# The Organocatalytic Three-Step Total Synthesis of (+)-Frondosin B

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## Electronic supplementary information (ESI)

**General Information**. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[S1] All solvents were purified according to the method of Grubbs.[S2] Chromatographic purification of products was accomplished using force-flow chromatography on Silicycle silica gel according to the method of Still.[S3] Thin-layer chromatography (TLC) was performed on Silicycle 250 mm silica gel plates. Visualization of the developed chromatogram was performed by fluorescence quenching and potassium permanganate or cerium ammonium molybdate stain. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian Mercury 400 (400 MHz or 100 MHz), or a Bruker 500 (500 MHz and 125 MHz) as noted, and are internally referenced to residual protio solvent signals (note: $CDCl_3$ referenced at d 7.26). Data for $^{1}H$ NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for $^{13}C$ NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption ($cm^{-1}$). Mass spectra were obtained from the California Institute of Technology Mass Spectral Facility and the Princeton Mass Spectroscopy Facility. Gas liquid chromatography (GLC) was performed on Hewlett-

[S1] Perrin, D. D. & Armarego, W. L. F. (1998) *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford.

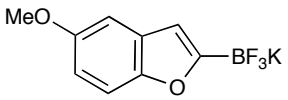
[S2] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K. & Timmers, F. J. (1996) *Organometallics,* **15**, 1518-1520.

[S3] Still, W. C.; Kahn, M. & Mitra, A. J. (1978) *J. Org. Chem.* **43**, 2923-2925.

Packard 6850 and 6890 Series gas chromatographs equipped with split-mode capillary injection system and flame ionization detectors using Bodman Chiraldex Γ-TA (30 m × 0.25 mm) column. Supercritical fluid chromatography (SFC) was performed on a Berger Minigram equipped with a diode array UV detector ( λ = 214–258 nm) using a chiral column (25 cm) and guard column (5 cm) as noted for each compound.

For the synthesis and full characterization of (*R*)-3-(5-methoxybenzofuran-2-yl)butan-1-ol ((*R*)-**12**) and X-ray crystallographic data of the corresponding 4-bromobenzoate, see reference S4.

**2-(5-methoxybenzofuranyl)trifluoroborate (6a).**



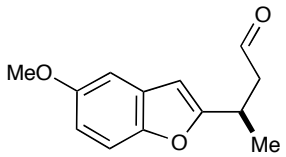

**6a**

Prepared according to a procedure adopted from Molander *et al*.[S5] commercially available 2-(5-methoxybenzofuranyl) boronic acid **2** (1.75 g, 9.00 mmol, 1.00 equiv.) was dissolved in anhydrous methanol (25 mL). Potassium hydrogenfluoride (2.44 g, 31.0 mmol, 3.40 equiv.) was added and the resulting suspension was sonicated for 5 min before being cooled down to 0 °C. Water (8mL) was added dropwise over 45 min using a syringe pump. A heavy white precipitate was deposited. The resulting suspension was stirred at room temperature for 2 h and then concentrated *in vacuo* and azeotroped five times with methanol. The resulting white solid was dried under high vacuum for 2 h, before being taken up with hot acetone and filtered. The filtrate was cooled to room temperature and concentrated *in vacuo*. Ethyl ether was added to triturate the product as a white solid. $^{1}$H NMR (400 MHz, $d_6$-acetone) δ 7.18 (d, 1H, *J* = 8.7 Hz, Ar**H**), 6.92 (d, 1H, *J* = 2.4 Hz, aryl **H**), 6.64 (dd, 1H, *J* = 8.7, 2.4 Hz, Ar**H**), 6.45 (s, 1H, Ar**H**), 3.54 (s, 3H, C$\mathbf{H_3}$); $^{13}$C NMR (125 MHz, $d_6$-acetone) δ 155.5, 151.5, 130.5, 110.7, 110.2, 107.6, 102.9, 55.3; $^{19}$F NMR

[S4] Lee, S. & MacMillan, D. W. C. (2007) *J. Am. Chem. Soc.* **129**, 15438-15439.
[S5] Molander, G. A. & Ito, T. (2001) *Org. Lett.* **3**, 393-396.

(282 MHz, $d_6$-acetone) δ −143.1 (br d, $J$ = 44 Hz); HRMS (ES−) calcd for $C_9H_7O_2BF_3$ $[M]^-$ $m/z$ 215.0491, found $m/z$ 215.0462.

**(*R*)-3-(5-methoxybenzofuran-2-yl)butanal (7a).**



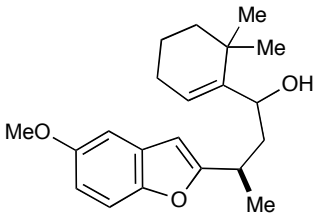

(*R*)-**7a**

**From trifluoroborate 6a:** To a plastic vial (Wheaton HDPE) was added aqueous HF (48 wt%, 6.25 mg, 0.150 mmol, 1.00 equiv.) followed by 1,2-dimethoxyethane (450 mL, 1M relative to aldehyde) and a magnetic stir bar. Imidazolidinone catalyst (*S*, *S*)-**4a** (10.9 mg, 0.0300 mmol, 0.200 equiv.) and acid co-catalyst HCl (4M in 1,4-dioxane, 7.5 μL, 0.030 mmol, 0.200 equiv.) were added and the reaction mixture was cooled to −20 °C. Crotonaldehyde (37.5 μL, 0.450 mmol, 3.00 equiv.) was added to the reaction mixture followed by potassium 2-(5-methoxybenzofuranyl) trifluoroborate **6a** (42.4 mg, 0.150 mmol, 1.00 equiv.). The reaction was stirred at −20 °C for 24 h and diluted with $CHCl_3$ (1.5 mL), quenched with 1M HCl (1.0 mL) and stirred at ambient temperature for 30 min. The aqueous layer was extracted with $CHCl_3$ (2 × 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 10% EtOAc in hexanes) yielded the title compound as clear oil (30.7 mg, 94% yield, 92% ee).

**From boronic acid 2:** To a plastic vial (Wheaton HDPE) was added HF (48 wt%, 58.4 mg, 1.40 mmol, 1.00 equiv.) followed by EtOAc (14 mL, 0.1M relative to boronic acid) and a magnetic stir bar. Imidazolidinone catalyst (*S*,*S*)-**4a** (105 mg, 0.280 mmol, 0.200 equiv.) and acid co-catalyst dichloroacetic acid (23.1 μL, 0.280 mmol, 0.200 equiv.) were added and the reaction mixture was stirred for 15 min at room temperature. Crotonaldehyde (348 μL, 4.20 mmol, 3.00 equiv.) was added to the reaction mixture followed by boronic acid **2** (269 mg, 1.40 mmol, 1.00 equiv.). The reaction was stirred at room temperature for 36 h and diluted with $CH_2Cl_2$ (17 mL), quenched with water (8 mL) and stirred at ambient

temperature for 1 h. The aqueous layer was extracted with $CH_2Cl_2$ (2 × 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 10% $Et_2O$ in hexanes) yielded the title compound as a clear oil (255 mg, 84% yield, 93% ee): $[\alpha]^{20}_D = -8.5$ (*c* = 1.3, $CHCl_3$); IR (film) 1724, 1475, 1205, 1030 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 9.78 (t, 1H, *J* = 1.5 Hz, C**H**O), 7.29 (d, 1H, *J* = 8.4 Hz, Ar**H**), 6.98 (d, 1H, *J* = 2.4 Hz, Ar**H**), 6.81 (dd, 1H, *J* = 9.0, 2.4 Hz, Ar**H**), 6.38 (d, 1H, *J* = 0.9 Hz, Ar**H**), 3.01 (s, 3H, OC**H**$_3$), 3.54 (m, 1H, C**H**$CH_3$), 2.79 (ddd, 2H, *J* = 17.4, 6.6, 1.5 Hz, C**H**$_2$), 1.39 (d, 3H, *J* = 0.9 Hz, C**H**$_3$); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 201.0, 162.1, 155.8, 149.5, 129.0, 112.0, 111.2, 103.2, 101.5, 55.9, 48.8, 28.2, 18.8; HRMS (EI+) calcd for $C_{13}H_{14}O_3$ $[M]^{+\bullet}$ *m*/*z* 218.0943, found *m*/*z* 218.0944. The enantiomeric excess was determined by SFC using a Chiracel OJ-H column (5% to 10% MeCN, linear gradient, 100 bar, 35 °C oven, flow = 4.0 mL/min); (*S*) isomer $t_r$ = 5.17 min, (*R*) isomer $t_r$ = 5.61 min.

**(*R*)-1-(6,6-dimethylcyclohex-1-enyl-)-3-(5-methoxybenzofuran-2-yl)butan-1-ol (10).**



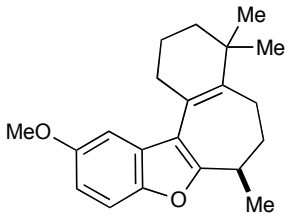

**10**

To a solution of 2,4,6-triisopropylbenzenesulfonyl hydrazone (**9**)[S6] (320 mg, 0.780 mmol, 1.00 equiv.) in anhydrous THF (1.5 ml) was added *t*-BuLi (1.30 ml, 1.3M, 1.72 mmol, 2.20 equiv.) dropwise over 15 min at −78 °C. The resultant solution was stirred at −78 °C for 30 min and then at 0 °C for 15 min, upon which $N_2$ evolution was observed. Upon cooling back down to −78°C, aldehyde (*R*)-**7a** (290 mg, 1.32 mmol, 1.69 equiv.) in THF (1.0 ml) was added *via* cannula. The resulting reaction mixture was then stirred at 0° C for 1 h and at room temperature for 3 h and quenched with sat. $NH_4Cl$ solution. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*.

[S6] Törmäkangas O. P.; Toivola R. J.; Karvinen E. K. & Koskinen A. M. P. (2002) *Tetrahedron* **58**, 2175-2181.

Purification by flash chromatography (silica gel, 10% EtOAc in hexanes) yielded the title compound as a yellow oil in a 1:1 mixture of diastereomers (220 mg, 86% yield). IR (film) 3475, 1617, 1475, 1205, 1030 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 1H, *J* = 8.8 Hz, Ar**H**, dia 1), 7.23 (d, 1H, *J* = 8.8 Hz, Ar**H**, dia 2), 6.93 (d, 1H, *J* = 2.8 Hz, Ar**H**, dia 1), 6.92 (d, 1H, *J* = 2.8 Hz, Ar**H**, dia 2), 6.78 (dt, 1H, *J* = 8.8, 2.8 Hz, Ar**H**, dia 1&2), 6.35 (s, 1H, Ar**H**, dia 1), 6.30 (s, 1H, Ar**H**, dia 2), 5.82 (t, 1H, *J* = 4.0 Hz, C=C**H**, dia 1), 5.80 (t, 1H, *J* = 4.0 Hz, C=C**H**, dia 2), 4.26 (dd, 1H, *J* = 10.0, 2.8 Hz, C**H**OH, dia 1), 4.02 (dd, 1H, *J* = 10.0, 2.8 Hz, C**H**OH, dia 2), 3.80 (s, 3H, OC$\mathbf{H}_3$, dia 1), 3.79 (s, 3H, OC$\mathbf{H}_3$, dia 2), 3.18 (m, 1H, C**H**$CH_3$, dia 1&2), 2.08 (ddd, 1H, *J* = 13.6, 9.2, 4.4 Hz, CHOHC$\mathbf{H}_2$, dia 1), 1.98 (t, 2H, *J* = 2.4 Hz, C=CC$\mathbf{H}_2$, dia 1&2), 1.91 (ddd, 1H, *J* = 13.6, 10.0, 2.8 Hz, CHOHC$\mathbf{H}_2$, dia 2), 1.76 (ddd, 1H, *J* = 13.4, 10.0, 4.8 Hz, CHOHC$\mathbf{H}_2$, dia 2), 1.65 (ddd, 1H, *J* = 13.6, 9.2, 2.8 Hz, CHOHC$\mathbf{H}_2$, dia 1), 1.55 (m, 2H, C=C$CH_2$C$\mathbf{H}_2$, dia 1&2), 1.40 (m, 2H, C$(CH_3)_2$C$\mathbf{H}_2$, dia 1&2), 1.32 (d, 3H, *J* = 6.9 Hz, CHC$\mathbf{H}_3$, dia 1), 1.31 (d, 3H, *J* = 6.9 Hz, CHC$\mathbf{H}_3$, dia 2), 1.08 (s, 3H, C(C$\mathbf{H}_3)_2$, dia 1), 0.94 (s, 3H, C(C$\mathbf{H}_3)_2$, dia 2), 0.93 (s, 3H, C(C$\mathbf{H}_3)_2$, dia 1) 0.80 (s, 3H, C(C$\mathbf{H}_3)_2$, dia 2); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 165.2, 164.2, 155.9, 149.8, 129.6, 129.5, 122.7, 122.4, 111.7, 111.6, 111.3, 103.5, 101.8, 100.8, 67.9, 67.1, 56.2, 44.9, 44.2, 39.8, 39.7, 34.0, 33.9, 31.6, 31.0, 28.6, 28.5, 28.3, 28.2, 26.0, 20.1, 19.3, 18.5; HRMS (EI+) calcd for $C_{21}H_{28}O_3$ $[M]^{+\bullet}$ *m/z* 328.2038, found *m/z* 328.2043.

