour, and the reaction mixture was concentrated under reduced pressure. The crude product was recrystallized from isopropyl alcohol-water to give 21 (215.2 mg, 0.543 mmol, 72.4% over 2 steps) as off-white
crystals. The mother liquid was purified by preparative TLC (dichloromethane/hexane = 1/1) to give 21 (45.2 mg, 0.114 mmol, 15.2%) as a white solid.

$$\left[\alpha\right]_{D}^{23} = -70.3 \text{ (c 1.21, CHCl}_{3}\text{). mp 153.0-154.3 °C (ethanol).}$$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.81 (1H, s), 5.89 (1H, m), 5.56 (1H, d, $J = 11.3$ Hz), 5.53 (1H, d, $J = 26.0$ Hz), 5.28 (1H, brd, $J = 17.2$ Hz), 5.20 (1H, d, $J = 10.3$ Hz), 4.54 (2H, m), 4.21 (2H, q, $J = 7.1$ Hz), 4.11 (1H, q, $J = 8.7$ Hz), 3.99 (1H, brd, $J = 7.1$ Hz), 3.86 (1H, m), 3.38 (1H, quintet, $J = 5.7$ Hz), 2.77 (1H, dd, $J = 18.1$, 4.8 Hz), 2.36 (1H, dd, $J = 18.1$, 9.0 Hz), 1.98 (s, 3H), 1.52 (4H, m), 1.29 (3H, t, $J = 7.1$ Hz), 0.90 (6H, dt, $J = 8.8$, 7.2 Hz).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.0, 165.9, 156.6, 137.3, 132.7, 129.2, 117.4, 82.1, 75.3, 65.4, 60.9, 54.0, 49.9, 30.6, 26.1, 25.7, 23.2, 14.1 9.4, 9.2. IR (neat, cm$^{-1}$): 3299, 3278, 1729, 1685, 1643, 1248, 1055. Anal. Calcd for C$_{20}$H$_{32}$N$_2$O$_6$: C, 60.59; H, 8.14; N, 7.07; Found: C, 60.36; H, 8.18; N, 7.04.

(-)-oseltamivir phosphate (1)

A stirred mixture of 21 (566.2 mg, 1.428 mmol), 1,3-dimethylbarbituric acid (272.1 mg, 1.743 mmol), triphenylphosphine (15.0 mg, 0.0571 mmol), and 5% Pd/C (E3, 50% wet, provided by Degussa, 64.0 mg, 0.0143 mmol) in ethanol (11.3 ml) was heated at 80 °C for an hour. The reaction mixture was then filtered and concentrated under reduced pressure. To the solution of the crude product in ethanol (5.80 ml) was added a 1.0 M solution of phosphoric acid in ethanol (1.70 ml, 1.70 mmol). The resulting solution was warmed to 50 °C and seed crystals of 1 were added to initiate the crystallization. The mixture was slowly cooled to room temperature and stirred overnight. The resulting suspension was cooled to –18 °C, stirred for an additional 3 hours, filtered and washed successively with acetone (seven times) and hexane (three times) to give 1 (445.1 mg, 1.085 mmol, 76.0%) as white crystals.

$$\left[\alpha\right]_{D}^{23} = -31.2 \text{ (c 1.00, H}_2\text{O). mp 184.0-186.2 °C (ethanol).}$$

$^1$H NMR (400 MHz, D$_2$O): $\delta$ 6.83 (1H, d, $J = 2.1$ Hz), 4.32 (1H, m), 4.23 (2H, m), 4.04 (1H, m), 3.55 (2H, m), 2.95 (1H, m), 2.51 (1H, m), 2.07 (3H, s), 1.54 (4H, m), 1.45 (2H, m), 1.37 (1H, ddt, $J = 14.0$, 2.3, 1.6 Hz), 0.87 (3H, m), 0.82 (3H, m). $^{13}$C NMR (100 MHz, D$_2$O): $\delta$ 175.2, 167.3, 137.8, 84.2, 75.0, 62.3, 52.5, 49.1, 28.1, 25.4, 25.0, 22.3, 13.2, 8.5, 8.4. $^{31}$P NMR (162 MHz, D$_2$O): $\delta$ 0.6. IR (KBr, cm$^{-1}$): 3352, 1718, 1660, 1552, 1375, 1296, 1246, 1128, 1066, 1028, 947. Anal. Calcd for C$_{16}$H$_{31}$N$_2$O$_8$P: C, 46.83; H, 7.61; N, 6.83; Found: C, 46.55; H, 7.36; N, 6.86.
To a stirred solution of pyridine (8) (5.00 g, 63.2 mmol) in methanol (50 ml) was added sodium borohydride (2.63 g, 69.5 mmol) at −78 °C. To this was added benzyl chloroformate (10.24 g, 60.0 mmol) dropwise over a period of 90 minutes at such a rate that inner temperature was maintained under −69 °C. After stirring for 100 minutes, water (50 ml) and diethyl ether (50 ml) were added to the reaction mixture. The resulting mixture was warmed to room temperature, and the organic layer was separated. The aqueous layer was extracted with ether (50 ml), and the combined organic extracts were washed with 1 N HCl (50 ml), 1 N NaOH (50 ml), water (20 ml), and brine (20 ml), respectively, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the crude dihydropyridine 9 (9.84 g) as a pale yellow oil, which was used for the next step without further purification.

