Supporting Information

On the Synergism Between Neutral Water and a Pyran Template in the Regioselective Cyclization of an Epoxy Alcohol

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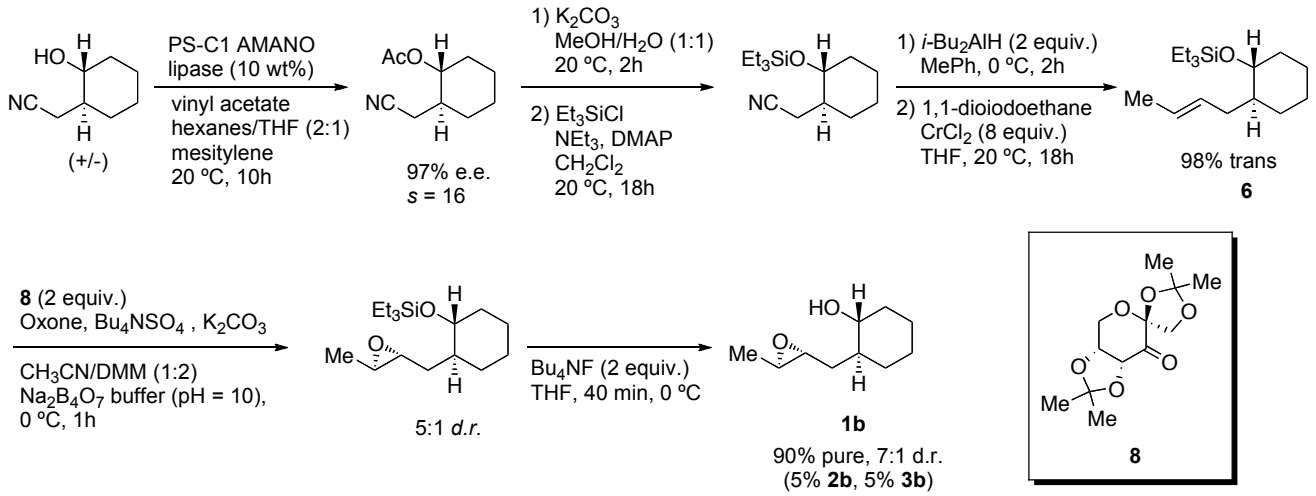
I. Synthetic Procedures

Synthesis of **1a** was carried as previously described.[1] Synthesis of **1b** was accomplished according to Scheme S-1. It was necessary to synthesize enantioenriched olefin, **6**, rather than racemic **6** because directed epoxidation of the latter yielded poor diastereoselectivities and separation of the diastereomers by column chromatography was not possible. Enantiomeric enrichment was achieved by lipase resolution of nitrile **7**, which originated from cyclohexene oxide and could be elaborated to **6** in 5 straightforward steps. Although good E:Z ratios were observed during the Takai olefination[2] used to form **6**, elimination of virtually all of the *cis*-olefin isomer was possible with a silver nitrate-impregnated silica gel column. Shi epoxidation[3] of **6** proceeded with good diastereoselectivity, and deprotection of the triethylsilyl protecting group with tetrabutylammonium fluoride proceeded efficiently at 0 ºC to give **1b**. Unfortunately, undesired spontaneous cyclization of **1b** could not be avoided; thus, **1a** contained 10–12 % cyclized material (~1:1 **2b**:**3b**). Kinetic analysis and **2b**:**3b** ratios were determined after correcting for the amount of **2b** and **3b** that had prematurely cyclized.

Scheme S-1. Synthesis of **1b**



General Considerations. Unless otherwise stated, all manipulations were carried under a nitrogen or argon atmosphere using standard Schlenk line or glovebox techniques. Tetrahydrofuran was either freshly distilled from sodium/benzophenone or obtained after passage through aluminum columns. Toluene and dichloromethane were freshly distilled from calcium hydride. All other solvents were used without further purification. All reagents were purchased from Aldrich with the exception of

triethylsilyl chloride and vinyl acetate, which were obtained from Alfa. The Shi epoxidation catalyst **8**,[4] 1,1-diiodoethane,[5] and racemic 2-(2-hydroxycyclohexyl)acetonitrile[6] were synthesized as previously reported. Nuclear magnetic resonance (NMR) spectra for characterization of new compounds were taken on Bruker 400 MHz (broadband probe) or Varian Inova 500 MHz (inverse or broadband probe) spectrometers. Gas chromatograms (GC) were obtained on an Agilent 7890A GC-FID (Agilent HP-5 column, 30 m x 0.32 mm x 0.25 μm) or, for enantioassays, on a Varian CP-3800 GC-FID (Chiraldex β-DA column, 20 m x 0.25 mm). pH was measured using a Symphony Posi-pHlo Ag/AgCl pH glass electrode calibrated at the reaction temperature with standard solutions. Fourier transform infrared (FT-IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR spectrometer. High resolution mass spectra (HR-MS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Dr. Li Li of the MIT Department of Chemistry Instrumentation Facility. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm.

Synthesis of (1R,2S)-2-(cyanomethyl)cyclohexyl acetate. In air, a 500 mL round bottom flask was charged with (*rac*)-2-(2-hydroxycyclohexyl)acetontrile (20.59 g, 148.0 mmol), THF (42 mL), hexanes (83 mL), vinyl acetate (68.0 mL, 63.7 g, 740 mmol). Mesitylene (2.10 mL, 1.74 g, 14.4 mmol) was added to the reaction as an internal standard. The mixture was stirred for five minutes and an aliquot was removed for HPLC analysis. At room temperature, AMANO PS-C1 lipase ceramic beads (2.06 g) were added to the reaction. The reaction was monitored by thin layer chromatography (TLC) (40% ethyl acetate/hexanes) and by periodic analysis of aliquots by HPLC (ODH column, 100% hexanes for 10 minutes then 7% isopropanol in hexanes for 35 minutes). After 9 h, the reaction was stopped by filtration and washing with 2:1 hexanes/THF (25 mL). Removal of the solvent gave a yellow oil that was purified by column chromatography (SiO_2, $R_f = 0.50$, 40% ethyl acetate/hexanes) to give a colorless oil. Yield = 6.86 g (25.6 %, e.e. = 97%, $s = 16$).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.44 (ddd, ^3J = 4.3, 10.5, 10.5 Hz, 1H, C*H*OAc), 2.41 (dd, ^3J = 5.0, ^2J = 16.9 Hz, 1H, CH_2CN), 2.19 (dd, ^3J = 7.6, ^2J = 16.9 Hz, 1H, CH_2CN), 2.00 (s, 3H, CH_3), 1.97 (m, 2H), 1.74 (m, 3H), 1.23 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 170.45, 118.35, 75.53, 39.21, 39.21, 31.54, 30.63, 24.80, 24.19, 21.16, 20.89. FT-IR (neat, cm^{-1}): 2938, 2862, 2247, 1781, 1739, 1452, 1428, 1373, 1239, 1127, 1032, 968, 944, 909, 875, 846, 816, 648, 607. HRMS-ESI (m/z): $[M+Na]^+$ calc'd for $C_{10}H_{15}NO_2Na$, 204.0995; found, 204.0998. $[\alpha]_D^{20}$ = –41.3 (c = 2.0, CH_2Cl_2).

Synthesis of 2-((1S,2R)-2-hydroxycyclohexyl)acetonitrile. In a 500 mL round bottom flask, (1R,2S)-2-(cyanomethyl)cyclohexyl acetate (6.53 g, 36.0 mmol) was dissolved in methanol (150 mL) and diluted with water (150 mL). At 0 ºC, potassium carbonate (17.44 g, 126.1 mmol) was added portionwise to the reaction portionwise over 10 min. The reaction was stirred at 0 ºC for 10 min. then brought to room temperature for 2 h. Reaction was complete by TLC (40 % ethyl acetate/hexanes, R_f = 0.178). Acidified reaction mixture with 1N HCl (300 mL) to pH = 5 and extracted with ethyl acetate (4 x 125 mL). The organic layer was dried with magnesium sulfate and the solvent was removed to give a yellow oil. The product was used without further purification. Yield = 4.73 g (94.4 %). ^{1}H NMR is identical to the racemic compound.[5]

Synthesis of 2-((1S,2R)-2-(triethylsilyloxy)cyclohexyl)acetonitrile. In a 500 mL round bottom flask, (1*R*,2*S*)-2-(cyanomethyl)cyclohexyl) acetate (4.73 g, 34.0 mmol) was dissolved in dichloromethane (300 mL). Dimethylaminopyridine (0.417g, 3.41 mmol) and triethylamine (16.5 mL, 12.0 g, 118 mmol) was added to the reaction. At 0 ºC, triethylsilylchloride (6.9 mL, 6.19 g, 41.1 mmol) was added dropwise to the reaction and stirred for 30 min. The reaction was brought to room temperature and stirred an additional 5 h. The reaction was quenched with saturated sodium bicarbonate (300 mL). The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organics were washed with brine (300 mL) then dried over magnesium sulfate. The solvent was removed to give a yellow-orange oil. The product was purified by column chromatography (SiO_2, 20% ethyl acetate/hexanes) to

give a pale yellow oil, which was the desired product containing a trace amount of triethyldisiloxane. Yield = 8.11 g (94.1 %).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.32 (ddd, ^3J = 4.4, 9.7 9.7 Hz, 1H, C*H*OSiEt$_3$), 2.54 (dd, ^3J = 3.9, ^2J = 16.6 Hz, 1H, C*H*$_2$CN), 2.42 (dd, ^{3}J = 7.2, ^2J = 16.6 Hz, 1H, C*H*$_2$CN), 1.90 (m, 2H), 1.71 (m, 2H), 1.58 (m, 1H), 1.24 (m, 4H), 0.95 (t, ^{3}J = 7.9 Hz, 9H, OSi(CH$_2$C*H*$_3$)$_3$), 0.60 (q, ^3J = 7.8 Hz, 6H, OSi(C*H*$_2$CH$_3$)$_3$). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 119.16, 73.94, 42.48, 35.90, 30.60, 25.31, 24.91, 20.91, 7.08, 5.27. FT-IR (neat, cm^{-1}): 2936, 2877, 2247, 1450, 1417, 1379, 1362, 1239, 1206, 1097, 1055, 1043, 1009, 962, 946, 886, 859, 876, 834, 822, 794, 744, 724, 679. HRMS-ESI (m/z): [M+Na]$^+$ calc'd for $C_{14}H_{27}NOSiNa$, 276.1754; found, 276.1753. $[\alpha]_D^{20} = -48.6$ (c = 2.0, CH_2Cl_2).

Synthesis of 2-((1S,2R)-2-(triethylsilyloxy)cyclohexyl)acetaldehyde. In a 500 mL round bottom flask, toluene (300 mL) was added to 2-((1*S*,2*R*)-2-(triethylsilyloxy)cyclohexyl)acetonitrile (7.90 g, 31.2 mmol). At -78 ºC, 1M diisobutyl aluminum hydride solution (47 mL, 47 mmol) was added dropwise over 1 h. The reaction was brought to 0 ºC for 3 h. The mixture was treated with Rochelle's salt (200 mL) and stirred at room temperature for 2 h. Filtered biphasic mixture through celite and isolated aqueous phase. The aqueous layer was extracted with ethyl acetate (4 x 75 mL). The combined organics were washed with brine (200 mL) then dried over magnesium sulfate. The solvent was removed to give a yellow oil. The product was purified by column chromatography (SiO_2, R_f = 0.43, CH_2Cl_2) to give a colorless oil. Yield = 3.1479 g (39.3 %, 59.6 % based on recovered starting material).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.71 (t, ^3J = 2.5 Hz, 1H, CO*H*), 3.25 (ddd, ^3J = 4.0, 9.7, 9.7 Hz, 1H, C*H*OSiEt$_3$), 2.65 (ddd, ^3J = 2.5, 6.0, ^2J = 16.0 Hz, C*H*$_2$COH), 2.11 (ddd, ^3J = 2.5, 7.2, ^2J = 16.0 Hz, C*H*$_2$COH), 1.91 (m, 2H), 1.74 (m, 2H), 1.62 (m, 1H), 1.28 (m, 3H), 1.03 (m, 1H), 0.94 (t, ^3J = 8.0 Hz, 9H, OSi(CH$_2$C*H*$_3$)$_3$, 0.58 (q, ^3J = 7.8 Hz, 6H, OSi(C*H*$_2$C*H*$_3$)$_3$. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 203.34, 75.72, 48.41, 41.39, 36.09, 31.75, 25.58, 25.15, 7.09, 5.28. FT-IR (neat, cm^{-1}): 2934, 2876, 2714, 1727, 1460, 1449, 1414, 1378, 1240, 1141, 1092, 1008, 976, 962, 947, 871, 805, 784, 742, 725.

