Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Ir-Na Cooperativity Controls the Diastereoselectivity of Borrowing Hydrogen C-C Alkylation on Isosorbide: Synthesis Methodology and Mechanistic Investigation

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Supplementary Information

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General Note

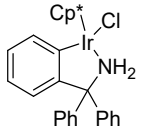
Reagents and solvents were supplied by Aldrich, TCI, or Alfa Aesar and purchased at the highest commercial quality to be used without further purification. NMR spectra were recorded on a Bruker 300 (^{1}H: 300 MHz; ^{13}C: 75 MHz) or Bruker 400 (^{1}H: 400 MHz; ^{13}C: 100 MHz) spectrometers at 298 K, using $CDCl_3$ as solvent. The chemical shifts (δ, ppm) are referenced to the residual solvent peak and coupling constants (*J*) are reported in the standard fashion. The residual peak of $CHCl_3$ was set at 7.26 ppm for ^{1}H NMR and the central peak of $CDCl_3$ was set at 77.16 ppm for ^{13}C NMR. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q =quartet, m = multiplet, br = broad. NMR peak assignments were performed for each compound using classical 1D and 2D NMR (COSY, HSQC, HMBC). For better clarity, a mean of close measured coupling constants for correlated protons are displayed in NMR assignments. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on a Thermo Finnigan LCQ Advantage mass spectrometer. Infrared (IR) spectra were recorded with an IRAffinity-1 Shimadzu spectrometer using attenuated total reflectance (ATR Miracle 10), and the wave-numbers were expressed in cm^{-1}. Optical rotations were measured with a Perkin−Elmer 241 polarimeter with a 5 cm cell (concentration *c* expressed in g/100 mL). High-resolution mass spectra (HRMS) were recorded on a Finnigan Mat 95xL mass spectrometer using either the electrospray (ESI) or atmospheric pressure chemical ionization (APCI) technique. Analytical thin-layer chromatography was carried out on silica gel Merck 60 D254 (0.25 mm). Flash chromatography was performed on Merck Si 60 silica gel (40−63µm).

General procedure for the borrowing hydrogen reaction

To a 10 mL Biotage® microwave vial equipped with a stirrer bar were introduced mono-protected isosorbide (1.0 eq.), pentamethylacetophenone (1.1 eq.), base (2.0 eq.), catalyst (5 mol %) and 1,3,5-trimethoxybenzene as standard in the open vessel. The vial was placed under inert atmosphere by performing 3 cycles vacuum / N_2. Then, toluene [1.0 M] was introduced and the vial was sealed with a microwave vial cap. The vial was heated at 120 °C for 24 h in a preheated tray. The mixture was cooled down to room temperature and few drops of water (100 µL) were added. The reaction vessel was washed with DCM (10 mL) and concentrated under reduced pressure. Purification by flash column chromatography packed with silica afforded the title compound.

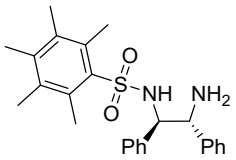
Preparation of catalysts

[Cp*-Ir-NTr · HCl] (Ir-1):



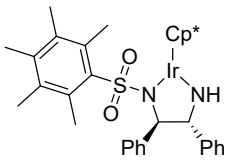
NaOAc (55 mg, 0.67 mmol, 2.7 eq.) was added to a mixture of $[Cp^*IrCl_2]_2$ (200 mg, 0.25 mmol, 1.0 eq.) and $TrNH_2$ (144 mg, 0.56 mmol, 2.2 eq.) in DCM (10 mL). After stirring at r.t. for 20 h, the solution was concentrated. The crude mixture was diluted with toluene (50 mL) and filtered off on a celite© pad and washed with toluene (50 mL). Evaporation of the filtrate to dryness afforded the iridacycle [Cp*Ir-NTr·HCl] product as a yellow to orange powder (335 mg, quant.). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 15H, $C(CH_3)_5$), 7.03-7.40 (m, 14H, CH_{Ph}). NMR spectrum was consistent with the literature.[1]

***N*-((*1R,2R*)-2-Amino-1,2-diphenylethyl)-2,3,4,5,6-pentamethylbenzenesulfonamide**



To a solution of (*R, R*)-1, 2-diphenylethylenediamine (750 mg, 3.53 mmol, 1.0 eq.) in anhydrous DCM (40 mL) under an argon atmosphere at 0 °C was introduced triethylamine (540 µL, 3.89 mmol, 1.1 eq.). After stirring for 20 min., pentamethylbenzenesulfonyl chloride (960 mg, 1.1 mmol) in anhydrous DCM (5 mL) was added dropwise to the reaction mixture at 0 °C. The solution was allowed to stir at r.t. for 18 h. After complete conversion, water (30 mL) was added and the aqueous phase was extracted with DCM (4 x 20 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO_2, pentane/EtOAc, 1/1) to afford the title compound as a white solid (1.19 g, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 6H, 2 CH_3), 2.12 (s, 3H, CH_3), 2.36 (s, 6H, 2 CH_3), 4.36 (bs, 1H), 5.95 (bs, 1H), 6.86–7.13 (m, 10H, 10 CH_{Ph}). NMR spectrum was consistent with the literature.[2]

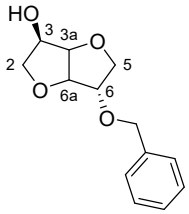
[Cp*Ir(Ts*-dpen)(*R,R*)] (Ir-2)



A mixture of N-((*1R,2R*)-2-amino-1,2-diphenylethyl)-2,3,4,5,6-pentamethylbenzenesulfonamide (200 mg, 0.50 mmol, 1.0 eq.), $[Cp^*IrCl_2]_2$ (200 mg, 0.25 mmol, 0.5 eq.) and KOH (140 mg, 2.5 mmol, 5 eq.) in DCM (6 ml) and water (6 ml) was stirred for 30 minutes under Ar atmosphere at r.t.. The aqueous phase was extracted with DCM (3 x 10 mL) and the organic phases were dried over Na_2SO_4. The purple organic layer was filtered off on a Celite© pad and washed with Et_2O (20 mL). The filtrate was concentrated under reduced pressure to afford the desired product [Cp*Ir(Ts*-dpen)(*R,R*)] as a dark purple powder (363 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96 (s, 6H, 2 CH_3), 1.97 (s, 6H, 2 CH_3), 2.03 (s, 15H, $C(CH_3)_5$), 2.13 (s, 3H, CH_3), 3.92 (s, 1H), 3.96 (s, 1H), 5.14 (bs, 1H, NH), 7.08–7.41 (m, 10H, 10 CH_{Ph}). NMR spectrum was consistent with the literature.[2]

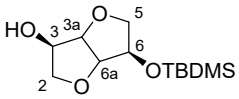
Substrates

(3*R*,6*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-ol (1)



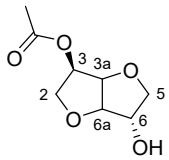
To a solution of isosorbide (5.0 g, 34.2 mmol, 1.0 eq.) in distilled water (15 mL) was introduced a 50%wt/H_2O solution of CsOH (5.96 mL, 34.2 mmol, 1.0 eq.) and benzyl chloride (3.94 mL, 34.2 mmol, 1.0 eq.). The biphasic solution was stirred at 80°C for 22 h. The reaction was quenched with HCl (2N) until neutral pH. Then, the water phase was extracted with EtOAc (3 x 30 mL). The organic layers were combined and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting yellow solid was washed with cold Et_2O (100 mL) and gave the title compound **1** as a white solid (1.52 g, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (d, *J* = 7.2, 1H, OH), 3.56 (dd, *J* = 9.5, 5.7, 1H, H_2), 3.82–3.92 (m, 2H, H_2, H_5), 4.05–4.16 (m, 2H, H_6, H_5), 4.25–4.33 (m, 1H, H_3), 4.53 (app dt, *J* = 4.8, 1.0, 1H, H_{6a}), 4.55 (d, *J* = 12.0, 1H, C$\underline{H}_2$Ph), 4.61 (d, *J* = 12.0, 1H, C$\underline{H}_2$Ph), 4.65 (app t, *J* = 4.8, 1H, H_{3a}). 7.30–7.38 (m, 5H, H_{Ph}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 71.7 ($\underline{C}H_2$Ph), 72.4 (C_3), 73.5 (C_5), 73.8 (C_2), 81.9 (C_{3a}), 83.6 (C_6), 86.1 (C_{6a}), 127.9 (2 CH_{Ph}), 128.1 (C_{Ph}), 128.7 (2 CH_{Ph}), 137.6 (C_{qPh}). MS (ESI/BS) $[M + Na]^+$: calcd. for $C_{13}H_{16}O_4Na$: 259.1, found 259.1, $[2M + Na]^+$: calcd. for $C_{26}H_{32}O_8Na_2$: 495.1, found 495.1. NMR spectra were consistent with the literature.[3]

(3*R*,6*R*)-6-((*Tert*-butyldimethylsilyl)oxy)hexahydrofuro[3,2-*b*]furan-3-ol (6)



To a solution of isomannide (3.01 g, 20.60 mmol, 1 eq) in DMF (22.5 mL), TBDMSCl (3.40 g, 22.56 mmol, 1.1 eq) then imidazole (3.37 g, 45.40 mmol, 2.4 eq) were added. The reaction was stirred at r.t. under an argon atmosphere for 5 hours. After completion, water (250 ml) was added. The aqueous phase was extracted with diethyl ether (3 x 100 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, pentane/EtOAc, 9:1) afforded compound **6** as white crystals (2.19 g, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 3H, CH_3), 0.12 (s, 3H, CH_3), 0.90 (s, 9H, $C(CH_3)_3$), 3.17 (bs, 1H, OH), 3.72 (dd, *J* = 5.5, 3.4, 1H, H_2), 3.74 (dd, *J* = 5.5, 4.0, 1H, H_2), 3.93 (dd, *J* = 5.5, 3.4, 1H, H_5), 3.96 (dd, *J* = 6.1, 3.4, 1H, H_5), 4.18 (m, 1H, H_6), 4.26 (app q, *J* = 5.3, 1H, H_{6a}), 4.41 (app t, *J* = 4.6, 1H, H_{3a}), 4.49 (app t, *J* = 5.6, 1H, H_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.0 (CH_3), -4.6 (CH_3), 18.5 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 71.9 (C_6), 73.5 (C_{6a}), 74.3 (C_2), 75.8 (C_5), 81.7 (C_3), 82.2 (C_{3a}). NMR spectra were consistent with the literature.[4]

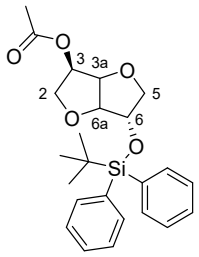
(3*R*,6*S*)-6-Hydroxyhexahydrofuro[3,2-*b*]furan-3-yl acetate



In a round bottom flask under Ar, isosorbide (3.65 g, 25 mmol, 1.0 eq.), lead oxide (112 mg, 0.5 mmol, 0.02 eq.) and acetic anhydride (2.8 mL, 30.0 mmol, 1.2 eq.) were introduced. The mixture became viscous after 30 min and anhydrous DCM (5 mL) was added. Then the solution was allowed to stir for 2 h at r.t. The mixture was concentrated with toluene as co-solvent (3 x 20 mL) under reduced pressure to remove the unreacted acetic anhydride and the acetic acid formed. The crude was purified on flash column chromatography (SiO_2, DCM/MeOH, 95:5, R_f = 0.13) affording the title compound as a yellow

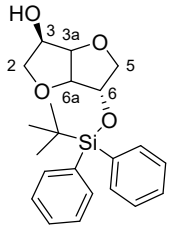
oil (4.11 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 3H, CH_3), 3.68 (dd, J = 5.3, 9.7, 1H, H_2), 3.75-3.88 (m, 3H, H_2, H_5), 4.22-4.23 (m, 1H, H_6), 4.31 (d, J = 4.6, 1H, H_{6a}), 4.75 (dd, J = 5.3, 4.6, 1H, H_{3a}), 5.04-5.08 (m, 1H, H_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.6 ($\underline{C}H_3$), 70.0 (C_2), 74.2 (C_3), 75.5 (C_5), 75.9 (C_6), 80.3 (C_{3a}), 88.1 (C_{6a}), 170.7 (C=O). MS (ESI/BS) $[M + Na]^+$: calcd. for $C_8H_{12}O_5Na$: 211.1, found 211.0 $[M + H]^+$: calcd. for $C_8H_{13}O_5$: 189.1, found 189.1.

(3*R*,6*S*)-6-((*Tert*-Butyldiphenylsilyl)oxy)hexahydrofuro[3,2-*b*]furan-3-yl acetate



(3*R*,6*S*)-6-Hydroxyhexahydrofuro[3,2-*b*]furan-3-yl acetate (1.06 g, 5.63 mmol, 1.0 eq.) was introduced in a 25 mL round-bottom flask. After 3 cycles vacuum/N_2, anhydrous DMF (5 mL) and imidazole (0.58 g, 8.45 mmol, 1.5 eq.) were introduced under inert atmosphere. The solution was cooled to 0 °C and *tert*-butyl(chloro)diphenylsilane (2.2 mL, 8.45 mmol, 1.5 eq.) was added dropwise. At the end of the addition, the mixture was allowed to stir at r.t. for 22 h. The mixture turned white and two phases were obtained. An aqueous saturated solution of NH_4Cl (100 mL) was added to the mixture. Then, the aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. Purification of the residue was performed by flash column chromatography (SiO_2, Pentane/Et_2O, 8/2, R_f = 0.26) affording the title compound as a colorless oil (1.79 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H, 3 CH_3), 2.09 (s, 3H, CH_3-Ac), 3.61 (dd, J = 9.4, 6.5, 1H, H_2), 3.68 (dd, J = 9.7, 3.3, 1H, H_5), 3.84 (d, J = 9.7, 1H, H_5), 3.89 (dd, J = 9.4, 6.5, 1H, H_2), 4.30–4.31 (m, 1H, H_6), 4.40 (d, J = 4.2, 1H, H_{6a}), 4.88 (app t, J = 4.6, 1H, H_{3a}), 5.10 (app td, J = 6.5, 4.6, 1H, H_3), 7.33–7.49 (m, 6H, H_{Ph}), 7.59–7.67 (m, 4H, H_{Ph}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.8 ($\underline{C}H_3$), 26.9 (3 $\underline{C}H_3$), 69.5 (C_2), 74.4 (C_3), 76.0 (C_5), 77.9 (C_6), 80.6 (C_{3a}), 88.5 (C_{6a}), 127.9 and 128.0 (4 *m*-$\underline{C}H_{Ph}$), 130.0 and 130.1 (2 *p*-$\underline{C}H_{Ph}$), 133.3 and 133.5 (2 $\underline{C}_{qPh}$), 135.8 (4 *o*-$\underline{C}H_{Ph}$), 170.6 (C=O). MS (ESI/HRMS) $[M + Na]^+$: calcd. for $C_{24}H_{30}O_5SiNa$: 449.1755, found 449.1755.

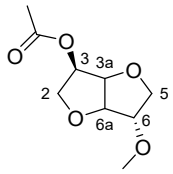
(3*R*,6*S*)-6-((*Tert*-butyldiphenylsilyl)oxy)hexahydrofuro[3,2-*b*]furan-3-ol (7)



(3*R*,6*S*)-6-((*tert*-Butyldiphenylsilyl)oxy)hexahydrofuro[3,2-*b*]furan-3-ylacetate (1.0 g, 2.3 mmol, 1.0 eq.) was dissolved with EtOH (2 mL) in a 25 mL round-bottom flask. Then, KOH (0.2 g, 3.6 mmol, 1.5 eq., in 1.5 mL of EtOH) was added to the reaction mixture. The mixture was refluxed at 50 °C for 30 min. The solution obtained was cooled to r.t. and HCl (1M) was added until pH neutral. The aqueous layer was extracted with EtOAc (5 x 10 mL) and the organic layers were combined, dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, Pentane/Et_2O, 1:1) affording the title compound **7** as a colorless oil (100 mg, 17%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H, *t*-Bu), 2.65 (d, J = 7.8, 1H, O$\underline{H}$), 3.41 (dd, J = 9.4, 6.3, 1H, H_2), 3.66 (dd, J = 9.7, 3.2, 1H, H_5), 3.81 (dd, J = 9.4, 6.3, 1H, H_2), 3.88 (d, J = 9.7, 1H, H_5), 4.23–4.32 (m, 1H, H_3), 4.34–4.37 (m, 1H, H_6), 4.39 (dt, J = 4.1, 1.0, 1H, H_{6a}), 4.70 (dd, J = 5.3, 4.1, 1H, H_{3a}),

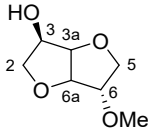
7.36–7.48 (m, 6H, 6 H_{Ph}), 7.61–7.67 (m, 4H, 4 H_{Ph}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 19.3 ($C_{q\textit{t}\text{-Bu}}$), 27.0 (3 $\underline{C}H_3$), 72.5 (C_3), 73.5 (C_2), 76.0 (C_5), 78.3 (C_6), 81.9 (C_{3a}), 88.3 (C_{6a}), 127.9 and 128.0 (2 C_{Ph}), 130.09 and 130.13 (2 C_{Ph}), 133.2 and 133.5 (2 C_{qPh}),135.76 and 135.77 (2 C_{Ph}). MS (ESI/HRMS) $[M + Na]^+$: calcd. for $C_{22}H_{28}NaO_4Si$: 407.1649 found 407.1642. $[2M + Na]^+$: calcd. for $C_{44}H_{56}NaO_8Si_2$: 791.3406 found 791.3400.

(3*R*,6*S*)-6-Methoxyhexahydrofuro[3,2-*b*]furan-3-yl acetate



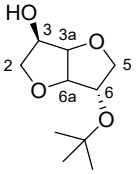
In a 100 mL round bottom flask was added (3*R*,6*S*)-6-hydroxyhexahydrofuro[3,2-*b*]furan-3-yl acetate (1.5 g, 8.0 mmol, 1.0 eq.) in iodomethane (15 mL, 241 mmol, 30 eq). Then, silver oxide (2.4 g, 10.4 mmol, 1.3 eq.) and calcium sulfate (6.0 g, 44 mmol, 5.5 eq.) were added to the mixture. The flask was protected from the light and the suspension was stirred for 2 days in the dark at r.t. The mixture was diluted with ether (100 mL) and filtered through a celite pad. The filtrate was concentrated under reduced pressure. The crude was purified on flash column chromatography (SiO_2, Pentane/Et_2O, 7/3, R_f = 0.13) affording the title compound as a yellowish oil (1.18 g, 73%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.01 (s, 3H, CH_3), 3.27 (s, 3H, OCH_3), 3.65 (dd, *J* = 9.6, 5.6, 1H, H_2), 3.73–3.81 (m, 2H, H_5, H_6), 3.80–3.91 (m, 2H, H_5, H_2), 4.36 (d, *J* = 4.8, 1H, H_{6a}), 4.66 (app t, *J* = 4.8, 1H, H_{3a}), 5.03 (app q, *J* = 5.6, 1H, H_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.5 ($\underline{C}H_3$), 56.9 ($O\underline{C}H_3$), 69.8 (C_2), 72.7 (C_5), 74.0 (C_3), 80.4 (C_{3a}), 85.2 (C_6), 85.5 (C_{6a}), 170.1 (C=O). MS (ESI/BS) $[M + Na]^+$: calcd. for $C_9H_{14}O_5Na$: 225.1, found 225.0, $[M + H]^+$: calcd. for $C_9H_{15}O_5$: 203.1, found 203.1. NMR spectrum was consistent with the literature.[3]

(3*R*,6*S*)-6-Methoxyhexahydrofuro[3,2-*b*]furan-3-ol (8)



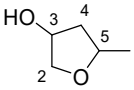
In a round bottom flask topped by a condenser, (3*R*,6*S*)-6-methoxyhexahydrofuro[3,2-*b*]furan-3-yl acetate (750 mg, 3.71 mmol, 1.0 eq.) was introduced in a solution of potassium hydroxide (312 mg, 5.56 mmol, 1.5 eq.) in EtOH (1M, 6 mL). The reaction mixture was stirred at 50 °C for 30 min. Then, the solution obtained was neutralized with aq. HCl (1M) until pH 7. The aqueous phase was extracted with EtOAc (5 x 10 mL). All the organic layers were collected and dried over $MgSO_4$. After filtration and concentration under reduced pressure, the crude was purified by flash column chromatography (SiO_2, Pentane/Et_2O, 7/3) affording the title compound **8** as a colorless oil (100 mg, 17%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.64 (d, *J* = 7.0, 1H, OH), 3.39 (s, 3H, CH_3), 3.57 (dd, *J* = 9.5, 5.6, 1H, H_2), 3.79–3.96 (m, 3H, H_5, H_2), 4.05 (dd, *J* = 9.8, 1.1, 1H, H_6), 4.22–4.34 (m, 1H, H_3), 4.46 (dd, *J* = 4.8, 1.1, 1H, H_{6a}), 4.60 (app t, *J* = 4.8, 1H, H_{3a}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 57.3 ($\underline{C}H_3$), 72.4 (C_3), 73.1 (C_6), 73.8 (C_2), 81.9 (C_{3a}), 85.6 (C_{6a}), 85.8 (C_5). MS (ESI/BS) $[M + Na]^+$: calcd. for $C_7H_{12}O_4Na$: 183.2, found 183.1, $[M + H]^+$: calcd. for $C_7H_{13}O_4$: 161.2, found 161.1. NMR spectrum was consistent with the literature.[3]

(3*R*,6*S*)-6-(*Tert*-butoxy)hexahydrofuro[3,2-*b*]furan-3-ol (9)



In a 50 mL round bottom flask was introduced isosorbide (5.0 g, 34.2 mmol, 1.0 eq.) and dissolved in *tert*-butanol (20.3 g, 274 mmol, 8 eq.). Then, Amberlyst-15 (2g, ratio $m_{amberlyst}/m_{isosorbide} = 0.4$) was added and the reaction mixture was refluxed at 70 °C for 6 h. The Amberlyst was filtered off, washed by DCM (200 mL) and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, Pentane/Et_2O, 6/4) affording the title compound **9** as a yellow liquid (0.85 g, 12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 9H, 3 CH_3), 2.67 (d, *J* = 7.4, 1H, OH), 3.52–3.57 (m, 1H, H_2), 3.77–3.88 (m, 2H, H_5, H_2), 3.92–3.97 (m, 1H, H_5), 4.11–4.18 (m, 1H, H_6), 4.20–4.30 (m, 1H, H_3), 4.33 (app d, *J* = 4.6, 1H, H_{6a}), 4.58 (dd, *J* = 5.1, 4.6, 1H, H_{3a}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.3 (3$\underline{C}H_3$), 72.4 (C_3), 73.4 (C_2), 74.8 ($\underline{C}(CH_3)_3$)75.8 (C_5), 76.9 (C_6), 81.7 (C_{3a}), 88.8 (C_{6a}). MS (ESI/BS) $[M + Na]^+$: calcd. for $C_{10}H_{18}O_4Na$: 225.2, found 225.1, $[2M + Na]^+$: calcd. for $C_{20}H_{36}O_8Na$: 427.5, found 427.2. NMR spectrum was consistent with the literature.[5]

5-Methyltetrahydrofuran-3-ol

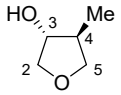


In a 50 mL round-bottom flask, under nitrogen, was introduced 4-penten-2-ol (0.50 g, 5.81 mmol, 1.0 eq.) and triethylamine (2.30 mL, 8.72 mmol, 1.5 eq.) in anhydrous DCM (15 mL) at 0 °C. Then, *p*-toluenesulfonyl chloride (1.66 g, 8.72 mmol, 1.5 eq.) and DMAP (0.07 g, 0.58 mmol, 10 mol%) were added sequentially under inert atmosphere in the cooled solution. The reaction mixture was allowed to warm up to r.t. and stirred overnight. After completion, an aqueous saturated solution of NH_4Cl (30 mL) was added to the mixture and the aqueous phase was extracted with DCM (3 x 10 mL). The organic phases were washed with a brine solution (50 mL), dried over Na_2SO_4, filtrated and concentrated under reduced pressure. Filtration through silica column with DCM gave 4-penten-2-tosylate as a colorless oil (1.36 g, 97%). CAS: 52753-86-3. NMR spectra were consistent with the literature.[6]

To a stirred solution of OsO_4 (0.05 mL, 4%wt/H_2O, 0.5 mol%) and NMO (194 mg, 1.66 mmol, 1.0 eq.) in *t*-BuOH/H_2O (15 mL, 1:1) at 0 °C was added 4-penten-2-tosylate (400 mg, 1.66 mmol, 1.0 eq.). The solution obtained was allowed to warm up to r.t. and was stirred for 24 h. After the addition of solid sodium sulfite (800 mg), the reaction mixture was stirred for an additional 1 h. The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were dried over Na_2SO_4, filtrated and concentrated. The crude obtained was purified by flash column chromatography (SiO_2, Pentane/EtOAc, 1:1) and gave the title compound as a mixture of two diastereoisomers (117 mg, 70%, dr 57:43 determined by ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, *J* = 6.1, 3H, CH_3, dia 1), 1.35 (d, *J* = 6.1, 3H, CH_3, dia 2), 1.48 (dddd, *J* = 13.4, 7.5, 3.0, 1.3, 1H, H_4, dia 2), 1.60 (ddd, *J* = 13.3, 9.7, 5.6, 1H, H_4, dia 1), 1.77 (bd, *J* = 4.4, 1H, OH, dia 1), 1.81 (bd, *J* = 6.4, 1H, OH, dia 2), 2.00 (app ddt, *J* = 13.3, 5.5, 1.2, 1H, H_4, dia 1), 2.37 (ddd, *J* = 13.4, 7.5, 6.7, 1H, H_4, dia 2), 3.63–3.72 (m, 2H, 2 H_2, dia 1 and 2), 3.85 (app. dt, *J* = 10.0, 1.6, 1H, H_2, dia 2), 3.95 (app tq, *J* = 7.5, 6.2, 1H, H_5, dia 2), 4.06 (dd, *J* = 9.9, 4.6, 1H, H_2, dia 1), 4.18–4.31 (m, 1H, H_4, dia 1), 4.45 (bs, 1H, H_1, dia 2), 4.51 (bs, 1H, H_1, dia 1). ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.7 ($\underline{C}H_3$, dia 1), 21.8 ($\underline{C}H_3$, dia 2), 43.2 (C_4, dia 2), 43.6 (C_4, dia 1), 73.1 (C_5, dia 1), 73.2 (C_5, dia 2), 74.1 (C_2, dia 1), 75.2 (C_2, dia 2),

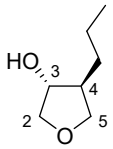
75.6 (C_3, dia 1), 75.8 (C_3, dia 2). MS (ESI/HRMS) $[M + Na]^+$: calcd. for $C_5H_{10}NaO_2$: 125.0573, found 125.0575. CAS: 29848-43-9. Journal of Catalysis (1999), 182(2), 349-356.

(3*R*,4*S*)-4-Methyltetrahydrofuran-3-ol (±)



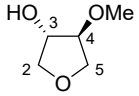
To a solution of CuI (273 mg, 1.4 mmol, 20 mol%), under Argon, in THF [0.5M] was added methyl magnesium bromide (3 M in THF, 4.8 mL, 14.3 mmol, 2 eq.) at - 78 °C. The resulting solution was stirred at - 78 °C before the addition of 3,6-dioxabicyclo[3.1.0]hexane (500 µL, 7.2 mmol, 1 eq.). The mixture was then allowed to warm up to r.t. and stirred for 18 h. The mixture obtained was quenched with a saturated aqueous ammonium chloride solution (15 mL). Then, diluted with water (15 mL) and extracted with diethyl ether (5 x 30 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, dichloromethane/methanol, 10/1) afforded the title compound (105 mg, 14% yield) as a slight yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (d, J = 7.1, 3H, Me), 2.16–2.24 (m, 1H, H_4), 3.41 (dd, J = 8.5, 4.6, 1H, H_5), 3.70 (dd, J = 9.8, 2.3, 1H, H_2), 3.91 (dd, J = 9.8, 4.7, 1H, H_2), 4.02 (app dt, J = 4.7, 2.3, 1H, H_3), 4.11 (dd, J = 8.5, 6.5, 1H, H_5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.7 (C_{Me}), 42.9 (C_4), 73.9 (C_5), 74.5 (C_2), 78.8 (C_3). MS (ESI/HRMS) $[M + Na]^+$: calcd. for $C_5H_{10}O_2Na$: 125.0573, found 125.0574. CAS: 387357-58-6. NMR spectra were consistent with the literature.[7]

(3*R*,4*S*)-4-Propyltetrahydrofuran-3-ol (±)



To a solution of CuI (82 mg, 0.43 mmol, 20 mol%), under Argon, in THF (1 mL) was added propyl magnesium chloride (1.6 mL, 3.23 mmol, 2 M in Et_2O, 1.5 eq.),at - 30 °C. The resulting solution was stirred at - 30 °C before the addition of 3,6-dioxabicyclo[3.1.0]hexane (150 µL, 2.16 mmol, 1.0 eq). The mixture was then allowed to warm up to r.t. and stirred for 16 h. The mixture obtained was quenched with a saturated aqueous ammonium chloride solution (5 mL). Then, diluted with water (10 mL) and extracted with diethyl ether (4 x 5 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, EtOAc, 100%) afforded the title compound (254 mg, 90%) as a pale-yellow liquid.
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J = 7.0, 3H, CH_3), 1.21–1.52 (m, 4H, 2 CH_2), 1.81 (bs, 1H, OH), 2.10 (m, 1H, H_4), 3.46 (dd, J = 8.7, 5.3, 1H, H_5), 3.72 (dd, J = 9.8, 2.4, 1H, H_2), 3.87 (dd, J = 9.8, 4.6, 1H, H_2), 4.04–4.18 (m, 2H, H_3, H_5). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 ($\underline{C}H_3$), 21.2 ($\underline{C}H_2$), 34.0 ($\underline{C}H_2$), 48.5 (C_4), 72.5 (C_5), 74.6 (C_2), 77.6 (C_3). MS (ESI/HRMS) $[M + Na]^+$: calcd. for $C_7H_{14}O_2Na$: 153.0886, found: 153.0888.

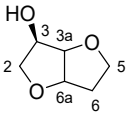
(3*S*,4*S*)-4-Methoxytetrahydrofuran-3-ol (±)



Sodium (830 mg, 36 mmol, 13 eq.) was carefully introduced in a flask containing freshly distilled MeOH (7 mL) at 0 °C under inert atmosphere. After vigorous stirring and complete dissolution of solid sodium, 3,6-dioxabicyclo[3.1.0]hexane (243 mg, 2.82 mmol, 1.0 equiv.) in MeOH (1M, 2.8 mL) was added dropwise. The mixture obtained was heated at 45 °C for 14 h. Then, the solution was cooled down to 0 °C and acetic acid was added until pH 7. The reaction mixture was concentrated and the solid obtained was taken in EtOAc. The organic phase obtained was washed with $NaHCO_3$ (15 mL), dried over Na_2SO_4

and concentrated *in vacuo*. The purification was performed by flash column chromatography on silica gel using EtOAc as eluent affording the title compound as a colorless syrup (245 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38 (s, 3H, OMe), 3.69–3.82 (m, 3H, H_2, H_4, H_5), 3.93 (dd, J = 10.0, 3.9, 1H, H_2), 4.05 (dd, J = 9.7, 4.4, 1H, H_5), 4.29 (ddd, J = 3.9, 1.8, 1.3, 1H, H_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 57.3 (O<u>Me</u>), 71.3 (C_5), 74.0 (C_2), 75.1 (C_3), 87.0 (C_4). MS (ESI/HRMS) $[M + H]^+$: calcd. for $C_5H_{11}O_3$: 119.0703, found 119.0703, $[M + Na]^+$: calcd. for $C_5H_{10}O_3Na$: 141.0522, found 141.0522.

