Catalyst Repurposing Sequential Catalysis by Harnessing Regenerated Prolinamide Organocatalysts as Transfer Hydrogenation Ligands

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1 General Information

All chemicals were reagent grade and used without further purification. Unless otherwise stated all reactions were carried out in oven dried glassware and under an atmosphere of argon. Solvents used for extraction and chromatography were HPLC grade. Cyclohexane was technical grade and distilled prior to use. Column chromatography was carried out on Silicycle SiliaFlash P60 (230-400 mesh) and analytical thin layer chromatography on pre-coated Merck silica gel 60 F254 plates (0.25 mm), visualized with UV (254 nm) or potassium permanganate stain. Preparative thin-layer chromatography was carried out on pre-coated Merck silica gel 60 F254 plates. Extracts were dried over Na_2SO_4 and products dried at $4*10^{-1}$ mbar and room temperature. Enantiomeric excess was determined by HPLC on a Chiralcel AD-H column. Gas chromatography (GC) for conversion determination was carried out with a Thermo Fisher Scientific Trace 1300 gas chromatograph on an Agilent HP-ULTRA 1 column (25 m, 0.2 mm inner diameter) at 140 °C (isotherm, 5 min) with Helium as carrier gas. NMR spectra were recorded on BrukerAdvance III (500 MHz) and BrukerAvance (400 MHz) spectrometers at 298 K. Chemical shifts (δ) were reported in ppm and the multiplicities in Hz as: s = singlet, br = broad singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Optical rotations were measured at 297 K on a JASCO P-2000 polarimeter with a 100 mm cell (1.00 mL) and concentrations (c) are reported in g/100 mL. Melting points (m.p.) were measured on a Büchi M-565 and are uncorrected. Infrared (IR) spectra were recorded on an ATR Varian Scimitar 800 and are reported in cm^{-1}. The intensities of the bands are reported as w = weak, m = medium and s = strong. High resolution mass spectrometry (HR-ESI) was performed by Sylvie Mittelheisser and Dr. Michael Pfeffer on a Bruker maXis 4G QTOF ESI mass spectrometer. X-ray crystallography was performed by Dr. Alessandro Prescimone on a STOE StadiVari with Dectris Pilatus 300K-detector and Excillum MetalJet D2 Ga-Kα (λ=1.340 Å).

2 Catalyst Preparation

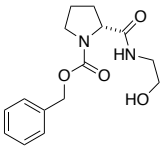
General Procedure A: Synthesis of Catalyst Precursors

Prepared according to modified literature procedure.[1] An oven-dried flask was charged with Cbz-L-proline or Cbz-D-proline (1.00 eq.) and dry CH_2Cl_2 (0.20 mol/L). The solution was cooled to 0 °C in an ice bath and triethylamine (1.00 eq.) and isobutyl chloroformate (1.00 eq.) were added. The mixture was stirred for 0.5 h, the amine (1.00 eq.) was added the mixture warmed to RT and stirred until complete conversion (monitored by TLC, ethyl acetate). The mixture was washed with aq. sat. NH_4Cl, aq. sat. $NaHCO_3$ and brine. Each aqueous layer was reextracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude products were purified as specified.

General Procedure B: Synthesis of Prolineamide Catalysts

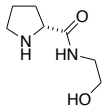
Prepared according to modified literature procedure.[1] Catalyst precursor (1.00 eq.) was dissolved in MeOH (0.40 mol/L), the flask was flushed with argon three times and Pd/C (10.0 wt.%, 5.00 mol%) was added in one portion. The mixture was evacuated and flushed with hydrogen five times. The black suspension was stirred at RT under a hydrogen atmosphere until complete conversion (monitored by TLC, ethyl acetate). The reaction mixture was filtered over a plug of celite and rinsed with methanol.

(R)-2-((2-Hydroxyethyl)carbamoylbenzyl)pyrrolidine-1-carboxylate



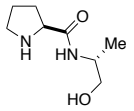
Prepared according to general procedure **A** using Cbz-D-proline (2.49 g, 10.0 mmol, 1.00 eq.), triethylamine (1.41 mL, 10.0 mmol, 1.00 eq.), isobutyl chloroformate (1.30 mL, 10.0 mmol, 1.00 eq.) and ethanolamine (1.21 mL, 10.0 mmol, 1.00 eq.). Recrystallization from hexane/ethanol (10:1, 220 mL) to yield the title compound as a white, crystalline solid (2.08 g, 71%, m.p. = 102 – 104 °C); $[\alpha]_D$ = +39.3 (*c* 1.00, $CHCl_3$); ν_{max} (neat) = 3418m, 3291m, 2954w, 2922w, 2880w, 2361w, 1681s, 1644s, 1543m, 1500w, 1461w, 1426s, 1360s, 1322w, 1278w, 1243w, 1201w, 1169w, 1135m, 1091m, 1028w, 995w, 951w, 922w, 890w, 768w, 735s, 666m, 608m; ^{1}H NMR (500 MHz, dmso-d_6): δ = 7.92 – 7.85 (1H, m, N7*H*), 7.38 – 7.27 (5H, m, Ar*H*), 5.10 – 4.96 (2H, m, C12H_2), 4.62 (1H, t, ^3J 5.3, O*H*), 4.19 – 4.14 (1H, m, C2*H*), 3.50 – 3.28 (4H, m, C5H_2, C9H_2), 3.17 – 3.04 (2H, m, C8H_2), 2.19 – 2.00 (1H, m, C3*H*), 1.89 – 1.71 (3H, m, C3*H*, C4H_2); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.1, 171.9 (*C6*), 154.0, 153.8 (*C11*), 137.0 (*C13*), 128.4, 128.2, 127.8, 127.5, 127.4, 127.0 (*C14*, *C15*, *C16*), 65.8, 65.7 (*C12*), 60.0, 59.8 (*C2*), 59.8, 59.5 (*C9*), 47.1, 46.5 (*C5*), 41.4 (*C8*), 31.3, 30.2 (*C3*), 23.8, 23.1 (*C4*); ESI-MS: m/z $C_{15}H_{20}N_2O_4Na^+$ 315.1315 found 315.1318 [M+Na$^+$].

(R)-N-(2-Hydroxyethyl)pyrrolidine-2-carboxamide ((R)-11)



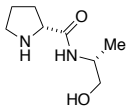
Prepared according to general procedure **B** using (*R*)-2-((2-hydroxyethyl)carbamoyl-benzyl)pyrrolidine-1-carboxylate (2.03 g, 6.94 mmol, 1.00 eq.) and Pd/C (10.0 wt.%, 368 mg, 347 µmol, 5.00 mol%) to yield product (*R*)-**11** as a colorless liquid (1.10 g, quant.); $[\alpha]_D$ = +42.1 (*c* 1.00, $CHCl_3$); ν_{max} (neat) = 3293w, 2943w, 2873w, 2361w, 1643s, 1528s, 1427m, 1360w, 1245w, 1069m, 996w, 873w, 734w, 666w; ^{1}H NMR (500 MHz, $CDCl_3$) = 8.01 (1H, br, N7*H*), 3.77 (1H, dd, ^3J 5.5, 9.1 C2*H*), 3.69 (2H, t, ^3J 5.03, C9*H*), 3.44 – 3.34 (2H, m, C8*H*), 3.07 (2H, br, N1*H*, O10*H*), 3.02 (1H, dt, ^2J 10.2, ^3J 7.0, C5*H*), 2.92 (1H, dt, ^2J 10.2, ^3J 6.4 C5*H*), 2.14 (1H, ddt, ^2J 12.8, ^3J 9.1, 7.4 C3*H*), 1.93 – 1.86 (1H, m, C3*H*), 1.77 – 1.66 (2H, m, C4*H*); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.7 (*C6*), 62.8 (*C9*), 60.6 (*C2*), 47.4 (*C5*), 42.5 (*C8*), 30.8 (*C3*), 26.3 (*C4*); ESI-MS: m/z $C_7H_{14}N_2O_2H^+$ 159.1128 found 159.1130 [M+H$^+$].

(S)-N-((R)-1-Hydroxypropan-2-yl)pyrrolidine-2-carboxamide (37)



Prepared according to general procedures **A** and **B** using Cbz-L-proline (620 mg, 2.50 mmol, 1.00 eq.), triethylamine (350 µL, 2.50 mmol, 1.00 eq.), isobutyl chloroformate (330 µL, 2.50 mmol, 1.00 eq.), (*R*)-(–)-2-amino-1-propanol (200 µL, 2.50 mmol, 1.00 eq.) and Pd/C (10.0 wt.%, 133 mg, 125 µmol, 5.00 mol%). Recrystallization from hexane/ethanol (10:1, 50 mL) yielded the product as a white crystalline solid (384 mg, 89%, m.p. = 135 –136 °C); $[\alpha]_D$ = –26.6 (*c* 1.00, $CHCl_3$); ν_{max} (neat) = 3254m, 3068w, 2974w, 2931w, 2868w, 2789w, 2707w, 2602w, 2537w, 1663s, 1559s, 1454m, 1370w, 1330w, 1238m, 1183w, 1149w, 1111w, 1053s, 989m, 924w, 884m, 856m, 690s; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.71 (1H, br, N7*H*), 3.97 (1H, ddq, ^3J 3.5, 6.9, 14.2, C8*H*), 3.72 (1H, dd, ^3J 5.4, 9.3, C2*H*), 3.63 (1H, dd, ^2J 10.8, ^3J 3.4, C9*H*), 3.50 (1H, dd, ^2J 11.0, ^3J 7.1, C9*H*), 3.01(1H, dt, ^2J 10.3, ^3J 7.0, C5*H*), 2.93 – 2.88 (1H, dt, ^2J 10.3, ^3J 6.6 C5*H*), 2.62 (2H, br, N1*H*, O10*H*), 2.14(1H, ddt, ^2J 12.5, ^3J 9.1, 7.5, C3*H*), 1.94 – 1.88 (1H, m, C3*H*), 1.77 – 1.65 (2H, m, C4*H*), 1.17 (3H, d, ^3J 6.8, C11*H*); 13C NMR (126 MHz, $CDCl_3$): δ = 176.6 (*C6*), 68.2 (*C9*), 60.6 (*C2*), 48.2 (*C8*), 47.4 (*C5*), 31.0 (*C3*), 26.3 (*C4*), 17.0 (*C11*); ESI-MS: m/z $C_8H_{16}N_2O_2H^+$ 173.1285 found 173.1286 [M+H$^+$].

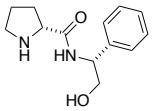
(R)-N-((R)-1-Hydroxypropan-2-yl)pyrrolidine-2-carboxamide (9)



Prepared according to general procedures **A** and **B** using Cbz-D-proline (620 mg, 2.50 mmol, 1.00 eq.), triethylamine (350 µL, 2.50 mmol, 1.00 eq.), isobutyl chloroformate (330 µL, 2.50 mmol, 1.00 eq.), (*R*)-(–)-2-amino-1-propanol (200 µL, 2.50 mmol, 1.00 eq.) and Pd/C (10.0 wt.%, 133 mg, 125 µmol, 5.00 mol%). Recrystallization from hexane/ethanol (15:1, 50 mL) yielded the product as a white crystalline solid (372 mg, 86%, m.p. = 88 – 92 °C); $[\alpha]_D$ = +41.5 (*c* 1.00, $CHCl_3$); ν_{max} (neat)

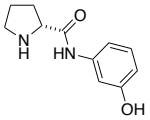
= 3278m, 3073w, 2981w, 2935w, 2877w, 2790w, 2690w, 2586w, 2361w, 1665s, 1555s, 1438m, 1364m, 1236s, 1148w, 1109w, 1047s, 987w, 920w, 885w, 839w, 676s; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.74 (1H, br, N7*H*), 3.98(1H, ddq, ^{3}J 3.4, 6.9, 14.3, C8*H*), 3.75 (1H, dd, ^{3}J 5.4, 9.0, C2*H*), 3.66 (1H, dd, ^{2}J 11.0, ^{3}J 3.4, C9*H*), 3.53 (1H, dd, ^{2}J 11.0, ^{3}J 7.0, C9*H*), 3.02 (1H, dt, ^{2}J 10.3, ^{3}J 6.7, C5*H*), 2.89 (1H, dt, ^{2}J 10.2, ^{3}J 6.3 C5*H*), 2.62 (2H, br, N1*H*, O10*H*), 2.15 (1H, ddt, ^{2}J 12.9, ^{3}J 9.2, 7.5, C3*H*), 1.93 – 1.86 (1H, m, C3*H*), 1.77 – 1.65 (2H, m, C4*H*), 1.17 (3H, d, ^{3}J 7.0, C11*H*); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.5 (*C6*), 68.2 (*C9*), 60.6 (*C2*), 48.2 (*C8*), 47.4 (*C5*), 30.8(*C3*), 26.4 (*C4*), 17.1 (*C11*); ESI-MS: m/z $C_8H_{16}N_2O_2H^+$ 173.1285 found 173.1286 [M+H$^+$].

(R)-N-((R)-1-Hydroxypropan-2-yl)pyrrolidine-2-carboxamide ((R)-38)



Prepared according to general procedures **A** and **B** using Cbz-D-proline (620 mg, 2.50 mmol, 1.00 eq.), triethylamine (350 µL, 2.50 mmol, 1.00 eq.), isobutyl chloroformate (330 µL, 2.50 mmol, 1.00 eq.), (*R*)-(–)-2-phenylglycinol (343 mg, 2.50 mmol, 1.00 eq.) and Pd/C (10.0 wt.%, 133 mg, 125 µmol, 5.00 mol%) yielded the product as a white crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.32 (1H, d, ^{3}J 7.0, N7*H*), 7.38 – 7.35 (2H, m, C13*H*), 7.32 – 7.29 (3H, m, C12*H*, C14*H*), 5.02 – 4.98 (1H, m, C8*H*), 3.89 – 3.81 (3H, m, C2*H*, C9H_2), 3.05 (1H, dt, ^{2}J 10.2, ^{3}J 6.8, C5*H*), 2.97 (1H, dt, ^{2}J 10.2, ^{3}J 6.6, C5*H*), 2.66 (2H, br, N*H*, O*H*), 2.23 – 2.16 (1H, m, C3*H*), 2.02 – 1.96 (1H, m, C3*H*), 1.84 – 1.70 (2H, m, C4*H*); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.1 (*C6*), 139.0 (*C11*), 129.1 (*C13*), 128.1 (*C14*), 126.9 (*C12*), 67.6 (*C9*), 60.7 (*C2*), 56.7 (*C8*), 47.4 (*C5*), 31.1 (*C3*), 26.3 (*C4*). Analytical data is in agreement with literature.[1]

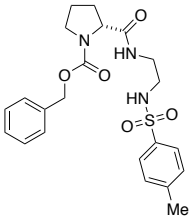
(R)-N-(3-Hydroxyphenyl)pyrrolidine-2-carboxamide (8)



Prepared according to general procedures **A** and **B** using Cbz-D-proline (249 mg, 1.0 mmol, 1.00 eq.), triethylamine (140 µL, 1.00 mmol, 1.00 eq.), isobutyl chloroformate (140 µL, 1.00 mmol, 1.00 eq.), 3-aminophenol (109 mg, 1.00 mmol, 1.00 eq.) and Pd/C (10.0 wt.%, 53.0 mg, 50.0 µmol, 5.00 mol%). Column chromatography (SiO_2 deactivated with NH_4OH, 5% methanol in CH_2Cl_2) yielded the product as a white crystalline solid (159 mg, 77%, m.p. = 113 – 115 °C); $[\alpha]_D$ = +66.1 (*c* 1.00, $CHCl_3$); ν_{max} (neat) = 3360w, 3185w, 2977w, 2873w, 2751w, 1643m, 1605m, 1531s, 1449s, 1282m, 1238m, 1157w, 1100w, 977w, 875m, 769m, 732m, 688m, 617w; ^{1}H NMR (500 MHz, CD_2Cl_2) = 9.82 (1H, s, N7*H*), 8.12 (1H, t, ^{4}J 2.2, C9*H*), 7.07 (1H, t, ^{3}J 8.1, C12*H*), 6.51 (1H, ddd, ^{3}J 8.1, ^{4}J 2.4, 0.9, C11*H*), 6.45 (1H, ddd, ^{3}J 8.0, ^{4}J 2.0, 0.9, C13*H*), 3.81 (1H, dd, ^{3}J 9.3, 5.5, C2*H*), 3.00 (1H, dt, ^{2}J 10.2, ^{3}J 6.6, C5*H*), 2.88 (1H, dt, ^{2}J 10.3, ^{3}J 6.4, C5*H*), 2.18 (1H, ddt, ^{2}J 12.3, ^{3}J 9.3, 7.3, C3*H*), 1.90 (1H, m, C3*H*), 1.67 (2H, m, C4*H*); ^{13}C NMR (126 MHz, CD_2Cl_2): δ = 175.4 (*C6*), 158.6 (*C10*), 138.9 (*C8*), 130.0 (*C12*), 111.8 (*C11*), 110.3 (*C13*), 107.0 (*C9*), 61.3 (*C2*), 47.7 (*C5*), 31.1 (*C3*), 26.9 (*C4*);

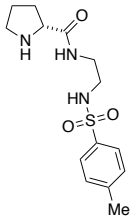
ESI-MS: m/z $C_{11}H_{14}N_2O_4H^+$ 207.1128 found 207.1130 [M+H$^+$]. Analytical data is in agreement with literature.[2]

(R)-2-((2-((4-Methylphenyl)sulfonamido)ethyl)carbamoylbenzyl)pyrrolidine-1-carboxylate



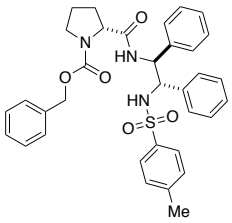
Prepared according to general procedure **A** using Cbz-D-proline (249 mg, 1.00 mmol, 1.00 eq.), triethylamine (141 µL, 10.0 mmol, 1.00 eq.), isobutyl chloroformate (130 µL, 1.00 mmol, 1.00 eq.) and *N*-(2-aminoethyl)-4-methylbenzenesulfonamide (214 mg, 1.00 mmol, 1.00 eq.). The crude product was washed with methanol to yield the product as a white solid (252 mg, 81%, m.p. = 132.5 – 133.2 °C); $[\alpha]_D$ = +40.0 (*c* 0.25, $CHCl_3$); ν_{max} (neat) = 3306w, 3111w, 2981w, 2934w, 2889w, 1670s, 1561w, 1425m, 1330m, 1285w, 1246w, 1160m, 1117m, 943w, 814w, 753m; ^{1}H NMR (500 MHz, dmso-d_6): δ = 7.98 – 7.92 (1H, m, N7*H*), 7.68 – 7.64 (2H, m, C12*H*), 7.63 – 7.55 (1H, m, N10*H*), 7.39 (2H, d, ^3J 7.7, C13*H*), 7.37 – 7.21 (5H, m, C18*H*, C19*H*, C20*H*), 5.09 – 4.92 (2H, m, C17H_2), 4.11 – 4.05 (1H, m, C2*H*), 3.47 – 3.32 (2H, m, C5H_2), 3.12 – 3.06 (2H, m, C8H_2), 2.75 – 2.64 (2H, m, C9H_2), 2.38 (3H, s, C15H_3), 2.11 – 2.00 (1H, m, C3*H*), 1.77 – 1.74 (3H, m, C3*H*, C4H_2); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.7, 172.4 (*C6*), 154.6, 154.3 (*C16*), 143.2 (*C14*), 138.0 (*C11*), 137.4 (*C18*), 130.2 (*C13*), 128.9, 128.6, 128.3, 128.0, 127.9, 127.4, 127.0, 126.9 (*C12*), 66.4, 66.2 (*C17*), 60.7, 60.1 (*C2*), 47.5, 47.0 (*C5*), 42.3 (*C9*), 38.8 (*C8*), 31.6, 30.5 (*C3*), 24.3, 23.5 (*C4*), 21.4 (*C15*); ESI-MS: m/z $C_{22}H_{27}N_3O_5SNa^+$ 468.1564 found 468.1568 [M+Na$^+$].

(R)-N-(2-((4-Methylphenyl)sulfonamido)ethyl)pyrrolidine-2-carboxamide (7)



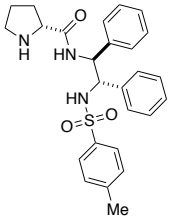
Prepared according to general procedure **B** using (*R*)-2-((2-((4-methylphenyl)sulfonamido)ethyl)carbamoylbenzyl)pyrrolidine-1-carboxylate (100 mg, 220 µmol, 1.00 eq.) and Pd/C (10.0 wt.%, 11.9 mg, 11.2 µmol, 5.00 mol%) in EtOH (10.0 mL) yielded the product as a sticky white solid (70.0 mg, quant.); $[\alpha]_D$ = +23.2 (*c* 0.25, $CHCl_3$); ν_{max} (neat) = 3302w, 2925w, 2871w, 2362w, 1646m, 1524m, 1430w, 1324m, 1155s, 1091m, 814m, 658m; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.94 (1H, br, N7*H*), 7.74 (2H, d, ^3J 8.0, C12*H*), 7.29 (2H, d, ^3J 8.0, C13*H*), 3.72 (1H, dd, ^3J 9.2, 5.1, C2*H*), 3.34 – 3.32 (2H, m, C8H_2), 3.07 (2H, t, ^3J 5.5, C9H_2), 3.00 (1H, dt, ^2J 10.2, ^3J 7.0, C5*H*), 2.89 (1H, dt, ^2J 10.2, ^3J 6.3, C5*H*), 2.41 (3H, s, C15H_3), 2.16 – 2.08 (1H, m, C3*H*), 1.88 – 1.82 (1H, m, C3*H*), 1.72 – 1.66 (2H, m, C4H_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.6 (*C6*), 143.3 (*C14*), 137.1 (*C11*), 129.7 (*C13*), 127.1 (*C12*), 60.4 (*C2*), 47.2 (*C5*), 43.7 (*C9*), 38.8 (*C8*), 30.7 (*C3*), 26.15 (*C4*), 21.5 (*C15*); ESI-MS: m/z $C_{14}H_{21}N_3O_3SH^+$ 312.1376 found 312.1379 [M+H$^+$]. Analytical data is in agreement with literature.[3]

(R)-2-(((1S,2S)-2-((4-Methylphenyl)sulfonamidobenzyl)-1,2-diphenylethyl)carbamoyl)pyrrolidine-1-carboxylate



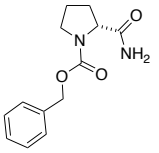
Prepared according to general procedure **A** using Cbz-D-proline (113 mg, 453 µmol, 1.00 eq.), triethylamine (63.7 µL, 453 µmol, 1.00 eq.), isobutyl chloroformate (58.9 µL, 453 µmol, 1.00 eq.) and (1*R*,2*S*)-1,2-diphenyl-3-tosylpropan-1-amine (166 mg, 453 µmol, 1.00 eq.). Recrystallization from hexane/ethanol yielded the title compound as a white solid (204 mg, 77%, m.p. = 160.3 – 164.6 °C); $[\alpha]_D$ = +19.7 (*c* 0.50, $CHCl_3$); ν_{max} (neat) = 3304w, 2953w, 2882w, 2363w, 1699m, 1650m, 1517w, 1454w, 1407m, 1328m, 1157s, 1088m, 919w, 810w, 774w, 698s, 669m, 620w; ^{1}H NMR (500 MHz, dmso-d_6): δ = 8.37 (1H, d, ^3J 9.5, N10*H*), 8.04 (1H, m, N7*H*), 7.44 – 7.00 (19H, m, Ar*H*), 5.29 – 5.18 (1H, m, C8*H*), 5.14, 4.85 (2H, d, ^2J 11.7, C25*H*), 4.86 – 4.73 (1H, m, C9*H*), 4.09 (1H, m, C2H), 3.57 – 3.46 (1H, m, C5*H*), 3.43 – 3.35 (1H, m, C5*H*), 2.25 (3H, s, C15*H*), 1.98 (1H, m, C3*H*), 1.78 – 1.51 (2H, m, C4H_2), 1.50 – 1.35 (1H, m, C3*H*); ^{13}C NMR (126 MHz, dmso-d_6): δ = 170.8, 170.6 (*C6*), 154.1, 153.8 (*C24*), 141.2, 141.0, 139.0, 138.6, 138.2, 137.8, 136.4, 136.0, 128.4, 128.2, 127.8, 127.6, 127.2, 127.0, 126. 8, 126.7, 126.6, 126.4, 126.3, 126.0, 125.4, 125.3, 65.6 (*C25*), 60.6, 60.5 (*C9*), 60.2, 59.8 (*C2*), 56.4 (*C8*), 46.6, 46.1 (*C5*), 30.2, 29.0 (*C3*), 23.0, 22.1 (*C4*), 20.2 (*C15*); ESI-MS: m/z $C_{34}H_{35}N_3O_5SNa^+$ 620.2190 found 620.2194 [M+Na^+].

(R)-N-((1S,2S)-2-((4-Methylphenyl)sulfonamido)-1,2-diphenylethyl)pyrrolidine-2-carboxamide (3)



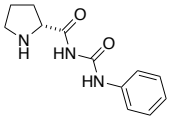
Prepared according to general procedure **B** using (*R*)-2-(((1*S*,2*S*)-2-((4-methylphenyl) sulfonamidobenzyl)-1,2-diphenylethyl)carbamoyl)pyrrolidine-1-carboxylate (100 mg, 171 µmol, 1.00 eq.) and Pd/C (10.0 wt.%, 9.10 mg, 8.55 µmol, 5.00 mol%) in EtOH (10.0 mL) yielded the product as a white solid (50.3 mg, 65%, m.p. = 136.8 – 139.1 °C); $[\alpha]_D$ = –8.10 (*c* 0.5, $CHCl_3$); ν_{max} (neat) = 3288w, 2962w, 2362m, 1647m, 1498m, 1455w, 1324m, 1155s, 1089m, 926w, 810w, 698s, 667m; ^{1}H NMR (500 MHz, $CDCl_3$) = 6.89 (1H, N7*H*), 7.45 – 6.78 (15H, m, Ar*H*, N9*H*), 5.12 (1H, m, C8*H*), 4.68 (1H, d, ^3J 9.7, C9*H*), 3.86 (1H, m, C2*H*), 3.09 (2H, t, ^3J 6.1, C5*H*), 2.30 – 2.19 (1H, m, C3*H*), 2.26 (3H, s, C15*H*), 2.18 – 2.11 (1H, m, C3*H*), 1.99 – 1.91 (1H, m, C4*H*), 1.81 – 1.74 (1H, m, C4*H*); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.7 (*C6*), 142.5, 138.3, 138.0, 129.4, 129.1, 128.7, 128.2, 128.1, 128.0, 127.7, 127.6, 127.3, 127.2, 126.9, 64.5 (*C9*), 60.6 (*C2*), 58.4 (*C8*), 47.5 (*C5*), 31.0 (*C3*), 26.4 (*C4*), 21.5 (*C15*); ESI-MS: m/z $C_{26}H_{29}N_3O_3SH^+$ 464.2002 found 464.2005 [M+H^+]. Analytical data is in agreement with literature.[4]

Benzyl (R)-2-carbamoylpyrrolidine-1-carboxylate



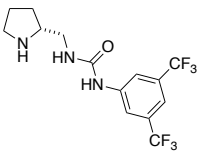
To a solution of Cbz-D-proline (3.99 g, 16.0 mmol, 1.00 eq.) in THF (80 mL) were added 1-hydroxybenzotriazole hydrate (3.24 g, 24.0 mmol, 1.50 eq.) and EDC hydrochloride (3.07 g, 16.0 mmol, 1.00 eq.). The mixture was stirred at room temperature for 30 minutes whereupon aqueous ammonia (32%, 11 mL) was slowly added by syringe. The reaction mixture was stirred for an additional 24h. Sat. aq. ammonium chloride (100 mL) was added and the aqueous layer extracted with ethyl acetate. The combined organic layers were dried, filteres and evaporated. The residue was purified by column chromatography (25:1, ethyl acetate:pentane) to yield the desired product (3.15 g, 79%) as a white crystalline solid. Analytical data is in agreement with literature.[5]

(R)-N-(Phenylcarbamoyl)pyrrolidine-2-carboxamide (48)



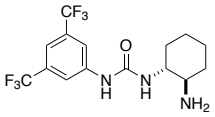
Prepared according to literature procedure.[6] To a suspension of Cbz-prolineamide (497 mg, 2.00 mmol, 1.00 eq.) in toluene (4.0 mL) was added phenyl isocyanate (238 mg, 219 µL, 2.00 mmol, 1.00 eq.). The mixture was heated to 110 °C in an oil bath and stirred for 40 h. The solvent was evaporated and the residue purified by column chromatography (4:1, cyclohexane:ethyl acetate) to obtain the intermediate (512 mg, 70%) as a white crystalline solid. The obtained intermediate (300 mg, 817 µmol, 1.00 eq.) was dissolved in MeOH (5 mL). The flask was flushed with argon before Pd/C (10.0 wt.%, 43.5 mg, 40.9 µmol, 5.00 mol%) was added in one portion. The mixture was evacuated and flushed with hydrogen (4x). The suspension was stirred under a hydrogen atmosphere for 17h. The reaction mixture was filtered through a plug of celite and washed with methanol. The filtrate was concentrated under reduced pressure to obtain the desired product (178 mg, 93%) as a yellow sticky solid. Analytical data is in agreement with literature.[6]

(R)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(pyrrolidin-2-ylmethyl)urea (49)



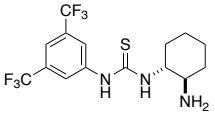
Prepared according to literature procedure.[7] To a solution of (*R*)-1-Boc-2-(aminomethyl)pyrrolidine (200 mg, 1.00 mmol, 1.00 eq.) in dry DCM (7 mL) was added 3,5-bis(trifluoromethyl)phenyl isocyanate (260 mg, 1.00 mmol, 1.00 eq). The reaction mixture was stirred for 12 h at 25°C. Excess of solvent was removed and the crude product redissolved in a TFA/DCM mixture (6 mL, 1:5). The solution was stirred at 25°C for 2 h and the solvent removed under reduced pressure. The pH was adjusted to 8 using aq. sat. $NaHCO_3$ to afford a white precipitate which was collected and washed with H_2O. The product was dried to afford the desired product (342 mg, 96%) as an off-white solid. Analytical data is in agreement with literature.[7]

1-((1*R*,2*R*)-2-Aminocyclohexyl)-3-(3,5-bis(trifluoromethyl)phenyl)urea (51)



Prepared according to literature procedure.[8] To a solution of (1*R*,2*R*)-(+)-1,2-cyclohexanediamine L-tartrate (793 mg, 3.00 mmol, 3.00 eq.) in CH_2Cl_2 was added an aqueous solution of sodium hydroxide (4M). The biphasic mixture was stirred at 25 °C for 15 minutes. The phases were separated and the aqueous layer washed with CH_2Cl_2 (3x 2 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C in an ice bath. A solution of 3,5-bis(trifluoromethyl)isocyanate) (255 mg, 1.00 mmol, 1.00 eq.) in CH_2Cl_2 (1 mL) was added dropwise and the solution stirred at 25 °C for 3 h. The solvent was removed and the residue purified by column chromatography (CH_2Cl_2/MeOH/NH_3, 95:5:1 → 90:10:1) yielding the desired product (101 mg, 273 µmol, 27%) as an off-white solid. R_f = 0.20 (CH_2Cl_2/MeOH/NH_3, 90:10:1). Analytical data is in agreement with literature.[8]

1-((1*R*,2*R*)-2-Aminocyclohexyl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (52)

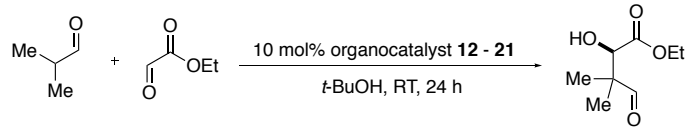


Prepared according to literature procedure.[8] To a solution of (1*R*,2*R*)-(+)-1,2-cyclohexanediamine L-tartrate (793 mg, 3.00 mmol, 3.00 eq.) in CH_2Cl_2 was added an aqueous solution of sodium hydroxide (4M). The biphasic mixture was stirred at 25 °C for 15 minutes. The phases were separated and the aqueous layer washed with CH_2Cl_2 (3x 2 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C in an ice bath. A solution of 3,5-bis(trifluoromethyl)isothiocyanate) (271 mg, 1.00 mmol, 1.00 eq.) in CH_2Cl_2 (1 mL) was added dropwise and the solution stirred at 25 °C for 3 h. The solvent was removed and the residue purified by column chromatography (CH_2Cl_2/MeOH/NH_3, 95:5:1 → 90:10:1) yielding the desired product (193 mg, 501 µmol, 50%) as an off-white solid. R_f = 0.27 (CH_2Cl_2/MeOH/NH_3, 90:10:1). Analytical data is in agreement with literature.[8]

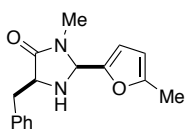
3 Development of the Aldol Addition Step

Effect of Organocatalysts in the Asymmetric Aldol Addition

To a vial containing the organocatalyst (0.01 mmol, 10.0 mol%) 0.20 mL of a stock solution of isobutanal (91.0 µL, 1.00 mmol) and ethyl glyoxalate (50.0 wt.% in toluene, 198 µL, 1.00 mmol) in *t*-BuOH (2.00 mL) was added. The mixtures were stirred at RT for 24 h. The results are summarized in the following tables.



(*R*)-**2a**



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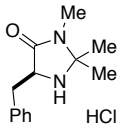
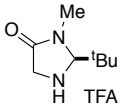


13



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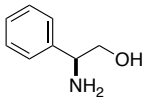

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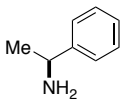

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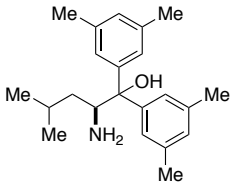

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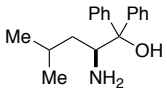

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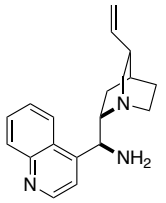

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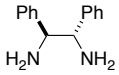

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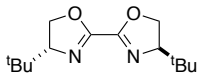
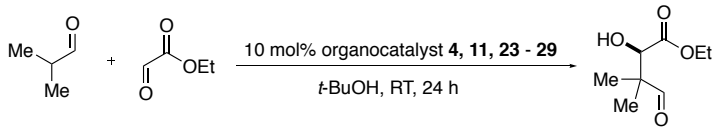


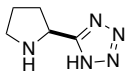
21

Entry	Catalyst	Conversion[a]	Enantiomeric ratio (*R*):(*S*)
1	**12**	0%	n/a
2	**13**	0%	n/a
3	**14**	75%	59:41
4	**15**	1%	n/a
5	**16**	>99%	76:24
6	**17**	>99%	70:30
7	**18**	0%	n/a
8	**19**	0%	n/a
9	**20**	3%	49:51
10	**21**	4%	11:89

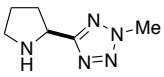
[a] Conversions were determined by NMR spectroscopy of the crude reaction mixture based on consumed starting material.



(*R*)-**2a**



(*S*)-**4**



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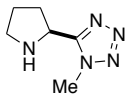

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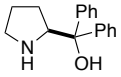

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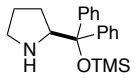

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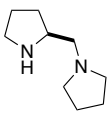

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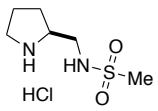

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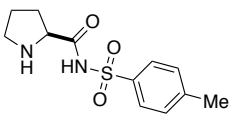

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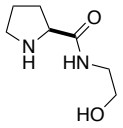
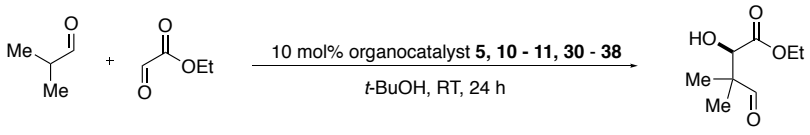


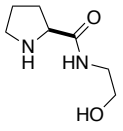
(*S*)-**11**

Entry	Catalyst	Conversion[a]	Enantiomeric ratio (*R*):(*S*)
1	**(*S*)-4**	88%	12:88
2	**22**	77%	66:34
3	**23**	39%	56:44
4	**24**	0%	n/a
5	**25**	0%	n/a
6	**26**	21%	33:67
7	**27**	0%	n/a
8	**28**	0%	n/a
9	**(*S*)-11**	>99%	13:87

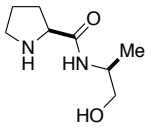
[a] Conversions were determined by NMR spectroscopy of the crude reaction mixture based on consumed starting material.



(*R*)-**2a**



(*S*)-**11**



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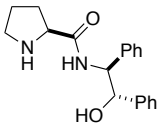

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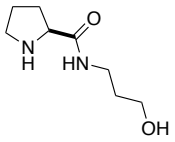

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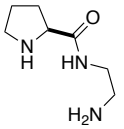

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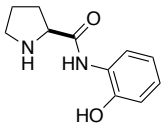

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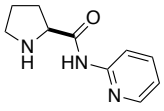

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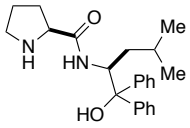

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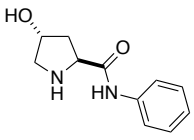

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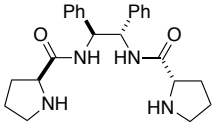

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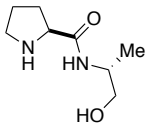

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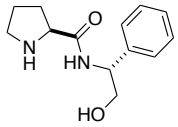
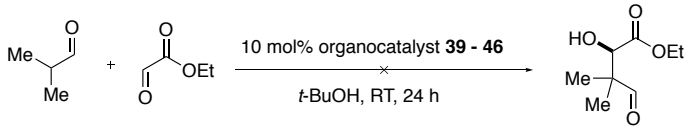


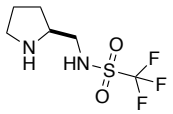
38

Entry	Catalyst	Conversion[a]	Enantiomeric ratio (*R*):(*S*)
1	**(*S*)-11**	>99%	13:87
2	**30**	>99%	15:85
3	**31**	90%	21:79
4	**32**	94%	18:82
5	**33**	>99%	45:55
6	**34**	5%	n/a
7	**35**	1%	n/a
8	**5**	93%	75:25
9	**10**	54%	19:81
10	**36**	88%	55:45
11	**37**	>99%	28:72
12	**38**	40%	21:79

[a] Conversions were determined by NMR spectroscopy of the crude reaction mixture based on consumed starting material.



(*R*)-**2a**



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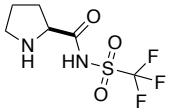

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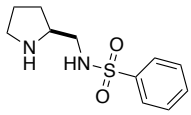

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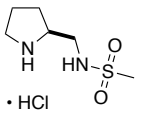

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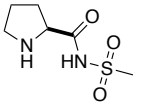

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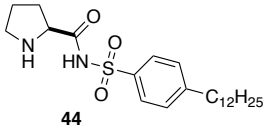

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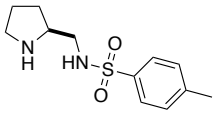

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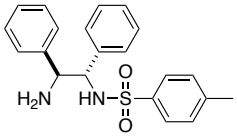

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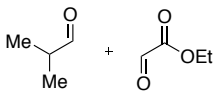
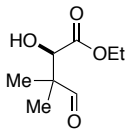
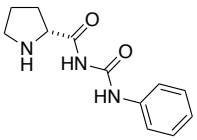


10 mol% organocatalyst **47** - **56**

t-BuOH, RT, 24 h



(*R*)-**2a**



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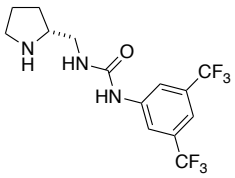

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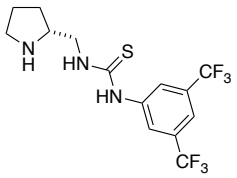

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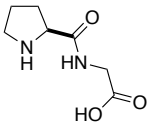

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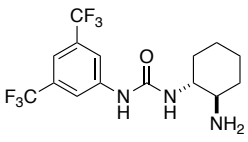

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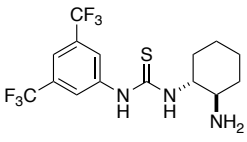

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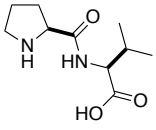

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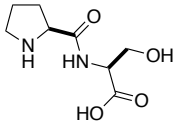

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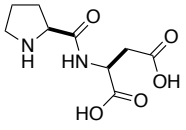

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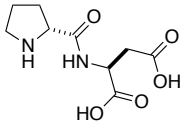


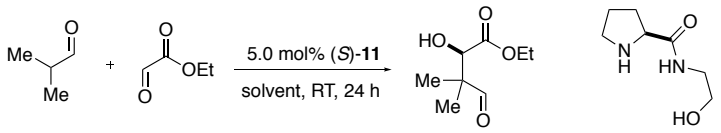
56

Entry	Catalyst	Conversion[a]	Enantiomeric ratio (*R*):(*S*)
1	**47**	5%	n/a
2	**48**	21%[b]	n/a
3	**49**	48%[b]	40:60
4	**50**	>99%	27:73
5	**51**	>99%	75:25
6	**52**	>99%	55:45
7	**53**	19%	45:55
8	**54**	18%	46:54
9	**55**	81%	44:56
10	**56**	10%	65:35

[a] Conversions were determined by NMR spectroscopy of the crude reaction mixture based on consumed starting material [b] Conversion after 48h.

Effect of isopropanol

In preparation for a possible combination of aldol addition and Noyori-type transfer hydrogenation, solvent mixtures of *t*-BuOH with *i*-PrOH were tested on their applicability for the direct asymmetric aldol addition.



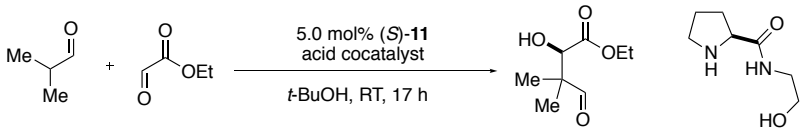
(*R*)-**2a** (*S*)-**11**

Entry	Solvent mixture *t*-BuOH/*i*-PrOH	Conversion[a]	Enantiomeric ratio (*R*):(*S*)
1	*t*-BuOH	89%	13:87
2	9/1	84%	13:87
3	5/1	70%	13:87
4	2/1	74%	13:87
5	1/1	67%	13:87
6	1/2	68%	14:86
7	1/5	63%	14:86
8	1/9	59%	14:86
9	*i*-PrOH	56%	15:85

[a] Conversions were determined by NMR spectroscopy of the crude reaction mixture based on consumed starting material.

Effect of Acid Cocatalysts

To a vial containing (*S*)-*N*-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*S*)-**11**, 1.58 mg, 10.0 µmol, 10.0 mol%) a stock solution (0.20 mL) of isobutanal (91.0 µL, 1.00 mmol), ethyl glyoxalate (50.0 wt.% in toluene, 198 µL, 1.00 mmol) in *t*-BuOH (2.00 mL) and acid (0.10 – 1.00 mmol) was added. The reaction mixture was stirred at RT for 17 h.



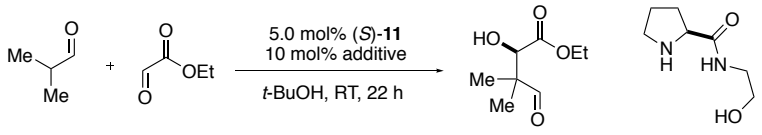
(*R*)-**2a** (*S*)-**11**

Entry	Acid Cocatalyst	Cocatalyst Loading	Conversion[a]	Enantiomeric ratio (*R*):(*S*)
1	TFA	10 mol%	>99%	13:87
2	TFA	50 mol%	84%	13:87
3	TFA	100 mol%	67%	14:86
4	Formic acid	10 mol%	50%	13:87
5	Formic acid	50 mol%	69%	13:87
6	Formic acid	100 mol%	80%	15:85
7	Benzoic acid	10 mol%	51%	13:87
8	Benzoic acid	50 mol%	60%	13:87
9	Benzoic acid	100 mol%	72%	15:85
10	Acetic acid	10 mol%	52%	14:86
11	Acetic acid	50 mol%	44%	13:87
12	Acetic acid	100 mol%	52%	13:87

[a] Conversions were determined by NMR spectroscopy of the crude reaction mixture based on consumed starting material.

Effect of Additives

To a vial containing (*S*)-*N*-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*S*)-**11**, 790 µg, 50.0 µmol, 5.00 mol%) a stock solution (0.20 mL) of isobutanal (91.0 µL, 1.00 mmol), ethyl glyoxalate (50.0 wt.% in toluene, 198 µL, 1.00 mmol) in *t*-BuOH (2.00 mL) was added. Subsequently additives (10.0 µmol, 0.10 eq.) was added. The reaction mixture was stirred at RT for 24 h.



(*R*)-**2a** (*S*)-**11**

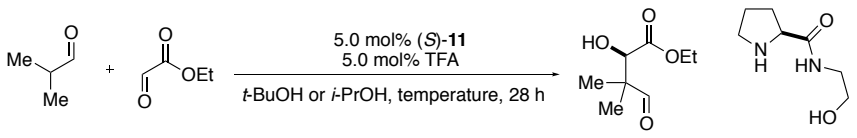
Entry	Additive	Conversion[a]	Enantiomeric ratio (*R*):(*S*)
1	$MgCl_2$	34%	31:69
2	KCl	>99%	13:87
3	Ag(OAc)	16%	n/a
4	$FeCl_3$	0%	n/a
5	$AlCl_3$	20%	n/a

Entry	Base cocatalyst	Converison[a]	Enantiomeric ratio (*R*):(*S*)
1	Et_3N	21%	50:50
2	NMM	5%	22:78
3	pyridine	81%	15:85
4	piperidine	14%	41:59
5	2,6-lutidine	36%	16:84
6	urea	8%	16:84
7	aq. KOH	5%	n/a

[a] Conversions were determined by NMR spectroscopy of the crude reaction mixture based on consumed starting material.

Effect of Reaction Temperature

To a solution of (*S*)-*N*-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*S*)-**11**, 3.96 mg, 25 µmol, 5.00 mol%) in *t*-BuOH or *i*-PrOH (0.50 mL), isobutanal (46.0 µL, 50.0 µmol, 1.00 eq.), ethyl glyoxalate (50.0 wt.% in toluene, 99.0 µL, 50.0 µmol, 1.00 eq.) and TFA (1.85 µL, 25.0 µmol, 0.05 eq.) were added. The mixture was stirred at various temperatures for 24 h.



(*R*)-**2a** (*S*)-**11**

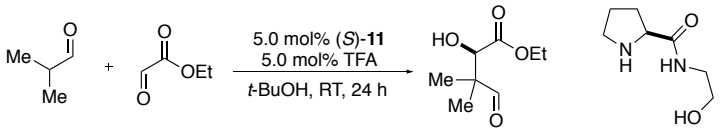
Entry	Solvent	Temperature	Conversion[a]	Enantiomeric ratio (*R*):(*S*)
1	*t*-BuOH	40 °C	89%	15:85
2	*t*-BuOH	RT	86%	14:86
3	*i*-PrOH	40 °C	58%	16:84
4	*i*-PrOH	RT	42%	15:85
5	*i*-PrOH	4 °C	19%	14:86
6	*i*-PrOH	–20 °C	0%	n/a

[a] Conversions were determined by NMR spectroscopy of the crude reaction mixture based on consumed starting material.

Influence of Substrate Ratios

To a solution of (*S*)-*N*-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*S*)-**11**, 791 µg, 5.00 µmol, 5.00 mol%) in *t*-BuOH (0.10 mL), isobutanal (11.0 – 46.0 µL, 12.0 – 50.0 µmol, 1.20 – 5.00 eq. with reference to ethyl glyoxalate, ethyl glyoxalate (50.0 wt.% in toluene, 19.8 µL, 100 µmol, 1.00 eq.) and TFA (0.37 µL, 5.00 µmol, 0.05 eq.) were added. The mixture was stirred at RT for 24 h.

To a solution of (*S*)-*N*-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*S*)-**11**, 3.96 mg, 25.0 µmol, 5.00 mol%) in *t*-BuOH (0.50 mL), isobutanal (46.0 µL, 50.0 µmol, 1.00 eq.), ethyl glyoxalate (50.0 wt.% in toluene, 119 – 496 µL, 60.0 – 250 µmol, 1.20 – 5.00 eq. with reference to isobutanal and TFA (1.85 µL, 25.0 µmol, 0.05 eq.) were added. The mixture was stirred at RT for 24 h.

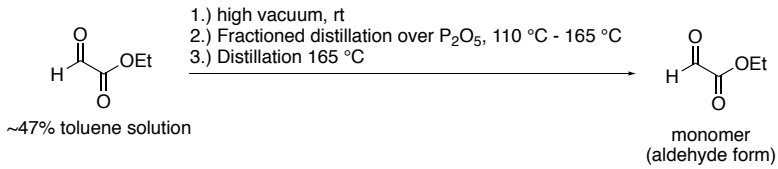


1.0 - 5.0 eq. 1.0 - 5.0 eq.

(*R*)-**2a** (*S*)-**11**

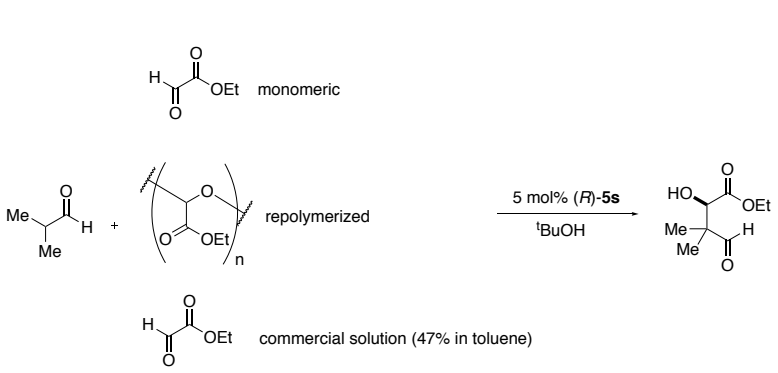
Entry	Isobutanal (3)	Ethyl glyoxalate (4)	Enantiomeric ratio (*R*):(*S*)
1	1.2 eq.	1.0 eq.	20:80
2	2.0 eq.	1.0 eq.	32:68
3	5.0 eq.	1.0 eq.	46:54
4	5.0 eq.[b]	1.0 eq.	16:84
5	1.0 eq.	1.2 eq.	14:86
6	1.0 eq.	2.0 eq.	14:86
7	1.0 eq.	5.0 eq.	17:83
8	1.0 eq.	5.0 eq.[c]	14:86

Cracking and purification of ethyl glyoxalate

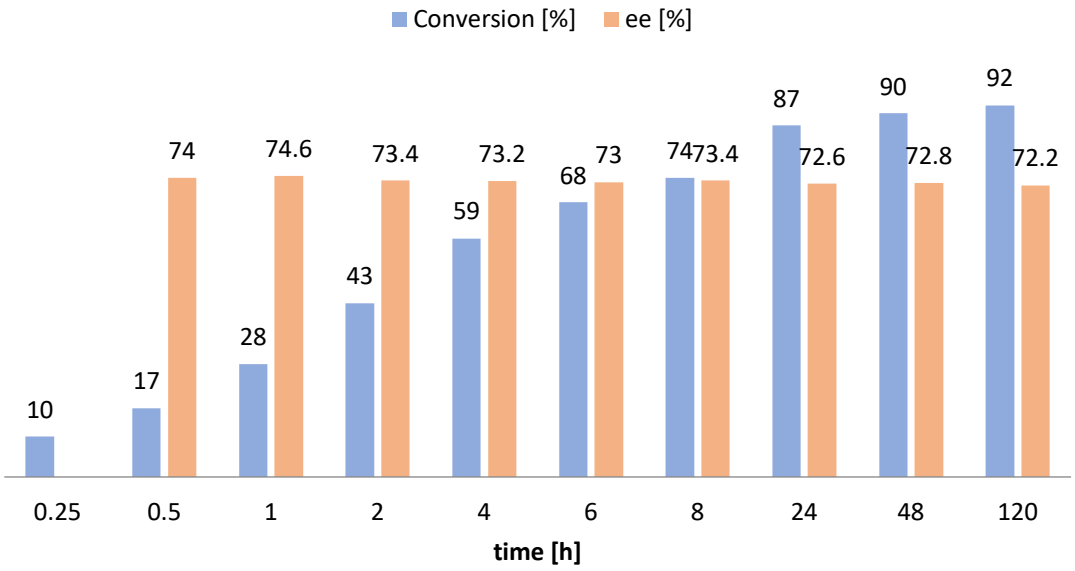


A commercial solution of ethyl glyoxalate (~47% in toluene) was transferred into an oven-dried flask, placed into a water bath (25 °C) and attached to a cold trap (– 196 °C). The solution was concentrated under vacuum until about half of the volume was removed. Phosphorus pentoxide was added to the remaining highly viscous colorless liquid. After a fractioned distillation ranging from 110 °C – 165 °C the desired product was again subjected to distillation over phosphorus pentoxide at 165 °C. The monomeric ethyl glyoxalate was collected in a Schlenk flask as a pale yellow low-viscosity liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.40 (1H, s, C1*H*), 4.39 (2H, q, ^{3}J 7.2, C3H_2), 1.40 (3H, t, ^{3}J 7.2, C4H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 184.1 (*C1*), 159.6 (*C2*), 62.9 (*C3*), 14.0 (*C4*).

