Supplementary Material

for the article

Figure S1. Crystal structure of compound 20. Chiral center is depicted in yellow color.

Crystallographic data for 20 were collected on Nonius KappaCCD diffractometer equipped with Bruker APEX-II CCD detector by monochromatized MoKα radiation (λ = 0.71073 Å) at a temperature of 150(2) K. The structure was solved by direct methods (SHELXT) and refined by full matrix least squares based on $F^2$ (SHELXL-2018). The absorption correction was carried on using multi-scan method. The hydrogen atoms were found on difference Fourier map and were recalculated into idealized positions. All hydrogen atoms were refined as fixed (riding model) with assigned temperature factors $H_{iso}(H) = 1.2 \ U_{eq}$ (pivot atom) or 1.5 $U_{eq}$ for methyl moiety. The absolute configuration was assigned along known chirality on carbon.
Crystal data for **20**: C_{28}H_{39}N_{3}O_{9}, \( M_r = 561.62 \); Tetragonal, \( P4_12_12_1 \) (No. 92), \( a = 17.9556 \, (10) \, \text{Å}, \ c = 18.6157 \, (11) \, \text{Å}, \ V = 6001.8 \, (8) \, \text{Å}^3, \ Z = 8, \ D_x = 1.243 \, \text{Mg m}^{-3}, \) colourless prism 0.35 × 0.26 × 0.21 mm, multi-scan absorption correction (\( \mu = 0.09 \, \text{mm}^{-1} \)) \( T_{\text{min}} = 0.76, \ T_{\text{max}} = 0.98; \) a total of 28913 measured reflections (\( \theta_{\text{max}} = 25.7^\circ \)), from which 5697 were unique (\( R_{\text{int}} = 0.048 \)) and 4288 observed according to the \( I > 2\sigma(I) \) criterion. The refinement converged (\( \Delta/\sigma_{\text{max}} = 0.001 \) to \( R = 0.042 \) for observed reflections and \( wR(F^2) = 0.109, \) GOF = 1.01 for 367 parameters and all 5697 reflections. The final difference Fourier map displayed no peaks of chemical significance, (\( \Delta \rho_{\text{max}} = 0.21, \Delta \rho_{\text{min}} = -0.21 \, \text{e.Å}^{-3} \)). Absolute structure parameter -0.3 (5).

The crystallographic data have been deposited at the Cambridge Crystallographic Data Centre with CCDC 1832673. Copies of the data can be obtained, free of charge by application to the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
Experimental procedures

**General:** Unless otherwise noted, all reactions were carried out under argon in oven-dried glassware. The solvents used for reactions were freshly distilled from the appropriate drying agent and were transferred under argon: THF (Na/benzophenone); toluene (Na); DCM (CaH₂). Chromatography was performed either using classical methods or using HPFC Biotage Isolera One system, using Fluka silica gel 60 (0.040 - 0.063mm) or Merck silica gel 60 RP-18 F₂₅₄ coated aluminium sheets. The spots were detected both in UV and by the solution of Ce(SO₄)₂·4H₂O (1%) and H₃P(Mo₃O₁₀)₄ (2%) in 10% sulfuric acid (10%). All starting materials were used as received (Sigma Aldrich, Alfa Aesar, Strem Chemicals, TCI), unless otherwise indicated. Oseltamivir phosphate was purchased from Santiago. All tested inhibitors were purified using preparative HPLC of Jasco brand (flow rate 10 mL/min; gradient 2-100 % ACN in 50 minutes), with column Waters SunFire C18 OBD Prep Column, 5 μm, 19 x 150 mm. The purity of compounds was tested on analytical Jasco PU-1580 HPLC (flow rate 1 mL/min, invariable gradient 2-100 % ACN in 30 minutes) with column Watrex C18 Analytical Column, 5 μm, 250x5 mm. The final inhibitors were all >95 % purity. The ¹H-NMR spectra were measured at 400.13 or 600.13 MHz, the ¹³C-NMR spectra at 100.61 or 150.90 MHz in CDCl₃ or (CD₃)₂SO, with tetramethylsилane or residual solvent peaks as an internal standard. The chemical shifts are given in δ-scale, coupling constants J are given in Hz. The EI mass spectra were determined at an ionizing voltage of 70 eV, the m/z values are given alone with their relative intensities (%). The ESI mass spectra were recorded using ZQ micromass mass spectrometer (Waters) equipped with an ESCi multimode ion source and controlled by MassLynx software. Methanol was used as solvent.

(6-Azidohexyl) (3R,4R,5S)-4-acetylamino-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-phosphonic acid (1)
(6-azidohexyl) (3R,4R,5S)-4-acetylamino-5-[(tert-butoxycarbonyl)-amino]-3-(1-ethylpropoxy)-1-cyclohexene-1-phosphonic acid 17 was dissolved in trifluoroacetic acid (3 mL) and stirred for 2 h at room temperature. The solution was dried under reduced pressure and the resulting residue was purified by preparative HPLC to afford the deprotected phosphonic acid 1.

\[\text{H NMR (500 MHz, Methanol-d}_4\text{) } \delta 6.42 (dd, J = 19.4, 1.0 Hz, 1H), 4.14 – 4.06 (m, 1H), 3.95 (dd, J = 11.2, 8.3 Hz, 1H), 3.83 (q, J = 6.5 Hz, 2H), 3.50 – 3.36 (m, 2H), 3.31 – 3.23 (m, 2H), 2.82 – 2.69 (m, 1H), 2.39 (ddd, J = 17.0, 10.1, 2.9 Hz, 1H), 2.03 (s, 3H), 1.69 – 1.56 (m, 4H), 1.55 – 1.46 (m, 4H), 1.45 – 1.37 (m, 4H), 0.91 (dt, J = 15.0, 7.4 Hz, 6H). \]
\[\text{C NMR (126 MHz, Methanol-d}_4\text{) } \delta 174.7, 137.1, 131.6 (d, J = 175.9 Hz), 83.4, 76.3 (d, J = 18.9 Hz), 65.7 (d, J = 5.4 Hz), 54.6, 52.4, 51.4, 31.8 (d, J = 6.8 Hz), 30.4 (d, J = 10.4 Hz), 29.9, 27.5, 27.3, 26.6, 26.5, 23.1, 9.9, 9.6. \]
\[\text{P NMR (162 MHz, Methanol-d}_4\text{) } \delta 13.01. \]

HR-ESI-MS calculated for C\(_{19}\)H\(_{35}\)O\(_5\)N\(_5\)P = 444.2381, found 444.2373.

\[(3R,4R,5S)-4-Acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-phosphonate (2)\]

Bromotrimethylsilane (0.41 mL, 3.18 mmol) and 2,6-lutidine (0.44 mL, 3.81 mmol) were added to a solution of the Boc-protected phosphonic acid 16 (0.14 g, 0.318 mmol) in DCM (10 mL) and the reaction was allowed to stir for 9 h at room temperature. The solvent was evaporated and TFA (50% in water, 10 mL) was added. Then the reaction was allowed to stir for 1 h and the solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC.
All spectral properties matched literature values\textsuperscript{15}. HR-ESI-MS calculated for C\textsubscript{13}H\textsubscript{25}O\textsubscript{5}N\textsubscript{2}NaP (M+Na\textsuperscript{+}) 343.1393, found 343.1395.

