Synthesis of α-alkylated γ-butyrolactones with concomitant anhydride kinetic resolution using a sulfamide-based catalyst

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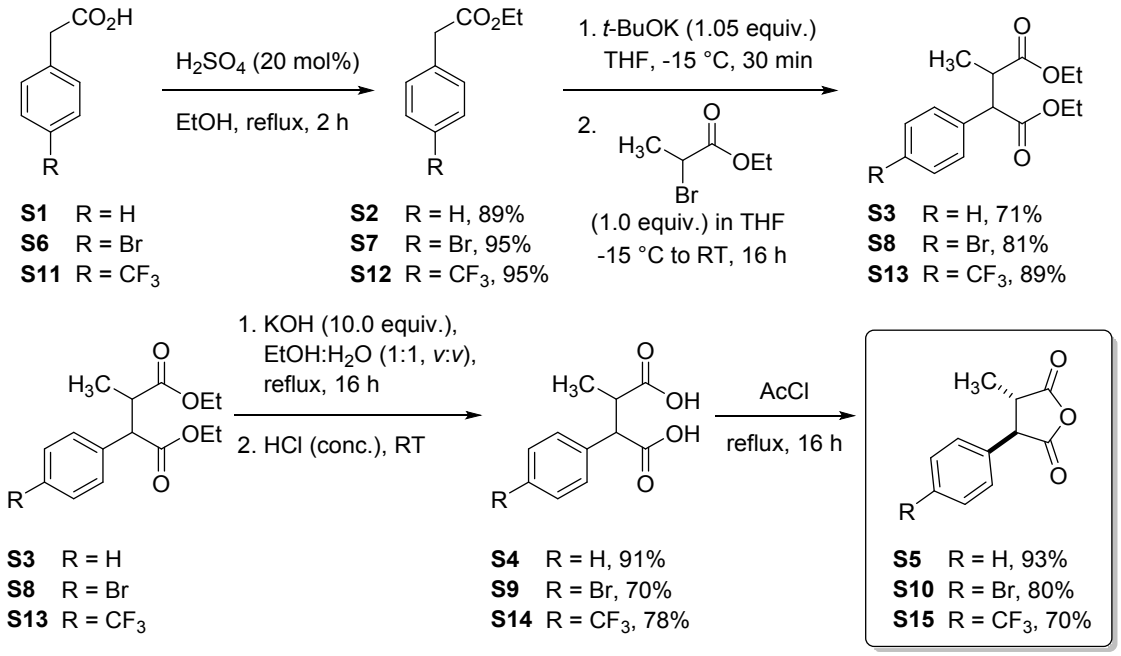
1. General

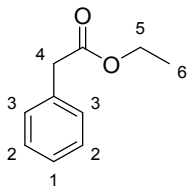
Proton Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker DPX 400 MHz and Bruker Avance II 600MHz spectrometers, using as solvent $CDCl_3$, DMSO-d_6 or D_2O and referenced relative to residual $CHCl_3$ (δ = 7.26 ppm) DMSO (δ = 2.50 ppm) or H_2O (δ = 4.79 ppm). Chemical shifts are reported in ppm and coupling constants (*J*) in Hertz. Carbon NMR spectra were recorded on the same instruments (100.6 MHz and 150.9 MHz respectively) with total proton decoupling. Fluorine NMR spectra were recorded on the Bruker DPX400 machine (376.5 MHz). HSQC, HMBC, TOCSY NOE and ROESY NMR experiments were used to aid assignment of NMR peaks when required. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. ESI mass spectra were acquired using a Waters Micromass LCT- time of flight mass spectrometer (TOF), interfaced to a Waters 2690 HPLC. The instrument was operated in positive or negative mode as required. EI mass spectra were acquired using a GCT Premier Micromass time of flight mass spectrometer (TOF). The instrument was operated in positive mode. Chemical Ionization (CI) mass spectra were determined using a GCT Premier Micromass mass spectrometer in CI mode utilising methane as the ionisation gas. APCI experiments were carried out on a Bruker microTOF-Q III spectrometer interfaced to a Dionex UltiMate 3000 LC or direct insertion probe. The instrument was operated in positive or negative mode as required. Agilent tuning mix APCI-TOF was used to calibrate the system. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated $60F_{254}$ slides, and visualized by UV irradiation and $KMnO_4$ staining. Optical rotation measurements are quoted in units of 10^{-1} deg cm^2 g^{-1}. Toluene was distilled over calcium hydride and stored under argon. Anhydrous acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), tetrahydrofuran (THF) and diethyl ether (Et_2O) were obtained by using Pure Solv MD-4EN Solvent Purification System. Methanol (MeOH) and isopropyl alcohol (*i*-PrOH) were dried over activated 3Å molecular sieves. Commercially available anhydrous *t*-butyl methyl ether (MTBE) was used. Analytical CSP-HPLC was performed on Daicel Chiralpak, AD, AD-H, IA, or Chiralcel OD, OD-H, OJ-H (4.6 mm x 25 cm) columns or ACQUITY UPC2 on chiral Trefoil AMY1, CEL1, CEL2 (2,5 µm, 3.0 x 150mm) columns.

2. Synthesis of anhydrides: procedures



Scheme 1 Synthesis of anhydrides **S5**, **S10** and **S15**.

Ethyl 2-phenylacetate (S2)



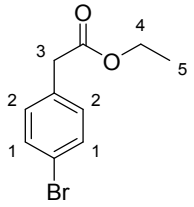
A 250 mL round-bottomed flask containing a stirring bar was charged with phenylacetic acid (**S1**) (10.00 g, 73.45 mmol). EtOH (100 mL) followed by conc. H_2SO_4 (0.8 mL) were added, the flask was fitted with a condenser and the resulting mixture was stirred under reflux for 2 h. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in Et_2O (150 mL), washed with a saturated $NaHCO_3$ solution until basic pH was reached. The mixture was extracted with Et_2O (3 x 100 mL), the combined organic fractions were washed with deionised water, dried over $MgSO_4$ and the solvent was removed *in vacuo* to afford **S2** pure as a colourless liquid (10.80 g, 65.77 mmol, 89%). TLC (hexanes:EtOAc, 4:1 *v*/*v*): R_f = 0.90.

Spectral data for this compound were consistent with those in the literature.[1]

δ_H (400 MHz, $CDCl_3$): 7.36-7.25 (5 H, m, H-1, H-2 and H-3), 4.16 (2 H, q, *J* 7.1, H-5), 3.63 (2 H, s, H-4), 1.27 (3 H, t, *J* 7.1, H-6).

HRMS (*m/z* - APCI): Found: 165.0900 $(M+H)^+$ $C_{10}H_{13}O_2$ Requires: 165.0910.

Ethyl 2-(4-bromophenyl)acetate (S7)



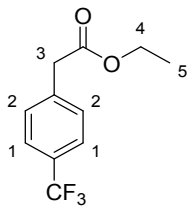
A 250 mL round-bottomed flask containing a stirring bar was charged with 4-bromophenylacetic acid (**S6**, 12.5 g, 58.13 mmol). EtOH (50 mL) followed by conc. H_2SO_4 (0.11 mL) were added, the flask was fitted with a condenser and the resulting mixture was stirred under refluxed overnight. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (150 mL), washed with a saturated $NaHCO_3$ solution until basic pH was reached. The mixture was extracted with CH_2Cl_2 (3 x 100 mL), the combined organic fractions were washed with deionised water, dried over $MgSO_4$ and the solvent was removed *in vacuo* to afford **S7** pure as a white solid (13.41 g, 55.16 mmol, 95%). M.p. 32-34 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): $R_f = 0.44$.

Spectral data for this compound were consistent with those in the literature.[2]

δ_H (400 MHz, $CDCl_3$): 7.43 (2 H, d, *J* 8.4, H-1), 7.15 (2 H, d, J 8.4, H-2), 4.14 (2 H, q, *J* 7.1, H-4), 3.55 (2 H, s, H-3), 1.24 (3 H, t, *J* 7.1, H-5).

HRMS (*m/z* - APCI): Found: 240.9867 $(M-H)^-$ $C_{10}H_{10}BrO_2$ Requires: 240.9869.

Ethyl 2-(4-(trifluoromethyl)phenyl)acetate (S12)



A 250 mL round-bottomed flask containing a stirring bar was charged with 4-trifluoromethylphenylacetic acid (**S11**) (5.0 g, 24.49 mmol). EtOH (50 mL) followed by conc. H_2SO_4 (0.5 mL) were added, the flask was fitted with a condenser and the resulting mixture was stirred under refluxed overnight. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (150 mL), washed with a saturated $NaHCO_3$ solution until basic pH was reached. The mixture was extracted with CH_2Cl_2 (3 x 100 mL), the combined organic fractions were washed with deionised water, dried over $MgSO_4$ and the solvent was removed *in vacuo* to afford **S12** pure as a colourless oil that solidified upon standing at room temperature (5.4 g, 23.26 mmol, 95%). M.p. 34-36 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): $R_f = 0.51$.

Spectral data for this compound were consistent with those in the literature.[3]

δ_H (400 MHz, $CDCl_3$): 7.58 (2 H, d, *J* 8.1, H-1), 7.40 (2 H, d, *J* 8.1, H-2), 4.16 (2 H, q, *J* 7.1, H-4), 3.67 (2 H, s, H-3), 1.26 (3 H, t, *J* 7.1, H-5).

HRMS (*m/z* - APCI): Found: 231.0646 $(M-H)^-$ $C_{11}H_{10}F_3O_2$ Requires: 231.0638.

<u>General procedure I:</u> Synthesis of anhydrides precursors S4, S9 and S14

A 500 mL oven dried round-bottomed flask containing a stirring bar was charged with the relevant ethyl-ester (**S2**, **S7** or **S12**, 1.0 equiv.). The flask was flushed with argon, fitted with a septum and placed under an argon atmosphere. Dry THF was added *via* syringe and the resulting stirring solution was cooled to -15 °C. To the stirred solution, potassium *tert*-butoxide (1.05 equiv.) was added portion wise and the mixture was allowed to stir for 30 min. After 30 min, a cooled solution of ethyl 2-bromopropionate (1.0 equiv.) in dry THF was slowly added *via* syringe over a 10-min period. The reaction mixture was allowed to come back to room temperature and stirred for 16 h. The solvent was then concentrated under reduced pressure, deionised water was added to the residue and the product was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic extracts were washed with deionised water, dried over $MgSO_4$ and the solvent was removed *in vacu*o to afford a mixture of the crude esters **S3**, **S8** or **S13**. The crude products were purified with a plug on silica gel (eluting with 50% of EtOAc in hexanes)

affording almost analytically pure material that was used into the next step without further purification.

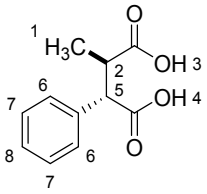
The crude mixture of diastereomers (**S2**, **S7** or **S12**, 1 equiv.) was transferred into a 500 mL round-bottomed flask containing a stirring bar and dissolved in a solution of KOH (10 equiv.) in EtOH:H_2O (50:50 *v*/*v*, 200 mL). The flask was fitted with a condenser and the solution was stirred under reflux for 16 h. The solution was allowed to cool to room temperature, the excess of EtOH was concentrated under reduced pressure and the remaining aqueous solution was washed several times with Et_2O. The organic layer was discarded and the aqueous solution layer was cooled to 0 °C. Acidification with conc. HCl (added dropwise until pH 1 was reached) generally results in the precipitation of the sole, analytically pure, *trans*-isomer. The solid is then filtrated and washed with a little warmed water, transferred to a 250 mL round-bottomed flask followed by an addition of Et_2O (30 mL). The solvent was removed *in vacuo* to help removing residual water to afford the pure *trans*- products. When the product doesn't precipitate as a single diastereomer, the resulting mixture of diacids is dissolved in the minimum amount of a dilute sodium hydroxide solution and the pH of the solution is adjusted to pH 5 with dilute HCl before being stored in a freezer. The monosodium salt of the *trans*- succinic acid generally crystalizes out, the solid is filtered and the free acid is recovered by redisolving the monosodium salt in dilute sodium hydroxide until basic pH is reached followed by acidification with conc. HCl until pH 1 is reached, resulting in the precipitation of the pure *trans*- isomer. The solid is then filtrated and washed with a little warmed water before being dried under high vacuum.

General procedure II: Synthesis of anhydrides S5, S10 and S15

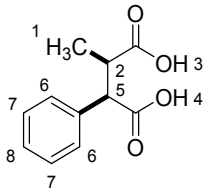
A 25 mL oven dried two-neck round-bottomed flask containing a stirring bar was charged with the appropriate succinic acid derivative **S4**, **S9** or **S14** (1.0 equiv.). The flask was then fitted with a condenser and a septum and flushed with argon. Freshly distilled acetyl chloride (≈ 15 mL/g of product) was added to the flask, the flask was flushed with argon for an additional 2 min and then kept under an argon atmosphere (balloon). The reaction mixture was heated under reflux for 16 h, and then concentrated *in vacuo*. The crude solid was triturated in dry Et_2O (≈ 10 mL/g of product) to get rid of

the remaining acetyl chloride/acetic acid, cooled to 0 °C, filtered and dried under high vacuum to yield **S5**, **S10** or **S15**.

2-Methyl-3-phenylsuccinic acid (S4)



trans-**S4**



cis-**S4**

Prepared according to general procedure I, using potassium *tert*-butoxide (4.45 g, 39.65 mmol), ethyl 2-phenylacetate (6.20 g, 37.76 mmol) in 80 mL of dry THF and ethyl 2-bromopropionate (6.84 g, 37.76 mmol) in 50 mL of dry THF. After hydrolysis of the esters and work up as described in the general procedure I, *trans*-**S4** was obtained as a white solid (5.1 g, 64% over 2 steps, combined yield for both diastereomers). M.p. 174-175 °C (lit, M.p. 192-193 °C).

Spectral data for this compound were consistent with those in the literature.[4]

trans-**S4**:

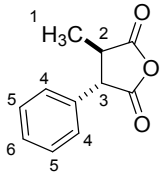
δ_H (400 MHz, DMSO-d_6): 12.3 (2 H, bs, H-3 and H-4), 7.36-7.26 (5 H, m, H-6, H-7 and H-8), 3.59 (1 H, d, *J* 11.2, H-5), 2.95-2.87 (1 H, m, H-2), 0.83 (3 H, d, *J* 7.3, H-1).

δ_C (100 MHz, DMSO-d_6): 177.1 (C=O), 174.6 (C=O), 137.6 (q), 129.1, 128.7, 127.8 (q), 54.2, 42.2, 15.7.

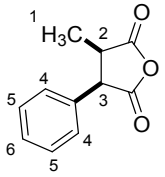
ν_{max} (neat)/cm^{-1}: 2985, 1690, 1421, 1313, 1275, 1253, 1204, 917, 900, 723, 698.

HRMS (*m/z* - ESI): Found: 207.0654 $(M+H)^+$ $C_{11}H_{11}O_4$ Requires: 207.0657.

3-Methyl-4-phenyldihydrofuran-2,5-dione (S5)



trans-**S5**



cis-**S5**

Prepared according to general procedure II, using *trans*-**S4** (0.940 g, 4.51 mmol) and freshly distilled acetyl chloride (≈ 15 mL). After work up as described in general procedure II, *trans*-**S5** was obtained as a white solid (0.804 g, 93%). M.p. 79-81 °C. TLC (hexanes:EtOAc, 4:1 *v/v*): $R_f = 0.42$ (*trans*-**S5**).

trans-**S5:**

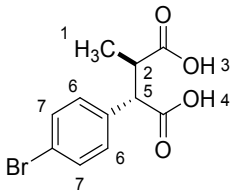
δ_H (600 MHz, $CDCl_3$): 7.60-7.49 (3 H, m, H-5 and H-6), 7.43-7.34 (2 H, m, H-4), 4.02 (1 H, d, *J* 8.4, H-3), 3.38 (1 H, m, H-2), 1.62 (3 H, d, *J* 7.1, H-1).

δ_C (100 MHz, $CDCl_3$): 172.4 (C=O), 170.6 (C=O), 133.7 (q), 129.4, 128.7, 127.7, 54.5, 44.3, 14.3.

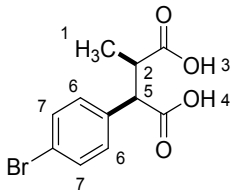
ν_{max} (neat)/cm^{-1}: 2923, 1835, 1772, 1695, 1498, 1455, 1259, 1217, 1102, 983, 924, 763, 739, 699, 589.

HRMS (*m/z* - ESI): Found: 189.0556 $(M-H)^-$ $C_{11}H_9O_3$ Requires: 189.0552.

(4-Bromophenyl)-3-methylsuccinic acid (S9)



trans-**S9**



cis-**S9**

Prepared according to general procedure I, using potassium *tert*-butoxide (1.05 g, 9.37 mmol – 1.1 equiv.), ethyl 2-(4-bromophenyl)acetate (2.09 g, 8.52 mmol) in 20 mL of dry THF and ethyl 2-bromopropionate (1.1 mL, 8.52 mmol) in 10 mL of dry THF. After

hydrolysis of the esters and work up as described in the general procedure I, *trans*-**S9** was obtained as a white solid (1.4 g, 57% over 2 steps). M.p. 175-178 °C.

trans-**S9:**

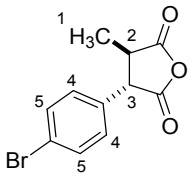
δ_H (400 MHz, DMSO-d_6): 12.37 (2 H, bs, H-3 and H-4), 7.54 (2 H, *J* 8.4, H-7), 7.25 (2 H, *J* 8.4, H-6), 3.62 (1 H, d, *J* 11.1, H-5), 2.93-2.85 (1 H, m, H-2), 0.83 (3 H, d, *J* 7.3, H-1).

δ_C (100 MHz, DMSO-d_6): 176.8 (C=O), 174.2 (C=O), 137.1 (q), 132.0, 131.0, 121.0 (q), 53.5, 42.0, 15.6.

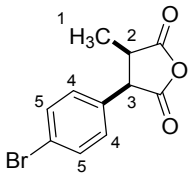
ν_{max} (neat)/cm^{-1}: 2982, 2601, 1694, 1489, 1458, 1408, 1280, 1198, 1074, 1012, 918, 809, 750, 646, 582.

HRMS (*m/z* - APCI): Found: 284.9765 $(M-H)^-$ $C_{11}H_{10}BrO_4$ Requires: 284.9767.

(4-Bromophenyl)-4-methyldihydrofuran-2,5-dione (S10)



trans-**S10**



cis-**S10**

Prepared according to general procedure II, using *trans*-**S9** (500 mg, 1.74 mmol) and freshly distilled acetyl chloride (≈ 10 mL). After work up as described in general procedure II, *trans*-**S10** was obtained as a white solid (372 mg, 80%). M.p. 116-118 °C.

trans-**S10:**

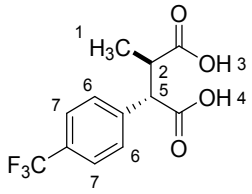
δ_H (400 MHz, $CDCl_3$): 7.56 (2 H, d, *J* 8.4, H-5), 7.14 (2 H, d, *J* 8.4, H-4), 3.86 (1 H, d, *J* 9.1, H-3), 3.24-3.16 (1 H, m, H-2), 1.49 (3 H, d, *J* 7.1, H-1).

δ_C (100 MHz, $CDCl_3$): 171.9 (C=O), 170.0 (C=O), 132.6, 132.4 (q), 129.4, 123.0 (q), 54.0, 44.1, 14.3.

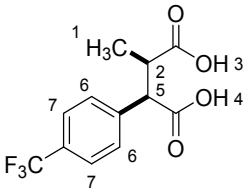
ν_{max} (neat)/cm^{-1}: 2988, 2942, 2894, 1867, 1768, 1493, 1448, 1409, 1382, 1260, 1217, 1112, 1076, 1014, 978, 907, 851, 835, 804, 741, 702, 626.

HRMS (*m/z* - APCI): Found: 266.9649 $(M-H)^-$ $C_{11}H_8BrO_3$ Requires: 266.9662.

2-Methyl-3-(4-(trifluoromethyl)phenyl)succinic acid (S14)



trans-**S14**



cis-**S14**

Prepared according to general procedure I, using potassium *tert*-butoxide (0.761 g, 6.68 mmol), ethyl 2-(4-(trifluoromethyl)phenyl)acetate (1.5 g, 6.46 mmol) in 40 mL of dry THF and ethyl 2-bromopropionate (1.17 g, 6.46 mmol) in 20 mL of dry THF. After hydrolysis of the esters and work up as described in the general procedure I, *trans*-**S14** was obtained as a white solid (1.26 g, 69% over 2 steps). M.p. 160-162 °C.

trans-**S14:**

δ_H (400 MHz, DMSO-d_6): 12.47 (2 H, bs, H-3 and H-4), 7.70 (2 H, *J* 8.2, H-7), 7.53 (2 H, *J* 8.2, H-6), 3.77 (1 H, d, *J* 11.1, H-5), 3.01-2.93 (1 H, m, H-2), 0.84 (3 H, d, *J* 7.3, H-1).

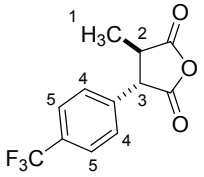
δ_C (100 MHz, DMSO-d_6): 176.8 (C=O), 174.0 (C=O), 142.4 (q), 129.7, 128.5 (q) (q, ^2J 31.8 Hz), 125.9 (q, ^3J 3.5 Hz), 124.6 (q) (q, ^1J 272.0 Hz), 54.0, 42.0, 15.5.

δ_F (376.5 MHz, DMSO-d_6): - 61.07.

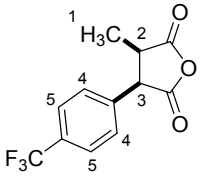
ν_{max} (neat)/cm^{-1}: 3245, 2994, 2575, 1747, 1672, 1461, 1421, 1324, 1202, 1173, 1161, 1128, 1107, 1067, 1020, 915, 833, 724, 676.

HRMS (*m/z* - APCI): Found: 275.0525 $(M-H)^-$ $C_{12}H_{10}F_3O_4$ Requires: 275.0536.

3-Methyl-4-(4-(trifluoromethyl)phenyl)dihydrofuran-2,5-dione (S15)



trans-**S15**



cis-**S15**

Prepared according to general procedure II, using *trans*-**S14** (650 mg, 2.35 mmol) and freshly distilled acetyl chloride (≈ 10 mL). After work up as described in general procedure II, *trans*-**S15** was obtained as a white solid (421.6 mg, 70%). TLC (hexanes:EtOAc, 1:1 *v/v*): $R_f = 0.79$ (*trans*-**S15**). M.p. 80-82 °C.

trans-**S15:**

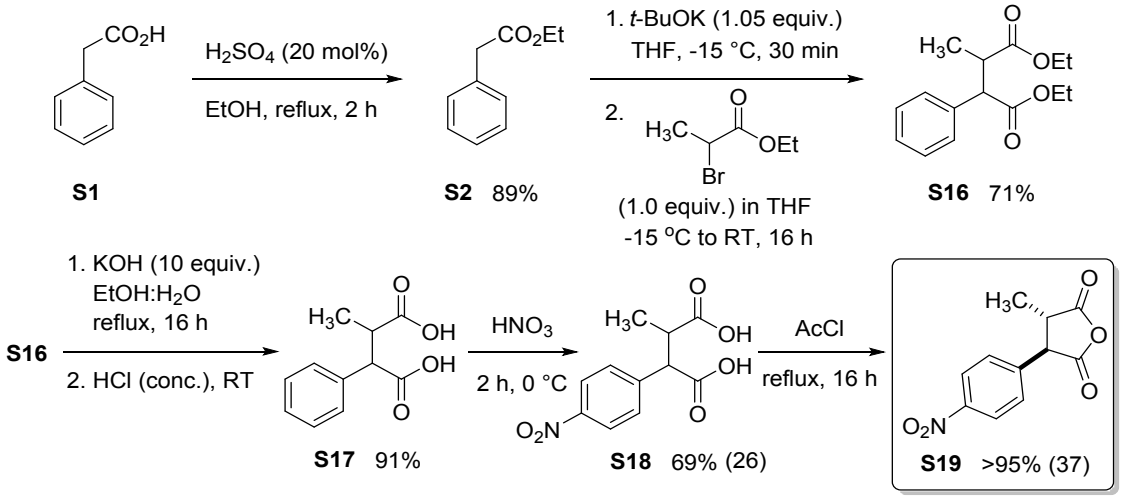
δ_H (400 MHz, $CDCl_3$): 7.70 (2 H, *J* 8.1, H-5), 7.40 (2 H, *J* 8.1, H-4), 3.96 (1 H, d, *J* 9.2, H-3), 3.29-3.22 (1 H, dq, *J* 7.1, *J* 9.2, H-2), 1.52 (3 H, d, *J* 7.1, H-1).

δ_C (100 MHz, $CDCl_3$): 171.7 (C=O), 169.8 (C=O), 137.4 (q), 131.2 (q) (q, ^2J 32.7 Hz), 128.4, 126.5 (q, ^3J 3.7 Hz), 123.7 (q) (q, ^1J 272.3 Hz), 54.2, 44.1, 14.3.

δ_F (376.5 MHz, $CDCl_3$): - 62.89.

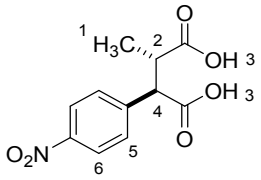
ν_{max} (neat)/cm^{-1}: 2942, 1871, 1846, 1773, 1422, 1324, 1264, 1227, 1166, 1111, 1067, 985, 926, 839, 751, 726, 628.

HRMS (*m/z* - APCI): Found: 257.0422 $(M-H)^-$ $C_{12}H_8F_3O_3$ Requires: 257.0431.



Scheme 2 Synthesis of anhydride **S19**.

2-Methyl-3-(4-nitrophenyl)succinic acid (S18)



A 25 mL oven-dried round-bottomed flask fitted with a thermometer and containing a magnetic stirring bar was charged with fuming nitric acid (≈ 4 mL) and cooled to 0 °C. 2-methyl-3-phenylsuccinic acid (**S17**, 1.0 g, 4.8 mmol) was added portion wise while keeping the temperature < 20 °C. The solution was allowed to stir for 2 h, at 0 °C, then crushed ice (≈ 10 g) and water (≈ 5 mL) were added to the reaction mixture. A pale yellow solid precipitate formed. The solid was filtered and washed with cold water. The crude product was obtained as a mixture of diastereomers in a 45:55 ratio (*cis*:*trans*) (0.840 g, 69%). The crude product was recrystallised from boiling water to obtain *trans*-**S18** as a white solid (320 mg, 26%). M.p. >200 °C (decomposition).

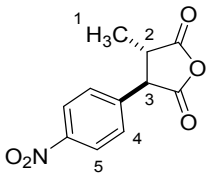
δ_H (400 MHz, DMSO-d_6): 12.34 (2 H, bs, H-3), 8.18 (2 H, *J* 8.8, H-6), 7.59 (2 H, *J* 8.8, H-5), 3.83 (1 H, d, *J* 10.2, H-4), 3.11-3.03 (1 H, dq, *J* 6.7, *J* 10.2, H-2), 1.21 (3 H, d, *J* 6.7, H-1).

δ_C (100 MHz, DMSO-d_6): 175.2 (C=O), 172.8 (C=O), 147.2 (q), 145.8 (q), 130.2, 123.9, 54.6, 43.1, 16.5.

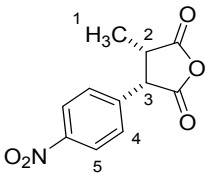
ν_{max} (neat)/cm^{-1}: 2920, 2916, 1696, 1599, 1519, 1423, 1351, 1296, 1196, 913, 836, 733, 697, 650.

HRMS (*m/z* - APCI): Found: 252.0505 $(M-H)^-$ $C_{11}H_{10}NO_6$ Requires: 252.0513.

3-Methyl-4-(4-nitrophenyl)dihydrofuran-2,5-dione (S19)



trans-**S19**



cis-**S19**

Prepared according to general procedure II, using **S18** (273.0 mg, 1.08 mmol) and freshly distilled acetyl chloride (≈ 5 mL). After work up as described in general procedure II, **S19** was obtained as a brown crude residue (241.3 mg – 95% (crude)). The residue was stirred in boiling Et_2O (4 mL) and the resulting solution was separated from the insoluble remaining residue. The organic solvent was transferred to a small vial and stored in a freezer. After overnight, a yellow solid had formed. The solid was filtered and dried under high vacuum to yield **S19** as a mixture of diastereomers in the ratio 83:17 (*trans*:*cis*) (93.6 mg, 37%). TLC (hexanes:EtOAc, 1:1 *v/v*): R_f = 0.68 (**S19**). M.p.* 88-90 °C.

trans-**S19:**

δ_H (400 MHz, $CDCl_3$): 8.28 (2 H, *J* 8.4, H-5), 7.37 (2 H, *J* 8.4, H-4), 4.59 (1 H, *J* 10.0, H-3), 3.61-3.52 (1 H, *J* 7.7, *J* 10.0, H-2), 1.02 (3 H, *J* 7.7, H-1).

δ_C (100 MHz, $CDCl_3$): 172.4 (C=O), 170.0 (C=O), 138.8 (q), 147.9 (q), 138.8 (q), 129.9, 124.4, 50.8, 40.3, 12.6.

cis-**S19:**

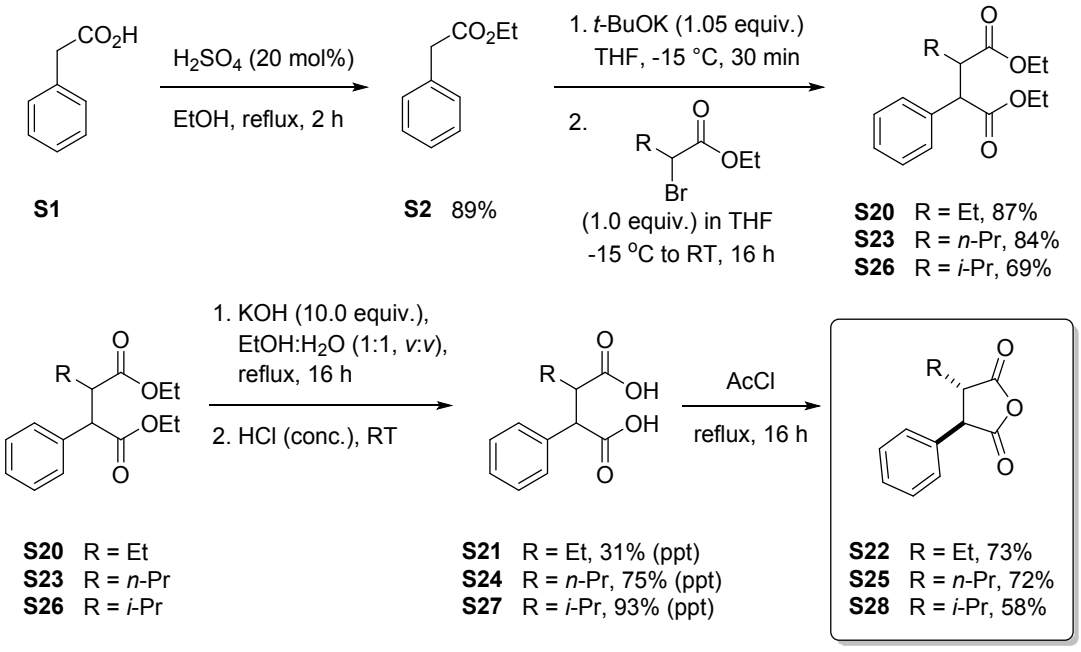
δ_H (400 MHz, $CDCl_3$): 8.30 (2 H, *J* 8.5, H-5), 7.48 (2 H, *J* 8.5, H-4), 4.05 (1 H, *J* 9.3, H-3), 3.33-3.25 (1 H, *J* 7.1, *J* 9.3, H-2), 1.54 (3 H, *J* 7.1, H-1).

δ_C (100 MHz, $CDCl_3$): 171.2 (C=O), 169.3 (C=O), 142.5 (q), 140.3 (q), 128.9, 124.6, 54.0, 44.0, 14.3.

