An aldol approach to the enantioselective synthesis of (-)-oseltamivir phosphate

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Electronic Supplementary Information

Contents

General Experimental S2

Synthesis of (S)-4-Benzyl-3-(2-(pentyl-3-oxy)acetyl)oxazolidin-2-one 4 S2
• 2-(Pentyl-3-oxy)acetic acid 5 S2
• (S)-4-Benzyl-3-(2-(pentyl-3-oxy)acetyl)oxazolidin-2-one 4 S2

Synthesis of (S)-Ethyl 4-(tert-butoxycarbonylamino)-5-oxopentanoate 3 S3
• (S)-Ethyl 4-(tert-butoxycarbonylamino)-5-(ethylthio)-5-oxopentanoate 7 S3
• (S)-Ethyl 4-(tert-butoxycarbonylamino)-5-oxopentanoate 3 S3

Synthesis of oseltamivir phosphate S4
• (4S,5R,6S)-ethyl 7-((S)-4-benzyl-2-oxooxazolidin-3-yl)-4-((tert-butoxycarbonyl)amino)-5-hydroxy-7-oxo-6-(pentan-3-yloxy)heptanoate 8 S4
• (4S,5R)-tert-butyl 5-((S)-2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxo-1-(pentan-3-yloxy)ethyl)-4-(3-ethoxy-3-oxopropyl)-2,2-dimethylloxazolidine-3-carboxylate 9 S4
• (4R,5R)-tert-butyl 5-((R)-2-hydroxy-1-(pentan-3-yloxy)ethyl)-4-(3-hydroxypropyl)-2,2-dimethylloxazolidine-3-carboxylate 12 S5
• (3aS,7R,7aR)-tert-butyl 5-formyl-2,2-dimethyl-7-(pentan-3-yloxy)-3a,4,7,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate 14 S6
• (3R,4R,5S)-ethyl 5-((tert-butoxycarbonyl)amino)-4-hydroxy-3-(pentan-3-yloxy)cyclohex-1-ene carboxylate 1 S6
• (3R,4S,5S)-ethyl 5-((tert-butoxycarbonyl)amino)-4-hydroxy-3-(pentan-3-yloxy)cyclohex-1-ene carboxylate 15 S7

References S7

Scanned spectra S8
General experimental

All chromatographic separations\(^1\) were performed on Silica, 10-18, 60A, ICN Biomedicals. Standard techniques were used for the purification of reagents and solvents.\(^2\) NMR spectra were recorded on a Varian Gemini 200, \(^1\)H NMR at 200 MHz, \(^{13}\)C NMR at 50 MHz, for samples in deuterated chloroform), and on Bruker Avance III 500 \(^1\)H NMR at 500 MHz, \(^{13}\)C NMR at 125 MHz). Chemical shifts are expressed in ppm (\(\delta\)) using tetramethylsilane as internal standard. IR spectra were recorded on a Nicolet 6700 FT instrument, and are expressed in cm\(^{-1}\). Mass spectra were obtained on Agilent technologies 6210 TOF LC/MS instrument (LC: series 1200). Microanalyses were performed at the Vario EL III instrument CHNOS Elementar Analyzer, Elementar Analysensysteme GmbH, Hanau-Germany. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Synthesis of (S)-4-Benzyl-3-(2-(pentyl-3-oxy)acetyl)oxazolidin-2-one 4

2-(Pentyl-3-oxy)acetic acid 5\(^3\)