**Methyl (3\textit{R},4\textit{R},5\textit{S})-4-acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-phosphonate (3)**

![Methyl (3\textit{R},4\textit{R},5\textit{S})-4-acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-phosphonate (3)](image)

The phosphonic acid 16 (0.05 g, 1.14 mmol) was stirred with trifluoroacetic acid (50\% in water, 4 mL) at room temperature for 1 h. The solution was evaporated under reduced pressure and later residue was purified by preparative HPLC to furnish the title compound 3 (0.02 g, 43\% yield).

\textsuperscript{1}H NMR (600 MHz, D\textsubscript{2}O) \(\delta\) 6.38 (d, \(J = 19.4\) Hz, 1H), 4.28 (d, \(J = 7.5\) Hz, 1H), 4.14 – 4.01 (m, 1H), 3.65 – 3.55 (m, 2H), 3.53 (d, \(J = 10.8\) Hz, 3H), 2.82 – 2.72 (m, 1H), 2.49 – 2.40 (m, 1H), 2.09 (s, 3H), 1.60 – 1.45 (m, 4H), 0.90 (t, \(J = 7.2\) Hz, 3H), 0.85 (t, \(J = 7.2\) Hz, 3H). \textsuperscript{13}C NMR (151 MHz, D\textsubscript{2}O) \(\delta\) 175.8, 137.9 (d, \(J = 6.8\) Hz), 129.7 (d, \(J = 174.4\) Hz), 84.9, 76.5 (d, \(J = 19.4\) Hz), 53.5, 52.5 (d, \(J = 5.1\) Hz), 50.3 (d, \(J = 14.1\) Hz), 29.8 (d, \(J = 11.0\) Hz), 26.1, 25.8, 22.9, 9.2, 9, 1. HR-ESI-MS calculated for C\textsubscript{14}H\textsubscript{28}O\textsubscript{5}N\textsubscript{2}P (M+H\textsuperscript{+}) 335.1730, found 335.1732.

**Oseltamivir carboxylate (4)**

![Oseltamivir carboxylate (4)](image)
An aqueous solution of NaOH (0.5 M; 1.9 mL) was added dropwise to a stirred solution of oseltamivir phosphate 5 (0.2 g, 0.48 mmol) in 1,4-dioxane (1.9 mL). The reaction was stirred for 24 h at room temperature. The pH was adjusted to neutral by addition of Amberlite IR 120 hydrogen form. After removal of Amberlite by filtration, the filtrate was concentrated under reduced pressure and the formed residue was purified by preparative HPLC to furnish the free base derivative 4 (0.12 g, 88% yield).

1H NMR (400 MHz, MeOD) δ 6.64 (s, 1H), 4.11 (d, J = 8.5 Hz, 1H), 3.83 (dd, J = 11.4, 8.7 Hz, 1H), 3.40 (td, J = 10.8, 5.5 Hz, 1H), 3.34 – 3.22 (m, 1H), 3.16 (dt, J = 3.3, 1.6 Hz, 1H), 2.80 (dd, J = 17.3, 5.1 Hz, 1H), 2.38 – 2.18 (m, 1H), 1.91 (s, 3H), 1.47 – 1.28 (m, 4H), 0.75 (dt, J = 12.6, 7.4 Hz, 6H). 13C NMR (101 MHz, MeOD) δ 174.9, 169.6, 138.4, 129.8, 83.7, 76.0, 54.5, 50.5, 30.0, 27.2, 26.6, 23.4, 9.8, 9.6. HR-ESI-MS calculated for C14H23O4N2 (M-H+) 283.1663, found 283.1656.

**Ethyl (3R,4R,5S)-4-acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (5)**

To a solution of oseltamivir phosphate (1.0 g, 2.43 mmol) in water (30 mL) was added a saturated solution of sodium bicarbonate (10 mL). The reaction mixture was stirred for 5 min at room temperature. The mixture was extracted with DCM/MeOH mixture (3:1; 4x10 mL). The combined organic phase was washed with brine, dried over anhydrous Na2SO4 and concentrated under reduced pressure to furnish the free base of oseltamivir (0.75 g, 98% yield). The product 5 was used without further purification.

1H NMR (300 MHz, CDCl3) δ 6.78 (t, J = 2.1 Hz, 1H), 6.26 (d, J = 8.3 Hz, 1H), 4.34 – 4.10 (m, 3H), 3.55 (dt, J = 10.3, 8.4 Hz, 1H), 3.37 (dd, J = 17.7, 12.0 Hz, 1H), 3.26 – 3.08 (m, 1H), 2.76 (dd, J = 17.7, 5.1 Hz, 1H), 2.26 – 2.08 (m, 1H), 2.04 (s, 3H), 1.58 (s, 2H), 1.55 – 1.44 (m, 4H),
1.29 (t, $J = 7.1$ Hz, 3H), 0.90 (td, $J = 7.4$, 3.8 Hz, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.1, 166.4, 137.8, 129.5, 81.7, 77.6, 77.2, 76.7, 75.0, 60.8, 58.9, 49.3, 33.7, 26.2, 25.7, 23.6, 14.2, 9.6, 9.3. HR-ESI-MS calculated for C$_{16}$H$_{29}$O$_4$N$_2$ (M+H)$^+$ 313.2122, found 313.2122.

**(3R,4R,5S)-4-Acetamido-5-guanidino-3-(1-ethylpropoxy)-1-cyclohexene-1-phosphonate (6)**

![Chemical Structure](image)

Neat bromotrimethylsilane (1.49 g, 9.68 mmol) was added to a solution of the phosphonate (0.07 g, 0.121 mmol) in DCM (5 mL) at 0 °C and the reaction was allowed to stir for 24 h at room temperature. The solvent was evaporated under reduced pressure; the remaining residue was quenched with water (4 mL) and then the mixture was stirred for 2 h. The solution was evaporated to dryness and later was purified by preparative HPLC to afford the free guanidine 6 (0.09 g, 21% yield).

