Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Synthesis and pharmacological evaluation of arctigenin analogues as antagonists of AMPA and kainate receptors

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1. General Experimental Details

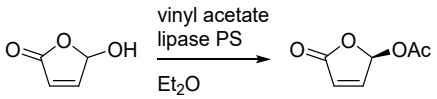
Unless otherwise noted, chemicals were purchased from commercial suppliers and were used without further purification. All moisture or air sensitive reactions were carried out in flame-dried glassware under a positive pressure of N_2 using syringe/septa techniques. Dry solvents (THF, DCM, Et_2O, CH_3CN, toluene) were obtained by passing through a modified Grubbs system of alumina columns, manufactured by Anhydrous Engineering. DMF was purchased as an anhydrous solvent from Acros Organics.

Column chromatography was performed on silica gel 60 from Sigma Aldrich (40-63 µm) and a suitable eluent. For thin layer chromatography (TLC) aluminium backed silica gel from Merck (silica gel 60, F254) with a suitable solvent system was used. Spots were visualised with UV light (254 nm) and/or developed with a potassium permanganate solution and heat.

Melting points were determined on an Electrothermal IA6301 melting point apparatus. Optical rotations were recorded on a Bellingham and Stanley ADP220 polarimeter at 20°C, irradiating with sodium D line (λ=589 nm) and $[\alpha]_D$ values are reported in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FTIR with an ATR accessory in the solid or liquid state. Only significant frequencies are reported in wavenumbers (cm^{-1}). ^1H and ^{13}C spectra were recorded in solutions on JNM-ECS 300, JNM-ECS 400, Varian

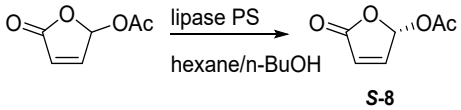
400, Bruker 400, Varian VNMR 500 or Bruker 500 Cryo spectrometers at ambient temperature unless otherwise indicated and were referenced to the residual solvent peaks. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are in Hertz (Hz). Coupling constants are rounded to the nearest half integer. DEPT-135, COSY, HSQC and HMBC NMR spectra were routinely used to definitively assign the signals of ^{1}H and ^{13}C NMR spectra. Electrospray (ESI) mass spectra were recorded on a VG Analytical Quattro mass spectrometer. Chiral SFC was performed using Diacel Chiralpak IA column (4.6 x 250 mm x 5 µm) or Whelk O-1 column (4.6 x 250 mm x 5 µm) on a Waters TharSFC system and monitored by DAD (Diode Array Detector).

The following compounds were prepared according to literature methods: (*RS*)-5-acetoxydihydrofuran-2-(5*H*)-one,[1] (*R*)-5-acetoxydihydrofuran-2-(5*H*)-one,[2] (*S*)-5-acetoxydihydrofuran-2-(5*H*)-one[3] and 4-toluenesulfonyl azide.[4] The resolution to give **8** was achieved as follows:



***R*-8**

Hydroxyfuranone (5.00 g, 50.0 mol) was dissolved in diethyl ether (750 ml) and vinyl acetate (115 ml, 1.25 mol) and immobilised lipase PS (30 w/w% on Celite, 5.00 g) were added.[2,3] The reaction mixture was stirred at room temperature and the conversion was determined by ^{1}H-NMR. When the reaction was finished (after ca. 2 days) the enzyme was filtered off and the solvent was evaporated. The crude product was purified by column chromatography (petroleum ether:EtOAc = 2:1) to give compound ***R*-8** as a colourless oil (5.48 g, 77%, 95:5 er). ν_{max} (neat)/cm^{-1} 3110, 1788, 1752, 1612; δ_H (300 MHz, $CDCl_3$) 2.16 (3H, s, CH_3), 6.31 (1H, dd, *J* 5.5, 1.5, 3-H), 6.99 (1H, *app* t, *J* 1.5, 5-H), 7.32 (1H, dd, *J* 5.5, 1.5, 4-H); δ_C (75 MHz, $CDCl_3$) 20.8 (CH_3), 93.9 (C-5), 125.4 (C-3), 149.8 (C-4), 169.0 (C=O), 169.7 (C=O). The enantiomeric excess was determined by SFC analysis on a chiral phase Whelk-01 column (50% isopropanol/hexane, 4 ml/min, 40 °C, 125 bar). The retention times of ***R*-8** and its enantiomer ***S*-8** are 2.95 and 2.58 minutes, respectively (see page 72). $[\alpha]_D$ -27 (*c* 1.0, $CHCl_3$), *lit.*[3b] $[\alpha]_D$ -23.2 (*c* 1.11, $CHCl_3$).

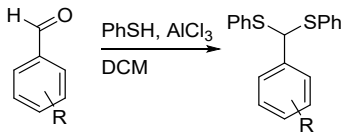


***S*-8**

Acetoxyfuranone (2.32 g, 16.3 mmol) was dissolved in hexane (300 ml) and *n*-BuOH (100 ml). Immobilised lipase PS (30 w/w% on Celite, 870 mg) was added and the reaction mixture was stirred at room temperature for 48 hours. When the conversion was over 50% (determined by ^{1}H-NMR) the enzyme was filtered off and the solvent was evaporated. The crude product was purified by column chromatography (petroleum ether:EtOAc = 2:1) to give compound ***S*-8** as a colourless oil (666 mg, 29%, 98:2 er.). The enantiomeric excess was determined by HPLC analysis on a chiral phase Chiralpak IC column (15% isopropanol/hexane, 0.75 ml/min, 210 nm) (see page 74). $[\alpha]_D$ +29 (*c* 1.0, $CHCl_3$), *lit.*[3a] $[\alpha]_D$ +25.4 (*c* 1.0, $CHCl_3$); Spectral data see above.

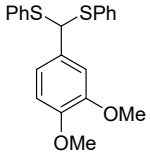
2 Synthetic procedures

General procedure A for the preparation of substituted (phenylmethylene)bis(phenylsulfanes)



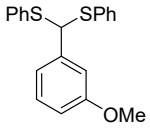
Thiophenol (2.5 equiv.) was added to a solution of the corresponding aldehyde (1 equiv.) in DCM (1.5 ml/mmol aldehyde) at room temperature under a nitrogen atmosphere, followed by the slow addition of $AlCl_3$ (0.3 equiv.). The solution turned immediately cloudy. After 10-15 minutes the reaction was finished and quenched with water. The two phases were separated and the aqueous phase was extracted with DCM and the combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. If possible, the crude product was recrystallised from EtOH.

9a [(3,4-Dimethoxyphenyl)methylene]-bis(phenylsulfane)



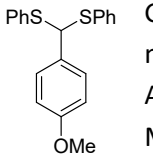
General procedure A gave compound **9a** as a white solid (3.50 g, 79%) starting from 4-methoxybenzaldehyde (2.00 g, 12.00 mmol) and thiophenol (3.00 ml, 3.32 g, 30.10 mmol). All spectral data were consistent with literature.[2] m.p. 66-68 °C (from EtOH), *lit.*[5] 68-69 °C; δ_H (400 MHz, $CDCl_3$) 3.81 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.41 (1H, s, $(PhS)_2CH$), 6.73 (1H, d, *J* 8.0, ArH), 6.87 (1H, dd, *J* 8.0, 2.0, ArH), 6.90 (1H, d, *J* 2.0, ArH), 7.21-7.29 (6H, m, ArH), 7.32-7.39 (4H, m, ArH); δ_C (100 MHz, $CDCl_3$) 56.0 (OCH_3), 60.2 ($(PhS)_2CH$), 110.8 (Ar-C), 110.9 (Ar-C), 120.4 (Ar-C), 127.9 (Ar-C), 129.0 (Ar-C), 132.2 (Ar-C), 132.7 (Ar-C), 134.7 (Ar-C), 148.8 (Ar-C), 148.9 (Ar-C).

9b [(3-Methoxyphenyl)methylene]-bis(phenylsulfane)



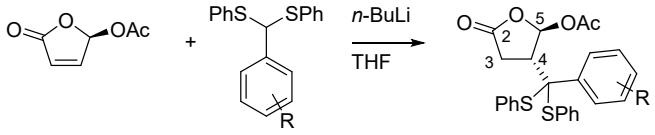
General procedure A gave compound **9b** as a yellow oil (2.44 g, 98%) starting from 3-methoxybenzaldehyde (0.89 ml, 1.00 g, 7.35 mmol) and thiophenol (1.88 ml, 2.02 g, 18.36 mmol). The product was used in the next step without further purification. All spectral data were consistent with literature.[6] δ_H (400 MHz, $CDCl_3$) 3.76 (3H, s, OCH_3), 5.41 (1H, s, $(PhS)_2CH$), 6.80 (1H, ddd, *J* 8.0, 2.5, 1.0, ArH), 6.93 (1H, t, *J* 2.5, ArH), 6.96 (1H, *app* dt, *J* 8.0, 1.0, ArH), 7.20 (1H, t, *J* 8.0, ArH), 7.24-7.31 (6H, m, ArH), 7.33-7.41 (4H, m, ArH); δ_C (100 MHz, $CDCl_3$) 55.4 (OCH_3), 60.5 ($(PhS)_2C$), 113.1 (Ar-C), 114.2 (Ar-C), 120.4 (Ar-C), 127.9 (Ar-C), 129.0 (Ar-C), 129.6 (Ar-C), 132.6 (Ar-C), 134.7 (Ar-C), 141.3 (Ar-C), 159.4 (Ar-C).

9c [(4-Methoxyphenyl)methylene]-bis(phenylsulfane)



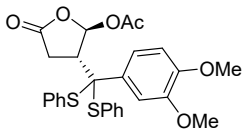
General procedure A gave compound **9c** as a white solid (2.27 g, 91%) starting from 4-methoxybenzaldehyde (0.89 ml, 1.00 g, 7.35 mmol) and thiophenol (1.88 ml, 2.02 g, 18.36 mmol). All spectral data were consistent with literature.[7] m.p. 79-81 °C (from EtOH), *lit.*[8] 79-80 °C; δ_H (400 MHz, $CDCl_3$) 3.79 (3H, s, OCH_3), 5.43 (1H, s, $(PhS)_2CH$), 6.81 (2H, d, *J* 9.0, ArH), 7.19-7.40 (12H, m, ArH); δ_C (100 MHz, $CDCl_3$) 55.4 (OCH_3), 59.9 ($(PhS)_2CH$), 113.9 (Ar-C), 127.8 (Ar-C), 128.9 (Ar-C), 129.2 (Ar-C), 131.8 (Ar-C), 132.5 (Ar-C), 134.9 (Ar-C), 159.4 (Ar-C).

General procedure B for the conjugate addition of thioacetals to 5-acetoxyfuran-2-(5H)-one



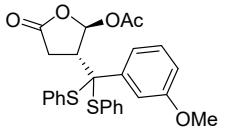
n-BuLi (1.2 equiv.) was added dropwise to a solution of the appropriate thioacetal in dry THF (3.5 ml/mmol thioacetal) at -78 °C under a nitrogen atmosphere. If necessary, the reaction mixture was allowed to warm to -20 °C to complete deprotonation. Then, a solution of (*R*)-5-acetoxydihydrofuran-2-(5*H*)-one **8** (1 equiv.) in dry THF (1 mL/mmol furanone) was added dropwise at -78 °C and the reaction mixture was stirred for 2 hours at the same temperature. The reaction was quenched with 1M HCl and extracted with DCM. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography.

10a (4*R*,5*R*)-5-Acetoxy-4-[(3,4-dimethoxyphenyl)-bis(phenylthio)methyl]dihydrofuran-2(3*H*)-one



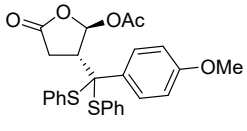
General procedure B gave compound **10a** as a yellow oil (2.03 g, 56%) starting from (*R*)-5-acetoxydihydrofuran-2-(5*H*)-one (1.00 g, 7.04 mmol) and thioacetal **9a** (2.85 g, 7.74 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 4:1). All spectral data were consistent with literature.[2] $[\alpha]_D$ -11 (*c* 1.0, $CHCl_3$), *lit.*[2] $[\alpha]_D$ -15 (*c* 1.13, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.07 (3H, s, CH_3), 2.86 (1H, dd, *J* 19.0, 10.0, 3-*H*H), 2.98 (1H, dd, *J* 19.0, 3.5, 3-H*H*), 3.11 (1H, ddd, *J* 10.0, 3.5, 1.5, 4-H), 3.77 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.74 (1H, d, *J* 8.5, ArH), 6.88 (1H, d, *J* 1.5, 5-H), 7.01 (1H, dd, *J* 8.5, 2.5, ArH), 7.20-7.41 (11H, m, ArH); δ_C (100 MHz, $CDCl_3$) 21.0 (CH_3), 31.7 (C-3), 49.3 (C-4), 56.0 (OCH_3), 56.1 (OCH_3), 70.8 ($(PhS)_2C$), 96.3 (C-5), 110.4 (Ar-C), 113.3 (Ar-C), 120.9 (Ar-C), 128.96 (Ar-C), 129.01 (Ar-C), 129.38 (Ar-C), 129.39 (Ar-C), 131.0 (Ar-C), 135.3 (Ar-C), 135.4 (Ar-C), 148.8 (Ar-C), 149.2 (Ar-C), 168.6 (C=O), 174.1 (C=O).

10b (4*R*,5*R*)-5-Acetoxy-4-[(3-methoxyphenyl)-bis(phenylthio)methyl]dihydrofuran-2(3*H*)-one



General procedure B gave compound **10b** as a yellow oil (907 mg, 54%) starting from (*R*)-5-acetoxydihydrofuran-2-(5*H*)-one (500 mg, 3.52 mmol) and thioacetal **9b** (1.31 g, 3.87 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 4:1). $[\alpha]_D$ -16 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3058, 2938, 2836, 1796, 1759, 1597; δ_H (400 MHz, $CDCl_3$) 2.07 (3H, s, CH_3), 2.86 (1H, dd, *J* 19.0, 10.0, 3-*H*H), 2.96 (1H, dd, *J* 19.0, 4.0, 3-H*H*), 3.15 (1H, ddd, *J* 10.0, 4.0, 1.5, 4-H), 3.74 (3H, s, OCH_3), 6.83 (1H, ddd, *J* 7.5, 2.5, 1.5, ArH), 6.87 (1H, d, *J* 1.5, 5-H), 7.16-7.37 (11H, m, ArH), 7.37-7.43 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 21.0 (CH_3), 31.6 (C-3), 49.3 (C-4), 55.5 (OCH_3), 70.5 ($(PhS)_2C$), 96.2 (C-5), 114.2 (Ar-C), 115.5 (Ar-C), 121.2 (Ar-C), 128.93 (Ar-C), 128.9 (Ar-C), 129.4 (Ar-C), 129.5 (Ar-C), 129.6 (Ar-C), 130.7 (Ar-C), 130.8 (Ar-C), 135.4 (Ar-C), 135.5 (Ar-C), 139.5 (Ar-C), 159.7 (Ar-C), 168.6 (C=O), 174.2 (C=O); Found (ESI) 503.0955 $[MNa]^+$, (required $C_{26}H_{24}NaO_5S_2$ 503.0957).

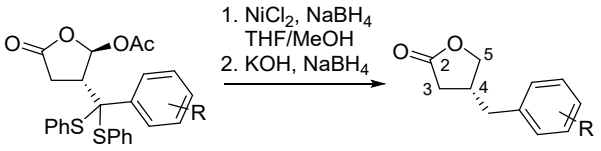
10c (4*R*,5*R*)-5-Acetoxy-4-[(4-methoxyphenyl)-bis(phenylthio)methyl]dihydrofuran-2(3H)-one



General procedure B gave compound **10c** as a yellow oil (1.00 g, 60%) starting from (*R*)-5-acetoxydihydrofuran-2-(5*H*)-one (500 mg, 3.52 mmol) and thioacetal **9c** (1.31 g, 3.87 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 4:1). $[\alpha]_D$ -18 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 2933, 2838, 1796, 1760, 1605; δ_H (400 MHz, $CDCl_3$) 2.06 (3H, s, CH_3), 2.84 (1H, dd, *J* 19.0, 10.0, 3-*H*H), 2.94 (1H, dd, *J* 19.0, 3.5, 3-H*H*), 3.08 (1H, ddd, *J* 10.0, 3.5, 1.5, 4-H), 3.81 (3H, s, OCH_3), 6.83 (2H, d, *J* 9.0, ArH), 6.86 (1H, d, *J* 1.5, 5-H), 7.19-7.34 (8H, m, ArH), 7.37-7.43 (2H, m, ArH), 7.59 (2H, d, *J* 9.0, ArH); δ_C (100 MHz, $CDCl_3$) 21.0 (CH_3), 31.5 (C-3), 49.3 (C-4), 55.5

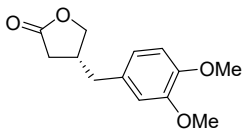
(OCH_3), 70.6 ($(PhS)_2C$), 96.2 (C-5), 114.0 (Ar-C), 128.9 (Ar-C), 129.0 (Ar-C), 129.3 (Ar-C), 129.4 (Ar-C), 130.5 (Ar-C), 130.9 (Ar-C), 131.0 (Ar-C), 135.3 (Ar-C), 135.4 (Ar-C), 159.6 (Ar-C), 168.6 (C=O), 174.2 (C=O); Found (ESI) 503.0955 $[MNa]^+$, (required $C_{26}H_{24}NaO_5S_2$ 503.0957).

General procedure C for the preparation of substituted 4-benzyl-furan-2(3*H*)-ones



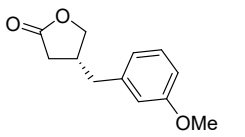
$NiCl_2$ (5 equiv.) was added to a solution of furanone (1 equiv.) in THF/MeOH (11 ml, 10:1, 25 ml/mmol furanone) and the solution was cooled to 0 °C. $NaBH_4$ (20 equiv.) was added portionwise so that the temperature did not exceed 10 °C. The reaction mixture turned black immediately. When the addition of $NaBH_4$ was finished, the reaction mixture was basified with 2M KOH to a pH of ~8 (approx. 2 equiv.) and more $NaBH_4$ (35 mg, 0.938 mmol) was added. The reaction was stirred at room temperature for 3 hours. The black precipitate was removed by filtration over celite and the solvent was evaporated. 1M HCl was added and the aqueous phase was extracted with DCM. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography.

11a (*R*)-4-(3,4-Dimethoxybenzyl)-dihydrofuran-2(3*H*)-one



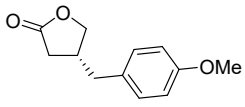
General procedure C gave compound **11a** as a yellow oil (552 mg, 62%) starting from compound **10a** (1.93 g, 3.78 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 4:1). All spectral data were consistent with literature.[2] $[\alpha]_D$ +4 (*c* 1.0, $CHCl_3$), *lit.*[2] $[\alpha]_D$ +8.3 (*c* 1.33, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.27 (1H, dd, *J* 17.5, 7.0, 3-*H*H), 2.59 (1H, dd, *J* 17.5, 8.0, 3-H*H*), 2.64-2.76 (2H, m, CH_2Ar), 2.76-2.88 (1H, m, 4-H), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.02 (1H, dd, *J* 9.0, 6.0, 5-*H*H), 4.32 (1H, dd, *J* 9.0, 7.0, 5-H*H*), 6.65 (1H, d, *J* 2.0, ArH), 6.68 (1H, dd, *J* 8.0, 2.0, ArH), 6.80 (1H, d, *J* 8.0, ArH); δ_C (100 MHz, $CDCl_3$) 34.3 (C-3), 37.4 (C-4), 38.7 (*C*H_2Ar), 55.99 (OCH_3), 56.02 (OCH_3), 72.7 (C-5), 111.5 (Ar-C), 111.9 (Ar-C), 120.7 (Ar-C), 130.9 (Ar-C), 148.0 (Ar-C), 149.2 (Ar-C), 177.0 (C-2).

11b (*R*)-4-(3-Methoxybenzyl)-dihydrofuran-2(3*H*)-one



General procedure C gave compound **11b** as a yellow oil (133 mg, 49%) starting from compound **10b** (630 mg, 1.31 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 4:1). All spectral data were consistent with literature.[9] $[\alpha]_D$ +5 (*c* 1.0, $CHCl_3$), *lit.*[9] $[\alpha]_D$ +6.4 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.29 (1H, dd, *J* 17.5, 7.0, 3-*H*H), 2.61 (1H, dd, *J* 17.5, 8.0, 3-H*H*), 2.69-2.78 (2H, m, CH_2Ar), 2.79-2.92 (1H, m, 4-H), 3.80 (3H, s, OCH_3), 4.04 (1H, dd, *J* 9.0, 6.0, 5-*H*H), 4.34 (1H, dd, *J* 9.0, 7.0, 5-H*H*), 6.69 (1H, t, *J* 2.0, ArH), 6.72-6.81 (2H, m, ArH), 7.20-7.26 (1H, m, ArH); δ_C (100 MHz, $CDCl_3$) 34.4 (C-3), 37.2 (C-4), 39.1 (*C*H_2Ar), 55.3 (OCH_3), 72.8 (C-5), 112.0 (Ar-C), 114.8 (Ar-C), 121.1 (Ar-C), 129.9 (Ar-C), 139.9 (Ar-C), 160.0 (Ar-C), 176.9 (C-2).

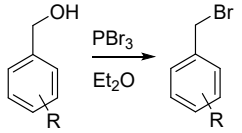
11c (*R*)-4-(4-Methoxybenzyl)-dihydrofuran-2(3*H*)-one



General procedure C gave compound **11c** as a yellow oil (222 mg, 54%) starting from compound **10c** (950 mg, 1.98 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 4:1). All spectral data were consistent with literature.[10] $[\alpha]_D$ +2 (*c* 1.0, $CHCl_3$), *lit.*[9] $[\alpha]_D$ +5.4 (*c* 6.8, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.28 (1H, dd, *J* 17.5, 7.0, 3-*H*H), 2.59 (1H, dd, *J* 17.5, 8.0, 3-H*H*), 2.66-2.75 (2H, m, CH_2Ar), 2.75-2.87 (1H, m, 4-H),

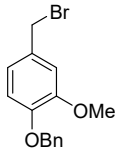
3.79 (3H, s, OCH_3), 4.02 (1H, dd, *J* 9.0, 6.0, 5-*H*H), 4.32 (1H, dd, *J* 9.0, 7.0, 5-H*H*), 6.85 (2H, d, *J* 8.5, ArH), 7.07 (2H, d, *J* 8.5, ArH); δ_C (100 MHz, $CDCl_3$) 34.3 (C-3), 37.5 (C-4), 38.2 (*C*H_2Ar), 55.4 (OCH_3), 72.8 (C-5), 114.3 (Ar-C), 129.8 (Ar-C), 130.3 (Ar-C), 158.6 (Ar-C), 177.0 (C-2).

General procedure D for the preparation of substituted benzylbromides



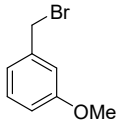
PBr_3 (2 equiv.) was added dropwise to a solution of benzyl alcohol (1 equiv.) in dry Et_2O (2.5 ml/mmol alcohol) at 0 °C under a nitrogen atmosphere. The cloudy suspension turned clear immediately. After 20 minutes the reaction was quenched with sat. aq. $NaHCO_3$ and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

12a 4-Benzyloxy-3-methoxybenzyl bromide



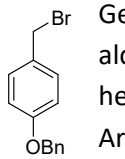
General procedure D gave bromide **12a** as a white solid (1.27 g, 93%) starting from 4-benzyl-3-methoxybenzyl alcohol (1.00 g, 5.94 mmol). All spectral data were consistent with literature.[11] m.p. 70-72 °C (from hexane), *lit.*[11] 70-72 °C; δ_H (400 MHz, $CDCl_3$) 3.91 (3H, s, OCH_3), 4.48 (2H, s, CH_2Br), 5.16 (2H, s, O*C*H_2Ph), 6.81 (1H, d, *J* 8.0, ArH), 6.88 (1H, dd, *J* 8.0, 2.0, ArH), 6.93 (1H, d, *J* 2.0, ArH), 7.27-7.33 (1H, m, ArH), 7.33-7.40 (2H, m, ArH), 7.40-7.46 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 34.5 (CH_2Br), 56.2 (OCH_3), 71.1 (O*C*H_2Ph), 112.7 (Ar-C), 113.8 (Ar-C), 121.6 (Ar-C), 127.3 (Ar-C), 128.0 (Ar-C), 128.7 (Ar-C), 130.8 (Ar-C), 137.0 (Ar-C), 148.5 (Ar-C), 149.8 (Ar-C).

12b 3-Methoxybenzyl bromide



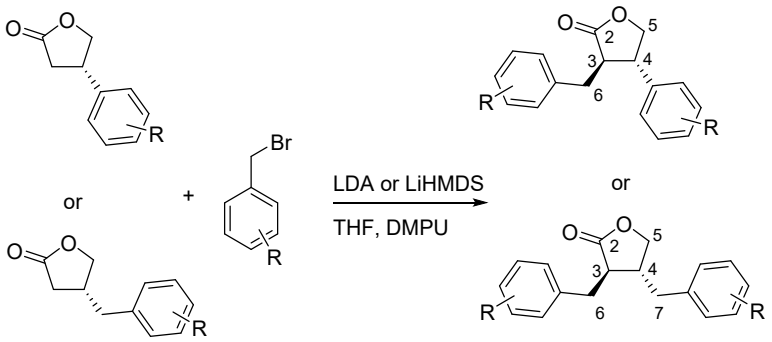
General procedure D gave bromide **12b** as a colourless oil (539 mg, 28%) starting from 3-methoxybenzyl alcohol (1.30 g, 9.41 mmol). All spectral data were consistent with literature.[12] δ_H (400 MHz, $CDCl_3$) 3.81 (3H, s, OCH_3), 4.46 (2H, s, CH_2Br), 6.83 (1H, ddd, *J* 8.5, 2.5, 1.0, ArH), 6.90-6.94 (1H, m, ArH), 6.95-6.99 (1H, m, ArH), 7.21-7.27 (1H, m, ArH); δ_C (100 MHz, $CDCl_3$) 33.6 (CH_2Br), 55.4 (OCH_3), 114.3 (Ar-C), 114.6 (Ar-C), 121.4 (Ar-C), 130.0 (Ar-C), 139.3 (Ar-C), 159.9 (Ar-C).

12c 4-Benzyloxybenzyl bromide



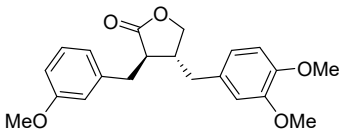
General procedure D gave bromide **12c** as a white solid (1.06 g, 63%) starting from 4-benzyloxybenzyl alcohol (1.30 g, 5.32 mmol). All spectral data were consistent with literature.[13] m.p. 87-90 °C (from hexane), *lit.*[13] 84-86 °C; δ_H (400 MHz, $CDCl_3$) 4.50 (2H, s, CH_2Br), 5.07 (2H, s, O*C*H_2Ph), 6.94 (2H, d, *J* 9.0, ArH), 7.29-7.46 (7H, m, ArH); δ_C (100 MHz, $CDCl_3$) 34.0 (CH_2Br), 70.2 (O*C*H_2Ph), 115.3 (Ar-C), 127.6 (Ar-C), 128.2 (Ar-C), 128.8 (Ar-C), 130.4 (Ar-C), 130.6 (Ar-C), 136.8 (Ar-C), 159.0 (Ar-C).

General procedure E for the alkylation of 4-aryl and 4-benzylfuran-2(3H)-ones



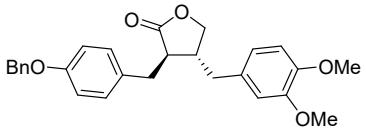
A solution of furanone (1 equiv.) in dry THF (2 ml/mmol furanone) was added to a freshly prepared solution of LDA or LiHMDS (1.2-1.6 equiv.) in dry THF at -78 °C under a nitrogen atmosphere. The reaction mixture was stirred for 30 minutes and then DMPU (1.2-1.6 equiv.) was added followed by a solution of bromide (1.2-1.6 equiv.) in dry THF (1 ml/mmol bromide). The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched with 1M HCl and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography. The products were used in the next step without further purification.

13b (=3b) (3*R*,4*R*)-3-(3-Methoxybenzyl)-4-(3,4-dimethoxybenzyl)-dihydrofuran-2(3*H*)-one



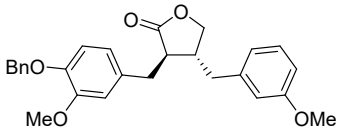
General procedure E gave compound **3b** as a yellow oil (49 mg, 22%) starting from compound **11a** (150 mg, 0.64 mmol), bromide **12b** (153 mg, 0.76 mmol) and LDA (0.62M in THF, 1.23 ml, 0.76 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 9:1-2:1). $[\alpha]_D$ -19 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3002, 2923, 2852, 1766, 1601; δ_H (400 MHz, $CDCl_3$) 2.42-2.64 (4H, m, 3-H+4-H+7-H_2), 2.85-2.93 (1H, m, 6-*H*H), 3.05 (1H, dd, *J* 14.0, 5.0, 6-H*H*), 3.77 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.83-3.90 (1H, m, 5-*H*H), 4.13 (1H, dd, *J* 9.0, 7.0, 5-H*H*), 6.45 (1H, d, *J* 2.0, ArH), 6.53 (1H, dd, *J* 8.0, 2.0, ArH), 6.69-6.81 (4H, m, ArH), 7.20 (1H, t, *J* 8.0, ArH); δ_C (100 MHz, $CDCl_3$) 35.3 (C-6), 38.3 (C-7), 41.6 (C-4), 46.4 (C-3), 55.3 (OCH_3), 55.9 (OCH_3), 56.0 (OCH_3), 71.4 (C-5), 111.4 (Ar-C), 111.8 (Ar-C), 112.3 (Ar-C), 115.1 (Ar-C), 120.7 (Ar-C), 121.7 (Ar-C), 129.7 (Ar-C), 130.6 (Ar-C), 139.5 (Ar-C), 148.0 (Ar-C), 149.1 (Ar-C), 160.0 (Ar-C), 178.7 (C-2); Found (ESI) 379.1517 $[MNa]^+$, (required $C_{21}H_{24}NaO_5$ 379.1516).

13c (3*R*,4*R*)-3-(4-Benzyloxybenzyl)-4-(3,4-dimethoxybenzyl)-dihydrofuran-2(3*H*)-one



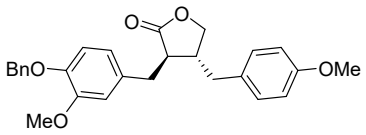
General procedure E gave compound **13c** as a yellow oil (101 mg, 42%) starting from compound **11a** (130 mg, 0.55 mmol), bromide **12c** (244 mg, 0.88 mmol) and LDA (0.64M in THF, 1.38 ml, 0.88 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 9:1-2:1). $[\alpha]_D$ -12 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3017, 2923, 2854, 1766, 1609; δ_H (400 MHz, $CDCl_3$) 2.42-2.69 (4H, m, 3-H+4-H+7-H_2), 2.86-3.04 (2H, m, 6-H_2), 3.82 (3H, s, OCH_3), 3.83-3.90 (1H, m, 5-*H*H), 3.86 (3H, s, OCH_3), 4.11 (1H, dd, *J* 9.0, 6.5, 5-H*H*), 5.04 (2H, s, O*CH*$_2$Ph), 6.48 (1H, d, *J* 2.0, ArH), 6.56 (1H, dd, *J* 8.0, 2.0, ArH), 6.76 (1H, d, *J* 8.0, ArH), 6.90 (2H, d, *J* 8.5, ArH), 7.07 (2H, d, *J* 8.5, ArH), 7.28-7.48 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$) 34.2 (C-6), 38.3 (C-7), 41.3 (C-4), 46.6 (C-3), 55.9 (OCH_3), 56.0 (OCH_3), 70.1 (C-5), 71.3 (O*CH*$_2$Ph), 111.4 (Ar-C), 111.9 (Ar-C), 115.0 (Ar-C), 120.7 (Ar-C), 127.6 (Ar-C), 128.1 (Ar-C), 128.7 (Ar-C), 130.1 (Ar-C), 130.4 (Ar-C), 130.6 (Ar-C), 137.0 (Ar-C), 147.9 (Ar-C), 149.1 (Ar-C), 157.8 (Ar-C), 178.7 (C-2); Found (ESI) 455.1840 $[MNa]^+$, (required $C_{27}H_{28}NaO_5$ 455.1829).

13d (3*R*,4*R*)-3-(4-Benzyloxy-3-methoxybenzyl)-4-(3-methoxybenzyl)-dihydrofuran-2(3*H*)-one



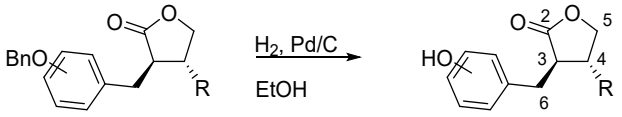
General procedure E gave compound **13d** as a yellow oil (22 mg, 41%) starting from compound **11b** (25 mg, 0.12 mmol), bromide **12a** (52 mg, 0.17 mmol) and LDA (0.62M in THF, 0.27 ml, 0.17 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 9:1-6:1). $[\alpha]_D$ -15 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3012, 2921, 2853, 1765, 1601; δ_H (400 MHz, $CDCl_3$) 2.46-2.69 (4H, m, 3-H+4-H+7-H_2), 2.86-3.00 (2H, m, 6-H_2), 3.76 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.82-3.88 (1H, m, 5-*H*H), 4.10 (1H, dd, *J* 9.0, 6.5, 5-H*H*), 5.13 (2H, s, O*C*H_2Ph), 6.53 (1H, t, *J* 2.0, ArH), 6.58 (1H, dd, *J* 8.0, 2.0, ArH), 6.61 (1H, dd, *J* 8.0, 2.0, ArH), 6.71 (1H, d, *J* 2.0, ArH), 6.75 (1H, dd, *J* 8.0, 2.0, ArH), 6.80 (1H, d, *J* 8.0, ArH), 7.17 (1H, t, *J* 8.0, ArH), 7.27-7.32 (1H, m, ArH), 7.32-7.38 (2H, m, ArH), 7.38-7.45 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 34.7 (C-6), 38.7 (C-7), 41.0 (C-4), 46.7 (C-3), 55.3 (OCH_3), 56.1 (OCH_3), 71.2+71.3 (C-5+O*C*H_2Ph), 111.8 (Ar-C), 113.0 (Ar-C), 114.3 (Ar-C), 114.8 (Ar-C), 121.0 (Ar-C), 121.5 (Ar-C), 127.4 (Ar-C), 127.9 (Ar-C), 128.6 (Ar-C), 129.8 (Ar-C), 130.9 (Ar-C), 137.3 (Ar-C), 139.7 (Ar-C), 147.2 (Ar-C), 149.9 (Ar-C), 159.9 (Ar-C), 178.7 (C-2); Found (ESI) 455.1812 $[MNa]^+$, (required $C_{27}H_{28}NaO_5$ 455.1829).

13e (3*R*,4*R*)-3-(4-Benzyloxy-3-methoxybenzyl)-4-(4-methoxybenzyl)-dihydrofuran-2(3*H*)-one



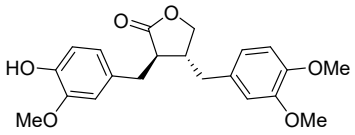
General procedure E gave compound **13e** as a yellow oil (227 mg, 56%) starting from compound **11c** (194 mg, 0.94 mmol), bromide **12a** (405 mg, 1.32 mmol) and LDA (0.62M in THF, 2.13 ml, 1.32 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 9:1-3:1). $[\alpha]_D$ -8 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3007, 2922, 2852, 1766, 1610; δ_H (400 MHz, $CDCl_3$) 2.41-2.74 (4H, m, 3-H+4-H+7-H_2), 2.85-2.99 (2H, m, 6-H_2), 3.78 (3H, s, OCH_3), 3.81-3.88 (1H, m, 5-*H*H), 3.84 (3H, s, OCH_3), 4.09 (1H, dd, *J* 9.0, 7.0, 5-H*H*), 5.13 (2H, s, O*C*H_2Ph), 6.61 (1H, dd, *J* 8.0, 2.0, ArH), 6.70 (1H, d, *J* 2.0, ArH), 6.74-6.82 (3H, m, ArH), 6.89 (2H, d, *J* 8.0, ArH), 7.28-7.32 (1H, m, ArH), 7.32-7.38 (2H, m, ArH), 7.38-7.46 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 34.7 (C-6), 37.8 (C-7), 41.3 (C-4), 46.7 (C-3), 55.4 (OCH_3), 56.1 (OCH_3), 71.3+71.4 (C-5+O*C*H_2Ph), 113.0 (Ar-C), 114.2 (Ar-C), 114.3 (Ar-C), 121.5 (Ar-C), 127.4 (Ar-C), 128.0 (Ar-C), 128.7 (Ar-C), 129.7 (Ar-C), 130.0 (Ar-C), 131.0 (Ar-C), 137.3 (Ar-C), 147.2 (Ar-C), 149.9 (Ar-C), 158.5 (Ar-C), 178.8 (C-2); Found (ESI) 455.1834 $[MNa]^+$, (required $C_{27}H_{28}NaO_5$ 455.1829).

General procedure F for the deprotection of the phenol-group



Palladium on carbon (10% w/w) was added to a solution of the benzyl-protected phenol (1 equiv.) in EtOH (15 ml/mmol). The solution was put under a hydrogen atmosphere and stirred for 30 minutes. The catalyst was filtered off over celite and the solvent was evaporated. The crude product was purified by column chromatography.

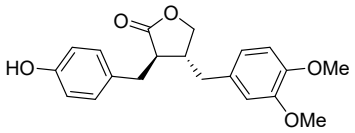
1(=3a) (3*R*,4*R*)-3-(4-Hydroxy-3-methoxybenzyl)-4-(3,4-dimethoxybenzyl)-dihydrofuran-2(3*H*)-one [(-)-Arctigenin]



General procedure E and F gave compound **3a** as a yellow oil (33 mg, 16%) over two steps starting from compound **11a** (130 mg, 0.55 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 5:1-3:1). All spectral data were consistent with literature.[14] $[\alpha]_D$ -22 (*c* 1.0, $CHCl_3$), *lit.*[15] $[\alpha]_D$ -16.6 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.41-2.67 (4H, m, 3-H+4-H+7-H_2), 2.84-2.99 (2H, m,

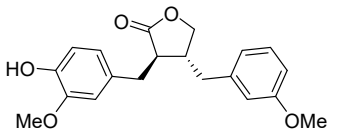
6-H_2), 3.80 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.85-3.88 (1H, m, 5-*H*H), 4.13 (1H, dd, *J* 9.0, 7.0, 5-H*H*), 5.59 (1H, s, OH), 6.46 (1H, d, *J* 2.0, ArH), 6.54 (1H, dd, *J* 8.0, 2.0, ArH), 6.60 (1H, dd, *J* 8.0, 2.0, ArH), 6.63 (1H, d, *J* 2.0, ArH), 6.74 (1H, d, *J* 8.0, ArH), 6.81 (1H, d, *J* 8.0, ArH); δ_C (100 MHz, $CDCl_3$) 34.6 (C-6), 38.3 (C-7), 41.0 (C-4), 46.7 (C-3), 55.9 (OCH_3), 55.96 (OCH_3), 56.01 (OCH_3), 71.5 (C-5), 111.4 (Ar-C), 111.7 (Ar-C), 111.9 (Ar-C), 114.3 (Ar-C), 120.7 (Ar-C), 122.2 (Ar-C), 129.6 (Ar-C), 130.6 (Ar-C), 144.7 (Ar-C), 146.8 (Ar-C), 147.9 (Ar-C), 149.13 (Ar-C), 178.9 (C-2).

3c (3*R*,4*R*)-3-(4-Hydroxybenzyl)-4-(3,4-dimethoxybenzyl)-dihydrofuran-2(3*H*)-one



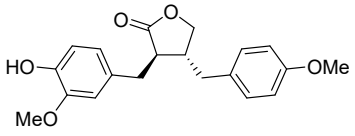
General procedure F gave compound **3c** as a colourless oil (51 mg, 64%) starting from compound **13c** (101 mg, 0.23 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 2:1). All spectral data were consistent with literature.[16] $[\alpha]_D$ -14 (*c* 1.0, $CHCl_3$), *lit.*[16] $[\alpha]_D$ -29.5 (*c* 0.27, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.41-2.67 (4H, m, 3-H+4-H+7-H_2), 2.82-2.99 (2H, m, 6-H_2), 3.80 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.84-3.91 (1H, m, 5-*H*H), 4.12 (1H, dd, *J* 9.0, 7.0, 5-H*H*), 6.05 (1H, s, OH), 6.45 (1H, d, *J* 2.0, ArH), 6.56 (1H, dd, *J* 8.0, 2.0, ArH), 6.71-6.79 (3H, m, ArH), 6.97 (2H, d, *J* 8.5, ArH); δ_C (100 MHz, $CDCl_3$) 34.2 (C-6), 38.3 (C-7), 41.2 (C-4), 46.7 (C-3), 55.9 (OCH_3), 56.0 (OCH_3), 71.6 (C-5), 111.5 (Ar-C), 111.9 (Ar-C), 115.6 (Ar-C), 120.8 (Ar-C), 129.4 (Ar-C), 130.5 (Ar-C), 130.6 (Ar-C), 147.9 (Ar-C), 149.1 (Ar-C), 155.0 (Ar-C), 179.3 (C-2).

3d (3*R*,4*R*)-3-(4-Hydroxy-3-methoxybenzyl)-4-(3-methoxybenzyl)-dihydrofuran-2(3*H*)-one



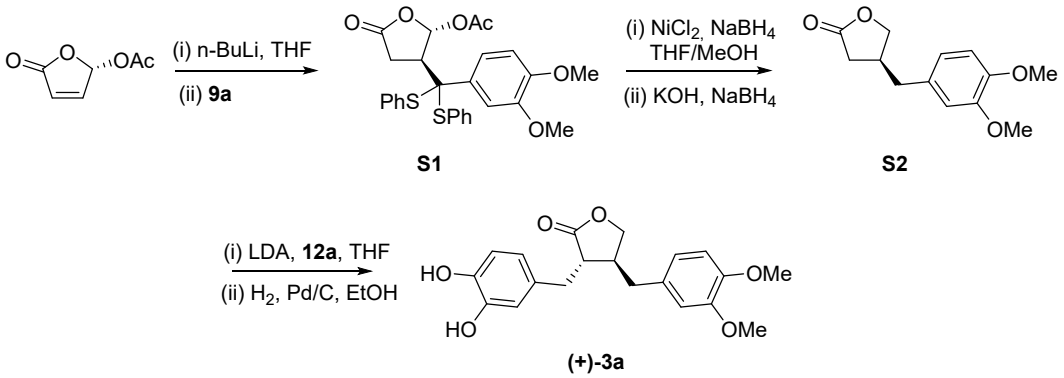
General procedure F gave compound **3d** as a colourless oil (16 mg, 80%) starting from compound **13d** (25 mg, 0.06 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 4:1). $[\alpha]_D$ -10 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3428, 3002, 2923, 2840, 1765, 1602; δ_H (400 MHz, $CDCl_3$) 2.45-2.73 (4H, m, 3-H+4-H+7-H_2), 2.87-2.98 (2H, m, 6-H_2), 3.77 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.84-3.89 (1H, m, 5-*H*H), 4.11 (1H, dd, *J* 9.0, 6.5, 5-H*H*), 5.55 (1H, s, OH), 6.54 (1H, t, *J* 2.0, ArH), 6.58-6.64 (2H, m, ArH), 6.66 (1H, d, *J* 2.0, ArH), 6.75 (1H, dd, *J* 8.0, 2.0, ArH), 6.83 (1H, d, *J* 8.0, ArH), 7.18 (1H, t, *J* 8.0, ArH); δ_C (100 MHz, $CDCl_3$) 34.6 (C-6), 38.7 (C-7), 40.9 (C-4), 46.8 (C-3), 55.3 (OCH_3), 56.0 (OCH_3), 71.4 (C-5), 111.7 (Ar-C), 111.9 (Ar-C), 114.4 (Ar-C), 114.7 (Ar-C), 121.1 (Ar-C), 122.3 (Ar-C), 129.6 (Ar-C), 129.8 (Ar-C), 139.7 (Ar-C), 144.7 (Ar-C), 146.8 (Ar-C), 159.9 (Ar-C), 178.8 (C-2); Found (ESI) 343.1543 $[MH]^+$, (required $C_{20}H_{23}O_5$ 343.1540).

3e (3*R*,4*R*)-3-(4-Benzyloxy-3-methoxybenzyl)-4-(4-methoxybenzyl)-dihydrofuran-2(3H)-one

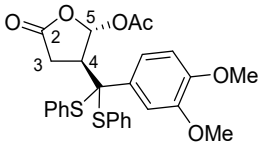


General procedure F gave compound **3e** as a colourless oil (49 mg, 62%) starting from compound **13e** (100 mg, 0.23 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 5:1). All spectral data were consistent with literature.[17] $[\alpha]_D$ -5 (*c* 1.0, $CHCl_3$), *lit.*[17] $[\alpha]_D$ -24 (*c* 3.3, $CHCl_3$); ν_{max}/cm^{-1} 3427, 3008, 2924, 2839, 1759, 1610; δ_H (400 MHz, $CDCl_3$) 2.43-2.69 (4H, m, 3-H+4-H+7-H_2), 2.85-2.98 (2H, m, 6-H_2), 3.78 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.84-3.89 (1H, m, 5-*H*H), 4.10 (1H, dd, *J* 9.0, 7.0, 5-H*H*), 5.58 (1H, s, OH), 6.62 (1H, dd, *J* 8.0, 2.0, ArH), 6.65 (1H, d, *J* 2.0, ArH), 6.79 (2H, d, *J* 8.5, ArH), 6.83 (1H, d, *J* 8.0, ArH), 6.91 (2H, d, *J* 8.5, ArH); δ_C (100 MHz, $CDCl_3$) 34.6 (C-6), 37.7 (C-7), 41.1 (C-4), 46.7 (C-3), 55.4 (OCH_3), 56.0 (OCH_3), 71.4 (C-5), 111.7 (Ar-C), 114.2 (Ar-C), 114.3 (Ar-C), 122.2 (Ar-C), 129.6 (Ar-C), 129.7 (Ar-C), 130.0 (Ar-C), 144.6 (Ar-C), 146.8 (Ar-C), 158.5 (Ar-C), 178.9 (C-2).

