Supporting Information for
Water Overcomes Methyl Group Directing Effects in Epoxide-Opening Cascades

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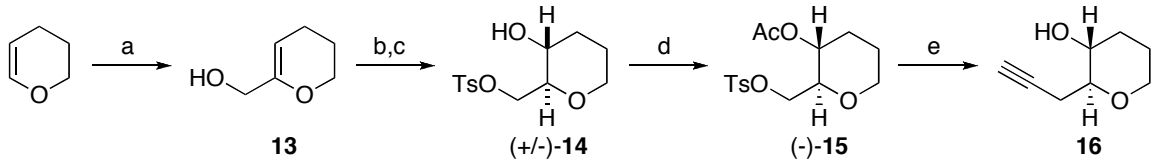
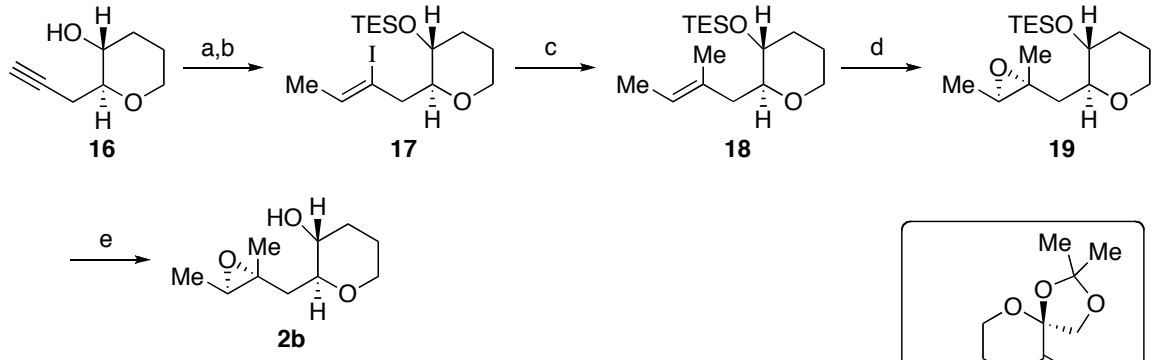
Schematic Summary of Synthetic Operations

Preparation of bishomopropargylic alcohol **16**:



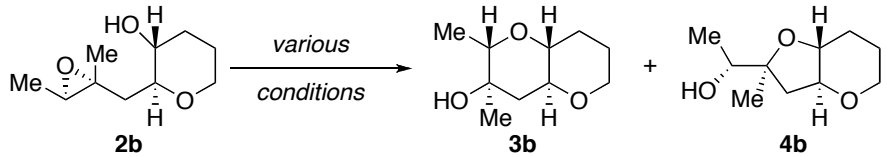
Reagents and conditions: (a) nBuLi, TMEDA; THF; $(CH_2O)_n$, **68%**; (b) BH_3•DMS, THF; TMANO•$2H_2O$; (c) TsCl, Et_3N, Me_3N•HCl, CH_2Cl_2, **27%** over 2 steps; (d) vinyl acetate, AMANO lipase PS-C I, hexanes/THF, **44%**; (e) LiCCH•EDA, THF/DMPU, **47%**.

Preparation of proximally Me-substituted epoxy alcohol alcohol **2b**:

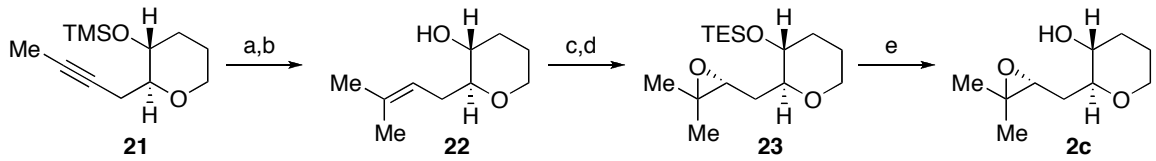


Reagents and conditions: (a) $TiCl_4$, $AlMe_3$, CH_2Cl_2; I_2; (b) TESCl, imid., DMF, **47%** over 2 steps; (c) Me_2Zn, $Pd(PPh_3)_4$, THF/PhMe, **85%**; (d) Shi asymmetric epoxidation[S1]: **20**, Oxone, nBu_4NHSO_4, K_2CO_3, $Na_2B_4O_7$ buffer, DMM/MeCN, **71%**, 2.8:1 dr; (e) TBAF, THF, **94%**.

Epoxide-opening cyclization reactions of proximally Me-substituted epoxy alcohol **2b**:

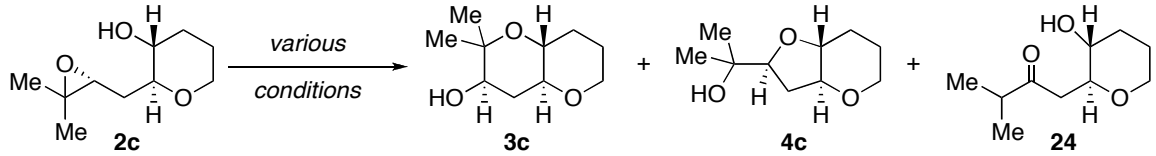


Preparation of distally Me-substituted epoxy alcohol alcohol **2c**:

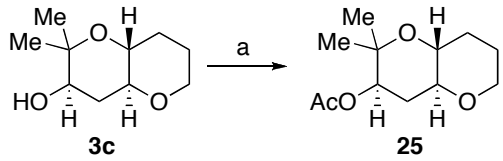


Reagents and conditions: (a) HCl, H_2O/THF; (b) $TiCl_4$, $AlMe_3$, CH_2Cl_2; MeOH, **67%** over 2 steps; (c) TESCl, imid., DMF, **74%**; (d) Shi asymmetric epoxidation[S1]: **20**, Oxone, nBu_4NHSO_4, K_2CO_3, $Na_2B_4O_7$ buffer, DMM/MeCN, **78%**, 5.8:1 dr; (e) TBAF, THF, **98%**.

Epoxide-opening cyclization reactions of distally Me-substituted epoxy alcohol **2c**:

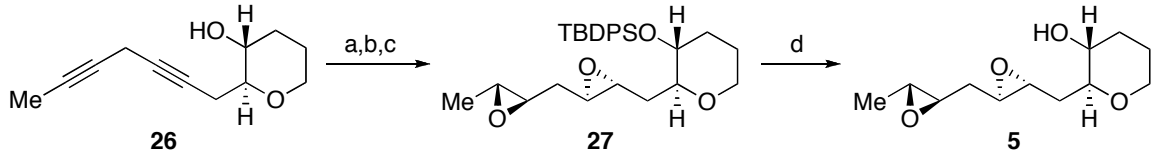


Acetylation of bis-THP diad **3c**:



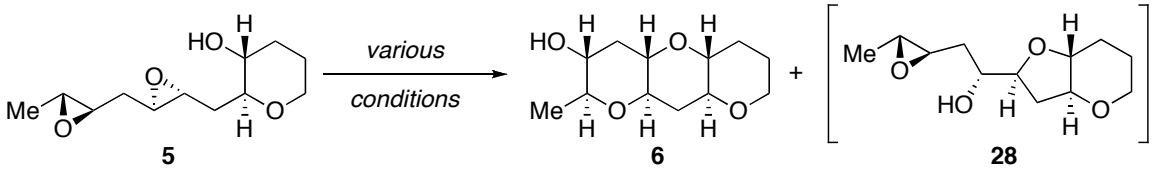
Reagents and conditions: (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, **87%**.

Preparation of diepoxy alcohol **5**:

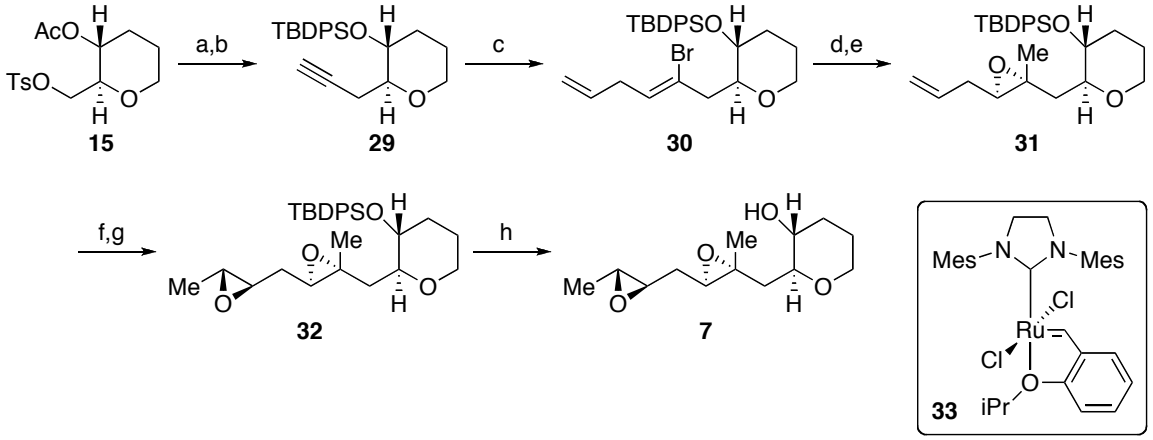


Reagents and conditions: (a) Li^0, NH_3, MeOH, THF; (b) TBDPSCl, imid., DMF; (c) Shi asymmetric epoxidation[S1]: **20**, Oxone, nBu_4NHSO_4, K_2CO_3, $Na_2B_4O_7$ buffer, DMM/MeCN, **28%** over 3 steps, 2.5:1 overall dr; (d) TBAF, THF, **99%**.

Epoxide-opening cyclization reactions of diepoxy alcohol **5**:

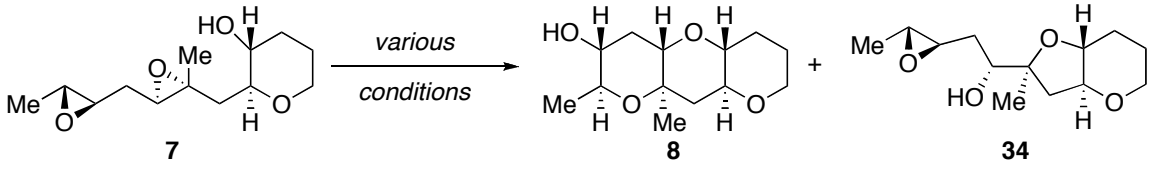


Preparation of diepoxy alcohol **7**:

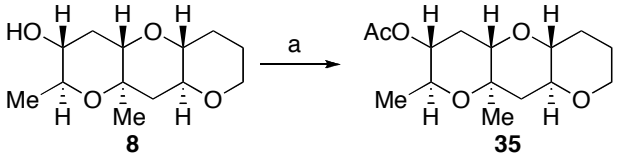


Reagents and conditions: (a) LiCCH•EDA, THF/DMPU; (b) TBDPSCl, imid., **51%** over 2 steps; (c) allyl bromide, $PdCl_2(PhCN)_2$, $NaHCO_3$, THF, **88%**; (d) Me_2Zn, $Pd(PPh_3)_4$, THF/PhMe; (e) Shi asymmetric epoxidation[S1]: **20**, Oxone, nBu_4NHSO_4, K_2CO_3, $Na_2B_4O_7$ buffer, DMM/MeCN, **48%** over 2 steps, 4:1 dr; (f) *cis*-2-butene, Grubbs-Hoveyda 2nd gen. catalyst **33**, CH_2Cl_2, 4.1:1 *E*/*Z*; (g) Shi asymmetric epoxidation[S1]: **20**, Oxone, nBu_4NHSO_4, K_2CO_3, $Na_2B_4O_7$ buffer, DMM/MeCN, **90%** over 2 steps, 2.7:1 overall dr; (h) TBAF, THF, **98%**.

Epoxide-opening cyclization reactions of diepoxy alcohol **7**:

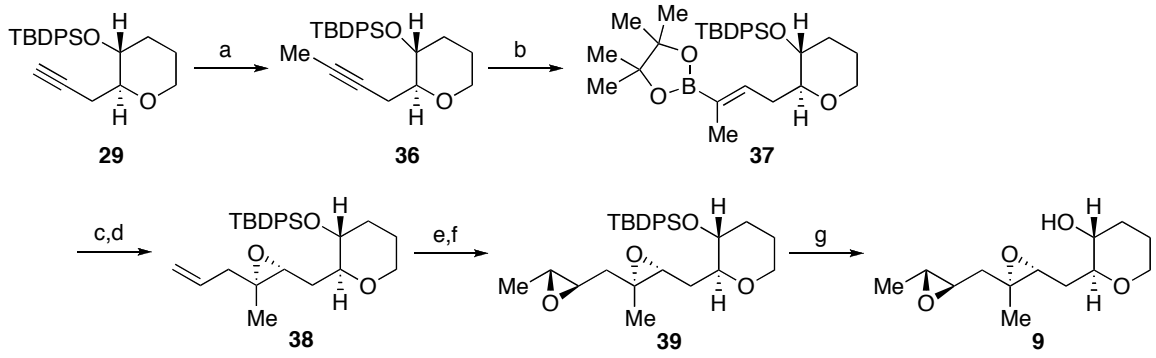


Acetylation of tris-THP diad **8**:



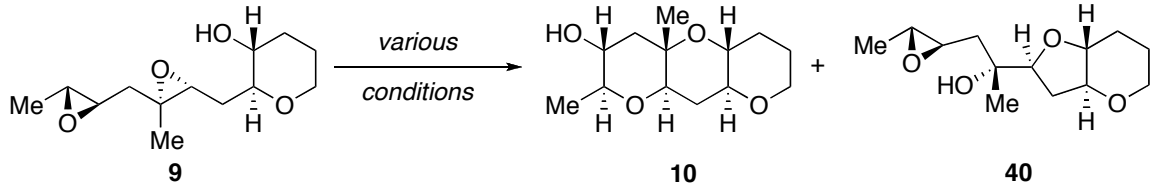
Reagents and conditions: (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, **83%**.

Preparation of diepoxy alcohol **9**:

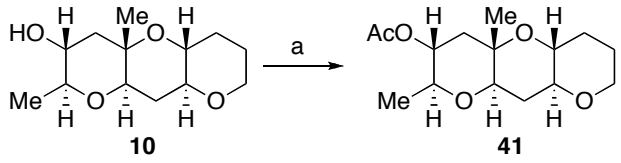


Reagents and conditions: (a) nBuLi, THF; MeI, **99%**; (b) HBpin, $Cp_2Zr(H)Cl$, Et_3N, **29%**; (c) allyl bromide, $PdCl_2(dppf)$, K_3PO_4, H_2O, THF; (d) Shi asymmetric epoxidation[S1]: **20**, Oxone, nBu_4NHSO_4, K_2CO_3, $Na_2B_4O_7$ buffer, DMM/MeCN, **53%** over 2 steps, 3:1 dr; (e) *cis*-2-butene, Grubbs-Hoveyda 2nd gen. catalyst **33**, CH_2Cl_2, 4.2:1 *E*/*Z*; (f) Shi asymmetric epoxidation[S1]: **20**, Oxone, nBu_4NHSO_4, K_2CO_3, $Na_2B_4O_7$ buffer, DMM/MeCN, **85%** over 2 steps, 1.5:1 overall dr; (g) TBAF, THF, **95%**.

Epoxide-opening cyclization reactions of diepoxy alcohol **9**:

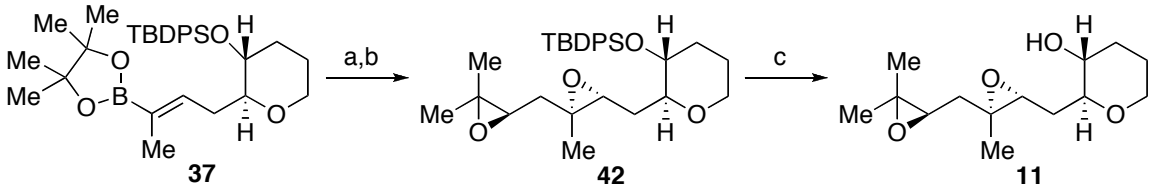


Acetylation of tris-THP diad **10**:



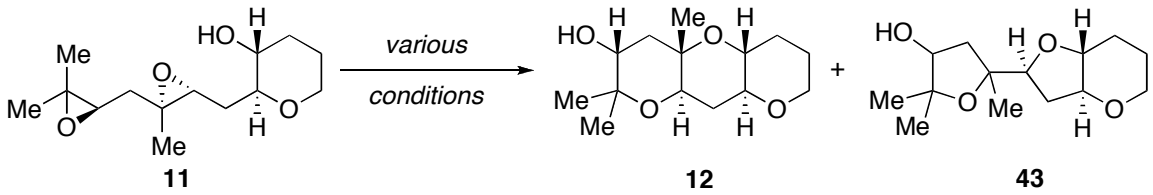
Reagents and conditions: (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, **92%**.

Preparation of diepoxy alcohol **11**:

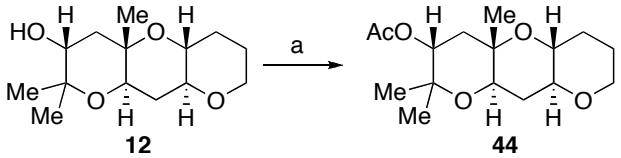


Reagents and conditions: (a) prenyl bromide, $PdCl_2$(dppf), K_3PO_4, H_2O, THF, **75%**, 2.5:1 S_N2:S_N2'; (b) Shi asymmetric epoxidation[S1]: **20**, Oxone, nBu_4NHSO_4, K_2CO_3, $Na_2B_4O_7$ buffer, DMM/MeCN, **65%**, 3.5:1 overall dr; (c) TBAF, THF, **92%**.

Epoxide-opening cyclization reactions of diepoxy alcohol **11**:



Acetylation of tris-THP diad **12**:



Reagents and conditions: (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, **88%**.

Experimental Section

General Information. Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon with rigid exclusion of moisture from reagents and glassware. Reactions were magnetically stirred unless otherwise stated. All temperatures are reported in °C.

Except were noted, dichloromethane was either distilled from calcium hydride or purified via an SG Water USA solvent column system. Except were noted, tetrahydrofuran (THF) and Et_2O were either distilled from a blue solution of benzophenone ketyl or purified via an SG Water USA solvent column system. Triethylamine was purified via an SG Water USA solvent column system. 1,3-Dimethyl-3,4,6,5-tetrahydro-2(1H)-pyrimidinone (DMPU) and tetramethylethylenediamine (TMEDA) were distilled from calcium hydride under argon. Reactions in water used deionized water without further purification. The pH of all aqueous buffers was checked within 24 hours of use.

Me_3N•HCl was pumped on under high vacuum for at least 15 minutes before use, to remove some water. Methyl iodide and allyl bromide were purified by filtration through basic alumina before use. Cs_2CO_3, NaI, and K_3PO_4 were oven-dried overnight before use. Chiral ketone **20**, used in Shi asymmetric epoxidation[S1a] was prepared from D-fructose according to the procedure of Vidal-Ferran and coworkers.[S1b]

All other reagents and solvents were used as obtained, without further purification.

Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F254 plates. The developed chromatogram was analyzed by UV lamp (254 nm) and ceric ammonium molybdate (CAM). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh). Analytical HPLC was performed on the column phase indicated on a Hewlett-Packard 1100 Series HPLC. Preparative HPLC was performed on the column phase indicated on an Agilent 1200 Series HPLC.

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise noted, on a Varian Inova-500 MHz spectrometer, a Bruker AVANCE-400 MHz spectrometer, or a Bruker AVANCE-600 MHz spectrometer. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual $CHCl_3$ in $CDCl_3$ (7.27 ppm), C_6HD_5 in C_6H_6 (7.15 ppm), or CH_2Cl_2 in CD_2Cl_2 (5.32 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and app = apparent), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.2 ppm), C_6D_6 (128.6 ppm), or CD_2Cl_2 (54.0 ppm) on the δ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 2000 FT-IR. High Resolution mass spectra (HR-MS) were obtained on a Bruker Daltonics APEXIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer by Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Optical rotations were measured on a Jasco Model 1010 polarimeter at 589 nm. An X-ray structure of **6** was collected on a Siemens three-circle Platform Diffractometer coupled to a Bruker-APEX CCD detector at the MIT Department of Chemistry X-Ray Diffraction Facility.

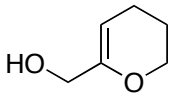
General Procedures for Cascade Reactions of 5, 7, 9, and 11.

Representative procedure for reaction in **water**:
A sample of diepoxy alcohol was dissolved in deionized water to 0.02 M in a 20 mL vial. The threads of the vial were lined with Teflon tape, the cap was sealed and covered with parafilm, and the solution was heated to 60° under air for 3 d. The solution was then cooled to rt and concentrated *in vacuo* (10 torr, 40°). The crude product mixture was chromatographed (30% EtOAc in hexanes or 50% EtOAc in hexanes, depending on product polarity, see individual procedures vide infra) to separate the desired tris-THP product (always the least polar and therefore the first off the column) from undesired cyclization products.

Representative procedure for reaction promoted by **Cs_2CO_3:**
A sample of diepoxy alcohol was dissolved in anhydrous MeOH to 0.02 M in a 20 mL vial. The threads of the vial were lined with Teflon tape, the cap was sealed and covered with parafilm, and the solution was stirred under air at rt for 3 d. The solution was then diluted with Et_2O, quenched with sat. NH_4Cl, and the aqueous layer was extracted with Et_2O. The combined organics were concentrated *in vacuo* without drying, and the crude product mixture was chromatographed (30% EtOAc in hexanes or 50% EtOAc in hexanes, depending on product polarity, see individual procedures vide infra) to separate the desired tris-THP product (always the least polar and therefore the first off the column) from undesired cyclization products.

Representative procedure for reaction promoted by **CSA:**
A sample of diepoxy alcohol was dissolved in CH_2Cl_2 to 0.02 M in an oven-dried round-bottom flask. To this was added (+/-)-CSA (1 equiv), and the solution was stirred under argon at rt for 4 h. The solution was then quenched with sat. $NaHCO_3$, and the aqueous layer was extracted with Et_2O. The combined organics were concentrated *in vacuo* without drying, and the crude product mixture was chromatographed (30% EtOAc in hexanes or 50% EtOAc in hexanes, depending on product polarity, see individual procedures vide infra) to separate the desired tris-THP product (always the least polar and therefore the first off the column) from undesired cyclization products.

Representative procedure for reaction promoted by **BF_3:**
A sample of diepoxy alcohol was dissolved in CH_2Cl_2 to 0.02 M in an oven-dried round-bottom flask and cooled to -78°. To this was added, dropwise, a 0.1 M solution of BF_3•OEt_2 in CH_2Cl_2 (0.25 equiv), and the solution was stirred at -78° under argon for 30 min. The solution was then allowed to warm gradually to rt over 5 min. and quenched with sat. $NaHCO_3$. The aqueous layer was extracted with Et_2O, and the combined organics were concentrated *in vacuo* without drying. The crude product mixture was chromatographed (30% EtOAc in hexanes or 50% EtOAc in hexanes, depending on product polarity, see individual procedures vide infra) to separate the desired tris-THP product (always the least polar and therefore the first off the column) from undesired cyclization products.



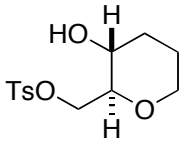
13

Allylic alcohol 13: Allylic alcohol **13** was prepared according to a procedure modified from that developed by Lebouc, Delaunay, and Riobé.[S2] 3,4-Dihydro-2H-pyran (120 mL, 112 g, 1.32 mol) was added to a 2 L round-bottom flask, followed by TMEDA (138 mL, 107 g, 0.92 mol). We have found that the reaction works even with undistilled TMEDA directly from the bottle, although yields are approximately 5% higher with TMEDA freshly distilled from CaH_2. After cooling to 0°, a 2.5 M solution of *n*BuLi in hexane (370 mL, 0.92 mol) was added slowly, over 15 min. Over the course of addition, the clear, pale yellow solution became cloudier as white solid precipitated, and the color evolved through darker yellow to orange. The reaction was stirred 45 minutes more at 0°, over which time the solution turned a vivid, opaque orange. The reaction was then warmed to room temperature and stirred 20 h. Dry THF (600 mL) was then added, at which point the solution turned red-brown. After cooling again to 0°, paraformaldehyde ($(CH_2O)_n$) (90 g, 2.96 mol) was added slowly, portionwise, with vigorous stirring, beginning with ~1 g, then ~2 g, then ~4 g, etc., pausing approximately 5 minutes between additions to prevent exotherm. After the addition of paraformaldehyde was complete, the reaction was allowed to warm gradually to room temperature over 20 h., at which point the solution had become a milky, opaque, pale yellow. The reaction was quenched slowly, at room temperature, with sat. NH_4Cl (200 mL) and stirred 15 minutes. The mixture was then diluted with 500 mL of Et_2O. The organic layer was separated, poured over an aqueous solution of $CuSO_4 \cdot 5H_2O$ (250 g in 700 mL H_2O), and stirred vigorously for 30 minutes. The organic layer was then decanted off, washed with sat. $NaHCO_3$ (3 x 50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by vacuum distillation (5 torr, bp = 65-71°), and **13** was collected as a clear, colorless oil with an aromatic, woodsy aroma (72 g, 630 mmol, 68%). Allylic alcohol **13** appears unstable to $CDCl_3$ (Cambridge Isotope Laboratories), even after treatment of $CDCl_3$ with K_2CO_3. It is therefore recommended that NMR spectra be recorded in C_6D_6 or another solvent. R_f = 0.61 (50% EtOAc in hexanes). Spectral data was consistent with the sample prepared by Riobé and coworkers. [S2]

IR (thin film, NaCl) 3412, 2934, 2874, 1678, 1449, 1239, 1089, 1063, 1025, 893, cm^{-1}

^1H NMR (400 MHz, C_6D_6) δ 4.74 (t, J = 3.8 Hz, 1H), 4.00-3.94 (broad s, 3H), 3.76 (app t, J = 5.1 Hz, 2 H), 1.78 (app q, J = 6.4, 4.0 Hz, 2 H), 1.47 (app quintet, J = 5.2 Hz, 4.4 Hz, 2 H); ^{13}C NMR (100 MHz, C_6D_6) δ 154.7, 97.1, 66.7, 63.6, 23.3, 20.8.

HR-MS (ESI) *m/z* calcd for $C_6H_{11}O_2$ $(M+Na)^+$: 137.0573, found 137.0579.



14

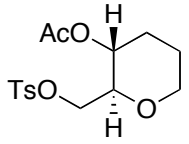
Tosylate 14: To a stirred solution of allylic alcohol **13** (51.4 g, 450 mmol) in THF (1100 mL, used directly from the bottle, without drying) maintained at 0° was added neat BH_3•DMS (135 mL, 1350 mmol) gradually, over 20 min. The reaction was stirred 1.5 h. at 0° and then warmed to room temperature for 30 min. After recooling to 0°, trimethylamine *N*-oxide dihydrate (TMANO•$2H_2O$)[S3] (130 g, 1170 mmol) was added slowly, portionwise, with vigorous stirring, beginning with ~3-5 g portions, pausing approximately 5 minutes between additions to prevent exotherm. The reaction was heated to vigorous reflux for 5 h.; over this period white solid clumped along the sides of the flask. The reaction was vacuum filtered while hot to remove all solids; these solids were washed with acetone (4 x 100 mL), and the combined acetone washes and reaction solution were concentrated *in vacuo*. The crude 1,3-diol was used without further purification (R_f = 0.23 in 100% EtOAc).

To a solution of crude diol in CH_2Cl_2 (500 mL, used directly from the bottle, without drying) was added Et_3N (115 g, 158 mL, 1125 mmol). After cooling to 0°, TsCl (44g, 230 mmol) and Me_3N•HCl[S4] (4.3 g, 45 mmol) were added. The solution was maintained at 0° for 1 h., at which point TLC analysis (50% EtOAc in hexanes) implied that conversion was approx. 40-50%, with evidence of a trace of ditosylation (R_f of 1,3-diol starting material = 0.07, R_f of tosylate **14** = 0.35, R_f of ditosylate = 0.62). Further TsCl (15 g, 79 mmol) was added and the reaction was maintained at 0° for 1 h. TLC analysis implied conversion of approx. 60-70%. Further TsCl (10 g, 53 mmol) was added and the reaction was maintained at 0° for 1 h. TLC analysis implied conversion of approx. 75-90%. At this point, TLC should show the 1,3-diol starting material more strongly than distosylate; larger quantities of ditosylate complicate purification. The reaction was quenched at 0° with sat. NH_4Cl (150 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 x 150 mL). The combined organics were washed with sat. NaCl (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Crude **14**, a foul-odored, thin yellow-brown oil, was purified by column chromatography (gradient 30% to 50% to 100% EtOAc in hexanes) to yield tosylate **14** as an odorless, heavy, pale yellow oil that crystallized on standing (35 g, 122 mmol, 27% over 2 steps): R_f = 0.35 (50% EtOAc in hexanes). Spectral data were consistent with that reported for an enantioenriched sample prepared by Delgado and Martin.[S5]

IR (KBr pellet) 3532, 3376, 3058, 2948, 2856, 1599, 1342, 1178, 1099, 961, 931 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.34 (dd, *J* = 11.0, 4.5 Hz, 1H), 4.21 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.91-3.87 (m, 1H), 3.60-3.53 (m, 1H), 3.33-3.27 (m, 1H), 3.22 (ddd, *J* = 9.3, 4.5, 2.0 Hz, 1H), 2.45 (s, 3H), 2.27 (d, *J* = 5.5 Hz, 1H), 2.17-2.11 (m, 1H), 1.68-1.63 (m, 2H), 1.47-1.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 132.9, 130.0, 128.1, 80.3, 70.1, 68.0, 65.9, 32.5, 25.3, 21.8.

HR-MS (ESI) *m/z* calcd for $C_{13}H_{18}O_5S$ $(M+Na)^+$: 309.0767, found 309.0777.



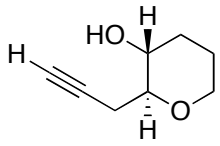
15

Acetate 15: To a vigorously stirred solution of alcohol **14** (32 g, 112 mmol) in vinyl acetate (48 g, 51 mL, 560 mmol) was added 100 mL of a 3:1 v/v hexanes:THF solution (both directly from the bottle, without drying), followed by Amano lipase PS-C I[S6] (immobilized on ceramic, Aldrich catalog #534897) (4.8 g). After having stirred 7 h. at room temperature, the solid beads were filtered off[S7] and the filtrate concentrated *in vacuo*. Acetate **15** was separated from **14** via column chromatography (gradient 25% to 30% to 50% to 100% EtOAc in hexanes) to yield enantioenriched acetate **15** as a heavy, pale yellow oil that crystallized on standing (16.2 g, 49 mmol, 44%): R_f = 0.67 (50% EtOAc in hexanes); $[\alpha]^{22}_D$ = -42.9 (*c* = 8.4, $CHCl_3$). The enantiomeric excess of **15** was determined to be >95% by chiral analytical HPLC analysis (Chiracel OD-H; 12% *i*PrOH in hexanes, 1.30 mL/min; t_R(major) = 12.10 min., t_R(minor) = 13.36 min.).

IR (KBr pellet) 3053, 2978, 2954, 2851, 1733, 1597, 1459, 1360, 1246, 1176, 1062, 1045, 973 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 4.58 (ddd, *J* = 10.8, 9.8, 4.8 Hz, 1H), 4.14 (dd, *J* = 10.7, 2.4 Hz, 1H), 4.06 (dd, *J* = 10.7, 5.6 Hz, 1H), 3.93-3.88 (m, 1H), 3.49 (ddd, *J* = 9.8, 5.6, 2.4 Hz, 1H), 3.33 (app td, *J* = 11.6, 2.9 Hz, 1H), 2.45 (s, 3H), 2.26-2.20 (m, 1H), 2.00 (s, 3H), 1.76-1.62 (m, 2H), 1.47-1.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 145.0, 132.9, 129.9, 128.2, 76.9, 69.1, 68.1, 68.0, 29.2, 24.8, 21.8, 21.1.

HR-MS (ESI) *m/z* calcd for $C_{15}H_{20}O_6S$ $(M+Na)^+$: 351.0873, found 351.0873.

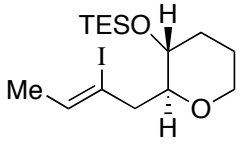


16

Alkyne 16: This compound has been synthesized in racemic form by Bowman and McDonald[S8a] and in antipodal form by Nakata and coworkers.[S8b,c] Our group previously reported a longer but higher-yielding synthesis of the desired (2*S*,3*R*) enantiomer.[S8d]
To a flame-dried flask containing fresh lithium acetylide-ethylenediamine complex (10 g,

109 mmol) was added dry THF (210 mL) and freshly distilled DMPU (25 mL) to afford a dusty gray-brown slurry.[S9] After cooling to 0°, to this solution was added slowly tosylate **15** (5.9 g, 18.1 mmol), over 5 minutes, as a solution in 30 mL DMPU. Any remaining **15** was dissolved with a further 10 mL THF and added via syringe. After stirring 1 h. at 0°, the reaction was warmed to room temperature for 34 h. Over time, the solution developed a bright cherry red color, which matured into a rich burgundy red color. Upon recooling to 0°, the reaction was quenched with H_2O (150 mL). The aqueous layer was extracted with Et_2O (3 x 100 mL), and the combined organics were washed with sat. NaCl (100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (gradient 20% to 40% EtOAc in hexanes) to remove most DMPU and afford bishomopropargylic alcohol **16** as a pale orange oil (1.20 g, 8.6 mmol, 47%): R_f of **16** = 0.55 (50% EtOAc in hexanes); $[\alpha]^{22}_D$ = -16.8 (*c* = 1.9, $CDCl_3$).
Residual DMPU may be removed by further aqueous washes, but **16** is moderately water soluble, and isolated yield will therefore be reduced. Prior to chromatography, crude **16** can be protected as a silyl ether without purification away from DMPU. Residual DMPU promotes silylation, and purification of the much less polar silyl ether is straightforward, resulting in improved yield over this 2-step process; see the synthesis of **29**, vide infra.

Spectral data for **16** were consistent with that reported by Bowman and McDonald.[S8a]



17

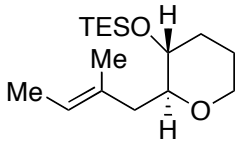
Alkenyl iodide 17: To a solution of bishomopropargylic alcohol **16** (265 mg, 1.89 mmol) in CH_2Cl_2 (20 mL) at -78° was added slowly a 2 M solution of $AlMe_3$ in hexanes (2.08 mL, 4.16 mmol).[S10] This solution was warmed for 3 min. by removing the flask from its cold bath to ensure complete deprotonation. After recooling to -78°, a 1 M solution of $TiCl_4$ in CH_2Cl_2 (2.08 mL, 2.08 mmol) was added dropwise, during which time the solution turned maroon, then a deep red. The solution was stirred 2 h. at -78° and then quenched with a solution of I_2 (2.4 g, 9.45 mmol) in Et_2O (20 mL). The reaction flask was then wrapped in foil and allowed to warm to room temperature for 10 h., at which point H_2O (2 mL) was added. The quenched reaction solution was diluted with Et_2O (100 mL) and washed with aqueous 3 M $NaHSO_3$ (40 mL) until the organic layer was colorless. The aqueous layer was extracted with Et_2O (3 x 40 mL), and the combined organics were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo.* The crude alkenyl iodide was carried forward without purification; R_f = 0.72 (50% EtOAc in hexanes), UV active.
Upon dissolution of this crude alkenyl iodide in DMF (1 mL), imidazole (322 mg, 4.73 mmol) and TESCl (380 μL, 342 mg, 2.27 mmol) were added, and the solution was stirred 2 h. at room temperature. The reaction was applied directly to column of SiO_2 and

chromatographed (2% EtOAc in hexanes) to afford protected alkenyl iodide **17** (310 mg, 0.78 mmol, 41% over 2 steps), which was isolated along with some silylated bishomopropargylic alcohol (43 mg, 0.17 mmol). R_f of **17** = 0.60 (10% EtOAc in hexanes), UV active; $[\alpha]^{22}_D$ = -19.2 (*c* = 4.0, $CHCl_3$).

IR (thin film, NaCl) 2955, 2876, 1461, 1415, 1274, 1239, 1127, 1102, 1004 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 5.64 (app qt, *J* = 6.3, 0.7 Hz, 1H), 3.90-3.85 (m, 1H), 3.39-3.28 (m, 3H), 3.04 (app d, *J* = 14.8 Hz, 1H), 2.41 (dd, *J* = 14.8, 9.1 Hz, 1H), 2.02 (m, 1H), 1.75 (d, *J* = 6.3 Hz, 3H), 1.68-1.62 (m, 2H), 1.54-1.44 (m, 1H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.59 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.5, 107.3, 81.3, 70.8, 68.1, 47.8, 33.8, 25.8, 22.5, 7.1, 5.3.

HR-MS (ESI) *m/z* calcd for $C_{15}H_{29}IO_2Si$ $(M+Na)^+$: 419.0874, found 419.0893.



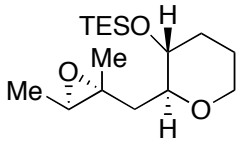
18

Trisubstituted alkene 18: To a sealed tube charged with $Pd(PPh_3)_4$ (60 mg, 0.045 mmol) was added 5 mL THF to provide a clear lemon yellow solution. Upon cooling to 0°, alkenyl iodide **17** (410 mg, 1.03 mmol) was added as a solution in THF (2 mL), followed immediately by a 2.0 M solution of Me_2Zn in PhMe (1.55 mL, 3.10 mmol) to provide a paler yellow solution. The tube was sealed and the temperature was maintained at 0° for 1 h. and then warmed to room temperature for 12 h. The reaction was diluted with Et_2O (10 mL) and quenched by pouring slowly over 10 mL H_2O. The aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organics were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to give an orange-brown crude oil. This crude product was purified by column chromatography (gradient 1% to 2.5% to 10% EtOAc in hexanes) to afford **18** as a colorless oil (250 mg, 0.88 mmol, 85%): R_f = 0.66 (10% EtOAc in hexanes); $[\alpha]^{22}_D$ = -17.8 (*c* = 0.38, $CDCl_3$).

IR (thin film, NaCl) 2952, 2924, 2876, 1460, 1127, 1098, 1017 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 5.29 (app q, *J* = 6.7 Hz, 1H), 3.91-3.87 (m, 1H), 3.32-3.26 (m, 2H), 3.19 (ddd, *J* = 10.4, 8.7, 2.2, 1H), 2.62 (app d, *J* = 14.3 Hz, 1H), 2.04-1.99 (m, 1H), 1.95 (dd, *J* = 14.4, 10.1, 1H), 1.72-1.58 (m, 8H), 1.51-1.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.6, 120.4, 81.2, 71.7, 68.0, 42.7, 33.9, 25.9, 15.8, 13.8, 7.1, 5.3.

HR-MS (ESI) *m/z* calcd for $C_{16}H_{32}O_2Si$ $(M+Na)^+$: 307.2064, found 307.2067.



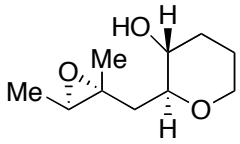
19

Epoxide 19: To a solution of alkene **19** (224 mg, 0.79 mmol) in 2:1 v/v DMM:MeCN (25.7 mL) was added a 0.05 M solution of $Na_2B_4O_7 \bullet 10H_2O$ in 4 x 10^{-4} Na_2EDTA (16.6 mL), $n Bu_4HSO_4$ (54 mg, 0.16 mmol), and chiral ketone **20** (405 mg, 1.57 mmol). This biphasic mixture was stirred vigorously at 0°. To this mixture was added, simultaneously over 30 min. via syringe pump, a solution of Oxone (1.94 g, 3.16 mmol) in 4 x 10^{-4} Na_2EDTA (13.1 mL) and a 0.89 M solution of K_2CO_3 (13.1 mL, 11.7 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 25 min., at which point it was diluted with EtOAc (40 mL). The aqueous layer was extracted with EtOAc (3 x 40 mL), and the combined organics were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to provide **19** in a 2.8:1 diastereomeric mixture. The desired diastereomer (R_f = 0.55, 20% EtOAc in hexanes) was separated from the undesired diastereomer (R_f = 0.59, 20% EtOAc in hexanes) and ketone catalyst **20** by patient column chromatography (gradient 2% to 3% to 5% EtOAc in hexanes) to afford **19** in >15:1 dr as a colorless oil (159 mg, 0.53 mmol, 67%): R_f = 0.55 (20% EtOAc in hexanes); $[\alpha]^{22}_D$ = -37.8 (*c* = 0.45, $CDCl_3$).

IR (thin film, NaCl) 2956, 2877, 1458, 1127, 1099, 1009 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 3.91-3.86 (m, 1H), 3.34-3.23 (m, 2H), 3.12 (app td, *J* = 8.9, 1.7 Hz, 1H), 2.89 (q, *J* = 5.5 Hz, 1H), 2.09 (dd, *J* = 14.6, 1.6 Hz, 1H), 2.04-1.98 (m, 1H), 1.72-1.61 (m, 2H), 1.57 (dd, *J* = 14.6, 9.9 Hz, 1H), 1.49-1.36 (m, 1H), 1.30 (s, 3H), 1.29 (d, *J* = 5.5 Hz, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.59 (q, *J* = 8.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 80.4, 71.1, 67.7, 59.8, 58.2, 40.6, 33.8, 25.8, 17.6, 14.3, 7.1, 5.3.

HR-MS (ESI) *m/z* calcd for $C_{16}H_{32}O_3Si$ $(M+Na)^+$: 323.2013, found 323.2010.



2b

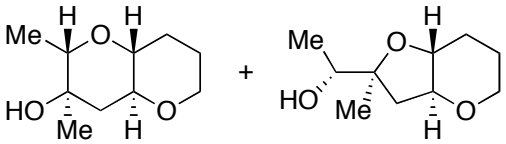
Epoxy alcohol 2b: To a solution of TES-protected epoxy alcohol **19** (17.5 mg, 0.058 mmol, in >20:1 dr) in THF (1.0 mL) cooled to 0° was added a 1 M THF solution of TBAF (70 μL, 0.070 mmol). The reaction was stirred for 20 min. at 0°. While still cold,

the crude product in THF was applied directly to a SiO_2 column (SiO_2 packed in 2% Et_3N dissolved in 20% EtOAc in hexanes, run with a gradient from 2% Et_3N dissolved in 20% EtOAc in hexanes to 50% EtOAc in hexanes) and concentrated *in vacuo* to afford epoxy alcohol **2b** as a colorless oil (9.8 mg, 0.053 mmol, 90%): R_f = 0.54 (100% EtOAc); $[\alpha]^{22}_D$ = -9.7 (*c* = 0.20, $CDCl_3$). This material is highly sensitive to acid. Exposure to even traces of acid will induce cyclization. We found it essential to neutralize $CDCl_3$ with K_2CO_3 before collecting NMR data. **2b** cyclizes very slowly on standing at -4° in aprotic organic solvents (CH_2Cl_2 or EtOAc/hexanes) and somewhat faster on standing at -4° as a neat oil. For extended periods, **2b** is best stored frozen in benzene at -4°.

IR (thin film, NaCl) 3417, 2926, 2851, 1723, 1462, 1381, 1274, 1096 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 3.94-3.88 (m, 1H), 3.48 (app td, *J* = 9.9, 4.1 Hz, 1H), 3.34-3.27 (m, 1H), 3.13 (ddd, *J* = 9.3, 6.8, 2.8 Hz, 1H), 2.96 (q, *J* = 5.5 Hz, 1H), 2.61 (broad s, 1H), 2.20-2.09 (m, 2H), 1.77-1.65 (m, 3H), 1.45-1.33 (m, 4H), 1.31 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.5, 69.8, 68.1, 60.1, 59.0, 40.5, 32.6, 26.0, 17.6, 14.0.

HR-MS (ESI) *m/z* calcd for $C_{10}H_{18}O_3$ $(M+Na)^+$: 209.1148, found 209.1153.



3b **4b**

2b cyclization products 3b and 4b:

Representative procedure for reaction in **<u>aqueous media</u>:**

Epoxy alcohol **2b** (1 mg, 0.0054 mmol) was dissolved either in deionized water (270 μL) or 1 M solution of potassium phosphate buffer in deionized water (270 μL) and stirred at rt under air for 3 d. At this point the crude product mixture was extracted with EtOAc (5x2 mL) and concentrated *in vacuo* without drying. The crude product mixture was analyzed by ^1H NMR spectroscopy to determine the ratio of **3b** to **4b**. For reactions in deionized water, **3b**:**4b** was found to be 4.9:1 (average of 6 experiments).

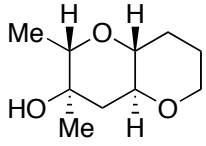
Table S1. Dependence of Regioselectivity on pH in Reactions of **2b**		
entry	pH (1 M KP_i buffer)	**3b**:**4b** observed
1	1.8	0.11:1
2	3.9	0.14:1
3	6.0	0.51:1
4	7.0	1.9:1
5	7.2	2.0:1
6	7.2	1.9:1

7	8.0	4.3:1
8	8.0	4.4:1
9	8.5	5.3:1
10	9.0	3.4:1
11	9.4	5.9:1
12	9.5	5.8:1
13	10.0	4.3:1
14	10.7	3.0:1
15	11.0	4.0:1
16	11.8	2.3:1
17	12.0	3.6:1
18	12.5	2.1:1
19	12.5	2.9:1

Procedure for reaction under **Cs_2CO_3 promotion:**
To a solution of epoxy alcohol **2b** (1 mg, 0.0054 mmol) in MeOH (270 μL) was added Cs_2CO_3 (53 mg, 0.16 mmol) and stirred at rt under air for 3 d. At this point the crude product mixture was diluted with deionized water (500 μL), extracted with EtOAc (5x2 mL) and concentrated *in vacuo* without drying. The crude product mixture was analyzed by ^{1}H NMR spectroscopy to determine the ratio of **3b** to **4b** to be 3.0:1.

Procedure for reaction under **CSA promotion:**
To a solution of epoxy alcohol **2b** (1 mg, 0.0054 mmol) in CH_2Cl_2 (270 μL) was added (+/-)-CSA (1.3 mg, 0.0056 mmol) and stirred at rt under argon for 4 h. At this point the crude product mixture was diluted with CH_2Cl_2 (2 mL) and washed with sat. $NaHCO_3$ (500 μL). The aqueous layer was extracted with CH_2Cl_2 (5x2 mL) and concentrated *in vacuo* without drying. The crude product mixture was analyzed by ^{1}H NMR spectroscopy to determine the ratio of **3b** to **4b** to be 1:5.2.

Procedure for reaction under **BF_3 promotion:**
To a solution of epoxy alcohol **2b** (1 mg, 0.0054 mmol) in CH_2Cl_2 (270 μL) cooled to -78° was added, dropwise, a stock solution of 0.1 M BF_3•OEt_2 in CH_2Cl_2 (14 μL, 0.0014 mmol) and stirred at -78° under argon for 30 min. At this point the reaction was allowed to warm gradually to rt over 5 min., diluted with CH_2Cl_2 (2 mL), and quenched with sat. $NaHCO_3$ (500 μL). The aqueous layer was extracted with CH_2Cl_2 (5x2 mL) and concentrated *in vacuo* without drying. The crude product mixture was analyzed by ^{1}H NMR spectroscopy to determine the ratio of **3b** to **4b** to be 1:11.



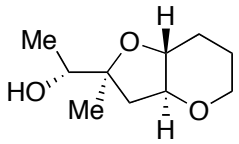
3b

bis-THP 3b: The connectivity of **3b** was confirmed by gCOSY (see p. S55-56).
R_f = 0.55 (100% EtOAc); $[\alpha]^{22}_D$ = -12.7 (*c* = 0.87, $CDCl_3$).

IR (thin film, NaCl) 3434, 2941, 2867, 1717, 1457, 1377, 1354, 1286, 1106, 1077, 1031, 964, 943 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 3.94-3.88 (m, 1H), 3.41-3.34 (m, 2H), 3.07-2.97 (m, 2H), 2.12 (dd, *J* = 11.5, 4.2 Hz, 1H), 2.10-2.04 (m, 1H), 1.75-1.68 (m, 2H), 1.57 (app t, *J* = 11.3 Hz, 1H), 1.50-1.41 (m, 2H), 1.23 (s, 3H), 1.18 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.5, 78.9, 77.2, 71.5, 68.1, 45.9, 29.6, 25.8, 21.3, 14.4.

HR-MS (ESI) *m/z* calcd for $C_{10}H_{18}O_3$ $(M+Na)^+$: 209.1148, found 209.1157.



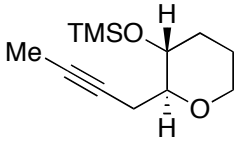
4b

6,5-fused 4b: R_f = 0.45 (100% EtOAc); $[\alpha]^{22}_D$ = -29.0 (*c* = 0.03, $CDCl_3$).

IR (thin film, NaCl) 3436, 2923, 2850, 1728, 1463, 1377, 1261, 1126, 1068 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$) δ 4.00 (app dd, *J* = 11.6, 4.8 Hz, 1H), 3.77 (qd, *J* = 6.5, 3.0 Hz, 1H), 3.48 (app td, *J* = 11.9, 3.1 Hz, 1H), 3.37 (ddd, *J* = 11.1, 9.1, 3.8 Hz, 1H), 3.31 (ddd, *J* = 11.1, 9.0, 6.3 Hz, 1H), 2.24-2.20 (m, 1H), 2.16 (app t, *J* = 11.0 Hz, 1H), 1.82 (dd, *J* = 11.1, 6.3 Hz, 1H), 1.74-1.61 (m, 2H), 1.56-1.48 (m, 1H), 1.22 (s, 3H), 1.15 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.7, 81.0, 80.0, 73.6, 69.0, 35.1, 30.4, 25.7, 24.8, 17.7.

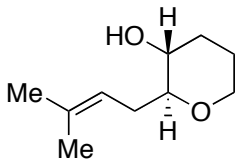
HR-MS (ESI) *m/z* calcd for $C_{10}H_{18}O_3$ $(M+Na)^+$: 209.1154, found 209.1153.



21

Internal alkyne 21: This compound was prepared via a previously published 2-step

procedure from **16**.[S11]



22

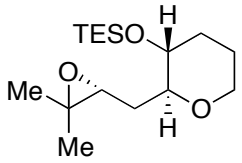
Trisubstituted alkene 22: To a solution of TMS ether **21** (207 mg, 0.92 mmol) in THF (9 mL) was added a 1 M aqueous solution of HCl (7 mL, 7 mmol). The mixture was stirred at room temperature for 15 min., diluted with Et_2O (30 mL), and then quenched with sat. $NaHCO_3$ (15 mL). The aqueous layer was extracted with Et_2O (3 x 25 ml), and the combined organics were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo*. The crude free alcohol (R_f = 0.56 in 50% EtOAc in hexanes) was pumped on under high vacuum for 2 h. to remove residual TMSOH and then carried forward without further purification.

To a solution of this crude bishomopropargylic alcohol in CH_2Cl_2 (10 mL) at 0° was added slowly a 2 M solution of $AlMe_3$ in hexanes (0.96 mL, 1.93 mmol).[S10] This solution was stirred for 3 min. and then recooled to -78°. A 1 M solution of $TiCl_4$ in CH_2Cl_2 (0.96 mL, 0.96 mmol) was added dropwise, during which time the solution turned maroon, then a deep red. The solution was stirred 2 h. at -78° and then quenched with cold MeOH (1 mL), upon which the solution turned pale yellow. The solution was diluted with Et_2O (10 mL) and washed with a saturated solution of Rochelle's salt (10 mL). The aqueous layer was extracted with Et_2O (3 x 20 ml), dried over $MgSO_4$, and concentrated *in vacuo*, and this crude product was purified by column chromatography (25% EtOAc in hexanes) to afford trisubstituted alkene **22** as a colorless oil (105 mg, 0.62 mmol, 67% over 2 steps): R_f = 0.38 (30% EtOAc in hexanes); $[\alpha]^{22}_D$ = -19.4 (*c* = 1.2, $CDCl_3$). Some unreacted bishomopropargylic alcohol (16 mg, 0.10 mmol, 12%) was also recovered.

IR (thin film, NaCl) 3412, 2928, 2855, 1451, 1376, 1340, 1277, 1095, 1036, 944 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 5.29 (app t, *J* = 7.0 Hz, 1H), 3.94-3.89 (m, 1H), 3.42-3.30 (m, 2H), 3.08 (ddd, *J* = 8.7, 7.2, 4.5 Hz, 1H), 2.52 (app dt, *J* = 15.0, 5.8 Hz, 1H), 2.24 (app dt, *J* = 15.0, 7.0 Hz, 1H), 2.10 (m, 1H), 1.73 (s, 3H), 1.72-1.64 (m, 5H), 1.40 (dddd, *J* = 17.4, 11.3, 6.3, 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 120.5, 82.4, 70.9, 67.9, 32.8, 31.6, 26.1, 25.7, 18.2.

HR-MS (ESI) *m/z* calcd for $C_{10}H_{18}O_2$ $(M+Na)^+$: 193.1199, found 193.1194.



23

Epoxide 23: Upon dissolution of bishomoallylic alcohol **22** in DMF (1 mL), imidazole (105 mg, 1.54 mmol) and TESCl (130 μL, 116 mg, 0.77 mmol) were added, and the solution was stirred 6 h. at room temperature. The reaction was applied directly to a plug of SiO_2 and quickly flushed (3% EtOAc in hexanes) to afford the bishomopropargylic silyl ether (128 mg, 0.45 mmol, 74%), which was carried forward without further purification.

To a solution of this protected bishomopropargylic silyl ether (125 mg, 0.45 mmol) in 2:1 v/v DMM:MeCN (14.7 mL) was added a 0.05 M solution of $Na_2B_4O_7 \bullet 10H_2O$ in 4 x 10^{-4} Na_2EDTA (9.5 mL), $n$$Bu_4HSO_4$ (31 mg, 0.09 mmol), and chiral ketone **20** (232 mg, 0.91 mmol). This biphasic mixture was stirred vigorously at 0°. To this mixture was added, simultaneously over 30 min. via syringe pump, a solution of Oxone (1.12 g, 1.82 mmol) in 4 x 10^{-4} Na_2EDTA (7.5 mL) and a 0.89 M solution of K_2CO_3 (7.5 mL, 6.7 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 25 min., at which point it was diluted with EtOAc (25 mL). The aqueous layer was extracted with EtOAc (3 x 25 mL), and the combined organics were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to provide a 5.8:1 diastereomeric mixture of epoxides. The desired epoxide diastereomer was inseparable from the undesired, but the combined epoxide diastereomers were separated from ketone catalyst **23** by column chromatography (5% EtOAc in hexanes) to afford epoxide **23** in 5.8:1 dr as a colorless oil (110 mg, 0.37 mmol, 73% combined): R_f = 0.66 (20% EtOAc in hexanes).

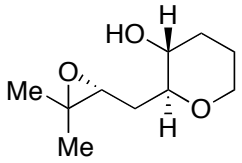
All characterization was obtained on this 5.8:1 mixture of diastereomers: $[\alpha]^{22}_D$ = -44.6 (c = 2.85, $CDCl_3$).

IR (thin film, NaCl) 2956, 2877, 1458, 1377, 1240, 1099, 1016 cm^{-1}

Tabulated ^1H and ^{13}C NMR shifts and coupling constants are reported for the major diastereomer:

^1H NMR (500 MHz, $CDCl_3$) δ 3.93-3.87 (m, 1H), 3.38-3.29 (m, 2H), 3.14 (app td, J = 8.9, 2.7 Hz, 1H), 2.94 (app t, J = 3.0 Hz, 1H), 2.06-1.98 (m, 2H), 1.72-1.60 (m, 3H), 1.49-1.38 (m, 1H), 1.31 (s, 3H), 1.26 (s, 3H), 0.94 (t, J = 7.9 Hz, 9H), 0.59 (q, J = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.6, 71.3, 67.9, 62.0, 57.5, 33.8, 32.2, 25.8, 25.1, 18.9, 7.0, 5.3.

HR-MS (ESI) *m/z* calcd for $C_{16}H_{32}O_3Si$ $(M+Na)^+$: 323.2013, found 323.2023.



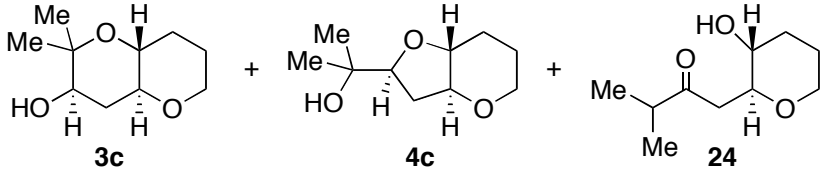
2c

Epoxy alcohol 2c: To a solution of TES-protected epoxy alcohol **23** (33 mg, 0.11 mmol, in a 5.8:1 diastereomeric mixture) in THF (1.5 mL) cooled to 0° was added a 1 M THF solution of TBAF (130 μL, 0.13 mmol). The reaction was stirred for 10 min. at 0°. While still cold, the crude product in THF was applied directly to a SiO_2 column (SiO_2 packed in 2% Et_3N dissolved in 20% EtOAc in hexanes, run with a gradient from 2% Et_3N dissolved in 20% EtOAc in hexanes to 50% EtOAc in hexanes) and concentrated *in vacuo* to afford epoxy alcohol **2c** as a colorless oil (20 mg, 0.11 mmol, 98%) as an inseparable 5.8:1 mixture of diastereomers: R_f = 0.54 (100% EtOAc in hexanes). This material is highly sensitive to acid. Exposure to even traces of acid will induce cyclization. We found it essential to neutralize $CDCl_3$ with K_2CO_3 before collecting NMR data. Epoxy alcohol **2c** cyclizes very slowly on standing at -4° in aprotic organic solvents (CH_2Cl_2 or EtOAc/hexanes) and somewhat faster on standing at -4° as a neat oil. For extended periods, **2c** is best stored frozen in benzene at -4°.
All characterization for epoxy alcohol **2c** was obtained on this 5.8:1 mixture of diastereomers: $[\alpha]^{22}_D$ = -2.1 (*c* = 1.0, $CDCl_3$).

IR (thin film, NaCl) 3427, 2930, 2854, 1656, 1461, 1379, 1347, 1273, 1097, 1042, 971 cm^{-1}.

Tabulated ^1H and ^{13}C NMR shifts and coupling constants are reported for the major diastereomer:
^1H NMR (500 MHz, $CDCl_3$) δ 3.96-3.90 (m, 1H), 3.61-3.54 (m, 1H), 3.37 (app td, *J* = 11.3, 3.7 Hz, 1H), 3.24 (ddd, *J* = 9.0, 5.7, 3.1 Hz, 1H), 3.03 (dd, *J* = 8.8, 3.1 Hz, 1H), 2.37-2.33 (m, 1H), 2.15-2.05 (m, 2H), 1.80-1.66 (m, 4H), 1.48-1.38 (m, 1H), 1.33 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.2, 69.7, 68.2, 61.2, 58.3, 32.4, 31.7, 26.0, 25.0, 19.0.

HR-MS (ESI) *m/z* calcd for $C_{10}H_{18}O_3$ $(M+Na)^+$: 209.1148, found 209.1155.



3c **4c** **24**

2c cyclization products 3c, 4c, and 2c rearrangement product 24:
Representative procedure for reaction in **<u>aqueous media</u>:**

Epoxy alcohol **2c** (1.5 mg, 0.0080 mmol) was dissolved either in deionized water (420 μL) or 1 M solution of potassium phosphate buffer in deionized water (420 μL) and stirred at rt under air for 3 d. At this point the crude product mixture was extracted with EtOAc (5x2 mL) and concentrated *in vacuo* without drying. The crude product mixture was analyzed by ^{1}H NMR spectroscopy to determine the ratio of **3c** to **4c**. For reactions in deionized water, **3c**:**4c** was found to be 25:1, 30:1, and 34:1 in separate experiments, with no **24** observed.

Table S2. Dependence of Regioselectivity on pH in Reactions of **2c**

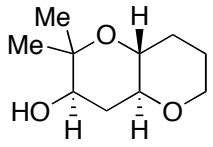
entry	pH (1 M KP_i buffer)	**3c**:**4c**:**24**
1	1.8	22:1:1
2	3.9	24:1:1
3	6.0	32:1:1
4	7.1	19:1:0
5	7.2	37:1:0
6	8.0	26:1:0
7	8.1	25:1:0
8	9.0	14:1:0
9	9.9	3.5:1:0
10	10.0	2.8:1:0
11	10.5	1.0:1:0
12	10.9	0.49:1:0
13	11.8	0.14:1:0
14	12.0	0.29:1:0

Procedure for reaction under **Cs_2CO_3 promotion:**
To a solution of epoxy alcohol **2c** (1.5 mg, 0.0080 mmol) in MeOH (420 μL) was added Cs_2CO_3 (78 mg, 0.24 mmol) and stirred at rt under air for 3 d. At this point the crude product mixture was diluted with deionized water (500 μL), extracted with EtOAc (5x2 mL) and concentrated *in vacuo* without drying. The crude product mixture was analyzed by ^{1}H NMR spectroscopy to determine the ratio of **3c** to **4c** to be 1:17, with no trace of **24**.

Procedure for reaction under **CSA promotion:**
To a solution of epoxy alcohol **2c** (1.5 mg, 0.0080 mmol) in CH_2Cl_2 (420 μL) was added (+/-)-CSA (1.9 mg, 0.0080 mmol) and stirred at rt under argon for 4 h. At this point the crude product mixture was diluted with CH_2Cl_2 (2 mL) and washed with sat. $NaHCO_3$ (500 μL). The aqueous layer was extracted with CH_2Cl_2 (5x2 mL) and concentrated *in vacuo* without drying. The crude product mixture was analyzed by ^{1}H NMR spectroscopy to determine the ratio **3c**:**4c**:**24** to be 5.8:1:0.5.

Procedure for reaction under **BF_3 promotion:**
To a solution of epoxy alcohol **2c** (1.5 mg, 0.0080 mmol) in CH_2Cl_2 (420 μL) cooled to -78° was added, dropwise, a stock solution of 0.1 M BF_3•OEt_2 in CH_2Cl_2 (20 μL, 0.0020 mmol) and stirred at -78° under argon for 30 min. At this point the reaction was allowed

to warm gradually to rt over 5 min., diluted with CH_2Cl_2 (2 mL), and quenched with sat. $NaHCO_3$ (500 μL). The aqueous layer was extracted with CH_2Cl_2 (5x2 mL) and concentrated *in vacuo* without drying. The crude product mixture was analyzed by ^1H NMR spectroscopy to determine the ratio of **3c** to **24** to be 2.2:1, with no trace of **4c**.



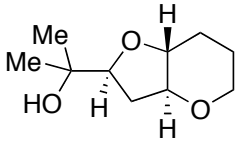
3c

bis-THP 3c: The connectivity of **3c** was confirmed via gCOSY of its acetate derivative **25** (see pp. S57-S58). R_f = 0.54 (100% EtOAc); $[\alpha]^{22}_D$ = +15.8 (*c* = 0.85, $CDCl_3$).

IR (thin film, NaCl) 3440, 2943, 2868, 1711, 1464, 1377, 1281, 1217, 1159, 1068, 1030, 998, 940 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.94-3.88 (m, 1H), 3.53 (app dt, *J* = 11.6, 4.7 Hz, 1H), 3.41-3.34 (m, 1H), 3.21 (ddd, *J* = 11.0, 9.2, 4.2 Hz, 1H), 2.96 (ddd, *J* = 11.6, 9.2, 4.4 Hz, 1H), 2.13 (app dt, *J* = 11.6, 4.5 Hz, 1H), 1.99-1.93 (m, 1H), 1.77-1.68 (m, 2H), 1.66-1.55 (m, 2H), 1.43-1.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.0, 75.9, 73.5, 70.7, 68.2, 35.1, 29.9, 28.0, 25.9, 16.8.

HR-MS (ESI) *m/z* calcd for $C_{10}H_{18}O_3$ $(M+Na)^+$: 209.1148, found 209.1152.



4c

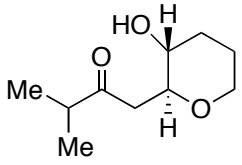
6,5-fused 4c: R_f = 0.50 (100% EtOAc); $[\alpha]^{22}_D$ = -5.8 (*c* = 0.41, $CDCl_3$).

IR (thin film, NaCl) 3447, 2945, 2871, 1465, 1382, 1278, 1127, 1085, 1068, 967 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 4.02-3.97 (m, 1H), 3.92 (dd, *J* = 9.9, 6.3 Hz, 1H), 3.47 (app td, *J* = 11.9, 3.2 Hz, 1H), 3.33-3.21 (m, 2H), 2.25-2.19 (m, 1H), 2.13 (app dt, *J* = 11.2, 6.1 Hz, 1H), 1.97 (broad s, 1H), 1.90 (app q, *J* = 10.8 Hz, 1H), 1.75-1.60 (m, 1H), 1.52 (app qd, *J* = 11.5, 4.7 Hz, 1H), 1.24 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 83.6, 81.4, 79.0, 72.5, 68.9, 31.2, 30.0, 26.6, 24.7, 24.1.

