Decarboxylative, trienamine mediated cycloaddition for the synthesis of 3,4-dihydrocoumarin derivatives

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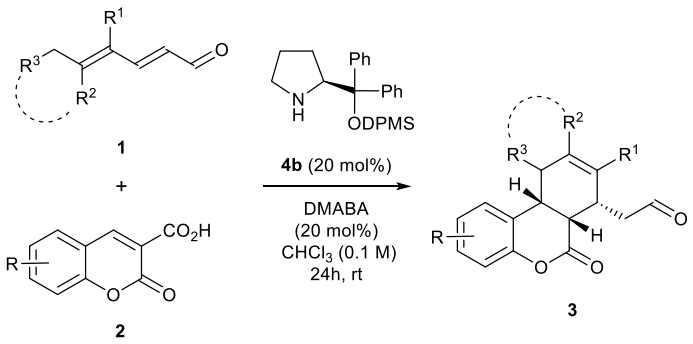
1. General methods

NMR spectra were acquired on a Bruker Ultra Shield 700 instrument, running at 700 MHz for ^{1}H and 176 MHz for ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$: 7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR). Mass spectra were recorded on a Bruker Maxis Impact spectrometer using electrospray (ES+) ionization (referenced to the mass of the charged species). Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or I_2 stain. Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. For flash chromatography (FC) silica gel (Silica gel 60, 230-400 mesh, Fluka). The enantiomeric ratio (er) of the products were determined by Ultra Performance Convergence Chromatography (UPC^2) or HPLC using Daicel Chiralpak IA, IB, ID and IG columns as chiral stationary phases. Aldehydes **1** were synthetized according to the literature procedure.[1] Coumarin-3-carboxylic acids **2** were prepared from the corresponding substituted 2-hydroxy-benzaldehydes following the literature procedure.[2]

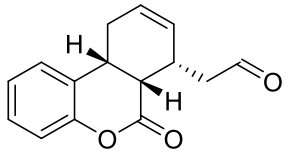
[1] A. Skrzyńska, P. Drelich, S. Frankowski and Ł. Albrecht, *Chem. Eur. J*. 2018, **24**, 16543.

[2] A. Song, X. Wang and K. S. Lam, *Tetrahedron Lett.* 2003, **44**, 1755.

2. Decarboxylative, trienamine mediated cycloaddition – general procedure

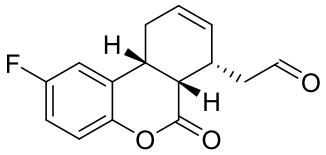


An ordinary screw-cap vial was charged with a magnetic stirring bar, the corresponding coumarin-3-carboxylic acid **2** (0.2 mmol, 1 equiv), $CHCl_3$ (2 mL), catalyst **4b** (0.04 mmol, 0.2 equiv), 4-(dimethylamino)benzoic acid (0.04 mmol, 6.6 mg) and the corresponding 2,4-dienal **1** (0.4 mmol, 2 equiv). The reaction mixture was stirred at room temperature and monitored by ^{1}H NMR spectroscopy. After complete consumption of the coumarin-3-carboxylic acid **2** the mixture was directly subjected to FC on silica gel (hexane:diethyl ether 4:1) to afford pure product **3**.



(3a) 2-((6a*S*,7*S*,10a*R*)-6-Oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

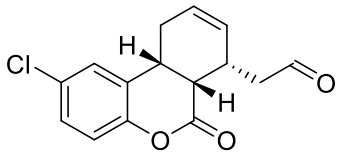
Pure product was isolated by flash chromatography on silica gel (hexane:diethyl ether 4:1) as yellow crystals in 93% yield, 2:1 dr. ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.86 (d, *J* = 0.7 Hz, $1H_{major}$), 9.84 (dd, *J* = 2.2, 1.1 Hz, $1H_{minor}$), 7.29 (tdd, *J* = 7.3, 1.6, 0.8 Hz, $1H_{minor}$), 7.28 – 7.26 (m, $1H_{minor}$), 7.25 (dd, *J* = 8.1, 1.6 Hz, $1H_{major}$), 7.20 – 7.19 (m, $1H_{major}$), 7.17 (td, *J* = 7.5, 1.2 Hz, $1H_{minor}$), 7.10 (td, *J* = 7.4, 1.2 Hz, $1H_{major}$), 7.07 (dd, *J* = 8.0, 1.2 Hz, $1H_{minor}$), 7.04 (dd, *J* = 8.1, 1.2 Hz, $1H_{major}$), 5.87 (ddt, *J* = 10.2, 5.9, 2.2 Hz, $1H_{minor}$), 5.71 – 5.64 (m, $1H_{major}$), 5.59 – 5.54 (m, $1H_{major+minor}$), 3.42 (ddd, *J* = 19.4, 7.7, 0.6 Hz, $1H_{major}$), 3.31 – 3.27 (m, $1H_{minor}$), 3.27 – 3.20 (m, $3H_{major+minor}$), 3.05 (ddd, *J* = 19.4, 6.3, 0.7 Hz, $1H_{major}$), 2.86 (dt, *J* = 17.1, 1.7 Hz, $1H_{minor}$), 2.59 (ddd, *J* = 17.2, 8.5, 2.2 Hz, $1H_{minor}$), 2.47 – 2.36 (m, $2H_{major+minor}$), 2.28 – 2.19 (m, $1H_{minor}$), 2.09 – 2.00 (m, $1H_{major}$). ^{13}C NMR (176 MHz, $CDCl_3$) δ_{major} 201.4, 168.7, 151.0, 129.0, 128.7, 128.4, 126.8, 125.4, 124.9, 116.8, 47.0, 41.3, 36.4, 31.0, 29.8. δ_{minor} 201.1, 170.0, 150.8, 129.0, 128.6, 128.6, 126.3, 124.6, 124.5, 116.6, 49.0, 43.2, 32.7, 31.8, 28.6. HRMS: calculated for $[C_{15}H_{14}O_3+H^+]$: 243.1016, found: 243.1027. The er was determined by UPC^2 using a chiral Chiralpack IG column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; detection wavelength = 245 nm; τ_{major} = 3.68 min, τ_{minor} = 3.73 min, (93:7 er) for major dastaereoisomer, detection wavelength = 245 nm; τ_{major} = 3.21 min, τ_{minor} = 3.27 min, (96:4 er) for minor diastereoisomer.



(3b) 2-((6a*S*,7*S*,10a*R*)-2-Fluoro-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

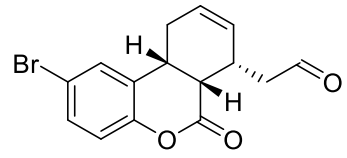
Pure product was isolated by flash chromatography on silica gel (hexane:diethyl ether 4:1) as yellow oil in 73% yield, 2:1 dr. ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.84 (s, $1H_{major}$), 9.83 (dd, *J* = 2.1, 1.1 Hz, $1H_{minor}$ 7.04 – 6.98 (m, $1H_{major}$ and $2H_{minor}$), 6.97 – 6.93 (m, $1H_{major+minor}$), 6.91 (dd, J = 8.0, 2.9 Hz, $1H_{major}$), 5.86 (ddt, J = 10.1, 5.8, 2.3 Hz, $1H_{minor}$), 5.71 – 5.66 (m, $1H_{major + minor}$), 5.58 – 5.54 (m, $1H_{major}$), 3.43 (ddd, J = 19.4, 7.9, 0.6 Hz, $1H_{major}$), 3.28 (dddq, J = 10.2, 6.1, 4.1, 1.9 Hz, $1H_{minor}$), 3.25 – 3.19 (m, $1H_{major}$ + $2H_{minor}$), 3.17 – 3.08 (m, $1H_{major}$), 3.08 – 2.99 (m, $1H_{major}$), 2.84 – 2.76 (m, $1H_{minor}$), 2.61 (ddd, J = 17.3, 8.5, 2.1 Hz, $1H_{minor}$), 2.43 (dd, J = 14.6, 9.9 Hz, $1H_{major}$), 2.42 – 2.39 (m, $1H_{major + minor}$), 2.27 –

2.17 (m, $1H_{minor}$), 2.10 – 2.00 (m, $1H_{major}$). ^{13}C NMR (176 MHz, $CDCl_3$) δ_{major} 201.3, 168.3, 158.9 (d, *J* = 244.1 Hz), 146.9 (d, *J* = 2.6 Hz), 130.1 (d, *J* = 8.0 Hz), 128.8, 124.6, 118.1 (d, *J* = 8.5 Hz), 115.0 (d, *J* = 23.5 Hz), 113.5 (d, *J* = 23.7 Hz), 46.9, 40.9, 36.5, 30.9, 29.5. δ_{minor} 200.9, 169.6, 159.4 (d, d, *J* = 242.9 Hz), 146.8 (d, *J* = 2.5 Hz), 129.2, 128.1 (d, *J* = 7.6 Hz), 124.1, 117.9 (d, *J* = 8.4 Hz), 115.2 (d, *J* = 23.5 Hz), 112.4 (d, *J* = 24.7 Hz), 48.8, 42.7, 32.8, 31.8 , 28.5. HRMS: calculated for $[C_{15}H_{13}FO_3+H^+]$: 261.0921, found: 261.0909. For major diastereoisomer the er was determined by UPC[2] using a chiral Chiralpack IG column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; detection wavelength = 245 nm; τ_{major} = 2.83 min, τ_{minor} = 3.04 min, (92:8 er). For minor diastereoisomer the er was determined by UPC[2] using a chiral Chiralpack IG column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; detection wavelength = 245 nm; τ_{major} = 3.18 min, τ_{minor} = 3.32 min, (96:4 er).



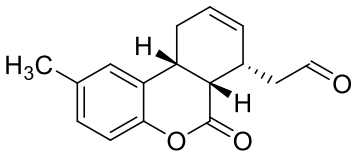
(3c) 2-((6a*S*,7*S*,10a*R*)-2-Chloro-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

Pure product was isolated by flash chromatography on silica gel (hexane:diethyl ether 4:1) as yellow crystals in 78% yield, 2:1 dr. ^1H NMR (700 MHz, $CDCl_3$) δ 9.84 (s, $1H_{major}$), 9.83 (dd, *J* = 2.1, 1.1 Hz, $1H_{minor}$), 7.25 – 7.20 (m, $1H_{major+minor}$), 7.18 (t, *J* = 2.7 Hz, $1H_{major+minor}$), 7.01 – 6.96 (m, $1H_{major+minor}$), 5.86 (ddt, *J* = 10.2, 5.8, 2.3 Hz, $1H_{minor}$), 5.71 – 5.65 (m, $1H_{major}$), 5.65 – 5.60 (m, $1H_{minor}$), 5.56 (dq, *J* = 10.2, 1.2 Hz, $1H_{major}$), 3.45 – 3.34 (m, $1H_{major}$), 3.31 – 3.15 (m, $3H_{major+minor}$), 3.12 – 3.07 (m, $1H_{minor}$), 3.07 – 2.97 (m, $1H_{major+minor}$), 2.91 (dd, *J* = 17.3, 6.9 Hz, $1H_{minor}$), 2.81 (dddd, *J* = 13.4, 9.5, 6.6, 5.0 Hz, $1H_{minor}$), 2.68 – 2.49 (m, $1H_{minor}$), 2.46 – 2.34 (m, $1H_{major+minor}$), 2.09 – 1.94 (m, $1H_{major}$). ^{13}C NMR (176 MHz, $CDCl_3$) δ_{major} 201.3, 168.1, 149.5, 130.1, 129.3 128.7, 128.5, 128.4, 126.8, 124.6, 118.2, 46.8, 40.9, 36.3, 30.9, 29.6. δ_{minor} 200.9, 167.8, 149.5, 130.1, 129.3,128.8, 128.5 125.7, 124.1, 118.0, 48.8, 42.8, 33.3, 32.8, 31.8. HRMS: calculated for $[C_{15}H_{13}ClO_3+H^+]$: 277.0626, found: 277.0632. For major diastereoisomer the er was determined by UPC[2] using a chiral Chiralpack IA column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; detection wavelength = 245 nm; τ_{major} = 2.84 min, τ_{minor} = 3.04 min, (91:9 er). For minor diastereoisomer the er was determined by UPC[2] using a chiral Chiralpack IA column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; detection wavelength = 245 nm; τ_{major} = 3.25 min, τ_{minor} = 3.40 min, (98:2 er).



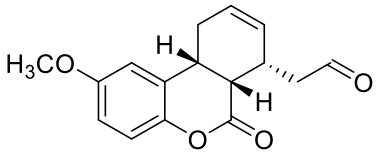
(3d) 2-((6a*S*,7*S*,10a*R*)-2-Bromo-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

Pure product was isolated by flash chromatography on silica gel (hexane:diethyl ether 4:1) as yellow oil in 65% yield, 2:1 dr. ^1H NMR (700 MHz, $CDCl_3$) δ 9.84 (s, $1H_{major}$), 9.83 (dd, *J* = 2.1, 1.1 Hz, $1H_{minor}$), 7.42 – 7.34 (m, $1H_{major+minor}$), 7.33 (d, *J* = 2.4 Hz, $1H_{major}$), 6.93 (dd, *J* = 15.9, 8.6 Hz, $1H_{major+minor}$), 5.86 (ddt, *J* = 10.2, 5.9, 2.2 Hz, $1H_{minor}$), 5.69 – 5.64 (m, $1H_{major+minor}$), 5.59 – 5.50 (m, $1H_{major}$), 3.42 (dd, *J* = 17.3, 3.6, 1.1 Hz $1H_{major}$), 3.29 – 3.24 (m, $1H_{minor}$), 3.24 – 3.17 (m, $3H_{major}$), 3.10 (ddd, *J* = 19.4, 7.7 Hz, $1H_{minor}$), 3.03 (ddd, *J* = 19.5, 6.1, 0.6 Hz, $1H_{major}$), 2.85 – 2.78 (m, $1H_{minor}$), 2.60 (ddd, *J* = 17.3, 8.4, 2.1 Hz, $1H_{minor}$), 2.47 – 2.35 (m, $1H_{major+minor}$), 2.27 – 2.18 (m, $1H_{minor}$), 2.07 – 1.97 (m, $1H_{major}$). ^{13}C NMR (176 MHz, $CDCl_3$) δ_{major} 201.2, 168.0, 150.0, 131.4, 129.7, 128.7, 124.6, 118.6, 116.77, 46.8, 40.9, 36.3, 30.8, 29.6. δ_{minor} 200.9, 169.3, 149.9, 131.6, 129.1, 128.6, 127.1, 124.1, 118.4, 117.4, 48.8, 42.8, 32.7, 31.7, 28.5. HRMS: calculated for $[C_{15}H_{13}BrO_3+H^+]$: 321.0121, found: 321.0132. For major diastereoisomer the er was determined by UPC[2] using a chiral Chiralpack IG column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; detection wavelength = 245 nm; τ_{major} = 3.46 min, τ_{minor} = 3.79 min, (90:10 er).



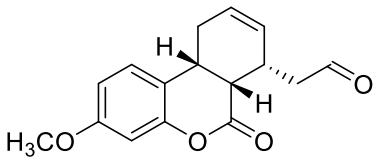
(3e) 2-((6a*S*,7*S*,10a*R*)-2-Methyl-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

Pure product was isolated by flash chromatography on silica gel (hexane:diethyl ether 4:1) as yellow oil in 92% yield, 2:1 dr. Major diastereoisomer was isolated by FC in 58% yield. ^{1}H NMR (700 MHz, $CDCl_3$) δ_{major} 9.82 (t, *J* = 1.7 Hz, 1H), 7.09 (ddd, *J* = 8.3, 2.2, 0.8 Hz, 1H), 7.02 (d, *J* = 2.1 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 5.84 – 5.66 (m, 2H), 3.58 (s, 1H), 3.09 (ddd, *J* = 16.1, 10.6, 5.8 Hz, 1H), 2.82 (d, *J* = 2.7 Hz, 1H), 2.69 (ddd, *J* = 17.1, 6.3, 1.6 Hz, 1H), 2.60 (ddd, *J* = 17.1, 8.2, 1.9 Hz, 1H), 2.33-2.37 (m, 1H), 2.33 (s, 3H), 2.16 – 2.02 (m, 1H). ^{13}C NMR (176 MHz, CDCl3) δ_{major} 200.3, 169.3, 148.8, 134.1, 129.0, 127.9, 127.5, 127.1, 125.4, 116.8, 48.3, 42.6, 30.8, 28.7, 28.3, 20.8. HRMS: calculated for [$C_{16}H_{16}O_3$+H^+]: 257.1172, found: 257.1160. For major diastereoisomer the er was determined by HPLC using a Chiralpak IG column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} =11.7 min; τ_{minor} = 15.4 min (80:20 er). For minor diastereoisomer the er was determined by HPLC using a Chiralpak IG column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} =16.9 min; τ_{minor} = 18.2 min (93:7er).



(3f) 2-((6a*S*,7*S*,10a*R*)-2-Methoxy-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

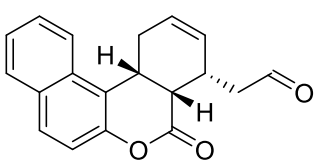
Pure product was isolated by flash chromatography on silica gel (hexane:diethyl ether 4:1) as yellow powder in 95% yield, 2:1 dr. ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.84 (d, *J* = 1.3 Hz, $1H_{major}$), 9.83 – 9.80 (m, $1H_{minor}$), 6.98 (dd, *J* = 8.8, 1.6 Hz, $1H_{minor}$), 6.95 (dd, *J* = 8.8, 1.4 Hz, $1H_{major}$), 6.82 – 6.78 (m, $1H_{minor}$), 6.78 – 6.74 (m, $1H_{major+minor}$), 6.71 (d, *J* = 2.9 Hz, $1H_{major}$), 5.85 (ddd, *J* = 10.2, 5.1, 2.5 Hz, $1H_{minor}$), 5.71 – 5.62 (m, $1H_{major+minor}$), 5.54 (ddt, *J* = 10.0, 2.5, 1.3 Hz, $1H_{major}$), 3.79 (s, $3H_{minor}$), 3.79 (s, $3H_{major}$), 3.39 (ddd, *J* = 19.3, 7.8, 2.0 Hz, $1H_{major}$), 3.26 (dddd, *J* = 8.2, 6.2, 4.1, 2.3 Hz, $1H_{minor}$), 3.23 – 3.16 (m, $3H_{major}$), 3.04 (ddd, *J* = 19.4, 6.5, 0.7 Hz, $1H_{major}$), 3.07 – 3.03 (m, $1H_{minor}$), 2.80 (dtd, *J* = 17.0, 5.6, 5.2, 2.5 Hz, $1H_{minor}$), 2.57 (dddd, *J* = 17.2, 8.5, 2.1, 1.3 Hz, $1H_{minor}$), 2.43 – 2.32 (m, $1H_{major}$), 2.25 – 2.17 (m, $1H_{minor}$), 2.07 – 1.95 (m, $1H_{minor}$). ^{13}C NMR (176 MHz, $CDCl_3$) δ_{major} 201.4, 168.9, 156.1, 144.8, 129.6, 128.8, 124.8, 117.5, 113.2, 112.2, 55.7, 47.0, 41.3, 36.7, 31.0, 29.7. δ_{minor} 201.1, 170.1, 156.4, 144.7, 129.1, 127.4, 124.3, 117.2, 112.9, 111.3, 55.7, 48.9, 43.0, 32.8, 31.7, 28.6. HRMS: calculated for [$C_{16}H_{16}O_4$+H^+]: 273.1121, found: 273.1109. The er was determined by UPC^2 using a chiral Chiralpack IA column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; detection wavelength = 245 nm; τ_{major} = 2.9 min, τ_{minor} =3.18 min, (94:6 er) for major diastereoisomer and τ_{major} = 3.39 min, τ_{minor} =3.50 min, (98:2 er) for minor diastereoisomer.



(3g) 2-((6a*S*,7*S*,10a*R*)-3-Methoxy-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

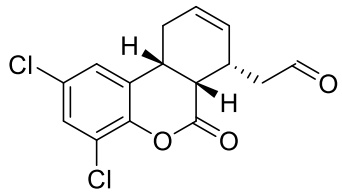
Pure product was isolated by flash chromatography on silica gel (hexane:diethyl ether 4:1) as white powder in 87% yield, 2:1 dr. ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.84 (s, $1H_{major}$), 9.83 (dd, J = 2.2, 1.1 Hz, $1H_{minor}$), 7.11 (dd, J = 8.6, 1.2 Hz, $1H_{minor}$), 7.08 (d, J = 8.3 Hz, $1H_{major}$), 6.71 (dd, J = 8.6, 2.6 Hz, $1H_{minor}$), 6.64 (dd, J = 8.3, 2.5 Hz, $1H_{minor}$), 6.58-6.61 (m, $1H_{majo+rminor}$), 5.89 – 5.81 (m, $1H_{minor}$), 5.64-5.68 (m, $1H_{major+minor}$), 5.56 – 5.51 (m, $1H_{major}$), 3.79 (s, $3H_{minor}$), 3.78 (s, $3H_{major}$), 3.38 (dd, 20.8, 7.3 Hz, $1H_{major}$), 3.17-3.21 (m, $1H_{minor}$), 3.23 – 3.15 (m, $2H_{major+minor}$), 3.14 – 3.07 (m, $1H_{major}$), 3.03 (ddd, J = 19.4, 6.4, 0.7 Hz, $1H_{major}$), 3.07 – 3.03 (m, $1H_{minor}$), 2.85 – 2.76 (m, $1H_{major}$), 2.57 (ddd, J = 17.1, 8.5, 2.2 Hz, $1H_{minor}$), 2.43 – 2.33 (m, $1H_{minor+minor}$), 2.21 – 2.13 (m, $1H_{minor}$), 2.04 – 1.90 (m, $1H_{major}$). ^{13}C NMR (176 MHz, $CDCl_3$) δ_{major} 201.3, 168.7, 159.8, 151.7, 128.6, 127.2, 125.0, 120.6, 110.1, 102.52, 55.5, 46.9, 41.6, 35.7, 31.1, 30.1. δ_{minor} 201.1, 170.1, 159.8, 151.5, 129.0, 126.0, 124.5, 118.3, 110.6, 102.2, 55.6, 48.93, 43.6, 32.3, 31.6, 28.9. HRMS: calculated for [$C_{16}H_{16}O_4$+H^+]: 273.1121, found: 273.1134. For

major diastereoizomer the er was determined by UPC^2 using a chiral Chiralpack IB column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; detection wavelength = 245 nm; τ_{major} = 2.81 min, τ_{minor} = 3.70 min, (96:4 er).



