Supporting Information for

Evidence That Epoxide-Opening Cascades Promoted by Water Are Stepwise and Become Faster and More Selective After the First Cyclization

Christopher J. Morten, Jeffery A. Byers, and Timothy F. Jamison*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Table of Contents

I. Schematic Summary of Synthetic Operations. S2-S3

II. Experimental Procedures and Data for Compounds **7-24**. S4-S23

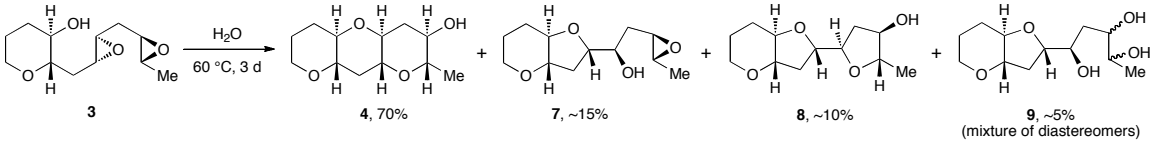
III. Kinetics Procedures, Data, and Analysis S24-S30

IV. ^{1}H and ^{13}C Spectra for Compounds **7-24**. S31-S63
(including ^{1}H spectra of **3**, **4**, **7**, **8**, **9a**, **9b**, **10**, and **11** in D_2O at 70°)

V. Supporting Information References. S64

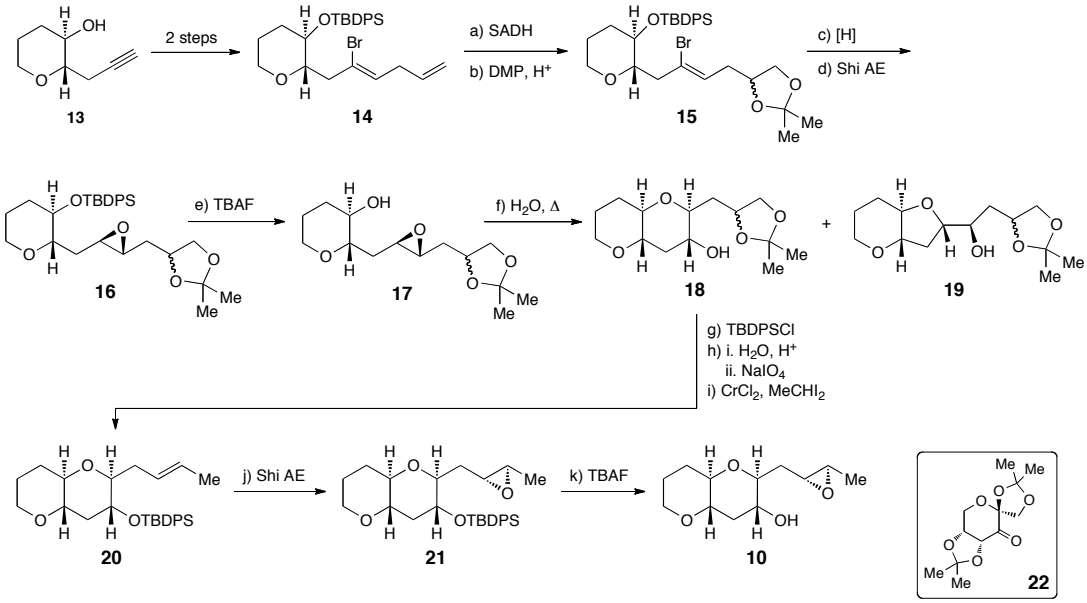
I. Schematic Summary of Synthetic Operations

Water-promoted cascade reaction of diepoxy alcohol **3**:



The preparation of diepoxy alcohol **3** from 2,3-dihydropyran followed a ten-step route previously published.[S1]

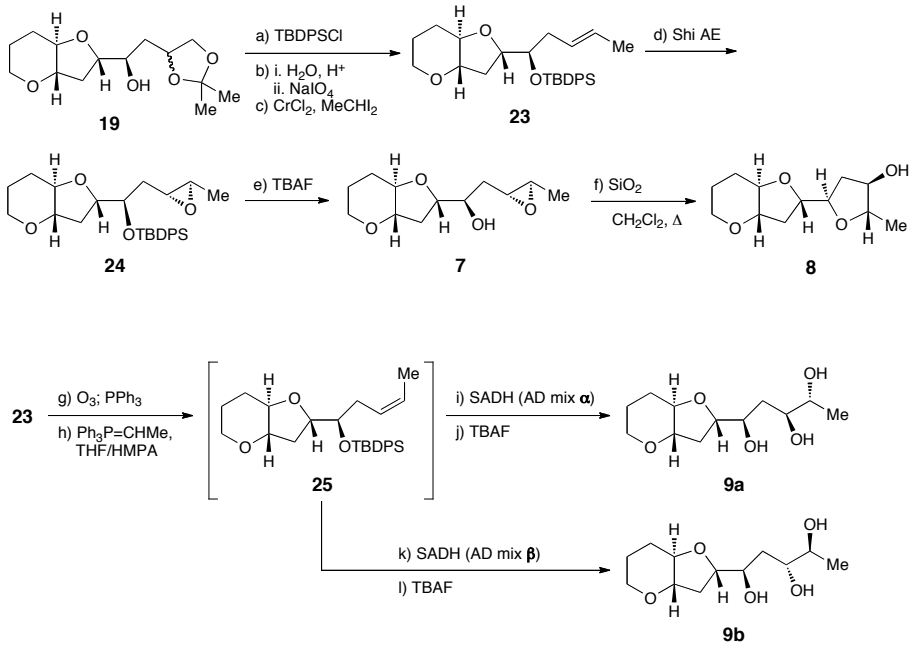
Independent preparation of THP diad-templated epoxy alcohol intermediate **10**:



The preparation of alkenyl bromide **14** from alkyne **13** followed a 2-step protocol previously published.[S1]

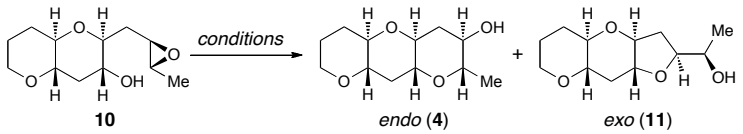
Reagents and conditions: a) *Sharpless asymmetric dihydroxylation*[S2]: AD mix β (1.4 g per mmol **14**), *t*BuOH/H_2O, 4 °C, 27 h., 2.8:1 dr; b) 2,2-dimethoxypropane (1200%), PPTS (10%), CH_2Cl_2, rt, 23 h.; c) *Pd-cat. vinyl bromide reduction*[S3]: HCO_2H (200%), Bu_3N (300%), $Cl_2Pd(PPh_3)_2$ (5%), DMF, 40 °C, 41 h.; d) *Shi asymmetric epoxidation*[S4]: **22** (200%), Oxone (1000%), nBu_4HSO_4, K_2CO_3, $Na_2B_4O_7$ buffer, DMM/MeCN, 0 °C, 70 min., 2 subjections, **40%** over 4 steps, 6:1 dr at the epoxide, 2:1 overall dr; e) TBAF (200%), THF, 40 °C, 2 h., **89%**; f) pH 7 buffer (0.1 M KP_i), 70 °C, 23 h., **38% 18** + **25% 19**; g) TBDPSCl (200%), imid. (400%), DMF, 50 °C, 17 h.; h) i. TFA (600%), THF/H_2O, 35 °C, 24 h.; ii. $NaIO_4$ (300%), THF/H_2O, 0 °C, 2 h.; i) *Takai olefination*[S5]: $CrCl_2$ (1200%), $MeCHI_2$ (300%), THF, rt, 20 h., **86%** over 3 steps; j) *Shi asymmetric epoxidation*[S4]: **22** (100%), Oxone (500%), nBu_4HSO_4, K_2CO_3, $Na_2B_4O_7$ buffer, DMM/MeCN, 0 °C, 55 min., **95%**, 5:1 dr; k) TBAF (250%), THF, 35°, 1.25 h., **97%**.

Independent preparation of *exo* side products **7**, **8**, and **9**:



Reagents and conditions: a) TBDPSCl (260%), imid. (500%), DMF, 50 °C, 36 h., **61%**; b) i. TFA (500%), THF/H_2O, 35 °C, 19 h.; ii. $NaIO_4$ (300%), THF/H_2O, 0 °C to rt, 3 h.; c) *Takai olefination*[S5]: $CrCl_2$ (1200%), $MeCHI_2$ (300%), THF, rt, 20 h., **91%** over 2 steps; d) *Shi asymmetric epoxidation*[S4]: **22** (100%), Oxone (500%), nBu_4HSO_4, K_2CO_3, $Na_2B_4O_7$ buffer, DMM/MeCN, 0 °C, 50 min., **72%**, 6:1 dr; e) TBAF (250%), THF, 40 °C, 6 h., **88%**; f) SiO_2 (100 mg per mg **7**), CH_2Cl_2, 90 °C (microwave), 3 h., 50%; g) $O_{3(g)}$, CH_2Cl_2, -78 °C, 3 min.; PPh_3 (150%), -78 °C to rt, 15 min., **85%**; h) *Z-selective Wittig*[S6]: Ph_3PEtBr (140%), KHMDS (130%), THF/HMPA, rt, 30 min.; then aldehyde, -78 °C to rt, 5 h. i) *Sharpless asymmetric dihydroxylation*[S2]: AD mix α (1.4 g per mmol alkene), *t*BuOH/H_2O, 4 °C, 18 h., **10%** over 2 steps, 67:33 dr; j) TBAF (250%), THF, rt, 16 h., **66%**. k) *Sharpless asymmetric dihydroxylation*[S2]: AD mix β (1.4 g per mmol alkene), *t*BuOH/H_2O, 4 °C, 18 h., **9%** over 2 steps, 55:45 dr; l) TBAF (250%), THF, rt, 16 h., **80%**.

Cyclization reactions of THP diad-templated epoxy alcohol **10**:



Conditions and results:

entry	promoter/ solvent	T (°C)	time	regioselectivity (**4**:**11**) [a]
1	Cs_2CO_3/MeOH [b]	rt	18 h	0.64:1
2	CSA/CH_2Cl_2 [c]	rt	18 h	1.4:1
3	BF_3•OEt_2/CH_2Cl_2 [d]	-78 to rt	30 min	1.5:1
4	H_2O [e]	rt	19 d	>20:1
5	D_2O [f] (pD 7, 0.1 M KP*i*)	70	24 h	19:1

[a] Regioselectivity determined by ^1H NMR spectroscopy. Results are the average of at least 2 experiments.
[b] Cs_2CO_3 (30 equiv), 0.02 M. [c] (±)-CSA (1 equiv), 0.02 M. [d] BF_3·OEt_2 (0.25 equiv), 0.02 M.
[e] Deionized water, 0.02 M. [f] D_2O buffered to pD 7.0 with 0.1 M K_2HPO_4/KH_2PO_4.

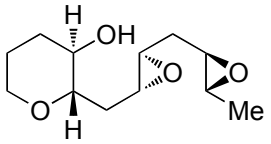
II. Experimental Procedures and Data for Compounds 7-24.

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. Except where noted, dichloromethane, tetrahydrofuran (THF), Et_2O, and triethylamine were purified via an SG Water USA solvent column system. Anhydrous dimethylformamide (DMF) from Aldrich was used without further purification. Reactions in water used deionized water without further purification. Cyclization reactions carried out in Millipore water showed results identical to those in deionized water. Chiral ketone **22**, used in Shi asymmetric epoxidation,[S2] was prepared from D-fructose according to the procedure of Vidal-Ferran and coworkers.[S7] 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.

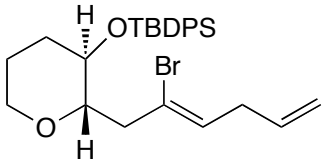
Infrared (IR) spectra were recorded on a Perkin-Elmer Model 2000 FT-IR. High resolution mass spectra (HR-MS) were obtained on a Bruker Daltonics APEXIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer by Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Optical rotations were measured on a Jasco Model 1010 polarimeter at 589 nm.

^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded in $CDCl_3$, C_6D_6, or D_2O, as indicated, on a Varian Inova-500 MHz spectrometer, a Bruker AVANCE-400 MHz spectrometer, or a Bruker AVANCE-600 MHz spectrometer. Chemical shifts in routine ^{1}H 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 HOD in D_2O (4.79 ppm) (all at room temperature). 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 (128.4 ppm), or, for carbon spectra in D_2O, from the resonance from an added drop of methanol (49.5 ppm),[S8] on the δ scale. All kinetic data were determined by NMR using a Varian Inova-500 MHz spectrometer (*vide infra*).



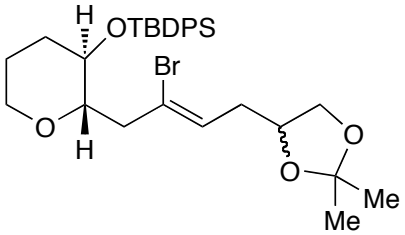
3

Diepoxide 3: This compound was prepared according to previously reported procedures; please see ref. S1.



14

Alkenyl bromide 14: This compound was prepared according to previously reported procedures; please see ref. S1.



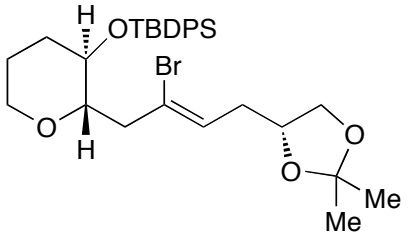
15

Acetonide 15: A commercial sample of AD mix β (984 mg) was dissolved in a mixture of *t*BuOH (3.5 mL) and H_2O (3.5 mL). This cloudy, bright orange solution was cooled to 4 °C. Meanwhile, skipped diene **14** (351 mg, 0.70 mmol) was dissolved in THF (700 μL), and this solution was cooled to 0 ºC. After cooling, the solution of **14** was added to the AD mix, and the resulting suspension was stirred 27 h. at 4 °C. The reaction was then quenched with addition of solid Na_2SO_3 (1.06 g, 8.4 mmol). The mixture was warmed to room temperature and allowed to stir 30 min.; over this time, the color changed from vivid yellow-orange to a pale tan. The mixture was diluted with H_2O (~15 mL) and Et_2O (~30 mL). The aqueous layer was separated and extracted with Et_2O (2x~40 mL), and the combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material (545 mg) was carried forward into acetonide protection without further purification. Major and minor diol diastereomers cospot; R_f = 0.45 (100% EtOAc) or 0.18 (50% EtOAc in hexanes).

This crude diol was dissolved in CH_2Cl_2 (1.45 mL) and 2,2-dimethoxypropane (1.04 mL, 874 mg, 8.4 mmol). Solid pyridinium *p*-toluenesulfonate (17.6 mg, 0.070 mmol) was added at room temperature, and the solution was stirred 23 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (2 mL) and diluted with H_2O (~5 mL) and CH_2Cl_2 (~5 mL). The aqueous layer was extracted three times with CH_2Cl_2 (20 mL each), and the combined organics

were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford the crude acetonide **15** as a pale yellow oil (400 mg). The crude product could be used without further purification. Major and minor diastereomers cospot; R_f = 0.57 (20% EtOAc in hexanes). However, a small portion of **15** was later purified for purposes of characterization. The diastereomers were inseparable by hand chromatography but could be purified away from other impurities (10% EtOAc in hexanes). The diastereomers could then be separated by preparative HPLC (Supelco SUPELCOSIL LC-SI, 20 mm diameter achiral SiO_2 column, 5μm particle size, 25 cm length; 99.6:0.4 hexanes:*i*PrOH, 20 mL/min) to afford major diastereomer **15a** (t_R = 8.3 min.) and minor diastereomer **15b** (t_R = 6.1 min.). The diastereomeric ratio (d.r.) of crude **15** was found to be 2.8:1 by HPLC.

Please note: The stereochemical assignments of major diastereomer **15a** and minor diastereomer **15b** are made purely on the basis of Sharpless's rules for stereochemical induction in the asymmetric dihydroxylation of monosubstituted olefins.[S2] The eventual destruction of the stereocenter in question makes this issue trivial, as the two diastereomers ultimately converge on a single product.



15a (major diastereomer)

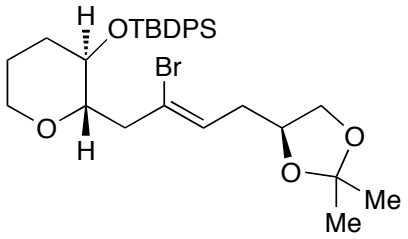
$[\alpha]^{22}_D$ = -13.4 (*c* = 0.70, $CDCl_3$).

IR (thin film, NaCl) 2932, 2857, 1472, 1428, 1369, 1257, 1215, 1103, 1060 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.67 (m, 4H), 7.47-7.36 (m, 6H), 5.70 (app t, *J* = 6.7 Hz, 1H), 4.19 (app quintet, *J* = 6.3 Hz, 1H), 4.02 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.81-3.75 (m, 1H), 3.60 (dd, *J* = 8.0, 7.2 Hz, 1H), 3.54-3.48 (m, 1H), 3.36 (app td, *J* = 9.4, 4.6 Hz, 1H), 3.31-3.25 (m, 1H), 3.12 (app d, *J* = 14.7, 1H), 2.58-2.51 (m, 1H), 2.49-2.42 (m, 1H), 2.22 (dd, *J* = 14.8, 10.1 Hz, 1H), 1.88-1.82 (m, 1H), 1.54-1.33 (m, 3H), 1.43 (s, 3H), 1.36 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 136.1, 134.5, 133.7, 130.0, 130.0, 127.9, 127.7, 127.6, 125.7, 109.2, 80.1, 74.9, 72.0, 69.0, 67.9, 44.8, 35.8, 33.6, 27.2, 27.0, 25.9, 25.7, 19.5.

HR-MS (ESI) *m/z* calcd for $C_{30}H_{41}BrO_4Si$ $(M+Na)^+$: 595.1850, found 595.1846.



15b (minor diastereomer)

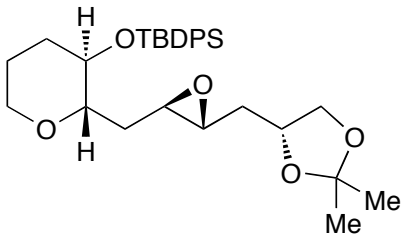
$[\alpha]^{22}_{D}$ = -3.4 (*c* = 0.23, CH_2Cl_2).

IR (thin film, NaCl) 2928, 2856, 1737, 1428, 1369, 1103 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.66 (m, 4H), 7.47-7.36 (m, 6H), 5.73 (app t, *J* = 6.8 Hz, 1H), 4.18 (app quintet, *J* = 6.4 Hz, 1H), 4.02 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.81-3.76 (m, 1H), 3.61 (dd, *J* = 7.9, 7.3 Hz, 1H), 3.53-3.48 (m, 1H), 3.36 (app td, *J* = 9.4, 4.6 Hz, 1H), 3.31-3.25 (m, 1H), 3.12 (app d, *J* = 14.9 Hz, 1H), 2.55-2.44 (m, 2H), 2.24 (dd, *J* = 14.7, 10.0 Hz, 1H), 1.88-1.81 (m, 1H), 1.58-1.34 (m, 3H), 1.42 (s, 3H), 1.36 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 136.1, 134.5, 133.7, 130.0, 129.9, 127.9, 127.7, 127.7, 125.6, 109.2, 80.2, 74.9, 72.0, 69.0, 67.9, 44.8, 35.6, 33.6, 27.2, 27.0, 26.0, 25.7, 19.5.

HR-MS (ESI) *m/z* calcd for $C_{30}H_{41}BrO_4Si$ $(M+Na)^+$: 595.1850, found 595.1841.



16

Epoxide 16: Reduction of the vinyl bromide was carried out according to the procedure of Cacchi and coworkers for the reduction of enol triflates.[3] Crude alkenyl bromide **15** (400 mg, ~0.7 mmol) was dissolved in DMF (930 μL). A dry flask was charged with $Cl_2Pd(PPh_3)_2$ (24.6 mg, 0.035 mmol), to which was added the solution of **15** in DMF. To this lemon yellow solution was added Bu_3N (389 mg, 500 μL, 2.1 mmol) and then HCO_2H (64 mg, 53 μL, 1.4 mmol). The reaction solution smoked upon addition of the formic acid. It was stirred 15 min. at room temperature, during which time it turned brown, then warmed to 40 °C for 41 h. The solution was then cooled to room temperature and filtered through a short pad of SiO_2 using 15% EtOAc in hexanes as an eluent to give a brown oil. NMR analysis of the crude reaction mixture revealed a 63:37 mixture of disubstituted alkene (the reduced product) and unreacted **15** (product cospots with **15** by TLC, R_f = 0.59 (20% EtOAc/hexanes)).

To this crude mixture in a mixture of dimethoxymethane (DMM)/MeCN (2:1 v/v, 56 mL) was added a 0.05 M solution of $Na_2B_4O_7$•$10H_2O$ in 4 x 10^{-4} M Na_2EDTA (38 mL), nBu_4HSO_4 (115

mg, 0.34 mmol), and chiral ketone **22** (346 mg, 1.34 mmol). The biphasic mixture was stirred vigorously at 0 ºC while Oxone (4.1 g, 6.7 mmol) in 4 x 10^{-4} M aqueous Na_2EDTA (18.8 mL) was added simultaneously with an aqueous solution of K_2CO_3 (0.89 M, 18.8 mL, 16.8 mmol) via syringe pump addition over 30 minutes. The resulting mixture was stirred an additional 30 min at 0 ºC, at which point it was diluted with EtOAc (~100 mL) and water (~50 mL). The aqueous layer was separated and extracted three times with EtOAc (100 mL each). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. NMR and TLC evidence at this point indicated approx. 35% conversion of the alkene. The reaction mixture was then resubjected to identical epoxidation conditions and worked up as before. Resubjection afforded approx. 80% overall conversion to epoxide **16**. The product was purified by column chromatography using a gradient of solvents (10% to 20% EtOAc in hexanes) to provide **16**, a colorless oil, as an inseparable mixture of diastereomers (207 mg of a 6:1 mixture of diastereomers at the epoxide (~2:1 overall d.r.), 0.305 mmol combined, 40% over 3 steps, R_f = 0.50 (25% EtOAc/hexanes)) as well as an inseparable mixture of vinyl bromide **15** (37 mg, 0.065 mmol) and disubstituted alkene (59 mg, 0.119 mmol), R_f = 0.62 (25% EtOAc in hexanes). Epoxide **16** could be 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, 20 mL/min.; t_R of major diastereomer = 12.4 min.) to afford **16** in a d.r. of 20:1, which was characterized.

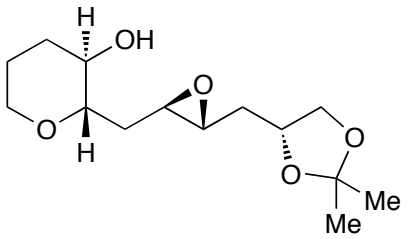
$[\alpha]^{22}_D$ = -15.0 (*c* = 0.10, $CDCl_3$).

IR (thin film, NaCl) 3072, 2931, 2857, 1732, 1472, 1428, 1369, 1260, 1214, 1103 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69-7.66 (m, 4H), 7.46-7.41 (m, 2H), 7.41-7.36 (m, 4H), 4.26 (app quint, *J* = 6.4 Hz, 1H), 4.09 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.83-3.79 (m, 1H), 3.60 (app t, *J* = 7.7 Hz, 1H), 3.40 (app td, *J* = 9.2, 4.4 Hz, 1H), 3.33-3.27 (m, 2H), 2.82 (app td, *J* = 5.7, 2.1 Hz, 1H), 2.77 (ddd, *J* = 6.9, 4.2, 2.2 Hz, 1H), 2.03 (ddd, *J* = 14.3, 6.0, 2.6 Hz, 1H), 1.95 (ddd, *J* = 13.9, 6.7, 4.3, 1H), 1.84-1.79 (m, 1H), 1.67 (ddd, *J* = 14.3, 8.9, 5.4, 1H), 1.61-1.53 (m, 2H), 1.50-1.40 (m, 5H), 1.39 (s, 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, 127.7, 109.0, 80.9, 74.0, 72.3, 69.5, 67.8, 56.9, 55.0, 36.6, 34.8, 33.5, 27.2, 27.1, 25.9, 25.6, 19.5.

HR-MS (ESI) *m/z* calcd for $C_{30}H_{42}O_5Si$ $(M+Na)^+$: 533.2694, found 533.2692.



17

Epoxy alcohol 17: To a solution of silyl ether **16** (2.10 g, 4.1 mmol) in THF (6 mL) was added tetrabutylammonium fluoride (TBAF, 1M in THF, 8.2 mL, 8.2 mmol). The reaction was warmed

to 40° for 2 h., cooled, and applied directly to a column of SiO_2. The SiO_2 was packed with 25% EtOAc in hexanes to which had been added 2% Et_3N, and the column was run with a gradient from 25% EtOAc in hexanes to 100% EtOAc to afford alcohol **17** as a pale yellow oil (990 mg, 3.6 mmol, 89%, R_f = 0.51 (EtOAc)).

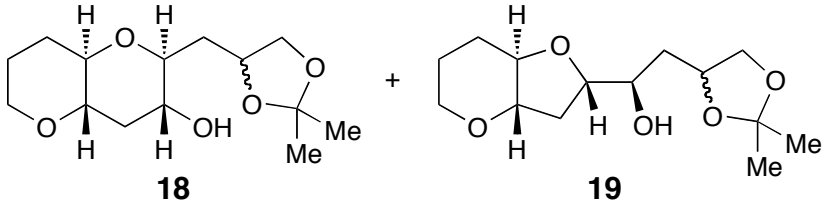
$[\alpha]^{22}_D$ = +10.9 (*c* = 0.095, CH_2Cl_2)

IR (thin film, NaCl) 3427, 2924, 2853, 1653, 1456, 1370, 1213, 1159, 1094, 1058 cm^{-1}.

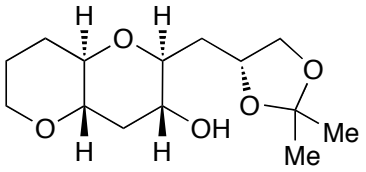
^{1}H NMR (600 MHz, C_6D_6) δ 4.04 (app dq, *J* = 7.3, 5.8, 5.8, 5.8 Hz, 1H), 3.78 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.71-3.67 (m, 1H), 3.47-3.40 (m, 1H), 3.36 (app t, *J* = 7.6 Hz, 1H), 3.08 (ddd, *J* = 9.0, 5.6, 3.5 Hz, 1H), 3.06-3.00 (m, 1H), 2.97 (ddd, *J* = 6.7, 4.0, 2.2 Hz, 1H), 2.67 (ddd, *J* = 6.9, 4.2, 2.2 Hz, 1H), 1.98 (app dt, *J* = 14.7, 3.8 Hz, 1H), 1.90-1.83 (m, 2H), 1.73 (ddd, *J* = 14.6, 7.0, 5.8 Hz, 1H), 1.65 (ddd, *J* = 13.7, 7.8, 4.3 Hz, 1H), 1.47-1.37 (m, 4H), 1.32 (s, 3H), 1.29-1.16 (m, 3H);

^{13}C NMR (100 MHz, C_6D_6) δ 109.3, 81.3, 74.2, 70.3, 69.9, 68.1, 56.3, 55.9, 37.2, 35.6, 33.2, 27.6, 26.5, 26.3.

HR-MS (ESI) *m/z* calcd for $C_{14}H_{24}O_5$ $(M+Na)^+$: 295.1516, found 295.1527.



THP diad 18 and 6,5-fused 19: Epoxy alcohol **17** (990 mg, 3.6 mmol) was dissolved in 0.1 M potassium phosphate buffer (pH = 7.0, 180 mL) and the resulting slightly cloudy solution was heated to 70 °C for 23 h. The solution was then cooled to room temperature and extracted four times with EtOAc (400 mL each). The combined organics were washed with a small amount of brine (~30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. ^{1}H NMR analysis of the crude reaction mixture indicated an approximately 1.1:1 ratio of **18**:**19**. The mixture was purified by column chromatography using a gradient of solvents (50% to 100% EtOAc/hexanes), which resulted in fractions containing pure **18** (380 mg, 1.40 mmol, 38%, R_f = 0.52 (100% EtOAc)) and **19** (252 mg, 0.93 mmol, 25%, R_f = 0.44 (100% EtOAc)), along with fractions containing a significant quantity of both products (344 mg, 1.26 mmol, 35%).



18 (characterization of major diastereomer only)

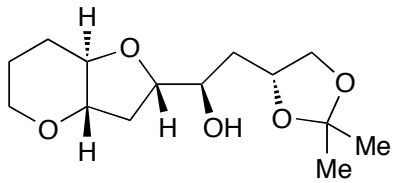
$[\alpha]^{22}_{D}$ = -17.9 (*c* = 0.13, CH_2Cl_2).