HR-MS (ESI) *m/z* calcd for $C_{10}H_{18}O_3$ $(M+Na)^+$: 209.1148, found 209.1156.



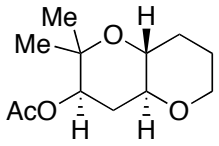
24

Isopropyl ketone 24: R_f = 0.56 (100% EtOAc); $[\alpha]^{22}_D$ = -15.3 (*c* = 0.08, $CDCl_3$).

IR (thin film, NaCl) 3415, 2925, 2853, 1708, 1466, 1383, 1273, 1096, 1028, 947 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$) δ 3.89-3.84 (m, 1H), 3.52 (ddd, *J* = 9.1, 6.8, 4.8 Hz, 1H), 3.38-3.29 (m, 2H), 2.90 (dd, *J* = 16.3, 4.7 Hz, 1H), 2.74 (dd, *J* = 16.3, 6.8 Hz, 1H), 2.67 (septet, *J* = 6.9 Hz, 1H), 2.18-2.12 (m, 1H), 1.98 (d, *J* = 6.2 Hz, 1H), 1.75-1.66 (m, 2H), 1.46-1.38 (m, 1H), 1.12 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4, 78.8, 71.1, 68.0, 44.5, 41.8, 33.5, 29.9, 25.8, 18.1.

HR-MS (ESI) *m/z* calcd for $C_{10}H_{18}O_3$ $(M+Na)^+$: 209.1148, found 209.1156.



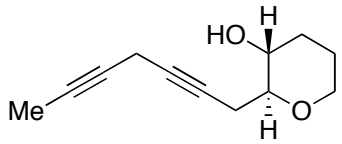
25

Acetylated bis-THP 25: To a solution of alcohol **3c** (7.9 mg, 0.042 mmol) in CH_2Cl_2 (300 μL) was added Et_3N (48 μL, 35 mg, 0.35 mmol), DMAP (0.8 mg, 0.007 mmol), and Ac_2O (13 μL, 14 mg, 0.14 mmol). The resulting solution was stirred at rt for 2 h. and quenched with sat. $NaHCO_3$. The aqueous layer was separated and extracted with Et_2O, and the combined organics were concentrated *in vacuo*. This wet, crude acetate **25** was purified by column chromatography (20% EtOAc in hexanes) to afford clean acetate **25** (8.4 mg, 0.037 mmol, 87%): R_f = 0.60 (30% EtOAc in hexanes); $[\alpha]^{22}_D$ = -8.6 (*c* = 0.40, $CDCl_3$). The connectivity of **25** was confirmed by gCOSY (see pp. S57-58).

IR (thin film, NaCl) 2943, 2851, 1744, 1465, 1370, 1237, 1166, 1103, 1048, 1030, 942 cm^{-1}.

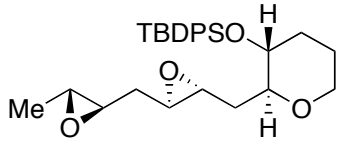
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.71 (dd, *J* = 11.9, 4.6 Hz, 1H), 3.93-3.88 (m, 1H), 3.42-3.34 (m, 1H), 3.29-3.23 (m, 1H), 3.02 (ddd, *J* = 11.9, 9.3, 4.4 Hz, 1H), 2.18 (app dt, *J* = 11.5, 4.5 Hz, 1H), 2.07 (s, 3H), 1.99-1.93 (m, 1H), 1.79-1.69 (m, 2H), 1.60 (app q, *J* = 11.7 Hz, 1H), 1.40 (app qd, *J* = 11.6, 5.6 Hz, 1H), 1.26 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 77.5, 74.3, 74.2, 70.9, 68.2, 31.7, 29.9, 27.9, 25.8, 21.4, 18.0.

HR-MS (EI) *m/z* calcd for $C_{12}H_{21}O_4$ $(M+H)^+$: 229.1440, found 229.1436.



26

Diyne 26: This compound was prepared via a previously published 1-step procedure from terminal alkyne **16**.[S11]



27

Diepoxide 27: A solution of diyne **26** (540 mg, 2.81 mmol) in THF (5 mL) was cooled to -40°, into which flask NH_3 gas was condensed (~60 mL). To this solution was added dry MeOH (2.3 mL, 1.8 g, 56 mmol). Lithium metal (120 mg, 18.6 mmol, cut into 10-20 mg pieces from Li^0 wire washed with hexanes) was added portionwise, allowing one minute between additions. With each addition, a blue "tail" developed behind each piece of Li^0 as the metal swirled and dissolved into solution. The blue color gradually disappeared as the metal was consumed, at which point the next piece of Li^0 was added. With the addition of the last piece, the blue was more persistent, lasting 3-5 min. before disappearing, at which point the reaction was quenched (vide infra). At no point did the reaction solution become a completely homogenous deep blue color. We believe that overreduction of the diene can be a major problem, resulting in low or even 0% yields, and that it is therefore critical to use a smaller excess of Li^0 than is typically used in dissolving metal reductions. The reaction was quenched at -40^0 via slow addition of solid NH_4Cl (~20 g) and allowed to warm gradually to room temperature. The resulting solid residue was dissolved in Et_2O (50 mL) and water (25 mL). The aqueous layer was

separated and extracted with Et_2O (3x50 mL), and combined organics were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to afford a crude mixture of 1,4-diene as well as some monoene overreduction products as a colorless oil: R_f for all = 0.68 (50% EtOAc in hexanes). This moderately unstable material was carried forward into silyl protection without further purification.

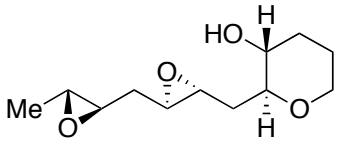
To a solution of this crude diene in DMF (3 mL) was added imidazole (478 mg, 7.0 mmol) and TBDPSCl (860 μL, 920 mg, 3.37 mmol), and the resulting solution was stirred at rt for 1 h., at which point it was quenched with sat. $NaHCO_3$ (~3 mL) and diluted with Et_2O (~10 mL) and water (~10 mL). The aqueous layer was separated and extracted with Et_2O (3x40 mL), and combined organics were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to afford the moderately unstable crude silyl-protected 1,4-diene: R_f = 0.70 (10% EtOAc in hexanes), which was carried forward into Shi epoxidation without further purification.

To this crude mixture in 2:1 v/v DMM:MeCN (237 mL) was added a 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} Na_2EDTA (158 mL), nBu$_4HSO_4$ (238 mg, 0.70 mmol), and chiral ketone **20** (1.45 g, 5.6 mmol). This biphasic mixture was stirred vigorously at 0°. To this mixture was added, simultaneously over 30 min. via syringe pump, a solution of Oxone (17.3 g, 28 mmol) in 4 x 10^{-4} Na_2EDTA (79 mL) and a 0.89 M solution of K_2CO_3 (79 mL, 70 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 30 min., at which point it was diluted with EtOAc (~400 mL) and water (~100 mL). The aqueous layer was separated and extracted with EtOAc (3x500 mL), and the combined organics were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. NMR and TLC evidence at this point indicated approx. 75% conversion of the diene. This partially oxidized reaction mixture was then subjected again to identical epoxidation conditions and worked up as before. After resubjection, crude diepoxide **27** was chromatographed (gradient 10% to 20% to 30% EtOAc in hexanes) to provide **27**, a colorless oil, as an inseparable mixture of diastereomers (371 mg of a 2.5:1 overall diastereomeric mixture, 0.79 mmol combined, 28% over 3 steps): R_f = 0.29 (20% EtOAc in hexanes). Diepoxide **27** was further purified via preparative HPLC (Supelco SUPELCOSIL LC-SI, 20 mm diameter achiral SiO_2 column, 5 μm particle size, 25 cm length; 0.6% *i*PrOH in hexanes, 30 mL/min.; t_R of desired diastereomer = 9.0 min.) to afford **27** in 20:1 overall dr: $[\alpha]^{22}_D$ = +4.2 (*c* = 2.4, $CDCl_3$).

IR (thin film, NaCl) 3072, 2958, 2931, 2857, 1472, 1428, 1380, 1361, 1103 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.65 (m, 4H), 7.47-7.36 (m, 6H), 3.84-3.78 (m, 1H), 3.43-3.36 (m, 1H), 3.33-3.26 (m, 2H), 2.86-2.79 (m, 4H), 2.05 (ddd, *J* = 14.4, 5.6, 2.6 Hz, 1H), 1.84-1.76 (m, 2H), 1.72-1.62 (m, 2H), 1.51-1.37 (m, 3H), 1.33 (d, *J* = 5.1 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 136.1, 134.7, 133.6, 130.0, 129.8, 127.9, 127.6, 80.8, 72.2, 67.8, 56.9, 56.5, 55.0, 54.6, 35.4, 34.7, 33.5, 27.2, 25.6, 19.5, 17.8.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{38}O_4Si$ $(M+Na)^+$: 489.2432, found 489.2447.

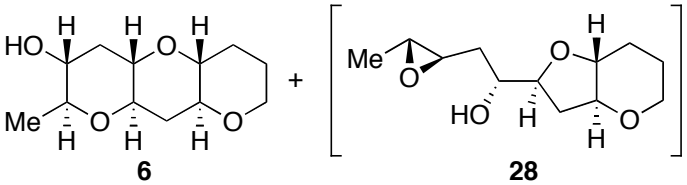


5

Diepoxy alcohol 5: To a solution of silyl ether **27** (66 mg, 0.14 mmol, in 20:1 overall dr) in THF (900 μL) was added a 1 M solution of TBAF in THF (280 μL, 0.28 mmol). The reaction was warmed to 30° for 2 h., cooled, and filtered through a pad of SiO_2 (gradient 20% to 50% to 100% EtOAc in hexanes) to yield free diepoxy alcohol **5** as a colorless oil (32.8 mg, 0.14 mmol, 99%): R_f = 0.41 (100% EtOAc); $[\alpha]^{22}_D$ = +39.4 (*c* = 1.6, $CDCl_3$).[S12] This material is highly sensitive to acid. Exposure to even traces of acid will induce cyclization. We found it essential to neutralize $CDCl_3$ with K_2CO_3 before collecting NMR data. **5** cyclizes very slowly on standing at -4° in aprotic organic solvents (CH_2Cl_2 or EtOAc/hexanes) and somewhat faster on standing at -4° as a neat oil. For extended periods, **5** is best stored frozen in benzene at -4°.

IR data was consistent with that previously reported.[S11]

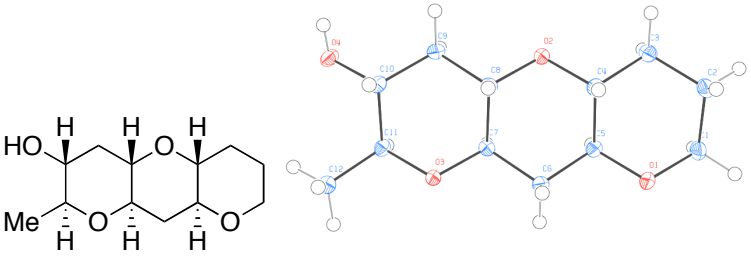
^{1}H NMR data was consistent with that previously reported.[S11] We nevertheless retabulate ^{1}H NMR data here, as the improved diastereopurity of **5** has enabled the determination of coupling constants not previously measurable: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93-3.88 (m, 1H), 3.52 (ddd, *J* = 10.8, 9.5, 4.5 Hz, 1H), 3.38-3.31 (m, 1H), 3.18 (ddd, *J* = 9.2, 5.9, 3.4 Hz, 1H), 2.99 (ddd, *J* = 7.7, 3.1, 2.5 Hz, 1H), 2.89 (ddd, *J* = 6.8, 4.6, 2.3 Hz, 1H), 2.83-2.78 (m, 2H), 2.28 (broad s, 1H), 2.16-2.07 (m, 2H), 1.82-1.65 (m, 5H), 1.41 (dddd, *J* = 12.2, 11.6, 11.1, 5.3 Hz, 1H), 1.31 (d, *J* = 5.0 Hz, 3H). ^{13}C NMR data was consistent with that previously reported.[S11] However, all ^{13}C shift values for **5** in ref. S12 are off by 0.4-0.5 ppm due to an incorrectly referenced $CDCl_3$ center peak. We therefore retabulate ^{13}C NMR data here: ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.6, 69.9, 68.1, 56.7, 55.8, 55.4, 54.7, 35.1, 34.9, 32.6, 26.0, 17.7.



6 **28**

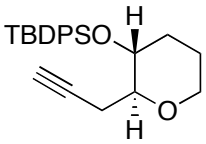
Cascade of diepoxy alcohol 5 to tris-THP 6:
Reaction in **<u>water</u>**: Diepoxy alcohol **5** (22.8 mg, 0.100 mmol, in 20:1 dr) was dissolved in deionized water (5.0 mL) in a 20 mL vial. The threads of the vial were lined with Teflon tape, the cap was sealed and covered with parafilm, and the solution was heated to 60° under air for 3 d. The solution was then cooled to rt and concentrated *in vacuo* (10 torr,

40°). The crude product mixture was chromatographed (50% EtOAc in hexanes) to separate the desired tris-THP **6** (16.8 mg, 0.074 mmol, 74% (78% adjusted for 20:1 dr), a white crystalline solid) from tentatively assigned 6,5-fused structure **28** (~15%). The tentatively assigned **28** could not be isolated cleanly, as it was contaminated with traces of another *exo* cyclization product.



6

tris-THP 6: Spectral data were consistent with that previously reported.[S11,S13] We have corroborated the connectivity and the relative and absolute configurations of this compound via X-ray structure (see pp. S47-S54). A sample of the solid (c. 15 mg) was crystallized using slow vapor diffusion of hexanes into CH_2Cl_2. A .cif file of the X-ray structure is included with this Supporting Information.



29

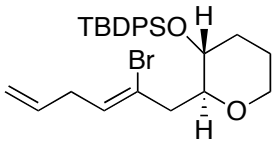
Silyl-protected bishomopropargylic alcohol 29: To a flame-dried flask containing fresh lithium acetylide-ethylenediamine complex (23.2 g, 252 mmol) was added dry THF (450 mL) and freshly distilled DMPU (80 mL) to afford a dusty gray-brown slurry.[S9] After cooling to 0°, to this solution was added slowly tosylate **15** (13.8 g, 42 mmol), over 5 minutes, as a solution in 40 mL DMPU and 20 mL THF. Any remaining **15** was dissolved with a further 10 mL THF and added via syringe. After stirring 1 h. at 0°, the reaction was warmed to room temperature for 41 h. Over time, the solution developed a bright cherry red color, which matured into a rich burgundy red color. After recooling to 0°, Et_3N (50 mL, 36.3 g, 358 mmol) was added, followed immediately by slow addition of a 1 M solution of HCl in Et_2O (270 mL, 270 mmol). The solution was stirred 10 minutes and vacuum filtered to remove solids; these solids were washed with Et_2O (4 x 100 mL). The combined washes and filtrate were concentrated *in vacuo* to yield a dark red-brown, viscous solution of crude bishomopropargylic alcohol **16** in DMPU, which was used without further purification; R_f of **16** = 0.55 (50% EtOAc in hexanes).

To this solution of alcohol **16** in DMPU was added imidazole (8.6 g, 126 mmol) and TBDPSCl (16.1 mL, 17.3 g, 63 mmol). After warming to 40° and stirring for 5 h., the red-brown solution was cooled, diluted with Et_2O (300 mL), and washed with water (400 mL). The aqueous layer was extracted with Et_2O (3 x 150 mL), and the combined organics were washed with sat. NaCl (100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was separated from TBDPSOH by column chromatography (gradient 3% to 5% to 10% to 15% EtOAc in hexanes) to afford silyl ether **29** as a pale yellow oil (8.10 g, 21.4 mmol, 51% over 2 steps): R_f = 0.45 (10% EtOAc in hexanes); $[\alpha]^{22}_D$ = -27.4 (*c* = 1.3, $CDCl_3$).

IR (thin film, NaCl) 3310, 2931, 2856, 1428, 1100, 1047 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 7.74-7.68 (m, 4H), 7.47-7.42 (m, 2H), 7.39 (app t, *J* = 7.1 Hz, 4 H), 3.91-3.86 (m, 1H), 3.55 (ddd, *J* = 9.6, 4.7, 4.7 Hz, 1H), 3.38-3.31 (m, 2H), 2.77 (app dt, *J* = 16.9, 2.9 Hz, 1H), 2.48 (ddd, *J* = 16.9, 6.8, 2.7 Hz, 1H), 1.98 (app t, *J* = 2.7 Hz, 1H), 1.81-1.73 (m, 1H), 1.49-1.40 (m, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 136.1, 134.7, 133.4, 130.0, 129.8, 127.9, 127.6, 81.6, 80.8, 71.4, 69.7, 68.2, 33.3, 27.2, 25.5, 22.5, 19.5.

HR-MS (ESI) *m/z* calcd for $C_{24}H_{30}O_2Si$ $(M+Na)^+$: 401.1907, found 401.1924.



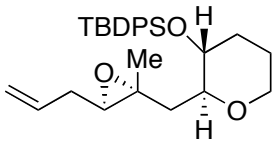
30

Alkenyl bromide 30: To $PdCl_2(PhCN)_2$ (40 mg, 0.11 mmol) and $NaHCO_3$ (880 mg, 10.5 mmol) was added allyl bromide (9 mL, 105 mmol). The resulting solution was stirred 15 minutes at room temperature, over which time the color changed from an initial yellow-orange to a deeper red-brown. Alkyne **29** (795 mg, 2.1 mmol) as a solution in THF (2 mL) was then added dropwise at ambient temperature via syringe pump over 90 min.[S14] After addition the reaction was stirred a further 30 min., directly concentrated *in vacuo*, and chromatographed (gradient 2% to 3% to 5% EtOAc in hexanes) to afford alkenyl bromide **30** (920 mg, 1.84 mmol, 88%): R_f = 0.54 (10% EtOAc in hexanes); $[\alpha]^{22}_D$ = -11.5 (*c* = 27.0, $CDCl_3$). We have found that the presence of silanol impurities (ie *t*-butyldiphenylsilanol, TBDPSOH) in starting material **29** does not adversely affect the bromoallylation reaction, and, in fact, purification away from TBDPSOH is easier after this step than after the synthesis of **29**.

IR (thin film, NaCl) 3072, 3011, 2933, 2858, 1639, 1472, 1428, 1362, 1218, 1127, 1103, 1048 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (app t, *J* = 8.4 Hz, 4H), 7.56-7.46 (m, 6H), 5.92 (dddd, *J* = 16.5, 10.1, 6.2, 6.2 Hz, 1H), 5.85 (app t, *J* = 6.8 Hz, 1H), 5.22 (dd, *J* = 17.1, 1.7 Hz, 1H), 5.13 (dd, *J* = 10.1, 1.5 Hz, 1H), 3.92-3.87 (m, 1H), 3.71 (app td, *J* = 9.2, 1.5 Hz, 1H), 3.55 (ddd, *J* = 10.2, 9.1, 4.6 Hz, 1H), 3.39 (app td, *J* = 11.3, 2.7 Hz, 1H), 3.32 (app d, *J* = 14.7 Hz, 1H), 3.13-3.02 (m, 2H), 2.43 (dd, *J* = 14.8, 10.0 Hz, 1H), 2.05-2.00 (m, 1H), 1.70-1.62 (m, 1H), 1.60-1.48 (m, 2H), 1.23 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 135.9, 134.9, 134.3, 133.5, 129.9, 129.7, 127.8, 127.6, 126.0, 115.5, 80.0, 71.9, 67.6, 44.5, 35.8, 33.5, 27.1, 25.5, 19.3.

HR-MS (ESI) *m/z* calcd for $C_{27}H_{35}BrO_2Si$ $(M+Na)^+$: 521.1482, found 521.1489.



31

Epoxide 31: To a dried, cooled sealed tube was added $Pd(PPh_3)_4$ (218 mg, 0.19 mmol). The tube was pumped out under high vacuum and backfilled with argon three times. A 2.0 M solution of dimethylzinc in toluene (6.75 mL, 13.5 mmol) was then added to afford a lemon yellow solution, which was cooled to 0°. Alkenyl bromide **30** (1.35 g, 2.7 mmol) was then added gradually as a solution in THF (10 mL). The tube was then capped and heated to 85° for 48 h. After cooling, the reaction was quenched by pouring over a mixture of ~60 g of ice and ~20 g of NaCl. The aqueous layer was separated and extracted Et_2O (3x75 mL), and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude diene product, a vivid yellow-orange oil containing the desired methylated, trisubstituted alkene along with traces of triphenylphosphine and a proton-quenched, disubstituted alkene impurity, was carried forward without further purification (R_f of trisubstituted and disubstituted alkenes = 0.60 (10% EtOAc in hexanes)).

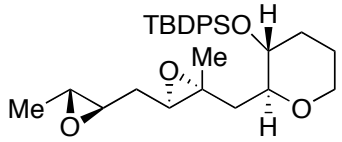
To this crude mixture in 2:1 v/v DMM:MeCN (34 mL) was added a 0.05 M solution of $Na_2B_4O_7$•$10H_2O$ in 4 x 10^{-4} Na_2EDTA (23 mL), *n*Bu_4HSO_4 (153 mg, 0.45 mmol), and chiral ketone **20** (613 mg, 2.37 mmol). This biphasic mixture was stirred vigorously at 0°. To this mixture was added, simultaneously over 30 min. via syringe pump, a solution of Oxone (1.46 g, 2.37 mmol) in 4 x 10^{-4} Na_2EDTA (11.4 mL) and a 0.89 M solution of K_2CO_3 (11.4 mL, 10.2 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 20 min., at which point it was diluted with EtOAc (50 mL). The aqueous layer was separated and extracted with EtOAc (3x120 mL), and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. NMR and TLC evidence indicated only partial conversion of starting material. This partially oxidized reaction mixture was then subjected again to identical epoxidation conditions and worked up as before. For reasons unknown, attempting to force full conversion in a single subjection by using greater than 1-1.05 equivalents of Oxone

appears to lead to epoxidation of the disubstituted alkene side product as well, forming an undesired disubstituted epoxide side product difficult to remove from the desired product. The desired trisubstituted epoxide **31** (R_f = 0.39 (10% EtOAc in hexanes)) was partially separated from its undesired diastereomer (crude dr ≅ 2:1, R_f of undesired diastereomer = 0.45 (10% EtOAc in hexanes)) via column chromatography (gradient 2% to 3% to 5% to 10% EtOAc in hexanes) to afford epoxy alkene **31** (580 mg of a 4:1 diastereomeric mixture, 1.29 mmol combined, 48% over 2 steps (38% over 2 steps for desired diastereomer)): $[\alpha]^{22}_D$ of desired diastereomer in 20:1 dr = -9.4 (*c* = 0.19, $CDCl_3$).

IR (thin film, NaCl) 3070, 2931, 2857, 1471, 1428, 1100 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.69-7.65 (m, 4H), 7.46-7.41 (m, 2H), 7.41-7.36 (m, 4H), 5.88 (dddd, *J* = 16.8, 10.3, 6.4, 6.4 Hz, 1H), 5.17 (app dq, *J* = 17.3, 1.7 Hz, 1H), 5.11 (app dq, *J* = 10.3, 1.5 Hz, 1H), 3.81-3.76 (m, 1H), 3.35-3.22 (m, 3H), 2.84 (app t, *J* = 6.4 Hz, 1H), 2.38 (dddd, *J* = 15.3, 15.3, 1.4, 1.4 Hz, 1H), 2.30-2.22 (m, 2H), 1.85-1.79 (m, 1H), 1.50-1.38 (m, 4H), 1.30 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 136.1, 134.7, 134.2, 133.7, 130.0, 129.8, 127.9, 127.7, 117.0, 79.9, 72.1, 67.5, 61.0, 59.7, 40.3, 33.5, 33.3, 27.2, 25.6, 19.5, 17.9.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{38}O_3Si$ $(M+Na)^+$: 473.2482, found 473.2476.



32

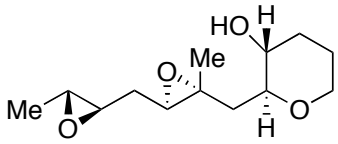
Diepoxide 32: To a solution of Grubbs-Hoveyda 2nd generation catalyst[15] **33** (80 mg, 0.13 mmol) in CH_2Cl_2 (3 mL) at -78° was added condensed *cis*-2-butene[S16] (approx. 3.5 mL, approx. 2.2 g, approx. 39 mmol). The resulting bright green solution was warmed to -15°, and epoxy alkene **31** (580 mg, 1.29 mmol, in 4:1 dr) was added as a solution in CH_2Cl_2 (21 mL). The reaction turned brown and then black over the course of a few minutes. After stirring for 4 h., the reaction was quenched at -15° with ethyl vinyl ether (8 mL, 6 g, 84 mmol), stirred 15 min., and then allowed to warm gradually to room temperature. After concentration *in vacuo* to yield a heavy black tar, the crude product was purified via filtration through a short pad of SiO_2 (10% EtOAc in hexanes) to afford the crude disubstituted alkene product, a mixture of *E* and *Z* alkene isomers in ~4.1:1 *E*:*Z* stereoisomeric ratio, as a pale gray oil (600 mg, 99%): R_f = 0.39 (10% EtOAc in hexanes). This crude mixture was carried forward without further purification.
To this crude mixture in 2:1 v/v DMM:MeCN (48 mL) was added a 0.05 M solution of $Na_2B_4O_7$•$10H_2O$ in 4 x 10^{-4} Na_2EDTA (24 mL), nBu_4HSO_4 (221 mg, 0.65 mmol), and chiral ketone **20** (503 mg, 1.95 mmol). This biphasic mixture was stirred vigorously at 0°. To this mixture was added, simultaneously over 45 min. via syringe pump, a solution of

Oxone (4.8 g, 7.8 mmol) in 4 x 10^{-4} Na_2EDTA (16.1 mL) and a 0.89 M solution of K_2CO_3 (16.1 mL, 14.3 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 30 min., at which point it was diluted with EtOAc (50 mL). The aqueous layer was separated and extracted with EtOAc (3x75 mL), and the combined organics were washed with brine, dried over Na_2SO_4, concentrated *in vacuo*, and chromatographed (15% EtOAc in hexanes) to achieve some separation of diepoxide diastereomers. Diepoxide **32**, a colorless oil, was obtained as a mixture of diastereomers (560 mg of a 2.7:1 overall diastereomeric mixture, 1.17 mmol combined, 90% (66% of desired diastereomer)): R_f = 0.36 (20% EtOAc in hexanes). The diastereomeric enrichment of this mixture was determined by achiral analytical HPLC analysis (Supelco SUPELCOSIL LC-SI, 5 μm particle size, 25 cm length; 0.5% *i*PrOH in hexanes, 1.00 mL/min; t_R(major) = 12.14 min., t_R(minor) = 10.64 min., 13.13 min., 14.20 min.). Diepoxide **32** was further purified via preparative HPLC (Supelco SUPELCOSIL LC-SI, 20 mm diameter achiral SiO_2 column, 5 μm particle size, 25 cm length; 0.5% *i*PrOH in hexanes, 20 mL/min.; t_R of desired diastereomer = 10.6 min.) to afford **32** in 20:1 overall dr: $[\alpha]^{22}_D$ = -1.4 (*c* = 6.6, $CDCl_3$).

IR (thin film, NaCl) 3071, 2932, 2858, 1473, 1428, 1381, 1102 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.70-7.65 (m, 4H), 7.46-7.36 (m, 6H), 3.82-3.77 (m, 1H), 3.35-3.24 (m, 3H), 2.92 (dd, *J* = 7.6, 4.8 Hz, 1H), 2.87-2.82 (m, 2H), 2.27 (dd, *J* = 14.7, 1.2 Hz, 1H), 1.86-1.79 (m, 2H), 1.75 (ddd, *J* = 14.5, 7.6, 4.7 Hz, 1H), 1.50-1.36 (m, 4H), 1.34 (d, *J* = 4.9 Hz, 3H), 1.28 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 136.1, 134.6, 133.7, 130.0, 129.8, 127.9, 127.6, 79.8, 72.2, 67.5, 59.6, 58.9, 57.3, 54.7, 40.3, 33.5, 32.0, 27.2, 25.6, 19.5, 18.0, 17.8.

HR-MS (ESI) *m/z* calcd for $C_{29}H_{40}O_4Si$ $(M+Na)^+$: 503.2588, found 503.2580.



7

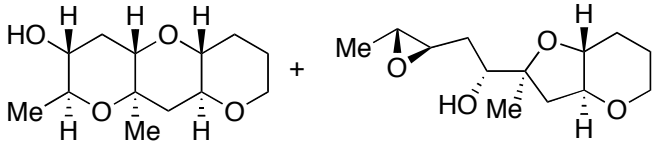
Diepoxy alcohol 7: To a solution of silyl ether **32** (130 mg, 0.27 mmol, in 20:1 overall dr) in THF (2 mL) was added a 1 M solution of TBAF in THF (540 μL, 0.54 mmol). The reaction was warmed to 40° for 3 h., cooled, and filtered through a pad of SiO_2 (gradient 20% to 50% to 100% EtOAc in hexanes) to yield free diepoxy alcohol **7** as a colorless oil (64 mg, 0.26 mmol, 98%): R_f = 0.49 (100% EtOAc); $[\alpha]^{22}_D$ = +29.0 (*c* = 1.55, $CDCl_3$). This material is highly sensitive to acid. Exposure to even traces of acid will induce cyclization. We found it essential to neutralize $CDCl_3$ with K_2CO_3 before collecting NMR data. Diepoxy alcohol **7** cyclizes very slowly on standing at -4° in aprotic organic solvents (CH_2Cl_2 or EtOAc/hexanes) and somewhat faster on standing at -4° as a neat oil.

For extended periods, **7** is best stored frozen in benzene at -4°.

IR (thin film, NaCl) 3429, 2924, 2852, 1443, 1382, 1094 cm^{-1}.

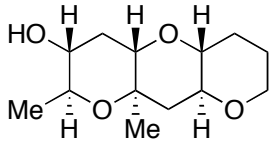
^1H NMR (500 MHz, $CDCl_3$) δ 3.93-3.88 (m, 1H), 3.46-3.38 (m, 1H), 3.33-3.27 (m, 1H), 3.14 (ddd, *J* = 9.6, 7.3, 2.8 Hz, 1H), 2.99 (dd, *J* = 7.3, 5.1 Hz, 1H), 2.86-2.81 (m, 2H), 2.48 (d, *J* = 4.7 Hz, 1H), 2.16 (dd, *J* = 15.1, 2.8 Hz, 1H), 2.14-2.08 (m, 1H), 1.84-1.64 (m, 5H), 1.44-1.34 (m, 4H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.3, 69.9, 68.0, 60.0, 60.0, 57.1, 54.8, 40.6, 32.7, 31.8, 25.9, 17.9, 17.7.

HR-MS (ESI) *m/z* calcd for $C_{13}H_{22}O_4$ $(M+Na)^+$: 265.1410, found 265.1406.



8 **34**

Cascade of diepoxy alcohol 7 to tris-THP 8:
Reaction in **<u>water</u>**: Diepoxy alcohol **7** (15.0 mg, 0.062 mmol, in 20:1 dr) was dissolved in deionized water (3.1 mL) in a 20 mL vial. The threads of the vial were lined with Teflon tape, the cap was sealed and covered with parafilm, and the solution was heated to 60° under air for 3 d. The solution was then cooled to rt and concentrated *in vacuo* (10 torr, 40°). The crude product mixture was chromatographed (30% EtOAc in hexanes) to separate the desired tris-THP **8** (4.7 mg, 0.0194 mmol, 31% (33% adjusted for 20:1 dr), a white solid) from 6,5-fused side product **34** (4.4 mg, 0.0182 mmol, 29%).



8

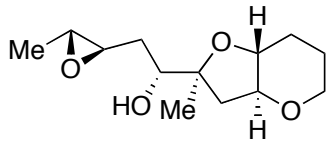
bis-THP 8: The connectivity and relative stereochemistry of **8** were confirmed via gCOSY and NOESY of its acetate derivative **35** (see pp. S59-61). R_f = 0.51 (100% EtOAC); $[\alpha]^{22}_D$ = -34.0 (*c* = 0.44, $CDCl_3$).

IR (thin film, NaCl) 3434, 2944, 2871, 1463, 1378, 1337, 1284, 1110, 1077, 1053, 1040, 1008 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.96-3.91 (m, 1H), 3.55 (dq, *J* = 9.3, 6.0 Hz, 1H), 3.43-

3.31 (m, 2H), 3.22-3.09 (m, 3H), 2.16 (ddd, J = 11.6, 4.6, 4.3 Hz, 1H), 2.14-2.06 (m, 2H), 1.82-1.70 (m, 2H), 1.66-1.57 (m, 2H), 1.55-1.45 (m, 2H), 1.29 (s, 3H), 1.26 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.3, 79.3, 77.6, 73.2, 72.8, 70.3, 68.4, 43.8, 34.0, 29.7, 25.9, 18.7, 16.2.

HR-MS (ESI) *m/z* calcd for $C_{13}H_{22}O_4$ $(M+Na)^+$: 265.1410, found 265.1416.



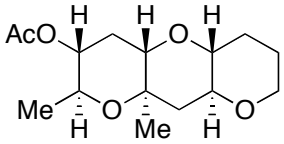
34

6,5-fused 34: R_f = 0.48 (100% EtOAC); $[\alpha]^{22}_D$ = -8.9 (c = 0.065, $CDCl_3$).

IR (thin film, NaCl) 3417, 2956, 2921, 2863, 1465, 1373, 1119, 1104, 1063, 858 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02-3.97 (m, 1H), 3.79-3.74 (m, 1H), 3.47 (app td, J = 11.9, 3.2 Hz, 1H), 3.35 (ddd, J = 11.0, 9.0, 3.9 Hz, 1H), 3.28 (ddd, J = 11.0, 9.0, 6.4 Hz, 1H), 2.95 (ddd, J = 6.4, 4.0, 2.3 Hz, 1H), 2.91 (qd, J = 5.2, 2.3 Hz, 1H), 2.48 (d, J = 1.8 Hz, 1H), 2.24-2.18 (m, 1H), 2.10 (app t, J = 11.1 Hz, 1H), 1.83 (dd, J = 11.1, 6.4 Hz, 1H), 1.77-1.46 (m, 5H), 1.34 (d, J = 5.2 Hz, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 83.7, 80.9, 79.8, 74.9, 69.0, 57.9, 55.1, 36.4, 33.8, 30.3, 25.1, 24.8, 17.8.

HR-MS (ESI) *m/z* calcd for $C_{13}H_{22}O_4$ $(M+Na)^+$: 265.1410, found 265.1415.



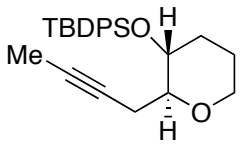
35

Acetate 35: To a solution of alcohol **8** (10.3 mg, 0.043 mmol) in CH_2Cl_2 (300 μL) was added Et_3N (59 μL, 43 mg, 0.43 mmol), DMAP (1.0 mg, 0.008 mmol), and Ac_2O (12 μL, 13 mg, 0.13 mmol). The resulting solution was stirred at rt for 2 h. and quenched with sat. $NaHCO_3$. The aqueous layer was separated and extracted with Et_2O, and the combined organics were concentrated *in vacuo*. This wet, crude acetate **35** was purified by column chromatography (20% EtOAc in hexanes) to afford clean acetate **35**, a white solid (10.1 mg, 0.036 mmol, 87%): R_f = 0.62 (50% EtOAc in hexanes); $[\alpha]^{22}_D$ = -66.2 (c = 0.55, $CDCl_3$). The connectivity and relative stereochemistry of **35** were confirmed by gCOSY and NOESY (see pp. S59-61).

IR (thin film, NaCl) 2962, 2946, 2919, 2849, 1742, 1471, 1376, 1247, 1107, 1090, 1076, 1042, 1027 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 4.51 (ddd, *J* = 11.1, 9.8, 5.2 Hz, 1H), 3.95-3.90 (m, 1H), 3.73 (dq, *J* = 9.8, 6.0 Hz, 1H), 3.38 (app td, *J* = 11.4, 3.6 Hz, 1H), 3.24 (dd, *J* = 12.6, 3.9 Hz, 1H), 3.18-3.09 (m, 2H), 2.23 (ddd, *J* = 11.4, 4.8, 4.3 Hz, 1H), 2.13-2.04 (m, 5H), 1.81-1.68 (m, 2H), 1.61 (app q, *J* = 12.0 Hz, 1H), 1.57-1.43 (m, 2H), 1.30 (s, 3H), 1.14 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 80.4, 78.8, 77.6, 73.5, 73.3, 68.4, 67.4, 43.7, 30.5, 29.6, 25.9, 21.3, 18.6, 16.1

HR-MS (ESI) *m/z* calcd for $C_{15}H_{24}O_5$ $(M+Na)^+$: 307.1516, found 307.1516.



36

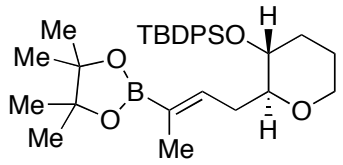
Internal alkyne 36: To a cooled flame-dried 50 mL round-bottomed flask was added terminal alkyne **29** (600 mg, 1.58 mmol). The flask was pumped down under high vacuum and backfilled with argon, and this procedure was repeated once. Dry THF (16 mL) was then added, and the solution was cooled to -78°. A 2.5 M solution of nBuLi in hexanes (710 μL, 1.77 mmol) was added slowly, dropwise. As equivalence was approached, the solution turned from a very pale yellow to a slightly deeper yellow. Within one minute after the addition of the last drop of nBuLi, the solution changed color more dramatically to a deeper orange. The authors advise that nBuLi addition proceed very gradually towards the end, as any excess equivalents of nBuLi result in a proportionate amount of decomposition. nBuLi addition should end immediately upon evolution of an orange color. After nBuLi addition, the solution was warmed for 5 min. by removing it from the -78° bath, during which time it developed an orange-brown color. After recooling to -78°, MeI (490 μL, 7.9 mmol) was added dropwise, over 2 min. The reaction was allowed to warm gradually to room temperature over 14 h., at which point it was quenched with sat. $NaHCO_3$ (15 mL) and diluted with Et_2O (20 mL). The aqueous layer was extracted with Et_2O (2 x 20 mL), and the combined organics were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo*. The nearly pure crude oil was pulled through a short pad of SiO_2 (10% EtOAc in hexanes) to yield internal alkyne **36** as a colorless oil (615 mg, 1.56 mmol, 99%): R_f = 0.45 (10% EtOAc in hexanes); $[\alpha]^{22}_D$ = -17.0 (*c* = 2.6, $CDCl_3$).

IR (thin film, NaCl) 3072, 2932, 2857, 1590, 1472, 1428, 1362, 1099, 1047 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 7.74-7.68 (m, 4H), 7.47-7.42 (m, 2H), 7.39 (app t, *J* = 7.4

Hz, 4 H), 3.90-3.85 (m, 1H), 3.59-3.53 (m, 1H), 3.36-3.30 (m, 1H), 3.28 (ddd, J = 9.3, 6.5, 3.1 Hz, 1H), 2.70 (app dp, J = 16.8, 2.6 Hz, 1H), 2.47 (ddq, J = 16.8, 6.8, 2.6 Hz, 1H), 1.79 (app t, J = 2.6 Hz, 3H), 1.77-1.70 (m, 1H), 1.47-1.37 (m, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 136.1, 134.9, 133.5, 129.9, 129.7, 127.8, 127.6, 81.2, 77.1, 76.0, 71.3, 68.2, 33.3, 27.1, 25.5, 22.8, 19.5, 4.1.

HR-MS (ESI) *m/z* calcd for $C_{25}H_{32}O_2Si$ $(M+Na)^+$: 415.2064, found 415.2065.



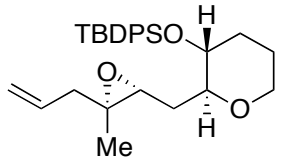
37

Alkenyl boronate ester 37: Internal alkyne **36** (616 mg, 1.56 mmol) was added to a dry, cooled sealed tube. The tube was pumped under high vacuum and then backfilled with argon, and this cycle repeated two times more. Pinacolborane (287 μL, 253 mg, 1.98 mmol) was added, followed by Et_3N (22 μL, 16 mg, 0.16 mmol) and Schwartz's reagent (41 mg, 0.16 mmol).[S17] The resulting beige slurry was heated to 60° and stirred vigorously for 28 h. while protected from light. On heating, the solid dissolves to afford a clear orange solution. After cooling, the crude reaction mixture was filtered through a short pad of SiO_2 (100% Et_2O) and concentrated *in vacuo* to a very pale yellow heavy oil containing a 2:1 mixture of pinacolate **37** (R_f = 0.36, 10% EtOAc in hexanes) and its regioisomer (R_f = 0.38, 10% EtOAc in hexanes), along with unreacted **36**, traces of a proton quench product, and borate and other impurities. These were separated via careful column chromatography (gradient 3% to 5% EtOAc in hexanes) to afford **37** (235 mg, 0.45 mmol, 29% (39% based on recovered **36**) in >20:1 regioisomeric purity along with unreacted **36** (163 mg, 26%): $[\alpha]^{22}_D$ = -2.1 (c = 1.9, $CDCl_3$).

IR (thin film, NaCl) 3072, 2932, 2246, 1632, 1472, 1428, 1371, 1301, 1103 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.67 (m, 4H), 7.45-7.36 (m, 6H), 6.43 (app tq, J = 6.4, 1.5 Hz, 1H), 3.81-3.76 (m, 1H), 3.45-3.39 (m, 1H), 3.30-3.24 (m, 2H), 2.81-2.75 (m, 1H), 2.08-2.00 (m, 1H), 1.82-1.77 (m, 1H), 1.63 (d, J = 1.5 Hz, 3H), 1.49-1.38 (m, 3H), 1.27 (app s, 12H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.43, 136.1, 136.1, 134.9, 133.9, 129.9, 129.7, 127.9, 127.6, 83.3, 82.4, 72.6, 67.9, 33.6, 32.1, 27.2, 25.8, 25.1, 25.0, 19.5, 14.5 (no signal was observed for the boron-bound carbon).

HR-MS (ESI) *m/z* calcd for $C_{31}H_{46}BO_4Si$ $(M+Na)^+$: 543.3089, found 543.3089.



38

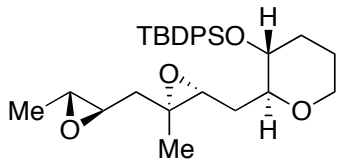
Epoxy alkene 38: [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II) ($PdCl_2$(dppf)) (35 mg, 0.048 mmol) was added to a flame-dried, cooled sealed tube. Oven-dried potassium phosphate (1.53 g, 7.2 mmol) was added, and the tube was pumped on vacuum and backfilled with argon. This cycle was repeated two further times, and then alkenyl boronate ester **37** (500 mg, 0.96 mmol) was added as a solution in dry THF (1.5 mL). The mixture was allowed to stir under Ar for 5 min. to afford a heterogeneous orange solution. Degassed water (35 mg, 35 μL, 1.9 mmol, degassed via sparging) was then added, followed immediately by allyl bromide (581 mg, 415 μL, 4.8 mmol). The sealed tub was capped, and the mixture was heated to 80° and stirred vigorously for 44 h., at which point it had become a chunky, pale yellow slurry. After cooling and dilution with Et_2O (5 mL), the crude product was filtered through SiO_2 (washed with Et_2O) and concentrated *in vacuo* to yield the crude 1,4-diene as a yellow oil (R_f = 0.60, 10% EtOAc in hexanes). This material was carried forward into Shi epoxidation without further purification.
To this crude diene in 2:1 v/v DMM:MeCN (14.2 mL) was added a 0.05 M solution of $Na_2B_4O_7$•$10H_2O$ in 4 x 10^{-4} Na_2EDTA (9.5 mL), *n*Bu_4HSO_4 (64 mg, 0.19 mmol), and chiral ketone **20** (248 mg, 0.96 mmol). This biphasic mixture was stirred vigorously at 0°. To this mixture was added, simultaneously over 25 min. via syringe pump, a solution of Oxone (652 mg, 1.06 mmol) in 4 x 10^{-4} Na_2EDTA (4.75 mL) and a 0.89 M solution of K_2CO_3 (4.75 mL, 4.22 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 30 min., at which point it was diluted with EtOAc (20 mL). The aqueous layer was separated and extracted with EtOAc (3x50 mL), and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. NMR and TLC evidence indicated ~90% conversion of the starting material. The desired trisubstituted epoxide **38** (R_f = 0.31 (10% EtOAc in hexanes)) was separated from unreacted diene via column chromatography (gradient 5% to 10% EtOAc in hexanes) to afford recovered diene (35 mg, 0.08 mmol, 8%) and epoxy alkene **38** (230 mg of an inseparable 3:1 diastereomeric mixture, 0.51 mmol, 53% over 2 steps (58% based on recovered starting material)). A small portion of this sample of **37** was purified further via preparative HPLC (Supelco SUPELCOSIL LC-SI, 20 mm diameter achiral SiO_2 column, 5 μm particle size, 25 cm length; 0.5% *i*PrOH in hexanes, 20 mL/min.; t_R of desired diastereomer = 5.8 min.): R_f = 0.31 (10% EtOAc in hexanes), $[\alpha]^{22}_D$ of desired diastereomer in >20:1 dr = -25.6 (*c* = 0.60, $CDCl_3$).

IR (thin film, NaCl) 3072, 2931, 2857, 1473, 1428, 1382, 1100 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.65 (m, 4H), 7.46-7.41 (m, 2H), 7.41-7.36 (m, 4H), 5.80 (dddd, *J* = 17.2, 10.3, 7.0, 7.0 Hz, 1H), 5.14-5.07 (m, 2H), 3.86-3.80 (m, 1H), 3.46-3.40 (m, 1H), 3.33-3.24 (m, 2H), 2.93 (app t, *J* = 6.1 Hz, 1H), 2.35 (app dd, *J* = 14.2, 7.3 Hz, 1H), 2.18 (app dd, *J* = 14.2, 6.7 Hz, 1H), 2.10 (ddd, *J* = 14.4, 6.2, 2.7 Hz, 1H), 1.86-

1.76 (m, 1H), 1.61-1.39 (m, 4H), 1.24 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 136.1, 134.7, 134.0, 133.6, 130.0, 129.8, 127.9, 127.6, 117.8, 81.6, 72.5, 67.9, 60.9, 59.5, 43.4, 33.5, 32.0, 27.2, 25.6, 19.5, 16.9.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{38}O_3Si$ $(M+Na)^+$: 473.2482, found 473.2485.



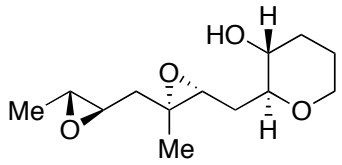
39

Diepoxide 39: To a solution of Grubbs-Hoveyda 2nd generation catalyst **33**[S15] (23 mg, 0.037 mmol) in CH_2Cl_2 (3 mL) at -78° was added condensed *cis*-2-butene[S16] (approx. 3 mL, approx. 1.9 g, approx. 33 mmol). The resulting bright green solution was warmed to -15°, and epoxy alkene **38** (335 mg, 0.74 mmol, in 3:1 dr) was added dropwise as a solution in CH_2Cl_2 (7 mL) over 5 minutes. The reaction turned brown and then black over the course of the addition. After stirring for 5 additional min., a further portion of *cis*-2-butene was added (approx. 2 mL, approx. 1.2 g, approx. 22 mmol) and the reaction was stirred for 1.5 h. at -10° to -5°. The reaction was quenched at -15° with ethyl vinyl ether (10 mL, 7.5 g, 100 mmol), stirred 15 min., and then allowed to warm gradually to room temperature. After concentration *in vacuo* to yield a heavy black tar, the crude disubstituted alkene product was purified via filtration through a short pad of SiO_2 (10% EtOAc in hexanes) to afford an inseparable mixture of *E* and *Z* alkene isomers in ~4.2:1 *E*:*Z* stereoisomeric ratio, as a colorless oil (245 mg, 71%): R_f = 0.34 (10% EtOAc in hexanes). This mixture was carried forward without further purification.
To this crude mixture in 2:1 v/v DMM:MeCN (19.7 mL) was added a 0.05 M solution of $Na_2B_4O_7$•$10H_2O$ in 4 x 10^{-4} Na_2EDTA (9.8 mL), $n$$Bu_4HSO_4$ (44 mg, 0.13 mmol), and chiral ketone **20** (207 mg, 0.80 mmol). This biphasic mixture was stirred vigorously at 0°. To this mixture was added, simultaneously over 45 min. via syringe pump, a solution of Oxone (1.97 g, 3.2 mmol) in 4 x 10^{-4} Na_2EDTA (6.55 mL) and a 0.89 M solution of K_2CO_3 (6.55 mL, 5.83 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 30 min., at which point it was diluted with EtOAc (30 mL). The aqueous layer was separated and extracted with EtOAc (3x50 mL), and the combined organics were washed with brine, dried over Na_2SO_4, concentrated *in vacuo*, and chromatographed (15% EtOAc in hexanes) to provide diepoxide **39**, a colorless oil, as an inseparable mixture of diastereomers (220 mg of a 1.5:1 overall diastereomeric mixture, 0.46 mmol combined, 86%): R_f = 0.37 (20% EtOAc in hexanes). Diepoxide **39** was further purified via preparative HPLC (Supelco SUPELCOSIL LC-SI, 20 mm diameter achiral SiO_2 column, 5 μm particle size, 25 cm length; 0.4% *i*PrOH in hexanes, 30 mL/min.; t_R of desired diastereomer = 13.5 min.) to afford **39** in 7.5:1 to 10:1 overall dr (depending on the batch): $[\alpha]^{22}_D$ of a 9:1 mixture = -2.5 (*c* = 4.6, $CDCl_3$).

IR (thin film, NaCl) 2932, 2857, 1589, 1473, 1428, 1382, 1362, 1101 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.71-7.66 (m, 4H), 7.46-7.36 (m, 6H), 3.86-3.81 (m, 1H), 3.43 (app td, *J* = 8.8, 4.5 Hz, 1H), 3.33-3.27 (m, 2H), 2.91 (app t, *J* = 6.1 Hz, 1H), 2.80-2.75 (m, 2H), 2.12 (ddd, *J* = 14.4, 6.2, 2.7 Hz, 1H), 1.86-1.79 (m, 1H), 1.77-1.65 (m, 2H), 1.58 (ddd, *J* = 14.6, 9.4, 6.0 Hz, 1H), 1.51-1.40 (m, 3H), 1.34-1.31 (m, 6H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 136.1, 134.6, 133.5, 130.0, 129.8, 127.9, 127.6, 81.4, 72.5, 67.9, 61.3, 58.4, 56.7, 54.3, 41.6, 33.4, 31.8, 27.2, 25.6, 19.5, 17.7, 17.3.

HR-MS (ESI) *m/z* calcd for $C_{29}H_{40}O_4Si$ $(M+Na)^+$: 503.2588, found 503.2600.



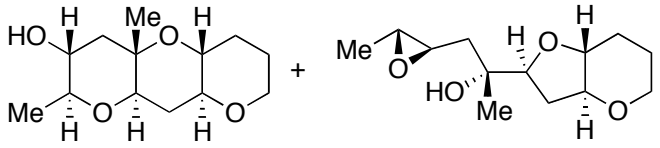
9

Diepoxy alcohol 9: To a solution of silyl ether **39** (113 mg, 0.24 mmol, in 7.5:1 overall dr) in THF (1 mL) was added a 1 M solution of TBAF in THF (470 μL, 0.47 mmol). The reaction was warmed to 30° for 2 h., cooled, and filtered through a pad of SiO_2 (gradient 20% to 50% to 100% EtOAc in hexanes) to yield free diepoxy alcohol **9** as a colorless oil (54 mg, 0.22 mmol, 95%): R_f = 0.55 (100% EtOAc); $[\alpha]^{22}_D$ of a 9:1 mixture of diastereomers = +25.0 (*c* = 2.0, $CDCl_3$). This material is highly sensitive to acid. Exposure to even traces of acid will induce cyclization. We found it essential to neutralize $CDCl_3$ with K_2CO_3 before collecting NMR data. **9** cyclizes very slowly on standing at -4° in aprotic organic solvents (CH_2Cl_2 or EtOAc/hexanes) and somewhat faster on standing at -4° as a neat oil. For extended periods, **9** is best stored frozen in benzene at -4°.

IR (thin film, NaCl) 3431, 2932, 2855, 1441, 1384, 1272, 1096 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.95-3.89 (m,1H), 3.55-3.47 (m, 1H), 3.35 (app td, *J* = 11.3, 4.0 Hz, 1 H), 3.22 (ddd, *J* = 9.3, 6.1, 3.4 Hz, 1H), 3.04 (dd, *J* = 8.2, 3.7 Hz, 1H), 2.80-2.73 (m, 2H), 2.37 (d, *J* = 4.1 Hz, 1H), 2.14-2.05 (m, 2H), 1.82-1.74 (m, 2H), 1.74-1.61 (m, 3H), 1.47-1.34 (m, 4H), 1.30 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.0, 69.8, 68.1, 60.6, 59.1, 56.5, 54.4, 41.6, 32.6, 31.5, 25.9, 17.6, 17.2.

HR-MS (ESI) *m/z* calcd for $C_{13}H_{22}O_4$ $(M+Na)^+$: 265.1410, found 265.1413.



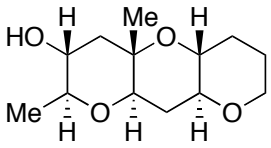
10 **40**

Cascades of diepoxy alcohol 9 to tris-THP 10:

Reaction in **water**: Diepoxy alcohol **9** (14.5 mg, 0.060 mmol, in 9:1 dr) was dissolved in deionized water (3.0 mL) in a 20 mL vial. The threads of the vial were lined with Teflon tape, the cap was sealed and covered with parafilm, and the solution was heated to 60° under air for 3 d. The solution was then cooled to rt and concentrated *in vacuo* (10 torr, 40°). The crude product mixture was chromatographed (30% EtOAc in hexanes) to separate the desired tris-THP **10** (8.0 mg, 0.033 mmol, 55% (61% adjusted for 9:1 dr), a white solid) from 6,5-fused side product **40** (4.1 mg, 0.017 mmol, 28%).

Reaction promoted by **CSA**: To a solution of diepoxy alcohol **9** (9.8 mg, 0.040 mmol, in 7.5:1 dr) in CH_2Cl_2 (2.0 mL) was added (+/-)-CSA (9.4 mg, 0.040 mmol) and stirred at rt under argon for 4 h. At this point the crude product mixture was diluted with CH_2Cl_2 (5 mL) and transferred to a separatory funnel. The reaction flask was washed out with EtOAc (3x6 mL) and H_2O (3x3 mL), and these combined washes were added to the separatory funnel. The organic layer was washed with sat. $NaHCO_3$ (2 mL), and the combined aqueous layers were extracted with EtOAc (3x40 mL). The combined organics were concentrated *in vacuo* without drying, and the crude product mixture was chromatographed (30% EtOAc in hexanes) to afford the desired tris-THP **10** (4.3 mg, 0.018 mmol, 44% (50% adjusted for 7.5:1 dr), a white solid).

Reaction promoted by **BF_3**: To a solution of diepoxy alcohol **10** (10.8 mg, 0.045 mmol, in 7.5:1 dr) in CH_2Cl_2 (2.24 mL) cooled to -78° was added, dropwise, a stock solution of 0.1 M BF_3•OEt_2 in CH_2Cl_2 (111 μL, 0.0011 mmol) and stirred at -78° under argon for 30 min. At this point the reaction was allowed to warm gradually to rt over 5 min., diluted with CH_2Cl_2 (5 mL), and quenched with sat. $NaHCO_3$ (800 μL). The resulting biphasic mixture was transferred to a separatory funnel. The reaction flask was washed out with EtOAc (3x6 mL) and H_2O (3x3 mL), and these combined washes were added to the separatory funnel. The aqueous layer was separated and extracted with EtOAc (3x40 mL), and the combined organics were concentrated *in vacuo* without drying. The crude product mixture was chromatographed (30% EtOAc in hexanes) to afford the desired tris-THP **10** (6.3 mg, 0.026 mmol, 58% (66% adjusted for 7.5:1 dr), a white solid).



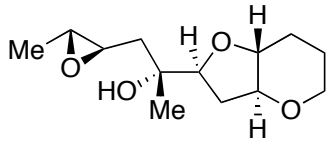
10

tris-THP 10: The connectivity of **10** was confirmed via gCOSY of its acetate derivative **41** (see pp. S62-63). R_f = 0.51 (100% EtOAc); $[\alpha]^{22}_D$ = +16.1 (*c* = 0.38, $CDCl_3$).

IR (thin film, NaCl) 3466, 2971, 2947, 2862, 1371, 1266, 1131, 1096, 1070, 1050, 1032, 947 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.96-3.90 (m, 1H), 3.53-3.45 (m, 1H), 3.43-3.35 (m, 2H), 3.27 (dq, *J* = 9.2, 6.1 Hz, 1H), 3.20 (dd, *J* = 12.3, 3.9 Hz, 1H), 3.02 (ddd, *J* = 11.4, 9.3, 4.5 Hz, 1H), 2.21 (dd, *J* = 11.6, 5.1 Hz, 1H), 2.11 (app td, *J* = 11.4, 4.2 Hz, 1H), 2.01-1.94 (m, 1H), 1.82-1.70 (m, 2H), 1.64 (app q, *J* = 11.7 Hz, 1H), 1.52-1.38 (m, 3H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.1, 79.3, 78.9, 73.7, 71.6, 70.5, 68.4, 47.0, 31.3, 30.0, 26.0, 18.4, 16.2.

HR-MS (ESI) *m/z* calcd for $C_{13}H_{22}O_4$ $(M+Na)^+$: 265.1410, found 265.1421.



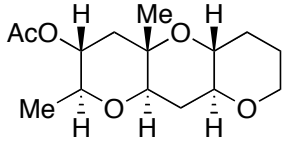
40

6,5-fused 40: R_f = 0.45 (100% EtOAc); $[\alpha]^{22}_D$ = +19.1 (*c* = 0.14, $CDCl_3$).

IR (thin film, NaCl) 3451, 2925, 2853, 1738, 1452, 1381, 1250, 1126, 1081, 966 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 4.05-3.97 (m, 2H), 3.47 (app td, *J* = 11.9, 3.1 Hz, 1H), 3.30-3.22 (m, 2H), 2.90 (ddd, *J* = 8.0, 3.3, 2.4 Hz, 1H), 2.77 (qd, *J* = 5.2, 2.3 Hz, 1H), 2.25-2.09 (m, 3H), 1.97-1.87 (m, 2H), 1.76-1.46 (m, 4H), 1.34 (s, 3H), 1.32 (d, *J* = 5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.9, 81.4, 79.1, 74.3, 68.9, 56.2, 54.3, 39.6, 30.8, 30.0, 24.7, 24.0, 17.7.

HR-MS (ESI) *m/z* calcd for $C_{13}H_{22}O_4$ $(M+Na)^+$: 265.1410, found 265.1438.



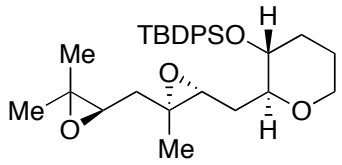
41

Acetate 41: To a solution of alcohol **10** (8.7 mg, 0.036 mmol) in CH_2Cl_2 (300 μL) was added Et_3N (74 μL, 54 mg, 0.53 mmol), DMAP (1.0 mg, 0.008 mmol), and Ac_2O (25 μL, 27 mg, 0.26 mmol). The resulting solution was stirred at rt for 2 h. and quenched with sat. $NaHCO_3$. The aqueous layer was separated and extracted with Et_2O, and the combined organics were concentrated *in vacuo*. This wet, crude acetate **41** was purified by column chromatography (20% EtOAc in hexanes) to afford clean acetate **41**, a white solid (9.5 mg, 0.033 mmol, 92%): R_f = 0.52 (30% EtOAc in hexanes); $[\alpha]^{22}_D$ = -18.4 (*c* = 0.45, $CDCl_3$). The connectivity of **41** was confirmed by gCOSY (see pp. S62-63).

IR (thin film, NaCl) 2939, 2851, 1743, 1463, 1377, 1238, 1100, 1077, 1045, 1032, 947 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 4.70 (ddd, *J* = 11.3, 9.7, 5.3 Hz, 1H), 3.96-3.90 (m, 1H), 3.46 (dq, *J* = 9.7, 6.2 Hz, 1H), 3.42-3.34 (m, 2H), 3.22 (dd, *J* = 12.3, 3.9 Hz, 1H), 3.01 (ddd, *J* = 11.4, 9.3, 4.5 Hz, 1H), 2.25 (dd, *J* = 11.5, 5.2 Hz, 1H), 2.10 (app dt, *J* = 11.4, 4.2 Hz, 1H), 2.06 (s, 3H), 2.00-1.94 (m, 1H), 1.82-1.70 (m, 2H), 1.65 (app q, *J* = 11.7 Hz, 1H), 1.49 (app t, *J* = 11.7 Hz, 1H), 1.41 (app qd, *J* = 12.0, 5.1 Hz, 1H), 1.32 (s, 3H), 1.21 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 79.5, 78.9, 77.2, 73.4, 72.5, 70.5, 68.5, 43.2, 31.3, 29.9, 26.0, 21.3, 18.4, 16.0.

HR-MS (ESI) *m/z* calcd for $C_{15}H_{24}O_5$ $(M+Na)^+$: 307.1516, found 307.1519.



42

Diepoxide 42: [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II) ($PdCl_2$(dppf)) (73 mg, 0.10 mmol) was added to a flame-dried, cooled sealed tube. Oven-dried potassium phosphate (1.83 g, 8.63 mmol) was added, and the tube was pumped on vacuum and backfilled with argon. This cycle was repeated two further times, and then alkenyl boronate **37** (600 mg, 1.15 mmol) was added as a solution in dry THF (2 mL). The mixture was allowed to stir under Ar for 5 min. to afford a heterogeneous orange solution. Degassed water (42 mg, 42 μL, 2.3 mmol, degassed via sparging) was then added, followed immediately by prenyl bromide (859 mg, 666 μL, 5.76 mmol). The sealed tub was capped, and the mixture was heated to 80° and stirred vigorously for 42 h., at which point it had become a chunky, pale yellow slurry. After cooling and dilution with Et_2O (5 mL), the crude product was filtered through SiO_2 (washed with Et_2O) and concentrated *in vacuo* to yield a mixture of the desired S_N2 product as well as an undesired S_N2' product, as a yellow oil. These inseparable skipped diene isomers were purified away from phosphine and other impurities via column chromatography (gradient

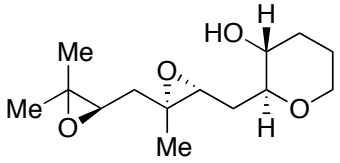
2% to 3% EtOAc in hexanes) to give a 2.5:1 (S_N2:S_N2') mixture of diene isomers (400 mg, 0.86 mmol, 75% combined yield, R_f = 0.63, 10% EtOAc in hexanes). This mixture was carried forward into Shi epoxidation without further purification.

To a solution of these dienes (400 mg, 0.86 mmol) in 2:1 v/v DMM:MeCN (23.2 mL) was added a 0.05 M solution of $Na_2B_4O_7$•$10H_2O$ in 4 x 10^{-4} Na_2EDTA (15.5 mL), $n$$Bu_4HSO_4$ (75 mg, 0.22 mmol), and chiral ketone **20** (222 mg, 0.86 mmol). This biphasic mixture was stirred vigorously at 0°. To this mixture was added, simultaneously over 30 min. via syringe pump, a solution of Oxone (1.06 g, 1.73 mmol) in 4 x 10^{-4} Na_2EDTA (7.75 mL) and a 0.89 M solution of K_2CO_3 (7.75 mL, 6.9 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 20 min., at which point it was diluted with EtOAc (25 mL). The aqueous layer was extracted with EtOAc (3 x 25 mL), and the combined organics were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to provide desired diepoxide **42** and diastereomers. The undesired S_N2' cross-coupling product formed in the previous step, which contains a monosubstituted alkene, is only partially oxidized under these conditions, to a monoepoxide (R_f = 0.77, 20% EtOAc in hexanes) that is readily separable from the desired diepoxide **42**. Column chromatography (15% EtOAc in hexanes) afforded diepoxide **42** in 3.5:1 overall dr as a colorless oil (276 mg, 0.56 mmol, 65% (49% yield over 2 steps), R_f = 0.54 (20% EtOAc in hexanes)) contaminated with a small quantity of ketone **20**. Diepoxide **42** was further purified via preparative HPLC (Supelco SUPELCOSIL LC-SI 20 mm achiral SiO_2 column, 5 μm particle size; 99.5:0.5 hexanes:iPrOH, 20 mL/min.; t_R of desired diastereomer = 11.9 min.) to afford **42** free of **20** and in 15:1 to 20:1 overall dr (depending on batch): $[\alpha]^{22}_D$ for a sample in 20:1 dr = -7.5 (*c* = 3.3, $CDCl_3$).

