

Synthesis of deoxy sugar esters: a chemoenzymatic stereoselective approach affording deoxy sugar derivatives also in the form of aldehyde

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1. General Methods

HPLC determination of the enantiomeric ratio of 3,4-dideoxy ribose 2-octenoic acid esters was performed using a Daicel Chiralcel OD-H column.

^1H and ^{13}C NMR spectra were recorded in CDCl_3 solutions on a 500 MHz spectrometer. All signals were referenced relatively to solvent signal (7.27 ppm for ^1H and 77.00 ppm for ^{13}C). 2D FT methods were used for the full assignment of NMR spectra.

TLC was performed using DC-Alufolien Kieselgel 60 F₂₅₄ (Merck) silica gel plates and analyzed by staining upon heating with anisaldehyde solution (3 ml anisaldehyde, 10 ml conc. H_2SO_4 in 90 ml EtOH).

Column chromatography was performed on Merck silica gel 60 (230-400 mesh).

Commercial reagents were used without purification.

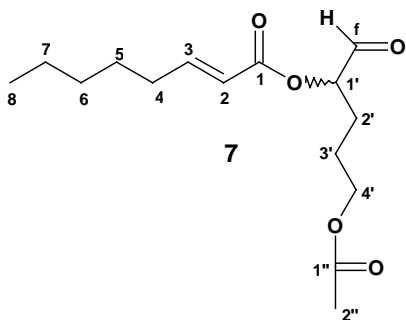
General procedures A, B and C are described in the experimental section of the note.

General Procedure D: *O*-alkylation of a carboxylic acid. The carboxylic acid (1 mmol) was dissolved in acetonitrile (8 mL), 4 eq of DIPEA was added, followed by 0.7 mmol of bromoaldehyde **6** dissolved in 2 mL of acetonitrile. After stirring for 24 h the solution was diluted with Et_2O , was washed with water, 1M NaHSO_4 , water and brine, dried over anhydrous Na_2SO_4 . The product was evaporated and purified by column chromatography over silica.

General Procedure E: removal of THP-blocking group. 2.5 mL of 0.5 N H_2SO_4 was added to the solution of 0.4 mmol of **20a** or **20b** in 7.5 mL of acetonitrile. After stirring for 24 h at rt the reaction mixture was diluted with EtOAc, washed with NaHCO_3 , water and brine, dried over anhydrous Na_2SO_4 . The product was evaporated and purified by column chromatography over silica (eluent: 20% to 30% of EtOAc in toluene).

2. Compound characterization data

2.1. (*E*)-Oct-2-enoic acid 4'-acetoxy-1'-formyl-butyl ester (**7**)



The reaction was carried out following the General Procedure D starting with 1 mmol of (*E*)-oct-2-enoic acid to yield 272 mg (96%) of **7**.

^1H NMR (500 MHz, CDCl_3) δ 9.55, 7.09, 5.92, 5.06, 2.25, 2.05, 1.95, 1.78, 1.49, 1.48, 1.32, 1.26, 0.90 ppm. ^{13}C NMR (500 MHz, CDCl_3) δ 198.4 (C_f), 171.1 ($\text{C}_{1''}$), 166.0 (C_1), 151.9 (C_3), 119.7 (C_2), 74.4 ($\text{C}_{1'}$), 63.6 (C_4), 32.3 (C_4), 31.2 (C_6), 27.5 (C_5), 25.5 (C_2), 24.1 (C_3), 22.3 (C_7), 20.8 ($\text{C}_{2''}$), 13.8 (C_8) ppm.

MS (m/z): 285.35, 225.30, 143.15, 125.05, 100.05.

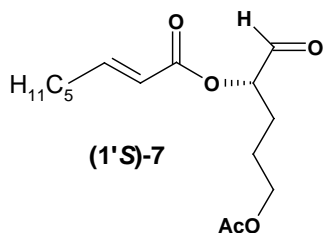
IR (neat, cm^{-1}): 1049, 1170, 1243, 1366, 1457, 1653, 1740.

Anal. Calcd for $\text{C}_{15}\text{H}_{24}\text{O}_5$ (284.39): C, 63.35; H, 8.52. Found: C, 63.18; H, 8.51.

TLC: R_f =0.35 (eluent: 30% EtOAc/hexane).

Flash chromatography eluent: 15% EtOAc/hexane.

2.2. (*E*)-Oct-2-enoic acid 4'-acetoxy-(1'*S*)-1'-formyl-butyl ester ((1'*S*)-**7**)



The reaction was carried out following the General Procedure B to yield 84 mg (32%) of (1'S)-7.

NMR: see sections 2.1 and 3.1.

MS: see section 2.1.

IR (neat, cm^{-1}): see section 2.1.

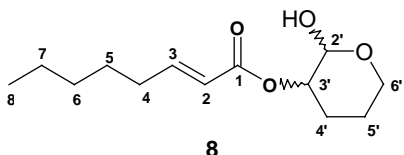
$[\alpha]_{546}^{20} = -12$ (c 1.5, EtOAc).

Anal. Calcd for $\text{C}_{15}\text{H}_{24}\text{O}_5$ (284.39): C, 63.35; H, 8.52. Found: C, 63.14; H, 8.50.

TLC: $R_f=0.24$ (eluent: 20% EtOAc/hexane).

Flash chromatography eluent: 10% EtOAc/hexane.

2.3. (E)-Oct-2-enoic acid 2'-hydroxy-tetrahydropyran-3'-yl ester (8)



The reaction was carried out following the General Procedure A starting with 1 mmol of (E)-Oct-2-enoic acid to yield 227 mg (94%) of 2 to 1 mixture of *trans* and *cis* isomers of **8** (yield from “one-pot synthesis”). Incubation time 48 h. The crude product was used in the further synthesis without purification.

^1H NMR (500 MHz, CDCl_3) δ *trans*: 7.00, 5.84, 4.77, 4.70, 4.00, 3.53, 2.19, 2.09, 1.79, 1.67, 1.54, 1.43, 1.30, 1.29, 0.88 ppm; *cis*: 7.00, 5.84, 5.09, 4.86, 3.95, 3.54, 2.19, 2.00, 1.80, 1.72, 1.61, 1.43, 1.30, 1.29, 0.88 ppm. ^{13}C NMR (500 MHz, CDCl_3) δ *trans*: 166.5 (C_1), 150.55 (C_3), 120.8 (C_2), 94.6 ($\text{C}_{2'}$), 70.6 ($\text{C}_{3'}$), 62.8 ($\text{C}_{6'}$), 32.1 (C_4), 31.2 (C_6), 27.51 (C_5), 25.5 ($\text{C}_{4'}$), 22.5 ($\text{C}_{5'}$), 22.3 (C_7), 13.8 (C_8) ppm; *cis*: 166.2 (C_1), 150.59 (C_3), 120.7 (C_2), 91.6 ($\text{C}_{2'}$), 70.0 ($\text{C}_{3'}$), 61.1 ($\text{C}_{6'}$), 32.1 (C_4), 31.2 (C_6), 27.49 (C_5), 24.1 ($\text{C}_{4'}$), 22.9 ($\text{C}_{5'}$), 22.3 (C_7), 13.8 (C_8) ppm.

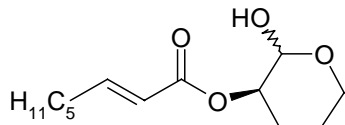
MS (m/z): 225.35, 196.40, 182.45, 171.05, 167.20, 143.05, 125.00, 100.05.

Anal. Calcd for $\text{C}_{13}\text{H}_{22}\text{O}_4$ (242.35): C, 64.42; H, 9.17. Found: C, 64.36; H, 9.19.

TLC: $R_f=0.51$ (eluent: 40% EtOAc/hexane).

Flash chromatography eluent: 18% EtOAc/hexane.

2.4. (*E*)-Oct-2-enoic acid (3'*R*)-2'-hydroxy-tetrahydropyran-3'-yl ester ((3'*R*)-8)



(3'*R*)-8

The reaction was carried out starting from **15** and following the General Procedure C to yield 98 mg (92%) of **(3'*R*)-8**.

NMR: see sections 2.3 and 3.3.

MS: see section 2.3.

$[\alpha]_{546}^{25} = -3.9$ (c 1.5, EtOAc).

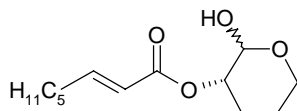
Chiral HPLC: see section 4.

Anal. Calcd for C₁₃H₂₂O₄ (242.35): C, 64.42; H, 9.17. Found: C, 64.20; H, 9.19.

TLC: R_f=0.51 (eluent: 40% EtOAc/hexane).

Flash chromatography eluent: 20% EtOAc/hexane.

2.5. (*E*)-Oct-2-enoic acid (3'*S*)-2'-hydroxy-tetrahydropyran-3'-yl ester ((3'*S*)-8)



(3'*S*)-8

The reaction was carried out starting from **(1'*S*)-7** and following the General Procedure C to yield 67 mg (94%) of **(3'*S*)-8**.

NMR: see sections 2.3 and 3.4.

MS: see section 2.3.

$[\alpha]_{546}^{25} = +3.8$ (c 1.5, EtOAc).

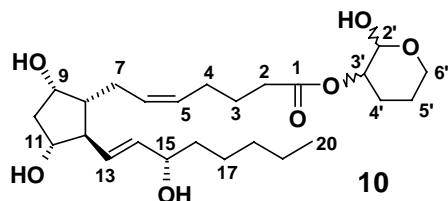
Chiral HPLC: see section 4.

Anal. Calcd for C₁₃H₂₂O₄ (242.35): C, 64.42; H, 9.17. Found: C, 64.33; H, 9.18.

TLC: R_f=0.51 (eluent: 40% EtOAc/hexane).

Flash chromatography eluent: 20% EtOAc/hexane.

2.6. Prostaglandin F_{2α} 2'-hydroxy-tetrahydropyran-3'-yl ester (**10**)



The reaction was carried out following the General Procedure A starting with 1 mmol of PGF_{2α} to yield 272 mg (60%) of **10** (yield from “one-pot synthesis”).

NMR: see sections 2.7 and 3.6.

MS (*m/z*): 419.30, 391.40, 301.40, 225.35, 177.10, 143.15, 117.05.

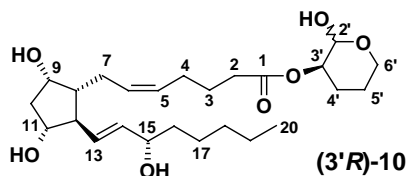
IR (neat, cm⁻¹): 1029, 1081, 1143, 1456, 1731, 3382.

Anal. Calcd for C₂₅H₄₂O₇ (454.67): C, 66.04; H, 9.33. Found: C, 65.86; H, 9.35.

TLC: R_f = 0.29 (eluent: 10% MeOH/CHCl₃).

Flash chromatography eluent: 5% isopropanol/hexane.

2.7. Prostaglandin F_{2α} (3'R)-2'-hydroxy-tetrahydropyran-3'-yl ester ((3'R)-**10**)



The reaction was carried out following the General Procedure C starting from 80 mg of **16** to yield 24 mg (36%) of 2 to 1 mixture of *trans* and *cis* isomers of (3'R)-**10** and 36 mg (49%) of **16a** during 72h of incubation.

¹H NMR (500 MHz, CDCl₃) δ *trans*: 5.55, 5.44, 5.39, 5.35, 4.75, 4.67, 4.12, 4.04, 4.02, 3.88, 3.51, 2.36, 2.30, 2.26, 2.23, 2.20, 2.17, 2.04, 2.02, 1.70, 1.67, 1.65, 1.61, 1.50, 1.42, 1.30, 1.28, 0.89 ppm; *cis*: 5.55, 5.44, 5.39, 5.35, 5.09, 4.85, 4.12, 4.04, 3.96, 3.88, 3.53, 2.36, 2.30, 2.26, 2.23, 2.17, 2.02, 1.85, 1.70, 1.67, 1.65, 1.61, 1.50, 1.42, 1.30, 1.28, 0.89 ppm. ¹³C NMR (500 MHz, CDCl₃) δ *trans*: 173.5 (C₁), 135.27 (C₁₄), 132.7 (C₁₃), 129.52 (C₅), 129.3 (C₆), 94.4 (C₂), 77.70 (C₁₁), 73.10 (C₉), 72.67 (C₁₅), 71.0 (C₃), 63.1 (C₆), 55.48 (C₁₂), 49.82 (C₈), 42.7 (C₁₀), 37.03 (C₁₆), 33.4 (C₂), 31.7 (C₁₈), 26.3 (C₄), 25.7 (C₄), 25.58 (C₇), 25.2 (C₁₇), 24.57 (C₃), 22.7 (C₅), 22.6 (C₁₉), 14.0 (C₂₀) ppm; *cis*: 173.4 (C₁), 135.33 (C₁₄), 132.7 (C₁₃), 129.59 (C₅), 129.4 (C₆), 91.2 (C₂), 77.72 (C₁₁), 73.12

(C₉), 72.68 (C₁₅), 70.2 (C_{3'}), 60.9 (C_{6'}), 55.53 (C₁₂), 49.79 (C₈), 42.7 (C₁₀), 37.05 (C₁₆), 33.29 (C₂), 31.7 (C₁₈), 26.3 (C₄), 25.62 (C₇), 25.2 (C₁₇), 24.51 (C₃), 24.1 (C_{4'}), 23.0 (C_{5'}), 22.6 (C₁₉), 14.0 (C₂₀) ppm.

MS: see section 2.6.

IR (neat, cm⁻¹): see section 2.6.

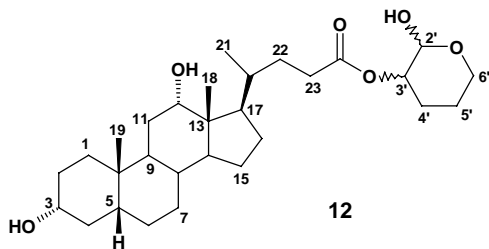
[α]₅₈₉²⁰ = +19.6 (c 0.7, EtOAc).

Anal. Calcd for C₂₅H₄₂O₇ (454.67): C, 66.04; H, 9.33. Found: C, 65.83; H, 9.36.

TLC: R_f = 0.13 (eluent: 5% isopropanol / EtOAc).

Flash chromatography eluent: 5% isopropanol/hexane.

2.8. Deoxycholic acid 2'-hydroxy-tetrahydropyran-3'-yl ester (**12**)



The reaction was carried out following the General Procedure A starting with 1 mmol of DCA to yield 325 mg (66%) of **12** (yield from “one-pot synthesis”).

NMR: see section 2.9.

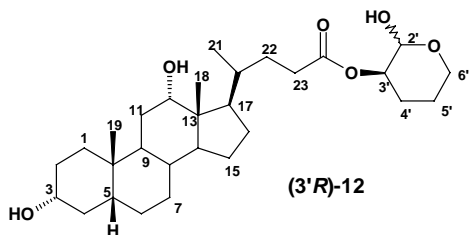
MS (*m/z*): 429.15, 358.40, 319.25, 255.20, 225.30, 175.15, 149.25, 106.05.

Anal. Calcd for C₂₉H₄₈O₆ (492.77): C, 70.68; H, 9.48. Found: C, 70.43; H, 9.86.

TLC: R_f = 0.32 (eluent: 20% isopropanol/hexane).

Flash chromatography eluent: 18% isopropanol/ 1% water/ hexane.

2.9. Deoxycholic acid (3'R)-2'-hydroxy-tetrahydropyran-3'-yl ester ((3'R)-**12**)



The reaction was carried out following the General Procedure C to yield 85 mg (71%) of 2 to 1 mixture of *trans* and *cis* isomers of (**3'R**)-**12**. Incubation time 72 h.

¹H NMR (500 MHz, CDCl₃) δ 5.08, 4.85, 4.74, 4.67, 4.00, 3.60, 3.54, 2.44, 2.28, 2.09, 1.99, 1.87, 1.84, 1.78, 1.74, 1.70, 1.65, 1.61, 1.57, 1.51, 1.41, 1.26, 1.13, 1.07, 0.98, 0.91, 0.68 ppm. ¹³C NMR (500 MHz, CDCl₃) δ 174.2>173.8 (C₂₄), 94.8>91.6 (C₂), 73.18>73.17 (C₁₂), 71.8 (C₃), 70.9>70.2 (C_{3'}), 63.1>61.2 (C₆), 48.25>48.23 (C₁₄), 47.30>47.24 (C₁₇), 46.5 (C₁₃), 42.1 (C₅), 36.4 (C₄), 36.1 (C₂₀), 35.3 (C₁), 35.06>35.08 (C₈), 34.1 (C₁₀), 33.7 (C₉), 31.4>31.3 (C₂₃), 30.8 (C₂₂), 30.5 (C₂), 28.64 (C₁₁), 27.46<27.44 (C₁₆), 27.1 (C₆), 26.1 (C₇), 25.8>24.2 (C_{4'}), 23.7 (C₁₅), 23.1 (C₁₉), 22.8>23.0 (C_{5'}), 17.29<17.27 (C₂₁), 12.7 (C₁₈) ppm.

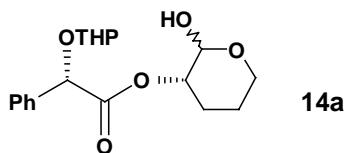
[α]_D²⁰ = +26.5 (c 0.5, EtOAc).

Anal. Calcd for C₂₉H₄₈O₆ (492.77): C, 70.68; H, 9.84. Found: C, 70.46; H, 9.86.

TLC: R_f = 0.32 (eluent: 20% isopropanol/hexane).

Flash chromatography eluent: 18% isopropanol/ 1% water/ hexane.

2.10. Tetrahydropyranyl-(*S*)-mandelic acid (3'*S*)-2'-hydroxy-tetrahydropyran-3'-yl ester (**14a**)



The reaction was carried out following the General Procedure A starting with 2 mmol of THP-protected MA to yield 124 mg (43%) of **14a** and 105 mg (37%) of **14b** (yields determined from separate synthesis).