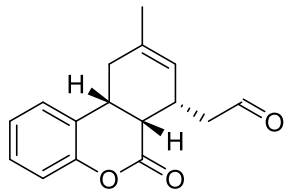
(3h) 2-((4*S*,4a*S*,12c*R*)-5-Oxo-4,4a,5,12c-tetrahydro-1*H*-dibenzo[c,f]chromen-4-yl)acetaldehyde

Pure product was isolated by flash chromatography on silica gel (hexane:diethyl ether 4:1) as yellow crystals in 95% yield, >20:1 dr. ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.94 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.86 (ddt, *J* = 8.2, 1.3, 0.6 Hz, 1H), 7.83 – 7.73 (m, 1H), 7.58 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.47 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 5.75 (ddt, *J* = 10.1, 5.0, 2.6 Hz, 1H), 5.63 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 3.94 (ddd, *J* = 11.4, 6.3, 4.8 Hz, 1H), 3.47 (ddd, *J* = 19.3, 7.9, 0.6 Hz, 1H), 3.38 – 3.32 (m, 1H), 3.31 (t, J = 4.8 Hz, 1H), 3.12 (ddd, *J* = 19.3, 6.5, 0.6 Hz, 1H), 2.72 – 2.58 (m, 1H), 2.06 – 2.12 (m, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 201.4, 168.8, 148.5, 130.8, 130.2, 128.9, 128.8, 128.7, 127.3, 125.1, 124.9, 122.4, 121.9, 117.2, 47.0, 41.0, 32.7, 31.0, 28.7. HRMS: calculated for [$C_{19}H_{16}O_3$+H^+]: 293.1172, found: 293.1180. The er was determined by UPC^2 using a chiral Chiralpack IG column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; detection wavelength = 245 nm; τ_{major} = 3.89 min, τ_{minor} = 4.37 min, (57:43 er).



(3i) 2-((6a*S*,7*S*,10a*R*)-2,4-Dichloro-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

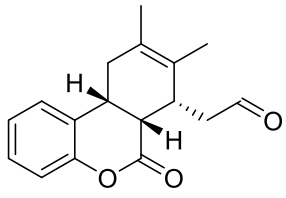
Pure product was isolated by flash chromatography on silica gel (hexane:diethyl ether 4:1) as yellow crystals in 78% yield, 2:1 dr. ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.85 (d, J = 0.5 Hz, $1H_{major}$), 9.83 (dd, J = 2.0, 1.0 Hz, $1H_{minor}$), 7.38 (dd, J = 2.4, 1.0 Hz, $1H_{minor}$), 7.34 (d, J = 2.4 Hz, $1H_{major}$), 7.13 (dd, J = 2.4, 1.3 Hz, $1H_{minor}$), 7.10 (dd, J = 2.4, 0.5 Hz, $1H_{major}$), 5.89 – 5.82 (m, $1H_{minor}$), 5.66-5.69 (m, $1H_{major+minor}$), 5.59 – 5.53 (m, $1H_{major}$), 3.50 – 3.36 (m, $1H_{major+minor}$), 3.33 – 3.19 (m, $3H_{major+minor}$), 3.11 (ddd, J = 17.4, 3.6, 1.0 Hz, $1H_{minor}$), 3.03 (ddd, J = 19.4, 6.1, 0.5 Hz, $1H_{major}$), 2.63 (ddd, J = 17.5, 8.4, 2.0 Hz, $1H_{minor}$), 2.51 – 2.36 (m, $1H_{major}$), 2.05 – 1.98 (m, $1H_{major+minor}$).^{13}C NMR (176 MHz, $CDCl_3$) δ_{major} 201.1, 166.7, 145.7, 131.2, 129.3, 128.9, 128.7, 125.3, 124.3 122.6, 46.7, 40.7, 36.7, 30.7, 29.3. δ_{minor} 200.7, 168.2, 145.6, 131.2, 129.3, 129.1, 128.0, 124.5, 124.2, 123.9, 48.5, 42.4, 33.1, 31.7, 28.5. HRMS: calculated for [$C_{15}H_{12}Cl_2O_3$+H^+]: 311.0236, found: 311.0248. The er was determined by UPC^2 using a chiral Chiralpack IG column gradient from 100% CO_2 up to 40%; acetonitril, 2.5 mL/min; detection wavelength = 245 nm; τ_{major} = 3.34 min, τ_{minor} = 3.53 min, (60:40 er) for major diastereoisomer.



(3j) 2-((6a*S*,7*S*,10a*R*)-9-Methyl-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-7-yl)acetaldehyde

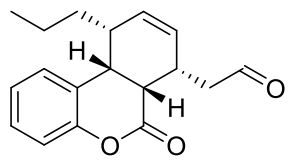
Pure product was isolated by flash chromatography on silica gel (hexane:diethyl ether 4:1) as yellow crystals in 67% yield, 1:1 dr. ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.85 (s, $1H_{minor}$), 9.83 (dd, *J* = 2.4, 1.1 Hz, $1H_{major}$), 7.30 – 7.26 (m, $1H_{major + minor}$), 7.25 (td, *J* = 7.5, 1.4 Hz, $1H_{major}$), 7.18 (dd, *J* = 7.5, 1.7 Hz, $1H_{minor}$), 7.16 (td, *J* = 7.5, 1.3 Hz, $1H_{major}$), 7.09 (td, *J* = 7.4, 1.2 Hz, $1H_{minor}$), 7.05 (dd, *J* = 8.1, 1.3 Hz, $1H_{major}$), 7.03 (dd, *J* = 8.1, 1.1 Hz, $1H_{minor}$), 5.36 – 5.34 (m, $1H_{major}$), 5.26 – 5.24 (m, $1H_{minor}$), 3.36 (dd, *J* = 19.2, 7.4 Hz, $1H_{minor}$), 3.27 – 3.20 (m, $1H_{major + minor}$), 3.20 – 3.12 (m, $2H_{major}$ and $1H_{minor}$), 3.10 (ddd, *J* = 17.0, 3.7, 1.2 Hz, $1H_{major}$), 3.02 (ddd, *J* = 19.3, 6.5, 0.7 Hz, $1H_{minor}$), 2.67 (dd, *J* = 17.0, 5.7 Hz, $1H_{minor}$), 2.51 (ddd, *J* = 17.0, 8.6, 2.4 Hz, $1H_{major}$), 2.33 (dd, J = 14.1, 9.9 Hz, $1H_{major}$), 2.26 – 2.17 (m, $1H_{major + minor}$), 2.01 – 1.93 (m, $1H_{minor}$), 1.79 (s, $3H_{major}$), 1.65 (s, $3H_{minor}$). ^{13}C NMR (176 MHz,

$CDCl_3$) δ_{major} 201.5, 170.1, 150.9, 132.0, 128.5, 126.8, 125.4, 124.6, 123.2, 116.6, 49.4, 43.0, 33.5, 33.1, 31.9, 23.4. δ_{minor} 201.7, 168.8, 151.0, 132.3, 128.5, 128.4, 126.4, 124.3, 122.9, 116.8, 47.3, 41.2, 36.7, 34.6, 31.2, 23.0. HRMS: calculated for [$C_{16}H_{16}O_3$+H^+]: 256.1099, found: 256.1107. The er was determined by HPLC using a Chiralpak ID column [hexane/i-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} =10.7 min; τ_{minor} = 11.8 min, (86:14 er) for major diastereoisomer and τ_{major} =15.5 min; τ_{minor} = 17.2 min, (99:1 er) for minor diastereoisomer.



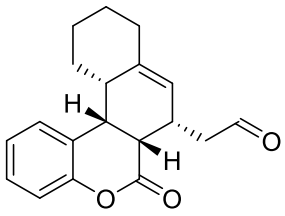
(3k) 2-((6a*S*,7*R*,10a*R*)-8,9-Dimethyl-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-7-yl)acetaldehyde

Pure product was isolated by flash chromatography on silica gel (hexane:diethyl ether 4:1) as yellow solid in 56% yield, 2:1 dr. ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.88 (s, $1H_{major}$), 9.78 (t, J = 2.3 Hz, $1H_{minor}$), 7.29 – 7.26 (m, $2H_{minor}$), 7.24 (ddd, J = 8.1, 7.4, 1.6 Hz, $1H_{major}$), 7.18 – 7.14 (m, $1H_{major + minor}$), 7.08 (td, J = 7.4, 1.2 Hz, $1H_{major}$), 7.06 (dd, J = 8.0, 1.3 Hz, $1H_{minor}$), 7.02 (dd, J = 8.1, 1.1 Hz, $1H_{major}$), 3.34 (ddd, J = 18.9, 7.9, 0.8 Hz, $1H_{major}$), 3.26 – 3.21 (m, $2H_{major}$ and $1H_{minor}$), 3.20 – 3.12 (m, $2H_{major}$), 3.05 – 2.96 (m, $1H_{minor}$), 2.89 – 2.77 (m, $1H_{major + minor}$), 2.65 (dd, J = 16.3, 5.0 Hz, $1H_{minor}$), 2.57 (dd, J = 14.3, 9.6 Hz, $1H_{minor}$), 2.30 – 2.19 (m, $1H_{major + minor}$), 2.08 (ddtd, J = 16.0, 11.7, 2.1, 1.0 Hz, $1H_{minor}$), 1.81 – 1.76 (m, $3H_{minor}$), 1.73 – 1.68 (m, $3H_{minor}$), 1.65 (s, $3H_{major}$), 1.65 – 1.61 (s, $3H_{major}$). ^{13}C NMR (176 MHz, $CDCl_3$) δ_{major} 202.1, 169.1, 151.0, 128.3, 126.8, 126.4, 125.3, 125.2, 124.21, 116.7, 45.4, 42.4, 36.4, 36.4, 34.8, 19.6, 16.0. δ_{minor} 202.2, 170.6, 151.0, 128.6, 128.5, 126.6, 125.8, 125.2, 124.2, 116.6, 46.7, 44.6, 37.0, 34.9, 32.9, 20.0, 16.8. HRMS: calculated for [$C_{17}H_{18}O_3$+H^+]: 270.1256, found: 270.1242. The er was determined by HPLC using a chiral Chiralpack IA column; [hexane/i-PrOH (95:5)]; flow rate 1.0 mL/min τ_{major} = 10.0 min, τ_{minor} = 11.0 min, (69:31 er), for major diastereoisomer, and τ_{major} = 12.6 min, τ_{minor} = 13.2 min, (68:32) for minor diastereoisomer.



(3l) 2-((6a*S*,7*S*,10*R*,10a*R*)-6-Oxo-10-propyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-7-yl)acetaldehyde

Pure product was isolated by flash chromatography on silica gel (hexane:diethyl ether 4:1) as yellow crystals in 84% yield, 10:1 dr. ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.88 (d, *J* = 0.5 Hz, 1H), 7.30 (ddd, *J* = 8.1, 7.4, 1.7 Hz, 1H), 7.22 – 7.18 (m, 1H), 7.15 (td, *J* = 7.4, 1.2 Hz, 1H), 7.08 – 7.05 (m, 1H), 5.91 (ddd, *J* = 10.4, 4.5, 3.0 Hz, 1H), 5.58 – 5.55 (m, 1H), 3.49 (dd, *J* = 19.6, 8.3 Hz, 1H), 3.47 (t, *J* = 6.1 Hz, 1H), 3.22 – 3.17 (m, 1H), 3.16 (td, *J* = 5.5, 1.1 Hz, 1H), 3.04 (ddd, *J* = 19.3, 6.3, 0.6 Hz, 1H), 2.38 (dddt, *J* = 11.0, 6.3, 4.2, 2.0 Hz, 1H), 1.43 – 1.35 (m, 1H), 1.18 – 1.08 (m, 1H), 1.03 (dddd, *J* = 13.1, 9.7, 7.3, 5.8 Hz, 1H), 0.96 – 0.89 (m, 1H), 0.72 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 201.4, 169.8, 152.1, 129.6, 128.5, 127.5, 127.5, 126.8, 124.3, 116.5, 46.9, 40.2, 38.4, 37.8, 32.9, 30.6, 20.9, 13.9. HRMS: calculated for [$C_{18}H_{20}O_3$+H+]: 285.1485, found: 285.1499. The er was determined by HPLC Chiralpak ID column [hexane/i-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 8.15 min, τ_{minor} = 9.36 min, (97:3 er).



(3m) 2-((6a*S*,7*S*,12a*S*,12b*R*)-6-Oxo-6a,7,9,10,11,12,12a,12b-octahydro-6*H*-naphtho[2,1-c]chromen-7-yl)acetaldehyde

Pure product was isolated by flash chromatography on silica gel (hexane:diethyl ether 4:1) as yellow solid in 56% yield, 2:1 dr. ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.86 (d, J = 3.7 Hz, $1H_{major + minor}$), 7.27 – 7.23 (m, $1H_{major + minor}$), 7.21 (dt, J = 7.8, 1.5 Hz, $1H_{minor}$), 7.17 (dd, J = 7.5, 1.7 Hz, $1H_{major}$), 7.15 (td, J = 7.6, 1.3 Hz, $1H_{minor}$), 7.11 (td, J = 7.4, 1.2 Hz, $1H_{major}$), 7.02 (ddd, J = 9.3, 8.1, 1.2 Hz, $1H_{major + minor}$), 5.23 (q, J = 1.5 Hz, $1H_{major + minor}$), 3.45 (dd, J = 7.4, 5.7 Hz, $1H_{major}$),

3.41 – 3.36 (m, $1H_{major}$), 3.26 – 3.18 (m, $1H_{minor}$), 3.19 (ddd, *J* = 16.9, 3.5, 1.1 Hz, $1H_{minor}$), 3.15 (dtd, J = 6.6, 3.6, 1.5 Hz, $1H_{major}$), 3.07 (td, J = 5.3, 4.9, 1.1 Hz, $1H_{major+minor}$), 3.04 (dd, J = 6.8, 0.7 Hz, $1H_{minor}$), 2.68 (dt, J = 12.8, 3.3 Hz, $1H_{minor}$), 2.66 – 2.61 (m, $1H_{minor}$), 2.61 – 2.57 (m, $1H_{minor}$), 2.32 – 2.19 (m, $2H_{major}$), 2.08 (td, J = 12.7, 6.0 Hz, $1H_{minor}$), 2.00 – 1.90 (m, $1H_{major}$), 1.91 – 1.81 (m, $1H_{major}$), 1.73 (ddq, J = 12.1, 4.2, 2.3 Hz, $1H_{major}$), 1.67 – 1.59 (m, $1H_{major + minor}$), 1.50 – 1.57 (m, $1H_{minor}$), 1.16-1.36 (m, $3H_{major}$ and $2H_{minor}$), 0.99-1.13 (m, $1H_{major+minor}$). ^{13}C NMR (176 MHz, $CDCl_3$) δ_{major} 201.7, 169.5, 152.0, 140.6, 128.3, 127.5, 124.3, 119.7, 116.5, 47.4, 41.3, 40.1, 39.0, 36.4, 30.4, 29.7, 28.5, 27.0. δ_{minor} 201.6, 170.0, 151.8, 142.7, 128.3, 127.1, 124.1, 122.2, 119.0, 117.0, 49.3, 39.9, 38.6, 37.2, 36.6, 32.8, 30.1, 28.8, 26.7. HRMS: calculated for $[C_{19}H_{20}O_3+H^+]$: 296.1412, found: 296.1417. The er was determined by HPLC using a chiral Chiralpack ID column [hexane/i-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 12.91 min, τ_{minor} = 13.92 min, (99:1 er).

3. Crystal and X-ray data

The single crystal X-ray diffraction studies at 100 K revealed that compounds major-*ent*-**3e** ($C_{16}H_{16}O_3$) and minor-**3f** ($C_{16}H_{16}O_4$) and crystallize in the non-centrosymmetric monoclinic space group $P2_1$ (Z = 2) and the crystal structures consist of one crystallographically independent formula unit in the unit cell (Figure X).

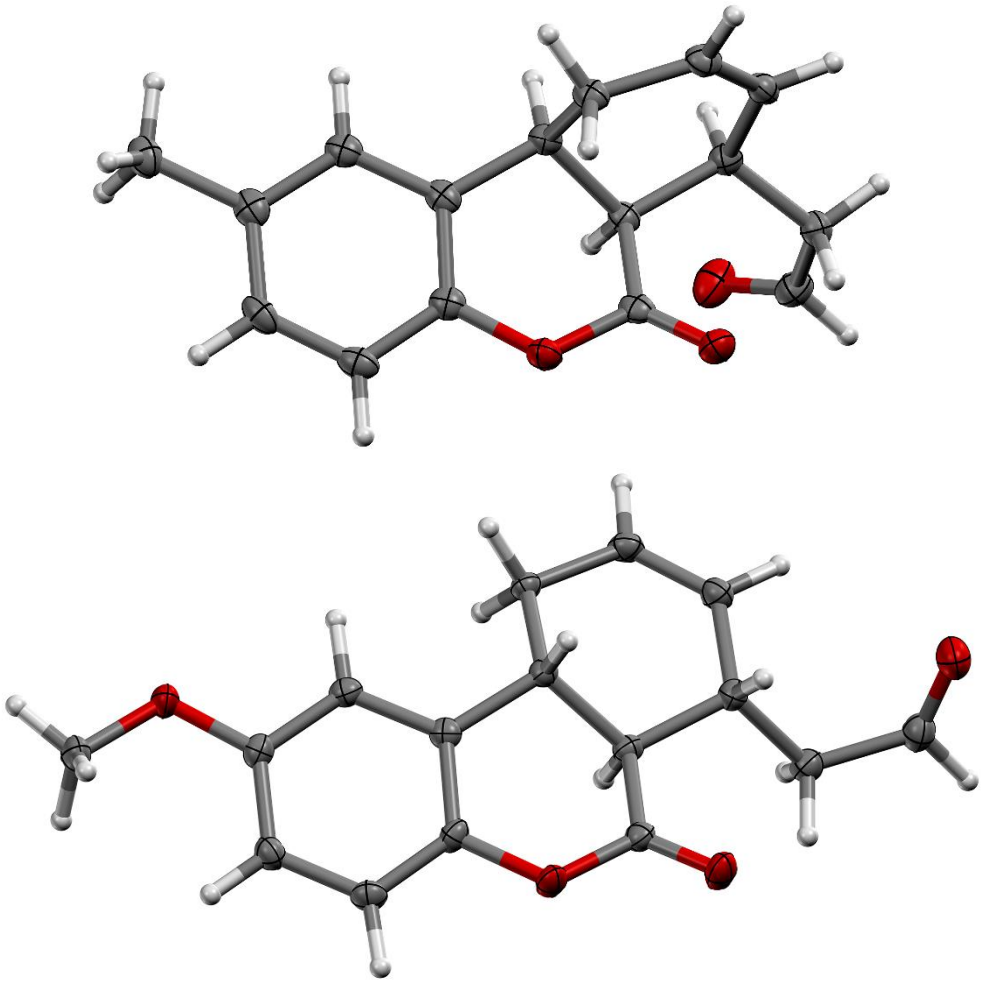


Figure X. The molecular structures of the compound major-*ent*-**3e** and minor-**3f**, showing 50% probability displacement ellipsoids. Hydrogen atoms are drawn with an arbitrary radius.

Single crystal X-ray diffraction data were collected at 100 K by the ω-scan technique using a RIGAKU XtaLAB Synergy, Dualflex, Pilatus 300K diffractometer[3] with PhotonJet micro-focus X-ray Source Cu-Kα (λ = 1.54184 Å). Data collection, cell refinement, data reduction and absorption correction were performed using CrysAlis PRO software[3]. The crystal structure was solved by using direct methods with the SHELXT 2018/2 program[4]. Atomic scattering factors were taken from the International Tables for X-ray Crystallography. Positional parameters of

[3] Rigaku OD. CrysAlis PRO. Rigaku Oxford Diffraction Ltd, Yarnton, Oxfordshire, England, 2019
[4] G. M. Sheldrick, *Acta Cryst.* 2015, **A71**, 3

non-H-atoms were refined by a full-matrix least-squares method on F^2 with anisotropic thermal parameters by using the SHELXL 2018/3 program[5]. All hydrogen atoms were placed in calculated positions (C–H = 0.95–1.00 Å) and included as riding contributions with isotropic displacement parameters set to 1.2–1.5 times the U_{eq} of the parent atom.

