

## Supporting Information

### **Total Synthesis of (–)-Strictosidine and Interception of Aryne Natural Product Derivatives “Strictosidyne” and “Strictosamidyne”**

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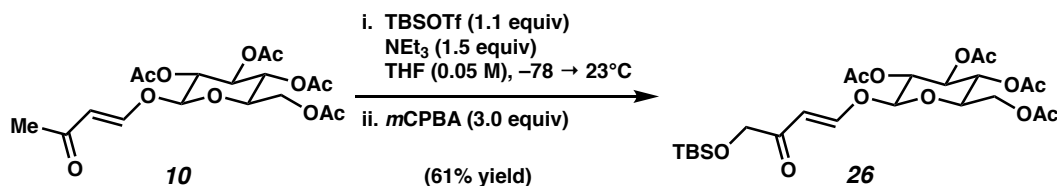
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**Materials and Methods.** Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). Commercially obtained reagents were used as received unless otherwise specified. Dess–Martin periodinane (DMP) was purchased from Combi–Blocks and used as received. Celite® was purchased from Fisher Scientific and used as received. TBSOTf was purchased from Oakwood and distilled prior to use. *m*CPBA (70–75%) was purchased from Acros Organics, dissolved in anhydrous THF and dried over Na<sub>2</sub>SO<sub>4</sub> immediately prior to use. Furan was purchased from Acros Organics and dried over MgSO<sub>4</sub> prior to use. NiCl<sub>2</sub>(DME) was purchased from Sigma–Aldrich and used as received. TBAF was purchased as a 1 M solution in THF from Sigma–Aldrich and used as received. CeCl<sub>3</sub>•7H<sub>2</sub>O was purchased from Acros Organics and used as received. NaBH<sub>4</sub> (>98%, powder) was purchased from Sigma–Aldrich and used as received. Vinylogous ester **10** was synthesized according to known procedures.<sup>1</sup> Pseudo–diene **8** was synthesized according to known procedures.<sup>2</sup> Reaction temperatures were controlled using an IKA Mag temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 °C). Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV (254 nm), anisaldehyde, iodine, phosphomolybdic acid and cerium (IV) sulfate in water with sulfuric acid (Seebach), and potassium permanganate staining. Silicycle P60 (particle size 0.040–0.063 mm) silica gel was used for flash column chromatography. <sup>1</sup>H NMR spectra were recorded on Bruker spectrometers (600, 500, 400 MHz) and are reported relative to deuterated solvent signals (7.26 ppm for CDCl<sub>3</sub>, 7.16 ppm for C<sub>6</sub>D<sub>6</sub>, 3.31 ppm for CD<sub>3</sub>OD). Data for <sup>1</sup>H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. <sup>13</sup>C NMR spectra were recorded on Bruker spectrometers (125 MHz) and are reported relative to deuterated solvent signals (77.16 ppm for CDCl<sub>3</sub>, 128.06 ppm for C<sub>6</sub>D<sub>6</sub>, 49.00 ppm for CD<sub>3</sub>OD). Data for <sup>13</sup>C NMR spectra are reported in terms of chemical shift, and when necessary, multiplicity, coupling constant (Hz) and carbon type. IR spectra were recorded on a Perkin-Elmer 100 spectrometer and are reported in terms of frequency of absorption (cm<sup>-1</sup>). DART-MS spectra were collected on a Thermo Exactive Plus MSD (Thermo Scientific) equipped with an ID-CUBE ion source and a Vapur Interface (IonSense Inc.).

Both the source and MSD were controlled by Excalibur software v. 3.0. The analyte was spotted onto OpenSpot sampling cards (IonSense Inc.) using  $\text{CHCl}_3$  or  $\text{CH}_2\text{Cl}_2$  as the solvent. Ionization was accomplished using UHP He plasma with no additional ionization agents. Mass calibration was carried out using Pierce LTQ Velos ESI (+) and (-) Ion calibration solutions (Thermo Fisher Scientific). ESI-TOF measurements were carried out on a Waters LCT-Premier XE Time of Flight Instrument controlled by MassLynx 4.1 software (Waters Corporation, Milford MA). The instrument was equipped with the Multi Mode Ionization source operated in the electrospray mode. A solution of Leucine Enkephalin (Sigma Chemical, L9133) was used in the Lock-Spray to obtain accurate mass measurements. Samples were infused using direct loop injection on a Waters Acquity UPLC system. Optical rotations were measured with a Rudolf Autopol III Automatic Polarimeter. Melting points were determined using a DigiMelt MPA160. Reaction optimization of the Diels–Alder cycloaddition was carried out on a Mettler Toledo SFC (supercritical fluid chromatography) using Daicel ChiralPak OD-H, Daicel ChiralPak IA-3, Daicel ChiralPak IC-3, Daicel ChiralPak AD-3, and Daicel ChiralPak OJ-H columns.

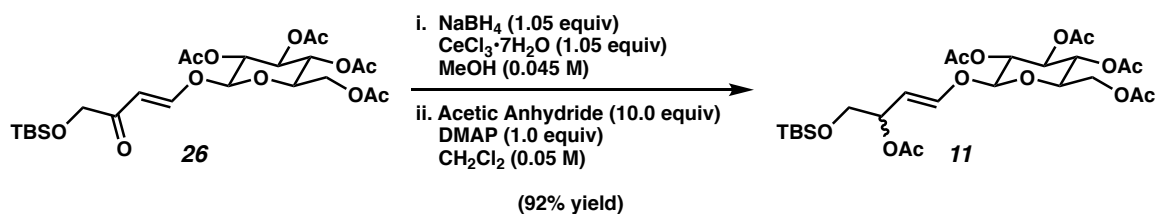
## Experimental Procedures.

### A. Synthesis of Strictosidine (4).



**$\alpha$ -Silyloxy ketone 26.** To a solution of vinylogous ester **10** (8.70 g, 1.00 equiv, 20.9 mmol) in THF (418 mL, 0.0500 M) was added triethylamine (4.34 mL, 1.50 equiv, 31.3 mmol). The mixture was cooled to  $-78^\circ\text{C}$  and TBSOTf (5.28 mL, 1.10 equiv, 23.0 mmol) was added dropwise over 10 min. The reaction mixture was then allowed to warm to  $23^\circ\text{C}$ . During this time, the reaction was monitored by TLC analysis. Upon consumption of the starting material, the reaction was cooled back down to  $-78^\circ\text{C}$ . In a

separate flask, a solution of *m*CPBA (15.5 g, 3.00 equiv, 62.7 mmol, >70% *m*CPBA) in THF (104 mL, 0.200 M) was dried over Na<sub>2</sub>SO<sub>4</sub>. The *m*CPBA mixture was added to the reaction dropwise over 10 min. The reaction was warmed to 23 °C and then allowed to stir at this temperature for an additional for 3 h. The reaction was then quenched by the addition of aq. sat. sodium thiosulfate (50 mL) and diluted with water (100 mL) and diethyl ether (200 mL). The layers were separated and the organic layer was washed with sat. aq. NaHCO<sub>3</sub> (3 x 300 mL) and brine (1 x 200 mL). The organic layer was then dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (5:1 to 1:1 hexanes:EtOAc) to afford  $\alpha$ -silyloxy ketone **26** (7.0 g, 61% yield) as a white solid.  $\alpha$ -Silyloxy ketone **26**: R<sub>f</sub> 0.50 (1:1 EtOAc:Hexanes); mp: 101.5 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.59 (d, *J* = 12.4, 1H), 6.18 (d, *J* = 12.4, 1H), 5.26–5.22 (m, 1H), 5.17–5.12 (m, 2H), 4.92 (d, *J* = 7.9, 1H), 4.29 (dd, *J* = 12.5, 4.8, 1H), 4.19 (s, 2H), 4.12 (dd, *J* = 12.5, 2.2, 1H), 3.80 (dq, *J* = 10.0, 2.3, 1H), 2.10–2.09 (m, 1H), 2.09 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 0.92 (s, 9H), 0.09 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) (19 of 21 carbon signals observed):  $\delta$  199.4, 170.6, 170.2, 169.3, 169.1, 159.0, 105.8, 100.5, 72.8, 72.4, 70.6, 69.0, 67.6, 61.5, 25.8, 20.7, 20.6, 18.3, –5.44; IR (film): 2931, 2856, 1750, 1367, 1206, 1070, 1033, 837 cm<sup>-1</sup>; HRMS–APCI (m/z) [M + H]<sup>+</sup> calcd for C<sub>24</sub>H<sub>39</sub>O<sub>12</sub>Si<sup>+</sup>, 547.2205; found 547.2182; [ $\alpha$ ]<sub>D</sub><sup>25.9</sup> –120.0° (c = 0.1, CH<sub>2</sub>Cl<sub>2</sub>).

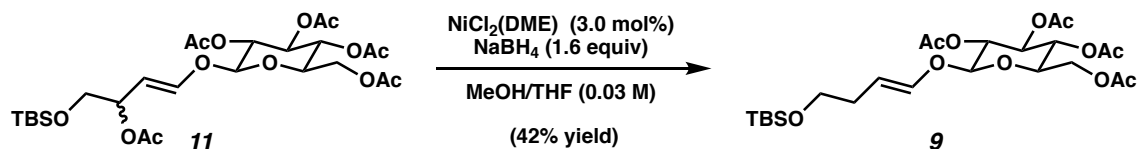


**Allylic acetate 11.** To a solution of  $\alpha$ -silyloxy ketone **26** (4.70 g, 1.00 equiv, 8.60 mmol) in methanol (191 mL, 0.0450 M) was added cerium trichloride heptahydrate (3.63 g, 1.05 equiv, 9.03 mmol). Sodium borohydride (341 mg, 1.05 equiv, 9.03 mmol) was then added over 1 min and the reaction mixture was stirred for 3 min. After consumption of the starting material, as determined via TLC analysis, acetone (6.30 mL, 10.0 equiv, 86.0 mmol) was added and the volatiles were removed under reduced pressure and the

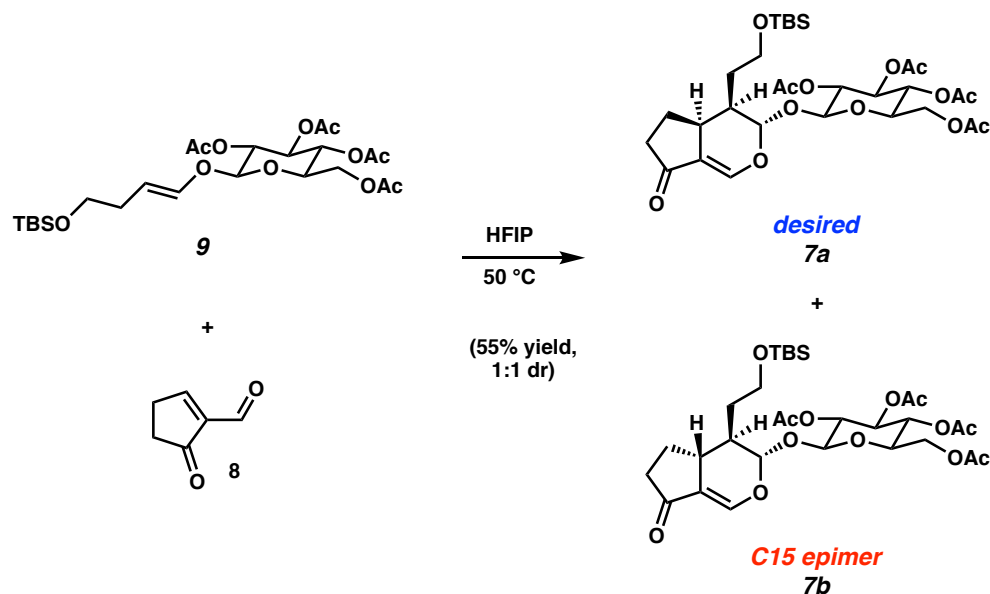


resulting residue was left under high vacuum (1 mbar) for 1 h. Dichloromethane (150 mL) was added to the mixture and concentrated under reduced pressure. Dichloromethane (172 mL, 0.0500 M), triethylamine (10.0 mL, 8.50 equiv, 73.1 mmol), DMAP (1.34 g, 1.0 equiv, 11.0 mmol), and acetic anhydride (8.13 mL, 10.0 equiv, 86.0 mmol) were then added sequentially. The reaction was stirred at 23 °C and monitored by TLC analysis for reaction completion. After 15 min, the reaction was quenched by the addition of sat. aq. NaHCO<sub>3</sub> (100 mL) and diluted with brine (100 mL). The layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 mL). The organic layers were combined, washed with brine (1 x 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The resulting crude mixture was purified by flash column chromatography (10:1 to 3:1 Hexanes:EtOAc) to afford allylic acetate **11** (4.69 g, 92% yield) as a yellow oil and an inseparable mixture of diastereomers. Allylic acetate **11** (1:1 mixture of diastereomers): R<sub>f</sub> 0.55 (1:1 Hexanes:EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 6.55 (app dd, *J* = 16.2, 12.3, 1H), 5.27–5.19 (m, 2H), 5.13–5.06 (m, 3H), 4.76 (app dd, *J* = 8.0, 1.0, 1H), 4.30–4.25 (m, 1H), 4.12 (app ddd, *J* = 12.4, 5.1, 2.3, 1H), 3.78–3.74 (m, 1H), 3.69–3.62 (m, 2H), 2.09 (s, 3H), 2.04–2.02 (m, 9H), 2.01 (s, 3H), 0.87 (app d, *J* = 0.85, 9H), 0.04 (app d, *J* = 1.7, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) (37 of 46 carbon signals observed): δ 170.7, 170.6, 170.4, 170.3, 170.22, 170.20, 169.4, 169.3, 169.22, 169.17, 148.18, 148.16, 105.7, 105.5, 99.7, 99.6, 72.60, 72.59, 72.5, 72.3, 72.2, 70.8, 67.99, 67.95, 65.02, 64.99, 61.8, 61.7, 25.8, 21.4, 21.3, 20.7, 20.63, 20.59, 20.58, 18.3, –5.3; IR (film): 2931, 2858, 1745, 1214, 1368, 1034 cm<sup>-1</sup>; HRMS–APCI (*m/z*) [*M* + H]<sup>+</sup> calcd for C<sub>26</sub>H<sub>43</sub>O<sub>13</sub>Si<sup>+</sup>, 591.24674; found 591.24539; [α]<sup>24.1</sup><sub>D</sub> –80.0° (*c* = 0.1, CH<sub>2</sub>Cl<sub>2</sub>).

*Note: Diastereomer signals were integrated and reported together in the <sup>1</sup>H NMR spectrum. Diastereomer signals were reported separately in the <sup>13</sup>C NMR spectrum.*



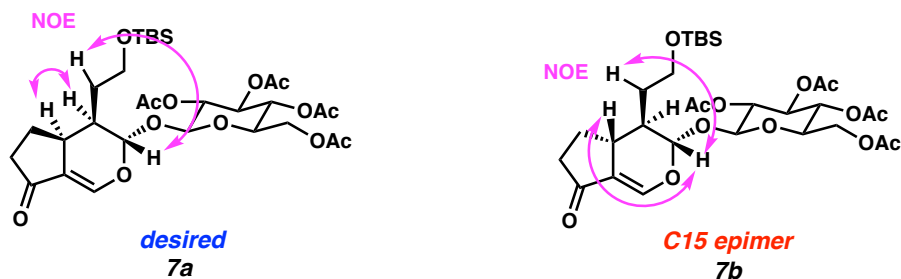
**Enol ether 9.** To a solution of allylic acetate **11** (1.91 g, 1.00 equiv, 3.23 mmol) in a 3:1 mixture of THF/methanol (107 mL, 0.0300 M) was added NiCl<sub>2</sub> (DME) (21.3 mg, 3.00 mol%, 97.0 μmol). To this mixture, NaBH<sub>4</sub> (195.6 mg, 1.60 equiv, 5.17 mmol) was added in three portions over 2 min. After stirring for 10 min at 23 °C, the reaction was quenched by addition of water (30 mL). The mixture was diluted with diethyl ether (50 mL) and brine (50 mL). The layers were then separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (10:1 to 2:1 hexanes:EtOAc) to yield enol ether **9** (726 mg, 42% yield) as a clear oil. Enol ether **9**: R<sub>f</sub> 0.63 (1:1 EtOAc:Hexanes); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 6.23 (dt, *J* = 12.4, 1.1, 1H), 5.23 (t, *J* = 9.5, 1H), 5.14–5.05 (m, 3H), 4.72 (d, *J* = 7.9, 1H), 4.27 (dd, *J* = 12.4, 4.7, 1H), 4.13 (dd, *J* = 12.4, 2.4, 1H), 3.74 (dq, *J* = 10.0, 2.4, 1H), 3.58 (td, *J* = 6.7, 1.6, 2H), 2.15–2.10 (m, 2H), 2.08 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 170.8, 170.4, 169.5, 169.4, 144.2, 107.3, 99.7, 72.9, 72.2, 71.1, 68.3, 63.4, 62.0, 31.2, 26.1, 20.9, 20.78, 20.75, 20.7, 18.5, –5.1; IR (film): 2930, 2858, 1755, 1367, 1219, 1041, 837 cm<sup>-1</sup>; HRMS–APCI (*m/z*) [*M* – H]<sup>+</sup> calcd for C<sub>24</sub>H<sub>40</sub>O<sub>11</sub>Si<sup>-</sup>, 531.22562; found 531.23482; [α]<sub>D</sub><sup>24.8</sup> –1220.0° (*c* = 0.1, CH<sub>2</sub>Cl<sub>2</sub>).



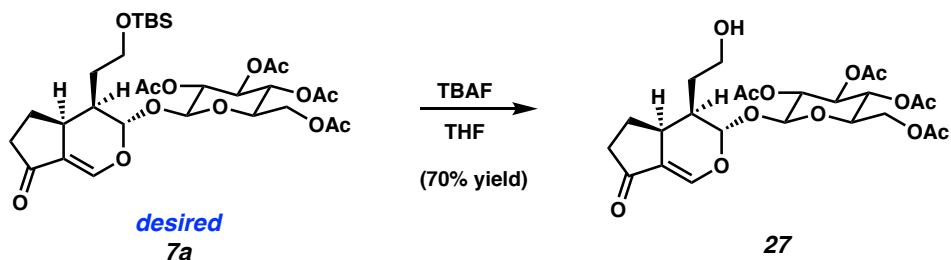
**Cycloadducts 7a and 7b.** A solution of enol ether **9** (480 mg, 1.00 equiv, 901  $\mu\text{mol}$ ) and enal **8** (595 mg, 6.00 equiv, 5.41 mmol) in 1,1,1,3,3,3-hexafluoropropan-2-ol (2.00 mL, 0.450 M) was heated to 50 °C. The reaction was stirred at this temperature for 16 h and then cooled to 23 °C. The reaction was then diluted with EtOAc (1 mL), filtered over a 2 inch pad of silica with EtOAc (10 mL), and the volatiles were concentrated under reduced pressure. By analysis of the crude mixture, a 1:1 mixture of diastereomers was obtained. The crude mixture was purified by column chromatography (10:1 to 1:1 hexanes:EtOAc) and preparative TLC (1:1 hexanes:EtOAc) to afford cycloadduct **7a** (158 mg, 27% yield) as a white solid and cycloadduct **7b** (163 mg, 28% yield) as a clear oil. Cycloadduct **7a** (desired):  $R_f$  0.54 (1:1 EtOAc:Hexanes); mp: 101.9 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.21 (d,  $J = 2.8$ , 1H), 5.46 (d,  $J = 1.8$ , 1H), 5.21 (t,  $J = 9.7$ , 1H), 5.09 (t,  $J = 9.7$ , 1H), 4.98 (dd,  $J = 9.7$ , 8.14, 1H), 4.87 (d,  $J = 8.14$ , 1H), 4.28 (dd,  $J = 12.4$ , 4.2, 1H), 4.12–4.09 (m, 1H), 3.72 (dq,  $J = 10.0$ , 2.14, 1H), 3.65 (t,  $J = 6.3$ , 2H), 3.05–3.00 (m, 1H), 2.31–2.26 (m, 2H), 2.08 (s, 3H), 2.03–2.00 (m, 4H), 1.99–1.95 (m, 4H), 1.89 (s, 3H), 1.60–1.53 (m, 2H), 1.22–1.13 (m, 1H), 0.86 (s, 9H), 0.03 (app d,  $J = 1.0$ , 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  205.0, 170.7, 170.2, 169.5, 169.4, 144.6, 117.8, 96.3, 96.1, 72.4, 72.3, 70.5, 68.2, 61.8, 61.0, 39.0, 32.2, 32.0, 27.6, 26.0 (3C), 22.2, 20.9, 20.7 (2C), 20.6, 18.3, –5.29; IR (film): 2955, 2858, 1756, 1714, 1638, 1367, 1221, 1069, 1042, 836  $\text{cm}^{-1}$ ; HRMS–APCI ( $m/z$ )  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{30}\text{H}_{47}\text{O}_{13}\text{Si}^+$ , 643.2780; found

643.2759;  $[\alpha]^{20.0}_{\text{D}} -400^{\circ}$  ( $c = 0.1$ ,  $\text{CH}_2\text{Cl}_2$ ). Cycloadduct **7b** (C15 epimer):  $R_f$  0.42 (1:1 EtOAc:hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.31 (d,  $J = 2.4$ , 1H), 5.23 (t,  $J = 9.5$ , 1H), 5.15–5.08 (m, 2H), 5.03 (dd,  $J = 9.5$ , 8.1, 1H), 4.95 (d,  $J = 8.1$ , 1H), 4.25 (dd,  $J = 12.4$ , 4.2, 1H), 4.12 (dd,  $J = 12.4$ , 2.4, 1H), 3.80–3.76 (m, 1H), 3.73 (dq,  $J = 10.0$ , 2.3, 1H), 3.68–3.64 (m, 1H), 2.68–2.62 (m, 1H), 2.35–2.28 (m, 3H), 2.07 (s, 3H), 2.03 (s, 6H), 2.00 (s, 3H), 1.78–1.72 (m, 1H), 1.73–1.67 (m, 1H), 1.53–1.46 (m, 1H), 1.44–1.34 (m, 1H), 0.88 (s, 9H), 0.053 (d,  $J = 1.3$  Hz, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  204.5, 170.7, 170.3, 169.6, 169.4, 146.7, 118.2, 101.1, 97.1, 72.7, 72.3, 70.9, 68.4, 61.9, 61.1, 39.6, 39.4, 39.0, 32.5, 27.3, 26.1 (3C), 20.9, 20.8, 20.7 (2C), 18.4,  $-5.2$  (2C); IR (film): 2922, 2852, 1751, 1713, 1367, 1218, 1064, 1035  $\text{cm}^{-1}$ ; HRMS–APCI ( $m/z$ )  $[\text{M} + \text{H}_2\text{O}]^+$  calcd for  $\text{C}_{30}\text{H}_{47}\text{O}_{13}\text{Si}^+$ , 643.2780; found 643.4323;  $[\alpha]^{20.7}_{\text{D}} -960^{\circ}$  ( $c = 0.1$ ,  $\text{CH}_2\text{Cl}_2$ ).

The following NOE correlations were observed:

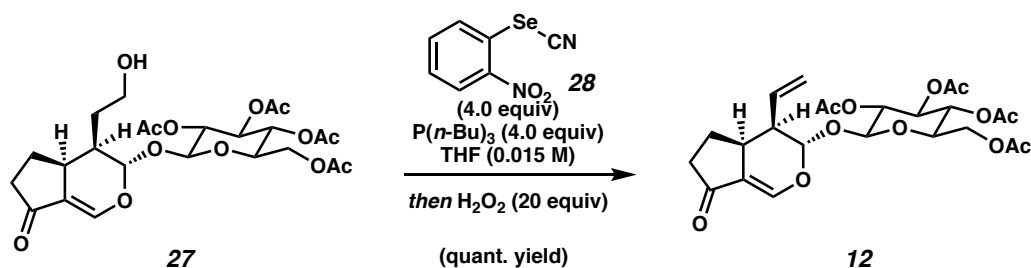


The absolute stereochemistry of **7a** was verified by carrying it forward to the natural products (–)-secologanin and (–)-strictosidine. The determination of the absolute stereochemistry of **7b** is described in section D.



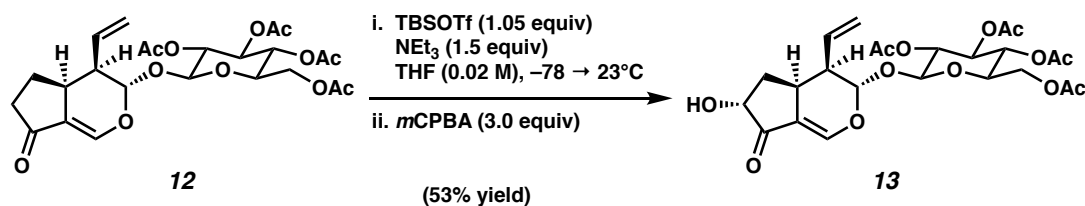
**Alcohol 27.** To a solution of cycloadduct **7a** (75.2 mg, 1.00 equiv, 117  $\mu\text{mol}$ ) in THF (1.95 mL, 0.0600 M) was added TBAF (234  $\mu\text{L}$ , 1 M in THF, 2.00 equiv, 234  $\mu\text{mol}$ ). The reaction was stirred for 1 h, then quenched by the addition of water (1 mL) and

diluted with diethyl ether (1 mL). The layers were separated and the aqueous layer was extracted with Et<sub>2</sub>O (3 x 1 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the volatiles were removed under reduced pressure. The crude residue was purified by flash column chromatography (2:1 hexanes:EtOAc to 100% EtOAc) to afford alcohol **27** (43.0 mg, 70% yield) as a clear oil. Alcohol **27**: R<sub>f</sub> 0.18 (4:1 EtOAc:hexanes); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 7.23 (d, *J* = 2.8, 1H), 5.46 (d, *J* = 1.8, 1H), 5.22 (t, *J* = 9.6, 1H), 5.09 (t, *J* = 9.7, 1H), 4.98 (dd, *J* = 9.6, 8.1, 1H), 4.88 (d, *J* = 8.1, 1H), 4.30 (dd, *J* = 12.4, 4.4, 1H), 4.16 (dd, *J* = 12.4, 2.3, 1H), 3.77–3.68 (m, 3H), 3.09–3.01 (m, 1H), 2.35–2.25 (m, 3H), 2.11 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.90 (s, 3H), 1.64–1.56 (m, 3H), 1.31–1.22 (m, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) (23 of 24 carbon signals observed): δ 204.9, 170.9, 170.2, 169.6, 169.4, 144.5, 117.8, 96.2, 96.1, 72.41, 72.35, 70.6, 68.3, 61.8, 60.9, 39.0, 32.2, 32.1, 27.8, 22.3, 20.9, 20.7, 20.6; IR (film): 3358, 3308, 2919, 2850, 1754, 1632, 1468, 1224 cm<sup>-1</sup>; HRMS–APCI (*m/z*) [M + H]<sup>+</sup> calcd for C<sub>24</sub>H<sub>33</sub>O<sub>13</sub><sup>+</sup>, 529.1916; found 529.1926; [α]<sup>22.3</sup><sub>D</sub> –600.0° (c = 0.1, CH<sub>2</sub>Cl<sub>2</sub>).



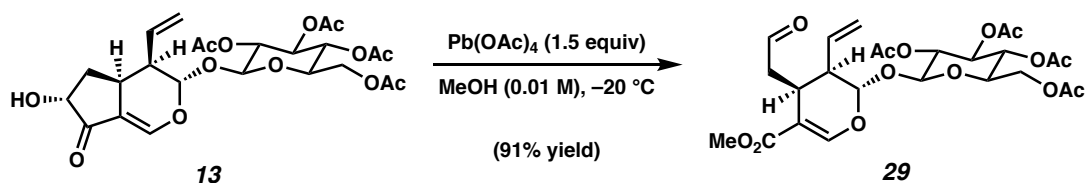
**Alkene 12.** To a solution of alcohol **27** (43.0 mg, 1.00 equiv, 81.4 μmol) in THF (5.4 mL, 0.015 M) was added tributylphosphine (80.3 μL, 4.00 equiv, 325 μmol) and selenide **28** (73.9 mg, 4.00 equiv, 325 μmol), sequentially. The reaction was allowed to stir for 20 min at 23 °C and then diluted with additional THF (5.4 mL, 0.015 M) and cooled to 0 °C. Hydrogen peroxide (166 μL, 30% by weight, 20.0 equiv, 1.63 mmol) was added dropwise over 1 min and then the reaction was allowed to warm to 23 °C and stir for 16 h. The mixture was then cooled to 0 °C, then quenched with sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (1 mL) and diluted with water (10 mL) and EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the volatiles were removed under reduced pressure. The crude

residue was then purified by flash column chromatography (3:1 Hexanes:EtOAc to 100% EtOAc) to afford alkene **12** (41.5 mg, quant. yield) as a yellow solid. Alkene **12**:  $R_f$  0.40 (1:1 EtOAc:hexanes); mp: 141.4 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.27 (br s, 1H), 5.46–5.37 (m, 1H), 5.30–5.21 (m, 4H), 5.10 (t,  $J = 9.8$ , 1H), 5.00 (dd,  $J = 9.5, 8.1$ , 1H), 4.90 (d,  $J = 8.1$ , 1H), 4.30 (dd,  $J = 12.2, 4.5$ , 1H), 4.15 (dd,  $J = 12.2, 2.3$ , 1H), 3.75 (dq,  $J = 10.1, 2.3$ , 1H), 3.03–2.97 (m, 1H), 2.85–2.82 (m, 1H), 2.32–2.28 (m, 2H), 2.10 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.99–1.95 (m, 1H), 1.92 (s, 3H), 1.64–1.57 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  205.1, 170.8, 170.2, 169.6, 169.5, 144.6, 131.8, 120.7, 117.6, 96.7, 96.0, 72.42, 72.40, 70.6, 68.3, 61.8, 41.0, 38.8, 31.5, 22.8, 20.91, 20.86, 20.7, 20.6; IR (film): 2922, 2852, 1751, 1713, 1367, 1218, 1064, 1035  $\text{cm}^{-1}$ ; HRMS–APCI ( $m/z$ ) [ $\text{M} + \text{H}$ ] $^+$  calcd for  $\text{C}_{24}\text{H}_{31}\text{O}_{12}^+$ , 511.1810; found 511.1818;  $[\alpha]^{24.6}_{\text{D}} -21.3^\circ$  ( $c = 0.1, \text{CH}_2\text{Cl}_2$ ).

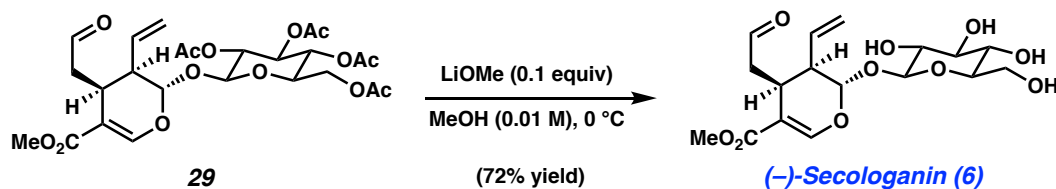


**$\alpha$ -ketol 13.** To a solution of alkene **12** (15.2 mg, 1.00 equiv, 29.8  $\mu\text{mol}$ ) in THF (1.49 mL, 0.0200 M) was added triethylamine (6.20  $\mu\text{L}$ , 1.50 equiv, 44.7  $\mu\text{mol}$ ). The mixture was cooled to  $-78^\circ\text{C}$  and TBSOTf (7.18  $\mu\text{L}$ , 1.05 equiv, 31.3  $\mu\text{mol}$ ) was added dropwise over 1 min. The mixture was then warmed to  $23^\circ\text{C}$  and stirred for 10 min before being cooled back to  $-78^\circ\text{C}$ . A solution of *m*CPBA (22.0 mg, 3.00 equiv, 62.7 mmol, >70% *m*CPBA) in THF (149  $\mu\text{L}$ , 0.200 M) was dried over  $\text{Na}_2\text{SO}_4$  and then added to the reaction dropwise over 2 min. The reaction was warmed to  $23^\circ\text{C}$  and stirred for 30 min before being quenched by the addition of aq. sat.  $\text{Na}_2\text{S}_2\text{O}_3$  (1 mL) and diluted with ethyl acetate (1 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 1 mL). The combined organic layers were washed with sat. aq.  $\text{NaHCO}_3$  (3 x 3 mL) and brine (1 x 5 mL). The organic layer was then dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude residue was purified by column chromatography (1:2 to 2:1 EtOAc:Hexanes) to afford  $\alpha$ -ketol **13** (8.3 mg, 53% yield) as a yellow oil.  $\alpha$ -ketol **13**:  $R_f$  0.50 (3:1 EtOAc:Hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$

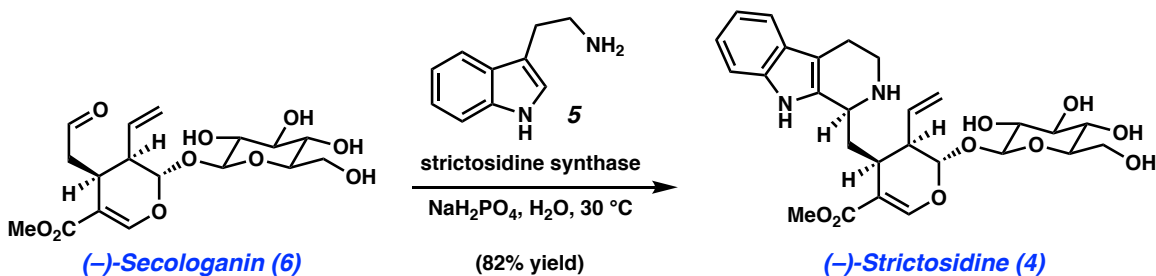
7.35 (d,  $J = 2.5$ , 1H), 5.35–5.27 (m, 4H), 5.23 (t,  $J = 9.5$ , 1H), 5.11 (t,  $J = 9.5$ , 1H), 5.02 (dd,  $J = 9.5$ , 7.9, 1H), 4.91 (d,  $J = 7.9$ , 1H), 4.30 (dd,  $J = 12.2$ , 4.7, 1H), 4.15 (dd,  $J = 12.2$ , 1.8, 1H), 4.03 (dd,  $J = 6.1$ , 2.8, 1H), 3.75 (dq,  $J = 9.9$ , 2.3, 1H), 3.32–3.27 (m, 1H), 2.83 (t,  $J = 8.3$ , 1H), 2.14 (d,  $J = 2.3$ , 1H), 2.10 (s, 3H), 2.03–2.00 (m, 4H), 2.00 (s, 3H), 1.94 (s, 3H), 1.77–1.71 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  202.9, 170.8, 170.3, 169.6, 169.5, 146.8, 131.2, 121.4, 115.9, 96.6, 95.6, 74.1, 72.5, 72.4, 70.6, 68.3, 61.8, 40.8, 31.0, 29.0, 20.9, 20.7 (2 C), 20.6; IR (film): 3425, 2922, 2852, 1748, 1632, 1368, 1221, 1061, 1035, 1016, 795  $\text{cm}^{-1}$ ; HRMS–APCI ( $m/z$ )  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{24}\text{H}_{31}\text{O}_{13}^+$ , 527.1759; found 527.1771;  $[\alpha]^{25.6}_{\text{D}} -16.0^\circ$  ( $c = 0.1$ ,  $\text{CH}_2\text{Cl}_2$ ).



**Aldehyde 29.** To a solution of  $\alpha$ -ketol **13** (6.0 mg, 1.0 equiv, 11  $\mu\text{mol}$ ) in methanol (1.1 mL, 0.010 M) at  $-20^\circ\text{C}$  was added lead (IV) acetate (7.6 mg, 1.5 equiv, 17  $\mu\text{mol}$ ). The reaction mixture was stirred at  $-20^\circ\text{C}$  for 1.5 h, after which the reaction was quenched with sat. aq.  $\text{NaHCO}_3$  (2 mL) and sat. aq.  $\text{NaCl}$  (5 mL). The layers were separated and the aqueous layer was extracted with  $\text{EtOAc}$  (3 x 5 mL). The organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The crude mixture was purified by column chromatography (1:4 to 1:1  $\text{EtOAc}$ :Hexanes) to afford aldehyde **29** (5.8 mg, 91% yield) as a colorless oil. Aldehyde **29**:  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.70 (t,  $J = 1.4$ , 1H), 7.41 (d,  $J = 2.0$ , 1H), 5.55–5.44 (m, 1H), 5.27 (d,  $J = 3.0$ , 1H), 5.26–5.20 (m, 3H), 5.11 (t,  $J = 9.7$ , 1H), 5.02 (dd,  $J = 8.24$ , 9.56, 1H), 4.88 (d,  $J = 8.1$ , 1H), 4.27 (dd,  $J = 12.3$ , 16.7, 1H), 4.14 (dd,  $J = 2.1$ , 12.3, 1H), 3.73 (dq,  $J = 2.4$ , 9.9, 1H), 3.68 (s, 3H), 3.33–3.26 (m, 1H), 2.91 (ddd,  $J = 2.1$ , 5.5, 17.9, 1H), 2.83–2.77 (m, 1H), 2.39 (ddd,  $J = 1.0$ , 7.8, 17.9, 1H), 2.10 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.90 (s, 3H). Characterization data for aldehyde **29** have been previously reported.<sup>3</sup>



**(–)-Secologanin 6.** To a vial containing aldehyde **29** (5.80 mg, 1.00 equiv, 10.4  $\mu\text{mol}$ ) at 0  $^\circ\text{C}$  was added a solution of LiOMe (39.6  $\mu\text{g}$ , 0.100 equiv, 1.00  $\mu\text{mol}$ ) in methanol (1.0 mL, 0.01 M). The reaction was stirred for 5 h at 0  $^\circ\text{C}$ . At that point, the reaction was diluted with EtOAc (2 mL) and filtered through a plug of silica gel with 30% MeOH in EtOAc as an eluent (15 mL). The volatiles were removed and the resulting crude residue was purified by preparative TLC (40% MeOH in EtOAc) to afford (–)-secologanin (**6**) (2.9 mg, 72% yield) as a white solid. The spectral data for synthetic **6** was consistent with a commercial sample from Sigma Aldrich. (–)-Secologanin (**6**):  $R_f$  0.70 (3:7 MeOH:EtOAc);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.73 (s, 1H), 7.46 (d,  $J = 1.6$ , 1H), 5.57–5.50 (m, 1H), 5.35 (d,  $J = 3.5$ , 1H), 5.24–5.20 (m, 2H), 4.69 (d,  $J = 7.8$ , 1H), 3.85 (br s, 2H), 3.68 (s, 3H), 3.64–3.52 (m, 3H), 3.45–3.40 (m, 2H), 2.93 (dd,  $J = 17.5, 5.6$ , 1H), 2.80–2.75 (m, 1H), 2.41 (dd,  $J = 17.5, 7.5$ , 1H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  201.5, 167.3, 152.3, 132.9, 120.7, 108.7, 98.3, 96.1, 76.0, 75.95, 73.0, 69.5, 61.5, 51.5, 43.8, 43.6, 25.6; IR (film): 3361, 2922, 2853, 1701, 1628, 1288, 1070, 1019  $\text{cm}^{-1}$ ; HRMS–APCI (m/z)  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{25}\text{O}_{10}^+$ , 389.1442; found 389.1449;  $[\alpha]^{26.7}_{\text{D}} -10.0^\circ$  ( $c = 0.1, \text{CH}_2\text{Cl}_2$ ).