3-Pentanol (3.26 g; 4.0 mL; 37 mmol) was added dropwise to a cold (0 °C) suspension of sodium hydride (4.4 g; 183.3 mmol) and potassium iodide (500 mg; 3.01 mmol) in THF (50 mL), and the reaction mixture was stirred 15 min under an argon atmosphere. A solution of bromoacetic acid (7.74 g; 55.7 mmol) in THF (5 mL) was added dropwise and the reaction mixture was heated to reflux for 24 h. Upon cooling (0 °C) excess sodium hydride was destroyed by careful addition of water, then water (30 mL) was added, the aqueous layer was separated, washed with EtOAc (3 x 20 mL), acidified with 1.5 M HCl (pH 2-3) and extracted with EtOAc (4 x 20 mL). Combined organic extract was washed with brine, dried over MgSO\(_4\) anh., filtered and concentrated under reduced pressure. The crude acid 5 was purified by distillation under reduced pressure, to afford 3.66 g (68%) of the title compound 5, as a colorless liquid, bp 130-140 °C/1 mmHg. Physical data for 5\(^3\): \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\): 9.74 (bs, 1H), 4.13 (s, 2H), 3.31 (quint., \(J = 5.8\) Hz, 1H), 1.58 (q, \(J = 7.2\) Hz, 2H), 1.55 (q, \(J = 7.2\) Hz, 2H), 0.92 (t, \(J_2 = 7.2\) Hz, 6H). \(^{13}\)C NMR (50 MHz, CDCl\(_3\)) \(\delta\): 174.5 (C), 83.5 (CH), 65.8 (CH\(_2\)), 25.5 (CH\(_2\)), 9.3 (CH\(_3\)). IR (ATR): 2968, 2937, 2880, 1734, 1240, 1124, 920. HRMS (ESI): calcd. for [C\(_7\)H\(_{14}\)O\(_3\) + NH\(_4\)]\(^+\): 164.1281; found: 164.1282.

(S)-4-Benzyl-3-(2-(pentyl-3-oxy)acetyl)oxazolidin-2-one 4

Pivaloyl chloride (218 mg; 0.24 mL; 1.81 mmol) was added dropwise to a cold (-78 °C) solution of acid 5 (250 mg; 1.71 mmol) and triethylamine (182 mg; 0.25 mL; 1.79 mmol) in diethyl ether (15 mL), under an argon atmosphere. After 5 min of stirring at that temperature, the reaction mixture was allowed to reach 0 °C within 1 h. To this reaction mixture, cooled to -78 °C, was added via cannula a solution of a lithium salt of (S)-4-benzyloxazolidinone (obtained by treatment of (S)-4-benzyloxazolidinone (281 mg; 1.72 mmol) in THF (4.5 mL) with n-BuLi (1.3 mL of 1.45 M solution in hexane) at -78 °C, for 15 min). Reaction mixture was allowed to reach 0 °C with stirring (~ 30 min), then quenched with water and extracted with diethyl ether (3 x 50 mL). The combined organic extract was washed with brine, dried over anh. MgSO\(_4\), and concentrated under reduced pressure. Purification by dry-flash
chromatography (SiO$_2$; eluent: petroleum-ether:EtOAc = 4:1) afforded 448 mg (86%) of the title compound 4, as a colorless oil. Physical data for 4: $^1$H NMR (200 MHz, CDCl$_3$) $\delta$: 7.39-7.28 (m, 3H), 7.27-7.19 (m, 2H), 4.78-4.57 (m, 1H), 4.69 (s, 2H), 4.32-4.18 (m, 2H), 3.39-3.25 (m, 2H), 2.81 (dd, $J = 12.8, 9.4$ Hz, 1H), 1.60 (quint., $J = 7.2$ Hz, 4H), 0.95 (t, $J = 7.4$ Hz, 6H). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$: 170.6 (C), 153.4 (C), 135.0 (C), 129.4 (CH), 128.9 (CH), 127.3 (CH), 83.0 (CH$_2$), 68.6 (CH$_2$), 67.1 (CH$_2$), 54.8 (CH), 37.7 (CH$_2$), 25.5 (CH$_2$), 25.4 (CH$_2$), 9.4 (CH$_3$), 9.3 (CH$_3$). IR (ATR): 3063, 3028, 2966, 2934, 2877, 1781, 1718, 1392, 1352, 1260, 1216, 1131. HRMS (ESI): calcd. for [C$_{17}$H$_{23}$NO$_4$ + H]$^+$: 306.1700; found: 306.1701. $\left[\alpha\right]_{D}^{20} +57.2$ (c 0.67, CHCl$_3$).