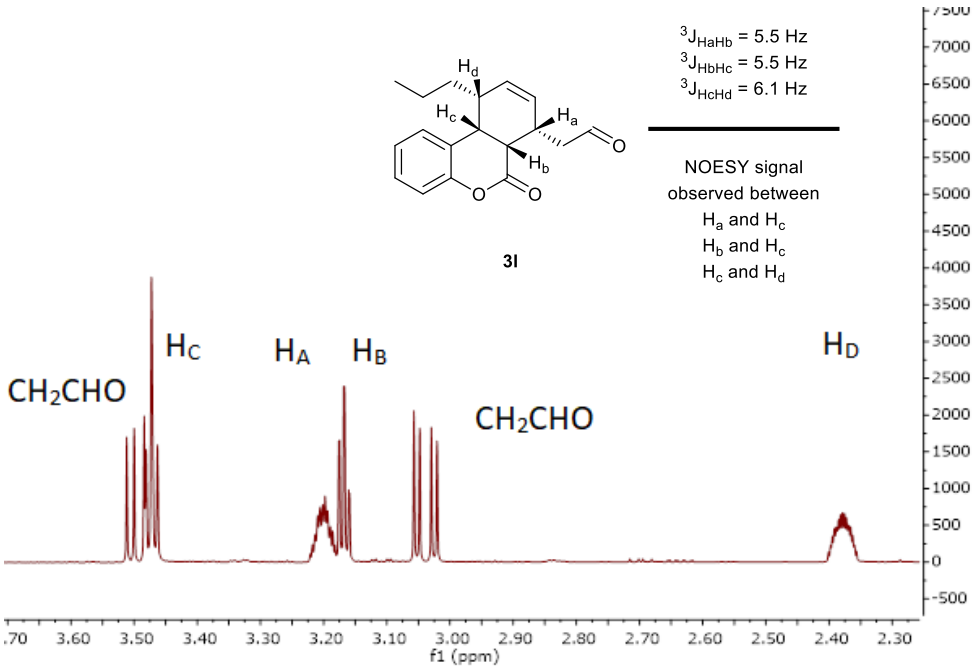
major-*ent*-**3e**: Formula $C_{16}H_{16}O_3$, monoclinic, space group $P2_1$, Z = 2, unit cell constants a = 8.5399(1), b = 7.2817(1), c = 10.6201(1) Å, □ = 105.546(1)°, V = 636.250(13) Å^3. The integration of the data yielded a total of 15530 reflections with θ angles in the range of 4.32 to 66.59°, of which 2246 unique (R_{int} = 1.60%) and 2241 were greater than 2σ(F^2). The final anisotropic full-matrix least-squares refinement on F^2 with 174 parameters converged at R_1 = 2.17% for the observed 2σ(F^2) data and wR_2 = 5.56% for all data. The largest peak in the final difference electron density synthesis was 0.147 e Å^{-3} and the largest hole was -0.116 e Å^{-3}. The goodness-of-fit was 1.054. The absolute configuration was unambiguously determined from anomalous scattering, by calculating the x Flack parameter [4] of 0.029(2) using 1020 quotients.

minor-**3f**: Formula $C_{16}H_{16}O_4$, orthorhombic, space group $P2_1$, Z = 2, unit cell constants a = 7.92142(4), b = 7.19257(4), c = 11.36141(5) Å, β = 97.7125(4)°, V = 641.465(6) Å^3. The integration of the data yielded a total of 34348 reflections with θ angles in the range of 5.64 to 68.17°, of which 2327 unique (R_{int} = 2.03%) and 2322 were greater than 2σ(F^2). The final anisotropic full-matrix least-squares refinement on F^2 with 182 parameters converged at R_1 = 2.37% for the observed 2σ(F^2) data and wR_2 = 6.26% for all data. The largest peak in the final difference electron density synthesis was 0.199 e Å^{-3} and the largest hole was -0.189 e Å^{-3}. The goodness-of-fit was 1.006. The absolute configuration was unambiguously determined from anomalous scattering, by calculating the x Flack parameter[6] of 0.01(3) using 1046 quotients.

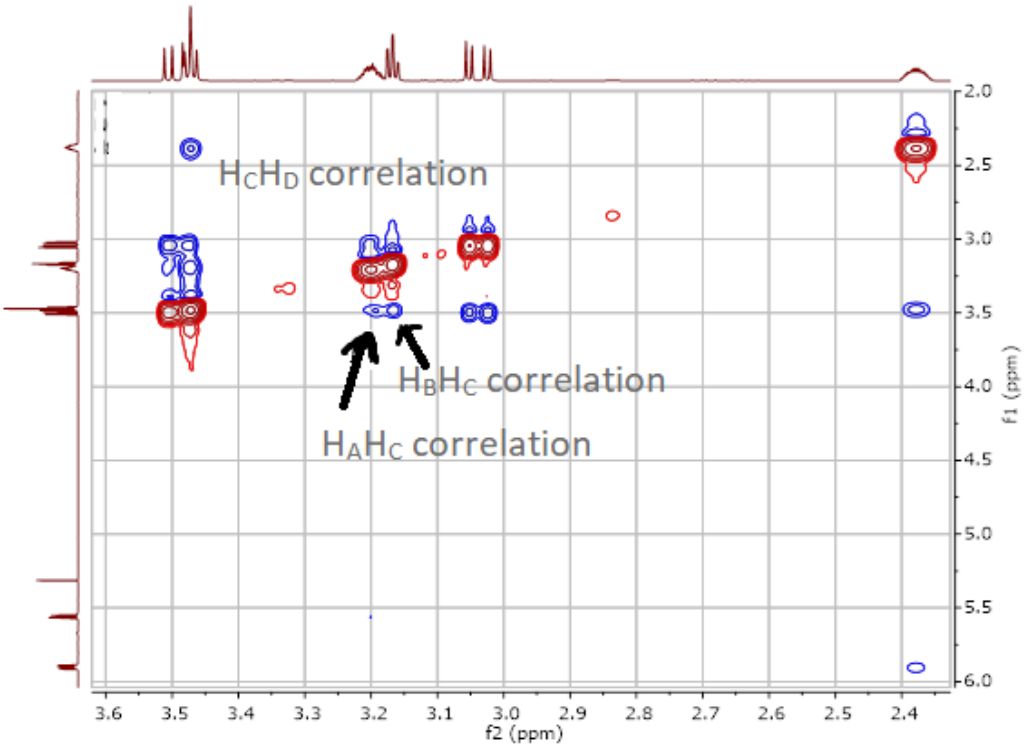
CCDC 1902497 (major-*ent*-**3e**) and 1896414 (minor-**3f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

[5] G. M. Sheldrick, *Acta Cryst.* 2015, **C71**, 3
[6] S. Parsons, H. D. Flack and T. Wagner, *Acta Cryst.* 2013, **B69**, 249

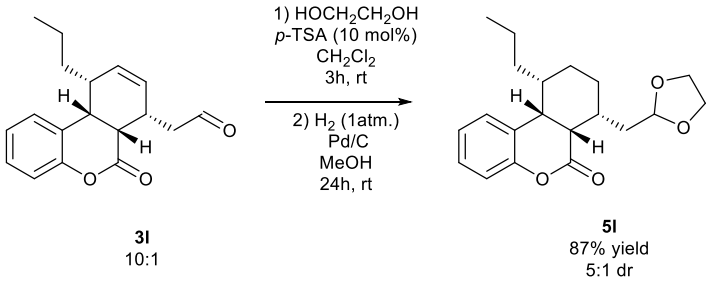
4. Relative configuration assignment



3.49 (dd, *J* = 19.6, 8.3 Hz, 1H, C<u>H</u>$_2$CHO), 3.47 (t, *J* = 6.1 Hz, 1H, H_C), 3.22–3.17 (m, 1H, H_A), 3.16 (td, *J* = 5.5, 1.1 Hz, 1H, H_B), 3.04 (ddd, *J* = 19.3, 6.3, 0.6 Hz, 1H, C<u>H</u>$_2$CHO), 2.38 (dddt, *J* = 11.0, 6.3, 4.2, 2.0 Hz, 1H, H_D).



5. Synthesis of (6a*S*,7*R*,10*R*,10a*R*)-7-((1,3-dioxolan-2-yl)methyl)-10-propyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-6-one 5l

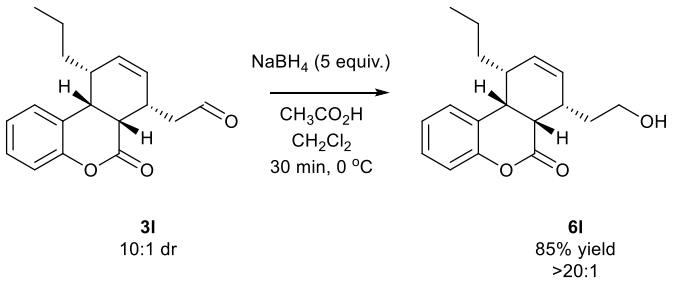


3l
10:1

5l
87% yield
5:1 dr

To a solution of the aldehyde **3l** (0.15 mmol) in CH_2Cl_2 (0.1 mL), ethylene glycol (0.30 mmol, 2 equiv.) and *p*-TSA•H_2O (0.015 mmol, 0.1 equiv.) were added. The reaction mixture was stirred for 2h at room temperature after which it was complete as confirmed by ^{1}H NMR spectroscopy. Hereafter, CH_2Cl_2 (10 mL), H_2O (5 mL), and sat. aq. $NaHCO_3$ (5 mL) were added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3x10 mL) and the combined organic extracts were concentrated under reduced pressure. Then 10% Pd/C (28.4 mg, 50 w/w%) was added and the solution was subjected to hydrogenolysis (1 atm.) for 20h. Subsequently, the reaction mixture was filtered through a short pad of Celite using CH_3OH (50 mL) as eluent. After removal of the solvents under reduced pressure, the residue was purified by FC on silica gel (hexane:diethyl ether 9:1) to afford pure product **5l** as white oil in 87% yield, 5:1 dr. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, $1H_{major + minor}$), 7.13 (dd, J = 7.6, 1.8 Hz, $1H_{major + minor}$), 7.11 – 7.07 (m, $1H_{major + minor}$), 7.01 (dd, J = 8.1, 1.2 Hz, $1H_{major + minor}$), 5.01 – 4.85 (m, $1H_{major + minor}$), 3.99 – 3.86 (m, $2H_{major + minor}$), 3.87 – 3.76 (m, $2H_{major + minor}$), 3.19 – 3.05 (m, $1H_{major + minor}$), 2.98 – 2.85 (m, $1H_{major}$), 2.52 – 2.42 (m, $1H_{minor}$), 2.34 (ddd, J = 14.4, 7.5, 5.3 Hz, $1H_{major + minor}$), 2.31 – 2.18 (m, $2H_{minor}$), 2.16 – 2.11 (m, $1H_{minor}$), 2.09 – 2.03 (m, $1H_{major + minor}$), 1.97 – 1.89 (m, $2H_{major}$), 1.85 (dtt, J = 11.8, 4.7, 2.4 Hz, $1H_{major}$), 1.79 (qd, J = 13.3, 3.2 Hz, $1H_{major}$), 1.72 (dt, J = 15.2, 7.4 Hz, $1H_{minor}$), 1.65 – 1.55 (m, $1H_{major + minor}$), 1.55 – 1.46 (m, $1H_{major}$), 1.37 – 1.22 (m, $2H_{major + minor}$), 1.20 – 1.11 (m, $1H_{minor}$), 0.96 – 0.85 (m, $1H_{major + minor}$), 0.85 – 0.77 (m, $1H_{major}$), 0.75 (t, J = 7.4 Hz, $3H_{minor}$), 0.68 (t, J = 7.2 Hz, $3H_{major}$). ^{13}C NMR (176 MHz, $CDCl_3$) δ_{major} 170.1, 151.9, 128.1, 127.5, 127.0, 124.1, 116.4, 103.8, 64.8, 64.7, 44.0, 40.5, 38.9, 37.5, 35.4, 28.8, 27.4, 22.9, 21.3, 13.9. δ_{minor} 168.8, 150.8, 135.1, 129.4, 128.5, 123.9, 116.7, 103.8, 64.8, 64.7, 42.1, 42.0, 38.9, 37.6, 36.4, 33.4, 31.9, 29.1, 21.4, 13.7. HRMS: calculated for [$C_{20}H_{26}O_4$+H^+]: 331.1904, found: 331.1913.

6. Synthesis of (6a*S*,7*S*,10*R*,10a*R*)-7-(2-hydroxyethyl)-10-propyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-6-one 6l

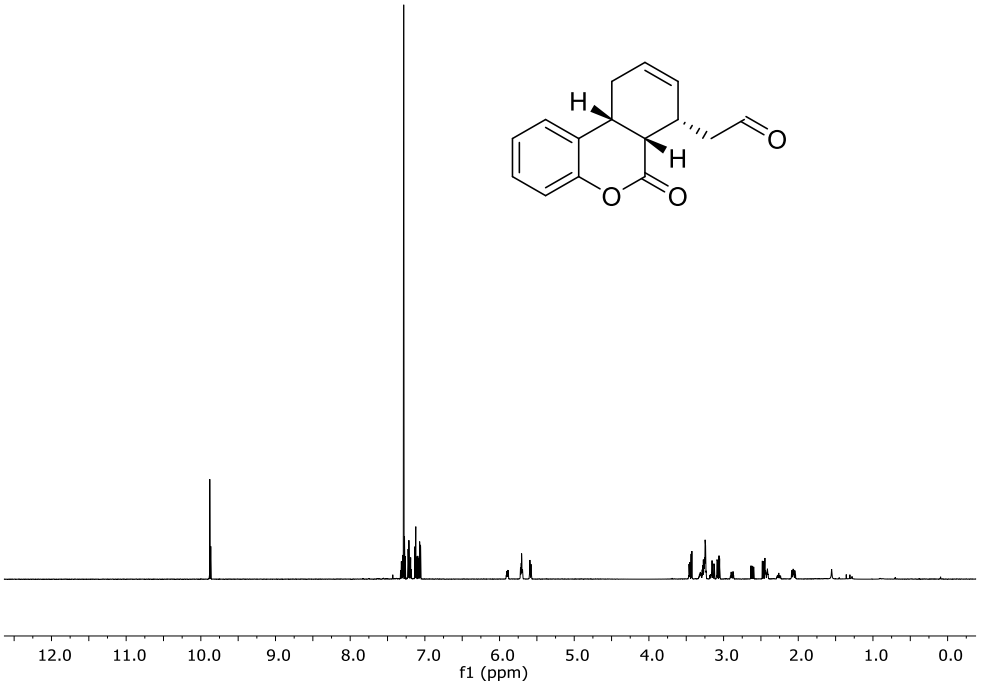


In an ordinary 4 mL glass vial, equipped with magnetic stirring bar aldehyde **3l** (1 equiv, 0.1 mmol) was dissolved in CH_2Cl_2 (0.2 mL) and glacial acetic acid (0.4 mL) and the resulting solution was cooled in cold water bath. Subsequently, sodium borohydride (5 equiv, 19 mg) was added, and reaction was stirred for 30 min. at room temperature. Reaction was quenched with water (5 mL), extracted with dichloromethane (3x10 mL). Combined organic layers were washed with saturated aqueous solution of sodium bicarbonate (1x5 mL) and water (1x5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. Pure product **6l** was isolated by flash chromatography on silica gel (eluent: hexane:acetone 80:20) as a white oil in 85% yield, >20:1 dr. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.25 – 7.22 (m, 1H), 7.13 (dd, J = 7.5, 1.7 Hz, 1H), 7.08 (td, J = 7.4, 1.2 Hz, 1H), 7.01 (dd, J = 8.2, 1.1 Hz, 1H), 5.88 – 5.76 (m, 1H), 5.70 – 5.60 (m, 1H), 3.74 (ddd, J = 6.7, 5.6, 1.4 Hz, 2H), 3.38 (dd, J = 7.2, 5.5 Hz, 1H), 2.93 (td, J = 5.4, 1.1 Hz, 1H), 2.75 (dtt, J = 10.2, 5.0, 2.6 Hz, 1H), 2.33 (ddt, J = 11.5, 7.2, 2.3 Hz, 1H), 2.28 (dddd, J = 14.1, 8.4, 6.5, 5.6 Hz, 1H), 2.09 – 2.03 (m, 1H), 1.30 – 1.36 (m, 2H), 1.11 – 1.05 (m, 1H), 1.01 – 0.93 (m, 1H), 0.90 – 0.86 (m, 1H), 0.66 (t, J = 7.3 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.7, 152.3, 128.6, 128.6, 128.3, 127.5, 127.2, 124.1, 116.5, 60.9, 40.7, 39.1, 38.0, 35.2, 33.6, 33.0, 21.0, 13.9. HRMS: calculated for [$C_{18}H_{22}O_3$+H^+]: 287.1642, found: 287.1639.

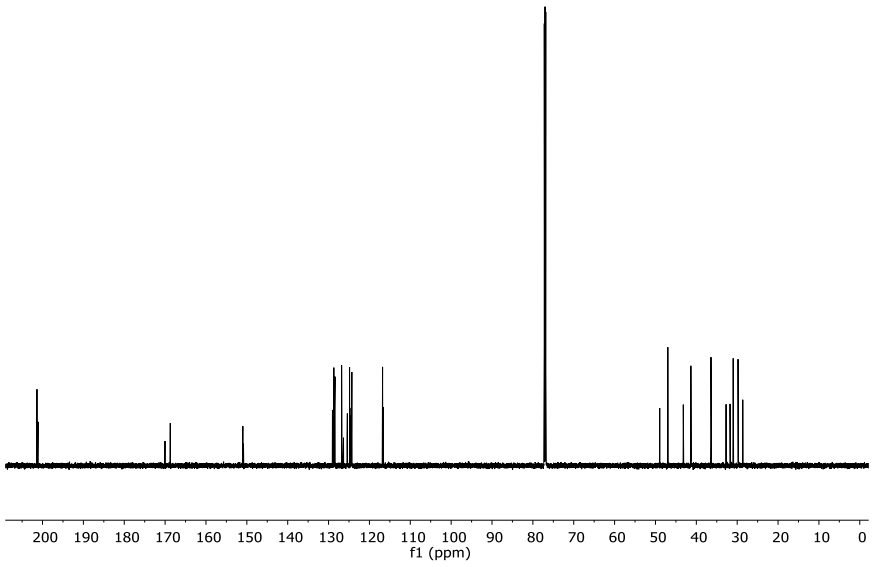
7. NMR Data

(3a) 2-((6a*S*,7*S*,10a*R*)-6-Oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

^{1}H NMR

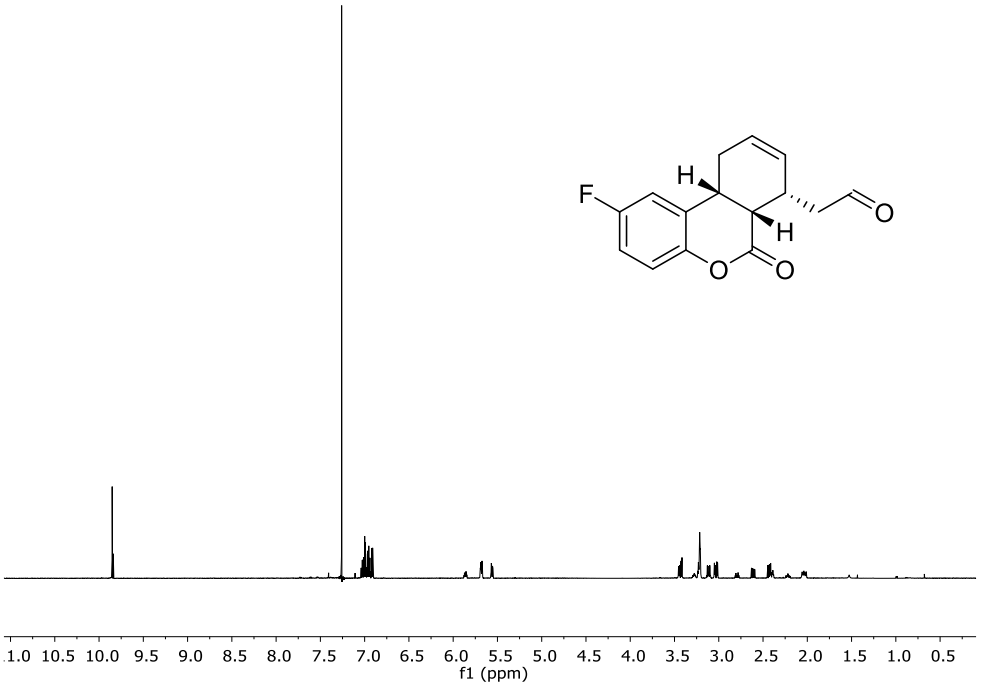


^{13}C NMR

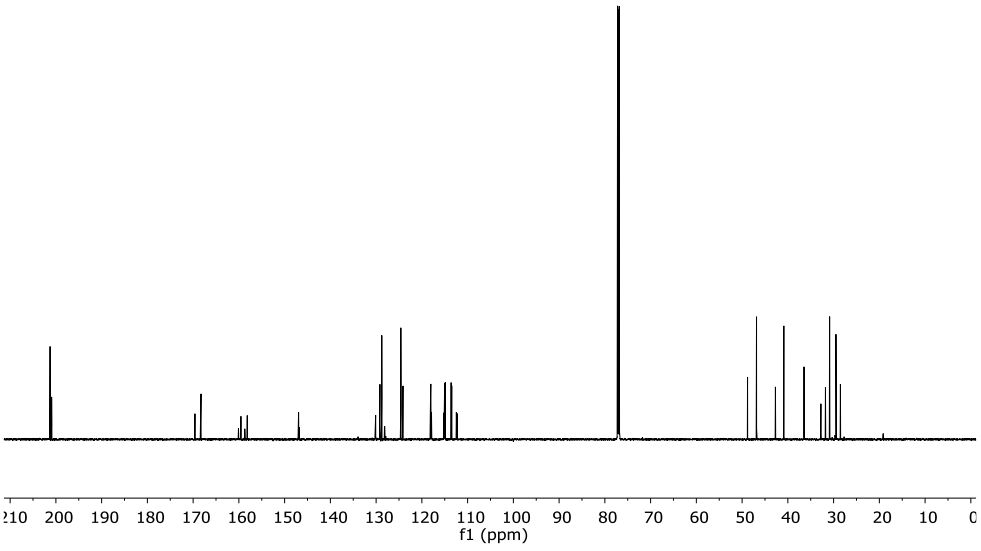


(3b) 2-((6a*S*,7*S*,10a*R*)-2-Fluoro-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