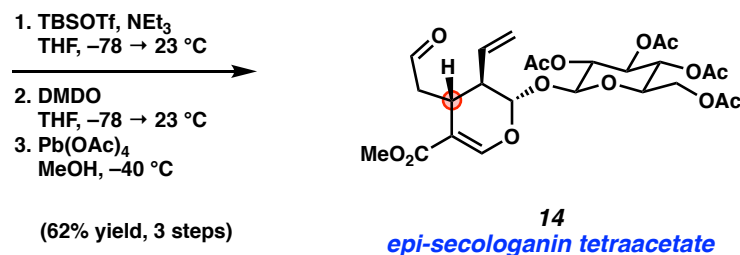
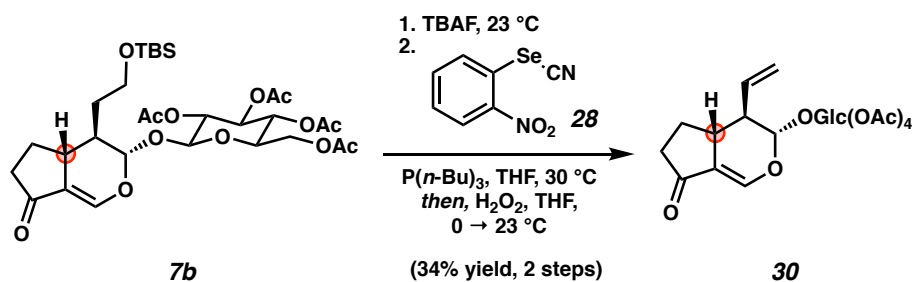


**(–)-Strictosidine 4.** To a solution of (–)-secologanin (**6**) (4.80 mg, 1.00 equiv, 12.0  $\mu\text{mol}$ ) and tryptamine (**5**) (2.00 mg, 1.0 equiv, 12  $\mu\text{mol}$ ) in 100 mM aq.  $\text{NaH}_2\text{PO}_4$  (1.0 mL) was added a powder of crude cell lysate of strictosidine synthase (4.7 mg). The reaction was stirred for 2 h at 30  $^\circ\text{C}$ . After 2 h, the volatiles were removed under reduced



pressure. The solids were suspended in MeOH (1 mL) and filtered through celite with MeOH as an eluent (10 mL). The volatiles were removed and the crude residue was purified further by preparative TLC (30% MeOH in CHCl<sub>3</sub>) to afford (–)-strictosidine (**4**) (5.4 mg, 82% yield). The spectral data for synthetic **4** was consistent with literature reports.<sup>4,5</sup> (–)-Strictosidine (**4**): R<sub>f</sub> 0.29 (3:7 MeOH:EtOAc); <sup>1</sup>H NMR (600 MHz, MeOD): δ 7.71 (s, 1H), 7.39 (d, *J* = 7.8, 1H), 7.26 (d, *J* = 8.2, 1H), 7.05 (t, *J* = 7.8, 1H), 7.96 (t, *J* = 7.6, 1H), 5.89–5.82 (m, 2H), 5.35 (d, *J* = 17.2, 1H), 5.26 (d, *J* = 10.7, 1H), 4.78 (d, *J* = 7.9, 1H), 4.09 (t, *J* = 9.4, 1H), 3.97 (dd, *J* = 11.8, 2.0, 1H), 3.76 (s, 3H), 3.65 (dd, *J* = 11.9, 6.8, 1H), 3.42–3.35 (m, 3H), 3.26–3.21 (m, 2H), 3.07–3.03 (m, 2H), 2.90–2.85 (m, 1H), 2.79–2.76 (m, 1H), 2.71–2.67 (m, 1H), 2.16–2.07 (m, 1H), 2.05–2.00 (m, 1H); <sup>13</sup>C NMR (125 MHz, MeOD): δ 171.0, 156.5, 138.1, 135.6, 131.8, 127.7, 123.1, 120.4, 119.6, 119.0, 112.2, 109.5, 107.5, 100.4, 97.4, 78.8, 78.0, 74.7, 71.7, 63.0, 52.8, 52.5, 45.6, 42.8, 35.4, 32.5, 20.3; IR (film): 3308, 2922, 2854, 1680, 1628, 1561, 1437, 1314, 1077 cm<sup>-1</sup>; HRMS–APCI (*m/z*) [*M* + *H*]<sup>+</sup> calcd for C<sub>27</sub>H<sub>35</sub>N<sub>2</sub>O<sub>9</sub><sup>+</sup>, 531.2337; found 531.2353; [α]<sup>19.8</sup><sub>D</sub> –90.0° (*c* = 0.1, MeOH).

### B. Synthesis epi-Strictosidine **15**, “Strictosidyne” precursor **19**, and “Strictosamidyne” precursor **20**

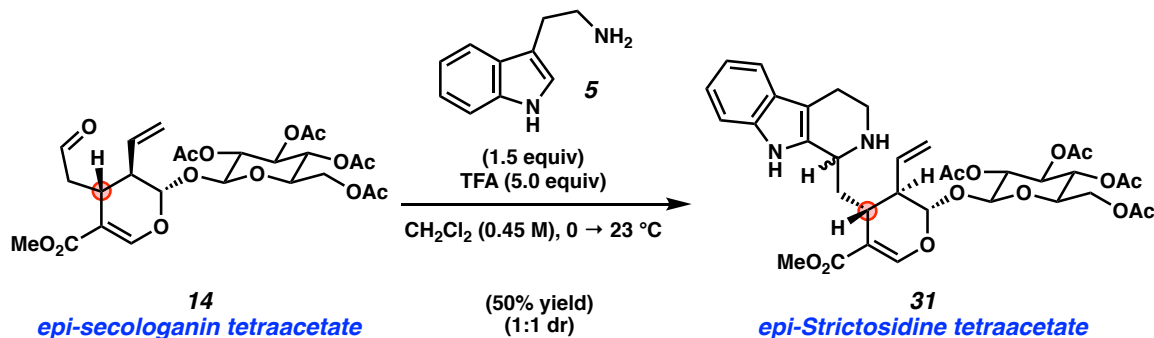


**Epi-secologanin tetraacetate 14.** To a solution of cycloadduct **7b** (140 mg, 1.00 equiv,

218  $\mu\text{mol}$ ) in THF (3.60 mL, 0.060 M) was added TBAF (545  $\mu\text{L}$ , 1.00 M, 2.50 equiv, 544  $\mu\text{mol}$ ). The reaction was stirred at 23  $^{\circ}\text{C}$  for 24 h and then quenched by the addition of water (1 mL) and diluted with diethyl ether (1 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 1 mL). The organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The crude material was purified by preparative TLC (2:1 EtOAc:Hexanes) to afford the free alcohol as an oil. To a solution of the free alcohol (56.0 mg, 1.00 equiv, 106  $\mu\text{mol}$ ) in THF (4.20 mL, 0.0250 M) was added selenide **28** (96.2 mg, 4.00 equiv, 424  $\mu\text{mol}$ ), and tributylphosphine (105  $\mu\text{L}$ , 4.00 equiv, 424  $\mu\text{mol}$ ). The mixture was stirred for 20 min, and was then diluted with additional THF (7.00 mL, 0.0150 M) and cooled to 0  $^{\circ}\text{C}$ .  $\text{H}_2\text{O}_2$  (108  $\mu\text{L}$ , 30% wt in water, 10.0 equiv, 1.05 mmol) was added dropwise over 1 min and the reaction was stirred at 0  $^{\circ}\text{C}$  for 1 h. The cold bath was removed and the reaction was stirred at 23  $^{\circ}\text{C}$  for 16 h. The reaction was then cooled to 0  $^{\circ}\text{C}$  and quenched with sat. aq.  $\text{Na}_2\text{S}_2\text{O}_3$  (1 mL) and diluted with water (2 mL) and EtOAc (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The product was purified by preparative TLC (1:1 EtOAc:Hexanes) to afford alkene **30** (41.0 mg, 34% yield over 2 steps) as an oil.

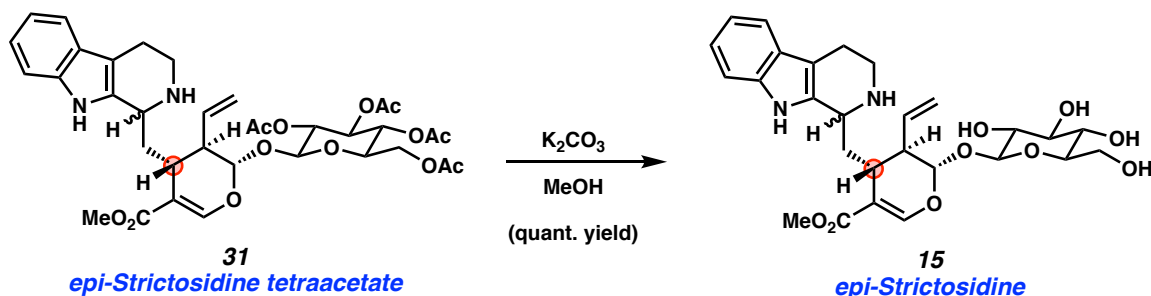
To a solution of alkene **30** (15.8 mg, 1.00 equiv, 31.0  $\mu\text{mol}$ ) in THF (3.10 mL, 0.0100 M) was added  $\text{Et}_3\text{N}$  (43.0  $\mu\text{L}$ , 10.0 equiv, 310  $\mu\text{mol}$ ) and the mixture was cooled to  $-78$   $^{\circ}\text{C}$ . TBSOTf (14.2  $\mu\text{L}$ , 2.00 equiv, 61.9  $\mu\text{mol}$ ) was added dropwise over 30 seconds. The reaction was then warmed to 23  $^{\circ}\text{C}$  and diluted with sat. aq.  $\text{NaHCO}_3$  (1 mL) and  $\text{CH}_2\text{Cl}_2$  (1 mL). The layers were separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 1 mL). The organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The crude mixture was used without further purification in the next step. To a solution of the silyl enol ether (19.3 mg, 1.00 equiv, 30.9  $\mu\text{mol}$ ) in THF (1.54 mL, 0.200 M) at  $-78$   $^{\circ}\text{C}$  was added freshly prepared DMDO (3.09 mL, 0.0300 M, 3.00 equiv, 92.7  $\mu\text{mol}$ ) in one portion. The reaction was warmed to 23  $^{\circ}\text{C}$  and after 10 min, the volatiles were removed under reduced pressure. The crude mixture was purified by preparative TLC (1:1 Hexanes:EtOAc) to afford the desired  $\alpha$ -

hydroxy ketone in quantitative yield. A solution of  $\alpha$ -hydroxy ketone (15.8 mg, 1.00 equiv, 30.0  $\mu\text{mol}$ ) in methanol (3.00 mL, 0.0100 M) was cooled to  $-40\text{ }^\circ\text{C}$ .  $\text{Pb}(\text{OAc})_4$  (15.0 mg, 1.50 equiv, 33.9  $\mu\text{mol}$ ) was added and the reaction mixture was stirred at  $-40\text{ }^\circ\text{C}$  for 10 min, then transferred to a  $-20\text{ }^\circ\text{C}$  cooling bath and stirred for an additional 30 min. The reaction was quenched with sat. aq.  $\text{NaHCO}_3$  (2 mL) and brine (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The crude residue was purified by preparative TLC (1:1 Hexanes:EtOAc) to afford epi-secologanin tetraacetate **14** (7.8 mg, 62% yield over 3 steps) as a film. Epi-secologanin tetraacetate **14**:  $R_f$  0.40 (1:1 Hexanes:EtOAc);  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.76 (s, 1H), 7.47 (s, 1H), 5.67–5.57 (m, 1H), 5.33 (d,  $J = 1.3$ , 1H), 5.27 (dt,  $J = 1.1$ , 17.3, 1H), 5.21 (t,  $J = 9.6$ , 1H), 5.16 (dt,  $J = 1.0$ , 10.5, 1H), 5.09 (t,  $J = 10.0$ , 1H), 5.04–4.98 (m, 1H), 4.85 (d,  $J = 8.0$ , 1H), 4.29 (dd,  $J = 4.4$ , 7.8, 1H), 4.11 (dd,  $J = 2.2$ , 10.2, 1H), 3.75–3.68 (m, 4H), 3.07–2.95 (m, 2H), 2.78 (d,  $J = 7.73$ , 1H), 2.72–2.61 (m, 1H), 2.09 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  201.4, 170.8, 170.3, 169.5, 169.45, 167.1, 151.0, 135.4, 117.9, 109.1, 96.44, 96.39, 72.7, 72.4, 70.7, 68.1, 61.8, 51.7, 47.1, 41.9, 27.5, 20.9, 20.75, 20.72, 20.6; IR (film): 2960, 2923, 2850, 1754, 1711, 1640, 1368, 1222, 1039  $\text{cm}^{-1}$ ; HRMS–APCI ( $m/z$ )  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{25}\text{H}_{33}\text{O}_{14}^+$ , 557.1865; found 557.1868,  $[\alpha]^{22.6}_{\text{D}} -780.0^\circ$  ( $c = 0.1$ ,  $\text{CH}_2\text{Cl}_2$ ).

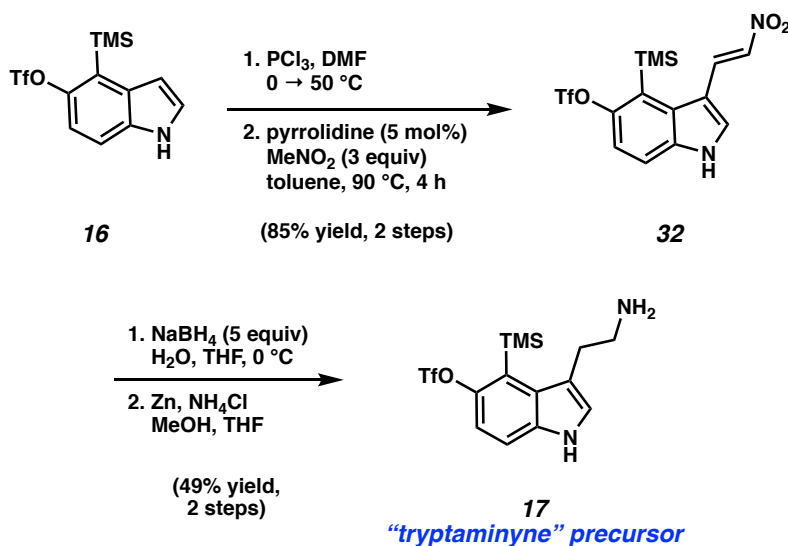


**Epi-strictosidine tetraacetate 31.** To a vial containing epi-secologanin tetraacetate **14** (2.50 mg, 1.00 equiv, 4.49  $\mu\text{mol}$ ) was added tryptamine (**5**) (1.08 mg, 1.5 equiv, 6.74  $\mu\text{mol}$ ) as a solution in  $\text{CH}_2\text{Cl}_2$  (0.450 mL, 0.0100 M) and oven-dried 4Å molecular sieves. The mixture was cooled to  $0\text{ }^\circ\text{C}$  and TFA (1.73  $\mu\text{L}$ , 5.00 equiv, 22.5  $\mu\text{mol}$ ) was added dropwise over 30 seconds. The reaction was stirred at  $0\text{ }^\circ\text{C}$  for 1 h and then

warmed to 23 °C and stirred for an additional 1 h. The reaction was filtered through celite and the filtrate was quenched with sat. aq. NaHCO<sub>3</sub> (1.5 mL). The layers were separated and then the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 1 mL). The combined organic layers were then dried with Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure, and purified by preparative TLC (1:1 Hexanes:EtOAc) to afford epi-strictosidine tetraacetate **31** (1.4 mg, 50% yield, 1:1 dr).

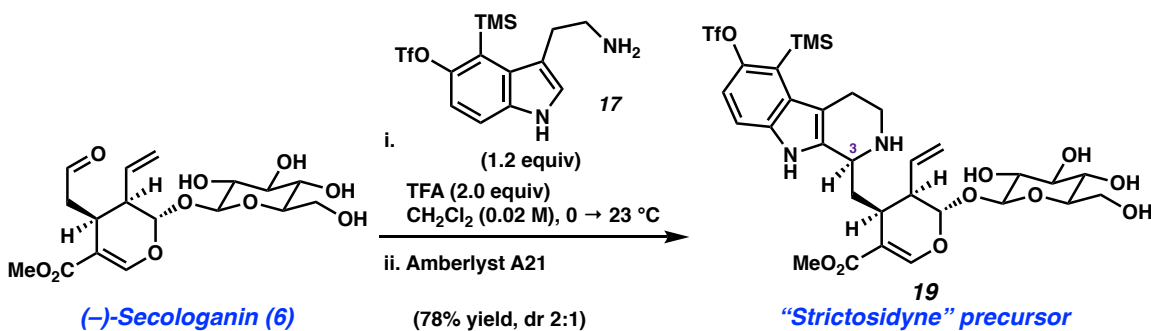


**Epi-strictosidine 15.** To a solution of epi-strictosidine tetraacetate **31** (1.1 mg, 1.0 equiv, 1.6  $\mu$ mol) in methanol (0.16 mL, 0.010 M) at 0 °C was added K<sub>2</sub>CO<sub>3</sub> (0.33 mg, 1.5 equiv, 2.4  $\mu$ mol). The reaction was stirred for 2 h at 0 °C and then filtered through a plug of silica gel (1 in) with MeOH as the eluent (15 mL). The volatiles were removed and the mixture was purified by preparative TLC (30% MeOH in EtOAc) to afford epi-strictosidine **15** (0.9 mg, quant. yield). Epi-strictosidine **15**: R<sub>f</sub> 0.20 (30% MeOH in EtOAc); <sup>1</sup>H NMR (500 MHz, MeOD) (29 of 34 protons detected):  $\delta$  8.54 (s, 1H), 7.42–7.34 (m, 2H), 7.33–7.26 (m, 1H), 7.11–7.03 (m, 1H), 7.02–6.94 (m, 1H), 5.71–5.60 (m, 1H), 5.36–5.24 (m, 3H), 5.16–5.06 (m, 4H), 4.68–4.63 (m, 1H), 3.70–3.62 (m, 1H), 3.61–3.51 (m, 3H), 3.42–3.41 (m, 3H), 2.99–2.88 (m, 1H), 2.85–2.76 (m, 1H), 2.73–2.62 (m, 1H), 2.22–2.14 (m, 4H); <sup>13</sup>C NMR (125 MHz, MeOD):  $\delta$  149.1, 134.3, 133.1, 121.1, 118.7, 118.3, 110.8, 98.6, 97.6, 76.8, 76.6, 73.3, 70.2, 62.9, 56.1, 54.8, 54.2, 46.1, 43.4, 31.7, 30.9, 29.4, 22.3, 20.8, 15.9, 15.7, 13.0; IR (film): 3364, 2959, 2922, 2851, 1631, 1560, 1422, 1258, 1080, 1029, 798 cm<sup>-1</sup>; HRMS–APCI (m/z) [M + H]<sup>+</sup> calcd for C<sub>27</sub>H<sub>35</sub>N<sub>2</sub>O<sub>9</sub><sup>+</sup>, 531.2337; found 531.2341, [ $\alpha$ ]<sup>21.9</sup><sub>D</sub> –40.0° (c = 0.1, MeOH).



**"Tryptaminyne" precursor 17.** To a flask containing DMF (4.80 mL, 30.0 equiv, 62.0 mmol) at 0 °C was added PCl<sub>3</sub> (217 μL, 1.20 equiv, 2.48 mmol) dropwise over 2 min. The mixture was then warmed to 23 °C and stirred for 30 min, and then cooled to 0 °C. Indolyne precursor **16** (697 mg, 1.00 equiv, 2.07 mmol) in a solution of DMF (4.80 mL, 30.0 equiv, 62.0 mmol) was added dropwise over 1 min at 0 °C and the mixture was heated to 50 °C and stirred for 2 h. The reaction was then cooled to 0 °C and sat. aq. sodium bicarbonate (10 mL) was added dropwise over 5 min and then warmed to 23 °C and stirred for 30 min. The solution was then diluted with EtOAc (10 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with water (3 x 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and then concentrated to dryness. The crude aldehyde was then used in the next step without further purification. To a flask containing the crude aldehyde (74.0 mg, 1.00 equiv, 203 μmol) was added toluene (506 μL, 0.400 M), pyrrolidine (0.832 μL, 0.0500 equiv, 10.1 μmol), and nitromethane (32.8 μL, 3.00 equiv, 607 μmol), sequentially. The vial was sealed, heated to 90 °C, and stirred for 4 h. The mixture was then cooled to 23 °C and quenched with brine (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 3 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude mixture was then purified by preparative TLC (1:1 Hexanes:EtOAc) to afford alkene **32** (34.7 mg, 85% yield over two steps).

A flask containing sodium borohydride (16.1 mg, 5.00 equiv, 424  $\mu\text{mol}$ ), THF (2.80 mL, 0.0300 mmol), and water (283  $\mu\text{L}$ , 0.300 M) was cooled to 0  $^{\circ}\text{C}$ , and alkene **32** (34.7 mg, 1.00 equiv, 84.9  $\mu\text{mol}$ ) was added as a solution in THF (849  $\mu\text{L}$ , 0.100 M). The reaction was stirred at 0  $^{\circ}\text{C}$  for 35 min and then quenched by the addition of aq. 1 M HCl (1 mL) and diluted with EtOAc (3 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$ , and purified by preparative TLC (1:1 Hexanes:EtOAc) to afford the nitroalkane. To a vial containing the nitroalkane (30.0 mg, 1.00 equiv, 73.1  $\mu\text{mol}$ ) was added methanol (1.5 mL, 0.0500 M) and THF (1.50 mL, 0.0500 M). Zinc (71.7 mg, 15.0 equiv, 1.10 mmol) and ammonium chloride (58.6 mg, 15.0 equiv, 1.10 mmol) were added sequentially, and the reaction was stirred at 23  $^{\circ}\text{C}$  for 2.5 h. The reaction was then filtered over Celite with methanol (15 mL). The methanol was evaporated under reduced pressure, and the resulting crude material was dissolved in  $\text{CH}_2\text{Cl}_2$  (5 mL) and washed with aq. 1.0 M NaOH (10 mL). The resulting crude material was purified by preparative TLC (1.1: EtOAc:MeOH) to afford “tryptaminyne” precursor **17** (15.9 mg, 49% yield over two steps) as a clear oil. “Tryptaminyne” precursor **17**:  $R_f$  0.22 ( $\text{CH}_2\text{Cl}_2$ :MeOH:sat. aq.  $\text{NH}_4\text{OH}$  9:1:0.15);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.29 (s, 1H), 7.37 (d,  $J = 9.21$ , 1H), 7.25–7.23 (m, 1H), 7.05 (d,  $J = 9.21$ , 1H), 3.05–3.00 (m, 2H), 2.99–2.94 (m, 2H), 0.51 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) (11 of 12 carbon signals observed):  $\delta$  149.0, 134.8, 132.0, 125.3, 125.0, 116.8, 115.4, 113.8, 43.6, 32.1, 3.0;  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ): –72.61; IR (film): 2903, 1405, 1389, 1202, 1141, 1124, 825, 605  $\text{cm}^{-1}$ ; HRMS–APCI ( $m/z$ )  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_3\text{SSi}^+$ , 381.09105; found 381.08991.



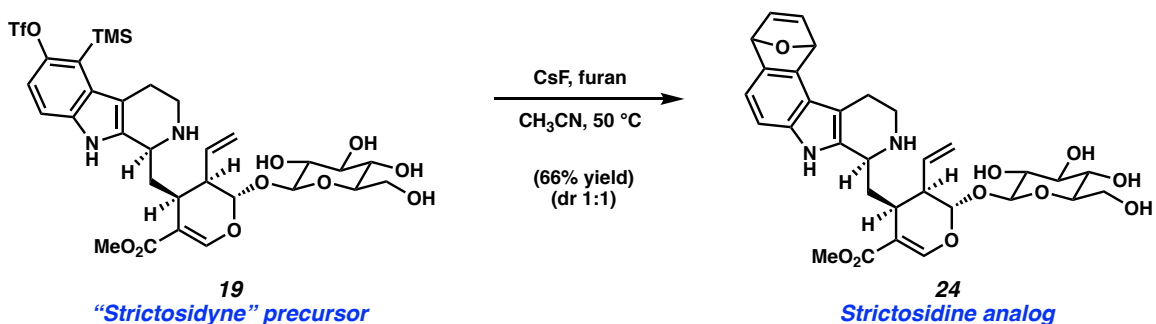
**(–)-Strictosidyne precursor 19.** (–)-Secologanin (**6**) (10.3 mg, 1.00 equiv, 26.5  $\mu\text{mol}$ )

was charged in a vial under N<sub>2</sub> atmosphere. Tryptaminyne **17** (12.80 mg, 1.27 equiv, 33.6 μmol) was added as a solution in CH<sub>2</sub>Cl<sub>2</sub> (1.33 mL, 0.0200 molar) and the solution was cooled to 0 °C. Trifluoroacetic acid (9.07 mg, 6.13 μL, 2.00 equiv, 79.6 μmol) was added in one portion. The reaction was stirred for 30 min at 0 °C, warmed to 23 °C, and then stirred for 30 min, while monitoring the consumption of starting material via TLC analysis. Amberlyst A21 (15 mg) was then added, the reaction was stirred for 2 min, filtered, and the filtrate was concentrated under vacuum. By analysis of the crude mixture, a ~2:1 mixture of diastereomers was obtained, favoring (–)-“strictosidine” precursor **19**. The crude mixture was purified by preparative TLC (2:1 EtOAc:MeOH) to afford (–)-“strictosidyne” precursor **19** (10.3 mg, 52% yield) as a white amorphous solid. Characterization data is reported for the major isomer. “Strictosidyne” precursor **19**. R<sub>f</sub> 0.60 (4:1 EtOAc:MeOH); <sup>1</sup>H NMR (MeOD, 500 MHz) (35 of 41 protons detected, NH and OH protons not detected): δ 7.68 (d, *J* = 1.06, 1H), 7.37–7.33 (m, 1H), 6.95 (d, *J* = 8.8, 1H), 5.88–5.80 (m, 2H), 5.30 (dd, *J* = 1.1, 17.3, 1H), 5.21 (dd, *J* = 0.9, 10.6, 1H), 4.78 (dd, *J* = 7.9, 0.9, 1H), 4.01 (br d, *J* = 9.1, 1H), 3.94 (d, *J* = 11.4, 1H), 3.75 (s, 3H), 3.65–3.61 (m, 1H), 3.41–3.37 (m, 4H), 3.27–3.20 (m, 3H), 3.07–3.01 (m, 1H), 3.00–2.95 (m, 1H), 2.89–2.84 (m, 2H), 2.67–2.63 (m, 1H), 2.06–1.98 (m, 2H), 0.47 (s, 9H). <sup>13</sup>C NMR (MeOD, 125 MHz): δ 170.1, 155.4, 149.9, 140.3, 136.1, 136.0, 133.2, 124.0, 119.2, 119.0 (q, *J* = 320.0 Hz), 114.7, 114.4, 110.81, 110.75, 100.3, 97.6, 78.7, 78.0, 74.7, 71.7, 63.0, 52.1, 52.0, 45.9, 43.8, 37.5, 32.6, 30.8, 27.3, 3.3 (3C); <sup>19</sup>F NMR (MeOD, 376 MHz): –74.36; IR (film): 3310, 2925, 2853, 1693, 1631, 1405, 1244, 1210, 1142, 1077, 841 cm<sup>–1</sup>; HRMS (ESI) (*m/z*) [M + H]<sup>+</sup> calcd for C<sub>31</sub>H<sub>42</sub>F<sub>3</sub>N<sub>2</sub>O<sub>12</sub>SSi<sup>+</sup>, 751.2174; found: 751.2219; [α]<sup>21.2</sup><sub>D</sub> –360° (c = 0.5, MeOH).

*Note: The stereochemistry at C3 was assigned by comparison of the <sup>1</sup>H NMR spectrum of strictosidine and its C3 epimer (vincoside). “Strictosidyne” precursor **19** overlapped with strictosidine and the C3 epimer of “Strictosidyne” precursor **19** overlapped with vincoside. Additionally, we observed similar selectivity when running the Pictet–Spengler reaction of secologanin and tryptamine with the same conditions (2:1, favoring strictosidine). Collectively, this led us to assign the C3 stereocenter as is depicted. Only*

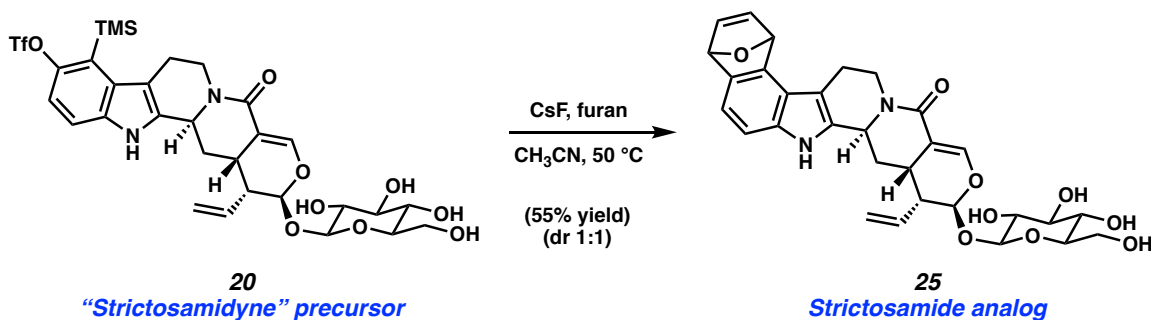






**Strictosidine analog 24.** In a glovebox, CsF (8.07 mg, 7.00 equiv, 53.1  $\mu\text{mol}$ ) was transferred to a flame dried vial. Out of the glovebox, the vial charged with a stir bar under nitrogen atmosphere. “Strictosidyne” precursor **19** (5.70 mg, 1.00 equiv, 7.59  $\mu\text{mol}$ ) was added as a solution in dry  $\text{CH}_3\text{CN}$  (400  $\mu\text{L}$ , 0.019 molar). Furan (**21**) (5.17 mg, 5.52  $\mu\text{L}$ , 10.0 equiv, 75.9  $\mu\text{mol}$ , previously dried over  $\text{MgSO}_4$ ) was added in one portion. The vial was sealed and heated to 50  $^\circ\text{C}$  for 2 h. The crude mixture was then directly filtered on silica gel (monster pipet, 1 cm tall) with MeOH (7 mL) and concentrated under vacuum. Purification by preparative TLC ( $\text{CH}_2\text{Cl}_2$ :MeOH:aq. sat.  $\text{NH}_4\text{OH}$  9:2.5:0.15) afforded strictosidine analog **24** (3.0 mg, 66% yield, 1:1 dr) as an amorphous white solid. Characterization data is reported for the 1:1 mixture of inseparable isomers. Strictosidine analog **24**:  $R_f$  0.54 (9:2.5:0.15  $\text{CH}_2\text{Cl}_2$ :MeOH:sat. aq.  $\text{NH}_4\text{OH}$ );  $^1\text{H}$  NMR (MeOD, 500 MHz) (2 isomers integrated as 1, 31 of 36 protons detected):  $\delta$  7.67 (s, 1H), 7.09–7.03 (m, 3H), 6.83 (d,  $J = 7.82$ , 1H), 6.02 (d,  $J = 11.43$ , 1H), 5.88–5.79 (m, 2H), 5.72 (s, 1H), 5.32–5.28 (m, 1H), 5.20 (app q,  $J = 5.35$  Hz, 1H), 4.76 (d,  $J = 7.87$ , 1H), 3.94–3.90 (m, 2H), 3.74 (s, 3H), 3.65–3.63 (m, 1H), 3.40–3.34 (m, 3H), 3.25–3.21 (m, 3H), 3.02–2.92 (m, 3H), 2.88–2.93 (m, 1H), 2.67–2.66 (m, 1H), 2.00–1.95 (m, 2H);  $^{13}\text{C}$  NMR (MeOD, 125 MHz):  $\delta$  170.1 (2C), 155.3 (2C), 145.4 (2C), 144.04, 143.99, 140.93, 140.89, 140.69 (2C), 138.7, 138.6, 137.3 (2C), 136.1 (2C), 124.01, 123.99, 119.1 (2C), 114.9 (2C), 110.8 (2C), 106.8 (2C), 106.6, 100.3 (2C), 97.6 (2C), 84.0 (2C), 82.9, 82.7, 78.7 (2C), 78.0 (2C), 74.7 (2C), 71.7 (2C), 62.9 (2C), 52.1 (2C), 51.7, 51.6, 46.0 (2C), 43.3, 43.1, 37.02 (2C), 36.97, 33.1, 32.72, 32.69, 30.9, 30.80, 30.77, 30.5, 27.9, 24.2, 23.7, 23.5; IR (film): 3350, 2923, 2851, 1735, 1555, 1463, 1380, 1081  $\text{cm}^{-1}$ ; HRMS (ESI) ( $m/z$ )  $[\text{M} + \text{H}]^+$  calcd. for  $\text{C}_{31}\text{H}_{37}\text{N}_2\text{O}_{10}^+$ , 597.2443; found: 597.2456,  $[\alpha]^{20.9}_{\text{D}}$  40 (value measured for the mixture of isomers,  $c = 0.5$ , MeOH).

Strictosidine analog **24** was characterized as a mixture of diastereomers and the  $^1\text{H}$  NMR spectrum was integrated as such. The dr was determined by comparing the peaks at 6.01 and 6.04, which integrated in a 1:1 ratio.



