

The Organocatalytic Three-Step Total Synthesis of (+)-Fronodosin 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. ¹H and ¹³C 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: CDCl₃ referenced at d 7.26). Data for ¹H 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 ¹³C 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.

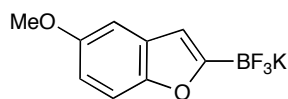
^{S2} Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K. & Timmers, F. J. (1996) *Organometallics*, **15**, 1518-1520.

^{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 \times 0.25 mm) column. Supercritical fluid chromatography (SFC) was performed on a Berger Minigram equipped with a diode array UV detector ($\lambda = 214$ – 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

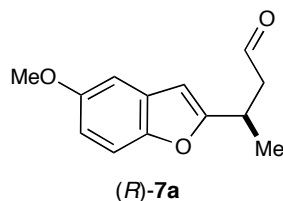
Prepared according to a procedure adopted from Molander *et al.*^{S5} commercially available 2-(5-methoxybenzofuranyl) boronic acid **2** (1.75 g, 9.00 mmol, 1.00 equiv.) was dissolved in anhydrous methanol (25 mL). Potassium hydrogenfluoride (2.44 g, 31.0 mmol, 3.40 equiv.) was added and the resulting 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. ¹H NMR (400 MHz, d₆-acetone) δ 7.18 (d, 1H, $J = 8.7$ Hz, ArH), 6.92 (d, 1H, $J = 2.4$ Hz, aryl H), 6.64 (dd, 1H, $J = 8.7, 2.4$ Hz, ArH), 6.45 (s, 1H, ArH), 3.54 (s, 3H, CH₃); ¹³C NMR (125 MHz, d₆-acetone) δ 155.5, 151.5, 130.5, 110.7, 110.2, 107.6, 102.9, 55.3; ¹⁹F 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).

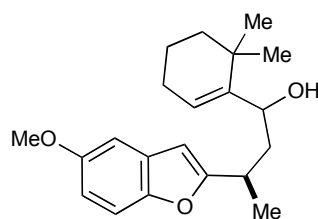


From trifluoroborate 6a: To a plastic vial (Wheaton HDPE) was added aqueous HF (48 wt%, 6.25 mg, 0.150 mmol, 1.00 equiv.) followed by 1,2-dimethoxyethane (450 mL, 1M relative to aldehyde) and a magnetic stir bar. Imidazolidinone catalyst (*S,S*)-**4a** (10.9 mg, 0.0300 mmol, 0.200 equiv.) and acid co-catalyst HCl (4M in 1,4-dioxane, 7.5 μ L, 0.030 mmol, 0.200 equiv.) were added and the reaction mixture was cooled to -20 °C. Crotonaldehyde (37.5 μ L, 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 \times 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 μ L, 0.280 mmol, 0.200 equiv.) were added and the reaction mixture was stirred for 15 min at room temperature. Crotonaldehyde (348 μ L, 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 CH₂Cl₂ (2 × 15 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 10% Et₂O in hexanes) yielded the title compound as a clear oil (255 mg, 84% yield, 93% ee): [α]_D²⁰ = -8.5 (c = 1.3, CHCl₃); IR (film) 1724, 1475, 1205, 1030 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.78 (t, 1H, *J* = 1.5 Hz, CHO), 7.29 (d, 1H, *J* = 8.4 Hz, ArH), 6.98 (d, 1H, *J* = 2.4 Hz, ArH), 6.81 (dd, 1H, *J* = 9.0, 2.4 Hz, ArH), 6.38 (d, 1H, *J* = 0.9 Hz, ArH), 3.01 (s, 3H, OCH₃), 3.54 (m, 1H, CHCH₃), 2.79 (ddd, 2H, *J* = 17.4, 6.6, 1.5 Hz, CH₂), 1.39 (d, 3H, *J* = 0.9 Hz, CH₃); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₃H₁₄O₃ [M]⁺ *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).



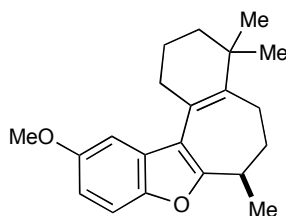
10

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 N₂ 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. NH₄Cl solution. The aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL), dried over MgSO₄, 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, ArH, dia 1), 7.23 (d, 1H, $J = 8.8$ Hz, ArH, dia 2), 6.93 (d, 1H, $J = 2.8$ Hz, ArH, dia 1), 6.92 (d, 1H, $J = 2.8$ Hz, ArH, dia 2), 6.78 (dt, 1H, $J = 8.8, 2.8$ Hz, ArH, dia 1&2), 6.35 (s, 1H, ArH, dia 1), 6.30 (s, 1H, ArH, dia 2), 5.82 (t, 1H, $J = 4.0$ Hz, C=CH, dia 1), 5.80 (t, 1H, $J = 4.0$ Hz, C=CH, dia 2), 4.26 (dd, 1H, $J = 10.0, 2.8$ Hz, CHOH, dia 1), 4.02 (dd, 1H, $J = 10.0, 2.8$ Hz, CHOH, dia 2), 3.80 (s, 3H, OCH₃, dia 1), 3.79 (s, 3H, OCH₃, dia 2), 3.18 (m, 1H, CHCH₃, dia 1&2), 2.08 (ddd, 1H, $J = 13.6, 9.2, 4.4$ Hz, CHOHCH₂, dia 1), 1.98 (t, 2H, $J = 2.4$ Hz, C=CCH₂, dia 1&2), 1.91 (ddd, 1H, $J = 13.6, 10.0, 2.8$ Hz, CHOHCH₂, dia 2), 1.76 (ddd, 1H, $J = 13.4, 10.0, 4.8$ Hz, CHOHCH₂, dia 2), 1.65 (ddd, 1H, $J = 13.6, 9.2, 2.8$ Hz, CHOHCH₂, dia 1), 1.55 (m, 2H, C=CCH₂CH₂, dia 1&2), 1.40 (m, 2H, C(CH₃)₂CH₂, dia 1&2), 1.32 (d, 3H, $J = 6.9$ Hz, CHCH₃, dia 1), 1.31 (d, 3H, $J = 6.9$ Hz, CHCH₃, dia 2), 1.08 (s, 3H, C(CH₃)₂, dia 1), 0.94 (s, 3H, C(CH₃)₂, dia 2), 0.93 (s, 3H, C(CH₃)₂, dia 1), 0.80 (s, 3H, C(CH₃)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 C₂₁H₂₈O₃ [M]⁺ m/z 328.2038, found m/z 328.2043.

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

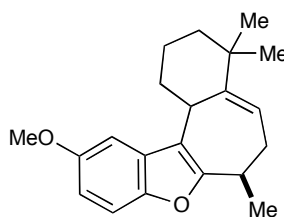


11

A round-bottom flask was charged with allylic alcohol **10** (100 mg, 0.300 mmol, 1.00 equiv.) and $[\text{Mo}(\text{CO})_4\text{Br}_2]_2$ (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 Et₂O 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, CDCl₃) δ 7.25 (d, 1H, *J* = 8.8 Hz, ArH), 7.12 (d, 1H, *J* = 2.5 Hz, ArH), 6.77 (dd, 1H, *J* = 8.8, 2.5 Hz, ArH), 3.82 (s, 3H, OCH₃), 3.15 (q, 1H, *J* = 8.5 Hz, CHCH₃), 2.55 (t, 2H, *J* = 7.5 Hz, C=CCH₂), 2.15 (m, 1H, CH₂C=C), 2.11 (m, 1H, CH₂C=C), 2.08 (m, 1H, C=CCH₂CH₂), 1.82 (m, 1H, C=CCH₂CH₂), 1.60 (m, 4H, CH₂CH₂C(CH₃)₂), 1.32 (d, 3H, *J* = 8.5 Hz, CHCH₃), 1.06 (s, 3H, C(CH₃)₂), 1.02 (C(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₁H₂₆O₂ [M]⁺ *m/z* 310.1933, found *m/z* 310.1928.

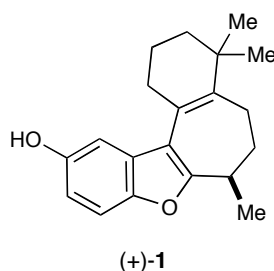
(R)-O-Methyl frondosin B, non-conjugated olefin isomer.