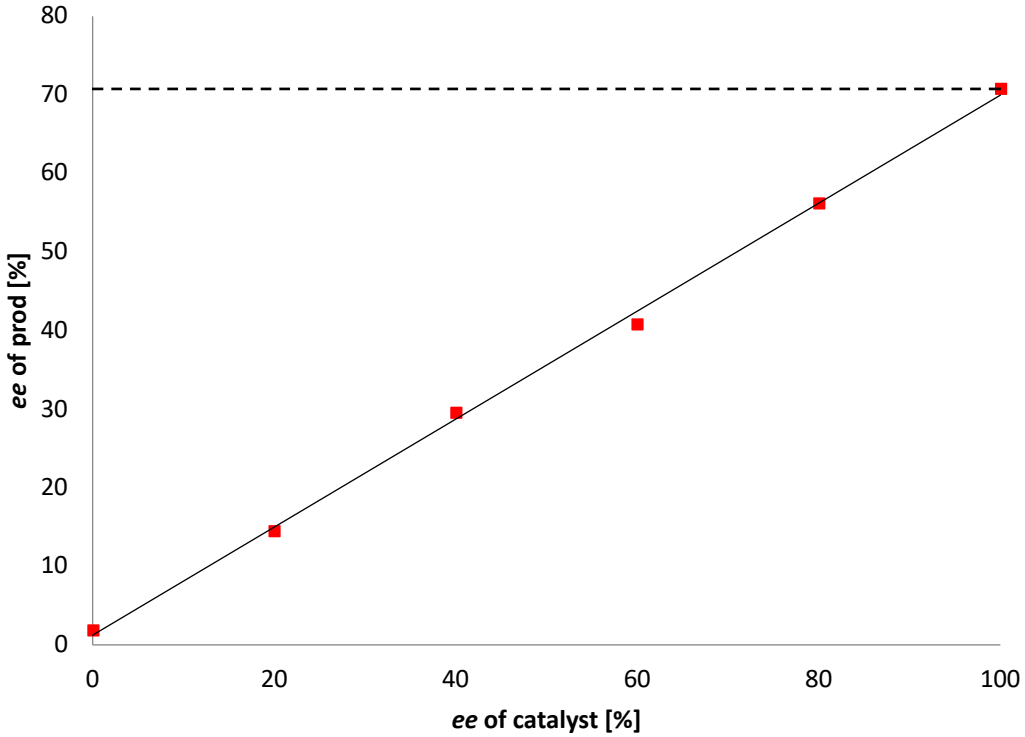
After 1 week of storage at – 18 °C an equilibrium between monomeric and polymerized form was reached. The different forms of ethyl glyoxalate (solution, monomeric, repolymerized) were compared in reactivity and selectivity.



Reaction Monitoring of Organocatalytic Aldol Addition



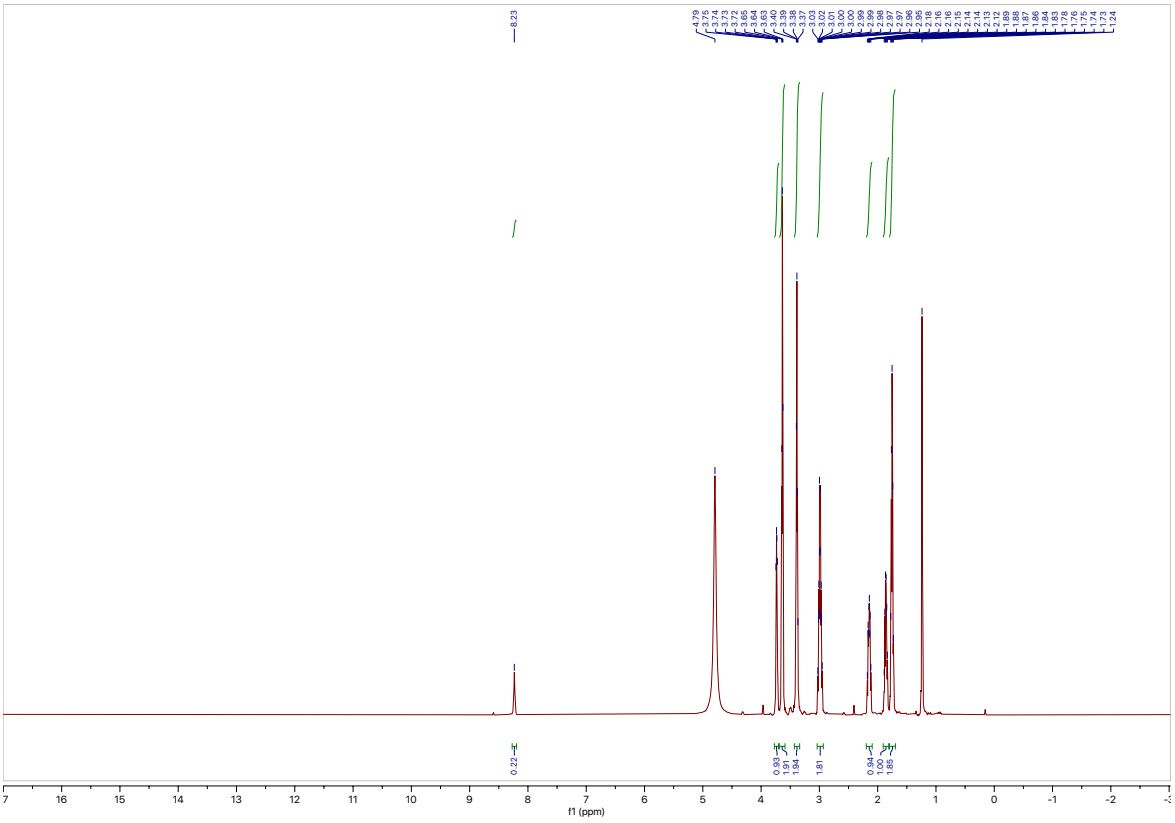
Investigation of Non-Linear Effect for the Asymmetric Aldol Addition



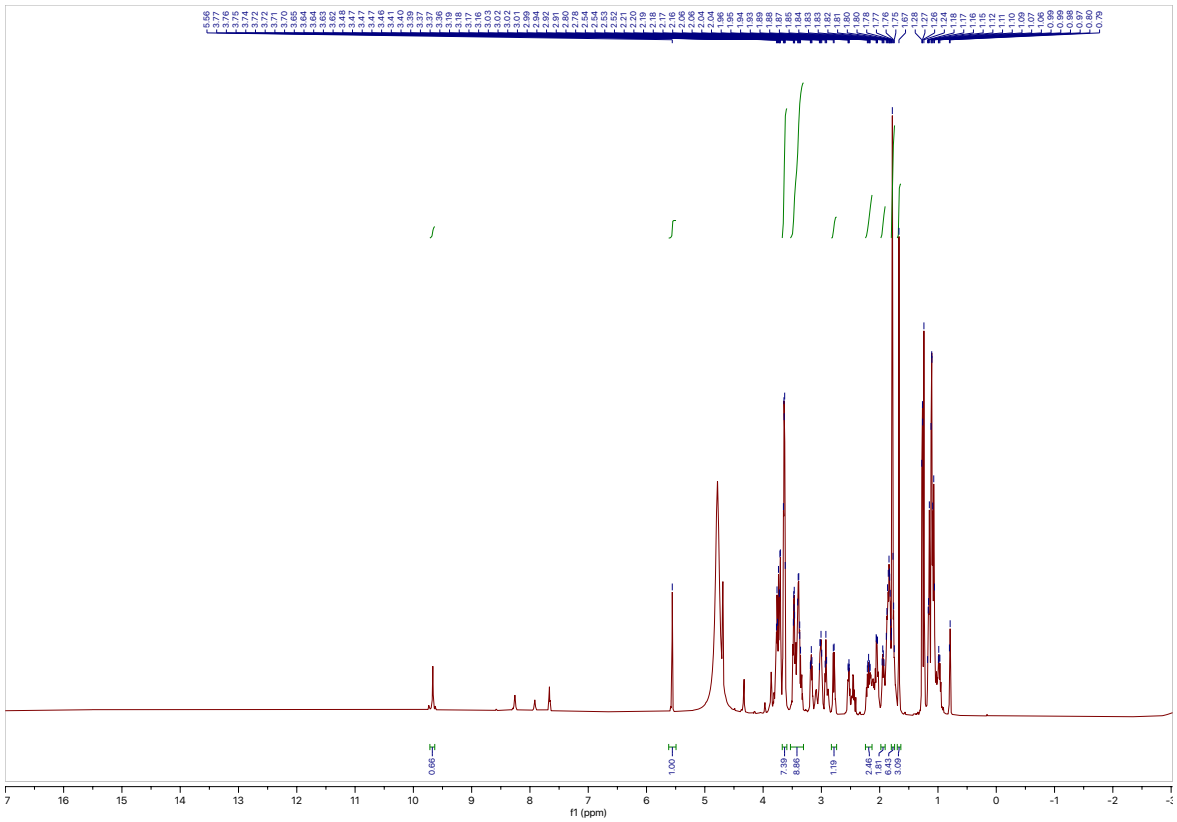
NMR Study of Enamine Formation with Isobutanal and Catalyst (*R*)-11

To a solution of (*R*)-*N*-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 15.8 mg, 100 µmol, 1.00 eq.) in *tert*-butanol-d10 (0.20 mL) was added isobutanal (7.21 mg, 9.10 µL, 1.00 mmol, 1.00 eq.). The obtained compound mixture was immediately analyzed by NMR spectroscopy. No further change was observed only minutes after addition of the aldehyde (aldehyde form: enamine form, 40:60). The major compound could be assigned to the enamine form and complete assignment was accomplished by 2D NMR spectroscopy (HMBC, HMQC, NOESY).

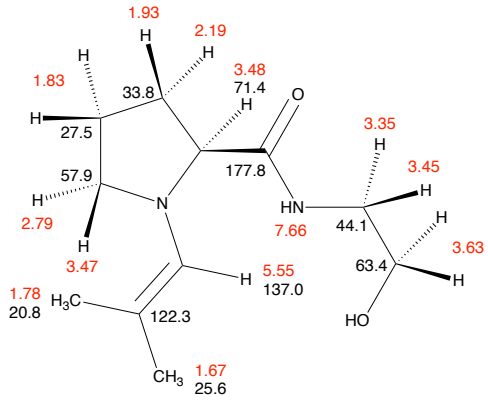
NMR spectra of catalyst (*R*)-**11** in *tert*-butanol-d10



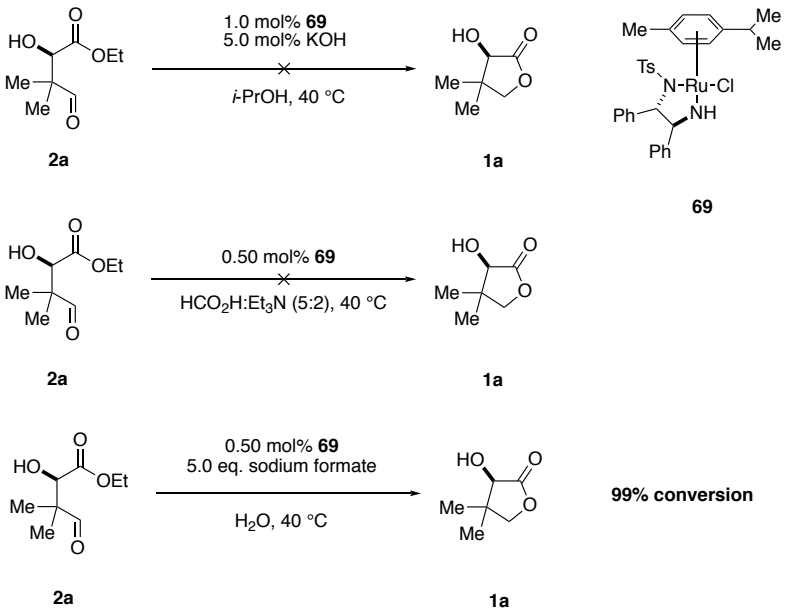
^{1}H-NMR of reaction mixture



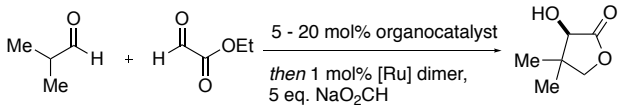
Assignment of the enamine species in *tert*-butanol-d10



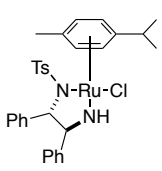
4 Development of the Transfer Hydrogenation Step



5 Combination for Catalyst-Repurposing Sequential Catalysis



1a



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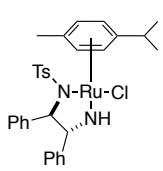

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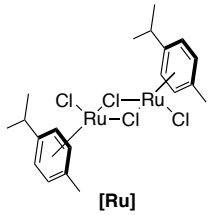
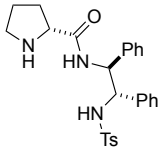


[Ru]



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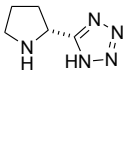
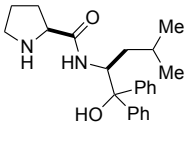


(*R*)-**4**



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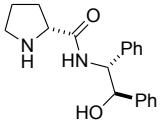

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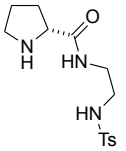

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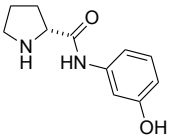

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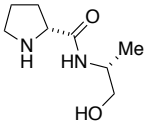

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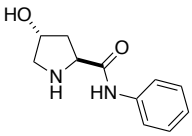

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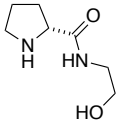


(*R*)-**11**

Entry	Catalyst	precursor loading [mol%]	t [h]	Conversion[a]	Enantiomeric ratio (*R*):(*S*)
1	**11/66**	1	1	99	-
2	**11/67**	1	1	99	-
3	**[Ru]**	2.5	24	9	-
4	**3**	2.5	<18	99	82:18
5	(*R*)-**4**	2.5	-	-	-
6	**5**	2.5	-	-	-
7	**6**	2.5	<18	99	79:21
8	**7**	2.5	<18	99	85:15

9	**8**	2.5	<18	99	84:16
10	**9**	1	18	99	85:15
11	**10**	1	2	99	19:81
12	(*R*)-**11**	1	4	99	86:14

[a] Conversions were determined by GC based on consumed starting material and formed product.

Control Experiment: Preparation of (*R*)-pantolactone with pre-formed catalyst 12

To a solution of ethyl (*R*)-2-hydroxy-3,3-dimethyl-4-oxobutanoate **2a** (174 mg, 1.00 mmol, 1.00 eq.) in degassed water was added sodium formate (340 mg, 5.00 mmol, 5.00 eq.) and Ir-complex **12** (520 µg, 1.00 µmol, 0.10 mol%). The mixture was heated to 40 °C in an oil bath and stirred for 18 h. After addition of aq. HCl (1 mol/L, 2 mL) the mixture was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 2:1) yielding the desired product (**1a**, 112.3 mg, 86%) as a white solid.

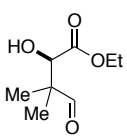
General Procedure C: Synthesis of Aldehyde Intermediates

To a solution of catalyst (*R*)-**11** (5.0 – 20 mol%) in ^{t}BuOH were added aldehyde (1.00 eq.) and glyoxalate (1.00 eq.). The mixture was stirred at 25°C for the indicated time. The solvent was removed *in vacuo* and the residue purified by column chromatography.

General Procedure D: Synthesis of α-hydroxy-γ-butyrolactones by CRSC

To a solution of catalyst (*R*)-**11** in ^{t}BuOH at 25°C was added aldehyde (1.00 eq.) and ethyl glyoxalate (47% in toluene, 1.00 eq.). The mixture was stirred at 25°C for the indicated time. Water (5:1, water: ^{t}BuOH) was added and the solution degassed with argon for 1 h, before $(IrCl_2(Cp^*))_2$ (0.10 mol%) and sodium formate (5.00 eq.) were added. The reaction mixture was heated to 40 °C in an oil bath and stirred for 15 h. After addition of aq. HCl (1.0 molL^{-1}), the mixture was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography.

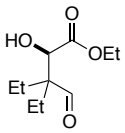
Preparation of Compound 2a



Prepared according to general procedure **C** using (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 79.1 mg, 500 µmol, 5.00 mol%) in ^{t}BuOH (10.0 mL), isobutanal (740 mg, 910 µL, 10.0 mmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 1.98 mL, 10.0 mmol, 1.00 eq.). The mixture was stirred at 25°C for 17 h. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 4:1) yielding the desired product (**2a**, 1.47 g, 84%) as a colorless oil. R_f = 0.17 (cyclohexane/ ethyl acetate, 4:1); ν_{max} (neat): 3463m, 2947m, 1734s, 1436w, 1370w, 1207m, 1102m, 1026w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.57 (1H, s, C1*H*), 4.32 (1H, s, C3*H*), 4.30 – 4.18 (2H, m, C6H_2), 3.06 (1H, br, O*H*), 1.27 (3H, t, ^3J 7.15, C7H_3), 1.14 (3H, s,

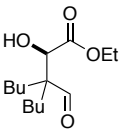
C5H_3), 1.05 (3H, s, C5'H_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 202.5 (*C1*), 172.9 (*C4*), 73.6 (*C3*), 62.3 (*C6*), 50.4 (*C2*), 18.3 (*C5*), 16.9 (*C5'*), 14.1 (*C7*).

Preparation of Compound 2b



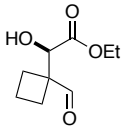
Prepared according to general procedure **C** using (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 31.6 mg, 200 µmol, 20.0 mol%) in ^{t}BuOH (1.00 mL), 2-ethylbutyraldehyde (100 mg, 123 µL, 1.00 mmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 210 µL, 1.00 mmol, 1.00 eq.). The mixture was stirred at 25°C for 3 days. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 4:1) yielding the desired product (**2b**,186 mg, 92%) as a colorless oil which solidified upon storage in the fridge. R_f = 0.36 (cyclohexane/ ethyl acetate, 4:1); v_{max} (neat): 3486m, 2974m, 2361w, 1731s, 1462w, 1385w, 1264w, 1216w, 1098w, 1025w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.61 (1H, s, C1*H*), 4.42 (1H, d, ^3J 5.5, C3*H*), 4.31 – 4.21 (2H, dq, ^2J 10.8, ^3J 7.2, C7H_2), 3.06 (1H, d, ^3J 5.5, O*H*), 1.76 – 1.64 (4H, m, C5H_2, C5´H_2), 1.29 (3H, t, ^3J 7.2, C8H_3), 0.9 (3H, t, ^3J 7.6, C6H_3), 0.89 (3H, t, ^3J 7.6, C6´H_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 204.2 (*C1*), 173.7 (*C4*), 72.8 (*C3*), 62.4 (*C7*), 56.0 (*C2*), 22.8 (*C5*), 21.9 (*C5´*), 14.2 (*C8*), 8.2 (*C6´*), 8.1 (*C6*).

Preparation of Compound 2c



Prepared according to general procedure **C** using (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 15.8 mg, 100 µmol, 10.0 mol%) in ^{t}BuOH (1.00 mL), 2-*n*-butylhexanal (156 mg, 1.00 mmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 211 µL, 1.00 mmol, 1.00 eq). The mixture was stirred at 25°C for 5 days. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 4:1 → 2:1) yielding the desired product (**2c**, 222 mg, 86 %) as a colorless oil. R_f = 0.39 (cyclohexane/ ethyl acetate, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.61 (1H, s, C1*H*), 4.41 (1H, d, ^{3}J 5.7, C3*H*), 4.32 – 4.24 (1H, dq, ^2J 10.7, ^3J 7.2, C9*H*), 4.28 – 4.20 (1H, dq, ^2J 10.7, ^{3}J 5.9, C9*H*), 2.93 (1H, d, ^3J 5.7, O*H*), 1.68 – 1.57 (3H, m, C5H2, C5´H), 1.33 – 1.19 (9H, m, C5´H, C6H2, C6´H2, C7H2, C7´H2), 1.30 (3H, t, ^3J 7.2, C10H_3), 0.90 (6H, t, ^3J 7.1, C8H_3, C8´H_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 204.4 (*C1*), 173.6 (*C4*), 73.2 (*C3*), 62.4 (*C9*), 55.7 (*C2*), 30.3 (*C5*), 29.6 (*C5´*), 25.8 (*C6*/*C6´*), 25.7 (*C6*/*C6´*), 23.7 (*C7*/*C7´*), 23.6 (*C7*/*C7´*), 14.2 (*C10*), 14.0 (*C8*, *C8´*).

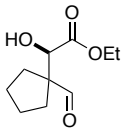
Preparation of Compound 2d



Prepared according to general procedure **C** using (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 15.8 mg, 100 µmol, 5.00 mol%) in ^{t}BuOH (2.00 mL), cyclobutane-carboxaldehyde (168 mg, 180 µL, 2.00 mmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 420 µL, 2.00 mmol, 1.00 eq.). The mixture was stirred at 25°C for 17 h. The residue was purified

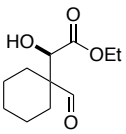
by column chromatography (cyclohexane/ethyl acetate, 4:1) yielding the desired product (**2d**, 342 mg, 92 %) as a colorless oil. R_f = 0.24 (cyclohexane/ ethyl acetate, 4:1); ν_{max} (neat): 3463m, 2947m, 1734s, 1436w, 1370w, 1207m, 1102m, 1026w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.73 (1H, s, C1*H*), 4.38 (1H, d, ^3J 5.3, C3*H*), 4.29 – 4.22 (1H, dq, ^2J 10.7, ^3J 7.1, C7*H*), 4.22 – 4.16 (1H, dq, ^2J 10.7 Hz, ^3J 7.1, C7*H*), 3.07 (1H, d, ^3J 5.4, O*H*), 2.36 – 2.28 (1H, m, C5*H*), 2.30 – 2.24 (1H, m, C5´*H*), 2.18 – 2.12 (1H, m, C5*H*), 2.16 – 2.08 (1H, m, C5´*H*), 1.92 – 1.85 (2H, m, C6H_2), 1.19 (t, ^3J 7.1, C8H_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 200.8 (*C1*), 173.1 (*C4*), 72.0 (*C3*), 62.3 (*C7*), 55.8 (*C2*), 24.9 (*C5*), 22.8 (*C5´*), 15.5 (*C6*), 14.2 (*C8*).

Preparation of Compound 2e



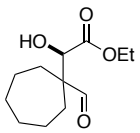
Prepared according to general procedure **C** using (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 15.8 mg, 100 µmol, 5.00 mol%) in ^{t}BuOH (2.00 mL), cyclopentane-carboxaldehyde (196 mg, 210 µL, 2.00 mmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 420 µL, 2.00 mmol, 1.00 eq.). The mixture was stirred at 25°C for 17 h. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 4:1) yielding the desired product (**2e**, 342 mg, 85 %) as a colorless oil. R_f = 0.32 (cyclohexane/ ethyl acetate, 4:1); ν_{max} (neat): 3464w, 2957m, 2873w, 1731s, 1451w, 1269w, 1200m, 1130m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.57 (1H, s, C1*H*), 4.35 (1H, s, C3*H*), 4.30 – 4.23 (1H, dq, ^2J 10.7, ^3J 7.1, C7*H*), 4.24 – 4.18 (1H, dq, ^2J 10.7, ^3J 7.1, C7*H*), 3.09 (1H, br, O*H*), 1.98 – 1.84 (3H, m, C5H_2, C5´*H*), 1.74 – 1.52 (5H, m, C5´*H*, C6H_2, C6´H_2), 1.27 (t, ^3J 7.1, C8H_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 201.8 (*C1*), 173.4 (*C4*), 72.5 (*C3*), 62.4 (*C7*), 61.8 (*C2*), 30.4 (*C5*), 28.3 (*C5´*), 26.1 (*C6*), 25.8 (*C6´*), 14.2 (*C8*).

Preparation of Compound 2f



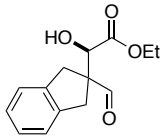
Prepared according to general procedure **C** using (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 15.8 mg, 100 µmol, 5.00 mol%) in ^{t}BuOH (2.00 mL), cyclohexane-carboxaldehyde (224 mg, 240 µL, 2.00 mmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 420 µL, 2.00 mmol, 1.00 eq.). The mixture was stirred at 25°C for 72 h. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 4:1) yielding the desired product (**2f**, 406 mg, 95 %) as a colorless oil. R_f = 0.38 (cyclohexane/ ethyl acetate, 4:1); ν_{max} (neat): 3496w, 2934m, 2859w, 1732s, 1452w, 1370w, 1268w, 1217w, 1001w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.58 (1H, s, C1*H*), 4.31 – 4.24 (1H, dq, ^2J 10.7, ^3J 7.2, C8*H*), 4.26 – 4.20 (1H, dq, ^2J 10.7, ^3J 7.2, C8*H*), 4.14 (1H, d, ^3J 5.9, C3*H*), 2.95 (1H, d, ^3J 5.9, O*H*), 2.00 – 1.92 (1H, m, C5*H*), 1.83 – 1.76 (1H, m, C5´*H*), 1.69 – 1.57 (4H, m, C5*H*, C6*H*, C6´*H*, C7*H*), 1.55 – 1.49 (1H, m, C5´*H*), 1.46 – 1.36 (1H, m, C7*H*), 1.29 (3H, t, ^3J 7.2, C9H_3), 1.26 – 1.17 (2H, m, C6*H*, C6´*H*). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 204.6 (*C1*), 173.0 (*C4*), 74.0 (*C3*), 62.4 (*C8*), 53.7 (*C2*), 28.0 (*C5*), 26.1 (*C5´*), 25.3 (*C6*), 22.4 (*C6´*), 22.2 (*C7*), 14.3 (*C9*).

Preparation of Compound 2g



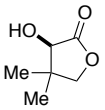
Prepared according to general procedure **C** using (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 15.8 mg, 100 µmol, 5.00 mol%) in ^{t}BuOH (2.00 mL), cycloheptane-carboxaldehyde (252 mg, 270 µL, 2.00 mmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 420 µL, 2.00 mmol, 1.00 eq.). The mixture was stirred at 25°C for 72 h. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 4:1) yielding the desired product (**2g**, 98 mg, 22 %) as a colorless oil. R_f = 0.4 (cyclohexane/ ethyl acetate, 4:1); ν_{max} (neat): 3450w, 2930s, 2860m, 1706s, 1461w, 1193w, 1107w, 1047w, 936w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.51 (1H, s, C1*H*), 4.28 – 4.21 (3H, m, C3*H*, C9*H*$_2$), 3.04 (1H, br, O*H*), 1.98 – 1.44 (12H, m, C5*H*$_2$, C5´*H*$_2$, C6*H*$_2$, C6´*H*$_2$, C7*H*$_2$, C7´*H*$_2$), 1.29 (3H, t, ^{3}*J* 7.2, C9*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 202.8 (*C1*), 173.2 (*C4*), 74.9 (*C3*), 62.5 (*C8*), 56.9 (*C2*), 30.8, 29.5, 28.5, 26.4, 23.7, 23.4, 14.2 (*C9*).

Preparation of Compound 2h



Prepared according to general procedure **C** using (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 1.58 mg, 10.0 µmol, 5.00 mol%) in ^{t}BuOH (200 µL), 2,3-dihydro-1*H*-indene-2-carbaldehyde (29.2 mg, 200 µmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 42.2 µL, 200 µmol, 1.00 eq.). The mixture was stirred at 25°C for 16 h. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 4:1) yielding the desired product (**2h**, 42 mg, 85 %) as a colorless oil. R_f = 0.27 (cyclohexane/ ethyl acetate, 4:1); ν_{max} (neat): 3473w, 2914w, 2849w, 1723s, 1442w, 1210m, 1112m, 1021m, 866w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.68 (1H, s, C1*H*), 7.20 – 7.15 (4H, m, C7*H*, C7'*H*, C8*H*, C8'*H*), 4.47 (1H, d, ^{3}*J* 5.6, C3*H*), 4.18 – 4.12 (1H, dq, ^{2}*J* 10.8, ^{3}*J* 7.2, C10*H*), 4.11 – 4.05 (1H, dq, ^{2}*J* 10.8, ^{3}*J* 7.2, C8*H*), 3.35 (1H, d, ^{2}*J* 16.7 Hz, C5*H*), 3.31 (1H, d, ^{2}*J* 16.6, C5'*H*), 3.28 (1H, d, ^{2}*J* 16.7, C5*H*), 3.24 (1H, d, ^{2}*J* 16.6, C5'*H*), 3.18 (1H, d, ^{3}*J* 5.6, O*H*), 1.21 (3H, t, ^{3}*J* 7.2 Hz, C11*H*$_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 201.4 (*C1*), 173.0 (*C4*), 140.3 (*C6*/*C6'*), 140.2 (*C6*/*C6'*), 127.2 (*C8*/*C8'*), 127.1 (*C8*/*C8'*), 124.8 (*C7*/*C7'*), 124.7 (*C7*/*C7'*), 72.5 (*C3*), 62.6 (*C10*), 61.7 (*C2*), 36.4 (*C5*), 35.9 (*C5'*), 14.1 (*C11*).

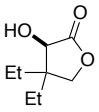
Preparation of (*R*)-pantolactone, (*R*)-1a



Prepared according to general procedure **D**. To a solution of (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 7.91 mg, 50.0 µmol, 5.00 mol%) in ^{t}BuOH (1.00 mL), isobutanal (72.1 mg, 89 µL, 1.00 mmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 211 µL, 1.00 mmol, 1.00 eq.) were added. The mixture was stirred at room temperature for 15 h. Water (5 mL) was added and the solution degassed with argon for 1 h, before $(IrCl_2(Cp^*))_2$ (0.80 mg, 1.00 µmol, 0.10 mol%) and sodium formate (340 mg, 5.00 mmol, 5.00 eq.) were added. The reaction mixture was heated to 40 °C and stirred for 15 h. After addition of aq. HCl (1M, 2 mL) the

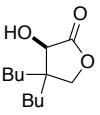
mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 2:1) yielding the desired product (**1a**, 80.7 mg, 620 µmol, 62%, e.r. 86:14 by HPLC, m.p. 90.1 – 91.8 °C) as a white crystalline solid. R_f = 0.16 (cyclohexane / ethyl acetate, 2:1); $[\alpha]_D$ = – 11.9 (*c* 1.00, $CHCl_3$); ν_{max} (neat): ; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.11 (1H, s, C2*H*), 4.03 (1H, d, ^2J 8.9, C4*H*), 3.95 (1H, dd, ^2J 8.9, ^4J 0.64, C4*H*), 2.58 (1H, br, O*H*), 1.24 (3H, s, C5*H*$_3$), 1.08, (3H, s, C5´*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 177.8 (*C1*), 76.6 (*C4*), 75.9 (*C2*), 41.0 (*C3*), 23.0 (*C5*), 18.9 (*C5´*); ESI-MS: m/z calcd. For $C_6H_{10}NaO_3$ 153.0522 found 153.0523 [$MNa^{\cdot+}$]; The e.r. was determined by HPLC using a Chiralcel AD-H column (1.00 mL/min^{-1}, *n*-heptane:*i*PrOH 90:10): (+)-(*S*)-**1a** t_R = 9.07 min and (–)-(*R*)-**1a** t_R = 12.73 min. The absolute configuration was assigned by HPLC using an authentic sample of (*R*)-pantolactone (Sigma-Aldrich, Lot # 1445151V). Recrystallization of (*R*)-pantolactone **1a** (500 mg, 3.84 mmol, e.r. 86:14 by HPLC) from diethylether/petroleum ether yielded enantiomerically enriched (*R*)-pantolactone **1a** (353 mg, 2.71 mmol, e.r. 97:3 by HPLC) as a white crystalline solid.

Preparation of (*R*)-4,4-diethyl-3-hydroxydihydrofuran-2(3*H*)-one, (*R*)-1b



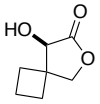
Prepared according to general procedure **D**. To a solution of (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 15.8 mg, 100 µmol, 10.0 mol%) in ^{t}BuOH (1.00 mL), 2-ethylbutyraldehyde (100 mg, 82 µL, 1.00 mmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 211 µL, 1.00 mmol, 1.00 eq.) were added. The mixture was stirred at room temperature for 72 h. Water (5 mL) was added and the solution degassed with argon for 1 h, before $(IrCl_2(Cp^*))_2$ (0.80 mg, 1.00 µmol, 0.10 mol%) and sodium formate (340 mg, 5.00 mmol, 5.00 eq.) were added. The reaction mixture was heated to 40 °C and stirred for 15 h. After addition of aq. HCl (1M, 2 mL) the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 2:1) yielding the desired product (**1b**, 71 mg, 449 µmol, 45%, e.r. 81:19 by HPLC) as a colorless oil. R_f = 0.31 (cyclohexane / ethyl acetate, 2:1); $[\alpha]_D$ = – 6.8 (*c* 0.25, $CHCl_3$) (reference:[9] $[\alpha]_D$ = – 13.2 (*c* 1.00, $CHCl_3$)); ν_{max} (neat): 3384w, 2967w, 2870w, 1758s, 1456w, 1288w, 1200m, 1100m, 990m, 874m, 722w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.21 (1H, d, ^3J 3.2, C2*H*), 4.15 (1H, d, ^2J 9.3, C4*H*), 3.87 (1H, d, ^2J 9.3, C4*H*), 2.86 (1H, d, ^3J 3.2, O*H*), 1.60 – 1.42 (4H, m, C5*H*$_2$, C5'*H*$_2$), 0.98 (3H, t, ^3J 7.5, C6*H*$_3$), 0.90 (3H, t, ^3J 7.5, C7'*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 178.5 (*C1*), 74.9 (*C2*), 73.3 (*C4*), 46.8 (*C3*), 28.3 (*C5*), 21.7 (*C5'*), 8.6 (*C6*), 8.2 (*C6'*); ESI-MS: m/z calcd. For $C_8H_{14}NaO_3$ 181.0835 found 181.0834 [$MNa^{\cdot+}$]; The e.r. was determined by HPLC using a Chiralcel AD-H column (1.00 mL/min^{-1}, *n*-heptane:*i*PrOH 90:10): (+)-(*S*)-**1b** t_R = 8.23 min and (–)-(*R*)-**1b** t_R = 9.32 min.

Preparation of (*R*)-4,4-dibutyl-3-hydroxydihydrofuran-2(3*H*)-one, (*R*)-1c



Prepared according to general procedure **D**. To a solution of (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 15.8 mg, 100 µmol, 10.0 mol%) in ^{t}BuOH (1.00 mL), n-butylhexanal (156 mg, 1.00 mmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 211 µL, 1.00 mmol, 1.00 eq.) were added. The mixture was stirred at room temperature for 7 days. Water (5 mL) was added and the solution degassed with argon for 1 h, before $(IrCl_2(Cp^*))_2$ (0.80 mg, 1.00 µmol, 0.10 mol%) and sodium formate (340 mg, 5.00 mmol, 5.00 eq.) were added. The reaction mixture was heated to 40 °C and stirred for 15 h. After addition of aq. HCl (1M, 2 mL) the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 4:1) yielding the desired product (**1c**, 143 mg, 667 µmol, 67%, e.r. 70:30 by HPLC) as a colorless oil. R_f = 0.5 (cyclohexane / ethyl acetate, 2:1); $[\alpha]_D$ = – 2.6 (*c* 1.00, $CHCl_3$); ν_{max} (neat): 3449w, 2931m, 2863w, 1764s, 1464w, 1379w, 1178w, 1115m, 1006m, 667w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.20 (1H, s, C2*H*), 4.15 (1H, d, ^2J 9.2, C4*H*), 3.87 (1H, d, ^2J 9.2, C4*H*), 1.58 – 1.14 (12H, m, C5*H*$_2$, C5´*H*$_2$, C6*H*$_2$, C6´*H*$_2$, C7*H*$_2$, C7´*H*$_2$), 0.90 (3H, t, ^3J 7.0, C8*H*$_3$), 0.98 (3H, t, ^3J 7.0, C8´*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 178.9 (C1), 75.1, 74.0, 46.3, 36.9, 29.3, 26.3, 26.0, 23.5, 23.4, 14.1, 14.0; ESI-MS: m/z calcd. For $C_{12}H_{22}NaO_3$ 237.1461 found 237.1461 [MNa$^{\cdot+}$]; The e.r. was determined by HPLC using a Chiralcel AD-H column (1.00 mL/min^{-1}, *n*-heptane:*i*PrOH 99:1): (+)-(*S*)-**1c** t_R = 23.71 min and (–)-(*R*)-**1c** t_R = 27.07 min.

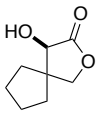
Preparation of (*R*)-8-hydroxy-6-oxaspiro[3.4]octan-7-one, (*R*)-1d



Prepared according to general procedure **D**. To a solution of (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 7.91 mg, 50.0 µmol, 5.00 mol%) in ^{t}BuOH (1.00 mL), cyclobutane-carboxaldehyde (84.1 mg, 1.00 mmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 211 µL, 1.00 mmol, 1.00 eq.) were added. The mixture was stirred at room temperature for 15 h. Water (5 mL) was added and the solution degassed with argon for 1 h, before $(IrCl_2(Cp^*))_2$ (0.80 mg, 1.00 µmol, 0.10 mol%) and sodium formate (340 mg, 5.00 mmol, 5.00 eq.) were added. The reaction mixture was heated to 40 °C and stirred for 15 h. After addition of aq. HCl (1M, 2 mL) the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 2:1) yielding the desired product (**1d**, 101.5 mg, 714 µmol, 71%, e.r. 93:7 by HPLC, m.p. 68.0 – 68.9 °C) as a white crystalline solid. R_f = 0.21 (cyclohexane / ethyl acetate, 2:1); $[\alpha]_D$ = – 13.2 (*c* 1.00, $CHCl_3$); ν_{max} (neat): 3411w, 2959w, 2892w, 1762s, 1473w, 1404w, 1289m, 1194m, 1117s, 1089m, 987s, 875m, 717w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.41 (1H, d, ^2J 9.1, C4*H*), 4.18 (1H, d, ^3J 3.3, C2*H*), 4.10 (1H, dd, ^2J 9.1, ^4J 0.9, C4*H*), 2.98 (1H, d, ^3J 3.4, O*H*), 2.57 – 2.50 (1H, m, C5'*H*), 2.34 – 2.27 (1H, m, C5*H*), 2.03 – 1.97 (1H, m, C5*H*), 1.97 – 1.89 (2H, m, C6*H*$_2$), 1.81 – 1.75 (1H, m, C5'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ

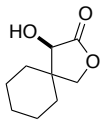
= 177.1 (*C1*), 75.4 (*C4*), 73.1 (*C2*), 46.6 (*C3*), 26.3 (*C5*), 25.1 (*C5'*), 15.8 (*C6*); ESI-MS: m/z calcd. For $C_7H_{10}NaO_3$ 165.0522 found 165.0520 [$MNa^{\cdot+}$]; The e.r. was determined by HPLC using a Chiralcel AD-H column (1.00 mL/min^{-1}, *n*-heptane:*i*PrOH 90:10): (+)-(*S*)-**1d** t_R = 10.15 min and (–)-(*R*)-**1d** t_R = 14.95 min.

Preparation of (*R*)-4-hydroxy-2-oxaspiro[4.4]nonan-3-one, (*R*)-1e



Prepared according to general procedure **D**. To a solution of (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 7.91 mg, 50.0 µmol, 5.00 mol%) in ^{t}BuOH (1.00 mL), cyclopentane-carboxaldehyde (98.1 mg, 1.00 mmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 211 µL, 1.00 mmol, 1.00 eq.) were added. The mixture was stirred at room temperature for 15 h. Water (5 mL) was added and the solution degassed with argon for 1 h, before $(IrCl_2(Cp^*))_2$ (0.80 mg, 1.00 µmol, 0.10 mol%) and sodium formate (340 mg, 5.00 mmol, 5.00 eq.) were added. The reaction mixture was heated to 40 °C and stirred for 15 h. After addition of aq. HCl (1M, 2 mL) the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 2:1) yielding the desired product (**1e**, 114.2 mg, 730 µmol, 73%, e.r. 92:8 by HPLC, m.p. 104 – 105 °C) as a white crystalline solid. R_f = 0.18 (cyclohexane / ethyl acetate, 2:1); $[\alpha]_D$ = – 13.8 (*c* 1.00, $CHCl_3$) (reference:[10] $[\alpha]_D$ = – 12.0 (*c* 0.19, $CHCl_3$)); ν_{max} (neat): 3383m, 2952w, 2869w, 1759s, 1427w, 1288w, 1200m, 1142m, 1095m, 988s, 873m, 724w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.27 (1H, d, ^3J 3.2, C2*H*), 4.12 (1H, d, ^2J 8.8, C4*H*), 4.02 (1H, dd, ^2J 8.8, ^4J 0.9, C4*H*), 2.71 (1H, d, ^3J 3.3, O*H*), 2.03 – 1.97 (1H, m, C5*H*), 1.91 – 1.87 (1H, m, C5´*H*), 1.81 – 1.77 (1H, m, C6*H*/C6´*H*), 1.69 – 1.58 (4H, m, C5´*H*, C6*H*/C6`*H*), 1.45 – 1.40 (1H, m, C5*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 177.5 (*C1*), 76.1 (*C4*), 73.9 (*C2*), 51.8 (*C3*), 33.8 (*C5´*), 29.3 (*C5*), 25.2 (*C6/C6´*), 25.1 (*C6/C6´*); ESI-MS: m/z calcd. For $C_8H_{12}NaO_3$ 179.0679 found 179.0676 [$MNa^{\cdot+}$]; The e.r. was determined by HPLC using a Chiralcel AD-H column (1.00 mL/min^{-1}, *n*-heptane:*i*PrOH 90:10): (+)-(*S*)-**1e** t_R = 9.48 min and (–)-(*R*)-**1e** t_R = 12.55 min.

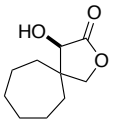
Preparation of (*R*)-4-hydroxy-2-oxaspiro[4.5]decan-3-one, (*R*)-1f



Prepared according to general procedure **D**. To a solution of (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 7.91 mg, 50.0 µmol, 5.00 mol%) in ^{t}BuOH (1.00 mL), cyclohexane-carboxaldehyde (98.1 mg, 1.00 mmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 211 µL, 1.00 mmol, 1.00 eq.) were added. The mixture was stirred at room temperature for 72 h. Water (5 mL) was added and the solution degassed with argon for 1 h, before $(IrCl_2(Cp^*))_2$ (0.80 mg, 1.00 µmol, 0.10 mol%) and sodium formate (340 mg, 5.00 mmol, 5.00 eq.) were added. The reaction mixture was heated to 40 °C and stirred for 15 h. After addition of aq. HCl (1M, 2 mL) the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried

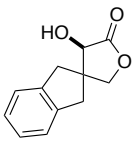
over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 2:1) yielding the desired product (**1f**, 122 mg, 717 µmol, 72%, e.r. 88:12 by HPLC, m.p. 83.4 – 85.5 °C) as a white crystalline solid. R_f = 0.26 (cyclohexane / ethyl acetate, 2:1); $[\alpha]_D$ = – 10.9 (*c* 1.00, $CHCl_3$) (reference:[11] $[\alpha]_D$ = + 12.2 (*c* 0.85, $CHCl_3$, (*S*)-configuration); ν_{max} (neat): 2284m, 2950w, 2867w, 1758s, 1447w, 1288w, 1200m, 1144m, 1096m, 988s, 873m, 726w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.35 (1H, d, ^2J 9.2, C4*H*), 4.07 (1H, s, C2*H*), 3.88 (1H, dd, ^2J 9.2, ^4J 1.5, C4*H*), 2.60 (1H, br, O*H*), 1.79 – 1.73 (2H, m, C5*H*, C6*H*), 1.71 – 1.56 (4H, m, C5'*H*, C6*H*, C6'*H*, C7*H*), 1.45 – 1.36 (2H, m, C5'*H*, C8*H*), 1.31 – 1.19 (2H, m, C5'*H*, C6'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 177.7 (*C1*), 75.9 (*C2*), 73.8 (*C4*), 44.3 (*C3*), 34.0 (*C5*), 26.0 (*C7*), 25.5 (*C6'*), 23.1 (*C5'*), 22.0 (*C5*); ESI-MS: m/z calcd. For $C_9H_{14}NaO_3$ 193.0835 found 193.0834 [$MNa^{\cdot+}$]; The e.r. was determined by HPLC using a Chiralcel AD-H column (1.00 mL/min^{-1}, *n*-heptane:*i*PrOH 90:10): (+)-(*S*)-**1f** t_R = 9.55 min and (–)-(*R*)-**1f** t_R = 10.65 min.

Preparation of (*R*)-4-hydroxy-2-oxaspiro[4.6]undecan-3-one, (*R*)-1g



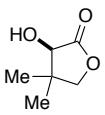
Prepared according to general procedure **D**. To a solution of (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 7.91 mg, 50.0 µmol, 10.0 mol%) in ^{t}BuOH (500 µL), cycloheptane-carboxaldehyde (63.1 mg, 500 µmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 105 µL, 500 µmol, 1.00 eq.) were added. The mixture was stirred at room temperature for 24 h. Water (2.5 mL) was added and the solution degassed with argon for 1 h, before $(IrCl_2(Cp^*))_2$ (0.40 mg, 500 nmol, 0.10 mol%) and sodium formate (170 mg, 2.50 mmol, 5.00 eq.) were added. The reaction mixture was heated to 40 °C and stirred for 15 h. After addition of aq. HCl (1M, 1 mL) the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 4:1) yielding the desired product (**1g**, 16.4 mg, 89.0 µmol, 18%, e.r. 72:28 by HPLC; m.p. 94.1 – 96.4 °C) as a white crystalline solid. R_f = 0.18 (cyclohexane / ethyl acetate, 4:1); $[\alpha]_D$ = – 10.8 (*c* 0.60, $CHCl_3$); ν_{max} (neat): 3396 (m), 2924 (m), 2852 (w), 1755 (s), 1460 (w), 1425 (w), 1319 (w), 1224 (w), 1180 (w), 1142 (m), 1114 (m), 1000 (m), 915 (w);^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.15 (1H, d, ^2J 9.0, C4*H*), 4.15 (1H, s, C2*H*), 3.85 (1H, dd, ^2J 9.0, ^4J 1.4, C4*H*), 2.90 (1H, br, O*H*), 1.91 – 1.83 (2H, m, C5*H*, C5´*H*), 1.71 – 1.57 (5H, m, $C_{alkyl}H$), 1.53 – 1.40 (5H, m, $C_{alkyl}H$); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 178.1 (C1), 77.7 (C2), 75.2 (C4), 47.4 (C3), 36.9 (C5), 30.2, 30.1, 29.3 (C5´), 23.4, 22.9; ESI-MS: m/z calcd. For $C_{10}H_{16}NaO_3$ 207.0992 found 207.0991 [$MNa^{\cdot+}$]; The e.r. was determined by HPLC using a Chiralcel AD-H column (1.00 mL/min^{-1}, *n*-heptane:*i*PrOH, ramp 90:10 to 80:20): (+)-(*S*)-**1g** t_R = 9.73 min and (–)-(*R*)-**1g** t_R = 10.18 min.

Preparation of (*R*)-4-hydroxy-1',3'-dihydro-2*H*-spiro[furan-3,2'-inden]-5(4*H*)-one, (*R*)-1h



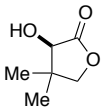
Prepared according to general procedure **D**. To a solution of (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 800 µg, 5.00 µmol, 5.00 mol%) in ^{t}BuOH (100 µL), 2,3-dihydro-1*H*-indene-2-carbaldehyde (15.0 mg, 100 µmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 21.1 µL, 100 µmol, 1.00 eq.) were added. The mixture was stirred at room temperature for 16 h. Water (500 µL) was added and the solution degassed with argon for 1 h, before $(IrCl_2(Cp^*))_2$ (160 µg, 100 nmol, 0.10 mol%) and sodium formate (34.0 mg, 500 µmol, 5.00 eq.) were added. The reaction mixture was heated to 40 °C and stirred for 15 h. After addition of aq. HCl (1M, 200 µL) the mixture was extracted with CH_2Cl_2 (3 x 1 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by preparative thin-layer chromatography (cyclohexane/ethyl acetate, 4:1) yielding the desired product (**1h**, 14.5 mg, 71.0 µmol, 64%, e.r. 62:38 by HPLC) as a white crystalline solid. R_f = 0.17 (cyclohexane / ethyl acetate, 4:1); $[\alpha]_D$ = – 12.8 (*c* 0.07, $CHCl_3$); ν_{max} (neat): 3395m, 2921w, 1744s, 1473w, 1370w, 1300w, 1236m, 1080m, 993s, 889m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.23 – 7.17 (4H, m, C7*H*, C7´*H*, C8*H*, C8´*H*), 4.42 (1H, s, C2*H*), 4.26 (1H, d, 2J 9.1, C4*H*), 4.10 (1H, d, 2J 9.1, C4*H*), 3.45 (1H, d, ^{2}*J* 16.1, C5*H*), 3.32 (1H, d, ^{2}*J* 16.1, C5´*H*), 2.93 (1H, d, ^{2}*J* 16.1, C5´*H*), 2.73 (1H, d, ^{2}*J* 16.1, C5*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 176.9 (*C1*), 140.8 (*C6*/*C6´*), 140.2 (*C6*/*C6´*), 127.3 (*C8*), 127.1 (*C8´*), 125.2 (*C7*), 124.7 (*C7´*), 76.1 (*C4*), 72.8 (*C2*), 52.5 (*C3*), 39.7 (*C5´*), 35.8 (*C5*); ESI-MS: m/z calcd. For $C_{12}H_{12}NaO_3$ 227.0679 found 227.0678 [$MNa^{\cdot+}$]; The e.r. was determined by HPLC using a Chiralcel AD-H column (1.00 mL/min^{-1}, *n*-heptane:*i*PrOH 90:10): (+)-(*S*)-**1h** t_R = 11.73 min and (–)-(*R*)-**1h** t_R = 13.33 min.

Gram-Scale preparation of (*R*)-Pantolactone using $(RuCl_2(cymene))_2$



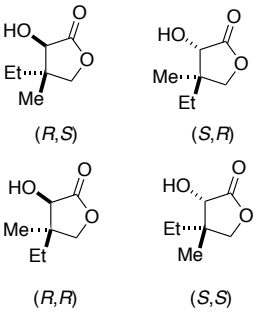
To a solution of (*R*)-*N*-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 237 mg, 1.50 mmol, 5.00 mol%) in *t*-BuOH (30.0 mL), isobutanal (2.74 mL, 30 mmol, 1.00 eq.) and ethyl glyoxalate (50.0 wt.% in toluene, 5.95 mL, 30.0 mmol, 1.00 eq.) were added. The mixture was stirred at RT for 24 h. Water (150 mL) was added and the solution was degassed with argon for 1 h, before $(RuCl_2(cymene))_2$ (91.9 mg, 150 mmol, 0.50 mol%) and sodium formate (10.2 g, 150 mmol, 5.00 eq.) were added. The mixture was stirred overnight. A solution of aq. HCl (1M, 200 mL) was added and the reaction mixture extracted with MTBE (3x 600 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 2:1) yielding the product ((*R*)-**1a**, 2.41 g, 62%, 86:14 e.r.) as a white solid. Analytical data in accordance with reference sample.