IR (thin film, NaCl) 3428, 2926, 2852, 1723, 1454, 1370, 1219, 1095, 1060, 1026 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.36 (dddd, *J* = 7.8, 7.7, 6.2, 4.1 Hz, 1H), 4.09 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.94-3.90 (m, 1H), 3.67-3.61 (m, 1H), 3.57 (app t, *J* = 8.0 Hz, 1H), 3.41-3.36 (m, 1H), 3.26 (ddd, *J* = 8.9, 5.3, 3.3 Hz, 1H), 3.04-2.98 (m, 2H), 2.66 (s, 1H), 2.35 (app dt, *J* = 11.5, 4.0 Hz, 1H), 2.06-2.00 (m, 2H), 1.96 (app dt, *J* = 15.0, 3.6 Hz, 1H), 1.76-1.69 (m, 2H), 1.51 (app q, *J* = 11.3 Hz, 1H), 1.46-1.40 (m, 4H), 1.38 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 109.4, 79.9, 78.4, 77.4, 72.5, 69.7, 68.8, 68.1, 38.3, 35.6, 29.5, 27.1, 26.0, 25.7.

HR-MS (ESI) *m/z* calcd for $C_{14}H_{24}O_5$ $(M+Na)^+$: 295.1516, found 295.1522.



19 (characterization of major diastereomer only)

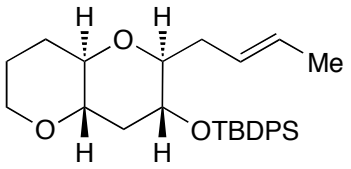
$[\alpha]^{22}_{D}$ = -11.9 (*c* = 0.20, $CDCl_3$).

IR (thin film, NaCl) 3440, 2939, 2869, 1453, 1369, 1222, 1041 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.36 (dddd, *J* = 7.4, 7.4, 6.4, 5.0 Hz, 1H), 4.11 (dd, *J* = 8.2, 6.0 Hz, 1H), 4.06 (ddd, *J* = 9.2, 6.2, 5.1 Hz, 1H), 4.03-3.95 (m, 2H), 3.61 (app t, *J* = 7.8 Hz, 1H), 3.50-3.44 (m, 1H), 3.32-3.21 (m, 2H), 2.50 (d, *J* = 4.1 Hz, 1H), 2.24-2.15 (m, 2H), 1.97 (app q, *J* = 10.8 Hz, 1H), 1.78 (ddd, *J* = 14.2, 7.5, 2.9 Hz, 1H), 1.74-1.60 (m, 3H), 1.50 (app qd, *J* = 11.3, 4.7 Hz, 1H), 1.42 (s, 3H), 1.37 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 109.1, 81.5, 79.6, 78.7, 73.8, 71.1, 69.8, 69.0, 35.7, 30.8, 29.9, 27.1, 25.9, 24.7.

HR-MS (ESI) *m/z* calcd for $C_{14}H_{24}O_5$ $(M+Na)^+$: 295.1516, found 295.1518.



20

Alkene 20: To a solution of alcohol **18** (380 mg, 1.39 mmol) in DMF (1 mL) was added imidazole (380 mg, 5.58 mmol) followed by *tert*-butyldiphenylchlorosilane (TBDPSCl, 714 μL, 767 mg, 2.79 mmol). The reaction was warmed to 50° for 17 h., then cooled and filtered through a short pad of SiO_2 (10% to 15% EtOAc in hexanes) to yield the desired silyl ether (R_f = 0.55 (20% EtOAc in hexanes)) as a mixture with TBDPSOH (R_f = 0.69 (20% EtOAc in hexanes)), a colorless oil (678 mg). This crude product was carried forward into the acetonide cleavage without further purification.

The crude silyl ether was dissolved in THF (5.1 mL), and deionized H_2O (1.3 mL) was added. Trifluoroacetic acid (568 μL, 876 mg, 7.68 mmol) was added slowly, resulting in smoking. The reaction was warmed to 35° for 24 h., then cooled to room temperature and quenched with NH_4OH (~2 mL, ~1.8 g, ~50 mmol). The solution was concentrated *in vacuo* (40°, 2 torr) to provide the crude diol (R_f = 0.11 (30% EtOAc/hexanes) or 0.40 (50% EtOAc in hexanes)) as a viscous colorless oil that crystallized upon standing. This crude was carried forward into periodate oxidation without further purification.

The crude diol was dissolved in a 1:1 mixture of THF:H_2O (6.4 mL) and cooled to 0° C, at which point $NaIO_4$ (821 mg, 3.84 mmol) was added. The mixture was stirred vigorously for 2 h., then diluted with H_2O (~25 mL) and extracted four times with Et_2O (50mL each). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the aldehyde (R_f = 0.65 (30% EtOAc in hexanes)). This crude aldehyde, which appeared nearly pure by ^{1}H NMR, was used without further purification. For prolonged storage of this aldehyde, it is recommended that the compound be frozen in benzene.

Olefination was carried out according to the procedure developed by Takai and coworkers.[S5] To a solution of this crude aldehyde in dry THF (7 mL) was added 1,1-diiodoethane (1.08 g, 3.84 mmol). A dry flask was charged with $CrCl_2$ (1.89 g, 15.4 mmol) to which was added dry THF (25 mL) to give a pale green slurry. The aldehyde and 1,1-diiodoethane solution were added dropwise by syringe to the $CrCl_2$ slurry over 5 min., at which point the reaction flask was covered with aluminum foil (to protect it from light) and stirred at rt for 20 h. The brown reaction solution was then quenched by pouring into a mixture of hexane (~50 mL) and H_2O (~50 mL). The aqueous layer was separated and extracted three times with Et_2O (50 mL each). The combined organics were washed twice with brine (15 mL each), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide crude alkene **20** as a yellow oil. The product was purified by column chromatography using a gradient of solvents (5% to 40% EtOAc in hexanes) to provide **20** as a pale yellow oil (495 mg, 1.10 mmol, 86% over 3 steps, *E*:*Z* = 8:1, R_f = 0.58 (10% EtOAc in hexanes)).

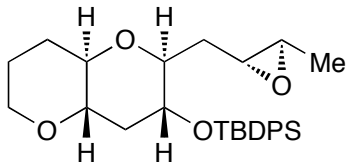
$[\alpha]^{22}_D$ = -29.5 (*c* = 0.81, $CDCl_3$)

IR (thin film, NaCl) 3071, 2933, 2856, 1590, 1473, 1463, 1451, 1428, 1361, 1281, 1100, 1081 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72-7.64 (m, 4H), 7.46-7.34 (m, 6H), 5.53-5.38 (m, 2H), 3.84-3.78 (m, 1H), 3.42 (ddd, *J* = 10.9, 9.0, 4.6 Hz, 1H), 3.30-3.22 (m, 2H), 2.96 (ddd, *J* = 11.2, 8.9, 4.4 Hz, 1H), 2.70 (ddd, *J* = 11.6, 8.9, 4.2 Hz, 1H), 2.63-2.56 (m, 1H), 2.09 (app dt, *J* = 11.5, 4.4 Hz, 1H), 2.05-1.96 (m, 2H), 1.70-1.61 (m, 5H), 1.54 (app q, *J* = 11.4 Hz, 1H), 1.32 (app dq, *J* = 11.6, 5.5 Hz, 1H), 1.06 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 136.1, 134.3, 133.5, 130.0, 129.8, 127.9, 127.7, 127.7, 82.7, 77.7, 76.9, 71.1, 67.9, 39.7, 34.9, 29.4, 27.2, 25.6, 19.5, 18.3.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{38}O_3Si$ $(M+Na)^+$: 473.2482, found 473.2498.



21

Epoxide 21: To a solution of alkene **20** (100 mg, 0.22 mmol) in 2:1 v/v DMM:MeCN (7.5 mL) was added a 0.05 M aqueous solution of $Na_2B_4O_7$•$10H_2O$ in 4 x 10^{-4} M Na_2EDTA (5.0 mL), $n$$Bu_4HSO_4$ (23 mg, 0.066 mmol), and chiral ketone **22** (57 mg, 0.22 mmol). The biphasic mixture was stirred vigorously at 0° C. To this mixture was added, simultaneously over 35 min. via syringe pump, a solution of Oxone (682 mg, 1.11 mmol) in 4 x 10^{-4} Na_2EDTA (2.5 mL) and a 0.89 M solution of K_2CO_3 (2.5 mL, 2.2 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 20 min at 0° C, at which point it was diluted with water (~10 mL). The aqueous layer was extracted four times with EtOAc (40 mL each), and the combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude epoxide **21** was purified by column chromatography using a gradient of solvents (5% to 40% EtOAc in hexanes) to provide **21**, a colorless oil, as an inseparable mixture of diastereomers (98 mg of a 5:1 mixture of epoxide diastereomers, 0.21 mmol combined, 95%), R_f = 0.60 (20% EtOAc in hexanes). Epoxide **21** could be 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 major diastereomer = 8.1 min.) to afford **21** in a d.r. of 20:1, which was characterized.

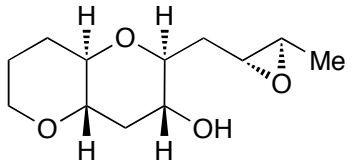
$[\alpha]^{22}_D$ = -30.7 (c = 1.29, $CDCl_3$).

IR (thin film, NaCl) 3072, 2931, 2857, 1739, 1590, 1473, 1428, 1361, 1281, 1098, 1032 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.64 (m, 4H), 7.46-7.35 (m, 6H), 3.84-3.79 (m, 1H), 3.46 (ddd, J = 10.7, 9.0, 4.6 Hz, 1H), 3.37 (app td, J = 8.8, 2.5 Hz, 1H), 3.28-3.22 (m, 1H), 2.98 (ddd, J = 11.2, 9.0, 4.4 Hz, 1H), 2.80-2.68 (m, 3H), 2.09 (app dt, J = 11.5, 4.4 Hz, 1H), 2.04-1.97 (m, 2H), 1.72-1.60 (m, 3H), 1.53 (app q, J = 11.2, 1H), 1.36-1.25 (m, 4H), 1.03 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 136.1, 134.1, 133.3, 130.1, 129.9, 127.9, 127.7, 80.4, 77.7, 76.7, 71.4, 67.9, 57.4, 54.2, 39.7, 34.3, 29.4, 27.2, 27.2, 25.6, 19.5, 17.9.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{38}O_4Si$ $(M+Na)^+$: 489.2437, found 489.2430.



10

Epoxy alcohol 10: To a solution of silyl ether **21** (6.9 mg, 0.015 mmol) in dry THF (300 μL) was added TBAF (1M in THF, 37 μL, 0.037 mmol). The reaction was warmed to 35 °C for 1.25 h, then cooled to room temperature and applied directly to a column of SiO_2. The silica was packed with 25% EtOAc in hexanes to which 2% Et_3N had been added, and the column run with a gradient of solvents from 25% to 100% EtOAc in hexanes, providing free alcohol **10** as a colorless oil (3.3 mg, 0.0145 mmol, 97%): R_f = 0.51 (100% EtOAc). Epoxy alcohol **10** cyclizes slowly if stored at room temperature as a neat oil. It is therefore best stored as a frozen benzene solution.

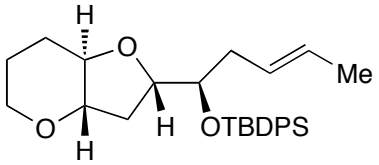
$[\alpha]^{22}_D$ = +15.1 (*c* = 0.045, $CDCl_3$).

IR (thin film, NaCl) 3407, 2923, 2850, 1454, 1095 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6) δ 3.70-3.65 (m, 1H), 3.64-3.57 (m, 1H), 3.21 (ddd, *J* = 9.1, 5.4, 3.5 Hz, 1H), 3.02 (app td, *J* = 11.9, 2.3 Hz, 1H), 2.91-2.85 (m, 2H), 2.82 (ddd, *J* = 11.3, 8.9, 4.2 Hz, 1H), 2.46-2.39 (m, 2H), 2.18 (s, 1H), 2.03 (app dt, *J* = 14.8, 3.5 Hz, 1H), 1.92-1.87 (m, 1H), 1.69-1.59 (m, 2H), 1.42 (app qt, *J* = 13.0, 4.2 Hz, 1H), 1.33-1.25 (m, 1H), 1.17 (app dd, *J* = 13.4, 2.0 Hz, 1H), 0.98 (d, *J* = 5.2 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 80.3, 78.3, 77.3, 69.0, 68.1, 56.7, 54.6, 38.5, 34.4, 29.5, 25.7, 17.7.

HR-MS (ESI) *m/z* calcd for $C_{12}H_{20}O_4$ $(M+Na)^+$: 251.1254, found 251.1263.



23

Alkene 23: To a solution of alcohol **19** (350 mg, 1.29 mmol) in DMF (3 mL) was added first imidazole (440 mg, 6.46 mmol) and then TBDPSCl (860 μL, 920 mg, 3.36 mmol). The reaction was warmed to 50 °C for 36 h., then cooled and applied directly to a column of SiO_2. Purification with a gradient of solvents (10% to 20% EtOAc in hexanes) yielded the desired silyl ether (R_f = 0.29 (20% EtOAc in hexanes), 404 mg, 0.79 mmol, 61%) as a colorless oil that solidified upon storage at -20 °C.

This acetonide (360 mg, 0.70 mmol) was dissolved in THF (2.8 mL), and deionized H_2O (0.7 mL) was added. Trifluoroacetic acid (261 μL, 402 mg, 3.52 mmol) was added slowly, resulting in smoking. The reaction was warmed to 35 °C for 19 h., then cooled to rt and quenched with NH_4OH (~1 mL, ~0.9 g, ~25 mmol). The reaction solution was concentrated *in vacuo* (40 ºC, 2 torr) to provide the crude diol (R_f = 0.50 (100% EtOAc)) as a viscous, colorless oil. The crude product was carried forward into periodate oxidation without further purification.

The crude diol was dissolved in a 1:1 mixture of THF:H_2O (3.5 mL) and cooled to 0 °C, at which point $NaIO_4$ (452 mg, 2.1 mmol) was added. The mixture was stirred vigorously for 2 h, then warmed to room temperature and stirred for an additional hour. The reaction was then diluted with H_2O (~25 mL) and extracted three times with Et_2O (40mL each). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude aldehyde (R_f = 0.65 (30% EtOAc in hexanes)) as a golden brown oil. The crude aldehyde was used without further purification. For prolonged storage of this crude aldehyde, it is recommended that the compound be frozen in benzene.

Olefination was carried out according to the procedure developed by Takai and coworkers.[S5] To a solution of this crude aldehyde in dry THF (7.6 mL) was added 1,1-diiodoethane (596 mg, 2.12 mmol). A dry flask was charged with $CrCl_2$ (1.04 g, 8.46 mmol), to which was added dry THF (10 mL) to give a pale green slurry. The aldehyde and 1,1-diiodoethane solution was added dropwise to the $CrCl_2$ slurry over 5 min., at which point the reaction flask was covered with aluminum foil (to protect it from light) and stirred at room temperature for 20 h. The brown reaction solution was then quenched by pouring into a mixture of hexane (~50 mL) and H_2O (~50 mL). The aqueous layer was extracted three times with Et_2O (50 mL each). The combined organics were washed twice with brine (15 mL each), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide crude alkene **23** as a yellow oil. The product was purified by column chromatography using a gradient of solvents (5% to 40% EtOAc in hexanes) to provide **23** as a pale yellow oil (290 mg, 0.64 mmol, 91% over 3 steps, *E*:*Z* = 9:1, R_f = 0.67 (20% EtOAc in hexanes)).

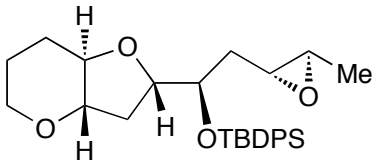
$[\alpha]^{22}_D$ = -22.7 (*c* = 0.68, CH_2Cl_2)

IR (thin film, NaCl) 3071, 3049, 2932, 2856, 1589, 1473, 1427, 1127, 1112, 1086, 1070 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79-7.69 (m, 4H), 7.45-7.35 (m, 6H), 5.17 (app dq, *J* = 15.2, 6.2 Hz, 1H), 5.07 (app dtd, *J* = 15.2, 7.1, 1.3 Hz, 1H), 4.10 (ddd, *J* = 9.5, 6.5, 3.4 Hz, 1H), 4.05 (ddd, *J* = 8.3, 4.9, 3.5 Hz, 1H), 3.99 (app dd, *J* = 11.5, 4.8 Hz, 1H), 3.46 (app td, *J* = 12.0, 2.8 Hz, 1H), 3.39 (ddd, *J* = 11.2, 8.9, 3.9 Hz, 1H), 3.21 (ddd, *J* = 11.1, 9.0, 6.6 Hz, 1H), 2.21-2.06 (m, 3H), 2.01-1.89 (m, 2H), 1.71-1.65 (m, 1H), 1.65-1.54 (m, 1H), 1.49 (dd, *J* = 6.2, 1.1 Hz, 3H), 1.46 (app qd, *J* = 11.8, 4.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 136.2, 134.9, 134.0, 129.8, 127.9, 127.7, 127.7, 126.4, 81.6, 78.8, 78.2, 75.4, 69.0, 37.6, 29.8, 29.7, 27.3, 24.8, 19.7, 18.1.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{38}O_3Si$ $(M+Na)^+$: 473.2482, found 473,2495.



24

Epoxide 24: To a solution of alkene **23** (120 mg, 0.27 mmol) in DMM:MeCN (2:1 v/v, 9.0 mL) was added a 0.05 M aqueous solution of $Na_2B_4O_7$•$10H_2O$ in 4 x 10^{-4} M Na_2EDTA (6.0 mL), *n*Bu_4HSO_4 (27 mg, 0.080 mmol), and chiral ketone **22** (69 mg, 0.27 mmol). The biphasic mixture was stirred vigorously at 0 °C, and Oxone (818 mg, 1.33 mmol) dissolved in a 4 x 10^{-4} M Na_2EDTA aqueous solution (3.0 mL) was simultaneously added with an aqueous solution of K_2CO_3 (0.89 M, 3.0 mL, 2.67 mmol) over 30 min. via syringe pump. The resulting mixture was stirred an additional 20 min. at 0 °C, at which point it was diluted with water (~10 mL). The aqueous layer was separated and extracted three times with Et_2O (40 mL each), and the combined organics were washed with brine (~10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude epoxide **24** was purified by column chromatography using a gradient of solvents (5% to 60% EtOAc in hexanes) to provide a small amount of unreacted alkene **23** (10 mg, 0.022 mmol, 8%) and the desired epoxide **24**, a colorless oil, as an inseparable mixture of diastereomers (89 mg of an approximately 6:1 mixture of epoxide diastereomers, 0.19 mmol combined, 72%), R_f = 0.21 in 20% EtOAc in hexanes and R_f = 0.38 in 30% EtOAc in hexanes. Epoxide **24** could be further purified via preparative HPLC (Supelco SUPELCOSIL LC-SI, 20 mm diameter achiral SiO_2 column, 5 μm particle size, 25 cm length; 3.0% *i*PrOH in hexanes, 20 mL/min.; t_R of major diastereomer = 5.7 min.., with the highest purity material collected on the trailing edge (i.e., the right side) of this peak) to afford **24** in a d.r. of 20:1, which was characterized:

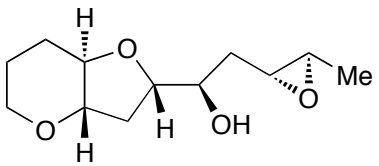
$[\alpha]^{22}_D$ = -20.3 (*c* = 0.34, $CDCl_3$).

IR (thin film, NaCl) 2933, 2857, 1751, 1428, 1383, 1112, 1076 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79-7.75 (m, 2H), 7.72-7.69 (m, 2H), 7.46-7.42 (m, 2H), 7.42-7.37 (m, 4H), 4.19 (ddd, *J* = 9.2, 6.5, 3.8 Hz, 1H), 4.14 (app quint, *J* = 4.1 Hz, 1H), 4.00-3.96 (m, 1H), 3.46 (app td, *J* = 12.0, 2.6 Hz, 1H), 3.35 (ddd, *J* = 11.2, 9.0, 3.9 Hz, 1H), 3.21 (ddd, *J* = 11.0, 8.9, 6.6 Hz, 1H), 2.41-2.37 (m, 2H), 2.17-2.11 (m, 2H), 2.06 (app td, *J* = 11.0, 9.2 Hz, 1H), 1.71-1.65 (m, 1H), 1.64-1.53 (m, 2H), 1.53-1.43 (m, 2H), 1.11 (d, *J* = 4.9 Hz, 3H), 1.09 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 136.1, 134.5, 133.6, 129.9, 127.8, 127.8, 81.5, 79.4, 78.4, 74.1, 69.0, 56.3, 54.7, 37.1, 30.5, 29.8, 27.2, 24.8, 19.7, 17.6.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{38}O_4Si$ $(M+Na)^+$: 489.2432, found 489.2445.



7

Epoxy alcohol 7: To a solution of silyl ether **24** (22 mg, 0.047 mmol, 20:1 dr) in dry THF (300 μL) was added TBAF (1M in THF, 118 μL, 0.118 mmol). The reaction was warmed to 40 °C for 6 h., then cooled to room temperature and applied directly to a pad of SiO_2. The silica was packed in 25% EtOAc in hexanes to which 2% Et_3N had been added, and the column run with a gradient of solvents from 25% to 100% EtOAc in hexanes, providing free alcohol **7** (R_f = 0.44 (100% EtOAc), 9.4 mg, 0.047 mmol, 88%) as a colorless oil which solidified upon storage at 4 °C. Spectral data and other characterization were consistent with that already reported by our group.[S9b] However, as that earlier report describes epoxy alcohol **7** in relatively low diastereopurity, we collected characterization data for a sample of **7** in 20:1 d.r. and report it here:

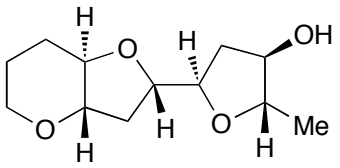
$[\alpha]^{22}_D$ = +18.8 (*c* = 0.47, CH_2Cl_2)

IR (thin film, NaCl) 3406, 2975, 2945, 2902, 2851, 1451, 1307, 1275, 1152, 1123, 1086, 1072, 1041 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6) δ 3.93-3.86 (m, 2H), 3.77-3.72 (m, 1H), 3.25 (ddd, *J* = 10.8, 8.9, 3.9 Hz, 1H), 3.10 (app td, *J* = 11.9, 2.8 Hz, 1H), 3.02 (ddd, *J* = 10.8, 8.9, 6.9 Hz, 1H), 2.67 (ddd, *J* = 6.9, 3.6, 2.2 Hz, 1H), 2.51 (qd, *J* = 5.2, 2.2 Hz, 1H), 2.43 (s, 1H), 2.11-1.97 (m, 3H), 1.63 (ddd, *J* = 14.2, 8.9, 3.7 Hz, 1H), 1.39 (ddd, *J* = 14.2, 7.1, 3.1 Hz, 1H), 1.35-1.26 (m, 2H), 1.18-1.10 (m, 1H), 1.00 (d, *J* = 5.2 Hz, 3H);

^{13}C NMR (100 MHz, C_6D_6) δ 82.3, 80.1, 79.1, 71.9, 68.9, 57.2, 54.5, 35.5, 31.5, 30.6, 25.2, 17.9.

HR-MS (ESI) *m/z* calcd for $C_{12}H_{20}O_4$ $(M+Na)^+$: 251.1254, found 251.1258.



8

THF side product 8: A solution of epoxy alcohol **7** (3.0 mg, 0.015 mmol) in CH_2Cl_2 (2 mL) was transferred into a 5 mL microwave reaction vial, along with a magnetic stir bar. To this was added silica gel (300 mg) that had been dried in the oven overnight and then cooled in a dessicator. The tube was capped and the mixture heated by microwave irradiation to 90 °C for 3 h. After cooling to room temperature, the slurry was filtered through a glass frit, and the silica gel was washed repeatedly with ~10 mL of a 10% solution of MeOH in EtOAc. The organic solution was concentrated *in vacuo* and purified by column chromatography (100% EtOAc) to afford **8** (1.5 mg, 0.0075 mmol, 50%) as a colorless oil (R_f = 0.28 (100% EtOAc)).

$[\alpha]^{22}_D$ = -17.5 (*c* = 0.075, CH_2Cl_2)

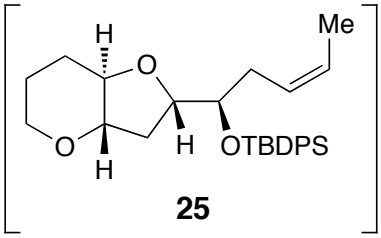
IR (thin film, NaCl) 3418, 2924, 2853, 1726, 1461, 1378, 1277, 1125, 1066, 1013 cm^{-1}.

^{1}H NMR (500 MHz, D_2O) δ 4.26 (m, 2H), 4.07-4.00 (m, 2H), 3.94 (app quintet, *J* = 6.1 Hz, 1H), 3.56 (app td, *J* = 12.2, 2.6 Hz, 1H), 3.42-3.34 (m, 2H), 2.46 (app dt, *J* = 13.0, 6.6 Hz, 1H), 2.36

(app td, J = 11.2, 5.8 Hz, 1H), 2.21-2.15 (m, 1H), 1.83-1.71 (m, 3H), 1.64 (app qt, J = 13.1, 4.5 Hz, 1H), 1.53 (app qd, J = 11.4, 4.5 Hz, 1H), 1.21 (d, J = 6.3 Hz, 3H).

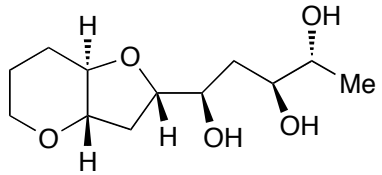
^{13}C NMR (125 MHz, D_2O) δ 81.6, 80.6, 79.4, 79.3, 79.0, 76.6, 69.5, 35.5, 31.6, 29.1, 24.4, 17.9.

HR-MS (ESI) *m/z* calcd for $C_{12}H_{20}O_4$ $(M+Na)^+$: 251.1254, found 251.1263.



***cis*-Alkene 25:** A solution of *trans*-alkene **23** (54 mg, 0.12 mmol) was dissolved in CH_2Cl_2 (2.4 mL) and cooled to -78 °C. Ozone was bubbled through the reaction mixture until a blue color remained, about 5 min. Pure oxygen gas was then bubbled through the reaction mixture for 2 min., followed by argon for 2 min. Triphenyl phosphine (47 mg, 0.18 mmol) was added to the reaction, and the solution was allowed to warm gradually to room temperature over approximately 15 min. The solution was then concentrated to provide the crude aldehyde (R_f = 0.32 (20% EtOAc in hexanes)) as a yellow-brown oil, which was filtered through a short plug of silica (5% to 40% EtOAc in hexanes) to remove unreacted PPh_3. The resulting crude aldehyde was used without further purification.

The *Z*-selective Wittig olefination was carried out according to the procedure of Denmark and coworkers.[S6] A dry flask was charged with KHMDS (26 mg, 0.13 mmol) and ethyltriphenylphosphonium bromide (Ph_3PEtBr) (52 mg, 0.14 mmol). To this was added THF (200 μL) and freshly distilled hexamethylphosphoramide (HMPA, 50 μL), and the mixture was stirred at room temperature for 30 min. to provide a clear orange-yellow solution. In a second flask, the crude aldehyde from the preceding step was dissolved in THF (150 μL). Upon cooling the newly-formed phosphorane solution to -78 °C, the aldehyde solution was slowly added dropwise over approximately 3 min. The flask containing the aldehyde was washed out with a further 100 μL, and this was added dropwise to the phosphorane solution. The yellow solution was allowed to warm gradually to room temperature over 5 h, at which point it was quenched with water (5 mL), diluted with Et_2O, extracted three times with Et_2O, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to provide the crude alkene **25** in >20:1 *Z*:*E* by ^{1}H NMR. Crude **25** was carried forward into dihydroxylation without further purification.



9a

Triol 9a: One half of the crude *cis*-alkene **25** prepared in the previous step was dissolved in THF (100 μL). In a separate vial, AD mix α (70 mg) was dissolved in a mixture of *t*BuOH (250 μL) and H_2O (250 μL). This solution was cooled to 4 °C and stirred 15 min. The solution of crude **25** was then added, and the resulting orange solution stirred vigorously at 4 °C for 18 h, at which point it was diluted with H_2O and Et_2O. The aqueous layer was extracted three times with Et_2O, and the combined organics were concentrated *in vacuo* without drying to provide the crude diol (R_f = 0.54 (100% EtOAc)). ^{1}H NMR analysis at this point indicated a 67:33 mixture of diastereomers, with the configuration of the major diastereomer assumed, based on Sharpless's rules for induction in asymmetric dihydroxylation.[S2] This crude mixture was carried into desilylation without further purification.