To a stirred solution of 9 (3.00 g) in acetonitrile (14.2 ml) and water (0.75 ml) were added the MacMillan’s catalyst 10 (0.36 g, 1.4 mmol) and acrolein (2.8 ml, 42 mmol) at room temperature. After stirring for 16 hours, the reaction mixture was diluted with diethyl ether (50 ml), and washed with water (50 ml). The aqueous layer was extracted with diethyl ether (50 ml). The combined organic extracts were washed with brine (50 ml), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give aldehyde 11 (7.77 g) as a pale yellow oil, which was used for the next step without further purification.

To a stirred solution of aldehyde 11 (5.00 g) in ethanol (25 ml) was added sodium borohydride (1.40 g, 37.0 mmol). After stirring for 30 minutes, the reaction was quenched with aqueous HCl (100 ml). The reaction mixture was extracted twice with ethyl acetate, and the combined organic extracts were washed with brine, filtered, and concentrated under reduced pressure to give the crude product (2.42 g). One gram of the crude product was purified by silica gel column chromatography to give 24 (284 mg, 28.1% over 3 steps) as a colorless viscous oil and 25 (79 mg, 7.8% over 3 steps) as a white amorphous solid.

24:

\[ \alpha_D^{23} = 70.2 \ (c \ 1.09, \ CHCl_3) \]

^1H NMR (400 MHz, CDCl_3): δ 7.33 (5H, m), 6.37 (2H, m), 5.11 (2H, m), 4.90 (2/5)1H, brs), 4.84 (2/5)1H, brs), 3.28 (2H, m), 3.18 (1H, m), 3.02 (1H, m), 2.73 (1H, m), 2.36 (1H, m), 1.76 (1H, m), 0.83 (1H, m), 0.83 (1H, m), 1.3C NMR (100 MHz, CDCl_3): δ 155.2, 154.9, 137.0, 136.9, 135.0, 134.6, 130.5, 130.0, 128.4, 128.4, 127.7, 127.7, 127.7, 66.7, 66.7, 65.6, 65.5, 47.3, 47.2, 46.9, 46.9, 46.6, 46.6, 41.6, 41.6, 30.8, 30.6, 26.1, 26.1. IR (neat, cm⁻¹): 3429, 2935, 2873, 1695, 1419, 1344, 1300, 1113, 1053. HRMS Calcd for C_{16}H_{19}NO_3: 274.1443 (M+H⁺); Found: 274.1441.

25:

\[ \alpha_D^{23} = -141 \ (c \ 1.00, \ CHCl_3) \]

^1H NMR (400 MHz, CDCl_3): δ 7.35 (5H, m), 5.99 (1H, dd, J = 9.4, 5.2 Hz), 5.85 (1H, d, J = 4.4 Hz), 5.64 (1H, dd, J = 9.4, 5.6 Hz), 5.12 (2H, m), 4.98 (1H, brs), 4.06 (2H, s), 3.21 (1H, m), 3.12 (1H, m), 2.46 (1H, m), 2.31 (1H, m), 2.23 (2H, m). 13C NMR (100 MHz, CDCl_3): δ 157.0, 137.1, 136.4, 128.5, 128.1, 128.1, 126.7, 125.5, 119.2, 66.8, 66.0, 42.9, 33.9, 26.6. IR (neat, cm⁻¹): 3334, 3033, 2925, 2864, 1699, 1537, 1454, 1259.
1140, 997. Anal. Calcd for C$_6$H$_{19}$NO$_3$: C, 70.31; H, 7.01; N, 5.12; Found: C, 70.01; H, 6.90; N, 5.08.
Selected $^1$H and $^{13}$C NMR Spectra