A round-bottom flask was charged with allylic alcohol **10** (33 mg, 0.088 mmol, 1.00 equiv.) and [Mo(CO)₄Br₂]₂ (34 mg, 0.044 mmol, 0.050 equiv.). Freshly distilled and degassed CH₂Cl₂ (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 Et₂O 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, CDCl₃) δ 7.27 (d, 1H, *J* = 8.8 Hz, ArH, dia 1), 7.25 (d, 1H, *J* = 8.8 Hz, ArH, dia 2), 6.87 (d, 1H, *J* = 3.0 Hz, ArH, dia 1&2), 6.80 (dd, 1H, *J* = 9.0, 2.5 Hz, ArH, dia 1), 6.78 (dd, 1H, *J* = 9.0, 2.5 Hz, ArH, dia 2), 5.59 (dd, 1H, *J* = 6.4, 4.4 Hz, C=CH, dia 1), 5.55 (dd, 1H, *J* = 7.6, 6.4 Hz, C=CH, dia 2), 3.85

(s, 3H, OCH₃, dia 1&2), 3.70 (m, 1H, CHC=C, dia 1), 3.68 (m, 1H, CHC=C, dia 2), 3.20 (dq, 1H, *J* = 7.2, 7.2, 6.4 Hz, CHCH₃, dia 1), 3.14 (qd, 1H, *J* = 7.2, 7.2, 2.8 Hz, CHCH₃, dia 2), 2.55 (dq, 1H, *J* = 16.4, 4.4, 2.2 Hz, CHCH₃CH₂, dia 1), 2.41 (ddd, *J* = 16.4, 7.2, 2.4 Hz, CHCH₃CH₂, dia 2), 2.42 (m, 2H, CHCH₂), 1.86 (m, 1H, CHCH₂CH₂), 1.66 (m, 1H, CHCH₂CH₂), 1.58 (m, 2H, CH₂C(CH₃)₂), 1.34 (d, 3H, *J* = 7.2 Hz, CHCH₃, dia 1&2), 1.18 (s, 3H, C(CH₃)₂, dia 1&2), 1.14 (s, 3H, C(CH₃)₂, dia 1), 1.12 (s, 3H, C(CH₃)₂, dia 2); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₁H₂₆O₂ [M]⁺ *m/z* 310.1933, found *m/z* 310.1928.

(R)- (+)-Fronodosin B (1).

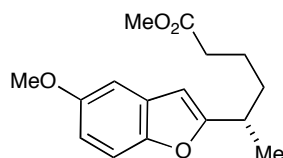


From *O*-methyl frondosin B (11): To a solution of (*R*)-*O*-methyl frondosin B (11) and its conjugated olefin isomer (2.5:1, 125 mg, 0.400 mmol, 1.00 equiv.) in CH₂Cl₂ (2 mL) was added BBr₃ (1M in CH₂Cl₂, 1.28 mL, 1.28 mmol, 3.20 equiv.) dropwise at -78 °C. After being stirred at -78 °C for 30 min, the solution was warmed to 0 °C. After 1 h, the reaction mixture was then quenched with sat. aqueous NaHCO₃ and diluted with EtOAc (6 mL). The organic layer was washed with sat. aqueous NaHCO₃ and brine, dried over Na₂SO₄ 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 CH₂Cl₂ (10 mL) was

added BBr_3 (1M in CH_2Cl_2 , 1.22 mL, 1.22 mmol, 3.50 equiv.) dropwise at $-78\text{ }^\circ\text{C}$. The resultant mixture was stirred at $-78\text{ }^\circ\text{C}$ for 30 min and was then allowed to reach $-15\text{ }^\circ\text{C}$ (acetone/ice). After 3 h, the reaction mixture was quenched with sat. aqueous NaHCO_3 (5 mL) and aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (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: $[\alpha]_D^{20} = +16.3$ ($c = 0.12$, MeOH) [lit. $[\alpha]_D^{20} = +18.6$ ($c = 0.17$, MeOH),^{S7} $[\alpha]_D^{20} = +15.2$ ($c = 0.13$, 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, ArH), 7.09 (d, 1H, $J = 2.5$ Hz, ArH), 6.67 (dd, 1H, $J = 8.8, 2.5$ Hz, ArH), 4.51 (s, 1H, OH), 3.17 (q, 1H, $J = 8.5$ Hz, CHCH_3), 2.51 (t, 2H, $J = 6.0$ Hz, $\text{C}=\text{CCH}_2$), 2.15 (m, 1H, $\text{ArC}=\text{CCH}_2$), 2.11 (m, 1H, $\text{CH}(\text{CH}_3)\text{CH}_2$), 2.08 (m, 1H, $\text{ArC}=\text{CCH}_2$), 1.72 (m, 2H, $\text{C}=\text{CCH}_2\text{CH}_2$), 1.54 (m, 3H, $\text{CH}(\text{CH}_3)\text{CH}_2$, $\text{CH}_2\text{C}(\text{CH}_3)_2$), 1.32 (d, 3H, $J = 8.5$ Hz, CHCH_3), 1.05 (s, 6H, $\text{C}(\text{CH}_3)_2$); ^{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 $\text{KO}t\text{-Bu}$ (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 $0\text{ }^\circ\text{C}$. 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

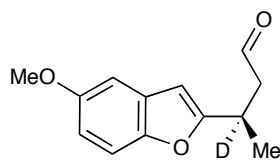
^{S7} Patil, A. D.; Freyer, A. J.; Killmer, L.; Offen, P.; Carte, B.; Jurewicz, A. J. & Johnson, R. K. (1997) *Tetrahedron* **53**, 5047-5060.

^{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 Et₂O (2 ml) and quenched upon slow addition of water (1 mL). The layers were separated and the aqueous phase was extracted with Et₂O (3 × 5 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄ 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 Ca₂CO₃, 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% Et₂O in pentanes) to give the title compound (40 mg, 88% yield over two steps): [α]_D²⁰ = +19.6 (*c* = 0.10, CHCl₃) [lit. [α]_D²⁰ = -20.4 (*c* = 0.104, CDCl₃) for (*R*)-**13** (84% ee)^{S8}]; IR (film) 1735, 1475, 1205, 1030 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.29 (d, 1H, *J* = 9.0 Hz, ArH), 6.96 (d, 1H, *J* = 2.7 Hz, Ar-H), 6.80 (dd, 1H, *J* = 9.0, 2.7 Hz, ArH), 6.32 (s, 1H, ArH), 3.83 (s, 3H, OCH₃), 3.66 (s, 3H, CO₂CH₃), 2.92 (m, 1H, CHCH₃), 2.32 (t, 2H, *J* = 7.0 Hz, CH₂CO₂Me; 1.80 (m, 1H, CH₂CH₂CO₂Me), 1.66 (m, 3H, CHCH₃CH₂CH₂), 1.32 (d, 3H, *J* = 7.0 Hz, CHCH₃); ¹³C NMR (CDCl₃, 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*)-[²H]-3-(5-methoxybenzofuran-2-yl)butanal ([²H]-8).

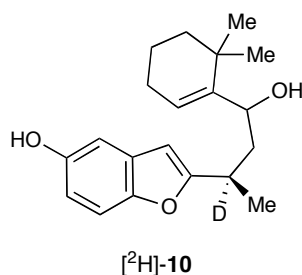


(*R*)-[²H]-8

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 $-20\text{ }^{\circ}\text{C}$. Crotonaldehyde [^2H]-**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 $-20\text{ }^{\circ}\text{C}$ 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 ($2 \times 15\text{ mL}$), 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). $[\alpha]_{\text{D}}^{20} = -13.7$ ($c = 1.3$, CHCl_3); IR (film) 1725, 1476, 1206, 1031 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.80 (t, $J = 1.7\text{ Hz}$, 1H, CHO), 7.30 (d, $J = 8.9\text{ Hz}$, 1H, ArH), 6.96 (d, $J = 2.5\text{ Hz}$, 1H, ArH), 6.83 (dd, $J = 8.9, 2.6\text{ Hz}$, 1H, ArH), 6.36 (s, 1H, ArH), 3.82 (s, 3H, OCH_3), 2.92 (d, $J = 17.4\text{ Hz}$, 1H, CH_2), 2.68 (d, $J = 17.2\text{ Hz}$, 1H, CH_2), 1.39 (s, 3H, CH_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 $\text{C}_{13}\text{H}_{14}\text{DO}_3$ $[\text{M}+\text{H}]^+$ 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, $35\text{ }^{\circ}\text{C}$ oven, flow = 4.0 mL/min); (*S*) isomer $t_{\text{r}} = 4.52\text{ min}$, (*R*) isomer $t_{\text{r}} = 4.90\text{ min}$.