IR (thin film, NaCl) 3072, 2958, 2930, 2857, 1590, 1472, 1462, 1428, 1379, 1102 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.66 (m, 4H), 7.46-7.41 (m, 2H), 7.40-7.36 (m, 4H), 3.85-3.80 (m, 1H), 3.43 (ddd, *J* = 9.3, 4.8, 4.5 Hz, 1H), 3.29 (app td, *J* = 9.3, 2.5 Hz, 1H), 2.93 (app t, *J* = 6.1 Hz, 1H), 2.89 (app t, *J* = 6.0 Hz, 1H), 2.11 (ddd, *J* = 14.4, 6.4, 2.7 Hz, 1H), 1.85-1.80 (m, 1H), 1.77-1.73 (m, 2H), 1.60 (ddd, *J* = 14.9, 9.5, 5.8 Hz, 1H), 1.51-1.39 (m, 3H), 1.33 (app s, 6H), 1.27 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 136.1, 134.7, 133.6, 130.0, 129.8, 127.9, 127.7, 81.4, 72.5, 67.9, 61.3, 61.2, 58.8, 58.0, 38.2, 33.5, 31.8, 27.2, 25.6, 24.9, 19.5, 19.0, 17.3.

HR-MS (ESI) *m/z* calcd for $C_{30}H_{42}O_4Si$ $(M+Na)^+$: 517.2745, found 517.2751.



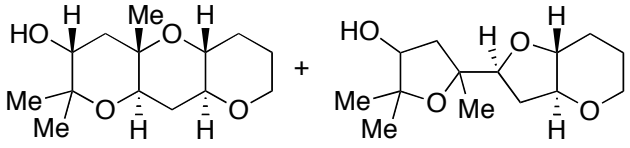
11

Diepoxy alcohol 11: To a solution of silyl ether **42** (64 mg, 0.13 mmol, in 20:1 overall dr) in dry THF (2 mL) was added a 1 M THF solution of TBAF (520 μL, 0.52 mmol). The reaction was warmed to 40° and stirred for 2 h. After cooling, the crude product was pulled directly through a SiO_2 plug (gradient 20% to 50% EtOAc in hexanes) and concentrated *in vacuo* to afford diepoxy alcohol **11** as a pale yellow oil (31 mg, 0.12 mmol, 92%): R_f = 0.58 (100% EtOAc); $[\alpha]^{22}_D$ = +17.8 (*c* = 2.0, $CDCl_3$). This material is highly sensitive to acid. Exposure to even traces of acid will induce cyclization. We found it essential to neutralize $CDCl_3$ with K_2CO_3 before collecting NMR data. **11** cyclizes very slowly on standing at -4° in aprotic organic solvents (CH_2Cl_2 or EtOAc/hexanes) and somewhat faster on standing at -4° as a neat oil. For extended periods, **11** is best stored frozen in benzene at -4°.

IR (thin film, NaCl) 3439, 2928, 2854, 1459, 1379, 1251, 1096, 1043 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.94-3.89 (m, 1H), 3.51 (ddd, *J* = 10.9, 9.2, 4.5 Hz, 1H), 3.38-3.32 (m, 1H), 3.22 (ddd, *J* = 9.3, 6.1, 3.4 Hz, 1H), 3.06 (dd, *J* = 8.0, 3.9 Hz, 1H), 2.89 (dd, *J* = 7.2, 4.8 Hz, 1H), 2.41 (broad s, 1H), 2.14-2.05 (m, 2H), 1.84-1.77 (m, 2H), 1.74-1.65 (m, 3H), 1.47-1.38 (m, 1H), 1.38 (s, 3H), 1.32 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.0, 69.9, 68.1, 61.1, 60.7, 59.4, 58.1, 38.3, 32.6, 31.5, 25.9, 24.9, 19.0, 17.2.

HR-MS (ESI) *m/z* calcd for $C_{14}H_{24}O_4$ $(M+Na)^+$: 279.1567, found 279.1566.



12 **43**

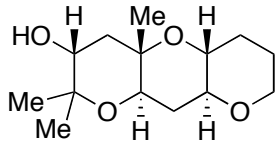
Cascades of diepoxy alcohol 11 to tris-THP 12:

Reaction in **water**: Diepoxy alcohol **11** (13.7 mg, 0.053 mmol, in 15:1 dr) was dissolved in deionized water (2.7 mL) in a 20 mL vial. The threads of the vial were lined with Teflon tape, the cap was sealed and covered with parafilm, and the solution was heated to 60° under air for 3 d. The solution was then cooled to rt and concentrated *in vacuo* (10 torr, 40°). The crude product mixture was chromatographed (50% EtOAc in hexanes) to separate the desired tris-THP **12** (6.9 mg, 0.027 mmol, 50% (54% adjusted for 15:1 dr), a white solid) from 6,5-fused side product **43** (5.4 mg, 0.021 mmol, 39%).

Reaction promoted by **CSA**: To a solution of diepoxy alcohol **11** (13.1 mg, 0.051 mmol, in 20:1 dr) in CH_2Cl_2 (2.5 mL) was added (+/-)-CSA (11.8 mg, 0.051 mmol) and stirred at rt under argon for 4 h. At this point the crude product mixture was diluted with CH_2Cl_2 (5 mL) and transferred to a separatory funnel. The reaction flask was washed out with

EtOAc (3x6 mL) and H_2O (3x3 mL), and these combined washes were added to the separatory funnel. The organic layer was washed with sat. $NaHCO_3$ (2 mL), and the combined aqueous layers were extracted with EtOAc (3x40 mL). The combined organics were concentrated *in vacuo* without drying, and the crude product mixture was chromatographed (50% EtOAc in hexanes) to afford the desired tris-THP **12** (3.5 mg, 0.018 mmol, 27% (29% adjusted for 20:1 dr), a white solid).

Reaction promoted by **BF_3**: To a solution of diepoxy alcohol **11** (15.1 mg, 0.059 mmol, in 15:1 dr) in CH_2Cl_2 (3.0 mL) cooled to -78° was added, dropwise, a stock solution of 0.1 M BF_3•OEt_2 in CH_2Cl_2 (147 μL, 0.015 mmol) and stirred at -78° under argon for 30 min. At this point the reaction was allowed to warm gradually to rt over 5 min., diluted with CH_2Cl_2 (5 mL), and quenched with sat. $NaHCO_3$ (800 μL). The resulting biphasic mixture was transferred to a separatory funnel. The reaction flask was washed out with EtOAc (3x6 mL) and H_2O (3x3 mL), and these combined washes were added to the separatory funnel. The aqueous layer was separated and extracted with EtOAc (3x40 mL), and the combined organics were concentrated *in vacuo* without drying. The crude product mixture was chromatographed (50% EtOAc in hexanes) to afford the desired tris-THP **12** (8.0 mg, 0.031 mmol, 53% (57% adjusted for 15:1 dr), a white solid) along with 6,5-fused side product **43** (3.8 mg, 0.015 mmol, 25%).



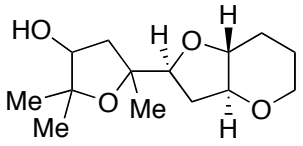
12

tris-THP 12: The connectivity and relative stereochemistry of **12** were confirmed via gCOSY and NOESY of its acetate derivative **44** (see pp. S64-66). R_f = 0.61 (100% EtOAc); $[\alpha]^{22}_D$ = +54.8 (*c* = 1.0, $CDCl_3$).

IR (thin film, NaCl) 3449, 2968, 2934, 2877, 1419, 1379, 1354, 1268, 1218, 1128, 1097, 1069, 1026, 949, 940 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.95-3.89 (m, 1H), 3.66 (dd, *J* = 11.7, 4.6 Hz, 1H), 3.42-3.34 (m, 3H), 3.03 (ddd, *J* = 11.3, 9.3, 4.5 Hz, 1H), 2.01-1.93 (m, 3H), 1.81-1.68 (m, 2H), 1.64-1.54 (m, 3H), 1.42 (ddd, *J* = 11.9, 11.9, 5.3 Hz, 1H), 1.31 (s, 3H), 1.27 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 79.2, 76.8, 74.3, 73.1, 71.7, 70.5, 68.5, 43.4, 31.5, 30.0, 28.4, 26.0, 17.0, 15.6.

HR-MS (ESI) *m/z* calcd for $C_{14}H_{24}O_4$ $(M+Na)^+$: 279.1567, found 279.1574.



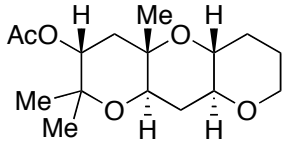
43

6,5-fused 43: R_f = 0.56 (100% EtOAc); $[\alpha]^{22}_D$ = -41.7 (*c* = 0.48, $CHCl_3$).

IR (thin film, NaCl) 3366, 2964, 2935, 2850, 1453, 1371, 1277, 1141, 1117, 1068, 1059, 1040, 1021, 974 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 4.76 (d, *J* = 11.8 Hz, 1H), 4.05 (dd, *J* = 10.9, 5.9 Hz, 1H), 4.01-3.96 (m, 1H), 3.82 (dd, *J* = 11.7, 5.3 Hz, 1H), 3.50-3.38 (m, 2H), 3.29 (ddd, *J* = 11.2, 9.1, 5.9 Hz, 1H), 2.29-2.17 (m, 3H), 2.11 (d, *J* = 14.5 Hz, 1H), 1.75-1.52 (m, 4H), 1.30 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 85.3, 85.0, 83.2, 80.3, 79.5, 78.1, 68.9, 40.9, 33.6, 29.7, 27.8, 26.8, 24.6, 23.2.

HR-MS (ESI) *m/z* calcd for $C_{14}H_{24}O_4$ $(M+Na)^+$: 279.1567, found 279.1571.



44

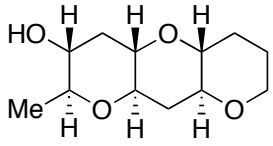
Acetate 44: To a solution of alcohol **12** (25.8 mg, 0.10 mmol) in CH_2Cl_2 (0.80 mL) was added Et_3N (70 μL, 51 mg, 0.50 mmol), DMAP (1.0 mg, 0.008 mmol), and Ac_2O (24 μL, 25 mg, 0.25 mmol). The resulting solution was stirred at rt for 8 h. and quenched with sat. $NaHCO_3$. The aqueous layer was separated and extracted with Et_2O, and the combined organics were concentrated *in vacuo*. This wet, crude acetate **44** was purified by column chromatography (20% EtOAc in hexanes) to afford clean acetate **44**, a white solid (26.4 mg, 0.088 mmol, 88%) R_f = 0.68 (50% EtOAc in hexanes); $[\alpha]^{22}_D$ = +5.5 (*c* = 1.3, $CDCl_3$). The connectivity and relative stereochemistry of **44** were confirmed by gCOSY and NOESY (see pp. S64-66).

IR (thin film, NaCl) 2974, 2946, 2882, 2859, 1736, 1464, 1384, 1374, 1366, 1283, 1235, 1129, 1099, 1077, 1025 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 4.88 (dd, *J* = 12.0, 5.1 Hz, 1H), 3.95-3.90 (m, 1H), 3.45-3.35 (m, 3H), 3.04 (ddd, *J* = 11.4, 9.3, 4.6, 1H), 2.06-2.01 (m, 4H), 2.00-1.94 (m, 2H), 1.81-1.68 (m, 2H), 1.66-1.55 (m, 2H), 1.42 (app qd, *J* = 12.1, 4.9 Hz, 1H), 1.33 (s, 3H), 1.27 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 79.2, 75.2, 74.0, 74.0, 71.9, 70.6, 68.5, 39.7, 31.4, 30.0, 28.4, 26.0, 21.4, 18.3, 15.5.

HR-MS (ESI) *m/z* calcd for $C_{16}H_{26}O_5$ $(M+Na)^+$: 321.1672, found 321.1677.

X-Ray Crystallographic Data for tris-THP 6:



6

All thermal ellipsoid images were generated using Ortep-3 for Windows v. 2.02.

Figure 1. "Overhead" view of 6. Displacement ellipsoids are scaled to 50% probability.

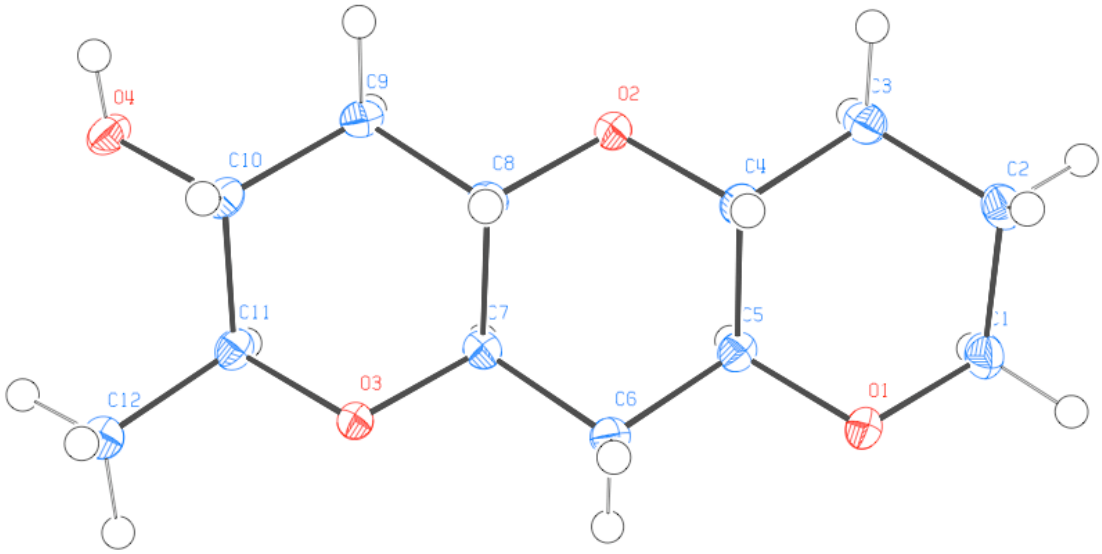


Figure 2. "Side-on" view A of 6. Displacement ellipsoids are scaled to 50% probability.

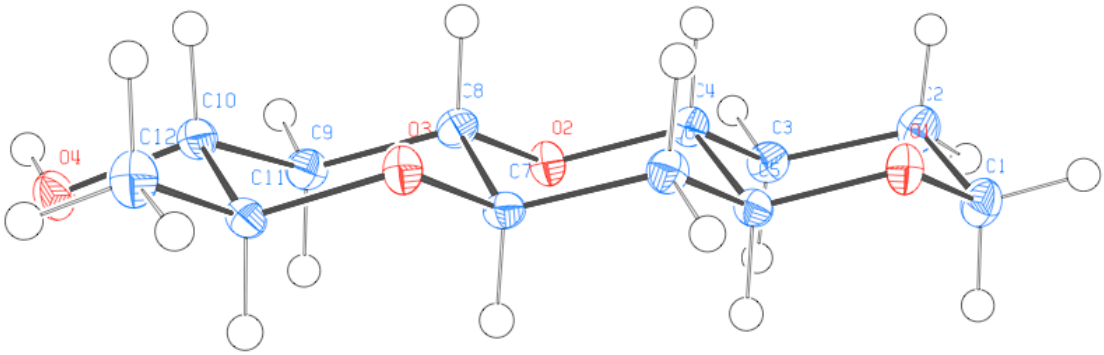


Figure 3. "Side-on" view B of 6. Displacement ellipsoids are scaled to 50% probability.

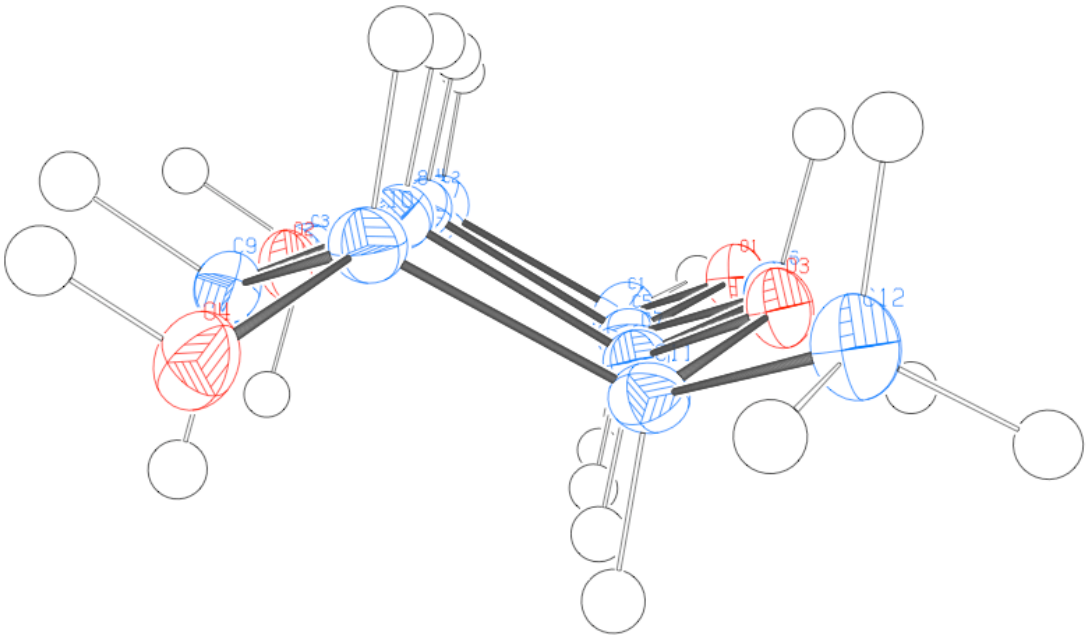


Table 3. Crystal data and structure refinement for d09014.

Identification code	d09014	
Empirical formula	C12 H20 O4	
Formula weight	228.28	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 10.4928(3) Å	a= 90°.
	b = 5.17550(10) Å	b= 112.4120(10)°.
	c = 11.2885(3) Å	g = 90°.
Volume	566.72(2) Å^3	
Z	2	
Density (calculated)	1.338 Mg/m^3	
Absorption coefficient	0.814 mm^{-1}	
F(000)	248	
Crystal size	0.48 x 0.12 x 0.10 mm^3	
Theta range for data collection	4.24 to 67.66°.	
Index ranges	-12<=h<=12, -6<=k<=6, -13<=l<=13	
Reflections collected	10799	
Independent reflections	2028 [R(int) = 0.0185]	
Completeness to theta = 67.66°	99.7 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9230 and 0.6959
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2028 / 2 / 150
Goodness-of-fit on F^2	1.102
Final R indices [I>2sigma(I)]	R1 = 0.0281, wR2 = 0.0839
R indices (all data)	R1 = 0.0283, wR2 = 0.0842
Absolute structure parameter	0.07(13)
Extinction coefficient	0.0103(11)
Largest diff. peak and hole	0.251 and -0.176 e.$Å^{-3}$

Table 4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for d09014. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	3624(1)	4664(2)	7603(1)	17(1)
O(2)	3314(1)	8093(2)	4647(1)	15(1)
O(3)	-30(1)	4731(2)	3433(1)	14(1)
O(4)	-272(1)	7648(2)	409(1)	18(1)
C(1)	5069(1)	5023(3)	8330(1)	19(1)
C(2)	5558(1)	7711(3)	8131(1)	19(1)
C(3)	5197(1)	8208(2)	6701(1)	17(1)
C(4)	3664(1)	7752(2)	5994(1)	15(1)
C(5)	3284(1)	5011(2)	6263(1)	14(1)
C(6)	1745(1)	4540(3)	5554(1)	15(1)
C(7)	1420(1)	5017(2)	4144(1)	13(1)
C(8)	1870(1)	7744(2)	3937(1)	14(1)
C(9)	1561(1)	8150(2)	2527(1)	15(1)
C(10)	32(1)	7624(2)	1757(1)	15(1)
C(11)	-381(1)	4944(2)	2078(1)	14(1)
C(12)	-1914(1)	4438(3)	1412(1)	19(1)

Table 5. Bond lengths [Å] and angles [°] for d09014.

O(1)-C(5)	1.4274(12)
O(1)-C(1)	1.4351(13)
O(2)-C(8)	1.4295(12)

O(2)-C(4)	1.4325(13)
O(3)-C(7)	1.4320(12)
O(3)-C(11)	1.4345(12)
O(4)-C(10)	1.4308(13)
O(4)-H(4)	0.814(13)
C(1)-C(2)	1.5284(17)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-C(3)	1.5322(16)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.5172(14)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(5)	1.5346(16)
C(4)-H(4A)	1.0000
C(5)-C(6)	1.5241(14)
C(5)-H(5)	1.0000
C(6)-C(7)	1.5154(14)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.5342(15)
C(7)-H(7)	1.0000
C(8)-C(9)	1.5128(15)
C(8)-H(8)	1.0000
C(9)-C(10)	1.5298(14)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.5367(16)
C(10)-H(10)	1.0000
C(11)-C(12)	1.5159(15)
C(11)-H(11)	1.0000
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800

C(5)-O(1)-C(1)	111.82(8)
C(8)-O(2)-C(4)	111.57(8)
C(7)-O(3)-C(11)	112.09(8)
C(10)-O(4)-H(4)	107.9(10)
O(1)-C(1)-C(2)	112.01(9)
O(1)-C(1)-H(1A)	109.2
C(2)-C(1)-H(1A)	109.2
O(1)-C(1)-H(1B)	109.2
C(2)-C(1)-H(1B)	109.2
H(1A)-C(1)-H(1B)	107.9

C(1)-C(2)-C(3)	110.20(10)
C(1)-C(2)-H(2A)	109.6
C(3)-C(2)-H(2A)	109.6
C(1)-C(2)-H(2B)	109.6
C(3)-C(2)-H(2B)	109.6
H(2A)-C(2)-H(2B)	108.1
C(4)-C(3)-C(2)	108.36(9)
C(4)-C(3)-H(3A)	110.0
C(2)-C(3)-H(3A)	110.0
C(4)-C(3)-H(3B)	110.0
C(2)-C(3)-H(3B)	110.0
H(3A)-C(3)-H(3B)	108.4
O(2)-C(4)-C(3)	109.33(9)
O(2)-C(4)-C(5)	110.05(9)
C(3)-C(4)-C(5)	110.05(10)
O(2)-C(4)-H(4A)	109.1
C(3)-C(4)-H(4A)	109.1
C(5)-C(4)-H(4A)	109.1
O(1)-C(5)-C(6)	108.80(8)
O(1)-C(5)-C(4)	110.31(9)
C(6)-C(5)-C(4)	110.31(9)
O(1)-C(5)-H(5)	109.1
C(6)-C(5)-H(5)	109.1
C(4)-C(5)-H(5)	109.1
C(7)-C(6)-C(5)	107.10(9)
C(7)-C(6)-H(6A)	110.3
C(5)-C(6)-H(6A)	110.3
C(7)-C(6)-H(6B)	110.3
C(5)-C(6)-H(6B)	110.3
H(6A)-C(6)-H(6B)	108.5
O(3)-C(7)-C(6)	109.74(8)
O(3)-C(7)-C(8)	109.42(9)
C(6)-C(7)-C(8)	110.53(9)
O(3)-C(7)-H(7)	109.0
C(6)-C(7)-H(7)	109.0
C(8)-C(7)-H(7)	109.0
O(2)-C(8)-C(9)	109.18(8)
O(2)-C(8)-C(7)	110.66(9)
C(9)-C(8)-C(7)	109.46(9)
O(2)-C(8)-H(8)	109.2
C(9)-C(8)-H(8)	109.2
C(7)-C(8)-H(8)	109.2
C(8)-C(9)-C(10)	109.33(9)
C(8)-C(9)-H(9A)	109.8
C(10)-C(9)-H(9A)	109.8
C(8)-C(9)-H(9B)	109.8

C(10)-C(9)-H(9B)	109.8
H(9A)-C(9)-H(9B)	108.3
O(4)-C(10)-C(9)	111.29(9)
O(4)-C(10)-C(11)	106.83(9)
C(9)-C(10)-C(11)	110.82(9)
O(4)-C(10)-H(10)	109.3
C(9)-C(10)-H(10)	109.3
C(11)-C(10)-H(10)	109.3
O(3)-C(11)-C(12)	107.92(8)
O(3)-C(11)-C(10)	109.85(9)
C(12)-C(11)-C(10)	112.35(9)
O(3)-C(11)-H(11)	108.9
C(12)-C(11)-H(11)	108.9
C(10)-C(11)-H(11)	108.9
C(11)-C(12)-H(12A)	109.5
C(11)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(11)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 6. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for d09014. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	16(1)	20(1)	13(1)	3(1)	3(1)	-1(1)
O(2)	15(1)	18(1)	12(1)	1(1)	5(1)	-2(1)
O(3)	13(1)	18(1)	12(1)	1(1)	4(1)	-1(1)
O(4)	25(1)	16(1)	13(1)	2(1)	7(1)	-2(1)
C(1)	17(1)	19(1)	16(1)	1(1)	2(1)	0(1)
C(2)	16(1)	20(1)	19(1)	0(1)	3(1)	-2(1)
C(3)	16(1)	16(1)	18(1)	0(1)	6(1)	-1(1)
C(4)	16(1)	15(1)	14(1)	1(1)	6(1)	1(1)
C(5)	17(1)	13(1)	13(1)	0(1)	6(1)	1(1)
C(6)	15(1)	15(1)	15(1)	1(1)	6(1)	0(1)
C(7)	13(1)	12(1)	15(1)	-1(1)	5(1)	0(1)
C(8)	13(1)	14(1)	16(1)	0(1)	6(1)	0(1)
C(9)	18(1)	13(1)	16(1)	1(1)	8(1)	-1(1)
C(10)	17(1)	15(1)	13(1)	1(1)	7(1)	2(1)
C(11)	17(1)	14(1)	12(1)	-1(1)	6(1)	1(1)

C(12)	17(1)	22(1)	16(1)	2(1)	6(1)	-2(1)

Table 7. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for d09014.

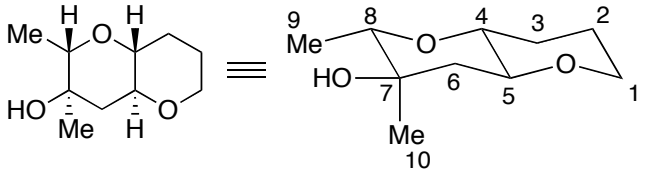
	x	y	z	U(eq)
H(4)	-149(15)	9110(30)	209(14)	22
H(1A)	5596	3702	8071	23
H(1B)	5259	4773	9251	23
H(2A)	6568	7844	8600	23
H(2B)	5113	9034	8477	23
H(3A)	5433	10008	6568	21
H(3B)	5729	7026	6373	21
H(4A)	3140	9033	6295	18
H(5)	3810	3730	5964	17
H(6A)	1509	2742	5690	18
H(6B)	1207	5731	5871	18
H(7)	1926	3722	3830	16
H(8)	1346	9042	4229	17
H(9A)	2131	6966	2245	18
H(9B)	1788	9947	2380	18
H(10)	-534	8974	1964	18
H(11)	135	3596	1807	17
H(12A)	-2138	2764	1689	28
H(12B)	-2164	4418	482	28
H(12C)	-2429	5806	1634	28

Table 8. Hydrogen bonds for d09014 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(4)-H(4)...O(4)#1	0.814(13)	2.066(13)	2.8772(7)	174.0(14)

Symmetry transformations used to generate equivalent atoms:
#1 -x,y+1/2,-z

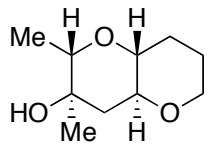
Assignment of bis-THP Diad 3b by ^{1}H-^{1}H gCOSY:



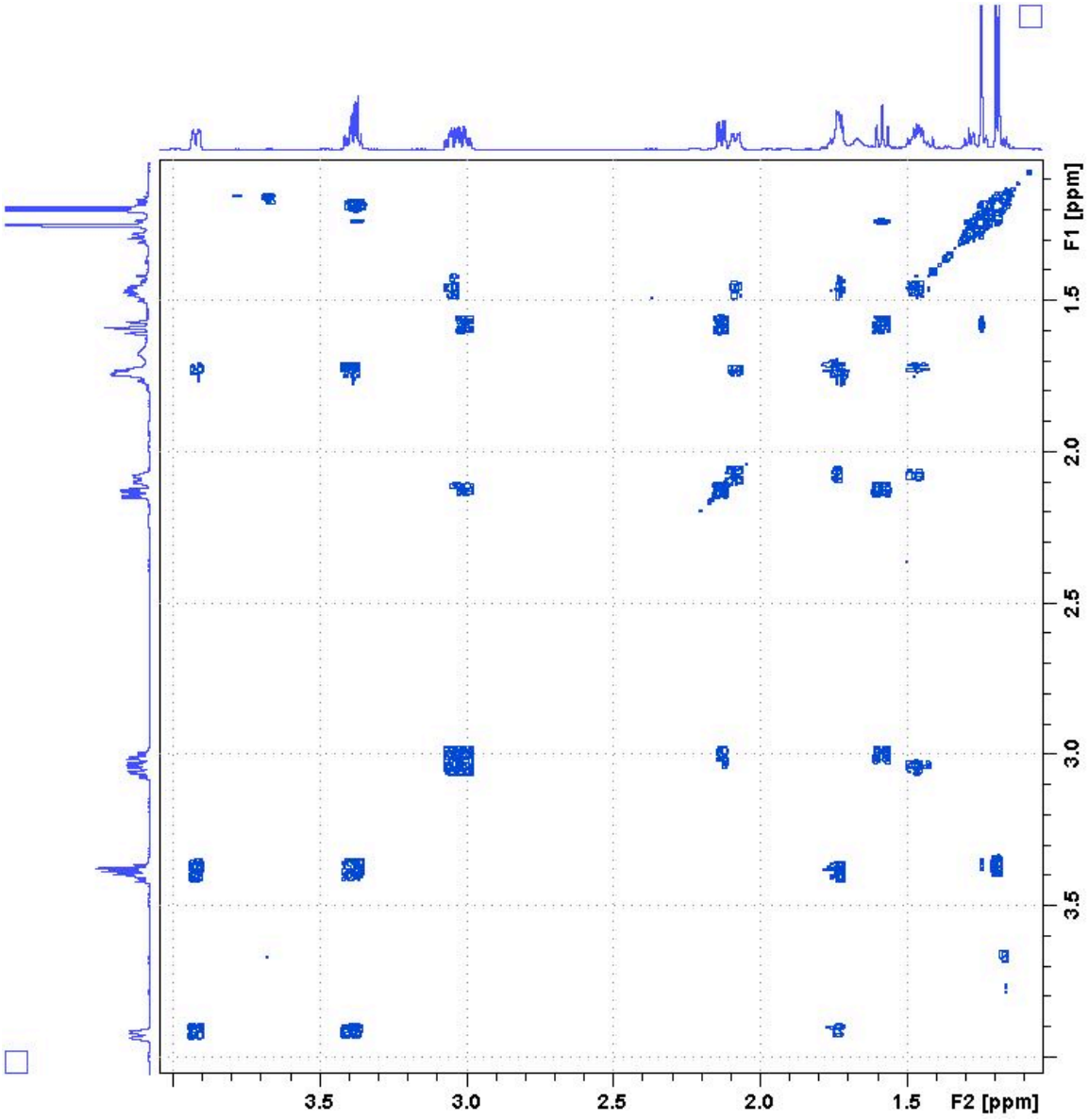
3b

chemical shift (δ)	**^{1}H-^{1}H gCOSY assignment**
3.94-3.88 (m, 1H)	1eq
3.41-3.34 (m, 2H)	1ax, 8ax
3.07-2.97 (m, 2H)	4ax, 5ax
2.12 (dd, *J* = 11.5, 4.2 Hz, 1H)	6eq
2.10-2.04 (m, 1H)	3eq
1.75-1.68 (m, 2H)	2eq, 2ax
1.57 (app t, *J* = 11.3 Hz, 1H)	6ax
1.50-1.41 (m, 2H)	3ax, OH
1.23 (s, 3H)	10Me
1.18 (d, *J* = 6.4 Hz, 3H)	9Me

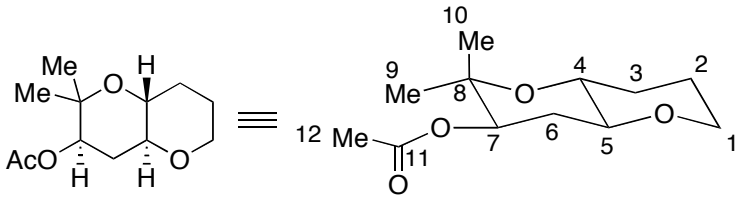
gCOSY of 3b



3b



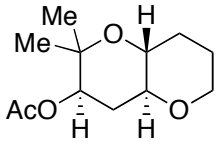
Assignment of acetylated bis-THP Diad 25 by ^{1}H-^{1}H gCOSY:



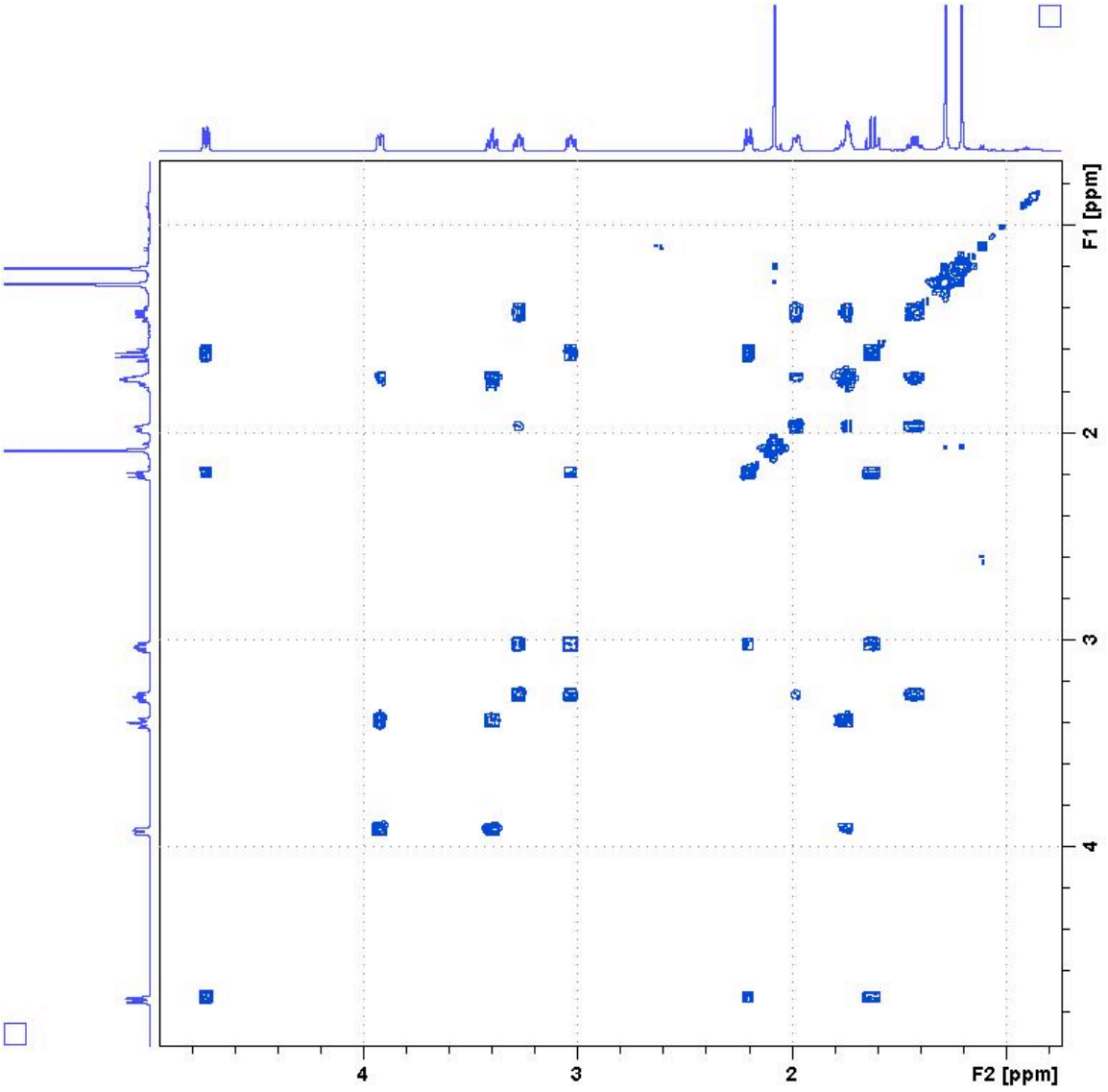
25

chemical shift (δ)	**^{1}H-^{1}H gCOSY assignment**
4.71 (dd, *J* = 11.9, 4.6 Hz, 1H)	7ax
3.93-3.88 (m, 1H)	1eq
3.42-3.34 (m, 1H)	1ax
3.29-3.23 (m, 1H)	4ax
3.02 (ddd, *J* = 11.9, 9.3, 4.4 Hz, 1H)	5ax
2.18 (app dt, *J* = 11.5, 4.5 Hz, 1H)	6eq
2.07 (s, 3H)	12Me
1.99-1.93 (m, 1H)	3eq
1.79-1.69 (m, 2H)	2eq, 2ax
1.60 (app q, *J* = 11.7 Hz, 1H)	6ax
1.40 (app dq, *J* = 11.6, 5.6 Hz, 1H)	3ax
1.26 (s, 3H); 1.18 (s, 3H)	9Me and 10Me

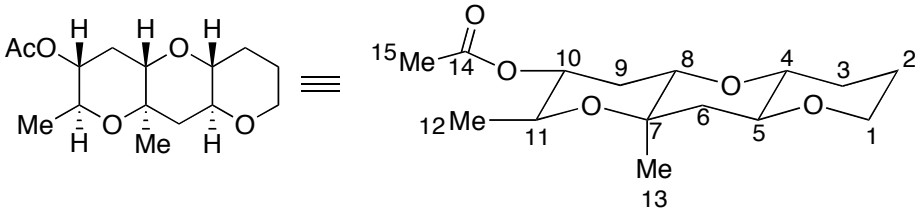
gCOSY of 25



25



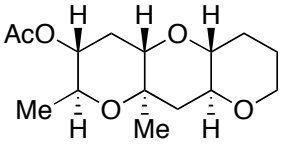
Assignment of acetylated bis-THP Diad 35 by ^{1}H-^{1}H gCOSY:



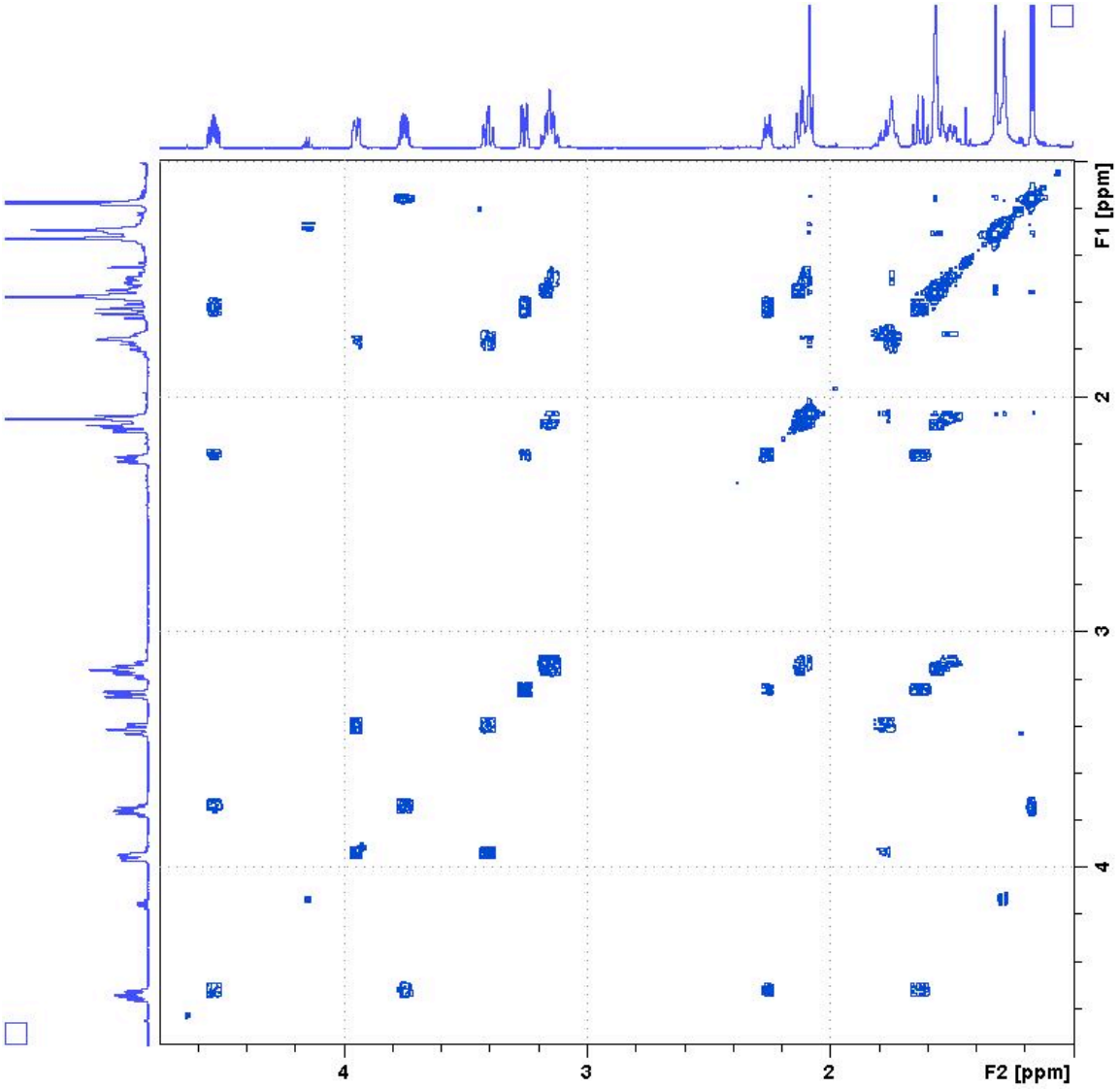
35

chemical shift (δ)	**^{1}H-^{1}H gCOSY assignment**
4.51 (ddd, *J* = 11.1, 9.8, 5.2 Hz, 1H)	10ax
3.95-3.90 (m, 1H)	1eq
3.73 (dq, *J* = 9.8, 6.0 Hz, 1H)	11ax
3.38 (app dt, *J* = 11.4, 3.6 Hz, 1H)	1ax
3.24 (dd, *J* = 12.6, 3.9 Hz, 1H)	8ax
3.18-3.09 (m, 2H)	4ax, 5ax
2.23 (ddd, *J* = 11.4, 4.8, 4.3 Hz, 1H)	9eq
2.13-2.04 (m, 5H)	3eq, 6eq, 15Me
1.81-1.68 (m, 2H)	2ax, 2eq
1.61 (app q, *J* = 12.0 Hz, 1H)	9ax
1.57-1.43 (m, 2H)	3ax, 6ax
1.30 (s, 3H)	13Me
1.14 (d, *J* = 6.0 Hz, 3H)	12Me

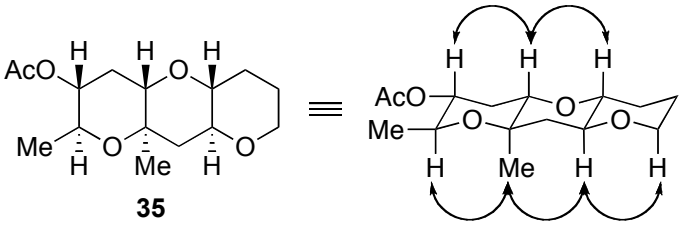
gCOSY of 35

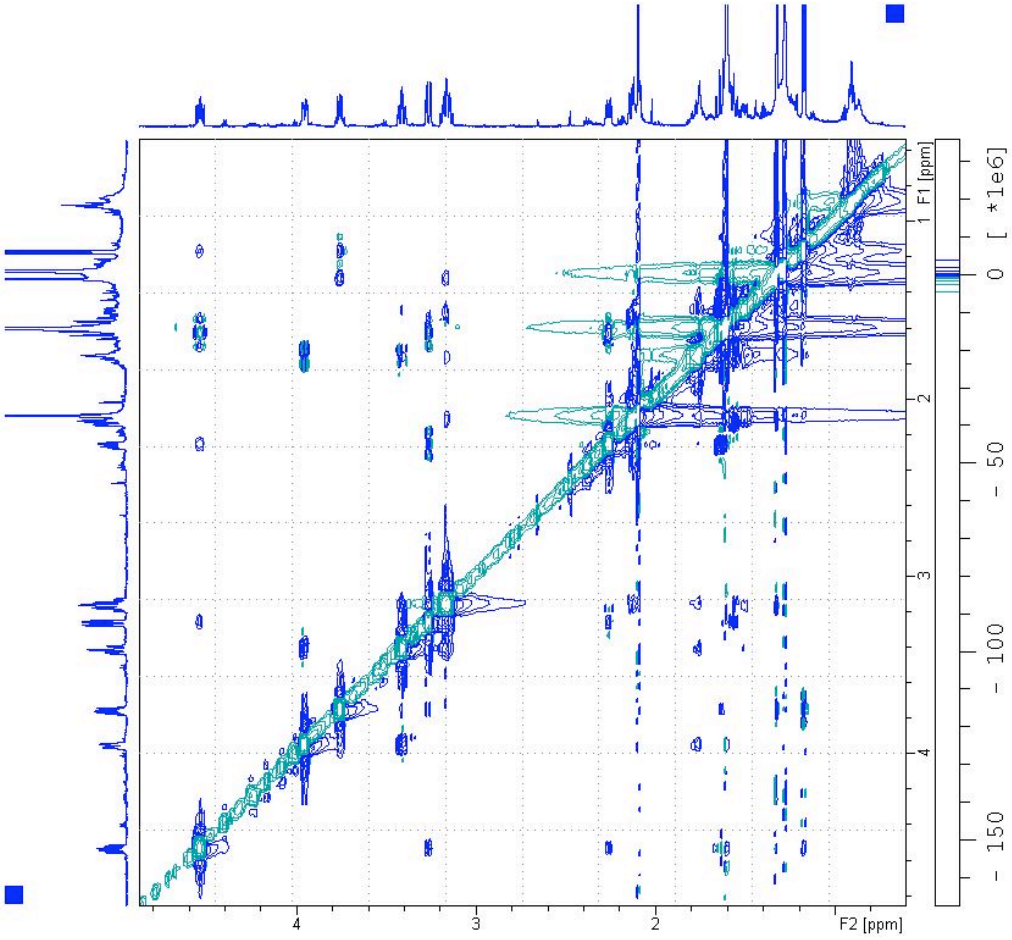


35

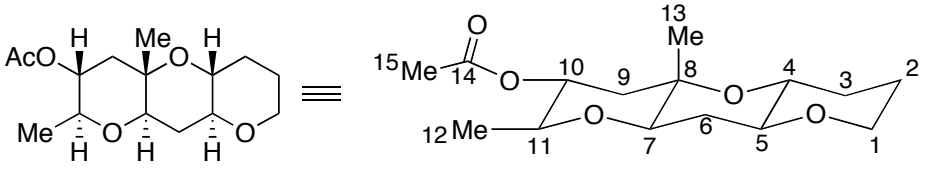


Corroboration of the relative stereochemistry of tri-THP triad 35 by NOESY





Assignment of acetylated tris-THP Triad 41 by ^{1}H-^{1}H gCOSY:



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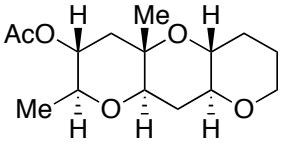
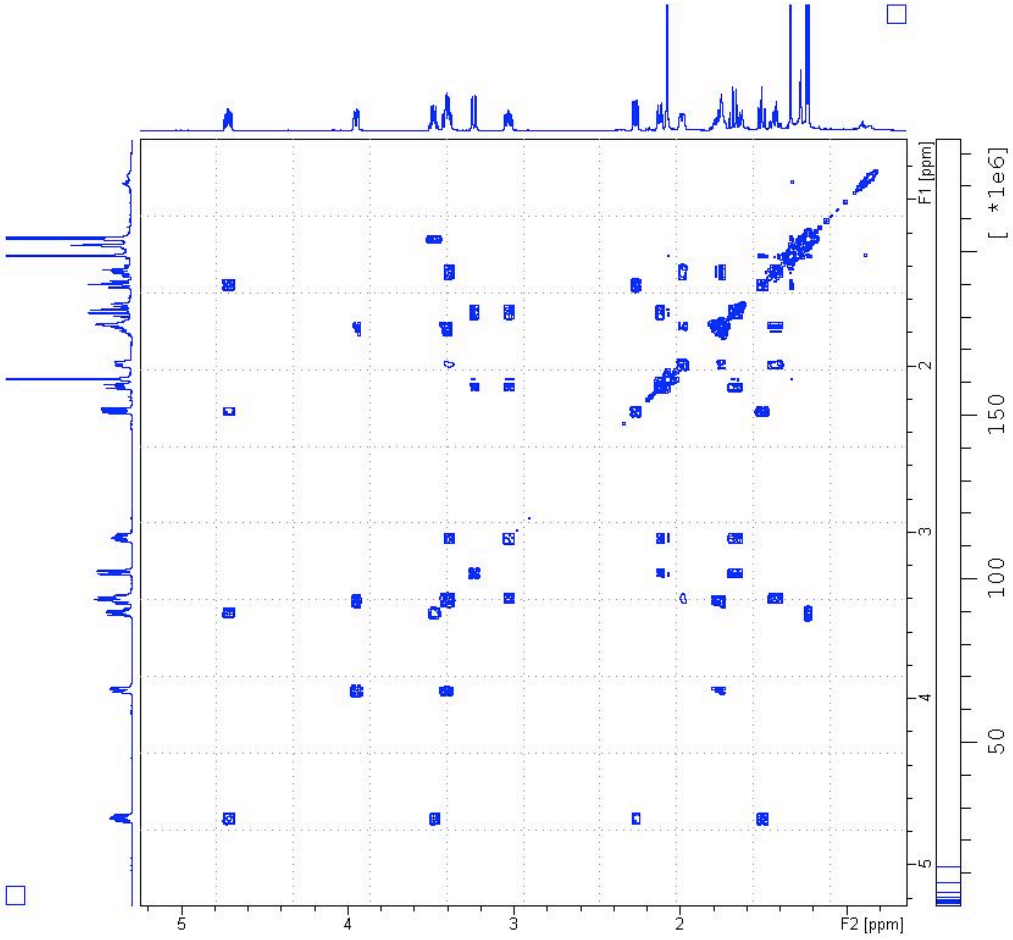
chemical shift (δ)	**^{1}H-^{1}H gCOSY assignment**
4.70 (ddd, *J* = 11.3, 9.7, 5.3 Hz, 1H)	10ax
3.96-3.90 (m, 1H)	1eq
3.46 (dq, *J* = 9.7, 6.2 Hz, 1H)	11ax
3.42-3.34 (m, 2H)	1ax, 4ax
3.22 (dd, *J* = 12.3, 3.9 Hz, 1H)	7ax
3.01 (ddd, *J* = 11.4, 9.3, 4.5 Hz, 1H)	5ax
2.25 (dd, *J* = 11.5, 5.2 Hz, 1H)	9eq
2.10 (app dt, *J* = 11.4, 4.2 Hz, 1H)	6eq
2.06 (s, 3H)	15Me
2.00-1.94 (m, 1H)	3eq
1.82-1.70 (m, 2H)	2ax, 2eq
1.65 (app q, *J* = 11.7 Hz, 1H)	6ax
1.49 (app t, *J* = 11.7 Hz, 1H)	9ax
1.41 (app dq, *J* = 12.0, 5.1 Hz, 1H)	3ax
1.32 (s, 3H)	13Me
1.21 (d, *J* = 6.2 Hz, 3H)	12Me

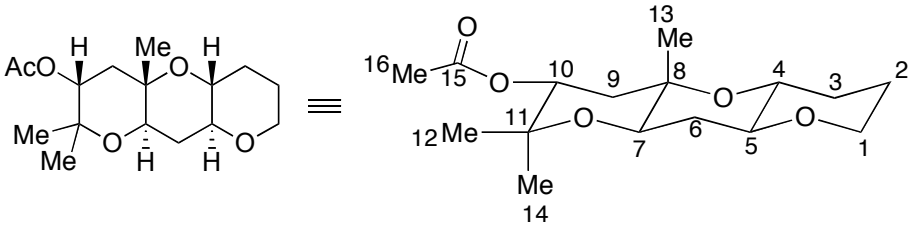
gCOSY of 41



41



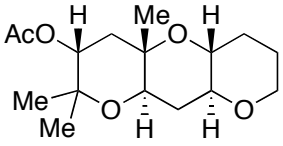
Assignment of acetylated tris-THP Triad 44 by ^{1}H-^{1}H gCOSY:



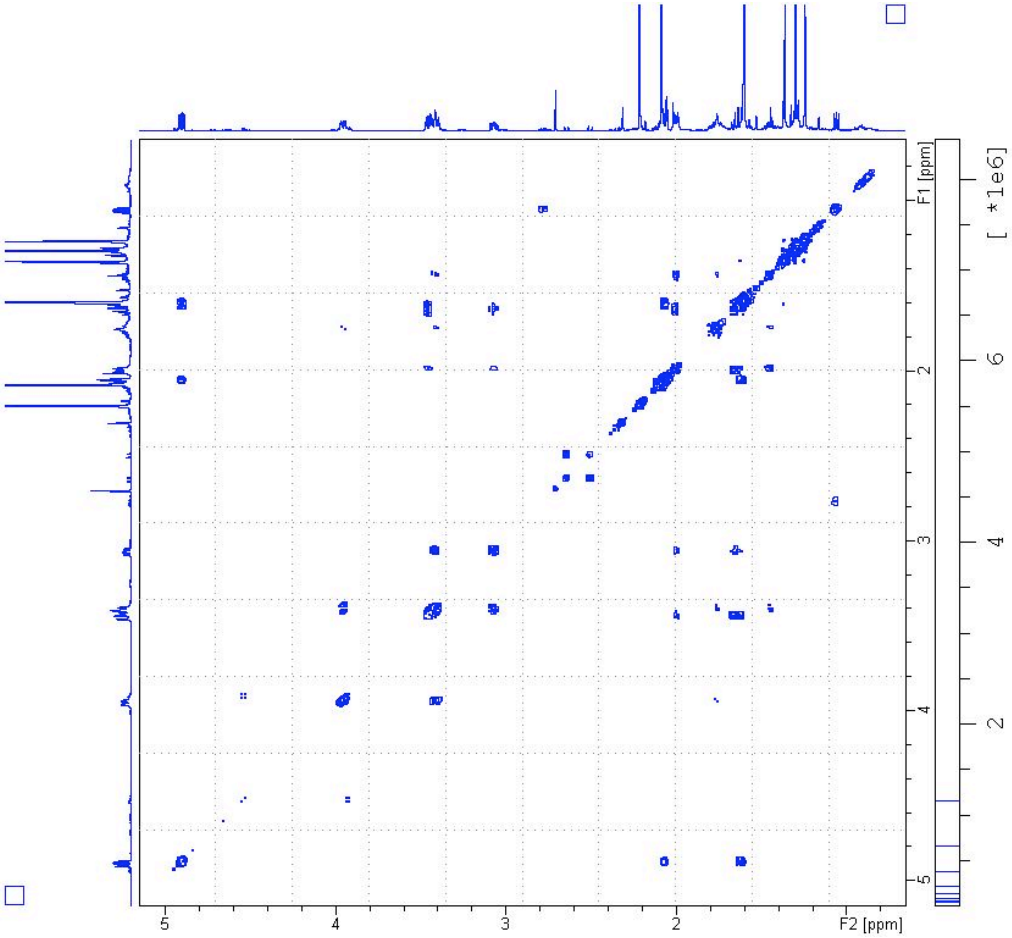
44

chemical shift (δ)	**^{1}H-^{1}H gCOSY assignment**
4.88 (dd, *J* = 12.0, 5.1 Hz, 1H)	10ax
3.95-3.90 (m, 1H)	1eq
3.45-3.35 (m, 3H)	1ax, 4ax, 7ax
3.04 (ddd, *J* = 11.4, 9.3, 4.6, 1H)	5ax
2.06-2.01 (m, 4H)	9eq, 16Me
2.00-1.94 (m, 2H)	6eq, 3eq
1.81-1.68 (m, 2H)	2ax, 2eq
1.66-1.55 (m, 2H)	6ax, 9ax
1.47-1.37 (m, 1H)	3ax
1.33 (s, 3H), 1.27 (s, 3H), 1.21 (s, 3H)	12Me, 13Me, and 14Me

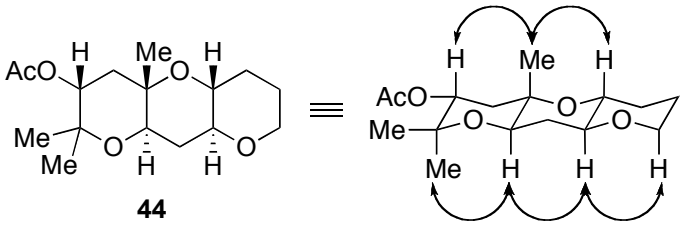
gCOSY of 44

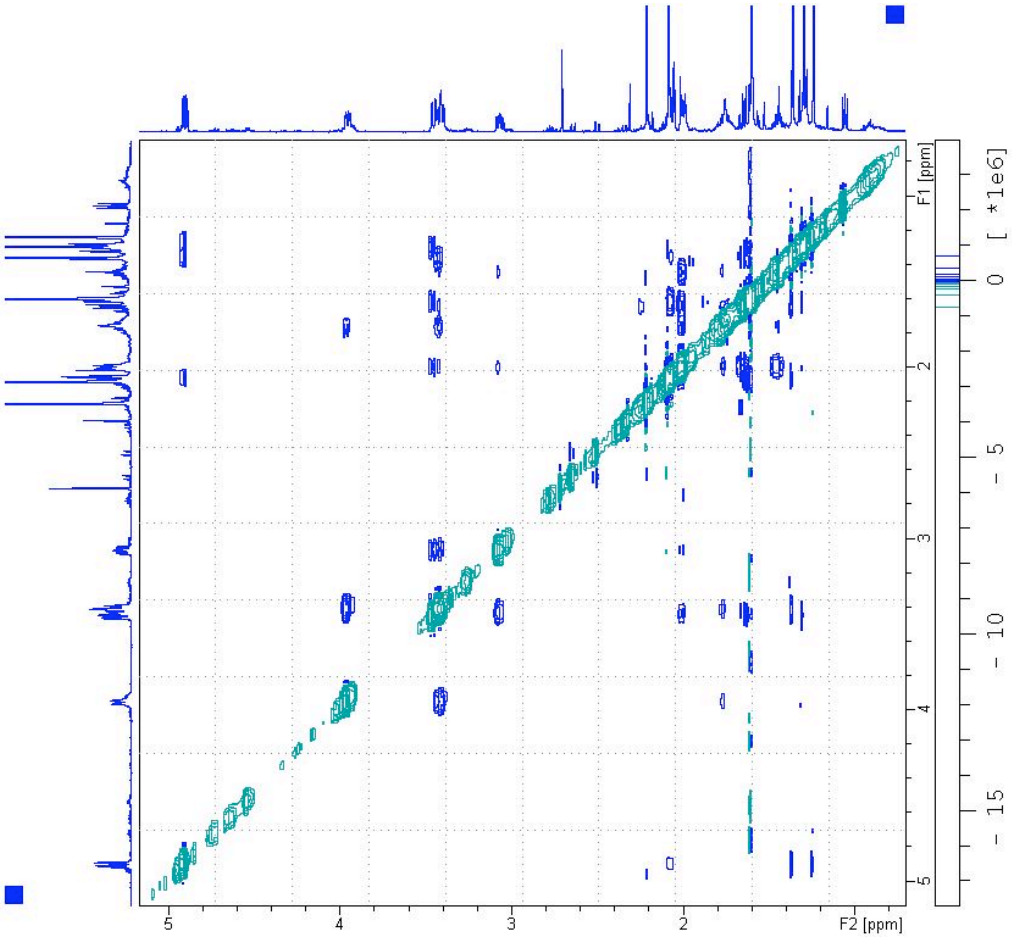


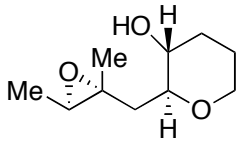
44



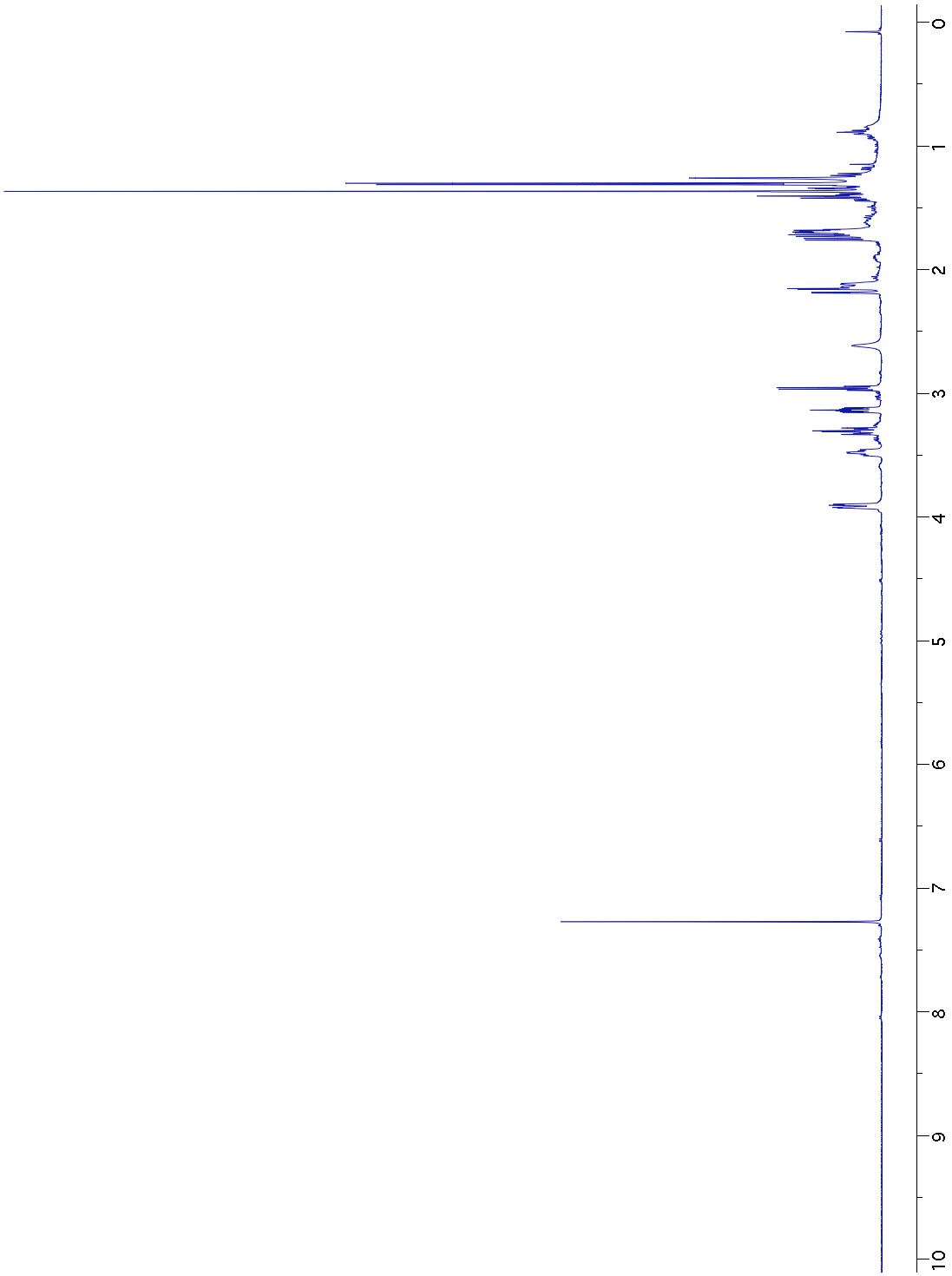
Corroboration of the relative stereochemistry of tri-THP triad 35 by NOESY