NMR: (**14a** is a mixture of four diastereomers) see section 3.8.

MS (*m/z*): 235.20, 189.25, 118.10, 85.15.

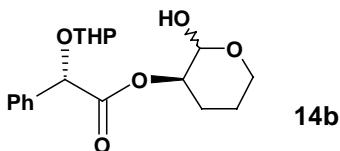
IR (neat, cm⁻¹): 698, 1080, 1123, 1455, 1496, 1603, 1746, 3417.

Anal. Calcd for C₁₈H₂₄O₆ (336.42): C, 64.26; H, 7.21. Found: C, 64.14; H, 7.28.

TLC: R_f = 0.35 (eluent: 30% EtOAc/toluene).

Flash chromatography eluent: 10% to 25% EtOAc/ toluene.

2.11. Tetrahydropyranyl-(S)-mandelic acid (3'R)-2'-hydroxy-tetrahydropyran-3'-yl ester (14b)



The reaction was carried out following the General Procedure A starting with 2 mmol of THP-protected MA to yield 105 mg (37%) of **14b** and 124 mg (43%) of **14a**.

NMR: (14b is a mixture of four diastereomers) see section 3.9.

MS: see section 2.10.

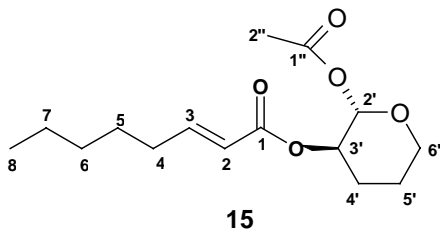
IR (neat, cm^{-1}): 698, 1080, 1123, 1457, 1496, 1604, 1746, 3418.

Anal. Calcd for $\text{C}_{18}\text{H}_{24}\text{O}_6$ (336.42): C, 64.26; H, 7.21. Found: C, 64.09; H, 7.30.

TLC: R_f = 0.27 (eluent: 30% EtOAc/toluene).

Flash chromatography eluent: 10% to 25% EtOAc/ toluene.

2.12. (E)-Oct-2-enoic acid (2'S,3'R)-2'-acetoxy-tetrahydropyran-3'-yl ester (15)



The reaction was carried out following the General Procedure B to yield 126 mg (48%) of **15**.

^1H NMR (500 MHz, CDCl_3) δ 7.0, 5.87, 5.82, 4.79, 3.88, 3.70, 2.20, 2.10, 2.04, 1.93, 1.82, 1.53, 1.46, 1.31, 1.29, 0.89 ppm. ^{13}C NMR (500 MHz, CDCl_3) δ 169.1 ($\text{C}_{1''}$), 165.5 (C_1), 150.7 (C_3), 120.7 (C_2), 91.5 ($\text{C}_{2'}$), 67.3 ($\text{C}_{3'}$), 62.8 ($\text{C}_{6'}$), 32.2 (C_4), 31.3 (C_6), 27.5 (C_5), 24.3 ($\text{C}_{4'}$), 22.4 (C_7), 20.9 ($\text{C}_{5'}$), 20.9 ($\text{C}_{2''}$), 13.9 (C_8) ppm.

MS (m/z): 225.05, 168.25, 142.30, 125.15, 100.10.

IR (neat, cm^{-1}): 1198, 1264, 1362, 1440, 1468, 1654, 1723, 1757.

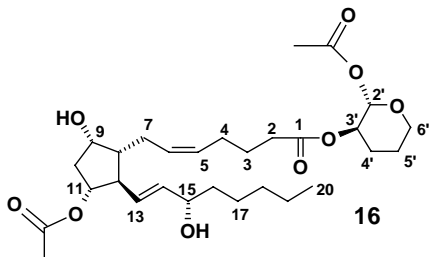
$[\alpha]_{546}^{20} = -63$ (c 1.8, EtOAc).

Anal. Calcd for $\text{C}_{15}\text{H}_{24}\text{O}_5$ (284.39): C, 63.35; H, 8.52. Found: C, 63.21; H, 8.54.

TLC: R_f = 0.46 (eluent: 20% EtOAc/hexane).

Flash chromatography eluent: 15% EtOAc/hexane.

2.13. 11-Acetyl-prostaglandin F_{2α} (2'S,3'R)-2'-acetoxy-tetrahydropyran-3'-yl ester (16)



The reaction was carried out following the General Procedure B starting with 180 mg of **10** to yield 110 mg (52%) of **16**.

¹H NMR (500 MHz, CDCl₃) δ 5.80, 5.56, 5.49, 5.43, 5.38, 4.87, 4.73, 4.14, 4.05, 3.84, 3.69, 2.54, 2.38, 2.34, 2.23, 2.10, 2.09, 2.08, 2.04, 2.02, 1.91, 1.77, 1.69, 1.66, 1.51, 1.49, 1.30, 1.28, 0.88 ppm. ¹³C NMR (500 MHz, CDCl₃) δ 172.7 (C₁), 170.9 (C_{11Ac}), 169.2 (C_{2'Ac}), 135.8 (C₁₄), 131.0 (C₁₃), 129.6 (C₅), 128.9 (C₆), 91.1 (C_{2'}), 78.9 (C₁₁), 72.6 (C₁₅), 71.6 (C₉), 67.4 (C_{3'}), 62.5 (C_{6'}), 51.2 (C₁₂), 49.4 (C₈), 40.8 (C₁₀), 37.0 (C₁₆), 33.6 (C₂), 31.6 (C₁₈), 26.5 (C₄), 25.0 (C₁₇), 24.9 (C₇), 24.7 (C₃), 24.0 (C_{4'}), 22.5 (C₁₉), 21.2 (C_{11Ac}), 20.9 (C_{2'Ac}), 20.6 (C_{5'}), 14.0 (C₂₀) ppm.

IR (neat, cm⁻¹): 984, 1075, 1225, 1294, 1382, 1433, 1709, 1739, 1758, 3399.

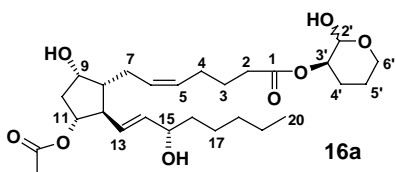
[α]_D²⁰ = -4.9 (c 1.5, EtOAc).

Anal. Calcd for C₂₉H₄₆O₉ (538.75): C, 64.66; H, 8.61. Found: C, 64.48; H, 8.60.

TLC: R_f = 0.26 (eluent: 50% EtOAc/toluene).

Flash chromatography eluent: 30% EtOAc/toluene.

2.14. 11-Acetyl-prostaglandin F_{2α} (3'R)-2'-hydroxy-tetrahydropyran-3'-yl ester (16a)



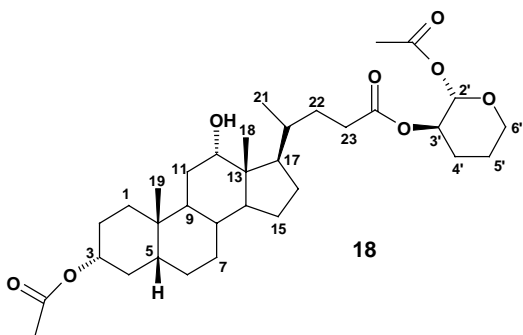
The reaction was carried out following the General Procedure C starting from 80 mg of **16** to yield 36 mg (49%) of 2 to 1 mixture of *trans* and *cis* isomers of **16a** and 24 mg (36%) of (**3'R**)-**10**.

¹H NMR (500 MHz, CDCl₃) δ *trans*: 5.55, 5.53, 5.42, 5.38, 4.88, 4.71, 4.66, 4.18, 4.09, 4.02, 3.53, 2.55, 2.40, 2.37, 2.27, 2.23, 2.10, 2.04, 1.81, 1.71, 1.70, 1.64, 1.61, 1.58, 1.55, 1.42, 1.32, 1.31, 1.29, 0.90 ppm; *cis*: 5.55, 5.53, 5.42, 5.38, 5.07, 4.88, 4.85, 4.18, 4.09, 3.97, 3.56, 2.55, 2.40, 2.37, 2.27, 2.23, 2.04, 1.99, 1.81, 1.78, 1.71, 1.70, 1.61, 1.58, 1.55, 1.42, 1.32, 1.31, 1.29, 0.90 ppm. ¹³C NMR (500 MHz, CDCl₃) δ *trans*: 173.6 (C₁), 135.6 (C₁₄), 130.88 (C₁₃), 129.97 (C₅), 128.8 (C₆), 94.9 (C_{2'}), 78.97 (C₁₁), 72.61 (C₁₅), 71.88 (C₉), 71.1 (C_{3'}), 63.4 (C_{6'}), 51.2 (C₁₂), 49.39 (C₈), 40.82 (C₁₀), 37.10 (C₁₆), 33.61 (C₂), 31.7 (C₁₈), 26.44 (C₄), 26.0 (C_{4'}), 25.1 (C₁₇), 25.0 (C₇), 24.71 (C₃), 22.91 (C_{5'}), 22.6 (C₁₉), 14.0 (C₂₀) ppm; *cis*: 173.3 (C₁), 135.7 (C₁₄), 130.91 (C₁₃), 129.96 (C₅), 129.9 (C₆), 91.6 (C_{2'}), 78.96 (C₁₁), 72.64 (C₁₅), 71.92 (C₉), 70.3 (C_{3'}), 61.3 (C_{6'}), 51.3 (C₁₂), 49.36 (C₈), 40.78 (C₁₀), 37.11 (C₁₆), 33.56 (C₂), 31.7 (C₁₈), 26.47 (C₄), 25.1 (C₇), 25.1 (C₁₇), 24.70 (C₃), 24.2 (C_{4'}), 22.90 (C_{5'}), 22.6 (C₁₉), 14.0 (C₂₀) ppm.

[α]_D²⁰ = +21.8 (c 1.0, EtOAc).

TLC: R_f = 0.5 (eluent: 5% isopropanol / EtOAc).

2.15. 3-Acetyl-deoxycholic acid (2'S,3'R)-2'-acetoxy-tetrahydropyran-3'-yl ester (**18**)



The reaction was carried out following the General Procedure B to yield 144 mg (38%) of **18** and 174 mg (46%) of **19**. Due to the inactivation of the enzyme observed during the acetylation, 0.2 g of Novozym® 435 was added to the reaction mixture every 24 h (during 120 h) in order to reach 80% of conversion of the starting material **12**.

^1H NMR (500 MHz, CDCl_3) δ 5.82, 4.73, 4.70, 3.99, 3.88, 3.70, 2.41, 2.28, 2.11, 2.06, 2.01, 1.93, 1.86, 1.82, 1.78, 1.76, 1.68, 1.61, 1.56, 1.52, 1.45, 1.41, 1.37, 1.28, 1.24, 1.11, 1.06, 1.03, 0.98, 0.91, 0.68 ppm. ^{13}C NMR (500 MHz, CDCl_3) δ 173.2 (C_{24}), 170.7 ($\text{C}_{3\text{Ac}}$), 169.1 ($\text{C}_{2'\text{Ac}}$), 91.4 ($\text{C}_{2'}$), 74.3 (C_3), 73.1 (C_{12}), 67.4 ($\text{C}_{3'}$), 62.7 ($\text{C}_{6'}$), 48.2 (C_{14}), 47.3 (C_{17}), 46.5 (C_{13}), 41.8 (C_5), 35.9 (C_{20}), 35.0 (C_8), 34.8 (C_1), 34.1 (C_{10}), 33.6 (C_9), 32.1 (C_4), 31.3 (C_{23}), 30.8 (C_{22}), 28.6 (C_{11}), 27.4 (C_{16}), 26.9 (C_7), 26.4 (C_2), 26.0 (C_6), 24.2 ($\text{C}_{4'}$), 23.6 (C_{15}), 23.1 (C_{19}), 21.4 ($\text{C}_{3\text{Ac}}$), 20.9 ($\text{C}_{2'\text{Ac}}$), 20.8 ($\text{C}_{5'}$), 17.2 (C_{21}), 12.7 (C_{18}) ppm.

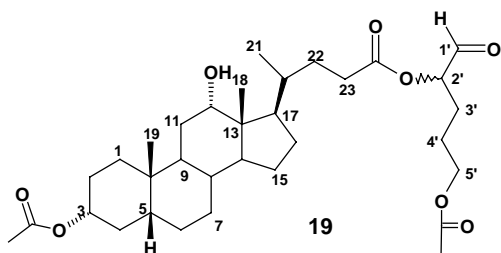
$[\alpha]_{589}^{20} = +16$ (c 1.4, EtOAc).

Anal. Calcd for $\text{C}_{33}\text{H}_{52}\text{O}_8$ (576.85): C, 68.71; H, 9.10. Found: C, 68.55; H, 9.11.

TLC: $R_f = 0.63$ (eluent: 30% EtOAc/toluene).

Flash chromatography eluent: 10% to 25% EtOAc/toluene.

2.16. 3-Acetyl-deoxycholic acid 4'-acetoxy-1'-formyl-butyl ester (**19**)



The reaction was carried out following the General Procedure B to yield 174 mg (46%) of **19** and 144 mg (38%) of **18**. Due to the inactivation of the enzyme observed during the acetylation, 0.2 g of Novozym® 435 was added to the reaction mixture every 24 h (during 120 h) in order to reach 80% of conversion of the starting material **12**.

^1H NMR (500 MHz, CDCl_3) δ 9.51, 5.01, 4.69, 4.07, 3.98, 2.48, 2.36, 2.04, 2.00, 1.93, 1.86, 1.84, 1.82, 1.78, 1.75, 1.70, 1.66, 1.61, 1.53, 1.50, 1.44, 1.41, 1.27, 1.24, 1.10, 1.05, 1.02, 0.99, 0.90, 0.67 ppm. ^{13}C NMR (500 MHz, CDCl_3) δ 197.96 ($\text{C}_{1'}$), 173.7 (C_{24}), 173.7 ($\text{C}_{5'\text{Ac}}$), 170.6 ($\text{C}_{3\text{Ac}}$), 77.45>77.42 ($\text{C}_{2'}$), 74.2 (C_3), 73.0 (C_{12}), 63.5 ($\text{C}_{5'}$), 48.23 (C_{14}), 47.20<47.22 (C_{17}), 46.5 (C_{13}), 41.8 (C_5), 35.9 (C_8), 34.97<35.00 (C_{20}), 34.8 (C_1), 34.1 (C_{10}), 33.6 (C_9), 32.1 (C_4), 30.8 (C_{22}), 30.78<30.82 (C_{23}), 28.7 (C_{11}), 27.4 (C_{16}), 26.9

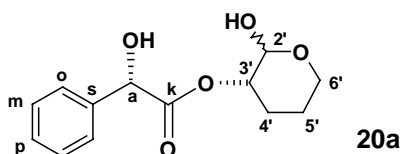
(C₇), 26.5 (C₂), 26.0 (C₆), 25.4 (C_{3'}), 24.2 (C_{4'}), 23.5 (C₁₅), 23.0 (C₁₉), 21.4 (C_{3Ac}), 20.8 (C_{5'Ac}), 17.28>17.26 (C₂₁), 12.7 (C₁₈) ppm.

Anal. Calcd for C₂₃H₅₂O₈ (576.85): C, 68.71; H, 9.10. Found: C, 68.49; H, 9.12.

TLC: R_f = 0.39 (eluent: 30% EtOAc/toluene).

Flash chromatography eluent: 10% to 25% EtOAc/toluene.

2.17. (S)-Mandelic acid (3'S)-2'-hydroxy-tetrahydropyran-3'-yl ester (20a)



The reaction was carried out following the General Procedure E to yield 78 mg (85%) of 3 to 2 mixture of *trans* and *cis* isomers of **20a**.

¹H NMR (500 MHz, CDCl₃) δ *trans*: 7.47, 7.38, 7.35, 5.24, 4.73, 4.61, 3.98, 3.61 (OH), 3.50, 3.14 (2'-OH), 2.12, 1.79, 1.73, 1.60 ppm; *cis*: 7.48, 7.38, 7.35, 4.88, 3.95, 3.78 (OH), 3.54, 2.92 (2'-OH), 2.06, 1.84, 1.74, 1.61 ppm. ¹³C NMR (500 MHz, CDCl₃) δ *trans*: 173.1 (C_k), 138.1 (C_s), 128.7 (C_m), 128.5 (C_p), 126.5 (C_o), 94.1 (C_{2'}), 73.07 (C_a), 72.5 (C_{3'}), 62.9 (C_{6'}), 25.5 (C_{4'}), 22.5 (C_{5'}) ppm; *cis*: 172.9 (C_k), 138.3 (C_s), 128.6 (C_m), 128.3 (C_p), 126.3 (C_o), 91.4 (C_{2'}), 73.09 (C_a), 71.9 (C_{3'}), 61.9 (C_{6'}), 24.4 (C_{4'}), 22.3 (C_{5'}) ppm.

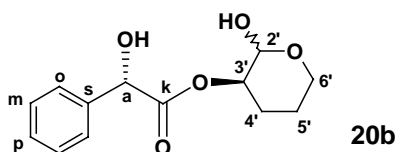
[α]₅₄₆²⁵ = +37.3 (c 1.0, EtOAc).

Anal. Calcd for C₁₃H₁₆O₅ (252.29): C, 61.89; H, 6.41. Found: C, 61.64; H, 6.43.

TLC: R_f = 0.28 (eluent: 50% EtOAc/ toluene).

Flash chromatography eluent: 20% to 30% EtOAc/ toluene.

2.18. (S)-Mandelic acid (3'R)-2'-hydroxy-tetrahydropyran-3'-yl ester (20b)



The reaction was carried out following the General Procedure E to yield 68 mg (86%) of 5 to 3 mixture of *trans* and *cis* isomers of **20b**.