^{1}H NMR

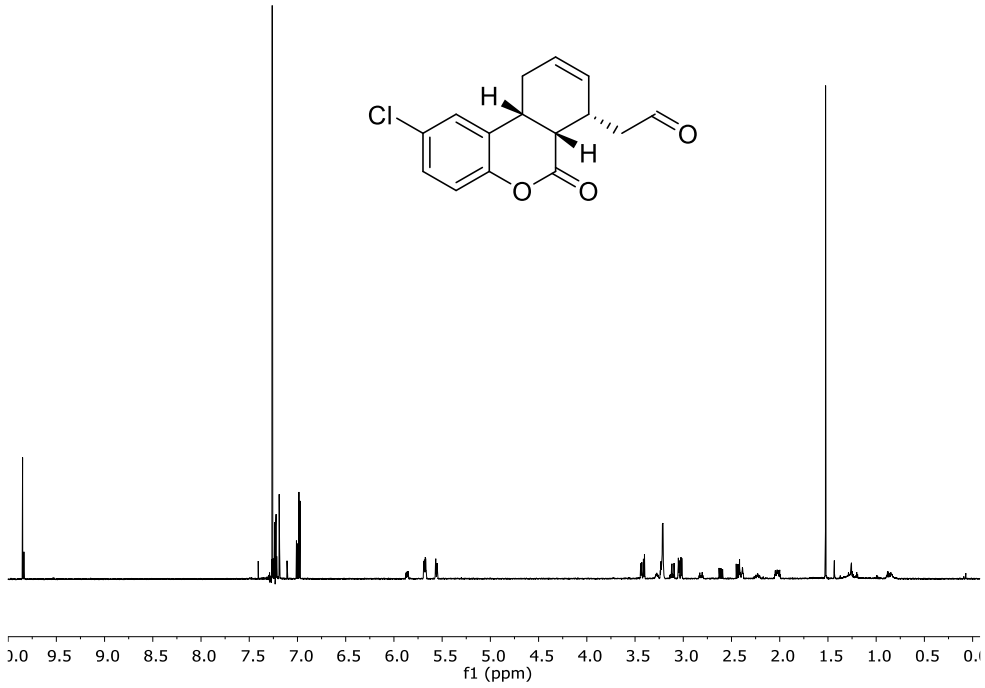


^{13}C NMR

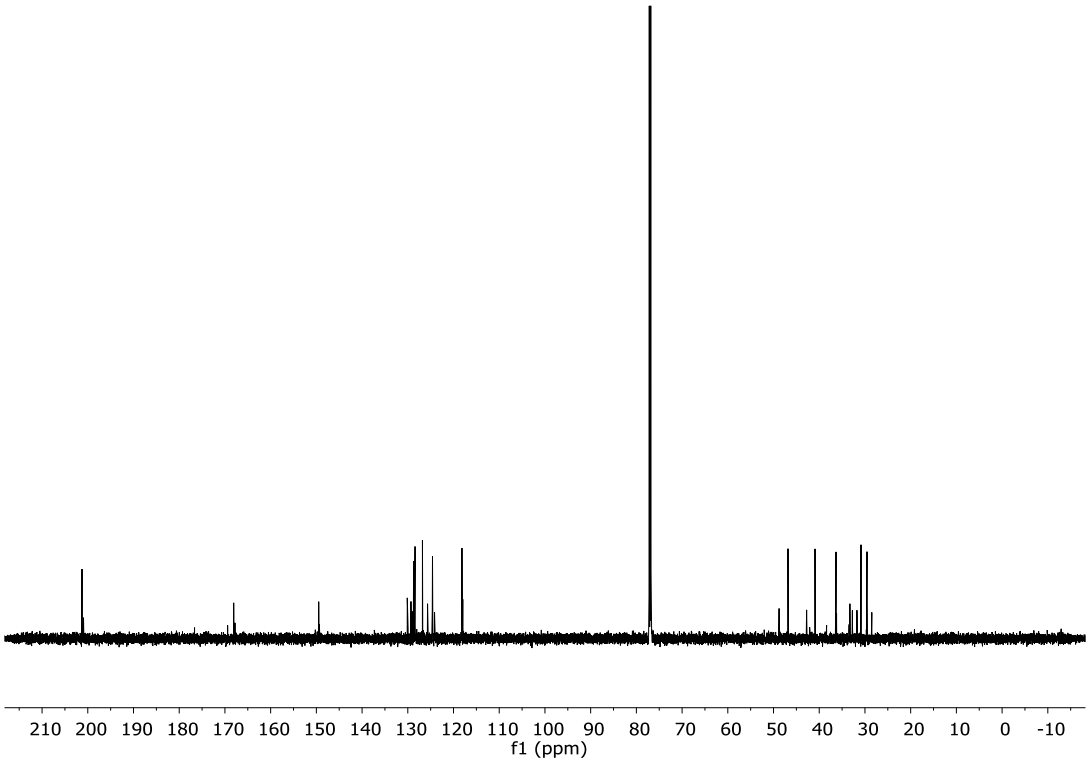


(3c) 2-((6a*S*,7*S*,10a*R*)-2-Chloro-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

^{1}H NMR

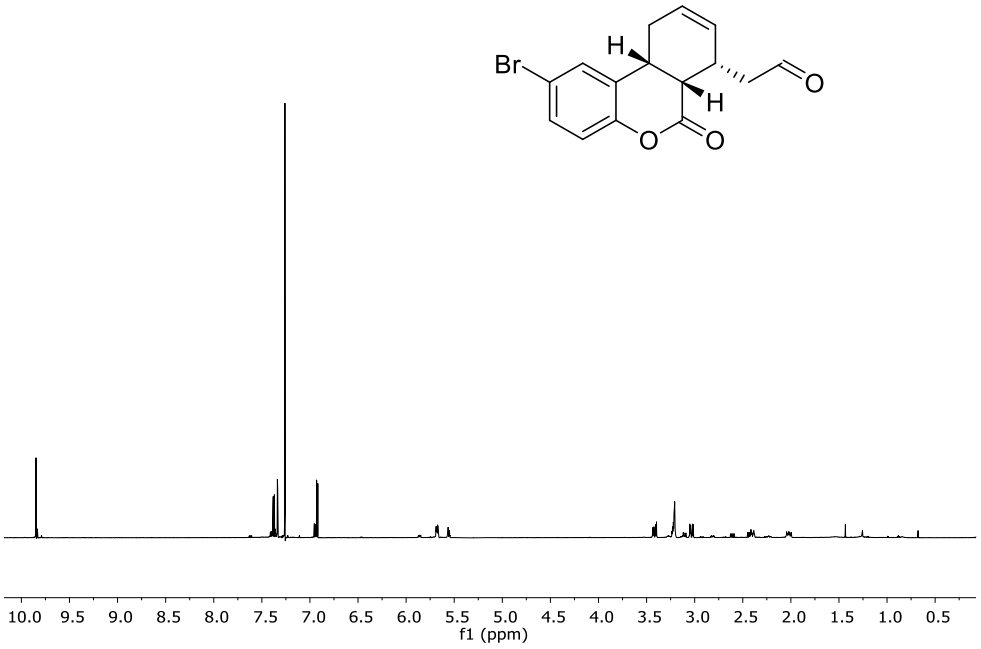


^{13}C NMR

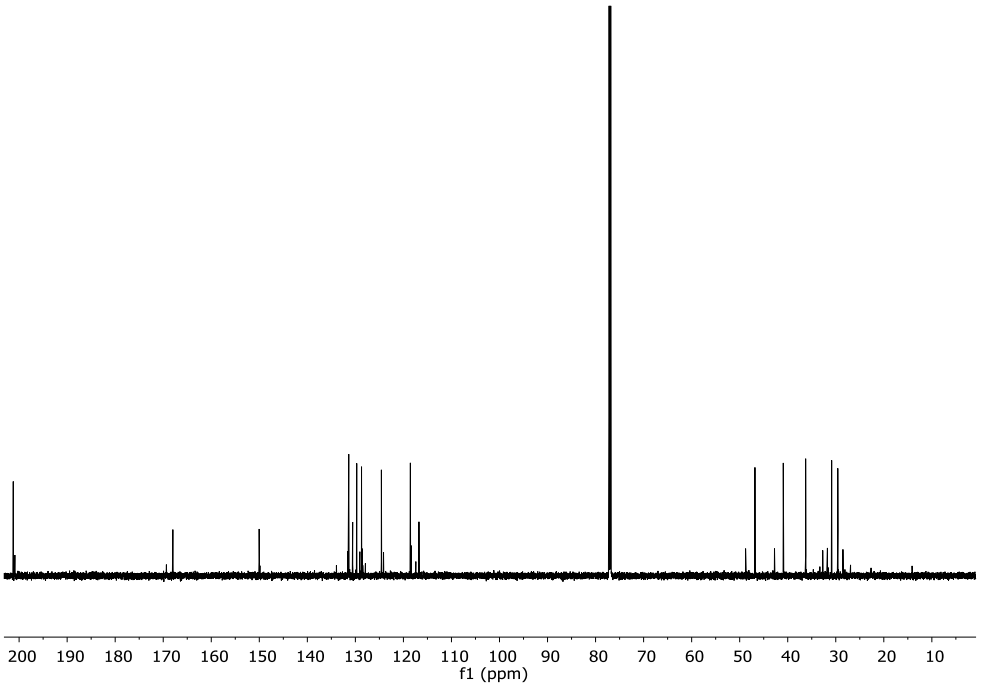


(3d) 2-((6a*S*,7*S*,10a*R*)-2-Bromo-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

^{1}H NMR

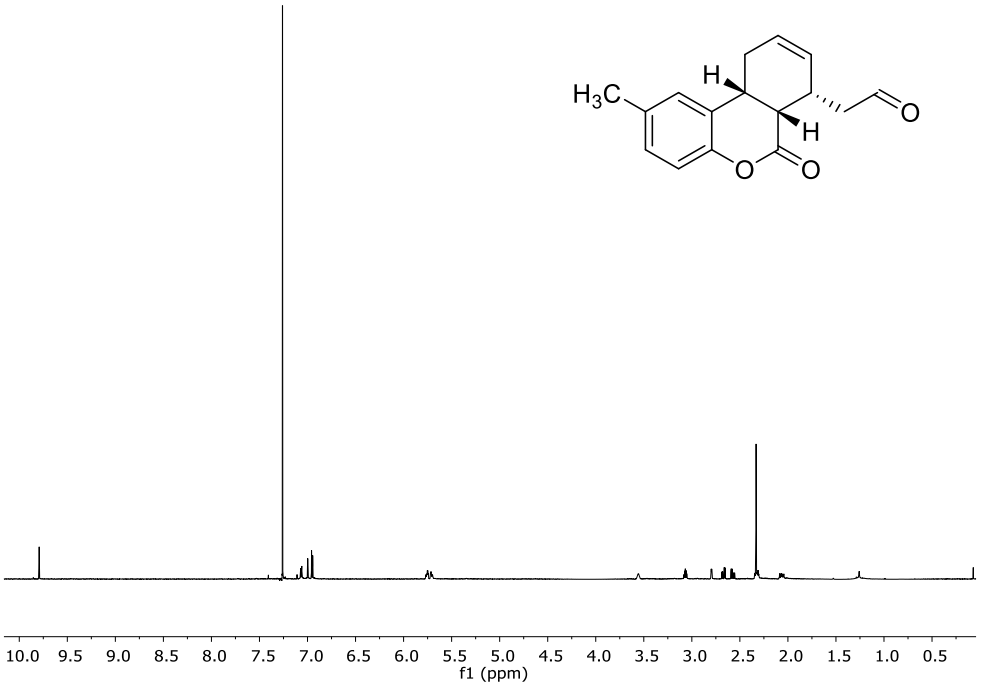


^{13}C NMR

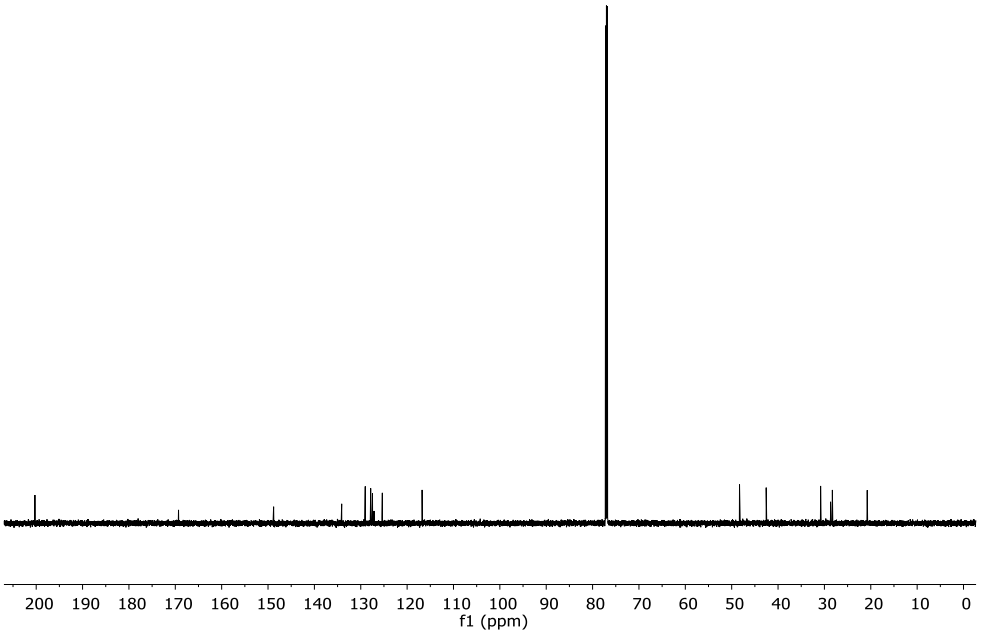


(3e) 2-((6a*S*,7*S*,10a*R*)-2-Methyl-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

^{1}H NMR

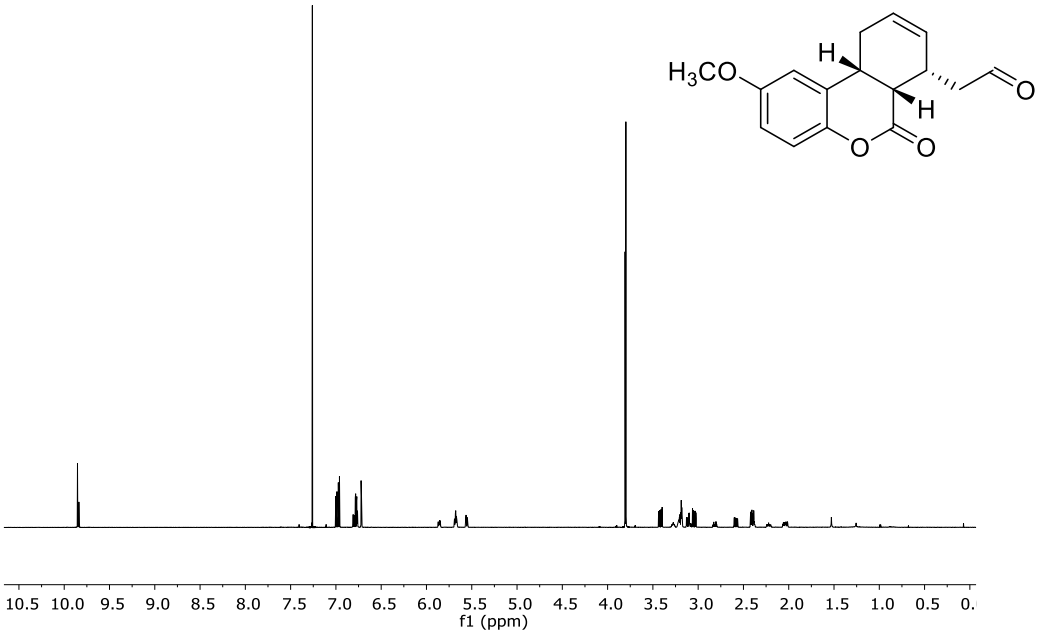


^{13}C NMR

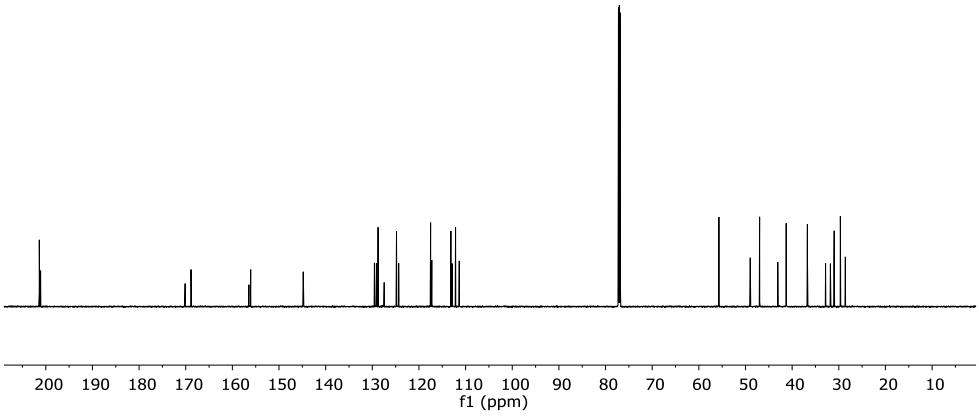


(3f) 2-((6a*S*,7*S*,10a*R*)-2-Methoxy-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

^{1}H NMR

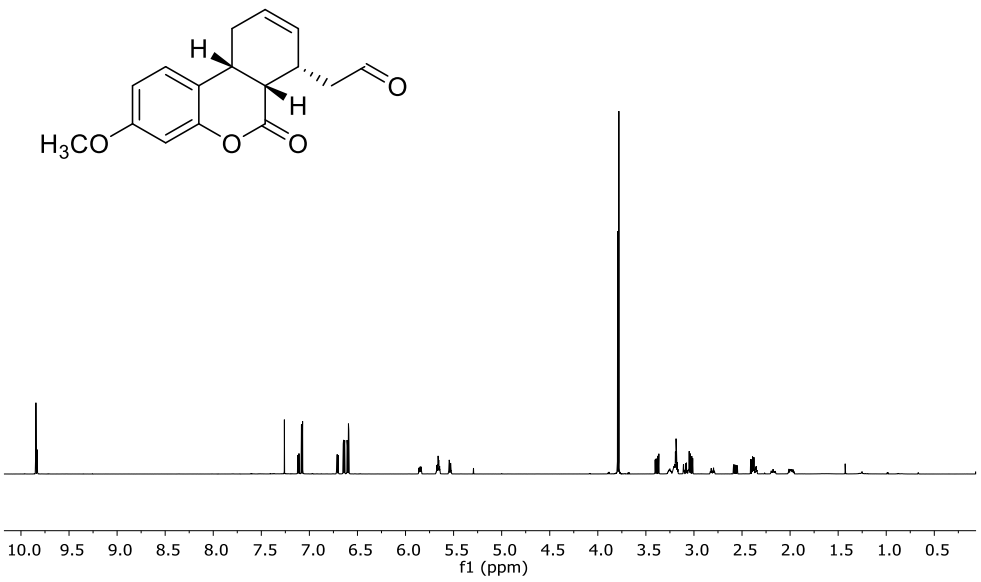


^{13}C NMR

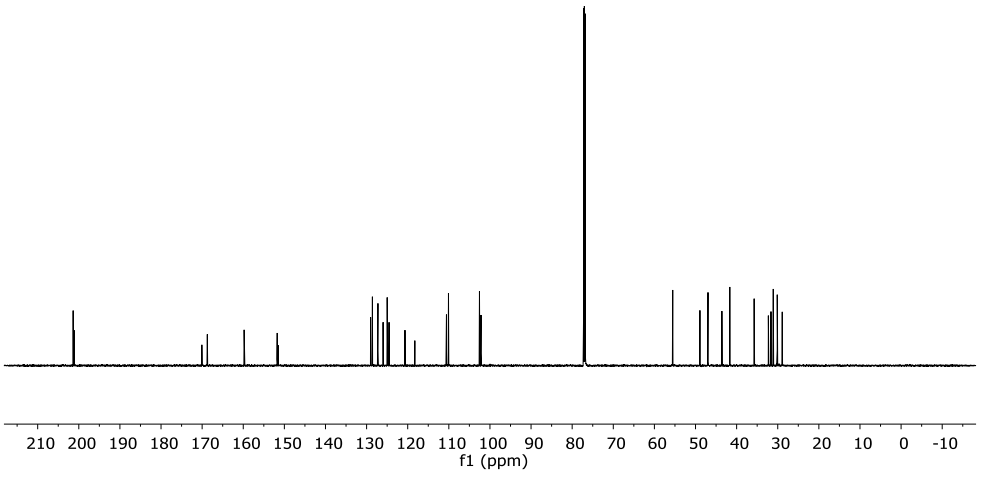


(3g) 2-((6a*S*,7*S*,10a*R*)-3-Methoxy-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