ν_{max} (neat)/cm^{-1}:* 2894, 1859, 1779, 1602, 1521, 1456, 1348, 1219, 1093, 981, 917, 853, 832, 698.

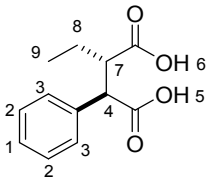
HRMS (*m/z* - APCI):* Found: 234.0419 $(M-H)^-$ $C_{11}H_8NO_5$ Requires: 234.0407.

* Refers to mixture of *trans*-**S19**:*cis*-**S19** in the ratio 83:17.

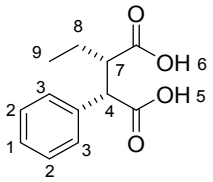


Scheme 3 Synthesis of anhydrides **S22**, **S25** and **S28**.

2-ethyl-3-phenylsuccinic acid (S21)



trans-**S21**



cis-**S21**

Prepared according to general procedure I, using potassium *tert*-butoxide (3.02 g, 26.92 mmol), ethyl 2-bromobutyrate (5.0 g, 25.63 mmol) in 100 mL of dry THF and ethyl 2-bromopropionate (4.21 g, 25.63 mmol) in 50 mL of dry THF. After hydrolysis of the esters and work up as described in the general procedure I, **S21** was obtained as a mixture of diastereomers in a 45:55 (*cis*:*trans*) ratio as a white solid (1.54 g, 27%, over 2 steps). M.p. >200 °C.*

trans-**S21:**

δ_H (400 MHz, DMSO-d_6): 12.32 (2 H, bs, H-5 and H-6), 7.36-7.22 (5 H, m, H-1, H-2 and H-3), 3.68 (1 H, d, *J* 11.6, H-4), 2.92-2.86 (1 H, m, H-7), 1.67-1.52 (2 H, m, H-8), 0.72 (3 H, t, *J* 7.5, H-9).

cis-**S21:**

δ_H (400 MHz, DMSO-d_6): 12.32 (2 H, bs, H-5 and H-6), 7.36-7.22 (5 H, m, H-1, H-2 and H-3), 3.58 (1 H, d, *J* 11.4, H-4), 2.92-2.86 (1 H, m, H-7), 1.37-1.28 (1 H, m, H-8), 1.16-1.08 (1 H, m, H-8), 0.90 (3 H, t, *J* 7.4, H-9).

cis-**S21** + *trans*-**S21:**

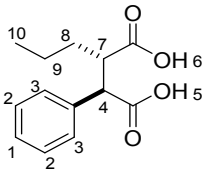
δ_C (100 MHz, DMSO-d_6):* 176.0 (C=O), 174.60 (C=O), 174.58 (C=O), 173.8 (C=O), 137.9 (q), 137.6 (q), 129.8, 129.1, 128.75, 128.7, 127.83, 127.77, 54.3, 52.3, 50.7, 48.4, 24.8, 22.2, 12.0, 10.6.

ν_{max} (neat)/cm^{-1}:* 2969, 1688, 1499, 1456, 1405, 1278, 1195, 934, 695, 633.

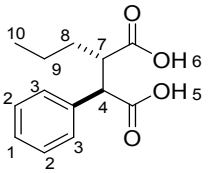
HRMS (*m/z* - ESI):* Found: 221.0810 $(M-H)^-$ $C_{12}H_{13}O_4$ Requires: 221.0819.

* Refers to mixture of *trans*-**S21**:*cis*-**S21** in the ratio 55:45.

2-Phenyl-3-propylsuccinic acid (S24)



trans-**S24**



cis-**S24**

Prepared according to general procedure I, using potassium *tert*-butoxide (2.22 g, 19.74 mmol), ethyl 2-phenylacetate (3.09 g, 18.80 mmol) in 80 mL of dry THF and ethyl 2-bromovalerate (3.93 g, 18.80 mmol) in 50 mL of dry THF. After hydrolysis of the esters and work up as described in the general procedure I, **S24** was obtained as a white solid as a mixture of diastereomers in the ratio 43:57 (*cis*:*trans*) (3.2 g, 63%, over 2 steps, combined yield for both diastereomers). M.p. 184-188 °C.

cis-**S24** + *trans*-**S24:**

δ_H (400 MHz, DMSO-d_6):* 12.31 (2 H, bs, H-5 and H-6), 7.37-7.23 (5 H, m, H-1, H-2 and H-3), 3.66 (1 H, d, *J* 11.6, H-4$_{(trans)}$), 3.57 (1 H, d, *J* 11.1, H-4$_{(cis)}$), 3.00-2.88 (1 H, m, H-7$_{(cis+trans)}$), 1.62-1.47 (1 H, m, H-8$_{(trans)}$), 1.62-1.47 (1 H, m, H-8$_{(cis)}$), 1.37-1.22 (1 H, m, H-8$_{(trans)}$), 1.20-1.04 (1 H, m, H-9$_{(cis+trans)}$), 0.89 (3 H, t, *J* 7.3, H-10$_{(cis)}$), 0.68 (3 H, t, *J* 7.0, H-10$_{(trans)}$).

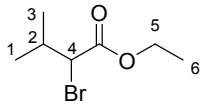
δ_C (100 MHz, DMSO-d_6):* 176.3 (C=O), 174.8 (C=O), 174.5 (C=O), 173.8 (C=O), 137.8 (q), 137.7 (q), 129.8, 129.1, 128.8, 128.75, 127.85, 127.78, 54.6, 53.0, 49.0, 47.3, 33.9, 31.7, 20.6, 19.4, 14.3, 14.2.

ν_{max} (neat)/cm^{-1}:* 2961, 1690, 1411, 1280, 1198, 934, 725, 697.

HRMS (*m/z* - ESI):* Found: 259.0950 $(M+Na)^+$ $C_{13}H_{16}NaO_4$ Requires: 259.0940.

* Refers to mixture of *trans*-**S24**:*cis*-**S24** in the ratio 57:43.

Ethyl 2-bromo-3-methylbutanoate (S29)



A 250 mL round-bottomed flask containing a stirring bar was charged with commercially available 2-bromo-3-methylbutyric acid (10.0 g, 55.24 mmol). MeOH (100 mL) followed by conc. H_2SO_4 (0.8 mL) were added, the flask was fitted with a condenser and the resulting mixture was stirred under reflux for 16 h. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL), washed with a saturated $NaHCO_3$ solution until basic pH was reached. The mixture was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic fractions were washed with deionised water, dried over $MgSO_4$ and the solvent was removed *in vacuo* to afford **S29** pure as a colourless liquid (10.6 g, 50.7 mmol, 92%). TLC (hexanes:EtOAc, 9:1 *v*/*v*): $R_f = 0.76$.

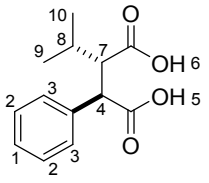
Spectral data for this compound were consistent with those in the literature.[5]

δ_H (400 MHz, $CDCl_3$): 4.23 (2 H, q, *J* 7.1, H-5), 4.03 (1 H, d, *J* 7.9, H-4), 2.27-2.19 (1 H, m, H-2), 1.29 (3 H, t, *J* 7.1, H-6), 1.09 (3 H, s, *J* 6.6, H-3), 1.03 (3 H, d, *J* 6.7, H-1).

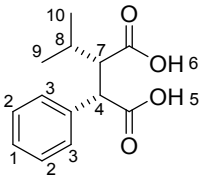
δ_C (100 MHz, $CDCl_3$): 169.5 (C=O), 61.8, 54.7, 32.3, 19.98, 19.89, 14.0.

HRMS (*m/z* - APCI): Found: 209.0171 $(M+H)^+$ $C7H17BrO_2$ Requires: 209.0172.

2-Isopropyl-3-phenylsuccinic acid (S27)



trans-**S27**



cis-**S27**

Prepared according to general procedure I, using potassium *tert*-butoxide (2.15 g, 19.18 mmol), ethyl 2-bromo-3-methylbutyrate (3.82 g, 18.27 mmol) in 80 mL of dry THF and ethyl 2-bromopropionate (3.0 g, 18.27 mmol) in 20 mL of dry THF. After hydrolysis of the esters and work up as described in the general procedure I, **S27** was obtained as a

mixture of diastereomers in a 22:78 (*cis*:*trans*) ratio as a white solid (0.750 g, 64%, over 2 steps, combined yield for both diastereomers). M.p. >200 °C.

trans-**S27:**

δ_H (400 MHz, DMSO-d_6): 12.24 (2 H, bs, H-5 and H-6), 7.36-7.22 (5 H, m, H-1, H-2 and H-3), 3.76 (1 H, d, *J* 11.8, H-4), 2.90 (1 H, dd, *J* 2.8, 11.8, H-7), 1.40-1.33 (1 H, m, H-8), 0.88 (3 H, d, *J* 6.9, H-9), 0.73 (3 H, d, *J* 6.8, H-10).

cis-**S27:**

δ_H (400 MHz, DMSO-d_6): 12.24 (2 H, bs, H-5 and H-6), 7.36-7.22 (5 H, m, H-1, H-2 and H-3), 3.74 (1 H, d, *J* 11.3, H-4), 3.02 (1 H, dd, *J* 4.3, 11.3, H-7), 2.01-1.93 (1 H, m, H-8), 0.99 (3 H, d, *J* 6.9, H-9), 0.96 (3 H, d, *J* 6.8, H-10).

trans-**S27:**

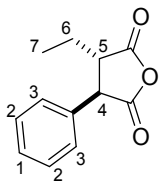
δ_C (100 MHz, DMSO-d_6):* 174.70 (C=O), 174.67 (C=O), 137.8 (q), 129.2, 128.7, 127.8, 53.0, 51.7, 26.5, 22.4, 17.2.

ν_{max} (neat)/cm^{-1}:* 3216, 1699, 1418, 1070, 944, 796, 725, 698.

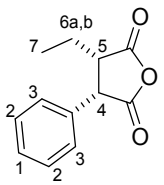
HRMS (*m/z* - ESI):* Found: 235.0967 $(M-H)^-$ $C_{13}H_{15}O_4$ Requires: 235.0975.

* Refers to mixture of *trans*-**S27**:*cis*-**S27** in the ratio 78:22.

2-Ethyl-3-phenylsuccinic acid anhydride (S22)



trans-**S22**



cis-**S22**

Prepared according to general procedure II, using **S21** (1.7 g, 7.64 mmol) and freshly distilled acetyl chloride (≈ 20 mL). After work up as described in general procedure II, **S22** was obtained as a brown liquid. The residue was filtered through a small pad of

silica eluting with 100% EtOAc. After evaporation of the solvent the product was dried under high *vacuum* to yield **S22** as a mixture of pure diastereomers in the ratio 52:48 (*trans*:*cis*) (1.14 g, 73%).

trans-**S22**:

δ_H (400 MHz, $CDCl_3$): 7.43-7.15 (5 H, m, H-1, H-2 and H-3), 4.00 (1 H, d, *J* 7.7, H-4), 3.24-3.19 (1 H, m, H-5), 2.04-1.89 (2 H, m, H-6), 1.09 (3 H, t, *J* 7.3, H-7).

δ_C (100 MHz, $CDCl_3$): 172.7 (C=O), 172.0 (C=O), 134.6 (q), 129.5, 128.7, 127.7, 52.1, 50.3, 20.3, 10.8.

cis-**S22**:

δ_H (400 MHz, $CDCl_3$): 7.43-7.15 (5 H, m, H-1, H-2 and H-3), 4.43 (1 H, d, *J* 9.5, H-4), 3.28-3.23 (1 H, m, H-5), 1.72-1.60 (1 H, m, H-6a), 1.37-1.26 (1 H, m, H-6b), 0.91 (3 H, t, *J* 7.5, H-7).

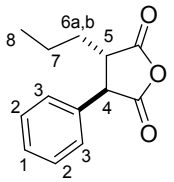
δ_C (100 MHz, $CDCl_3$): 171.04 (C=O), 171.01 (C=O), 131.6 (q), 129.2, 128.70, 128.66, 50.9, 47.3, 23.2, 11.7.

ν_{max} (neat)/cm^{-1}:* 2972, 2939, 1863, 1775, 1496, 1455, 1208, 1107, 1080, 1208, 1034, 1017, 914, 763, 698, 735.

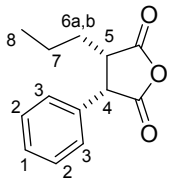
HRMS (*m/z* - APCI):* Found: 203.0707 $(M-H)^-$ $C_{12}H_{11}O_3$ Requires: 203.0713.

* Refers to mixture of *trans*-**S22**:*cis*-**S22** in the ratio 52:48.

2-Phenyl-3-propylsuccinic acid anhydride (S25)



trans-**S25**



cis-**S25**

Prepared according to general procedure II, using **S24** (2.3 g, 9.78 mmol) and freshly distilled acetyl chloride (≈ 20 mL). After work up as described in general procedure II,

S25 was obtained as a brown liquid. The residue was filtered through a small pad of silica eluting with 100% EtOAc. After evaporation of the solvent the product was dried under high *vacuum* to yield **S25** as a mixture of pure diastereomers in the ratio 64:36 (*trans*:*cis*) (1.52 g, 72%).

trans-**S25**:

δ_H (400 MHz, $CDCl_3$): 7.43-7.14 (5 H, m, H-1, H-2 and H-3), 3.98 (1 H, d, *J* 7.5, H-4, 3.28-3.23 (1 H, m, H-5), 2.02-1.94 (1 H, m, H-6a), 1.87-1.77 (1 H, m, H-6b), 1.58-1.39 (2 H, m, H-7), 0.91 (3 H, t, *J* 7.3, H-8).

δ_C (100 MHz, $CDCl_3$): 172.3 (C=O), 171.0 (C=O), 134.6 (q), 129.5, 128.66, 127.7, 52.8, 48.8, 32.3, 19.8, 13.6.

cis-**S25**:

δ_H (400 MHz, $CDCl_3$): 7.43-7.14 (5 H, m, H-1, H-2 and H-3), 4.40 (1 H, d, *J* 9.6, H-4, 3.37-3.31 (1 H, m, H-5), 1.66-1.57 (1 H, m, H-6a), 1.45-1.36 (1 H, m, H-6b), 1.28-1.17 (2 H, m, H-7), 0.79 (3 H, t, *J* 7.2, H-8).

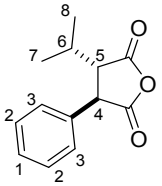
δ_C (100 MHz, $CDCl_3$): 172.9 (C=O), 171.0 (C=O), 131.7 (q), 129.2, 128.72, 128.63, 51.1, 45.5, 28.6, 20.3, 13.5.

ν_{max} (neat)/cm^{-1}:* 2963, 2935, 1862, 1776, 1498, 1455, 1208, 1051, 1038, 927, 769, 731, 698, 596.

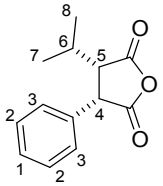
HRMS (*m/z* - APCI):* Found: 217.0861 $(M-H)^-$ $C_{13}H_{13}O_3$ Requires: 217.0870.

* Refers to mixture of *trans*-**S25**:*cis*-**S25** in the ratio 64:36.

2-Isopropyl-3-phenylsuccinic acid anhydride (S28)



trans-**S28**



cis-**S28**

Prepared according to general procedure II, using **S27** (0.750 g, 3.17 mmol) and freshly distilled acetyl chloride (≈ 10 mL). After work up as described in general procedure II, **S28** was obtained as a brown liquid. The residue was filtered through a small pad of silica eluting with 100% EtOAc. After evaporation of the solvent the product was dried under high *vacuum* to yield **S28** as a mixture of analytically pure diastereomers in the ratio 86:14 (*trans*:*cis*) (0.408 g, 58%).

trans-**S28**:

δ_H (400 MHz, $CDCl_3$): 7.42-7.22 (5 H, m, H-1, H-2 and H-3), 4.02 (1 H, d, *J* 6.4, H-4), 3.19-3.36 (1 H, m, H-5), 2.40-2.32 (1 H, m, H-6), 1.10 (3 H, d, *J* 6.9, H-7), 1.04 (3 H, d, *J* 6.9, H-8).

δ_C (100 MHz, $CDCl_3$): 171.7 (C=O), 171.3 (C=O), 135.5 (q), 129.5, 128.58, 127.5, 55.3, 49.7, 29.4, 19.4, 18.9.

cis-**S28**:

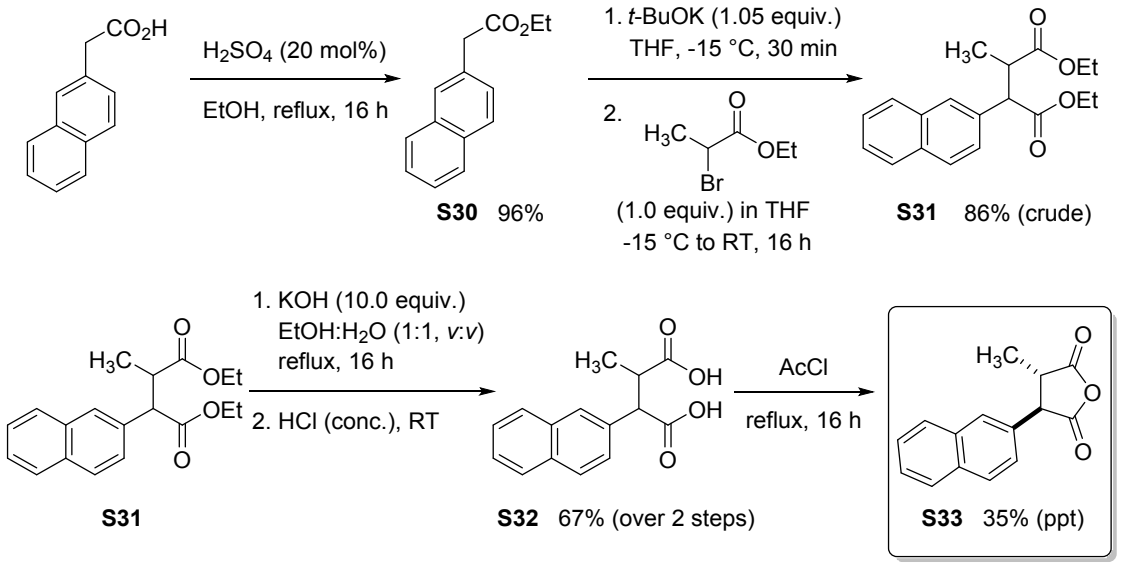
δ_H (400 MHz, $CDCl_3$): 7.42-7.22 (5 H, m, H-1, H-2 and H-3), 4.44 (1 H, d, *J* 9.4, H-4), 3.19-3.36 (1 H, m, H-5), 1.81-1.72 (1 H, m, H-6), 0.97 (3 H, d, *J* 6.7, H-7), 0.92 (3 H, d, *J* 6.8, H-8).

δ_C (100 MHz, $CDCl_3$): 171.2 (C=O), 170.5 (C=O), 131.1 (q), 129.2, 128.63, 128.57, 52.2, 50.4, 26.4, 21.3, 18.7.

ν_{max} (neat)/cm^{-1}:* 2966, 2931, 1862, 1775, 1499, 1455, 1209, 1063, 1038, 924, 771, 742, 697.

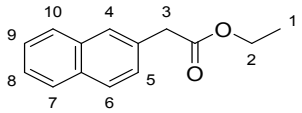
HRMS (*m/z* - APCI):* Found: 217.0878 $(M-H)^-$ $C_{13}H_{13}O_3$ Requires: 217.0870.

* Refers to mixture of *trans*-**S28**:*cis*-**S28** in the ratio 86:14.



Scheme 3 Synthesis of anhydrides **S33**.

Ethyl 2-(naphthalen-2-yl)acetate (S30)



A 250 mL round-bottomed flask containing a stirring bar was charged with commercially available 2-naphthaleacetic acid (5.46 g, 29.32 mmol). MeOH (50 mL) followed by conc. H_2SO_4 (0.4 mL) were added, the flask was fitted with a condenser and the resulting mixture was stirred under reflux for 16 h. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL), washed with a saturated $NaHCO_3$ solution until basic pH was reached. The mixture was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic fractions were washed with deionised water, dried over $MgSO_4$ and the solvent was removed *in vacuo* to afford **S30** pure as a colourless liquid (6.05 g, 28.24 mmol, 96%). TLC (hexanes:EtOAc, 9:1 *v*/*v*): $R_f = 0.49$.

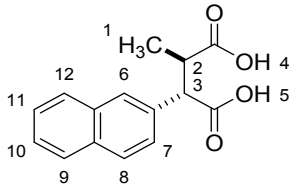
Spectral data for this compound were consistent with those in the literature.[6]

δ_H (400 MHz, $CDCl_3$): 7.84-7.80 (3 H, m, H-6, H-7 and H-10), 7.74 (1 H, bs, H-4), 7.50-7.42 (3 H, m, H-5, H-8 and H-9), 4.18 (2 H, q, *J* 7.2, H-2), 3.78 (2 H, s, H-3), 1.26 (3 H, t, *J* 7.2, H-1).

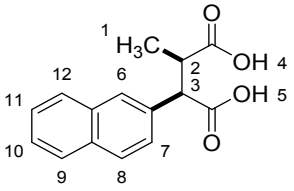
δ_C (100 MHz, $CDCl_3$): 177.7 (C=O), 133.5 (q), 132.5 (q), 131.7 (q), 128.2, 127.9, 127.71, 127.68, 127.4, 126.2, 125.8, 61.0, 41.7, 14.2.

HRMS (*m/z* - APCI): Found: 213.0922 $(M-H)^-$ $C_{14}H_{13}O_2$ Requires: 213.0921.

2-Methyl-3-(naphthalen-2-yl)succinic acid (S32)



trans-**S32**



cis-**S32**

Prepared according to general procedure I, using potassium *tert*-butoxide (3.33 g, 29.65 mmol), ethyl 2-(naphthalen-2-yl)acetate (6.05 g, 28.24 mmol) in 100 mL of dry THF and ethyl 2-bromopropionate (5.11 g, 28.24 mmol) in 10 mL of dry THF. After hydrolysis of the esters and work up as described in the general procedure I, **S32** was obtained as a white solid as a mixture of diastereomers (*trans*:*cis*) in the ratio 63:37 (4.87 g, 67% over 2 steps, combined yield for both diastereomers). M.p. 102-104 °C.*

trans-**S32**:

δ_H (400 MHz, DMSO-d_6): 12.42 (2 H, bs, H-4 and H-5), 7.91-7.87 (3 H, m, H-8, H-9 and H-12), 7.84 (1 H, bs, H-6), 7.53-7.42 (3 H, m, H-7, H-10 and H-11), 3.80 (1 H, d, *J* 11.2, H-3), 3.12-3.04 (1 H, m, *J* 7.2, 11.2, H-2), 0.88 (3 H, d, *J* 7.2, H-1).

δ_C (100 MHz, DMSO-d_6): 177.2 (C=O), 174.6 (C=O), 135.2 (q), 133.4 (q), 132.7 (q), 128.8, 128.1, 128.0, 127.8, 126.85, 126.83, 126.4, 55.1, 43.3, 16.8.

cis-**S32**:

δ_H (400 MHz, DMSO-d_6): 12.42 (2 H, bs, H-4 and H-5), 7.91-7.87 (3 H, m, H-8, H-9 and H-12), 7.81 (1 H, bs, H-6), 7.53-7.42 (3 H, m, H-7, H-10 and H-11), 3.82 (1 H, d, *J* 10.8, H-3), 3.20-3.13 (1 H, m, *J* 6.9, 10.8, H-2), 1.27 (3 H, d, *J* 6.9, H-1).

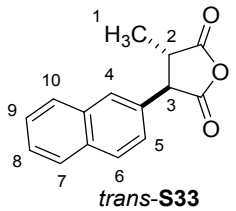
δ_C (100 MHz, DMSO-d_6): 175.6 (C=O), 173.7 (C=O), 135.8 (q), 133.2 (q), 132.7 (q), 128.3, 128.2, 127.91, 127.89, 127.5, 126.7, 126.5, 54.4, 42.2, 15.8.

ν_{max} (neat)/cm^{-1}:* 2886, 2598, 1693, 1421, 1306, 1195, 934, 818, 747.

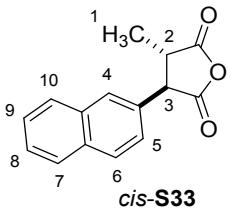
HRMS (*m/z* - ESI):* Found: 281.0787 $(M+Na)^+$ $C_{15}H_{14}NaO_4$ Requires: 281.0784.

* Refers to mixture of *trans*-**S32**:*cis*-**S32** in the ratio 63:37.

3-Methyl-4-(naphthalen-2-yl)dihydrofuran-2,5-dione (S33)



trans-**S33**



cis-**S33**

Prepared according to general procedure II, using **S32** (3.8 g, 14.71 mmol) and freshly distilled acetyl chloride (≈ 40 mL). After work up as described in general procedure II, **S33** was obtained as a brown crude residue. The residue was triturated in dry Et_2O (≈ 10 mL). The remaining solid was filtered and dried under high vacuum to yield **S33** as a mixture of pure diastereomers in the ratio 81:19 (*trans*:*cis*) (1.25 g, 35%). The mother liquor containing the remaining anhydride was stored under in a vial under Argon atmosphere. M.p.* 135-137 °C.

trans-**S33**:

δ_H (400 MHz, $CDCl_3$): 7.91 (1 H, d, *J* 8.6, H-6), 7.87-7.81 (2 H, m, H-7 and H-10), 7.72 (1 H, bs, H-4), 7.56-7.51 (2 H, m, H-8 and H-9), 7.31 (1 H, d, *J* 8.6, H-5), 4.05 (1 H, d, *J* 8.8, H-3), 3.38-3.31 (1 H, dq, *J* 7.2, 8.8, H-2), 1.52 (3 h, d, *J* 7.2, H-1).

δ_C (100 MHz, DMSO-d_6): 172.5 (C=O), 170.7 (C=O), 133.3 (q), 133.1 (q), 130.9 (q), 129.6, 129.3, 127.9, 127.8, 127.4, 126.97, 126.88, 124.7, 54.8, 44.4, 14.4.

cis-**S33**:

δ_H (400 MHz, $CDCl_3$): 7.87-7.81 (3 H, m, H-6, H-7 and H-10), 7.64 (1 H, bs, H-4), 7.56-7.51 (2 H, m, H-8 and H-9), 7.16 (1 H, d, *J* 8.4, H-5), 4.57 (1 H, d, *J* 10.2, H-3), 3.57-3.49 (1 H, dq, *J* 7.5, 10.2, H-2), 1.02 (3 H, d, *J* 7.5, H-1).

δ_C (100 MHz, DMSO-d_6): 173.7 (C=O), 171.2 (C=O), 133.3 (q), 132.96 (q), 129.31 (q), 129.26, 128.2, 127.9, 127.8, 126.9, 126.89, 125.6, 51.5, 40.64, 12.0.

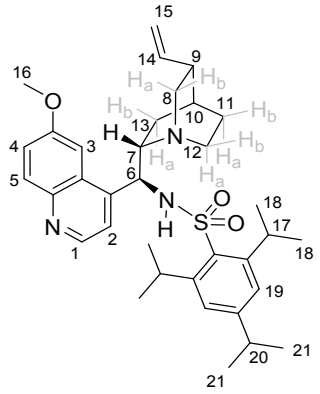
ν_{max} (neat)/cm^{-1}:* 1838, 1771, 1255, 1229, 1103, 993, 955, 925, 814, 760, 737.

HRMS (*m/z* - ESI):* Found: 263.0675 $(M+Na)^+$ $C_{15}H_{12}NaO_4$ Requires: 263.0678.

* Refers to mixture of *trans*-**S33**:*cis*-**S33** in the ratio 81:19.

3. Synthesis of catalysts: procedures

2,4,6-Triisopropyl-*N*-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)benzenesulfonamide (42)



A 50 mL round-bottomed flask containing a stirring bar was charged with quinine·3HCl salt (900.0 mg, 2.08 mmol) and suspended in 20 mL of dry CH_2Cl_2. The solution was cooled to 0 °C and dry triethylamine (1.45 mL, 10.4 mmol) was added. To the resulting clear solution 2,4,6-triisopropyl-phenyl sulphonyl chloride (629.8 mg, 2.08 mmol) was added portion wise as a solid. The reaction was allowed to come back to room temperature and stirred for overnight. After 16 h, the reaction was diluted with 20 mL of water and extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were combined, washed successively with brine (30 mL), water (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product. The catalyst was purified by flash column chromatography eluting with 50% EtOAc in hexanes, to afford the product as a white solid (940.0 mg, 77%). M.p. 110-112 °C. TLC (hexanes:EtOAc, 50:50 *v/v*): $R_f = 0.48$.

Spectral data for this compound were consistent with those in the literature.[7]

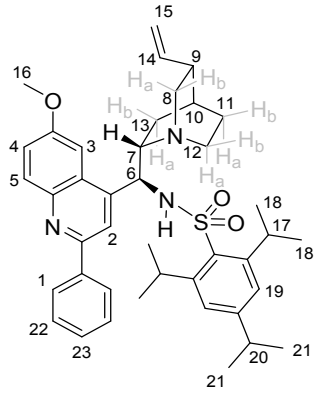
^1H and ^{13}C analysis showed the presence of two rotameric species in the ratio 78:22.

Major rotamer:

δ_H (400 MHz, DMSO-d_6): 8.51 (1 H, d, *J* 4.4, H-1), 7.90 (1 H, d, *J* 9.8, H-5), 7.49-7.41 (2 H, m, H-3 and H-4), 7.39 (1 H, d, *J* 4.4, H-2), 6.98 (2 H, s, H-19), 5.77-5.64 (1 H, m, H-14), 5.15 (1 H, d, *J* 10.5, H-6), 4.99-4.80 (2 H, m, H-15), 3.94 (3 H, s, H-16), 3.89-3.85 (3 H, m, H-9 and H-17), 3.12-3.00 (1 H, m, H-8a), 2.97-

2.74 (3 H, m, H-7, H-12a and H-20), 2.68-2.60 (1 H, m, H-8b), 2.50-2.39 (1 H, m, H-12b), 2.23-2.13 (1 H, m, H-10), 1.55-1.38 (3 H, m, H-11a, H-11b and H-13a), 1.18-1.06 (12 H, m, H-18), 0.86 (6 H, d, *J* 6.5, H-21), 0.76-0.71 (1 H, m, H-13b).

2,4,6-Triisopropyl-*N*-((*S*)-(6-methoxy-2-phenylquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)benzenesulfonamide (43)



A 50 mL round-bottomed flask containing a stirring bar was charged with C-2'-phenyl-9-amino-*epi*-quinine hydrochloride salt (250.0 mg, 0.49 mmol) and suspended in 20 mL of dry CH_2Cl_2. The solution was cooled to 0 °C and dry triethylamine (0.31 mL, 2.21 mmol) was added. To the resulting clear solution 2,4,6-triisopropyl-phenyl sulphonyl chloride (148.78 mg, 0.49 mmol) was added portion wise as a solid. The reaction was allowed to come back to room temperature and stirred for overnight. After 16 h, the reaction was diluted with 20 mL of water and extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were combined, washed successively with brine (30 mL), water (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product. The catalyst was purified by flash column chromatography eluting with the solvent system hexanes:EtOAc:Et_3N (80:15:5 *v*:*v*), to afford the product as a white solid (220.0 mg, 68%). M.p. 81-83 °C. TLC (hexanes:EtOAc:Et_3N, 80:18:2 *v/v*): R_f = 0.17; $[\alpha]_D^{20}$ = -10.4 (*c* = 0.5, $CHCl_3$).

^1H and ^{13}C analysis showed the presence of two rotameric species in the ratio 89:11.