General scheme for the synthesis of (+)-arctigenin (+)-3a

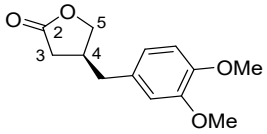


S1 (4*S*,5*S*)-5-Acetoxy-4-[(3,4-dimethoxyphenyl)-bis(phenylthio)methyl]dihydrofuran-2(3*H*)-one



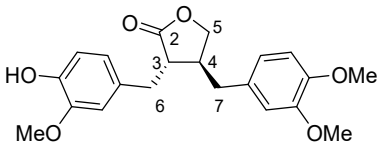
n-BuLi (1.47 M, 7.6 ml, 11.20 mmol) was added dropwise to a solution of thioacetal **9a** (3.79 g, 10.30 mmol) in dry THF (25 ml) at -78 °C under a nitrogen atmosphere. Then, a solution of acetoxyfuranone (1.33 g, 9.36 mmol) in dry THF (5 ml) was added dropwise at -78 °C and the reaction mixture was stirred for 3 hours at the same temperature. The reaction was quenched with 1M HCl (30 ml) and extracted with DCM (4x30 ml). The combined organic phases were washed dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether:EtOAc = 3:1) to give compound **S1** as a yellow oil (1.65 g, 35%). $[\alpha]_D$ +13 (*c* 1.0, $CHCl_3$); Spectral data identical with compound **10a**.

S2 (*S*)-4-(3,4-Dimethoxybenzyl)-dihydrofuran-2(3*H*)-one



$NiCl_2$ (2.03 g, 15.70 mmol) was added to a solution of compound **S1** (1.6 g, 3.13 mmol) in THF/MeOH (11 ml, 10:1) and the solution was cooled to 0 °C. Then $NaBH_4$ (2.37 g, 62.70 mmol) was added portion-wise so that the temperature did not exceed 10 °C. The reaction mixture turned black immediately. When the addition of $NaBH_4$ was finished, the reaction mixture was basified with 2M KOH to a pH of ~8 (approx. 30 ml) and more $NaBH_4$ (296 mg, 7.83 mmol) was added. The reaction was stirred at room temperature for 3 hours. The black precipitate was removed by filtration over celite and the solvent was evaporated. 1M HCl was added to a pH of ~ 1 and the aqueous phase was extracted with DCM (3x100 ml). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether:EtOAc = 4:1) to give compound **S2** as a colourless oil (541 mg, 73%). $[\alpha]_D$ -3 (*c* 1.0, $CHCl_3$), *lit.*[18] $[\alpha]_D$ -5.8 (*c* 0.5, $CHCl_3$); Spectral data identical with compound **11a**.

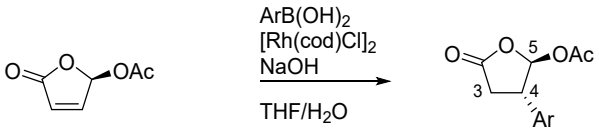
(+)-3a (3*S*,4*S*)-3-(4-Hydroxy-3-methoxybenzyl)-4-(3,4-dimethoxybenzyl)-dihydrofuran-2(3H)-one



A freshly prepared solution of LDA (0.62M in THF, 5.35 ml, 3.32 mmol) was added to a solution of compound **S2** (490 mg, 2.074 mmol) in dry THF (10 ml) at -78 °C under a nitrogen atmosphere. The reaction mixture was stirred for 30 minutes at -78 °C and then DMPU (0.4 ml, 3.318 mmol) was added followed by a solution of bromide **12a** (1.02 g, 3.32 mmol) in dry THF (4 ml). The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched with 1M HCl (15 ml) and the aqueous phase was extracted with EtOAc (3x20 ml). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether:EtOAc = 6:1) and the product was used in the next step without further purification.

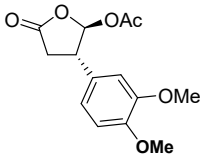
Palladium on charcoal (50% wet with H_2O, 10% w/w, 120 mg) was added to a solution of the benzyl-protected phenol (591 mg) in EtOH. The solution was put under a H_2-atmosphere and stirred for 30 minutes. The catalyst was filtered off over celite and the solvent was evaporated. The crude product was purified by column chromatography (petroleum ether:EtOAc = 4:1) to give compound **(+)-3a** as a colourless oil (453 mg, 59% over two steps). $[\alpha]_D$ +24 (*c* 1.0, $CHCl_3$); Spectral data identical with compound **1** and literature.[19,20]

General procedure G for the conjugate addition of boronic acids to 5-acetoxy-dihydrofuran-2(3*H*)-one



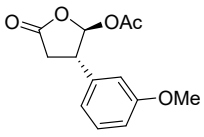
(*R*)-5-Acetoxydihydrofuran-2-(5*H*)-one (1 equiv.), arylboronic acid (1.6 equiv.) and $[Rh(cod)Cl]_2$ (5 mol%) were dissolved in THF/H_2O (9:1, 5 ml/mmol furanone). 1M NaOH (1 equiv.) was added dropwise, and the reaction mixture turned from bright yellow to dark orange. The reaction mixture was stirred at 70 °C (oil bath temperature) and monitored by TLC. When the reaction was finished, the reaction mixture was partitioned between EtOAc and H_2O. The aqueous phase was extracted with EtOAc (3x) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography.

14a (4*S*,5*R*)-5-Acetoxy-4-(3-methoxyphenyl)-dihydrofuran-2(3*H*)-one



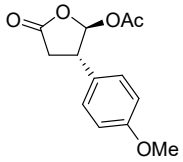
General procedure G gave compound **14a** as a yellow oil (617 mg, 63%) starting from (*R*)-5-acetoxydihydrofuran-2-(5*H*)-one (500 mg, 3.52 mmol) and 3,4-dimethoxyphenylboronic acid (1.02 g, 5.63 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 5:1). $[\alpha]_D$ -27 (*c* 1.0, $CHCl_3$), ν_{max} (neat)/cm^{-1} 2938, 2838, 1793, 1756; δ_H (400 MHz, $CDCl_3$) 2.16 (3H, s, $COCH_3$), 2.65 (1H, dd, *J* 18.0, 4.0, 3-*H*H), 3.14 (1H, dd, *J* 18.0, 9.0, 3-H*H*), 3.59 (1H, ddd, *J* 9.0, 4.0, 2.0, 4-H), 3.87 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.49 (1H, d, *J* 2.0, 5-H), 6.68 (1H, d, *J* 2.0, ArH), 6.74 (1H, dd, *J* 8.0, 2.0, ArH), 6.84 (1H, d, *J* 8.0, ArH); δ_C (100 MHz, $CDCl_3$) 21.1 (CH_3), 34.4 (C-3), 45.8 (C-4), 56.1 (OCH_3), 100.1 (C-5), 109.9 (ArH), 111.8 (ArH), 118.8 (ArH), 130.9 (ArH), 149.0 (ArH), 149.7 (ArH), 169.1 (C=O), 174.9 (C=O), Found (ESI) 303.0841 $[MNa]^+$, (required $C_{14}H_{16}NaO_6$ 303.0839).

14b (4*S*,5*R*)-5-Acetoxy-4-(3-methoxyphenyl)-dihydrofuran-2(3H)-one



General procedure G gave compound **14b** as a yellow oil (546 mg, 62%) starting from (*R*)-5-acetoxydihydrofuran-2-(5*H*)-one (500 mg, 3.52 mmol) and 3-methoxyphenylboronic acid (855 mg, 5.63 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 5:1). $[\alpha]_D$ -36 (*c* 1.0, $CHCl_3$), ν_{max} (neat)/cm^{-1} 3005, 2840, 1794, 1757, 1602; δ_H (400 MHz, $CDCl_3$) 2.15 (3H, s, CH_3), 2.67 (1H, dd, *J* 18.0, 4.0, 3-*H*H), 3.14 (1H, dd, *J* 18.0, 9.0, 3-H*H*), 3.62 (1H, ddd, *J* 9.0, 4.0, 2.0, 4-H), 3.81 (3H, s, OCH_3), 6.52 (1H, d, *J* 2.0, 5-H), 6.73 (1H, t, *J* 2.0, ArH), 6.78 (1H, ddd, *J* 8.0, 2.0, 1.0, ArH), 6.85 (1H, ddd, *J* 8.0, 2.0, 1.0, ArH), 7.29 (1H, t, *J* 8.0, ArH); δ_C (100 MHz, $CDCl_3$) 21.0 (CH_3), 34.4 (C-3), 46.1 (C-4), 55.5 (OCH_3), 99.7 (C-5), 112.9 (ArH), 113.4 (ArH), 118.9 (ArH), 130.6 (ArH), 139.9 (ArH), 160.4 (ArH), 169.0 (C=O), 174.7 (C=O), Found (ESI) 273.0735 $[MNa]^+$, (required $C_{13}H_{14}NaO_5$ 273.0733).

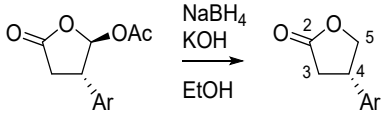
14c (4*S*,5*R*)-5-Acetoxy-4-(4-methoxyphenyl)-dihydrofuran-2(3H)-one



General procedure G gave compound **14c** as a yellow oil (102 mg, 58%, 96% ee) starting from (*R*)-5-acetoxydihydrofuran-2-(5*H*)-one (100 mg, 0.704 mmol) and 4-methoxyphenylboronic

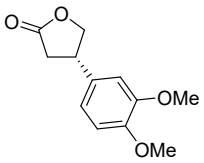
acid (171 mg, 1.13 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 5:1). $[\alpha]_D$ -45 (*c* 1.0, $CHCl_3$), ν_{max} (neat)/cm^{-1} 3008, 2941, 2840, 1785, 1758, 1613; δ_H (400 MHz, $CDCl_3$) 2.14 (3H, s, CH_3), 2.63 (1H, dd, *J* 18.0, 4.0, 3-*H*H), 3.13 (1H, dd, *J* 18.0, 9.0, 3-H*H*), 3.66 (1H, ddd, *J* 9.0, 4.0, 2.0, 4-H), 3.80 (3H, s, OCH_3), 6.46 (1H, d, *J* 2.0, 5-H), 6.86-6.92 (2H, m, ArH), 7.08-7.15 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 21.0 (CH_3), 34.5 (C-3), 45.4 (C-4), 55.5 (OCH_3), 100.0 (C-5), 114.8 (ArH), 127.9 (ArH), 130.3 (ArH), 159.5 (ArH), 169.1 (C=O), 174.8 (C=O), Found (ESI) 273.0733 $[MNa]^+$, (required $C_{13}H_{14}NaO_5$ 273.0733).

General procedure H for the cleavage of the acetyl group to prepare (*S*)-4-aryl-dihydrofuran-2(3*H*)-ones



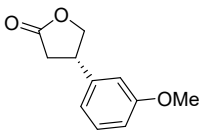
A 0.4M solution of KOH in ethanol (1.5 equiv.) was added to a solution of acetate (1 equiv.) in ethanol (5 ml/mmol acetate) and the pH was checked to be at ~8. $NaBH_4$ (7 equiv.) was added portion-wise at 0 °C. The solution was stirred for 1 hour at room temperature. If the reaction was not finished, another 3.5 equiv. of $NaBH_4$ was added. Once the reaction was finished, the reaction mixture was acidified with 1M HCl and stirred for another 30 minutes. The aqueous phase was then extracted with DCM and the combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was dissolved in $CHCl_3$ and refluxed overnight to cyclise. The solvent was evaporated off and the product was obtained without further purification.

15a (*S*)-4-(3,4-Dimethoxyphenyl)-dihydrofuran-2(3*H*)-one



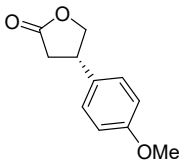
General procedure H gave compound **15a** as a white solid (291 mg, 75%) starting from compound **14a** (487 mg, 1.74 mmol). All spectral data were consistent with literature,[21] however the compound has not been fully characterised in literature. m.p. 84-86 °C; $[\alpha]_D$ +11.0 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3003, 2960, 2839, 1764, 1592; δ_H (400 MHz, $CDCl_3$) 2.65 (1H, dd, *J* 17.5, 9.0, 3-*H*H), 2.91 (1H, dd, *J* 17.5, 9.0, 3-H*H*), 3.73 (1H, *app* p, *J* 8.5, 4-H), 3.87 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.25 (1H, dd, *J* 9.0, 8.0, 5-*H*H), 4.65 (1H, dd, *J* 9.0, 8.0, 5-H*H*), 6.71 (1H, d, *J* 2.0, ArH), 6.78 (1H, dd, *J* 8.0, 2.0, ArH), 6.85 (1H, d, *J* 8.0, ArH); δ_C (100 MHz, $CDCl_3$) 36.0 (C-3), 40.9 (C-4), 56.0 (OCH_3), 74.3 (C-5), 110.0 (ArH), 111.7 (ArH), 118.8 (ArH), 132.0 (ArH), 148.6 (ArH), 149.5 (ArH), 176.6 (C-2).

15b (*S*)-4-(3-Methoxyphenyl)-dihydrofuran-2(3*H*)-one



General procedure H gave compound **15b** as a brown oil (177 mg, 88%) starting from compound **14b** (263 mg, 1.05 mmol). All spectral data were consistent with literature.[22] $[\alpha]_D$ +34.0 (*c* 1.0, $CHCl_3$), lit.[22] $[\alpha]_D$ +44.9 (*c* 1.0, $CHCl_3$, 98 % ee); ν_{max} (neat)/cm^{-1} 2913, 1770, 1602; δ_H (400 MHz, $CDCl_3$) 2.67 (1H, dd, *J* 17.5, 9.0, 3-*H*H), 2.91 (1H, dd, *J* 17.5, 9.0, 3-H*H*), 3.75 (1H, m, 4-H), 3.81 (3H, s, OCH_3), 4.26 (1H, dd, *J* 9.0, 8.0, 5-*H*H), 4.65 (1H, dd, *J* 9.0, 8.0, 5-H*H*), 6.76 (1H, t, *J* 7.0, ArH), 6.79-6.86 (2H, m, ArH), 7.28 (1H, t, *J* 8.0, ArH); δ_C (100 MHz, $CDCl_3$) 35.7 (C-3), 41.2 (C-4), 55.4 (OCH_3), 74.0 (C-5), 112.7 (ArH), 113.0 (ArH), 118.9 (ArH), 130.3 (ArH), 141.1 (ArH), 160.2 (ArH), 176.5 (C-2).

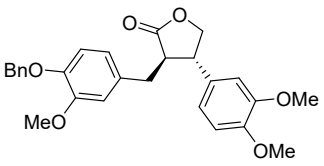
15c (*S*)-4-(4-Methoxyphenyl)-dihydrofuran-2(3*H*)-one



General procedure H gave compound **15c** as a white solid (485 mg, 94%) starting from compound **14c** (675 mg, 2.70 mmol). All spectral data were consistent with literature.[23] m.p. 67-69 °C, *lit.*[24] 68-70 °C; $[\alpha]_D$ +45.0 (*c* 1.0, $CHCl_3$), lit.[23] $[\alpha]_D$ +36.8 (*c* 0.6, $CHCl_3$, 91% ee); ν_{max} (neat)/cm^{-1} 2999, 2900, 2841, 1765, 1609; δ_H (400 MHz, $CDCl_3$) 2.63 (1H, dd, *J* 17.5, 9.0, 3-

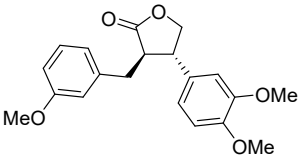
*H*H), 2.89 (1H, dd, *J* 17.5, 8.5, 3-H*H*), 3.75 (1H, *app* p, *J* 8.5, 4-H), 3.80 (3H, s, OCH_3), 4.22 (1H, dd, *J* 9.0, 8.0, 5-*H*H), 4.63 (1H, dd, *J* 9.0, 8.0, 5-H*H*), 6.89 (2H, d, *J* 8.5, ArH), 7.15 (2H, d, *J* 8.5, ArH); δ_C (100 MHz, $CDCl_3$) 36.0 (C-3), 40.6 (C-4), 55.5 (OCH_3), 74.4 (C-5), 114.6 (ArH), 127.9 (ArH), 131.4 (ArH), 159.2 (ArH), 176.6 (C-2).

16a (3*R*,4*S*)-3-(4-Benzyloxy-3-methoxybenzyl)-4-(3,4-dimethoxyphenyl)-dihydrofuran-2(3*H*)-one



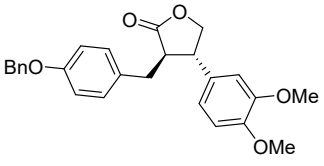
General procedure E gave compound **16a** as a yellow oil (96 mg, 24%) starting from compound **15a** (200 mg, 0.90 mmol), bromide **12a** (332 mg, 1.08 mmol) and LDA (0.65M in THF, 1.7 ml, 1.11 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 9:1-3:1). $[\alpha]_D$ +1 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 2923, 2851, 1769, 1591; δ_H (400 MHz, $CDCl_3$) 2.89 (1H, dd, *J* 14.0, 5.0, 6-*H*H), 3.01 (1H, dt, *J* 10.5, 5.0, 3-H), 3.09 (1H, dd, *J* 14.0, 5.0, 6-H*H*), 3.28 (1H, *app* td, *J* 10.5, 8.0, 4-H), 3.79 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.04 (1H, *app* t, *J* 9.5, 5-*H*H), 4.37 (1H, *app* t, *J* 8.5, 5-H*H*), 5.10 (2H, s, O*C*H_2Ph), 6.56-6.63 (2H, m, ArH), 6.68-6.73 (2H, m, ArH), 6.76 (1H, d, *J* 8.0, ArH), 6.81 (1H, d, *J* 8.0, ArH), 7.27-7.31 (1H, m, ArH), 7.31-7.39 (2H, m, ArH), 7.39-7.46 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 33.2 (C-6), 45.2 (C-4), 48.0 (C-3), 55.96 (OCH_3), 55.99 (OCH_3), 56.03 (OCH_3), 71.2 (O*C*H_2Ph), 72.5 (C-5), 110.5 (Ar-C), 111.6 (Ar-C), 113.4 (Ar-C), 114.1 (Ar-C), 119.6 (Ar-C), 121.8 (Ar-C), 127.3 (Ar-C), 127.9 (Ar-C), 128.6 (Ar-C), 130.4 (Ar-C), 130.5 (Ar-C), 137.3 (Ar-C), 147.1 (Ar-C), 148.6 (Ar-C), 149.4 (Ar-C), 149.6 (Ar-C), 177.8 (C-2); Found (ESI) 449.1959 $[MH]^+$, (required $C_{27}H_{29}O_6$ 449.1959).

16b (=4b) (3*R*,4*S*)-3-(3-Methoxybenzyl)-4-(3,4-dimethoxyphenyl)-dihydrofuran-2(3H)-one



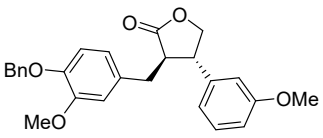
General procedure E gave compound **4b** as a yellow oil (153 mg, 50%) starting from compound **15a** (200 mg, 0.90 mmol), bromide **12b** (217 mg, 1.08 mmol) and LDA (0.65M in THF, 1.7 ml, 1.11 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 9:1-3:1). $[\alpha]_D$ +3 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 2921, 2851, 1767, 1593; δ_H (400 MHz, $CDCl_3$) 2.94-3.12 (3H, m, 6-H_2+3-H), 3.29 (1H, br *app* q, *J* 9.0, 4-H), 3.72 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.06 (1H, *app* t, *J* 9.5, 5-*H*H), 4.39 (1H, dd, *J* 9.0, 8.0, 5-H*H*), 6.57 (1H, d, *J* 2.0, ArH), 6.66-6.74 (4H, m, ArH), 6.81 (1H, d, *J* 8.0, ArH), 7.13 (1H, t, *J* 8.0, ArH); δ_C (100 MHz, $CDCl_3$) 34.0 (C-6), 45.6 (C-4), 48.2 (C-3), 55.3 (OCH_3), 56.0 (OCH_3), 56.1 (OCH_3), 72.5 (C-5), 110.6 (Ar-C), 111.7 (Ar-C), 112.4 (Ar-C), 115.4 (Ar-C), 119.5 (Ar-C), 122.1 (Ar-C), 129.6 (Ar-C), 130.5 (Ar-C), 139.0 (Ar-C), 148.6 (Ar-C), 149.4 (Ar-C), 159.8 (Ar-C), 177.8 (C-2); Found (ESI) 343.1534 $[MH]^+$, (required $C_{20}H_{23}O_5$ 343.1540).

16c (3*R*,4*S*)-3-(4-Benzyloxybenzyl)-4-(3,4-dimethoxyphenyl)-dihydrofuran-2(3H)-one



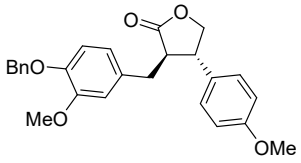
General procedure E gave compound **16c** as a yellow oil (277 mg, 57%) starting from compound **15a** (260 mg, 1.17 mmol), bromide **12c** (389 mg, 1.40 mmol) and LDA (0.65M in THF, 2.2 ml, 1.43 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 9:1-3:1). $[\alpha]_D$ +1 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 2916, 2836, 1765, 1608; δ_H (400 MHz, $CDCl_3$) 2.92 (1H, dd, *J* 14.0, 5.5, 6-*H*H), 3.00 (1H, *app* dt, *J* 10.0, 5.0, 3-H), 3.11 (1H, dd, *J* 14.0, 5.0, 6-H*H*), 3.30 (1H, td, *J* 10.0, 8.0, 4-H), 3.84 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.06 (1H, *app* t, *J* 9.0, 5-*H*H), 4.37 (1H, dd, *J* 9.0, 8.0, 5-H*H*), 5.02 (2H, s, O*C*H_2Ph), 6.59 (1H, d, *J* 2.0, ArH), 6.72 (1H, dd, *J* 8.0, 2.0, ArH), 6.80-6.90 (3H, m, ArH), 7.07 (2H, d, *J* 8.5, ArH), 7.29-7.35 (1H, m, ArH), 7.35-7.45 (4H, m, ArH); δ_C (100 MHz, $CDCl_3$) 32.9 (C-6), 45.3 (C-4), 48.4 (C-3), 56.08 (OCH_3), 56.12 (OCH_3), 70.2 (O*C*H_2Ph), 72.5 (C-5), 110.5 (Ar-C), 111.7 (Ar-C), 115.0 (Ar-C), 119.6 (Ar-C), 127.6 (Ar-C), 128.1 (Ar-C), 128.7 (Ar-C), 129.7 (Ar-C), 130.6 (Ar-C), 130.9 (Ar-C), 137.1 (Ar-C), 148.7 (Ar-C), 149.5 (Ar-C), 157.9 (Ar-C), 177.8 (C-2); Found (ESI) 441.1672 $[MNa]^+$, (required $C_{26}H_{26}NaO_5$ 441.1654).

16d (3*R*,4*S*)-3-(4-Benzyloxy-3-methoxybenzyl)-4-(3-methoxyphenyl)-dihydrofuran-2(3*H*)-one



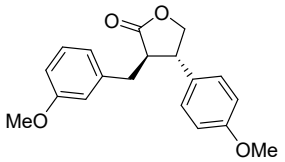
General procedure E gave compound **16d** as a yellow oil (175 mg, 42%) starting from compound **15b** (190 mg, 0.99 mmol), bromide **12a** (364 mg, 1.19 mmol) and LDA (0.62M in THF, 1.9 ml, 1.18 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 9:1-7:1). $[\alpha]_D$ +8 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3060, 2922, 2850, 1770, 1602; δ_H (400 MHz, $CDCl_3$) 2.91 (1H, dd, *J* 14.0, 5.5, 6-*H*H), 3.00-3.14 (2H, m, 3-H+6-H*H*), 3.32 (1H, td, *J* 10.0, 8.0, 4-H), 3.78 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 4.07 (1H, dd, *J* 10.0, 9.0, 5-*H*H), 4.39 (1H, dd, *J* 9.0, 8.0, 5-H*H*), 5.11 (2H, s, O*C*H_2Ph), 6.60 (1H, dd, *J* 8.0, 2.0, ArH), 6.64-6.70 (2H, m, ArH), 6.71-6.78 (2H, m, ArH), 6.80 (1H, ddd, *J* 8.0, 2.5, 1.0, ArH), 7.21-7.25 (1H, m, ArH), 7.27-7.33 (1H, m, ArH), 7.33-7.40 (2H, m, ArH), 7.40-7.46 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 33.4 (C-6), 45.6 (C-4), 48.1 (C-3), 55.4 (OCH_3), 56.0 (OCH_3), 71.3 (O*C*H_2Ph), 72.4 (C-5), 112.7 (Ar-C), 113.4 (Ar-C), 113.8 (Ar-C), 114.2 (Ar-C), 119.6 (Ar-C), 121.9 (Ar-C), 127.4 (Ar-C), 127.9 (Ar-C), 128.7 (Ar-C), 130.3 (Ar-C), 130.4 (Ar-C), 137.4 (Ar-C), 139.7 (Ar-C), 147.2 (Ar-C), 149.7 (Ar-C), 160.2 (Ar-C), 177.8 (C-2); Found (ESI) 441.1676 $[MNa]^+$, (required $C_{26}H_{26}NaO_5$ 441.1672).

16e (3*R*,4*S*)-3-(4-Benzyloxy-3-methoxybenzyl)-4-(4-methoxyphenyl)-dihydrofuran-2(3*H*)-one



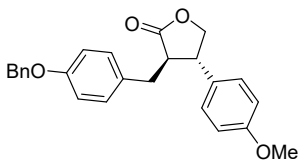
General procedure E gave compound **16e** as a yellow oil (478 mg, 55%) starting from compound **15c** (400 mg, 2.08 mmol), bromide **12a** (767 mg, 2.50 mmol) and LDA (0.43M in THF, 5.8 ml, 2.49 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 9:1-3:1). $[\alpha]_D$ +5 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3002, 2918, 2836, 1770, 1611; δ_H (400 MHz, $CDCl_3$) 2.87 (1H, dd, *J* 14.0, 5.5, 6-*H*H), 3.00 (1H, *app* dt, *J* 10.5, 5.0, 3-H), 3.10 (1H, dd, *J* 14.0, 5.0, 6-H*H*), 3.29 (1H, *app* td, *J* 10.5, 8.0, 4-H), 3.80 (6H, s, OCH_3), 4.02 (1H, dd, *J* 10.0, 9.0, 5-*H*H), 4.37 (1H, *app* t, *J* 8.5, 5-H*H*), 5.11 (2H, s, O*C*H_2Ph), 6.59 (1H, dd, *J* 8.0, 2.0, ArH), 6.69 (1H, d, *J* 2.0, ArH), 6.76 (1H, d, *J* 8.0, ArH), 6.86 (2H, d, *J* 8.5, ArH), 7.07 (2H, d, *J* 8.5, ArH), 7.27-7.33 (1H, m, ArH), 7.33-7.40 (2H, m, ArH), 7.40-7.46 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 33.1 (C-6), 44.9 (C-4), 48.2 (C-3), 55.5 (OCH_3), 56.0 (OCH_3), 71.3 (O*C*H_2Ph), 72.6 (C-5), 113.5 (Ar-C), 114.2 (Ar-C), 114.6 (Ar-C), 121.9 (Ar-C), 127.4 (Ar-C), 127.9 (Ar-C), 128.5 (Ar-C), 128.6 (Ar-C), 129.8 (Ar-C), 130.5 (Ar-C), 137.4 (Ar-C), 147.1 (Ar-C), 149.7 (Ar-C), 159.2 (Ar-C), 177.9 (C-2); Found (ESI) 419.1849 $[MH]^+$, (required $C_{26}H_{27}O_5$ 419.1853).

16f (=4f) (3*R*,4*S*)-3-(3-Methoxybenzyl)-4-(4-methoxyphenyl)-dihydrofuran-2(3*H*)-one



General procedure E gave compound **4f** as a colourless oil (11 mg, 14%) starting from compound **15c** (50 mg, 0.26 mmol), bromide **12b** (84 mg, 0.42 mmol) and LiHMDS (1M, 0.42 ml, 0.42 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 15:1). $[\alpha]_D$ +4.0 (*c* 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3006, 2962, 2920, 2836, 1770, 1611; δ_H (400 MHz, $CDCl_3$) 2.93 (1H, dd, *J* 13.5, 5.0, 6-*H*H), 3.02 (1H, *app* dt, *J* 10.5, 5.0, 3-H), 3.12 (1H, dd, *J* 13.5, 5.0, 6-H*H*), 3.31 (1H, br *app* td, *J* 10.5, 8.0, 4-H), 3.80 (3H, s, OCH_3), 4.04 (1H, dd, *J* 9.0, 8.0, 5-*H*H), 4.38 (1H, dd, *J* 9.0, 8.0, 5-H*H*), 6.67-6.77 (3H, m, ArH), 6.86 (2H, d, *J* 8.5, ArH), 7.08 (2H, d, *J* 8.0, ArH), 7.15 (1H, t, *J* 8.0, ArH); δ_C (100 MHz, $CDCl_3$) 33.7 (C-6), 45.0 (C-4), 48.0 (C-3), 55.2 (OCH_3), 55.4 (OCH_3), 72.6 (C-5), 112.6 (Ar-C), 114.6 (Ar-C), 115.2 (Ar-C), 122.2 (Ar-C), 128.5 (Ar-C), 129.6 (Ar-C), 129.8 (Ar-C), 138.9 (Ar-C), 159.2 (Ar-C), 159.8 (Ar-C), 177.8 (C-2); Found (ESI) 335.1257 $[MNa]^+$, (required $C_{19}H_{20}NaO_4$ 335.1254).

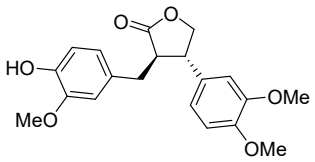
16g (3*R*,4*S*)-3-(4-Benzyloxybenzyl)-4-(4-methoxyphenyl)-dihydrofuran-2(3*H*)-one



General procedure E gave compound **16g** as a colourless oil (186 mg, 61%) starting from compound **15c** (150 mg, 0.78 mmol), bromide **12c** (345 mg, 1.25 mmol) and

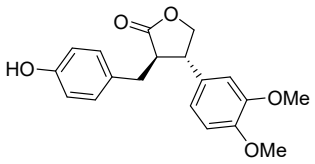
LDA (1M in THF, 1.25 ml, 1.25 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 9:1-5:1). $[\alpha]_D$ +5.0 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3066, 3035, 2915, 1768, 1611; δ_H (400 MHz, $CDCl_3$) 2.88 (1H, dd, *J* 14.0, 5.0, 6-*H*H), 2.99 (1H, *app* dt, *J* 10.0, 5.0, 3-H), 3.12 (1H, dd, *J* 14.0, 5.0, 6-H*H*), 3.31 (1H, br *app* td, *J* 10.0, 8.0, 4-H), 3.81 (3H, s, OCH_3), 4.03 (1H, dd, *J* 10.0, 9.0, 5-*H*H), 4.39 (1H, dd, *J* 9.0, 8.0, 5-H*H*), 5.03 (2H, s, O*C*H_2Ph), 6.83-6.91 (4H, m, ArH), 7.03-7.12 (4H, m, ArH), 7.29-7.36 (1H, m, ArH), 7.36-7.46 (4H, m, ArH); δ_C (100 MHz, $CDCl_3$) 32.6 (C-6), 44.8 (C-4), 48.3 (C-3), 55.4 (OCH_3), 70.1 (O*C*H_2Ph), 72.6 (C-5), 114.6 (Ar-C), 115.0 (Ar-C), 127.6 (Ar-C), 128.1 (Ar-C), 128.5 (Ar-C), 128.7 (Ar-C), 129.6 (Ar-C), 129.8 (Ar-C), 130.9 (Ar-C), 137.2 (Ar-C), 157.8 (Ar-C), 159.2 (Ar-C), 177.8 (C-2); Found (ESI) 411.1568 $[MNa]^+$, (required $C_{25}H_{24}NaO_4$ 411.1567).

4a (3*R*,4*S*)-3-(4-Hydroxy-3-methoxybenzyl)-4-(3,4-dimethoxyphenyl)-dihydrofuran-2(3*H*)-one



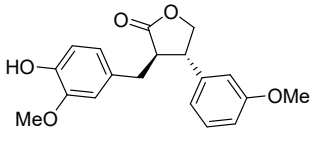
General procedure F gave compound **4a** as a colourless oil (40 mg, 64%) starting from compound **16a** (78 mg, 0.17 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 3:1). $[\alpha]_D$ +4 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3448, 3015, 2937, 2839, 1762, 1601; δ_H (400 MHz, $CDCl_3$) 2.89 (1H, dd, *J* 14.0, 5.5, 6-*H*H), 3.00 (1H, *app* dt, *J* 10.5, 5.0, 3-H), 3.09 (1H, dd, *J* 14.0, 5.0, 6-H*H*), 3.28 (1H, td, *J* 10.5, 8.0, 4-H), 3.78 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.05 (1H, *app* t, *J* 9.5, 5-*H*H), 4.37 (1H, *app* t, *J* 8.5, 5-H*H*), 5.55 (1H, s, OH), 6.57-6.62 (2H, m, ArH), 6.67 (1H, d, *J* 2.0, ArH), 6.72 (1H, dd, *J* 8.0, 2.0, ArH), 6.76-6.85 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 33.3 (C-6), 45.2 (C-4), 48.3 (C-3), 55.9 (OCH_3), 56.0 (OCH_3), 56.1 (OCH_3), 72.5 (C-5), 110.6 (Ar-C), 111.7 (Ar-C), 112.2 (Ar-C), 114.2 (Ar-C), 119.6 (Ar-C), 122.6 (Ar-C), 129.2 (Ar-C), 130.5 (Ar-C), 144.6 (Ar-C), 146.6 (Ar-C), 148.6 (Ar-C), 149.4 (Ar-C), 177.9 (C-2); Found (ESI) 359.1492 $[MH]^+$, (required $C_{20}H_{23}O_6$ 359.1489).

4c (3*R*,4*S*)-3-(4-Hydroxybenzyl)-4-(3,4-dimethoxyphenyl)-dihydrofuran-2(3H)-one



General procedure F gave compound **4c** as a colourless oil (74 mg, 47%) starting from compound **16c** (200 mg, 0.48 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 5:1-3.1). $[\alpha]_D$ +6 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3402, 3018, 2926, 2838, 1757, 1614; δ_H (400 MHz, $CDCl_3$) 2.90 (1H, dd, *J* 14.0, 5.5, 6-*H*H), 3.01 (1H, *app* dt, *J* 10.5, 5.0, 3-H), 3.08 (1H, dd, *J* 14.0, 5.0, 6-H*H*), 3.26-3.36 (1H, m, 4-H), 3.84 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.07 (1H, *app* t, *J* 9.0, 5-*H*H), 4.39 (1H, dd, *J* 9.0, 8.0, 5-H*H*), 5.61 (1H, s, OH), 6.59 (1H, d, *J* 2.0, ArH), 6.68-6.75 (3H, m, ArH), 6.83 (1H, d, *J* 8.0, ArH), 7.00 (2H, d, *J* 8.5, ArH); δ_C (100 MHz, $CDCl_3$) 32.9 (C-6), 45.2 (C-4), 48.4 (C-3), 56.07 (OCH_3), 56.11 (OCH_3), 72.7 (C-5), 110.6 (Ar-C), 111.8 (Ar-C), 115.5 (Ar-C), 119.6 (Ar-C), 129.1 (Ar-C), 130.5 (Ar-C), 131.0 (Ar-C), 148.6 (Ar-C), 149.4 (Ar-C), 154.9 (Ar-C), 178.3 (C-2); Found (ESI) 441.1672 $[MNa]^+$, (required $C_{26}H_{26}NaO_5$ 441.1654).

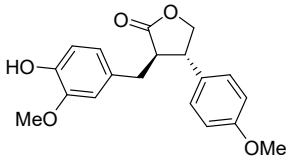
4d (3*R*,4*S*)-3-(4-Hydroxy-3-methoxybenzyl)-4-(3-methoxyphenyl)-dihydrofuran-2(3*H*)-one



General procedure F gave compound **4d** as a colourless oil (63 mg, 80%) starting from compound **16d** (100 mg, 0.24 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 5:1). $[\alpha]_D$ +6 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3441, 3008, 2932, 2840, 1762, 1602; δ_H (400 MHz, $CDCl_3$) 2.89 (1H, dd, *J* 14.0, 5.0, 6-*H*H), 3.00-3.08 (1H, m, 3-H), 3.11 (1H, dd, *J* 14.0, 5.0, 6-H*H*), 3.33 (1H, *app* td, *J* 10.0, 8.0, 4-H), 3.79 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.07 (1H, *app* t, *J* 9.0, 5-*H*H), 4.39 (1H, *app* t, *J* 9.0, 5-H*H*), 5.52 (1H, s, OH), 6.60 (1H, dd, *J* 8.0, 2.0, ArH), 6.65-6.70 (2H, m, ArH), 6.73-6.84 (3H, m, ArH), 7.21-7.30 (1H, m, ArH); δ_C (100 MHz, $CDCl_3$) 33.3 (C-6), 45.5 (C-4), 48.1 (C-3), 55.3 (OCH_3), 55.9 (OCH_3), 72.3 (C-5), 112.2 (Ar-C), 112.7 (Ar-

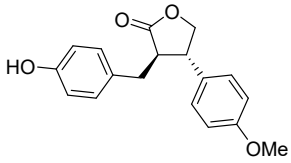
C), 113.7 (Ar-C), 114.2 (Ar-C), 119.6 (Ar-C), 122.6 (Ar-C), 129.0 (Ar-C), 130.2 (Ar-C), 139.7 (Ar-C), 144.5 (Ar-C), 146.6 (Ar-C), 160.1 (Ar-C), 177.9 (C-2); Found (ESI) 329.1370 $[MH]^+$, (required $C_{19}H_{21}O_5$ 329.1384).

4e (3*R*,4*S*)-3-(4-Hydroxy-3-methoxybenzyl)-4-(4-methoxyphenyl)-dihydrofuran-2(3*H*)-one



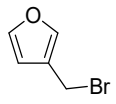
General procedure F gave compound **4e** as a colourless oil (40 mg, 51%) starting from compound **16e** (100 mg, 0.24 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 5:1). $[\alpha]_D$ +5 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3436, 3005, 2925, 2839, 1762, 1612; δ_H (400 MHz, $CDCl_3$) 2.85 (1H, dd, *J* 14.0, 5.5, 6-*H*H), 3.00 (1H, *app* dd, *J* 10.5, 5.5, 3-H), 3.11 (1H, dd, *J* 14.0, 5.0, 6-H*H*), 3.30 (1H, *app* td, *J* 10.5, 8.0, 4-H), 3.80 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.03 (1H, dd, *J* 10.0, 9.0, 5-*H*H), 4.37 (1H, *app* t, *J* 8.5, 5-H*H*), 5.53 (1H, s, OH), 6.59 (1H, dd, *J* 8.0, 2.0, ArH), 6.68 (1H, d, *J* 2.0, ArH), 6.79 (1H, d, *J* 8.0, ArH), 6.87 (2H, d, *J* 8.5, ArH), 7.09 (2H, d, *J* 8.5, ArH); δ_C (100 MHz, $CDCl_3$) 33.1 (C-6), 44.7 (C-4), 48.3 (C-3), 55.5 (OCH_3), 56.0 (OCH_3), 72.6 (C-5), 112.3 (Ar-C), 114.2 (Ar-C), 114.6 (Ar-C), 122.7 (Ar-C), 128.6 (Ar-C), 129.1 (Ar-C), 129.8 (Ar-C), 144.6 (Ar-C), 146.6 (Ar-C), 159.2 (Ar-C), 178.0 (C-2); Found (ESI) 329.1379 $[MH]^+$, (required $C_{19}H_{21}O_5$ 329.1384).

4g (3*R*,4*S*)-3-(4-Hydroxybenzyl)-4-(4-methoxyphenyl)-dihydrofuran-2(3*H*)-one



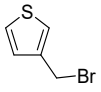
General procedure F gave compound **4g** as a colourless oil (97 mg, 68%) starting from compound **16g** (186 mg, 0.48 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 5:1). $[\alpha]_D$ +4.0 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3368, 3015, 2961, 2918, 2836; δ_H (400 MHz, $CDCl_3$) 2.85 (1H, dd, *J* 14.0, 5.0, 6-*H*H), 3.00 (1H, *app* dt, *J* 10.5, 5.0, 3-H), 3.11 (1H, dd, *J* 14.0, 5.0, 6-H*H*), 3.31 (1H, br *app* td, *J* 10.5, 8.0, 4-H), 3.81 (3H, s, OCH_3), 4.04 (1H, dd, *J* 10.0, 9.0, 5-*H*H), 4.37 (1H, dd, *J* 9.0, 8.0, 5-H*H*), 6.73 (2H, d, *J* 8.0, ArH), 6.88 (2H, d, *J* 8.5, ArH), 7.00 (2H, d, *J* 8.0, ArH), 7.09 (2H, d, *J* 8.5, ArH); δ_C (100 MHz, $CDCl_3$) 32.5 (C-6), 44.7 (C-4), 48.4 (C-3), 55.5 (OCH_3), 72.8 (C-5), 114.6 (Ar-C), 115.5 (Ar-C), 128.6 (Ar-C), 129.0 (Ar-C), 129.8 (Ar-C), 131.1 (Ar-C), 154.8 (Ar-C), 159.2 (Ar-C), 178.4 (C-2); Found (ESI) 321.1100 $[MNa]^+$, (required $C_{18}H_{18}NaO_4$ 321.1097).

S3 3-(Bromomethyl)-furan



$NaBH_4$ (197 mg, 5.20 mmol) was added to a solution of furan-3-carbaldehyde (1.00 g, 10.4 mmol) in MeOH (20 ml) at 0 °C. The reaction was stirred for 15 minutes at 0 °C and the reaction was quenched with H_2O (20 ml) and extracted with EtOAc (3x20 ml). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was obtained as a pale yellow oil (984 mg, 96%) and was used in the next step without further purification. PBr_3 (0.38 ml, 4.094 mmol) was added dropwise to the crude product (590 mg) in dry Et_2O (10 ml) at 0 °C under nitrogen. After 20 minutes the reaction was quenched with sat. aq. $NaHCO_3$ (10 ml) and the aqueous phase was extracted with Et_2O (3x10 ml). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Compound **S3** was obtained as a dark oil (514 mg, 52%) and was used in the next step without further purification. All spectral data were consistent with literature.[25] δ_H (400 MHz, $CDCl_3$) 4.38 (2H, s, CH_2), 6.45 (1H, m, ArH), 7.40 (1H, t, *J* 2.0, ArH), 7.48 (1H, dd, *J* 2.0, 1.0, ArH); δ_C (100 MHz, $CDCl_3$) 23.7 (CH_2), 111.0 (Ar-C), 122.7 (Ar-C), 140.9 (Ar-C), 143.9 (Ar-C).

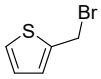
S4 3-(Bromomethyl)-thiophene



$NaBH_4$ (167 mg, 4.46 mol) was added to a solution of thiophene-3-carbaldehyde (1.00 g, 8.92 mmol) in MeOH (20 ml) at 0 °C. The reaction was stirred for 15 minutes at 0 °C and then quenched with

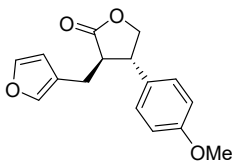
H_2O (20 ml) and extracted with EtOAc (3x20 ml). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was obtained as a pale yellow oil (943 mg, 93%) and was used in the next step without further purification. PBr_3 (0.42 ml, 4.44 mmol) was added dropwise the crude product (760 mg) in dry Et_2O (10 ml) at 0 °C under nitrogen. After 20 minutes the reaction was quenched with sat. aq. $NaHCO_3$ (10 ml) and the aqueous phase was extracted with Et_2O (3x10 ml). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Compound **S4** was obtained as a dark oil (965 mg, 82%) and was used in the next step without further purification. All spectral data were consistent with literature.[26] δ_H (400 MHz, $CDCl_3$) 4.53 (2H, s, CH_2), 7.13 (1H, dd, *J* 5.0, 2.0, ArH), 7.28-7.35 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 27.5 (CH_2), 124.4 (Ar-C), 126.8 (Ar-C), 128.2 (Ar-C), 138.2 (Ar-C).

S5 2-(Bromomethyl)-thiophene



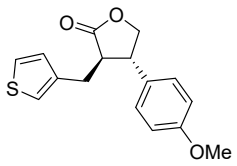
General procedure D gave bromide **S5** as a yellow oil (1.29 g, 83%) starting from 2-thiophenemethanol (1.00 g, 8.76 mmol). All spectral data were consistent with literature.[27] δ_H (400 MHz, $CDCl_3$) 4.76 (2H, s, CH_2), 6.94 (1H, dd, *J* 5.0, 3.5, ArH), 7.10-7.13 (1H, m, ArH), 7.32 (1H, dd, *J* 5.0, 1.0, ArH); δ_C (100 MHz, $CDCl_3$) 26.9 (CH_2), 127.2 (Ar-C), 128.2 (Ar-C), 140.5 (Ar-C).

5a (3*R*,4*S*)-3-(3-Furfuryl)-4-(4-methoxyphenyl)-dihydrofuran-2(3H)-one



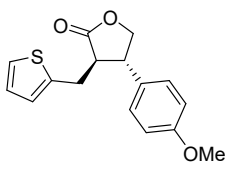
General procedure E gave compound **5a** as a pale yellow oil (21 mg, 30%) starting from compound **15c** (50 mg, 0.26 mmol), bromide **S3** (67 mg, 0.416 mmol) and LiHMDS (0.5M, 0.84 ml, 0.42 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 5:1). $[\alpha]_D$ +3.0 (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3003, 2961, 2917, 2839, 1772, 1613; δ_H (400 MHz, $CDCl_3$) 2.72 (1H, dd, *J* 14.5, 5.0, 6-*H*H), 2.92 (1H, *app* dt, *J* 11.0, 5.0, 3-H), 2.99 (1H, dd, *J* 14.5, 5.0, 6-H*H*), 3.36 (1H, br *app* td, *J* 11.0, 8.0, 4-H), 3.81 (3H, s, OCH_3), 4.07 (1H, dd, *J* 10.0, 9.0, 5-*H*H), 4.42 (1H, *app* t, *J* 9.0, 5-H*H*), 6.22 (1H, dd, *J* 2.0, 1.0, ArH), 6.90 (2H, d, *J* 8.5, ArH), 7.13 (2H, d, *J* 8.0, ArH), 7.22 (1H, t, *J* 1.0, ArH), 7.32 (1H, t, *J* 2.0, ArH); δ_C (100 MHz, $CDCl_3$) 22.6 (C-6), 44.8 (C-4), 47.4 (C-3), 55.4 (OCH_3), 72.4 (C-5), 111.8 (Ar-C), 114.7 (Ar-C), 120.2 (Ar-C), 128.6 (Ar-C), 129.6 (Ar-C), 140.9 (Ar-C), 143.2 (Ar-C), 159.3 (Ar-C), 177.7 (C-2); Found (ESI) 295.0944 $[MNa]^+$, (required $C_{16}H_{16}NaO_4$ 295.0941).