$^1$H NMR (400 MHz, D$_2$O) δ 6.31 (d, $J = 19.8$ Hz, 1H), 4.26 (d, $J = 8.5$ Hz, 1H), 4.01 – 3.88 (m, 1H), 3.80 (td, $J = 10.4$, 5.2 Hz, 1H), 3.60 – 3.47 (m, 1H), 2.85 – 2.66 (m, 1H), 2.46 – 2.31 (m, 1H), 2.04 (s, 3H), 1.65 – 1.50 (m, 3H), 1.45 (dt, $J = 14.4$, 7.2 Hz, 1H), 0.87 (dt, $J = 19.5$, 7.4 Hz, 6H). $^{13}$C NMR (151 MHz, H$_2$O+D$_2$O+tert-butyl alcohol) δ 175.3, 157.6, 157.5, 135.3, 135.3, 134.0, 132.8, 85.0, 77.0, 76.9, 70.5 (C), 55.9, 55.9, 51.8, 51.7, 31.5, 31.4, 30.2 (CH$_3$), 26.3, 26.0, 22.7, 22.6, 9.3, 9.2. $^{31}$P NMR (162 MHz, D$_2$O) δ 11.13. All spectral properties matched literature values. HR-ESI-MS calculated for C$_{14}$H$_{28}$O$_5$N$_4$P (M+H)$^+$ 363.1792, found 363.1794.

**(3R,4R,5S)-4-Acetamido-5-guanidino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid (7)**
(3R,4R,5S)-4-Acetamido-5-[N^2,N^3-bis(tert-butoxycarbonyl)guanidino]-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid (0.07 g, 0.13 mmol) was stirred with trifluoroacetic acid (50% in water, 5 mL) at room temperature for 1 h. The solution was evaporated under reduced pressure and purified by preparative HPLC to furnish the guanidine derivative 7 (0.02 g, 43%).

\[^1\text{H}\text{ NMR (400 MHz, Methanol-}d_4\text{)}\delta 7.28 (d, J = 9.0 \text{ Hz, 1H}), 6.79 (s, 1H), 4.15 (dd, J = 5.3, 2.1 \text{ Hz, 1H}), 3.93 – 3.73 (m, 2H), 3.42 – 3.31 (m, 1H), 2.77 (dd, J = 17.6, 5.0 \text{ Hz, 1H}), 2.37 – 2.20 (m, 1H), 1.94 (s, 3H), 1.48 (tdd, J = 12.9, 6.2, 4.5 \text{ Hz, 4H}), 0.86 (dt, J = 12.8, 7.4 \text{ Hz, 6H}).\] \[^{13}\text{C NMR (101 MHz, Methanol-}d_4\text{)}\delta 174.2, 169.0, 158.6, 138.8, 129.8, 83.8, 76.1, 55.8, 51.7, 31.3, 27.2, 26.8, 22.8, 9.8, 9.7.\] All spectral properties matched literature values \(^3\). HR-ESI-MS calculated for C\(_{15}\)H\(_{27}\)O\(_4\)N\(_4\) (M+H)\(^+\) 327.2027, found 327.2028.

(3R,4R,5S)-4-Acetamido-5-[(S)-1-carboxyethyl]amino]-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid (8)

A solution of aqueous NaOH (1 mL, 0.5 M) was added dropwise to a solution of the A diastereomer (S) 18 (0.025 g, 0.06 mmol) in THF (1 mL) and the reaction mixture was stirred overnight at room temperature. The pH was adjusted to neutral by addition of Amberlite IR 120 hydrogen form. Amberlite was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC.
$^1$H NMR (401 MHz, Methanol-$d_4$) δ 6.90 (d, $J = 1.4$ Hz, 1H), 4.26 – 4.11 (m, 2H), 3.77 (dd, $J = 13.9, 7.1$ Hz, 1H), 3.64 – 3.58 (m, 1H), 3.48 – 3.39 (m, 1H), 2.99 – 2.90 (m, 1H), 2.67 – 2.55 (m, 1H), 2.04 (s, 3H), 1.64 – 1.42 (m, 7H), 0.99 – 0.84 (m, 6H). $^{13}$C NMR (101 MHz, Methanol-$d_4$) δ 174.7, 173.8, 168.7, 137.7, 129.3, 83.6, 75.2, 57.3, 55.1, 53.2, 27.7, 27.1, 26.6, 23.1, 15.9, 9.9, 9.5. HR-ESI-MS calculated for $C_{17}H_{28}N_2O_6Na$ (M+Na)$^+$ 379.1840, found 379.1839.

(3R,4R,5S)-4-Acetamido-5-[(R)-1-carboxyethyl]amino]-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid (9)

A solution of aqueous NaOH (2 mL, 0.5 M) was added dropwise to a solution of the diastereomer B (R) 19 (0.05 g, 0.12 mmol) in THF (2 mL) and the reaction mixture was stirred overnight at room temperature. The pH was adjusted to neutral by addition of Amberlite IR 120 hydrogen form. Amberlite was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC.

$^1$H NMR (401 MHz, Methanol-$d_4$) δ 6.92 – 6.80 (m, 1H), 4.21 – 4.05 (m, 2H), 3.82 (q, $J = 7.2$ Hz, 1H), 3.52 – 3.39 (m, 2H), 3.08 – 2.95 (m, 1H), 2.52 – 2.39 (m, 1H), 2.09 (s, 3H), 1.59 – 1.47 (m, 7H), 0.91 (dt, $J = 11.2, 7.4$ Hz, 6H). $^{13}$C NMR (101 MHz, Methanol-$d_4$) δ 175.1, 173.6, 168.5, 138.8, 128.7, 83.9, 76.1, 57.3, 57.2, 53.5, 27.8, 27.2, 26.6, 23.2, 16.9, 9.8, 9.6. HR-ESI-MS calculated for $C_{17}H_{28}N_2O_6Na$ (M+Na)$^+$ 379.1840, found 379.1839.

((1S,5R,6R)-6-Acetamido-3-carboxy-5-(pentan-3-ylxoy)cyclohex-3-en-1-yl)aspartic acid (10)
An aqueous solution of NaOH (0.5 M; 7.2 mL) was added dropwise to a stirred solution of the ester 21 (0.09 g, 0.19 mmol) in THF (3 mL). The reaction was stirred for 24 h at room temperature. The pH was adjusted to neutral by addition of Amberlite IR 120 hydrogen form. Amberlite was filtered off, the filtrate was concentrated under reduced pressure and purified by flash chromatography (DCM/MeOH 80:20) to furnish the free carboxylic acid derivative 10 (0.053 g, 70%).