Synthesis of (S)-Ethyl 4-(tert-butoxycarbonylamino)-5-oxopentanoate 3

(S)-Ethyl 4-(tert-butoxycarbonylamino)-5-(ethylthio)-5-oxopentanoate 7

Isobutyl chloroformate (575 mg; 0.55 mL; 4.21 mmol) and triethylamine (436 mg; 0.60 mL; 4.3 mmol) were added to a cold (0 °C) solution of (S)-2-((tert-butoxycarbonyl)amino)-5-ethoxy-5-oxopentanoic acid (1.07 g; 3.88 mmol) in dichloromethane (11 mL), under an argon atmosphere. The reaction mixture was vigorously stirred for 15 min at 0 °C, then ethane thiol (587 mg; 0.70 mL; 9.45 mmol) and triethylamine (436 mg; 0.60 mL; 4.3 mmol) were added. The resulting solution was stirred for 30 min at 0 °C and 45 min at rt. The reaction mixture was diluted with dichloromethane (25 mL), washed with 1.5 M HCl (15 mL), 1M NaOH (15 mL), water (15 mL) and brine (15 mL), dried over anh. MgSO$_4$, concentrated under reduced pressure and purified by dry-flash chromatography (SiO$_2$; eluent: petroleum-ether:EtOAc = 4:1) to give 1.16 g (93%) of the title compound 7, as colorless crystals. Physical data for 7: mp 63 °C. $^1$H NMR (200 MHz, CDCl$_3$) $\delta$: 5.28 (bd, $J = 8.5$ Hz, 1H), 4.42-4.31 (m, 1H), 4.15 (q, $J = 7.1$ Hz, 2H), 2.88 (q, $J = 7.4$ Hz, 2H), 2.47-2.39 (m, 2H), 2.30-2.13 (m, 1H), 2.02-1.87 (m, 1H), 1.45 (s, 9H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.25 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$: 201.0 (C), 172.8 (C), 155.2 (C), 80.1 (C), 60.6 (CH$_2$), 59.1 (CH), 29.7 (CH$_2$), 23.1 (CH$_2$), 14.3 (CH$_3$), 14.0 (CH$_3$). IR (ATR): 3352, 2985, 2931, 1728, 1679, 1511, 1250, 1152, 1019. HRMS (ESI): calcd. for [C$_{14}$H$_{25}$NO$_5$S + Na]$^+$: 342.1346; found: 342.1349. $\left[\alpha\right]_{D}^{20} -18.5$ (c 0.21, CHCl$_3$).

(S)-Ethyl 4-(tert-butoxycarbonylamino)-5-oxopentanoate 3

Triethylsilane (1.82 g; 2.5 mL; 15.65 mmol) was added during 1 h to a suspension of thioester 7 (2.5 g; 7.83 mmol), 2.6-lutidine (1.26 g; 1.37 mL; 11.76 mmol) and 10% palladium on charcoal (417 mg; 0.392 mmol) in acetone (39 mL), at rt, under an argon atmosphere. Upon the completion of the addition, the reaction mixture was stirred for additional 15 min, then filtered and concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 mL), washed with 1.5 M HCl (25 mL), sat. NaHCO$_3$ (25 mL) and brine (25 mL), dried over anh. MgSO$_4$, concentrated under reduced pressure and purified by dry-flash chromatography (SiO$_2$; eluent: petroleum-ether:EtOAc = 4:1) to give 1.64 g (81%) of the title compound 3, as a colorless oil. Physical data for 3: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 9.59 (s, 1H), 5.31-5.28 (m, 1H), 4.27-4.24 (m,1H), 4.14 (q, $J = 7.1$ Hz, 2H), 2.49-2.37 (m, 2H), 2.29-2.25 (m, 1H), 1.93-1.85 (m, 1H), 1.45 (s, 9H), 1.26 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 199.1 (CH), 172.8 (C), 155.5 (C), 80.1(C), 60.6 (CH$_2$), 59.1 (CH), 29.7 (CH$_2$), 28.2 (3 x CH$_3$), 27.5 (CH$_2$), 23.1 (CH$_2$), 14.3 (CH$_3$), 14.0 (CH$_3$). IR (ATR): 3360, 2978, 2931, 1728, 1679, 1511, 1250, 1152, 1019. HRMS (ESI): calcd. for [C$_{14}$H$_{25}$NO$_5$S + Na]$^+$: 342.1346; found: 342.1349. $\left[\alpha\right]_{D}^{20} -18.5$ (c 0.21, CHCl$_3$).
1729, 1710, 1688, 1514, 1248, 1162, 1026. HRMS (ESI): calcd. for [C\textsubscript{12}H\textsubscript{21}NO\textsubscript{5} + Na\textsuperscript{+}]: 282.1312; found: 282.1316. [\alpha]D\textsuperscript{20} +1.02 (c 0.49, CHCl\textsubscript{3}).