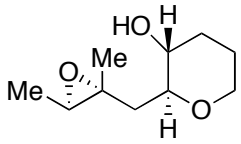






2b





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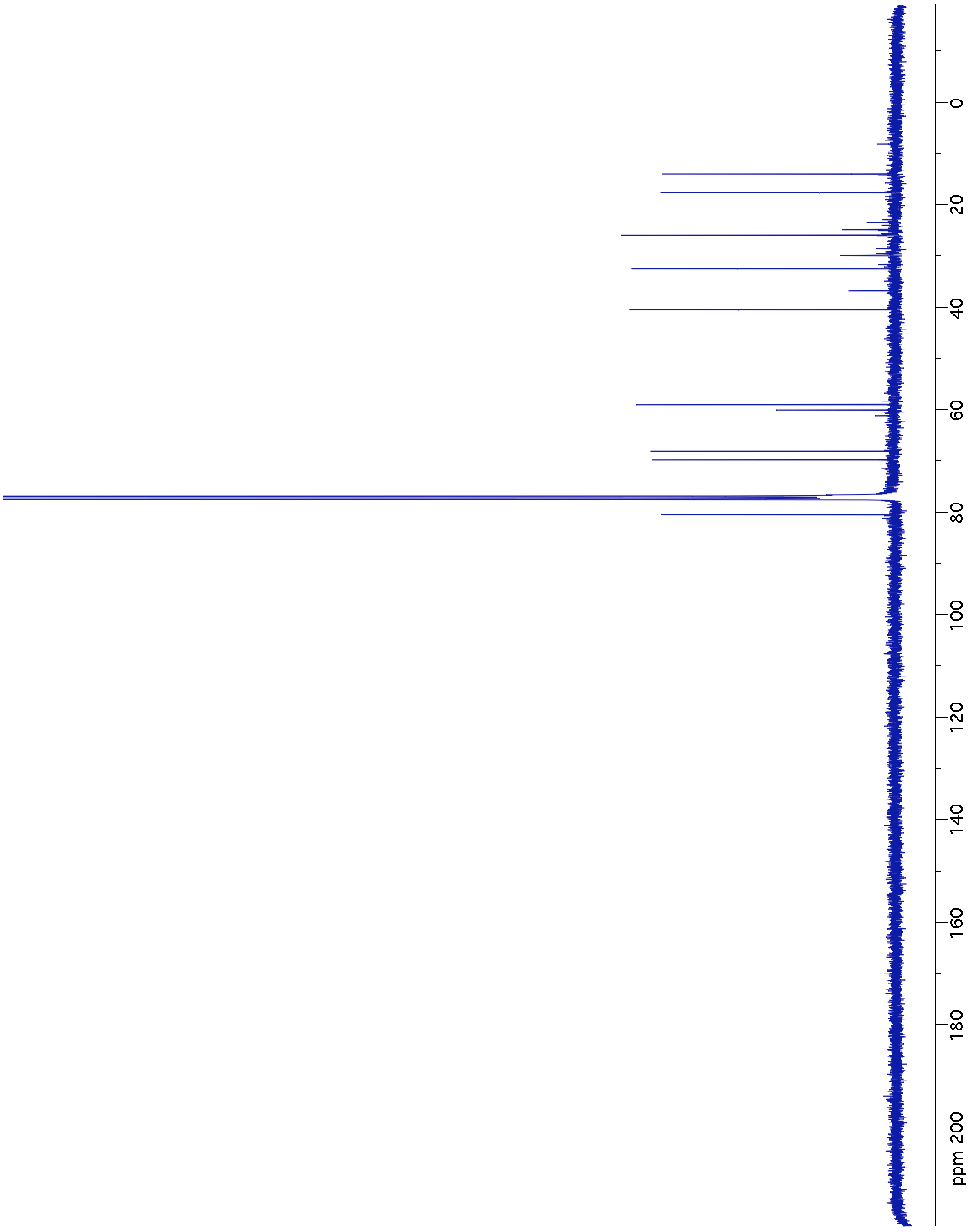

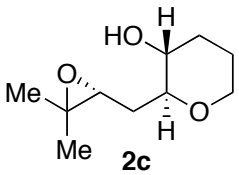

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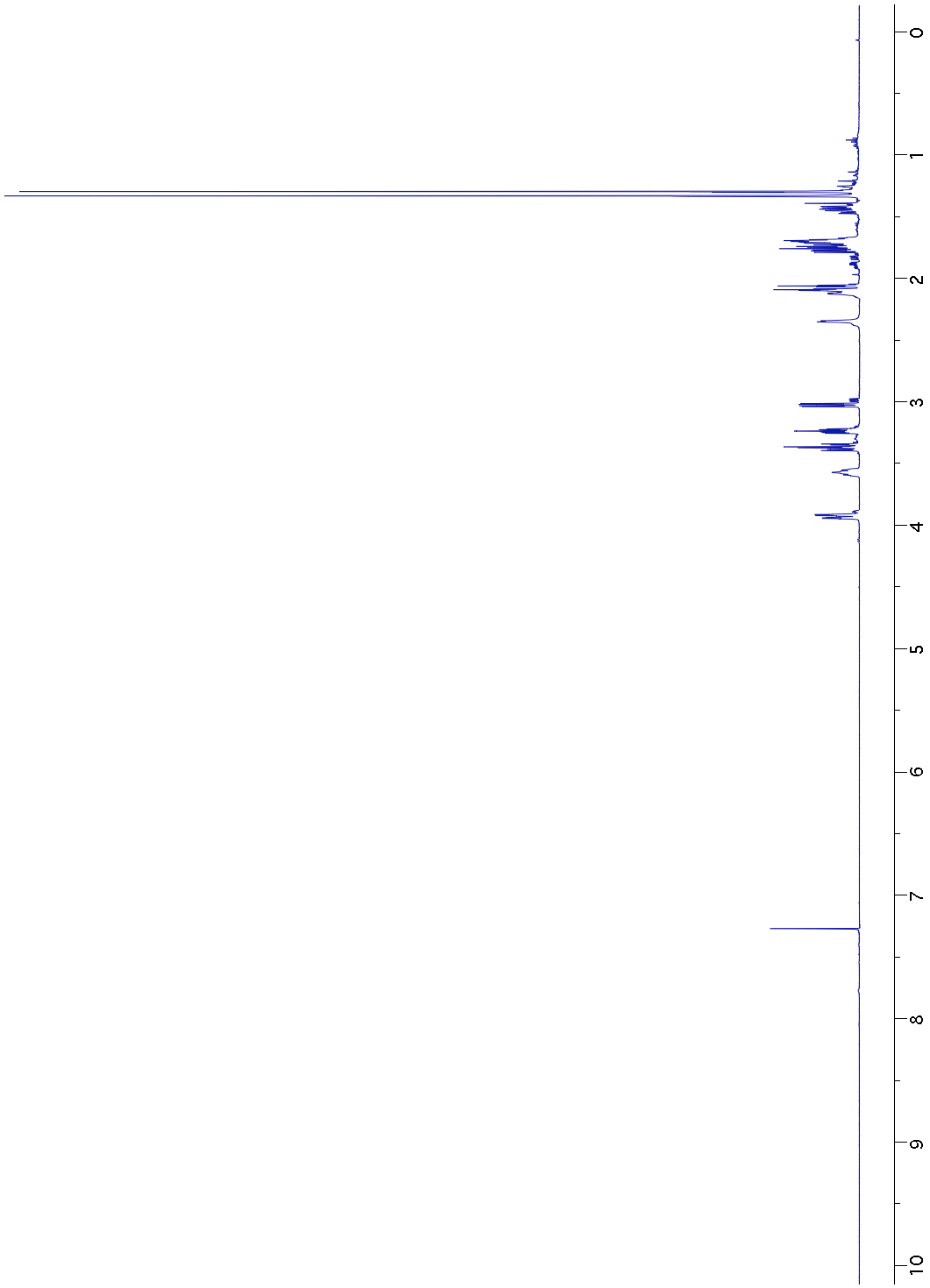

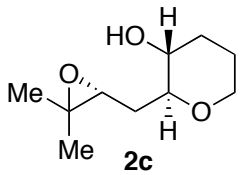
H
HO
O
Me
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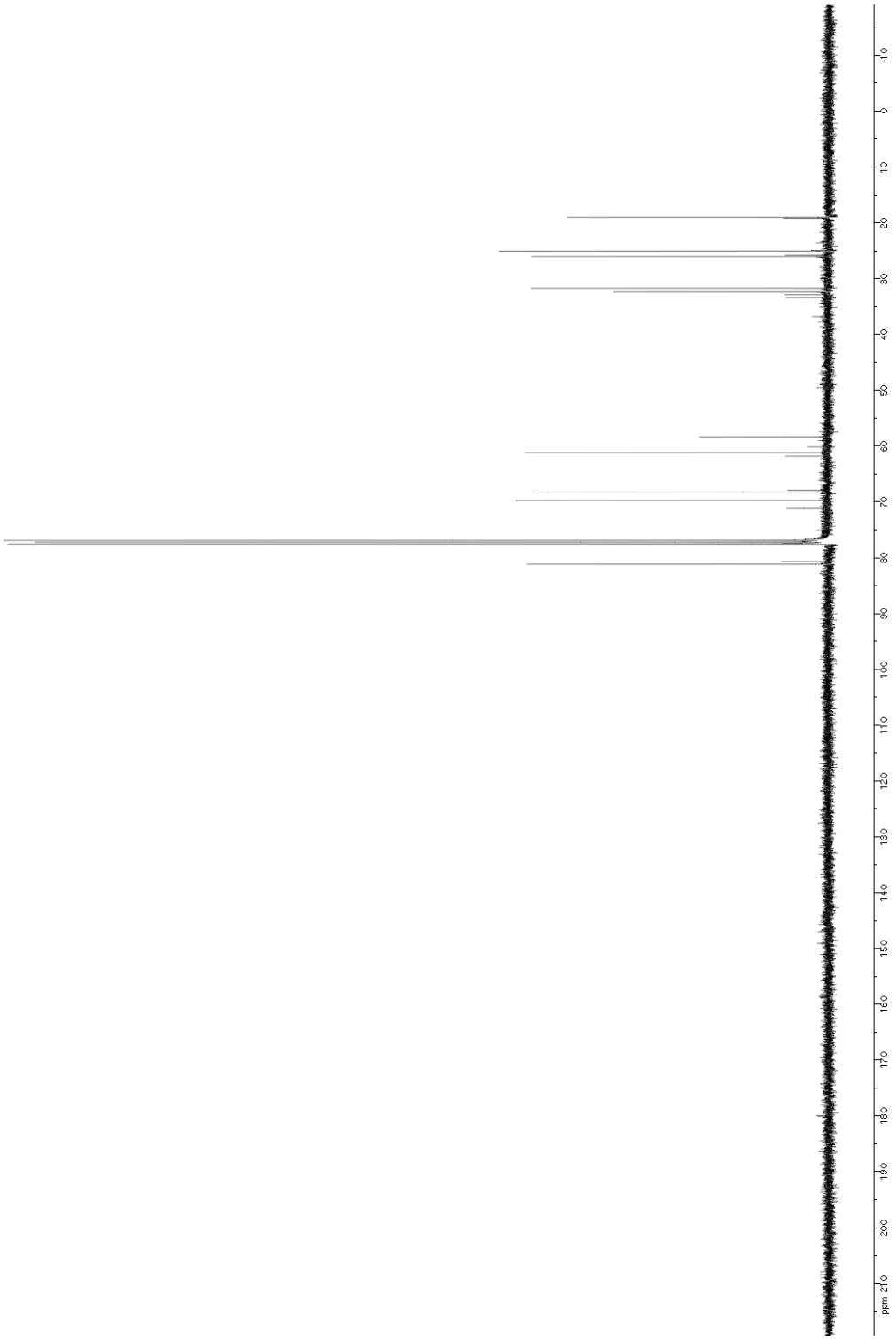
H
Me

2c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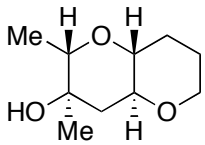

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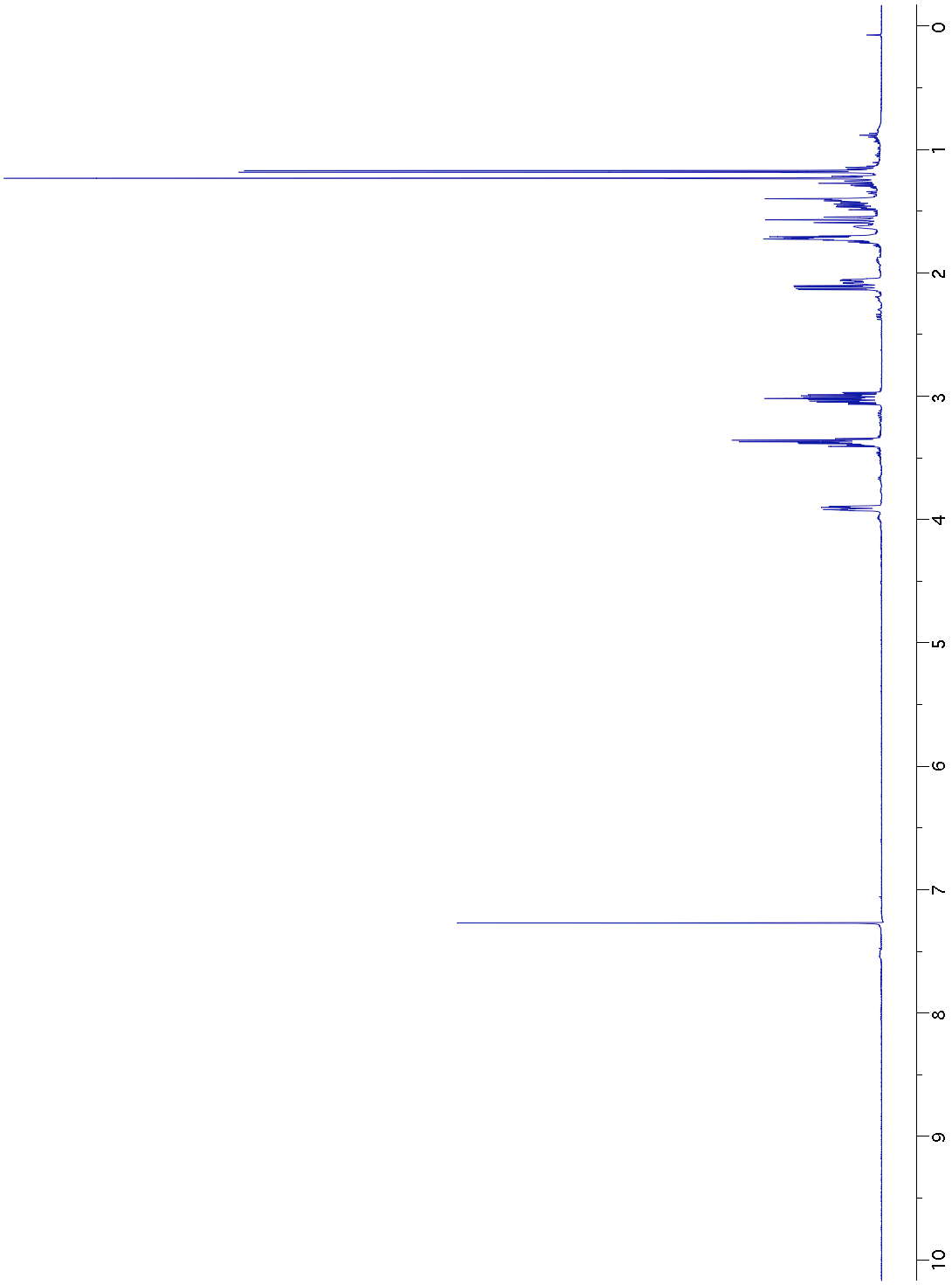

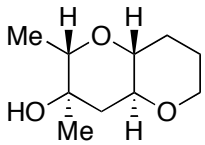

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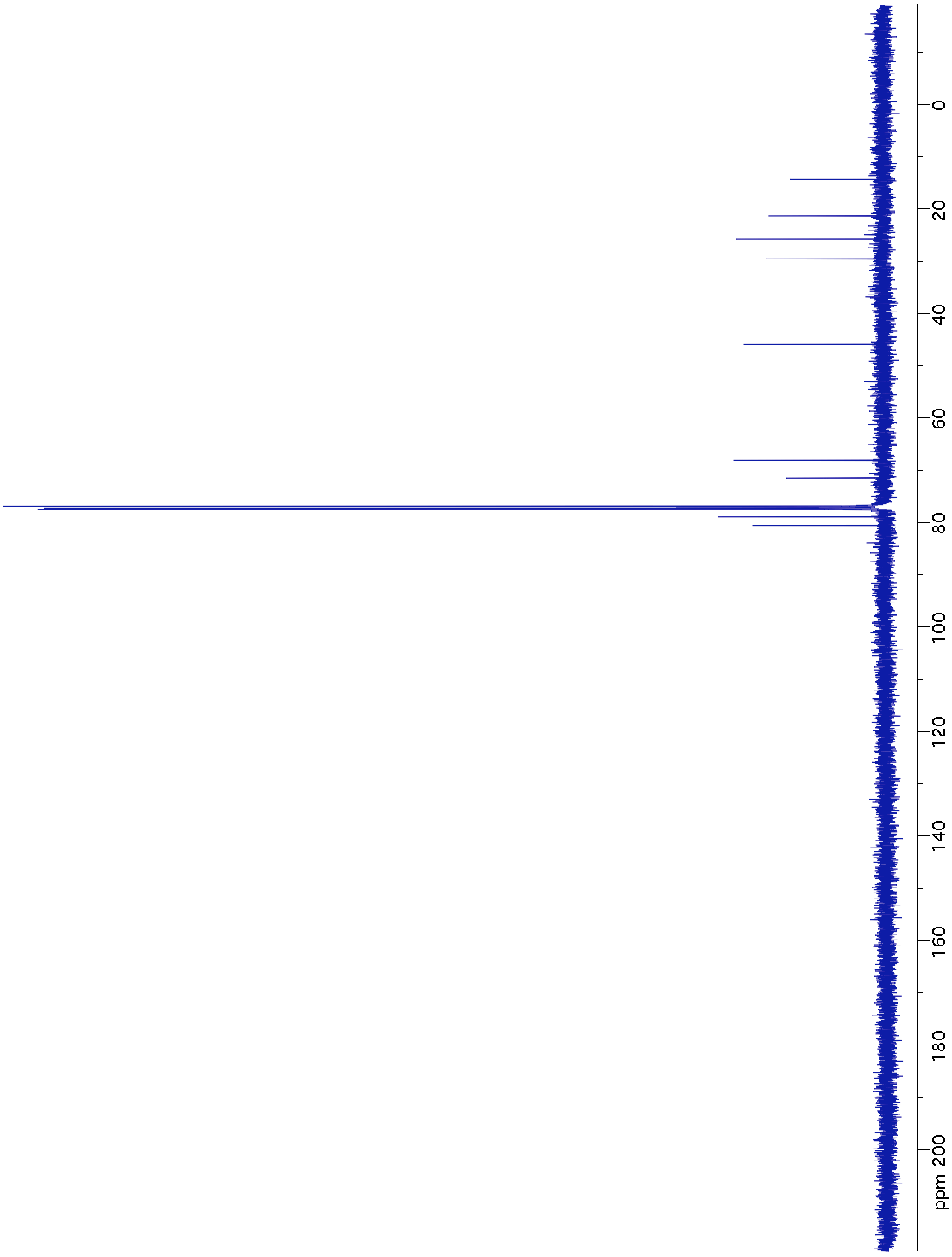

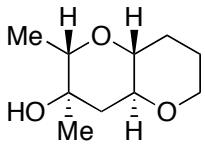

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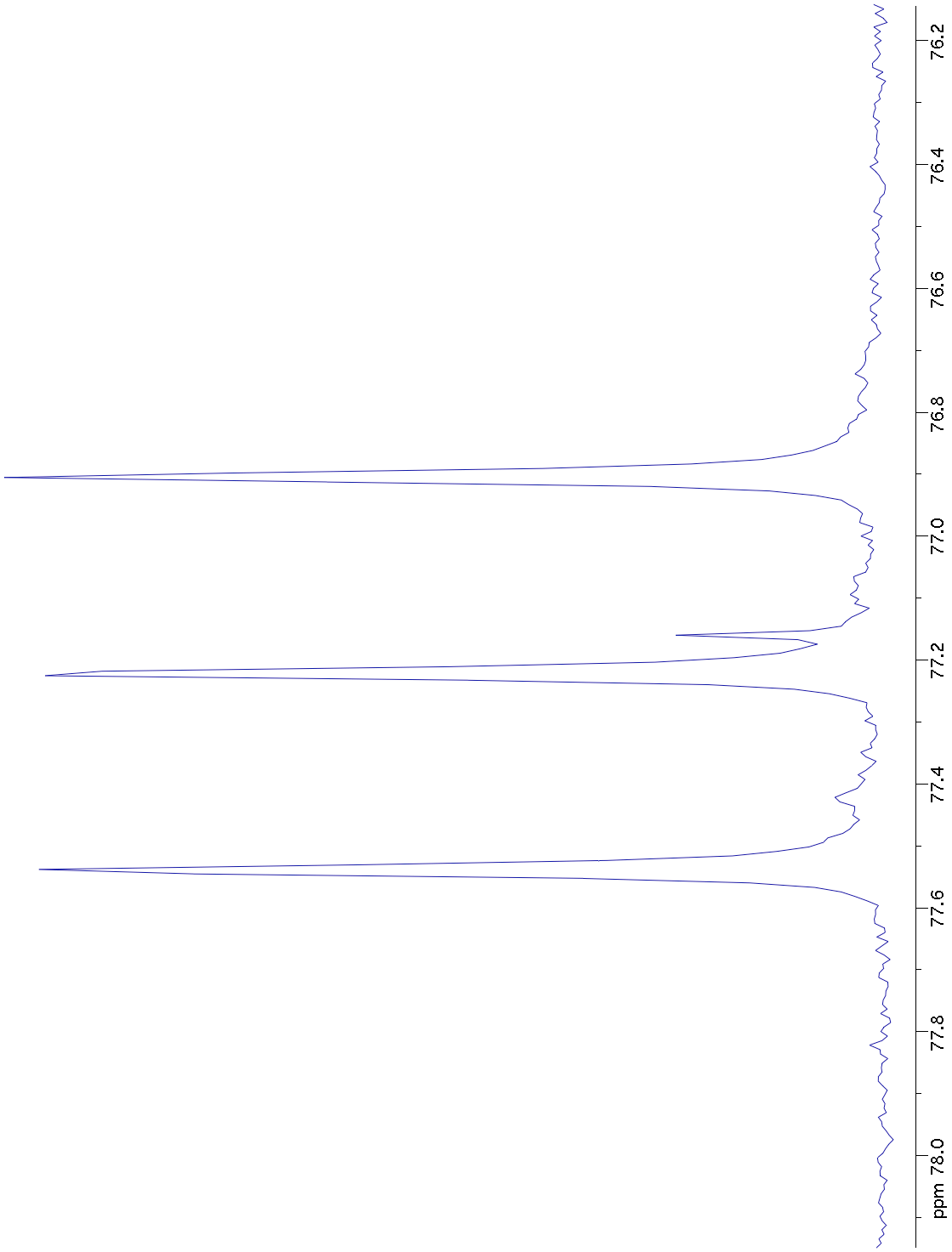

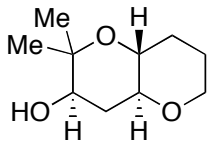

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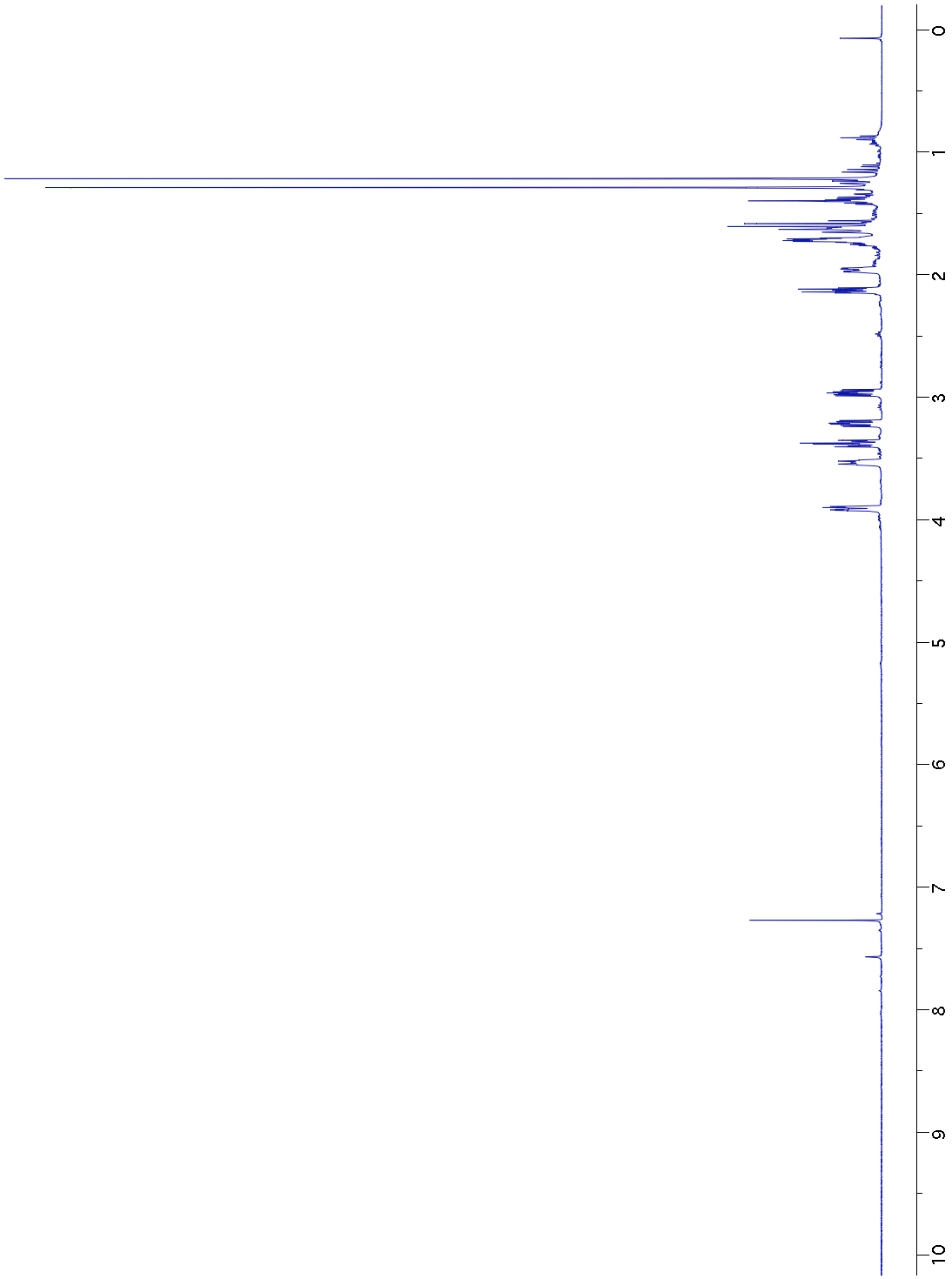
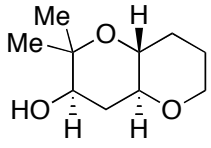
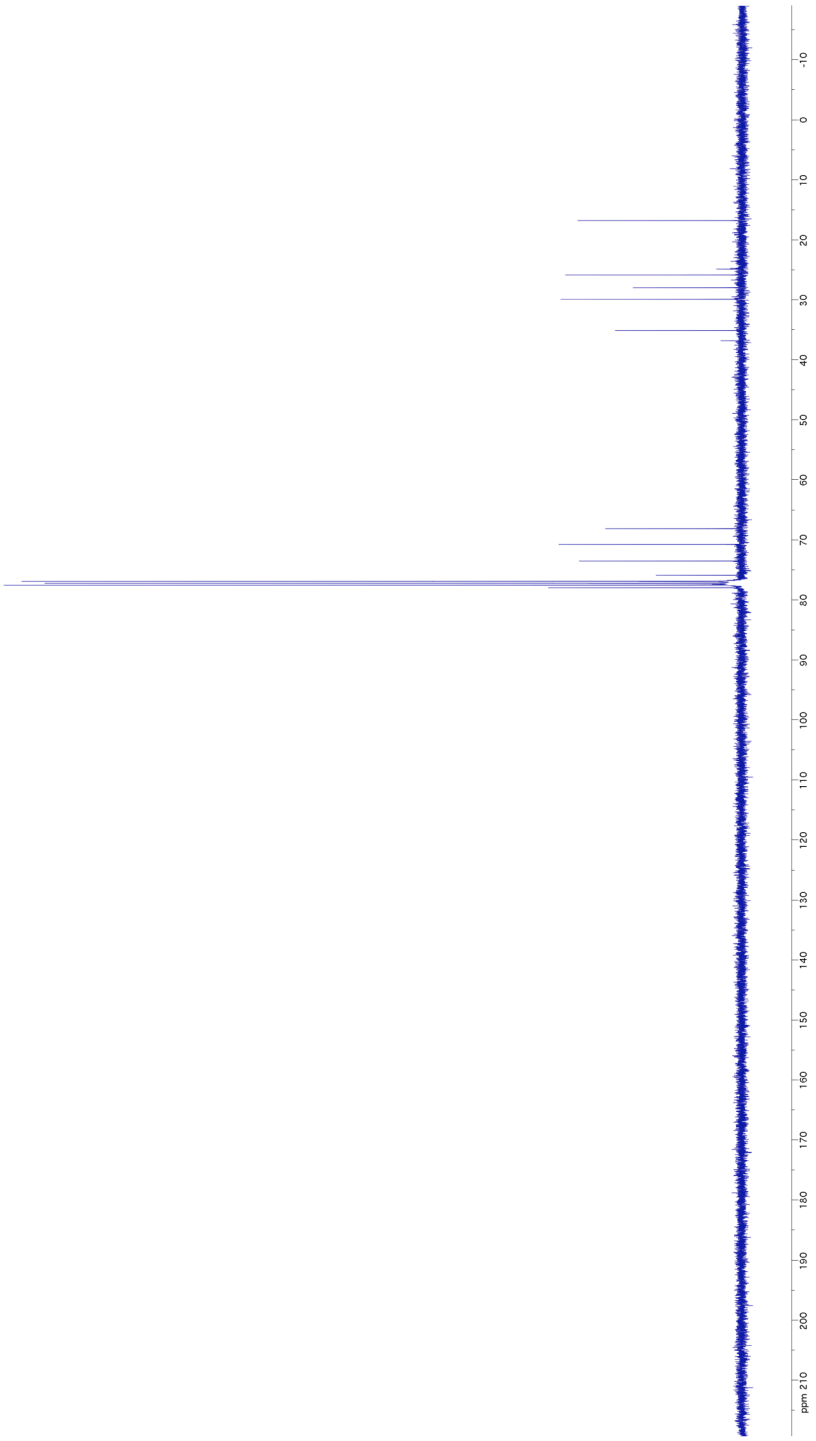



Me
Me
O
H
HO
H
H
O

3c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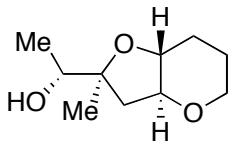

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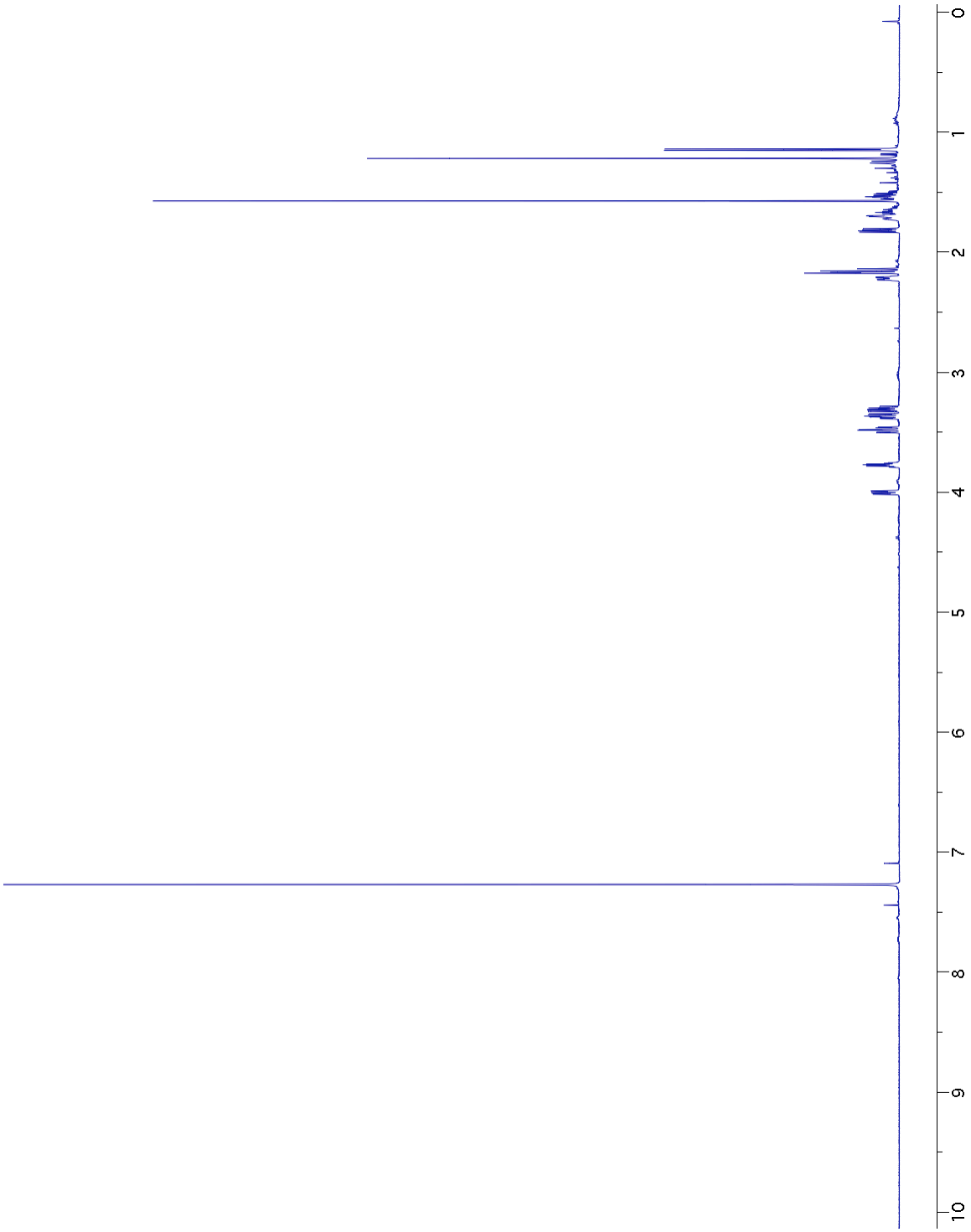

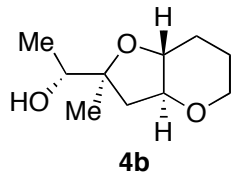

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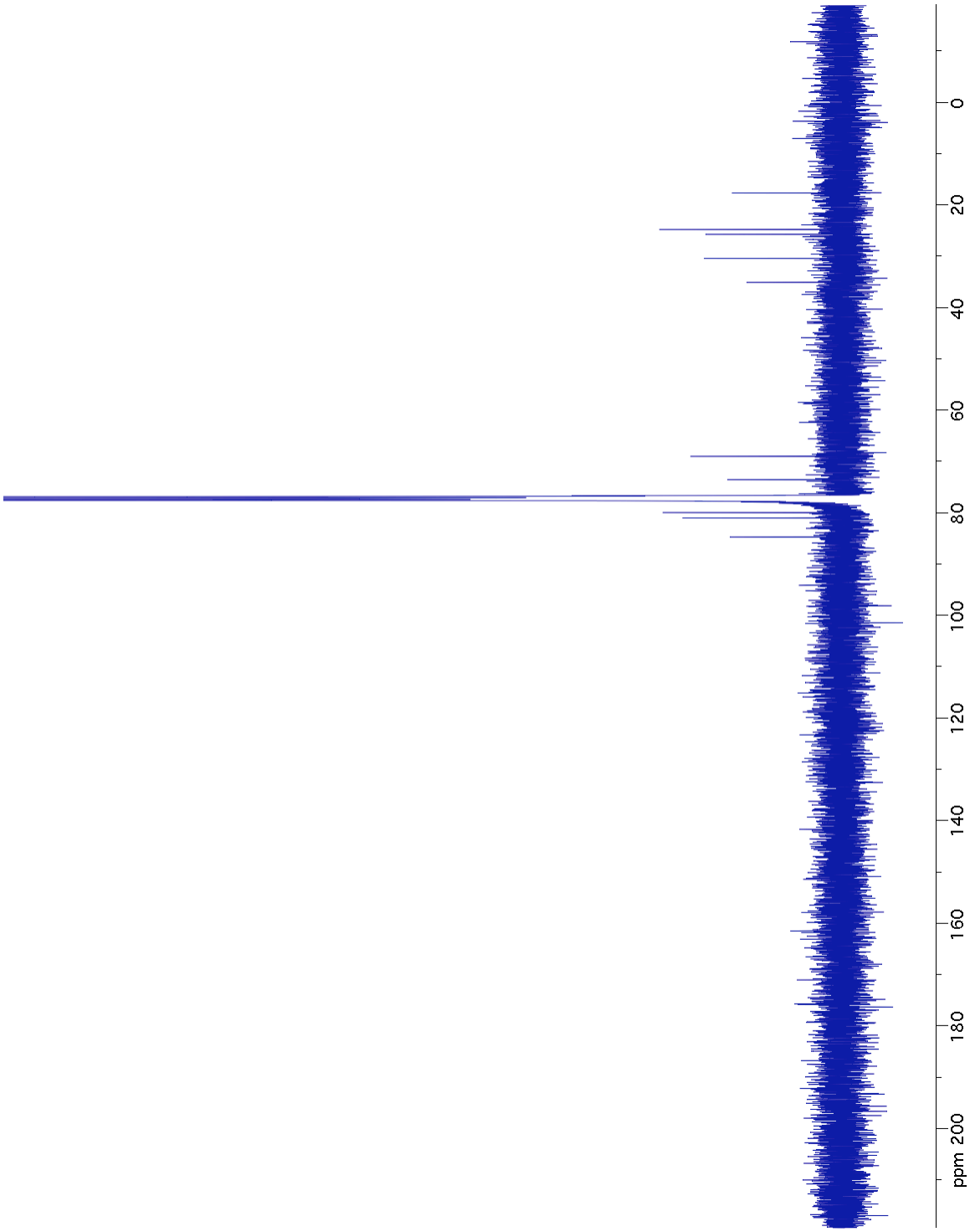

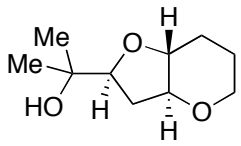

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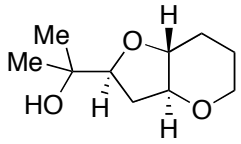

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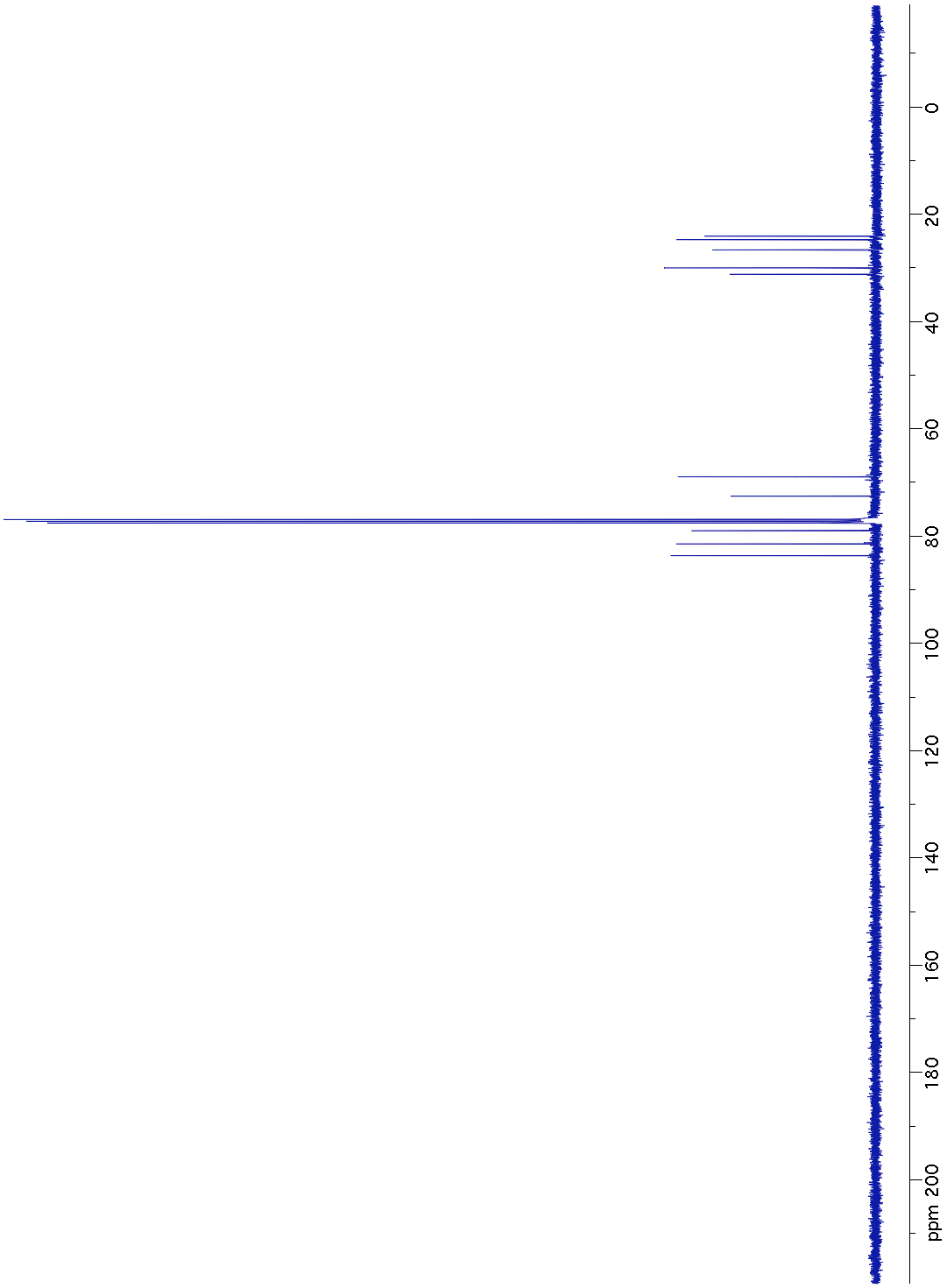

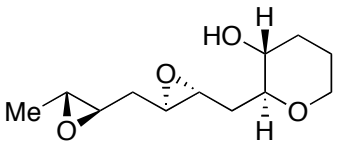

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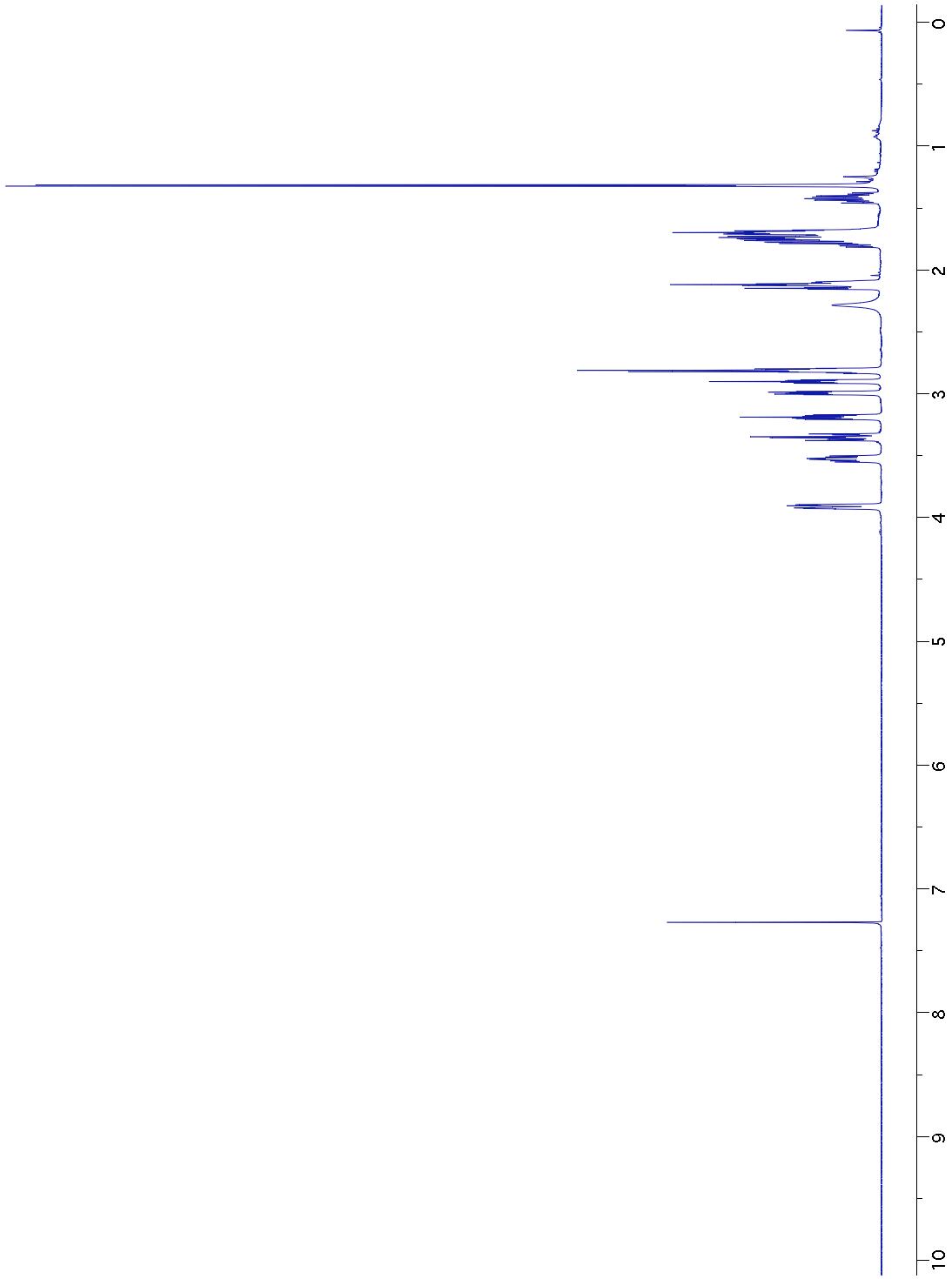

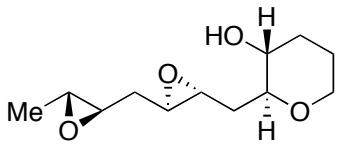

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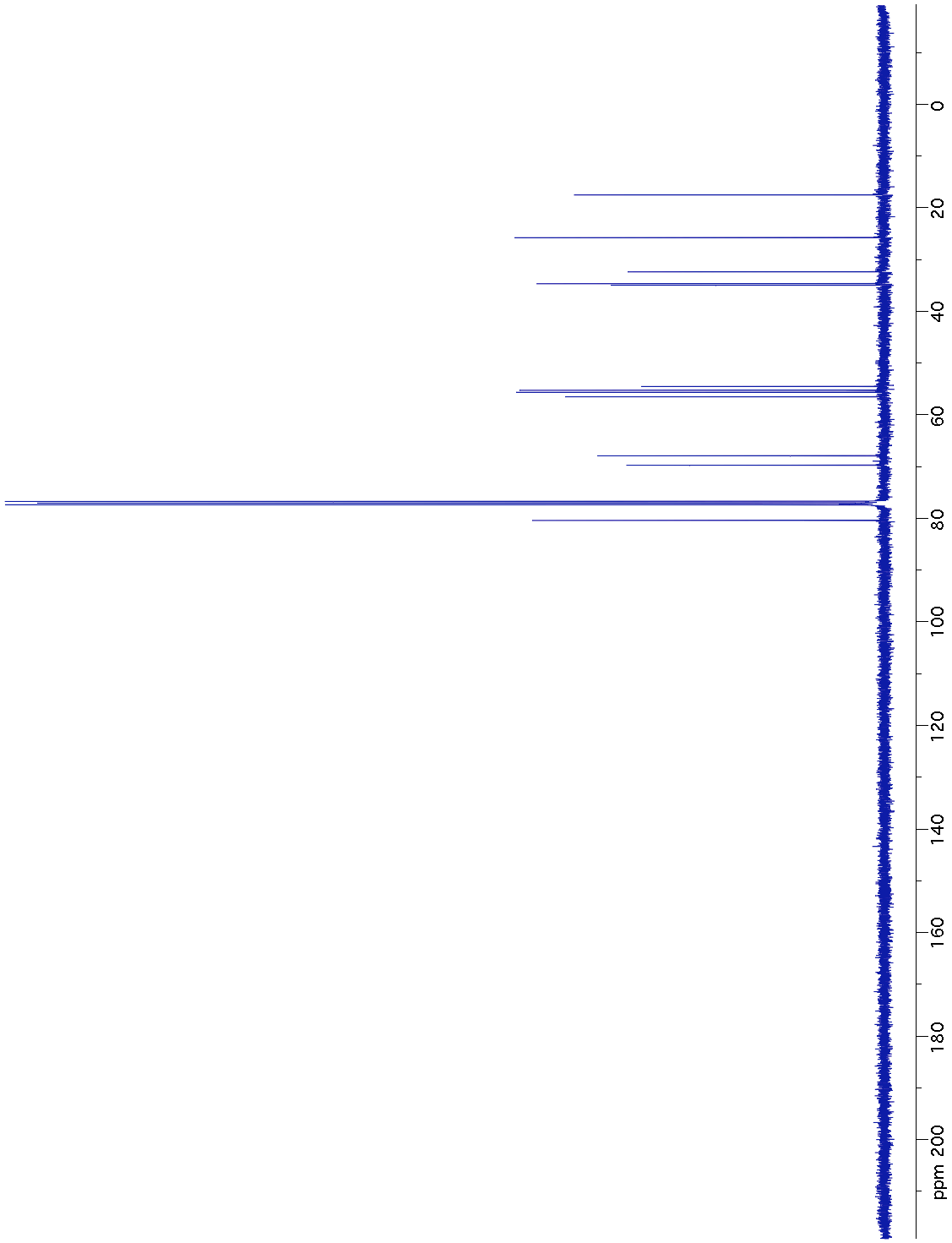

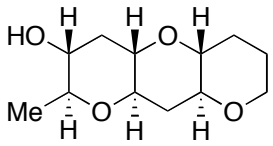

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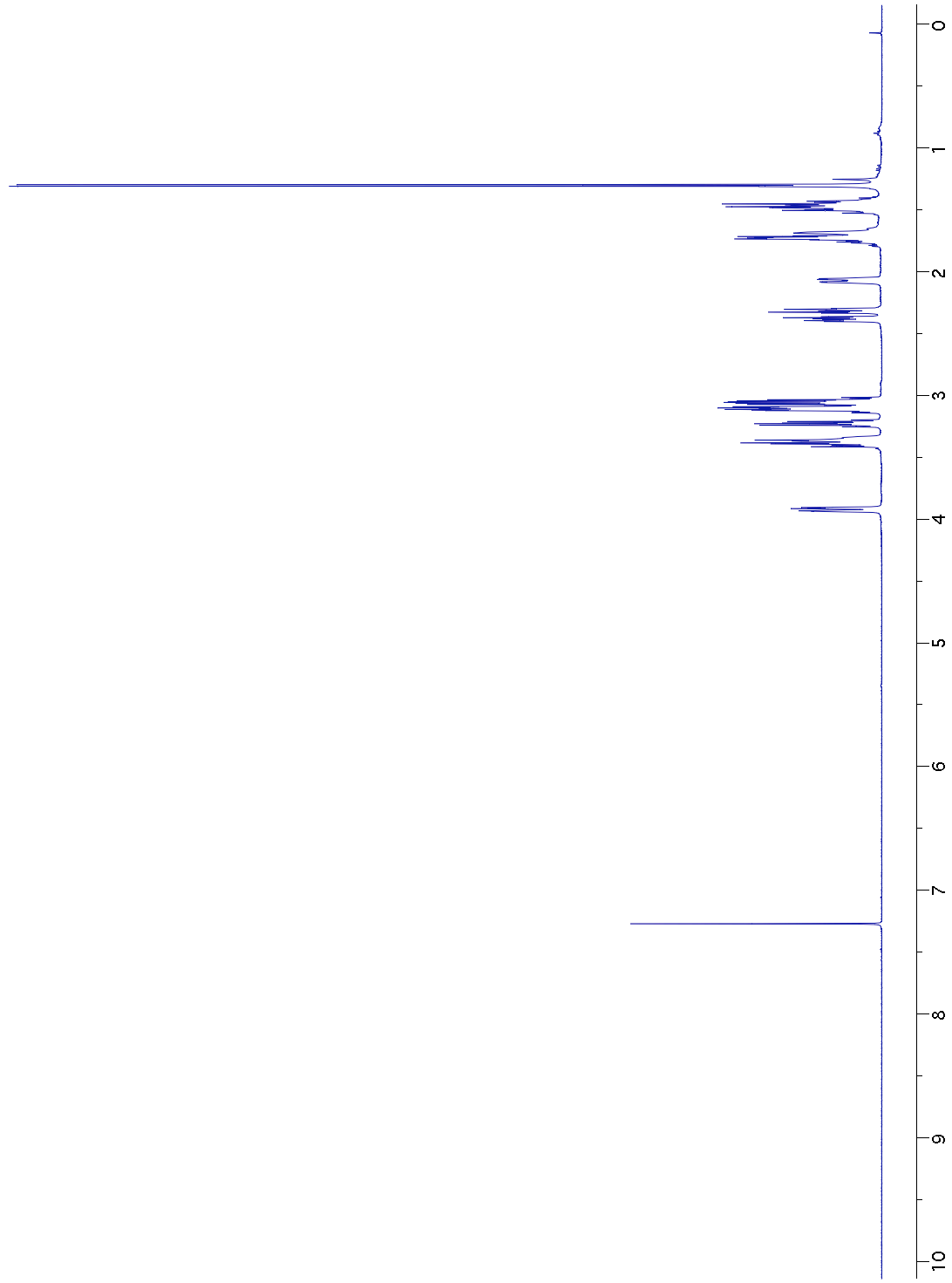

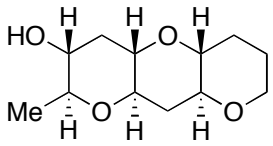

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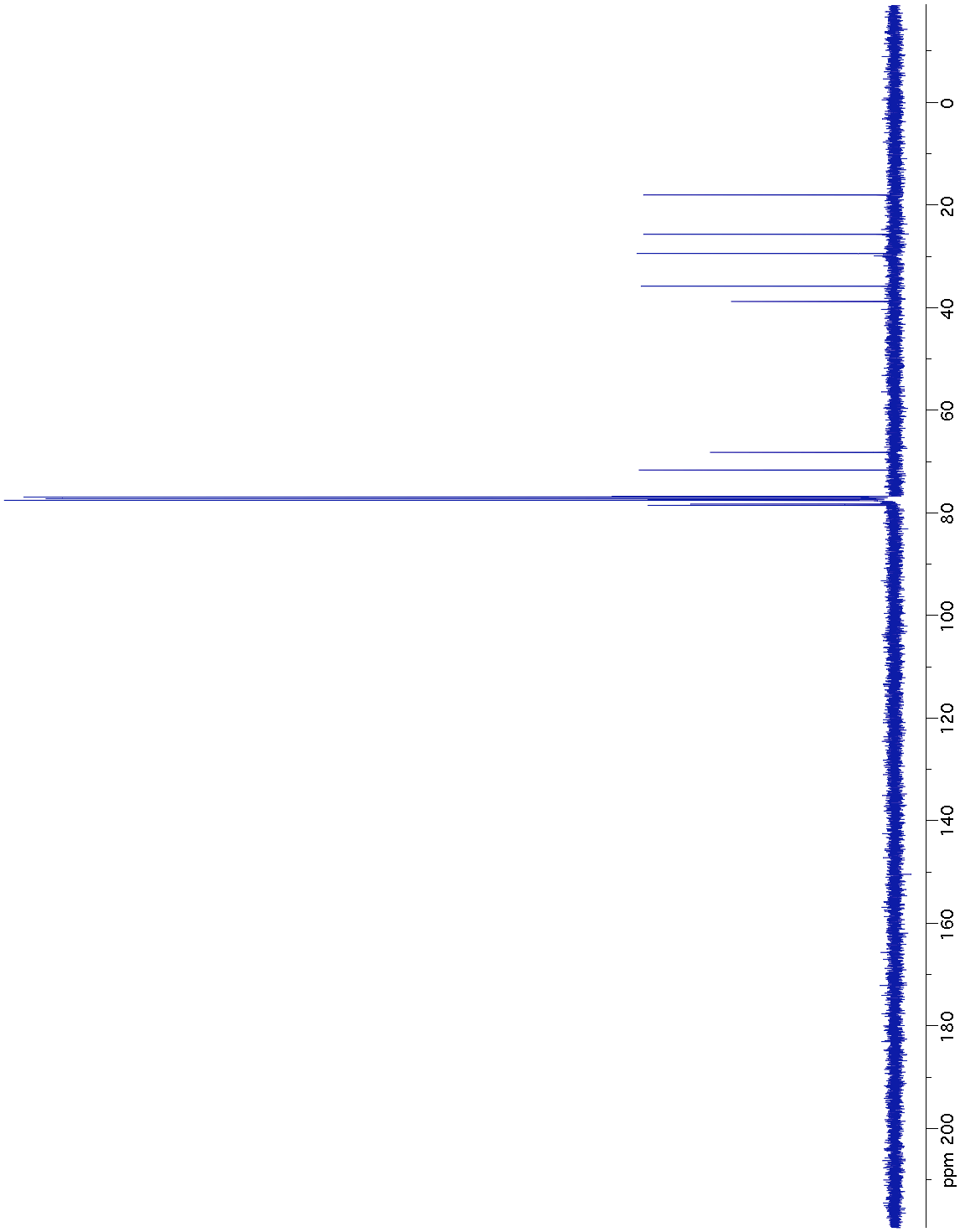

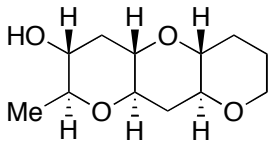
HO
H
H
O
H
Me
O
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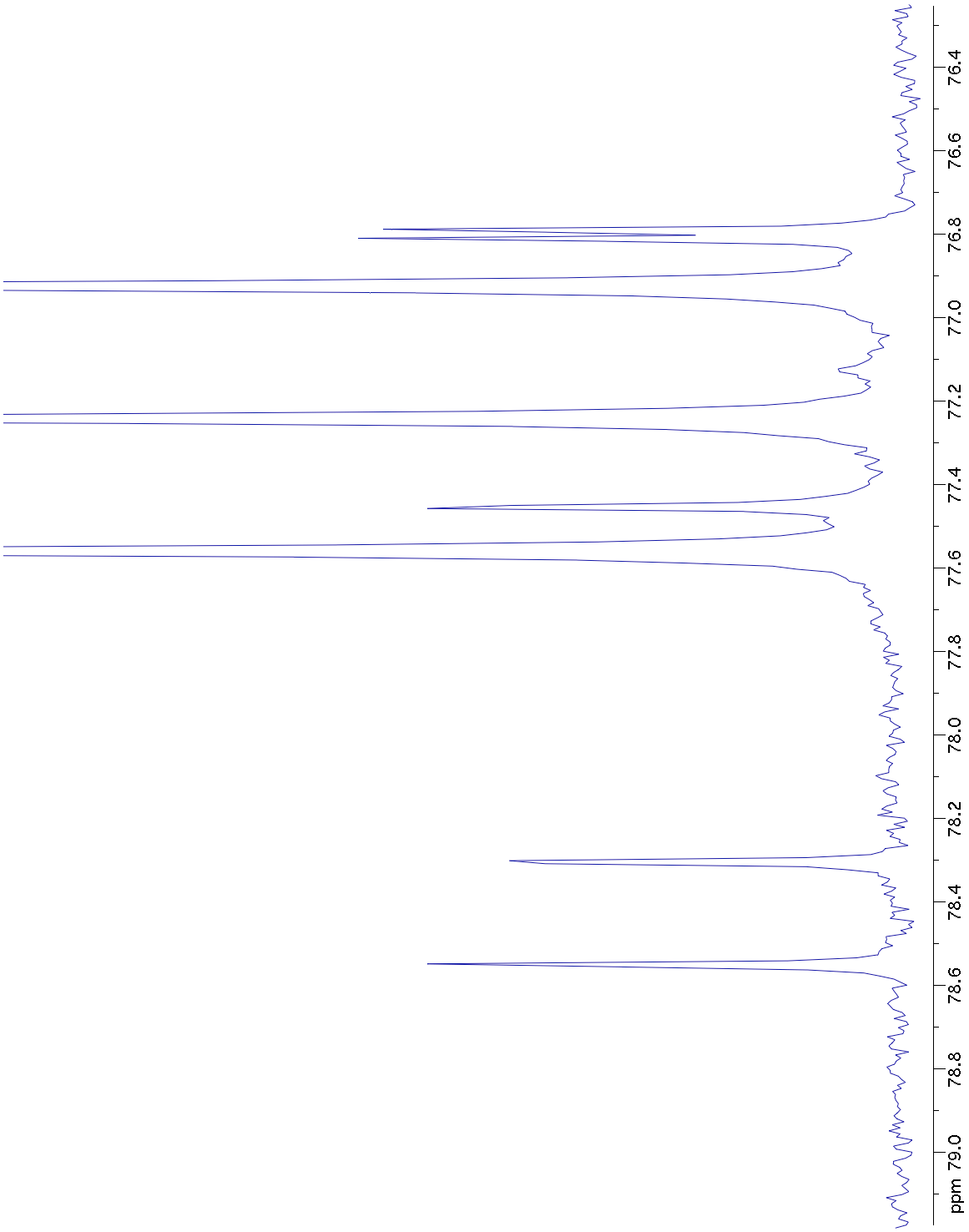
H

6


76.4
76.6
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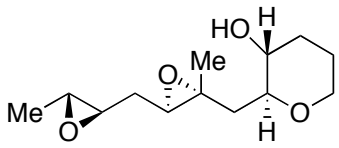
77.2
77.4
77.6
77.8
78.0
78.2
78.4
78.6
78.8
79.0
ppm



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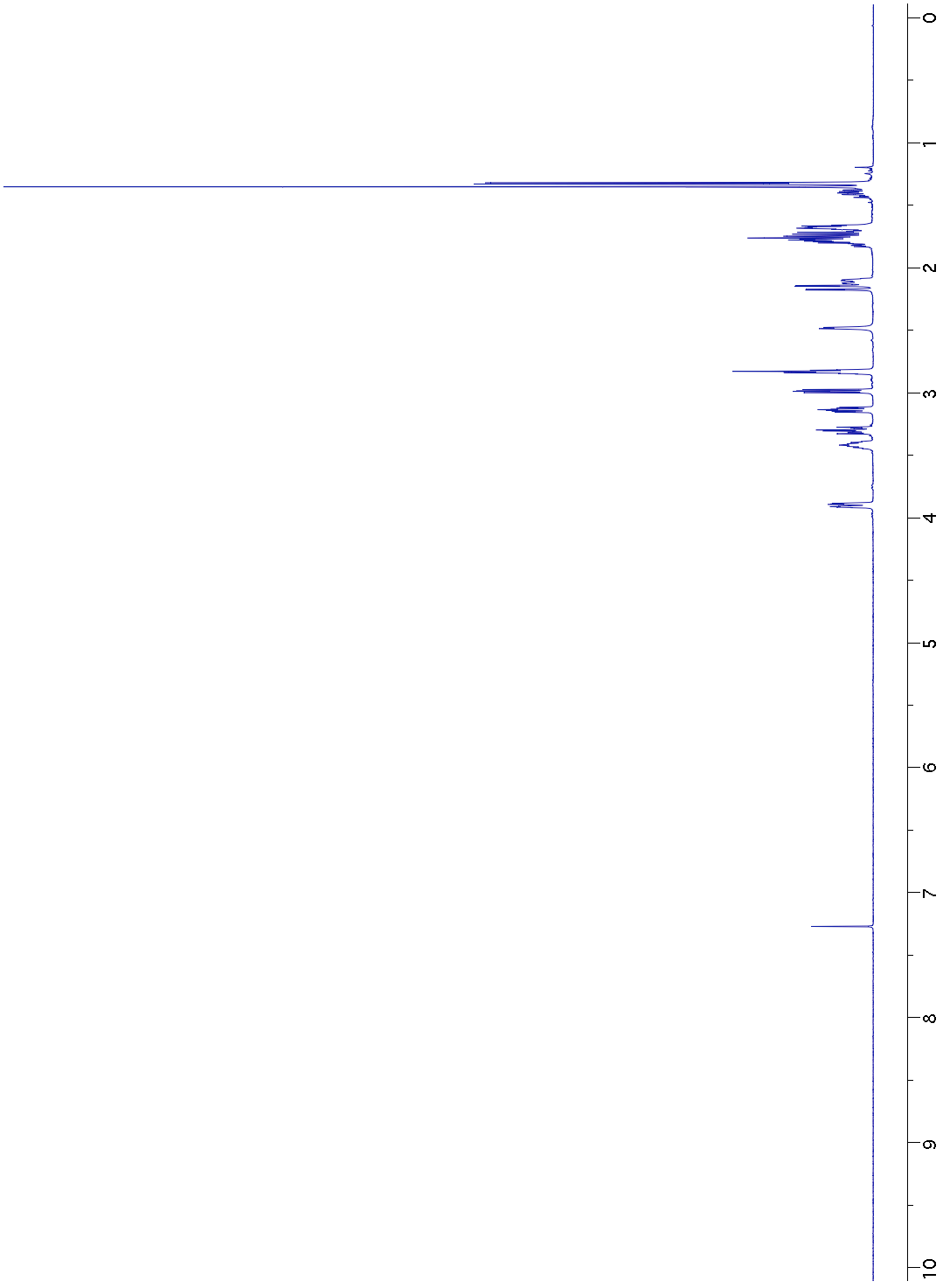