**(*R*)-*O*-Methyl frondosin B (11).**

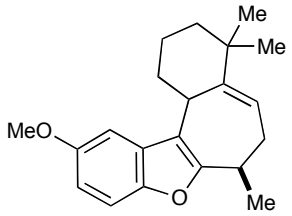



**11**

A round-bottom flask was charged with allylic alcohol **10** (100 mg, 0.300 mmol, 1.00 equiv.) and $[Mo(CO)_4Br_2]_2$ (22.4 mg, 0.0300 mmol, 0.100 equiv.). Freshly distilled and degassed $CH_2Cl_2$ (2 mL) was added and the reaction was stirred at room temperature for 6 h upon which it had reached completion, as judged by TLC. The reaction mixture was diluted

with $Et_2O$ and filtered through a plug of florisil. The organic solvent was concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5% EtOAc in hexanes) yielded the title compound as pale yellow oil (77 mg, 83% yield) as a 2.5:1 mixture with its conjugated olefin isomer. IR (film) 1613, 1475, 1205, 1030 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 1H, *J* = 8.8 Hz, Ar**H**), 7.12 (d, 1H, *J* = 2.5 Hz, Ar**H**), 6.77 (dd, 1H, *J* = 8.8, 2.5 Hz, Ar**H**), 3.82 (s, 3H, OC**H**$_3$), 3.15 (q, 1H, *J* = 8.5 Hz, C**H**$CH_3$), 2.55 (t, 2H, *J* = 7.5 Hz, C=CC**H**$_2$), 2.15 (m, 1H, C**H**$_2$C=C), 2.11 (m, 1H, C**H**$_2$C=C), 2.08 (m, 1H, C=C$CH_2$C**H**$_2$), 1.82 (m, 1H, C=C$CH_2$C**H**$_2$), 1.60 (m, 4H, C**H**$_2$C**H**$_2$C$(CH_3)_2$), 1.32 (d, 3H, *J* = 8.5 Hz, CHC**H**$_3$), 1.06 (s, 3H, C(C**H**$_3)_2$), 1.02 (C(C**H**$_3)_2$); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 160.2, 155.5, 149.3, 144.6, 129.5, 124.1, 116.9, 111.1, 111.0, 105.6, 56.3, 39.8, 39.0, 36.0, 34.9, 30.8, 29.2, 28.2, 26.3, 20.3, 20.0; HRMS (EI+) calcd for $C_{21}H_{26}O_2$ $[M]^{+\bullet}$ *m/z* 310.1933, found *m/z* 310.1928.

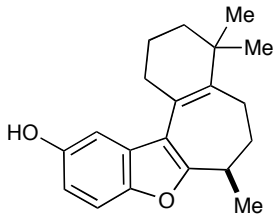
**(*R*)-*O*-Methyl frondosin B, non-conjugated olefin isomer.**




A round-bottom flask was charged with allylic alcohol **10** (33 mg, 0.088 mmol, 1.00 equiv.) and $[Mo(CO)_4Br_2]_2$ (34 mg, 0.044 mmol, 0.050 equiv.). Freshly distilled and degassed $CH_2Cl_2$ (2 mL) was added and the reaction was stirred at –20 °C for 12 h, upon which it had reached completion, as judged by TLC. The reaction mixture was diluted with $Et_2O$ and filtered through a plug of florisil. The organic solvent was concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5% EtOAc in hexanes) yielded the title compound as pale yellow oil (27 mg, 98% yield) as a 1:1 mixture of diastereomers. IR (film) 1613, 1475, 1205, 1030 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.27 (d, 1H, *J* = 8.8 Hz, Ar**H**, dia 1), 7.25 (d, 1H, *J* = 8.8 Hz, Ar**H**, dia 2), 6.87 (d, 1H, *J* = 3.0 Hz, Ar**H**, dia 1&2), 6.80 (dd, 1H, *J* = 9.0, 2.5 Hz, Ar**H**, dia 1), 6.78 (dd, 1H, *J* = 9.0, 2.5 Hz, Ar**H**, dia 2), 5.59 (dd, 1H, *J* = 6.4, 4.4 Hz, C=C**H**, dia 1), 5.55 (dd, 1H, *J* = 7.6, 6.4 Hz, C=C**H**, dia 2), 3.85

(s, 3H, OC**H**$_3$, dia 1&2), 3.70 (m, 1H, C**H**C=C, dia 1), 3.68 (m, 1H, C**H**C=C, dia 2), 3.20 (dqd, 1H, *J* = 7.2, 7.2, 6.4 Hz, C**H**CH$_3$, dia 1), 3.14 (qd, 1H, *J* = 7.2, 7.2, 2.8 Hz, C**H**CH$_3$, dia 2), 2.55 (dqd, 1H, *J* = 16.4, 4.4, 2.2 Hz, CHCH$_3$C**H**$_2$, dia 1), 2.41 (ddd, *J* = 16.4, 7.2, 2.4 Hz, CHCH$_3$C**H**$_2$, dia 2), 2.42 (m, 2H, CHC**H**$_2$), 1.86 (m, 1H, CHCH$_2$C**H**$_2$), 1.66 (m, 1H, CHCH$_2$C**H**$_2$), 1.58 (m, 2H, C**H**$_2$C(CH$_3$)$_2$), 1.34 (d, 3H, *J* = 7.2 Hz, CHC**H**$_3$, dia 1&2), 1.18 (s, 3H, C(C**H**$_3$)$_2$, dia 1&2), 1.14 (s, 3H, C(C**H**$_3$)$_2$, dia 1), 1.12 (s, 3H, C(C**H**$_3$)$_2$, dia 2); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 159.53, 158.9, 155.7, 148.6, 148.3, 147.3, 131.2, 131.1, 117.3, 116.1, 115.6, 115.3, 111.3, 111.2, 110.7, 110.6, 102.4, 56.4, 43.1, 42.9, 39.2, 39.0, 36.9, 36.7, 35.8, 35.7, 34.9, 33.6, 33.1, 31.0, 30.8, 26.8, 26.6, 23.7, 23.6, 19.7, 18.4; HRMS (EI+) calcd for $C_{21}H_{26}O_2$ $[M]^{+\bullet}$ *m*/*z* 310.1933, found *m*/*z* 310.1928.

**(*R*)- (+)-Frondosin B (1).**



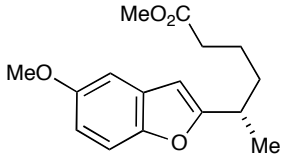

(+)-**1**

**From *O*-methyl frondosin B (11):** To a solution of (*R*)-*O*-methyl frondosin B (**11**) and its conjugated olefin isomer (2.5:1, 125 mg, 0.400 mmol, 1.00 equiv.) in $CH_2Cl_2$ (2 mL) was added $BBr_3$ (1M in $CH_2Cl_2$, 1.28 mL, 1.28 mmol, 3.20 equiv.) dropwise at −78 °C. After being stirred at −78 °C for 30 min, the solution was warmed to 0 °C. After 1 h, the reaction mixture was then quenched with sat. aqueous $NaHCO_3$ and diluted with EtOAc (6 mL). The organic layer was washed with sat. aqueous $NaHCO_3$ and brine, dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5% EtOAc in hexanes) yielded the title compound and its conjugated olefin isomer as a pale yellow oil (2.5:1, 105 mg, 90% total yield).

**From allylic alcohol 10 by one-pot cyclization/isomerization/deprotection:** To a solution of allylic alcohol **10** (114 mg, 0.347 mmol, 1.00 equiv.) in $CH_2Cl_2$ (10 mL) was

added $BBr_3$ (1M in $CH_2Cl_2$, 1.22 mL, 1.22 mmol, 3.50 equiv.) dropwise at −78 °C. The resultant mixture was stirred at −78 °C for 30 min and was then allowed to reach −15 °C (acetone/ice). After 3 h, the reaction mixture was quenched with sat. aqueous $NaHCO_3$ (5 mL) and aqueous $Na_2S_2O_3$ (1M, 5 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 × 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5% $Et_2O$ in hexanes) yielded the title compound as pale yellow oil (71.0 mg, 69% yield) and its conjugated olefin isomer (19.8 mg, 19% yield). (*R*)-(+)-frondosin B: $[\alpha]^{20}_D = +16.3$ (*c* = 0.12, MeOH) [lit. $[\alpha]^{20}_D = +18.6$ (*c* = 0.17, MeOH),[S7] $[\alpha]^{20}_D = +15.2$ (*c* = 0.13, MeOH)[S8]]; IR (film) 3300, 2930, 1620, 1460, 1189 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.21 (d, 1H, *J* = 8.8 Hz, Ar**H**), 7.09 (d, 1H, *J* = 2.5 Hz, Ar**H**), 6.67 (dd, 1H, *J* = 8.8, 2.5 Hz, Ar**H**), 4.51 (s, 1H, O**H**), 3.17 (q, 1H, *J* = 8.5 Hz, C**H**$CH_3$), 2.51 (t, 2H, *J* = 6.0 Hz, C=CC$\mathbf{H}_2$), 2.15 (m, 1H, ArC=CC$\mathbf{H}_2$), 2.11 (m, 1H, $CH(CH_3)C\mathbf{H}_2$), 2.08 (m, 1H, ArC=CC$\mathbf{H}_2$), 1.72 (m, 2H, $C{=}CCH_2C\mathbf{H}_2$), 1.54 (m, 3H, $CH(CH_3)C\mathbf{H}_2$, $C\mathbf{H}_2C(CH_3)_2$), 1.32 (d, 3H, *J* = 8.5 Hz, $CHC\mathbf{H}_3$), 1.05 (s, 6H, $C(C\mathbf{H}_3)_2$); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 160.4, 150.9, 149.3, 144.6, 129.8, 124.0, 116.7, 111.3, 111.1, 107.5, 39.7, 38.7, 35.9, 34.9, 30.8, 29.2, 28.2, 26.3, 20.3, 20.0.