To a solution this crude silyl ether in THF (300 μL) was added TBAF (1 M in THF, 13 μL, 0.013 mmol). The reaction solution was stirred at room temperature for 16 h., then applied directly to a pad of SiO_2. The column was run with a gradient of solvents from 5% to 15% MeOH in EtOAc, providing cleanly triol **9a** as the major product (0.8 mg, 0.0032 mmol, 6% over 4 steps, R_f = 0.24 (10% MeOH in EtOAc)) as well as some of the diastereomeric triol **9b** (R_f = 0.32 (10% MeOH in EtOAc)).

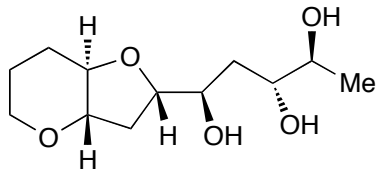
$[\alpha]^{22}_D$ = +2.2 (*c* = 0.040, EtOAc)

IR (thin film, NaCl) 3377, 2924, 2855, 1996, 1642, 1379, 1123, 1061 cm^{-1}.

^{1}H NMR (500 MHz, D_2O) δ 4.08 (ddd, *J* = 9.3, 6.6, 4.4 Hz, 1H), 4.01-3.94 (m, 2H), 3.76-3.70 (m, 2H), 3.52 (app td, *J* = 12.2, 2.5 Hz, 1H), 3.39-3.30 (m, 2H), 2.23 (app dt, *J* = 11.2, 6.3 Hz, 1H), 2.18-2.12 (m, 1H), 1.87-1.72 (m, 2H), 1.60 (app qt, *J* = 13.0, 4.6 Hz, 1H), 1.54-1.41 (m, 3H), 1.11 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (125 MHz, D_2O) δ 80.9, 80.7, 78.9, 71.6, 71.3, 70.1, 69.5, 34.7, 30.0, 29.1, 24.4, 17.0.

HR-MS (ESI) *m/z* calcd for $C_{12}H_{22}O_5$ $(M+Na)^+$: 269.1359, found 269.1364.



9b

Triol 9b: One half of the crude *cis*-alkene **25** prepared in the procedure above was dissolved in THF (100 μL). In a separate vial, AD mix β (70 mg) was dissolved in a mixture of *t*BuOH (250 μL) and H_2O (250 μL). This solution was cooled to 4 °C and stirred 15 min. The solution of

crude **25** was then added, and the resulting orange solution stirred vigorously at 4 °C for 18 h, at which point it was diluted with H_2O and Et_2O. The aqueous layer was extracted three times with Et_2O, and the combined organics were concentrated *in vacuo* without drying to provide the crude diol (R_f = 0.54 (100% EtOAc)). ^{1}H NMR analysis at this point indicated a 55:45 mixture of diastereomers, with the configuration of the major diastereomer assumed, based on Sharpless's rules for induction in asymmetric dihydroxylation.[S2] This crude mixture was carried into desilylation without further purification.

To a solution this crude silyl ether in THF (300 μL) was added TBAF (1 M in THF, 13 μL, 0.013 mmol). The reaction solution was stirred at room temperature for 16 h., then applied directly to a pad of SiO_2. The column was run with a gradient of solvents from 5% to 15% MeOH in EtOAc, providing cleanly triol **9b** as the major product (0.9 mg, 0.0037 mmol, 6% over 4 steps, R_f = 0.32 (10% MeOH in EtOAc)) as well as some of the diastereomeric triol **9a** (R_f = 0.24 (10% MeOH in EtOAc)).

$[\alpha]^{22}_D$ = -13.2 (*c* = 0.040, EtOAc)

IR (thin film, NaCl) 3377, 2924, 2855, 1996, 1604, 1378, 1123, 1063 cm^{-1}.

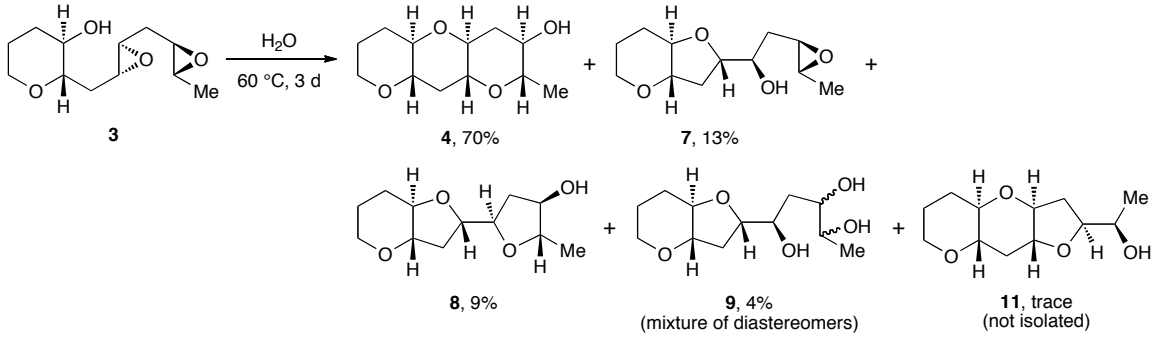
^{1}H NMR (500 MHz, D_2O) δ 4.12 (ddd, *J* = 9.3, 6.5, 4.5 Hz, 1H), 4.01-3.94 (m, 2H), 3.77-3.67 (m, 2H), 3.52 (app td, *J* = 12.1, 2.5 Hz, 1H), 3.39-3.29 (m, 2H), 2.23 (app dt, *J* = 11.2, 6.3 Hz, 1H), 2.17-2.11 (m, 1H), 1.84 (app q, *J* = 10.3 Hz, 1H), 1.79-1.70 (m, 2H), 1.60 (app qt, *J* = 13.1, 4.6 Hz, 1H), 1.54-1.44 (m, 2H), 1.11 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (125 MHz, D_2O) δ 80.9, 80.0, 78.9, 73.7, 71.8, 70.6, 69.5, 35.2, 29.8, 29.1, 24.4, 17.0.

HR-MS (ESI) *m/z* calcd for $C_{12}H_{22}O_5$ $(M+Na)^+$: 269.1359, found 269.1369.

Experimental Procedures for Cyclizations and Cascade Reactions in Batch:

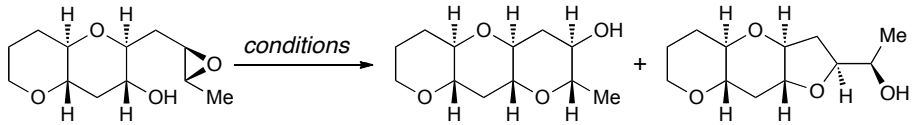
Cascade reaction of THP-templated diepoxy alcohol **3** promoted by neutral water:



Diepoxy alcohol **3** (20:1 d.r., 24.7 mg, 0.108 mmol) was dissolved in deionized water (5.4 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 °C under air for 3 d. The solution was then cooled to room temperature and concentrated *in vacuo* (2 torr, 40 °C). The crude product mixture was purified by column chromatography using a gradient of solvents (50% EtOAc in hexanes to 100% EtOAc in 10% MeOH in EtOAc) to separate THP triad **4** (17.2 mg, 0.075 mmol, 70%, R_f = 0.51 (EtOAc)), a white crystalline solid, from 6,5-fused epoxy alcohol **7** (3.3 mg, 13%, R_f = 0.44 (EtOAc)), THF side product **8** (2.1 mg, 0.009 mmol, 9%, R_f = 0.28 (EtOAc)), and two diastereomeric hydrolysis products **9a** and **9b** (1.0 mg of an approximately 2:1 mixture of **9a**:**9b**, 0.004 mmol, 4%, R_f of **9a** = 0.24 (10% MeOH in EtOAc) and R_f of **9b** = 0.32 (10% MeOH in EtOAc)). The configurations of **9a** and **9b** could not be determined by NMR spectroscopy. However, we prepared **9a** and **9b** independently via asymmetric dihydroxylation (*vide supra*). Following Sharpless's rules of asymmetric induction in asymmetric dihydroxylation,[S2] we were able to assign the configurations of **9a** and **9b**.

The ratio of **4**:**11**:**8** in the crude cascade product mixture could be determined by gas chromatography (GC). To the crude mixture was added EtOAc, and the slurry of solid buffer residue was sonicated in an ultrasound bath. The organic solution was then filtered through a PTFE syringe filter. The sample was injected into an Agilent 7890A GC-FID equipped with an Agilent HP-5 column (30 m x 0.32 mm, 0.25 μm) using the following program: 2 mL/min. flow rate, initial T = 35 °C hold for 5 min., then heat 20 °C/min. to 250 °C, then hold 5 min. at 250 °C. t_R(**4**) = 14.08 min., t_R(**11**) = 14.16 min., t_R(8) = 14.19 min. From reactions in D_2O at pD 7.0 at 70 °C (0.1 M KP_i buffer, 2-4 d. reaction time), the ratio of **4**:**11** was found to be 15.5:1 (average of 3 experiments).

Cyclization reactions of THP diad-templated epoxy alcohol **10**:



Conditions and results:

entry	promoter/ solvent	T (°C)	time	regioselectivity (**4**:**11**) [a]
1	Cs_2CO_3/MeOH [b]	rt	18 h	0.64:1
2	CSA/CH_2Cl_2 [c]	rt	18 h	1.4:1
3	BF_3•OEt_2/CH_2Cl_2 [d]	-78 to rt	30 min	1.5:1
4	H_2O [e]	rt	19 d	>20:1
5	D_2O [f] (pD 7, 0.1 M KP*i*)	70	24 h	19:1

[a] Regioselectivity determined by ^{1}H NMR spectroscopy. Results are the average of at least 2 experiments.
[b] Cs_2CO_3 (30 equiv), 0.02 M. [c] (±)-CSA (1 equiv), 0.02 M. [d] BF_3·OEt_2 (0.25 equiv), 0.02 M.
[e] Deionized water, 0.02 M. [f] D_2O buffered to pD 7.0 with 0.1 M K_2HPO_4/KH_2PO_4.

Reaction of 10 promoted by Cs_2CO_3/MeOH: To a sample of epoxy alcohol **10** (0.6 mg, 0.0024 mmol) in a 2 mL vial was added a 0.60 M aqueous solution of Cs_2CO_3 in MeOH (120 μL, 0.072 mmol, prepared by dissolving 235 mg Cs_2CO_3 to 1.2 mL volume in anhydrous methanol). The resulting clear, colorless solution was stirred under air at room temperature for 18 h, at which point it was quenched with the addition of sat. $NH_4Cl_{(aq)}$ (~200 μL). The reaction solution was concentrated *in vacuo* (40 °C, 2 torr) without drying to afford a solid residue. To the crude product mixture was added $CDCl_3$ (700 μL), and the resulting slurry was placed in an ultrasound bath for 5 min. The chloroform solution was then analyzed by ^{1}H NMR to determine **4**:**11**.

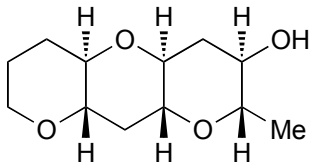
Reaction of 10 promoted by CSA in CH_2Cl_2: To a sample of epoxy alcohol **10** (0.6 mg, 0.0024 mmol) in a 2 mL vial was added CH_2Cl_2 (125 μL). To this was added (+/-)-CSA (0.6 mg, 0.0024 mmol), and the resulting clear, colorless solution was stirred under air at room temperature for 18 h. The reaction was then quenched with sat. $NaHCO_{3(aq)}$ (2 drops). The reaction solution was concentrated *in vacuo* (40 °C, 2 torr) without drying to afford a trace of residue, which was taken up into $CDCl_3$ (700 μL) and analyzed by ^{1}H NMR to determine **4**:**11**.

Reaction of 10 promoted by BF_3 in CH_2Cl_2: A solution of epoxy alcohol **10** (0.6 mg, 0.0024 mmol) in CH_2Cl_2 (110 μL) in a dried 5 mL round bottom flask was cooled to -78 °C. To this was added a 0.05 M solution of BF_3•OEt_2 (12 μL, 0.0006 mmol, prepared from the dissolution of 71 mg of BF_3•OEt_2 in 10 mL CH_2Cl_2), and the reaction was stirred at -78 °C for 30 min. The dry ice bath was removed, and the reaction was allowed to warm for 1 min., at which point it was quenched with sat. $NaHCO_{3(aq)}$ (2 drops). The reaction solution was concentrated *in vacuo* (40 °C, 2 torr) without drying to afford a trace of residue, which was taken up into $CDCl_3$ (700 μL) and analyzed by ^{1}H NMR to determine **4**:**11**.

Representative procedure for the reaction of 10 in aqueous media: Epoxy alcohol **10** (0.9 mg, 0.0040 mmol, >20:1 dr) was dissolved either in deionized water (200 μL) or 0.1 M solution of potassium phosphate buffer in deionized water (200 μL) and stirred at room temperature under air for 13-19 d. The reaction solutions were concentrated *in vacuo* (40 °C, 2 torr) without drying. The crude product mixture was analyzed by ^{1}H NMR to determine the ratio of **4:11**. For reactions of **10** in deionized water at room temperature, **4**:**11** was found to be 22:1 (average of 2 experiments).

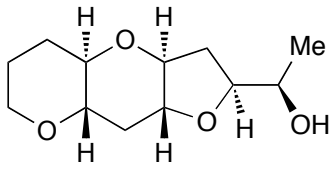
Dependence of Regioselectivity on pH in Reactions of **10**		
entry	pH (0.1 M KP_i buffer)	*endo*:*exo* selectivity (**4:11**)
1	2.0	2.6:1
2	2.0	3.1:1
3	3.0	2.8:1
4	4.0	6.2:1
5	4.0	5.0:1
6	5.0	13:1
7	6.0	20:1
8	6.0	28:1
9	7.0	28:1
10	7.0	24:1
11	8.0	15:1
12	8.0	17:1
13	9.0	6.3:1
14	10.0	3.2:1
15	10.0	2.9:1
16	11.0	1.1:1
17	12.0	1.0:1
18	12.0	1.0:1

Protocol for the separation of 4 and 11: The crude product mixture of **4** and **11** can be separated by column chromatography (load crude mixture as solution in CH_2Cl_2, pack column in 50% EtOAc in hexanes, run 50% EtOAc in hexanes) to afford analytically pure samples of **4** (R_f = 0.51 (100% EtOAc) and **11** (R_f = 0.42 (100% EtOAc)).



4

THP triad 4: This compound has already been characterized.[S1,S9]



11

6,6,5-fused triad 11: R_f = 0.42 (EtOAc)

$[\alpha]^{22}_{D}$ = -9.4 (*c* = 0.18, CH_2Cl_2)

IR (thin film, NaCl) 3430, 2924, 2852, 1739, 1462, 1341, 1068, 1025 cm^{-1}.

^{1}H NMR (500 MHz, D_2O (referenced H_2O peak at 4.79 ppm) δ 4.15 (dddd, *J* = 10.5, 6.4, 4.6, 0.7 Hz, 1H), 3.99-3.90 (m, 2H), 3.59 (ddd, *J* = 10.7, 9.6, 6.5 Hz, 1H), 3.48-3.41 (m, 2H), 3.35 (ddd, *J* = 10.9, 9.4, 3.9 Hz, 1H), 3.22 (ddd, *J* = 11.4, 10.1, 4.5 Hz, 1H), 2.43 (app dt, *J* = 10.3, 4.1 Hz, 1H), 2.24 (dt, *J* = 11.1, 6.5 Hz, 1H), 2.11-2.04 (m, 1H), 1.86-1.65 (m, 3H), 1.56-1.46 (m, 2H), 1.12 (dd, *J* = 6.5, 0.7 Hz, 3H).

^{13}C NMR (125 MHz, D_2O (referenced to MeOH (1 μL) added to sample, at 49.50 ppm) δ 82.8, 80.9, 79.7, 69.6, 69.0, 35.0, 29.3, 29.1, 25.3, 17.8.

`HR-MS (DART) *m/z* calcd for $C_{12}H_{20}O_4$ $(M+H)^+$: 229.1434, found 229.1425.

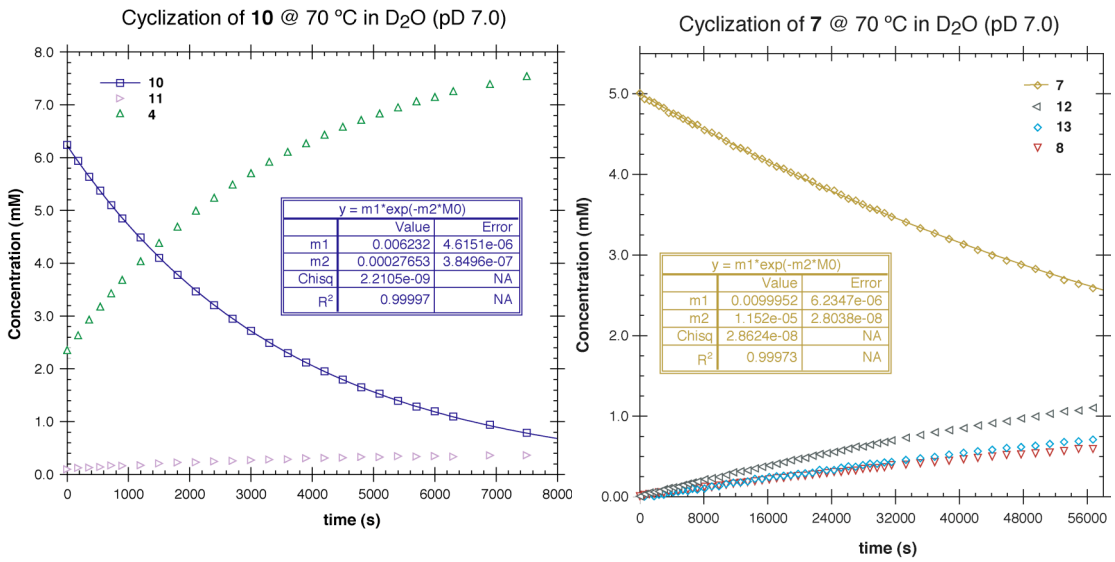
III. Kinetic Procedures, Data, and Analysis

General experimental considerations. Kinetic measurements were made using ^{1}H NMR spectroscopy on a Varian Inova 500 MHz spectrometer equipped with an inverse broadband gradient probe (gHX) thermostated at 70 ºC. The temperature of the spectrometer was calibrated using an ethylene glycol external standard. Unless otherwise stated, kinetic data was obtained in triplicate to three half lives in deuterated 0.1 M potassium phosphate buffer (pD 7.0). The rate constants determined from regression analysis or from computer simulation are reported in Scheme 2 and Tables S1-S3 as an average of the three experiments with the average error reported in parenthesis. Buffers were prepared at room temperature, and their pD was adjusted to 7.0 using 0.1 M solutions of K_2DPO_4 or KD_2PO_4 at the reaction temperature using a Symphony™ Posi-pHlo Ag/AgCl pH glass electrode. The pH electrode was calibrated at the reaction temperature with standard pH solutions. A correction factor was applied to all measurement to account for the solvent isotope effect inherent to the glass electrode (pD = measured pH + 0.4).[S10] All chemical shifts are reported in ppm and are referenced against the HDO peak (4.310 ppm at 70 °C).[S8]

General experimental procedure. The substrate (0.7-1.5 mg) was dissolved in pD 7.0 buffer (0.7 mL) containing a small amount of DMSO (2.0 μL, 2.2 mg, 28 μmol) as an internal standard. The mixture was stirred briefly, then filtered through a PTFE syringe filter into a J. Young tube. The J. Young tube was filled from the bottom, taking care not to scratch the tube. Samples in scratched tubes appear prone to undergoing degassing upon heating, which is severely detrimental to the NMR signal. To further prevent degassing, the J. Young tube was pressurized with argon (2-5 atm). The NMR tube was injected into the thermostated spectrometer and allowed to warm to 70 ºC. After three minutes, the spectrometer was shimmed and kinetic data was obtained using the array function on the pre acquisition delay parameter (Varian). The concentrations of all species were determined by integration of the methyl resonances relative to the DMSO standard. The overlapping resonances for cyclizations of **3** were deconvoluted as described in the text. All measurements were made in triplicate using substrates in at least 20:1 d.r. (*vide supra*). The rate constants reported in Scheme 2 and Tables S1-S3 are reported as average values from these experiments. Error is reported as average error in the measurement.

Determination of rate constants from concentration vs. time data. Determination of rate constants for cyclizations of independently prepared monoepoxides **7** and **10** was straightforward from concentration vs. time data (see Figure S1 for representative examples). The raw data were fit to a two-parameter exponential function ($f(t)=ae^{-kt}$) using the "General Fit" function in the Kaleidagraph™ v. 3.6 software (based on the Levenberg-Marquardt algorithm[S11]). Elementary rate constants were determined from the observed rate constant and the selectivity of the reaction determined at the end of the reaction by NMR. Due to the very slow reaction of **7**, data was only collected for the first half-life and was repeated only once. These data appear in the text and in Table S3 for comparison with rate constants determined from diepoxide **3** by simulation of the concentration vs. time data (*vide infra*).

Figure S1. *Representative concentration vs. time plots and first order fits for cyclizations of* ***10*** *(left) and* ***7*** *(right) in D_2O (pD 7.0) at 70 ºC.*



Due to competing side reactions, determination of all rate constants for cyclizations of diepoxide **3** could not be achieved in a similar fashion as for the monoepoxides. However, most rate constants could be estimated from concentration vs. time data determined for species **3**, **4**, **10**, and **7** using the following procedure. The observed rate constant for the first step ($k_{obs}^{\mathbf{3}}$) could be obtained in a straightforward fashion by linear regression analysis from ln([**3**]) vs. time data. The second step kinetics was more complicated. The observed rate constant for the formation of **4** and **11** ($k_{obs}^{\mathbf{10}}$) could be determined either from concentration vs. time data of the intermediate (**10**) or the major product (**4**) using equations (S-1) or (S-2), which describe intermediate and product formation in a consecutive reaction mechanism, respectively [S12]:

$$[\mathbf{10}]_t = \frac{[\mathbf{3}]_0 * k_{obs}^{\mathbf{3}}}{k_{obs}^{\mathbf{10}} - k_{obs}^{\mathbf{3}}}\left[e^{-k_{obs}^{\mathbf{3}} * t} - e^{-k_{obs}^{\mathbf{10}} * t}\right] \qquad \text{(S-1)}$$

$$[\mathbf{4}]_t = [\mathbf{3}]_0 + \frac{[\mathbf{3}]_0}{k_{obs}^{\mathbf{3}} - k_{obs}^{\mathbf{10}}}\left[k_{obs}^{\mathbf{10}} * e^{-k_{obs}^{\mathbf{3}} * t} - k_{obs}^{\mathbf{3}} * e^{-k_{obs}^{\mathbf{10}} * t}\right] \qquad \text{(S-2)}$$

Equations S-1 and S-2 are valid only when [**10**] and [**4**] are negligible at t = 0. However, this approximation is inaccurate in our case, as the cascade reaction had invariably proceeded to a significant extent by the time we could begin collecting kinetics data. To ensure sufficiently good shims for the long reaction times, data collection could not be initiated until 30-60 minutes after the sample reached the reaction temperature. Therefore, to use equations x and y, the actual t = 0 was estimated from extrapolation of the ln([**3**]) to the total concentration of all species measured in solution, in accordance with the law of mass conservation. Substituting $k_{obs}^{\mathbf{3}}$ determined from ln([**3**]) vs. time data in equations x and y and adjusting the time for the calculated t = 0 allowed for $k_{obs}^{\mathbf{10}}$ to be determined from a two parameter fit to either equation using the "General Fit" function in the Kaleidagraph™ v. 3.6 software (based on the Levenberg-Marquardt algorithm). The $k_{obs}^{\mathbf{10}}$ that is reported in Table S2 is a composite average of the two rate constants determined from [**4**] and [**10**] vs. time data. The observed rate constants for the formation of **8** and **9** via

intermediate **7** (k_{obs}^{7}) could be estimated in a similar fashion using equation x and [**7**] vs. time data, but fits for the [**8**] vs. time data using equation y were poor. As discussed in the main text of the article, we believe that this is due to the competing direct pathway from **3** to **8** that is not accounted for by equation y. The elementary rate constants for all pathways were determined from the observed rate constants and the final concentration of species in solution as determined by NMR or by GC using equations (S-3)-(S-5):

$$\frac{k_6^{\mathbf{3}}}{k_5^{\mathbf{3}}} = \frac{[\mathbf{10}]+[\mathbf{11}]+[\mathbf{4}]}{[\mathbf{7}]+[\mathbf{8}]+[\mathbf{9}]} \tag{S-3}$$

$$\frac{k_6^{\mathbf{10}}}{k_5^{\mathbf{10}}} = \frac{[\mathbf{11}]}{[\mathbf{4}]} \tag{S-4}$$

$$\frac{k_5^{\mathbf{7}}}{k_{hydrolysis}^{\mathbf{7}}} = \frac{[\mathbf{8}]}{[\mathbf{9}]} \tag{S-5}$$

Representative data for the determination of $k_{obs}^{\mathbf{3}}$, $k_{obs}^{\mathbf{10}}$, and $k_{obs}^{\mathbf{7}}$ determined in this fashion appear in Figures S2, S3, and S4, and the average elementary rate constants appear in Table S2 for comparison with simulated data.

Figure S2. *Representative semilog plot and fit via regression analysis for species **3** in reaction of **3** in D_2O at 70 ºC.*

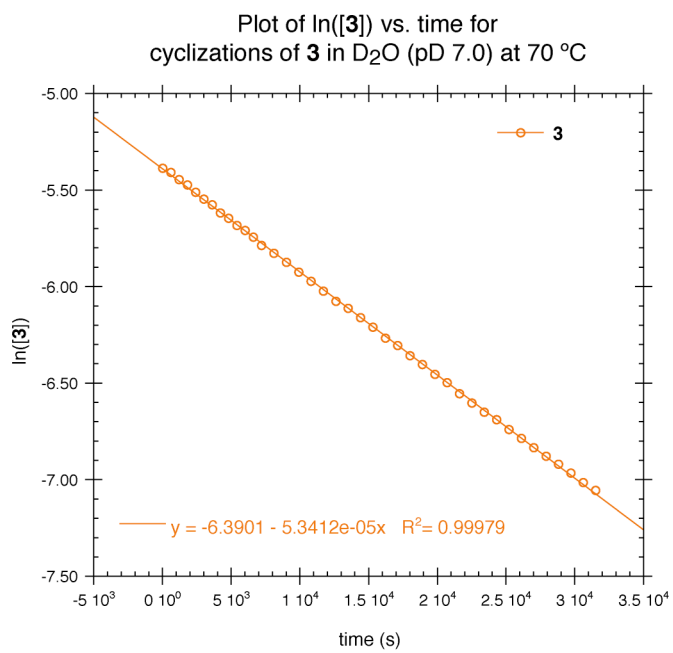


Figure S3. *Representative concentration vs. time data and fits via regression analysis for species* ***10*** *(left) and* ***4*** *(right) in cyclization of* ***3*** *in D_2O at 70 ºC.*

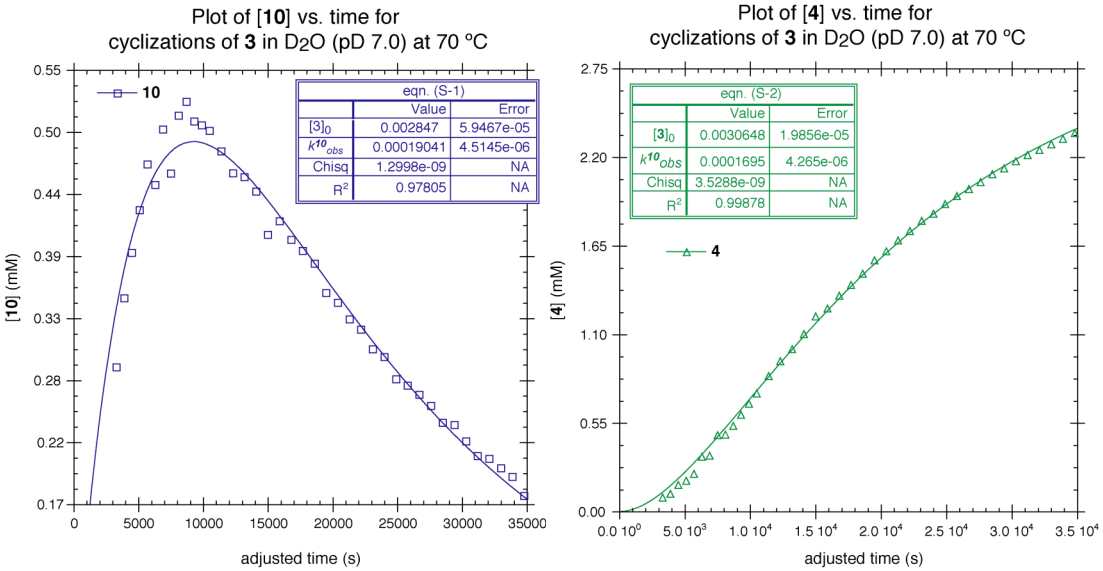
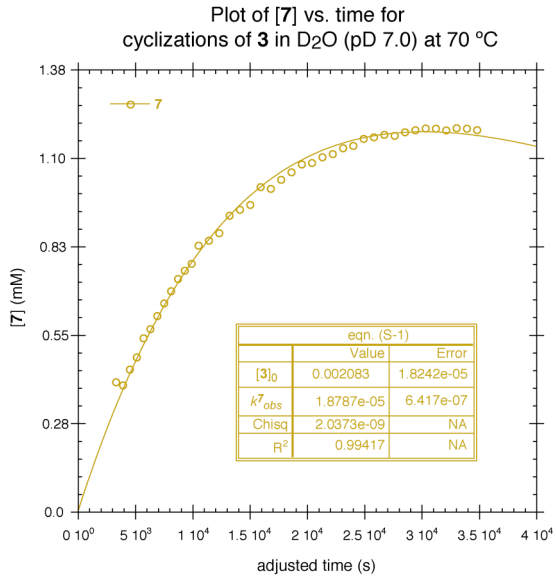


Figure S4. *Representative concentration vs. time data and fits via regression analysis for species* ***7*** *in cyclization of* ***3*** *in D_2O at 70 ºC.*



Determination of rate constants for cyclization of diepoxide 3 using computer simulation. Due to the complexity of the reaction, we reasoned that the best estimation of rate constants for the cyclization of diepoxide **3** would be obtained using the complex reaction simulation program COPASI.[S13] Rate constants for all steps could be determined from the concentration vs. time data for all species measured using the "Parameter Estimation" protocol assuming all reactions are irreversible. The method used for the simulation was the Levenberg-Marquardt method, with an iteration limit of 500 and a tolerance of $1x10^{-5}$. The initial concentration of all species was estimated using the first data point in the NMR data. The results from the simulations were the same regardless of whether each parameter was optimized individually or if all parameters were allowed to freely vary. To ensure that the estimated parameters were not local minima, each rate constant was randomly varied and the simulation was repeated. Simulations were also carried out

assuming that no direct pathway from **3** to **8** existed (i.e. without k_{55}^{3}), but the experimental data could not be satisfactorily simulated. Fits for [**8**] vs. time data were particularly poor when k_{55}^{3} was excluded (see Figure S5 and Table S1 for representative data and fits for a representative kinetics run).