Major rotamer:

δ_H (400 MHz, $CDCl_3$): 8.04 (1 H, d, *J* 9.2, H-5), 7.67 (2 H, d, *J* 6.9, H-1), 7.62 (1 H, s, H-2), 7.51 (1 H, s, H-3), 7.41-7.37 (4 H, m, H-4, H-22 and H-23), 6.87 (2 H, H-19), 5.67-5.58 (1 H, m, H-14), 5.43 (1 H, d, *J* 10.5, H-6), 4.94-4.87 (2 H, m, H-15), 4.02 (3 H, s, H-16), 3.83-3.74 (2 H, m, H-17), 3.3-3.24 (2 H, m, H-7 and H-8a), 2.85-2.72 (2 H, m, H-12a and H-20), 2.68-2.60 (2 H, m, H-9 and H-8b), 2.34-2.24 (1 H, m, H-12b), 1.71-1.61 (3 H, m, H-11a, H-11b and H-13a), 1.29-1.23 (2 H, m, H-10 and H-13b), 1.21-1.17 (4 H, m, H-18), 1.07-0.98 (8 H, m, H-18), 0.74 (6 H, d, *J* 6.6, H-21).

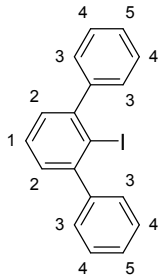
Major and minor rotamers:

δ_C (150.9 MHz, $CDCl_3$): 157.9 (q), 156.8 (q), 154.6 (q), 154.0 (q), 152.7 (q), 152.3 (q), 150.1 (q), 149.4 (q), 145.4 (q), 144.8 (q), 143.6 (q), 141.8 (q), 141.2, 141.1, 139.5 (q), 139.4 (q), 134.4 (q), 132.8 (q), 132.1, 132.0, 129.0, 128.8, 128.5, 127.5 (q), 127.3, 127.2, 126.0 (q), 123.4, 123.3, 121.5, 121.2, 120.6, 118.4, 114.7, 104.5, 101.4, 65.9, 62.5, 62.1, 56.6, 56.0, 55.9, 55.7, 55.6, 53.1, 40.4, 39.8, 39.7, 39.6, 34.0, 33.9, 29.9, 29.6, 28.0, 27.7, 27.6, 27.4, 26.9, 26.6, 25.2, 24.9, 24.7, 23.9, 23.5, 23.2, 15.3, 14.2.

ν_{max} (neat)/cm^{-1}: 2954, 2867, 1622, 1598, 1553, 1498, 1459, 1359, 1333, 1262, 1226, 1148, 1031, 882, 827, 776, 660.

HRMS (*m/z* - ESI): Found: 666.3730 $(M+H)^+$ $C_{41}H_{52}N_3O_3S$ Requires: 666.3729.

2'-Iodo-1,1':3',1''-terphenyl (S34)



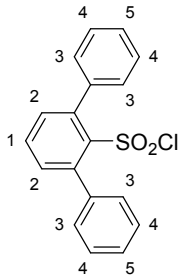
A 250 mL oven dried two-neck round-bottomed flask containing a stirring bar was placed under Argon atmosphere (balloon) and charged with 20 mL of dry Et_2O. To the solvent, a commercially available solution of PhLi (15.75 mL, 30 mmol: 1.9M in Et_2O) was added carefully *via* syringe. The resulting solution was cooled to 0 °C and 1,3-dichlorobenzene (0.85 mL, 7.5 mmol) was added dropwise to the mixture. The reaction was allowed to come back to room temperature and allowed to stir for 16 h. The mixture was cooled to 0 °C (ice bath) and a solution of I_2 (5.7 g, 22.5 mmol) in dry THF (15 mL) was slowly added. The reaction mixture was allowed to come back to room temperature and an aqueous saturated solution of Na_2SO_3 was added to quench the excess of iodine until its characteristic colour disappeared. The organic phase was separated and the aqueous phase extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (15 mL), water (15 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo* to afford the crude product that was purified by recrystallisation from boiling MeOH affording the product in form of pale yellow needles (2.67 g, 45%).

Spectral data for this compound were consistent with those in the literature.[8]

δ_H (400 MHz, $CDCl_3$): 7.45-7.35 (12 H, m, H-2, H-3, H-4 and H-5), 7.25-7.24 (1 H, m, H-1).

HRMS (*m/z* - APCI): Found: 356.0061 $(M+H)^+$ $C_{18}H_{13}I$ Requires: 356.0056.

[1,1':3',1''-Terphenyl]-2'-sulfonyl chloride (S35)



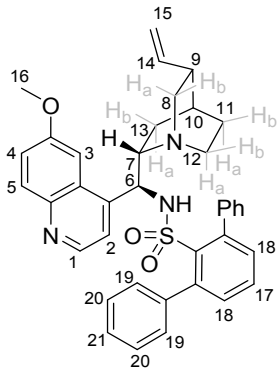
A 100 mL oven dried two-neck round-bottomed flask containing a stirring bar was charged with 2,6-diphenyliodobenzene (**S34**, 0.3 g, 0.842 mmol) and 10 mL of dry Et_2O. The mixture was placed under Argon atmosphere (balloon), cooled to 0 °C (ice bath) and *n*-BuLi (0.53 mL, 0.842 mmol, 1.6 M in hexanes) was added dropwise. The mixture turned yellow and a white solid precipitated. After the mixture was stirred for 8 h at room temperature, the reaction was cooled to -78 °C and freshly distilled sulfuryl chloride (0.136 mL, 1.68 mmol) was added slowly. The mixture was allowed to come back to room temperature and stirred for overnight, cooled to 0 °C and poured into a solution of hydrochloric acid (1.5N, ~ 20 mL). The mixture was diluted with 20 mL of water and the product extracted with Et_2O (3 x 30 mL). The organic layer was washed with brine (15 mL), water (15 mL), dried over $MgSO_4$, filtered and the solvent was concentrate under reduced pressure to afford the crude product that was purified by recrystallisation from a mixture hexanes-$CHCl_3$ (1:1, *v*:*v*) affording the product as a pale yellow solid (0.171 g, 62%). TLC (hexanes:EtOAc, 95:5 *v/v*): $R_f = 0.3$.

Spectral data for this compound were consistent with those in the literature.[9]

δ_H (400 MHz, $CDCl_3$): 7.68 (1 H, app.T, H-1), 7.50-7.41 (12 H, m, H-2, H-3, H-4 and H-5).

HRMS (*m/z* - ESI): Found: 327.0249 $(M-H)^-$ $C_{18}H_{12}O_2SCl$ Requires: 327.0247.

_N_-((_S_)-(6-Methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)-[1,1':3',1''-terphenyl]-2'-sulfonamide (44)



A 25 mL round-bottomed flask containing a stirring bar was charged with quinine (190.4 mg, 0.589 mmol) and 2,6-diphenylbenzene sulfonyl chloride (**S35**, 193.6 mg, 0.589 mmol) in 4 mL of CH_2Cl_2. The solution was cooled to 0 °C and 2N NaOH (0.29 mL, 0.589 mmol) was added. The reaction was allowed to come back to room temperature and stirred for overnight. After 16 h, the reaction was diluted with 20 mL of water and extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were combined, washed successively with brine (30 mL), water (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product. The catalyst was purified by flash column chromatography, eluting in gradient from 100% hexanes to 50% EtOAc in hexanes, to afford the product as a white solid (342.3 mg, 94%). M.p. 88-90 °C. TLC (hexanes:EtOAc, 1:1 *v/v*): $R_f = 0.18$; $[\alpha]_D^{20} = -85.2$ ($c = 0.05$, $CHCl_3$).

δ_H (600 MHz, $CDCl_3$): 8.41 (1 H, d, *J* 4.4, H-1), 7.98 (1 H, d, *J* 9.2, H-5), 7.39 (1 H, m, H-4), 7.39-7.19 (10 H, m, H-19, H-20 and H-21), 7.34 (1 H, t, *J* 7.8, H-17), 7.18 (1 H, bs, H-3), 7.07-7.06 (2 H, d, *J* 7.8, H-18), 6.91 (1 H, d, *J* 4.4, H-2), 5.67-5.59 (1 H, m, H-14), 4.93-4.90 (3 H, m, H-6 and H-15), 3.76 (3 H, s, H-16), 2.99-2.93 (1 H, m, H-7), 2.89-2.78 (1 H, m, H-8b), 2.52-2.32 (3 H, m, H-8a, H12a and H-12b), 2.20-2.11 (1 H, m, H-9), 1.53-1.30 (3 H, H-10, H11a and H11b), 1.18-1.12 (1 H, m, H13a), 0.59-0.54 (1 H, m, H-13b).

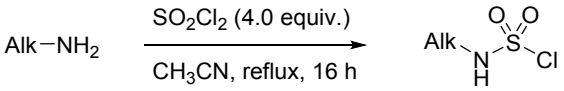
δ_C (150.9 MHz, $CDCl_3$): 157.9 (q), 146.6, 144.5 (q), 142.8 (q), 142.2 (q), 141.3, 141.0 (q), 139.4 (q), 131.4, 131.2, 130.0, 129.3 (q), 128.9

(q), 127.33, 127.27, 121.9, 119.4, 114.4, 101.6, 60.4, 55.56, 55.53, 52.9, 40.2, 39.4, 27.8, 27.2, 25.0.

ν_{max} (neat)/cm^{-1}: 2933, 1620, 1571, 1508, 1474, 1452, 1355, 1317, 1227, 1155, 1028, 909, 854, 808, 758, 748, 662, 592.

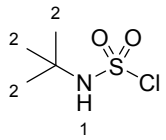
HRMS (*m/z* - ESI): Found: 616.2640 $(M+H)^+$ $C_{38}H_{38}N_3O_3S$ Requires: 616.2628.

<u>General procedure III:</u> Synthesis of sulfamoyl chlorides for aliphatic substrates S36 and S37



A 25 mL oven-dried two-neck round-bottomed flask containing a stirring bar was charged with the relevant amine (1.0 equiv.) in dry CH_3CN (10 mL per gram). To the resulting solution, sulfuryl dichloride (SO_2Cl_2, ~ 4.0 equiv.) was carefully added, at 0 °C (ice bath cooled). The flask was then flushed with argon, fitted with a condenser and placed under an inert atmosphere (Ar, balloon). The reaction mixture was heated under reflux for 48 h, cooled to room temperature and, the excess of sulfuryl dichloride was distilled off using a pump connected to a trap cooled with liquid nitrogen, the residue was diluted with dry CH_2Cl_2 and quickly filtered through a small plug of silica eluting with a mixture of 50% EtOAc in Hexanes. The solvent was removed under reduced pressure affording the crude sulfamoyl chloride, immediately used into the next step, as a crude material, without any further purifications.

***tert*-Butylsulfamoyl chloride (S36)**



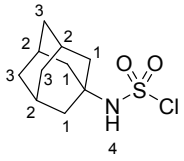
Prepared according to the general procedure III, using *tert*-butylamine (1.44 mL, 13.67 mmol), dry CH_3CN (4 mL) and SO_2Cl_2 (4 mL). The crude product was isolated as a yellow oil (0.941 mg, 40%). M.p. 20-22 °C (lit, M.p. 23-24 °C). The product was used into the next step without further purification and stored under Argon in a freezer.

Spectral data for this compound were consistent with those in the literature.[10]

δ_H (400 MHz, $CDCl_3$): 5.54 (1 H, bs, N-H, H-1), 1.47 (9 H, s, H-2).

δ_C (100 MHz, $CDCl_3$): 58.4 (q), 29.2.

(Adamantan-1-yl)sulfamoyl chloride (S37)



Prepared according to the general procedure III, using 1-adamantylamine (1 g, 6.61 mmol), dry CH_3CN (5 mL) and SO_2Cl_2 (2.7 mL, 33.06 mmol). The crude product was isolated as a white solid (1.09 g, 66%). M.p. 100-104 °C (lit, M.p. 104-106 °C). The product was used into the next step without further purification and was stored under Argon in a freezer.

Spectral data for this compound were consistent with those in the literature.[10]

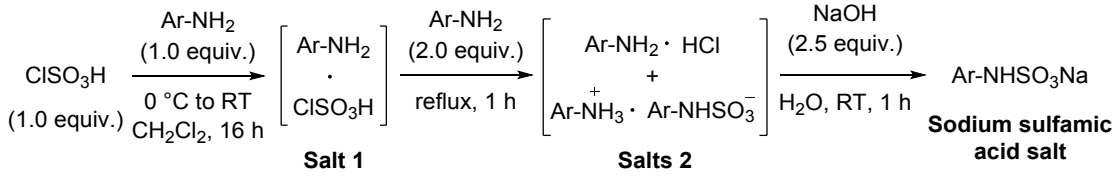
δ_H (400 MHz, $CDCl_3$): 5.45 (1 H, bs, N-H, H-4), 2.17 (3 H, app.S, H-2), 2.07 (6 H, m, H-1), 1.70 (6 H, m, H-3).

δ_C (100 MHz, $CDCl_3$): 58.9 (q), 41.9, 35.6, 29.5.

ν_{max} (neat)/cm^{-1}: 2993, 2923, 1403, 1362, 1348, 1319, 1275, 1244, 1169, 1080, 1049, 887, 617, 644, 617, 583.

HRMS (*m/z* - ESI): Found: 250.0665 $(M+H)^+$ $C_{10}H_{17}NO_2SCl$ Requires: 250.0669.

<u>General procedure IV:</u> Synthesis of sodium sulfamic acids S38 and S39

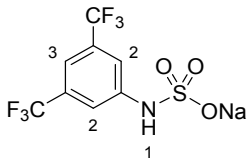


A 250 mL oven dried three-neck round-bottomed flask containing a stirring bar was carefully charged with chlorosulfonic acid (1.0 equiv.), fitted with a condenser, flushed with Argon and placed under an inert atmosphere (Argon, balloon). The flask was cooled to 0 °C (ice bath) and a solution of the relevant amine (1.0 equiv.), in dry CH_2Cl_2 (10 mL / 10 mmol of amine), was added dropwise *via* syringe. The mixture was allowed to come back to room temperature and stirred for 16 h. The chlorosulfonic salt (**Salt 1**) of the amine forms a suspension in the organic layer.

Over a 20-min period, a solution of the relevant amine (2.0 equiv.), in dry CH_2Cl_2 (10 mL / 10 mmol of amine), is added to the stirred suspension, at room temperature. After completion of the addition, the mixture is heated to reflux for 1 h. The **Salt 1** is converted to the mixture of **Salts 2**.

The reaction mixture is cooled to room temperature and, an aqueous solution of sodium hydroxide (2.5 equiv.) is added. After 3 h of stirring, the sodium sulfamic acid salt is formed, the organic layer is separated from the aqueous layer and washed with water (3 x 30 mL). The water washes were added to the water layer and the combined water layers washed with CH_2Cl_2 (3 x 20 mL). The aqueous layers were concentrated under reduced pressure. The white residue was suspended in ethanol (100 mL for 30 mmol of starting material of amine), stirred at room temperature for 30 min, then refluxed for 10 min. The boiling solution was filtered and the volatiles were concentrated under reduced pressure to afford the appropriate sodium sulfamate salt that is used into the next step without further purifications.

Sodium (3,5-bis(trifluoromethyl)phenyl)sulfamate (S38)

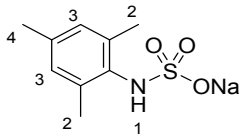


Prepared according to the general procedure IV, using 3,5-bis(trifluoromethyl)aniline (3.3 g – 2.25 mL, 14.42 mmol, *i.e.* 3.0 equiv.), chlorosulfonic acid (0.56 g – 0.32 mL, 4.81 mmol, *i.e.* 1.0 equiv.) and sodium hydroxide (0.48 g, 12.02 mmol, *i.e.* 2.5 equiv.). The sodium sulfamic acid salt was obtained as a white solid (1.5 g, 94%). M.p. > 200 °C, decomposition.

Spectral data for this compound were consistent with those in the literature.[11]

δ_H (400 MHz, DMSO-d_6): 7.59 (1 H, s, H-3), 7.25 (1 H, s, H-2), 6.99 (1 H, s, H-1).

Sodium mesitylsulfamate (S39)



Prepared according to the general procedure IV, using 2,4,6-trimethylaniline (12.2 g – 12.65 mL, 90.12 mmol, *i.e.* 3.0 equiv.), chlorosulfonic acid (3.5 g – 2.0 mL, 30.04 mmol, *i.e.* 1.0 equiv.) and sodium hydroxide (3.0 g, 75.1 mmol, *i.e.* 2.5 equiv.). When the aqueous layer was concentrated under reduced pressure, a white solid precipitated. The solid was filtered, washed with cold water and dried under high vacuum to yield the sodium sulfamic acid salt as a white solid (4.4 g, 62%). M.p. 190-200 °C.

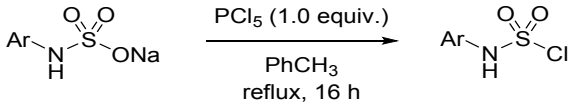
δ_H (400 MHz, DMSO-d_6): 6.70 (2 H, s, H-3), 5.85 (1 H, bs, H-1), 2.29 (6 H, s, H-2), 2.15 (3 H, s, H-4).

δ_C (100 MHz, DMSO-d_6): 137.2 (q), 136.2, 133.0 (q), 128.5, 20.8, 19.3.

ν_{max} (neat)/cm^{-1}: 3483, 3277, 1621, 1479, 1398, 1210, 1049, 880, 848, 815, 739, 689, 610.

HRMS (*m/z* - APCI): Found: 214.0534 $(M-Na)^-$ $C_9H_{12}NO_3S$ Requires: 214.0543.

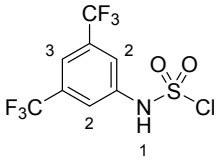
<u>General procedure V:</u> Synthesis of sulfamoyl chlorides for aromatic substrates S40 and S41



A 25 mL oven dried round-bottomed flask containing a stirring bar was charged with the relevant sodium sulfamic acid salt (1.0 equiv.) in dry toluene (10 mL per gram). To the resulting suspension, phosphorus pentachloride (PCl_5, 1.0 equiv.) was added portion wise, at room temperature. The flask was then flushed with argon, fitted with a condenser and placed under an inert atmosphere (Ar, balloon). The reaction mixture was heated under reflux for 16 h, cooled to room temperature, filtered through a celite pad and the filtrate was then concentrated *in vacuo* to provide almost analytically pure

material. The sulfamoyl chlorides synthesised were immediately used in the next step, as a crude material, without further purifications.

(3,5-bis(trifluoromethyl)phenyl)sulfamoyl chloride (S40)



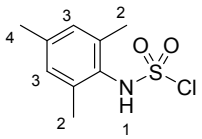
Prepared according to the general procedure V, using the sodium sulfamic acid salt of the 3,5-bis(trifluoromethyl)aniline (**S38**, 1.5 g, 4.53 mmol), phosphorus pentachloride (943 mg, 4.53 mmol) and dry toluene (15 mL). The sulfamoyl chloride was obtained as a brown residue that crystallises upon standing (701 mg, 47%).*

Spectral data for this compound were consistent with those in the literature.

δ_H (400 MHz, $CDCl_3$): 8.08 (1 H, bs, H-1), 7.89 (1 H, s, H-3), 7.82 (2 H, s, H-2).

* Full analysis for this compound cannot be reported as the entire batch was immediately employed as a crude material, in the next reaction step, due to its assumed instability.

Mesitylsulfamoyl chloride (S41)



Prepared according to the general procedure V, using the sodium sulfamic acid salt of the 2,4,6-trimethylaniline (1.0 g, 4.21 mmol), phosphorus pentachloride (878.0 mg, 4.21 mmol) and dry toluene (10 mL). The reaction mixture was refluxed for 3 h. The sulfamoyl chloride was obtained as a crude pale-yellow residue that solidifies upon standing (340 mg, 35%).*

δ_H (400 MHz, $CDCl_3$): 7.41 (1 H, bs, H-1), 6.95 (2 H, s, H-3), 2.41 (6 H, s, H-2), 2.29 (3 H, s, H-4).

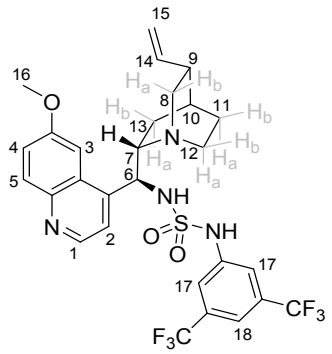
HRMS (*m/z* - APCI): Found: 232.0196 $(M-H)^-$ $C_9H_{11}ClNO_2S$ Requires: 232.0205.

* Full analysis for this compound cannot be reported as the entire batch was immediately employed as a crude material, in the next reaction step, due to its assumed instability.

General procedure VI: Synthesis of the sulfamide based catalysts 45-48

A 25 mL oven-dried round-bottomed flask containing a stirring bar was charged with the free quinine (1.0 equiv.) in dry CH_2Cl_2 (1 mL per 100 mg of quinine). The flask was flushed with Argon and placed under an inert atmosphere (Ar, balloon). Freshly distilled triethylamine (2.0 equiv.) was added to the solution *via* syringe at room temperature. The solution was cooled to 0 °C and the relevant freshly synthesised crude sulfamoyl chloride (1.0 to 5.0 equiv.) was added portion wise, directly as a solid. The reaction was monitored by TLC chromatography. If required an excess of sulfamoyl chloride (up to 4 more equivalents) was added to the reaction mixture until TLC analysis indicated completed disappearance of the quinine starting material. After the reaction was judged completed, as indicated by TLC analysis, the reaction was diluted with 20 mL of water and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The organic extracts were combined, washed successively with brine (30 mL) and water (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product. The catalyst was purified by flash column chromatography, eluting in gradient with the conditions as indicated for each case, to afford the relevant sulfamide based catalyst.

_N_-((_S_)-(6-Methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)-3,5-bis(trifluoromethyl)benzenesulfamide (45)



Prepared according to the general procedure VI, using the free quinine (306.0 mg, 0.94 mmol), TEA (0.26 mL, 1.9 mmol) and the sulfamoyl chloride **S40** (461.0 mg, 1.41 mmol) in dry CH_2Cl_2 (4 mL). The catalyst was purified by flash column chromatography, eluting in gradient from 1% CH_3OH in CH_2Cl_2 to 5% CH_3OH in CH_2Cl_2, to afford the product as a white solid (220.3 mg, 38%). M.p. 120-122 °C. TLC (CH_2Cl_2:CH_3OH, 95:5 *v:v*): $R_f = 0.18$; $[\alpha]_D^{20} = +40.0$ ($c = 0.05$, $CHCl_3$).

^1H, ^{13}C and ^{19}F analysis showed the presence of two rotameric species in the ratio 69:31.

Major rotamer:

δ_H (600 MHz, $CDCl_3$): 8.48 (1 H, d, *J* 4.3, H-1), 8.01 (1 H, d, *J* 9.2, H-5), 7.54 (1 H, s, H-3), 7.48 (1 H, s, H-18), 7.41 (1 H, d, *J* 9.2, H-4), 7.20 (1 H, s, H-17), 7.15-7.11 (1 H, m, H-2), 5.80-5.75 (1 H, m, H-14), 5.29 (1 H, d, *J* 11.5, H-6), 5.09-5.06 (2 H, m, H-15), 3.98 (3 H, s, H-16), 3.41-3.24 (2 H, m, H-7 and H-9), 2.92-2.81 (1 H, m, H-8a), 2.82-2.74 (1 H, m, H-8b), 2.47-2.39 (1 H, m, H-12a), 1.79-1.75 (1 H, m, H-12b), 1.73-1.52 (4 H, m, H-10, H-11a, H-11b and H-13a), 0.84-0.78 (1 H, m, H-13b).

Minor rotamer:

δ_H (600 MHz, $CDCl_3$): 8.61 (1 H, d, *J* 3.9, H-1), 7.86 (1 H, d, *J* 9.2, H-5), 7.27 (1 H, s, H-18), 7.26-7.24 (1 H, m, H-2), 7.22 (1 H, s, H-3), 7.16 (1 H, d, *J* 9.2, H-4), 6.84 (1 H, s, H-17), 5.61-5.55 (1

H, m, H-14), 4.49 (1 H, d, *J* 11.5, H-6), 4.95-4.87 (2 H, m, H-15), 3.63 (3 H, s, H-16), 3.38 (1 H, m, H-8a), 3.01-2.97 (2 H, m, H-7, H-8b), 2.77 (1 H, m, H-9), 2.35-2.28 (1 H, m, H-12a), 1.75-1.71 (1 H, m, H-12b), 1.34-1.22 (4 H, m, H-10, H-11a, H-11b and H-13b), 0.94-0.88 (1 H, m, H-13a).

Major and minor rotamers:

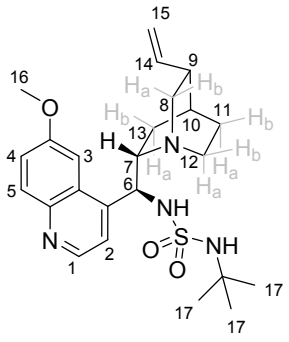
δ_C (150.9 MHz, $CDCl_3$): 158.7 (q), 156.8 (q), 147.1, 147.0, 144.8 (q), 144.6 (q), 141.1 (q), 140.8 (q), 140.1 (q), 139.5 (q), 139.1 (q), 138.4, 132.48 (q) (q, $^2J_{C\text{-}F}$ 32.6), 132.23 (q) (q, $^2J_{C\text{-}F}$ 33.3), 132.08, 131.87, 128.1, 128.09, 126.4, 125.6, 123.8, 123.78, 123.7, 122.7 (q) (q, $^1J_{C\text{-}F}$ 272.3), 122.2, 122.0, 121.0, 120.2, 119.2, 117.9, 116.6, 116.2, 115.6, 115.0, 102.9, 100.5, 63.1, 60.7, 55.9, 55.8, 55.7, 55.2, 55.1, 53.5, 40.8, 40.1, 39.3, 38.7, 27.4, 27.2, 27.1, 27.0, 26.2, 25.9.

δ_F (376.5 MHz, $CDCl_3$): -62.96 (minor), -63.08 (major).

ν_{max} (neat)/cm^{-1}: 3154, 2921, 1623, 1510, 1472, 1432, 1377, 1274, 1177, 1156, 1131, 982, 878, 693, 610.

HRMS (*m/z* - ESI): Found: 615.1876 $(M+H)^+$ $C_{28}H_{29}N_4O_3F_6S$ Requires: 315.1865.

_N_-((_S_)-(6-Methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)-2-methylpropane-2-sulfamide (46)



Prepared according to the general procedure VI, using the free quinine (417.0 mg, 0.94 mmol), TEA (0.36 mL, 2.6 mmol) and the sulfamoyl chloride **S36** (381.0 mg, 2.2 mmol) in dry CH_2Cl_2 (5 mL). The catalyst was purified by flash column chromatography, eluting in gradient from 1% CH_3OH in CH_2Cl_2 to 5% CH_3OH in CH_2Cl_2, to afford the product as a white solid (377.1 mg, 64%). M.p. 120-122 °C. TLC (CH_2Cl_2:CH_3OH, 95:5 *v:v*): $R_f = 0.18$; $[\alpha]_D^{20} = +151.2$ ($c = 0.05$, $CHCl_3$).

^1H and ^{13}C analysis showed the presence of two rotameric species in the ratio 80:20.

Major rotamer:

δ_H (600 MHz, $CDCl_3$): 8.75 (1 H, d, *J* 4.5, H-1), 7.98 (1 H, d, *J* 9.2, H-5), 7.57 (1 H, s, H-3), 7.42-7.34 (2 H, m, H-2 and H-4), 5.77-5.71 (1 H, m, H-14), 5.17 (1 H, d, *J* 10.7, H-6), 5.04-4.96 (2 H, m, H-15), 4.72 (1 H, bs, N-H), 3.95 (3 H, s, H-16), 3.37-3.28 (1 H, m, H-7), 3.27-3.19 (1 H, m, H-8a), 3.16-3.03 (1 H, m, H-8b), 2.84-2.74 (2 H, m, H-12a and H-12b), 2.35-2.28 (1 H, m, H-9), 1.69-1.63 (1 H, m, H-10), 1.65-1.63 (2 H, m, H-11a and H-11b), 1.50-1.44 (1 H, m, H-13a), 1.00 (9 H, s, H-17), 1.01-0.94 (1 H, m, H-13b).

Minor rotamer:

δ_H (600 MHz, $CDCl_3$): 8.75 (1 H, d, *J* 4.5, H-1), 8.00 (1 H, d, *J* 9.7, H-5), 7.75 (1 H, bs, H-3), 7.42-7.34 (2 H, m, H-2 and H-4), 5.62-5.57 (1 H, m, H-14), 4.44 (1 H, d, *J* 10.9, H-6), 4.96-4.83 (2 H, m, H-15), 3.89 (3 H, s, H-16), 3.57-3.43 (1 H, m, H-7), 3.27-3.19 (1 H, m, H-8a), 3.16-3.03 (1 H, m, H-8b), 2.74-2.65 (2 H, m, H-12a and H-12b), 2.30-2.24 (1 H, m, H-9), 1.69-1.63 (1 H, m, H-10), 1.65-1.63 (2 H, m, H-11a and H-11b), 1.32-1.24 (1 H, m, H-13b), 0.84 (9 H, s, H-17), 0.78-0.72 (1 H, m, H-13a).

Major rotamer:

δ_C (150.9 MHz, $CDCl_3$): 158.3 (q), 147.3, 144.6 (q), 143.5 (q), 141.2, 131.7, 128.9 (q), 122.0, 119.6, 114.7, 101.0, 60.7, 55.9, 55.5, 53.8, 53.4, 40.5, 39.4, 29.6, 27.7, 27.3, 26.1.

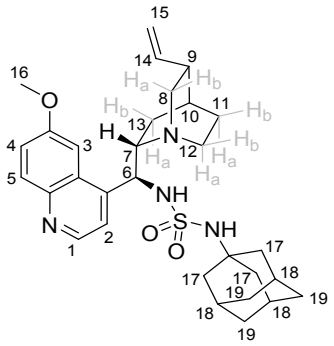
Minor rotamer:

δ_C (150.9 MHz, $CDCl_3$): 157.0 (q), 147.2, 145.2 (q), 144.5 (q), 141.3, 131.9, 127.1 (q), 123.9, 121.3, 114.6, 103.5, 63.2, 56.3, 55.9, 55.5, 54.1, 39.9, 39.7, 29.3, 27.7, 27.4, 26.5.

ν_{max} (neat)/cm^{-1}: 2941, 1618, 1475, 1435, 1299, 1239, 1227, 1083, 1057, 1016, 973, 857, 711, 660, 611.

HRMS (*m/z* - ESI): Found: 459.2430 $(M+H)^+$ $C_{24}H_{35}N_4O_3S$ Requires: 459.2430.

(3*R*,5*R*,7*R*)-*N*-((*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)adamantane-1-sulfamide (20)



Prepared according to the general procedure VI, using the free quinine (372.0 mg, 1.15 mmol), TEA (0.31 mL, 2.3 mmol) and the sulfamoyl chloride **S37** (574.0 mg, 2.3 mmol) in dry CH_2Cl_2 (4 mL). The catalyst was purified by flash column chromatography, eluting in gradient from 1% CH_3OH in CH_2Cl_2 to 5% CH_3OH in CH_2Cl_2, to afford the product as a white solid (252.0 mg, 41%). M.p. 118-120 °C. TLC (CH_2Cl_2:CH_3OH, 95:5 *v:v*): R_f = 0.21; $[\alpha]_D^{20}$ = +29.6 (*c* = 0.05, $CHCl_3$).

^1H and ^{13}C analysis showed the presence of two rotameric species in the ratio 77:23.

Major rotamer:

δ_H (600 MHz, $CDCl_3$): 8.78 (1 H, d, *J* 4.4, H-1), 8.02 (1 H, d, *J* 9.2, H-5), 7.62 (1 H, s, H-3), 7.44 (1 H, d, *J* 4.4, H-2), 7.42-7.36 (1 H, m, H-4), 5.83-5.75 (1 H, m, H-14), 5.21 (1 H, d, *J* 10.8, H-6), 5.05-5.01 (2 H, m, H-15), 3.98 (3 H, s, H-16), 3.40-3.32 (1 H, m, H-7), 3.30-3.23 (1 H, m, H-8a), 3.19-3.08 (1 H, m, H-8b), 2.87-2.77 (2 H, m, H-12a and H-12b), 2.38-2.32 (1 H, m, H-9), 1.97-1.91 (3 H, m, H-10, H-11a and H-11b), 1.74-1.22 (15 H, m, H-17, H-18 and H-19), 0.89-0.82 (1 H, m, H-13a), 0.80-0.75 (1 H, m, H-13b).

