# A General Synthesis of Aromatic and Heteroaromatic Lipoxin $B_4$ Analogs

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# Supporting Information

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# 1. General Experimental Considerations

**$^1$H-NMR Spectroscopy**: $^1$H and $^{13}$C NMR spectra were obtained using Varian VNMRS 300, 400, 500 and 600 MHz spectrometers at room temperature. Proton and carbon chemical shifts are quoted in ppm. $^1$H NMR spectra were recorded using an internal deuterium lock for the residual protons in $CDCl_3$ (δ 7.26). $^{13}$C NMR spectra were recorded using an internal deuterium lock in $CDCl_3$ (δ 77.0). Assignments were determined either on the basis of unambiguous chemical shift or coupling patterns, COSY, HSQC and/or NOESY experiments. Peak multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constants (*J*) are reported to the nearest 0.1 Hz.

**Infrared Spectroscopy:** Infrared spectra were recorded on a Varian 3100 FT-IR spectrometer with the sample being prepared as a thin film on a diamond ATR module. Absorption maxima ($\nu_{max}$) are quoted in wavenumbers ($cm^{-1}$).

**Supercritical Fluid Chromatography**: SFC was performed on a Waters UPC$^2$ using a Chiralcel-IA3, IB3, IC3 or ID3 column.

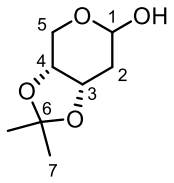
**Mass Spectrometry**: High-resolution mass spectra (HRMS) were recorded using a Waters Micromass LCT time-of-flight mass spectrometer.

**Optical Rotation**: Optical rotation measurements were recorded using a Schmidt-Haensch Unipol L2000 polarimeter at 589 nm and are quoted in units of deg $cm^3dm^{-1}g^{-1}$.

**Reagents, Solvents and Techniques**: Reagents were purchased from Sigma-Aldrich, Fischer, Acros or Fluorochem and used without further purification unless otherwise stated. Dry tetrahydrofuran was obtained from a Puresol Grubbs system unless otherwise stated. When appropriate, reactions were performed under a nitrogen atmosphere with oven dried glassware. Oxygen free nitrogen was supplied by BOC gases and used without further drying. Column chromatography was performed with Merck Kieselgel 60 F254 (230-400 mesh) silica gel. Thin-layer chromatography was performed on aluminium sheets pre-coated plates with silica gel 60 $F_{254}$, or aluminium oxide 60 $F_{254}$. The plates were realised with ultraviolet fluorescence. Solvent was removed from solutions using a Büchi rotary evaporator with an integrated vacuum pump. All reactions that required heating were heated in an oil bath unless otherwise stated. Reactions heated under microwave irradiation were carried out in a sealed 35 mL microwave vessel using a CEM Discover SP microwave reactor.

## 2. Experimental Procedures and Characterization Data

**(3a*R*,7a*S*)-2,2-dimethyltetrahydro-4*H*-[1,3]dioxolo[4,5-c]pyran-6-ol (13)**




**13**

To a flask equipped with stirrer bar was suspended 2-deoxy-D-ribose (5.00 g, 37.28 mmol) in acetone (125 mL). Conc. $H_2SO_4$ (3 drops) was added and the resulting mixture was stirred at rt for 2 h. $NaHCO_3$ was added until the pH was ~ 7, after which the solution was filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, cyclohexane/EtOAc, 1:1) afforded the desired product as a pale yellow oil (2.76 g, 42%). The product was isolated as a mixture of α- and β- anomers in a ratio of approx. 2:1.

*Minor diastereomer:*

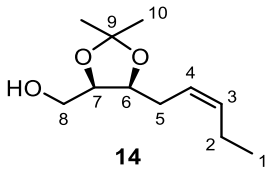
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 5.10 – 5.02 (1H, m, H1), 4.40 (1H, dt, *J* = 5.8, 4.7 Hz, H3), 4.23 – 4.11 (1H, m, H4), 3.97 – 3.94 (1H, m, H5), 3,90 (1H, broad s , -OH), 3.73 – 3.66 (1H, m, H5), 2.15 – 1.99 (2H, m, H2),1.56 (3H, s, H7), 1.35 (3H, s, H7). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 109.5, 91.6, 71.3, 70.8, 60.8, 32.5, 28.1, 25.7.

*Major diastereomer:*

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 5.25 (1H, dd, *J* = 7.1, 4.3 Hz, H1), 4.47 (1H, dt, *J* = 6.6, 4.3 Hz, H3), 4.23 – 4.11 (1H, m, H4), 3.94 – 3.91 (1H, m, H5), 3.74 – 3.65 (1H, m, H5), 3.04 (1H, broad s, -OH), 2.23 (1H, dt, *J* = 14.8, 4.3 Hz, H2), 1.77 (ddd, *J* = 14.8, 7.1, 4.3 Hz, H2), 1.49 (3H, s, H7), 1.34 (3H, s, H7). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 108.9, 91.1, 71.8, 70.5, 62.2, 32.3, 27.4, 25.5.

*Spectroscopic data in agreement with those previously reported.*[1]

**((4*R*,5*S*)-2,2-dimethyl-5-((*Z*)-pent-2-en-1-yl)-1,3-dioxolan-4-yl)methanol** (**14**)

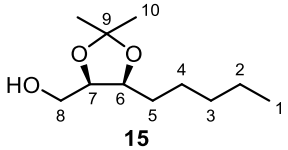


**14**

To a flame-dried two-necked flask under $N_2$ was suspended propylphosphonium bromide (5.31 g, 13.79 mmol) in dry THF (50 mL). The resulting mixture was cooled to –78 °C and NaHMDS (2.0 M in THF, 6.90 mL, 13.79 mmol) was added dropwise. The solution was stirred at –78 °C for 30 min, then warmed to 0 °C and stirred for a further 1 h. The solution was again cooled to –78 °C and a solution of **13** (1.72 g, 9.85 mmol) in dry THF (20 mL) was added dropwise. The resulting mixture was stirred at –78 °C for 1 h, then warmed to rt and stirred for a further 1 h. $NH_4Cl$ (aq. sat., 5 mL) was added followed by $H_2O$ (50 mL). The product was extracted into EtOAc (3 x 40 mL), and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, cyclohexane/EtOAc, 4:1) afforded the desired compound as a yellow oil (1.04 g, 53%).

**$R_f$** = 0.24 (cyclohexane/EtOAc, 4:1) [Vanillin]. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.51 (1H, dtt, *J* = 10.7, 7.3, 1.7 Hz, H3), 5.39 – 5.30 (1H, m, H4), 4.25 – 4.14 (2H, m, H6, H7), 3.71 – 3.58 (2H, m, H8), 2.43 – 2.34 (1H, m, H5), 2.33 – 2.23 (1H, m, H5), 2.14 – 1.99 (2H, m, H2), 1.89 (1H, dd, *J* = 7.2, 5.1 Hz, -OH), 1.48 (3H, s, H10), 1.37 (3H, s, H10), 0.98 (3H, t, *J* = 7.5 Hz, H1). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 134.6, 123.9, 108.3, 77.9, 61.8, 50.9, 28.3, 27.4, 25.6, 21.0, 14.2. **$[\alpha]_D$** = +19.06 ° (c = 1.00 g/100 $cm^3$). **IR** (film) $\nu_{max}/cm^{-1}$ 3446 (broad), 2963, 2934, 2875, 1379, 1370, 1247, 1041, 865. **HRMS** (ESI) $[M+Na]^+$ calc. 223.1305 for $[C_{11}H_{20}O_3Na]^+$; found 223.1303.

**((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)methanol** (**15**)

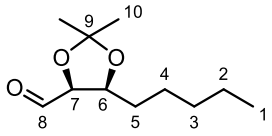


**15**

To a round-bottom flask was added **14** (1.49 g, 7.42 mmol) in EtOAc (20 mL). Pd/C (~10 wt. %, 1.2 g) was added and the flask was stoppered. The flask was evacuated under suction and the reaction mixture was placed under an atmosphere of $H_2$ using a balloon. The resulting mixture was stirred at rt for 24 h. The mixture was then filtered through a plug of silica and concentrated *in vacuo* to afford the desired compound as a colourless oil (1.45 g, 97%).

**$R_f$** = 0.22 (cyclohexane/EtOAc, 4:1) [Vanillin]. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 4.20 – 4.08 (2H, m, H6, H7), 3.65 – 3.54 (2H, m, H8), 1.95 (1H, t, *J* = 5.5 Hz, -OH), 1.62 – 1.38 (3H, m, H4, H5), 1.46 (3H, s, H10), 1.36 (3H, s, H10), 1.34 – 1.28 (5H, m, H2, H3, H4), 0.92 – 0.85 (3H, m, H1). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 108.2, 78.1, 77.2, 62.0, 32.0, 29.0, 28.4, 26.5, 25.7, 22.7, 14.1. **$[\alpha]_D$** = +32.04 ° (c = 0.95 g/100 $cm^3$). **IR** (film) $\nu_{max}/cm^{-1}$ 3451 (broad), 2933, 2862, 1379, 1370, 1247, 1218, 1043. **HRMS** (ESI) $[M+Na]^+$ calc. 225.1461 for $[C_{11}H_{22}O_3Na]^+$; found 225.1461.

**(4*S*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolane-4-carbaldehyde** (**16**)

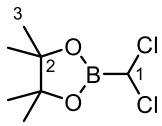



**16**

To a flame-dried round-bottom flask was added **15** (2.41 g, 11.91 mmol) in dry dichloromethane (20 mL). (Diacetoxyiodo)benzene (4.60 g, 14.29 mmol) and TEMPO (0.186 g, 1.19 mmol) were added in a single portion, and the resulting mixture was stirred vigorously at rt for 4 h. The solution was concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, cyclohexane/EtOAc, 9:1) afforded the desired compound as pale yellow oil (1.77 g, 74%).

**$R_f$** = 0.26 (cyclohexane/EtOAc, 9:1) [Vanillin]. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 9.63 (1H, dd, *J* = 3.6, 0.6 Hz, H8), 4.37 – 4.29 (1H, m, H6), 4.24 (1H, dd, *J* = 7.1, 3.6 Hz, H7), 1.58 (3H, s, H10), 1.57 – 1.44 (3H, m, H4, H5), 1.41 (3H, s, H10), 1.39 – 1.25 (5H, m, H2, H3, H4), 0.91 – 0.85 (3H, m, H1). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 202.2, 110.6, 82.2, 78.8, 31.7, 29.8, 27.8, 26.2, 25.4, 22.5, 14.1. **$[\alpha]_D$** = –14.53 ° (c = 1.14 g/100 $cm^3$). **IR** (film) $\nu_{max}/cm^{-1}$ 2934, 2861, 1733, 1380, 1371, 1217, 1065. **HRMS** (ESI) $[M+H]^+$ calc. 201.1485 for $[C_{11}H_{21}O_3]^+$; found 201.1486.

**2-(dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (17)**



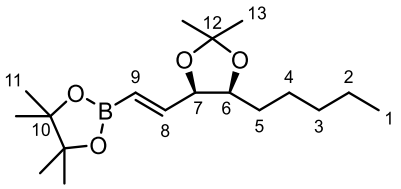

**17**

To a flame-dried two-necked flask under $N_2$ was added dry dichloromethane (3.2 mL, 50.0 mmol) in dry THF (70 mL). The solution was cooled to ─100 ˚C and *n*-BuLi (2.5 M in hexanes, 20.0 mL, 50.0 mmol) was added dropwise over 20 min. The resulting mixture was stirred at ─100 ˚C for 30 min. Trimethylborate (5.77 mL, 50.0 mmol) was added in a single portion and the resulting mixture was stirred at ─100 ˚C for a further 30 min. HCl (5 M, 50 mL) was added and the mixture was stirred vigorously and allowed to warm to rt. The product was extracted into $Et_2O$ (3 x 50 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was then dissolved in toluene (70 mL) and transferred to a flame-dried two-necked flask under $N_2$. With backflow of $N_2$, pinacol (5.91 g, 50.0 mmol) was added and the resulting mixture was stirred under reflux for 48 h. The resulting solution was concentrated *in vacuo*. Purification by reduced pressure distillation (b.p. 64 – 66 ˚C, 0.2 mbar) afforded the desired compound as a colorless oil (6.47 g, 61%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 5.34 (1H, s, H1), 1.33 (12H, s, H3). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 85.9, 24.6, (C1 gives a very broad signal between δ 57.5 and 52.2 barely detectable above the baseline).

*Spectroscopic data in agreement with those previously reported.*[1]

**2-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane** (**11**)

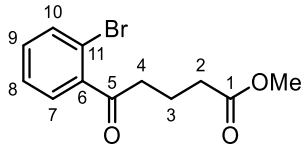



**11**

To a flame-dried Schlenk tube under $N_2$ was added **16** (1.360 g, 6.79 mmol) and boronate ester **17** (2.86 g, 13.58 mmol) in dry THF (50 mL). A solution of LiI (3.64 g, 27.16 mmol) in dry THF (20 mL) was added to the mixture dropwise. With backflow of $N_2$, $CrCl_2$ (5.00 g, 40.68 mmol) was added and the Schlenk tube was immediately stoppered. The resulting mixture was stirred at rt for 18 h. The mixture was then poured onto ice water (50 mL) and extracted into EtOAc (3 x 40 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, cyclohexane/EtOAc, 19:1) afforded the desired compound as a pale yellow oil (1.510 g, 69%).

**$R_f$** = 0.25 (pentane/EtOAc, 19:1) [Vanillin]. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 6.51 (1H, dd, *J* = 18.0, 6.9 Hz, H8), 5.69 (1H, dd, *J* = 18.0, 1.2 Hz, H9), 4.51 (1H, td, *J* = 6.6, 1.2 Hz, H7), 4.22 – 4.11 (1H, m, H6), 1.49 (3H, s, H13), 1.53 – 1.35 (3H, m, H4, H5), 1.36 (3H, s, H13), 1.33 – 1.22 (5H, m, H2, H3, H4), 1.26 (12H, s, H11), 0.91 – 0.83 (3H, m, H1). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 148.6, 108.4, 83.4, 80.7, 78.6, 31.9, 30.4, 28.3, 26.0, 25.8, 24.9, 24.8, 22.7, 14.2 (carbon adjacent to boron could not be observed). **$[\alpha]_D$** = +2.97 ° (c = 1.13 g/100 $cm^3$). **IR** (film) $\nu_{max}/cm^{-1}$ 2980, 2934, 2861, 1643, 1370, 1323, 1146, 1043, 849. **HRMS** (ESI) $[M+Na]^+$ calc. 347.2365 for $[C_{18}H_{33}BO_4Na]^+$; found 347.2367.

**Methyl 5-(2-bromophenyl)-5-oxopentanoate** (**20**)



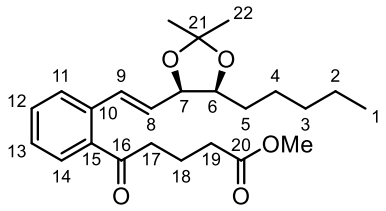

**20**

To a flame-dried two-necked flask under $N_2$ was added *i*-PrMgCl•LiCl (1.3 M in THF, 7.17 mL, 9.33 mmol). The solution was cooled to –15 °C and 1,2-dibromobenzene (1.01 mL, 8.48 mmol) was added dropwise. The resulting mixture was stirred at –15 °C for 3 h, then warmed to –10 °C. CuCN•2LiCl (1.0 M in THF, 9.33 mL, 9.33 mmol) was added and the mixture was

stirred at –10 °C for 20 min. A solution of acid chloride **19** (1.67 g, 10.17 mmol) in dry THF (5 mL) was added dropwise and the resulting mixture was allowed to warm slowly to rt over 1 h. $NH_4Cl$ (aq. sat., 5 mL) was added followed by $H_2O$ (20 mL), and the product was extracted into $Et_2O$ (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, cyclohexane/EtOAc, 4:1) afforded the desired compound as a pale yellow oil (1.77 g, 73%).

**$R_f$** = 0.43 (cyclohexane/EtOAc, 4:1) [UV/Vanillin]. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.59 (1H, dt, *J* = 7.9, 0.9 Hz, H7), 7.39 – 7.34 (2H, m, H9, H10), 7.32 – 7.27 (1H, m, H8), 3.67 (3H, s, -OMe), 2.99 (2H, t, *J* = 7.2 Hz, H4), 2.44 (2H, t, *J* = 7.2 Hz, H2), 2.05 (2H, p, *J* = 7.2 Hz, H3). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 203.6, 173.7, 141.8, 133.8, 131.7, 128.4, 127.6, 118.7, 51.8, 41.7, 33.1, 19.3. **IR** (film) $\nu_{max}/cm^{-1}$ 2951, 1732, 1700, 1433, 1209, 1027, 757. **HRMS** (ESI) $[M+H]^+$ calc. 285.0121 for $[C_{12}H_{14}{}^{79}BrO_3]^+$; found 285.0125, $[M+H]^+$ calc. 287.0101 for $[C_{12}H_{14}{}^{81}BrO_3]^+$; found 287.0105.

**Methyl 5-(2-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)phenyl)-5-oxopentanoate** (**21**)



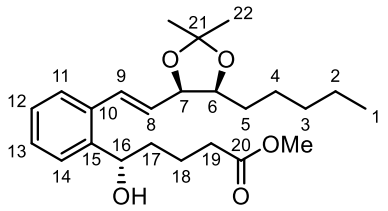

**21**

To a microwave vial was added **20** (0.080 g, 0.281 mmol) and **11** (0.127 g, 0.393 mmol) in 1,2-dimethoxyethane (2 mL). $K_2CO_3$ (2.0 M in $H_2O$, 0.42 mL, 0.842 mmol) was added followed by $Pd(PPh_3)_4$ (0.0162 g, 0.0140 mmol). The vial was placed in a microwave reactor and heated at 125 °C for 1 h. $NaHCO_3$ (aq. sat., 5 mL) was added and the product was extracted into EtOAc (3 x 10 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, cyclohexane/EtOAc, 9:1) afforded the desired compound as a pale yellow oil (0.094 g, 81%).

**$R_f$** = 0.30 (cyclohexane/EtOAc, 4:1) [UV/Vanillin]. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.59 (1H, dd, *J* = 7.7, 1.3 Hz, H14), 7.55 (1H, d, *J* = 7.8 Hz, H11), 7.46 – 7.41 (1H, m, H12), 7.32 (1H, td, *J* = 7.7, 1.3 Hz, H13), 7.05 (1H, d, *J* = 15.7 Hz, H9), 6.04 (1H, dd, *J* = 15.7, 8.3 Hz, H8), 4.67 (1H, ddd, *J* = 8.3, 6.1, 0.9 Hz, H7), 4.21 (1H, ddd, *J* = 8.6, 6.1, 4.4 Hz, H6), 3.67 (3H, s, -OMe), 3.03 – 2.88 (2H, m, H17), 2.42 (2H, t, *J* = 7.3 Hz, H19), 2.07 – 1.98 (2H, m, H18), 1.59 – 1.48 (1H, m, H5), 1.52 (3H, s, H22), 1.50 – 1.43 (2H, m, H5, H4), 1.39 (3H, s, H22),

1.37 – 1.24 (5H, m, H2, H3, H4), 0.90 – 0.83 (3H, m, H1). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 203.6, 173.7, 137.6, 136.4, 131.9, 131.5, 129.1, 128.3, 127.9, 127.6, 108.3, 79.7, 78.9, 51.7, 40.9, 33.2, 32.0, 30.6, 28.5, 26.1, 25.8, 22.7, 19.6, 14.1. **$[\alpha]_D$** = +6.44° (c = 1.13 g/100 $cm^3$). **IR** (film) $\nu_{max}/cm^{-1}$ 2985, 2933, 2860, 1736, 1686, 1437, 1368, 1213, 1042, 877, 755. **HRMS** (ESI) $[M+H]^+$ calc. 403.2479 for $[C_{24}H_{35}O_5]^+$; found 403.2478.

**methyl (*S*)-5-(2-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)phenyl)-5-hydroxypentanoate** (**22**)



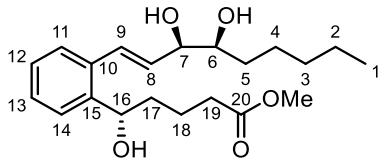

**22**

To a vial containing **21** (0.044 g, 0.109 mmol) in *i*-PrOH (0.5 mL) was added $K_2CO_3$ (0.023 g, 0.164 mmol) followed by $RuCl_2$[(*R*)-DM-BINAP][(*R*)-DAIPEN] (0.0067 g, 0.0055 mmol). $B(OiPr)_3$ (1 drop) was added and the vial was placed within a Parr high pressure reactor. The system was flushed with $H_2$ (3 x 20 bar) and stirred under $H_2$ (20 bar) at rt for 24 h. After venting the reactor, $H_2O$ (5 mL) was added and the product was extracted into EtOAc (3 x 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, cyclohexane/EtOAc, 4:1) afforded the desired compound as a pale yellow oil (0.017 g, 38%, 99.6% *de*).

**$R_f$** = 0.14 (cyclohexane/EtOAc, 4:1) [UV/Vanillin]. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.48 (1H, dd, *J* = 7.7, 1.4 Hz, H14), 7.42 (1H, dd, *J* = 7.7, 1.5 Hz, H11), 7.29 (1H, td, *J* = 7.5, 1.5 Hz, H13), 7.27 – 7.21 (1H, m, H11), 6.91 (1H, d, *J* = 15.6 Hz, H9), 6.03 (1H, dd, *J* = 15.6, 8.0 Hz, H8), 5.00 (1H, dd, *J* = 7.0, 5.1 Hz, H16), 4.67 (1H, ddd, *J* = 8.0, 6.1, 1.0 Hz, H7), 4.21 (1H, ddd, *J* = 8.5, 6.1, 4.5 Hz, H6), 3.65 (3H, s, -OMe), 2.35 (2H, t, *J* = 7.1 Hz, H19), 1.87 – 1.64 (4H, m, H18, H17), 1.60 – 1.48 (1H, m, H5), 1.52 (3H, s, H22), 1.50 – 1.41 (2H, m, H4, H5), 1.40 (3H, s, H22), 1.37 – 1.27 (5H, m, H2, H3, H4), 0.90 – 0.84 (3H, m, H1). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 174.1, 141.8, 134.6, 129.9, 129.0, 128.2, 127.7, 126.9, 125.6, 108.3, 79.7, 78.9, 70.6, 51.7, 37.7, 33.9, 32.0, 30.7, 28.5, 26.1, 25.8, 22.7, 21.5, 14.1. **$[\alpha]_D$** = –4.55° (c = 0.93 g/100 $cm^3$). **IR** (film) $\nu_{max}/cm^{-1}$ 3467 (broad), 2930, 2858, 1737, 1454, 1369, 1215, 1042, 791, 757. **HRMS** (ESI) $[M+Na]^+$ calc. 427.2455 for $[C_{24}H_{36}O_5Na]^+$; found 427.2456.

**SFC** (For Method B) *dr* = 99.8:0.2 (99.6% *de*) as determined by SFC (chiralpak ID column, $sCO_2$:*i*-PrOH, 99:1 for 0 – 1 min, gradient to 90:10 for 1 – 20 min, 3.00 mL/min, T = 35 °C); $R_T$ = 10.83 min [(*S*)-major], $R_T$ = 16.73 min [(*R*)-minor].

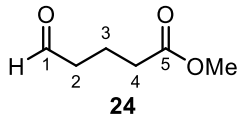
**methyl (*S*)-5-(2-((3*R*,4*S*,*E*)-3,4-dihydroxynon-1-en-1-yl)phenyl)-5-hydroxypentanoate** (**7**)




**7**

To a vial containing **22** (0.017 g, 0.042 mmol) in MeOH (1 mL) was added $ZrCl_4$ (0.0049 g, 0.0210 mmol). The resulting mixture was stirred at rt for 2 h. The solution was then concentrated *in vacuo* at room temperature. Purification by column chromatography ($SiO_2$, cyclohexane/EtOAc, 1:1) afforded the desired compound as a colourless oil (0.0078 g, 51%). **$R_f$** = 0.17 (cyclohexane/EtOAc, 1:1) [UV/Vanillin]. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.50 (1H, dd, *J* = 7.7, 1.5 Hz, H14), 7.41 (1H, dd, *J* = 7.7, 1.5 Hz, H11), 7.30 (1H, td, *J* = 7.5, 1.5 Hz, H13), 7.24 (1H, td, *J* = 7.5, 1.5 Hz, H12), 6.94 (1H, d, *J* = 15.7 Hz, H9), 6.13 (1H, dd, *J* = 15.7, 7.0 Hz, H8), 5.03 (1H, t, *J* = 5.6 Hz, H16), 4.29 – 4.22 (1H, m, H7), 3.80 (1H, dt, *J* = 8.5, 4.3 Hz, H6), 3.64 (3H, s, -OMe), 2.97 (1H, broad s, -OH), 2.47 – 2.36 (1H, m, H19), 2.35 – 2.26 (2H, m, H19, -OH), 2.08 (1H, broad s, -OH), 1.84 – 1.66 (4H, m, H17, H18), 1.58 – 1.43 (3H, m, H4, H5), 1.41 – 1.27 (5H, m, H2, H3, H4), 0.94 – 0.83 (3H, m, H1). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 174.7, 142.0, 134.9, 130.8, 130.3, 128.2, 127.6, 127.0, 125.2, 76.0, 74.5, 70.7, 51.9, 37.8, 33.4, 32.6, 32.0, 25.7, 22.8, 21.6, 14.2. **$[\alpha]_D$** = +22.99° (c = 0.70 g/100 $cm^3$). **IR** (film) $\nu_{max}$/$cm^{-1}$ 3402 (broad), 2927, 2857, 1721, 1438, 1068, 970, 758. **HRMS** (ESI) $[M+Na]^+$ calc. 387.2142 for $[C_{21}H_{32}O_5Na]^+$; found 387.2142.

**methyl 5-oxopentanoate** (**24**)



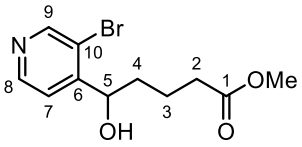

**24**

To a flame-dried Schlenk tube under $N_2$ was added δ-valerolactone (5.40 g, 53.9 mmol) in MeOH (50 mL). Conc. $H_2SO_4$ (10 drops) was added and the mixture was heated under reflux for 18 h. The solution was cooled to 0 °C and $NaHCO_3$ was added until the pH was ~7. The suspension was filtered, and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in dry $CH_2Cl_2$ (60 mL) and added to a flame-dried two-neck flask under $N_2$. With backflow of $N_2$, pyridinium chlorochromate (17.44 g, 80.9 mmol) was added and the resulting mixture was stirred at rt for 90 min. $Et_2O$ (100 mL) was added and the suspension was filtered under suction through a celite plug. The celite plug was washed with further $Et_2O$ (3 x 50 mL) and the filtrate was concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, cyclohexane/EtOAc, 4:1) afforded the desired compound as a colourless oil (3.176 g, 45%).

**$R_f$** = 0.19 (cyclohexane/EtOAc, 4:1) [$KMnO_4$].**$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.76 (1H, t, *J* = 1.3 Hz, H1), 3.66 (3H, s, -OMe), 2.52 (2H, td, *J* = 7.2, 1.3 Hz, H2), 2.36 (2H, t, *J* = 7.2 Hz, H4), 1.95 (2H, q, *J* = 7.2 Hz, H3). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 201.6, 173.5, 51.7, 43.0, 33.0, 17.4.

*Spectroscopic data in agreement with those previously reported.*[2]

**methyl 5-(3-bromopyridin-4-yl)-5-hydroxypentanoate** (**25**)



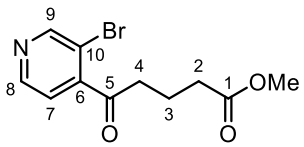

**25**

To a flame-dried two-necked flask under $N_2$ was added 2,2,6,6-tetramethylpiperidine (1.93 mL, 11.4 mmol) in dry THF (20 mL). The solution was cooled to –5 °C and *n*-BuLi (2.5 M in hexanes, 4.57 mL, 11.4 mmol) was added dropwise. The resulting mixture was stirred at –5 °C for 20 min then cooled to –85 °C. A solution of 3-bromopyridine (1.00 mL, 10.4 mmol) in dry THF (10 mL) was added dropwise and the resulting mixture was stirred at –85 °C for 25 min. A solution of **24** (2.03 g, 15.6 mmol) in dry THF (10 mL) was added in a single portion and the resulting mixture was stirred at –85 °C for 15 min. $NaHCO_3$ (aq. sat., 20 mL) was added

and the mixture was allowed to warm to rt. The product was extracted into EtOAc (3 x 20 mL) and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, cyclohexane/EtOAc, 2:3) afforded the desired compound as a yellow oil (1.806 g, 60%).

**$R_f$** = 0.28 (cyclohexane/EtOAc, 2:3) [UV/$KMnO_4$]. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.57 (1H, s, H9), 8.46 (1H, d, *J* = 5.0 Hz, H8), 7.52 (1H, d, *J* = 5.0 Hz, H7), 4.97 (1H, dd, *J* = 8.1, 2.5 Hz, H5), 3.66 (3H, s, -OMe), 3.21 (1H, s, -OH), 2.39 (2H, t, *J* = 7.1 Hz, H2), 1.94 – 1.74 (3H, m, H3, H4), 1.70 – 1.56 (1H, m, H4). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 174.3, 152.9, 151.7, 148.7, 122.2, 120.0, 71.5, 51.8, 36.4, 33.6, 20.9. **IR** (film) $\nu_{max}$/cm$^{-1}$ 3333 (broad), 2951, 1736, 1586, 1437, 1401, 1170, 1083, 1022. **HRMS** (ESI) $[M+H]^+$ calc. 288.0230 for $[C_{11}H_{15}{}^{79}BrNO_3]^+$; found 288.0232, $[M+H]^+$ calc. 290.0210 for $[C_{11}H_{15}{}^{81}BrNO_3]^+$; found 290.0212.

**methyl 5-(3-bromopyridin-4-yl)-5-oxopentanoate** (**26**)

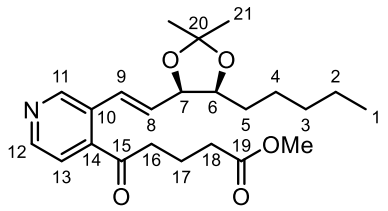



**26**

To a flask containing **25** (1.80 g, 6.25 mmol) in $CH_2Cl_2$ (60 mL) was added Dess-Martin periodinane (3.97 g, 9.37 mmol) and the resulting mixture was stirred at rt for 3 h. $Na_2S_2O_3$ (aq. sat., 20 mL) and $NaHCO_3$ (aq. sat., 20 mL) was added and the resulting biphasic mixture was stirred vigorously for 30 min. The product was extracted into $CH_2Cl_2$ (3 x 50 mL) and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, cyclohexane/EtOAc, 1:1) afforded the desired compound as a pale yellow oil (1.403 g, 78%).

**$R_f$** = 0.32 (cyclohexane/EtOAc, 1:1) [UV/$KMnO_4$]. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.75 (1H, d, *J* = 0.7 Hz, H9), 8.58 (1H, d, *J* = 4.9 Hz, H8), 7.22 (1H, dd, *J* = 4.9, 0.7 Hz, H7), 3.65 (3H, s, -OMe), 2.95 (2H, t, *J* = 7.1 Hz, H4), 2.42 (2H, t, *J* = 7.2 Hz, H2), 2.09 – 1.97 (2H, m, H3). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 201.7, 173.4, 153.0, 148.8, 148.1, 121.7, 116.0, 51.7, 41.4, 32.8, 18.7. **IR** (film) $\nu_{max}$/cm$^{-1}$ 2952, 1733, 1710, 1397, 1212, 1024, 836. **HRMS** (ESI) $[M+H]^+$ calc. 286.0073 for $[C_{11}H_{13}{}^{79}BrNO_3]^+$; found 286.0076, $[M+H]^+$ calc. 288.0054 for $[C_{11}H_{13}{}^{81}BrNO_3]^+$; found 288.0057.

**methyl 5-(3-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)pyridin-4-yl)-5-oxopentanoate** (**27**)

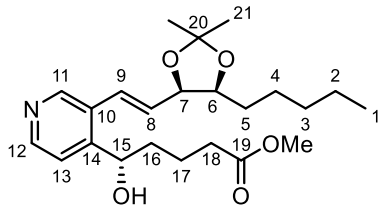



**27**

To a microwave vial was added **26** (0.087 g, 0.305 mmol) and **11** (0.128 g, 0.395 mmol) in 1,2-dimethoxyethane (2 mL). $K_2CO_3$ (2.0 M in $H_2O$, 0.46 mL, 0.91 mmol) was added followed by $Pd(PPh_3)_4$ (0.0176 g, 0.0152 mmol). The vial was placed in a microwave reactor and heated to 125 °C for 1 h. $NaHCO_3$ (aq. sat., 10 mL) was added and the product was extracted into EtOAc (3 x 10 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, cyclohexane/EtOAc, 1:1) afforded the desired compound as a pale yellow oil (0.096 g, 78%).