^{1}H NMR

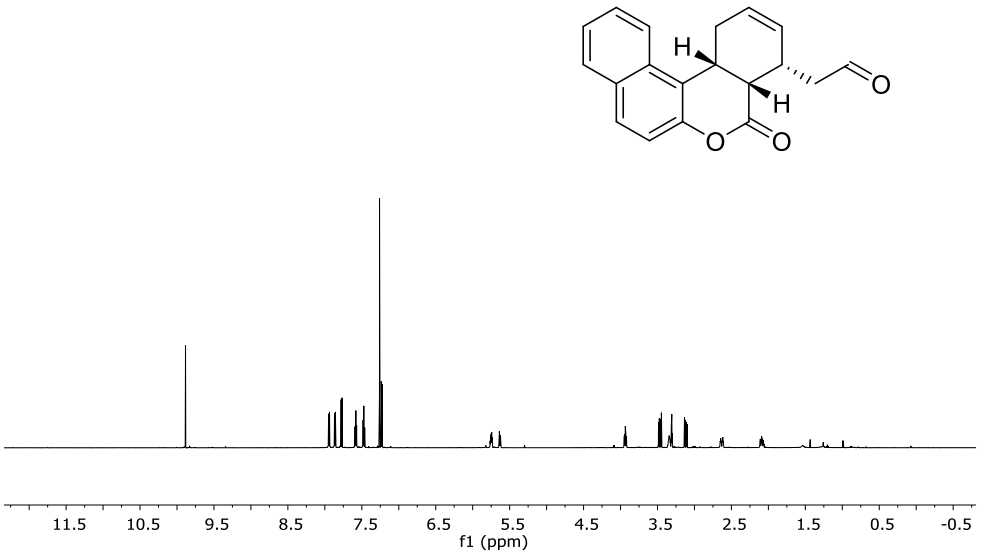


^{13}C NMR

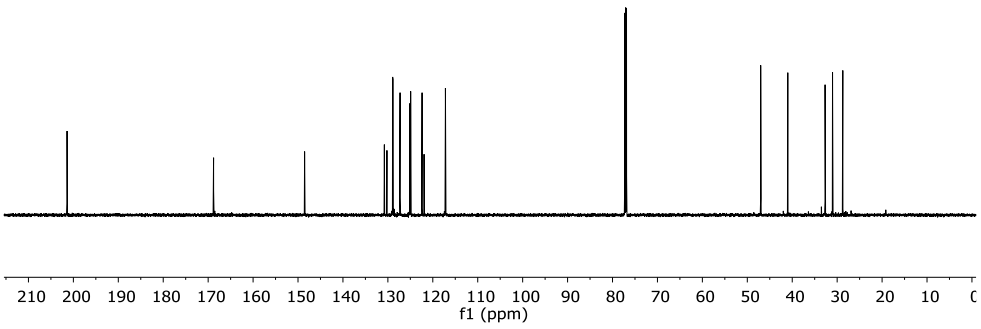


(3h) 2-((6a*S*,7*S*,10a*R*)-6-Oxo-6a,7,10,10a-tetrahydro-6*H*-dibenzo[c,h]chromen-7-yl)acetaldehyde

^{1}H NMR

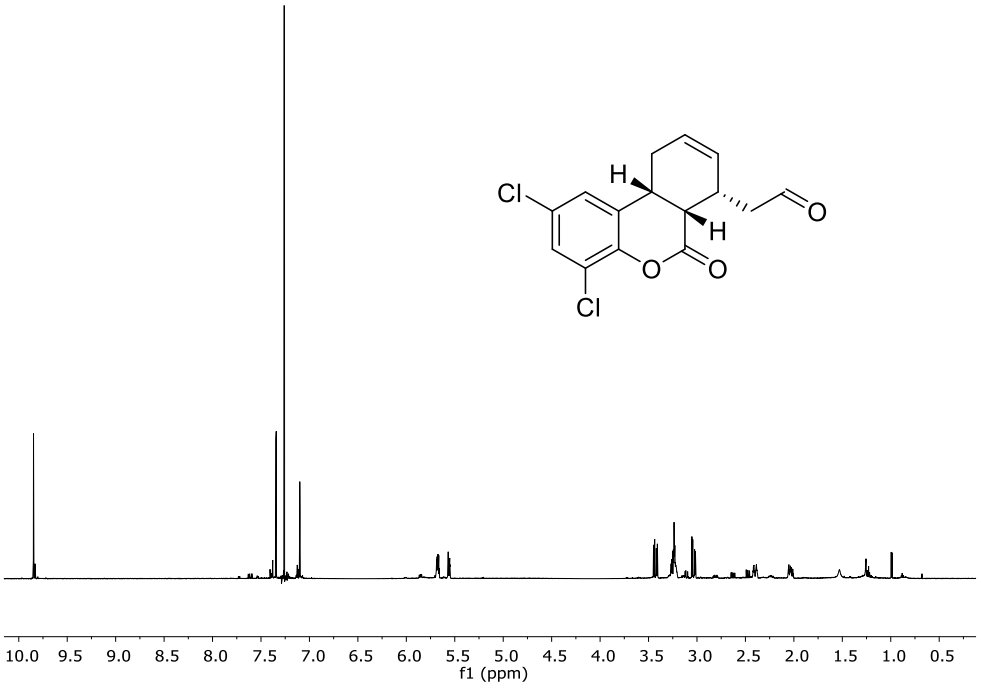


^{13}C NMR

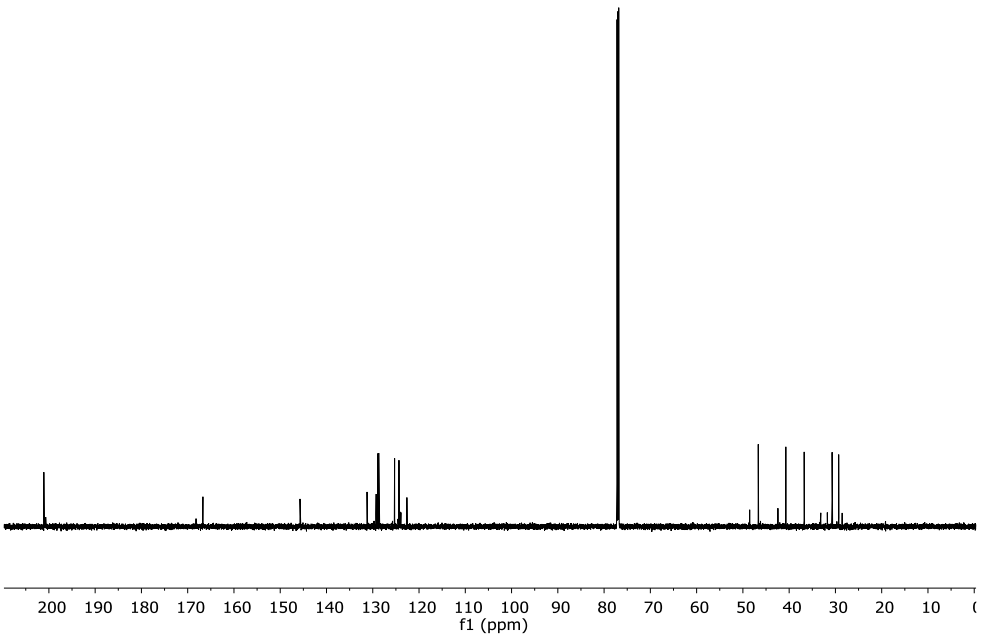


(3i) 2-((6a*S*,7*S*,10a*R*)-2,4-Dichloro-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

^{1}H NMR

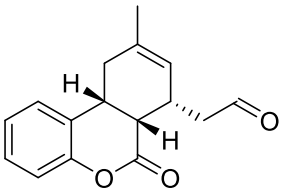


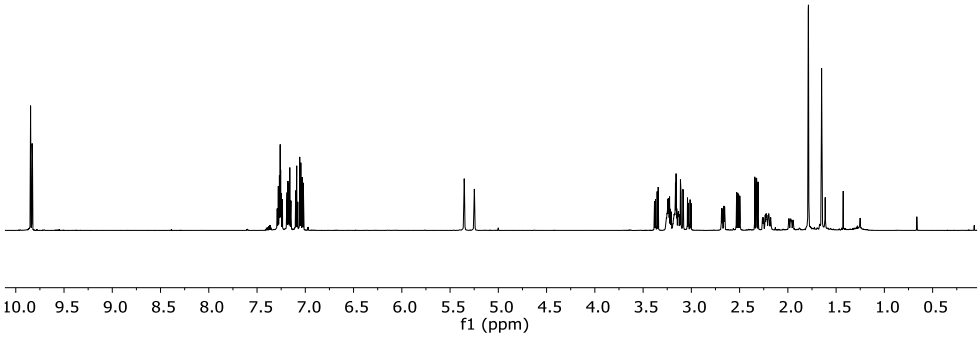
^{13}C NMR



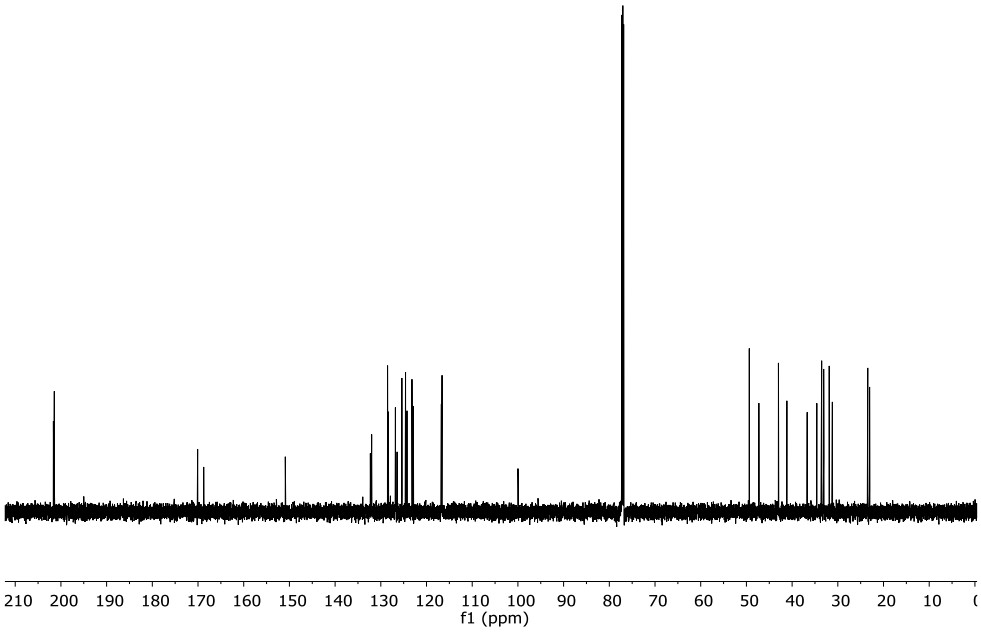
(3j) 2-((6a*S*,7*S*,10a*R*)-9-Methyl-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

^{1}H NMR



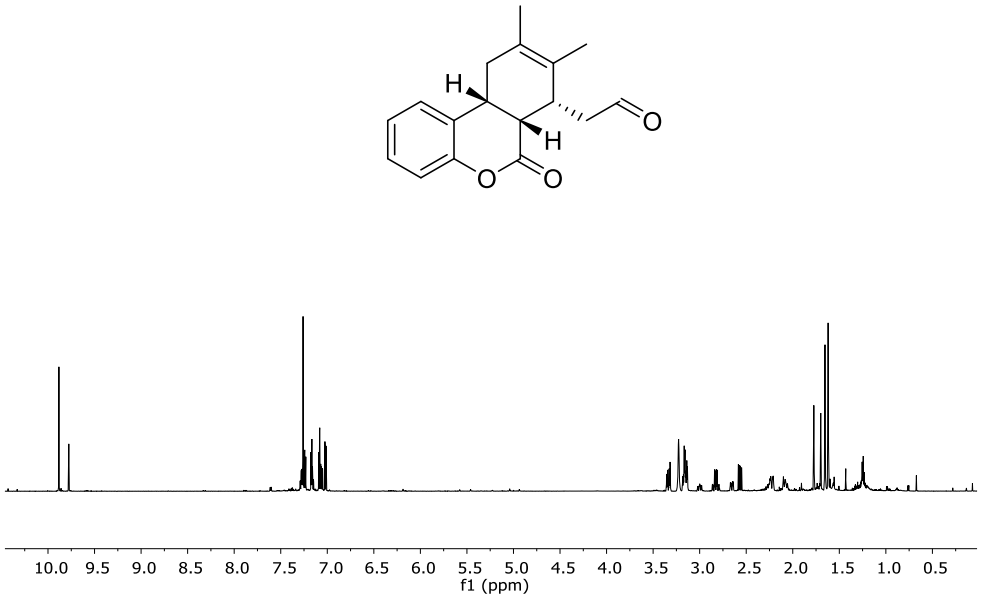


^{13}C NMR

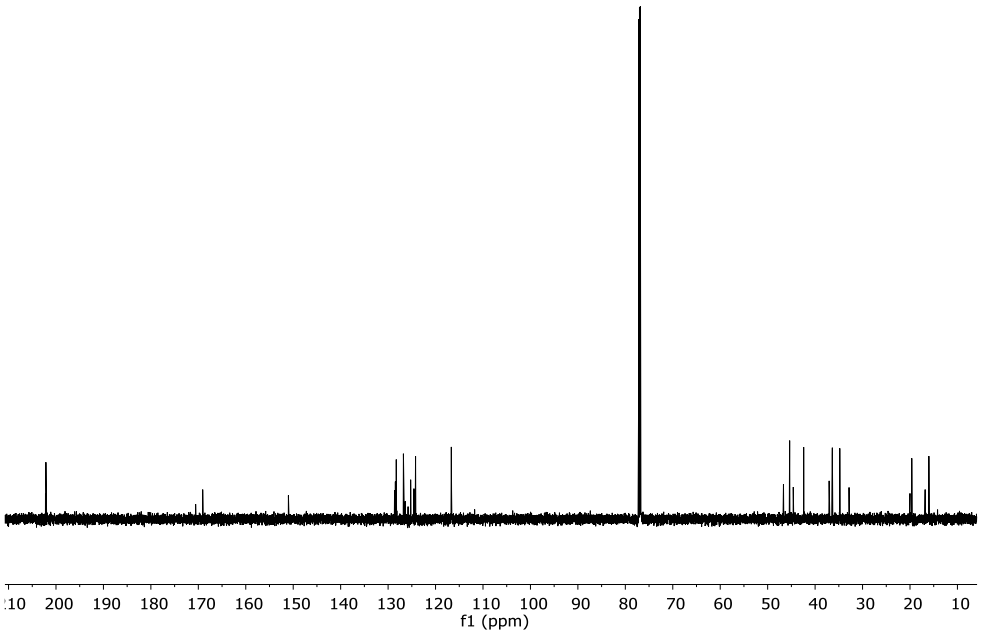


(3k) 2-((6a*S*,7*R*,*10aR*)-8,9-Dimethyl-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

^{1}H NMR

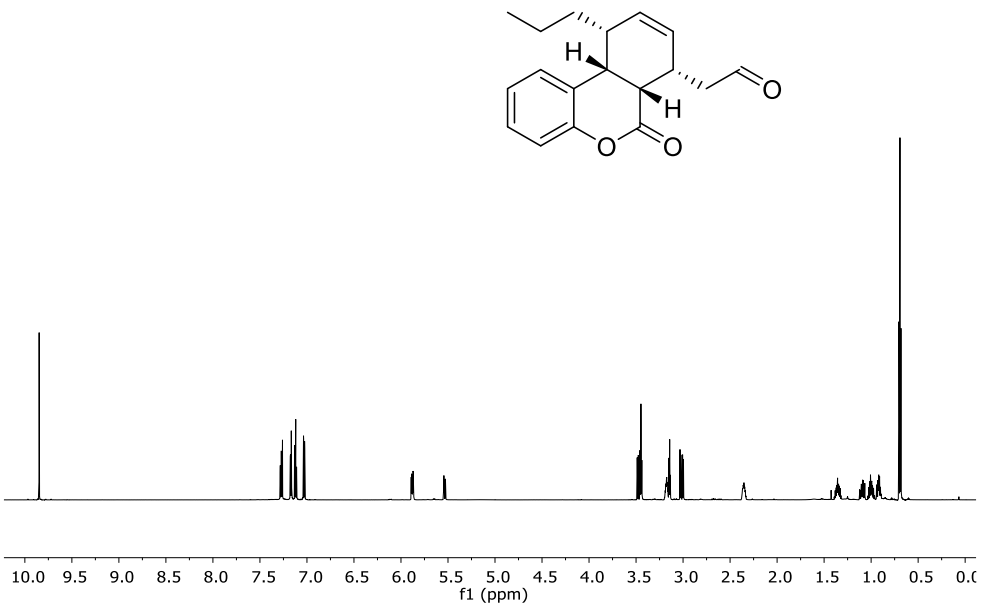


^{13}C NMR

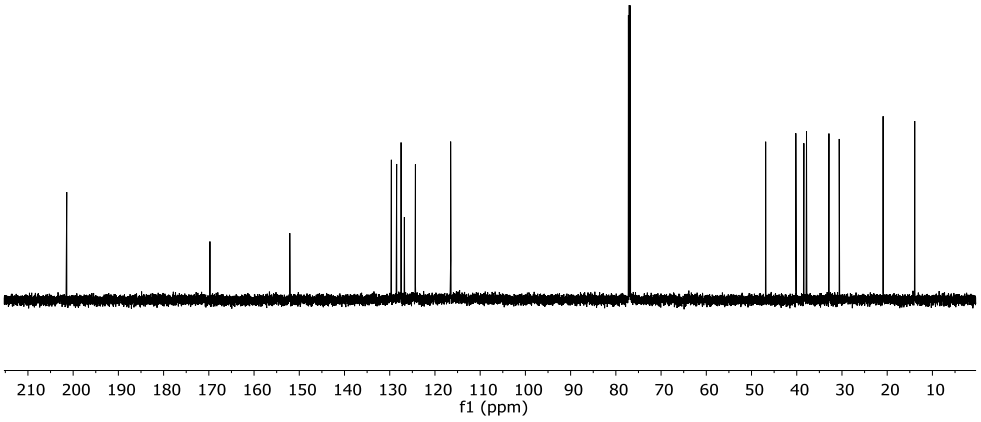


(3l) 2-((6a*S*,7*S*,10*R*,10a*R*)-6-Oxo-10-propyl-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