Gram-Scale preparation of (*R*)-Pantolactone using CRSC with $(IrCl_2(Cp^*))_2$



To a solution of (*R*)-*N*-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 158 mg, 1.00 mmol, 5.00 mol%) in *t*-BuOH (20.0 mL), isobutanal (1.83 mL, 20 mmol, 1.00 eq.) and ethyl glyoxalate (47.0 wt.% in toluene, 4.22 mL, 20.0 mmol, 1.00 eq.) were added. The mixture was stirred at RT for 24 h. Water (100 mL) was added and the solution was degassed with argon for 1 h, before $(IrCl_2(Cp^*))_2$ (15.9 mg, 20.0 µmol, 0.10 mol%) and sodium formate (6.80 g, 100 mmol, 5.00 eq.) were added. The mixture was heated to 40°C in an oil bath and stirred overnight. The reaction mixture was extracted with ethyl acetate (3x 150 mL) and the combined organic layers dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 2:1) yielding the product ((*R*)-**1a**, 2.03 g, 78%, 86:14 e.r.) as a white solid. Recrystallization of (*R*)-pantolactone **1a** (2.03 g, 15.6 mmol, e.r. 86:14 by HPLC) from diethylether/petroleum ether (80 mL/30 mL) yielded enantiomerically enriched (*R*)-pantolactone **1a** (1.43 g, 55%, e.r. 98:2 by HPLC) as a white crystalline solid.

Preparation of 4-ethyl-3-hydroxy-4-methyldihydrofuran-2(3*H*)-one, 1i

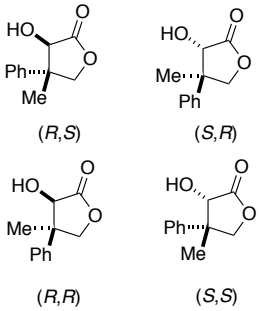


(*R*,*S*) (*S*,*R*) (*R*,*R*) (*S*,*S*)

Prepared according to general procedure **D**. To a solution of (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 15.8 mg, 50.0 µmol, 10.0 mol%) in ^{t}BuOH (1.00 mL), 2-methylbutanal (86.1 mg, 107 µL, 1.00 mmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 211 µL, 1.00 mmol, 1.00 eq.) were added. The mixture was stirred at room temperature for 24 h. A sample of 0.20 mL was taken from the reaction mixture and the solvent was evaporated. The crude was analyzed by HPLC to determine diastereo- and enantioselectivity of the aldehyde intermediate **2i** (d.r. 1.8 (*syn*):1 (*anti*), e.r. 93:7 (*syn*), 65:35 (*anti*). Water (4 mL) was added and the solution degassed with argon for 1 h, before $(IrCl_2(Cp^*))_2$ (0.65 mg, 0.80 µmol, 0.10 mol%) and sodium formate (272 mg, 4.00 mmol, 5.00 eq.) were added. The reaction mixture was stirred at 40 °C for 15 h. The reaction mixture was extracted with ethyl acetate and filtered over a short plug of silica. The solvent was removed under reduced pressure and the residue purified by column chromatography (cyclohexane / ethyl acetate, 4:1) yielding the desired product (**1i**, 63.8 mg, 443 µmol, 55%, d.r. 1.6 (*anti*):1 (*syn*), e.r. 94:6 (*anti*), 65:35 (*syn*) by HPLC) as a colorless liquid. R_f = 0.16 (cyclohexane / ethyl acetate, 4:1); $[\alpha]_D$ = – 11.3 (*c* 1.00, $CHCl_3$) (reference:[12] $[\alpha]_D$ = + 4.5 (*c* 0.25, $CHCl_3$, (*S*,*S*), $[\alpha]_D$ = + 25.7 (*c* 0.35, $CHCl_3$, (*S*,*R*)); ν_{max} (neat): 3424 (w), 3285 (w), 2968 (w), 1771 (s), 1691 (m), 1641 (w), 1544 (w), 1458 (m), 1322(w), 1264 (w), 1210 (m), 1108 (s), 995 (s), 875 (w), 694 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.20 (1H, d, ^2J 9.2, C4*H*, *syn*), 4.16 (1H, d, ^3J 3.3, C2*H*, *anti*), 4.14 (1H, d, ^3J 3.3, C2*H*, *syn*), 4.01 (1H, d, ^2J 9.0, C4*H*, *anti*), 3.96 (1H, dd, ^2J 9.0, ^4J 0.5, C4*H*, *anti*), 3.86 (1H, dd, ^2J 9.2, ^4J 0.7, C4*H*, *syn*), 2.51 (1H, d, ^3J

3.3, OH, *syn*), 2.49 (1H, d, ^{3}J 3.4, OH, *anti*), 1.70 – 1.40 (4H, m, C5*H*, *syn*/*anti*), 1.19 (3H, s, C7*H*, *syn*), 1.07 (3H, d, ^{4}J 0.5, C7*H*, *anti*), 0.98 (3H, t, ^{3}J 7.7, C6*H*, *anti*), 0.92 (3H, t, ^{3}J 7.5, C6*H*, *syn*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 177.8 (*C1*, *anti*), 177.7 (*C1*, *syn*), 76.1 (*C2*, *syn*), 75.7 (*C4*, *anti*), 75.3 (*C2*, *anti*), 73.8 (*C4*, *syn*), 44.4 (*C3*, *anti*), 43.8 (*C3*, *syn*), 30.4 (*C5*, *anti*), 24.3 (*C5*, *syn*), 21.1 (*C7*, *syn*), 16.1 (*C7*, *anti*), 8.8 (*C6*, *anti*), 8.5 (*C6*, *syn*); ESI-MS: m/z calcd. For $C_7H_{12}NaO_3$ 167.0679 found 167.0678 [$MNa^{\cdot+}$]; The e.r. of **2i** was determined by HPLC using a Chiralcel AD-H column (1.00 mL/min^{-1}, *n*-heptane:*i*PrOH 99:1): t_R = 29.0 min (*anti*), t_R = 31.1 min (*anti*), t_R = 35.9 min (*syn*), t_R = 42.3 min (*syn*); The e.r. of **1i** was determined by HPLC using a Chiralcel AD-H column (1.00 mL/min^{-1}, *n*-heptane:*i*PrOH 90:10): t_R = 8.3 min (*syn*), t_R = 9.1 min (*syn*), t_R = 9.7 min (*anti*), t_R = 15.1 min (*anti*). Analytical data was in accordance with literature.[9]

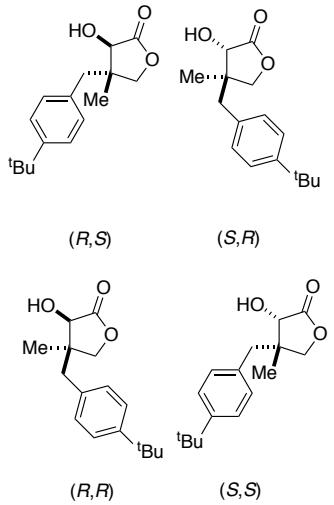
Preparation of 3-hydroxy-4-methyl-4-phenyldihydrofuran-2(3*H*)-one, 1j



Prepared according to general procedure **D**. To a solution of (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 15.8 mg, 50.0 µmol, 10.0 mol%) in ^{t}BuOH (1.00 mL), 2-phenylpropanal (134 mg, 167 µL, 1.00 mmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 211 µL, 1.00 mmol, 1.00 eq.) were added. The mixture was stirred at room temperature for 24 h. A sample of 0.20 mL was taken from the reaction mixture and the solvent was evaporated. The crude was analyzed by HPLC to determine diastereo- and enantioselectivity of the aldehyde intermediate **2j** (d.r. 1.3 (*syn*):1 (*anti*), e.r. 82:13 (*syn*), 53:47 (*anti*). Water (4 mL) was added and the solution degassed with argon for 1 h, before $(IrCl_2(Cp^*))_2$ (0.65 mg, 0.80 µmol, 0.10 mol%) and sodium formate (272 mg, 4.00 mmol, 5.00 eq.) were added. The reaction mixture was stirred at 40 °C for 15 h. The reaction mixture was extracted with ethyl acetate and filtered over a short plug of silica. The solvent was removed under reduced pressure and the residue purified by column chromatography (cyclohexane / ethyl acetate, 9:1 → 4:1) yielding the desired product as two diastereomers (*anti*-**1j** as an inseparable mixture with 2-phenylpropan-1-ol, 49.6 mg (+ 22.2 mg side product), 258 µmol, 26% and *syn*-**1j**, 36.0 mg, 187 mmol, 19%, e.r. 84:16 (*anti*), 51:49 (*syn*) by HPLC) m.p. 93.3 – 94.7 °C) as white solids. R_f = 0.32 (*anti*), 0.12 (*syn*) (cyclohexane/ethyl acetate, 4:1); $[\alpha]_D$ = + 1.1 (*c* 1.00, $CHCl_3$, *syn*); ν_{max} of *syn*-**1j** (neat): 3404 (m), 3006 (w), 1756 (s), 1485 (w), 1443 (w), 1325 (w), 1220 (m), 1165 (m), 1107 (s), 995 (s), 893 (w), 772 (w), 658 (m), 614 (w); ^{1}H NMR of *syn*-**1j** (500 MHz, $CDCl_3$) δ = 7.42 – 7.37 (2H, m, C7*H*), 7.35 – 7.30 (3H, m, C6*H*, C8*H*), 4.81 (1H, d, ^{2}J 9.4, C4*H*), 4.37 (1H, d, ^{3}J 6.7, C2*H*), 4.29 (1H, d, ^{2}J 9.4, C4*H*), 1.97 (1H, d, ^{3}J 6.8, O*H*), 1.63 (3H, s, C9*H*); ^{13}C NMR of *syn*-**1j** (126 MHz, $CDCl_3$) δ = 175.9 (C1), 138.0 (C5), 129.2 (C7), 128.1 (C8), 127.1 (C6), 76.4 (C2), 75.6 (C4), 48.1 (C3), 23.7 (C9); ^{1}H NMR of *anti*-**1j** (500 MHz, $CDCl_3$) δ = 7.41 – 7.36 (2H, m, C7*H*), 7. 35 – 7.28 (3H, m, C6*H*, C8*H*), 4.66 (1H, d, ^{3}J 2.9, C2*H*), 4.48 (1H, d, ^{2}J 9.1, C4*H*), 4.35

(1H, dd, ^{2}J 9.0, ^{4}J 0.7, C4*H*), 2.78 (1H, d, ^{3}J 3.0, O*H*), 1.42 (3H, d, ^{4}J 0.6, C9*H*); ^{13}C NMR of *anti*-**1j** (126 MHz, $CDCl_3$) δ = 177.1 (*C1*), 143.3 (*C5*), 129.2 (*C7*), 127.6 (*C8*), 125.4 (*C6*), 74.8 (*C4*), 74.5 (*C2*), 48.2 (*C3*), 21.3 (*C9*); ESI-MS: m/z calcd. For $C_{11}H_{12}NaO_3$ 215.0679 found 215.0680 [$MNa^{\cdot+}$]; The e.r. of **2j** was determined by HPLC using a Chiralcel AD-H column (0.70 mL/min^{-1}, *n*-heptane:*i*PrOH 98.5:1.5): t_R = 66.7 min (*syn*), t_R = 70.7 min (*anti*), t_R = 74.5 min (*anti*), t_R = 110.5 min (*syn*); The e.r. of **1j** was determined by HPLC using a Chiralcel AD-H column (1.00 mL/min^{-1}, *n*-heptane:*i*PrOH 98:2): t_R = 47.3 min (*anti*), t_R = 47.8 min (*syn*), t_R = 55.0 min (*anti*), t_R = 69.7 min (*syn*). Analytical data was in accordance with literature.[9]

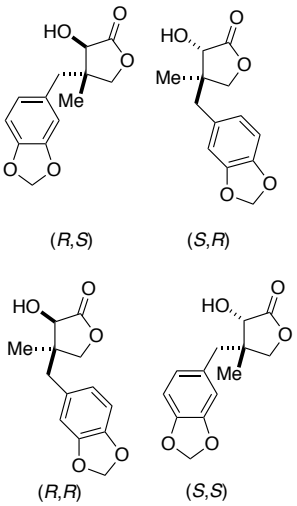
Preparation of 4-(4-(*tert*-butyl)benzyl)-3-hydroxy-4-methyldihydrofuran-2(3*H*)-one, 1k



Prepared according to general procedure **D**. To a solution of (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 15.8 mg, 50.0 µmol, 10.0 mol%) in ^{t}BuOH (1.00 mL), 2-(4-(*tert*-butyl)phenyl)propanal (204 mg, 167 µL, 1.00 mmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 211 µL, 1.00 mmol, 1.00 eq.) were added. The mixture was stirred at room temperature for 24 h. A sample of 0.20 mL was taken from the reaction mixture and the solvent was evaporated. The crude was analyzed by HPLC to determine diastereo- and enantioselectivity of the aldehyde intermediate **2k** (d.r. 1.4 (*syn*):1 (*anti*), e.r. 89:11 (*syn*), 57:43 (*anti*). Water (4 mL) was added and the solution degassed with argon for 1 h, before $(IrCl_2(Cp^*))_2$ (0.65 mg, 0.80 µmol, 0.10 mol%) and sodium formate (272 mg, 4.00 mmol, 5.00 eq.) were added. The reaction mixture was stirred at 40 °C for 15 h. The reaction mixture was extracted with ethyl acetate and filtered over a short plug of silica. The solvent was removed under reduced pressure and the residue purified by column chromatography (cyclohexane/ethyl acetate, 9:1 → 4:1) yielding the desired product (**1k**, 130 mg , 524 µmol, 52% d.r. 2 (*anti*): 1 (*syn*) ,e.r. 91:9 (*anti*), 58:42 (*syn*) by HPLC, m.p. 125.3 – 129.2 °C) as a white solid. R_f = 0.19 (cyclohexane / ethyl acetate, 4:1); $[\alpha]_D$ = + 7.3 (*c* 1.00, $CHCl_3$); ν_{max} (neat): 3408 (m), 2956 (m), 1765 (s), 1445 (w), 1366 (w), 1178 (m), 1109 (s), 999 (s), 837 (w), 614 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.34 (2H, d, ^{3}J 8.2, C8*H*, *anti*), 7.32 (2H, d, ^{3}J 8.2, C8*H*, *syn*), 7.09 (2H, d, ^{3}J 8.2, C7*H*, *syn*) 7.06 (2H, d, ^{3}J 8.2, C7*H*, *anti*), 4.28 (1H, d, ^{2}J 9.4, C4*H*, *syn*), 4.23 (1H, s, C2*H*, *syn*) 4.21 (1H, s, C2*H*, *anti*), 4.12 (1H, d, ^{2}J 8.8, C4*H*, *anti*), 3.93 (1H, d, ^{2}J 8.8, C4*H*, *anti*), 3.69 (1H, dd, ^{2}J 9.4, ^{4}J 1.0, C4*H*, *syn*), 2.85 (1H, d, ^{2}J 13.9, C5*H*, *anti*), 2.81 (1H, d, ^{2}J 13.9, C5*H*, *anti*), 2.78 (1H, d, ^{2}J 13.9, C5*H*, *syn*), 2.65 (1H, br, O*H*, *syn*), 2.54 (1H, d, ^{2}J 13.9, C5*H*, *syn*), 2.47 (1H, br, O*H*, *anti*), 1.31(4) (9H, s, C11*H*, *anti*) 1.31(2) (9H, s, C11*H*, *syn*), 1.18 (3H, s, C12*H*, *syn*), 1.11 (3H, s, C12*H*, *anti*); ^{13}C

NMR (126 MHz, $CDCl_3$) δ = 178.0 (*C1*, *syn*), 177.0 (*C1*, *anti*), 150.0 (*C6*, *anti*), 149.7 (*C6*, *syn*), 133.3 (*C9*, *syn*), 132.9 (*C9*, *anti*), 130.3 (*C7*, *syn*), 129.7 (*C7*, *anti*), 125.7 (*C8*, *anti*), 125.3 (*C8*, *syn*), 76.6 (*C2*, *syn*), 74.0 (*C4*, *anti*), 73.6 (*C2*, *anti*), 72.3 (*C4*, *syn*), 45.0 (*C3*, *anti*), 44.6 (*C3*, *anti*), 41.9 (*C5*, *anti*), 35.6 (*C5*, *syn*), 34.6 (*C10*, *anti*), 34.5 (C10, *syn*), 31.4 (*C11*, *syn*), 31.3 (*C11*, *anti*), 20.7 (*C12*, *syn*), 17.6 (*C12*, *anti*); ESI-MS: m/z calcd. For $C_{16}H_{22}NaO_3$ 285.1461 found 285.1461 [$MNa^{\cdot+}$]; The e.r. of **2k** was determined by HPLC using a Chiralcel AD-H column (0.70 mL/min^{-1}, *n*-heptane:*i*PrOH 98.5:1.5): t_R = 25.3 min (*anti*), t_R = 30.8 min (*anti*), t_R = 35.9 min, t_R = 42.3 min; The e.r. of **1k** was determined by HPLC using a Chiralcel AD-H column (1.00 mL/min^{-1}, *n*-heptane:*i*PrOH 99:1): t_R = 41.9 min (*anti*), t_R = 52.0 min (*anti*), t_R = 55.3 min (*syn*), t_R = 62.5 min (*syn*).

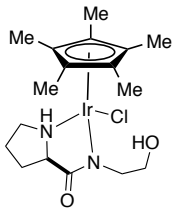
Preparation of 4-(benzo[*d*][1,3]dioxol-5-ylmethyl)-3-hydroxy-4-methyldihydrofuran-2(3*H*)-one, 1l



Prepared according to general procedure **D**. To a solution of (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 15.8 mg, 50.0 µmol, 10.0 mol%) in ^{t}BuOH (1.00 mL), 3-(benzo[*d*][1,3]dioxol-5-yl)-2-methylpropanal (192 mg, 192 µL, 1.00 mmol, 1.00 eq.) and ethyl glyoxalate (47% in toluene, 211 µL, 1.00 mmol, 1.00 eq.) were added. The mixture was stirred at room temperature for 24 h. A sample of 0.20 mL was taken from the reaction mixture and the solvent was evaporated. The crude was analyzed by HPLC to determine diastereo- and enantioselectivity of the aldehyde intermediate **2l** (d.r. 1.3 (*syn*):1 (*anti*), e.r. 89:11 (*syn*), 64:36 (*anti*). Water (4 mL) was added and the solution degassed with argon for 1 h, before $(IrCl_2(Cp^*))_2$ (0.65 mg, 0.80 µmol, 0.10 mol%) and sodium formate (272 mg, 4.00 mmol, 5.00 eq.) were added. The reaction mixture was stirred at 40 °C for 15 h. The reaction mixture was extracted with ethyl acetate and filtered over a short plug of silica. The solvent was removed under reduced pressure and the residue purified by column chromatography (cyclohexane/ethyl acetate, 9:1 → 2:1) yielding the desired product (**1l**, 105 mg , 420 µmol, 42% d.r. 1 (*anti*):1 (*syn*),e.r. 91:9 (*anti*), 64:36 (*syn*) by HPLC) as a yellowish sticky oil. R_f = 0.10 (cyclohexane / ethyl acetate, 4:1); $[\alpha]_D$ = + 6.1 (*c* 1.00, $CHCl_3$); ν_{max} (neat): 3441 (w), 2905 (w), 1775 (s), 1490 (s), 1442 (m) 1362 (w), 1242 (s), 1187 (m), 1099 (s), 1037 (s), 1000 (s), 927 (m), 879 (w), 817 (w), 652 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.77 (1H, d, ^3J 5.8, C10*H*, *syn*), 6.75 (1H, d, ^3J 5.8, C10*H*, *anti*), 6.65 (1H, d, ^4J 1.7, C7*H*, *syn*), 6.61 (1H, dd, ^3J 7.9, ^4J 1.7, C11*H*, *syn*), 6.61 (1H, d, ^4J 1.7, C7*H*, *anti*), 6.57 (1H, dd, ^3J 7.8, ^4J 1.7, C11*H*, *anti*), 5.96 (2H, s, C13*H*, *anti*), 5.94 (2H, s, C13*H*, *syn*), 4.26 (1H, d, ^2J 9.7, C4*H*, *syn*), 4.21

(1H, s, C2*H*, *anti*), 4.20 (1H, s, C2*H*, *syn*), 4.09 (1H, d, ^{2}J 8.9, C4*H*, *anti*), 3.92 (1H, d, ^{2}J 9.0, C4*H*, *anti*), 3.71 (1H, dd, ^{2}J 9.4, ^{4}J 1.1, C4*H*, *syn*), 2.79 (1H, d, ^{2}J 13.9, C5*H*, *anti*), 2.78 (1H, br, O*H*, *anti*), 2.76 (1H, d, 2J 13.9, C5H, *anti*), 2.72 (1H, d, ^{2}J 14.0, C5*H*, *syn*), 2.59 (1H, d, ^{3}J 3.4, O*H*, *syn*), 2.53 (1H, d, ^{2}J 14.0, C5*H*, *syn*), 1.17 (3H, s, C12*H*, *syn*), 1.08 (3H, s, C12*H*, *anti*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 177.4 (*C1*, *syn*), 177.2 (*C1*, *anti*), 148.0 (*C8*, *anti*) 147.8 (*C8*, *syn*), 146.8 (*C9*, *anti*) 146.7 (*C9*, *syn*), 130.0 (*C6*, *syn*) 129.8 (*C6*, *anti*), 123.7 (*C11*, *syn*), 123.1 (*C11*, *anti*), 110.9 (*C7*, *syn*), 110.4 (*C7*, *anti*), 108.5 (*C10*, *anti*), 108.3 (*C10*, syn), 101.3 (*C13*, *anti*), 101.1 (*C13*, *syn*), 76.5 (*C2*, *syn*), 74.2 (*C4*, *anti*), 73.7 (*C2*, *anti*), 72.6 (*C4*, *syn*), 45.2 (*C3*, *anti*), 44.8 (*C3*, *syn*), 42.3 (*C5*, *syn*), 36.3 (*C5*, *anti*), 21.0 (*C12*, *syn*), 17.6 (*C12*, *anti*); ESI-MS: m/z calcd. For $C_{13}H_{14}NaO_5$ 273.0733 found 273.0737 [$MNa^{\cdot +}$]; The e.r. of **2l** was determined by HPLC using a Chiralcel AD-H column (1.00 mL/min^{-1}, *n*-heptane:*i*PrOH 90:10): t_R = 16.9 min (*syn*), t_R = 18.2 min (*anti*), t_R = 19.5 min (*anti*), t_R = 23.1 min (*syn*); The e.r. of **1l** was determined by HPLC using a Chiralcel ID column (1.00 mL/min^{-1}, *n*-heptane:*i*PrOH 80:20): t_R = 10.6 min (*syn*), t_R = 12.4 min (*syn*), t_R = 14.9 min (*anti*), t_R = 16.7 min (*anti*).

Preparation of Transfer Hydrogenation Catalyst



To a solution of $(IrCl_2(Cp^*))_2$ (19.9 mg, 25.0 µmol, 1.00 eq.) in dry toluene was added (*R*)-N-(2-hydroxyethyl)pyrrolidine-2-carboxamide ((*R*)-**11**, 7.91 mg, 50.0 µmol, 2.00 eq.) and triethylamine (11.0 µL, 75.0 µmol, 3.00 eq.). The solution was stirred at room temperature for 4h. The solvent was decanted with a syringe to obtain a yellow precipitate. X-ray quality crystals (9.82 mg, 19.0 µmol, 76%, m.p. 168 °C (decomp.)) were obtained by recrystallization from hexane/chloroform by liquid diffusion technique. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.63 (1H, br, N*H*), 4.33 (1H, br, O*H*), 3.98 (1H, m, C2*H*), 3.79 (2H, m, C8*H*, C9*H*), 3.64 (1H, m, C9*H*), 3.58 (1H, br, C8*H*), 3.44 (1H, m, C5*H*), 3.13 (1H, m, C5*H*), 2.14 (1H, m, C3*H*), 2.02 (1H, m, C3*H*), 1.85 (1H, m, C4*H*), 1.78 (1H, m, C4*H*), 1.67 (15H, s, C12*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 181.5 (*C6*), 85.5 (*C10*), 65.1 (*C2*), 64.0 (*C9*), 54.3 (*C5*), 52.4 (*C8*), 29.8 (*C3*), 26.7 (*C4*), 9.5 (*C11*).

6 References

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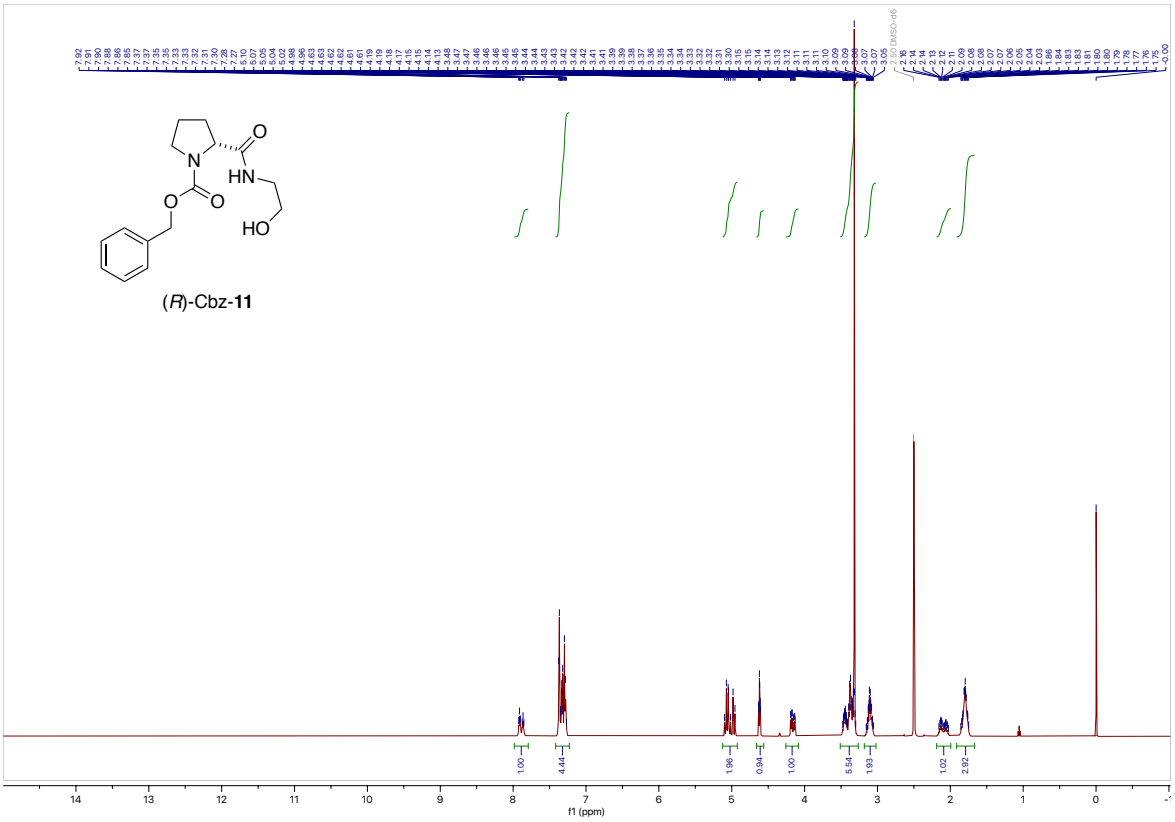
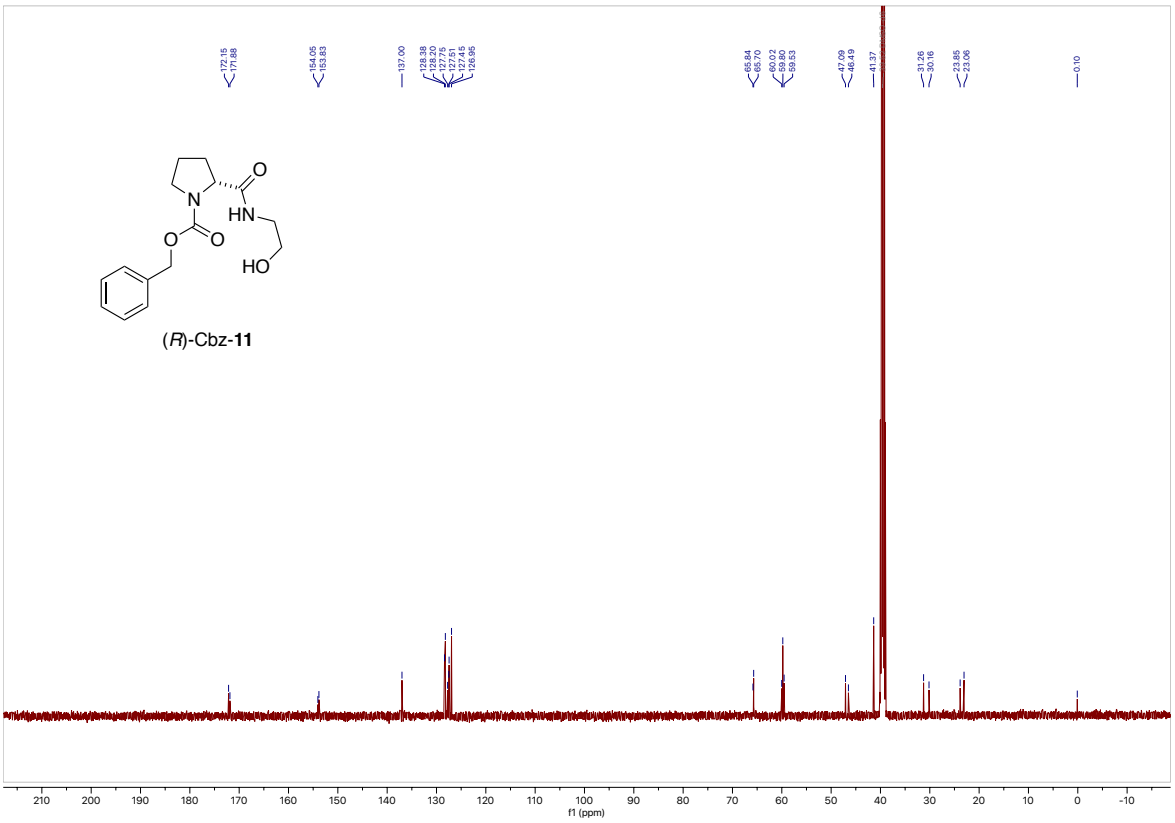
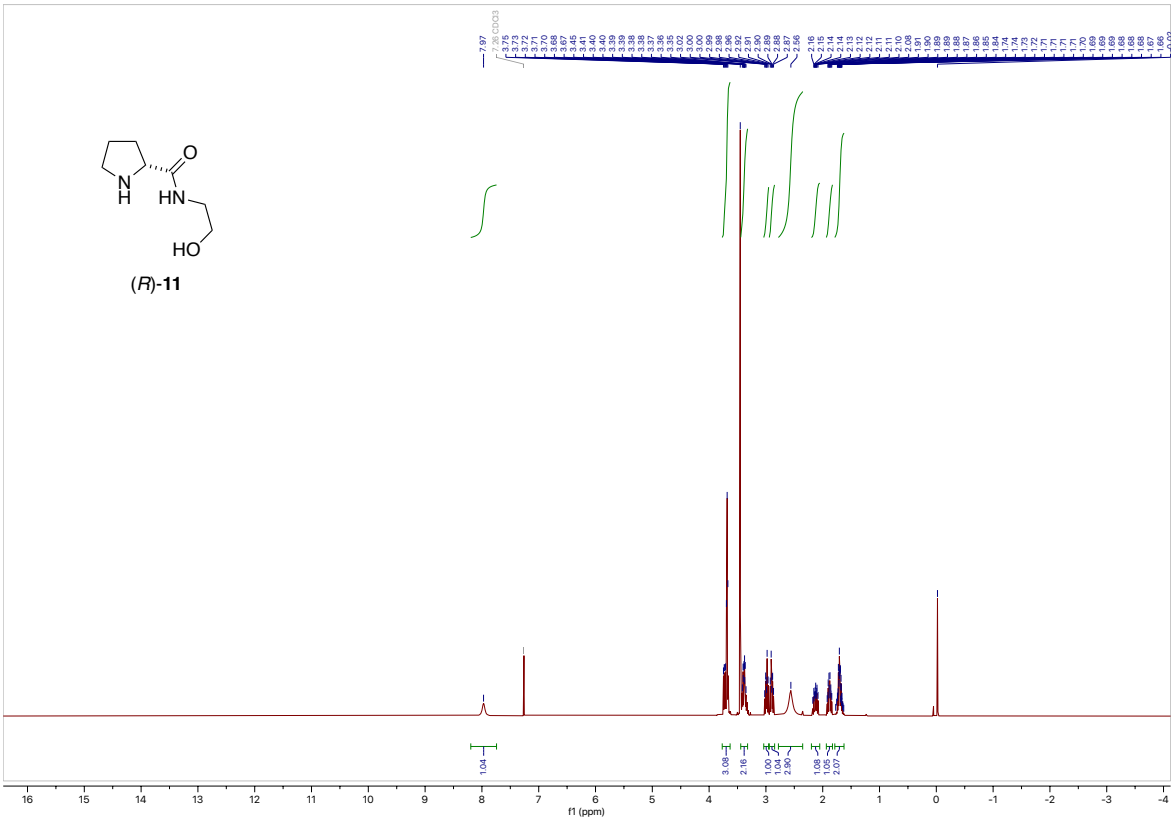
7 NMR Data