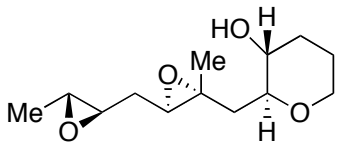

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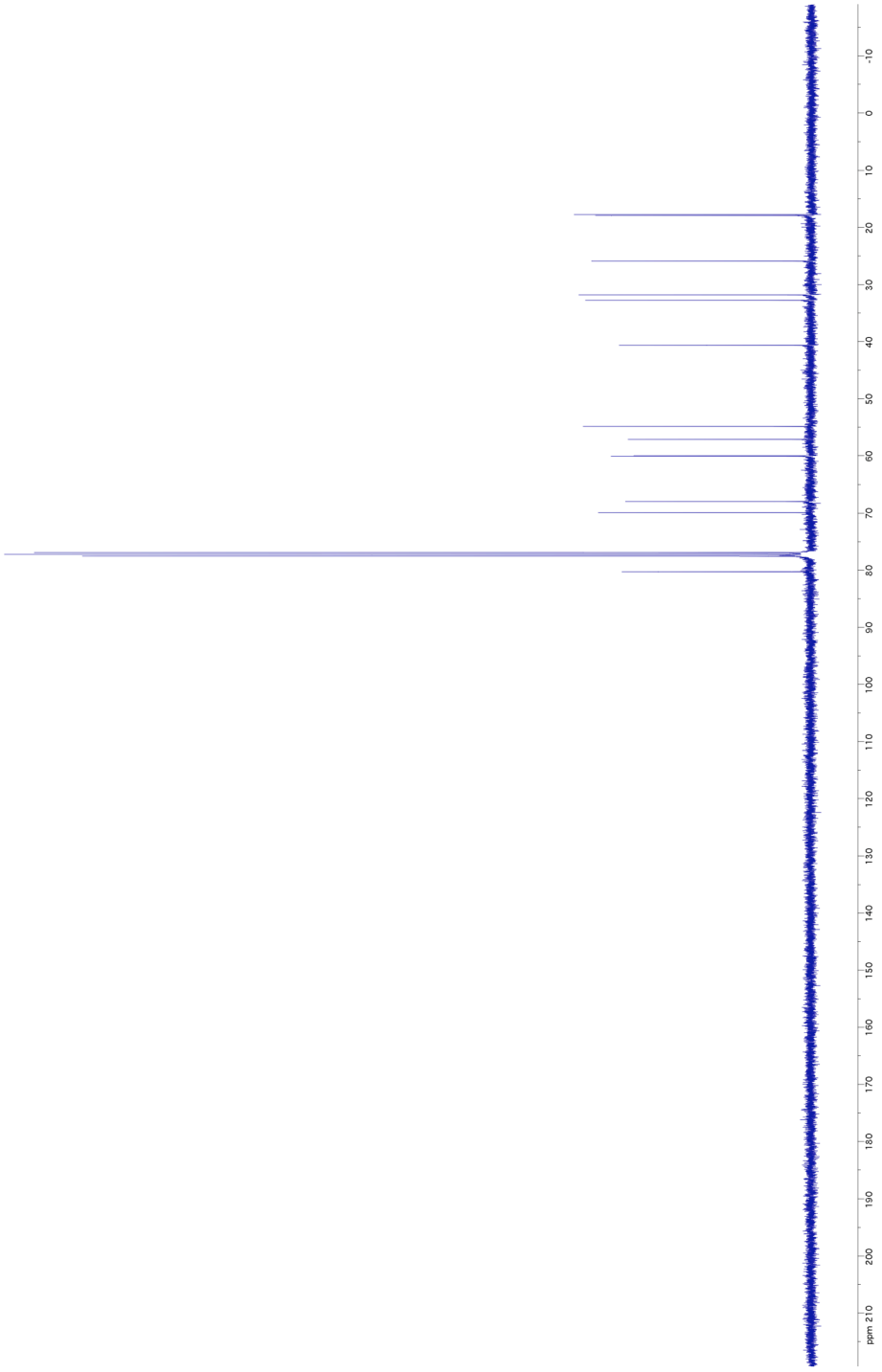

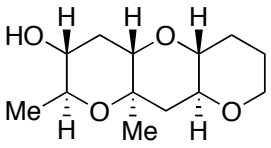

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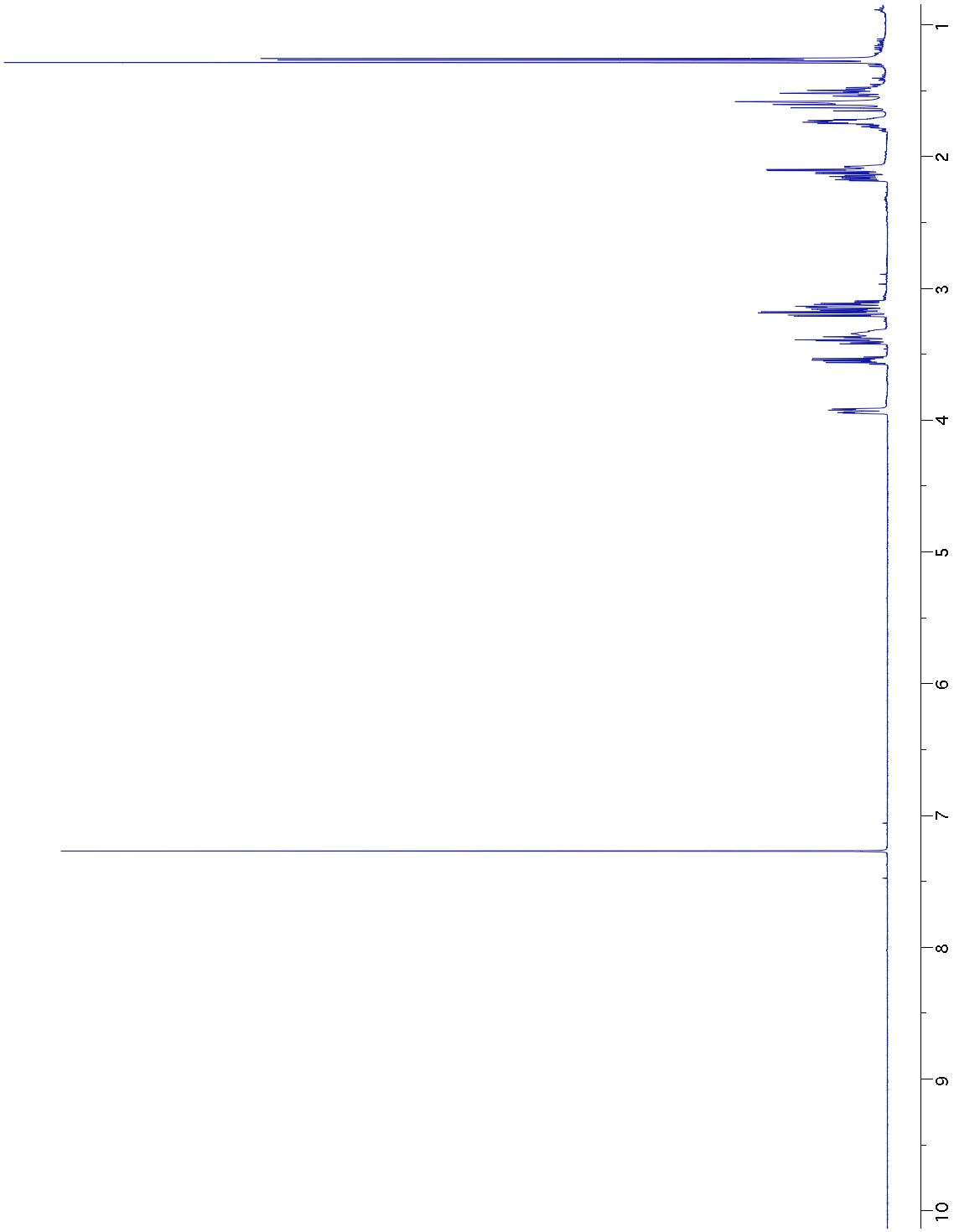

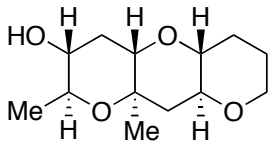
HO
H
H
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H
Me
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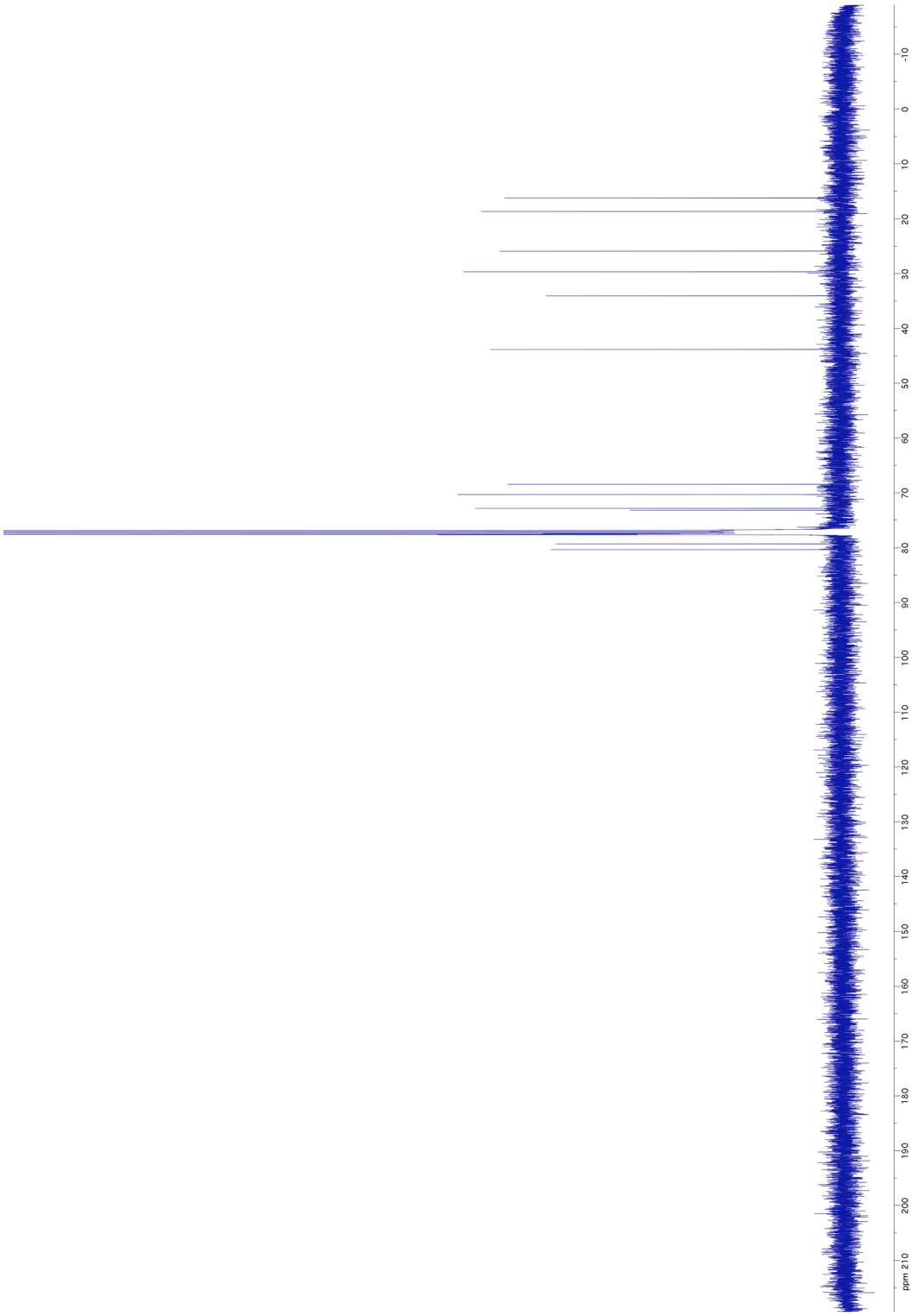
O
H
Me
H

8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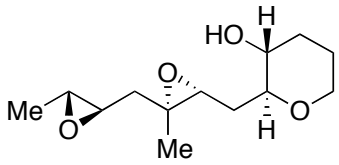
ppm 210



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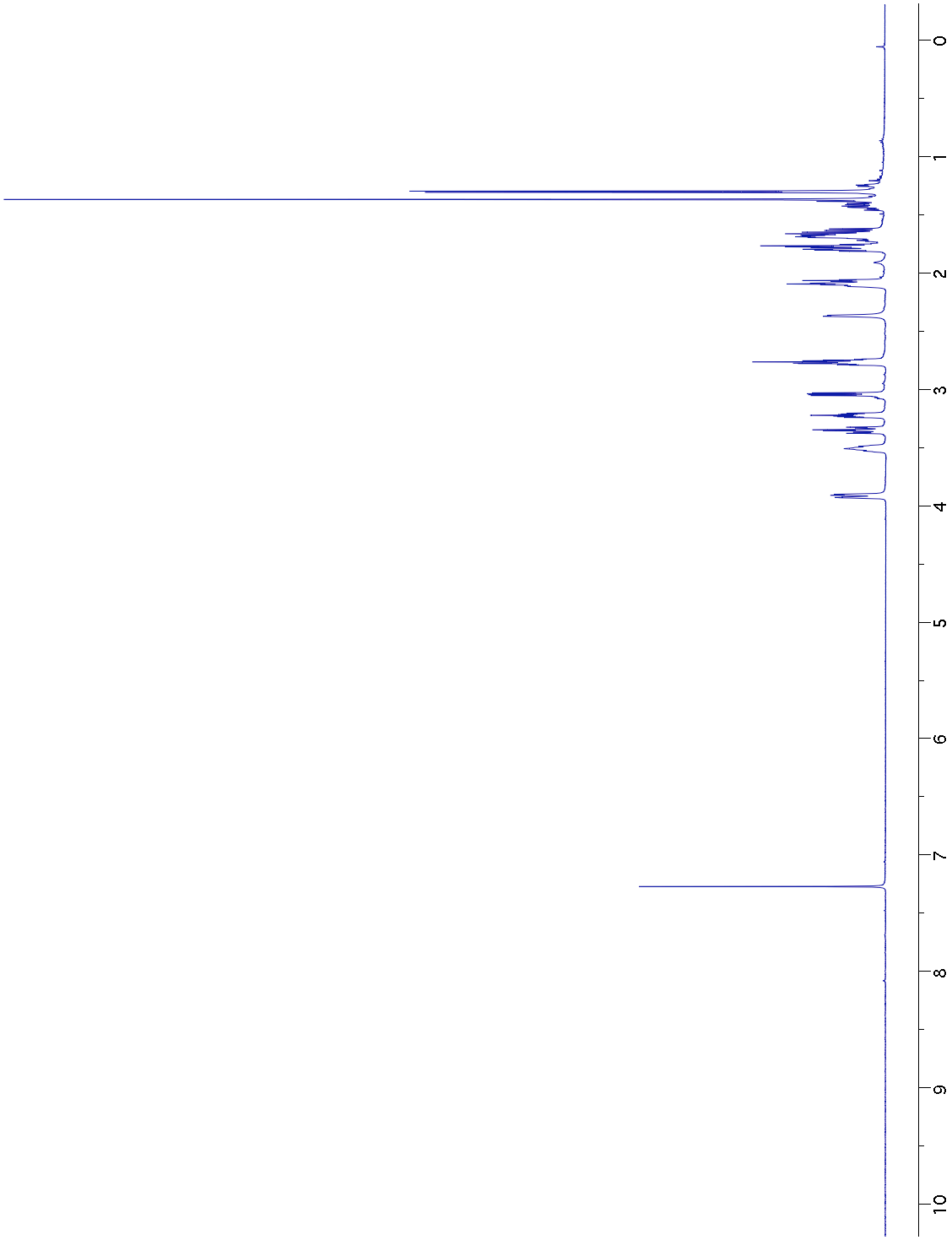
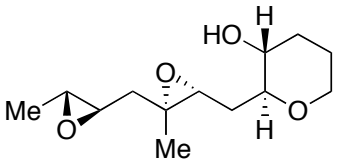
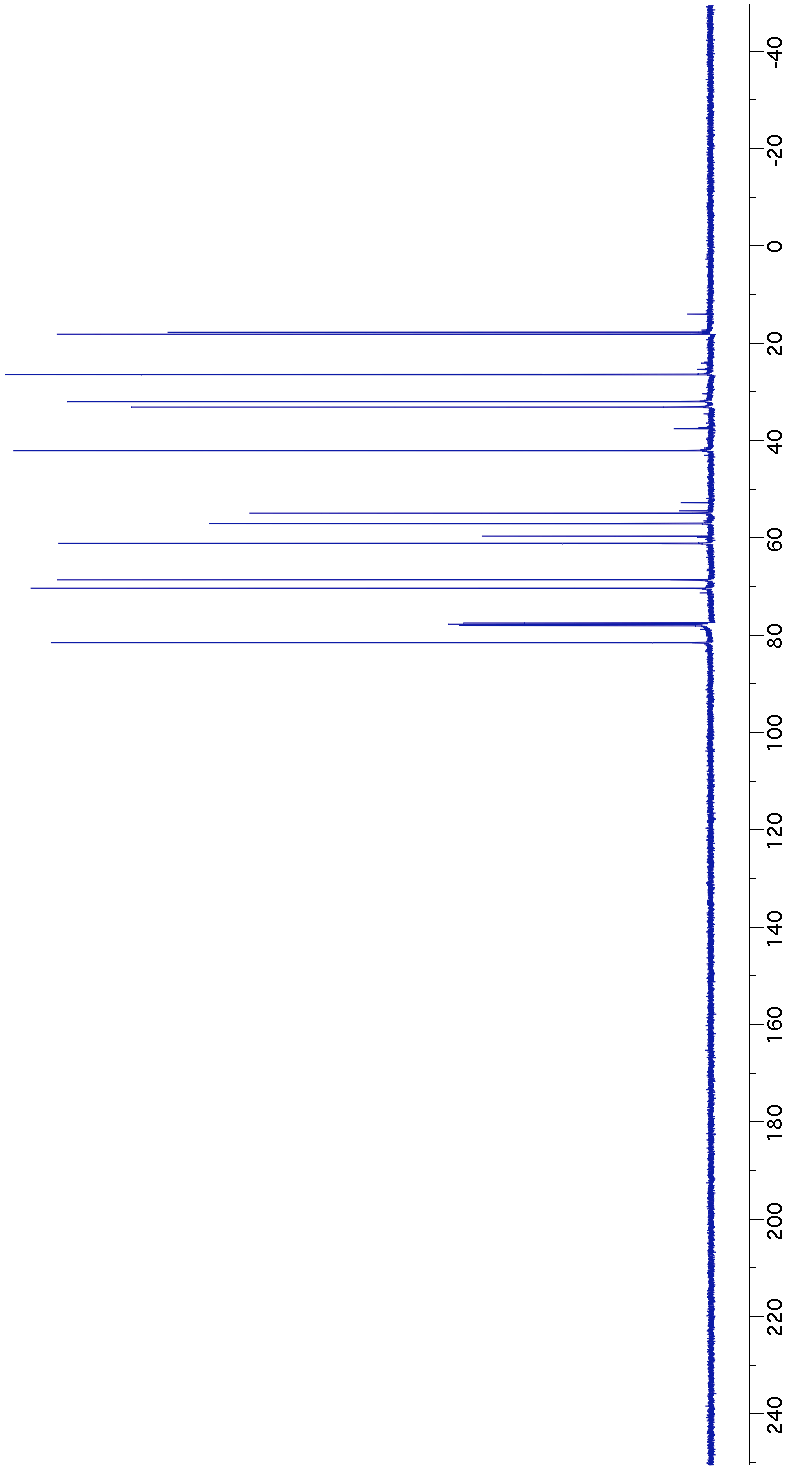
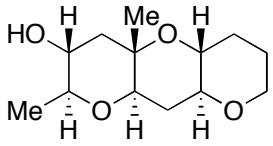




9





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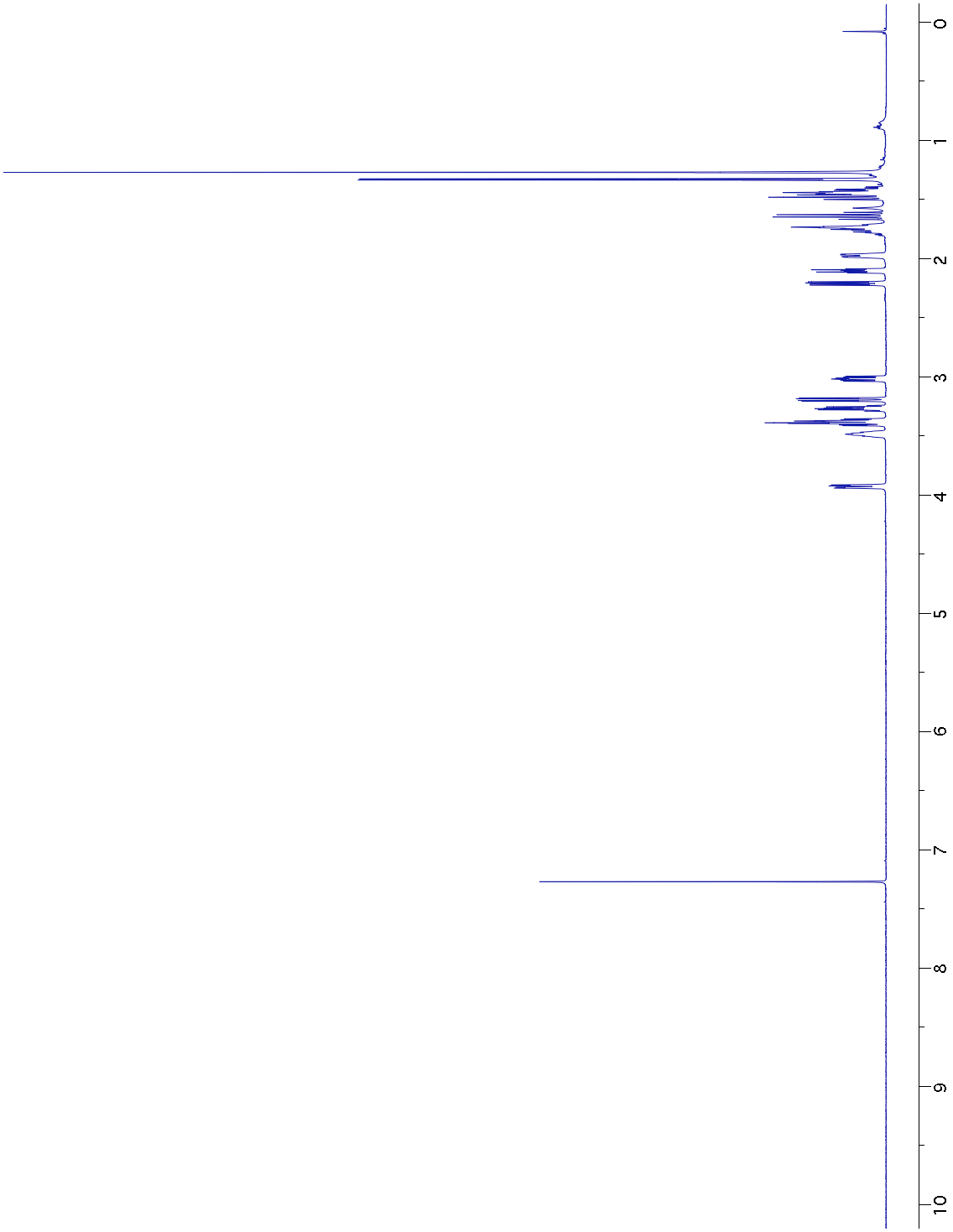

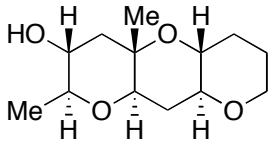

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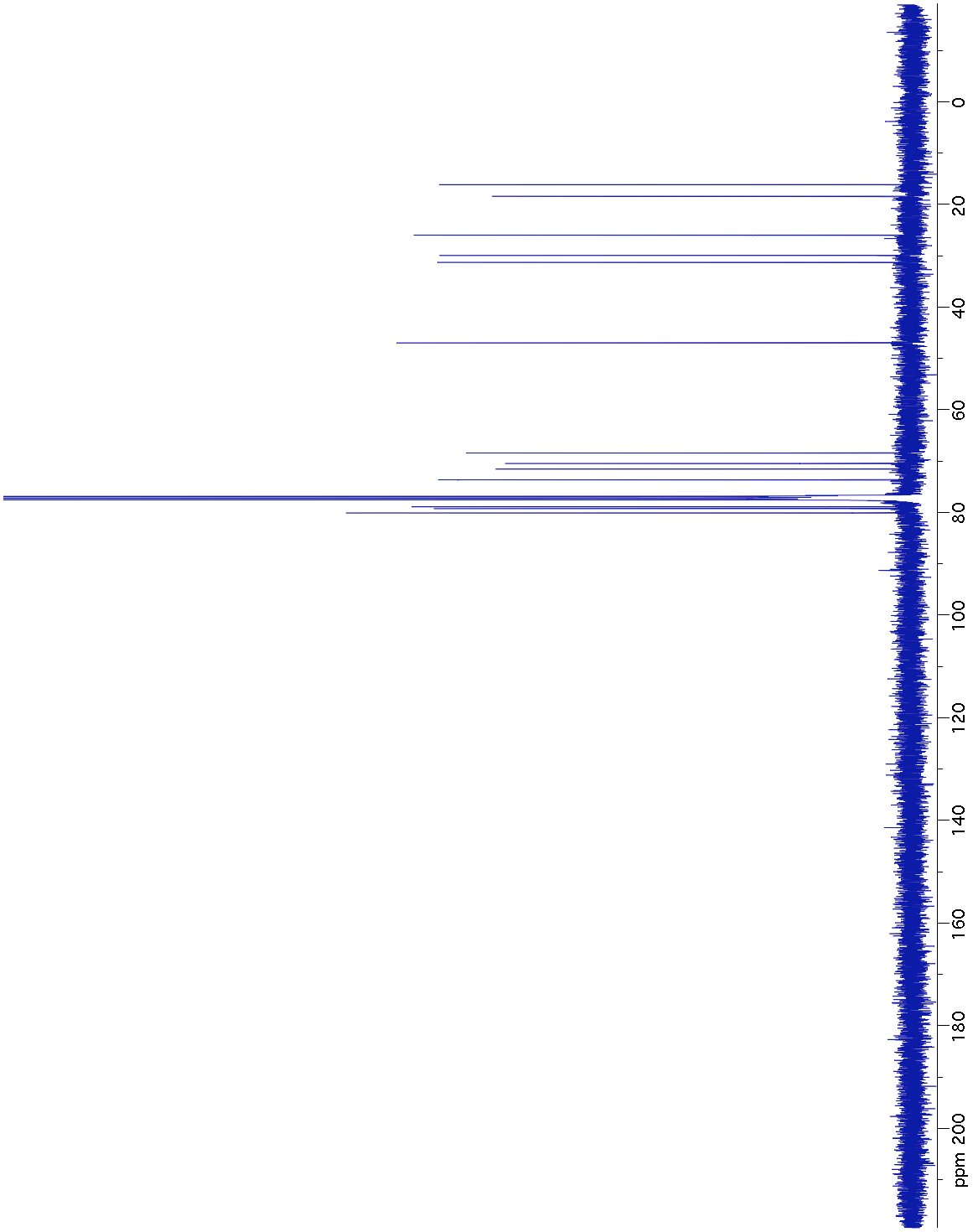

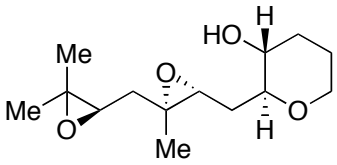

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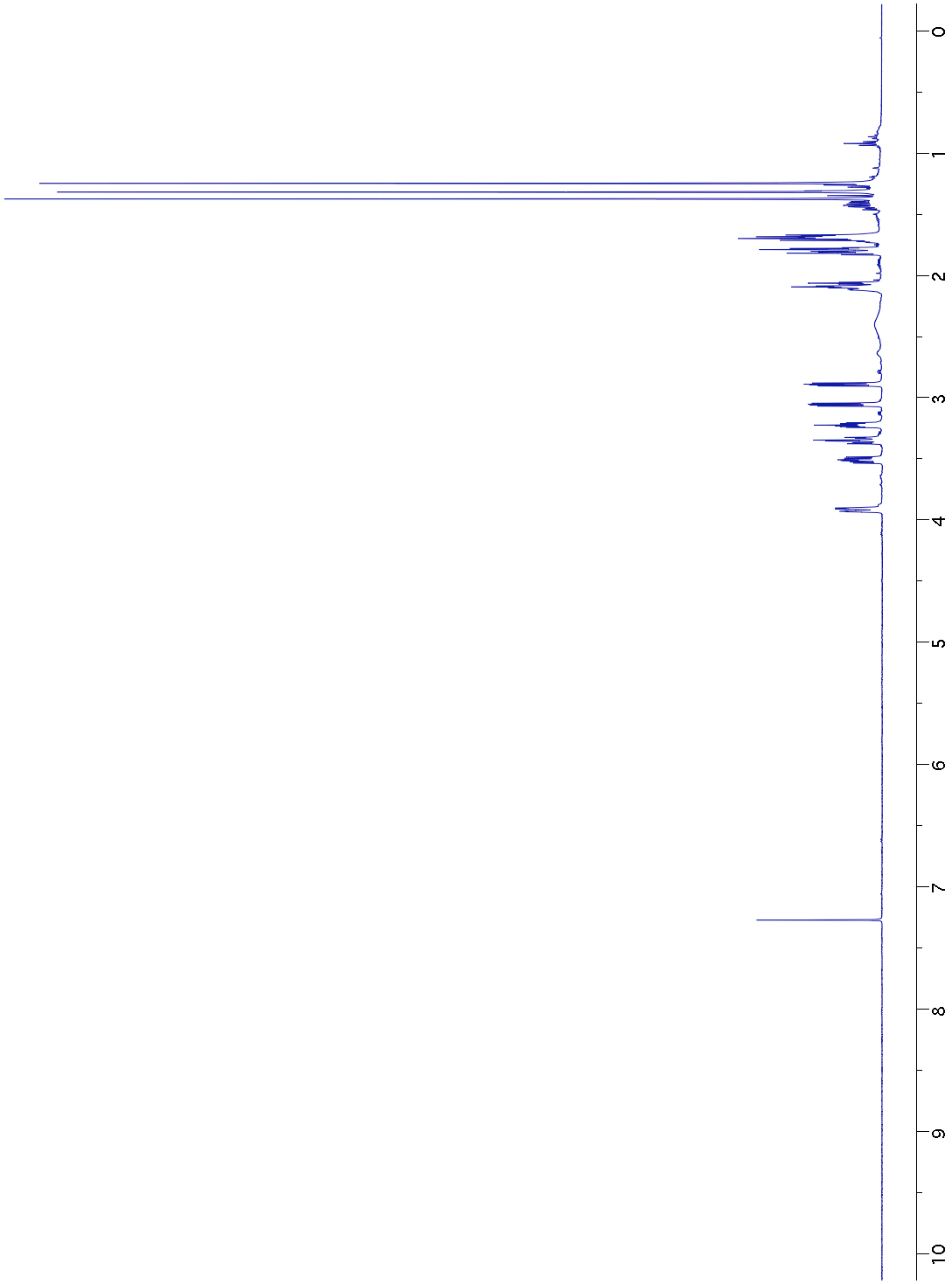

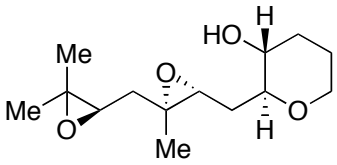

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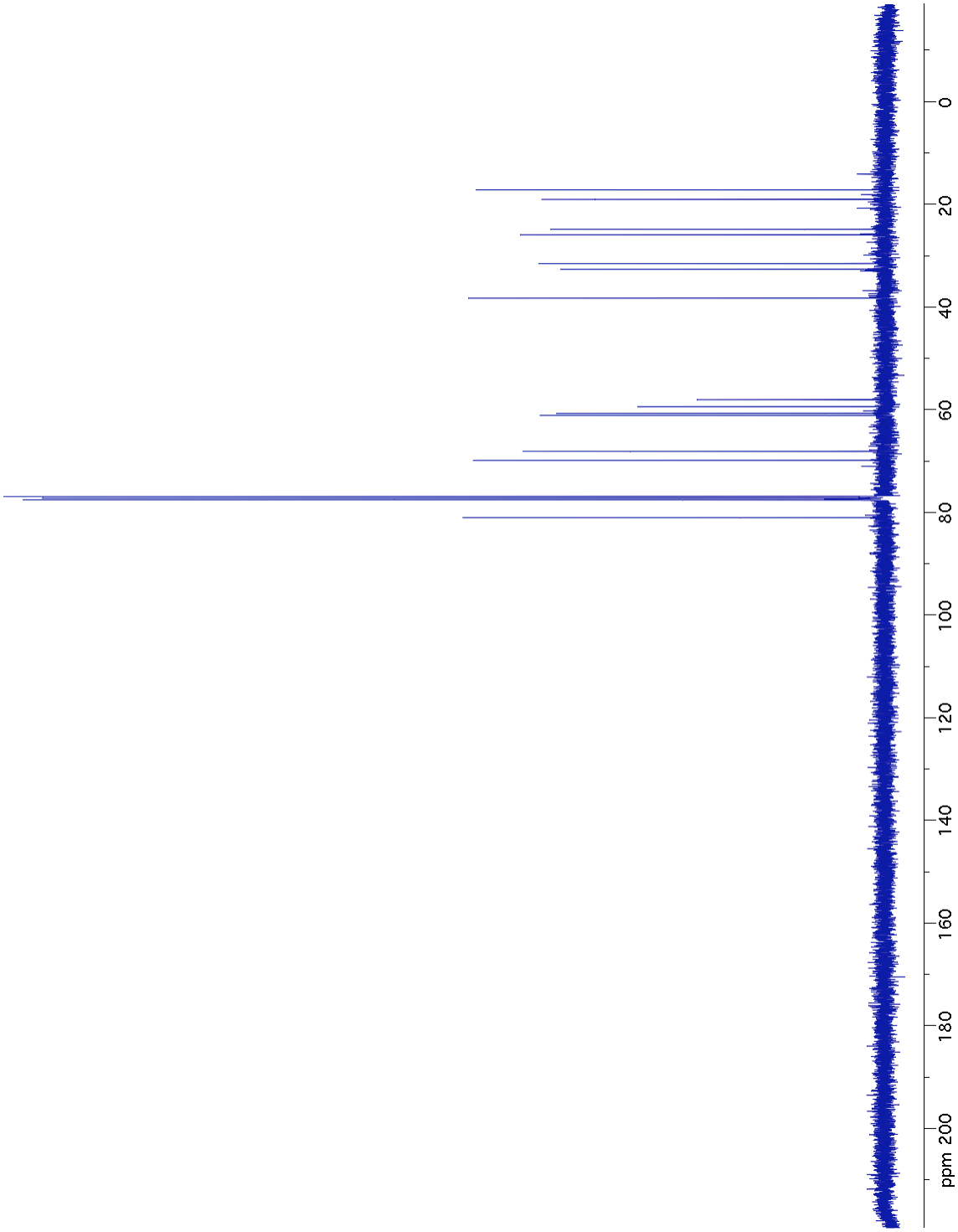

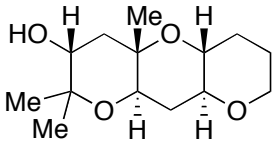

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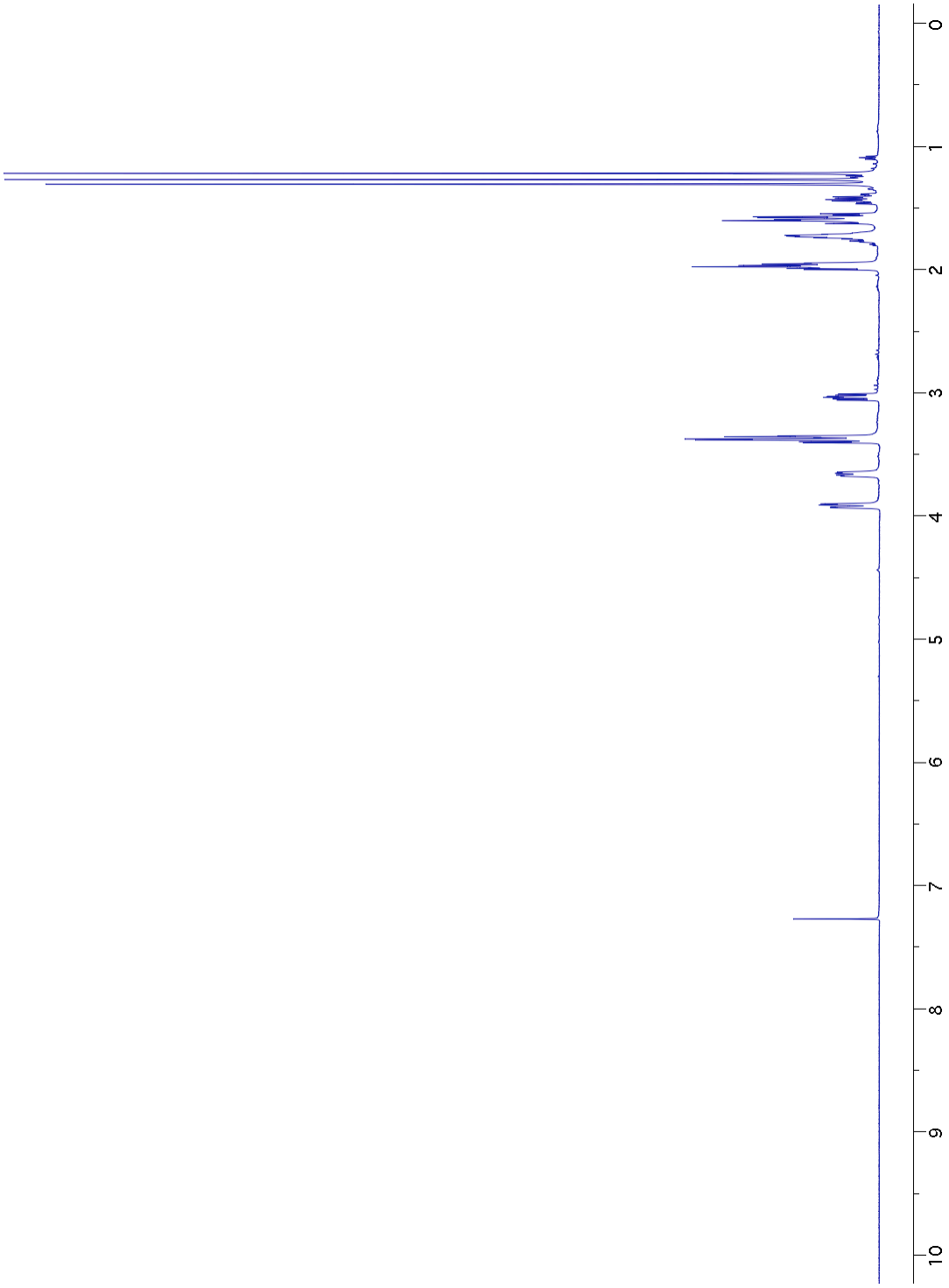

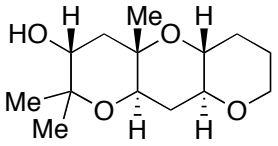

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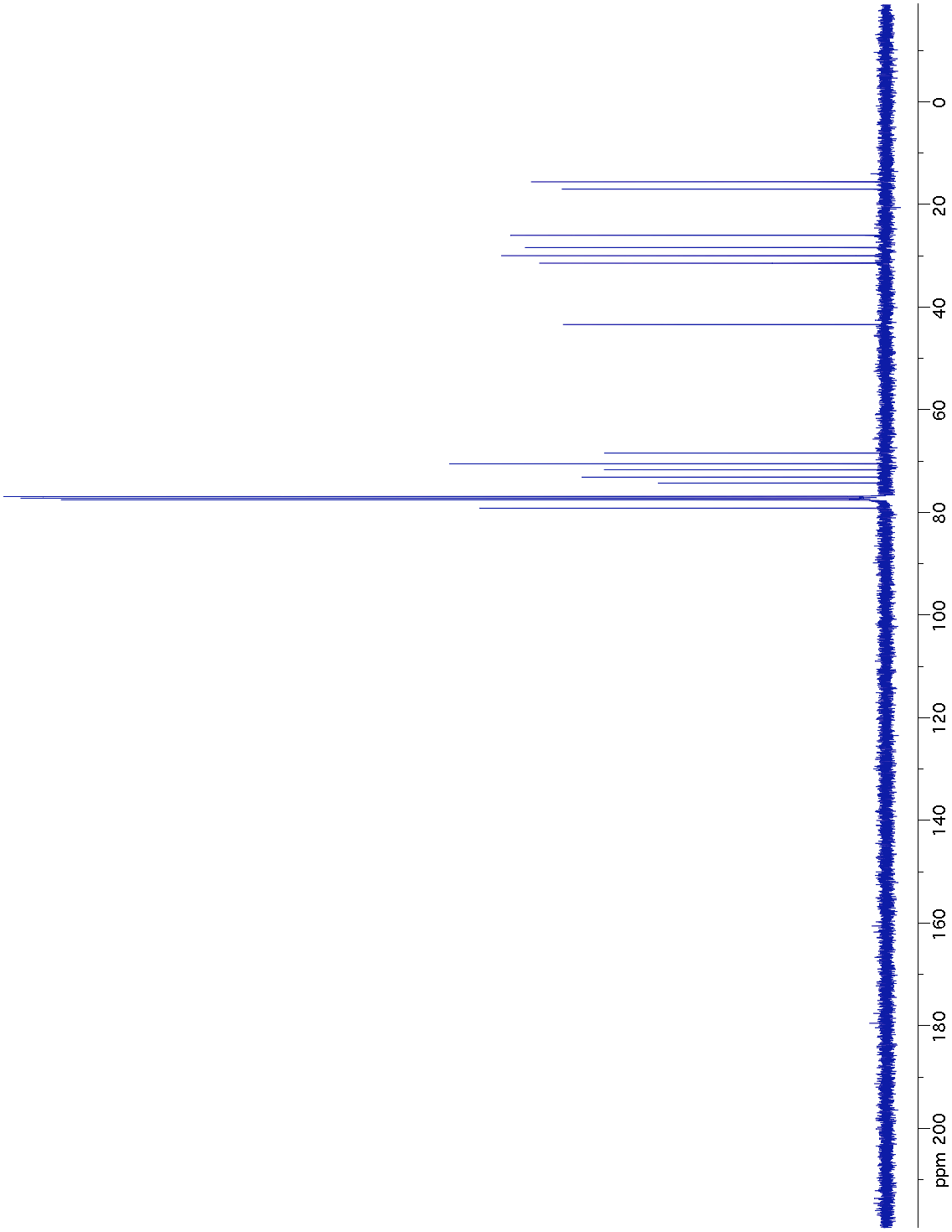

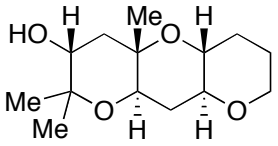
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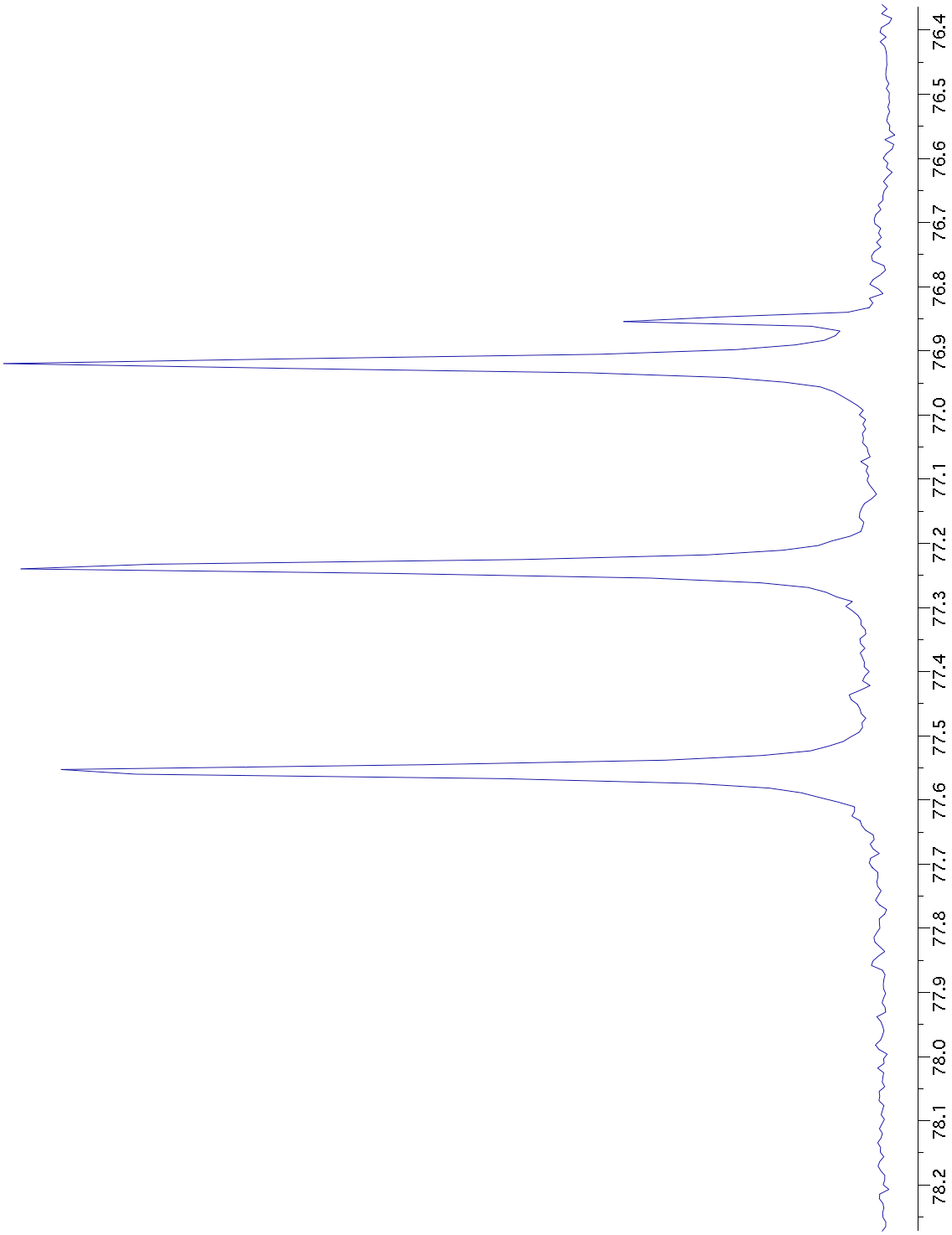
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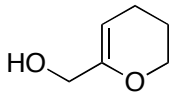

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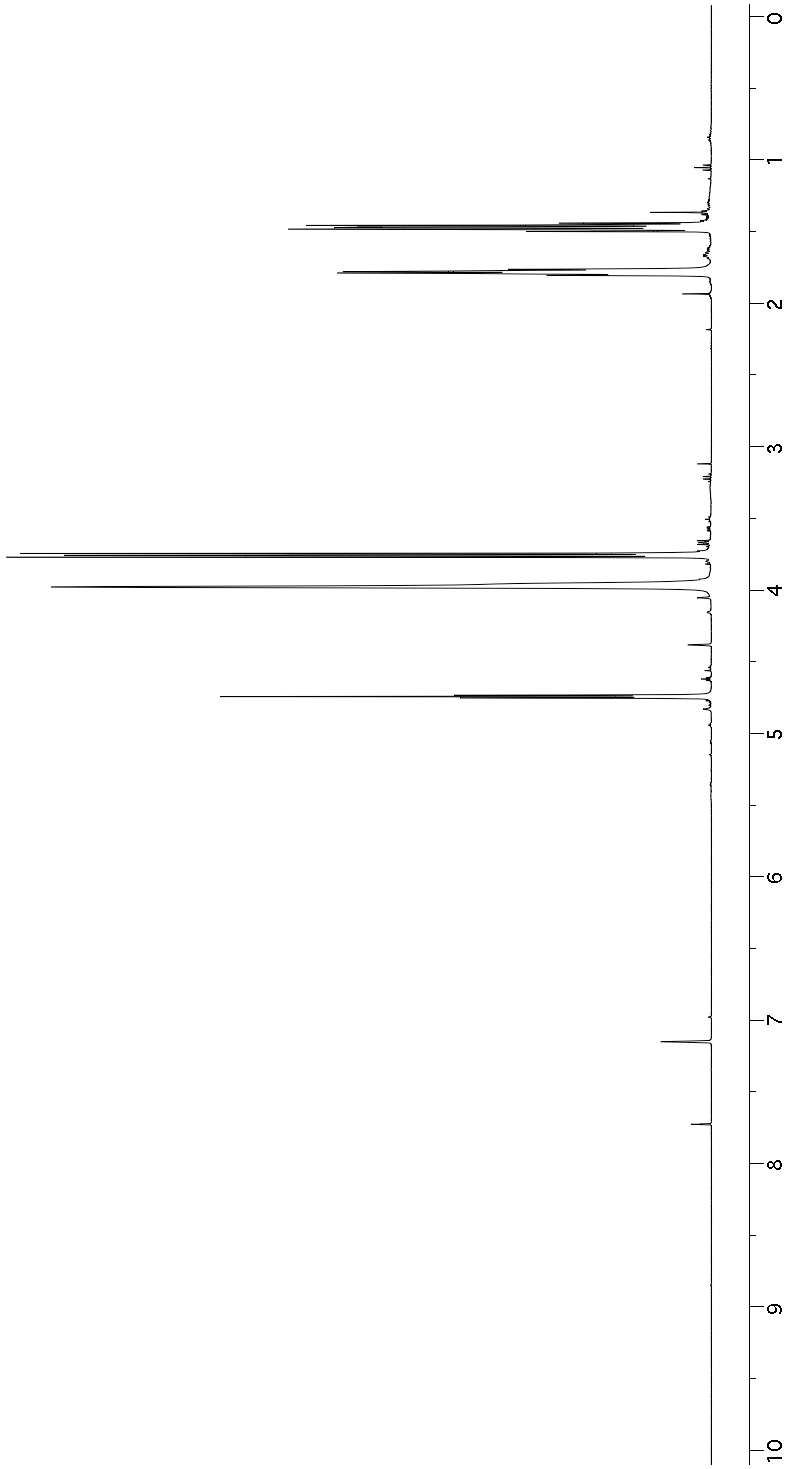

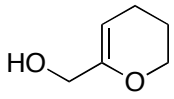

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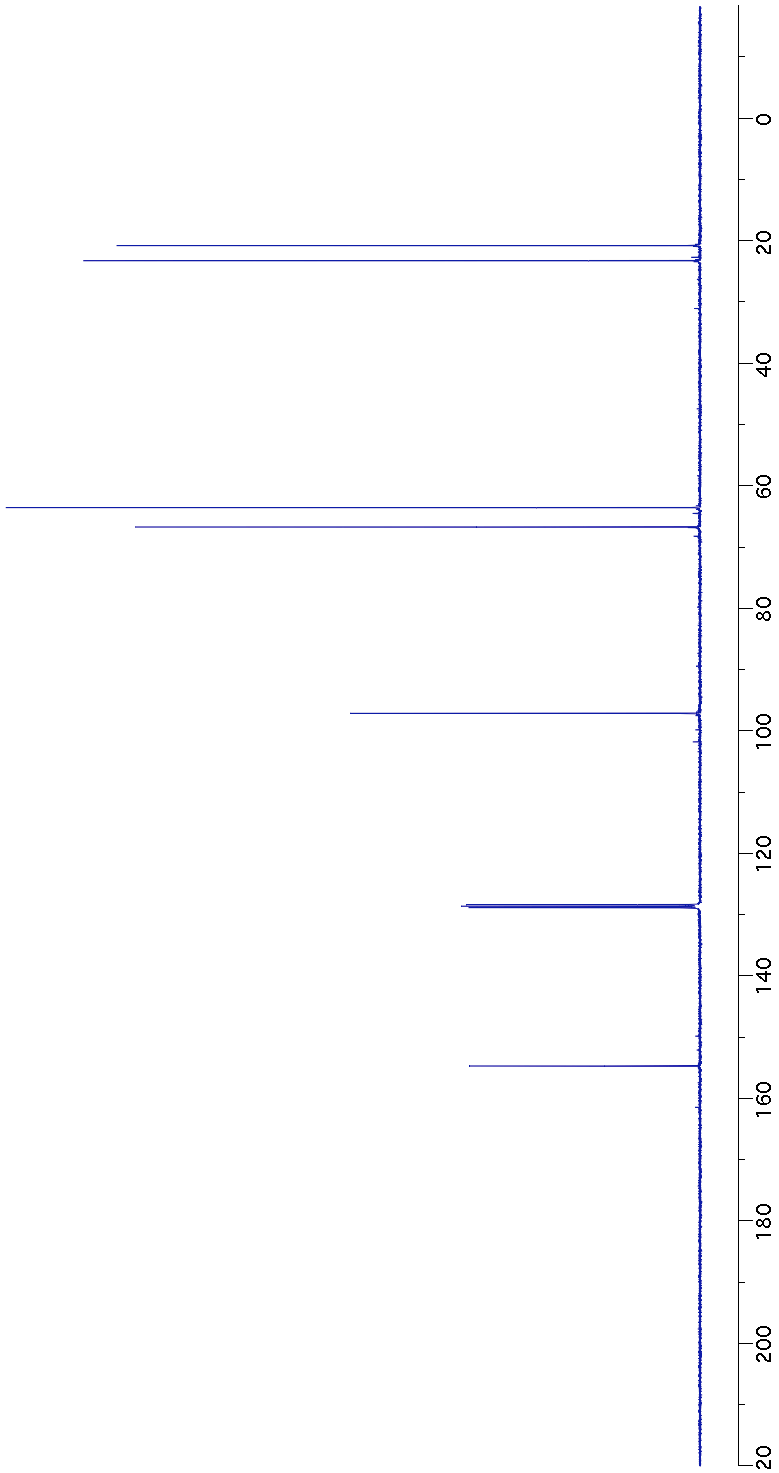

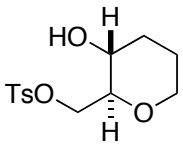

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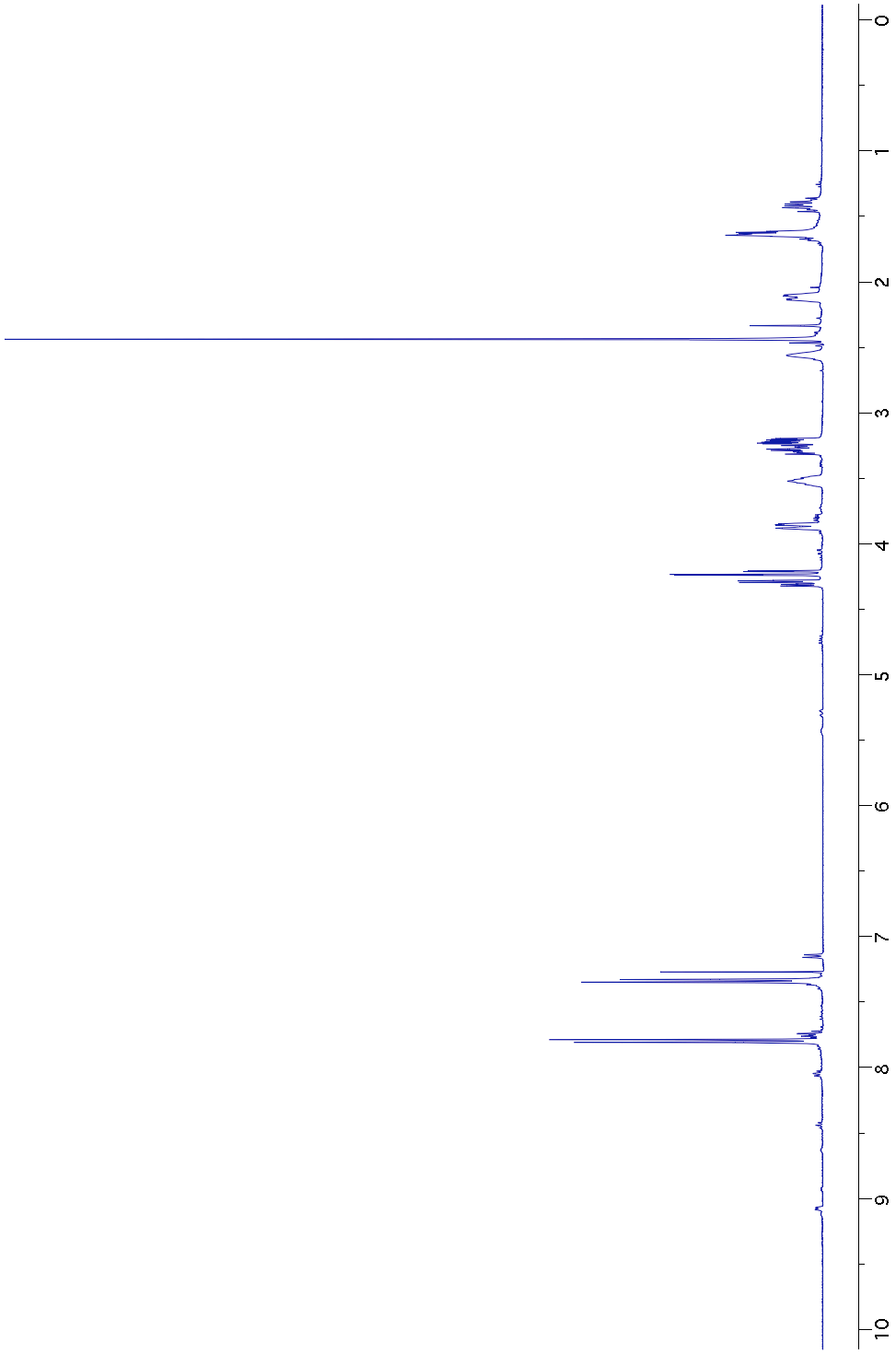

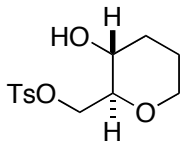

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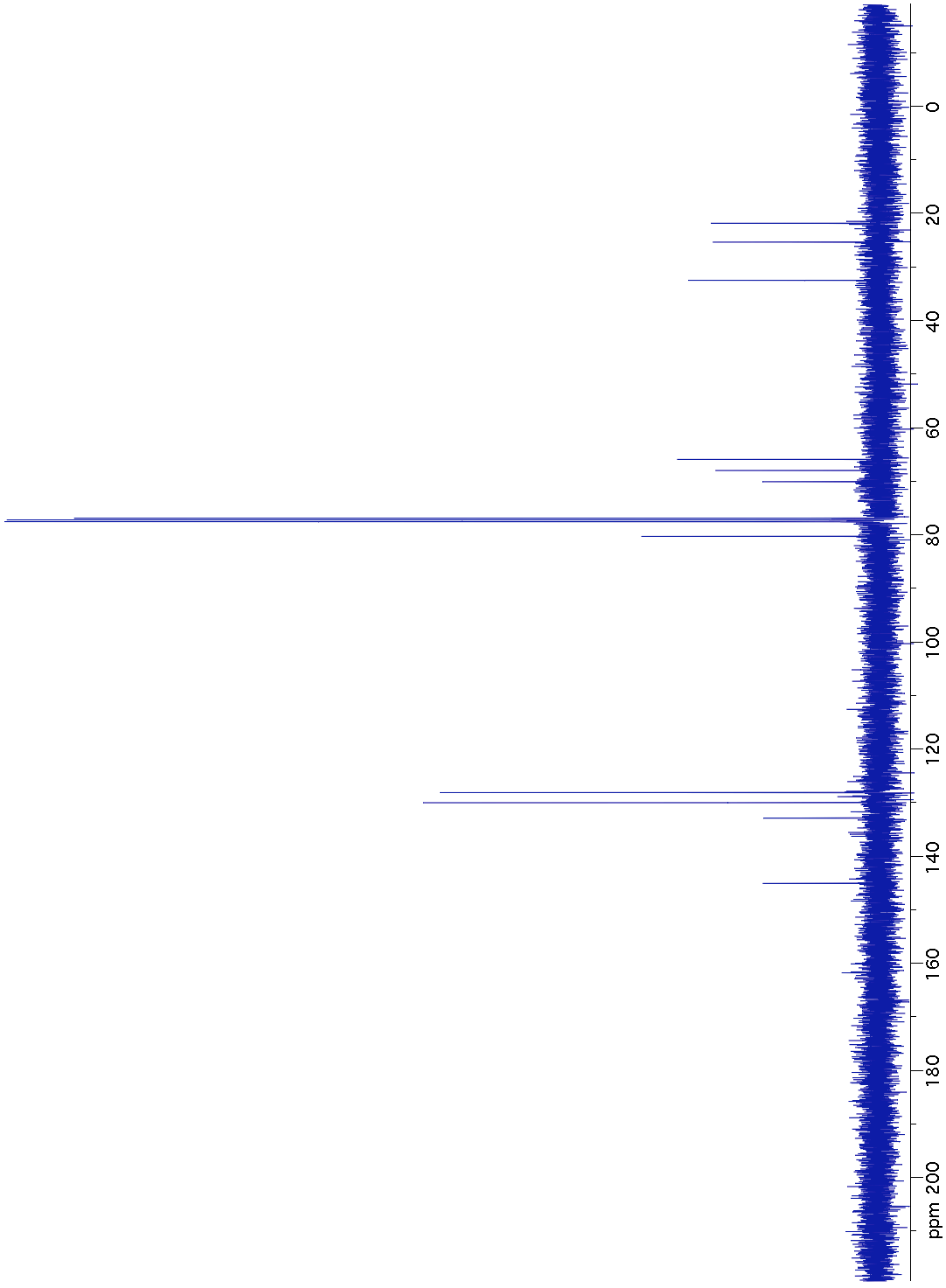