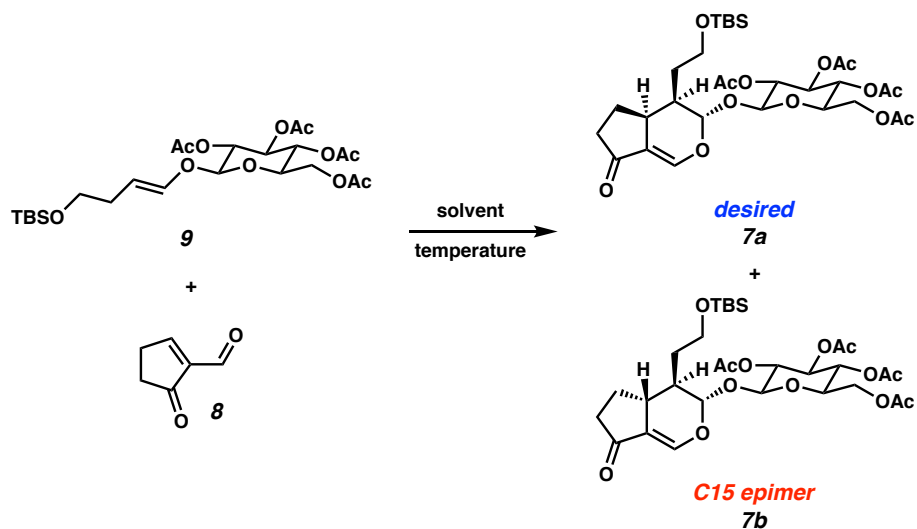
**Strictosamide analog 25.** To a vial containing "strictosamidyne" precursor **20** (2.30 mg, 1.00 equiv, 3.20  $\mu\text{mol}$ ) in MeCN (0.320 mL, 0.0100 M) was added furan (**21**) (2.30  $\mu\text{L}$ , 10.0 equiv, 32.0  $\mu\text{mol}$ , previously dried over  $\text{MgSO}_4$ ) and CsF (4.90 mg, 10.0 equiv, 32.0  $\mu\text{mol}$ ). The vial was sealed with Teflon tape, heated to 50  $^\circ\text{C}$ , and stirred for 2 h. The reaction was then cooled to 23  $^\circ\text{C}$  and filtered on a silica gel plug (monster pipet, 2.5 cm tall) with 1:1 EtOAc:MeOH (10 mL). The volatiles were removed under reduced pressure and the crude residue was purified by preparative TLC (4:1 EtOAc:MeOH) to afford strictosamide analog **25** (1.0 mg, 55% yield, 1:1 dr). Strictosamide analog **25**:  $R_f$  0.56 (4:1 EtOAc:MeOH);  $^1\text{H}$  NMR (MeOD, 500 MHz) (2 isomers, 27 of 32 protons detected, NH and OH peaks not detected):  $\delta$  7.38 (dd,  $J = 2.3, 7.0$ , 1H), 7.13–7.05 (m, 3H), 6.93 (dd,  $J = 7.90, 3.44$ , 1H), 6.06–5.97 (m, 1H), 5.77–5.73 (m, 1H), 5.70–5.59 (m, 1H), 5.41 (dd,  $J = 6.24, 1.74$ , 1H), 5.36 (dt,  $J = 17.2, 5.35$ , 1H), 5.32 (dd,  $J = 9.99, 5.31$ , 1H), 5.09–5.04 (m, 1H), 5.00–4.94 (m, 1H), 4.57 (dd,  $J = 8.00, 6.42$ , 1H), 3.88–3.82 (m, 1H), 3.65–3.60 (m, 1H), 3.26–3.22 (m, 2H), 3.21–3.15 (m, 2H), 3.15–3.10 (m, 1H), 2.99–2.91 (m, 1H), 2.90–2.73 (m, 2H), 2.71–2.64 (m, 1H), 2.48–2.41 (m, 1H), 2.09–1.98 (m, 1H);  $^{13}\text{C}$  NMR (MeOD, 125 MHz) (2 isomers):  $\delta$  167.1, 149.3, 145.6, 144.2, 137.3, 137.0, 134.4, 120.5, 115.4, 109.2, 108.4, 107.4, 100.54, 100.51, 98.1, 84.03, 83.99, 82.9, 82.7, 78.3, 78.0, 74.3, 71.4, 62.6, 57.6, 57.5, 57.3, 55.1, 49.6, 44.8, 30.8, 27.3, 25.0, 24.1, 23.7, 23.2, 22.9, 17.6, 17.4, 17.3, 17.1, 17.0, 14.4; IR (film): 3356, 2955, 2918, 2850, 1735, 1659, 1552, 1463, 1375, 1079  $\text{cm}^{-1}$ ; HRMS (ESI) ( $m/z$ )  $[\text{M} + \text{H}]^+$  calcd. for  $\text{C}_{30}\text{H}_{33}\text{N}_2\text{O}_9^+$ ,

565.2181; found: 565.2191,  $[\alpha]^{22.3}_{\text{D}} -20$  (value measured for the mixture of isomers,  $c = 0.1$ ,  $\text{CH}_2\text{Cl}_2$ ).

*Strictosamide analog 25 was characterized as a mixture of diastereomers and the  $^1\text{H}$  NMR spectrum was integrated as such. The dr was determined by comparing the peaks at 6.04 and 5.99, which integrated in a 1:1 ratio.*

### **C. Diels–Alder Reaction Optimization.**

**Cycloadducts 7a and 7b. General Procedure.** Enol ether **9** (1.00 equiv) and enal **8** (6.00 equiv) in a solution in the reported solvent were heated to the reported temperature. The reaction was stirred for the reported time and then cooled to 23 °C. The reaction was diluted with EtOAc (1 mL), filtered over a short pad of silica with EtOAc (10 mL), and the volatiles were concentrated under reduced pressure. The crude mixture was diluted with HPLC-grade isopropanol (5, 10, or 15 mL) and the crude mixture was analyzed by SFC. The yield and d.r. were determined by using generated calibration curves on an SFC. Chiral SFC: 250 mm Daicel ChiralPak IC-3, 5% MeOH, 3.5 mL/min,  $\lambda = 268$  nm, 35 °C, nozzle pressure = 100 bar  $\text{CO}_2$ ,  $t_{\text{R1}}$  (desired) = 3.80,  $t_{\text{R2}}$  (undesired) = 6.13 min.

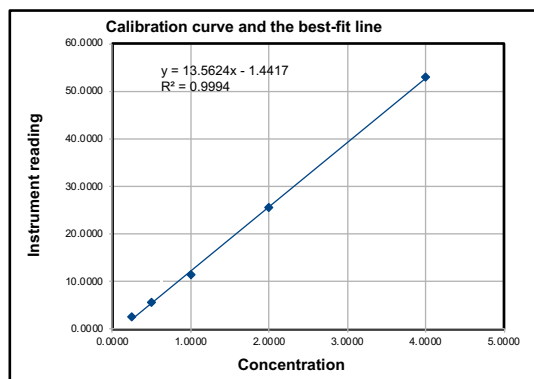
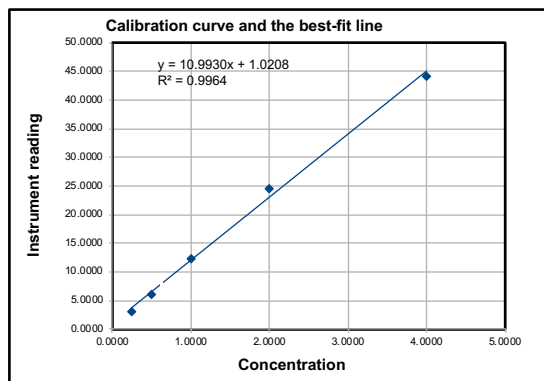
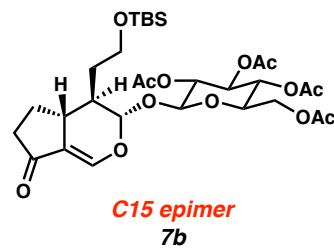
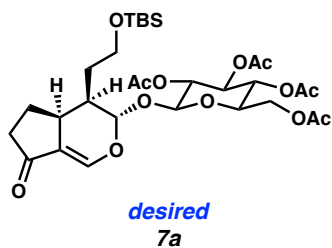


entry	time	solvent (M)	temperature (°C)	additive (equiv)	yield
1	16 h	DMF	130	-	<5 %
2	20 h	<i>i</i> PrOH	70	-	<5 %
3	14 h	trifluoroethanol	70	-	<5 %
4	16 h	PhMe	90	-	20% <b>7a</b> *, 18% <b>7b</b> *
5	2 days	PhMe	50	acetic acid (5.0)	16% <b>7a</b> , 33% <b>7b</b>
6	14 h	neat	70	-	30% <b>7a</b> , 37% <b>7b</b>
7	3 days	PhMe	50	CoCl <sub>2</sub> (1.2)	20% <b>7a</b> , 40% <b>7b</b>
8	16 h	HFIP	50	-	35% <b>7a</b> , 29% <b>7b</b>

\*Isolated yield

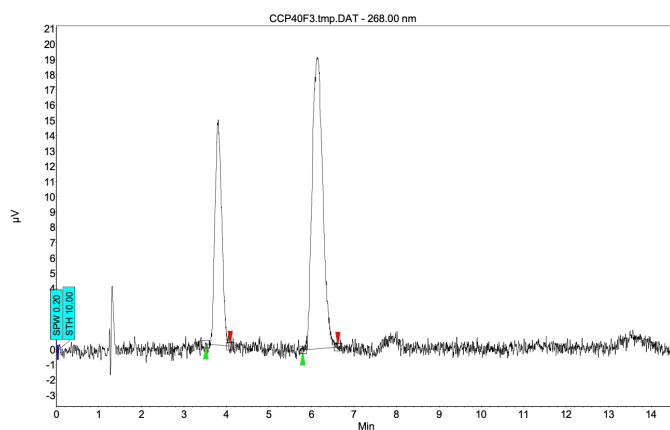
**Table SI-1. Select Results of Diels–Alder Reaction Optimization.** Reactions were run at 0.2 M.

### Calibration curves



## SFC traces

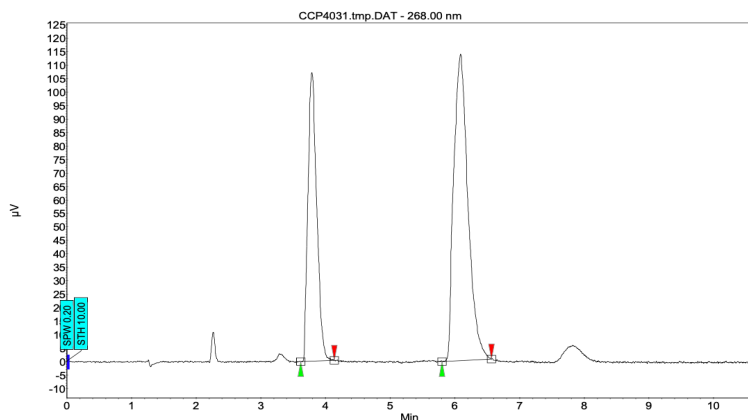
## Entry 5:



Index	Name	Start Time [Min]	Time [Min]	End [Min]	RT Offset [Min]	Quantity [% Area]	Height [ $\mu\text{V}$ ]	Area [ $\mu\text{V}\cdot\text{Min}$ ]	Area [%]
1	UNKNOWN	3.52	3.80	4.09	0.00	32.78	14.7	2.7	32.777
2	UNKNOWN	5.79	6.13	6.62	0.00	67.22	19.1	5.5	67.223
Total						100.00	33.7	8.2	100.000

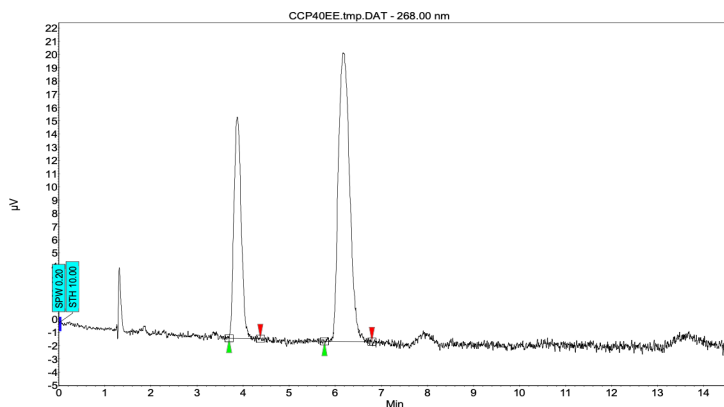
	Instrument Reading (Area)	Calculated Concentration (mg/mL)	Yield
<b>7a</b>	2.7	0.38	16%
<b>7b</b>	5.5	0.76	33%

## Entry 6:



Index	Name	Start [Min]	Time [Min]	End [Min]	RT Offset [Min]	Quantity [% Area]	Height [μV]	Area [μV.Min]	Area [%]
1	UNKNOWN	3.62	3.79	4.13	0.00	36.90	107.1	16.9	36.903
2	UNKNOWN	5.80	6.09	6.57	0.00	63.10	113.7	28.9	63.097
Total						100.00	220.8	45.8	100.000

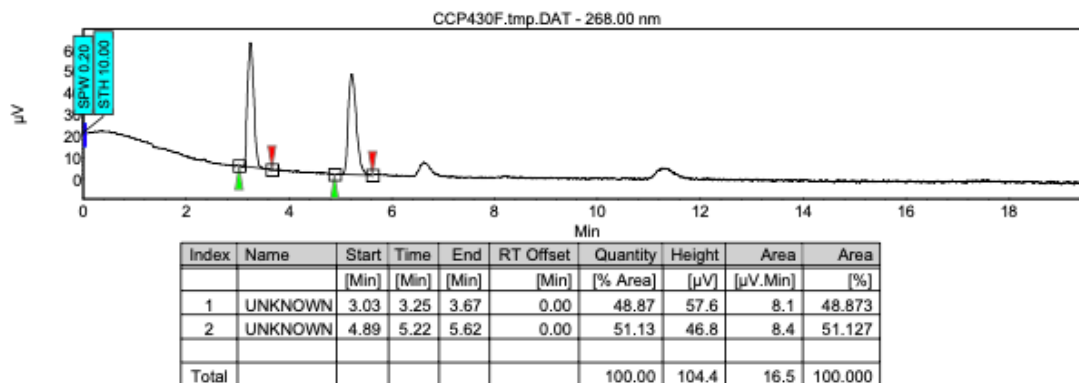
	<i>Instrument Reading (Area)</i>	<i>Calculated Concentration (mg/mL)</i>	<i>Yield</i>
<b>7a</b>	16.9	2.9	30%
<b>7b</b>	28.9	3.4	37%

**Entry 7:**

Index	Name	Start [Min]	Time [Min]	End [Min]	RT Offset [Min]	Quantity [% Area]	Height [μV]	Area [μV.Min]	Area [%]
1	UNKNOWN	3.70	3.87	4.38	0.00	32.97	16.7	3.0	32.968
2	UNKNOWN	5.76	6.17	6.79	0.00	67.03	21.8	6.2	67.032
Total						100.00	38.5	9.2	100.000

	<i>Instrument Reading (Area)</i>	<i>Calculated Concentration (mg/mL)</i>	<i>Yield</i>
<b>7a</b>	3.0	0.43	20%
<b>7b</b>	6.2	0.84	40%

**Entry 8:**



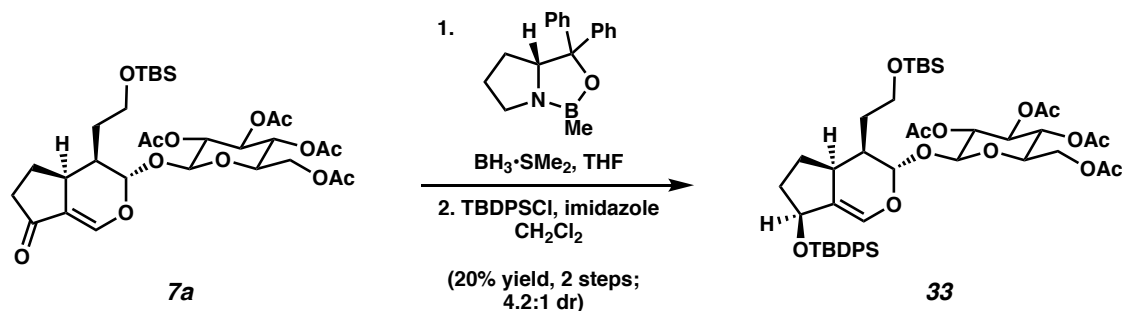
	Instrument Reading (Area)	Calculated Concentration (mg/mL)	Yield
<b>7a</b>	8.1	1.3	35%
<b>7b</b>	8.4	1.1	29%

Note: The d.r. for this reaction was 1.2:1, favoring the desired cycloadduct (**7a**) to the undesired cycloadduct (**7b**). The dr of the reaction was variable between 1.2–1.0 d.r., and in the isolated reaction described in section A, a 1:1 d.r. was obtained. We have reported the d.r. as 1:1 in the manuscript reflect the experiment where both products were isolated.

#### D. Determination of the Absolute Stereochemistry of Cycloadduct **7b**.

To determine the absolute stereochemistry of **7b**, several methods were attempted, including crystallization. Unfortunately, these attempts were futile. Therefore, a reduction of the ketone using the CBS-catalyst was performed. CBS reductions follow an established stereochemical model and can be used reliably to generate secondary alcohols with control of absolute stereochemistry.<sup>6</sup> Due to instability of the allylic alcohol, the free alcohol was protected as a silyl ether.

To ensure the carbonyl reduction was under reagent control, **7a** was first subjected to both enantiomers of catalyst and two different diastereomers were obtained and fully characterized (**33** and **34**). By analogy, **7b** was assumed to also be under reagent control and **7b** was also subjected to both enantiomers of the CBS catalyst and two different diastereomers were obtained (**35** and **36**). The NOE correlations shown were then used to determine the stereochemistry at C15, C20, and C21.



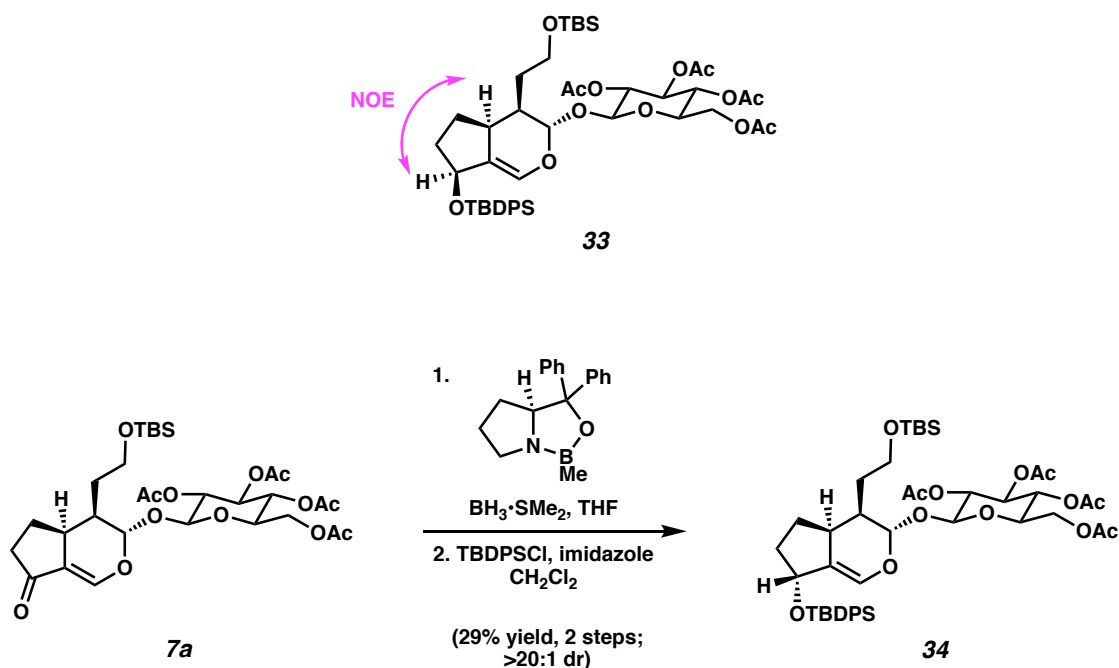
**Representative procedure toward secondary silyl ether (Synthesis of 33 is used as an example)**

**Silyl ether 33.** To a flame-dried dram vial containing cycloadduct **7a** (13.9 mg, 21.6  $\mu\text{mol}$ , 1.00 equiv), was added THF (1.0 mL, 0.20 M) and the mixture was cooled to 0 °C. A solution of (*R*)-CBS catalyst (3.00 mg, 10.8  $\mu\text{mol}$ , 0.500 equiv) in THF (1.0 mL, 0.20 M) was added in a single portion.  $\text{BH}_3\cdot\text{SMe}_2$  (16.2  $\mu\text{L}$ , 2.00 M in THF, 1.50 equiv) was added dropwise over 3 min. After stirring at 0 °C for an additional 5 min, the reaction was warmed to 23 °C and stirred for 10 min. The reaction was cooled back to 0 °C and quenched by the addition of methanol (0.5 mL). The reaction was diluted with EtOAc (0.5 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 x 1 mL). The combined organic layers were dried with  $\text{Na}_2\text{SO}_4$  and concentrated. The mixture was used without further purification. The resulting secondary alcohol was diluted with  $\text{CH}_2\text{Cl}_2$  (0.42 mL, 0.050 M) and imidazole (2.83 mg, 41.6  $\mu\text{mol}$ , 2.00 equiv) and TBDPSCl (8.0  $\mu\text{L}$ , 31.2  $\mu\text{mol}$ , 1.50 equiv) were added. The reaction was stirred for 2 h and then quenched by the addition of brine (1 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 1 mL). The organic layers were combined and dried over  $\text{Na}_2\text{SO}_4$ . The crude residue was purified by preparative TLC (3:1 Hexanes:EtOAc) to afford silyl ether **33** as a clear oil (3.7 mg, 20% yield over two steps). Silyl ether **33**:  $R_f$  0.48 (2:1 Hexanes:EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.66–7.62 (m, 4H), 7.44–7.39 (m, 2H), 7.38–7.34 (m, 4H), 6.00 (dd,  $J = 1.46, 1.6$ , 1H), 5.24 (d,  $J = 1.8$ , 1H), 5.19 (t,  $J = 9.4$ , 1H), 5.06 (t,  $J = 9.8$ , 1H), 4.95–4.90 (m, 1H), 4.84 (d,  $J = 8.33$ , 1H), 4.61–4.57 (m, 1H), 4.26 (dd,  $J = 4.38, 12.34$ , 1H), 4.09 (dd,  $J = 2.30, 12.34$ , 1H), 3.71–3.64 (m, 3H), 2.50–2.43 (m, 1H), 2.07–2.03 (m, 4H), 2.06–2.00 (m, 5H), 1.98 (s, 3H), 1.66 (s, 3H), 1.64–1.60 (m, 2H), 1.39–1.31 (m, 2H), 1.05 (s, 9H), 0.88 (s, 9H), 0.05 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.9, 170.4, 169.6, 169.3, 136.00,



135.98, 134.5, 134.3, 129.9, 129.8, 127.8, 127.7, 122.2, 95.7, 94.8, 73.0, 72.6, 72.1, 70.7, 68.5, 62.0, 61.7, 36.5, 32.7, 32.2, 28.0, 27.1, 26.1, 23.8, 20.9, 20.78, 20.75, 20.5, 19.4, 18.4, -5.2; IR (film): 2956, 2930, 2859, 1758, 1365, 1222, 1106, 1038, 703  $\text{cm}^{-1}$ ; ESI-HRMS  $m/z = 905.3934$  ( $[M + \text{Na}]^+$ ), calcd for  $\text{C}_{46}\text{H}_{66}\text{O}_{13}\text{Si}_2\text{Na} = 905.3934$ ,  $[\alpha]^{24.5}_{\text{D}} - 760.0^\circ$  ( $c = 0.1$ ,  $\text{CH}_2\text{Cl}_2$ ).

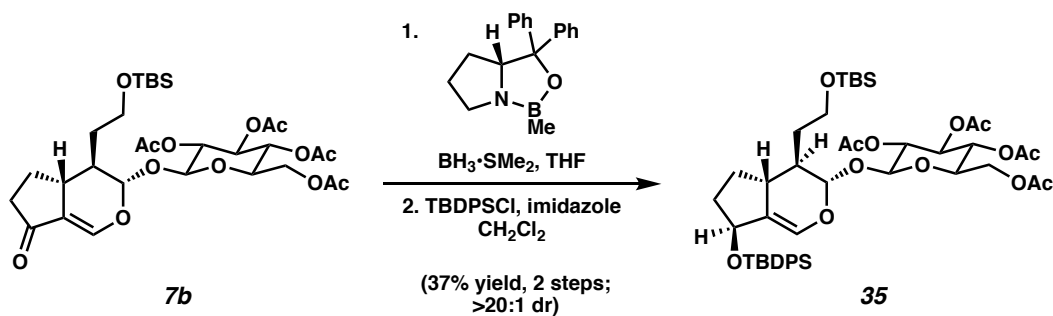
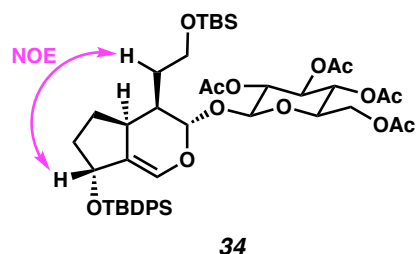
The following NOE correlations were observed:



**Silyl ether 34.** Purification by preparative TLC (3:1 Hexanes:EtOAc) afforded silyl ether **34** as a clear oil (4.4 mg, 29% yield over two steps). Silyl ether **34**:  $R_f$  0.50 (2:1 Hexanes:EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.68–7.64 (m, 4H), 7.45–7.36 (m, 6H), 6.09–6.06 (m, 1H), 5.27 (t,  $J = 9.6$ , 1H), 5.24 (d,  $J = 1.6$ , 1H), 5.12 (t,  $J = 9.7$ , 1H), 5.08–5.03 (m, 1H), 4.90 (d,  $J = 8.2$ , 1H), 4.57–4.53 (m, 1H), 4.28 (dd,  $J = 4.4$ , 12.3, 1H), 4.11 (dd,  $J = 2.39$ , 12.3, 1H), 3.73 (m, 1H), 3.55 (t,  $J = 6.61$ , 2H), 2.88–2.80 (m, 1H), 2.08 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.82–1.75 (m, 1H), 1.72–1.64 (m, 1H), 1.36–1.28 (m, 1H), 1.19–1.07 (m, 4H), 1.08 (s, 9H), 0.85 (s, 9H), -0.01 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.9, 170.4, 170.1, 169.6, 136.1, 136.0, 135.6, 134.3, 129.84, 129.82, 127.7, 120.8, 95.2, 93.8, 74.2, 72.7, 72.1, 70.6, 68.6, 62.0, 61.5, 36.1, 32.8, 32.6, 27.9, 27.2, 26.1, 24.4, 21.3, 20.9, 20.81, 20.78, 19.3, 18.4, -5.26, -5.28; IR (film): 2956, 2929,

2859, 1758, 1365, 1221, 1039, 833  $\text{cm}^{-1}$ ; ESI-HRMS  $m/z = 905.0396$  ( $[\text{M} + \text{Na}]^+$ ), calcd for  $\text{C}_{46}\text{H}_{66}\text{O}_{13}\text{Si}_2\text{Na} = 905.3934$ ,  $[\alpha]^{24.9}_{\text{D}} -520.0^\circ$  ( $c = 0.1$ ,  $\text{CH}_2\text{Cl}_2$ ).

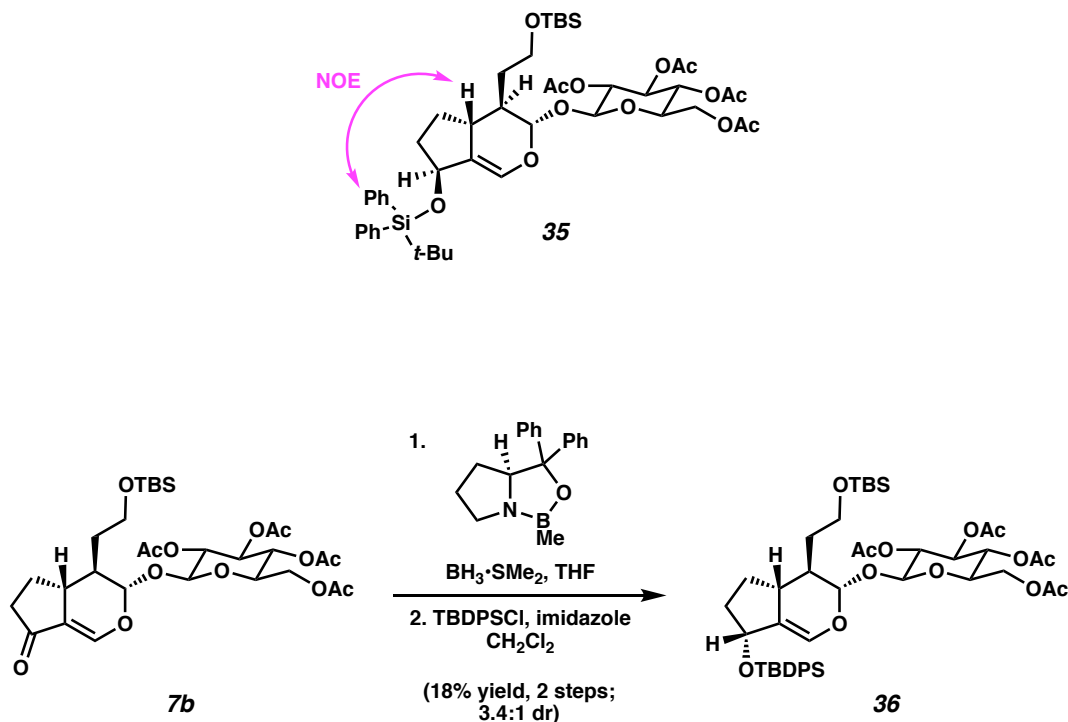
The following NOE correlations were observed:



**Silyl ether 35.** Purification by preparative TLC (3:1 Hexanes:EtOAc) generated silyl ether **35** as a clear oil (4.8 mg, 37% yield over two steps). Silyl ether **35**:  $R_f$  0.50 (2:1 Hexanes:EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.68–7.64 (m, 4H), 7.44–7.39 (m, 2H), 7.39–7.34 (m, 4H), 5.88 (d,  $J = 2.2$ , 1H), 5.21 (t,  $J = 9.5$ , 1H), 5.08 (t,  $J = 9.9$ , 1H), 5.00–4.95 (m, 1H), 4.86–4.82 (m, 2H), 4.56–4.53 (m, 1H), 4.27 (dd,  $J = 4.4, 12.3$ , 1H), 4.16 (dd,  $J = 2.5, 12.3$ , 1H), 3.76–3.69 (m, 2H), 3.63–3.58 (m, 1H), 2.50–2.42 (m, 1H), 2.09 (s, 3H), 2.08–2.05 (m, 1H), 2.03 (s, 3H), 2.00 (s, 3H), 1.95 (s, 3H), 1.92–1.84 (m, 1H), 1.77–1.65 (m, 2H), 1.63–1.57 (m, 1H), 1.12–1.08 (m, 1H), 1.04 (s, 9H), 0.88 (s, 9H), 0.05 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.8, 170.4, 169.6, 169.4, 137.0, 136.1, 136.0, 134.7, 134.6, 129.7, 129.6, 127.7, 127.6, 122.6, 99.7, 97.0, 73.5, 72.9, 72.1, 71.0, 68.6, 62.1, 61.5, 40.0, 39.3, 36.3, 34.0, 29.2, 27.1, 26.1, 20.9, 20.80, 20.77, 19.3, 18.4, –5.1, –5.2; IR (film): 2926, 2854, 1758, 1632, 1365, 1219, 1037, 801, 702  $\text{cm}^{-1}$ ; ESI-HRMS  $m/z = 905.0374$  ( $[\text{M} + \text{Na}]^+$ ), calcd for  $\text{C}_{46}\text{H}_{66}\text{O}_{13}\text{Si}_2\text{Na} = 905.3934$ ,  $[\alpha]^{22.8}_{\text{D}} -$

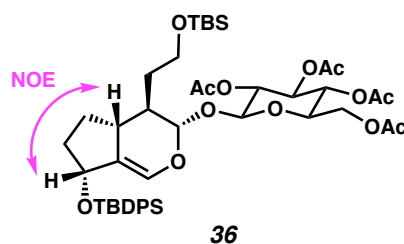
360.0° (c = 0.1, CH<sub>2</sub>Cl<sub>2</sub>).

The following NOE correlations were observed:



**Silyl ether 36.** Purification by preparative TLC (3:1 Hexanes:EtOAc) afforded silyl ether **36** as a clear oil (2.1 mg, 18% yield over two steps). Silyl ether **36**:  $R_f$  0.63 (2:1 Hexanes:EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.68–7.64 (m, 4H), 7.44–7.39 (m, 2H), 7.39–7.34 (m, 4H), 6.34 (t,  $J = 2.04$ , 1H), 5.21 (q,  $J = 9.5$ , 1H), 5.11–5.06 (m, 1H), 5.04–5.00 (m, 1H), 4.93–4.88 (m, 2H), 4.70–4.66 (m, 1H), 4.26–4.22 (m, 1H), 4.14–4.10 (m, 1H), 3.76–3.66 (m, 2H), 3.63–3.56 (m, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.80–1.72 (m, 1H), 1.70–1.64 (m, 2H), 1.63–1.59 (m, 2H), 1.48–1.39 (m, 2H), 1.06 (s, 9H), 0.88 (s, 9H), 0.05 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  170.8, 170.4, 169.6, 169.5, 136.1, 136.02, 135.96, 135.9, 135.5, 134.6, 134.2, 129.8, 129.7, 129.6, 127.8, 127.7, 127.6, 122.9, 99.8, 96.9, 73.1, 73.0, 72.1, 71.0, 68.6, 62.0, 61.6, 39.8, 39.6, 35.4, 33.9, 27.9, 27.1, 26.1, 20.92, 20.88, 20.8, 19.4, 18.4, –5.2; IR (film): 2958, 2934, 2859, 1757, 1375, 1222, 1040 cm<sup>-1</sup>; ESI-HRMS  $m/z = 905.0413$  ( $[\text{M} + \text{Na}]^+$ ), calcd for C<sub>46</sub>H<sub>66</sub>O<sub>13</sub>Si<sub>2</sub>Na = 905.3934,  $[\alpha]^{24.9}_D -40.0^\circ$  (c = 0.1, CH<sub>2</sub>Cl<sub>2</sub>).

The following NOE correlations were observed:



### E. Preparation of strictosidine synthase.

The gene encoding strictosidine synthase was obtained via DNA synthesis from Gen9. Protein expression in *E. coli* required the removal of a 30-residue N-terminal signal peptide, which was replaced with a HIS-tag for optional purification via Nickel-NTA. The codon optimized gene was amplified with primers adding NheI and SacI restriction sites. Following digestion of both the amplified gene and pET28a, ligation was carried out with T4 DNA Ligase. The ligation product was transformed into TOP10 (Invitrogen) for sequence confirmation, and then retransformed into SoluBL21 (Genlantis) for expression. An overnight culture was used to inoculate 1 L LB + 50 mg/L kanamycin. The culture was shaken at 250 rpm and 37 °C until an OD<sub>600</sub> of 0.6 was reached. The culture was cooled on ice prior to the addition of 100 μM IPTG for induction and then shaken at 16 °C for 18 h. Cells were harvested via centrifugation at 4,000 g for 20 min and stored at –80 °C for several hours. The thawed pellet was resuspended in 30 mL chilled lysis buffer (0.1 M NaH<sub>2</sub>PO<sub>4</sub>, 0.1 M NaCl, pH = 7.0), and lysed by sonication on ice (Qsonica, 500 W, 20 kHz, 50% amplitude, 5 cycles of 1 second on, 1 second off for 60 seconds). The lysate was then centrifuged at 40,000 g for 30 min to remove cell debris. The lysate was flash frozen and lyophilized in 1 mL aliquots, providing a shelf-stable enzymatic preparation that retained activity for at least 6 months.