(*3R*)-Hexahydrofuro[3,2-*b*]furan-3-ol



Isosorbide (3.0 g, 20.5 mmol, 1.0 eq.) was dissolved in dry DCM (20 mL) and Et_3N (1.1 mL, 8.2 mmol, 0.4 eq.) was added to the solution at r.t. Then, *O*-phenyl carbonochloridothioate (0.9 mL, 6.2 mmol, 0.3 eq.) was introduced dropwise and the reaction was stirred for 18 h at r.t. After completion of the reaction, the mixture was diluted with DCM (100 mL) and saturated aq. solution of $NaHCO_3$ (100 mL) was added. Then, the aqueous phase was extracted with DCM (3 x 30 mL). The organic phases were combined, washed with H_2O (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc, 1/1) to give the title compound as a white solid (383 mg, 22%). In a round bottom flask, under N_2, Tributyltin hydride (720 µL, 2.71 mmol, 2 eq.) and AIBN (22 mg, 0.136 mmol, 10 mol%) were refluxed in PhMe (10 mL) for 10 min. Then, *O*-((3*S*,6*R*)-6-hydroxyhexahydrofuro[3,2-*b*]furan-3-yl) *O*-phenyl carbonothioate (383 mg in 5 mL of PhMe, 1.36 mmol, 1 eq.) was added to the refluxed solution with an addition funnel over a period of 1 h. After complete addition, the reaction mixture was allowed to stir for 5 h at 110 °C. Then, the mixture was cooled at r.t. and the solvent was removed *in vacuo*. To the liquid obtained were added pentane (20 mL) and acetonitrile (20 mL) and the two phases were separated. The pentane phase was extracted with acetonitrile (3 x 20 mL). The acetonitrile layers were combined and concentrated under reduced pressure. The crude was purified on flash column chromatography (SiO_2, pentane/EtOAc, 1/1) affording the title compound as a colorless liquid (96 mg, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (dddd, J = 13.4, 10.6, 8.2, 4.9, 1H, H_6), 2.15 (dddd, J = 13.4, 5.8, 2.6, 1.3, 1H, H_6), 2.76 (d, J = 6.3, 1H, OH), 3.67 (dd, J = 9.7, 4.9, 1H, H_2), 3.76–3.90 (m, 2H, H_2, H_5), 4.05 (td, J = 8.2, 2.6, 1H, H_5), 4.25 (m, 1H, H_3), 4.47 (dd, J = 5.7, 4.9, 1H, H_{3a}), 4.59 (app td, J = 4.9, 1.3, 1H, H_{6a}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.7 (C_6), 69.7 (C_5), 72.4 (C_3), 74.5 (C_2), 82.6 (C_{3a}), 83.4 (C_{6a}). MS (ESI/HR) $[M + H]^+$: calcd. for $C_6H_{10}O_3Na$: 153.0522, found 153.0522.

Blank reactions:

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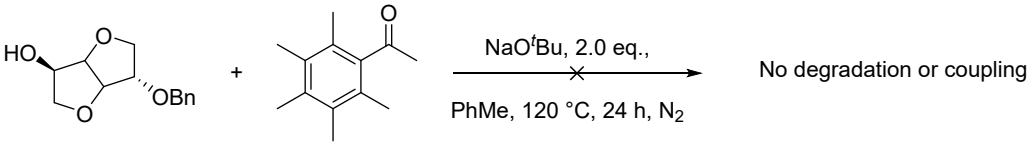
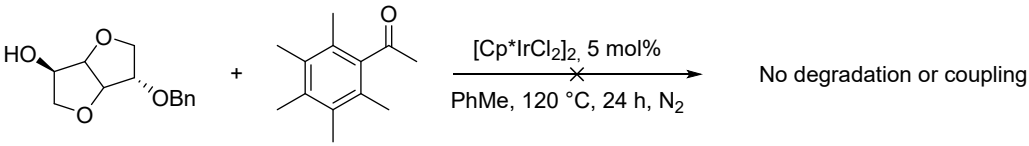


No Base



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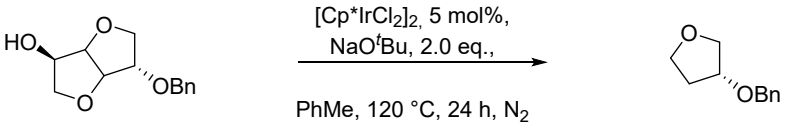

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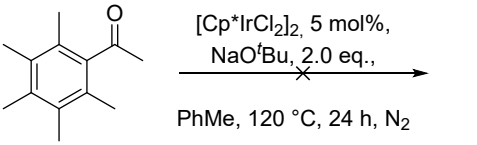
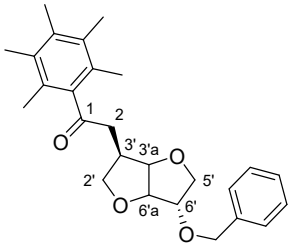


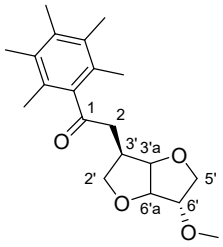
Products obtained from BH

2-((3*R*,6*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (2)



(3*R*,6*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-ol **1** (59 mg, 0.25 mmol, 1.0 eq.), pentamethylacetophenone (52 mg, 0.275 mmol, 1.1 eq.), NaO^{t}Bu (48 mg, 0.50 mmol, 2 eq.), [Cp*Ir(Ts*-dpen)(*R,R*)] (19 mg, 0.025 mmol, 10 mol%) were subjected to **General Procedure**. Purification by flash chromatography (SiO_2, solid load, pentane/EtOAc, 95:5 to 80:20) afforded the title compound **2** as a yellow solid (18 mg, 18%, dr >99:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 6H, 2 CH_3), 2.18 (s, 6H, 2 CH_3), 2.23 (s, 3H, CH_3), 2.66–2.87 (m, 2H, H_2, $H_{3'}$), 3.02–3.18 (m, 1H, H_2), 3.37 (dd, *J* = 10.6, 7.9, 1H, $H_{2'}$), 3.82 (dd, *J* = 10.0, 4.2, 1H, $H_{5'}$), 3.88 (dd, *J* = 10.0, 2.6, 1H, $H_{5'}$), 4.05 (ddd, *J* = 4.2, 2.6, 1.2, 1H, $H_{6'}$), 4.17 (app t, *J* = 7.9, 1H, $H_{2'}$), 4.57 (d, *J* = 11.9, 1H, C$\underline{H}_2$Ph), 4.63 (d, *J* = 11.9, 1H, C$\underline{H}_2$Ph), 4.63 (dd, *J* = 4.0, 1.2, 1H, $H_{6'a}$), 4.82 (app t, *J* = 4.0, 1H, $H_{3'a}$), 7.27–7.38 (m, 5H, H_{Ar}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.1 (2 $\underline{C}H_3$), 16.8 ($\underline{C}H_3$), 17.3 (2 $\underline{C}H_3$), 40.1 ($C_{3'}$), 42.4 (C_2), 71.7 ($\underline{C}H_2$Ph), 72.0 ($C_{2'}$), 73.0 ($C_{5'}$), 83.4 ($C_{3'a}$), 84.0 ($C_{6'}$), 86.9 ($C_{6'a}$), 127.4 (2 C_{qAr}), 127.9 (2 $\underline{C}H_{Ph}$), 128.0 ($\underline{C}H_{Ph}$), 128.6 (2 $\underline{C}H_{Ph}$), 133.2 (2 C_{qAr}), 135.6 (C_{qAr}), 137.9 (C_{qPh}), 140.3 (C_{qAr}), 210.6 (C_1). IR (ATR) ν 697, 736, 903, 929, 1012, 1028, 1096, 1206, 1273, 1306, 1382, 1453, 1697, 2864, 2925. $[\alpha]_D^{21}$ = + 26.7° (*c* 0.25 $CHCl_3$). MS (ESI/HRMS) $[M + Na]^+$: calcd. for $C_{26}H_{32}O_4Na$: 431.2193, found 431.2198, $[M + H]^+$: calcd. for $C_{26}H_{33}O_4$: 409.2373, found 409.2380.

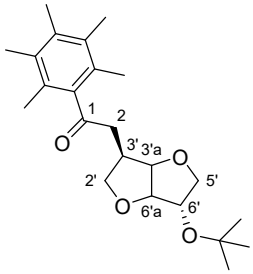
2-((3*R*,6*S*)-6-Methoxyhexahydrofuro[3,2-*b*]furan-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (10)



(3*R*,6*S*)-6-Methoxyhexahydrofuro[3,2-*b*]furan-3-ol **8** (50 mg, 0.31 mmol, 1.0 eq.), pentamethylacetophenone (65 mg, 0.34 mmol, 1.1 eq.), NaO^{t}Bu (60 mg, 0.62 mmol, 2 eq.) and [Ir-Noyo(*R,R*)] (12 mg, 0.0155 mmol, 5 mol%) were subjected to **General Procedure**. Purification by flash chromatography (SiO_2, solid load, pentane/EtOAc, 8/2) afforded the title compound **10** as a yellow solid (18 mg, 17%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 6H, 2 CH_3), 2.17 (s, 6H, 2 CH_3), 2.22 (s, 3H, CH_3), 2.68–2.83 (m, 2H, $H_{3'}$, H_2), 3.09 (dd, *J* = 18.2, 6.1, 1H), 3.36 (dd, *J* = 10.9, 8.1, 1H, $H_{2'}$), 3.40 (s, 3H, OMe), 3.75–3.90 (m, 3H, 2 $H_{5'}$, $H_{6'}$), 4.17 (app t, *J* = 8.1, 1H, $H_{2'}$), 4.57 (dd, *J* = 4.4, 1.1, 1H, $H_{6'a}$), 4.77 (app t, *J* = 4.4, 1H, $H_{3'a}$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.1 (2 CH_3), 16.8 (CH_3), 17.3 (2 CH_3), 40.1 ($C_{3'}$), 42.4 (C_2), 57.4 (C_{OMe}), 72.0 ($C_{2'}$), 72.6 ($C_{5'}$), 83.3 ($C_{3'a}$), 86.2 and 86.4 ($C_{6'a}$, $C_{6'}$), 127.4 (2 C_{qAr}), 133.2 (2 C_{qAr}), 135.6 (C_{qAr}), 140.3 (C_{qAr}), 210.6 (C_1). IR (ATR) ν 860, 887, 932, 1006, 1092, 1193, 1233, 1258, 1306, 1365, 1391, 1463, 1702, 1766, 2867, 2935, 2972. $[\alpha]_D^{21}$ =

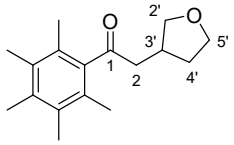
+ 46.5 ° (*c* 0.12 $CHCl_3$). MS (ESI/HRMS) $[M + Na]^+$: calcd. for $C_{20}H_{28}O_4Na$: 355.1880, found 355.1880, $[M + H]^+$: calcd. for $C_{20}H_{29}O_4$: 333.2060, found 333.2062.

2-((3*R*,6*S*)-6-(*Tert*-Butoxy)hexahydrofuro[3,2-*b*]furan-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (12)



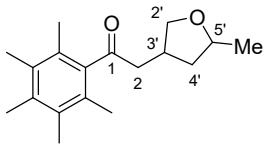
(3*R*,6*S*)-6-(*Tert*-Butoxy)hexahydrofuro[3,2-*b*]furan-3-ol **9** (91 mg, 0.45 mmol, 1.0 eq.), pentamethylacetophenone (94 mg, 0.495 mmol, 1.1 eq.), NaO^{t}Bu (43 mg, 0.45 mmol, 1 eq.) and [Cp*Ir(Ts*-dpen)(*R,R*)] (6.7 mg, 0.01 mmol, 2 mol%) were subjected to **General Procedure.** Purification by flash chromatography (SiO_2, solid load, pentane/EtOAc, 95:5 to 90:10) afforded the title compound **12** as a yellow solid (79 mg, 47%, dr >99:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H, ^{t}Bu-C$\underline{H}_3$), 2.10 (s, 6H, 2 CH_3), 2.17 (s, 6H, 2 CH_3), 2.22 (s, 3H, CH_3), 2.64–2.87 (m, 2H, H_2, $H_{3'}$), 3.09 (dd, J = 21.0, 8.7, 1H, H_2), 3.37 (dd, J = 10.3, 7.9, 1H, $H_{2'}$), 3.61 (dd, J = 9.4, 3.5, 1H, $H_{5'}$), 3.86 (dd, J = 9.4, 5.0, 1H, $H_{5'}$), 4.07 (ddd, J = 5.0, 3.5, 1.6, 1H, $H_{6'}$), 4.15 (app t, J = 7.9, 1H, $H_{2'}$), 4.43 (dd, J = 4.0, 1.6, 1H, $H_{6'a}$), 4.74 (app t, J = 4.0, 1H, $H_{3'a}$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.1 (2 $\underline{C}H_3$), 16.8 (2 $\underline{C}H_3$), 17.3 ($\underline{C}H_3$), 28.4 (3 $\underline{C}H_3$), 40.0 ($C_{3'}$), 42.4 (C_2), 71.6 ($C_{2'}$), 74.5 ($\underline{C}(CH_3)_3$), 74.9 ($C_{5'}$), 77.3 ($C_{6'}$), 83.3 ($C_{3'a}$), 89.7 ($C_{6'a}$), 127.4 (2 C_{qAr}), 133.2 (2 C_{qAr}), 135.6 (C_{qAr}), 140.4 (C_{qAr}), 210.7 (C_1). IR (ATR) ν 825, 890, 940, 1021, 1070, 1112, 1138, 1198, 1365, 1391, 1458, 1702, 2347, 2870, 2939, 2975. $[\alpha]_D^{21}$ = + 72.7° (*c* 0.47 $CHCl_3$). MS (ESI/HRMS) $[M + Na]^+$: calcd. for $C_{23}H_{34}O_4Na$: 397.2349, found 397.2330, $[M + H]^+$: calcd. for $C_{23}H_{35}O_4$: 375.2530, found 375.2512.

1-(2,3,4,5,6-Pentamethylphenyl)-2-(tetrahydrofuran-3-yl)ethanone (13)



Tetrahydrofuran-3-ol (22 mg, 0.25 mmol, 1.0 eq.), pentamethylacetophenone (52 mg, 0.275 mmol, 1.1 eq.), NaO^{t}Bu (48 mg, 0.50 mmol, 2.0 eq.), $[Cp^*IrCl_2]_2$ (10 mg, 0.013 mmol, 5 mol%) were subjected to **General Procedure**. Purification by flash column chromatography (SiO_2, solid load, pentane/Et_2O, 8/2) afforded the title compound **13** as a yellow solid (65 mg, >99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50–1.64 (m, 1H, $H_{4'}$), 2.08–2.12 (m, 6H, 2 CH_3), 2.18 (s, 6H, 2 CH_3), 2.23 (s, 3H, CH_3), 2.20–2.31 (m, 1H, $H_{4'}$), 2.70–2.91 (m, 3H, 2 H_2, $H_{3'}$), 3.40–3.49 (m, 1H, $H_{2'}$), 3.78 (app dt, J = 8.4, 7.4, 1H, $H_{5'}$), 3.86 (app td, J = 8.4, 4.9, 1H, $H_{5'}$), 4.04–4.12 (m, 1H, $H_{2'}$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.1 (2 $\underline{C}H_3$), 16.8 ($\underline{C}H_3$), 17.3 (2 $\underline{C}H_3$), 32.5 ($C_{4'}$), 34.1 ($C_{3'}$), 49.7 (C_2), 67.8 ($C_{5'}$), 73.3 ($C_{2'}$), 127.3 (2 C_{qAr}), 133.3 (2 C_{qAr}), 135.7 (C_{qAr}), 140.3 (C_{qAr}), 210.9 (C_1). IR (ATR) ν 663, 903, 934, 1057, 1070, 1129, 1362, 1402, 1448, 1695, 2870, 2941. MS (ESI/HRMS) $[M + Na]^+$: calcd. for $C_{17}H_{24}O_2Na$: 283.1669, found 283.1664, $[M + H]^+$: calcd. for $C_{17}H_{25}O_2$: 261.1849, found 261.1846.

2-(5-Methyltetrahydrofuran-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (14)



5-Methyltetrahydrofuran-3-ol (26 mg, 0.25 mmol, 1.0 eq.), pentamethylacetophenone (52 mg, 0.275 mmol, 1.1 eq.), NaO^{t}Bu (48 mg, 0.50 mmol, 2 eq.), $[Cp^*IrCl_2]_2$ (10 mg, 0.0125 mmol, 5 mol%) were subjected to **General Procedure**. Purification by flash chromatography (SiO_2, solid load, Pentane/EtOAc, 95/5 to 80/20) afforded the title compound **14** as a yellow solid, (44 mg, 64%, dr 61:39 determined by ^{1}H NMR).

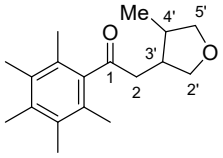
Major isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (ddd, *J* = 12.3, 9.4, 8.3, 1H, $H_{4'}$), 1.27 (d, *J* = 5.9, 3H, Me), 2.10 (s, 6H, 2 CH_3), 2.18 (s, 6H, 2 CH_3), 2.23 (s, 3H, CH_3), 2.37 (ddd, *J* = 12.3, 6.9, 5.8, 1H, $H_{4'}$), 2.71–2.93 (m, 3H, 2 H_2, $H_{3'}$), 3.57 (dd, *J* = 8.7, 6.2, 1H, $H_{2'}$), 3.99 (dqd, *J* = 9.4, 5.9, 5.8, 1H, $H_{5'}$), 4.04–4.12 (m, 1H, $H_{2'}$). ^{13}C NMR (101 M, $CDCl_3$) δ 16.1 (2 $\underline{C}H_3$), 16.8 ($\underline{C}H_3$), 17.3 (2 $\underline{C}H_3$), 21.1 (C_{Me}), 35.0 ($C_{3'}$), 40.6 ($C_{4'}$), 50.4 (C_2), 72.9 ($C_{2'}$), 75.7 ($C_{5'}$), 127.3 (2 C_{qAr}), 133.3 (2 C_{qAr}), 135.7 (C_{qAr}), 140.3 (C_{qAr}), 211.0 (C_1).

Minor isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, *J* = 6.1, 3H, Me), 1.73 (ddd, *J* = 12.6, 7.0, 5.6, 1H, $H_{4'}$), 1.84 (ddd, *J* = 12.6, 8.3, 6.9, 1H, $H_{4'}$), 2.10 (s, 6H, 2 CH_3), 2.18 (s, 6H, 2 CH_3), 2.23 (s, 3H, CH_3), 2.71–2.93 (m, 3H, 2 H_2, $H_{3'}$), 3.40 (dd, *J* = 8.8, 6.6, 1H, $H_{2'}$), 4.04–4.12 (m, 3H, $H_{5'}$), 4.23 (dd, *J* = 8.8, 6.8, 1H, $H_{2'}$). ^{13}C NMR (101 M, $CDCl_3$) δ 16.1 (2 $\underline{C}H_3$), 16.8 ($\underline{C}H_3$), 17.3 (2 $\underline{C}H_3$), 21.4 (C_{Me}), 34.0 ($C_{3'}$), 39.4 ($C_{4'}$), 49.7 (C_2), 73.3 ($C_{2'}$), 74.6 ($C_{5'}$), 127.3 (2 C_{qAr}), 133.3 (2 C_{qAr}), 135.7 (C_{qAr}), 140.3 (C_{qAr}), 210.9 (C_1). IR (ATR) ν 660, 749, 806, 822, 898, 935, 1024, 1039, 1090, 1108, 1133, 1275, 1302, 1353, 1378, 1402, 1451, 1698, 2871, 2928, 2970. MS (ESI/HRMS) $[M + Na]^+$: calcd. for $C_{18}H_{26}O_2Na$: 297.1825, found 297.1823, $[M + H]^+$: calcd. for $C_{18}H_{27}O_2$: 275.2006, found 275.2008.

2-(4-Methyltetrahydrofuran-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (15)



(3*R*,4*S*)-4-Methyltetrahydrofuran-3-ol (23 mg, 0.23 mmol, 1.0 eq.), pentamethylacetophenone (48 mg, 0.25 mmol, 1.1 eq.), NaO^{t}Bu (44 mg, 0.46 mmol, 2.0 eq.), [Cp*Ir(Ts-dpen)(*R,R*)] (8.6 mg, 0.0115 mmol, 5 mol%) were subjected to **General Procedure.** Purification by flash chromatography (SiO_2, solid load, pentane/EtOAc, 9/1) afforded the title compound **15** as a yellow solid, (41 mg, 65%, dr 70:30 determined by ^{1}H NMR).

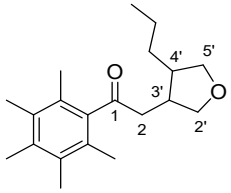
Major isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, *J* = 7.1, 3H, Me), 2.10 (s, 6H, 2 CH_3), 2.19 (s, 6H, 2 CH_3), 2.24 (s, 3H, CH_3), 2.41–2.51 (m, 1H, $H_{4'}$), 2.59–2.71 (m, 1H H_2), 2.75–2.88 (m, 2H, H_2, $H_{3'}$), 3.44 (dd, *J* = 8.2, 5.1, 1H, $H_{5'}$), 3.56 (dd, *J* = 8.5, 7.0, 1H, $H_{2'}$), 3.93–3.99 (m, 1H, $H_{5'}$), 4.16 (dd, *J* = 8.5, 7.1, 1H, $H_{2'}$).^{13}C NMR (101 MHz, $CDCl_3$) δ 13.5 (C_{Me}), 16.10 (2 $\underline{C}H_3$), 16.8 ($\underline{C}H_3$), 17.32 (2 $\underline{C}H_3$), 35.8 ($C_{4'}$), 37.2 ($C_{3'}$), 44.2 (C_2), 72.6 ($C_{2'}$), 74.8 ($C_{5'}$), 127.34 (2 C_{qAr}), 133.34 (2 C_{qAr}), 135.74 (C_{qAr}), 140.5 (C_{qAr}), 211.0 (C_1).

Minor isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, *J* = 6.7, 3H, Me), 1.85–1.96 (m, 1H, $H_{4'}$), 2.09 (s, 6H, 2 CH_3), 2.18 (s, 6H, 2 CH_3), 2.23 (s, 3H, CH_3), 2.27–2.36 (m, 1H, $H_{3'}$), 2.59–2.71 (m, 1H H_2), 2.97 (dd, *J* = 18.9, 4.2, 1H, H_2), 3.34 (app t, *J* = 8.1, 1H, $H_{5'}$), 3.51 (dd, *J* = 8.8, 7.1, 1H, $H_{2'}$), 3.96 (m, 1H, $H_{5'}$), 4.28 (dd, *J* = 8.8, 7.4, 1H, $H_{2'}$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.09 (2 $\underline{C}H_3$), 16.5 (C_{Me}), 16.8 ($\underline{C}H_3$), 17.29 (2 $\underline{C}H_3$), 39.9 ($C_{4'}$), 42.0 ($C_{3'}$), 49.1 (C_2), 73.8 ($C_{2'}$), 74.6 ($C_{5'}$), 127.30 (2 C_{qAr}), 133.31 (2 C_{qAr}), 135.72 (C_{qAr}), 140.4 (C_{qAr}), 211.1 (C_1). IR (ATR) ν 650, 922, 995, 1038, 1099, 1311, 1386, 1403, 1460, 1694, 2854, 2930, 2961. MS (ESI/HRMS) $[M + Na]^+$: calcd. for $C_{18}H_{26}O_2Na$: 297.1825, found 297.1820, $[M + H]^+$: calcd. for $C_{18}H_{27}O_2$: 275.2006, found 275.2001.

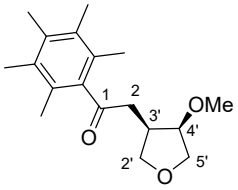
1-(2,3,4,5,6-Pentamethylphenyl)-2-(4-Propyltetrahydrofuran-3-yl)ethanone (16)



(3*R*,4*S*)-4-Propyltetrahydrofuran-3-ol (+/-)(33 mg, 0.25 mmol, 1.0 eq.), pentamethylacetophenone (52 mg, 0.275 mmol, 1.1 eq.), NaO^{t}Bu (48 mg, 0.50 mmol, 2 eq.), [Cp*Ir(Ts*-dpen)(*R,R*)] (9.4 mg, 0.0125 mmol, 5 mol%) were subjected to **General Procedure**. Purification by flash chromatography (SiO_2, solid load, pentane/EtOAc, 95:5 to 80:20) afforded the title compound **16** as a brown oil (53 mg, 70%, dr 1:1). The diastereoisomers were assigned when it was possible due to the overlap signals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (m, 6H, 2 $CH_2CH_2\underline{CH_3}$, dia 1 and 2), 1.18–1.41 (m, 7H, 2 $CH_2\underline{CH_2}CH_3$, $\underline{CH_2}CH_2CH_3$, dia 1 and 2), 1.53–1.81 (m, 2H, $\underline{CH_2}CH_2CH_3$, $H_{4'}$), 2.10 (s, 6H, 2 CH_3), 2.11 (s, 6H, 2 CH_3), 2.19 (2 s, 12H, 4 CH_3), 2.24 (2 s, 6H, 2 CH_3), 2.28–2.46 (m, 2H, $H_{3'}$, $H_{4'}$), 2.66 (m, 2H, 2 H_2), 2.75–2.87 (m, 2H, $H_{3'}$, H_2), 2.97 (dd, *J* = 18.9, 3.8, 1H, H_2), 3.35–3.47 (m, 2H, 2 $H_{5'}$), 3.52 (dd, *J* = 8.8, 6.5, 1H, $H_{2'}$, dia 1), 3.67 (dd, *J* = 8.7, 4.4, 1H, $H_{2'}$, dia 2), 3.95 (m, 2H, 2 $H_{5'}$), 4.11 (ddd, *J* = 8.7, 6.0, 1.0, 1H, $H_{2'}$, dia 2), 4.24 (dd, *J* = 8.8, 7.3, 1H, $H_{2'}$, dia 1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.38 and 14.40 ($CH_2CH_2\underline{CH_3}$, dia 1 and 2), 16.1 (4 CH_3), 16.8 (2 CH_3), 17.22 and 17. 24 (4 CH_3), 21.66 and 21.75 ($CH_2\underline{CH_2}CH_3$, dia 1 and 2), 30.2 ($\underline{CH_2}CH_2CH_3$, dia 1), 35.1 ($\underline{CH_2}CH_2CH_3$, dia 2), 36.5 and 40.5 ($C_{3'}$), 41.6 ($C_{4'}$), 43.8 (C_2, dia 2), 45.1 ($C_{4'}$), 49.8 (C_2, dia 1),72.3; 73.3; 73.5; 73.8 (2 $C_{2'}$, 2 $C_{5'}$), 127.28 and 127.33 (4 C_{qAr}), 133.26 and 133.31 (4 C_{qAr}), 135.66 and 135.69 (2 C_{qAr}), 140.3 (C_{qAr}), 140.6 (C_{qAr}), 211.1 (2 C_1). IR (ATR) ν 656, 694, 906, 933, 1000, 1027, 1051, 1101, 1315, 1381, 1401, 1465, 1698, 2870, 2927, 2956. MS (ESI/HRMS) $[M + Na]^+$: calcd. for $C_{20}H_{30}O_2Na$: 325.2138, found 325.2138, $[M + H]^+$: calcd. for $C_{20}H_{31}O_2$: 303.2319, found 303.2321.

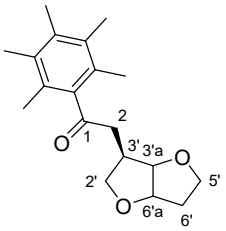
2-((3*R*,4*R*)-4-Methoxytetrahydrofuran-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (17)



(3*S*,4*S*)-4-Methoxytetrahydrofuran-3-ol (32 mg, 0.27 mmol, 1 eq.), pentamethylacetophenone (52 mg, 0.275 mmol, 1 eq.), NaO^{t}Bu (48 mg, 0.50 mmol, 2 eq.), [Cp*Ir(Ts*-dpen)(*R,R*)] (9.4 mg, 0.0125 mmol, 5mol%) were subjected to **General Procedure**. Purification by flash chromatography (SiO_2, solid load, pentane/EtOAc, 9/1) afforded the title compound **17** as a yellowish solid, (23 mg, 29%, dr >99:1, determined by ^{1}H NMR). After recrystallization from Et_2O/pentane at r.t. colourless needle crystals suitable for X-ray crystallography were obtained.

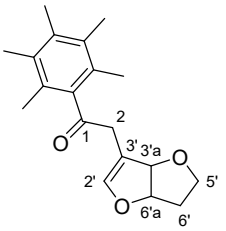
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 6H, 2 CH_3), 2.19 (s, 6H, 2 CH_3), 2.23 (s, 3H, CH_3), 2.72 (dd, *J* = 19.0, 5.7, 1H, H_2), 2.80 (m, 1H, $H_{3'}$), 3.10 (dd, *J* = 19.0, 7.7, 1H, H_2), 3.30 (s, 3H, OCH_3), 3.52 (dd, *J* = 9.7, 7.9, 1H, $H_{2'}$), 3.86 (dd, *J* = 10.0, 3.7, 1H, $H_{5'}$), 3.97 (dd, *J* = 10.0, 1.4, 1H, $H_{5'}$), 4.05–4.12 (m, 2H, $H_{2'}$, $H_{4'}$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.1 (2 $\underline{C}H_3$), 16.8 ($\underline{C}H_3$), 17.1 (2 $\underline{C}H_3$), 38.8 ($C_{3'}$), 42.1 (C_2), 57.0 (C_{Me}), 71.4 ($C_{2'}$), 71.7 ($C_{5'}$), 81.2 ($C_{4'}$), 127.4 (2 C_{qAr}), 133.2 (2 C_{qAr}), 135.6 (C_{qAr}), 140.5 (C_{qAr}), 211.0 (C_1). IR (ATR) ν 648, 713, 754, 838, 898, 937, 966, 1043, 1081, 1100, 1114, 1167, 1190, 1221, 1310, 1374, 1398, 1450, 1697, 1732, 2857, 2887, 2920. MS (ESI/HRMS) [M + Na]$^+$: calcd. for $C_{18}H_{26}O_3Na$: 313.1774, found 313.1772, [M + H]$^+$: calcd. for $C_{18}H_{27}O_3$: 291.1955, found 291.1954.

2-((3*R*)-Hexahydrofuro[3,2-*b*]furan-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (18)



(3*R*)-Hexahydrofuro[3,2-*b*]furan-3-ol (22 mg, 0.17 mmol, 1.0 eq.), pentamethylacetophenone (35 mg, 0.19 mmol, 1.1 eq.), NaO^{t}Bu (32 mg, 0.34 mmol, 2.0 eq.), [Cp*Ir(Ts*-dpen)(*R,R*)] (13 mg, 0.017 mmol, 10 mol%) were subjected to **General Procedure**. Purification by flash chromatography (SiO_2, solid load, Pentane/EtOAc, 95:5 to 90:10) afforded the title compound **18** as a yellow solid (6 mg, 12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02–2.09 (m, 2H, $H_{6'}$), 2.11 (s, 6H, 2 CH_3), 2.18 (s, 6H, 2 CH_3), 2.23 (s, 3H, CH_3), 2.67–2.87 (m, 2H, H_2, $H_{3'}$), 3.11 (dd, *J* = 18.3, 6.2, 1H, H_2), 3.42 (dd, *J* = 10.2, 8.0, 1H, $H_{2'}$), 3.75 (app td, *J* = 8.5, 7.1, 1H, $H_{5'}$), 3.85 (ddd, *J* = 8.5, 6.8, 4.9, 1H, $H_{5'}$), 4.12 (app t, *J* = 8.0, 1H, $H_{2'}$), 4.63 (app t, *J* = 4.3, 1H, $H_{3',a}$), 4.74 (app td, *J* = 4.3, 2.4, 1H, $H_{6',a}$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.1 (2 $\underline{C}H_3$), 16.8 ($\underline{C}H_3$), 17.3 (2 $\underline{C}H_3$), 35.4 ($C_{6'}$), 40.3 ($C_{3'}$), 42.6 (C_2), 68.9 ($C_{5'}$), 72.5 ($C_{2'}$), 84.0 ($C_{6',a}$), 84.1 ($C_{3',a}$), 127.4 (2 C_{qAr}), 133.2 (2 C_{qAr}), 135.6 (C_{qAr}), 140.4 (C_{qAr}), 210.8 (C_1). IR (ATR) ν 650, 820, 836, 882, 936, 1018, 1039, 1093, 1110, 1263, 1305, 1344, 1402, 1447, 1698, 2858, 2934. $[\alpha]_D^{21}$ = + 37.2° (*c* 0.12 $CHCl_3$). MS (ESI/HRMS) [M + Na]$^+$: calcd. for $C_{19}H_{26}O_3Na$: 325.1774, found 325.1776, [M + H]$^+$: calcd. for $C_{19}H_{27}O_3$: 303.1955, found 303.1958.