Figure S5. *Representative simulations for cyclization of **3** in D_2O (pD 7.0) at 70 ºC including (left) and excluding (right) k^{3}_{55} in the simulation.*

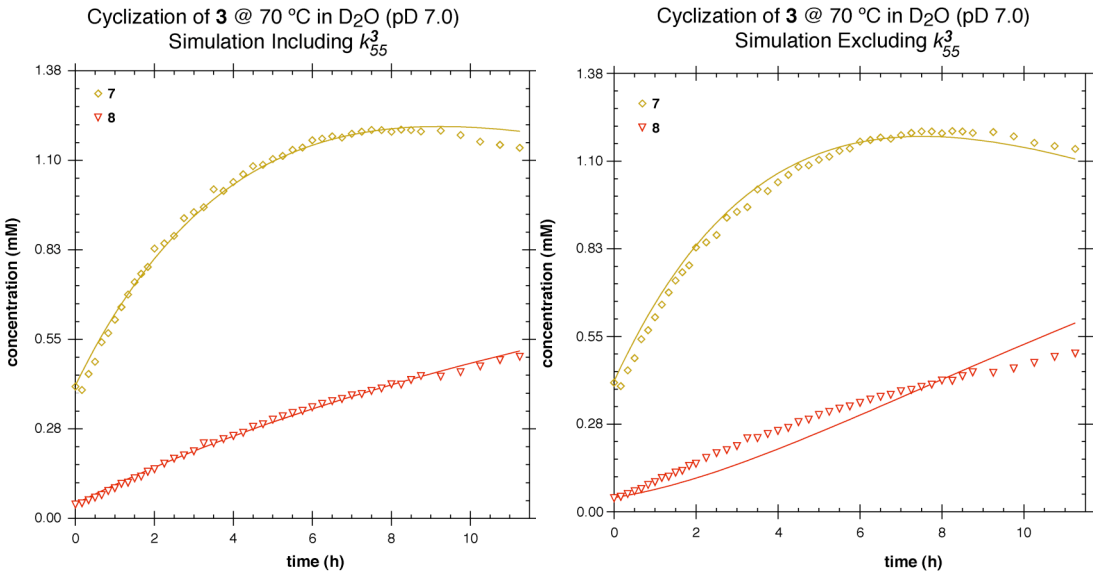


Table S1. *Comparison of simulations for cyclizations of* ***3*** *for simulations excluding and including* k^3_{55}.

		without k^3_{55}		with k^3_{55}	
		simulation	coeff. var.	simulation	coeff. var.
k^3	k_{obs}	5.31E-05	–	5.36E-05	–
	k_6/k_5	1.79	–	1.73	–
	k_6	3.26E-05	0.11	3.27E-05	0.05
	k_5	1.82E-05	0.40	1.57E-05	0.25
	k_{dir}	–	–	3.17E-06	1.22
	$k_{hydrolysis}$	2.30E-06	2.82	1.99E-06	1.66
k^{10}	k_{obs}	2.19E-04	–	2.19E-04	–
	k_6/k_5	15.1	–	15.1	–
	k_6	2.05E-04	0.27	2.05E-04	0.13
	k_5	1.36E-05	1.12	1.36E-05	0.54
k^7	k_{obs}	1.02E-05	–	1.02E-05	–
	$k_5/k_{hdyrolysis}$	3.50	–	1.17	–
	k_5	1.32E-05	0.45	5.49E-06	1.88
	$k_{hydrolysis}$	3.77E-06	7.43	4.68E-06	2.85
		objective	mean err.	objective	mean err.
species conc.	**3**	1.68E-10	5.56E-07	1.38E-10	-1.51E-07
	10	3.75E-10	-4.78E-07	3.78E-10	-5.77E-07
	7	4.56E-10	1.19E-06	2.79E-10	2.66E-07
	4	1.00E-10	6.18E-07	8.32E-11	3.86E-07
	11	6.62E-12	1.59E-07	5.51E-12	9.94E-08
	8	4.36E-09	-4.55E-06	1.29E-10	2.49E-07
	9+12	2.37E-10	-2.94E-07	2.25E-10	-7.18E-07
	expt.	5.70E-09	-3.98E-07	1.24E-09	-6.37E-08

Discussion of rate constants determined from simulation vs. regression analysis. Rate constants determined from the simulations including k^3_{55} appear in Table S2 for comparison with those determined from regression analysis. Rate constants determined from simulation agree reasonably well with those determined by regression analysis for the first step kinetics (k^3_x), with differences in elementary rate constants likely due to the inclusion of k^3_{55} and $k^3_{hydrolysis}$ in the simulation but not accounted for in the regression analysis. The data from the two methods agree less well for the "second step" kinetics (k^{10}_x and k^7_x), especially for k^7_x. Regression analysis consistently results in smaller k^{10}_{obs} and larger k^7_{obs} than what results from simulation. The discrepancies are likely due to the inclusion of the side reactions in the simulation and to the error associated with determining t = 0 for regression analysis (*vide supra*). Additionally, significant error in k^7_x is expected for both simulation and regression analysis, as this reaction had not sufficiently progressed during the data collection time frame. We therefore conclude that the rate constants determined from simulation and from regression analysis agree to first approximation.

Table S2. *Comparison of rate constants determined from regression analysis or by simulation for cyclizations of* ***3.***

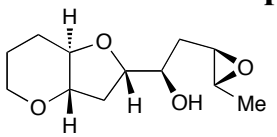
		regression analysis	avg. err.	simulated	avg. err.
k^3	k_{obs}	5.22E-05	1.93E-06	5.30E-05	1.45E-06
	k_6/k_5	1.59	0.03	1.97	0.15
	k_6	3.20E-05	1.37E-06	3.16E-05	1.22E-06
	k_5	2.02E-05	5.62E-07	1.61E-05	6.00E-07
	k_{55}	–	–	3.08E-06	2.51E-07
	$k_{hydrolysis}$	–	–	2.17E-06	5.80E-07
k^{10}	k_{obs}	1.83E-04	2.67E-06	2.33E-04	9.38E-06
	k_6/k_5	15.2	0.2	15.2	0.2
	k_6	1.71E-04	2.39E-06	2.18E-04	8.89E-06
	k_5	1.12E-05	2.73E-07	1.43E-05	6.44E-07
k^7	k_{obs}	1.92E-05	4.44E-07	1.04E-05	9.09E-07
	$k_5/k_{hydrolysis}$	1.35	0.04	1.50	0.12
	k_5	1.10E-05	2.97E-07	6.18E-06	3.22E-07
	$k_{hydrolysis}$	8.20E-06	1.88E-07	4.18E-06	5.87E-07

Comparison of rate constants from simulation with those obtained for monoepoxides. The "second step" rate constants (k_x^{10} and k_x^7) determined from simulation of data from cyclizations of **3** agree with rate constants determined from independent cyclizations of **7** and **10**. Observed and elementary rate constants determined for cyclization from isolated **10** are within experimental error as compared to those determined from simulation of diepoxide **3**. Although k_{obs}^7 determined for cyclization of isolated **7** are comparable to the equivalent rate constant determined from cyclization of diepoxide **3**, the elementary rate constants are different. This discrepancy is likely due to the overlapping resonances of **9** and **12** in spectra of the reaction of **3**, which results in significant error in determining the relative contributions of $k_{hydrolysis}^3$ and $k_{hydrolysis}^7$. Considering this complication, we consider the data obtained from the monoepoxides **7** and **10** to be in agreement with those obtained from diepoxide **3**.

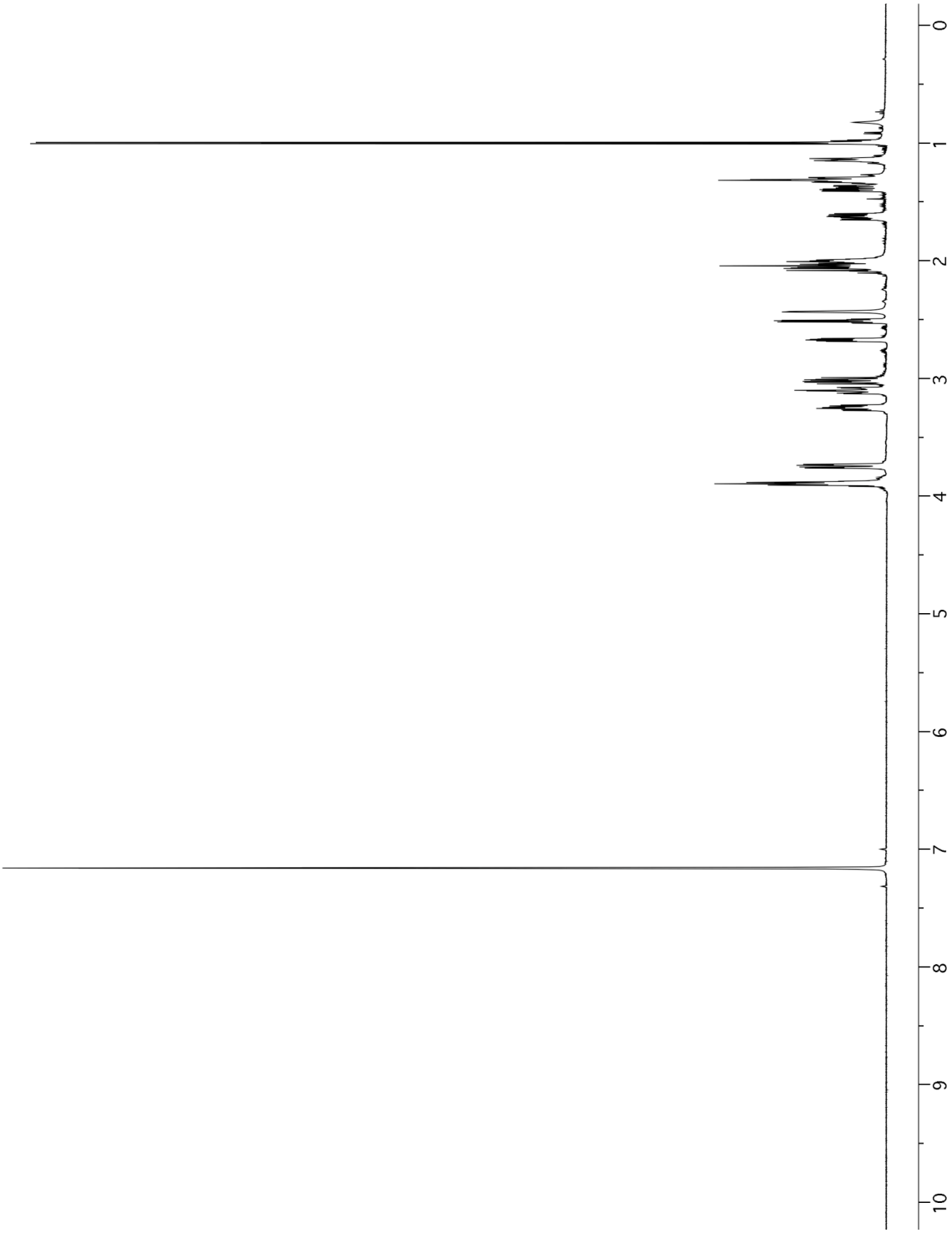
Table S3. *Comparison of rate constants determined from cyclizations of diepoxide **3** and monoepoxides **7** and **10.***

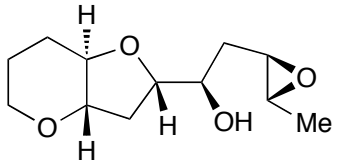
		avg. from **3**		avg. from **10** and **7**	
		k (s^{-1})	error	k (s^{-1})	error
k^{10}	k_{obs}	2.33E-04	9.38E-06	2.67E-04	2.62E-05
	k_6/k_5	15.2	0.2	18.5	1.3
	k_6	2.18E-04	8.89E-06	2.54E-05	2.58E-05
	k_5	1.43E-05	6.44E-07	1.36E-05	4.63E-07
k^7	k_{obs}	1.04E-05	9.09E-07	1.15E-05	1.00E-07
	$k_5/k_{hydrolysis}$	1.50	0.12	0.56	0.01
	k_5	6.18E-06	3.22E-07	2.90E-06	8.37E-08
	$k_{hydrolysis}$	4.18E-06	5.87E-07	5.15E-06	1.17E-07