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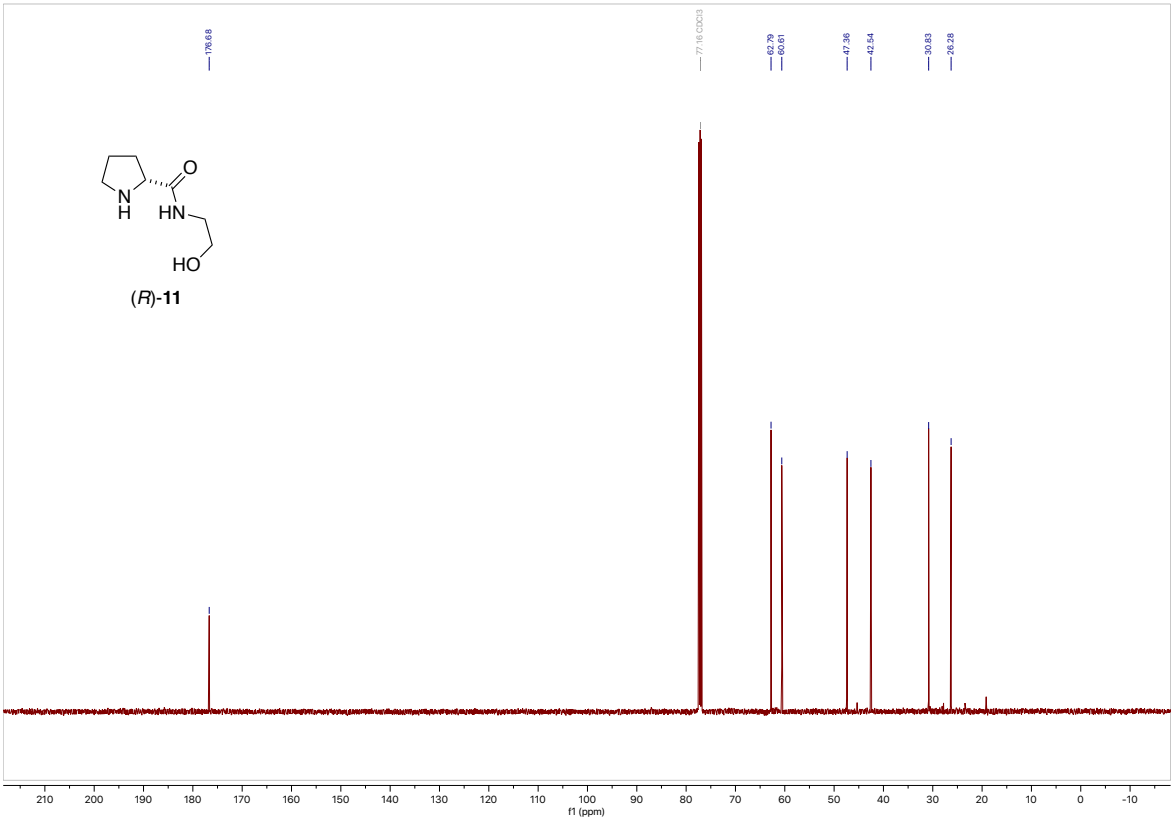
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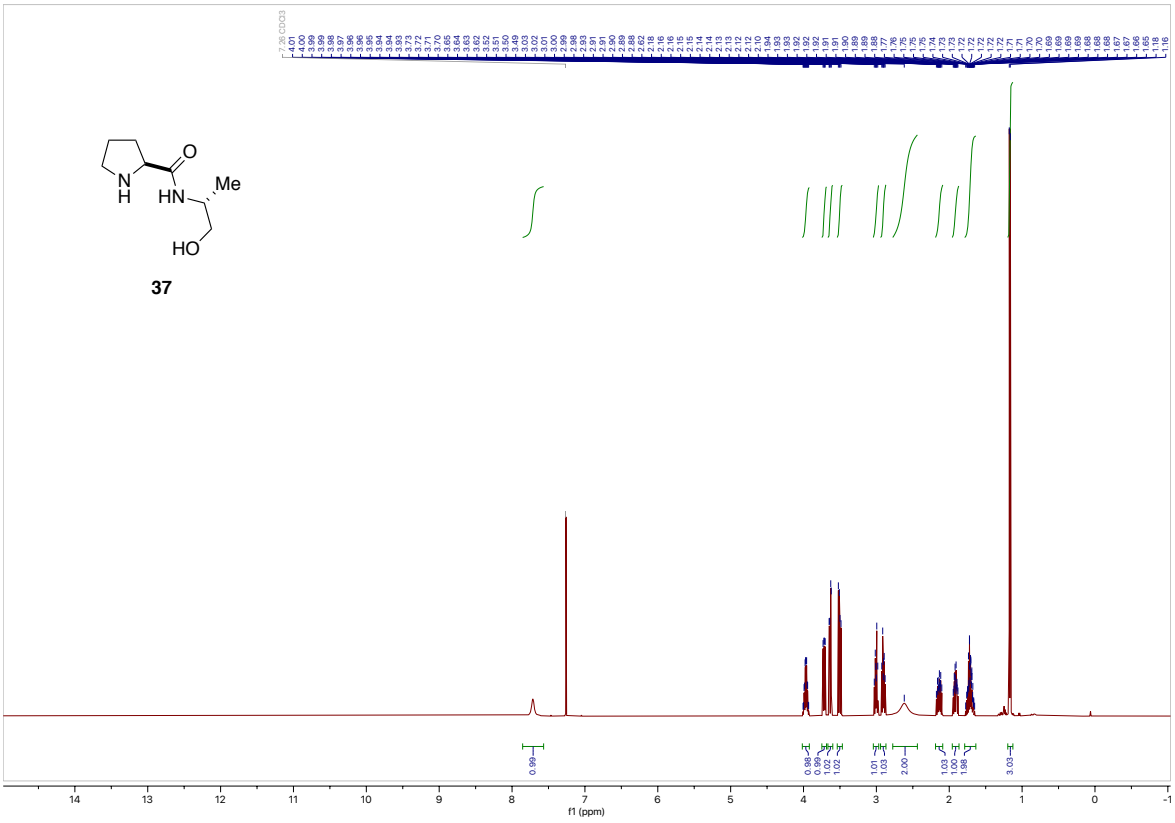
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H
HN
Me
HO
37
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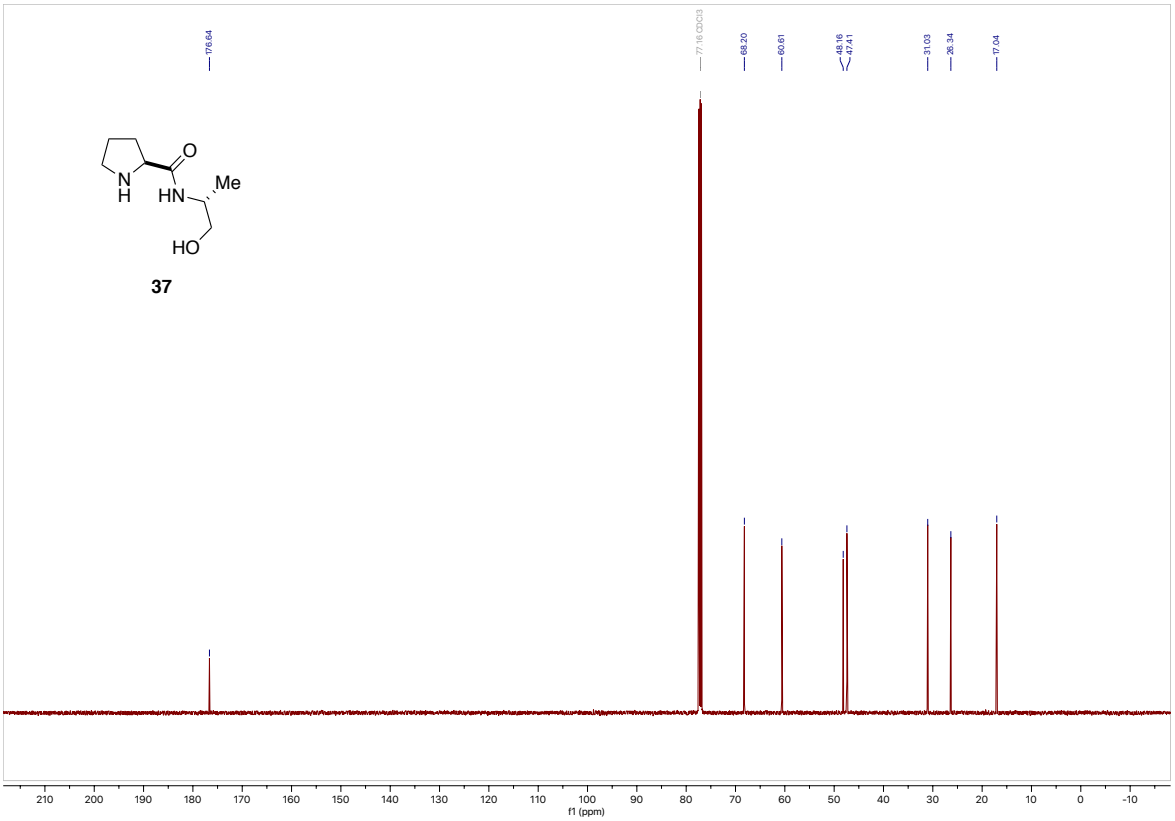
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Me
HO
37
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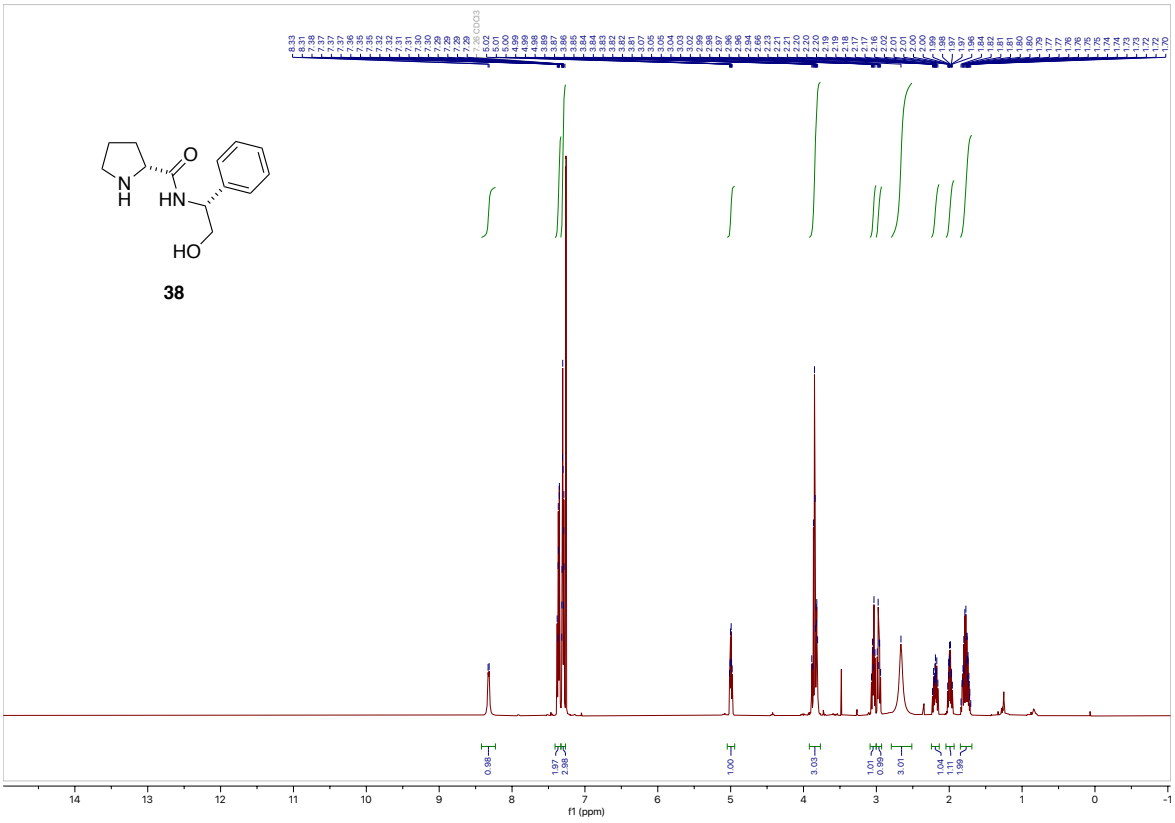
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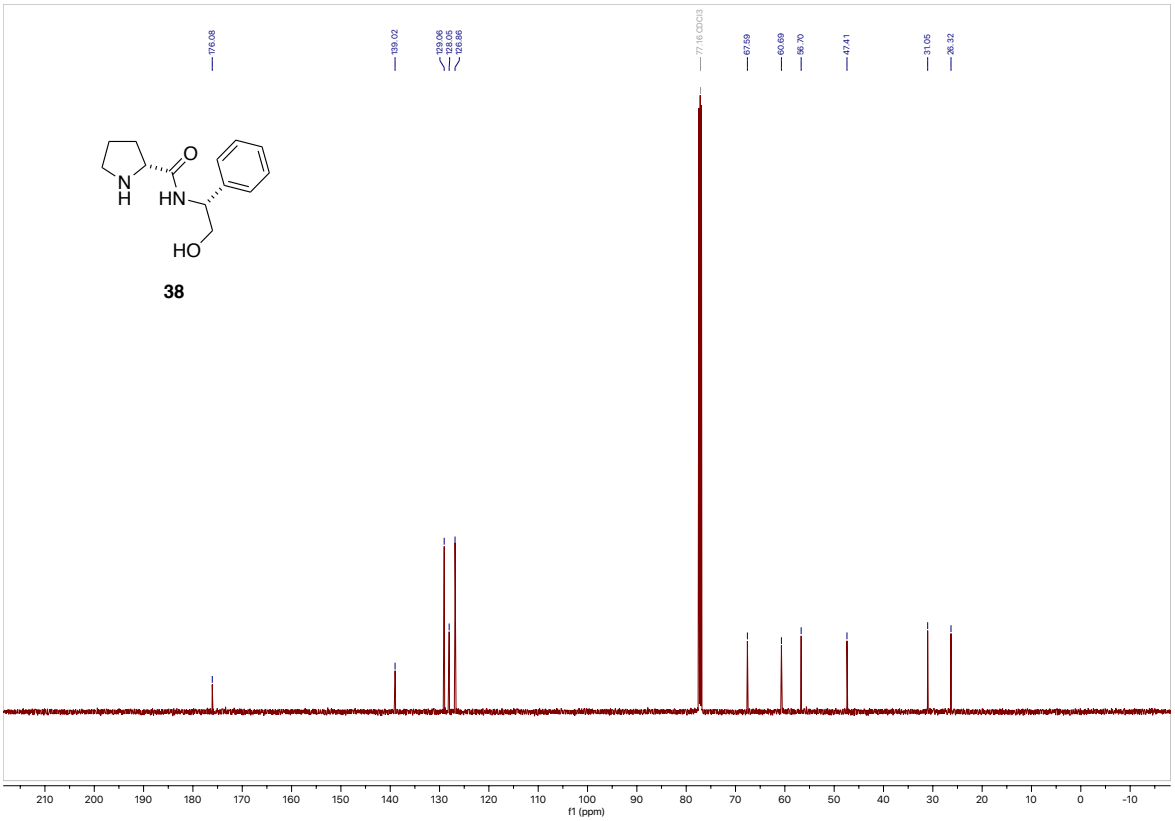
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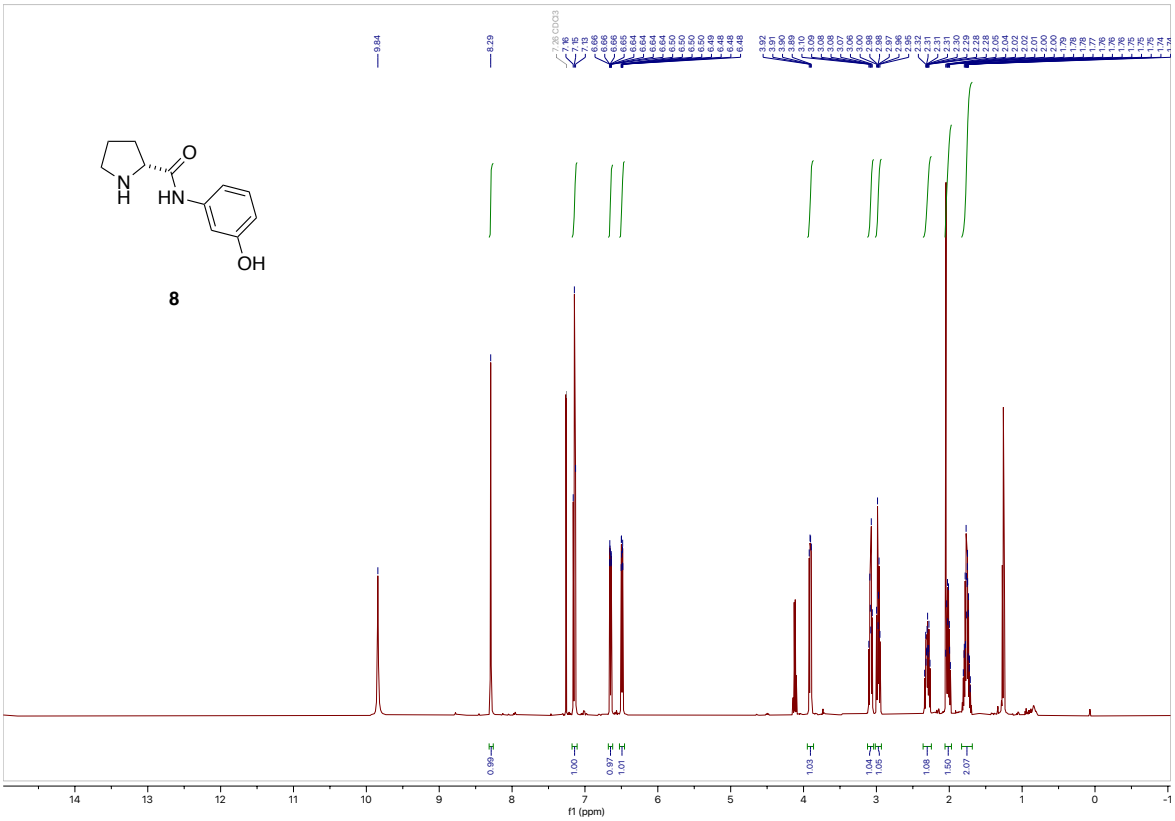
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6.65
6.64
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6.64
6.64
6.50
6.50
6.50
6.50
6.49
6.48
6.48
6.48
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3.91
3.90
3.89
3.10
3.09
3.08
3.08
3.07
3.06
3.00
2.99
2.98
2.98
2.97
2.96
2.95
2.32
2.31
2.31
2.30
2.30
2.29
2.28
2.28
2.06
2.04
2.02
2.02
2.01
2.00
2.00
1.79
1.78
1.78
1.77
1.76
1.76
1.76
1.75
1.75
1.75
1.74
1.74
0.99
1.00
0.97
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1.50
2.07
f1 (ppm)
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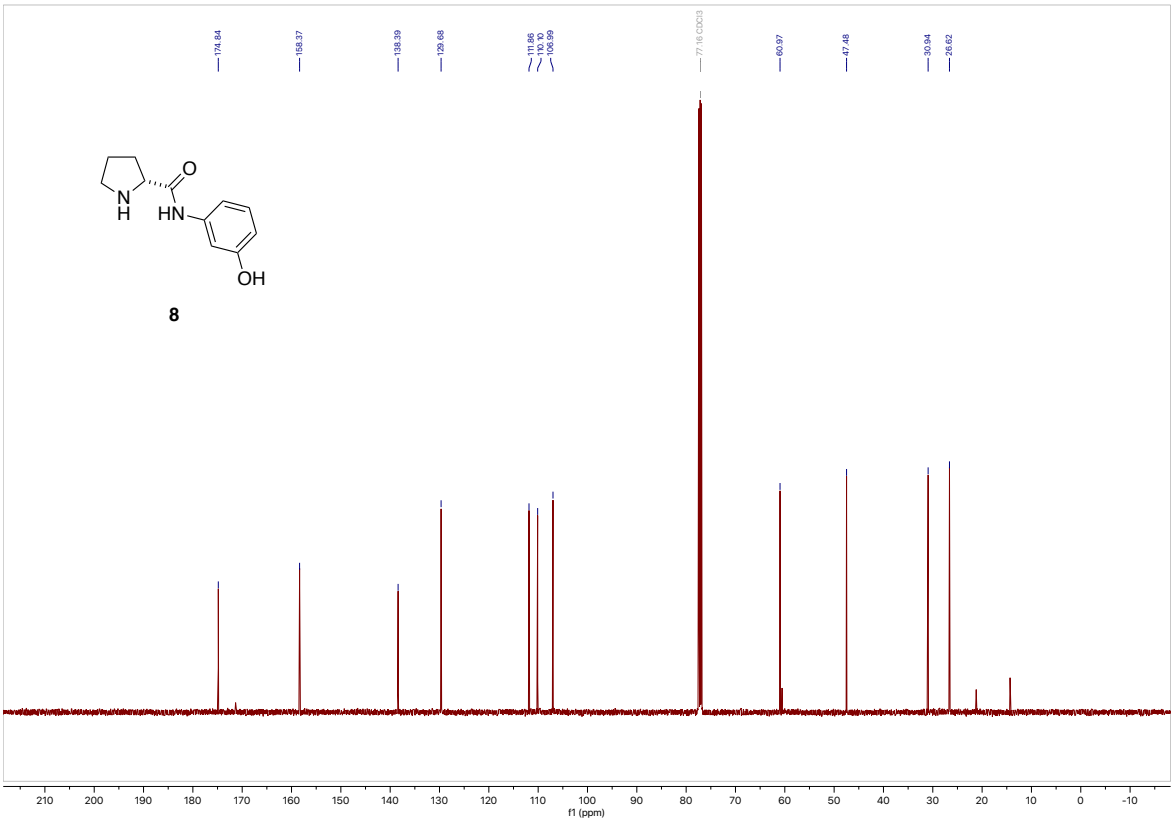
N
H
HN
OH
8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110.10
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26.62
f1 (ppm)
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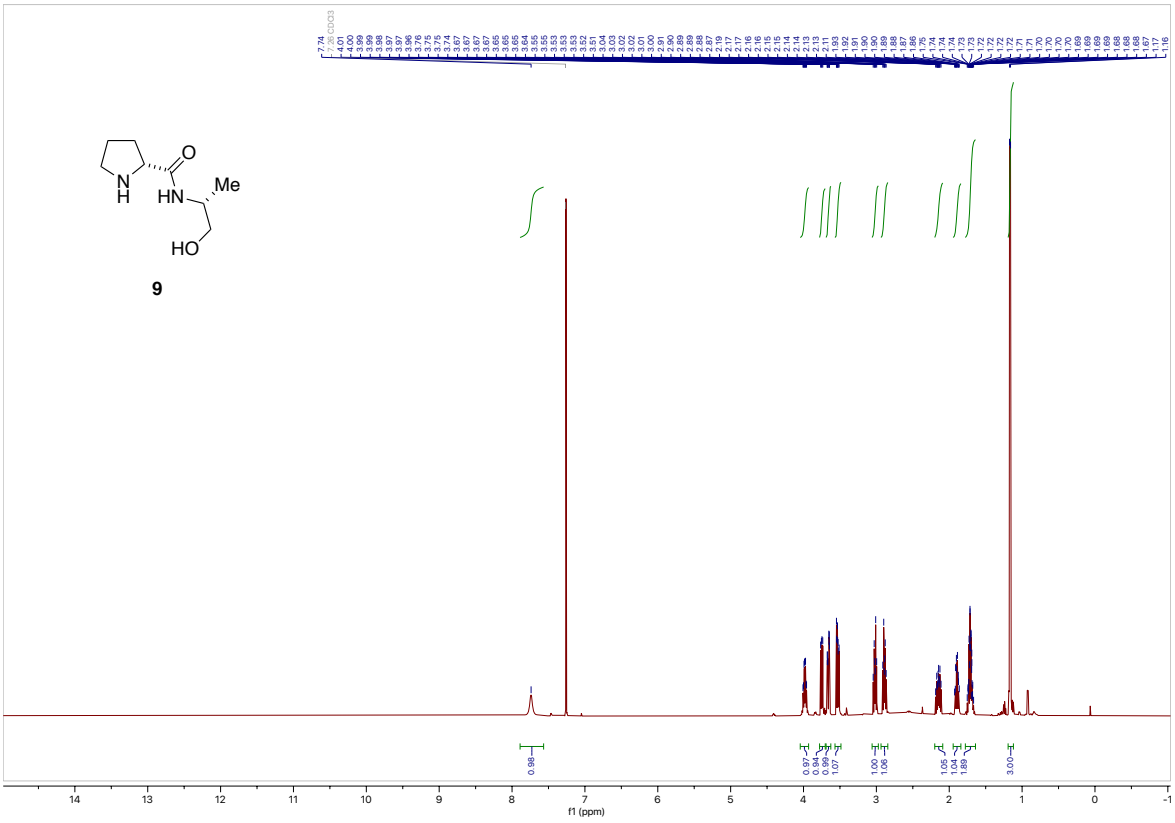
N
H
HN
OH
8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H
HN
Me
HO
9
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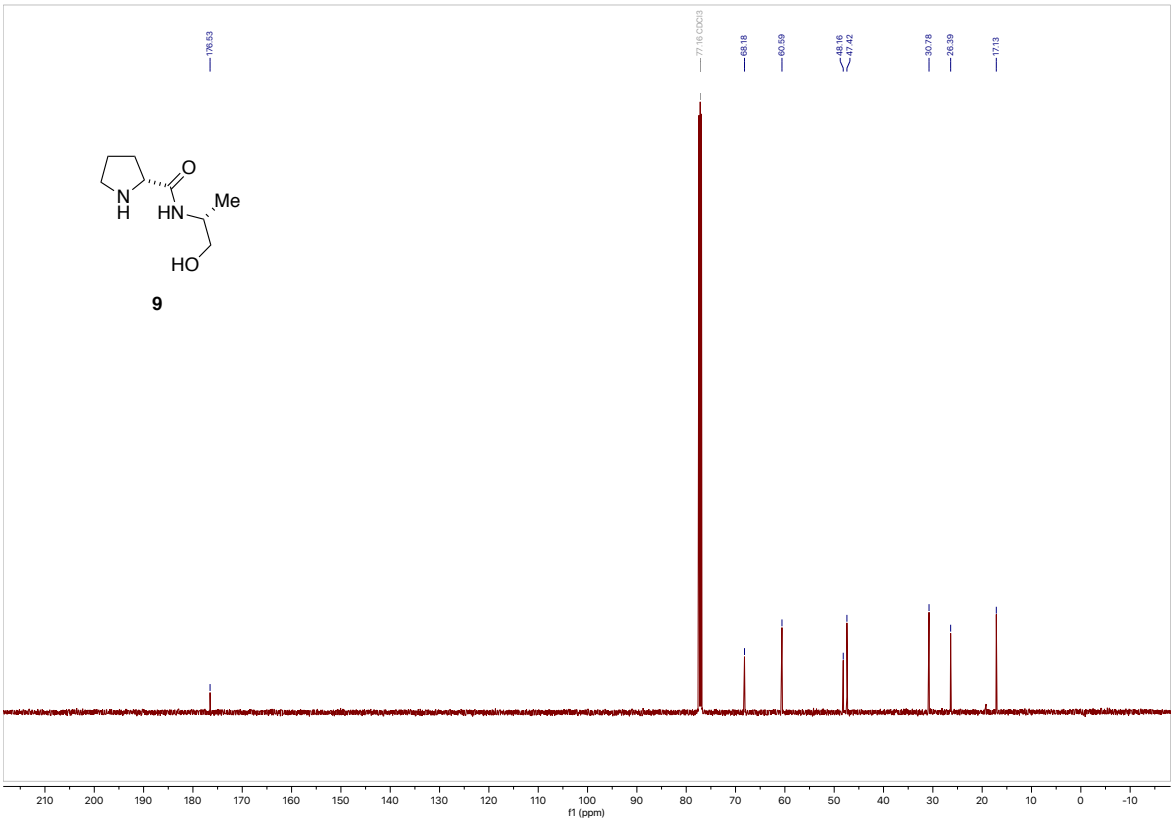
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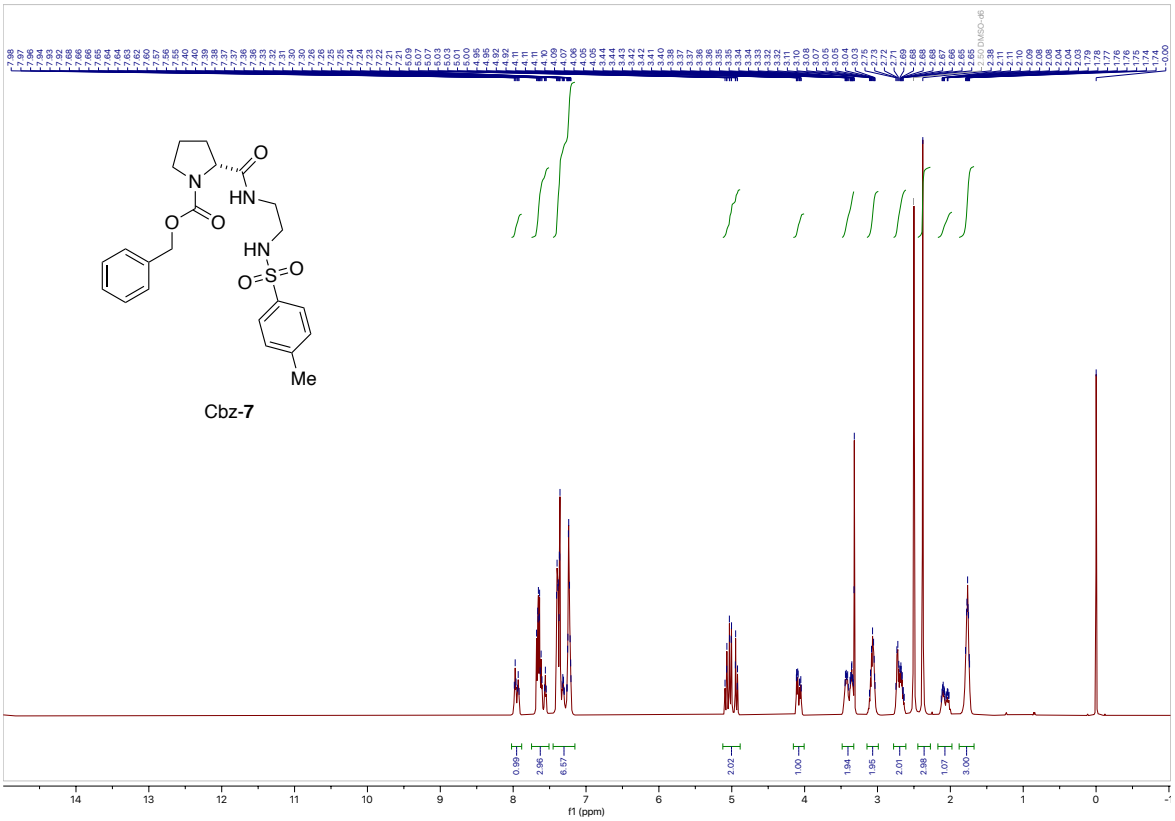
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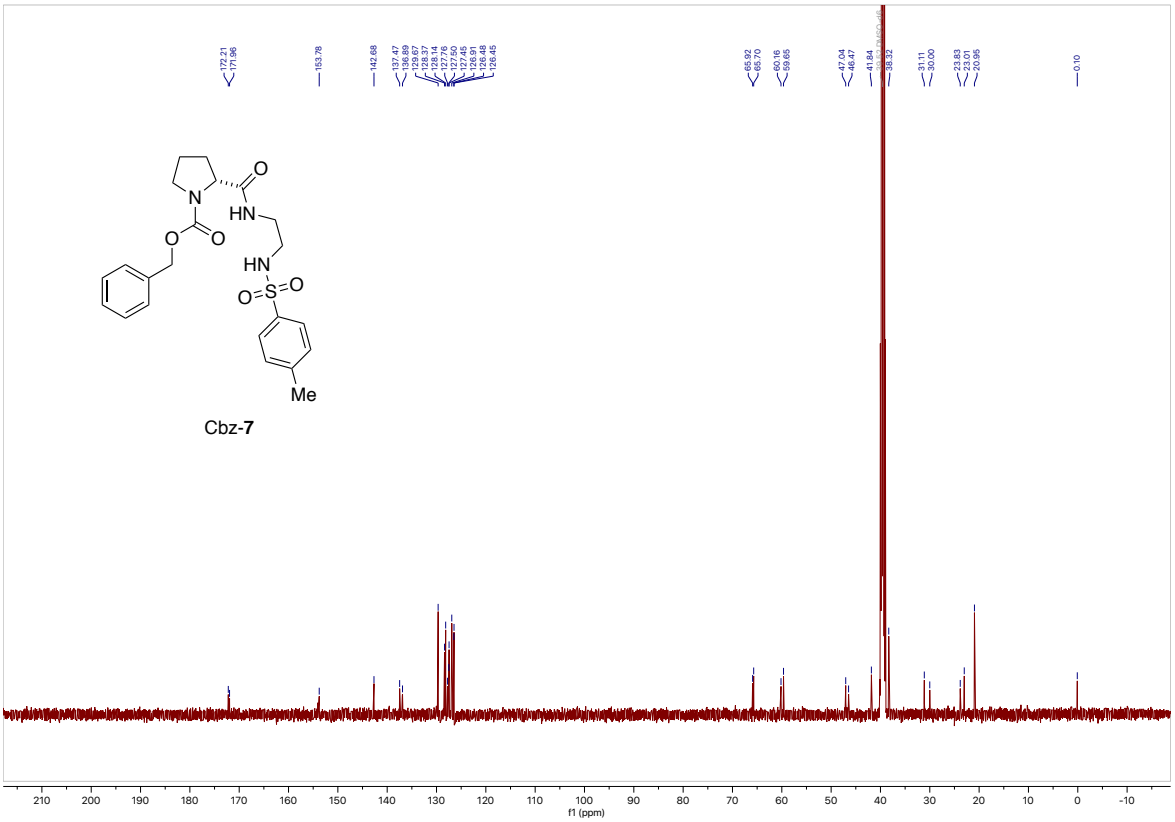
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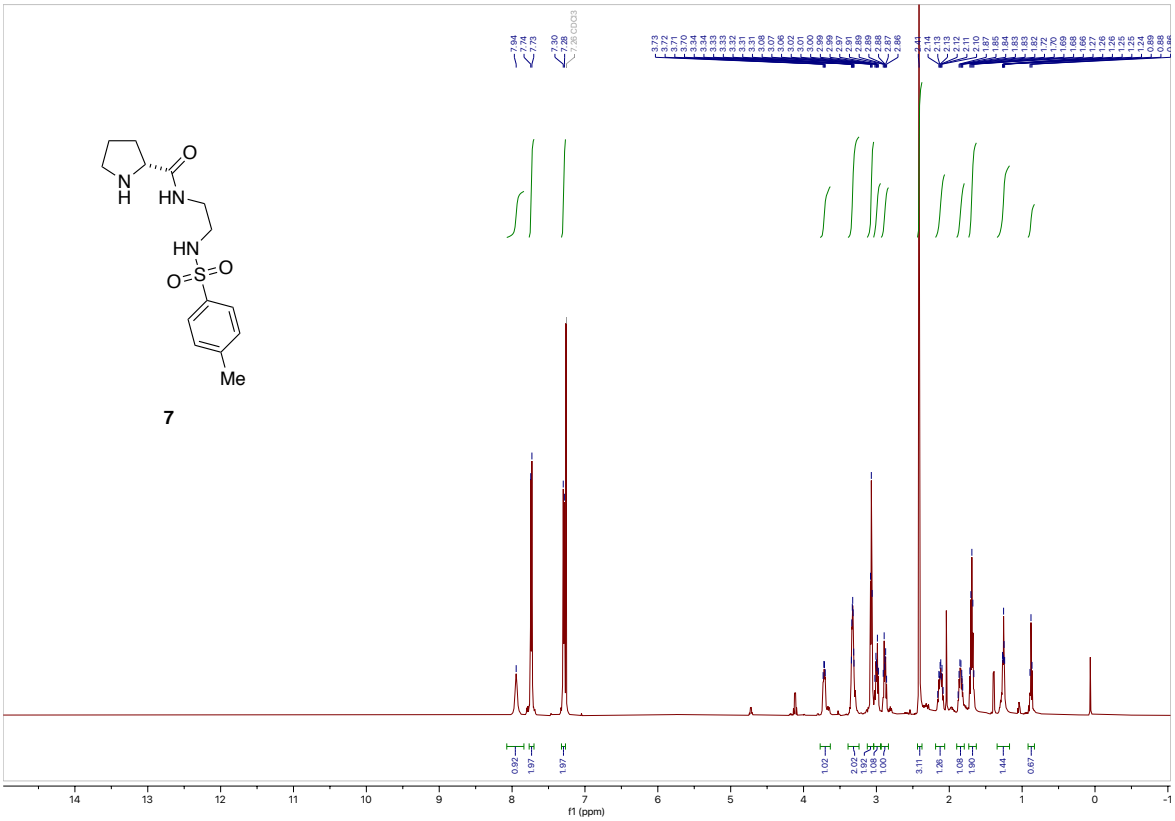
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3.73
3.72
3.71
3.70
3.34
3.33
3.32
3.31
3.07
3.06
3.02
3.01
3.00
2.99
2.97
2.91
2.89
2.88
2.87
2.86
3.41
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1.83
1.82
1.72
1.70
1.69
1.68
1.66
1.27
1.26
1.25
1.24
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1.97
1.02
2.02
1.92
1.08
1.00
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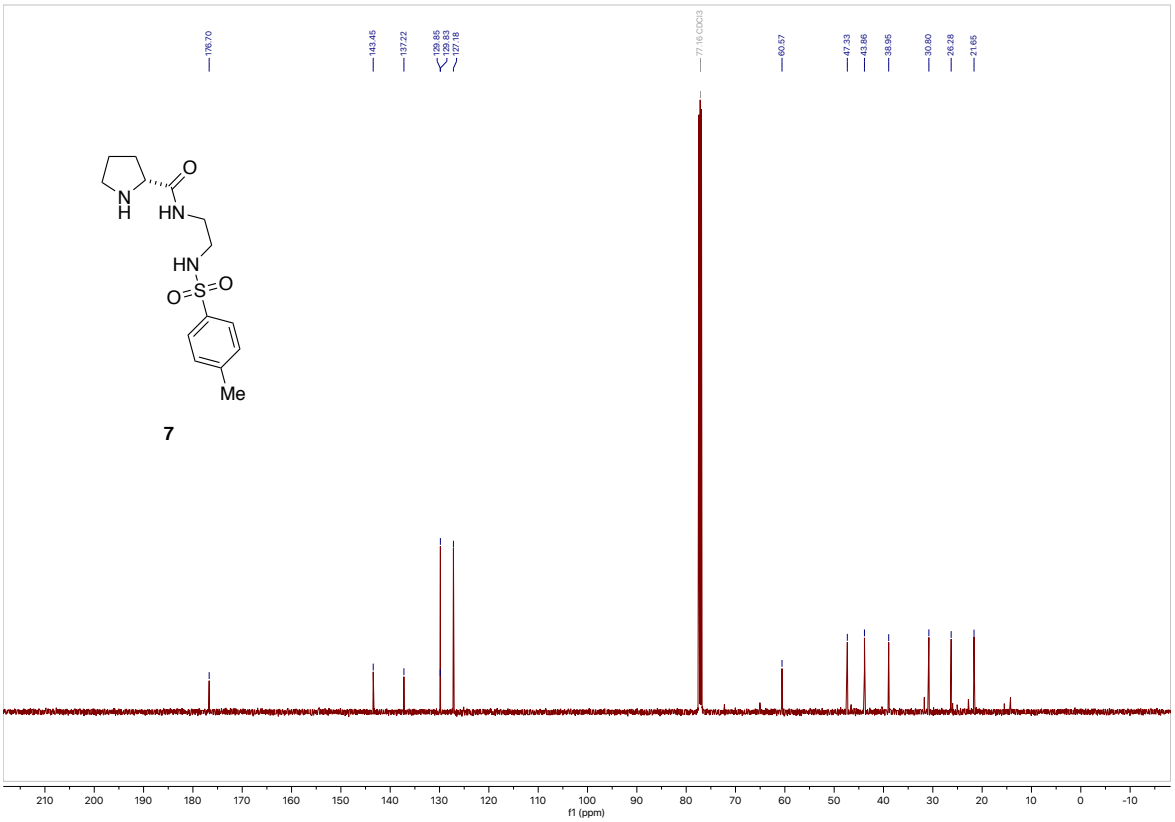
Me
7
f1 (ppm)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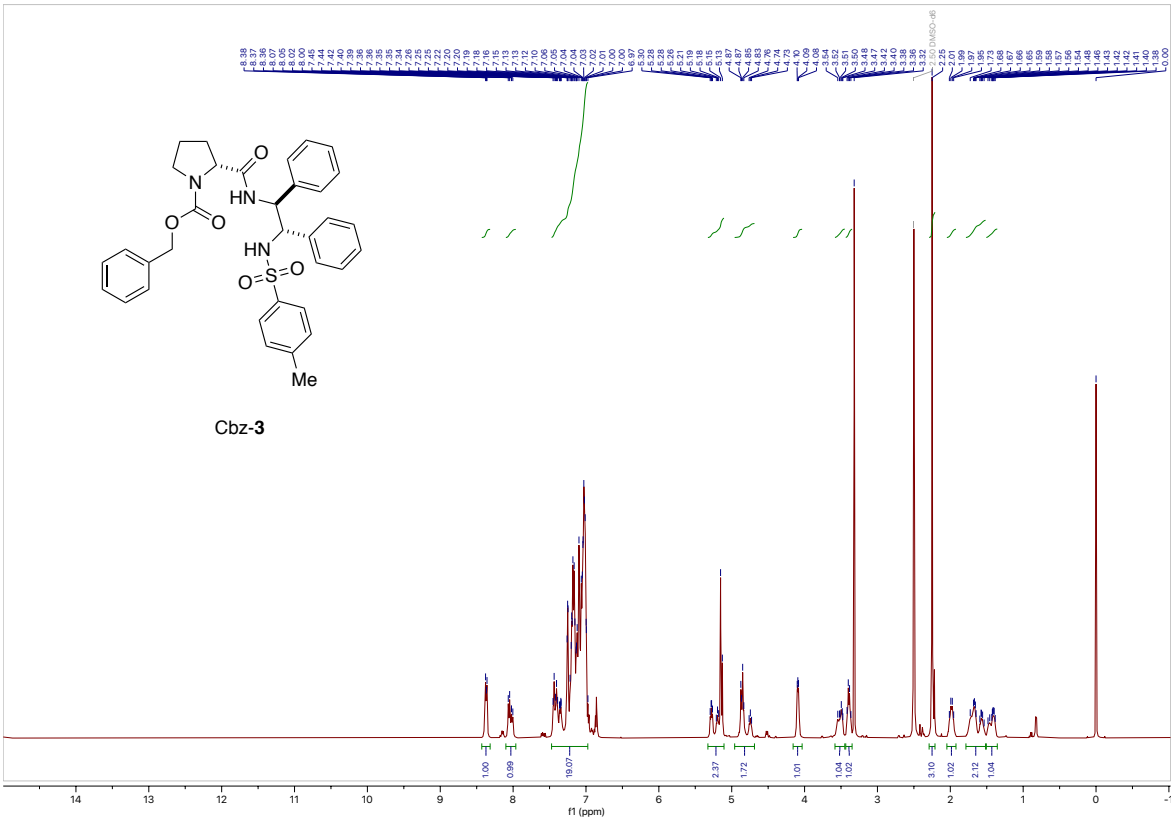
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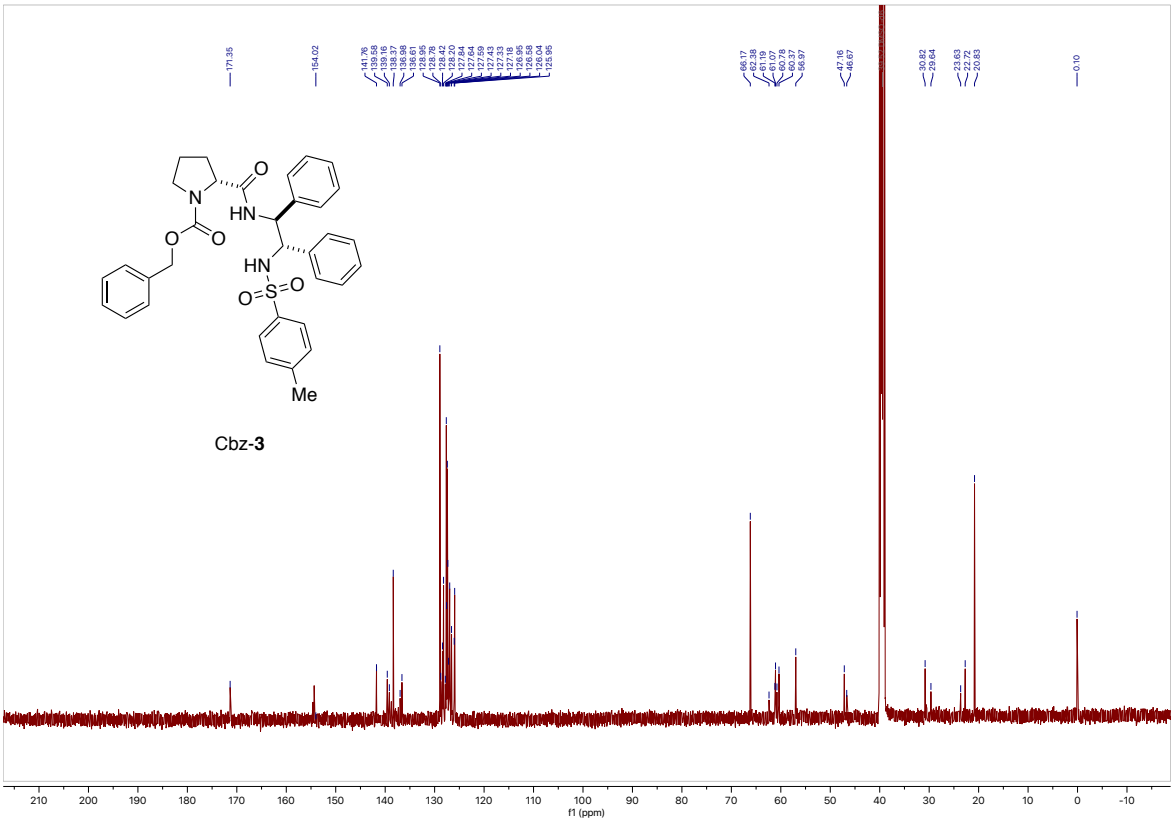
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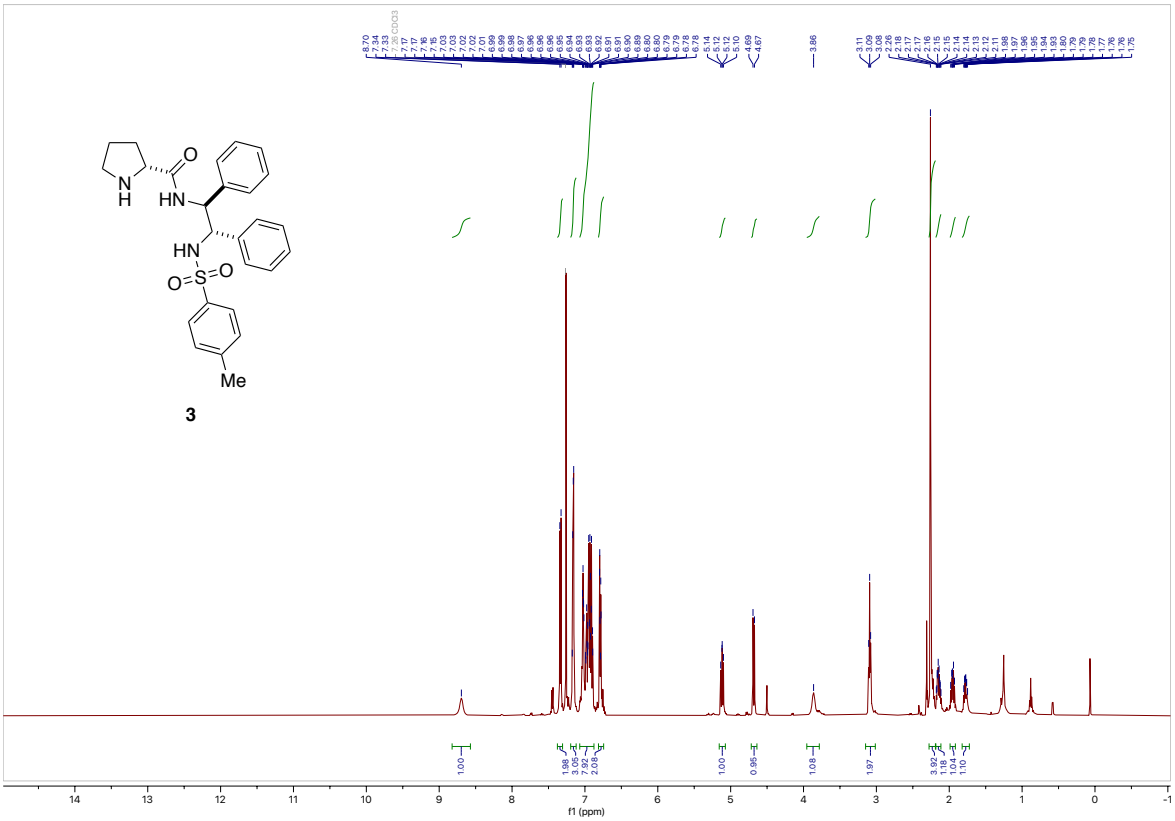
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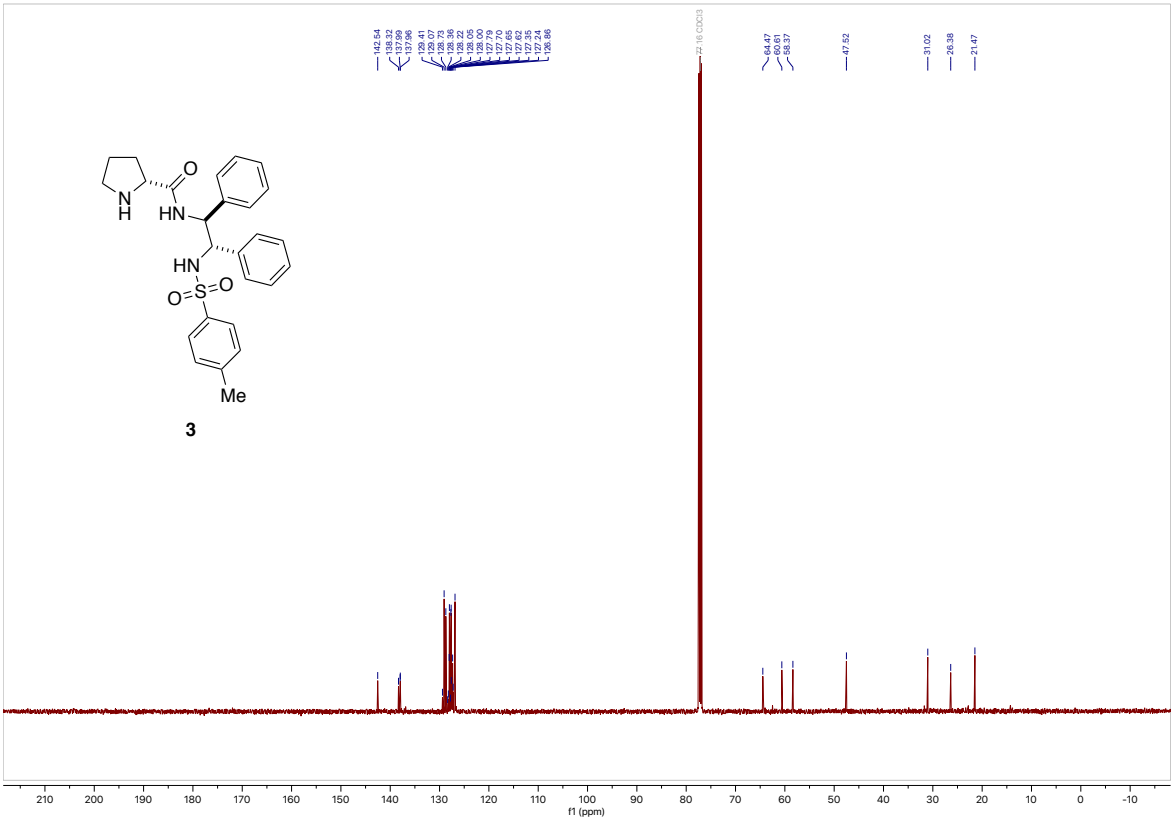
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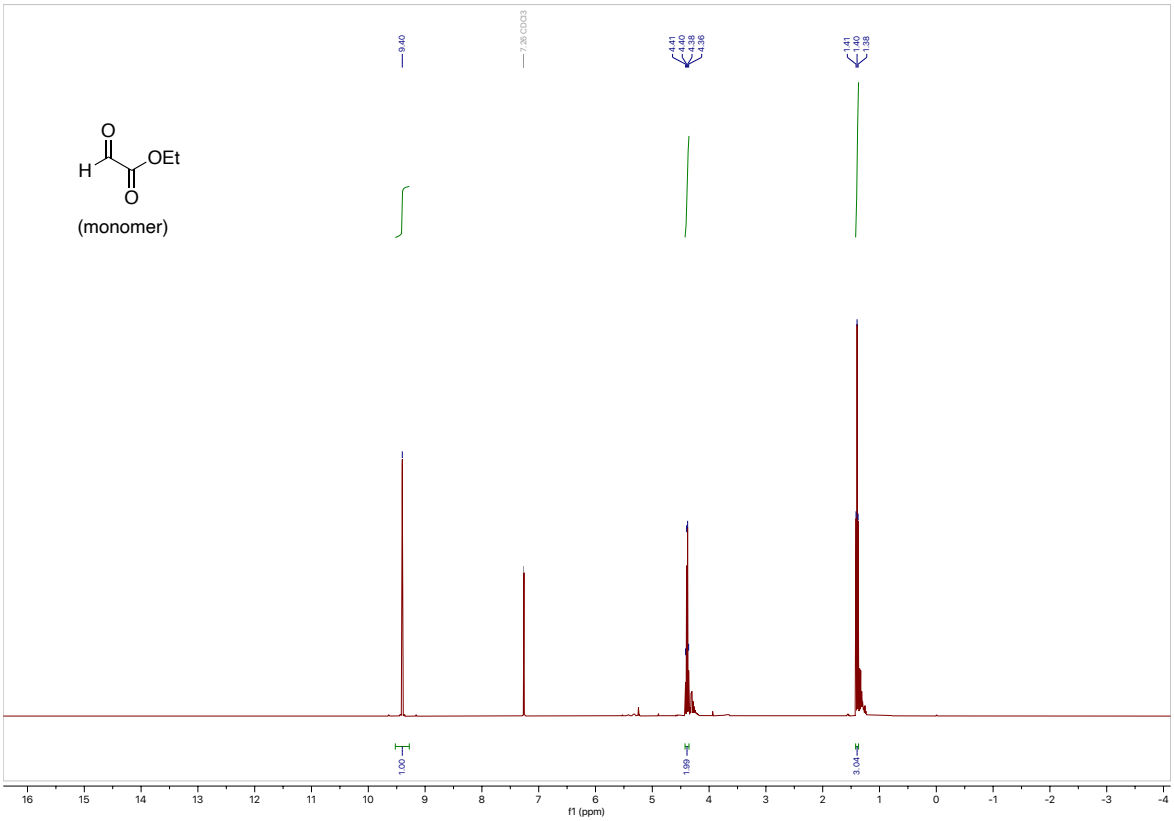
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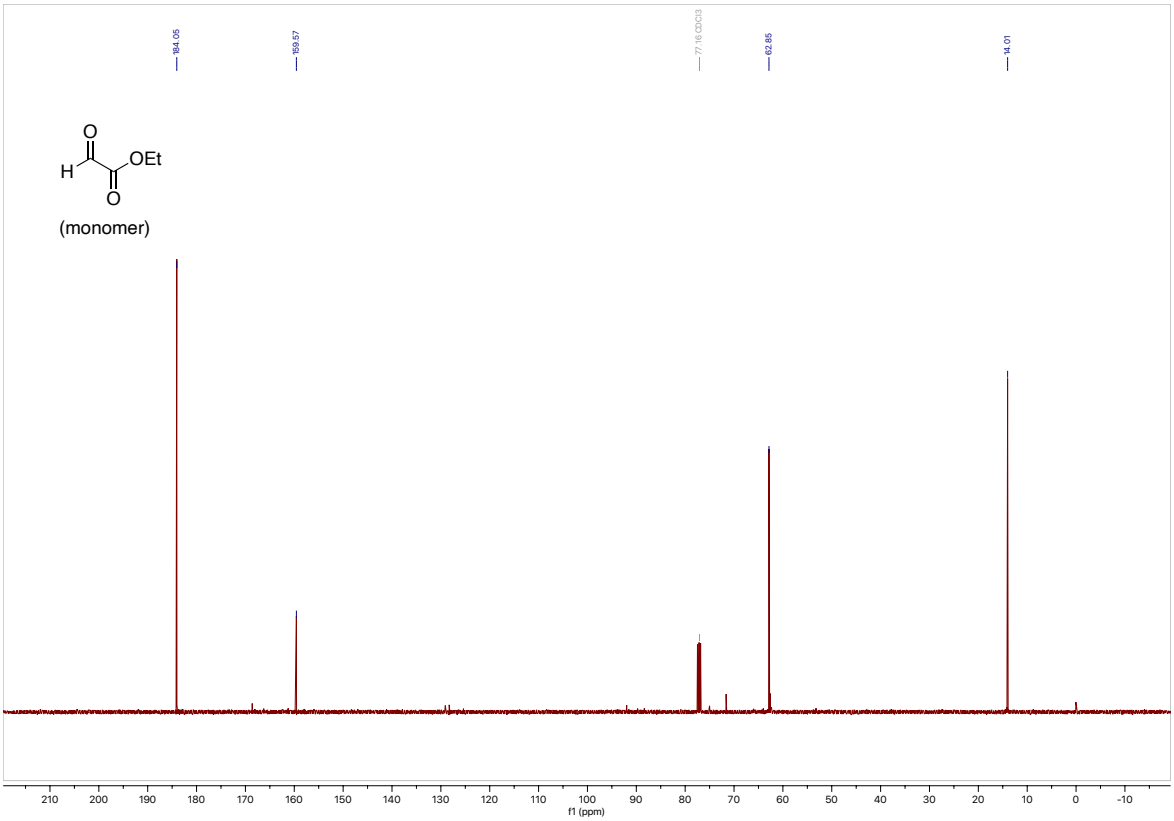
1.99
3.04
f1 (ppm)
(monomer)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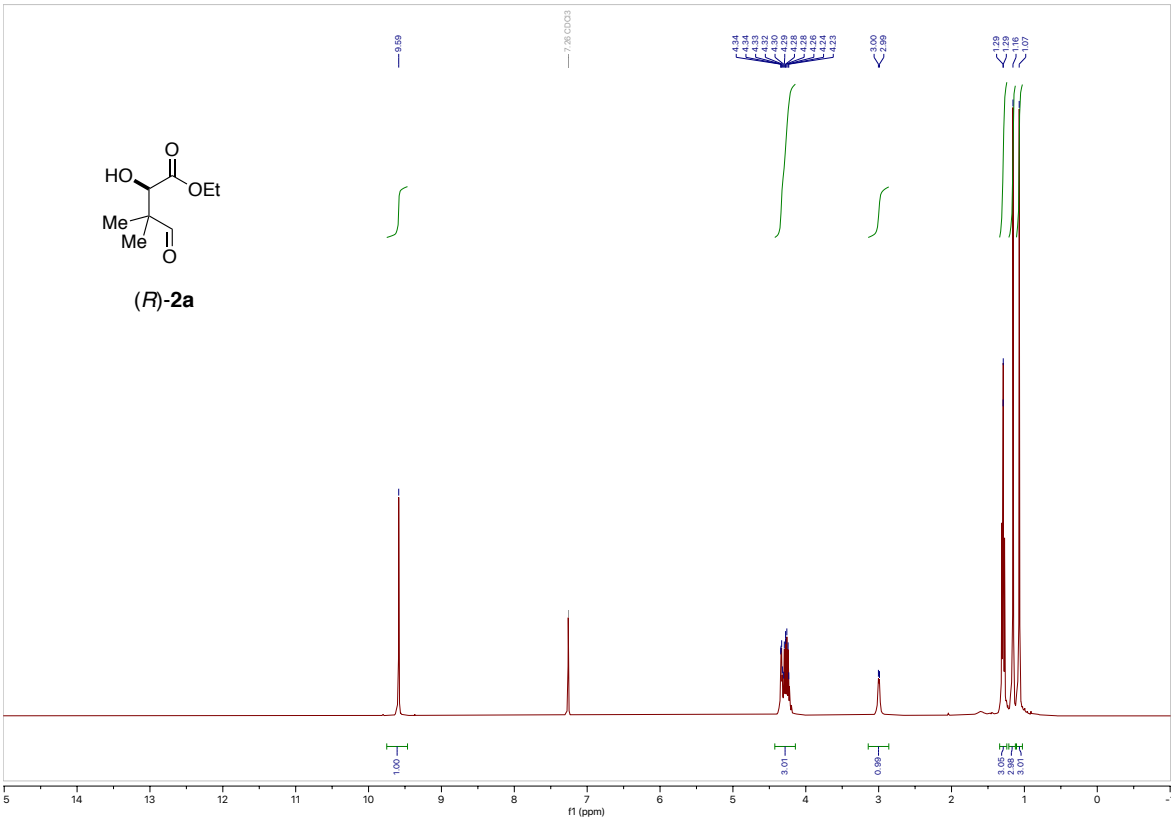
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4.28
4.26
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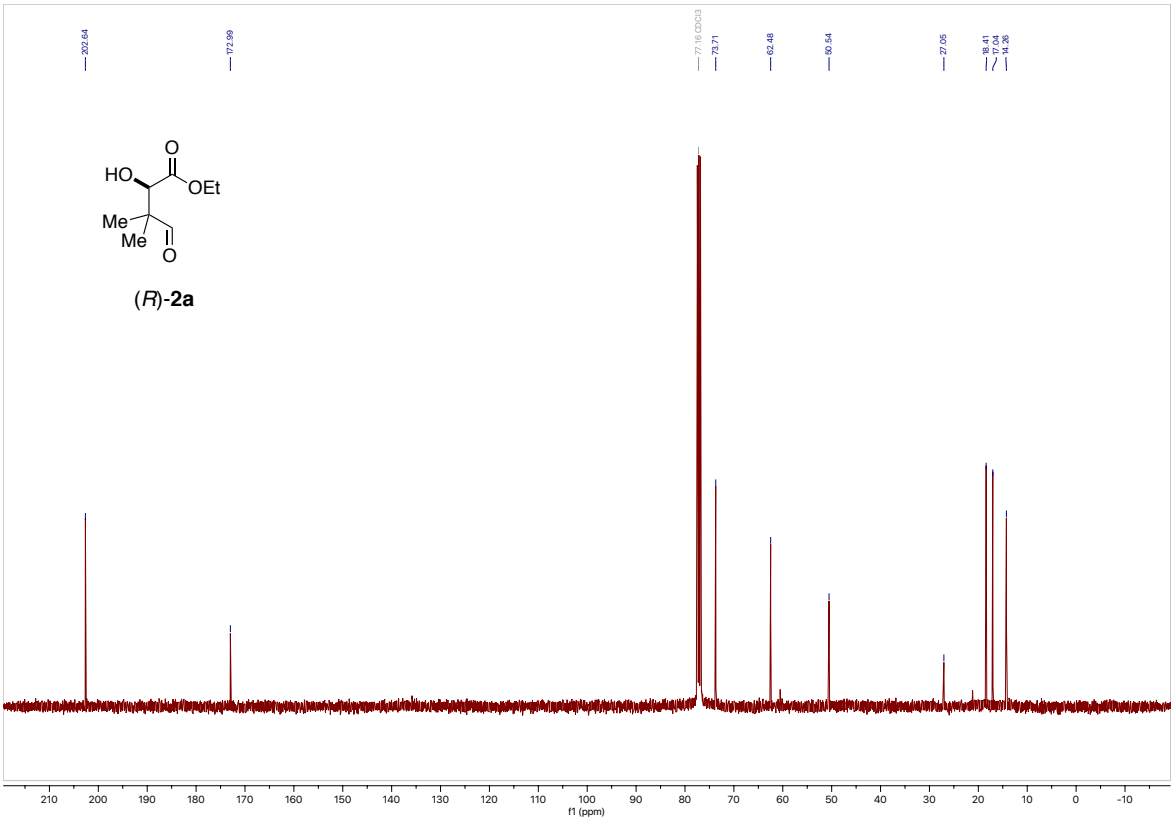
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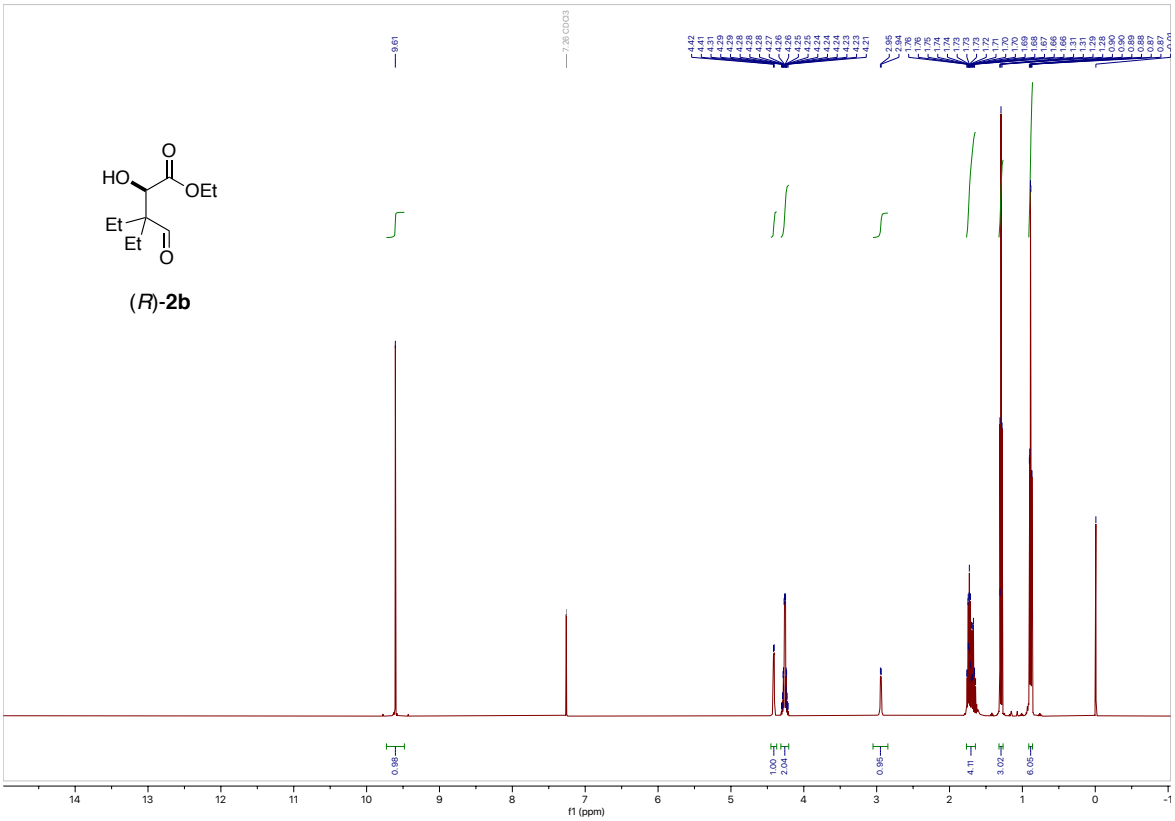
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Et
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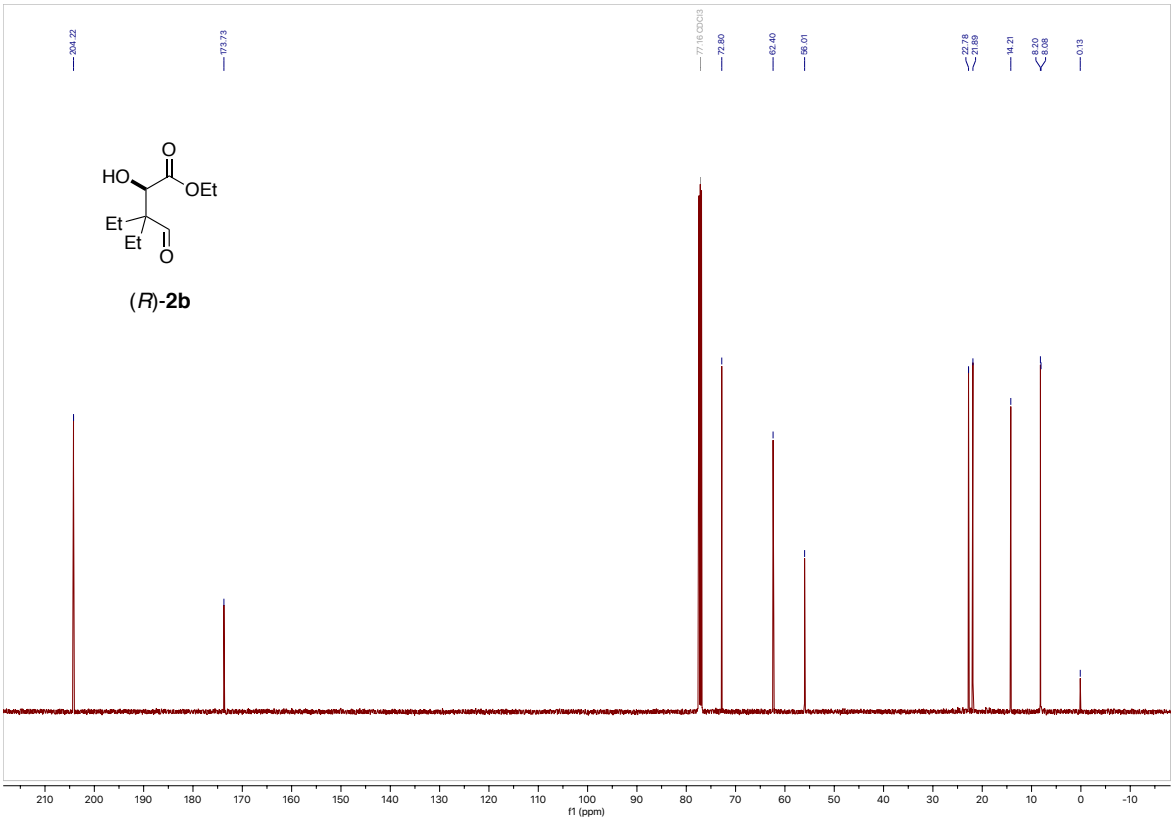
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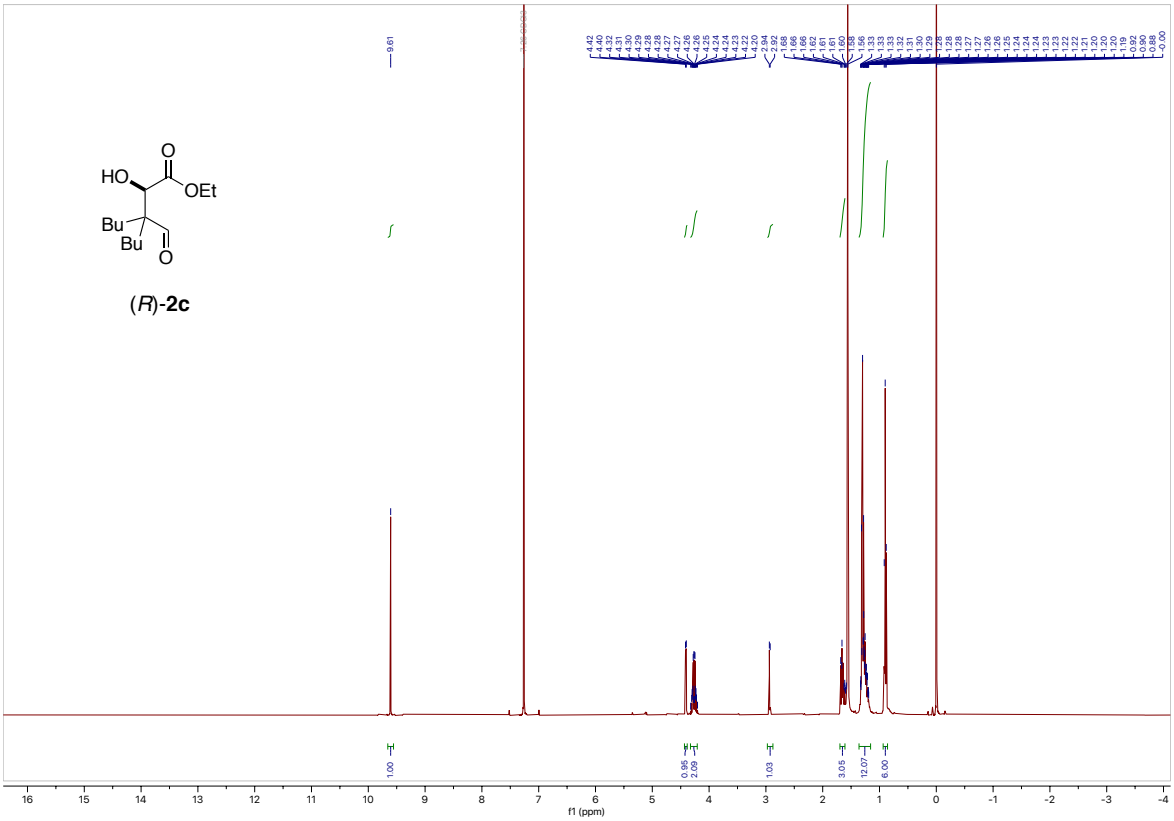
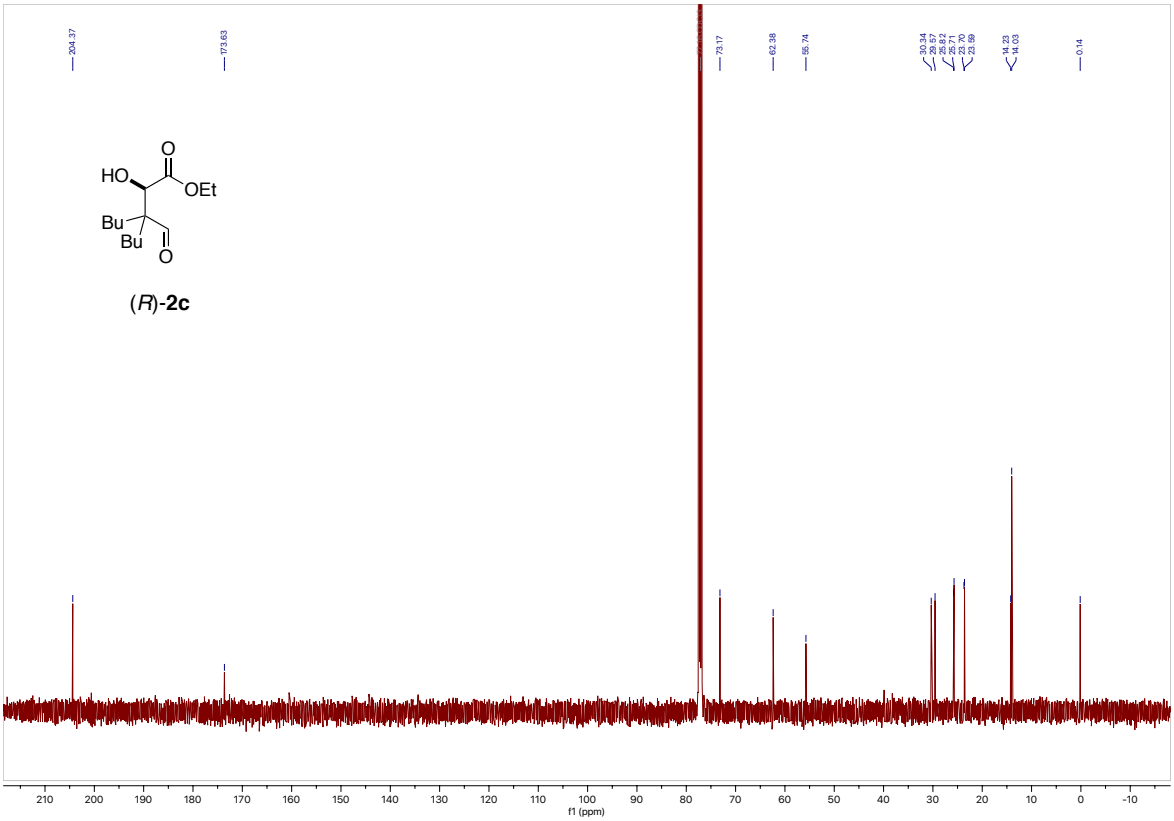
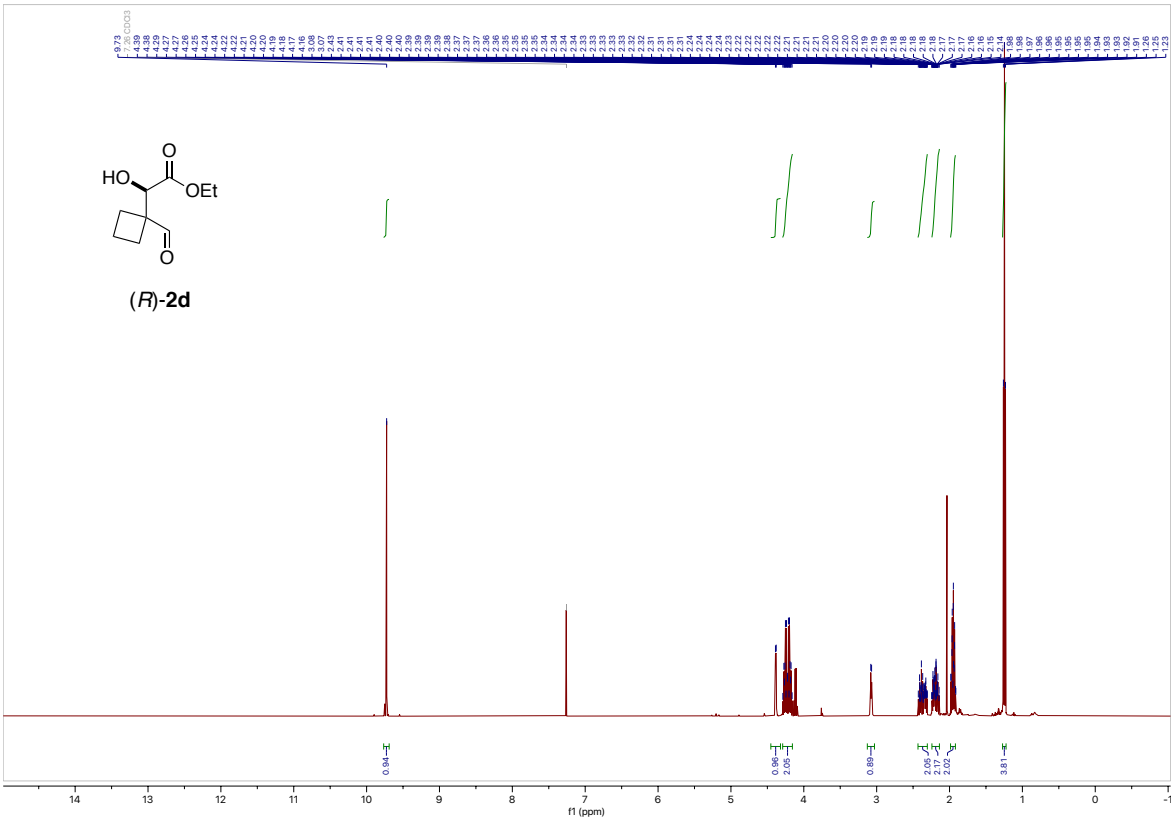
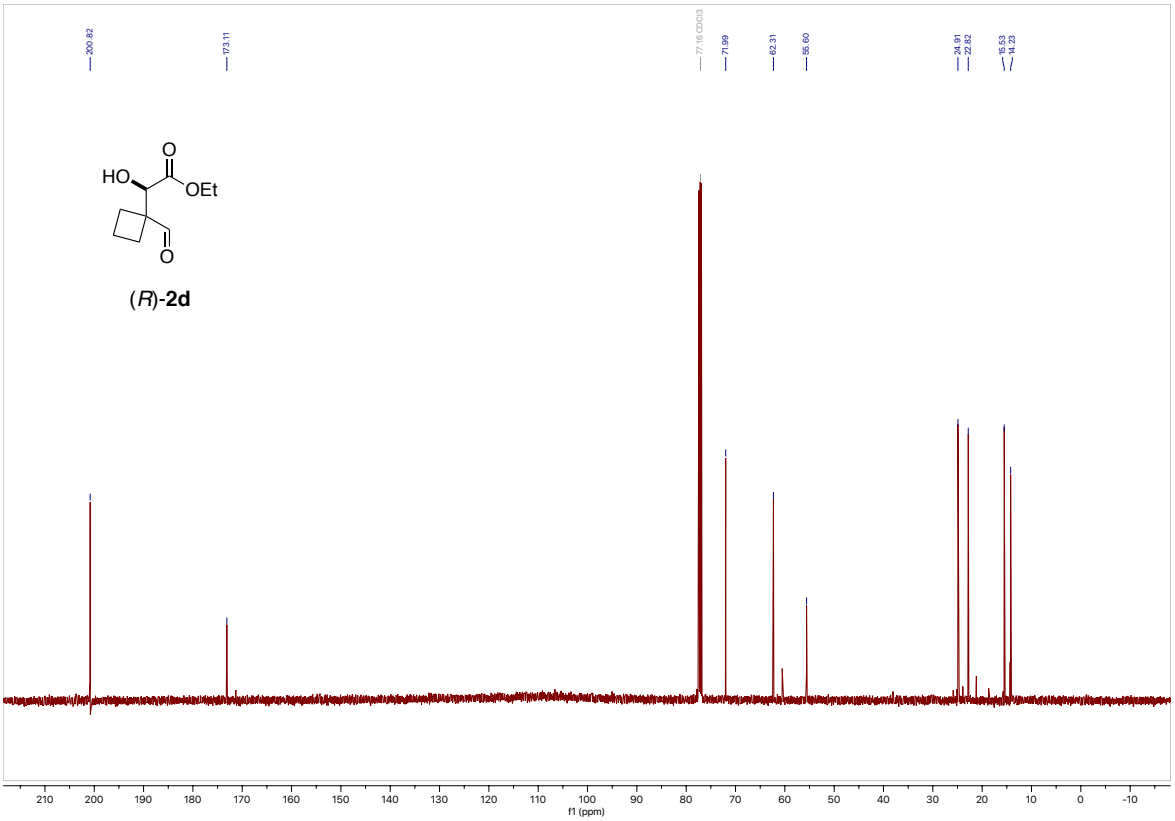
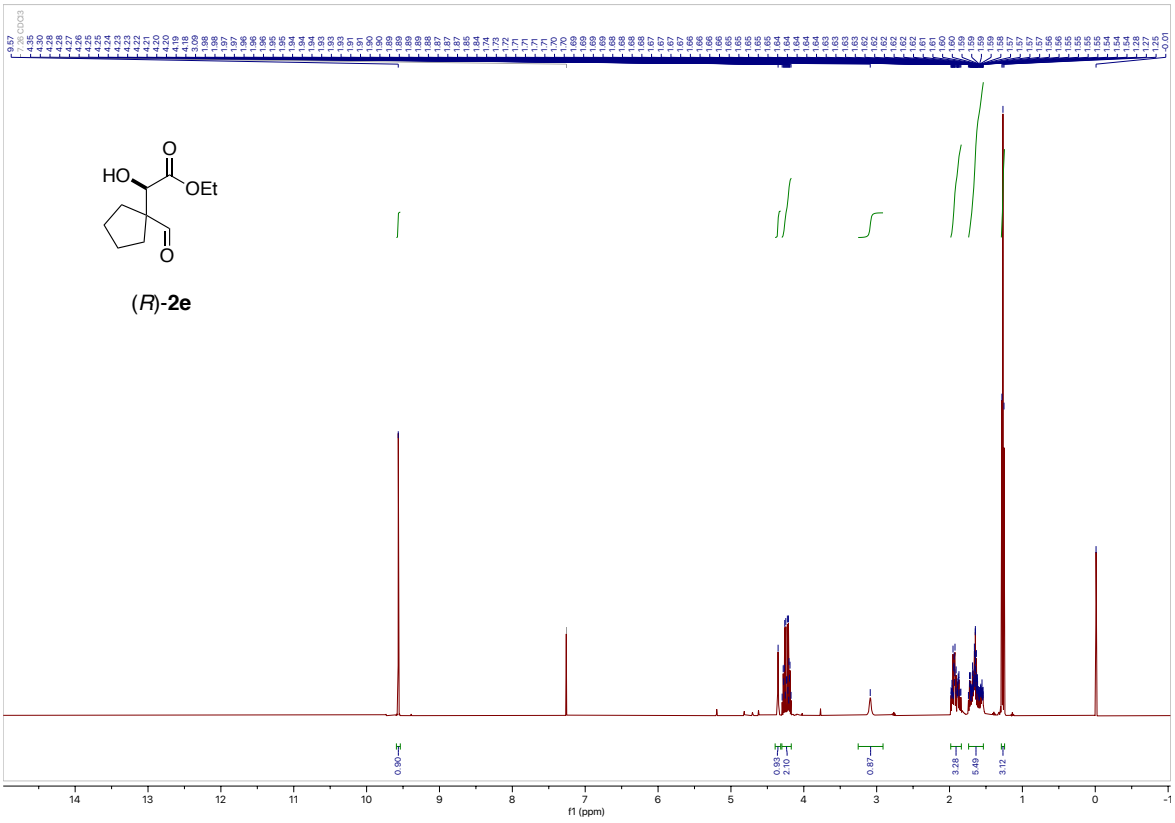
O
(R)-2b
f1 (ppm)