HRMS-ESI (m/z): $[M+Na]^+$ calc'd for $C_{14}H_{28}O_2SiNa$, 279.1748; found, 279.1747. $[\alpha]_D^{21} = -7.0$ (c = 2.0, CH_2Cl_2).

Synthesis of ((1R,2S)-2((E)-but-2-enyl)cyclohexyloxy)triethylsilane, **6**. In the glovebox, chromium dichloride (10.28 g, 83.6 mmol) was loaded in a 1 L three-neck flask. On the Schlenk line, THF (400 mL) was transferred via cannula onto the chromium dichloride and stirred 1.5 h to break up the aggregated chromium. In a 100 mL round bottom flask, 2-((1*S*,2*R*)-2-(triethylsilyloxy)cyclohexyl) acetaldehyde (4.29 g, 16.7 mmol) was combined with 1,1-diiodoethane (7.94 g, 28.2 mmol) and THF (90 mL). At room temperature, the aldehyde solution was cannulated onto the chromium slurry. The reaction gradually turned red after stirring for 1.5 d. The reaction was poured into brine (350 mL), and the isolated organics were repeatedly washed with brine (200 mL). The organics were dried over $MgSO_4$ and the solvent was removed to give a green oil. The product was purified by column chromatography using a solvent gradient (SiO_2, 0–20% ethyl acetate/hexanes) to give a colorless oil (R_f = 0.80 in 10% ethylacetate/hexanes). Yield = 2.91 g (64.8 %, E:Z = 10:1 by GC). The major biproduct (R_f = 0.20) was the deprotected alcohol (yield = 0.5768 g (22.4%)), which could be isolated and reprotectected using standard procedures. The E:Z ratio of the desired product could be further improved by running a 5% (wt/wt) silver nitrate impregnated silica column (2% ethyl acetate/hexanes). Yield = 2.32 g (51.2%, E:Z = 26:1 by GC).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 5.38 (m, 2H, alkenyl), 3.20 (ddd, ^3J = 4.1, 9.7, 9.7 Hz, 1H, C*H*OSiEt$_3$), 2.49 (m, 1H, C*H*$_2$CHCHCH$_3$), 1.83 (m, 2H), 1.73-1.56 (m, 6H), 1.34-1.06 (m, 4H), 0.96 (t, ^3J = 7.8 Hz, 9H, OSi(CH$_2$C*H*$_3$)$_3$), 0.60 (q, ^3J = 7.8 Hz, 6H, OSi(C*H*$_2$CH$_3$)$_3$. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 130.08, 126.21, 75.40, 45.59, 36.33, 35.82, 30.27, 25.68, 25.31, 18.22, 7.20, 5.39. FT-IR (neat, cm^{-1}): 2934, 2877, 2857, 1457, 1449, 1415, 1377, 1238, 1203, 1130, 1095, 1051, 1008, 967, 942, 881, 862, 804, 741, 724, 785, 674. $[\alpha]_D^{20} = -32.1$ (c = 2.0, CH_2Cl_2).

Synthesis of triethyl((1R,2S)-2-(((2R,3R)-3-methyloxiran-2-yl)methyl)cyclohexyloxy)silane. In a 500 mL three-neck flask in air, ((1*R*,2*S*)-2((E)-but-2-enyl)cyclohexyloxy)triethylsilane was dissolved in a 1:2 mixture of acetonitrile:dimethoxymethane (116 mL). Tetrabutylammonium sulfate (0.26 g, 0.768 mmol) and sodium borate buffer (pH 10, 77 mL) was added to the reaction. Two addition funnels, one containing oxone (9.50 g, 15.5 mmol) dissolved in a 0.4 mM aqueous EDTA solution (77 mL) and the other containing 0.89 M aqueous potassium carbonate solution (67 mL, 59.6 mmol). At 0 ºC, chiral ketone **7** (1.98 g, 7.67 mmol) was added to the reaction. The two solutions were simultaneously added to the reaction over twenty minutes. After the addition was complete, the reaction was brought to room temperature and allowed to stir an additional 40 min. The reaction was quenched with water (300 mL), and extracted with ethyl acetate (4 x 75 mL). The combined organics were dried over sodium sulfate and the solvent was removed to give a cloudy oil. The product was purified by column chromatography using a solvent gradient (SiO_2, 2%–5% ethyl acetate/hexanes) to give a colorless oil. Yield = 0.90 g (82%, d.r. = 5:1 by ^{1}H NMR).

Major diastereomer: ^{1}H NMR (500 MHz, C_6D_6, ppm): δ 3.24 (ddd, ^3J = 4.2, 9.8, 9.8 Hz, 1H, C*H*OSiEt$_3$), 2.55 (ddd, ^3J = 2.3, 4.5, 6.9 Hz, 1H, C*H*(O)CHCH$_3$), 2.51 (dq, ^3J = 2.1, 5.2 Hz, 1H, CH(O)C*H*CH$_3$), 2.12 (ddd, ^3J = 4.2, 4.2, ^2J = 13.9 Hz, 1H, C*H*$_2$CH(O)CHCH$_3$), 1.99 (m, 1H), 1.85 (m, 1H), 1.59 (m, 1H), 1.50 (m, 2H), 1.33 (m, 1H), 1.23 (ddd, ^3J = 8.9, 7.1 Hz, ^2J = 13.9 Hz, 1H, C*H*$_2$CH(O)CHCH$_3$), 1.09 (m, 1H), 1.05 (d, ^3J = 5.2 Hz, 3H, CH(O)CHC*H*$_3$), 1.02 (t, ^3J = 8.0 Hz, 9H, OSi(CH$_2$C*H*$_3$)$_3$), 0.61 (q, ^3J = 8.0 Hz, 6H, OSi(C*H*$_2$CH$_3$)$_3$). ^{13}C{^{1}H} NMR (125 Hz, C_6D_6, ppm): δ 75.76, 59.04, 53.63, 45.26, 36.78, 36.04, 31.48, 26.08, 25.47, 18.15, 7.67, 6.00. IR (neat, cm^{-1}): 2954, 2931, 2876, 2858, 1459, 1448, 1379, 1360, 1239, 1207, 1094, 1075, 1007, 969, 943, 896, 882, 860, 829, 800, 781, 742, 724, 666. HRMS-ESI (m/z): [M+Na]$^+$ calc'd for $C_{16}H_{32}O_2SiNa$, 307.2064; found, 307.2064. $[\alpha]_D^{20} = -15.8$ (c = 2.0, CH_2Cl_2).

Minor diastereomer: ^{1}H NMR (500 MHz, C_6D_6, ppm): δ 2.21 (ddd, ^3J = 3.9, 5.5, ^2J = 13.5 Hz, 1H, C*H*$_2$CH(O)CHCH$_3$), 1.78 (m, 1H), 0.84 (m, 1H) other resonances overlap with major diastereomer.

$^{13}C\{^{1}H\}$ NMR(125 MHz, C_6D_6, ppm): δ 58.21, 55.22, 43.55, 36.60, 36.11, 31.10, 25.93, 25.37, 18.17 other resonances overlap with major diastereomer.

Synthesis of (1R,2S)-2-(((2R,3R)-3-methyloxiran-2-yl)methyl)cyclohexanol, **1b**. In a 50 mL round bottom flask, triethyl((1*R*,2*S*)-2-(((2*R*,3*R*)-3-methyloxiran-2-yl)methyl)cyclohexyloxy)silane (0.24 g, 0.83 mmol) was dissolved in THF (8.5 mL). At 0 ºC, a 1M THF solution of tetrabutylammonium fluoride (1.6 mL, 1.6 mmol) was syringed onto the reaction. The reaction was stirred 40 min. then diluted with hexanes (12 mL). The mixture was filtered through a small plug of silica, which was flushed with 50% ethyl acetate/hexanes. The product was purified by repeated azeotropic distillation with benzene (5 x 2 mL) then dried *en vacuo* for a few hours to give a colorless oil. Yield = 0.13 g (93.8 %). The product contained a minor amount of cyclized products (5% **2b**, 5% **3b**). To prevent premature cyclization, **1b** was stored as a frozen benzene solution (~10 mg/mL) at -40 ºC.

Major diastereomer: ^{1}H NMR (500 MHz, C_6D_6, ppm): δ 3.15 (m, 1H, C*H*OH), 2.53 (ddd, ^{3}J = 2.3, 3.4, 7.2 Hz, 1H, C*H*(O)CHCH$_3$), 2.44 (dq, ^{3}J = 2.2, 5.1 Hz, 1H, CH(O)C*H*CH$_3$), 1.93 (br s, 1H, O*H*), 1.87 (m, 1H), 1.79 (ddd, ^{3}J = 3.5, 6.8, ^{2}J = 16.8 Hz, 1H, CH_2CH(O)CHCH$_3$), 1.64 (m, 1H), 1.56 (m, 1H), 1.47 (m, 1H), 1.31 (m, 1H), 1.2 (m, 1H), 1.07 (m, 2H), 1.02 (d, ^{3}J = 5.2 Hz, 1H, CH_3), 0.94 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 74.94, 59.09, 55.13, 44.37, 36.00, 35.97, 31.90, 26.42, 25.72, 18.24. FT-IR (neat, cm^{-1}): 3428, 2936, 2857, 1448, 1381, 1356, 1306, 1258, 1234, 1193, 1118, 1060, 1038, 967, 937, 893, 878, 857, 797, 720. HRMS-ESI (m/z): $[M+Na]^+$ calc'd for $C_{10}H_{18}O_2Na$, 193.1199; found, 193.1205. $[\alpha]_D^{20} = -45.6$ (c = 2.0, CH_2Cl_2).

Minor diastereomer: ^{1}H NMR(500 MHz, C_6D_6, ppm): δ 3.02 (m, 1H), 2.09 (m, 1H), 2.00 (m, 1H), 1.72 (m, 1H) other resonances overlap with major diastereomer.

*General procedure for the cyclization of **1b***. An aliquot of the **1b** stock solution (0.5 mL, 3–5 mg) was placed in a vial and the solvent was removed *en vacou* for 30 min. At room temperature, the solvent (see Table 1) was added to the vial and the vial was agitated for 1 minute at which time the reaction became homogeneous. After stirring the reaction for the allotted time (see Table 1), the

aqueous solution was extracted into dichloromethane (3 x 2 mL). The organic layer was dried over $MgSO_4$ and filtered through a small plug of celite. Removal of the solvent gave a colorless residue. Mass recovery for the reactions was generally >90%. The reaction mixture was analyzed by ^{1}H NMR in C_6D_6 (note: NMR analysis in $CDCl_3$ resulted in poor resolution of the starting material(s) from the product(s). There was an insignificant amount of cyclization in C_6D_6 even after several days at room temperature). The reactions were run in triplicate, the average of which are shown in Table 1, along with the average error in parentheses. **2b** (R_f = 0.38) could be separated from **3b** (R_f = 0.30) by column chromatography (SiO_2, 50% ethyl acetate/hexanes) and identification was possible by 2D NMR analysis and by observing downfield shifts of the appropriate resonances resulting from acetate functionalization.

2b: ^{1}H NMR (400 MHz, C_6D_6, ppm): δ 3.13 (m, 2H, OC*H*(CH_3)C*H*(OH)CH_2), 2.71 (ddd, ^3J = 4.1, 9.5, 11.0 Hz, 1H, CH_2C*H*COCH_2), 2.00 (m, 1H, CH_2C$HOCH_2$), 1.70 (ddd, ^3J = 4.1, 4.1, ^2J = 12.1 Hz, 1H, CH_2CHOH), 1.57 (m, 1H), 1.42 (m, 1H), 1.39 (d, ^3J = 5.91 Hz, 3H, CH_3), 1.30 (m, 2H), 0.88–1.14 (m, 4H), 0.77 (m, 1H). ^{13}C NMR (100 MHz, C_6D_6, ppm): δ 81.65, 79.19, 73.03, 42.16, 40.98, 32.94, 32.00, 26.16, 25.56, 19.14. FT-IR (KBr, cm^{-1}): 3416, 3371, 2986, 2972, 2926, 2912, 2858, 2880, 2822, 1473, 1460, 1443, 1433, 1386, 1377, 1372, 1358, 1350, 1332, 1306, 1280, 1250, 1213, 1171, 1140, 1111, 1095, 1069, 1047, 1031, 1018, 949, 939, 895, 872, 860, 842, 816, 782, 618, 577, 545, 509, 460. HRMS-ESI (m/z): $[M+Na]^+$ calc'd for $C_{10}H_{18}O_2Na$, 193.1199; found, 193.1204. $[\alpha]_D^{21} = -10.0$ (c = 2.0, CH_2Cl_2).