**(*S*)-Methyl-5-(5-methoxybenzofuran-2-yl)-hexanoate (13).**




(*S*)-**13**

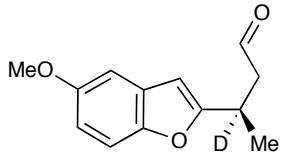
To a suspension of KO*t*-Bu (30.6 mg, 0.273 mmol, 1.30 equiv.) in dry THF (3 mL) was added methyl 2-(diethoxyphosphoryl)acetate (53.3 μL, 0.294 mmol, 1.40 equiv.) dropwise at 0 °C. The resulting reaction mixture was allowed to warm up to room temperature and stirred for an additional 15 min, before a solution of aldehyde (*S*)-**7a** (45.0 mg, 0.210

[S7] Patil, A. D.; Freyer, A. J.; Killmer, L.; Offen, P.; Carte, B.; Jurewicz, A. J. & Johnson, R. K. (1997) *Tetrahedron* **53**, 5047-5060.
[S8] Inoue, M.; Carson, M. W.; Frontier, A. J.; Danishefsky, S. J. (2001) *J. Am. Chem. Soc.* **123**, 1878-1889.

mmol, 1.00 equiv., 86% ee) in THF (2 mL) was added. After the reaction mixture was stirred for 12 h at room temperature, it was diluted with $Et_2O$ (2 ml) and quenched upon slow addition of water (1 mL). The layers were separated and the aqueous phase was extracted with $Et_2O$ (3 × 5 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$ and concentrated *in vacuo* to give the crude product (50 mg), which was used in the next step without further purification.

The crude (*S,E*)-methyl-(5-methoxybenzofuran-2-yl)-hexanoate (50 mg) was dissolved in methanol (3 mL) and Lindlar's catalyst (Pd on $Ca_2CO_3$, poisoned with Pb) (15.5 mg, 0.0700 mmol, 0.05 equiv.) was added and the system flushed with hydrogen. The mixture was stirred for 12 h at room temperature and then diluted with methanol and filtered through celite. The solvent was removed *in vacuo* and the obtained crude product was purified by flash chromatography (silica gel, 10% $Et_2O$ in pentanes) to give the title compound (40 mg, 88% yield over two steps): $[\alpha]^{20}_D$ = +19.6 (*c* = 0.10, $CHCl_3$) [lit. $[\alpha]^{20}_D$ = −20.4 (*c* = 0.104, $CDCl_3$) for (*R*)-**13** (84% ee)[S8]]; IR (film) 1735, 1475, 1205, 1030 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.29 (d, 1H, *J* = 9.0 Hz, Ar**H**), 6.96 (d, 1H, *J* = 2.7 Hz, Ar-**H**), 6.80 (dd, 1H, *J* = 9.0, 2.7 Hz, Ar**H**), 6.32 (s, 1H, Ar**H**), 3.83 (s, 3H, OC$\mathbf{H_3}$), 3.66 (s, 3H, $CO_2C\mathbf{H_3}$), 2.92 (m, 1H, C**H**$CH_3$), 2.32 (t, 2H, *J* = 7.0 Hz, C$\mathbf{H_2}CO_2Me$; 1.80 (m, 1H, C$\mathbf{H_2}CH_2CO_2Me$), 1.66 (m, 3H, $CHCH_3C\mathbf{H_2}C\mathbf{H_2}$), 1.32 (d, 3H, *J* = 7.0 Hz, CHC$\mathbf{H_3}$); $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 174.2, 164.3, 155.9, 149.7, 129.6, 111.7, 111.4, 103.5, 101.3, 56.2, 51.7, 35.0, 34.2, 33.7, 22.8, 19.2.

**(*R*)-[$^2$H]-3-(5-methoxybenzofuran-2-yl)butanal ([$^2$H]-8).**

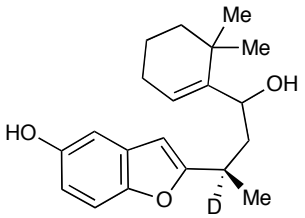



(*R*)-[$^2$H]-**8**

To a plastic vial (Wheaton HDPE) was added HF (48 wt%, 35.1 mg, 0.840 mmol, 1.00 equiv.) followed by 1,2-dimethoxyethane (1.7 mL, 1M relative to aldehyde) and a magnetic stir bar. The imidazolidinone catalyst (*S*,*S*)-**4b**·HCl (47.7 mg, 0.170 mmol, 0.200 equiv.)

were added and the reaction mixture was cooled to –20 °C. Crotonaldehyde [$^2$H]-**12**[S9] (120 mg, 1.69 mmol, 2.01 equiv., >95% D) was added to the reaction mixture followed by trifluoroborate **6a** (214 mg, 0.840 mmol, 1.00 equiv.). The reaction was stirred at –20 °C for 24 h and diluted with $CHCl_3$ (2.5 mL), quenched with 1M HCl (2.5 mL) and stirred at ambient temperature for 30 min. The aqueous layer was extracted with $CHCl_3$ (2 × 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 10% EtOAc in hexanes) yielded the title compound as clear oil (132.5 mg, 72% yield, 84% ee). $[\alpha]^{20}_D$ = –13.7 (*c* = 1.3, $CHCl_3$); IR (film) 1725, 1476, 1206, 1031 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 9.80 (t, *J* = 1.7 Hz, 1H, C**H**O), 7.30 (d, *J* = 8.9 Hz, 1H, Ar**H**), 6.96 (d, *J* = 2.5 Hz, 1H, Ar**H**), 6.83 (dd, *J* = 8.9, 2.6 Hz, 1H, Ar**H**), 6.36 (s, 1H, Ar**H**), 3.82 (s, 3H, OC**H**$_3$), 2.92 (d, *J* = 17.4 Hz, 1H, C**H**$_2$), 2.68 (d, *J* = 17.2 Hz, 1H, C**H**$_2$), 1.39 (s, 3H, C**H**$_3$); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 200.9, 162.0, 155.7, 149.5, 129.0, 111.9, 111.2, 103.2, 101.5, 55.8, 48.7, 18.7; HRMS (ESI+) calcd for $C_{13}H_{14}DO_3$ $[M+H]^+$ *m*/*z* 220.1079, found *m*/*z* 220.1073. The enantiomeric excess was determined by SFC using a Chiracel OJ-H column (5% to 10% MeCN, linear gradient, 100 bar, 35 °C oven, flow = 4.0 mL/min); (*S*) isomer $t_r$ = 4.52 min, (*R*) isomer $t_r$ = 4.90 min.

**(*R*)-[$^2$H]-1-(6,6-dimethylcyclohex-1-eyl-)-3-(5-methoxybenzofuran-2-yl)butan-1-ol ([$^2$H]-10)**.



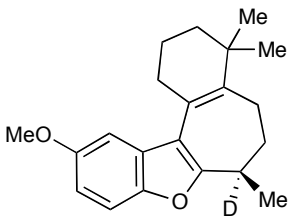

[$^2$H]-**10**

To a solution of 2,4,6-triisopropylbenzenesulfonyl hydrazone (**5**)[S6] (206 mg, 0.506 mmol, 1.00 equiv.) in anhydrous THF (2 mL) was added *t*-BuLi (600 μL, 1.7M, 1.01 mmol, 2.00 equiv.) dropwise over 15 min at –78 °C. The resultant solution was stirred at –78 °C for 30

[S9] Mariano, P. S. & Bay, E. (1980) *J. Org. Chem.* **45**, 1763-1769.

min and then at 0 °C for 15 min, upon which $N_2$ evolution was observed. Upon cooling back down to −78 °C, aldehyde [$^2$H]-**8** (166 mg, 0.760 mmol, 1.50 equiv.) in THF (1 mL) was added *via* cannula. The resulting reaction mixture was then stirred at 0 °C for 1 h and at room temperature for 3 h and quenched with sat. $NH_4Cl$ solution. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 10% $Et_2O$ in hexanes) yielded the title compound as a clear oil as 1:1 mixture of diastereomers (139 mg, 84% yield). The diastereomers can be separated for analytical purposes using preparative TLC (5% $Et_2O$ in hexanes, eluted twice). IR (film) 3442, 1617, 1476, 1205, 1032 cm$^{-1}$; HRMS (ESI+) calcd for $C_{21}H_{28}DO_3$ $[M+H]^+$ *m*/*z* 330.2174, found *m*/*z* 330.2168. Diastereomer 1: $[\alpha]^{20}_D$ = +11.9 (*c* = 0.088, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.9 Hz, 1H, Ar**H**), 6.95 (d, *J* = 2.5 Hz, 1H, Ar**H**), 6.80 (dd, *J* = 8.9, 2.6 Hz, 1H, Ar**H**), 6.34 (s, 1H, Ar**H**), 5.85 (t, *J* = 3.9 Hz, 1H, C=C**H**), 4.29 (dt, *J* = 9.3, 3.6 Hz, 1H, C**H**OH), 3.83 (s, 3H, OC**H**$_3$), 2.10 (dd, *J* = 14.1, 9.6 Hz, 1H, CHOHC**H**$_2$), 2.04-1.99 (m, 2H, C=CC**H**$_2$), 1.70 (dd, *J* = 14.1, 3.5 Hz, 1H, CHOHC**H**$_2$), 1.62-1.54 (m, 2H, C=CCH$_2$C**H**$_2$), 1.50-1.42 (m, 2H, C(CH$_3$)$_2$C**H**$_2$), 1.36 (s, 3H, CDC**H**$_3$), 1.12 (s, 3H, C(C**H**$_3$)$_2$), 0.97 (s, 3H, C(C**H**$_3$)$_2$); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 164.9, 155.6, 149.5, 149.4, 129.3, 122.5, 111.4, 111.1, 103.1, 100.6, 67.0, 55.9, 43.9, 39.5, 33.8, 29.7, 28.3, 28.2, 25.8, 19.0, 18.1. Diastereomer 2: $[\alpha]^{20}_D$ = −6.5 (*c* = 0.15, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.8 Hz, 1H, Ar**H**), 6.97 (d, *J* = 2.5 Hz, 1H, Ar**H**), 6.81 (dd, *J* = 8.8, 2.6 Hz, 1H, Ar**H**), 6.38 (s, 1H, Ar**H**), 5.83 (t, *J* = 3.9 Hz, 1H, C=C**H**), 4.04 (d, *J* = 9.7 Hz, 1H, C**H**OH), 3.84 (s, 3H, OC**H**$_3$), 2.03-1.98 (m, 2H, C=CC**H**$_2$), 1.93 (dd, *J* = 14.2, 2.4 Hz, 1H, CHOHC**H**$_2$), 1.78 (dd, *J* = 14.2, 10.0 Hz, 1H, CHOHC**H**$_2$), 1.59-1.52 (m, 2H, C=CCH$_2$C**H**$_2$), 1.44-1.38 (m, 2H, C(CH$_3$)$_2$C**H**$_2$), 1.33 (s, 3H, CDC**H**$_3$), 0.96 (s, 3H, C(C**H**$_3$)$_2$), 0.84 (s, 3H, C(C**H**$_3$)$_2$); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 163.8, 155.6, 149.9, 149.5, 129.3, 122.1, 111.4, 111.1, 103.1, 101.6, 67.6, 55.9, 44.6, 39.4, 33.6, 28.1, 28.1, 25.7, 20.5, 19.0.