^1H NMR (500 MHz, CDCl_3) δ *trans*: 7.46, 7.38, 7.36, 5.27, 4.85, 4.74, 3.98, 3.76 (OH), 3.65 (2'-OH), 3.51, 1.93, 1.60, 1.47, 1.45 ppm; *cis*: 7.47, 7.38, 7.35, 5.30, 5.08, 4.91, 3.94, 3.86 (OH), 3.74 (2'-OH), 3.54, 1.85, 1.66, 1.52 ppm. ^{13}C NMR (500 MHz, CDCl_3) δ *trans*: 173.3 (C_k), 138.2 (C_s), 128.5 (C_m), 128.4 (C_p), 126.5 (C_o), 93.7 ($\text{C}_{2'}$), 72.88 (C_a), 72.2 ($\text{C}_{3'}$), 62.6 ($\text{C}_{6'}$), 24.8 ($\text{C}_{4'}$), 22.0 ($\text{C}_{5'}$) ppm; *cis*: 173.1 (C_k), 138.2 (C_s), 128.5 (C_m), 128.3 (C_p), 126.43 (C_o), 91.6 ($\text{C}_{2'}$), 72.92 (C_a), 71.6 ($\text{C}_{3'}$), 61.9 ($\text{C}_{6'}$), 24.2 ($\text{C}_{4'}$), 22.1 ($\text{C}_{5'}$) ppm.

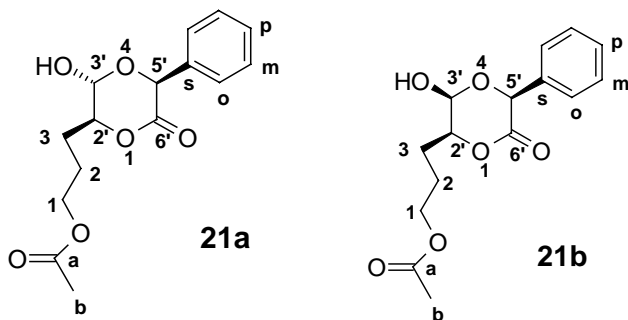
$[\alpha]_{546}^{25} = +49.5$ (c 1.2, EtOAc).

Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_5$ (252.29): C, 61.89; H, 6.41. Found: C, 61.67; H, 6.44.

TLC: R_f (15) = 0.23 (eluent 50% toluene/EtOAc).

Flash chromatography eluent: 20% to 30% EtOAc/ toluene.

2.19. Acetic acid 3-((2'S,3'R,5'S)-3'-hydroxy-6'-oxo-5'-phenyl-[1,4]dioxan-2'-yl)-propyl ester (21a) and acetic acid 3-((2'S,3'S,5'S)-3'-hydroxy-6'-oxo-5'-phenyl-[1,4]dioxan-2'-yl)-propyl ester (21b)



The reaction was carried out following the General Procedure B to yield 38 mg (92%) of **21a** containing about 8% of *cis*-hemiacetal **21b**.

21a: ^1H NMR (500 MHz, CDCl_3) δ 5.68, 5.48, 4.13, 3.87, 2.06, 1.94, 1.77, 1.74, 1.64.

^{13}C NMR (500 MHz, CDCl_3) δ 171.20 (C_a), 171.12 ($\text{C}_{6'}$), 133.8 (C_s), 129.1 (C_p), 128.9 (C_m), 126.0 (C_o), 105.3 ($\text{C}_{3'}$), 75.5 ($\text{C}_{5'}$), 72.1 ($\text{C}_{2'}$), 63.96 (C_1), 27.5 (C_3), 24.58 (C_2), 20.90 (C_b) ppm.

21b: ^1H NMR (500 MHz, CDCl_3) δ 5.57, 5.31, 3.90 ppm. ^{13}C NMR (500 MHz, CDCl_3) δ 171.24 (C_a), 171.15 ($\text{C}_{6'}$), 133.4 (C_s), 129.4 (C_p), 128.8 (C_m), 127.0 (C_o), 104.0 ($\text{C}_{3'}$), 76.4 ($\text{C}_{5'}$), 70.9 ($\text{C}_{2'}$), 64.02 (C_1), 27.4 (C_3), 24.57 (C_2), 20.93 (C_b) ppm.

MS (m/z): 252.30, 208.35, 144.25, 118.05, 107.10, 84.15.

IR (neat, cm^{-1}): 698, 1045, 1211, 1368, 1454, 1498, 1605, 1732, 1797, 3036, 3464.

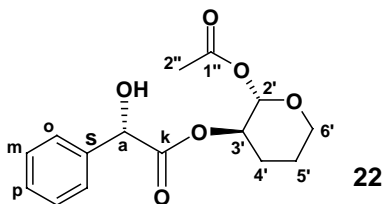
$[\alpha]^{20}_{589}$ (**21a**) = +53 (c 1.5, EtOAc).

Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_6$ (294.33): C, 61.21; H, 6.18. Found: C, 61.09; H, 6.20.

TLC: R_f (**21a**) = 0.44 (eluent 15% acetone / C_6H_6).

Flash chromatography eluent: 8% acetone/toluene.

2.20. (S)-Mandelic acid (2'S,3'R)-2'-acetoxy-tetrahydropyran-3'-yl ester (**22**)



The reaction was carried out following the General Procedure C to yield 64 mg (85%) of **22**.

^1H NMR (500 MHz, CDCl_3) δ 7.45, 7.37, 7.34, 5.87, 5.24, 4.80, 3.83, 3.63, 2.11, 1.94, 1.56, 1.54, 1.36 ppm. ^{13}C NMR (500 MHz, CDCl_3) δ 90.9 ($\text{C}_{2'}$), 69.3 ($\text{C}_{3'}$), 23.8 ($\text{C}_{4'}$), 20.4 ($\text{C}_{5'}$), 62.6 ($\text{C}_{6'}$), 169.1 ($\text{C}_{1'}$), 20.9 ($\text{C}_{2''}$), 172.7 (C_k), 72.8 (C_a), 138.1 (C_s), 126.4 (C_o), 128.6 (C_m), 128.5 (C_p) ppm.

MS (m/z): 277.25, 236.20, 217.20, 189.05, 143.10, 107.00, 84.00.

IR (neat, cm^{-1}): 1016, 1071, 1196, 1240, 1495, 1730-1745, 2956, 3387.

$[\alpha]^{20}_{589}$ (**22**) = -5.5 (c 6.4, EtOAc).

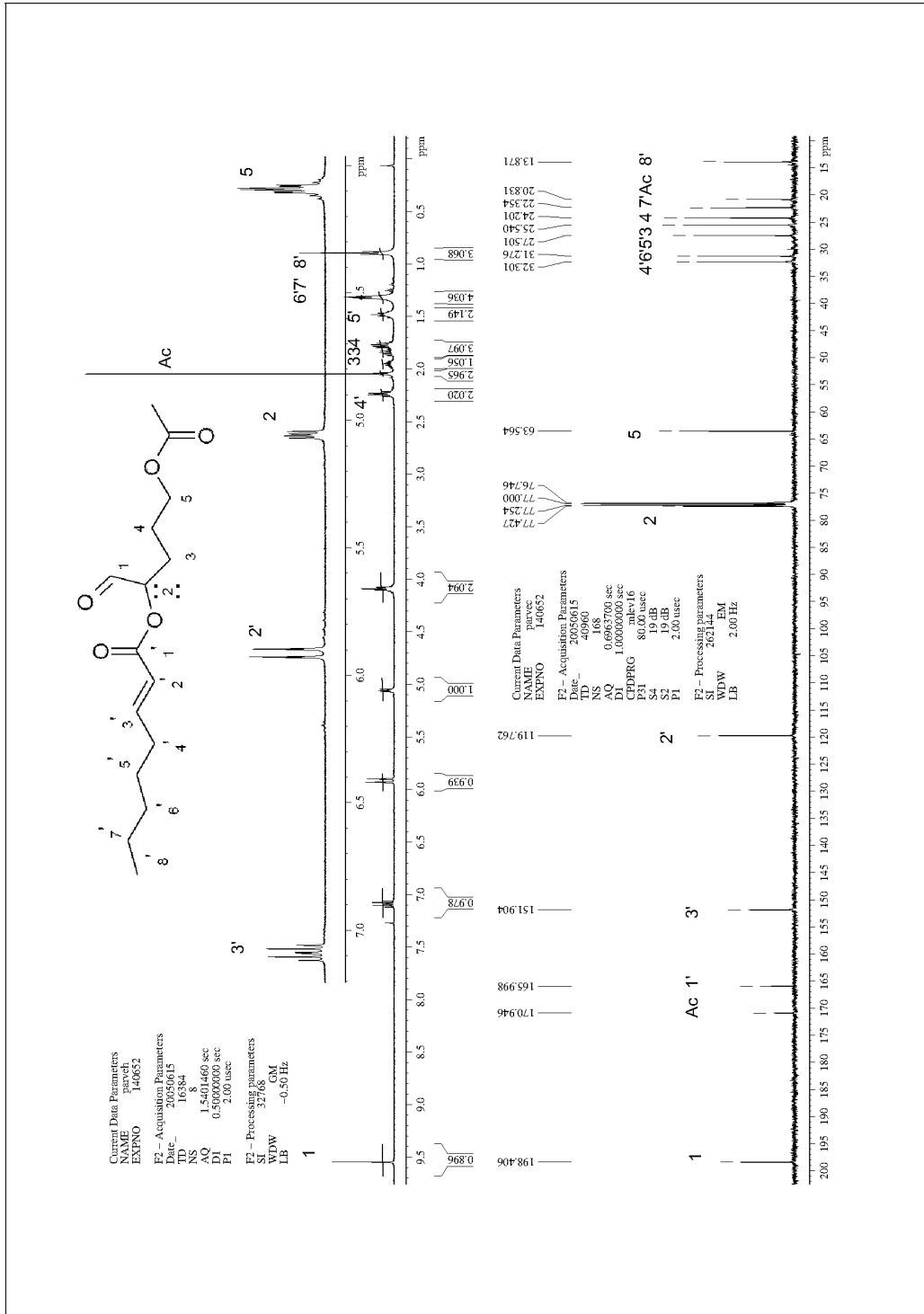
Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_6$ (294.33): C, 61.21; H, 6.18. Found: C, 61.10; H, 6.16.

TLC: R_f = 0.4 (eluent 15% acetone/toluene).

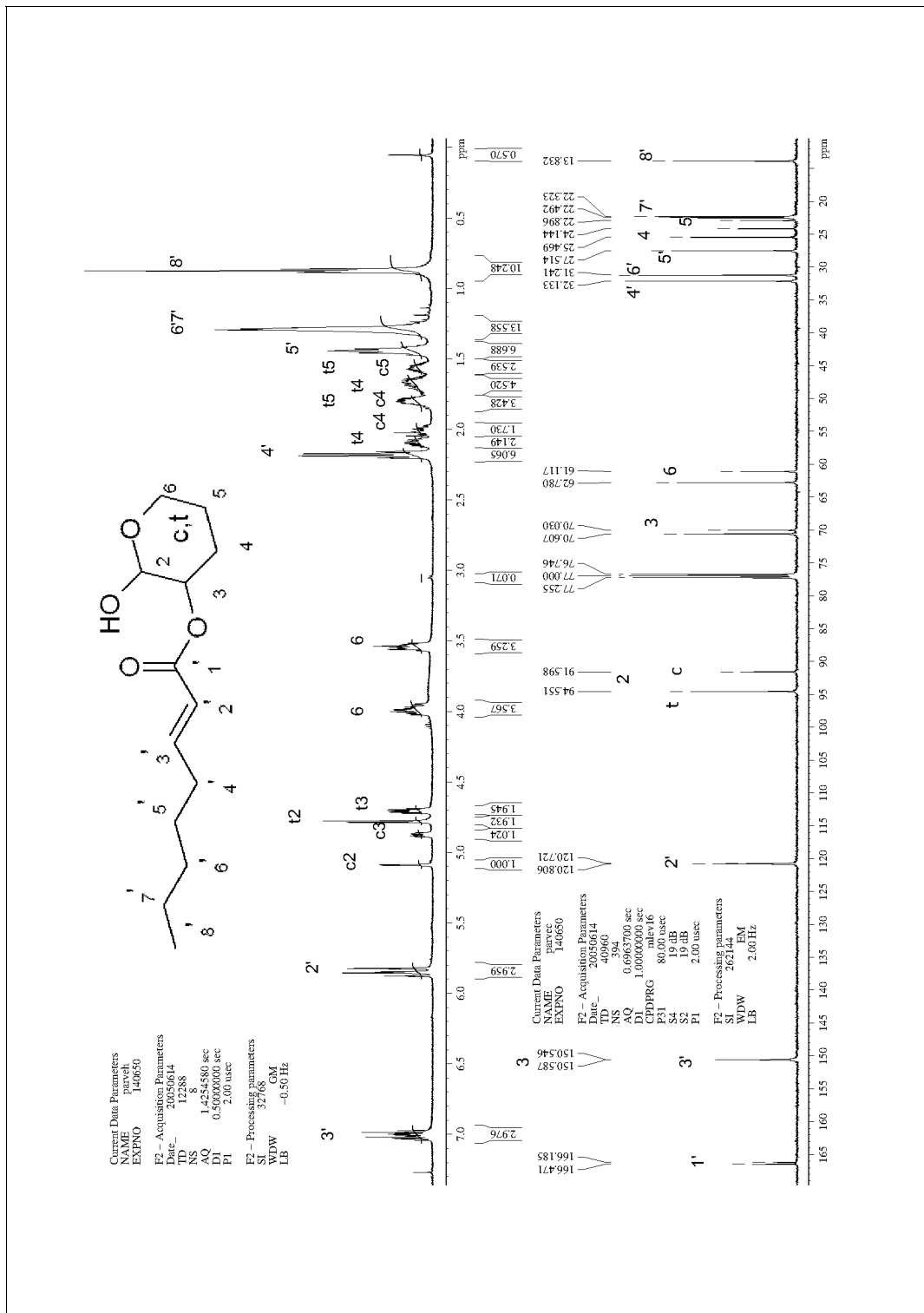
Flash chromatography eluent: 8% acetone/toluene.

3. Copies of ^1H and ^{13}C spectra

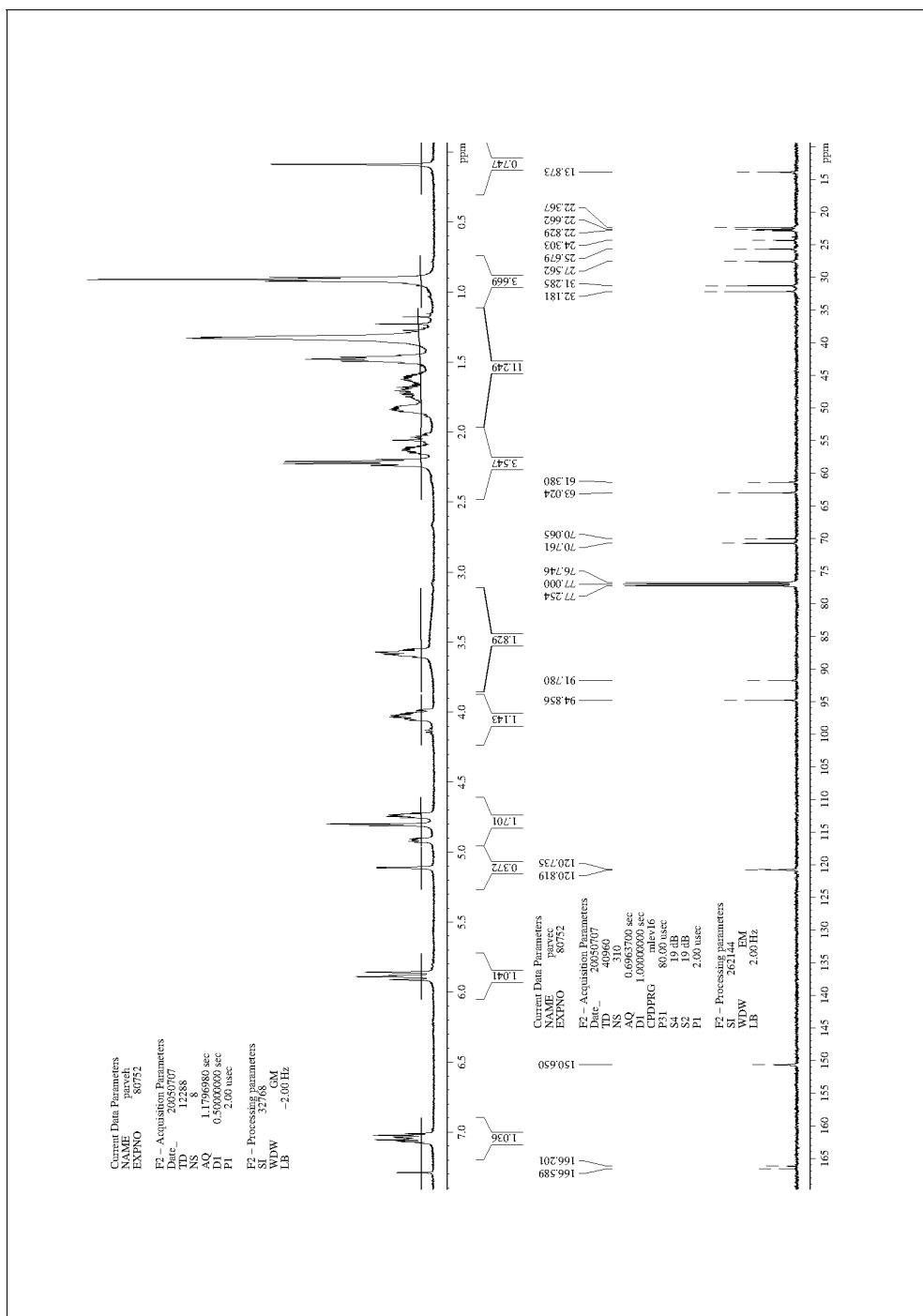
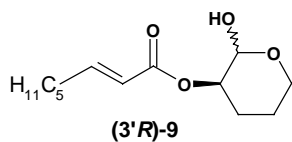
3.1. (E)-Oct-2-enoic acid 4'-acetoxy-1'-formyl-butyl ester (7)