^{1}H NMR

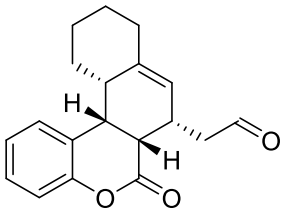


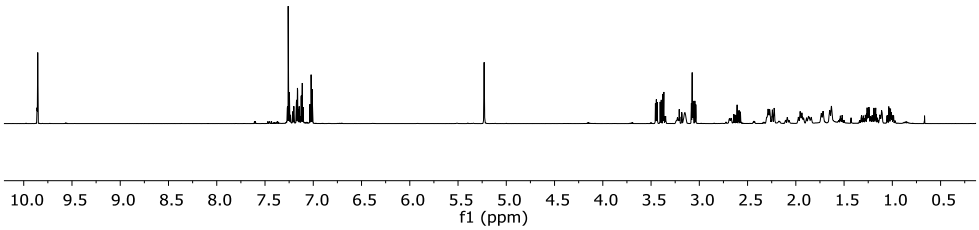
^{13}C NMR



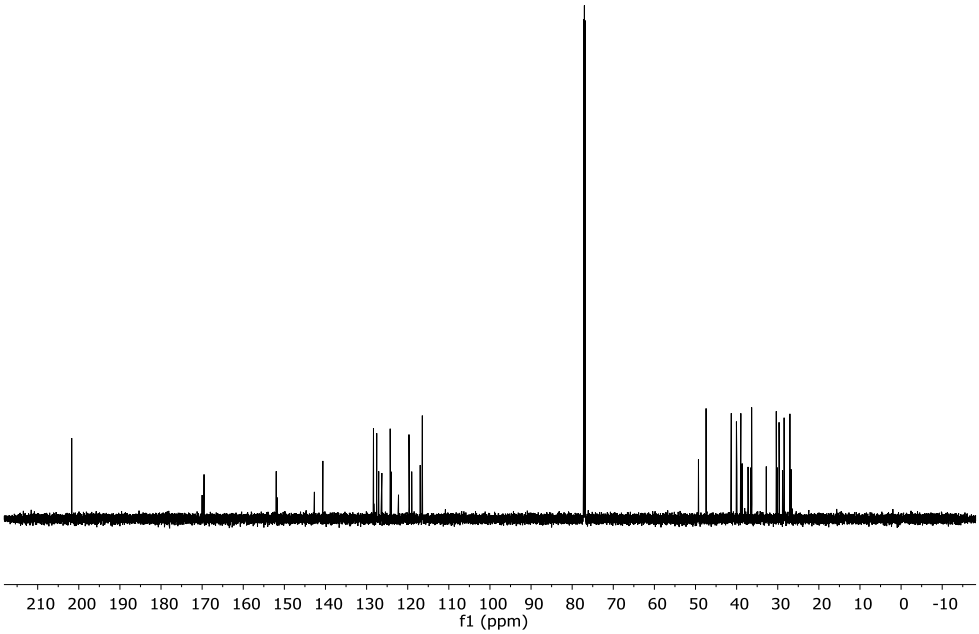
(3m) 2-((6a*S*,7*S*,12a*S*,12b*R*)-6-Oxo-6a,7,9,10,11,12,12a,12b-octahydro-6*H*-naphtho[2,1-c]chromen-7-yl)acetaldehyde

^{1}H NMR



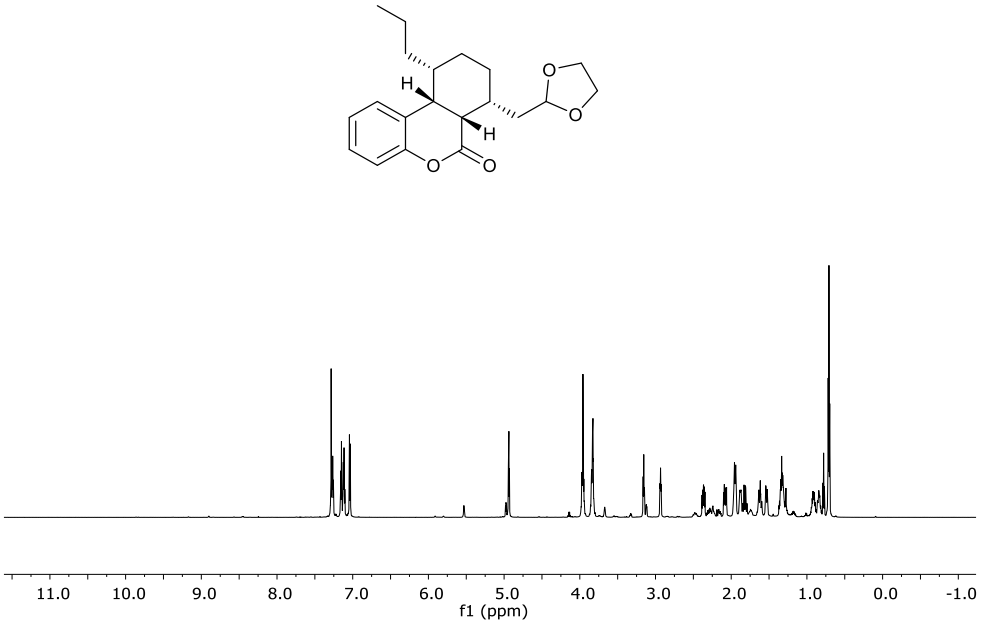


^{13}C NMR

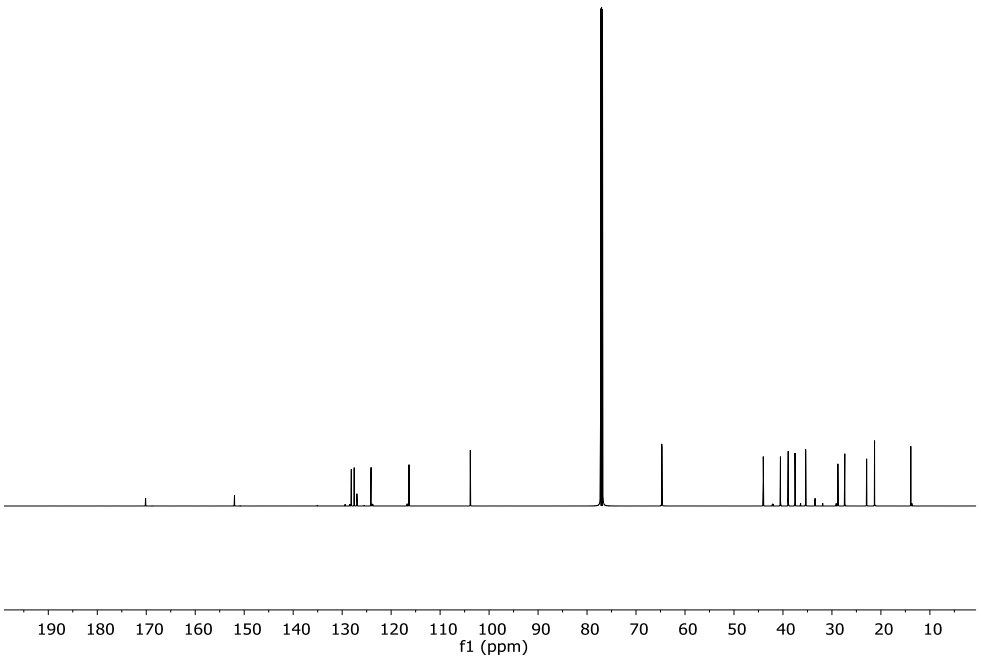


(5l) (6a*S*,7*R*,10*R*,10a*R*)-7-((1,3-Dioxolan-2-yl)methyl)-10-propyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-6-one

^{1}H NMR

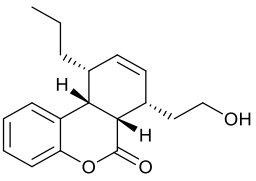


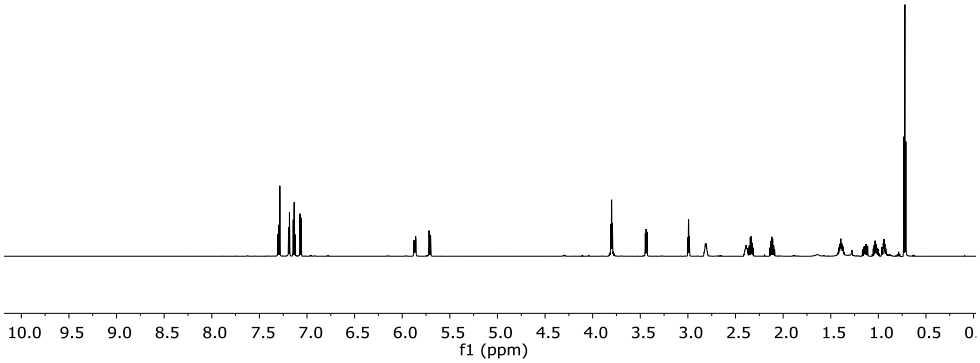
^{13}C NMR



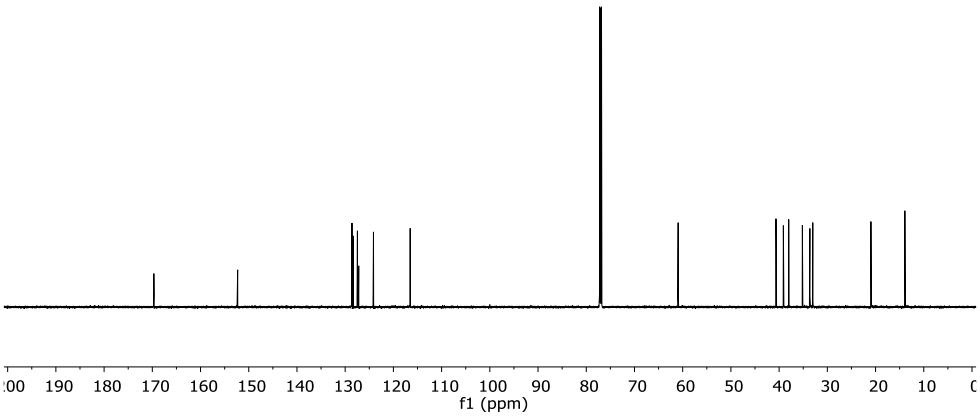
(6l) (6a*S*,7*S*,10*R*,10a*R*)-7-(2-Hydroxyethyl)-10-propyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-6-one

^{1}H NMR



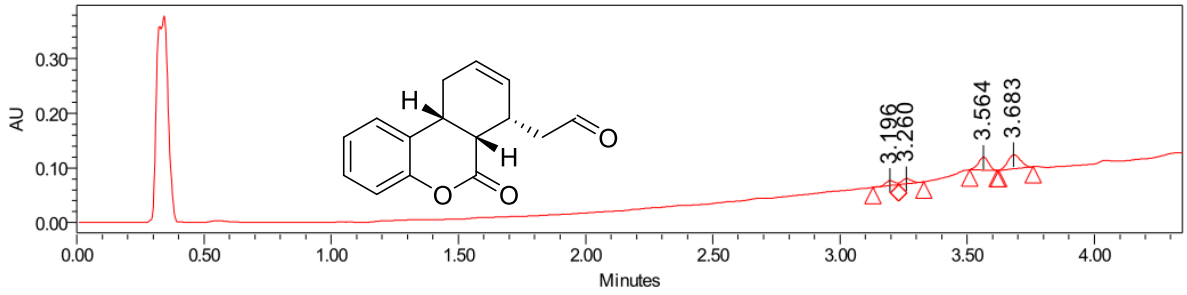


^{13}C NMR

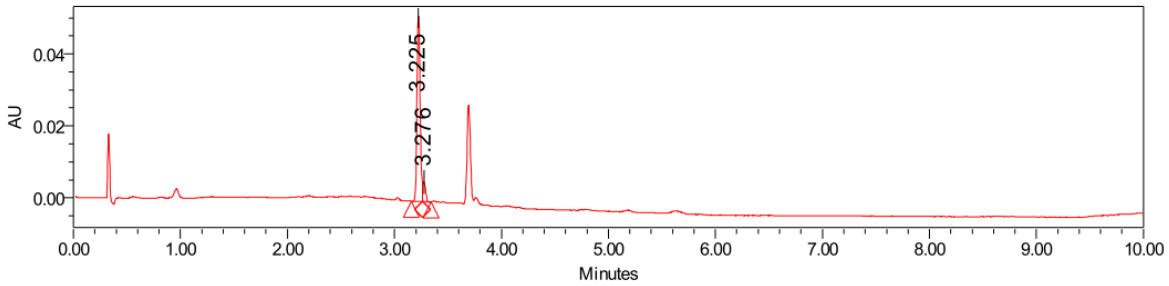


4. HPLC traces

(3a) 2-((6a*S*,7*S*,10a*R*)-6-Oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

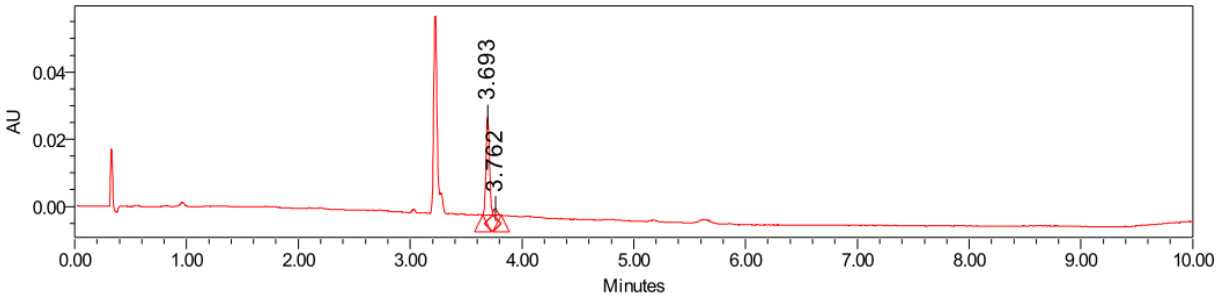


Major diastereoisomer



	RT	Area	% Area	Height
1	3.225	106960	93.48	51734
2	3.276	9956	6.52	5467

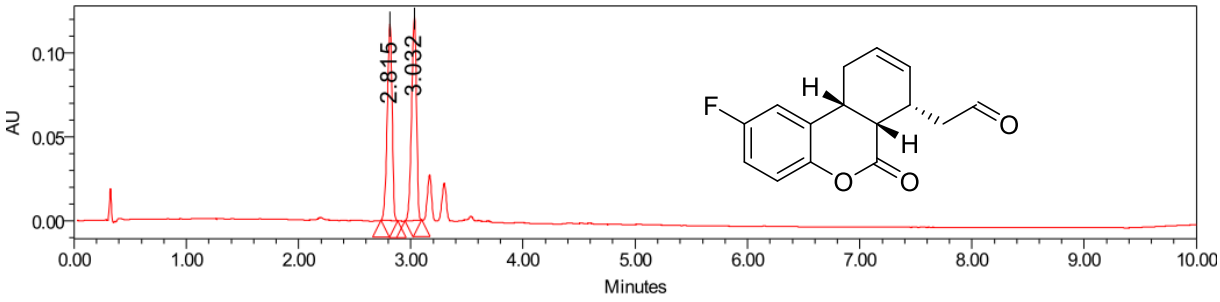
Minor diastereoisomer

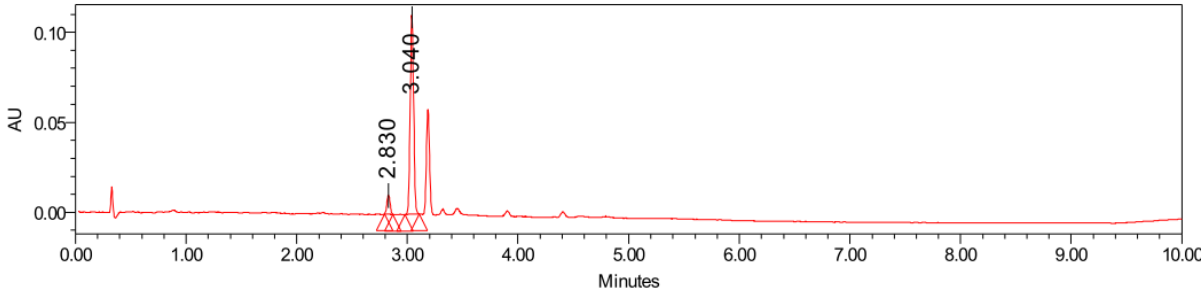


	RT	Area	% Area	Height
1	3.693	62893	96.52	29137
2	3.762	4360	3.48	1901

(3b) 2-((6a*S*,7*S*,10a*R*)-2-Fluoro-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

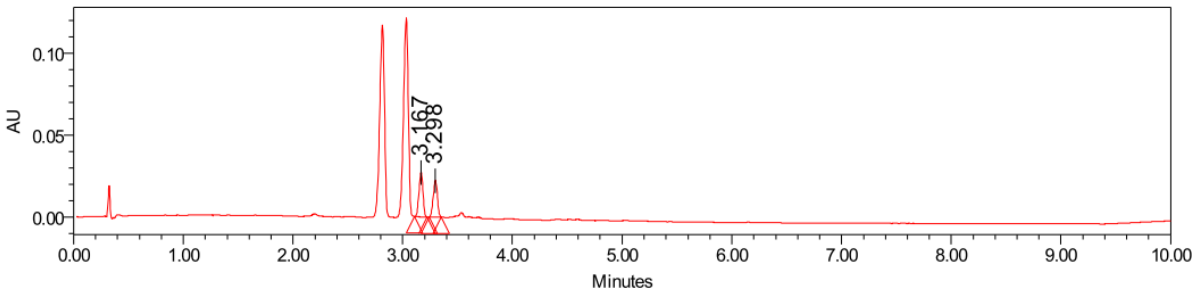
Major diastereoisomer

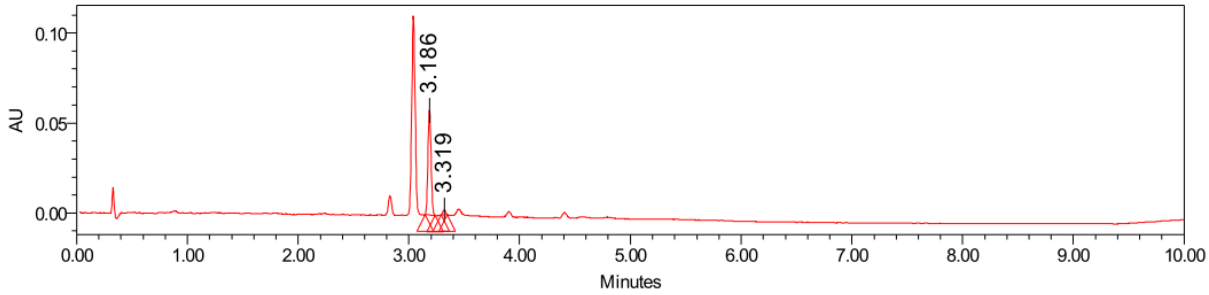




	RT	Area	% Area	Height
1	2.830	21165	8.14	10419
2	3.040	238691	91.86	110578

Minor diastereoisomer

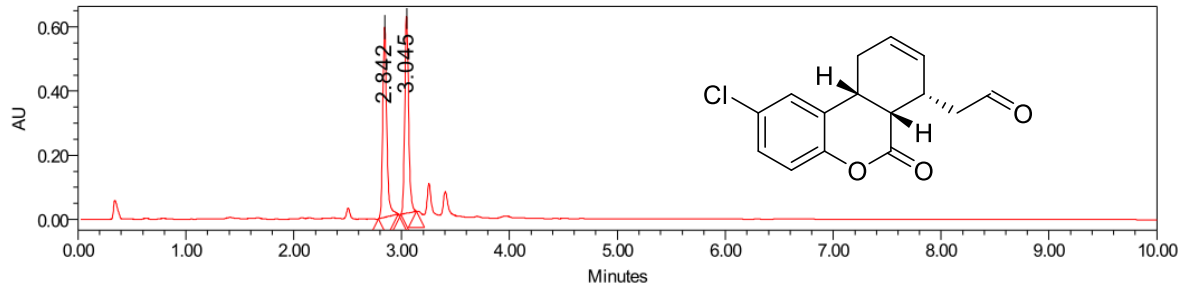


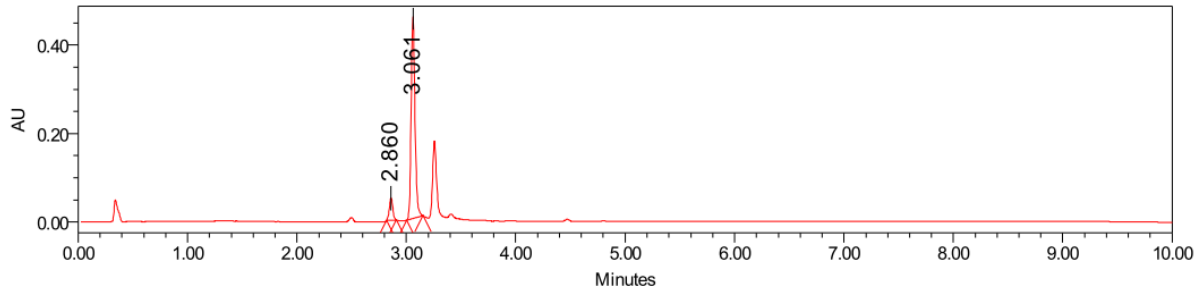


	RT	Area	% Area	Height
1	3.186	115153	96.07	58432
2	3.319	4709	3.93	2713

(3c) 2-((6a*S*,7*S*,10a*R*)-2-Chloro-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