Synthesis of oseltamivir phosphate

(4S,5R,6S)-ethyl 7-(((S)-4-benzyl-2-oxooxazolidin-3-yl)-4-((tert-butoxycarbonyl)amino)-5-hydroxy-7-oxo-6-(pentan-3-yl oxy)heptanoate \textsuperscript{8}

Di-\textit{n}-butylboron triflate (504 mg; 0.4 mL; 1.83 mmol) was added dropwise to a solution of oxazolidinone \textsuperscript{4} (437.4 mg; 1.43 mmol) and triethylamine (218 mg; 0.3 mL; 2.18 mmol) in cold (-78 °C) dichloromethane (7.2 mL), and the reaction mixture was stirred for 1 h at that temperature, then allowed to reach 0 °C within 1h, then again cooled to -78 °C. A solution of aldehyde \textsuperscript{3} (258.8 mg; 0.73 mmol) in dichloromethane (1 mL) was added and the reaction mixture was stirred for 15 min at that temperature, then allowe to reach -30 °C during 1 h and stirred at that temperature for 3 h. The reaction mixture was cooled to -40 °C and quenched by alternate additions of phosphate buffer (pH 7; 5.7 mL) and methanol (17.1 mL), while maintaining the temperature below -15 °C. Finally, a mixture of hydrogen peroxide and methanol (11.4 mL; v/v=1/2) was added, the reaction mixture was allowed to reach 0 °C and was stirred at that temperature for 1 h. The reaction mixture was extracted with dichloromethane (3 x 30 mL), the organic extract was washed with brine, dried over anh. MgSO\textsubscript{4}, concentrated under reduced pressure and purified by dry-flash chromatography (SiO\textsubscript{2}; eluent: benzene/EtOAc=4/1) to give 348.1 mg of the mixture of the title compound \textsuperscript{8} and aldehyde \textsuperscript{3}. Purification of this mixture by Lobar chromatography (SiO\textsubscript{2}; eluent: dichloromethane/methanol=39/1) afforded 250.6 mg (45%) of the title compound \textsuperscript{8}, as a colorless oil. Physical data for \textsuperscript{7}: ¹H NMR (500 MHz, CDCl\textsubscript{3}) δ: 7.34-7.23 (m, 5H), 5.36 (d, J = 7.5 Hz, 1H), 4.84 (d, J = 10 Hz, 1H, 4.65 (brt, J = 7.5 Hz, 1H), 4.35 (t, J = 8.0 Hz, 1H), 4.15-4.08 (m, 3H), 3.89 (bd, J = 7.5 Hz, 1H), 3.59-3.53 (m, 1H), 3.48 (quint, J = 6 Hz., 1H), 3.37 (dd, J = 13.5, 3.5 Hz, 1H), 2.77 (dd, J = 13.5, 10.0 Hz, 1H), 2.76 (dd, J = 3.0, 1.0 Hz, 1H), 2.35-2.29 (m, 2H), 1.96-1.83 (m, 2H), 1.71-1.64 (m, 1H, 1.60-1.45 (m, 3H), 1.40 (s, 9H), 1.24 (t, J = 7.5 Hz, 3H), 0.93 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H). ¹³C NMR (125 MHz, CDCl\textsubscript{3}) δ: 173.1 (C), 172.3 (C), 155.9 (C), 153.2 (C), 135.4 (C), 129.4 (CH), 128.9 (CH), 127.3 (CH), 82.8 (CH), 79.5 (C), 75.7 (CH), 75.1 (CH), 66.4 (CH\textsubscript{2}), 60.4 (CH\textsubscript{2}), 56.2 (CH), 49.7 (CH), 37.7 (CH\textsubscript{2}), 30.9 (CH\textsubscript{2}), 28.6 (CH\textsubscript{2}), 28.3 (3 x CH\textsubscript{3}), 26.3 (CH\textsubscript{2}), 25.6 (CH\textsubscript{2}), 14.2 (CH\textsubscript{3}), 9.5 (CH\textsubscript{3}), 9.4 (CH\textsubscript{3}). IR (ATR): 3448, 3371, 2971, 2932, 2877, 1784, 1731, 1699, 1388, 1172, 1112. HRMS (ESI) calcd. for [C\textsubscript{29}H\textsubscript{44}N\textsubscript{2}O\textsubscript{9} + Na\textsuperscript{+}]: 587.2939; found: 587.2944. [\alpha]D\textsuperscript{20} +8.4 (c 0.65, CHCl\textsubscript{3}).