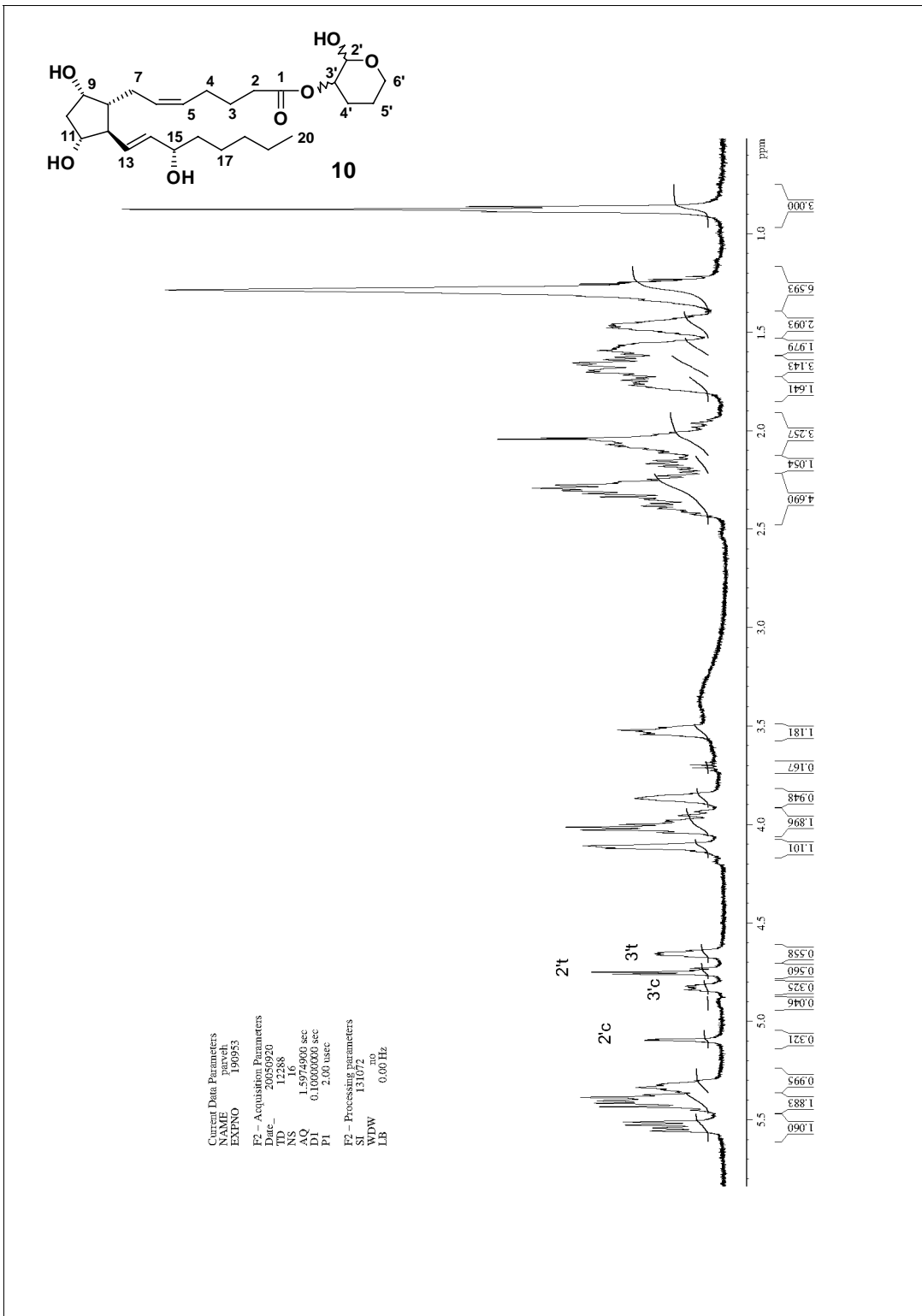
3.2. (E)-Oct-2-enoic acid 2'-hydroxy-tetrahydropyran-3'-yl ester (8)

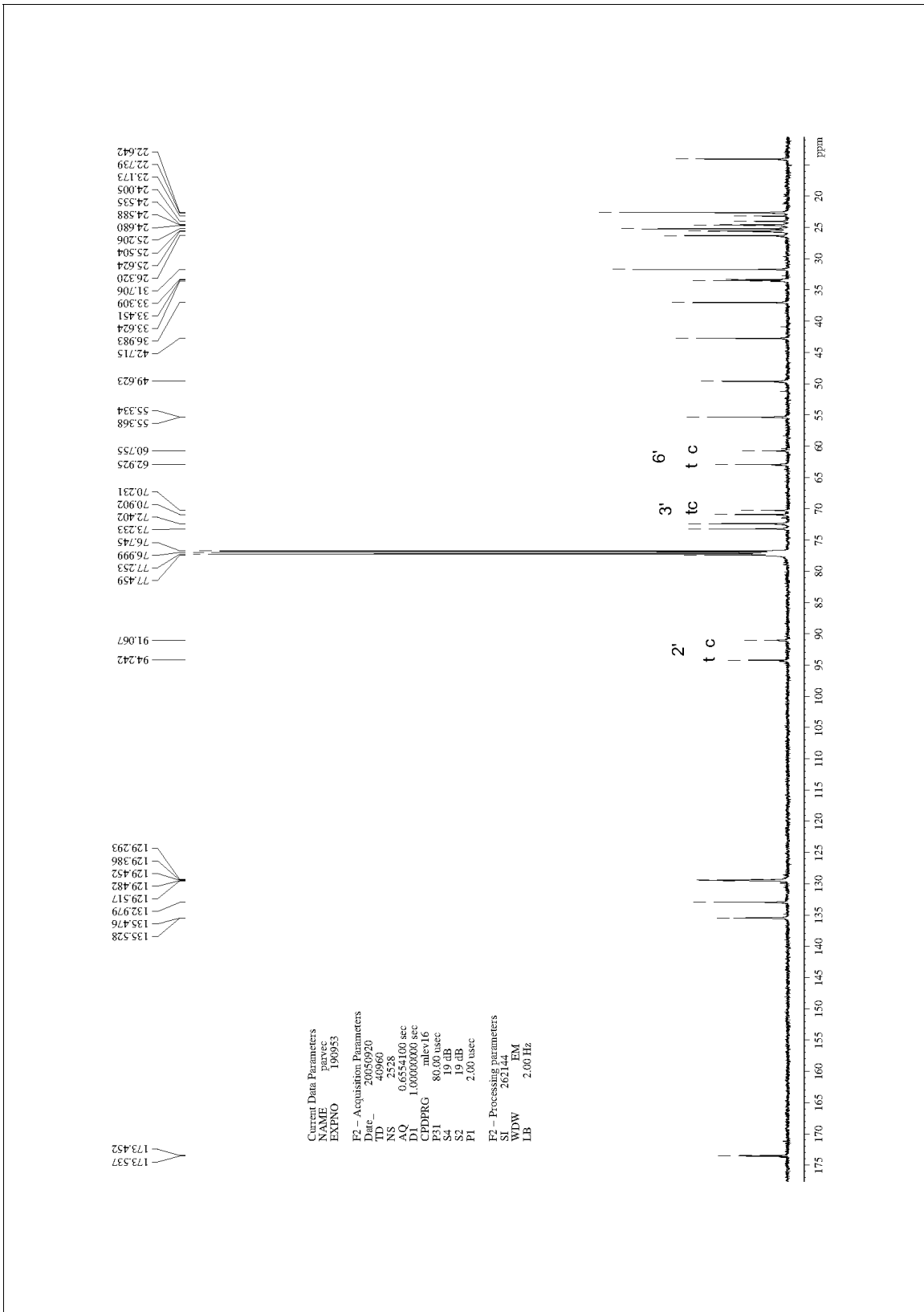


3.3. (E)-Oct-2-enoic acid (3'R)-2'-hydroxy-tetrahydropyran-3'-yl ester ((3'R)-8)

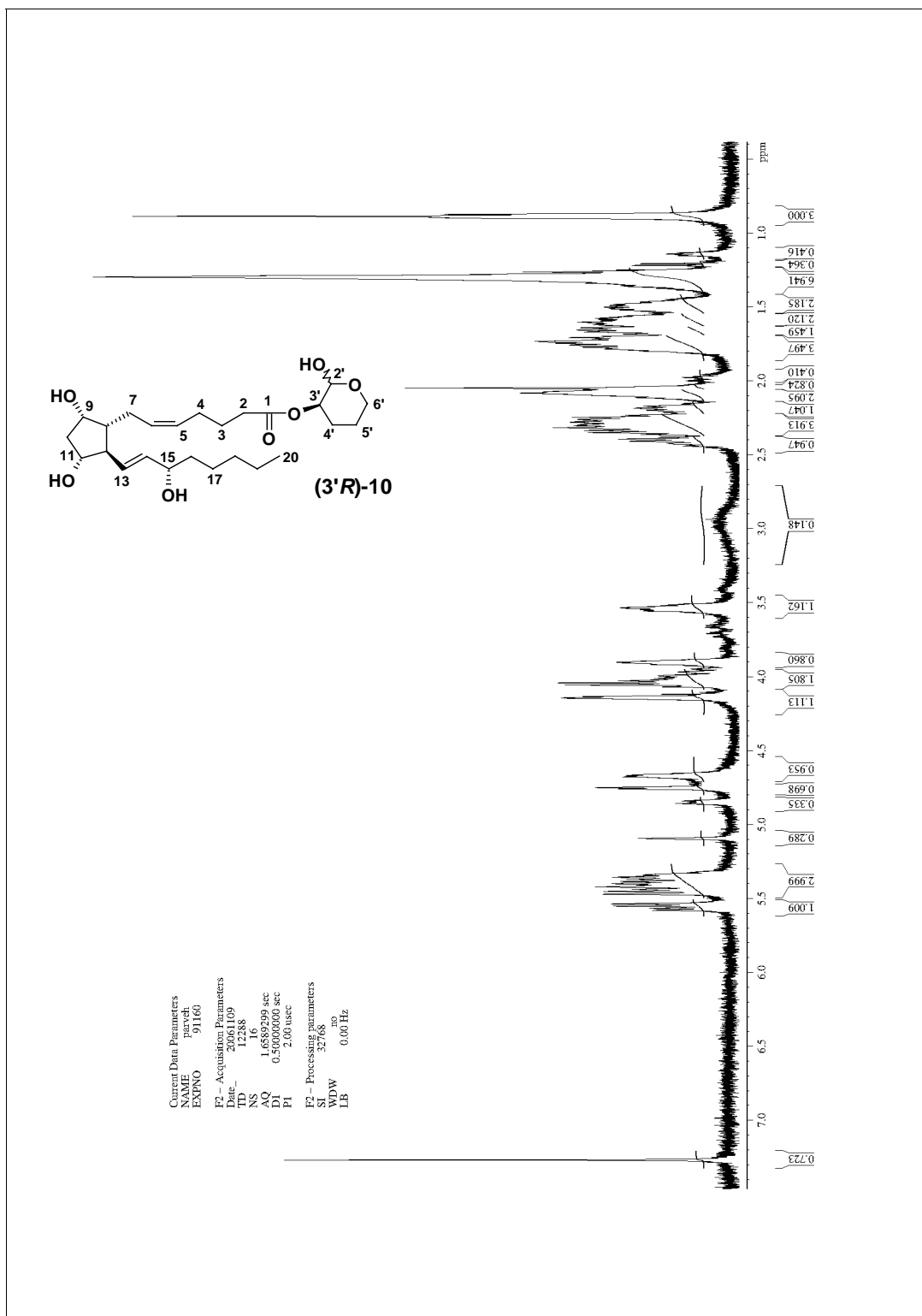


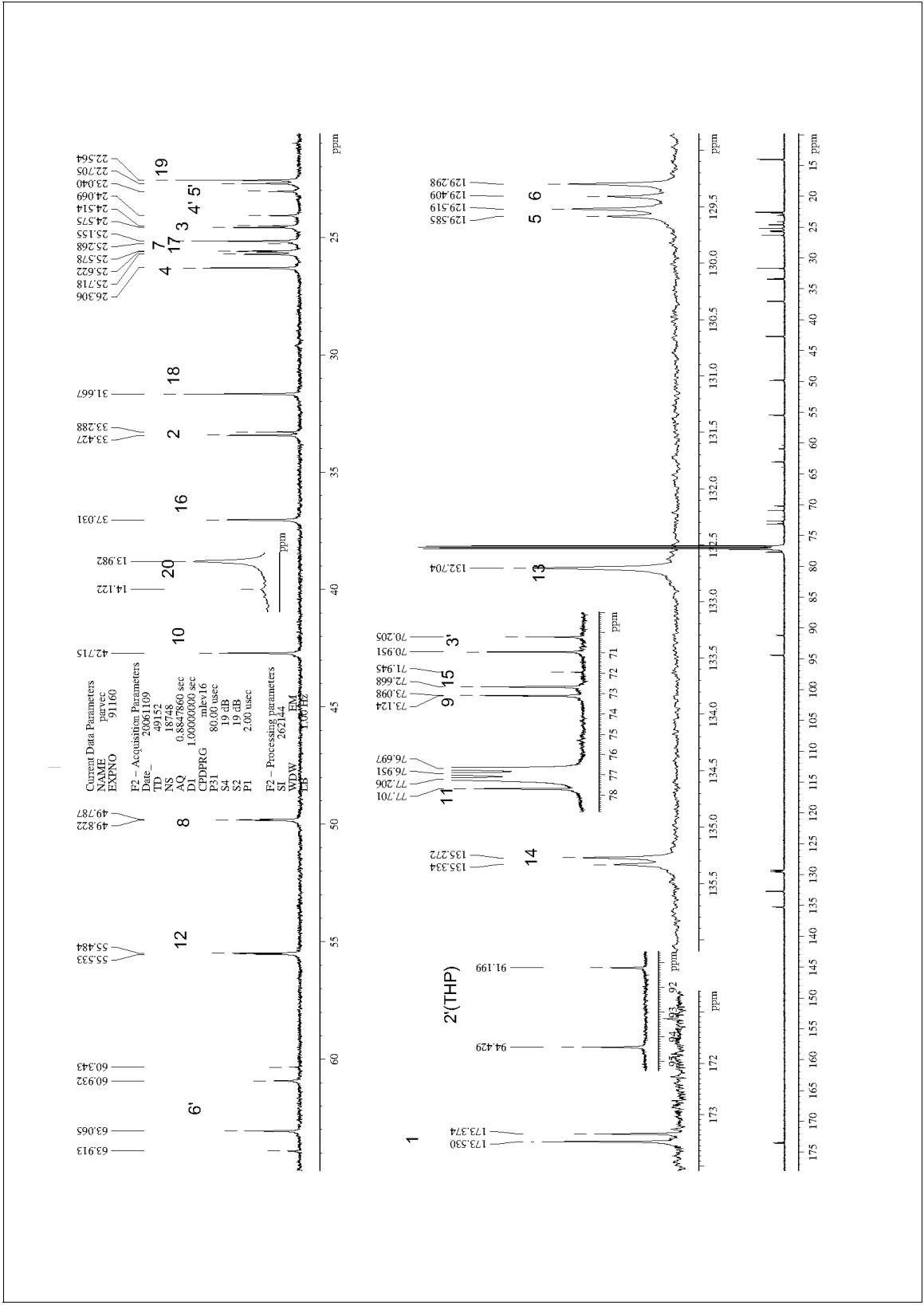
3.5. Prostaglandin F_{2α} 2'-hydroxy-tetrahydropyran-3'-yl ester (10)