Minor rotamer:

δ_H (600 MHz, $CDCl_3$): 8.67 (1 H, d, *J* 3.6, H-1), 8.05 (1 H, d, *J* 9.3, H-5), 7.79 (1 H, s, H-3), 7.29 (1 H, d, *J* 3.6, H-2), 7.42-7.36 (1 H, m, H-4), 5.68-5.60 (1 H, m, H-14), 4.97-4.89 (2 H, m, H-15), 4.48 (1 H, d, *J* 10.9, H-6), 3.92 (3 H, s, H-16), 3.59-3.45 (1 H, m, H-7), 3.51-3.46 (1 H, m, H-8a), 3.19-3.08 (1 H, m, H-8b), 2.77-2.68 (2 H, m, H-12a and H-12b), 2.32-2.27 (1 H, m, H-9), 1.84-1.78 (3 H, m, H-10, H-11a and H-11b), 1.74-1.22 (15 H, m, H-17, H-18 and H-19), 1.57-1.50 (1 H, m, H-13a), 1.31-1.28 (1 H, m, H-13b).

Major rotamer:

δ_C (150.9 MHz, $CDCl_3$): 158.4 (q), 147.4, 144.7 (q), 141.0 (q), 131.8, 129.0 (q), 122.1, 119.8, 114.9, 101.1, 60.6, 55.8, 55.6, 54.4, 53.4, 42.6, 40.7 (q), 39.3, 35.9, 34.7, 29.7, 29.5, 27.6, 27.4, 26.1.

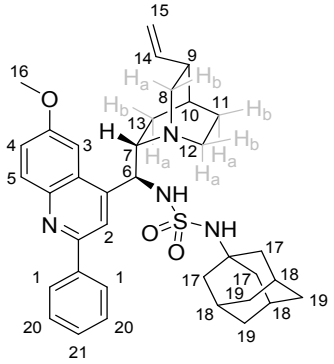
Minor rotamer:

δ_C (150.9 MHz, $CDCl_3$): 157.1 (q), 147.3, 143.5 (q), 141.3 (q), 132.1, 127.2 (q), 124.2, 121.3, 114.7, 103.9, 63.3, 56.3, 56.0, 54.6, 42.2, 40.1 (q), 39.7, 35.8, 34.5, 31.6, 29.3, 27.7, 27.5, 26.9, 26.6.

ν_{max} (neat)/cm^{-1}: 2904, 2848, 1620, 1508, 1453, 1358, 1308, 1229, 1150, 1087, 988, 911, 852, 824, 582, 569.

HRMS (*m/z* - ESI): Found: 537.2891 $(M+H)^+$ $C_{30}H_{41}N_4O_3S$ Requires: 537.2899.

(3*R*,5*R*,7*R*)-*N*-((*S*)-(6-Methoxy-2-phenylquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)adamantane-1-sulfonamide (48)



Prepared according to the general procedure VI, using the free quinine (85.0 mg, 0.21 mmol), TEA (57 μL, 0.43 mmol) and the sulfamoyl chloride **S37** (106.0 mg, 0.43 mmol) in dry CH_2Cl_2 (2 mL). The catalyst was purified by flash column chromatography, eluting in gradient from 1% CH_3OH in CH_2Cl_2 to 5% CH_3OH in CH_2Cl_2, to afford the product as a white solid (75.4 mg, 57%). M.p. 54-56 °C. TLC (CH_2Cl_2:CH_3OH, 95:5 *v:v*): $R_f = 0.34$; $[\alpha]_D^{20} = +280.0$ ($c = 0.102$, $CHCl_3$).

^1H and ^{13}C analysis showed the presence of two rotameric species in the ratio 76:24.

Major rotamer:

δ_H (600 MHz, $CDCl_3$): 8.15 (2 H, d, *J* 7.8, H-1), 8.11 (1 H, d, *J* 9.3, H-5), 7.97 (1 H, s, H-3), 7.61 (1 H, bs, H-2), 7.61-7.38 (4 H, m, H-4, H-20 and H-21), 5.79-5.74 (1 H, m, H-14),5.24 (1 H, d, *J* 10.8, H-6), 5.03-4.97 (2 H, m, H-15), 4.00 (3 H, s, H-16), 3.39-3.37 (1 H, m, H-7), 3.30-3.26 (1 H, m, H-8a), 3.17-3.16 (1 H, m, H-8b), 2.83-2.78 (2 H, m, H-12a and H-12b), 2.34-2.25 (1 H, m, H-9), 1.85-1.83 (1 H, m, H-10), 1.69-0.82 (13 H, m, H-11a, H-11b, H-13a, H-13b and H-17).

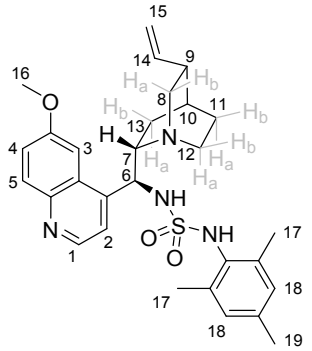
Major and minor rotamers:

δ_C (150.9 MHz, $CDCl_3$): 158.2 (q), 157.0 (q), 154.4 (q), 152.4 (q), 145.4 (q), 144.7 (q), 144.4 (q), 144.0 (q), 141.3 (q), 141.0 (q), 139.5 (q), 139.2 (q), 132.3, 132.1, 129.1, 128.9, 128.8, 128.0, 127.2, 127.1, 122.1, 122.0, 121.4, 117.9, 114.8, 114.7, 103.8, 100.9, 63.7, 60.6, 56.2, 55.9, 55.7, 55.6, 55.5, 54.5, 54.5, 53.6, 42.3, 42.1, 40.5 (q), 39.4 (q), 35.8, 35.7, 32.8, 31.9, 29.7, 29.6, 29.3, 29.3, 27.7, 27.4, 22.7, 14.1.

ν_{max} (neat)/cm^{-1}: 2919, 2848, 1622, 1600, 1497, 1450, 1358, 1308, 1229, 1149, 1084, 990, 897, 829, 693, 577, 555.

HRMS (*m/z* - ESI): Found: 613.3212 $(M+H)^+$ $C_{36}H_{45}N_4O_3S$ Requires: 613.3212.

_N_-((_S_)-(6-Methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)-2,4,6-trimethylbenzenesulfonamide (47)



Prepared according to the general procedure VI, using the free quinine (282.0 mg, 0.87 mmol), Et_3N (0.24 mL, 1.74 mmol) and the sulfamoyl chloride **S41** (305.0 mg, 1.3 mmol) in dry CH_2Cl_2 (3 mL). The catalyst was purified by flash column chromatography, eluting in gradient from 1% CH_3OH in CH_2Cl_2 to 5% CH_3OH in CH_2Cl_2, to afford the product as a white solid (194.4 mg, 43%). M.p. 88-90 °C. TLC (EtOAc:CH_3OH, 95:5 *v:v*): $R_f = 0.28$; $[\alpha]_D^{20} = +16.8$ ($c = 0.05$, $CHCl_3$).

^1H and ^{13}C analysis showed the presence of two rotameric species in the ratio 98:2.

Major rotamer:

δ_H (600 MHz, $CDCl_3$): 8.66 (1 H, d, *J* 4.2, H-1), 7.99 (1 H, d, *J* 9.2, H-5), 7.57 (1 H, bs, H-3), 7.37 (1 H, d, *J* 9.2, H-4), 7.25 (1 H, m, H-2), 6.75 (2 H, bs, H-18), 5.87-5.76 (1 H, m, H-14), 5.37 (1 H, d, *J* 10.8, H-6), 5.10-5.00 (2 H, m, H-15), 3.98 (3 H, s, H-16), 3.55-3.42 (1 H, m, H-7), 3.31-3.14 (2 H, m, H-8a, and H-9), 2.90-2.83 (1 H, m, H-8b), 2.40-2.31 (1 H, m, H-12a), 2.25 (6 H, s, H-17), 2.20 (3 H, s, H-19), 2.13-2.05 (1 H, m, H-12b), 1.75-1.70 (1 H, m, H-10), 1.68-1.54 (3 H, m, H-11a, H-11b and H-13a), 0.87-0.78 (1 H, m, H-13b).

Major rotamer:

δ_C (150.9 MHz, $CDCl_3$): 158.3 (q), 147.3, 144.7 (q), 142.8 (q), 141.0, 136.9 (q), 136.4, 131.6, 131.2 (q), 129.2, 128.4 (q), 122.2, 118.9, 115.0, 101.2, 61.2, 55.8, 54.3, 41.0, 39.3, 27.6, 27.3, 26.6, 20.8, 19.1, 17.6.

ν_{max} (neat)/cm^{-1}: 2919, 1620, 1508, 1474, 1310, 1227, 1143, 1029, 988, 911, 851, 828, 713, 610.

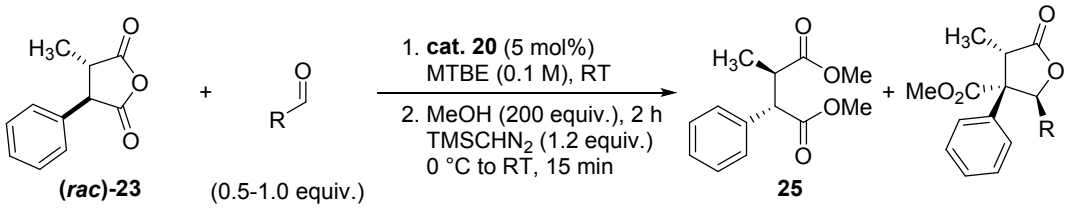
HRMS (*m/z* - APCI): Found: 519.2444 $(M-H)^-$ $C_{29}H_{35}N_4O_3S$ Requires: 519.2435.

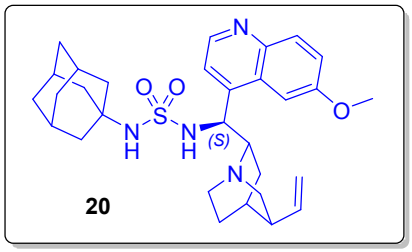
4. Synthesis of racemic lactones

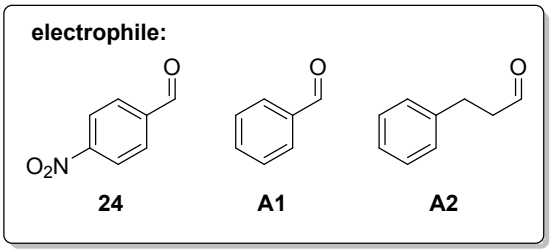
Racemic preparation of lactones 57-64

An oven-dried 5 mL reaction vessel containing a magnetic stirring bar under argon atmosphere was charged with the relevant anhydride (0.1 mmol). Anhydrous MTBE or THF (1.0 mL, 0.1 M) was added *via* syringe followed by recrystallized 4-nitro-benzaldehyde aldehyde (0.1 mmol). *N*,*N*-Diisopropylethylamine (3.6 μL, 20.0 μmol - 20 mol%) was added *via* syringe and the resulting mixture was allowed to stir for 48 h at room temperature. To the reaction mixture containing the corresponding crude carboxylic acids, anhydrous MeOH (202.3 μL, 5.0 mmol), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 60 μL, 0.12 mmol) were added *via* syringe and the reaction was allowed to stir for 15 min at 0 °C. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash column chromatography, eluting in gradient from 100% hexanes to 30% EtOAc in hexanes to isolate all of the 4 diastereomers combined. A sample of the purified diastereomer, isolated after column chromatography, was then re-purified by preparative TLC chromatography to produce racemic material for HPLC traces analysis.

5. Evaluation of aliphatic and aromatic resolving agents







entry	aldehyde	electrophile (equiv.)	time (d)	conv. (%)[a]	25 *ee* (%)[b]	S*[c]
1	**24**	0.5	7	48	64	10.5
2	**A1**	5	10	33	n.d.[d]	n.d.[d]
3	**A2**	10	10	27	n.d.[d]	n.d.[d]

[a]Conversion of starting material **(*rac*)-23** was determined by ^{1}H NMR spectroscopic analysis using 4-iodoanisole as an internal standard. [b]Determined by CSP-HPLC after derivatisation of the unreacted starting material **(*rac*)-23** by ring opening alcoholysis with MeOH followed by *in situ* esterification with $TMSCHN_2$. [c]S* = estimated selectivity factor calculated based on the starting material **(*rac*)-23** after derivatisation to **25** by using the conversion (C) determined by ^{1}H NMR spectroscopic analysis and using the formula: $S^* = \ln[(1-C)(1-ee_{25})]:\ln[(1-C)(1+ee_{25})]$. [d]Not determined.

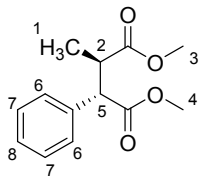
5. Catalyst evaluation (general procedures)

General procedure VI: Evaluation of the substrate scope with respect to the anhydride component and derivatisation procedure for the determination of the enantiomeric excess of the recovered starting materials 49-56.

A 10-25 mL two-neck oven-dried round-bottomed flask containing a magnetic stirring bar was charged with the relevant anhydride (0.1 mmol), recrystallised 4-nitrobenzaldehyde (0.5-0.7 equiv.) followed by the relevant catalyst (5-10 mol%). The air was evacuated from the reaction vessel by placing the reaction flask under vacuum and backfilling several times with argon before being placed under an argon atmosphere (balloon). Methyl *tert*-butyl ester (0.1 M) was added *via* syringe to the reaction vessel. The resulting mixture was allowed to stir, at the temperature and, for the time as indicated in each specific case. The enantiomeric excesses of the unreacted starting materials were determined by CSP-HPLC after derivatisation of the anhydrides following the procedure as follow: the conversion of the reaction was determined by ^{1}H NMR spectroscopy using 4-iodoanisole (0.5-0.7 equiv.) as an internal standard and the reaction was immediately quenched by adding to the reaction mixture, *via* syringe, hplc grade MeOH (200 equiv.). The reaction was allowed to stir for 2 h, at room temperature, after which time the starting material anhydrides have been determined to be fully converted to the corresponding methyl hemiester opened form. The reaction mixture containing both hemiester and the crude mixture of carboxylic acid lactones products was cooled to 0 °C, followed by the addition *via* syringe of trimethylsilyldiazomethane (1.2 equiv., 2 M solution in Et_2O). The reaction was allowed to stir for 15 min at 0 °C. The excess of solvent was removed under reduced pressure and the crude residue was immediately subjected to flash column chromatography to isolate unreacted starting material (as its open bis-methyl ester derivative) and the major lactone diastereomer, eluting the mixture in gradient from 100% hexanes to 20% EtOAc in hexanes.

6. Characterisation data

Dimethyl (2*R*,3*S*)-2-methyl-3-phenylsuccinate (49)



Prepared according to general procedure VI, using anhydride **S5** (100.0 mg, 0.525 mmol), recrystallized 4-nitrobenzaldehyde (39.7 mg, 0.263 mmol), 4-iodoanisole (61.5 mg, 0.263 mmol) and catalyst **20** (14.1 mg, 0.026 mmol – 5 mol%) in dry MTBE (5.25 mL – 0.1 M). The reaction was allowed to stir for 168 h, quenched with MeOH (4.25 mL, 105.1 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (315 µL, 0.631 mmol) the unreacted starting material (**49**) was isolated by flash column chromatography (as its open bis-methyl ester opened form) as a colourless liquid (47.4 mg, 37%). TLC (hexanes:EtOAc, 9:1 *v/v*): $R_f = 0.31$; $[\alpha]_D^{20} = +118.6$ ($c = 0.07$, $CHCl_3$).

trans-**49**:

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: 11.71 min (minor enantiomer) and 12.72 min (major enantiomer).

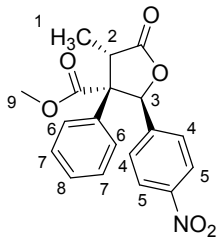
δ_H (400 MHz, $CDCl_3$): 7.34-7.24 (5 H, m, H-6, H-7 and H-8), 3.77 (1 H, d, *J* 11.3, H-5), 3.72 (3 H, s, H-3), 3.62 (3 H, s, H-4), 3.21-3.13 (1 H, dq, *J* 7.3, *J* 11.3, H-2), 0.95 (3 H, d, *J* 7.3, H-1).

δ_C (100 MHz, $CDCl_3$): 176.2 (C=O), 173.7 (C=O), 136.3 (q), 128.9, 128.4, 127.8, 54.1, 52.2, 52.0, 42.3, 15.4.

ν_{max} (neat)/cm^{-1}: 2953, 1730 (C=O), 1455, 1435, 1319, 1277, 1240, 1192, 1161, 1059, 1005, 735, 700.

HRMS (*m/z* - ESI): Found: 259.0944 $(M+Na)^+$ $C_{13}H_{16}NaO_4$ Requires: 259.0940.

Methyl 4-methyl-2-(4-nitrophenyl)-5-oxo-3-phenyltetrahydrofuran-3-carboxylate (57)



Prepared according to general procedure VI, using anhydride **S5** (100.0 mg, 0.525 mmol), recrystallized 4-nitrobenzaldehyde (39.7 mg, 0.263 mmol), 4-iodoanisole (61.5 mg, 0.263 mmol) and catalyst **20** (14.1 mg, 0.026 mmol – 5 mol%) in dry MTBE (5.25 mL – 0.1 M). The reaction was allowed to stir for 168 h to give a diastereomeric mixture of carboxylic acid lactones in a 95:5 (*major*:*others*) ratio, quenched with MeOH (4.25 mL, 105.1 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (125.2 μL, 0.250 mmol) the major diastereomer (**57**) was isolated by flash column chromatography as a white solid (75.2 mg, 40%). TLC (hexanes:EtOAc, 70:30 *v/v*): R_f = 0.39; $[\alpha]_D^{20}$ = +19.2 (*c* = 0.238, $CHCl_3$).

CSP-HPLC analysis. Chiralcel ODH (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 19.88 min (major enantiomer) and 29.75 min (minor enantiomer).

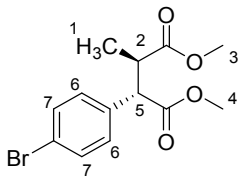
δ_H (400 MHz, $CDCl_3$): 7.90 (2 H, d, *J* 8.8, H-5), 7.20-7.07 (5 H, m, H-6, H-7 and H-8), 6.66 (2 H, d, *J* 8.8, H-4), 6.34 (1 H, s, H-3), 3.79 (3 H, s, H-9), 3.48 (1 H, q, *J* 7.6, H-2), 1.52 (3 H, d, *J* 7.6, H-1).

δ_C (100 MHz, $CDCl_3$): 176.8 (C=O), 171.8 (C=O), 147.6 (q), 141.9 (q), 135.3 (q), 128.6, 128.4, 127.7, 126.8, 122.7, 82.2, 64.0 (q), 52.8, 43.8, 13.2.

ν_{max} (neat)/cm^{-1}: 2935, 1781, 1730, 1603, 1521, 1436, 1346, 1315, 1272, 1250, 1221, 1174, 1043, 1021, 979, 861, 838, 718, 691.

HRMS (*m/z* - ESI): Found: 354.0975 $(M-H)^-$ $C_{19}H_{16}NO_6$ Requires: 354.0978.

Dimethyl (2*S*,3*R*)-2-(4-bromophenyl)-3-methylsuccinate (50)



Prepared according to general procedure VI, using anhydride **S10** (107.6 mg, 0.4 mmol), recrystallized 4-nitrobenzaldehyde (42.3 mg, 0.280 mmol), 4-iodoanisole (65.5 mg, 0.280 mmol) and catalyst **20** (10.7 mg, 0.02 mmol – 5 mol%) in dry MTBE (4.0 mL – 0.1 M). The reaction was allowed to stir for 3 days, quenched with MeOH (3.24 mL, 80.0 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (240 μL, 0.480 mmol) the unreacted starting material (*trans*-**50**) was isolated by flash column chromatography (as its open bis-methyl ester opened form) as a colourless liquid (38.6 mg, 31%). TLC (hexanes:EtOAc, 9:1 *v/v*): $R_f = 0.25$; $[\alpha]_D^{20} = +59.5$ ($c = 0.04$, $CHCl_3$).

trans-**50**:

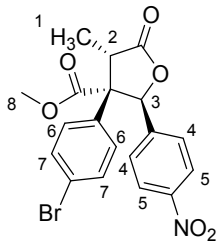
δ_H (400 MHz, $CDCl_3$): 7.46 (2 H, d, *J* 8.4, H-7), 7.14 (2 H, d, *J* 8.4, H-6), 3.74 (1 H, d, *J* 11.3, H-5), 3.72 (3 H, s, H-3), 3.62 (3 H, s, H-4), 3.17-3.09 (1 H, dq, *J* 7.3, *J* 11.3, H-2), 0.95 (3 H, d, *J* 7.3, H-1).

δ_C (100 MHz, $CDCl_3$): 175.8 (C=O), 173.2 (C=O), 135.3 (q), 132.0, 130.1, 121.8, 53.6, 52.3, 52.1, 42.2, 15.3.

ν_{max} (neat)/cm^{-1}: 2952, 1729 (C=O), 1488, 1434, 1312, 1273, 1238, 1193, 1161, 1072, 1009, 822, 769.

HRMS (*m/z* - ESI): Found: 337.0033 $(M+Na)^+$ $C_{13}H_{15}BrNaO_4$ Requires: 337.0045.

Methyl 3-(4-bromophenyl)-4-methyl-2-(4-nitrophenyl)-5-oxotetrahydrofuran-3-carboxylate (58)



Prepared according to general procedure VI, using anhydride **S10** (107.6 mg, 0.4 mmol), recrystallized 4-nitrobenzaldehyde (42.3 mg, 0.280 mmol), 4-iodoanisole (65.5 mg, 0.280 mmol) and catalyst **20** (10.7 mg, 0.02 mmol – 5 mol%) in dry MTBE (4.0 mL – 0.1 M). The reaction was allowed to stir for 3 days to give a diastereomeric mixture of carboxylic acid lactones in a 87.5:12.5 (*major*:*others*) ratio, quenched with MeOH (3.24 mL, 80.0 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (240 μL, 0.480 mmol) the major diastereomer (**58**) was isolated by flash column chromatography as a white solid (75.2 mg, 39%). TLC (hexanes:EtOAc, 70:30 *v/v*): R_f = 0.44; $[\alpha]_D^{20}$ = +21.1 (c = 0.189, $CHCl_3$).

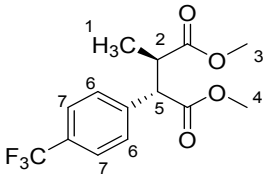
δ_H (400 MHz, $CDCl_3$): 7.98 (2 H, d, *J* 8.8, H-5), 7.26 (2 H, d, *J* 8.6, H-7), 7.22 (2 H, d, *J* 8.8, H-4), 6.54 (2 H, d, *J* 8.6, H-6), 6.33 (1 H, s, H-3), 3.79 (3 H, s, H-8), 3.42 (1 H, q, *J* 7.5, H-2), 1.51 (3 H, d, *J* 7.5, H-1).

δ_C (100 MHz, $CDCl_3$): 176.3 (C=O), 171.3 (C=O), 147.7 (q), 141.5 (q), 134.4 (q), 131.7, 128.5, 127.7, 122.9, 122.7 (q), 81.8, 63.7 (q), 52.9, 43.8, 13.2.

ν_{max} (neat)/cm^{-1}: 2920, 1776, 1731, 1605, 1517 1493, 1452, 1344, 1208, 1170, 1025, 1010, 857, 829, 780, 730, 695.

HRMS (*m/z* - APCI): Found: 432.0098 $(M-H)^-$ $C_{19}H_{15}BrNO_6$ Requires: 432.0088.

Dimethyl (2*R*,3*S*)-2-methyl-3-(4-(trifluoromethyl)phenyl)succinate (51)



Prepared according to general procedure VI, using anhydride **S15** (103.3 mg, 0.4 mmol), recrystallized 4-nitrobenzaldehyde (42.3 mg, 0.280 mmol), 4-iodoanisole (65.5 mg, 0.280 mmol) and catalyst **20** (10.7 mg, 0.02 mmol – 5 mol%) in dry MTBE (4.0 mL – 0.1 M). The reaction was allowed to stir for 2 days, quenched with MeOH (3.24 mL, 80.0 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (240 μL, 0.480 mmol) the unreacted starting material (*trans*-**51**) was isolated by flash column chromatography (as its open bis-methyl ester opened form) as a colourless liquid (42.3 mg, 35%). TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.28 (*trans*), R_f = 0.36 (*cis*); $[\alpha]_D^{20}$ = +149.2 (*c* = 0.05, $CHCl_3$).

trans-**51**:

δ_H (400 MHz, $CDCl_3$): 7.60 (2 H, d, *J* 8.1, H-7), 7.39 (2 H, d, *J* 8.1, H-6), 3.86 (1 H, d, *J* 11.2, H-5), 3.73 (3 H, s, H-3), 3.64 (3 H, s, H-4), 3.23-3.15 (1 H, dq, *J* 7.3, *J* 11.3, H-2), 0.96 (3 H, d, *J* 7.3, H-1).

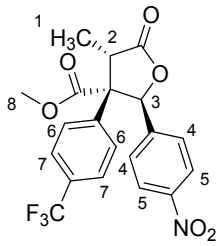
δ_C (100 MHz, $CDCl_3$): 175.7 (C=O), 173.0 (C=O), 140.3 (q), 130.1 (q) (q, ^2J 32.4 Hz), 128.9, 125.8 (q, ^3J 3.5 Hz), 123.9 (q) (q, ^1J 272.1 Hz), 53.9, 52.4, 52.1, 42.2, 15.3.

δ_F (376.5 MHz, $CDCl_3$): - 62.69.

ν_{max} (neat)/cm^{-1}: 2956, 1732 (C=O), 1619, 1459, 1436, 1421, 1322, 1278, 1244, 1161, 1122, 1066, 1018, 836, 602.

HRMS (*m/z* - APCI): Found: 305.0985 $(M+H)^+$ $C_{14}H_{16}F_3O_4$ Requires: 305.0995.

Methyl 4-methyl-2-(4-nitrophenyl)-5-oxo-3-(4-(trifluoromethyl)phenyl) tetrahydrofuran-3-carboxylate (59)



Prepared according to general procedure VI, using anhydride **S15** (103.3 mg, 0.4 mmol), recrystallized 4-nitrobenzaldehyde (42.3 mg, 0.280 mmol), 4-iodoanisole (65.5 mg, 0.280 mmol) and catalyst **20** (10.7 mg, 0.02 mmol – 5 mol%) in dry MTBE (4.0 mL – 0.1 M). The reaction was allowed to stir for 2 days to give a diastereomeric mixture of carboxylic acid lactones in a 83:17 (*major*:*others*) ratio, quenched with MeOH (3.24 mL, 80.0 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (240 μL, 0.480 mmol) the major diastereomer (**59**) was isolated by flash column chromatography as a white solid (72.5 mg, 43%). TLC (hexanes:EtOAc, 70:30 *v/v*): R_f = 0.41; $[\alpha]_D^{20}$ = +24.5 (c = 0.268, $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 7.95 (2 H, d, *J* 8.8, H-5), 7.39 (2 H, d, *J* 8.4, H-7), 7.21 (2 H, d, *J* 8.8, H-4), .39 (2 H, d, *J* 8.4, H-6), 6.37 (1 H, s, H-3), 3.81 (3 H, s, H-8), 3.48 (1 H, q, *J* 7.5, H-2), 1.54 (3 H, d, *J* 7.5, H-1).

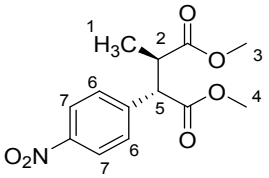
δ_C (100 MHz, $CDCl_3$): 176.1 (C=O), 171.1 (C=O), 147.8 (q), 141.3 (q), 139.4 (q), 130.7 (q) (q, ^2J 32.6 Hz), 127.6, 127.4, 125.5 (q, ^3J 3.6 Hz), 123.4 (q) (q, ^1J 272.5 Hz), 81.8, 64.0 (q), 53.1, 43.8.

δ_F (376.5 MHz, $CDCl_3$): - 62.91.

ν_{max} (neat)/cm^{-1}: 2956, 1786, 1735, 1608, 1522, 1349, 1325, 1220, 1168, 1125, 1069, 1026, 1014, 859, 751, 713.

HRMS (*m/z* - ESI): Found: 422.0872 $(M-H)^-$ $C20H15F_3NO_6$ Requires: 422.0856.

Dimethyl (2*R*,3*S*)-2-methyl-3-(4-nitrophenyl)succinate (52)



Prepared according to general procedure VI, using anhydride **S19** (30.5 mg, 0.129 mmol), recrystallized 4-nitrobenzaldehyde (13.7 mg, 0.091 mmol), 4-iodoanisole (21.2 mg, 0.091 mmol) and catalyst **20** (3.5 mg, 0.0068 mmol – 5 mol%) in dry MTBE (1.3 mL – 0.1 M). The reaction was allowed to stir for 1 days, quenched with MeOH (1.05 mL, 25.94 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (78 μL, 0.155 mmol) the unreacted starting material (*trans*-**52**) was isolated by flash column chromatography (as its open bis-methyl ester opened form) as a colourless liquid (12.3 mg, 34%). TLC (hexanes:EtOAc, 9:1 *v/v*): $R_f = 0.16$; $[\alpha]_D^{20} = +52.7$ ($c = 0.03$, $CHCl_3$).

trans-**52**:

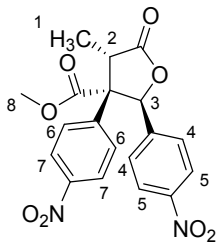
δ_H (400 MHz, $CDCl_3$): 8.16 (2 H, d, *J* 8.8, H-7), 7.52 (2 H, d, *J* 8.8, H-6), 3.93 (1 H, d, *J* 10.9, H-5), 3.69 (3 H, s, H-3), 3.45 (3 H, s, H-4), 3.31-3.23 (1 H, dq, *J* 6.9, *J* 10.9, H-2), 1.32 (3 H, d, *J* 6.9, H-1).

δ_C (100 MHz, $CDCl_3$): 173.9 (C=O), 171.6 (C=O), 143.98 (q), 130.3 (q), 129.4, 123.7, 54.4, 52.6, 51.8, 43.6, 16.5.

ν_{max} (neat)/cm^{-1}: 2967, 1727 (C=O), 1596, 1517, 1454, 1438, 1346, 1318, 1291, 1197, 1153, 1107, 1057, 1001, 973, 860, 737, 691.

HRMS (*m/z* - ESI): Found: 304.0781 $(M+H)^+$ $C_{13}H_{15}NNaO_6$ Requires: 304.0791.

Methyl 4-methyl-2,3-bis(4-nitrophenyl)-5-oxotetrahydrofuran-3-carboxylate (60)



Prepared according to general procedure VI, using anhydride **S19** (30.5 mg, 0.129 mmol), recrystallized 4-nitrobenzaldehyde (13.7 mg, 0.091 mmol), 4-iodoanisole (21.2 mg, 0.091 mmol) and catalyst **20** (3.5 mg, 0.0068 mmol – 5 mol%) in dry MTBE (1.3 mL – 0.1 M). The reaction was allowed to stir for 1 days to give a diastereomeric mixture of carboxylic acid lactones in a 87.5:12.5 (*major*:*others*) ratio, quenched with MeOH (1.05 mL, 25.94 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (78 μL, 0.155 mmol) the major diastereomer (**60**) was isolated by flash column chromatography as a white solid (19.8 mg, 38%). TLC (hexanes:EtOAc, 70:30 *v/v*): $R_f = 0.27$; $[\alpha]_D^{20} = +21.6$ ($c = 0.05$, $CHCl_3$).

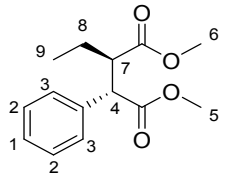
δ_H (400 MHz, $CDCl_3$): 8.00-7.96 (4 H, m, H-5 and H-7), 7.24 (2 H, d, *J* 8.6, H-6), 6.88 (2 H, d, *J* 8.8, H-4), 6.4 (1 H, d, H-3), 3.83 (3 H, s, H-8), 3.49 (1 H, q, *J* 7.5, H-2), 1.55 (3 H, d, *J* 7.5, H-1).