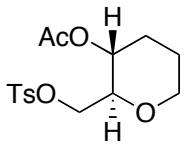

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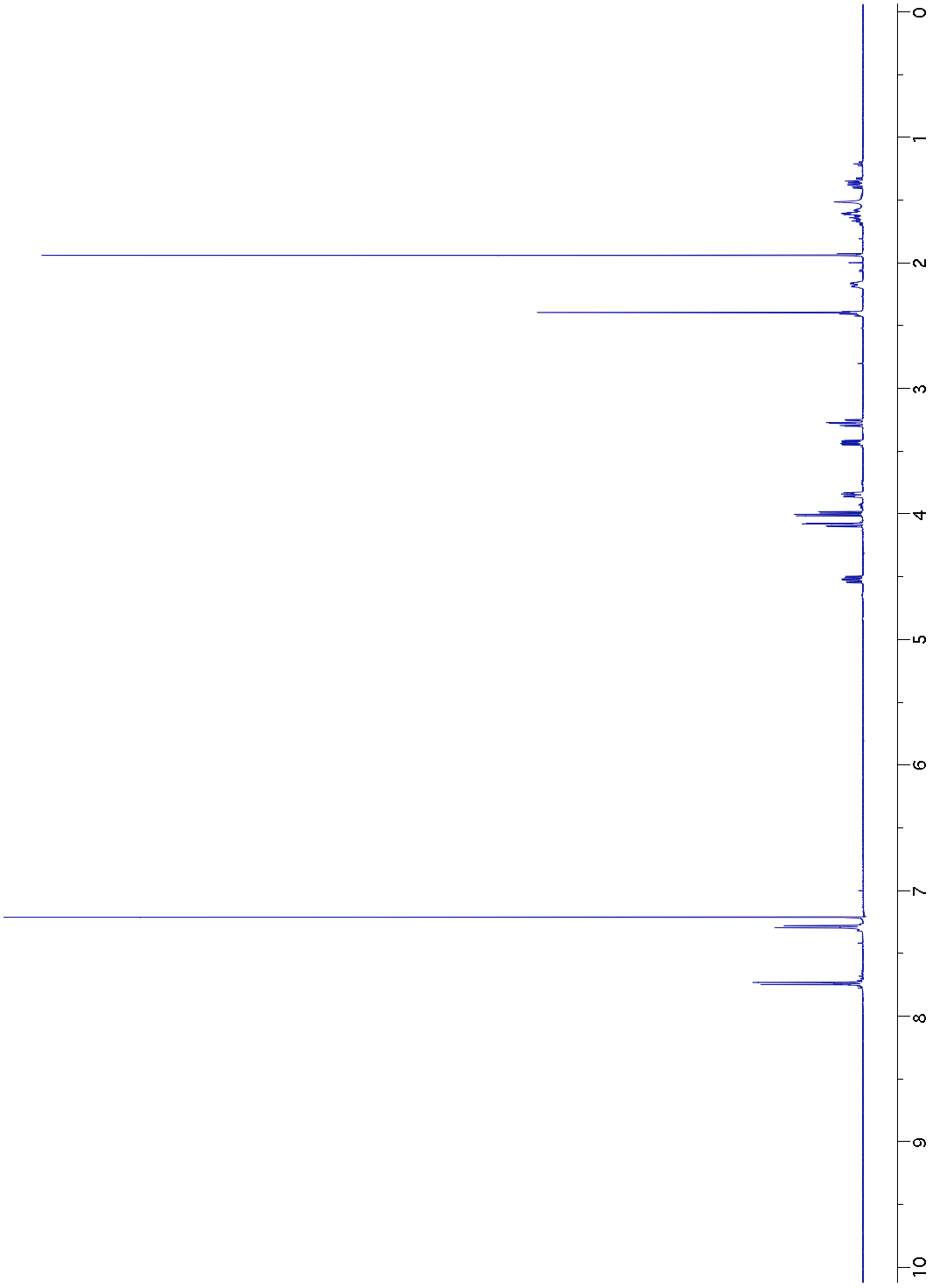

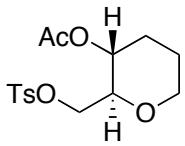

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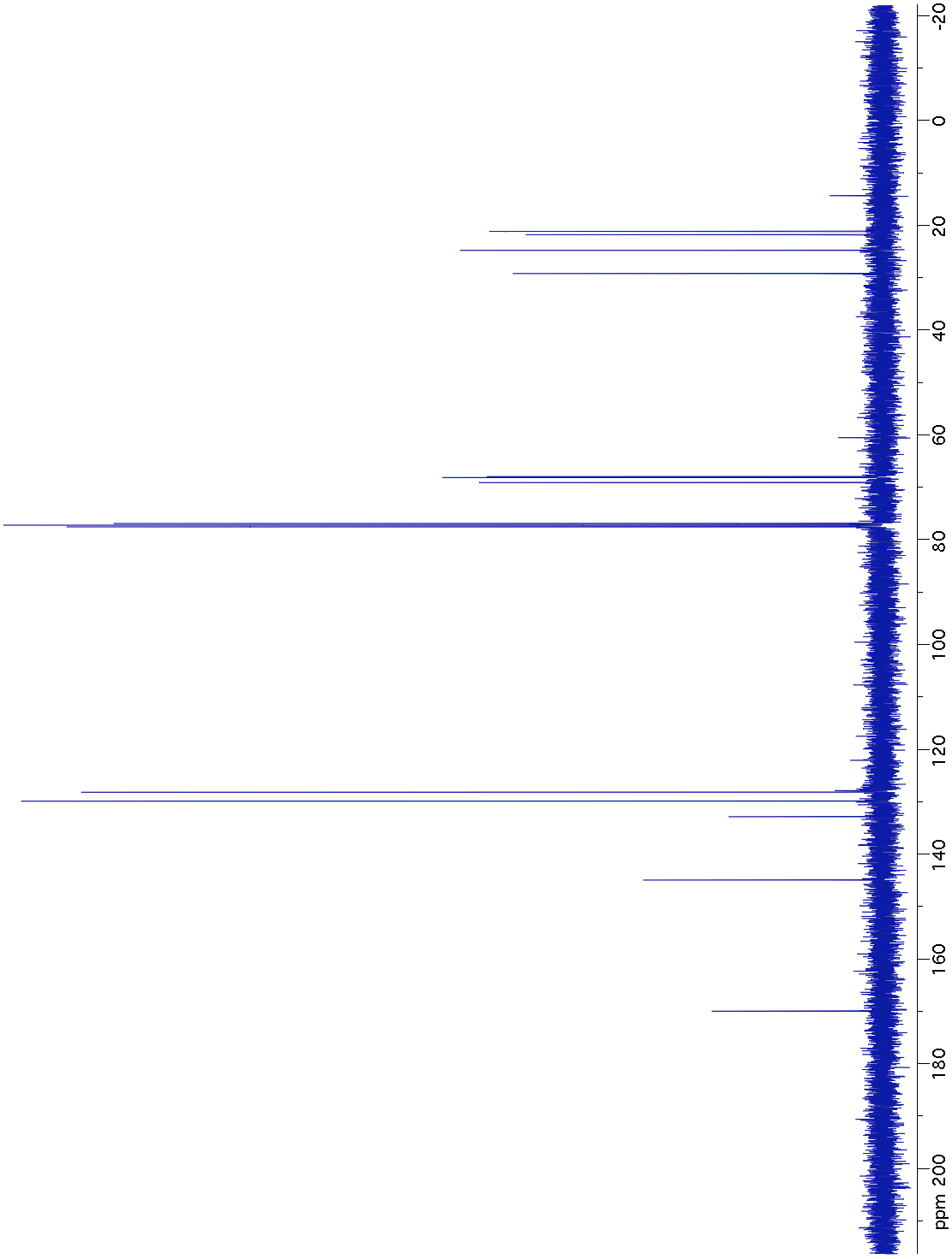

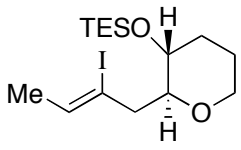

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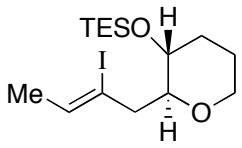

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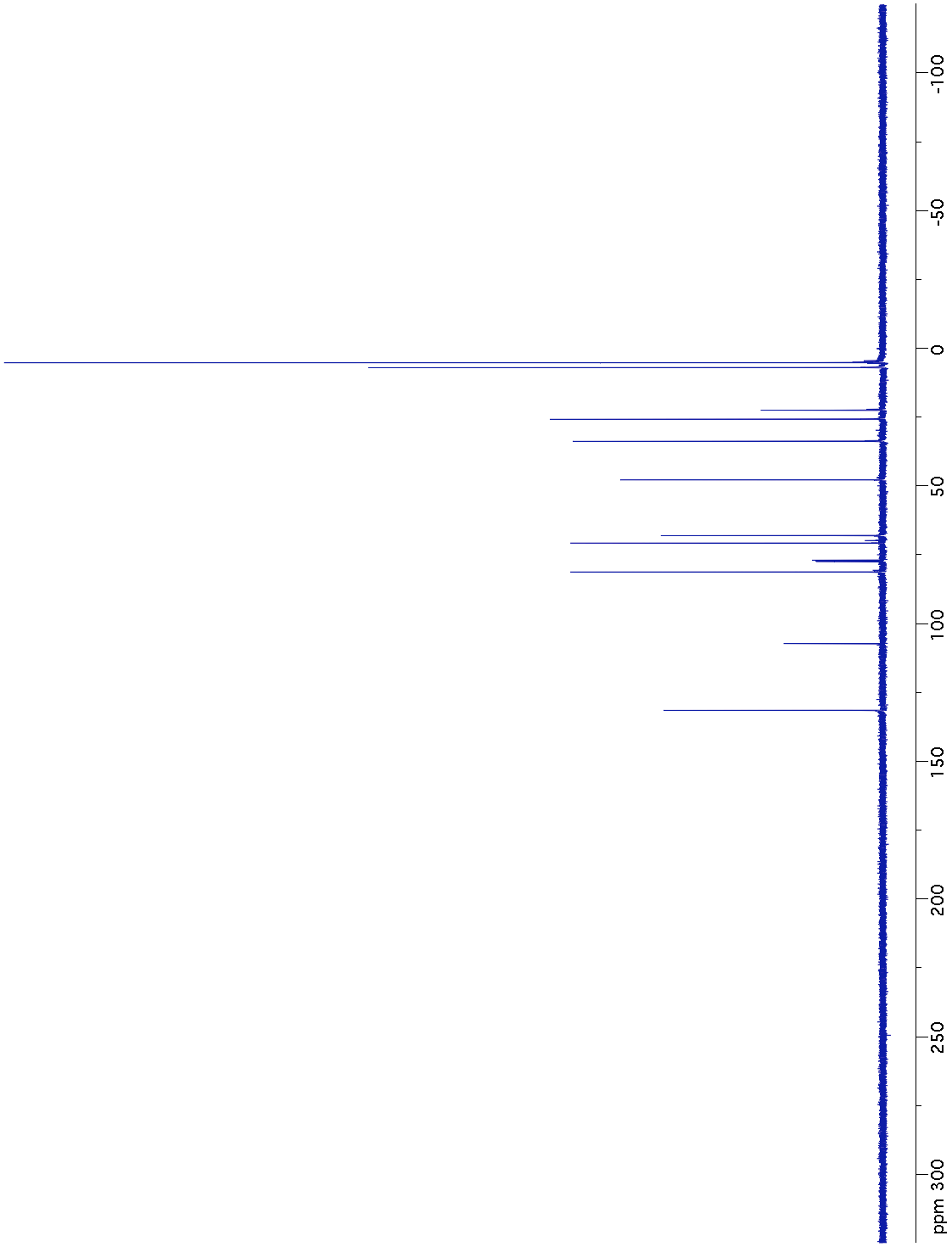

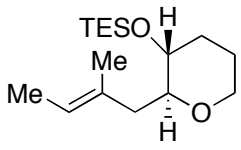

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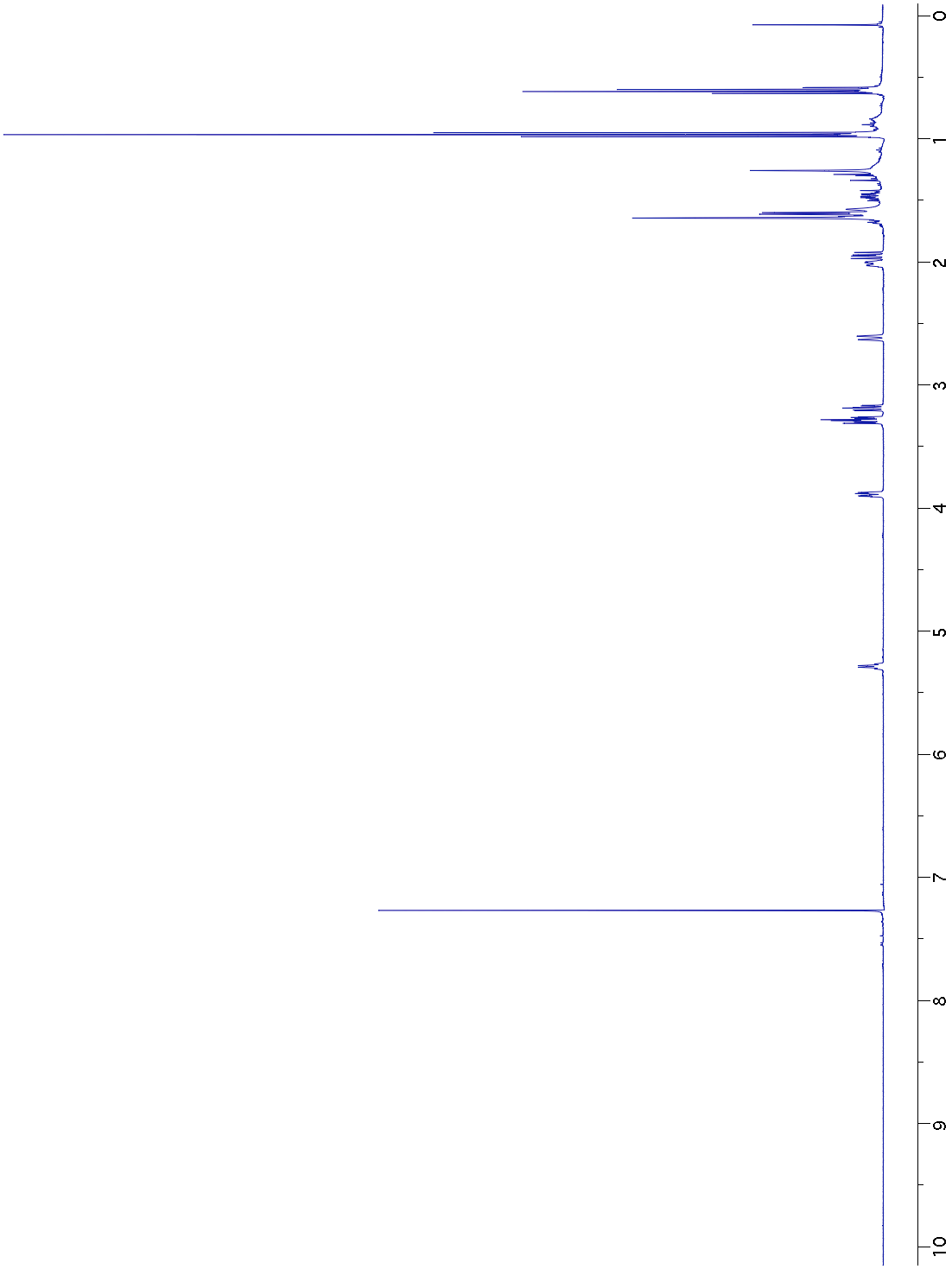

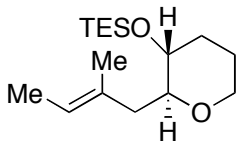

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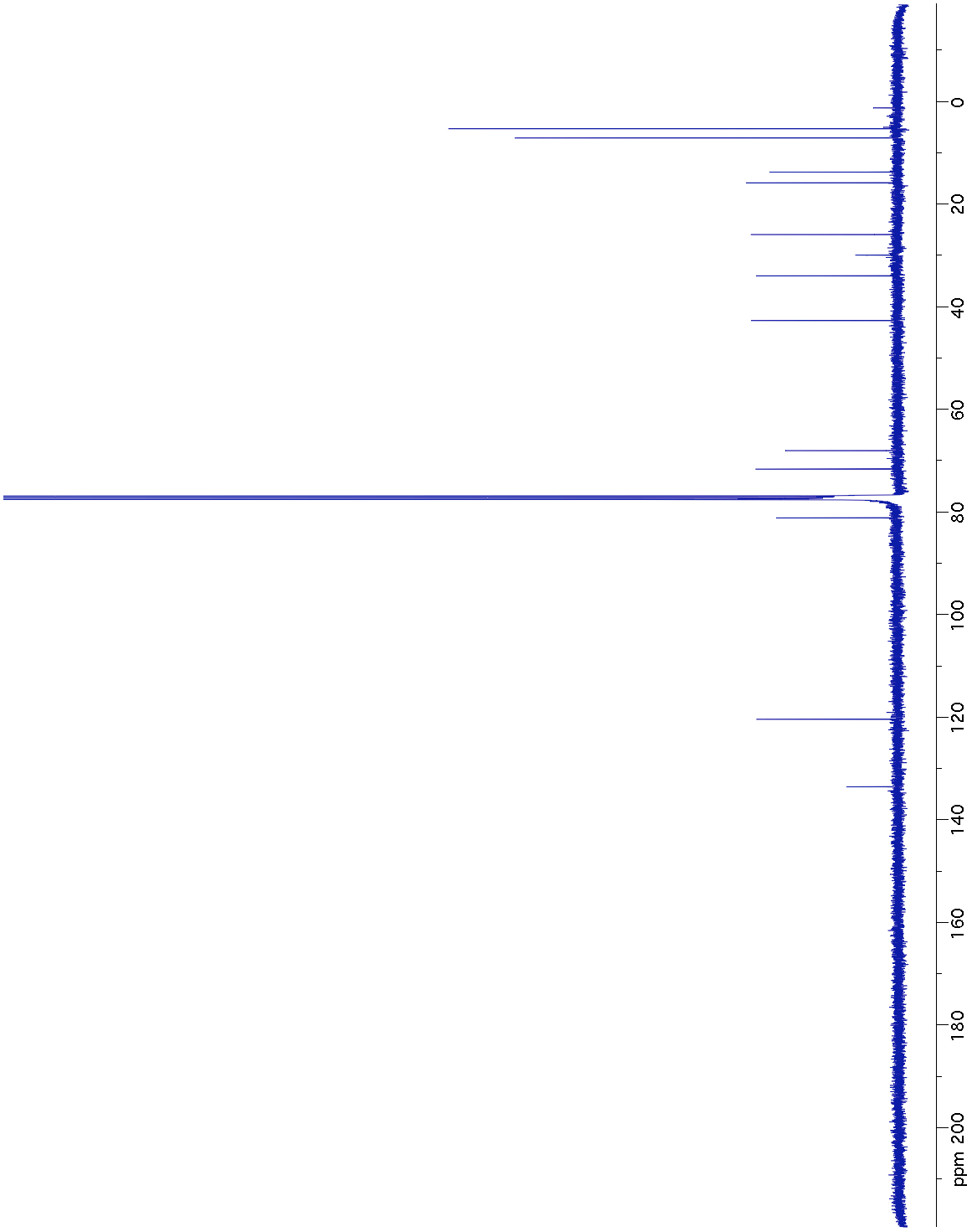

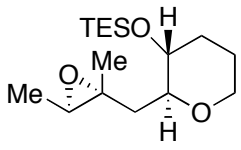

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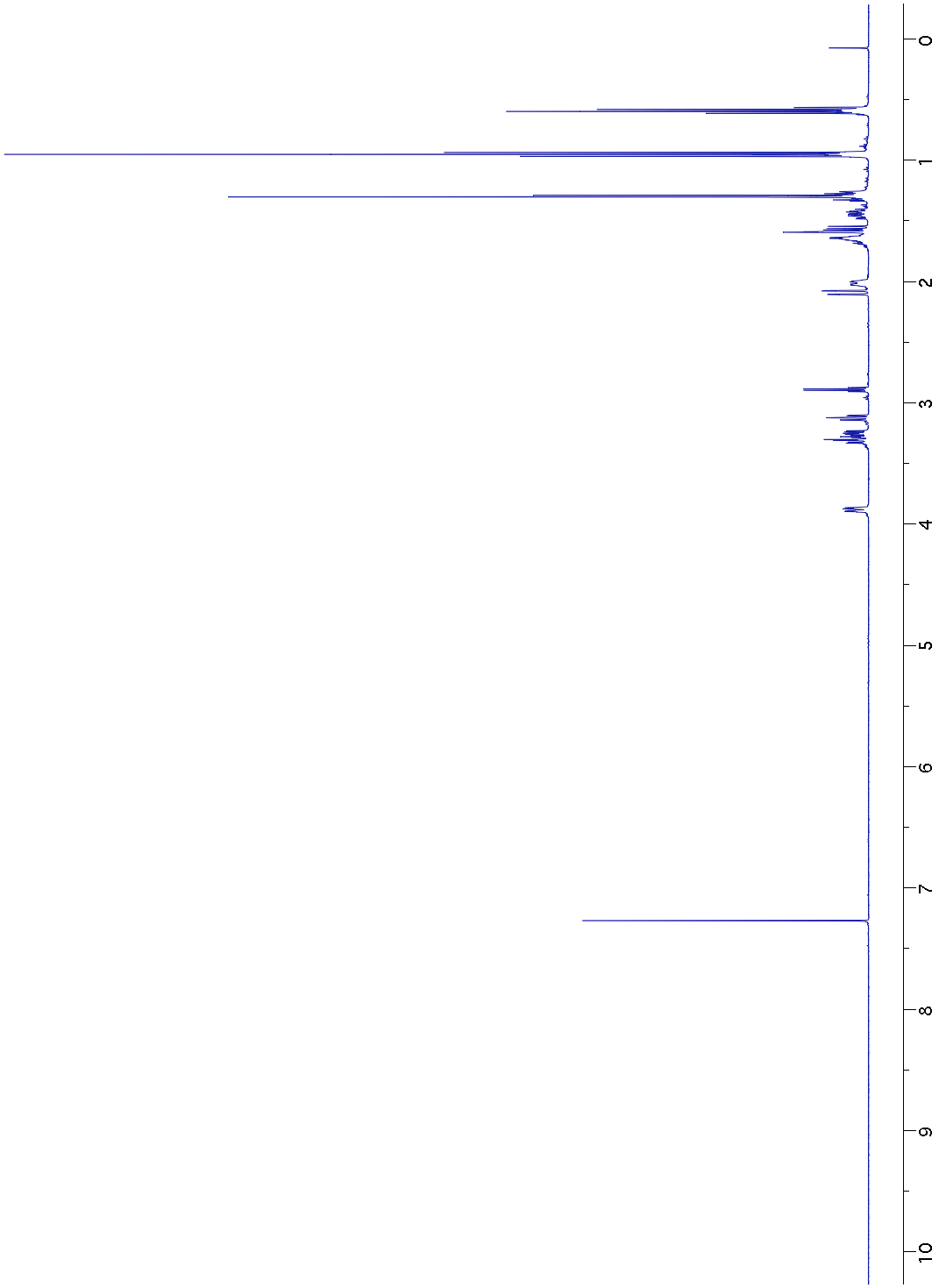

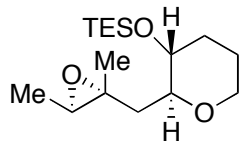

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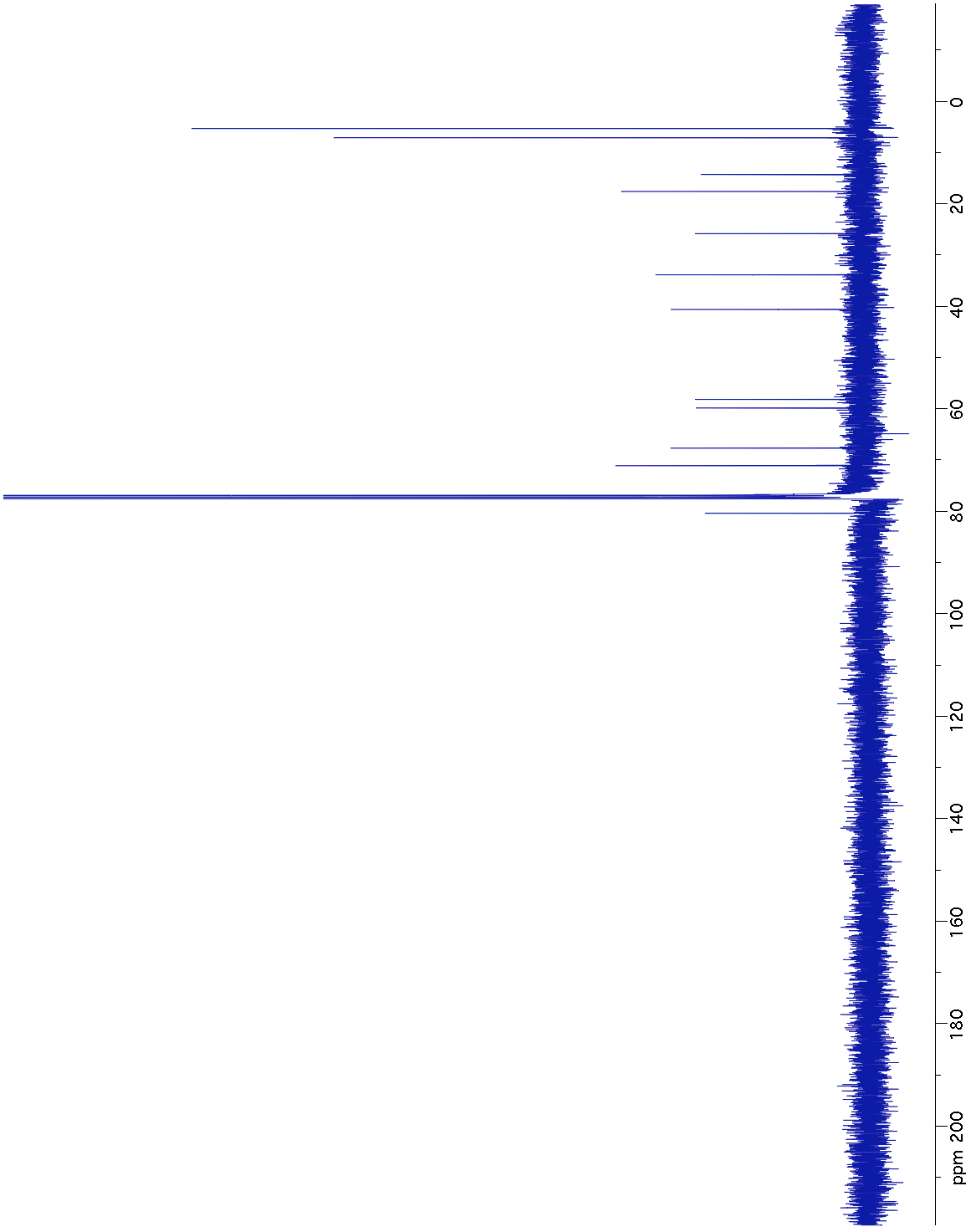

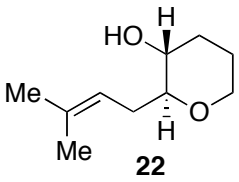

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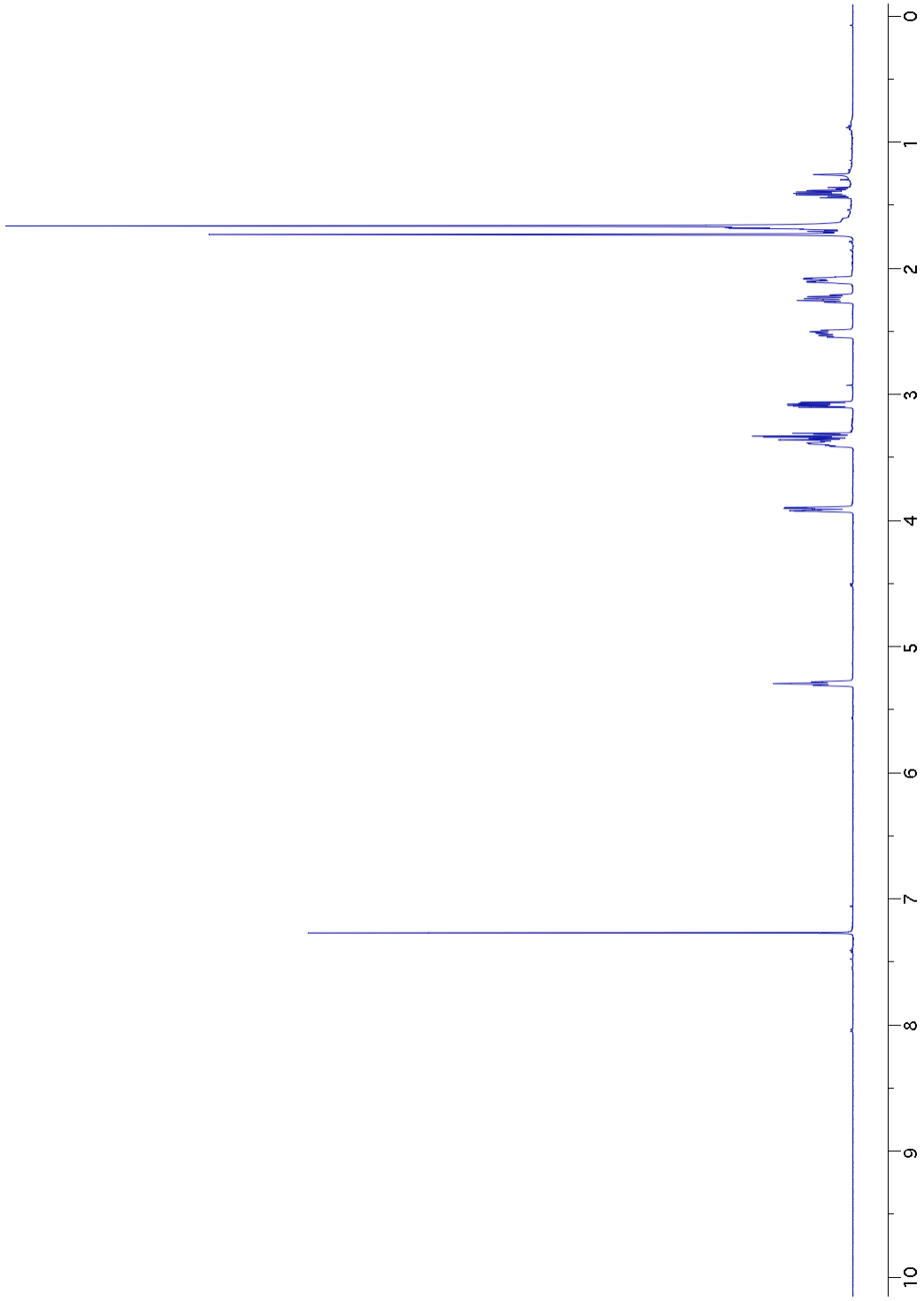

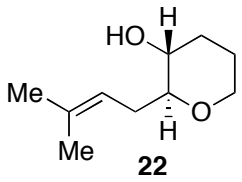

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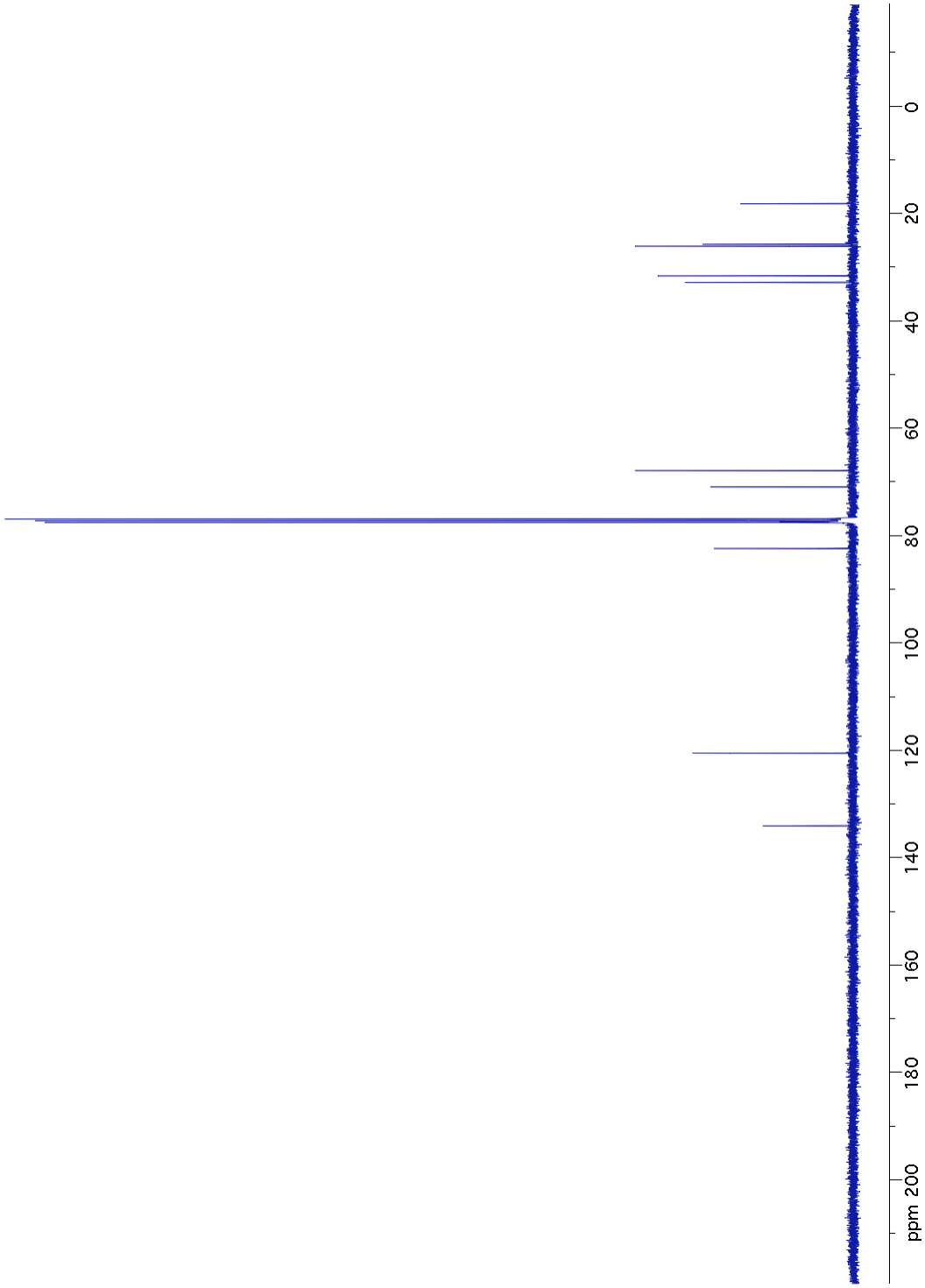

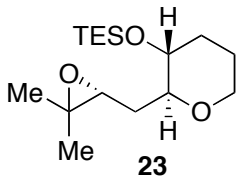

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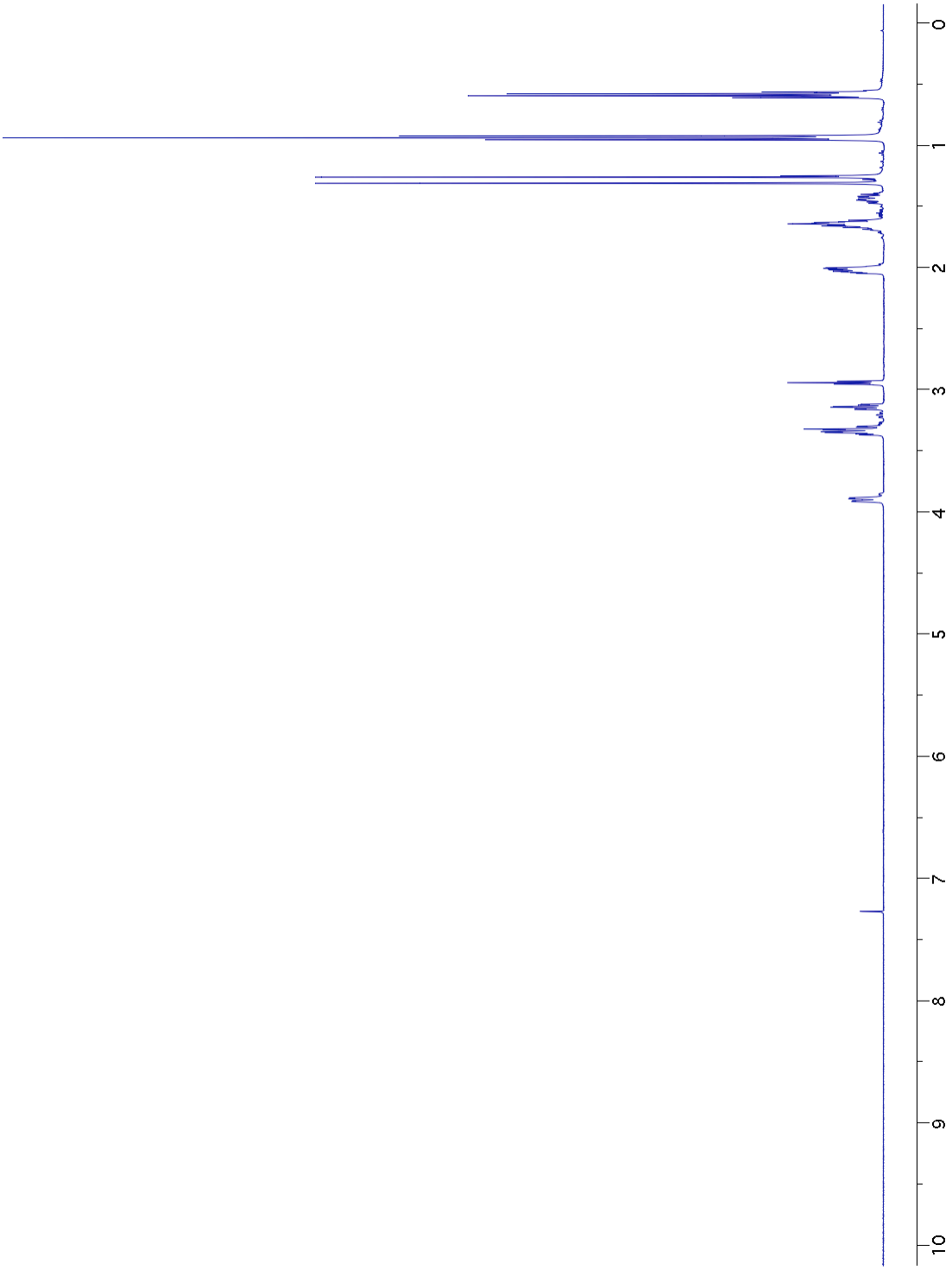

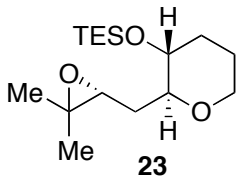

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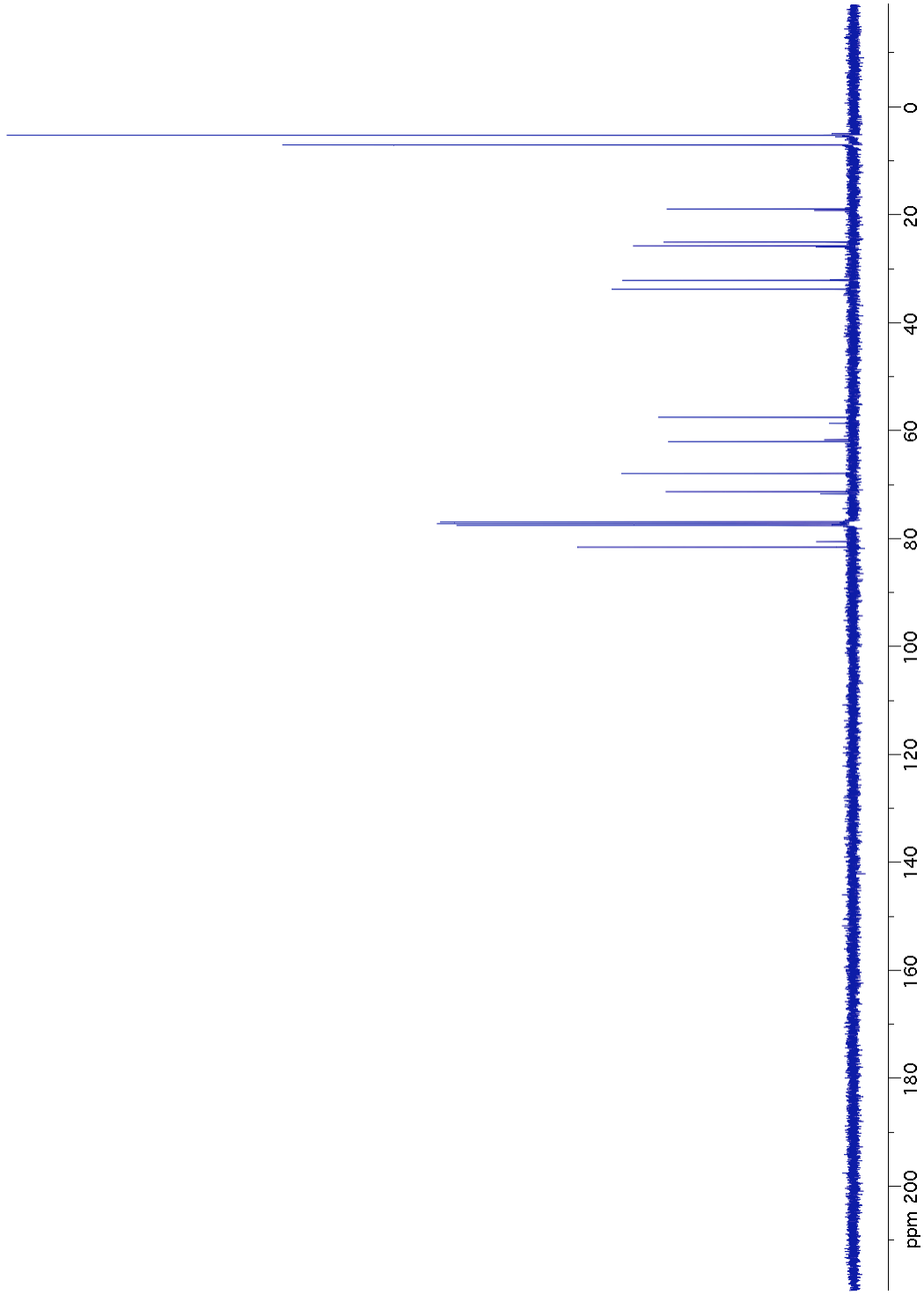

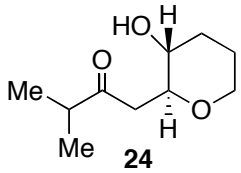

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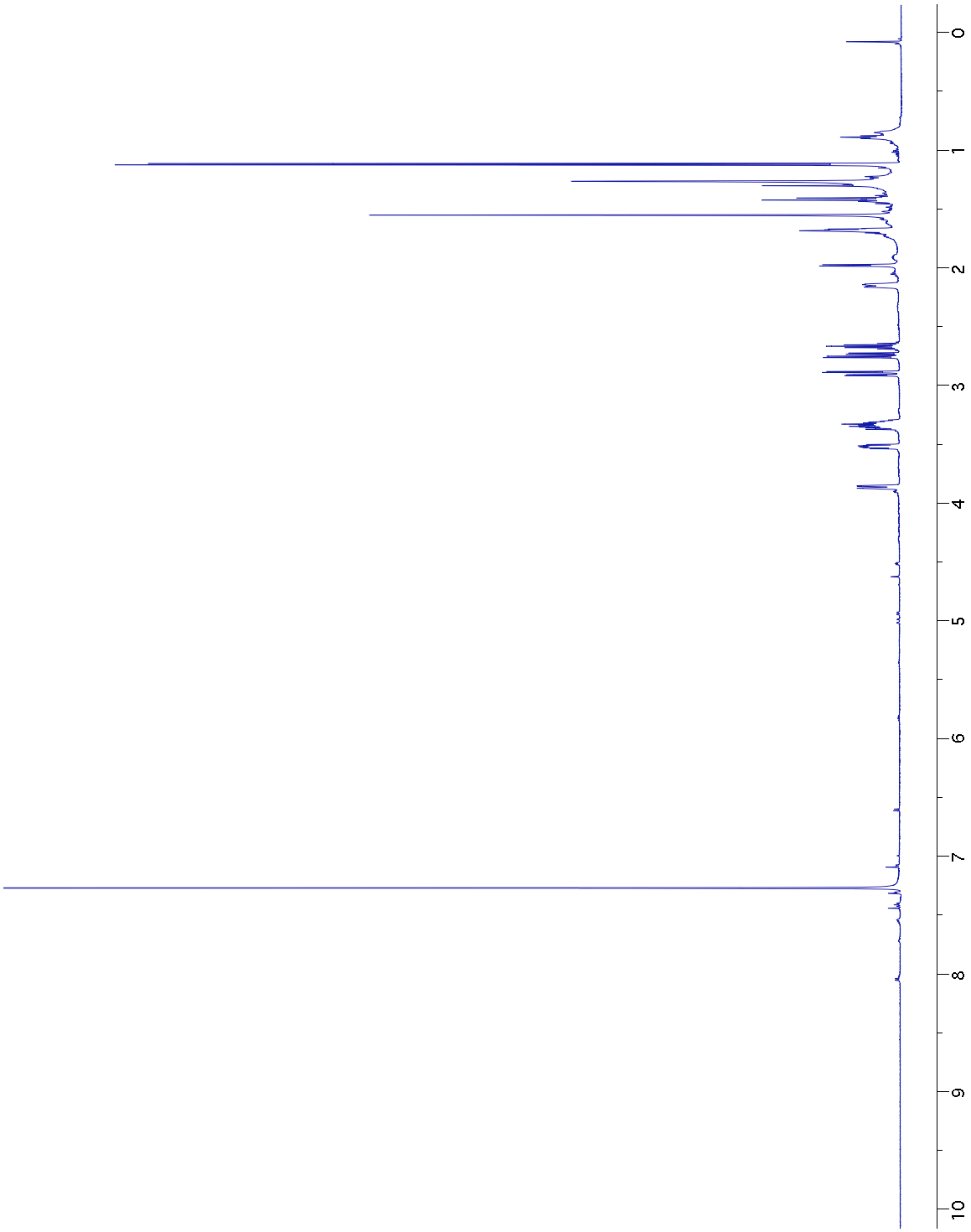

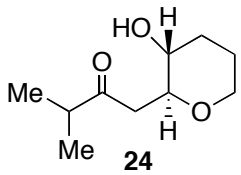

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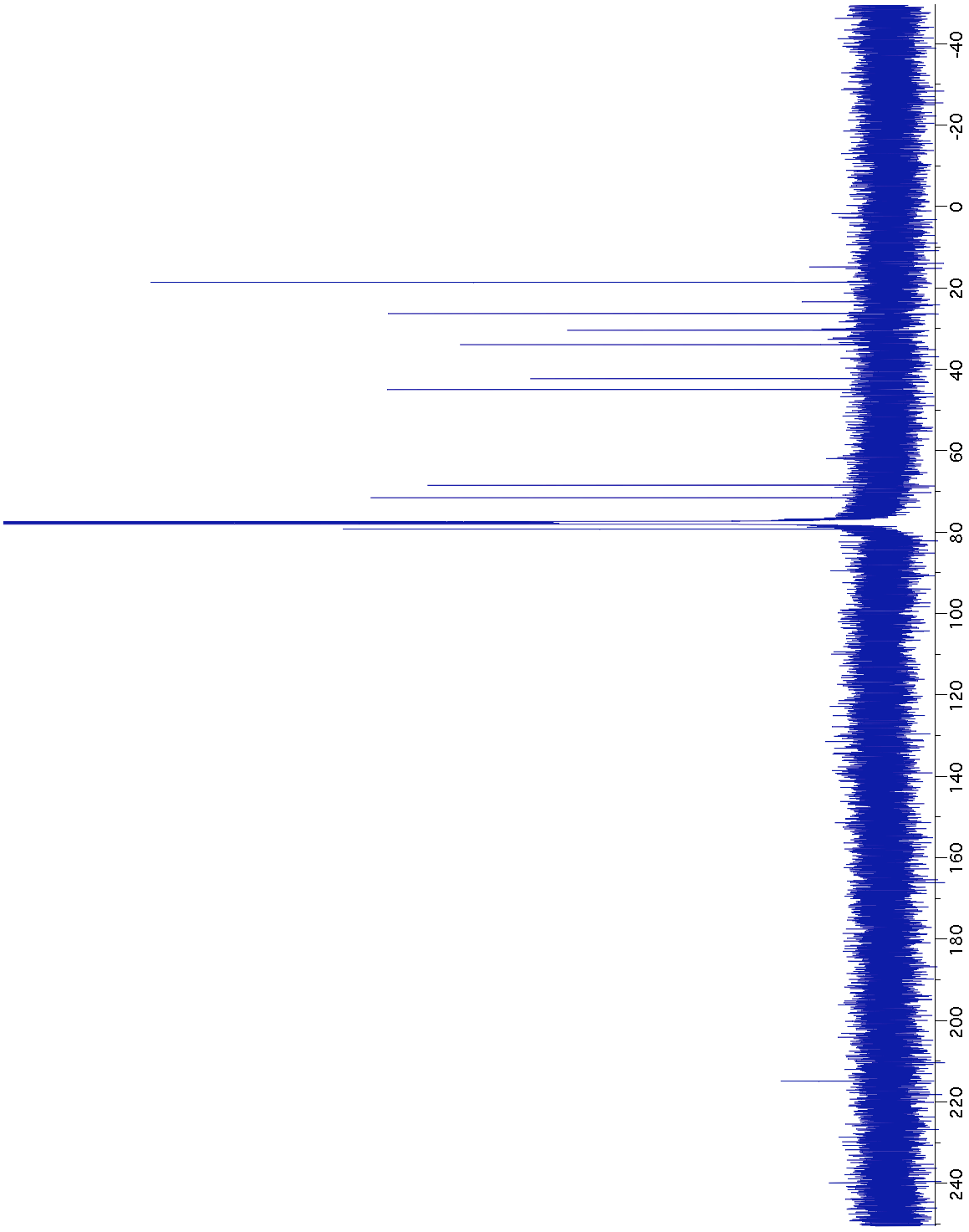

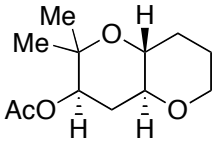

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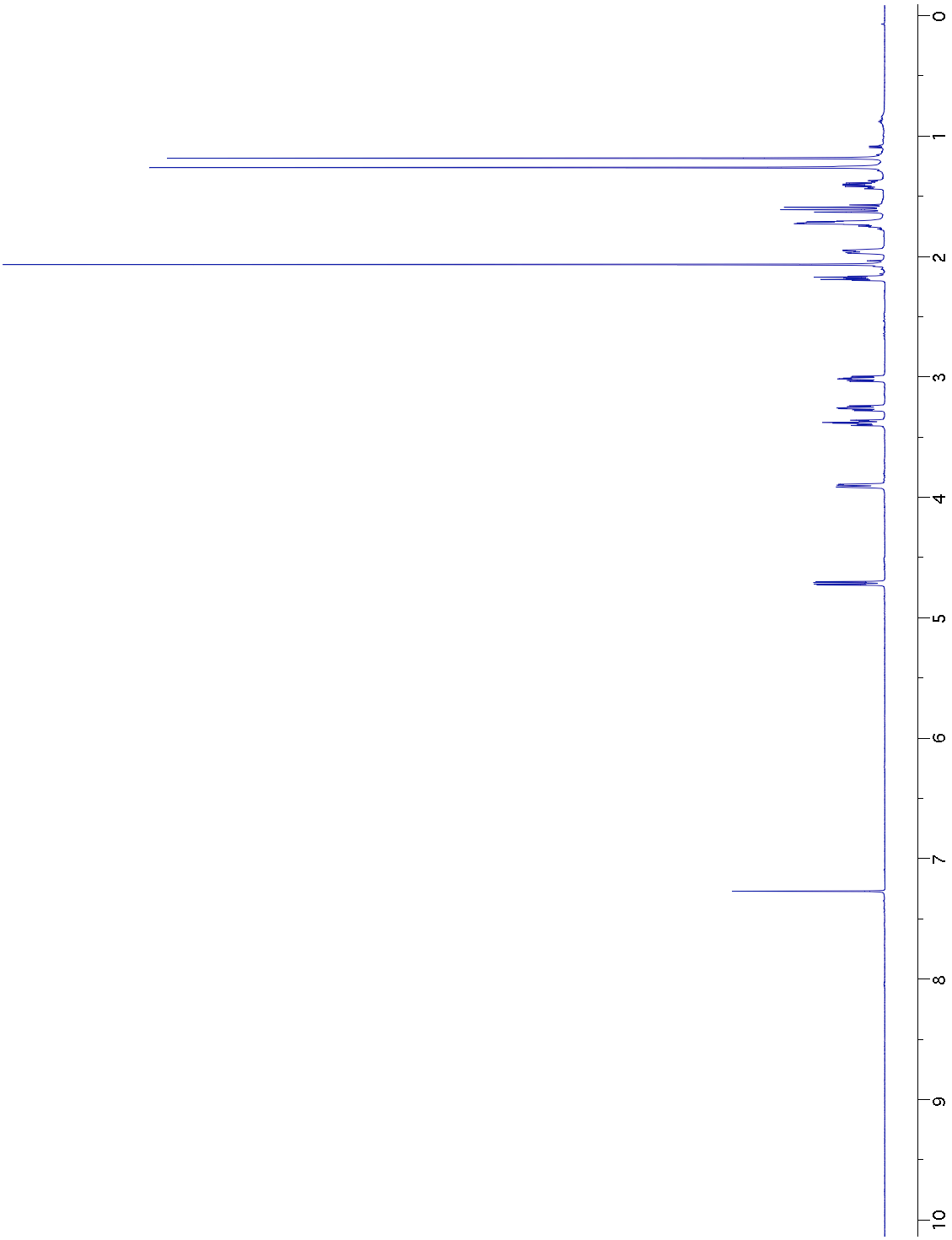

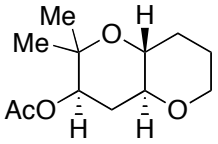

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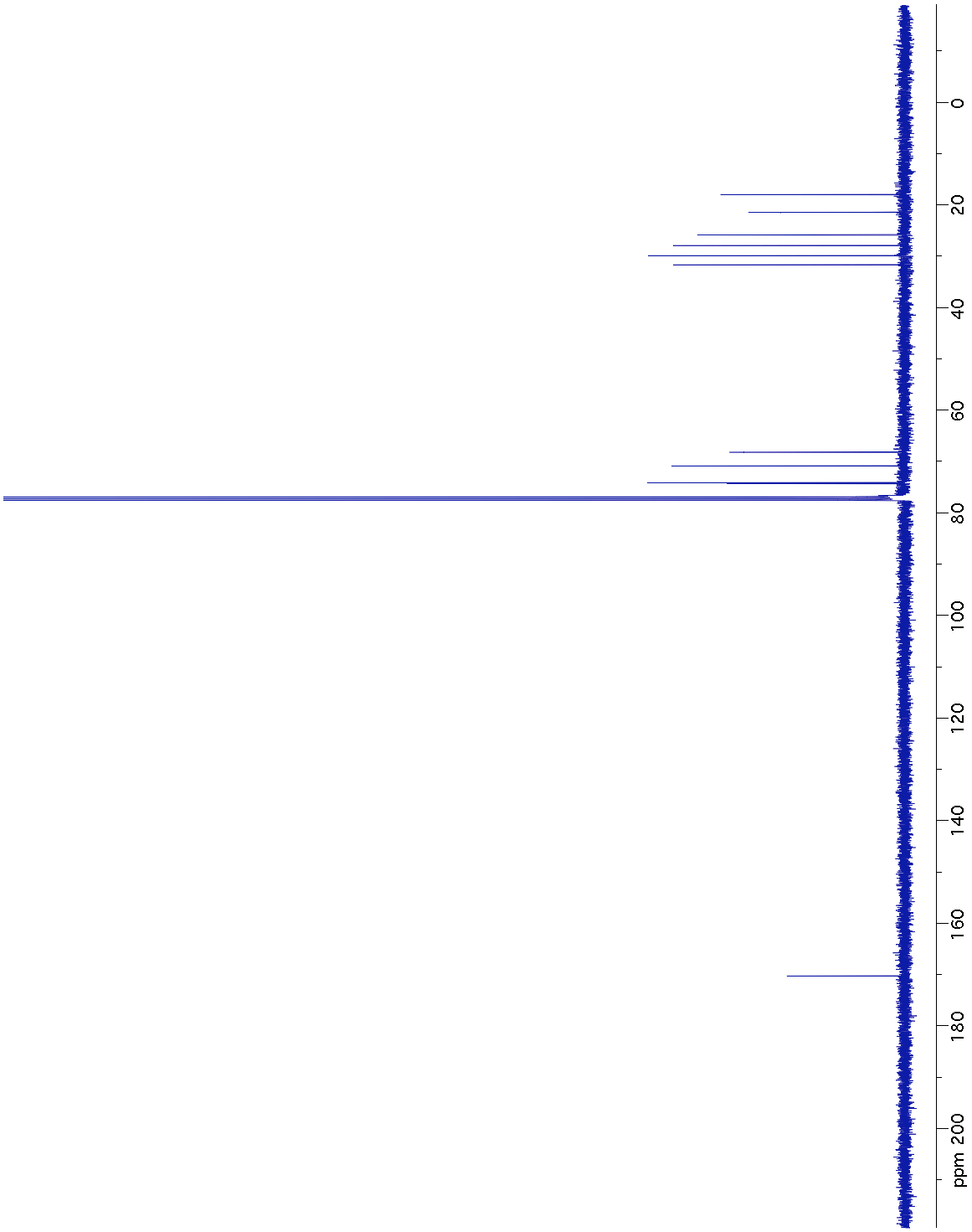

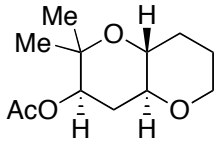

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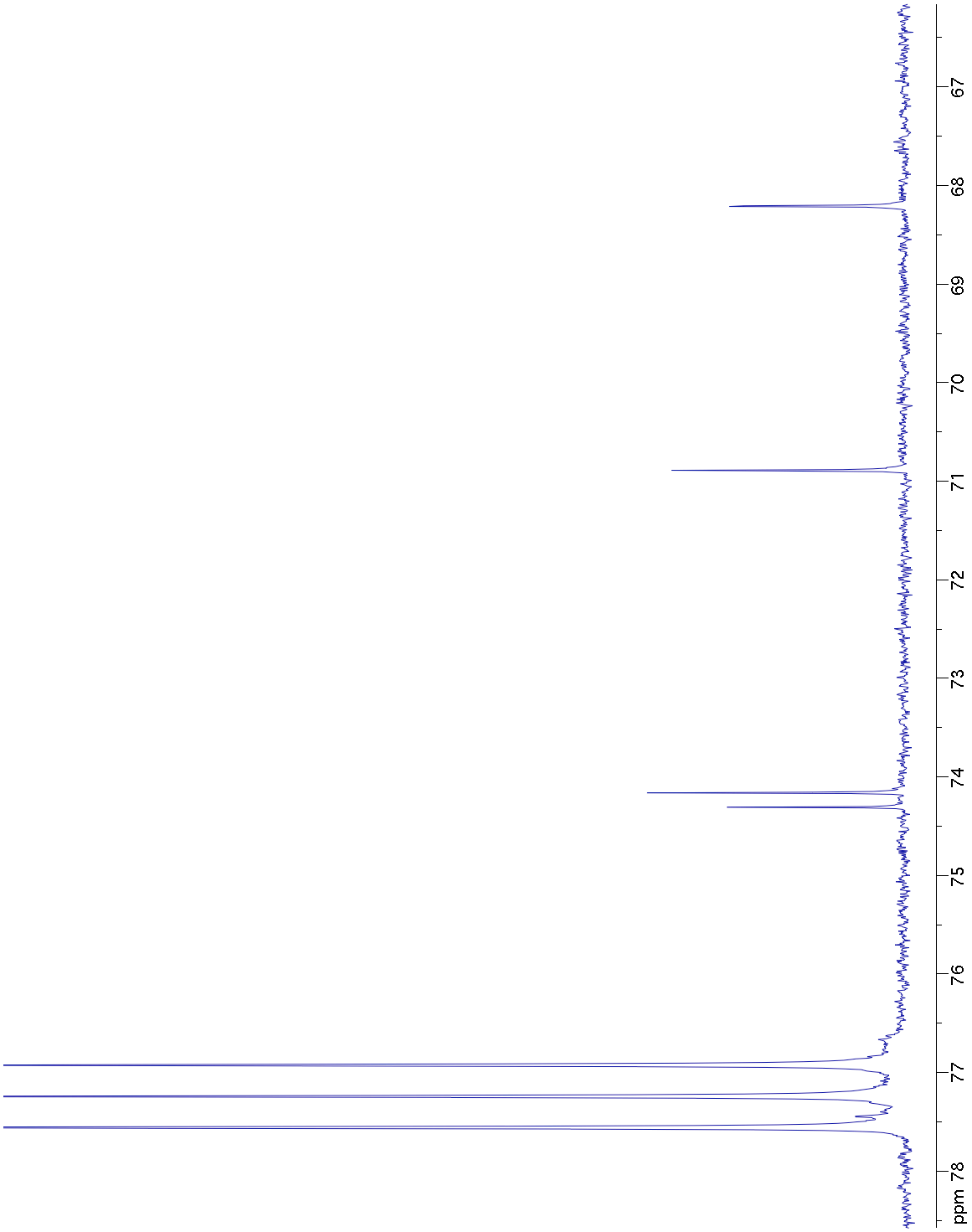

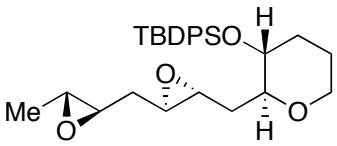

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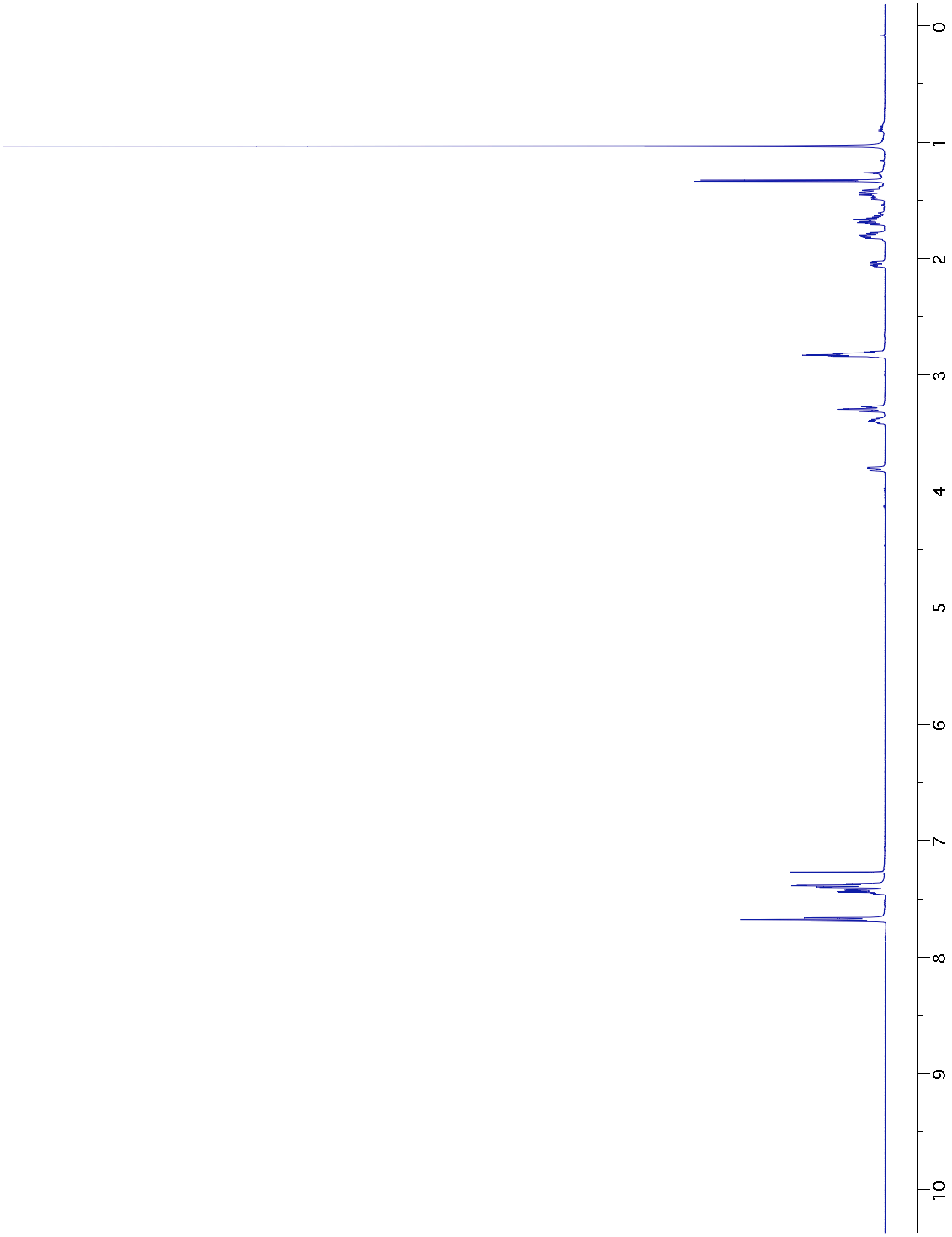