### DNA sequence of strictosidine synthase.

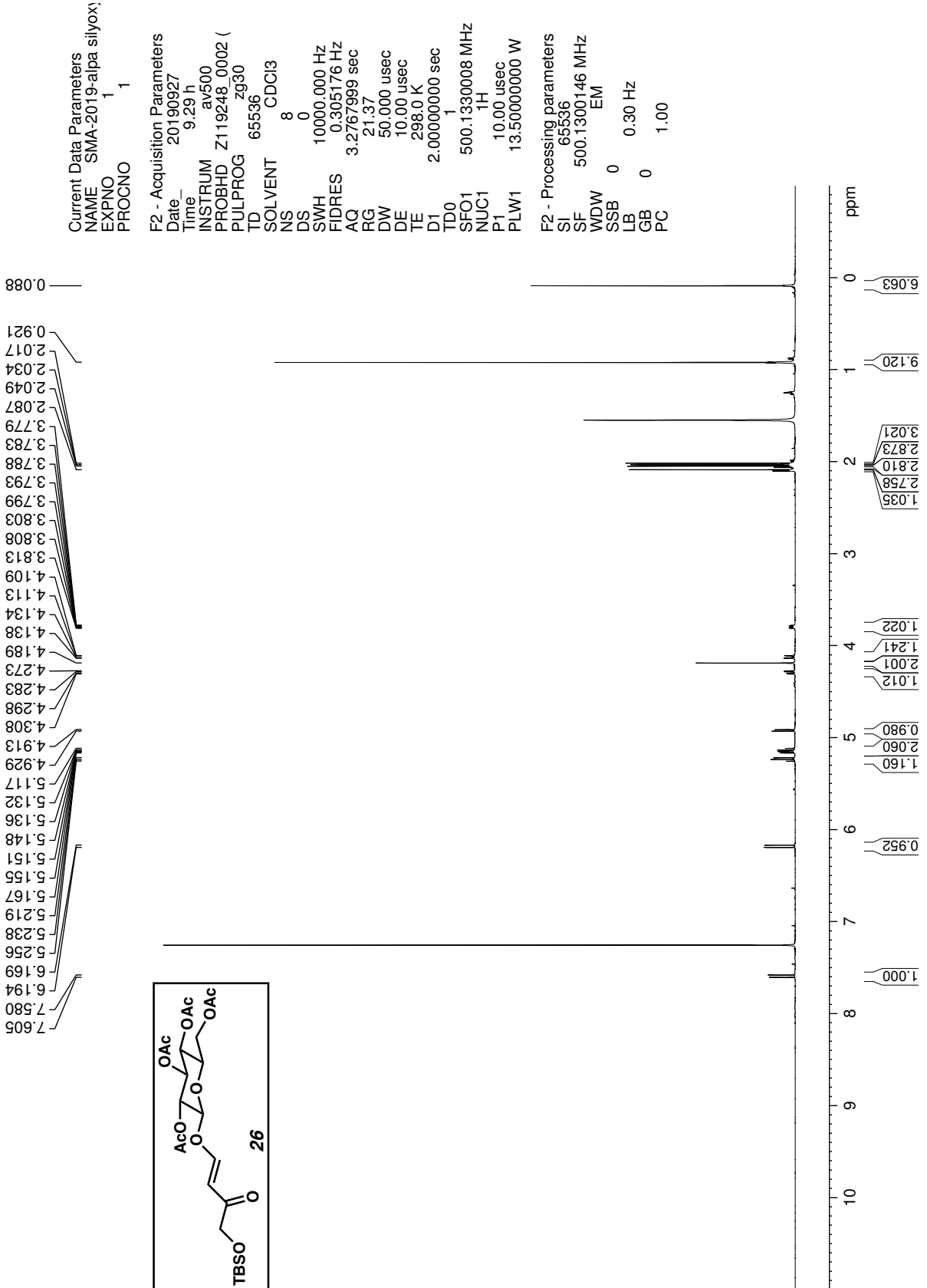
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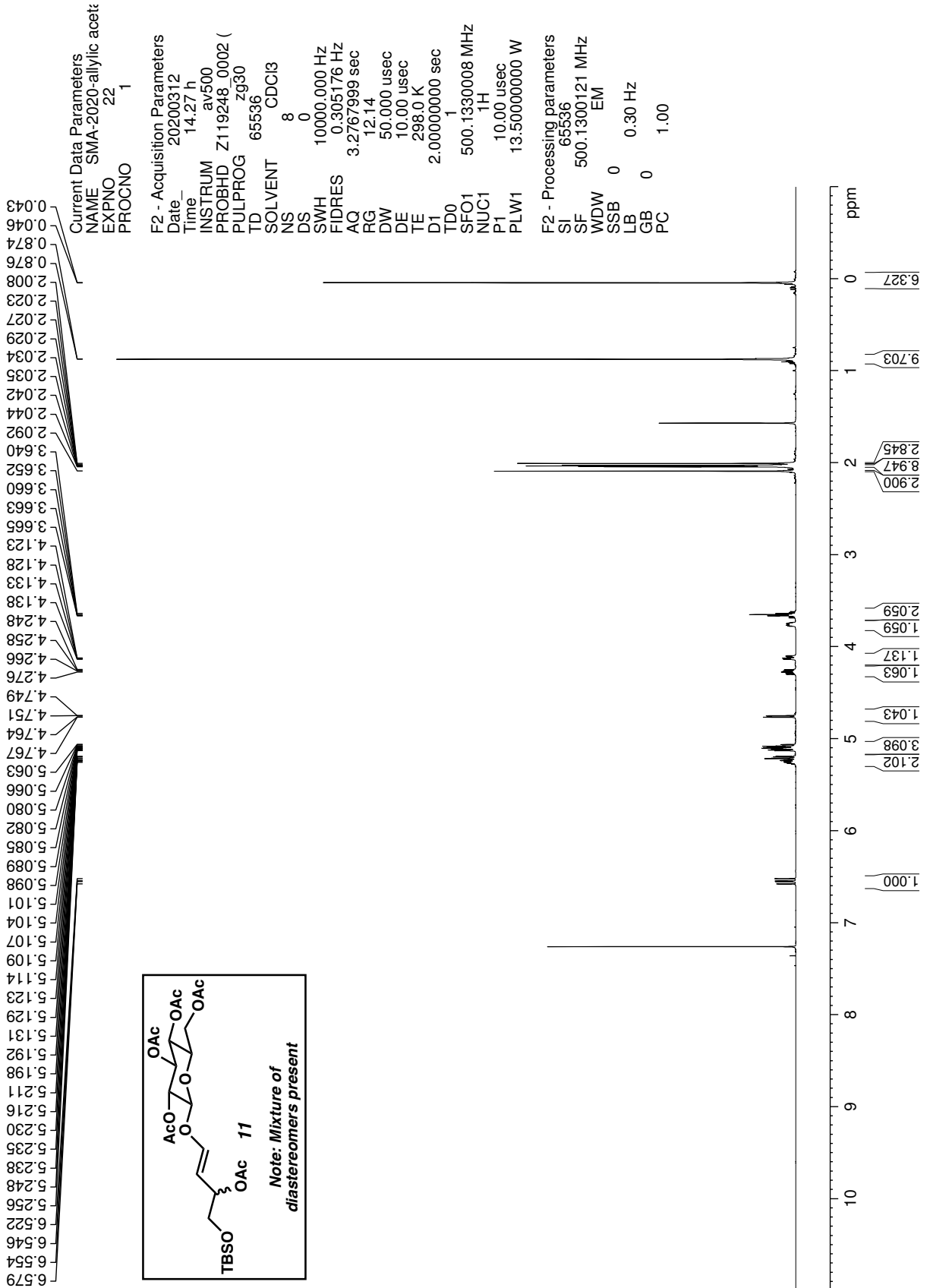
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**Protein sequence of strictosidine synthase.**

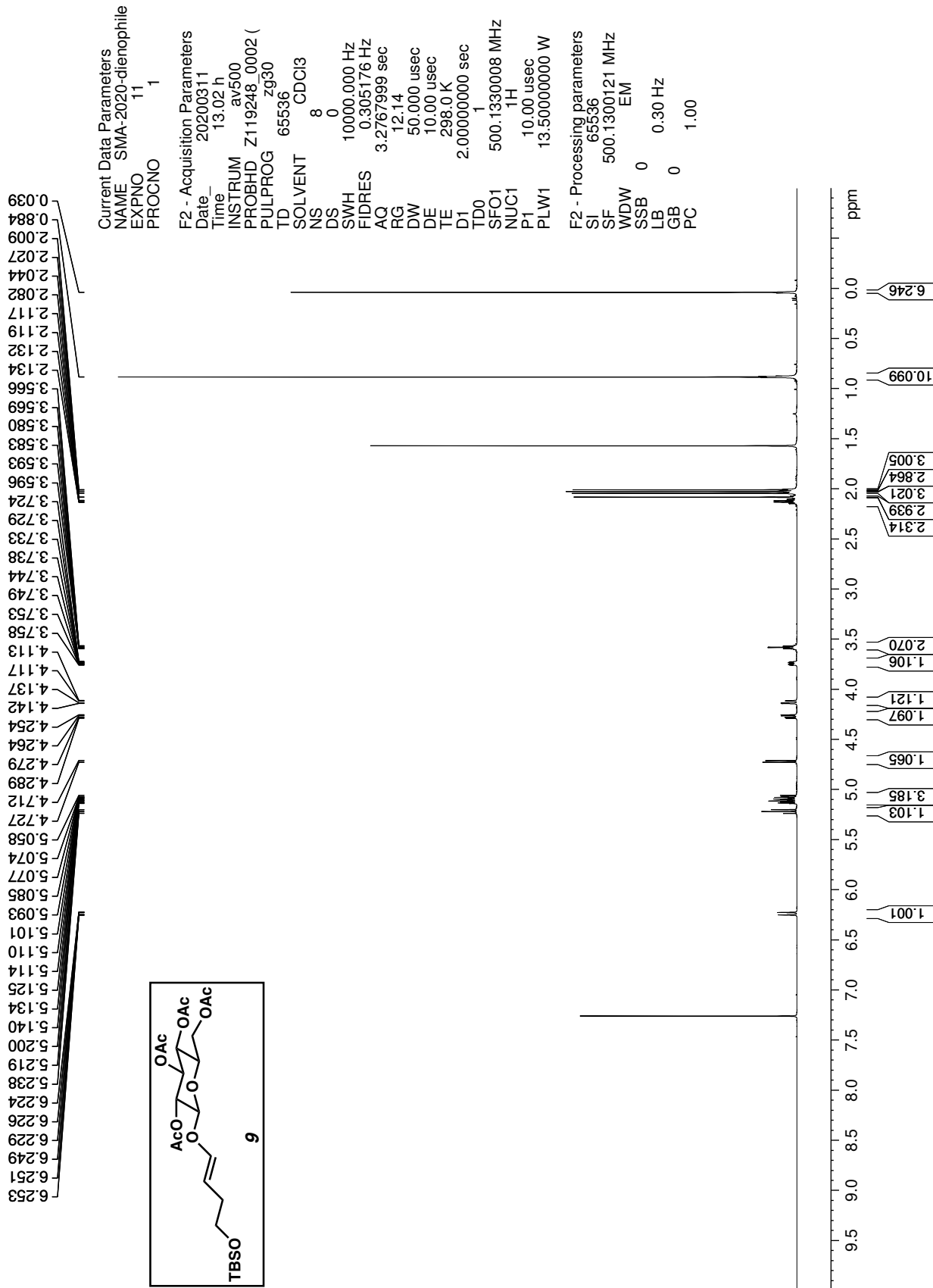
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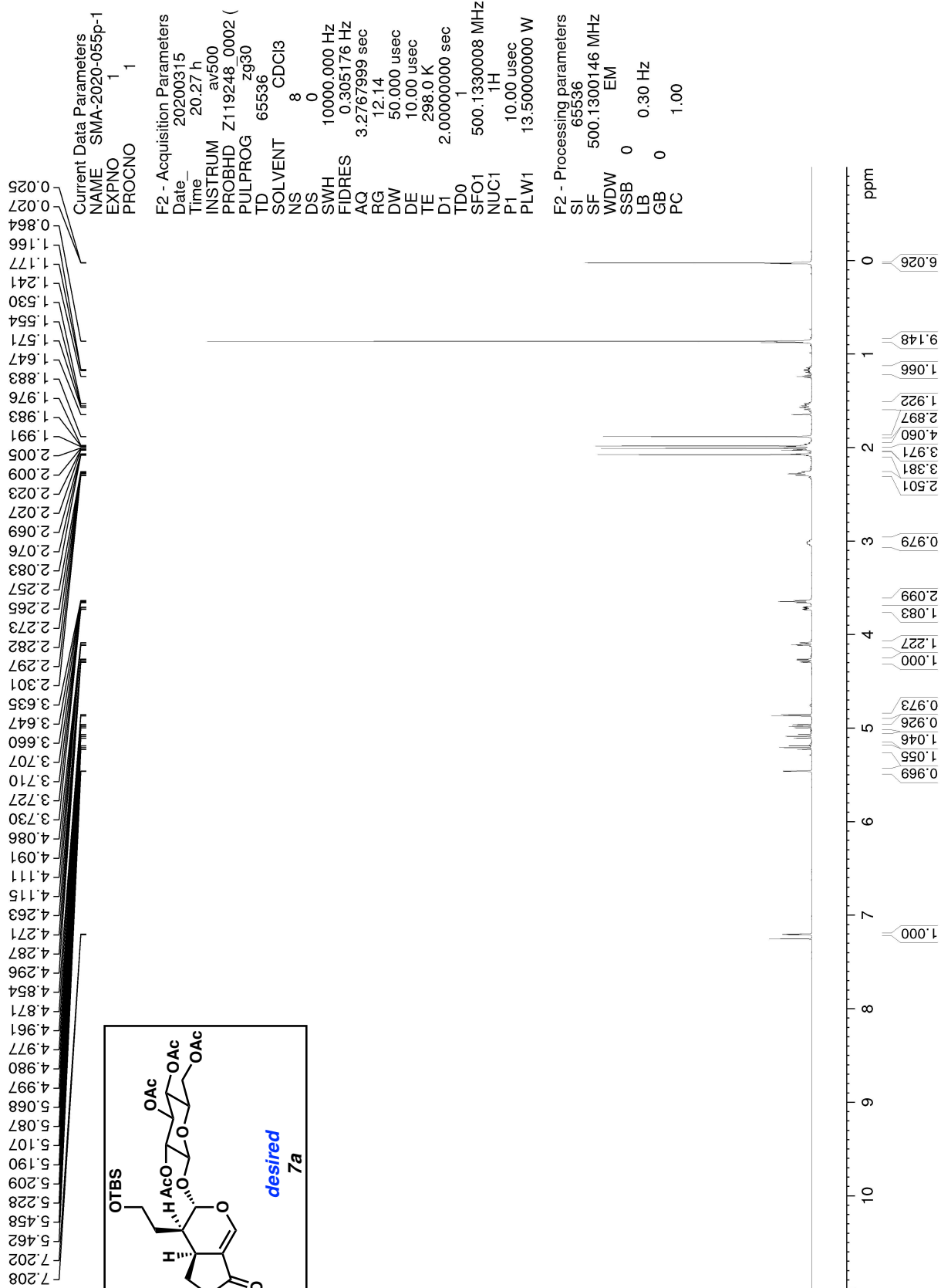
**$^1\text{H}$  NMR Spectra:**



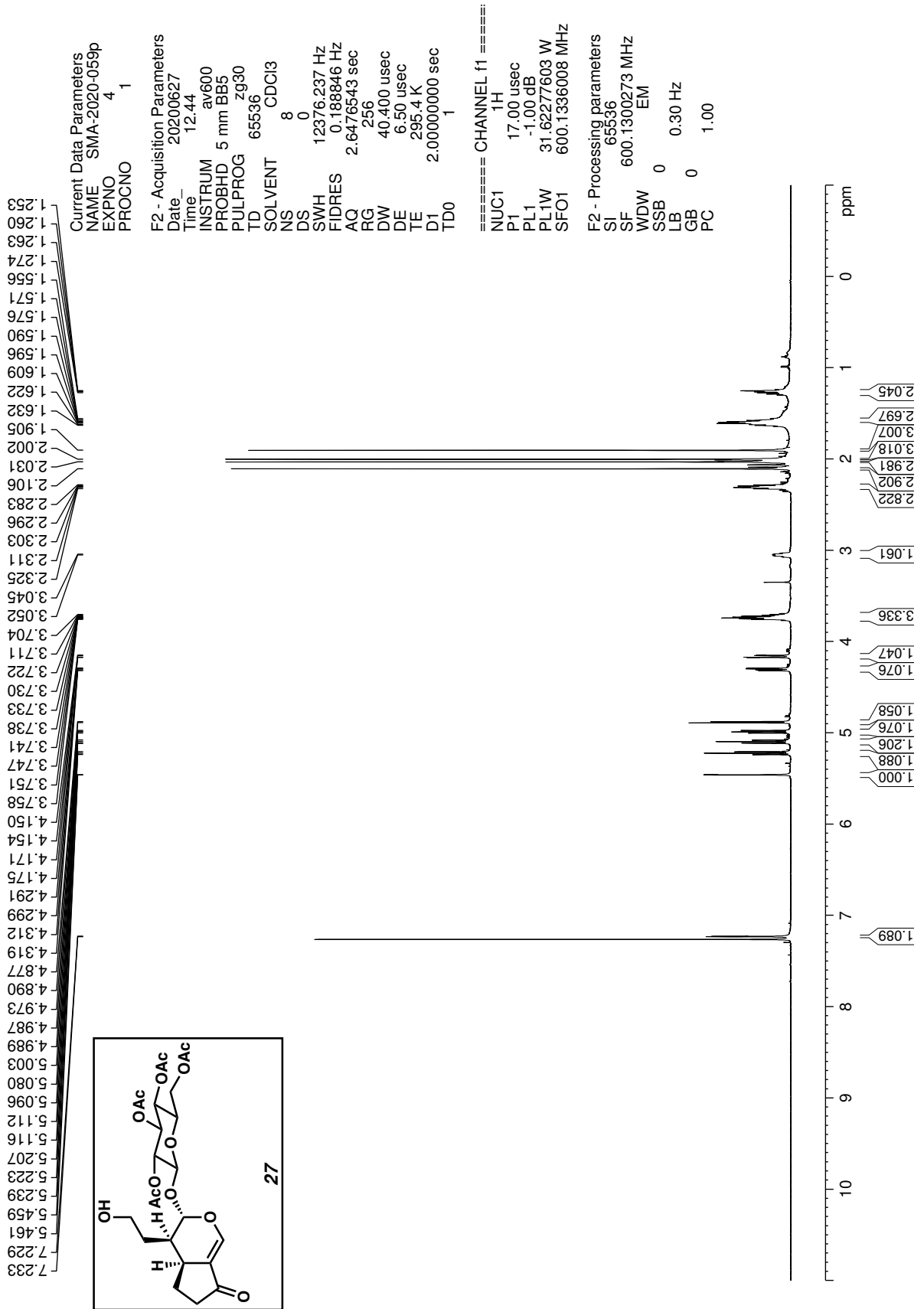


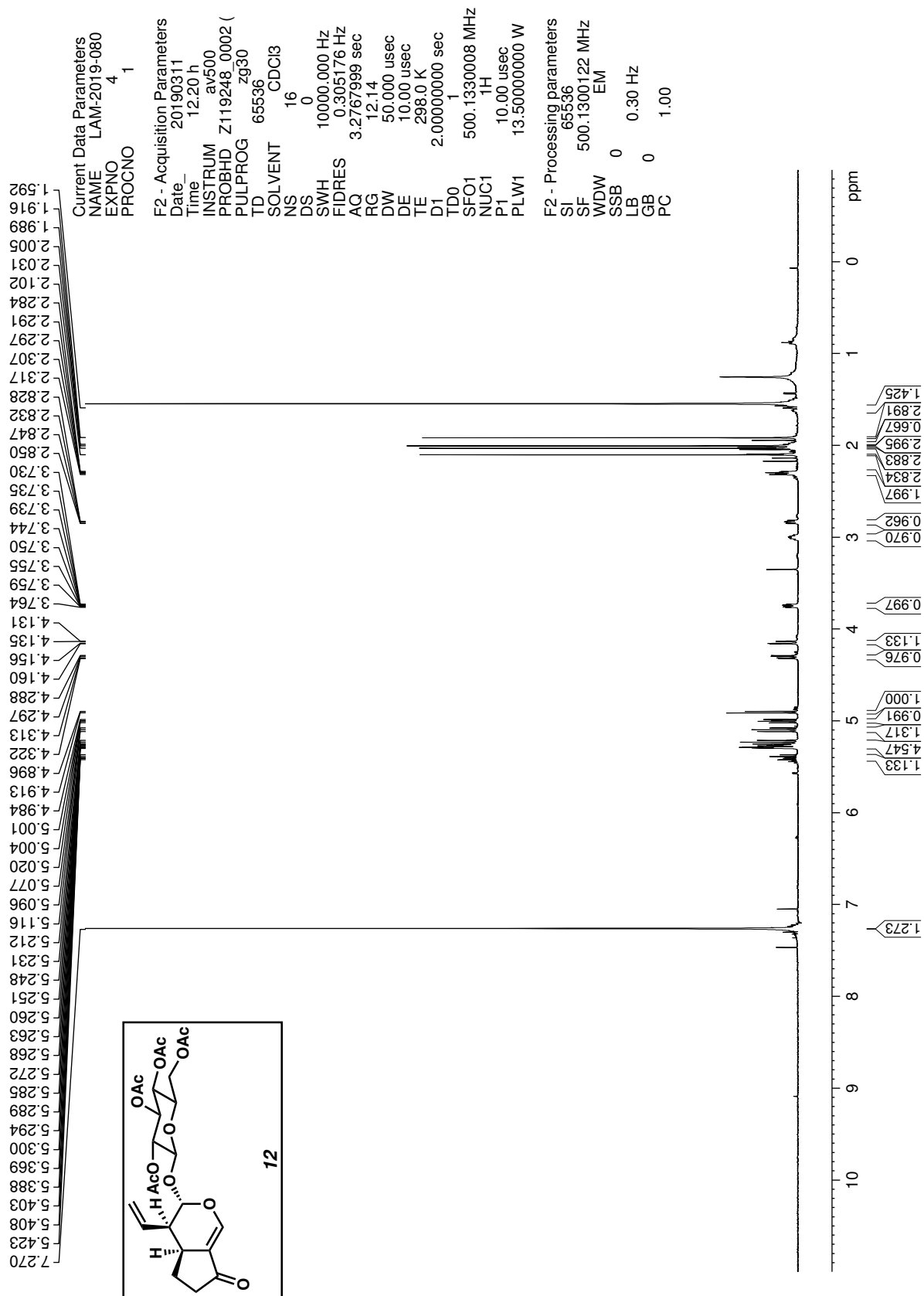


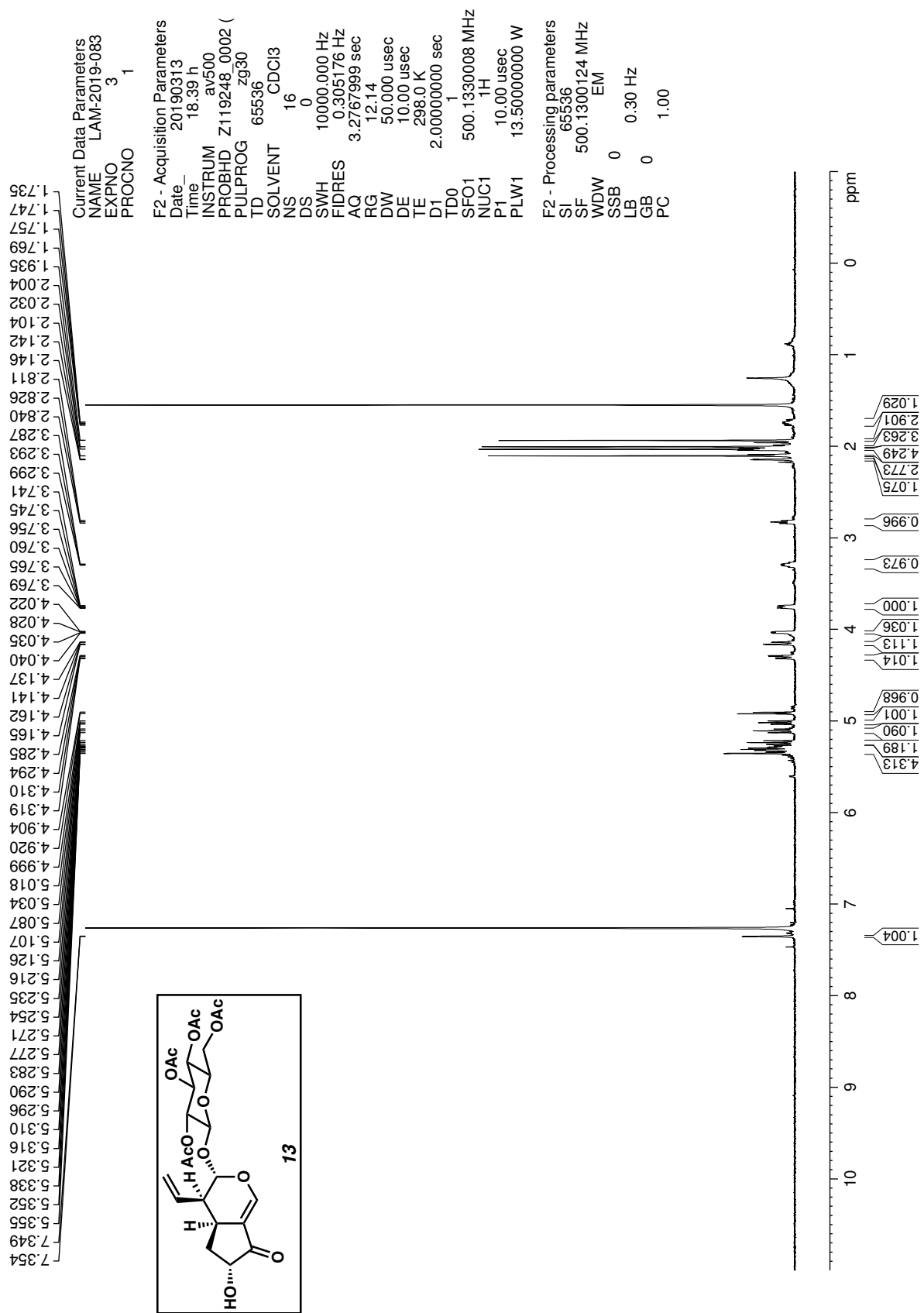


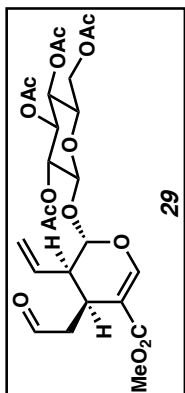
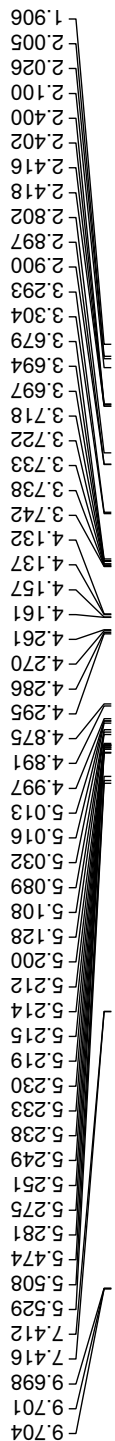








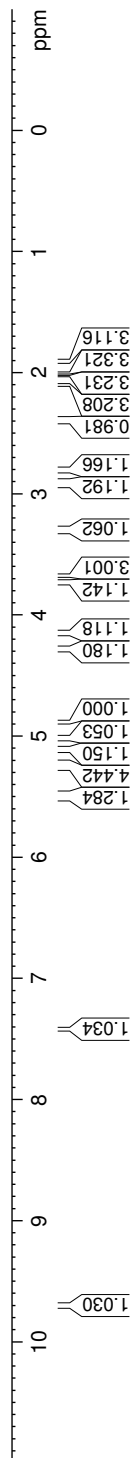




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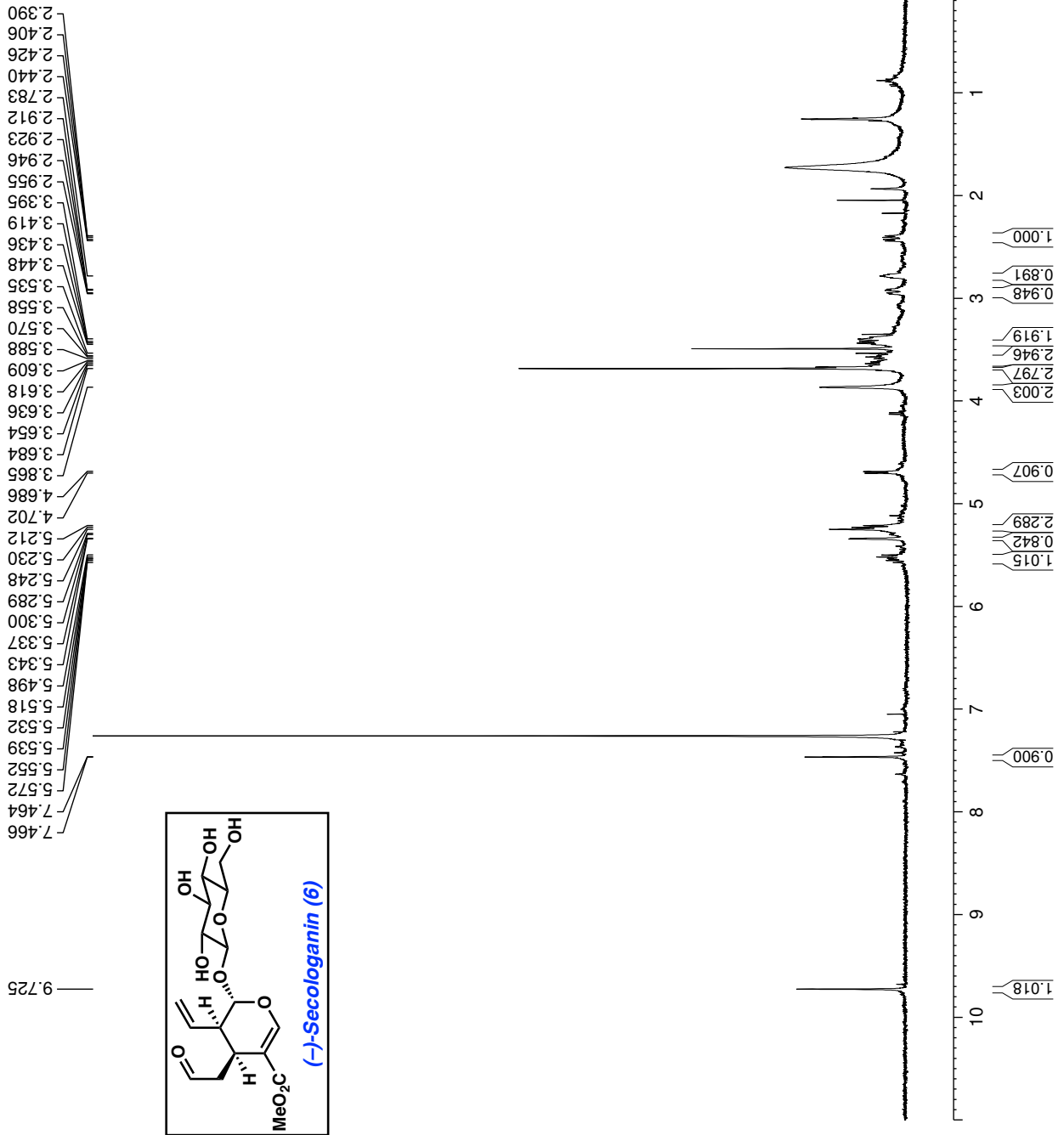


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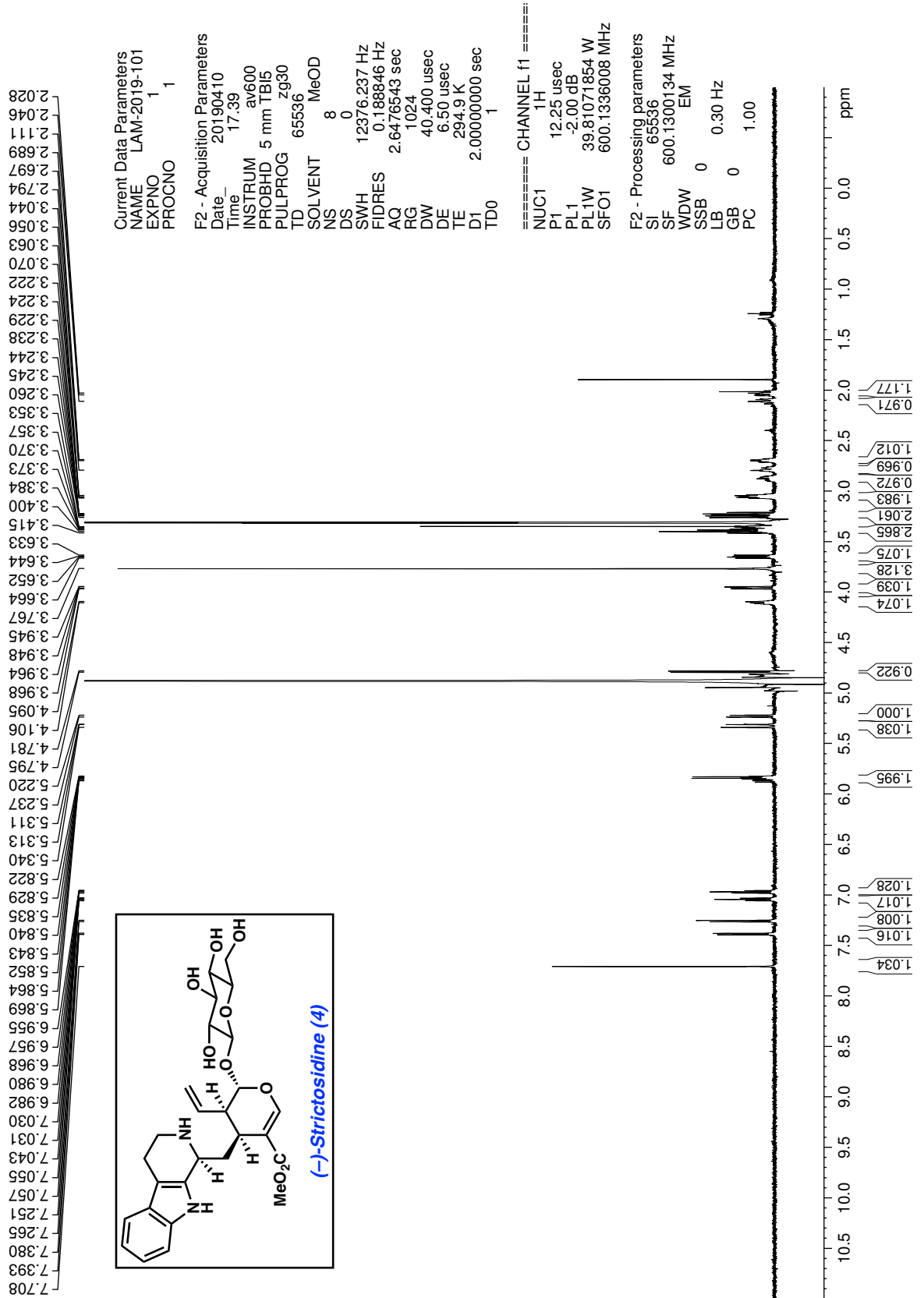
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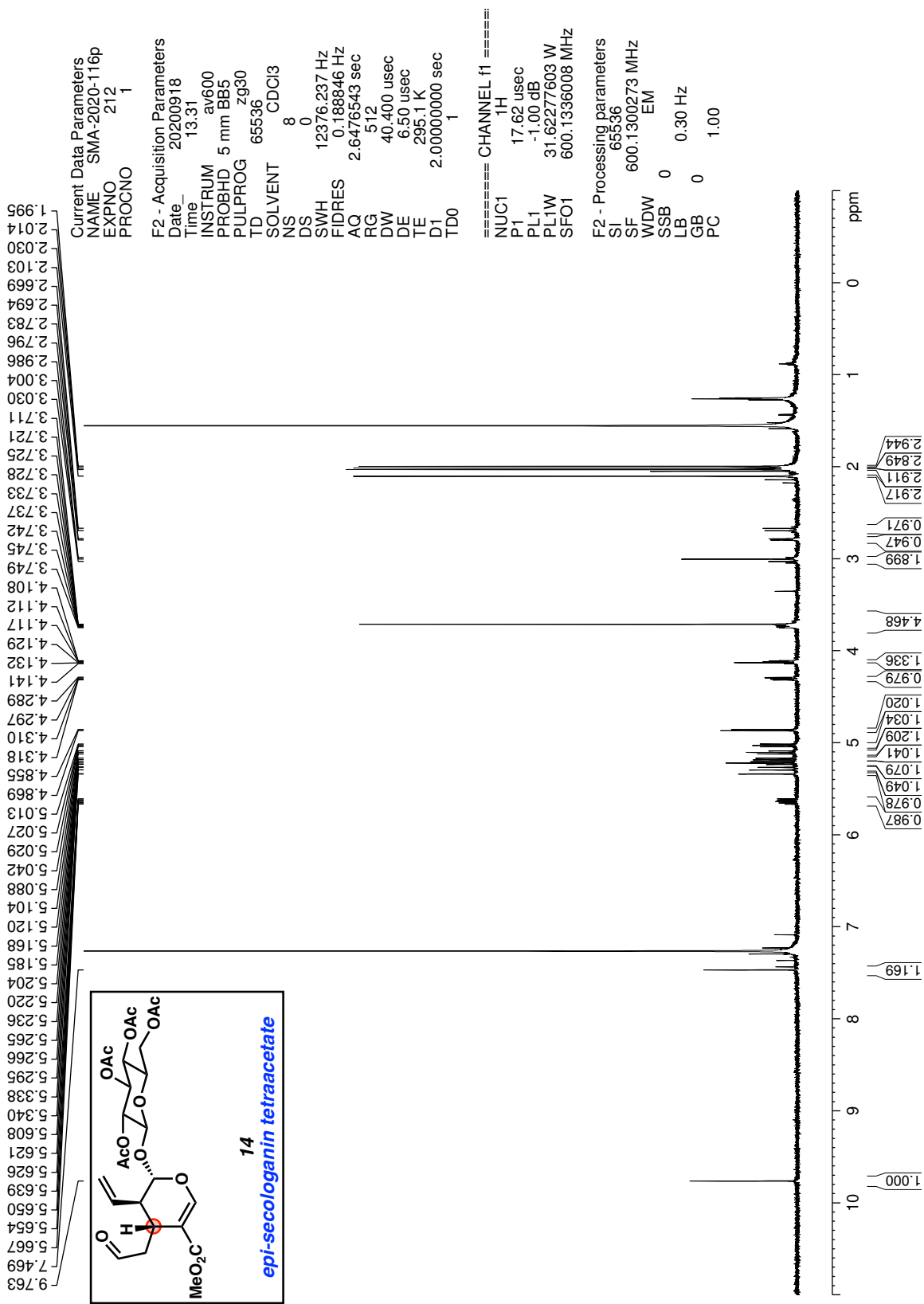
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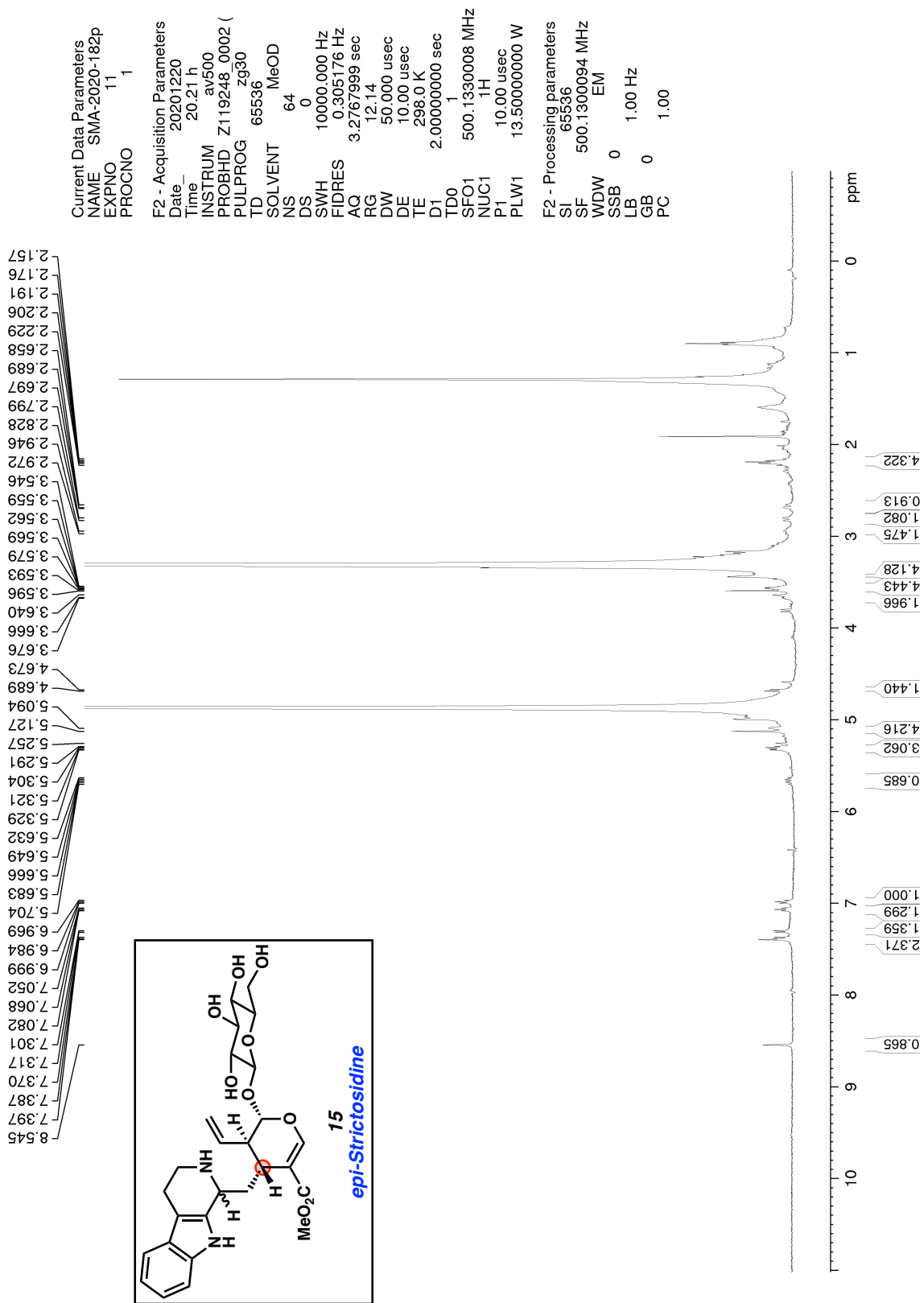
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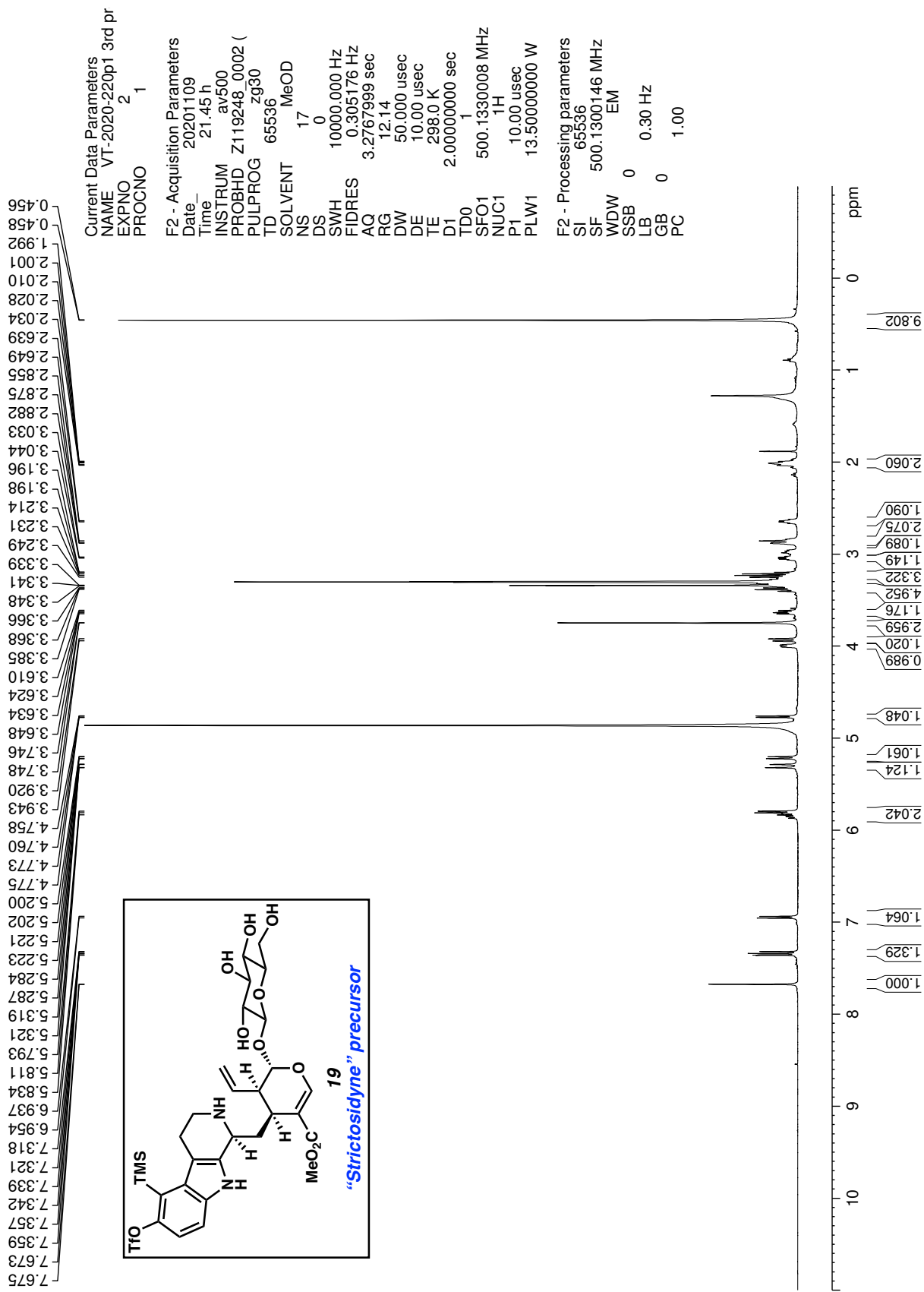