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

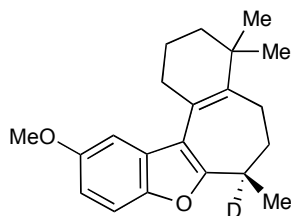


To a solution of 2,4,6-triisopropylbenzenesulfonyl hydrazone (**5**)^{S6} (206 mg, 0.506 mmol, 1.00 equiv.) in anhydrous THF (2 mL) was added *t*-BuLi (600 μL , 1.7M, 1.01 mmol, 2.00 equiv.) dropwise over 15 min at $-78\text{ }^{\circ}\text{C}$. The resultant solution was stirred at $-78\text{ }^{\circ}\text{C}$ 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 N₂ evolution was observed. Upon cooling back down to -78 °C, aldehyde [²H]-**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. NH₄Cl solution. The aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 10% Et₂O 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% Et₂O in hexanes, eluted twice). IR (film) 3442, 1617, 1476, 1205, 1032 cm⁻¹; HRMS (ESI+) calcd for C₂₁H₂₈DO₃ [M+H]⁺ *m/z* 330.2174, found *m/z* 330.2168. Diastereomer 1: [α]²⁰_D = +11.9 (*c* = 0.088, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.29 (d, *J* = 8.9 Hz, 1H, ArH), 6.95 (d, *J* = 2.5 Hz, 1H, ArH), 6.80 (dd, *J* = 8.9, 2.6 Hz, 1H, ArH), 6.34 (s, 1H, ArH), 5.85 (t, *J* = 3.9 Hz, 1H, C=CH), 4.29 (dt, *J* = 9.3, 3.6 Hz, 1H, CHOH), 3.83 (s, 3H, OCH₃), 2.10 (dd, *J* = 14.1, 9.6 Hz, 1H, CHOHCH₂), 2.04-1.99 (m, 2H, C=CCH₂), 1.70 (dd, *J* = 14.1, 3.5 Hz, 1H, CHOHCH₂), 1.62-1.54 (m, 2H, C=CCH₂CH₂), 1.50-1.42 (m, 2H, C(CH₃)₂CH₂), 1.36 (s, 3H, CDCH₃), 1.12 (s, 3H, C(CH₃)₂), 0.97 (s, 3H, C(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃) 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: [α]²⁰_D = -6.5 (*c* = 0.15, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.29 (d, *J* = 8.8 Hz, 1H, ArH), 6.97 (d, *J* = 2.5 Hz, 1H, ArH), 6.81 (dd, *J* = 8.8, 2.6 Hz, 1H, ArH), 6.38 (s, 1H, ArH), 5.83 (t, *J* = 3.9 Hz, 1H, C=CH), 4.04 (d, *J* = 9.7 Hz, 1H, CHOH), 3.84 (s, 3H, OCH₃), 2.03-1.98 (m, 2H, C=CCH₂), 1.93 (dd, *J* = 14.2, 2.4 Hz, 1H, CHOHCH₂), 1.78 (dd, *J* = 14.2, 10.0 Hz, 1H, CHOHCH₂), 1.59-1.52 (m, 2H, C=CCH₂CH₂), 1.44-1.38 (m, 2H, C(CH₃)₂CH₂), 1.33 (s, 3H, CDCH₃), 0.96 (s, 3H, C(CH₃)₂), 0.84 (s, 3H, C(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃) 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.

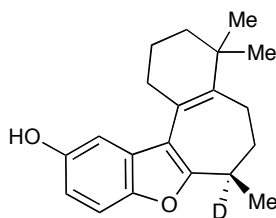
(R)-[²H]-O-Methyl frondosin B ([²H]-11).



[²H]-11

A round-bottom flask was charged with allylic alcohol [²H]-**10** (26.0 mg, 0.0800 mmol, 1.00 equiv.) and [Mo(CO)₄Br₂]₂ (11.6 mg, 0.0158 mmol, 0.200 equiv.). Freshly distilled and degassed CH₂Cl₂ (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 Et₂O 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; ¹H NMR (500 MHz, CDCl₃) δ 7.29 (d, *J* = 8.8 Hz, 1H, ArH), 7.15 (d, *J* = 2.5 Hz, 1H, ArH), 6.80 (dd, *J* = 8.8, 2.3 Hz, 1H, ArH), 3.84 (s, 3H, OCH₃), 2.57 (t, *J* = 5.9 Hz, 2H, C=CCH₂), 2.20-2.06 (m, 3H, CH₂C=C, C=CCH₂CH₂), 1.76-1.67 (m, 2H, C=CCH₂CH₂), 1.65-1.54 (m, 3H, CH₂H₂C(CH₃)₂), 1.34 (s, 3H, CDCH₃), 1.092 (s, 3H, CH₂CH₂C(CH₃)₂), 1.089 (s, 3H, CH₂CH₂C(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₁H₂₆DO₂ [M+H]⁺ *m/z* 312.2068, found *m/z* 312.2065.

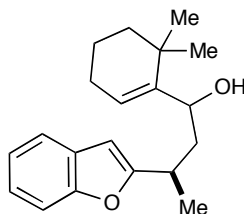
(R)-(+)-[²H]-Frondosin B ([²H]-(+)-1).



[²H]-(+)-1

To a solution of allylic alcohol [²H]-**10** (47.0 mg, 0.143 mmol, 1.00 equiv.) in CH₂Cl₂ (5 mL) was added BBr₃ (1M in CH₂Cl₂, 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 NaHCO₃ (5 mL) and aqueous Na₂S₂O₃ (1M, 5 mL). The aqueous layer was extracted with CH₂Cl₂ (2 × 10 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5% Et₂O 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*)-(+)-[²H]-frondosin B: [α]_D²⁰ = +6.5 (*c* = 1.5, CHCl₃); IR (film) 3300, 2927, 1591, 1457, 1198 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.24 (d, *J* = 8.7 Hz, 1H, ArH), 7.12 (d, *J* = 2.2 Hz, 1H, ArH), 6.70 (dd, *J* = 8.6, 2.1 Hz, 1H, ArH), 4.60 (s, 1H, ArOH), 2.59-2.48 (m, 2H, C=CCH₂), 2.21-2.03 (m, 3H, CH₂C=C, C=CCH₂CH₂), 1.75-1.66 (m, 2H, C=CCH₂CH₂), 1.64-1.52 (m, 3H, CH₂CH₂C(CH₃)₂), 1.33 (s, 3H, CDCH₃), 1.083 (s, 3H, C(CH₃)₂), 1.079 (s, 3H, C(CH₃)₂); ¹³C NMR (CDCl₃, 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 C₂₀H₂₄DO₂ [M+H]⁺ *m/z* 298.1912, found *m/z* 298.1914.

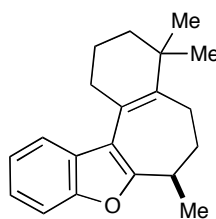
(*R*)-3-(benzofuran-2-yl)-1-(6,6-dimethylcyclohex-1-enyl)butan-1-ol.



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 N₂ 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, ArH, dia 1&2), 7.42 (d, $J = 7.7$ Hz, 2H, ArH, dia 1&2), 7.25-7.14 (m, 4H, ArH, dia 1&2), 6.44 (s, 1H, ArH, dia 1), 6.40 (s, 1H, ArH, dia 2), 5.86 (t, 1H, $J = 3.9$ Hz, C=CH, dia 1), 5.84 (t, 1H, $J = 3.9$ Hz, C=CH, dia 2), 4.31 (dd, 1H, $J = 9.6, 3.6$ Hz, CHOH, dia 1), 4.08 (dd, 1H, $J = 10.5, 3.3$ Hz, CHOH, dia 2), 3.33-3.14 (m, 2H, CHCH₃, dia 1&2), 2.14 (ddd, 1H, $J = 14.3, 9.6, 4.8$ Hz, CHOHCH₂, dia 1), 2.07-1.93 (m, 5H, C=CCH₂, dia 1&2, CHOHCH₂, dia 2), 1.81 (ddd, 1H, $J = 14.3, 9.9, 4.5$ Hz, CHOHCH₂, dia 2), 1.73 (ddd, 1H, $J = 13.9, 9.1, 3.7$ Hz, CHOHCH₂, dia 1), 1.63-1.52 (m, 4H, C=CCH₂CH₂, dia 1&2), 1.50-1.42 (m, 4H, C(CH₃)₂CH₂, dia 1&2), 1.39 (d, 3H, $J = 6.9$ Hz, CHCH₃, dia 1), 1.37 (d, 3H, $J = 7.0$ Hz, CHCH₃, dia 2), 1.13 (s, 3H, C(CH₃)₂, dia 1), 0.98 (s, 3H, C(CH₃)₂, dia 2), 0.97 (s, 3H, C(CH₃)₂, dia 1), 0.85 (s, 3H, C(CH₃)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 $\text{C}_{20}\text{H}_{26}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ m/z 321.1825, found m/z 321.1827.

