Vibrational Mode Assignment of α-Pinene by Isotope Editing: One Down, Seventy-One To Go

Mary Alice Upshur,[1] Hilary M. Chase,[1] Benjamin F. Strick,[1] Carlena J. Ebben,[1,2] Li Fu,[2]
Hongfei Wang,[2] Regan J. Thomson,[1,*] and Franz M. Geiger[1,*]

[1]Department of Chemistry, Northwestern University, Evanston, IL 60208, [2]now at the Department of Chemistry, University of California, Berkeley, CA 94720, and [3]William R. Wiley Environmental Molecular Sciences Laboratory, Pacific Northwest National Laboratory, Richland, WA 99352

Supporting Information

1. General Methods

All reactions were carried out under a nitrogen atmosphere in flame-dried glassware with magnetic stirring unless otherwise stated. THF, Et_2O and CH_2Cl_2 were purified by passage through a bed of activated alumina.[1] Reagents were purified prior to use unless otherwise stated following the guidelines of Armarego and Chai.[2] Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and anisaldehyde stain, ceric ammonium molybdate stain, or potassium permanganate stain followed by heating. Infrared spectra were recorded at 0.6 cm^{-1} resolution using a Bruker Tensor ATR spectrometer. ^{1}H-NMR spectra were recorded on a Bruker Avance III 500 (500 MHz) or a Varian Inova 400 (400 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as (app = apparent, obs = obscured, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, sep = septet, o = octet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled 13C-NMR spectra were recorded on a Bruker Avance III 500 (500

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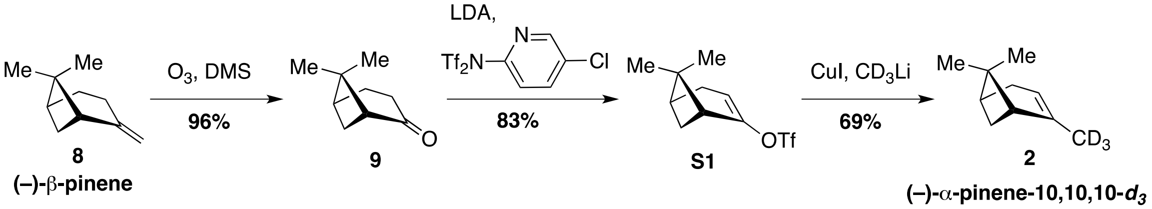
[1] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

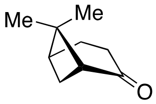
[2] Armarego, W. L. F. C., C. L. L. *Purification of Laboratory Chemicals*; 5th ed.; Butterworth-Heinemann, 2003.

MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.00 ppm). Mass spectrometric data were obtained on an Agilent 6210 Time-of-Flight LC/MS and a Thermo Finnegan Mat 900 XL High Resolution Magnetic Sector.

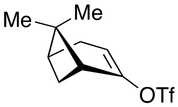
2. Experimental Procedures for the Synthesis of α-Pinene Derivatives

Scheme S1 Synthetic outline of (–)-α-pinene-10,10,10-*d*₃ (**2**)

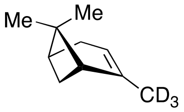




(1*R*)-6,6-Dimethylbicyclo[3.1.1]heptan-2-one (9): Ozone was bubbled through a solution of (–)-β-pinene (**8**, 40 g, 294 mmol) in methanol (70 mL) at -78 ºC. After 3 hours, O_2 was bubbled through for an additional 30 minutes. After addition of dimethyl sulfide (37 mL, 504 mmol) mixture was then allowed to warm to room temperature and stirred for an additional 12 hours. Reaction was transferred to a separatory funnel and diluted with CH_2Cl_2 (100 mL) and H_2O (100 mL). The organic phase was collected and aqueous layer extraced with CH_2Cl_2 (2 x 100 mL). The combined organics were washed with brine and dried using Na_2SO_4. Concentration under reduced pressure to afford an oil. Flash column chromatography on silica gel using 5% EtOAc in hexanes as the eluent afforded the title compound as a clear oil. (39.0 g, 282 mmol, 96% yield): 97:3 e.r. $[\alpha]^{20}D$ = +20.7 (c 2.9, $CHCl_3$); IR (film): 2951, 1710, 1460, 1200, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 2.58–2.51 (m, 3H); 2.34 (ddd, 1H, J = 19.1, 9.2, 2.0 Hz); 2.25 (m, 1H); 2.05 (m, 1H); 1.94 (m, 1H); 1.58 (d, 1H, J = 10.4 Hz); 1.33 (s, 3H); 0.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): □□□215.1, 57.9, 41.2, 40.3, 32.8, 25.9, 25.2, 22.1, 21.4; HRMS (EI): Exact mass calcd for $C_9H_{10}O$ $[M]^+$, 138.1045. Found 138.1035.

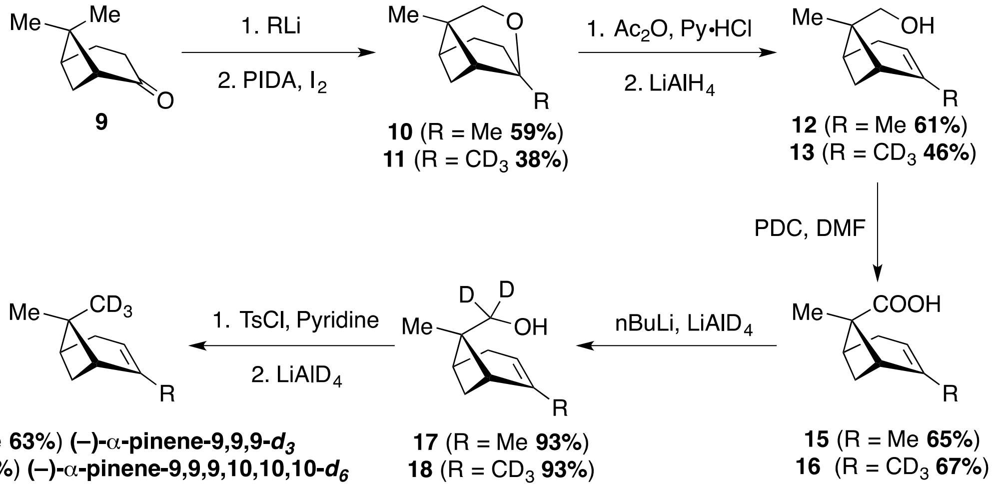


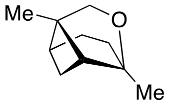
(1*R*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl trifluoromethanesulfonate (S1): To a solution of diisopropylamine (2 mL, 14.3 mmol) in THF (50 mL) at 0 ºC was added *n*-(6.67 mL, 13 mmol, 1.95 M in hexanes) and cooled to –78 ºC, under N_2. After 15 minutes, (1*R*)-6,6-dimethylbicyclo[3.1.1]heptan-2-one-3 (**9**) (1.8 g, 13 mmol) in THF (20 mL) was added dropwise into the solution of LDA and stirred for 1 hour. At this time, a solution of Comins' reagent (5.5 g, 14 mmol) in THF (20 mL) was added over a period of 15 minutes. The resulting mixture was warmed to 0 ºC and stirred for 2 hours. Reaction was diluted with H_2O (100 mL) and Et_2O (50 mL) and transferred to a separatory funnel. The organic phase was collected and the aqueous layer extracted with Et_2O (2 x 100 mL). The combined organics were dried with Na_2SO_4. Concentration under reduced pressure and flash column chromatography on silica gel in 10% EtOAc in hexanes as the eluent afforded the title compound (2.92 g, 10.8 mmol, 83% yield) as a clear oil: 97:3 e.r. $[\alpha]^{20}D$ = –53.4 (c 2.1, $CHCl_3$); IR (film): 2958, 1420, 1206, 1143, 859 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.54 (d, 1H, J = 3.3 Hz); 2.56 (dt, 1H, J = 9.2, 5.7 Hz); 2.39–2.27 (m, 3H); 2.14 (dd, 1H, J = 5.2, 2.7 Hz); 1.38 (d, 1H, J = 9.2 Hz); 1.34 (s, 3H); 0.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): □□□155.0, 118.5 (q, 1C, J = 320 Hz), 111.4, 46.3, 40.1, 39.7, 31.7, 28.2, 25.5, 20.8; HRMS (EI): Exact mass calcd for $C_{10}H_{13}F_3O_3S$ $[M]^+$, 270.0538. Found 270.0538.



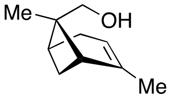
(1*S*)-6,6-Dimethy-2-(methyl-*d₃*)-bicyclo[3.1.1]hept-2-ene (2): Methyl-d_3-lithium (26.4 mL, 13.2 mmol, 0.5 M in Et_2O) was added to a slurry of CuI (1.74 g, 9.15 mmol) in THF (18 mL) at 0 ºC. After stirring for 10 minutes, a room temperature solution of (1*R*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl trifluoromethanesulfonate (1.02 g, 3.77 mmol) in THF (6 mL) was added dropwise by cannula. Reaction was cooled to –5 ºC and stirred overnight. After 14 hours, the reaction was warmed to room temperature and filtered through a plug of Florisil®, flushing with pentanes. Concentration under reduced pressure afforded the title compound (360 mg, 2.60 mmol, 69% yield) as a clear oil: 97:3 e.r. $[\alpha]^{20}D$ = –62.3 (c 2.8, $CHCl_3$); IR (film): 2917, 2220, 2189, 766 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.19 (d, 1H, J = 1.2 Hz); 2.33 (dt, 1H, J = 8.5, 5.6 Hz); 2.26–2.14 (m, 2H); 2.07 (m, 1H); 1.93 (td, 1H, J = 5.6, 1.1 Hz); 1.26 (s, 3H); 1.15 (d, 1H, J = 8.5 Hz); 0.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): □□□144.4, 116.0, 46.9, 40.7, 38.0, 31.4, 31.3, 26.3, 21.1 (sep, 1C, J = 19 Hz); HRMS (EI): Exact mass calcd for $C_{10}H_{13}D_3$ $[M]^+$, 139.1440. Found 139.1426.

Scheme S2 Synthetic outline of (–)-α-pinene-9,9,9-*d*₃ (**3**) and (–)-α-pinene-9,9,9,10,10,10-*d₆* (**4**)



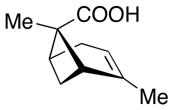


(1*R*, 3*S*, 6*R*, 9*S*)-6,9-Dimethyl-7-oxatricyclo[4.3.0.0^{3,9}]nonane (10): To a solution of (1*R*)-6,6-dimethylbicyclo[3.1.1]heptan-2-one (**9**) (12 g, 87.0 mmol) in THF (87 mL) at 78 ºC was added methyl lithium (65 mL, 104 mmol, 1.6 M in Et_2O) dropwise. After 3 hours, the reaction was warmed to 0 ºC and quenched by careful addition of sat. NH_4Cl solution (100 mL). The reaction mixture was transferred to a separatory funnel and diluted with Et_2O (100 mL). The organic phase was collected and the aqueous layer extracted with Et_2O (2 x 100 mL). The combined organics were washed with brine (150 mL) and dried with Na_2SO_4. Concentration under reduced pressure and flash column chromatography on silica gel in 5% EtOAc in hexanes as the eluent afforded a 2:1 mixture of desired methyl addition adduct to starting ketone (10.7 g) respectively. To the 2:1 mixture (10.7 g) in cyclohexane (600 mL) was added (diacetoxyiodo)benzene (27.9 g, 86.4 mmol) and iodine (20.0 g, 78.7 mmol). Reaction was placed under a UV lamp and stirred vigorously. After 7.5 hours, the reaction was poured into H_2O (400 mL). The organic phase was collected and the aqueous layer extracted with Et_2O (2 x 100 mL). The combined organics were washed with a sat. NaS_2O_3 solution (300 mL), brine (300 mL), and dried with Na_2SO_4. Concentration under reduced pressure and flash column chromatography on silica gel using 5% EtOAc in hexanes as the eluent afforded the title compound (7.12 g, 51.1 mmol, 59% yield) as a yellow oil: 97:3 e.r. $[\alpha]^{20}$D = +21.2 (c 2.9, $CHCl_3$); IR (film): 2949, 2924, 2865, 1032 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 3.81 (d, 1H, J = 8.8 Hz); 3.36 (d, 1H, J = 8.8 Hz); 2.10–2.00 (m, 3H); 1.85–1.75 (m, 2H); 1.66 (m, 2H); 1.43 (d, 1H, J = 10.0 Hz); 1.25 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): □□□87.0, 72.6, 52.1, 51.9, 41.2, 32.5, 25.4, 22.9, 22.7, 19.7; HRMS (EI): Exact mass calcd for $C_{10}H_{16}O$ $[M]^+$, 152.1201. Found 152.1178.

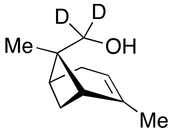


((1*S*,5*S*,6*S*)-2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-yl)methanol (12): Acetic anhydride (28 mL, 296 mmol) and pyridine hydrochloride (5.6 g, 48.4 mmol) were added to (1*R*, 3*S*, 6*R*, 9*S*)-6,9-dimethyl-7-oxatricyclo[4.3.0.0^{3,9}]nonane (**10**) (5.6 g, 36.8 mmol). Reaction was heated to 90 ºC and stirred vigorously for 7.5 hours. After cooling to room temperature, reaction was diluted with H_2O (100 mL) and pentane (100 mL) and transferred to a separatory funnel. The organic phase was collected and the aqueous layer extracted with pentanes (2 x 100 mL). Combined organics were washed with a sat. $NaHCO_3$ solution (150 mL) and dried with Na_2SO_4. Concentration under reduced pressure and flash column chromatography on silica gel using 5% EtOAc in hexanes afforded a mixture containing predominantly the desired acetate (6.08 g). Lithium aluminum hydride (1.54 g, 40.5 mmol) was slowly added to the mixture (6.08 g) in THF (200 mL) at 0 ºC. After 1 hour, the reaction was cautiously poured on ice, diluted with 1.0 M HCl (50 mL) and transferred to a separatory funnel. The organic phase was collected and the aqueous layer extracted with Et_2O (2 x 100 mL). The combined organics were washed with brine (200 mL) and dried with Na_2SO_4. Concentration under reduced pressure and flash column chromatography on silica gel using 10% ⋆ 20% EtOAc in hexanes as the eluent afforded the title compound (3.4 g, 22.3 mmol, 61%

yield) as a clear oil: 97:3 e.r. $[\alpha]^{20}$D = –62.5 (c 2.6, $CHCl_3$); IR (film): 3368, 2924, 1438, 1018 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 5.25 (t, 1H, J = 1.5 Hz); 3.56 (d, 1H, J = 10.5 Hz); 3.40 (d, 1H, J = 10.5 Hz); 2.38 (dt, 1H, J = 8.5, 5.5 Hz); 2.27–2.14(m, 3H); 2.04 (td, 1H, J = 5.5, 1.2 Hz); 1.70 (q, 3H, J = 1.8 Hz); 1.35 (s, 3H); 1.20 (d, 1H, J = 8.6 Hz); 0.99 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): □□□143.3, 116.6, 65.8, 44.5, 41.2, 39.0, 31.3, 31.0, 22.6, 21.1; HRMS (EI): Exact mass calcd for $C_{10}H_{16}O$ $[M]^+$, 152.1201. Found 152.1192.

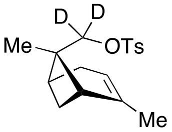


(1*S*,5*S*,6*S*)-2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-carboxylic acid (15): Pyridinium dichromate (14.5 g, 38.5 mmol) was added to a stirred solution of ((1*S*,5*S*,6*S*)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl)methanol (**12**) (1.67 g, 11 mmol) in DMF (40 mL). After 12 hours, the reaction was diluted with water (100 mL), Et_2O (100 mL), and transferred to a separatory funnel. The organic phase was collected and the aqueous layer extracted with Et_2O (2 x 100 mL). Combined organics were washed with brine (150 mL) and dried with Na_2SO_4. Concentration under reduced pressure and flash column chromatography on silica gel using 1% AcoH in dichloromethane as the eluent afforded the title compound (846 mg, 5.1 mmol, 46% yield) as a white solid. The aldehyde, also formed under these conditions, was resubmitted to the reaction conditions to afford the title compound (1.19 g, 7.2 mmol, 65% yield over three iterations) as a white solid: 97:3 e.r. $[\alpha]^{20}$D = +22.4 (c 1.9, $CHCl_3$); melting point (decomp) 144 °C; IR (film): 2944, 2573, 1693, 1303 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 5.14 (m, 1H); 2.63 (m, 1H); 2.51 (m, 1H); 2.31–2.21 (m, 3H); 1.72 (d, 3H, J = 1.9 Hz); 1.53 (s, 3H); 1.25 (d, 1H, J = 8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): □□□181.4, 146.5, 115.9, 49.4, 44.5, 40.7, 31.6, 29.0, 22.6, 21.7; HRMS (EI): Exact mass calcd for $C_{10}H_{14}O_2$ $[M]^+$, 166.0994. Found 166.0984.