**$R_f$** = 0.30 (cyclohexane/EtOAc, 1:1) [UV/Vanillin]. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.80 (1H, s, H11), 8.61 (1H, d, *J* = 5.1 Hz, H12), 7.38 (1H, dd, *J* = 5.1, 0.7 Hz, H13), 6.91 (1H, d, *J* = 15.9 Hz, H9), 6.14 (1H, dd, *J* = 15.9, 7.6 Hz, H8), 4.66 (1H, ddd, *J* = 7.6, 6.2, 1.1 Hz, H7), 4.22 (1H, ddd, *J* = 8.3, 6.2, 4.3 Hz, H6), 3.67 (3H, s, -OMe), 3.05 – 2.84 (2H, m, H16), 2.42 (2H, t, *J* = 7.2 Hz, H18), 2.02 (2H, p, *J* = 7.2 Hz, H17), 1.52 (3H, s, H21), 1.60 – 1.40 (3H, m, H4, H5), 1.39 (3H, s, H21), 1.34 – 1.25 (5H, m, H2, H3, H4), 0.92 – 0.80 (3H, m, H1). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 202.7, 173.5, 149.1, 148.7, 143.7, 132.0, 130.3, 127.5, 120.9, 108.6, 79.3, 78.8, 51.8, 41.0, 32.9, 31.9, 30.6, 28.4, 26.1, 25.7, 22.7, 19.0, 14.1. **$[\alpha]_D$** = +16.08° (c = 1.18 g/100 $cm^3$). **IR** (film) $\nu_{max}/cm^{-1}$ 2933, 1735, 1698, 1369, 1213, 1166, 1042, 974, 878. **HRMS** (ESI) $[M+H]^+$ calc. 404.2431 for $[C_{23}H_{34}NO_5]^+$; found 404.2437.

**methyl (*S*)-5-(3-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)pyridin-4-yl)-5-hydroxypentanoate** (**28**)

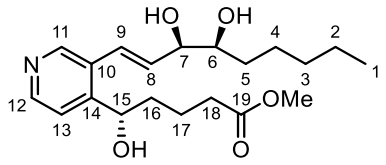



**28**

To a vial containing **27** (0.046 g, 0.114 mmol) in *i*-PrOH (0.5 mL) was added $K_2CO_3$ (0.024 g, 0.171 mmol) followed by $RuCl_2$[(*R*)-DM-BINAP][(*R*)-DAIPEN] (0.0070 g, 0.0057 mmol). B(O*i*Pr)$_3$ (1 drop) was added and the vial was placed within a Parr high pressure reactor. The system was flushed with $H_2$ (3 x 20 bar) and stirred under $H_2$ (20 bar) at rt for 20 h. After venting the reactor, $H_2O$ (5 mL) was added and the product was extracted into EtOAc (3 x 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, cyclohexane/EtOAc, 3:7) afforded the desired compound as a pale yellow oil (0.0265 g, 57%, 99.6% *de*).

**$R_f$** = 0.23 (cyclohexane/EtOAc, 3:7) [UV/Vanillin]. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.55 (1H, s, H11), 8.43 (1H, d, *J* = 5.1 Hz, H12), 7.43 (1H, d, *J* = 5.1 Hz, H13), 6.75 (1H, d, *J* = 15.8 Hz, H9), 6.08 (1H, dd, *J* = 15.8, 7.3 Hz, H8), 4.95 (1H, dd, *J* = 7.8, 3.8 Hz, H15), 4.67 (1H, ddd, *J* = 7.4, 6.2, 1.2 Hz, H7), 4.22 (1H, ddd, *J* = 8.7, 6.2, 4.5 Hz, H6), 3.65 (3H, s, -OMe), 3.03 (1H, broad s, -OH), 2.34 (2H, t, *J* = 7.0 Hz, H18), 1.88 – 1.60 (4H, m, H16, H17), 1.59 – 1.41 (3H, m, H4, H5), 1.51 (3H, s, H21), 1.39 (3H, s, H21), 1.34 – 1.23 (5H, m, H2, H3, H4), 0.89 – 0.83 (3H, m, H1). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 174.0, 150.6, 149.0, 147.7, 130.9, 130.1, 126.4, 120.0, 108.5, 79.2, 78.8, 69.4, 51.7, 37.2, 33.7, 31.9, 30.7, 28.4, 26.1, 25.7, 22.7, 21.1, 14.1. **$[\alpha]_D$** = –4.14° (c = 1.03 g/100 cm$^3$). **IR** (film) $\nu_{max}$/cm$^{-1}$ 3205 (broad), 2933, 2859, 1737, 1592, 1457, 1378, 1215, 1166, 1042, 974, 878, 843. **HRMS** (ESI) $[M+H]^+$ calc. 406.2588 for $[C_{23}H_{36}NO_5]^+$; found 406.2587. **SFC** *dr* = 99.8:0.2 (99.6% *de*) as determined by SFC (chiralpak ID column, $sCO_2$:MeOH, 99:1 for 0 – 1 min, gradient to 50:50 for 1 – 5 min, 3.00 mL/min, T = 35 °C); $R_T$ = 3.04 min [(*S*)-major], $R_T$ = 3.19 min [(*R*)-minor].

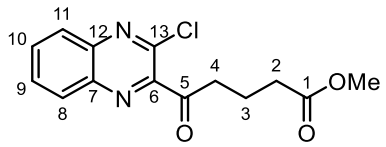
**methyl (*S*)-5-(3-((3*R*,4*S*,*E*)-3,4-dihydroxynon-1-en-1-yl)pyridin-4-yl)-5-hydroxypentanoate** (**8**)



**8**

To a vial containing **28** (0.040 g, 0.099 mmol) in MeOH (1 mL) was added $ZrCl_4$ (0.0115 g, 0.0493 mmol). The resulting mixture was stirred at rt for 4 h. The solution was then concentrated *in vacuo* at room temperature. Purification by column chromatography ($SiO_2$, $CH_2Cl_2$/MeOH, 9:1) afforded the desired compound as a pale yellow oil (0.0225 g, 62%).
**$R_f$** = 0.30 ($CH_2Cl_2$/MeOH, 9:1) [UV/Vanillin]. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.36 – 8.26 (2H, m, H11, H12), 7.40 (1H, d, *J* = 5.1 Hz, H13), 6.74 (1H, d, *J* = 15.8 Hz, H9), 6.09 (1H, dd, *J* = 15.9, 6.4 Hz, H8), 4.92 – 4.85 (1H, m, H15), 4.22 – 4.15 (1H, m, H7), 3.74 (1H, dt, *J* = 8.1, 3.9 Hz, H6), 3.63 (3H, s, -OMe), 2.41 – 2.22 (2H, m, H18), 1.81 – 1.71 (1H, m, H17), 1.71 – 1.59 (3H, m, H16, H17), 1.56 – 1.38 (3H, m, H4, H5), 1.38 – 1.26 (5H, m, H2, H3, H4), 0.87 (3H, t, *J* = 6.8 Hz, H1). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 174.6, 151.4, 148.3, 147.2, 133.5, 130.9, 126.0, 120.3, 75.6, 74.5, 69.6, 51.9, 36.9, 33.4, 32.8, 32.0, 25.7, 22.8, 21.3, 14.2. **$[\alpha]_D$** = +7.53° (c = 1.10 g/100 $cm^3$). **IR** (film) $\nu_{max}/cm^{-1}$ 3361 (broad), 2927, 2857, 1733, 1594, 1437, 1199, 1071, 971, 841, 582. **HRMS** (ESI) $[M+H]^+$ calc. 366.2275 for $[C_{20}H_{32}NO_5]^+$; found 366.2273.

**methyl 5-(3-chloroquinoxalin-2-yl)-5-oxopentanoate** (**30**)

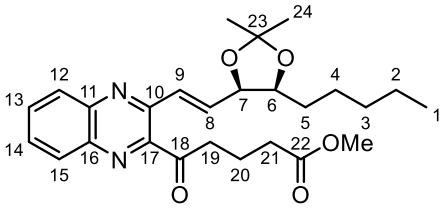


**30**

To a round-bottom flask containing 2-chloroquinoxaline (0.220 g, 1.34 mmol) in EtOAc (10 mL) was added **24** (0.696 g, 5.35 mmol) followed by trimethylsilyl azide (0.35 mL, 2.67 mmol). Bis(trifluoroacetoxy)iodo benzene (1.15 g, 2.67 mmol) was added portionwise and the resulting mixture was stirred at rt for 18 h. $NEt_3$ (1 mL) was added dropwise and the resulting mixture was stirred for a further 30 min. $NaHCO_3$ (aq. sat., 10 mL) was added and the product was extracted into EtOAc (3 x 10 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, cyclohexane/EtOAc, 4:1) afforded the desired compound as an orange solid (0.209 g, 53%).

**$R_f$** = 0.21 (cyclohexane/EtOAc, 4:1) [UV/$KMnO_4$]. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.14 (1H, ddd, *J* = 8.4, 1.6, 0.7 Hz, H8), 8.06 (1H, ddd, *J* = 8.4, 1.5, 0.6 Hz, H11), 7.89 (1H, ddd, *J* = 8.4, 6.9, 1.6 Hz, H10), 7.84 (1H, ddd, *J* = 8.4, 6.9, 1.5 Hz, H9), 3.69 (3H, s, -OMe), 3.31 (2H, t, *J* = 7.2 Hz, H4), 2.50 (2H, t, *J* = 7.2 Hz, H2), 2.13 (2H, p, *J* = 7.2 Hz, H3). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 199.7, 173.7, 147.5, 143.8, 142.6, 139.6, 133.0, 131.1, 129.8, 128.5, 51.8, 39.4, 33.1, 18.9. **m.p.** = 84 – 86 °C. **IR** (film) $\nu_{max}$/cm$^{-1}$ 1735, 1706, 1382, 1281, 1175, 953, 772. **HRMS** (ESI) $[M+H]^+$ calc. 293.0687 for $[C_{14}H_{14}{}^{35}ClN_2O_3]^+$; found 293.0690.

**methyl 5-(3-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)quinoxalin-2-yl)-5-oxopentanoate** (**31**)

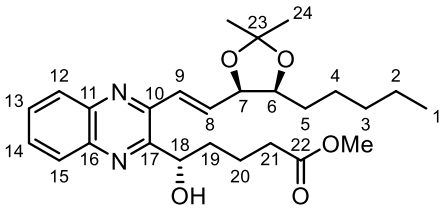



**31**

To a microwave vial was added **30** (0.100 g, 0.342 mmol) and **11** (0.144 g, 0.444 mmol) in 1,2-dimethoxyethane (2 mL). $K_2CO_3$ (2.0 M in $H_2O$, 0.51 mL, 1.02 mmol) was added followed by $Pd(PPh_3)_4$ (0.0197 g, 0.0171 mmol). The vial was placed in a microwave reactor and heated to 125 °C for 1 h. $NaHCO_3$ (aq. sat., 10 mL) was added and the product was extracted into EtOAc (3 x 10 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, cyclohexane/EtOAc, 9:1) afforded the desired compound as a pale yellow oil (0.116 g, 75%).

**$R_f$** = 0.43 (cyclohexane/EtOAc, 4:1) [UV/Vanillin]. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.05 (2H, dd, *J* = 8.3, 1.5 Hz, H12, H15), 7.81 (1H, ddd, *J* = 8.3, 6.9, 1.5 Hz, H13), 7.73 (1H, ddd, *J* = 8.3, 6.9, 1.5 Hz, H14), 7.54 (1H, dd, *J* = 15.2, 1.2 Hz, H9), 7.17 (1H, dd, *J* = 15.3, 7.5 Hz, H8), 4.80 (1H, ddd, *J* = 7.5, 6.2, 1.2 Hz, H7), 4.28 (1H, ddd, *J* = 8.7, 6.2, 4.4 Hz, H6), 3.68 (3H, s, -OMe), 3.46 – 3.32 (2H, m, H19), 2.48 (2H, t, *J* = 7.4 Hz, H21), 2.10 (2H, p, *J* = 7.4 Hz, H20), 1.60 (3H, s, H24), 1.65 – 1.55 (1H, m, H5), 1.55 – 1.46 (2H, m, H4, H5), 1.42 (3H, s, H24), 1.40 – 1.33 (1H, m, H4), 1.32 – 1.25 (4H, m, H2, H3), 0.87 – 0.81 (3H, m, H1). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 202.7, 173.7, 148.0, 146.5, 143.1, 140.1, 136.3, 132.1, 130.1, 129.8, 129.4, 127.9, 108.7, 79.1, 79.0, 51.7, 39.0, 33.3, 31.9, 30.6, 28.4, 26.1, 25.9, 22.6, 19.3, 14.1. **$[\alpha]_D$** = +5.98° (c = 1.08 g/100 cm$^3$). **IR** (film) $\nu_{max}$/cm$^{-1}$ 2933, 2859, 1738, 1701, 1370, 1213, 1167, 1043, 977, 763. **HRMS** (ESI) $[M+H]^+$ calc. 455.2540 for $[C_{26}H_{35}N_2O_5]^+$; found 455.2538.

**methyl (*S*)-5-(3-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)quinoxalin-2-yl)-5-hydroxypentanoate** (**32**)

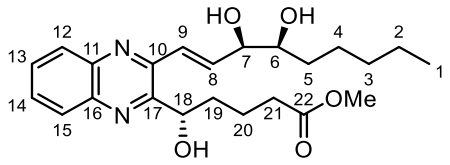



**32**

To a vial containing **31** (0.098 g, 0.216 mmol) in *i*-PrOH (0.5 mL) was added $K_2CO_3$ (0.045 g, 0.323 mmol) followed by $RuCl_2$[(*R*)-DM-BINAP][(*R*)-DAIPEN] (0.0132 g, 0.0108 mmol). B(O*i*Pr)$_3$ (1 drop) was added and the vial was placed within a Parr high pressure reactor. The system was flushed with $H_2$ (3 x 20 bar) and stirred under $H_2$ (20 bar) at rt for 20 h. After venting the reactor, $H_2O$ (5 mL) was added and the product was extracted into EtOAc (3 x 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, cyclohexane/EtOAc, 7:3) afforded the desired compound as a pale yellow oil (0.061 g, 62%, 99.6% *de*).

**$R_f$** = 0.24 (cyclohexane/EtOAc, 7:3) [UV/Vanillin]. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.08 – 8.05 (1H, m, H15), 8.03 – 8.00 (1H, m, H12), 7.75 – 7.68 (2H, m, H13, H14), 7.20 (1H, dd, *J* = 15.0, 6.4 Hz, H8), 6.94 (1H, dd, *J* = 15.0, 1.4 Hz, H9), 5.17 (1H, ddd, *J* = 8.6, 7.2, 2.8 Hz, H18), 4.85 (1H, td, *J* = 6.4, 1.4 Hz, H7), 4.73 (1H, d, *J* = 7.2 Hz, -OH), 4.31 (1H, ddd, *J* = 8.6, 6.4, 4.0 Hz, H6), 3.65 (3H, s, -OMe), 2.44 – 2.32 (2H, m, H21), 2.01 – 1.82 (3H, m, H19, H20), 1.60 (3H, s, H24), 1.64 – 1.53 (2H, m, H5, H19), 1.53 – 1.46 (2H, m, H4, H5), 1.44 (3H, s, H24), 1.42 – 1.34 (1H, m, H4), 1.33 – 1.26 (4H, m, H2, H3), 0.88 – 0.82 (3H, m, H1). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 173.8, 154.6, 147.1, 142.1, 139.9, 136.7, 130.0, 129.9, 129.3, 128.4, 125.1, 108.7, 79.0, 78.7, 69.7, 51.7, 37.4, 33.9, 31.9, 30.8, 28.4, 26.2, 25.8, 22.7, 21.3, 14.1. **$[\alpha]_D$** = –70.92° (c = 1.00 g/100 cm$^3$). **IR** (film) $\nu_{max}$/cm$^{-1}$ 3440 (broad), 2932, 1737, 1369, 1215, 1165, 1075, 1040, 762. **HRMS** (ESI) $[M+H]^+$ calc. 457.2697 for $[C_{26}H_{37}N_2O_5]^+$; found 457.2696. **SFC** *dr* = 99.8:0.2 (99.6% *de*) as determined by SFC (chiralpak ID column, $sCO_2$:MeOH, 99:1 for 0 – 1 min, gradient to 50:50 for 1 – 5 min, 3.00 mL/min, T = 35 °C); $R_T$ = 3.19 min [(*S*)-major], $R_T$ = 3.47 min [(*R*)-minor].

**methyl (*S*)-5-(3-((3*R*,4*S*,*E*)-3,4-dihydroxynon-1-en-1-yl)quinoxalin-2-yl)-5-hydroxypentanoate** (**9**)

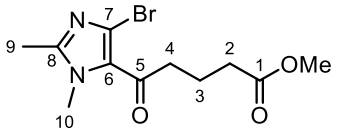


**9**

To a vial containing **32** (0.0310 g, 0.0679 mmol) in MeOH (1 mL) was added camphorsulfonic acid (0.0158 g, 0.0679 mmol). The resulting mixture was stirred at rt for 2 h. The solution was then concentrated *in vacuo* at room temperature. Purification by column chromatography ($SiO_2$, 100% EtOAc) afforded the desired compound as a colourless waxy solid (0.0229 g, 81%).

**$R_f$** = 0.20 (cyclohexane/EtOAc, 2:3) [UV/Vanillin]. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.07 – 8.04 (1H, m, H15), 8.01 – 7.98 (1H, m, H12), 7.74 – 7.68 (2H, m, H13, H14), 7.25 (1H, dd, *J* = 15.3, 5.1 Hz, H8), 7.05 (1H, dd, *J* = 15.3, 1.7 Hz, H9), 5.18 (1H, ddd, *J* = 9.0, 6.6, 2.7 Hz, H18), 4.84 (1H, d, *J* = 6.6 Hz, -OH), 4.49 – 4.43 (1H, m, H7), 3.88 (1H, dt, *J* = 7.8, 4.0 Hz, H6), 3.65 (3H, s, -OMe), 3.29 (1H, broad s, -OH), 2.52 (1H, broad s, -OH), 2.50 – 2.42 (1H, m, H21), 2.40 – 2.32 (1H, m, H21), 2.06 – 1.98 (1H, m, H19), 1.96 – 1.88 (1H, m, H20), 1.86 – 1.76 (1H, m, H20), 1.64 – 1.51 (4H, m, H19, H4, H5), 1.45 – 1.36 (1H, m, H5), 1.35 – 1.26 (4H, m, H2, H3), 0.91 – 0.85 (3H, m, H1). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 174.8, 154.7, 147.7, 142.0, 139.8, 138.7, 130.0, 129.9, 129.2, 128.4, 125.4, 75.3, 74.9, 69.8, 51.9, 36.9, 33.1, 32.7, 32.0, 25.9, 22.8, 21.2, 14.2. **$[\alpha]_D$** = –93.57° (c = 1.15 g/100 $cm^3$). **IR** (film) $\nu_{max}/cm^{-1}$ 3395 (broad), 2928, 2857, 1735, 1437, 1073, 762. **HRMS** (ESI) $[M+H]^+$ calc. 417.2384 for $[C_{23}H_{33}N_2O_5]^+$; found 417.2382.

**methyl 5-(4-bromo-1,2-dimethyl-1*H*-imidazol-5-yl)-5-oxopentanoate** (**34**)



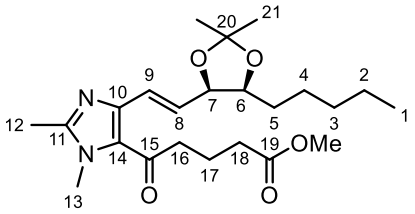
**34**

To a flame-dried Schlenk tube under $N_2$ was added *i*-PrMgCl•LiCl (1.3 M in THF, 3.33 mL, 4.33 mmol). The solution was cooled to –25 °C and a solution of 4,5-dibromo-1,2-dimethylimidazole (1.00 g, 3.94 mmol) in dry THF (6 mL) was added dropwise. The resulting

mixture was stirred at –25 °C for 30 min. A solution of acid chloride **19** (0.681 g, 4.14 mmol) in dry THF (4 mL) was added in a single portion and the resulting mixture was stirred at –25 °C for 1 h, then warmed to rt and stirred for a further 1 h. $NH_4Cl$ (aq. sat., 5 mL) was added followed by NaOH (0.1 M in $H_2O$, 10 mL). The product was extracted into EtOAc (3 x 10 mL) then the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 100% EtOAc) afforded the desired compound as a yellow oil (0.402 g, 34%).

**$R_f$** = 0.20 (cyclohexane/EtOAc, 2:3) [UV/$KMnO_4$]. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 3.79 (3H, s, H10), 3.67 (3H, s, -OMe), 3.07 (2H, t, *J* = 7.2 Hz, H4), 2.42 (2H, t, *J* = 7.4 Hz, H2), 2.39 (3H, s, H9), 2.03 (2H, p, *J* = 7.3 Hz, H3). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 190.5, 173.7, 150.1, 128.5, 123.1, 51.7, 40.9, 34.4, 33.3, 19.4, 13.6. **m.p.** = 78 – 80 °C. **IR** (film) $\nu_{max}$/cm$^{-1}$ 2954, 1737, 1657, 1510, 1429, 1376, 1274, 1153, 976, 879, 750. **HRMS** (ESI) $[M+H]^+$ calc. 303.0339 for $[C_{11}H_{16}{}^{79}BrN_2O_3]^+$; found 303.0339, $[M+H]^+$ calc. 305.0319 for $[C_{11}H_{16}{}^{81}BrN_2O_3]^+$; found 305.0318.

**methyl 5-(4-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)-1,2-dimethyl-1*H*-imidazol-5-yl)-5-oxopentanoate** (**35**)



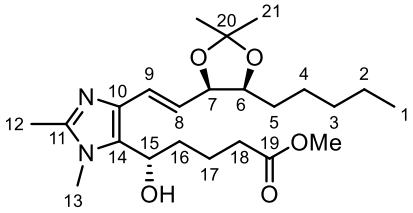

**35**

To a microwave vial was added **34** (0.050 g, 0.165 mmol) and **11** (0.070 g, 0.214 mmol) in 1,2-dimethoxyethane (1.5 mL). $K_2CO_3$ (2.0 M in $H_2O$, 0.25 mL, 0.49 mmol) was added followed by $Pd(PPh_3)_4$ (0.0095 g, 0.0083 mmol). The vial was placed in a microwave reactor and heated to 125 °C for 1 h. $NaHCO_3$ (aq. sat., 5 mL) was added and the product was extracted into EtOAc (3 x 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, cyclohexane/EtOAc, 3:7) afforded the desired compound as a yellow oil (0.047 g, 68%).

**$R_f$** = 0.20 (cyclohexane/EtOAc, 2:3) [UV/$KMnO_4$]. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.91 (1H, dd, *J* = 15.1, 1.3 Hz, H9), 6.63 (1H, dd, *J* = 15.1, 6.6 Hz, H8), 4.72 (1H, td, *J* = 6.6, 1.3 Hz, H7), 4.22 (1H, ddd, *J* = 8.7, 6.2, 3.9 Hz, H6), 3.74 (3H, s, H13), 3.67 (3H, s, -OMe), 2.88 (2H, t, *J* = 7.2 Hz, H16), 2.41 (2H, t, *J* = 7.2 Hz, H18), 2.39 (3H, s, H12), 2.03 (2H, p, *J* = 7.2 Hz,

H17), 1.59 – 1.49 (1H, m, H5), 1.52 (3H, s, H21), 1.50 – 1.41 (2H, m, H4, H5), 1.39 (3H, s, H21), 1.37 – 1.23 (5H, m, H2, H3, H4), 0.89 – 0.82 (3H, m, H1). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 190.8, 173.6, 150.2, 144.1, 131.3, 127.9, 123.3, 108.3, 79.0, 78.9, 51.7, 41.3, 33.7, 33.3, 31.9, 30.7, 28.4, 26.3, 25.8, 22.7, 19.6, 14.1, 13.7. **$[\alpha]_D$** = +37.39° (c = 0.98 g/100 $cm^3$). **IR** (film) $\nu_{max}/cm^{-1}$ 2932, 1736, 1643, 1378, 1213, 1166, 1044. **HRMS** (ESI) $[M+H]^+$ calc. 421.2697 for $[C_{23}H_{37}N_2O_5]^+$; found 421.2698.

**methyl (*S*)-5-(4-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)-1,2-dimethyl-1*H*-imidazol-5-yl)-5-hydroxypentanoate** (**36**)



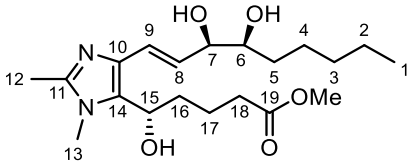

**36**

To a flame-dried Schlenk tube under $N_2$ was added triethylamine (1.21 mL, 8.68 mmol) followed by formic acid (0.82 mL, 21.7 mmol) dropwise at 0 °C. After warming to rt, [(*R*,*R*)-Teth-TsDpen]RuCl (0.0061 g, 0.0099 mmol) was added and the resulting mixture was stirred at rt for 15 min. A solution of **35** (0.083 g, 0.197 mmol) in $CH_2Cl_2$ (0.5 mL) was added and the resulting mixture was stirred at 40 °C for 18 h. $NaHCO_3$ (aq. sat., 5 mL) was added and the product was extracted into EtOAc (5 x 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, $CH_2Cl_2$/MeOH, 96:4) afforded the desired compound as a pale yellow oil (0.055 g, 66%, 90% *de*).

**$R_f$** = 0.17 ($CH_2Cl_2$/MeOH, 96:4) [UV/$KMnO_4$]. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.37 (1H, dd, *J* = 15.4, 1.1 Hz, H9), 6.18 (1H, dd, *J* = 15.4, 7.2 Hz, H8), 4.80 (1H, dd, *J* = 8.0, 6.2 Hz, H15), 4.64 – 4.58 (1H, m, H7), 4.14 (1H, ddd, *J* = 9.2, 6.0, 3.9 Hz, H6), 3.64 (3H, s, H13), 3.56 (3H, s, -OMe), 2.34 – 2.28 (2H, m, H18), 2.25 (3H, s, H12), 1.97 – 1.88 (1H, m, H16), 1.76 – 1.66 (2H, m, H16, H17), 1.58 – 1.45 (2H, m, H5, H17), 1.49 (3H, s, H21), 1.46 – 1.39 (2H, m, H4, H5), 1.37 (3H, s, H21), 1.33 – 1.23 (5H, m, H2, H3, H4), 0.87 – 0.82 (3H, m, H1). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 173.7, 146.3, 134.0, 130.0, 123.3, 122.7, 108.0, 79.7, 79.0, 65.3, 51.7, 35.5, 33.6, 31.9, 31.8, 30.6, 28.4, 26.2, 25.9, 22.7, 21.7, 14.1, 13.2. **$[\alpha]_D$** = +3.46° (c = 0.97 g/100 $cm^3$). **IR** (film) $\nu_{max}/cm^{-1}$ 3166 (broad), 2930, 2858, 1736, 1456, 1377, 1215, 1039, 878. **HRMS** (ESI) $[M+H]^+$ calc. 423.2854 for $[C_{23}H_{39}N_2O_5]^+$; found 423.2853. **SFC** *dr* = 95.0:5.0

(90.0% *de*) as determined by SFC (chiralpak IC column, $sCO_2$:MeOH, 99:1 for 0 – 1 min, gradient to 60:40 for 1 – 5 min, 3.00 mL/min, T = 35 °C); $R_T$ = 3.96 min [(*S*)-major], $R_T$ = 4.22 min [(*R*)-minor].

**methyl (*S*)-5-(4-((3*R*,4*S*,*E*)-3,4-dihydroxynon-1-en-1-yl)-1,2-dimethyl-1*H*-imidazol-5-yl)-5-hydroxypentanoate** (**10**)

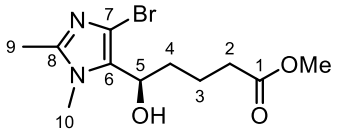



**10**

To a vial containing **36** (0.055 g, 0.130 mmol) in MeOH (1.5 mL) was added $ZrCl_4$ (0.015 g, 0.065 mmol). The resulting mixture was stirred at rt for 3 h. The solution was then concentrated *in vacuo* at room temperature. Purification by column chromatography ($SiO_2$, $CH_2Cl_2$/MeOH, 9:1) afforded the desired compound as a pale orange wax (0.038 g, 76%).

**$R_f$** = 0.21 ($CH_2Cl_2$/MeOH, 9:1) [UV/PMA]. **$^1$H NMR** (500 MHz, $CD_3OD$) δ 6.63 (1H, dd, *J* = 15.9, 1.3 Hz, H9), 6.31 (1H, dd, *J* = 15.9, 6.5 Hz, H8), 4.94 (1H, t, *J* = 7.3 Hz, H15), 4.11 (1H, ddd, *J* = 6.5, 4.8, 1.3 Hz, H7), 3.70 (3H, s, H13), 3.64 (3H, s, -OMe), 3.58 (1H, ddd, *J* = 8.8, 4.8, 3.3 Hz, H6), 2.44 (3H, s, H12), 2.39 – 2.33 (2H, m, H18), 1.99 – 1.91 (1H, m, H16), 1.84 – 1.74 (1H, m, H16), 1.74 – 1.66 (1H, m, H17), 1.64 – 1.47 (3H, m, H4, H5, H17), 1.46 – 1.39 (1H, m, H5), 1.39 – 1.27 (5H, m, H2, H3, H4), 0.94 – 0.86 (3H, m, H1). **$^{13}$C NMR** (126 MHz, $CD_3OD$) δ 175.5, 147.3, 132.5, 131.8, 130.2, 120.8, 76.9, 75.8, 65.8, 52.0, 36.6, 34.2, 33.6, 33.1, 32.4, 26.7, 23.7, 22.4, 14.4, 12.0. **$[\alpha]_D$** = +6.06° (c = 1.00 g/100 $cm^3$).**IR** (film) $\nu_{max}$/$cm^{-1}$ 3338 (broad), 2928, 2857, 1735, 1436, 1199, 1073, 1025. **HRMS** (ESI) $[M+H]^+$ calc. 383.2540 for $[C_{20}H_{35}N_2O_5]^+$; found 383.2539.

**methyl (*R*)-5-(4-bromo-1,2-dimethyl-1H-imidazol-5-yl)-5-hydroxypentanoate** (**37**)




(*R*)-**37**

To a flame-dried Schlenk tube under $N_2$ was added triethylamine (1.011 mL, 7.26 mmol) followed by formic acid (0.68 mL, 18.1 mmol) dropwise at 0 °C. After warming to rt, [(*S*,*S*)-Teth-TsDpen]RuCl (0.0102 g, 0.0165 mmol) was added and the resulting mixture was stirred

at rt for 15 min. A solution of **34** (0.100 g, 0.330 mmol) in $CH_2Cl_2$ (0.5 mL) was added and the resulting mixture was stirred at 40 °C for 24 h. $NaHCO_3$ (aq. sat., 5 mL) was added and the product was extracted into EtOAc (5 x 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, $CH_2Cl_2$/MeOH, 96:4) afforded the desired compound as a colourless waxy solid (0.046 g, 46%, 56% *ee*).

**$R_f$** = 0.20 (100% EtOAc) [$KMnO_4$]. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 4.77 (1H, t, *J* = 7.4 Hz, H5), 3.65 (3H, s, -OMe), 3.64 (3H, s, H10), 2.34 (2H, td, *J* = 7.1, 3.6 Hz, H2), 2.29 (3H, s, H9), 1.99 – 1.89 (1H, m, H4), 1.83 – 1.67 (2H, m, H3, H4), 1.60 – 1.51 (1H, m, H3). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 174.0, 146.1, 129.2, 112.4, 65.8, 51.7, 35.0, 33.6, 32.1, 21.4, 13.3. **$[\alpha]_D$** = +5.68° (c = 1.05 g/100 $cm^3$). **IR** (film) $\nu_{max}/cm^{-1}$ 3213 (broad), 2951, 1733, 1435, 1235, 1004. **HRMS** (ESI) $[M+H]^+$ calc. 305.0495 for $[C_{11}H_{18}{}^{79}BrN_2O_3]^+$; found 305.0495, calc. 307.0476 for $[C_{11}H_{18}{}^{81}BrN_2O_3]^+$; found 307.0474. **SFC** *er* = 78.0:22.0 (56.0% *ee*) as determined by SFC (chiralpak IC column, $sCO_2$:MeOH, 99:1 for 0 – 1 min, gradient to 60:40 for 1 – 5 min, 3.00 mL/min, T = 35 °C); $R_T$ = 3.93 min [(*R*)-major], $R_T$ = 4.06 min [(*S*)-minor].

## 2.1 Mosher's Ester Analysis of Compound 37

*Adapted from procedure described by Hoye et al.*[3] To a flame-dried Schlenk tube under $N_2$ was added **37** (78:22 *er* as determined by SFC analysis, 0.023 g, 0.0754 mmol) in dry $CH_2Cl_2$ (1 mL). (*S*)-(–)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (0.053 g, 0.226 mmol) was added followed by DCC (0.047 g, 0.226 mmol) and DMAP (0.028 g, 0.226 mmol). The resulting mixture was stirred at rt for 3 h. The solution was diluted with $CH_2Cl_2$ (5 mL), filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, cyclohexane/EtOAc, 2:3) afforded the desired product as a mixture of two diastereomers in a 78:22 ratio (0.020 g, 51%). $\mathbf{R_f}$ = 0.20 (cyclohexane/EtOAc, 2:3).