1-(2,3,4,5,6-Pentamethylphenyl)-2-(3a,5,6,6a-Tetrahydrofuro[3,2-*b*]furan-3-yl)ethanone (18')



(3*R*)-Hexahydrofuro[3,2-*b*]furan-3-ol (22 mg, 0.17 mmol, 1.0 eq.), pentamethylacetophenone (35 mg, 0.19 mmol, 1.1 eq.), NaO^{t}Bu (32 mg, 0.34 mmol, 2.0 eq.), [Cp*Ir(Ts*-dpen)(*R,R*)] (13 mg, 0.017 mmol, 10mol%) were subjected to **General Procedure.** Purification by flash chromatography (SiO_2, solid load, pentane/EtOAc, 95:5 to 90:10) afforded the title compound **18'** as a yellow solid (13 mg, 21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95–2.07 (m, 2H, $H_{6'}$), 2.13 (s, 6H, 2 CH_3), 2.19 (s, 6H, 2 CH_3), 2.23 (s, 3H, CH_3), 3.45 (s, 2H, H_2), 3.44–3.55 (m, 1H, $H_{5'}$), 3.92 (td, *J* = 8.1, 1.1, 1H, $H_{5'}$), 5.08 (app t, *J* = 6.3, 1H, $H_{6',a}$), 5.35 (d, *J* = 6.3, 1H, $H_{3',a}$), 6.56 (s, 1H, $H_{2'}$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.1 (2 $\underline{C}H_3$), 16.8 ($\underline{C}H_3$), 7.4 (2 $\underline{C}H_3$), 35.3 ($C_{6'}$), 40.5 (C_2), 64.2 ($C_{5'}$), 84.7 ($C_{6',a}$), 86.5 ($C_{3',a}$), 105.9 ($C_{3'}$), 127.6 (2 C_{qAr}), 133.2 (2 C_{qAr}), 135.7 (C_{qAr}), 140.5 (C_{qAr}), 147.7 ($C_{2'}$), 209.3 (C_1). IR (ATR) ν 586.4, 701.2, 793.7, 1013.6, 1070.5, 1259.6, 1696.5, 2854.8, 2924.2, 2962.8.

$[\alpha]_D^{21}$ = + 9° (*c* 0.06 $CHCl_3$). MS (ESI/BR) $[M + H]^+$: calcd. for $C_{19}H_{25}O_3$: 301.4, found 301.4, $[M + Na]^+$: calcd. for $C_{19}H_{24}O_3Na$: 323.4, found 323.4.

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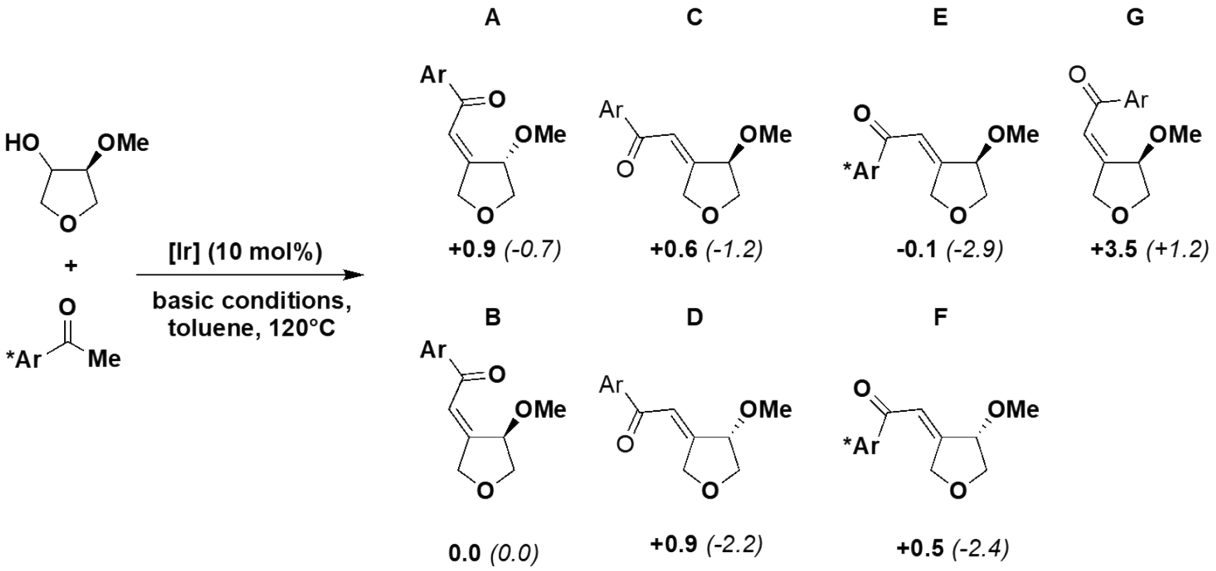
Computational Modelling:

Computational details:

All calculations were performed using the gaussian 09 software (revision D.01).[1] Electronic energies were computed at the M06 density functional level,[2] using an ultrafine grid to compute the integrals. This density functional was previously found to give reasonable results on the modelling of Ir-catalyzed reactions.[3] For geometry optimization the polarized split-valence basis set of Karlsruhe (def2SVP) was used for all atoms except for Ir for which the quasi-relativistic ECP60MWB pseudopotential from Stuttgart-Köln was used in association with its basis set (level **I**).[4] Electronic energies were then refined by performing single point calculations (level **II**) using the polarized triple-ζ basis sets def2TZVP for all atoms. The nature of the extrema was verified by an analytical frequency calculation. Transition states show only one imaginary frequency, and their connectivity were verified by following the intrinsic reaction coordinate (IRC) in both directions. Solvent effect were included both for geometry optimization and single points energy calculations, using the SMD model as defined for toluene.[5] Gibbs energies and enthalpies were estimated by adding the thermal and entropy corrections computed within the classical harmonic approximation 1 atm and 418K at the level **I** to the single point electronic energy computed at the level **II**.

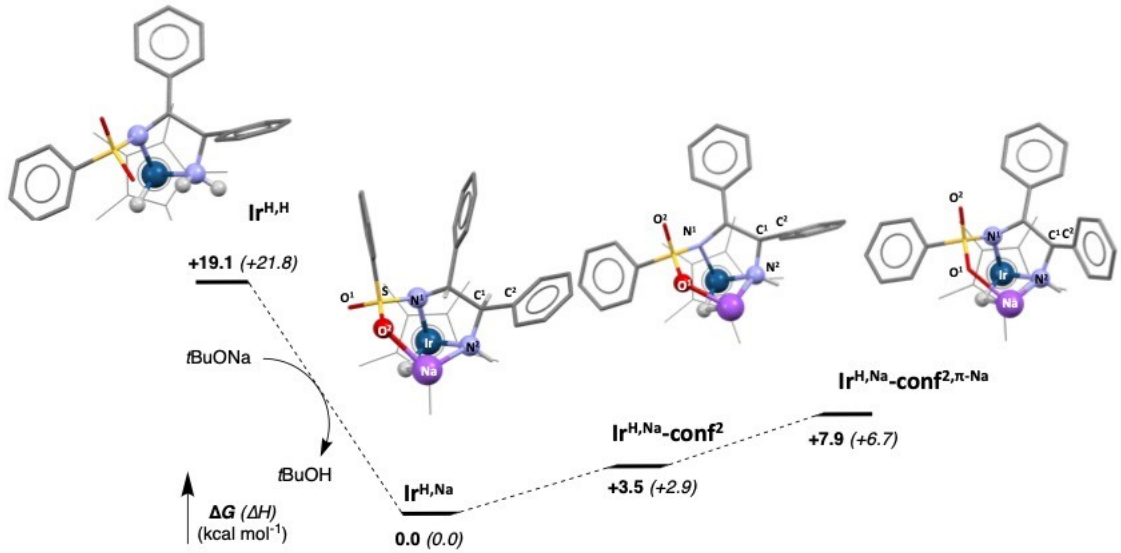
Speciation of [Ir^{III}] complex and substrates:

Since configuration isomerism and epimerization at the asymmetric carbon C* can occur under the reaction conditions (120°C, basic conditions), the speciation of the aldol products has been investigated as well **(Scheme S1)**. Up to 8 configuration isomers can coexist in solution. Ketone **E** is found to be the most stable one, especially it is more stable than ketone **A** (namely ***(Z,S)*-A** in the main text) by ΔG = 1.0 kcal mol^{-1}. As discussed in next section the conjugate addition at ketones **B** and **C** is kinetically less favorable than ketone **A** (**Scheme S3-5**).



Scheme S1: Speciation of the aldol condensation product. Energies are given in kcal mol^{-1}.

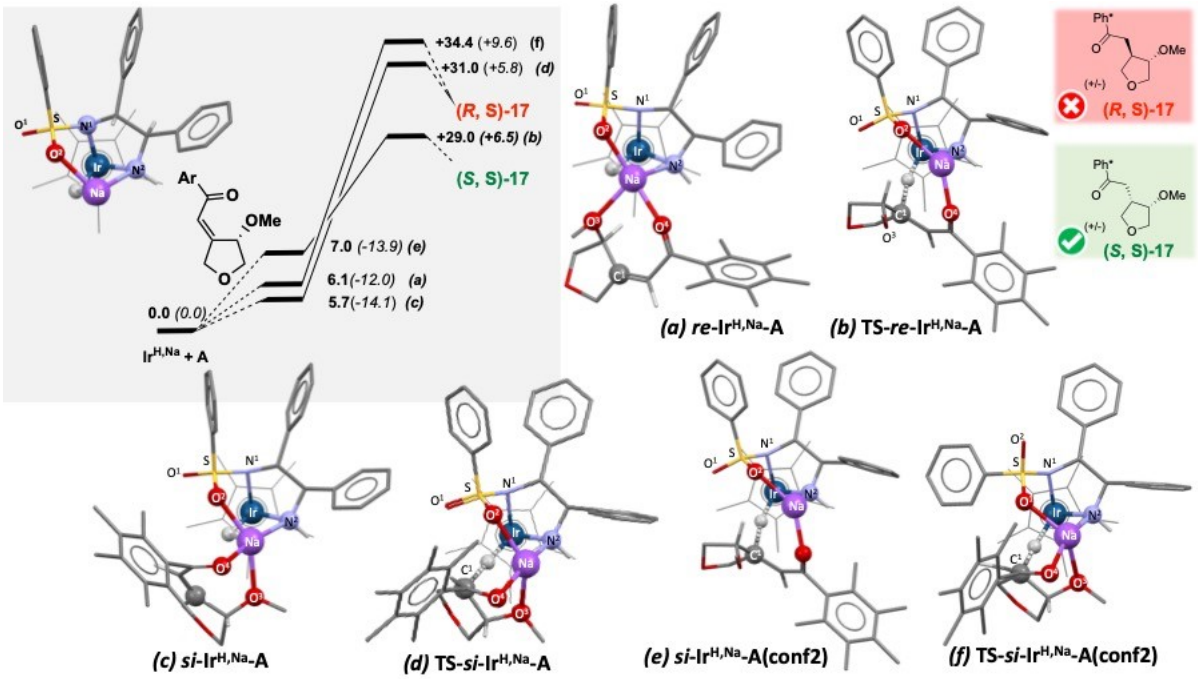
The speciation of the starting complex has been studied **(Scheme S2)**. In the presence of *t*BuONa, the **Ir^{H,H}** complex is deprotonated to give **Ir^{H,Na}**. This reaction is exergonic by ΔG = -19.1 kcal mol^{-1}. In the absence of substrate, the most stable intermediate is **Ir^{H,Na}**. **Ir^{H,Na}** enables π-π interactions between the phenyl rings of the dpen ligand. As can be seen in structure **Ir^{H,Na}-conf^{2}**, removing π-π interactions *via* rotation of the N^1-S or C^1-C^2 bonds destabilizes the Ir(III)-complex by ΔG = 3.5. As can be seen in structure **Ir^{H,Na}-conf$^{2,\pi\text{-}Na}$**, additional Na-π interaction destabilizes more **Ir^{H,Na}-conf^{2}** by 4.4 kcal mol^{-1}.



Scheme S2: Speciation of the [Ir^{III}] complex. Energies are given in kcal mol^{-1}.

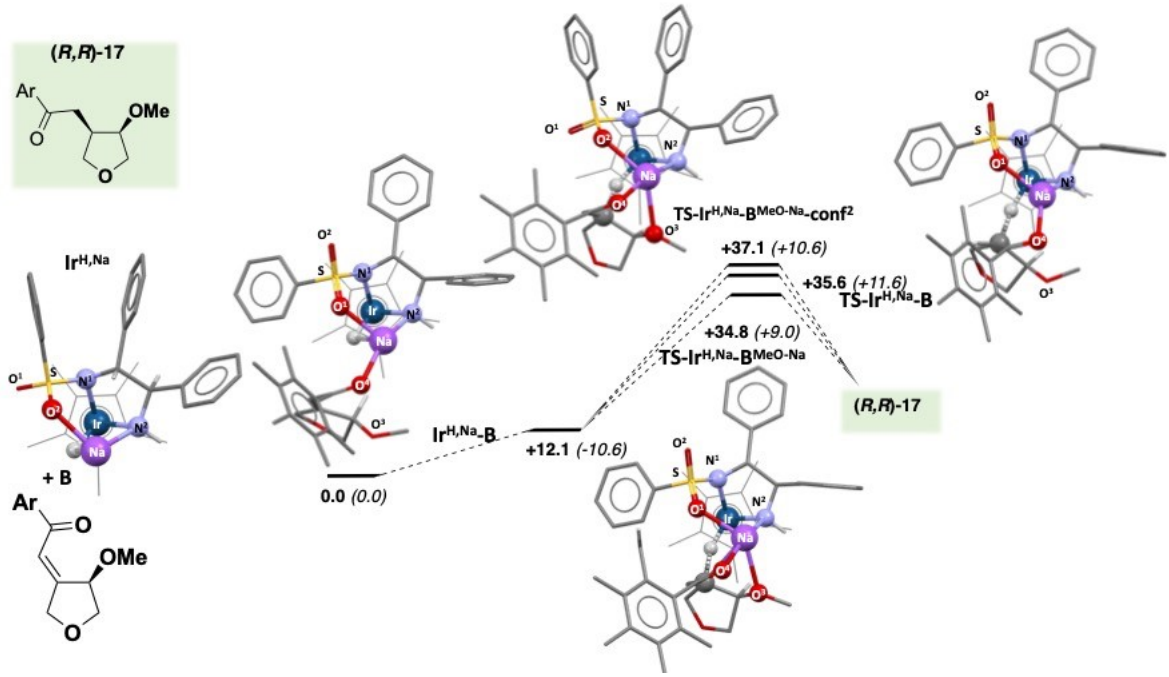
Alternative mechanisms:

The mechanisms involving aldol condensation products **A**, **B** and **C** have been studied. Starting from **Ir^{H,Na}** and **A** (**Scheme S3**) the lowest energy barrier is obtained when **Ir^{H,Na}** attacks **A** on the *re* side (**TS-*re*-Ir^{H,Na}-A**, $\Delta G^{\neq}$ = 29.0 kcal mol^{-1}) and leads to the experimentally observed +/-**(*S*,*S*)-17** product. When attacking on the opposite side of **A** (**TS-*si*-Ir^{H,Na}-A**), the free energy is higher by 2.0 kcal mol^{-1} compared to **TS-*re*-Ir^{H,Na}-A**. Rotation around the N^1-S bond to give **TS-*si*-Ir^{H,Na}-A(conf2)** – in which the sodium atom coordinates to the O^2 atom from TS-dpen ligand – leads to an even higher energy barrier ($\Delta G^{\neq}$ = 34.4 kcal mol^{-1}, compared to **Ir^{H,Na}** and **A**).



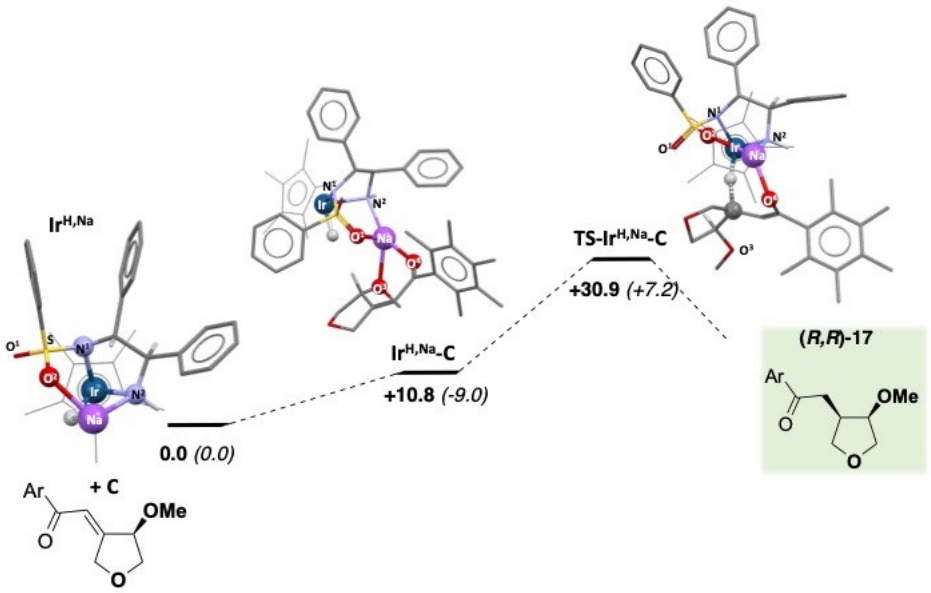
Scheme S3: Free energy profile computed for the formation of **(*S,S*)-17** using aldol condensation product **A**. Δ***G*** *(ΔH)* in kcal mol^{-1}.

The kinetic for the formation of the experimentally obtained product +/- **(*R,R*)-17** is very similar for the conjugated ketone **B** (Scheme S4). Indeed, the lowest energy barrier leading to ***(R,R)*-17** *via* **TS-Ir^{H,Na}-B^{MeONa}** is about 34.8 kcal mol^{-1} (*i.e.* 5.8 kcal mol^{-1} higher in energy than in the case of ketone **A**). Decoordination of the O^3 atom from the methoxy group to the sodium counter-ion has a detrimental effect on the kinetic of the reaction (**TS-Ir^{H,Na}-B**, $\Delta G^{\neq}$ = 35.6 kcal mol^{-1}). Adding new π-π interactions between the phenyl groups of the Ts-dpen ligand through rotation of the N^1-S bond was found detrimental (structure **TS-Ir^{H,Na}-B$^{MeO\text{-}NA}$-conf2** , $\Delta G^{\neq}$ = 37.1 kcal mol^{-1} starting from **Ir^{H,Na}** and **B**).



Scheme S4: Free energy profile computed for the formation of **(*R,R*)-17** using aldol condensation product **B**. Energies are given in kcal mol^{-1}.

The mechanism starting from conjugated ketone **C** and leading to the experimentally observed product +/- **(*R*,*R*)-17** is depicted in **figure S3**. The adduct formation is thermodynamically unfavorable (ΔG = 10.8 kcal mol^{-1}, starting from separated molecules **Ir^{H,Na}** and **C**). The energy barrier to reach **TS-Ir^{H,Na}-C** is about $\Delta G^{\neq}$ = 30.9 kcal mol^{-1}. This energy barrier is higher to that of **TS-*re*-(*Z*,*S*)-A-Ir^{H,Na}** by 1.9 kcal

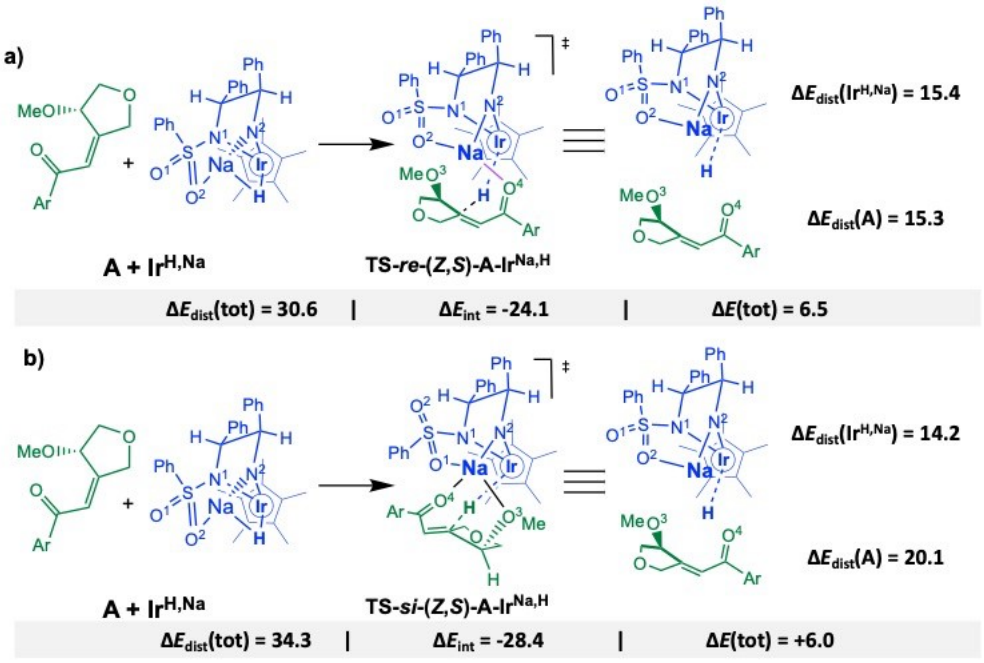


mol^{-1}.

Scheme S5: Free energy profile computed for the formation of **(*R*,*R*)-17** using aldol condensation product **C**. ΔG *(ΔH)* in kcal mol^{-1}.

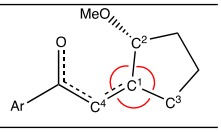
Interaction-distortion analyses:

The interaction-distortion analysis (IDA) was used to explain the selectivity of the hydride transfer (**Scheme S6**). For this purpose, we decomposed each transition state (**TS-*re*-(*Z*,*S*)-A-Ir^{H,Na}** and **TS-*si*-(*Z*,*S*)-A-Ir^{H,Na}**) into two fragments and used **A** and **Ir^{H,Na}** as a reference. When attacking at the *re* face (**TS-*re*-(*Z*,*S*)-A-Ir^{H,Na}**, **Scheme S5-a**), both the conjugated ketone **A** and the catalyst **Ir^{H,Na}** are disorted to the same extent (ΔE_{dist}(Ir^{H,Na}) =15.4, (ΔE_{dist}(A) = 15.3 kcal mol^{-1}, compared to separated **A** and **Ir^{H,Na}**). The TS is stabilized by ΔE_{int} = -24.1 kcal mol^{-1} in the transition state, and therefore the overall difference in electronic energy is ΔE = +6.5 kcal mol^{-1}. This transition state leads to the product **(*S*,*S*)-17**, which is the one experimentally observed. Interestingly, when attacking at the *si* face (**TS-*si*-(*Z*,*S*)-A-Ir^{H,Na}**, **Scheme S5-b**), the substrate is considerably more distorted (ΔE_{dist}(A) = 20.1 kcal mol^{-1}). The interaction contribution to the difference in electronic energy is also more important (ΔE_{int} = -28.4 kcal mol^{-1}, ΔE = 6.0 kcal mol^{-1} compared to **A** and **I^{H,Na}**) and fully compensates the distortion contribution. This transition state leads to the product **(*R*,*S*)-17**, which was not experimentally observed. Results of the Interaction-distortion analysis correlates with the geometries of the transition states presented in **Table S1**. It appears that distortion of the substrate and Ir-H bonds in the transition state are determinant parameters for the selectivity of the reaction. The most favorable transition state is the earliest one, *i.e.* where the substrate shows minimal distortion and the shortest Ir-H bond. It corresponds to **TS-*re*-(*Z*,*S*)-A-Ir^{H,Na}**.



Scheme S6: Interaction – Distortion analyses for **TS-*re*-(*Z*,*S*)-A-Ir^{H,Na}** and **TS-*si*-(*Z*,*S*)-A-Ir^{H,Na}**. All electronic energies (ΔE) are given in kcal mol^{-1}.

Table S1: Sum of the C^2-C^1-C^3, C^3-C^1-C^4 and C^4-C^1-C^2 angles, percentage of lengthening of the Ir-H bond in the TS compared to the pre-TS adduct and Gibbs free energies relative to **Ir^{H,Na}** and **A**. Angles are given in °, energies in kcal mol^{-1}.

	re-(*Z*,*S*)-A-Ir^{H,Na}	*si*-(*Z*,*S*)-A-Ir^{H,Na}	TS-*re*-(*Z*,*S*)-A-Ir^{H,Na}	TS-*si*-(*Z*,*S*)-A-Ir^{H,Na}	
Angles sum	358	359	345	332°	
Ir-H bond lenghtening	0.0	0.0	110%	115%	
ΔG	7.9	5.7	29.0	31.0	
	Adducts		**Transition states**		

Cartesian coordinates:

The cartesian coordinates for all discussed structures are available in additional XYZ file.

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[3] a) K. H. Hopmann, How Accurate is DFT for Iridium-Mediated Chemistry? *Organometallics* 2016, **35**, 3795; b) K. A. Moltved, K. P. Kepp, The Metal Hydride Problem of Computational Chemistry: Origins and Consequences, *J. Phys. Chem. A* 2019, **123**, 2888.

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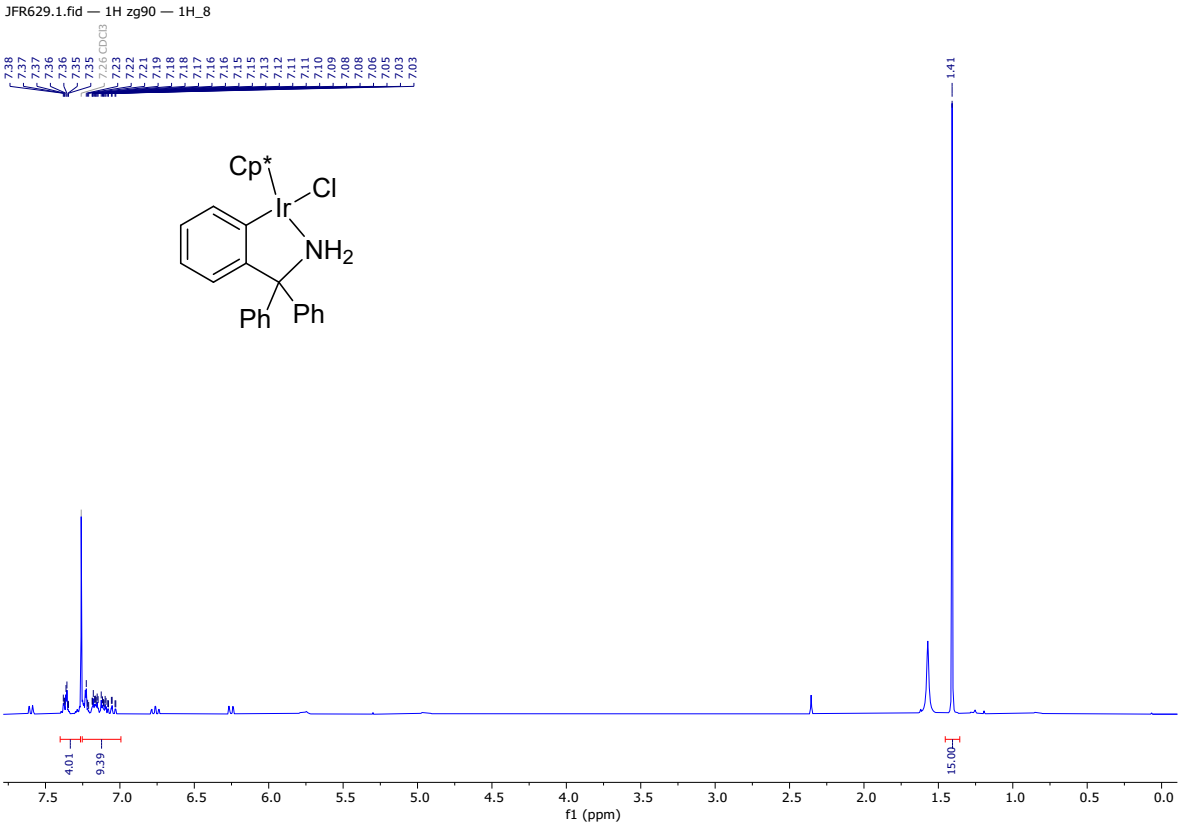
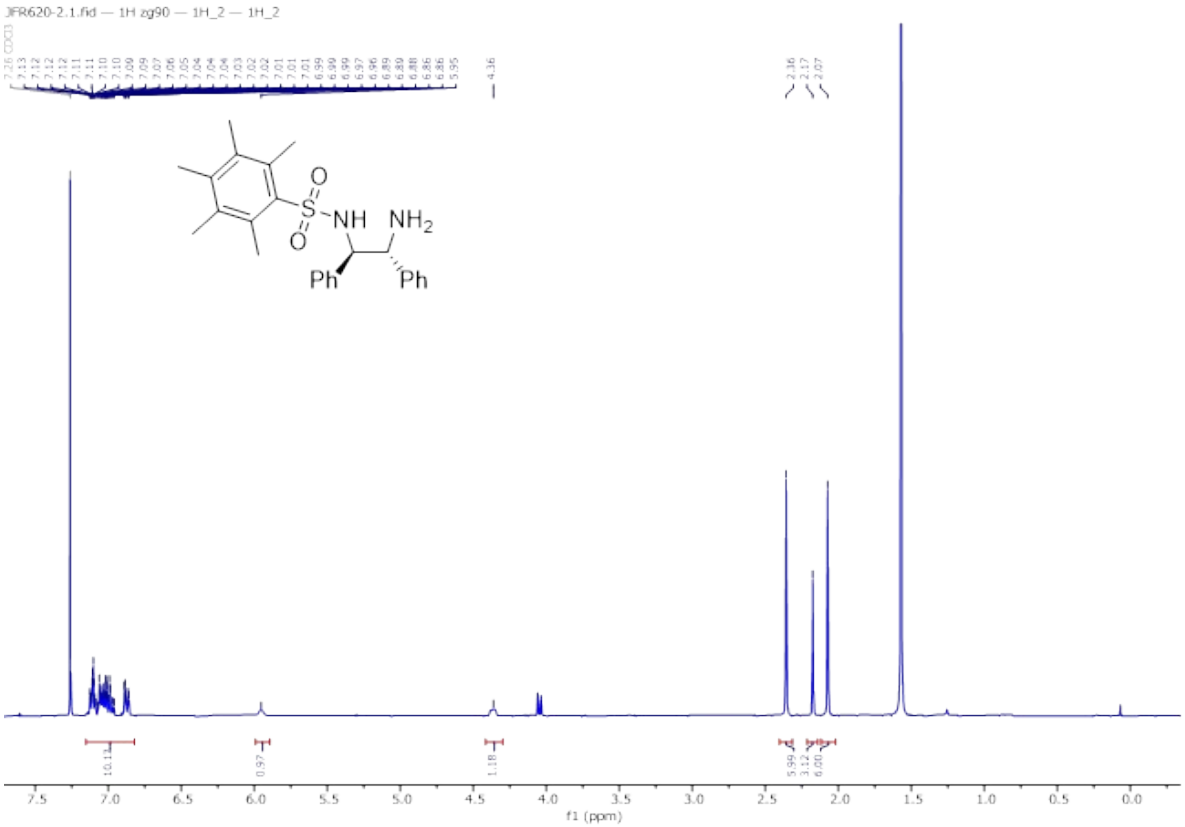
Spectral data:

^{1}H NMR spectrum of [Cp*-Ir-NTr · HCl] (Ir-1) (300 MHz, $CDCl_3$)

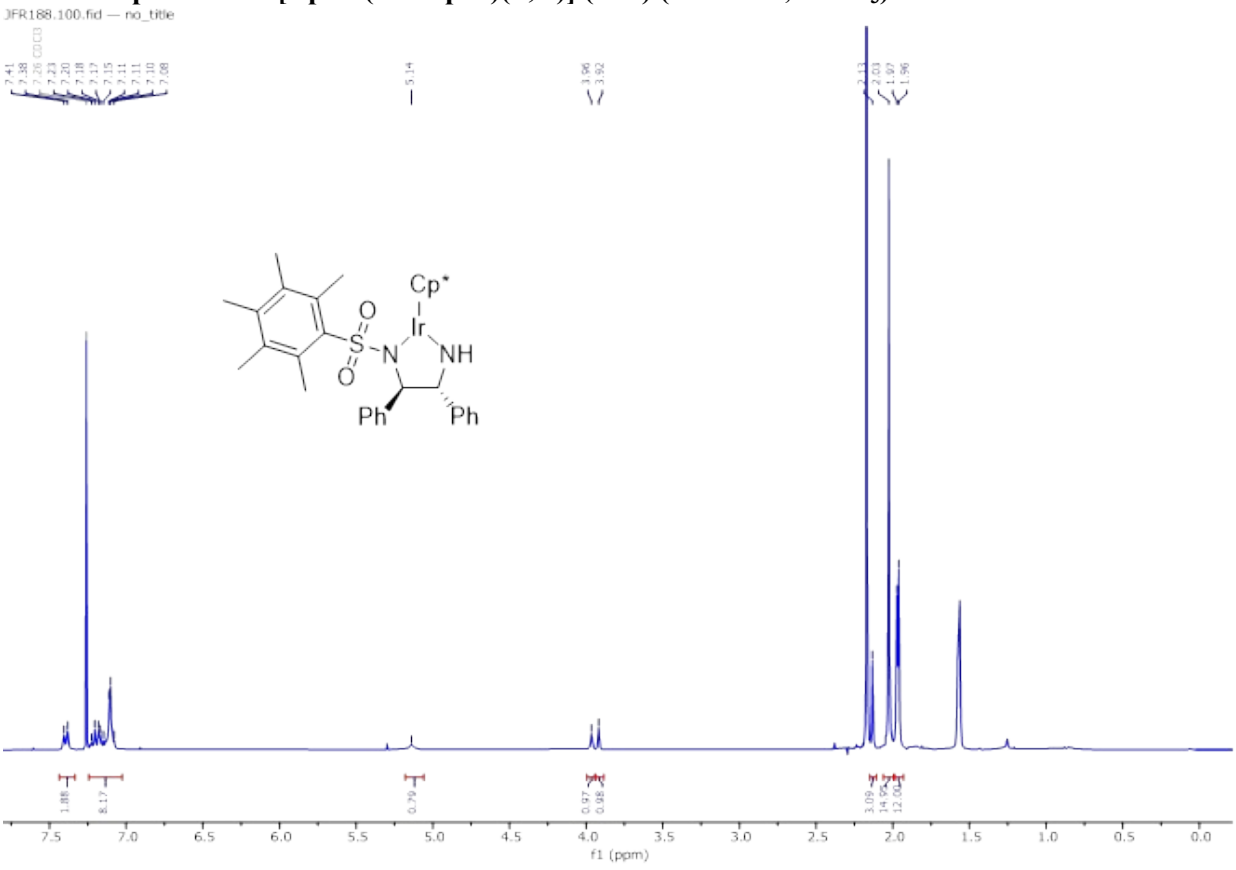


^{1}H NMR spectrum of *N*-((*1R,2R*)-2-amino-1,2-diphenylethyl)-2,3,4,5,6-

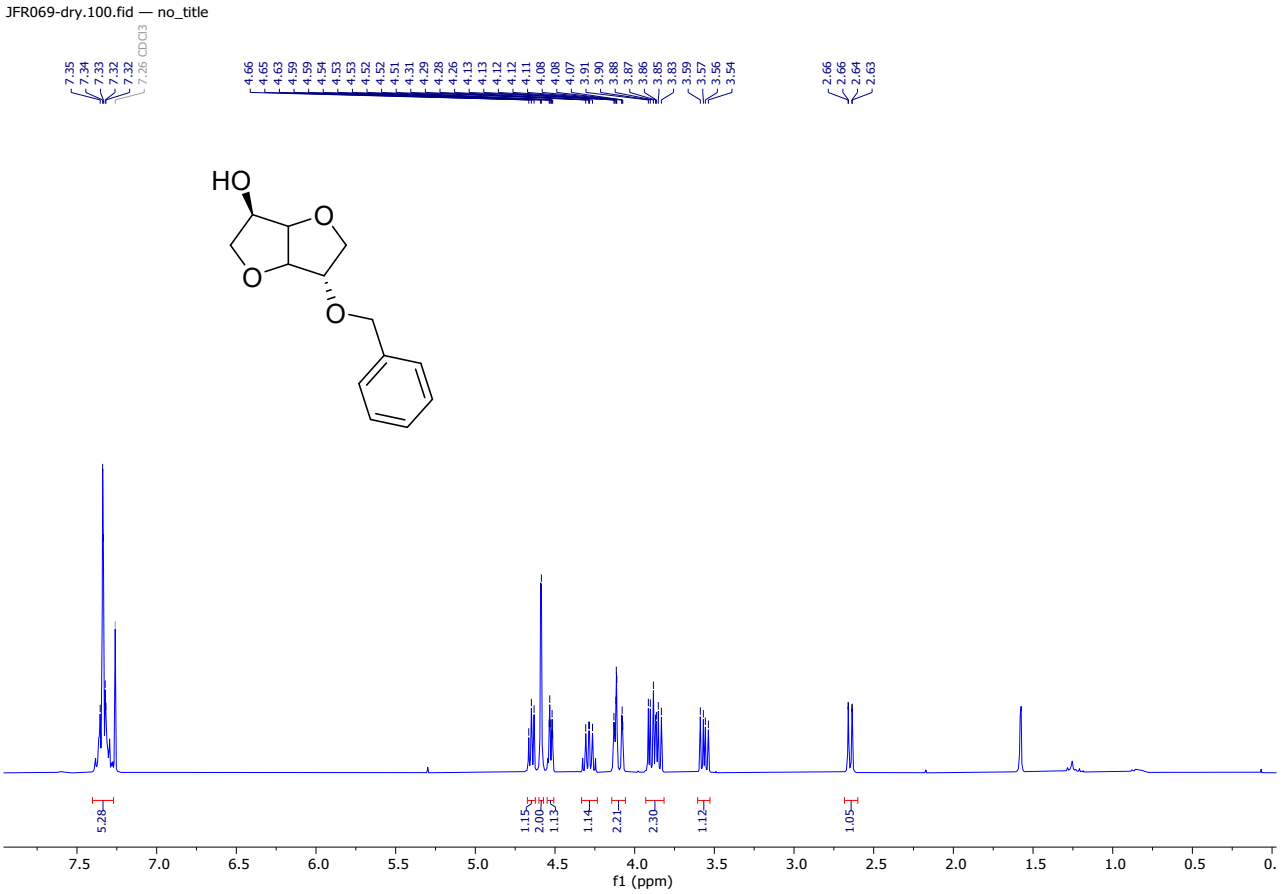


pentamethylbenzenesulfonamide (300 MHz, $CDCl_3$)

^{1}H NMR spectrum of [Cp*Ir(Ts*-dpen)(*R,R*)] (Ir-2) (300 MHz, $CDCl_3$)



^{1}H NMR spectrum of (3*R*,6*S*)-6-(benzyloxy)hexahydrofuro[3,2-*b*]furan-3-ol (1) (300 MHz, $CDCl_3$)



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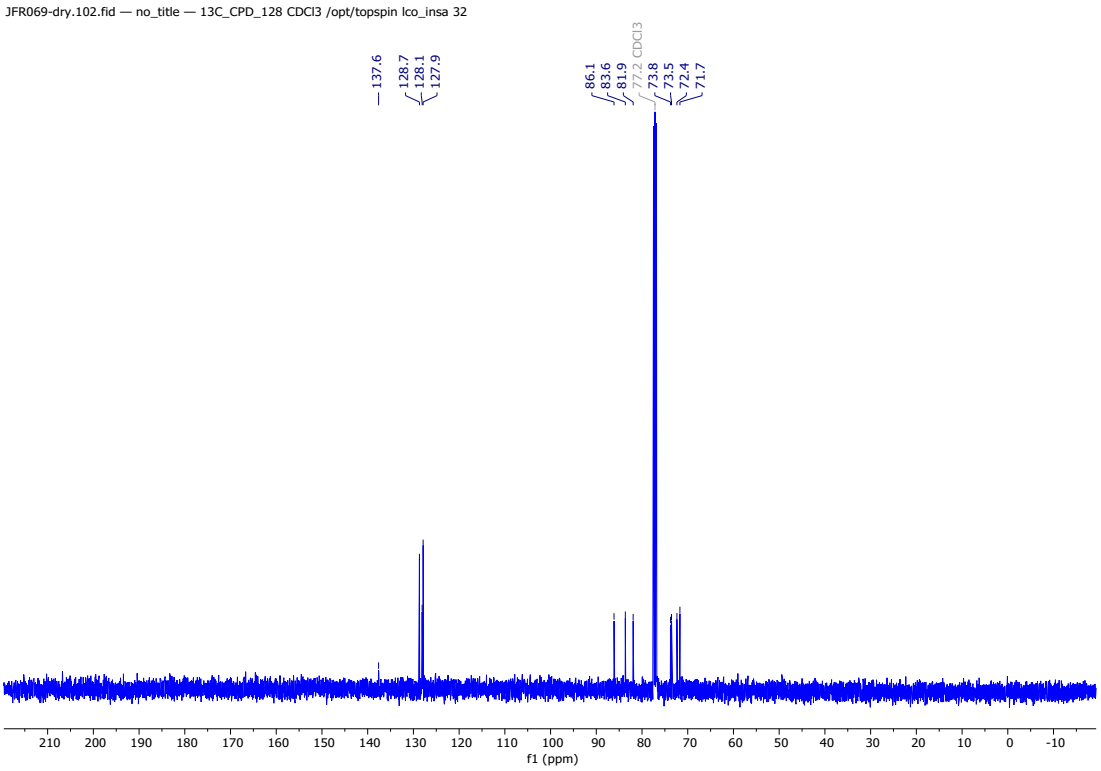
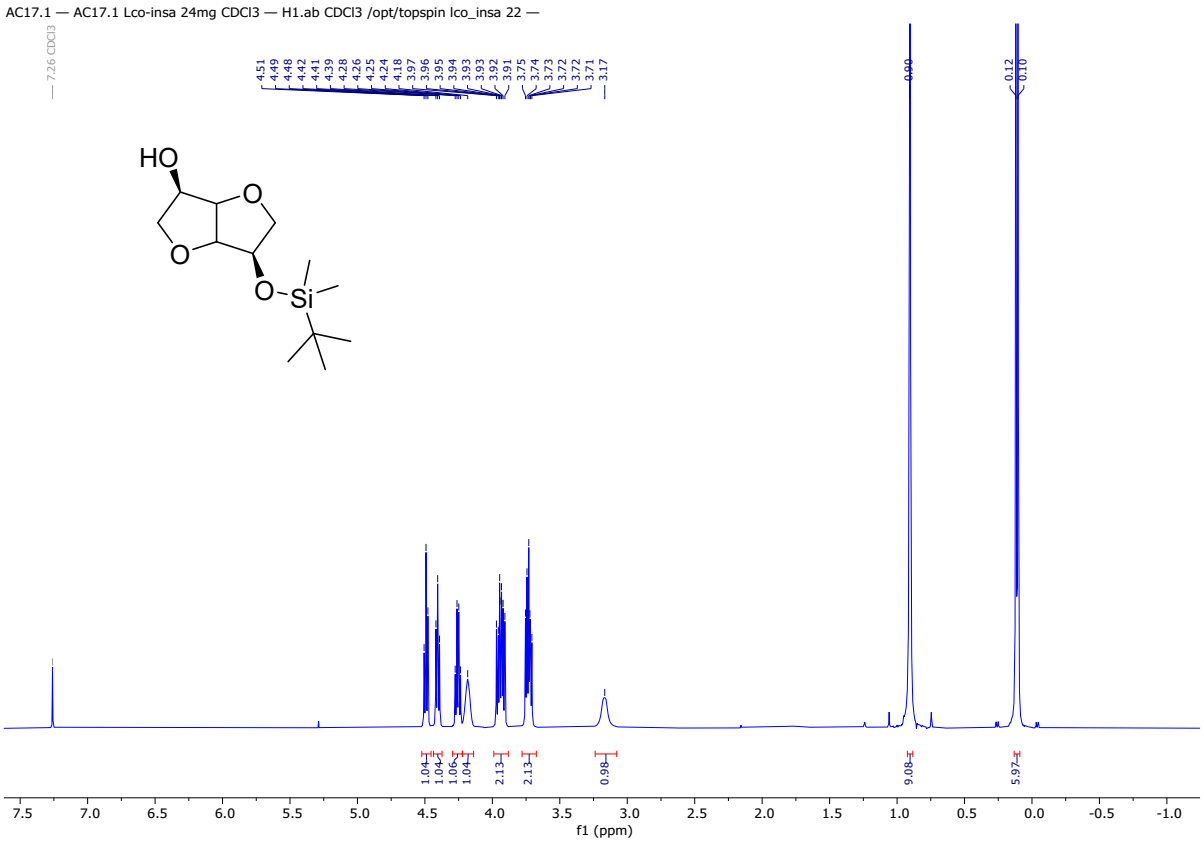
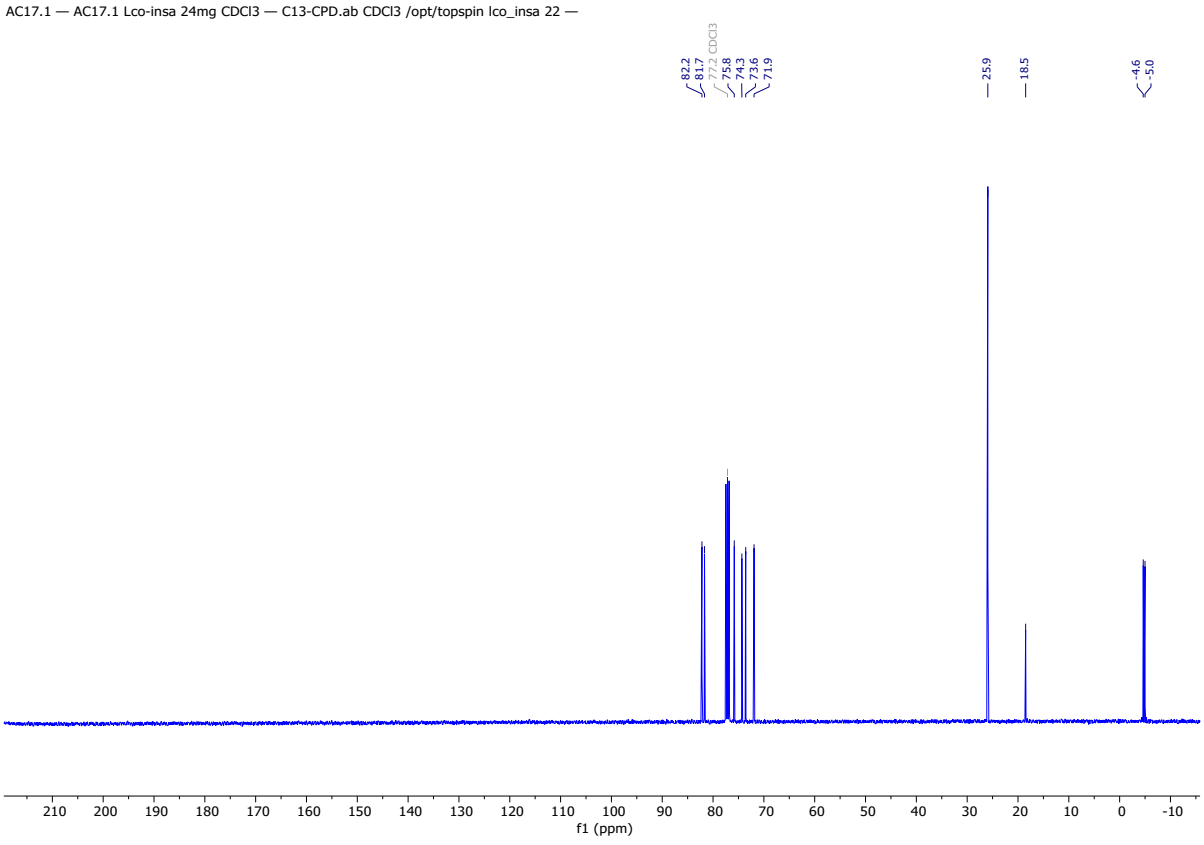


^{1}H NMR spectrum of (3*R*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)hexahydrofuro[3,2-*b*]furan-3-ol (6) (400 MHz, $CDCl_3$)



^{13}C NMR spectrum of (3*R*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)hexahydrofuro[3,2-*b*]furan-3-ol (6) (101 MHz, $CDCl_3$)



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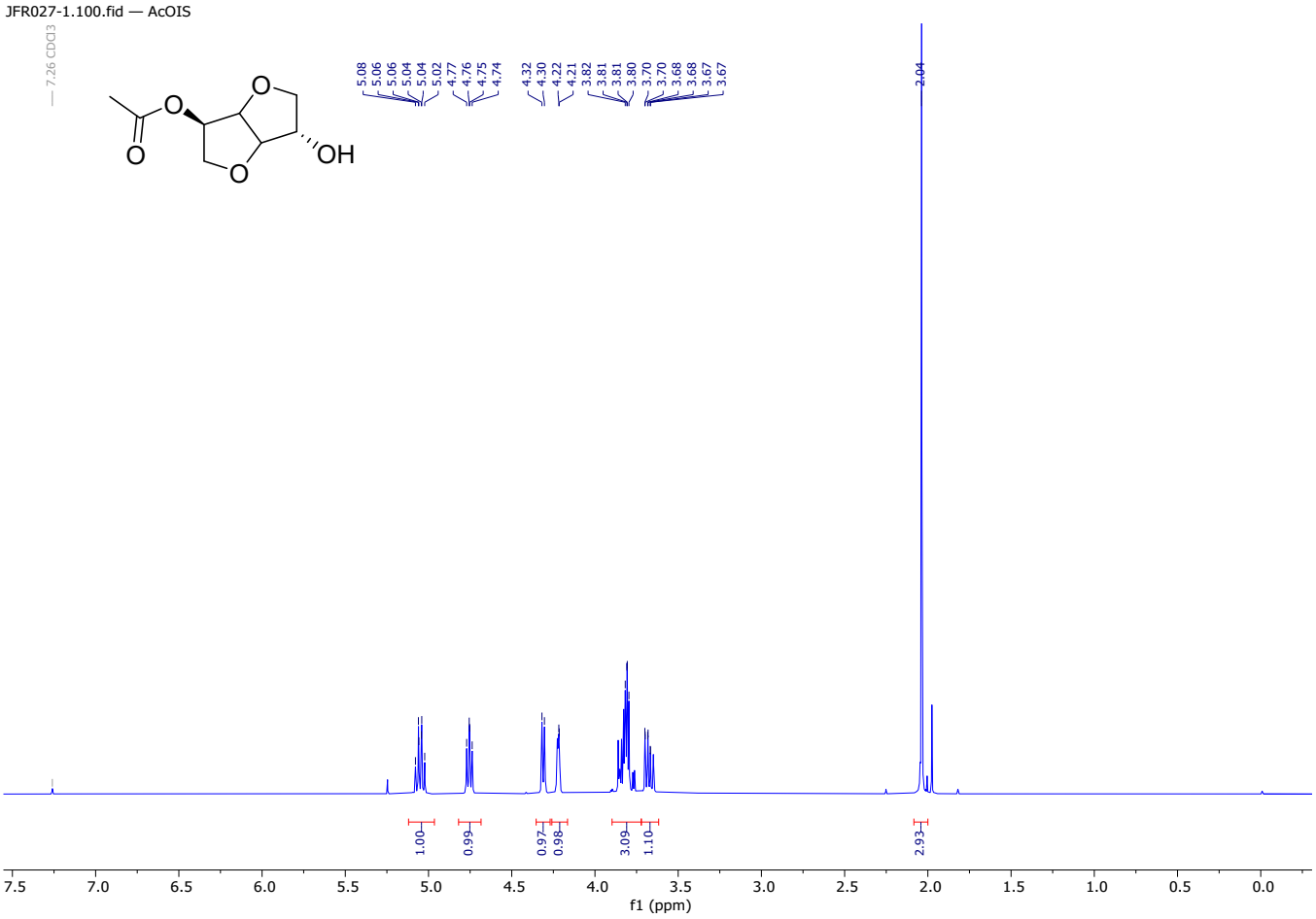

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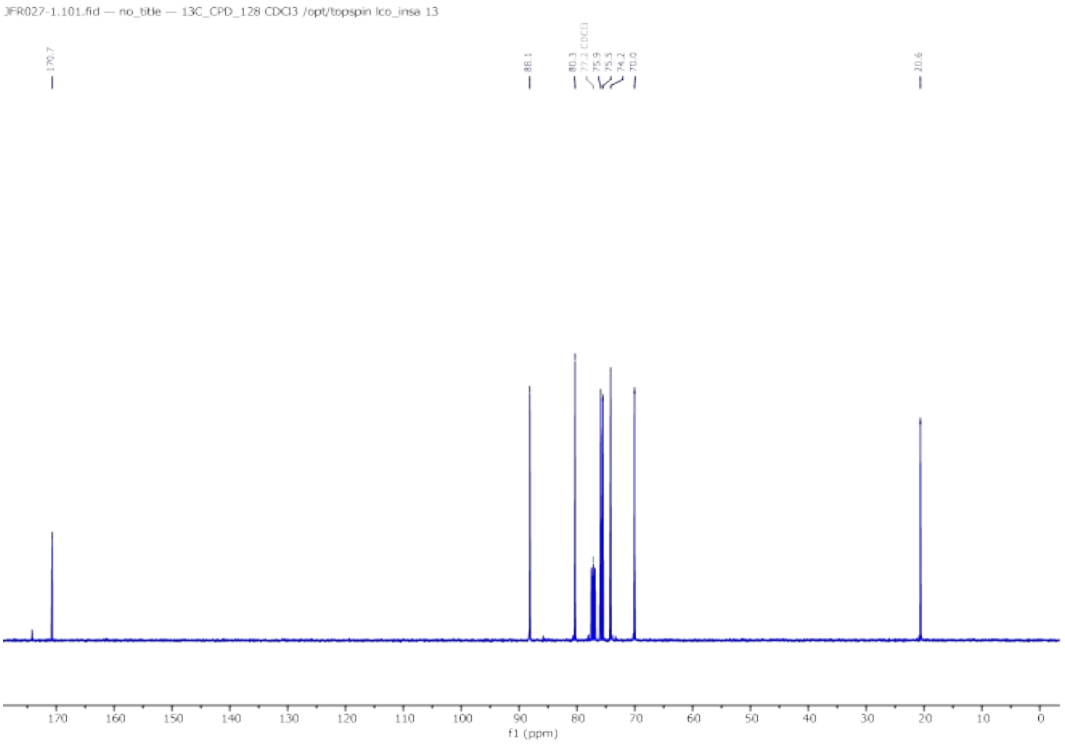

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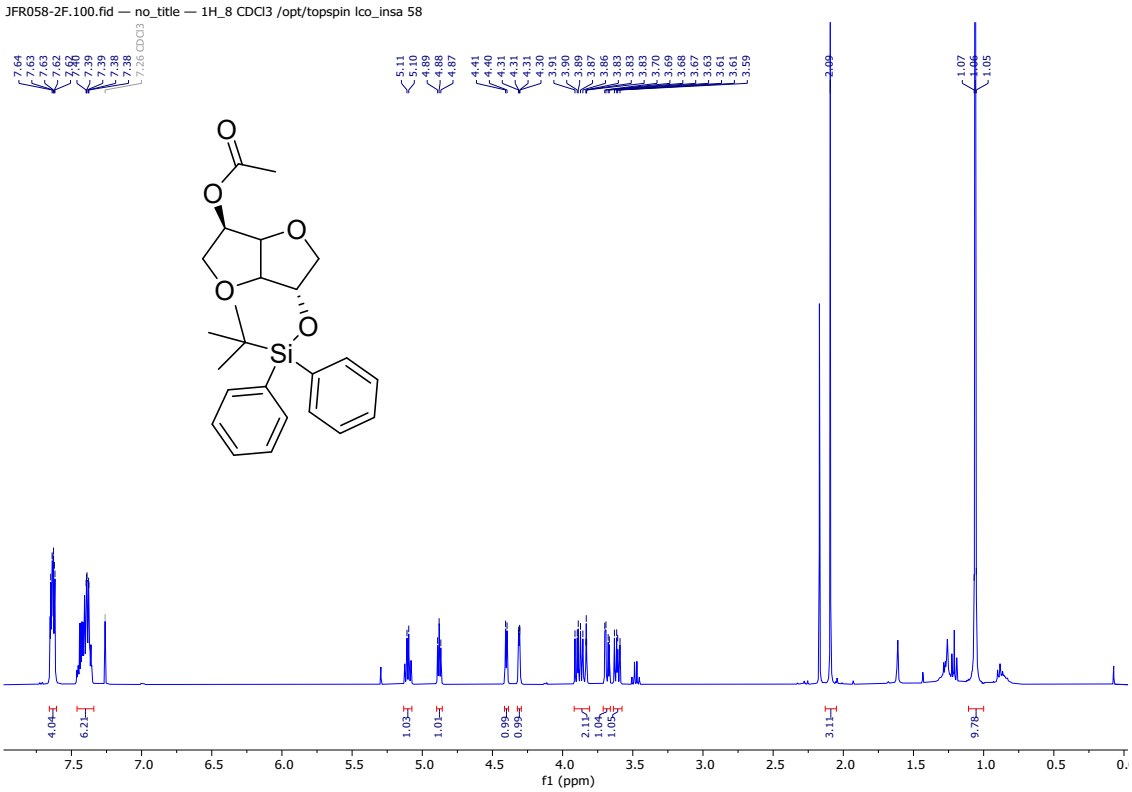
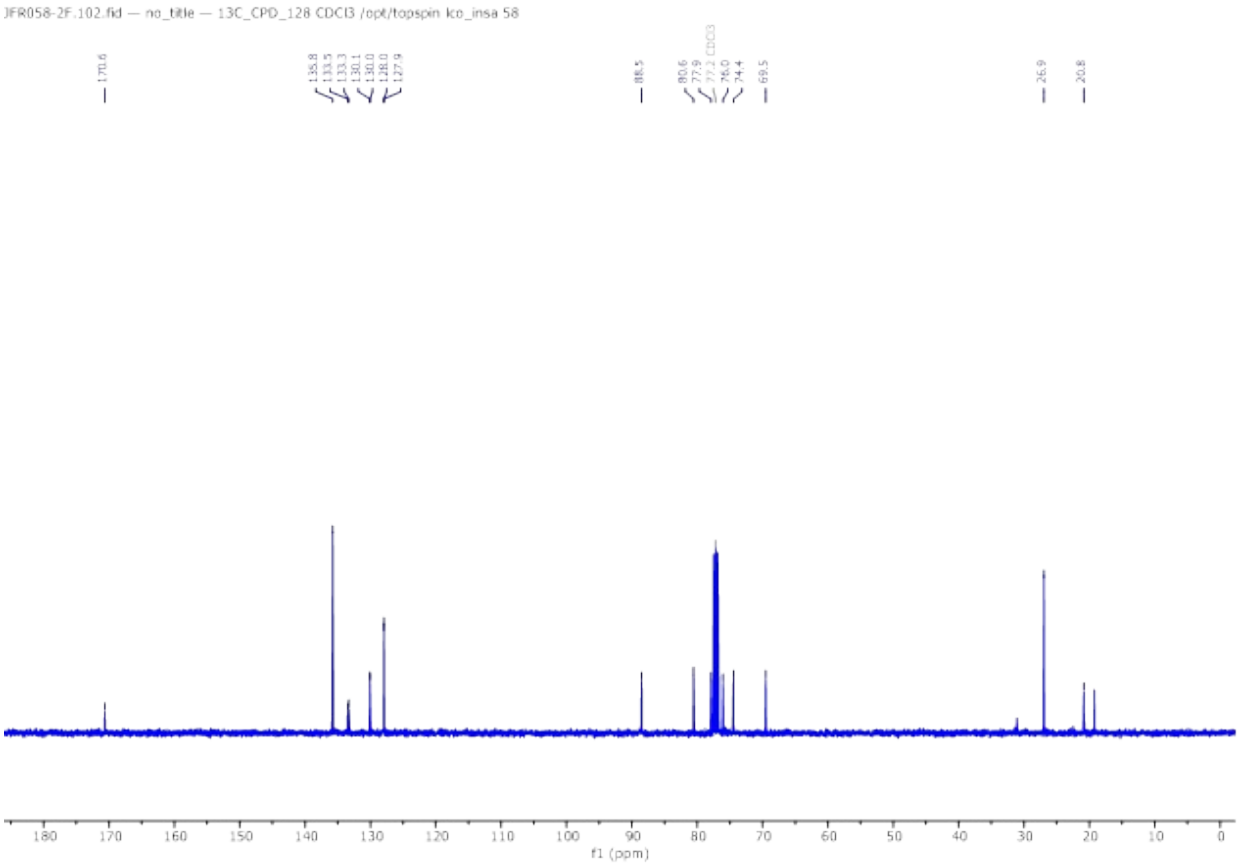