3b: ^{1}H NMR (400 MHz, C_6D_6, ppm): δ 3.92 (ddd, ^3J = 4.3, 6.4, 12.8 Hz, 1H, C*H*(OH)CH_3), 3.83 (ddd, ^3J = 3.2, 6.2, 10.4 Hz, 1H, OC*H*CH(OH)CH_3), 3.05 (ddd, ^3J = 3.8, 10.1, 11.0 Hz, 1H, CH_{bh}), 2.10 (m, 1H, CH_2CHOCH(OH)CH_3), 1.67 (m, 1H), 1.59 (m, 2H), 1.49 (m, 2H), 1.35-1.15 (m, 2H), 1.06 (d, ^3J = 6.41 Hz, 1H, CH_3), 1.03-0.82 (m, 2H). ^{13}C NMR (100 MHz, C_6D_6, ppm): δ 84.26, 83.09, 69.63, 46.77, 32.64, 32.01, 29.50, 26.42, 24.95, 18.94. IR (KBr, cm^{-1}): 3452, 2958, 2937, 2876, 1456, 1399, 1385, 1367, 1359, 1347, 1339, 1301, 1284, 1259, 1203, 1180, 1149, 1109, 1095, 1073, 1052, 1029, 978, 966,

955, 931, 918, 897, 859, 846, 838, 801, 788, 676, 633, 599, 555, 539, 482, 768. HRMS-ESI (m/z): $[M+Na]^+$ calc'd for $C_{10}H_{19}O_2Na$, 193.1199; found, 193.1203. $[\alpha]_D^{20} = -8.8$ (c = 1.0, CH_2Cl_2).

Synthesis of (2S,3R,4aS,8aR)-2-methyloctahydr-2H-chromen-3-yl acetate. In a 20 mL vial, **2b** (0.016 g, 0.094 mmol) was dissolved in pyridine (3.0 mL). *p*-Dimethylaminopyridine (~10 mg) was added to the reaction along with acetic anhydride (0.050 mL, 0.054 g, 0.53 mmol) was added. Stirred the reaction for 2 h. Diluted reaction with dichloromethane (10 mL) and extracted with 1N HCl (4 x 8 mL). Removed the solvent to give the product as a colorless solid. Yield = 0.018 g (90%).

^{1}H NMR (400 MHz, C_6D_6, ppm): δ 4.72 (ddd, ^3J = 4.8, 9.5, 10.4 Hz, 1H, C*H*OAc), 3.38 (dq, ^3J = 6.1, 9.5, 1H, C*H*CH_3), 2.69 (ddd, ^3J = 4.1, 9.2, 11.0 Hz, 1H, CH_2C*H*O), 2.02-1.92 (m, 2H), 1.68 (s, 3H, OCOC*H*$_3$), 1.54 (m, 1H), 1.37 (m, 1H), 1.29 (d, ^3J = 6.1 Hz, 3H, CHC*H*$_3$), 1.30-1.22 (m, 2H), 1.10-0.87 (m, 4H), 0.68 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 169.14, 81.19, 75.68, 74.00, 40.94, 36.66, 32.22, 31.16, 25.39, 24.90, 20.53, 18.39. FT-IR (KBr, cm^{-1}): 2935, 2876, 2710, 1727, 1460, 1449, 1414, 1378, 1240, 1143, 1092, 1008, 975, 964, 947, 871, 805, 784, 742, 726. HRMS-ESI (m/z): $[M+Na]^+$ calc'd for $C_{12}H_2O_3Na$, 235.1305; found, 235.1309. $[\alpha]_D^{20} = -20.4$ (c = 2.0, CH_2Cl_2).

Synthesis of (R)-1-((2S,3aS,7aR)-octahydrobenzofuran-2-yl)ethyl acetate. In a 20 mL vial, **3b** (0.067 g, 0.40 mmol) was dissolved in dichloromethane (8.0 mL). Pyridine (0.30 mL, 0.29 g, 3.7 mmol) followed by acetic anhydride (0.19 mL, 0.21 g, 2.0 mmol) and *p*-dimethylaminopyridine (0.005 g, 0.04 mmol) was added to the reaction. The mixture was stirred at room temperature for 1h. The reaction was diluted with dichloromethane (20 mL) then extracted with 1N HCl (3 x 30 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed to give a colorless oil. The product was purified by column chromatography (SiO_2, 25% ethyl acetate/hexanes, R_f = 0.67) to give a colorless oil. Yield = 0.072 g (85.5%)

^{1}H NMR (400 MHz, C_6D_6, ppm): δ 5.15 (dt, ^3J = 6.3, 12.3 Hz, 1H, C*H*OCOCH$_3$), 4.01 (m, 1H, C*H*CHOCOCH$_3$), 3.04 (ddd, ^3J = 3.8, 9.7, 11.0 Hz, 1H, C*H*(O)CHCHOCH$_3$), 2.12 (m, 1H,

CH_2CHCHOCOCH$_3$), 1.80 (m, 1H), 1.77 (s, 3H, COCH_3), 1.69 (m, 1H), 1.61 (m, 1H), 1.52 (m, 1H), 1.31 (d, ^3J = 6.3 Hz, CHCH_3), 1.36-1.25 (m, 2H), 1.13-0.83 (m, 3H). ^{13}C NMR (100 MHz, C_6D_6, ppm): δ 169.63, 83.43, 80.13, 73.03, 46.21, 34.35, 31.99, 28.98, 25.94, 24.44, 20.88, 16.70. IR (neat, cm^{-1}): 2935, 2859, 1739, 1454, 1373, 1310, 1242, 1143, 1060, 1046, 1021, 1000, 952, 938, 928, 866, 835, 813. HRMS-ESI (m/z): [M+Na]$^+$ calc'd for $C_{12}H_{20}O_3Na$, 235.1305; found, 235.1311. $[\alpha]_D^{21} = -20.5$ (c = 2.0, CH_2Cl_2).

II. Kinetic Procedures and Analysis

General considerations. Kinetic measurements were made using ^{1}H NMR spectroscopy on Varian Inova 500 MHz spectrometers equipped with an inverse broadband gradient probe (gHX). The spectrometer was brought to the desired reaction temperature and calibrated using an ethylene glycol external standard. For reactions in H_2O, suppression of the solvent peak was achieved by either presaturation of the solvent peak or with shaped pulse sequences using the "presat" or "wet1D" Varian macros, respectively. Measurements in deuterium oxide (or D_2O/DMSO-d_6 mixtures) were buffered using potassium phosphate buffer (0.1 M) maintained at pD 7.0. The pD of the solution was measured at the reaction temperature using a Symphony™ Posi-pHlo Ag/AgCl pH glass electrode calibrated at the reaction temperature with standard solutions. For reactions in D_2O, a correction for the solvent isotope effect that is typical for glass electrodes was applied ($pD = pH_{meter} + 0.4$).[7] pD of D_2O/DMSO-d_6 mixtures were measured according to established procedures.[8] The methyl resonances for epoxy alcohol **1a** (1.24 ppm, d, ^{3}J = 5.0 Hz, 3H, 70 ºC) and the products **2a** (1.18 ppm, d, ^{3}J = 5.6 Hz, 3H, 70 ºC) and **3a** (1.08 ppm, d, ^{3}J = 6.1 Hz, 3H, 70 ºC) were used to follow the cyclization reaction for **1a**. No other products or intermediates were observable. Overlapping resonances from the minor diastereomer were avoided by preparatory HPLC purification of the dimethylphenylsilyl-protected alcohol precursor (5% ethyl acetate/hexanes). Unfortunately, the analogous methyl resonances for **1b** were obstructed by resonances assigned to the cyclohexyl moeity. Instead, the epoxide protons of **1b** (2.98 ppm, m, 2H, 45 ºC) and the carbinol resonances of **2b** (3.10 ppm, ddd, ^{3}J = 4.2, 10.7, 10.7 Hz, 1H, 45 ºC) and **3b** (3.97-

3.85 ppm, m, 2H, 45 ºC) were used to follow the reaction. Resonances resulting from cyclization of the minor diastereomer overlap with **2b**, but a correction could be applied to integrations of **2b** by subtracting integrals of an unobstructed carbinol resonance assigned to the minor diastereomeric product (3.80 ppm, m, 1H, 45 ºC). All reactions with the exception of those carried out in H_2O were run in triplicate and are reported in Scheme S-3 (average error in parentheses).

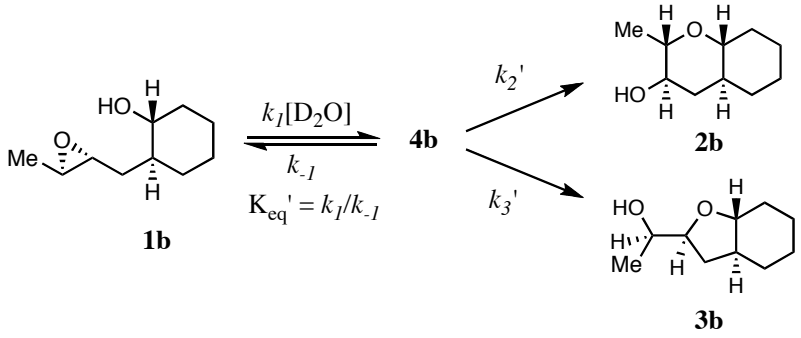
General procedure for kinetic experiments. In a 20 mL vial, the epoxy alcohol (2-5 mg) was dissolved in the appropriate solvent (0.8 mL) and shaken at room temperature for 1 min. The homogeneous mixture was gently heated for 30 s, and the solution (0.7 mL) was injected into a heated NMR tube. Bubbles were expelled by gently tapping the tube against a table before inserting into the spectrometer. After allowing the reaction to reach the reaction temperature (~3 min.), the sample was locked and shimmed. A "t = 0" spectrum was obtained, and iterative measurements were obtained by using the array function set for the pre-acquisition delay parameter (Varian). Reactions were monitored over at least 3 half-lives at which point a final spectrum was taken. The observed rate constants reported were obtained from following the disappearing starting material, but similar rate constants could also be obtained by observing the products. The raw data was fit to a three-parameter exponential function ($f(t) = a + be^{-ct}$) using the "General Fit" function in the Kaleidagraph™ v. 3.6 software (based on the Levenberg-Marquardt algorithm). Similar results were obtained by least-squares analysis. Representative kinetic curves for **1a** and **1b** are in Figures S-1 and S-2, respectively. The product ratios (S = [**2**]/[**3**]) were determined by subtracting the amount of premature cyclization products observed in the t = 0 spectrum from the final spectrum. Selectivity remained constant throughout all experiment once enough of each regioisomer was formed to be within measurement error (ca. 2-3%). The apparent rate constants k_2 and k_3 were obtained by the formulas $k_2 = k_{obs}[(S/S+1)]$ and $k_{obs} = k_2+k_3$.

Kinetic Analysis. A detailed treatment of the kinetic parameters obtainable from the experiments carried out in DMSO-d_6/D_2O mixtures is beyond the scope of this publication (and requires additional

experimentation), but a brief discussion of the mechanism proposed in Scheme 2 and a derivation of the associated kinetic rate is relevant.

For **1b**, it is proposed that an equilibrium between the ground state and an intermediate requiring one additional water molecule precedes rate-determining cyclization (Scheme S-2).

Scheme S-2. Proposed mechanism for **1b**. Waters of solvation and proton transfer step(s) are not shown for clarity.