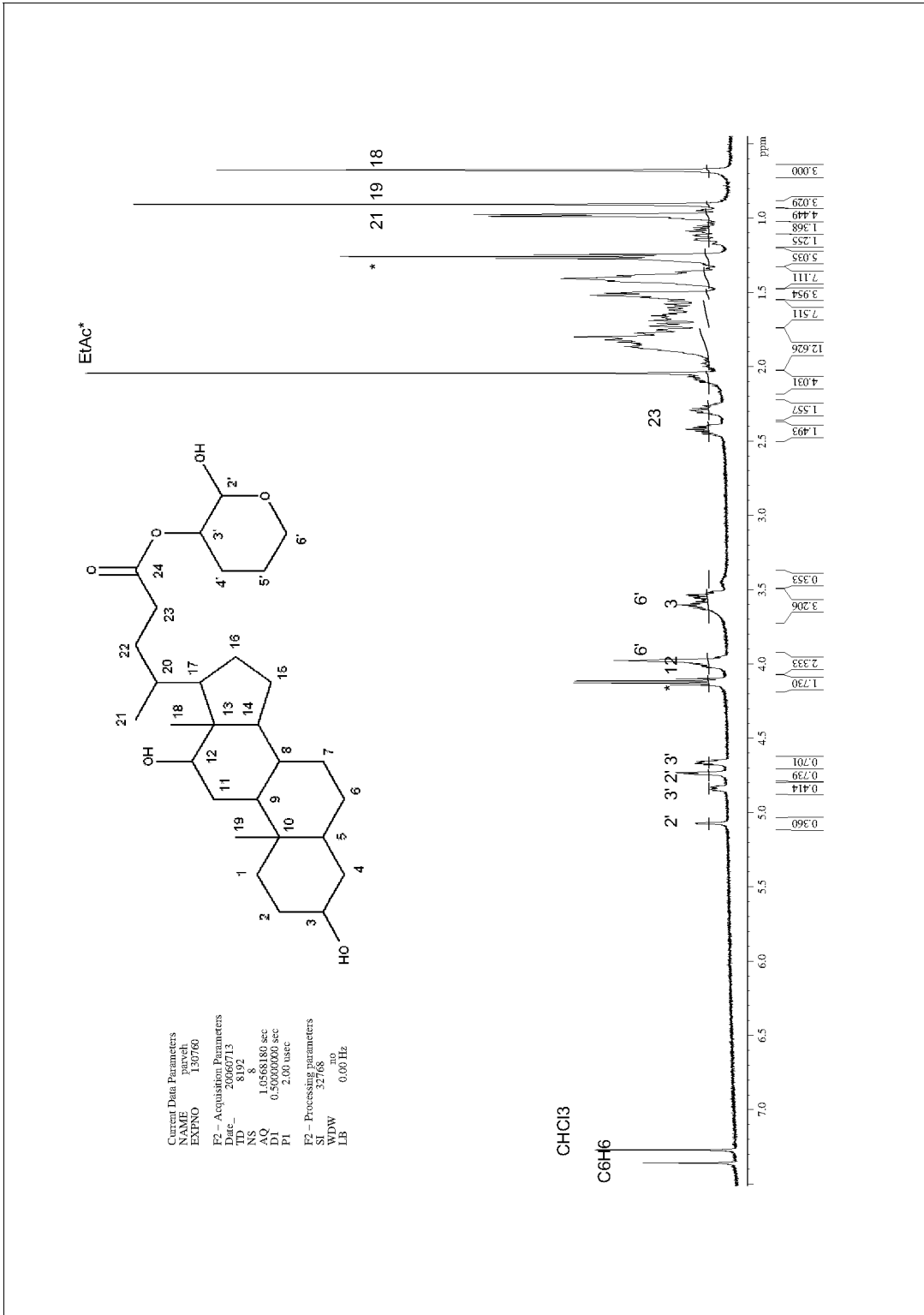


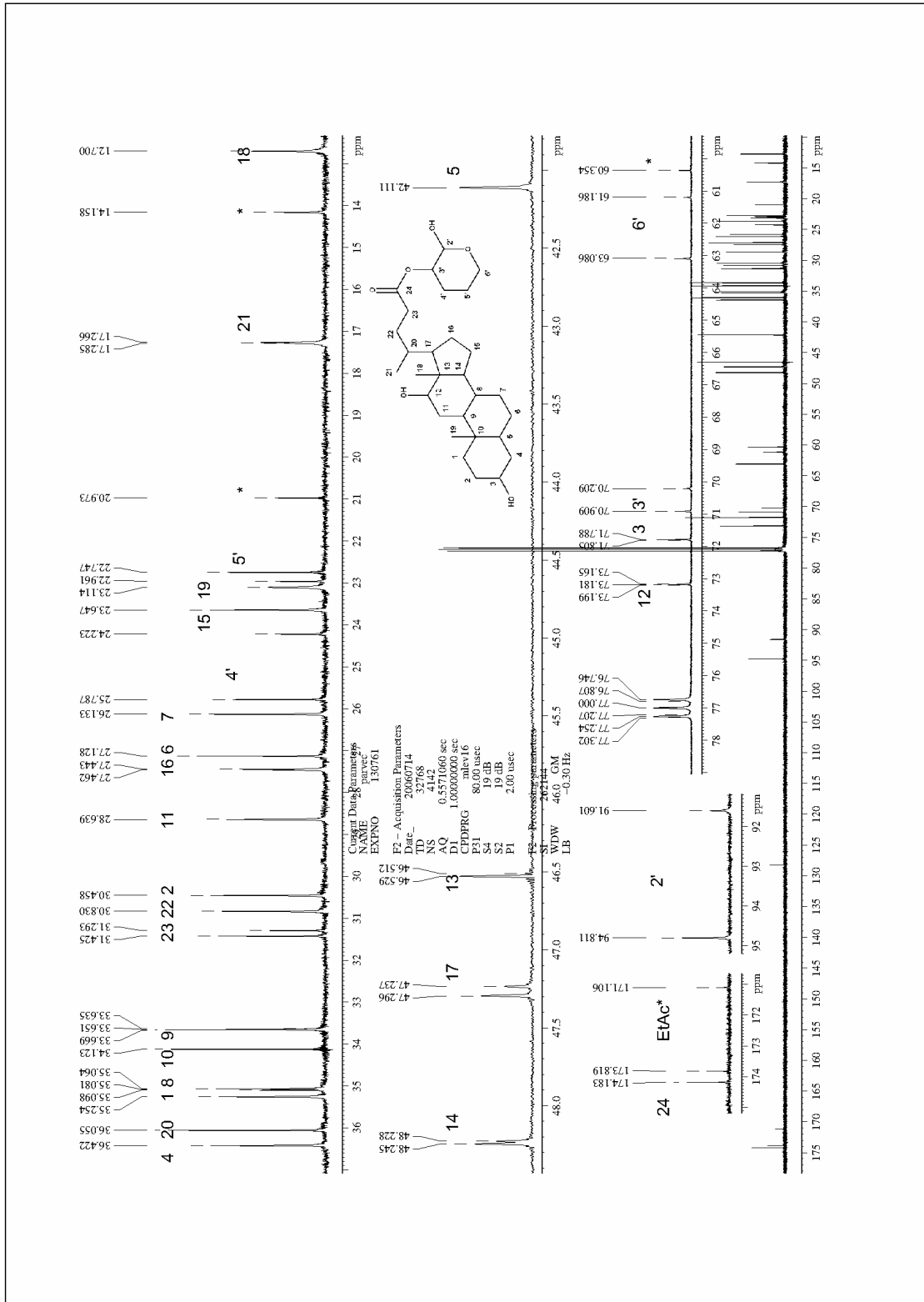
3.6. Prostaglandin F_{2α} (3'R)-2'-hydroxy-tetrahydropyran-3'-yl ester ((3'R)-10)



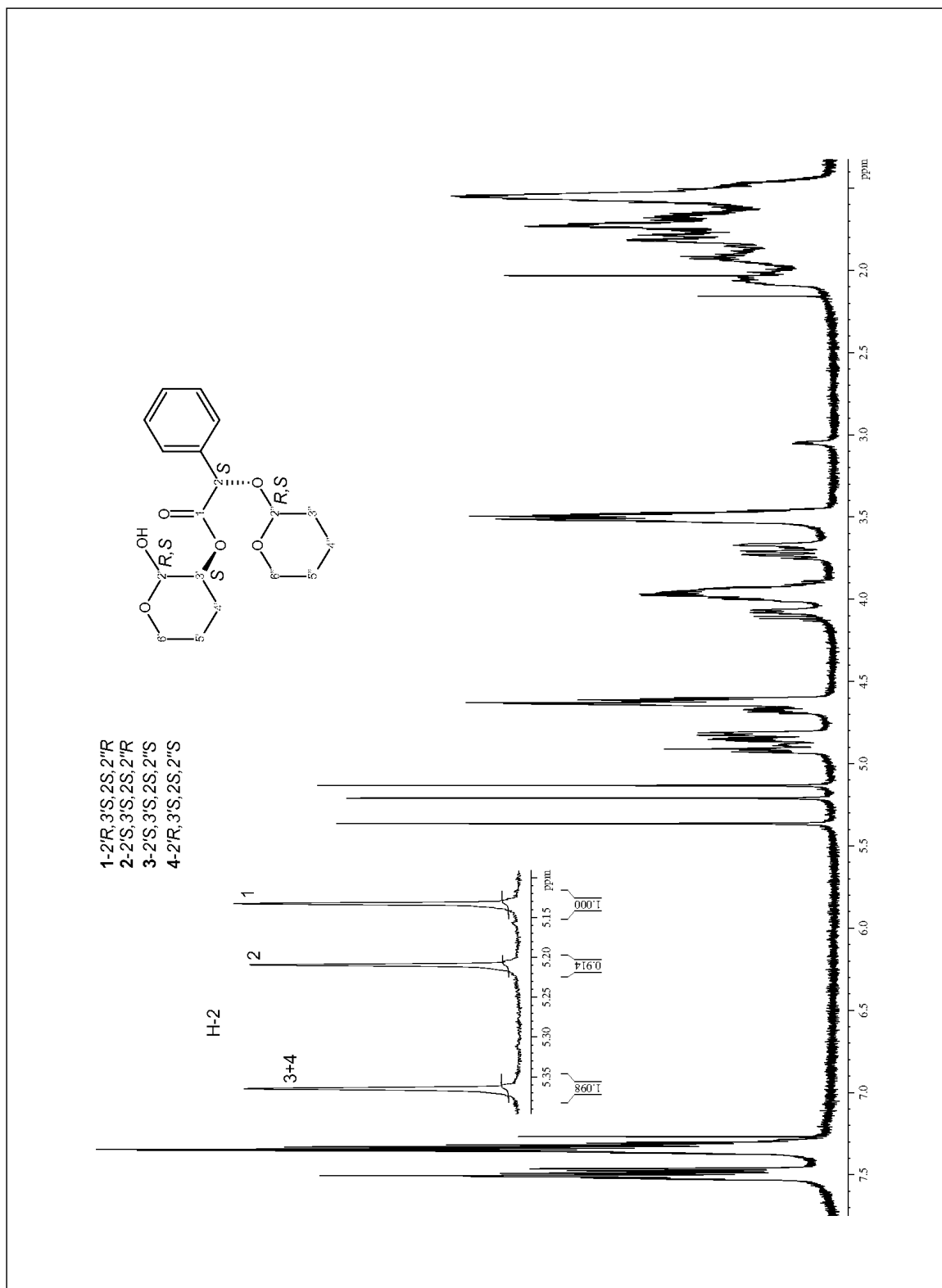


3.7. Deoxycholic acid (3'R)-2'-hydroxy-tetrahydropyran-3'-yl ester ((3'R)-12)

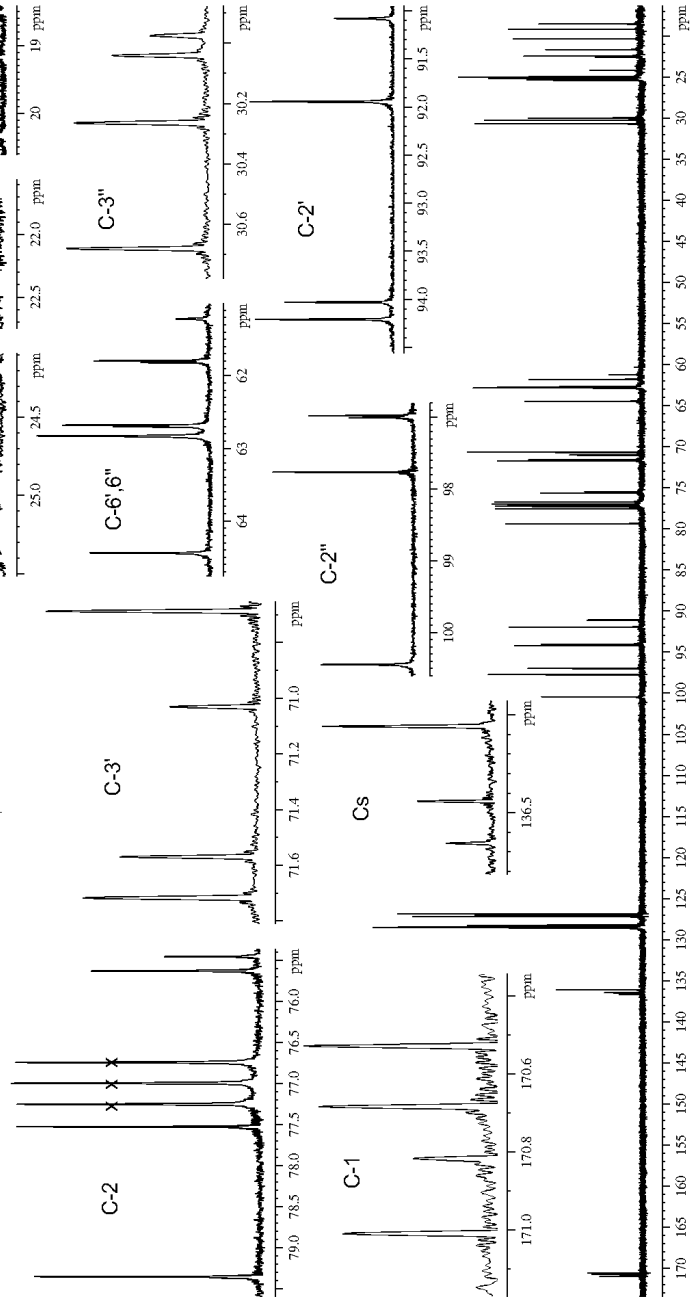
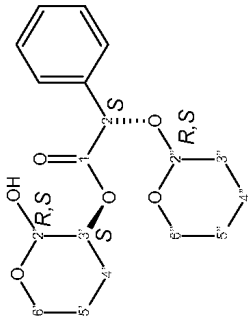




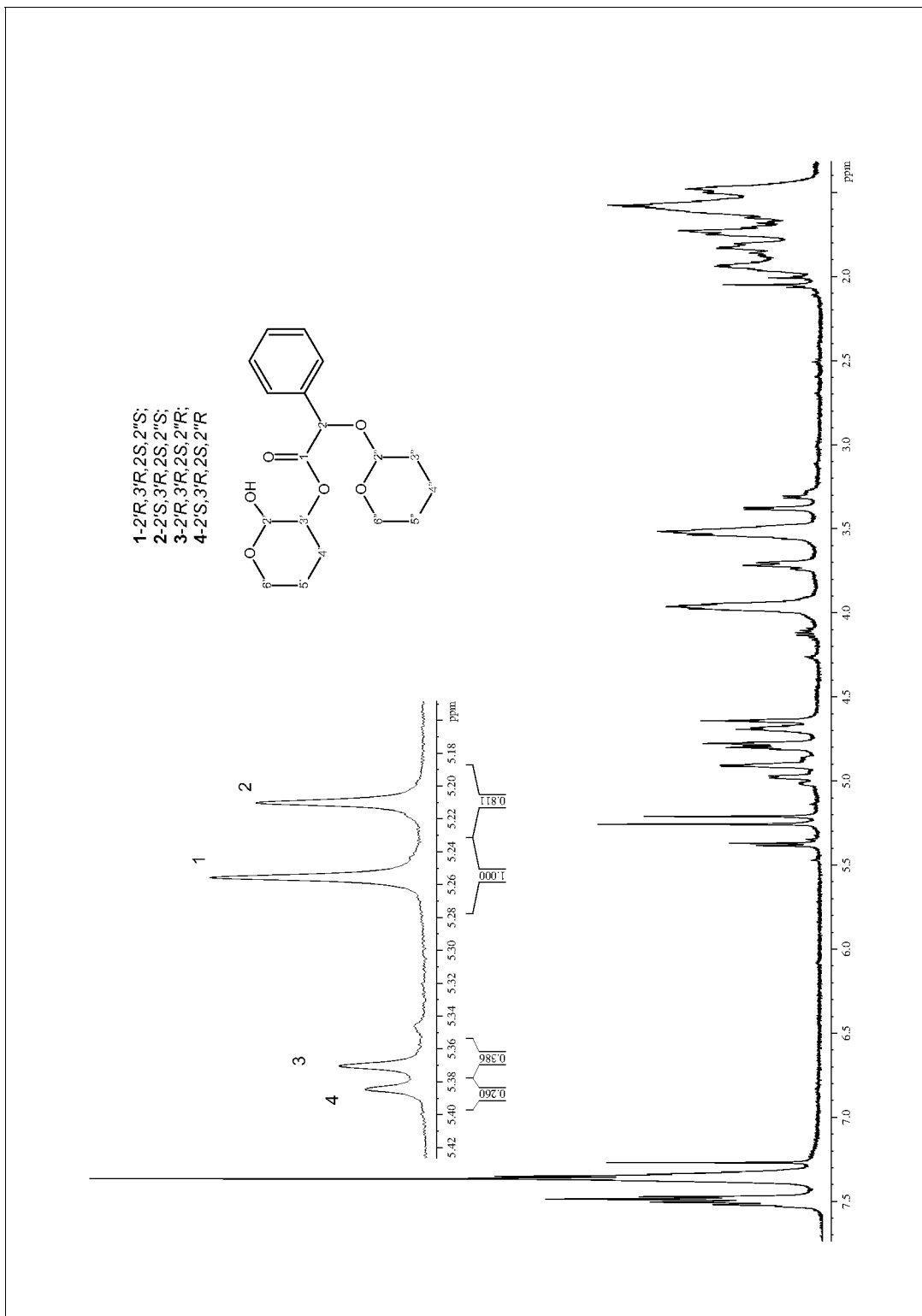
3.8. Tetrahydropyranyl-(S)-mandelic acid (3'S)-2'-hydroxy-tetrahydropyran-3'-yl ester (14a)