5b (3*R*,4*S*)-4-(4-Methoxyphenyl)-3-(3-thienylmethyl)-dihydrofuran-2(3*H*)-one



General procedure E gave compound **5b** as a colourless oil (39 mg, 52%) starting from compound **15c** (50 mg, 0.26 mmol), bromide **S4** (74 mg, 0.42 mmol) and LiHMDS (0.5M, 0.84 ml, 0.42 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 9:1). $[\alpha]_D$ +3.0 (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3106, 3002, 2918, 2838, 1770, 1612; δ_H (400 MHz, $CDCl_3$) 2.93-3.01 (2H, m, 3-H+6-*H*H), 3.13-3.22 (1H, m, 6-H*H*), 3.29 (1H, br *app* td, *J* 10.0, 8.0, 4-H), 3.81 (3H, s, OCH_3), 4.05 (1H, dd, *J* 10.0, 9.0, 5-*H*H), 4.39 (1H, dd, *J* 9.0, 8.0, 5-H*H*), 6.85-6.91 (3H, m, ArH), 6.95-7.01 (1H, m, ArH), 7.10 (2H, d, *J* 8.5, ArH), 7.22 (1H, dd, *J* 5.0, 2.0, ArH); δ_C (100 MHz, $CDCl_3$) 27.9 (C-6), 54.0 (C-4), 47.8 (C-3), 55.5 (OCH_3), 72.5 (C-5), 114.6 (Ar-C), 123.2 (Ar-C), 125.9 (Ar-C), 128.5 (Ar-C), 129.0 (Ar-C), 129.7 (Ar-C), 137.4 (Ar-C), 159.2 (Ar-C), 177.8 (C-2); Found (ESI) 311.0724 $[MNa]^+$, (required $C_{16}H_{16}NaO_3S$ 311.0712).

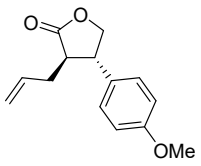
5c (3*R*,4*S*)-4-(4-Methoxyphenyl)-3-(2-thienylmethyl)-dihydrofuran-2(3*H*)-one



General procedure E gave compound **5c** as a pale yellow oil (41 mg, 54%) starting from compound **15c** (50 mg, 0.26 mmol), bromide **S5** (74 mg, 0.42 mmol) and LiHMDS (0.5M, 0.84 ml, 0.42 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 9:1-5:1). $[\alpha]_D$ +8.0 (*c* 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3003, 2962,

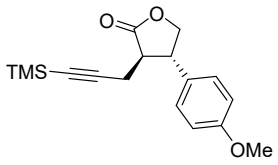
2917, 2840, 1773, 1612; δ_H (400 MHz, $CDCl_3$) 2.99 (1H, *app* dt, *J* 11.0, 5.0, 3-H), 3.12 (1H, dd, *J* 15.0, 5.0, 6-*H*H), 3.34-3.47 (2H, m, 6-H*H*+4-H), 3.81 (3H, s, OCH_3), 4.09 (1H, dd, *J* 10.0, 9.0, 5-*H*H), 4.41 (1H, *app* t, *J* 8.5, 5-H*H*), 6.83 (1H, dd, *J* 3.5, 1.0, ArH), 6.86-6.94 (3H, m, ArH), 7.10-7.17 (3H, m, ArH); δ_C (100 MHz, $CDCl_3$) 27.5 (C-6), 44.5 (C-4), 48.5 (C-3), 55.4 (OCH_3), 72.4 (C-5), 114.6 (Ar-C), 124.7 (Ar-C), 127.2 (Ar-C), 127.3 (Ar-C), 128.6 (Ar-C), 129.5 (Ar-C), 138.8 (Ar-C), 159.3 (Ar-C), 177.3 (C-2); Found (ESI) 311.0719 $[MNa]^+$, (required $C_{16}H_{16}NaO_3S$ 311.0712).

5d (3*R*,4*S*)-3-Allyl-4-(4-methoxyphenyl)-dihydrofuran-2(3*H*)-one



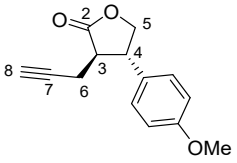
General procedure E gave compound **5d** as a colourless oil (478 mg, 53%) starting from compound **15c** (750 mg, 3.90 mmol), allyl iodide (0.39 ml, 4.29 mmol) and LiHMDS (0.5M, 8.6 ml, 4.30 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 9:1). $[\alpha]_D$ +5.0 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3003, 2964, 2908, 2838, 1769, 1612; δ_H (400 MHz, $CDCl_3$) 2.36-2.58 (2H, m, 6-H_2), 2.78 (1H, m, 3-H), 3.45 (1H, br *app* td, *J* 10.5, 8.0, 4-H), 3.81 (3H, s, OCH_3), 4.11 (1H, dd, *J* 10.0, 9.0, 5-*H*H), 4.51 (1H, dd, *J* 9.0, 8.0, 5-H*H*), 5.04-5.15 (2H, m, 8-H_2), 5.71 (1H, dddd, *J* 16.8, 10.0, 8.0, 6.5, 7-H), 6.90 (2H, d, *J* 8.5, ArH), 7.16 (2H, d, *J* 8.5, ArH); δ_C (100 MHz, $CDCl_3$) 32.4 (C-6), 45.5 (C-4), 46.5 (C-3), 55.3 (OCH_3), 72.3 (C-5), 114.5 (Ar-C), 118.5 (C-8), 128.4 (Ar-C), 129.8 (Ar-C), 133.7 (C-7), 159.2 (Ar-C), 177.5 (C-2); Found (ESI) 255.0995 $[MNa]^+$, (required $C_{14}H_{16}NaO_3$ 255.0992).

17 (3*R*,4*S*)-4-(4-Methoxyphenyl)-3-(3-(trimethylsilyl)propargyl)-dihydrofuran-2(3*H*)-one



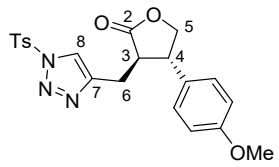
General procedure E gave compound **17** as a colourless oil (40 mg, 51%) starting from compound **15c** (50 mg, 0.26 mmol), TMS-propargyl bromide (67 µl, 0.42 mmol) and LiHMDS (0.5M, 0.84 ml, 0.42 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 5:1). $[\alpha]_D$ +3.0 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3003, 2959, 2909, 2839, 2178, 1774, 1613; δ_H (400 MHz, $CDCl_3$) 0.09 (9H, s, $Si(CH_3)_3$), 2.60 (1H, dd, *J* 17.0, 5.0, 6-*H*H), 2.71 (1H, dd, *J* 17.0, 6.0, 6-H*H*), 2.79 (1H, ddd, *J* 10.5, 6.0, 5.0, 3-H), 3.70 (1H, br *app* td, *J* 10.5, 8.0, 4-H), 3.80 (3H, s, OCH_3), 4.16 (1H, m, 5-*H*H), 4.56 (1H, *app* t, *J* 8.5, 5-H*H*), 6.90 (2H, d, *J* 8.5, ArH), 7.20 (2H, d, *J* 8.5, ArH); δ_C (100 MHz, $CDCl_3$) 0.06 ($Si(CH_3)_3$), 19.4 (C-6), 45.7 (C-4), 46.1 (C-3), 55.4 (OCH_3), 72.3 (C-5), 88.3 (C-8), 101.8 (C-7), 114.6 (Ar-C), 128.6 (Ar-C), 129.7 (Ar-C), 159.4 (Ar-C), 176.6 (C-2); Found (ESI) 325.1233 $[MNa]^+$, (required $C_{17}H_{22}NaO_3Si$ 325.1230).

18 (3*R*,4*S*)-4-(4-Methoxyphenyl)-3-(propargyl)-dihydrofuran-2(3H)-one



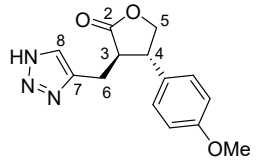
K_2CO_3 (41 mg, 0.30 mmol) was added to a solution of compound **17** (30 mg, 0.10 mmol) in MeOH (1 ml) at room temperature. The reaction was stirred for 1.5 hours and quenched with 1M HCl (3 ml). The aqueous phase was extracted with EtOAc (3x4 ml) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether:EtOAc = 5:1) to give compound **18** as a colourless oil (11 mg, 49%) $[\alpha]_D$ +12.0 (*c* 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3286, 3002, 2965, 2912, 2841, 1771, 1613; δ_H (400 MHz, $CDCl_3$) 2.03 (1H, t, *J* 2.5, 8-H), 2.47 (1H, m, 6-*H*H), 2.71-2.84 (2H, m, 3-H+6-H*H*), 3.75 (1H, m, 4-H), 3.81 (3H, s, OCH_3), 4.18 (1H, dd, *J* 10.5, 9.0, 5-*H*H), 4.58 (1H, dd, *J* 9.0, 8.0, 5-H*H*), 6.91 (2H, d, *J* 8.5, ArH), 7.21 (1H, d, *J* 8.5, ArH); δ_C (100 MHz, $CDCl_3$) 0.06 ($Si(CH_3)_3$), 17.6 (C-6), 45.1 (C-4), 46.0 (C-3), 55.5 (OCH_3), 71.7 (C-8), 72.1 (C-5), 79.5 (C-7), 114.7 (Ar-C), 128.6 (Ar-C), 129.1 (Ar-C), 159.4 (Ar-C), 176.3 (C-2); Found (ESI) 353.0838 $[MNa]^+$, (required $C_{14}H_{14}NaO_3$ 353.0835).

5e (3*R*,4*S*)-4-(4-Methoxyphenyl)-3-((1-tosyl-1H-1,2,3,-triazol-4-yl)methyl)-dihydrofuran-2(3H)-one



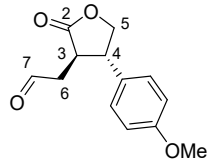
CuI (7 mg, 0.04 mmol) and 2,6-lutidine (50 µl, 0.43 mmol) were added to a solution of alkyne **18** (100 mg, 0.43 mmol) and tosyl azide (71 mg, 0.36 mmol) in $CHCl_3$ (1 ml) at 0 °C. The reaction was stirred overnight. The reaction mixture was filtered off and the solvent was removed. The crude product was purified by column chromatography (petroleum ether:EtOAc = 6:1) to give compound **5e** as a colourless oil (111 mg, 60%) $[\alpha]_D$ +6.0 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2962, 2911, 2839, 1771, 1613; δ_H (400 MHz, $CDCl_3$) 2.44 (3H, s, CH_3), 3.01 (1H, m, 3-H), 3.09 (2H, d, *J* 5.5, 6-H_2), 3.45 (1H, br ddd, *J* 11.0, 10.5, 8.0, 4-H), 3.79 (3H, s, OCH_3), 4.12 (1H, dd, *J* 10.5, 9.0, 5-*H*H), 4.43 (1H, dd, *J* 9.0, 8.0, 5-H*H*), 6.85 (2H, d, *J* 8.5, ArH), 7.16 (2H, d, *J* 8.5, ArH), 7.37 (2H, d, *J* 8.0, ArH), 7.90 (1H, s, 8-H), 7.94 (2H, d, *J* 8.0, ArH); δ_C (100 MHz, $CDCl_3$) 22.0 (CH_3), 23.7 (C-6), 45.7 (C-4), 47.0 (C-3), 55.4 (OCH_3), 72.1 (C-5), 114.7 (Ar-C), 122.7 (C-8), 128.65 (Ar-C), 128.68 (Ar-C), 128.8 (Ar-C), 130.5 (Ar-C), 133.2 (Ar-C), 143.5 (C-7), 147.35 (Ar-C), 159.4 (Ar-C), 176.9 (C-2); Found (ESI) 450.1094 $[MNa]^+$, (required $C_{21}H_{21}N_3NaO_5S$ 450.1094).

5f (3*R*,4*S*)-4-(4-Methoxyphenyl)-3-((1H-1,2,3,-triazol-4-yl)methyl)-dihydrofuran-2(3*H*)-one



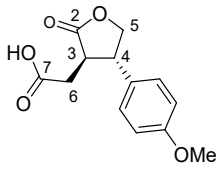
Magnesium powder (28 mg, 1.17 mmol) was added to a solution of triazole **5e** (50 mg, 0.12 mmol) in dry MeOH (1 ml) at 0 °C under a nitrogen atmosphere. The reaction was stirred for 4 hours and allowed to warm to room temperature. The reaction was quenched with 1M HCl (5 ml) and stirred until all of the remaining magnesium was dissolved. The reaction mixture was partitioned between water (5 ml) and EtOAc (5 ml). The phases were separated and the aqueous phase was extracted with EtOAc (2x5 ml). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether:EtOAc = 2:1) to give compound **5f** as a colourless oil (9 mg, 28%). $[\alpha]_D$ +12.0 (*c* 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3147, 2961, 2925, 2854, 1768, 1613; δ_H (400 MHz, $CDCl_3$) 3.00-3.12 (2H, m, 3-H+6-*H*H), 3.19 (1H, m, 6-H*H*), 3.44 (1H, br *app* td, *J* 10.5, 8.0, 4-H), 3.80 (3H, s, OCH_3), 4.15 (1H, dd, *J* 10.5, 9.0, 5-*H*H), 4.47 (1H, dd, *J* 9.0, 8.0, 5-H*H*), 6.89 (2H, d, *J* 8.5, ArH), 7.17 (2H, d, *J* 8.5, ArH), 7.52 (1H, s, 8-H); δ_C (100 MHz, $CDCl_3$) 23.1 (C-6), 45.5 (C-4), 47.2 (C-3), 55.5 (OCH_3), 72.4 (C-5), 114.8 (Ar-C), 128.6 (Ar-C), 128.9 (Ar-C), 159.4 (Ar-C), 177.7 (C-2); Found (ESI) 274.1186 $[MH]^+$, (required $C_{14}H_{16}N_3O_3$ 274.1186).

19 2-((3*R*,4*S*)-4-(4-Methoxyphenyl)-2-oxotetrahydrofuran-3-yl)-acetaldehyde



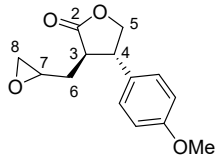
OsO_4 (1 crystal) was added to a solution of alkene **5d** (150 mg, 0.65 mmol) and sodium (meta)periodate (622 mg, 2.91 mmol) in THF/water (4 ml, 1:1). The reaction was stirred for 3.5 hours and then water (4 ml) was added to the reaction. The aqueous phase was extracted with EtOAc (3x10 ml) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether:EtOAc = 3:1) to give compound **19** as a colourless oil (90 mg, 60%). $[\alpha]_D$ +6.0 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3002, 2966, 2908, 2839, 1771, 1721, 1613; δ_H (400 MHz, $CDCl_3$) 2.75 (1H, dd, *J* 18.5, 5.5, 6-*H*H), 2.88 (1H, dd, *J* 18.5, 5.5, 6-H*H*), 3.16 (1H, *app* dt, *J* 12.0, 5.5, 3-H), 3.50 (1H, br ddd, *J* 12.0, 10.5, 8.0, 4-H), 3.80 (3H, s, OCH_3), 4.16 (1H, dd, *J* 10.5, 9.0, 5-*H*H), 4.59 (1H, dd, *J* 9.0, 8.0, 5-H*H*), 6.90 (2H, d, *J* 8.5, ArH), 7.17 (2H, d, *J* 8.5, ArH), 9.71 (1H, s, 7-H); δ_C (100 MHz, $CDCl_3$) 41.49 (C-6), 41.54 (C-3), 46.5 (C-4), 55.3 (OCH_3), 72.5 (C-5), 114.6 (Ar-C), 128.4 (Ar-C), 128.5 (Ar-C), 159.3 (Ar-C), 177.1 (C-2), 198.9 (C-7); Found (ESI) 257.0777 $[MNa]^+$, (required $C_{13}H_{14}NaO_4$ 257.0784).

5g 2-((3*R*,4*S*)-4-(4-Methoxyphenyl)-2-oxotetrahydrofuran-3-yl)-acetic acid



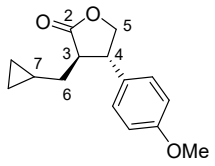
A solution of $NaClO_2$ (116 mg, 1.28 mmol) and $NaHPO_4$ (154 mg, 1.28 mmol) in water (0.25 ml) was added to a solution of aldehyde **19** (30 mg, 0.13 mmol) in 2-methylbut-2-ene (0.15 ml) and ^{t}BuOH (0.5 ml). The reaction was stirred for 1 hour and then water (1 ml) was added to the reaction. The aqueous phase was extracted with EtOAc (3x3 ml) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether:EtOAc = 2:1+1% AcOH) to give compound **5g** as a colourless oil (9 mg, 28%). $[\alpha]_D$ +8.0 (*c* 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3228, 2969, 2912, 2841, 1772, 1714, 1613; δ_H (400 MHz, $CDCl_3$) 2.71 (2H, d, *J* 5.5, 6-H_2), 3.05 (1H, dd, *J* 12.0, 5.5, 3-H), 3.57 (1H, br ddd, *J* 12.0, 10.5, 8.0, 4-H), 3.80 (3H, s, OCH_3), 4.17 (1H, dd, *J* 10.5, 9.0, 5-*H*H), 4.58 (1H, dd, *J* 9.0, 8.0, 5-H*H*), 6.91 (2H, d, *J* 8.5, ArH), 7.19 (2H, d, *J* 8.5, ArH); δ_C (100 MHz, $CDCl_3$) 32.0 (C-6), 43.5 (C-3), 46.3 (C-4), 55.5 (OCH_3), 72.5 (C-5), 114.6 (Ar-C), 128.5 (Ar-C), 128.6 (Ar-C), 159.6 (Ar-C), 176.0 (C-7), 177.0 (C-2); Found (ESI) 273.0734 $[MNa]^+$, (required $C_{13}H_{14}NaO_5$ 273.0733).

5h (3*R*,4*S*)-4-(4-Methoxyphenyl)-3-(((*RS*)-oxiran-2-yl)methyl)-dihydrofuran-2(3*H*)-one



3-Chloroperbenzoic acid (45 mg, 0.26 mmol) was added to a solution of alkene **10l** (50 mg, 0.22 mmol) in dry DCM (1 ml) at 0 °C. The reaction was stirred overnight and allowed to warm to room temperature. The reaction mixture was diluted with DCM (4 ml) washed with sat. aq. $Na_2S_2O_3$ (5 ml), 1M NaOH (5 ml), water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether:EtOAc = 4:1) to give compound **5h** as a colourless oil as a 1:1 mixture of diastereomers (21 mg, 39%). ν_{max} (neat)/cm^{-1} 2997, 2970, 2917, 2839, 1772, 1613; δ_H (400 MHz, $CDCl_3$) 1.62 (1H, m, 1x 6-*H*H), 1.84 (1H, ddd, *J* 14.5, 7.5, 5.0, 1x 6-*H*H), 1.98 (1H, ddd, *J* 14.5, 6.5, 4.0, 1x 6-H*H*), 2.07 (1H, ddd, *J* 14.5, 7.5, 4.5, 1x 6-H*H*), 2.40 (1H, dd, *J* 5.0, 2.5, 1x 8-*H*H), 2.44 (1H, dd, *J* 5.0, 2.5, 1x 8-*H*H), 2.64 (1H, dd, *J* 5.0, 4.0, 1x 8-H*H*), 2.72 (1H, dd, *J* 5.0, 4.0, 1x 8-H*H*), 2.83-2.95 (3H, m, 1x 3-H, 2x 7-H), 3.03-3.11 (1H, m, 1x 3-H), 3.45 (1H, *app* td, *J* 11.0, 8.0, 1x 4-H), 3.60 (1H, ddd, *J* 12.0, 10.5, 8.0, 1x 4-H), 3.80 (3H, s, 2x OCH_3), 4.07-4.15 (2H, m, 2x 5-*H*H), 4.50-4.58 (2H, m, 2x 5-H*H*), 6.87-6.93 (4H, m, ArH), 7.18-7.25 (4H, m, ArH); δ_C (100 MHz, $CDCl_3$) 31.6 (C-6), 32.6 (C-6), 44.6 (C-7), 44.8 (C-7), 47.01 (C-4), 47.03 (C-8), 47.4 (C-4), 47.8 (C-8), 49.6 (C-3), 50.0 (C-3), 55.4 (OCH_3), 72.5 (C-5), 72.7 (C-5), 114.66 (Ar-C), 114.69 (Ar-C), 128.50 (Ar-C), 128.55 (Ar-C), 129.0 (Ar-C), 129.1 (Ar-C), 159.38 (Ar-C), 159.40 (Ar-C), 177.5 (C-2), 177.7 (C-2); Found (ESI) 271.0937 $[MNa]^+$, (required $C_{14}H_{16}NaO_4$ 271.0941).

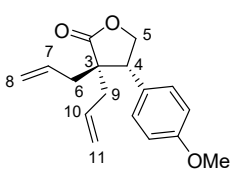
5i (3*R*,4*S*)-3-(Cyclopropylmethyl)-4-(4-methoxyphenyl)-dihydrofuran-2(3*H*)-one



Et_2Zn (1M, 1.08 ml, 1.08 mmol) was added dropwise to a solution of alkene **5d** (50 mg, 0.22 mmol) in dry DCM (4 ml) at -78 °C under a nitrogen atmosphere followed by CH_2I_2 (86 µl, 1.08 mmol). The reaction was stirred overnight and allowed to warm to room temperature. The reaction was quenched with sat. aq. NH_4Cl (4 ml) and 1M HCl (0.5 ml). The phases were separated, and the aqueous phase was extracted with DCM (2x5 ml). The combined organic phases were washed with sat. aq. $Na_2S_3O_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether:EtOAc = 6:1) to give compound **5i** as a colourless oil (9 mg, 17%). $[\alpha]_D$ +18.0 (*c* 0.33, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3079, 2997, 2970, 2912, 1773, 1613; δ_H (400 MHz, $CDCl_3$) -0.02-0.04 (2H, m, 2x C*H*H), 0.33-0.40 (2H, m, 2x CH*H*), 0.62-0.76 (1H, m, 7-H), 1.59-1.65 (2H, m, 6-H_2), 2.82 (1H, dt, *J* 10.5, 6.0, 3-H), 3.55 (1H, br *app* td, *J* 10.5, 8.0, 4-H), 3.81 (3H, s, OCH_3), 4.05 (1H, dd, *J* 10.5, 9.0, 5-*H*H), 4.52 (1H, dd, *J* 9.0, 8.0, 5-H*H*), 6.90 (2H, d, *J* 8.5, ArH), 7.20 (2H, d, *J* 8.5, ArH); δ_C

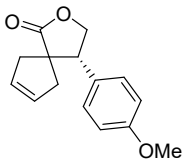
(100 MHz, $CDCl_3$) 5.0 (CH_2), 5.2 (CH_2), 8.6 (C-7), 33.8 (C-6), 46.9 (C-4), 47.03 (C-3), 55.5 (OCH_3), 72.7 (C-5), 114.6 (Ar-C), 128.5 (Ar-C), 130.2 (Ar-C), 159.3 (Ar-C), 178.5 (C-2); Found (ESI) 269.1143 $[MNa]^+$, (required $C_{15}H_{18}NaO_3$ 269.1148).

20 (3*R*,4*S*)-3,3-(Diallyl)-4-(4-methoxyphenyl)-dihydrofuran-2(3*H*)-one



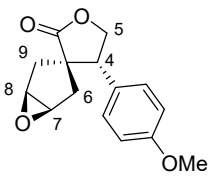
General procedure E gave compound **20** as a colourless oil (657 mg, 62%) starting from compound **15c** (750 mg, 3.90 mmol), allyl iodide (1.61 ml, 17.60 mmol) and LiHMDS (0.5M, 12.5 ml, 6.25 mmol). The crude product was purified by column chromatography (petroleum ether:EtOAc = 9:1). $[\alpha]_D$ +8.0 (*c* 0.5, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3076, 2976, 2913, 2839, 1768, 1612; δ_H (400 MHz, $CDCl_3$) 1.82 (1H, ddt, *J* 14.0, 7.5, 1.0, 9-*H*H), 2.17 (1H, ddt, *J* 14.0, 9.0, 1.0, 6-*H*H), 2.24 (1H, ddt, *J* 14.0, 7.0, 1.0, 9-H*H*), 2.63 (1H, ddt, *J* 14.0, 5.5, 1.5, 6-H*H*), 3.72 (1H, t, *J* 8.5, 4-H), 3.81 (3H, s, OCH_3), 4.48 (2H, m, 5-H_2), 4.94 (1H, ddt, *J* 17.0, 2.0, 1.0, 11-*H*H), 5.04 (1H, ddt, *J* 10.0, 2.0, 1.0, 11-H*H*), 5.21-5.29 (2H, m, 8-H_2), 5.64 (1H, dddd, *J* 17.0, 10.0, 7.5, 7.0, 10-H), 5.78 (1H, dddd, *J* 17.0, 9.5, 9.0, 5.5, 7-H), 6.89 (2H, d, *J* 8.5, Ar-H), 7.12 (2H, d, *J* 8.5, Ar-H); δ_C (100 MHz, $CDCl_3$) 36.7 (C-9), 38.5 (C-6), 46.6 (C-4), 49.9 (C-3), 55.4 (OCH_3), 69.1 (C-5), 114.3 (Ar-C), 119.4 (C-11), 120.4 (C-8), 127.6 (Ar-C), 129.6 (Ar-C), 132.4 (C-10), 133.6 (C-7), 159.2 (Ar-C), 179.0 (C-2); Found (ESI) 295.1307 $[MNa]^+$, (required $C_{17}H_{20}NaO_3$ 295.1305). The signals of the allyl groups were assigned using nOe studies irradiating signal assigned to 7-H.

6a (*R*)-4-(4-Methoxyphenyl)-2-oxaspiro[4.4]non-7-en-1-one



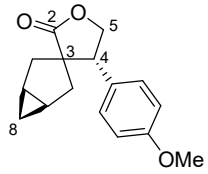
Hoveda-Grubbs second generation catalyst (101 mg, 0.12 mmol) was added to a solution of diallyl compound **20** (650 mg, 2.39 mmol) in DCM (200 ml). The reaction was refluxed overnight. The solvent was evaporated and the crude product was purified by column chromatography (petroleum ether:EtOAc = 5:1) to give compound **6a** as a brown oil (515 mg, 88%). $[\alpha]_D$ +8.0 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3064, 3000, 2961, 2939, 2909, 2845, 1768, 1612; δ_H (400 MHz, $CDCl_3$) 2.19 (1H, *app* dp, *J* 17.0, 2.0, 1x C*H*H), 2.52 (1H, *app* dp, *J* 17.0, 2.0, CH*H*), 2.68 (1H, *app* dp, *J* 16.5, 2.0, C*H*H), 2.94 (1H, *app* dp, *J* 16.5, 2.0, 1x CH*H*), 3.41 (1H, dd, *J* 6.5, 5.0, 4-H), 3.79 (3H, s, OCH_3), 4.44 (1H, dd, *J* 9.0, 5.0, 5-*H*H), 4.60 (1H, dd, *J* 9.0, 6.5, 5-H*H*), 5.61 (1H, dt, *J* 6.0, 2.0, 1x CH), 5.97 (1H, dt, *J* 6.0, 2.0, 1x CH), 6.85 (2H, d, *J* 8.5, Ar-H), 7.04 (2H, d, *J* 8.5, Ar-H); δ_C (100 MHz, $CDCl_3$) 37.9 (CH_2), 44.5 (CH_2), 51.7 (C-4), 52.6 (C-3), 55.4 (OCH_3), 70.9 (C-5), 114.4 (Ar-C), 127.3 (CH), 128.6 (Ar-C), 129.1 (CH), 130.5 (Ar-C), 159.1 (Ar-C), 182.0 (C-2); Found (ESI) 267.0985 $[MNa]^+$, (required $C_{15}H_{16}NaO_3$ 267.0992).

6b (4'*R*)-4'-(4-Methoxyphenyl)dihydro-2'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,3'-furan]-2'-one



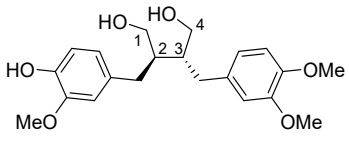
3-Chloroperbenzoic acid (71 mg, 0.41 mmol) was added to a solution of alkene **6a** (50 mg, 0.21 mmol) in dry DCM (1 ml) at 0 °C. The reaction was stirred overnight and allowed to warm to room temperature. The reaction mixture was diluted with DCM (4 ml) washed with sat. aq. $Na_2S_2O_3$ (5 ml), 1M NaOH (5 ml), water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether:EtOAc = 4:1) to give compound **6b** as a colourless oil (12 mg, 22%). $[\alpha]_D$ +16.0 (*c* 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2966, 2920, 2838, 1769, 1612; δ_H (400 MHz, $CDCl_3$) 1.65 (1H, d, *J* 15.0, 9-H), 2.01 (1H, dd, *J* 15.0, 1.0, 9-H), 2.02 (1H, dd, *J* 14.0, 1.5, 6-H), 2.39 (1H, d, *J* 14.0, 6-H), 3.34 (1H, d, *J* 6.0, 4-H), 3.47 (1H, dd, *J* 2.0, 1.0, 8-H), 3.65 (1H, d, *J* 2.0, 1.5, 7-H), 3.79 (3H, s, OCH_3), 4.49 (1H, d, *J* 9.0, 5-*H*H), 4.59 (1H, dd, *J* 9.0, 6.0, 5-H*H*), 6.86 (2H, d, *J* 8.5, ArH), 7.05 (2H, d, *J* 8.5, ArH); δ_C (100 MHz, $CDCl_3$) 32.9 (CH_2), 38.9 (CH_2), 50.7 (C-3), 52.7 (C-4), 55.4 (OCH_3), 55.8 (CH), 57.4 (CH), 72.4 (C-5), 114.5 (Ar-C), 129.2 (Ar-C), 132.4 (Ar-C), 158.9 (Ar-C), 181.0 (C-2); Found (ESI) 283.0936 $[MNa]^+$, (required $C_{15}H_{16}NaO_4$ 283.0941).

6c (4'*R*)-4' (4-Methoxyphenyl)dihydro-2'H-spiro[bicyclo[3.1.0]hexane-3,3'-furan]-2'-one



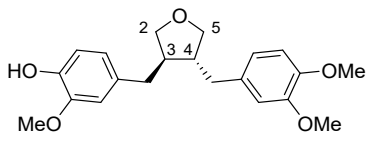
Et_2Zn (1M, 1.23 ml, 1.23 mmol) was added dropwise to a solution of alkene **6a** (30 mg, 0.12 mmol) in dry DCM (3 ml) at -78 °C under a nitrogen atmosphere followed by CH_2I_2 (98 µl, 1.23 mmol). The reaction was stirred overnight and allowed to warm to room temperature. The reaction was quenched with sat. aq. NH_4Cl (4 ml) and 1M HCl (0.5 ml). The phases were separated, and the aqueous phase was extracted with DCM (2x5 ml). The combined organic phases were washed with sat. aq. $Na_2S_3O_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether:EtOAc = 6:1) to give compound **6c** as a colourless oil (11 mg, 35%). $[\alpha]_D$ +8.0 (*c* 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3039, 3003, 2924, 2860, 2838, 1764, 1612; δ_H (400 MHz, $CDCl_3$) 0.48 (1H, m, 8-*H*H), 0.83 (1H, *app* q, *J* 4.0, 8-H*H*), 1.19 (1H, m, CH), 1.31 (1H, m, CH), 1.69 (1H, d, *J* 14.0, C*H*H), 1.83 (1H, dd, *J* 14.0, 5.5, CH*H*), 2.16-2.26 (2H, m, CH_2), 3.35 (1H, t, *J* 6.0, 4-H), 3.80 (3H, s, OCH_3), 4.32 (1H, dd, *J* 9.0, 6.0, 5-*H*H), 4.49 (1H, dd, *J* 9.0, 6.0, 5-H*H*), 6.87 (2H, d, *J* 8.5, ArH), 7.08 (2H, d, *J* 8.5, ArH); δ_C (100 MHz, $CDCl_3$) 12.1 (C-8), 18.0, (CH), 18.6 (CH), 33.5 (CH_2), 39.8 (CH_2), 53.3 (C-4), 55.2 (C-3), 55.4 (OCH_3), 70.6 (C-5), 114.3 (Ar-C), 129.2 (Ar-C), 130.2 (Ar-C), 159.2 (Ar-C), 182.4 (C-2); Found (ESI) 281.1145 $[MNa]^+$, (required $C_{16}H_{18}NaO_3$ 281.1148).

7a (2*R*,3*R*)-2-(3,4-Dimethoxybenzyl)-3-(4-hydroxy-3-methoxybenzyl)butane-1,4-diol



A solution of $LiBH_4$ (2M, 2.95 ml, 5.91 mmol) was added to a solution of (-)-arctigenin **1** (110 mg, 0.30 mmol) in dry THF (6 ml) under a nitrogen atmosphere. The reaction mixture was heated to reflux and stirred overnight. The reaction was allowed to cool to room temperature and quenched with 1M HCl (10 ml) and the aqueous phase was extracted with EtOAc (3x25 ml). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether:EtOAc = 1:4) to give compound **7a** as a colourless oil (85 mg, 77%). All spectral data were consistent with literature.[28] $[\alpha]_D$ -24 (*c* 1.0, $CHCl_3$), *lit.*[28] $[\alpha]_D$ -34 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.78-1.94 (2H, br s, 2-H+3-H), 2.57-2.83 (4H, m, 2x C*H*$_2$Ar), 2.86-3.13 (2H, br s, OH), 3.50-3.59 (2H, m, 1-*H*H+4-*H*H), 3.78-3.89 (2H, m, 1-H*H*+4-H*H*), 3.81 (6H, s, 2x OCH_3), 3.85 (3H, s, OCH_3), 5.55 (1H, br s, OH), 6.57-6.70 (4H, m, Ar-H), 6.76 (1H, d, *J* 8.0, Ar-H), 6.81 (1H, d, *J* 8.0, Ar-H); δ_C (100 MHz, $CDCl_3$) 35.97+36.04 (2x *C*H_2Ar), 43.94+44.07 (C-2+C-3), 55.93 (OCH_3), 55.96 (OCH_3), 56.04 (OCH_3), 60.8 (C-1+C-4), 111.2 (Ar-C), 111.5 (Ar-C), 112.2 (Ar-C), 114.3 (Ar-C), 121.1 (Ar-C), 121.8 (Ar-C), 132.5 (Ar-C), 133.3 (Ar-C), 144.0 (Ar-C), 146.6 (Ar-C), 147.4 (Ar-C), 149.0 (Ar-C).

7b (3*R*,4*R*)-3-(3,4-Dimethoxybenzyl)-4-(4-hydroxy-3-methoxybenzyl)-tetrahydrofuran



A solution of diol **7a** (42 mg, 0.112 mmol) and *p*-toluenesulfonic acid (1 mg) in dry DCM (2.5 ml) was refluxed under a N_2-atmosphere over the weekend. The reaction was allowed to cool to room temperature and the solvent was evaporated. The crude product was purified by column chromatography (petroleum ether:EtOAc = 1:1) to give compound **7b** as a colourless oil (38 mg, 95%). All spectral data were consistent with literature.[14] $[\alpha]_D$ -30 (*c* 1.0, $CHCl_3$), *lit.*[29] $[\alpha]_D$ -38 (*c* 0.7, MeOH); δ_H (400 MHz, $CDCl_3$) 2.11-2.24 (2H, m, 3-H+4-H), 2.46-2.67 (4H, m, 2x C*H*$_2$Ar), 3.48-3.58 (2H, m, 2-*H*H+5-*H*H), 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.88-3.95 (2H, m, 2-H*H*+5-H*H*), 5.59 (1H, br s, OH), 6.50-6.65 (4H, m, Ar-H), 6.75 (1H, d, *J* 8.0, Ar-H), 6.80 (1H, d, *J* 8.0, Ar-H); δ_C (100 MHz, $CDCl_3$) 39.20+39.25 (2x *C*H_2Ar), 46.6+46.7 (C-3+C-4), 55.9 (OCH_3), 56.0 (OCH_3), 73.4 (C-2+C-5), 111.2 (Ar-C), 112.0 (Ar-C), 114.3 (Ar-C), 120.6 (Ar-C), 121.4 (Ar-C), 132.4 (Ar-C), 133.1 (Ar-C), 144.0 (Ar-C), 146.5 (Ar-C), 147.5 (Ar-C), 148.9 (Ar-C).

3 Determination of the Relative Stereochemistry of Compound 6b

The stereochemistry of **6b** was determined by recording and analysing a 2D nOe spectrum (NOESY). From these data, the signal at δ 2.39 ppm can be assigned as 6_a-H due enhancement of 4-H (Figure S1, red circle). The CH-proton α to the oxygen in the epoxide ring (labelled 7) shows enhancement of both of the neighbouring CH_2 protons – the one below and the one above the five-membered ring (6_a and 6_b, green circle). The same is valid for the second CH-proton in the epoxide. It is therefore not clear which of the two protons of the methylene group is on the same side of the five-membered ring as 7-H.

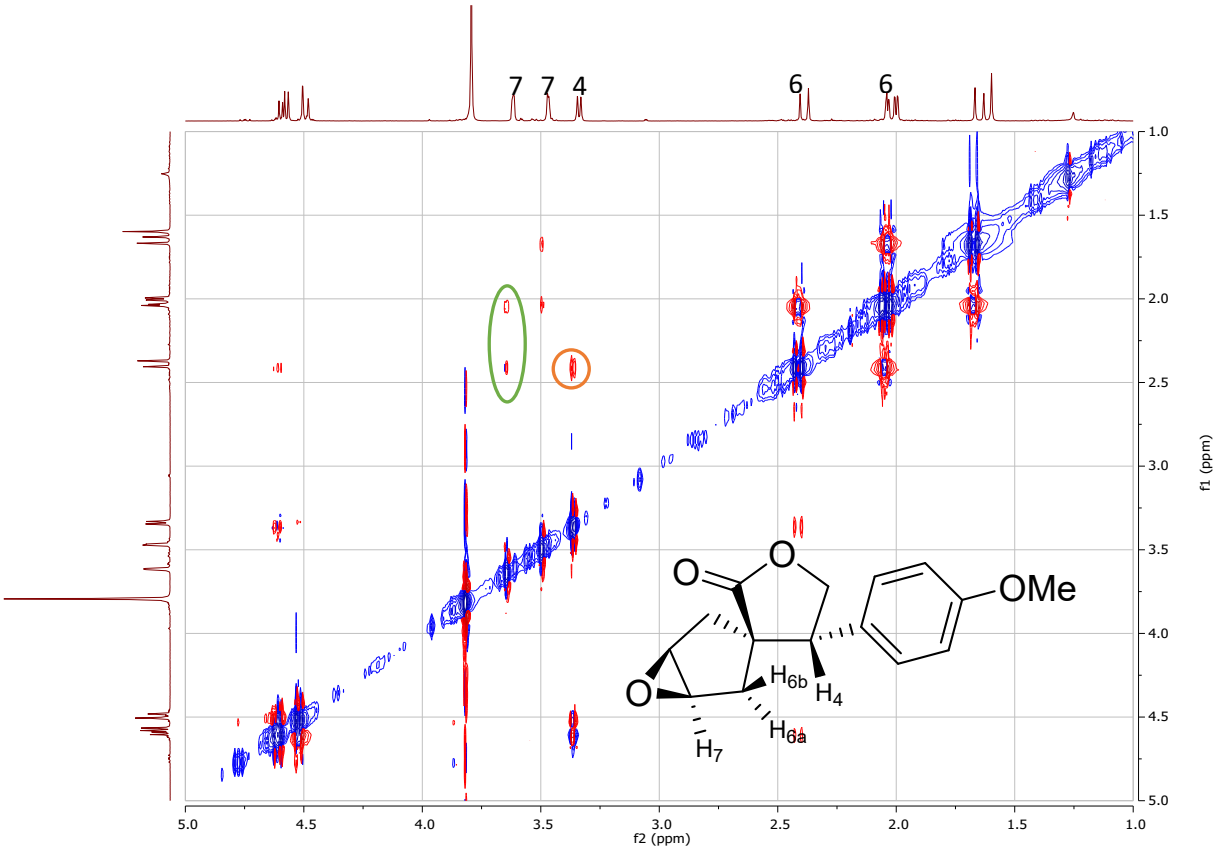


Figure S1: 2D-nOe spectrum of epoxide 6b. Red and green circles highlight important signals.

The distance between the two proton pairs 7-6_a and 7-6_b can be determined and compared to the distance in DFT calculations using previously reported nOe-based methodology.[30] Therefore, a F2-slice of the nOe spectrum was extracted at the F1-chemical shift of proton 7 (δ 3.61 ppm, Figure S2). According to the following equation, the ratio of the integrals of the relative nOe signals is proportional to the ratio of the interproton distances:

$$\eta_{7-6b}:\eta_{7-6a} = \left(r_{7-6b}:r_{7-6a}\right)^{-1/6}$$

The observed ratio of the integrals is $(\eta_{7\text{-}6b}:\eta_{7\text{-}6a})^{1/6} = (1.67:1)^{1/6} = 1.089$. This means that the distance of 7-H to 6_b-H is 8.9% longer than the distance of 7H-6_a.

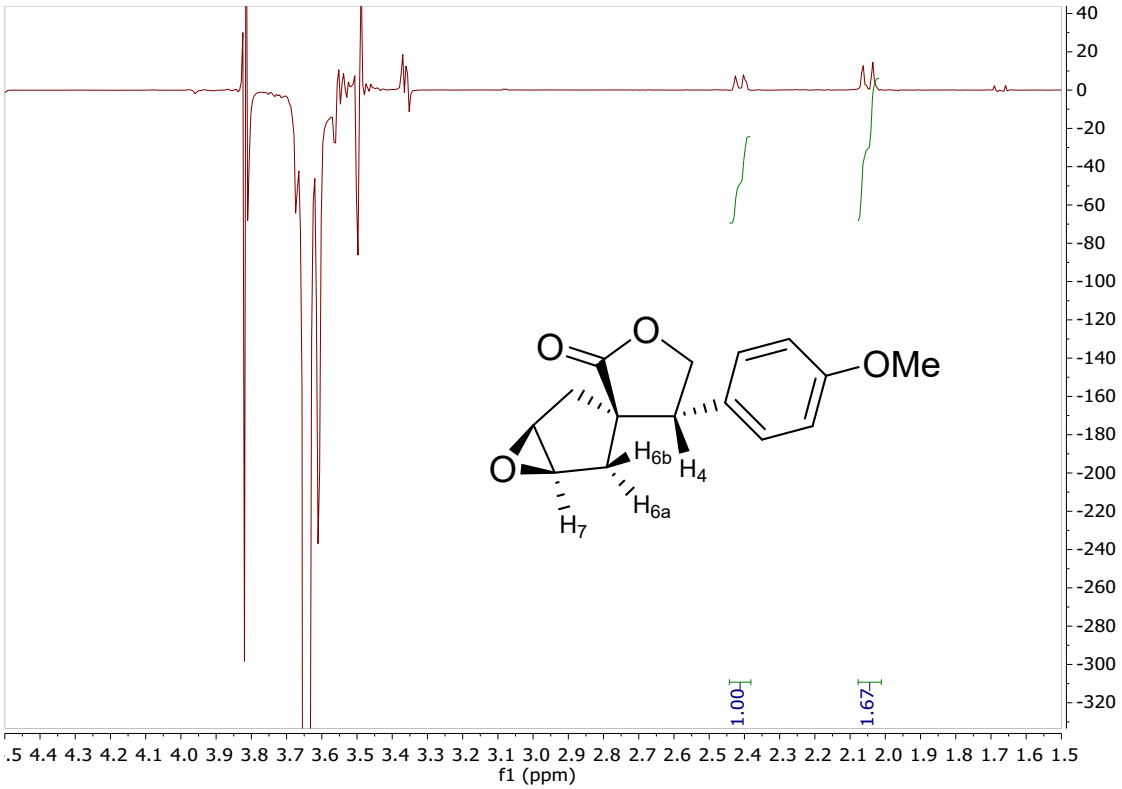


Figure S2: F2-slice of the 2D nOe spectrum in Figure S1 at the F1-chemical shift of proton 7 (δ 3.61 ppm)

Figure S3 shows the DFT calculations of the optimisation of the geometry for epoxide **6b**, where the 7-H and 6_a-H are in *cis* configuration. In this model, the distance between 7- and 6_b-H is 2.74358 Å and the distance between 7-H and 6_a-H is 2.53401 Å, the former being 8.2% longer than the latter. This is in accordance with the data obtained from the nOe spectrum and the stereochemistry of epoxide **6b** is suggested to be as depicted in Figure S3.

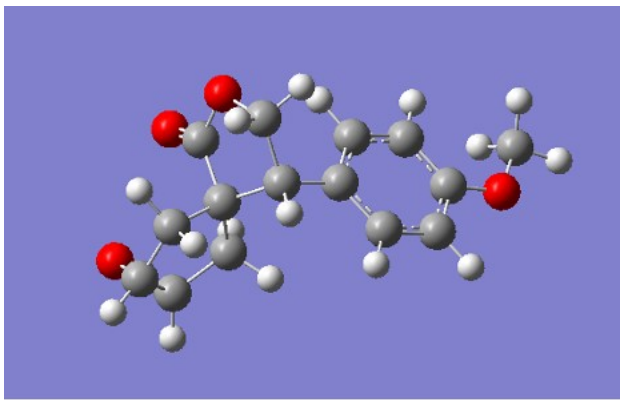


Figure S3: DFT-calculation of geometry optimisation of epoxide 6b

4 Molecular Modelling supplementary diagrams

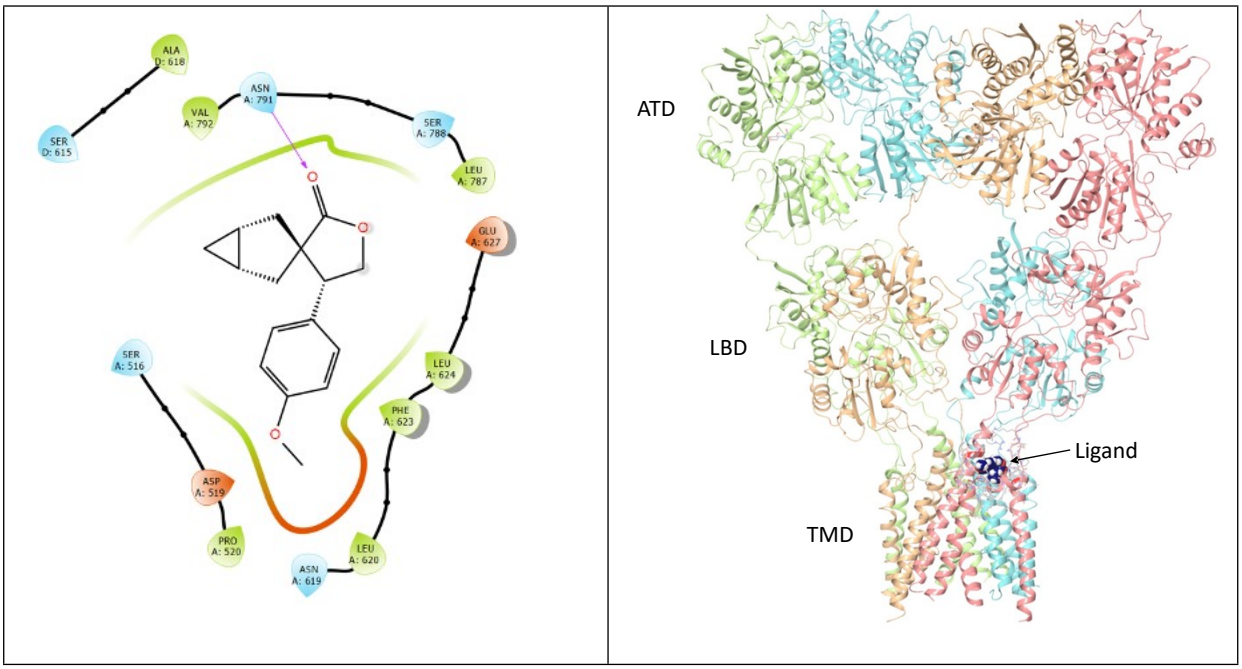


Figure S4: LEFT Ligand-residue interactions schematic showing the residues in the non-competitive antagonist binding site that interact with compound 6c. RIGHT Position of ligand (6c) in the non-competitive antagonist binding site in the full AMPAR tetramer. Each subunit contains a non-competitive antagonist binding site to which 6c can bind (only one binding site is shown occupied by 6c in this figure).