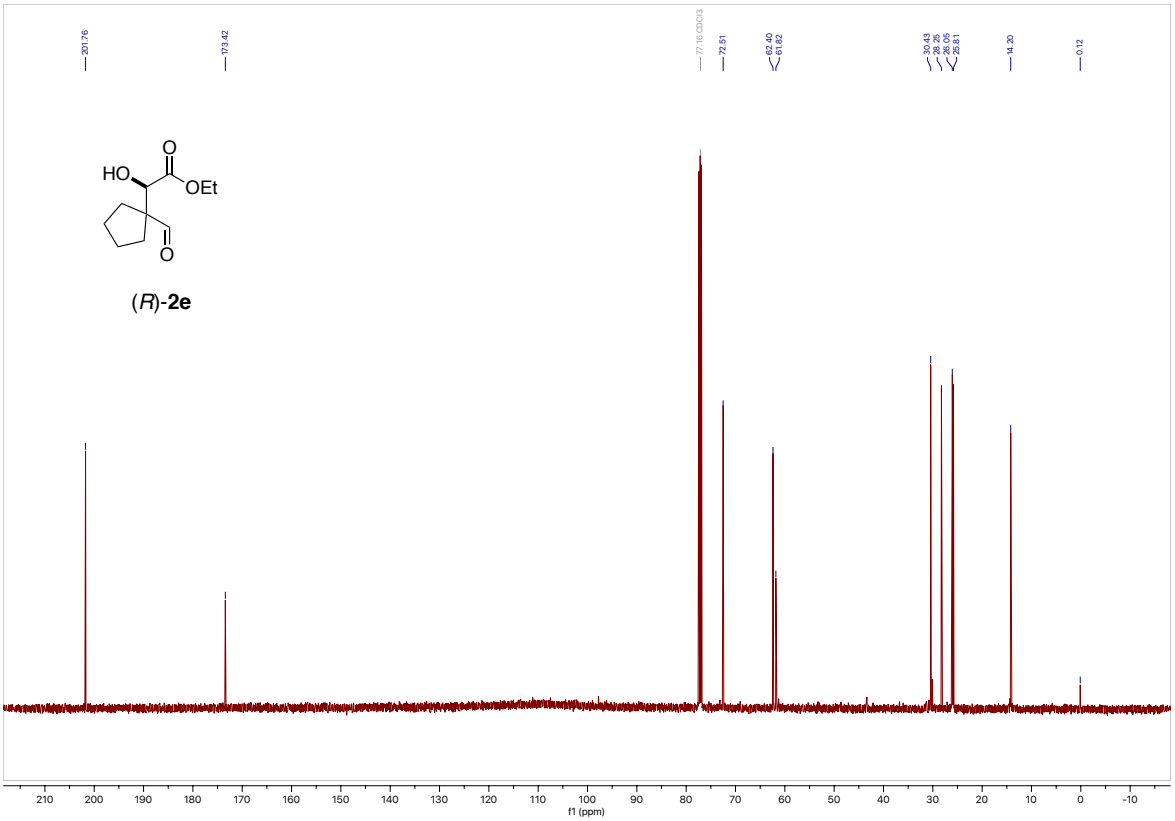

HO
O
OEt
Bu
Bu
O
(R)-2c
f1 (ppm)

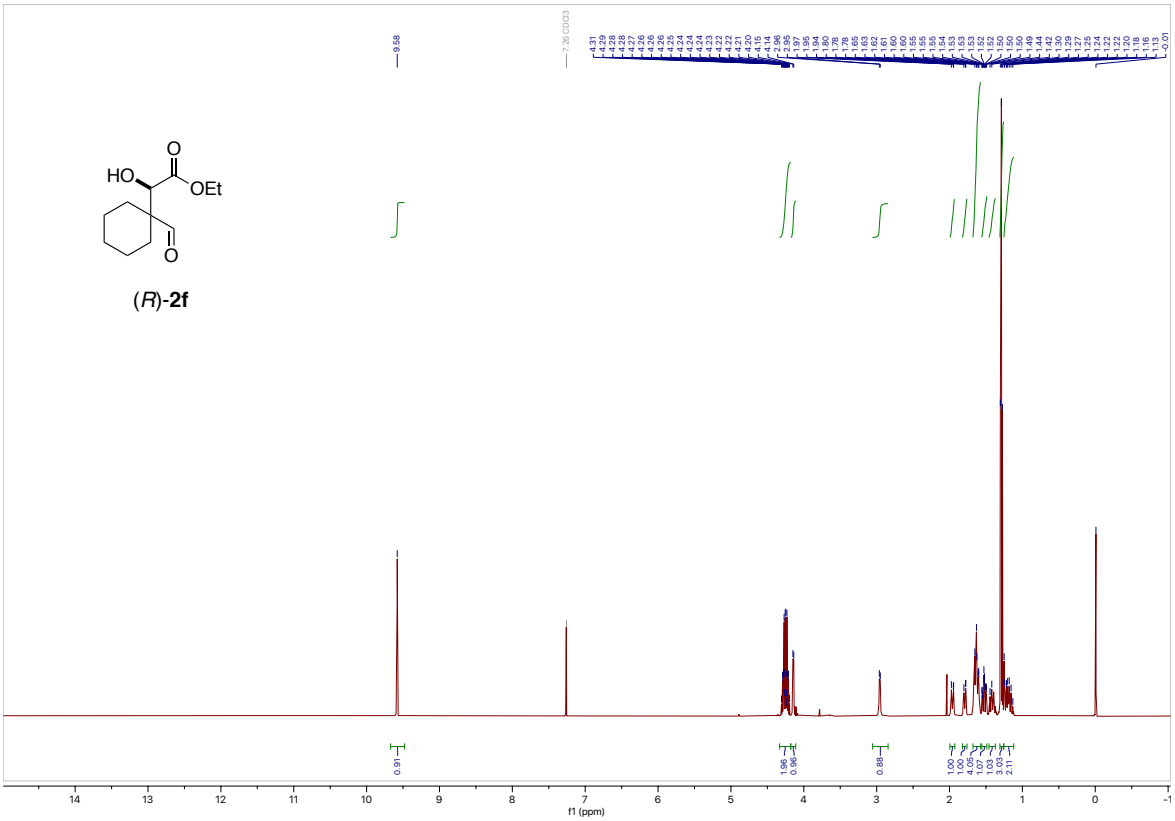

HO
O
OEt
Bu
Bu
O
(R)-2c
f1 (ppm)

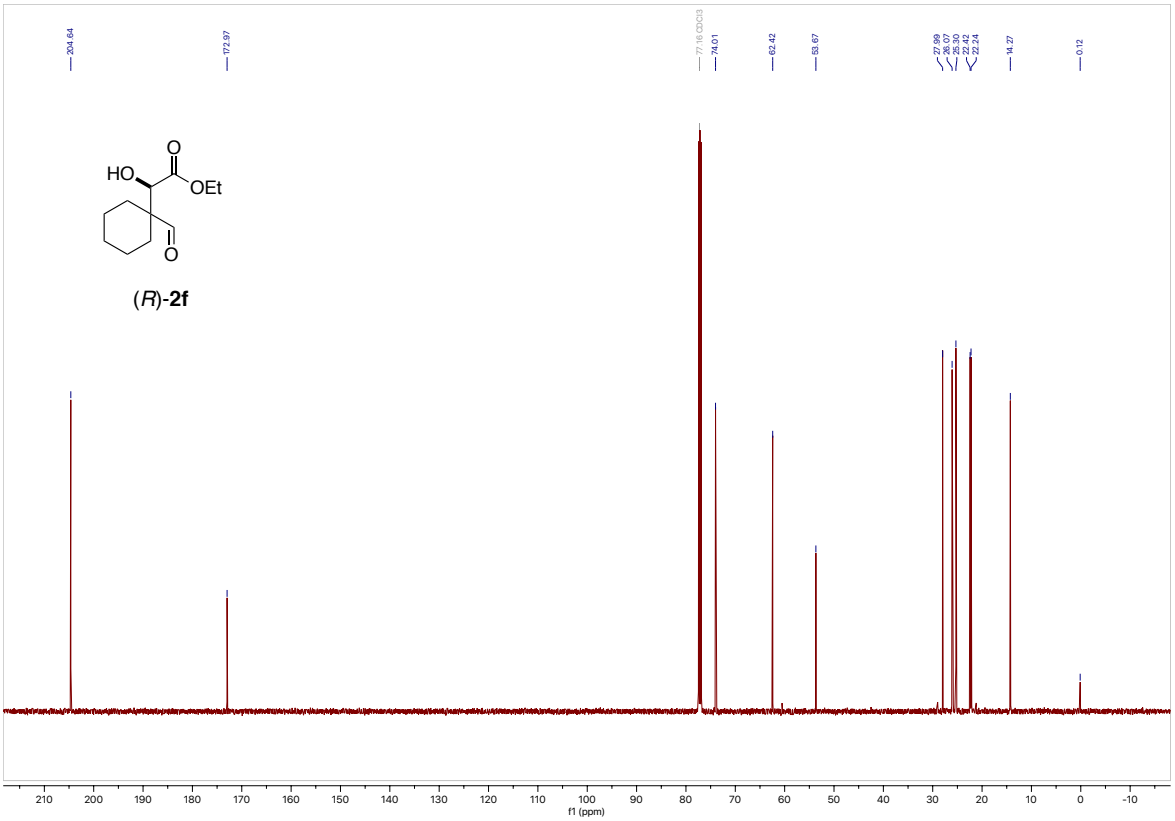

HO
O
OEt
O
(R)-2d
f1 (ppm)

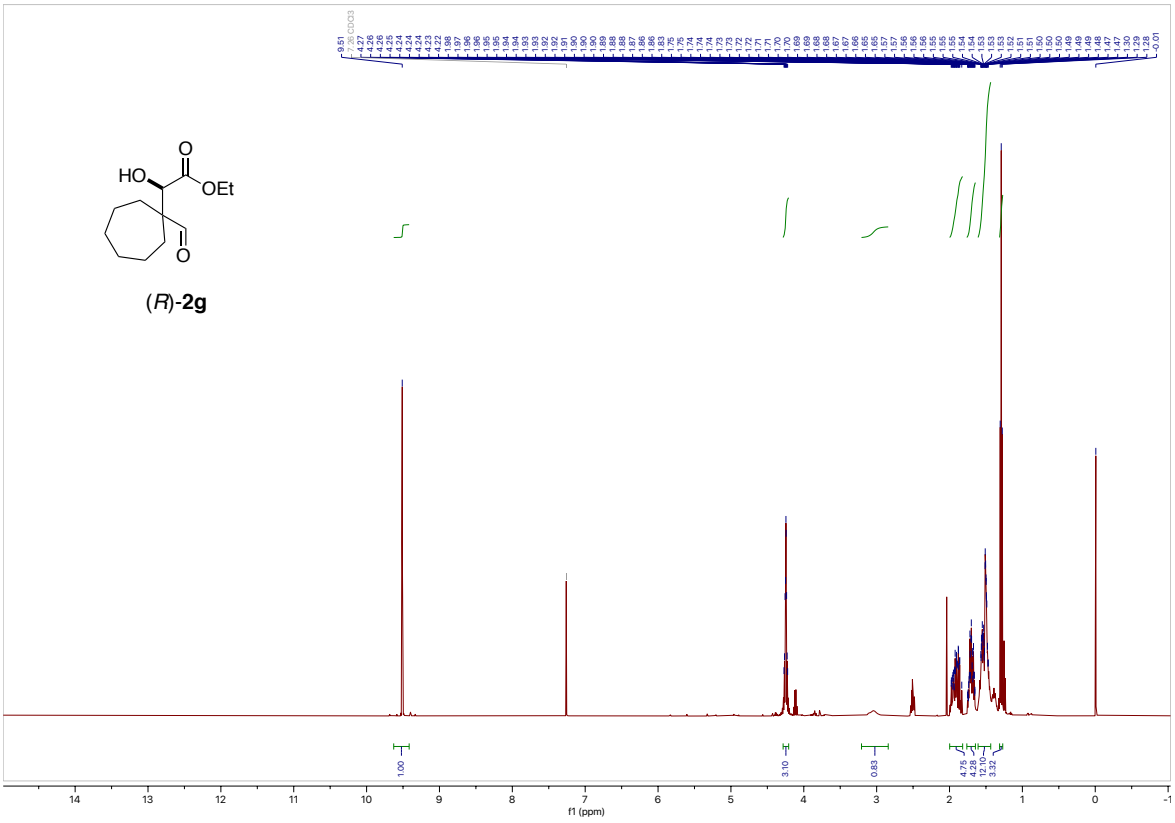

200.82
173.11
77.16 CDCl3
71.99
62.31
56.60
24.91
22.82
15.53
14.23
HO
O
OEt
O
(R)-2d
f1 (ppm)

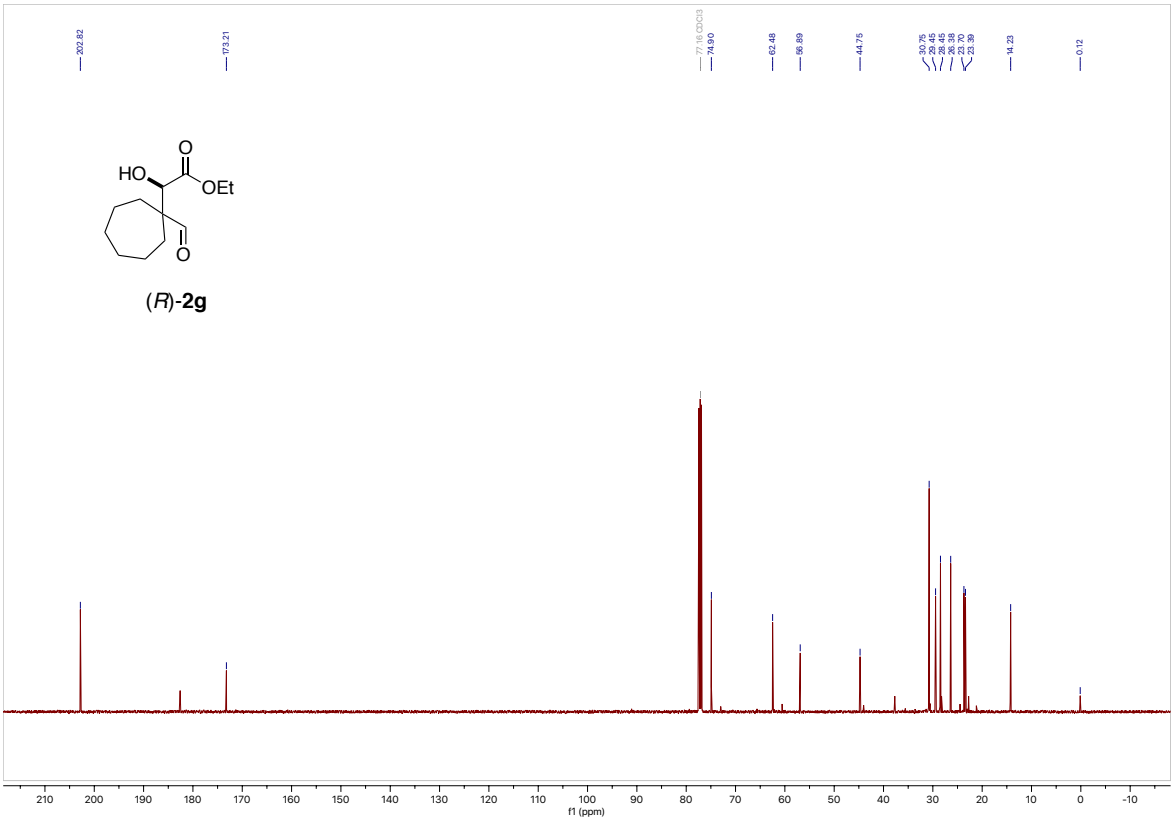

HO
O
OEt
O
(R)-2e
0.90
0.93
2.10
0.87
3.28
5.49
3.12
f1 (ppm)

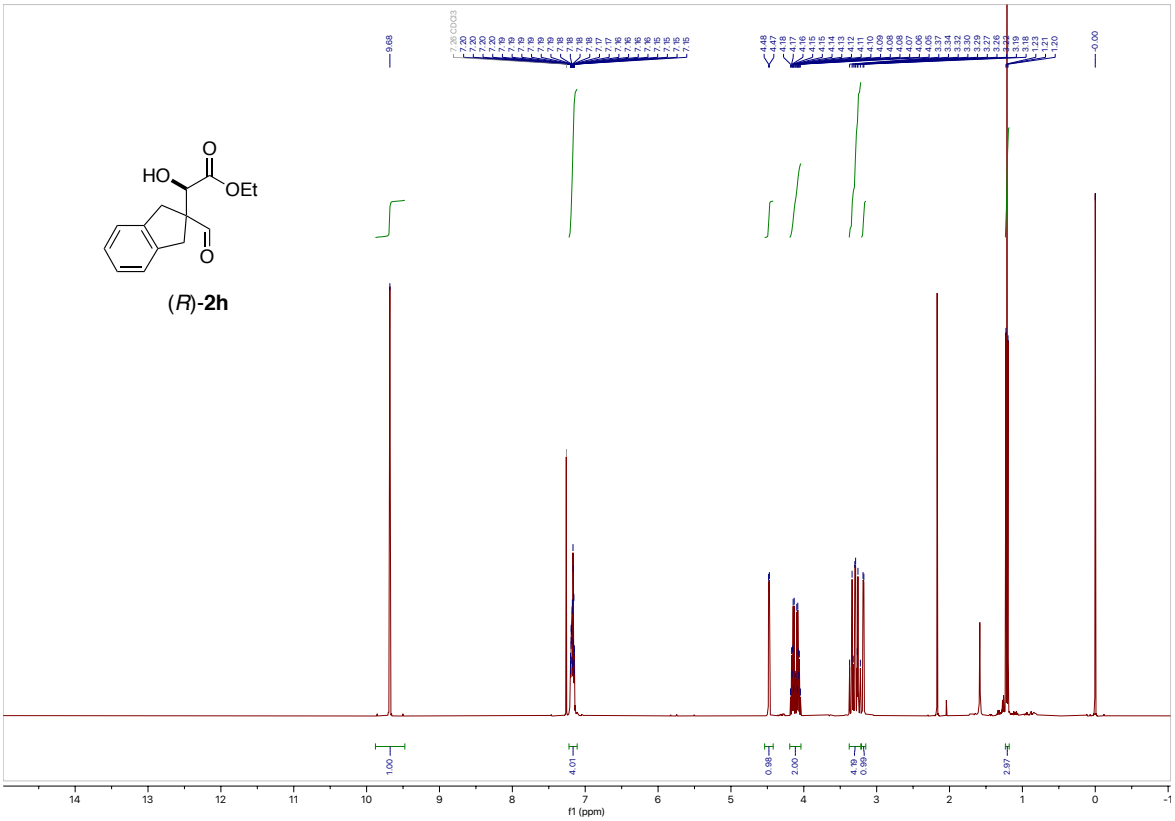

201.76
173.42
77.16 CDCl3
72.51
62.40
61.82
30.43
28.25
26.05
25.81
14.20
0.12
HO
O
OEt
O
(R)-2e
f1 (ppm)

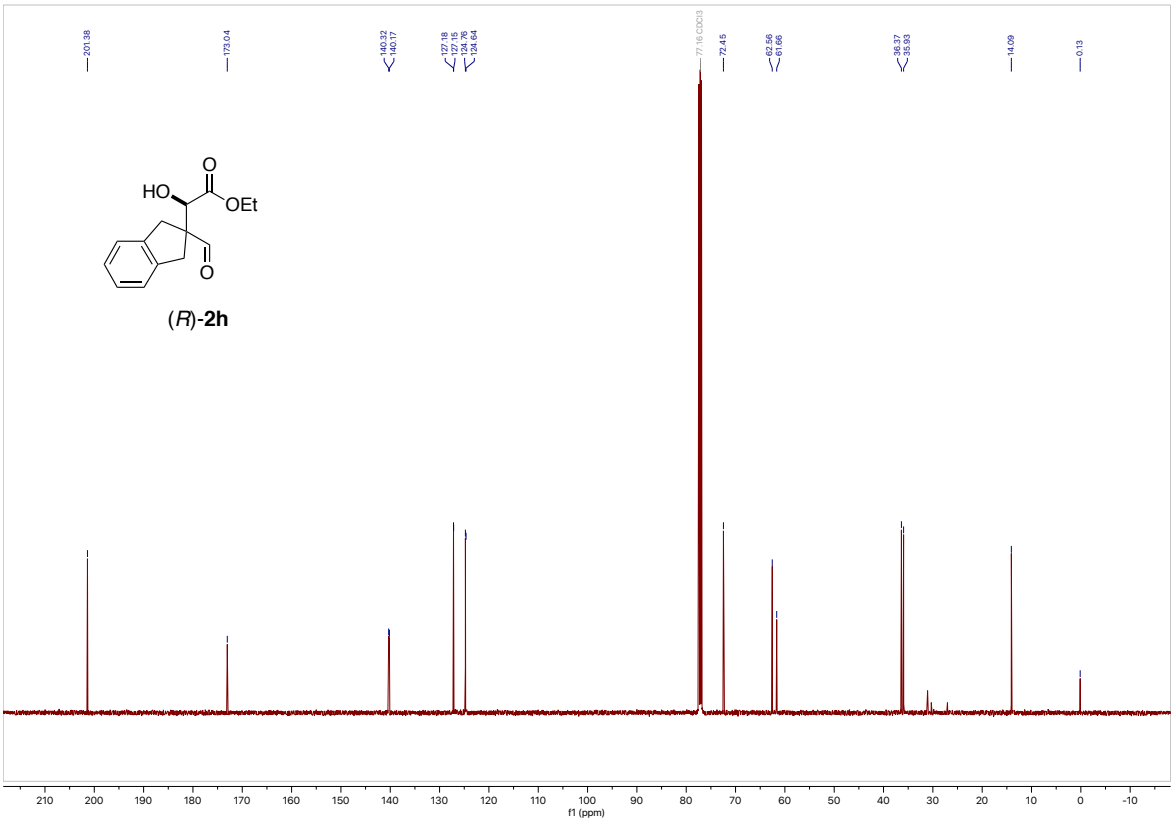

HO
O
OEt
O
(R)-2f
f1 (ppm)

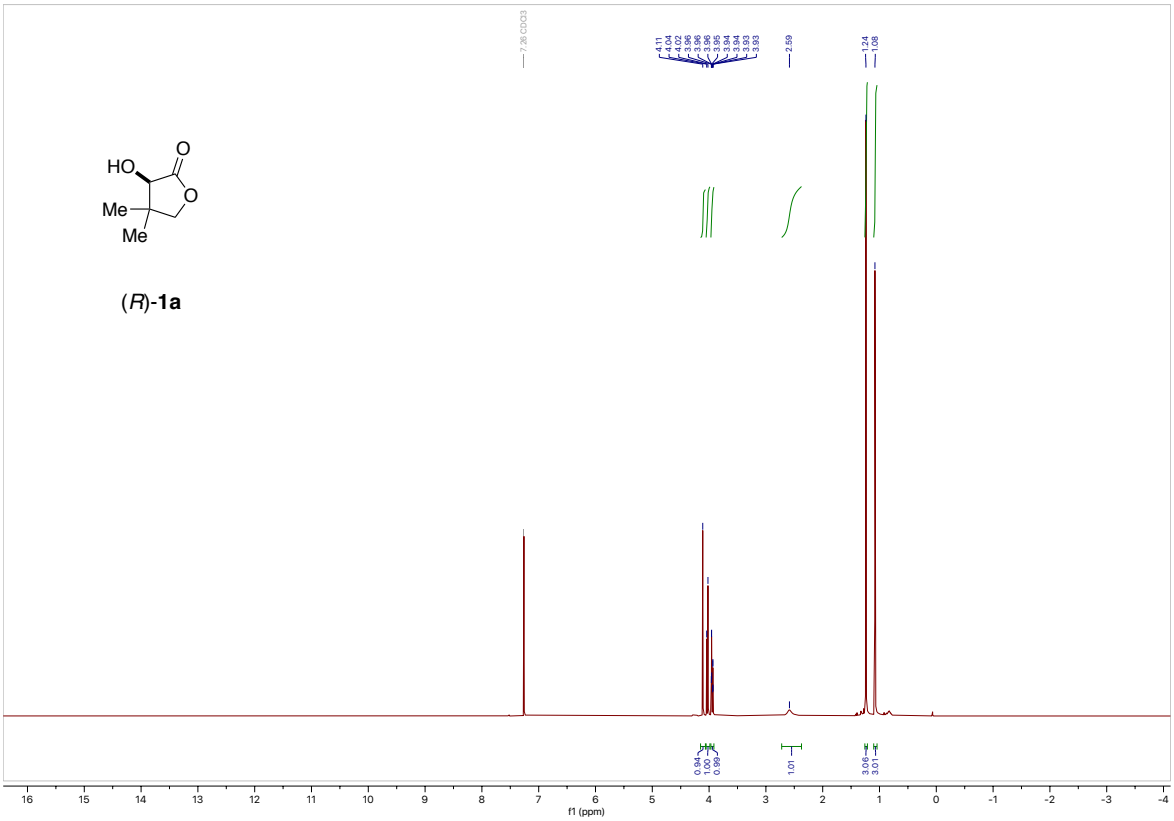

HO
O
OEt
O
(R)-2f
f1 (ppm)

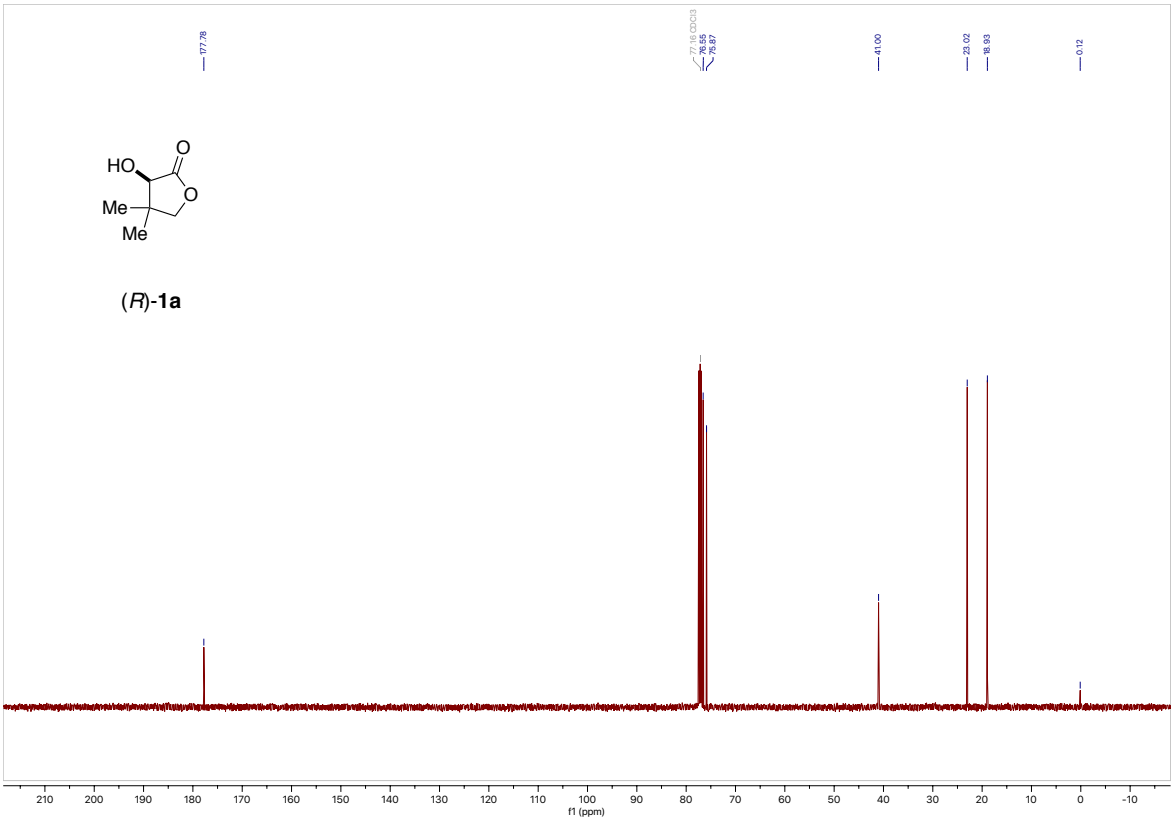

HO
OEt
O
O
(R)-2g
f1 (ppm)

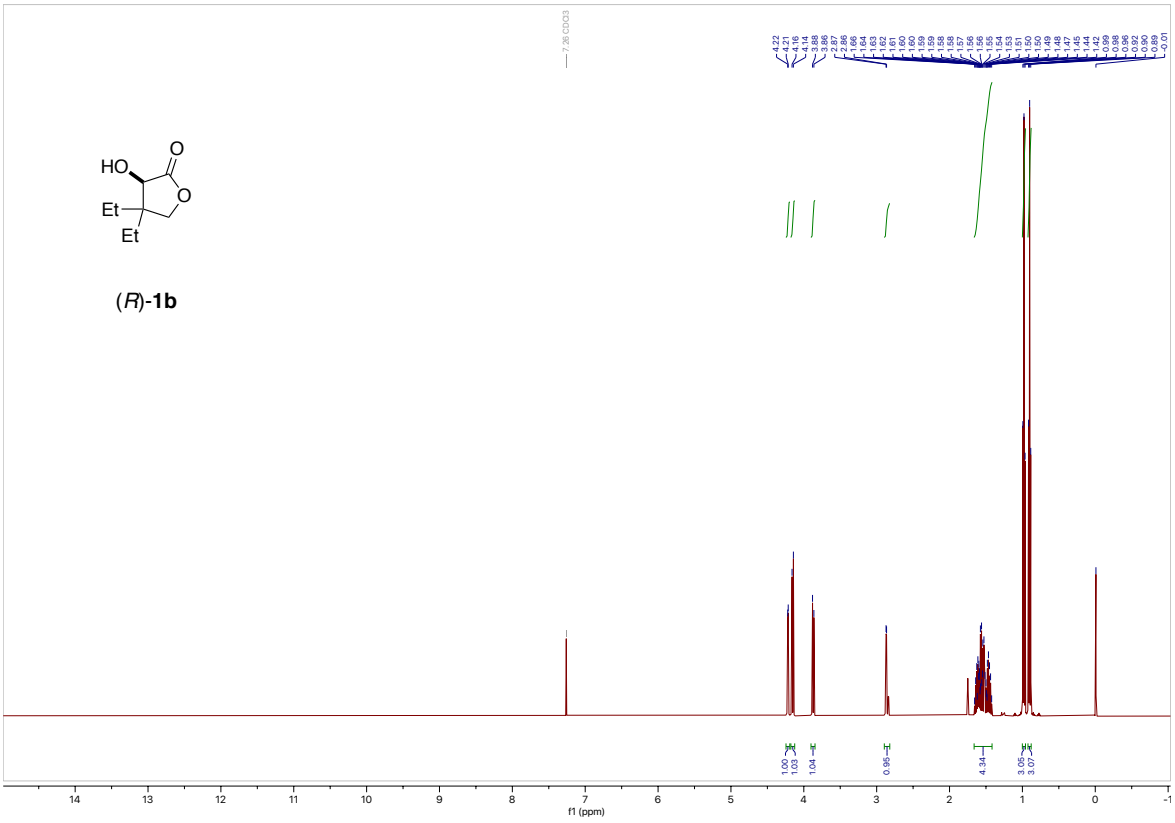

HO
OEt
O
O
(R)-2g
f1 (ppm)

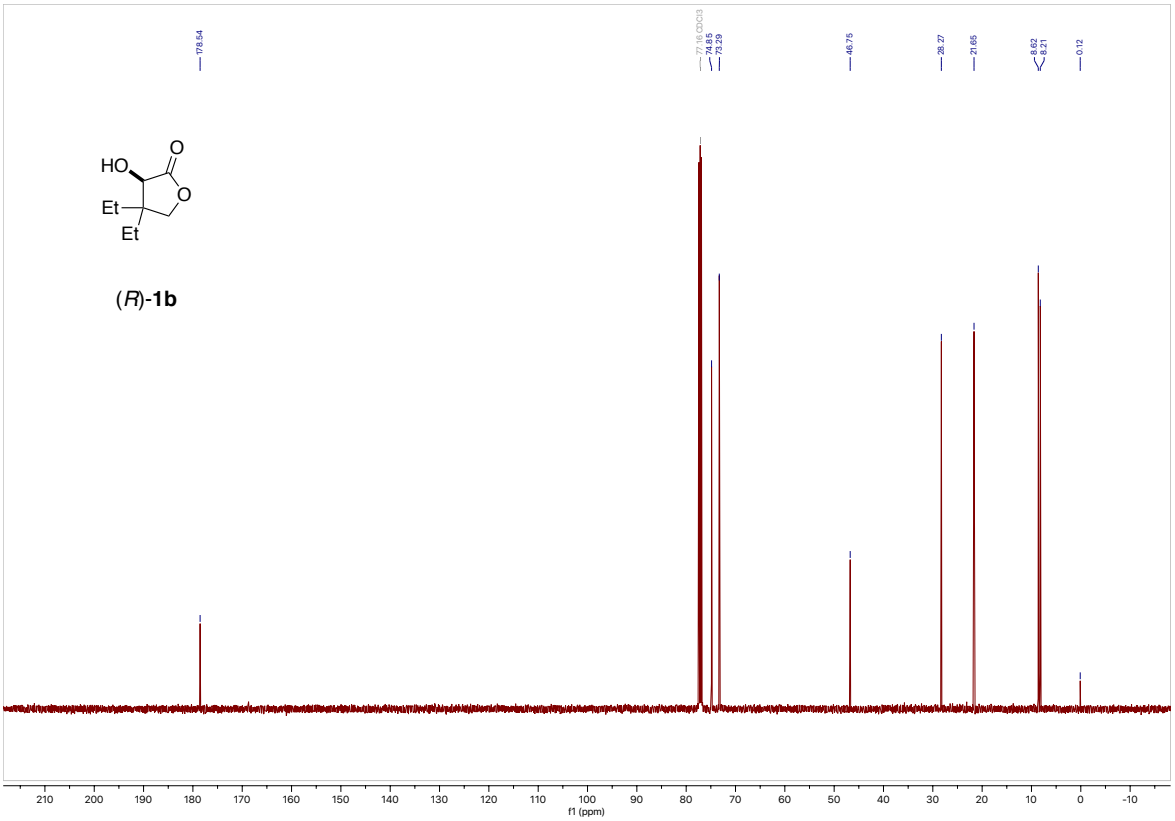

HO
O
OEt
O
(R)-2h
f1 (ppm)