^{13}C NMR spectrum of (3*R*,6*S*)-6-((*tert*-butyldiphenylsilyl)oxy)hexahydrofuro[3,2-*b*]furan-3-yl acetate (101 MHz, $CDCl_3$)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130.0
128.0
127.9
88.5
80.6
77.9
77.2 CDCl3
76.0
74.4
69.5
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180
170
160
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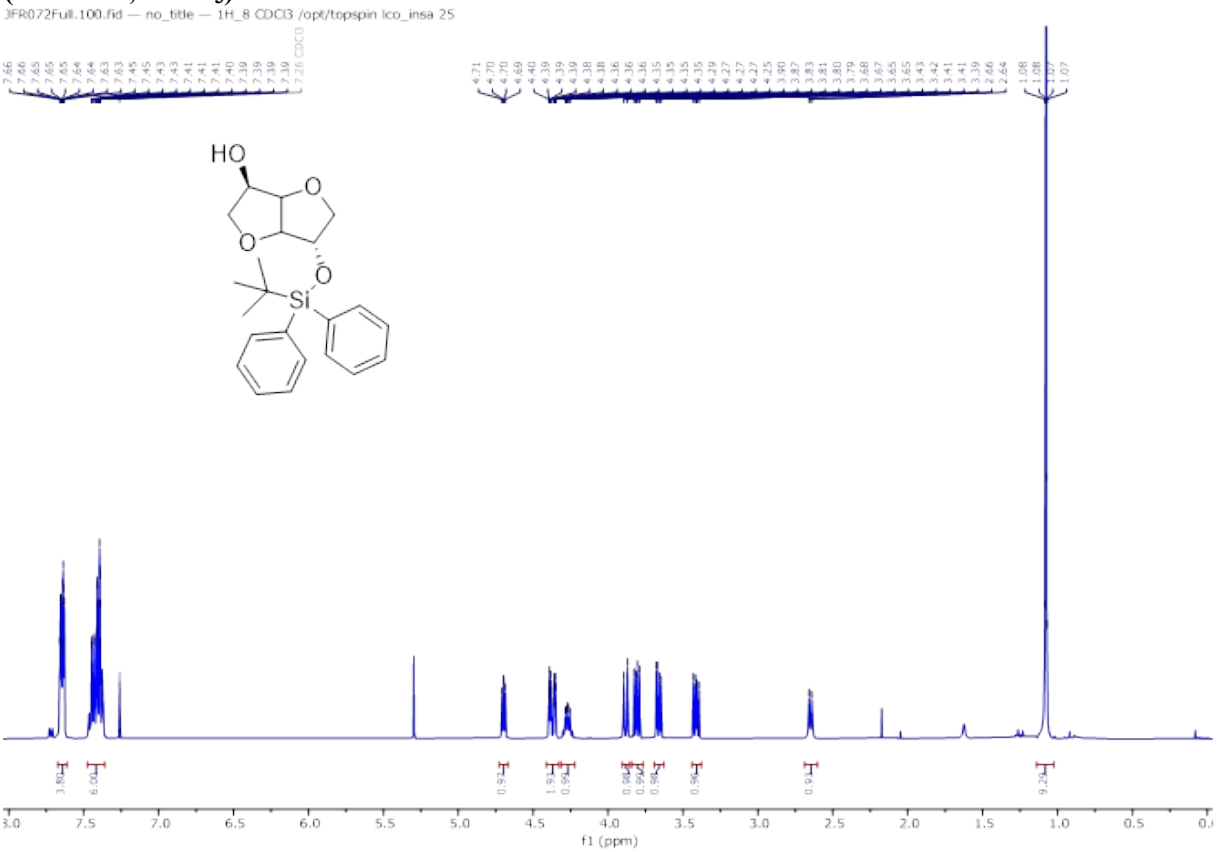
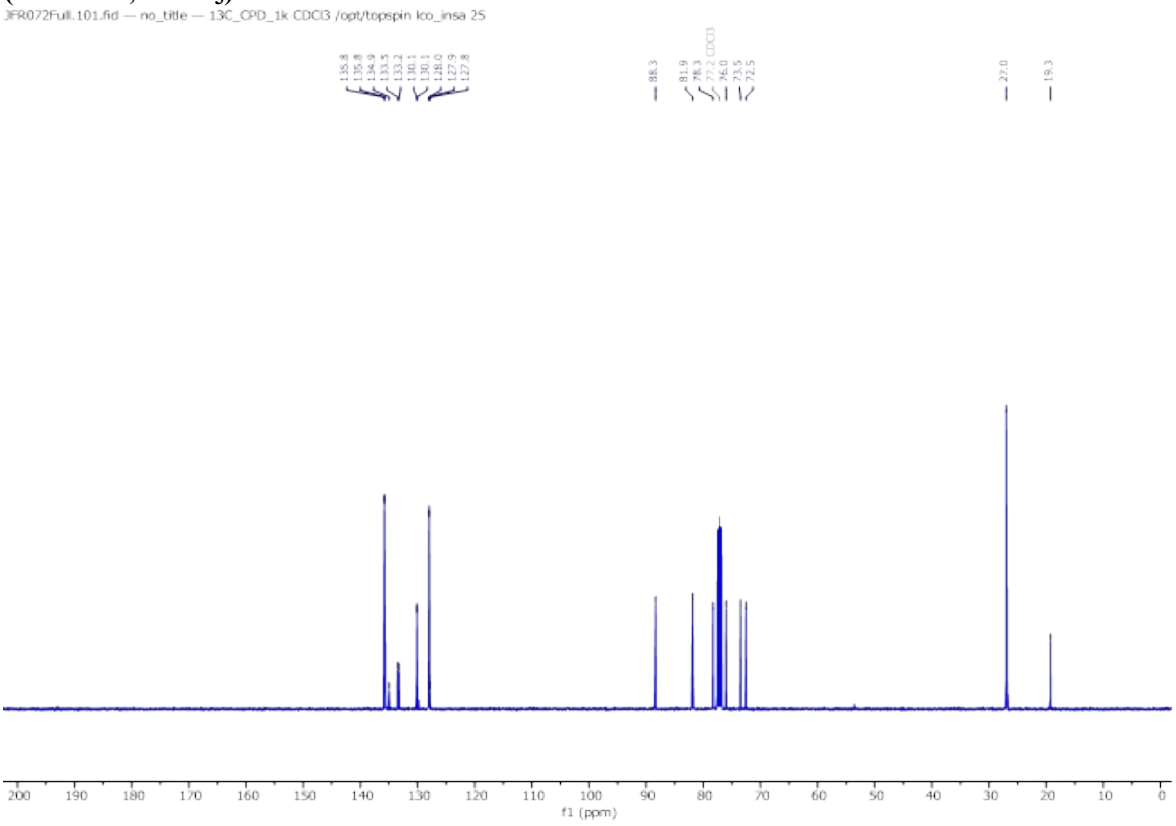
0
f1 (ppm)

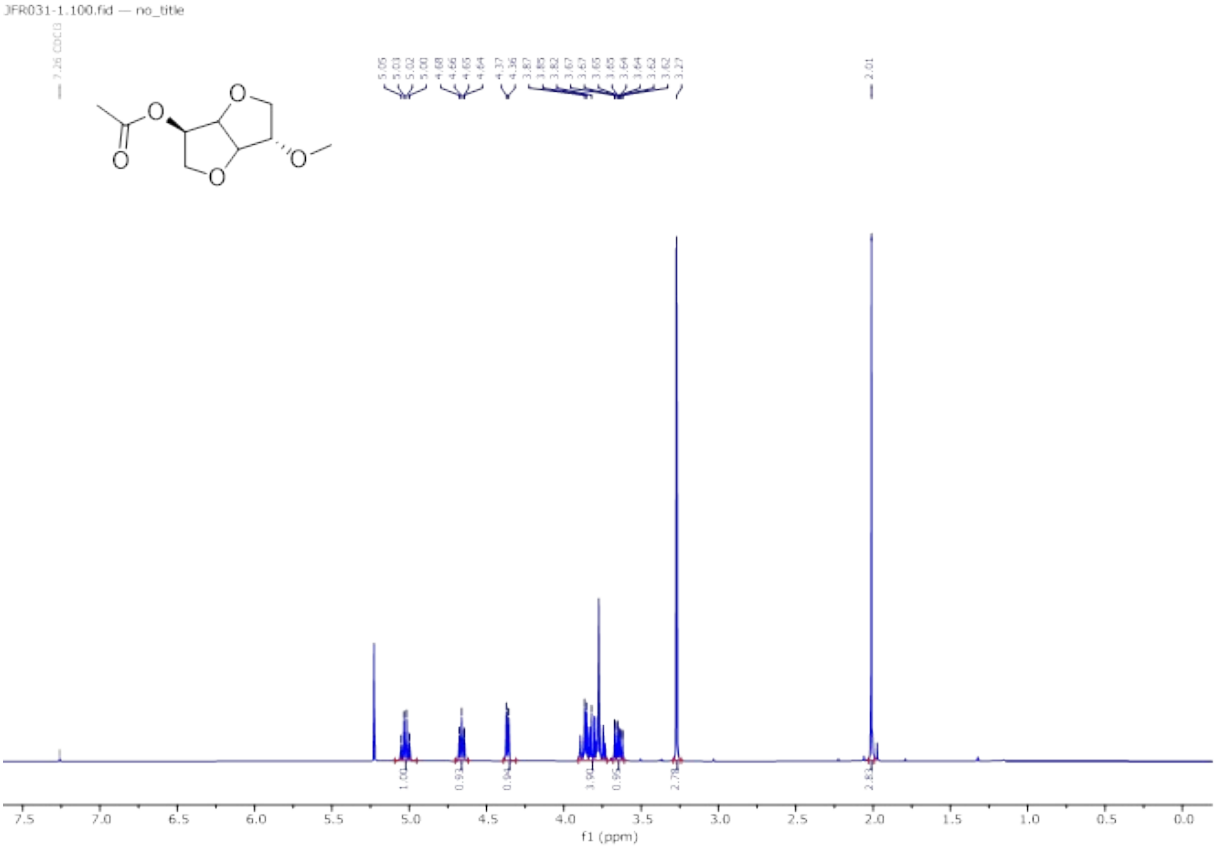
^{1}H NMR spectrum of (3*R*,6*S*)-6-((*tert*-butyldiphenylsilyl)oxy)hexahydrofuro[3,2-*b*]furan-3-ol (7) (400 MHz, $CDCl_3$)



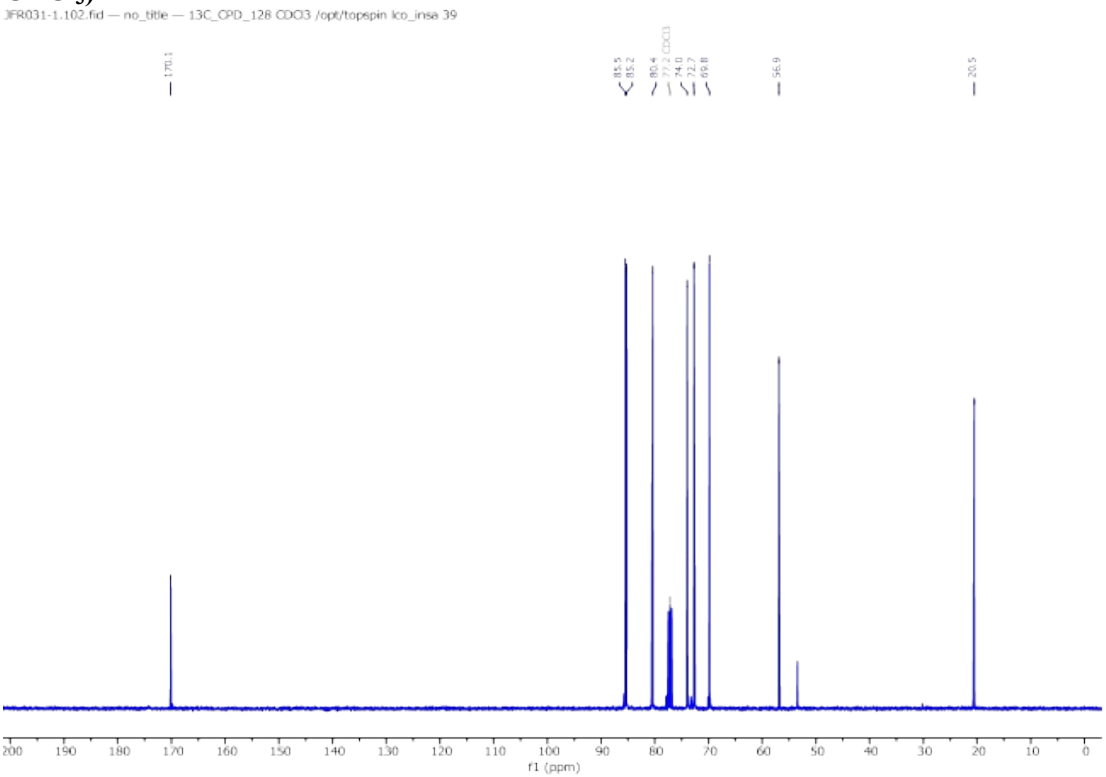
^{13}C NMR spectrum of (3*R*,6*S*)-6-((*tert*-butyldiphenylsilyl)oxy)hexahydrofuro[3,2-*b*]furan-3-ol (7) (101 MHz, $CDCl_3$)



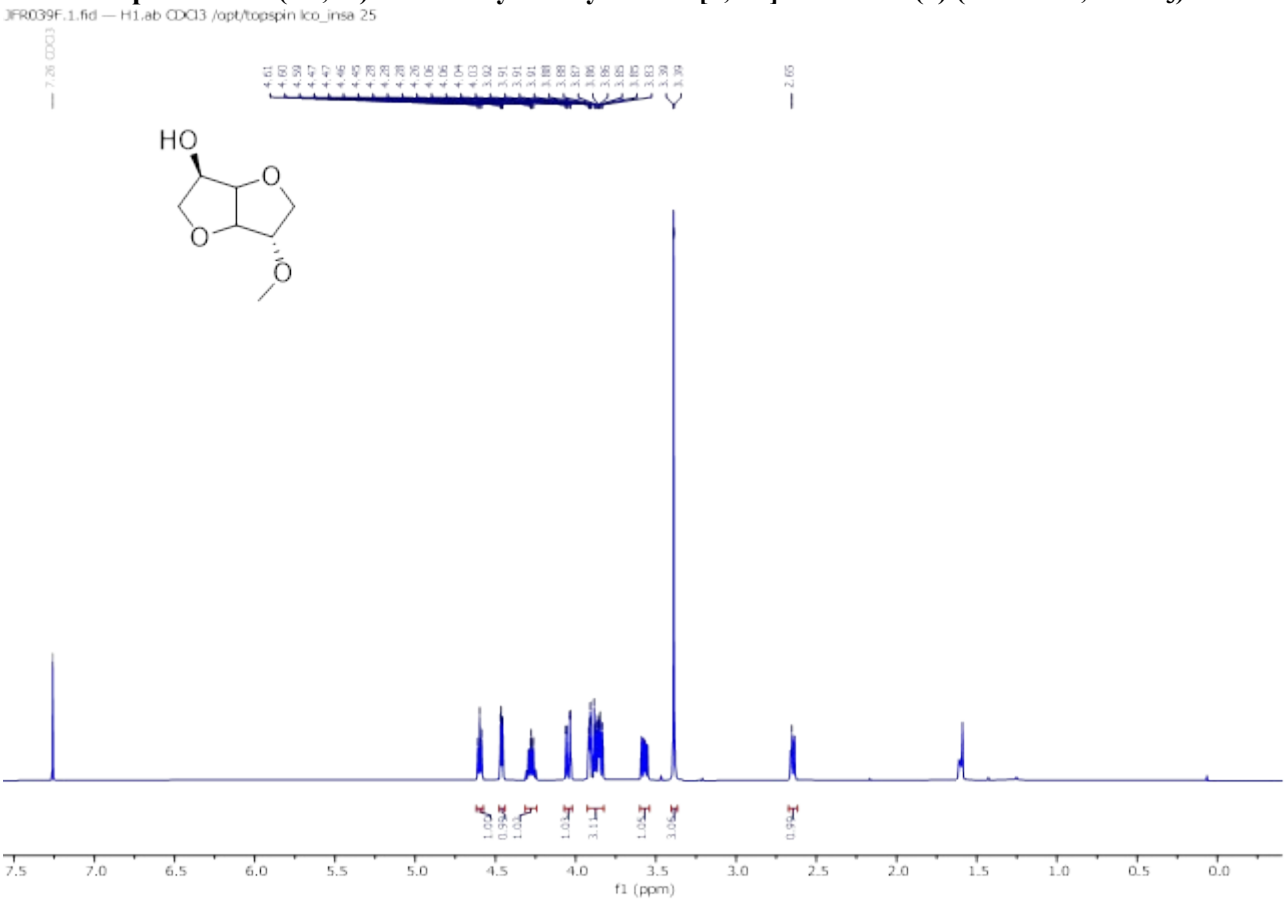
^{1}H NMR spectrum of (3R,6S)-6-Methoxyhexahydrofuro[3,2-b]furan-3-yl acetate (400 MHz, $CDCl_3$)



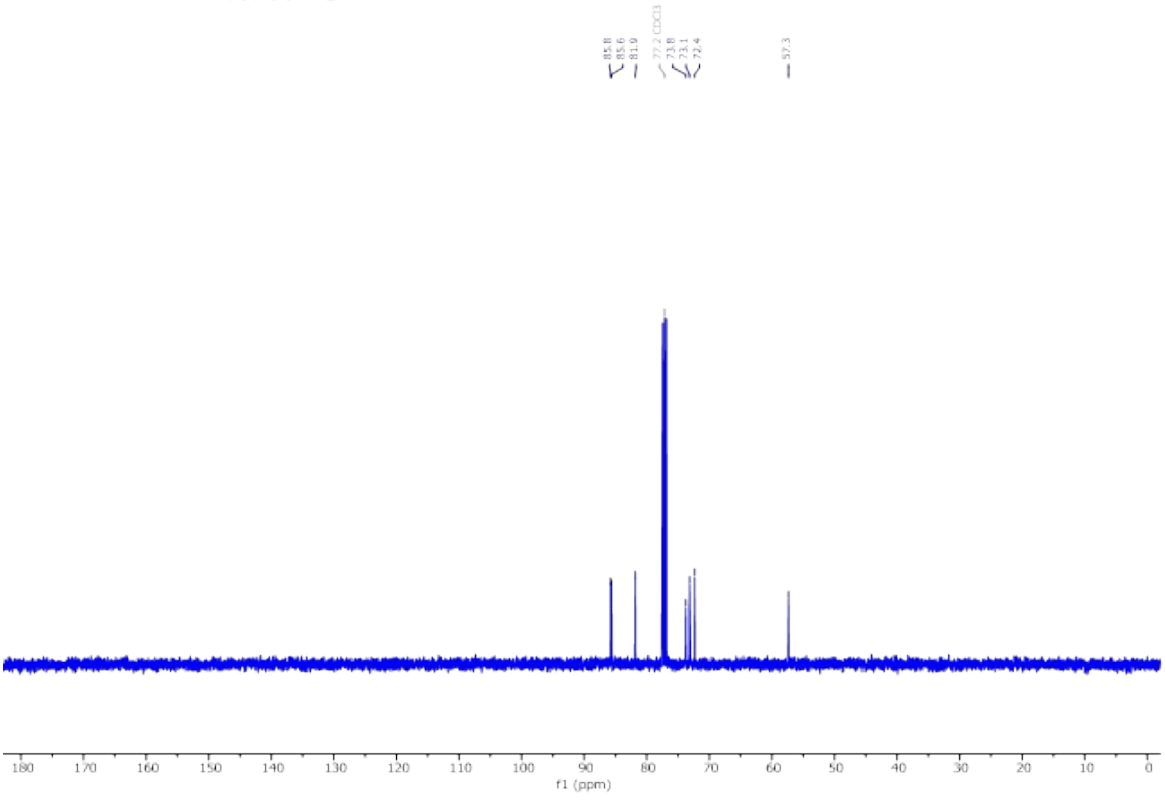
^{13}C NMR spectrum of (3*R*,6*S*)-6-Methoxyhexahydrofuro[3,2-*b*]furan-3-yl acetate (101 MHz, $CDCl_3$)



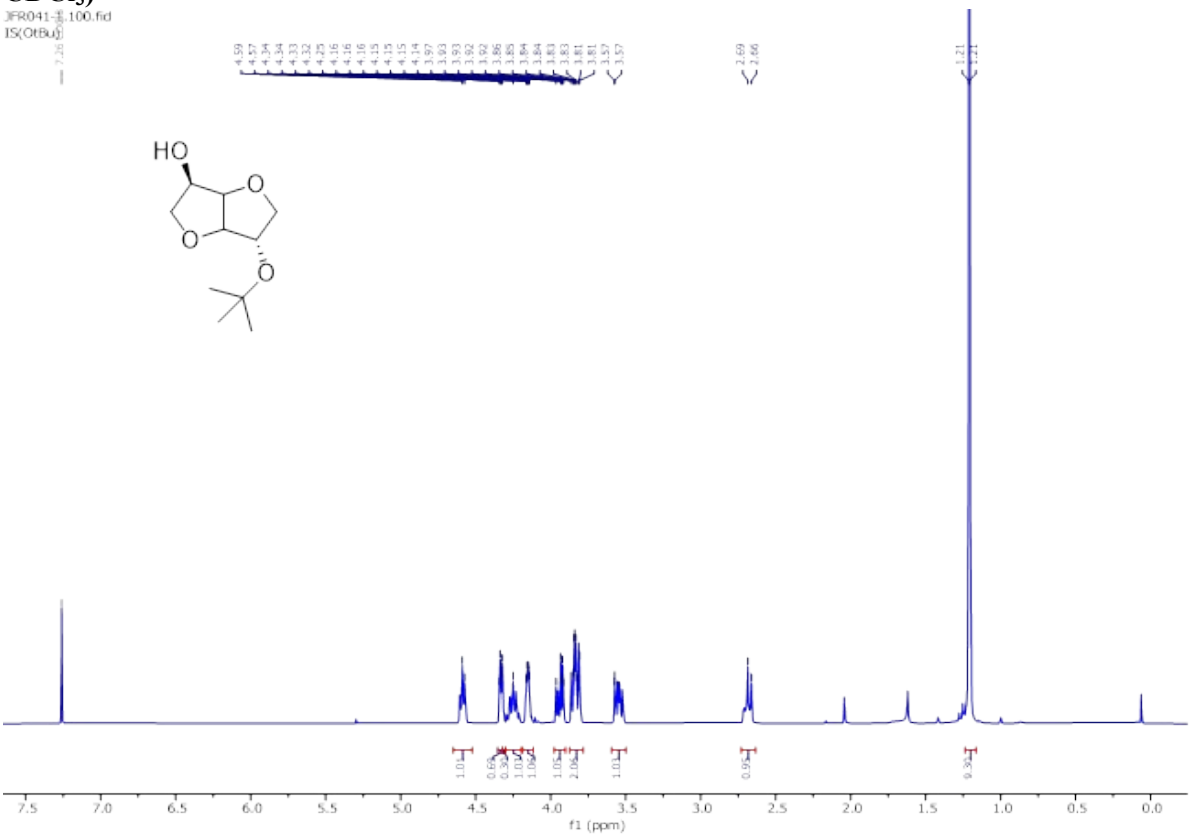
^{1}H NMR spectrum of (3*R*,6*S*)-6-methoxyhexahydrofuro[3,2-*b*]furan-3-ol (8) (400 MHz, $CDCl_3$)



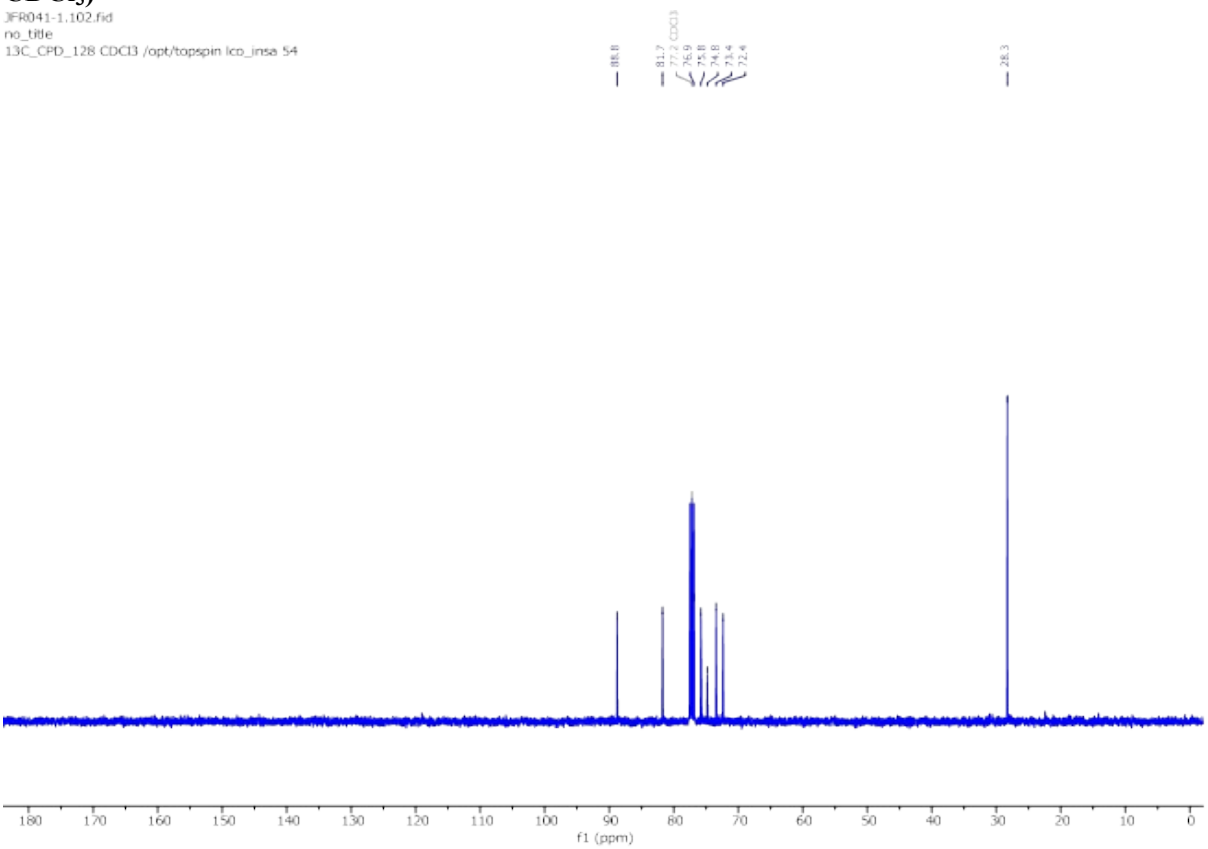
^{13}C NMR spectrum of (3*R*,6*S*)-6-methoxyhexahydrofuro[3,2-*b*]furan-3-ol (8) (101 MHz, $CDCl_3$)



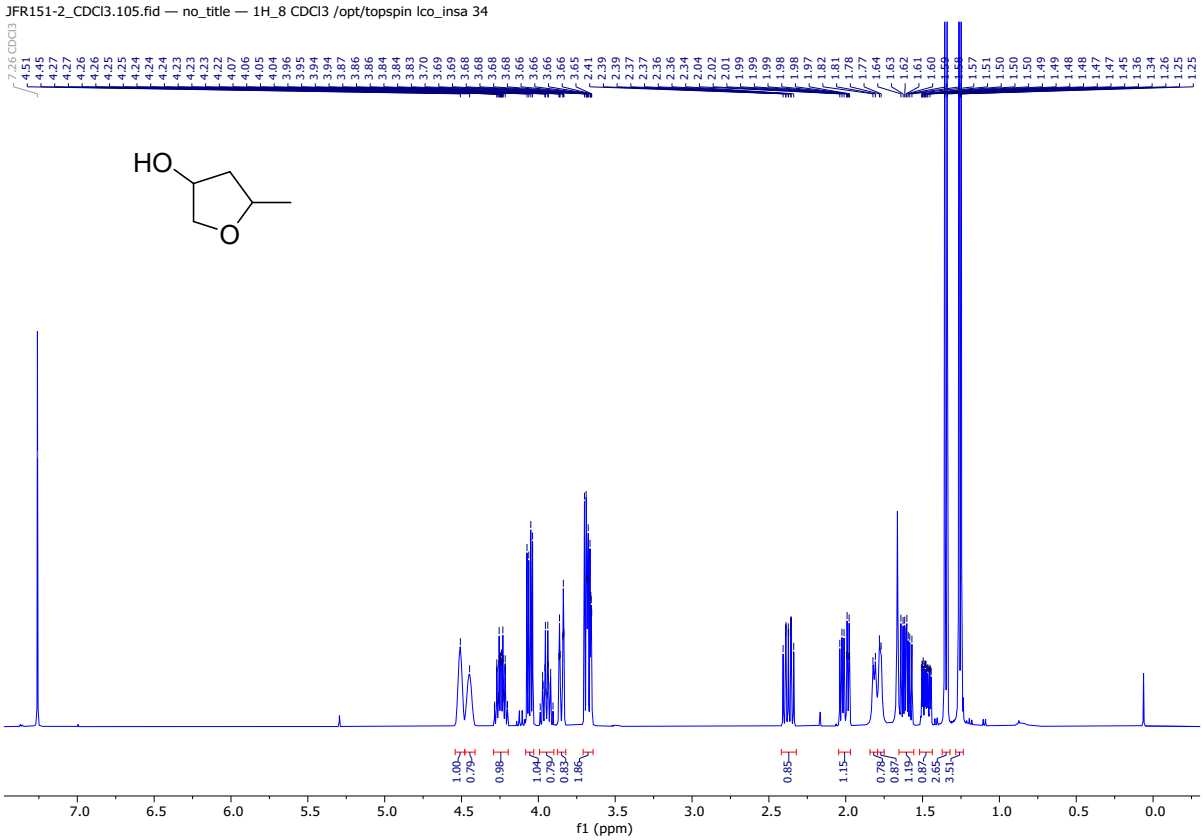
^{1}H NMR spectrum of (3*R*,6*S*)-6-(*tert*-butoxy)hexahydrofuro[3,2-*b*]furan-3-ol (9) (400 MHz, $CDCl_3$)



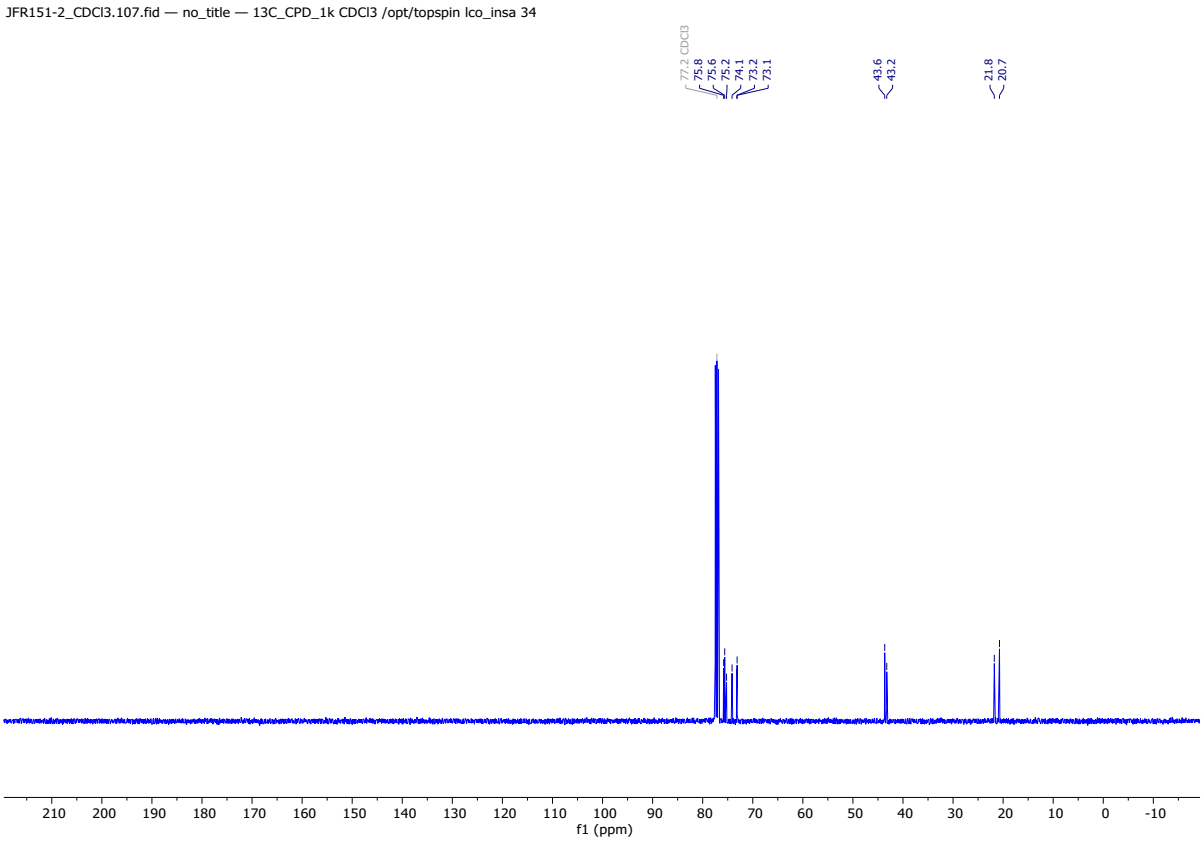
^{13}C NMR spectrum of (3*R*,6*S*)-6-(*tert*-butoxy)hexahydrofuro[3,2-*b*]furan-3-ol (9) (101 MHz, $CDCl_3$)