5 Calcium influx assay

Compound solutions

Test compounds were prepared as 10 mM stock solutions in DMSO and were diluted to working concentrations using Hanks Balanced Salt Solution supplemented with 5 mM $CaCl_2$ and 20 mM HEPES (sHBSS). Working solutions which exhibited precipitation have been indicated. Final concentrations of DMSO were between 0-3% with control experiments using the DMSO carrier were performed as indicated below.

Cell Culture

HEK293 cell lines stably expressing homomeric glutamate receptors (GluA1 and GluK2) were obtained from Eli Lilly and grown in DMEM (ThermoFisher) supplemented with 10% *v/v* fetal bovine serum (Sigma), 2 mM Glutamax™ (Gibco), 100 U/mL penicillin, 100 µg/mL streptomycin and 250 ng/mL amphotericin B (Sigma) in 5% CO_2 at 37 °C. Cells were passaged using TrypLE (Gibco) as required before confluency and periodically treated with selection antibiotics (GluK1, GluK2 hygromycin B, 200 µg/mL; GluA1 geneticinTM, 200 µg/mL).

Calcium influx fluorescence assay

Compounds were tested for activity against non-NMDA iGluRs using a calcium influx fluorescence assay as described previously.[31] 100k cells/well were seeded into a 96-well plate precoated with poly-L-lysine and incubated for 12-16 hours until fully confluent. The cell monolayer was washed twice with 100 µL Hanks Balanced Salt Solution supplemented with 5 mM $CaCl_2$ and 20 mM HEPES (sHBSS), then incubated for 2-4 hours with 100 µL working solution of Calcium 6 dye (Molecular Devices) supplemented with a desensitization blocker (GluK2 0.25 mg/mL concanavalin A, Sigma; GluA1 100 µM cyclothiazide, Sigma).

The time resolved fluorescence was recorded in a Flexstation 3 instrument (Molecular Devices). For each individual reading, the initial fluorescence of the well was measured for 20 seconds, after which the desired concentration of test antagonist was added followed by addition of the L-glutamate agonist 70 seconds later. The response is measured as the peak change in fluorescence upon addition of agonist. The viability of the cells was confirmed by determination of the concentration-response curve to the L-glutamate agonist and a standard antagonist for each plate. The response of antagonists was measured in the presence of the experimentally determined EC_{80} concentration of L-glutamate. Fluorescence traces were performed in triplicate on each plate with the median of these data used. Separate experiments (n) were performed on different passages of cells.

DMSO Control responses

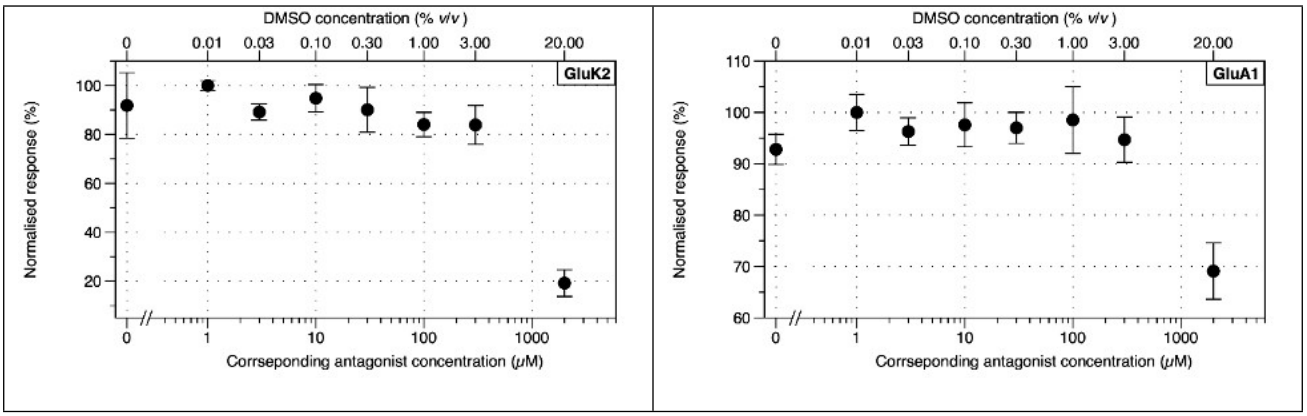


Figure S5: Concentration-Response curves with respect to DMSO carrier. Median of 3 experiments ± SEM. Top axes indicates absolute %*v/v* DMSO, Bottom axes indicate the corresponding concentration of antagonists. LEFT Concentration Response Curve for GluK2 homomeric receptors. RIGHT: Concentration Response Curve for GluA1 homomeric receptors

No significant change to the response of cells was observed between 0-3% DMSO concentrations. At 20% DMSO concentration a large decrease in response was observed (Figure S2). In the case of single concentration measurements, DMSO was added to the antagonist blank (negative control) solution such that the final concentration in the assay was 0.1%.

Data Processing

Single Concentration Experiments

For single concentration testing of compounds the % inhibition is calculated as:

$$\%\ \text{inhibition} = 100\% - \left[\frac{\text{response in presence of antagonist}}{\text{response in absence of antagonist}} \times 100\%\right]$$

Experiments were carried out between n=3-5 and the values reported as the mean ± SEM

Concentration-Response Relationships and IC_{50} determination

Concentration-response data was normalised with respect to the maximum response of the compound and the data fitted using a 2-parameter model from which the IC_{50} of compounds was determined:

$$\text{Response} = \frac{100}{(1 + \left(\frac{x}{IC_{50}}\right)^{H}}$$

where x is the concentration of antagonist and H is the Hill slope. The top and bottom of the slope were constrained to 100 and 0 % accordingly.

IC_{50} values were determined on a plate by plate basis and reported as the mean ± SEM.

Schild Plot Analysis

Concentration-response data with respect to the agonist was normalised with to the maximum experimental response of the *agonist-only* concentration response curve and modelled using a 3-parameter fit:

$$\text{Response} = \frac{A}{(1 + \left(\frac{x}{EC_{50}}\right)^{H}}$$

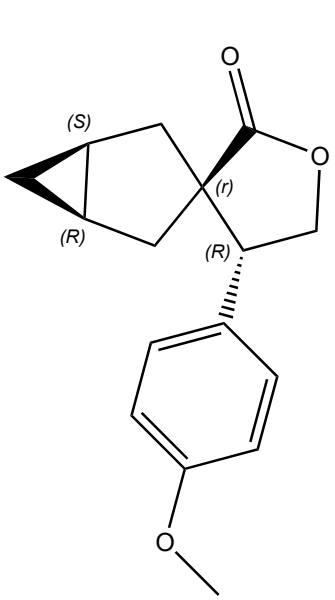
Where A is the curve maximum, x is the concentration of agonist, L-Glutamate, and H is the Hill slope. The bottom of the slope was constrained to 0% accordingly.

6 Molecular Modelling

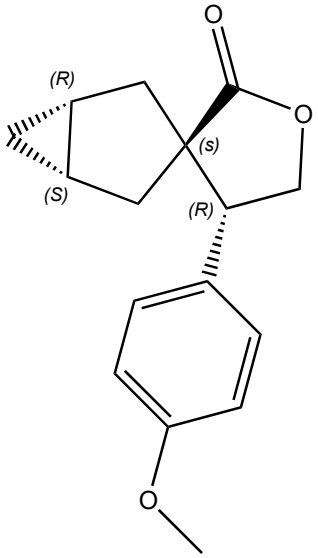
The structure of GYKI53655 was built in Maestro (Schrödinger LLC) and the two possible stereoisomers of **6c** were generated using Ligprep (Schrödinger LLC). All ligands were energy minimised using Macromodel (Schrödinger LLC) and the OPLS3e forcefield.

The protein structure of the GluA2 AMPAR tetramer in complex with GYKI53655 was imported from the protein databank (PDB code 5L1H) into the protein preparation wizard in Maestro. Missing side chains were added using Prime (Schrödinger LLC) and the GYKI molecules were deleted from their binding sites in chains B, C and D. The structure was energy minimised using the OPLS3e forcefield.

Docking of GYKI and the two possible stereoisomers of **6c** into the prepared GuA2 AMPAR tetramer was done using the Induced Fit module in Maestro. The area of interest was chosen to be the area of the receptor around the GYKI ligand in chain A (representing one subunit in the tetramer). Docking was carried out in extra precision (XP) mode and the programme was set to generate up to 10 poses for each ligand.



(1*R*,3*r*,4'*R*,5*S*)-4'-(4-methoxyphenyl)dihydro-2'*H*-spiro[bicyclo[3.1.0]hexane-3,3'-furan]-2'-one (**6c**)



(1*R*,3*s*,4'*R*,5*S*)-4'-(4-methoxyphenyl)dihydro-2'*H*-spiro[bicyclo[3.1.0]hexane-3,3'-furan]-2'-one

Figure S6 : Structure of stereoisomers of 6c used in molecular modelling studies

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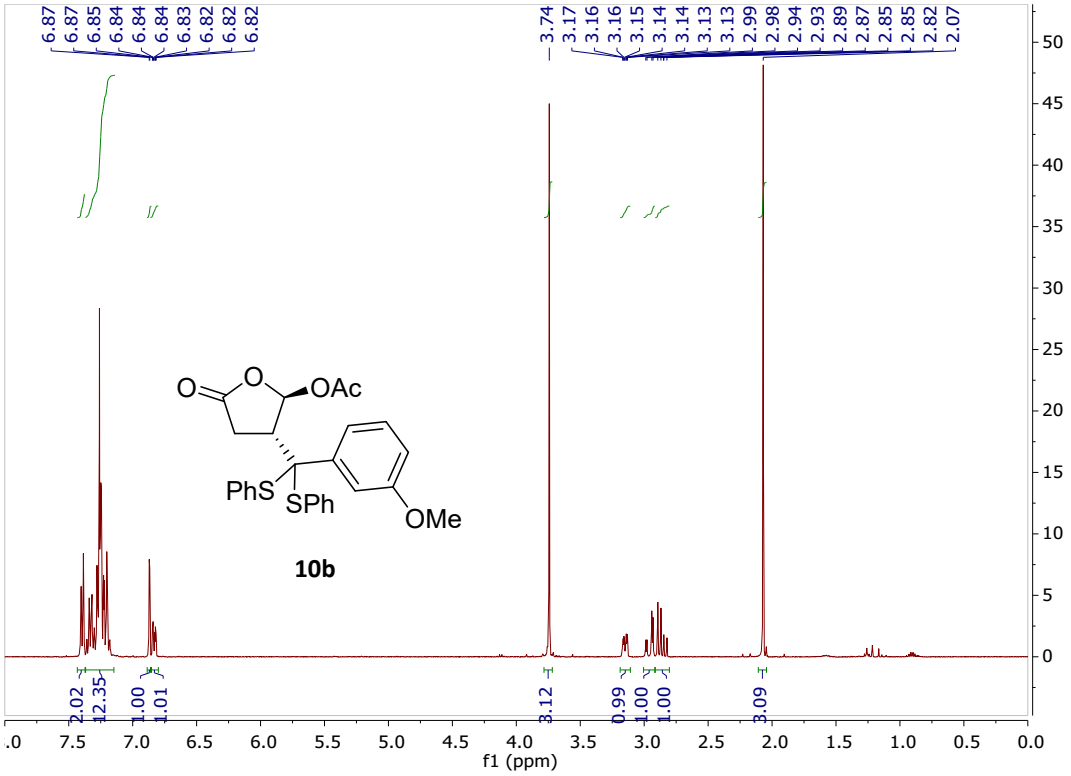
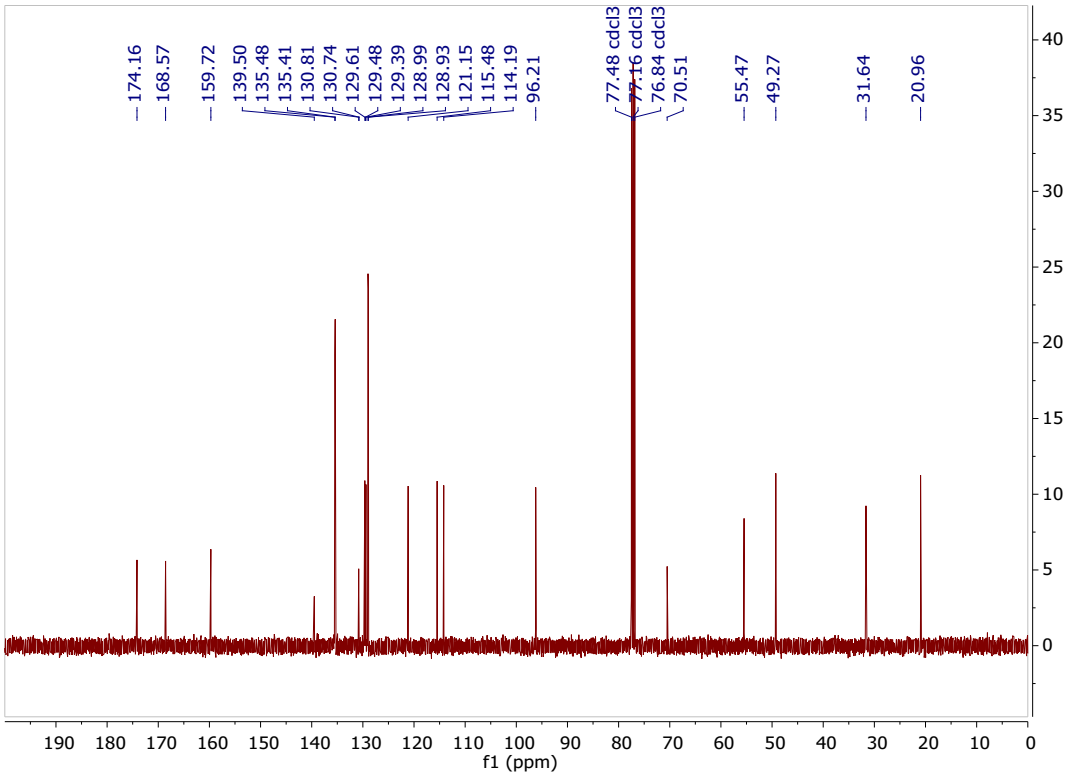
8 NMR spectra of novel compounds

^{1}H NMR ($CDCl_3$, 400 MHz)



^{13}C NMR ($CDCl_3$, 100 MHz)



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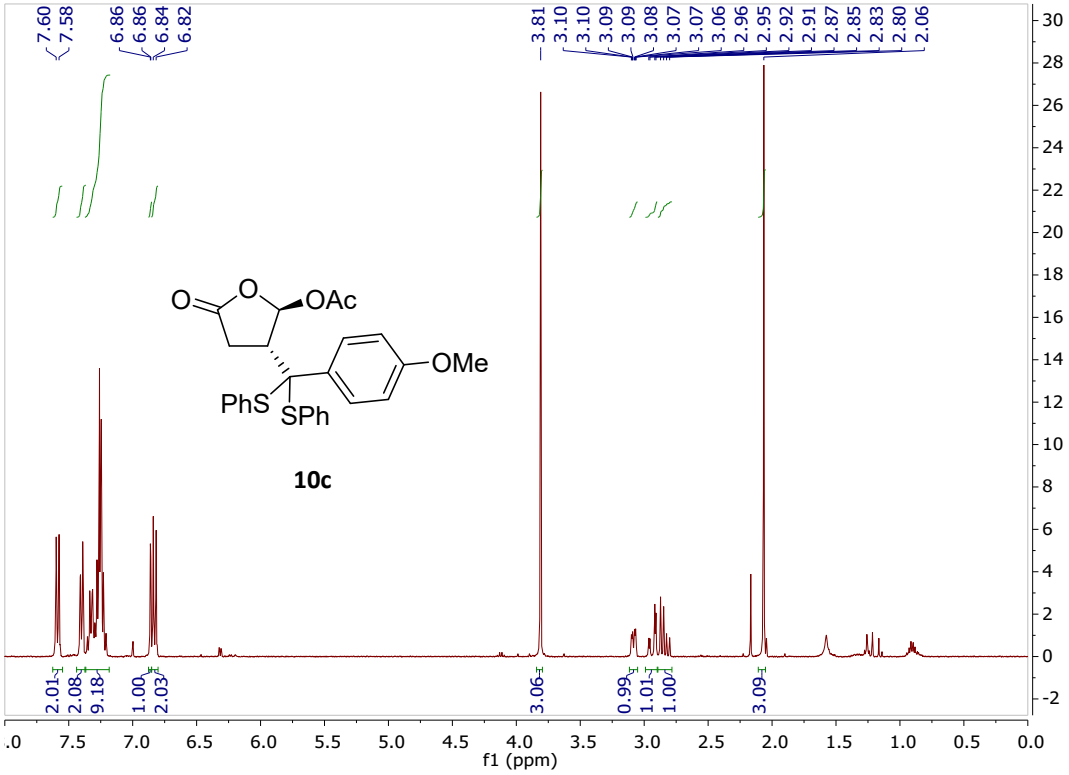

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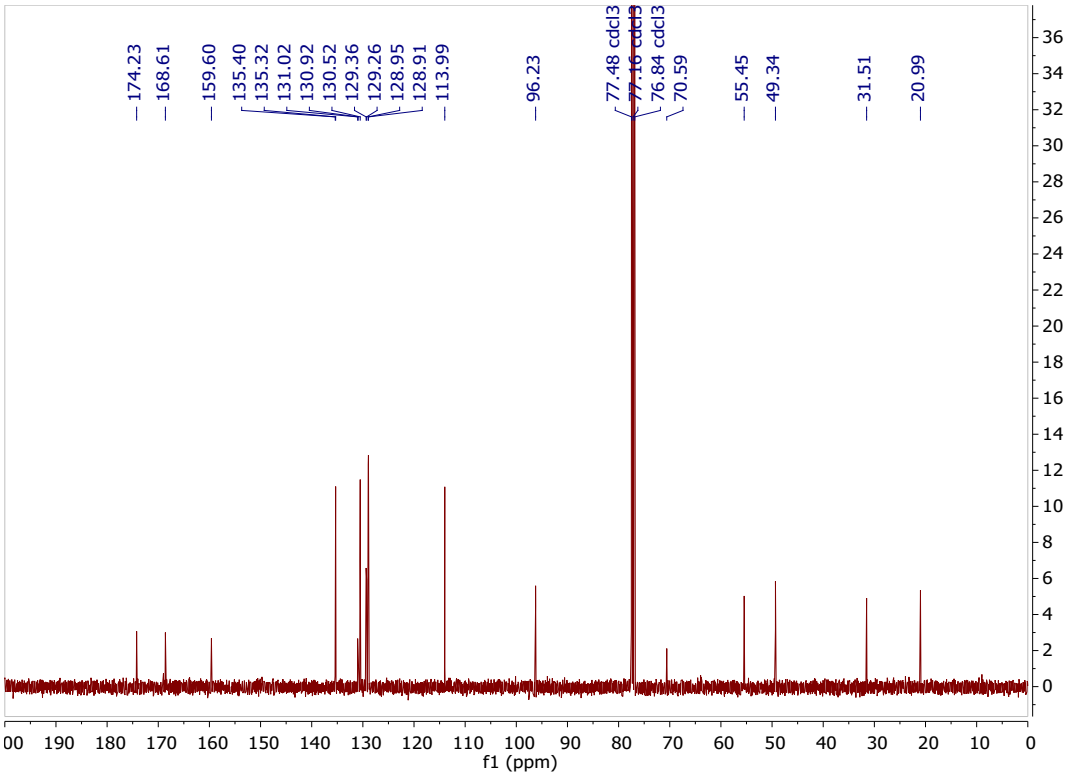

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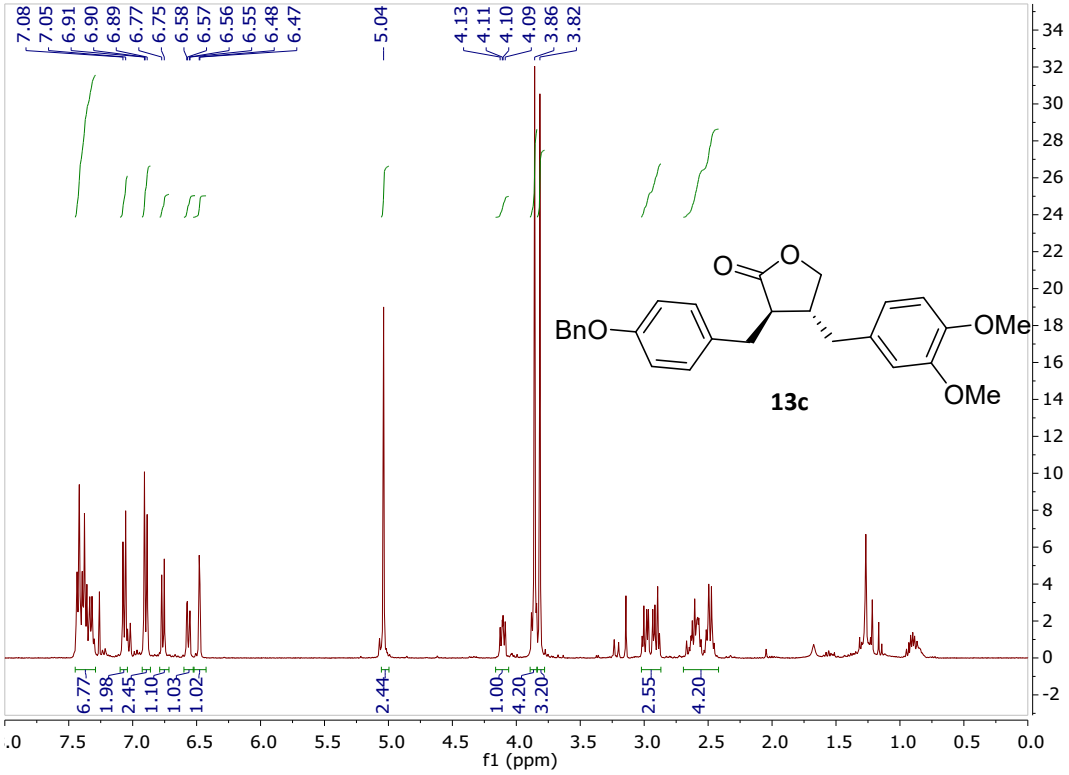

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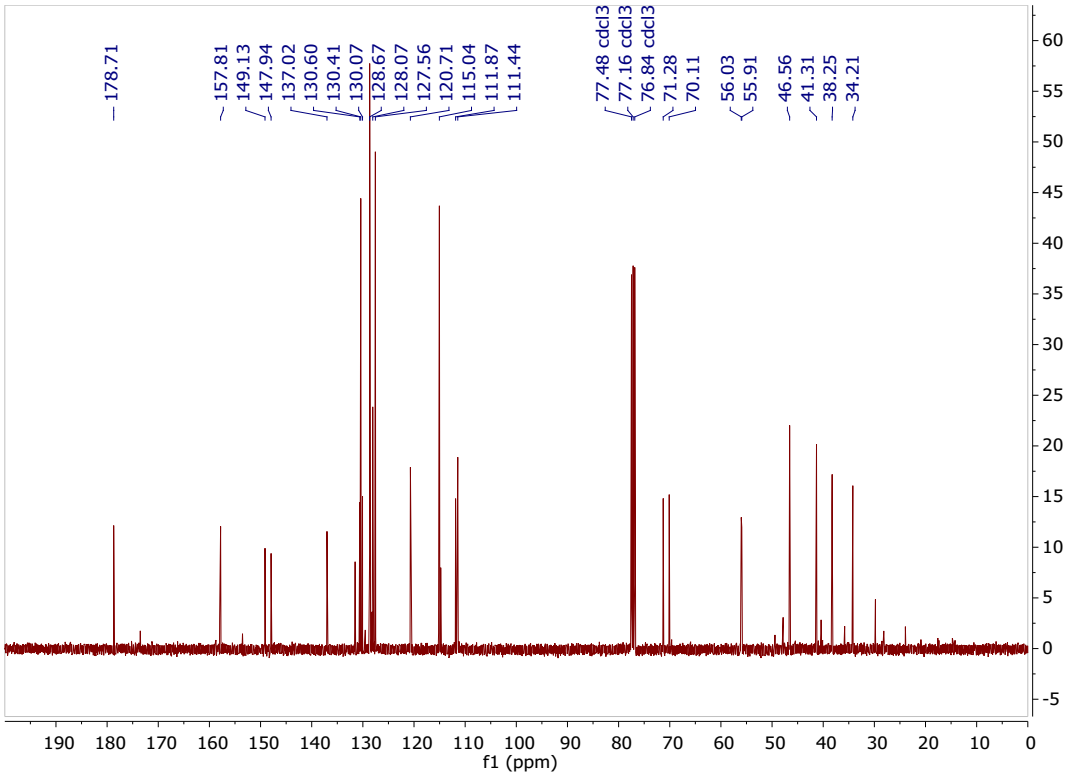

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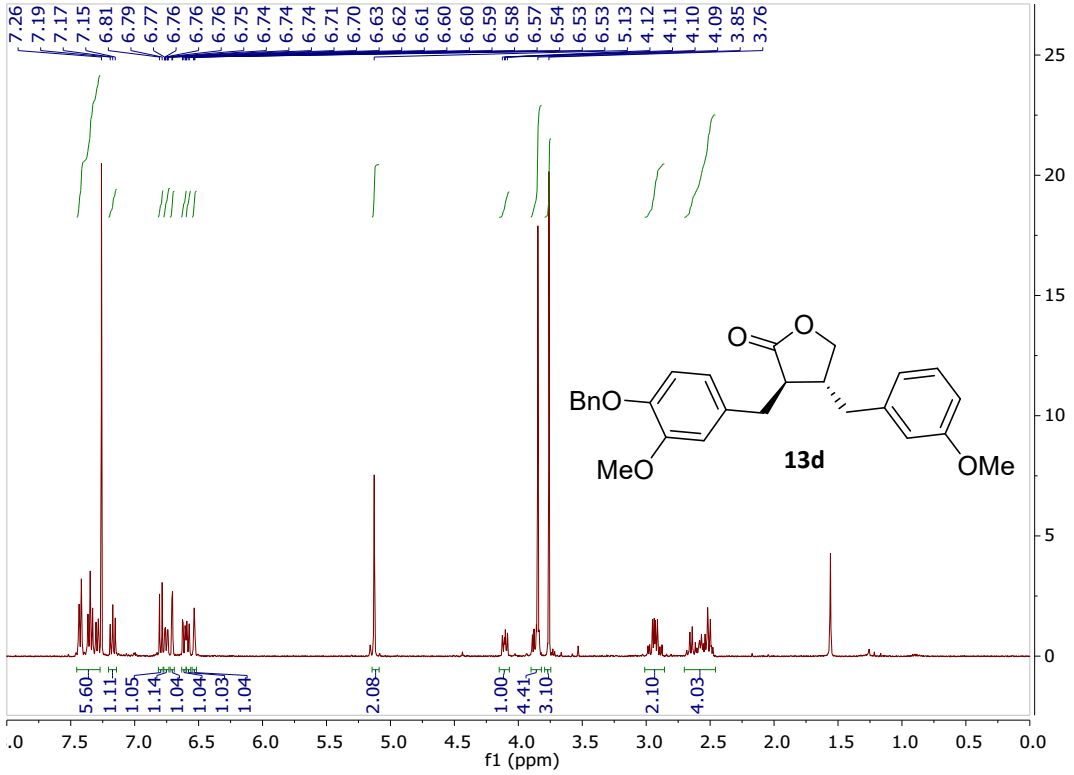
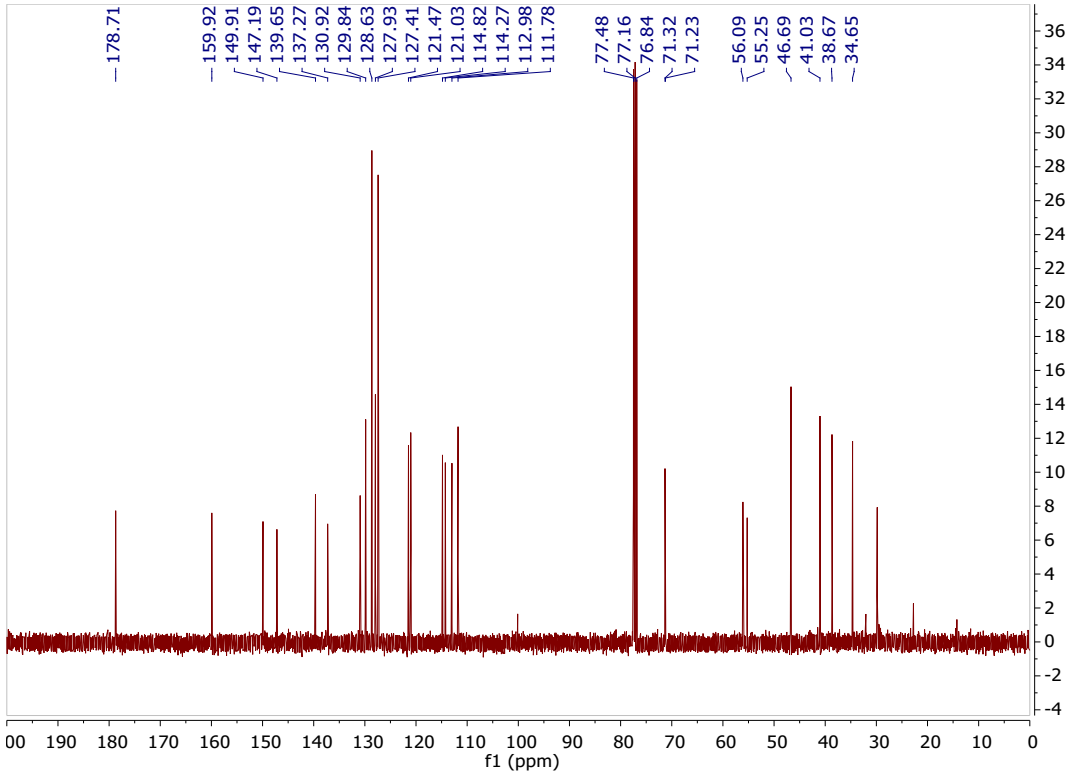
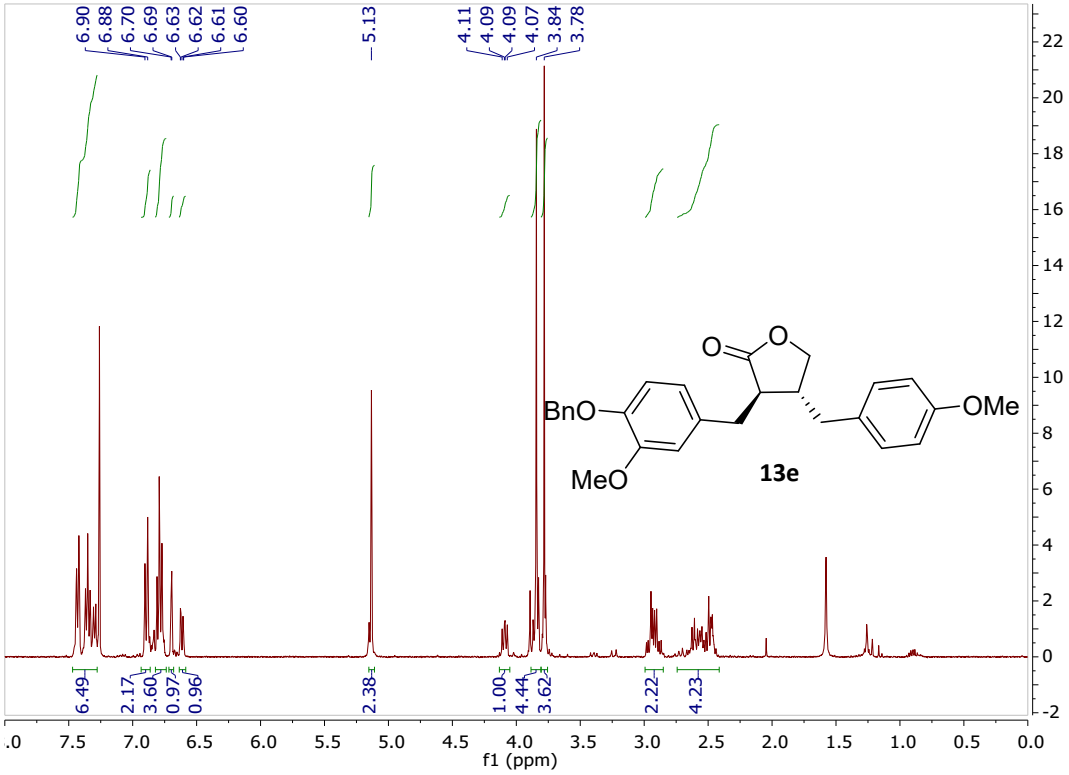


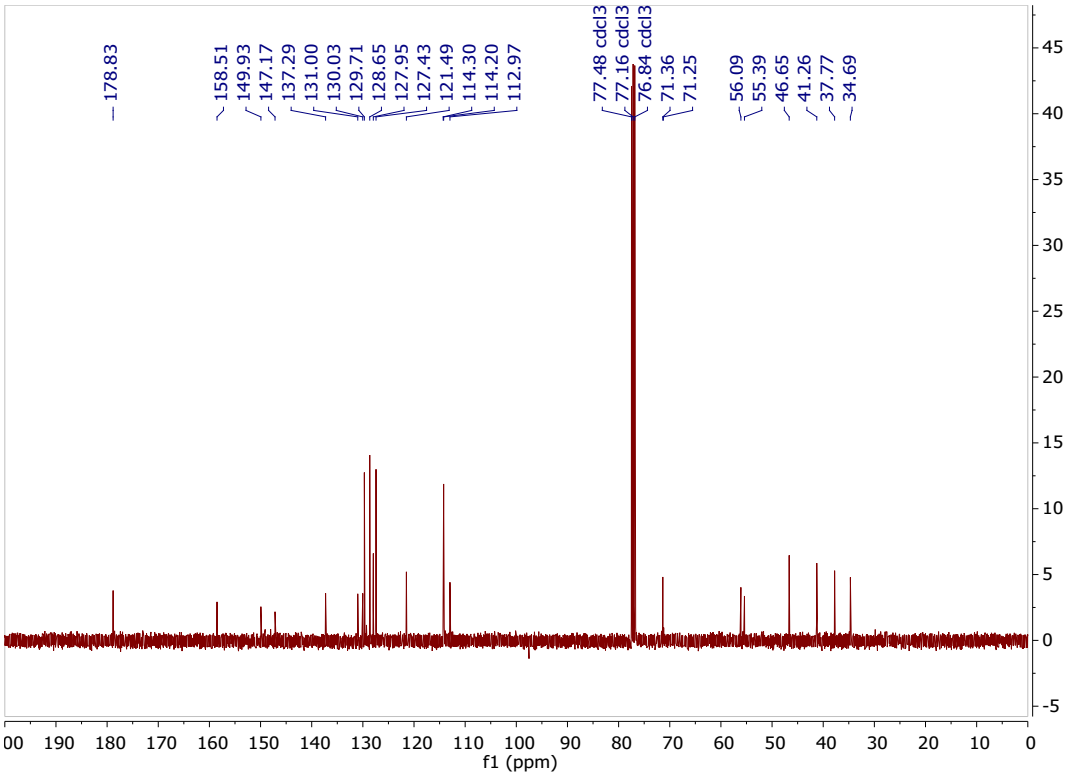
^{13}C NMR ($CDCl_3$, 100 MHz)



^{1}H NMR ($CDCl_3$, 400 MHz)



^{13}C NMR ($CDCl_3$, 100 MHz)



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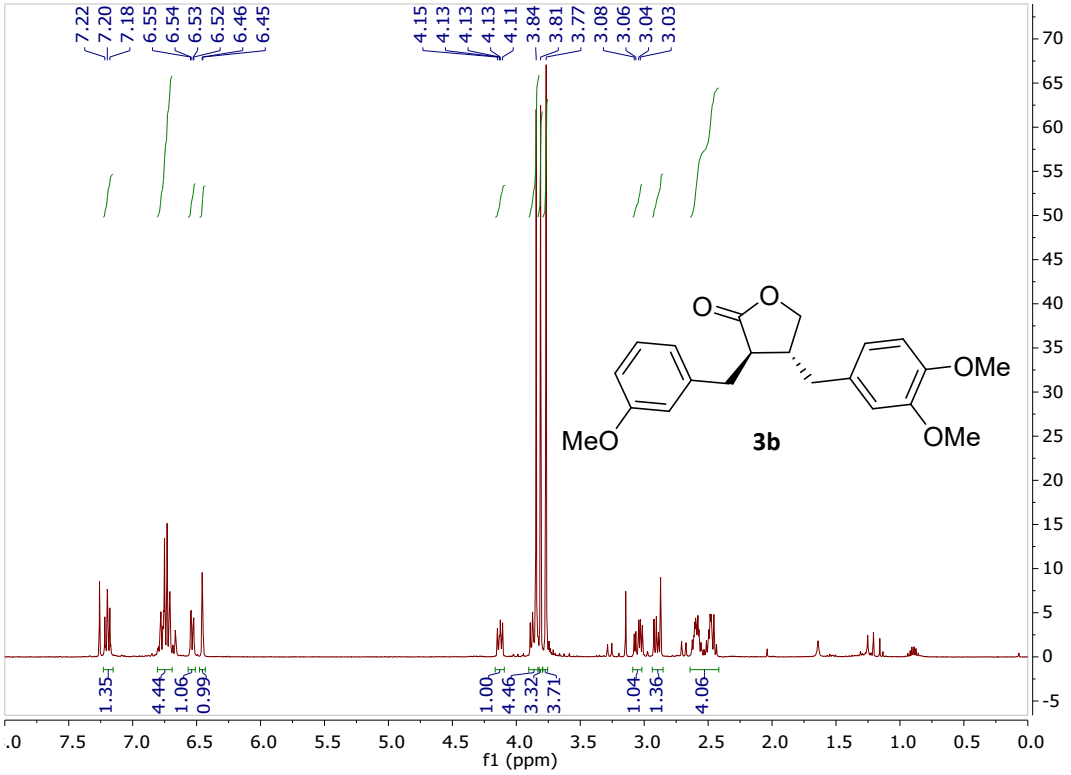

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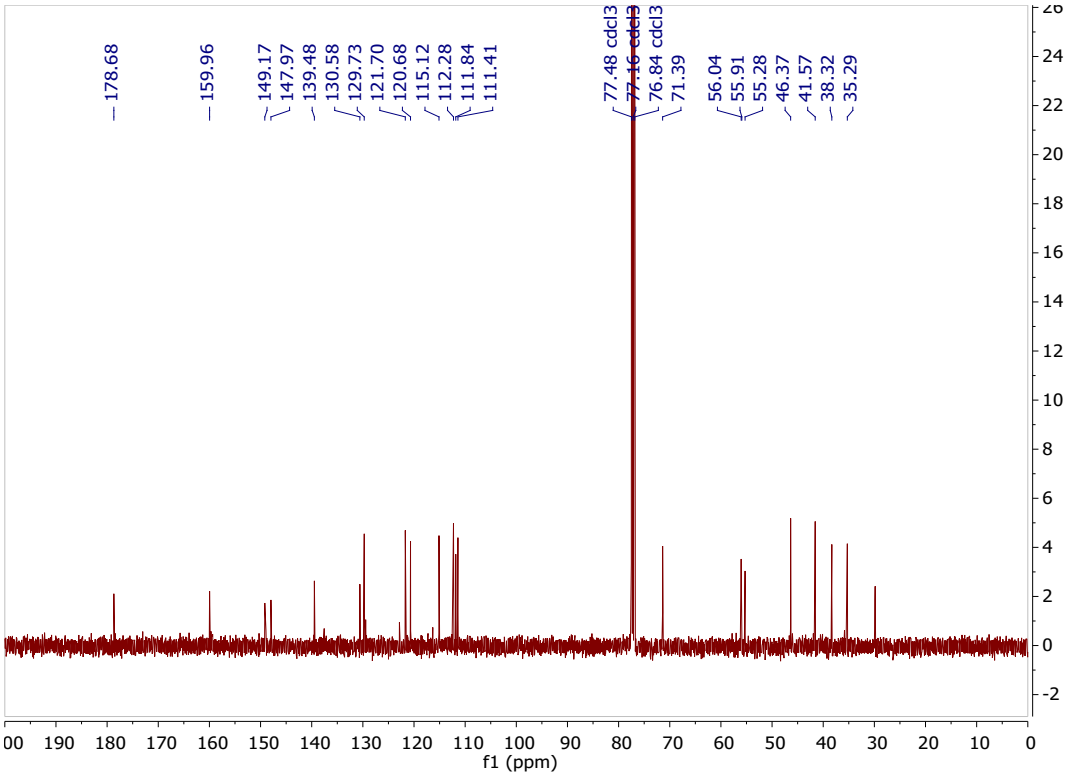

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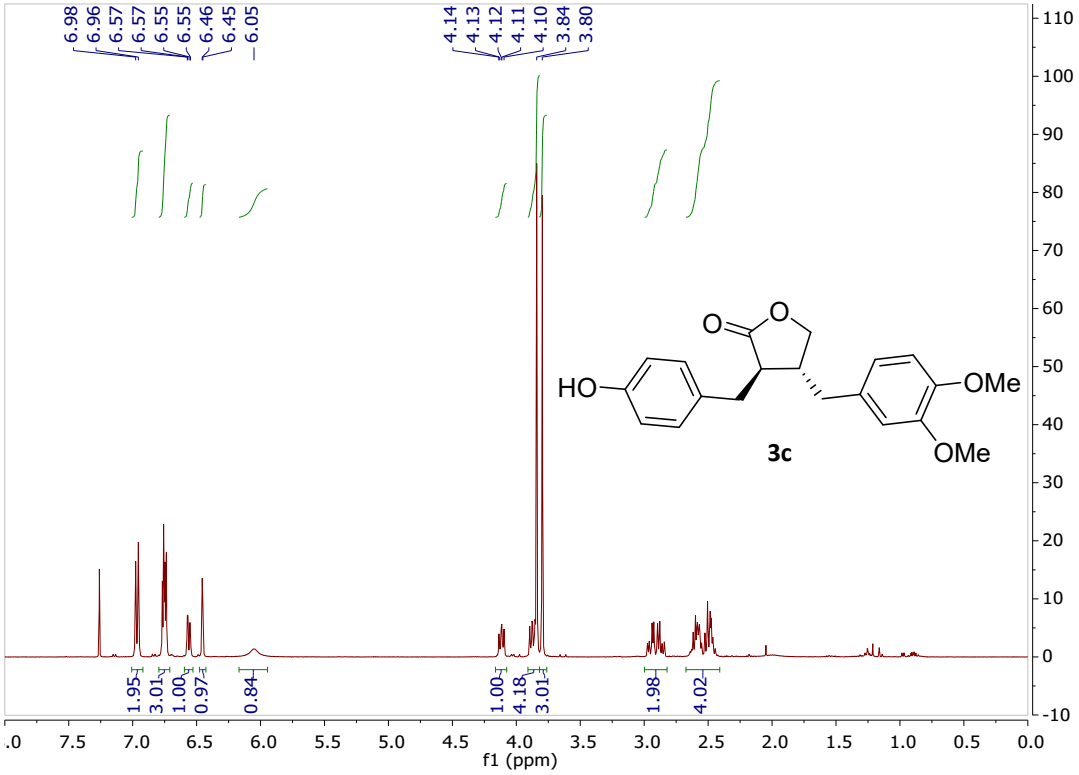

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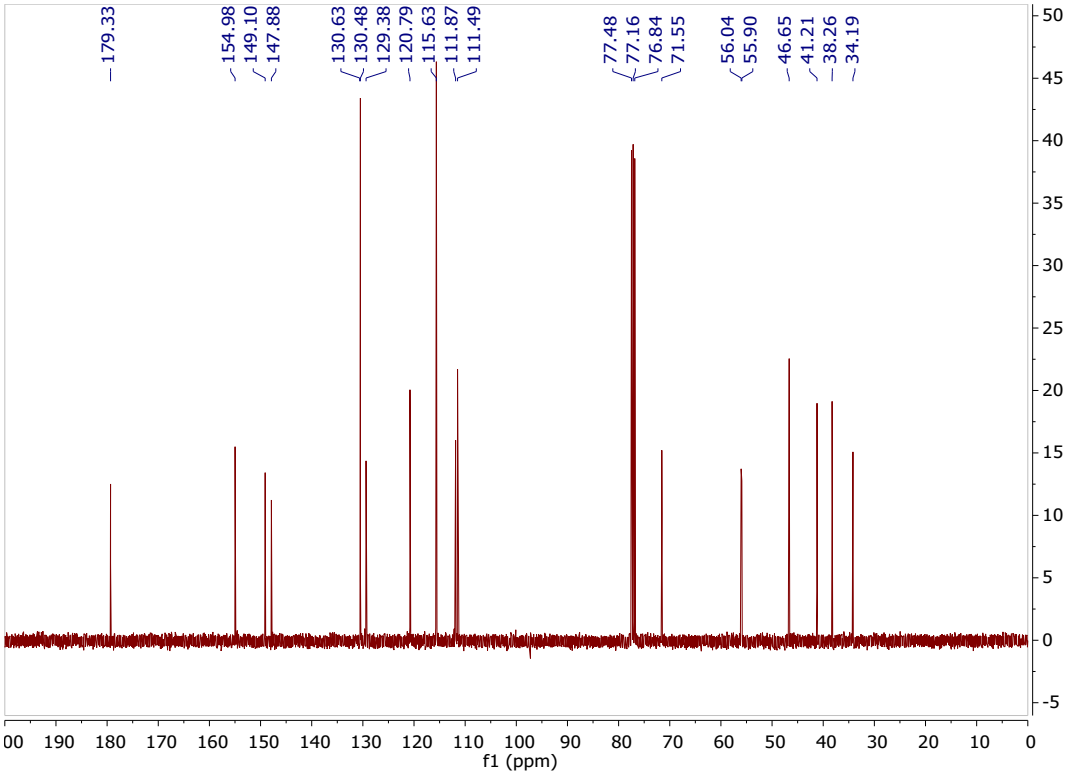
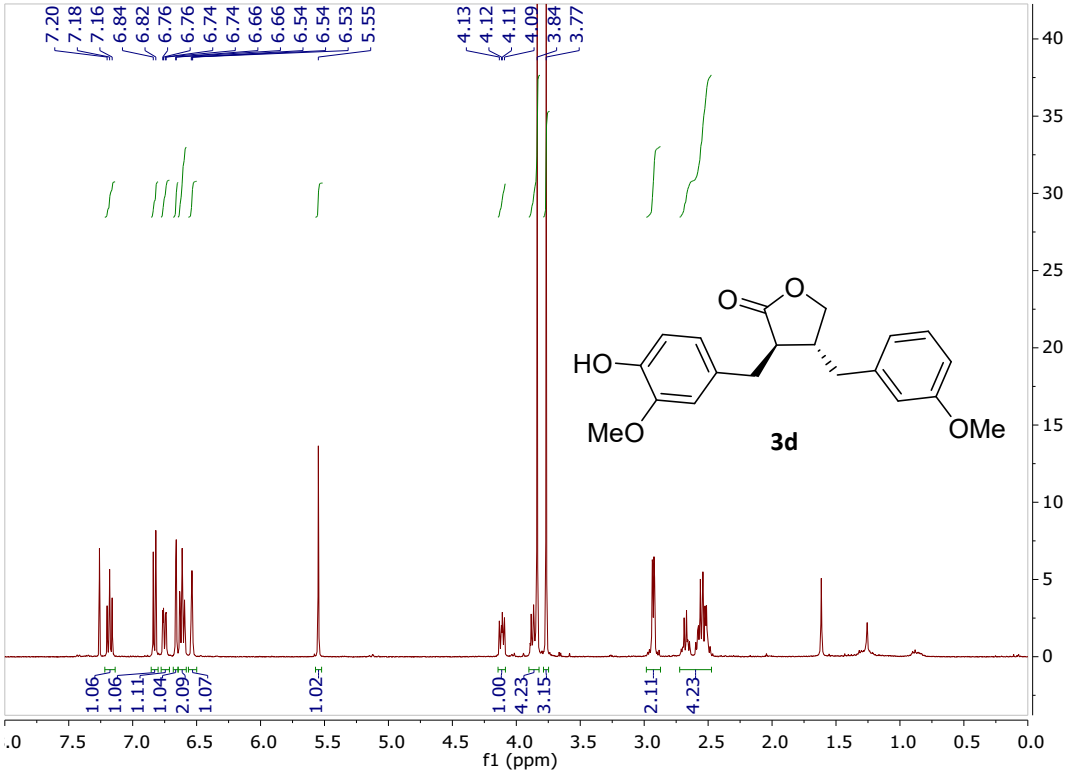