The full $^1$H-NMR spectrum of the mixture of diastereomers was difficult to interpret, and the mixture was not characterised fully. However, two sets of four 3H singlets could clearly be seen in a 78:22 ratio. These corresponded to the four methyl groups in each of the diastereomers, and their chemical shifts could be used to deduce the absolute stereochemistry of the major and minor diastereomers (**Figures S1 and S2**). Because of magnetic anisotropy, protons that are close in space to the phenyl substituent on the ester are shielded and thus have a lower chemical shift whilst protons that are close in space to the methoxy substituent on the ester are deshielded and thus have a higher chemical shift. The protons of the ester methoxy substituent can also be shielded if they are close in space to the imidazole ring.

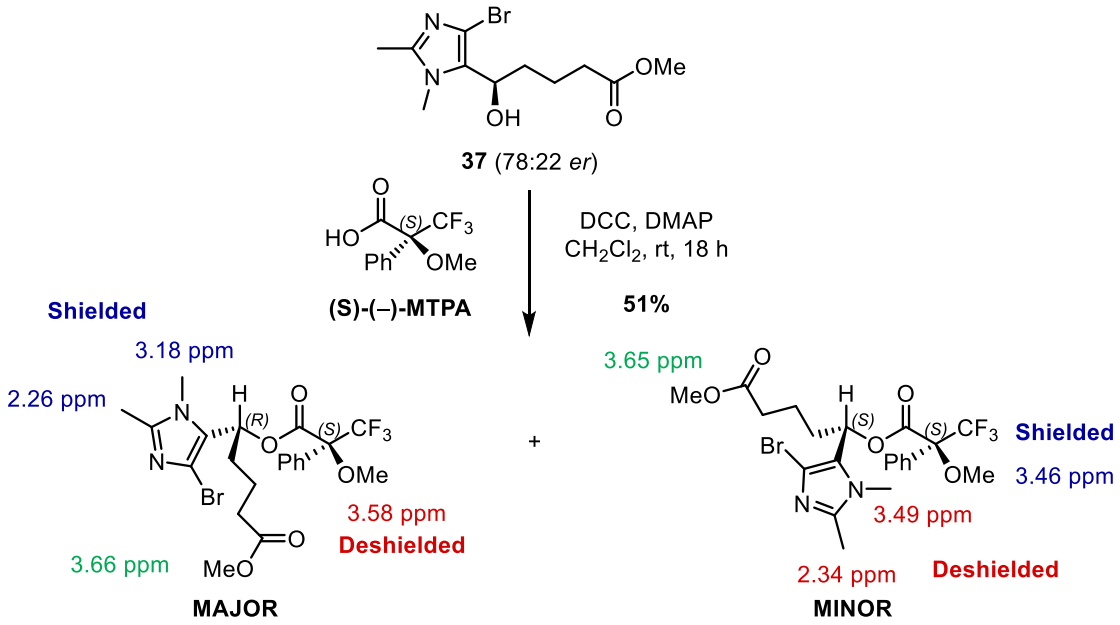



**Figure S1:** Mosher's ester analysis of **37** confirming the (*R*)-configuration of the major enantiomer.

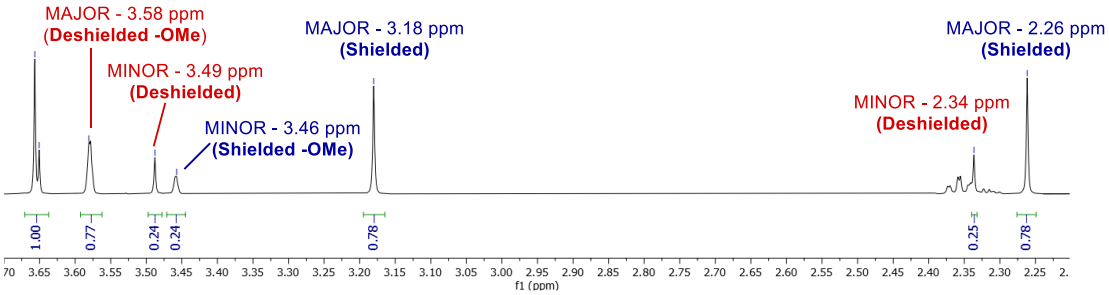
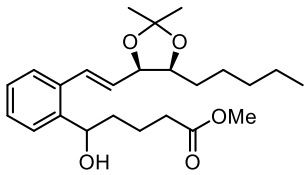


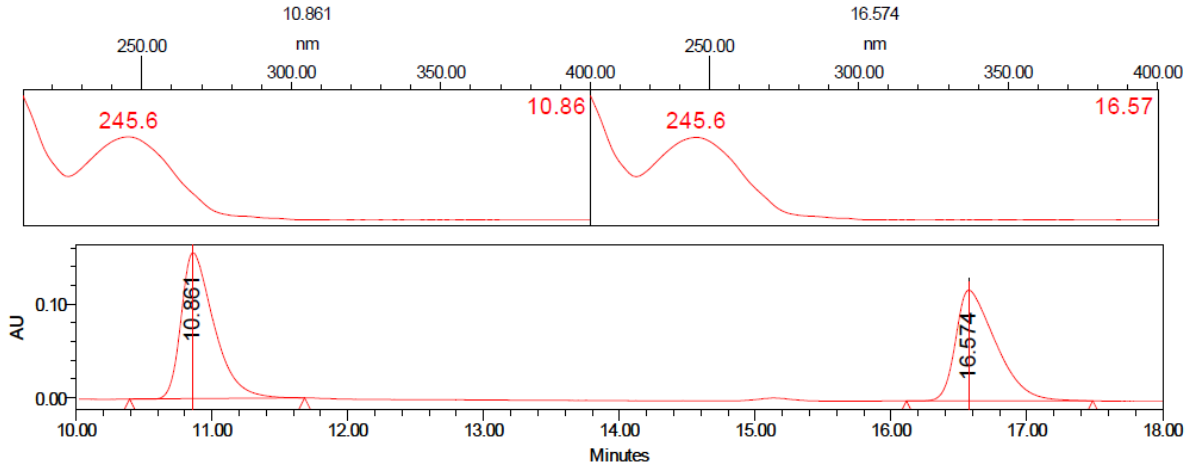

**Figure S2:** Section of the $^{1}$H-NMR spectrum showing the diagnostic 3H singlets and their chemical shifts.

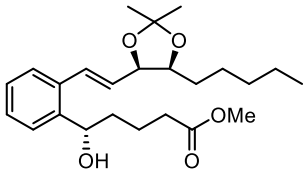
## 3. SFC Chromatograms

**methyl (*S*)-5-(2-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)phenyl)-5-hydroxypentanoate (22)**



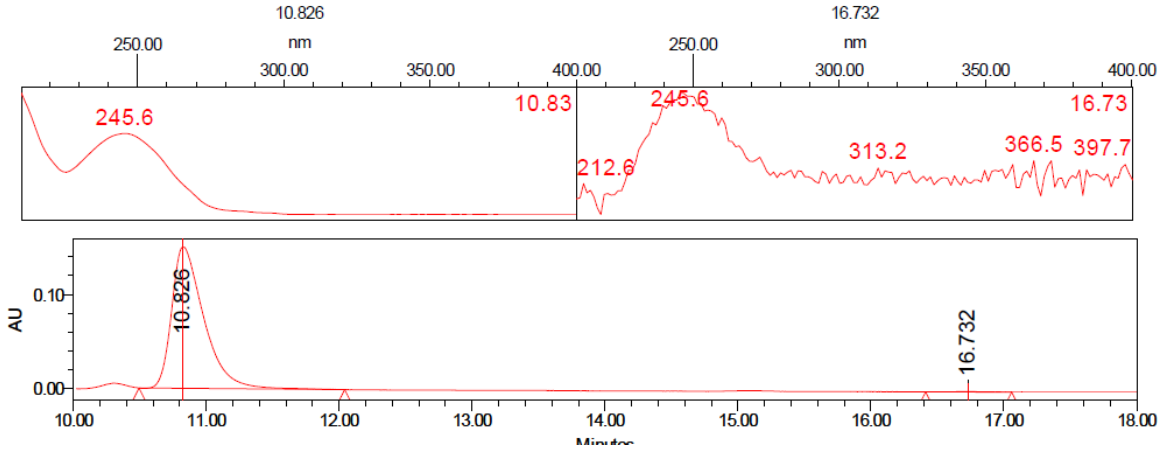

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 245.6 nm | 10.861 | 2620695 | 51.99 | 155825 |
| 2 | PDA 245.6 nm | 16.574 | 2420522 | 48.01 | 118323 |



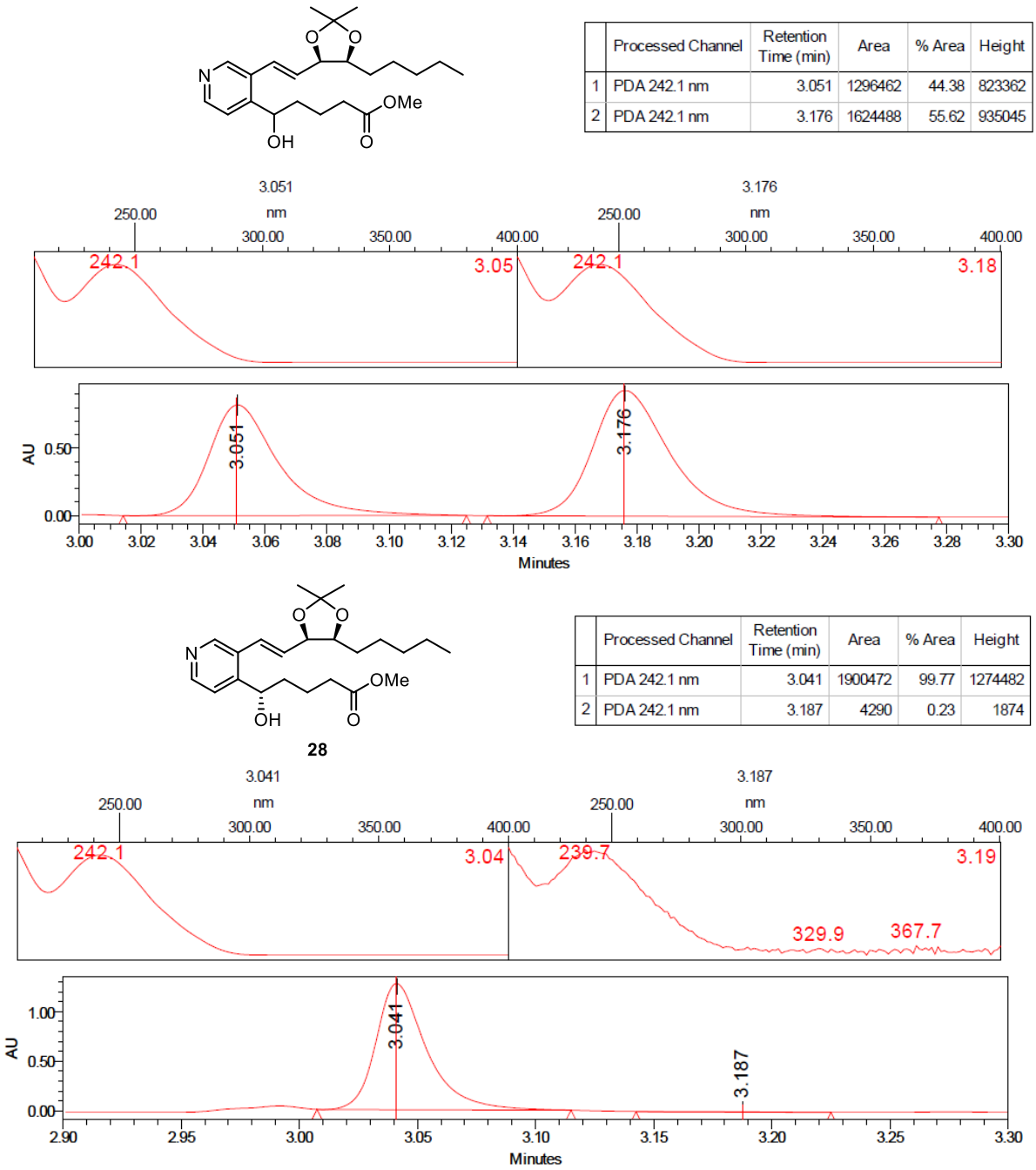

**22**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 245.6 nm | 10.826 | 2539414 | 99.80 | 151197 |
| 2 | PDA 245.6 nm | 16.732 | 5216 | 0.20 | 432 |



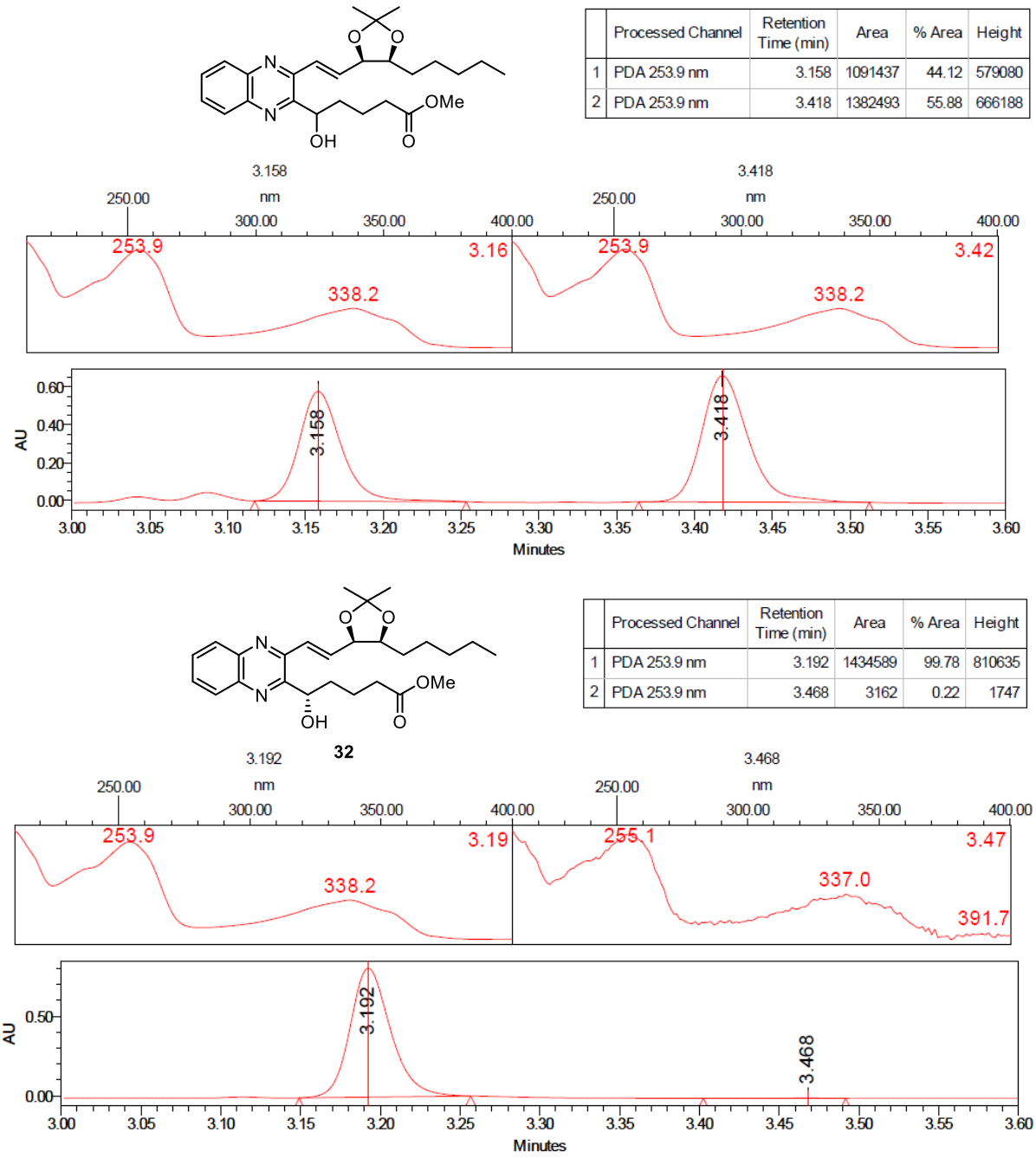

**SFC** *dr* = 99.8:0.2 (99.6% *de*) as determined by SFC (chiralpak ID column, $sCO_2$:*i*-PrOH, 99:1 for 0 – 1 min, gradient to 90:10 for 1 – 20 min, 3.00 mL/min, T = 35 °C); $R_T$ = 10.83 min [(*S*)-major], $R_T$ = 16.73 min [(*R*)-minor].

**methyl (*S*)-5-(3-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)pyridin-4-yl)-5-hydroxypentanoate (28)**




**SFC** *dr* = 99.8:0.2 (99.6% *de*) as determined by SFC (chiralpak ID column, $sCO_2$:MeOH, 99:1 for 0 – 1 min, gradient to 50:50 for 1 – 5 min, 3.00 mL/min, T = 35 °C); $R_T$ = 3.04 min [(*S*)-major], $R_T$ = 3.19 min [(*R*)-minor].

**methyl (*S*)-5-(3-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)quinoxalin-2-yl)-5-hydroxypentanoate (32)**




| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 253.9 nm | 3.158 | 1091437 | 44.12 | 579080 |
| 2 | PDA 253.9 nm | 3.418 | 1382493 | 55.88 | 666188 |

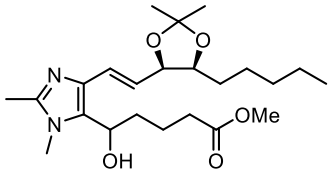



**32**

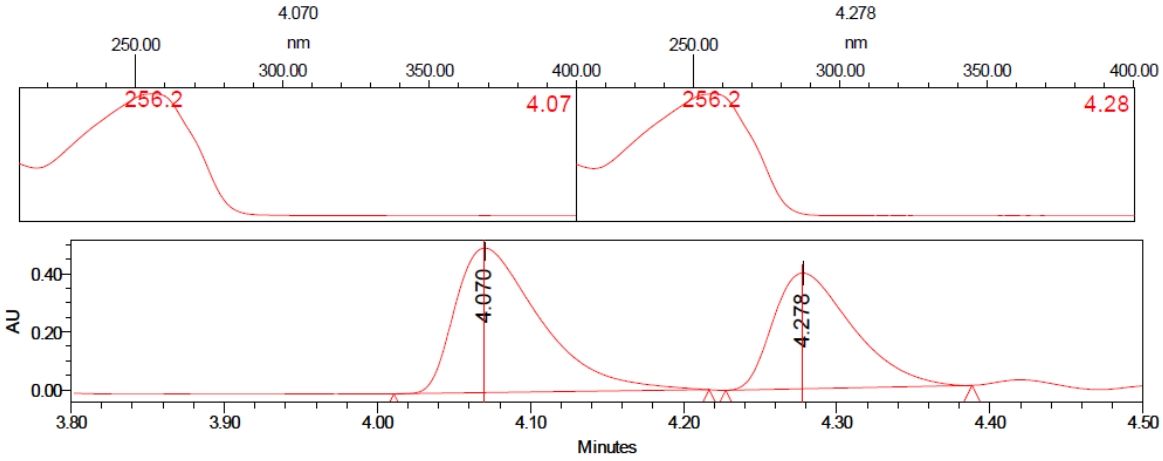
| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 253.9 nm | 3.192 | 1434589 | 99.78 | 810635 |
| 2 | PDA 253.9 nm | 3.468 | 3162 | 0.22 | 1747 |

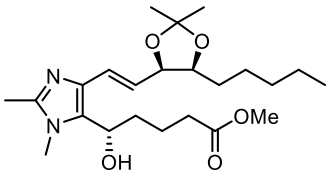
**SFC** *dr* = 99.8:0.2 (99.6% *de*) as determined by SFC (chiralpak ID column, $sCO_2$:MeOH, 99:1 for 0 – 1 min, gradient to 50:50 for 1 – 5 min, 3.00 mL/min, T = 35 °C); $R_T$ = 3.19 min [(*S*)-major], $R_T$ = 3.47 min [(*R*)-minor].

**methyl (*S*)-5-(4-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)-1,2-dimethyl-1*H*-imidazol-5-yl)-5-hydroxypentanoate (36)**



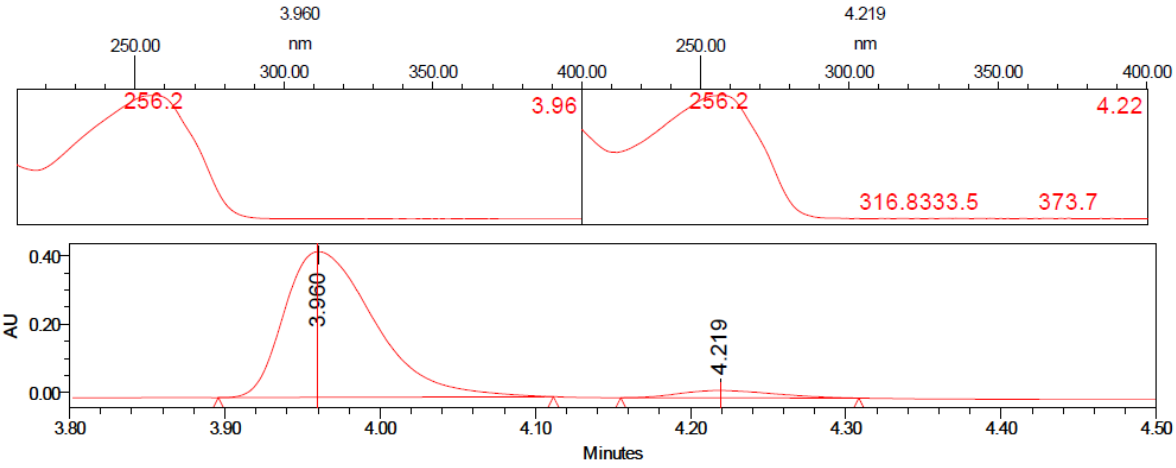

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 256.2 nm | 4.070 | 1921159 | 57.26 | 497251 |
| 2 | PDA 256.2 nm | 4.278 | 1433986 | 42.74 | 398067 |



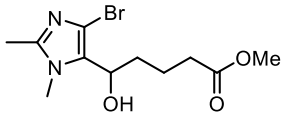

**36**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 256.2 nm | 3.960 | 1727755 | 95.01 | 427784 |
| 2 | PDA 256.2 nm | 4.219 | 90744 | 4.99 | 21541 |



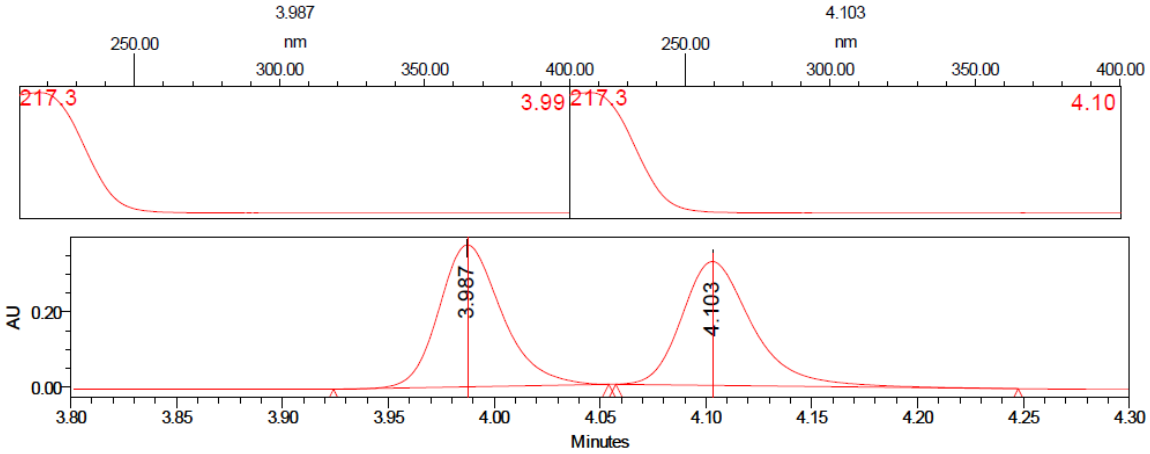

**SFC** *dr* = 95.0:5.0 (90.0% *de*) as determined by SFC (chiralpak IC column, $sCO_2$:MeOH, 99:1 for 0 – 1 min, gradient to 60:40 for 1 – 5 min, 3.00 mL/min, T = 35 °C); $R_T$ = 3.96 min [(*S*)-major], $R_T$ = 4.22 min [(*R*)-minor].

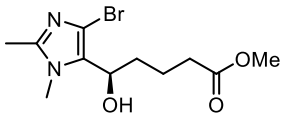
**methyl (*R*)-5-(4-bromo-1,2-dimethyl-1H-imidazol-5-yl)-5-hydroxypentanoate (37)**




*rac*-**37**

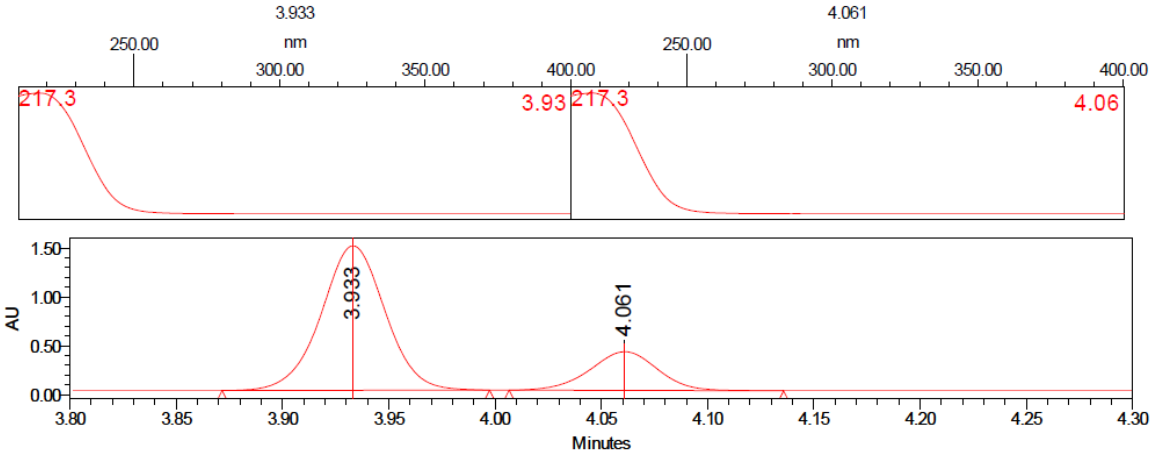
| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 217.3 nm | 3.987 | 787422 | 50.64 | 379778 |
| 2 | PDA 217.3 nm | 4.103 | 767654 | 49.36 | 331140 |



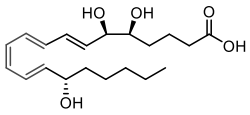

(*R*)-**37**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 217.3 nm | 3.933 | 3101639 | 78.01 | 1476959 |
| 2 | PDA 217.3 nm | 4.061 | 874148 | 21.99 | 395235 |

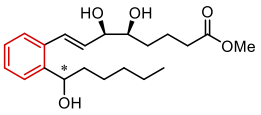



**SFC** *er* = 78.0:22.0 (56.0% *ee*) as determined by SFC (chiralpak IC column, $sCO_2$:MeOH, 99:1 for 0 – 1 min, gradient to 60:40 for 1 – 5 min, 3.00 mL/min, T = 35 °C); $R_T$ = 3.93 min [(*R*)-major], $R_T$ = 4.06 min [(*S*)-minor].

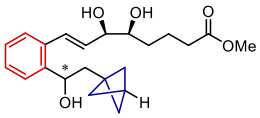
# 4. Summary of Previously Reported SAR Studies on Aromatic and Heteroaromatic $LXA_4$ Analogues



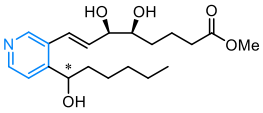
Native $LXA_4$ (**1**)



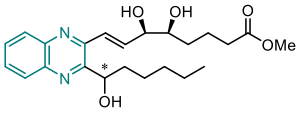
(*S*)-**3**
(*R*)-**3**



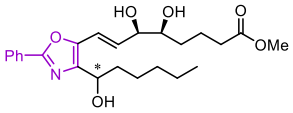
(*S*)-**S1**
(*R*)-**S1**



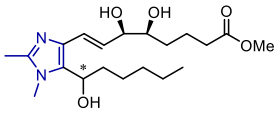
(*S*)-**4**
(*R*)-**4**



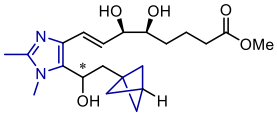
(*S*)-**5**
(*R*)-**5**



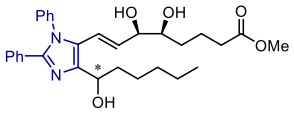
(*S*)-**S2**
(*R*)-**S2**



(*S*)-**6**
(*R*)-**6**



(*S*)-**S3**
(*R*)-**S3**



(*S*)-**S4**
(*R*)-**S4**

| Aromatic Ring | Compound | $I_{max}$ | Conc./ M |
|---|---|---|---|
| Native $LXA_4$ | (*S*)-**1** | 24 ± 1% | $10^{-7}$ |
| Benzene | (S)-**3** | - | - |
| | (*R*)-**3** | 20 ± 1% | $10^{-12}$ |
| | (S)-**S1** | 22 ± 11% | $10^{-10}$ |
| | (*R*)-**S1** | 18 ± 6% | $10^{-9}$ |
| Pyridine | (S)-**4** | - | - |
| | (*R*)-**4** | - | - |
| Quinoxaline | (*S*)-**5** | 34 ± 9% | $10^{-8}$ |
| | (*R*)-**5** | 38 ± 9% | $10^{-8}$ |
| Phenyl Oxazole | (*S*)-**S2** | 24 ± 10% | $10^{-12}$ |
| | (*R*)-**S2** | 14 ± 4% | $10^{-6}$ |
| Dimethyl Imidazole | (*S*)-**6** | 24 ± 12% | $10^{-6}$ |
| | (*R*)-**6** | 44 ± 9% | $10^{-12}$ |
| | (*S*)-**S3** | 46 ± 9% | $10^{-7}$ |
| | (*R*)-**S3** | 17 ± 3% | $10^{-8}$ |
| Diphenyl Imidazole | (*S*)-**S4** | 20 ± 1% | $10^{-10}$ |
| | (*R*)-**S4** | 16 ± 2% | $10^{-8}$ |

**Table S1**: Summary of the results of our previously reported SAR studies on aromatic and heteroaromatic $LXA_4$ analogues.[1,4,5]

For each analogue the maximum %inhibition of LPS-induced NF-κB activity ($I_{max}$) is shown alongside the concentration at which $I_{max}$ was observed. $I_{max}$ values significantly higher than that of native $LXA_4$ (**1**) are highlighted in blue. The labels (*S*)- and (*R*)- refer to the absolute configuration at the carbon indicated with an asterisk. LPS-induced NF-κB activity data are not available for compound (*S*)-**3** and pyridine-containing compounds (*S*)-**4** and (*R*)-**4**. The bioactivity of these compounds was evaluated and compared in a separate study.[6]

## 5. References


(1) de Gaetano, M.; Tighe, C.; Gahan, K.; Zanetti, A.; Chen, J.; Newson, J.; Cacace, A.; Marai, M.; Gaffney, A.; Brennan, E.; Kantharidis, P.; Cooper, M. E.; Leroy, X.; Perretti, M.; Gilroy, D.; Godson, C.; Guiry, P. J. Asymmetric Synthesis and Biological Screening of Quinoxaline-Containing Synthetic Lipoxin A4 Mimetics (QNX-SLXms). *J. Med. Chem.* **2021**, *64* (13), 9193–9216. https://doi.org/10.1021/acs.jmedchem.1c00403.

(2) Huckstep, M.; Taylor, R. J. K.; Caton, M. P. L. A Convenient Method of Preparing the Leukotriene Precursor Methyl 5-Oxopentanoate. *Synthesis* **1982**, *1982* (10), 881–882. https://doi.org/10.1055/s-1982-29988.

(3) Hoye, T. R.; Jeffrey, C. S.; Shao, F. Mosher Ester Analysis for the Determination of Absolute Configuration of Stereogenic (Chiral) Carbinol Carbons. *Nat. Protoc.* **2007**, *2* (10), 2451–2458. https://doi.org/10.1038/nprot.2007.354.