Assuming the reaction is carried out under pseudo-first order conditions and that the steady-state approximation is appropriate for **4b**, a rate law can be derived (eq 4) which can be further simplified assuming a rapid pre-equilibrium (i.e. $k_{-1} >> k_{cyc}$).

$$rate = \frac{k'_{cyc}k_1[D_2O][\mathbf{1b}]}{k_{-1} + k'_{cyc}} = k_{obs}[\mathbf{1b}] \quad (4)$$

$$\text{where : } k'_{cyc} = k'_2 + k'_3 \quad (5)$$

$$rate = k'_{cyc}K'_{eq}[D_2O][\mathbf{1b}] = k_{obs}[\mathbf{1b}] \quad (6)$$

Substituting (5) into (6), the apparent rate constants for the formation of **2** (k_2) and **3** (k_3) can be obtained straightforwardly from k_{obs} and the observed selectivity (S = [**2**]/[**3**]) using the equations $k_2 = k_{obs}$*[S/(S+1)] and $k_3 = k_{obs}$-k_2:

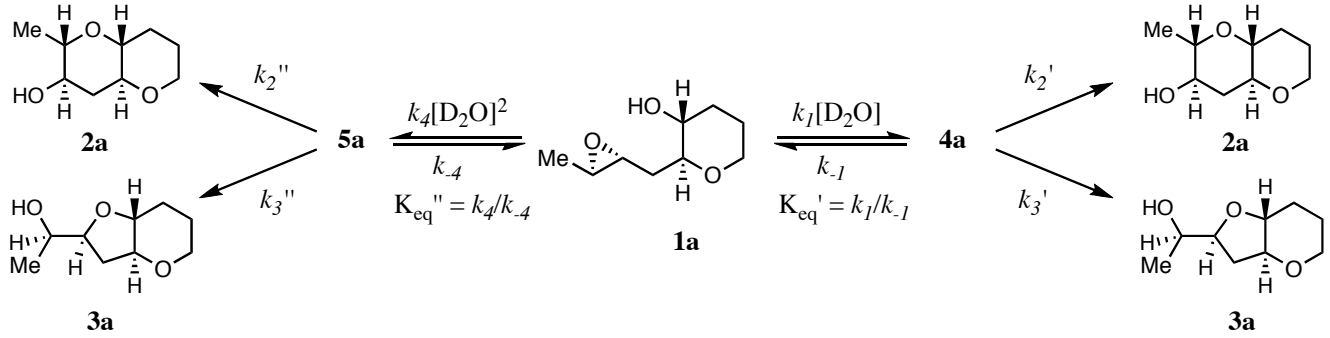
$$k_2 = k'_2K'_{eq}[D_2O] \quad (7)$$

$$k_3 = k'_3K'_{eq}[D_2O] \quad (8)$$

According to (7) and (8), plots of k_2 and k_3 vs. $[D_2O]$ should be linear (Figure 1).

The more complicated case is for **1a**, where a pre-equilibrium involving two additional water molecules is proposed to be in competition with a pre-equilibrium involving one additional water molecule; both pathways proceed to product by rate determining cyclizations (Scheme S-3).

Scheme S-3. Proposed mechanism for **1a**. Waters of solvation and proton transfer step(s) are not shown for clarity.



Again assuming the steady-state approximation on the two intermediates **4a** and **5a**, a kinetic rate law can be obtained (9), which can be simplified to (12) by applying the rapid pre-equilibrium constraint:

$$rate = \frac{k'_{cyc}k_1[D_2O][\mathbf{1a}]}{k_{-1} + k'_{cyc}} + \frac{k''_{cyc}k_4[D_2O]^2[\mathbf{1a}]}{k_{-4} + k''_{cyc}} = k_{obs}[\mathbf{1a}] \tag{9}$$

$$\text{where : } k'_{cyc} = k'_2 + k'_3 \tag{10}$$

$$k''_{cyc} = k''_2 + k''_3 \tag{11}$$

$$rate = k_{obs}[\mathbf{1a}] = \left(k'_{cyc}K'_{eq}[D_2O] + k''_{cyc}K''_{eq}[D_2O]^2\right)[\mathbf{1a}] \tag{12}$$

$$\text{where : } k_{obs} = k'_{cyc}K'_{eq}[D_2O] + k''_{cyc}K''_{eq}[D_2O]^2 \tag{13}$$

Assuming that the pathway that is second order in water is selective for **2a** and contributes little to the formation of **3a** (i.e., k_2''$[D_2O]^2 > k_3$''$[D_2O]^2 << k_3$'$[D_2O]$), apparent rate constants for the formation of the two products (k_2 and k_3) can be obtained from (13) and the relationships, $k_2 = k_{obs}$*[S/(S+1)] and $k_3 = k_{obs}$-k_2:

$$k_2 = k'_2K'_{eq}[D_2O] + k''_2K''_{eq}[D_2O]^2 \tag{14}$$

$$k_3 = k'_3K'_{eq}[D_2O] \tag{15}$$

From (14) and (15), it is apparent that plots of k_2 and k_3 vs $[D_2O]$ should have polynomial and linear dependences, respectively (Figure 2). Rearrangement of (13) gives:

$$\frac{k_2}{[D_2O]} = k_2'K'_{eq} + k_2''K''_{eq}[D_2O] \tag{16}$$

which predicts that plots of $k_2/[D_2O]$ should be linear (Figure 3).

Perhaps a more appropriate derivation of the kinetic law according to Scheme S-3 is achieved using principles of the Curtin-Hammett postulate.[9] Since the equilibrating species proposed in Scheme S-3 are conformational isomers (albeit solvent-assisted), it is possible that a significant amount of the intermediates **4a** and **5a** are present throughout the reaction and that changes in their concentration are significant. The consequence of this reality is that the steady-state approximation cannot be applied to intermediates **4a** and **5a**, and the resonances observed in the NMR are actually weighted average of **1a, 4a**, and **5a**. If rapid equilibrium precedes rate-determining cyclization (i.e. k_1, k_{-1}, k_2, $k_{-2} >> k_{cyc}'$, k_{cyc}''), then a Curtin-Hammett situation is established and the mole fraction of each equilibrating species (X_n) is constant or:

$$[\mathbf{1a}]_{ob} = [\mathbf{1a}] + [\mathbf{4a}] + [\mathbf{5a}] \tag{17}$$

$$\frac{[\mathbf{1a}]}{[\mathbf{1a}]_{ob}} = X_{\mathbf{1a}} = \text{const.} \tag{18}$$

$$\frac{[\mathbf{4b}]}{[\mathbf{1a}]_{ob}} = X_{\mathbf{4a}} = const. \tag{19}$$

$$\frac{[\mathbf{5b}]}{[\mathbf{1a}]_{ob}} = X_{\mathbf{5a}} = const. \tag{20}$$

A reaction operating under Curtin-Hammett conditions follows Winstein-Holness kinetics:

$$\text{rate} = k_{obs}[\mathbf{1a}]_{ob} = \left(k'_{cyc}X_{\mathbf{4a}} + k''_{cyc}X_{\mathbf{5a}}\right)[\mathbf{1a}]_{ob} \tag{21}$$

$$\text{where}: k_{obs} = k'_{cyc}X_{\mathbf{4a}} + k''_{cyc}X_{\mathbf{5a}} \tag{22}$$

k_{obs} is a constant under pseudo-first order conditions, because $X_{\mathbf{4a}}$ and $X_{\mathbf{5a}}$ are constant under the Curtin-Hammett constraints. This does not mean that $X_{\mathbf{4a}}$ and $X_{\mathbf{5a}}$ are constant under all reaction conditions. From Scheme S-3, expressions for the equilibrium constants can are obtained:

$$K'_{eq} = \frac{[\mathbf{4a}]}{[\mathbf{1a}][D_2O]} \tag{23}$$

$$K''_{eq} = \frac{[\mathbf{5a}]}{[\mathbf{1a}][D_2O]^2} \tag{24}$$

$$K_{tot} = \frac{K''_{eq}}{K'_{eq}} = \frac{[\mathbf{5b}]}{[\mathbf{4b}][D_2O]} \tag{25}$$

$X_{\mathbf{4a}}$ and $X_{\mathbf{5a}}$ can then be related to $[D_2O]$ by substituting rearranged versions of (23)-(25) into (18) and (19). After some algebraic manipulation one obtains:

$$X_{\mathbf{4a}} = \frac{K'_{eq}[D_2O]}{K'_{eq}[D_2O] + K''_{eq}[D_2O]^2 + 1} \tag{26}$$

$$X_{\mathbf{5a}} = \frac{K''_{eq}[D_2O]^2}{K'_{eq}[D_2O] + [D_2O]^2 + 1} \tag{27}$$

Substituting(26) and (27) into (22) gives an expression for k_{obs}:

$$k_{obs} = \frac{k'_{cyc}K'_{eq}[D_2O] + k''_{cyc}K''_{eq}[D_2O]^2}{K'_{eq}[D_2O] + K''_{eq}[D_2O]^2 + 1} \tag{28}$$

It is interesting to compare (28) to (13), the analogous equation obtained using the steady state approximation (Note: k_2 and k_3 can be obtained in a similar fashion as described above, the only difference between (28) and the analogous expressions for k_2 and k_3 being the subscripts. For the sake of brevity, the remainder of the discussion will refer to k_{obs}). The equations are identical except that the denominator term in (28) complicates the relationship between k_{obs} and $[D_2O]$. It is clear that equation (28) does not accurately reflect the reaction behavior under conditions where a significant amount of equilibrating species exists (i.e. $K'_{eq}[D_2O] \approx K''_{eq}[D_2O] \approx 1$). However, it is interesting to consider some

limiting situations. If the conditions are such that **4a** predominates among the equilibrating species, then $K'_{eq}[D_2O] >> K''_{eq}[D_2O] + 1$ and (28) simplifies to:

$$k_{obs} = k'_{cyc} + k''_{cyc}K^{tot}_{eq}[D_2O] \tag{29}$$

However, under these circumstances plots of k_{obs} vs. $[D_2O]$ should be linear while plots of $k_{obs}/[D_2O]$ vs. $[D_2O]$ should not. Another possibility is that the reaction conditions are such that **5a** predominates (i.e. $K''_{eq}[D_2O]^2 >> K'_{eq}[D_2O] + 1$). Equation (27) then simplifies to:

$$k_{obs} = \frac{k'_{cyc}}{K^{tot}_{eq}[H_2O]} + k''_{cyc} \tag{30}$$

This situation predicts a linear plot of k_{obs} vs. $1/[D_2O]$ rather than a linear plot $k_{obs}/[D_2O]$ vs. $[D_2O]$. It is possible that both **4a** and **5a** predominate (i.e. $K'_{eq}[D_2O] + K''_{eq}[D_2O]^2 >> 1$). Under such conditions, (28) reduces to:

$$k_{obs} = \frac{k'_{cyc} + k''_{cyc}K^{tot}_{eq}[D_2O]}{1 + K^{tot}_{eq}[D_2O]} \tag{31}$$

Once again, a complex relationship between k_{obs} and $[D_2O]$ results. Finally, it is possible that **1a** is the predominate species in the equilibrium (i.e. $K'_{eq}[D_2O] + K''_{eq}[D_2O]^2 << 1$). These conditions simplify (28) to (13), the equation derived from the steady state approximation. This is reasonable because the implied constraints on (28) are essentially the same constraints used in the steady state approximation. As mentioned above, this expression satisfactorily reproduces the observed rate behavior unlike any of the other expressions obtained using the Curtin-Hammett constraints. While a steady-state analysis of Scheme S-3 seems to be most consistent with the data, it is still necessary to justify its application in light of the assumed relative ease of isomerization compared to cyclization. One possibility is that entropic penalties undoubtedly incurred by interconverting **1a** to **4a** and **5a** significantly raise the energy of the intermediates and allow for the steady-state approximation to hold. A more likely justification, however, is that there is a large concentration of conformations that do not lead to productive reaction.

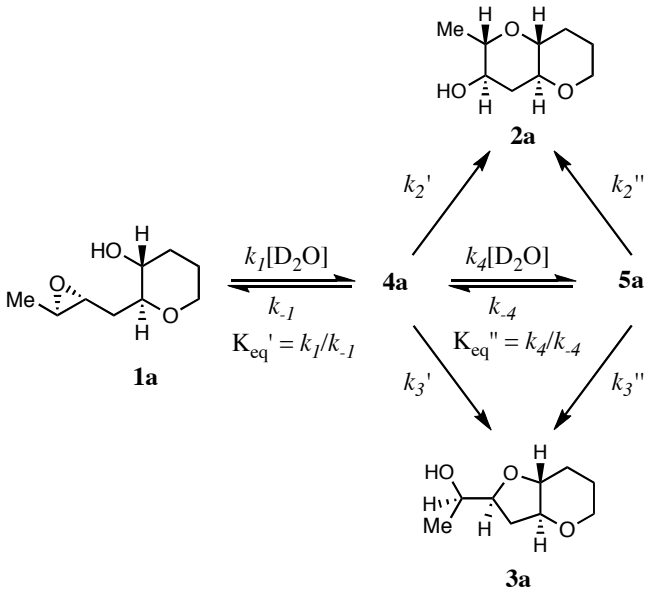
In order to satisify the definition in (18), $X_{\mathbf{1a}}$ is more accurately described as the mole fraction of all conformations that do not lead to reaction (not just the proposed ground state conformation **1a**). If $X_{\mathbf{1a}} >> X_{\mathbf{4a}}, X_{\mathbf{5a}}$, then (19) and (20) become:

$$X_{\mathbf{4a}} = K'_{eq}[D_2O] \tag{31}$$

$$X_{\mathbf{5a}} = K''_{eq}[D_2O]^2 \tag{32}$$

using the equilibrium expressions (23) and (24). Substituting (31) and (32) into (22) give the steady-state equation (13). To conclude, it is important to point out that Scheme S-3 is not the only kinetic scheme that can satisfactorily explain the experimental observations. For example, it is possible that the reactive intermediate that requires one additional water molecule is on the pathway to the reactive intermediate requiring two water molecules (Scheme S-4).