δ_C (151 MHz, $CDCl_3$): 175.7 (C=O), 170.7 (C=O), 147.9 (q), 147.4 (q), 142.5 (q), 141.0 (q), 128.1, 127.5, 123.6, 123.2, 81.7, 64.0 (q), 53.2, 44.0, 13.3

ν_{max} (neat)/cm^{-1}: 2921, 1785, 1734, 1606, 1517, 1348, 1221, 1171, 1026, 1012, 861, 724, 697.

HRMS (*m/z* - ESI): Found: 399.0839 $(M-H)^-$ $C_{19}H_{15}N_2O_8$ Requires: 399.0833.

Dimethyl 2-ethyl-3-phenylsuccinate (54)



Prepared according to general procedure VI, using anhydride **S22** (98.9 mg, 0.484 mmol), recrystallized 4-nitrobenzaldehyde (51.2 mg, 0.339 mmol), 4-iodoanisole (79.3 mg, 0.581 mmol) and catalyst **20** (13.0 mg, 0.024 mmol – 5 mol%) in dry MTBE (4.8 mL – 0.1 M). The reaction was allowed to stir for 5 days, quenched with MeOH (3.92 mL, 96.8 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (290 μL, 0.580 mmol) the unreacted starting material (*trans*-**54**) was isolated by flash column chromatography (as its open bis-methyl ester opened form) as a colourless liquid (41.2 mg, 34%). TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.46 (*cis*), R_f = 0.31 (*trans*); $[\alpha]_D^{20}$ = +243.6 (*c* = 0.123, $CHCl_3$).

trans-**54**:

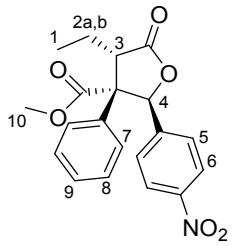
δ_H (400 MHz, $CDCl_3$): 7.28-7.19 (5 H, m, H-1, H-2 and H-3), 3.80 (1 H, d, *J* 11.4, H-4), 3.67 (3 H, s, H-6), 3.54 (3 H, s, H-5), 3.07-3.01 (1 H, m, H-7), 1.42-1.32 (1 H, m, H-8), 1.27-1.16 (1 H, m, H-8), 0.71 (3 H, t, *J* 7.5, H-9).

δ_C (100 MHz, $CDCl_3$): 175.4 (C=O), 173.7 (C=O), 136.4 (q), 128.9, 128.4, 127.7, 52.4, 52.2, 51.8, 48.8, 22.5, 10.5.

ν_{max} (neat)/cm^{-1}: 2953, 1730, 1454, 1434, 1256, 1235, 1160, 747, 734, 700.

HRMS (*m/z* - ESI): Found: 273.1091 $(M+Na)^+$ $C_{14}H_{18}NaO_4$ Requires: 273.1097.

Methyl 4-ethyl-2-(4-nitrophenyl)-5-oxo-3-phenyltetrahydrofuran-3-carboxylate (62)



Prepared according to general procedure VI, using anhydride **62** (98.9 mg, 0.484 mmol), recrystallized 4-nitrobenzaldehyde (51.2 mg, 0.339 mmol), 4-iodoanisole (79.3 mg, 0.581 mmol) and catalyst **20** (13.0 mg, 0.024 mmol – 5 mol%) in dry MTBE (4.8 mL – 0.1 M). The reaction was allowed to stir for 5 days to give a diastereomeric mixture of carboxylic acid lactones in a 91:9 (*major*:*others*) ratio, quenched with MeOH (3.92 mL, 96.8 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (290 μL, 0.580 mmol) the major diastereomer (**62**) was isolated by flash column chromatography as a white solid (76.6 mg, 43%). M.p. 152-154 °C. TLC (hexanes:EtOAc, 4:1 *v/v*): R_f = 0.34; $[\alpha]_D^{20}$ = +63.2 (*c* = 0.05, $CHCl_3$).

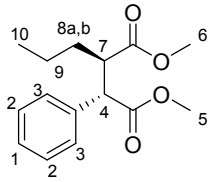
δ_H (400 MHz, $CDCl_3$): 7.91 (2 H, d, *J* 8.8, H-6), 7.18-7.15 (3 H, m, H-8 and H-9), 7.12-7.08 (2 H, m, H-7), 6.66 (2 H, d, *J* 8.8, H-5), 6.33 (1 H, s, H-4), 3.78 (1 H, s, H-3), 3.25 (1 H, dd, *J* 4.7, 10.9, H-3), 1.98-1.89 (1 H, m, H-2a), 1.87-1.77 (1 H, m, H-2b), 1.26 (3 H, t, *J* 7.4, H-1),

δ_C (100 MHz, $CDCl_3$): 175.4 (C=O), 171.8 (C=O), 147.5 (q), 142.0 (q), 135.5 (q), 128.5, 128.3, 127.7, 126.9, 122.7, 82.3, 64.5 (q), 52.7, 50.0, 21.4, 11.3.

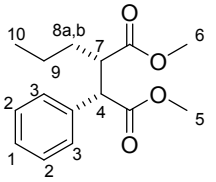
ν_{max} (neat)/cm^{-1}: 2945, 1770, 1743, 1608, 1516, 1435, 1348, 1250, 1202, 1167, 1125, 1072, 1011, 979, 875, 857, 846, 760, 715, 704, 693, 585.

HRMS (*m/z* - APCI): Found: 370.1288 $(M+H)^+$ $C_{20}H_{20}NO_6$ Requires: 370.1285.

Dimethyl 2-phenyl-3-propylsuccinate (55)



trans-**55**



cis-**55**

Prepared according to general procedure VI, using anhydride **S25** (148.6 mg, 0.680 mmol), recrystallized 4-nitrobenzaldehyde (72.0 mg, 0.476 mmol), 4-iodoanisole (111.5 mg, 0.476 mmol) and catalyst **20** (10.7 mg, 0.02 mmol – 5 mol%) in dry MTBE (4.0 mL – 0.1 M). The reaction was allowed to stir for 5 days, quenched with MeOH (5.5 mL, 136.17 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (408 µL, 0.817 mmol) the unreacted starting material (*trans*-**55**) was isolated by flash column chromatography (as its open bis-methyl ester opened form) as a colourless liquid (73.2 mg, 41%). TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.56 (*cis*), R_f = 0.36 (*trans*); $[\alpha]_D^{20}$ = +254.8 (*c* = 0.213, $CHCl_3$).

trans-**55**:

δ_H (400 MHz, $CDCl_3$): 7.36-7.26 (5 H, m, H-1, H-2 and H-3), 3.85 (1 H, d, *J* 11.6, H-4), 3.73 (3 H, s, H-6), 3.61 (3 H, s, H-5), 3.17-3.11 (1 H, m, H-7), 1.32-1.24 (3 H, m, H-9 and H-8a), 1.18-1.05 (1 H, m, H-8b), 0.74 (3 H, t, *J* 6.7, H-10).

δ_C (100 MHz, $CDCl_3$): 175.6 (C=O), 173.7 (C=O), 136.4 (q), 128.9, 128.4, 127.7, 53.0, 52.2, 51.8, 47.6, 31.7, 19.6, 13.8.

cis-**55**:

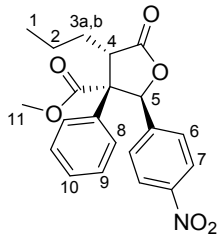
δ_H (400 MHz, $CDCl_3$): 7.32-7.23 (5 H, m, H-1, H-2 and H-3), 3.77 (1 H, d, *J* 11.2, H-4), 3.66 (3 H, s, H-6), 3.35 (3 H, s, H-5), 3.25-3.18 (1 H, m, H-7), 1.72-1.63 (1 H, m, H-8a), 1.58-1.49 (1 H, m, H-8b), 1.37-1.25 (2 H, m, H-9), 0.92 (3 H, t, *J* 7.4, H-10).

δ_C (100 MHz, $CDCl_3$): 174.0 (C=O), 172.8 (C=O), 136.4 (q), 128.5, 128.3, 127.7, 54.3, 52.2, 51.3, 49.6, 33.9, 20.7, 13.8.

ν_{max} (neat)/cm^{-1}: 2955, 1730, 1434, 1328, 1239, 1160, 1003, 782, 735, 700.

HRMS (*m/z* - ESI): Found: 287.1259 $(M+Na)^+$ $C_{15}H_{20}NaO_4$ Requires: 287.1253.

Methyl 2-(4-nitrophenyl)-5-oxo-3-phenyl-4-propyltetrahydrofuran-3-carboxylate (63)



Prepared according to general procedure VI, using anhydride **S25** (148.6 mg, 0.680 mmol), recrystallized 4-nitrobenzaldehyde (72.0 mg, 0.476 mmol), 4-iodoanisole (111.5 mg, 0.476 mmol) and catalyst **20** (10.7 mg, 0.02 mmol – 5 mol%) in dry MTBE (6.8mL – 0.1 M). The reaction was allowed to stir for 5 days to give a diastereomeric mixture of carboxylic acid lactones in a 90:10 (*major*:*others*) ratio, quenched with MeOH (5.5 mL, 136.17 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (408 μL, 0.817 mmol) the major diastereomer (**63**) was isolated by flash column chromatography as a white solid (109.4 mg, 42%). M.p. 150-152 °C. TLC (hexanes:EtOAc, 4:1 *v/v*): R_f = 0.40; $[\alpha]_D^{20}$ = +79.6 (*c* = 0.05, $CHCl_3$).

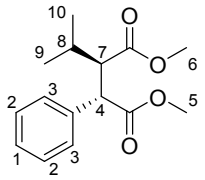
δ_H (400 MHz, $CDCl_3$): 7.90 (2 H, d, *J* 8.8, H-7), 7.19-7.15 (3 H, m, H-9 and H-10), 7.12-7.08 (2 H, m, H-8), 6.66 (2 H, d, *J* 8.8, H-6), 6.33 (1 H, s, H-5), 3.78 (3 H, s, H-11), 3.34 (1 H, dd, *J* 4.0, 10.6, H-4), 1.94-1.84 (1 H, m, H-3a), 1.84-1.74 (1 H, m, H-3b), 1.69-1.53 (2 H, m, H-2), 1.02 (3 H, t, *J* 6.9, H-1).

δ_C (100 MHz, $CDCl_3$): 175.5 (C=O), 171.8 (C=O), 147.5 (q), 142.0 (q), 135.5 (q), 128.5, 128.3, 127.7, 126.9, 122.7, 82.2, 64.5 (q), 52.7, 48.3, 29.9, 19.8, 13.8.

ν_{max} (neat)/cm^{-1}: 2947, 1771, 1744, 1664, 1595, 1518, 1458, 1434, 1349, 1204, 1167, 857, 716, 560.

HRMS (*m/z* - APCI): Found: 384.1454 $(M+H)^+$ $C_{21}H_{22}NO_6$ Requires: 384.1441.

Dimethyl 2-isopropyl-3-phenylsuccinate (56)



Prepared according to general procedure VI, using anhydride **S28** (90.8 mg, 0.416 mmol), recrystallized 4-nitrobenzaldehyde (44.0 mg, 0.291 mmol), 4-iodoanisole (68.2 mg, 0.291 mmol) and catalyst **20** (11.2 mg, 0.021 mmol – 5 mol%) in dry MTBE (4.2 mL – 0.1 M). The reaction was allowed to stir for 6 days, quenched with MeOH (3.37 mL, 83.2 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (250 µL, 0.499 mmol) the unreacted starting material (*trans*-**56**) was isolated by flash column chromatography (as its open bis-methyl ester opened form) as a colourless liquid (50.2 mg, 46%). TLC (hexanes:EtOAc, 9:1 *v/v*): $R_f = 0.33$ (*trans*); $[\alpha]_D^{20} = +129.9$ ($c = 0.145$, $CHCl_3$).

trans-**56**:

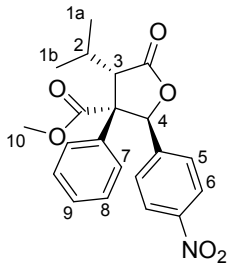
δ_H (400 MHz, $CDCl_3$): 7.35-7.27 (5 H, m, H-1, H-2 and H-3), 3.97 (1 H, d, *J* 11.9, H-4), 3.72 (3 H, s, H-6), 3.60 (3 H, s, H-5), 3.14 (1 H, dd, *J* 3.05, 11.9, H-7), 1.56-1.48 (1 H, m, H-8), 0.93 (3 H, d, *J* 6.9, H-9), 0.79 (3 H, d, *J* 6.9, H-10).

δ_C (100 MHz, $CDCl_3$): 173.93 (C=O), 173.91 (C=O), 136.5 (q), 128.9, 128.4, 127.7, 53.3, 52.2, 51.6, 51.4, 26.7, 22.0, 16.8.

ν_{max} (neat)/cm^{-1}: 2958, 1729, 1454, 1435, 1286, 1259, 1235, 1158, 1006, 734, 700.

HRMS (*m/z* - ESI): Found: 287.1252 $(M+Na)^+$ $C_{15}H_{20}NaO_4$ Requires: 287.1253.

Methyl 4-isopropyl-2-(4-nitrophenyl)-5-oxo-3-phenyltetrahydrofuran-3-carboxylate (64)



Prepared according to general procedure VI, using anhydride **S28** (90.8 mg, 0.416 mmol), recrystallized 4-nitrobenzaldehyde (44.0 mg, 0.291 mmol), 4-iodoanisole (68.2 mg, 0.291 mmol) and catalyst **20** (11.2 mg, 0.021 mmol – 5 mol%) in dry MTBE (4.2 mL – 0.1 M). The reaction was allowed to stir for 6 days to give a diastereomeric mixture of carboxylic acid lactones in a 86:14 (*major*:*others*) ratio, quenched with MeOH (3.37 mL, 83.2 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (250 μL, 0.499 mmol) the major diastereomer (**64**) was isolated by flash column chromatography as a white solid (54.6 mg, 34%). TLC (hexanes:EtOAc, 4:1 *v/v*): $R_f = 0.35$; $[\alpha]_D^{20} = +38.8$ ($c = 0.05$, $CHCl_3$).

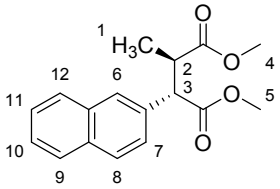
δ_H (400 MHz, $CDCl_3$): 7.89 (2 H, d, *J* 8.9, H-6), 7.18 (2 H, d, *J* 8.7, H-7), 7.13-7.05 (3 H, m, H-8 and H-9), 6.65 (2 H, d, *J* 8.9, H-5), 6.39 (1 H, s, H-4), 3.82 (3 H, s, H-10), 3.37 (1 H, d, *J* 2.8, H-3), 2.29-2.22 (1 H, m, H-2), 1.33 (1 H, d, *J* 6.8, H-1a), 1.22 (1 H, d, *J* 7.0, H-1b).

δ_C (100 MHz, $CDCl_3$): 174.8 (C=O), 172.0 (C=O), 147.4 (q), 142.4 (q), 136.8 (q), 128.4, 128.1, 127.5, 126.7, 122.6, 82.9, 64.4 (q), 55.4, 52.7, 29.0, 23.0, 18.7.

ν_{max} (neat)/cm^{-1}: 2920, 1771, 1729, 1522, 1349, 1263, 1199, 1162, 1099, 1028, 1013, 858, 848, 748, 701.

HRMS (*m/z* - ESI): Found: 406.1251 $(M+Na)^+$ $C_{21}H_{21}NNaO_6$ Requires: 406.1261.

Dimethyl 2-methyl-3-(naphthalen-2-yl)succinate (53)



Prepared according to general procedure VI, using anhydride **S33** (96.1 mg, 0.4 mmol), recrystallized 4-nitrobenzaldehyde (42.3 mg, 0.280 mmol), 4-iodoanisole (65.5 mg, 0.280 mmol) and catalyst **20** (10.7 mg, 0.02 mmol – 5 mol%) in dry MTBE (4.0 mL – 0.1 M). The reaction was allowed to stir for 6 days, quenched with MeOH (3.24 mL, 80.0 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (240 μL, 0.480 mmol) the unreacted starting material (*trans*-**53**) was isolated by flash column chromatography (as its open bis-methyl ester opened form) as a white solid (29.6 mg, 26%). TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.45 (*cis*), R_f = 0.36 (*trans*); $[\alpha]_D^{20}$ = +93.4 (*c* = 0.08, $CHCl_3$).

trans-**53**:

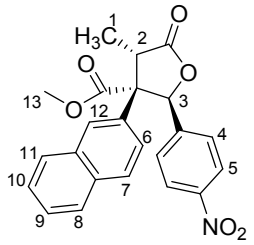
δ_H (400 MHz, $CDCl_3$): 8.83-8.81 (3 H, m, H-8, H-9 and H-12), 7.74 (1 H, bs, H-6), 7.52-7.45 (2 H, m, H-10 and H-11), 7.39-7.37 (1 H, m, H-7), 3.96 (1 H, d, *J* 11.2, H-3), 3.76 (3 H, s, H-4), 3.64 (3 H, s, H-5), 3.34-3.26 (1 H, m, *J* 7.2, 11.2, H-2), 0.99 (3 H, d, *J* 7.2, H-1).

δ_C (100 MHz, $CDCl_3$): 176.2 (C=O), 173.7 (C=O), 133.7 (q), 133.4 (q), 132.8 (q), 128.7, 127.82, 127.81, 127.7, 126.4, 126.1, 125.7, 54.3, 52.3, 52.0, 42.3, 15.5.

ν_{max} (neat)/cm^{-1}: 2955, 1728, 1454, 1433, 1375, 1316, 1281, 1233, 1170, 1154, 1063, 1007, 858, 817, 762.

HRMS (*m/z* - ESI): Found: 309.1096 $(M+Na)^+$ $C_{17}H_{18}NaO_4$ Requires: 309.1097.

Methyl 4-methyl-3-(naphthalen-2-yl)-2-(4-nitrophenyl)-5-oxotetrahydrofuran-3-carboxylate (61)



Prepared according to general procedure VI, using anhydride **S33** (96.1 mg, 0.4 mmol), recrystallized 4-nitrobenzaldehyde (42.3 mg, 0.280 mmol), 4-iodoanisole (65.5 mg, 0.280 mmol) and catalyst **20** (10.7 mg, 0.02 mmol – 5 mol%) in dry MTBE (4.0 mL – 0.1 M). The reaction was allowed to stir for 6 days to give a diastereomeric mixture of carboxylic acid lactones in a 90:10 (*major*:*others*) ratio, quenched with MeOH (3.24 mL, 80.0 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (240 μL, 0.480 mmol) the major diastereomer (**61**) was isolated by flash column chromatography as a white solid (52.4 mg, 40%). M.p. 155-157 °C. TLC (hexanes:EtOAc, 4:1 *v/v*): R_f = 0.18; $[\alpha]_D^{20}$ = +34.8 (*c* = 0.764, $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 7.84 (2 H, d, *J* 8.8, H-5), 7.75-7.68 (2 H, m, H-6 and H-7), 7.51-7.41 (4 H, m, H-8, H-9, H-10 and H-11), 7.20 (2 H, d, *J* 8.8, H-4), 6.41 (1 H, s, H-3), 6.39 (1 H, app. dd, H-12), 3.80 (3 H, s, H-13), 3.65 (1 H, q, *J* 7.4, H-2), 1.57 (3 H, d, *J* 7.4, H-1).

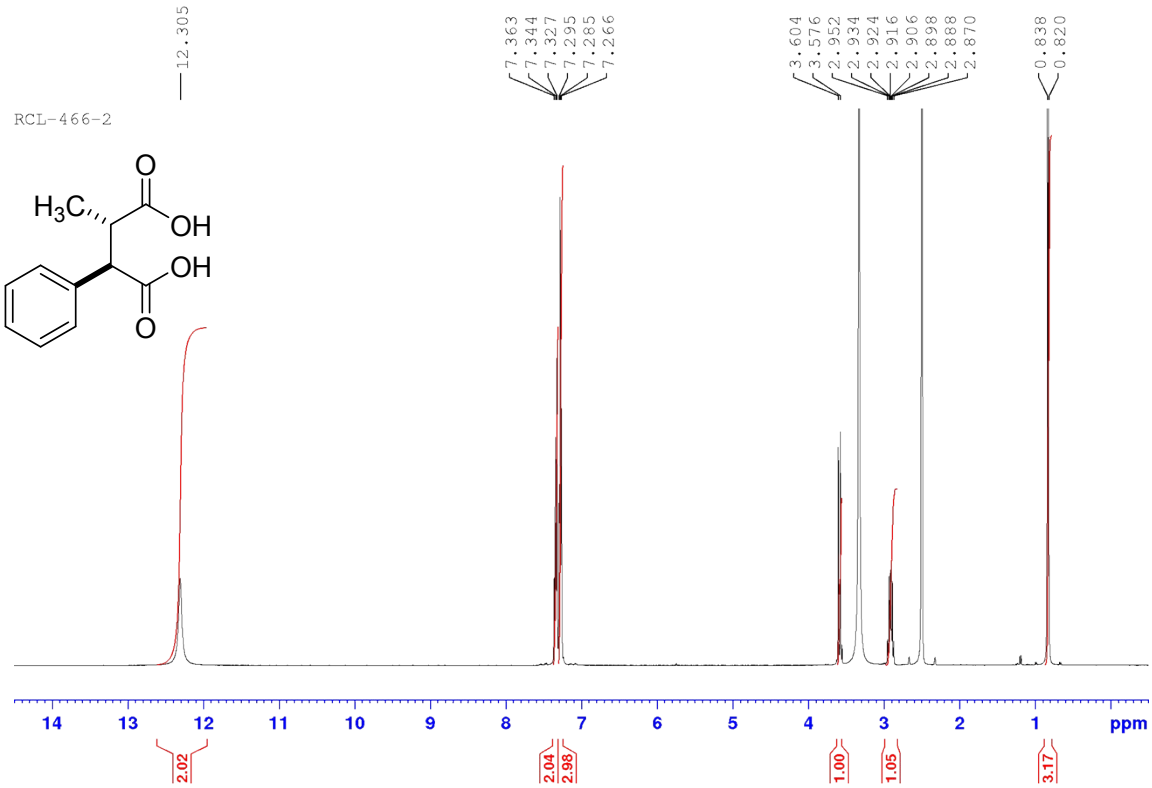
δ_C (151 MHz, $CDCl_3$): 176.8 (C=O), 171.8 (C=O), 147.6 (q), 141.7 (q), 132.65 (q), 132.62 (q), 132.3 (q), 128.08, 128.07, 127.9, 127.5, 127.1, 126.9, 125.5, 124.9, 122.8, 82.1, 64.1 (q), 52.9, 43.9, 13.3.

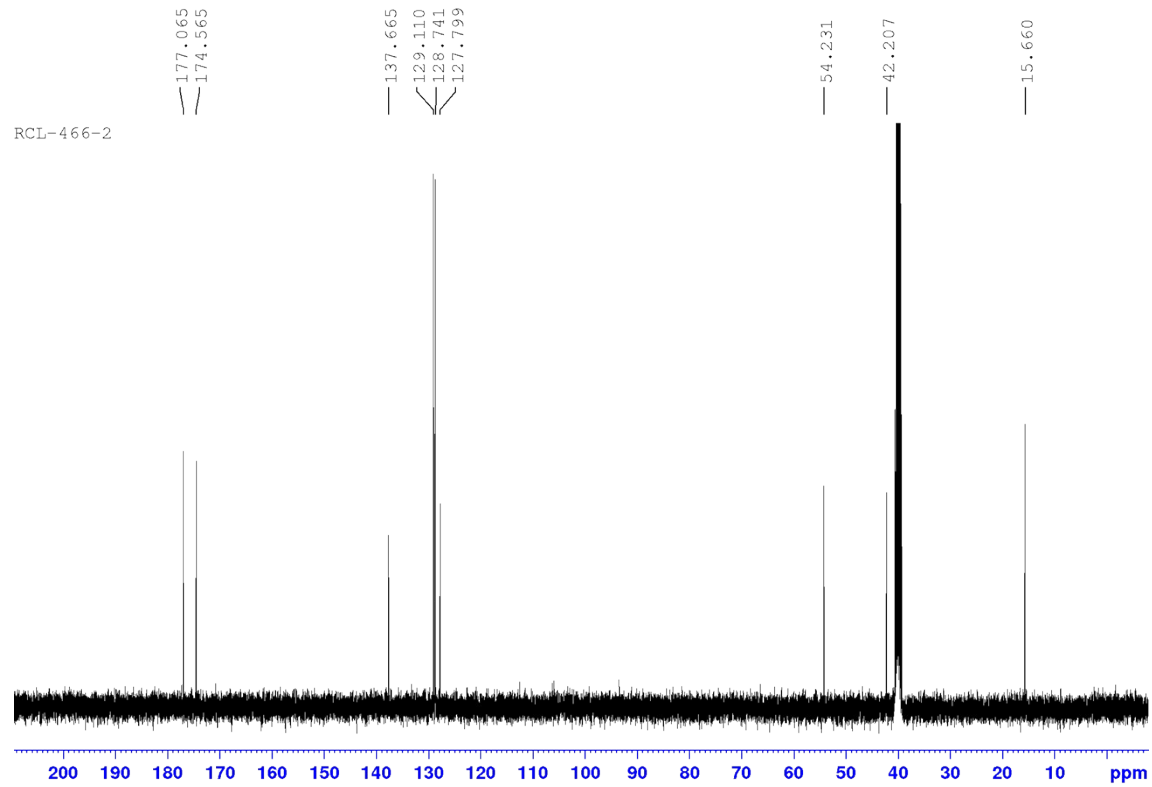
ν_{max} (neat)/cm^{-1}: 2950, 1784, 1721, 1607, 1518, 1463, 1437, 1351, 1253, 1200, 1162, 1013, 837, 787, 727, 745, 692.

HRMS (*m/z* - APCI): Found: 406.1292 $(M+H)^+$ $C_{23}H_{20}NO_6$ Requires: 406.1285

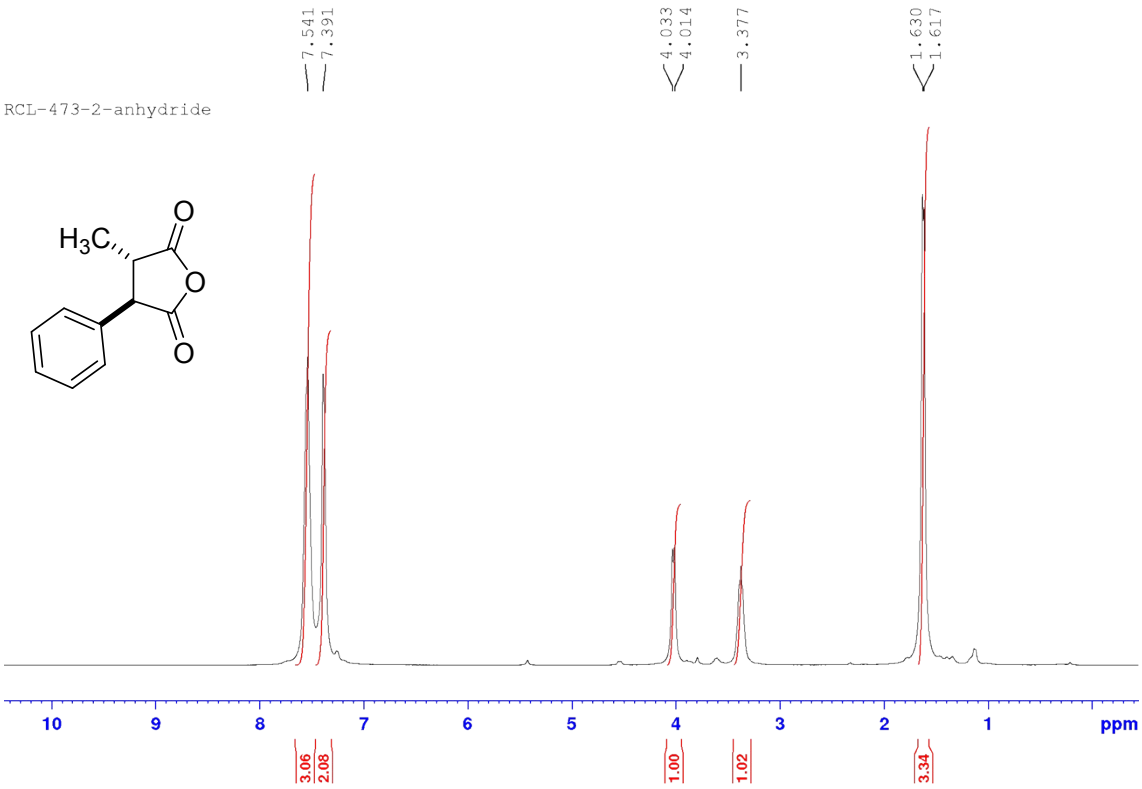
7. NMR spectra: ^{1}H and ^{13}C (anhydrides)

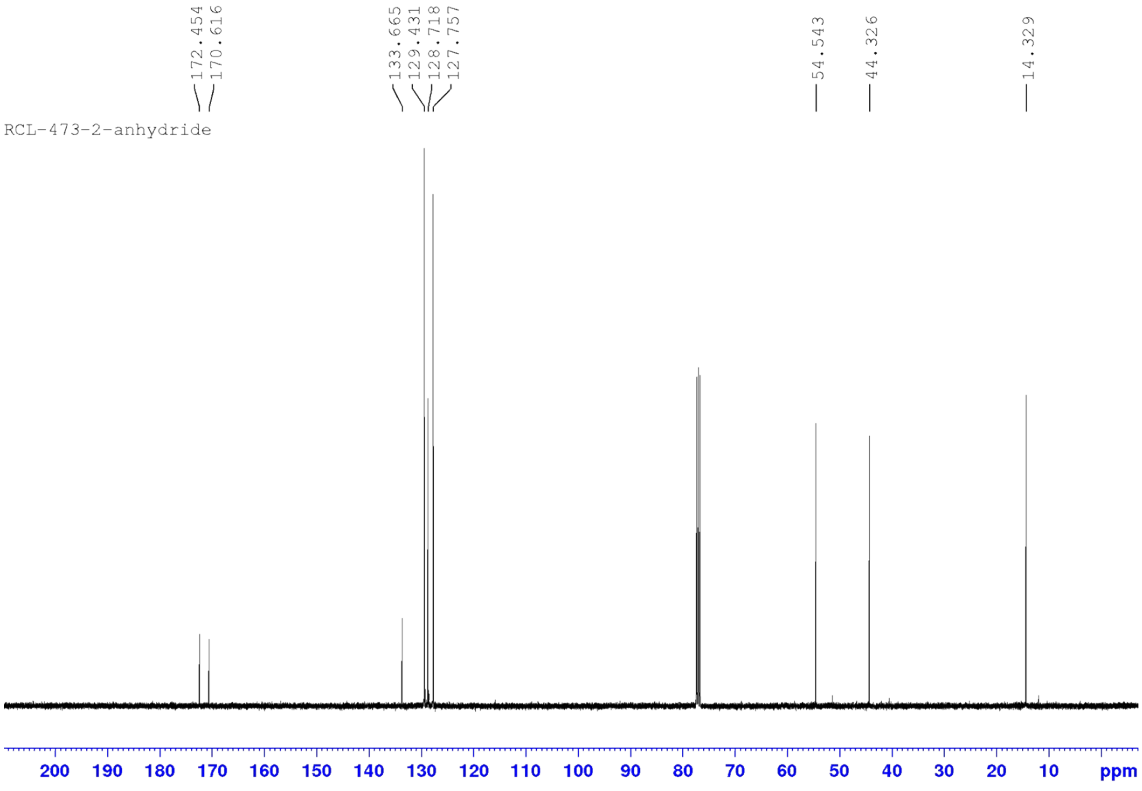
2-Methyl-3-phenylsuccinic acid (S4)