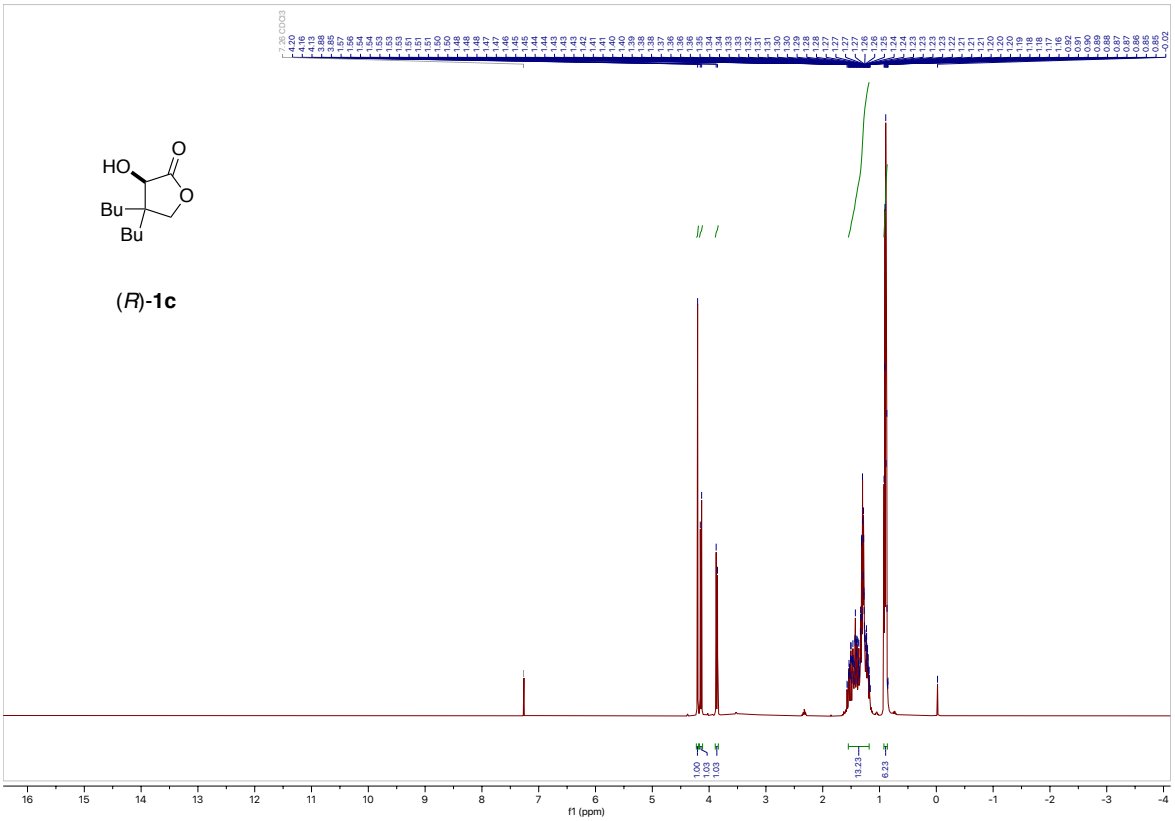

HO
O
OEt
O
(R)-2h
f1 (ppm)

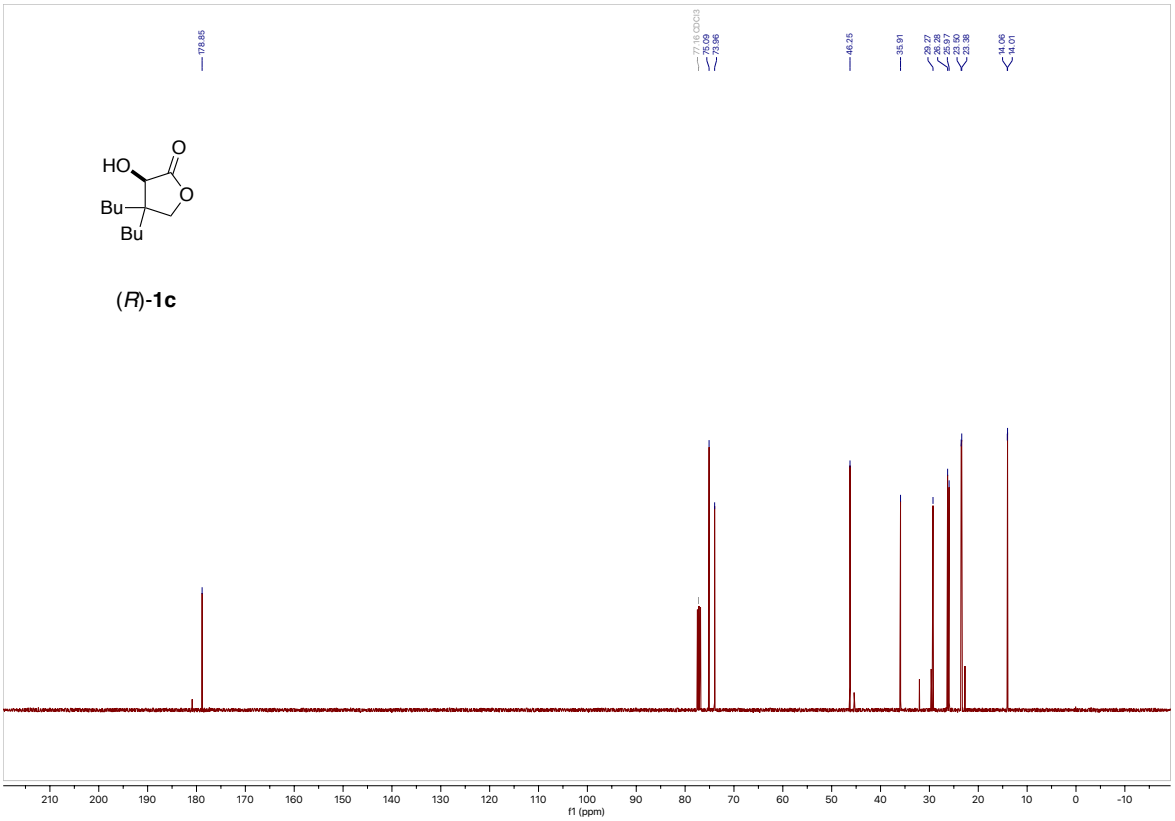

HO
O
O
Me
Me
(R)-1a
f1 (ppm)

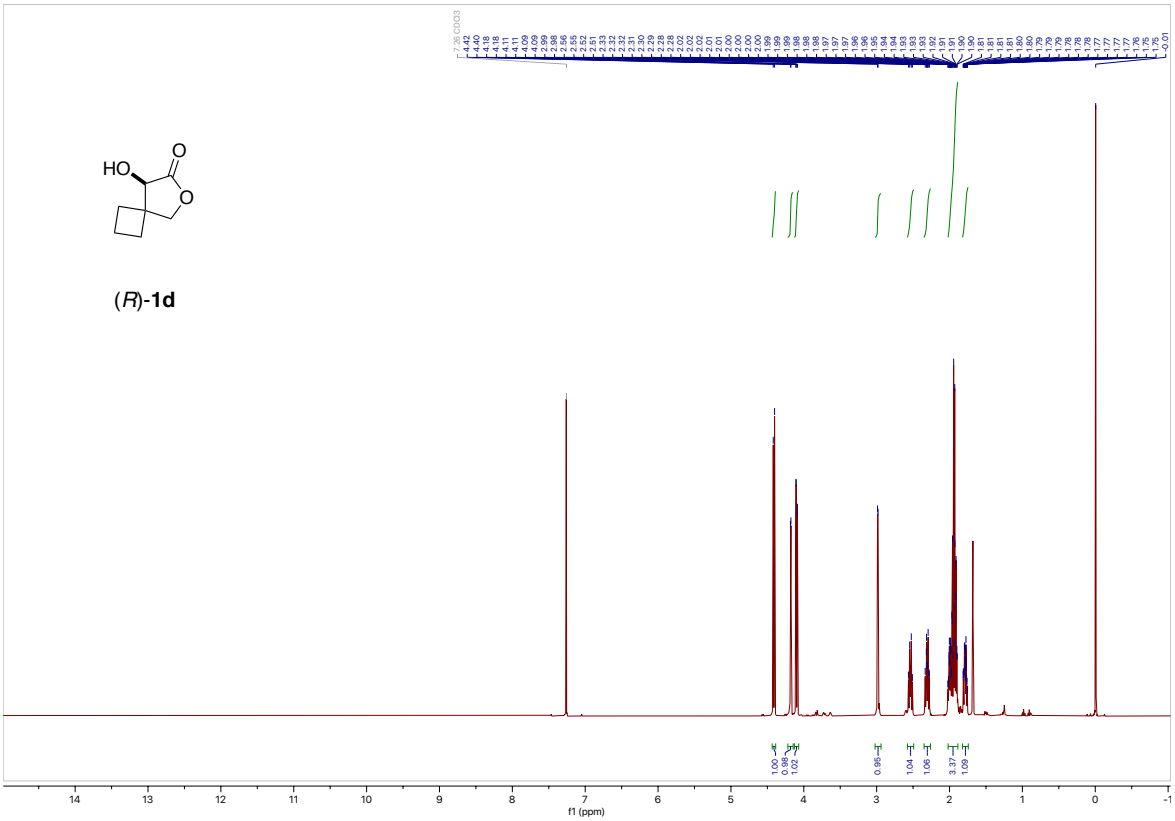

HO
O
O
Me
Me
(R)-1a
f1 (ppm)

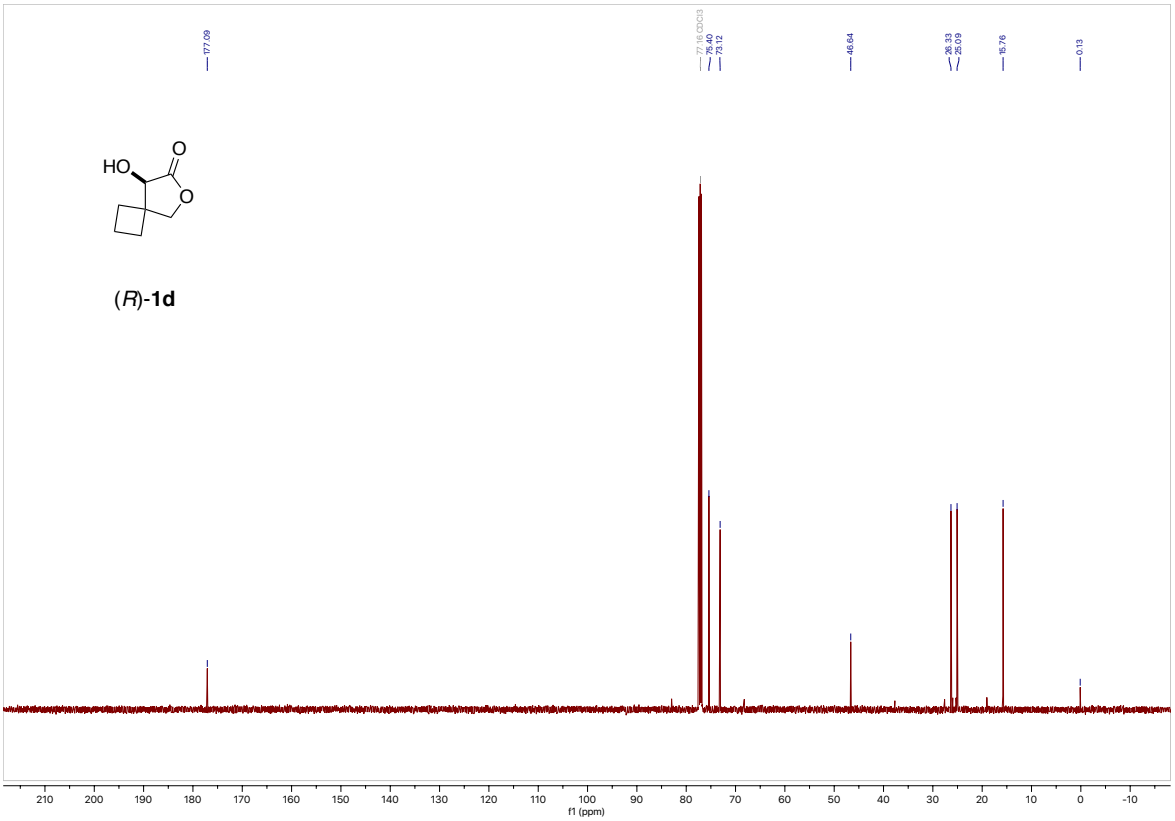

HO
O
O
Et
Et
(R)-1b
f1 (ppm)

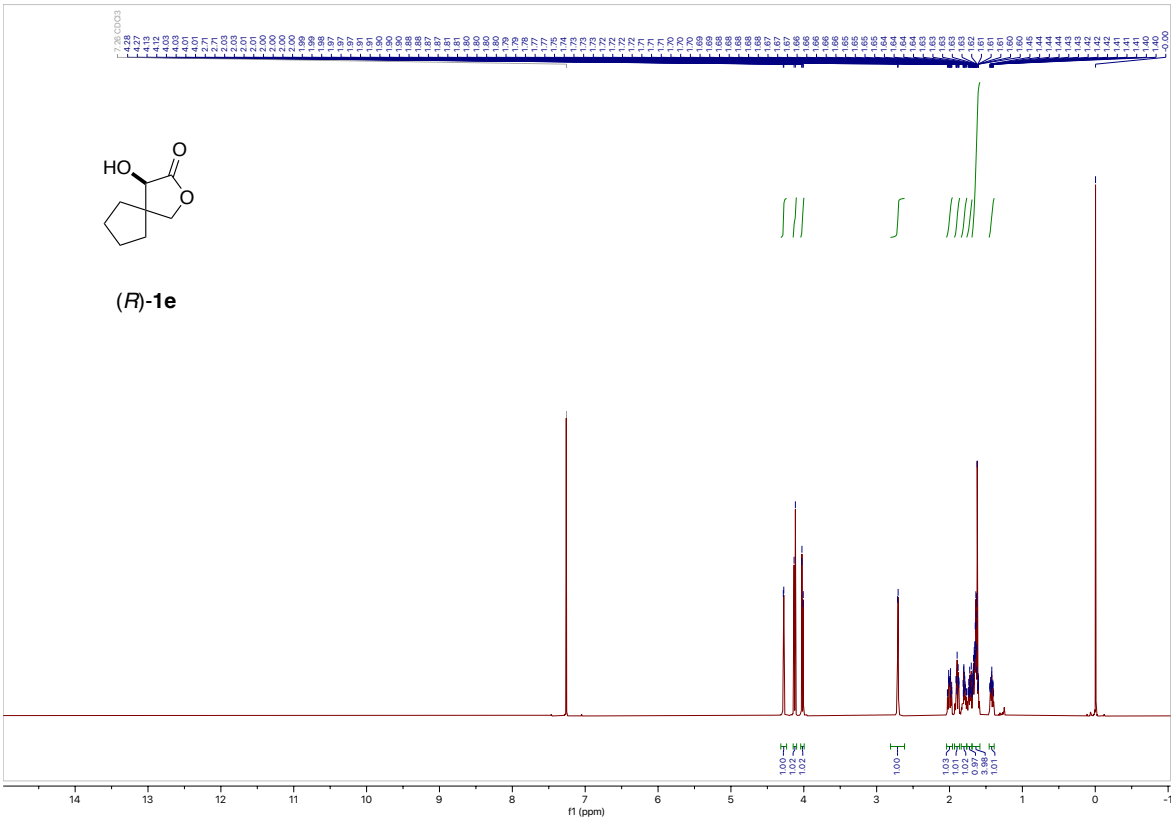

HO
O
O
Et
Et
(R)-1b
f1 (ppm)

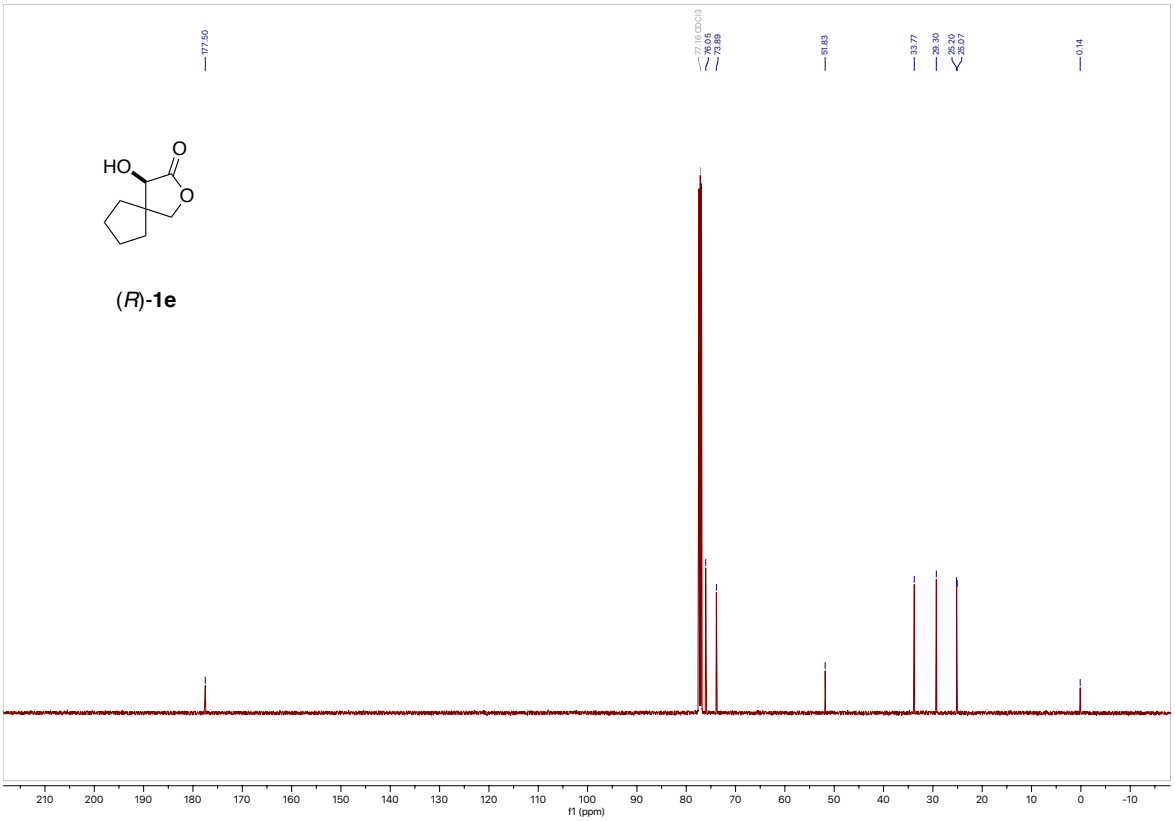

HO
O
O
Bu
Bu
(R)-1c
f1 (ppm)

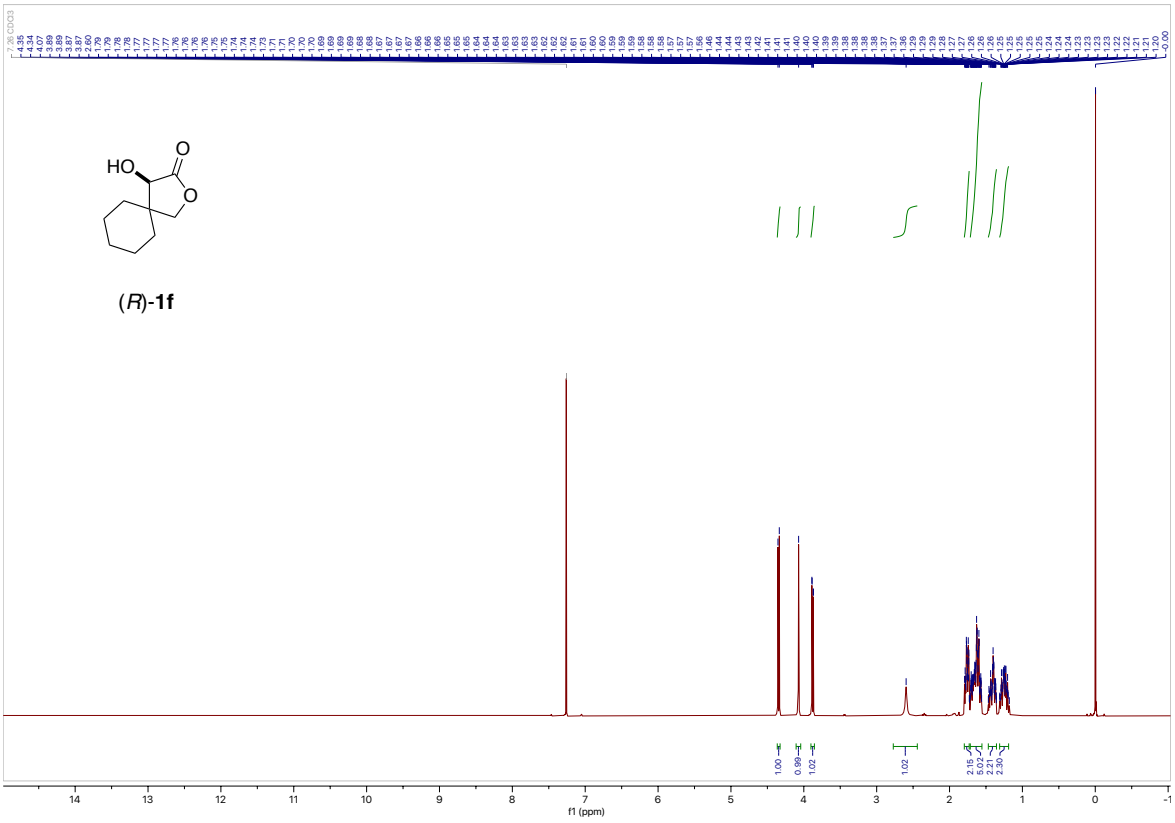

HO
O
O
Bu
Bu
(R)-1c
f1 (ppm)

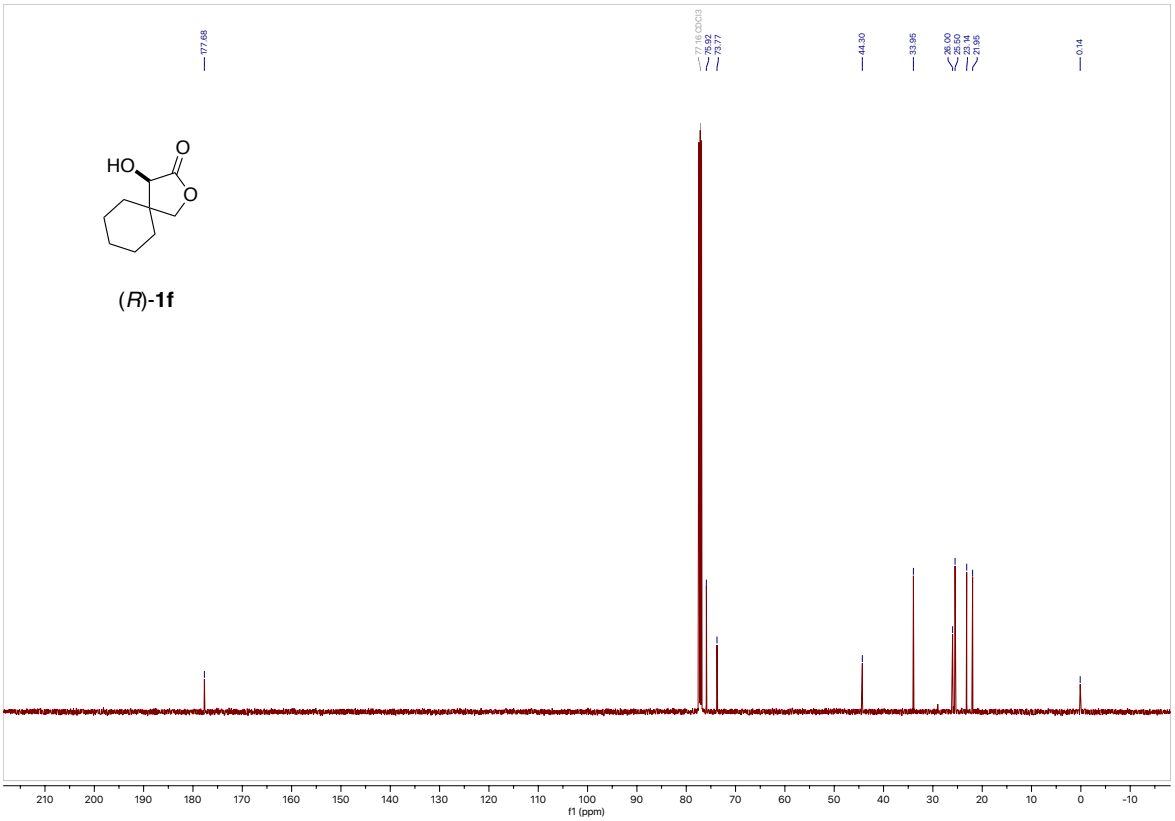

HO
O
O
(R)-1d
f1 (ppm)

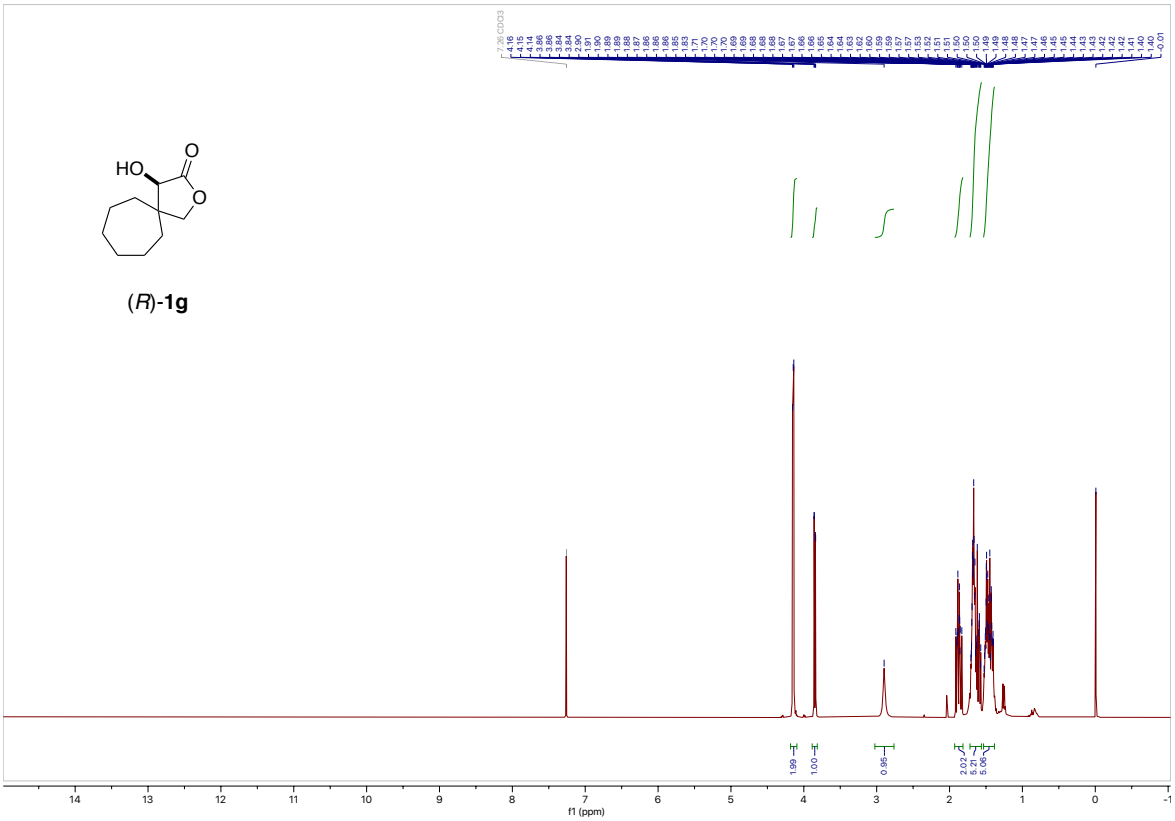

HO
O
O
(R)-1d
177.09
77.16 CDCl3
76.40
73.12
46.64
26.33
25.09
15.76
0.13
f1 (ppm)

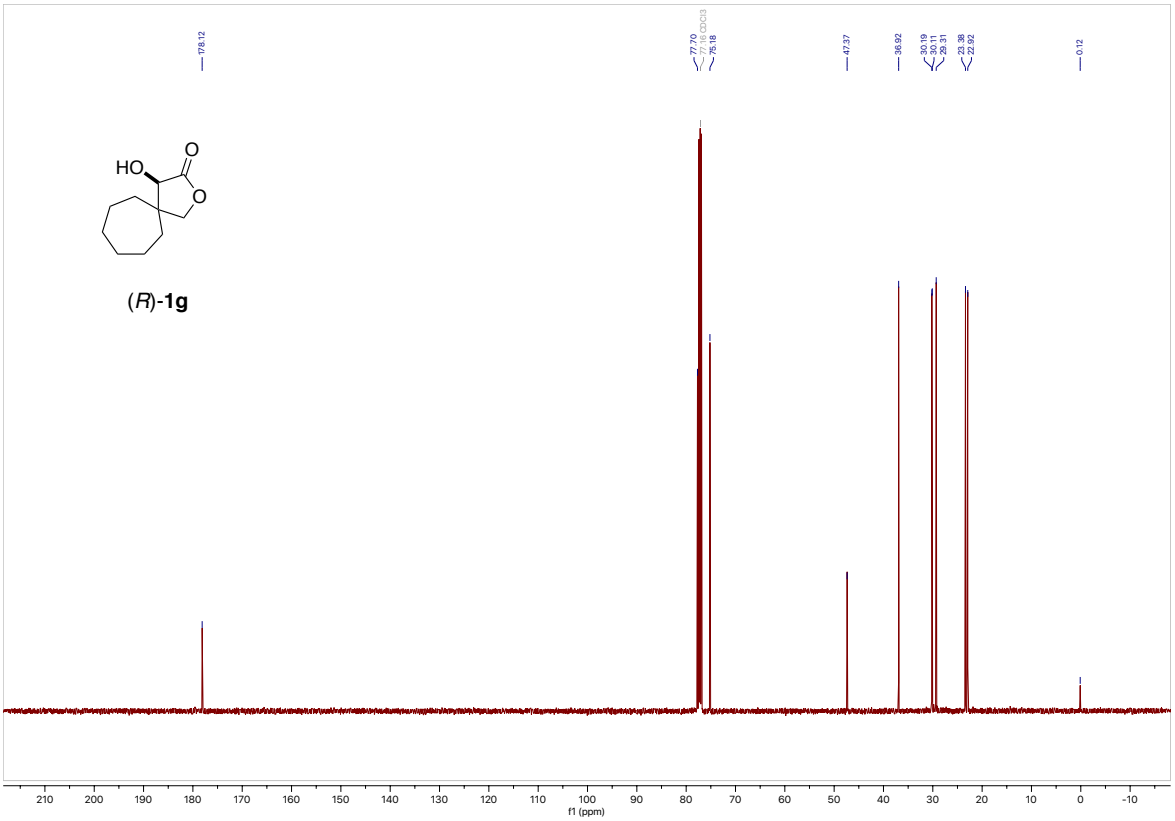

HO
O
O
(R)-1e
f1 (ppm)

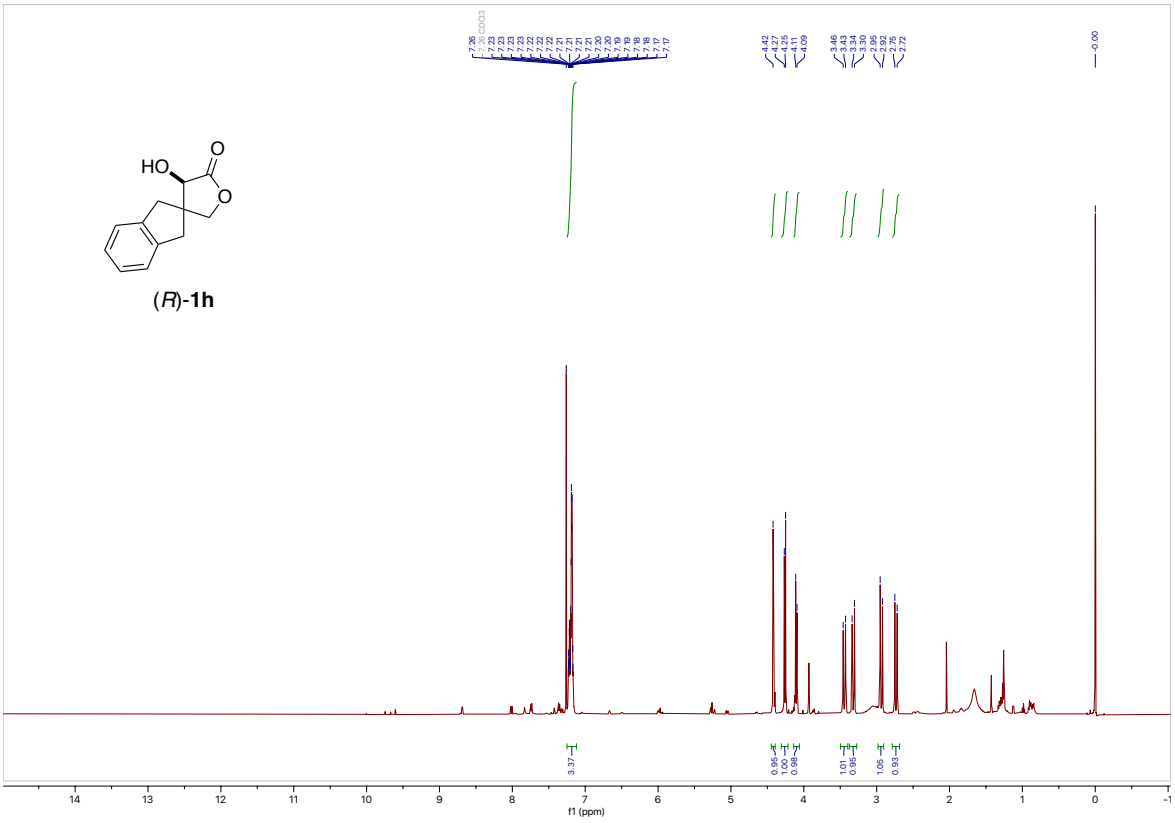

HO
O
O
(R)-1e
177.50
77.16 CDCl3
76.05
75.89
51.83
33.77
29.30
25.20
25.07
0.14
f1 (ppm)

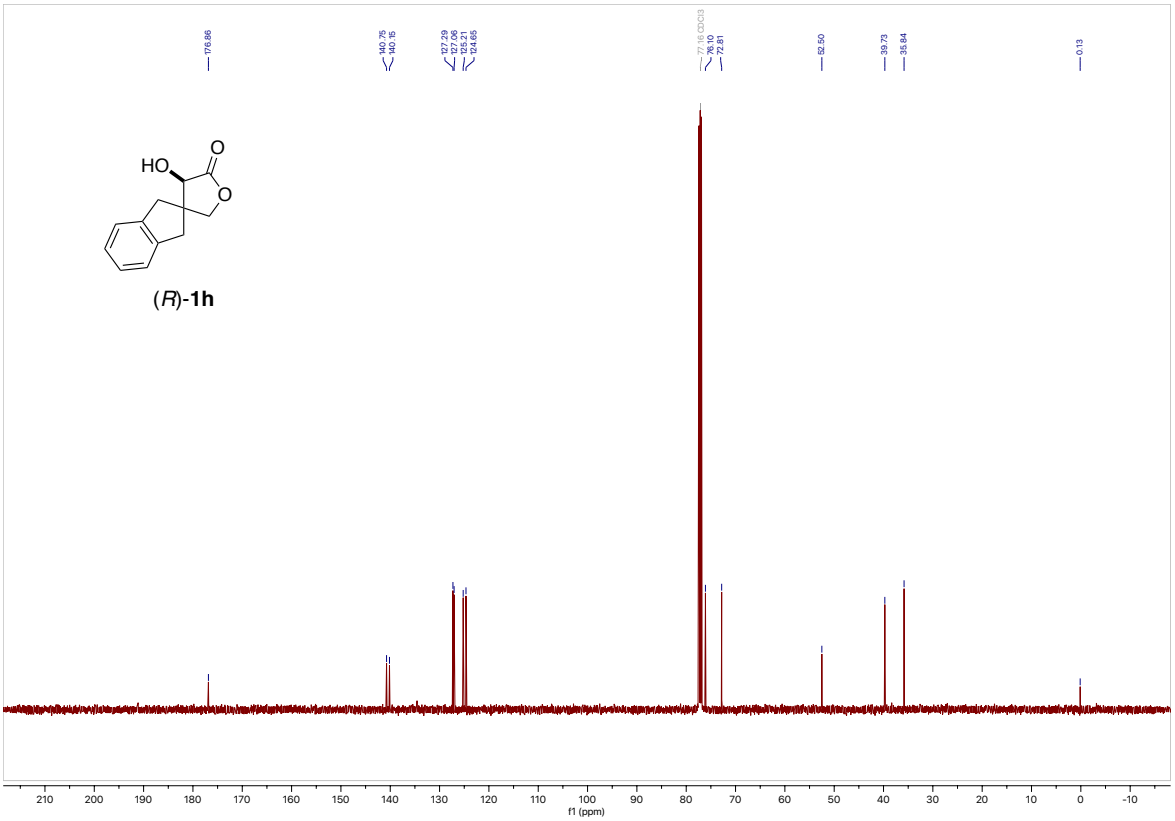

HO
O
O
(R)-1f
f1 (ppm)

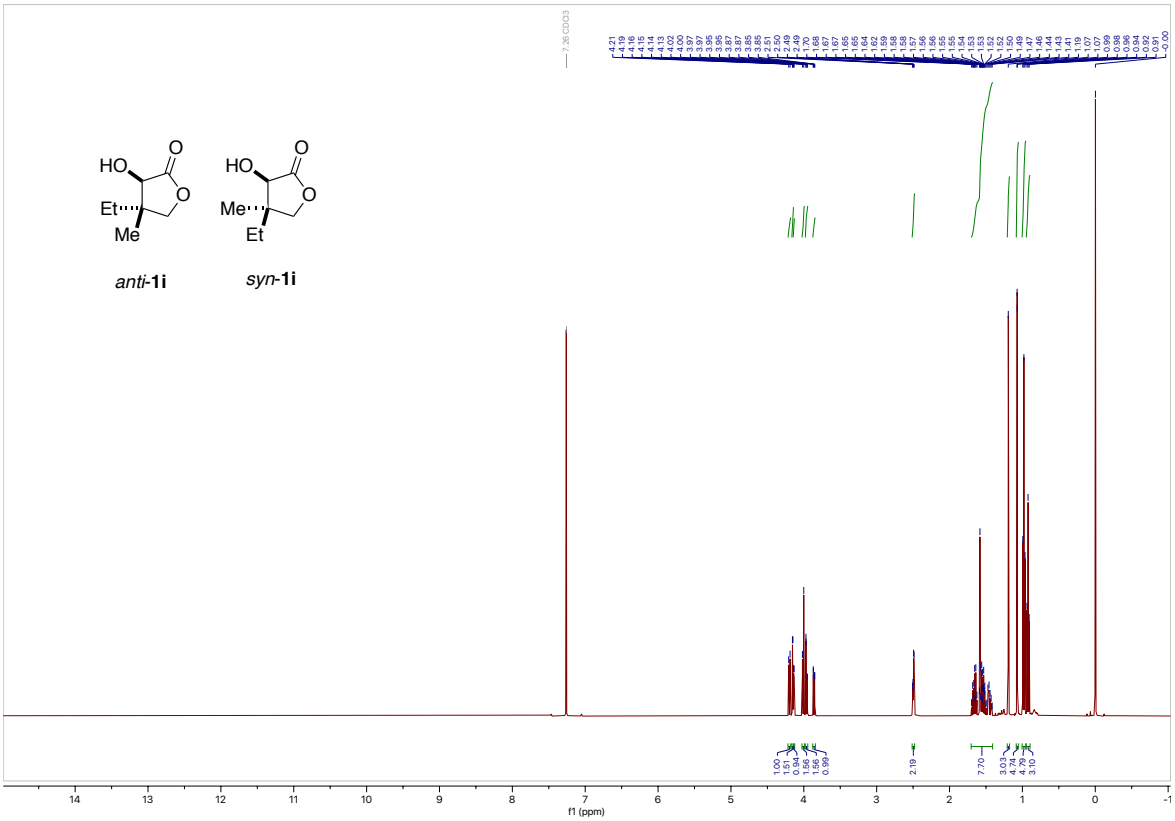

HO
O
O
(R)-1f
f1 (ppm)

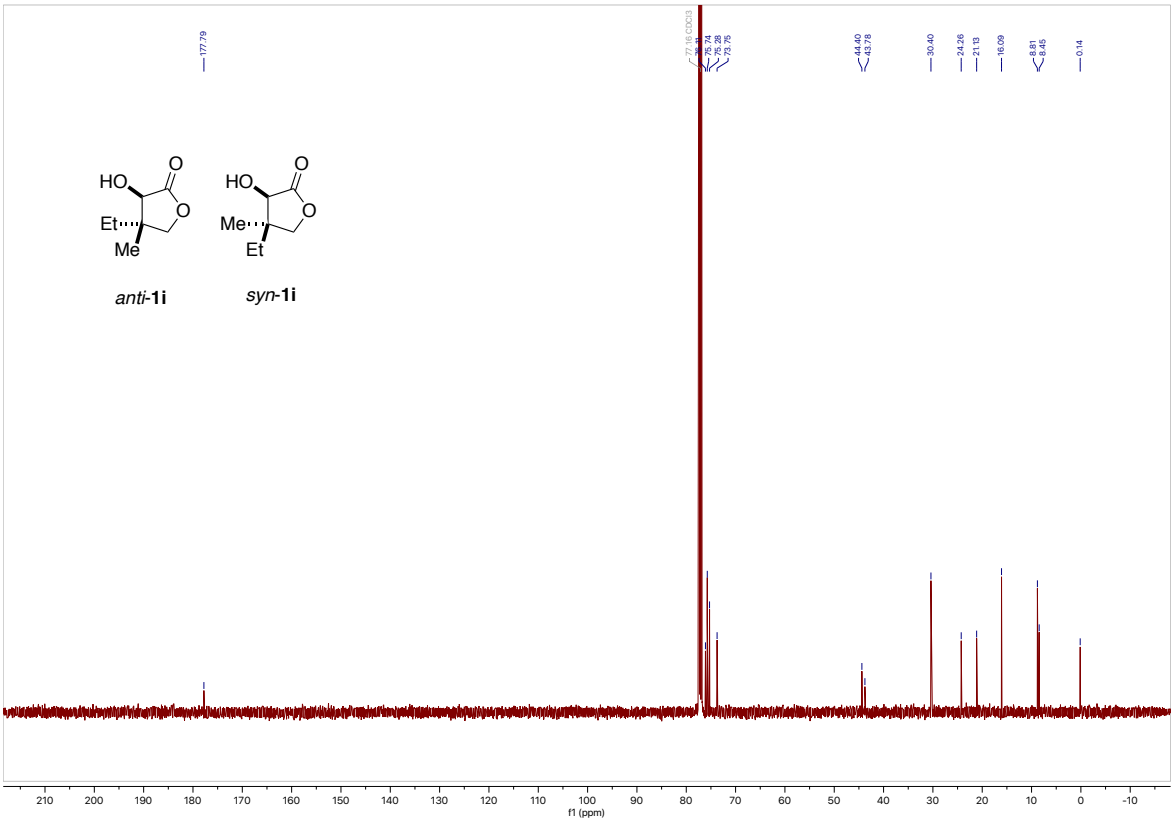

HO
O
O
(R)-1g
f1 (ppm)

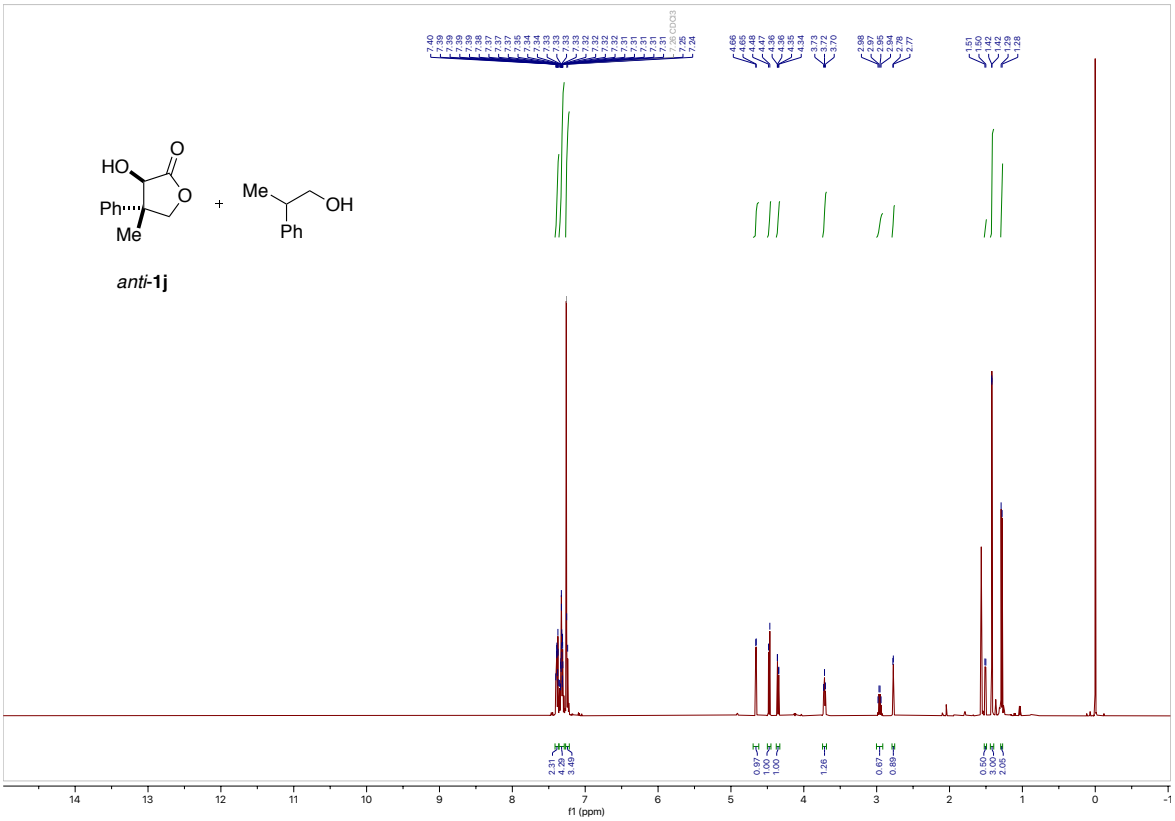

HO
O
O
(R)-1g
f1 (ppm)

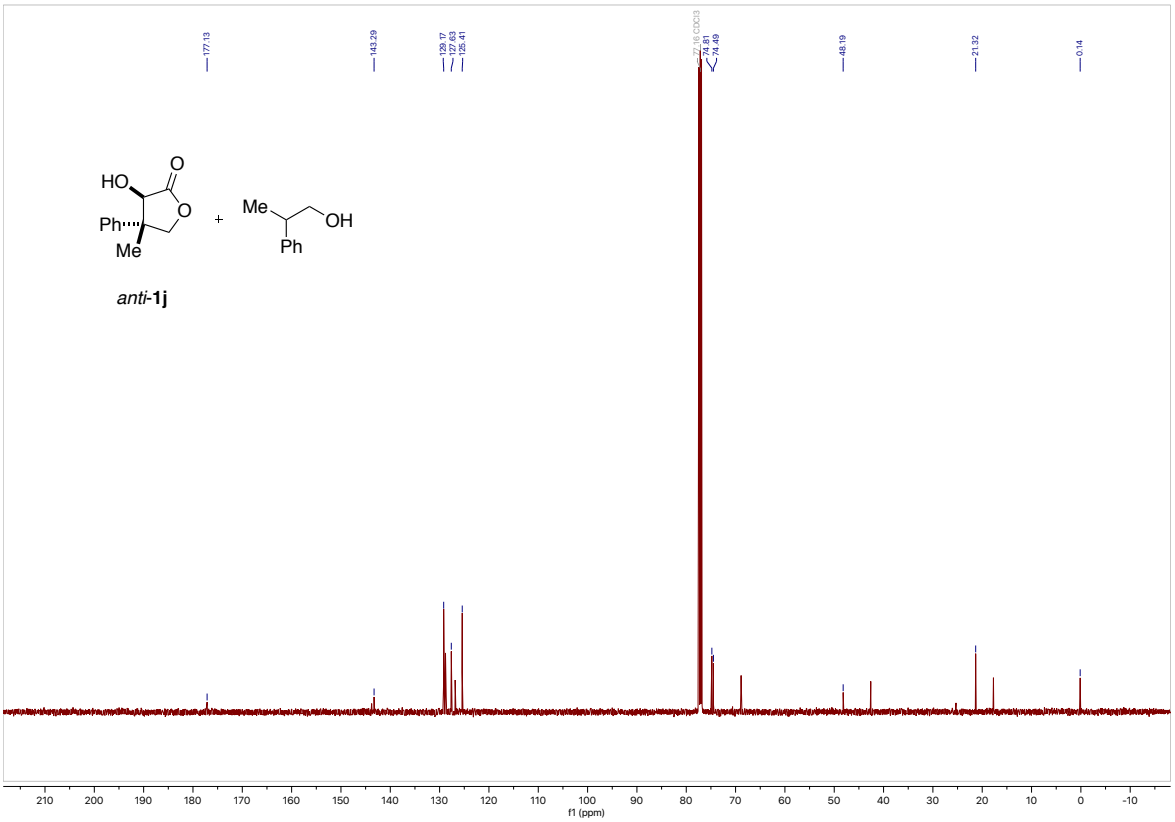

HO
O
O
(R)-1h
f1 (ppm)

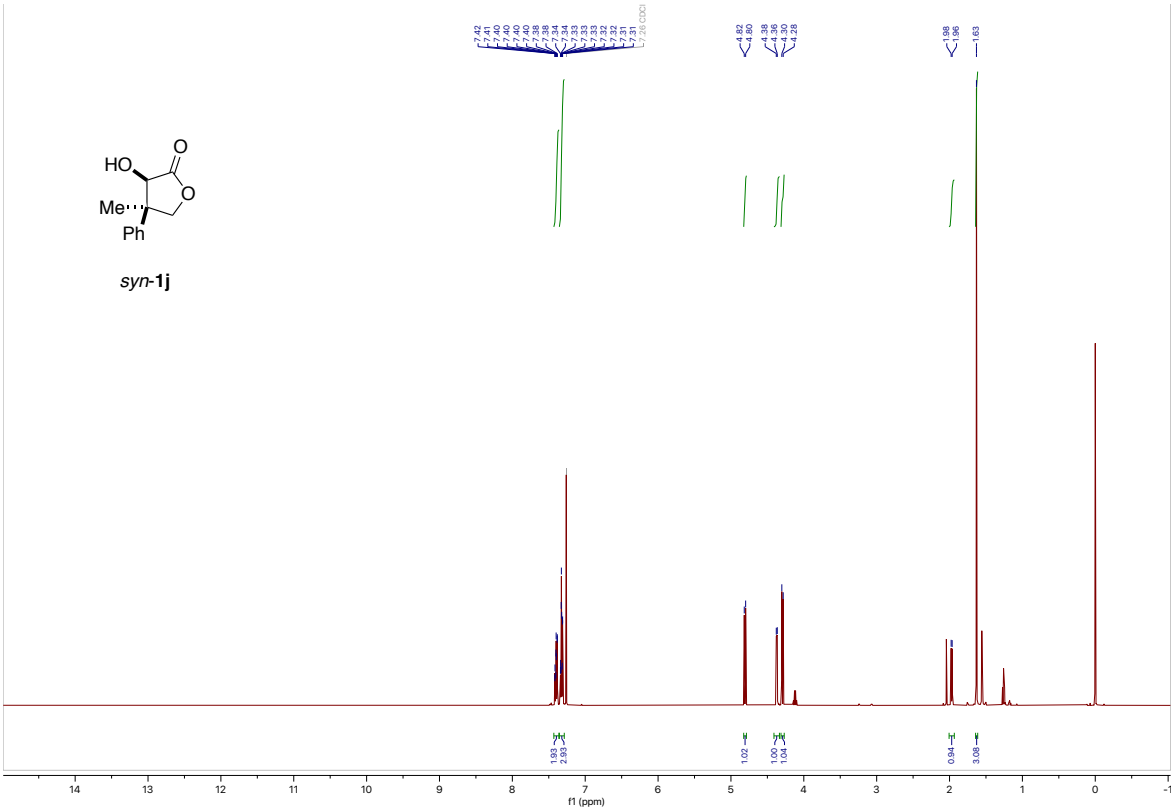

HO
O
O
(R)-1h
f1 (ppm)


HO
O
Et
Me
anti-1i
HO
O
Me
Et
syn-1i
f1 (ppm)