^{1}H NMR ($CDCl_3$, 400 MHz)



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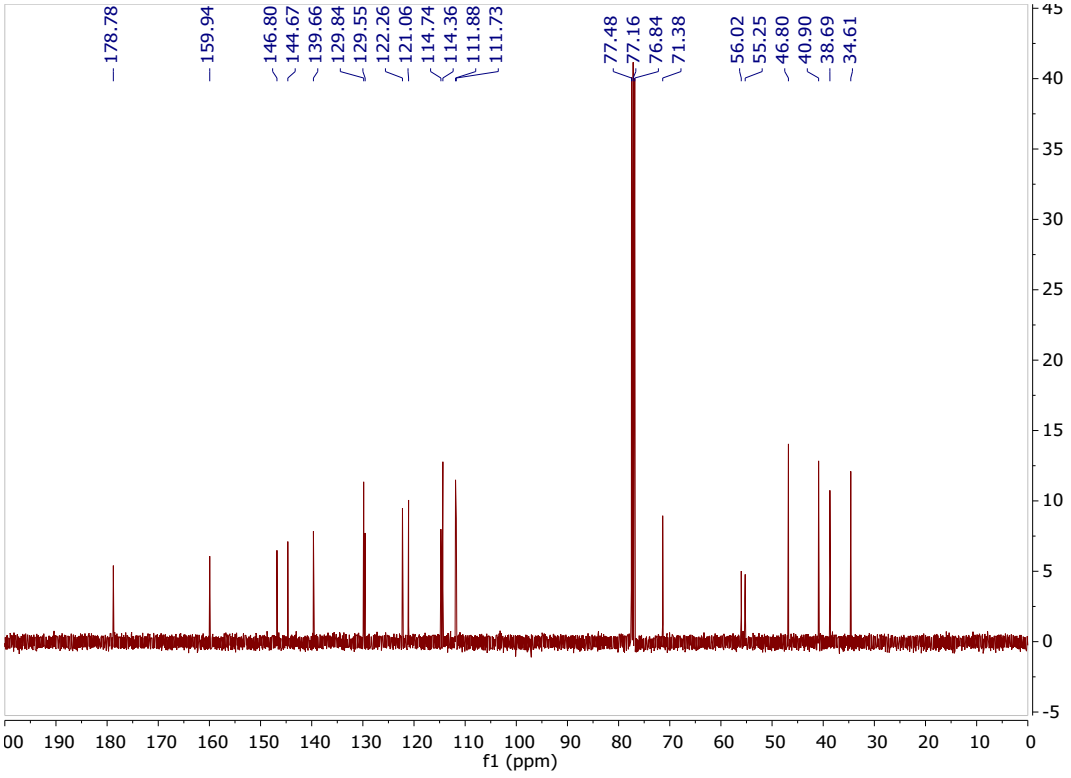

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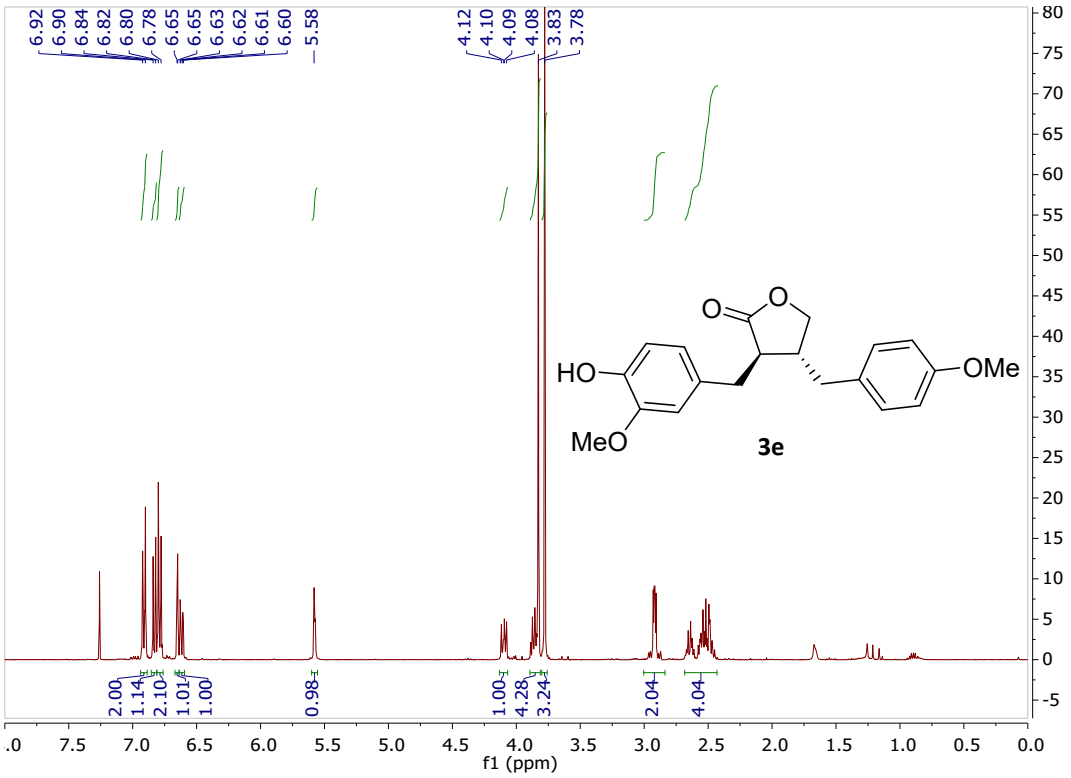

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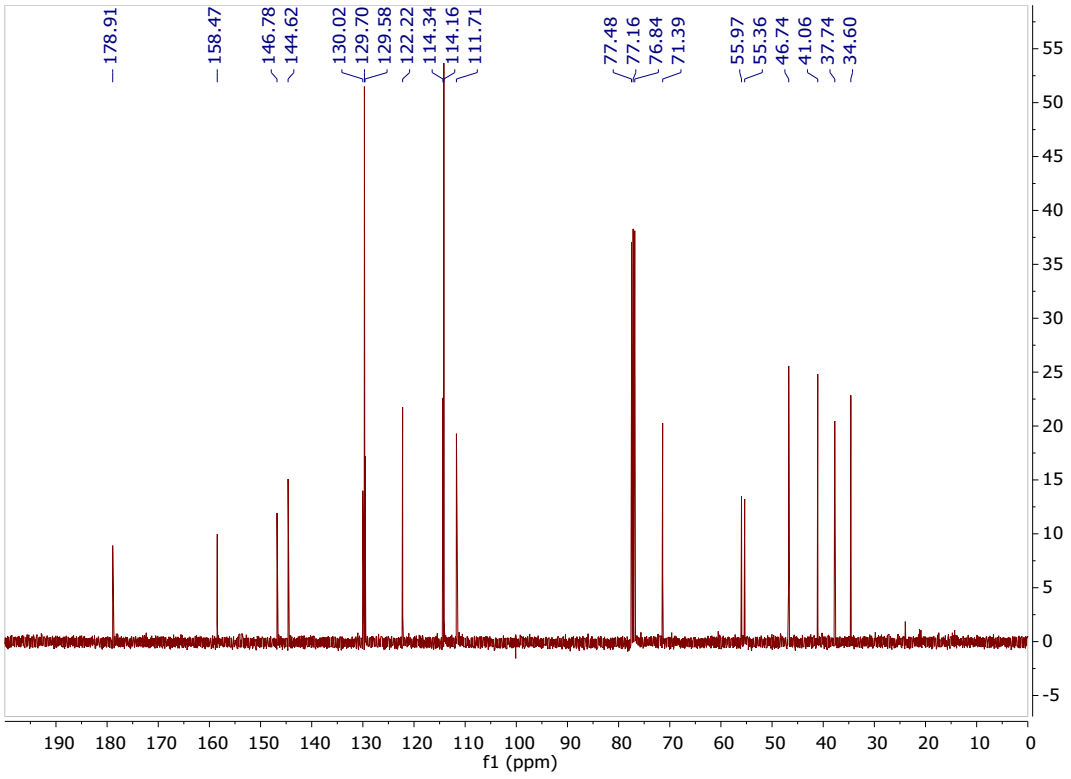

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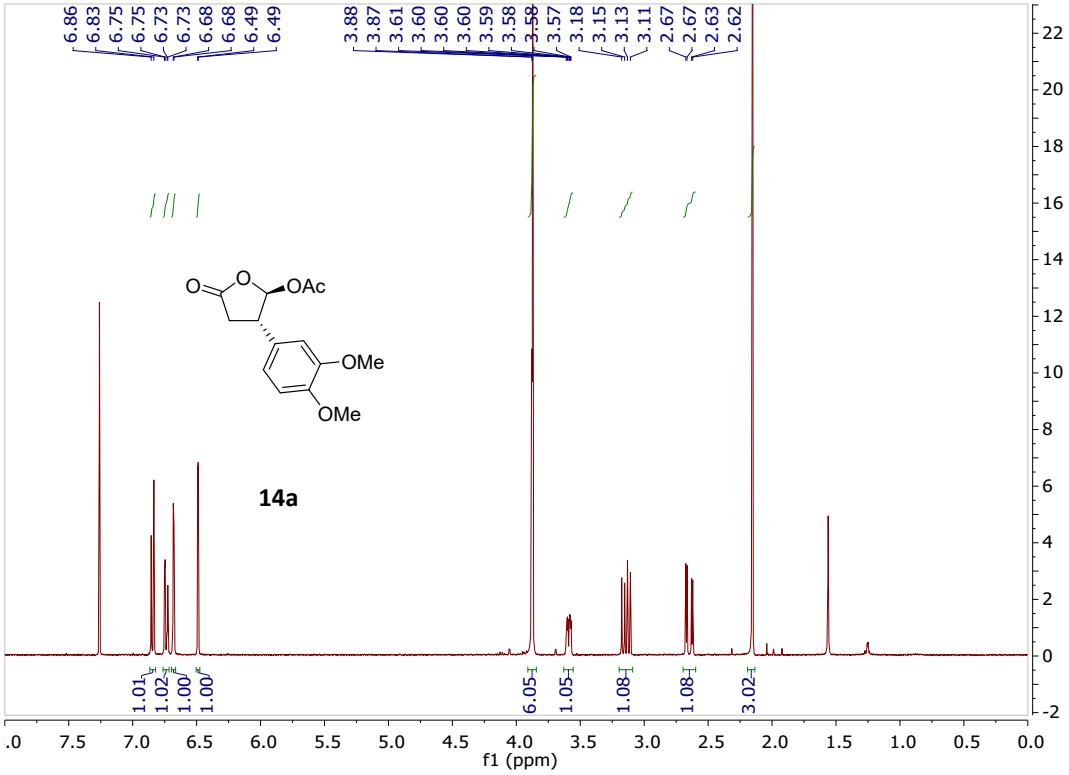
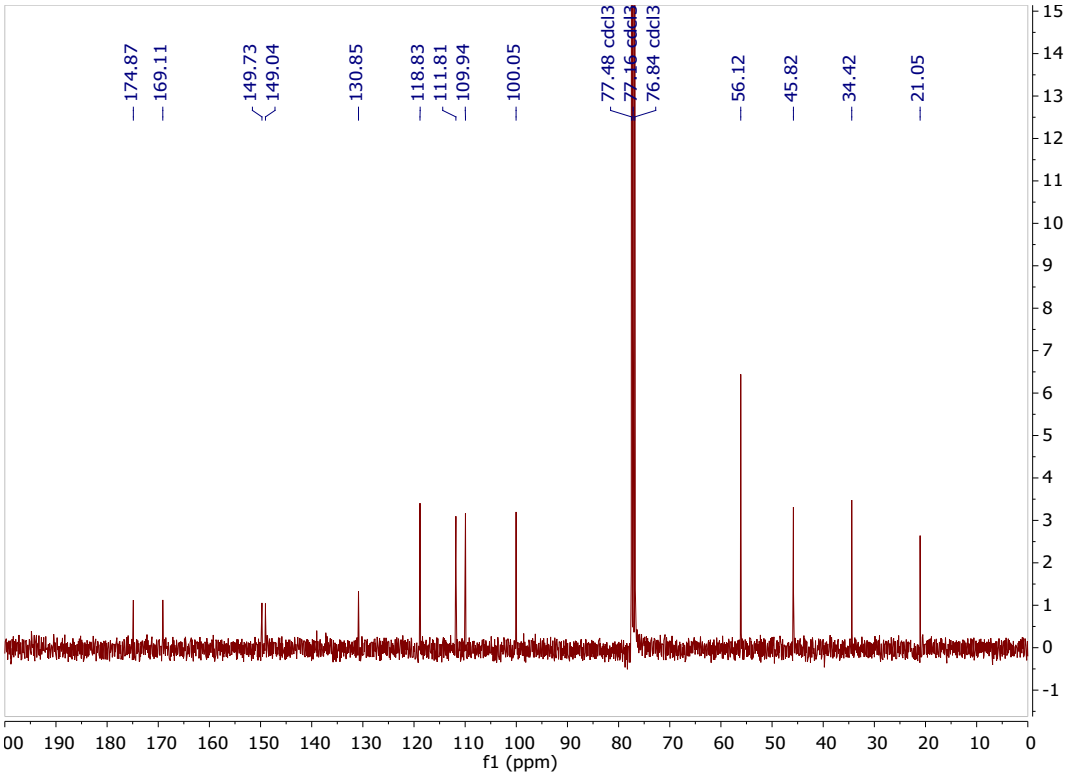


^{13}C NMR ($CDCl_3$, 100 MHz)



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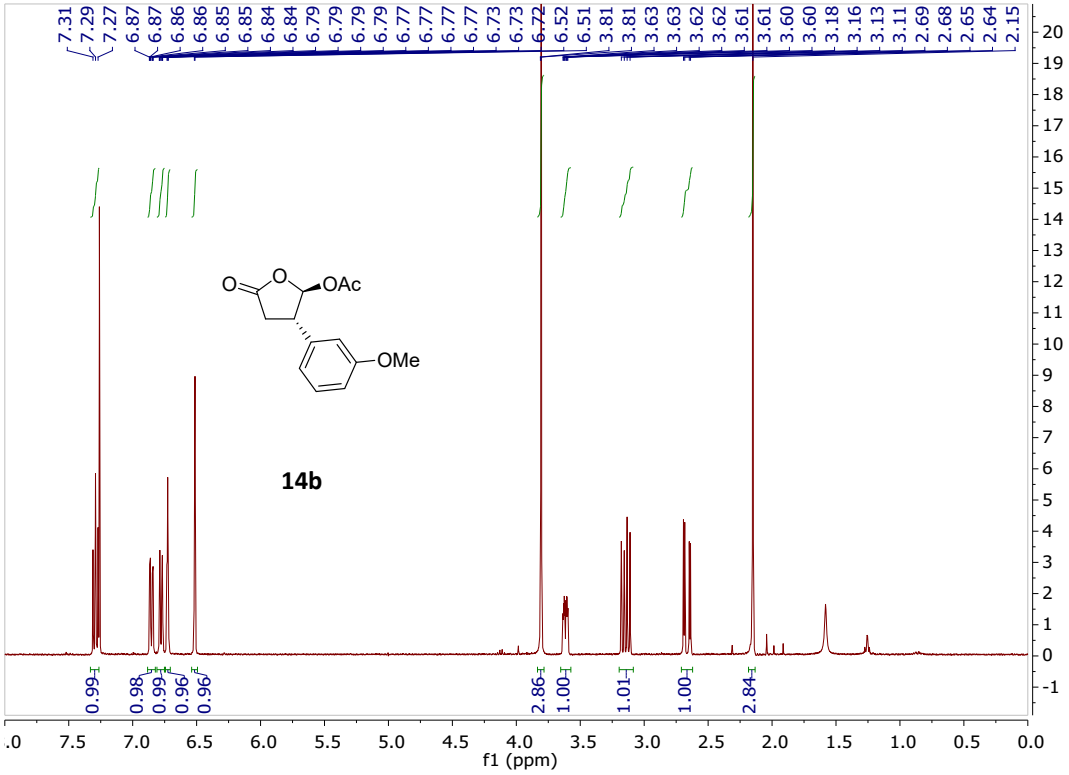

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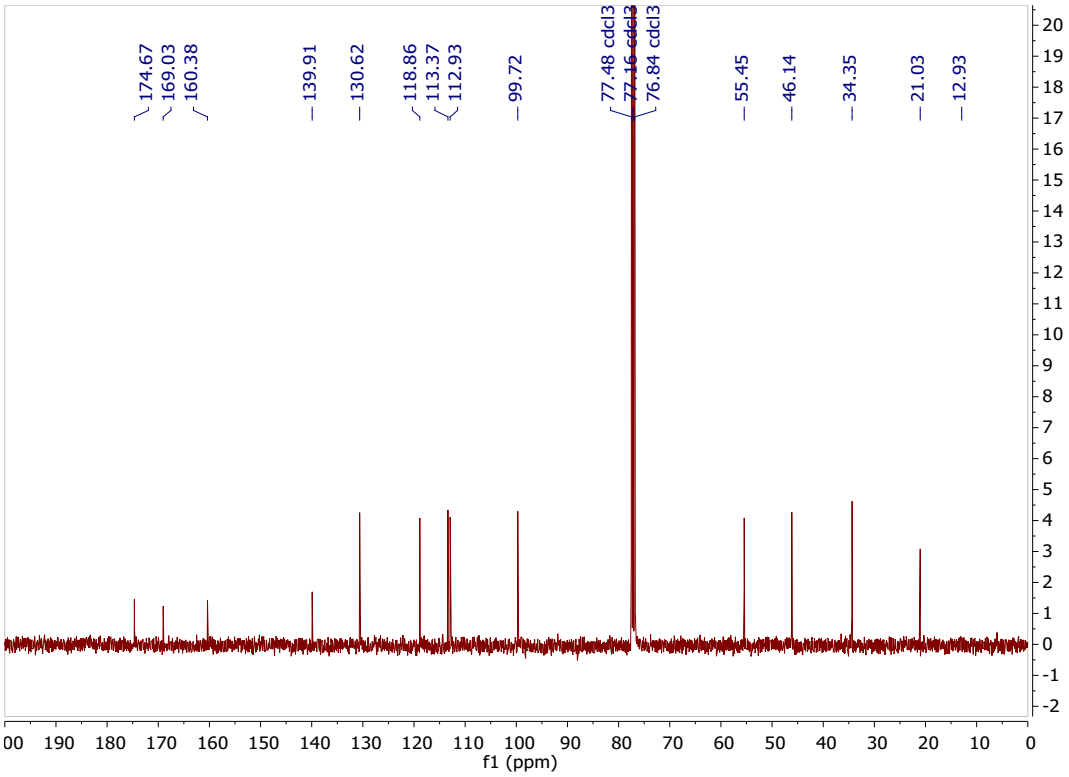

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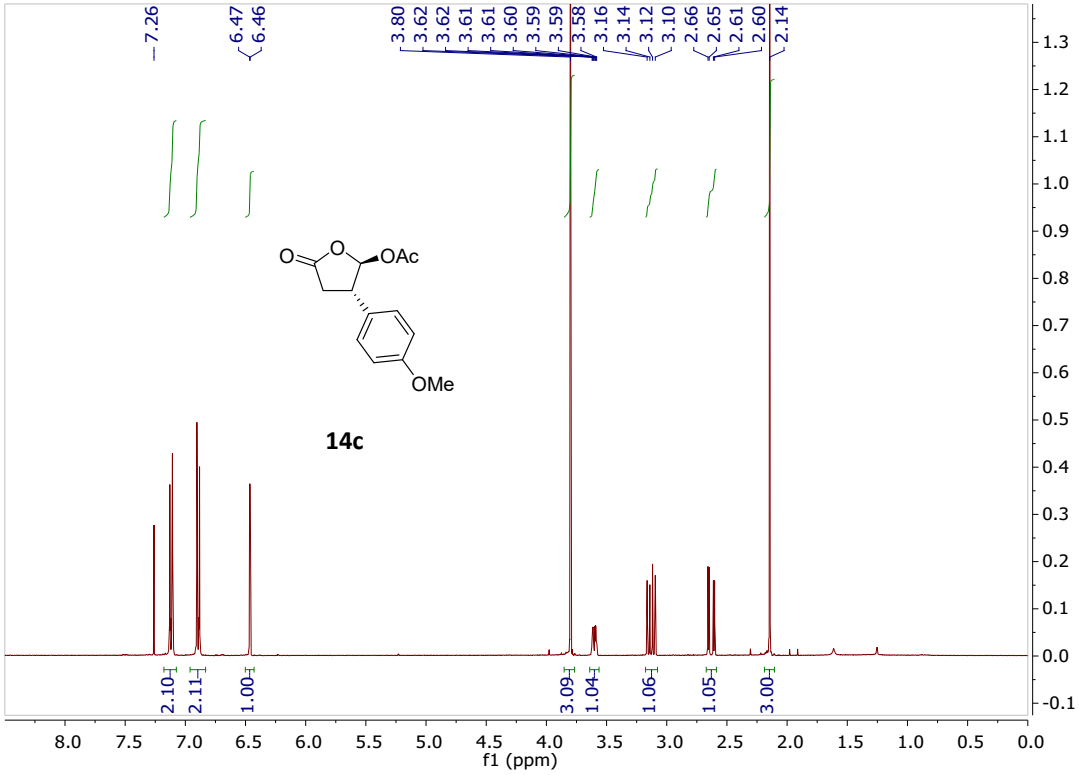

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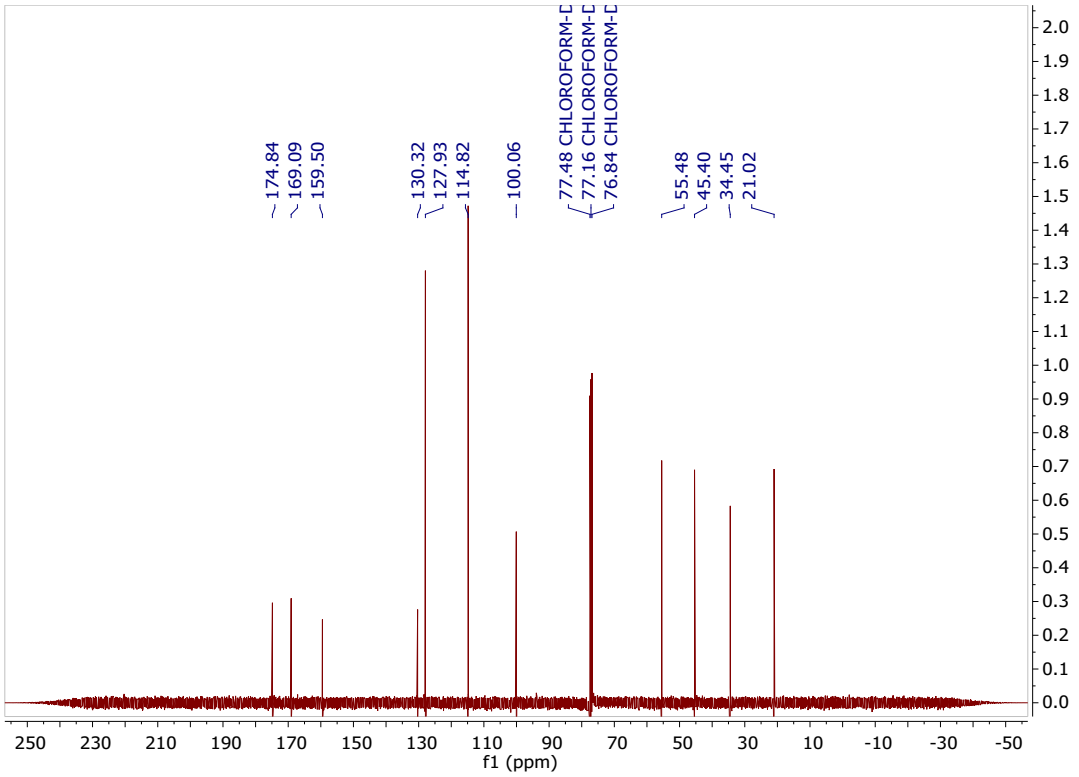

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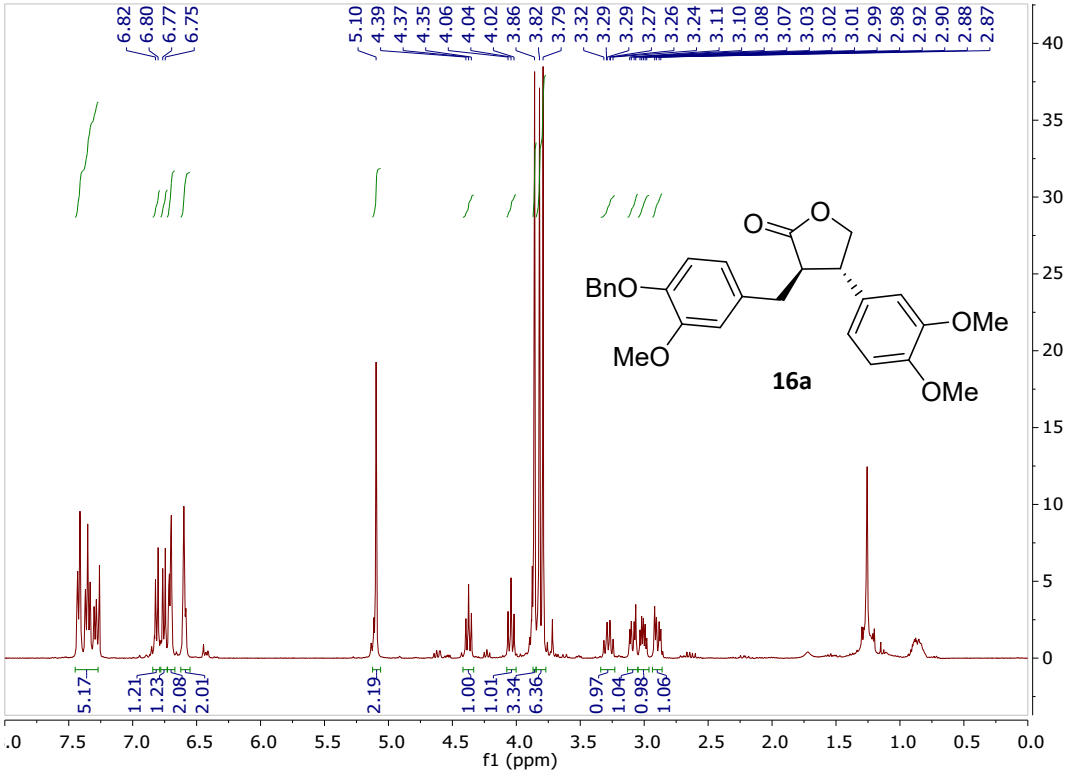

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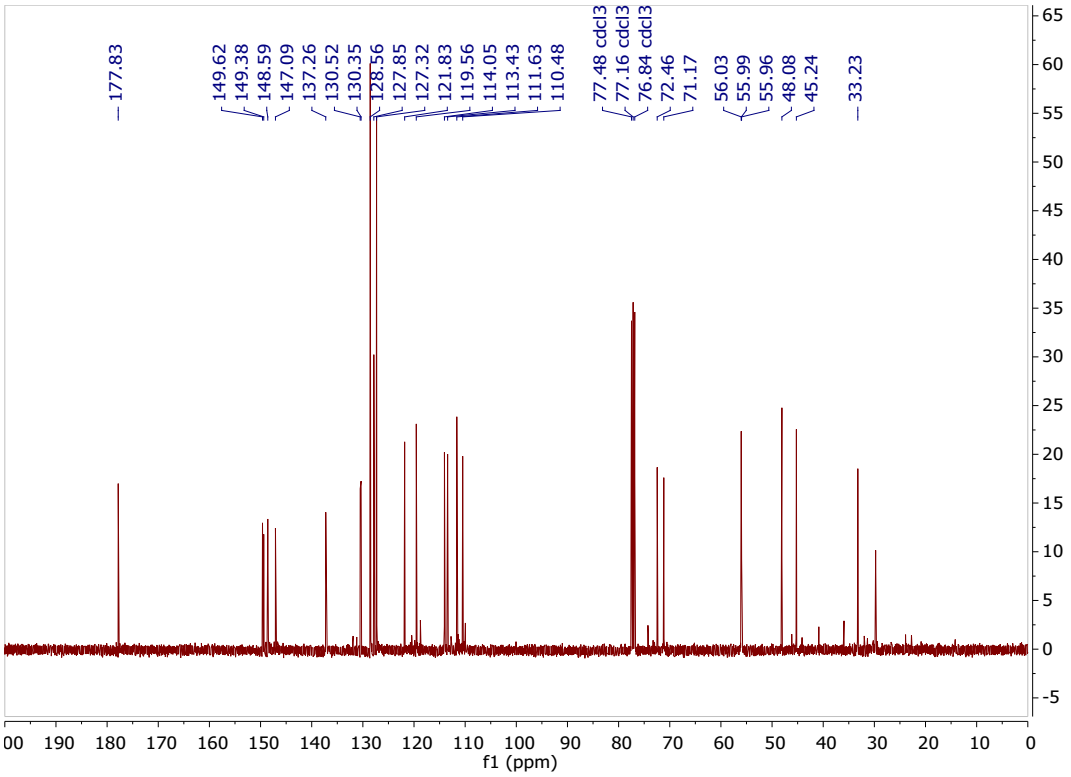

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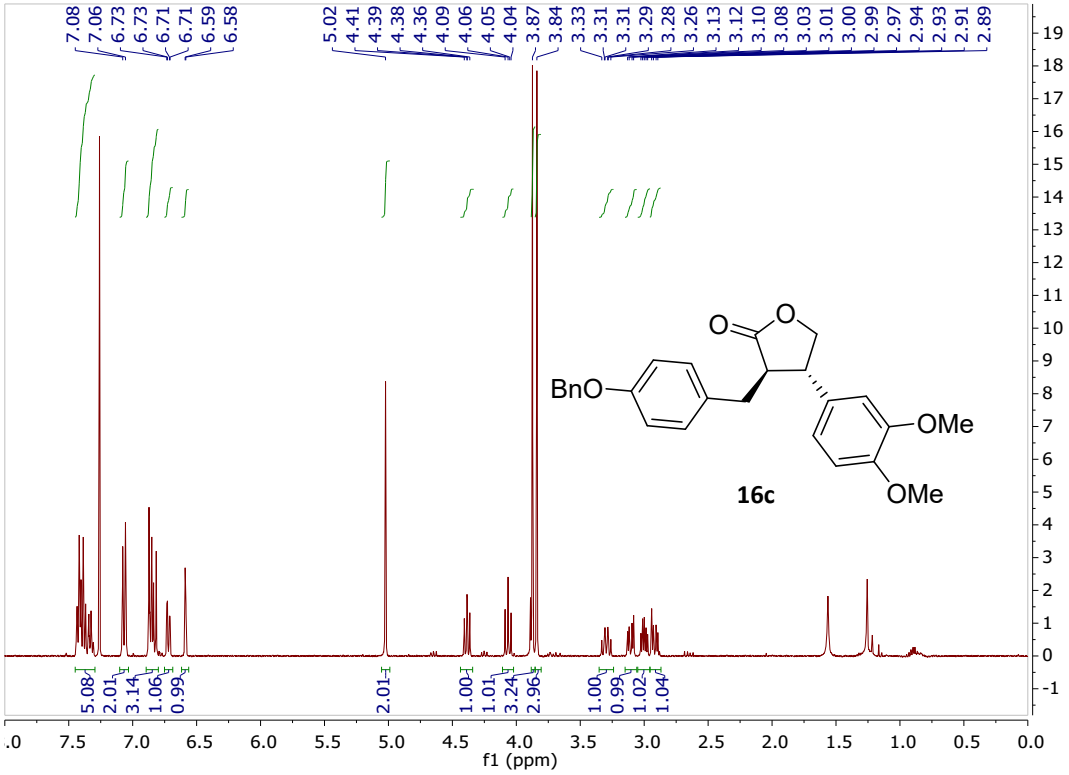

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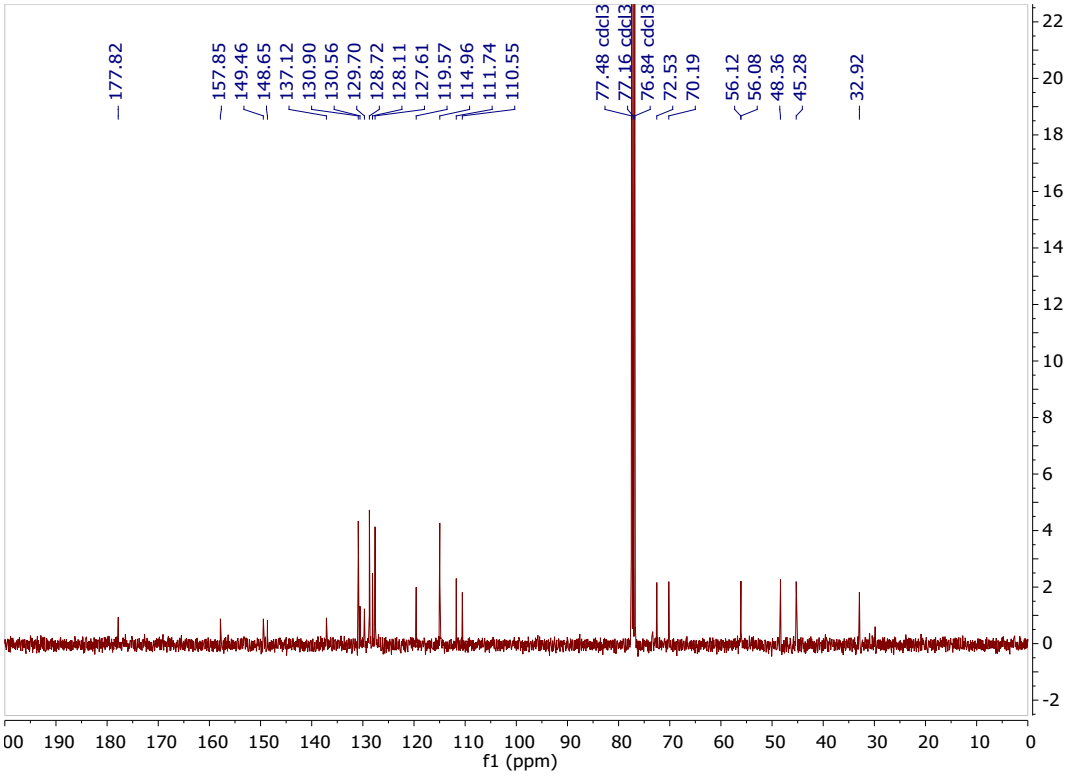

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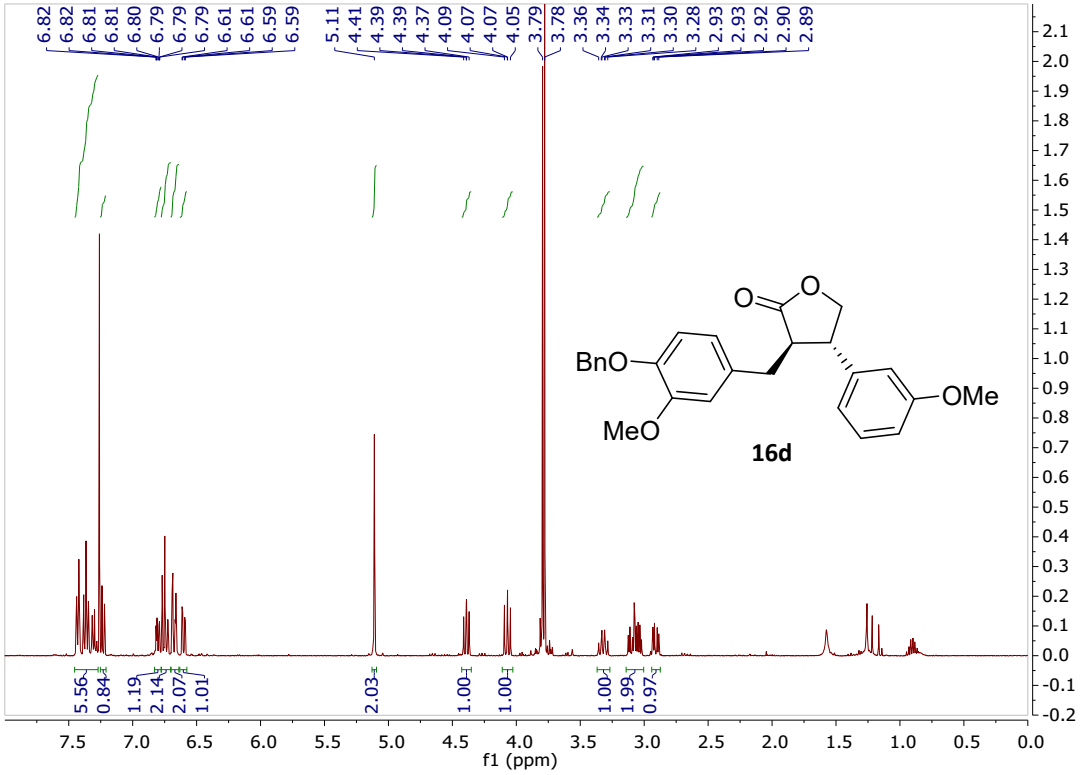

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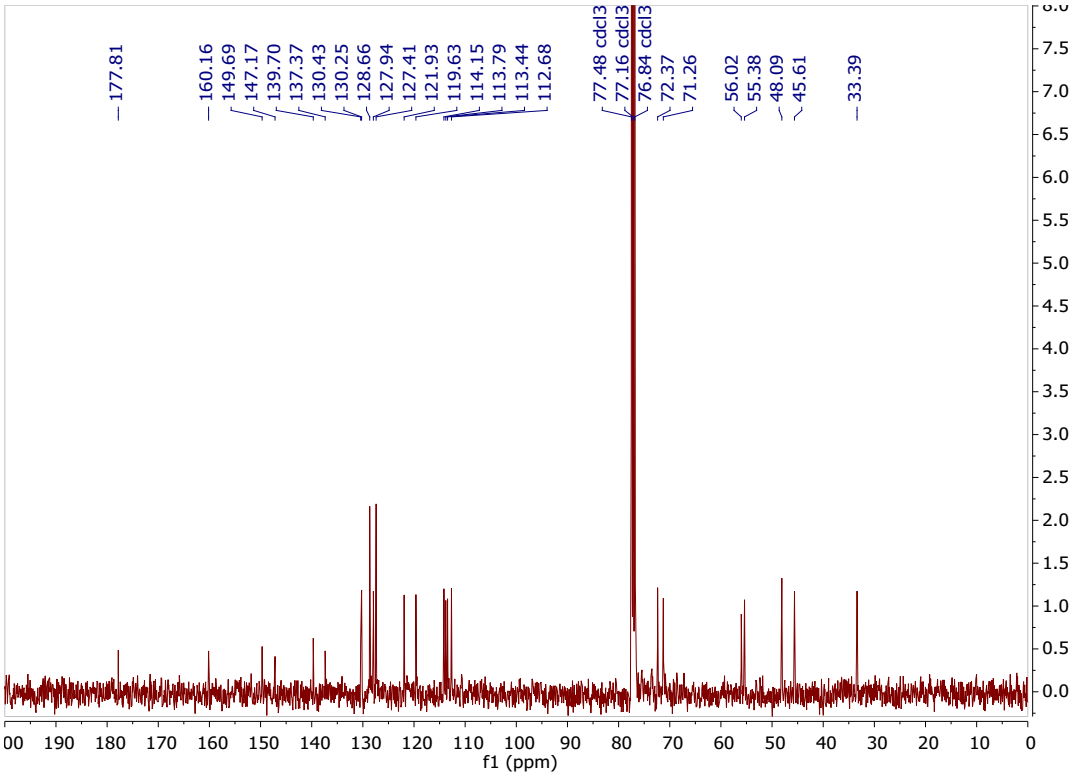

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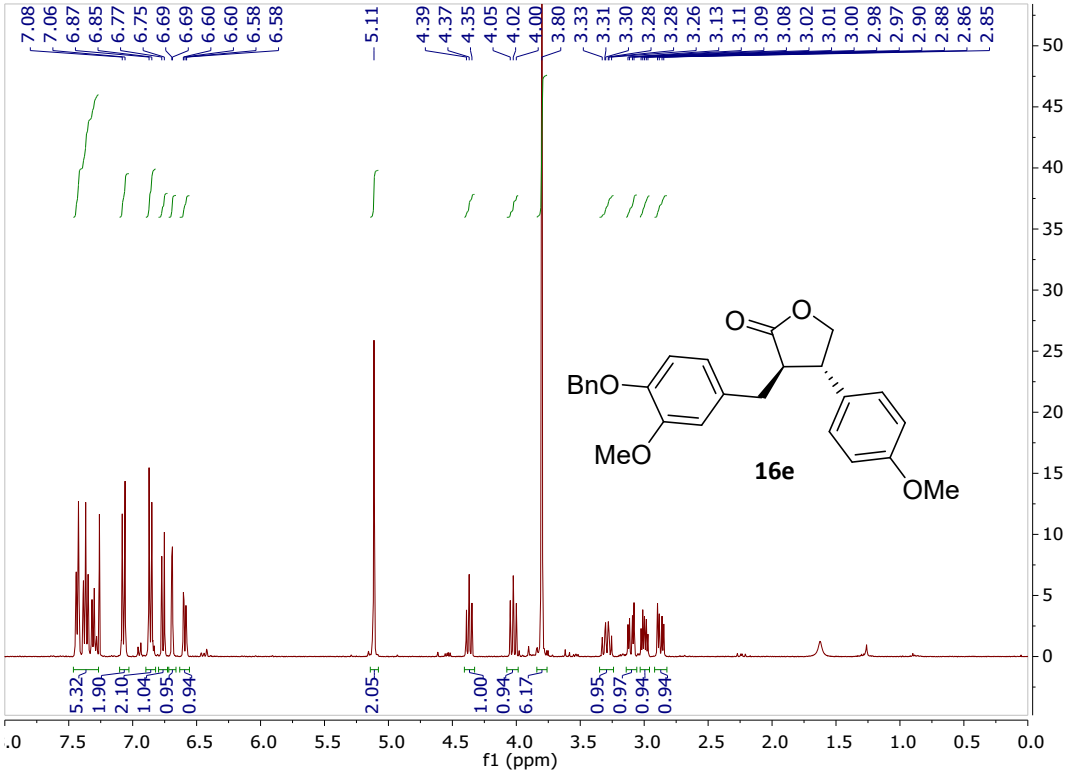

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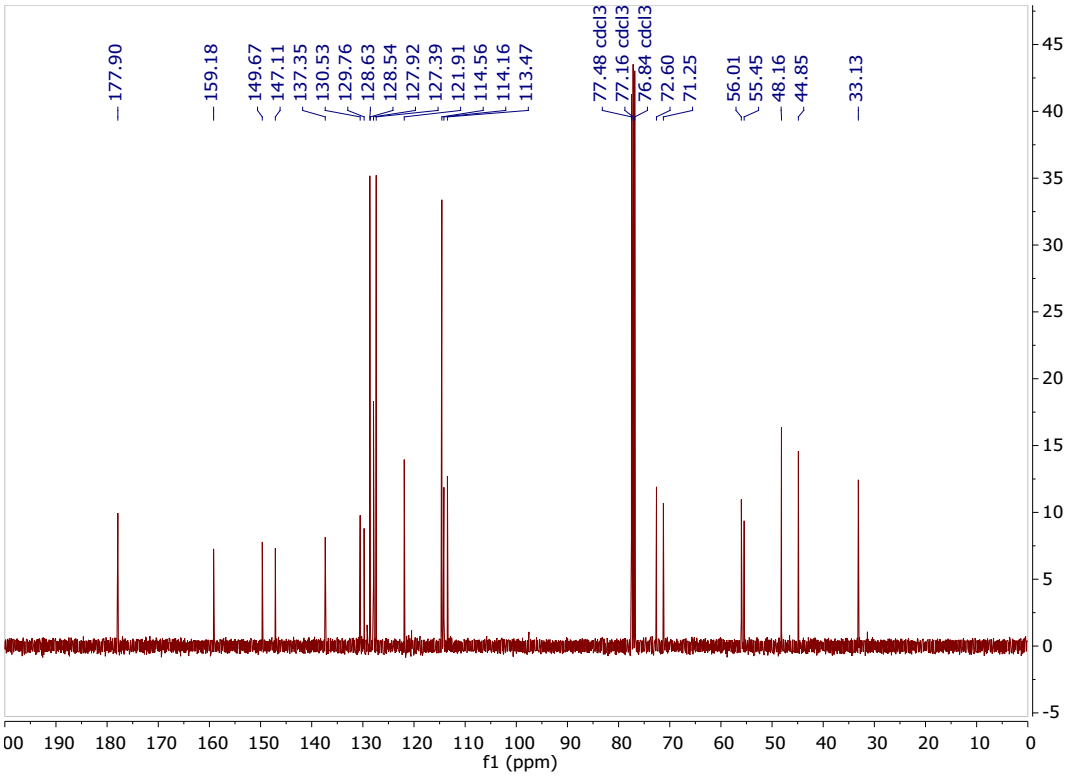