$^1$H NMR (401 MHz, Methanol-$d_4$) $\delta$ 6.87 (t, $J = 1.2$ Hz, 1H), 4.28 (dd, $J = 8.1$, 2.0 Hz, 1H), 4.07 (dd, $J = 10.7$, 8.1 Hz, 1H), 3.99 (t, $J = 5.1$ Hz, 1H), 3.67 (td, $J = 10.2$, 5.6 Hz, 1H), 3.48 – 3.39 (m, 1H), 3.05 – 2.91 (m, 3H), 2.62 – 2.52 (m, 1H), 2.04 (s, 3H), 1.60 – 1.49 (m, 4H), 0.92 (dt, $J = 10.4$, 7.4 Hz, 6H). $^{13}$C NMR (101 MHz, Methanol-$d_4$) for the major diastereomer $\delta$ 175.4, 175.0, 172.1, 168.7, 138.4, 129.1, 83.6, 75.3, 58.0, 55.5, 54.1, 33.6, 28.0, 27.2, 26.6, 23.2, 9.9, 9.5. $^{13}$C NMR (101 MHz, Methanol-$d_4$) for the minor diastereomer $\delta$ 175.4, 175.0, 173.9, 168.7, 138.9, 129.0, 83.9, 76.3, 57.8, 55.5, 53.9, 35.9, 28.0, 27.2, 26.7, 23.2, 9.8, 9.6. HR-ESI-MS calculated for $C_{18}H_{27}N_2O_8$ (M-H)$^-$ 399.1769, found 399.1773.

(3R,4R,5S)-4-Acetamido-5-{2-[2-(2-methoxyethoxy)ethoxy]acetamido}-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid (11)

An aqueous solution of NaOH (0.5 M; 0.88 mL) was added dropwise to a stirred solution of the ethyl ester 22 (0.104 g, 0.22 mmol) in 1,4-dioxane (0.88 mL). The reaction was stirred for 24 h at room temperature. The pH was adjusted to neutral by addition of Amberlite IR 120 hydrogen form. Amberlite was filtered off, rinsed with MeOH several times and the filtrate was then concentrated under reduced pressure. The residue was purified by flash chromatography (DCM/MeOH 80:20) to furnish the free carboxylic acid derivative 11 (0.069 g, 70% yield).
1H NMR (401 MHz, CDCl₃) δ 7.73 (d, J = 9.2 Hz, 1H), 6.92 (dt, J = 9.1, 4.6 Hz, 1H), 6.85 (d, J = 2.5 Hz, 1H), 5.74 (bs, 1H), 4.24 – 4.16 (m, 1H), 4.15 – 4.10 (m, 1H), 4.07 – 4.00 (m, 1H), 3.71 – 3.61 (m, 8H), 3.59 – 3.53 (m, 2H), 3.40 – 3.31 (m, 1H), 3.36 (s, 3H), 2.71 (dd, J = 18.0, 5.2 Hz, 1H), 2.47 – 2.32 (m, 1H), 1.95 (d, J = 1.7 Hz, 3H), 1.59 – 1.40 (m, 4H), 0.87 (m, 6H). 13C NMR (101 MHz, CDCl₃) δ 177.1, 176.7, 174.0, 144.6, 134.5, 87.9, 81.2, 77.3, 76.5, 76.1, 75.9, 64.5, 60.1, 56.0, 53.2, 35.9, 31.8, 31.1, 28.6, 15.2, 14.7. HR-ESI-MS calculated for C₂₁H₃₆O₈N₂ (M+Na)+ 467.2364, found 467.2363.

Ethyl (3R,4R,5S)-4-acetamido-5-[(tert-butoxycarbonyl)-amino]-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (12)

To a solution of oseltamivir free base 5 (0.38 g, 1.21 mmol) in DCM (3 mL) was added triethylamine (0.61 g, 6.08 mmol) followed by addition of di-tert-butyl dicarbonate (0.53 g, 2.42 mmol) and then the reaction mixture was stirred for 4 h at room temperature. The mixture was diluted with water (10 mL) and then extracted with DCM (3x10 mL). The combined organic phase was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluent DCM to DCM/MeOH, 20:1) to afford the protected amine 12 (0.49 g, 98% yield) as a white solid.

1H NMR (300 MHz, CDCl₃) δ 6.78 (s, 1H), 5.80 (d, J = 8.2 Hz, 1H), 5.11 (d, J = 9.0 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.13 – 4.00 (m, 1H), 3.97 (s, 1H), 3.79 (dd, J = 9.7, 5.1 Hz, 1H), 3.52 – 3.28 (m, 1H), 2.74 (dd, J = 18.1, 4.9 Hz, 1H), 2.29 (dd, J = 17.7, 9.6 Hz, 1H), 1.98 (s, 3H), 1.51 (dd, J = 5.5, 4.1 Hz, 4H), 1.42 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H), 0.88 (dd, J = 13.6, 7.3 Hz, 6H). 13C NMR (75 MHz, CDCl₃) δ 170.9, 166.1, 156.4, 137.7, 129.5, 82.3, 79.8, 76.0, 61.1, 54.5, 49.2, 31.1, 28.5, 26.3, 25.8, 23.5, 14.3, 9.6, 9.4. HR-ESI-MS calculated for C₂₁H₃₇O₈N₂ (M+H)+ 413.2646, found 413.2648.
An aqueous solution of NaOH (0.5 M; 8.7 mL) was added dropwise to a stirred solution of the ester 12 (0.9 g, 2.18 mmol) in 1,4-dioxane (8.7 mL). The reaction mixture was stirred for 24 h at room temperature. The pH was adjusted to neutral by addition of Amberlite IR 120 hydrogen form. Amberlite was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (eluent DCM/MeOH gradient 10:1 to 10:3) to furnish the free acid 13 (1.28 g, 95% yield) as a white solid.