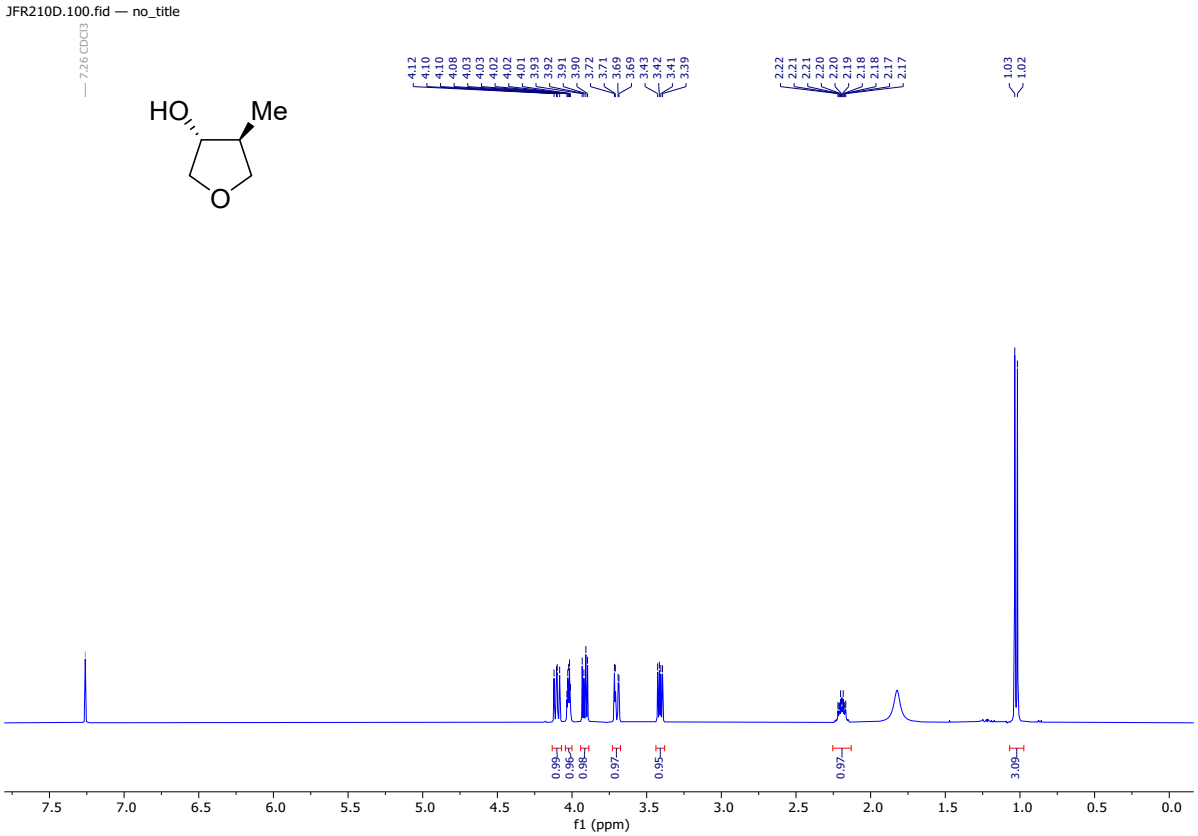
^{1}H NMR spectrum of 5-methyltetrahydrofuran-3-ol (400 MHz, $CDCl_3$)



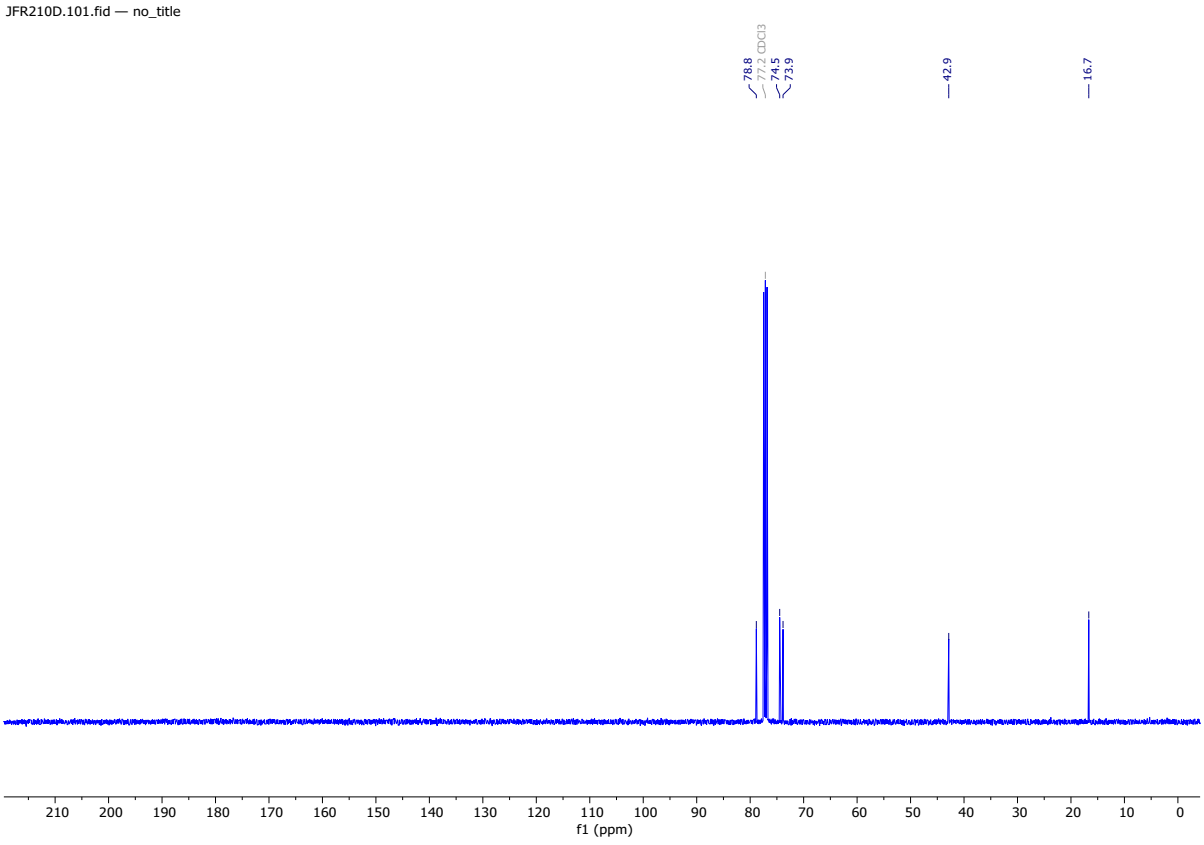
^{13}C NMR spectrum of (3*R*,4*S*)-4-methyltetrahydrofuran-3-ol (101 MHz, $CDCl_3$)



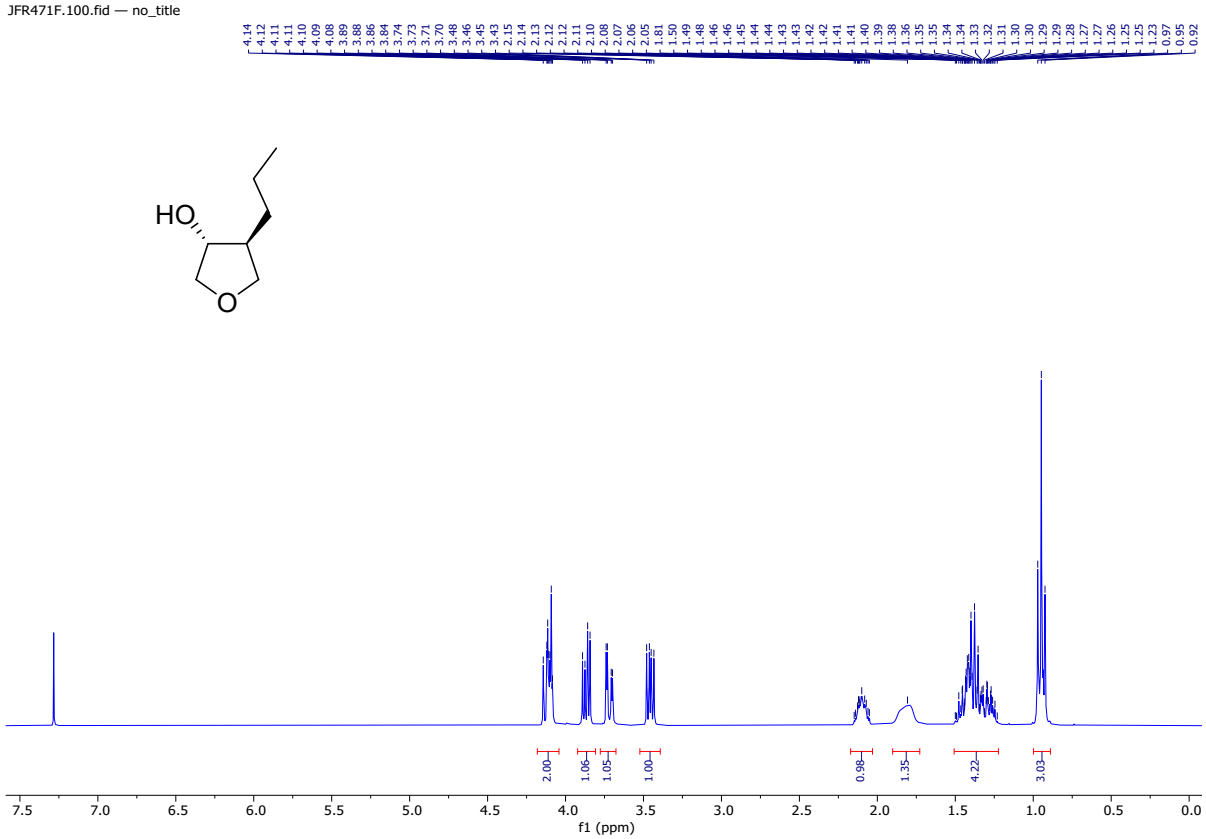
^{1}H NMR spectrum of (3*R*,4*S*)-4-methyltetrahydrofuran-3-ol (±) (400 MHz, $CDCl_3$)



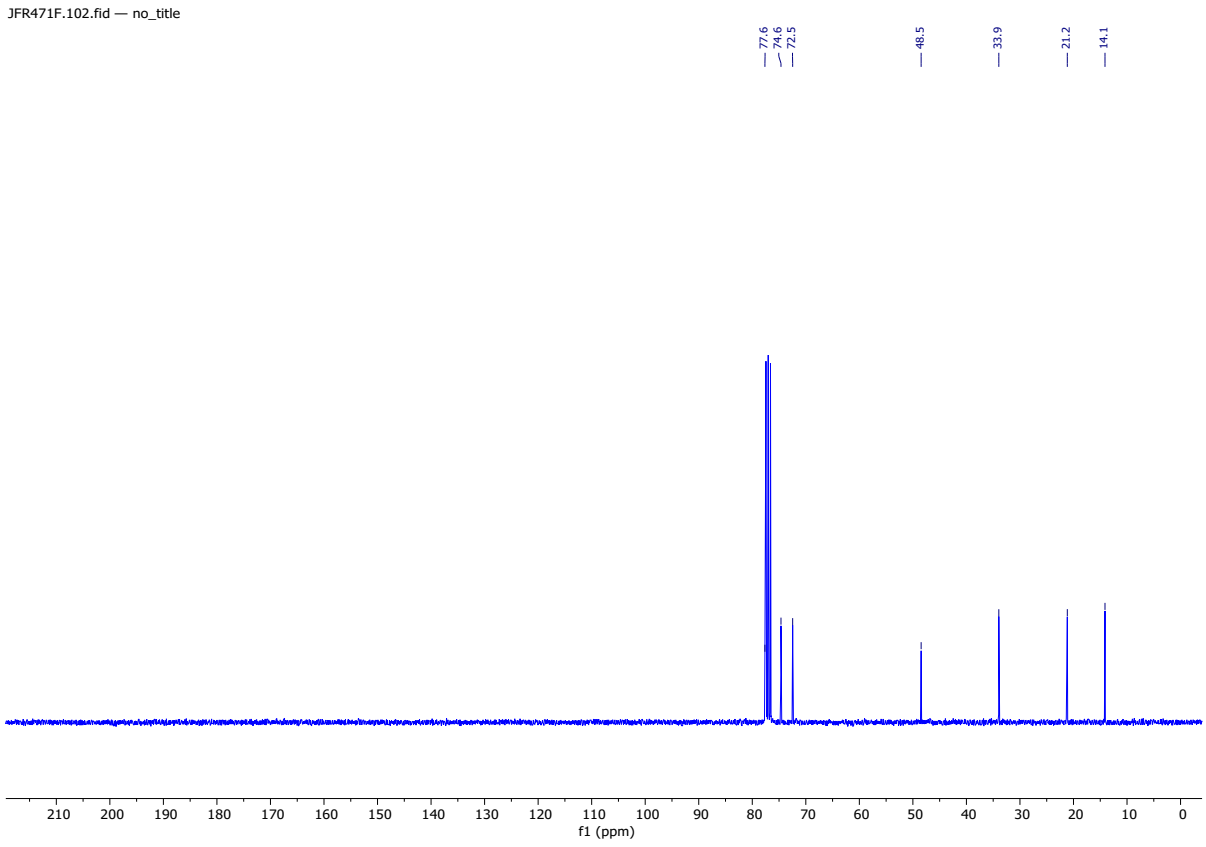
^{13}C NMR spectrum of (3*R*,4*S*)-4-methyltetrahydrofuran-3-ol (±) (101 MHz, $CDCl_3$)



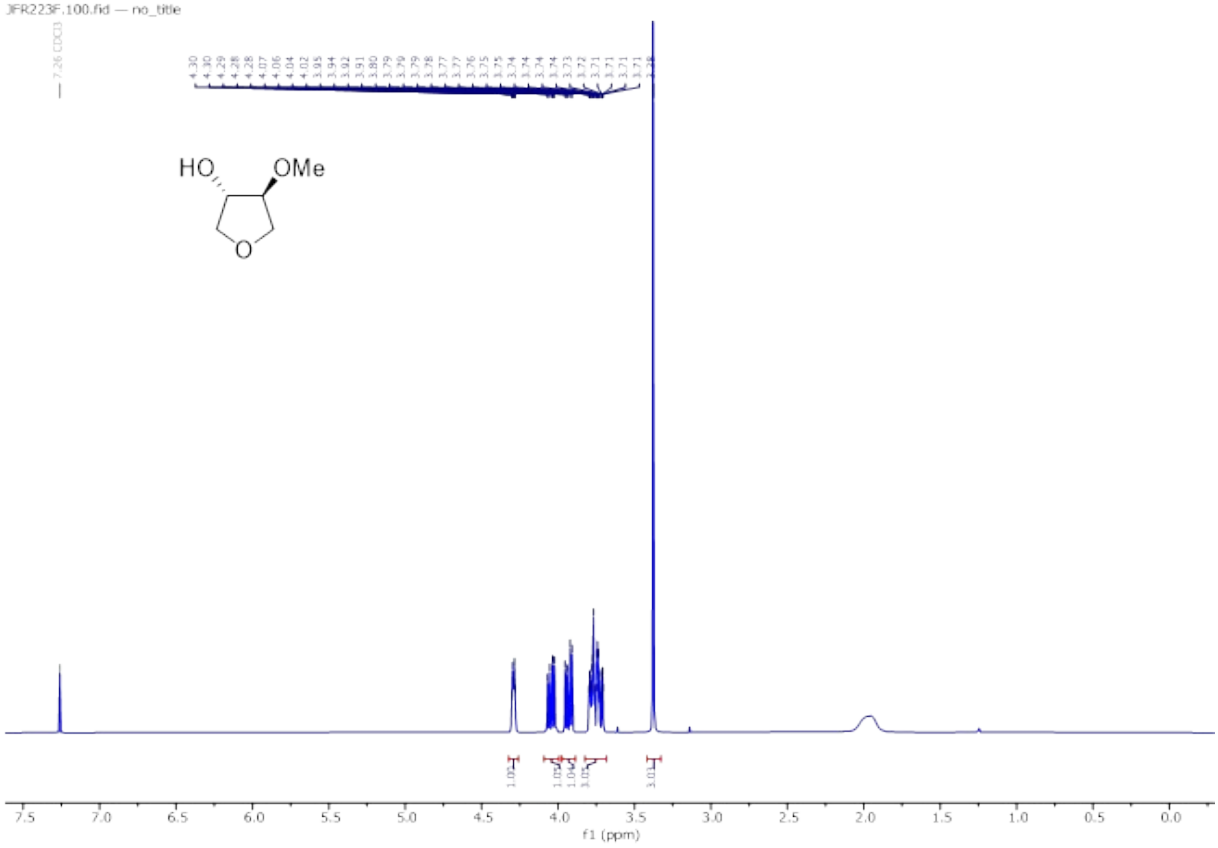
^{1}H NMR spectrum of (3*R*,4*S*)-4-propyltetrahydrofuran-3-ol (±) (300 MHz, $CDCl_3$)



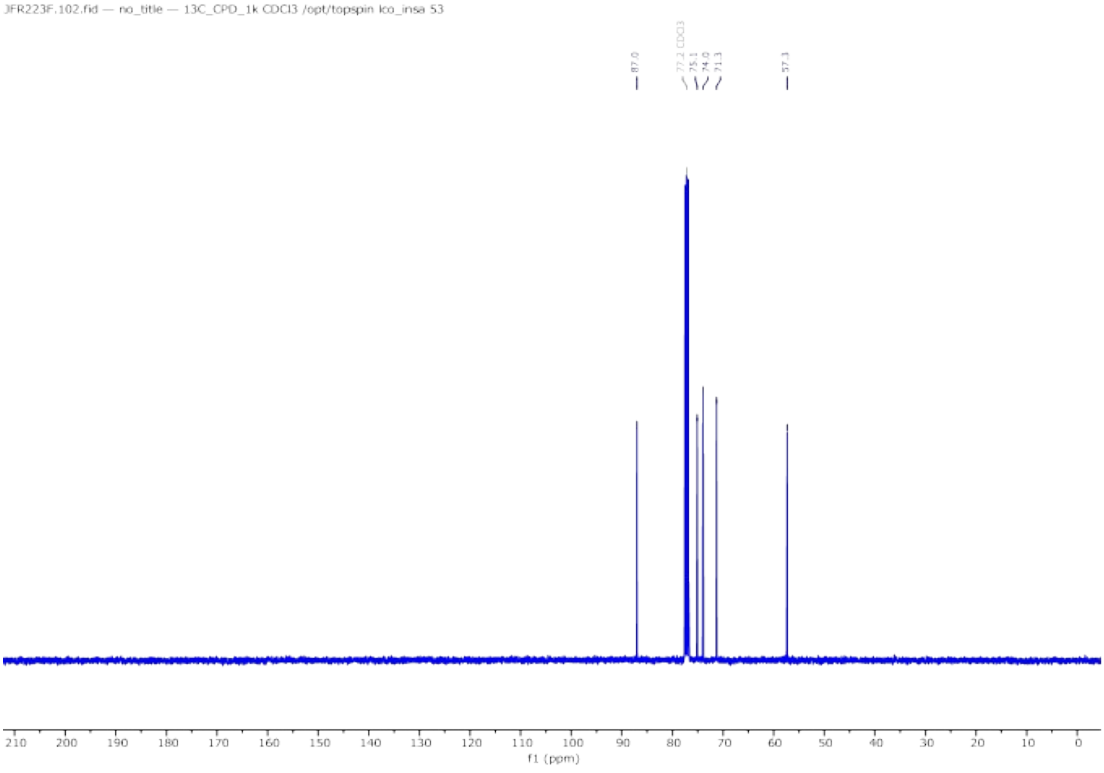
^{13}C NMR spectrum of (3*R*,4*S*)-4-propyltetrahydrofuran-3-ol (±) (75 MHz, $CDCl_3$)



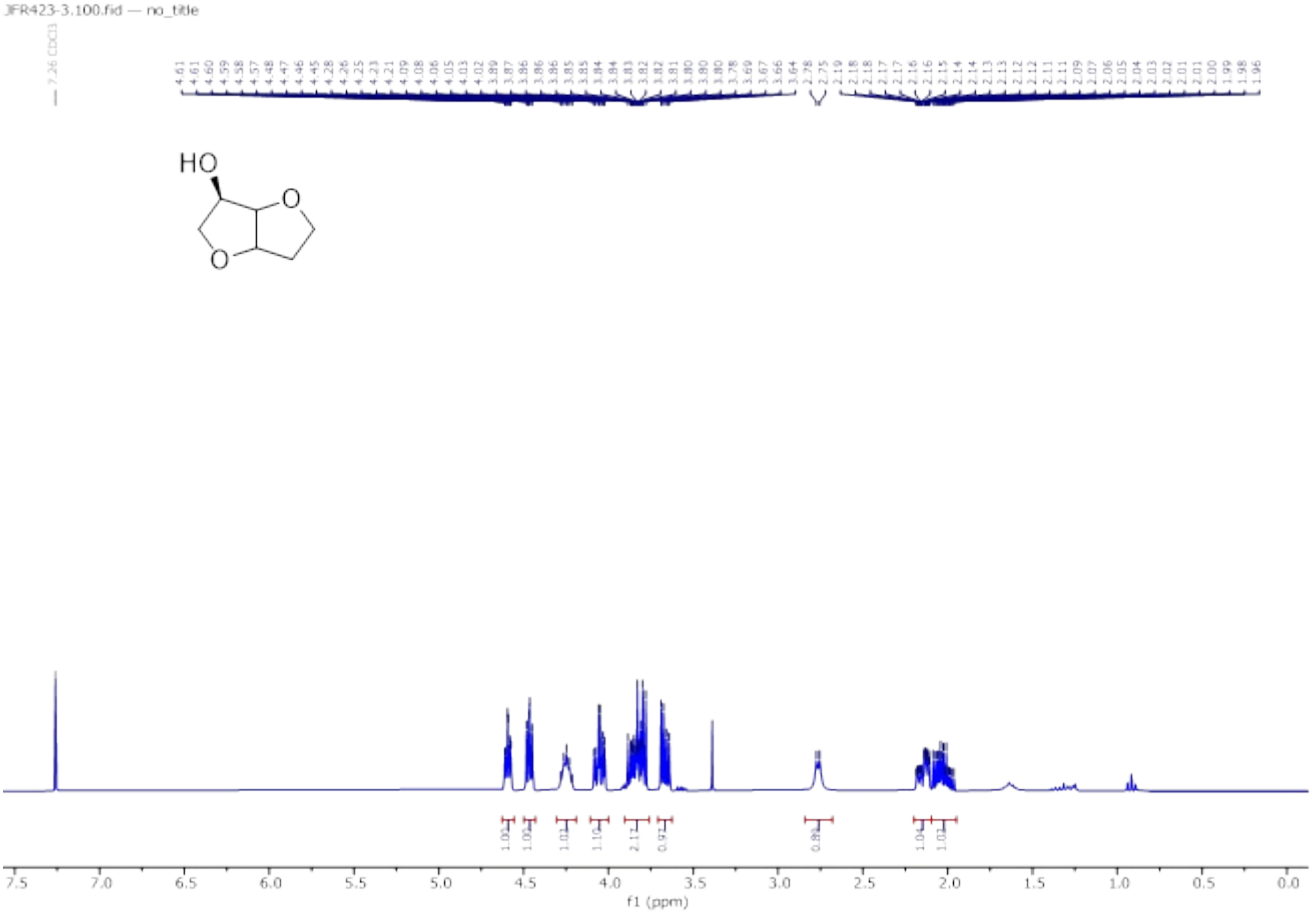
^{1}H NMR spectrum of (3*S*,4*S*)-4-methoxytetrahydrofuran-3-ol (±) (400 MHz, $CDCl_3$)



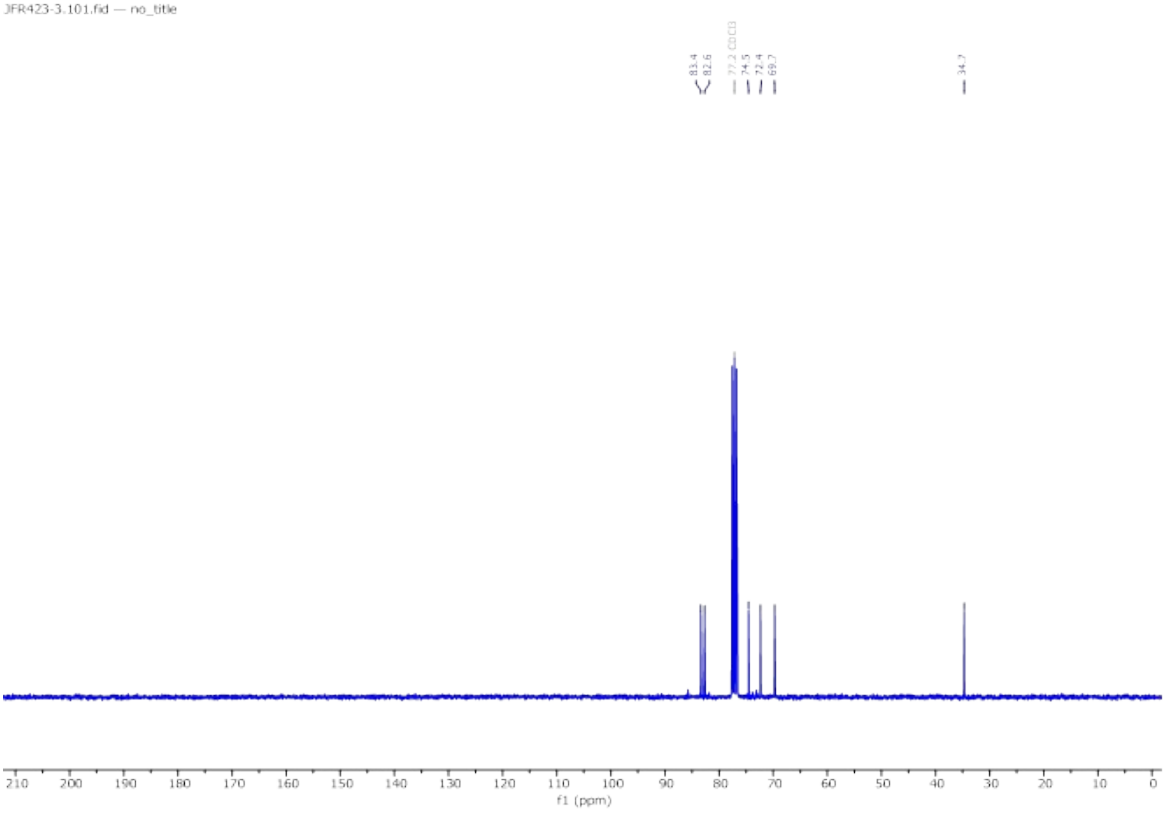
^{13}C NMR spectrum of (3*S*,4*S*)-4-methoxytetrahydrofuran-3-ol (±) (101 MHz, $CDCl_3$)



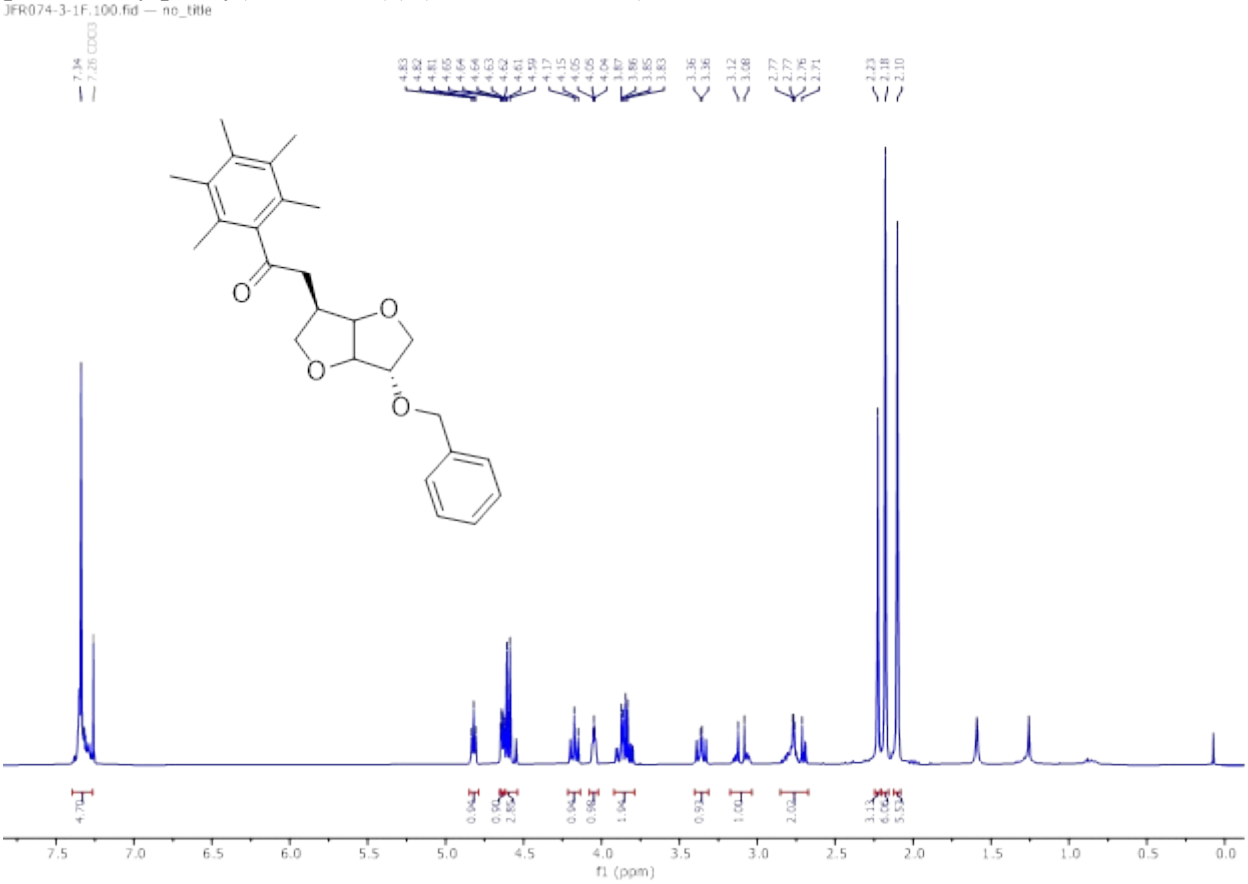
^{1}H NMR spectrum of (*3R*)-hexahydrofuro[3,2-*b*]furan-3-ol (300 MHz, $CDCl_3$)



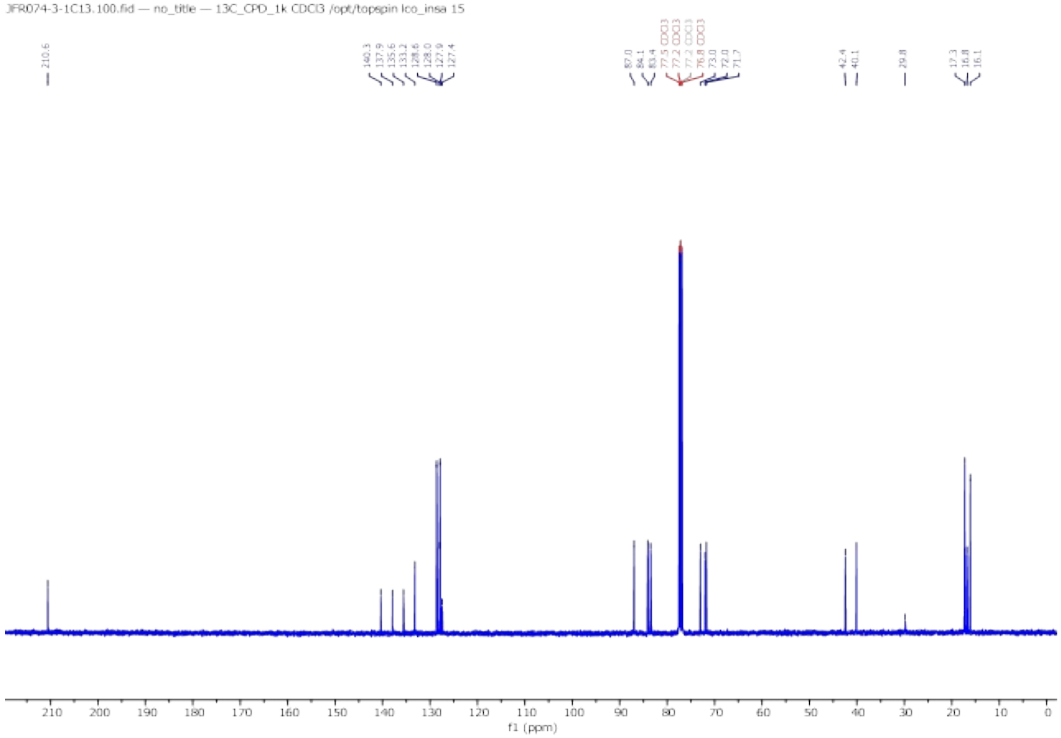
^{13}C NMR spectrum of (*3R*)-hexahydrofuro[3,2-*b*]furan-3-ol (75 MHz, $CDCl_3$)