IV. ^{1}H and ^{13}C Spectra for Newly Synthesized Compounds

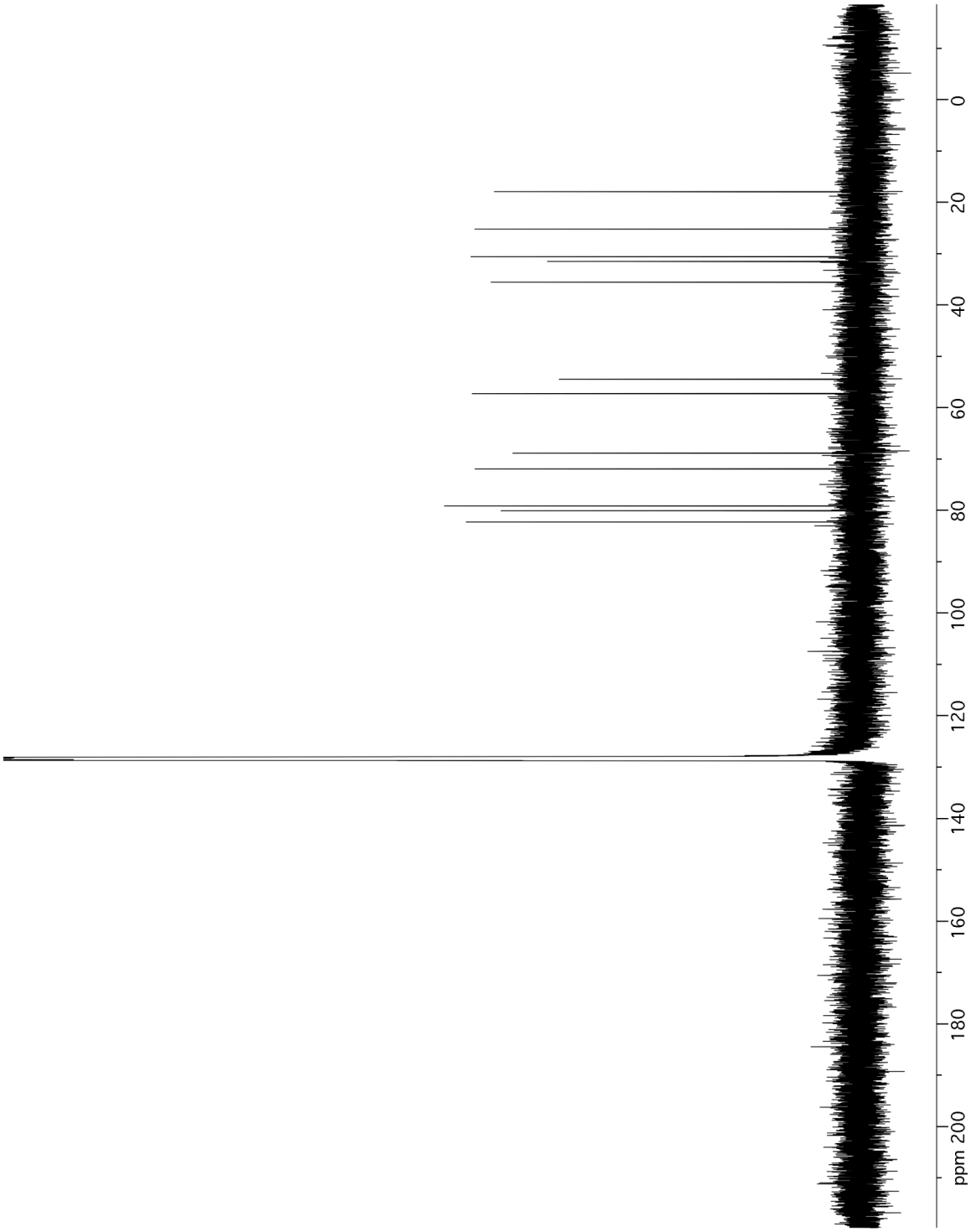


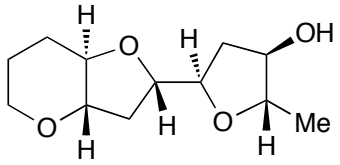
7



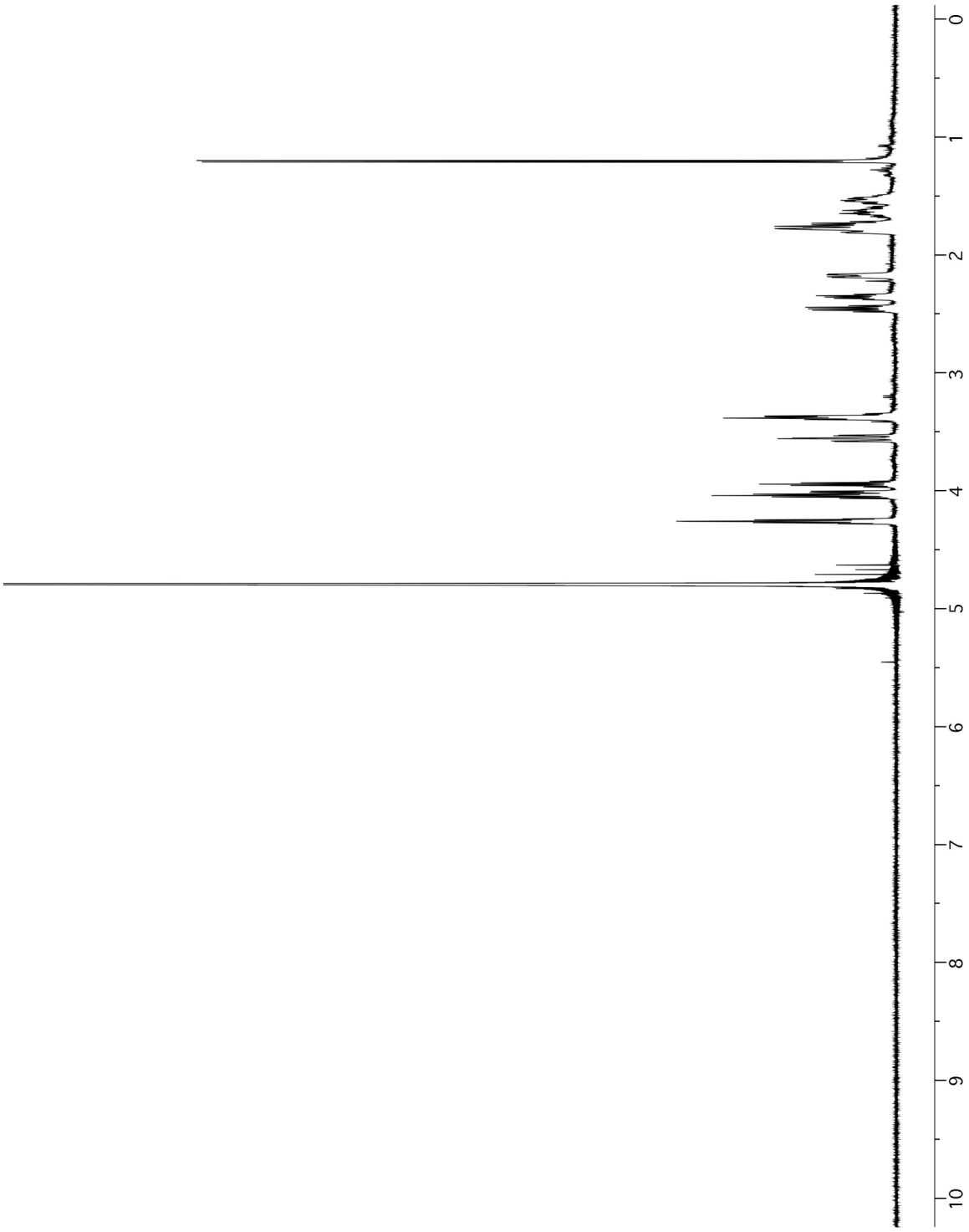


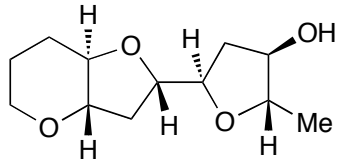
7



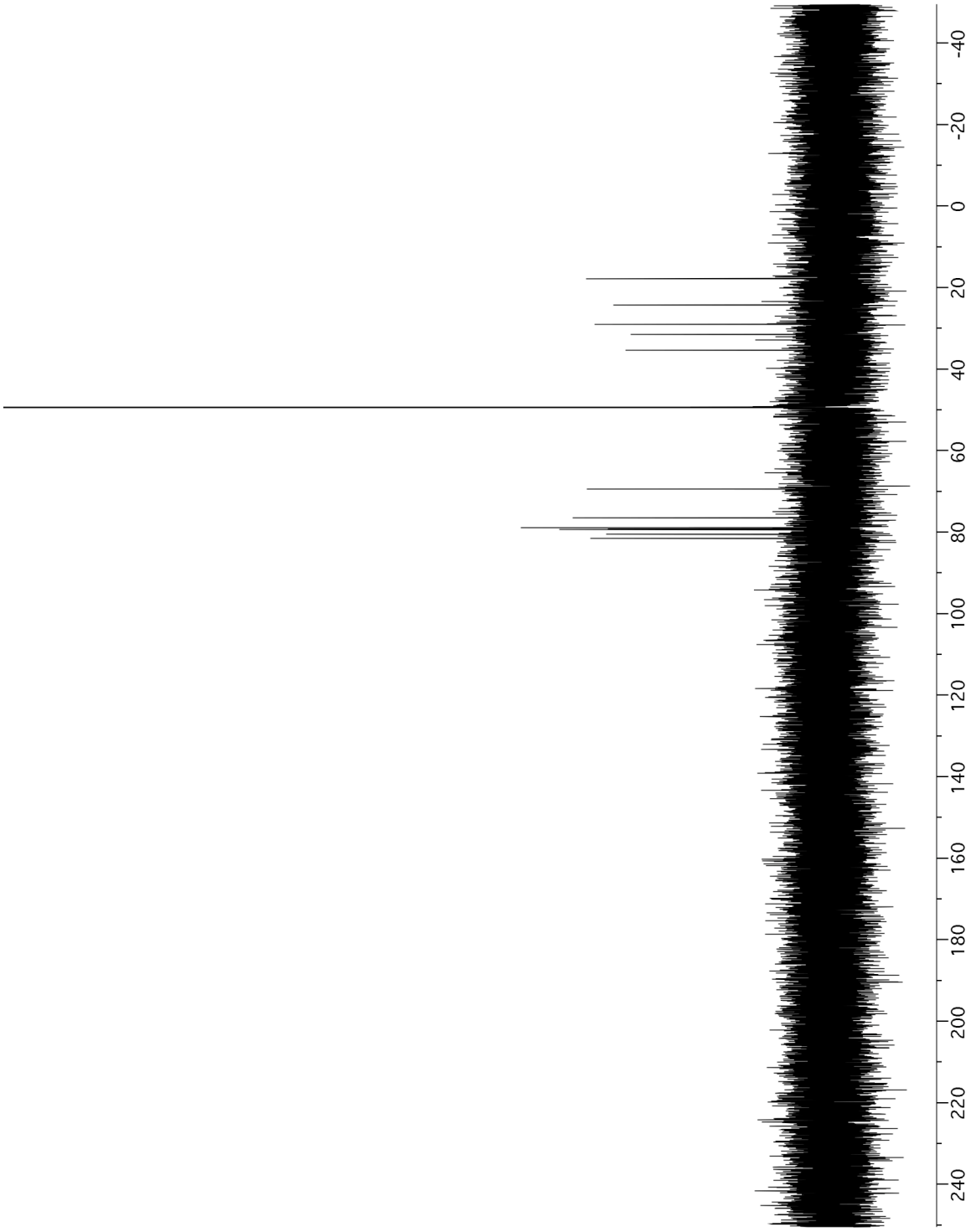


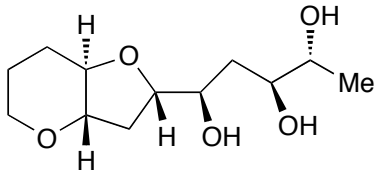
8



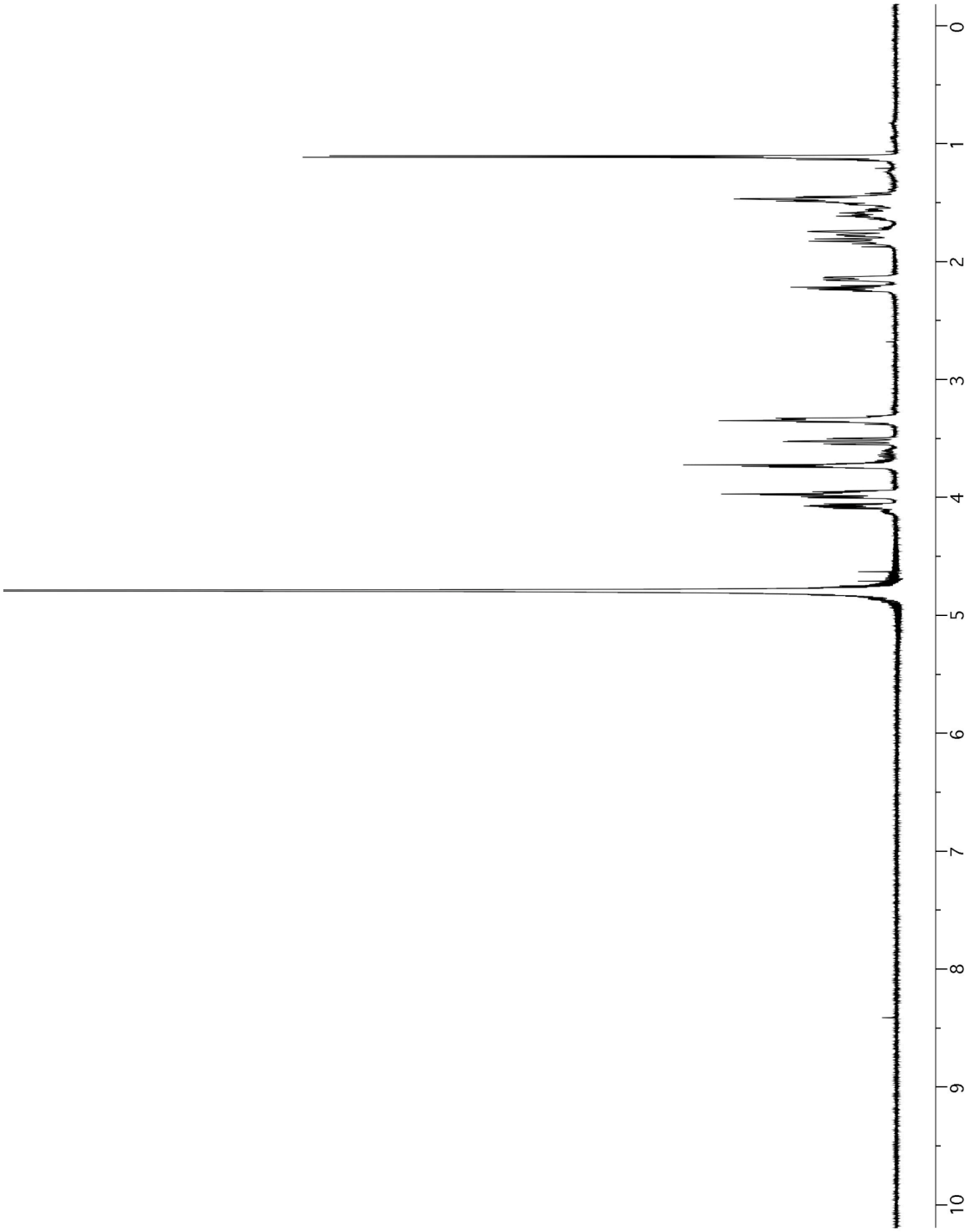


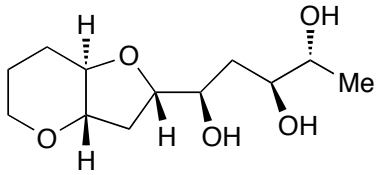
8



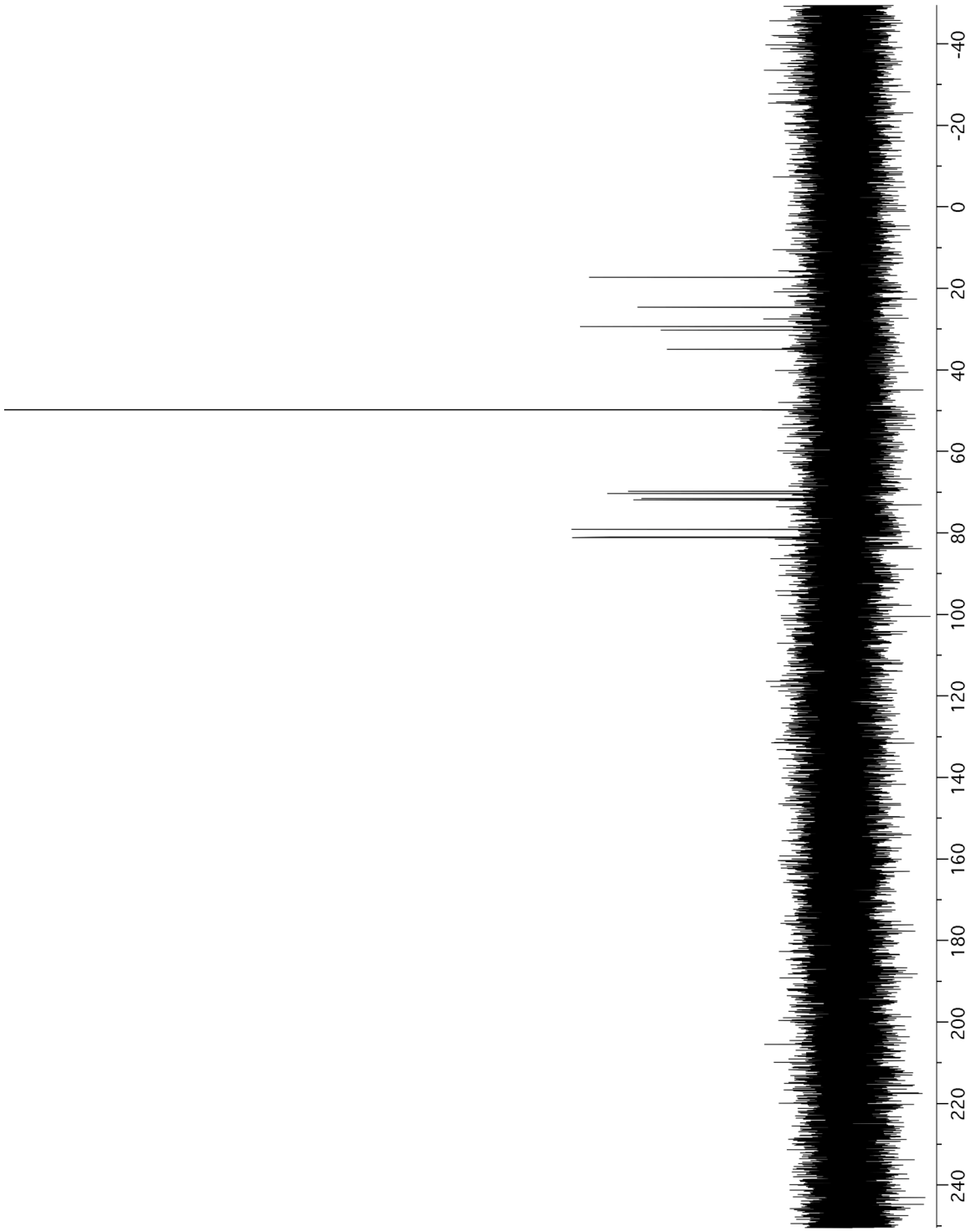


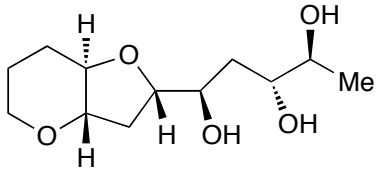
9a



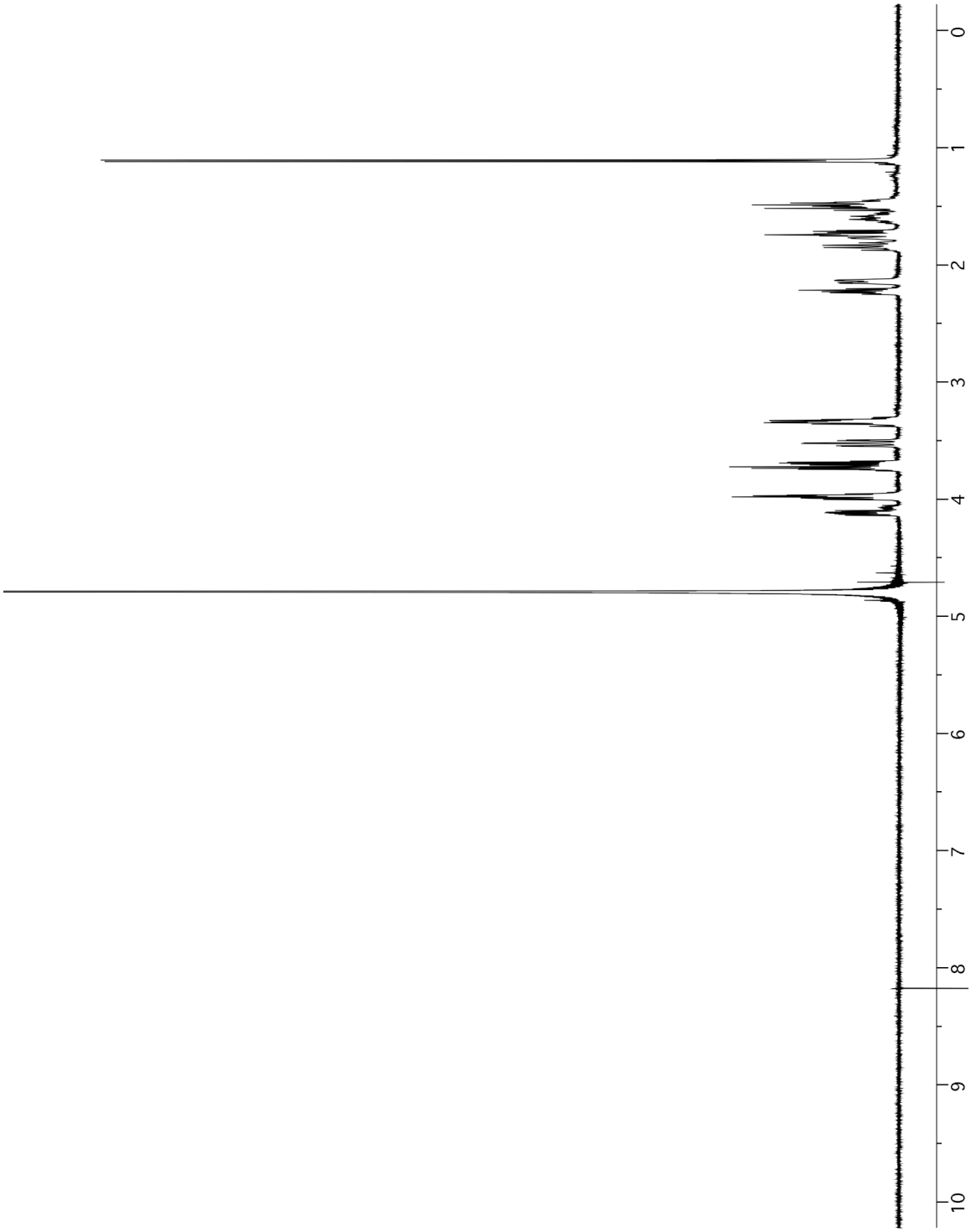

H
O
OH
Me
O
H
H
OH
OH

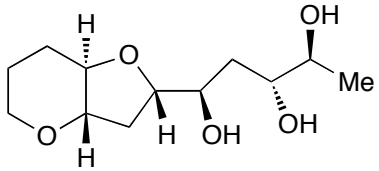
9a


-40
-20
0
20
40
60
80
100
120
140
160
180
200
220
240

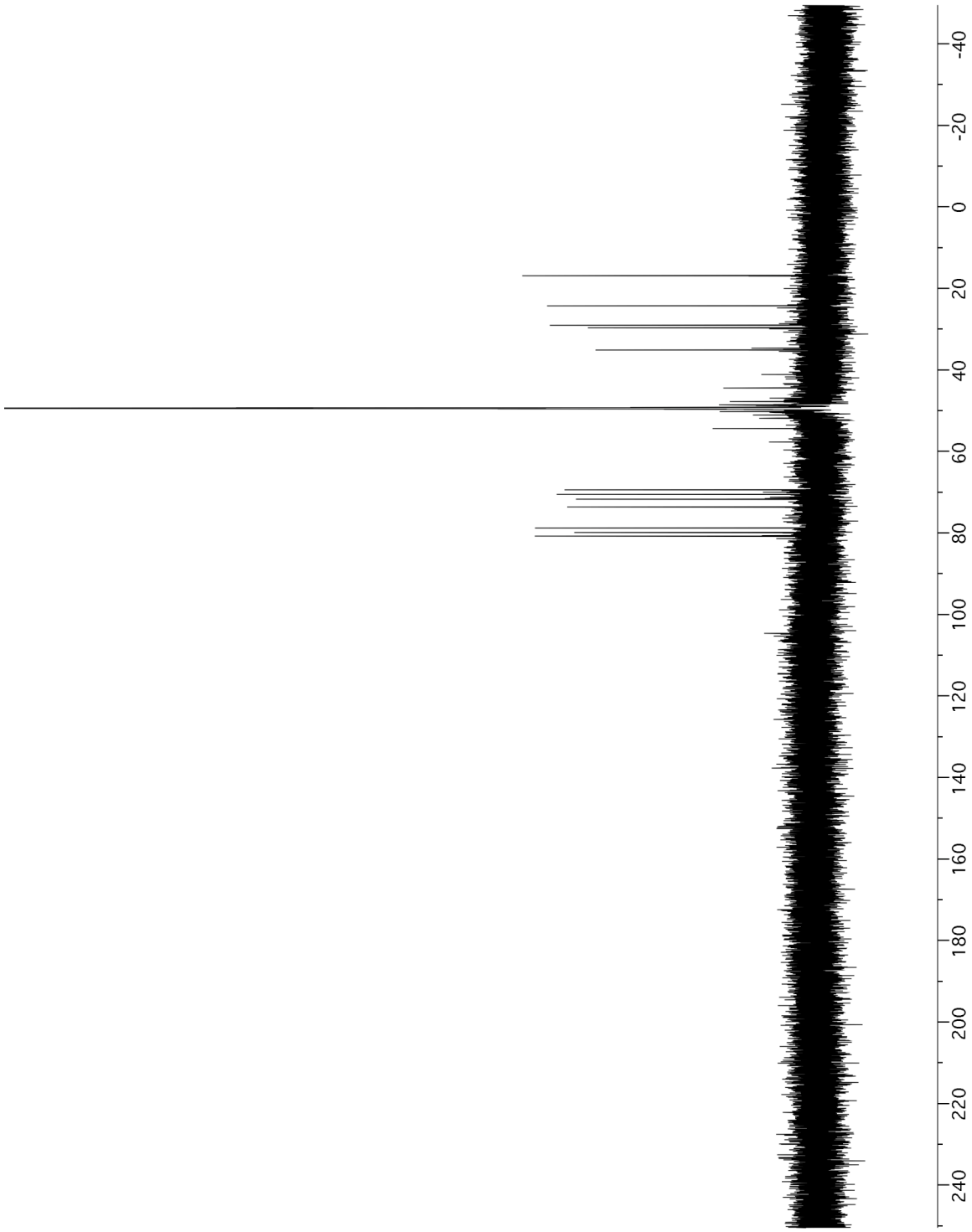


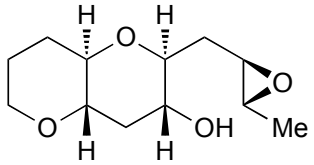
9b



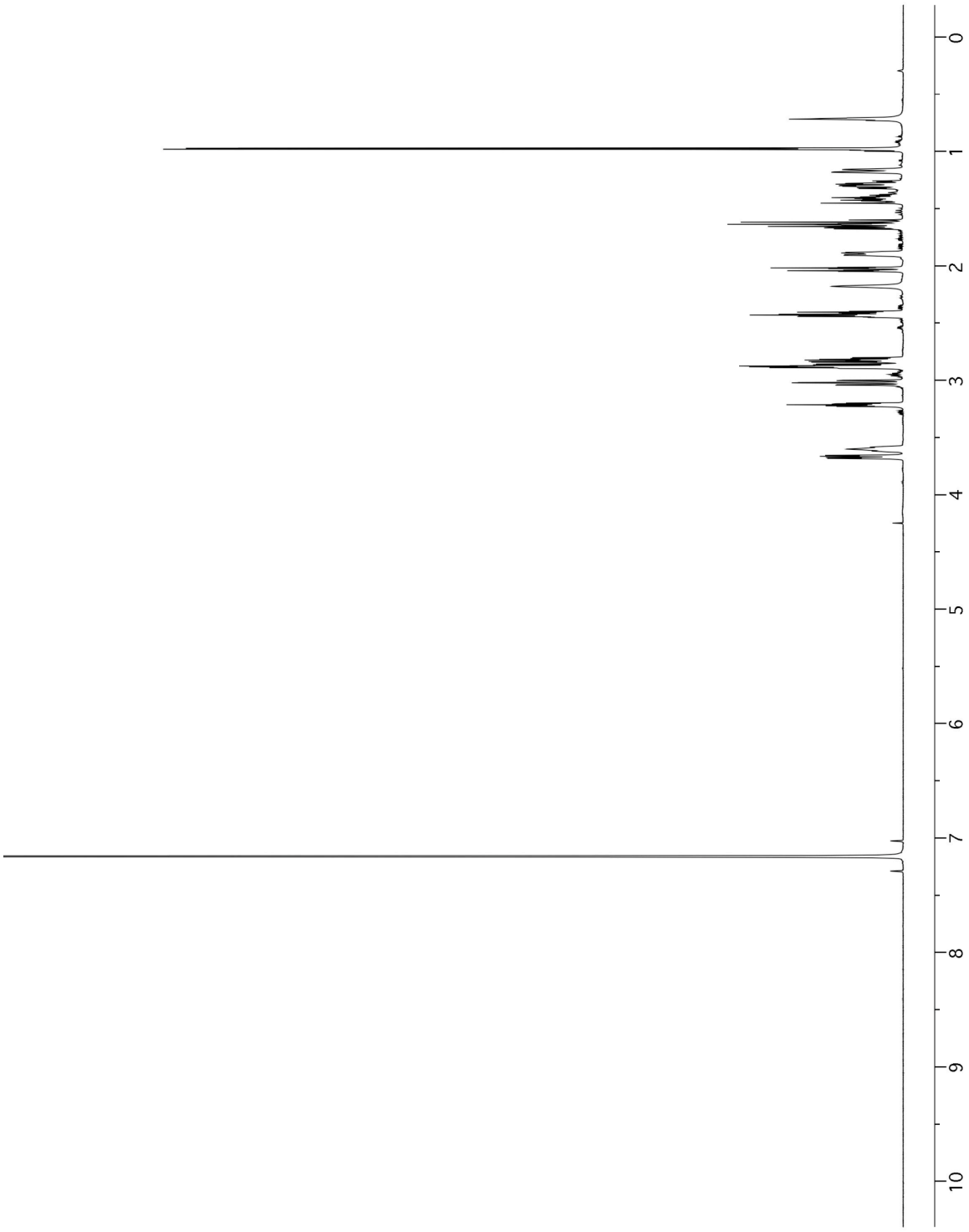

H
O
OH
Me
O
H
H
OH
OH

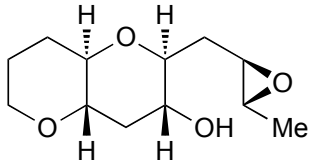
9b


-40
-20
0
20
40
60
80
100
120
140
160
180
200
220
240

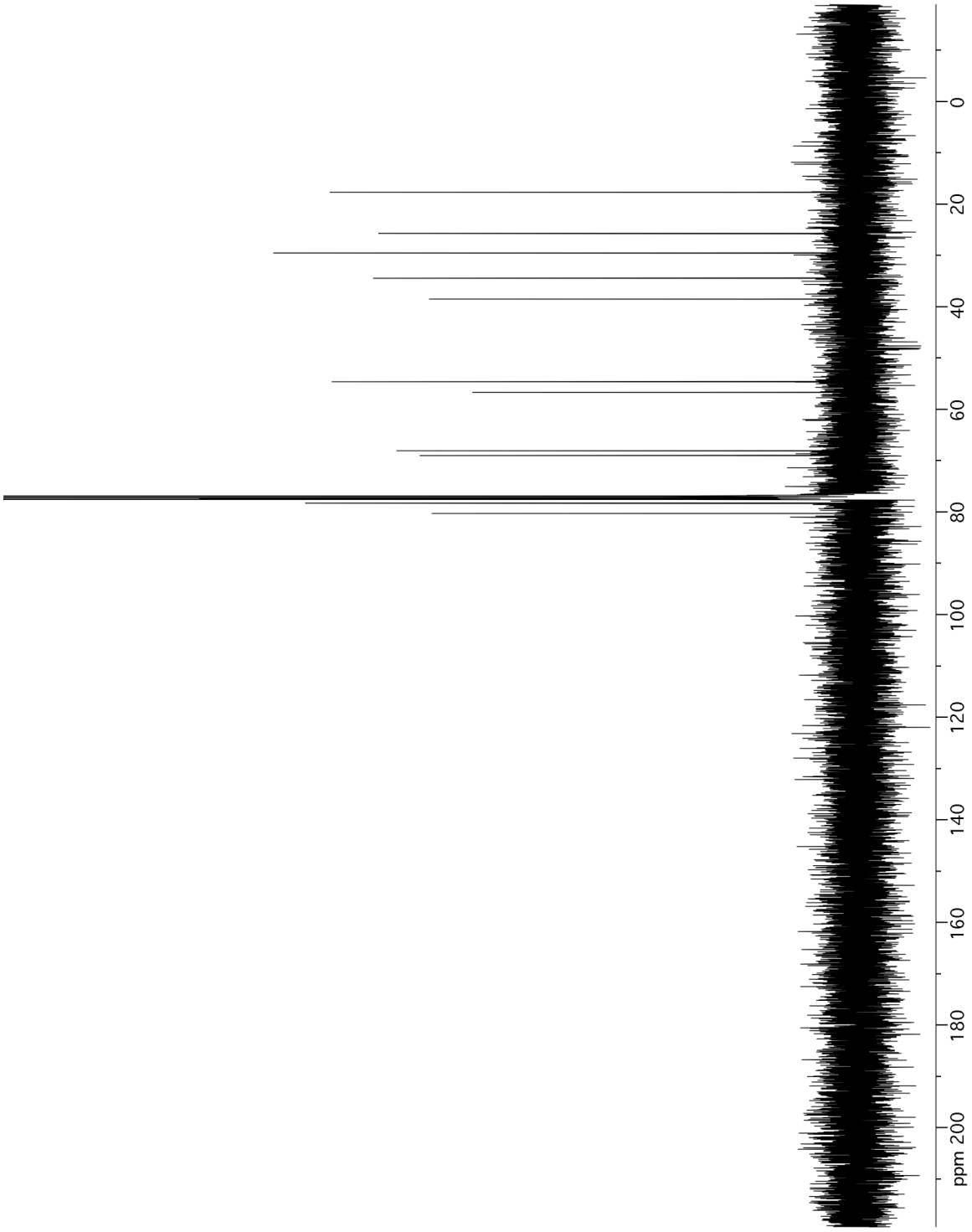


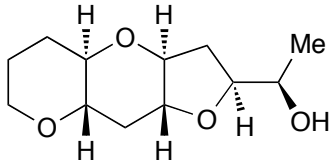
10



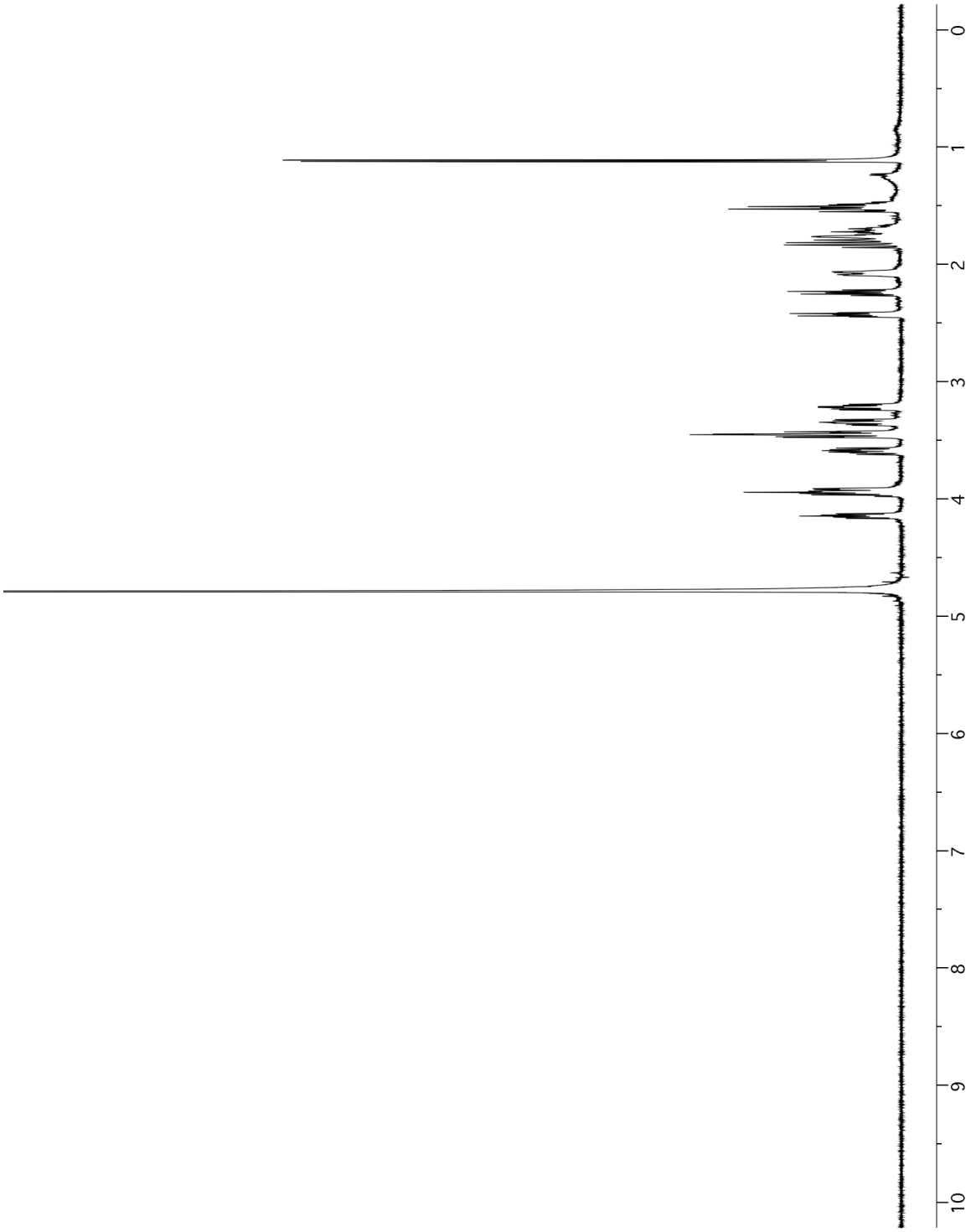


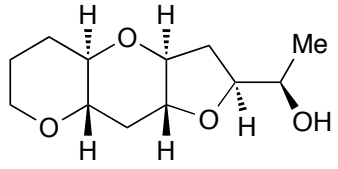
10



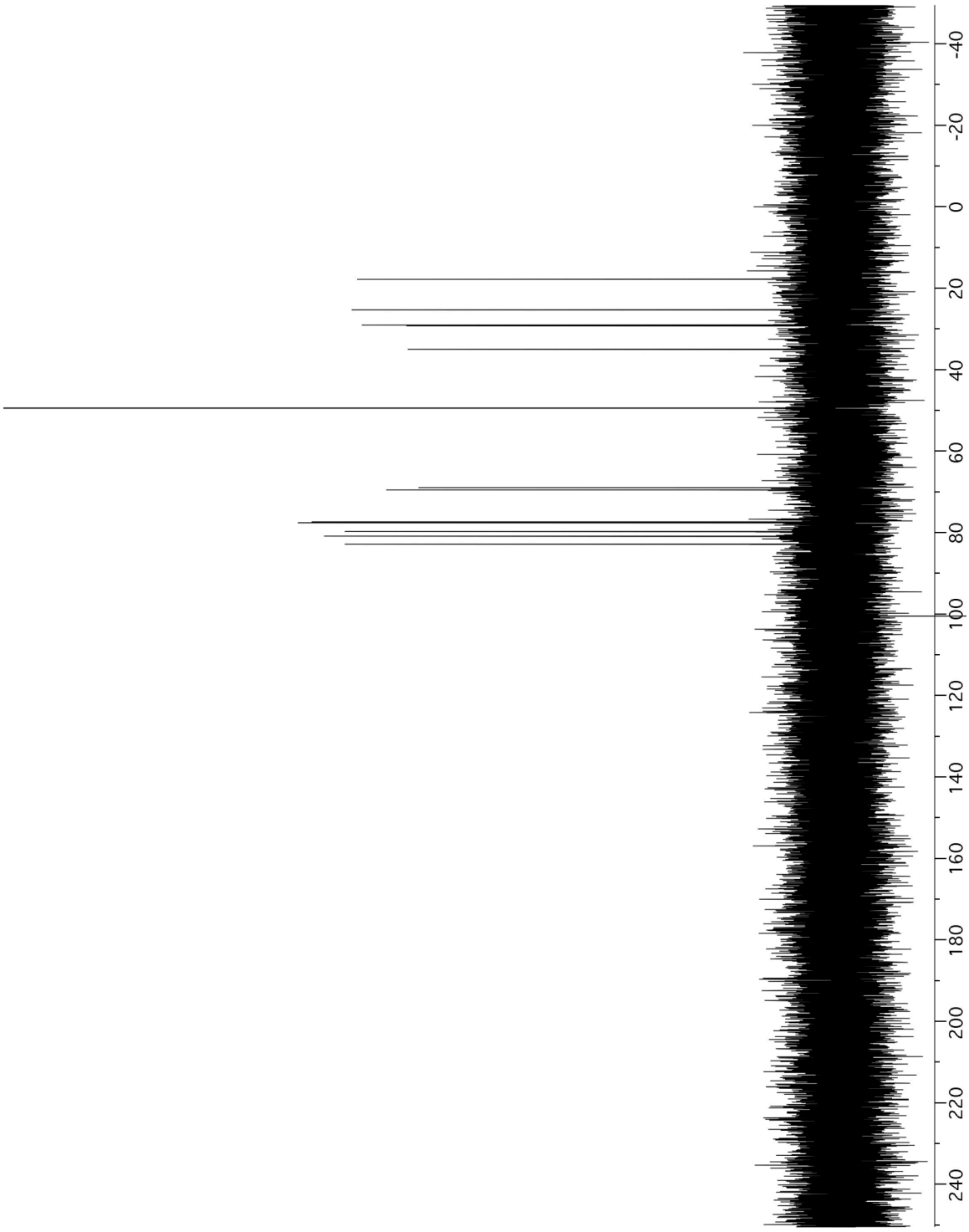


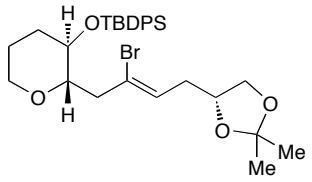
11



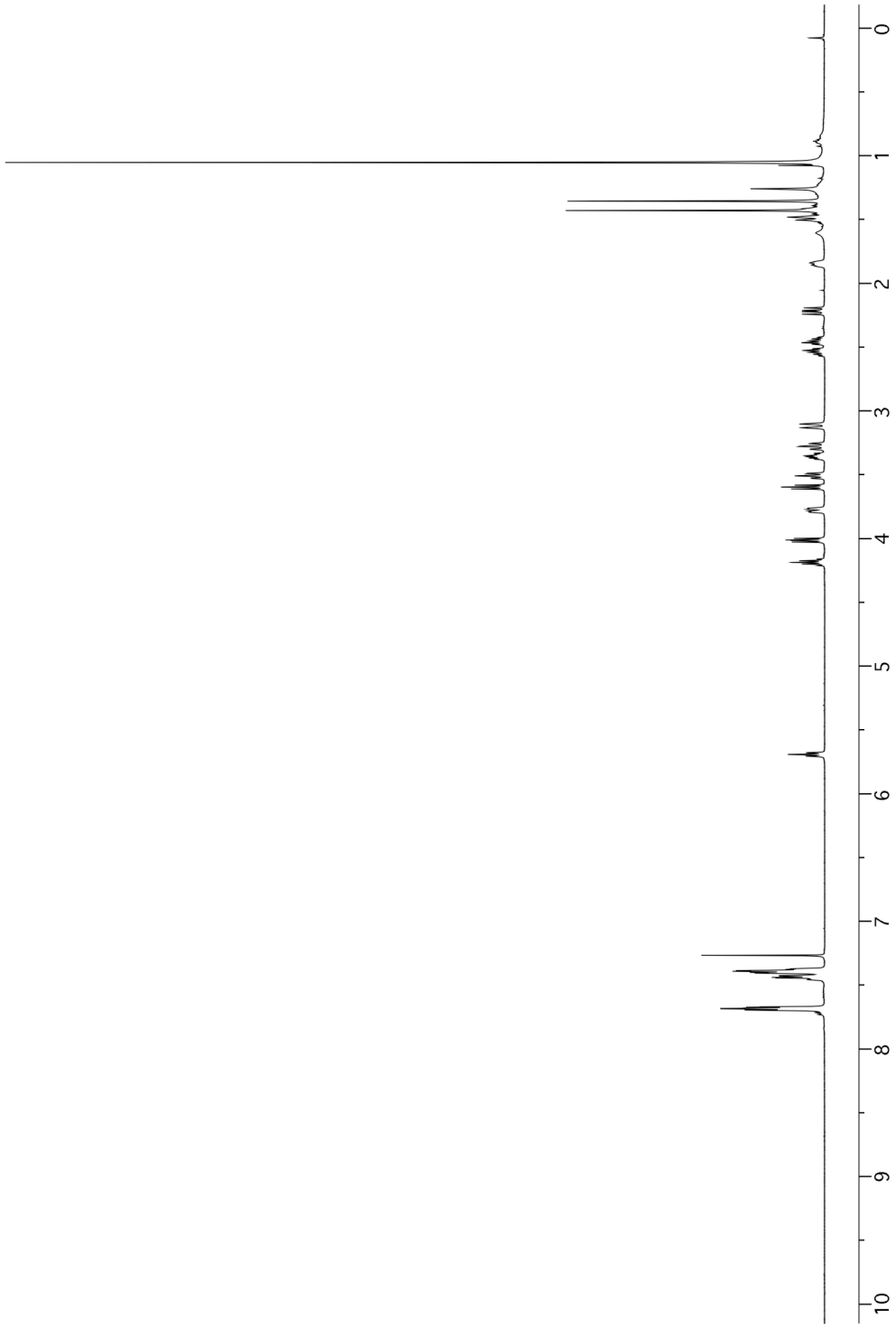