$^1$H NMR (300 MHz, CDCl$_3$)  δ 6.81 (s, 1H), 6.69 (s, 1H), 5.72 (d, $J = 9.3$ Hz, 1H), 4.02 (d, $J = 6.8$ Hz, 2H), 3.75 (dd, $J = 13.1$, 8.4 Hz, 1H), 3.39 – 3.26 (m, 1H), 2.70 (dd, $J = 17.5$, 5.0 Hz, 1H), 2.25 (dd, $J = 17.7$, 11.1 Hz, 1H), 1.99 (s, 3H), 1.49 (dd, $J = 14.0$, 6.7 Hz, 4H), 1.41 (s, 9H), 0.86 (dd, $J = 16.5$, 7.4 Hz, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.5, 169.1, 156.9, 139.2, 129.2, 82.3, 79.8, 76.2, 55.2, 49.6, 31.0, 28.5, 26.3, 25.7, 23.4, 9.8, 9.2. HR-ESI-MS calculated for C$_{19}$H$_{33}$O$_6$N$_2$ (M+H)$^+$ 385.2333, found 385.2335.
S-(1-Oxido-2-pyridyl)-N,N,N',N'-tetramethylthiuronium hexafluorophosphate (0.26 g, 0.70 mmol) was added to a solution of the free acid 13 (0.21 g, 0.54 mmol), triethylamine (0.22 mL, 1.61 mmol) and 4-(dimethylamino)pyridine (0.007 g, 0.054 mmol) in dry THF (4 mL). The reaction was stirred in the dark for 40 min at room temperature. The solvent was removed by evaporation under reduced pressure. The remaining green oil was dissolved in DCM (2 mL) and bromotrichloromethane (2 mL). The formed solution was irradiated (refluxed) with a flood lamp for 90 min. The mixture was concentrated and purified by flash column chromatography (eluent Toluene/EtOAc gradient 2:1 to 1:1) to afford the vinyl bromide 14 (0.18 g, 78% yield).

TLC (Toluene/EtOAc 1:1) \( R_f = 0.45 \). \(^1^H\) NMR (300 MHz, CDCl\(_3\)) \( \delta 6.07 \) (s, 1H), 5.52 (d, \( J = 9.4 \) Hz, 1H), 5.35 (d, \( J = 9.0 \) Hz, 1H), 4.09 (dd, \( J = 9.1, 6.8 \) Hz, 1H), 3.88 (dd, \( J = 7.9, 5.5 \) Hz, 1H), 3.83 (s, 1H), 3.39 – 3.25 (m, 1H), 2.68 (m, \( J = 26.0, 18.0, 6.8 \) Hz, 2H), 1.99 (s, 3H), 1.59 (s, 1H), 1.49 (dd, \( J = 7.3, 6.0 \) Hz, 3H), 1.42 (s, 9H), 0.88 (t, \( J = 7.4 \) Hz, 6H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta 171.5, 156.9, 129.2, 121.2, 82.3, 79.8, 76.2, 55.2, 50.9, 49.6, 28.5, 26.3, 25.7, 23.4, 9.7, 9.2. HR-ESI-MS calculated for C\(_{18}\)H\(_{31}\)BrO\(_4\)N\(_2\)Na (M+Na)\(^+\) 441.1359, found 441.1360.

**Dimethyl (3R,4R,5S)-4-acetamido-5-[(tert-butoxycarbonyl)-amino]-3-(1-ethylpropoxy)-1-cyclohexene-1-phosphonate (15)**
To a solution of the vinyl bromide 14 (0.18 g, 0.39 mmol) in toluene (10 mL) was added tetrakis(triphenylphosphine)palladium (0.07 g, 0.06 mmol), triethylamine (0.21 mL, 1.54 mmol) and dimethyl phosphite (0.14 mL, 1.54 mmol). The reaction mixture was stirred at 80 °C for 90 min. The reaction was quenched with a saturated solution of NH₄Cl (6 mL) and diluted with DCM (30 mL). The organic phase was washed with a saturated solution of NH₄Cl (6 mL) and brine (2x5 mL), dried over MgSO₄ and concentrated. The residue was purified by flash column chromatography (eluent EtOAc gradient to EtOAc/MeOH 6:1) to afford the phosphonate 15 (0.16 g, 86% yield).

TLC (EtOAc/MeOH 6:1) \( R_f = 0.42 \). \(^1\)H NMR (300 MHz, CDCl₃) \( \delta 6.59 (d, J = 21.8 \text{ Hz}, 1\text{H}), 6.02 (d, J = 8.8 \text{ Hz}, 1\text{H}), 5.17 (d, J = 9.0 \text{ Hz}, 1\text{H}), 4.11 - 3.99 (m, 1\text{H}), 3.94 (s, 1\text{H}), 3.77 (d, J = 11.9 \text{ Hz}, 1\text{H}), 3.72 (d, J = 2.4 \text{ Hz}, 3\text{H}), 3.69 (d, J = 2.4 \text{ Hz}, 3\text{H}), 3.39 - 3.27 (m, 1\text{H}), 2.67 - 2.49 (m, 1\text{H}), 2.28 - 2.11 (m, 1\text{H}), 1.97 (s, 3\text{H}), 1.56 - 1.44 (m, 4\text{H}), 1.40 (s, 9\text{H}), 0.86 (td, J = 7.4, 5.1 \text{ Hz}, 6\text{H}). \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta 171.2, 156.3, 141.9 (d, J = 6.8 \text{ Hz}), 129.3 (d, J = 180.4 \text{ Hz}), 81.8, 79.8, 76.0 (d, J = 20.2\text{Hz}), 54.1, 52.8 (d), 52.7 (d), 49.8 (d), 30.7 (d), 28.2, 25.9, 25.6, 23.1, 9.7, 9.3. HR-ESI-MS calculated for C₂₀H₃₇O₇NaN₂P (M+Na)\(^+\) 471.2231, found 471.2232.

Methyl \((3R,4R,5S)-4\text{-acetamido-5-[(tert-butoxycarbonyl)-amino]-3-(1-ethylpropoxy)-1-cyclohexene-1-phosphonate (16)}\)

An aqueous solution of NaOH (0.5M; 2.8 mL) was added to a stirred solution of the dimethoxyphosphonate 15 (0.31 g, 0.698 mmol) in 1,4-dioxane (2.8 mL). The reaction mixture was stirred for 18 h at room temperature. The pH was adjusted to neutral by addition of Amberlite IR 120 hydrogen form. Amberlite was removed by filtration and the filtrate was
concentrated under reduced pressure. The residue was purified by flash column chromatography (eluent EtOAc/MeOH gradient 6:1 to 1:2) to furnish phosphonic acid 16 (0.27 g, 91% yield) as a white solid.