Scheme S-4. Alternative mechanistic route for the cyclization of **1a**. Waters of solvation and proton transfer step(s) are omitted for clarity.



Using similar logic to what is presented above, a kinetic rate law can be derived that has the form:

$$\text{rate} = k_{obs}[\mathbf{1a}] = \left(K'_{eq}k'_{cyc}[D_2O] + K'_{eq}K''_{eq}k''_{cyc}[D_2O]^2\right)[\mathbf{1a}] \tag{33}$$

$$\text{where: } k_{obs} = K'_{eq}k'_{cyc}[D_2O] + K'_{eq}K''_{eq}k''_{cyc}[D_2O]^2 \tag{34}$$

Equations (33) and (34) are kinetically indistinguishable from (12) and (13). We currently do not strongly favor either of these possibilities.

III. Kinetic Plots and Data

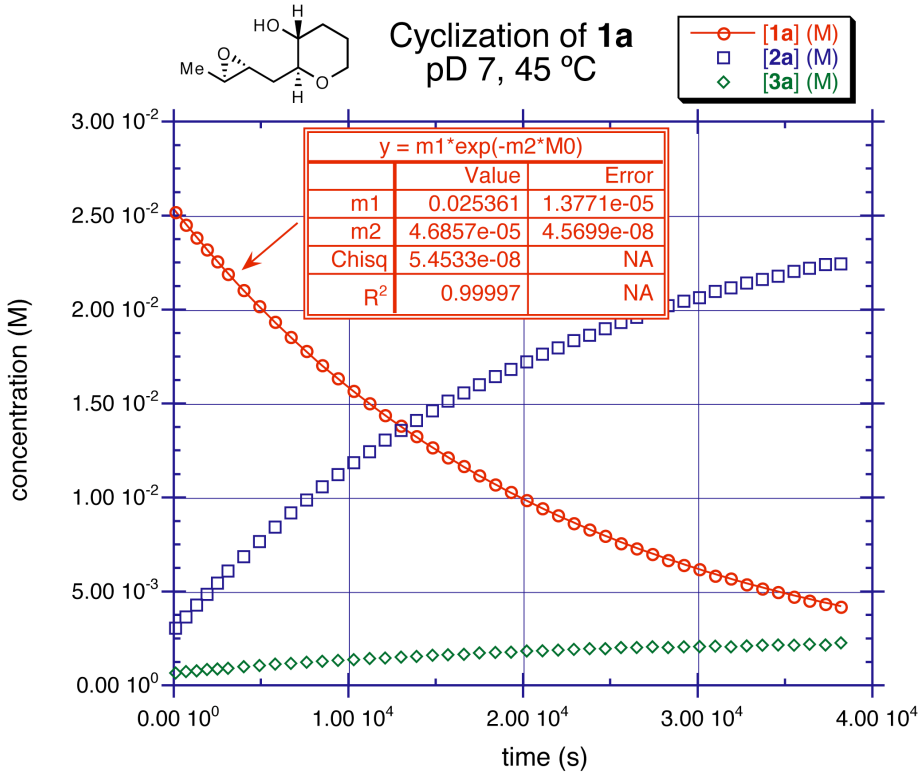


Figure S-1. Representative concentration vs. time plot for the cyclization of **1a** at 45 ºC and pD 7.

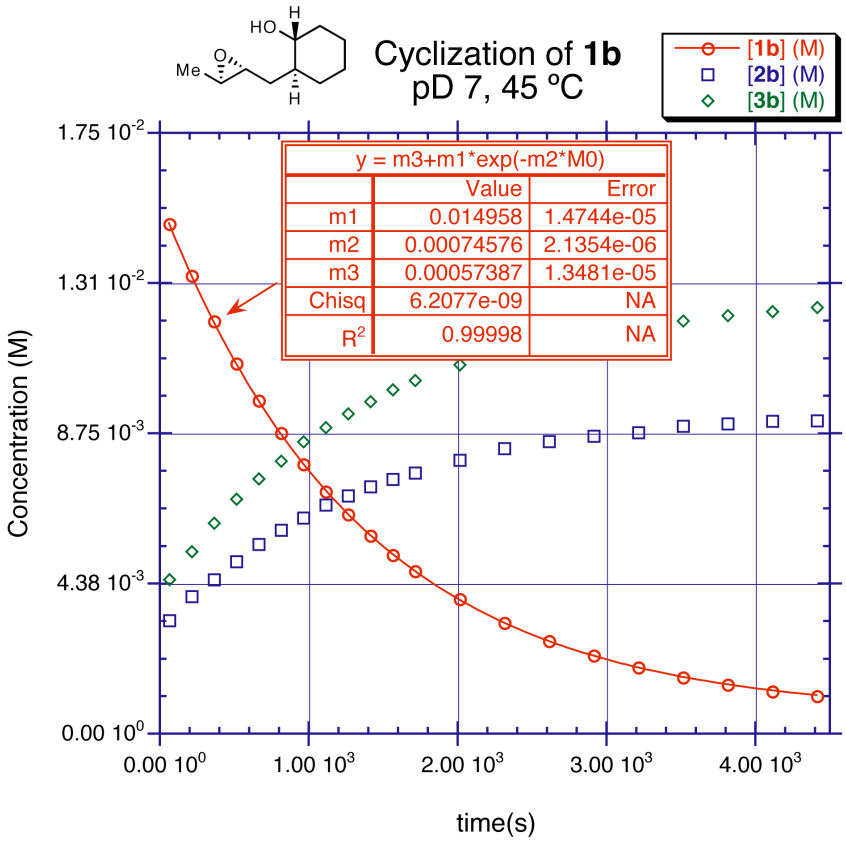


Figure S-2. Representative concentration vs. time plot for the cyclization of **1b** at 45 ºC and pD 7.

Table S-1. Summary of kinetic data. Values are an average of three kinetic runs with the average error in parentheses.

entry	X	T (ºC)	solvent, [water]	k_{obs}*10^4 (s^{-1})	**2**:**3**
1	O (**1a**)	45	H_2O, 54.6 M	0.62[a]	11.4
2	O (**1a**)	45	D_2O, 54.6 M	0.47[a]	10.3
3	O (**1a**)	70	D_2O, 54.6 M	3.10 (0.12)	10.8 (0.2)
4	O (**1a**)	70	D_2O/DMSO-d_6, 50.1 M	2.40 (0.03)	9.7 (0.5)
5	O (**1a**)	70	D_2O/DMSO-d_6, 45.2 M	1.86 (0.07)	9.1 (0.2)
6	O (**1a**)	70	D_2O/DMSO-d_6, 39.7 M	1.29 (0.01)	9.0 (0.6)
7	O (**1a**)	70	D_2O/DMSO-d_6, 34.9 M	0.85 (0.04)	8.0 (0.6)
8	CH_2 (**1b**)	45	H_2O, 54.6 M	10.5[a]	0.7
9	CH_2 (**1b**)	45	D_2O, 54.6 M	7.38 (0.15)	0.7 (0.1)
10	CH_2 (**1b**)	45	D_2O/DMSO-d_6, 50.1 M	6.03 (0.10)	0.7 (0.1)
11	CH_2 (**1b**)	45	D_2O/DMSO-d_6, 45.2 M	4.69 (0.06)	0.7 (0.1)
12	CH_2 (**1b**)	45	D_2O/DMSO-d_6, 39.7 M	2.96 (0.05)	0.8 (0.1)
13	CH_2 (**1b**)	45	D_2O/DMSO-d_6, 34.9 M	2.03 (0.06)	0.7 (0.1)

[a] Single kinetic measurement

Linear free energy relationships for the kinetics in DMSO-d_6/D_2O are shown in Figures S-3 through S-5 for **1a** and Figures S-6 through S-8 for **1b**, respectively. The Kamlett-Taft parameter for solvent polarizability (π*) and the relative permittivity (ε) vary little in the range of solvent composition examined. Reactions carried out in pure D_2O were used as the reference reaction (i.e. $k_s(0)$).

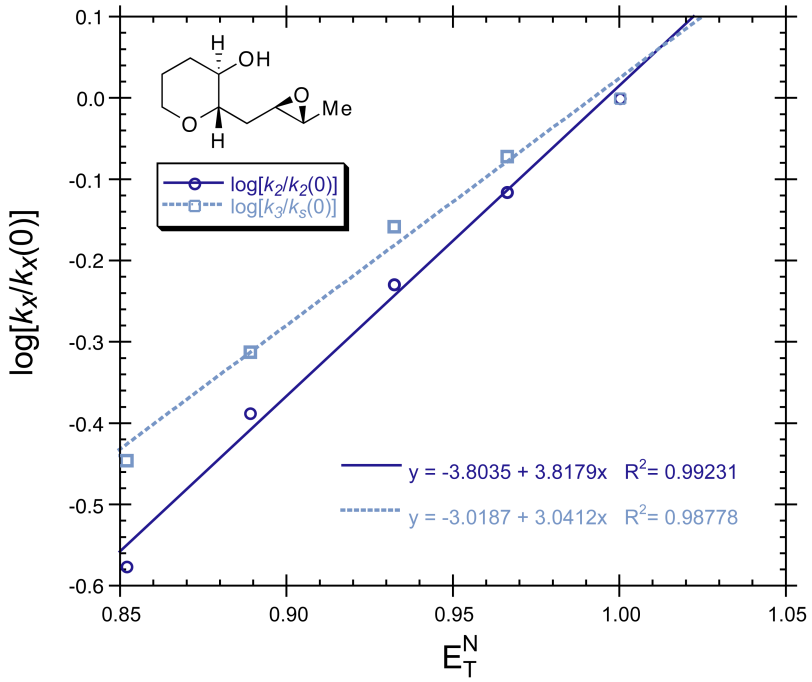


Figure S-3. Sensitivity of **1a** to Dimroth and Reichard's polarity scale[1] (E_T^N).[10]

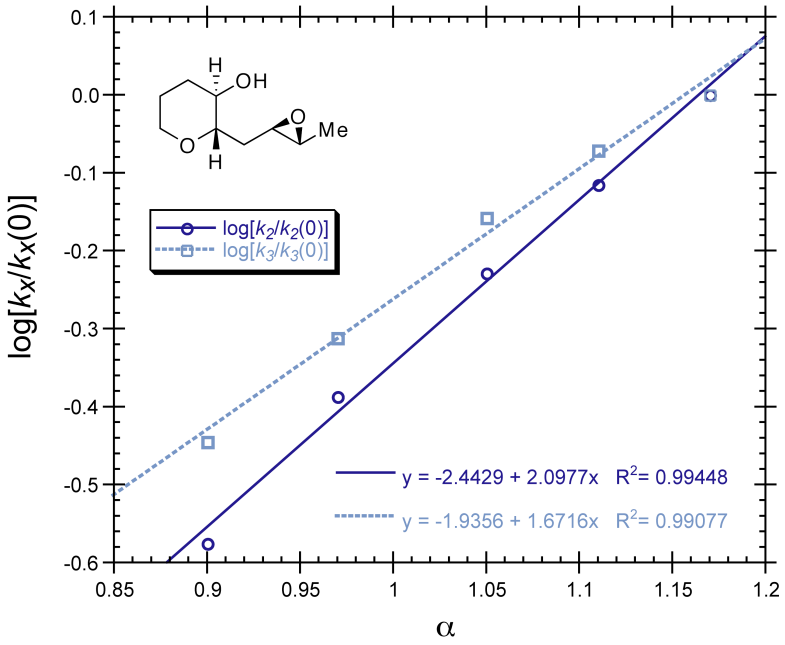


Figure S-4. Sensitivity of **1a** to Kamlet-Taft parameter for hydrogen-bond donation (α).[11]