(4S,5R)-tert-butyl 5-(((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxo-1-(pentan-3-yl oxy)ethyl)-4-(3-ethoxy-3-oxopropyl)-2,2-dimethyloxazolidine-3-carboxylate \textsuperscript{9}
A solution of aldol 8 (87.7 mg; 0.155 mmol), 2,2-dimethoxypropane (169 mg; 0.20 mL; 1.62 mmol) and p-toluenesulfonic acid (5.4 mg; 0.03 mmol) in dichloromethane (0.2 mL) is stirred for 1 h at rt, then concentrated under reduced pressure (when it turns red). The residue was diluted with dichloromethane, washed with sat. NaHCO₃, dried over anh. MgSO₄, and concentrated under reduced pressure. Purification of the crude product by dry-flash chromatography (SiO₂; eluent: petroleum-ether/EtOAc=7/3) afforded 62.6 mg (67%) of the title compound 9, as a colorless viscous oil. Physical data for 9: ¹H NMR (500 MHz, CDCl₃) δ: 7.35-7.30 (m, 2H), 7.30-7.27 (m, 1H), 7.25-7.21 (m, 2H), 5.34 (bs, 1H), 4.77-4.67 (m, 1H), 4.31 (dd, J = 4.0, 2.5 Hz, 1H), 4.28 (t, J = 8.5 Hz, 1H), 4.21 (dd, J = 9.0, 2.5 Hz, 1H), 4.11 (q, J = 7.0 Hz, 2H), 4.06 (m, 1H), 3.36 (dd, J = 13.0, 3.0 Hz, 1H), 3.27 (quint., J = 5.5 Hz, 1H), 2.80 (dd, J = 13.0, 10.0 Hz, 1H), 2.45-2.38 (m, 1H), 2.33-2.26 (m, 1H), 2.16-2.06 (m, 1H), 1.95 – 1.85 (m, 1H), 1.70 (s, 3H), 1.63 – 1.53 (m, 4H), 1.50 (s, 3H), 1.47 (s, 9H), 1.25 (t, J = 7.0 Hz, 3H), 0.93 (t, J = 7.4 Hz, 6H). ¹³C NMR (125 MHz, CDCl₃) δ: 172.9 (C), 170.4 (C), 153.5 (C), 151.3 (C), 135.1 (C), 129.4 (CH), 128.9 (CH), 128.3 (CH), 127.4 (CH), 96.1 (C), 82.7 (CH), 80.2 (CH), 79.8 (C), 77.0 (CH), 66.8 (CH₂), 60.3 (CH₂), 57.8 (CH), 55.7 (CH), 37.7 (CH₂), 30.6 (CH₂), 29.7 (CH₂), 28.3 (3 CH₃), 28.3 (CH₃), 25.8 (CH₃), 24.4 (CH₂), 14.2 (CH₃), 9.3 (CH₃), 9.1 (CH₃). IR (film): 2974, 2935, 2877, 1779, 1729, 1699, 1389, 1178, 1109. HRMS (ESI) calcd. for [C₃₂H₄₈N₂O₉ + Na⁺]: 627.3252; found: 627.3237. [α]D²⁰ -7.5 (c 0.64, CHCl₃).