TLC (DCM/MeOH 2:1), $R_f = 0.2$. $^1$H NMR (600 MHz, D$_2$O) $\delta$ 6.32 (d, $J = 19.7$ Hz, 1H), 4.25 (d, $J = 8.6$ Hz, 1H), 3.83 (t, $J = 10.0$ Hz, 1H), 3.75 (s, 1H), 3.52 (d, $J = 10.7$ Hz, 3H), 2.45 – 2.43 (m, 2H), 2.24 (s, 3H), 1.57 (dd, $J = 13.6, 6.7$ Hz, 4H), 1.51 – 1.34 (m, 9H), 0.88 (dt, $J = 34.7, 7.3$ Hz, 6H). $^{13}$C NMR (151 MHz, D$_2$O) $\delta$ 174.2, 157.6, 137.0, 131.6, 130.5, 84.2, 80.9, 76.9, 76.7, 55.6, 51.6, 49.3, 49.2, 31.1, 27.6, 25.6, 25.3, 22.2, 8.6, 8.5. $^{31}$P NMR (121 MHz, D$_2$O) $\delta$ 15.27. HR-ESI-MS calculated for C$_{19}$H$_{36}$O$_7$N$_2$P (M+H)$^+$ 435.2255, found 435.2256.

(6-Azidohexyl) (3R,4R,5S)-4-acetylamino-5-[(tert-butoxycarbonyl)-amino]-3-(1-ethylpropoxy)-1-cyclohexene-1-phosphonic acid (17)

Methyl (3R,4R,5S)-4-acetamido-5-[(tert-butoxycarbonyl)-amino]-3-(1-ethylpropoxy)-1-cyclohexene-1-phosphonate 16 (100 mg, 0.23 mmol) was dissolved in DMF (1.5 mL) followed by addition of DIPEA (0.16 mL, 0.92 mmol), 1-azido-6-bromohexane (120 mg, 0.57 mmol) and sodium iodide (5 mg, 0.034 mmol). The reaction was then purged with argon and heated to 60 °C for 48 h. The solvent was evaporated under reduced pressure and the crude mixture purified by flash chromatography (from EtOAc to EtOAc/MeOH 80:20) to yield the alkylated phosphonic acid 17 (72 mg, 56%).

$^1$H NMR (401 MHz, Methanol- $d4$) $\delta$ 6.36 (d, $J = 19.0$ Hz, 1H), 4.15 – 4.00 (m, 1H), 3.88 – 3.78 (m, 1H), 3.77 (t, $J = 6.4$ Hz, 1H), 3.70 (dd, $J = 10.0, 4.4$ Hz, 1H), 3.55 – 3.44 (m, 1H), 3.41 (t, $J = 5.4$ Hz, 1H), 3.28 (d, $J = 6.8$ Hz, 2H), 2.62 (d, $J = 17.1$ Hz, 1H), 2.22 (t, $J = 14.2$ Hz, 1H), 1.97 (s, 3H), 1.61 (m, 3H), 1.50 (ddd, $J = 16.4, 7.6, 6.1$ Hz, 4H), 1.43 (s, 12H), 1.34 (d, $J = 6.6$ Hz,
2H), 0.89 (dt, J = 15.1, 7.4 Hz, 6H). $^{13}$C NMR (101 MHz, Methanol-$d_4$) δ 172.4, 156.6, 136.0, 132.6 (d, J = 211.8 Hz), 82.1, 78.8, 76.5, 64.2, 55.2, 54.5, 51.0, 30.4, 28.5 (x3), 27.4, 26.2, 26.0, 25.4, 25.2, 21.7, 18.0, 8.6, 8.3. $^{31}$P NMR (162 MHz, Methanol-$d_4$) δ 13.12. HR-ESI-MS calculated for C$_{24}$H$_{43}$O$_7$N$_5$P = 544.2906, found 544.2906.

Ethyl (3R,4R,5S)-4-acetamido-5-$[N^2,N^3$-bis(tert-butoxycarbonyl)guanidino]-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate

Mercury(II) chloride (0.11 g, 0.40 mmol) was added portionwise to a solution of oseltamivir base 6 (0.10 g, 0.32 mmol), N,N′-di-(tert-butoxycarbonyl)thiourea (0.11 g, 0.40 mmol) and triethylamine (0.11 mL, 0.80 mmol) in DMF (15 mL) at 0 °C. The reaction mixture was stirred for 24 h at room temperature. The mixture was diluted with EtOAc (10 mL), filtered through a pad of Celite and concentrated under reduced pressure. The residue was diluted with water (30 mL) and extracted with EtOAc (3x10 mL). The combined organic phase was washed with water, brine, dried over Na$_2$SO$_4$, filtered and evaporated. The residue was purified by flash column chromatography (eluent Hexanes/EtOAc, 2:1) to afford the Boc-protected guanidine derivative 7 (0.16 g, 89%).

TLC (Hexanes/EtOAc 1:1) $R_f = 0.4$. $^1$H NMR (300 MHz, CDCl$_3$) δ 11.33 (s, 1H), 8.57 (d, J = 8.1 Hz, 1H), 6.76 (s, 1H), 6.16 (d, J = 8.9 Hz, 1H), 4.43 – 4.23 (m, 1H), 4.20 – 4.01 (m, 3H), 3.96 (d, J = 7.7 Hz, 1H), 3.36 – 3.21 (m, 1H), 2.72 (dd, J = 17.6, 5.3 Hz, 1H), 2.42 – 2.23 (m, 1H), 1.85 (s, 3H), 1.55 – 1.49 (m, J = 8.4, 4.7 Hz, 2H), 1.22 (dd, J = 12.6, 5.5 Hz, 3H), 0.82 (dt, J = 10.3, 7.4 Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 170.3, 166.0, 163.3, 157.0, 152.7, 138.1,
An aqueous solution of NaOH (0.5 M; 0.55 mL) was added to a solution of ester (0.15 g, 0.27 mmol) in 1,4-dioxane (0.55 mL). The reaction mixture was stirred overnight at room temperature. The pH was adjusted to neutral by addition of Amberlite IR 120 hydrogen form. Amberlite was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (Toluene/EtOAc/AcOH 1:1:0.5%) to afford the free acid (0.07 g, 48%).