Desoxyfrondosin B (14).

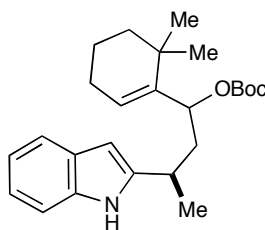


14

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 $[\text{Mo}(\text{CO})_4\text{Br}_2]_2$ (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 Et₂O 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. ¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, 1H, *J* = 7.5 Hz, ArH), 7.44-7.39 (m, 1H, ArH), 7.25-7.12 (m, 2H, ArH), 3.31-3.17 (m, 1H, CHCH₃), 2.71-2.54 (m, 2H, C=CCH₂), 2.26-2.05 (m, 3H, CH₂C=C, C=CCH₂CH₂), 1.78-1.69 (m, 2H, C=CCH₂CH₂), 1.67-1.53 (m, 3H, CH₂H₂C(CH₃)₂), 1.38 (d, 3H, *J* = 6.9 Hz, CHCH₃), 1.11 (s, 3H, C(CH₃)₂), 1.10 (s, 3H, C(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₀H₂₅O [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}**

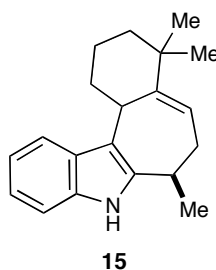


To a solution of 2,4,6-triisopropylbenzenesulfonyl hydrazone **9**^{S6} (77.7 mg, 0.191 mmol, 1.00 equiv.) in anhydrous THF (1.5 mL) was added *t*-BuLi (265 μL, 0.420 mmol, 1.6M in pentane, 2.20 equiv.) dropwise over 15 min at -78 °C. The resultant solution was stirred at -78 °C for 30 min and then at 0 °C for 15 min, upon which N₂ 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 NH₄Cl. The layers were separated and the aqueous phase was extracted Et₂O (2 × 10 mL), dried (MgSO₄) and concentrated *in vacuo*. Flash chromatography (2 → 5% Et₂O in hexane) of

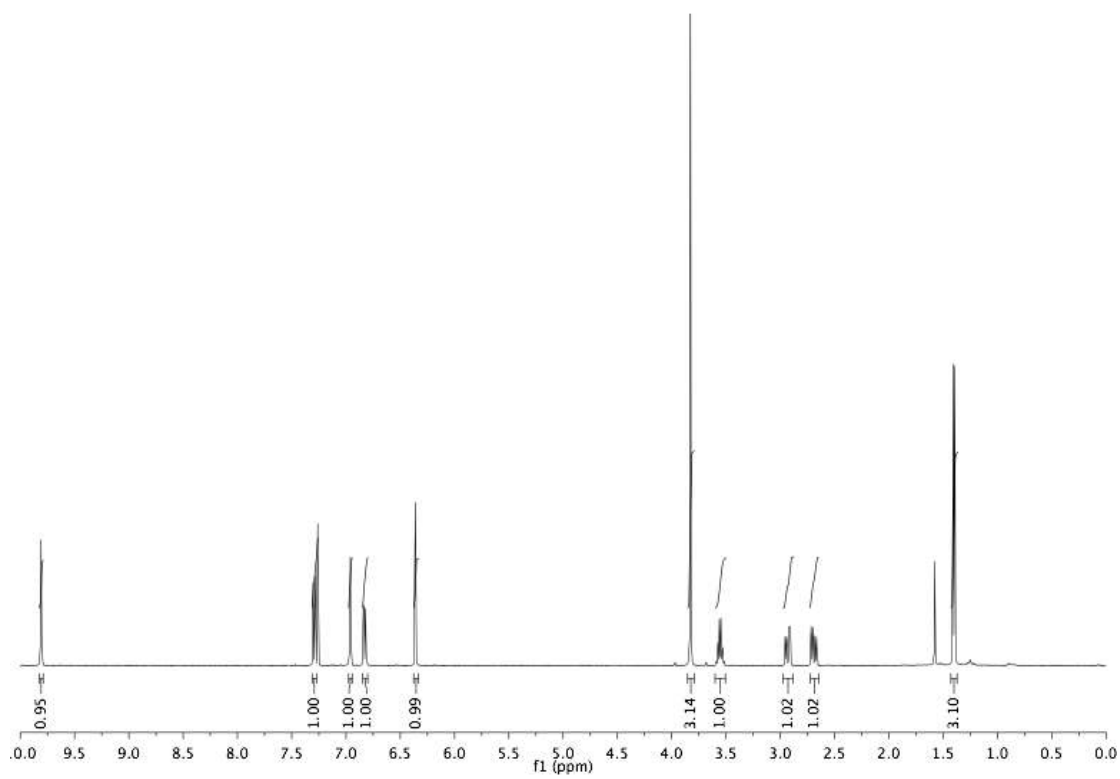
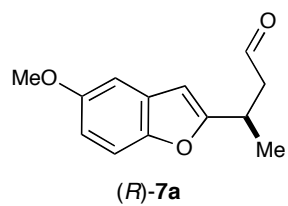
^{S10} Under the reaction conditions, a complete migration of the *tert*-butoxycarbonyl (Boc) group from the indole nitrogen to the secondary alcohol moiety was observed.