^{1}H NMR spectrum of 2-((3*R*,6*S*)-6-(benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (2) (400 MHz, $CDCl_3$)

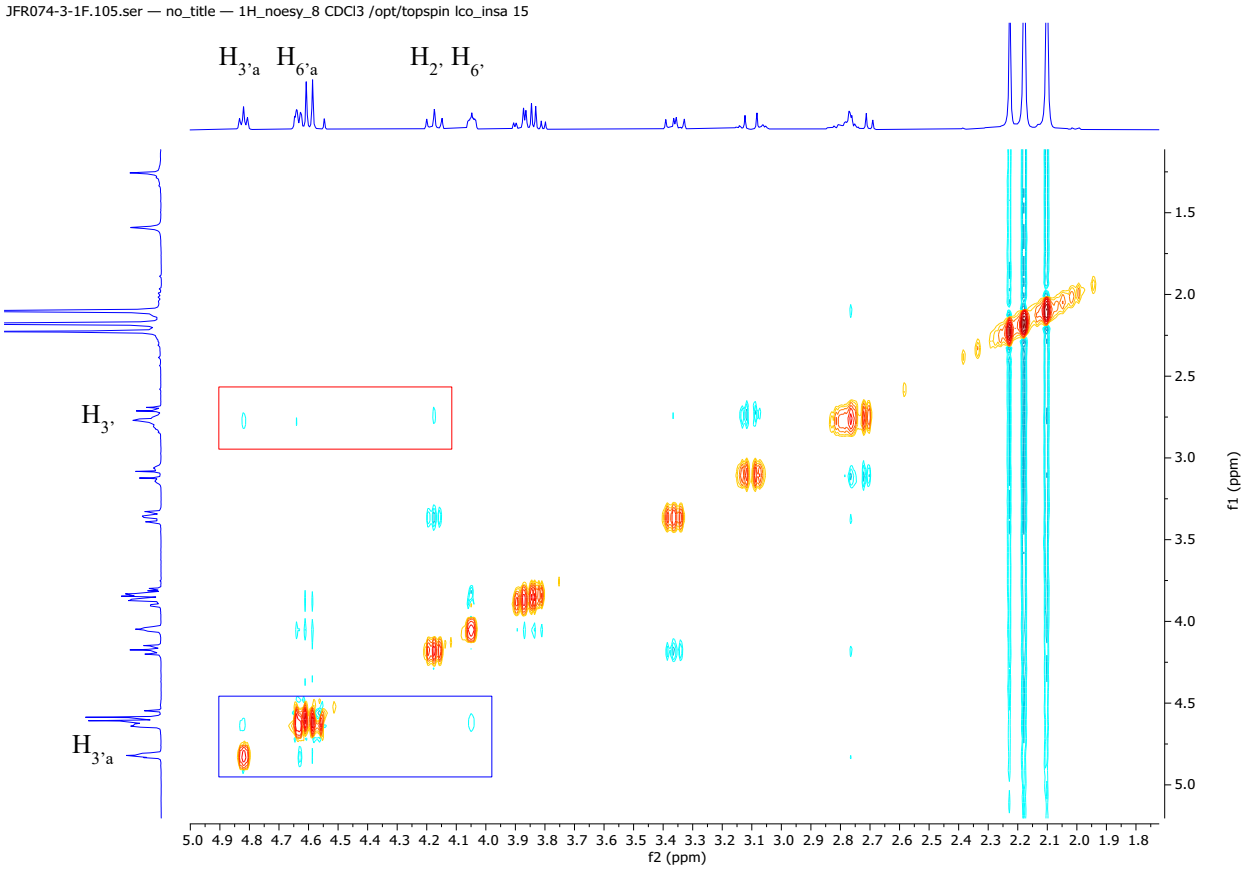


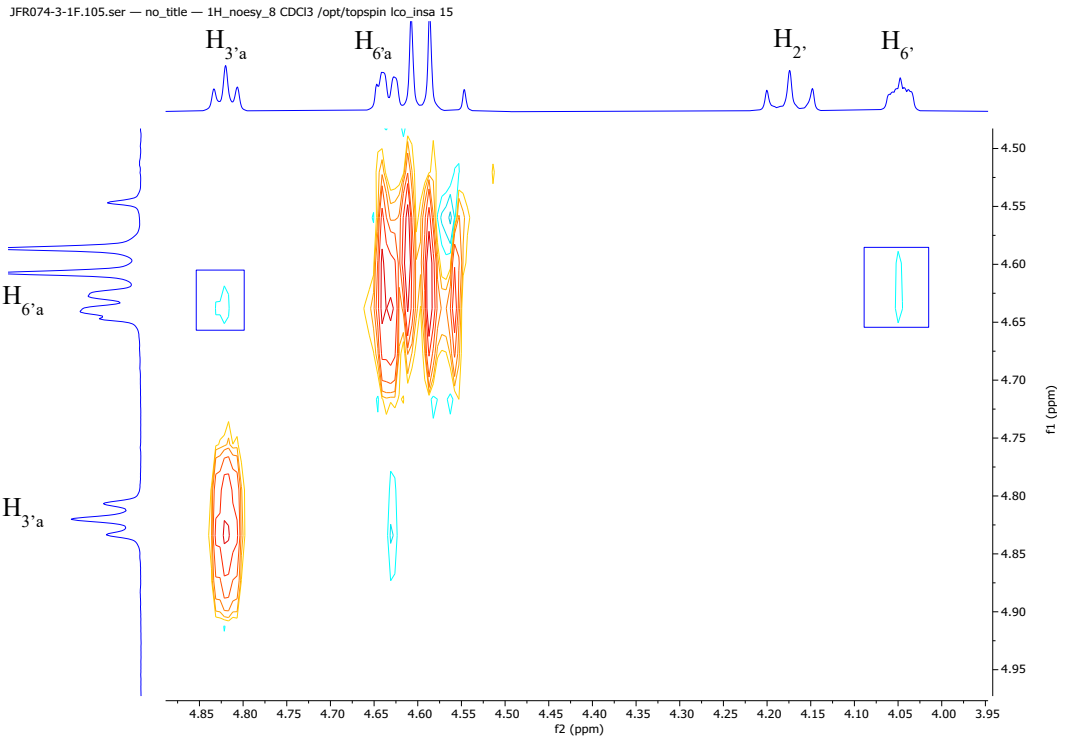
^{13}C NMR spectrum of 2-((3*R*,6*S*)-6-(benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (2) (101 MHz, $CDCl_3$)

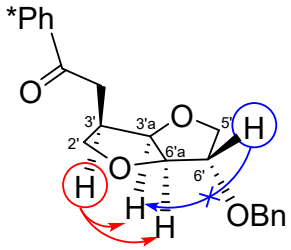


2-((3*R*,6*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (2) – S73

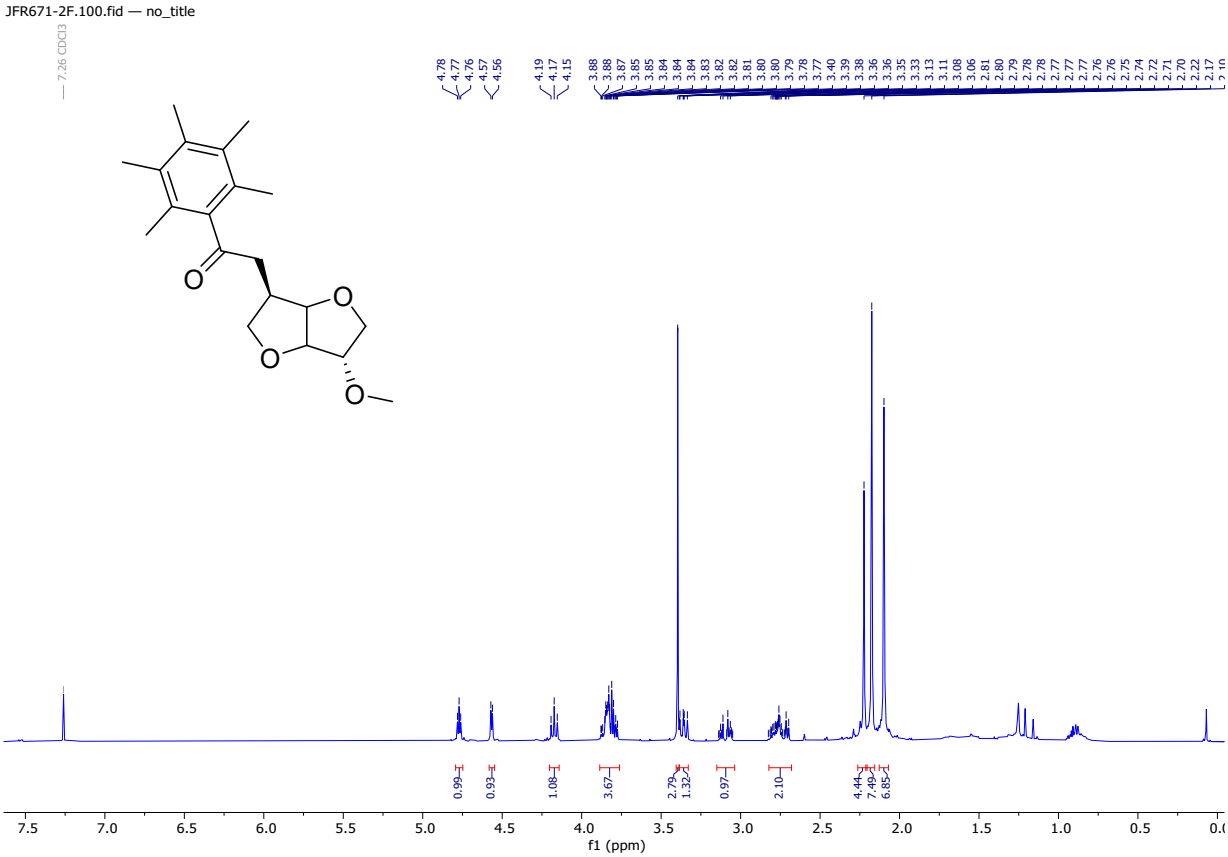
Determination of the absolute configuration of **2** by NOESY



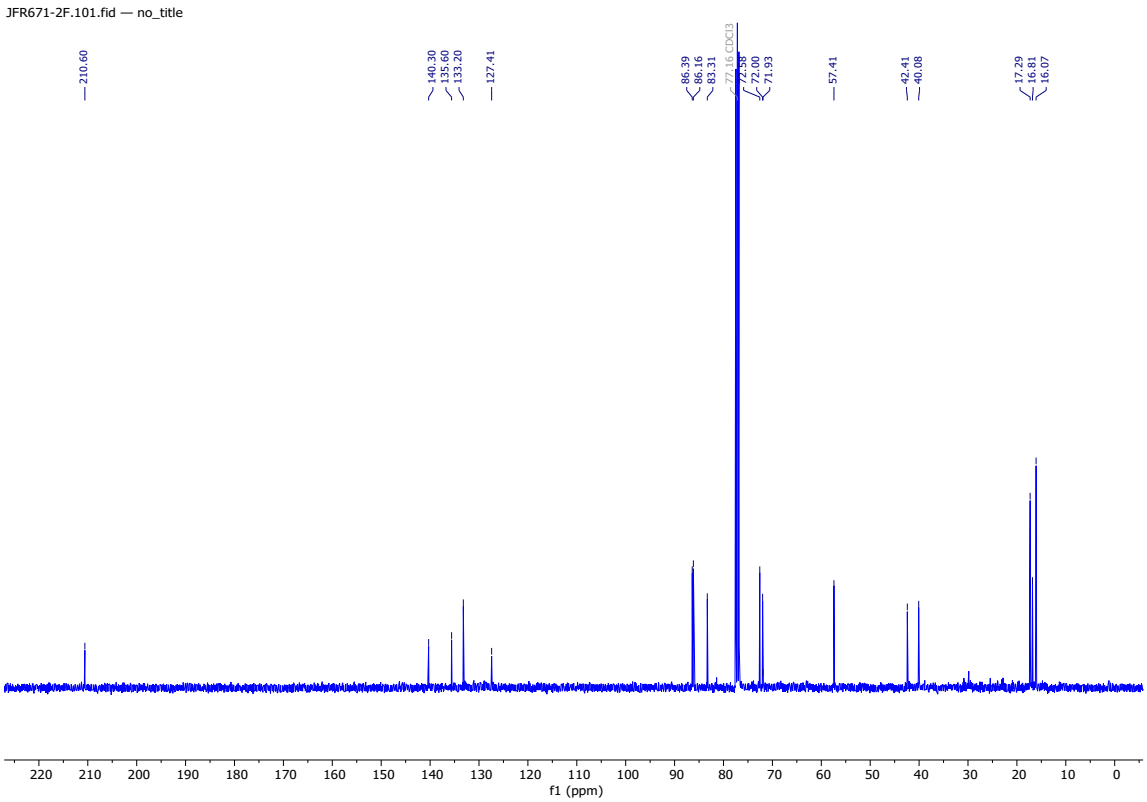




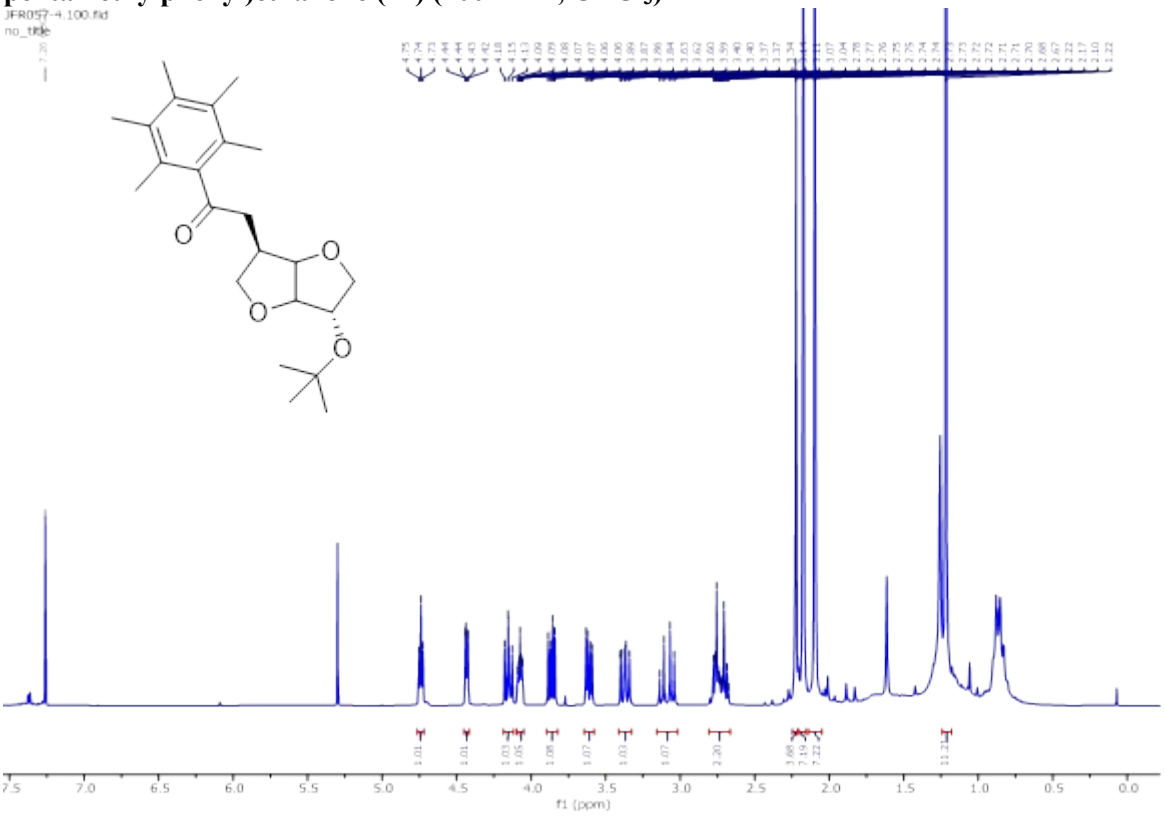
^{1}H NMR spectrum of 2-((3*R*,6*S*)-6-Methoxyhexahydrofuro[3,2-*b*]furan-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (10) (400 MHz, $CDCl_3$)



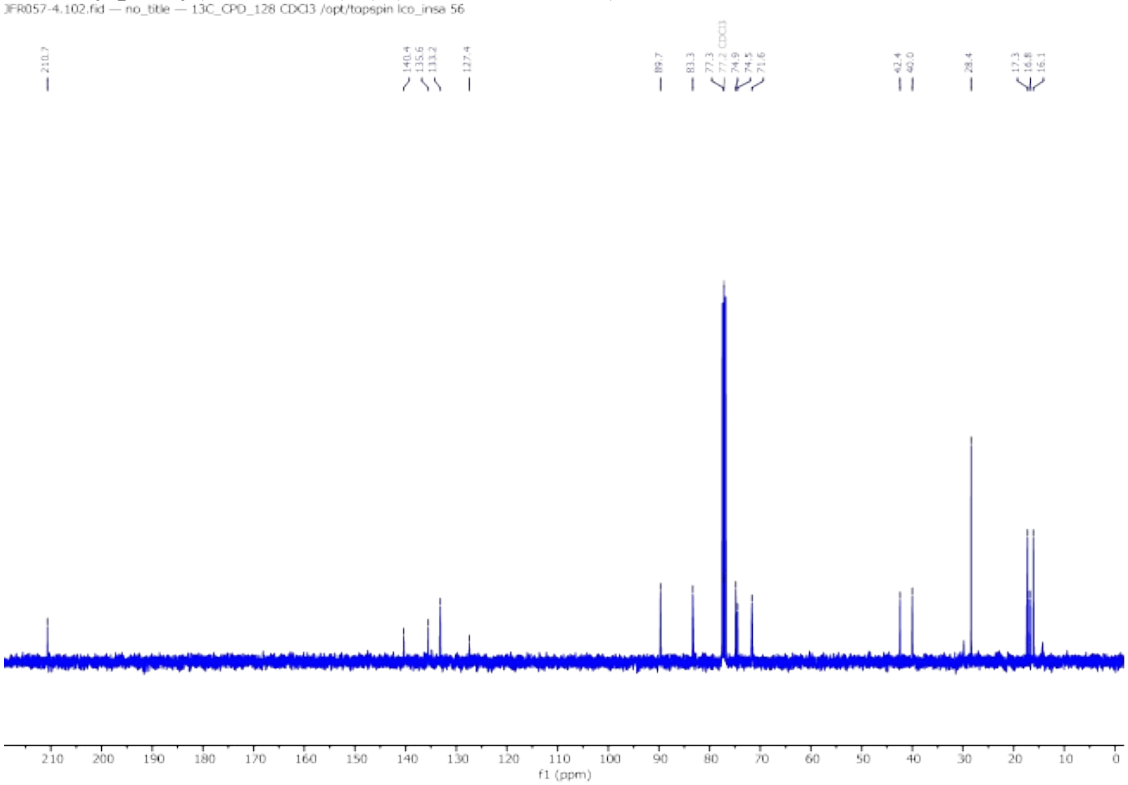
^{13}C NMR spectrum of 2-((3*R*,6*S*)-6-Methoxyhexahydrofuro[3,2-*b*]furan-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (10) (101 MHz, $CDCl_3$)



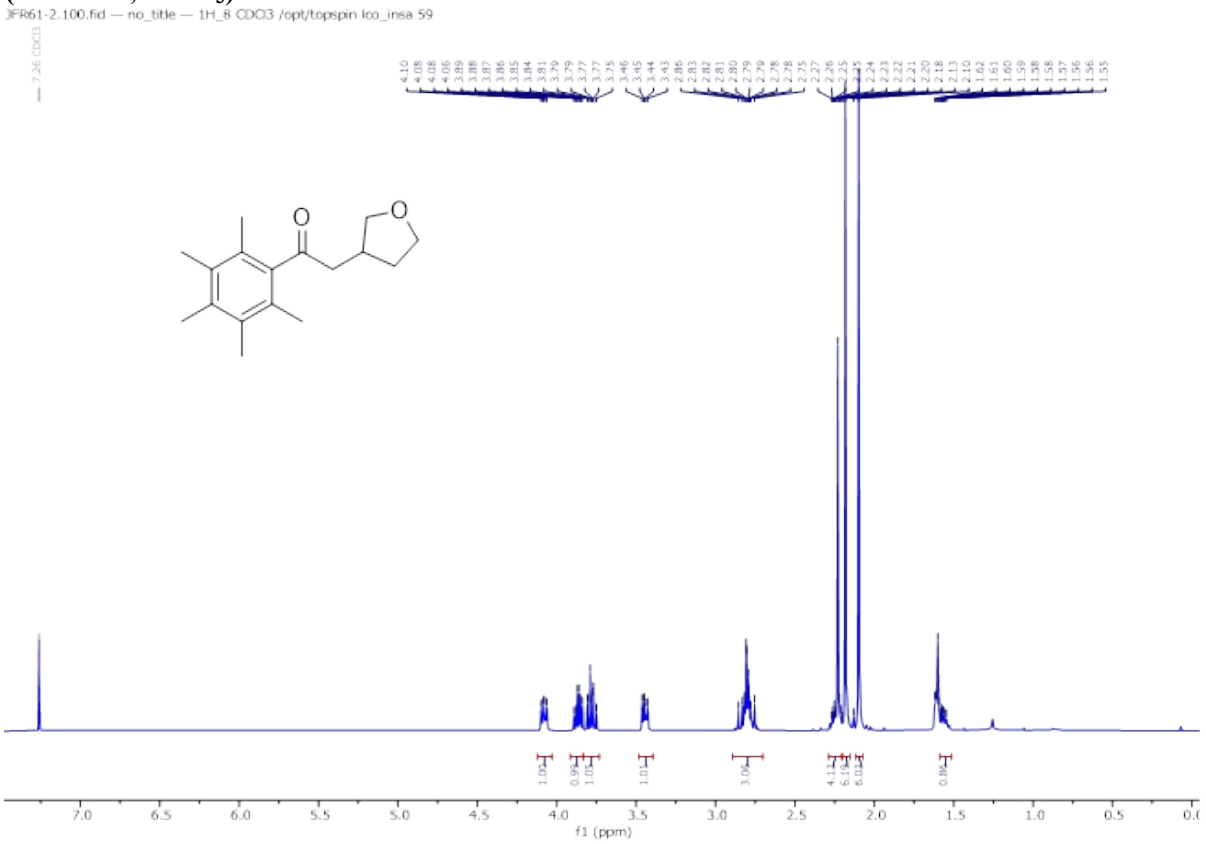
^{1}H NMR spectrum of 2-((3*R*,6*S*)-6-(*tert*-butoxy)hexahydrofuro[3,2-*b*]furan-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (12) (400 MHz, $CDCl_3$)



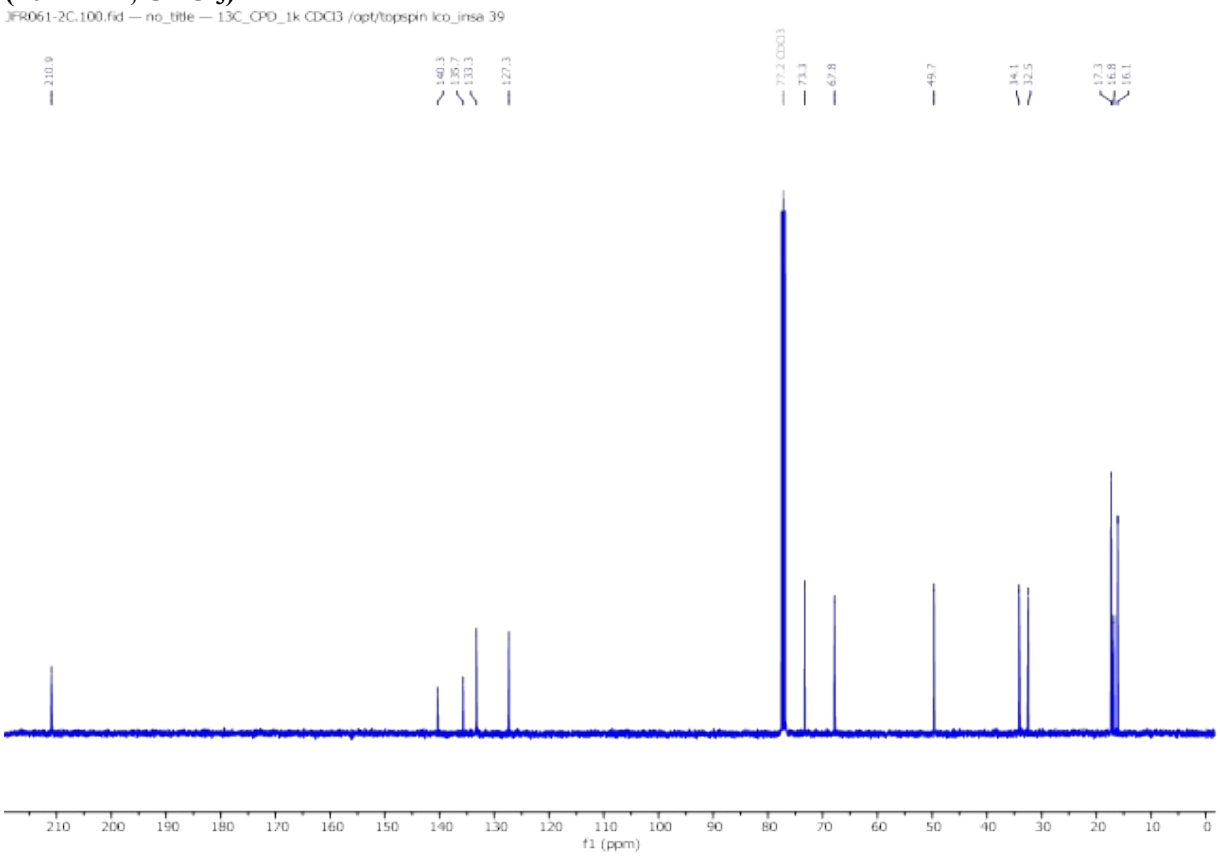
^{13}C NMR spectrum of 2-((3*R*,6*S*)-6-(*tert*-butoxy)hexahydrofuro[3,2-*b*]furan-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (12) (101 MHz, $CDCl_3$)



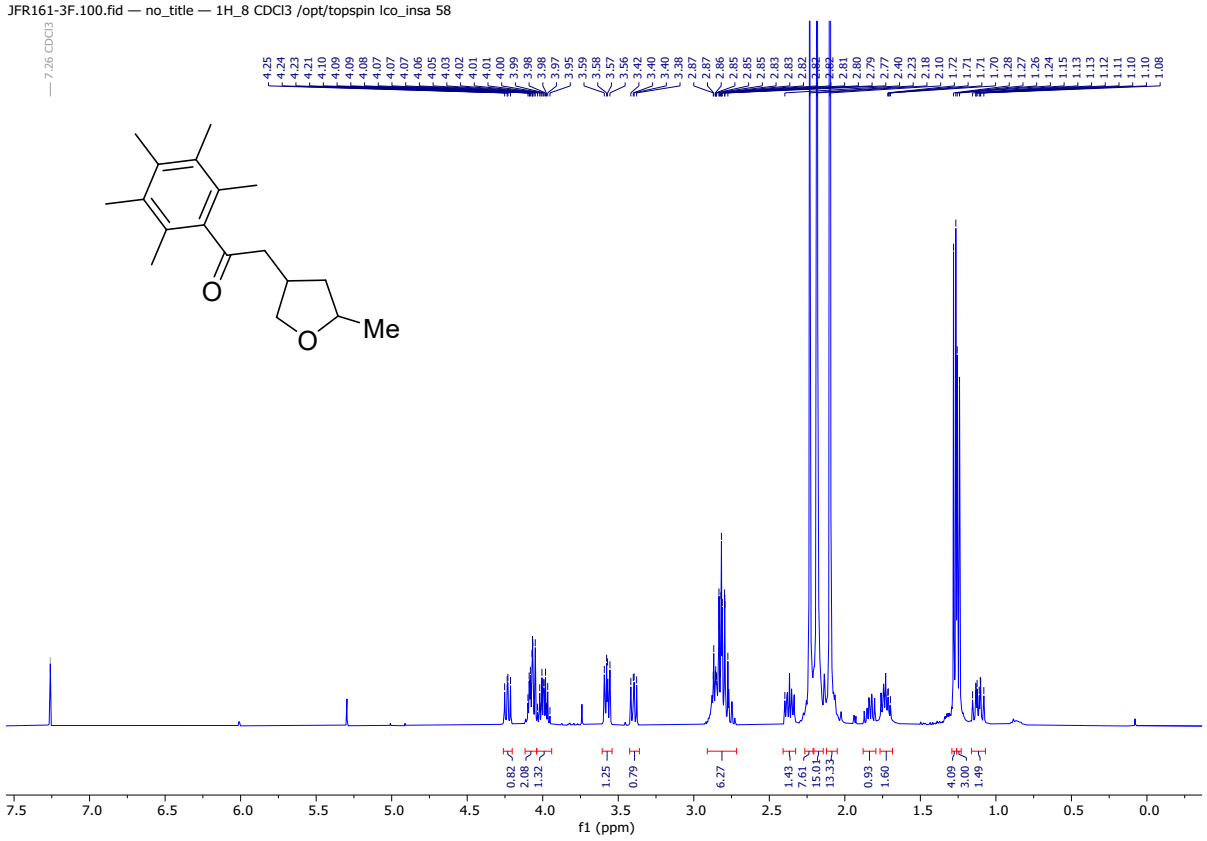
^{1}H NMR spectrum of 1-(2,3,4,5,6-pentamethylphenyl)-2-(tetrahydrofuran-3-yl)ethanone (13) (400 MHz, $CDCl_3$)



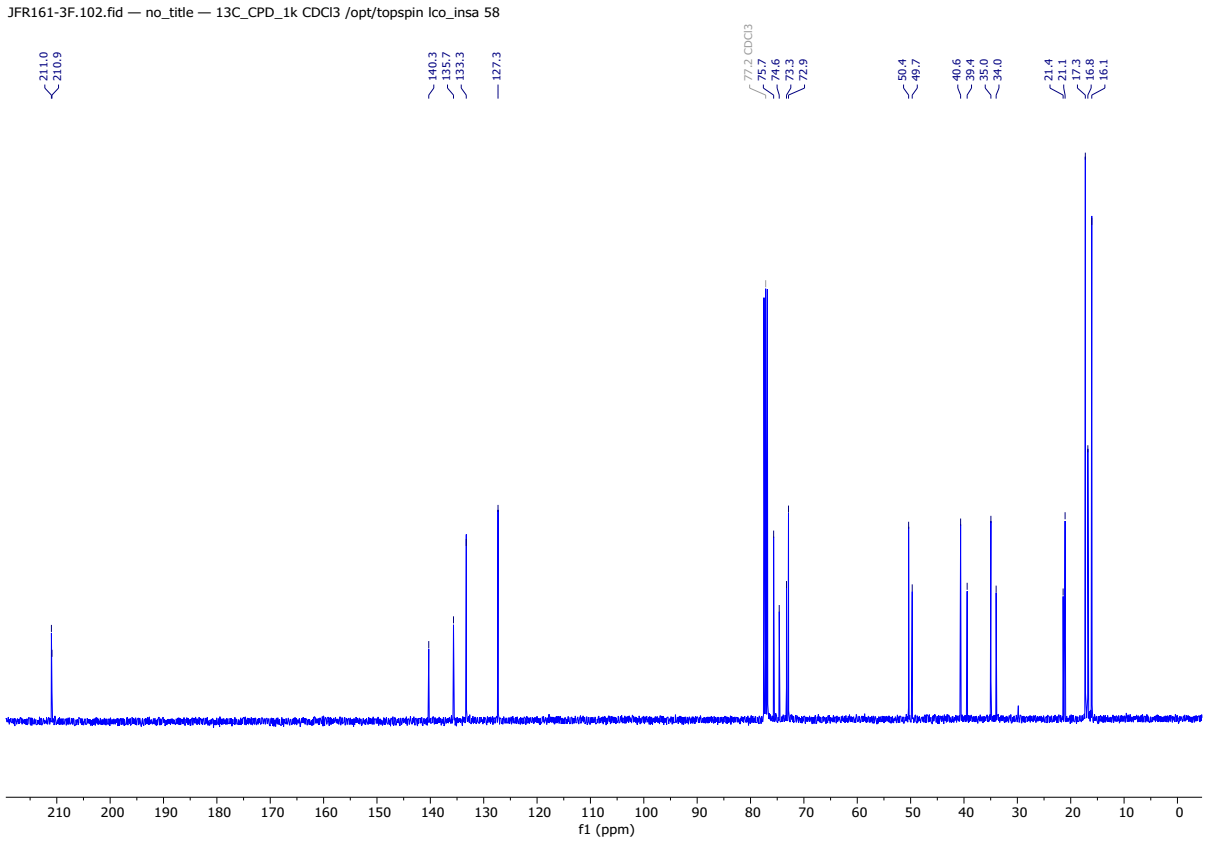
^{13}C NMR spectrum of 1-(2,3,4,5,6-pentamethylphenyl)-2-(tetrahydrofuran-3-yl)ethanone (13) (101 MHz, $CDCl_3$)