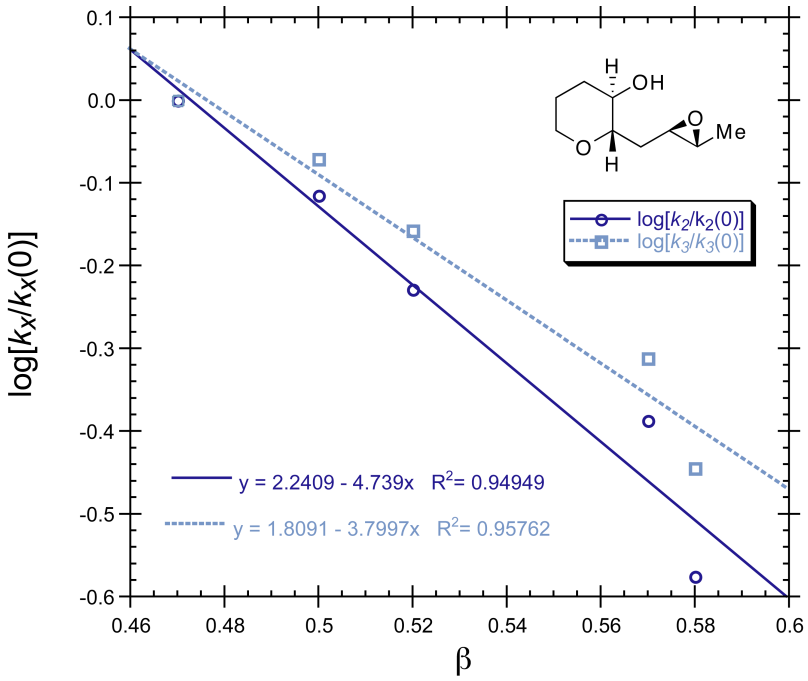


Figure S-5. Sensitivity of **1a** to Kamlet-Taft parameter for hydrogen-bond accepting (β).[11]

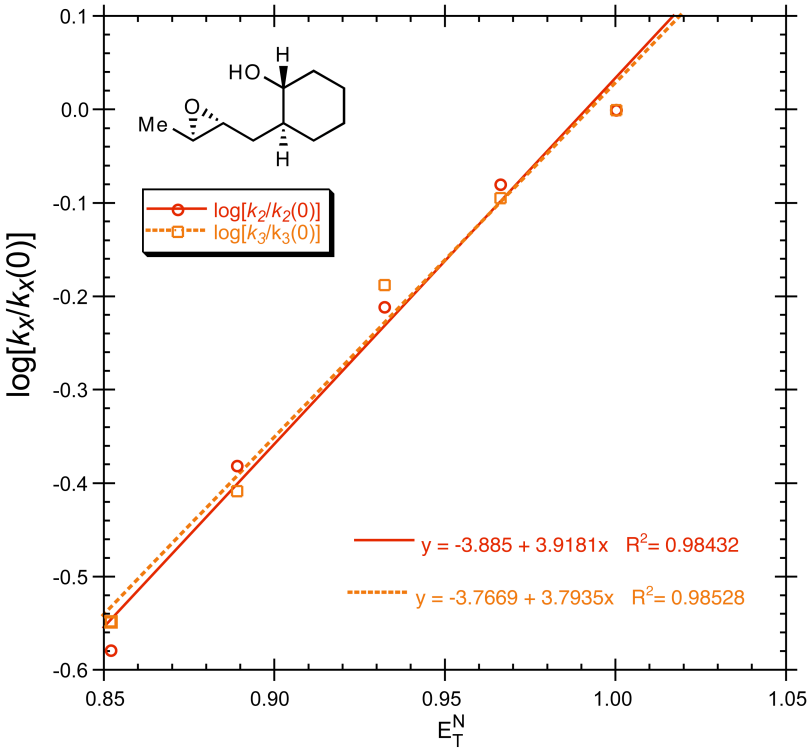


Figure S-6. Sensitivity of **1b** to Dimroth and Reichard's polarity scale (E_T^N).[10]

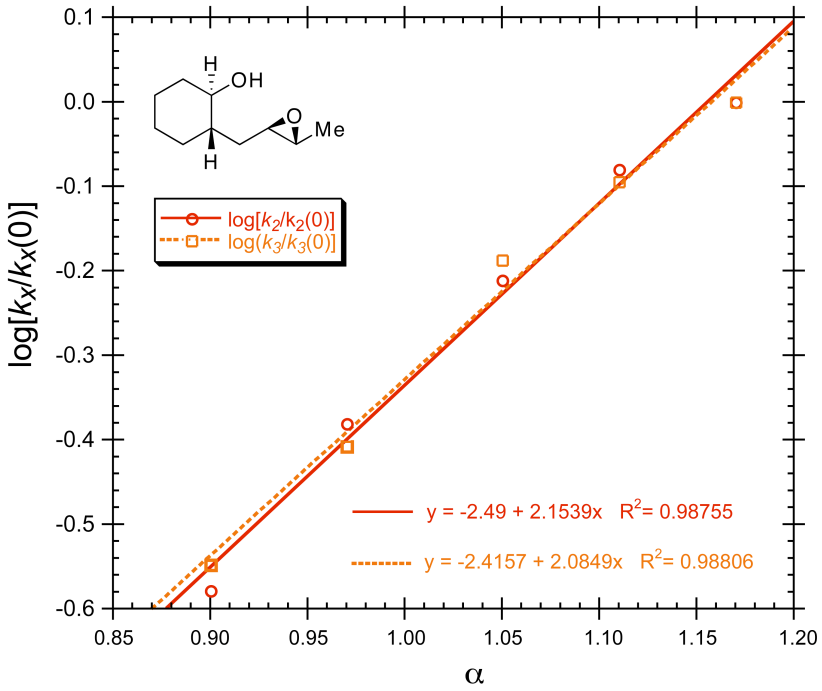


Figure S-7. Sensitivity of **1b** to Kamlet-Taft parameter for hydrogen-bond donation (α).[11]

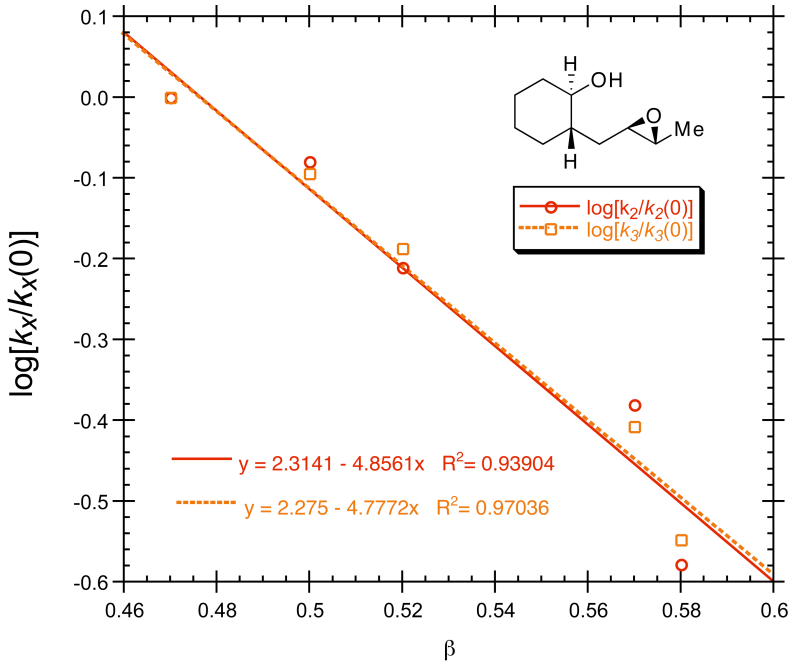
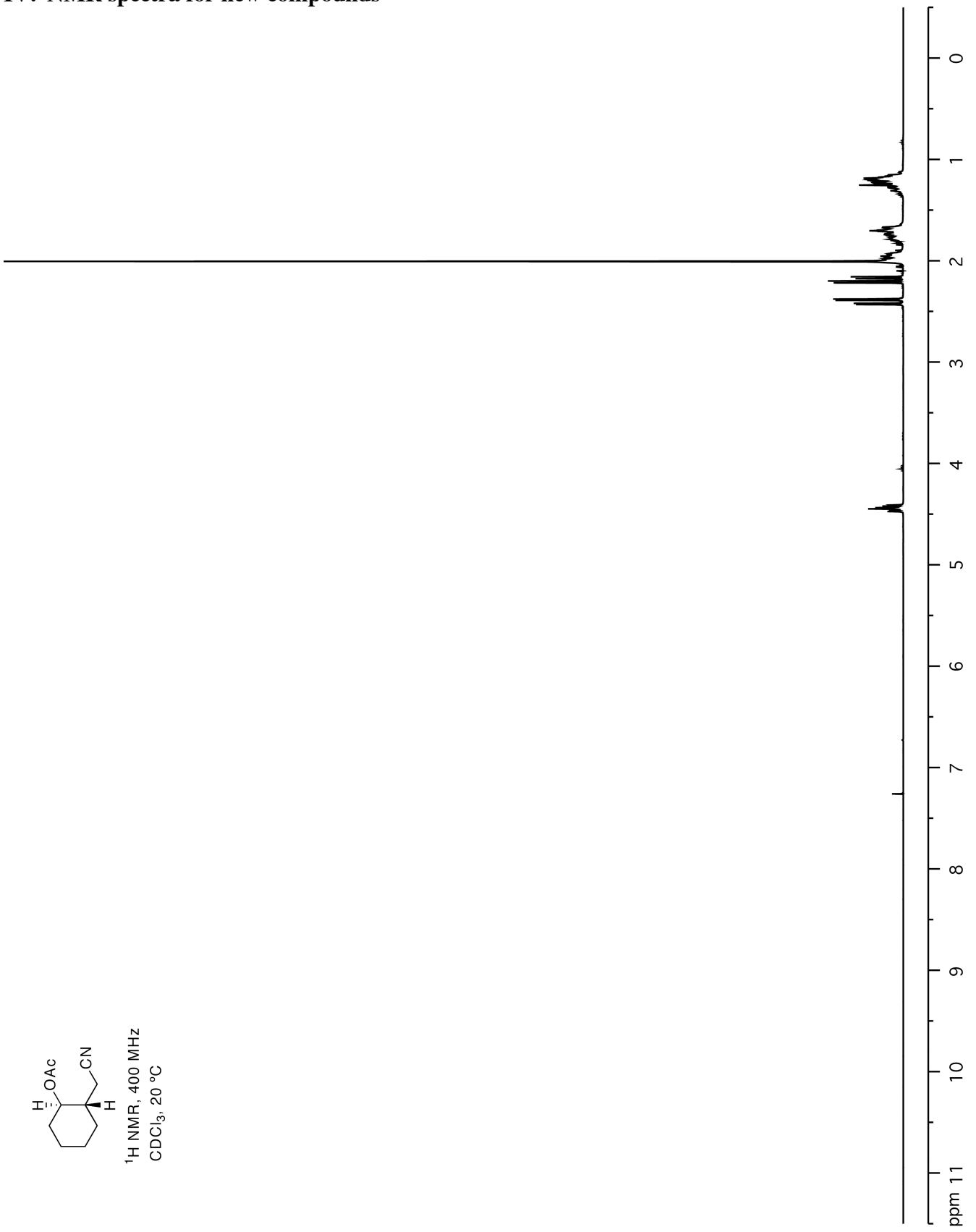
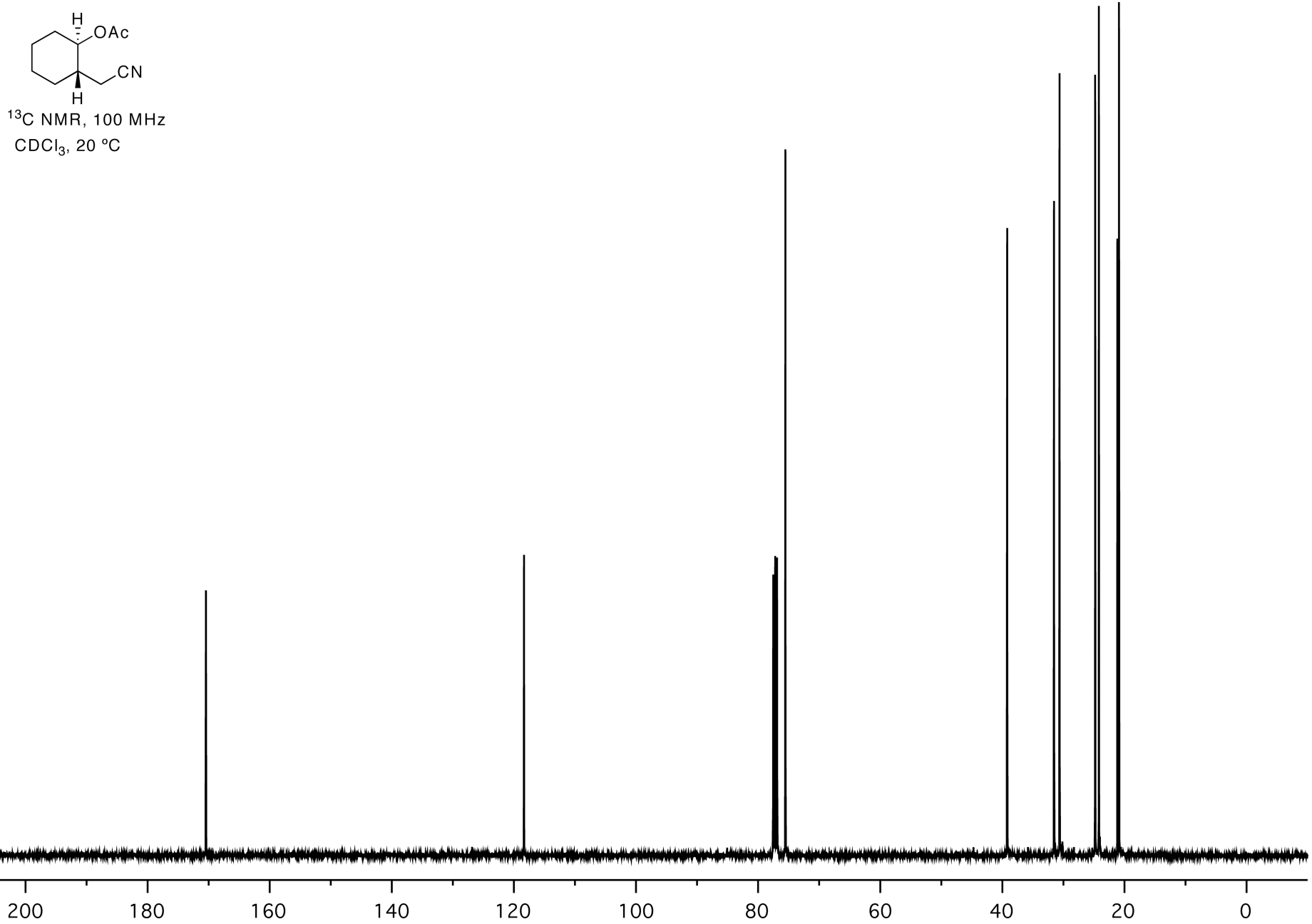
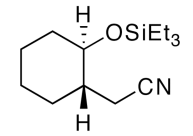