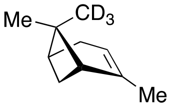


((1*S*,5*S*,6*S*)-2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-yl)dideuteromethanol (17): *n*–BuLi (2.87 mL, 6.95 mmol, 2.42 M in hexanes) was added dropwise to a solution of (1*S*,5*S*,6*S*)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-carboxylic acid (**15**) (1.16 g, 6.95 mmol) in THF (48 mL). After 1 minute, $LiAlD_4$ (6.95 mL, 6.95 mmol, 1.0 M in Et_2O) was added dropwise and reaction was heated to reflux for 3 hours. Reaction was cooled to room temperature and carefully quenched with a sat. NH_4Cl solution (20 mL) and 1.0 M HCl (20 mL). Resulting mixture was dilute with H_2O (50 mL), Et_2O (50 mL), and transferred to a separatory funnel. The organic phase was collected and the aqueous layer extracted with Et_2O (2 x 50 mL). Combined organics were washed with brine (75 mL) and dried over $MgSO_4$. Concentration under reduced pressure and flash column chromatography on silica gel using 10% EtOAc in hexanes as the eluent afforded the title compound (1.0 g, 6.5 mmol, 93% yield) as a clear oil: 97:3 e.r. $[\alpha]^{20}$D = –65.3 (c 2.9, $CHCl_3$); IR (film): 3357, 2925, 2088, 1069, 971 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 5.18 (dd, 1H, J = 3.0, 1.4 Hz); 2.41 (m, 1H); 2.27–2.20 (m, 3H); 2.07 (m, 1H); 1.73 (q, 3H, J = 1.9 Hz); 1.37 (s, 3H); 1.23 (d, 1H, J = 8.6 Hz); 0.96 (s, 1H); ^{13}C NMR (125 MHz,

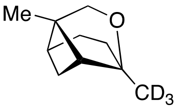
$CDCl_3$): □□□143.3, 116.6, 65.1 (p, 1C, J = 21 Hz), 44.5, 41.1, 38.9, 31.3, 31.0, 22.6, 21.0; HRMS (EI): Exact mass calcd for $C_{10}H_{14}D_2O$ $[M]^+$, 154.1327. Found 154.1351.



((1*S*,5*S*,6*S*)-2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-yl)dideuteromethyl 4-methylbenzenesulfonate (19): *p*-Toluenesulfonyl chloride (4.7 g, 24.6 mmol) was added to a stirred solution of ((1*S*,5*S*,6*S*)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl)dideuteromethanol (**17**) (950 mg, 6.16 mmol) in pyridine (28 mL) at 0 ºC. After 12 hours, the reaction was diluted with a sat. NH_4Cl solution (50 mL), dichloromethane (50 mL), and transferred to a separatory funnel. The organic phase was collected and the aqueous layer extracted with dichloromethane (2 x 50 mL). Combined organics were washed with brine (75 mL) and dried with Na_2SO_4. Concentration under reduced pressure and flash column chromatography on silica gel using 5% EtOAc in hexanes as the eluent afforded the title compound (1.53 g, 5.0 mmol, 81% yield) as a clear oil: 97:3 e.r. $[\alpha]^{20}D$ = –34.7 (c 3.7, $CHCl_3$); IR (film): 2931, 1361, 1179, 949 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.76 (d, 2H, J = 8.3 Hz); 7.33 (d, 2H, J = 7.9 Hz); 5.13 (t, 1H, J = 1.4 Hz); 2.45 (s, 3H); 2.36 (dt, 1H, J = 8.7, 5.5 Hz); 2.22–2.18 (m, 2H); 2.03–1.97 (m, 2H); 1.58 (d, 3H, J = 1.8 Hz); 1.27 (s, 3H); 1.19 (d, 1H, J = 8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): □□□144.5, 143.3, 133.0, 129.7, 127.9, 116.5, 73.2 (p, 1C, J = 21 Hz), 44.5, 39.1, 38.7, 31.4, 30.7, 22.3, 21.6, 20.8; HRMS (ESI): Exact mass calcd for $C_{12}H_{14}$ $[M+Na]^+$, 331.1313. Found 331.1303.

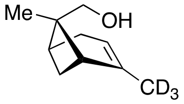


(1*S*,6*S*)-2,6-Dimethyl-6-(methyl-*d₃*)-bicyclo[3.1.1]hept-2-ene (3): $LiAlD_4$ (4.38 mL, 4.38 mmol, 1.0 M in Et_2O) was added to a solution of ((1*S*,5*S*,6*S*)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl)dideuteromethyl 4-methylbenzenesulfonate (**19**) (900 mg, 2.92 mmol) in Et_2O (15 mL). After 30 minutes, reaction was run through a plug of Florisil® with pentanes as an eluent. Careful concentration under reduced pressure afforded the title compound (316 mg, 2.3 mmol, 78% yield) as a clear oil: 97:3 e.r. $[\alpha]^{20}D$ = –58.5 (c 2.8, $CHCl_3$); IR (film): 2919, 2232, 2199, 788 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.19 (dd, 1H, J = 3.0, 1.5 Hz); 2.34 (dt, 1H, J = 8.5, 5.6 Hz); 2.26–2.14 (m, 2H); 2.07 (td, 1H, J = 2.9, 1.3 Hz); 1.67 (q, 3H, J = 1.9 Hz); 1.27 (s, 3H); 1.16 (d, 1H, J = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): □□□144.5, 116.0, 46.9, 40.6, 37.8, 31.5, 31.2, 26.3, 23.0, 19.9 (sep, 1C, J = 19 Hz); HRMS (EI): Exact mass calcd for $C_{10}H_{13}D_3$ $[M]^+$, 139.1440. Found 139.1416.

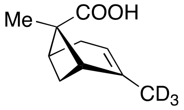


(1*R*,3*S*,6*R*,9*S*)-9-Methyl-6-(methyl-*d₃*)-7-oxatricyclo[4.3.0.0^{3,9}]nonane (11): To a solution of (1*R*)-6,6-dimethylbicyclo[3.1.1]heptan-2-one (**9**) (3.46 g, 25 mmol) in THF (25 mL) at –78 ºC was added methyl-d_3-lithium (50 mL, 25 mmol, 0.5 M in Et_2O)

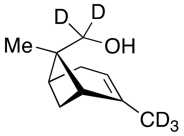
dropwise. After 3 hours, the reaction was warmed to 0 ºC and quenched by careful addition of sat. NH_4Cl solution (50 mL). The reaction mixture was transferred to a separatory funnel and diluted with Et_2O (50 mL). The organic phase was collected and the aqueous layer extracted with Et_2O (2 x 50 mL). The combined organics were washed with brine (100 mL) and dried with Na_2SO_4. Concentration under reduced pressure and flash column chromatography on silica gel in 5% EtOAc in hexanes as the eluent afforded a 2:1 mixture of desired methyl-d_3 addition adduct to starting ketone (3.38 g) respectively. To the 2:1 mixture (3.38 g) in cyclohexane (165 mL) was added (diacetoxyiodo)benzene (7.6 g, 23.6 mmol) and iodine (5.46 g, 21.5 mmol). Reaction was placed under a UV lamp and stirred vigorously. After 4 hours, the reaction was poured into H_2O (150 mL). The organic phase was collected and the aqueous layer extracted with Et_2O (2 x 100 mL). The combined organics were washed with a sat. NaS_2O_3 solution (150 mL), brine (150 mL), and dried with Na_2SO_4. Concentration under reduced pressure and flash column chromatography on silica gel using 5% EtOAc in hexanes as the eluent afforded the title compound (1.48 g, 9.5 mmol, 38% yield) as a yellow oil: 97:3 e.r. $[\alpha]^{20}D$ = +45.5 (c 3.0, $CHCl_3$); IR (film): 2948, 2922, 2865, 2223, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 3.80 (d, 1H, J = 8.8 Hz); 3.36 (d, 1H, J = 8.8 Hz); 2.10–2.01 (m, 3H); 1.89–1.74 (m, 2H); 1.70–1.61 (m, 2H); 1.42 (d, 1H, J = 10 Hz); 1.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): □□□86.9, 72.6, 52.1, 51.8, 41.2, 32.4, 22.8, 22.7, 19.7; HRMS (EI): Exact mass calcd for $C_{10}H_{13}D_3O$ $[M]^+$, 155.1390. Found 155.1372.



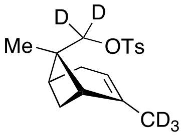
((1*S*,5*S*,6*S*)-6-Methyl-2-(methyl-*d_3*)-bicyclo[3.1.1]hept-2-en-6-yl)methanol (13): Acetic anhydride (11.7 mL, 124 mmol) and pyridine hydrochloride (2.35 g, 20.4 mmol) were added to (1*R*,3*S*,6*R*,9*S*)-9-methyl-6-(methyl-*d_3*)-7-oxatricyclo[4.3.0.0^{3,9}]nonane (**11**) (2.4 g, 15.5 mmol). Reaction was heated to 90 ºC and stirred vigorously for 12 hours. After cooling to room temperature, reaction was diluted with H_2O (100 mL) and pentane (100 mL) and transferred to a separatory funnel. The organic phase was colleced and the aquous layer extracted with pentanes (2 x 100 mL). Combined organics were washed with a sat. $NaHCO_3$ solution (150 mL) and dried with Na_2SO_4. Concentration under reduced pressure and flash column chromatography on silica gel using 5% EtOAc in hexanes afforded a mixture containing predominantly the desired acetate (2.16 g). Lithium aluminum hydride (0.50 g, 13.2 mmol) was slowly added to the mixture (2.16 g) in THF (60 mL) at 0 ºC. After 1 hour, the reaction was cautiously poured on ice, diluted with 1.0 M HCl (50 mL) and transferred to a separatory funnel. The organic phase was collected and the aqueous layer extracted with Et_2O (2 x 100 mL). The combined organics were washed with brine (200 mL) and dried with Na_2SO_4. Concentration under reduced pressure and flash column chromatography on silica gel using 10% ⋆ 20% EtOAc in hexanes as the eluent afforded the title compound (1.1 g, 7.1 mmol, 46% yield) as a clear oil: 97:3 e.r. $[\alpha]^{20}D$ = –63.5 (c 2.8, $CHCl_3$); IR (film): 3364, 2924, 2220, 2189, 1022 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.25 (dd, 1H, J = 2.8, 1.3 Hz); 3.56 (d, 1H, J = 10.5 Hz); 3.40 (d, 1H, J = 10.3 Hz); 2.38 (dt, 1H, J = 8.6, 5.6 Hz); 2.28–2.14 (m, 3H); 2.04 (m, 1H); 1.35 (s, 3H); 1.20 (d, 1H, J = 8.6 Hz); 0.99 (s, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) □□□143.2, 116.6, 65.8, 44.5, 41.2, 39.0, 31.3, 31.0, 21.9 (sep, 1C, J = 19 Hz), 21.1; HRMS (EI): Exact mass calcd for $C_{10}H_{13}D_3O$ $[M]^+$, 155.1390. Found 155.1385.



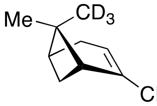
(1*S*,5*S*,6*S*)-6-Methyl-2-(methyl-*d*$_3$)-bicyclo[3.1.1]hept-2-en-6-carboxylic acid (16): Pyridinium dichromate (11.1 g, 29.0 mmol) was added to a stirred solution of ((1*S*,5*S*,6*S*)-6-methyl-2-(methyl-*d*$_3$)-bicyclo[3.1.1]hept-2-en-6-yl)methanol (**13**) (1.31 g, 8.45 mmol) in DMF (31 mL). After 12 hours, the reaction was diluted with water (100 mL), Et_2O (100 mL), and transferred to a separatory funnel. The organic phase was collected and the aqueous layer extracted with Et_2O (2 x 100 mL). Combined organics were washed with brine (150 mL) and dried with Na_2SO_4. Concentration under reduced pressure and flash column chromatography on silica gel using 1% AcoH in dichloromethane as the eluent afforded the title compound (635 mg, 3.8 mmol, 44% yield) as a white solid. The aldehyde, also formed under these conditions, was resubmitted to the reaction conditions to afford the title compound (959 mg, 5.7 mmol, 67% yield over three iterations) as a white solid: 97:3 e.r. $[\alpha]^{20}D = +27.0$ (c 2.6, $CHCl_3$); melting point (decomp) 144 °C; IR (film): 2945, 1693, 1316, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.14 (m, 1H); 2.63 (m, 1H); 2.51 (m, 1H); 2.31–2.21 (m, 3H); 1.53 (s, 3H); 1.25 (d, 1H, J = 8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): □□□181.3, 146.4, 116.0, 49.4, 44.4, 40.7, 31.6, 29.0, 21.7; HRMS (EI): Exact mass calcd for $C_{10}H_{11}D_3O_2$ $[M]^+$, 169.1182. Found 169.1192.



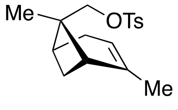
((1*S*,5*S*,6*S*)-6-Methyl-2-(methyl-*d*$_3$)-bicyclo[3.1.1]hept-2-en-6-yl)dideuteromethanol (18): *n*–BuLi (2.24 mL, 5.42 mmol, 2.42 M in hexanes) was added dropwise to a solution of (1*S*,5*S*,6*S*)-6-methyl-2-(methyl-*d*$_3$)-bicyclo[3.1.1]hept-2-en-6-carboxylic acid (**16**) (917 mg, 5.42 mmol) in THF (37 mL). After 1 minute, $LiAlD_4$ (5.42 mL, 5.42 mmol, 1.0 M in Et_2O) was added dropwise and reaction was heated to reflux for 2.5 hours. Reaction was cooled to room temperature and carefully quenched with a sat. NH_4Cl solution (20 mL) and 1.0 M HCl (20 mL). Resulting mixture was diluted with H_2O (50 mL), Et_2O (50 mL), and transferred to a separatory funnel. The organic phase was collected and the aqueous layer extracted with Et_2O (2 x 50 mL). Combined organics were washed with brine (75 mL) and dried over $MgSO_4$. Concentration under reduced pressure and flash column chromatography on silica gel using 10% EtOAc in hexanes as the eluent afforded the title compound (795 mg, 5.1 mmol, 93% yield) as a clear oil: 97:3 e.r. $[\alpha]^{20}D = –69.0$ (c 2.4, $CHCl_3$); IR (film): 3367, 2925, 2220, 2088, 1069, 971 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.25 (t, 1H, J = 1.3 Hz); 2.38 (m, 1H); 2.24–2.17 (m, 3H); 2.04 (m, 1H); 1.34 (s, 3H); 1.20 (d, 1H, J = 8.6 Hz); 0.96 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): □□□143.2, 116.6, 65.1 (p, 1C, J = 21 Hz), 44.4, 41.1, 39.0, 31.3, 31.0, 21.9 (sep, 1C, J = 19 Hz), 21.0; HRMS (EI): Exact mass calcd for $C_{10}H_{11}D_5O$ $[M]^+$, 157.1515. Found 157.1520.