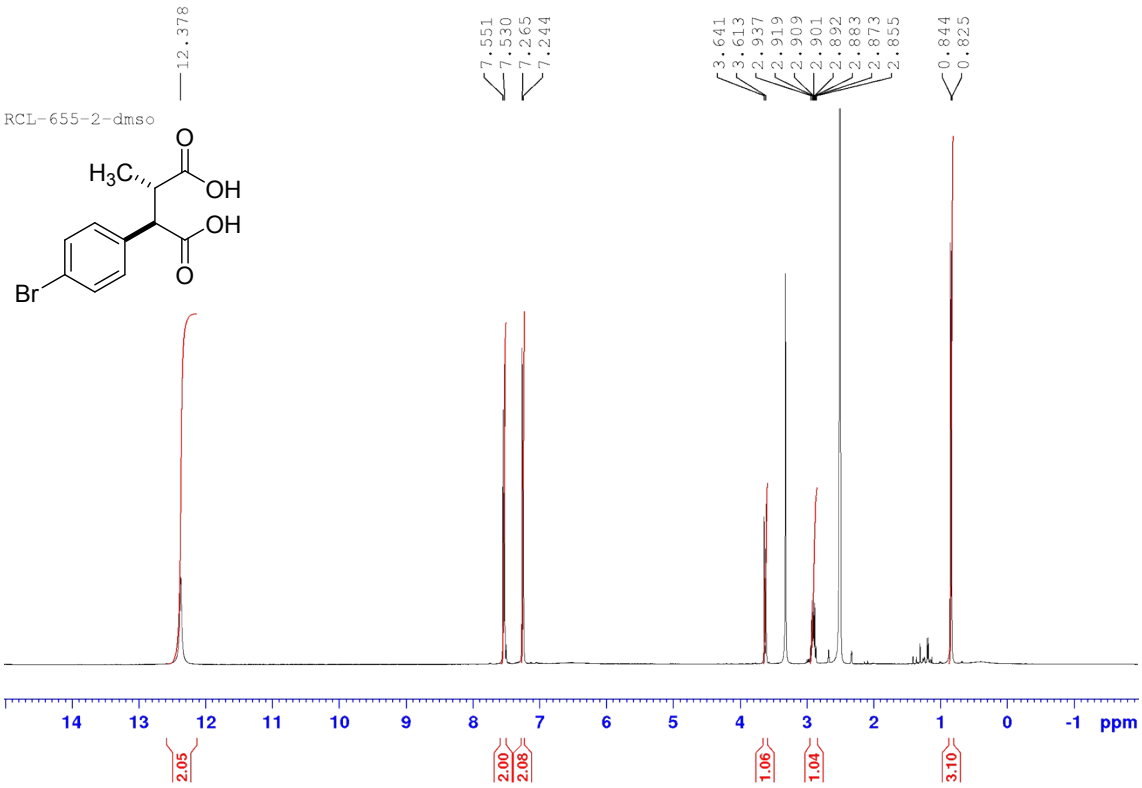


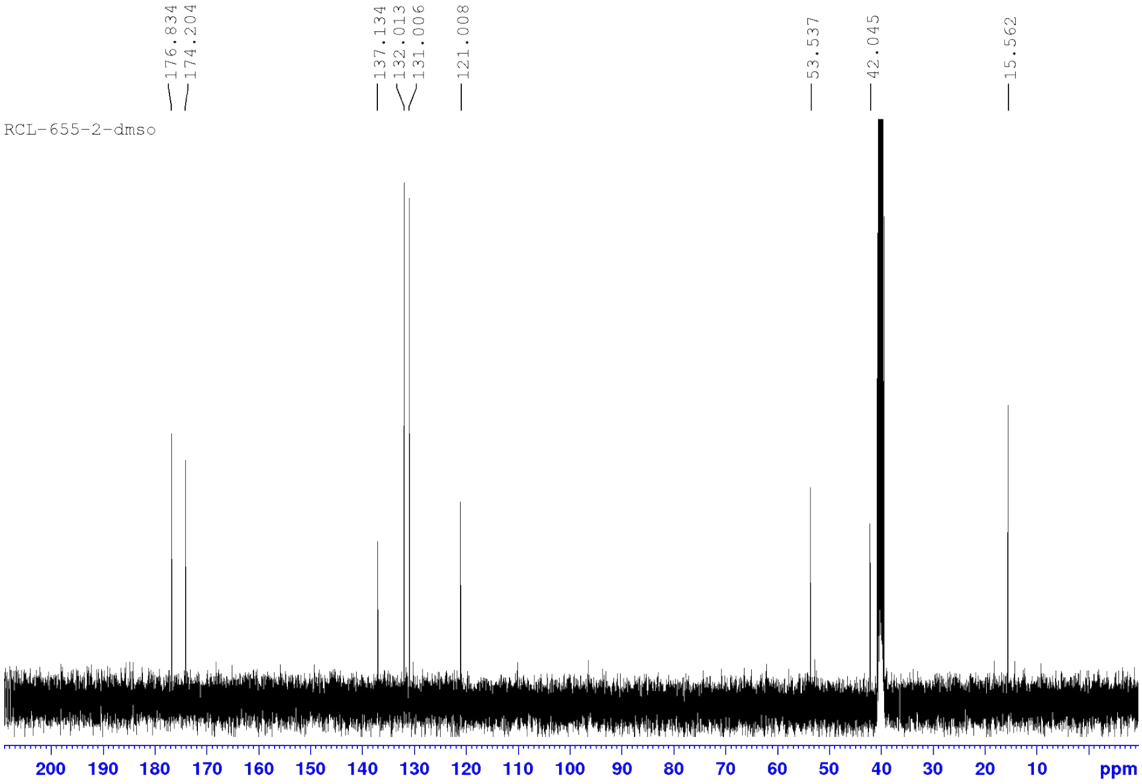
3-Methyl-4-phenyldihydrofuran-2,5-dione (S5)



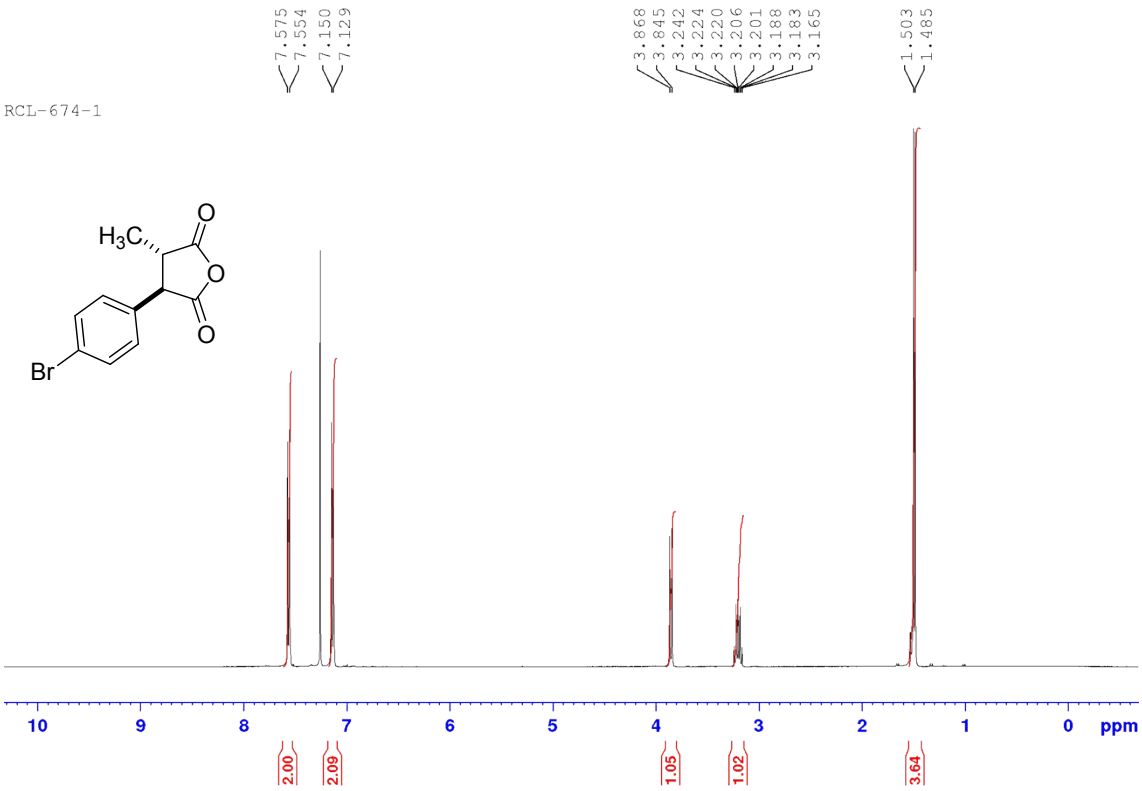


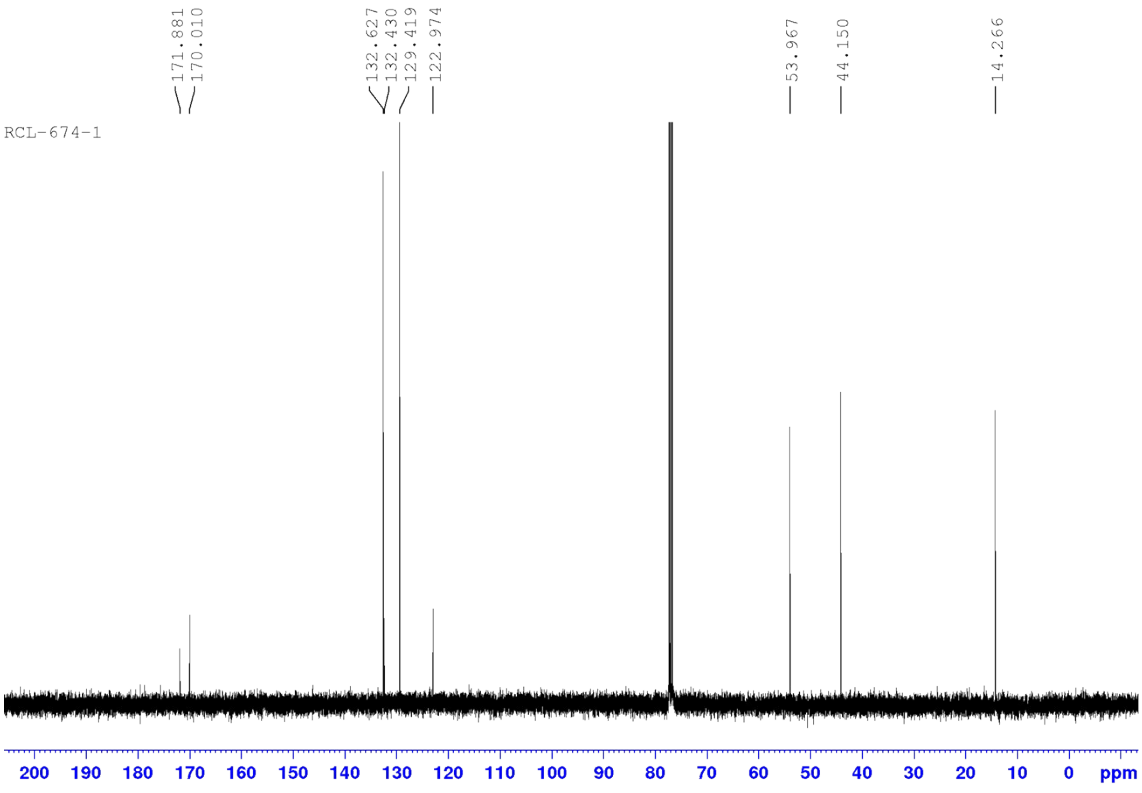
2-(4-bromophenyl)-3-methylsuccinic acid (S9)



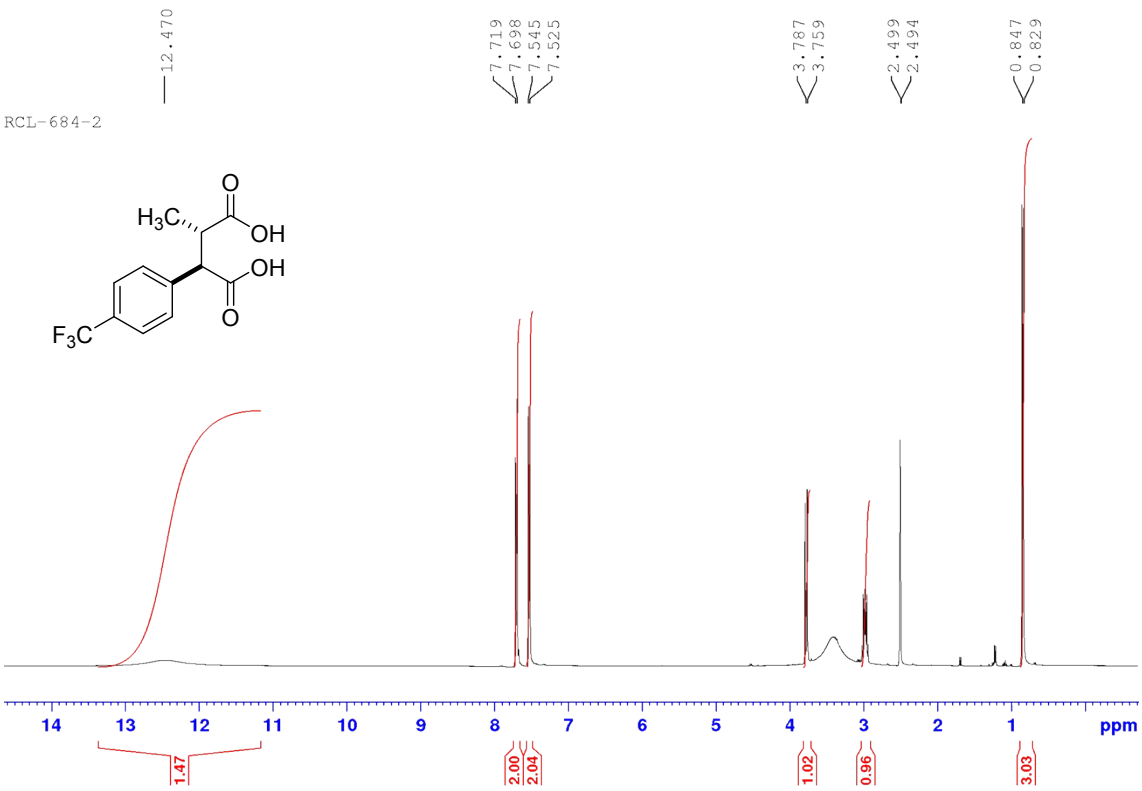


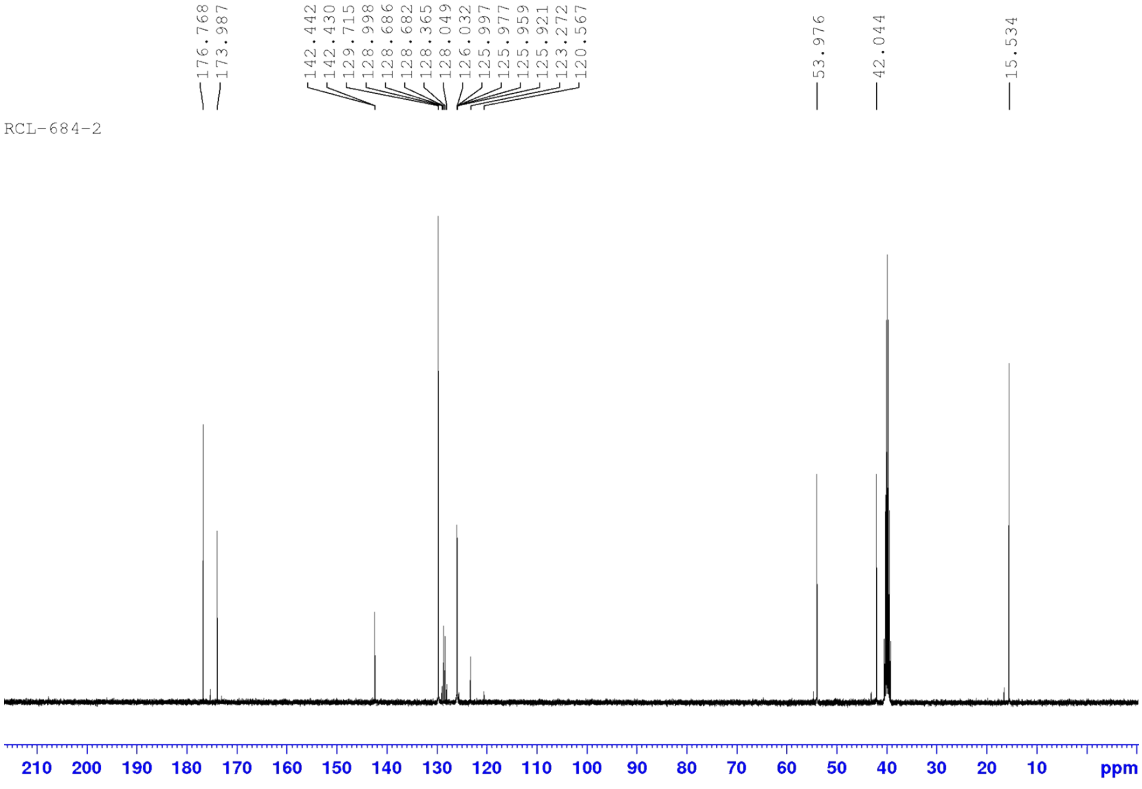
3-(4-Bromophenyl)-4-methyldihydrofuran-2,5-dione (S10)



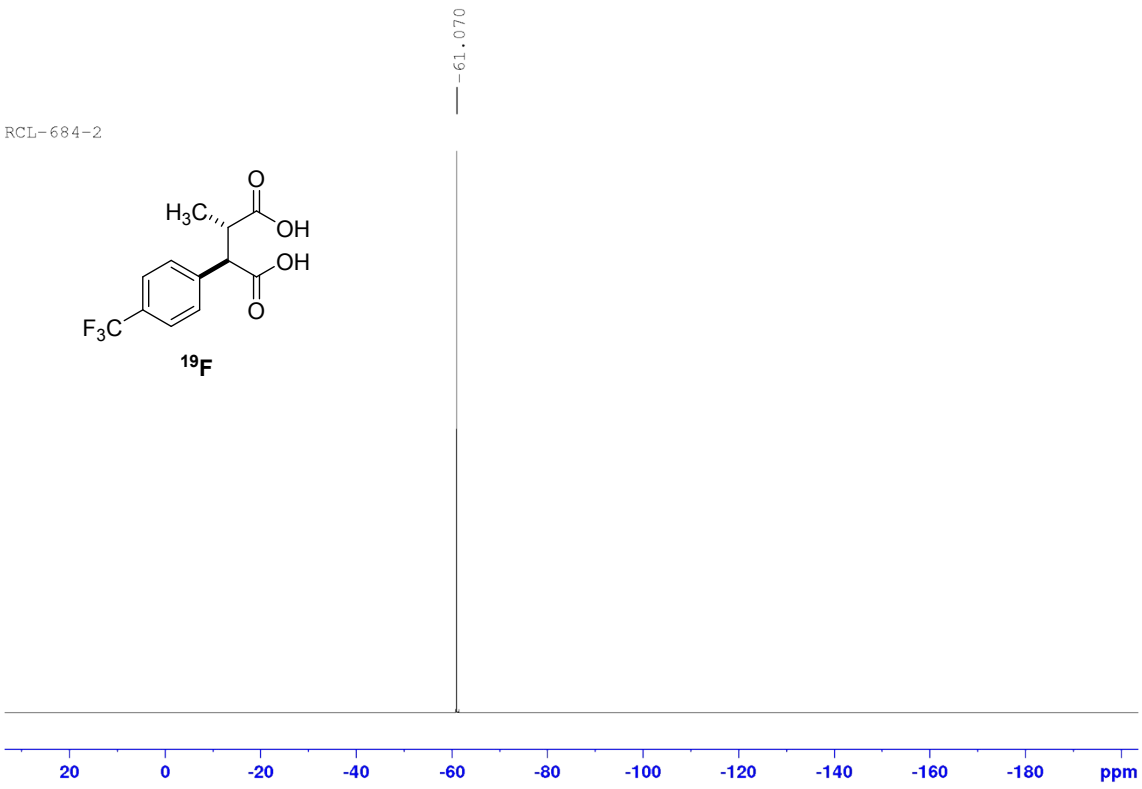


2-Methyl-3-(4-(trifluoromethyl)phenyl)succinic acid (S14)

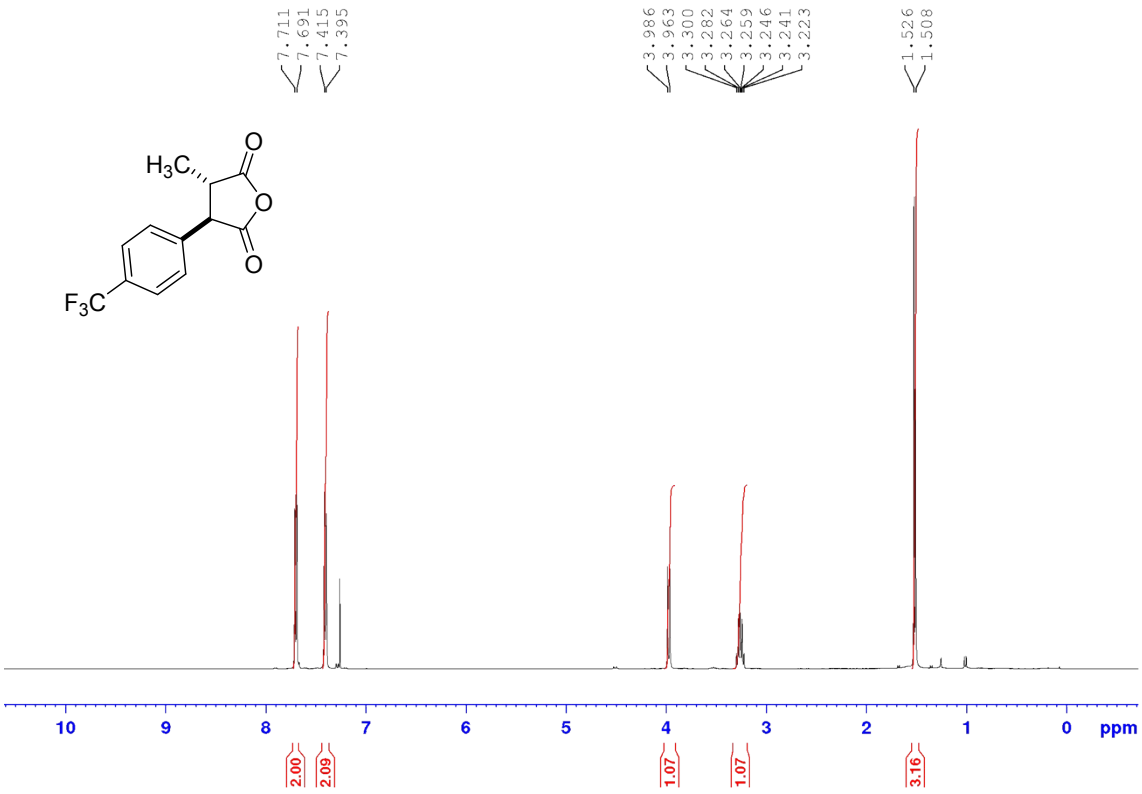


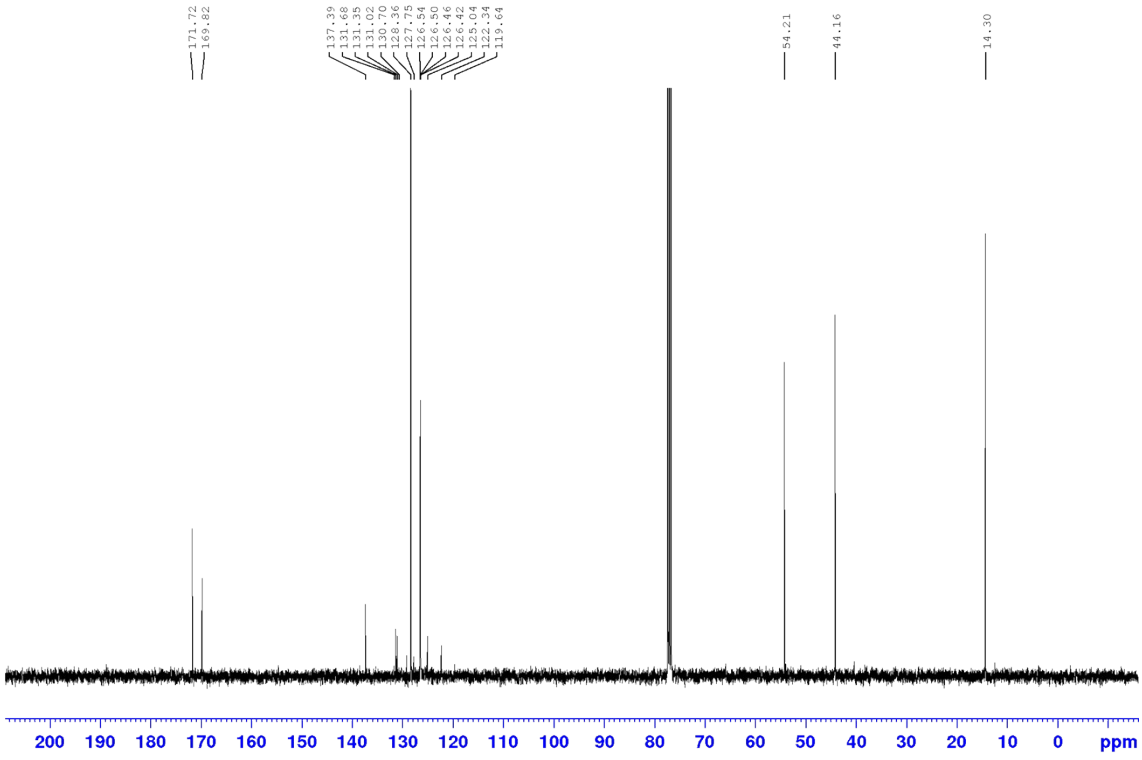


2-Methyl-3-(4-(trifluoromethyl)phenyl)succinic acid (S14)

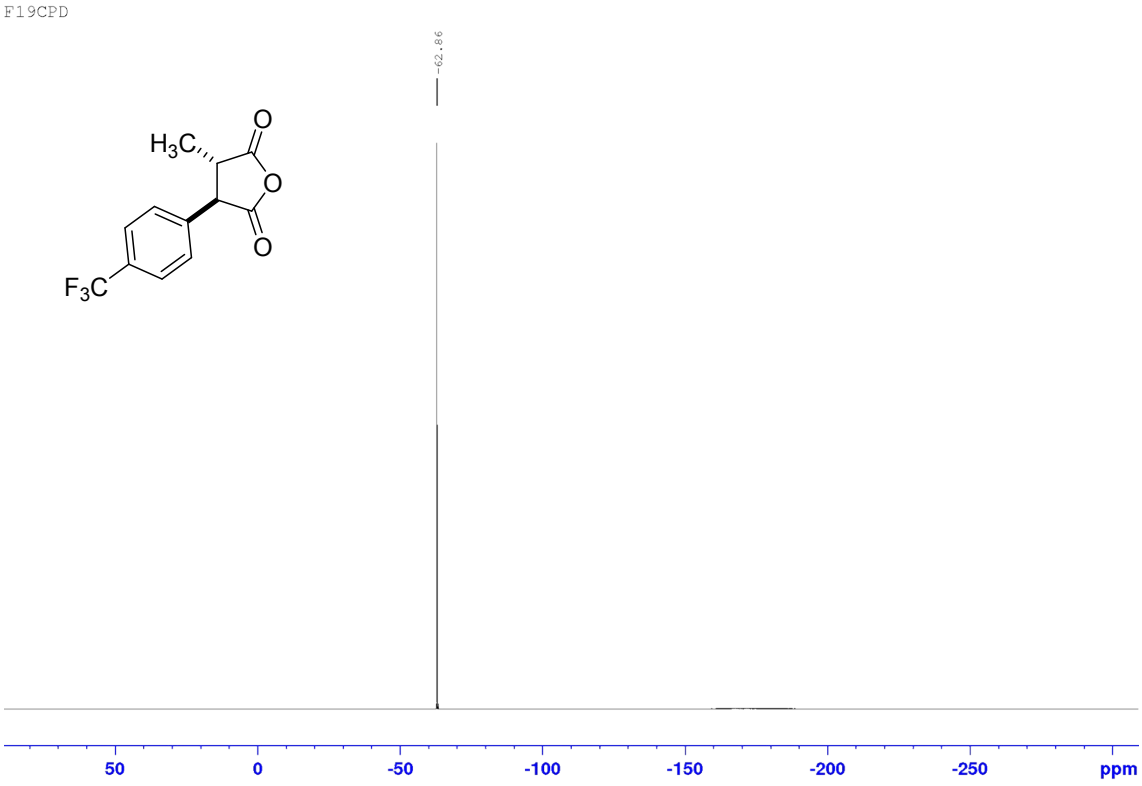


3-Methyl-4-(4-(trifluoromethyl)phenyl)dihydrofuran-2,5-dione (S15)

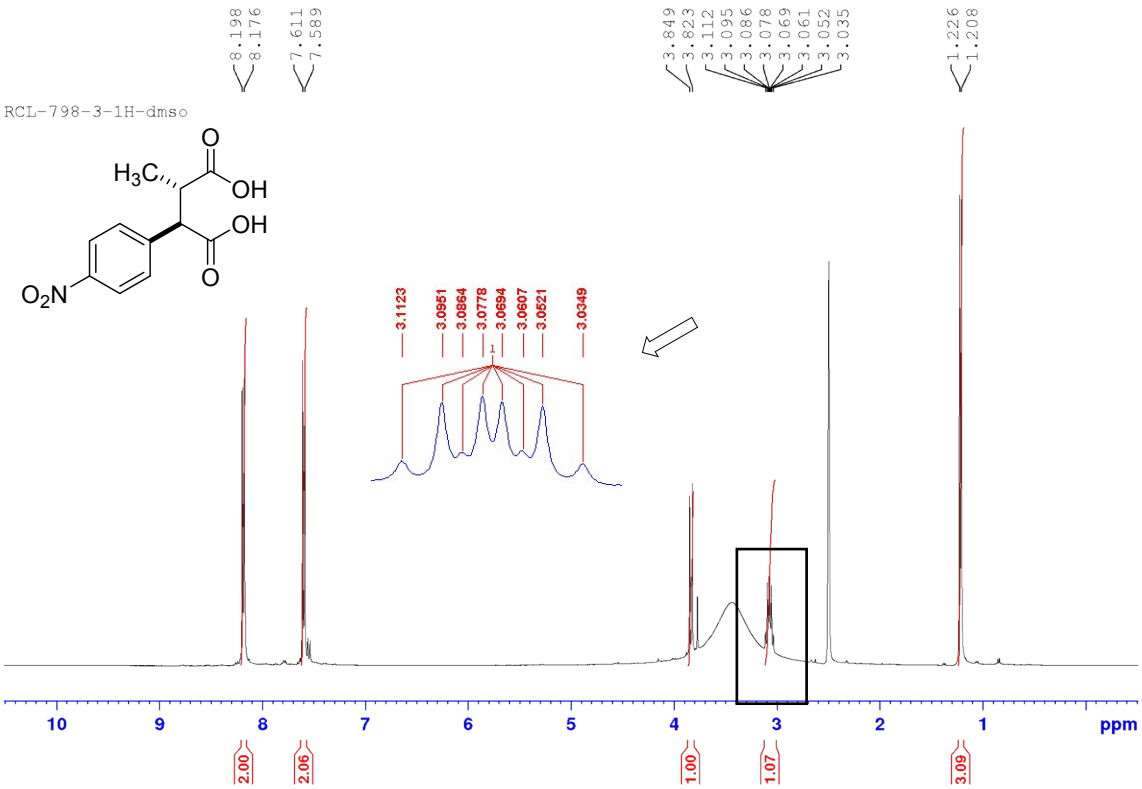


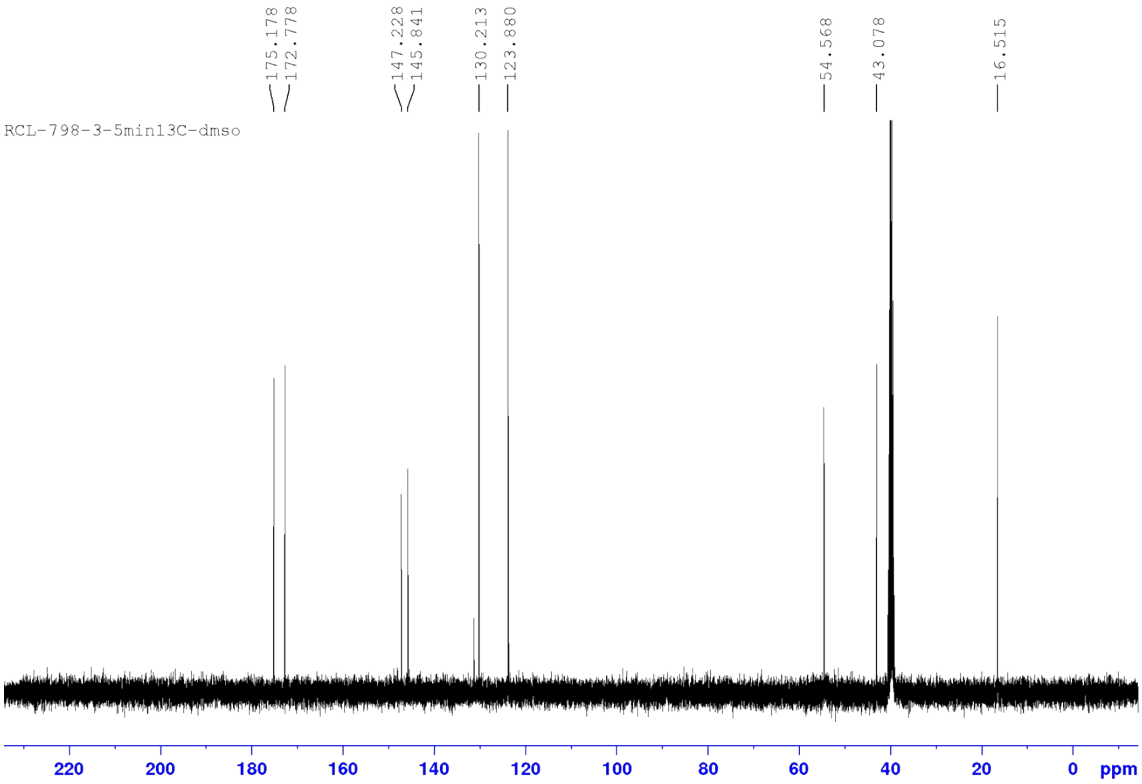


3-Methyl-4-(4-(trifluoromethyl)phenyl)dihydrofuran-2,5-dione (S15)