Figure S-8. Sensitivity of **1b** to Kamlet-Taft parameter for hydrogen-bond accepting (β).[11]

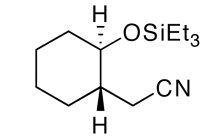
IV. NMR spectra for new compounds



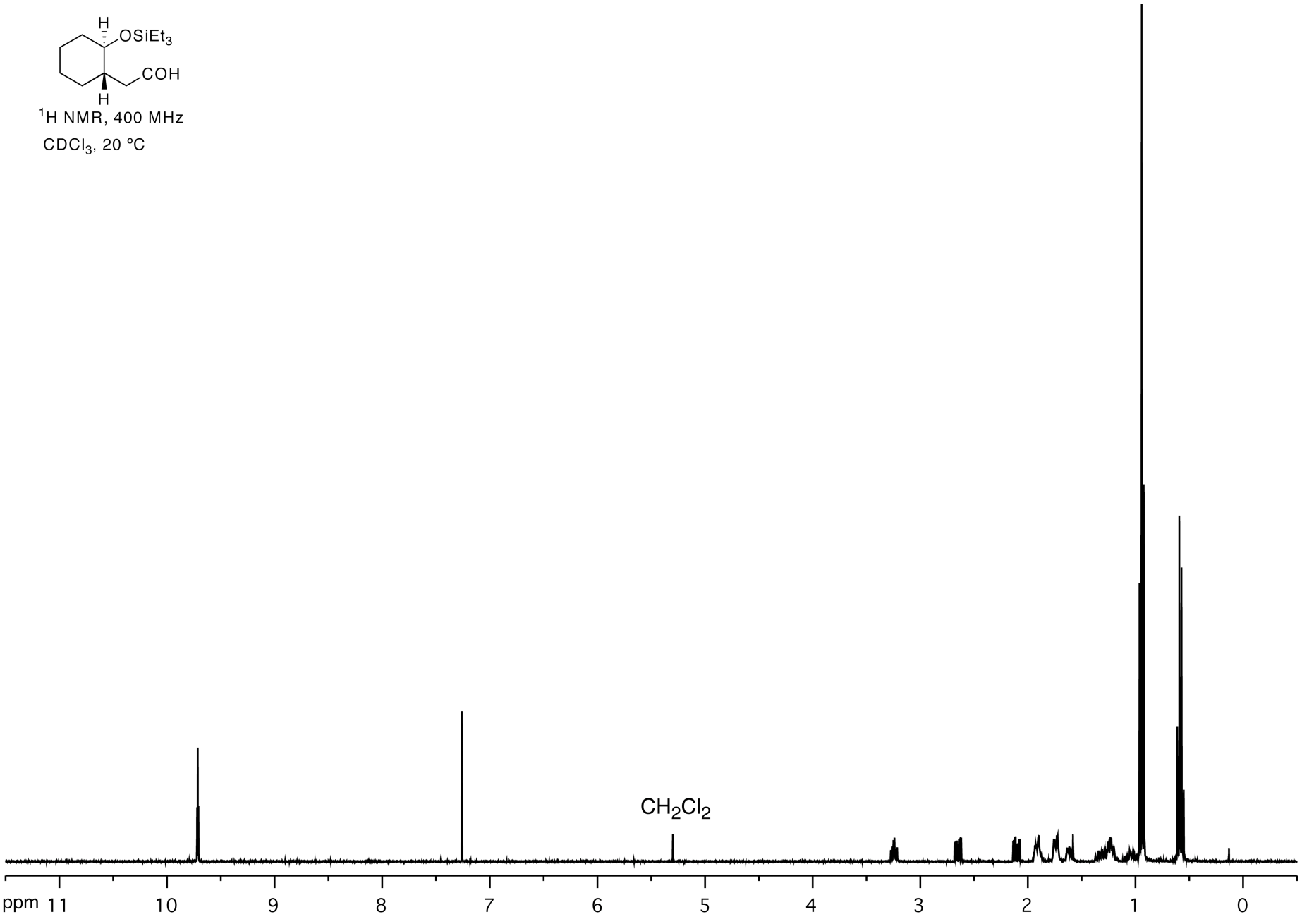

H
OAc
CN
H
13C NMR, 100 MHz
CDCl3, 20 °C
ppm
200
180
160
140
120
100
80
60
40
20
0

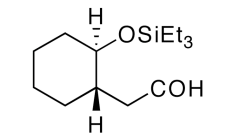


^{1}H NMR, 400 MHz
$CDCl_3$, 20 °C



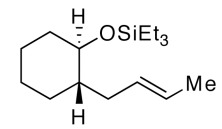
^{13}C NMR, 100 MHz
$CDCl_3$, 20 ºC


H
OSiEt3
COH
H
1H NMR, 400 MHz
CDCl3, 20 ºC
CH2Cl2
ppm 11
10
9
8
7
6
5
4
3
2
1
0

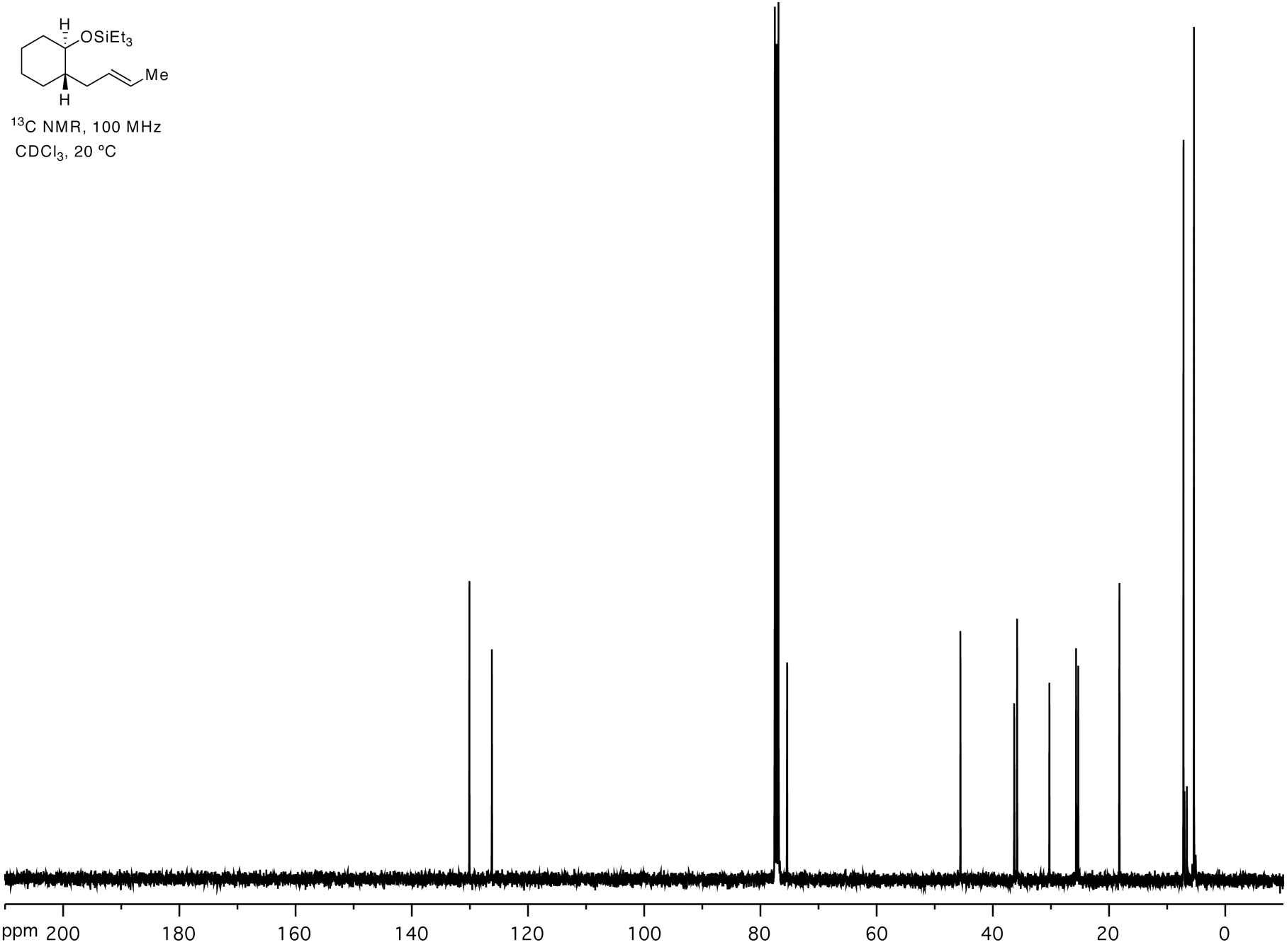


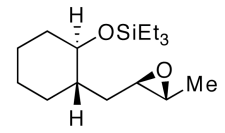
^{13}C NMR, 100 MHz

$CDCl_3$, 20 °C



^{1}H NMR, 400 MHz
$CDCl_3$, 20 °C

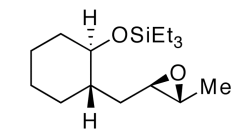

OSiEt3
Me
H
H
13C NMR, 100 MHz
CDCl3, 20 °C
ppm
200
180
160
140
120
100
80
60
40
20
0



5:1 d.r.

^{1}H NMR, 500 MHz

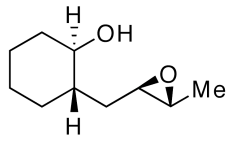
C_6D_6, 20 °C



5:1 d.r.

^{13}C NMR, 125 MHz

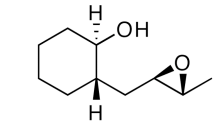
C_6D_6, 20 °C



5:1 d.r.