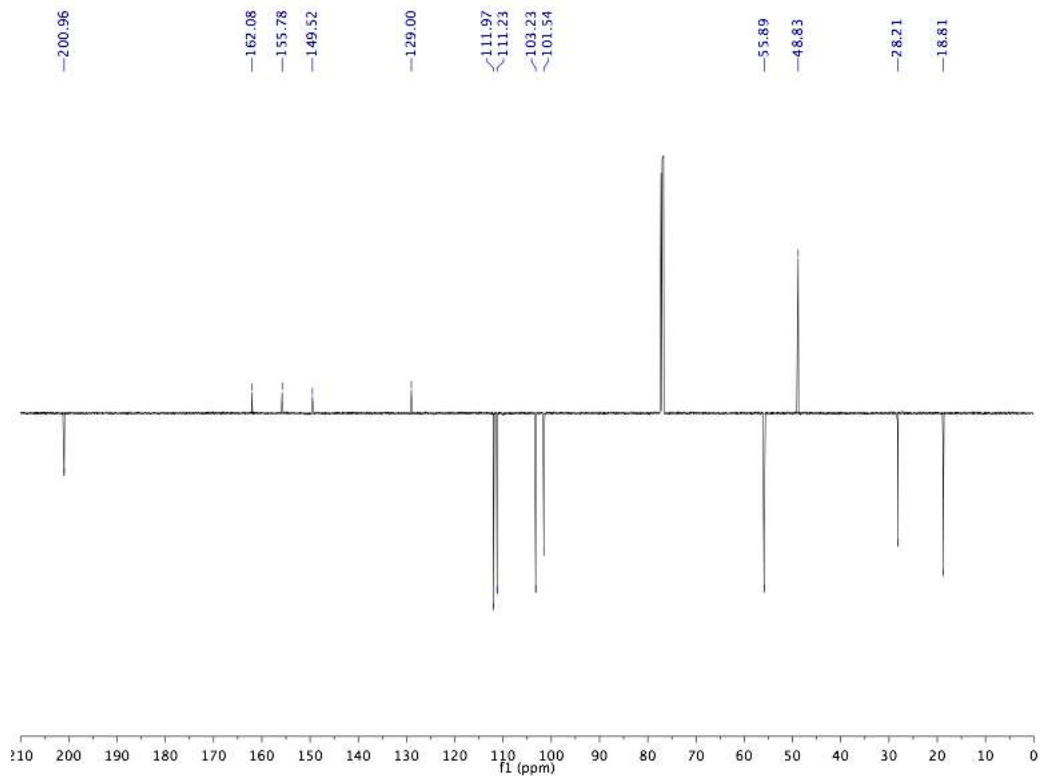
the residue gave the title compound (64.5 mg, 85% yield, 1:1 d.r.) as a clear oil. IR (film) 3423, 2938, 1733, 1281, 1156; Diastereomer 1: ^1H NMR (500 MHz, CDCl_3) δ 9.00 (s, 1H, NH), 7.55 (d, 1H, $J = 7.7$ Hz, ArH), 7.40 (d, 1H, $J = 8.0$ Hz, ArH), 7.13 (t, 1H, $J = 7.1$ Hz, ArH), 7.07 (t, 1H, $J = 7.4$ Hz, ArH), 6.27 (s, 1H, ArH), 5.84 (t, 1H, $J = 3.9$ Hz, C=CH), 5.30 (dd, 1H, $J = 10.2, 2.3$ Hz, CHOBoc), 2.89 (ddd, 1H, $J = 10.4, 7.0, 3.5$ Hz, CHCH₃), 2.11 (ddd, 1H, $J = 14.1, 10.2, 3.6$ Hz, CH(OBoc)CH₂), 2.06-1.92 (m, 2H, C=CCH₂), 1.80 (ddd, 1H, $J = 14.4, 10.4, 2.5$ Hz, CH(OBoc)CH₂), 1.56-1.50 (m, 2H, C=CCH₂CH₂), 1.53 (s, 9H, C(CH₃)₃) 1.40 (d, 3H, $J = 7.0$ Hz, CHCH₃), 1.39-1.35 (m, 2H, CH₂C(CH₃)₂), 0.96 (s, 3H, C(CH₃)₂), 0.69 (s, 3H, C(CH₃)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: ^1H NMR (500 MHz, CDCl_3) δ 8.29 (s, 1H, NH), 7.54 (d, 1H, $J = 7.7$, ArH), 7.34 (d, 1H, $J = 8.0$ Hz, ArH), 7.12 (t, 1H, $J = 7.5$ Hz, ArH), 7.06 (t, 1H, $J = 7.4$ Hz, ArH), 6.28 (d, 1H, $J = 1.2$ Hz, ArH), 5.88 (t, 1H, $J = 3.9$ Hz, C=CH), 5.26 (dd, 1H, $J = 8.7, 5.0$ Hz, CHOBoc), 3.02-2.92 (m, 1H, CHCH₃), 2.24 (ddd, 1H, $J = 14.8, 8.6, 6.4$ Hz, CH(OBoc)CH₂), 2.11-1.94 (m, 2H, C=CCH₂), 1.92 (ddd, 1H, $J = 14.2, 7.8, 14.2$ Hz, CH(OBoc)CH₂), 1.64-1.55 (m, 2H, C=CCH₂CH₂), 1.47 (s, 9H, C(CH₃)₃), 1.45-1.42 (m, 2H, CH₂C(CH₃)₂), 1.41 (d, 3H, $J = 6.9$ Hz, CHCH₃), 1.07 (s, 3H, C(CH₃)₂), 0.93 (s, 3H, C(CH₃)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 $\text{C}_{25}\text{H}_{36}\text{NO}_3$ $[\text{M}+\text{H}]^+$ m/z 398.2690, found m/z 398.2690.

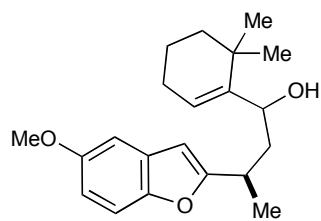
Indole derivative 15.



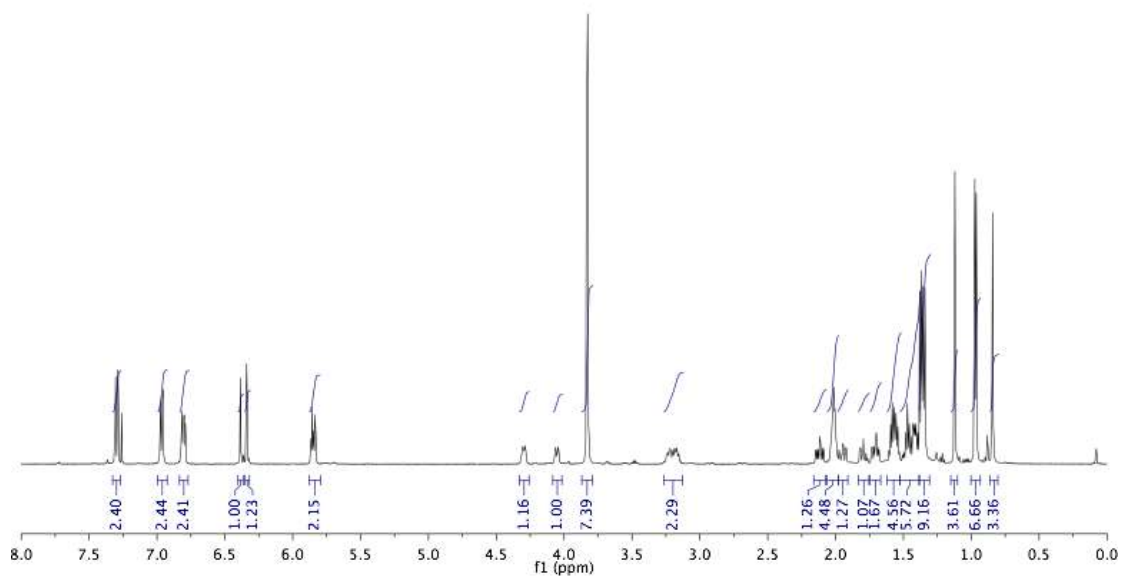
To a solution of the previously prepared allylic carbonate (27.5 mg, 0.0692 mmol, 1.00 equiv.) in CH_2Cl_2 (3 mL) was added trifluoroacetic acid (26.8 μL , 0.346 mmol, 5.00 equiv.) and the resultant dark solution was stirred at room temperature for 2 h. The reaction was quenched with sat. aqueous NaHCO_3 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; ^1H NMR (500 MHz, CDCl_3) δ 7.80 (s, 1H, **NH**, dia 1), 7.61 (s, 1H, **NH**, dia 2), 7.54-7.48 (m, 1H, **ArH**, dia 1&2), 7.36-7.24 (m, 1H, **ArH**, dia 1&2), 7.15-7.07 (m, 2H, **ArH**, dia 1&2), 5.63 (dd, 1H, $J = 7.8, 3.3$ Hz, **C=CH**, dia 1), 5.55 (d, 1H, $J = 8.2, 2.7$ Hz, **C=CH**, dia 2), 3.99 (d, 1H, $J = 12.4$ Hz, **CH=CCH**, dia 2), 3.97 (d, 1H, $J = 12.4$ Hz, **CH=CCH**, dia 1), 3.39-3.30 (m, 1H, **CHCH}_3**, dia 1), 3.07-2.98 (m, 1H, **CHCH}_3**, dia 2), 2.65 (dd, 1H, $J = 15.7, 2.8$ Hz, **C=CHCH}_2**, dia 2), 2.44-2.24 (m, 3H, **C=CHCH}_2**, dia 1&2), 2.20 (d, 1H, $J = 12.9$ Hz, **ArCHCH}_2**, dia 2), 2.11 (d, 1H, $J = 12.7$ Hz, **ArCHCH}_2**, dia 1), 2.01-1.81 (m, 2H, **CH}_2\text{CH}_2(\text{CH}_3)_2**, dia 1&2), 1.75-1.54 (m, 2H, **CH}_2(\text{CH}_3)_2**, dia 1&2), 1.51-1.42 (m, 1H, **C=CHCH}_2**, dia 1&2), 1.41 (d, 3H, $J = 5.0$ Hz, **CHCH}_3**, dia 1), 1.39 (d, 2H, $J = 5.0$ Hz, **CHCH}_3**, dia 2), 1.24 (s, 3H, **C(CH}_3)_2**, dia 1), 1.23 (s, 3H, **C(CH}_3)_2**, dia 2), 1.18 (s, 3H, **C(CH}_3)_2**, dia 2), 1.15 (s, 3H **C(CH}_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 $\text{C}_{20}\text{H}_{26}\text{N}$ $[\text{M}+\text{H}]^+$ m/z 280.2060, found m/z 280.2062.