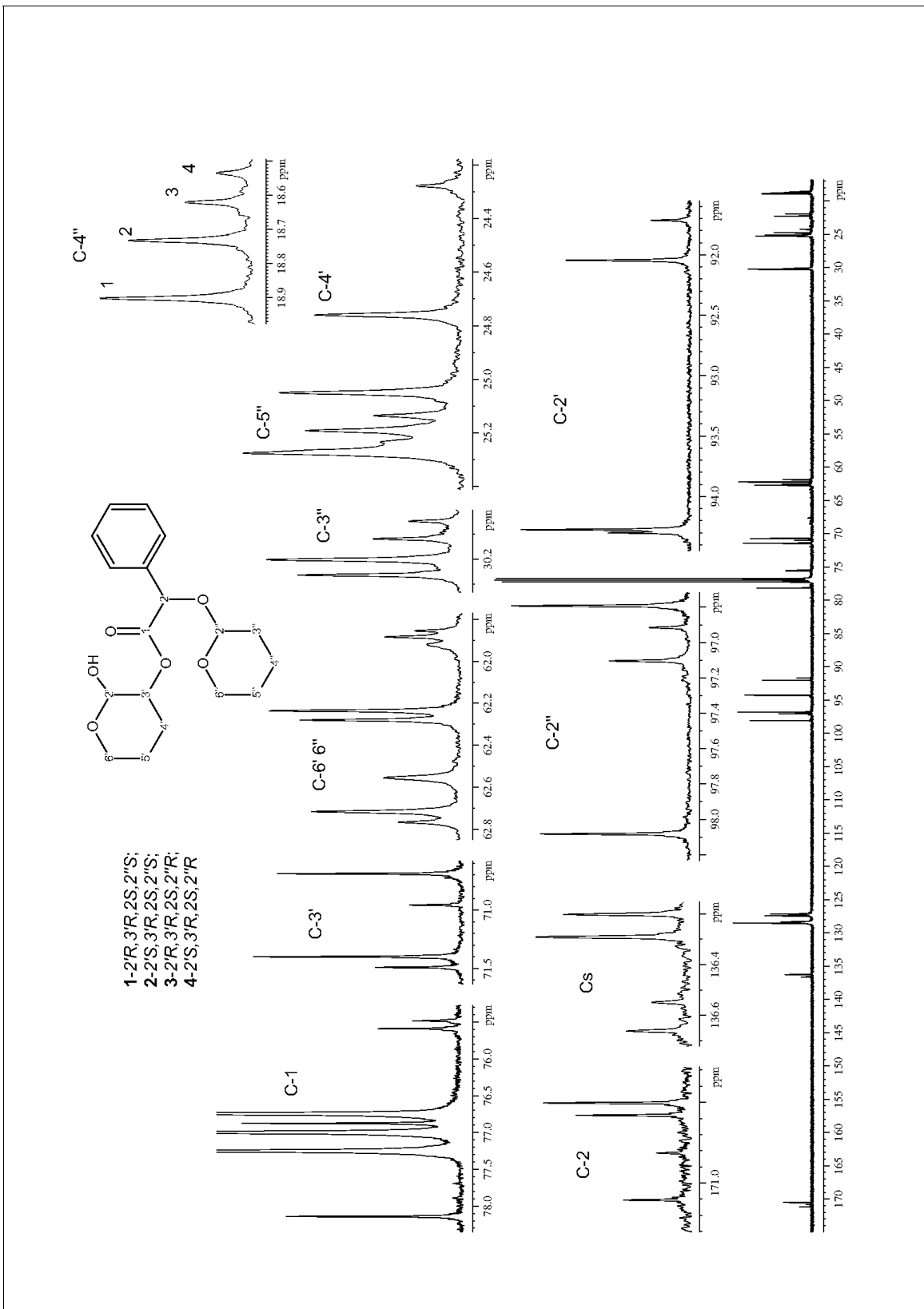


1-2'R,3'S,2S,2''R
 2-2'S,3'S,2S,2''R
 3-2'S,3'S,2S,2''S
 4-2'R,3'S,2S,2''S

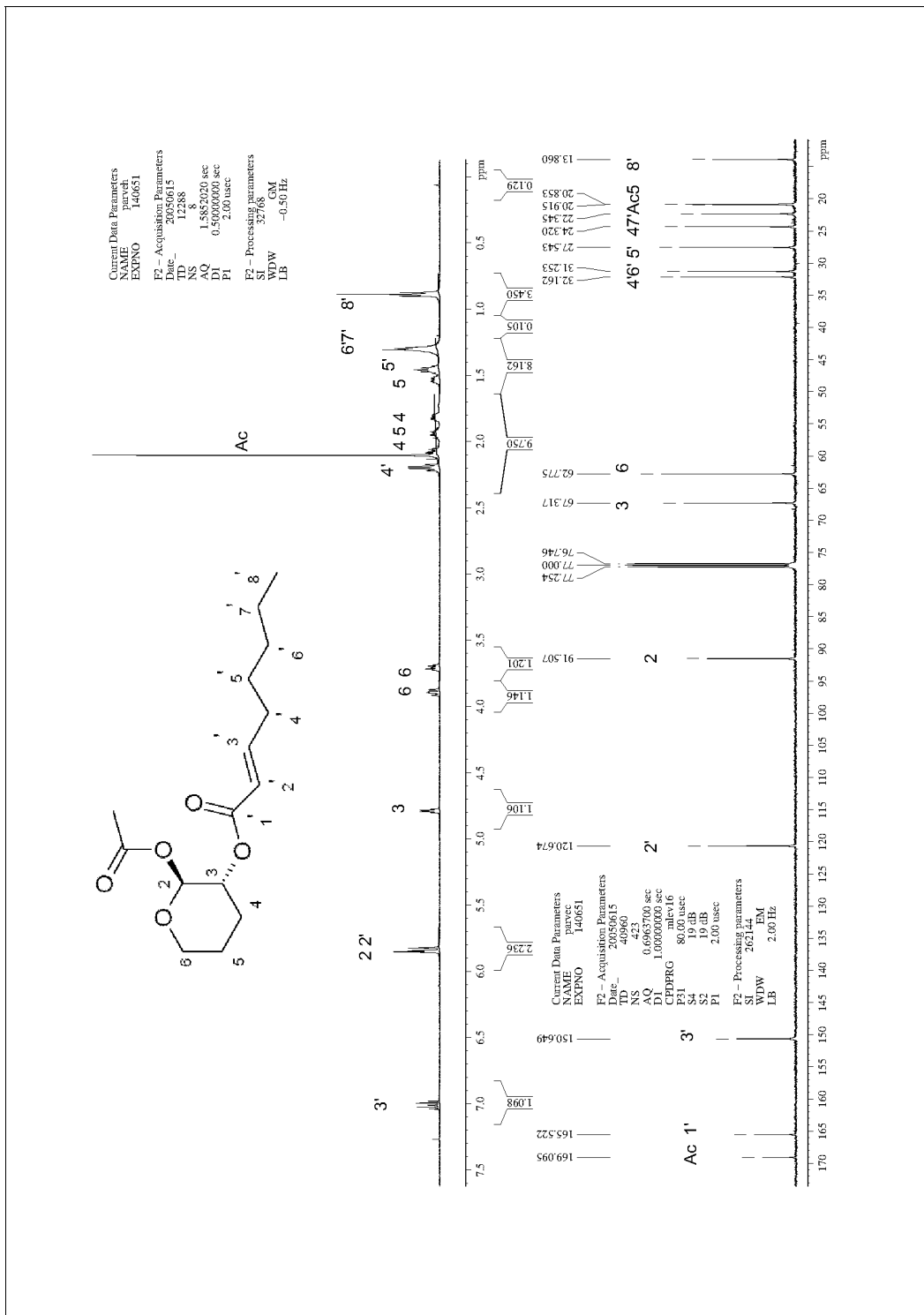


3.9. Tetrahydropyranyl-(S)-mandelic acid (3'R)-2'-hydroxy-tetrahydropyran-3'-yl ester (14b)



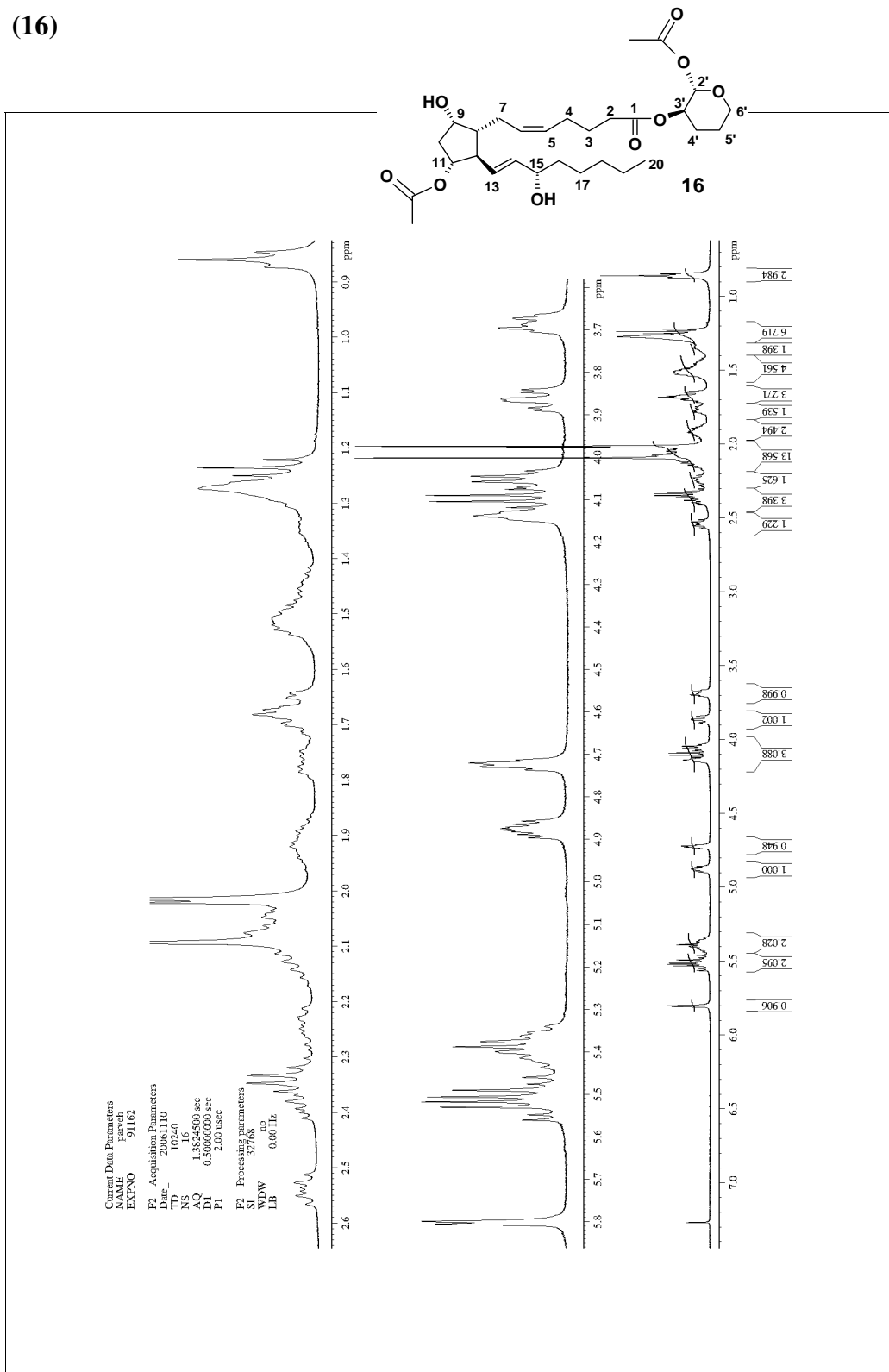


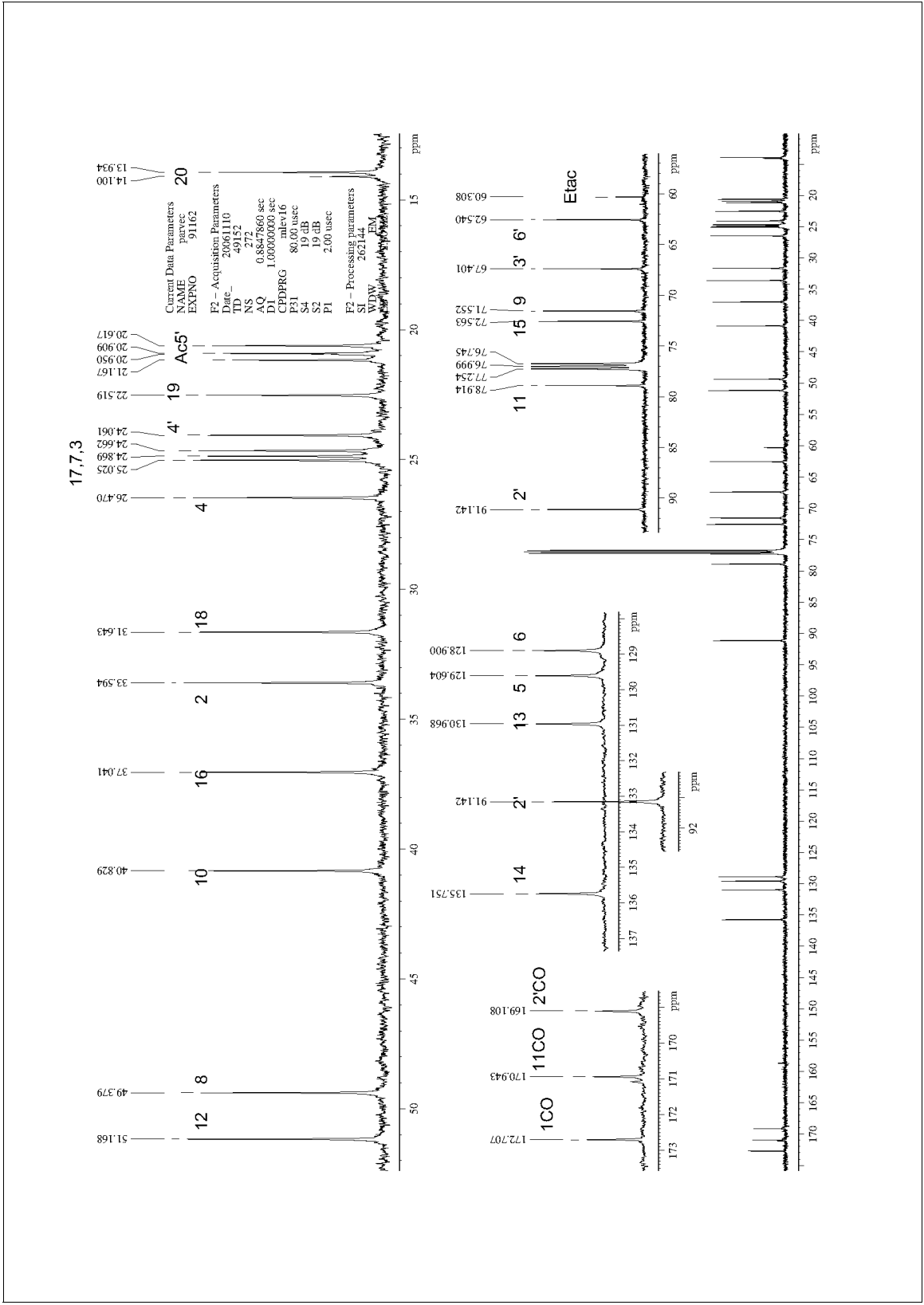
3.10. (*E*)-Oct-2-enoic acid (2'*S*,3'*R*)-2'-acetoxy-tetrahydropyran-3'-yl ester (15)



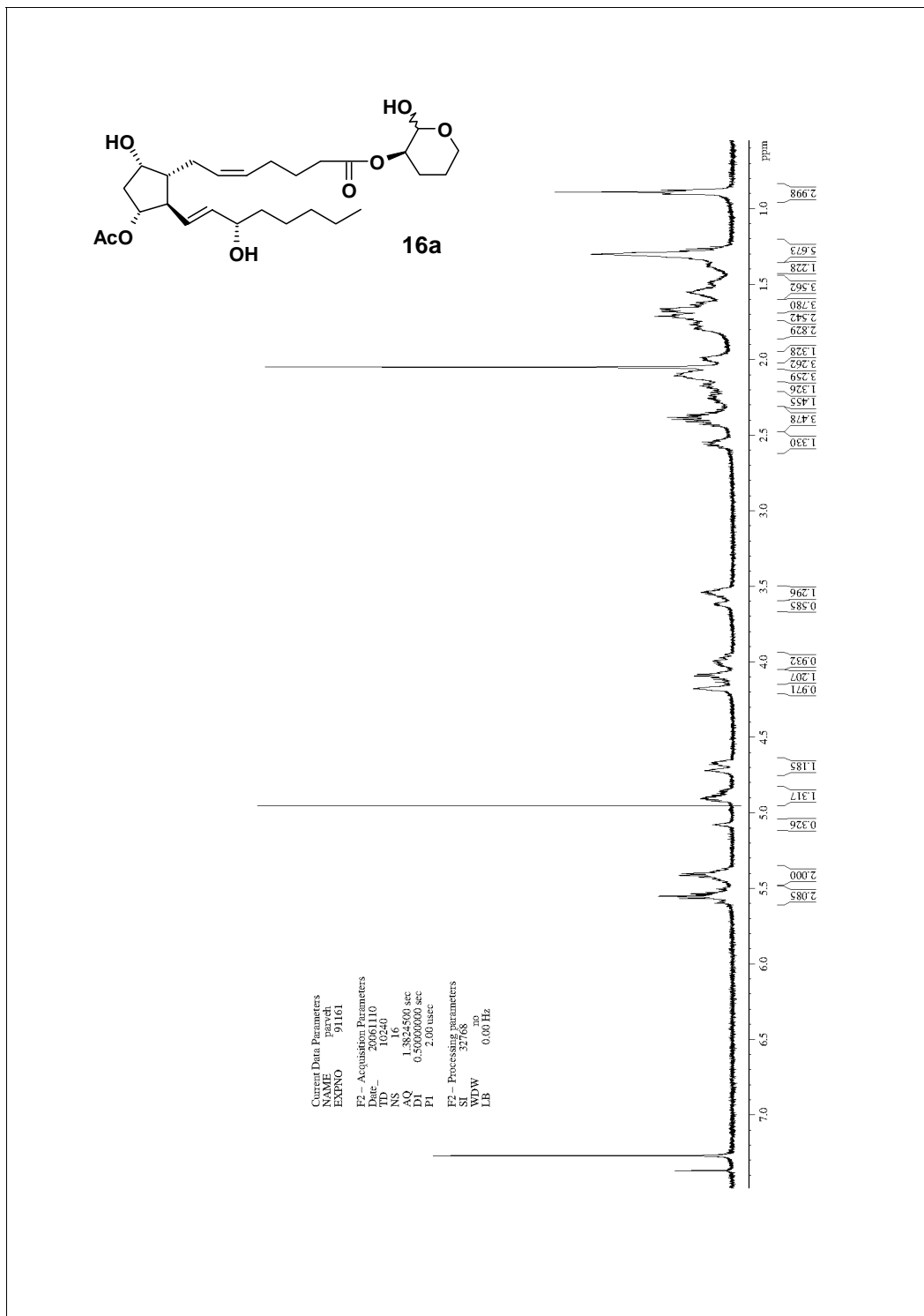
3.11. 11-Acetyl-prostaglandin F_{2α} (2'S,3'R)-2'-acetoxy-tetrahydropyran-3'-yl ester