(4) de Gaetano, M.; Butler, E.; Gahan, K.; Zanetti, A.; Marai, M.; Chen, J.; Cacace, A.; Hams, E.; Maingot, C.; McLoughlin, A.; Brennan, E.; Leroy, X.; Loscher, C. E.; Fallon, P.; Perretti, M.; Godson, C.; Guiry, P. J. Asymmetric Synthesis and Biological Evaluation of Imidazole- and Oxazole-Containing Synthetic Lipoxin A4 Mimetics (SLXms). *Eur. J. Med. Chem.* **2019**, *162*, 80–108. https://doi.org/10.1016/j.ejmech.2018.10.049.

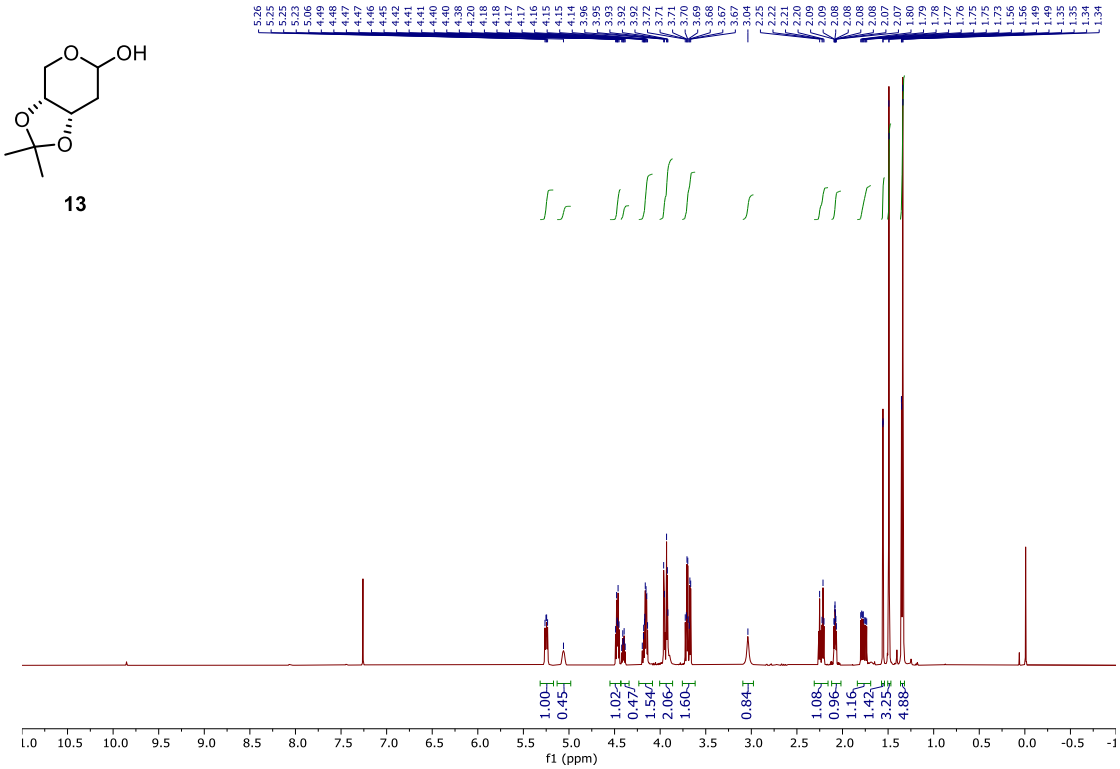
(5) Owen, B.; de Gaetano, M.; Gaffney, A.; Godson, C.; Guiry, P. J. Synthesis and Biological Evaluation of Bicyclo[1.1.1]Pentane-Containing Aromatic Lipoxin A4 Analogues. *Org. Lett.* **2022**, *24* (32), 6049–6053. https://doi.org/10.1021/acs.orglett.2c02345.

(6) Duffy, C. D.; Maderna, P.; McCarthy, C.; Loscher, C. E.; Godson, C.; Guiry, P. J. Synthesis and Biological Evaluation of Pyridine-Containing Lipoxin A4 Analogues. *ChemMedChem* **2010**, *5* (4), 517–522. https://doi.org/10.1002/cmdc.200900533.

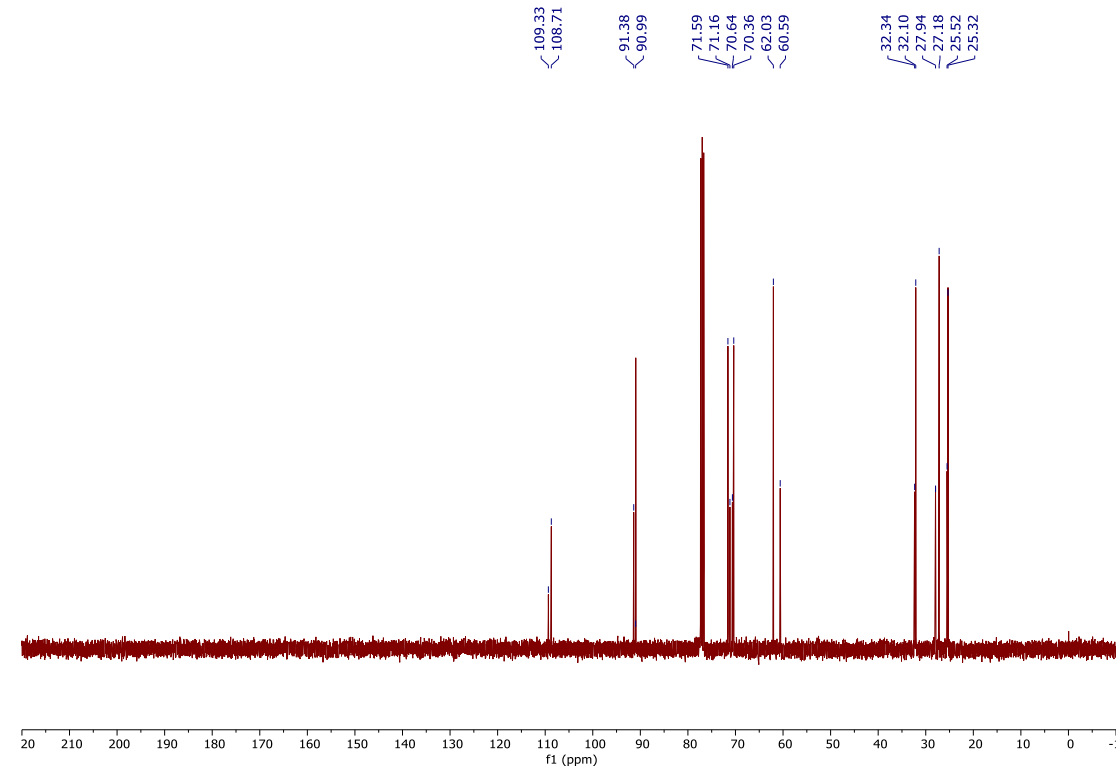
# 6. NMR Spectra

**(3aR,7aS)-2,2-dimethyltetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-6-ol (13)**

**$^{1}$H-NMR** (400 MHz, $CDCl_3$):

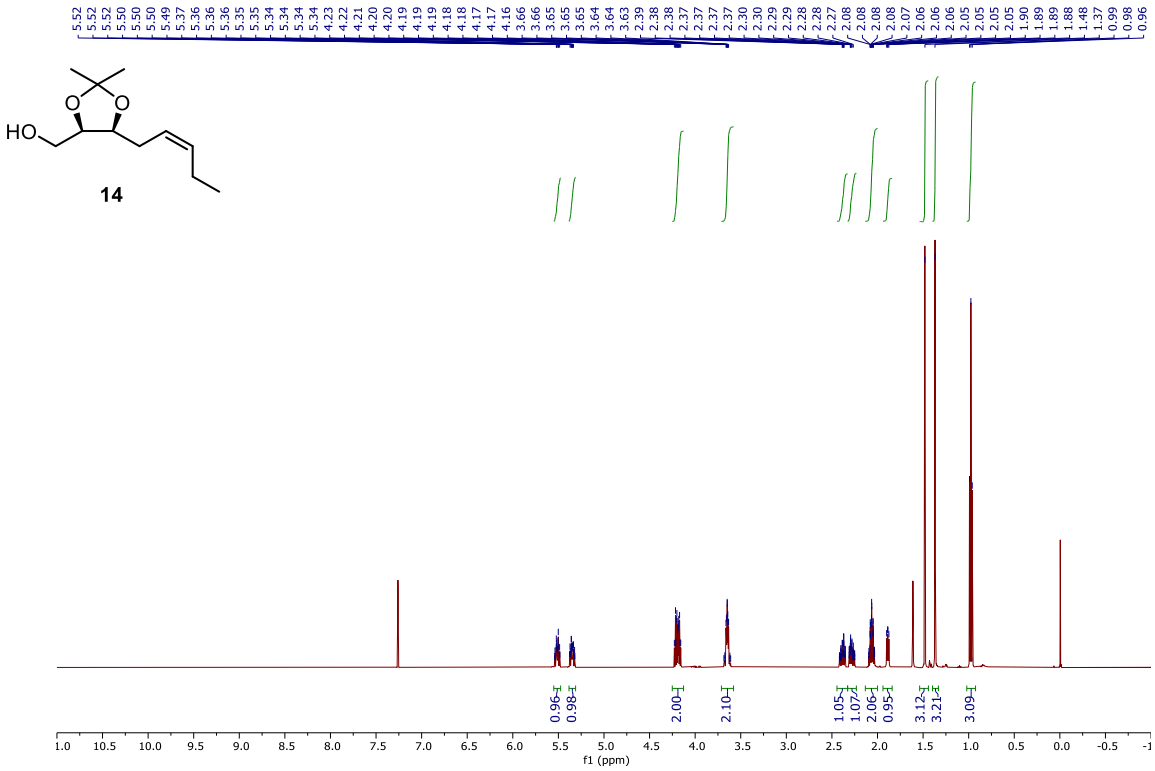



**$^{13}$C-NMR** (101 MHz, $CDCl_3$)**:**

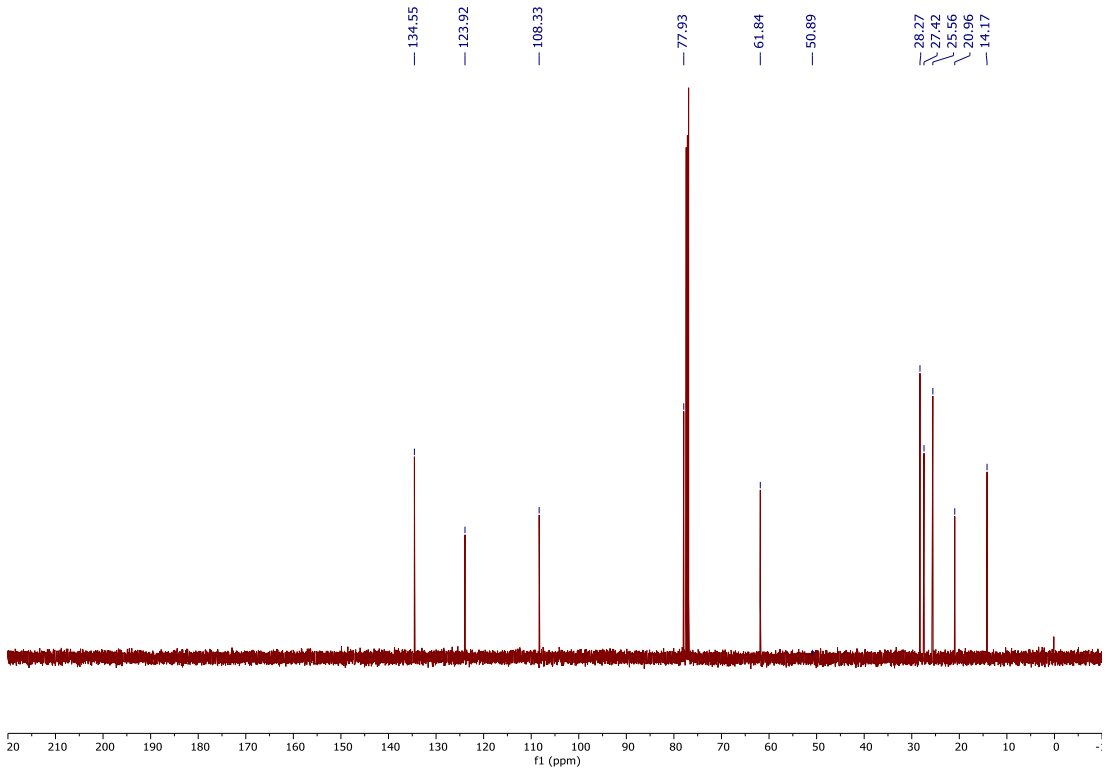


**((4*R*,5*S*)-2,2-dimethyl-5-((*Z*)-pent-2-en-1-yl)-1,3-dioxolan-4-yl)methanol (14)**

**$^{1}$H NMR** (500 MHz, $CDCl_3$):

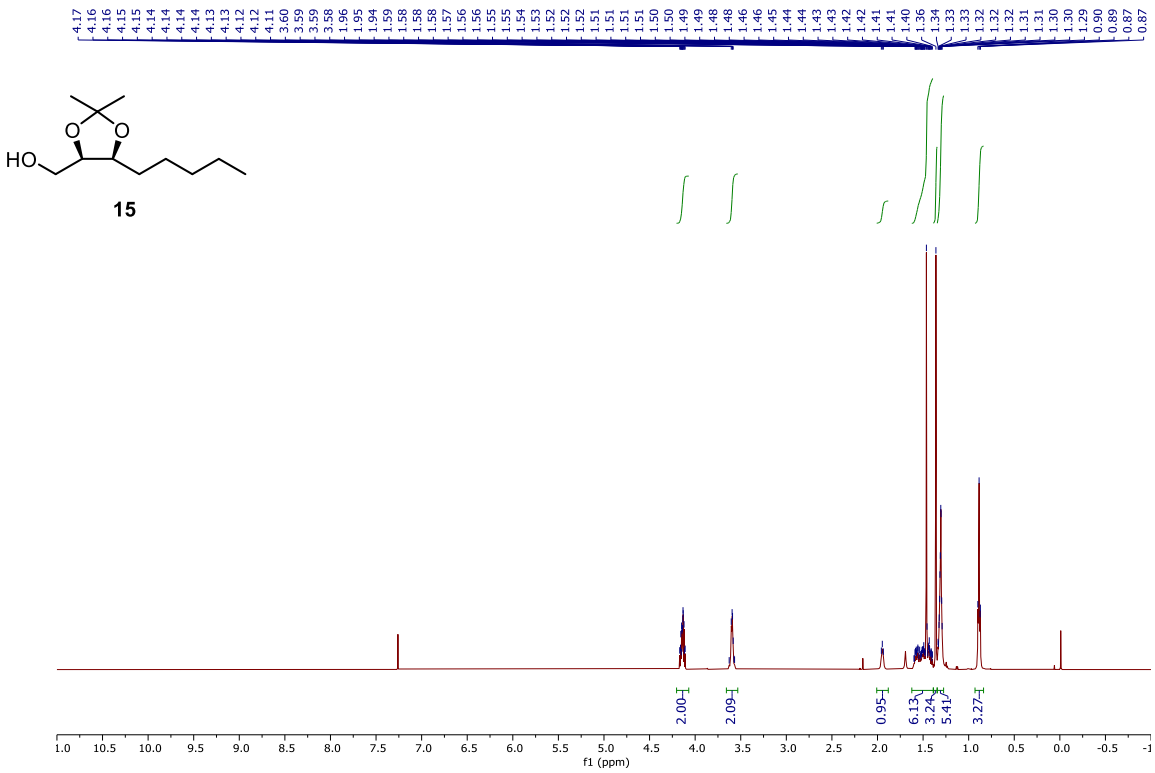



**$^{13}$C NMR** (126 MHz, $CDCl_3$):

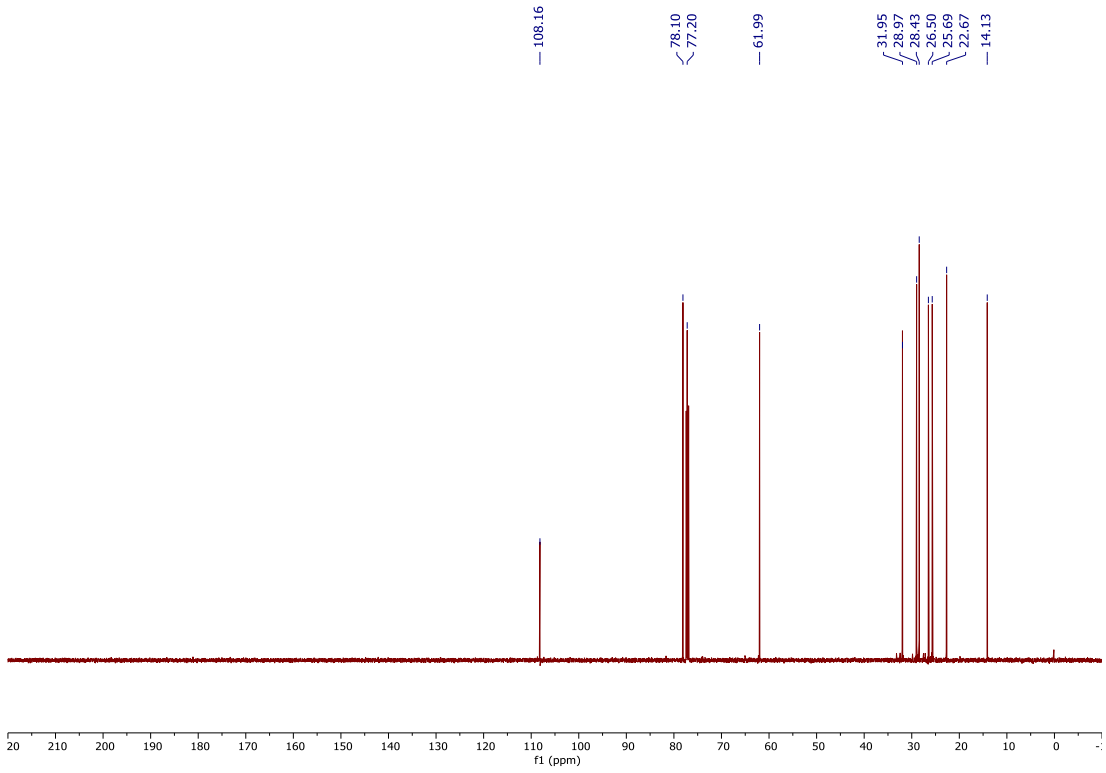


**((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)methanol** (**15**)

**$^{1}$H NMR** (500 MHz, $CDCl_3$):

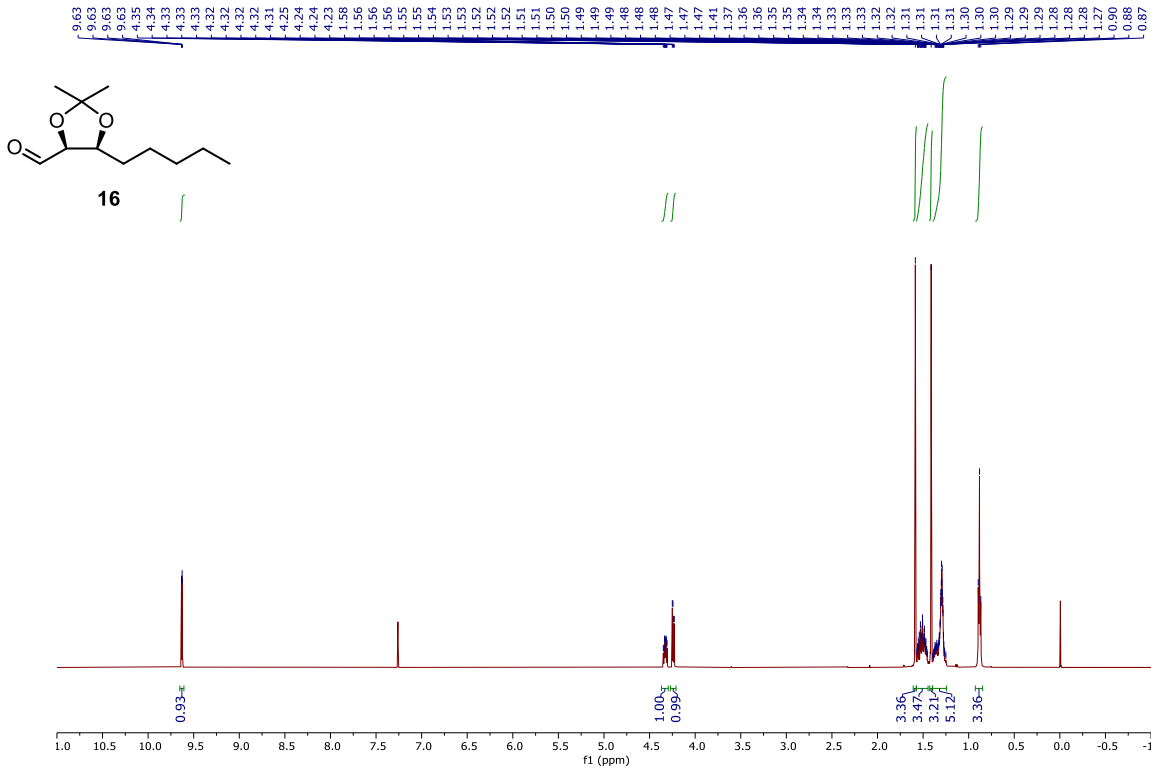



**$^{13}$C NMR** (126 MHz, $CDCl_3$):

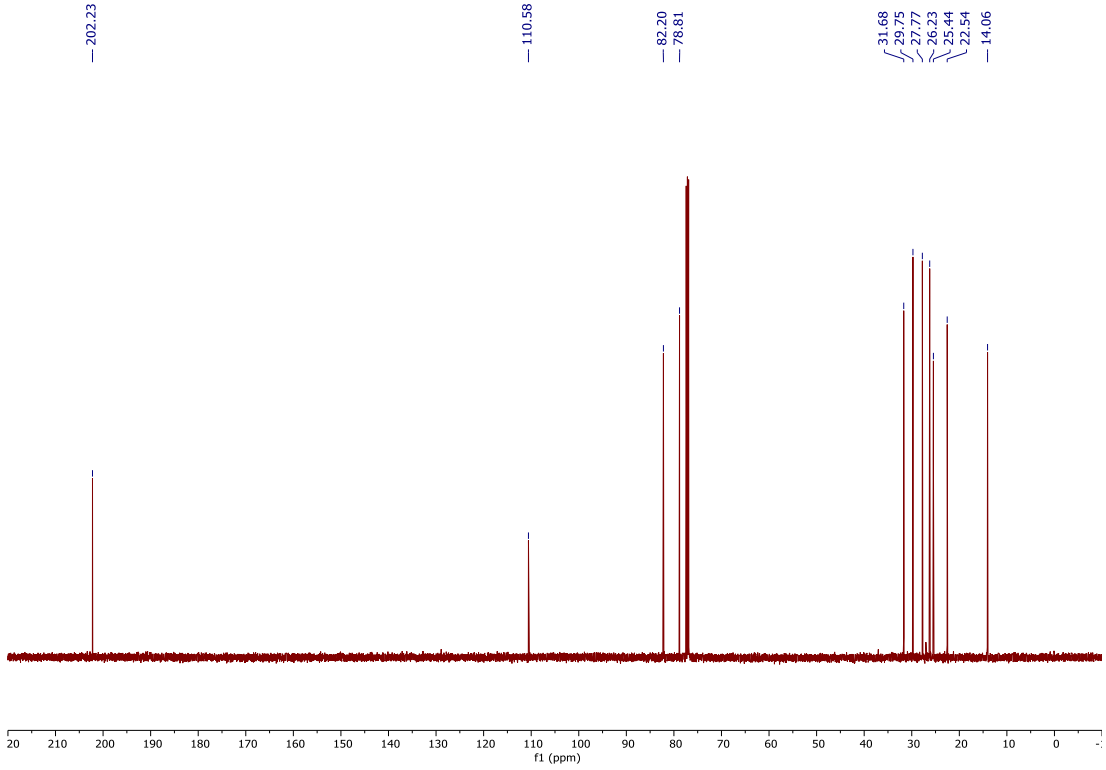


**(4*S*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolane-4-carbaldehyde (16)**

**$^{1}$H NMR** (500 MHz, $CDCl_3$):

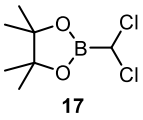



**$^{13}$C NMR** (126 MHz, $CDCl_3$):



**2-(dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (17)**

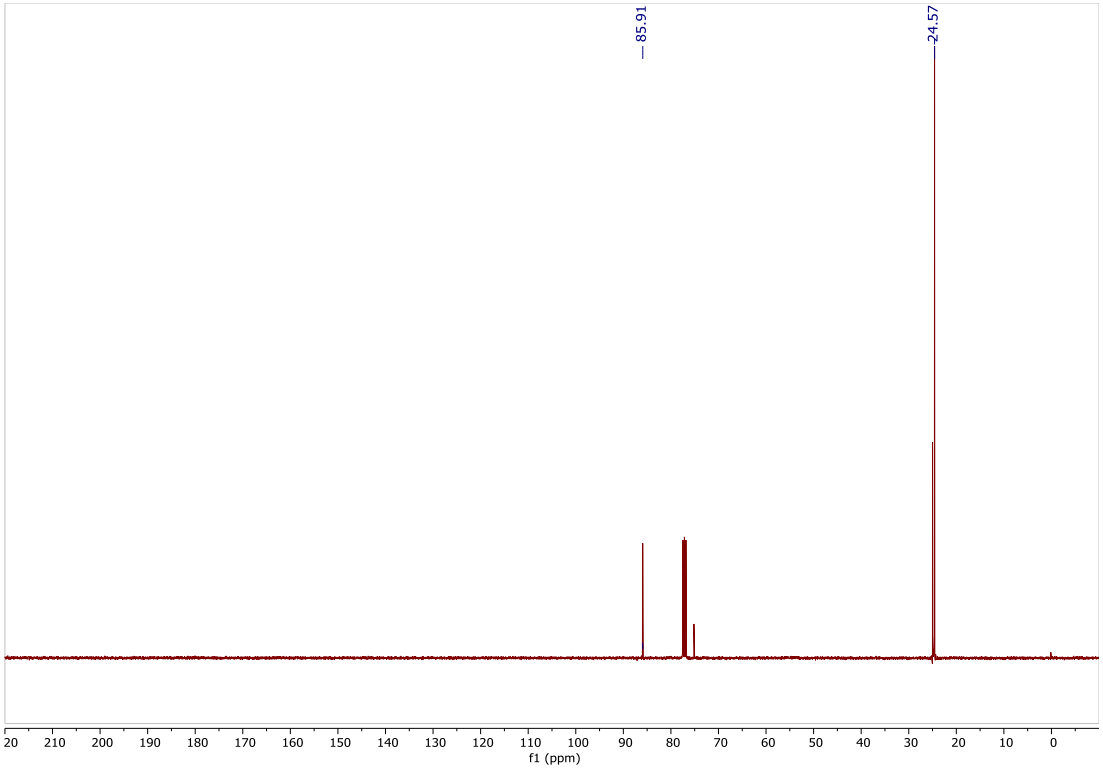
**$^{1}$H-NMR** (400 MHz, $CDCl_3$)**:**