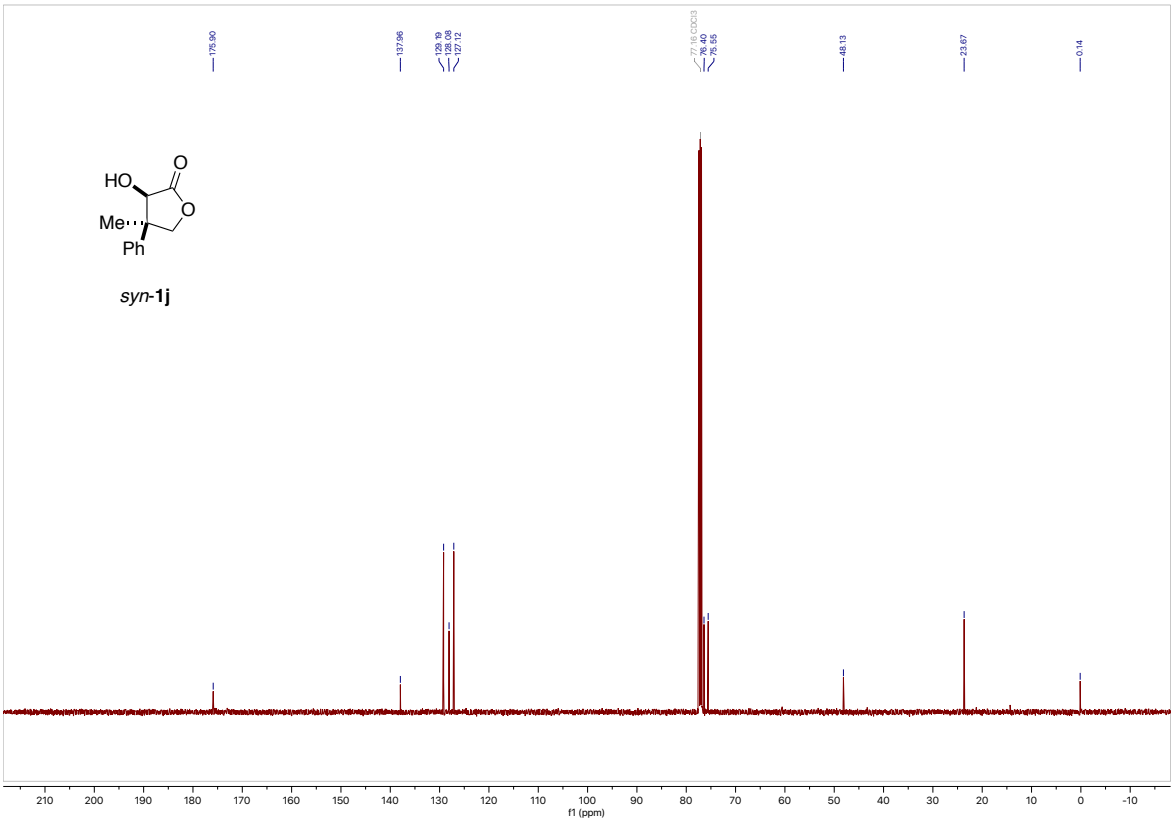

HO
O
Et
Me
anti-1i
HO
O
Me
Et
syn-1i
f1 (ppm)


HO
O
O
Ph
Me
+
Me
OH
Ph
anti-1j
f1 (ppm)

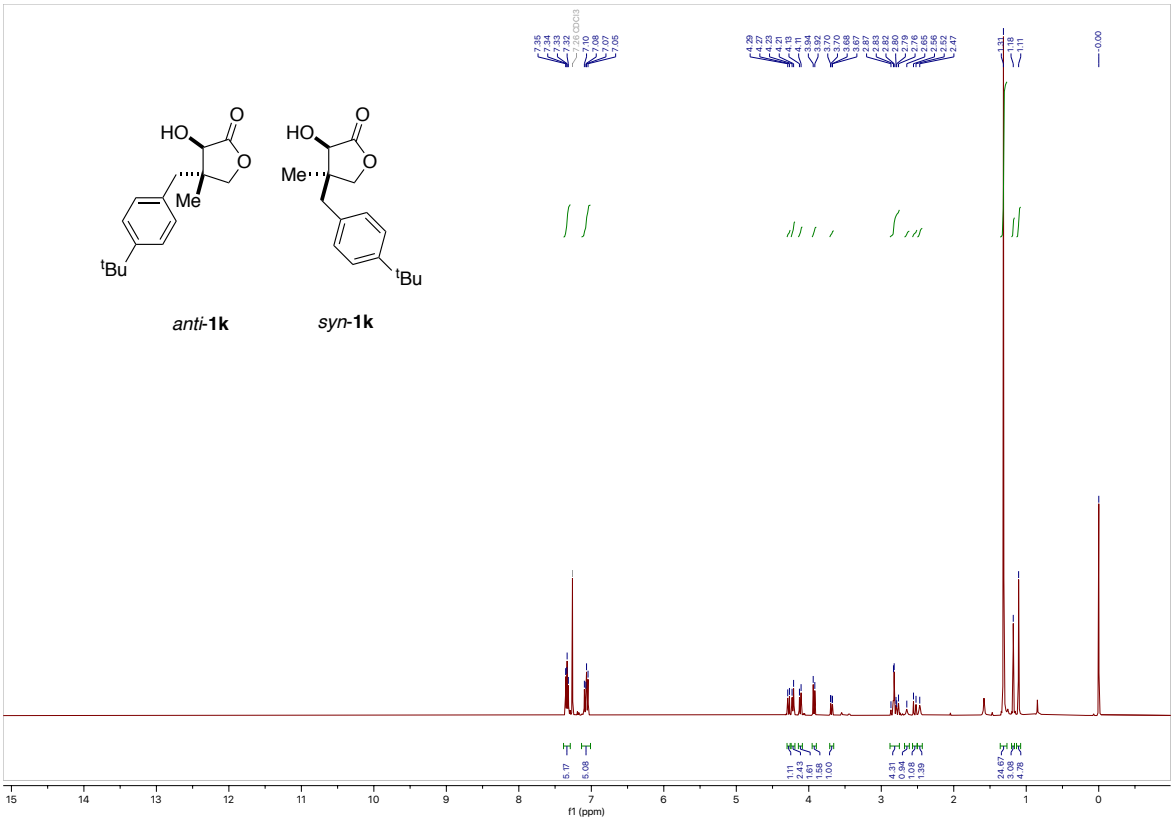

HO
O
O
Ph
Me
+
Me
OH
Ph
anti-1j
f1 (ppm)

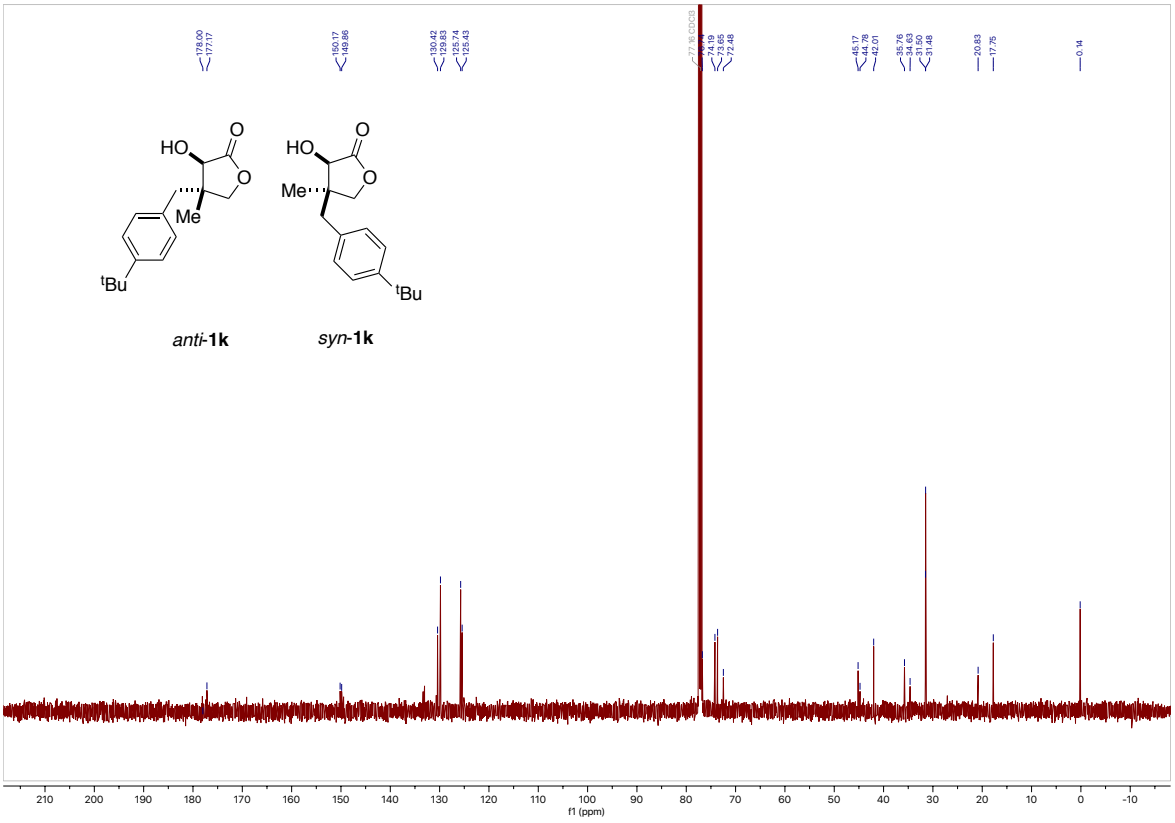

HO
O
O
Me
Ph
7.42
7.41
7.40
7.40
7.40
7.40
7.38
7.38
7.34
7.34
7.33
7.33
7.32
7.32
7.31
7.31
7.26 CDCl
4.82
4.80
4.38
4.35
4.30
4.28
1.98
1.96
1.63
1.93
2.93
1.02
1.00
1.04
0.94
3.08
f1 (ppm)

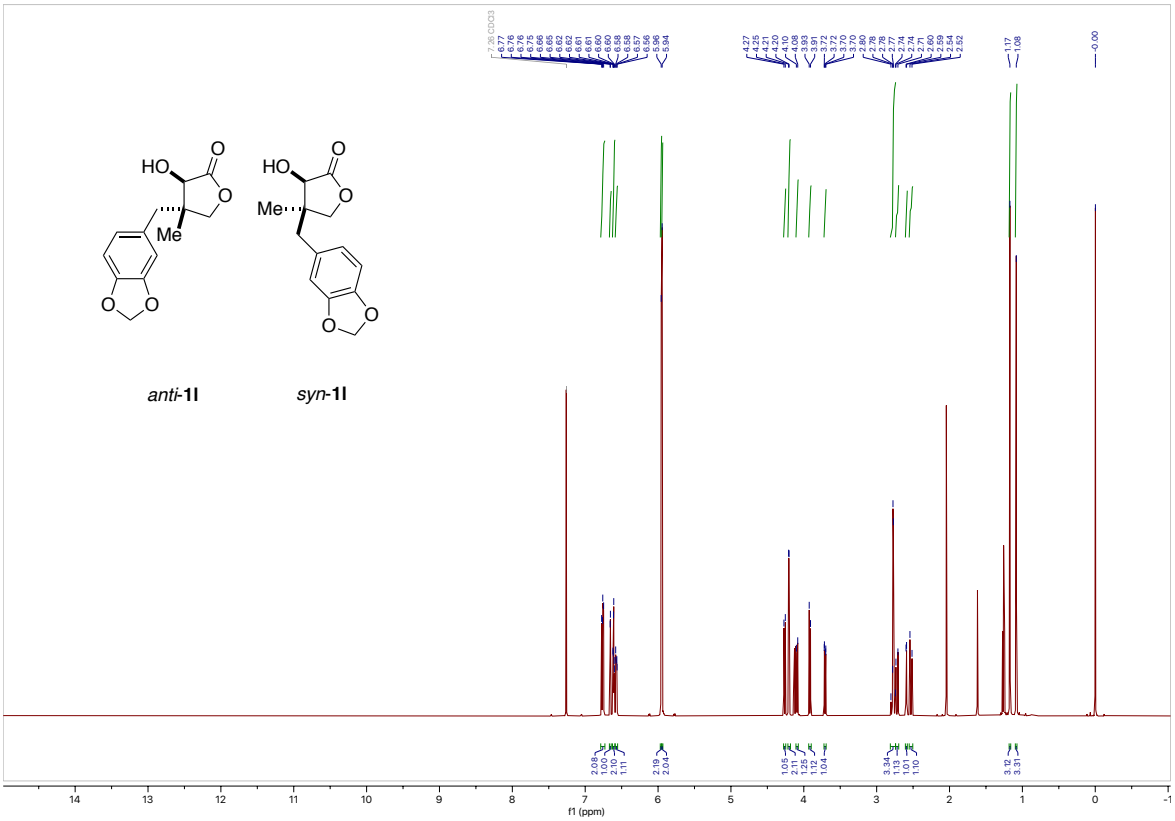
syn-**1j**

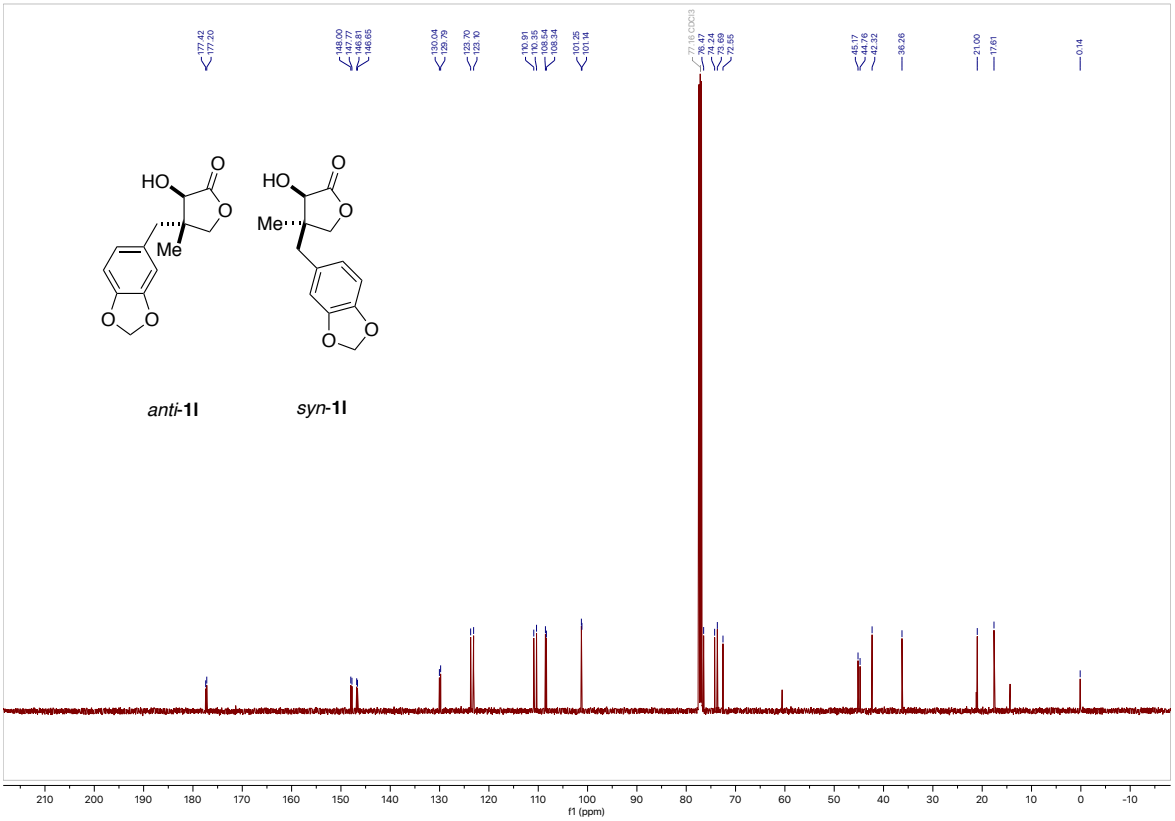

HO
O
O
Me
Ph
175.90
137.96
129.19
128.08
127.12
77.16 CDCl3
76.40
75.55
48.13
23.67
0.14
f1 (ppm)

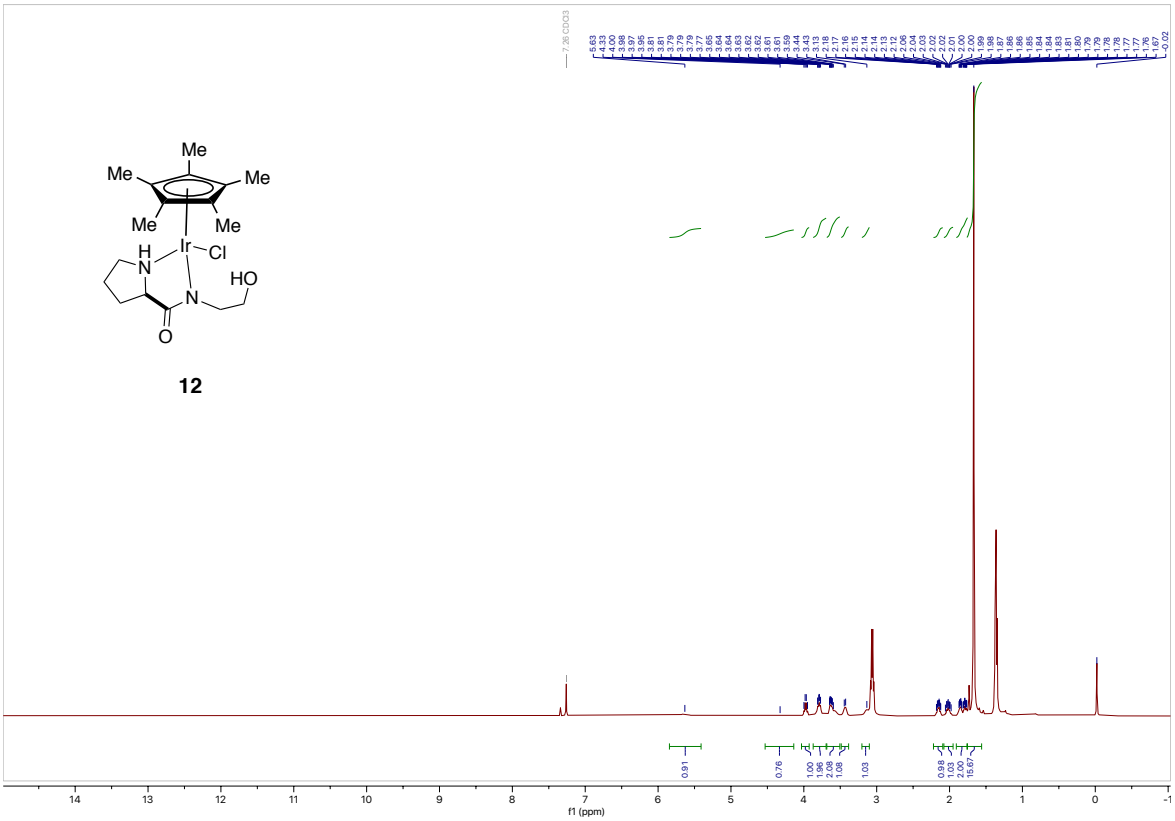
syn-**1j**

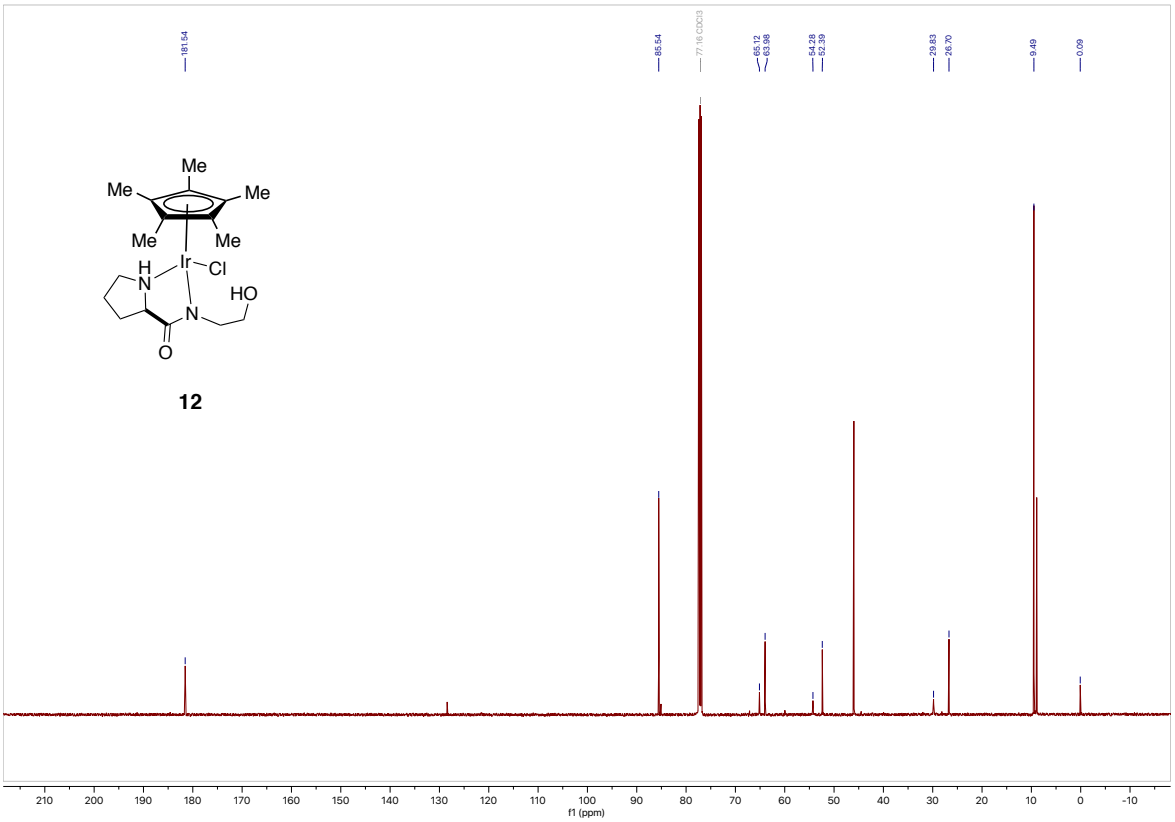

HO
O
O
Me
tBu
anti-1k
HO
O
O
Me
tBu
syn-1k
f1 (ppm)


HO
O
O
Me
tBu
anti-1k
HO
O
O
Me
tBu
syn-1k
f1 (ppm)

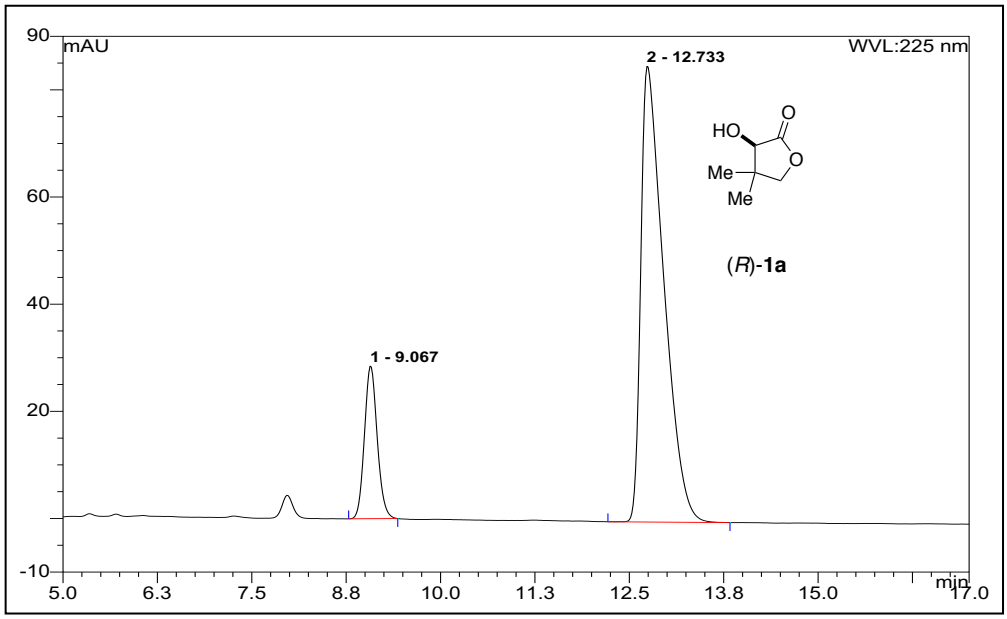

HO
O
O
Me
O
O
HO
O
Me
O
O
O
anti-1l
syn-1l
f1 (ppm)


HO
O
O
Me
O
O
HO
O
Me
O
O
O
anti-1l
syn-1l
f1 (ppm)

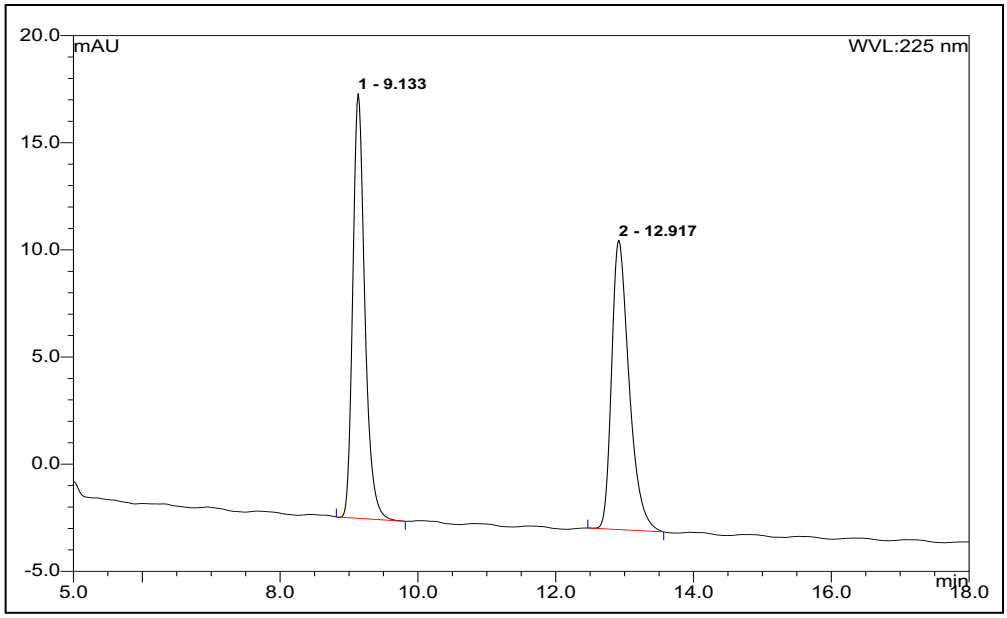

Me
Me
Me
Me
Me
H
N
Ir
Cl
HO
N
O
12
f1 (ppm)


Me
Me
Me
Me
Me
H
N
Ir
Cl
HO
N
O
12
f1 (ppm)

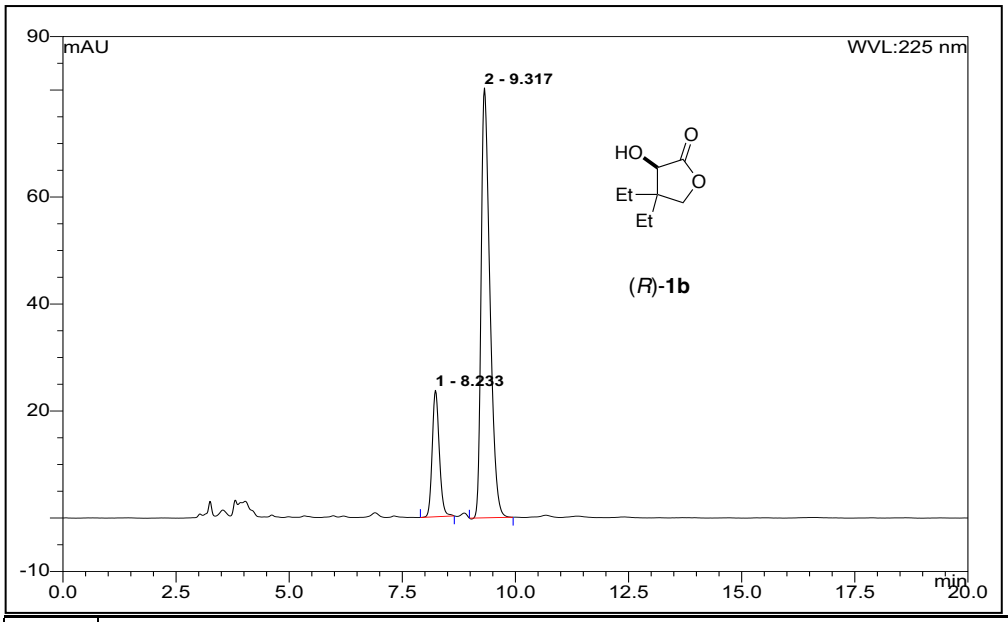
8 HPLC data



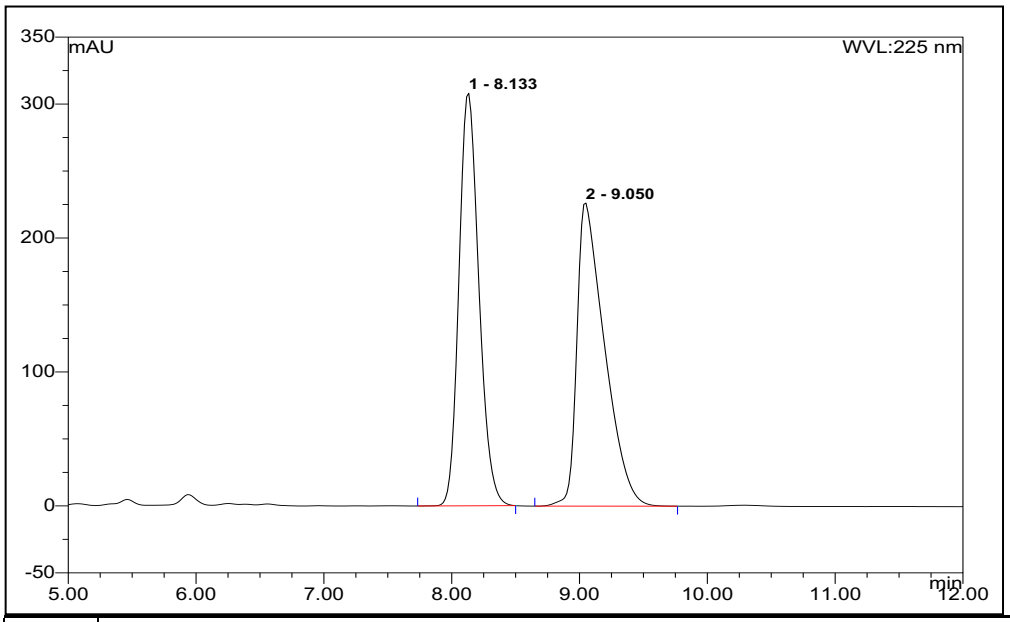
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	9.07	n.a.	26.422	4.659	13.43	n.a.	BMB*
2	12.73	n.a.	85.057	30.047	86.57	n.a.	BMB*
Total:			111.479	34.706	100.00	0.000	



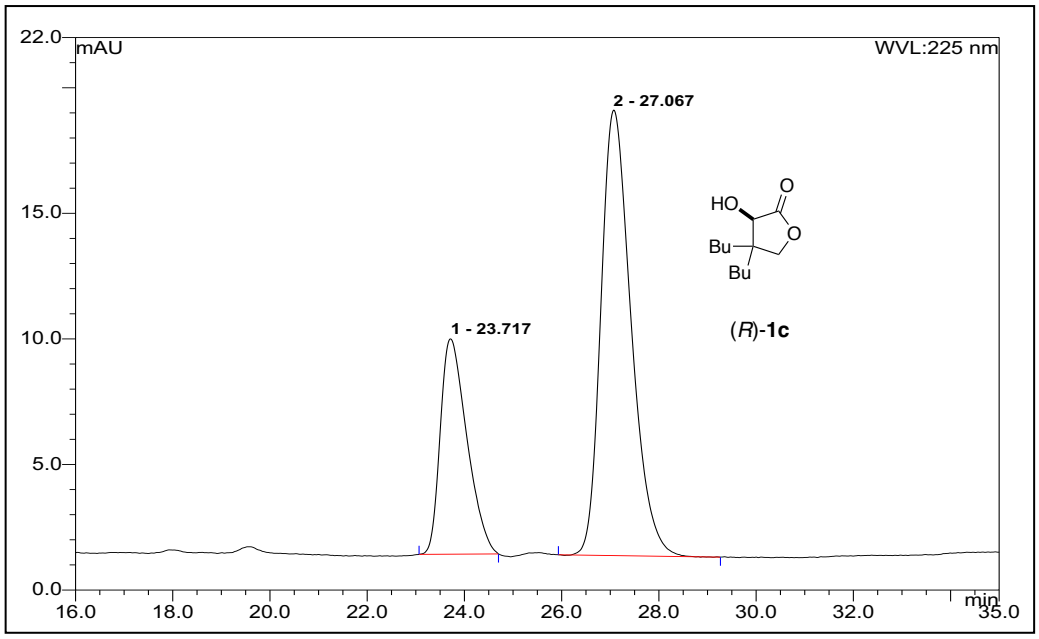
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	9.13	n.a.	19.817	4.012	50.22	n.a.	BMB*
2	12.92	n.a.	13.501	3.977	49.78	n.a.	BMB*
Total:			33.317	7.989	100.00	0.000	



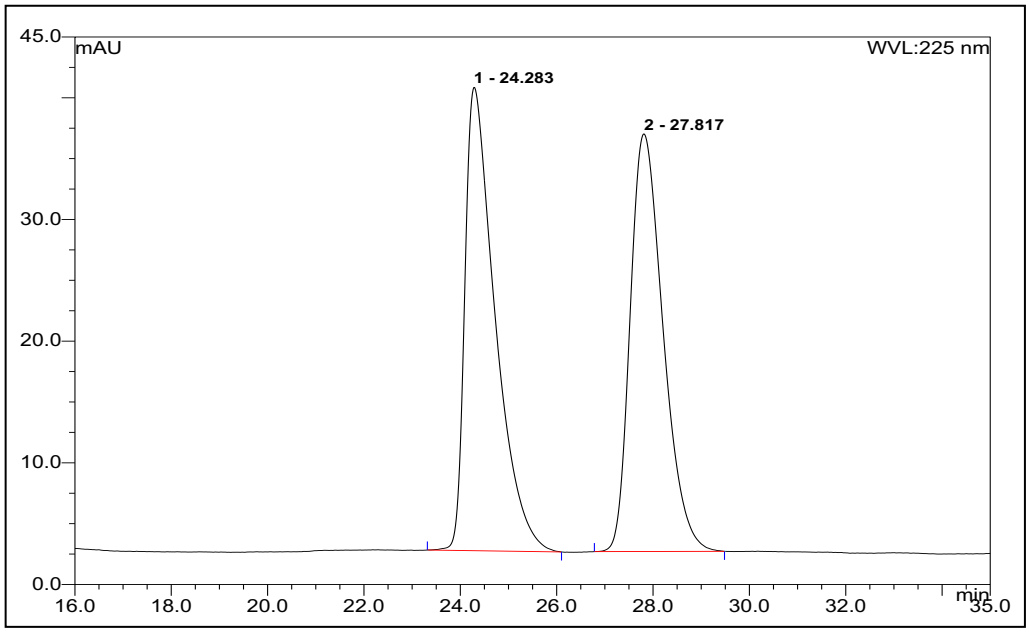
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	8.23	n.a.	23.643	4.276	19.15	n.a.	BMB*
2	9.32	n.a.	80.374	18.055	80.85	n.a.	BMB*
Total:			104.018	22.331	100.00	0.000	



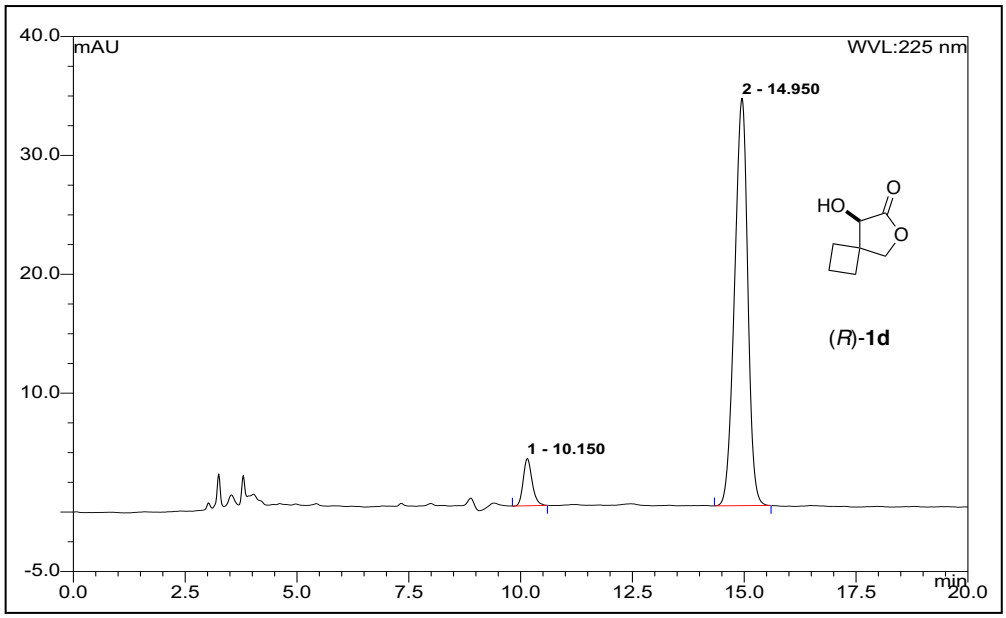
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	8.13	n.a.	308.113	55.721	49.53	n.a.	BMB*
2	9.05	n.a.	226.322	56.785	50.47	n.a.	BMB*
Total:			534.435	112.507	100.00	0.000	



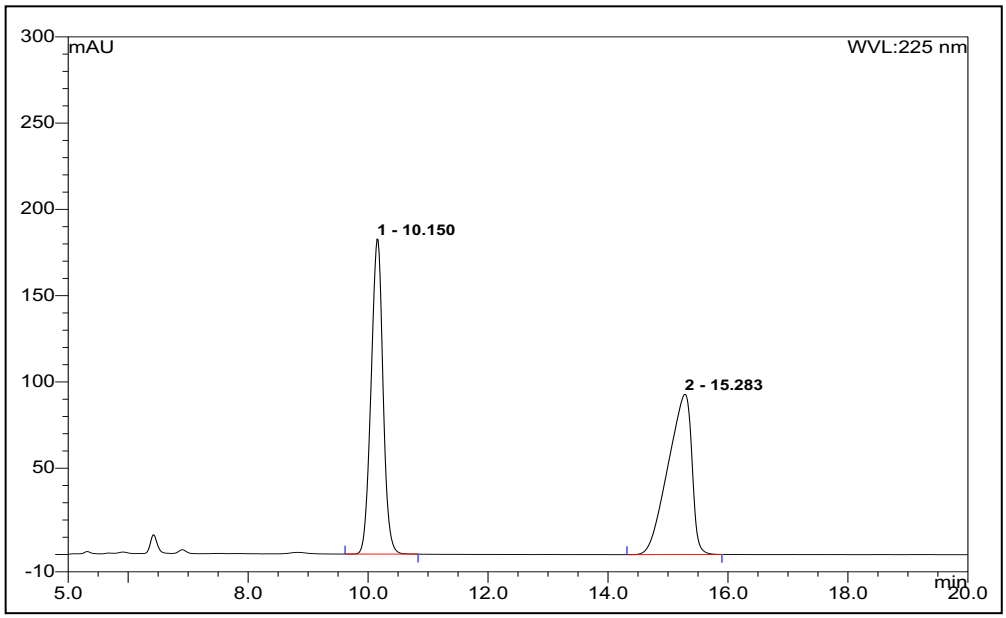
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	23.72 n.a.		8.576	5.431	29.87	n.a.	BMB*
2	27.07 n.a.		17.740	12.754	70.13	n.a.	BMB*
Total:			26.316	18.186	100.00	0.000	



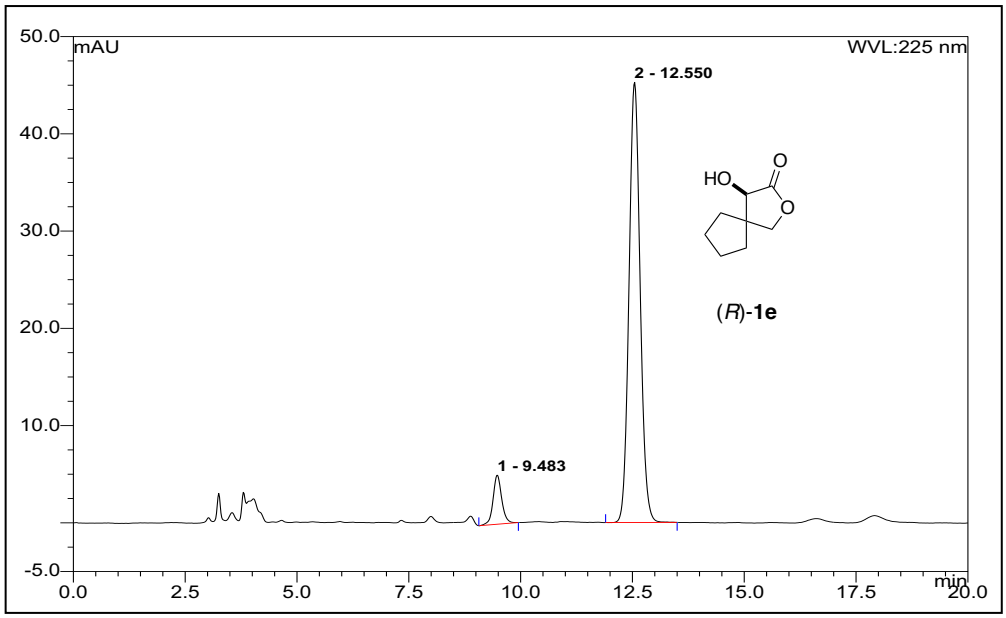
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	24.28 n.a.		38.083	27.686	50.49	n.a.	BMB*
2	27.82 n.a.		34.319	27.152	49.51	n.a.	BMB*
Total:			72.402	54.837	100.00	0.000	



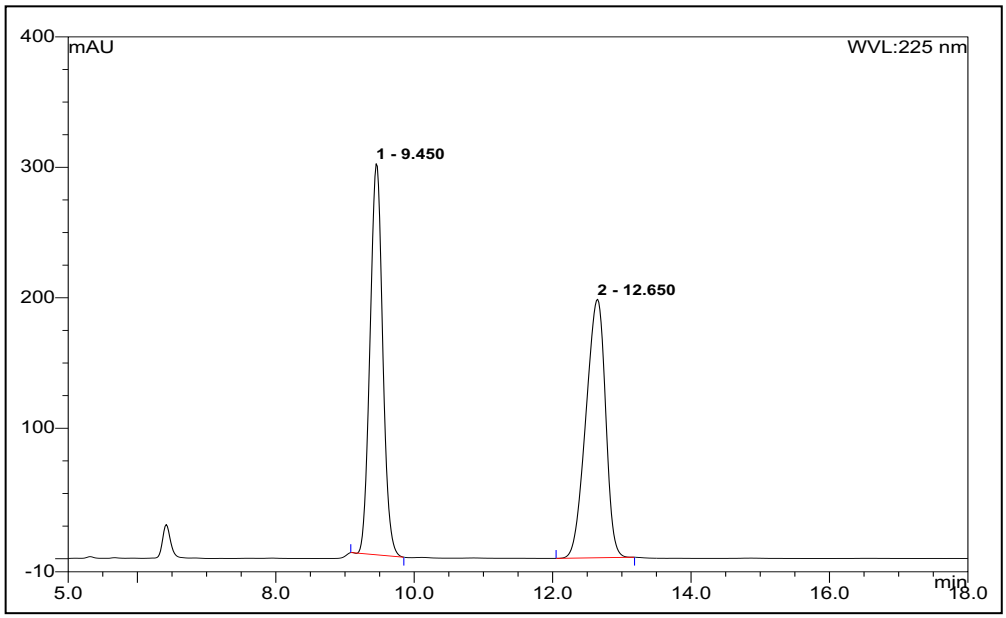
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	10.15 n.a.		3.982	0.918	7.25	n.a.	BMB*
2	14.95 n.a.		34.279	11.734	92.75	n.a.	BMB*
Total:			38.261	12.652	100.00	0.000	



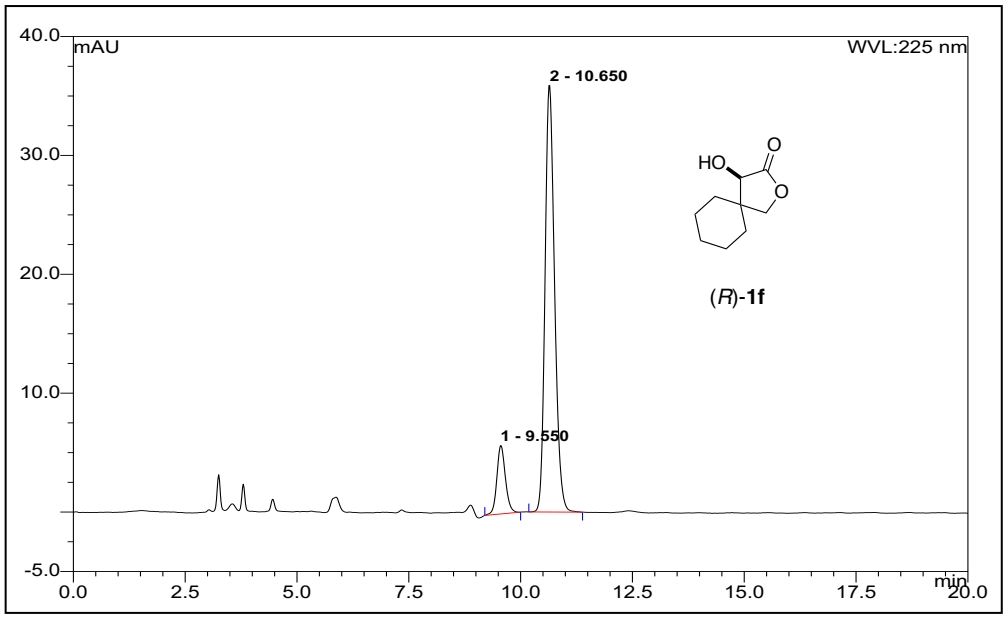
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	10.15 n.a.		182.689	42.095	49.67	n.a.	BMB*
2	15.28 n.a.		92.946	42.656	50.33	n.a.	BMB*
Total:			275.635	84.750	100.00	0.000	



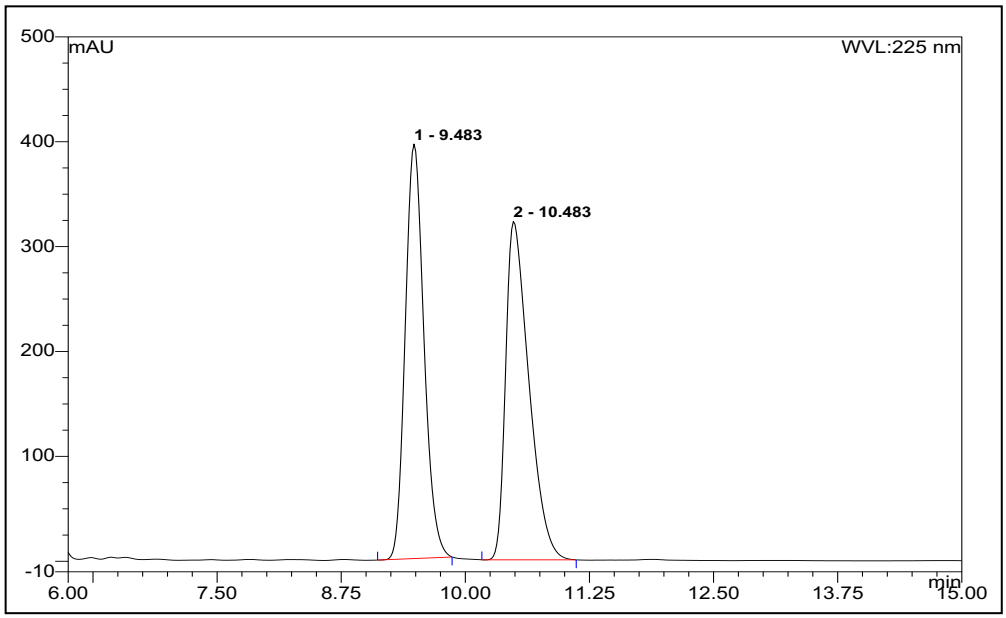
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	9.48 n.a.		5.040	1.132	7.98	n.a.	BMB*
2	12.55 n.a.		45.256	13.061	92.02	n.a.	BMB*
Total:			50.296	14.193	100.00	0.000	



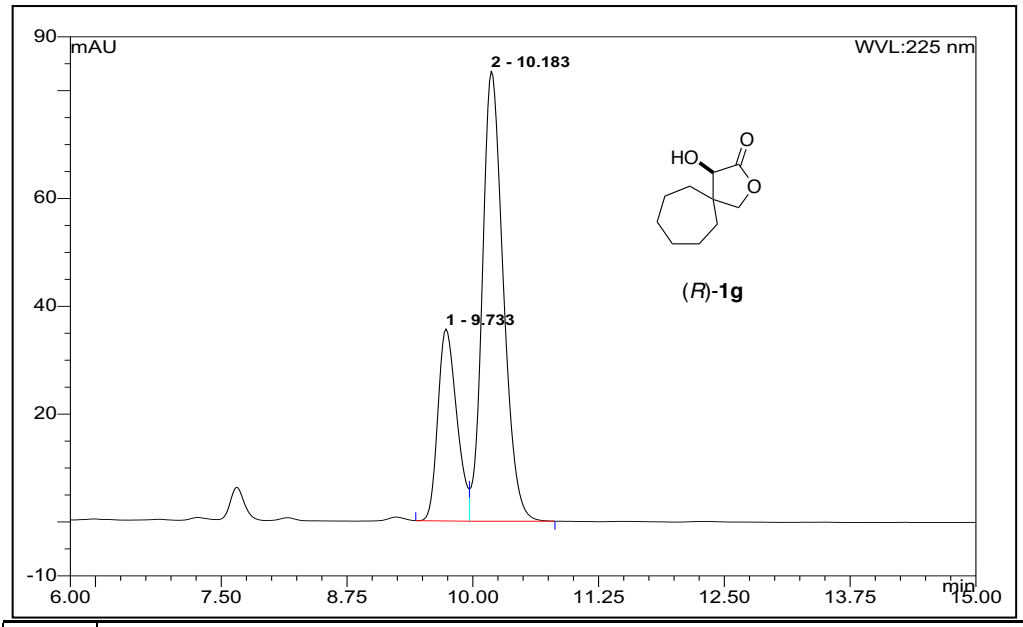
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	9.45 n.a.		299.767	63.575	49.49	n.a.	BMB*
2	12.65 n.a.		198.152	64.888	50.51	n.a.	BMB*
Total:			497.919	128.463	100.00	0.000	