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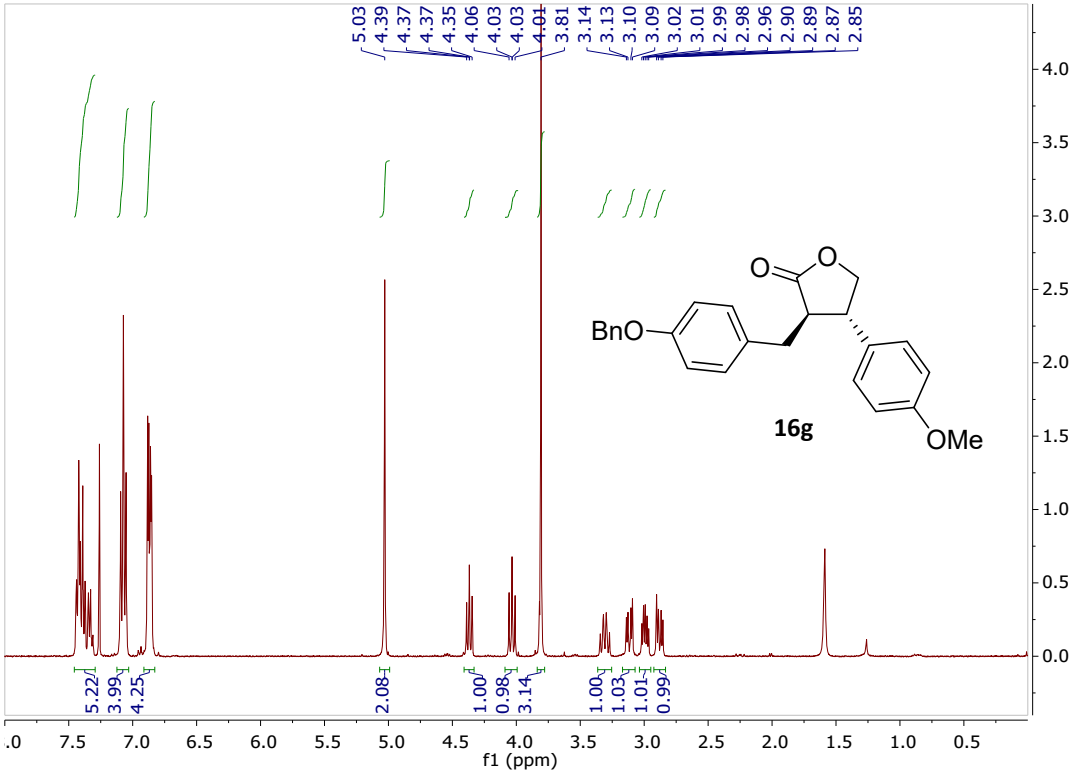

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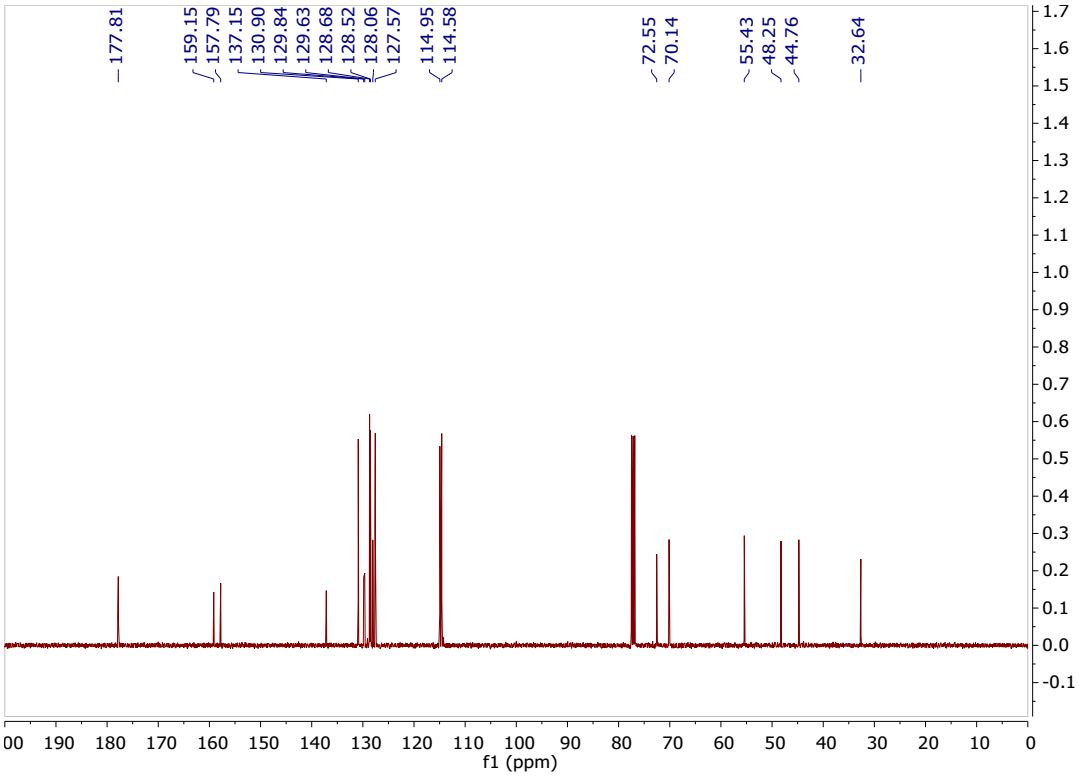

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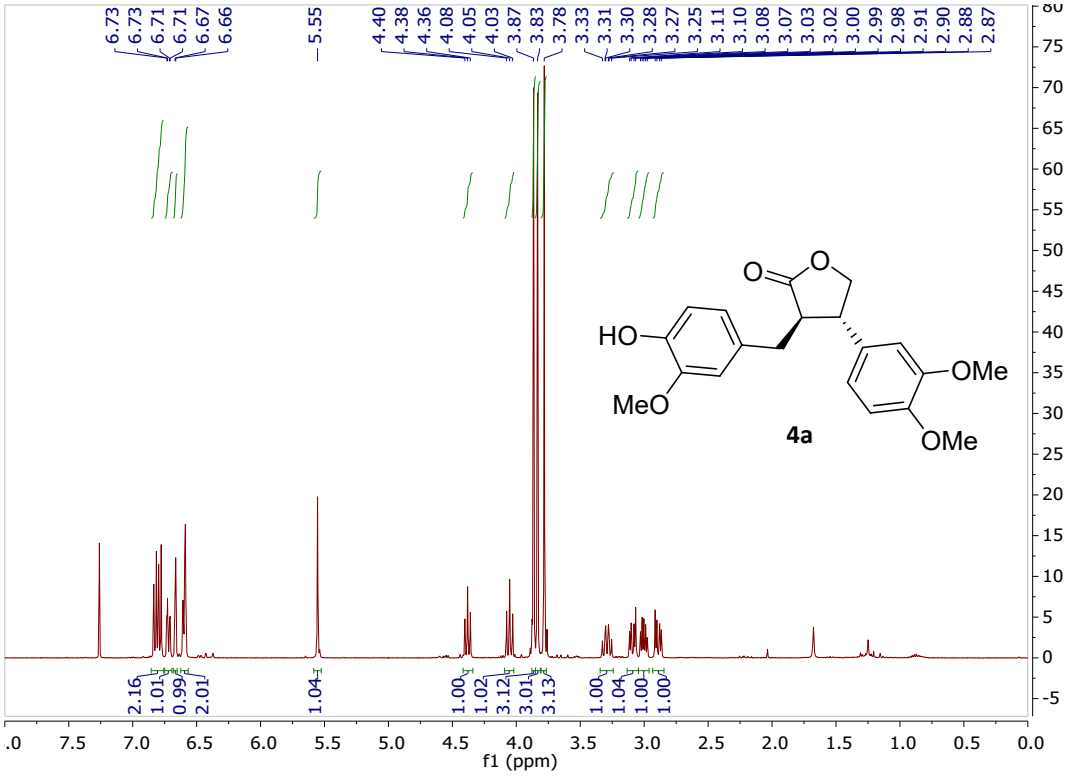

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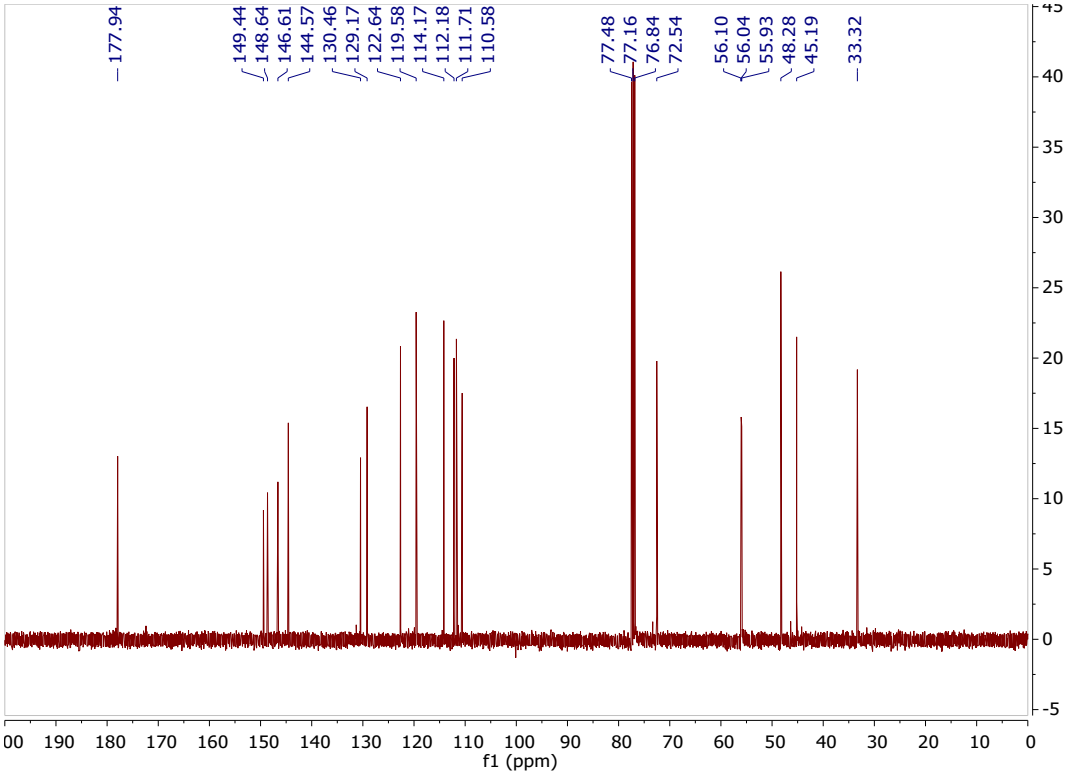

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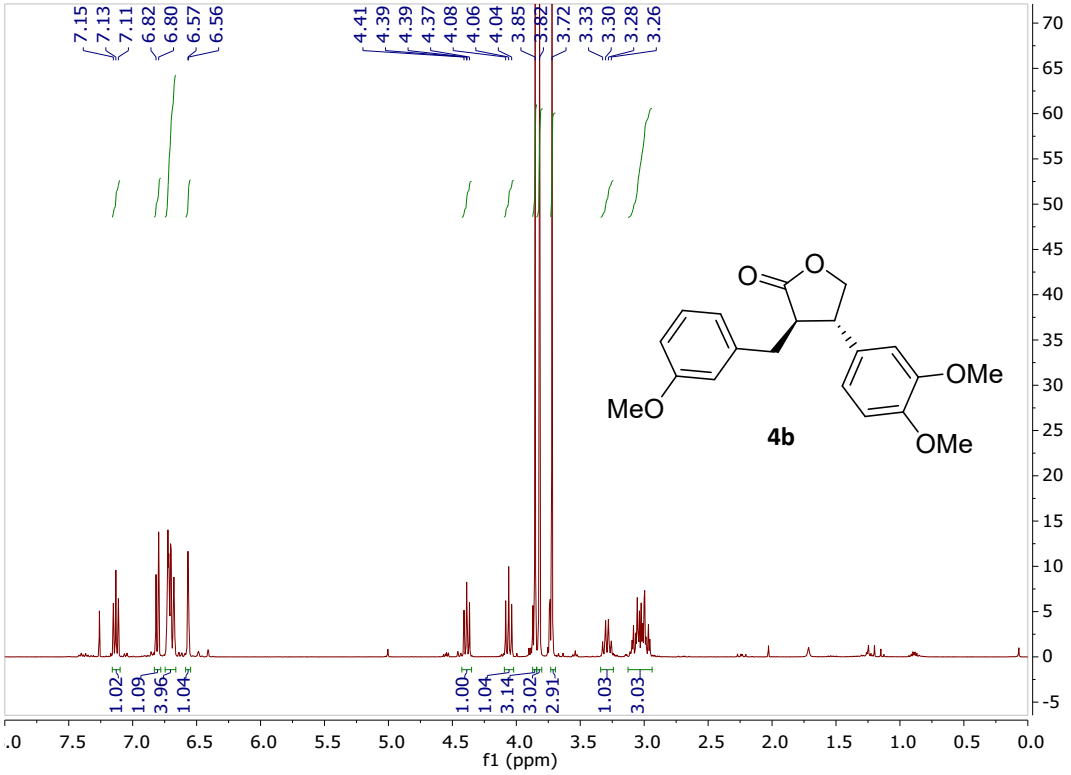

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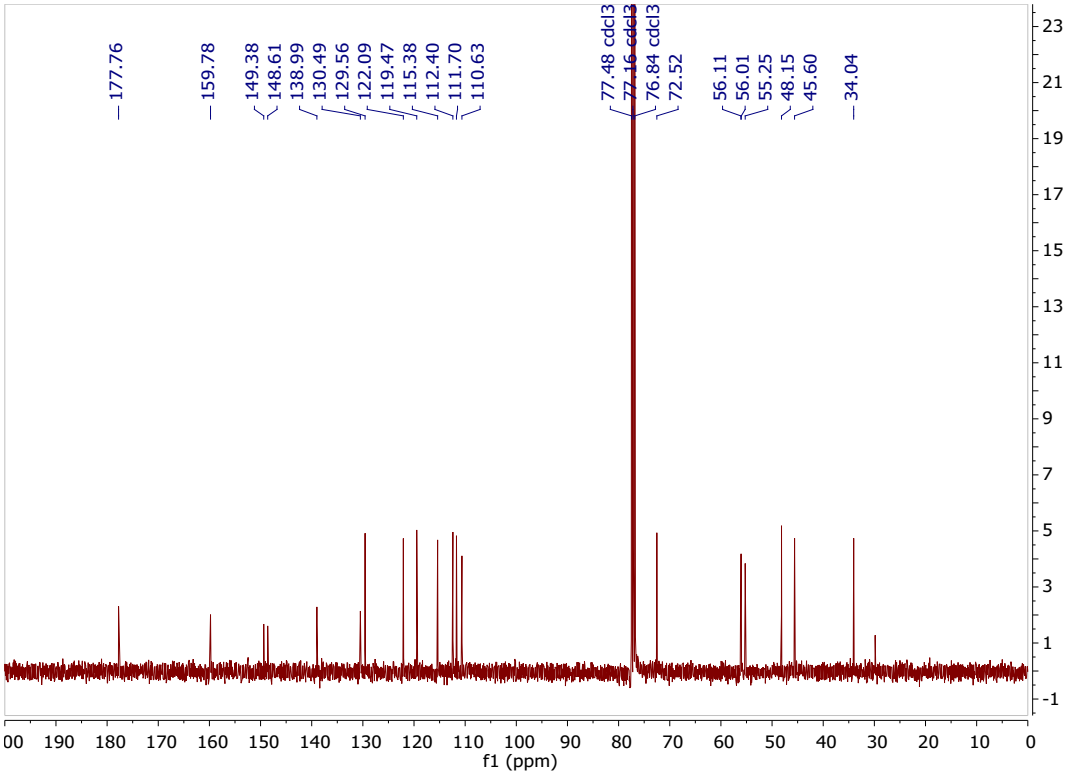

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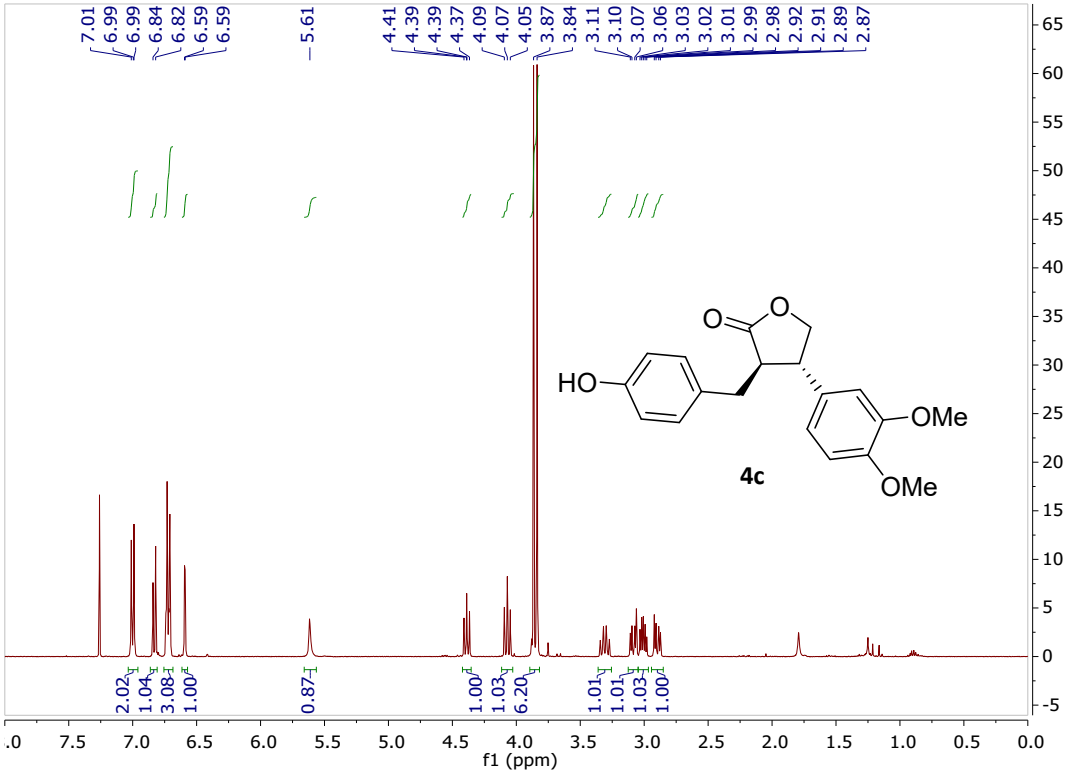

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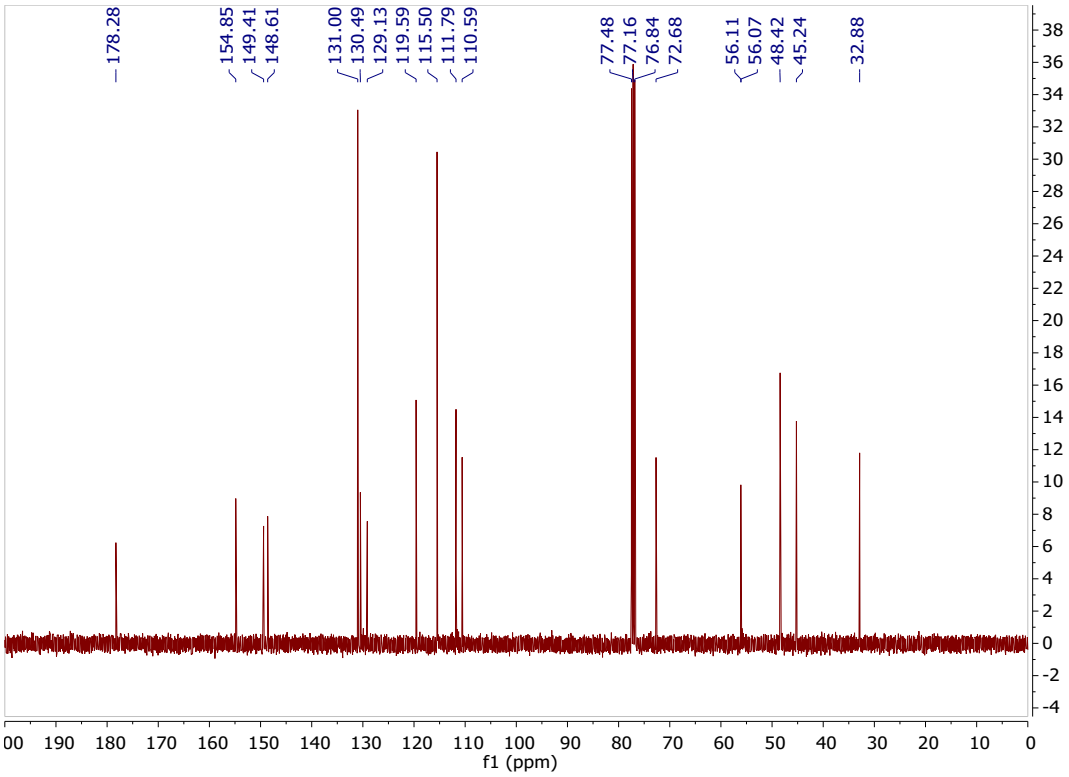

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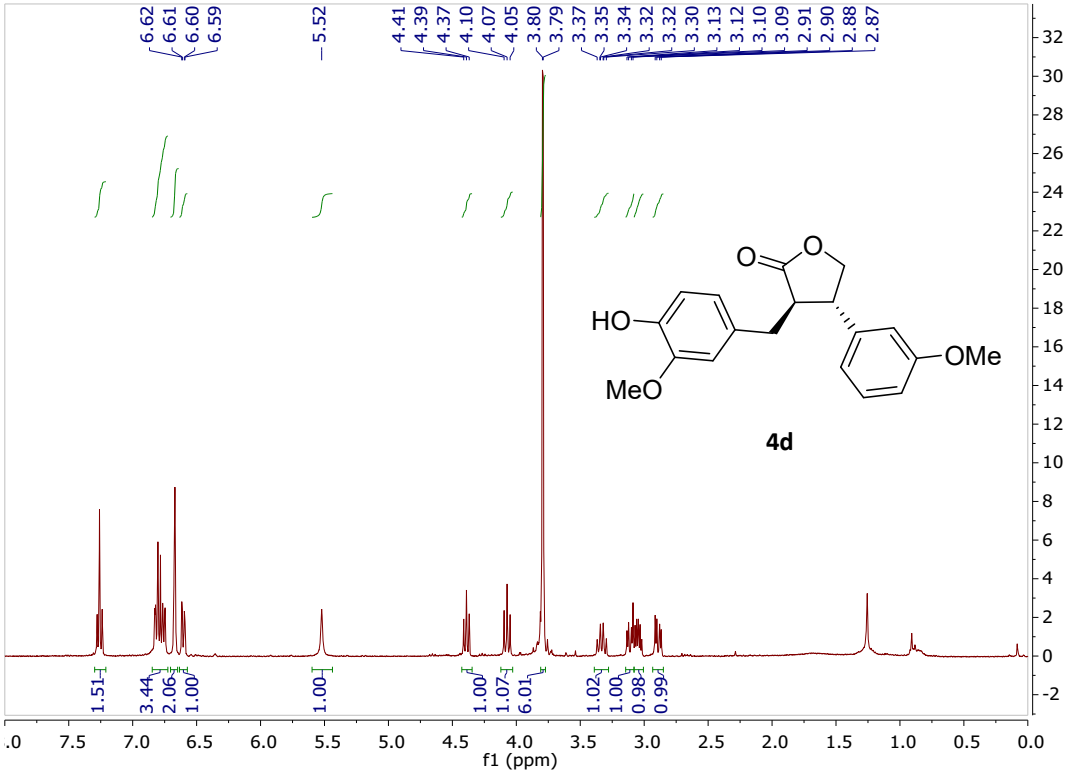

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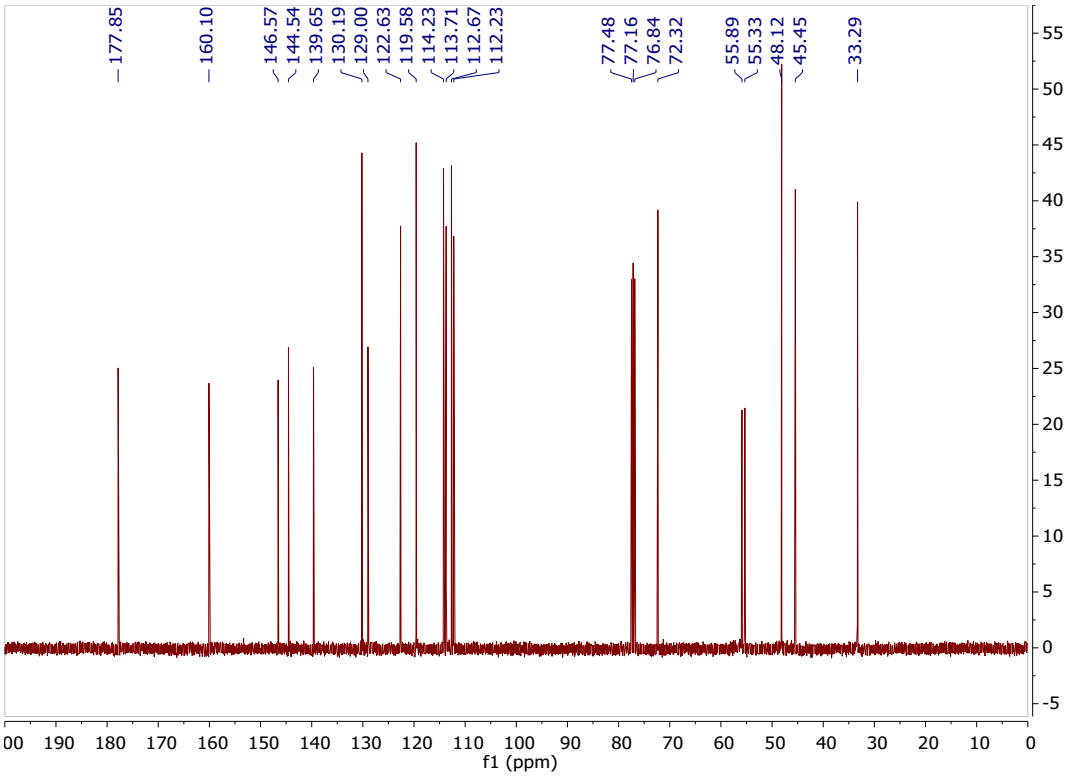

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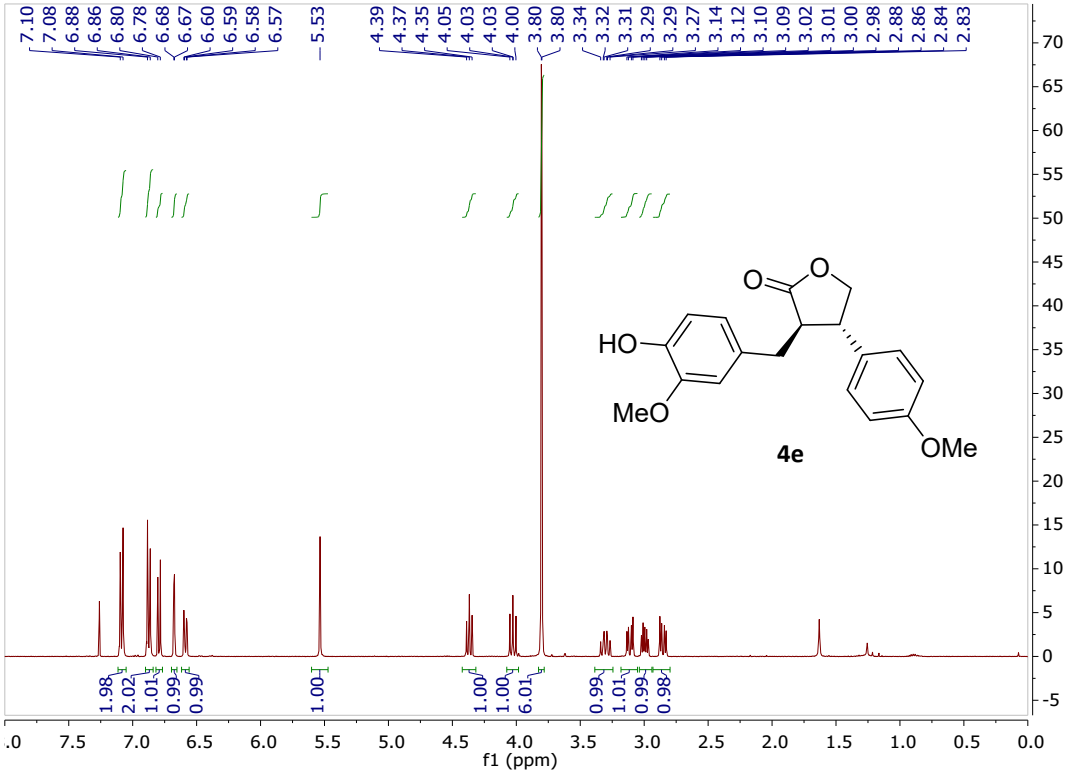

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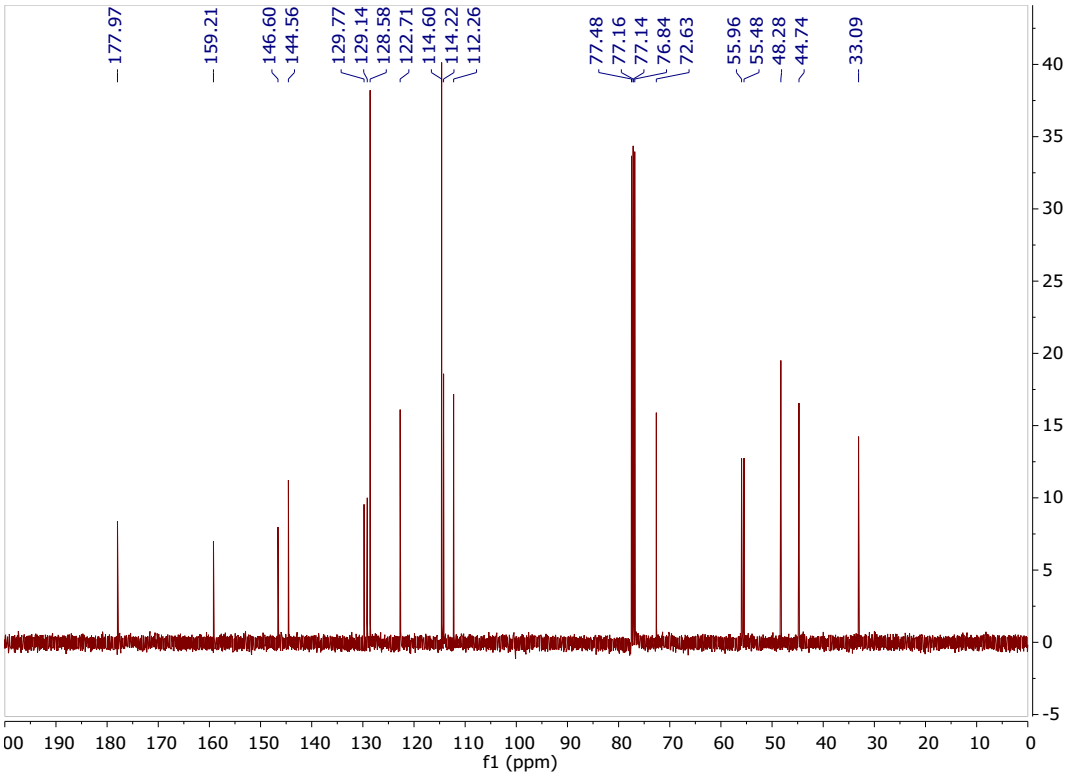

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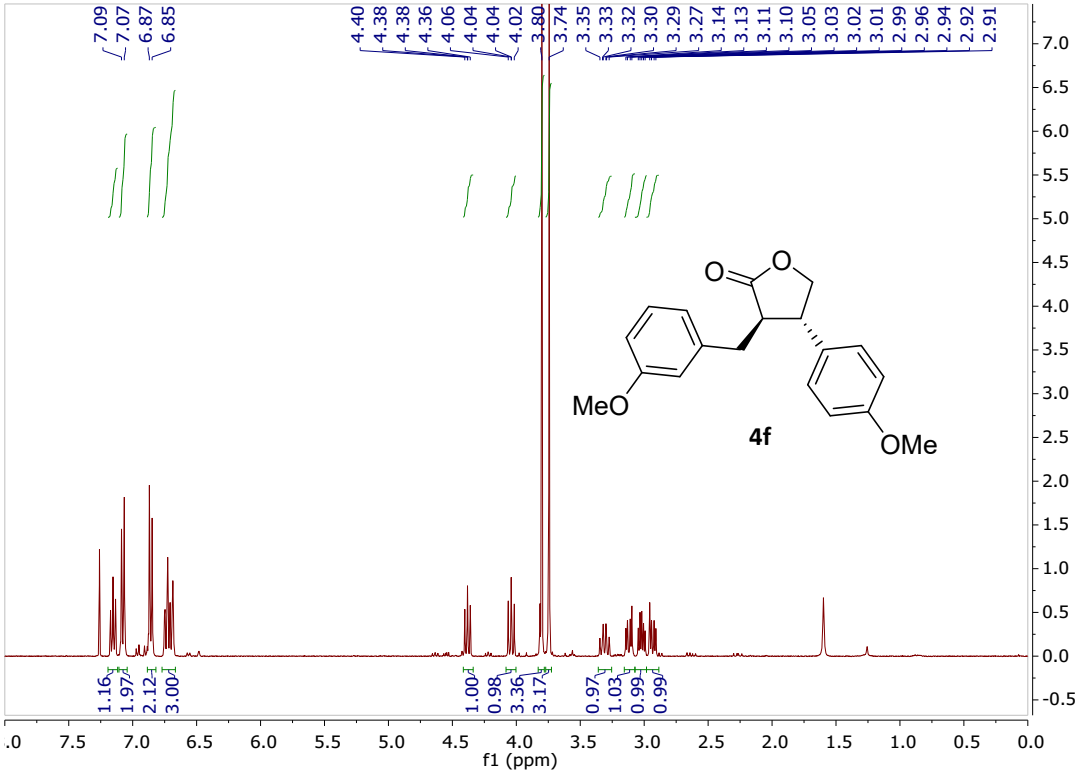

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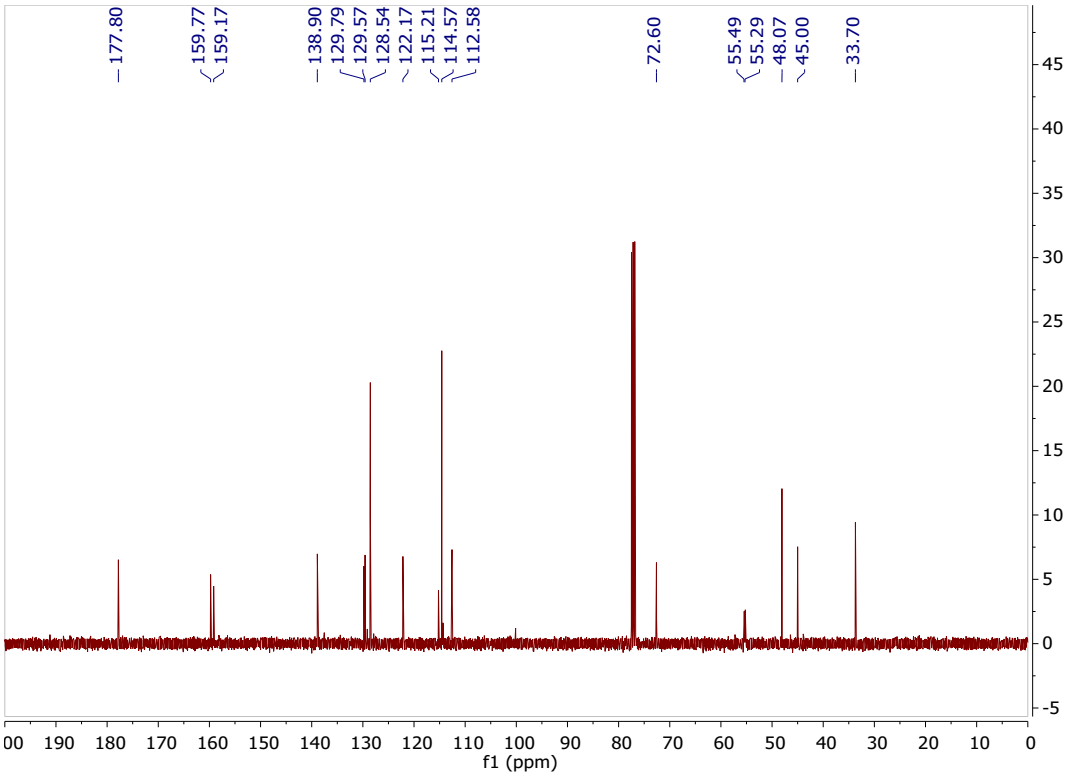

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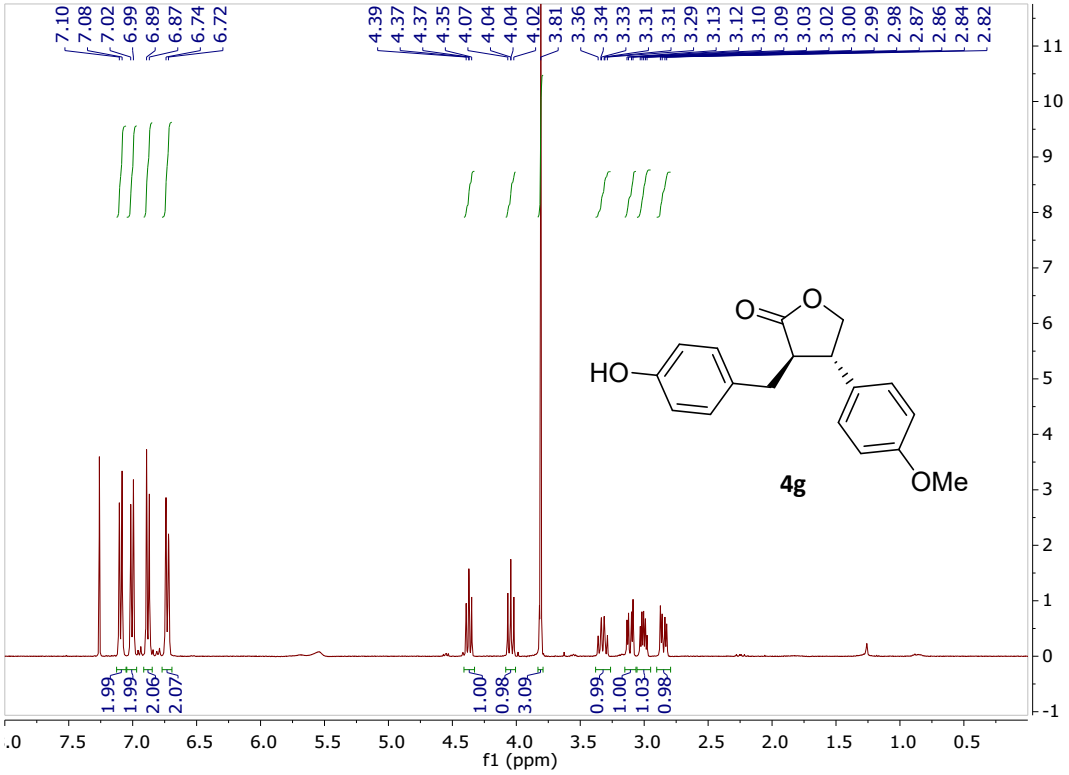

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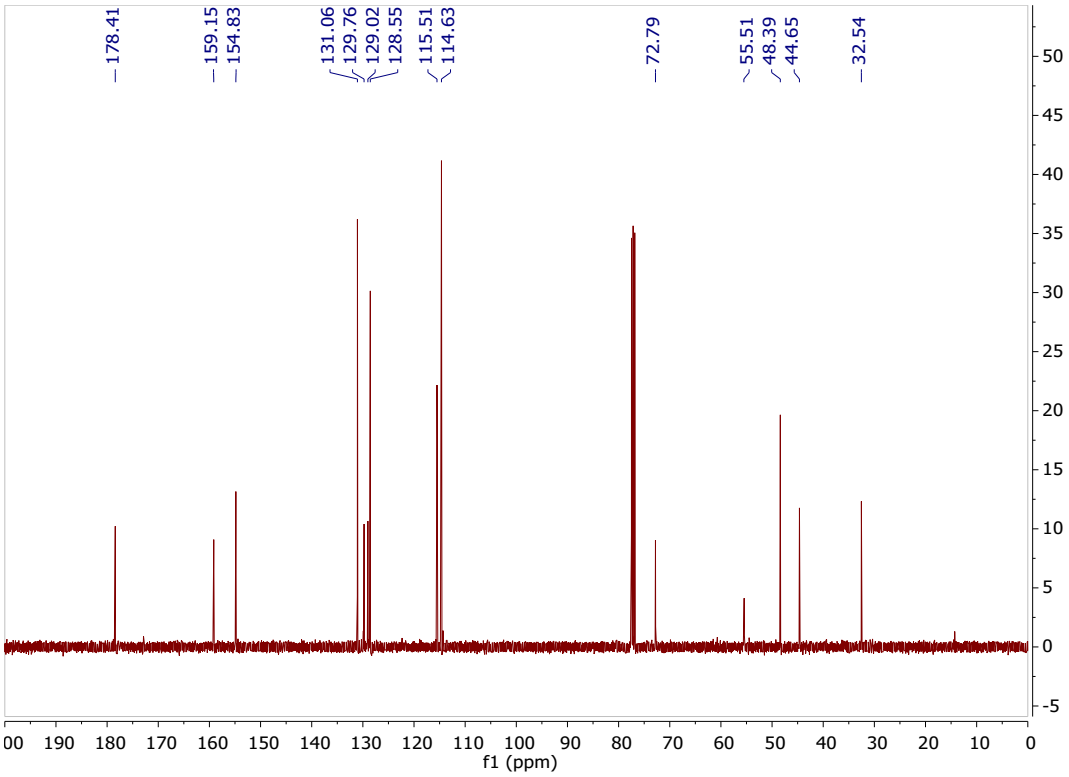

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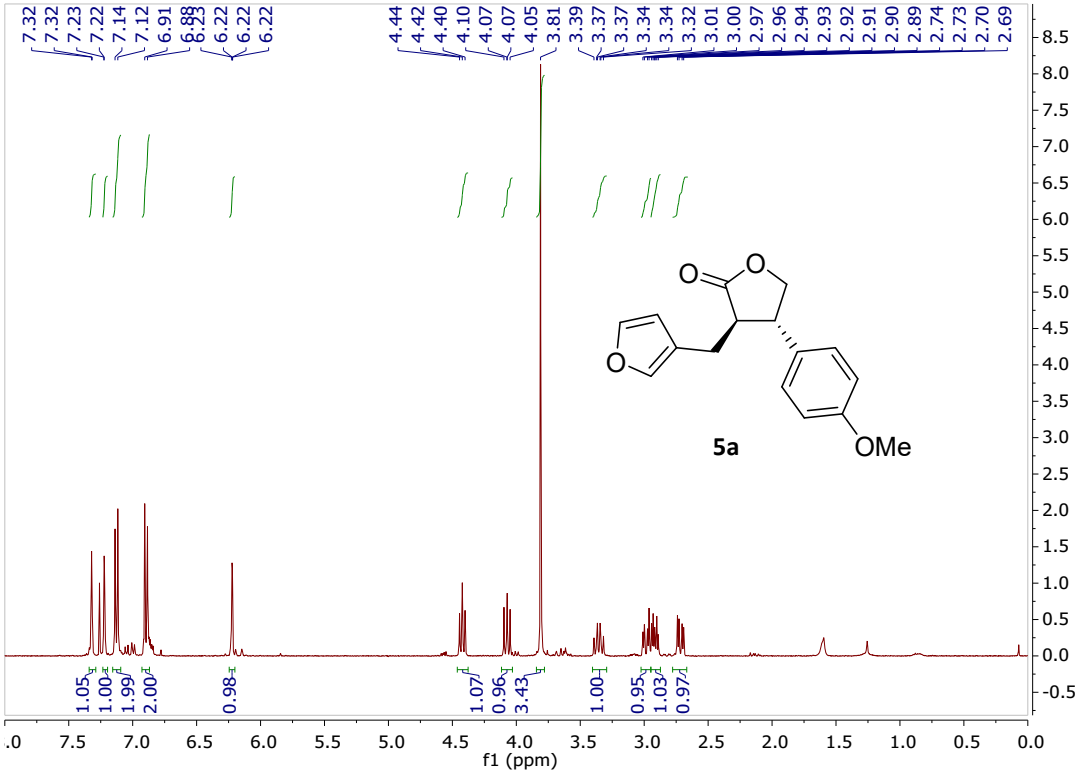

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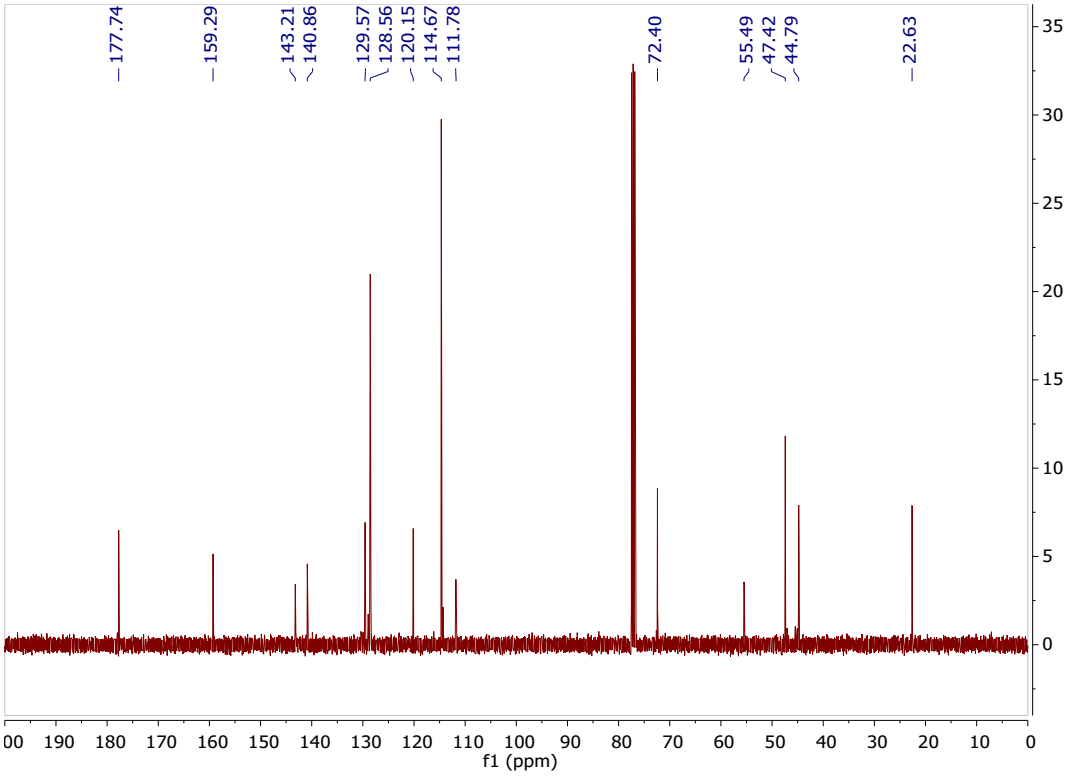