TLC (Toluene/EtOAc/AcOH 1:1:0.5%) $R_f = 0.2$. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.64 (d, $J = 8.1$ Hz, 1H), 6.82 (s, 1H), 6.23 (d, $J = 8.9$ Hz, 1H), 4.39 (dd, $J = 8.3$, 6.0 Hz, 1H), 4.26 – 4.16 (m, 2H), 4.16 – 4.08 (m, 1H), 4.06 – 3.98 (m, 1H), 3.41 – 3.29 (m, 1H), 2.78 (dd, $J = 17.6$, 5.3 Hz, 1H), 2.47 – 2.32 (m, 1H), 1.91 (s, 3H), 1.61 – 1.41 (m, 22H), 1.27 (dt, $J = 10.9$, 7.1 Hz, 4H), 0.89 (dt, $J = 10.3$, 7.4 Hz, 6H). $^{13}$C NMR (75 MHz, CD$_3$OD) $\delta$ 173.6, 169.3, 164.4, 157.7, 153.7, 138.7, 130.4, 84.6, 84.0, 80.5, 76.6, 54.6, 50.0, 31.4, 28.5, 28.2, 27.3, 26.9, 22.7, 9.9, 9.7. HR-ESI-MS calculated for C$_{25}$H$_{43}$O$_8$N$_4$ (M+H)$^+$ 527.3075, found 527.3076.
Dimethyl (3R,4R,5S)-4-acetamido-5-[N2,N3-bis(tert-butoxycarbonyl)guanidino]-3-(1-ethylpropoxy)-1-cyclohexene-1-phosphonate

The Boc-protected phosphonate 16 (0.12 g, 0.259 mmol) was treated with trifluoroacetic acid (100%, 1 mL) for 1 h and then the trifluoroacetic acid was removed by evaporation under reduced pressure. The residue was dissolved in acetonitrile (1.5 mL) and triethylamine (0.18 mL, 1.29 mmol) was added dropwise followed by the addition of N,N’-di-Boc-1H-pyrazole-1-carboxamidine (0.08 g, 0.26 mmol). The reaction mixture was stirred for 18 h at room temperature and then was evaporated to dryness. The residue was purified by flash column chromatography (eluent EtOAc gradient to EtOAc/MeOH 6:1) to afford the guanidine phosphonate (0.07 g, 47% yield).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 11.39 (s, 1H), 8.60 (d, $J = 7.3$ Hz, 1H), 6.64 (d, $J = 22.5$ Hz, 1H), 6.35 (d, $J = 9.2$ Hz, 1H), 4.41 (d, $J = 8.2$ Hz, 1H), 4.23 – 4.04 (m, 1H), 3.99 (s, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.39 – 3.27 (m, 1H), 2.72 – 2.58 (m, 1H), 2.36 – 2.22 (m, 1H), 1.92 (s, 3H), 1.58 – 1.41 (m, 22H), 0.88 (dd, $J = 16.2$, 7.4 Hz, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.6, 163.2, 157.0, 152.7, 143.2, 143.1, 132.2, 132.1, 126.6, 124.1, 83.7, 82.8, 79.8, 76.4, 76.1, 54.3, 52.8, 52.7, 52.6, 48.4, 48.2, 30.9, 30.8, 28.3, 28.1, 26.0, 25.7, 23.3, 9.6, 9.3. HR-ESI-MS calculated for C$_{26}$H$_{48}$O$_9$N$_4$P (M+H)$^+$ 591.3153, found 591.3153.
Ethyl (3R,4R,5S)-4-acetamido-5-[N-[dimethyl aspartyl]methyl]-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (21)

Dimethyl maleate (0.57 g, 4.0 mmol) was added to a stirred solution of oseltamivir free base 5 (0.22 g, 0.73 mmol) in methanol (3 mL) and the mixture was refluxed overnight. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (DCM/MeOH 90:10) to yield the mixture of diastereomers 21 (0.25 g, 75%).

$^{1}$H NMR (300 MHz, CDCl$_3$) δ 6.68 (s, 1H), 6.03 (d, $J = 7.5$ Hz, 1H), 4.26 (d, $J = 8.3$ Hz, 1H), 4.19 – 4.01 (m, 2H), 3.64 (s, 3H), 3.67 – 3.63 (m, 1H), 3.60 (s, 3H), 3.51 – 3.36 (m, 1H), 3.35 – 3.20 (m, 1H), 3.08 (dt, $J = 10.1$, 5.0 Hz, 1H), 2.96 – 2.86 (m, 1H), 2.72 – 2.52 (m, 3H), 2.10 – 1.95 (m, 1H), 1.92 (s, 3H), 1.42 (ddt, $J = 7.4$, 5.7, 1.9 Hz, 4H), 1.26 – 1.13 (m, 3H), 0.90 – 0.75 (m, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) of major diastereomer δ 174.2, 171.4, 170.9, 166.3, 137.7, 129.0, 81.7, 74.4, 60.7, 57.4, 56.1, 53.4, 52.3, 51.8, 37.8, 31.5, 26.2, 25.6, 23.6, 14.2, 9.5, 9.3.

$^{13}$C NMR (75 MHz, CDCl$_3$) of minor diastereomer δ 174.8, 171.3, 171.0, 166.5, 137.8, 129.1, 82.0, 75.9, 60.9, 55.9, 55.2, 53.8, 52.4, 52.0, 38.7, 31.7, 26.2, 25.7, 23.8, 14.3, 9.7, 9.4. HR-ESI-MS calculated for C$_{22}$H$_{36}$N$_2$O$_8$Na (M+Na)$^+$ 479.2364, found 479.2364.
Ethyl (3R,4R,5S)-4-Acetamido-5-[2-[2-(2-methoxyethoxy)ethoxy]acetamido]-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (22)

To a solution of 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.28 g, 0.87 mmol) and 2-[2-(2-methoxyethoxy)ethoxy]acetic acid (0.13 g, 0.72 mmol) in DMF (3 mL) was added triethylamine (0.5 ml, 3.6 mmol). The reaction mixture was stirred for 5 min at room temperature followed by addition of Oseltamivir phosphate 5 (0.15 g, 0.36 mmol) and the reaction was stirred for an additional for 16 h. The reaction mixture was quenched by addition of water (10 mL) and NaHCO₃ saturated solution (5 mL) until the pH was slightly basic. The aqueous solution was extracted with DCM and the combined organic phases were washed with water and brine, dried over Na₂SO₄, and evaporated to dryness under reduced pressure. Purification of the crude residue by flash column chromatography (eluent DCM/MeOH 90:10) furnished the amide 22 (0.16 g, 93%).

¹H NMR (401 MHz, CDCl₃) δ 7.33 (d, J = 8.6 Hz, 1H), 6.82 – 6.74 (m, 1H), 6.06 (d, J = 8.8 Hz, 1H), 4.19 (qd, J = 7.1, 1.0 Hz, 3H), 4.13 – 4.06 (m, 1H), 4.04 – 3.99 (m, 1H), 3.69 – 3.61 (m, 8H), 3.59 – 3.52 (m, 2H), 3.37 – 3.31 (m, 1H), 3.35 (s, 3H), 2.85 – 2.69 (m, 1H), 2.37 (dd, J = 17.7, 9.8 Hz, 1H), 1.92 (s, 3H), 1.56 – 1.43 (m, 4H), 1.27 (t, J = 7.1 Hz, 3H), 0.87 (dt, J = 10.4, 7.4 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 170.8, 170.7, 166.1, 137.9, 129.3, 82.4, 75.7, 72.0, 71.1, 70.7, 70.4, 70.4, 61.0, 59.1, 54.5, 47.5, 30.6, 26.3, 25.8, 23.4, 14.3, 9.7, 9.4. HR-ESI-MS calculated for C₂₃H₄₀O₈N₂ (M+H)⁺ 473.2865, found 473.2857.
Ethyl (3R,4R,5S)-4-acetamido-5-[(1-ethoxy-1-oxopropan-2-yl)amino]-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate.