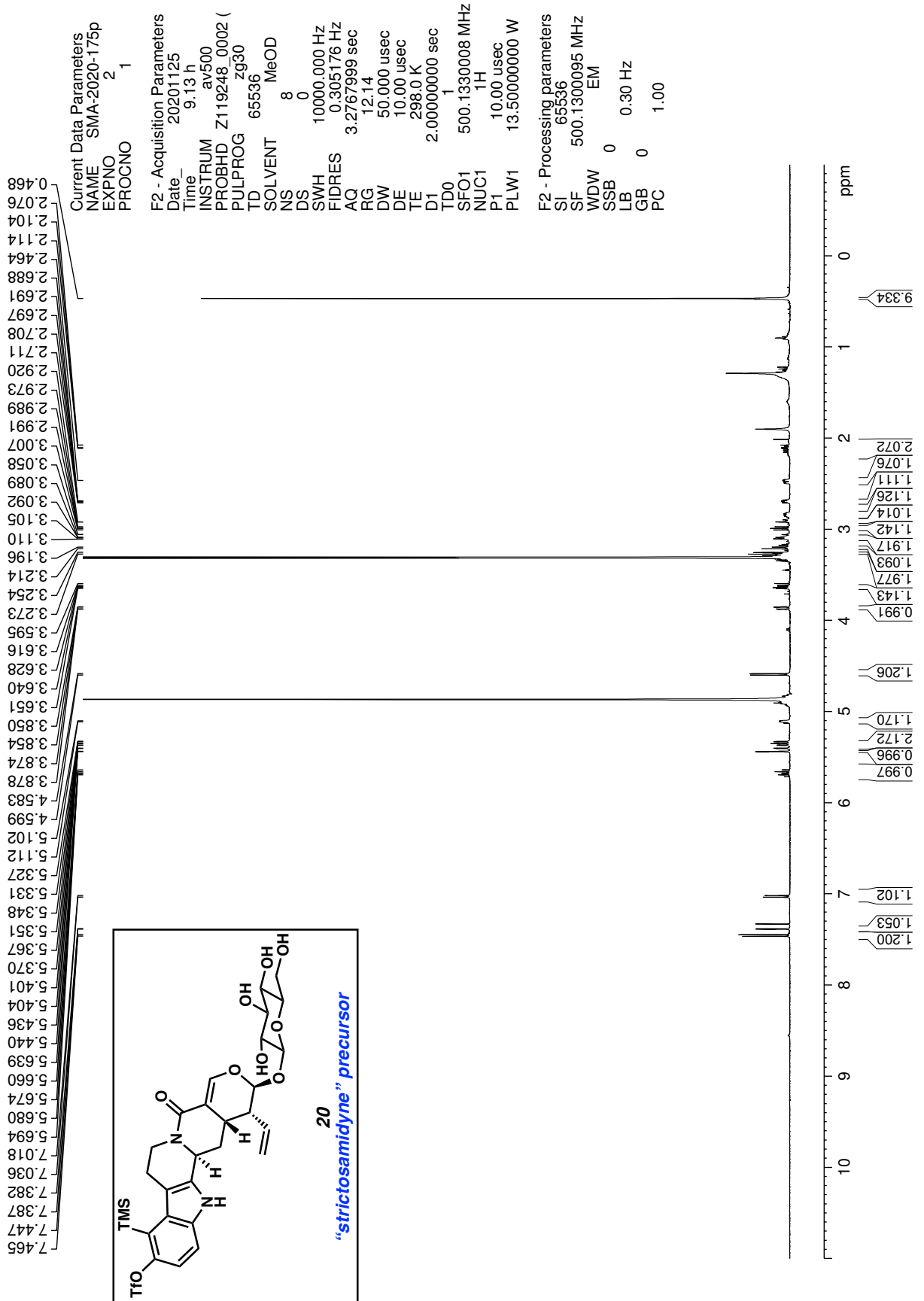


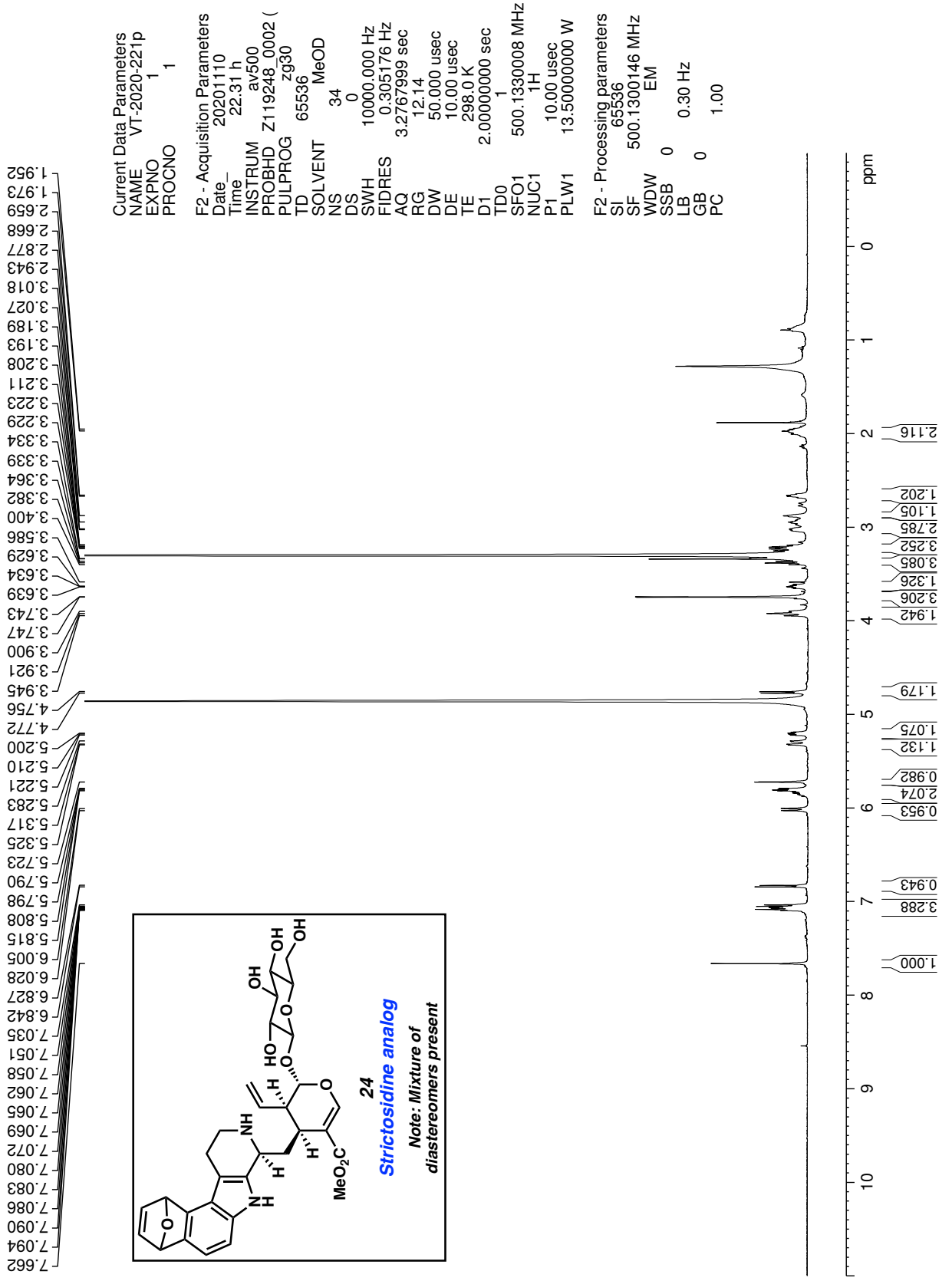






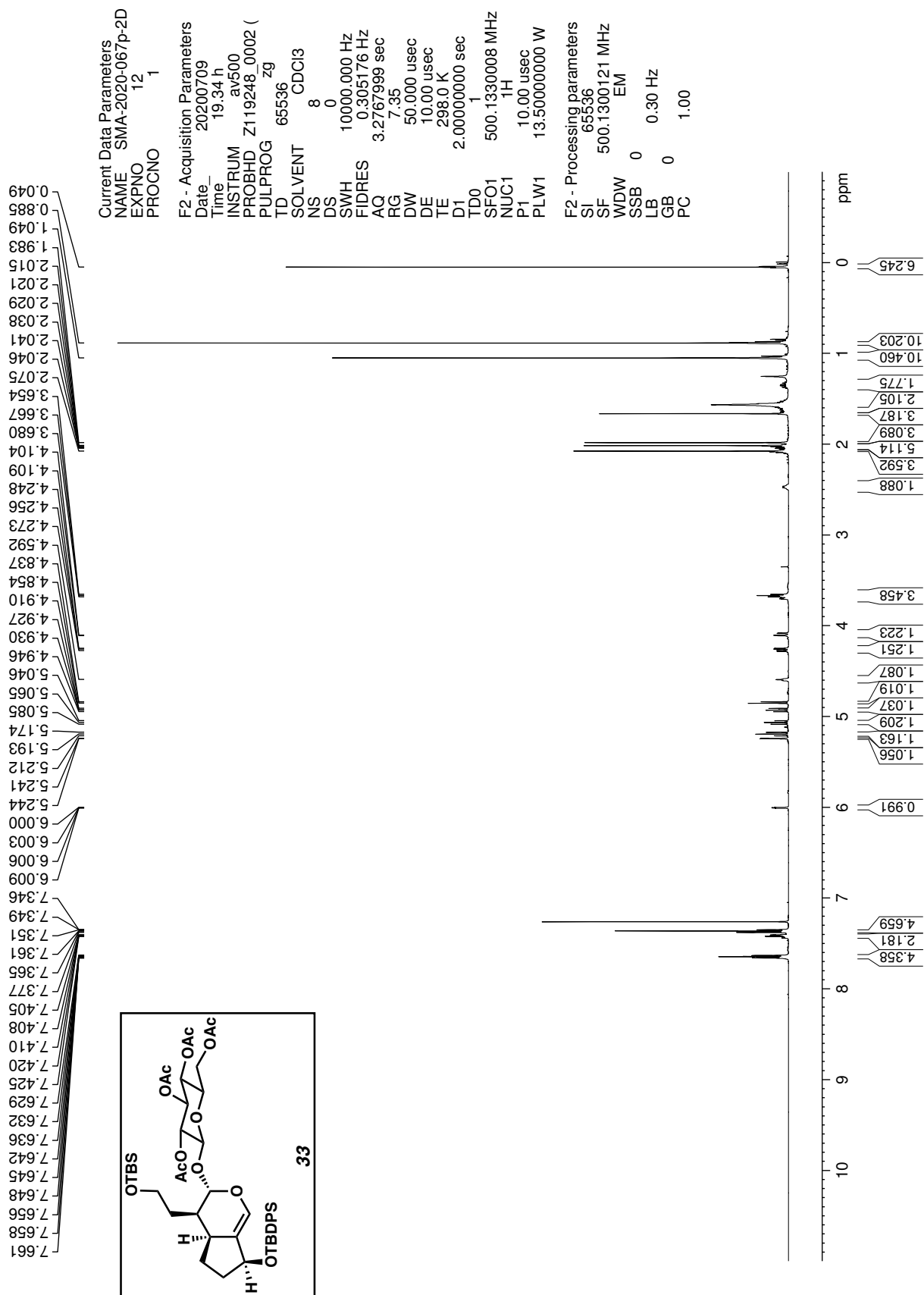


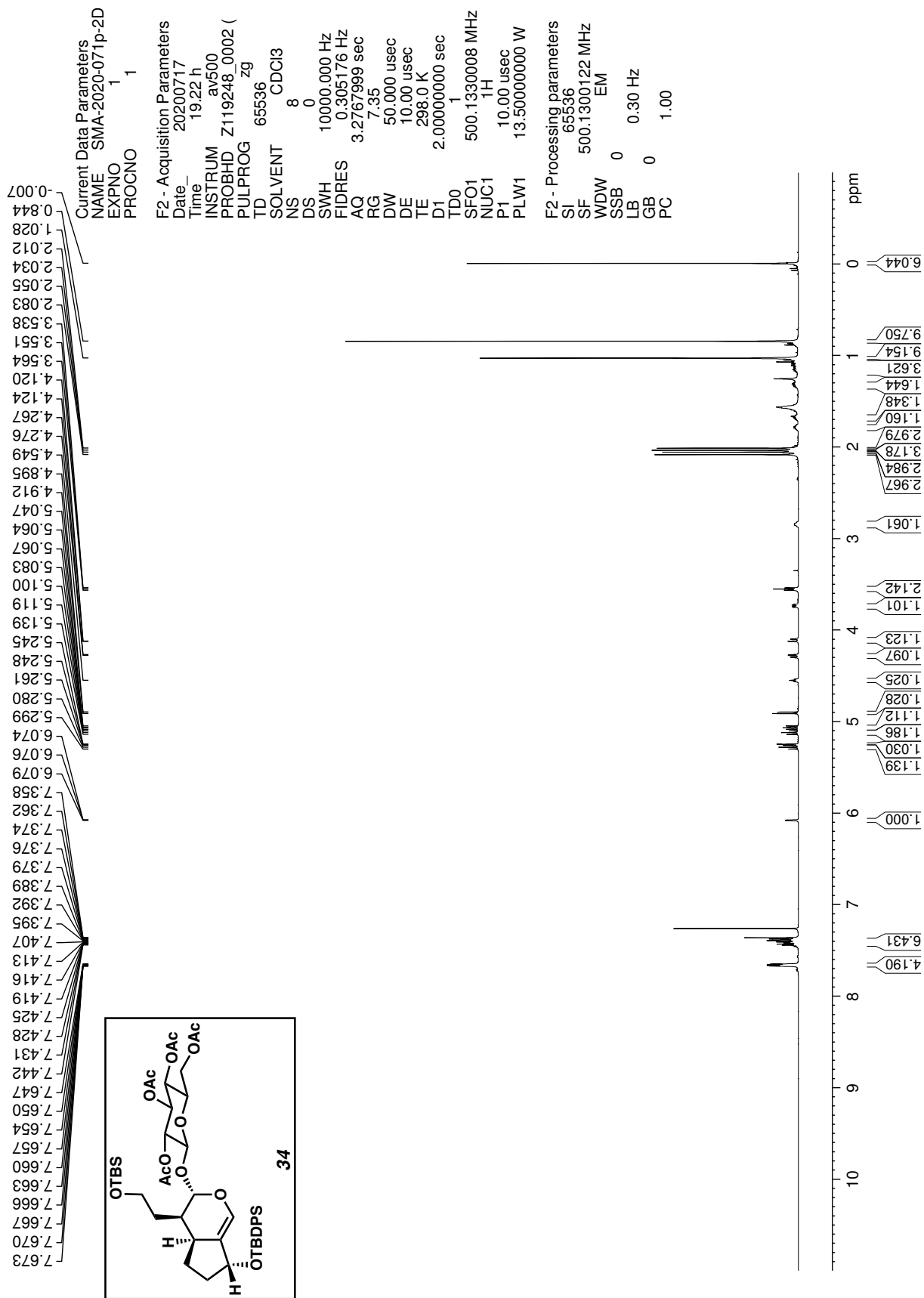


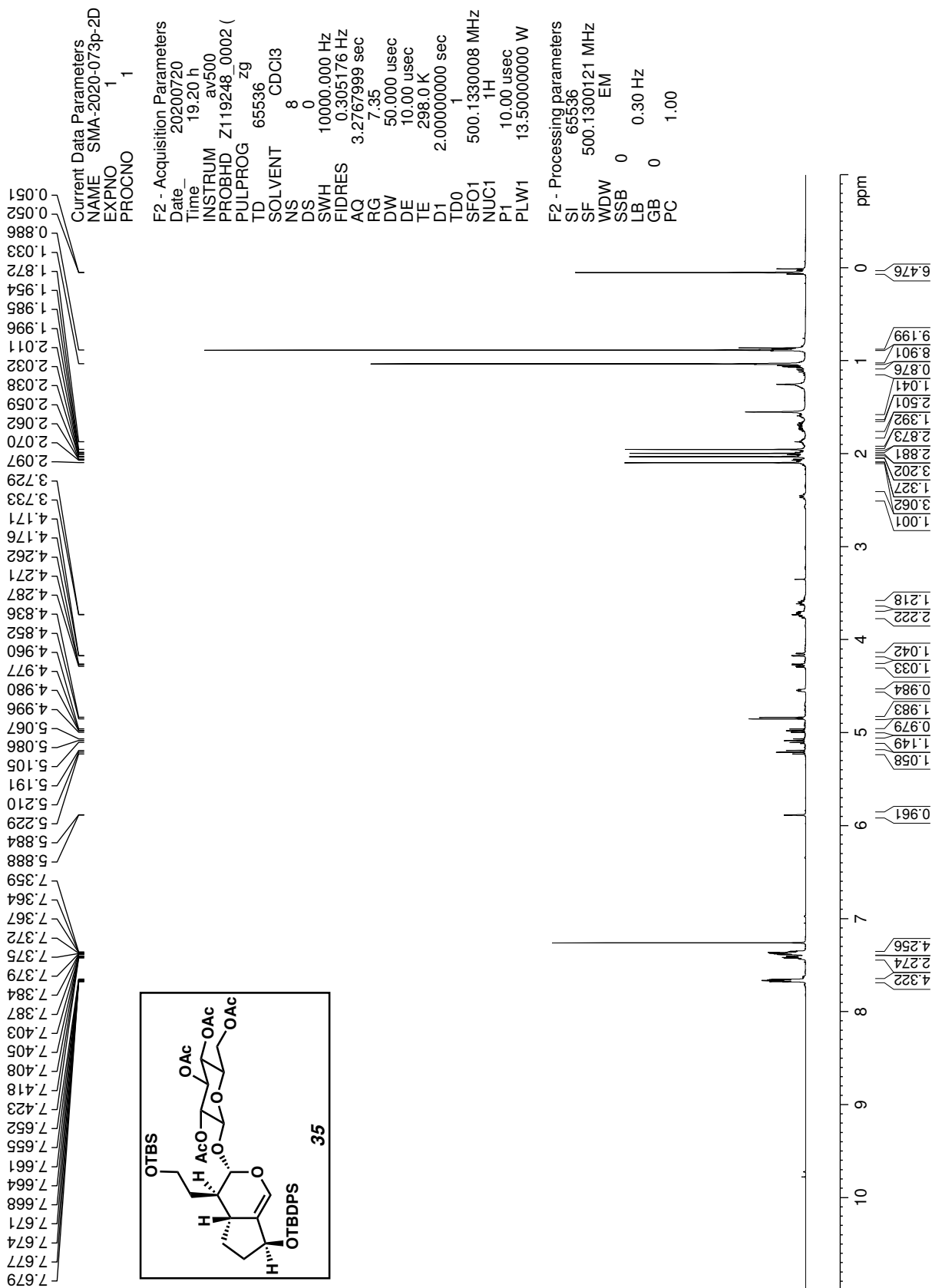


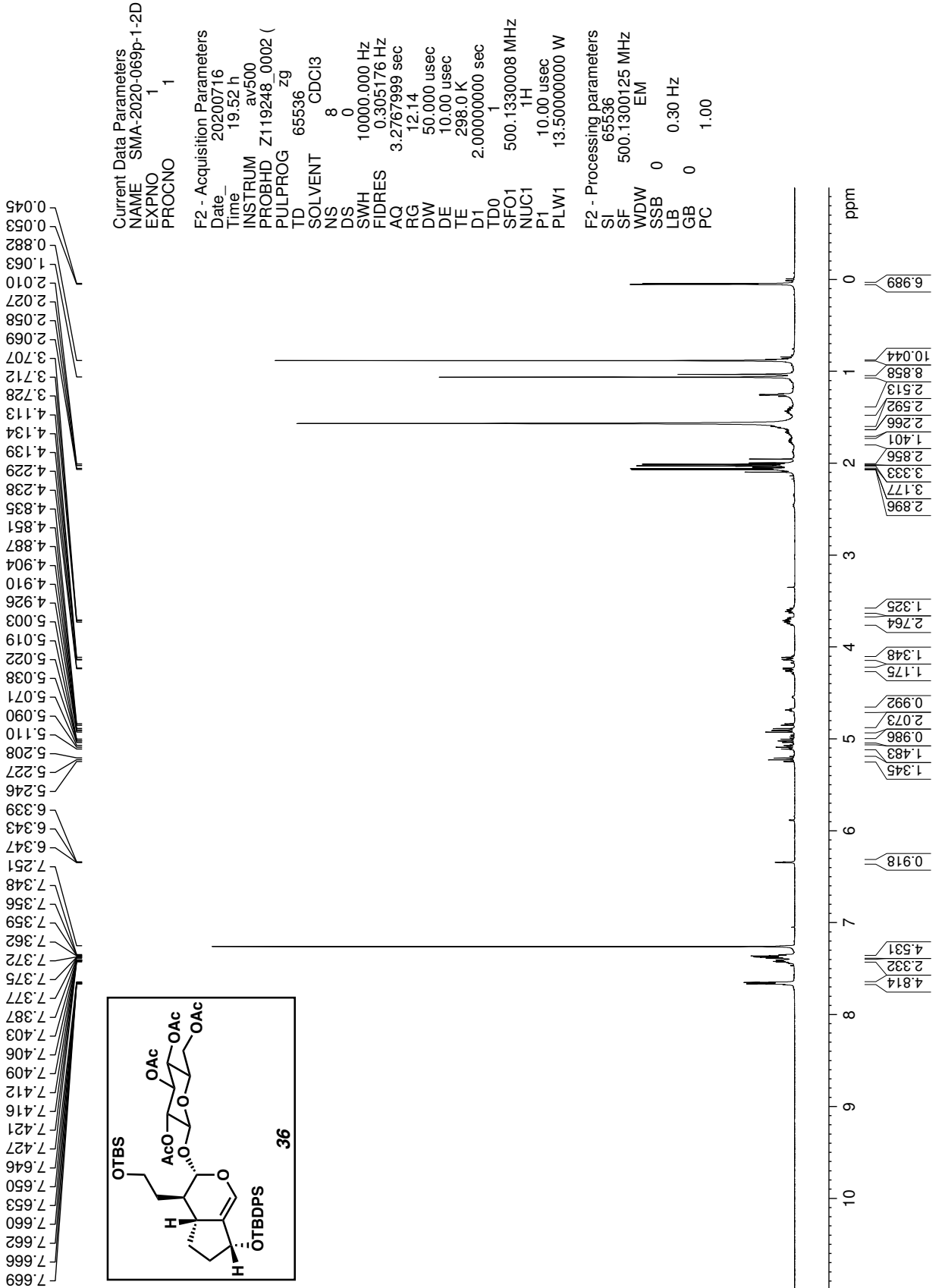










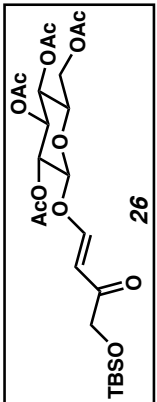
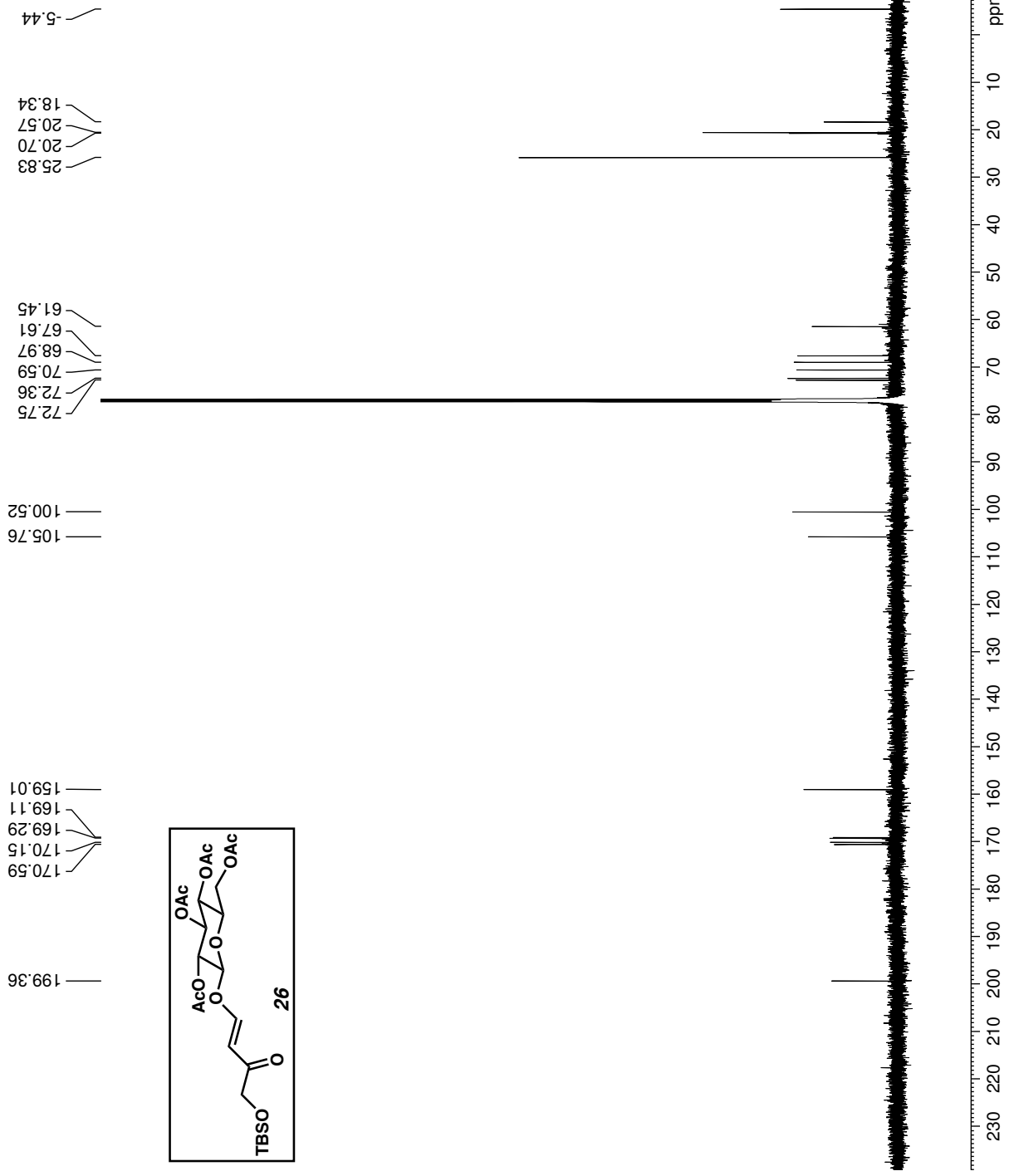


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 TE 298.0 K  
 D1 2.00000000 sec  
 D11 0.03000000 sec  
 TD0 1  
 SFO1 125.7722511 MHz  
 NUC1 13C  
 P1 10.50 usec  
 PLW1 23.00000000 W  
 SFO2 500.1330008 MHz  
 NUC2 1H  
 CPDPRG2 waltz16  
 PCPD2 80.00 usec  
 PLW2 13.50000000 W  
 PLW12 0.21094000 W  
 PLW13 0.10610000 W

F2 - Processing parameters  
 SI 131072  
 SF 125.7577892 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0

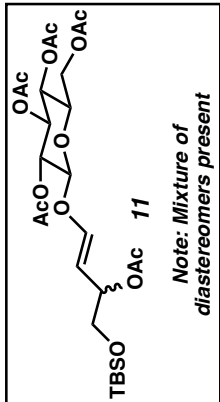
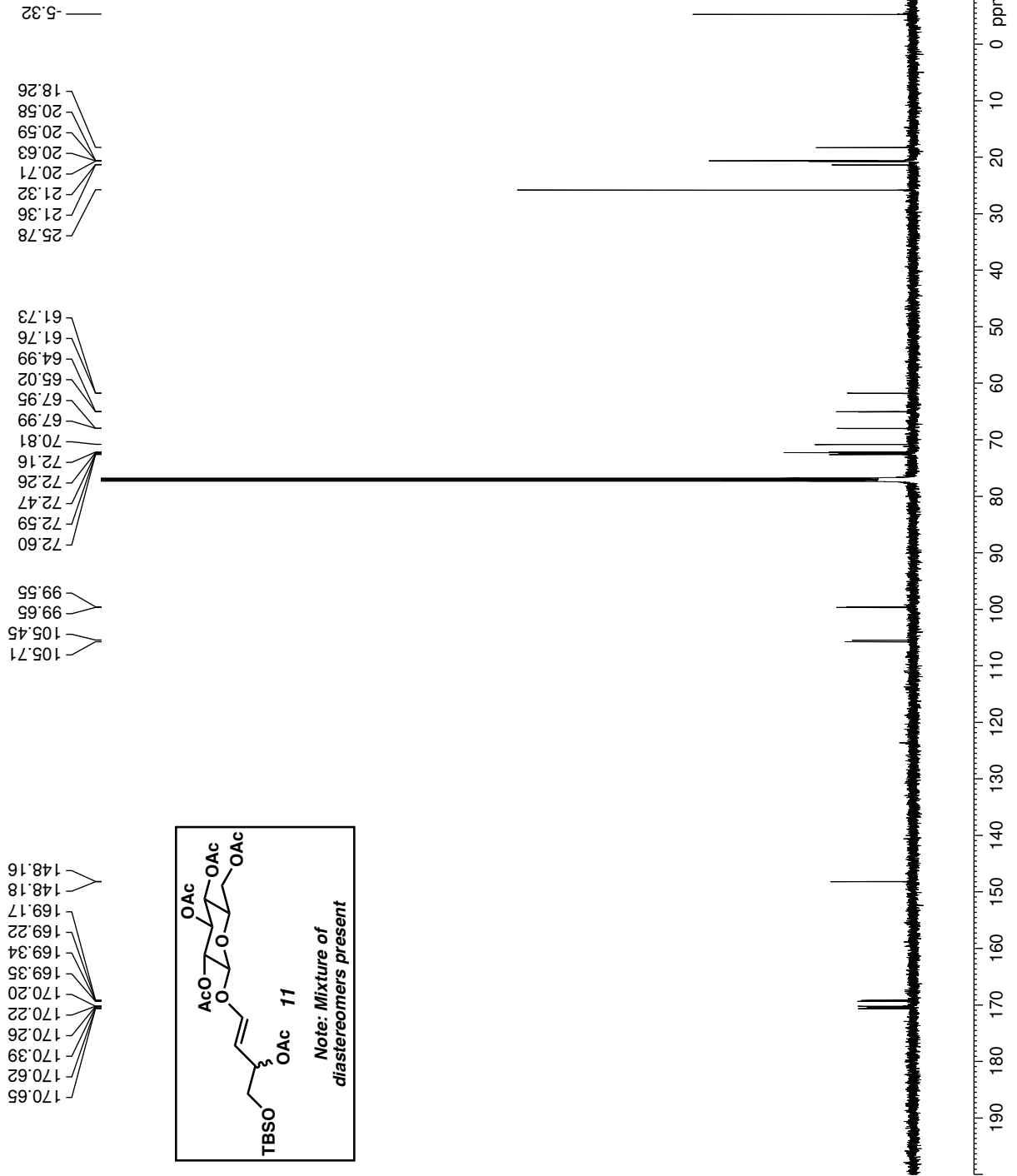