((1*S*,5*S*,6*S*)-6-Methyl-2-(methyl-*d*$_3$)-bicyclo[3.1.1]hept-2-en-6-yl)dideuteromethyl 4-methylbenzenesulfonate (20): *p*-Toluensulfonyl chloride (2.79 g, 14.6 mmol) was added to a stirred solution of ((1*S*,5*S*,6*S*)-6-methyl-2-(methyl-*d*$_3$)-bicyclo[3.1.1]hept-2-en-6-yl)dideuteromethanol (**18**) (767 mg, 4.9 mmol) in pyridine (22 mL) at 0 ºC. After 12 hours, the reaction was diluted with a sat. NH_4Cl solution (50 mL), dichloromethane (50 mL), and transferred to a separatory funnel. The organic phase was collected and the aqueous layer extracted with dichloromethane (2 x 50 mL). Combined organics were washed with brine (75 mL) and dried with Na_2SO_4. Concentration under reduced pressure and flash column chromatography on silica gel using 5% EtOAc in hexanes as the eluent afforded the title compound (1.17 g, 3.76 mmol, 77% yield) as a clear oil: 97:3 e.r. $[\alpha]^{20}D = -27.1$ (c 3.2, $CHCl_3$); IR (film): 2934, 1362, 1179, 949 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.76 (d, 2H, J = 8.3 Hz); 7.33 (d, 2H, J = 8.6 Hz); 5.13 (t, 1H, J = 1.3 Hz); 2.45 (s, 3H); 2.35 (dt, 1H, J = 8.7, 5.6 Hz); 2.23–2.17 (m, 2H); 2.03–1.97 (m, 2H); 1.26 (s, 3H); 1.19 (d, 1H, J = 8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): □□□144.5, 143.2, 133.0, 129.7, 127.9, 116.5, 44.4, 39.1, 38.7, 31.4, 30.7, 21.6, 20.9; HRMS (ESI): Exact mass calcd for $C_{17}H_{17}D_5O_3S$ $[M+Na]^+$, 334.1496. Found 334.1493.

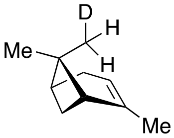


(1*S*,6*S*)-6-Methy-2,6-bis(methyl-*d*$_3$)-bicyclo[3.1.1]hept-2-ene (4): $LiAlD_4$ (4.38 mL, 4.38 mmol, 1.0 M in Et_2O) was added to a solution of ((1*S*,5*S*,6*S*)-6-methyl-2-(methyl-*d*$_3$)-bicyclo[3.1.1]hept-2-en-6-yl)dideuteromethyl 4-methylbenzenesulfonate (**20**) (900 mg, 2.89 mmol) in Et_2O (15 mL). After 30 minutes, reaction was run through a plug of Florisil® with pentanes as an eluent. Careful concentration under reduced pressure afforded the title compound (309 mg, 2.2 mmol, 75% yield) as a clear oil: 97:3 e.r. $[\alpha]^{20}D = -57.2$ (c 2.5, $CHCl_3$); IR (film): 2918, 2220, 2198, 1044, 771 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.19 (dd, 1H, J = 2.7, 1.4 Hz); 2.34 (dt, 1H, J = 8.4, 5.6 Hz); 2.26–2.14 (m, 2H); 2.07 (td, 1H, J = 2.9, 1.3 Hz) 1.94 (td, 1H, J = 5.6, 1.4 Hz); 1.27 (s, 3H); 1.16 (d, 1H, J = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): □□□144.5, 116.0, 46.8, 40.6, 37.8, 31.5, 31.3, 26.3, 22.3 (sep, 1C, J = 19 Hz), 19.9 (sep, 1C, J = 19 Hz); HRMS (EI): Exact mass calcd for $C_{10}H_{10}D_6$ $[M]^+$, 142.1629. Found 142.1600.

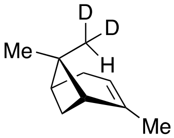


((1*S*,6*S*)-2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-yl)methyl 4-methylbenzenesulfonate (14): *p*-Toluensulfonyl chloride (5.0 g, 26.3 mmol) was added to a stirred solution of ((1*S*,5*S*,6*S*)-2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-yl)methanol **(12)** (1.0 g, 6.6 mmol) in pyridine (26 mL) at 0 ºC. After 12 hours, the reaction was diluted with a sat. NH_4Cl solution (50 mL), dichloromethane (50 mL), and transferred to a separatory funnel. The organic phase was collected and the aqueous layer extracted with dichloromethane (2 x 50 mL). Combined organics were washed with brine (75 mL) and dried with Na_2SO_4.

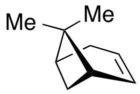
Concentration under reduced pressure and flash column chromatography on silica gel using 5% EtOAc in hexanes as the eluent afforded the title compound (1.51 g, 4.90 mmol, 75% yield) as a clear oil: 97:3 e.r. $[\alpha]^{20}$D = –28.8 (c 2.6, $CHCl_3$); IR (film): 2930, 1357, 1174, 943, 664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.76 (d, 2H, *J* = 8.3 Hz), 7.34 (d, 2H, *J* = 7.9 Hz), 5.14 (dt, 1H, *J* = 2.9, 1.4 Hz), 3.95 (d, 1H, *J* = 8.9 Hz), 3.85 (d, 1H, *J* = 8.9 Hz), 2.45 (s, 3H), 2.36 (dd, 1H, *J* = 8.7, 5.5 Hz), 2.21 (dd, 2H, *J* = 18.1, 2.3 Hz), 2.03 (td, 2H, *J* = 4.6, 1.6 Hz), 1.59 (q, 3H, *J* = 1.9 Hz), 1.28 (s, 3H), 1.20 (d, 1H, *J* = 8.7 Hz).; ^{13}C NMR (125 MHz, $CDCl_3$): □□□144.4, 143.3, 133.1, 129.7, 127.9, 116.5, 73.8, 44.6, 39.2, 38.9, 31.4, 30.7, 22.3, 21.6, 20.9; HRMS (ESI): Exact mass calcd for $C_{17}H_{22}O_3S$ $[M+Na]^+$, 329.1182. Found 329.1187.



(1*S*,6*S*)-2,6-Dimethyl-6-(methyl-*d*)bicyclo[3.1.1]hept-2-ene (5): $LiAlD_4$ (4.30 mL, 4.30 mmol, 1.0 M in Et_2O) was added to a solution of ((1*S*,6*S*)-2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-yl)methyl 4-methylbenzenesulfonate (**14**) (875 mg, 2.90 mmol) in Et_2O (15 mL). After 30 minutes, reaction was run through a plug of Florisil® with pentanes as an eluent. Careful concentration under reduced pressure afforded the title compound (303 mg, 2.2 mmol, 76% yield) as a clear oil: 97:3 e.r. $[\alpha]^{20}$D = –58.4 (c 1.7, $CHCl_3$); IR (film): 2947, 2917, 2173, 1446, 785 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.18 (t, J = 3.0 Hz), 2.33 (dt, 1H, J = 8.5, 5.6 Hz), 2.25–2.13 (m, 2H), 2.06 (dt, 1H, J = 5.8, 2.9 Hz), 1.93 (t, 1H, J = 5.6 Hz), 1.66 (q, 3H, J = 1.9 Hz), 1.26 (s, 3H), 1.16 (d, 3H, J = 8.5 Hz), 0.81 (t, 2H, J = 1.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): □□□144.5, 116.0, 46.9, 40.7, 37.9, 31.4, 31.2, 26.3, 23.0, 20.5 (t, 1C, J = 19 Hz); HRMS (EI): Exact mass calcd for $C_{10}H_{15}D$ $[M]^+$, 137.1315. Found 137.1288.



(1*S*,6*S*)-2,6-Dimethyl-6-(methyl-*d*$_2$)bicyclo[3.1.1]hept-2-ene (6): To a solution of $LiAlH_4$ (186 mg, 4.9 mmol) in Et_2O (8 mL) was cannulated a solution of ((1*S*,5*S*,6*S*)-2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-yl)dideuteromethyl 4-methylbenzenesulfonate (**19**) (1.0 g, 3.24 mmol) in Et_2O (7 mL). After 30 minutes, reaction was run through a plug of Florisil® with pentanes as an eluent. Careful concentration under reduced pressure afforded the title compound (370 mg, 2.7 mmol, 83% yield) as a clear oil: 97:3 e.r. $[\alpha]^{20}$D = –57.1 (c 2.1, $CHCl_3$); IR (film): 2913, 2880, 2195, 1455, 785 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.18 (t, 1H, J = 3.0 Hz), 2.33 (dt, 1H, J = 8.5, 5.6 Hz), 2.25–2.13 (m, 2H), 2.06 (dt, 1H, J = 5.8, 2.9 Hz), 1.93 (t, 1H, J = 5.6 Hz), 1.66 (q, 3H, J = 1.9 Hz), 1.26 (s, 3H), 1.15 (d, 3H, J = 8.5 Hz), 0.79 (t, 1H, J = 1.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): □144.5, 116.0, 46.9, 40.6, 37.8, 31.5, 31.2, 26.3, 23.0, 20.2 (p, 1C, J = 19 Hz); HRMS (EI): Exact mass calcd for $C_{10}H_{14}D_2$ $[M]^+$, 138.1378. Found 138.1340.



(1*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-ene (7): (*R*)-Myrtenal (5.0 g, 33.3 mmol) and palladium (10%) on barium sulfate (600 mg) were combined in a flask and fitted with a Dean–Stark apparatus. Mixture was heated to 185 ºC to afford the title compound (3.25 g, 26.6 mmol, 80% yield) in the Dean–Stark trap as a clear oil: 97:3 e.r. $[\alpha]^{20}$D = –52.7 (c 3.1, CHCl$_3$); IR (film): 3036, 2988, 2914, 2831, 1365, 720, 688 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): 6.15 (ddt, 1H, J = 8.4 6.5, 1.8 Hz), 5.54 (dtd, 1H, J = 8.4, 2.9, 1.4 Hz), 2.37 (dt, 1H, J = 8.5, 5.6 Hz), 2.34–2.22 (m, 2H), 2.15–2.08 (m, 2H), 1.27 (s, 3H), 1.20 (d, 1H, J = 8.5 Hz), 0.89 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): □□□136.5, 124.1, 41.9, 41.3, 38.0, 32.5, 32.1, 26.4, 21.3; HRMS (EI): Exact mass calcd for C_9H_{14} $[M+H]^+$, 123.1168. Found 123.1181.

3. Supplemental SFG and IR Spectra

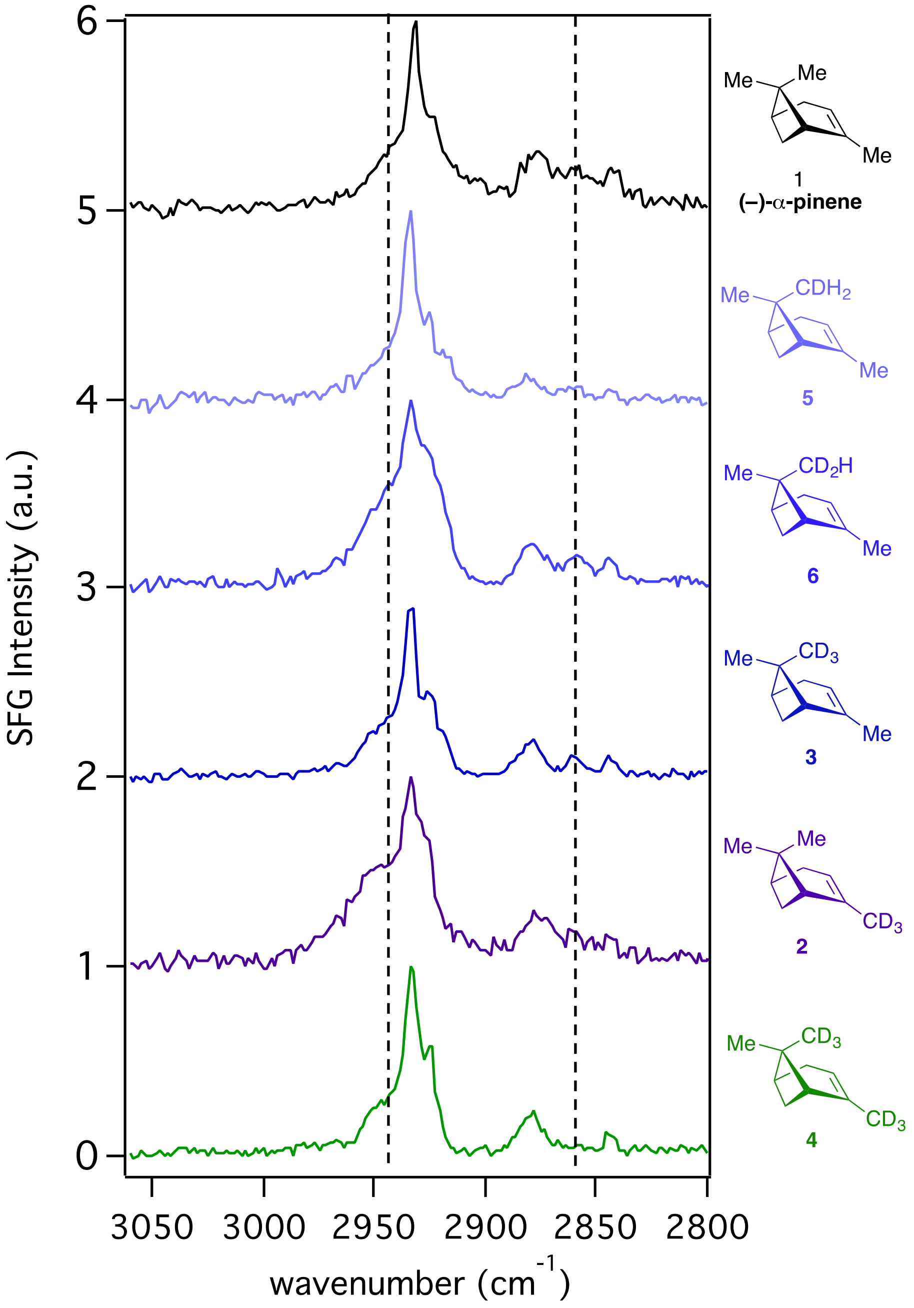


Figure S1. 0.6 cm^{-1}-resolution SFG spectra of (–)-α-pinene (**1**) and α-pinene analogues (**2-6**) vapor phases in contact with SiO_2. Spectra are offset and normalized to the highest intensity peak for clarity. Dashed lines indicate peak positions at 2940 and 2860 cm^{-1}.

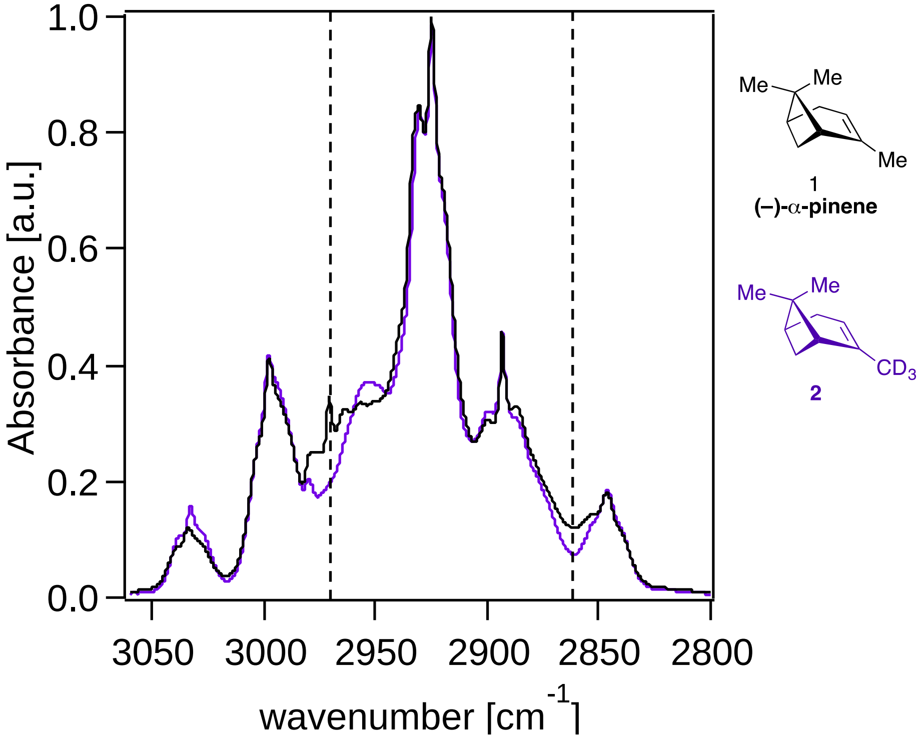


Figure S2. Comparison between IR spectra of vapor phase (–)-α-pinene (**1**) (black trace), and isotopologue **2** (purple trace). Spectra are normalized to the highest intensity peak. Dashed lines indicate peak positions at 2970 and 2860 cm^{-1}.