**17**

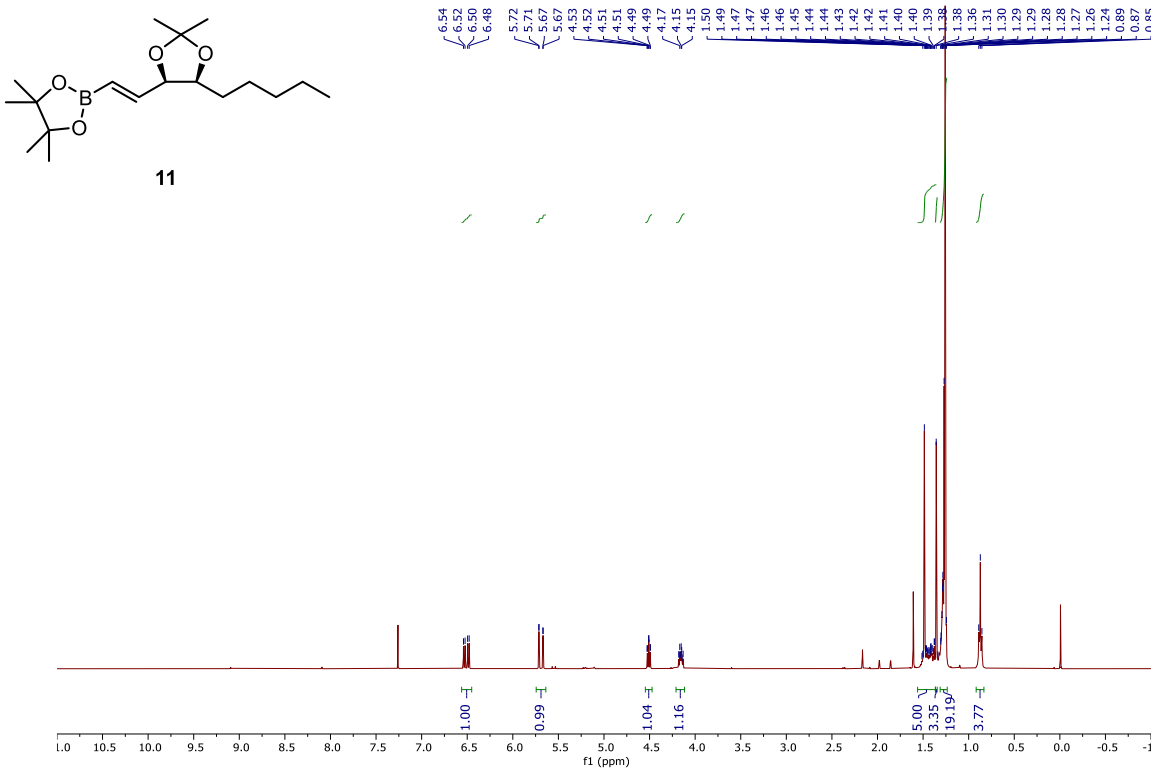



**$^{13}$C-NMR** (101 MHz, $CDCl_3$)**:**

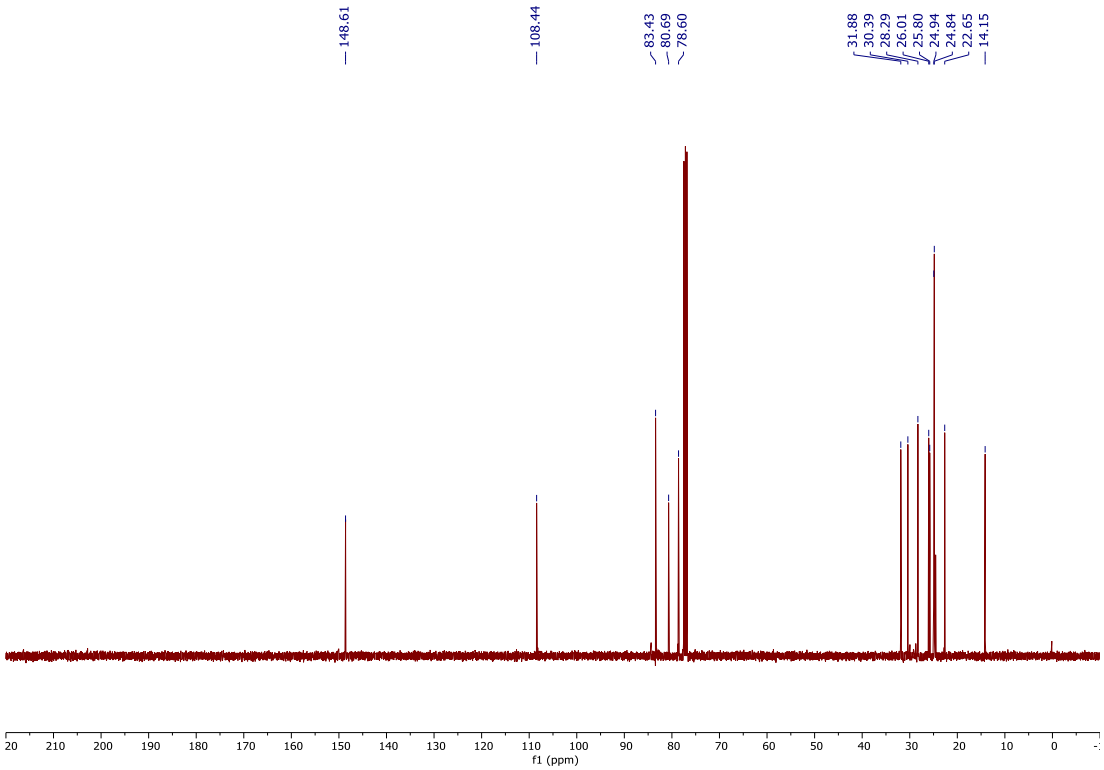


**2-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane** (**11**)

**$^{1}$H NMR** (400 MHz, $CDCl_3$):

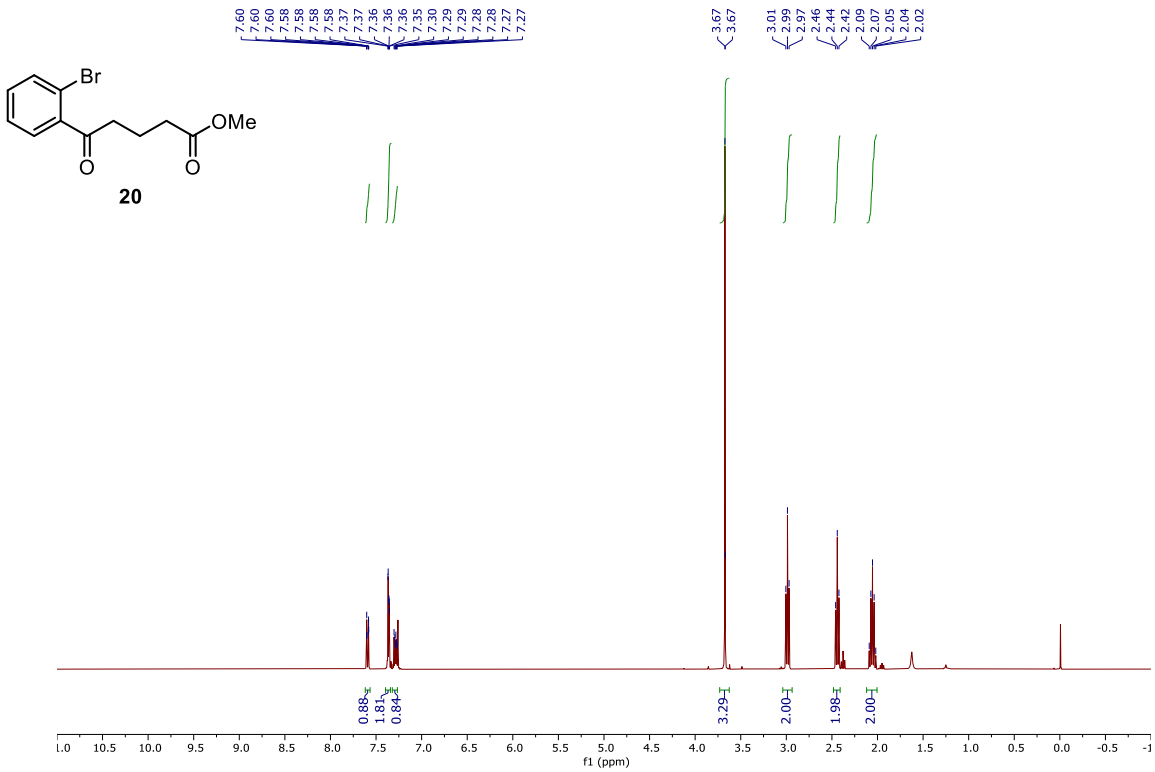



**$^{13}$C NMR** (101 MHz, $CDCl_3$):

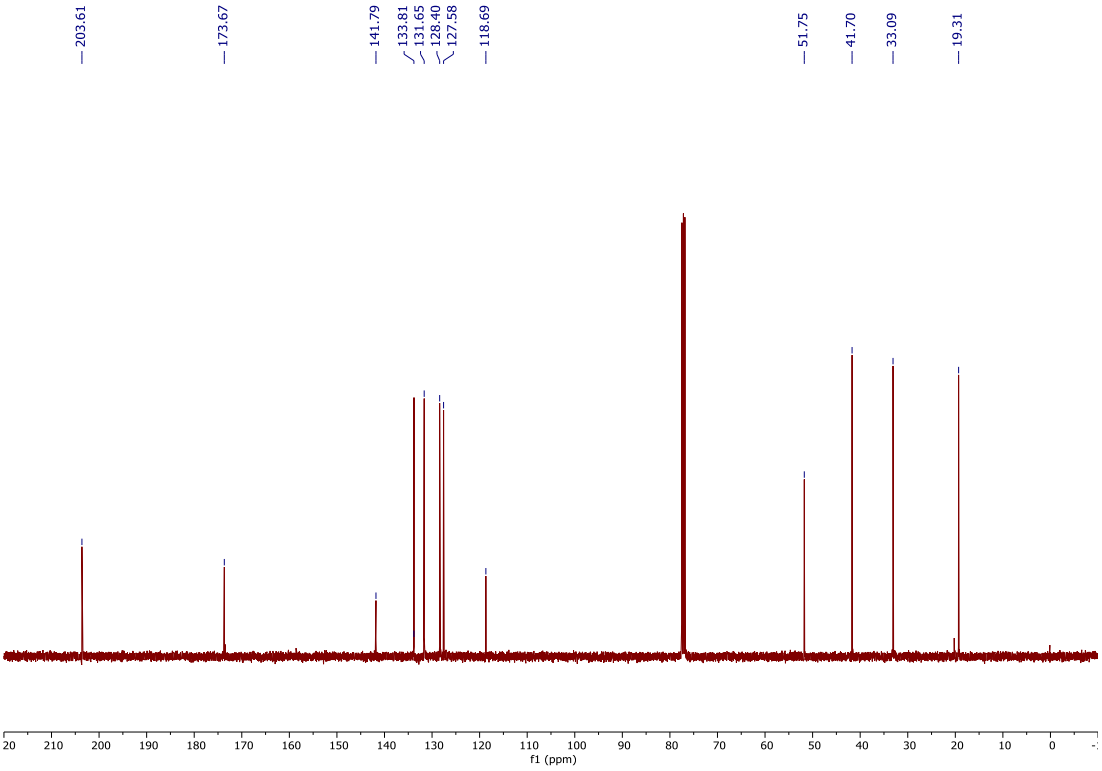


**Methyl 5-(2-bromophenyl)-5-oxopentanoate** (**20**)

**$^{1}$H NMR** (400 MHz, $CDCl_3$):

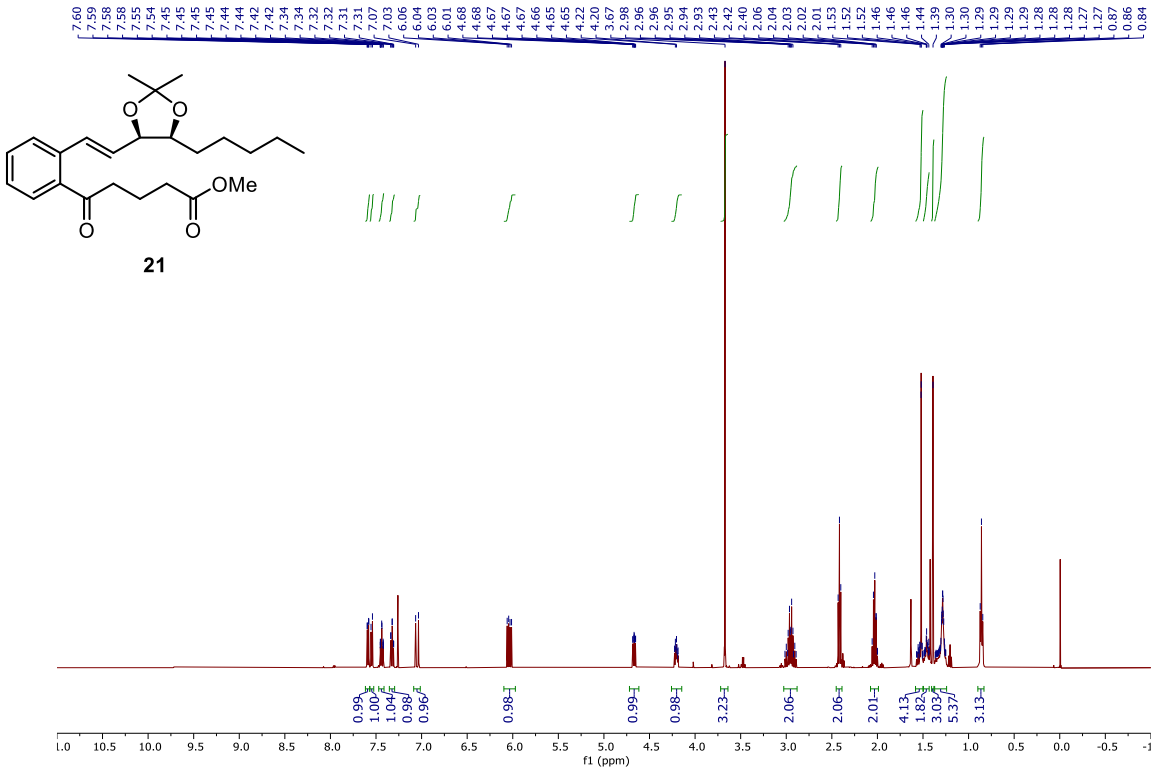



**$^{13}$C NMR** (101 MHz, $CDCl_3$):

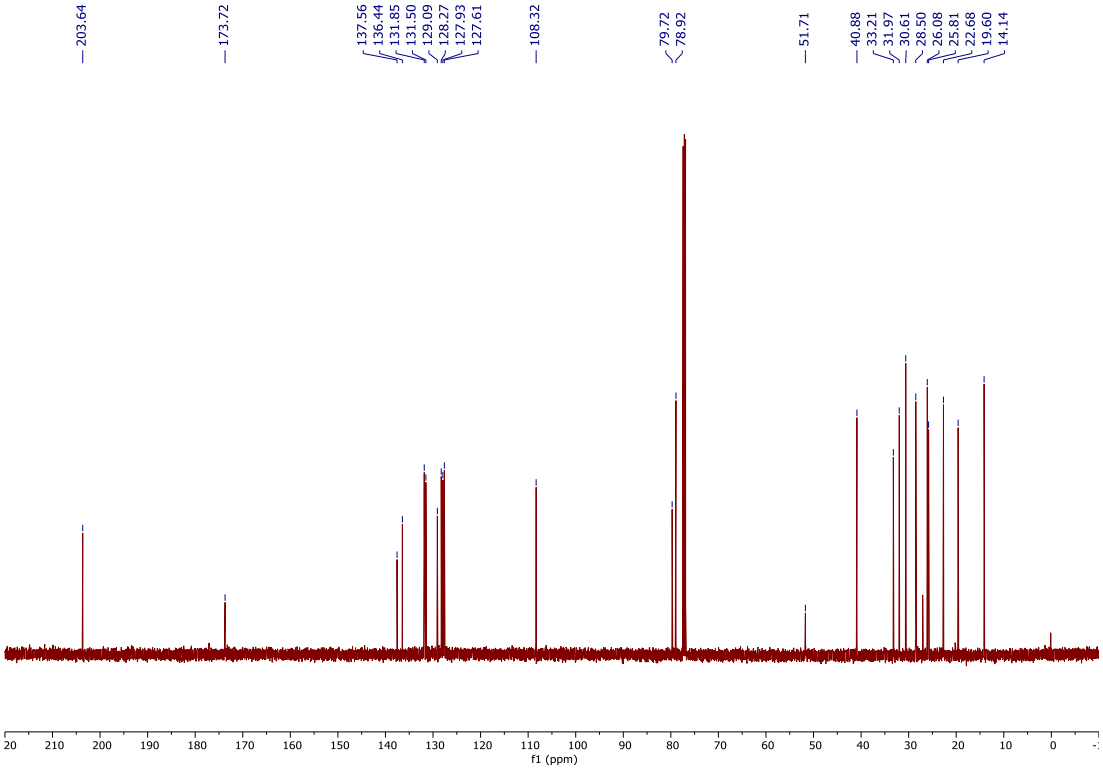


**methyl 5-(2-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)phenyl)-5-oxopentanoate** (**21**)

**$^{1}$H NMR** (500 MHz, $CDCl_3$):

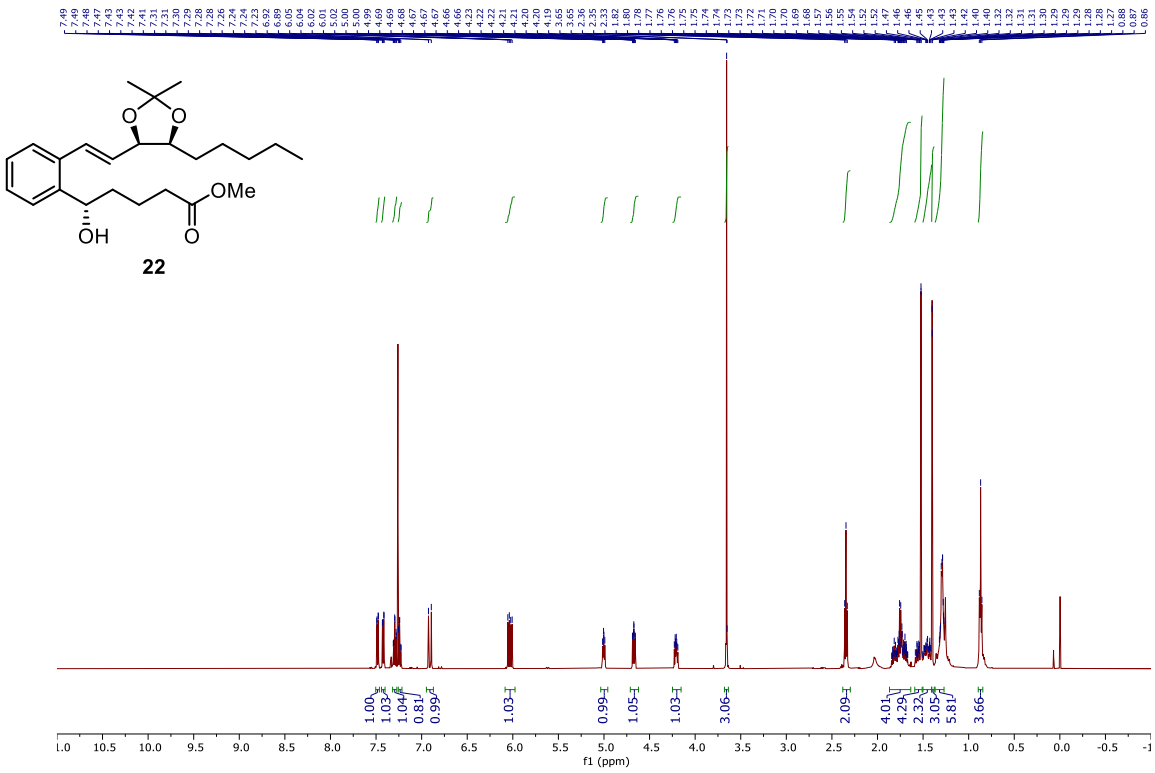



**$^{13}$C NMR** (126 MHz, $CDCl_3$):

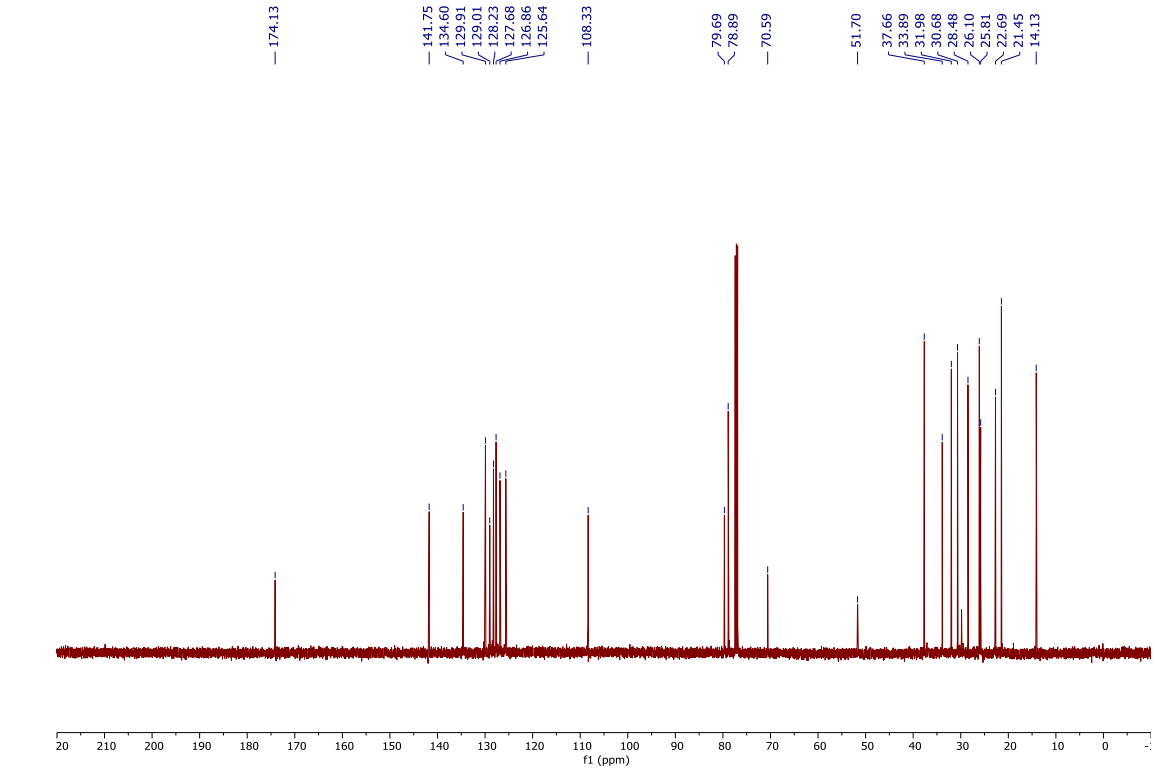


**methyl (*S*)-5-(2-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)phenyl)-5-hydroxypentanoate** (**22**)

**$^{1}$H NMR** (500 MHz, $CDCl_3$):

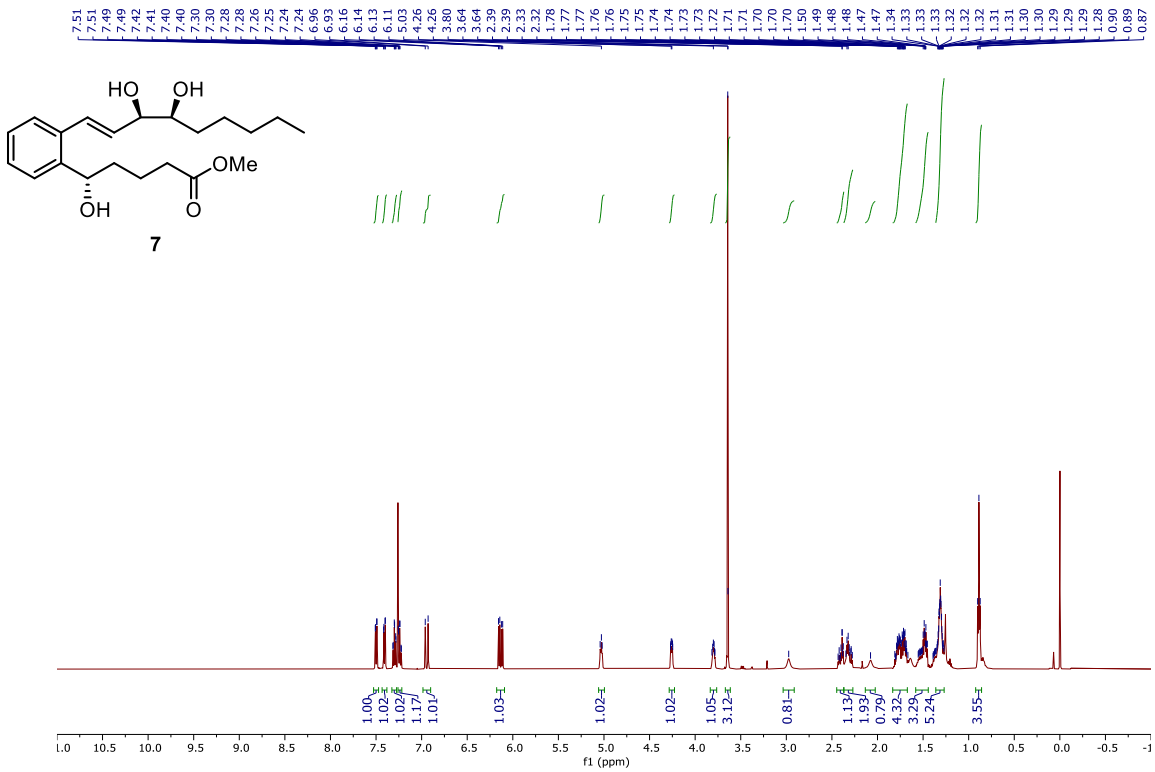



**$^{13}$C NMR** (126 MHz, $CDCl_3$):

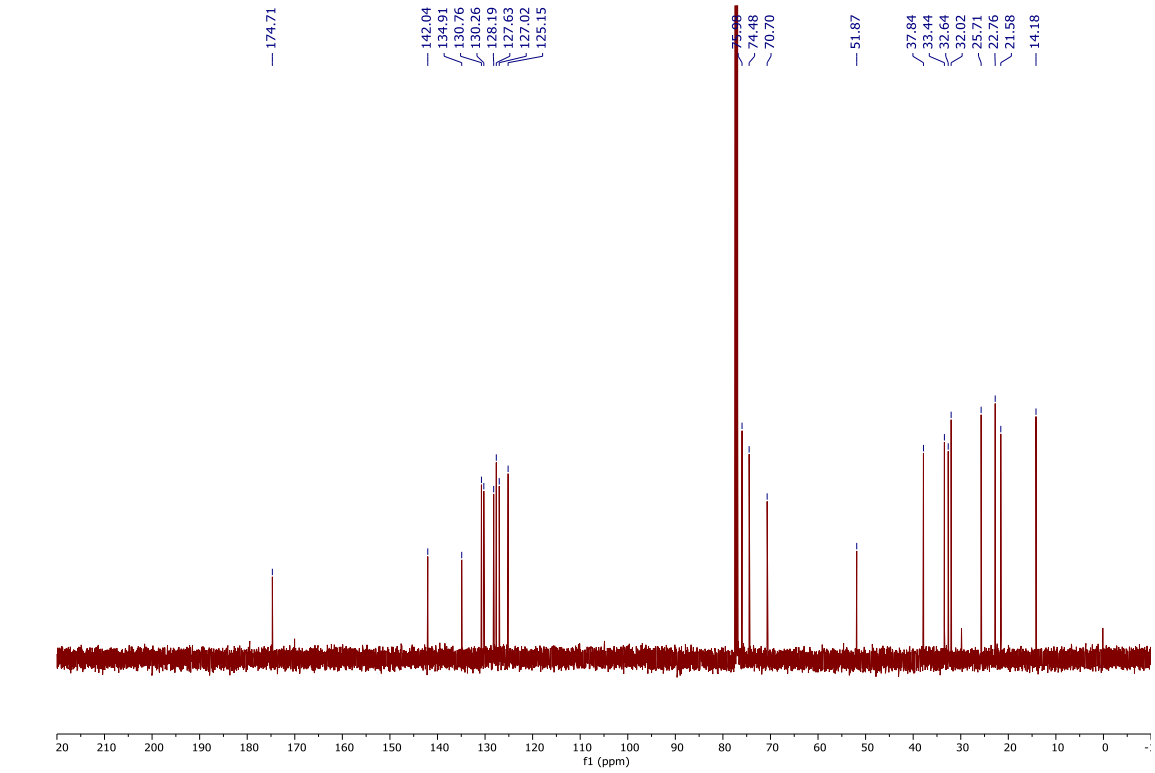


**methyl (*S*)-5-(2-((3*R*,4*S*,*E*)-3,4-dihydroxynon-1-en-1-yl)phenyl)-5-hydroxypentanoate** (**7**)

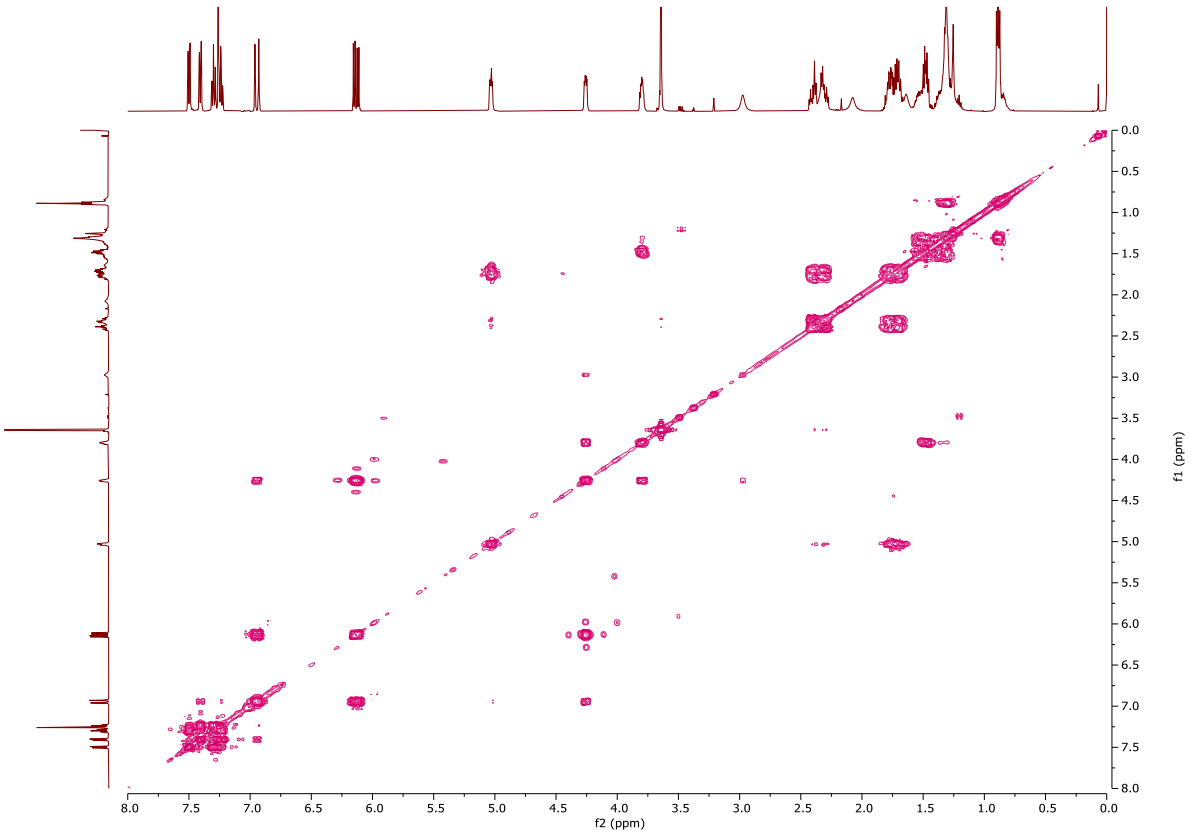
**$^{1}$H NMR** (500 MHz, $CDCl_3$):