(4R,5R)-tert-butyl 5-((R)-2-hydroxy-1-(pentan-3-yloxy)ethyl)-4-(3-hydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylate 12

Sodium borohydride (900 mg; 23.79 mmol) was added to a solution of aminoacetal 9 (900 mg; 1.49 mmol) in THF/water (10.65 mL; v/v=4/1) and the reaction mixture was stirred for 4 h at 65 °C. Upon cooling, the reaction mixture was quenched by addition of sat. NH₄Cl and stirred until excess sodium borohydride completely decomposed. The mixture was diluted with water, extracted with dichloromethane (3 x 100 mL), combined organic extract was dried over anh. MgSO₄ and concentrated under reduced pressure. Purification of the crude product by dry-flash chromatography (SiO₂; eluent: dichloromethane/MeOH=95/5) afforded 490 mg (85%) of the title compound 12, as a colorless, viscous oil. Physical data for 12: ¹H NMR (500 MHz, DMSO, 65 °C) δ: 4.38 (t, J = 5.3 Hz, 1H), 4.21 (t, J = 5.1 Hz, 1H), 4.03 (t, J = 3.6 Hz, 1H), 3.89-3.83 (m, 1H), 3.50 (m, 2H), 3.42 (dd, J = 11.7, 6.5 Hz, 2H), 3.36 (quint., J = 5.6 Hz, 1H), 3.27 (dd, J = 7.1, 5.0, 3.3 Hz, 1H), 1.78-1.69 (m, 1H), 1.67-1.56 (m, 1H), 1.53 (s, 3H), 1.51-1.35 (m, 6H), 1.42 (s, 3H), 1.41 (s, 9H), 0.85 (t, J = 7.5 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H). ¹³C NMR (125 MHz, DMSO, 65 °C) δ: 150.6, 93.4 (C), 79.9 (CH), 79.5 (CH), 78.3 (CH), 78.2 (C), 60.5 (CH₂), 60.3 (CH₂), 57.4 (CH), 29.9 (CH₂), 28.5 (CH₂), 27.8 (3 CH₃), 27.6 (CH₃), 25.4 (CH₃), 24.7 (CH₃), 24.7 (CH₃), 8.8 (CH₃), 8.5 (CH₃). IR (film): 3438, 2966, 2935, 2877, 1780, 1689, 1506, 1391, 1367, 1251, 1169, 1052. HRMS (ESI) calcd. for [C₂₀H₃₉NO₆ + Na⁺]: 412.2670; found 412.2677. [α]D²⁰ -11.2 (c 0.54, CHCl₃).
(3aS,7R,7aR)-tert-butyl 5-formyl-2,2-dimethyl-7-(pentan-3-yloxy)-3a,4,7,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate 14

A: (4R,5R)-tert-butyl 2,2-dimethyl-5-((S)-2-oxo-1-(pentan-3-yloxy)ethyl)-4-(3-oxopropyl)oxazolidine-3-carboxylate 13
A mixture of diol 12 (490 mg; 1.26 mmol) and Dess-Martin periodinane (3.2 g; 7.55 mmol) in dichloromethane (14 mL) was stirred for 30 min at rt. Reaction mixture was diluted with dichloromethane, quenched by addition of sat. aq. Na2S2O3 (10 mL) and sat. aq. NaHCO3 (10 mL) and stirred until clear. Extraction with dichloromethane (3 x 40 mL) followed by drying over anh. MgSO4 and concentration under reduced pressure afforded the crude product 13, which was used in the next step without further purification.

B: (3aS,7R,7aR)-tert-butyl 5-formyl-2,2-dimethyl-7-(pentan-3-yloxy)-3a,4,7,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate 14
A solution of dialdehyde 13 (~490 mg; 1,26 mmol) and dibenzylamine trifluoroacetate (445 mg; 1.45 mmol) in toluene (14 mL) was stirred at rt for 3 h. The mixture was diluted with dichloromethane, washed with water, dried over anh. MgSO4 and concentrated under reduced pressure. Purification by dry-flash chromatography (SiO2; eluent: benzene/EtOAc=9/1) afforded 250 mg (54%, calculated on the bases of starting diol 12) of the title compound 14, as a colorless viscous oil. Physical data for 14: 1H NMR (500 MHz, CDCl3) δ: 9.55 (s, 1H), 6.54 (s, 1H), 4.40-4.34 (m, 1H), 3.71 (dd, J = 10.0, 8.5 Hz, 1H), 3.58 (quint., J = 6.0 Hz, 1H), 3.45-3.20 (m, 2H), 2.11-2.01 (m, 1H), 1.64-1.52 (m, 10H), 1.49 (s, 9H), 0.96 (t, J = 7.0 Hz, 3H), 0.95 (t, J = 7.5 Hz, 3H). 13C NMR (125 MHz, CDCl3) δ: 192.5 (CH), 152.7 (C), 148.4 (CH), 140.5 (C), 96.4 (C), 82.4 (CH), 81.2 (CH), 80.3 (C), 75.6 (CH), 56.3 (CH), 28.4 (3 x CH3), 26.8 (CH3), 26.5 (CH2), 25.8 (CH2), 25.5 (CH2), 9.7 (CH3), 9.6 (CH3). IR (film): 2973, 2935, 2877, 1699, 1396, 1369, 1174, 1121, 1074. HRMS (ESI) calcd. for [C20H33NO5 + Na]+: 390.2251; found 390.2258. [α]D20 +130.9 (c 0.68, CHCl3).