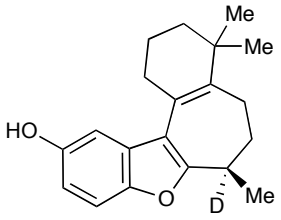
**(*R*)-[$^2$H]-*O*-Methyl frondosin B ([$^2$H]-11).**




[$^2$H]-**11**

A round-bottom flask was charged with allylic alcohol [$^2$H]-**10** (26.0 mg, 0.0800 mmol, 1.00 equiv.) and $[Mo(CO)_4Br_2]_2$ (11.6 mg, 0.0158 mmol, 0.200 equiv.). Freshly distilled and degassed $CH_2Cl_2$ (3 mL) was added and the reaction was stirred at room temperature for 6 h upon which it had reached completion, as judged by TLC. The reaction mixture was diluted with $Et_2O$ and filtered through a plug of florisil. The organic solvent was concentrated *in vacuo*. Purification by chromatography (silica gel, 5% EtOAc in hexanes) yielded the title compound as pale yellow oil (18.5 mg, 75% yield) as a 2.5:1 mixture with its conjugated olefin isomer. IR (film) 1613, 1475, 1205, 1030 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.8 Hz, 1H, Ar**H**), 7.15 (d, *J* = 2.5 Hz, 1H, Ar**H**), 6.80 (dd, *J* = 8.8, 2.3 Hz, 1H, Ar**H**), 3.84 (s, 3H, O**CH$_3$**), 2.57 (t, *J* = 5.9 Hz, 2H, C=CC**H$_2$**), 2.20-2.06 (m, 3H, C**H$_2$**C=C, C=CCH$_2$C**H$_2$**), 1.76-1.67 (m, 2H, C=CCH$_2$C**H$_2$**), 1.65-1.54 (m, 3H, C**H$_2$H$_2$**C(CH$_3$)$_2$), 1.34 (s, 3H, CDC**H$_3$**), 1.092 (s, 3H, CH$_2$CH$_2$C(C**H$_3$**)$_2$), 1.089 (s, 3H, CH$_2$CH$_2$C(C**H$_3$**)$_2$); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 160.0, 155.1, 149.0, 144.4, 129.2, 123.7, 116.6, 110.9, 110.8, 105.2, 56.1, 39.4, 38.5, 35.7, 30.5, 28.9, 27.8, 26.0, 20.0, 19.6; HRMS (ESI+) calcd for $C_{21}H_{26}DO_2$ $[M+H]^+$ *m/z* 312.2068, found *m/z* 312.2065.

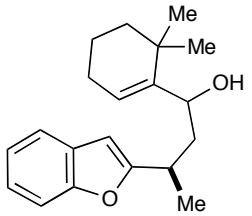
**(*R*)-(+)-[$^2$H]-Frondosin B ([$^2$H]-(+)1).**




[$^2$H]-(+)-**1**

To a solution of allylic alcohol [$^2$H]-**10** (47.0 mg, 0.143 mmol, 1.00 equiv.) in $CH_2Cl_2$ (5 mL) was added $BBr_3$ (1M in $CH_2Cl_2$, 500 μL, 0.499 mmol, 3.5 equiv.) dropwise at −78 °C. The resultant mixture was stirred at −78 °C for 30 min and was then allowed to reach −15 °C (acetone/ice). After 2 h, the reaction mixture was quenched with sat. aqueous $NaHCO_3$ (5 mL) and aqueous $Na_2S_2O_3$ (1M, 5 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 × 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5% $Et_2O$ in hexanes) yielded the title compound as a pale yellow oil (24.8 mg, 59% yield) and its conjugated olefin isomer (7.3 mg, 17% yield). (*R*)-(+)-[$^2$H]-frondosin B: $[\alpha]^{20}_D$ = +6.5 (*c* = 1.5, $CHCl_3$); IR (film) 3300, 2927, 1591, 1457, 1198 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 1H, Ar**H**), 7.12 (d, *J* = 2.2 Hz, 1H, Ar**H**), 6.70 (dd, *J* = 8.6, 2.1 Hz, 1H, Ar**H**), 4.60 (s, 1H, ArO**H**), 2.59-2.48 (m, 2H, C=CC**H**$_2$), 2.21-2.03 (m, 3H, C**H**$_2$C=C, C=CCH$_2$C**H**$_2$), 1.75-1.66 (m, 2H, C=CCH$_2$C**H**$_2$), 1.64-1.52 (m, 3H, C**H**$_2$**H**$_2$C(CH$_3$)$_2$), 1.33 (s, 3H, CDC**H**$_3$), 1.083 (s, 3H, C(C**H**$_3$)$_2$), 1.079 (s, 3H, C(C**H**$_3$)$_2$); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 160.2, 150.7, 149.1, 144.4, 129.6, 123.7, 116.5, 111.1, 110.9, 107.3, 39.5, 38.3, 35.7, 34.5, 34.3, 34.2, 30.6, 28.9, 27.9, 26.1, 20.0, 19.7; HRMS (ESI+) calcd for $C_{20}H_{24}DO_2$ $[M+H]^+$ *m*/*z* 298.1912, found *m*/*z* 298.1914.

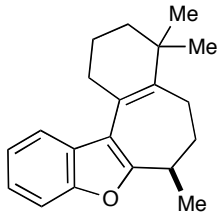
**(*R*)-3-(benzofuran-2-yl)-1-(6,6-dimethylcyclohex-1-enyl)butan-1-ol.**




To a solution of 2,4,6-triisopropylbenzenesulfonyl hydrazone **9**[S6] (160 mg, 0.400 mmol, 1.00 equiv.) in anhydrous THF (1.5 ml) was added *t*-BuLi (550 μL, 0.88 mmol, 1.6M in pentane, 2.20 equiv.) dropwise over 15 min at −78 °C. The resultant solution was stirred at −78 °C for 30 min and then at 0 °C for 15 min, upon which $N_2$ evolution was observed. Upon cooling back down to −78°C, aldehyde **6b**[S4] (130 mg, 0.690 mmol, 1.73 equiv.) in THF (1 mL) was added *via* cannula. The resulting reaction mixture was then stirred at 0 °C

for 1 h and at room temperature for 3 h and quenched with sat. $NH_4Cl$ solution. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (10% EtOAc in hexanes) of the residue gave the title compound (80 mg, 70% yield, 1:1 d.r.) as a yellow oil. IR (film) 3411, 2932, 1456, 1254 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.53-7.46 (m, 2H, Ar**H**, dia 1&2), 7.42 (d, *J* = 7.7 Hz, 2H, Ar**H**, dia 1&2), 7.25-7.14 (m, 4H, Ar**H**, dia 1&2), 6.44 (s, 1H, Ar**H**, dia 1), 6.40 (s, 1H, Ar**H**, dia 2), 5.86 (t, 1H, *J* = 3.9 Hz, C=C**H**, dia 1), 5.84 (t, 1H, *J* = 3.9 Hz, C=C**H**, dia 2), 4.31 (dd, 1H, *J* = 9.6, 3.6 Hz, C**H**OH, dia 1), 4.08 (dd, 1H, *J* = 10.5, 3.3 Hz, C**H**OH, dia 2), 3.33-3.14 (m, 2H, C**H**$CH_3$, dia 1&2), 2.14 (ddd, 1H, *J* = 14.3, 9.6, 4.8 Hz, CHOHC**H**$_2$, dia 1), 2.07-1.93 (m, 5H, C=CC**H**$_2$, dia 1&2, CHOHC**H**$_2$, dia 2), 1.81 (ddd, 1H, *J* = 14.3, 9.9, 4.5 Hz, CHOHC**H**$_2$, dia 2), 1.73 (ddd, 1H, *J* = 13.9, 9.1, 3.7 Hz, CHOHC**H**$_2$, dia 1), 1.63-1.52 (m, 4H, C=C$CH_2$C**H**$_2$, dia 1&2), 1.50-1.42 (m, 4H, C$(CH_3)_2$C**H**$_2$, dia 1&2), 1.39 (d, 3H, *J* = 6.9 Hz, CHC**H**$_3$, dia 1), 1.37 (d, 3H, *J* = 7.0 Hz, CHC**H**$_3$, dia 2), 1.13 (s, 3H, C(C**H**$_3$)$_2$, dia 1), 0.98 (s, 3H, C(C**H**$_3$)$_2$, dia 2), 0.97 (s, 3H, C(C**H**$_3$)$_2$, dia 1), 0.85 (s, 3H, C(C**H**$_3$)$_2$, dia 2); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 164.0, 163.0, 154.57, 154.51, 149.8, 149.6, 128.8, 123.08, 123.07, 122.5, 122.34, 122.31, 122.2, 120.30, 120.26, 110.75, 110.73, 101.4, 100.4, 67.7, 67.0, 44.7, 44.0, 39.53, 39.51, 33.8, 33.6, 31.2, 30.7, 29.31, 29.29, 28.3, 28.2, 28.10, 28.08, 25.76, 25.73, 20.6, 19.1, 18.2; HRMS (ESI+) calcd for $C_{20}H_{26}NaO_2$ $[M+Na]^+$ *m/z* 321.1825, found *m/z* 321.1827.

**Desoxyfrondosin B (14).**

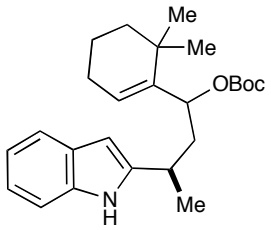



**14**

A round-bottom flask was charged with the allylic alcohol prepared in the previous step (55.0 mg, 0.180 mmol, 1.00 equiv.) and $[Mo(CO)_4Br_2]_2$ (40.7 mg, 0.055 mmol, 0.30 equiv.). Freshly distilled and degassed $CH_2Cl_2$ (2 mL) was added and the reaction was

stirred at room temperature for 6 h upon which it had reached completion, as judged by TLC. The reaction mixture was diluted with $Et_2O$ and filtered through a plug of florisil. The organic solvent was concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5% EtOAc in hexanes) yielded the title compound as a pale yellow oil (40 mg, 80% yield) as a 2.5:1 mixture with its conjugated olefin isomer. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 1H, *J* = 7.5 Hz, Ar**H**), 7.44-7.39 (m, 1H, Ar**H**), 7.25-7.12 (m, 2H, Ar**H**), 3.31-3.17 (m, 1H, C**H**$CH_3$), 2.71-2.54 (m, 2H, C=CC**H$_2$**), 2.26-2.05 (m, 3H, C**H$_2$**C=C, C=CCH$_2$C**H$_2$**), 1.78-1.69 (m, 2H, C=CCH$_2$C**H$_2$**), 1.67-1.53 (m, 3H, C**H$_2$H$_2$**C$(CH_3)_2$), 1.38 (d, 3H, *J* = 6.9 Hz, CHC**H$_3$**), 1.11 (s, 3H, C(C**H$_3$**)$_2$), 1.10 (s, 3H, C(C**H$_3$**)$_2$); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 158.9, 154.0, 144.4, 128.9, 122.8, 121.9, 121.8, 119.6, 116.5, 110.7, 39.5, 38.2, 35.7, 34.7, 30.7, 28.9, 27.9, 26.0, 20.1, 19.9; HRMS (ESI+) calcd for $C_{20}H_{25}O$ $[M+H]^+$ *m/z* 281.1900, found *m/z* 281.1902.