(16)





3.12. 11-Acetyl-prostaglandin F_{2α} (3'R)-2'-hydroxy-tetrahydropyran-3'-yl ester
(16a)



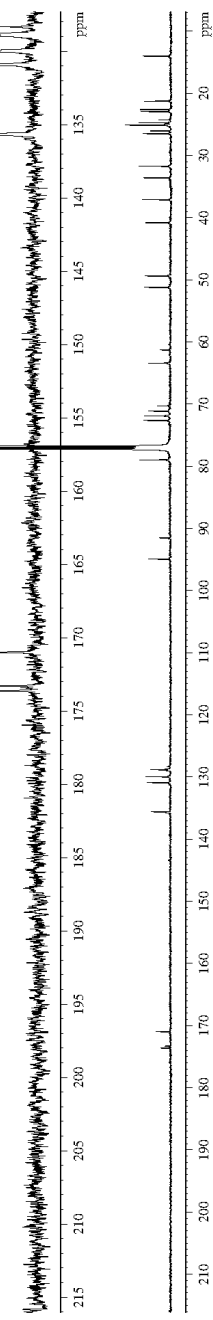
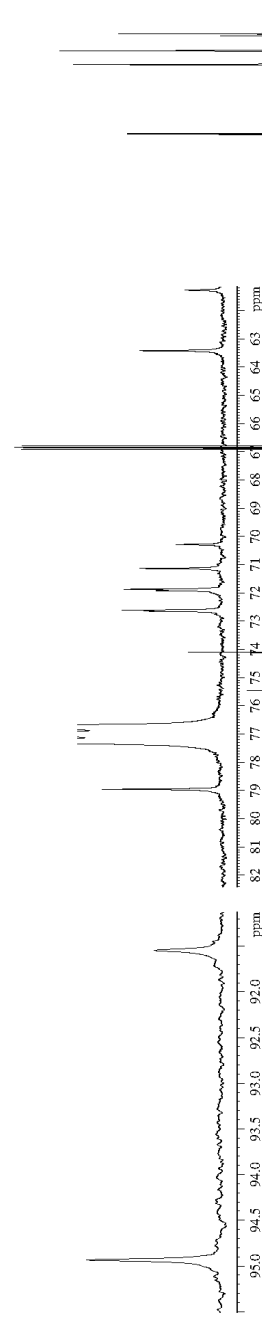
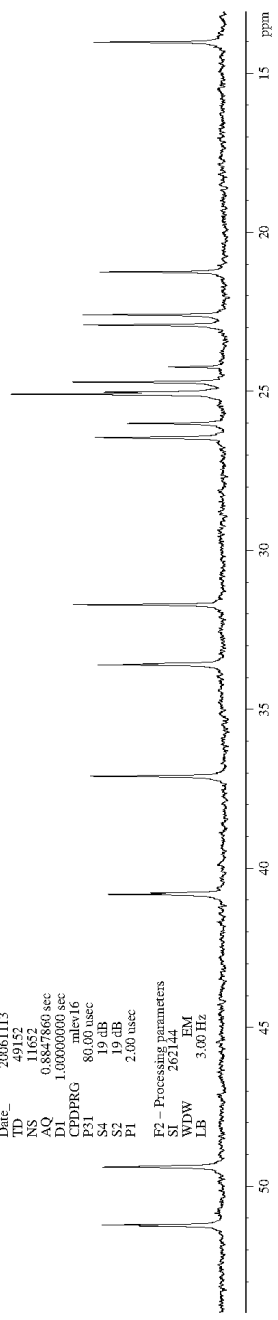
Current Data Parameters
NAME parvec
EXPNO 131161

F2 - Acquisition Parameters

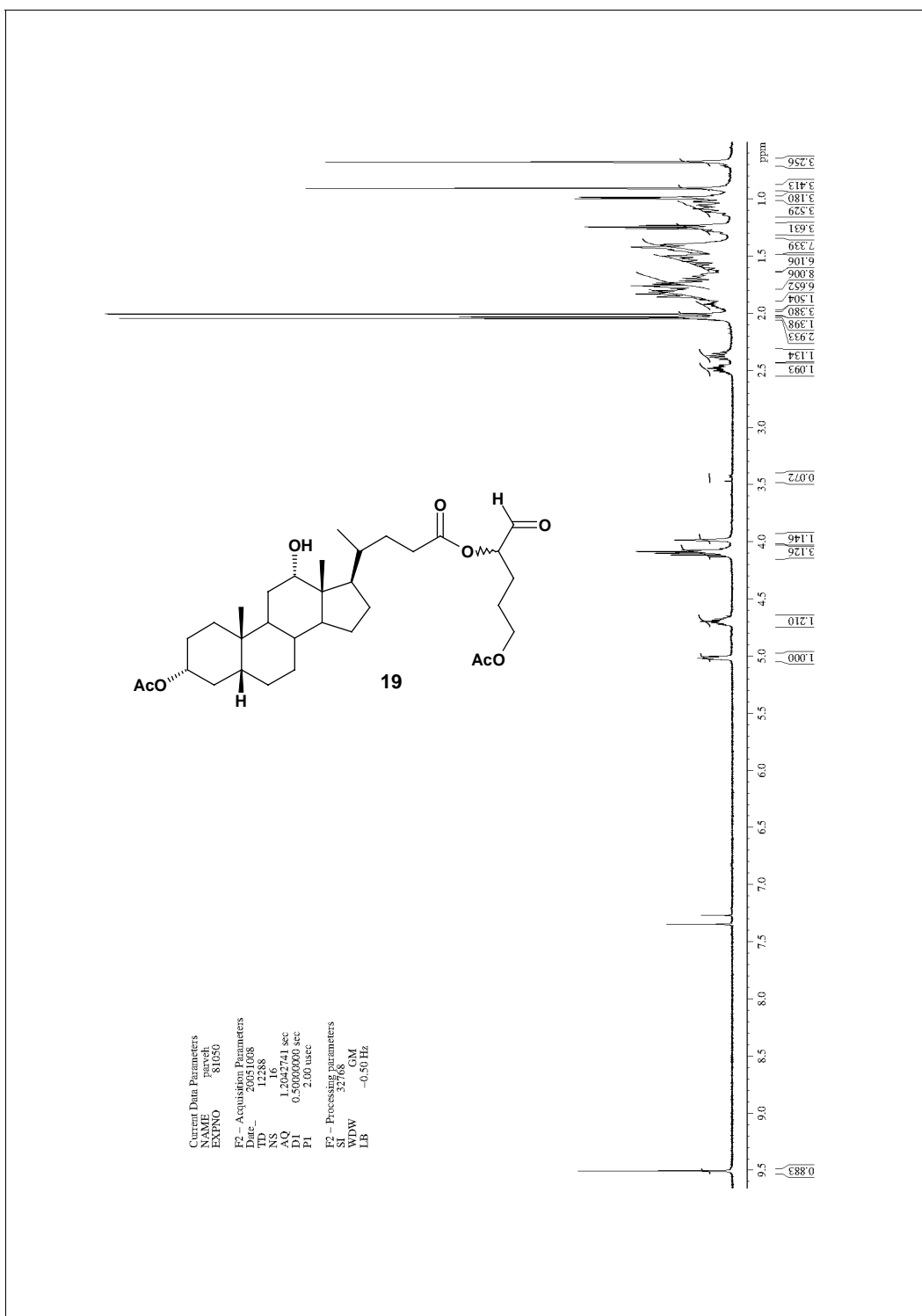
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DQ 1.00000000 sec
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S4 19 dB
S2 19 dB
P1 2.00 usec

F2 - Processing parameters

SI 262144
WDW EM
LB 3.00 Hz

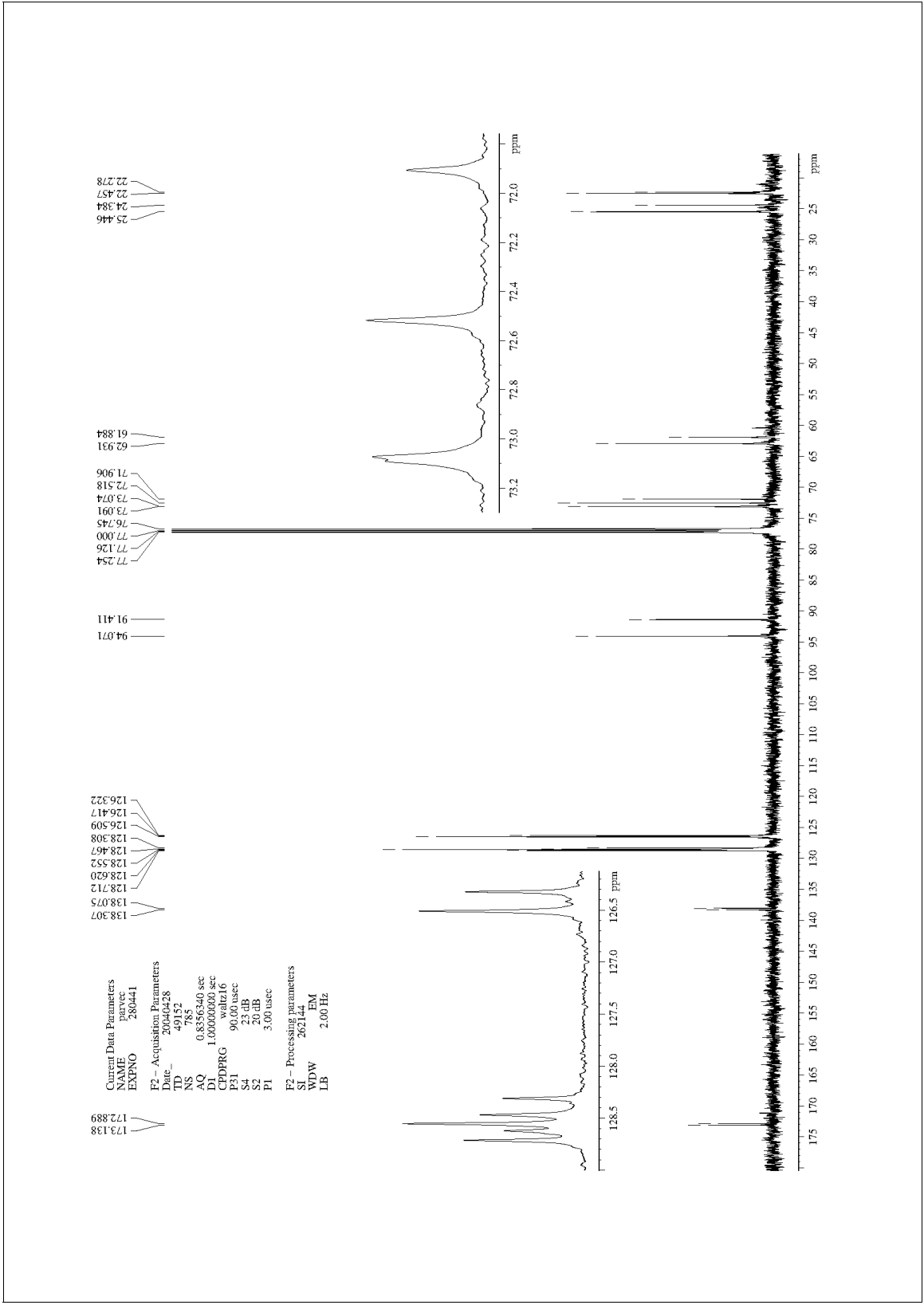


3.13. 3-Acetyl-deoxycholic acid 4'-acetoxy-1'-formyl-butyl ester (19)

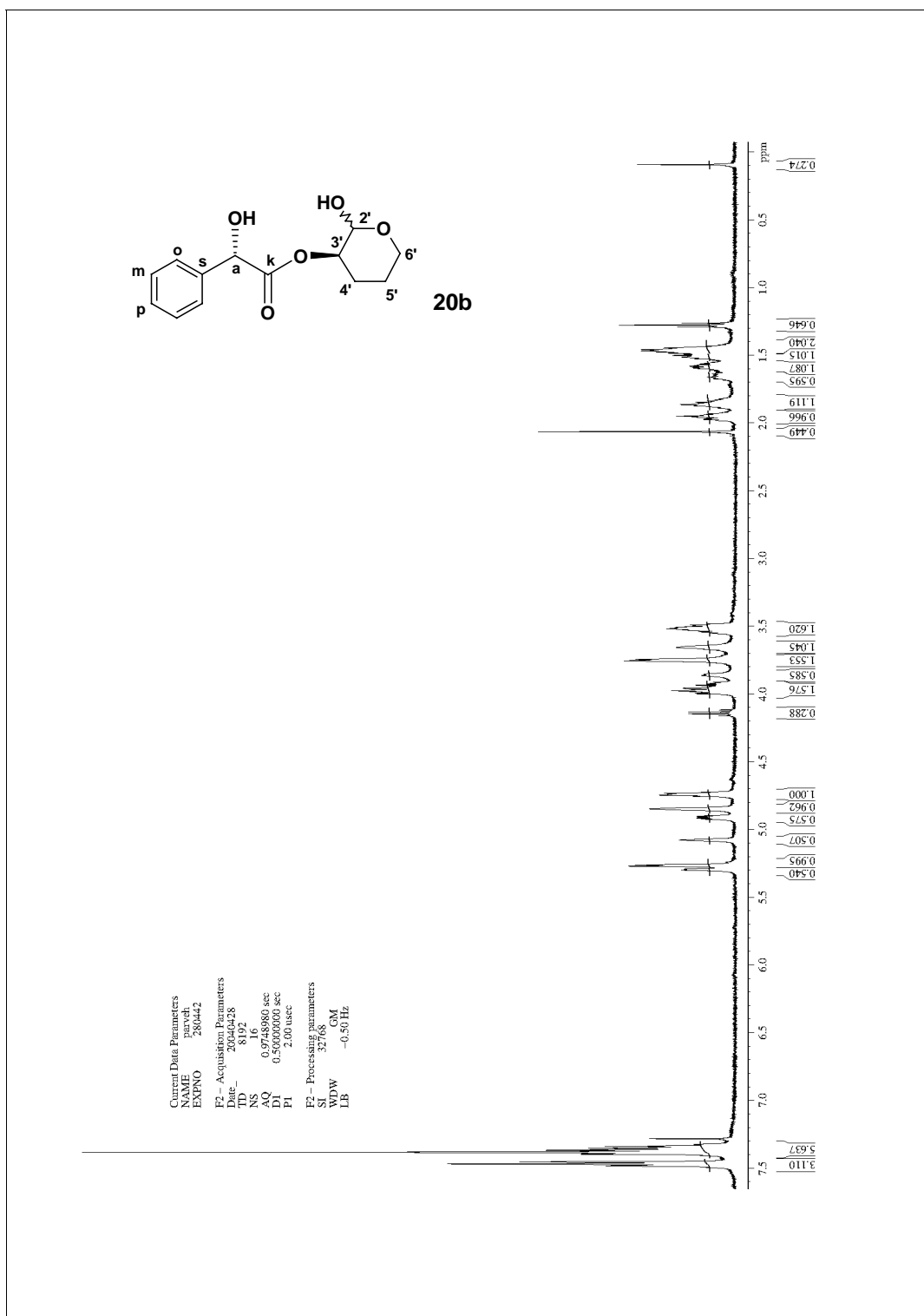


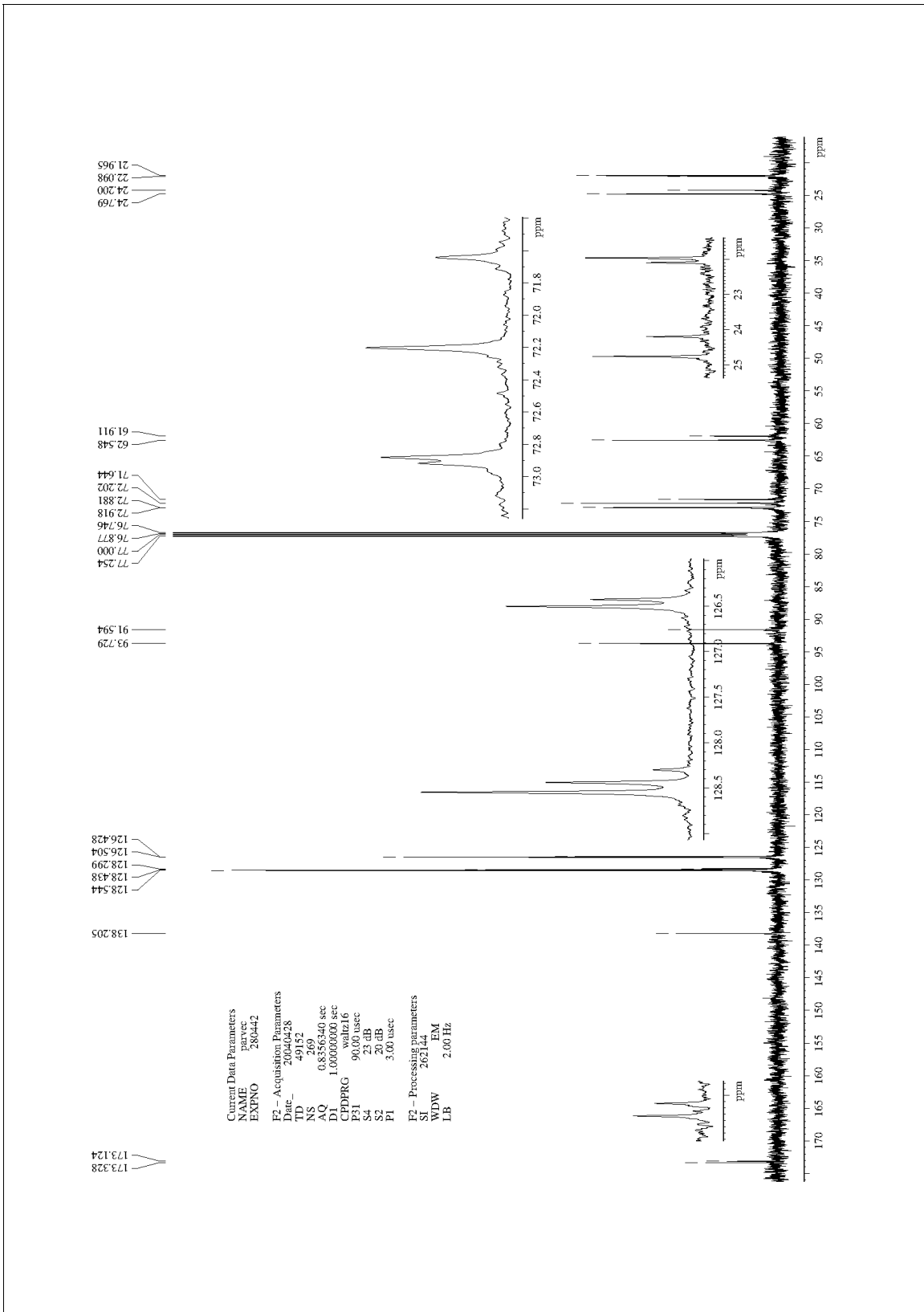
3.14. (S)-Mandelic acid (3'S)-2'-hydroxy-tetrahydropyran-3'-yl ester (20a)