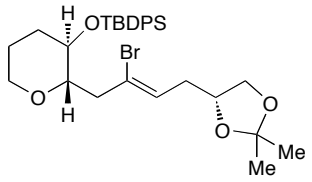
11



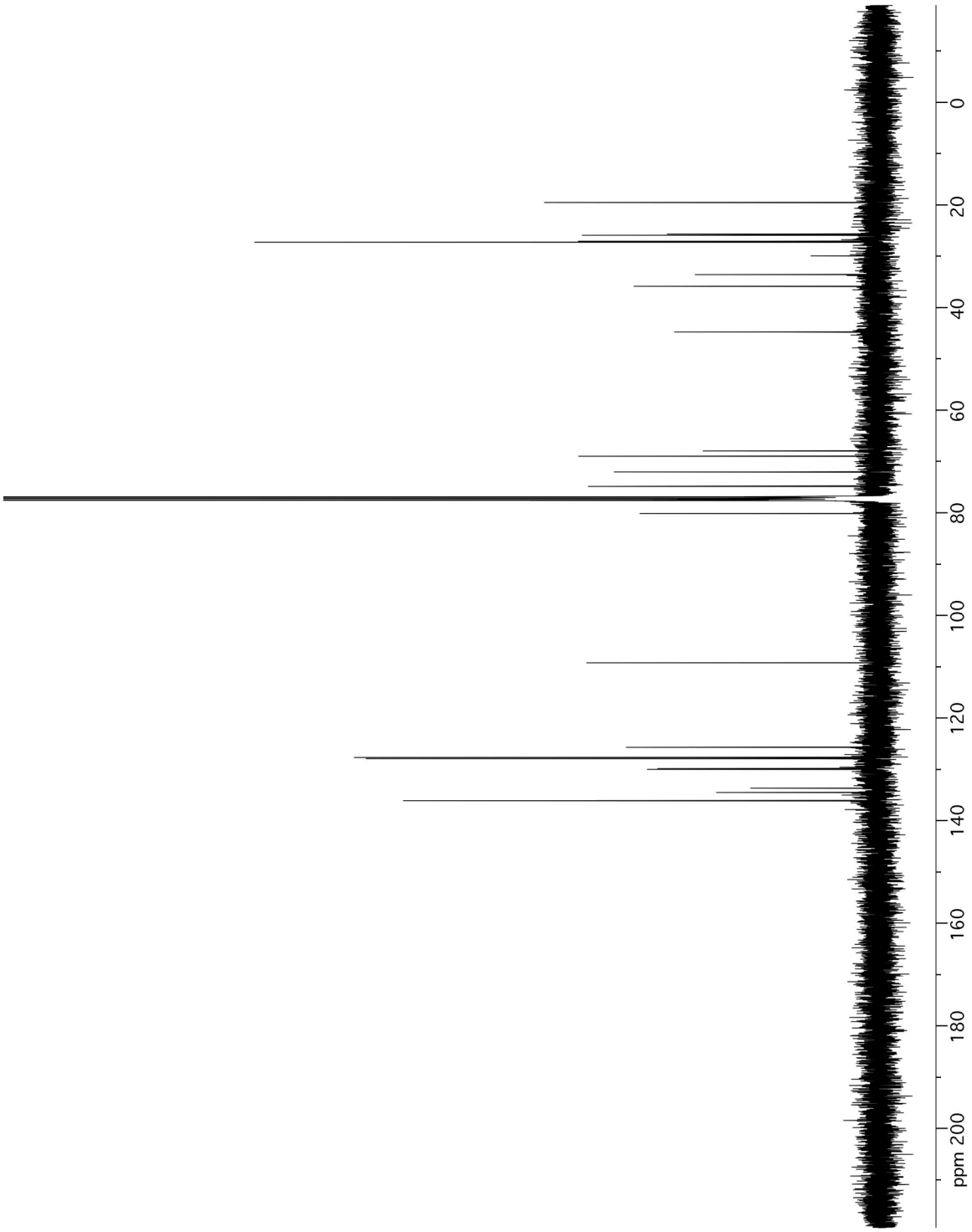


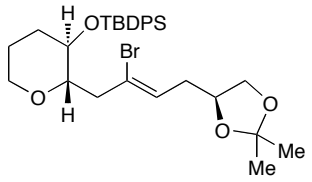
15a



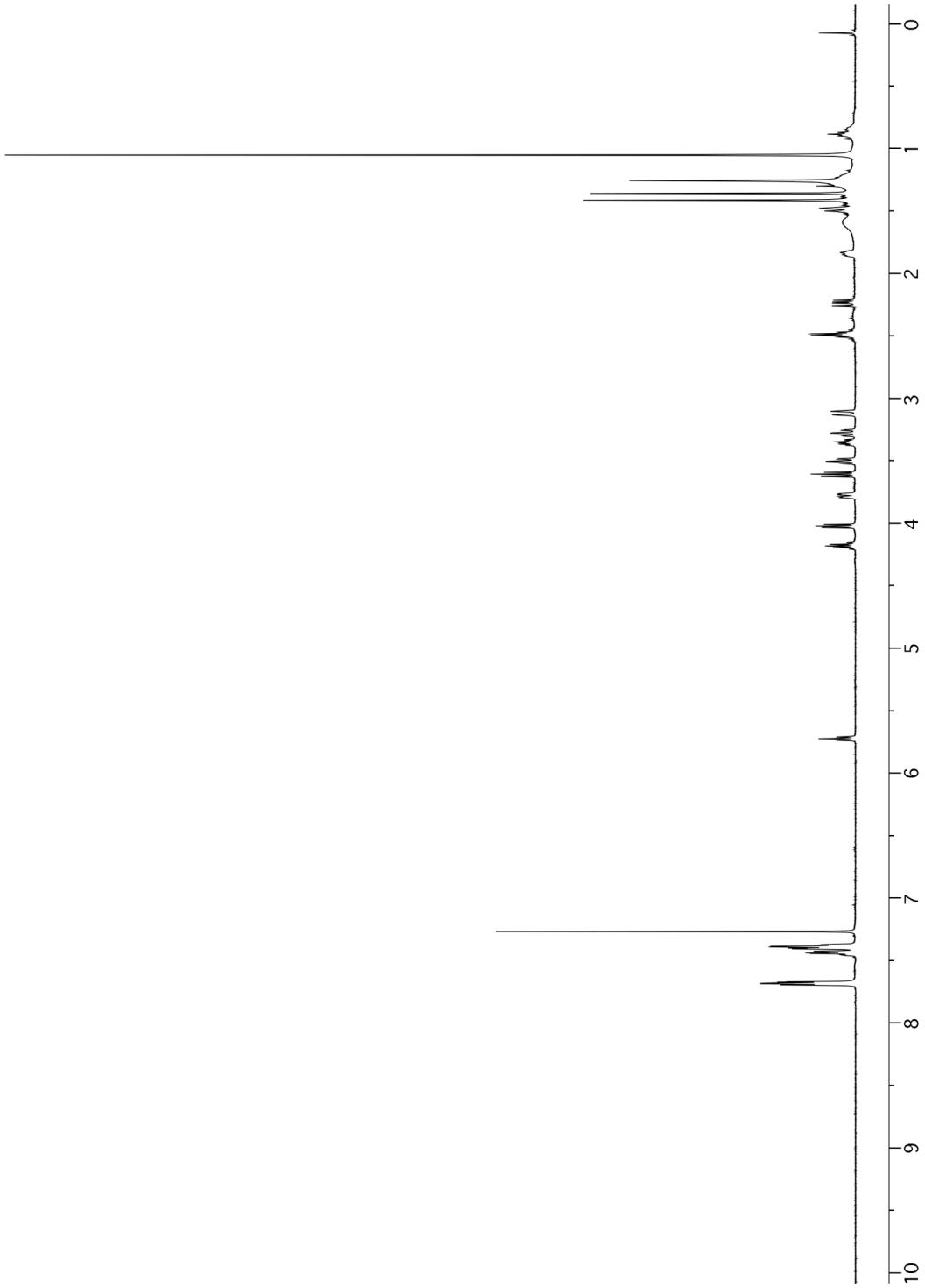


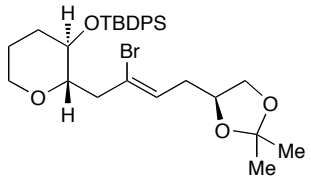
15a



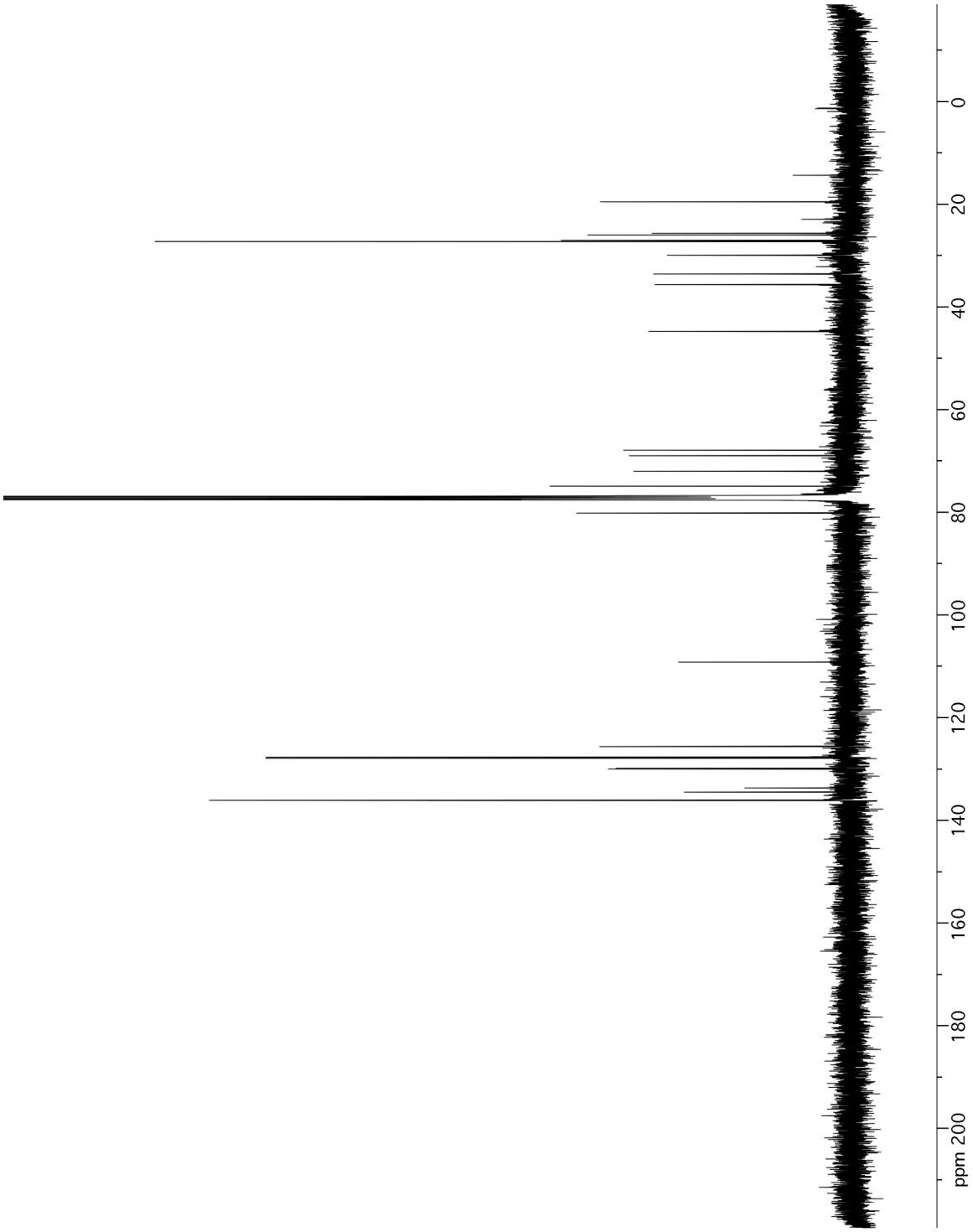


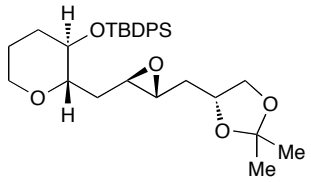
15b



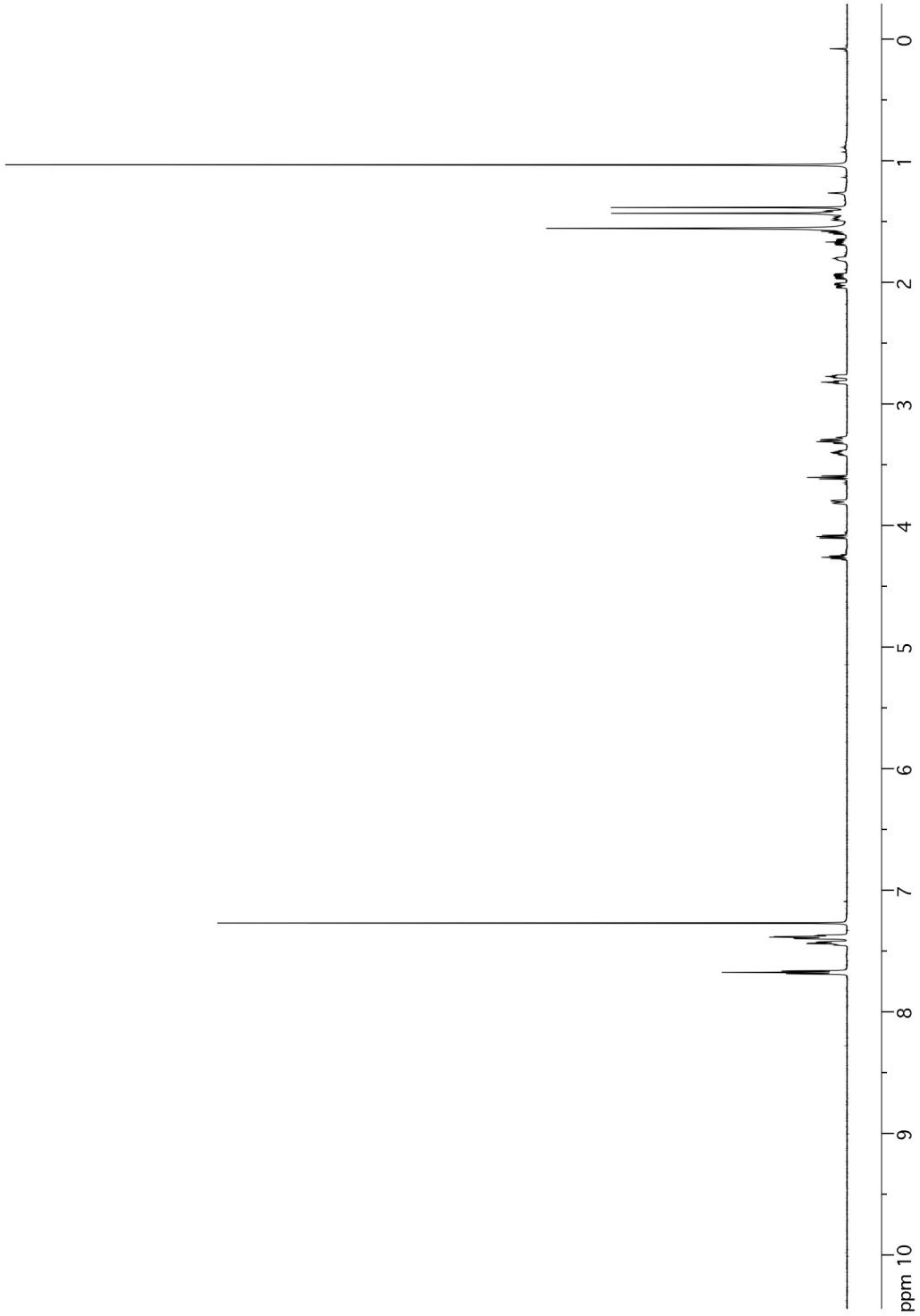


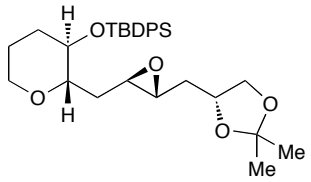
15b



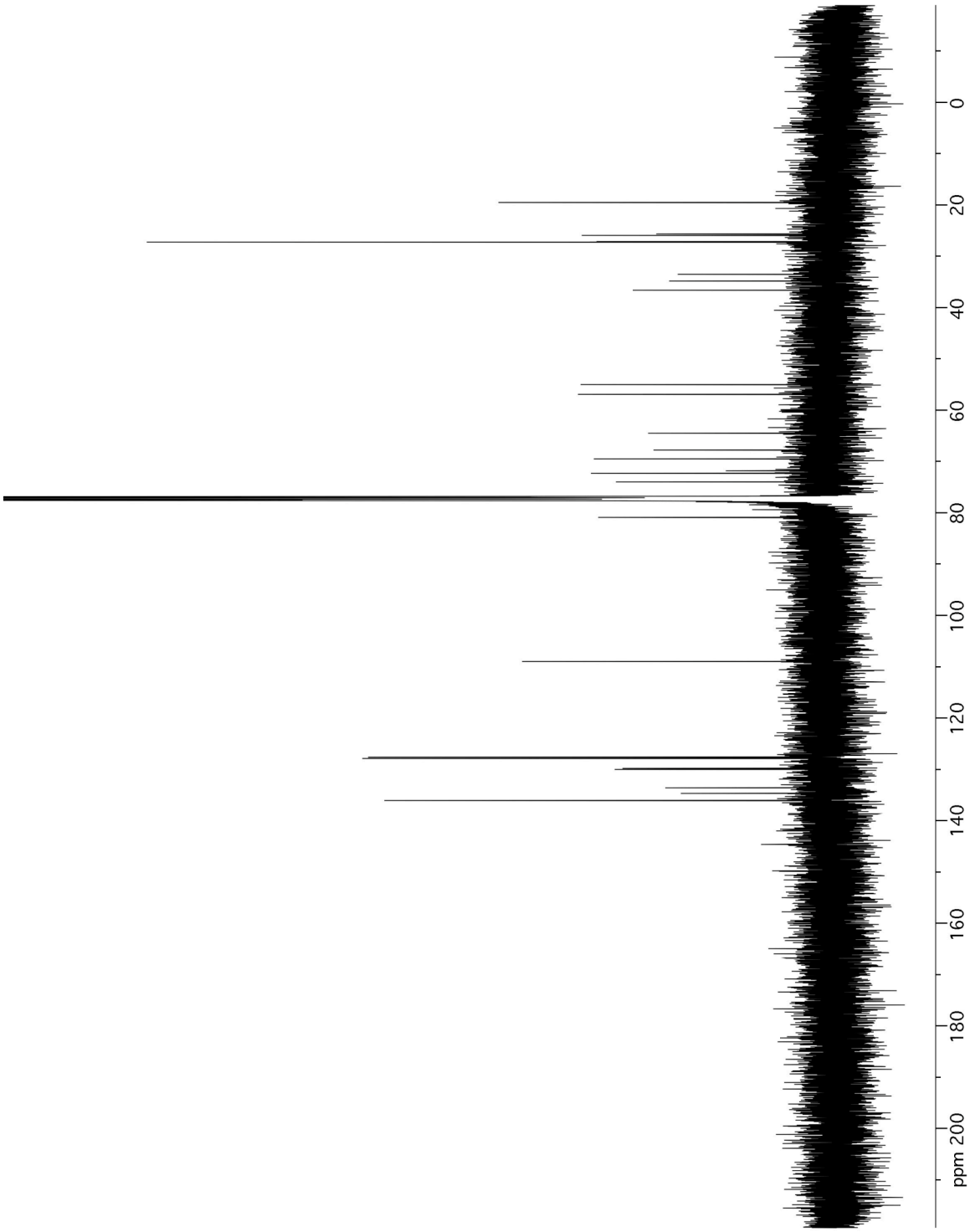


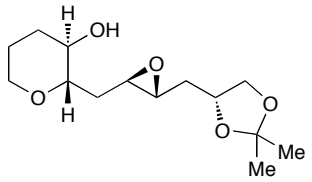
16



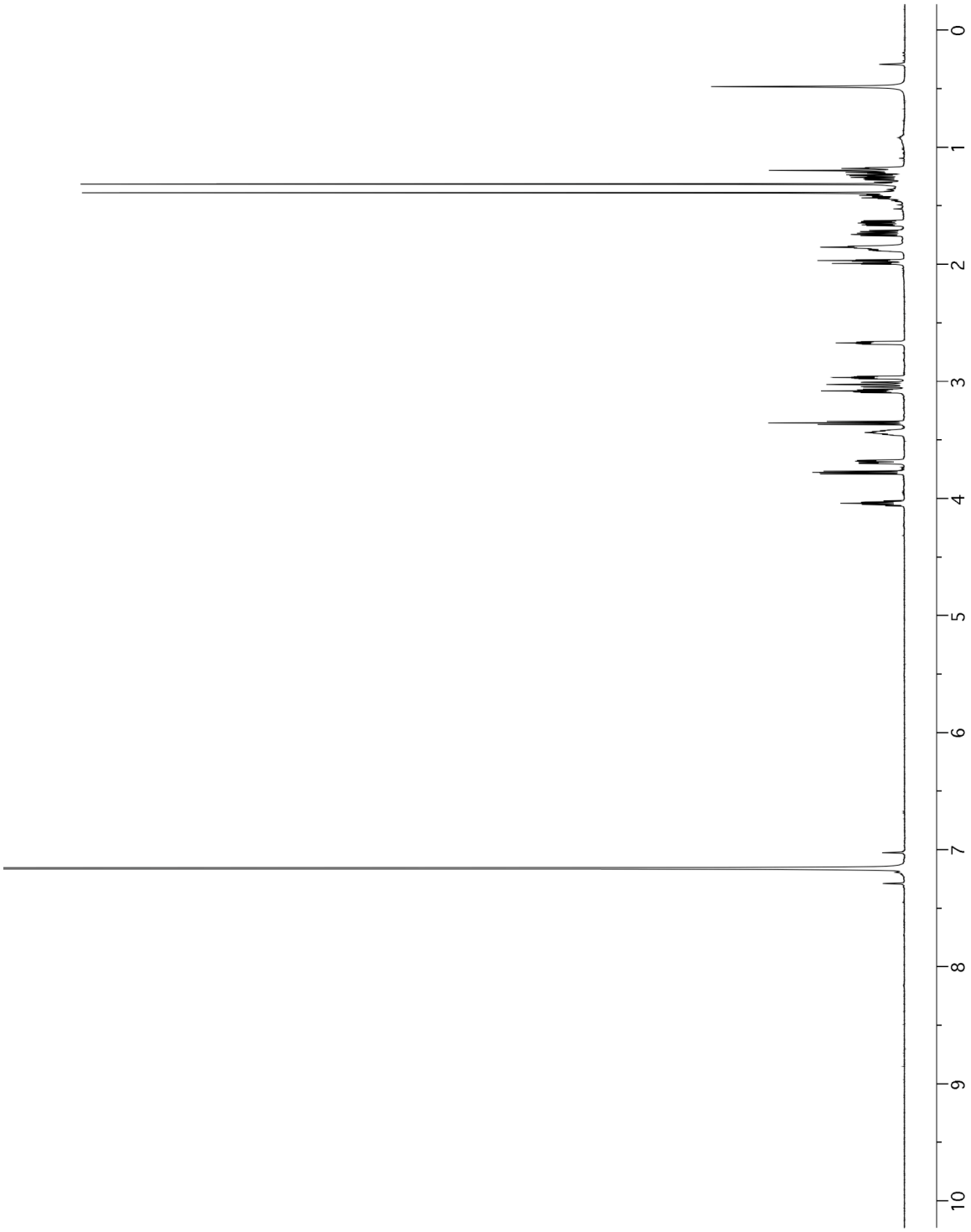


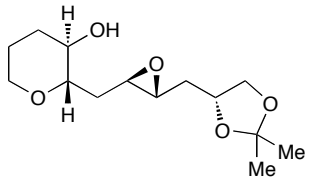
16



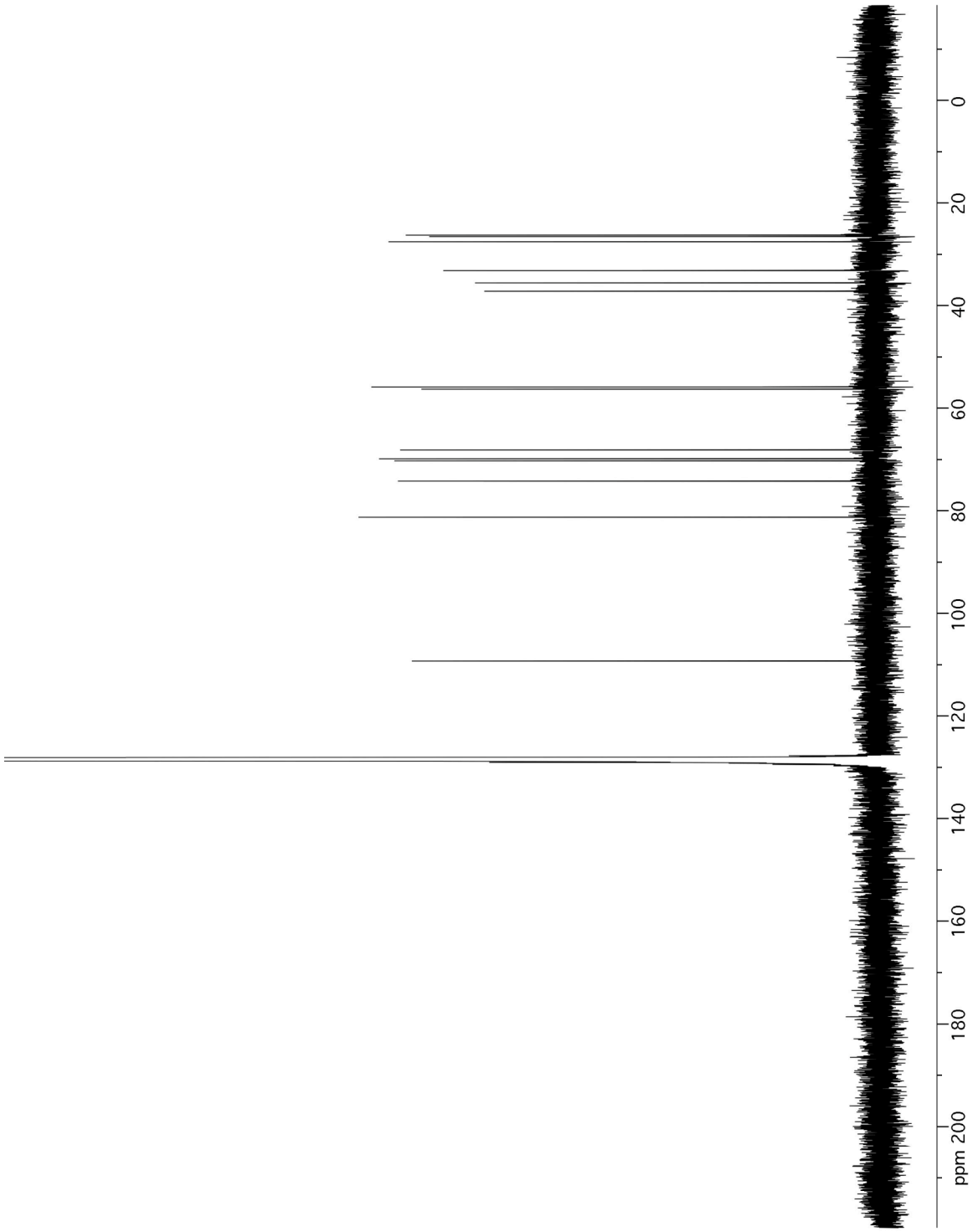


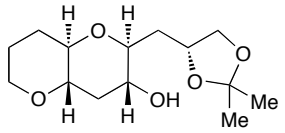
17



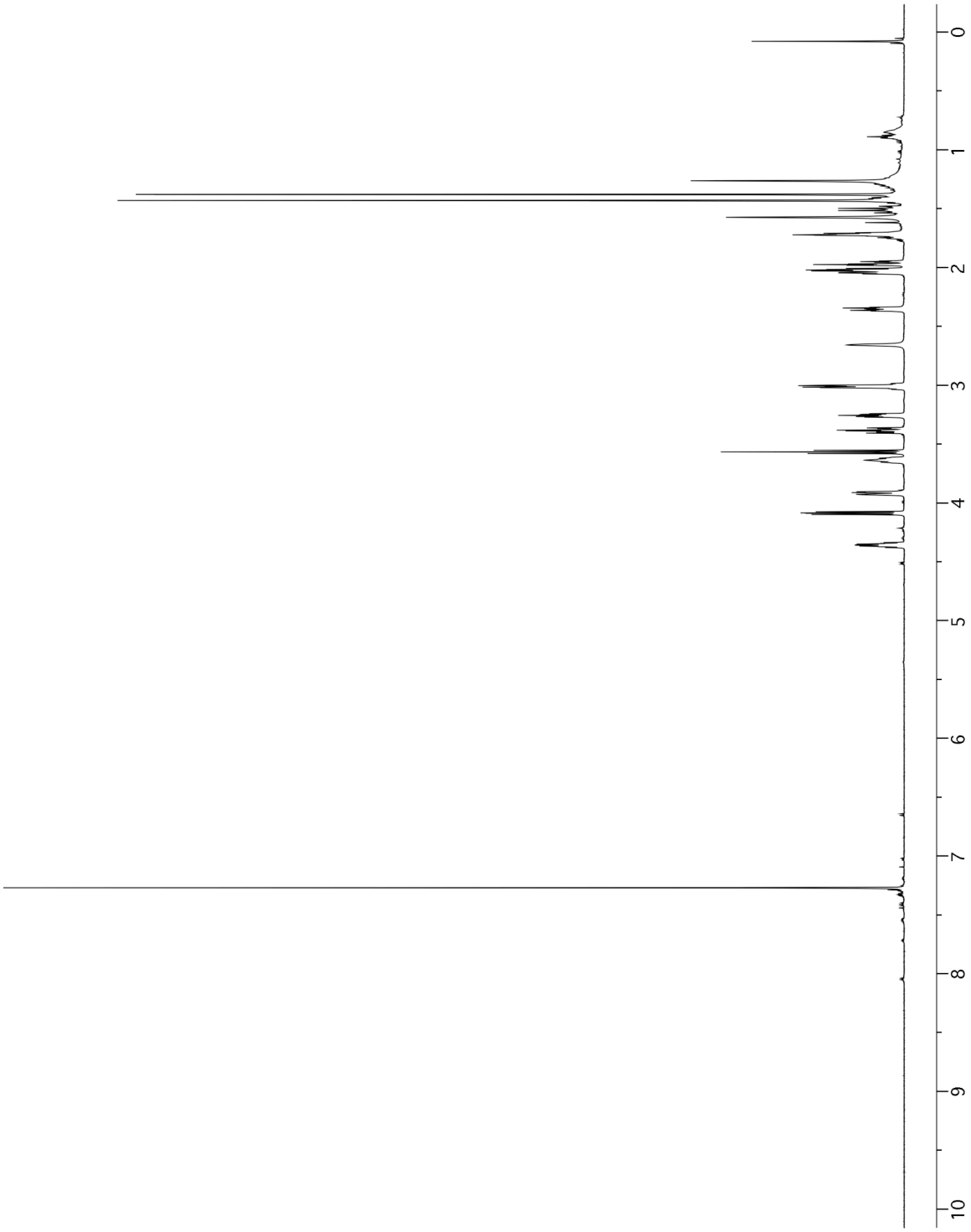


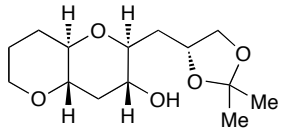
17



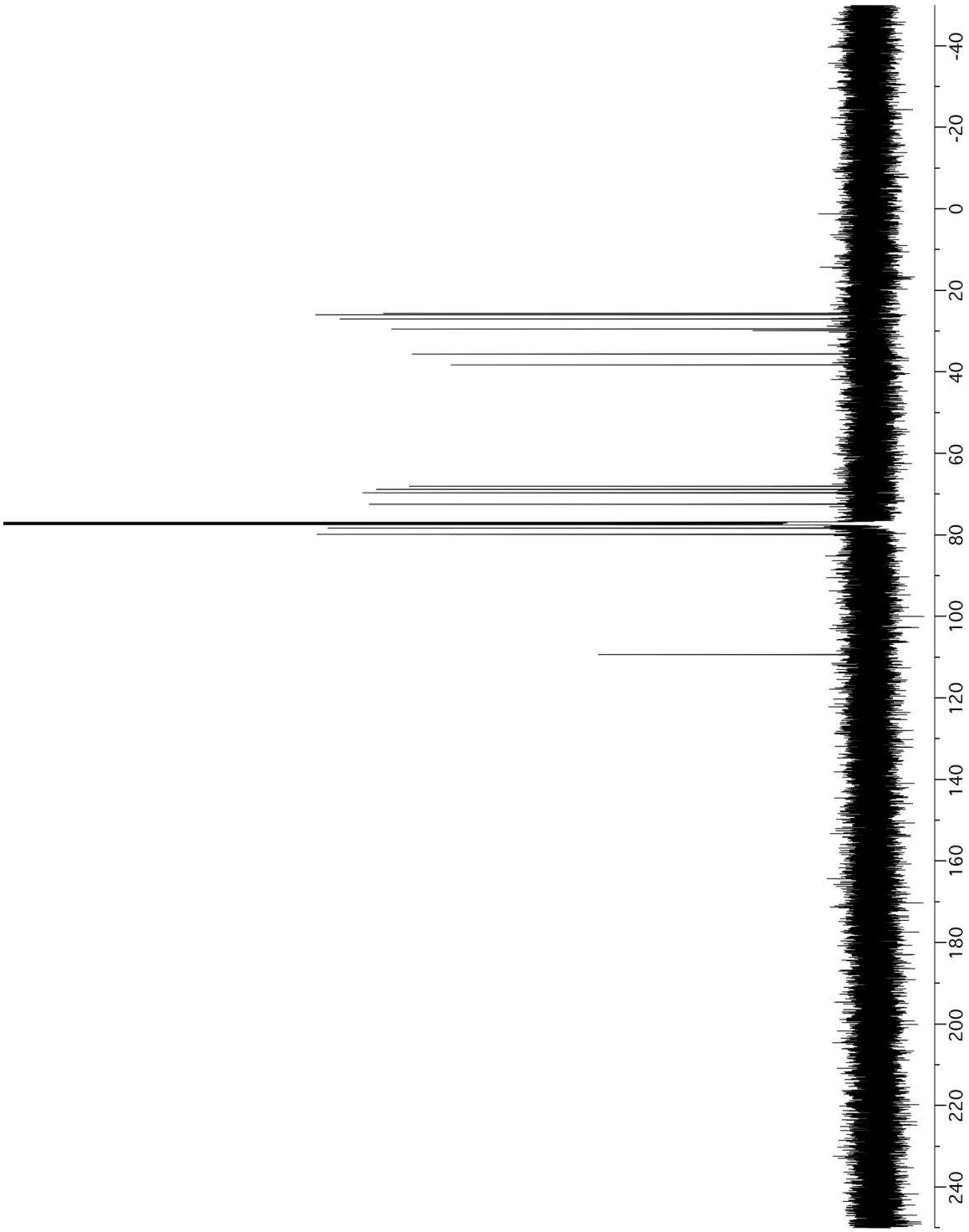


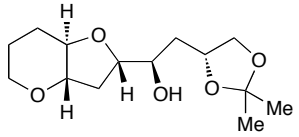
18



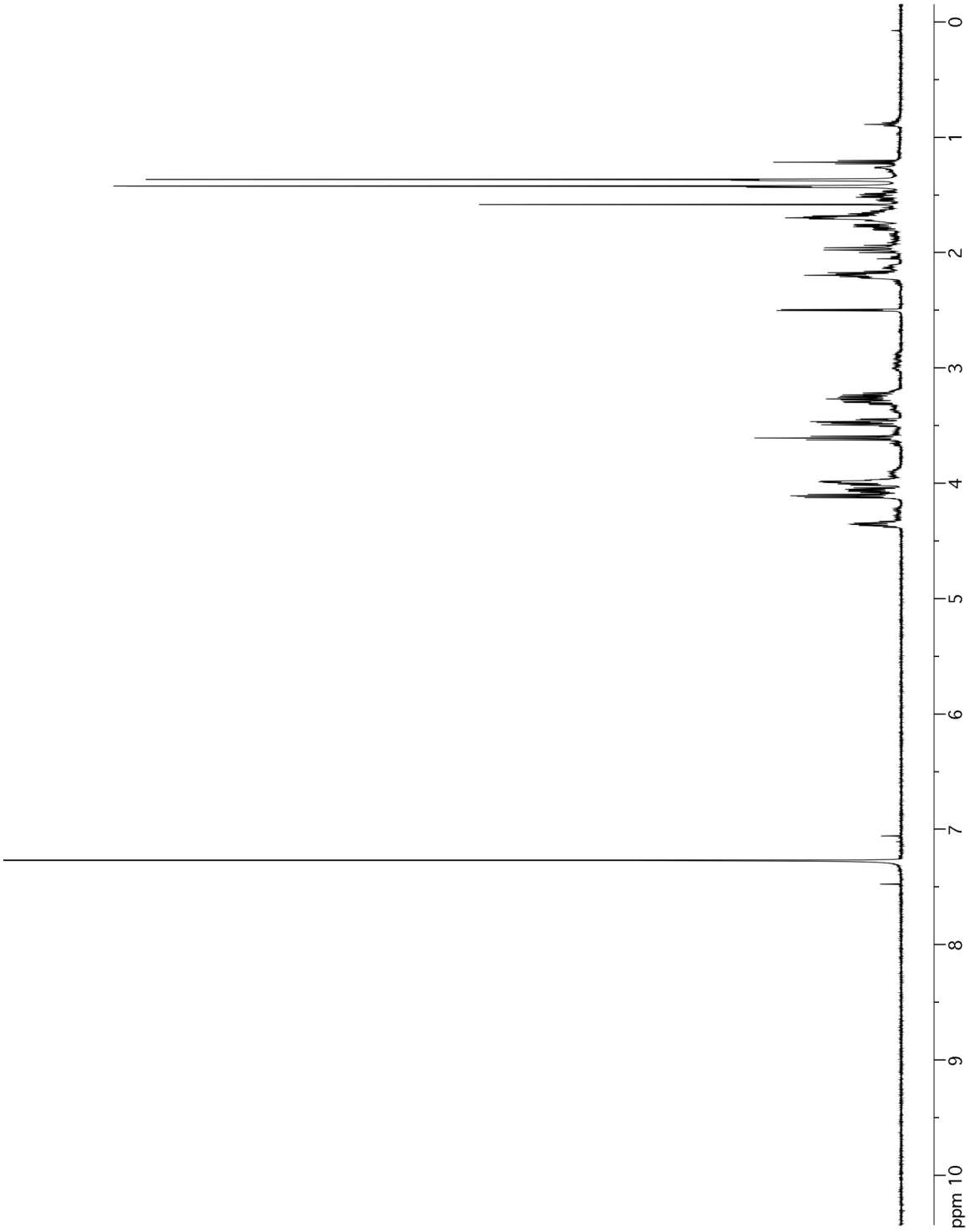

H
H
O
O
O
O
H
H
OH
Me
Me

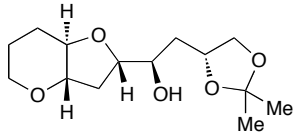
18


-40
-20
0
20
40
60
80
100
120
140
160
180
200
220
240

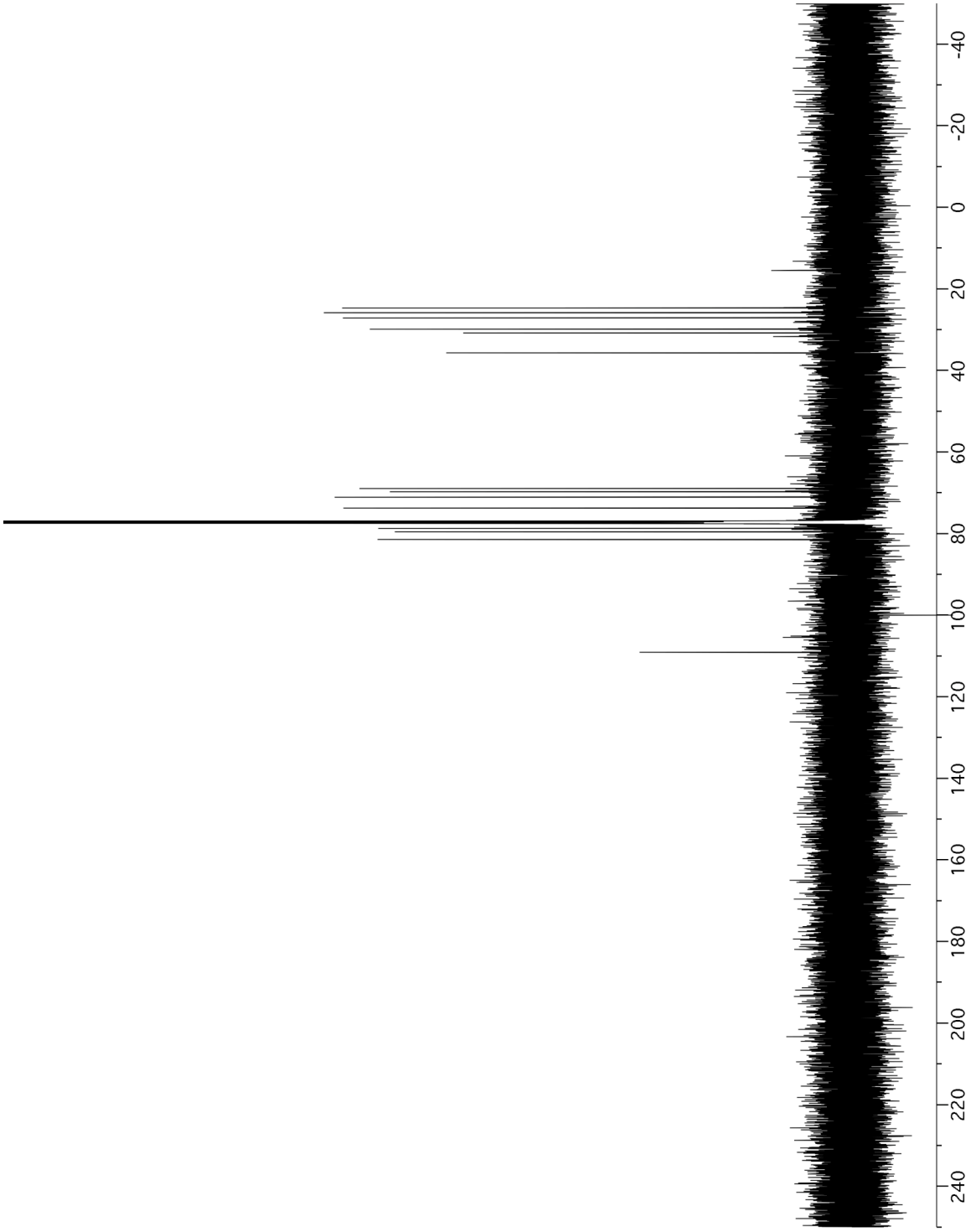


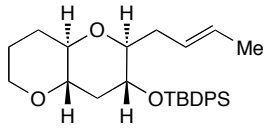
19



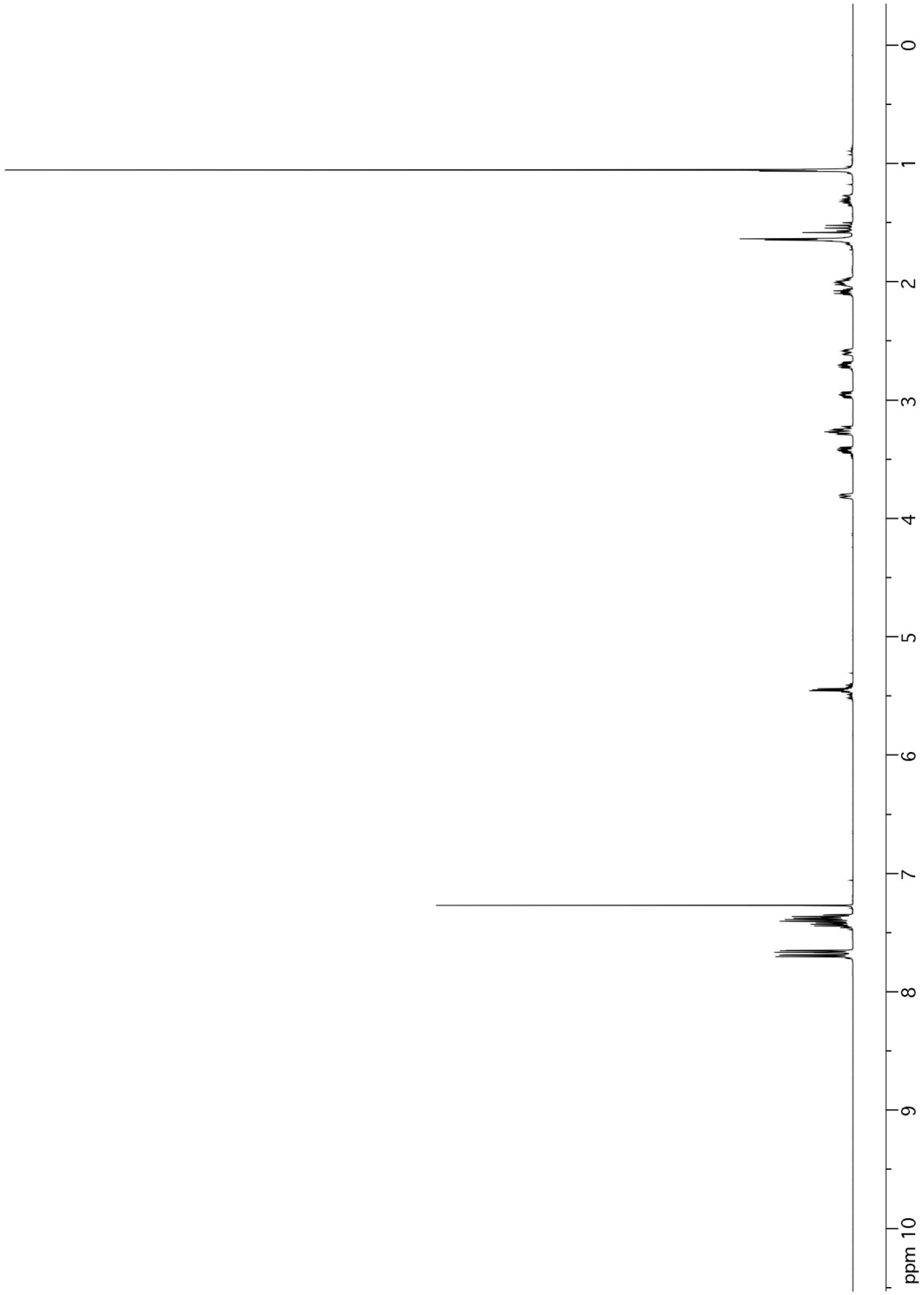

H
O
O
H
H
OH
O
O
Me
Me

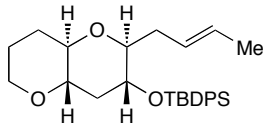
19


-40
-20
0
20
40
60
80
100