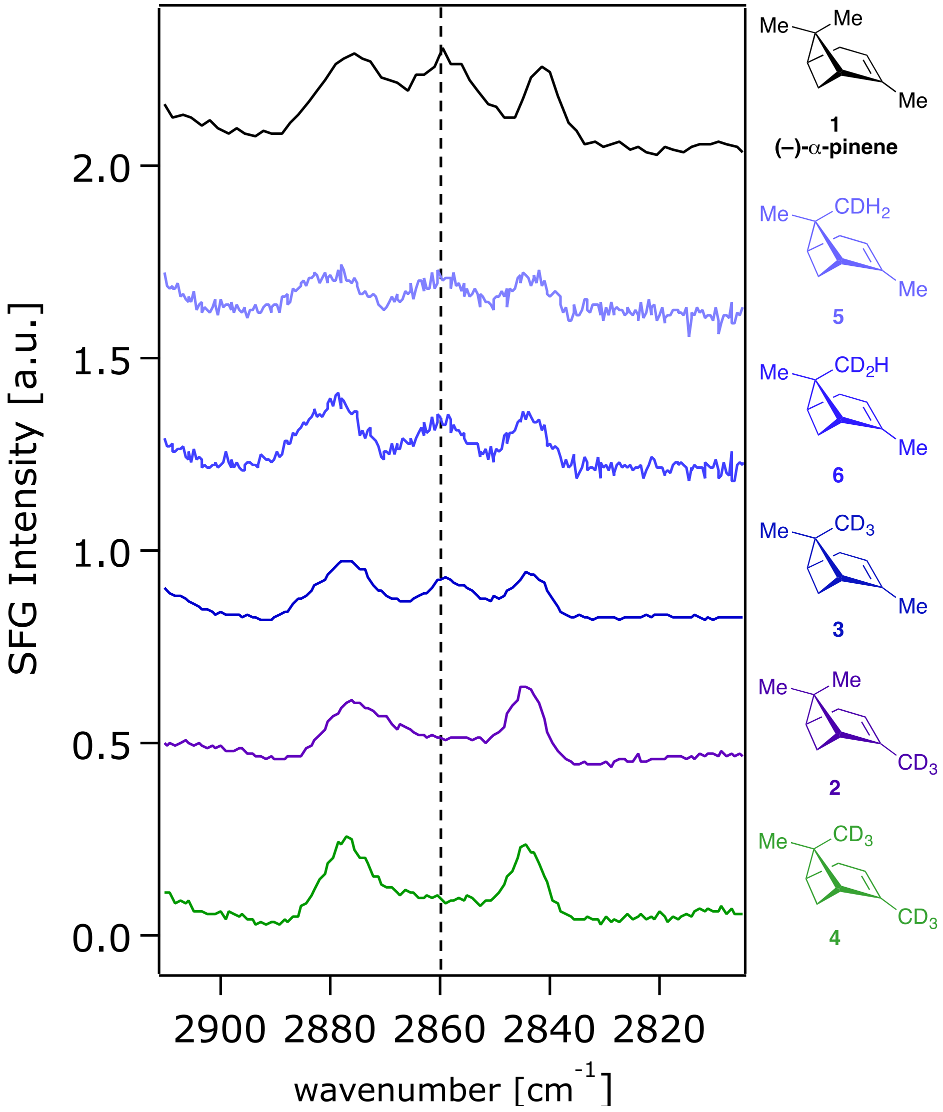


Figure S3. 0.6 cm^{-1}-resolution SFG spectra of (–)-α-pinene (**1**) and α-pinene isotopologues (**2-6**) as vapor phases in contact with CaF$_2$ zoomed in on the 2910-2810 cm^{-1} range in order to show clear differences in intensity at the 2860 cm^{-1} position indicated by the dashed line.

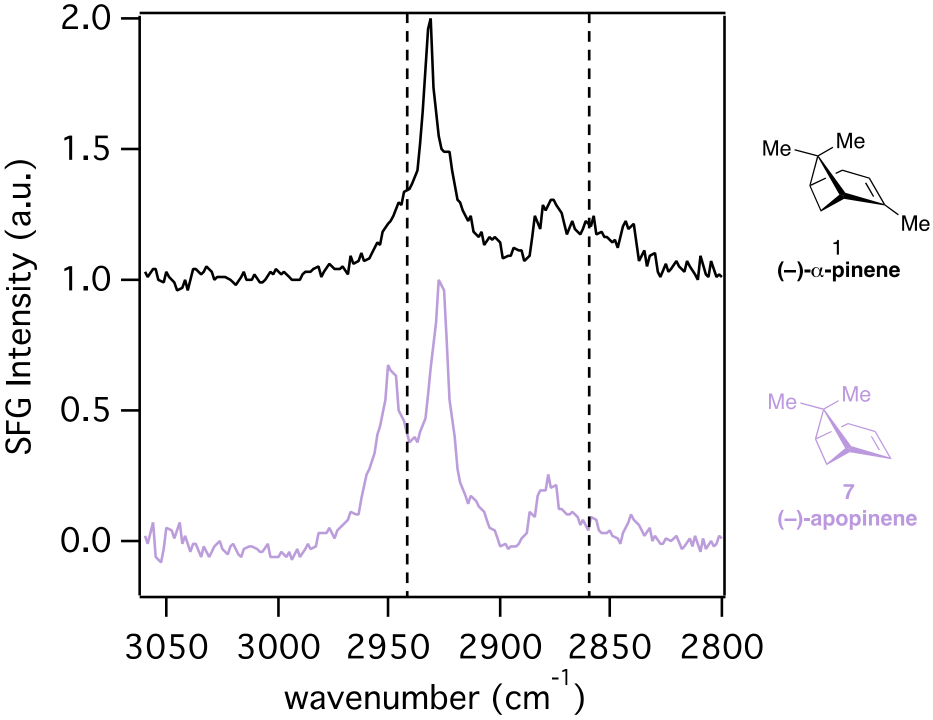
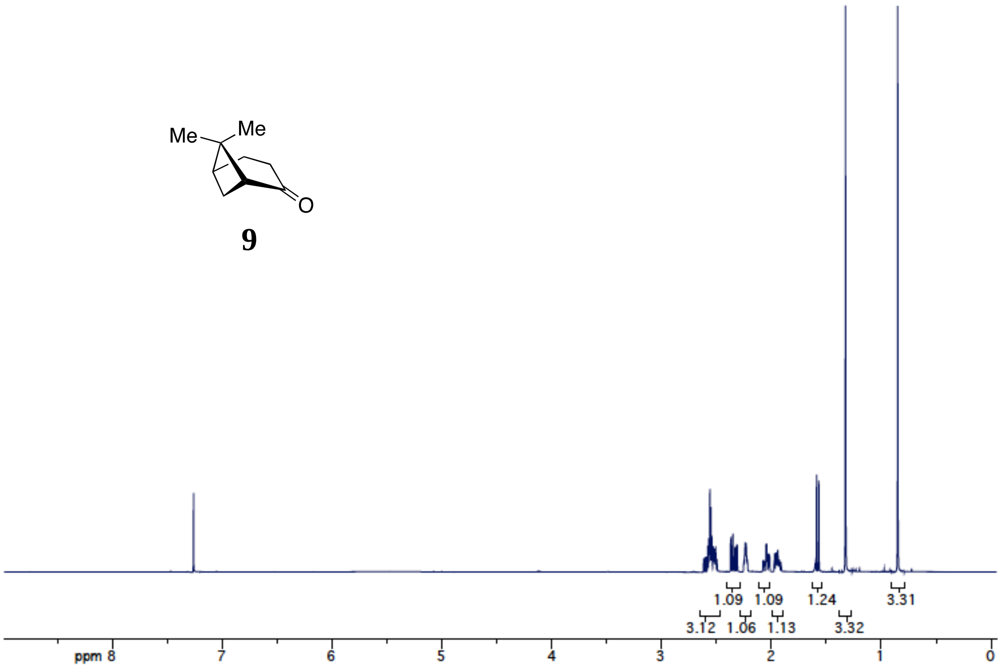


Figure S4. 0.6 cm^{-1}-resolution SFG spectra of (–)-α-pinene (**1**) and (–)-apopinene (**7**) as vapor phases in contact with SiO_2. Spectra are offset and normalized to the highest intensity peak for clarity. Dashed lines indicate peak positions at 2940 and 2860 cm^{-1}.

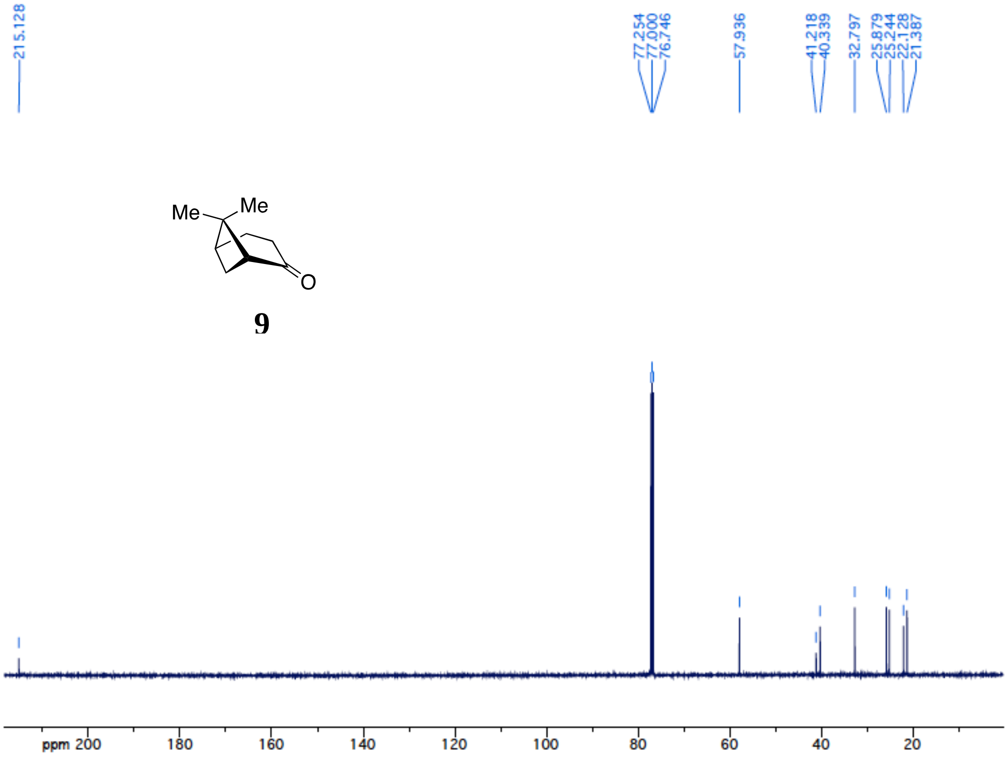
4. ^{1}H and ^{13}C NMR Spectra

(1*R*)-6,6-Dimethylbicyclo[3.1.1]heptan-2-one (9):

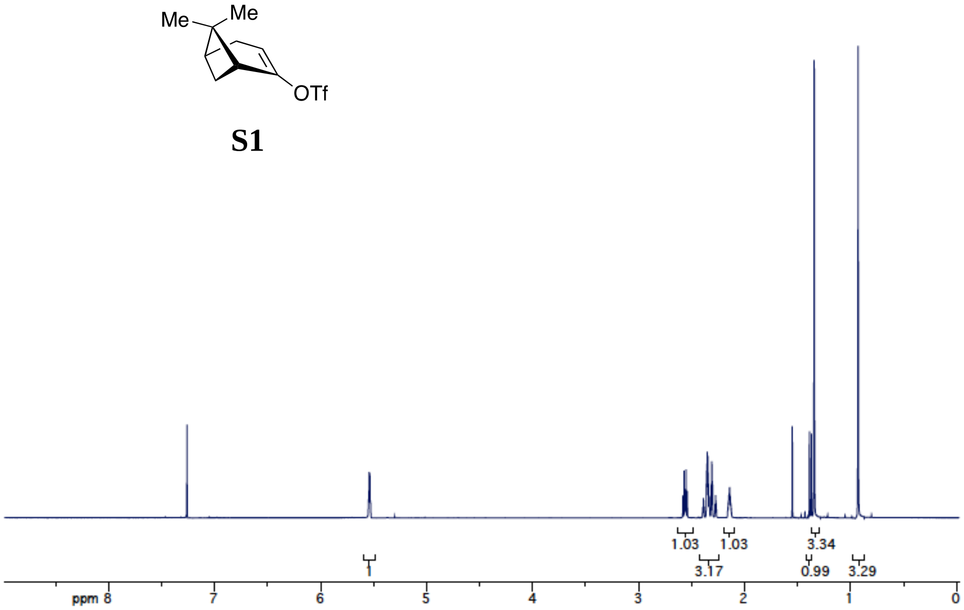
9

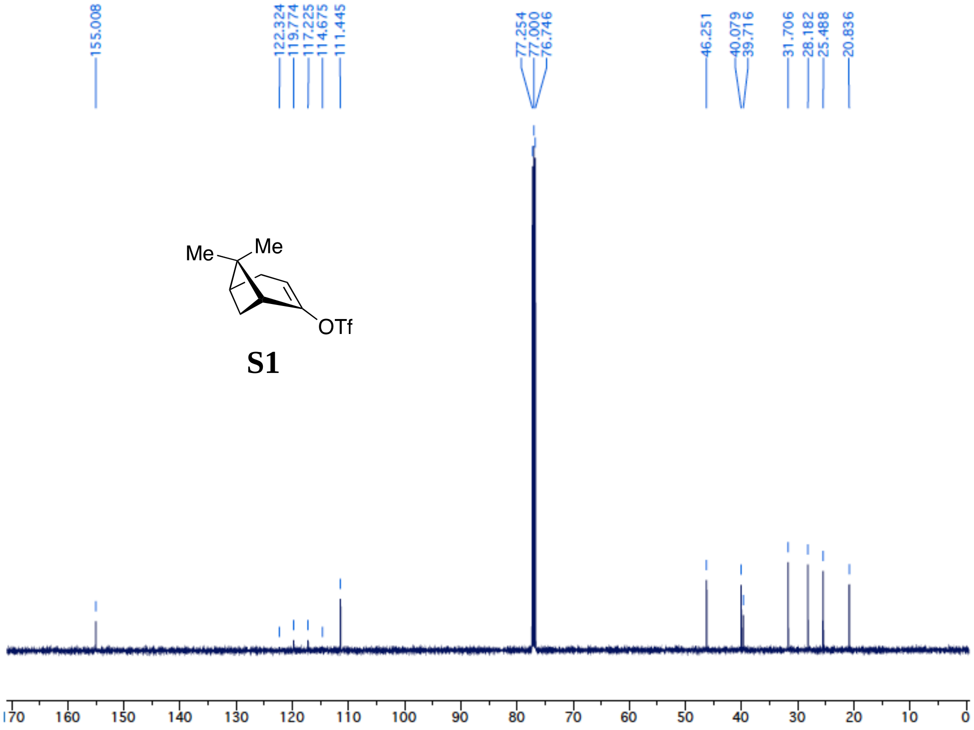


9

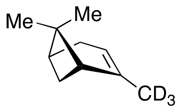


(1*R*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl trifluoromethanesulfonate:

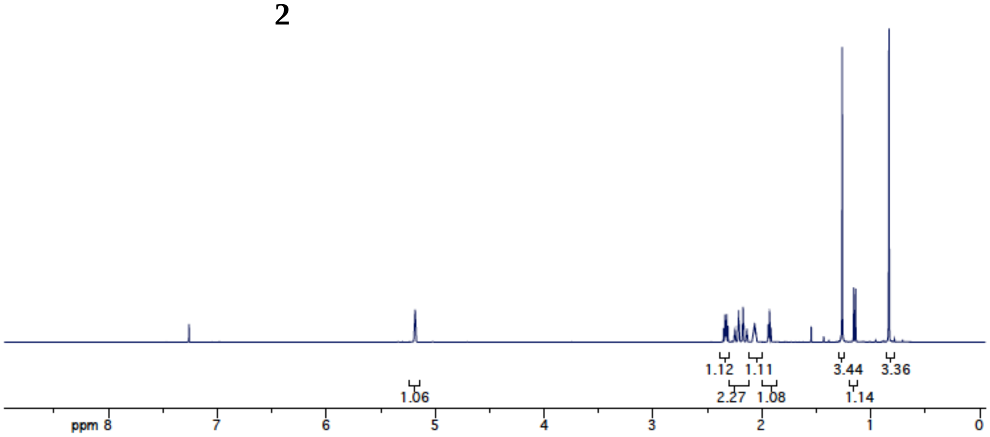


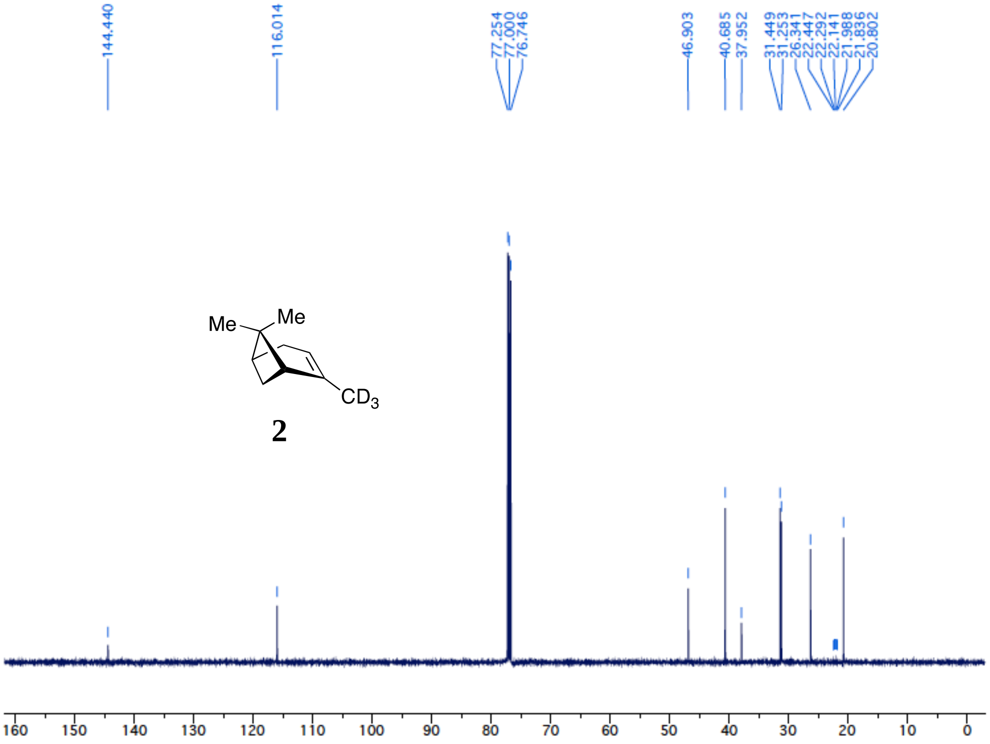


(1*S*)-6,6-Dimethy-2-(methyl-d_3)-bicyclo[3.1.1]hept-2-ene (2):

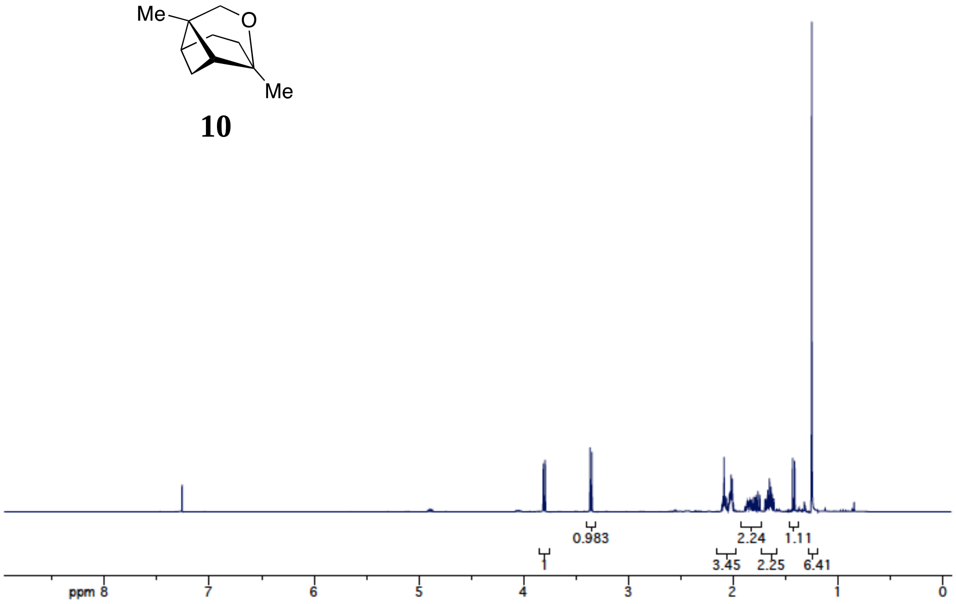


2

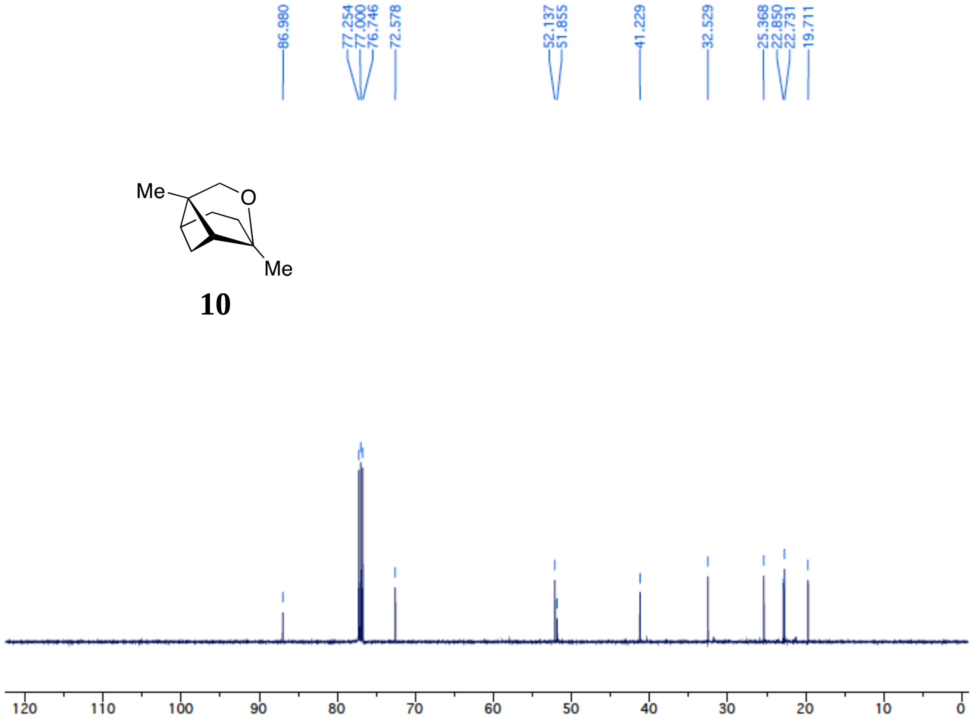




(1*R*, 3*S*, 6*R*, 9*S*)-6,9-Dimethyl-7-oxatricyclo[4.3.0.0^{3,9}]nonane (10):

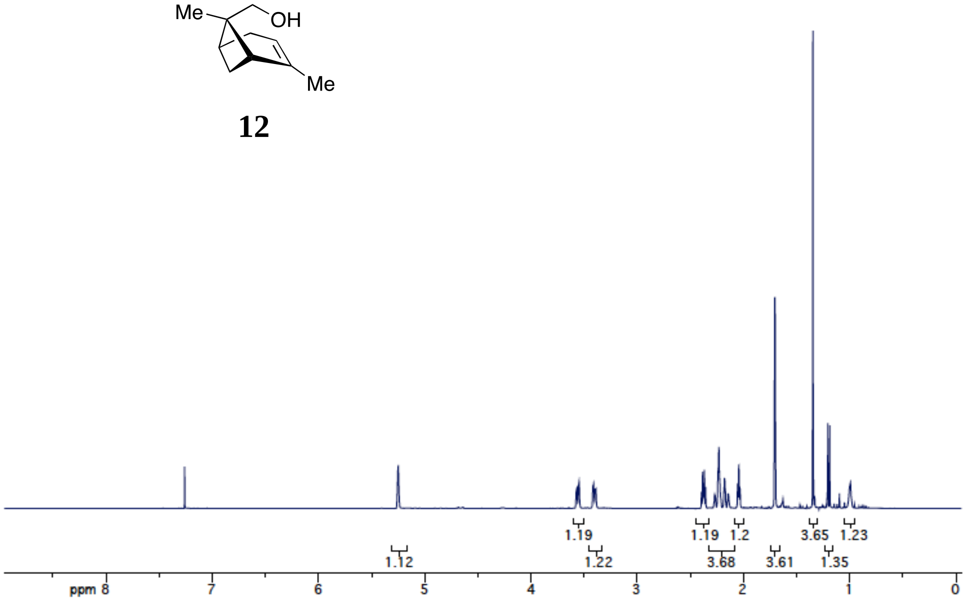


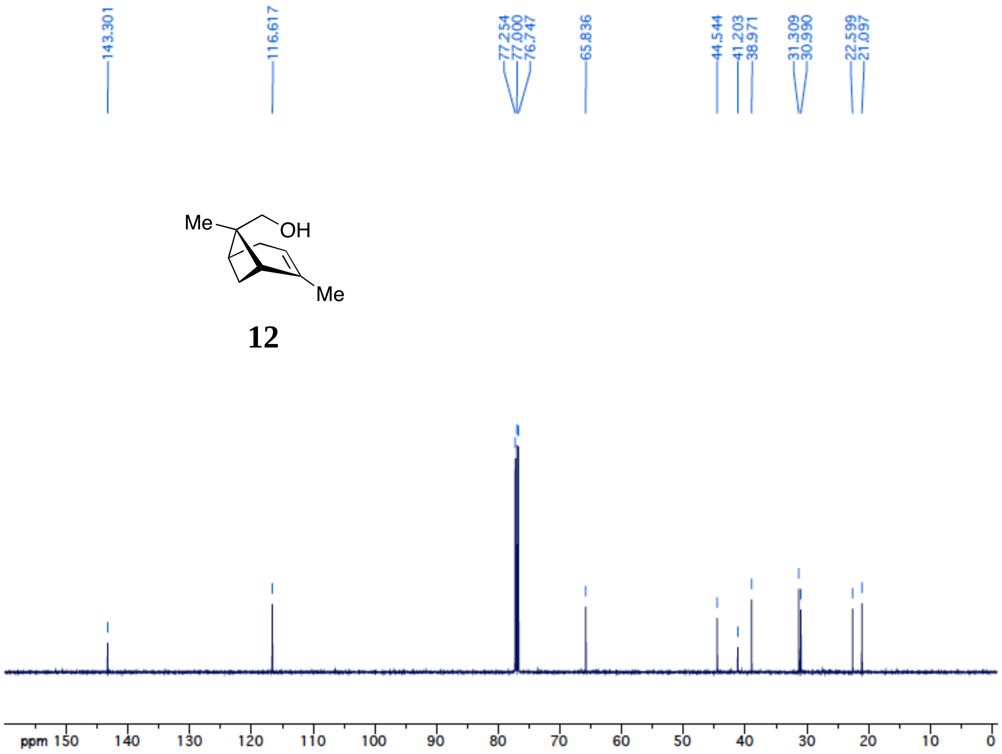
10



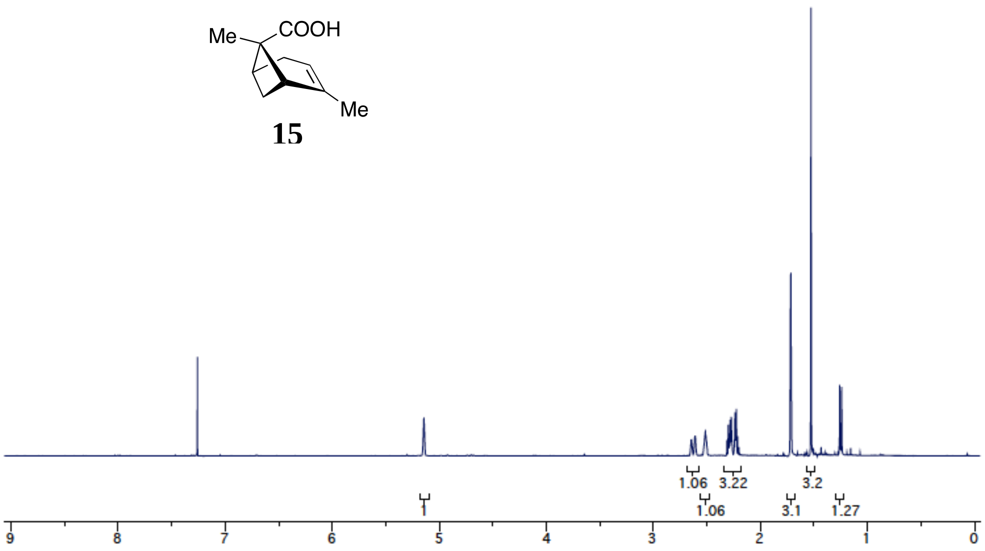
10

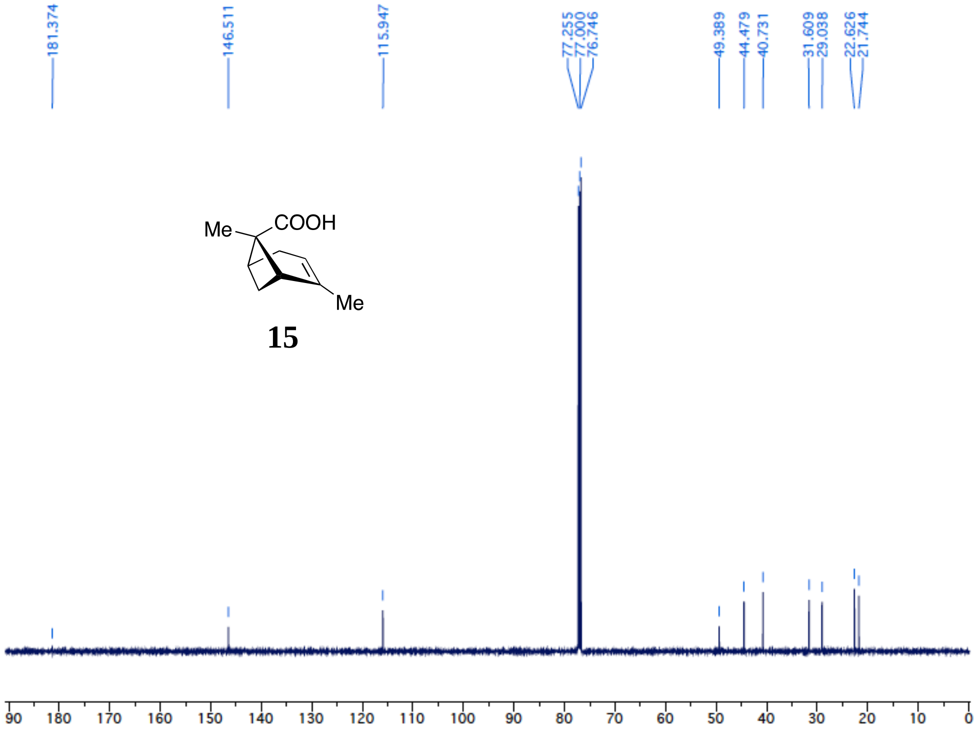
((1*S*,5*S*,6*S*)-2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-yl)methanol (II-21):