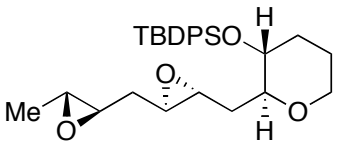

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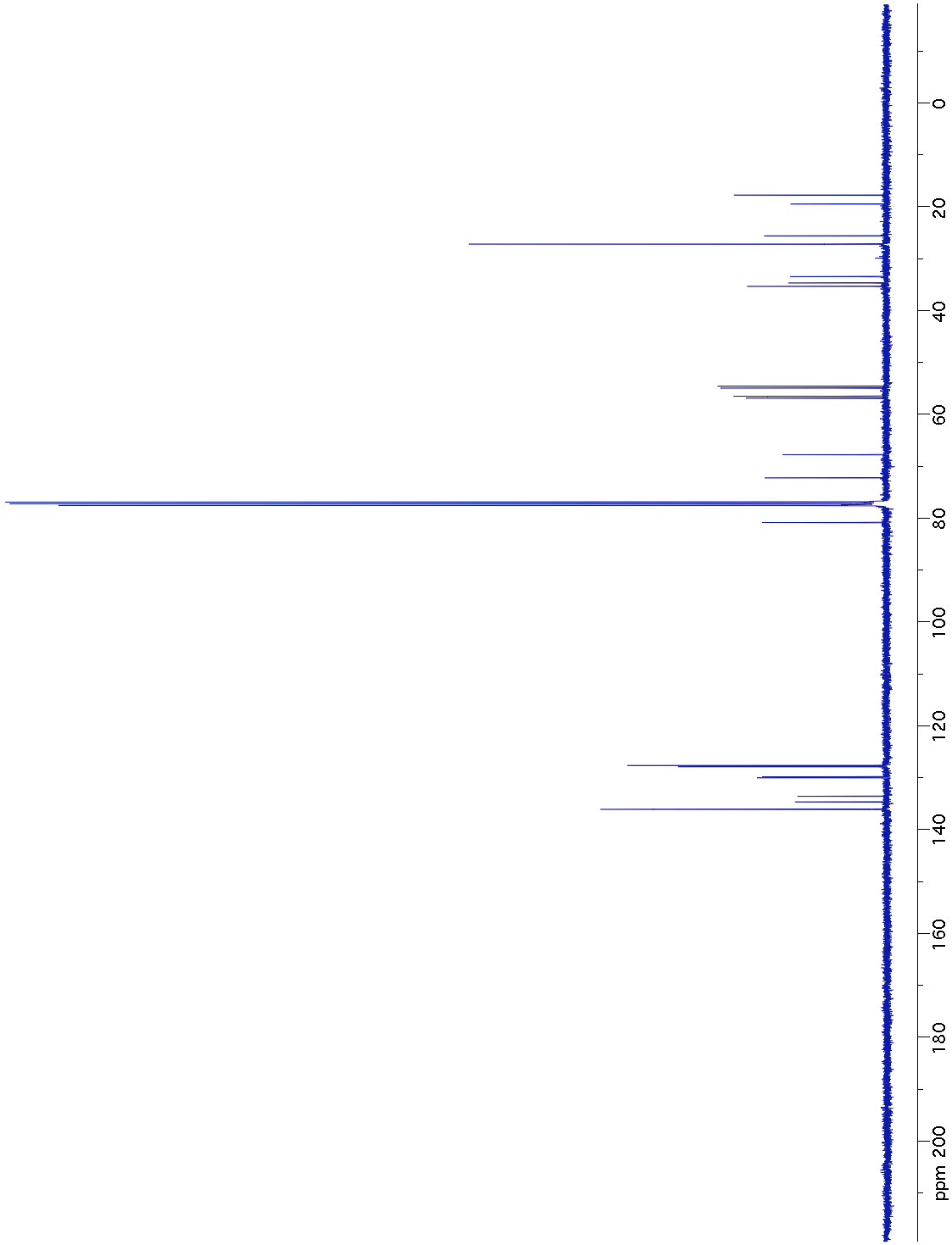

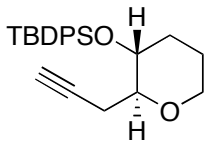

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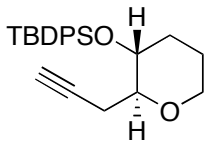
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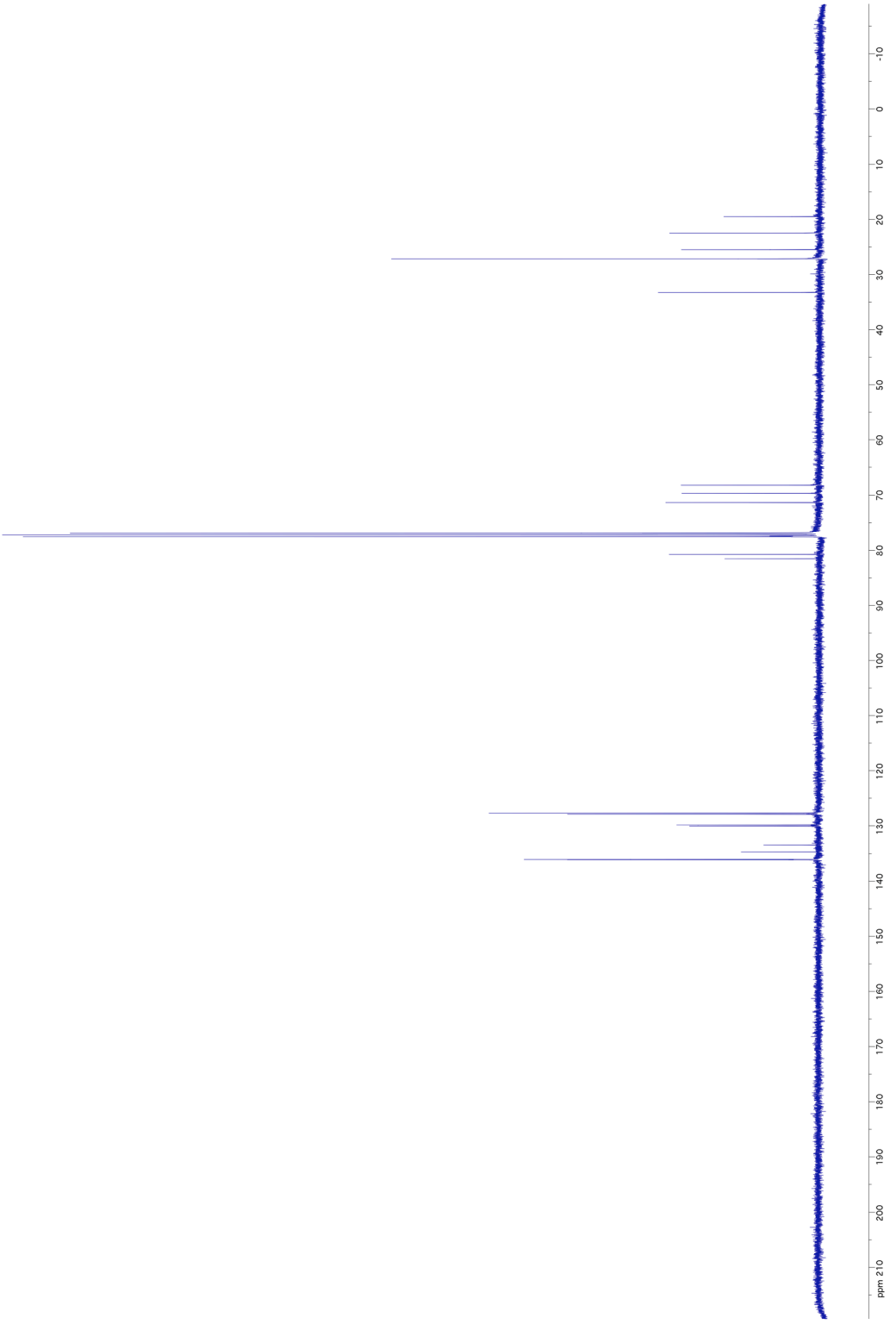
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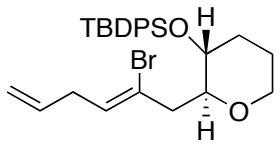

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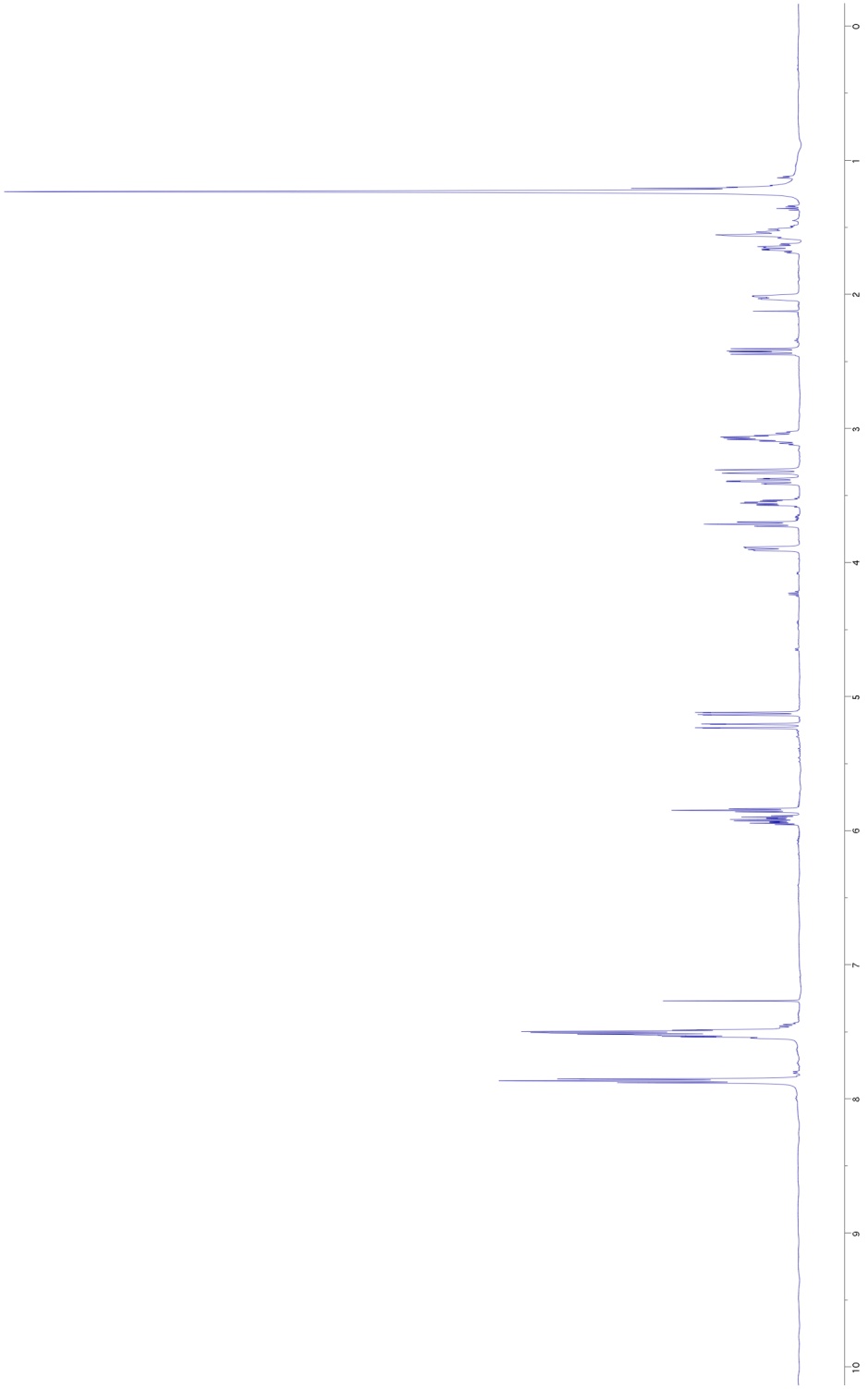

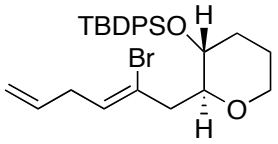

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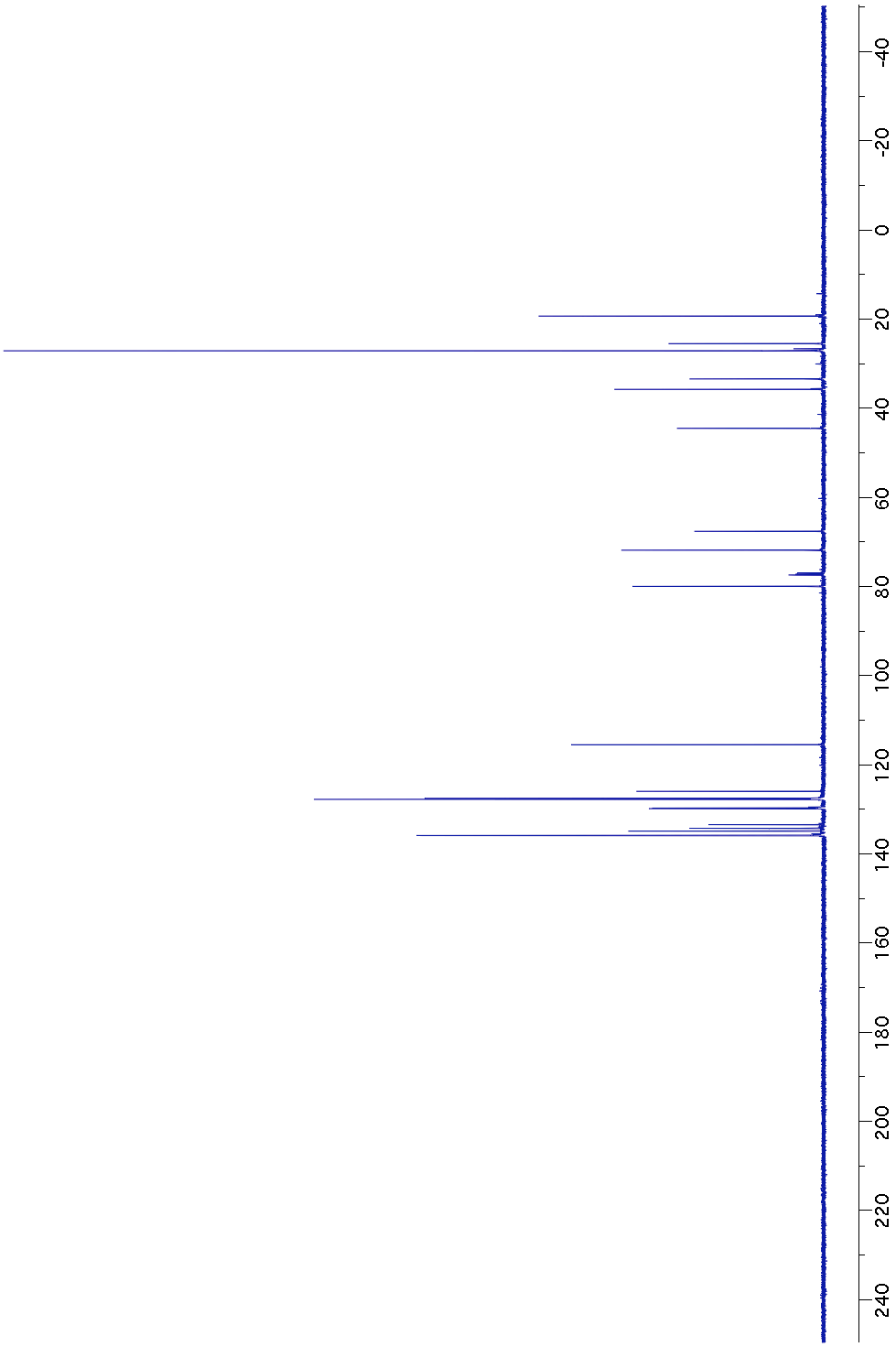

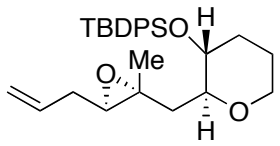

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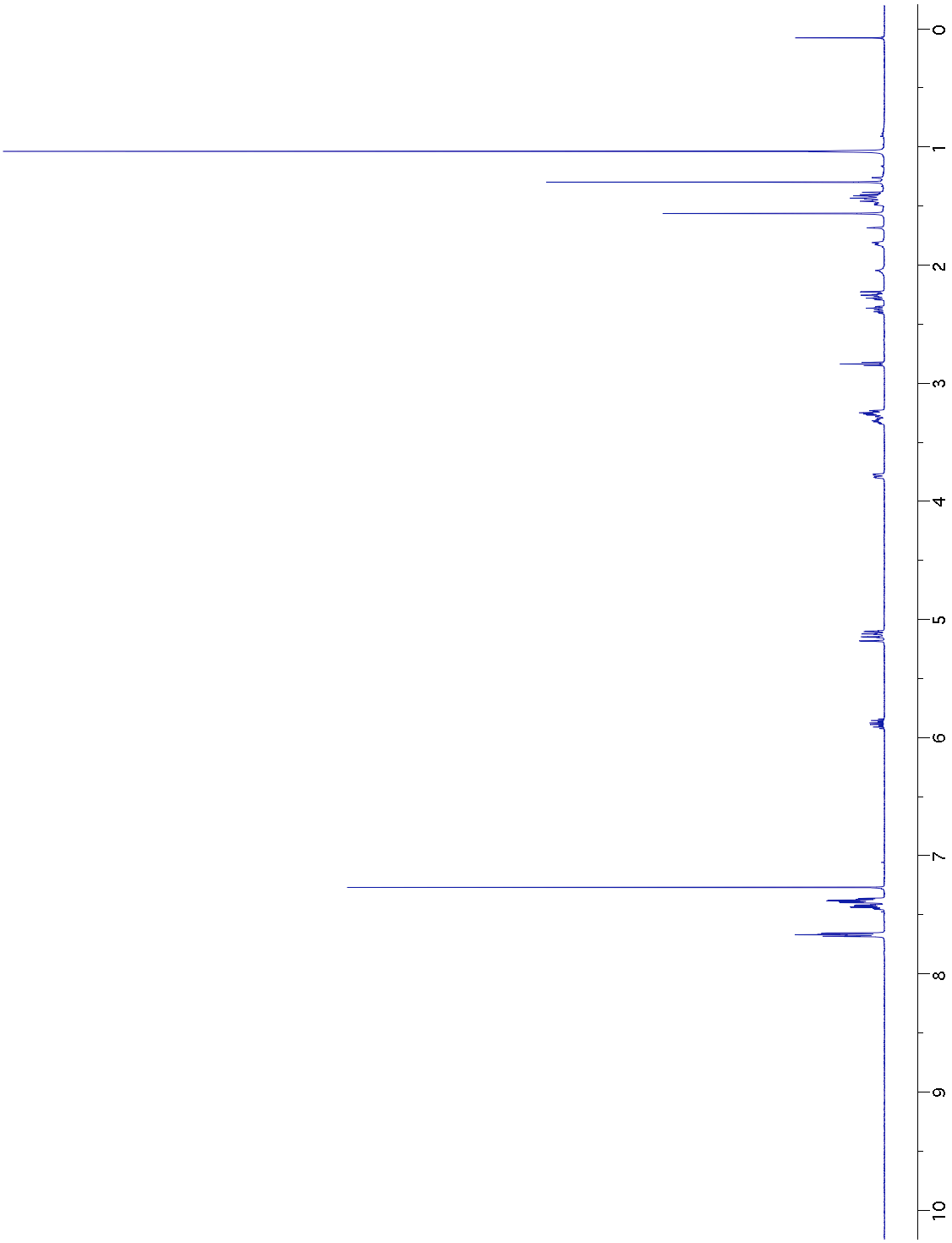

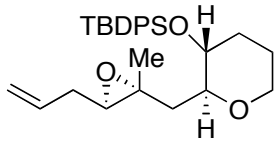

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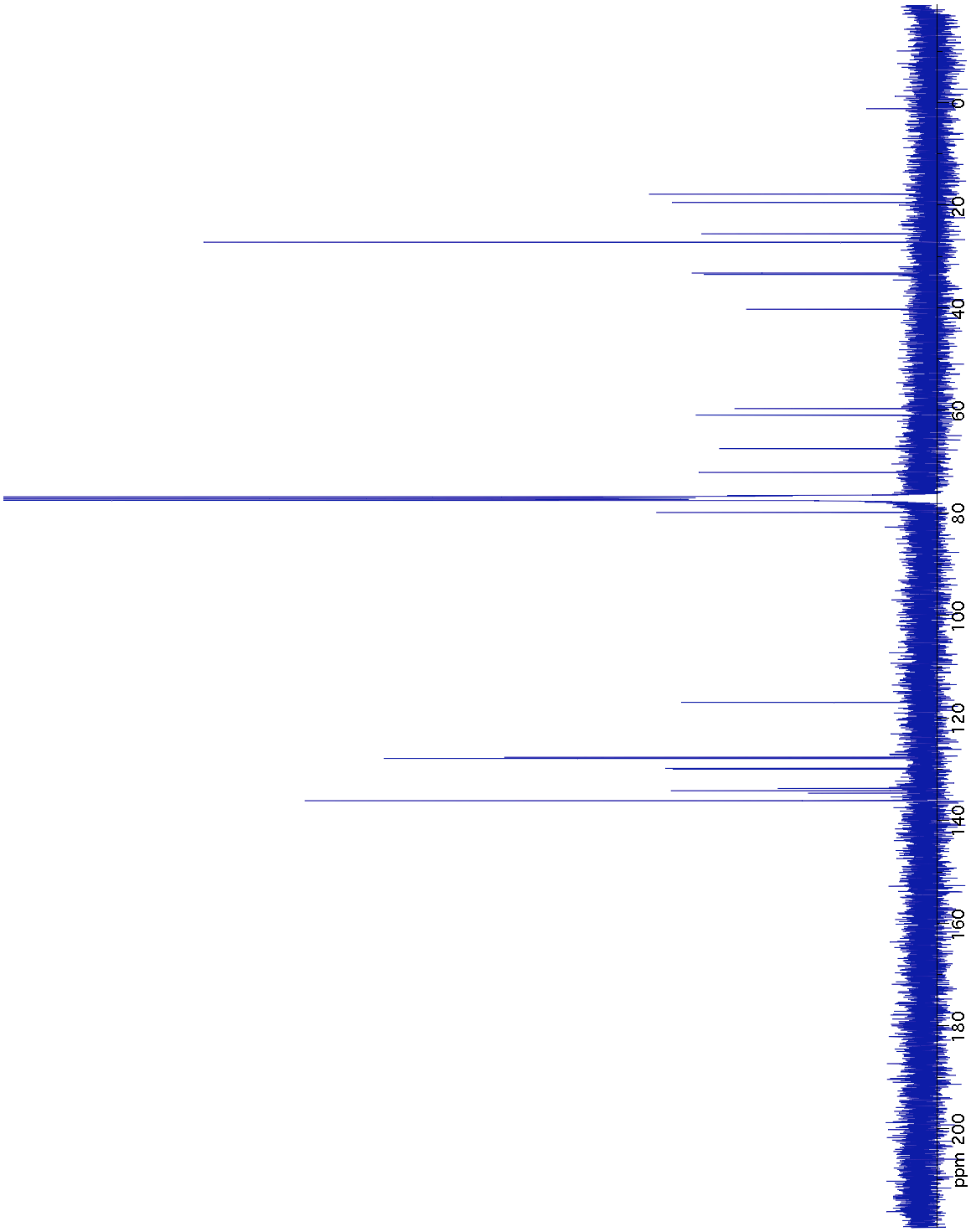

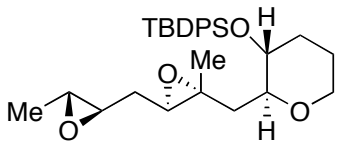

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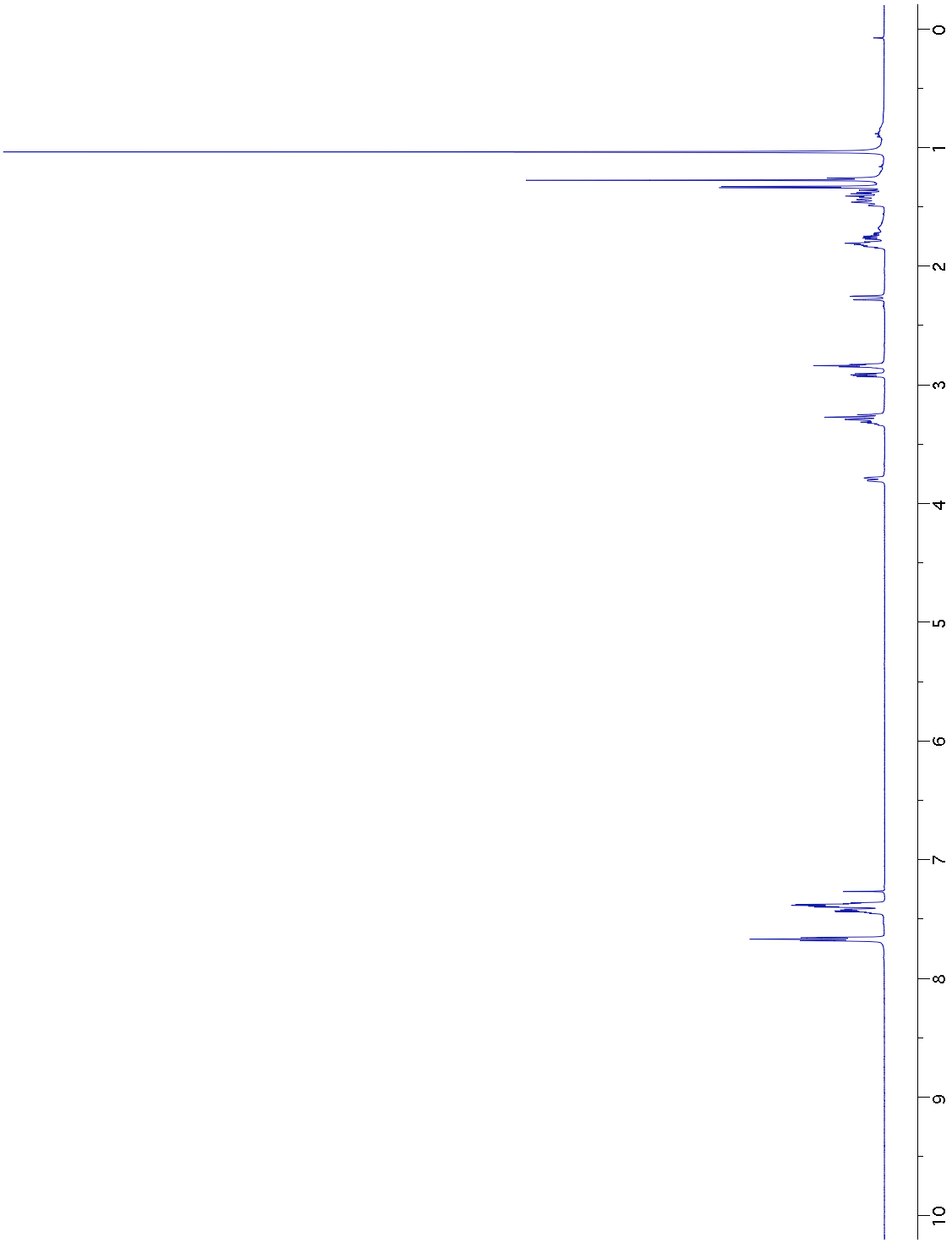

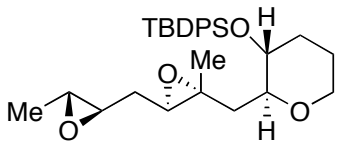

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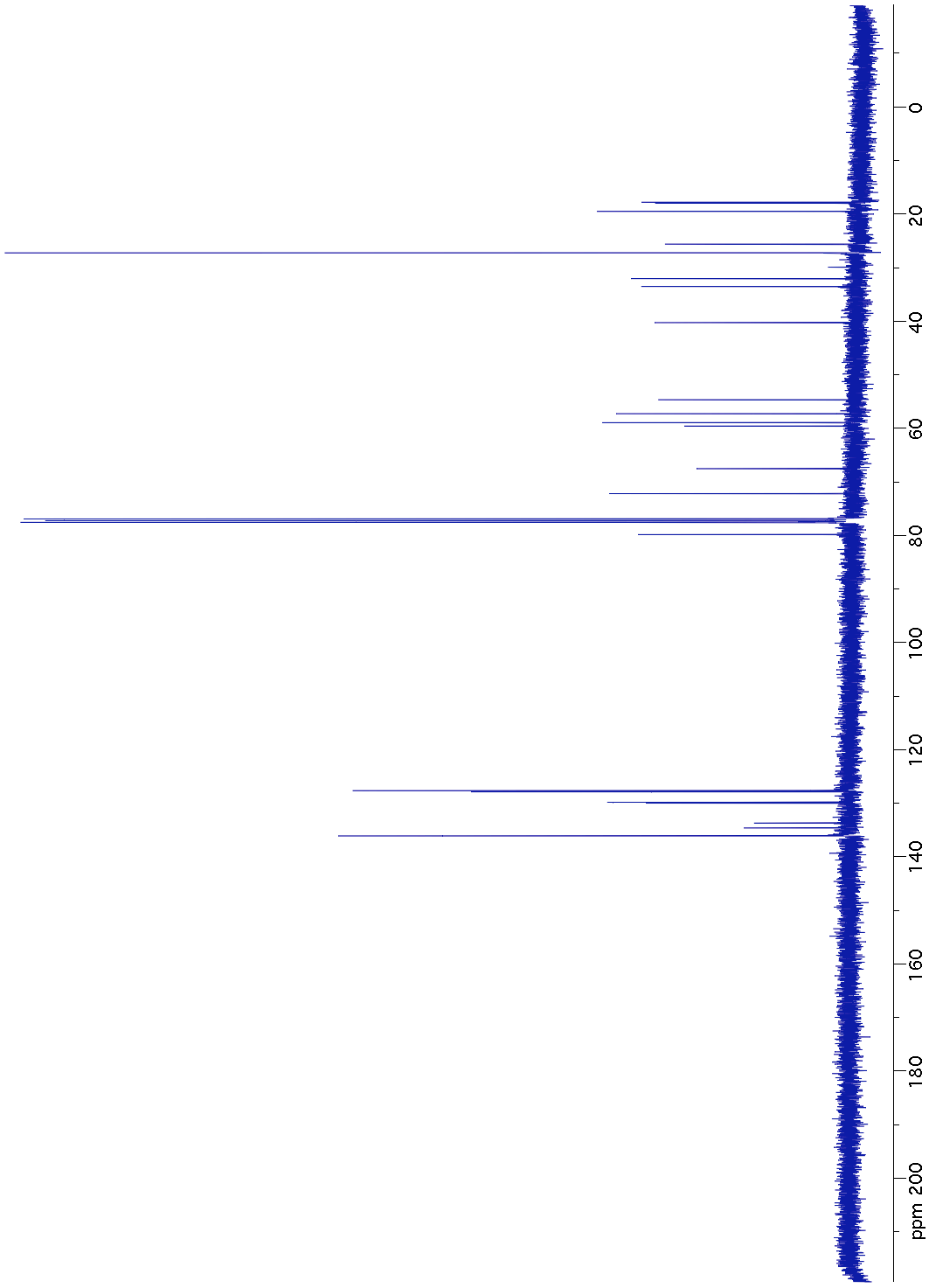

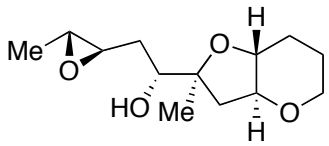

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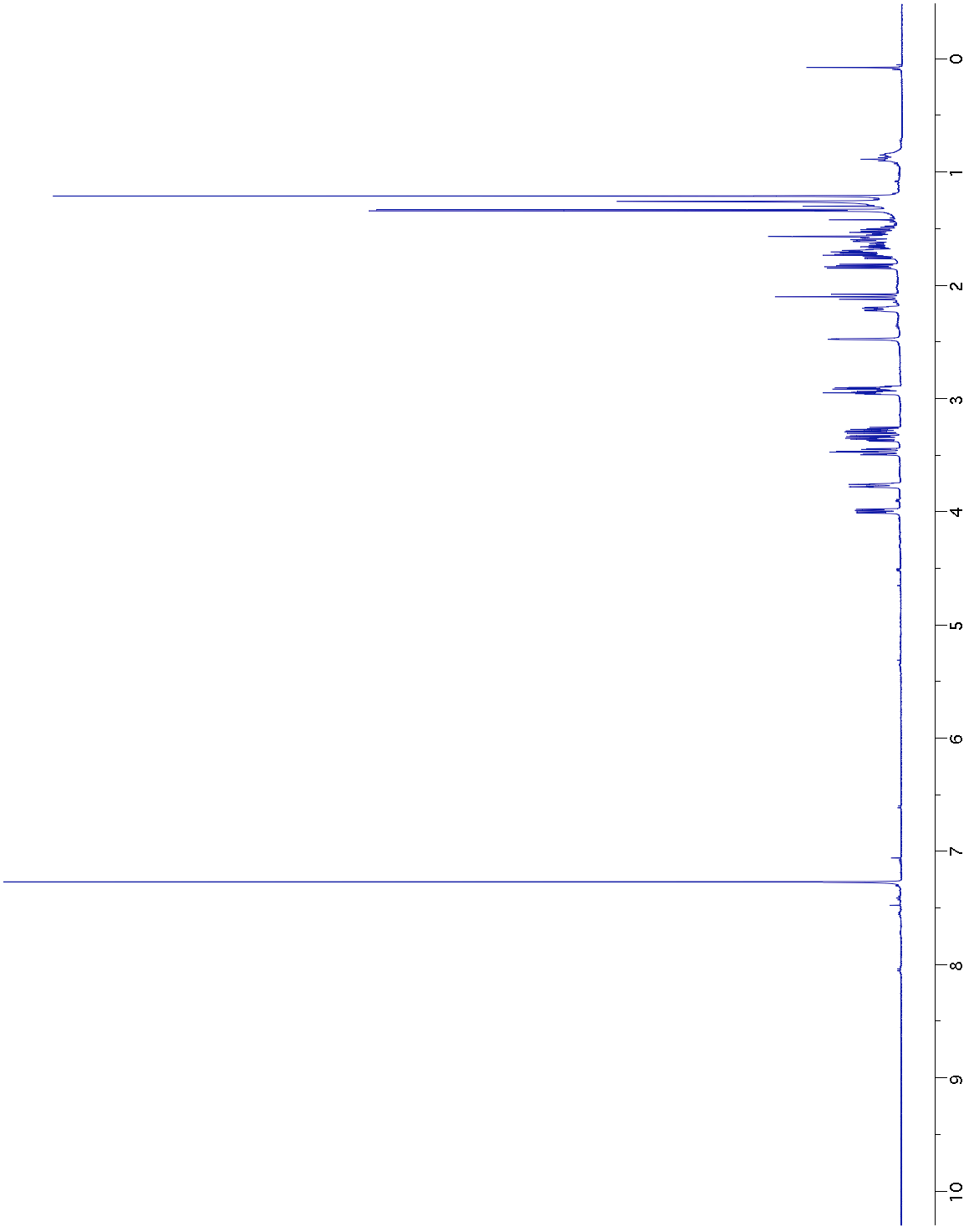

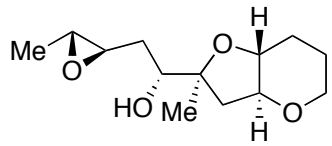

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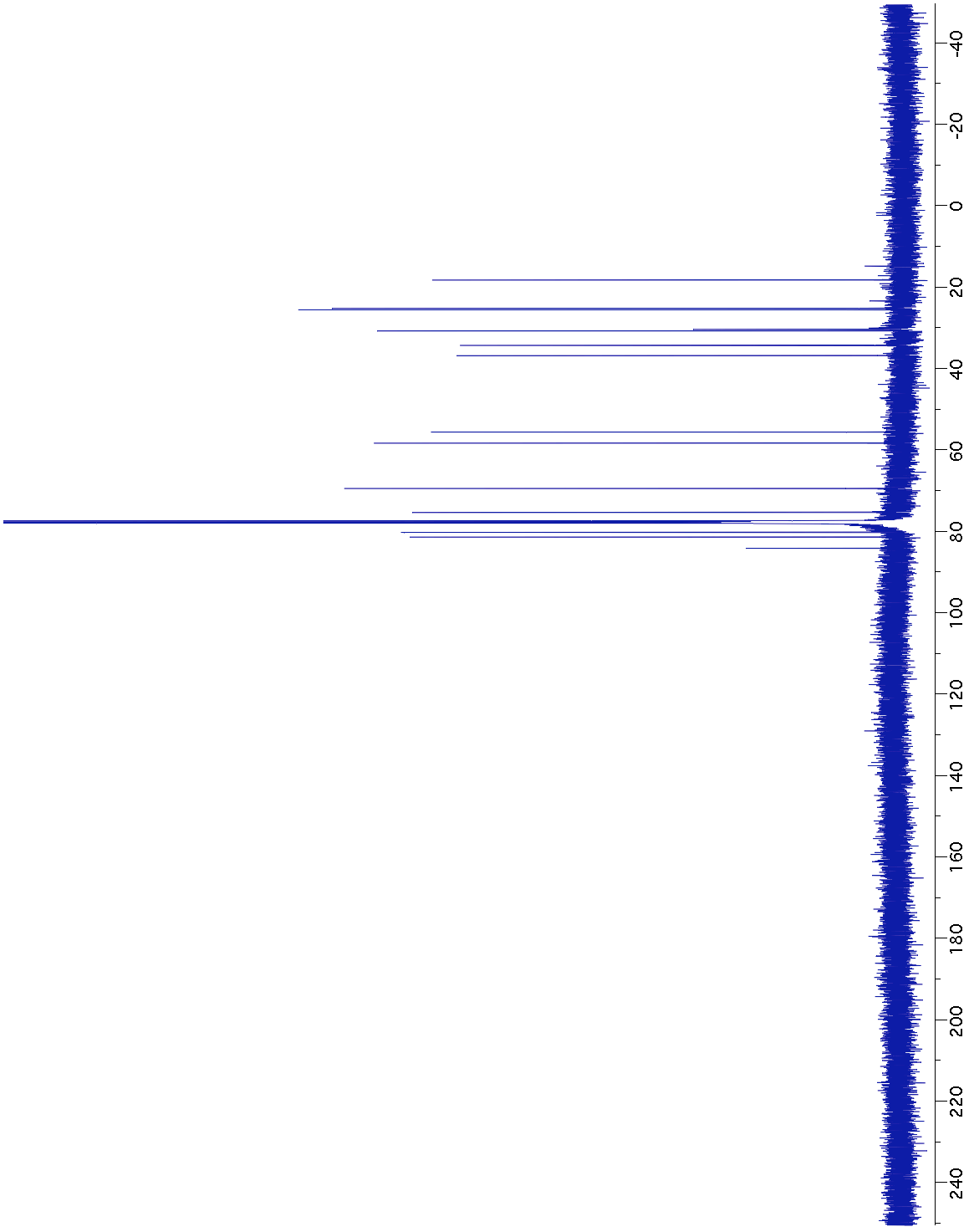

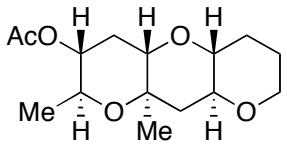

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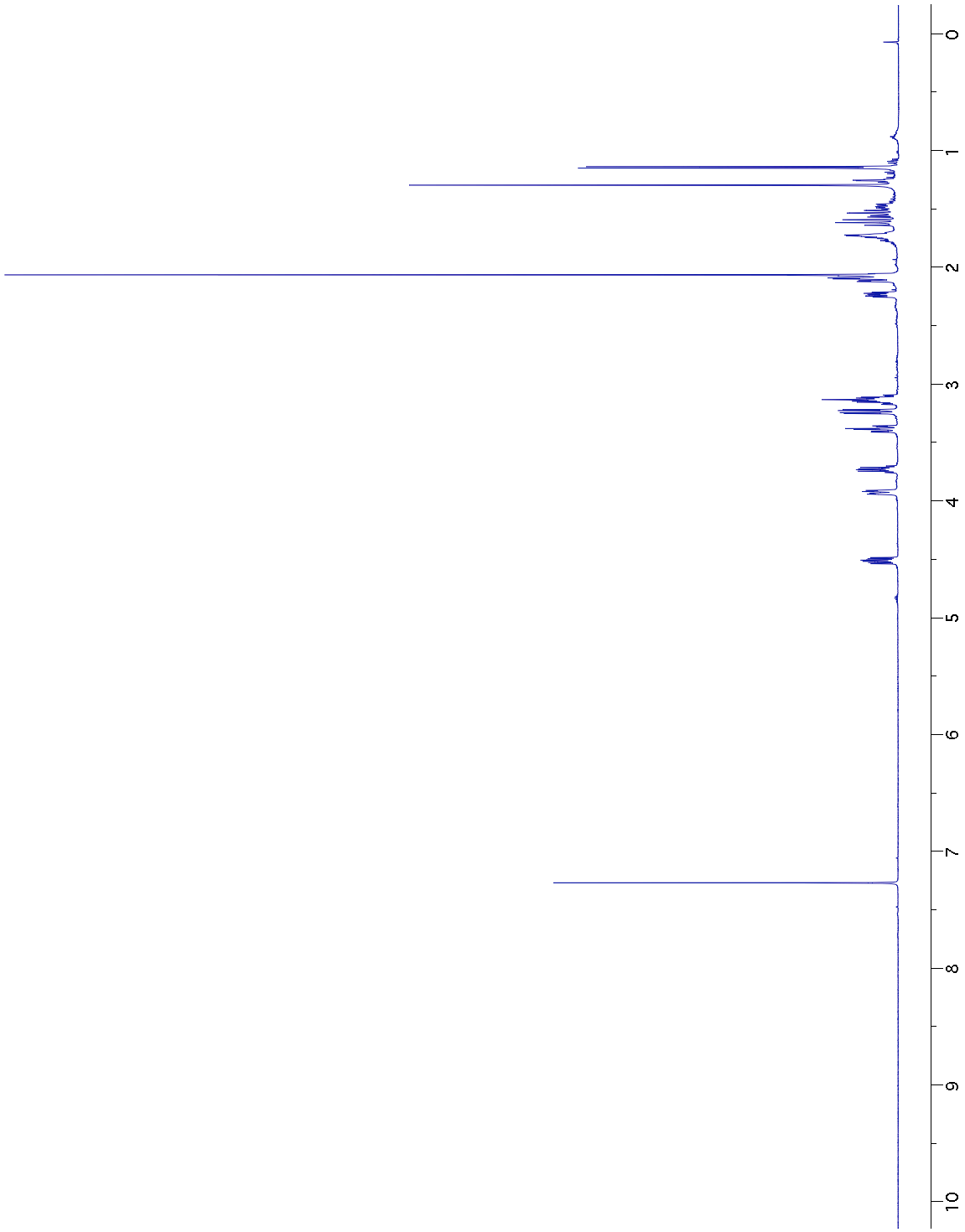

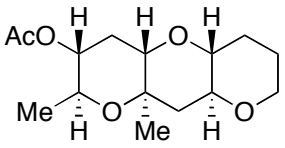
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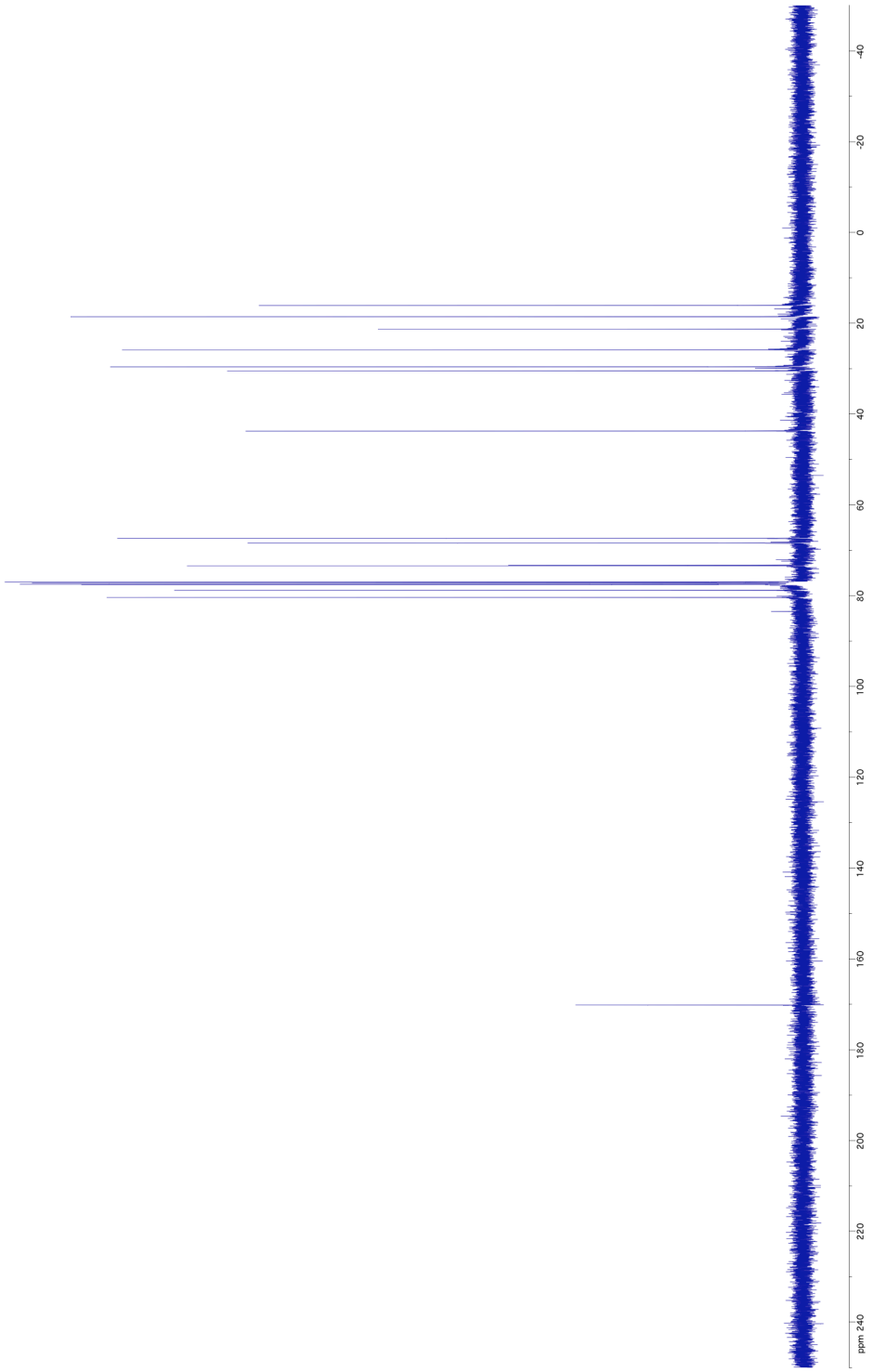
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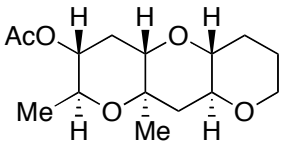
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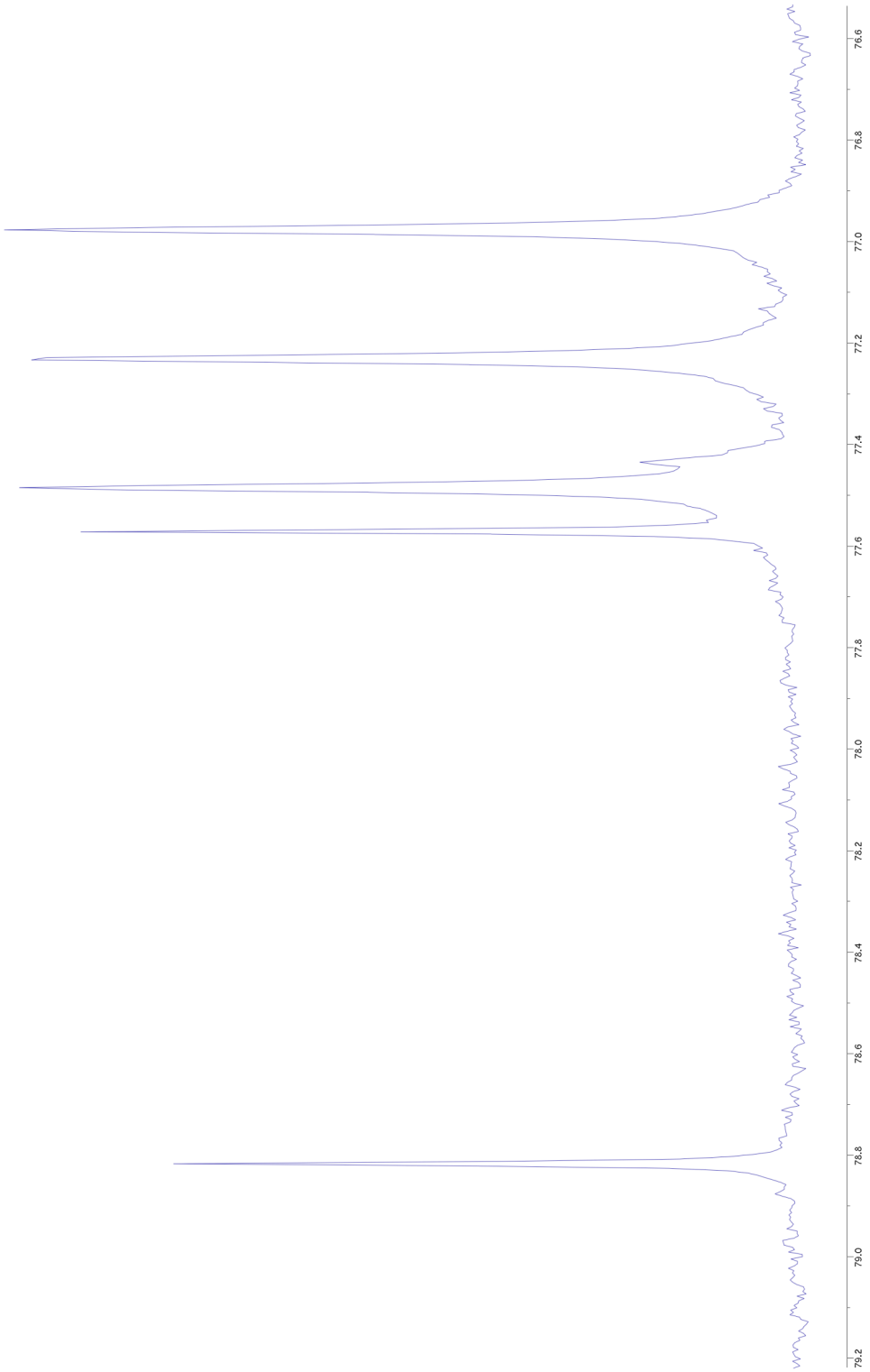
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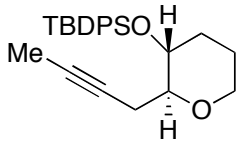

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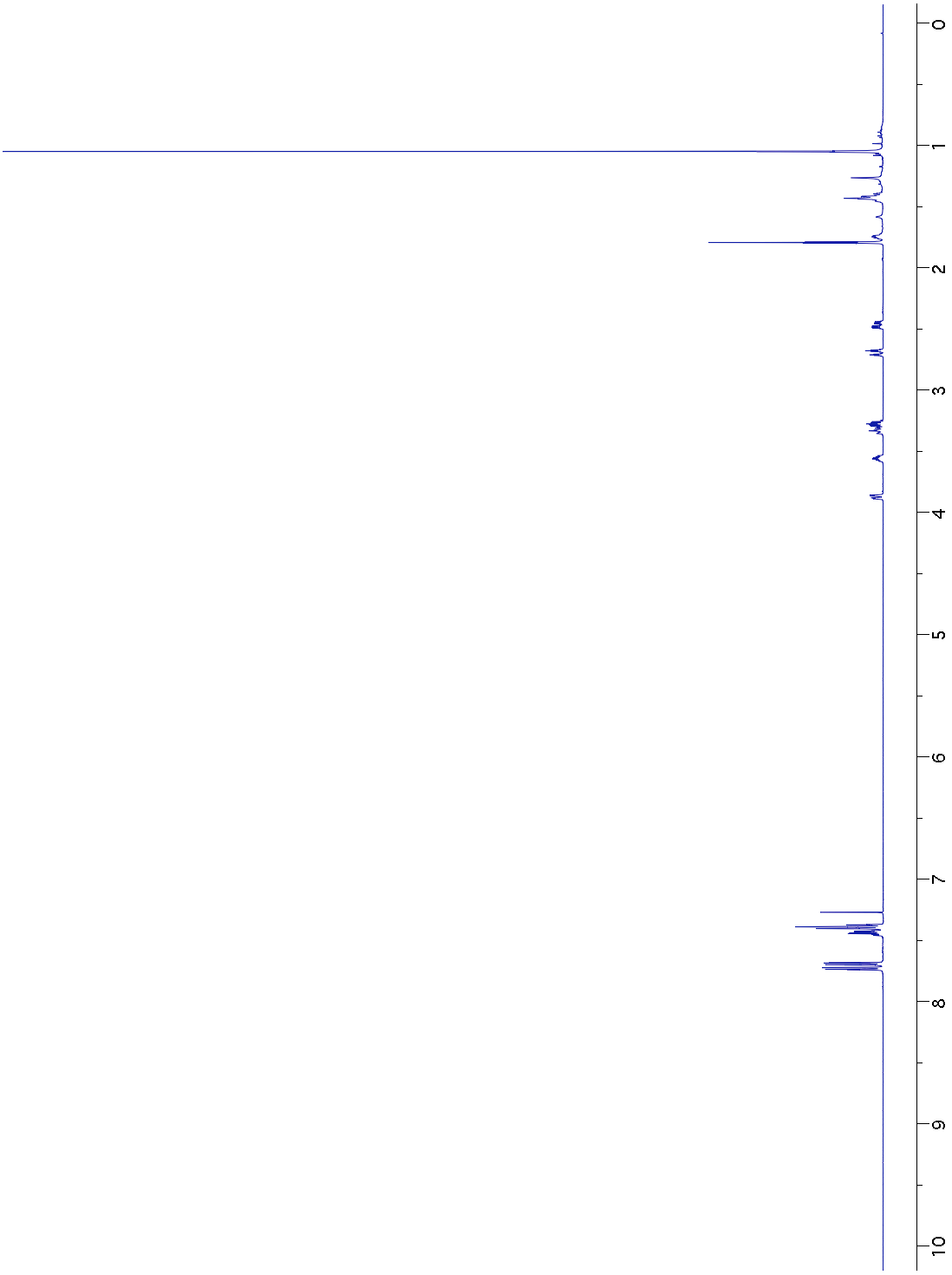

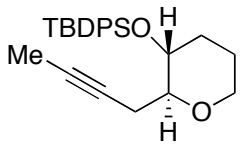

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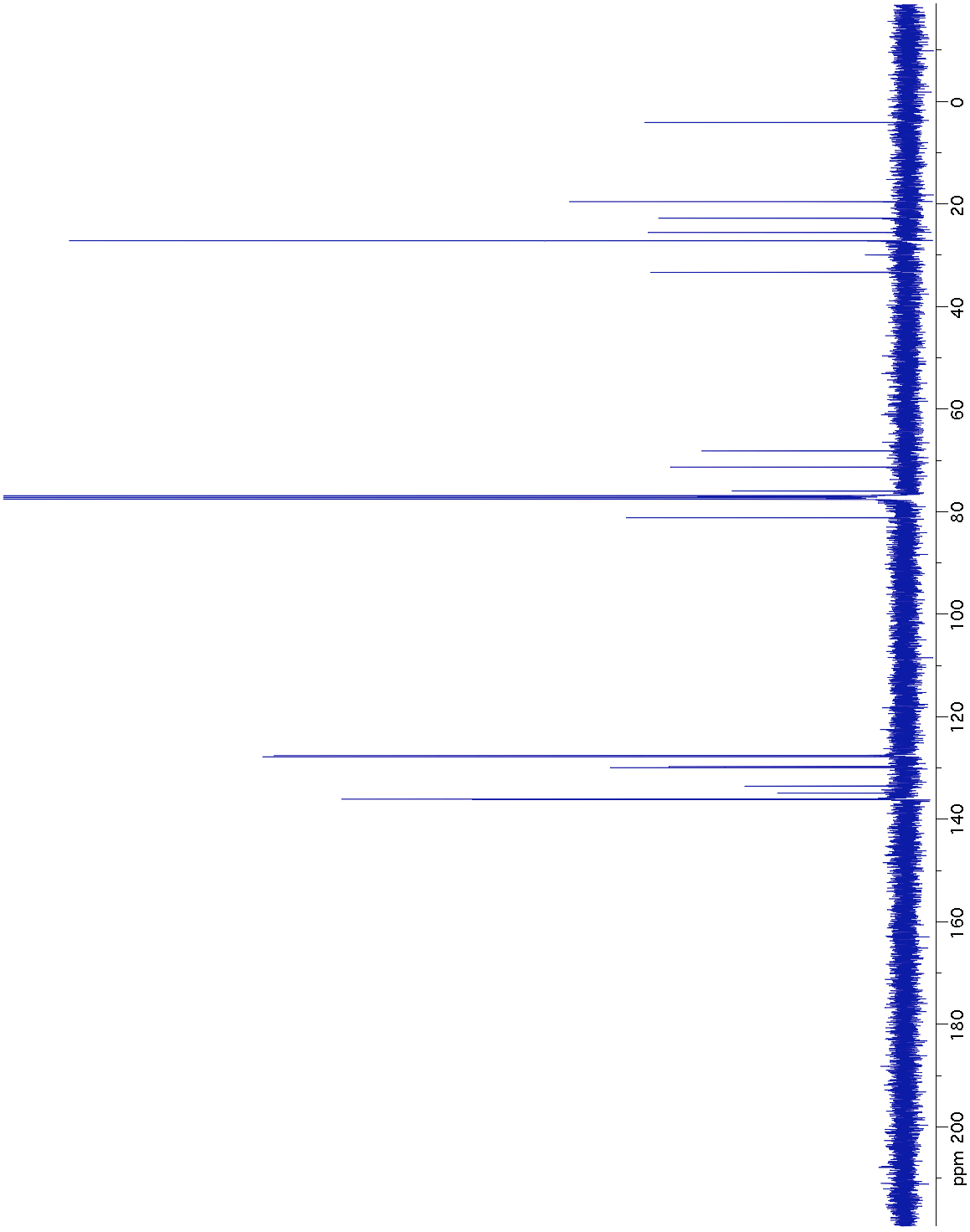

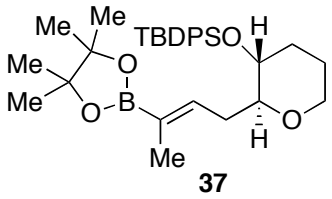

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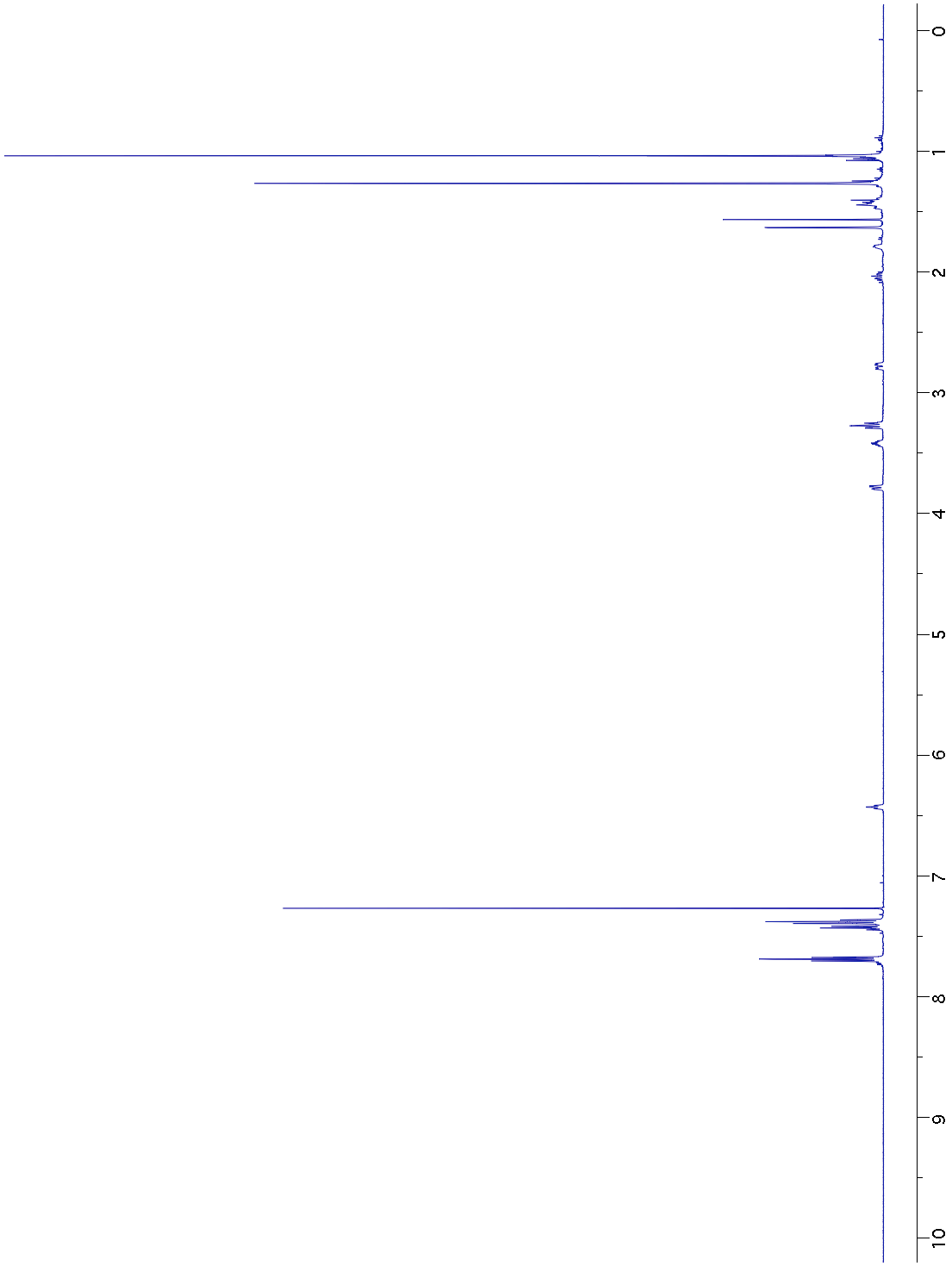

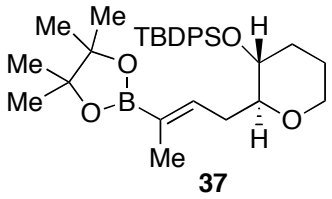
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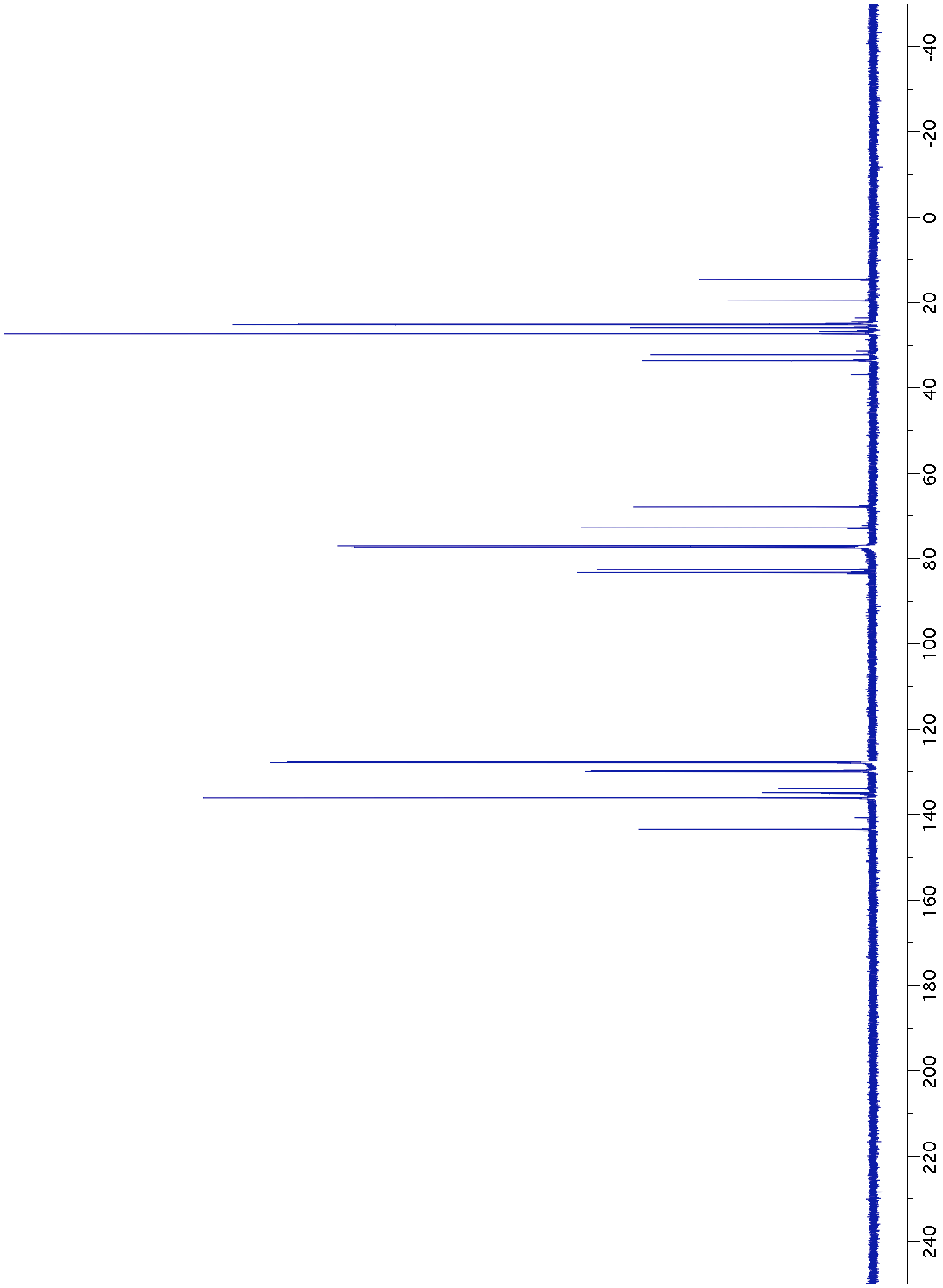
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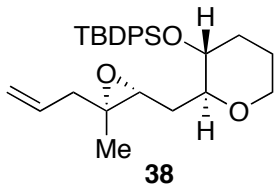