***tert*-Butyl (3*R*)-1-(6,6-dimethylcyclohex-1-enyl)-3-(1*H*-indol-2-yl)butyl carbonate.**[S10]

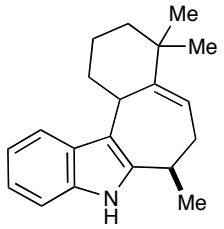



To a solution of 2,4,6-triisopropylbenzenesulfonyl hydrazone **9**[S6] (77.7 mg, 0.191 mmol, 1.00 equiv.) in anhydrous THF (1.5 mL) was added *t*-BuLi (265 μL, 0.420 mmol, 1.6M in pentane, 2.20 equiv.) dropwise over 15 min at –78 °C. The resultant solution was stirred at –78 °C for 30 min and then at 0 °C for 15 min, upon which $N_2$ evolution was observed. Upon cooling back down to –78 °C, aldehyde **6c**[S4] (83.3 mg, 0.290 mmol, 1.52 equiv.) in THF (1 mL) was added *via* cannula. The resulting reaction mixture was then stirred at 0 °C for 1 h and at room temperature for 3 h before it was quenched with sat. aqueous $NH_4Cl$. The layers were separated and the aqueous phase was extracted $Et_2O$ (2 × 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (2 → 5% $Et_2O$ in hexane) of

[S10] Under the reaction conditions, a complete migration of the tert-butoxycarbonyl (Boc) group from the indole nitrogen to the secondary alcohol moiety was observed.

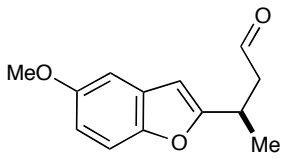
the residue gave the title compound (64.5 mg, 85% yield, 1:1 d.r.) as a clear oil. IR (film) 3423, 2938, 1733, 1281, 1156; Diastereomer 1: $^1$H NMR (500 MHz, $CDCl_3$) δ 9.00 (s, 1H, N**H**), 7.55 (d, 1H, *J* = 7.7 Hz, Ar**H**), 7.40 (d, 1H, *J* = 8.0 Hz, Ar**H**), 7.13 (t, 1H, *J* = 7.1 Hz, Ar**H**), 7.07 (t, 1H, *J* = 7.4 Hz, Ar**H**), 6.27 (s, 1H, Ar**H**), 5.84 (t, 1H, *J* = 3.9 Hz, C=C**H**), 5.30 (dd, 1H, *J* = 10.2, 2.3 Hz, C**H**OBoc), 2.89 (ddd, 1H, *J* = 10.4, 7.0, 3.5 Hz, C**H**$CH_3$), 2.11 (ddd, 1H, *J* = 14.1, 10.2, 3.6 Hz, CH(OBoc)C$\mathbf{H_2}$), 2.06-1.92 (m, 2H, C=CC$\mathbf{H_2}$), 1.80 (ddd, 1H, *J* = 14.4, 10.4, 2.5 Hz, CH(OBoc)C$\mathbf{H_2}$), 1.56-1.50 (m, 2H, C=C$CH_2$C$\mathbf{H_2}$), 1.53 (s, 9H, C(C$\mathbf{H_3}$)$_3$) 1.40 (d, 3H, *J* = 7.0 Hz, CHC$\mathbf{H_3}$), 1.39-1.35 (m, 2H, C$\mathbf{H_2}$C$(CH_3)_2$), 0.96 (s, 3H, C(C$\mathbf{H_3}$)$_2$), 0.69 (s, 3H, C(C$\mathbf{H_3}$)$_2$); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 154.1, 144.1, 144.0, 135.6, 128.6, 125.0, 120.8, 119.8, 119.3, 110.7, 97.5, 82.4, 73.7, 45.4, 39.3, 33.5, 29.9, 28.2, 28.1, 27.8, 27.6, 25.7, 21.0, 18.8. Diastereomer 2: $^1$H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H, N**H**), 7.54 (d, 1H, *J* = 7.7, Ar**H**), 7.34 (d, 1H, *J* = 8.0 Hz, Ar**H**), 7.12 (t, 1H, *J* = 7.5 Hz, Ar**H**), 7.06 (t, 1H, *J* = 7.4 Hz, Ar**H**), 6.28 (d, 1H, *J* = 1.2 Hz, Ar**H**), 5.88 (t, 1H, *J* = 3.9 Hz, C=C**H**), 5.26 (dd, 1H, *J* = 8.7, 5.0 Hz, C**H**OBoc), 3.02-2.92 (m, 1H, C**H**$CH_3$), 2.24 (ddd, 1H, *J* = 14.8, 8.6, 6.4 Hz, CH(OBoc)C$\mathbf{H_2}$), 2.11-1.94 (m, 2H, C=CC$\mathbf{H_2}$), 1.92 (ddd, 1H, *J* = 14.2, 7.8, 14.2 Hz, CH(OBoc)C$\mathbf{H_2}$), 1.64-1.55 (m, 2H, C=C$CH_2$C$\mathbf{H_2}$), 1.47 (s, 9H, C(C$\mathbf{H_3}$)$_3$), 1.45-1.42 (m, 2H, C$\mathbf{H_2}$C$(CH_3)_2$), 1.41 (d, 3H, *J* = 6.9 Hz, CHC$\mathbf{H_3}$), 1.07 (s, 3H, C(C$\mathbf{H_3}$)$_2$), 0.93 (s, 3H, C(C$\mathbf{H_3}$)$_2$); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 153.3, 144.1, 143.5, 135.7, 128.5, 125.0, 120.9, 119.9, 119.4, 110.5, 98.3, 81.9, 73.5, 42.6, 39.4, 33.6, 30.1, 28.4, 28.2, 27.8, 27.8, 25.8, 20.7, 18.8. HRMS (ESI+) calcd for $C_{25}H_{36}NO_3$ $[M+H]^+$ *m*/*z* 398.2690, found *m*/*z* 398.2690.