120
140
160
180
200
220
240

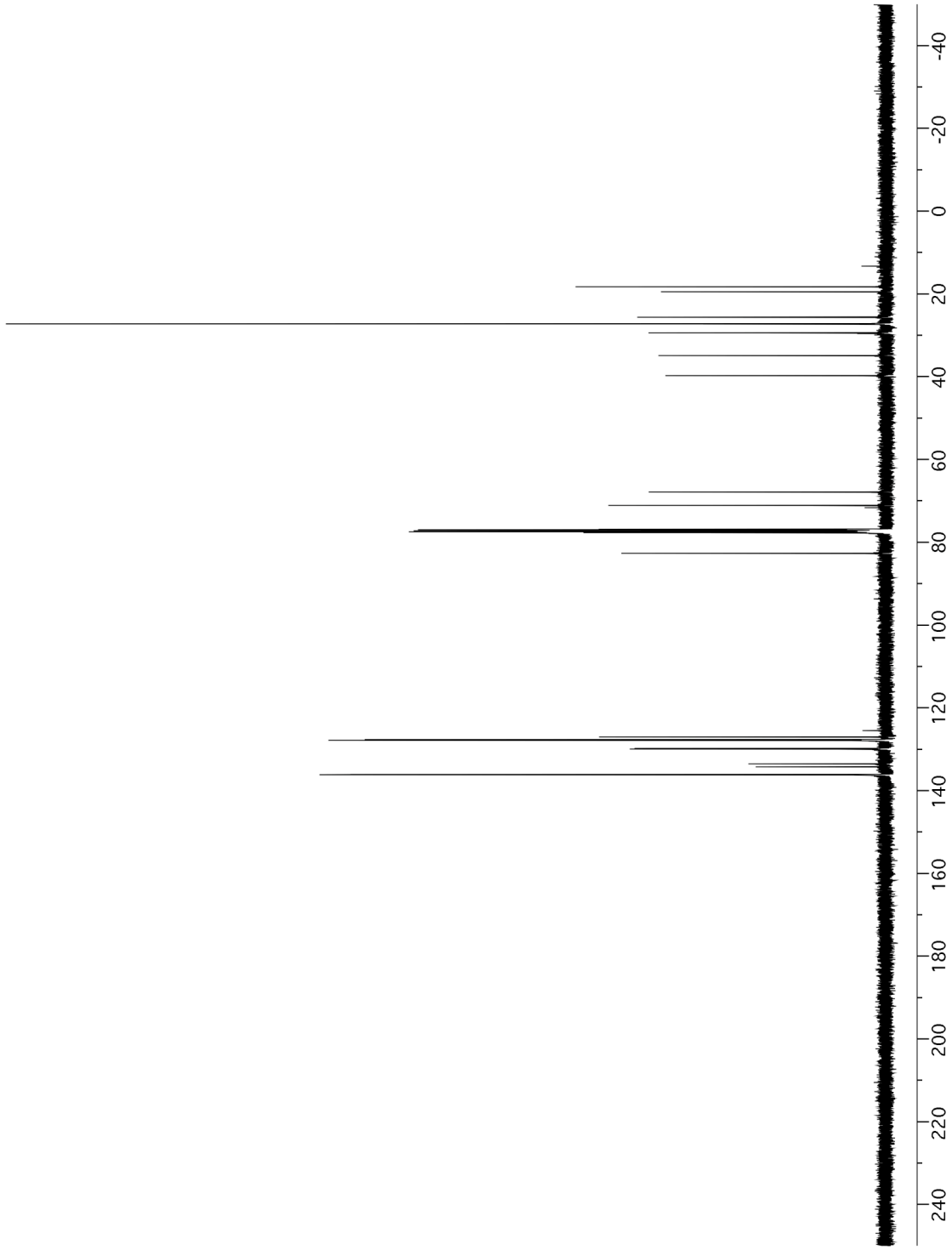


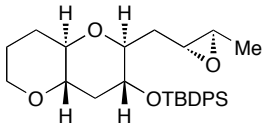
20



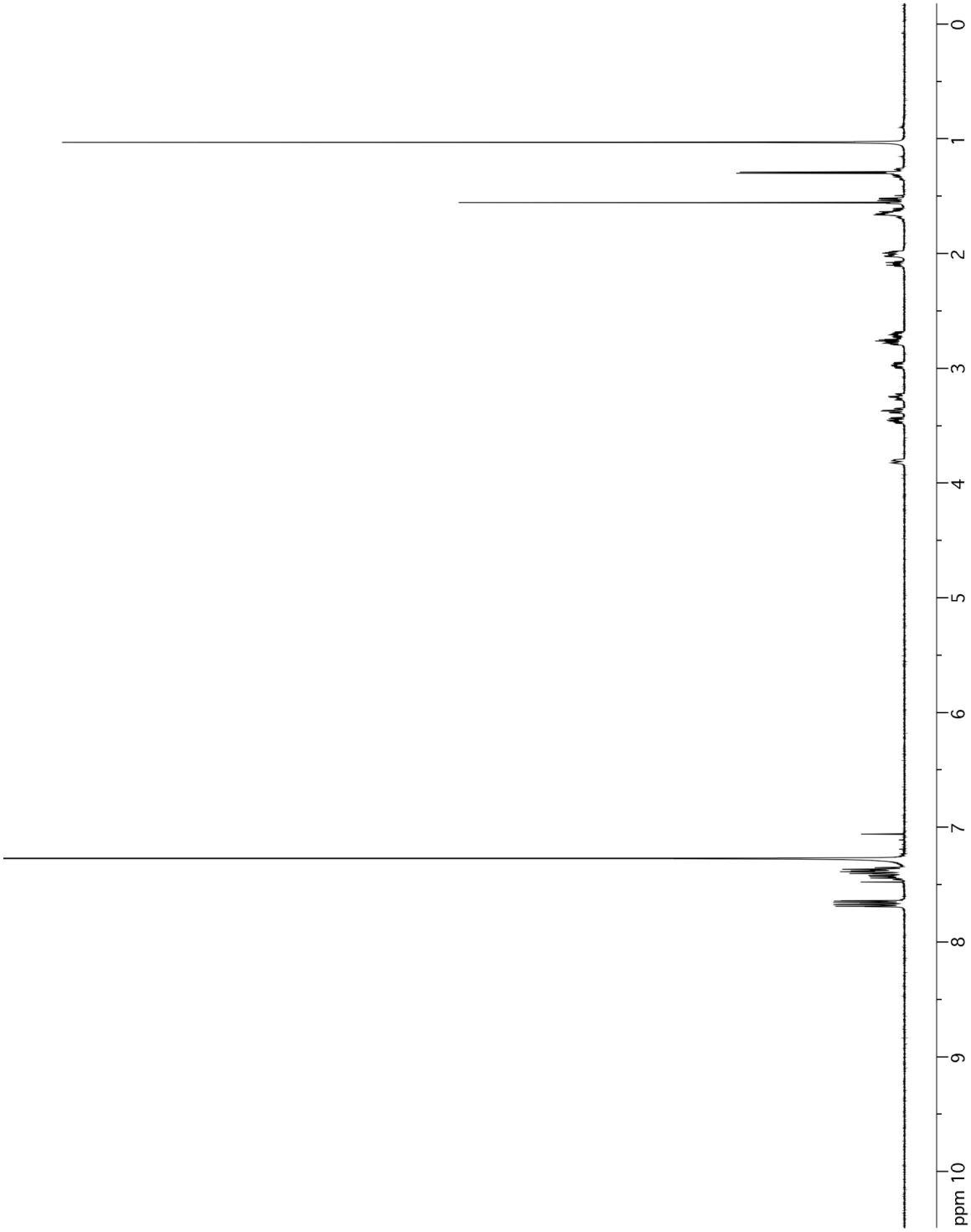

H
H
O
Me
O
OTBDPS
H
H

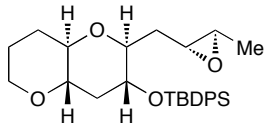
20


-40
-20
0
20
40
60
80
100
120
140
160
180
200
220
240

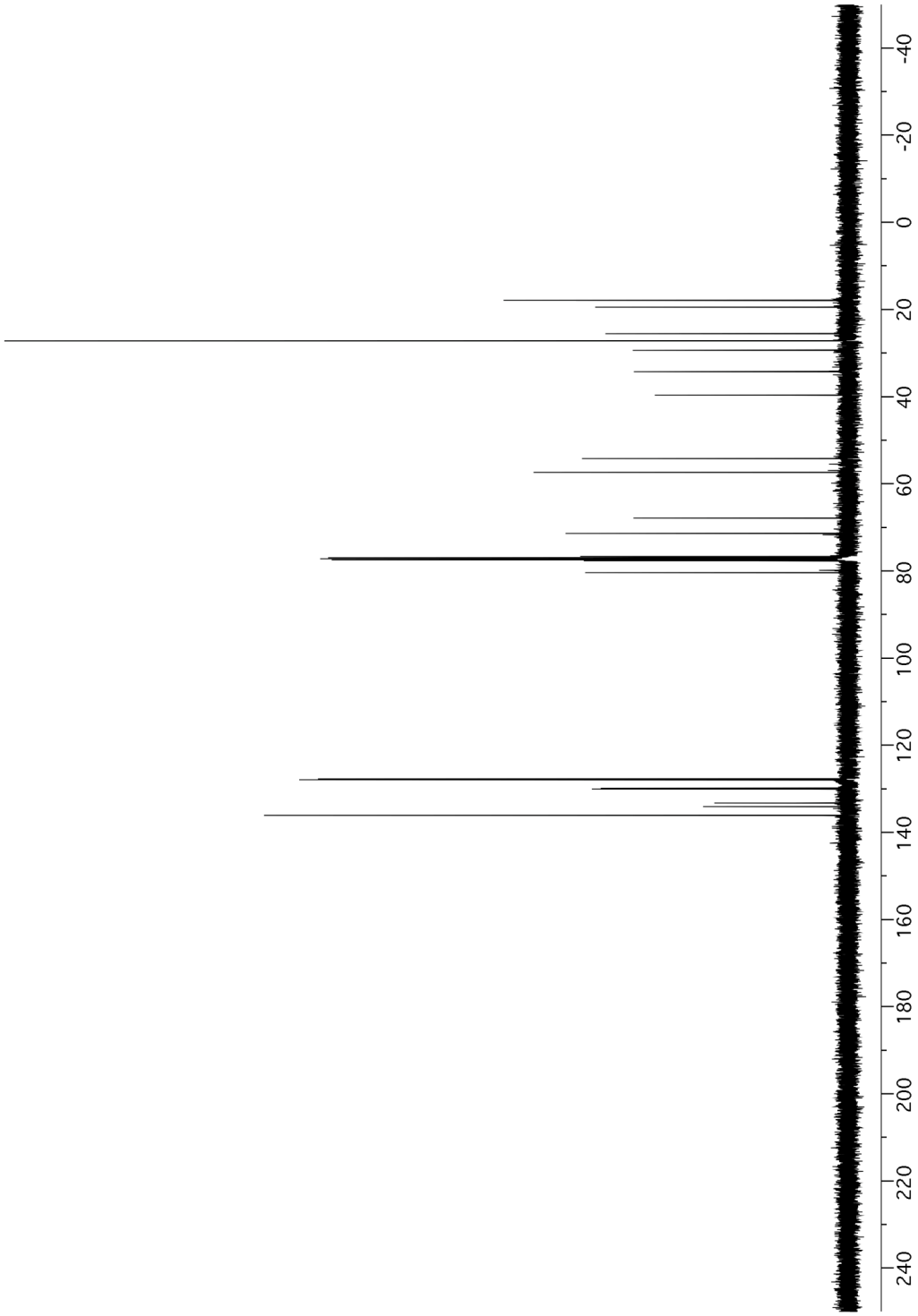


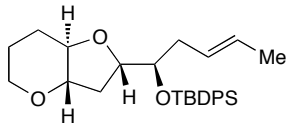
21



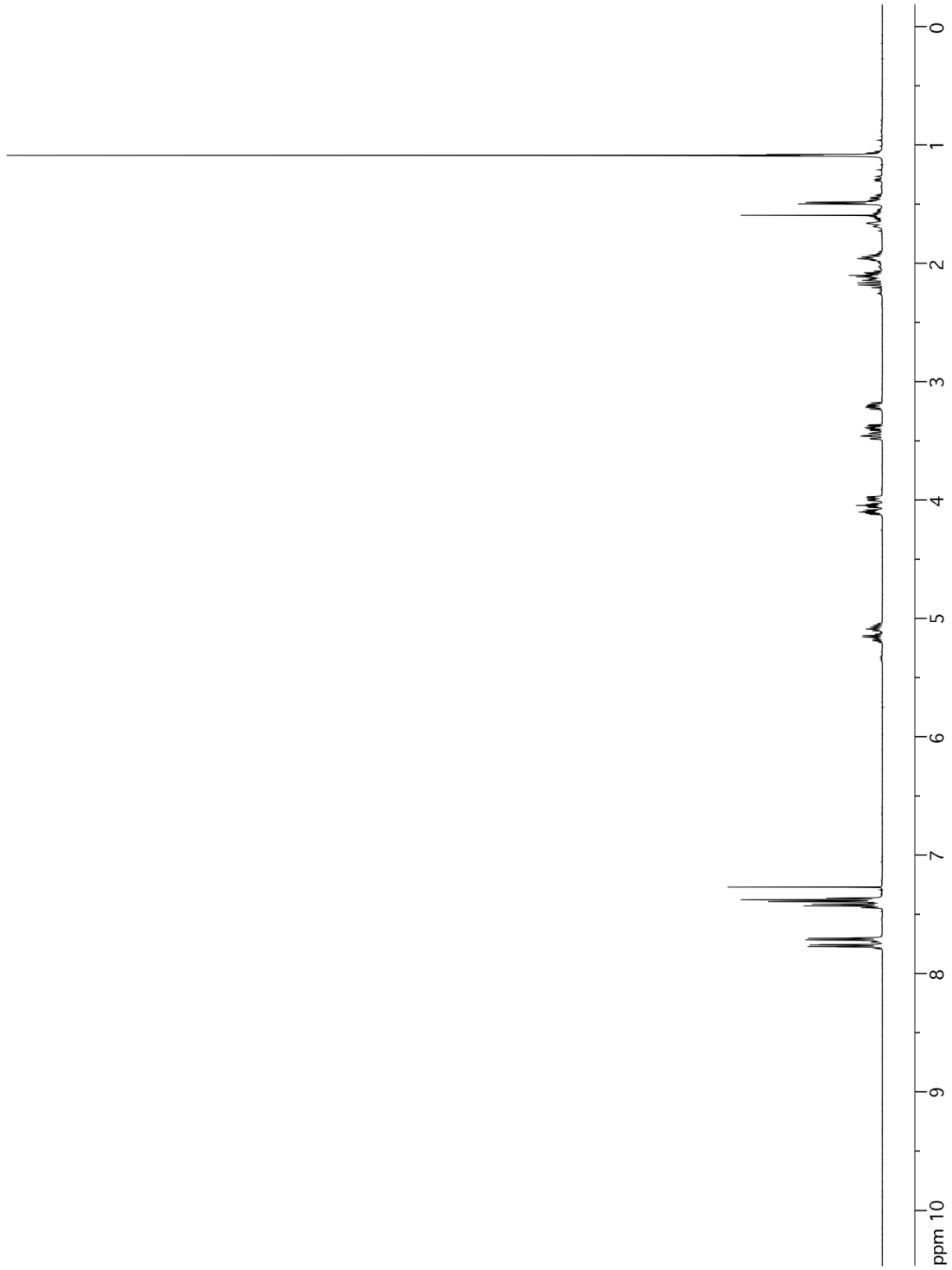

H
H
O
Me
O
O
OTBDPS
H
H

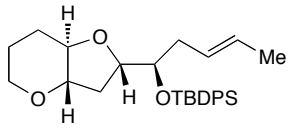
21


-40
-20
0
20
40
60
80
100
120
140
160
180
200
220
240

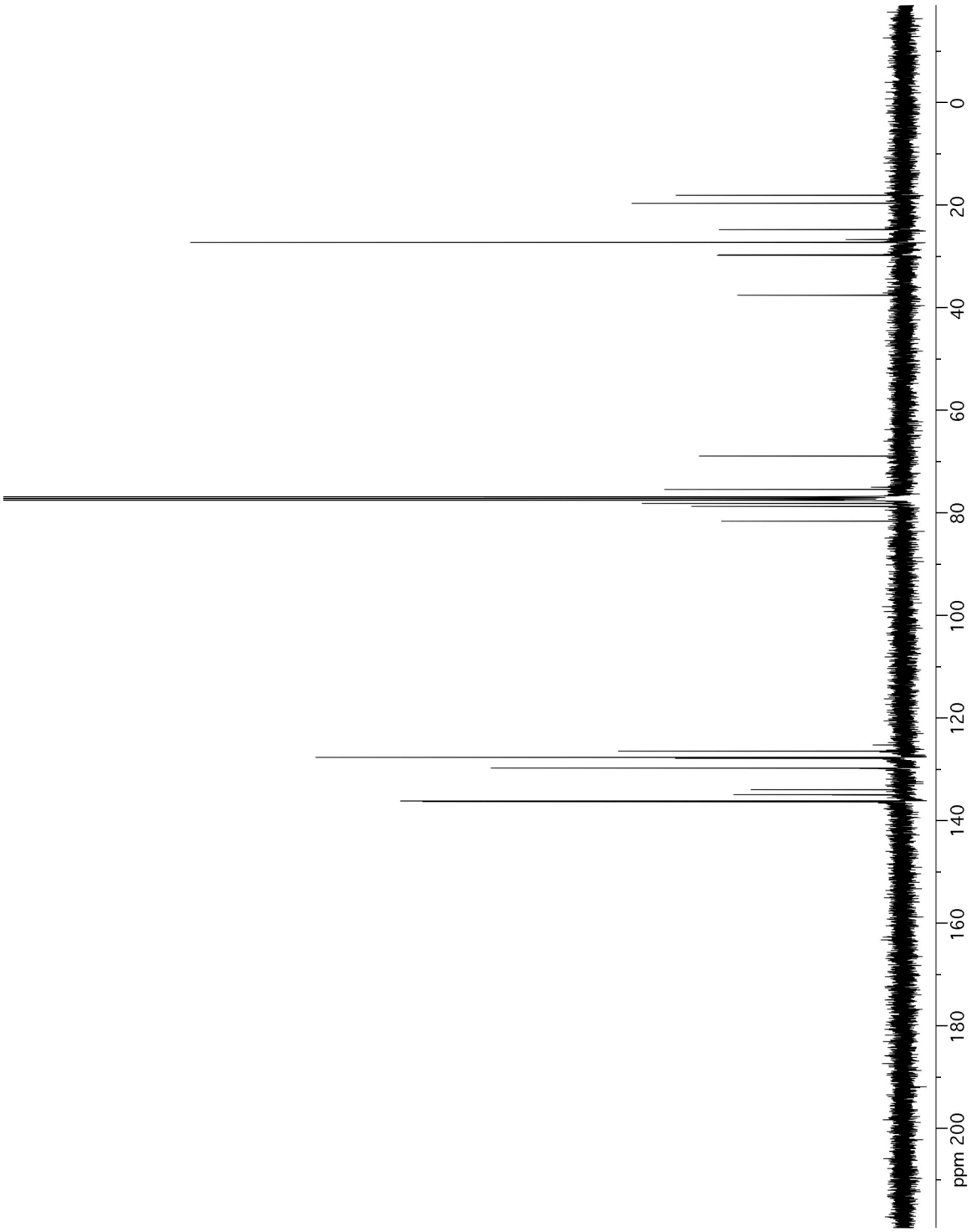


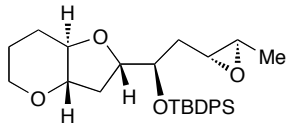
23



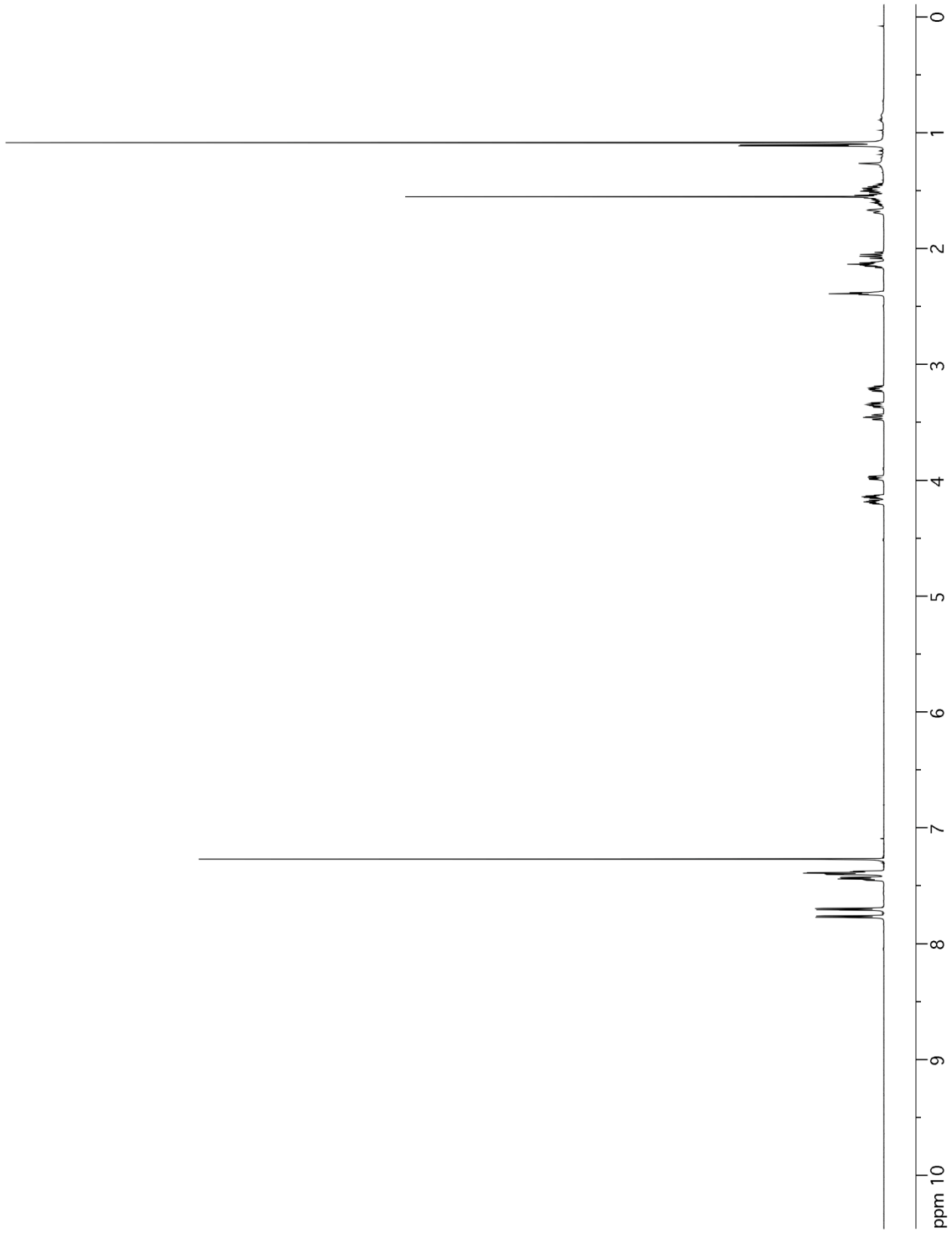


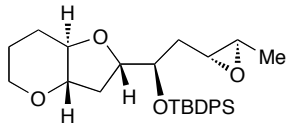
23



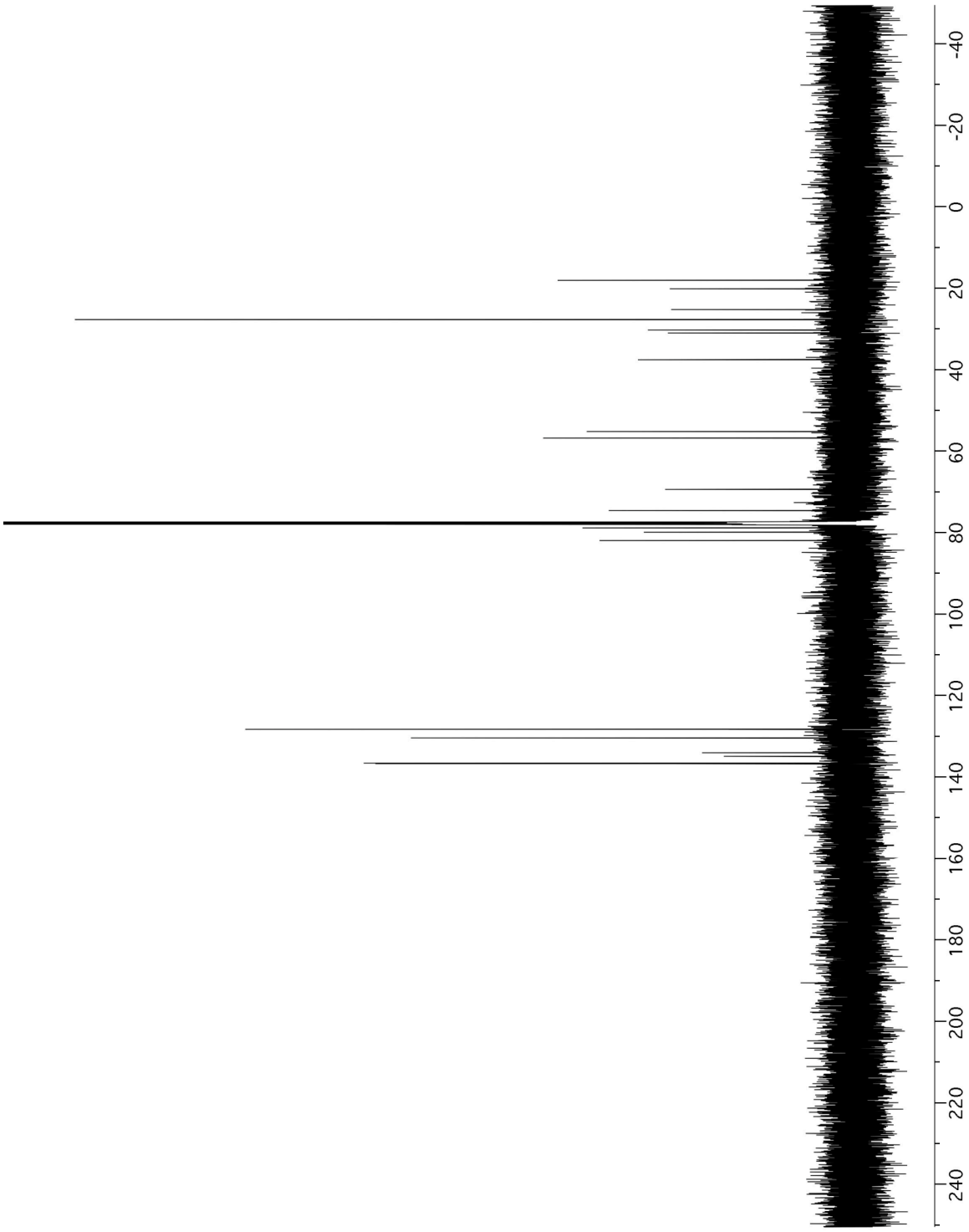


24

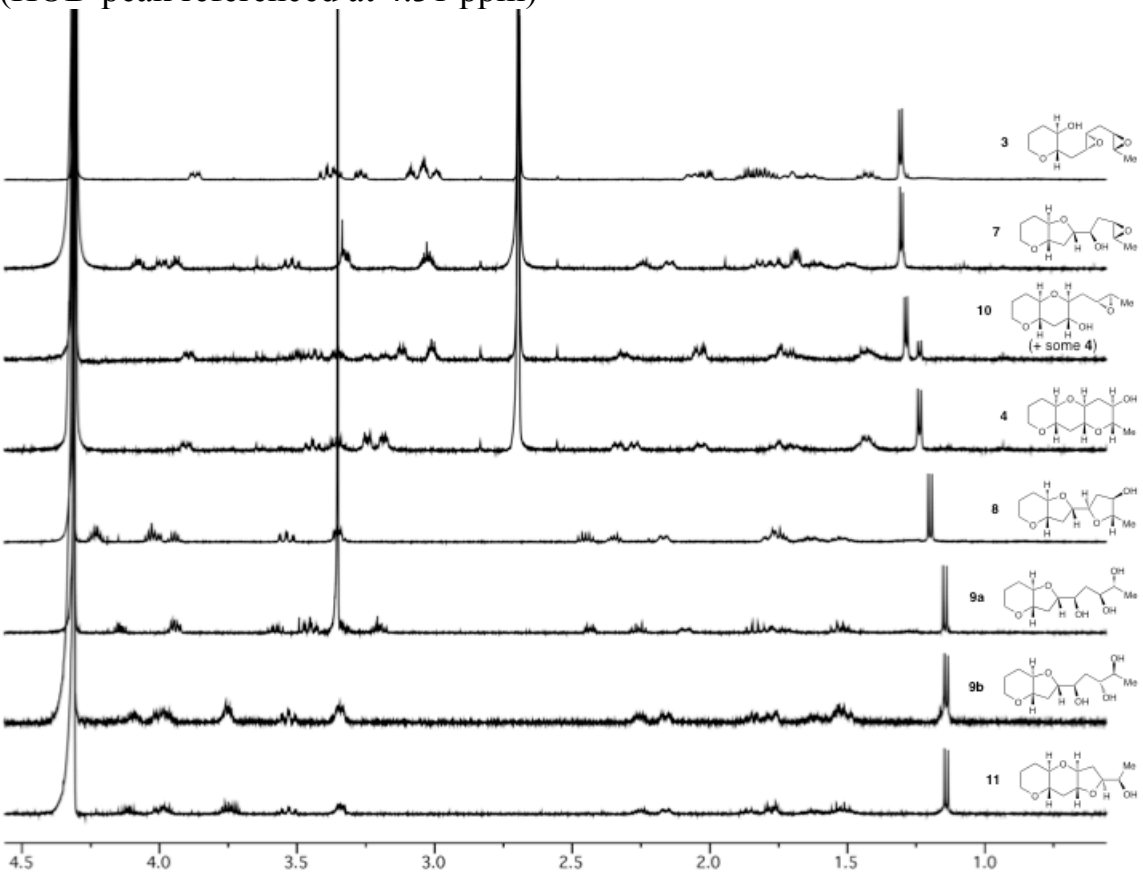


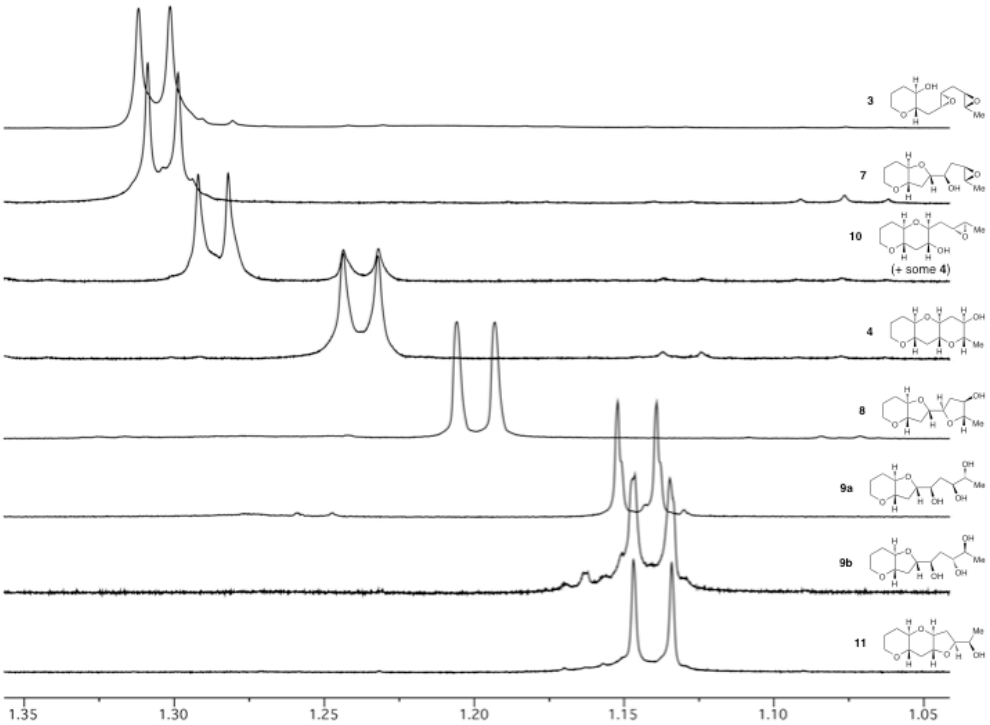

H
O
Me
O
O
H
H
OTBDPS

24


-40
-20
0
20
40
60
80
100
120
140
160
180
200
220
240

^{1}H spectra of compounds **3**, **4**, **7**, **8**, **9a**, **9b**, **10**, and **11** in D_2O at 70 °C
(HOD peak referenced at 4.31 ppm)





V. Supporting Information References

[S1] Morten, C. J.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6678-6679.
[S2] Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547.