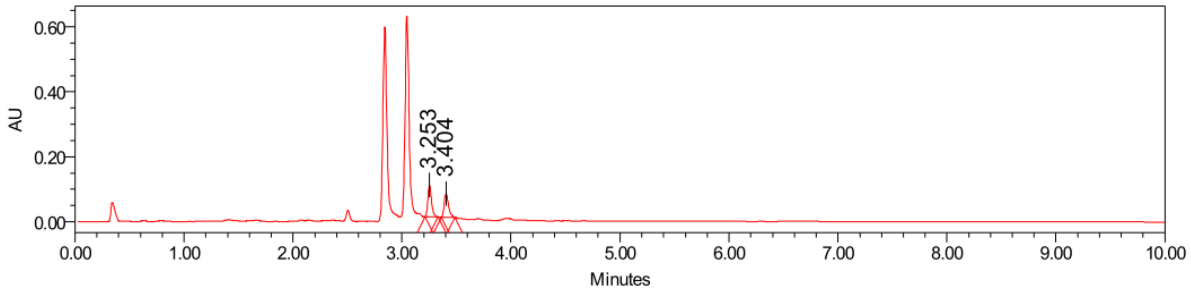
Major diastereoisomer

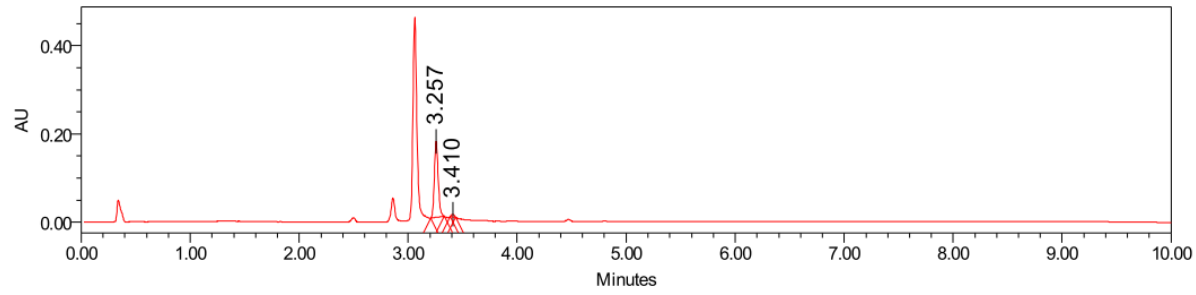




	RT	Area	% Area	Height
1	2.860	109570	8.99	49881
2	3.061	1108580	91.01	456789

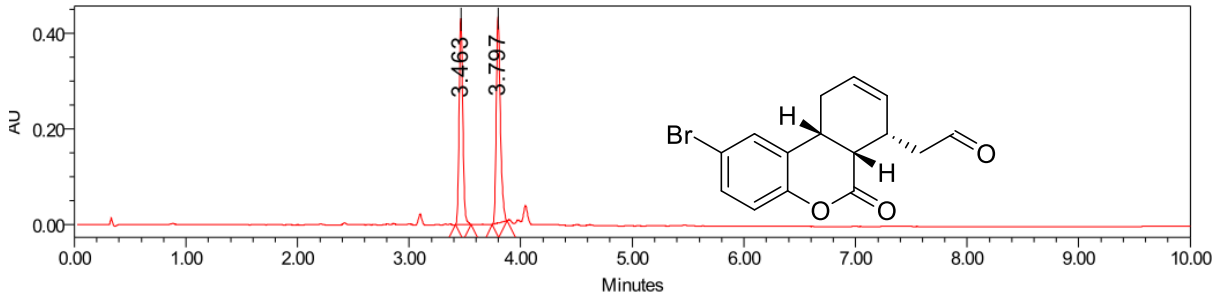
Minor diastereoisomer

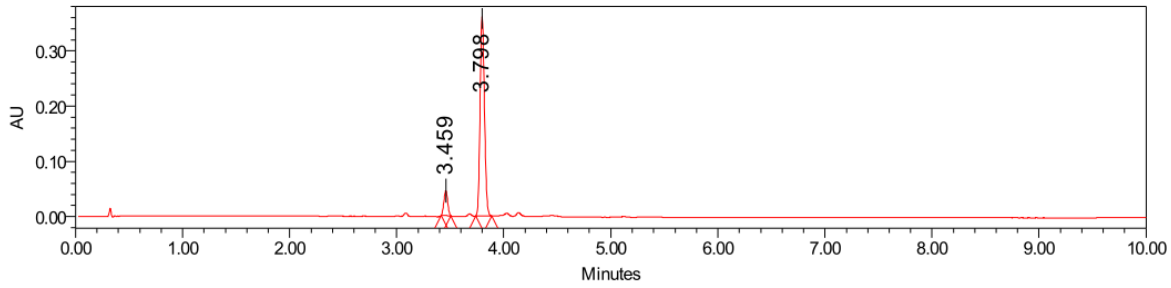




	RT	Area	% Area	Height
1	3.257	418345	97.59	172537
2	3.410	10341	2.41	5906

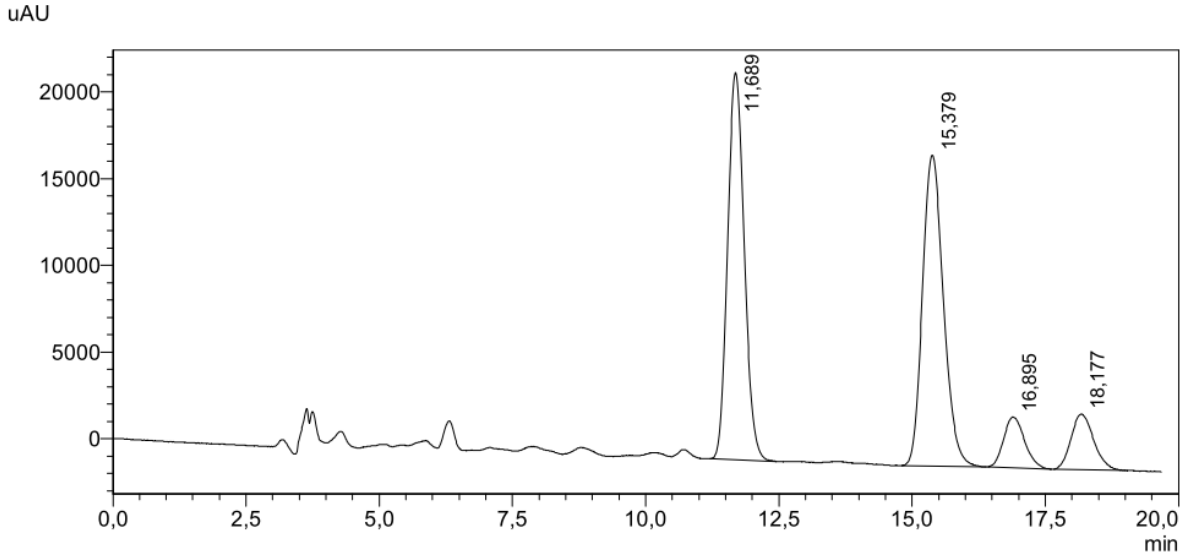
(3d) 2-((6a*S*,7*S*,10a*R*)-2-Bromo-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde



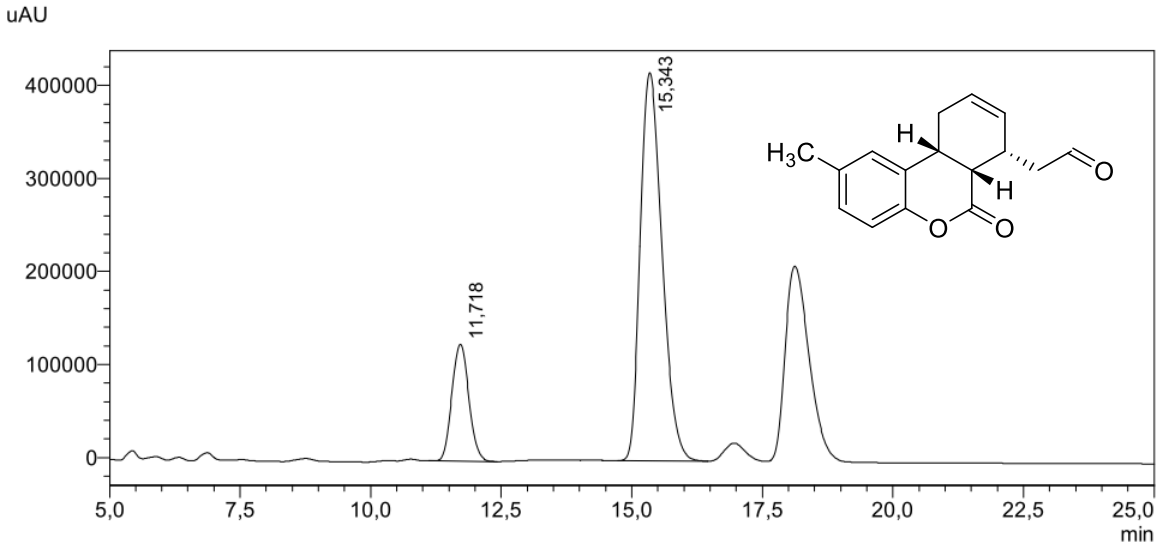


	RT	Area	% Area	Height
1	3.459	109802	9.63	44953
2	3.798	1030281	90.37	362226

(3e) 2-((6a*S*,7*S*,10a*R*)-2-Methyl-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

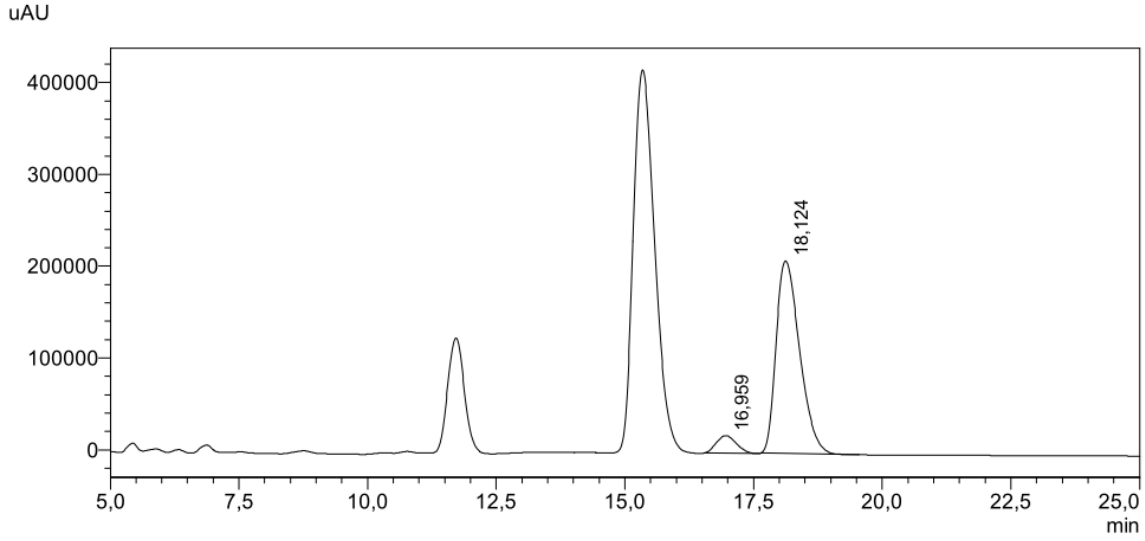


Major diastereoisomer



Peak#	Ret. Time	Area%
1	11,718	19,046
2	15,343	80,954
Total		100,000

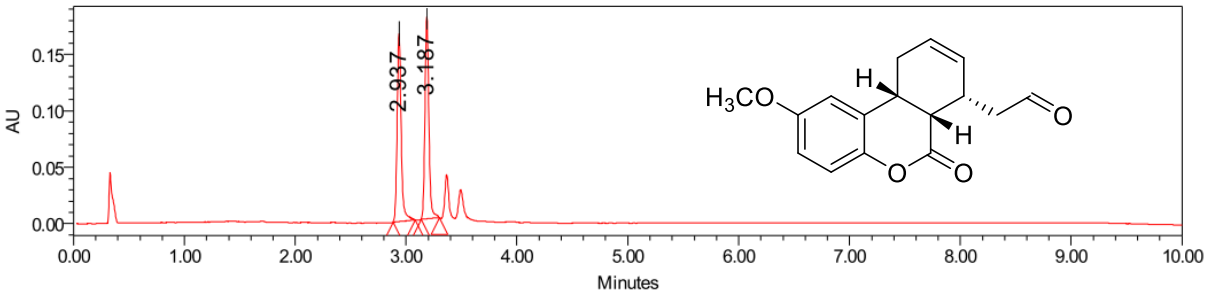
Minor diastereoisomer

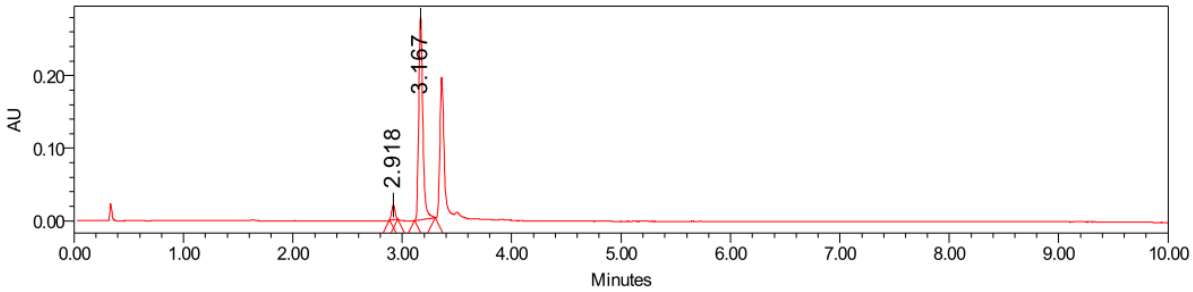


Peak#	Ret. Time	Area%
1	16,959	7,175
2	18,124	92,825
Total		100,000

(3f) 2-((6a*S*,7*S*,10a*R*)-2-Methoxy-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

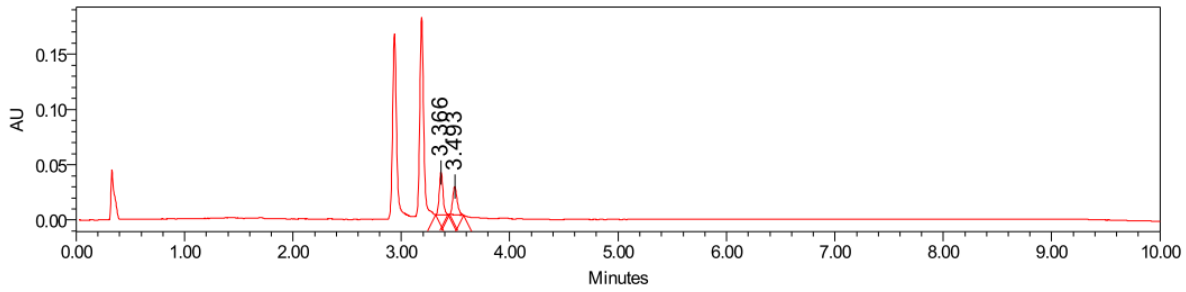
Major diastereoisomer

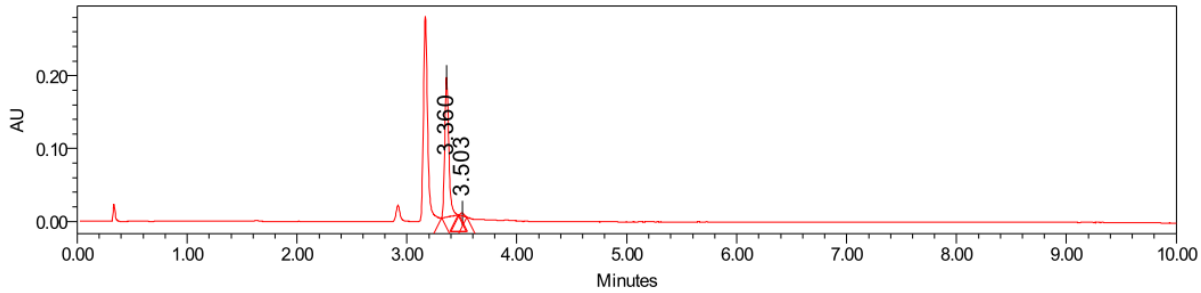




	RT	Area	% Area	Height
1	2.918	43992	5.72	20585
2	3.167	724587	94.28	279865

Minor diastereoisomer

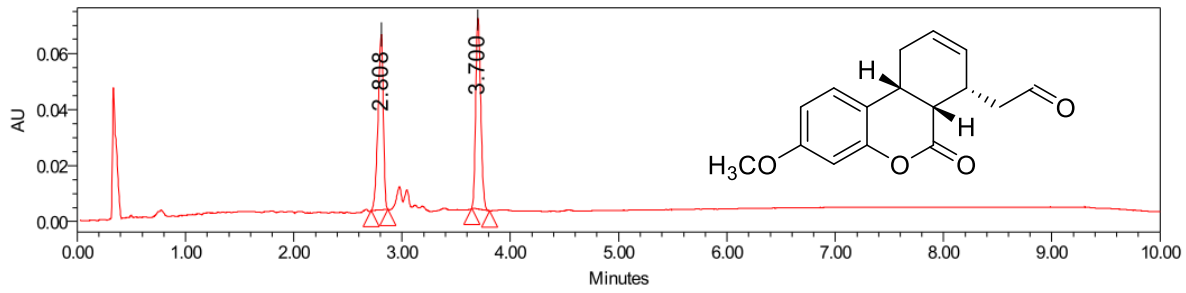


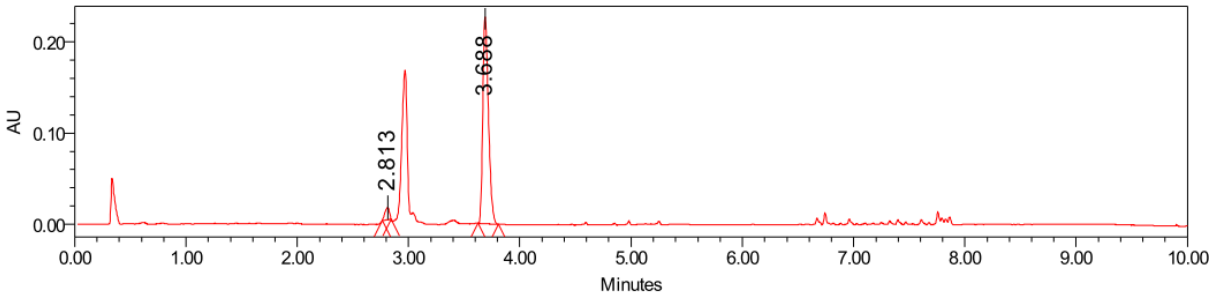


	RT	Area	% Area	Height
1	3.360	487857	98.22	191720
2	3.503	8827	1.78	3939

(3g) 2-((6a*S*,7*S*,10a*R*)-3-Methoxy-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

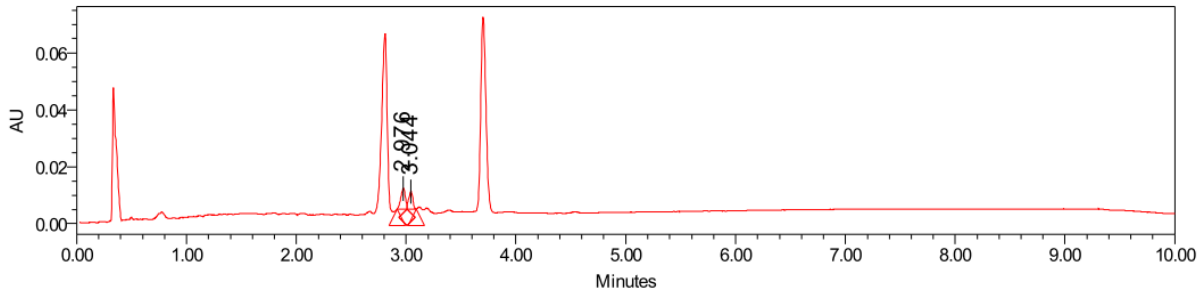
Major diastereoisomer

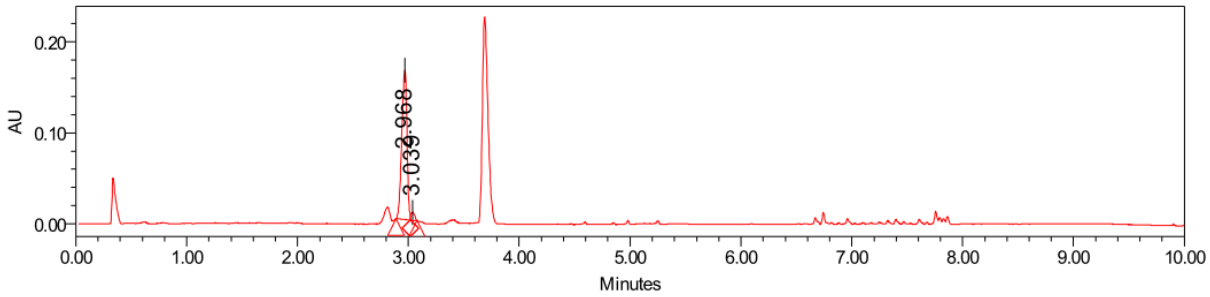




	RT	Area	% Area	Height
1	2.813	37210	4.45	13357
2	3.688	799462	95.55	226814

Minor diastereoisomer

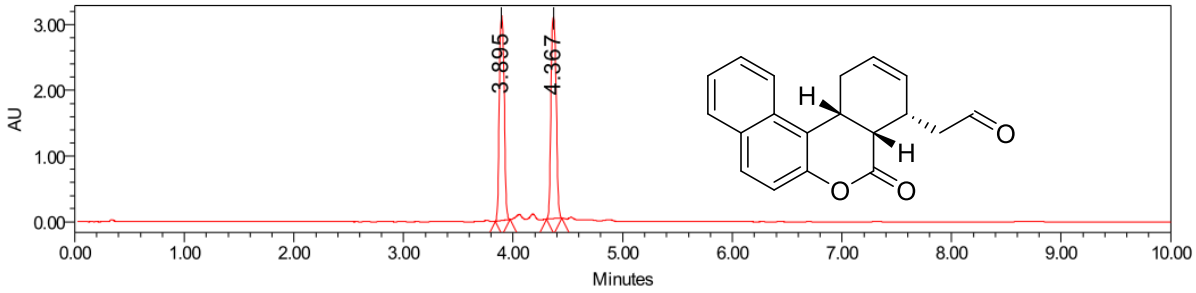


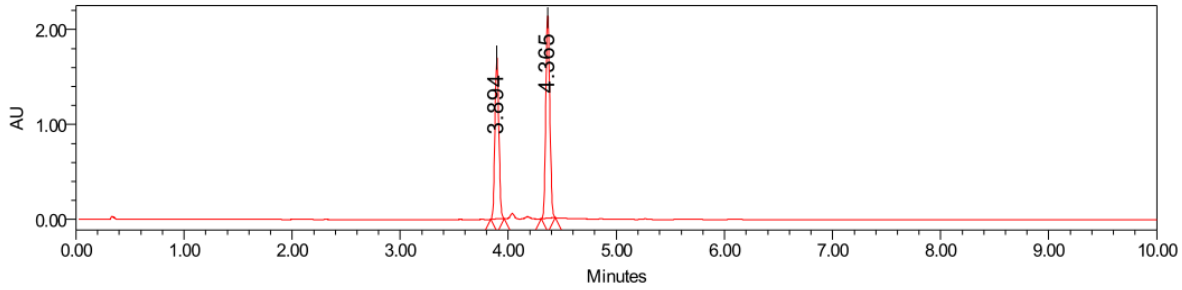


	RT	Area	% Area	Height
1	2.968	537049	96.50	164457
2	3.039	19506	3.50	8691

(3h) 2-((6a*S*,7*S*,10a*R*)-6-Oxo-6a,7,10,10a-tetrahydro-6*H*-dibenzo[c,h]chromen-7-yl)acetaldehyde