Current Data Parameters  
 NAME SMA-2020-allylic at  
 EXPNO 33  
 PROCNO 1

F2 - Acquisition Parameters

Date\_ 20200312  
 Time\_ 14.39 h  
 INSTRUM av500  
 PROBHD Z119248\_0002 (  
 PULPROG zgpg30  
 TD 65536  
 SOLVENT CDCl3  
 NS 48  
 DS 2  
 SWH 31250.000 Hz  
 FIDRES 0.953674 Hz  
 AQ 1.0485760 sec  
 RG 204.54  
 DW 16.000 usec  
 DE 28.00 usec  
 TE 298.0 K  
 D1 2.00000000 sec  
 D11 0.03000000 sec  
 TD0 1  
 SFO1 125.7722511 MHz  
 NUC1 13C  
 P1 10.50 usec  
 PLW1 23.00000000 W  
 SFO2 500.1330008 MHz  
 NUC2 1H  
 CPDPRG2 waltz16  
 PCPD2 80.00 usec  
 PLW2 13.50000000 W  
 PLW12 0.21094000 W  
 PLW13 0.10610000 W

F2 - Processing parameters  
 SI 131072  
 SF 125.7577892 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0



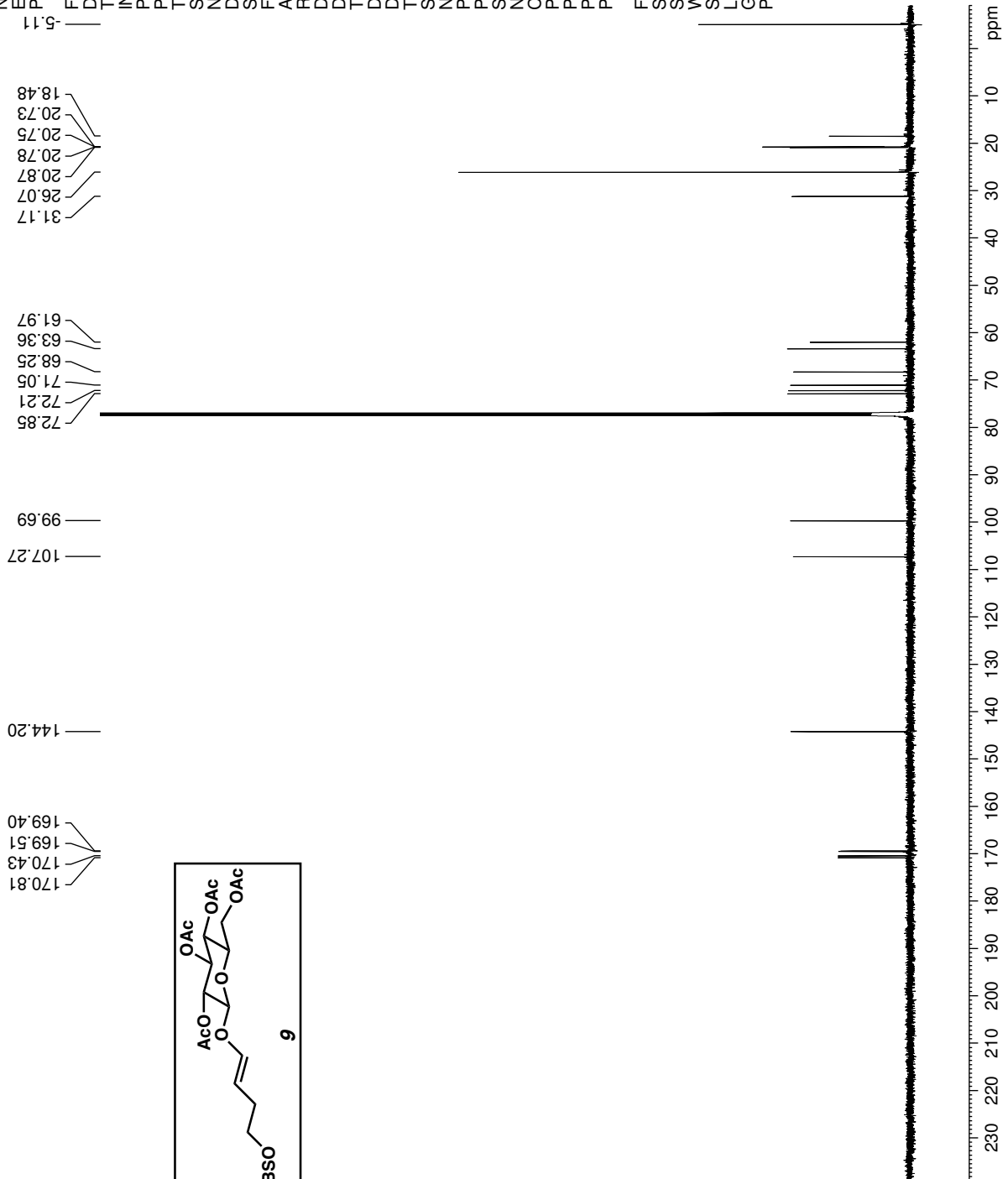
Current Data Parameters  
 NAME SMA-2020-dlenoq  
 EXPNO 13  
 PROCNO 1

F2 - Acquisition Parameter:

Date\_ 20200311  
 Time 13.11 h  
 INSTRUM av500  
 PROBHD Z119248\_0002  
 PULPROG zgpg30  
 TD 65536  
 SOLVENT CDCI3  
 NS 136  
 DS 2  
 SWH 31250.000 Hz  
 FIDRES 0.953674 Hz  
 AQ 1.0485760 sec  
 RG 204.54  
 DW 16.000 usec  
 DE 28.00 usec  
 TE 298.0 K  
 D1 2.00000000 sec  
 D11 0.03000000 sec  
 TD0 1  
 SFO1 125.7722511 MI  
 NUC1 13C  
 P1 10.50 usec  
 PLW1 23.00000000 W  
 SFO2 500.1330008 MI  
 NUC2 1H  
 CPDPRG2 waltz16  
 PCPD2 80.00 usec  
 PLW2 13.50000000 W  
 PLW12 0.21094000 W  
 PLW13 0.10610000 W

F2 - Processing parameter:

SI 131072  
 SF 125.757718 MHz  
 WDW EM  
 SSB 0  
 LB 0  
 GB 0  
 PC 1.40

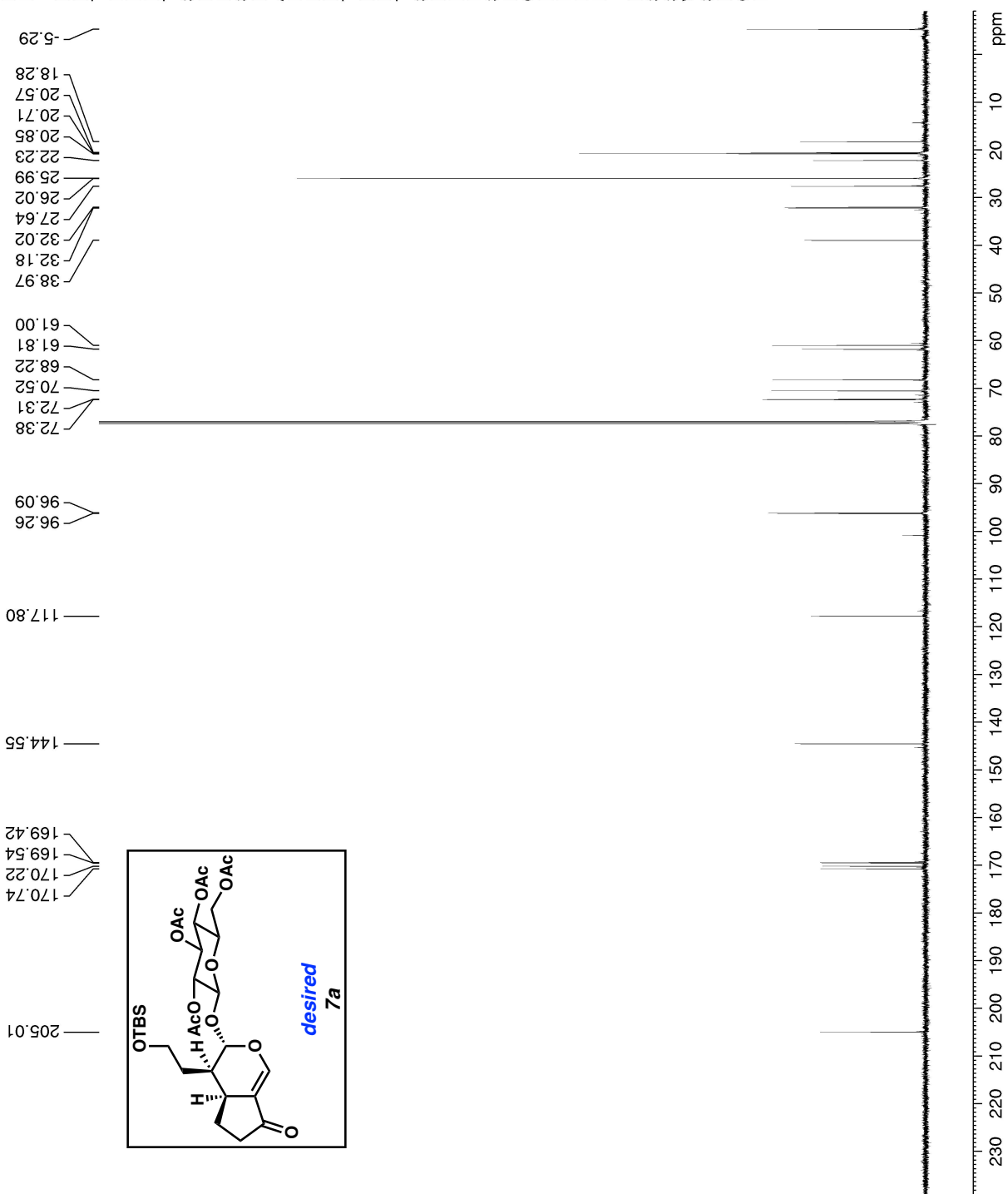




Current Data Parameters  
 NAME SMA-2020-055p-1  
 EXPNO 113  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20200315  
 Time 20.30 h  
 INSTRUM av500  
 PROBHD Z119248\_0002 (  
 PULPROG zgpg30  
 TD 65536  
 SOLVENT CDC13  
 NS 16  
 DS 2  
 SWH 31250.000 Hz  
 FIDRES 0.953674 Hz  
 AQ 1.0485760 sec  
 RG 204.54  
 DW 16.000 usec  
 DE 28.00 usec  
 TE 298.0 K  
 D1 2.00000000 sec  
 D11 0.03000000 sec  
 TD0 1  
 SFO1 125.7722511 MHz  
 NUC1 13C  
 P1 10.50 usec  
 PLW1 23.00000000 W  
 SFO2 500.1330008 MHz  
 NUC2 1H  
 CPDPRG2 waltz16  
 PCPD2 80.00 usec  
 PLW2 13.50000000 W  
 PLW12 0.21094000 W  
 PLW13 0.10610000 W

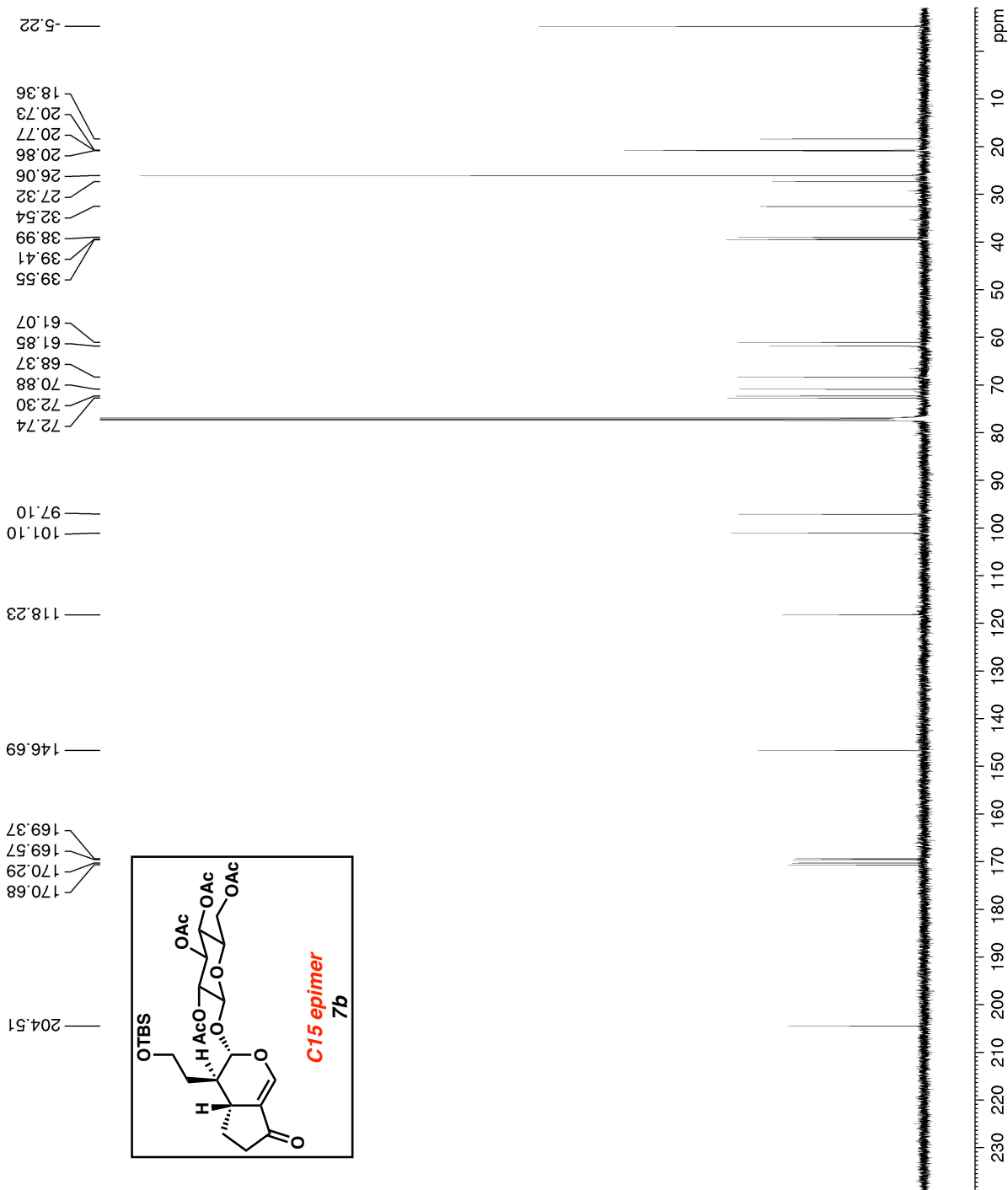
F2 - Processing parameters  
 SI 131072  
 SF 125.7577737 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.40



Current Data Parameters  
 NAME SMA-2020-055p  
 EXPNO 13  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20200315  
 Time 18.26 h  
 INSTRUM av500  
 PROBHD Z119248\_0002  
 PULPROG zgpg30  
 TD 65536  
 SOLVENT CDCI3  
 NS 24  
 DS 2  
 SWH 31250.000 Hz  
 FIDRES 0.953674 Hz  
 AQ 1.0485760 sec  
 RG 204.54  
 DW 16.000 usec  
 DE 28.00 usec  
 TE 298.0 K  
 D1 2.00000000 sec  
 D11 0.03000000 sec  
 TD0 1  
 SFO1 125.7722511 Mt  
 NUC1 13C  
 P1 10.50 usec  
 PLW1 23.00000000 W  
 SFO2 500.1330008 Mt  
 NUC2 1H  
 CPDPRG2 waitz16  
 PCPD2 80.00 usec  
 PLW2 13.50000000 W  
 PLW12 0.21094000 W  
 PLW13 0.10610000 W

F2 - Processing parameters  
 SI 131072  
 SF 125.7577730 MHz  
 WDW EM  
 SSB 0  
 LB 0 1.00 Hz  
 GB 0  
 PC 1.40



Current Data Parameters  
 NAME VT-2020-130  
 EXPNO 13  
 PROCNO 1

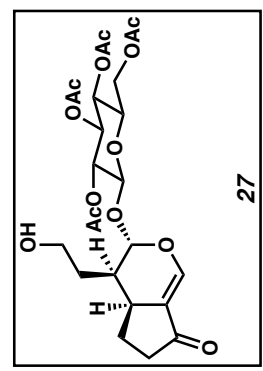
F2 - Acquisition Parameters

Date\_ 20201029  
 Time 17:57 h  
 INSTRUM av500  
 PROBHD Z119248\_0002 (  
 PULPROG zgpg30  
 TD 65536  
 SOLVENT CDCI3  
 NS 120  
 DS 2  
 SWH 31250.000 Hz  
 FIDRES 0.953674 Hz  
 AQ 1.0485760 sec  
 RG 204.54  
 DW 16.000 usec  
 DE 28.00 usec  
 TE 298.0 K  
 D1 2.00000000 sec  
 D11 0.03000000 sec  
 TD0 1  
 SFO1 125.7722511 MHz  
 NUC1 13C  
 P1 10.50 usec  
 PLW1 23.00000000 W  
 SFO2 500.1330008 MHz  
 NUC2 1H  
 CPDPRG[2] waltz16  
 PCPD2 80.00 usec  
 PLW2 13.50000000 W  
 PLW12 0.21094000 W  
 PLW13 0.10610000 W

F2 - Processing parameters

SI 131072  
 SF 125.757724 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.40

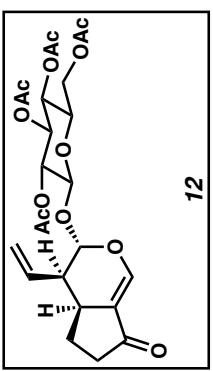
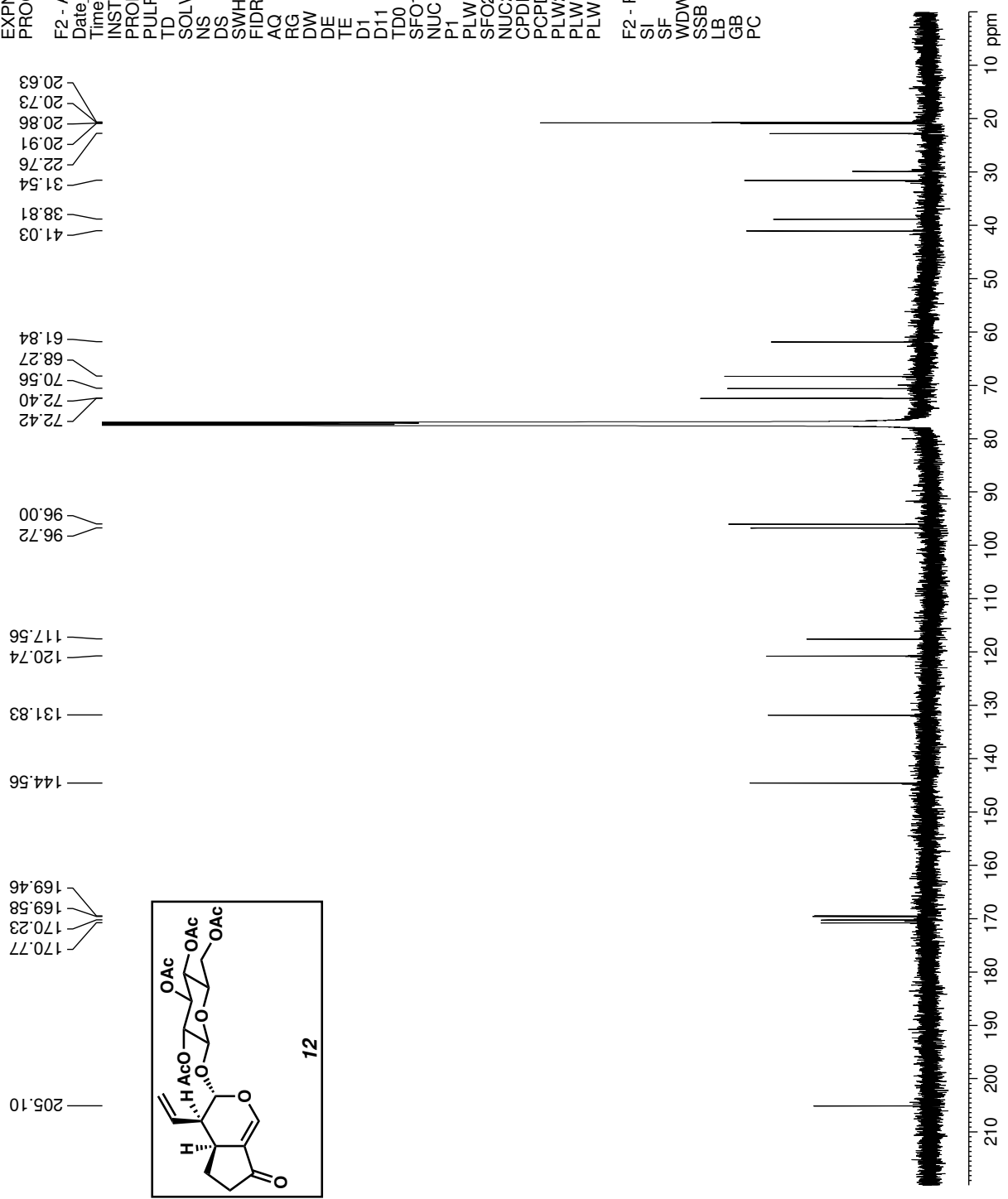
204.90  
 170.85  
 170.23  
 169.58  
 169.44  
 144.51  
 117.76  
 96.22  
 96.05  
 72.41  
 72.35  
 70.58  
 68.27  
 61.77  
 60.90  
 38.95  
 32.21  
 32.06  
 27.76  
 22.33  
 20.92  
 20.73  
 20.59



Current Data Parameters  
 NAME LAM-2019-080  
 EXPNO 7  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20190312  
 Time\_ 10.07 h  
 INSTRUM av500  
 PROBHD Z119248\_0002 (  
 PULPROG zgpg30  
 TD 65536  
 SOLVENT CDCI3  
 NS 1160  
 DS 2  
 SWH 31250.000 Hz  
 FIDRES 0.953674 Hz  
 AQ 1.0485760 sec  
 RG 204.54  
 DW 16.000 usec  
 DE 28.00 usec  
 TE 298.0 K  
 D1 2.00000000 sec  
 D11 0.03000000 sec  
 TD0 1  
 SFO1 125.7722511 MHz  
 NUC1 13C  
 P1 10.50 usec  
 PLW1 23.00000000 W  
 SFO2 500.1330008 MHz  
 NUC2 1H  
 CPDPRG2 waltz16  
 PCPD2 80.00 usec  
 PLW2 13.50000000 W  
 PLW12 0.21094000 W  
 PLW13 0.10610000 W

F2 - Processing parameters  
 SI 131072  
 SF 125.7577717 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.40



Current Data Parameters  
 NAME LAM-2019-083  
 EXPNO 4  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20190313  
 Time\_ 19.01 h  
 INSTRUM av500  
 PROBHD Z119248\_0002 (

PULPROG zgpg30  
 TD 65536  
 SOLVENT CDCI3  
 NS 384

DS 2  
 SWH 31250.000 Hz  
 FIDRES 0.953674 Hz  
 AQ 1.0485760 sec

RG 204.54  
 DW 16.000 usec  
 DE 28.00 usec  
 TE 298.0 K

D1 2.00000000 sec  
 D11 0.03000000 sec  
 TD0 1

SFO1 125.7722511 MHz  
 NUC1 13C

P1 10.50 usec  
 PLW1 23.0000000 W  
 SFO2 500.1330008 MHz

NUC2 1H  
 CPDPRG[2] waltz16  
 PCPD2 80.00 usec

PLW2 13.5000000 W  
 PLW12 0.21094000 W  
 PLW13 0.10610000 W

F2 - Processing parameters  
 SI 131072  
 SF 125.7577716 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.40

74.12  
 72.47  
 72.37  
 70.55  
 68.27  
 61.80  
 40.75  
 30.99  
 28.97  
 20.91  
 20.74  
 20.58

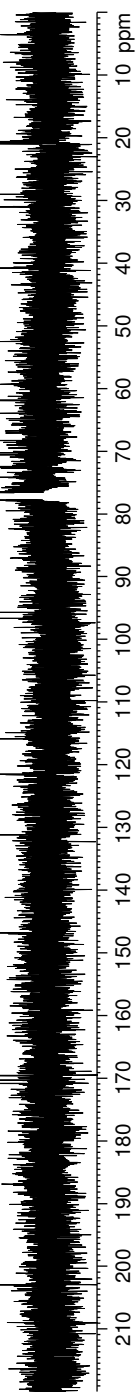
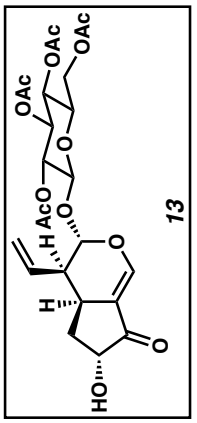
96.53  
 96.59

115.85  
 121.44  
 131.16

146.77

169.51  
 169.56  
 170.28  
 170.78

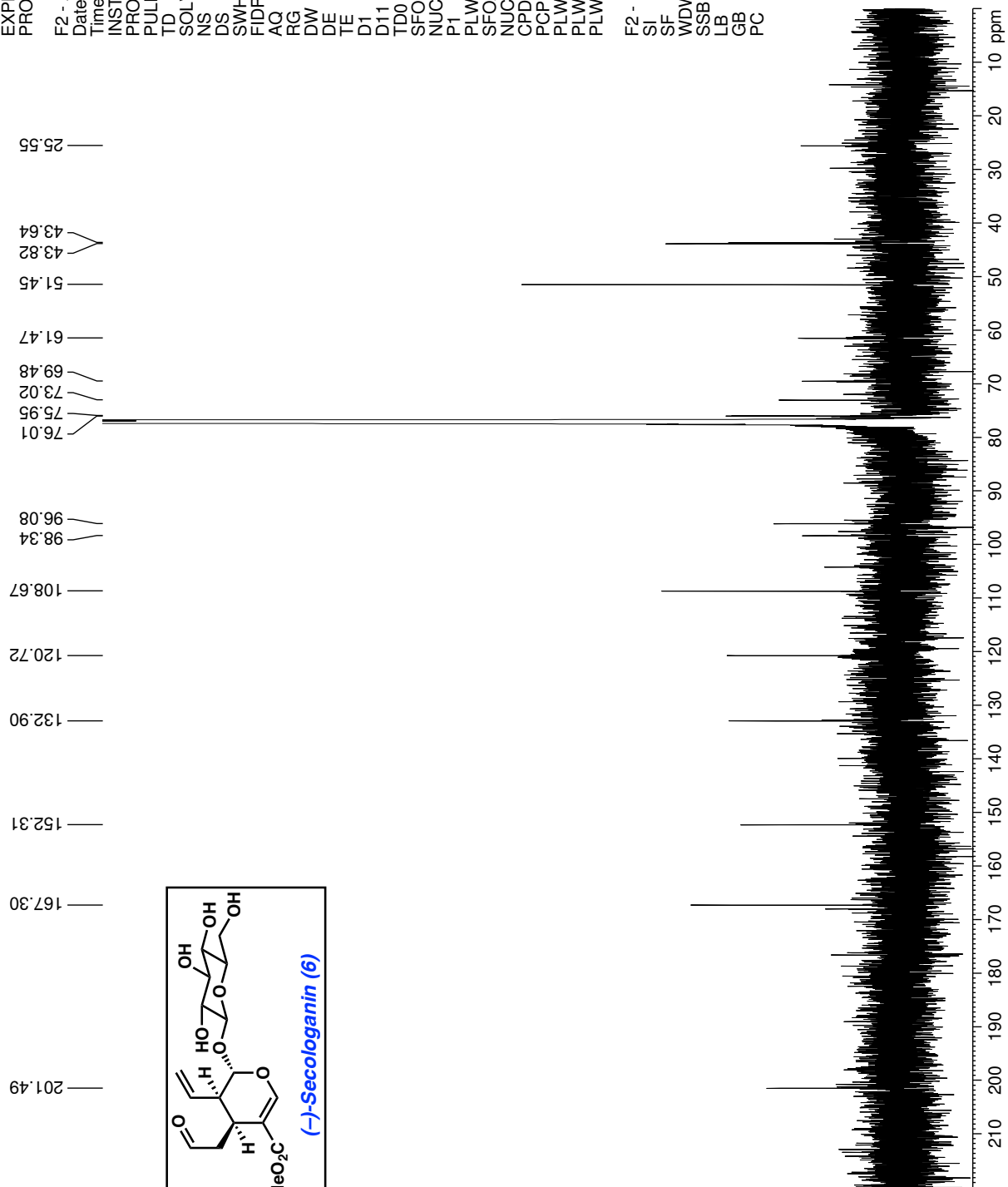
202.93



Current Data Parameters  
 NAME LAM-2019-087  
 EXPNO 4  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20190321  
 Time\_ 17.41 h  
 INSTRUM av500  
 PROBHD Z119248\_0002 (  
 PULPROG zgpg30  
 TD 65536  
 SOLVENT CDCI3  
 NS 592  
 DS 2  
 SWH 31250.000 Hz  
 FIDRES 0.953674 Hz  
 AQ 1.0485760 sec  
 RG 204.54  
 DW 16.000 usec  
 DE 28.00 usec  
 TE 298.0 K  
 D1 2.00000000 sec  
 D11 0.03000000 sec  
 TD0 1  
 SFO1 125.7722511 MHz  
 NUC1 13C  
 P1 10.50 usec  
 PLW1 23.00000000 W  
 SFO2 500.1330008 MHz  
 NUC2 1H  
 CPDPRG2 waltz16  
 PCPD2 80.00 usec  
 PLW2 13.50000000 W  
 PLW12 0.21094000 W  
 PLW13 0.10610000 W

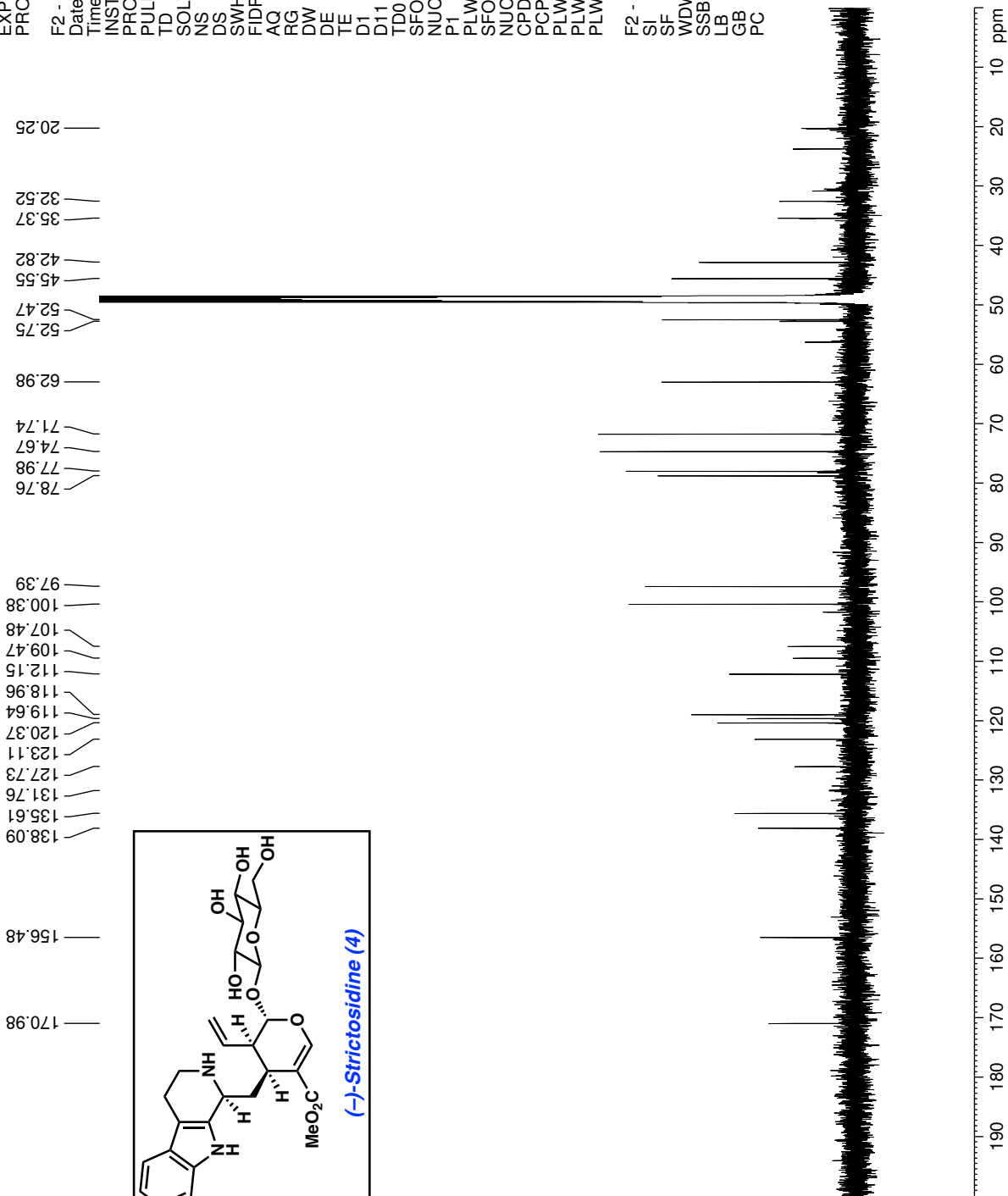
F2 - Processing parameters  
 SI 131072  
 SF 125.7577892 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.40



Current Data Parameters  
 NAME LAM-2019-100  
 EXPNO 6  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20190409  
 Time\_ 17.47 h  
 INSTRUM av500  
 PROBHD Z119248\_0002 ( zppg90  
 PULPROG zgpg30  
 TD 65536  
 SOLVENT MeOD  
 NS 648  
 DS 2  
 SWH 31250.000 Hz  
 FIDRES 0.953674 Hz  
 AQ 1.0485760 sec  
 RG 204.54  
 DW 16.000 usec  
 DE 28.00 usec  
 TE 298.0 K  
 D1 2.0000000 sec  
 D11 0.030000000 sec  
 TD0 1  
 SFO1 125.7722511 MHz  
 NUC1 13C  
 P1 10.50 usec  
 PLW1 23.00000000 W  
 SFO2 500.1330008 MHz  
 NUC2 1H  
 CPDPRG12 waltz16  
 PCPD2 80.00 usec  
 PLW2 13.50000000 W  
 PLW12 0.21094000 W  
 PLW13 0.10610000 W

F2 - Processing parameters  
 SI 131072  
 SF 125.7576123 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.40

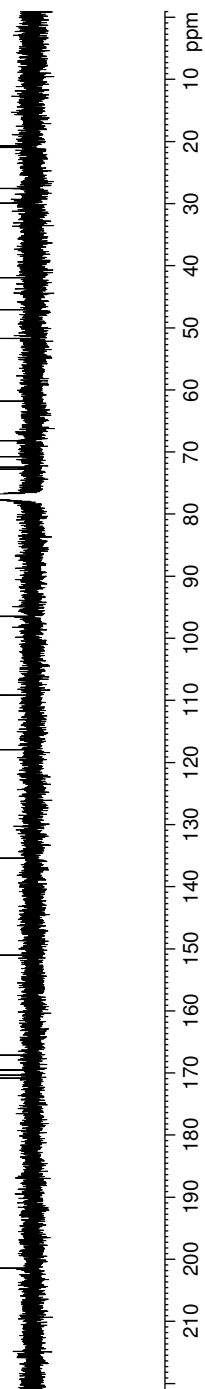
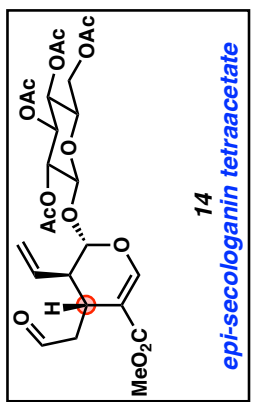


Current Data Parameters  
 NAME SMA-2020-122p  
 EXPNO 13  
 PROCNO 1

F2 - Acquisition Parameters  
 Date 20201005  
 Time 13.18 h  
 INSTRUM av500  
 PROBHD Z119248\_0002 (zpgp30)  
 PULPROG zgpg30  
 TD 65536  
 SOLVENT CDCI3  
 NS 270  
 DS 2  
 SWH 31250.000 Hz  
 FIDRES 0.953674 Hz  
 AQ 1.0485760 sec  
 RG 204.54  
 DW 16.000 usec  
 DE 28.00 usec  
 TE 298.0 K  
 D1 2.00000000 sec  
 D11 0.03000000 sec  
 TD0 1  
 SFO1 125.7722511 MHz  
 NUC1 13C  
 P1 10.50 usec  
 PLW1 23.00000000 W  
 SFO2 500.1330008 MHz  
 NUC2 1H  
 CPDPRG2 waltz16  
 PCPD2 80.00 usec  
 PLW2 13.50000000 W  
 PLW12 0.21094000 W  
 PLW13 0.10610000 W

F2 - Processing parameters  
 SI 131072  
 SF 125.7577717 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.40

201.37  
 170.78  
 170.31  
 169.51  
 169.45  
 167.10  
 150.96  
 135.36  
 117.92  
 109.10  
 96.44  
 96.39  
 72.71  
 72.40  
 70.70  
 68.14  
 61.76  
 51.65  
 47.07  
 41.91  
 27.53  
 20.90  
 20.74  
 20.72  
 20.64