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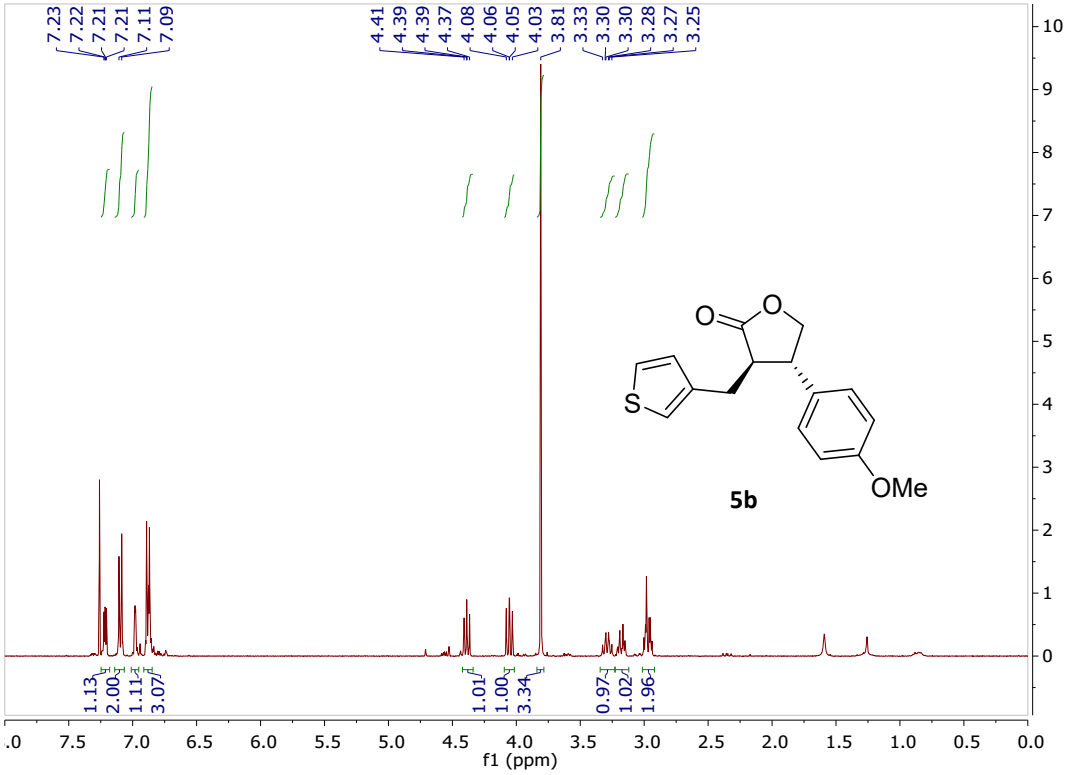

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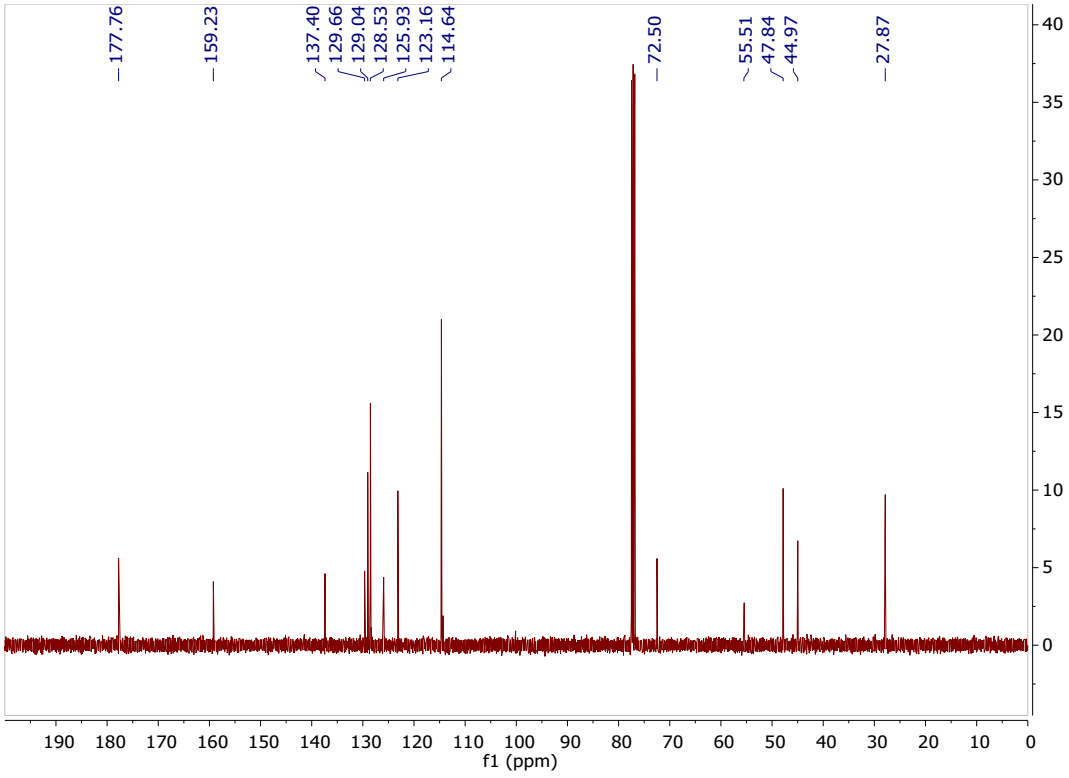

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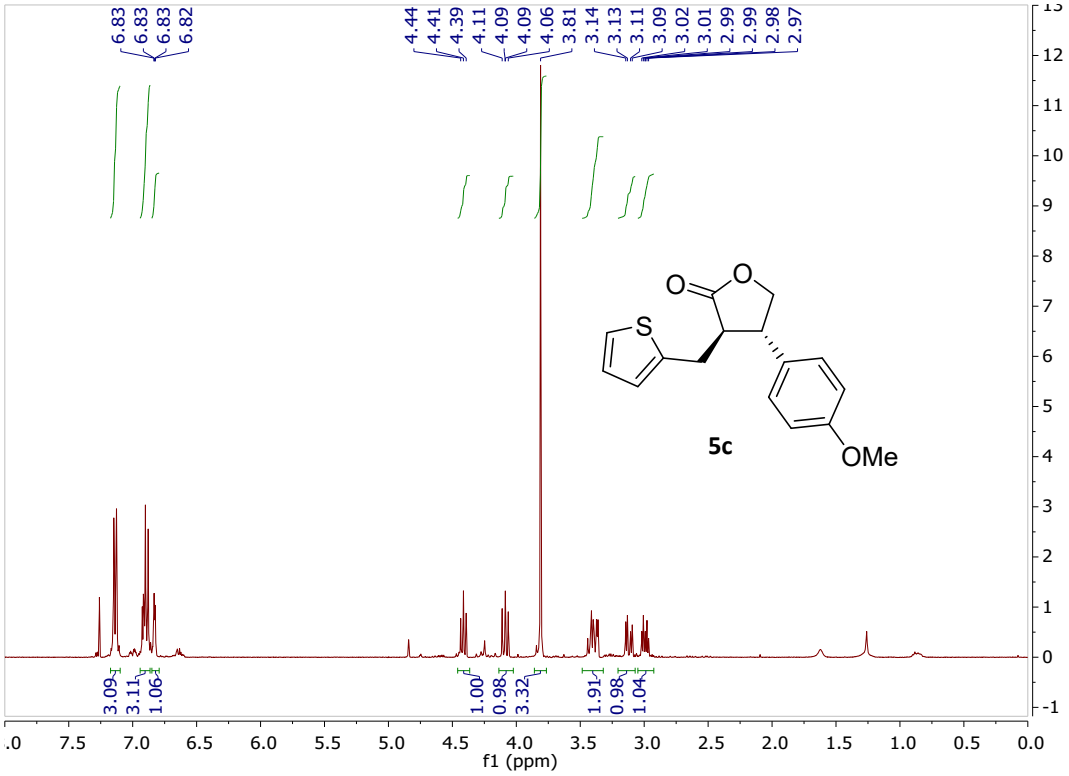

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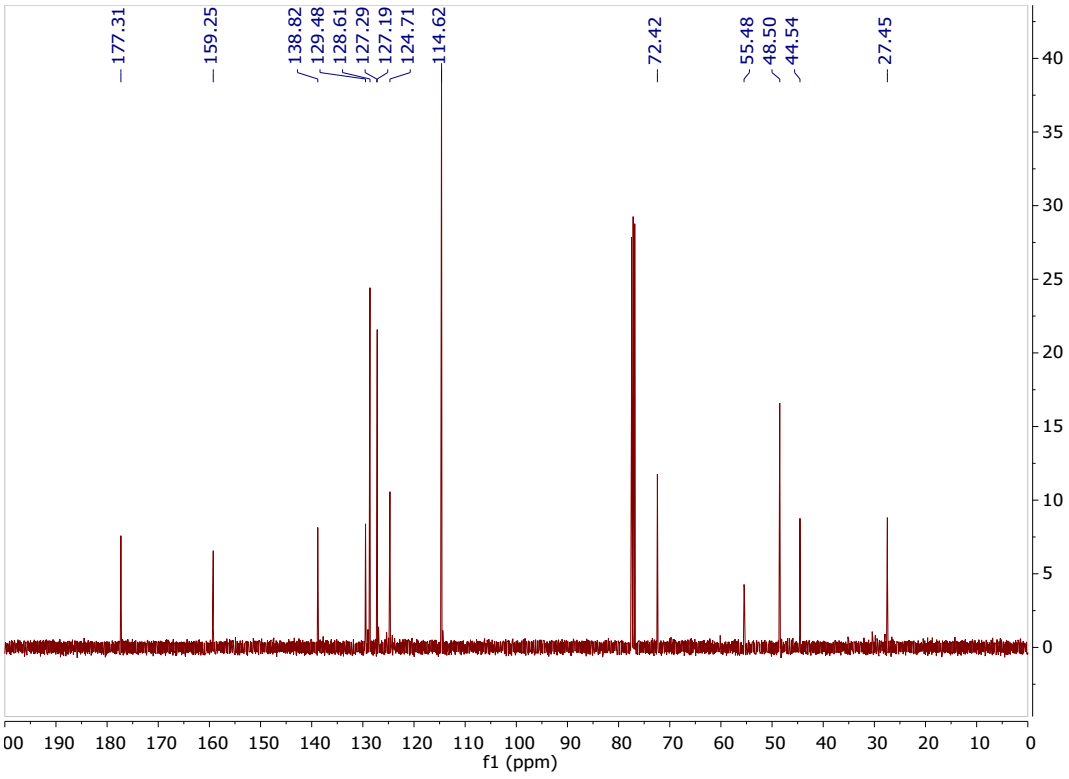

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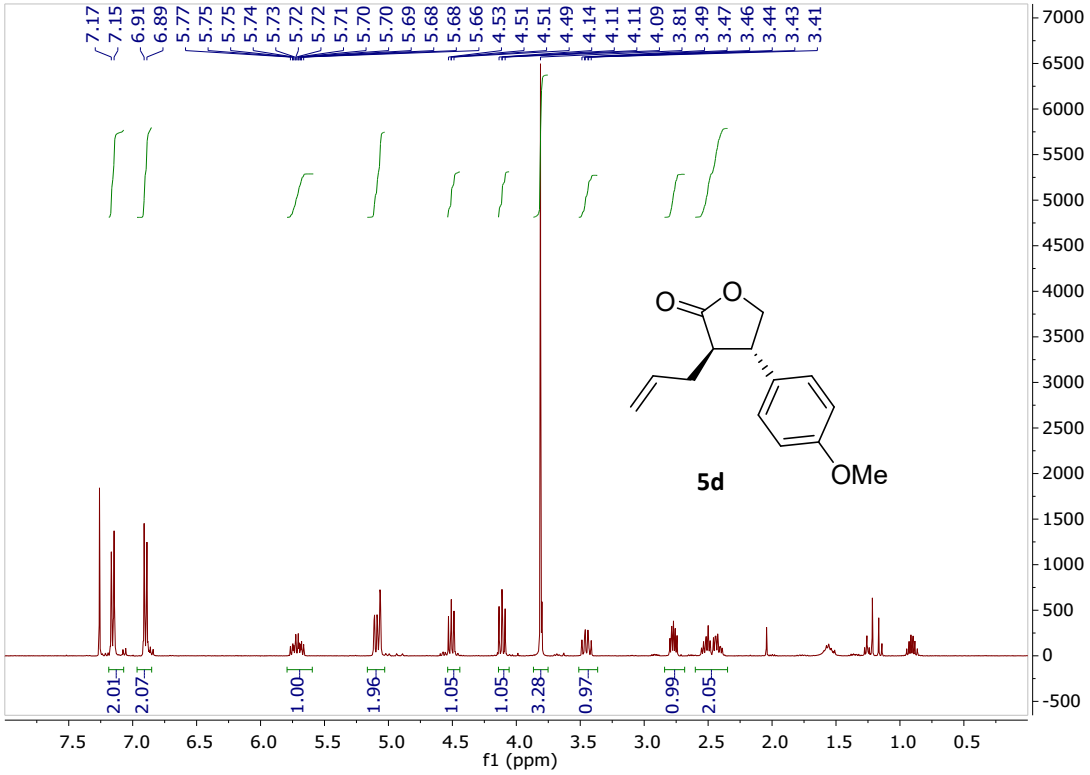

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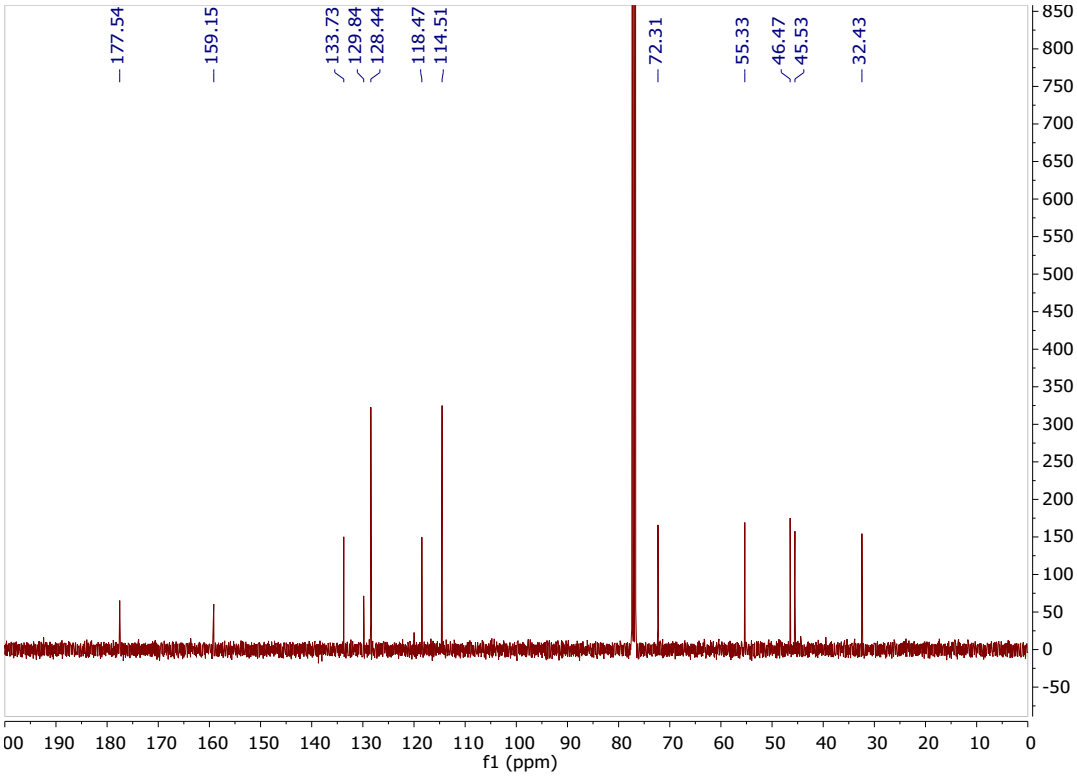

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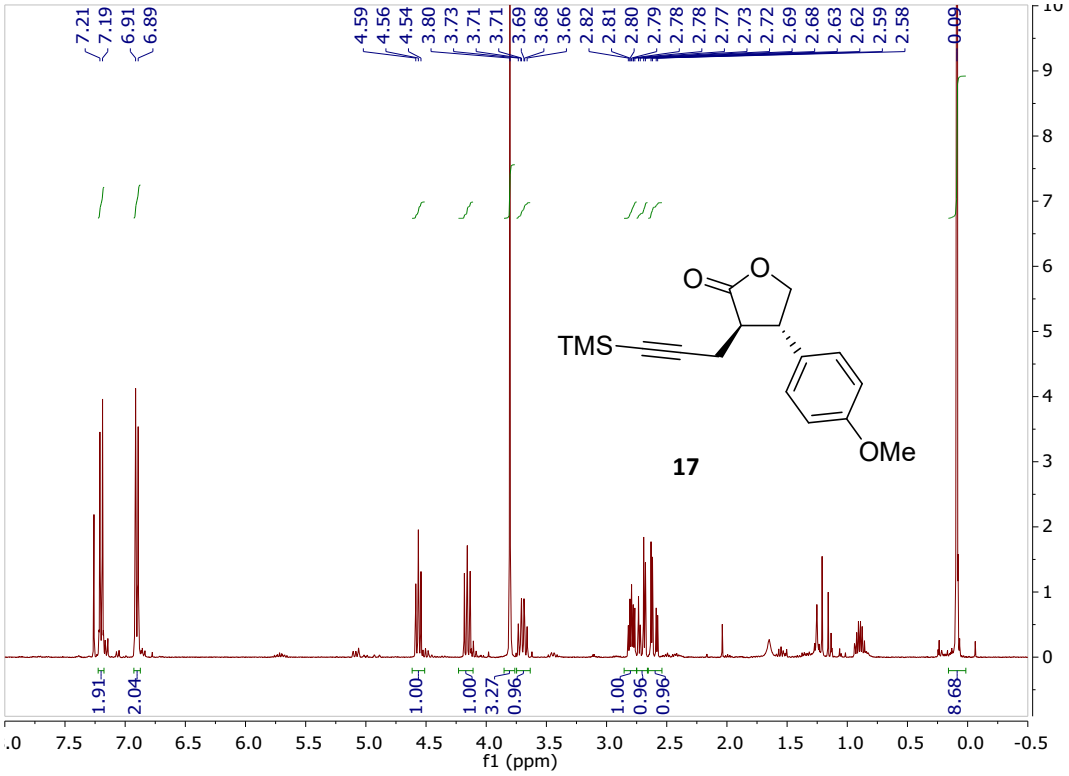

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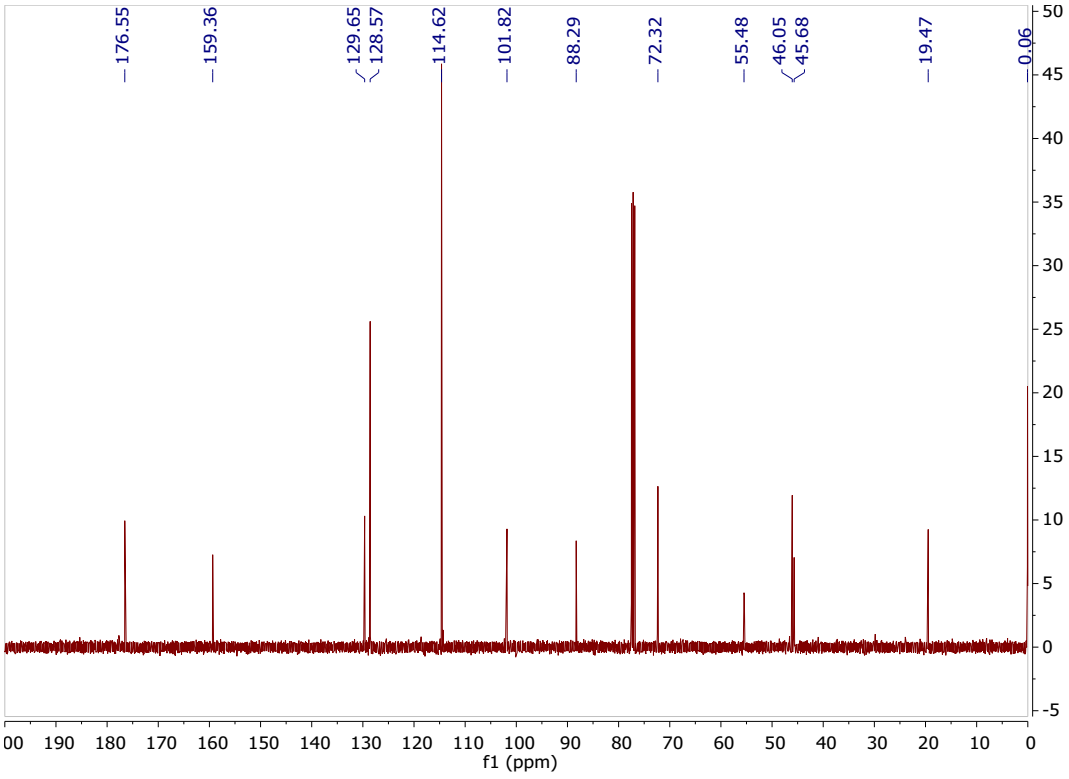

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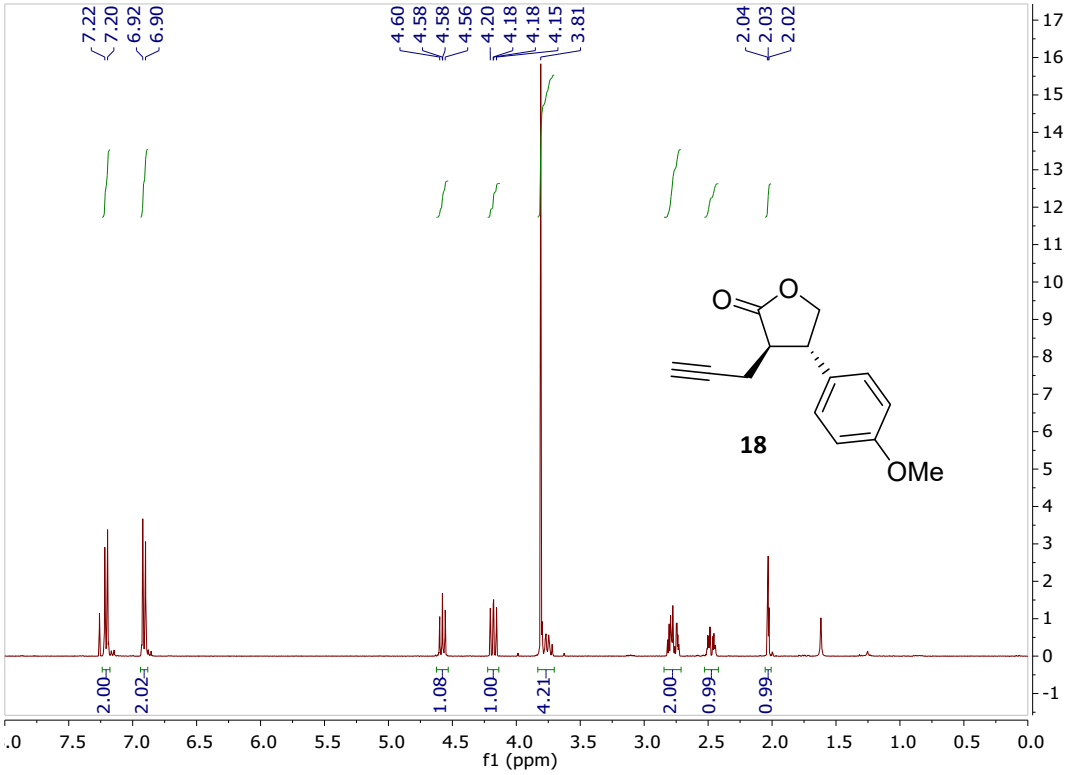

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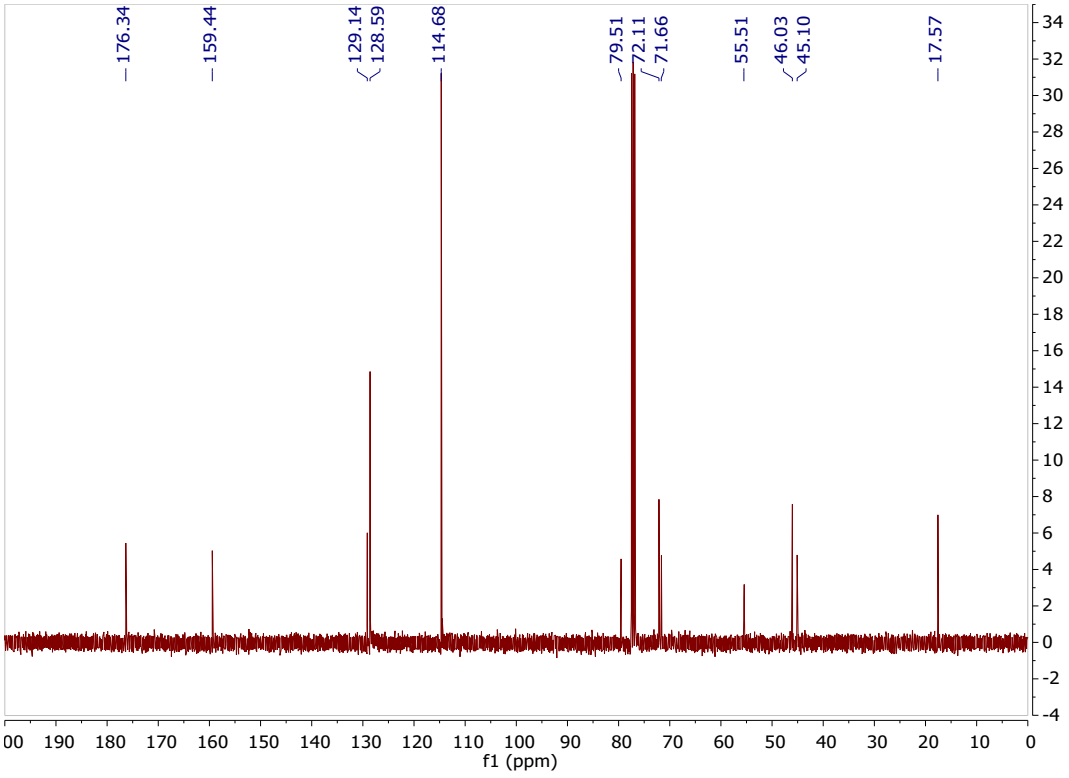

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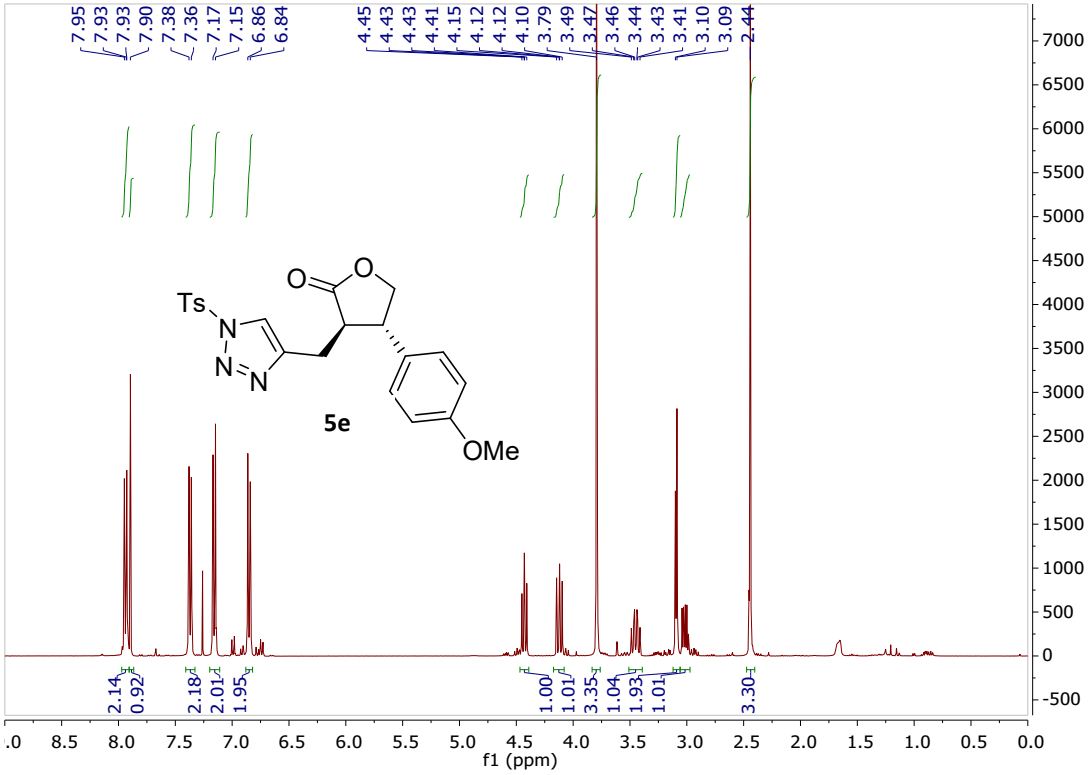
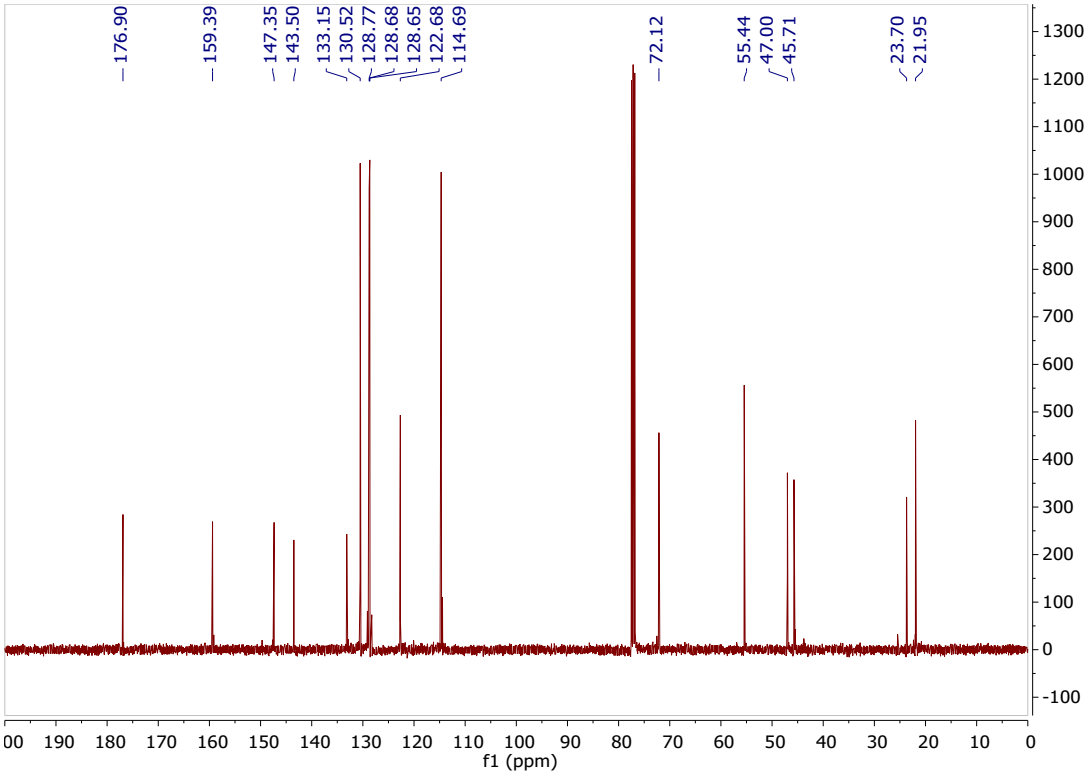
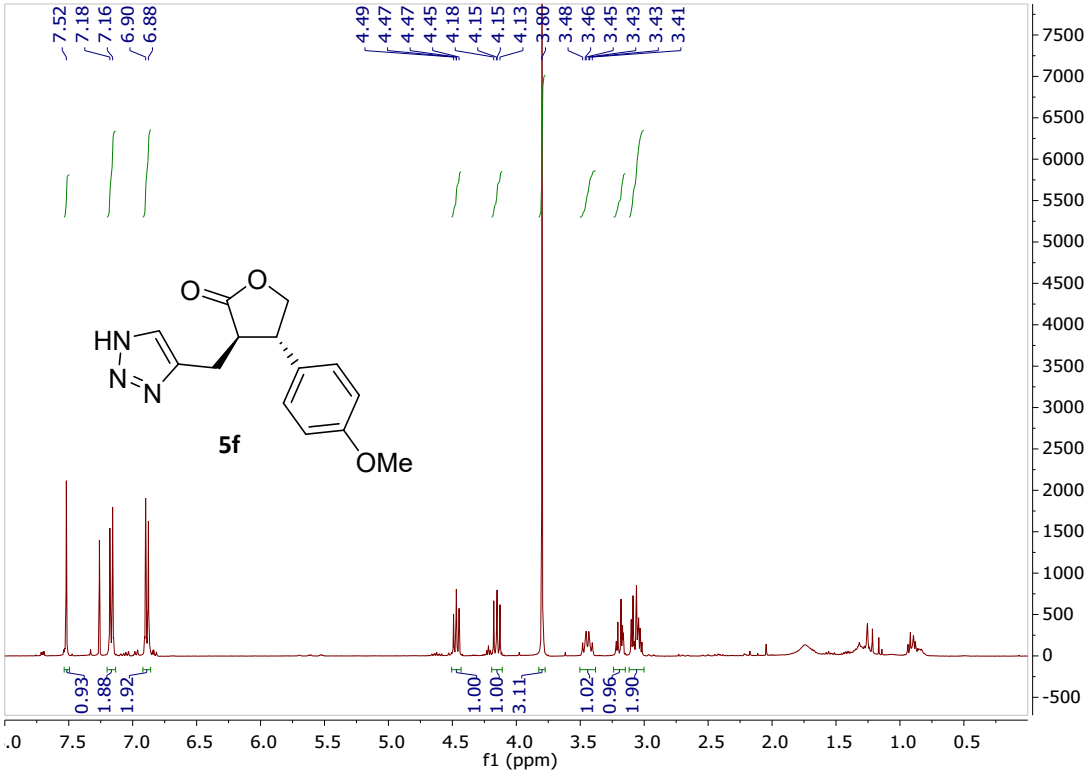


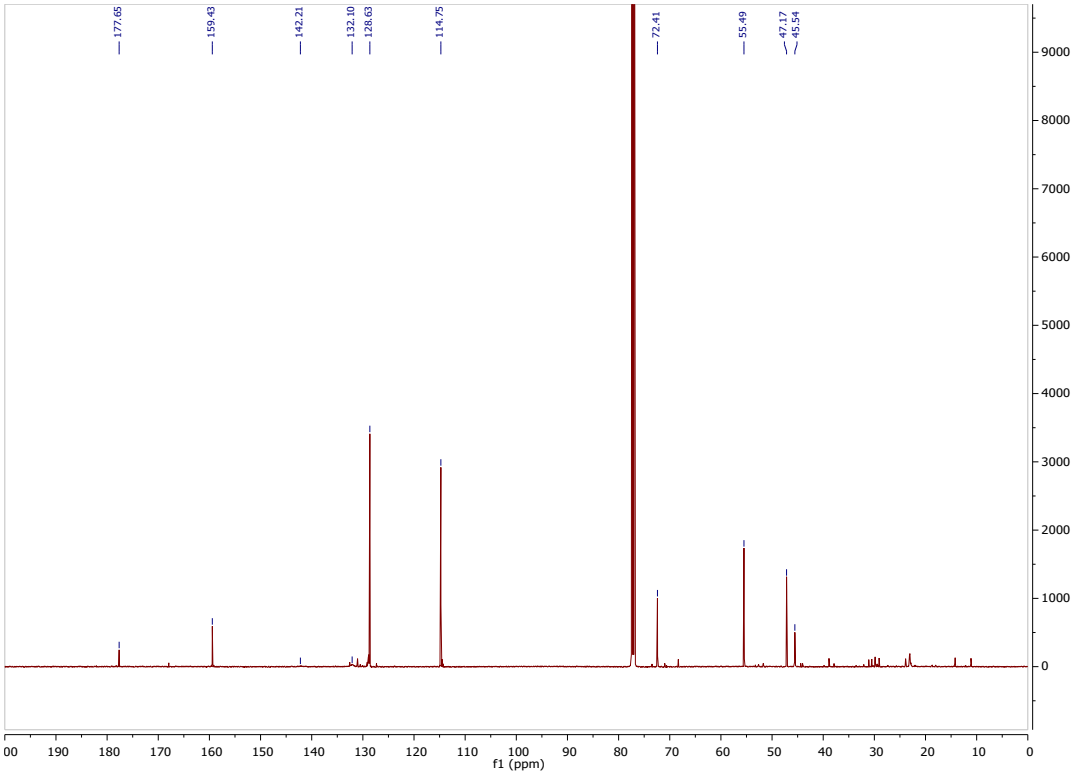
^{13}C NMR ($CDCl_3$, 100 MHz)



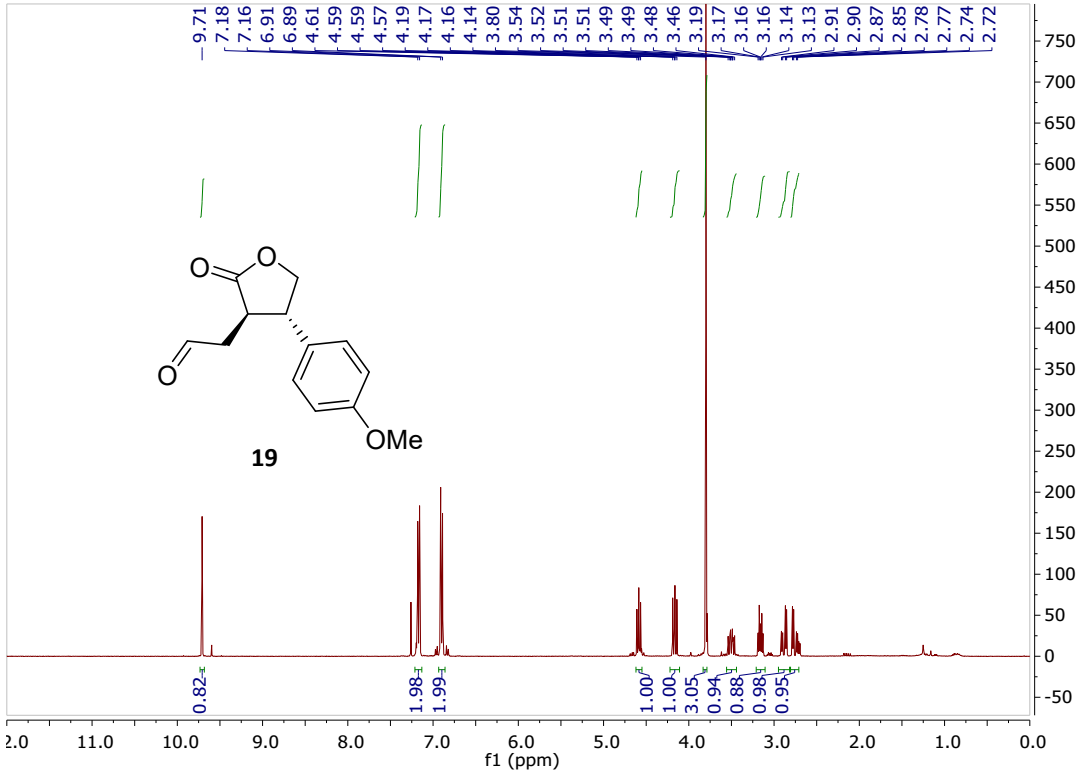
^{1}H NMR ($CDCl_3$, 400 MHz)



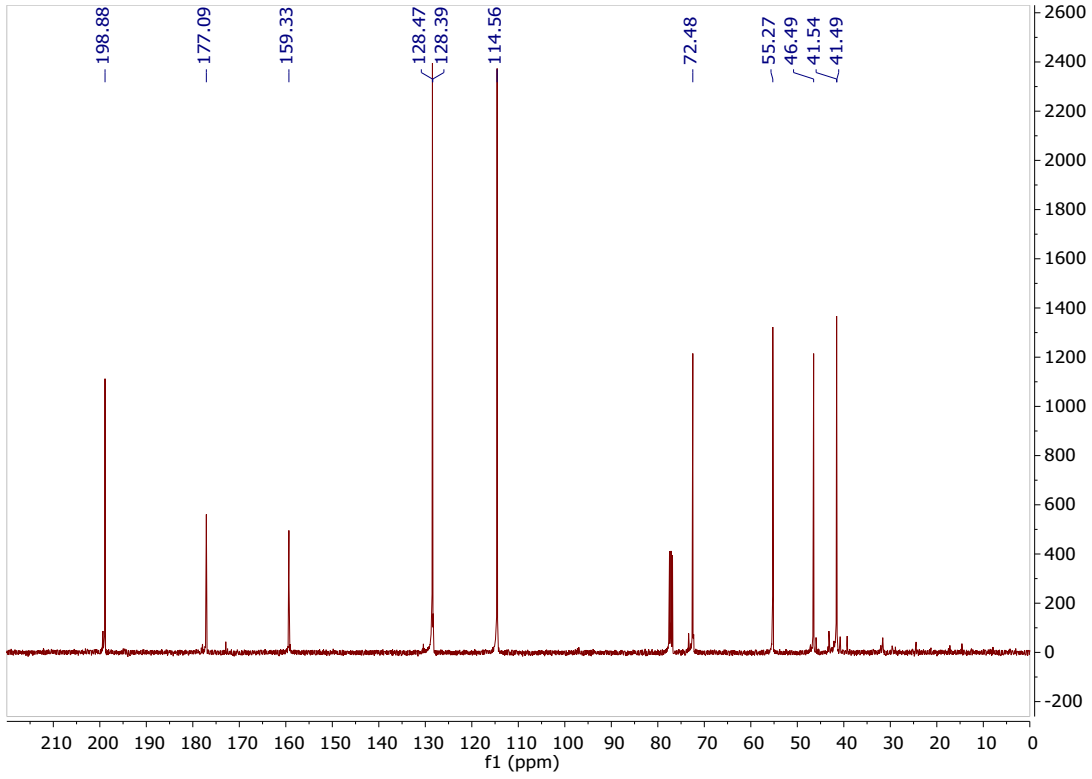
^{13}C NMR ($CDCl_3$, 125 MHz)



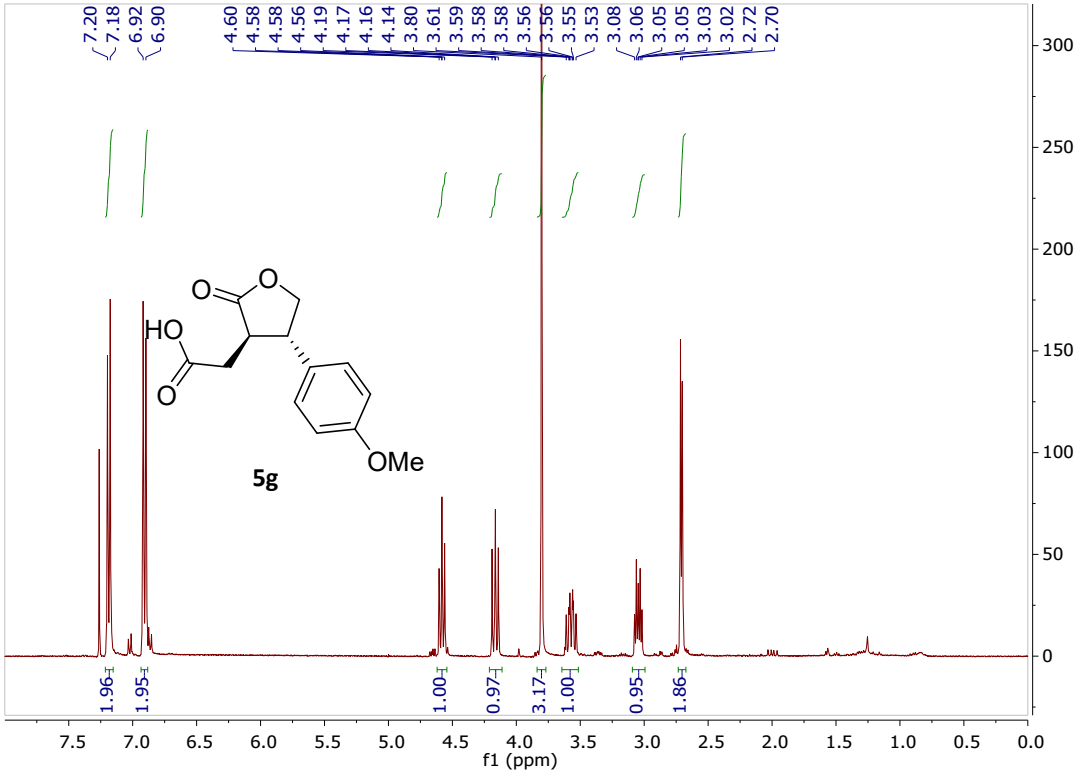
^{1}H NMR ($CDCl_3$, 400 MHz)