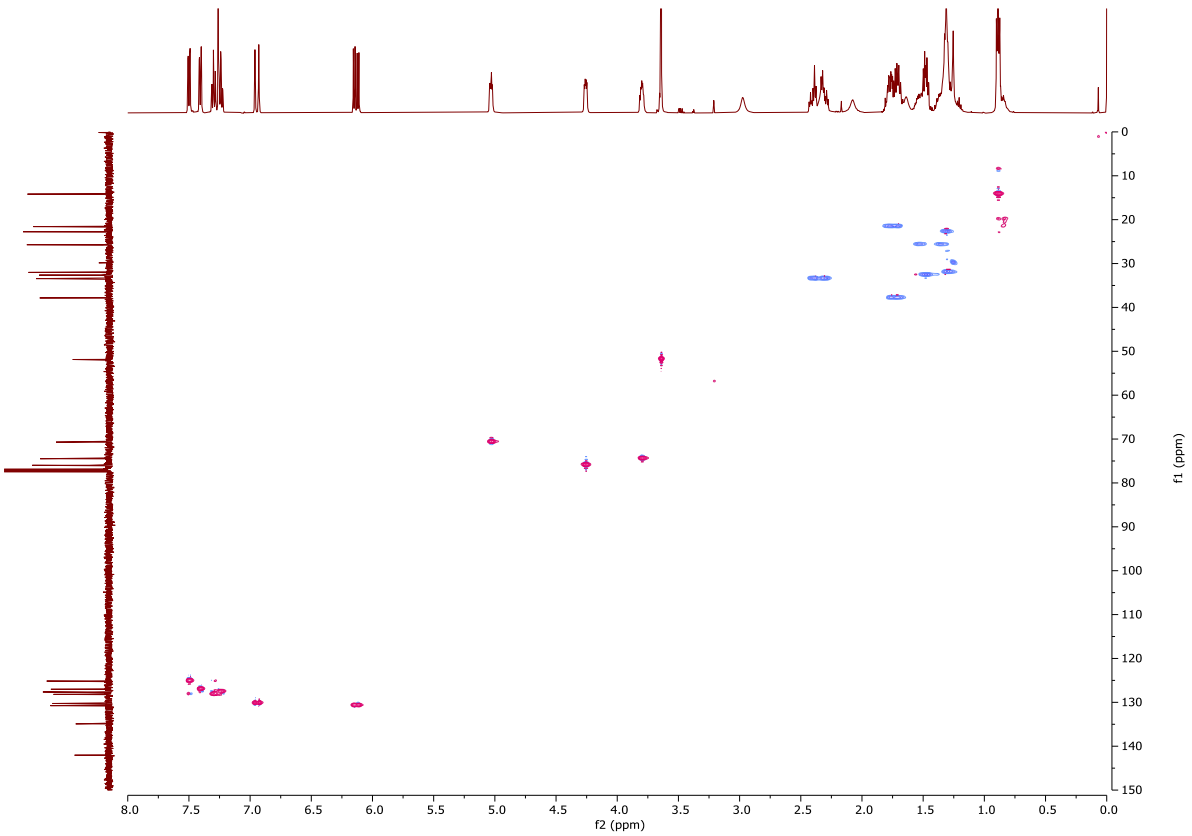

**$^{13}$C NMR** (126 MHz, $CDCl_3$):



**COSY:**

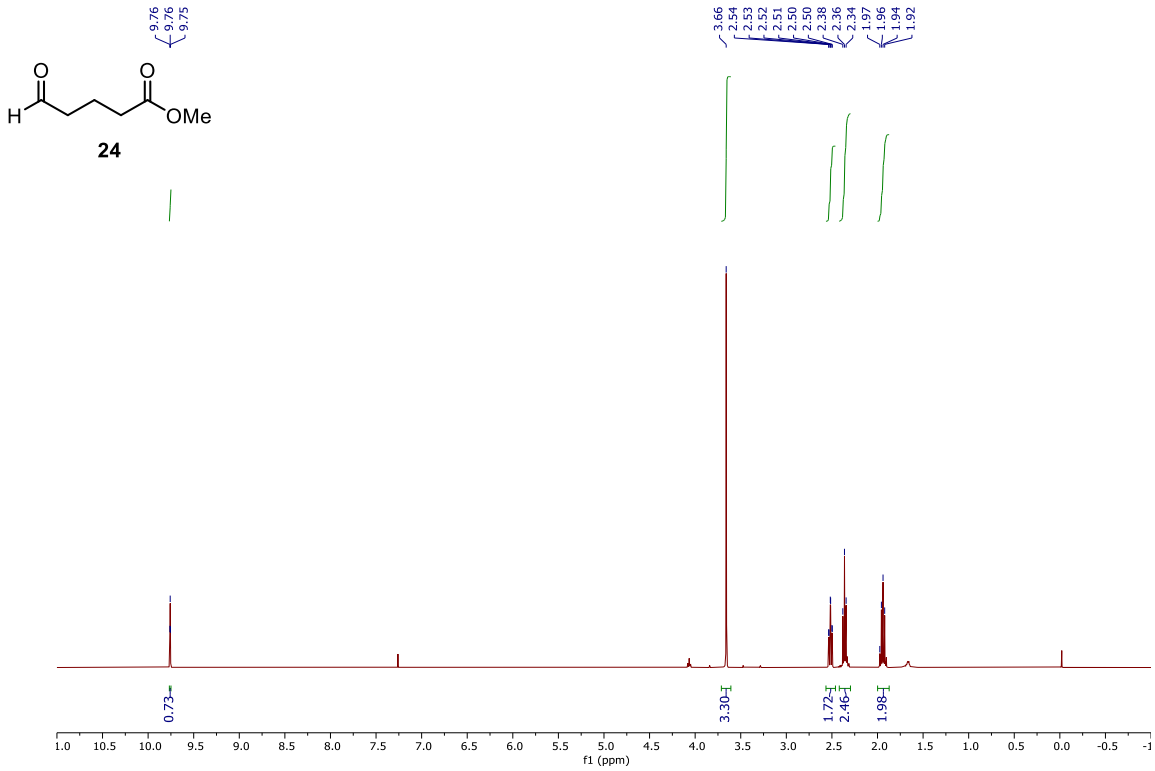



**HSQC:**

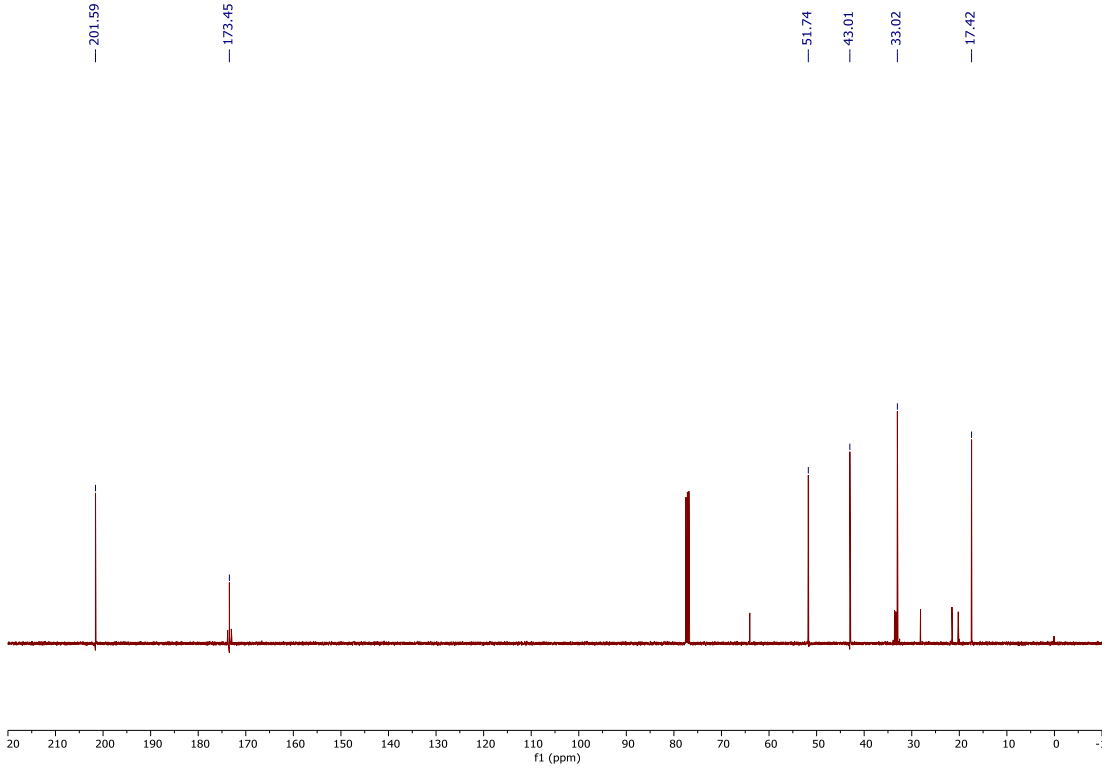


**methyl 5-oxopentanoate (24)**

**$^{1}$H NMR** (400 MHz, $CDCl_3$):

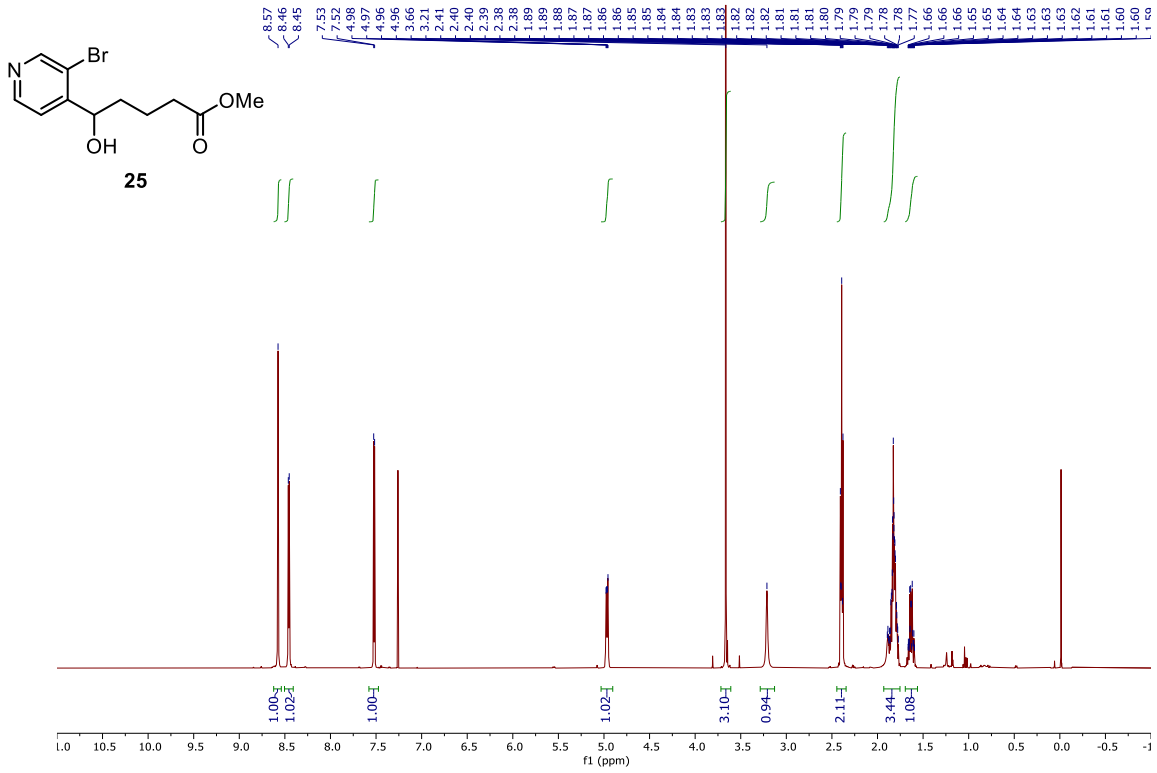



**$^{13}$C NMR** (101 MHz, $CDCl_3$):

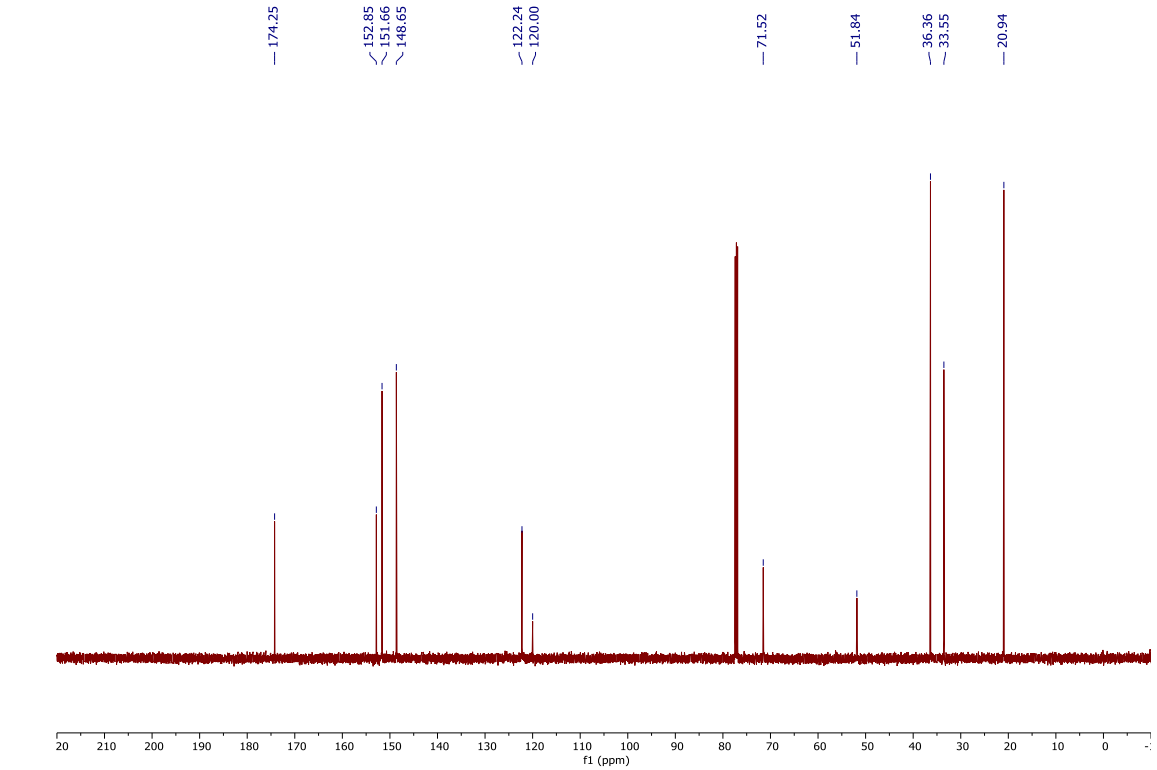


**methyl 5-(3-bromopyridin-4-yl)-5-hydroxypentanoate (25)**

**$^{1}$H NMR** (500 MHz, $CDCl_3$):

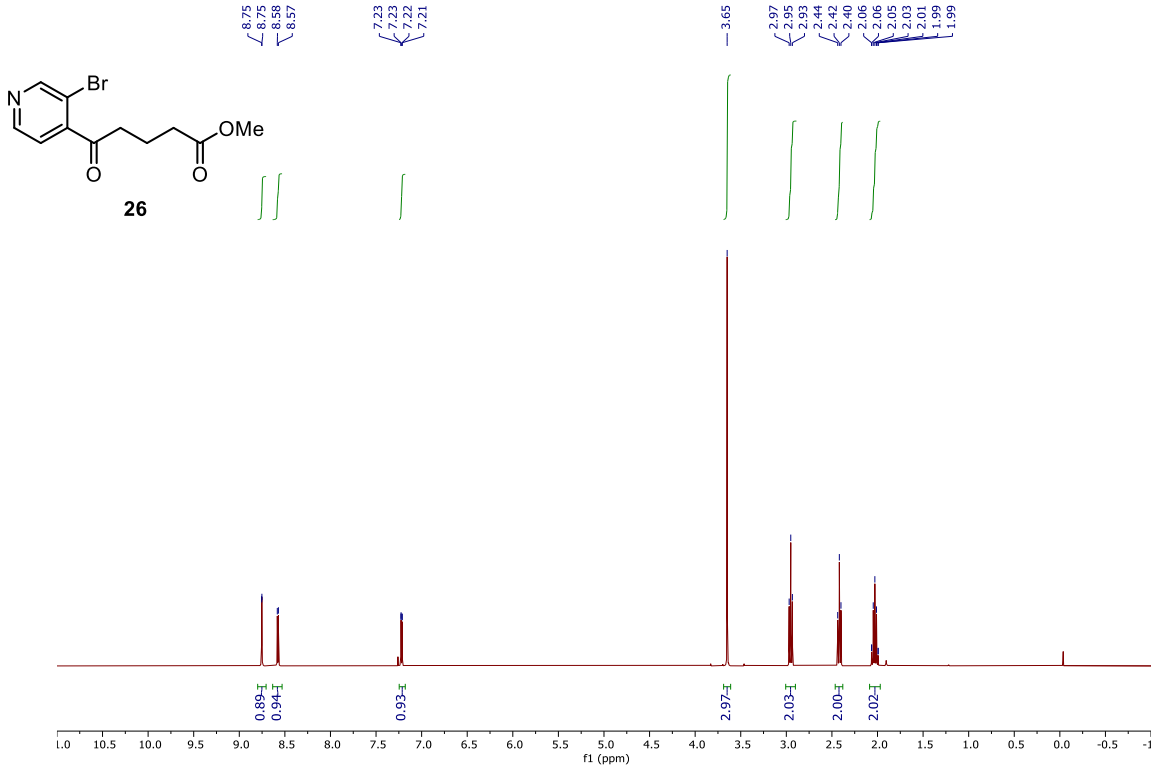



**$^{13}$C NMR** (126 MHz, $CDCl_3$):

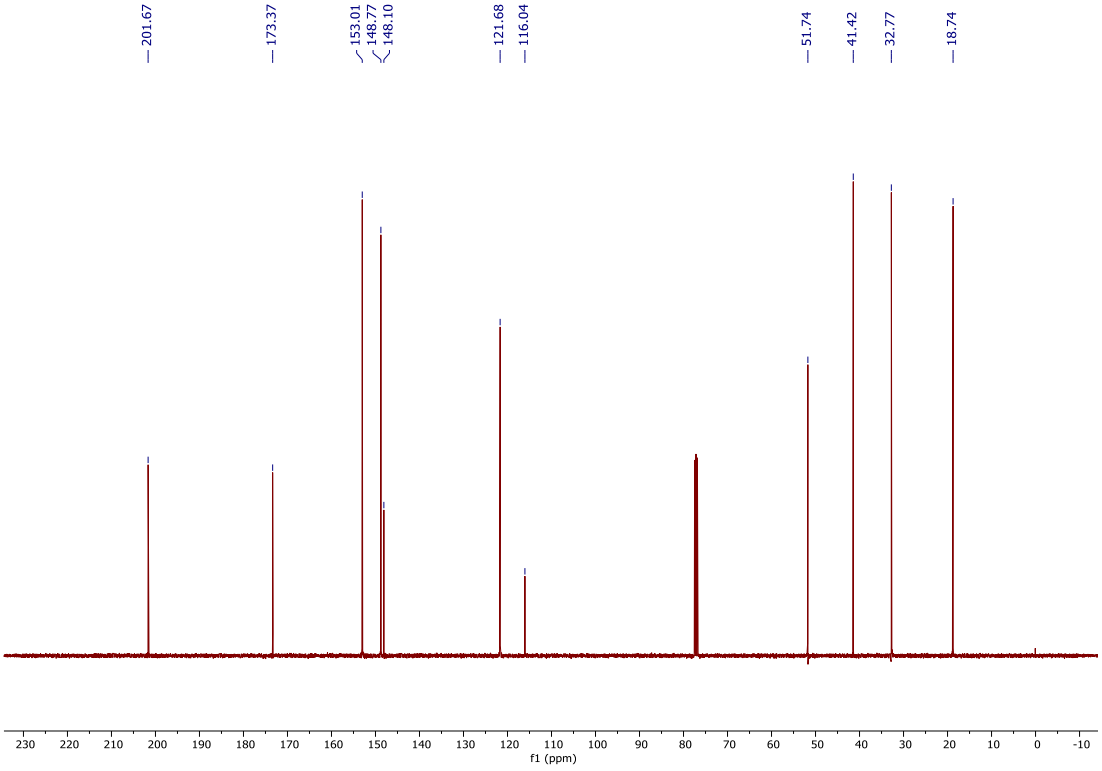


**methyl 5-(3-bromopyridin-4-yl)-5-oxopentanoate** (**26**)

**$^{1}$H NMR** (400 MHz, $CDCl_3$):

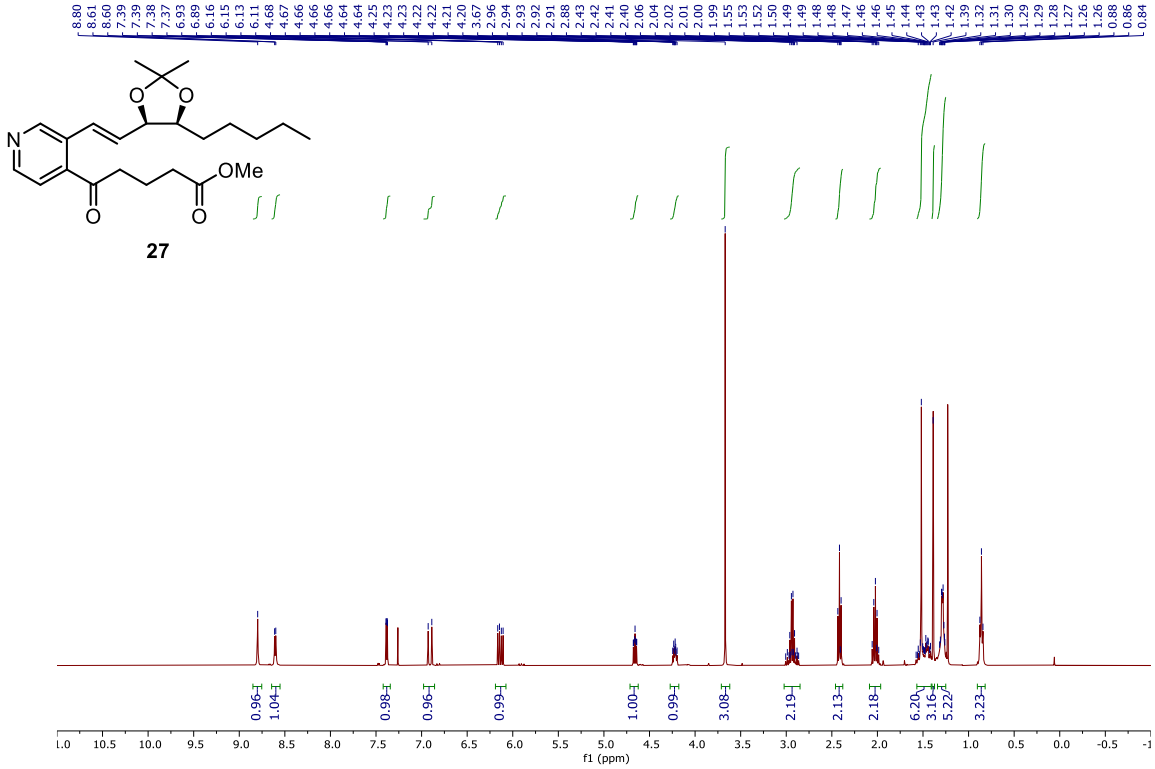



**$^{13}$C NMR** (101 MHz, $CDCl_3$):

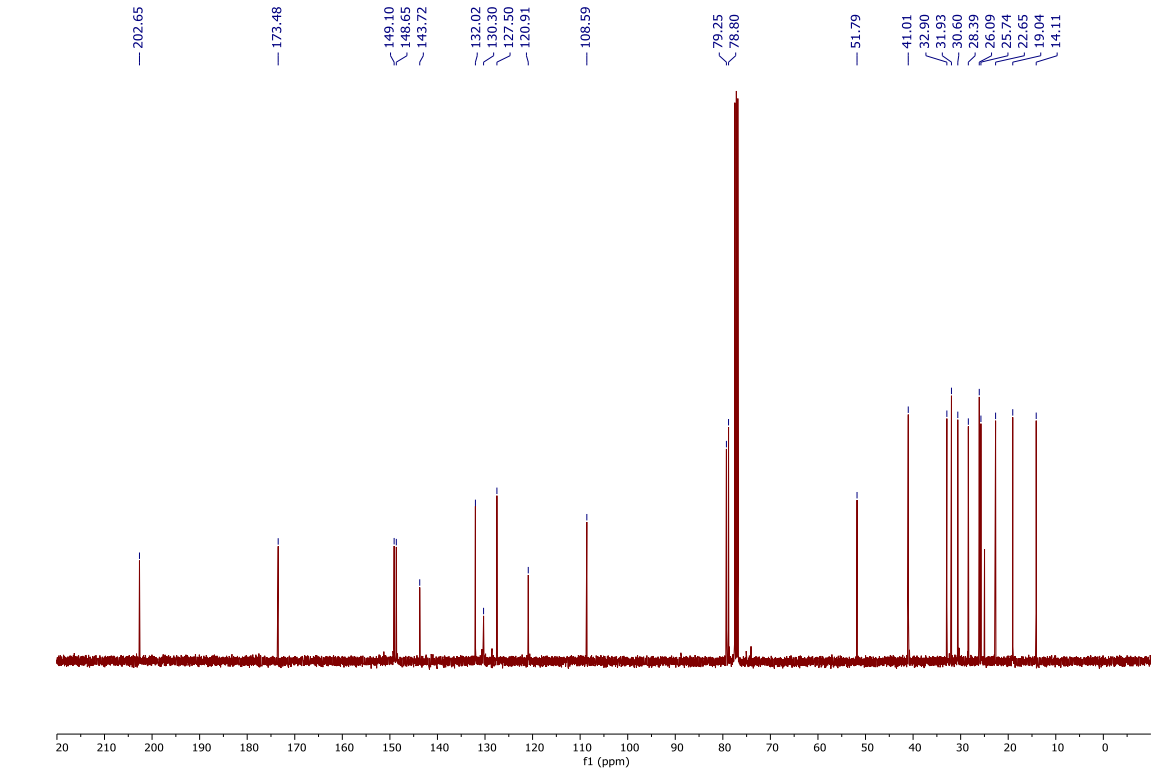


**methyl 5-(3-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)pyridin-4-yl)-5-oxopentanoate** (**27**)

**$^{1}$H NMR** (400 MHz, $CDCl_3$):

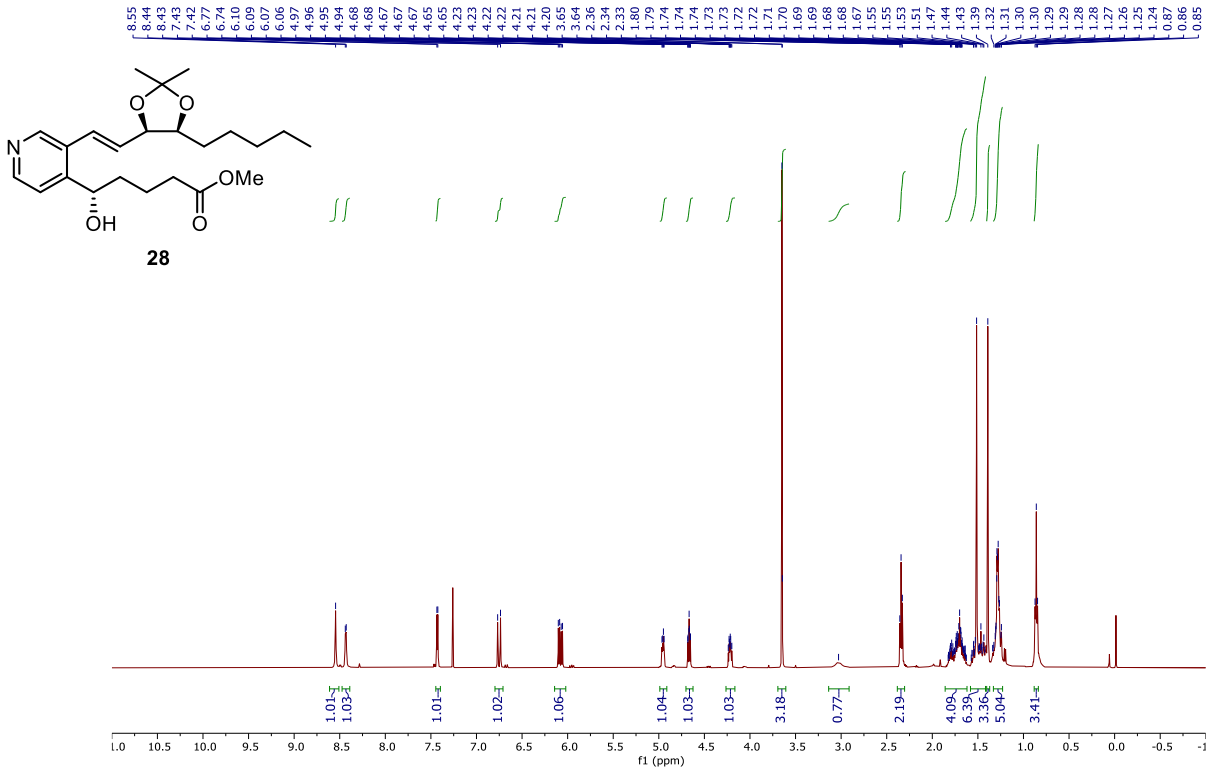



**$^{13}$C NMR** (101 MHz, $CDCl_3$):

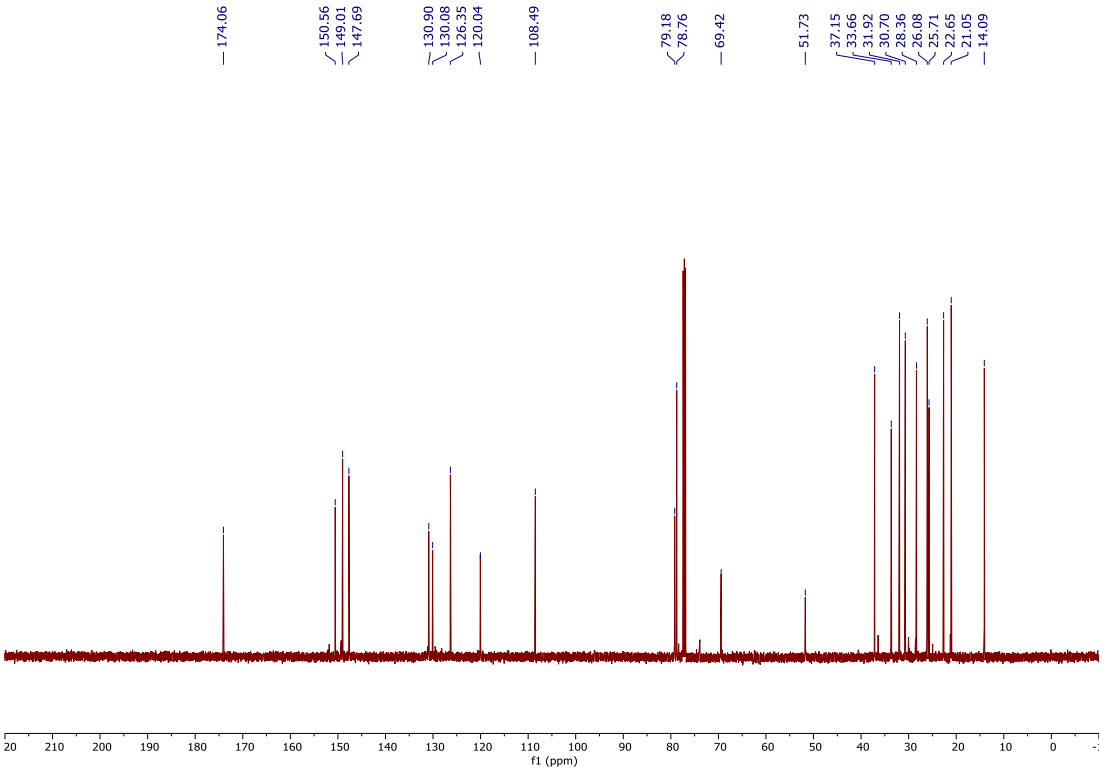


**methyl (*S*)-5-(3-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)pyridin-4-yl)-5-hydroxypentanoate (28)**

**$^{1}$H NMR** (500 MHz, $CDCl_3$):

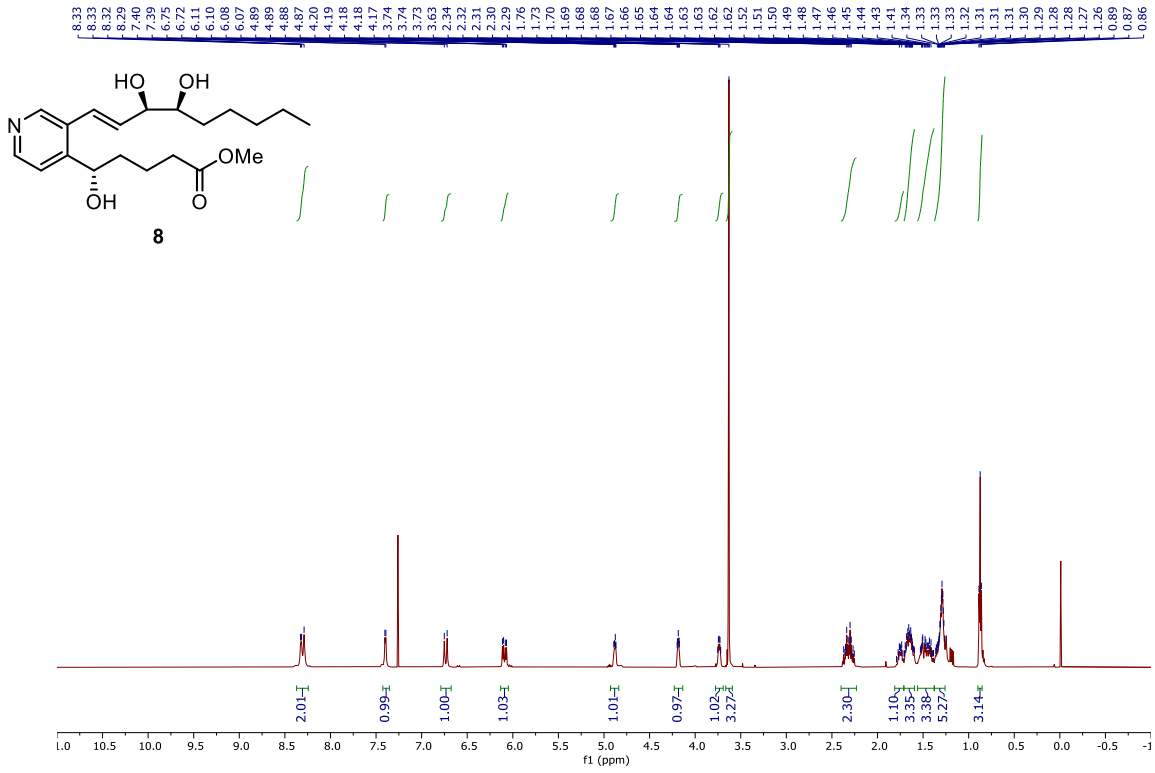



**$^{13}$C NMR** (126 MHz, $CDCl_3$):

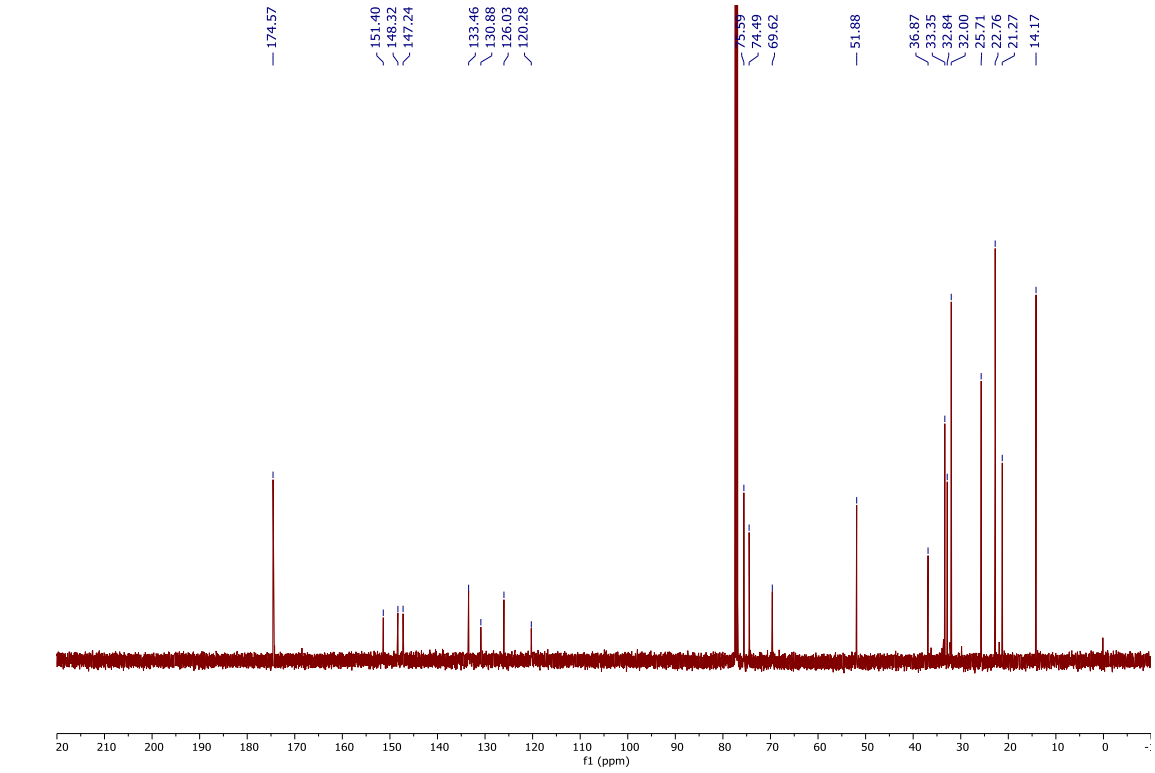


**methyl (*S*)-5-(3-((3*R*,4*S*,*E*)-3,4-dihydroxynon-1-en-1-yl)pyridin-4-yl)-5-hydroxypentanoate** (**8**)

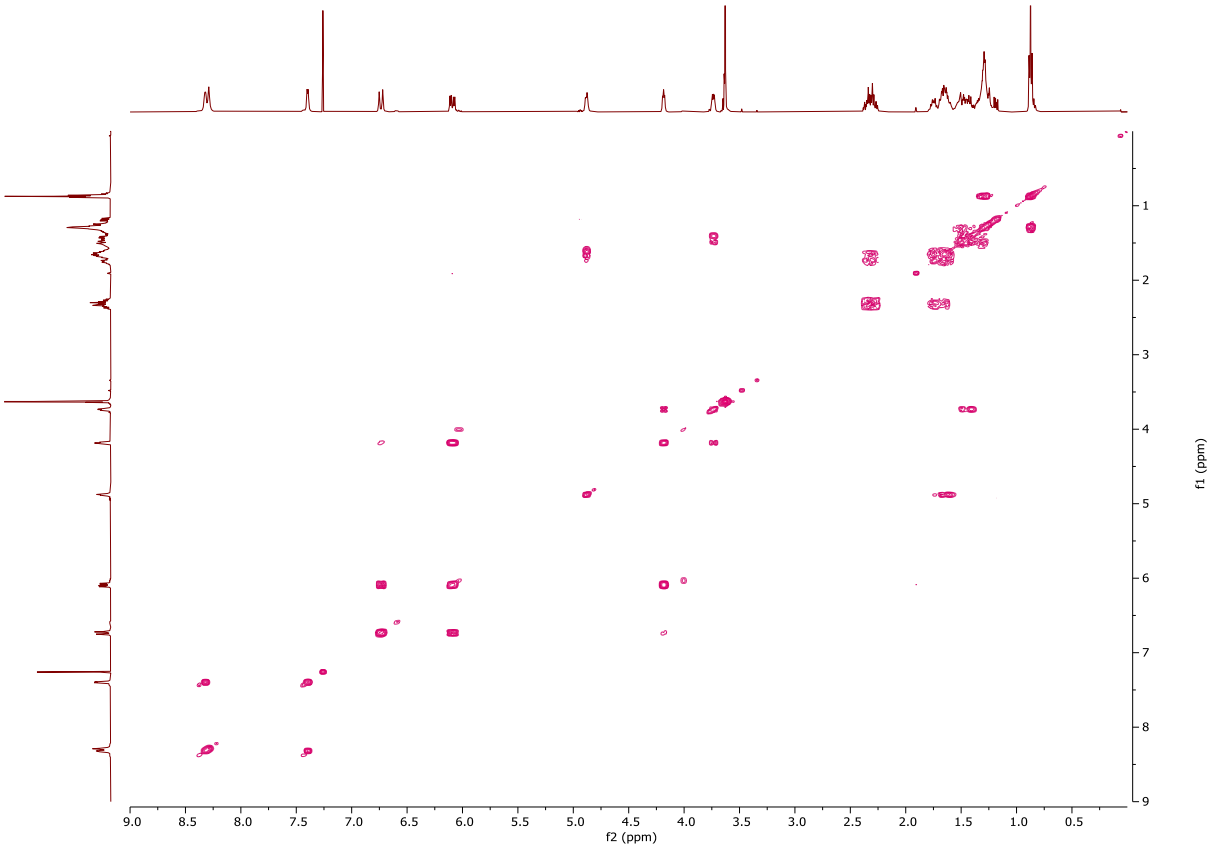
**$^{1}$H NMR** (500 MHz, $CDCl_3$):