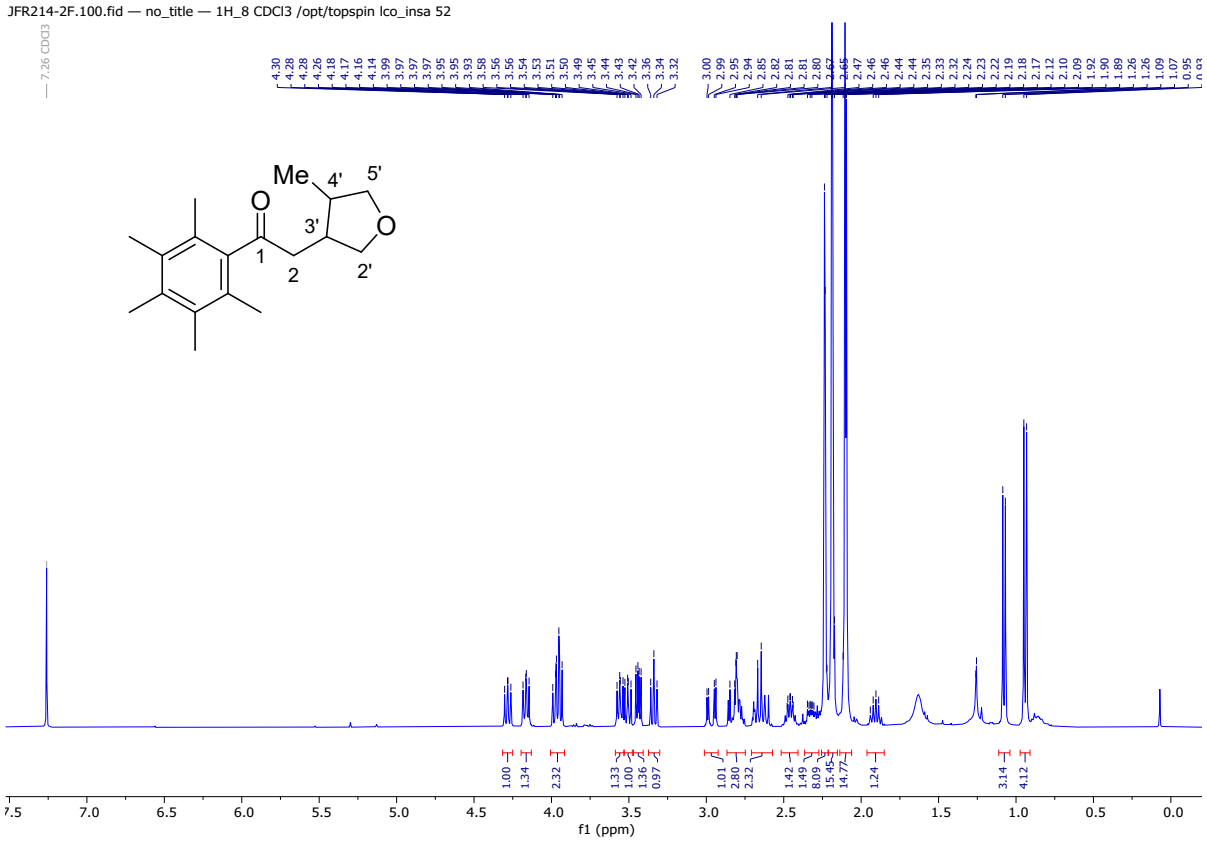
^{1}H NMR spectrum of 2-(5-methyltetrahydrofuran-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (14) (400 MHz, $CDCl_3$)



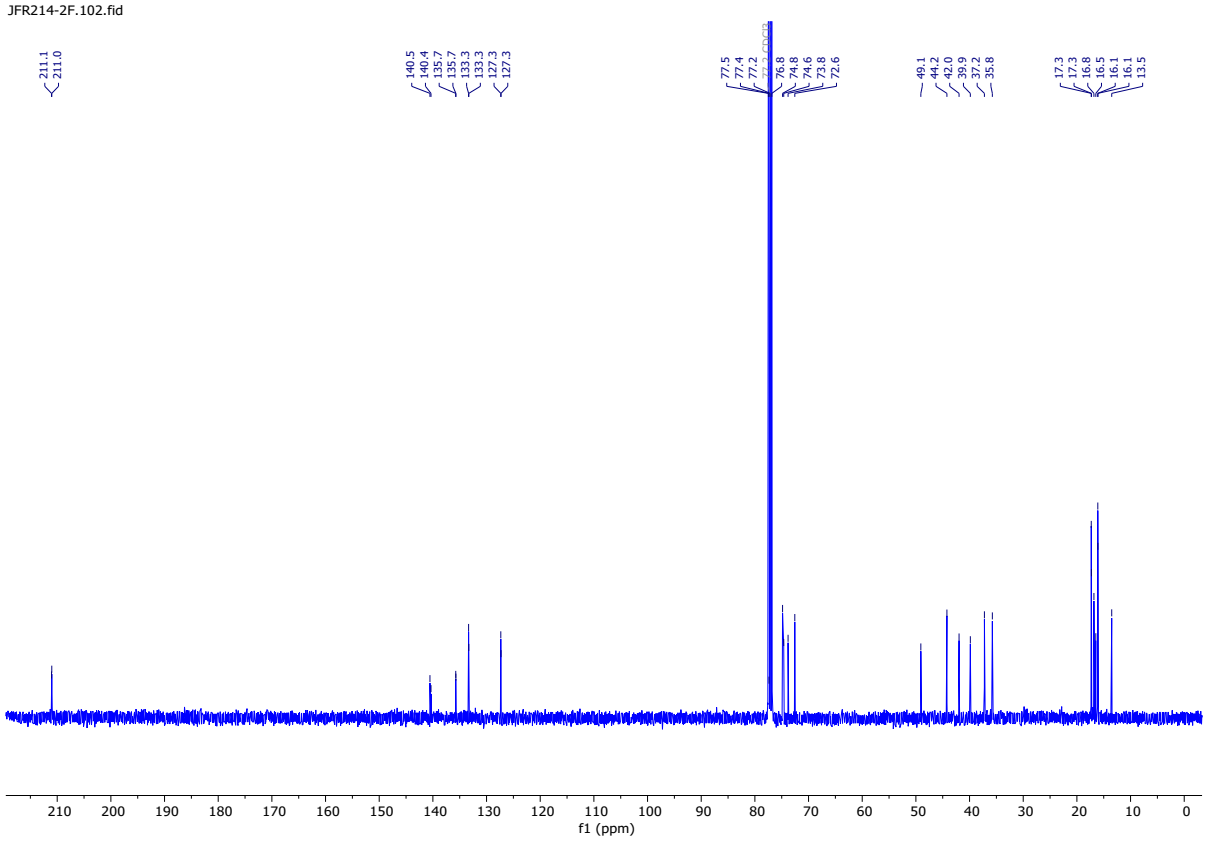
^{13}C NMR spectrum of 2-(5-methyltetrahydrofuran-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (14) (101 MHz, $CDCl_3$)



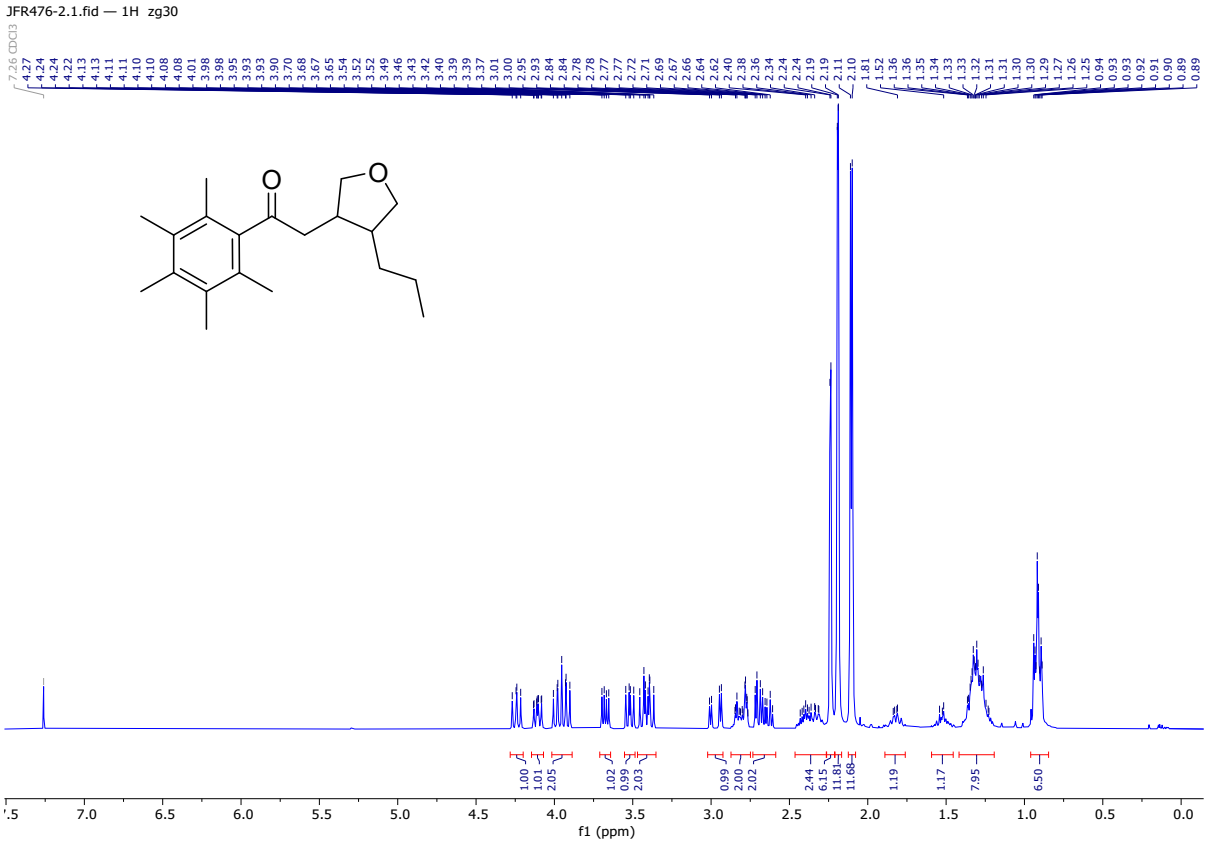
^{1}H NMR spectrum of 2-(4-methyltetrahydrofuran-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (15) (400 MHz, $CDCl_3$)



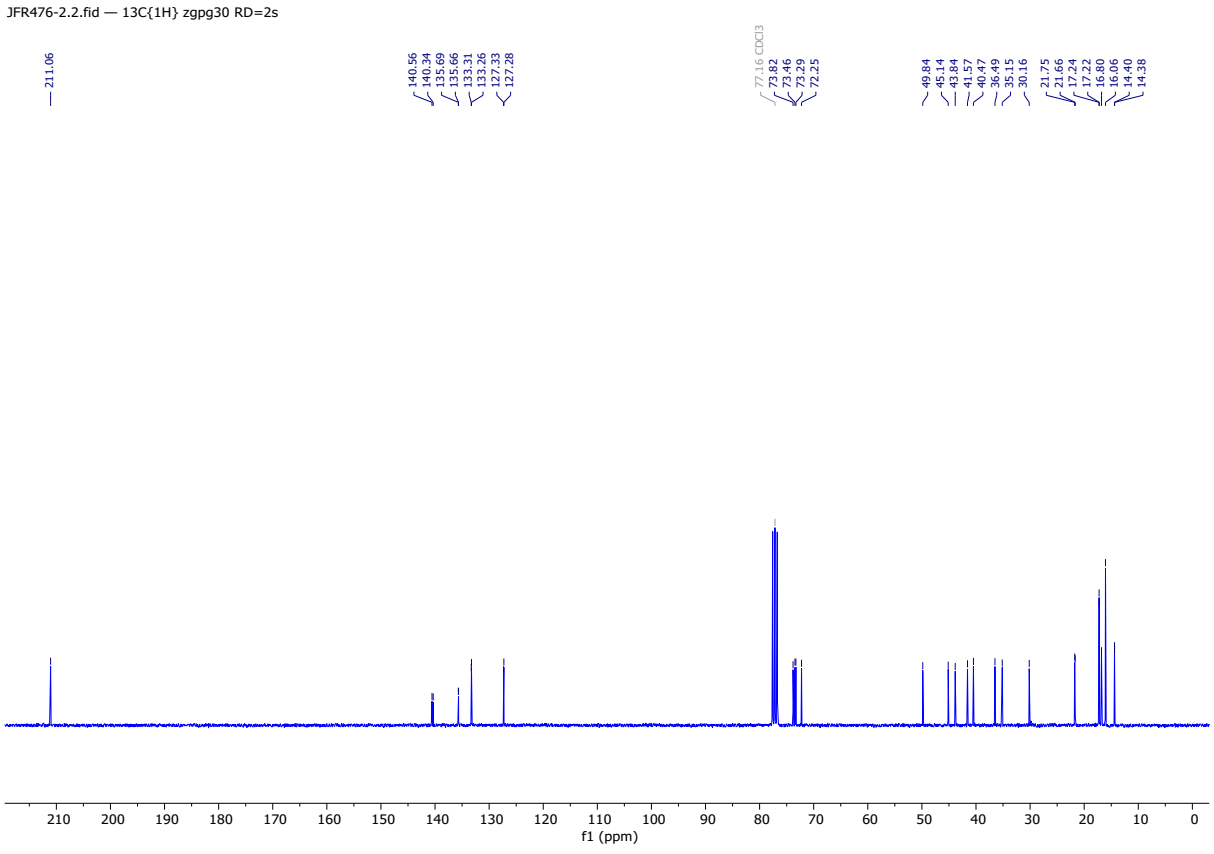
^{13}C NMR spectrum of 2-(4-methyltetrahydrofuran-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone 15 (101 MHz, $CDCl_3$)



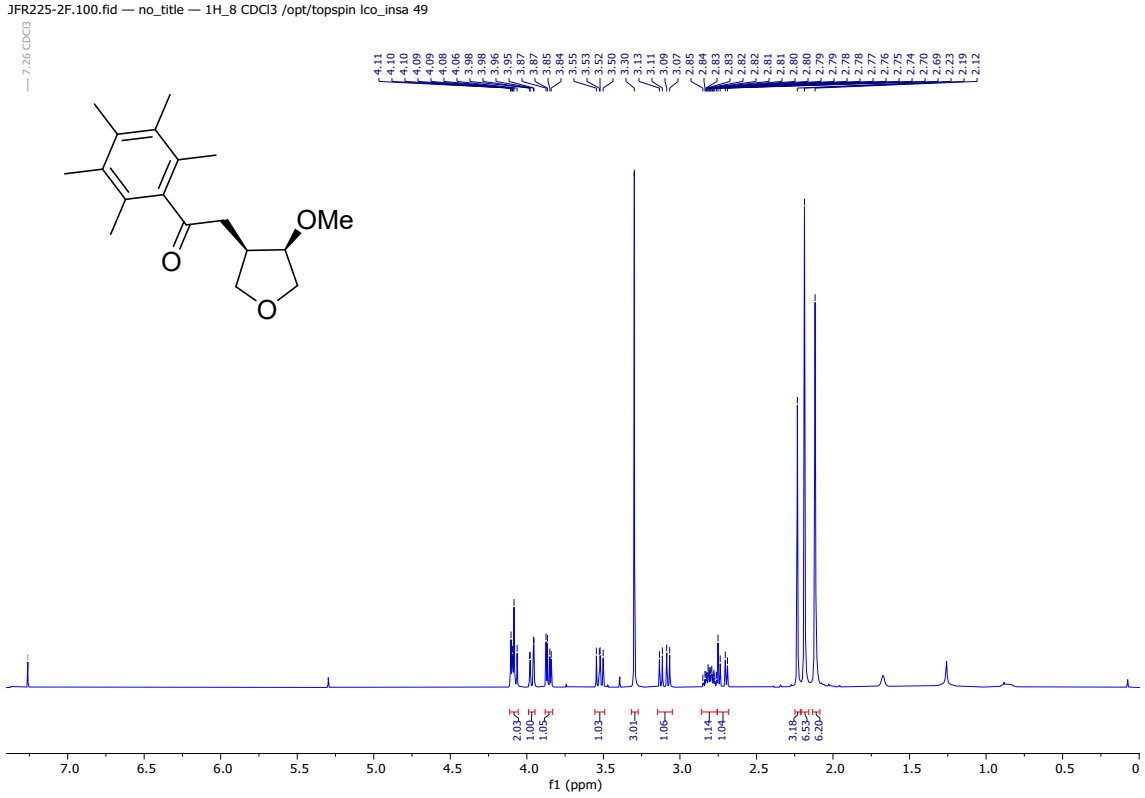
^{1}H NMR spectrum of 1-(2,3,4,5,6-pentamethylphenyl)-2-(4-propyltetrahydrofuran-3-yl)ethanone (16) (400 MHz, $CDCl_3$)

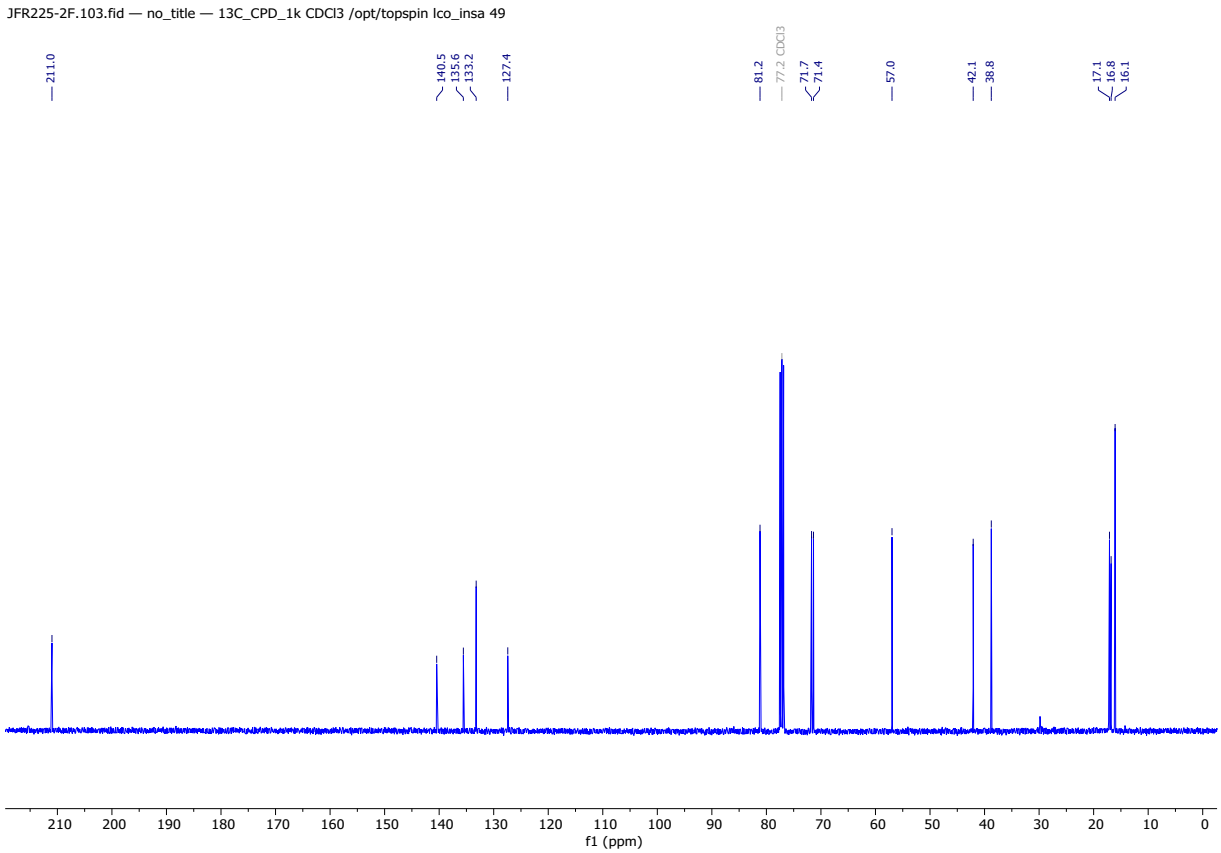


^{13}C NMR spectrum of 1-(2,3,4,5,6-pentamethylphenyl)-2-(4-propyltetrahydrofuran-3-yl)ethanone (16) (101 MHz, $CDCl_3$)



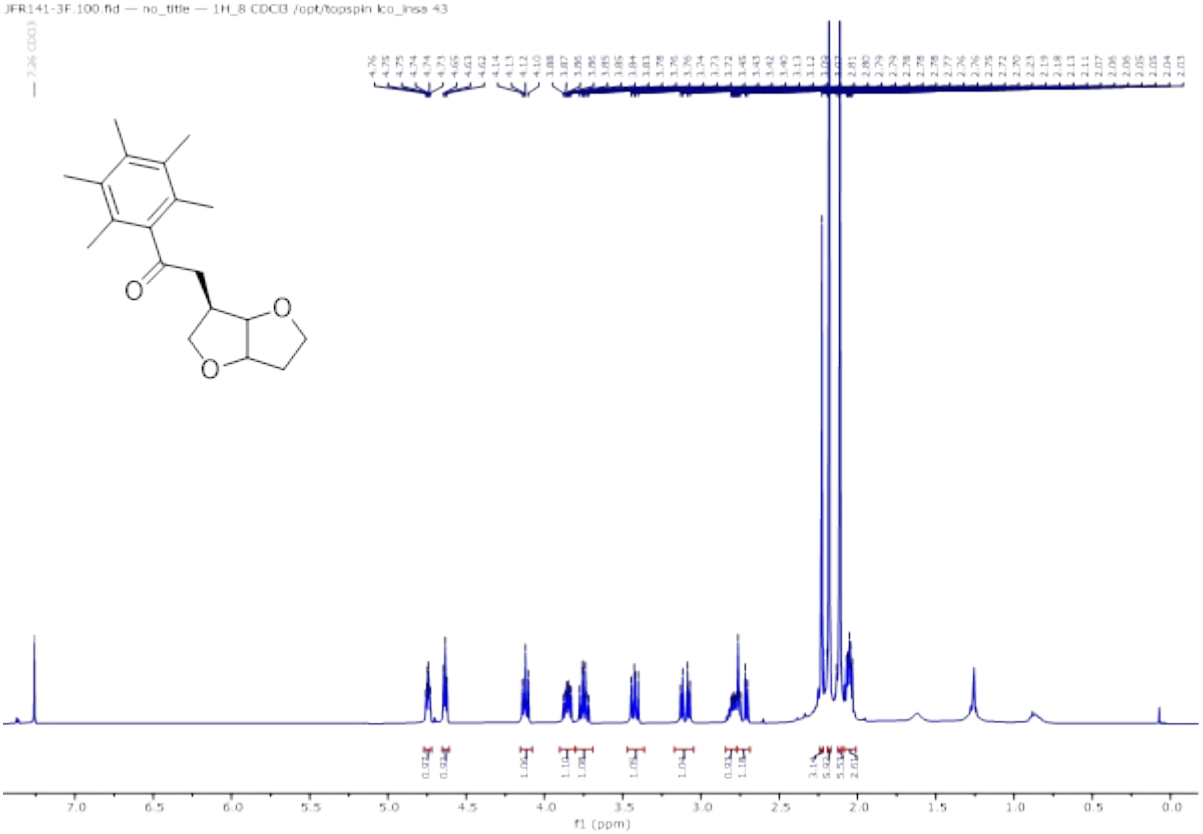
^{1}H NMR spectrum of 2-((3*R*,4*R*)-4-Methoxytetrahydrofuran-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (17) (400 MHz, $CDCl_3$)



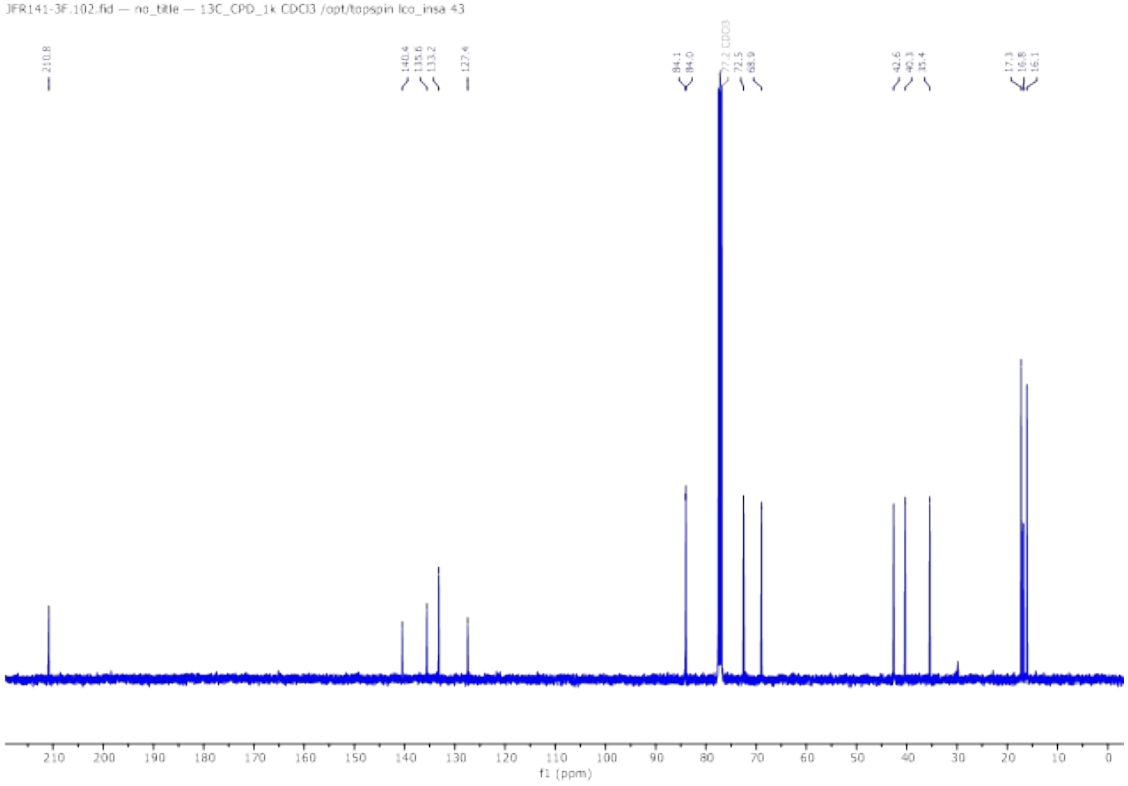


^{13}C NMR spectrum of 2-((3*R*,4*R*)-4-Methoxytetrahydrofuran-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (17) (101 MHz, $CDCl_3$)

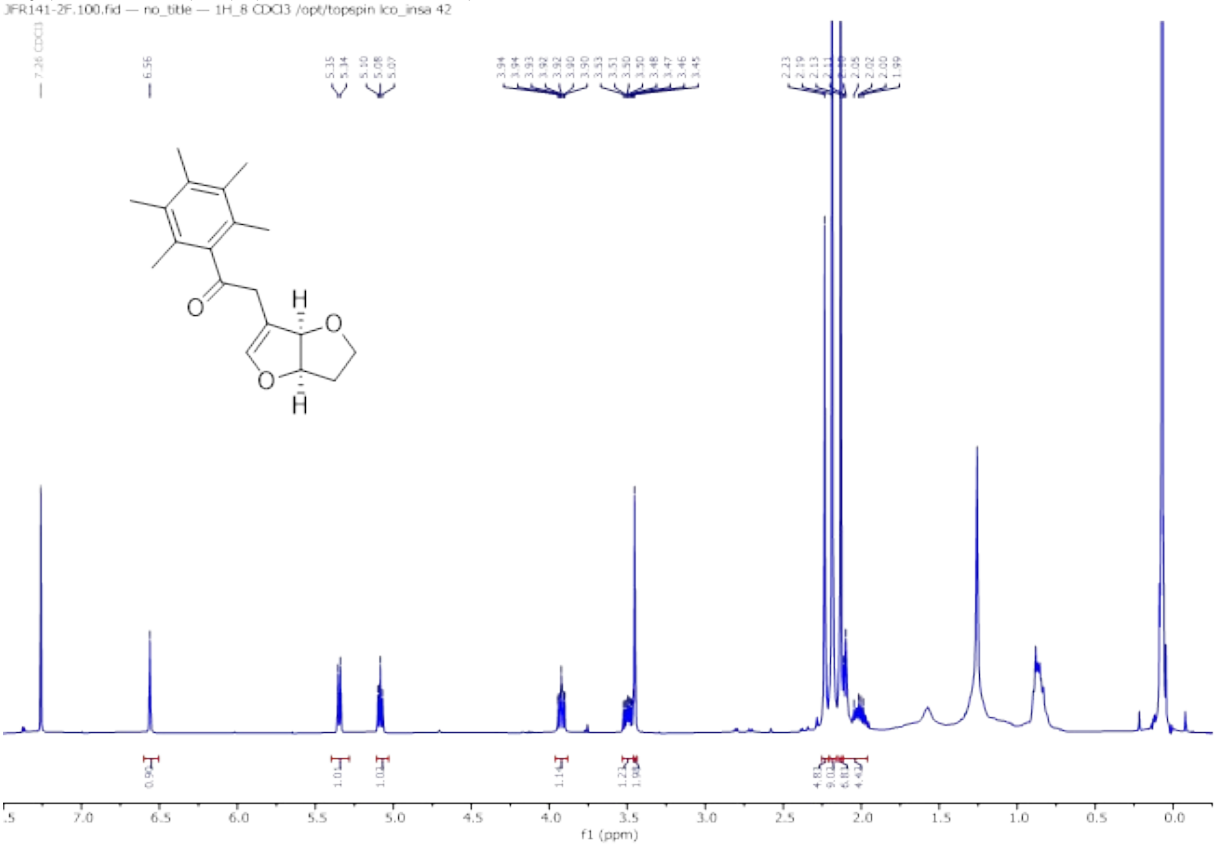
^{1}H NMR spectrum of 2-((3*R*)-hexahydrofuro[3,2-*b*]furan-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (18) (400 MHz, $CDCl_3$)



^{13}C NMR spectrum of 2-((3*R*)-hexahydrofuro[3,2-*b*]furan-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethanone (18) (101 MHz, $CDCl_3$)



^{1}H NMR spectrum of 1-(2,3,4,5,6-pentamethylphenyl)-2-(3a,5,6,6a-Tetrahydrofuro[3,2-*b*]furan-3-yl)ethanone (18') (400 MHz, $CDCl_3$)



^{13}C NMR spectrum of 1-(2,3,4,5,6-pentamethylphenyl)-2-(3a,5,6,6a-Tetrahydrofuro[3,2-*b*]furan-3-yl)ethanone (18') (101 MHz, $CDCl_3$)