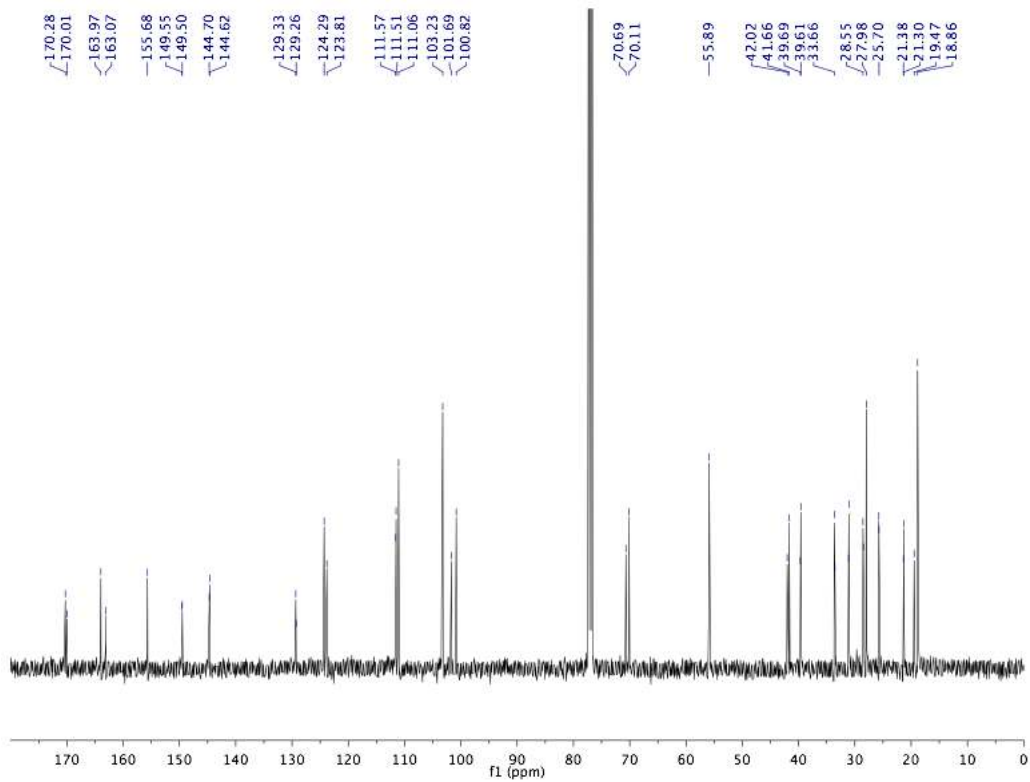


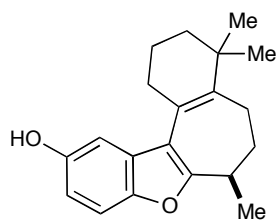




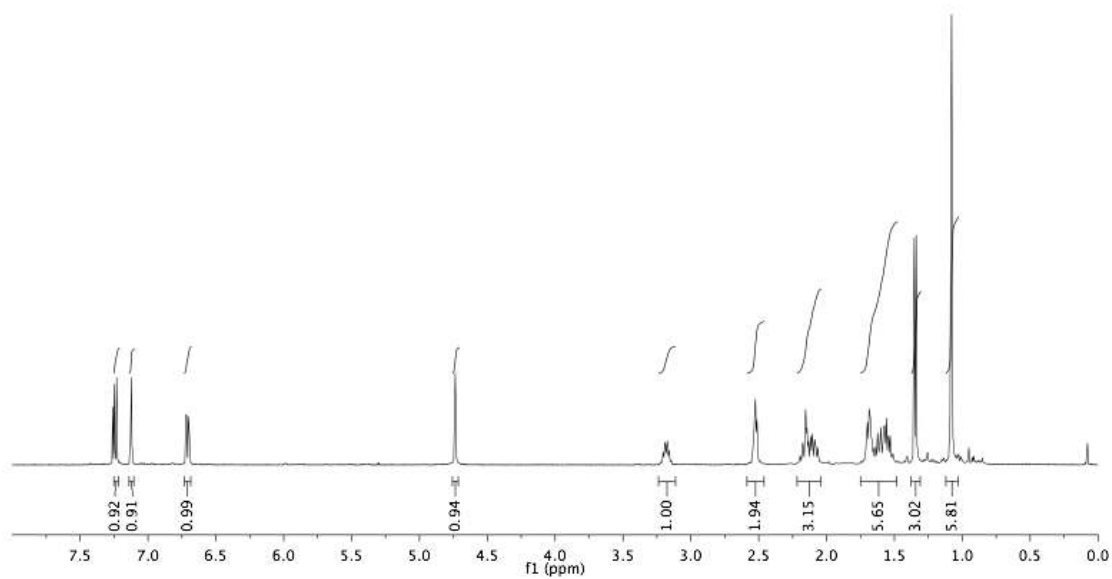
10: 1:1 dr

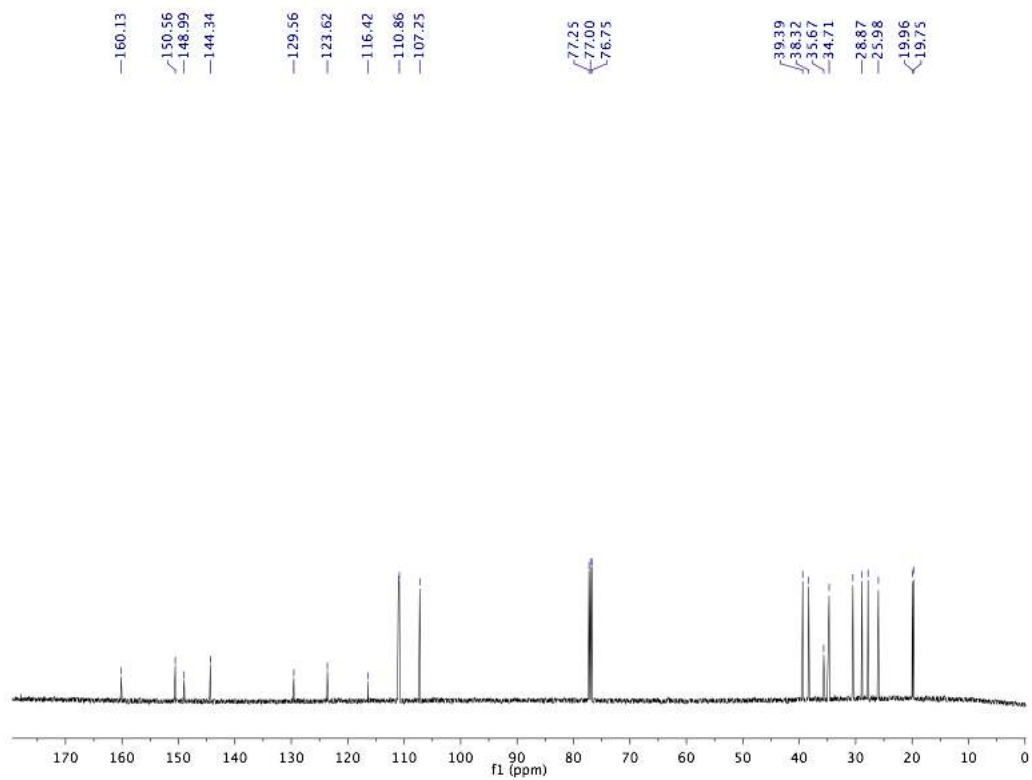


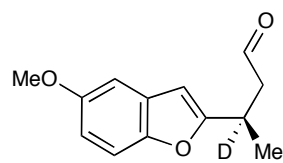