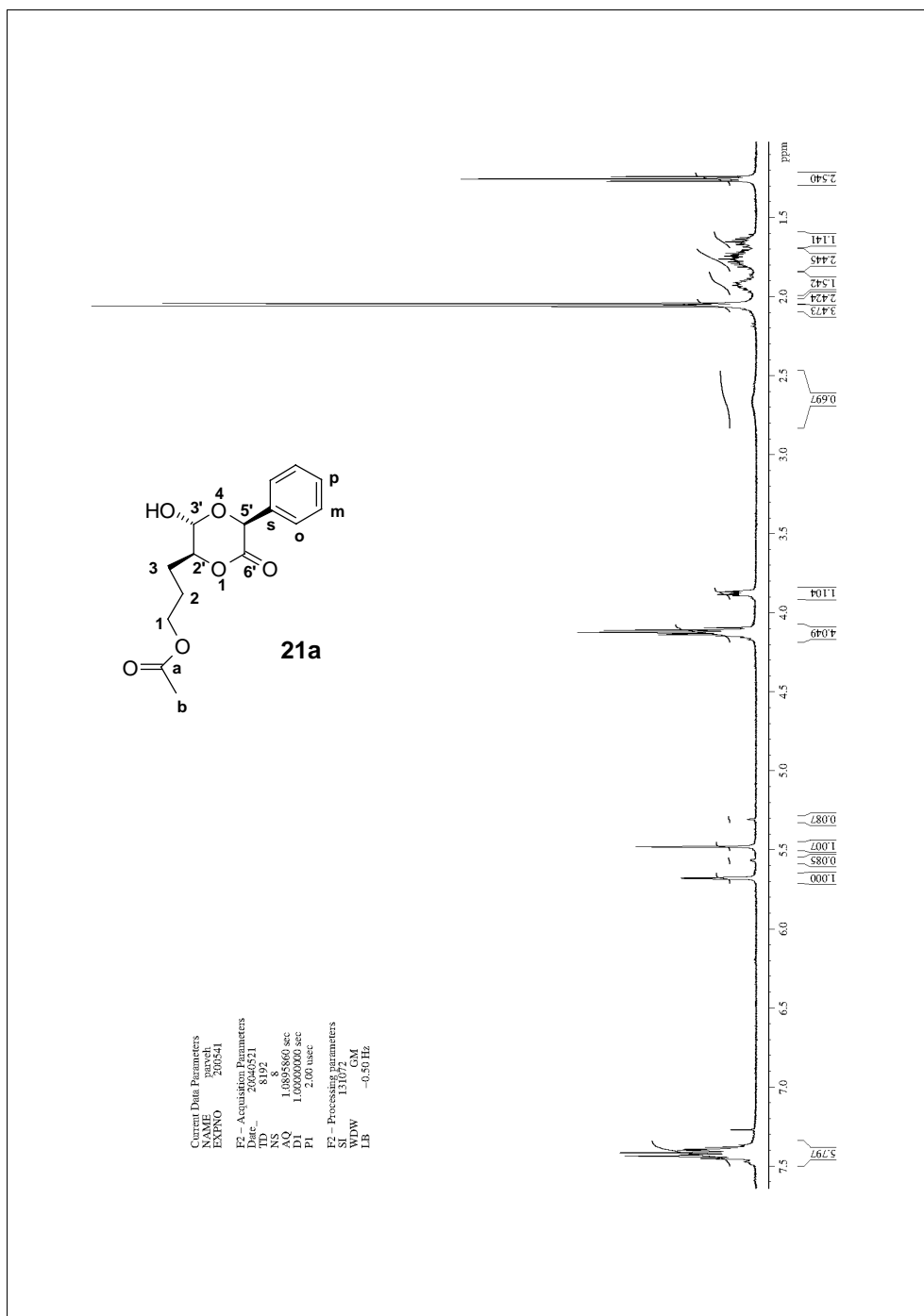


3.15. (S)-Mandelic acid (3'R)-2'-hydroxy-tetrahydropyran-3'-yl ester (20b)

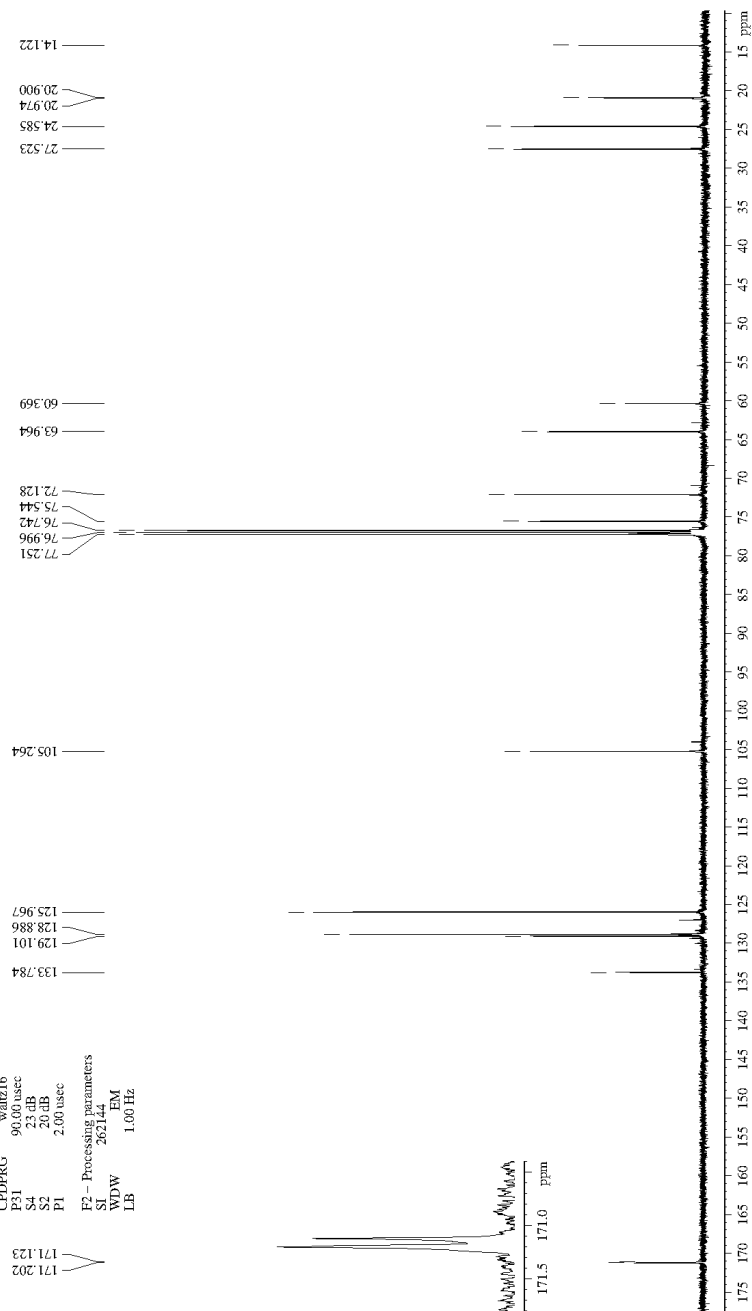




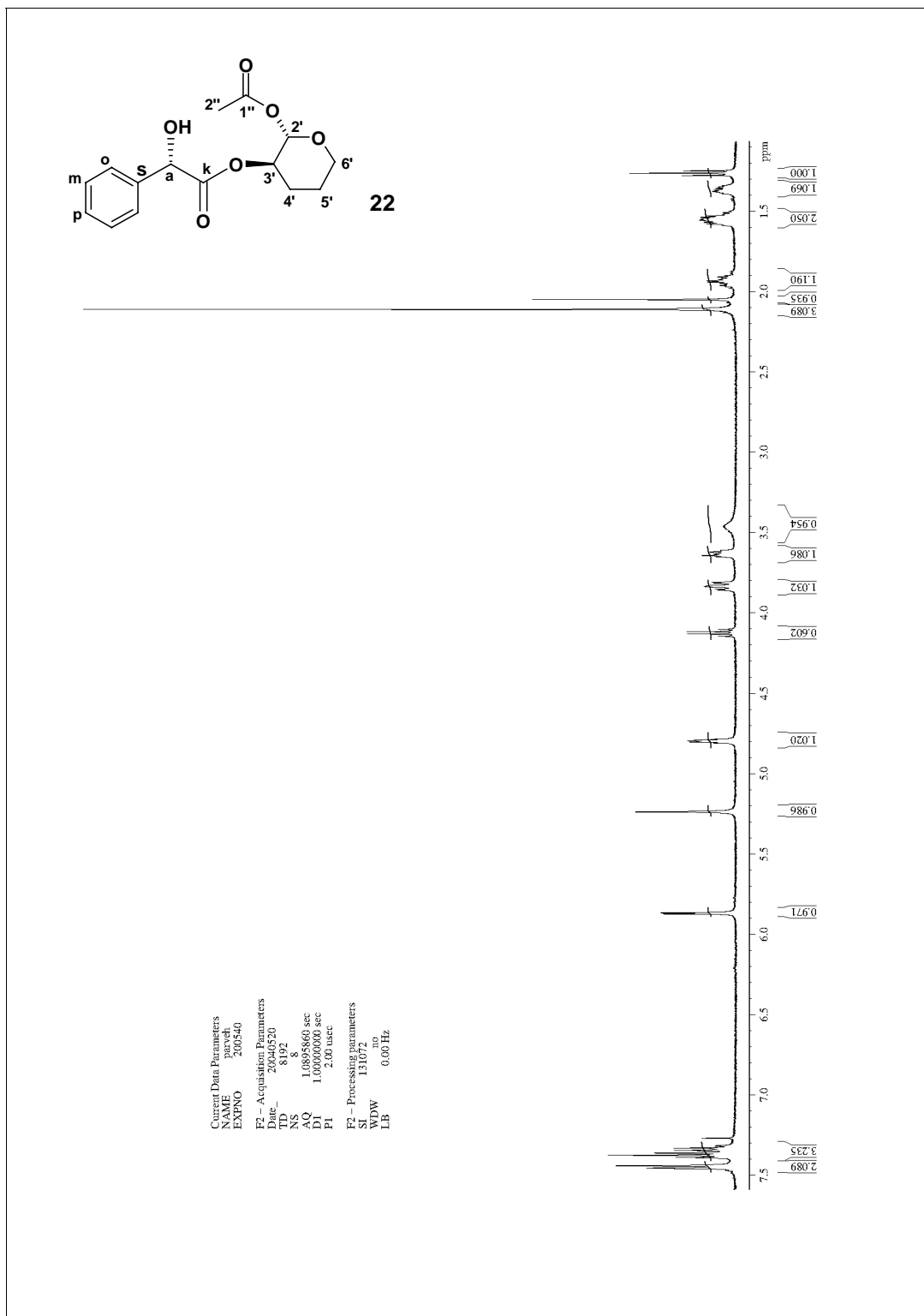
3.16. Acetic acid 3-((2'S,3'R,5'S)-3'-hydroxy-6'-oxo-5'-phenyl-[1,4]dioxan-2'-yl)-propyl ester (21a) and acetic acid 3-((2'S,3'S,5'S)-3'-hydroxy-6'-oxo-5'-phenyl-[1,4]dioxan-2'-yl)-propyl ester (21b)

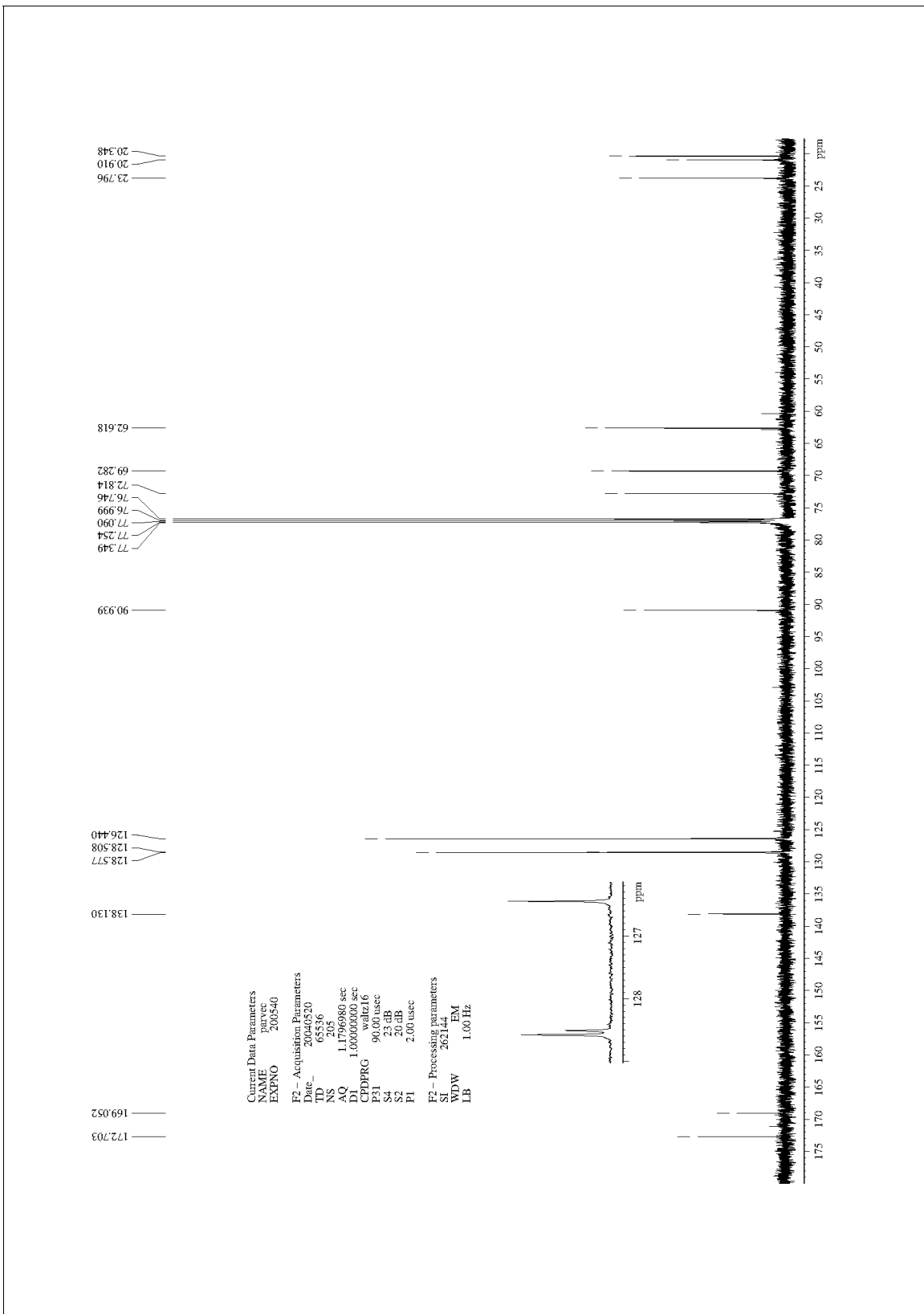


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 S3 20.00 usec
 P1 2.000 usec
 F2 - Processing parameters
 SI 262144
 WDW EM
 LB 1.00 Hz



3.17. (S)-Mandelic acid (2'S,3'R)-2'-acetoxy-tetrahydropyran-3'-yl ester (22)





4. Copies of chromatograms using chiral-HPLC

Separation of (*E*)-Oct-2-enoic acid (3'*R*)-2'-hydroxy-tetrahydropyran-3'-yl ester ((3'*R*)-8) and (*E*)-Oct-2-enoic acid (3'*S*)-2'-hydroxy-tetrahydropyran-3'-yl ester ((3'*S*)-8)

Conditions: eluent 2.5% of isopropanol in petrol ether

Flow rate 0.6 ml/min

Pressure 0.43 bar