**Indole derivative 15.**

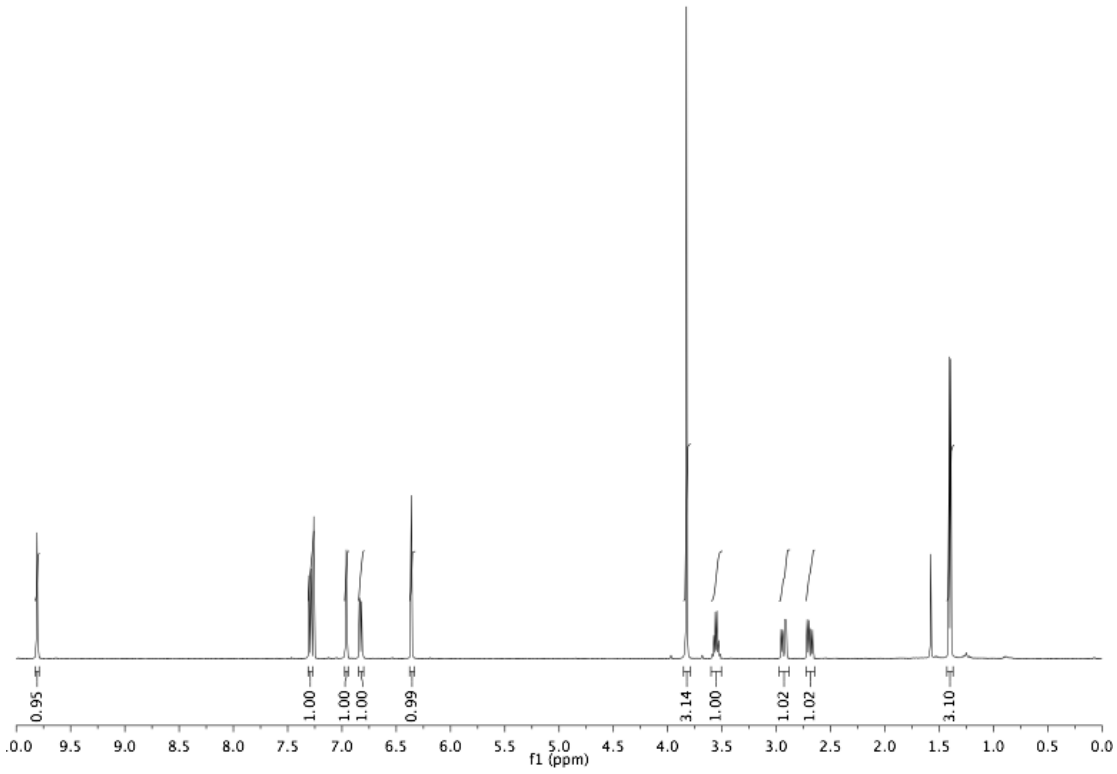


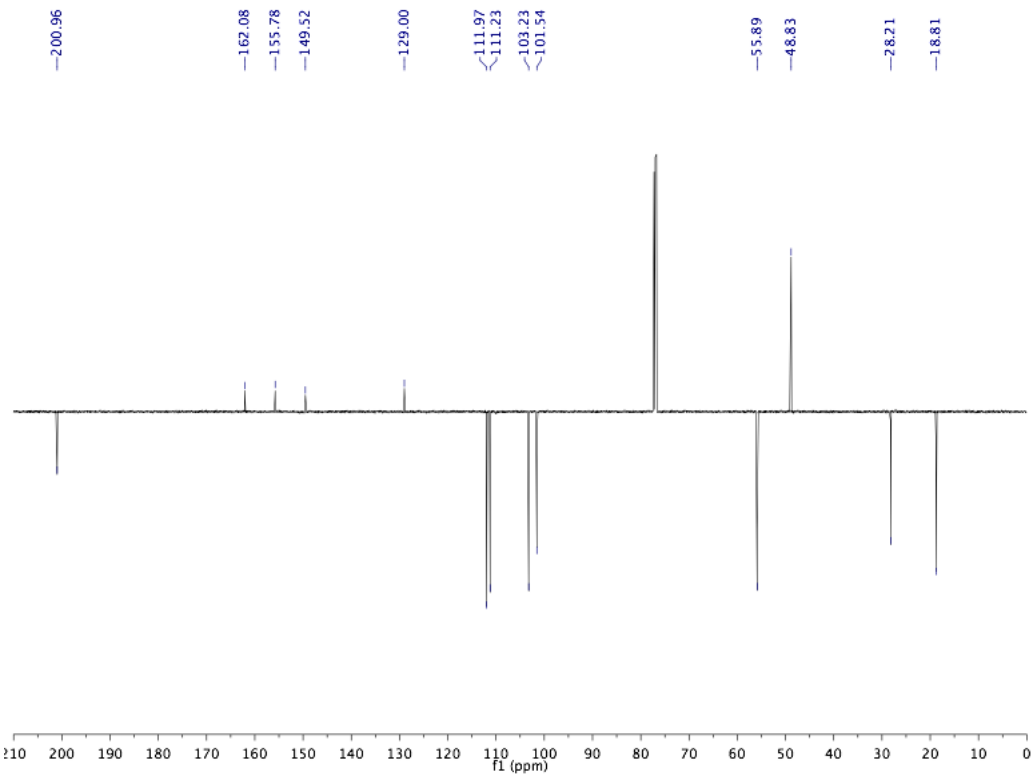

**15**

To a solution of the previously prepared allylic carbonate (27.5 mg, 0.0692 mmol, 1.00 equiv.) in $CH_2Cl_2$ (3 mL) was added trifluoroacetic acid (26.8 μL, 0.346 mmol, 5.00 equiv.) and the resultant dark solution was stirred at room temperature for 2 h. The reaction was quenched with sat. aqueous $NaHCO_3$ and the layers were separated. The aqueous phase was extracted with $CH_2Cl_2$ (2 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (2% $Et_2O$ in hexane) of the residue gave **15** (17.4 mg, 90% yield, 1.4:1 d.r.) as a clear oil. IR (film) 3409, 2925, 1459, 1319, 740; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1H, N**H**, dia 1), 7.61 (s, 1H, N**H**, dia 2), 7.54-7.48 (m, 1H, Ar**H**, dia 1&2), 7.36-7.24 (m, 1H, Ar**H**, dia 1&2), 7.15-7.07 (m, 2H, Ar**H**, dia 1&2), 5.63 (dd, 1H, *J* = 7.8, 3.3 Hz, C=C**H**, dia 1), 5.55 (d, 1H, *J* = 8.2, 2.7 Hz, C=C**H**, dia 2), 3.99 (d, 1H, *J* = 12.4 Hz, CH=CC**H**, dia 2), 3.97 (d, 1H, *J* = 12.4 Hz, CH=CC**H**, dia 1), 3.39-3.30 (m, 1H, C**H**$CH_3$, dia 1), 3.07-2.98 (m, 1H, C**H**$CH_3$, dia 2), 2.65 (dd, 1H, *J* = 15.7, 2.8 Hz, C=CHC**H$_2$**, dia 2), 2.44-2.24 (m, 3H, C=CHC**H$_2$**, dia 1&2), 2.20 (d, 1H, *J* = 12.9 Hz, ArCHC**H**$_2$, dia 2), 2.11 (d, 1H, *J* = 12.7 Hz, ArCHC**H**$_2$, dia 1), 2.01-1.81 (m, 2H, C**H**$_2$$CH_2(CH_3)_2$, dia 1&2), 1.75-1.54 (m, 2H, C**H**$_2(CH_3)_2$, dia 1&2), 1.51-1.42 (m, 1H, C=CHC**H**$_2$, dia 1&2), 1.41 (d, 3H, *J* = 5.0 Hz, CHC**H**$_3$, dia 1), 1.39 (d, 2H, *J* = 5.0 Hz, CHC**H**$_3$, dia 2), 1.24 (s, 3H, C(C**H**$_3)_2$, dia 1), 1.23 (s, 3H, C(C**H**$_3)_2$, dia 2), 1.18 (s, 3H, C(C**H**$_3)_2$, dia 2), 1.15 (s, 3H C(C**H**$_3)_2$, dia 1); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 147.6, 147.1, 140.2, 139.3, 134.5, 134.2, 129.3, 128.84, 120.77, 120.6, 119.0, 118.9, 117.5, 117.34, 115.1, 113.1, 113.0, 110.5, 110.3, 51.4, 50.4, 42.8, 42.7, 38.0, 37.8, 36.7, 36.6, 36.3, 34.3, 33.1, 31.9, 31.0, 30.7, 26.7, 26.3, 23.5, 23.4, 20.4, 18.3; HRMS (ESI+) calcd for $C_{20}H_{26}N$ $[M+H]^+$ *m*/*z* 280.2060, found *m*/*z* 280.2062.




(*R*)-**7a**

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129.00
111.97
111.23
103.23
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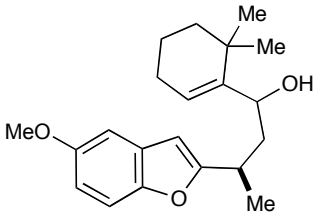
28.21
18.81
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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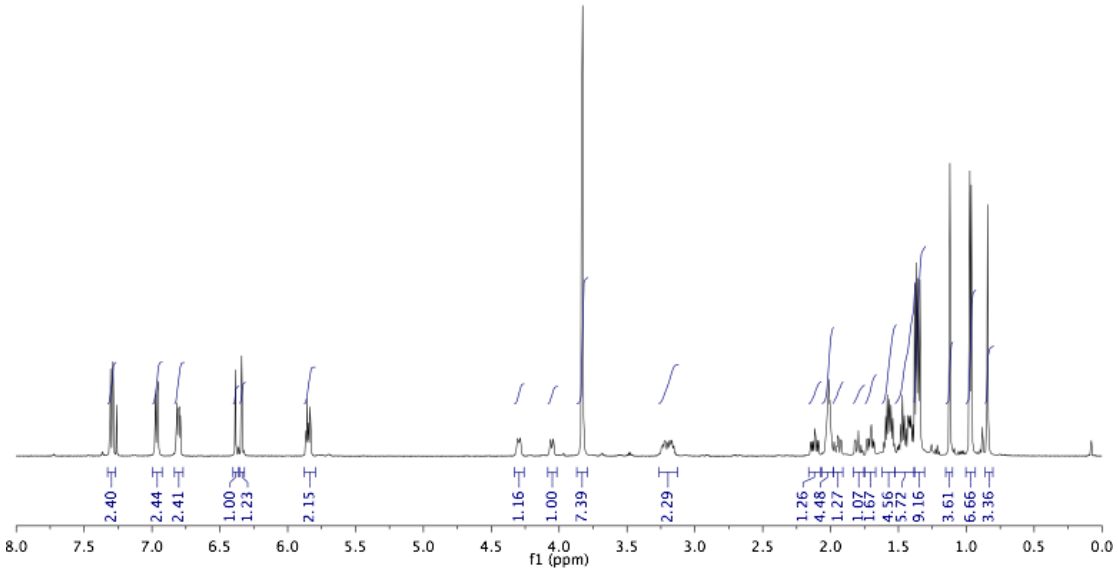
Me
OH
MeO
O
Me

**10**: 1:1 dr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1.00
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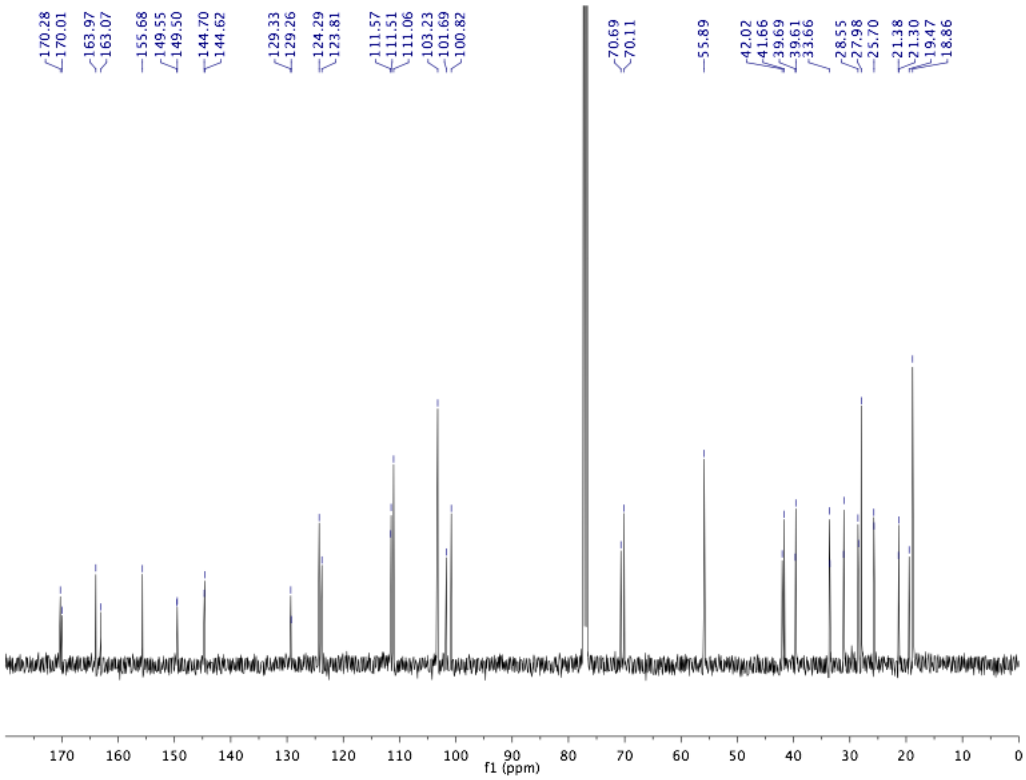
2.29
1.26
4.48
1.27
1.07
1.67
4.56
5.72
9.16
3.61
6.66
3.36
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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163.07
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149.55
149.50
144.70
144.62
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129.26
124.29
123.81
111.57
111.51
111.06
103.23
101.69
100.82
70.69
70.11
55.89
42.02
41.66
39.69
39.61
33.66
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21.30
19.47
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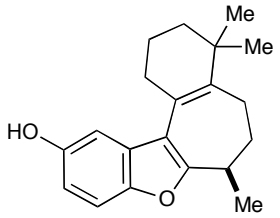
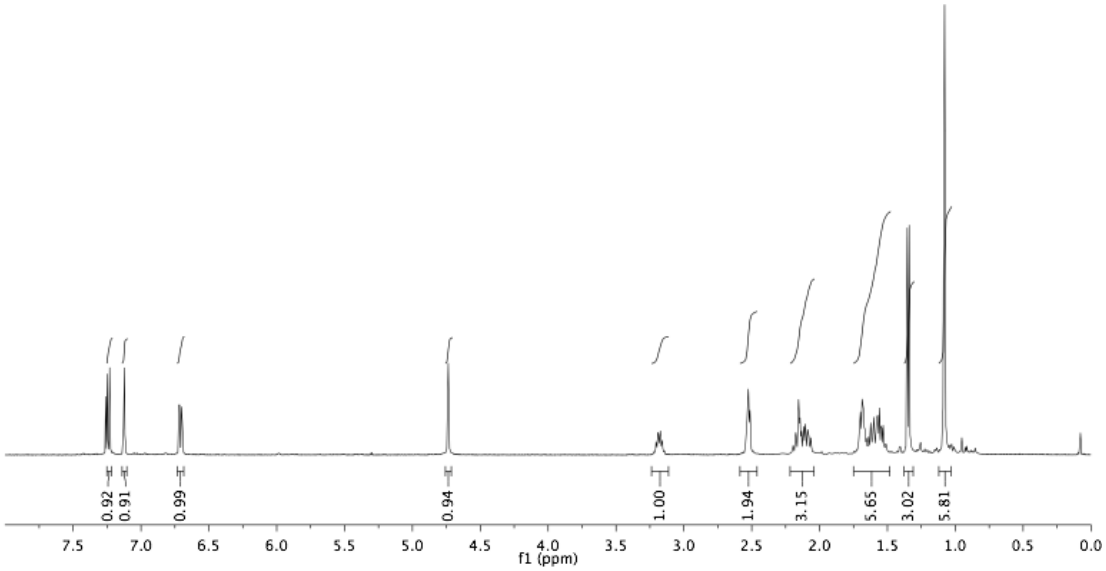
f1 (ppm)