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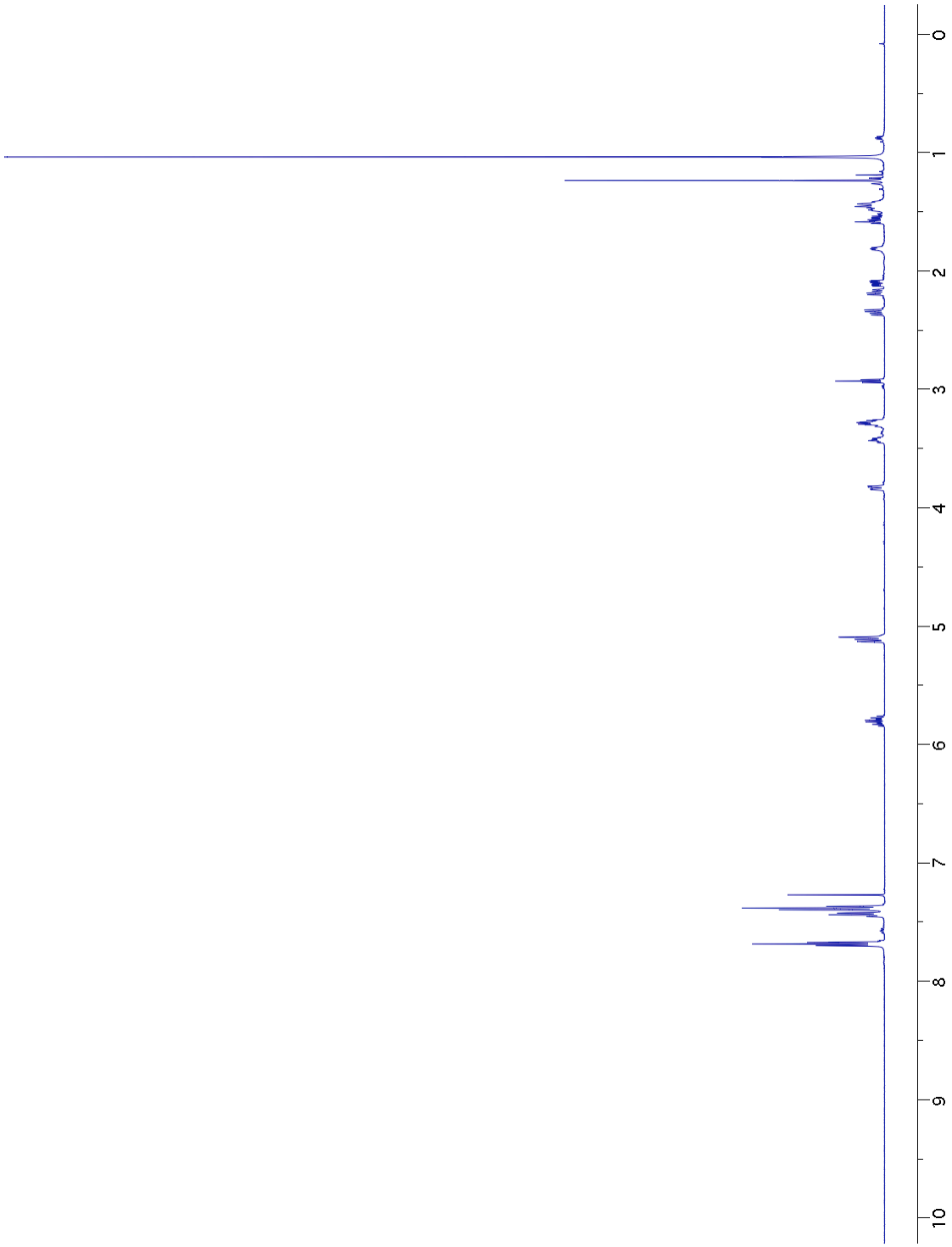

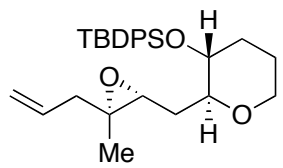

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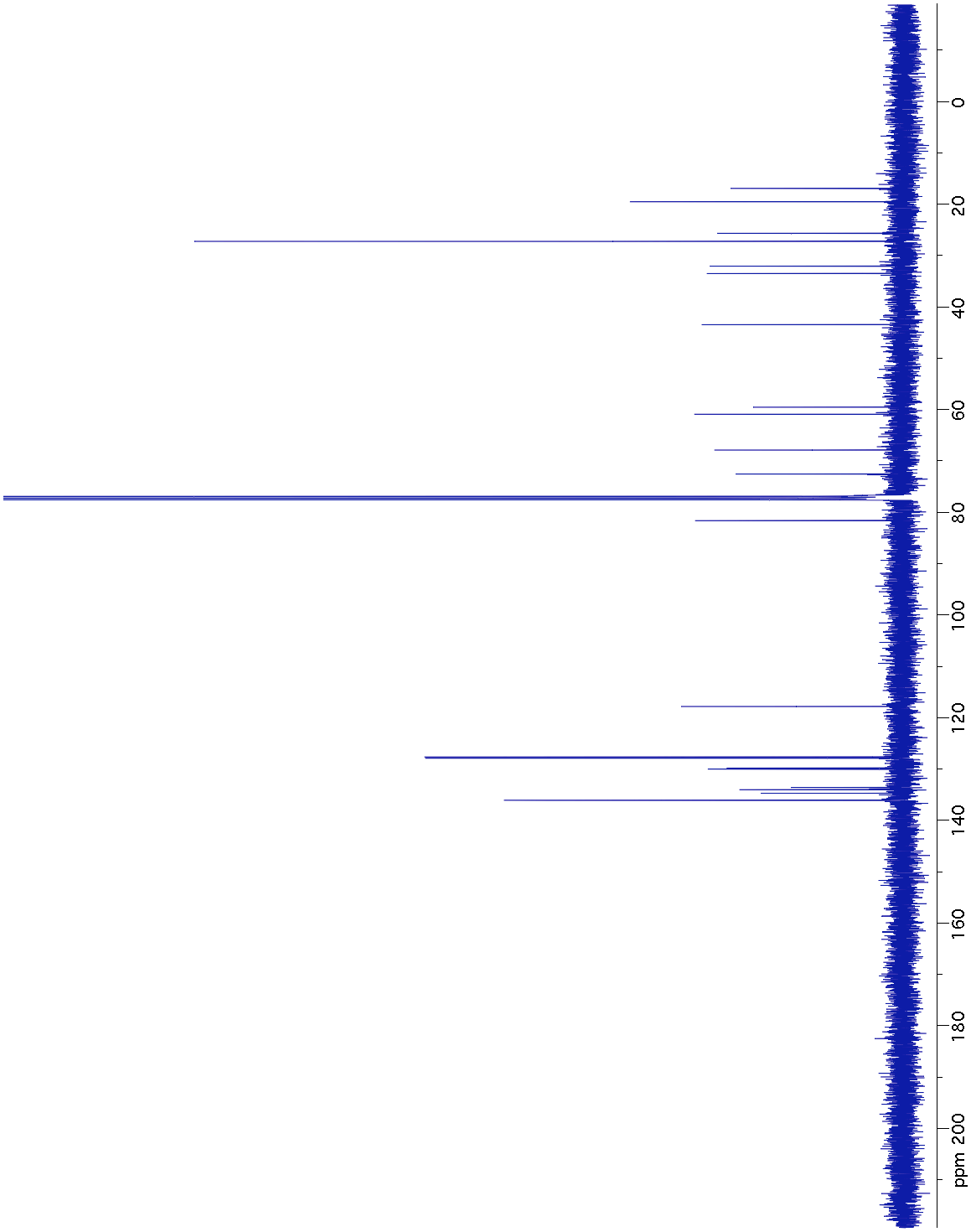

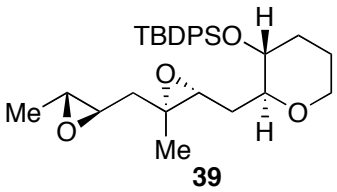

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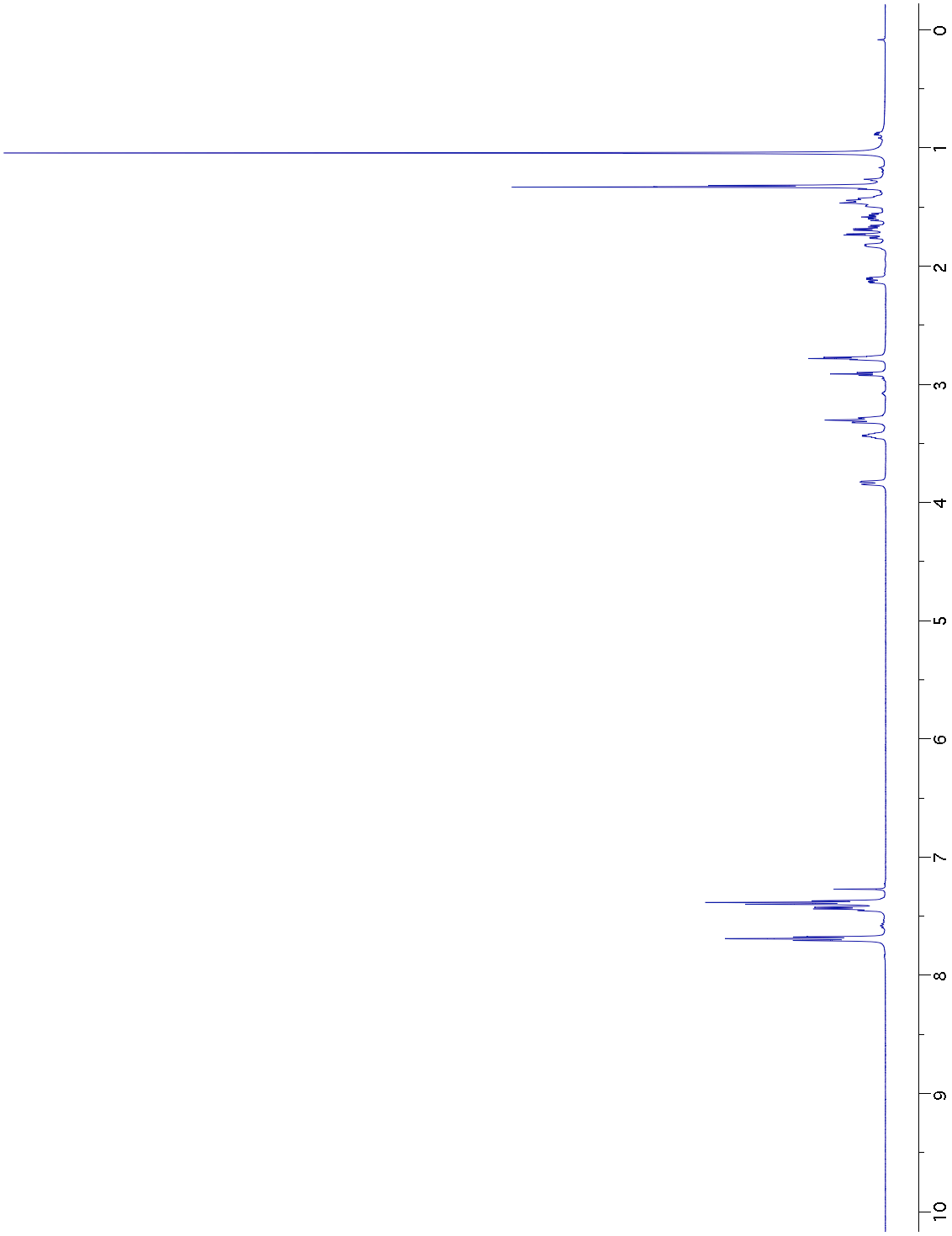

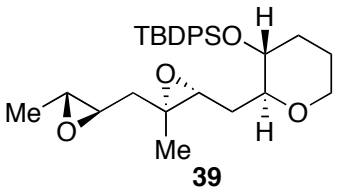

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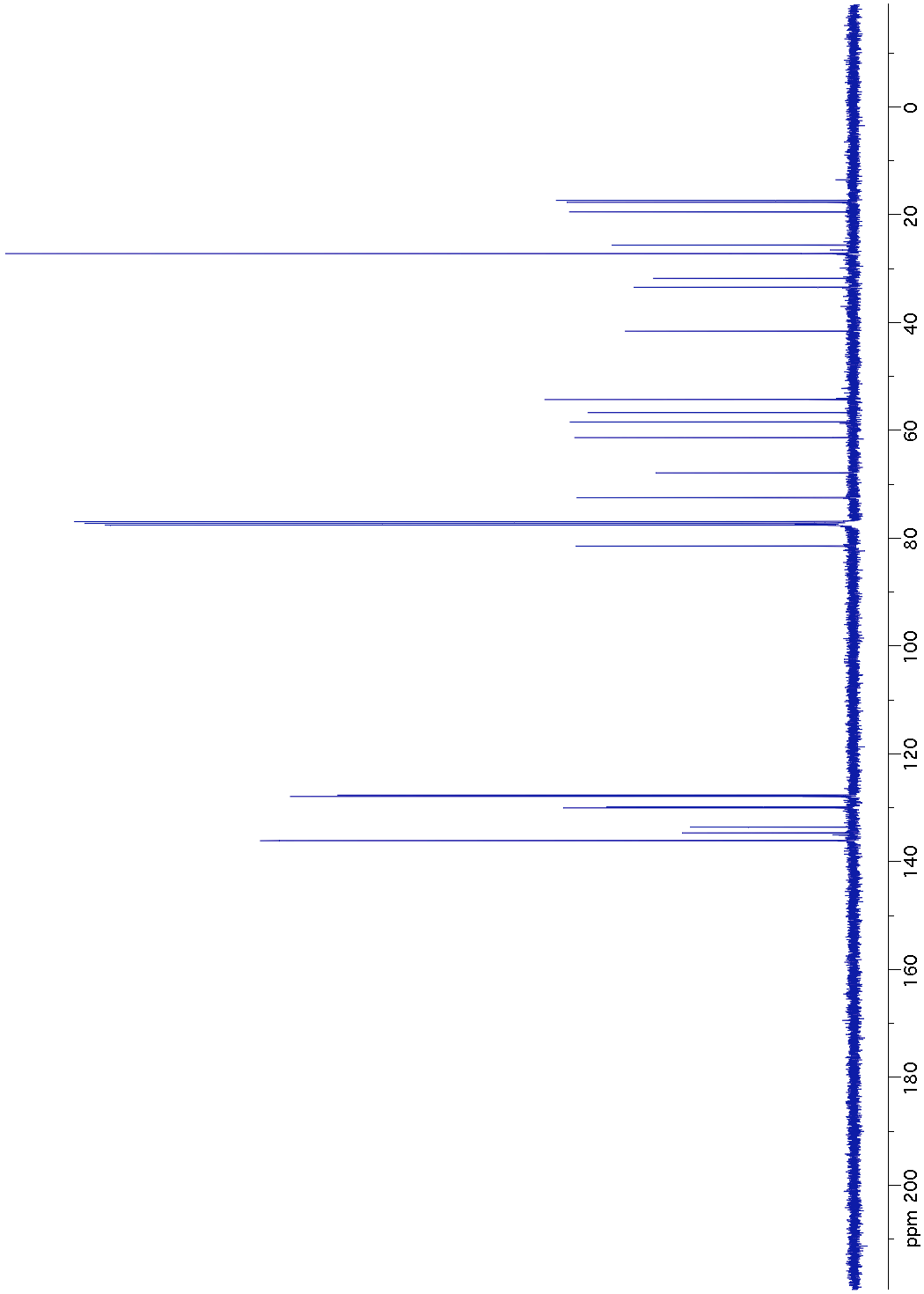

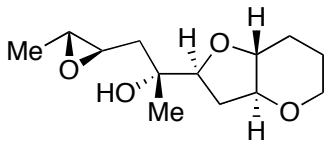

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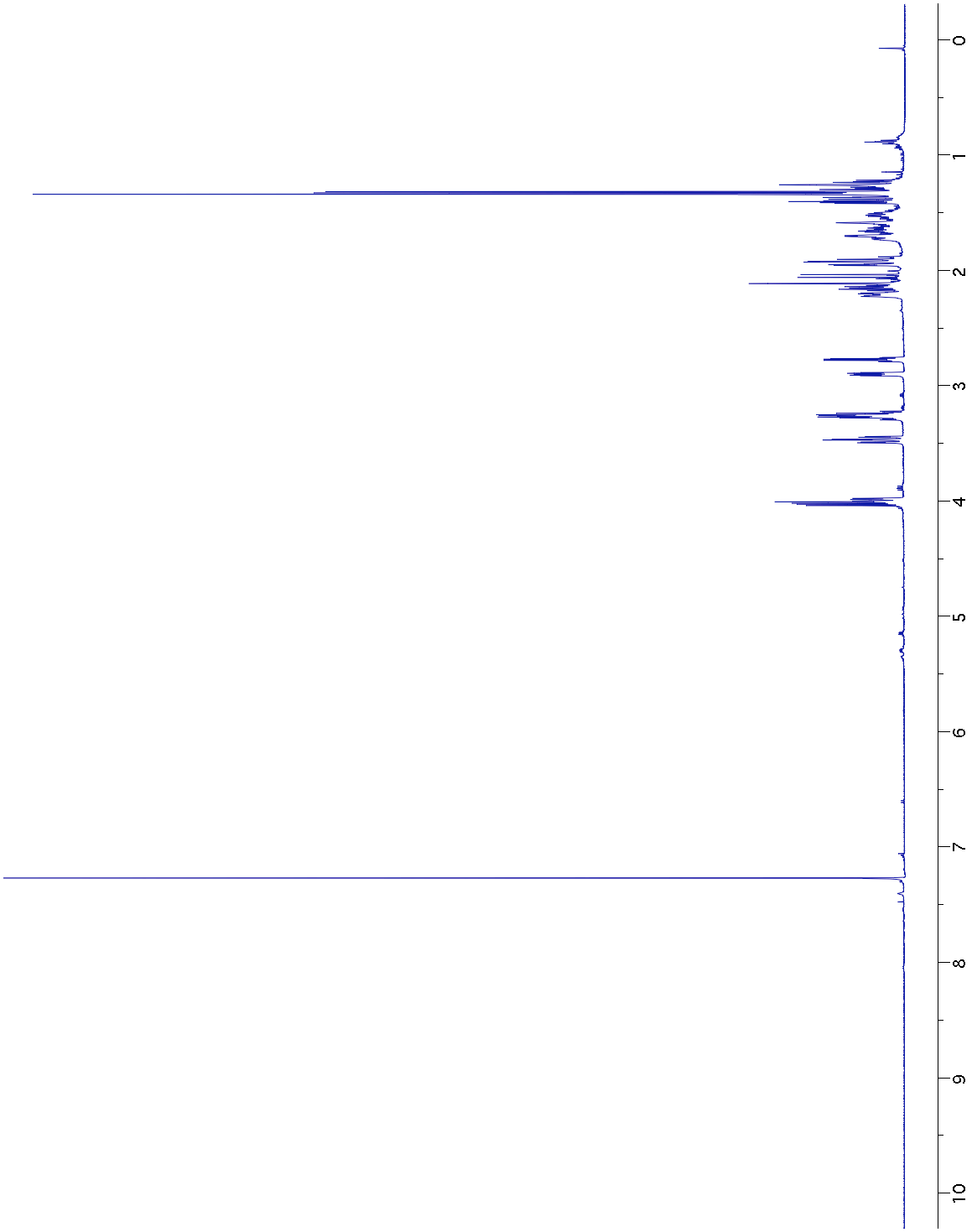

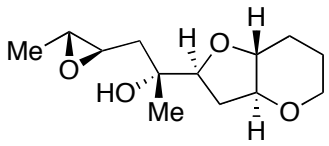

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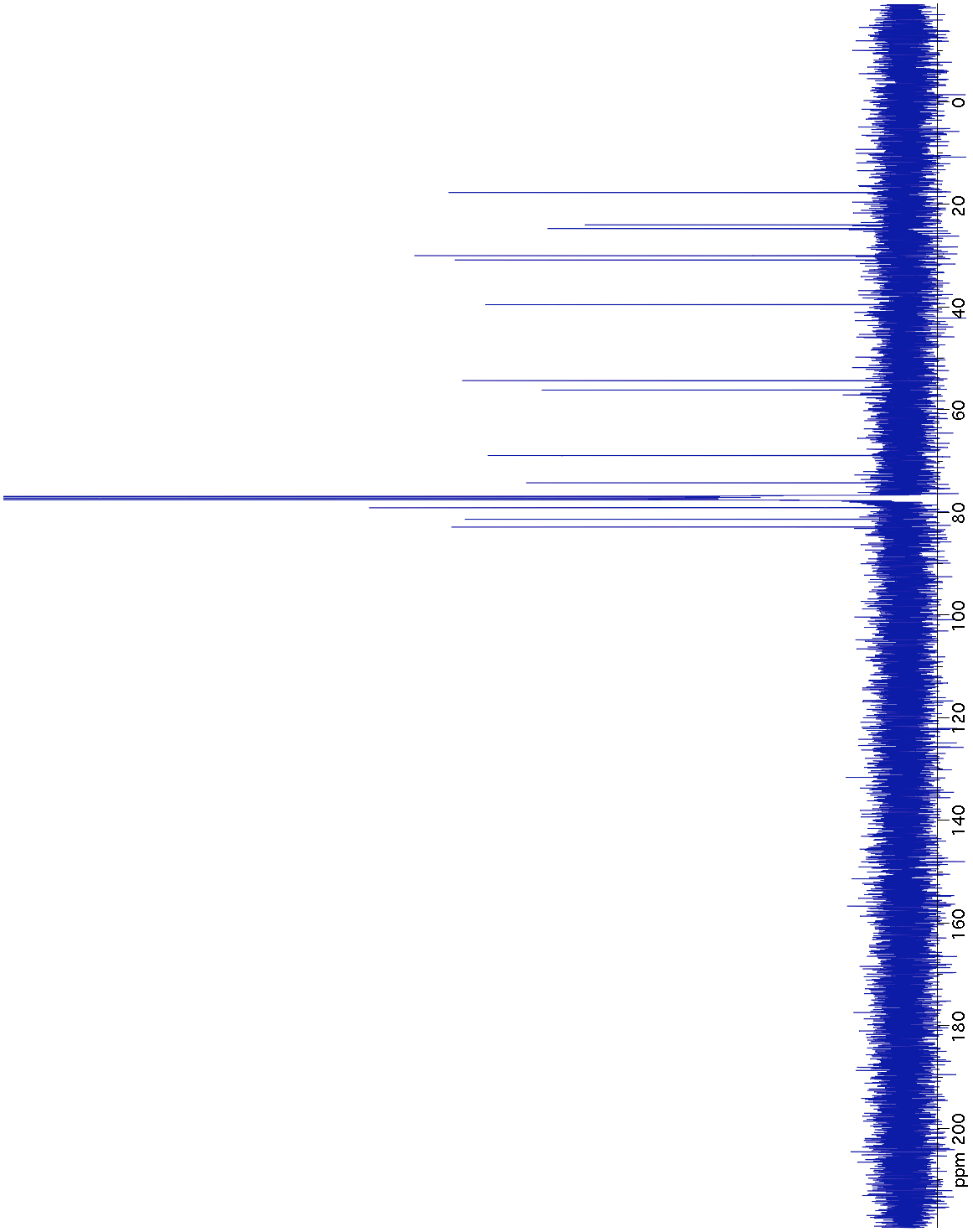

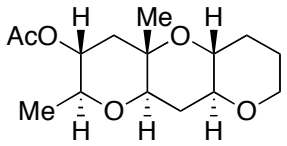

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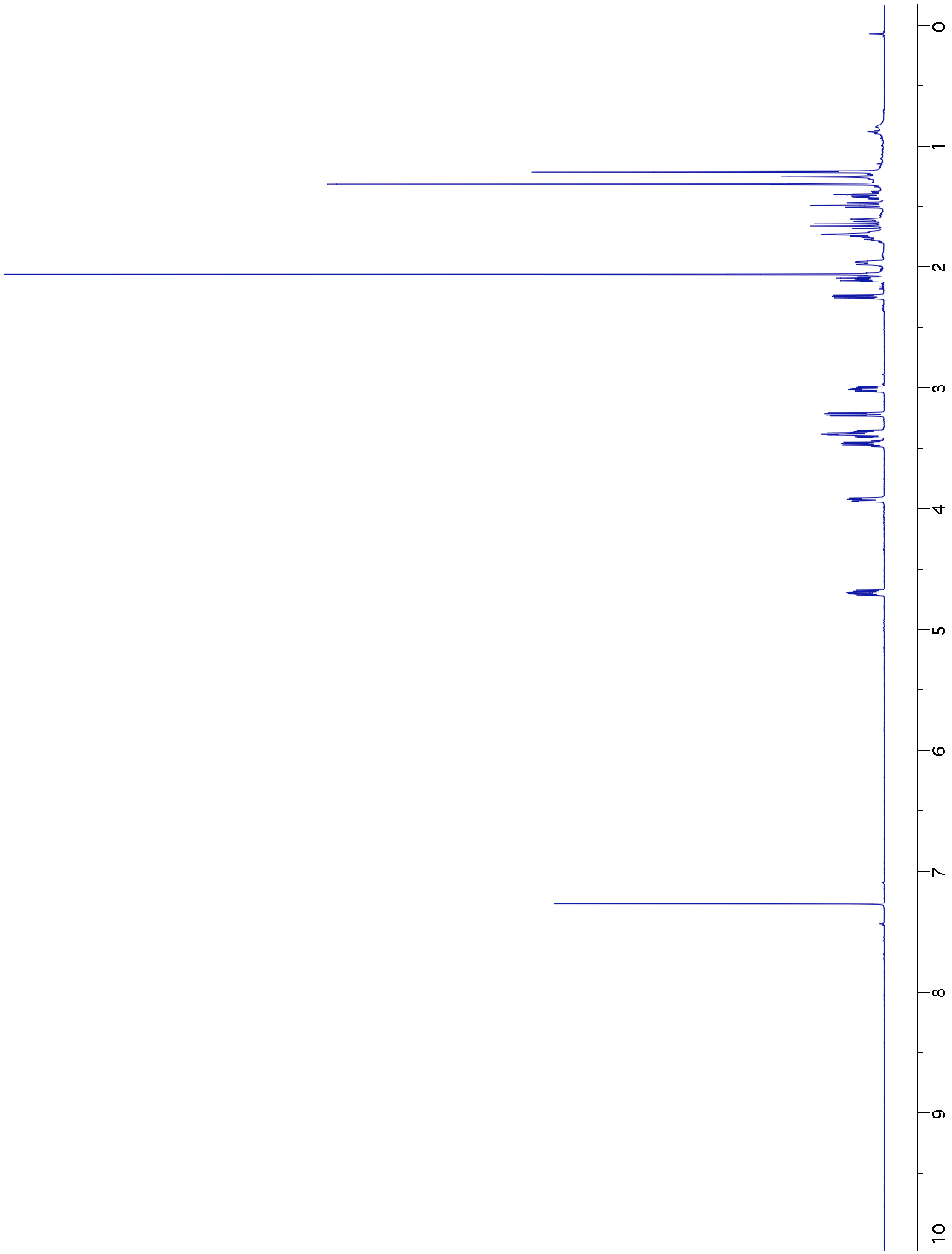

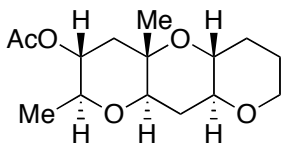
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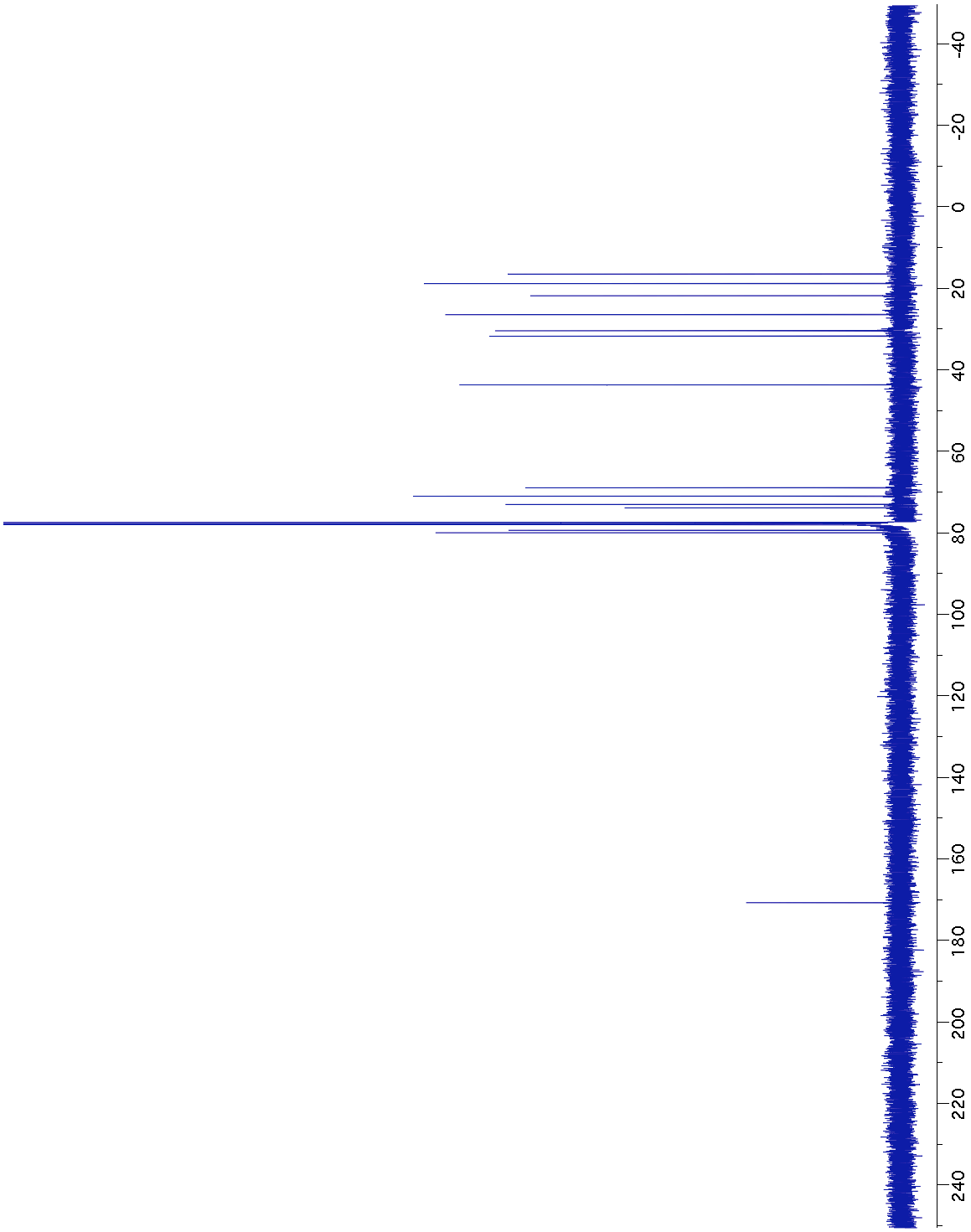
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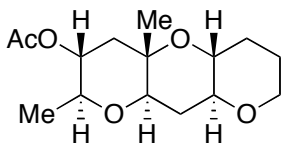
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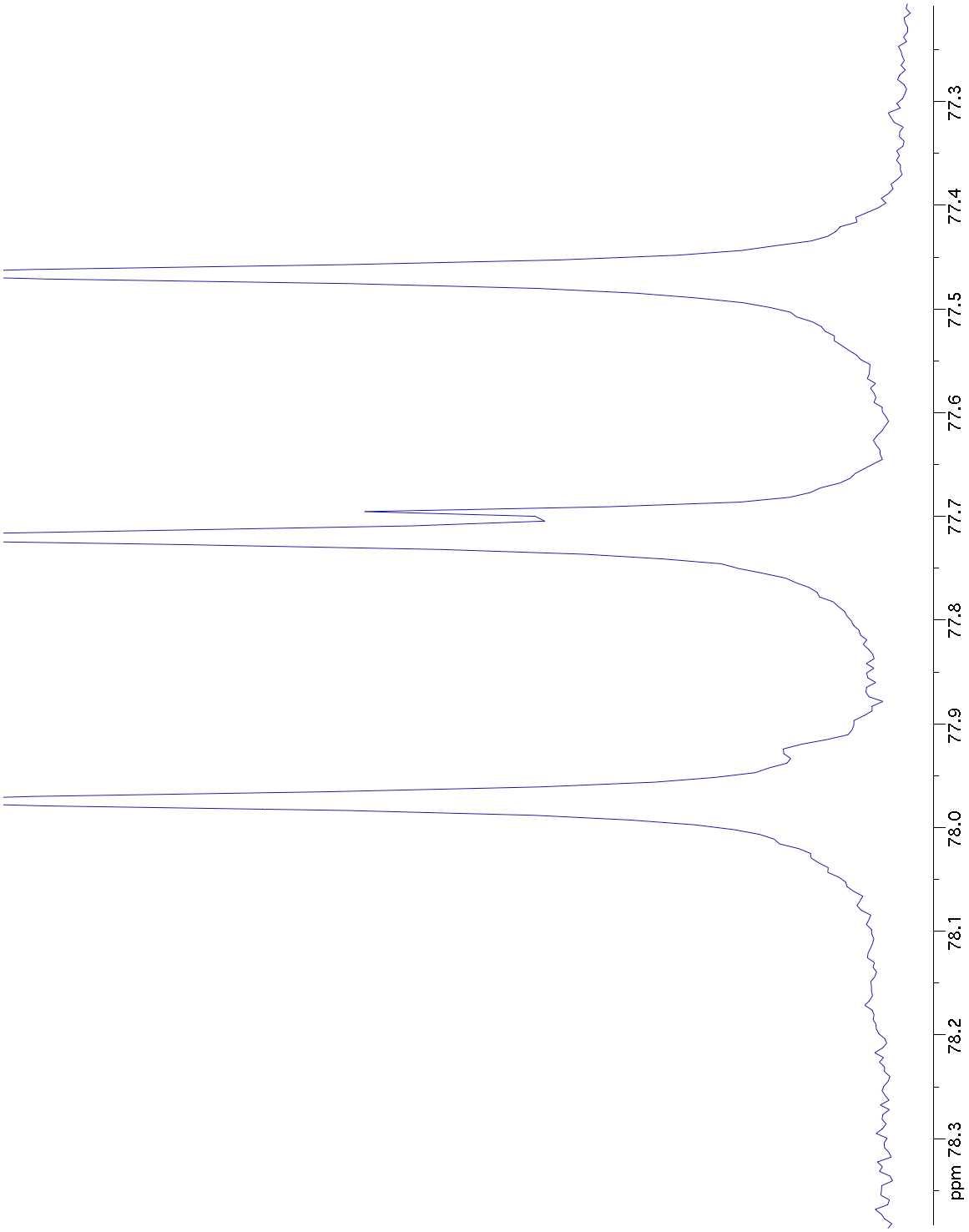
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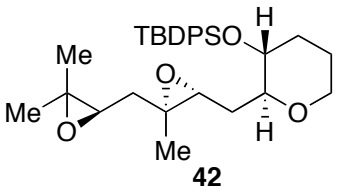

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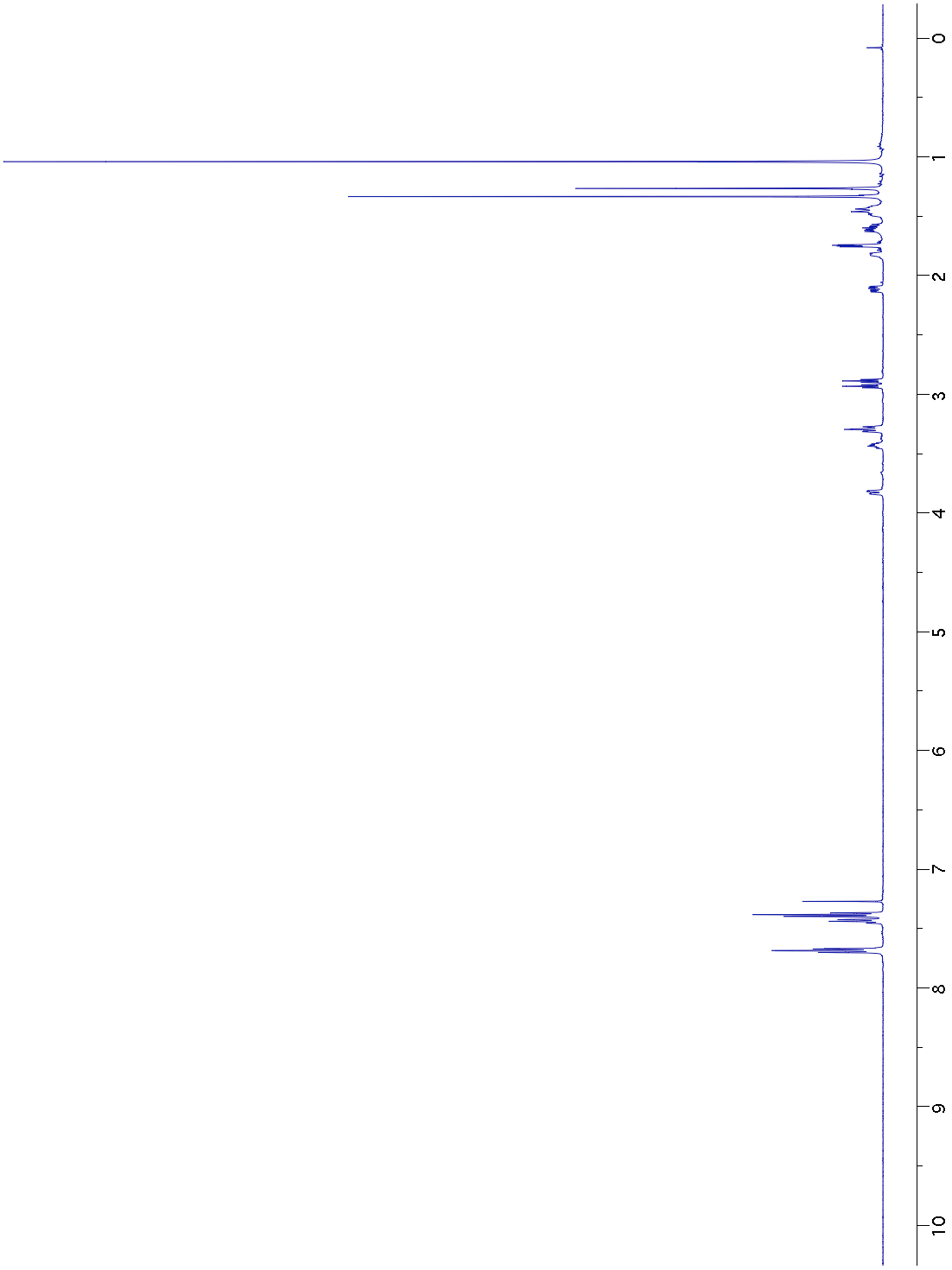

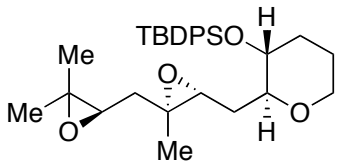

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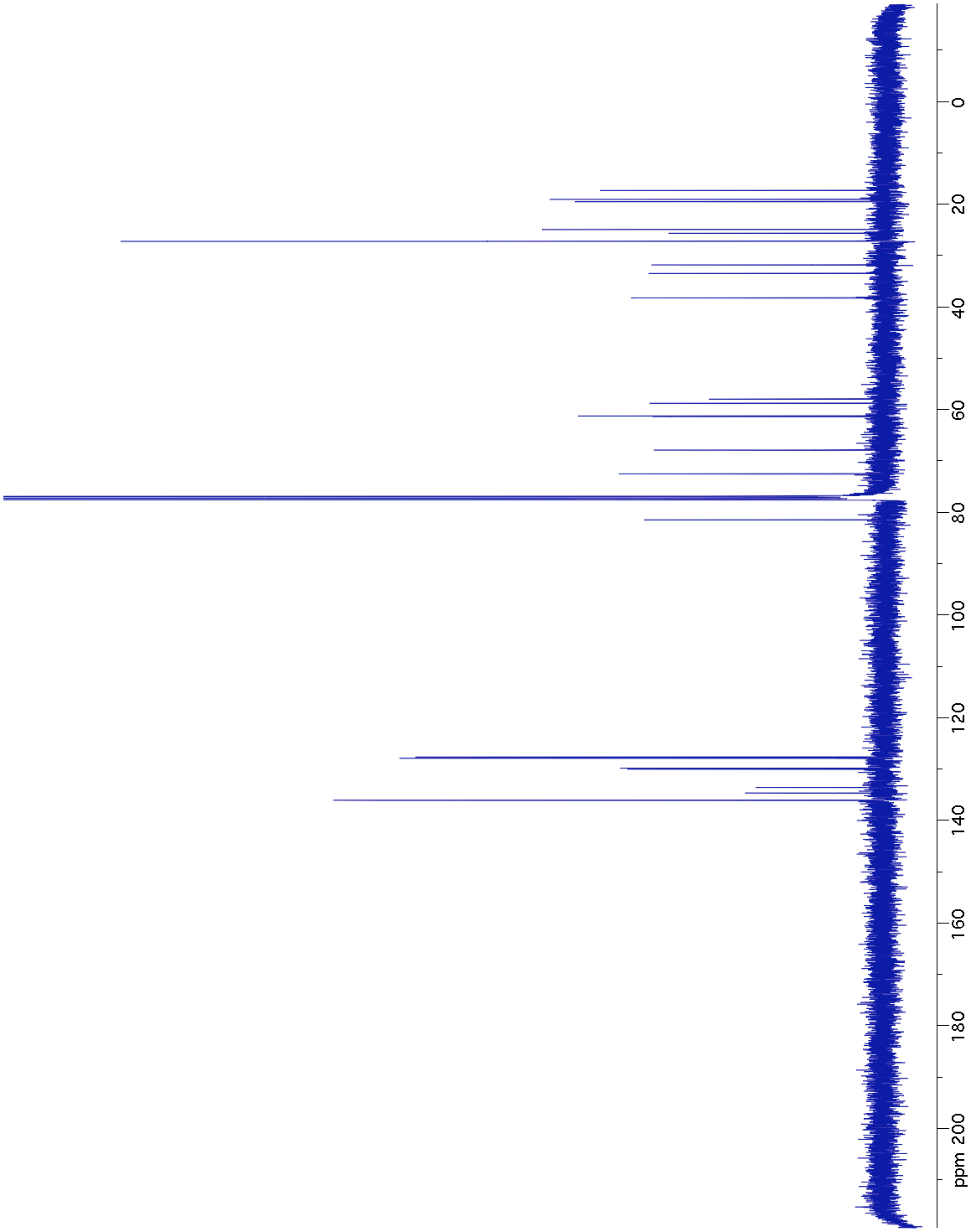

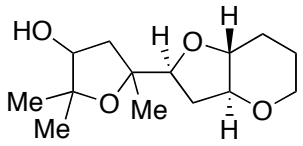

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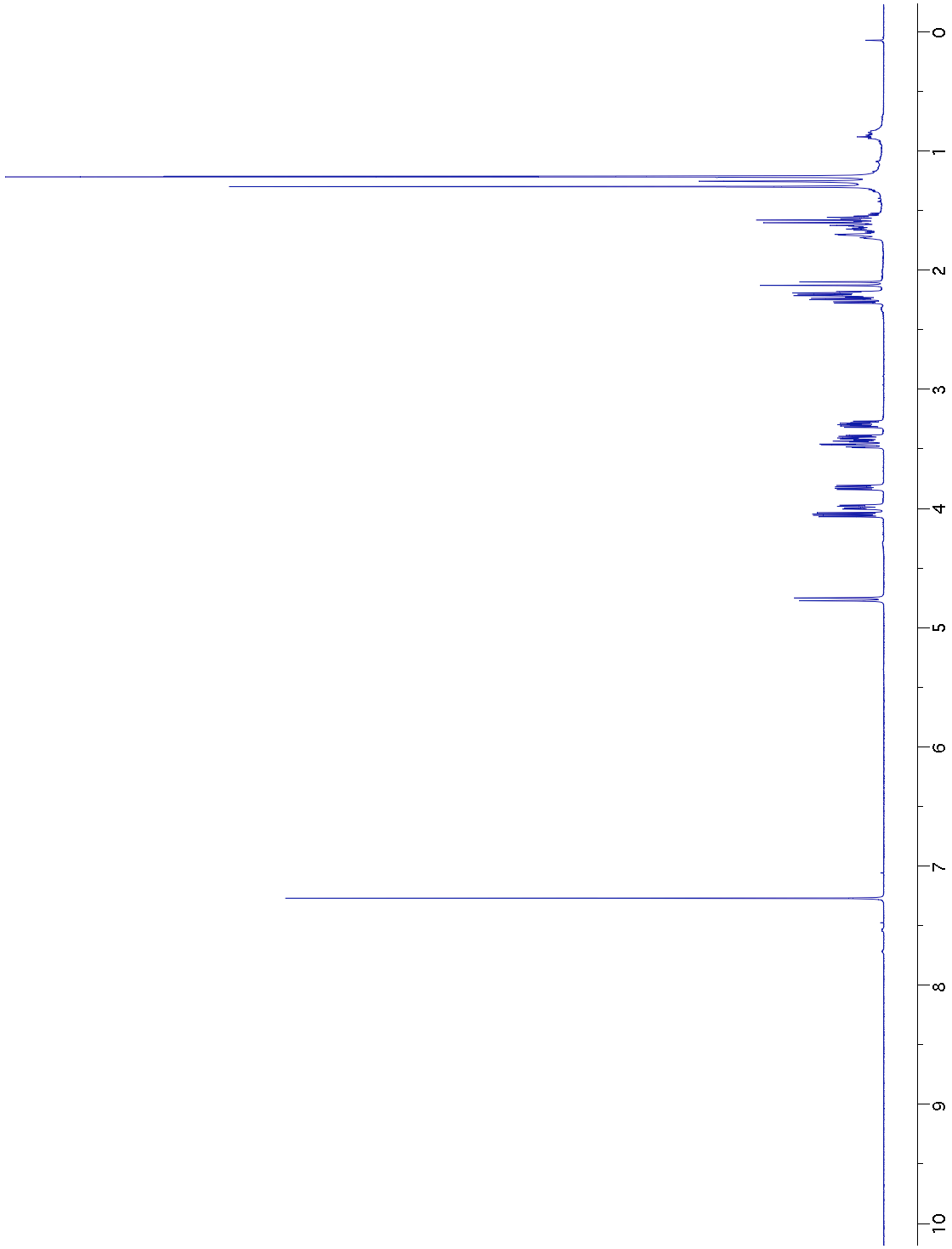

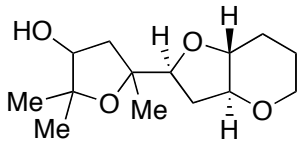
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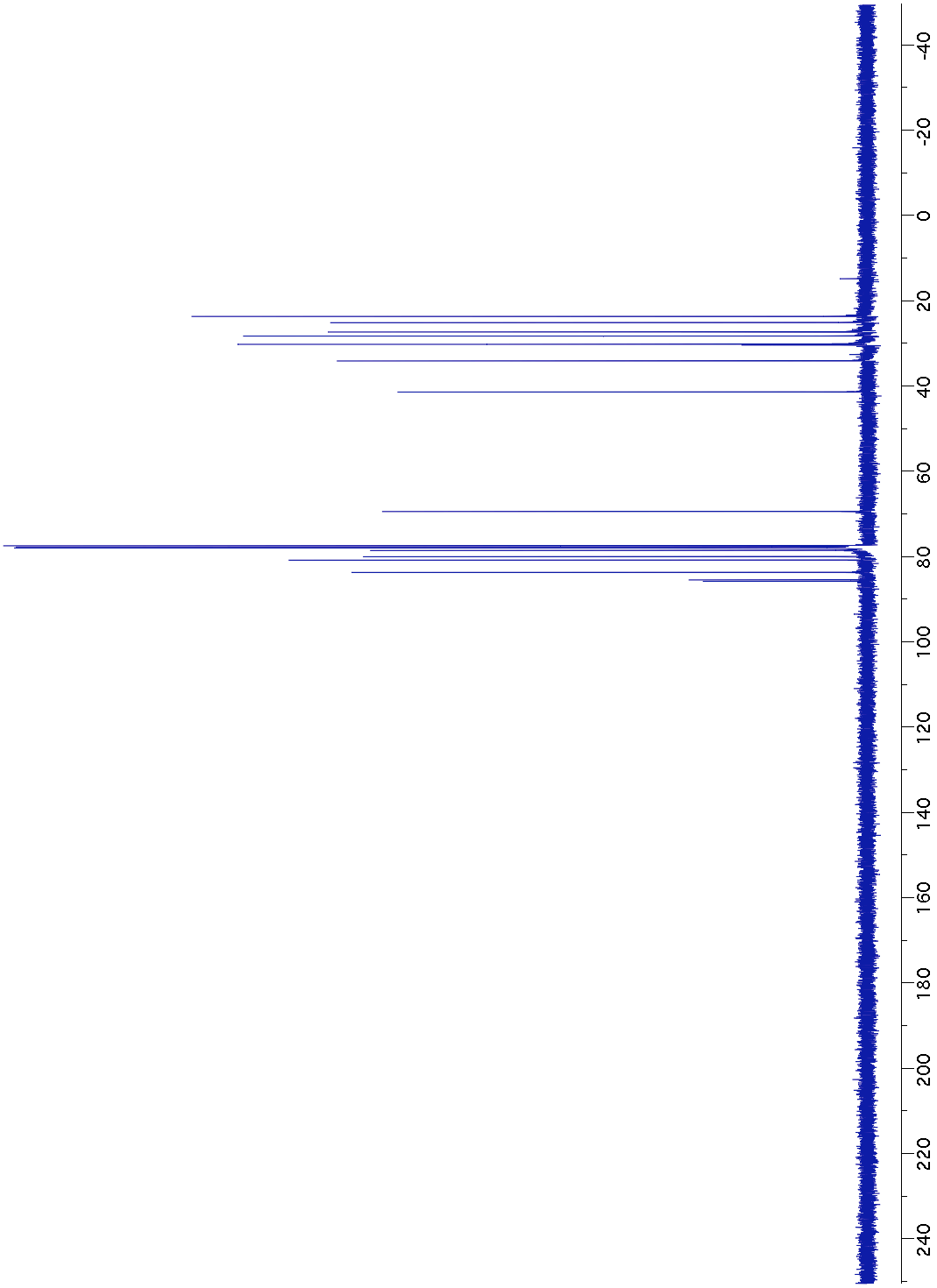
H
Me
O
Me
Me
O
H

43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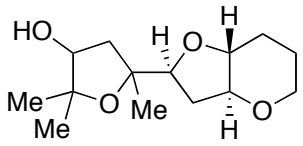
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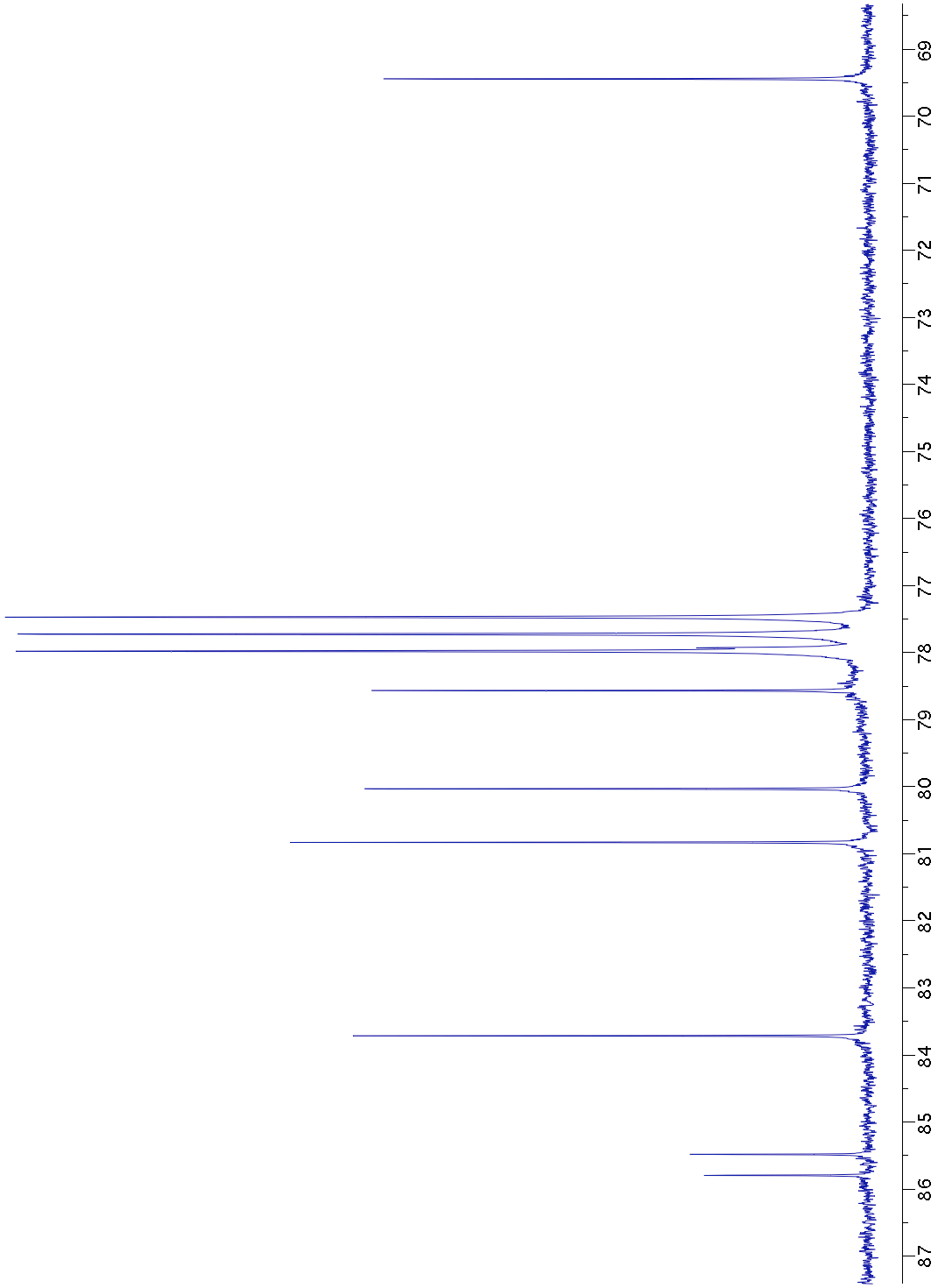
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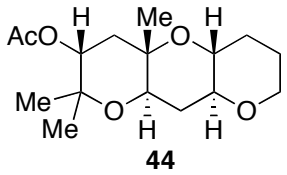

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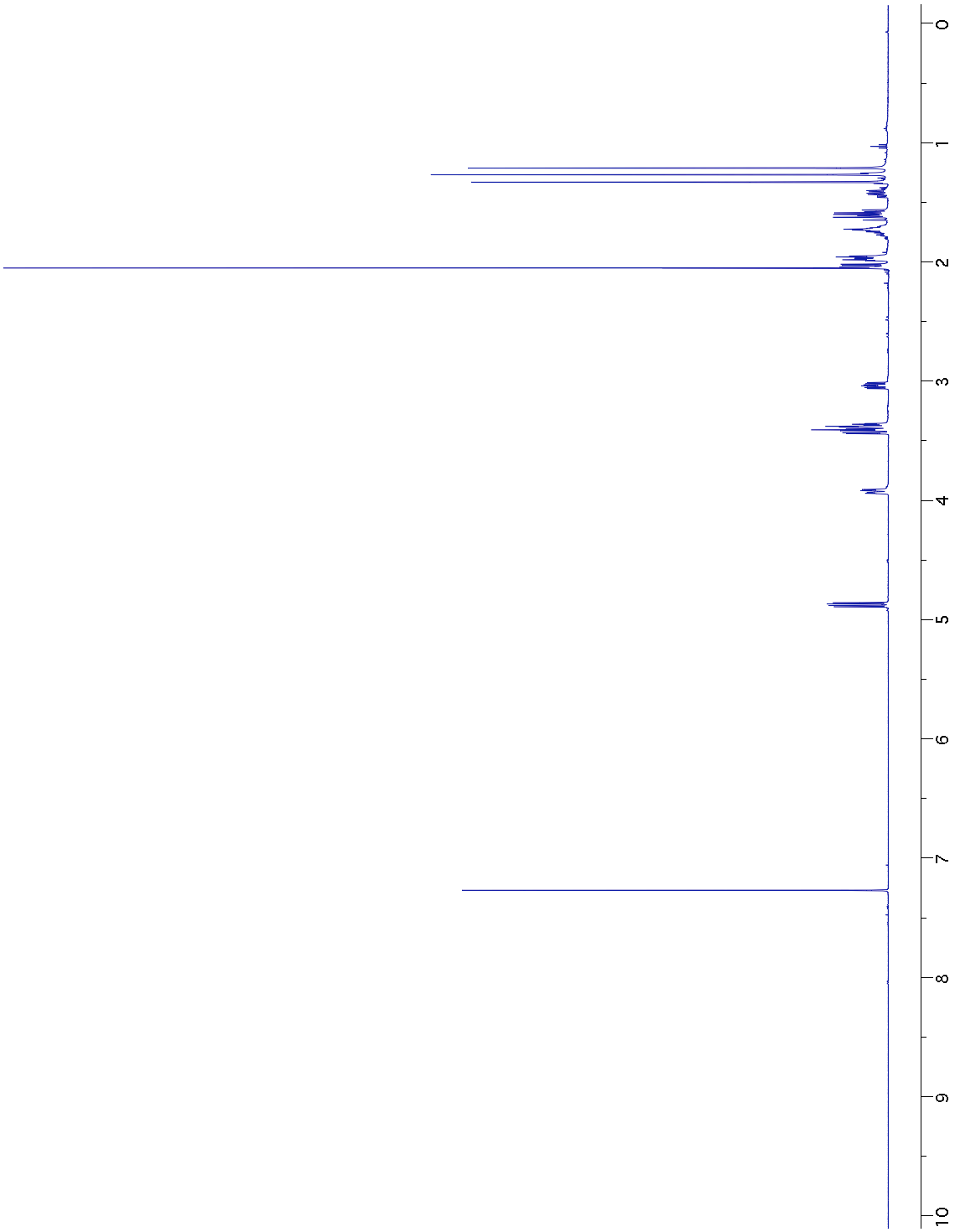

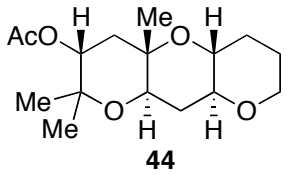
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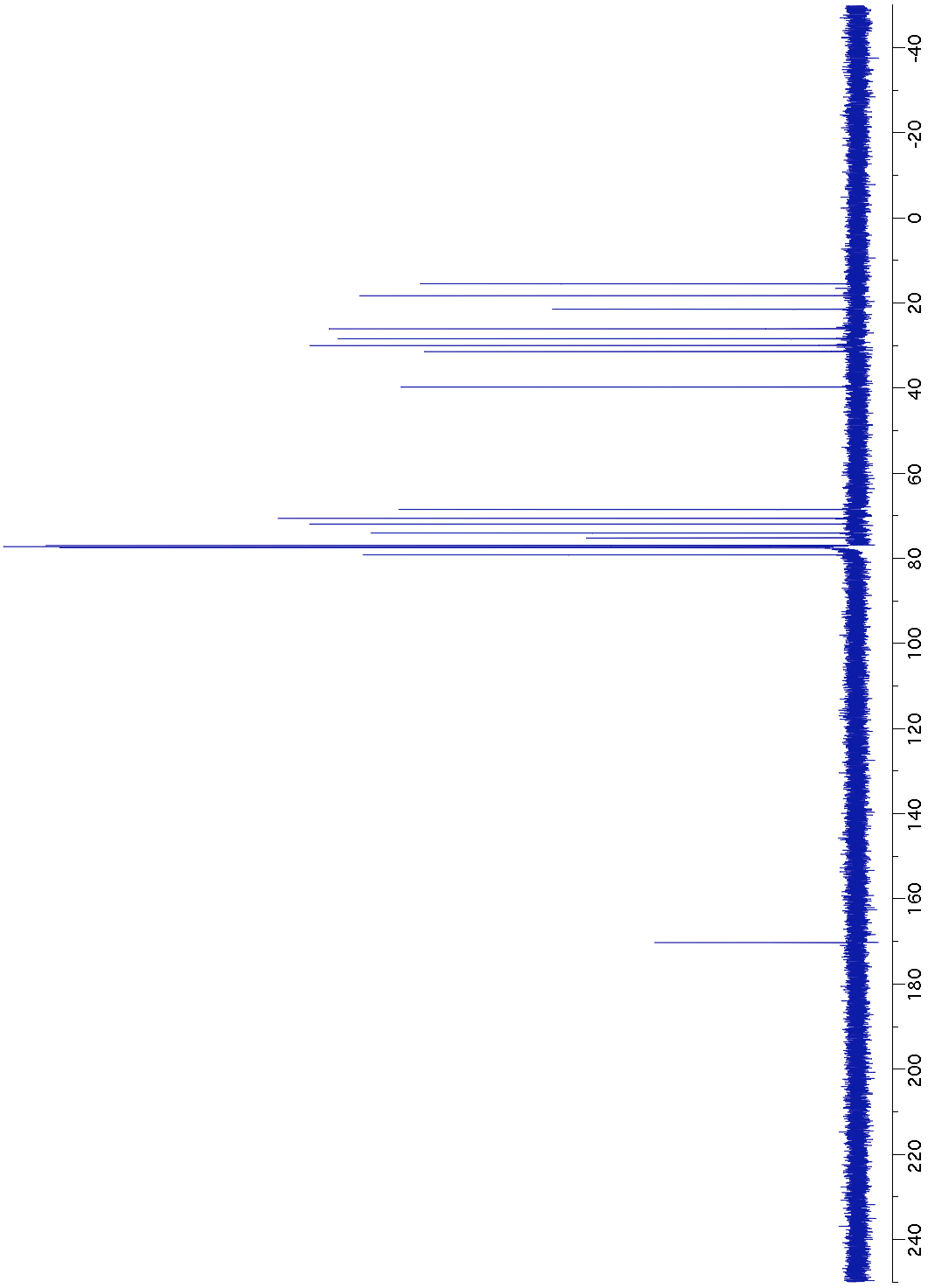
O

44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[S9] We have found that the yield of this reaction suffers when older lithium acetylide-ethylenediamine complex is used, even if it was stored in a glove box or in a dessicator under argon. Multiple samples of lithium acetylide-ethylenediamine complex sourced from both Alfa Aesar and Sigma-Aldrich have proved adequate, so long as they are used immediately after opening.

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[S12] This specific rotation ($[\alpha]^{22}_{D}$ = +39.4 (*c* = 1.6, $CDCl_3$)), measured on a sample of material in 20:1 diastereopurity, differs from the value reported earlier by our group, which was measured on a sample in 4:1 dr ($[\alpha]^{25}_{D}$ = +2.3 (c = 0.7, $CDCl_3$)).[S11]

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