Major diastereoisomer

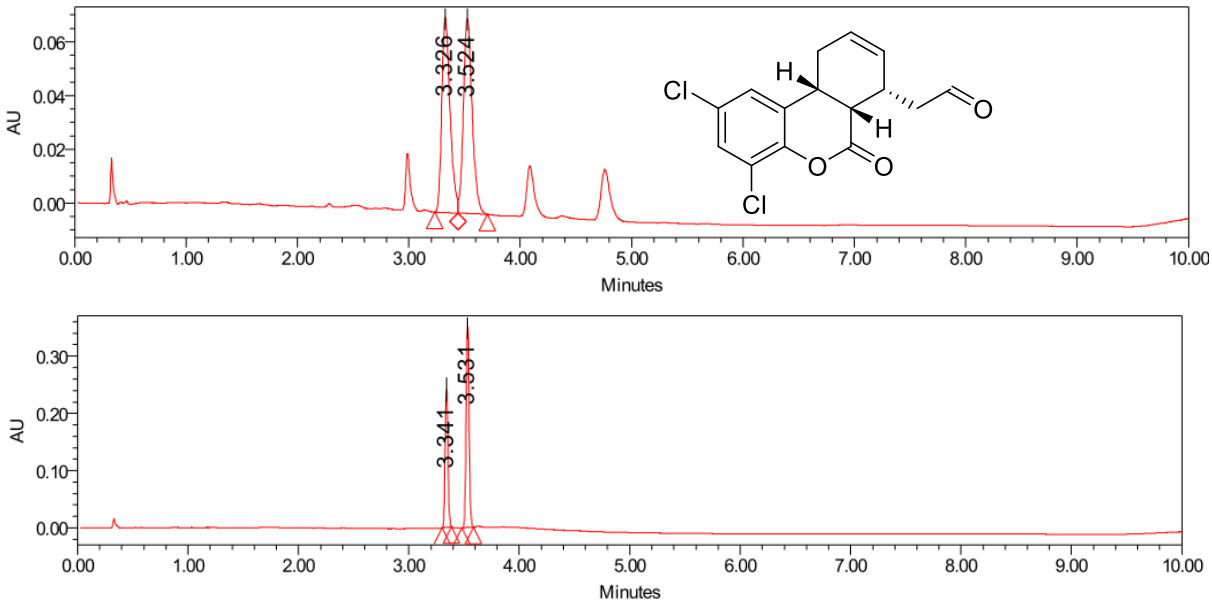




	RT	Area	% Area	Height
1	3.894	4295315	43.86	1704277
2	4.365	5497210	56.14	2135885

(3i) 2-((6a*S*,7*S*,10a*R*)-2,4-Dichloro-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

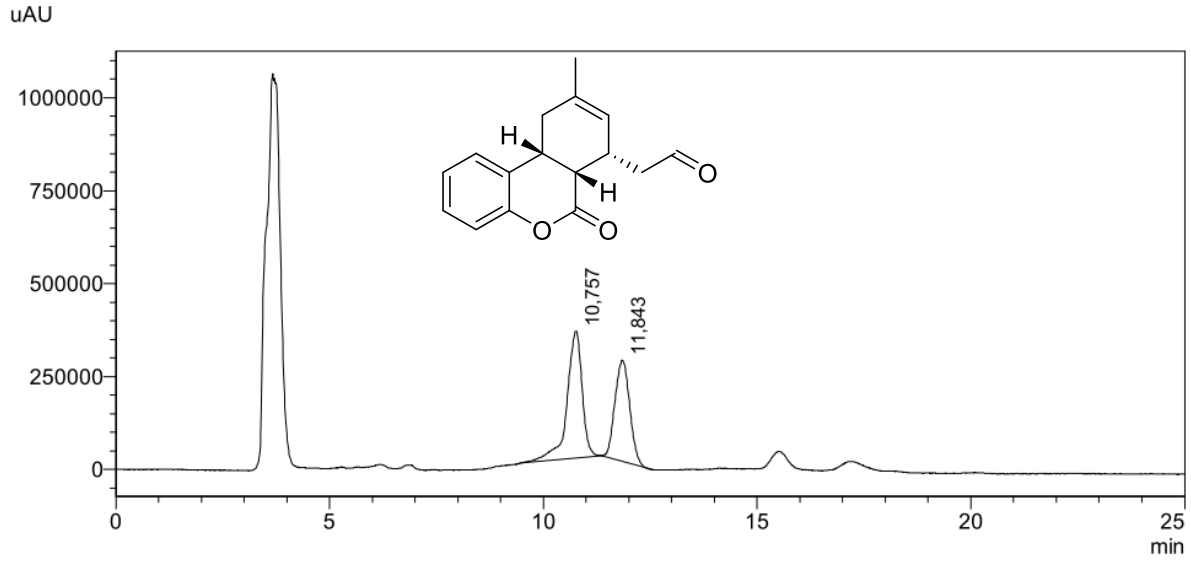
Major diastereoisomer

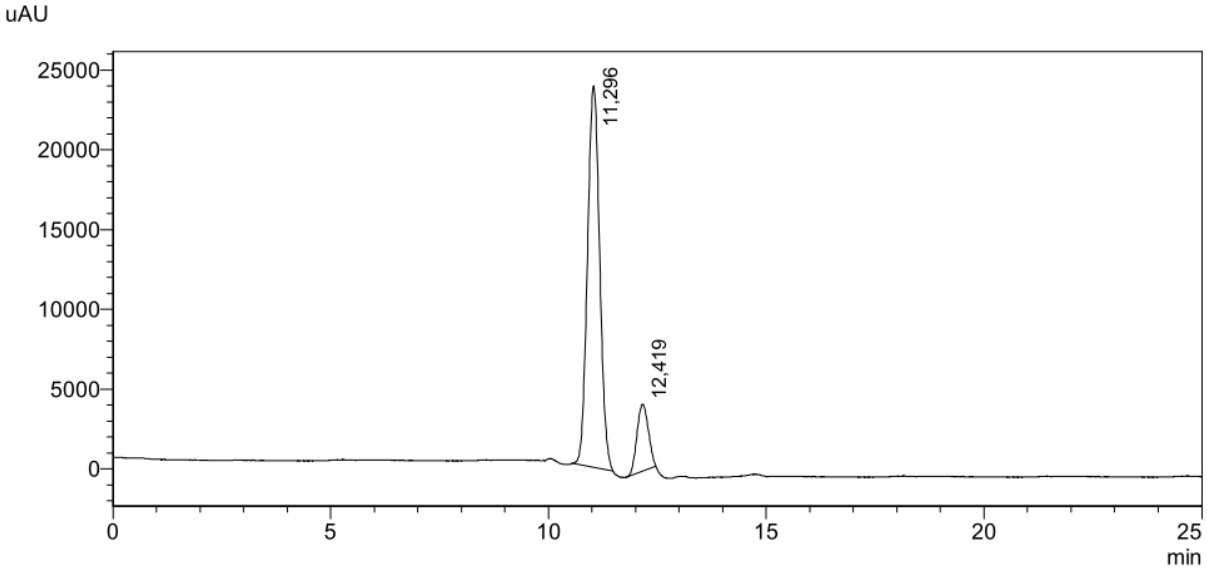


	RT	Area	% Area	Height
1	3.341	436407	39.88	242027
2	3.531	657856	60.12	353646

(3j) 2-((6a*S*,7*S*,10a*R*)-9-Methyl-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

Major diastereoisomer

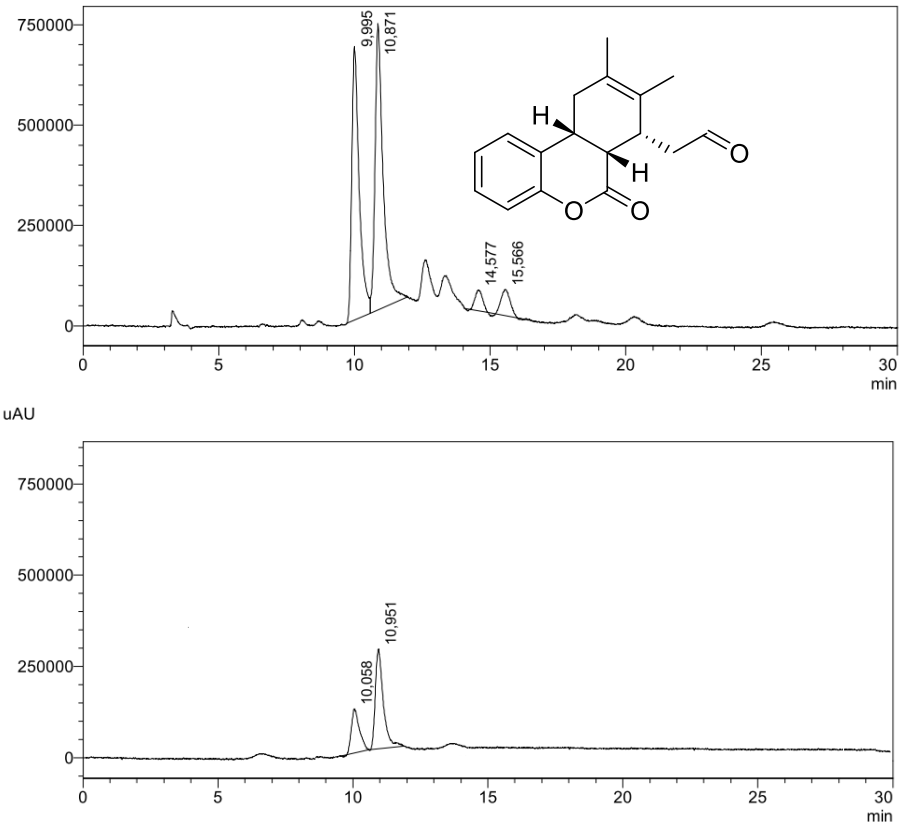




Peak#	Ret. Time	Area%
1	11,296	85,825
2	12,419	14,175
Total		100,000

(3k) 2-((6a*S*,7*R*,*10aR*)-8,9-Dimethyl-6-oxo-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

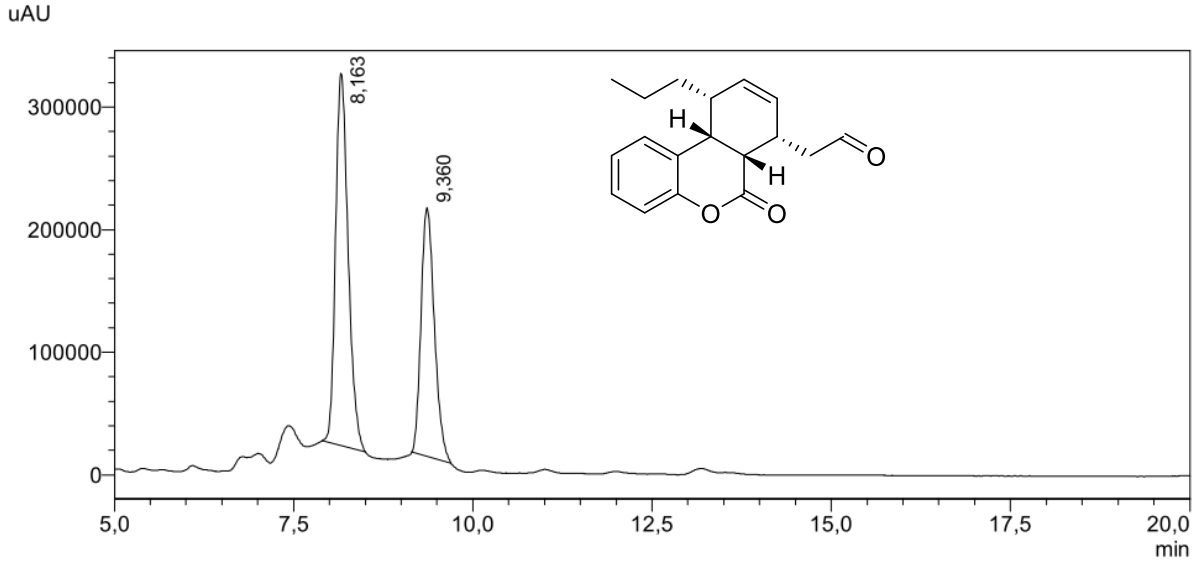
Major diastereoisomer

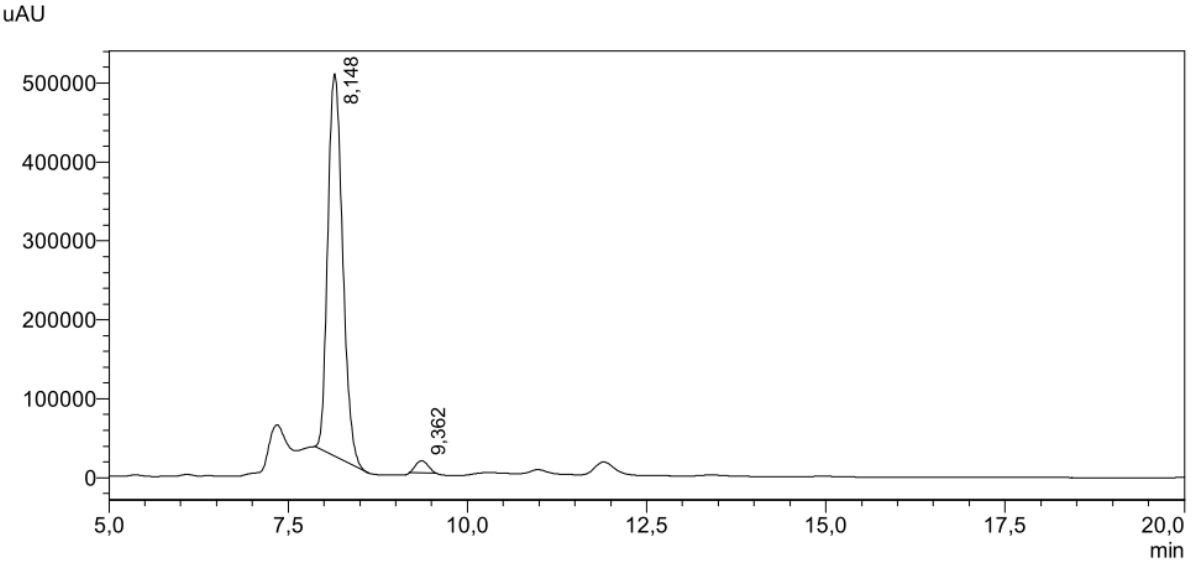


Peak#	Ret. Time	Area%
1	10,058	30,639
2	10,951	69,361
Total		100,000

(3l) 2-((6a*S*,7*S*,10*R*,10a*R*)-6-Oxo-10-propyl-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-7-yl)acetaldehyde

Major diastereoisomer

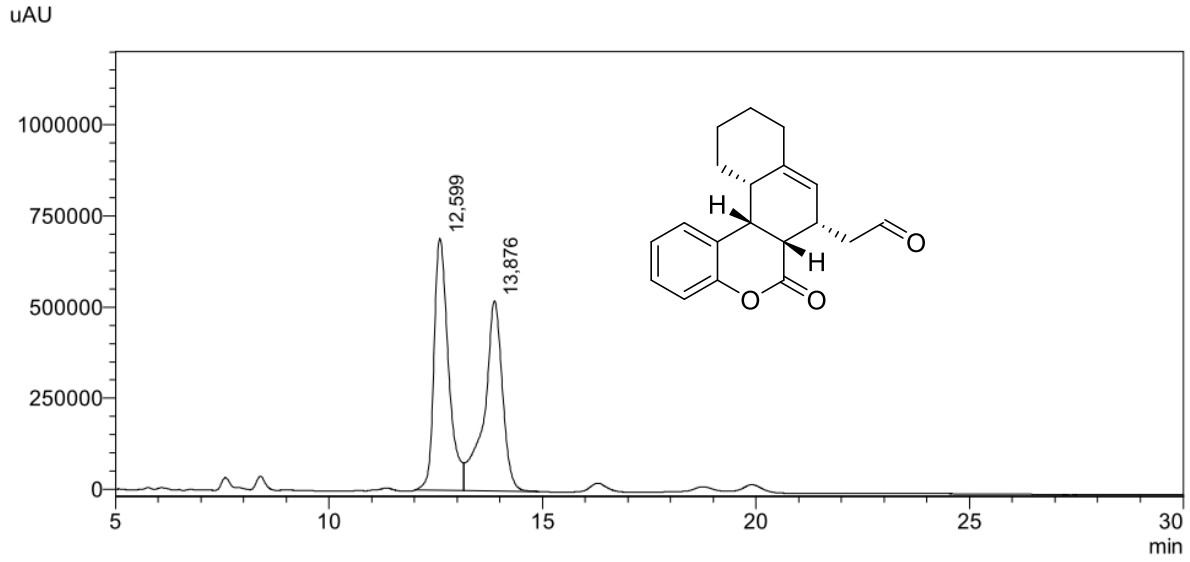


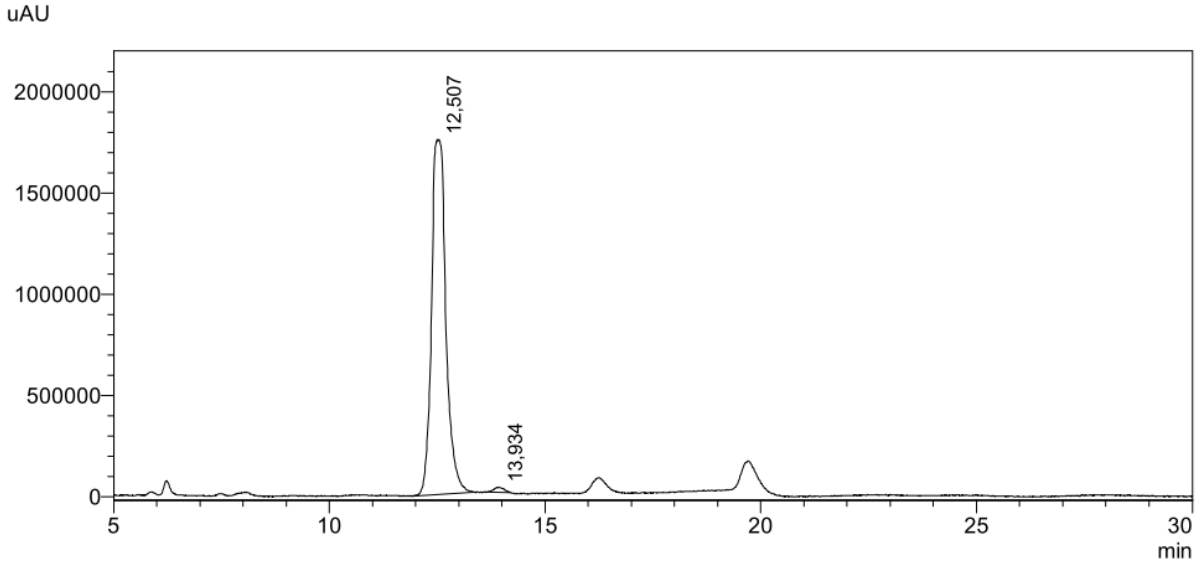


Peak#	Ret. Time	Area%
1	8,148	97,375
2	9,362	2,625
Total		100,000

(3m) 2-((6a*S*,7*S*,12a*S*,12b*R*)-6-Oxo-6a,7,9,10,11,12,12a,12b-octahydro-6*H*-naphtho[2,1-c]chromen-7-yl)acetaldehyde

Major diastereoisomer





Peak#	Ret. Time	Area%
1	12,507	98,950
2	13,934	1,050
Total		100,000