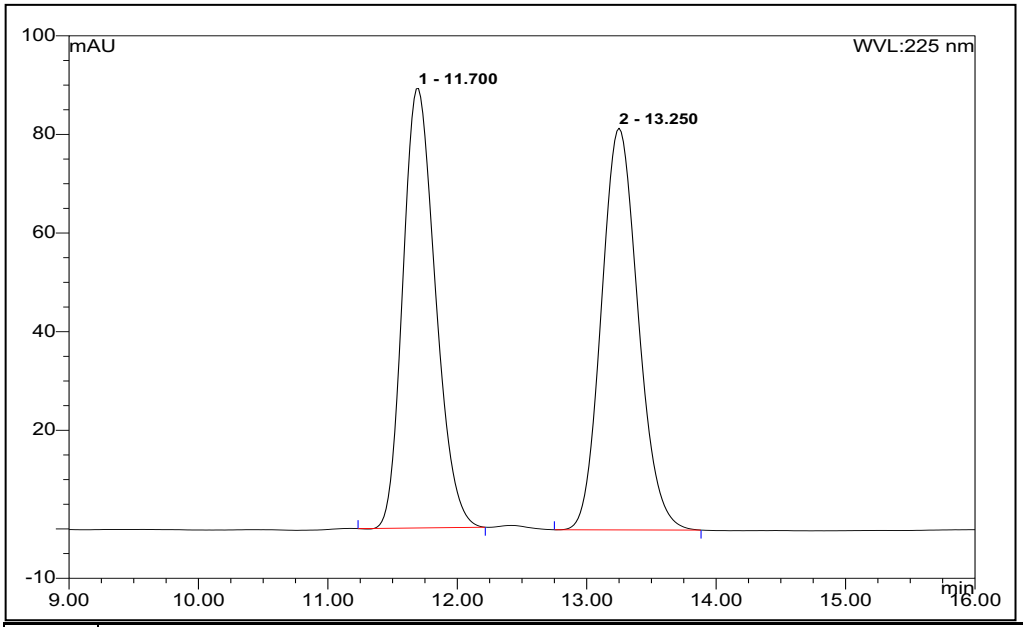
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	9.55	n.a.	5.748	1.278	12.58	n.a.	BMB*
2	10.65	n.a.	35.900	8.887	87.42	n.a.	BMB*
Total:			41.649	10.166	100.00	0.000	



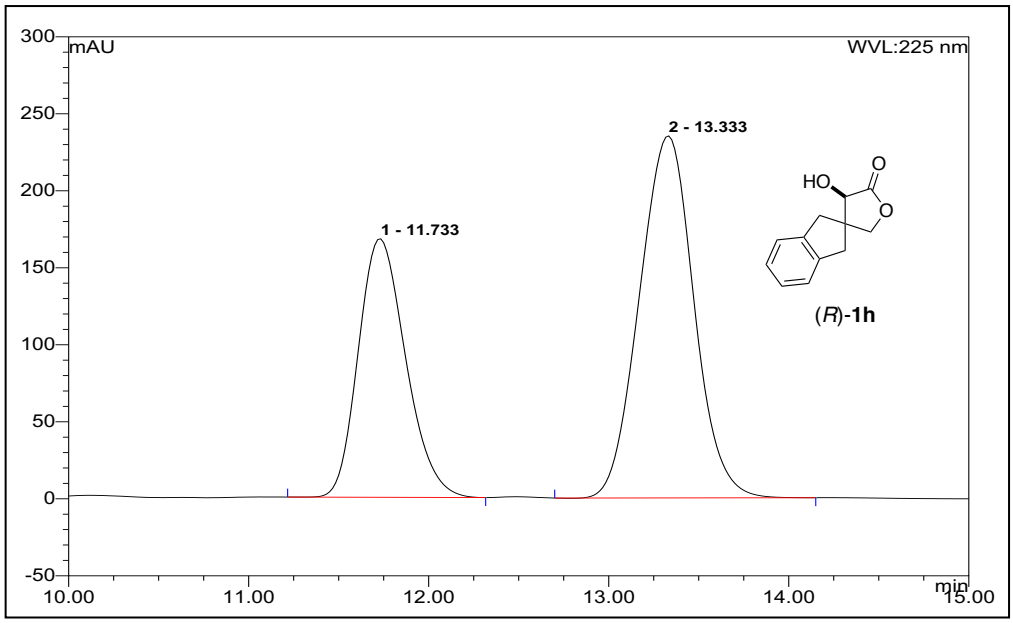
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	9.48	n.a.	395.283	86.115	49.65	n.a.	BMB*
2	10.48	n.a.	322.551	87.334	50.35	n.a.	BMB*
Total:			717.833	173.449	100.00	0.000	



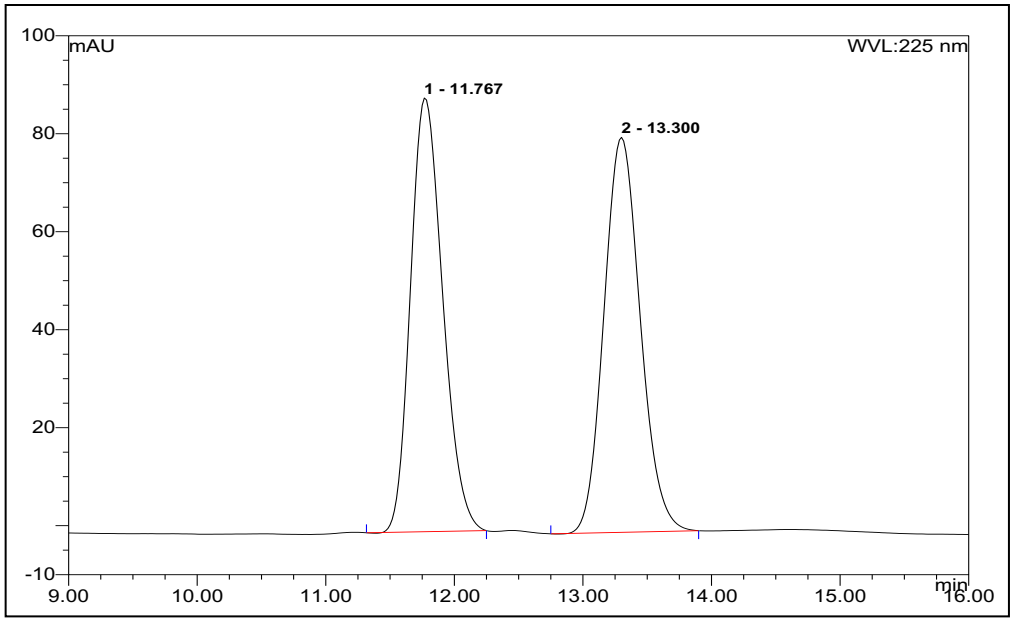
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	9.73	n.a.	35.649	7.787	27.88	n.a.	BM *
2	10.18	n.a.	83.521	20.143	72.12	n.a.	MB*
Total:			119.170	27.930	100.00	0.000	



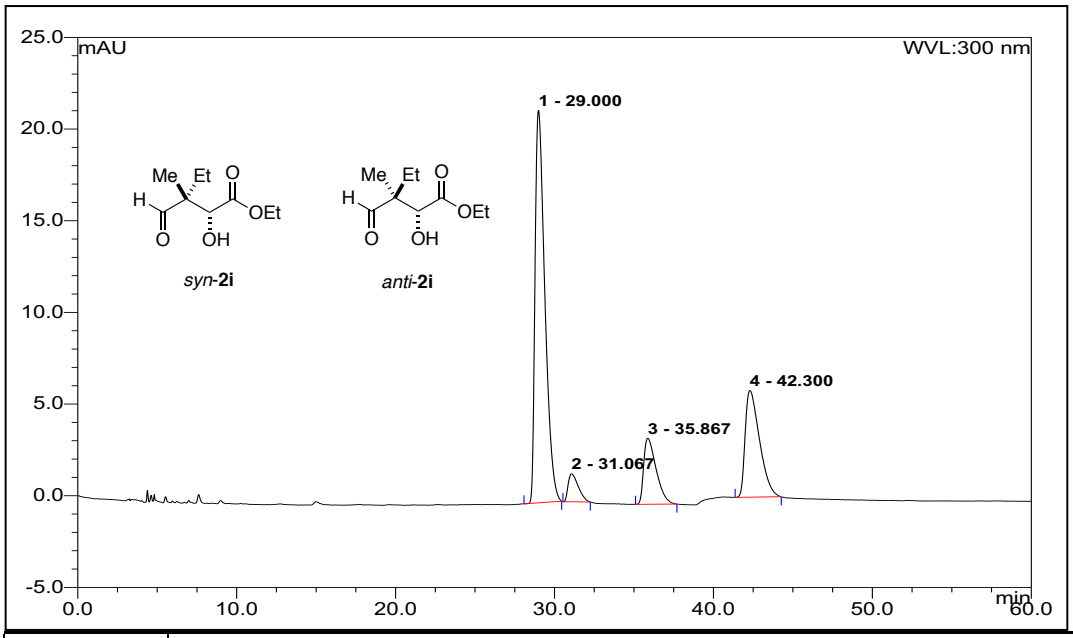
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	11.70	n.a.	89.119	25.974	49.24	n.a.	BMB*
2	13.25	n.a.	81.468	26.771	50.76	n.a.	BMB*
Total:			170.587	52.745	100.00	0.000	



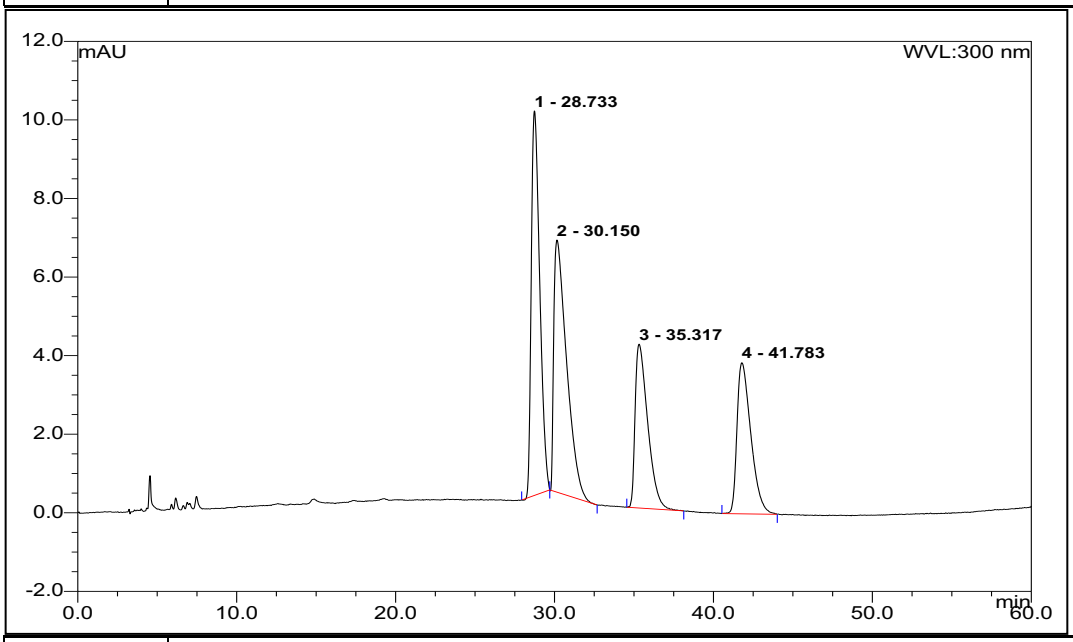
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	11.73	n.a.	167.872	51.155	38.31	n.a.	BMB*
2	13.33	n.a.	235.115	82.386	61.69	n.a.	BMB*
Total:			402.987	133.541	100.00	0.000	



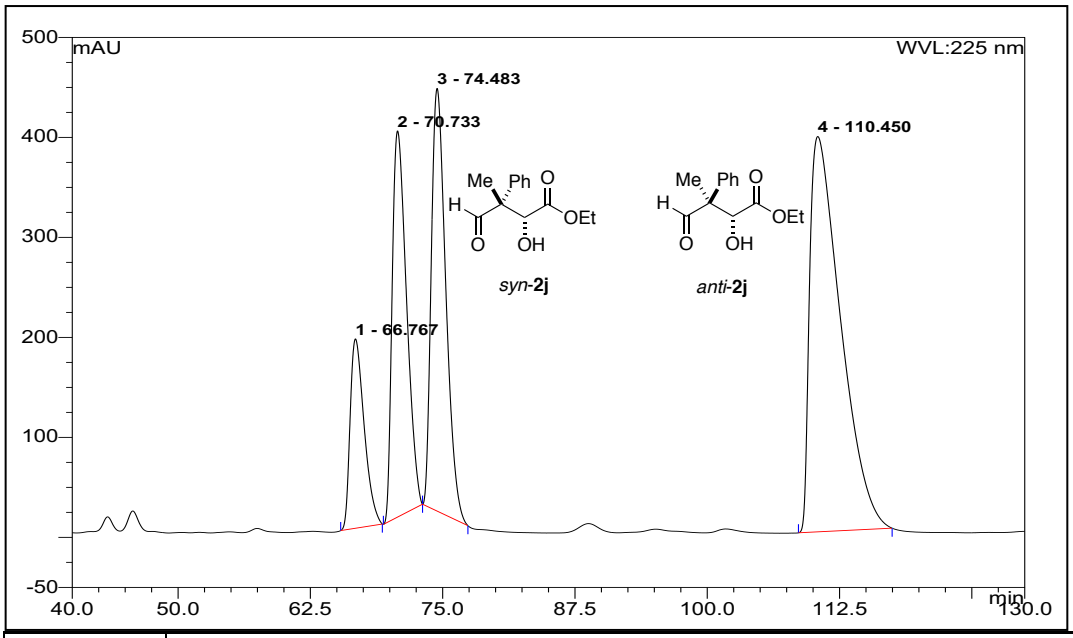
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	11.77	n.a.	88.540	25.680	49.35	n.a.	BMB*
2	13.30	n.a.	80.619	26.353	50.65	n.a.	BMB*
Total:			169.158	52.033	100.00	0.000	



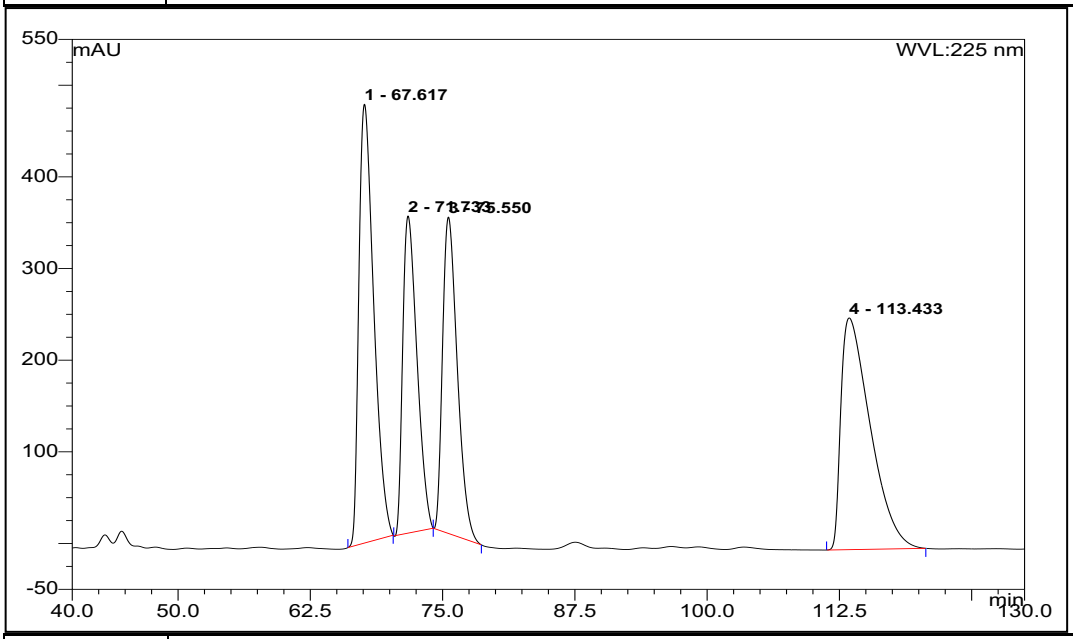
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	29.00	n.a.	21.411	15.331	59.37	n.a.	BMB*
2	31.07	n.a.	1.521	1.128	4.37	n.a.	BMB*
3	35.87	n.a.	3.603	3.280	12.70	n.a.	BMB*
4	42.30	n.a.	5.821	6.084	23.56	n.a.	BMB*
Total:			32.357	25.823	100.00	0.000	



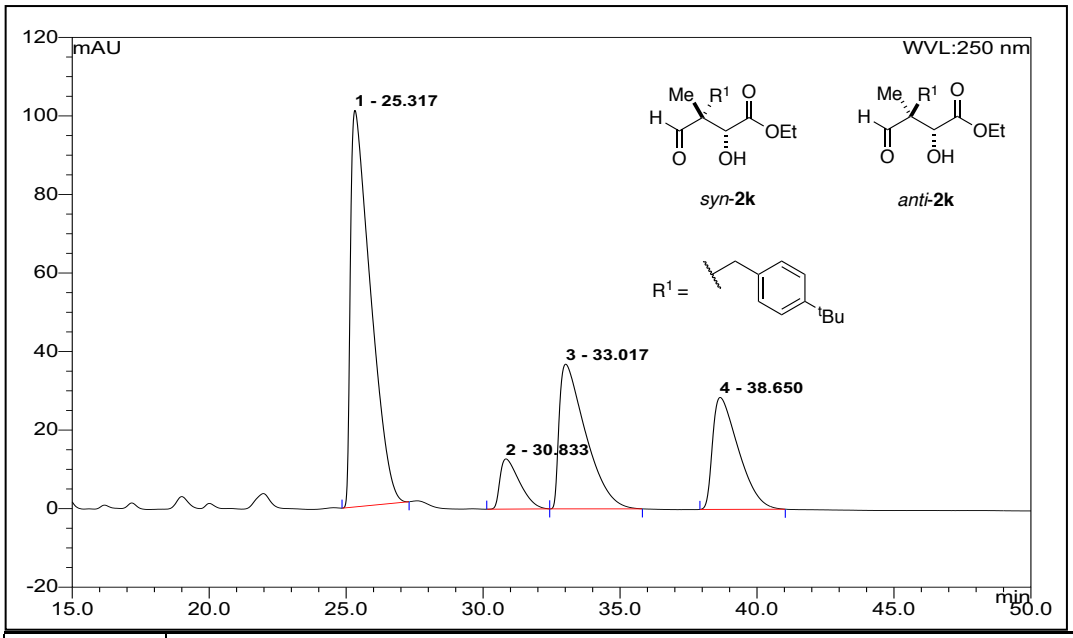
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	28.73	n.a.	9.787	6.041	30.54	n.a.	BMb*
2	30.15	n.a.	6.418	6.028	30.47	n.a.	bMB*
3	35.32	n.a.	4.171	3.828	19.35	n.a.	BMB*
4	41.78	n.a.	3.847	3.886	19.64	n.a.	BMB*
Total:			24.224	19.783	100.00	0.000	



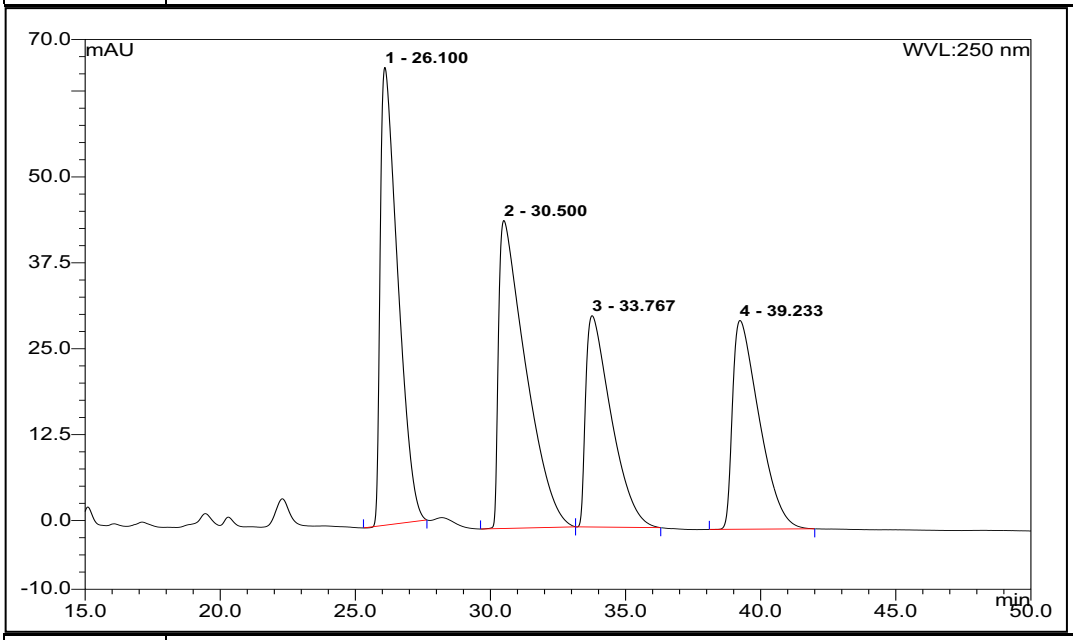
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%	n.a.	
1	66.77	n.a.	189.331	291.625	10.02	n.a.	BMB*
2	70.73	n.a.	386.232	607.821	20.88	n.a.	BMb*
3	74.48	n.a.	422.702	674.063	23.15	n.a.	bMB*
4	110.45	n.a.	395.329	1338.055	45.96	n.a.	BMB*
Total:			1393.595	2911.564	100.00	0.000	



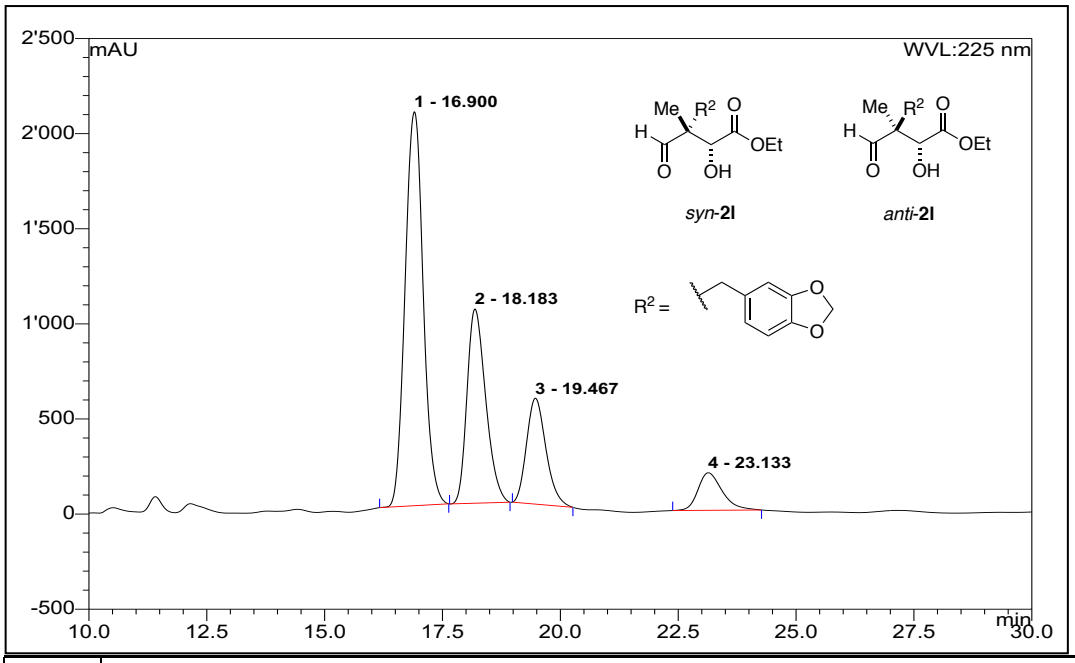
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%	n.a.	
1	67.62	n.a.	478.793	781.932	29.03	n.a.	BMB*
2	71.73	n.a.	346.040	540.095	20.05	n.a.	BMb*
3	75.55	n.a.	345.178	558.766	20.74	n.a.	bMB*
4	113.43	n.a.	252.777	812.797	30.18	n.a.	BMB*
Total:			1422.788	2693.591	100.00	0.000	



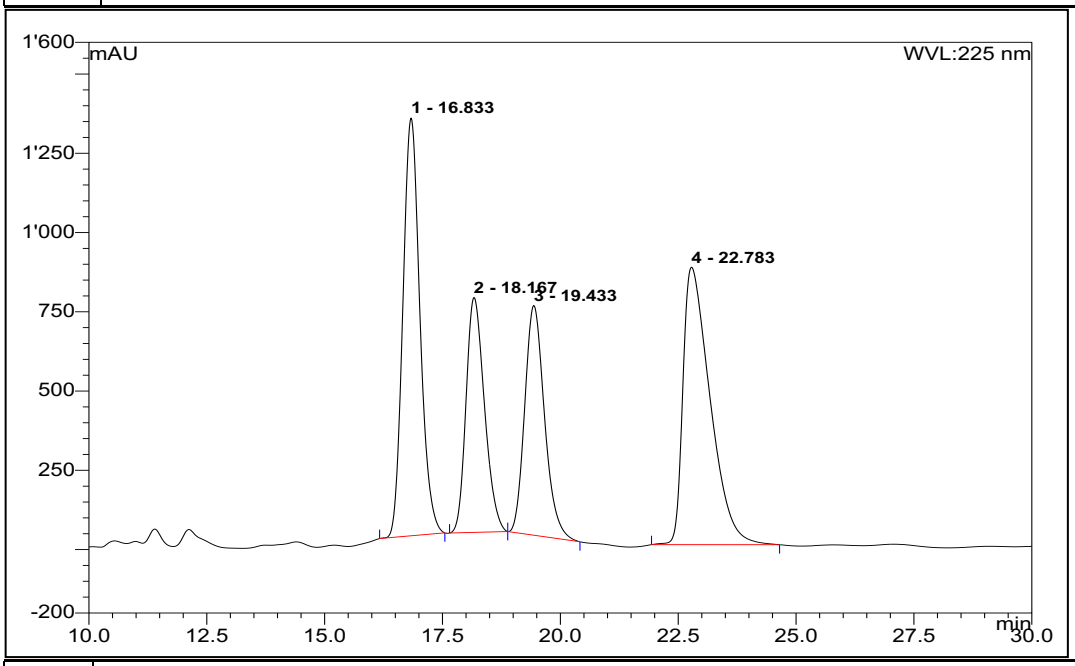
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	25.32	n.a.	100.983	85.951	50.86	n.a.	BMB*
2	30.83	n.a.	12.784	10.565	6.25	n.a.	BMb*
3	33.02	n.a.	36.850	41.268	24.42	n.a.	bMB*
4	38.65	n.a.	28.511	31.224	18.47	n.a.	BMB*
Total:			179.128	169.007	100.00	0.000	



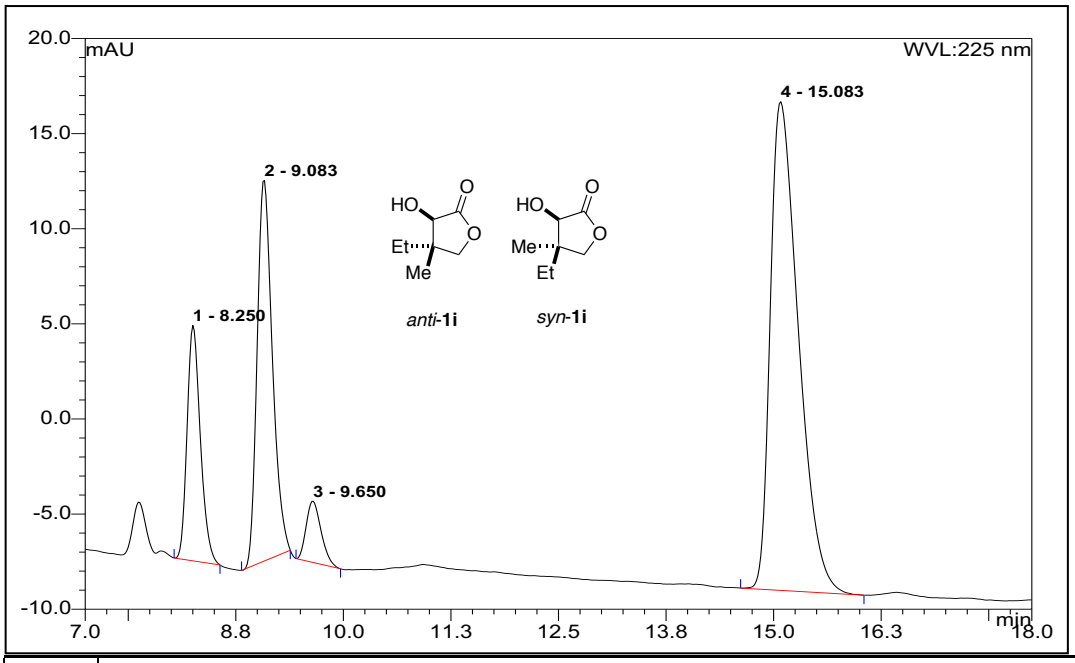
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	26.10	n.a.	66.611	50.365	29.47	n.a.	BMB*
2	30.50	n.a.	44.813	52.114	30.49	n.a.	BMb*
3	33.77	n.a.	30.743	33.736	19.74	n.a.	bMB*
4	39.23	n.a.	30.382	34.699	20.30	n.a.	BMB*
Total:			172.549	170.914	100.00	0.000	



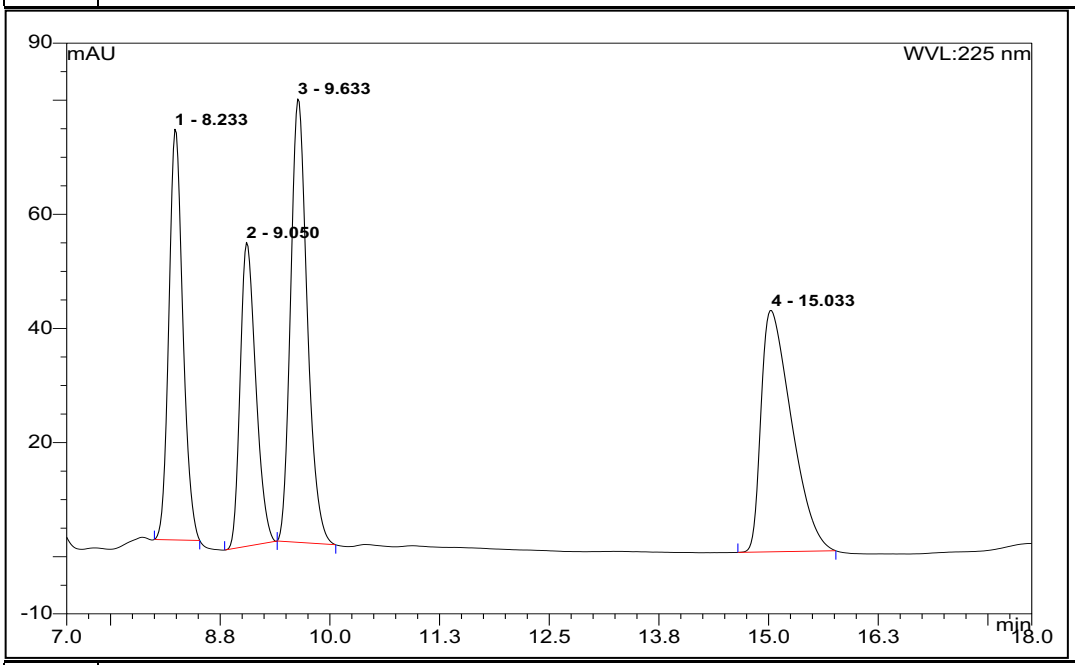
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	16.90	n.a.	2071.028	925.461	52.02	n.a.	BMB*
2	18.18	n.a.	1021.028	469.710	26.40	n.a.	BMB*
3	19.47	n.a.	557.103	266.220	14.96	n.a.	BMB*
4	23.13	n.a.	197.317	117.783	6.62	n.a.	BMB*
Total:			3846.475	1779.173	100.00	0.000	



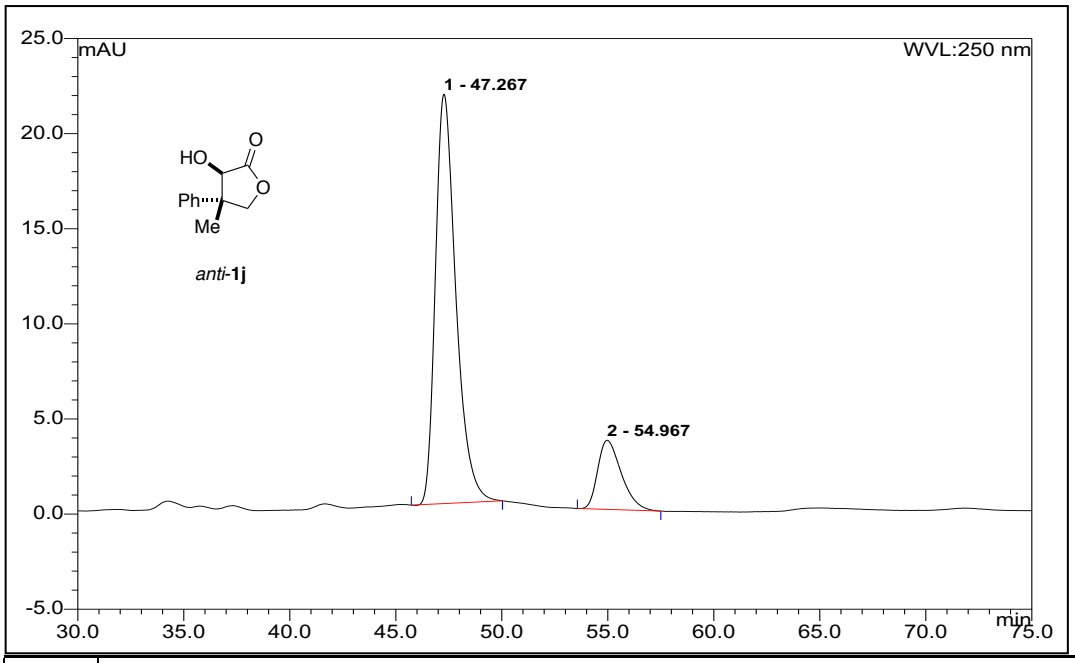
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	16.83	n.a.	1317.982	552.409	30.30	n.a.	BMB*
2	18.17	n.a.	741.047	335.381	18.39	n.a.	BMb*
3	19.43	n.a.	724.609	352.395	19.33	n.a.	bMB*
4	22.78	n.a.	875.401	583.216	31.99	n.a.	BMB*
Total:			3659.039	1823.401	100.00	0.000	



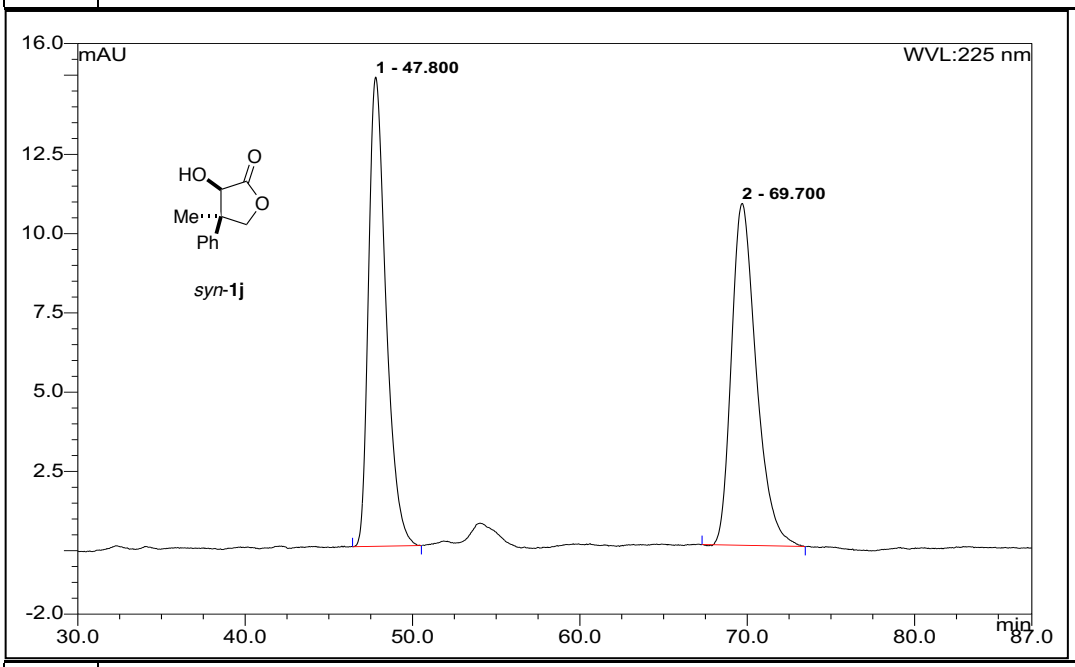
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	8.25	n.a.	12.382	2.220	13.28	n.a.	BMB*
2	9.08	n.a.	20.007	4.105	24.56	n.a.	BMB*
3	9.65	n.a.	3.227	0.649	3.88	n.a.	BMB*
4	15.08	n.a.	25.693	9.739	58.27	n.a.	BMB*
Total:			61.308	16.714	100.00	0.000	



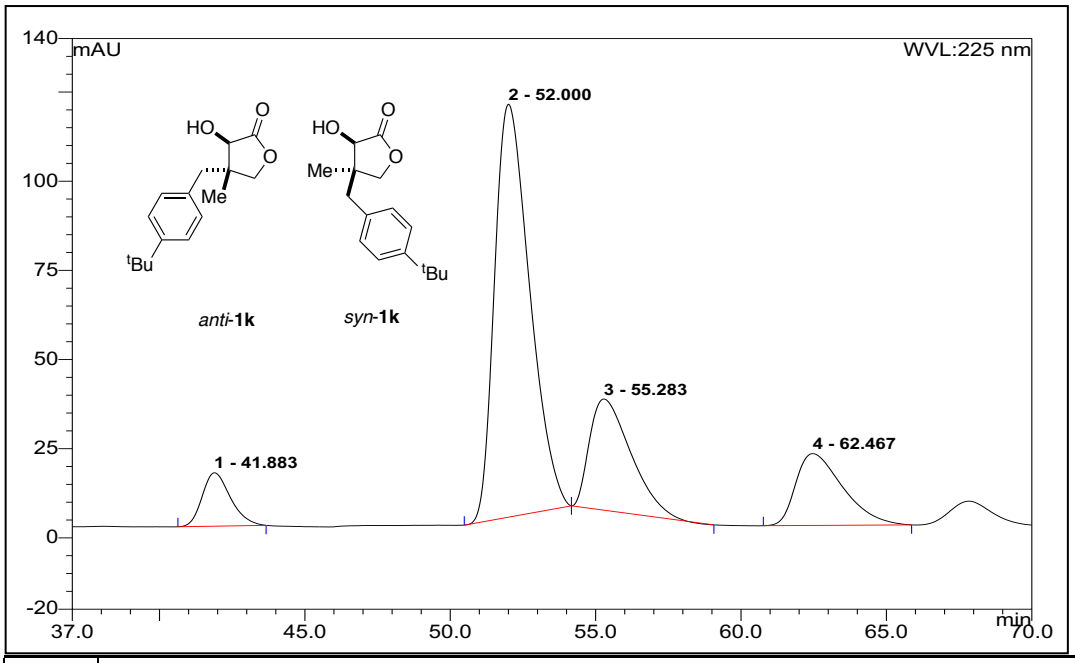
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	8.23	n.a.	71.986	13.308	22.78	n.a.	BMB*
2	9.05	n.a.	53.272	10.967	18.78	n.a.	BMb*
3	9.63	n.a.	77.709	17.118	29.31	n.a.	bMB*
4	15.03	n.a.	42.281	17.017	29.13	n.a.	BMB*
Total:			245.248	58.411	100.00	0.000	



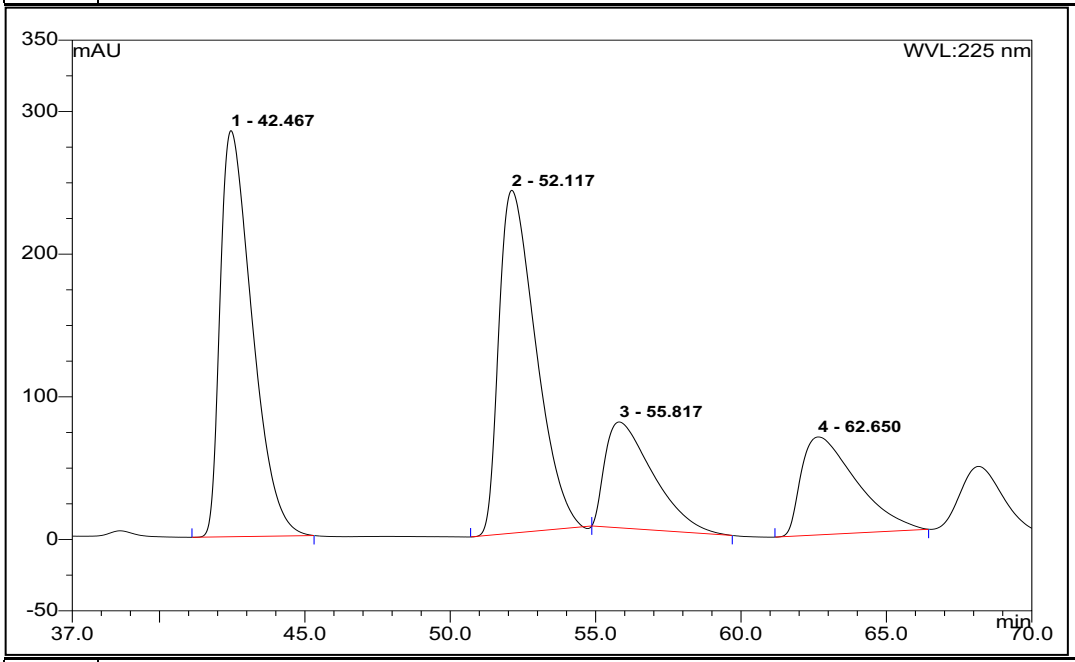
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	47.27	n.a.	21.521	24.127	83.72	n.a.	BMB*
2	54.97	n.a.	3.634	4.691	16.28	n.a.	BMB*
Total:			25.156	28.818	100.00	0.000	



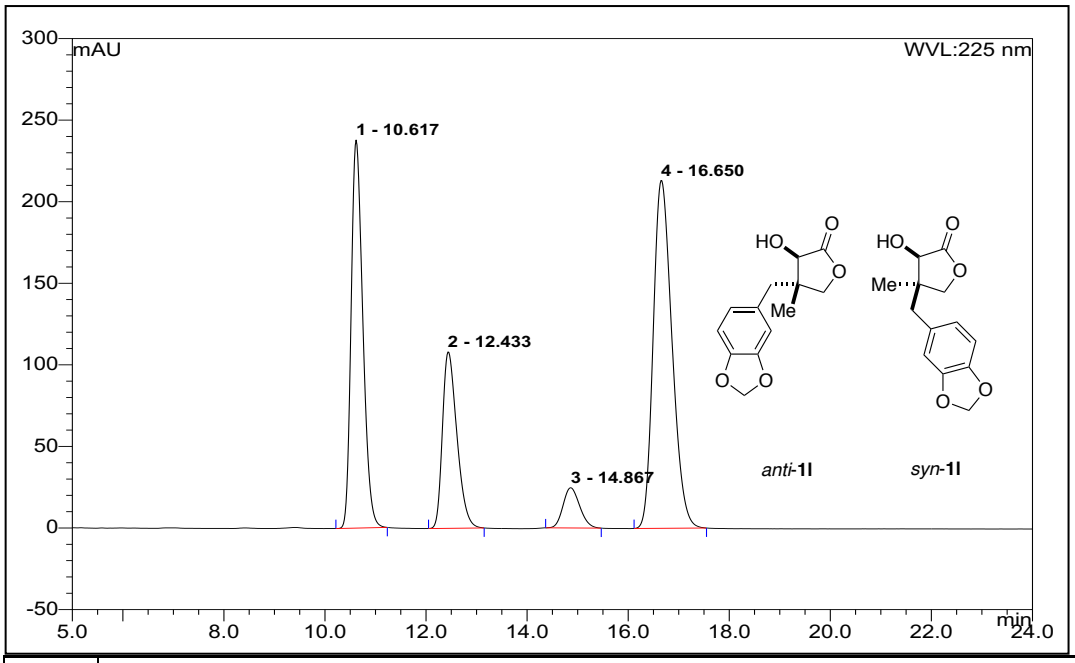
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	47.80	n.a.	14.803	17.929	49.22	n.a.	BMB*
2	69.70	n.a.	10.784	18.499	50.78	n.a.	BMB*
Total:			25.587	36.429	100.00	0.000	



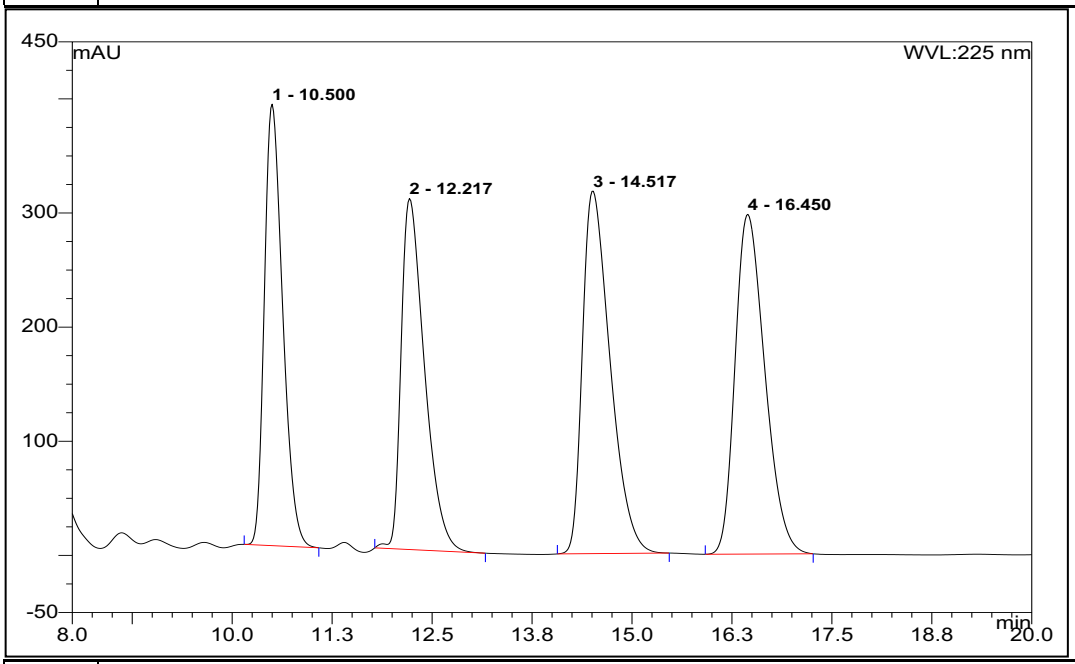
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	41.88	n.a.	14.976	16.884	6.29	n.a.	BMB*
2	52.00	n.a.	115.767	162.341	60.44	n.a.	BMb*
3	55.28	n.a.	31.155	51.611	19.22	n.a.	bMB*
4	62.47	n.a.	20.136	37.758	14.06	n.a.	BMB*
Total:			182.034	268.593	100.00	0.000	



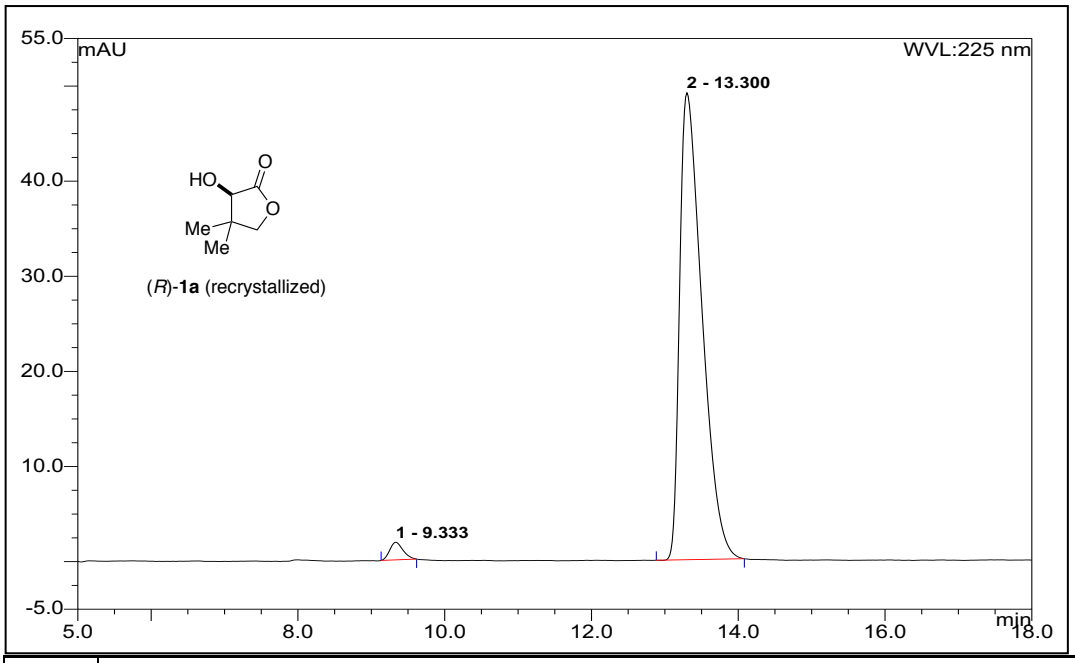
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	42.47	n.a.	284.635	363.392	35.99	n.a.	BMB*
2	52.12	n.a.	240.355	353.341	34.99	n.a.	BMb*
3	55.82	n.a.	74.186	142.172	14.08	n.a.	bMB*
4	62.65	n.a.	68.654	150.882	14.94	n.a.	BMB*
Total:			667.830	1009.786	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	10.62 n.a.		237.869	63.701	31.74	n.a.	BMB*
2	12.43 n.a.		108.122	35.822	17.85	n.a.	BMB*
3	14.87 n.a.		24.646	9.393	4.68	n.a.	BMB*
4	16.65 n.a.		213.251	91.774	45.73	n.a.	BMB*
Total:			583.888	200.689	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	10.50 n.a.		386.883	102.882	22.23	n.a.	BMB*
2	12.22 n.a.		307.602	104.099	22.49	n.a.	BMB*
3	14.52 n.a.		317.601	127.422	27.53	n.a.	BMB*
4	16.45 n.a.		297.645	128.373	27.74	n.a.	BMB*
Total:			1309.731	462.776	100.00	0.000	

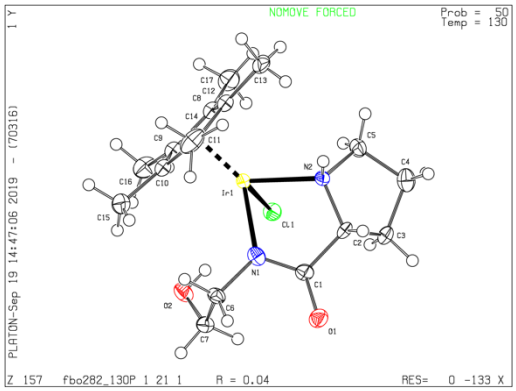


(*R*)-**1a** (recrystallized)

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	9.33 n.a.		1.856	0.388	2.19	n.a.	BMB*
2	13.30 n.a.		49.108	17.289	97.81	n.a.	BMB*
Total:			50.963	17.677	100.00	0.000	

9 X-ray Data CCDC1963845

Crystal data for IrClCp*((*R*)-11)



Chemical formula	$C_{17}H_{28}ClIrN_2O_2$
Formual weight	520.06
Z	2
$D_{calc.}$	1.916 g cm^{-3}
F(000)	506.0
Crystal description	yellow block
Crystal size	0.20x0.14x0.10 mm^3
Absorption coefficient	10.495 mm^{-1}
Min/max transmission	0.026 / 0.543
Temperature	130 K
Radiation (wavelength)	Ga *K*α (λ = 1.34143)
Crystal system	monoclinic
Space Group	P 2_1
Unit cell dimensions	a = 9.6777(5) Å
	b = 8.6576(3) Å
	c = 10.8681(5) Å
	α = 90°
	β = 98.892(4)°
	γ = 90°
Volume	899.65(7) $Å^3$
Min/max θ	3.581° / 55.387°
Number of collected reflections	9663
Number of independent reflections	2942 (merging r = 0.0267)
Number of observed reflections	2935 (I>2.0σ(I))
Number of refined parameters	191
R	0.0350
wR	0.0965
Goodness of fit	1.097
Flack	0.02(3)