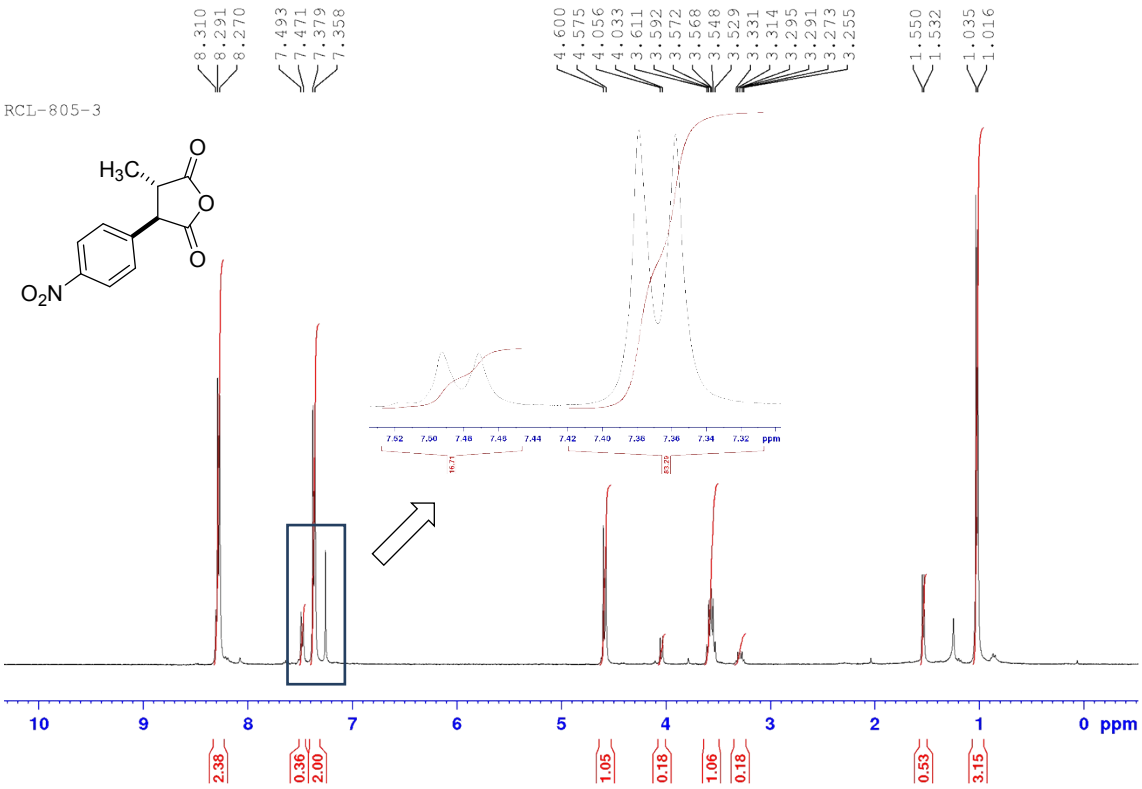


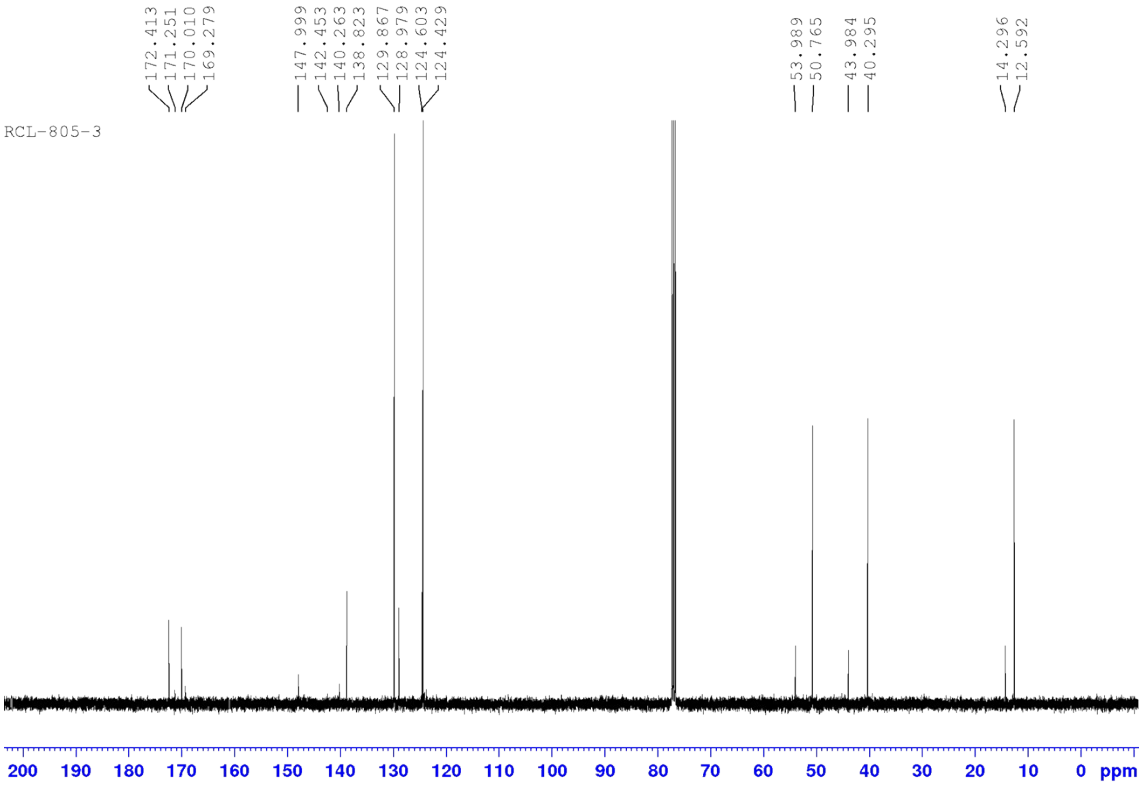
2-Methyl-3-(4-nitrophenyl)succinic acid (S18)



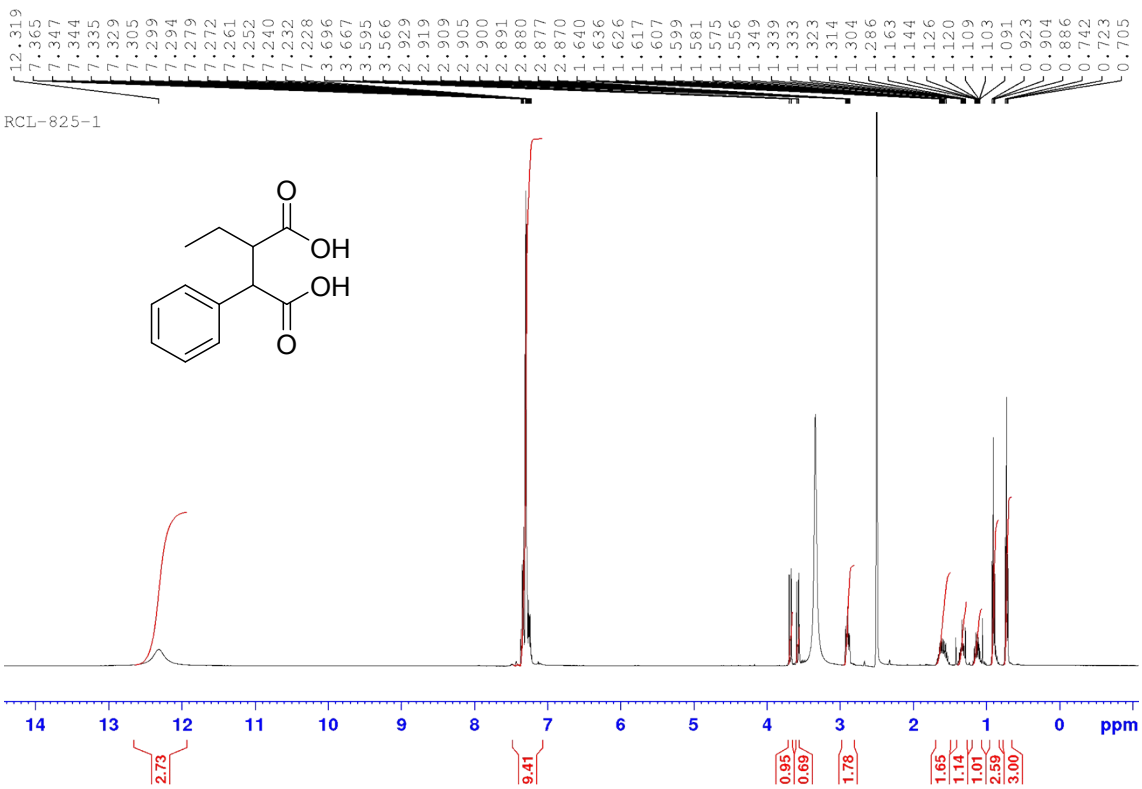


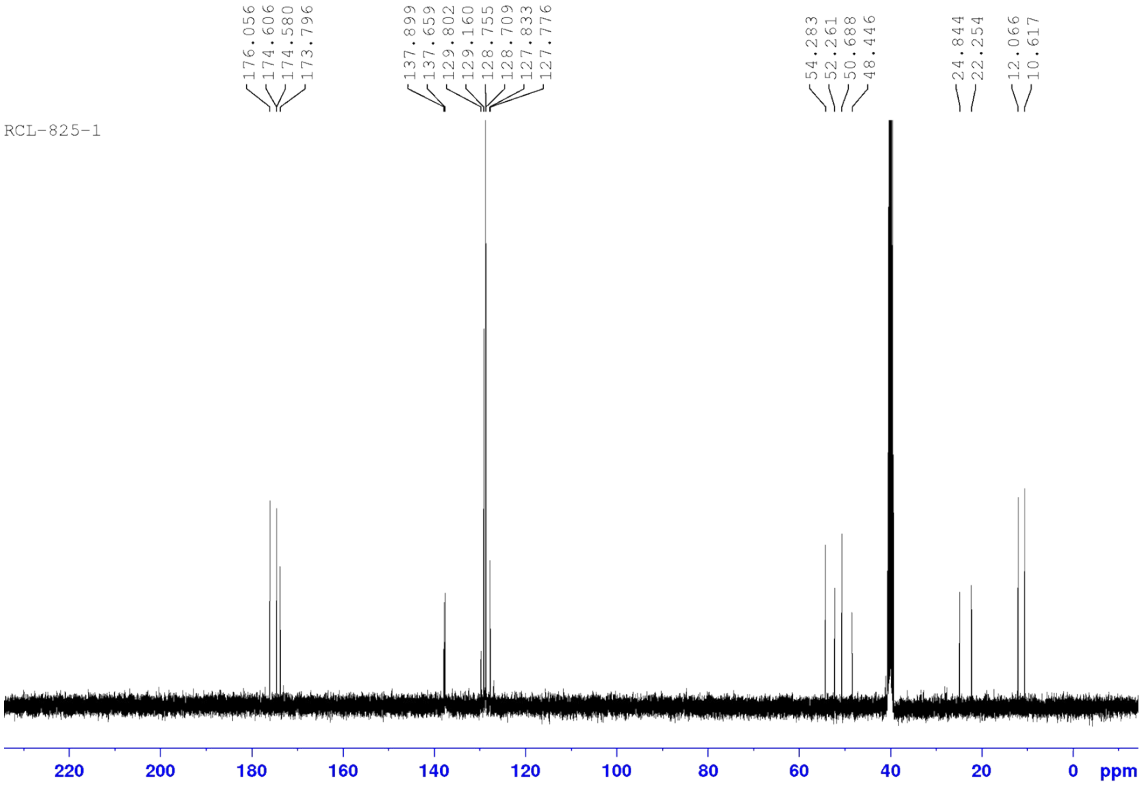
3-Methyl-4-(4-nitrophenyl)dihydrofuran-2,5-dione (S19)



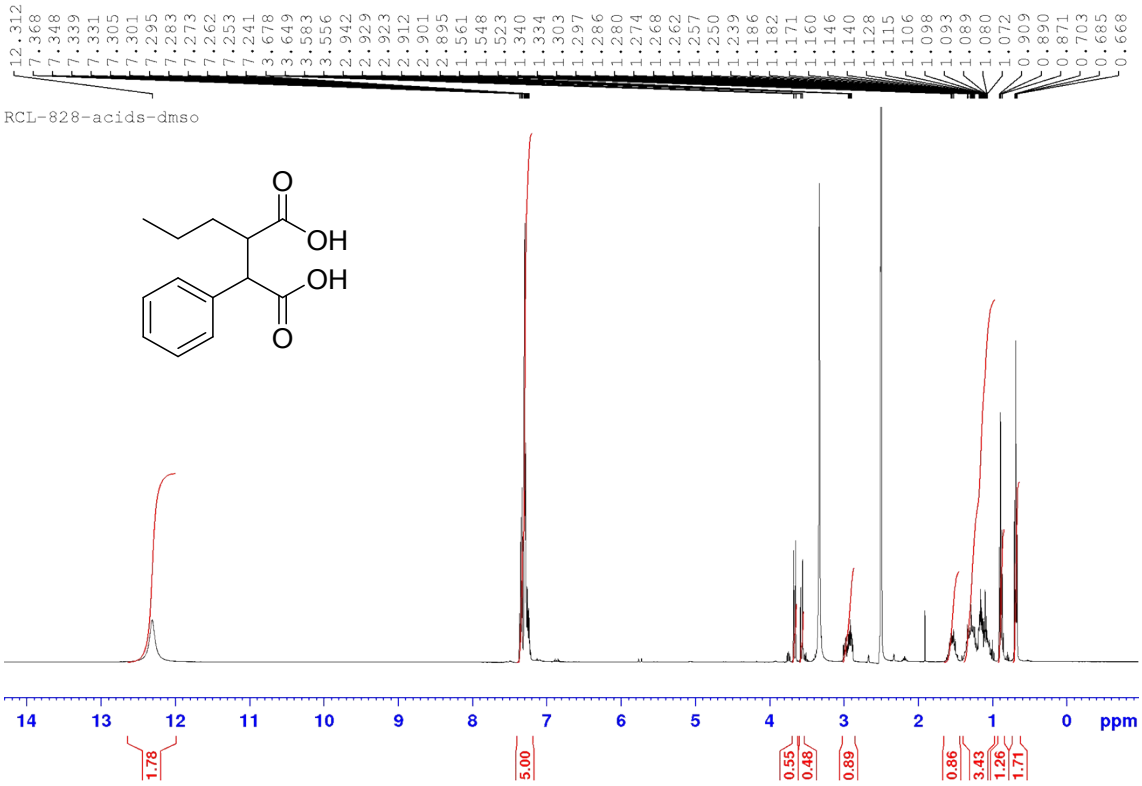


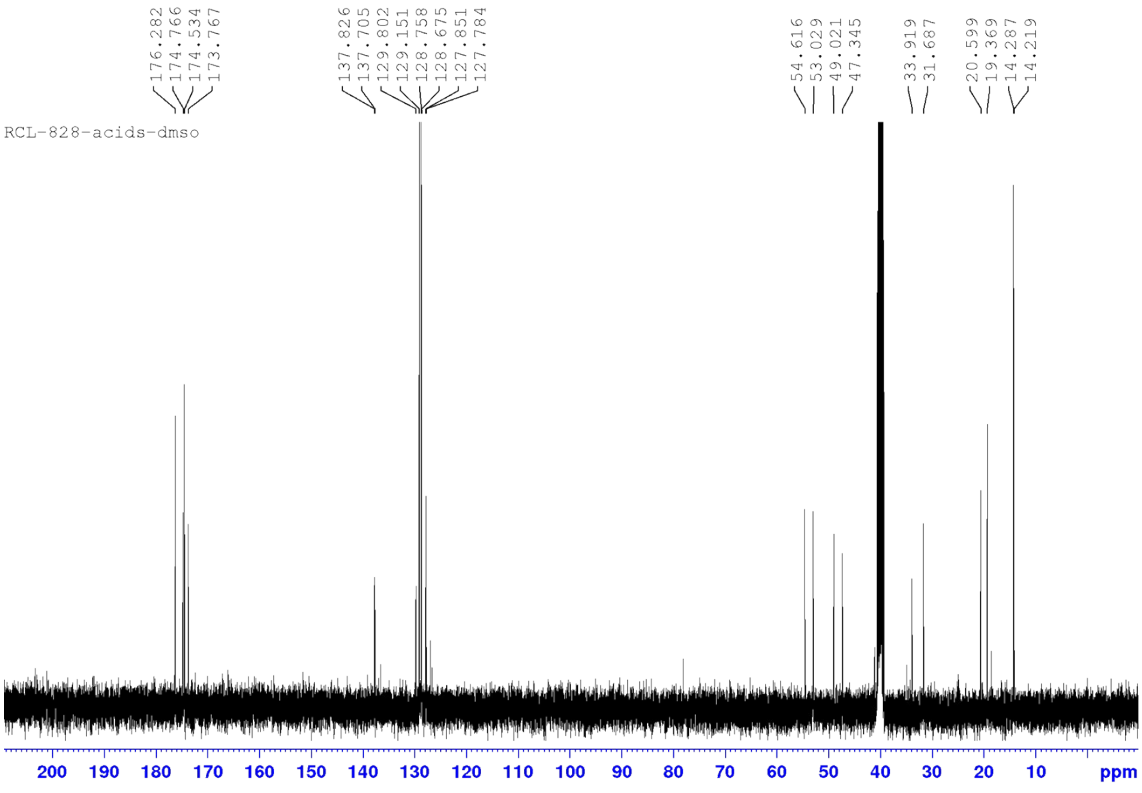
2-Ethyl-3-phenylsuccinic acid (S21)



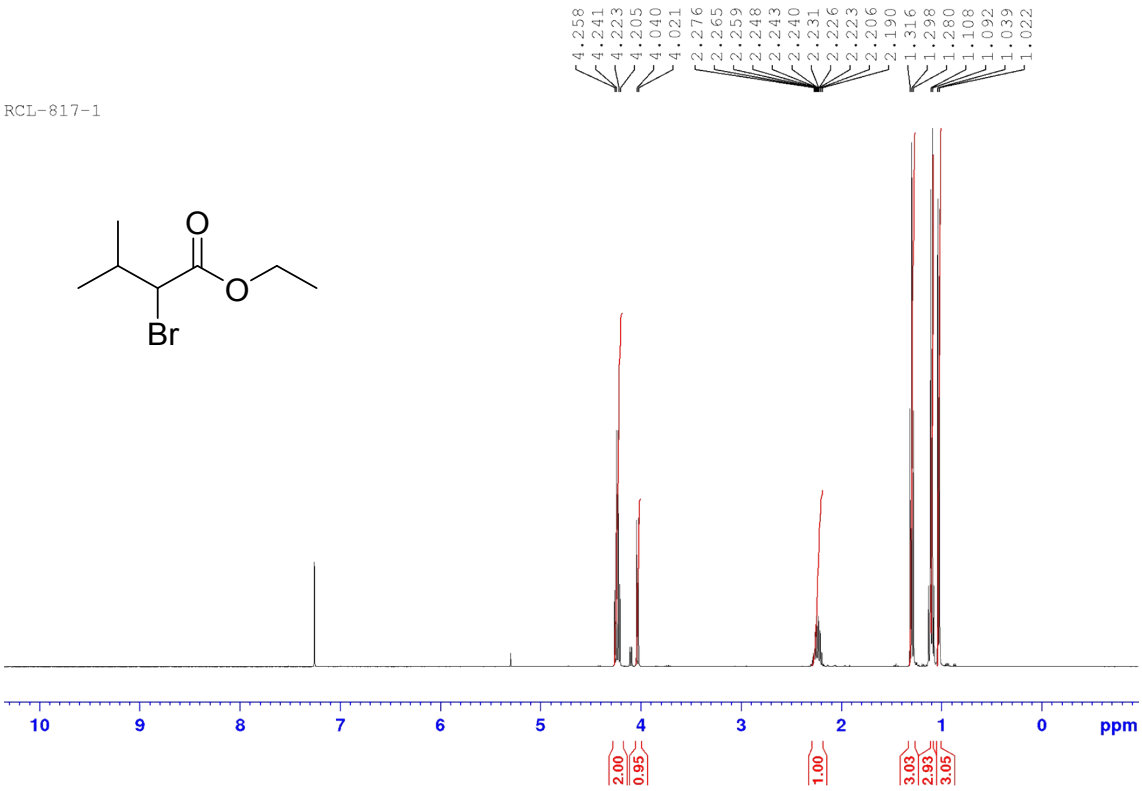


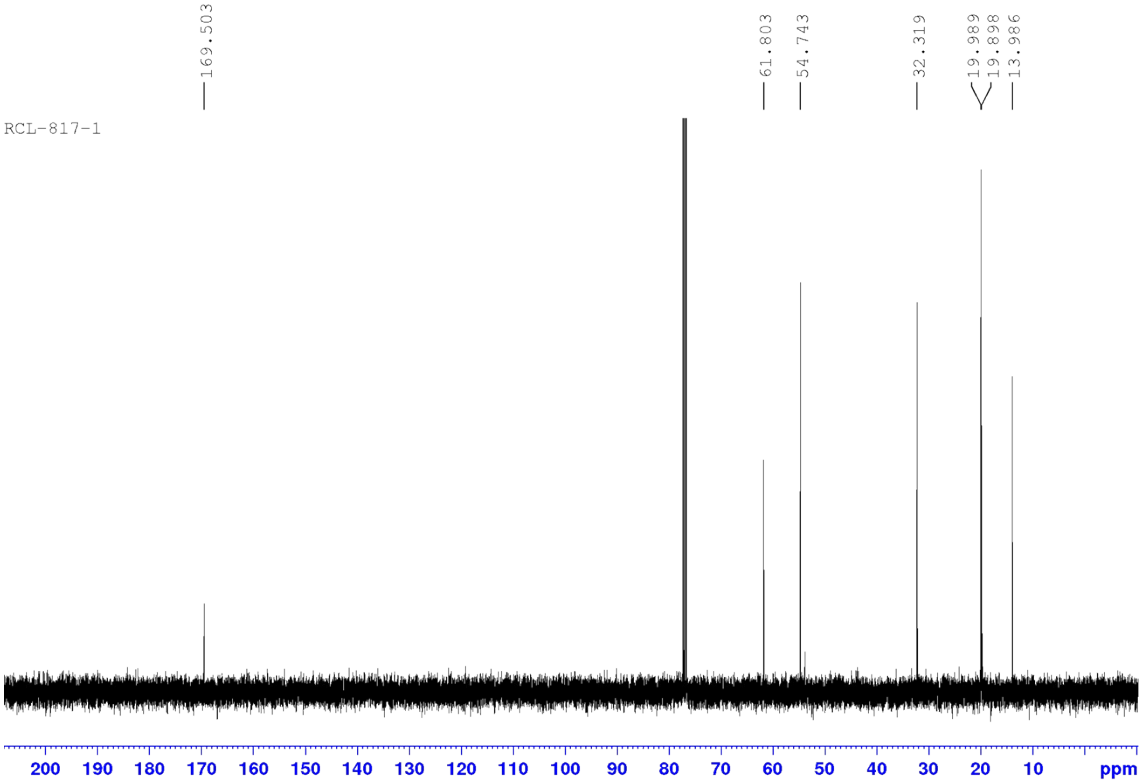
2-Phenyl-3-propylsuccinic acid (S24)



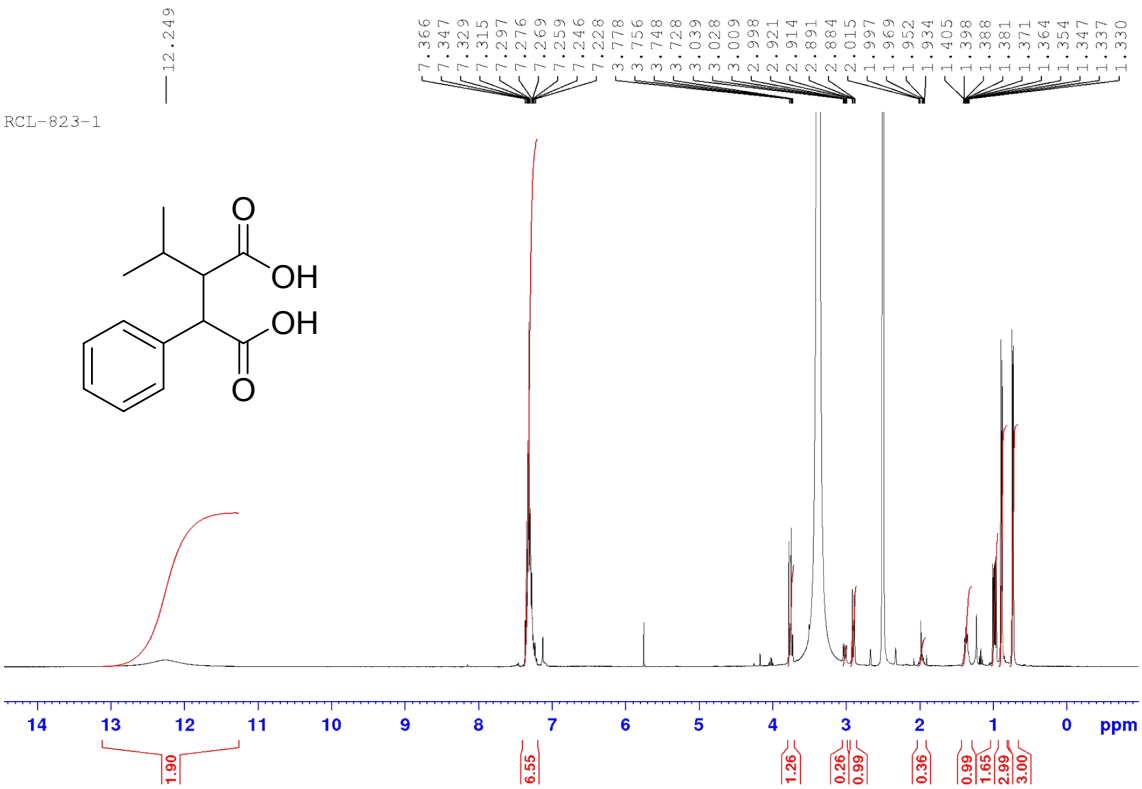


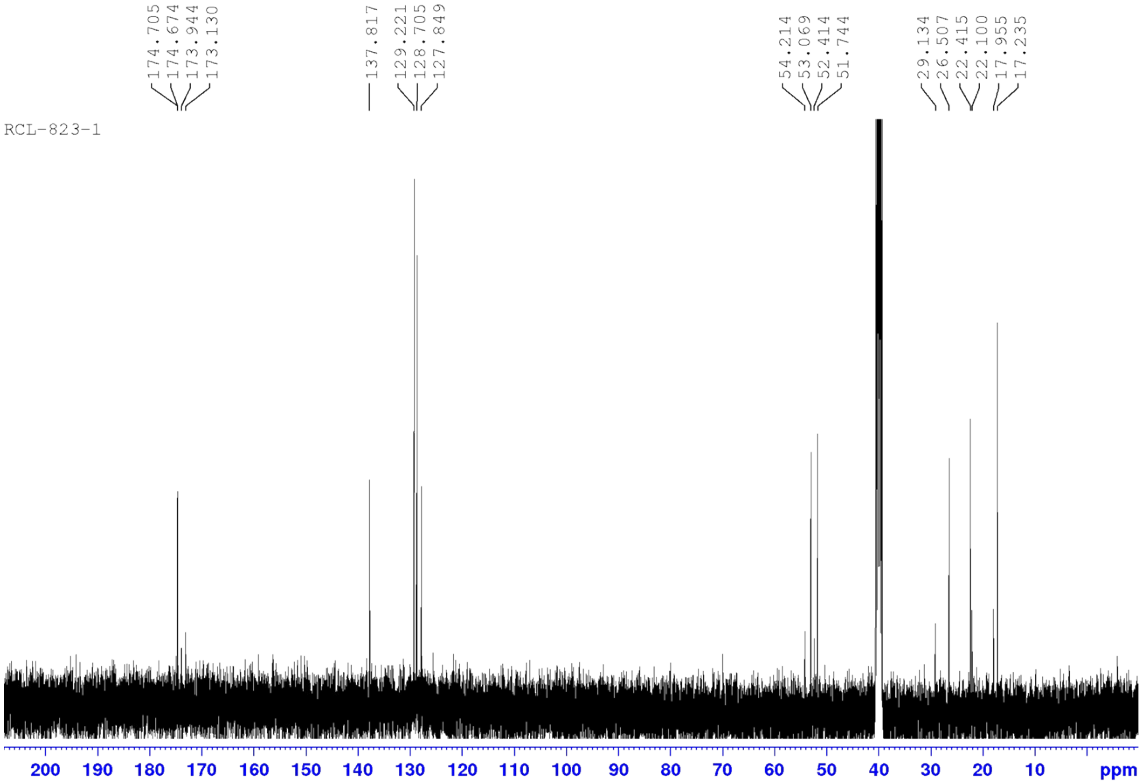
Ethyl 2-bromo-3-methylbutanoate (S29)