(3R,4R,5S)-ethyl 5-((tert-butoxycarbonyl)amino)-4-hydroxy-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate 1.

A mixture of aldehyde 14 (62.5 mg; 0.17 mmol), oxone (473 mg; 1.54 mmol) and DMF (3.15 mL) was stirred at rt for 18 h. The reaction mixture was diluted with EtOAc, the organic layer was washed twice with water, dried over anh. MgSO4, concentrated under reduced pressure and used in the next step without further purification.

A solution of the crude acid from the previous step (~58.4 mg; 0.17 mmol) and potassium carbonate (89 mg; 0.64 mmol) in ethanol/water (6 mL; v/v=5/1) was stirred for 30 min at rt. The solvent was removed under reduced pressure, the solid residue was dissolved in DMSO (6.8 mL), ethyl iodide (621 mg; 0.32 mL; 3.98 mmol) was added and the resulting solution was stirred for 40 h at rt. The reaction mixture was diluted with EtOAc, water and 1.5 M HCl were added (pH~3), the organic layer was washed three times with water, dried over anh.
MgSO₄, and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO₂; eluent: petroleum-ether/EtOAc=7/3) afforded 34.5 mg (55%) of the title compound 1, as a colorless oil. Physical data for 1. ¹H NMR (500 MHz, CDCl₃) δ: 6.77-6.74 (m, 1H), 4.87 (d, J = 6.5 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H), 4.06-4.00 (m, 1H), 3.87-3.78 (m, 1H), 3.61 (ddd, J = 10.5, 7.0, 3.5 Hz, 1H), 3.52-3.48 (quint., J = 6.0 Hz, 1H), 2.88 (dd, J = 18.0, 5.5 Hz, 1H), 2.66 (s, 1H), 2.25-2.15 (m, 1H), 1.64-1.48 (m, 6H), 1.45 (s, 9H), 1.29 (t, J = 7.0 Hz, 3H), 0.93 (t, J = 7.0 Hz, 3H), 0.93 (t, J = 7.0 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ: 166.1 (C), 156.3 (C), 136.7 (CH), 129.1 (C), 81.9 (CH), 79.9 (C), 77.8 (CH), 74.0 (CH), 60.9 (CH₂), 50.1 (CH), 30.6 (CH₂), 28.3 (3 x CH₃), 26.3 (CH₂), 26.0 (CH₂), 14.2 (CH₃), 9.6 (CH₃), 9.5 (CH₃). IR (film): 3397, 2970, 2931, 2877, 1716, 1695, 1517, 1389, 1248, 1170, 1077, 1050. HRMS (ESI) calcd. for [C₁₉H₃₃NO₆ + Na]⁺: 394.2200; found: 394.2196. [α]D²⁰ -20.4 (c 0.41, CHCl₃).

(3R,4S,5S)-ethyl 5-((tert-butoxycarbonyl)amino)-4-hydroxy-3-(pentan-3-yloxy)cyclohex-1-ene carboxylate 15.⁴,⁵

According to the literature procedure for the racemic compound 15.⁶ ¹H and ¹³C NMR spectra of 15 identical to those previously described in the literature,⁴ [α]D²⁰ -51 ° (c 0.16, CHCl₃); (lit.:⁵ [α]D²⁵ = -52.5 °).


Scanned spectra
$^{1}H$ NMR

EtO$_2$C$\xrightarrow{\text{NHBoc}}$COSEt

7
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$^1$H NMR

![Chemical Structure and NMR Spectrum](image-url)
Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry
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$^{13}$C NMR
$^{13}$C NMR

![NMR Spectrum]

15