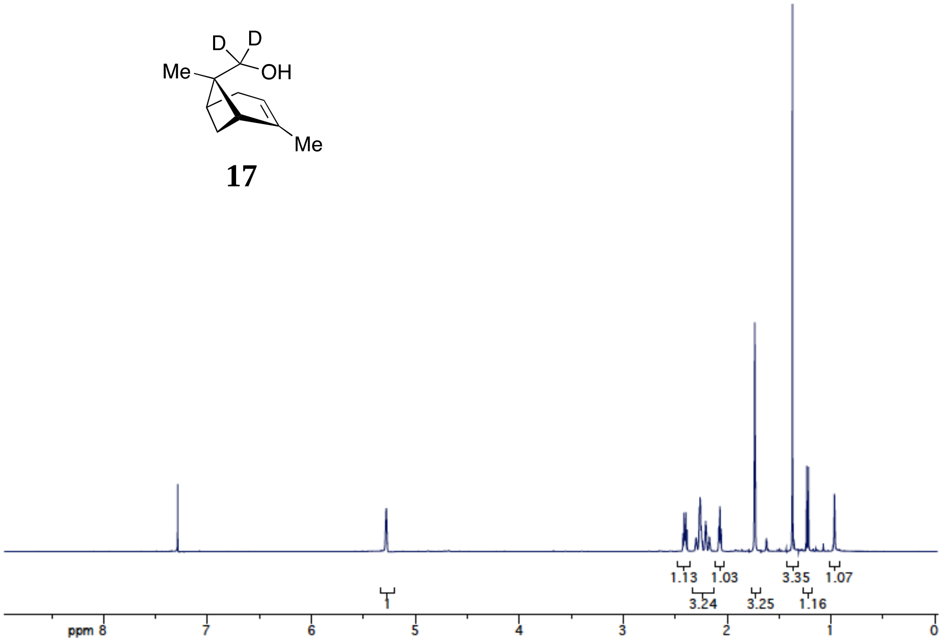


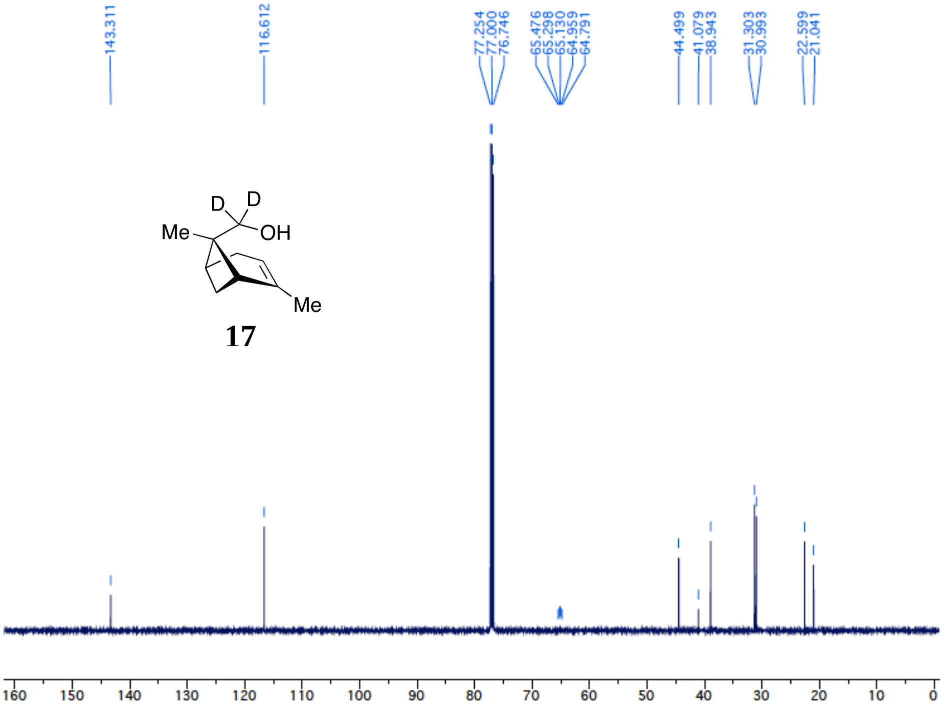
(1*S*,5*S*,6*S*)-2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-carboxylic acid (15):



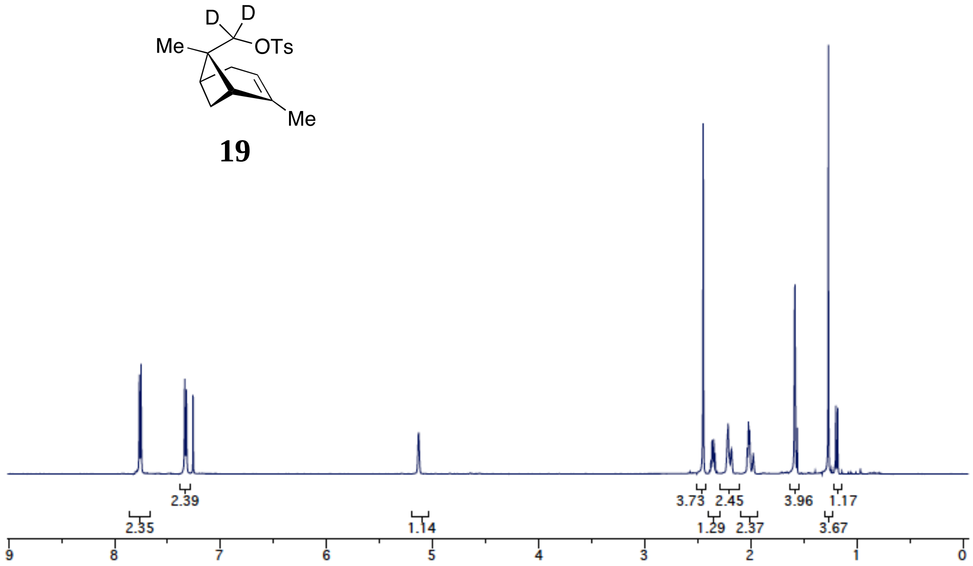


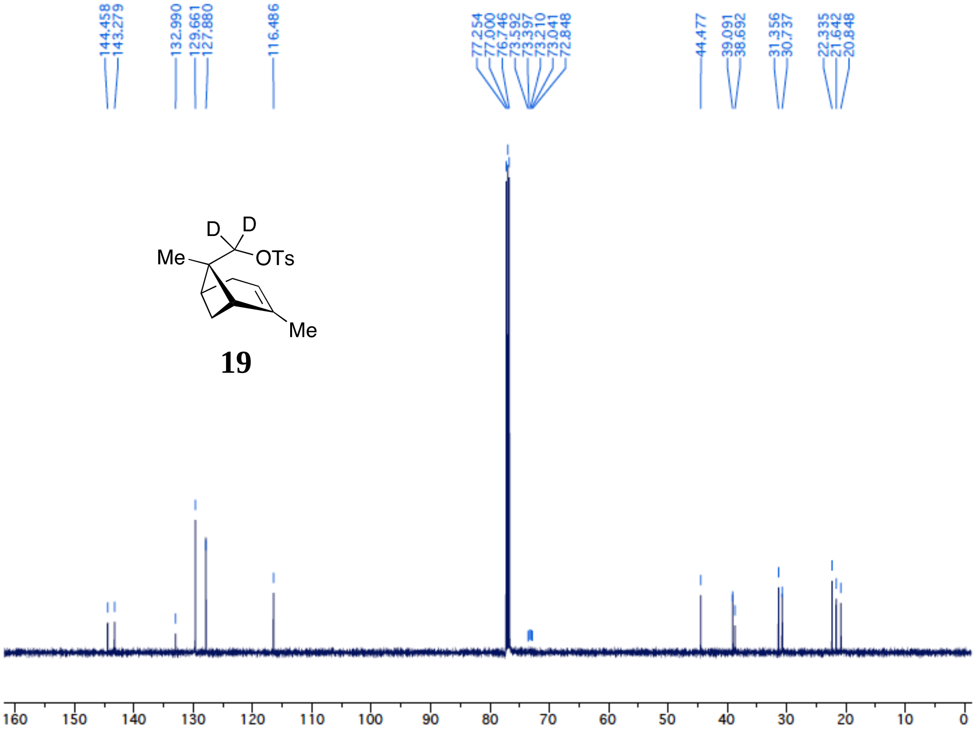
((1*S*,5*S*,6*S*)-2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-yl)dideuteromethanol (17):


17

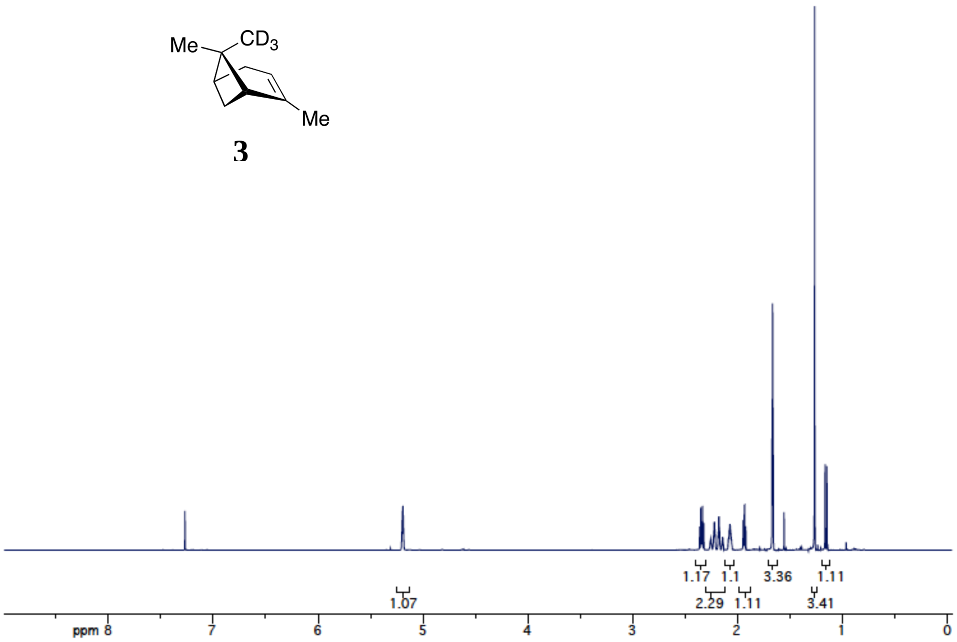

17

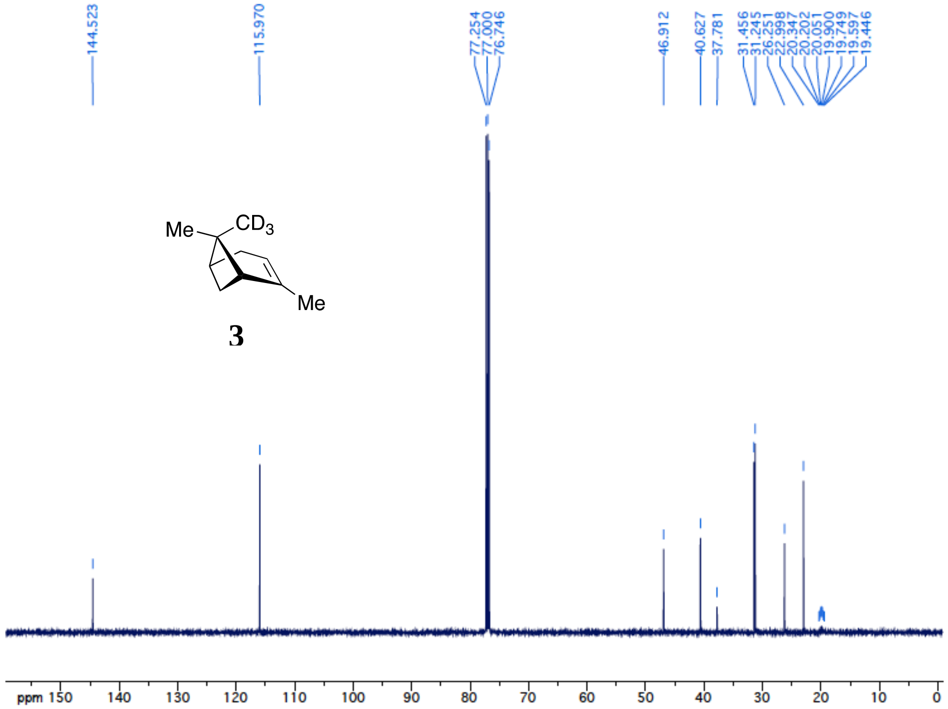
((1*S*,5*S*,6*S*)-2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-yl)dideuteromethyl 4-methylbenzenesulfonate (19):



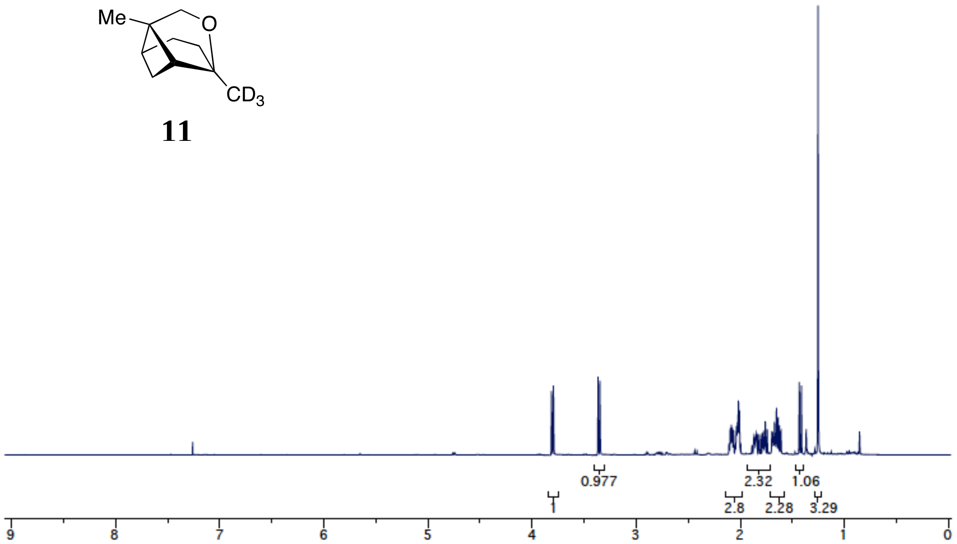


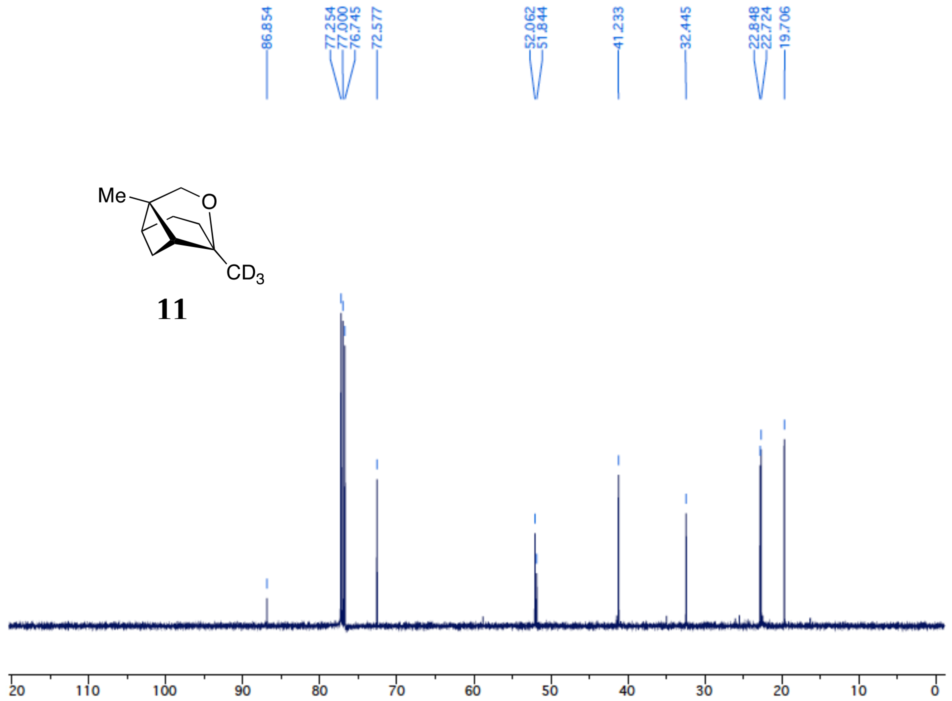
(1*S*)-6,6-Dimethy-2-(methyl-d_3)-bicyclo[3.1.1]hept-2-ene (3):