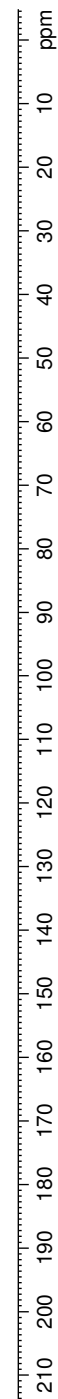
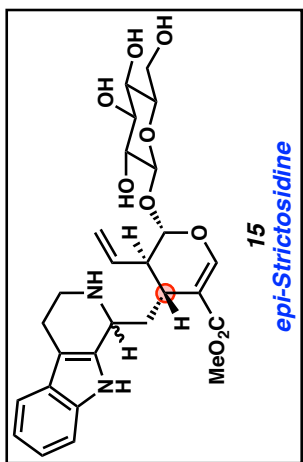


Current Data Parameters  
 NAME SMA-2020-182p  
 EXPNO 13  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20201221  
 Time 12.25 h  
 INSTRUM av500  
 PROBHD Z119248\_0002 (  
 PULPROG zgpg30  
 TD 65536  
 SOLVENT MeOD  
 NS 18519  
 DS 2  
 SWH 31250.000 Hz  
 FIDRES 0.953674 Hz  
 AQ 1.0485760 sec  
 RG 204.54  
 DW 16.000 usec  
 DE 28.00 usec  
 TE 298.0 K  
 D1 2.00000000 sec  
 D11 0.03000000 sec  
 TD0 1  
 SFO1 125.7722511 MHz  
 NUC1 13C  
 P1 10.50 usec  
 PLW1 23.0000000 W  
 SFO2 500.1330008 MHz  
 NUC2 1H  
 CPDPRG|2 waltz16  
 PCPD2 80.00 usec  
 PLW2 13.5000000 W  
 PLW12 0.21094000 W  
 PLW13 0.10610000 W

F2 - Processing parameters  
 SI 131072  
 SF 125.7577892 MHz  
 WDW EM  
 SSB 0  
 LB 0 1000.00 Hz  
 GB 0  
 PC 1.40

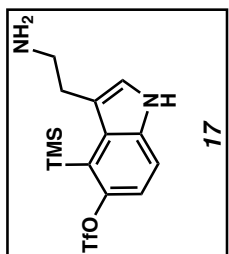
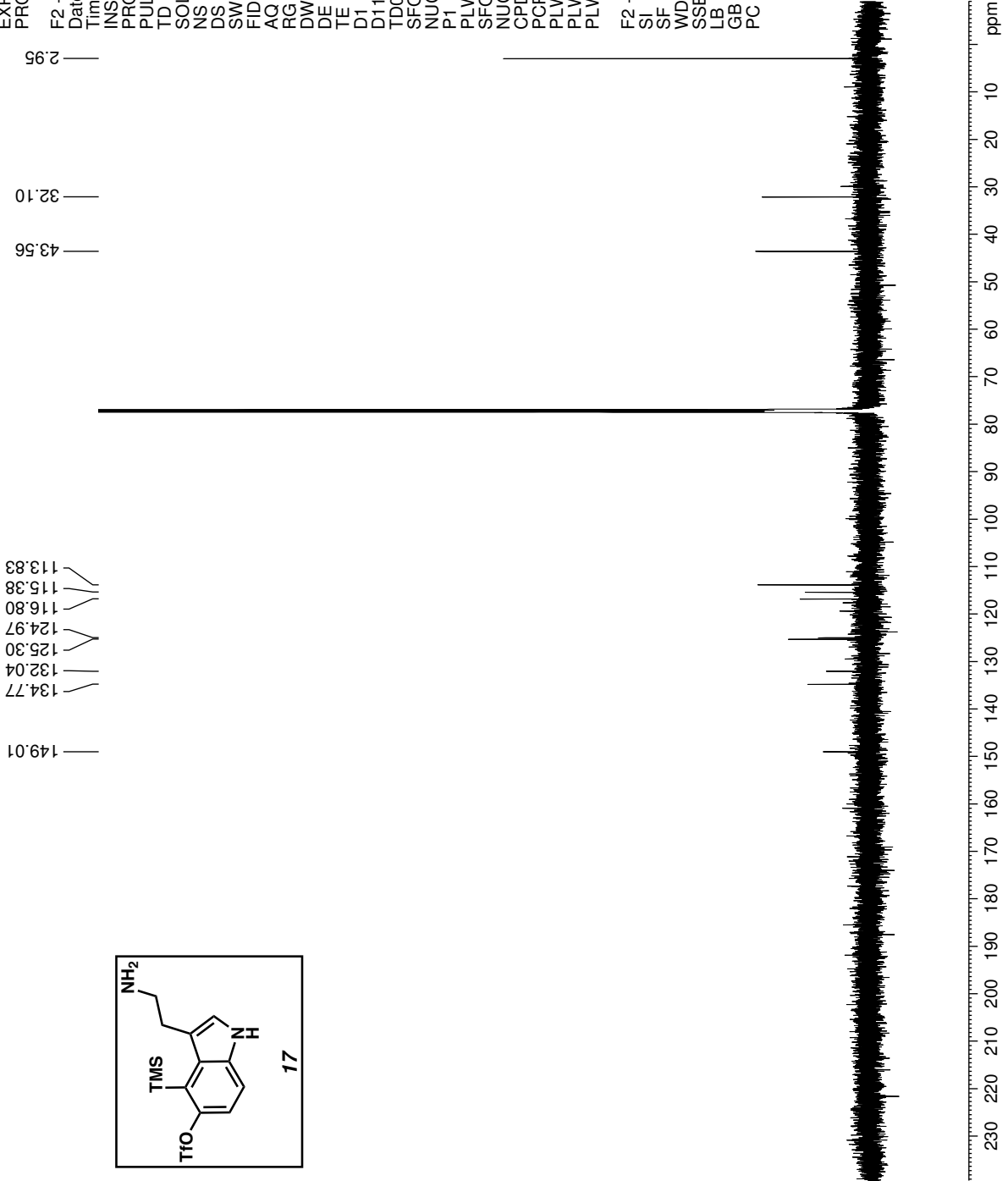
13.02  
 15.72  
 15.87  
 20.80  
 22.33  
 29.35  
 30.86  
 31.67  
 43.44  
 46.08  
 54.19  
 54.83  
 56.06  
 62.90  
 70.24  
 73.30  
 76.64  
 76.79  
 97.57  
 98.62  
 110.81  
 118.34  
 118.67  
 121.05  
 133.06  
 134.26  
 149.14



Current Data Parameters  
 NAME SMA-2020-154p  
 EXPNO 13  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20201104  
 Time\_ 16.12 h  
 INSTRUM av500  
 PROBHD Z119248\_0002 (Zggg30)  
 PULPROG zgpg30  
 TD 65536  
 SOLVENT CDCl3  
 NS 58  
 DS 2  
 SWH 31250.000 Hz  
 FIDRES 0.953674 Hz  
 AQ 1.0485760 sec  
 RG 204.54  
 DW 16.000 usec  
 DE 28.00 usec  
 TE 298.0 K  
 D1 2.00000000 sec  
 D11 0.03000000 sec  
 TD0 1  
 SFO1 125.7722511 MHz  
 NUC1 13C  
 P1 10.50 usec  
 PLW1 23.0000000 W  
 SFO2 500.1330008 MHz  
 NUC2 1H  
 CPDPRG2 waltz16  
 PCPD2 80.00 usec  
 PLW2 13.5000000 W  
 PLW12 0.21094000 W  
 PLW13 0.10610000 W

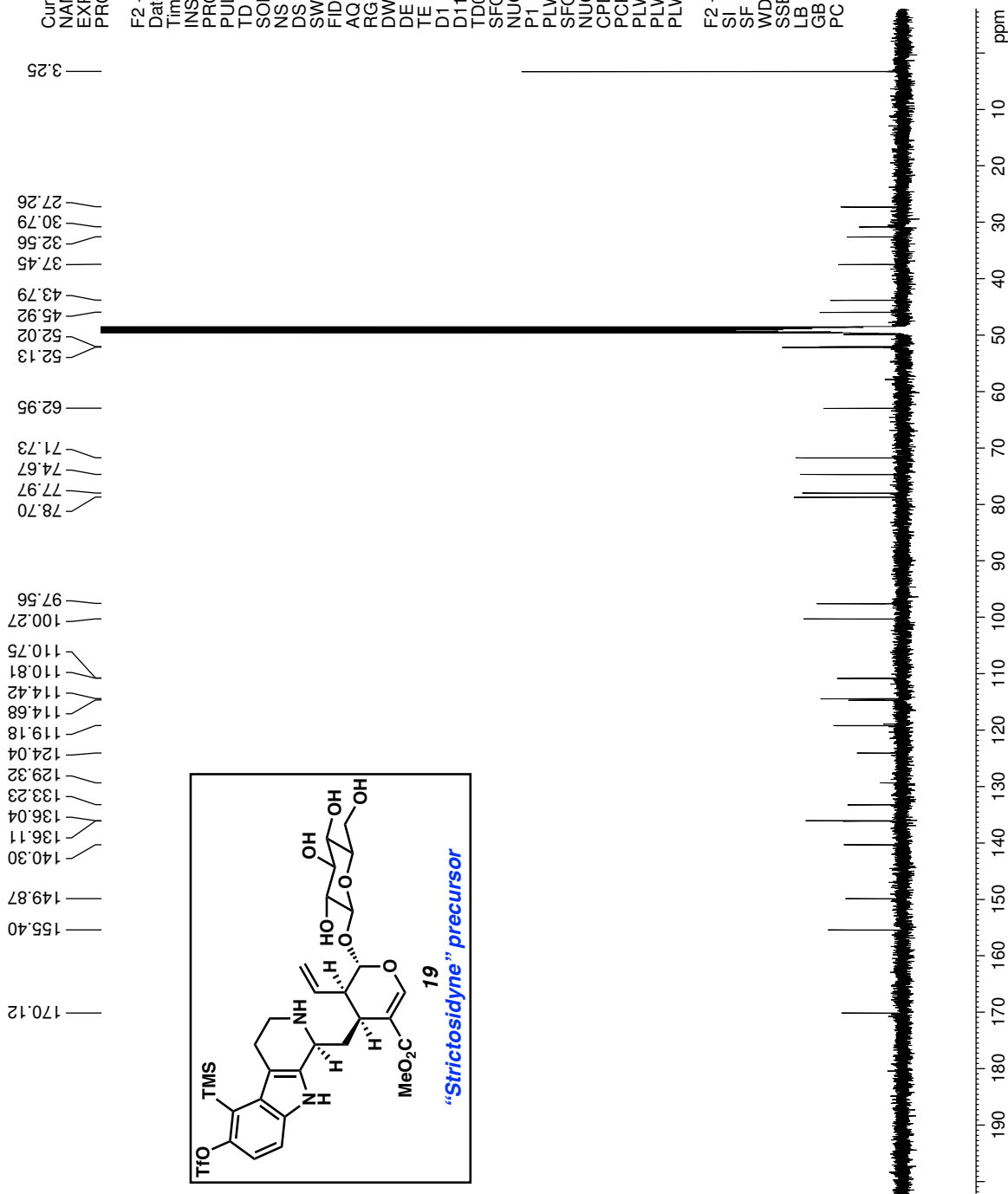
F2 - Processing parameters  
 SI 131072  
 SF 125.7577721 MHz  
 WDW EM  
 SSB 0  
 LB 0 1.00 Hz  
 GB 0  
 PC 1.40



Current Data Parameters  
 NAME VT-2020-220p1 3rd  
 EXPNO 3  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20201109  
 Time\_ 22.00 h  
 INSTRUM av500  
 PROBHD Z119248\_0002 ( zppg30  
 TD 65536  
 SOLVENT MeOD  
 NS 216  
 DS 2  
 SWH 31250.000 Hz  
 FIDRES 0.953674 Hz  
 AQ 1.0485760 sec  
 RG 204.54  
 DW 16.000 usec  
 DE 28.00 usec  
 TE 298.0 K  
 D1 2.0000000 sec  
 D11 0.03000000 sec  
 TD0 1  
 SFO1 125.7722511 MHz  
 NUC1 13C  
 P1 10.50 usec  
 PLW1 23.0000000 W  
 SFO2 500.1330008 MHz  
 NUC2 1H  
 CPDPRG2 waltz16  
 PCPD2 80.00 usec  
 PLW2 13.5000000 W  
 PLW12 0.21094000 W  
 PLW13 0.10610000 W

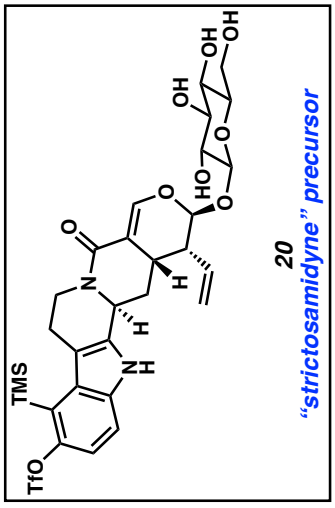
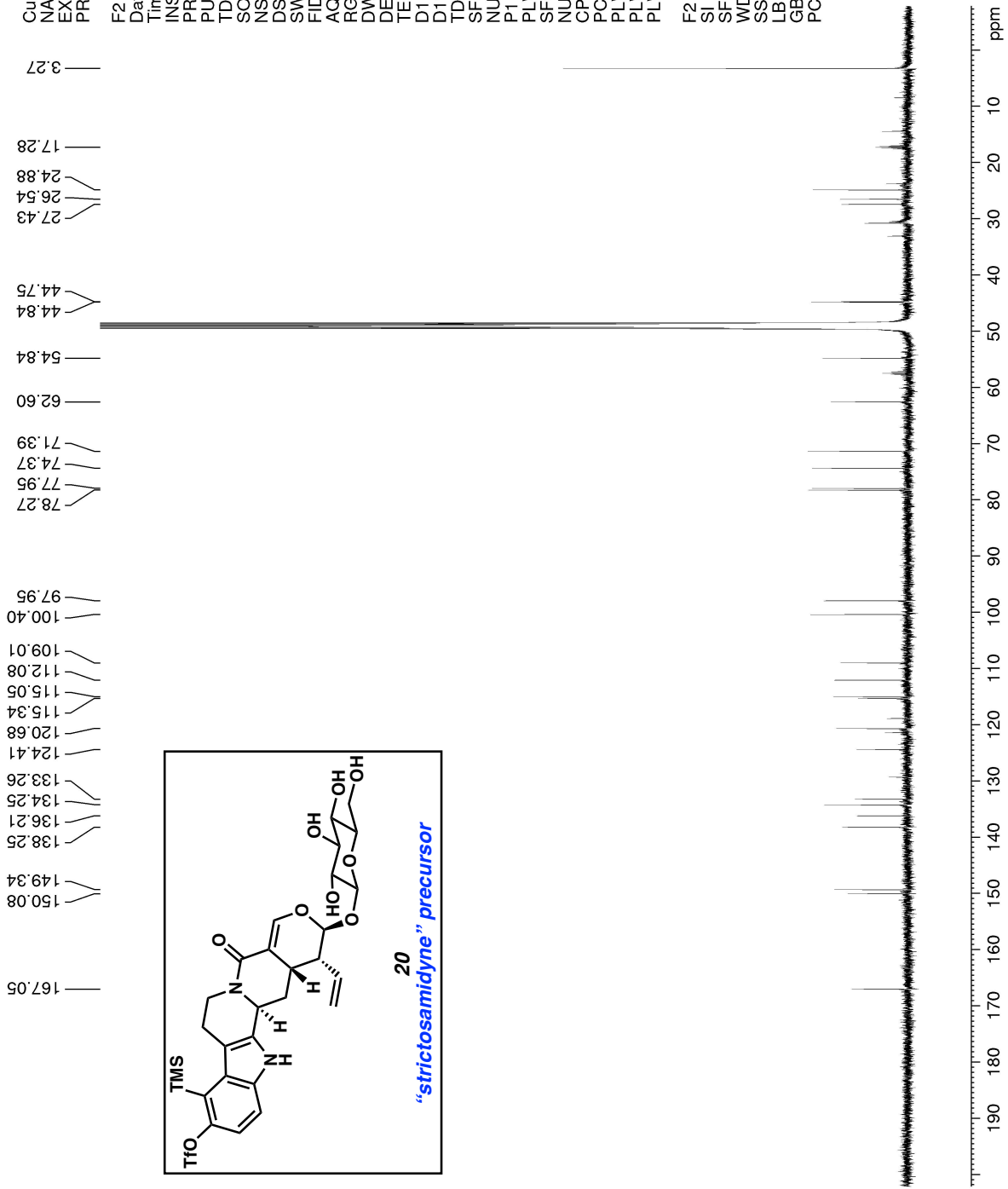
F2 - Processing parameters  
 SI 131072  
 SF 125.7576125 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.40



Current Data Parameters  
 NAME SMA-2020-175p  
 EXPNO 13  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20201125  
 Time\_ 12.32 h  
 INSTRUM av500  
 PROBHD Z119248\_0002 ( zpg930  
 TD 65536  
 SOLVENT MeOD  
 NS 3752  
 DS 2  
 SWH 31250.000 Hz  
 FIDRES 0.953674 Hz  
 AQ 1.0485760 sec  
 RG 204.54  
 DW 16.000 usec  
 DE 28.00 usec  
 TE 298.0 K  
 D1 2.00000000 sec  
 D11 0.030000000 sec  
 TD0 1  
 SFO1 125.7722511 MHz  
 NUC1 <sup>13</sup>C  
 P1 10.50 usec  
 PLW1 23.00000000 W  
 SFO2 500.1330008 MHz  
 NUC2 <sup>1</sup>H  
 CPDPRG2 waltz16  
 PCPD2 80.00 usec  
 PLW2 13.50000000 W  
 PLW12 0.21094000 W  
 PLW13 0.10610000 W

F2 - Processing parameters  
 SI 131072  
 SF 125.7576117 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.40

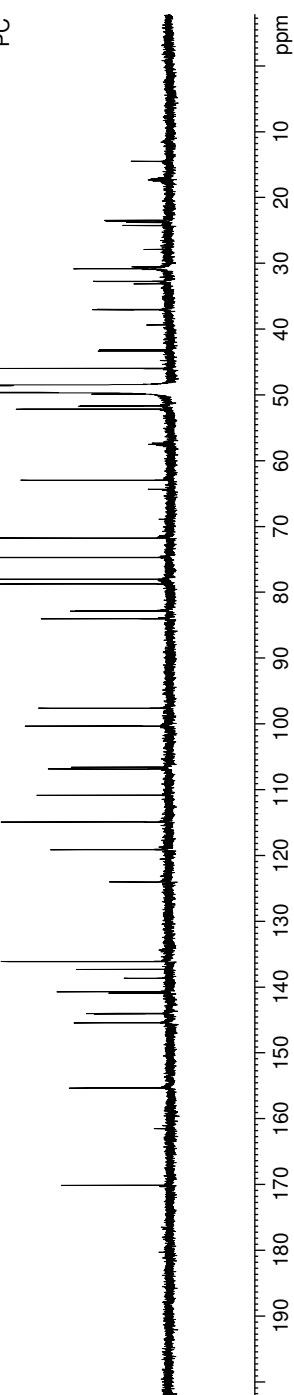
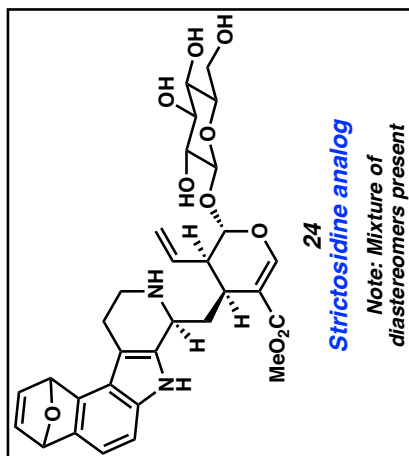


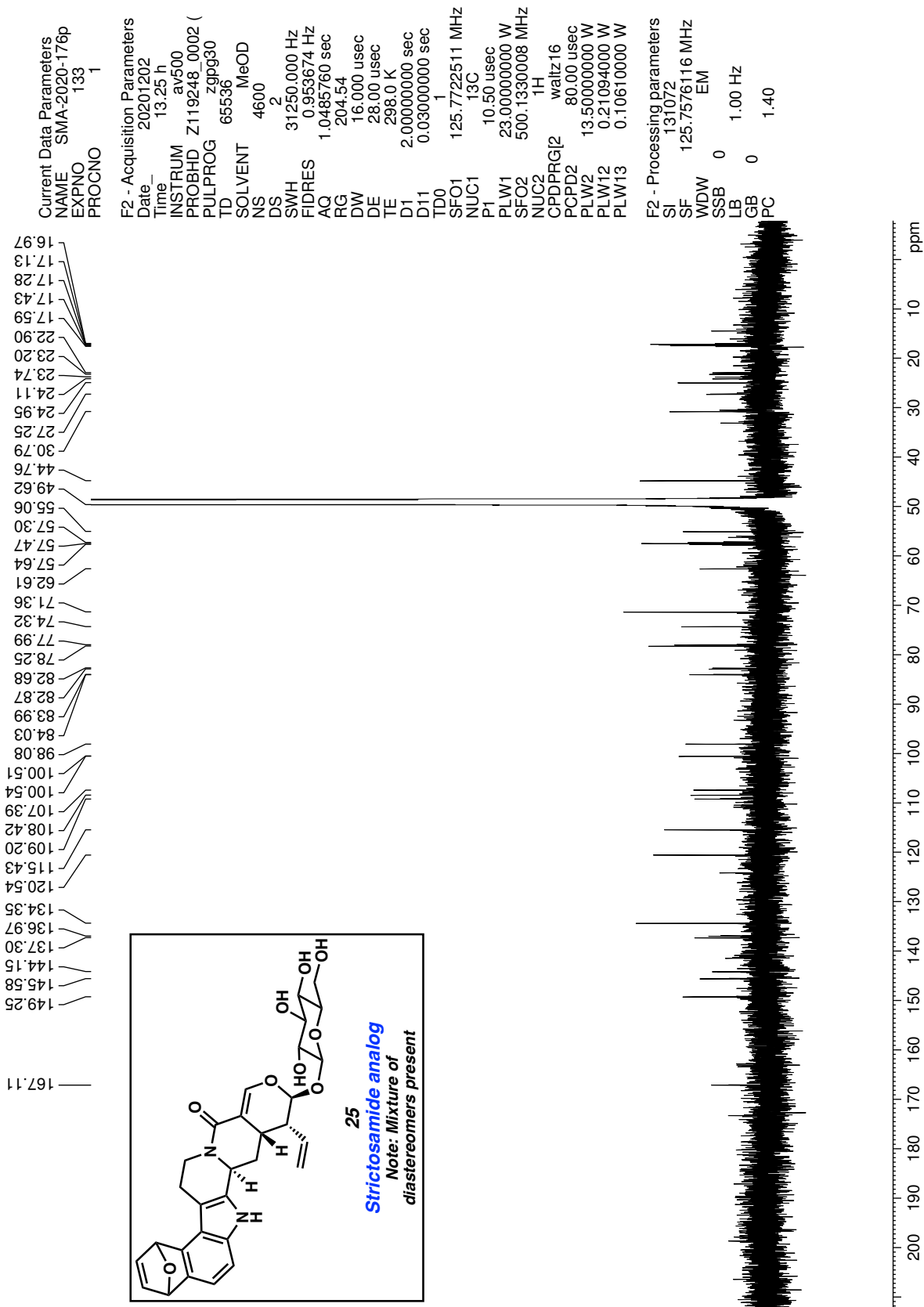
Current Data Parameters  
 NAME VI-2020-221p  
 EXPNO 2  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20201111  
 Time\_ 8.36 h  
 INSTRUM av500  
 PROBHD Z119248.0002 (  
 PULPROG zgpg30  
 TD 65536  
 SOLVENT MeOD  
 NS 11599  
 DS 2  
 SWH 31250.000 Hz  
 FIDRES 0.953674 Hz  
 AQ 1.0485760 sec  
 RG 204.54  
 DW 16.000 usec  
 DE 28.00 usec  
 TE 298.0 K  
 D1 2.0000000 sec  
 D11 0.0300000 sec  
 TD0 1  
 SFO1 125.7722511 MHz  
 NUC1 13C  
 P1 10.50 usec  
 PLW1 23.0000000 W  
 SFO2 500.1330008 MHz  
 NUC2 1H  
 CPDPRG2 waltz16  
 PCPD2 80.00 usec  
 PLW2 13.5000000 W  
 PLW12 0.21094000 W  
 PLW13 0.10610000 W

F2 - Processing parameters  
 SI 131072  
 SF 125.7576119 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.40

23.54  
 23.74  
 24.21  
 27.85  
 30.48  
 30.77  
 30.80  
 30.90  
 32.69  
 32.72  
 33.08  
 36.97  
 37.02  
 43.10  
 43.28  
 45.94  
 51.62  
 51.67  
 52.12  
 62.94  
 71.72  
 74.68  
 77.98  
 78.70  
 82.74  
 82.86  
 83.99  
 97.58  
 100.30  
 106.55  
 106.82  
 110.83  
 114.90  
 119.10  
 123.99  
 124.01  
 136.11  
 137.30  
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 140.93  
 143.99  
 144.04  
 145.41  
 155.32  
 170.12

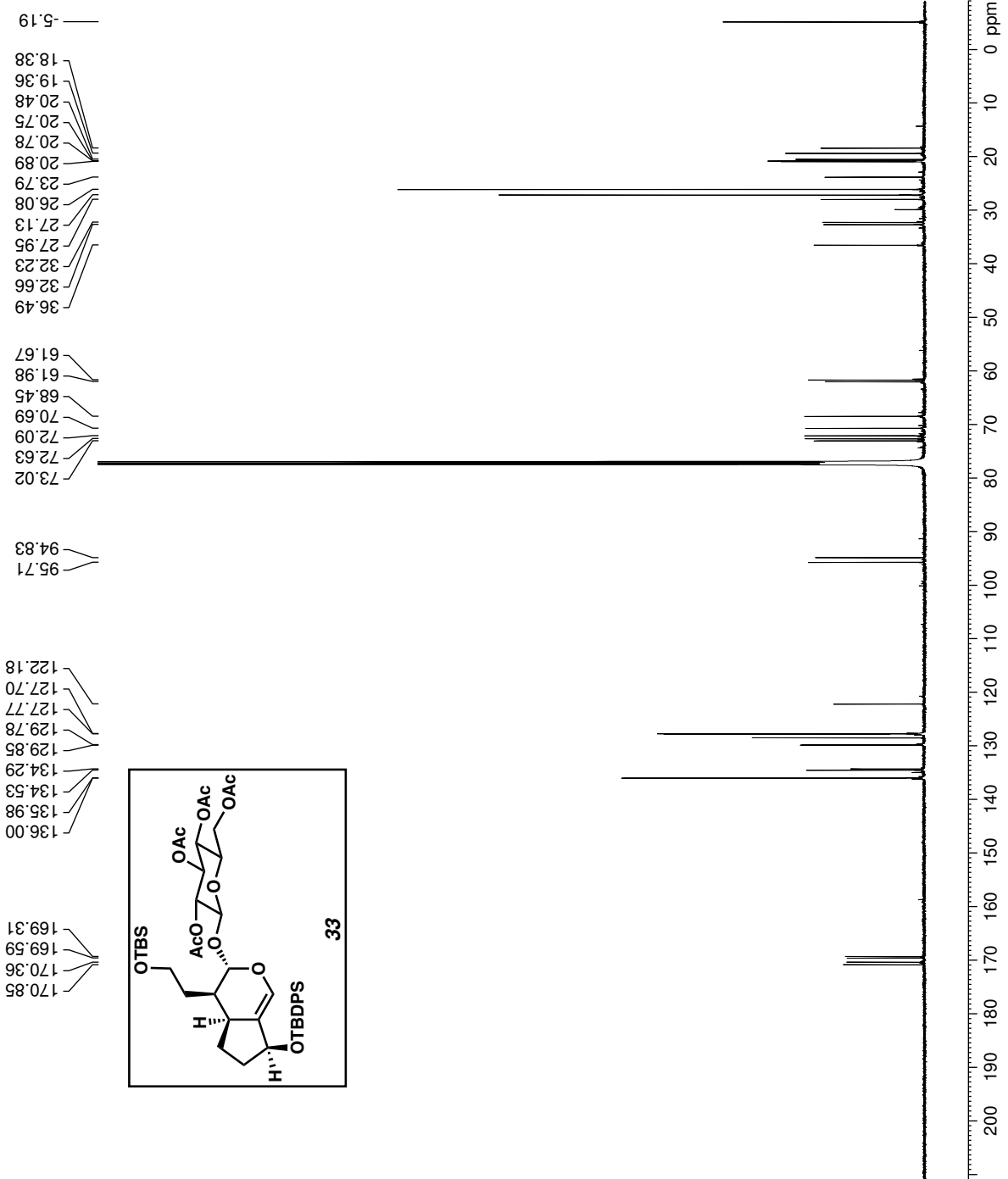


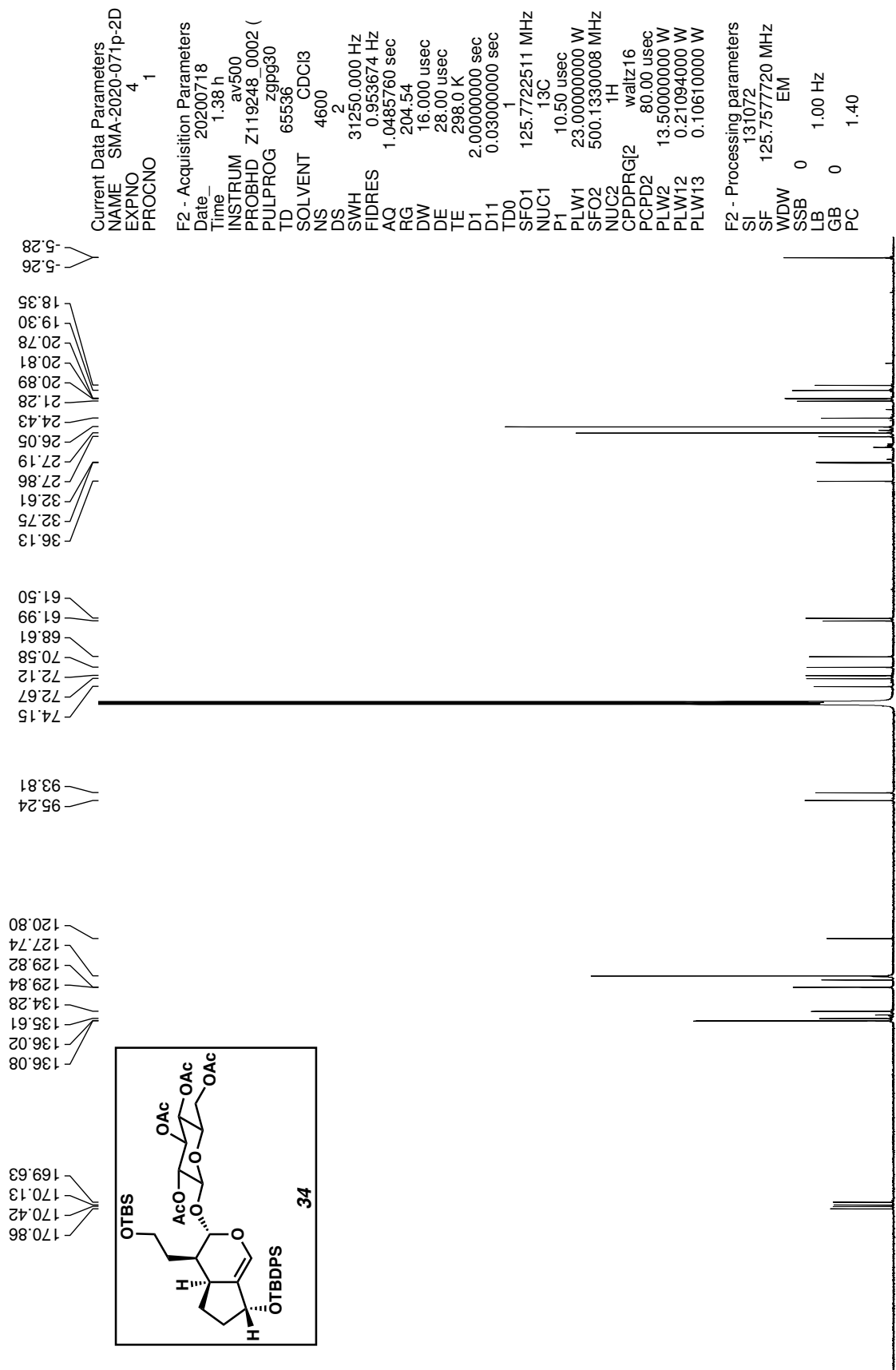


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 PROCNO 1

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 PROBHD Z119248\_000  
 PULPROG zgpg30  
 TD 65536  
 SOLVENT CDCI3  
 NS 4600  
 DS 2  
 SWH 31250.000 Hz  
 FIDRES 0.953674 Hz  
 AQC 1.0485760 sec  
 RG 204.54  
 DW 16.000 usec  
 DE 28.000 usec  
 TE 298.0 K  
 D1 2.00000000 sec  
 D11 0.030000000 sec  
 TD0 1  
 SFO1 125.7722511 MHz  
 NUC1 13C  
 P1 10.50 usec  
 PLW1 23.00000000 MHz  
 SFO2 500.1330008 MHz  
 NUC2 1H  
 CPDPRG2 waltz16  
 PCPD2 80.00 usec  
 PLW2 13.50000000 MHz  
 PLW12 0.21094000 MHz  
 PLW13 0.10610000 MHz

F2 - Processing parameters  
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 SF 125.7577719 MHz  
 WDW EM  
 SSB 0  
 LB 0  
 GB 0  
 PC 1.40





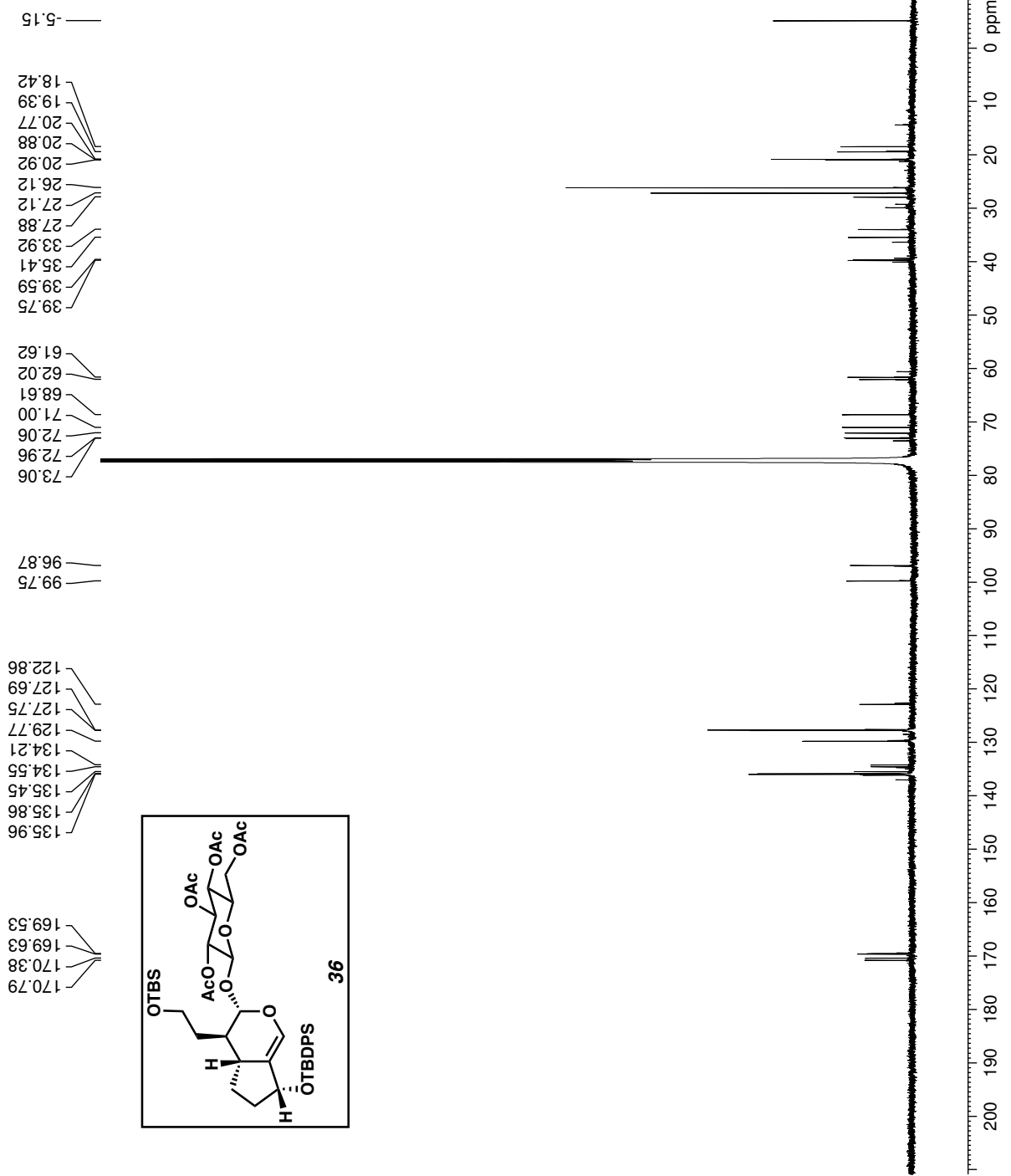




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 EXPNO 4  
 PROCNO 1

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 Time\_ 2.10 h  
 INSTRUM av500  
 PROBHD Z119248\_000;  
 PULPROG zgpg30  
 TD 65536  
 SOLVENT CDC13  
 NS 4600  
 DS 2  
 SWH 31250.000 Hz  
 FIDRES 0.953674 Hz  
 AQ 1.0485760 sec  
 RG 204.54  
 DW 16.000 usec  
 DE 28.00 usec  
 TE 298.0 K  
 D1 2.0000000 sec  
 D11 0.0300000 sec  
 TD0 1  
 SFO1 125.7722511 N  
 NUC1 13C  
 P1 10.50 usec  
 PLW1 23.00000000 V  
 SFO2 500.1330008 N  
 NUC2 1H  
 CPDPRG[2] waltz16  
 PCPD2 80.00 user  
 PLW2 13.50000000 V  
 PLW12 0.21094000 V  
 PLW13 0.10610000 V