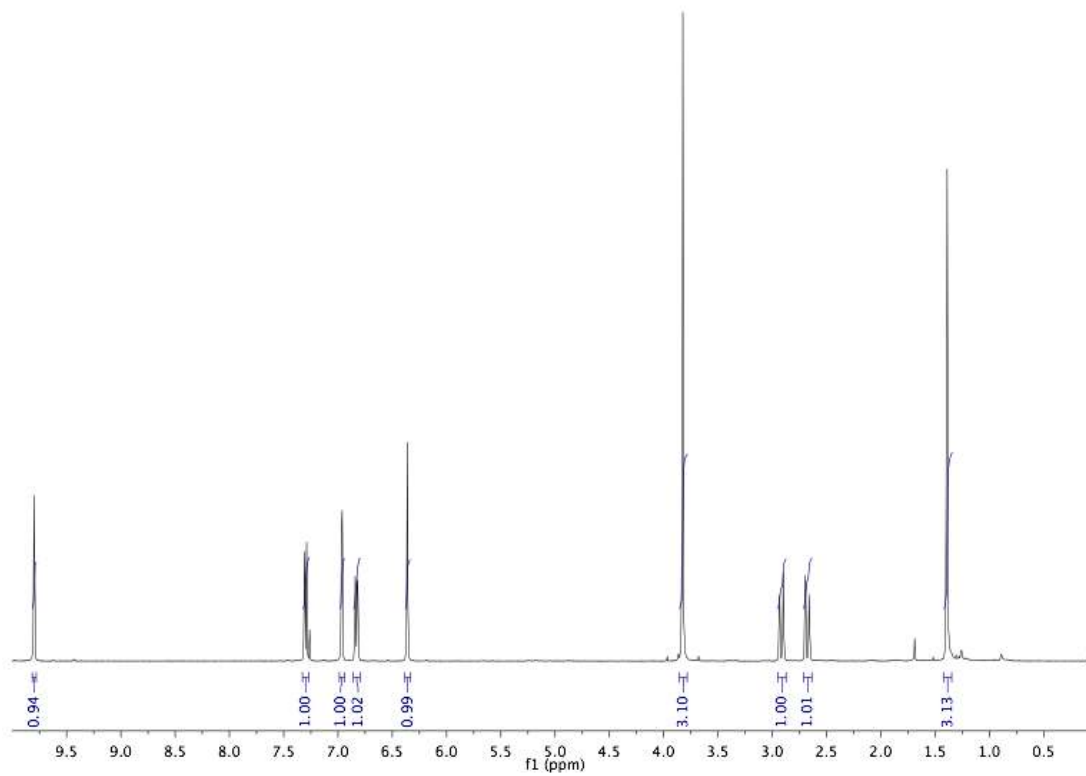
frondosin (+)-1

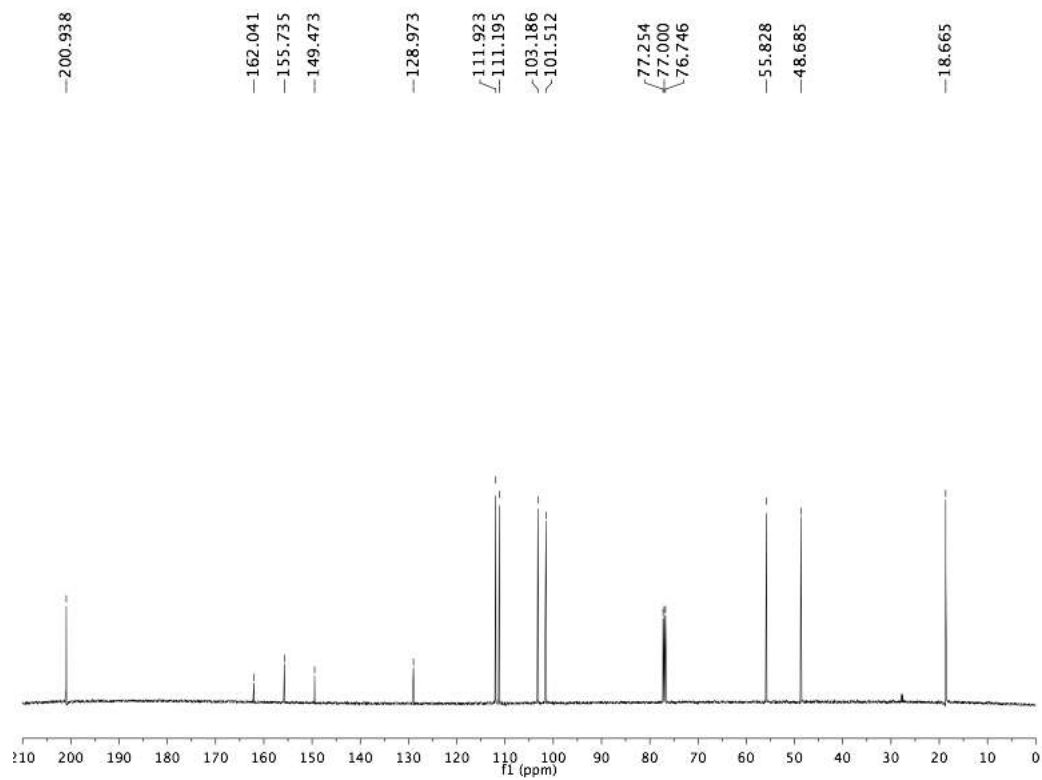


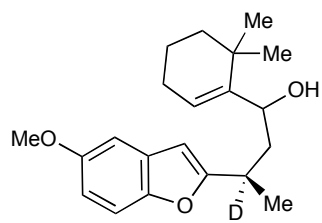




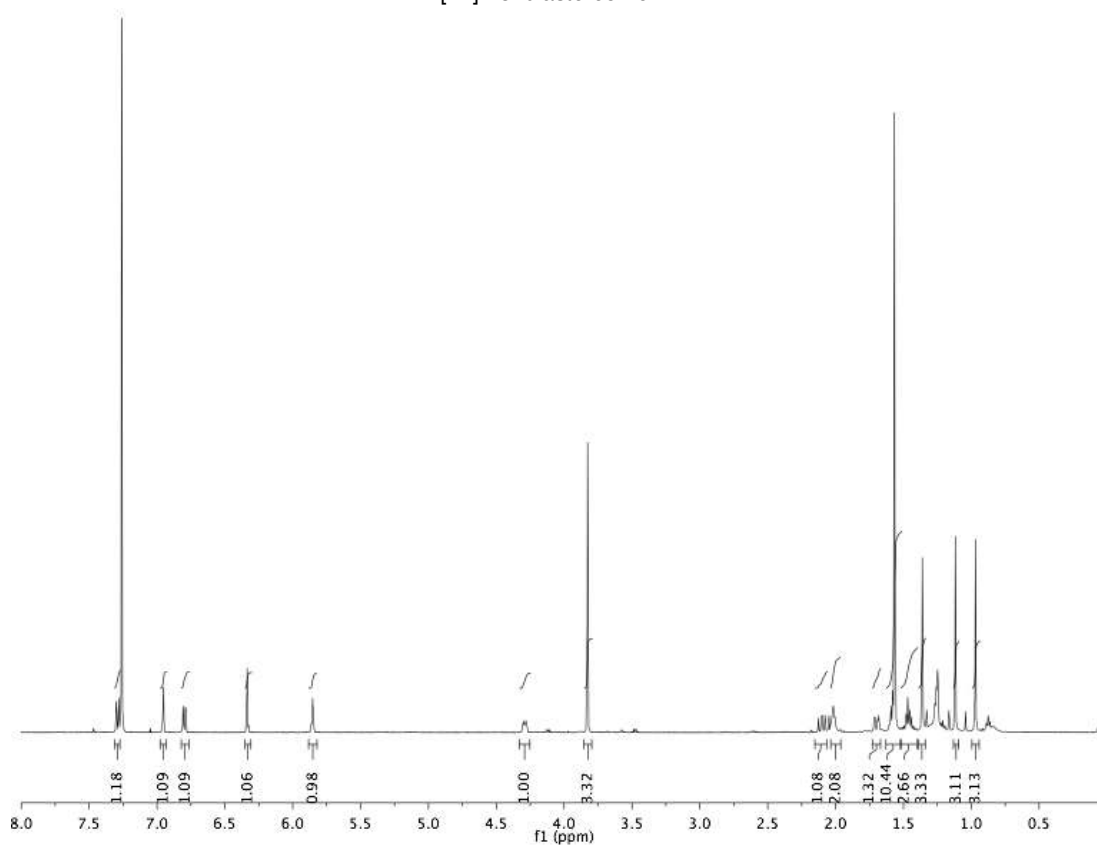
(*R*)-[²H]-8

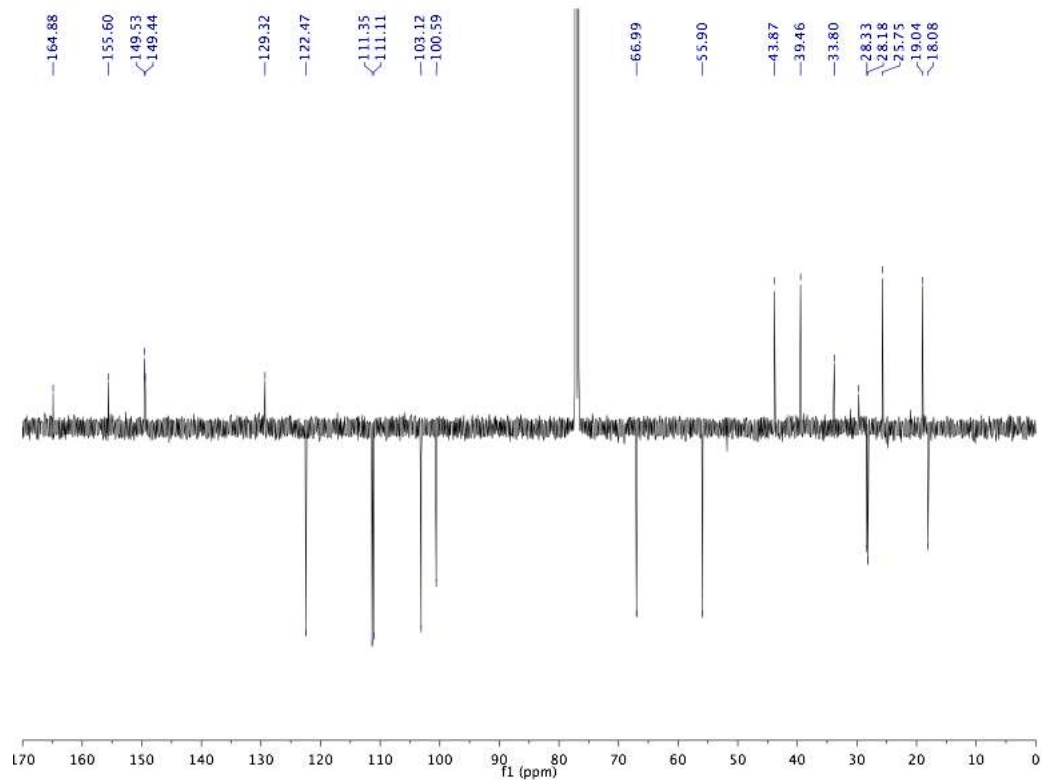