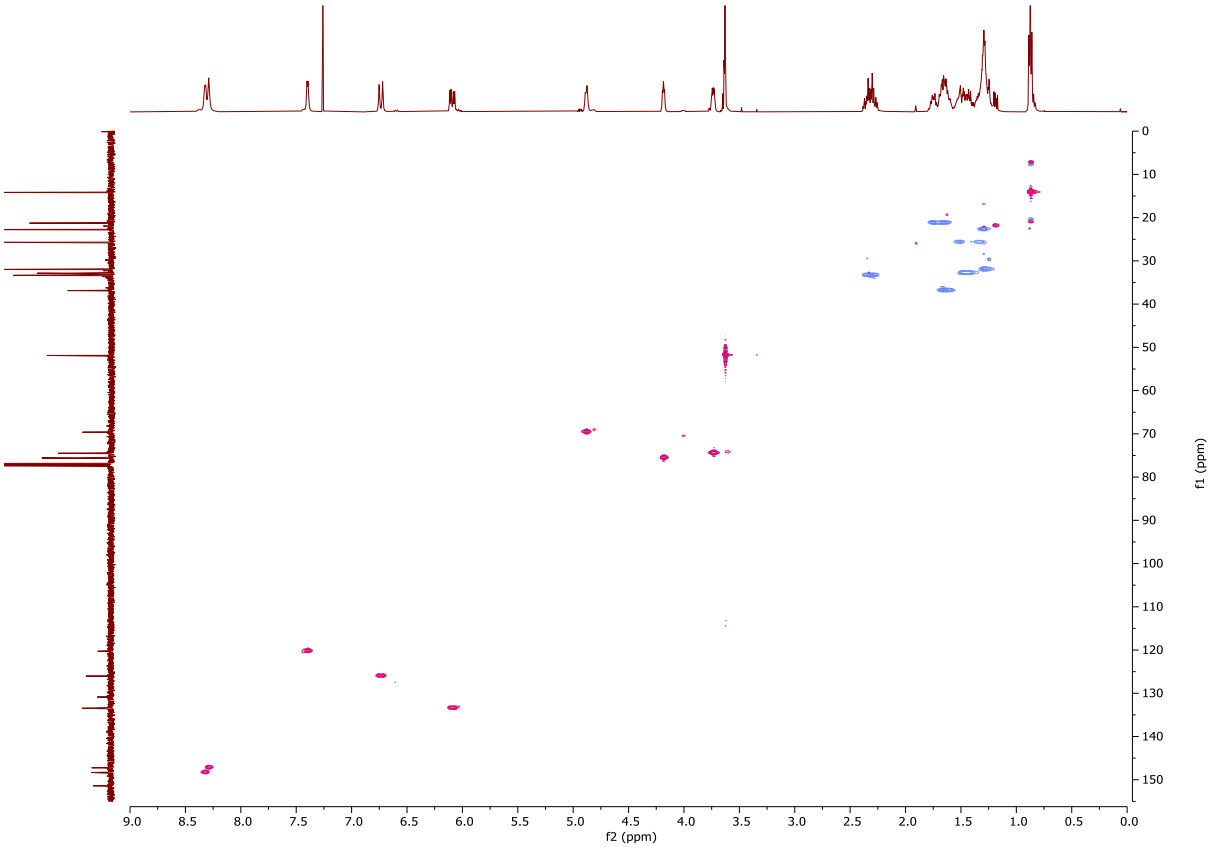

**$^{13}$C NMR** (126 MHz, $CDCl_3$):



**COSY**:

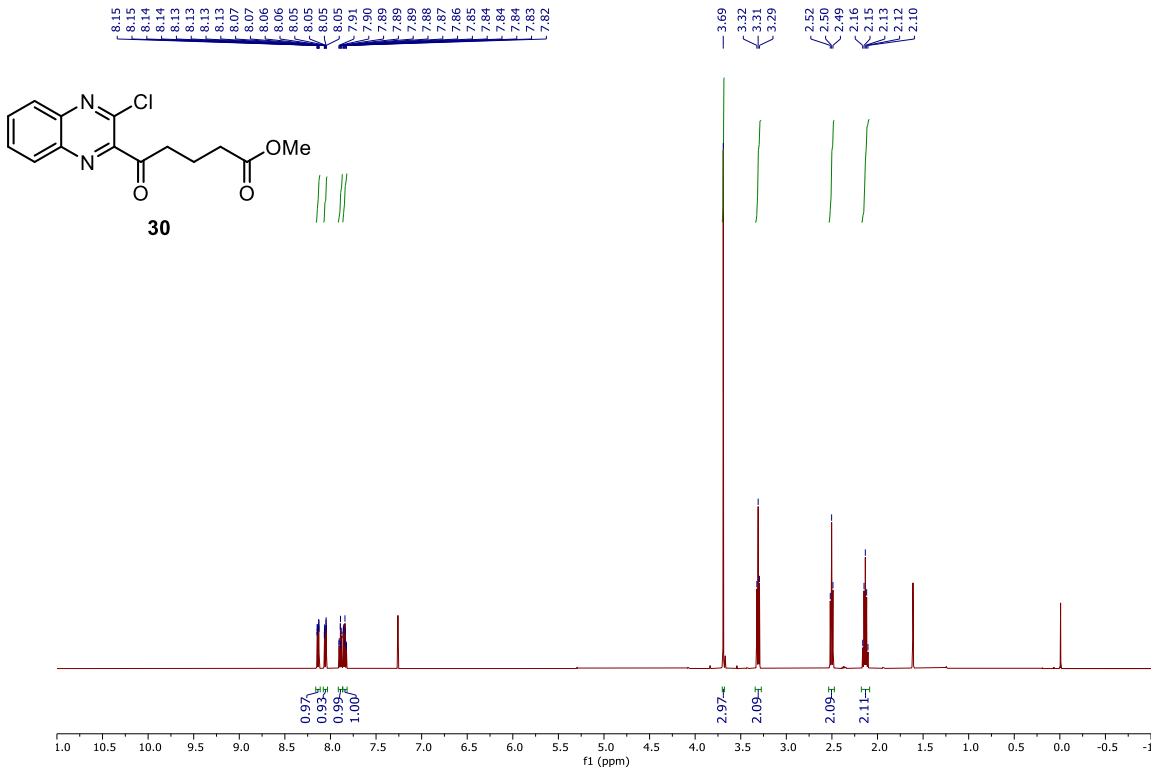



**HSQC**:

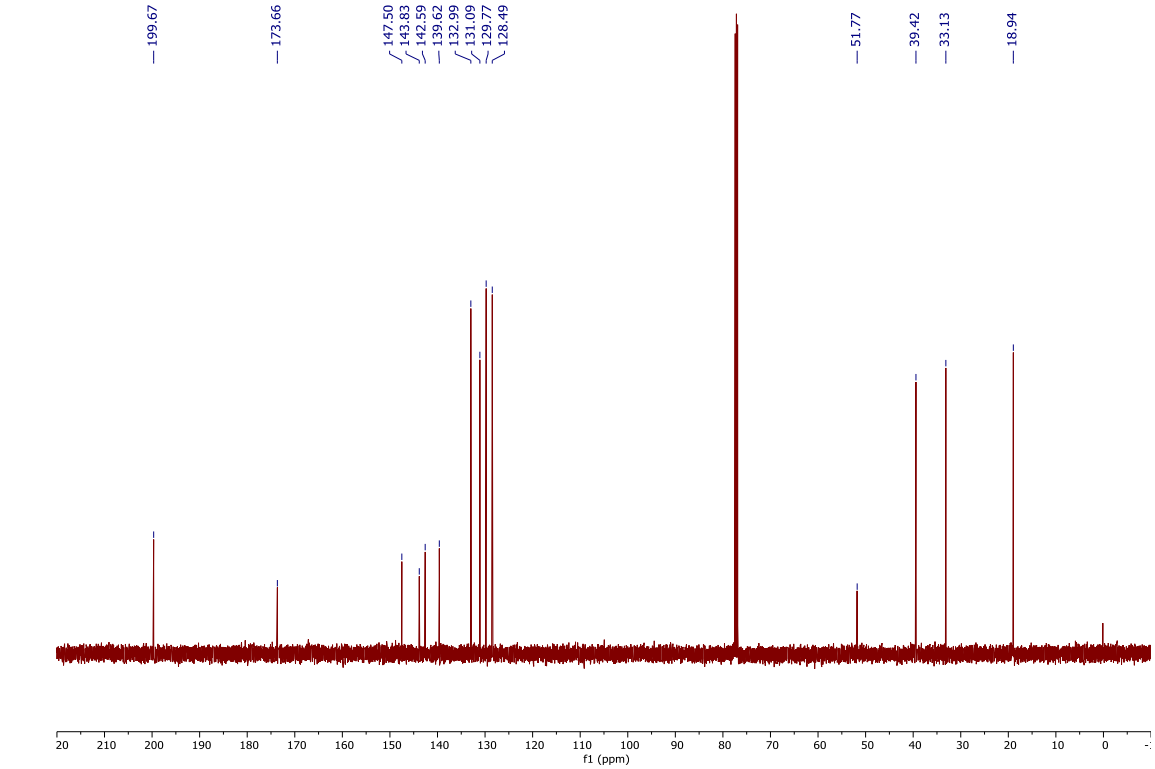


**methyl 5-(3-chloroquinoxalin-2-yl)-5-oxopentanoate** (**30**)

**$^{1}$H NMR** (500 MHz, $CDCl_3$):

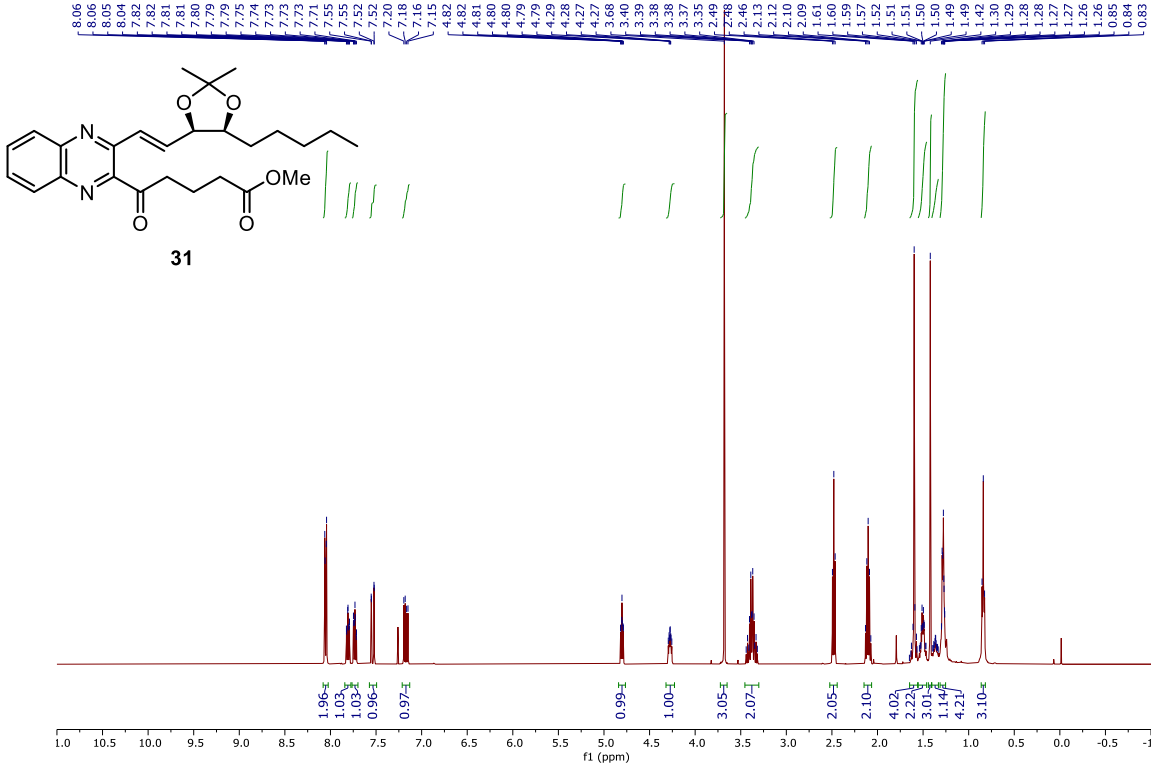



**$^{13}$C NMR** (126 MHz, $CDCl_3$):

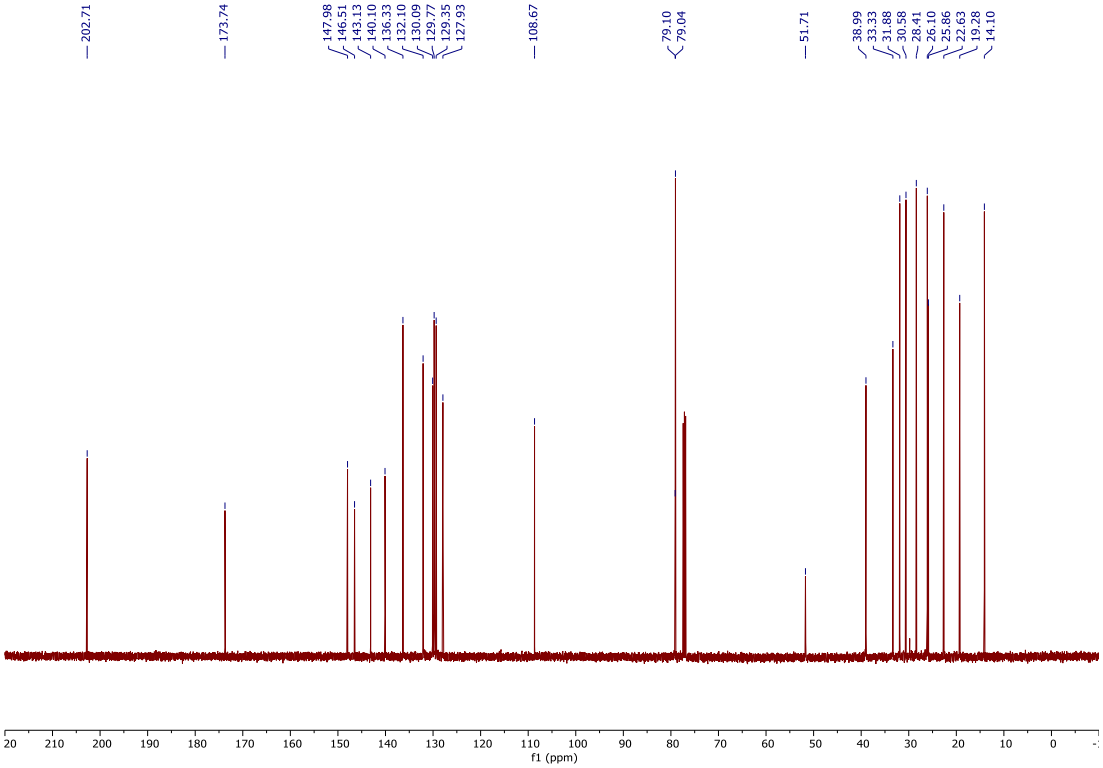


**methyl 5-(3-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)quinoxalin-2-yl)-5-oxopentanoate** (**31**)

**$^{1}$H NMR** (500 MHz, $CDCl_3$):

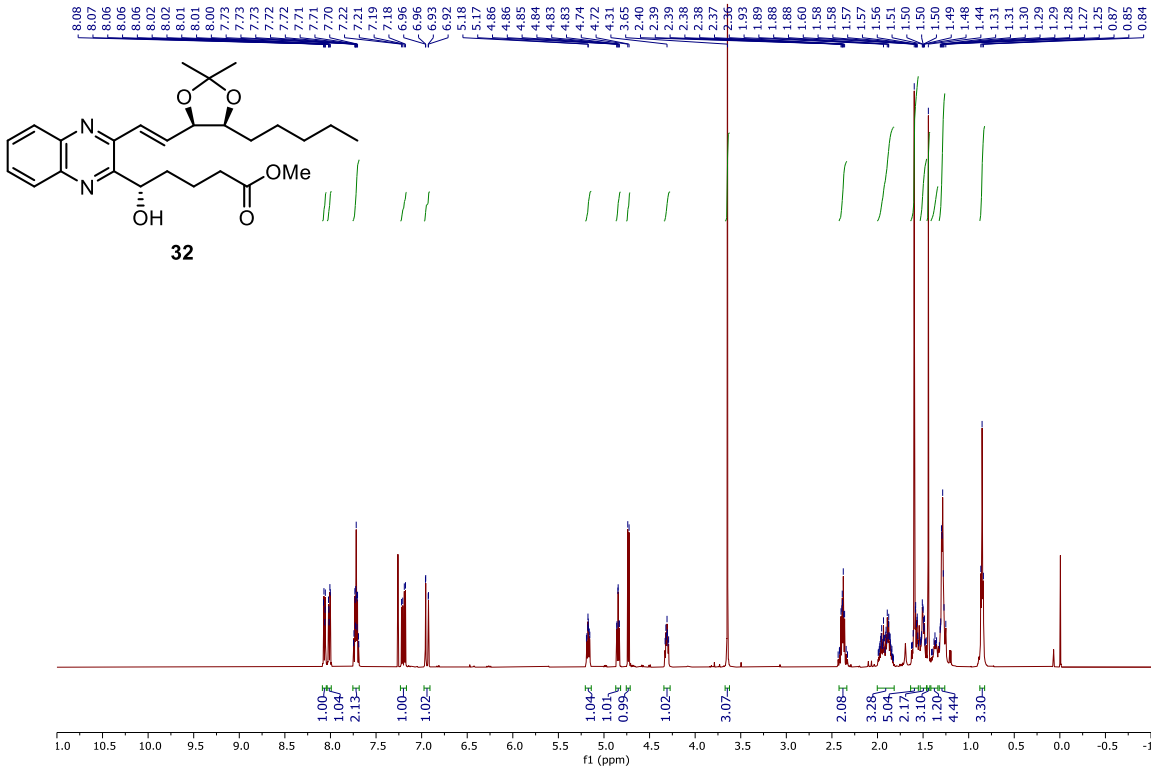



**$^{13}$C NMR** (126 MHz, $CDCl_3$):

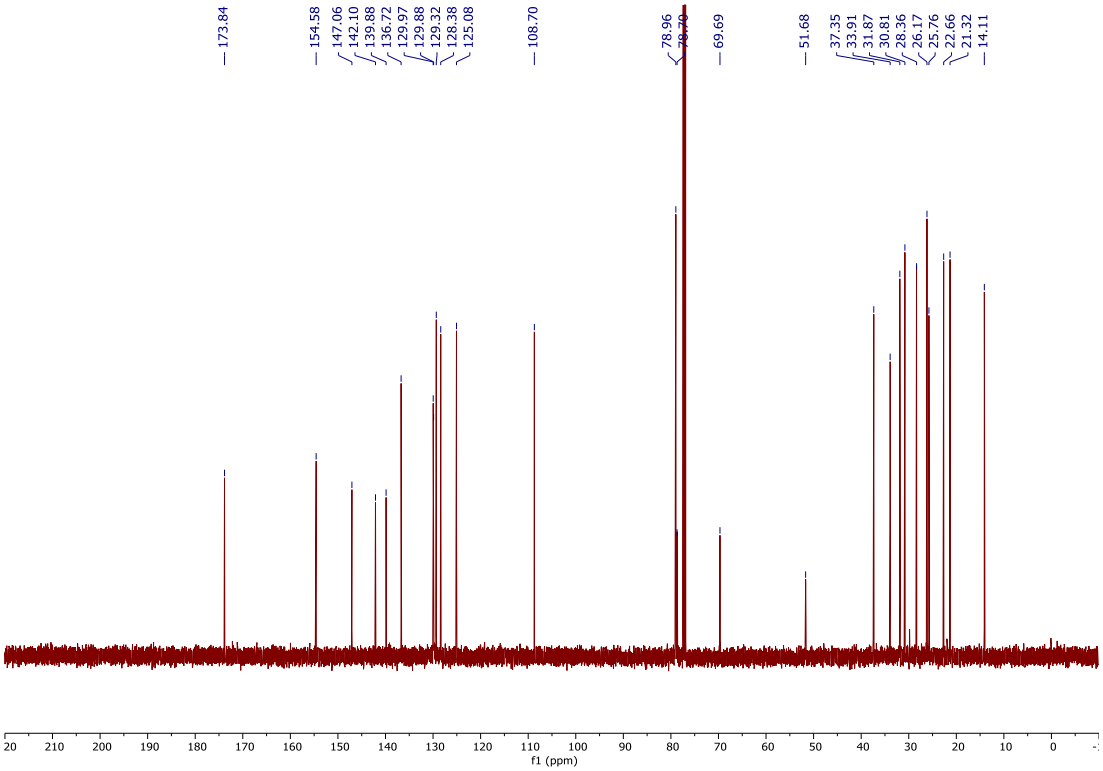


**methyl (*S*)-5-(3-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)quinoxalin-2-yl)-5-hydroxypentanoate** (**32**)

**$^{1}$H NMR** (500 MHz, $CDCl_3$):

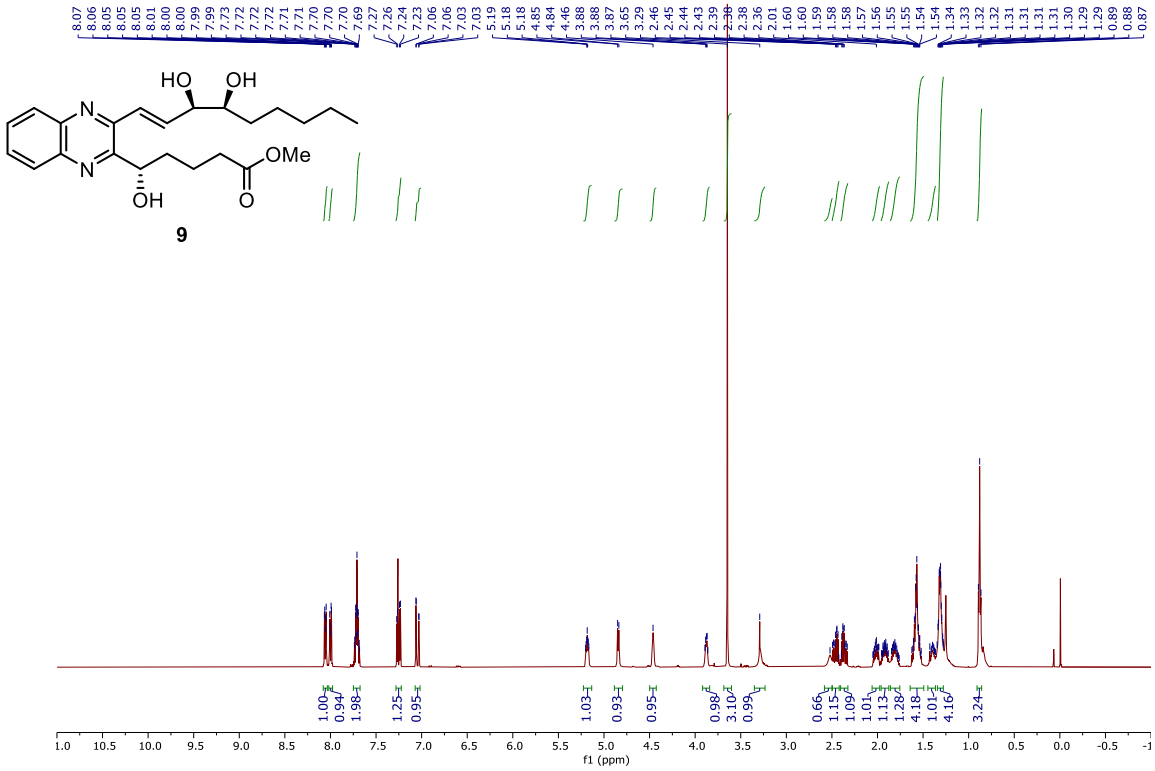



**$^{13}$C NMR** (126 MHz, $CDCl_3$):

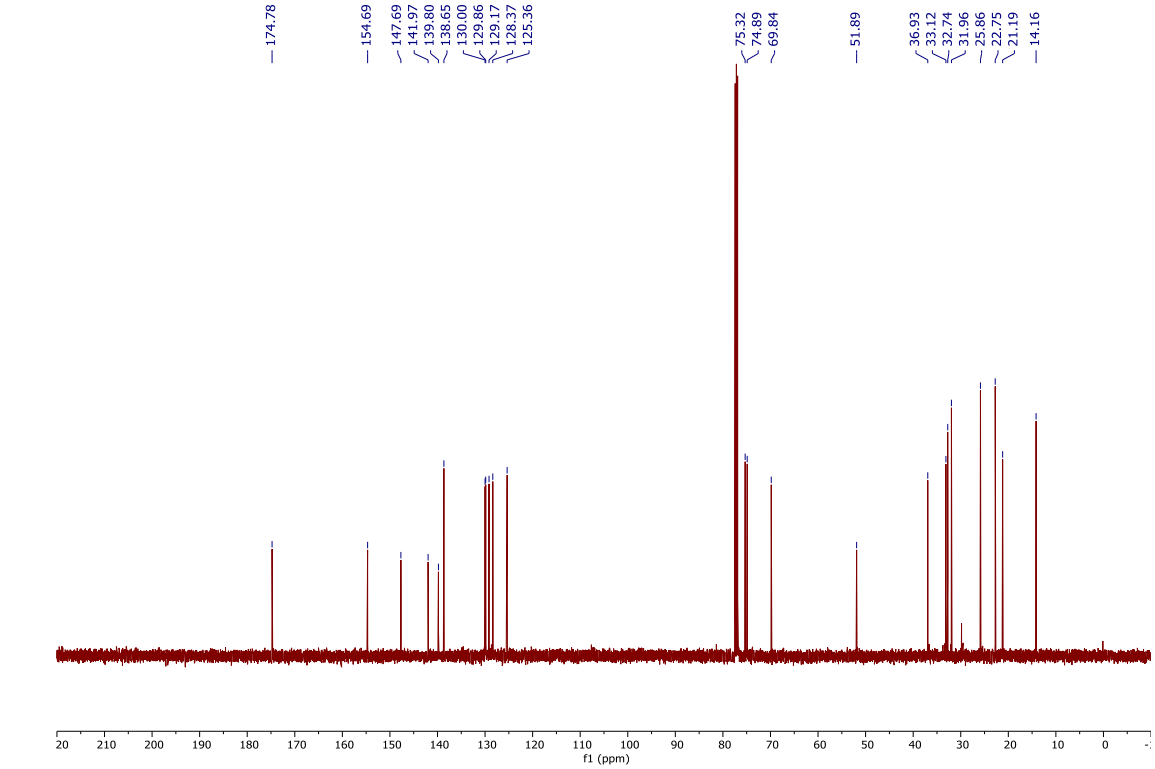


**methyl (*S*)-5-(3-((3*R*,4*S*,*E*)-3,4-dihydroxynon-1-en-1-yl)quinoxalin-2-yl)-5-hydroxypentanoate** (**9**)

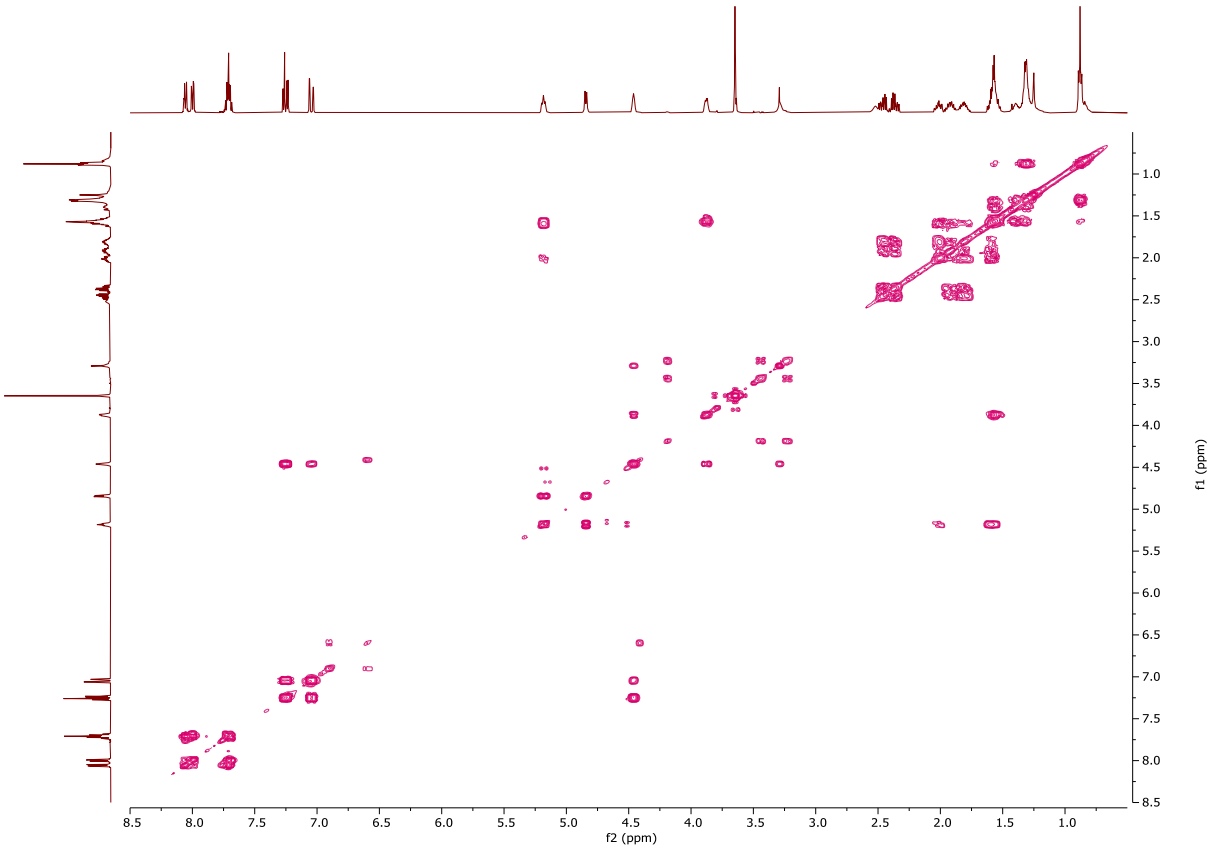
**$^{1}$H NMR** (500 MHz, $CDCl_3$):