F2 - Processing parameters  
 SI 131072  
 SF 125.7577717 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.40



**<sup>19</sup>F NMR Spectra:**

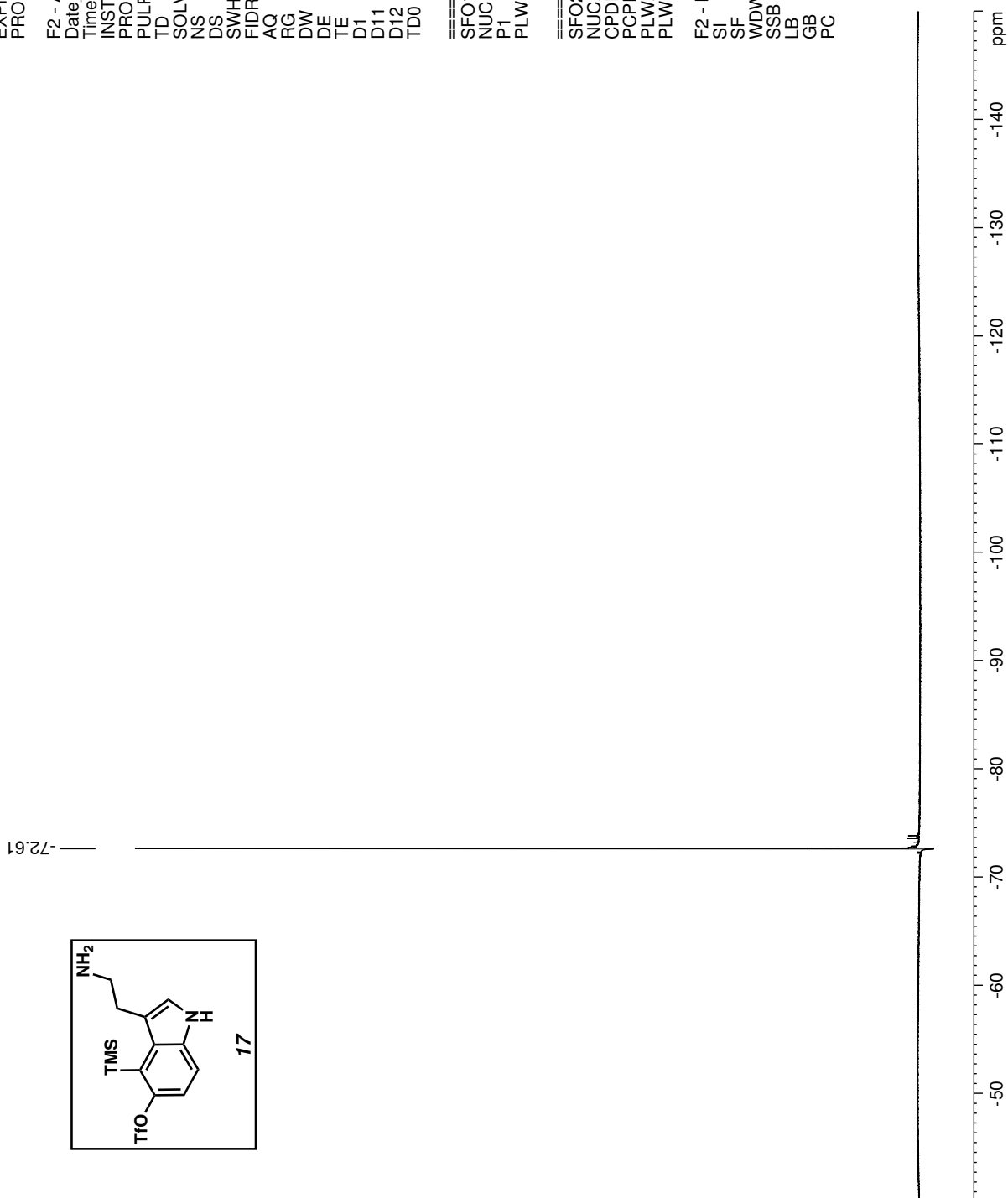
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 PROCNO 1

F2 - Acquisition Parameters  
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 INSTRUM av400  
 PROBHD 5 mm PABBO BB/  
 PULPROG zgfhgqn.2  
 TD 262144  
 SOLVENT CDCI3  
 NS 64  
 DS 0  
 SWH 75000.000 Hz  
 FIDRES 0.286102 Hz  
 AQ 1.7476267 sec  
 RG 189.85  
 DW 6.667 usec  
 DE 6.50 usec  
 TE 296.8 K  
 D1 1.00000000 sec  
 D11 0.03000000 sec  
 D12 0.00002000 sec  
 TD0 1

==== CHANNEL f1 =====  
 SFO1 376.4607162 MHz  
 NUC1 19F  
 P1 14.50 usec  
 PLW1 17.00000000 W

==== CHANNEL f2 =====  
 SFO2 400.1324008 MHz  
 NUC2 1H  
 CPDPRG2 waitz16  
 PCPD2 90.00 usec  
 PLW2 13.00000000 W  
 PLW12 0.3611000 W

F2 - Processing parameters  
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 SF 376.4983660 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.00



Current Data Parameters  
 NAME VT-2020-220p1 3rd p  
 EXPNO 170  
 PROCNO 1

## F2 - Acquisition Parameters

Date\_ 20201110  
 Time 15.41  
 INSTRUM av400  
 PROBHD 5 mm PABBO BB/  
 PULPROG zgpg30  
 TD 262144  
 SOLVENT MeOD  
 NS 64  
 DS 0  
 SWH 75000.000 Hz  
 FIDRES 0.286102 Hz  
 AQ 1.7476267 sec  
 RG 189.85  
 DW 6.667 usec  
 DE 6.50 usec  
 TE 296.4 K  
 D1 1.00000000 sec  
 D11 0.03000000 sec  
 D12 0.00002000 sec  
 TD0 1

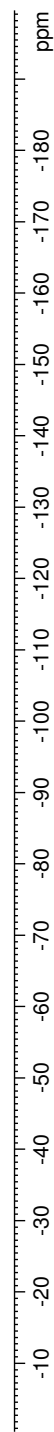
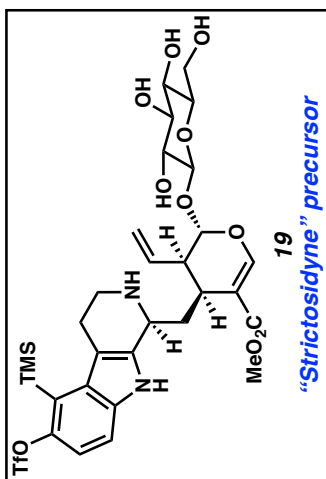
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 NUC1 19F  
 P1 14.50 usec  
 PLW1 17.00000000 W

==== CHANNEL f2 =====  
 SFO2 400.1324008 MHz  
 NUC2 1H  
 CPDPRG2 waltz16  
 PCPD2 90.00 usec  
 PLW2 13.00000000 W  
 PLW12 0.3611000 W

## F2 - Processing parameters

SI 262144  
 SF 376.4983660 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.00

—74.36



Current Data Parameters  
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 EXPNO 11  
 PROCNO 1

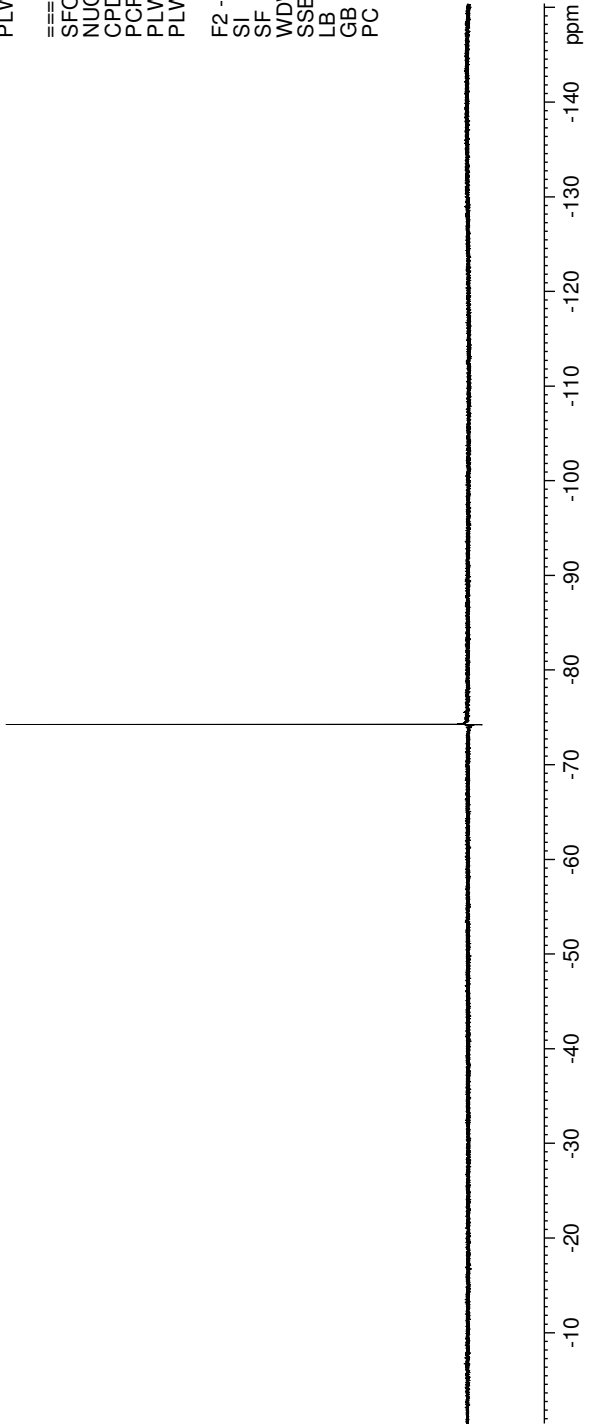
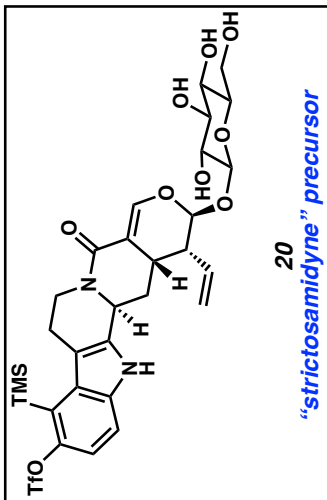
F2 - Acquisition Parameters  
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 Time\_ 17.39  
 INSTRUM av400  
 PROBHD 5 mm PABBO BB/  
 PULPROG zgfhgqn.2  
 TD 262144  
 SOLVENT MeOD  
 NS 32  
 DS 0  
 SWH 75000.000 Hz  
 FIDRES 0.286102 Hz  
 AQ 1.7476267 sec  
 RG 189.85  
 DW 6.667 usec  
 DE 6.50 usec  
 TE 296.2 K  
 D1 1.00000000 sec  
 D11 0.03000000 sec  
 D12 0.00002000 sec  
 TD0 1

==== CHANNEL f1 =====  
 SFO1 376.4607162 MHz  
 NUC1 19F  
 P1 14.50 usec  
 PLW1 17.00000000 W

==== CHANNEL f2 =====  
 SFO2 400.1324008 MHz  
 NUC2 1H  
 CPDPRG2 waltz16  
 PCPD2 90.00 usec  
 PLW2 13.00000000 W  
 PLW12 0.3611000 W

F2 - Processing parameters  
 SI 262144  
 SF 376.4983660 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.00

— -74.27



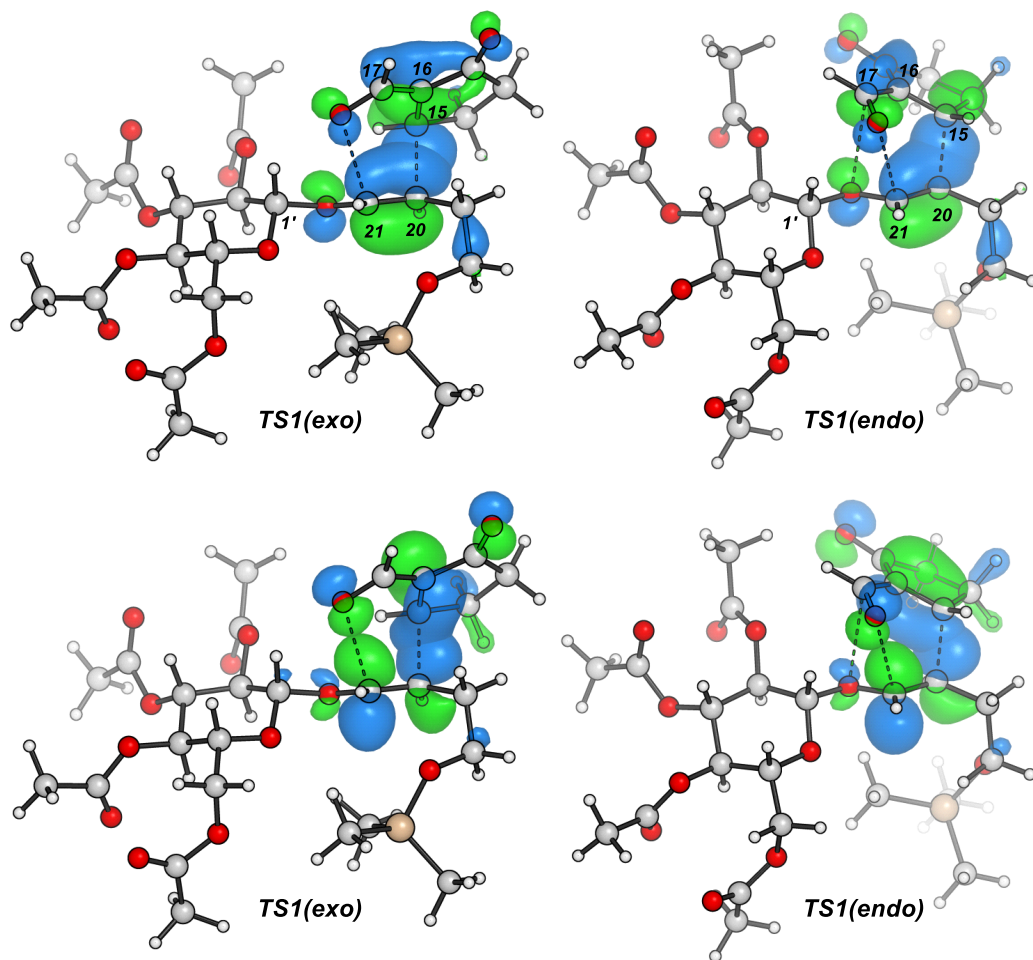
## **Part II: Computational Section**

### **Conformational Search**

Due to the conformational flexibility of the glycosyl enol ether dienophile, we performed extensive conformational searches using metadynamics approaches in Grimme's program CREST.<sup>7,8</sup> More than 1700 conformations were generated for the dienophile. In order to find what proved to be the most favored chair <sup>4</sup>C<sub>1</sub> conformation of the glycosyl group,<sup>9,10</sup> manual adjustments of the glycosyl group to the lowest energy <sup>4</sup>C<sub>1</sub> conformation were also required. Low energy conformations were reoptimized with M06-2X. The conformation of the pyranyl part was identical for all four stereoisomeric transition states.

### **DFT Calculation Procedure**

Density functional theory (DFT) calculations were performed with Gaussian 09.<sup>11</sup> The geometry of each species was optimized using the M06-2X functional<sup>12</sup> and the 6-31G(d,p) basis set with the SMD<sup>13</sup> solvation model for toluene. Frequency calculations were performed at the same theoretical level as for geometry optimizations to verify the stationary points as either minima or first-order saddle points on the potential energy surface, as well as to obtain thermal Gibbs free energy corrections. All reported Gibbs free energies are for 298K and are after quasi-harmonic correction using the GoodVibes program developed by the Paton group.<sup>14</sup> Single-point energy calculations were based on the optimized geometry and conducted at M06-2X/6-311++g(d,p)/SMD(toluene) level. All DFT calculations were with ultrafine integration grid. Optimized structures are presented using Pymol.<sup>15</sup>



**Figure S1.** Combination of the calculated frontier orbitals of diene and dienophile in each stereoisomeric transition state.

### XYZ Coordinates of the DFT Optimized Structure and the Corresponding Energies<sup>16</sup>

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**8**

E[M06-2X/6-31G(d,p)/SMD(toluene)] = -382.524358660

Zero-point correction = 0.108603

Thermal correction to Energy = 0.115829

Thermal correction to Enthalpy = 0.116773

Thermal correction to Gibbs Free Energy = 0.076571

E[M06-2X/6-311++g(d,p)/SMD(toluene)] = -382.631516673

C	1.975105	0.044659	0.001197
C	0.695131	0.878253	-0.000393
O	0.621846	2.086933	-0.000541
C	-0.449848	-0.069705	-0.000087



C	0.004236	-1.332912	-0.000332
C	1.504236	-1.418439	-0.000587
H	1.849974	-1.978073	0.875072
H	1.849373	-1.975447	-0.878198
H	-0.637868	-2.208955	-0.000441
C	-1.862931	0.357755	-0.000014
O	-2.793380	-0.418602	0.000500
H	-2.023118	1.451614	-0.000262
H	2.571073	0.304025	-0.877490
H	2.567260	0.302514	0.882954

**9**

E[M06-2X/6-31G(d,p)/SMD(toluene)]= -1937.12326939

Zero-point correction= 0.551788

Thermal correction to Energy= 0.590525

Thermal correction to Enthalpy= 0.591470

Thermal correction to Gibbs Free Energy= 0.477333

E[M06-2X/6-311++g(d,p)/SMD(toluene)]= -1937.61209376

C	3.506837	-2.565754	-0.570358
C	2.430133	-1.903690	-0.977007
C	5.713055	-1.387481	-0.534612
O	5.112002	-0.115050	-0.626708
Si	4.579477	0.770015	0.691214
C	3.666889	-0.284394	1.947257
C	3.406361	2.039136	-0.013806
C	6.064042	1.567416	1.519617
H	2.714980	-0.643602	1.543847
H	4.243902	-1.150924	2.286452
H	3.448847	0.324080	2.833093
H	3.090604	2.759476	0.747805
H	3.854564	2.593636	-0.844156
H	2.510453	1.524094	-0.374674
H	6.769823	0.811907	1.882478
H	6.603476	2.217535	0.823568
H	5.760347	2.173308	2.380094
C	0.199714	-1.257806	-0.832222
O	0.493668	0.120201	-0.752101
C	-0.526506	0.920125	-1.328349
C	-1.054926	-1.590624	-0.028299
C	-2.217097	-0.677851	-0.426011
C	-1.768256	0.774853	-0.451394
H	0.055338	-1.539217	-1.891329
C	-0.049774	2.355087	-1.425735
O	0.038732	2.930544	-0.122375

C	-0.761171	3.986828	0.149047
C	-0.626964	4.400018	1.583353
O	-1.492569	4.497696	-0.665066
H	-0.747252	0.571248	-2.351155
O	-2.810981	1.576623	-0.993315
C	-3.466797	2.409682	-0.144063
C	-4.490354	3.213807	-0.885674
O	-3.219878	2.489095	1.032295
H	-1.529762	1.107486	0.561882
H	0.948396	2.380354	-1.869876
H	-0.742904	2.932625	-2.038753
O	-3.267341	-0.758518	0.534600
C	-4.235594	-1.679795	0.340068
C	-5.191824	-1.688172	1.493596
O	-4.283430	-2.401385	-0.626695
H	-2.597199	-0.976309	-1.409549
O	-1.364001	-2.947067	-0.332457
C	-1.956832	-3.688788	0.628820
C	-2.288397	-5.055374	0.110887
H	-0.838560	-1.476169	1.038321
H	-1.150286	3.660413	2.195975
H	0.422326	4.416764	1.882306
H	-1.087097	5.376341	1.724754
H	-3.960106	3.928481	-1.520845
H	-5.096396	2.567705	-1.523353
H	-5.115487	3.750133	-0.174193
H	-5.448245	-0.669114	1.787545
H	-6.083028	-2.253747	1.227137
H	-4.688122	-2.168689	2.337446
H	-3.126307	-4.954387	-0.584938
H	-1.441303	-5.476132	-0.433159
H	-2.574266	-5.700271	0.939885
H	5.867768	-1.692989	0.511602
H	6.699987	-1.347241	-1.011826
O	-2.200541	-3.270950	1.733991
C	4.836113	-2.421464	-1.247224
H	5.367135	-3.379500	-1.276016
H	4.701762	-2.086131	-2.281454
H	3.442859	-3.153645	0.343239
O	1.251699	-1.963103	-0.273005
H	2.420280	-1.266963	-1.859797

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**TS1(endo)**


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E[M06-2X/6-31G(d,p)/SMD(toluene)] = -2319.63734362

Zero-point correction= 0.663387

Thermal correction to Energy= 0.708959

Thermal correction to Enthalpy= 0.709903

Thermal correction to Gibbs Free Energy= 0.580723

E[M06-2X/6-311++g(d,p)/SMD(toluene)]= -2320.23095622

C	3.429788	0.327839	-0.787021
C	2.120794	0.198887	-1.227465
C	3.972968	2.775641	-0.970610
O	4.128969	2.835776	0.432948
Si	2.933752	3.496841	1.409525
C	2.639669	5.280789	0.910155
C	3.601399	3.384428	3.148546
C	1.342100	2.519616	1.234322
H	3.558650	5.869766	0.992876
H	2.281482	5.362597	-0.121631
H	1.885617	5.745241	1.554724
H	2.886327	3.792887	3.870077
H	3.799972	2.345060	3.427783
H	4.536547	3.943693	3.248537
H	0.954205	2.508342	0.210168
H	1.469411	1.478943	1.550993
H	0.560340	2.961644	1.863460
C	-0.052224	-0.552887	-0.948265
O	-0.539830	0.753860	-1.087477
C	-1.878873	0.785242	-1.566450
C	-0.848384	-1.353530	0.074798
C	-2.347472	-1.271864	-0.233047
C	-2.761679	0.170050	-0.483954
H	-0.009932	-1.068573	-1.920360
C	-2.250060	2.220476	-1.877264
O	-2.368702	2.968956	-0.667754
C	-3.586615	3.479380	-0.368933
C	-3.576948	4.127549	0.981850
O	-4.544090	3.388395	-1.098546
H	-1.958733	0.203400	-2.498676
O	-4.112052	0.200850	-0.926588
C	-5.041389	0.697654	-0.067851
C	-6.396318	0.697191	-0.706161
O	-4.777085	1.097419	1.037169
H	-2.655982	0.751048	0.435903
H	-1.458776	2.678311	-2.475649
H	-3.192136	2.247617	-2.426050
O	-3.105732	-1.718912	0.885876
C	-3.441919	-3.028530	0.940043

C	-4.135368	-3.339131	2.230866
O	-3.178210	-3.817442	0.066461
H	-2.576251	-1.894490	-1.105320
O	-0.388999	-2.692984	-0.038833
C	-0.439192	-3.473220	1.074505
C	-0.047337	-4.878713	0.750167
H	-0.656535	-0.960048	1.078295
H	-3.642982	3.332202	1.730198
H	-2.650880	4.681206	1.141924
H	-4.443185	4.780092	1.077189
H	-6.393058	1.438974	-1.509223
H	-6.612000	-0.280373	-1.141471
H	-7.146779	0.962666	0.035970
H	-4.853554	-2.557044	2.481451
H	-4.622269	-4.310249	2.160900
H	-3.372568	-3.365804	3.014799
H	-0.658892	-5.235720	-0.081230
H	1.007126	-4.891904	0.457950
H	-0.197370	-5.503395	1.629233
H	4.644123	3.503691	-1.443646
H	2.945147	3.030950	-1.275270
O	-0.769804	-3.044301	2.152137
C	4.770357	-2.380768	0.934283
C	3.628979	-3.135582	0.245799
C	3.361347	-2.454854	-1.007552
C	4.238383	-1.354458	-1.191520
H	5.486397	-3.073228	1.381532
H	4.334351	-1.789325	1.748877
O	3.067871	-4.117373	0.712061
C	2.265607	-2.672673	-1.880070
H	1.611085	-3.538093	-1.676401
O	2.005130	-1.889862	-2.810204
C	4.297101	1.368744	-1.462653
H	5.351619	1.154123	-1.259587
H	4.157893	1.324356	-2.549587
H	3.527005	0.263979	0.296451
H	4.496582	-1.071941	-2.210285
C	5.363021	-1.486346	-0.161850
H	5.729667	-0.525452	0.207742
H	6.203626	-1.987998	-0.652935
O	1.266884	-0.429151	-0.444711
H	1.760972	0.549621	-2.191403

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**TS1(exo)**

---

E[M06-2X/6-31G(d,p)/SMD(toluene)] = -2319.63469113

Zero-point correction = 0.662903

Thermal correction to Energy = 0.708943

Thermal correction to Enthalpy = 0.709887

Thermal correction to Gibbs Free Energy = 0.578800

E[M06-2X/6-311++g(d,p)/SMD(toluene)] = -2320.22917028

C	-3.370331	0.259011	-0.606937
C	-2.171723	0.266065	0.088780
C	-4.075089	2.673399	-0.664031
O	-2.912096	3.097866	0.015938
Si	-1.640684	3.869628	-0.762376
C	-2.283958	5.403350	-1.629102
C	-0.841688	2.720637	-2.009056
C	-0.456634	4.286077	0.620147
H	-2.994187	5.154904	-2.424982
H	-2.790541	6.070182	-0.924061
H	-1.462793	5.964185	-2.088410
H	-0.088672	3.267528	-2.588475
H	-0.334235	1.889488	-1.509936
H	-1.563118	2.308521	-2.723150
H	-0.761356	5.186504	1.161736
H	-0.451821	3.453193	1.329827
H	0.565154	4.427563	0.254425
C	-0.013847	-0.567695	0.395684
O	0.586820	0.696348	0.515081
C	1.783611	0.642841	1.285030
C	0.890645	-1.556220	-0.334802
C	2.284424	-1.593792	0.293864
C	2.799618	-0.177470	0.492027
H	-0.325464	-0.950886	1.376445
C	2.272029	2.049178	1.556907
O	2.707066	2.655414	0.339471
C	4.005261	3.032702	0.261228
C	4.331899	3.537141	-1.111259
O	4.782897	2.939685	1.179813
H	1.582153	0.162206	2.255704
O	4.022087	-0.218932	1.215974
C	5.158055	0.105635	0.543207
C	6.339997	0.066106	1.462151
O	5.175583	0.404538	-0.623520
H	2.958783	0.296990	-0.479713
H	1.458905	2.654712	1.960863
H	3.095944	2.016667	2.270967
O	3.206355	-2.237691	-0.581531

C	3.366293	-3.574497	-0.460619
C	4.292108	-4.091138	-1.519117
O	2.804511	-4.236875	0.377267
H	2.246683	-2.129449	1.248779
O	0.248885	-2.820660	-0.219840
C	0.413567	-3.704423	-1.230699
C	-0.234879	-5.012768	-0.897066
H	0.972180	-1.261825	-1.386254
H	3.519899	4.150852	-1.503705
H	5.264400	4.098036	-1.079749
H	4.457766	2.666750	-1.762028
H	7.254848	0.166261	0.881144
H	6.253460	0.904455	2.158685
H	6.346227	-0.861337	2.037575
H	3.743452	-4.093883	-2.465601
H	5.155983	-3.433913	-1.629642
H	4.601702	-5.105041	-1.271753
H	-0.293871	-5.630054	-1.791727
H	0.387831	-5.509002	-0.146912
H	-1.224577	-4.855218	-0.465364
H	-3.935896	2.686864	-1.756591
H	-4.902106	3.355559	-0.430842
O	1.029426	-3.451246	-2.236634
C	-6.491058	-1.627769	-0.309210
C	-5.987220	-1.636103	1.139676
C	-4.533370	-1.615160	1.096972
C	-4.049430	-1.546145	-0.228578
H	-7.034913	-0.693875	-0.483747
H	-7.202707	-2.443899	-0.457350
O	-6.706544	-1.663061	2.124726
C	-3.673692	-1.451142	2.209734
H	-4.136382	-1.432052	3.211670
O	-2.450690	-1.274965	2.082499
C	-4.430231	1.258209	-0.217773
H	-5.391072	0.975031	-0.661539
H	-4.559700	1.252785	0.870807
H	-3.255819	0.046458	-1.670008
H	-3.094936	-2.009242	-0.476783
C	-5.230158	-1.759916	-1.179252
H	-5.143833	-2.770532	-1.591772
H	-5.220574	-1.072586	-2.029247
O	-1.153593	-0.411933	-0.422497
H	-2.018109	0.777712	1.032587

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**TS2(endo)**

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E[M06-2X/6-31G(d,p)/SMD(toluene)]= -2319.63370690  
 Zero-point correction= 0.663033  
 Thermal correction to Energy= 0.708683  
 Thermal correction to Enthalpy= 0.709628  
 Thermal correction to Gibbs Free Energy= 0.580161  
 E[M06-2X/6-311++g(d,p)/SMD(toluene)]= -2320.22829405

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C	3.285883	1.121364	-0.728416
C	2.071090	0.569207	-1.132561
C	5.048951	-0.674673	-0.923751
O	5.305986	-0.593723	0.464111
Si	4.669265	-1.730609	1.522374
C	2.796254	-1.645306	1.445697
C	5.315236	-1.271181	3.209976
C	5.234528	-3.445066	1.014251
H	2.410595	-0.719718	1.886404
H	2.456310	-1.675329	0.404317
H	2.333261	-2.487727	1.969898
H	4.920572	-1.945676	3.976733
H	6.407483	-1.326791	3.242624
H	5.022083	-0.251730	3.478744
H	4.879100	-3.714475	0.013561
H	6.326801	-3.516722	1.009864
H	4.852366	-4.199768	1.710118
C	-0.244135	0.387190	-0.782494
O	-1.066413	1.345357	-0.204391
C	-2.401627	1.246122	-0.685003
C	-0.640008	-1.012040	-0.315884
C	-2.102444	-1.250389	-0.710247
C	-2.965883	-0.094329	-0.216196
H	-0.252881	0.460990	-1.880635
C	-3.191125	2.431759	-0.162383
O	-3.492905	2.261167	1.222769
C	-4.794025	2.130456	1.566515
C	-4.931973	1.889547	3.039306
O	-5.703666	2.186560	0.773774
H	-2.401862	1.294983	-1.785998
O	-4.280345	-0.234731	-0.737576
C	-5.260528	-0.612415	0.125640
C	-6.585059	-0.651210	-0.572570
O	-5.064324	-0.850304	1.289775
H	-2.994328	-0.108649	0.876294
H	-2.581286	3.333715	-0.254809
H	-4.115274	2.541161	-0.730613

O	-2.626469	-2.420765	-0.093511
C	-2.494052	-3.594386	-0.749307
C	-3.037906	-4.720804	0.074707
O	-1.976901	-3.692316	-1.835929
H	-2.172232	-1.347193	-1.800002
O	0.243085	-1.905664	-0.988270
C	0.492725	-3.100782	-0.395389
C	1.398334	-3.938763	-1.245002
H	-0.514347	-1.096196	0.768512
H	-4.570909	0.880249	3.254763
H	-4.323381	2.600844	3.600285
H	-5.979966	1.968131	3.322568
H	-6.872776	0.377865	-0.803645
H	-6.508118	-1.206653	-1.509083
H	-7.327889	-1.101470	0.083221
H	-3.989433	-4.440251	0.529023
H	-3.147245	-5.609311	-0.544679
H	-2.322904	-4.917337	0.879084
H	0.782467	-4.414535	-2.014622
H	2.151629	-3.326121	-1.743079
H	1.865171	-4.706550	-0.629393
H	4.297705	-1.448205	-1.153419
H	5.971529	-0.954347	-1.447598
O	0.013841	-3.424977	0.661346
C	2.986917	4.138951	0.979136
C	1.640143	4.223287	0.247471
C	1.785090	3.463021	-0.982065
C	3.104234	2.945225	-1.128563
H	2.880675	3.405900	1.788612
H	3.251173	5.095024	1.435542
O	0.653750	4.813764	0.656823
C	0.747251	3.102616	-1.869518
H	-0.243691	3.559547	-1.701396
O	0.909722	2.261596	-2.773858
C	4.546420	0.669750	-1.435788
H	4.363996	0.602157	-2.515275
H	5.331947	1.418478	-1.285396
H	3.367702	1.212083	0.355148
H	3.491781	2.853865	-2.142467
C	3.978377	3.659298	-0.089515
H	4.448479	4.516112	-0.583594
H	4.781335	3.031463	0.305927
O	1.055223	0.714570	-0.315844
H	1.893981	0.107742	-2.100825

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<b>TS2(exo)</b>			
E[M06-2X/6-31G(d,p)/SMD(toluene)]= -2319.63268476			
Zero-point correction= 0.663345			
Thermal correction to Energy= 0.708967			
Thermal correction to Enthalpy= 0.709911			
Thermal correction to Gibbs Free Energy= 0.580723			
E[M06-2X/6-311++g(d,p)/SMD(toluene)]= -2320.22802055			
C	-3.165317	-0.799432	0.139304
C	-1.947508	-0.494993	-0.448502
C	-4.790606	0.964116	-0.633259
O	-5.006621	1.391547	0.698080
Si	-4.233406	2.745440	1.314724
C	-4.615384	4.235891	0.241603
C	-2.380336	2.450671	1.324365
C	-4.900889	2.965889	3.042395
H	-4.256918	4.106869	-0.785442
H	-5.692496	4.425548	0.196126
H	-4.134889	5.134151	0.644778
H	-1.834268	3.362941	1.588137
H	-2.091802	1.671326	2.037562
H	-2.036296	2.128229	0.335595
H	-5.981204	3.138847	3.027956
H	-4.710751	2.078565	3.653927
H	-4.429676	3.820831	3.538160
C	0.391101	-0.481649	-0.364143
O	1.155581	-1.454157	0.272387
C	2.413794	-1.619451	-0.368675
C	1.028709	0.898250	-0.212822
C	2.455593	0.856696	-0.766557
C	3.206989	-0.327908	-0.172080
H	0.240086	-0.729458	-1.423802
C	3.111719	-2.828066	0.221690
O	3.569667	-2.541330	1.544009
C	4.905452	-2.552772	1.756248
C	5.226919	-2.128298	3.157116
O	5.714014	-2.845848	0.908404
H	2.260685	-1.812585	-1.442682
O	4.462066	-0.461619	-0.826202
C	5.574665	-0.121922	-0.123551
C	6.805508	-0.373375	-0.939125
O	5.545169	0.296133	1.005754
H	3.360183	-0.161575	0.897203
H	2.400681	-3.654510	0.287466
H	3.955483	-3.111552	-0.408211

O	3.189676	2.019113	-0.394750
C	3.145515	3.086197	-1.221764
C	3.908013	4.235896	-0.637902
O	2.542375	3.090775	-2.267759
H	2.418989	0.779472	-1.859248
O	0.202101	1.777615	-0.972097
C	0.157503	3.078391	-0.592856
C	-0.685292	3.883400	-1.535046
H	1.035232	1.195295	0.840732
H	4.539455	-2.587902	3.868532
H	6.258165	-2.390206	3.387378
H	5.110096	-1.042069	3.211592
H	7.668629	0.058582	-0.436098
H	6.934752	-1.455415	-1.027463
H	6.692506	0.043536	-1.941496
H	3.308499	4.652004	0.177142
H	4.856719	3.895079	-0.220362
H	4.067404	4.995703	-1.400995
H	-1.084845	4.752929	-1.013692
H	-0.033494	4.220552	-2.347299
H	-1.487257	3.283013	-1.966252
H	-3.984459	1.538788	-1.118632
H	-5.704273	1.130043	-1.217264
O	0.753478	3.507861	0.362590
C	-5.187733	-3.842214	0.345364
C	-4.442677	-4.050036	-0.978454
C	-3.152018	-3.387692	-0.863523
C	-3.008914	-2.729168	0.380859
H	-5.524018	-4.807686	0.732130
H	-6.085167	-3.245662	0.153249
O	-4.880908	-4.671040	-1.932986
C	-2.222344	-3.204643	-1.912802
H	-2.445130	-3.687648	-2.880002
O	-1.217713	-2.480820	-1.792816
C	-4.423266	-0.515181	-0.646044
H	-4.299536	-0.852852	-1.682223
H	-5.256552	-1.082578	-0.218258
H	-3.205880	-0.609608	1.210540
H	-2.020981	-2.649911	0.833518
C	-4.184558	-3.137650	1.273777
H	-4.621466	-2.291013	1.809679
H	-3.800121	-3.827283	2.032154
O	-0.858320	-0.496365	0.299298
H	-1.830765	-0.269551	-1.505271

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<sup>14</sup> <https://github.com/bobbypaton/GoodVibes>

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<sup>16</sup> Note: TBS group was replaced with TMS group.