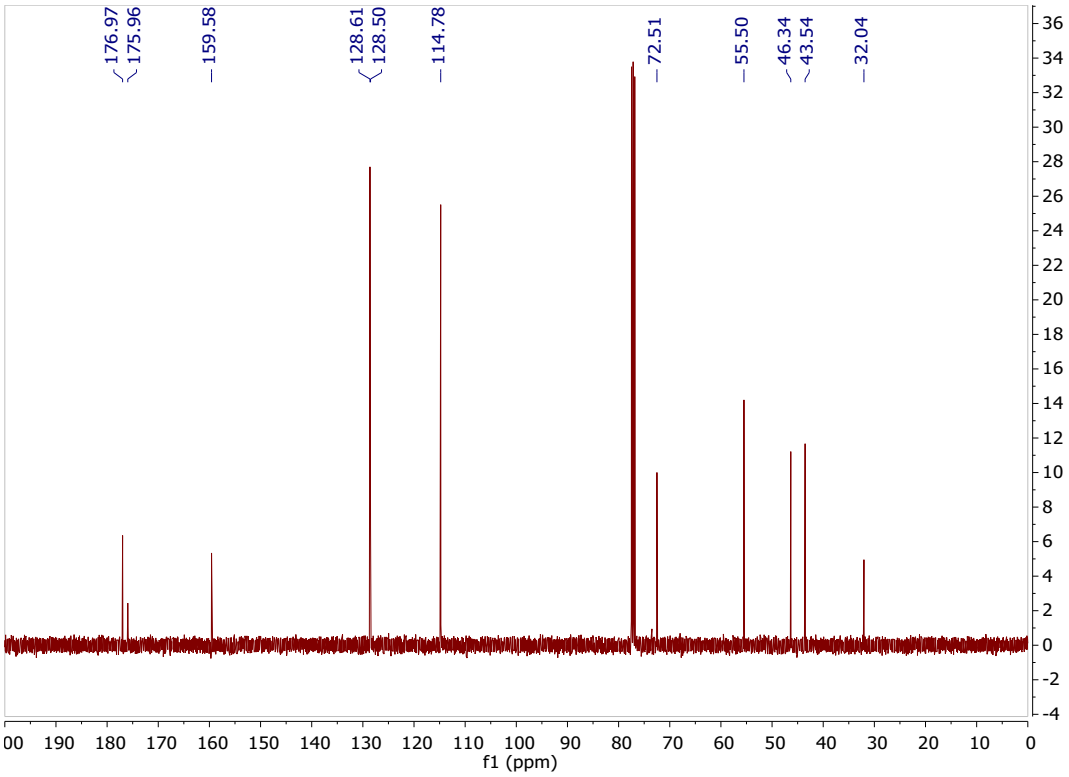
^{13}C NMR ($CDCl_3$, 100 MHz)



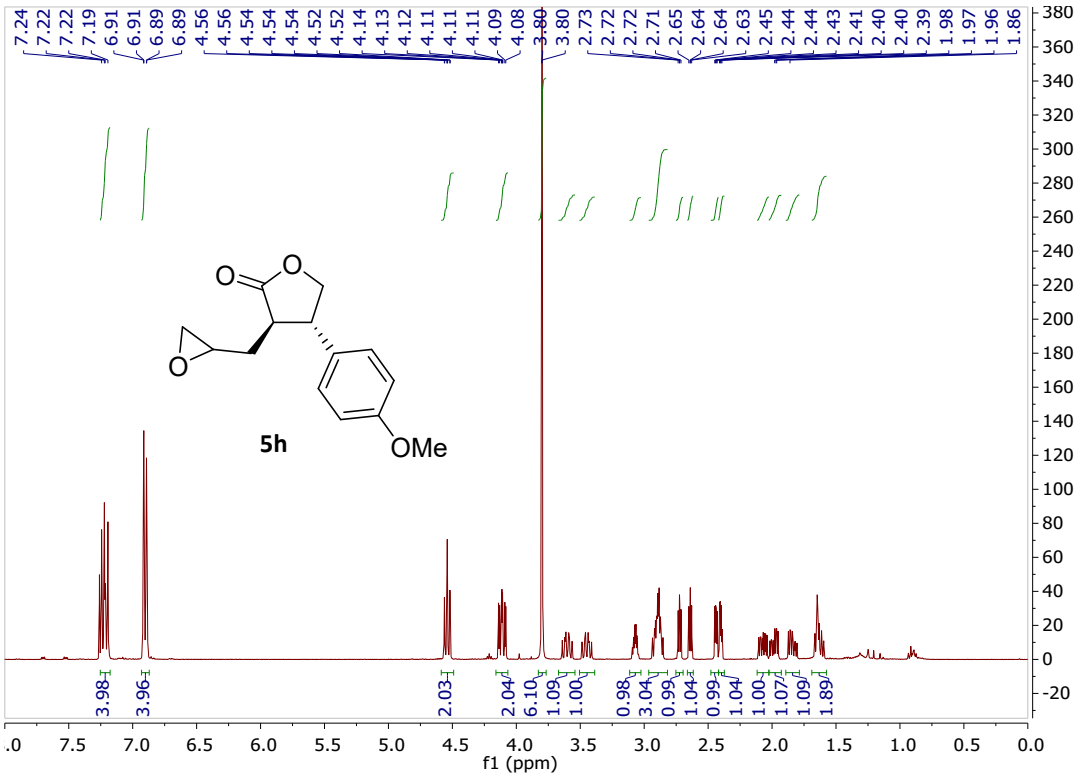
^{1}H NMR ($CDCl_3$, 400 MHz)



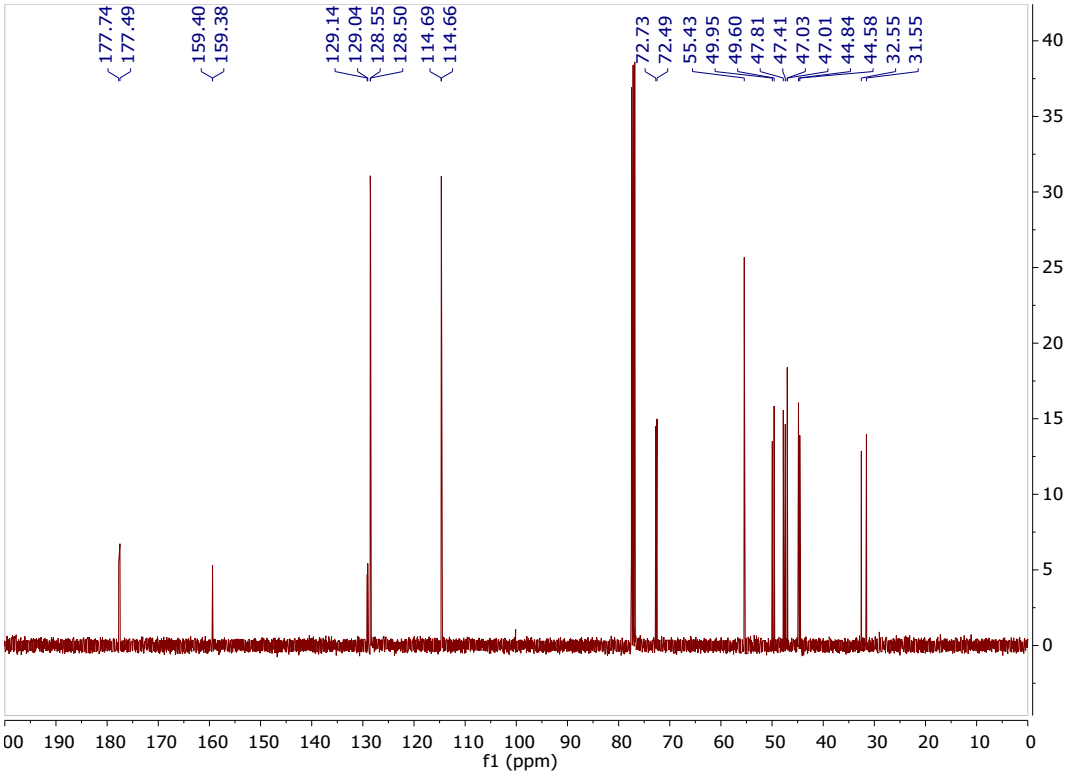
^{13}C NMR ($CDCl_3$, 100 MHz)



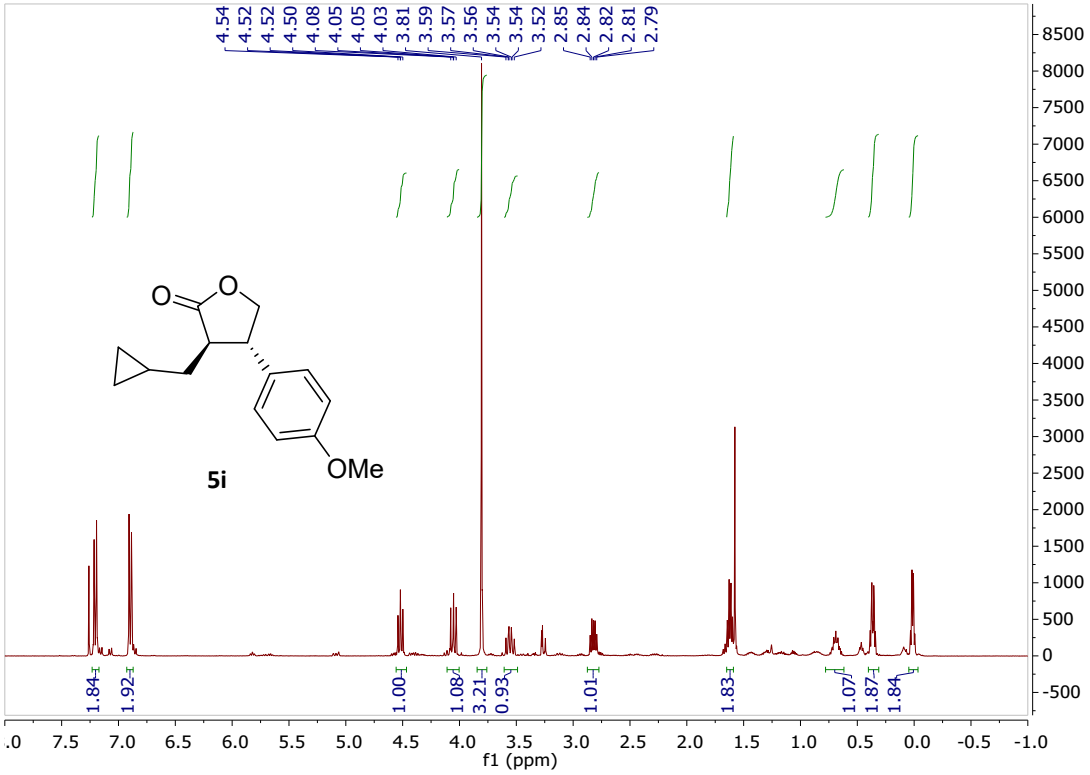
^{1}H NMR ($CDCl_3$, 400 MHz)



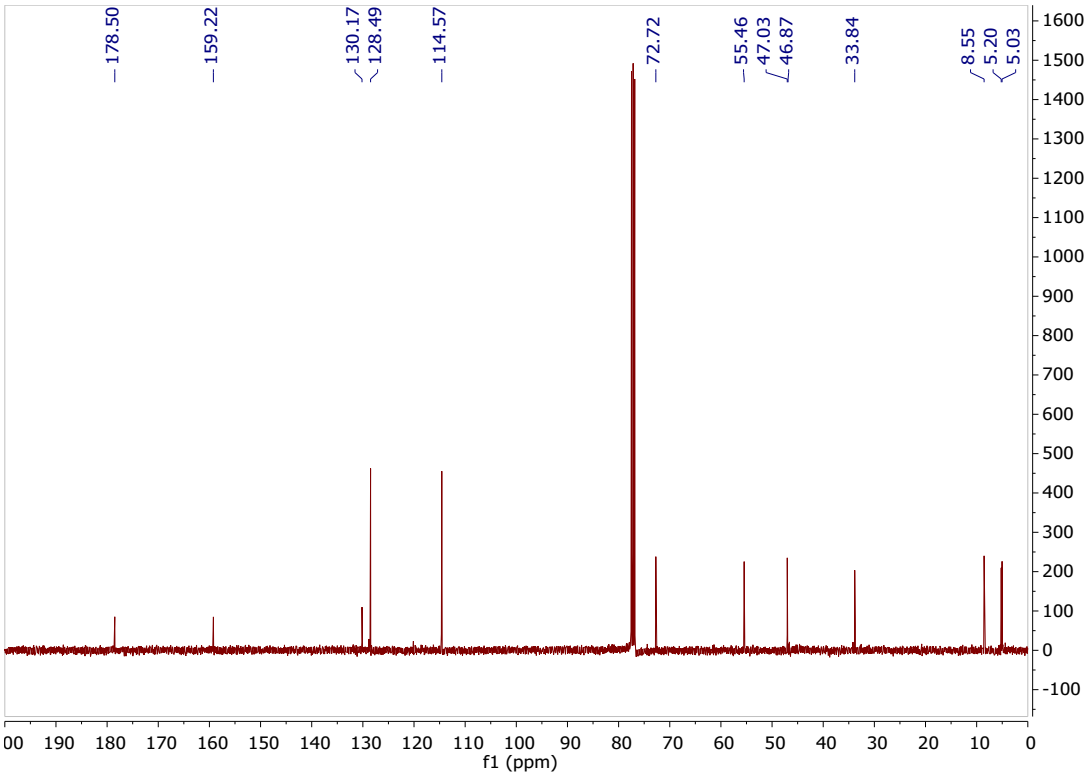
^{13}C NMR ($CDCl_3$, 100 MHz)



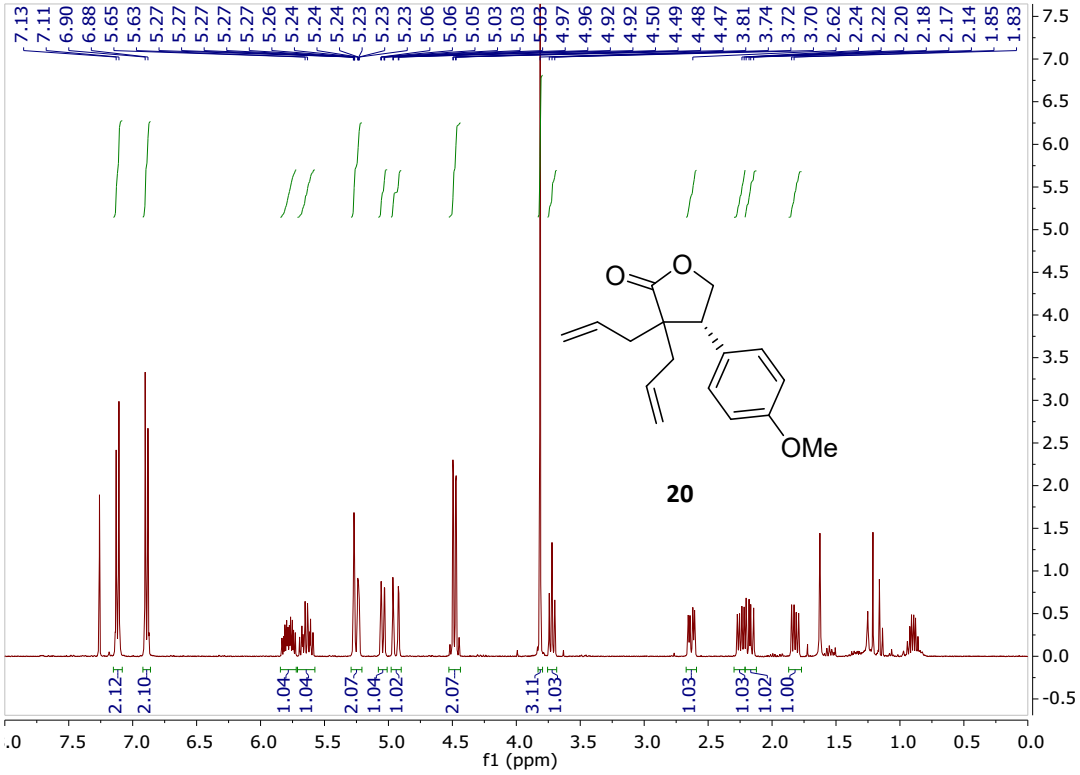
^{1}H NMR ($CDCl_3$, 400 MHz)



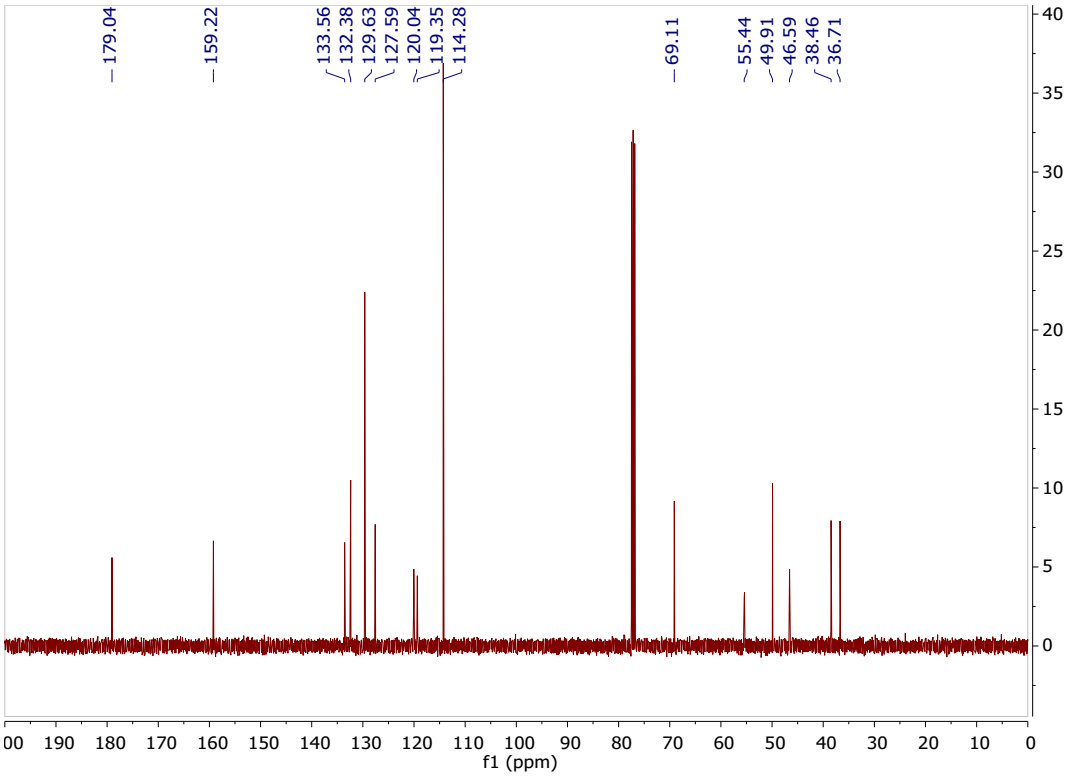
^{13}C NMR ($CDCl_3$, 100 MHz)



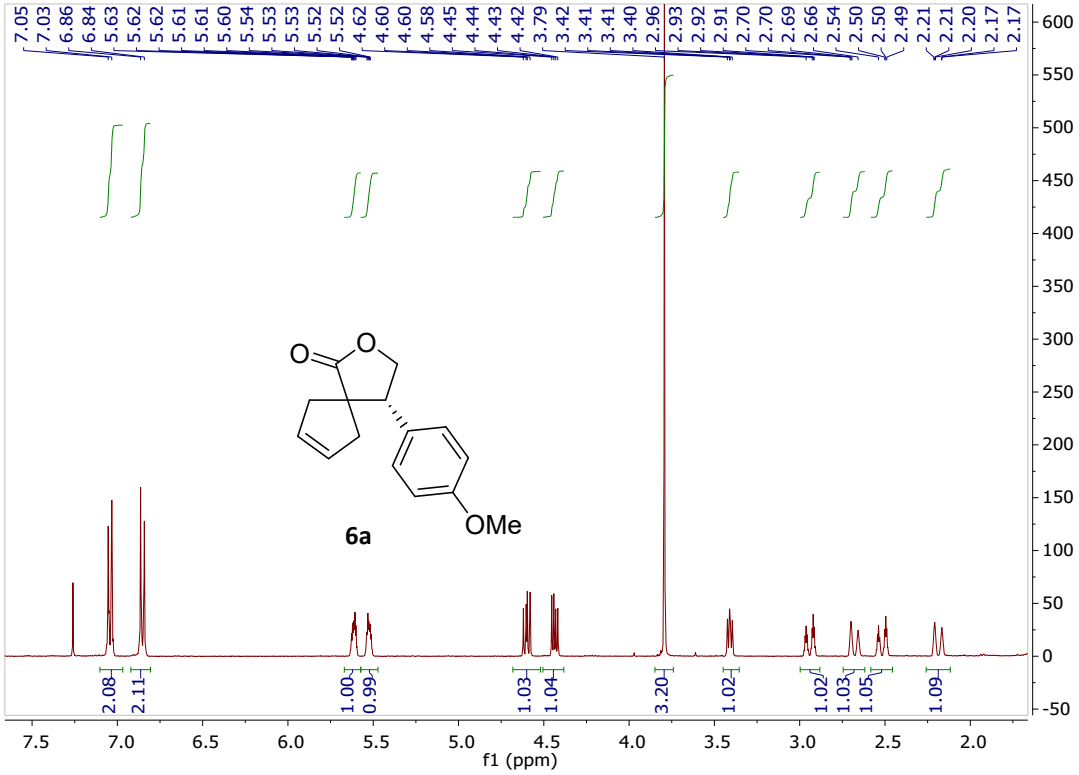
^{1}H NMR ($CDCl_3$, 400 MHz)



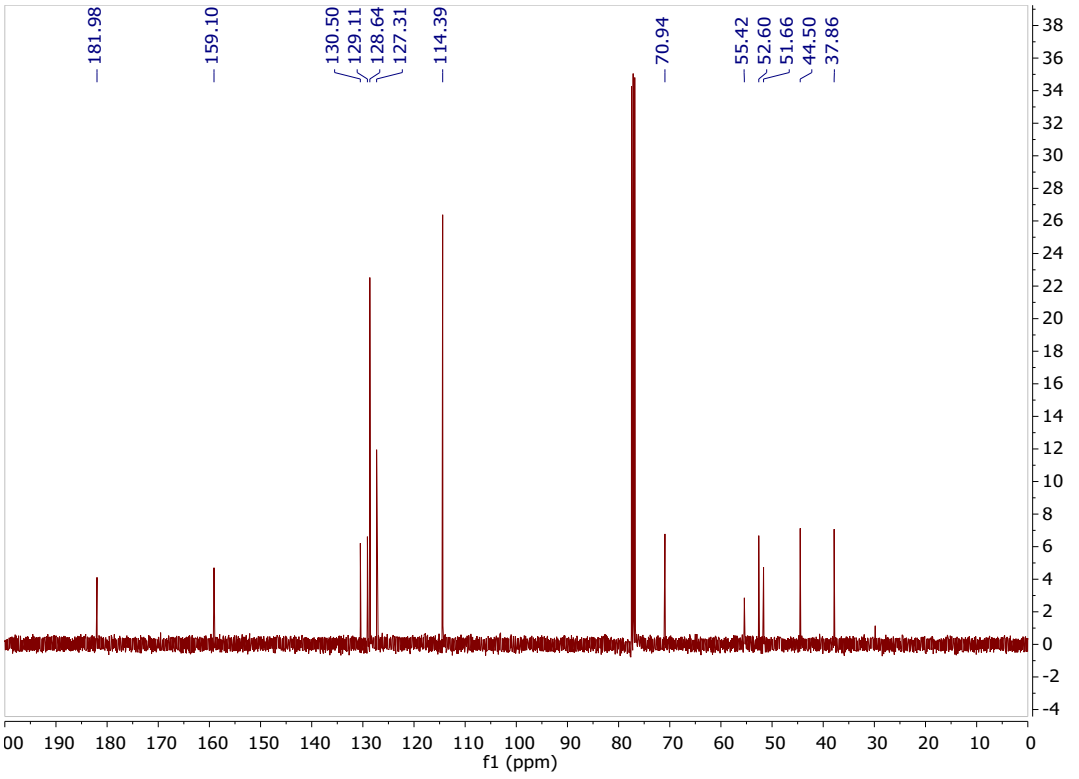
^{13}C NMR ($CDCl_3$, 100 MHz)



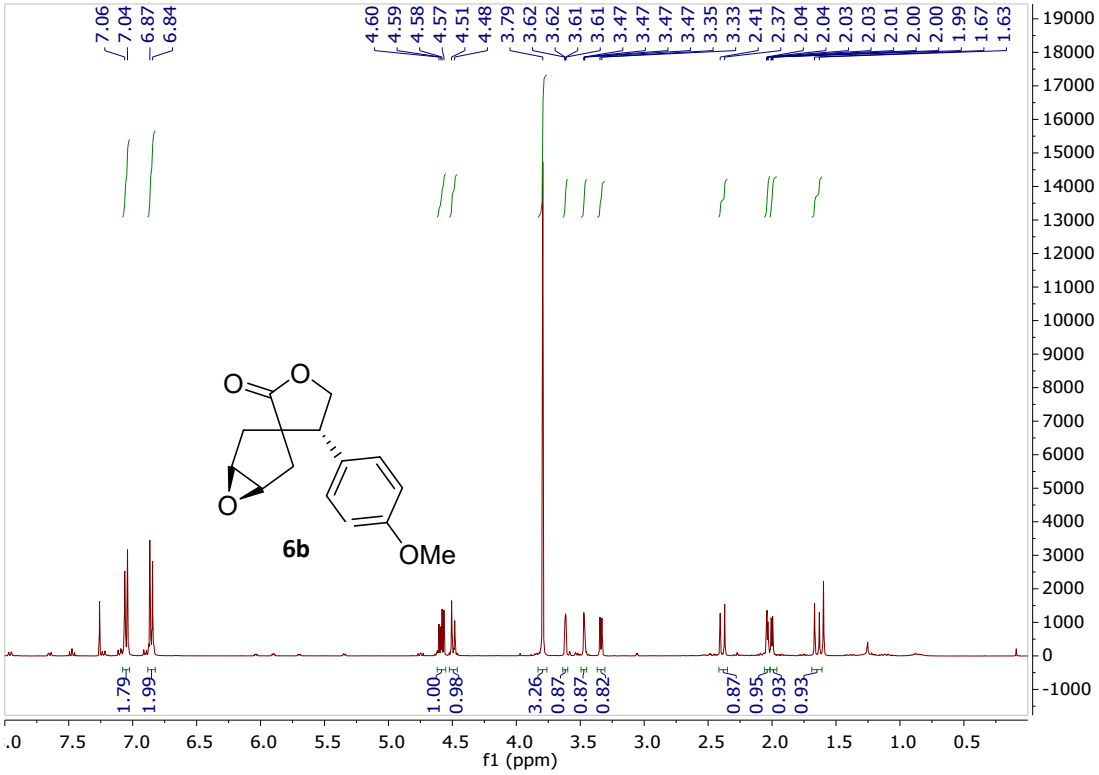
^{1}H NMR ($CDCl_3$, 400 MHz)



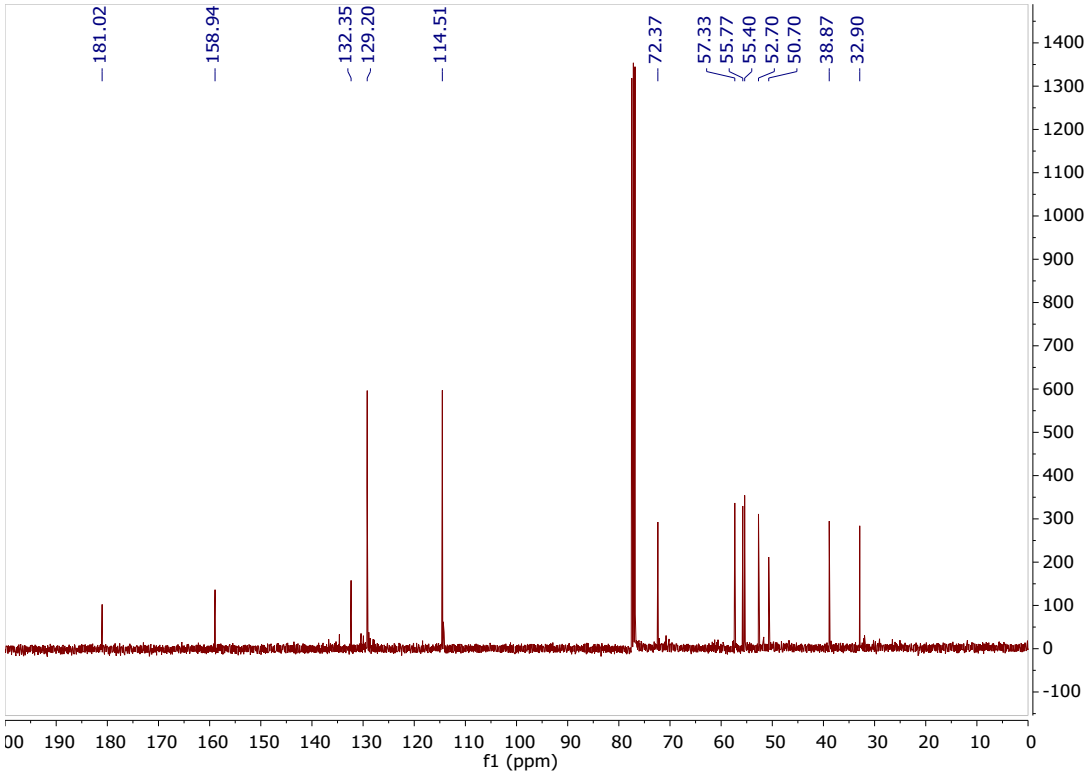
^{13}C NMR ($CDCl_3$, 100 MHz)



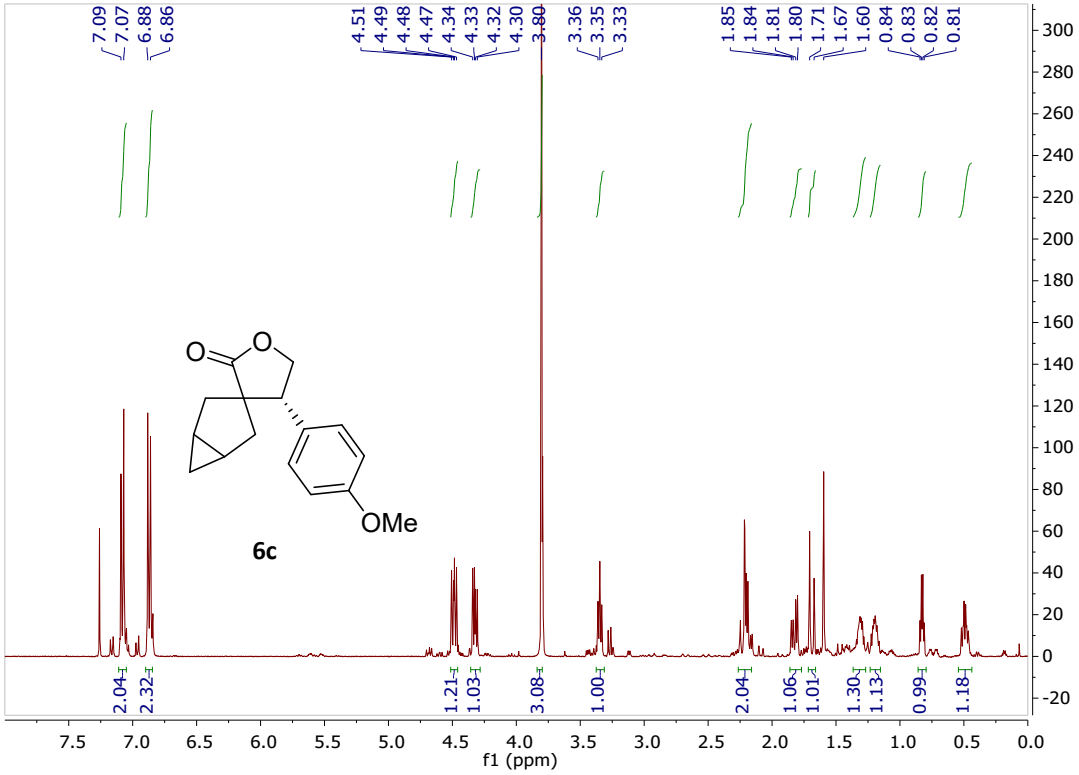
^{1}H NMR ($CDCl_3$, 400 MHz)



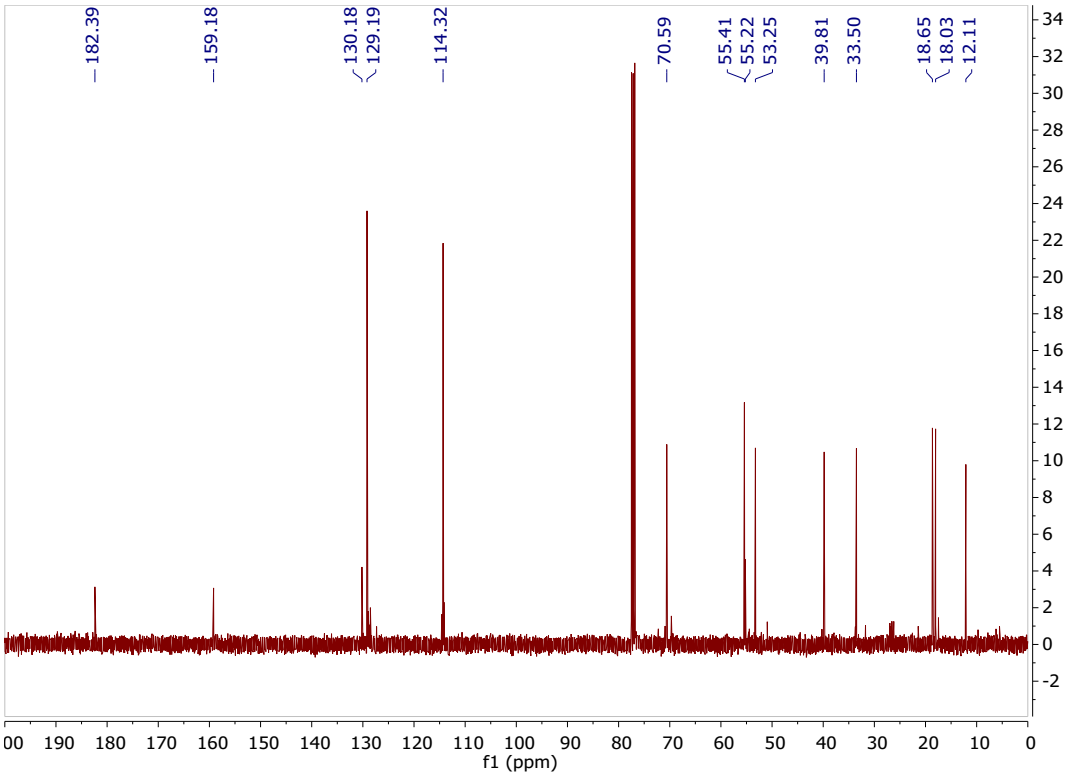
^{13}C NMR ($CDCl_3$, 100 MHz)



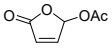
^{1}H NMR ($CDCl_3$, 400 MHz)



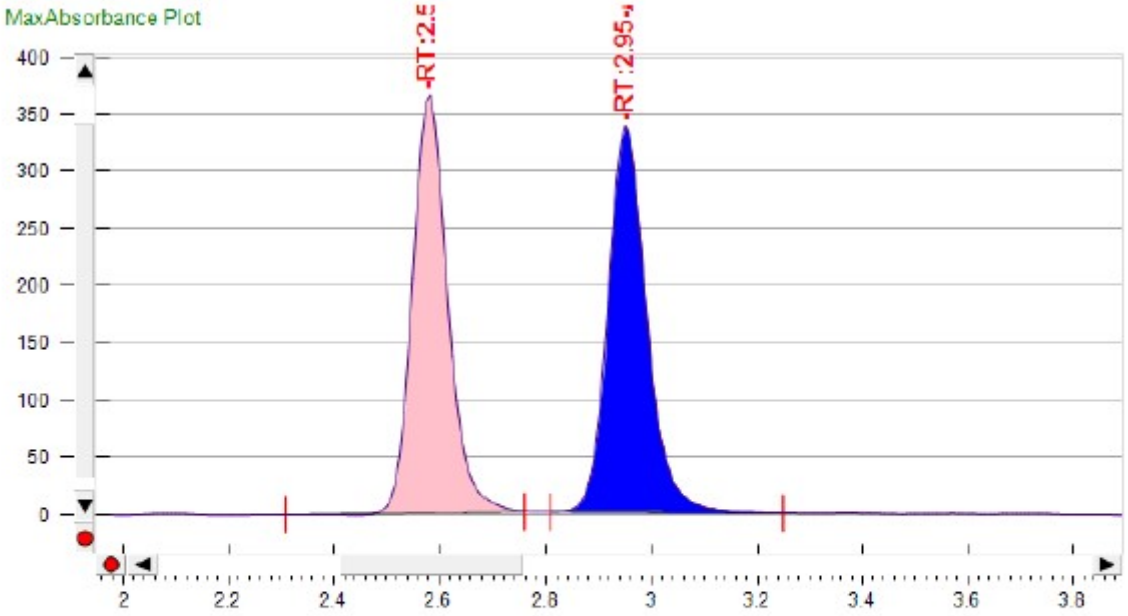
^{13}C NMR ($CDCl_3$, 100 MHz)



SFC-Chromatograms

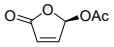


rac-**8**

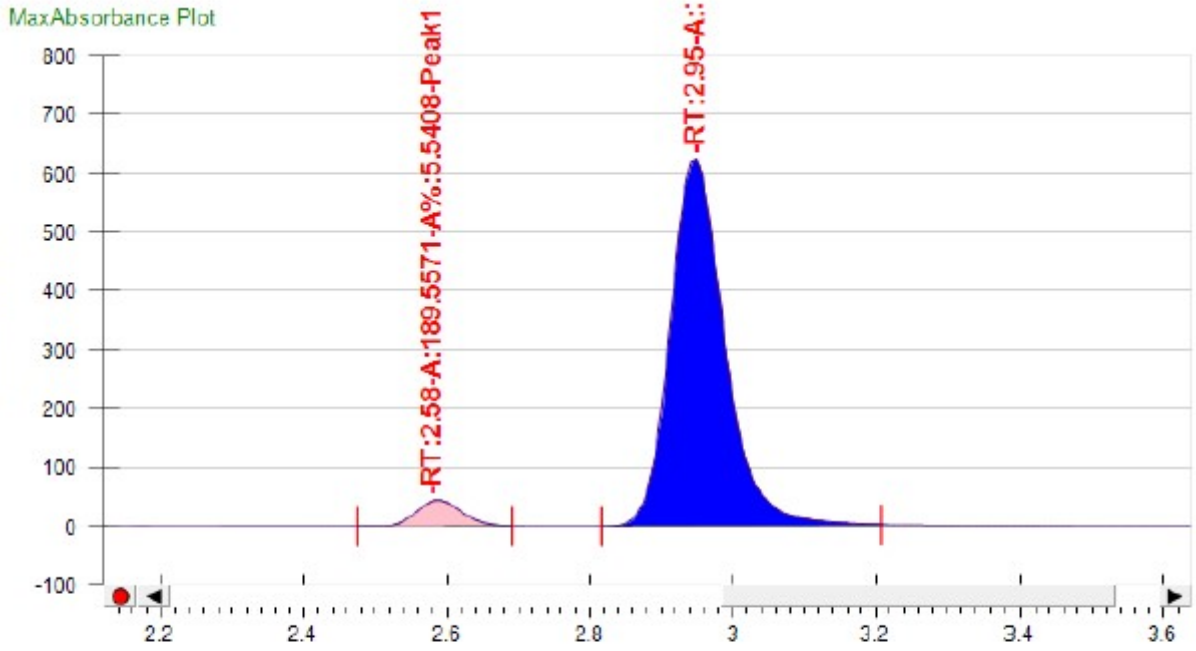


Peak Information

Peak No	% Area	Area	Ret. Time	Height	Cap. Factor
1	49.6843	1667.8689	2.58 min	364.9225	0
2	50.3157	1689.0642	2.95 min	337.5197	0

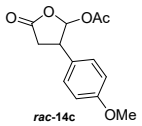


***R*-8**

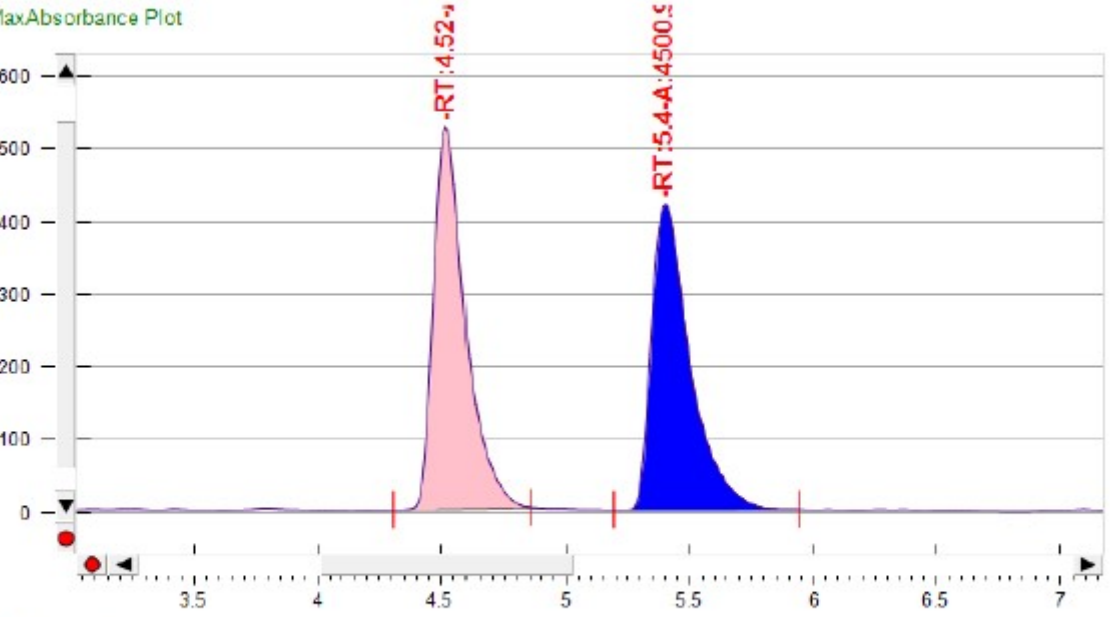


Peak Information

eak No	% Area	Area	Ret. Time	Height	Cap. Factor
	5.5408	189.5571	2.58 min	43.5517	2582.3
	94.4592	3231.5555	2.95 min	623.6076	2948.9667

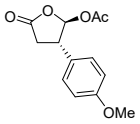


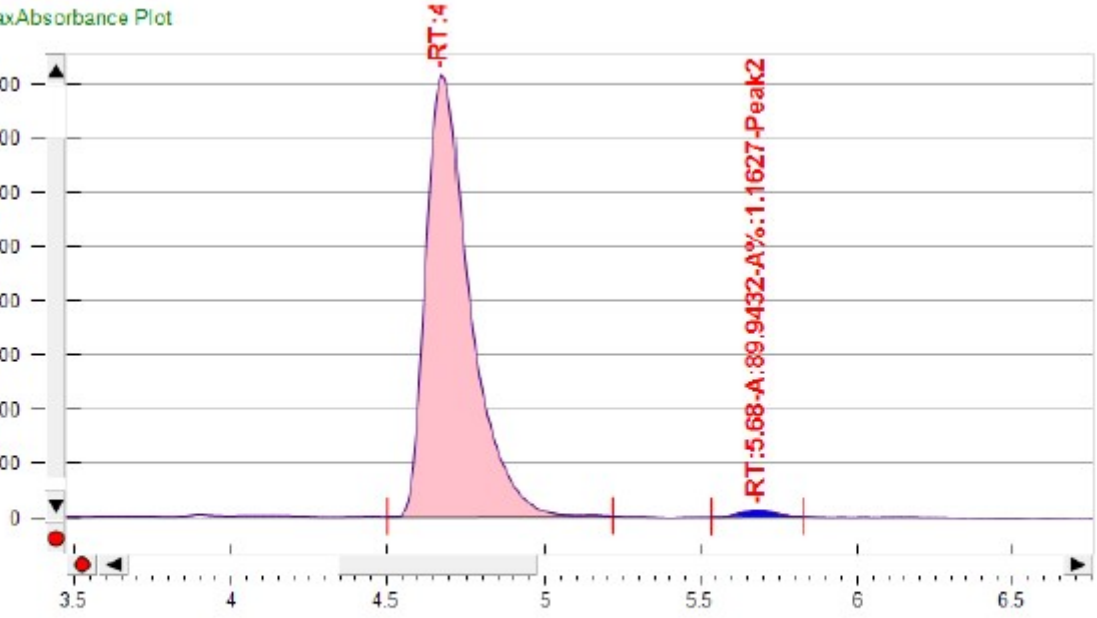
rac-14c



k Information

lo	% Area	Area	Ret. Time	Height	Cap. Factor
	50.1565	4529.2356	4.52 min	525.4369	4515.6
	49.8435	4500.9672	5.4 min	420.3029	5398.9167

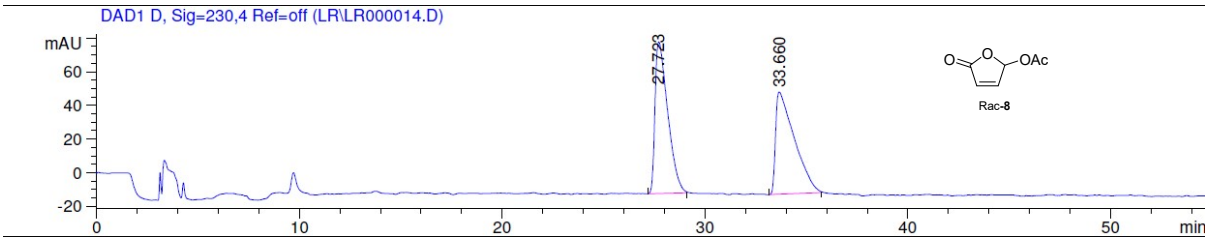




k Information

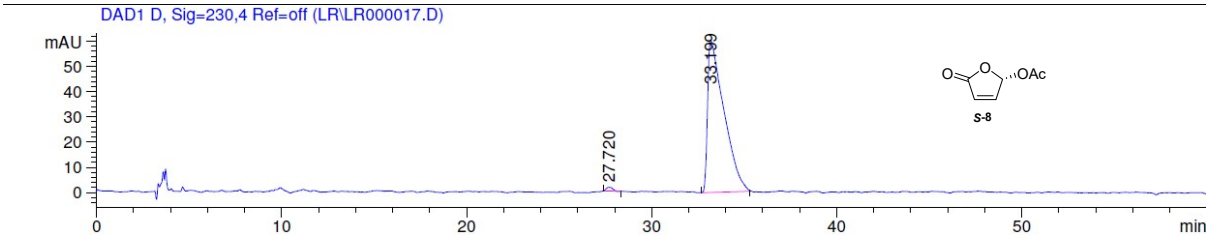
No	% Area	Area	Ret. Time	Height	Cap. Factor
	98.8373	7645.879	4.67 min	814.046	4673.9333
	1.1627	89.9432	5.68 min	12.5979	5682.25

HPLC Chromatograms



Signal 3: DAD1 D, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.723	PB	0.6374	3920.38306	90.13626	50.1001
2	33.660	PB	0.8478	3904.71582	60.75700	49.8999
Totals :				7825.09888	150.89326	



Signal 3: DAD1 D, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.720	BP	0.2879	36.47773	1.50948	0.9764
2	33.199	PB	0.8169	3699.53076	60.03873	99.0236
Totals :				3736.00849	61.54820	