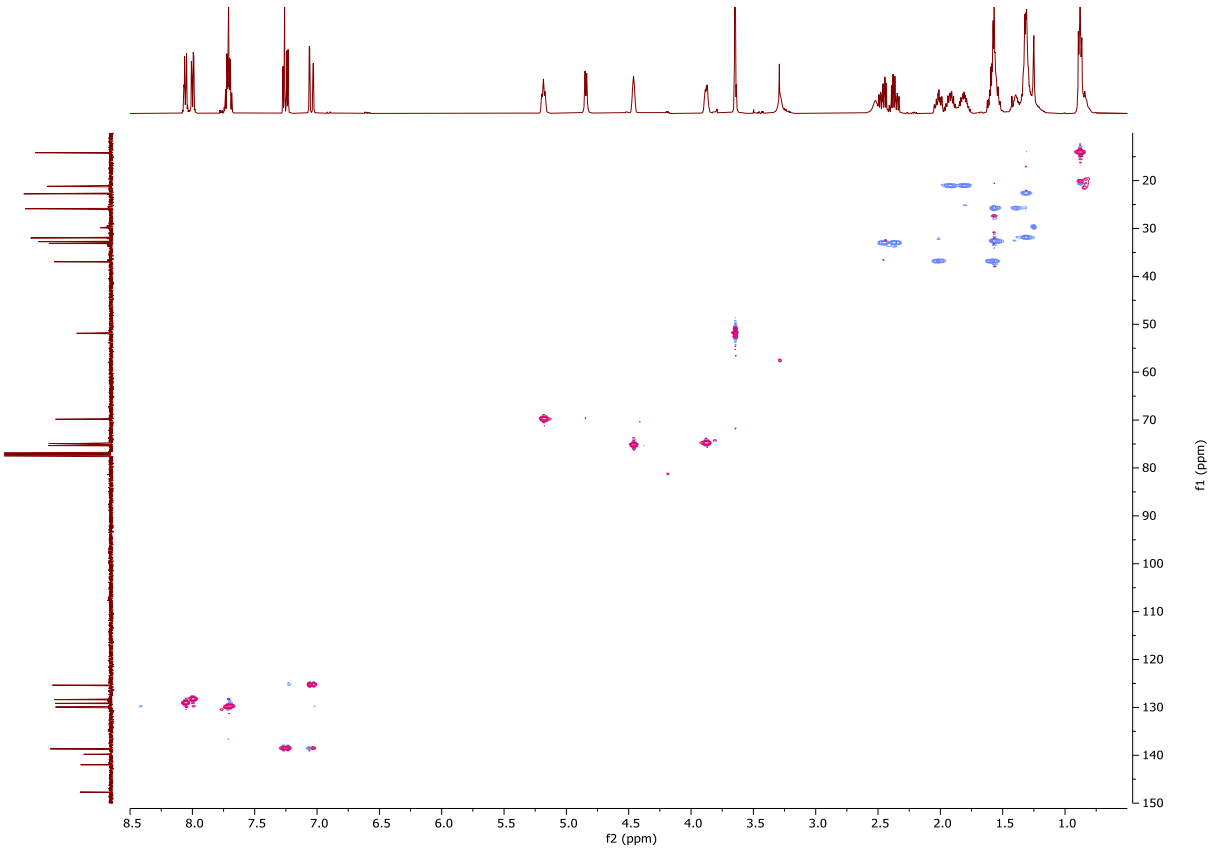

**$^{13}$C NMR** (126 MHz, $CDCl_3$):



**COSY:**

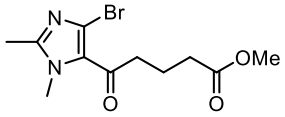



**HSQC:**



**methyl 5-(4-bromo-1,2-dimethyl-1*H*-imidazol-5-yl)-5-oxopentanoate (34)**

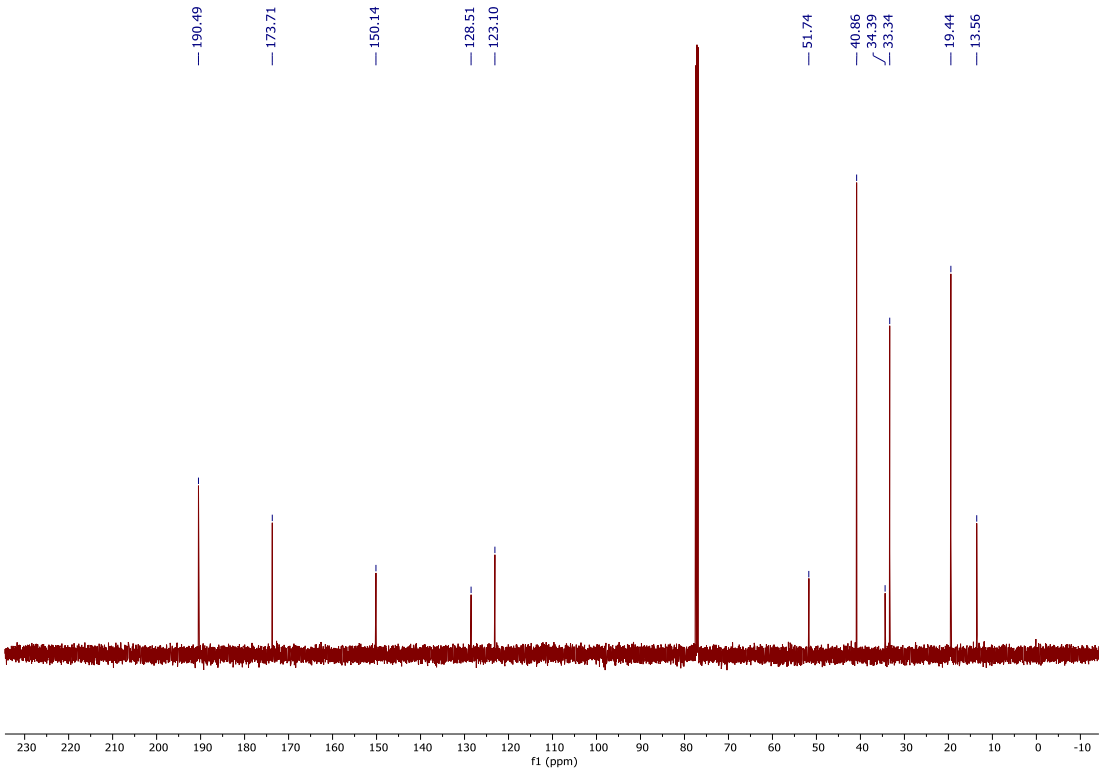
**$^{1}$H NMR** (500 MHz, $CDCl_3$):




**34**

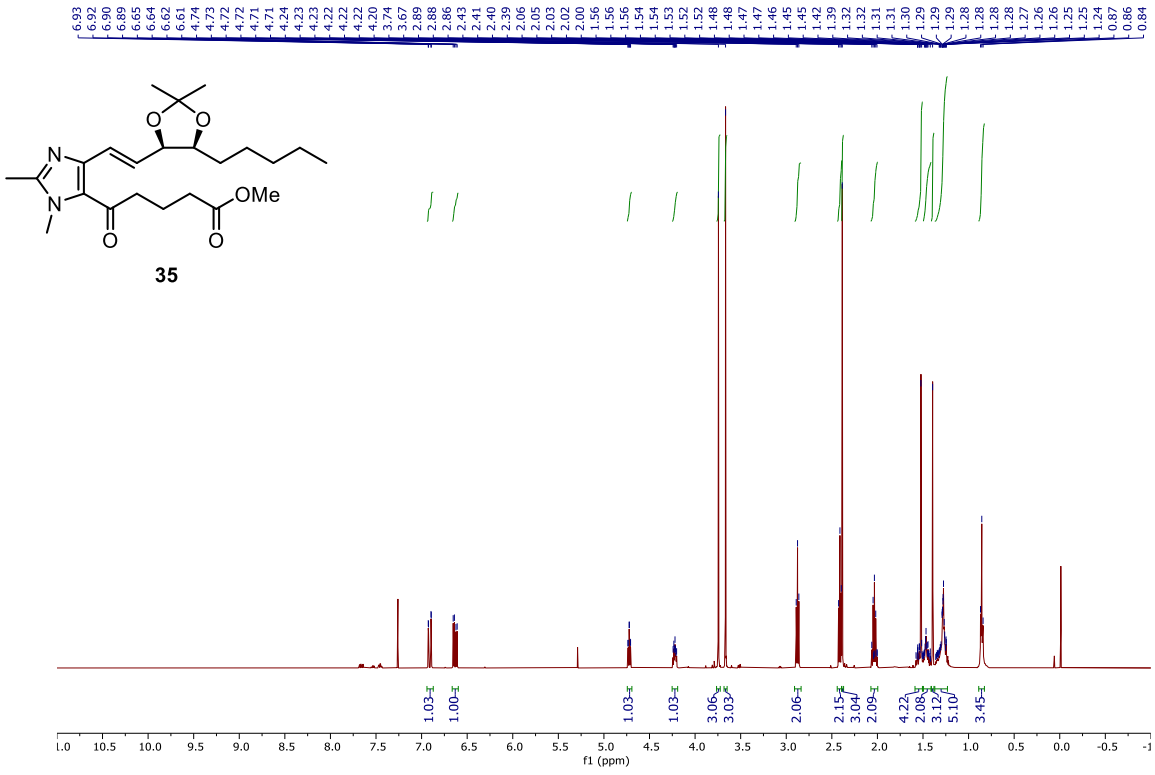



**$^{13}$C NMR** (126 MHz, $CDCl_3$):

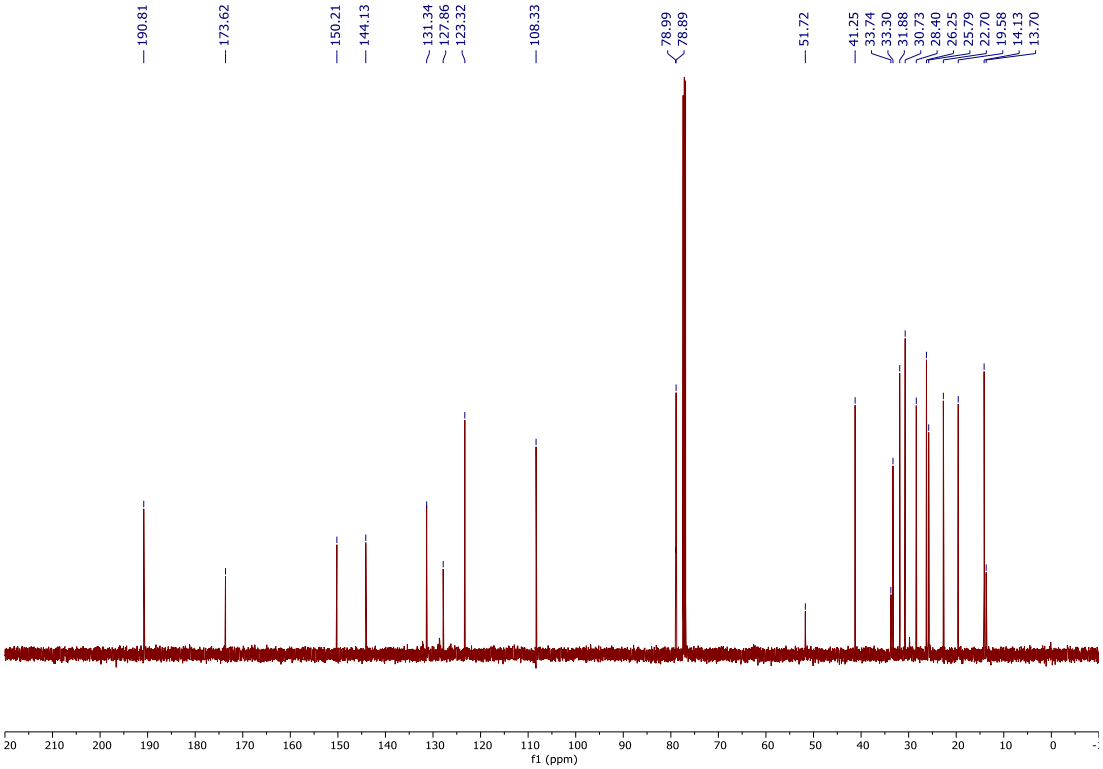


**methyl 5-(4-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)-1,2-dimethyl-1*H*-imidazol-5-yl)-5-oxopentanoate (35)**

**$^{1}$H NMR** (500 MHz, $CDCl_3$):

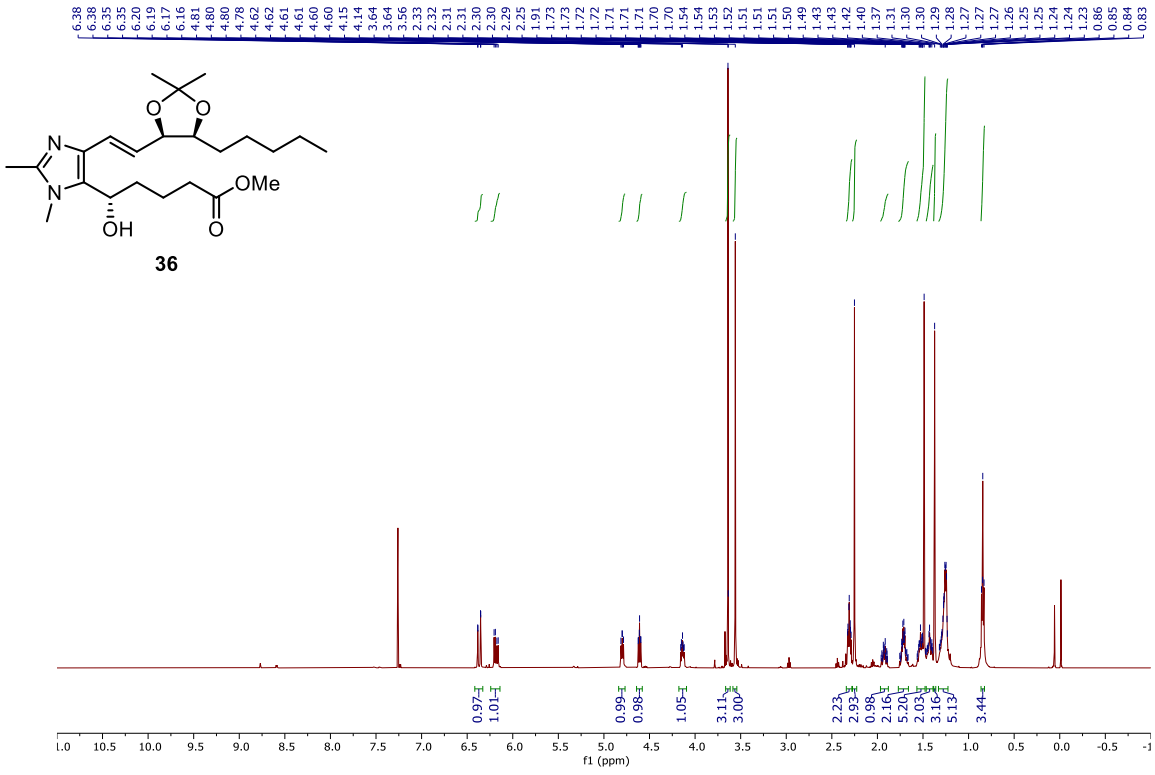



**$^{13}$C NMR** (126 MHz, $CDCl_3$):

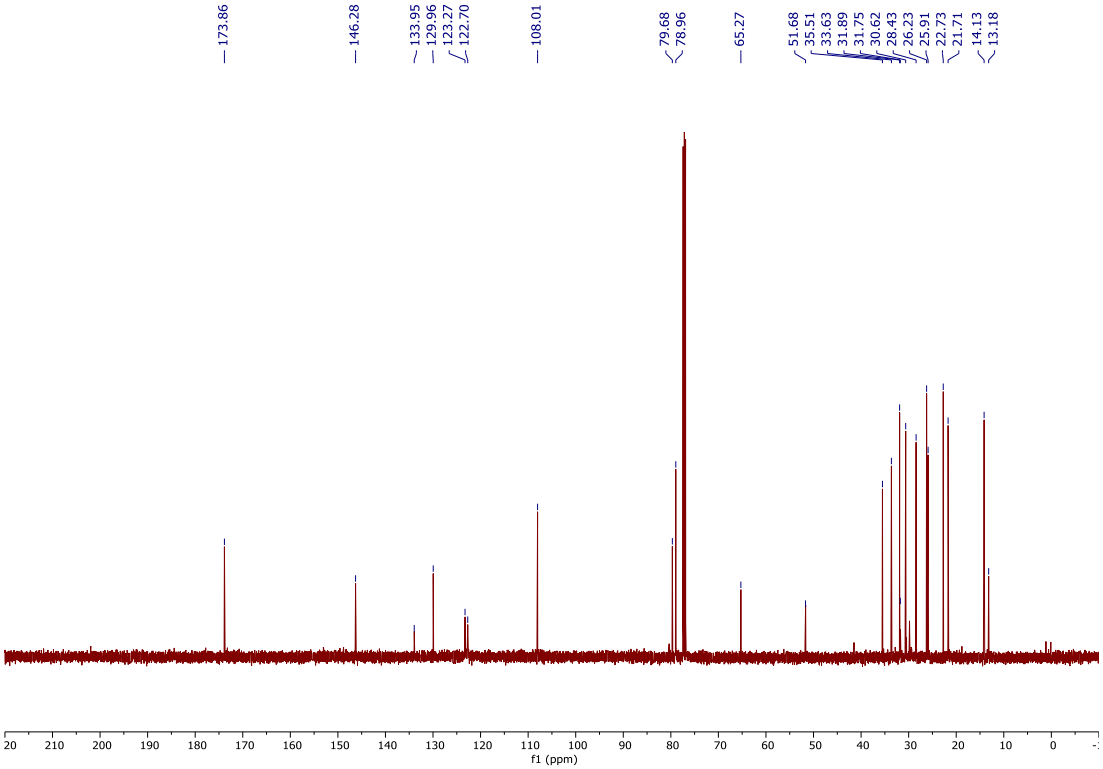


**methyl (*S*)-5-(4-((*E*)-2-((4*R*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)vinyl)-1,2-dimethyl-1*H*-imidazol-5-yl)-5-hydroxypentanoate (36)**

**$^{1}$H NMR** (500 MHz, $CDCl_3$):

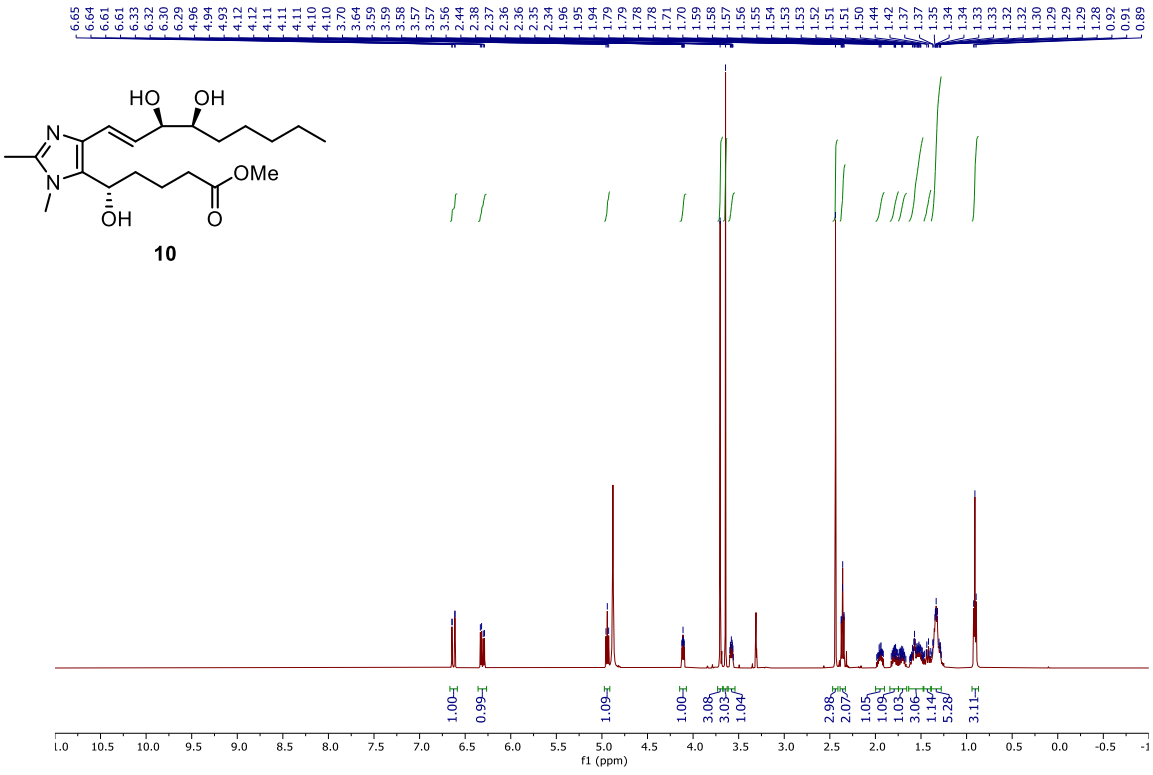



**$^{13}$C NMR** (126 MHz, $CDCl_3$):

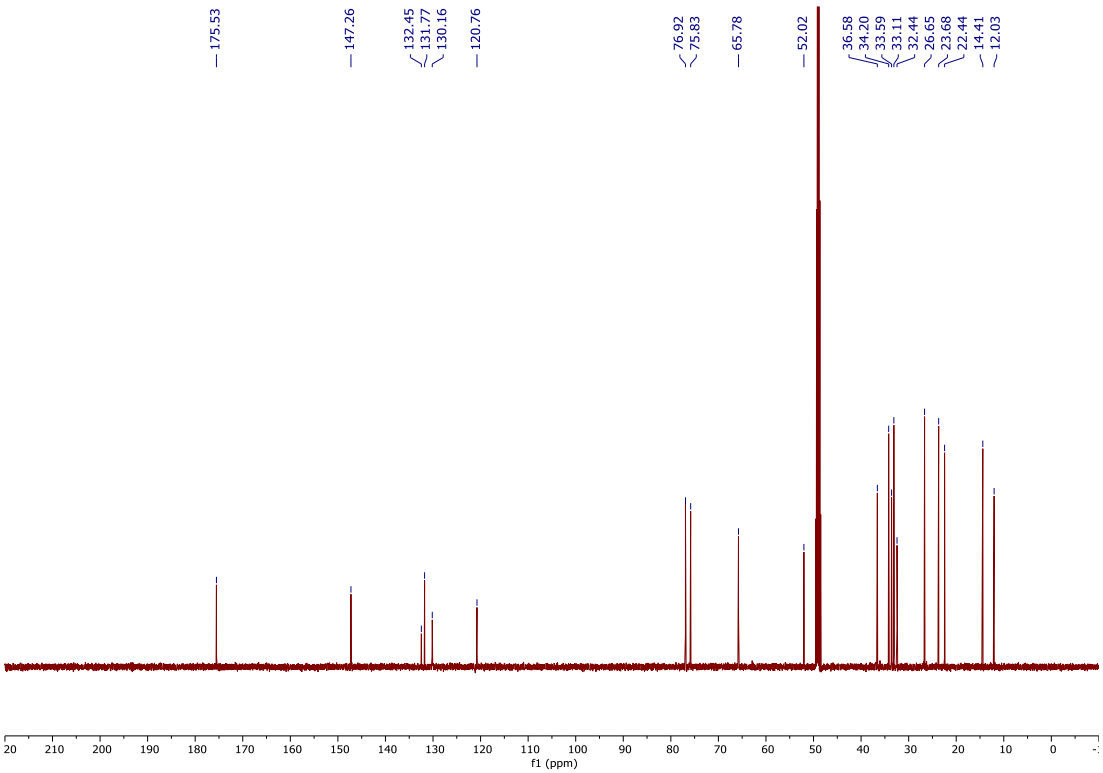


**methyl (*S*)-5-(4-((3*R*,4*S*,*E*)-3,4-dihydroxynon-1-en-1-yl)-1,2-dimethyl-1*H*-imidazol-5-yl)-5-hydroxypentanoate** (**10**)

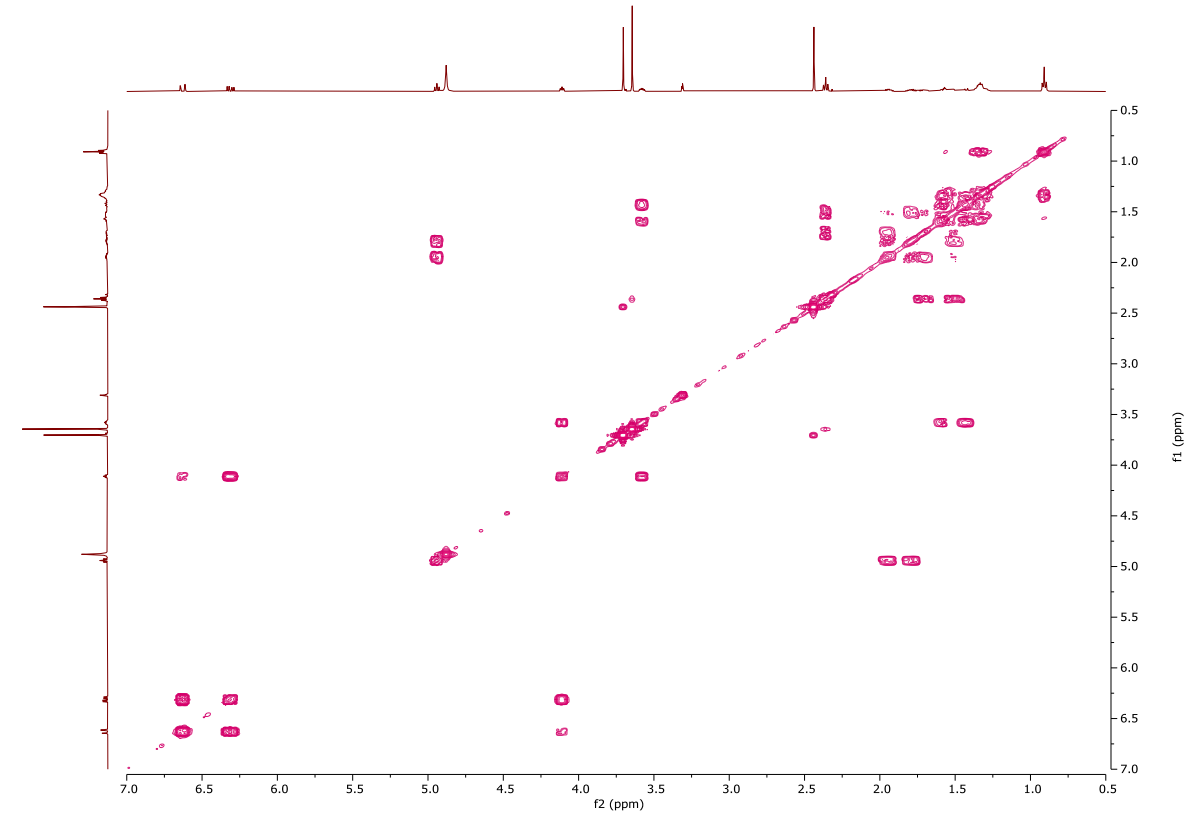
**$^{1}$H NMR** (500 MHz, $CD_3OD$):



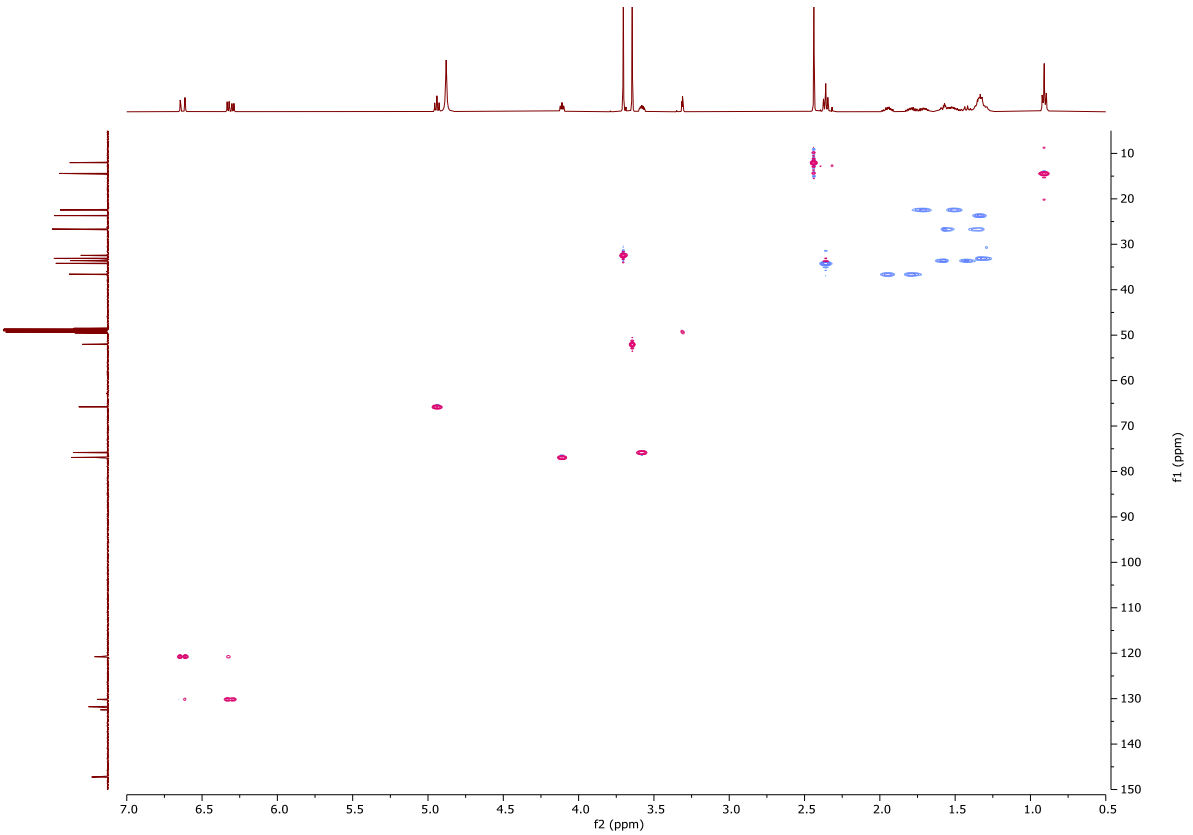

**$^{13}$C NMR** (126 MHz, $CD_3OD$):



**COSY:**

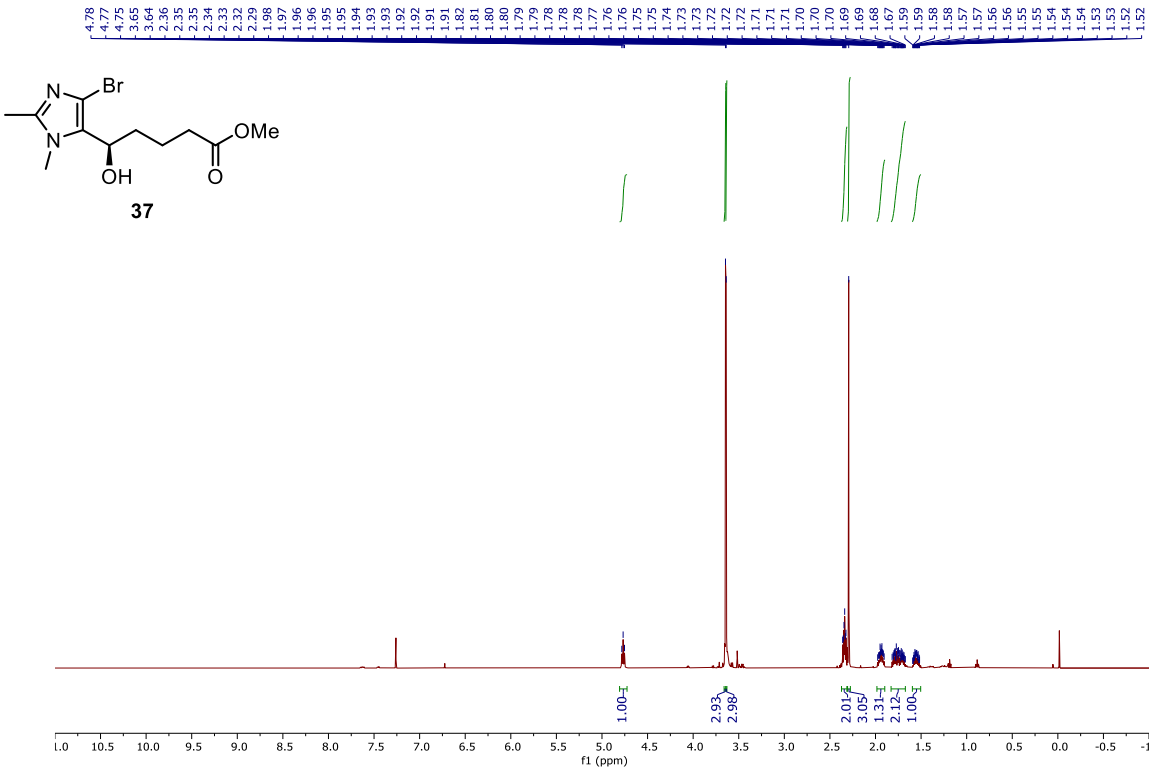



**HSQC:**



**methyl (*R*)-5-(4-bromo-1,2-dimethyl-1H-imidazol-5-yl)-5-hydroxypentanoate** (**37**)

**$^{1}$H NMR** (500 MHz, $CDCl_3$):




**$^{13}$C NMR** (126 MHz, $CDCl_3$):