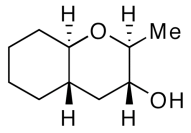
^{1}H NMR, 500 MHz

C_6D_6, 20 °C



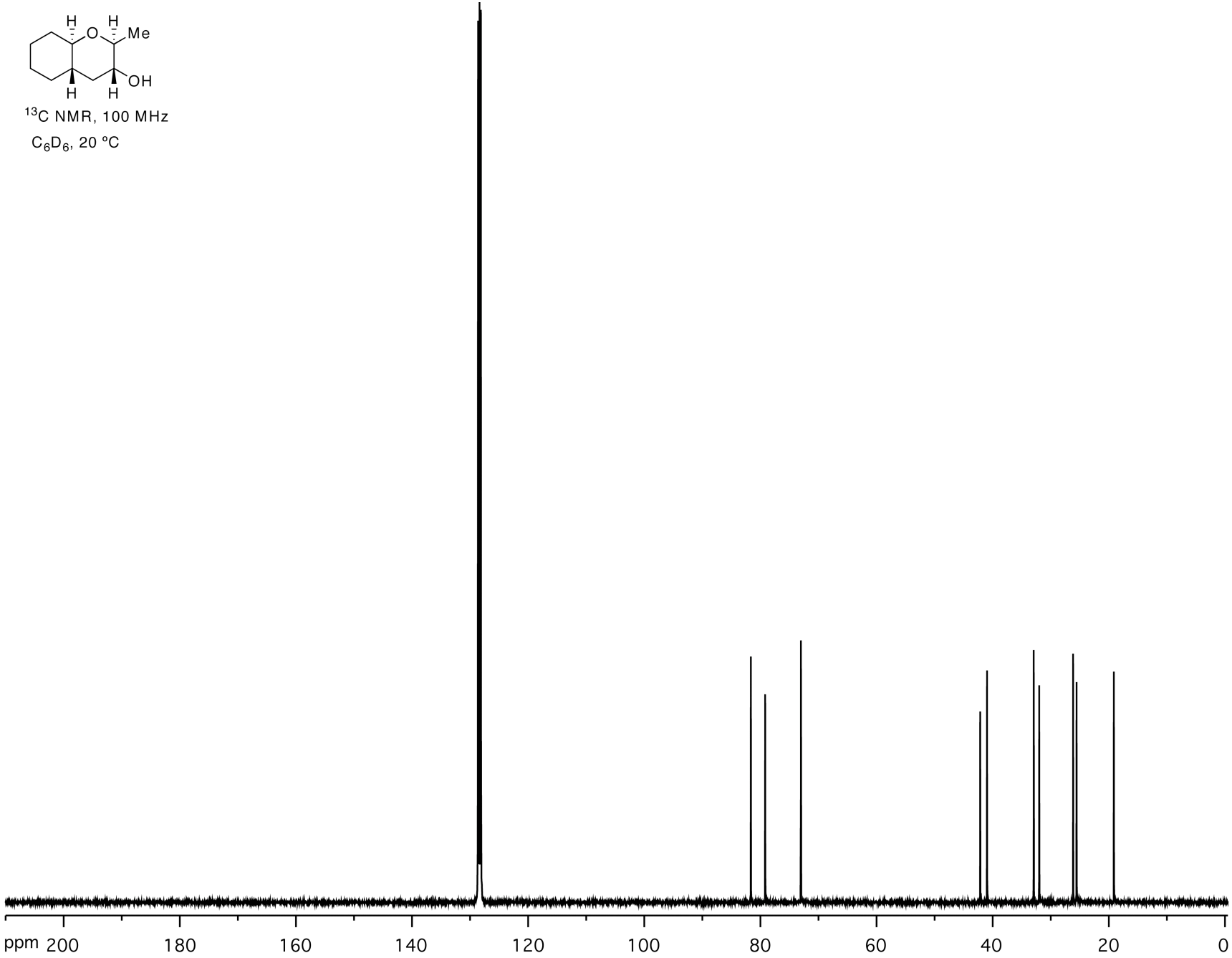
^{13}C NMR, 100 MHz

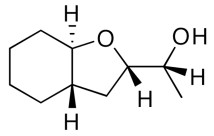
$CDCl_3$, 20 °C



^{1}H NMR, 400 MHz

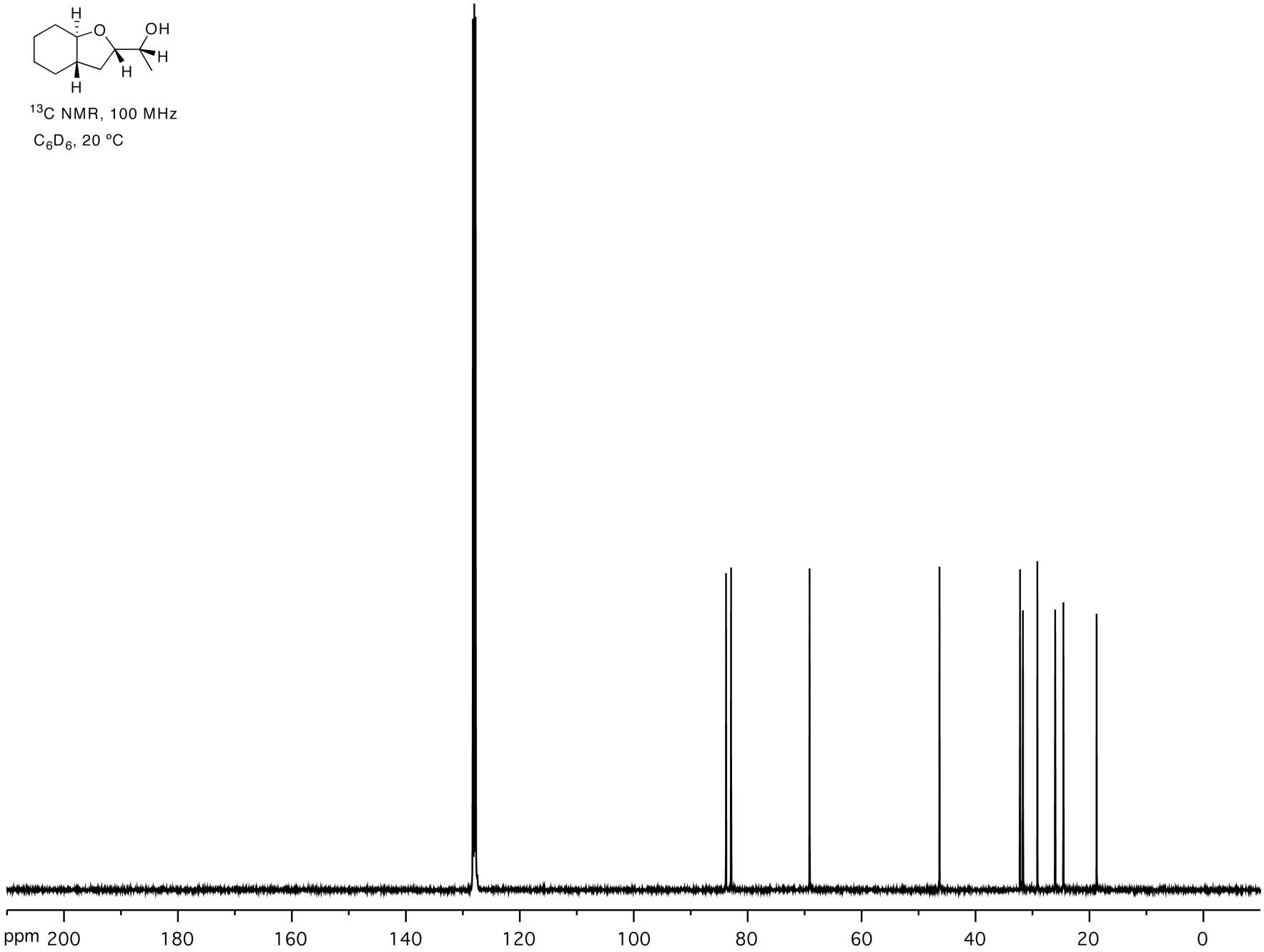
C_6D_6, 20 °C

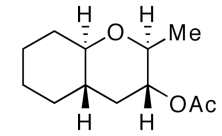

H
H
O
Me
OH
H
H
^{13}C NMR, 100 MHz
C_6D_6, 20 °C
ppm 200
180
160
140
120
100
80
60
40
20
0



^{1}H NMR, 400 MHz

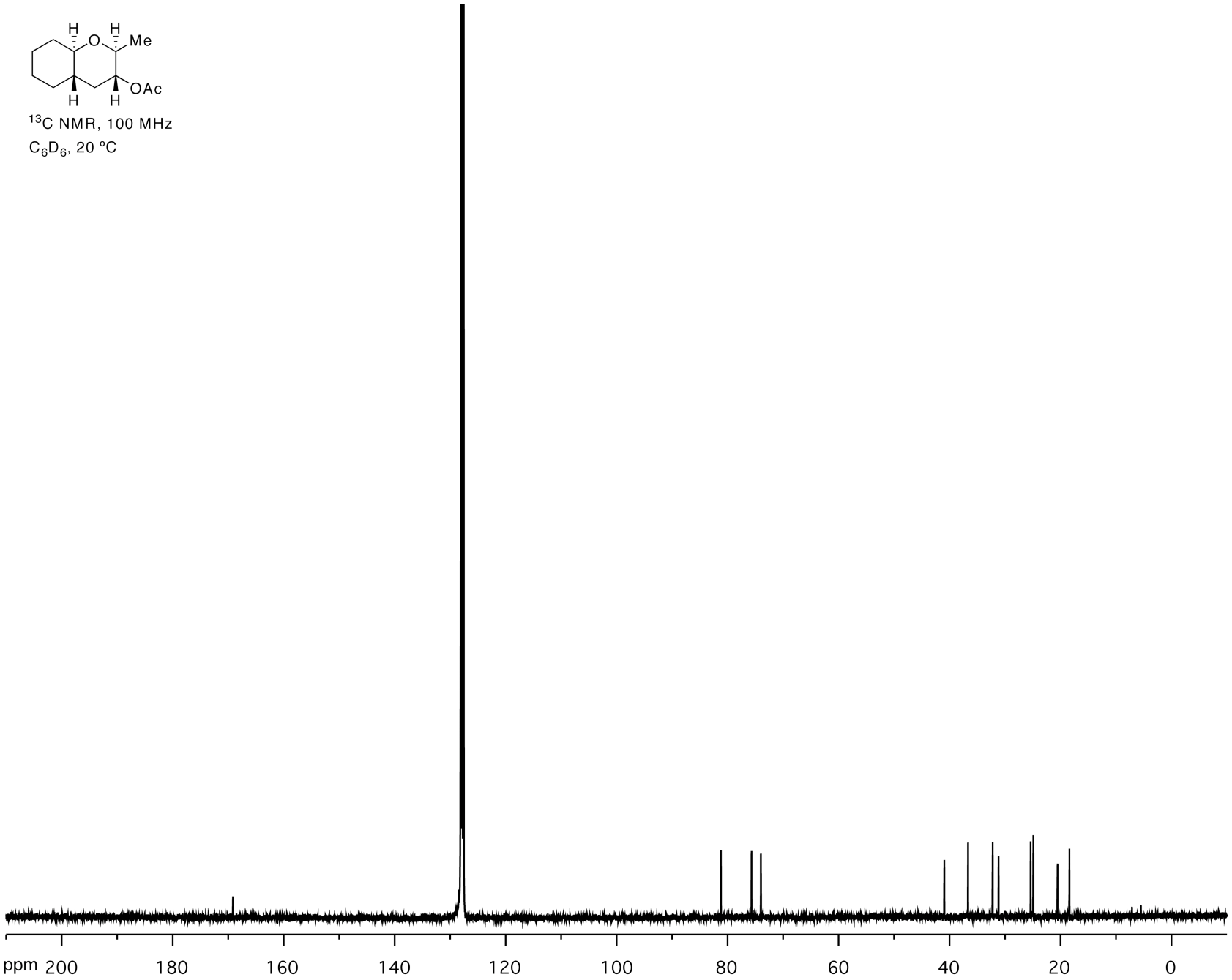
C_6D_6, 20 °C

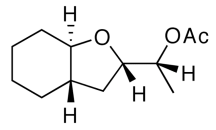

H
O
OH
H
H
H
13C NMR, 100 MHz
C6D6, 20 °C
ppm 200
180
160
140
120
100
80
60
40
20
0



^{1}H NMR, 500 MHz

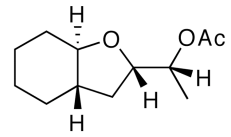
C_6D_6, 20 °C


H
H
O
Me
OAc
H
H
^{13}C NMR, 100 MHz
C_6D_6, 20 °C
ppm 200
180
160
140
120
100
80
60
40
20
0



^{1}H NMR, 400 MHz

C_6D_6, 20 °C



^{13}C NMR, 125 MHz

C_6D_6, 20 °C

V. References

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