[S3] (a) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 4821-4824. (b) Xu, J.; Burton, D. J. *J. Org. Chem.* **2005**, *70*, 4346-4353.
[S4] Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224-11235.
[S5] Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951-953.
[S6] Denmark, S. E.; Senanayake, C. B. W. *Tetrahedron* **1996**, *52*, 11579-11600.
[S7] Nieto, N.; Molas, P.; Benet-Buchholz, J.; Vidal-Ferran, A. *J. Org. Chem.* **2005**, *70*, 10143-10146.
[S8] Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512-7515.
[S9] (a) Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339-2342. (b) Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189-1192.
[S10] Cook, P. A.; Clelan, W. W. *Enzyme Kinetics and Mechanism*, Garland Science; New York, 2007.
[S11] (a) Levenberg, K. *Quart. Appl. Math.* **1944**, *2*, 164-168. (b) Marquardt, D. *SIAM J. Appl. Math.* **1963**, *11*, 431-441. (c) Bates, D. M.; Watts, D. G. *Nonlinear Regression and Its Applications*. New York: Wiley, 1988.
[S12] Connors, K. A. *Chemical Kinetics*; VCH: New York, NY, **1990**.
[S13] Hoops, S.; Sahle, S.; Gauges, R.; Lee, C.; Pahle, J.; Simus, N.; Singhal, M.; Xu, L.; Mendes, P.; Kummer, U. *Bioinformatics* **2006**, *22*, 3067-3074.