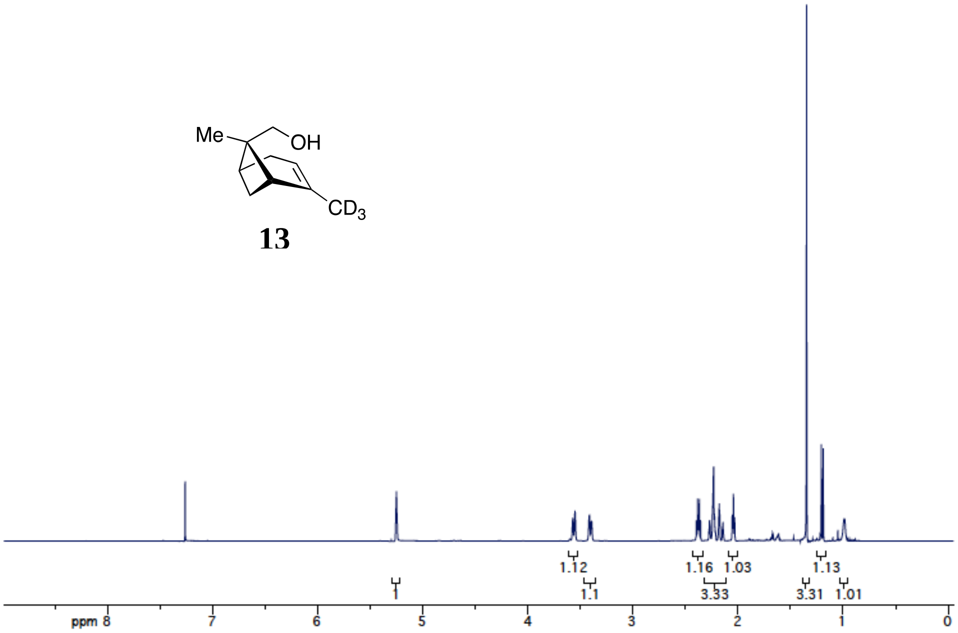


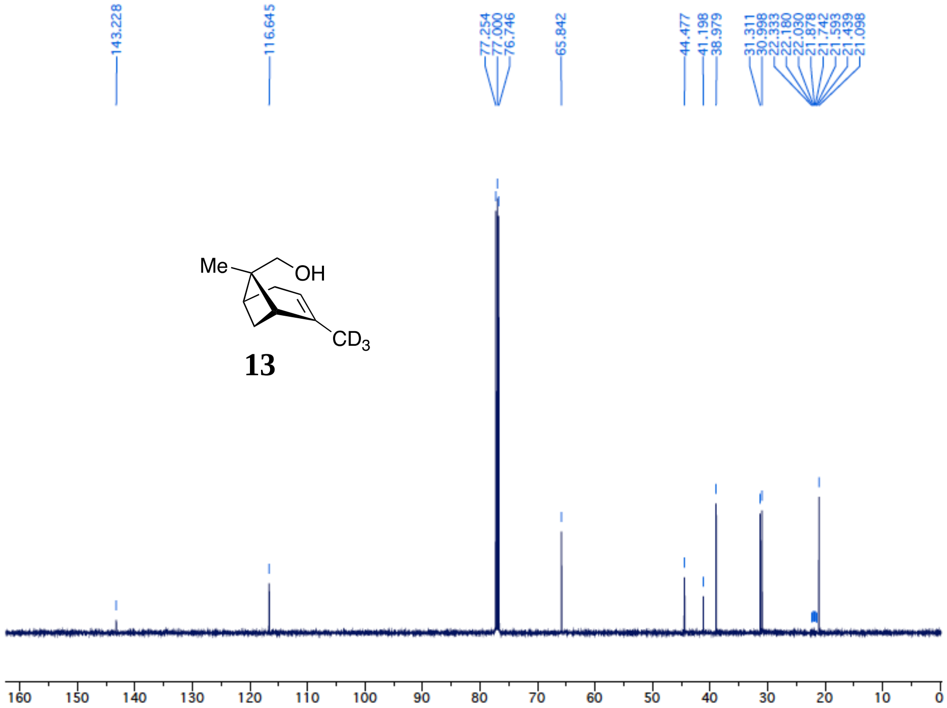
(1*R*,3*S*,6*R*,9*S*)-9-Methyl-6-(methyl-d_3)-7-oxatricyclo[4.3.0.0^{3,9}]nonane (11):



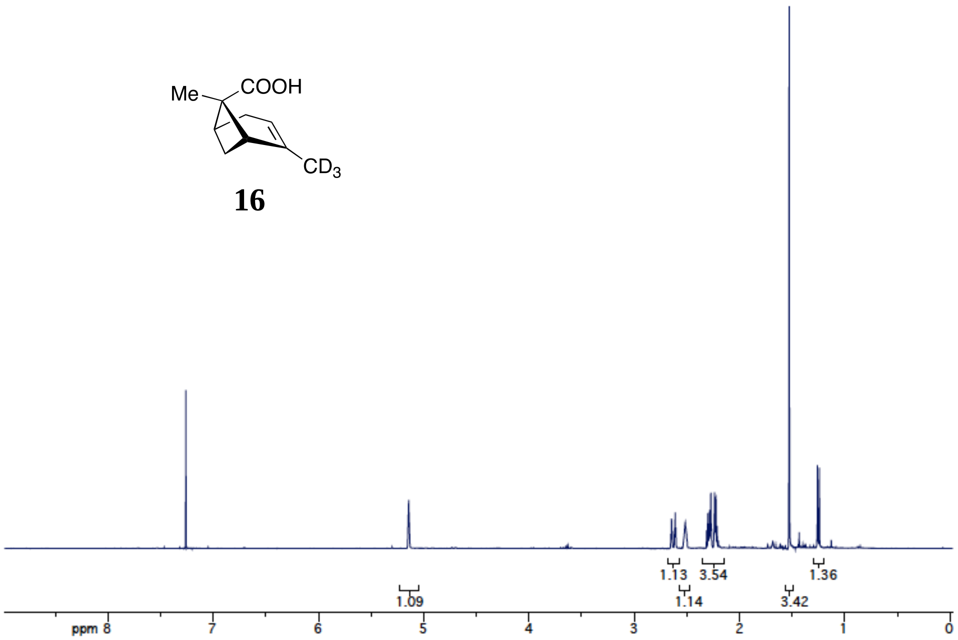


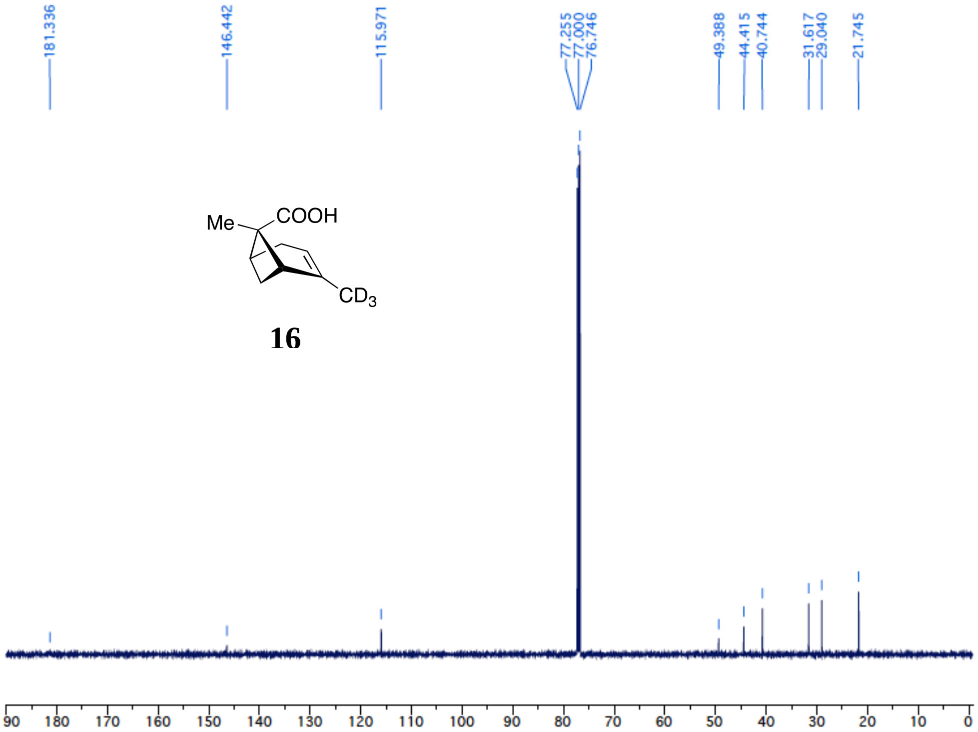
((1*S*,5*S*,6*S*)-6-Methyl-2-(methyl-d_3)-bicyclo[3.1.1]hept-2-en-6-yl)methanol (13):



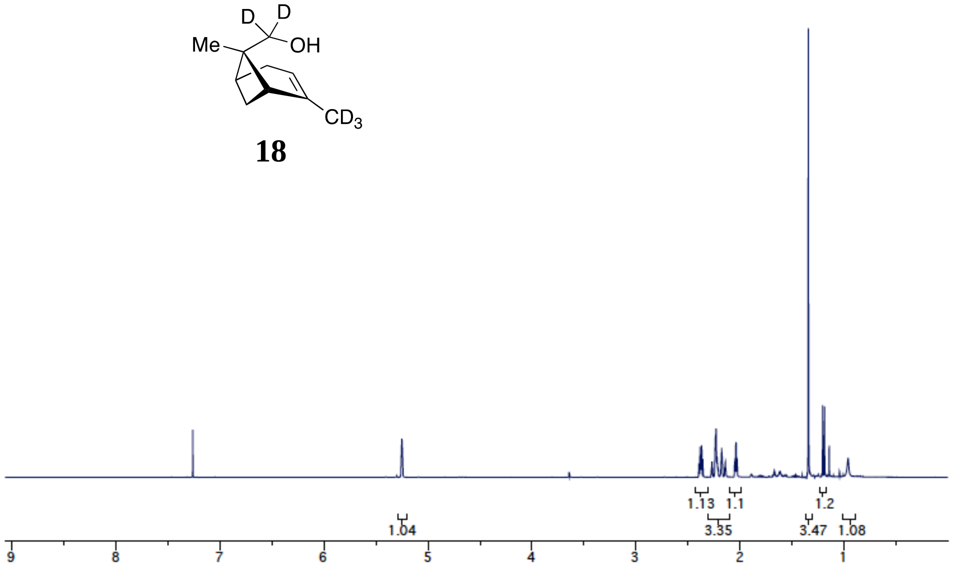


(1*S*,5*S*,6*S*)-6-Methyl-2-(methyl-d_3)-bicyclo[3.1.1]hept-2-en-6-carboxylic acid (16):

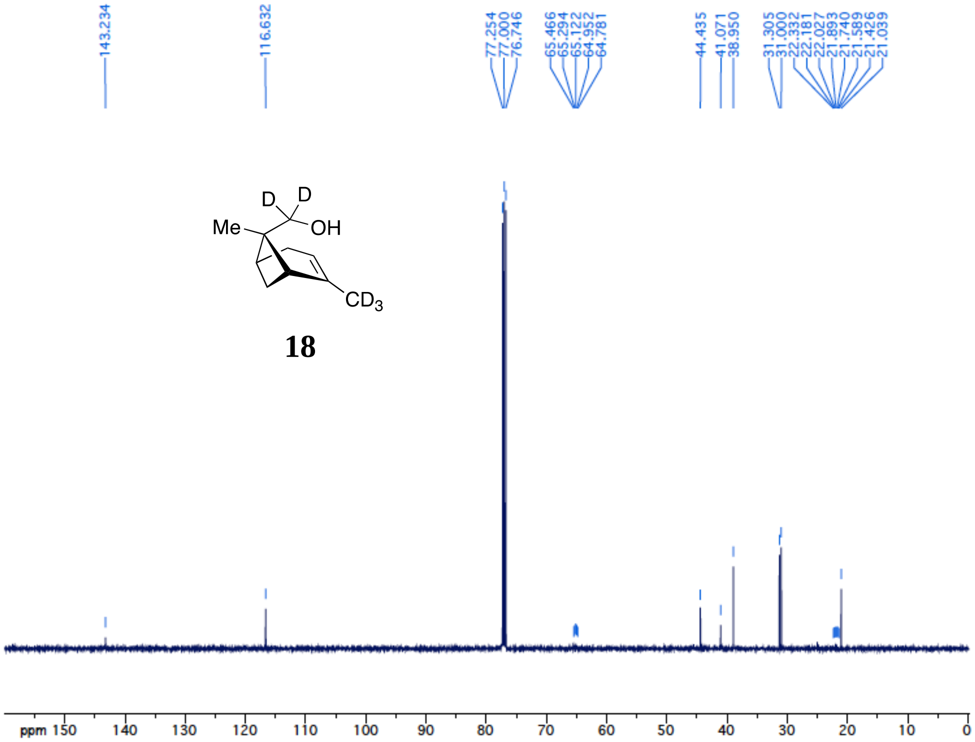




((1*S*,5*S*,6*S*)-6-Methyl-2-(methyl-d_3)-bicyclo[3.1.1]hept-2-en-6-yl)dideuteromethanol (18):