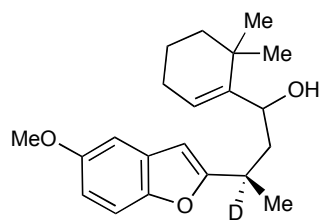




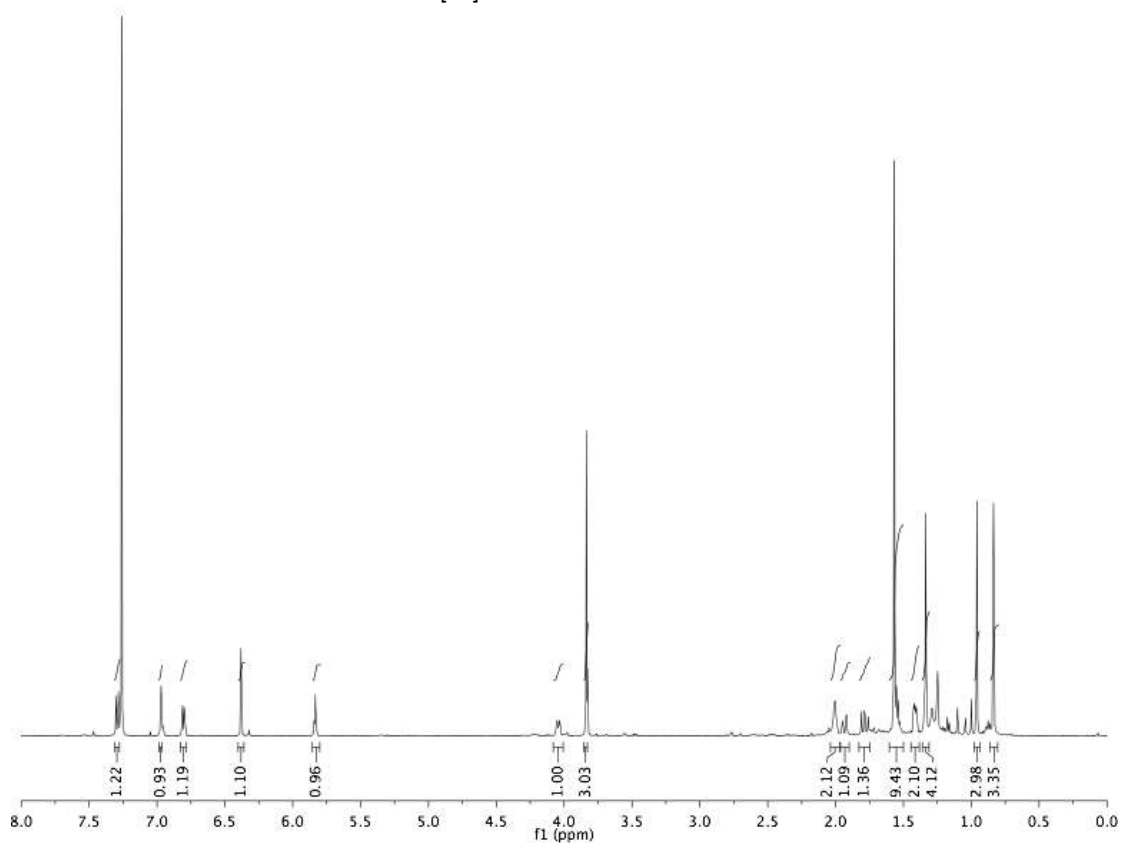
[²H]-10: diastereomer 1

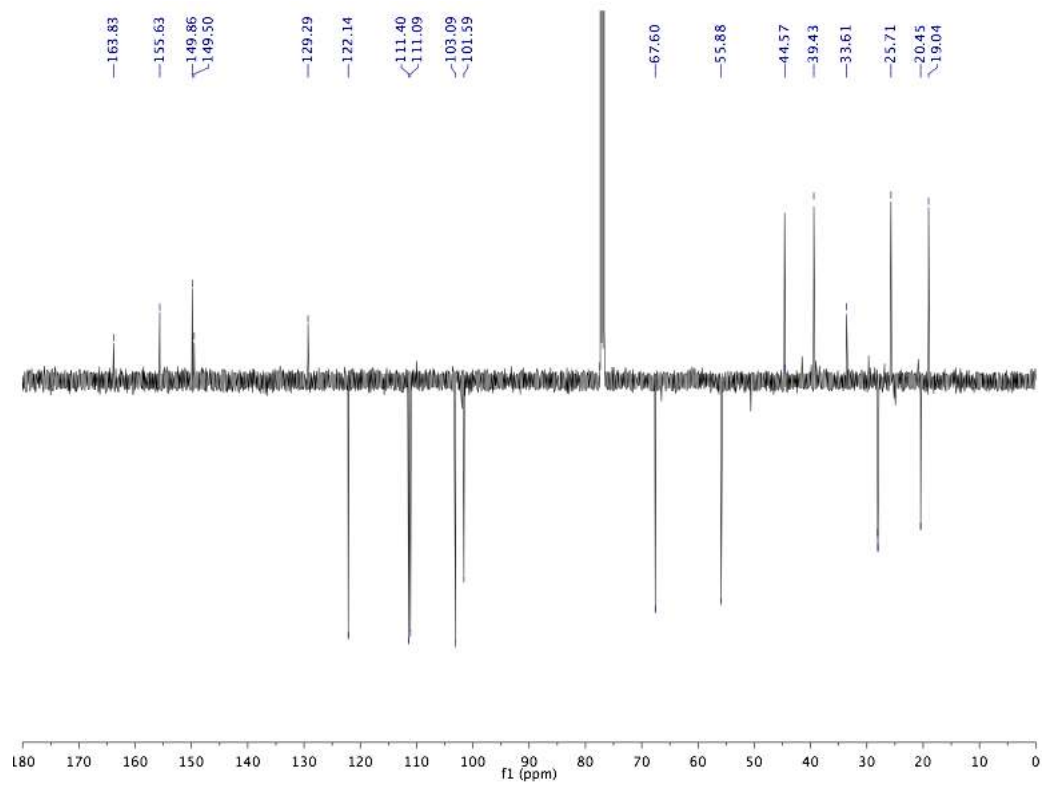


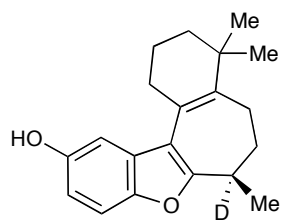




[²H]-10: diastereomer 2







[²H]-1