Me
Me
HO
O
Me

frondosin (+)-**1**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0.94
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1.94
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3.02
5.81
7.5
7.0
6.5
6.0
5.5
5.0
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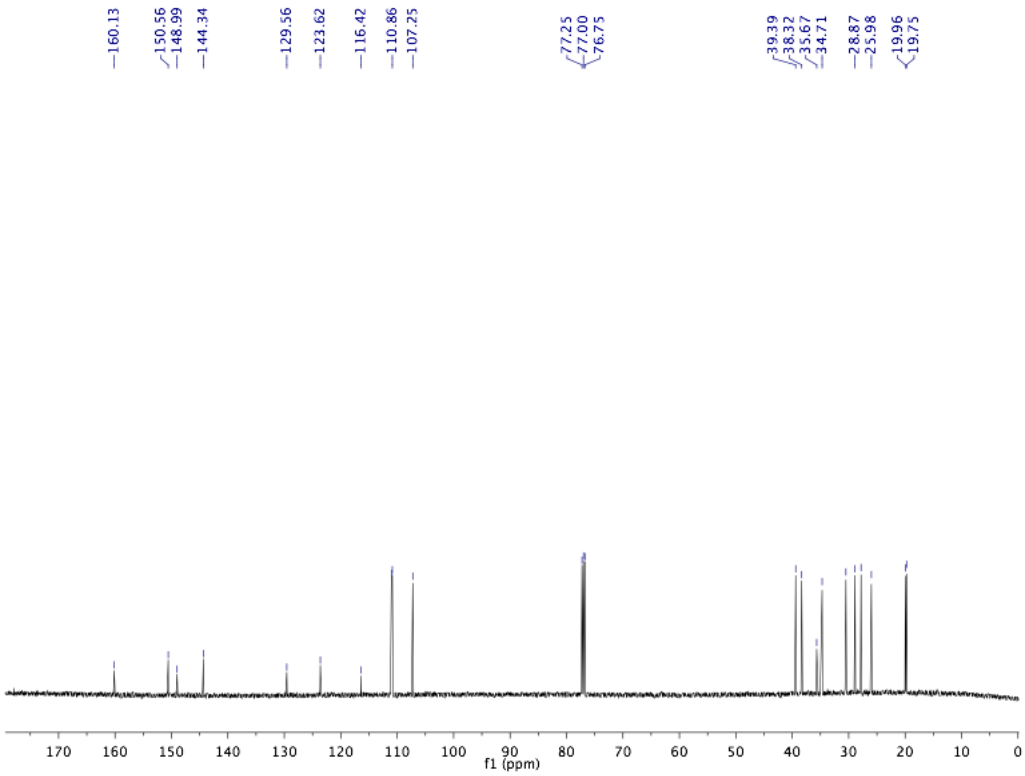
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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148.99
144.34
129.56
123.62
116.42
110.86
107.25
77.25
77.00
76.75
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38.32
35.67
34.71
28.87
25.98
19.96
19.75
170
160
150
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130
120
110
100
90
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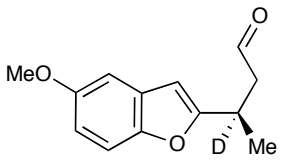
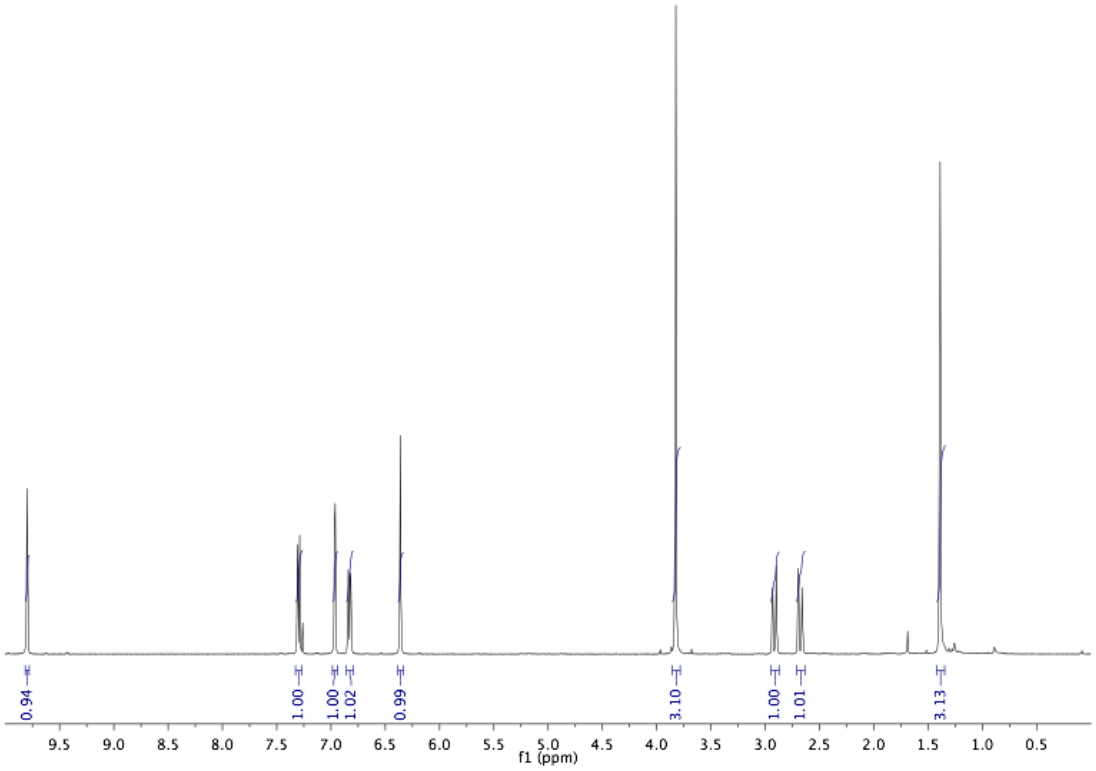
70
60
50
40
30
20
10
0
f1 (ppm)


MeO
O
O
D
Me

(*R*)-[$^2$H]-**8**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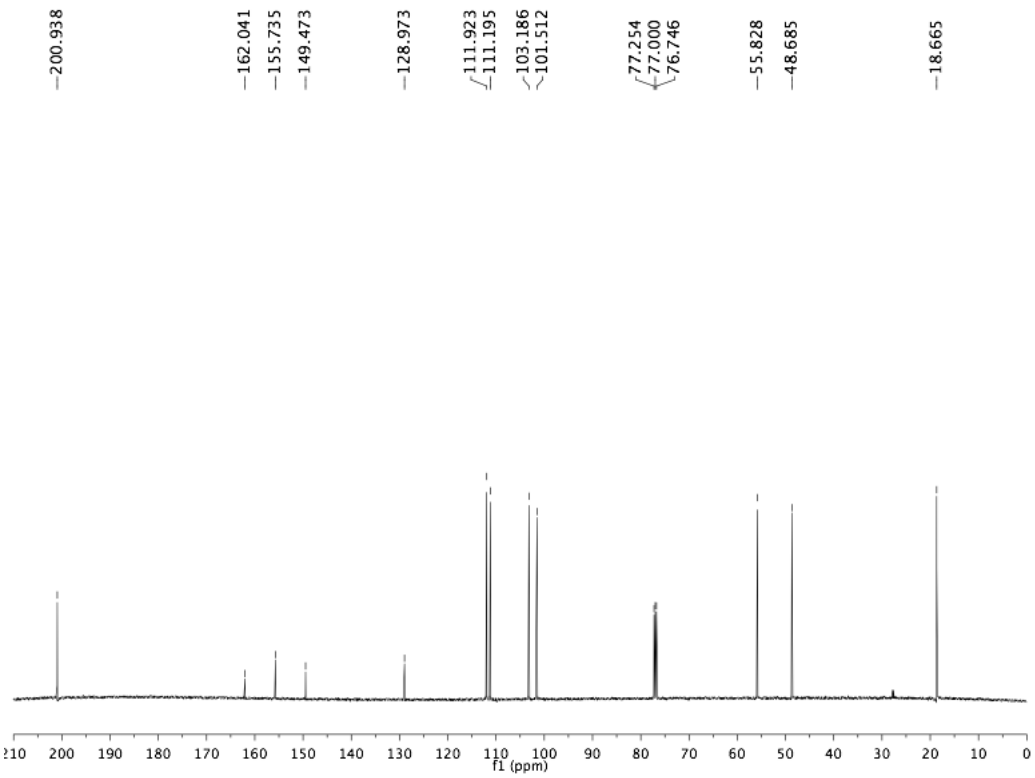
1.00
1.02
0.99
3.10
1.00
1.01
3.13
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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101.512
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77.000
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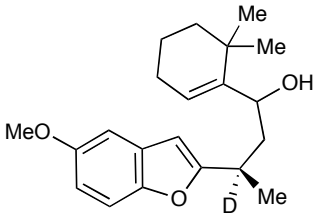
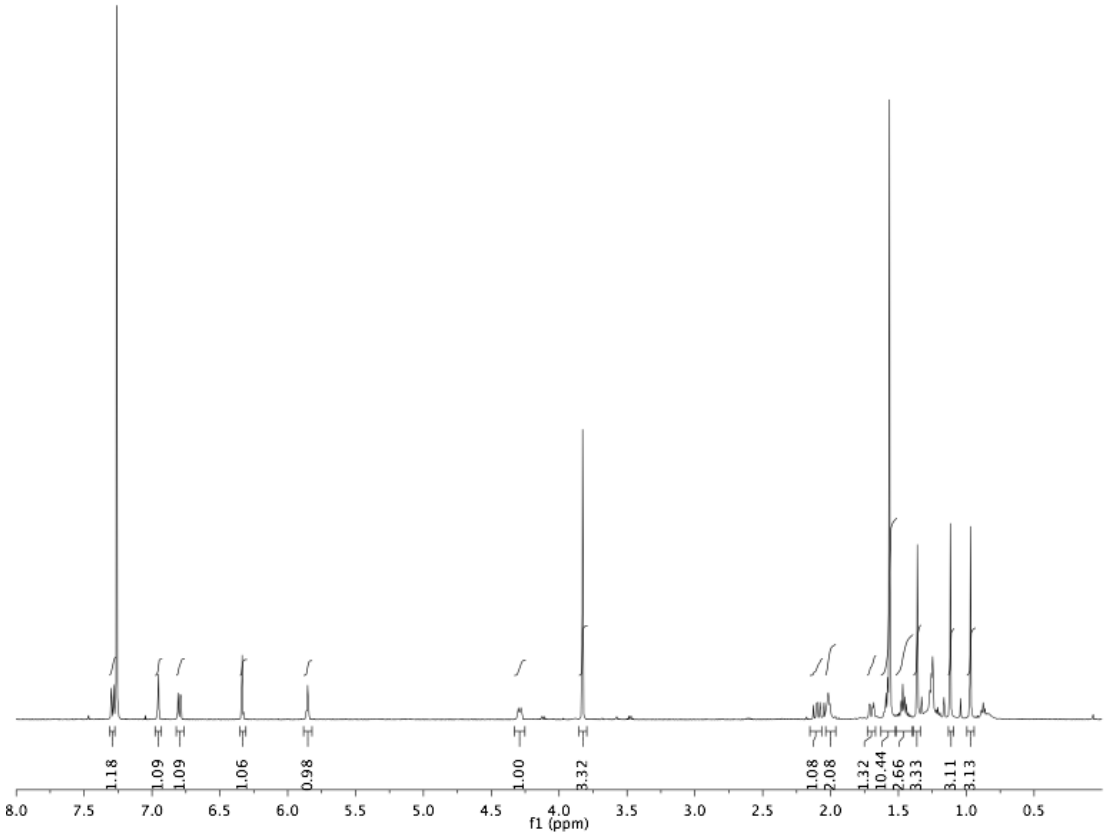
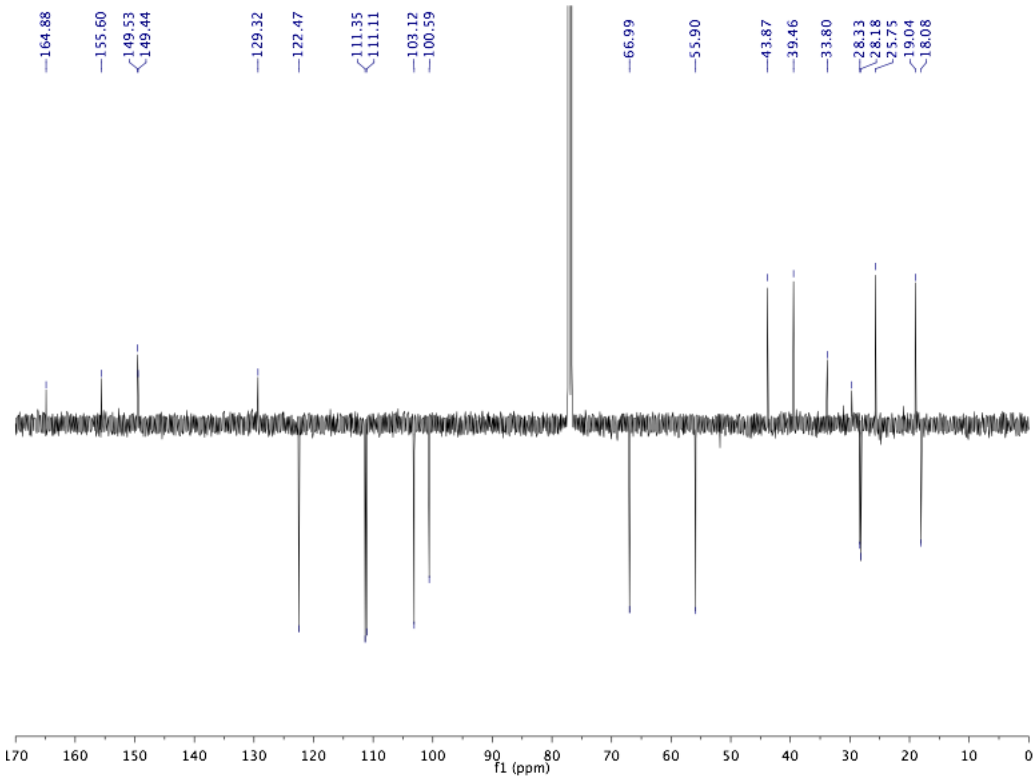
55.828
48.685
18.665
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)