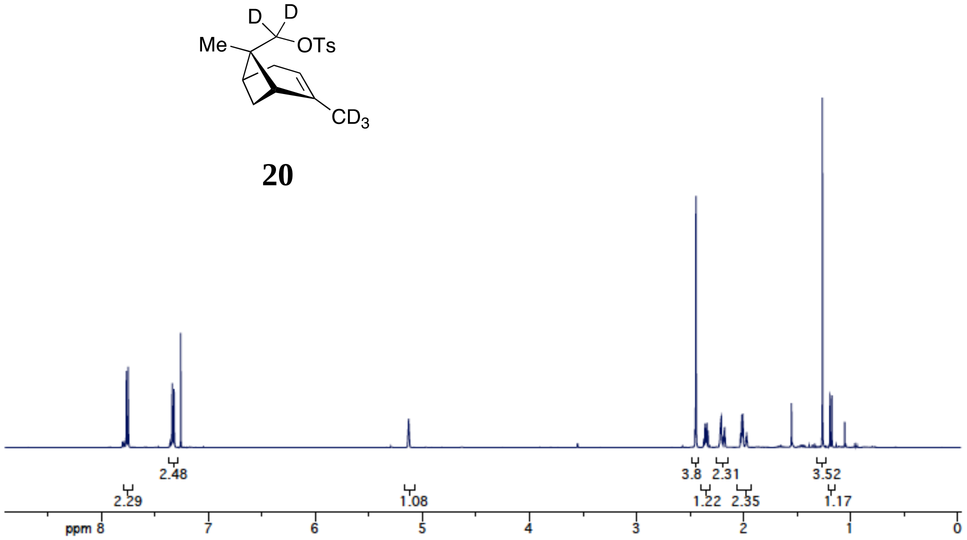


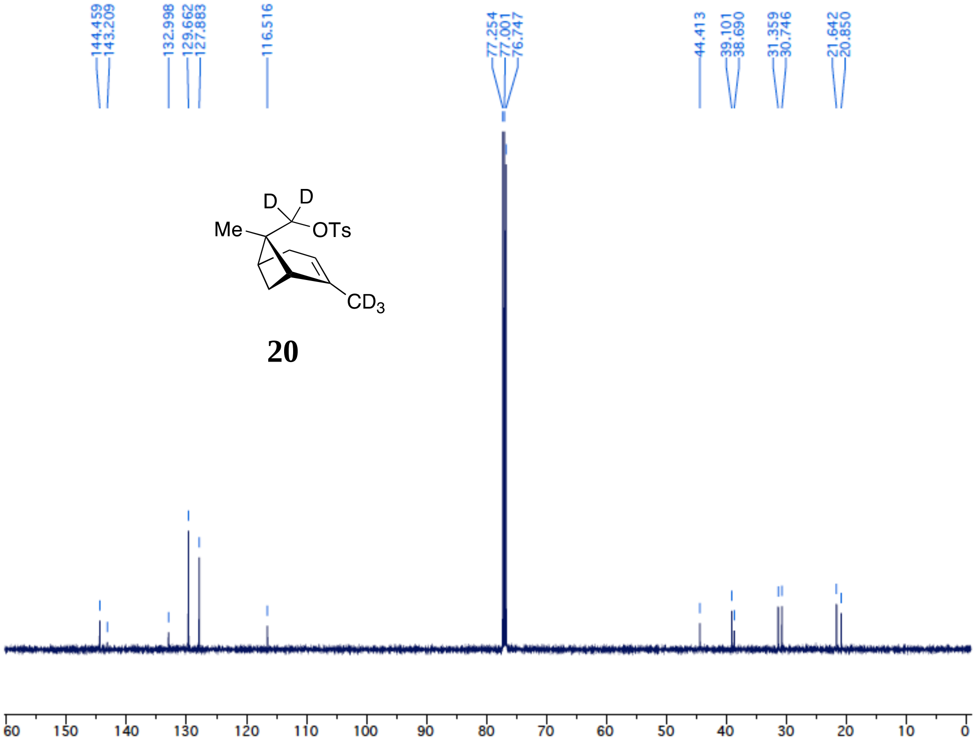
18



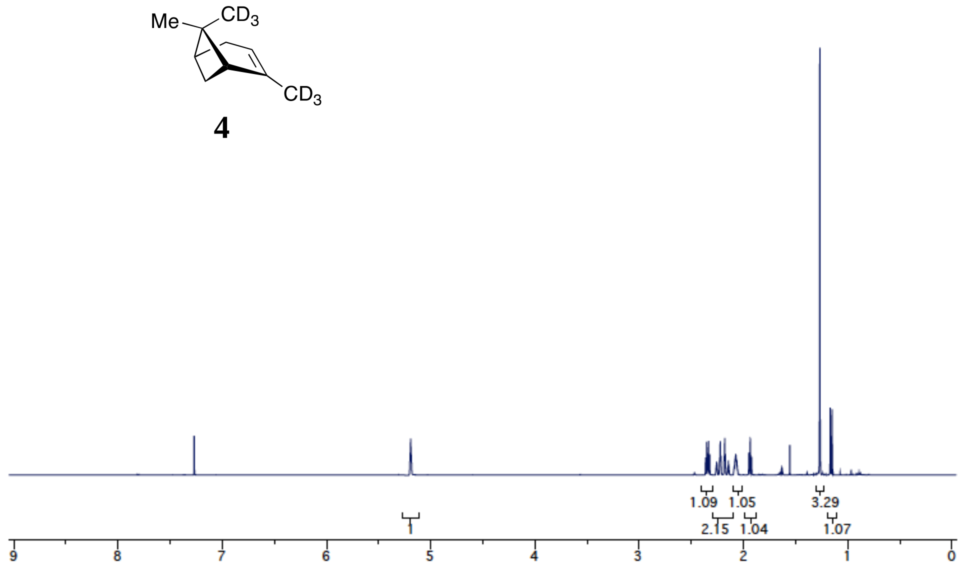
18

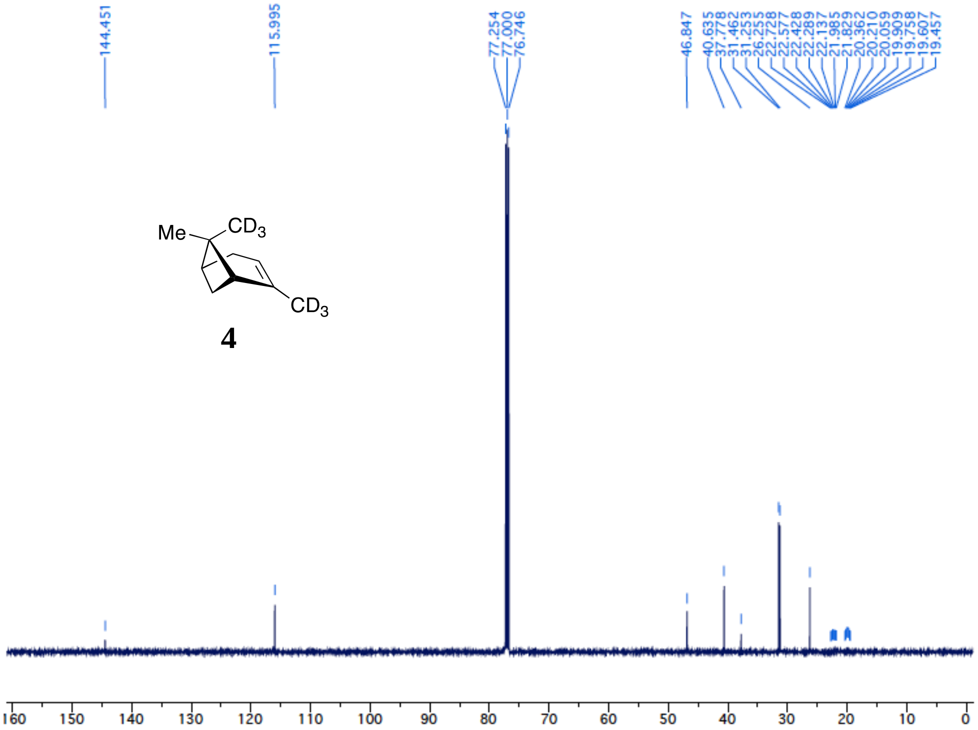
((1*S*,5*S*,6*S*)-6-Methyl-2-(methyl-*d_3*)-bicyclo[3.1.1]hept-2-en-6-yl)dideuteromethyl 4-methylbenzenesulfonate (20):



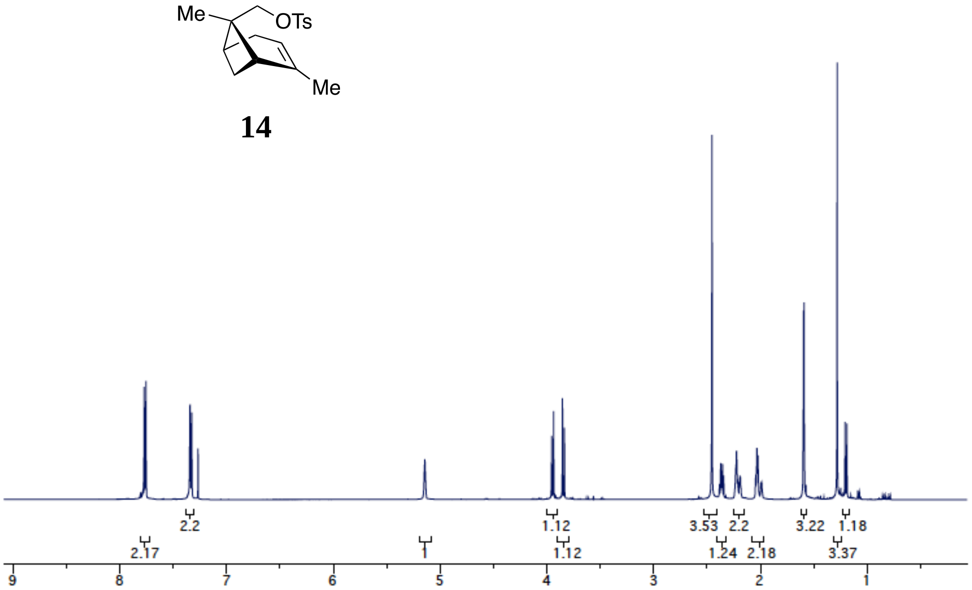


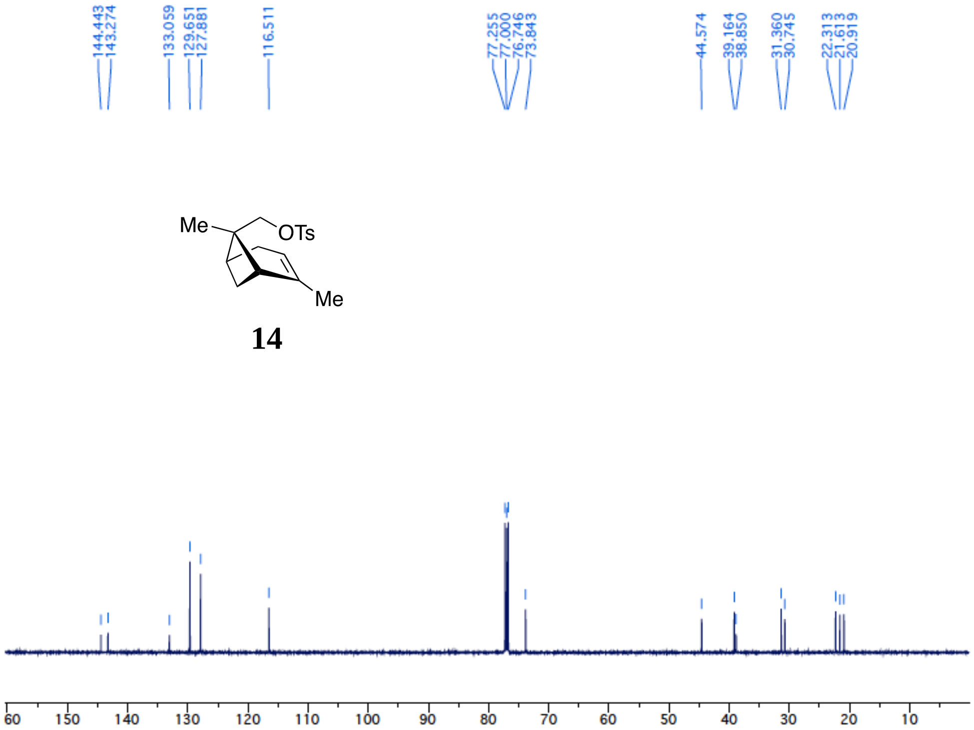
(1*S*,6*S*)-6-Methy-2,6-bis(methyl-d_3)-bicyclo[3.1.1]hept-2-ene (4):



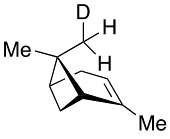


((1*S*,6*S*)-2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-yl)methyl 4-methylbenzenesulfonate (14):

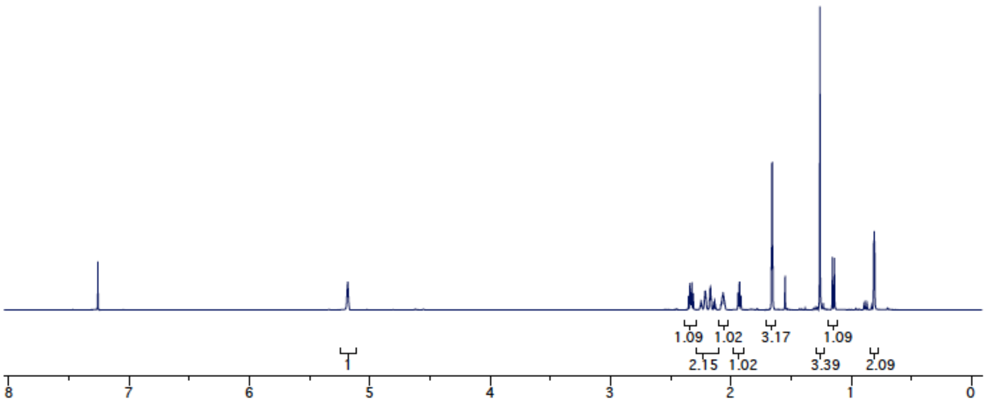


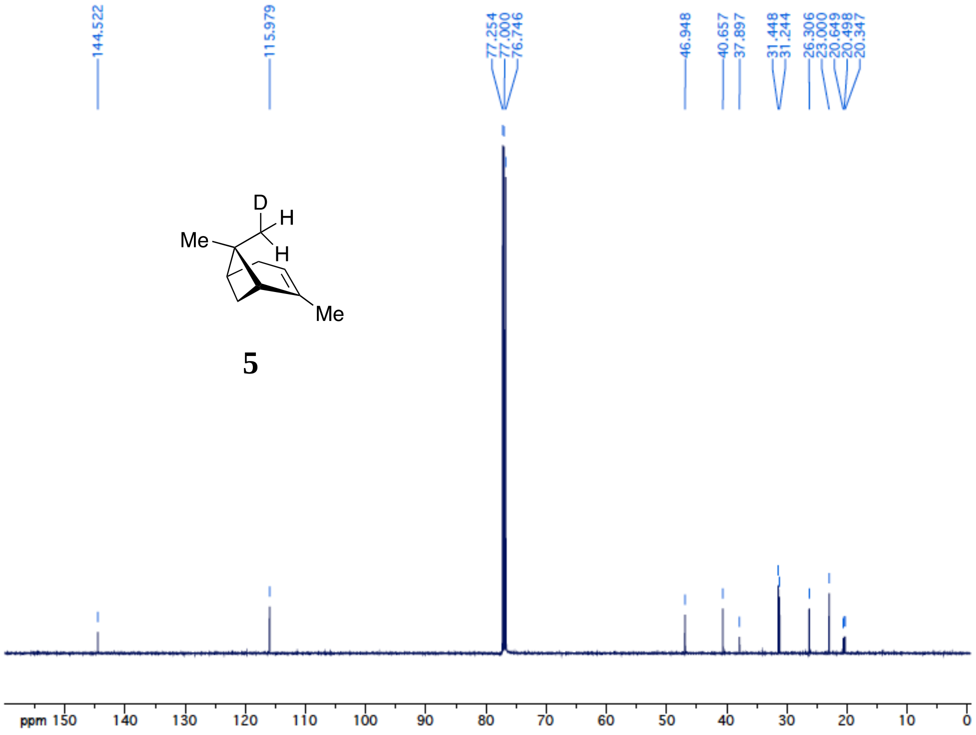


(1*S*,6*S*)-2,6-Dimethyl-6-(methyl-*d*)bicyclo[3.1.1]hept-2-ene (5):

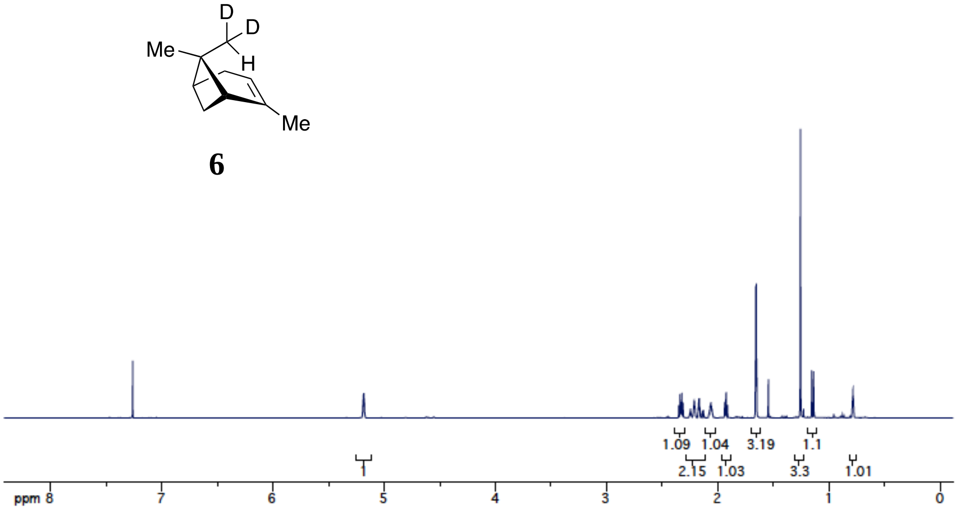


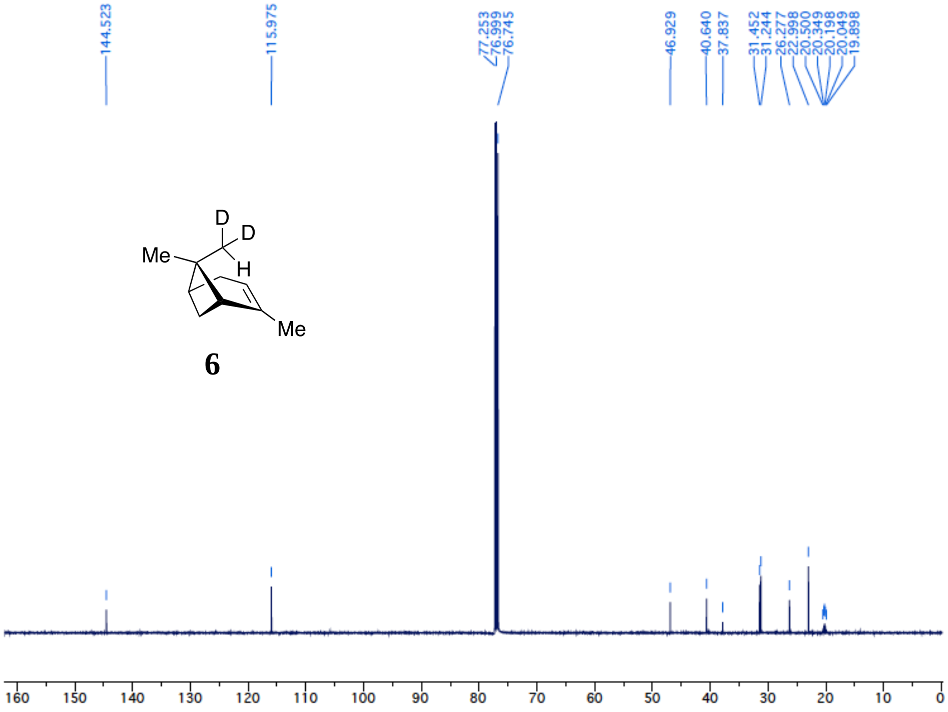
5





(1*S*,6*S*)-2,6-Dimethyl-6-(methyl-d_2)bicyclo[3.1.1]hept-2-ene (6):





(1*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-ene (7):