To a solution of oseltamivir phosphate 5 (0.2 g, 0.49 mmol) and ethyl 2-bromopropionate (0.11 g, 0.58 mmol) in DMF (3 mL) was added NaHCO₃ (0.25 g, 2.9 mmol) portionwise. The reaction mixture was stirred at 80 ºC overnight. The mixture was then quenched by the addition of water (5 mL) and extracted with EtOAc (3x 10 mL). The combined organic extracts was washed with water (2x 5 mL) and brine (3 mL), dried over anhydrous MgSO₄ and evaporated to dryness. The resulting residue was purified by flash chromatography (EtOAc) to yield 70 mg of the A diastereomer and 77 mg of the B diastereomer, (73 % combined yield).

A diastereomer, less polar (S) (18)

¹H NMR (300 MHz, CDCl₃) δ 6.82 – 6.70 (m, 1H), 5.66 (d, J = 7.9 Hz, 1H), 4.29 (ddd, J = 5.9, 2.9, 1.5 Hz, 1H), 4.17 (tt, J = 8.1, 7.1 Hz, 4H), 3.55 (dt, J = 9.7, 7.8 Hz, 1H), 3.46 (q, J = 7.0 Hz, 1H), 3.33 (q, J = 5.7 Hz, 1H), 3.15 (ddd, J = 9.8, 8.8, 5.3 Hz, 1H), 2.75 – 2.60 (m, 1H), 2.18 (ddt, J = 11.7, 5.5, 2.8 Hz, 1H), 2.13 – 2.02 (m, 1H), 1.99 (s, 3H), 1.57 – 1.40 (m, 4H), 1.32 – 1.19 (m, 9H), 0.88 (t, J = 7.4 Hz, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 176.0, 170.7, 166.5, 137.4, 129.5, 81.9, 74.3, 60.9 (2x OCH₂CH₃), 57.0, 55.1, 52.9, 31.5, 26.3, 25.9, 23.8, 19.4, 14.3 (2x OCH₂CH₃), 9.6, 9.5.

B diastereomer, more polar (R) (19)
1H NMR (300 MHz, CDCl$_3$) δ 6.73 (t, $J = 2.5$ Hz, 1H), 5.80 (d, $J = 6.6$ Hz, 1H), 4.15 (ddt, $J = 8.6$, 7.0, 3.3 Hz, 4H), 4.07 – 3.99 (m, 1H), 3.77 (dt, $J = 10.7$, 8.7 Hz, 1H), 3.49 – 3.38 (m, 1H), 3.35 – 3.24 (m, 1H), 2.83 – 2.70 (m, 1H), 2.70 – 2.60 (m, 1H), 2.09 (q, $J = 5.2$, 4.8 Hz, 2H), 2.03 (s, 3H), 1.56 – 1.38 (m, 4H), 1.25 (td, $J = 6.8$, 4.3 Hz, 9H), 0.95 – 0.76 (m, 6H).

13C NMR (75 MHz, CDCl$_3$) δ 176.4, 170.8, 166.4, 137.7, 129.0, 81.8, 75.8, 60.8 (2x OCH$_2$CH$_3$), 55.4, 53.8, 53.5, 31.4, 26.1, 25.6, 23.7, 19.8, 14.2 (2x OCH$_2$C$_3$H$_3$), 9.5, 9.2.

HR-ESI-MS calculated for C$_{21}$H$_{36}$N$_2$O$_6$Na (M+Na)$^+$ 435.2466, found 435.2466.

Ethyl (3R,4R,5S)-4-acetamido-5-[N-((R)-1-ethoxy-1-oxopropan-2-yl)-4-nitrobenzamido]-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (20)

4-Nitrobenzoyl chloride (0.086 g, 0.46 mmol) was added to a solution of the B diastereomer 19 (0.16 g, 0.39 mmol) and trimethylamine (0.1 mL, 0.77 mmol) in DCM (3 mL). The reaction mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (1.5 mL) and the resulting mixture was extracted with EtOAc (3x 10 mL). The combined organic extracts were washed with water, brine and were evaporated to dryness. The residue was purified by flash chromatography (Hex/EtOAc 1:2) which was followed by crystallization (EtOH) to furnish the desired compound 20 (79 mg, 36% yield).

1H NMR (401 MHz, Chloroform-$d_3$) δ 8.26 (d, $J = 8.7$ Hz, 2H), 7.48 (d, $J = 8.7$ Hz, 2H), 7.13 (d, $J = 6.1$ Hz, 1H), 6.75 (t, $J = 2.4$ Hz, 1H), 5.10 (ddd, $J = 7.3$, 3.5 Hz, 1H), 4.63 (td, $J = 10.9$, 6.2 Hz, 1H), 4.35 – 4.16 (m, 4H), 3.79 (q, $J = 6.8$ Hz, 1H), 3.25 (p, $J = 5.7$ Hz, 1H), 3.10 (ddd, $J = 11.3$, 8.5, 6.1 Hz, 1H), 2.89 – 2.77 (m, 1H), 2.56 – 2.43 (m, 1H), 1.96 (d, $J = 6.3$ Hz, 3H), 1.67 (d, $J = 6.8$ Hz, 3H), 1.55 – 1.40 (m, 4H), 1.39 – 1.27 (m, 6H), 0.95 – 0.80 (m, 6H).

13C NMR (101 MHz, CDCl$_3$) δ 171.7, 171.1, 169.8, 166.0, 148.8, 141.2, 138.9, 128.3, 127.9, 126.9, 124.1, 124.0, 82.1, 71.2, 62.2, 61.3, 56.7, 55.6, 52.6, 28.4, 26.5, 25.7, 24.3, 16.3, 14.4, 14.2, 9.8, 9.3.

HR-ESI-MS calculated for C$_{28}$H$_{39}$N$_3$O$_9$Na (M+Na)$^+$ 584.2578, found 584.2578.

X-ray analysis of the crystals determinates that the product obtained was the R diastereomer.
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