[$^2$H]-**10**: diastereomer 1

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122.47
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111.11
103.12
100.59
66.99
55.90
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33.80
28.33
28.18
25.75
19.04
18.08
170
160
150
140
130
120
110
100
90
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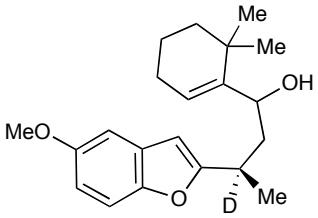
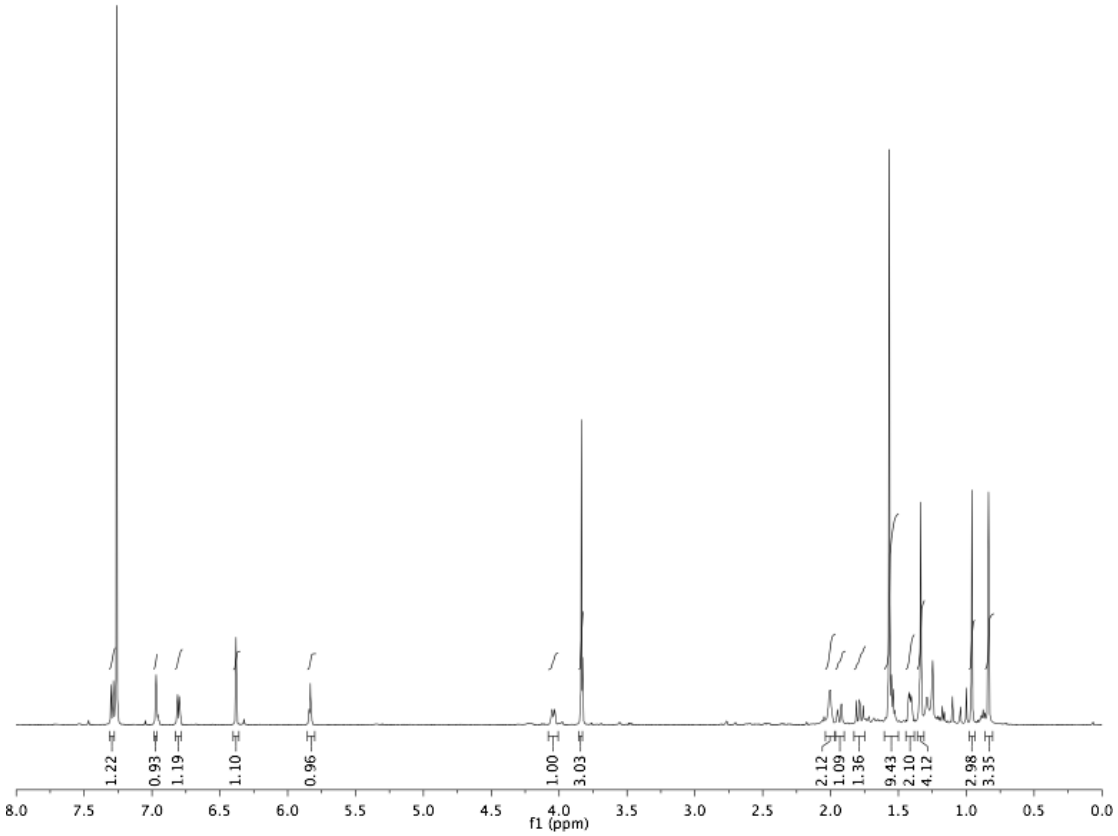
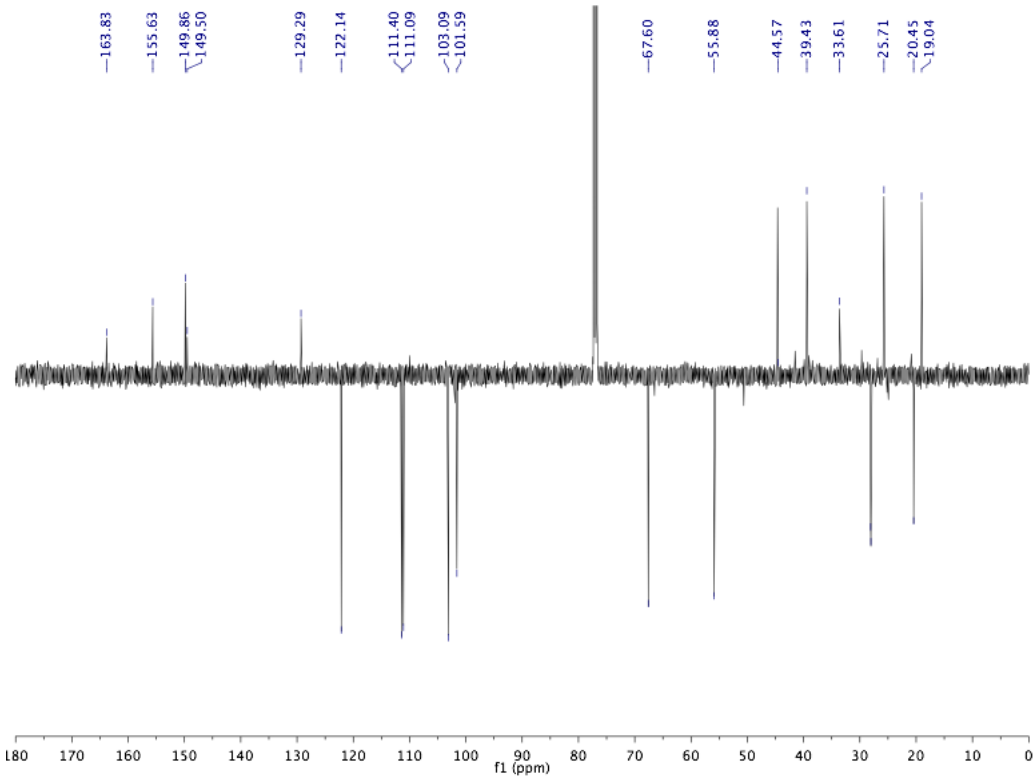
70
60
50
40
30
20
10
0
f1 (ppm)




[$^2$H]-**10**: diastereomer 2

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103.09
101.59
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20.45
19.04
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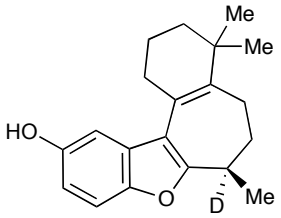
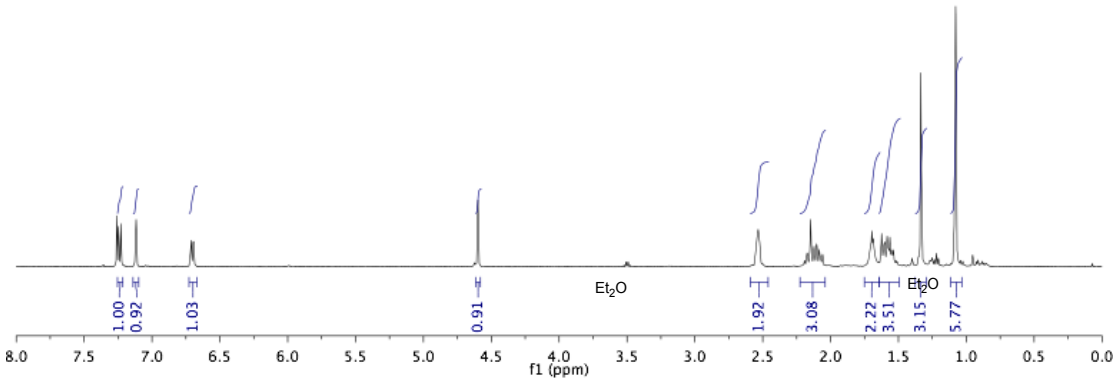
f1 (ppm)


Me
Me
HO
O
D
Me

[$^2$H]-**1**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6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
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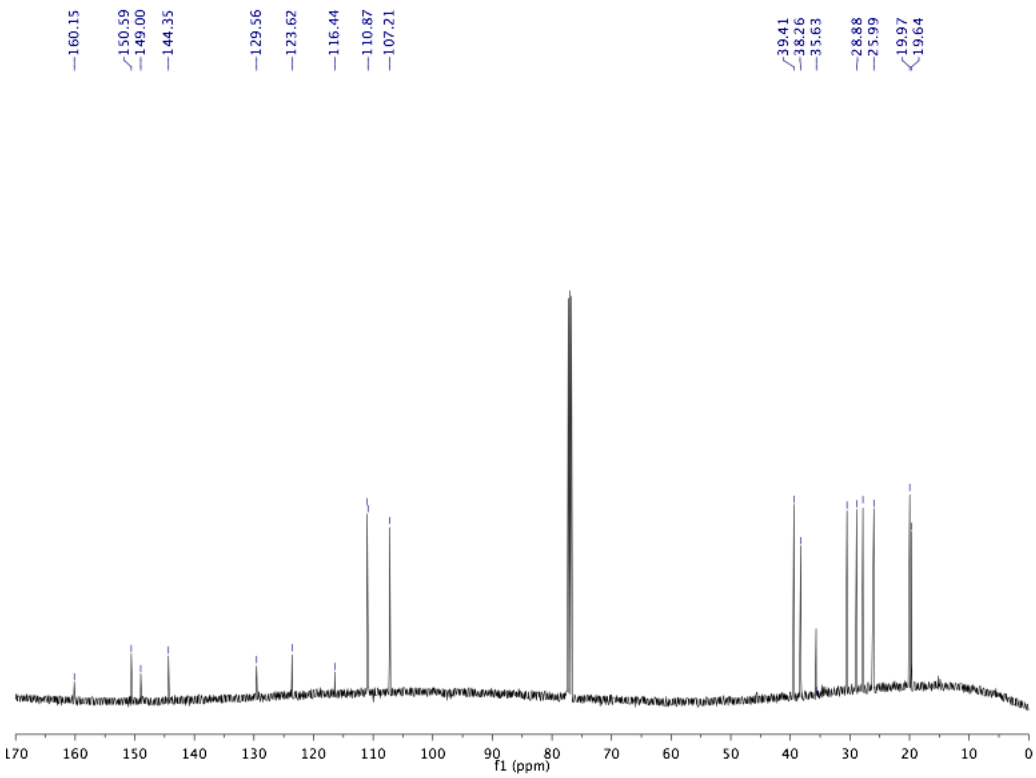
1.5
1.0
0.5
0.0
f1 (ppm)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150.59
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144.35
129.56
123.62
116.44
110.87
107.21
39.41
38.26
35.63
28.88
25.99
19.97
19.64
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)