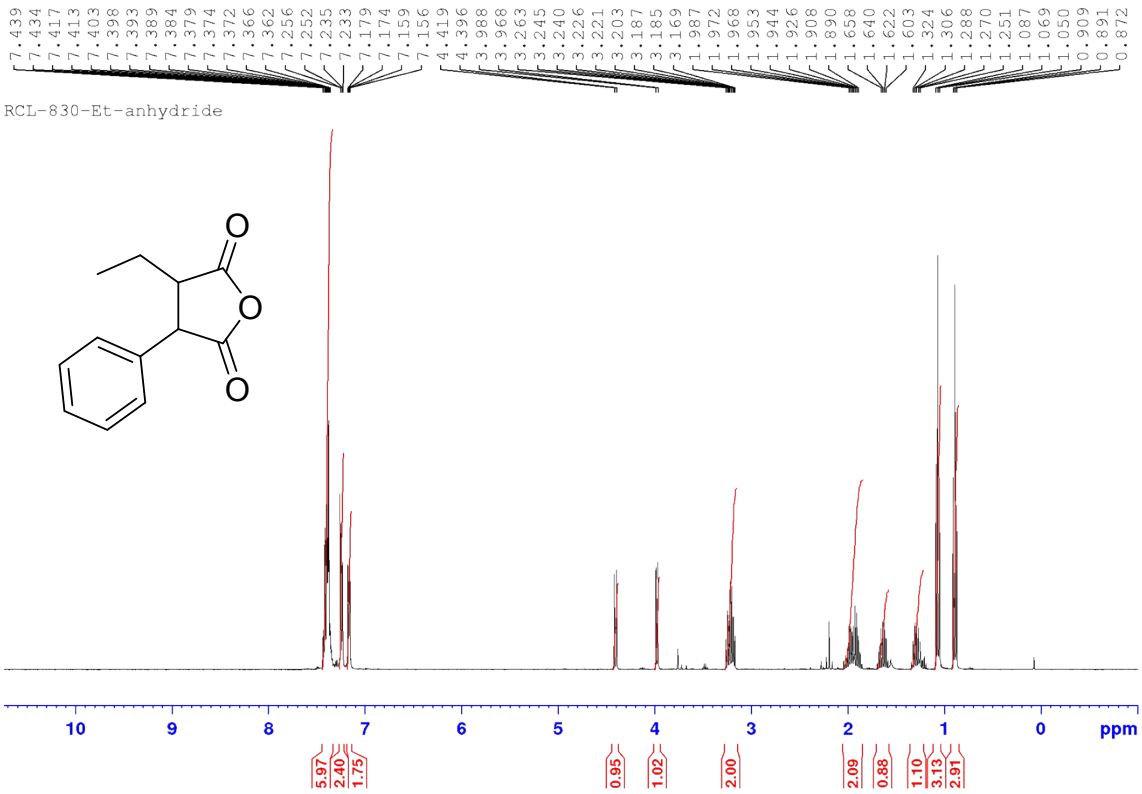


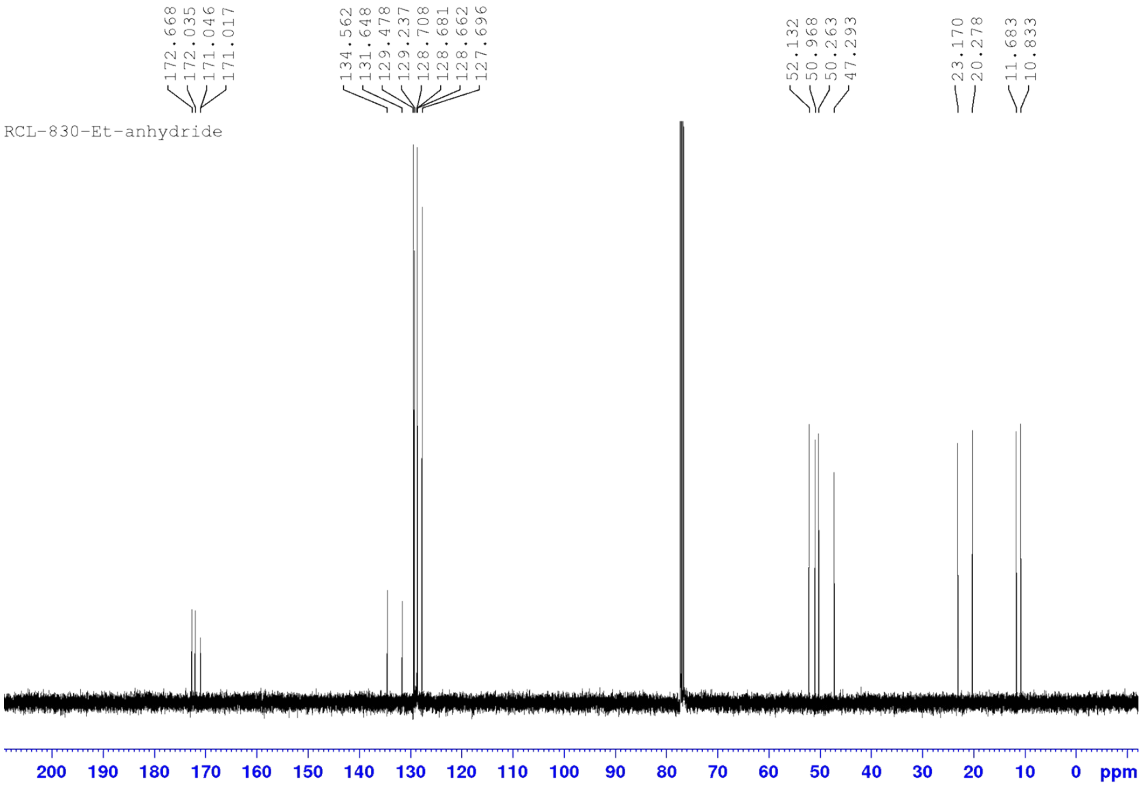
2-Isopropyl-3-phenylsuccinic acid (S27)



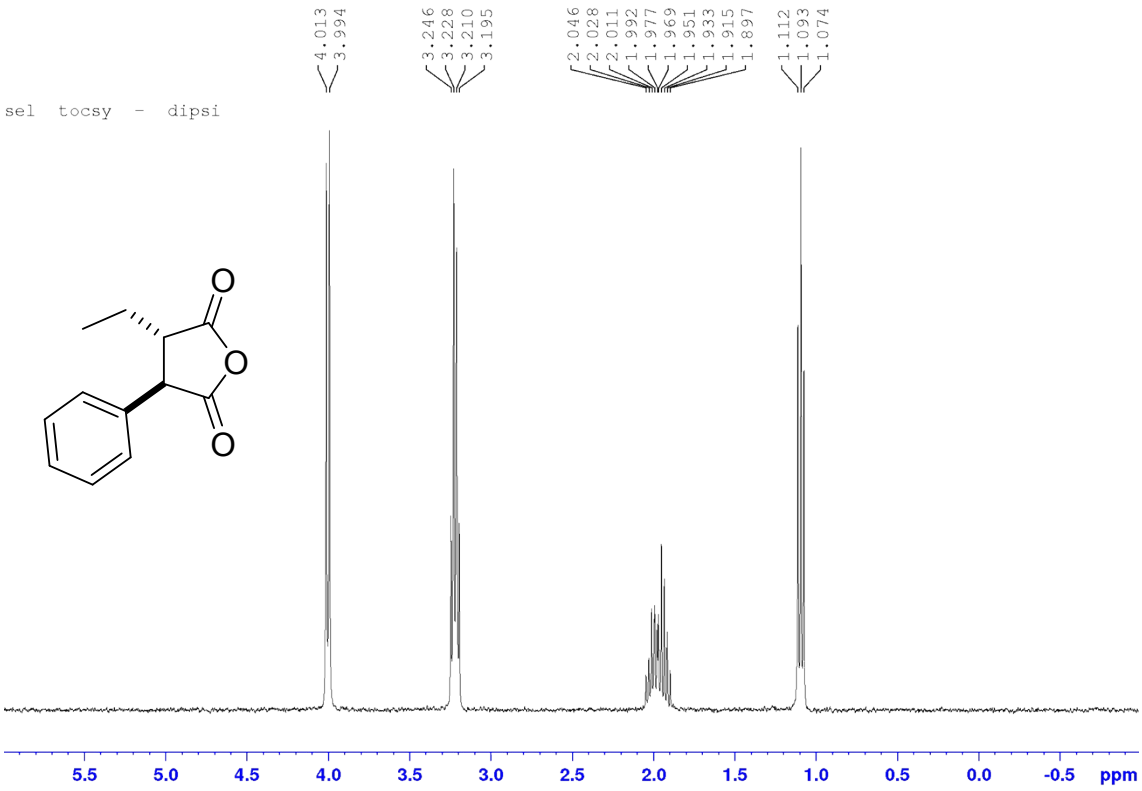


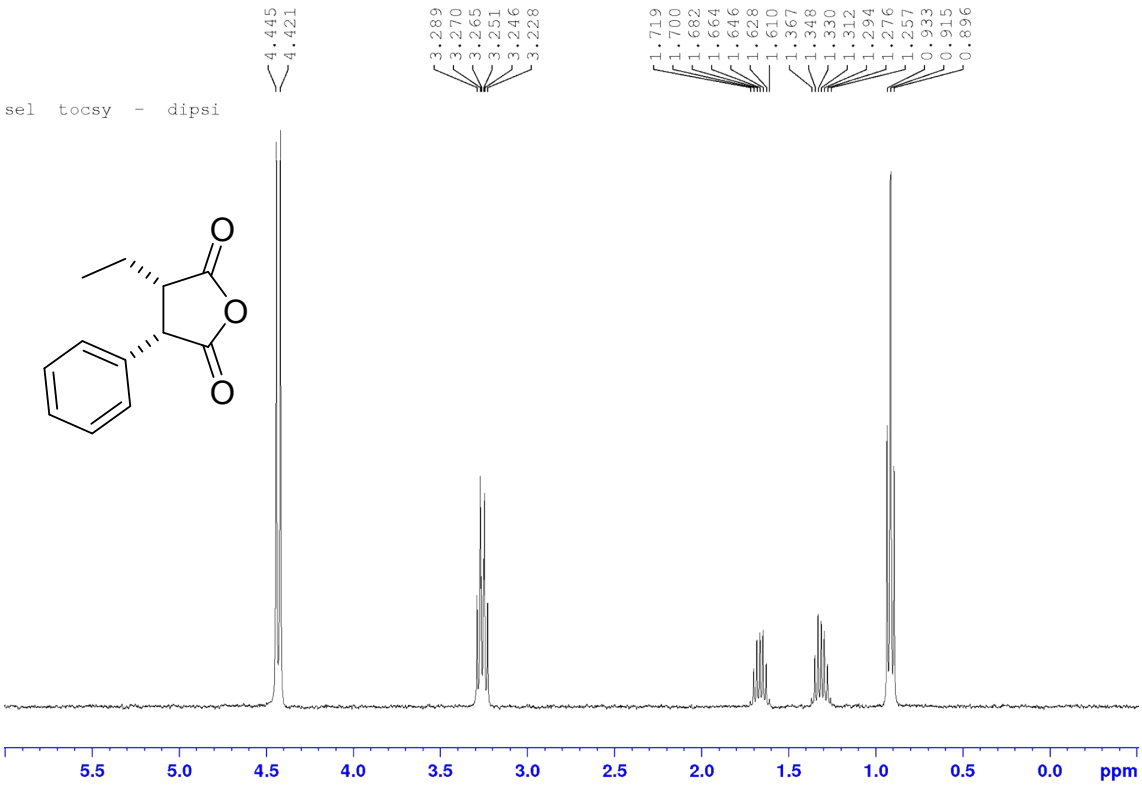
2-Ethyl-3-phenylsuccinic acid anhydride (S22)



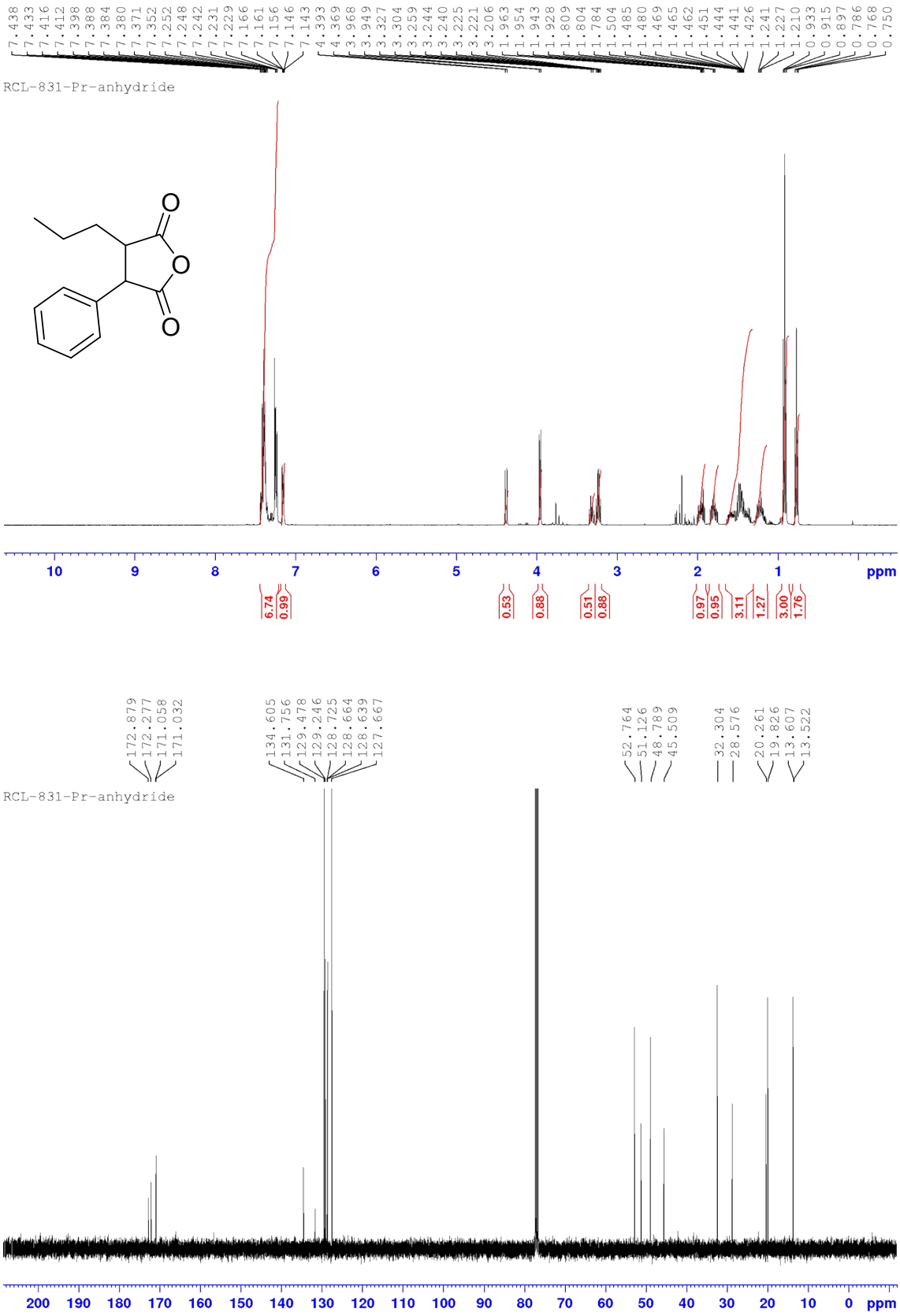


(S22): selectives TOCSY experiments

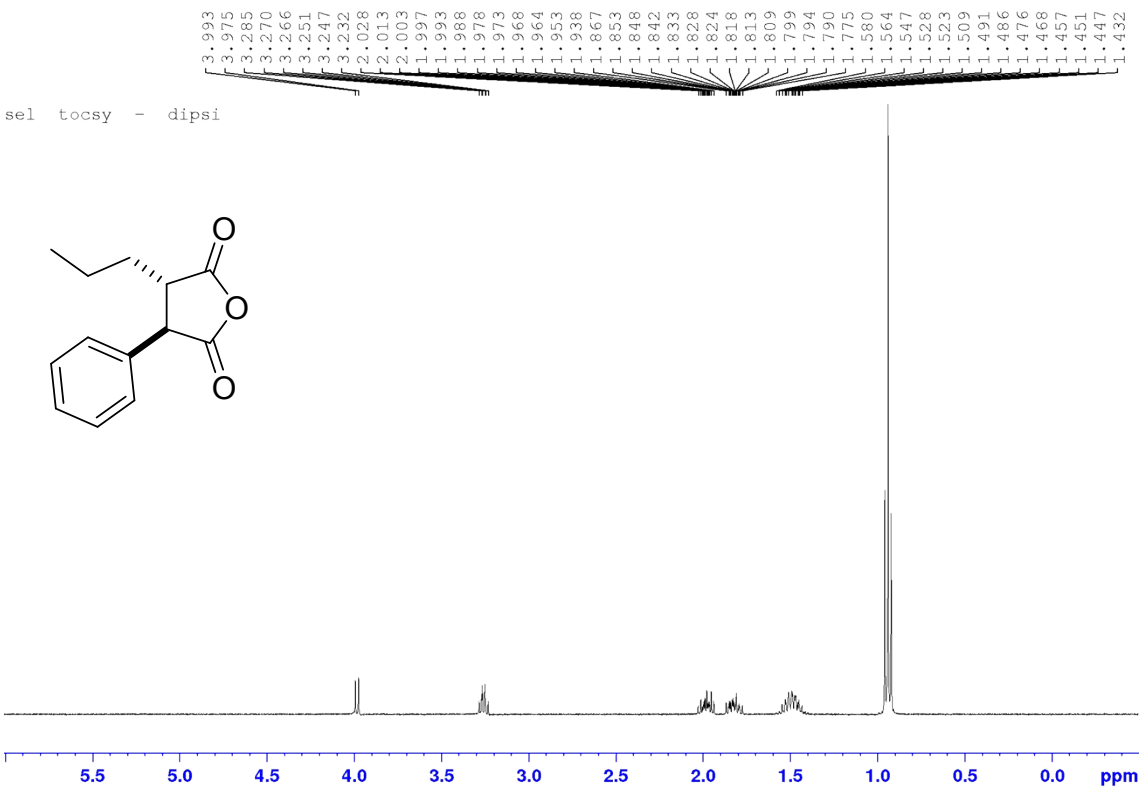


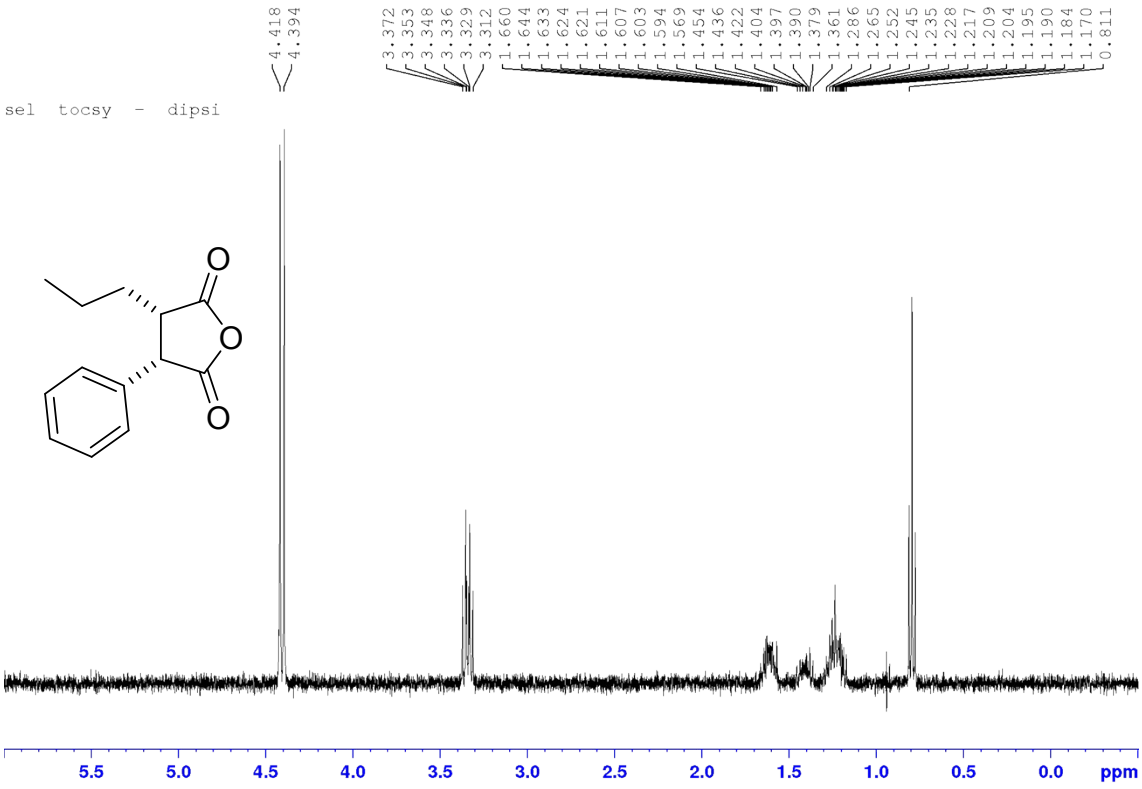


2-Phenyl-3-propylsuccinic acid anhydride (S25)

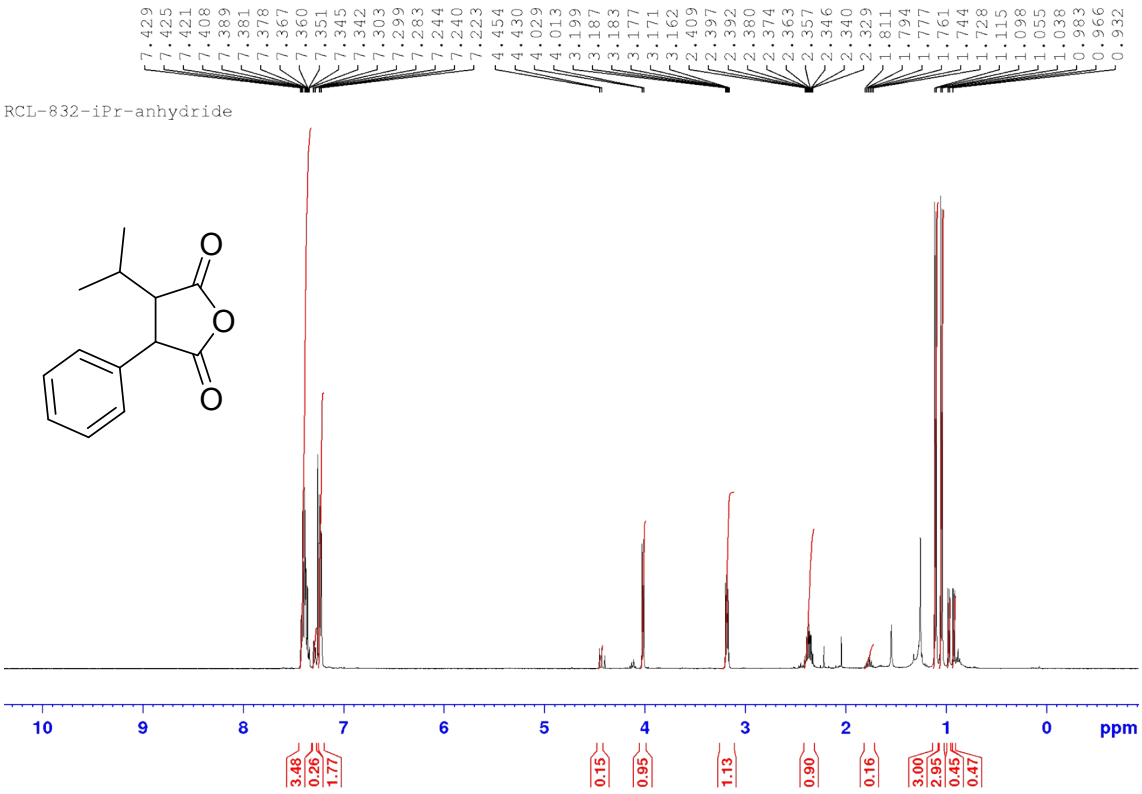


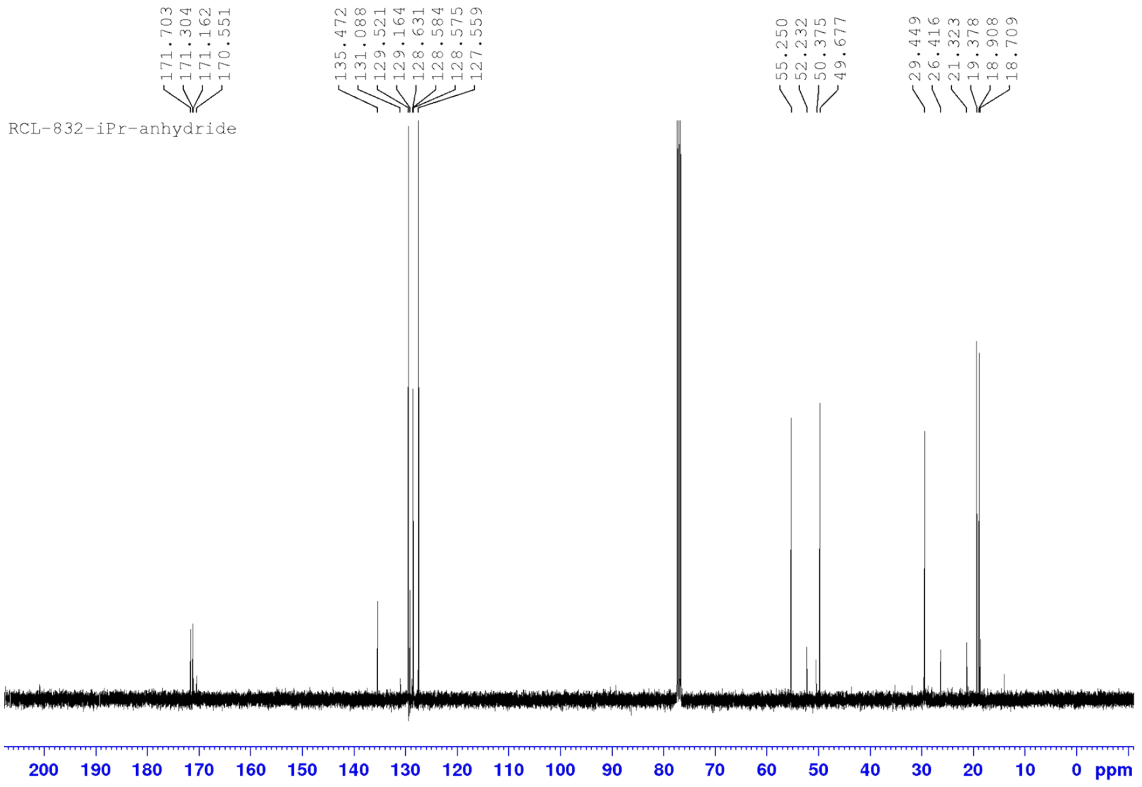
(S25): selectives TOCSY experiments



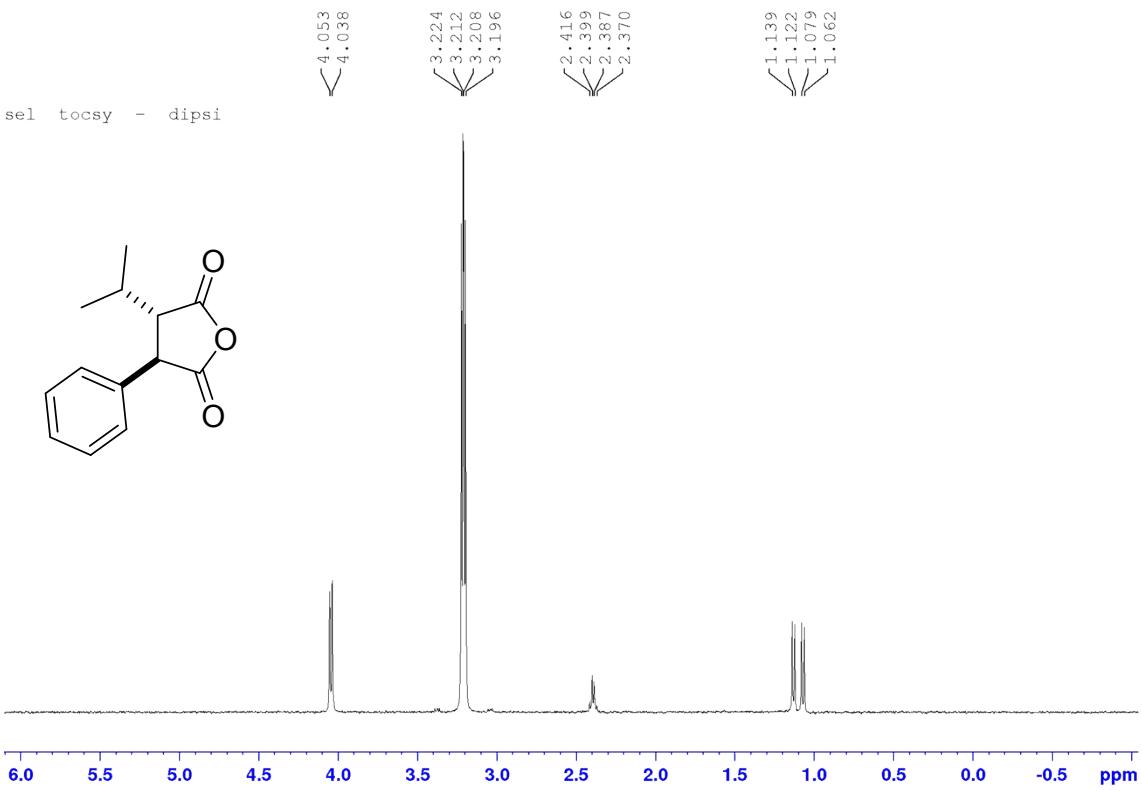


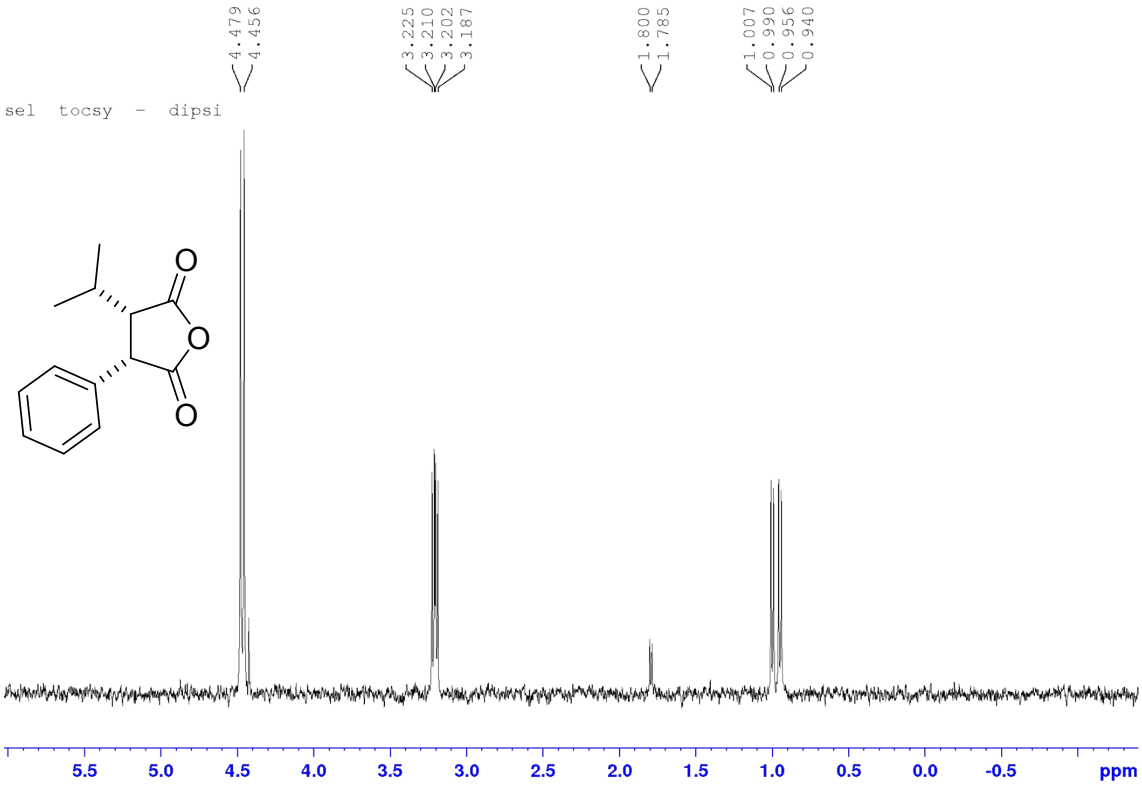
2-Isopropyl-3-phenylsuccinic acid anhydride (S28)



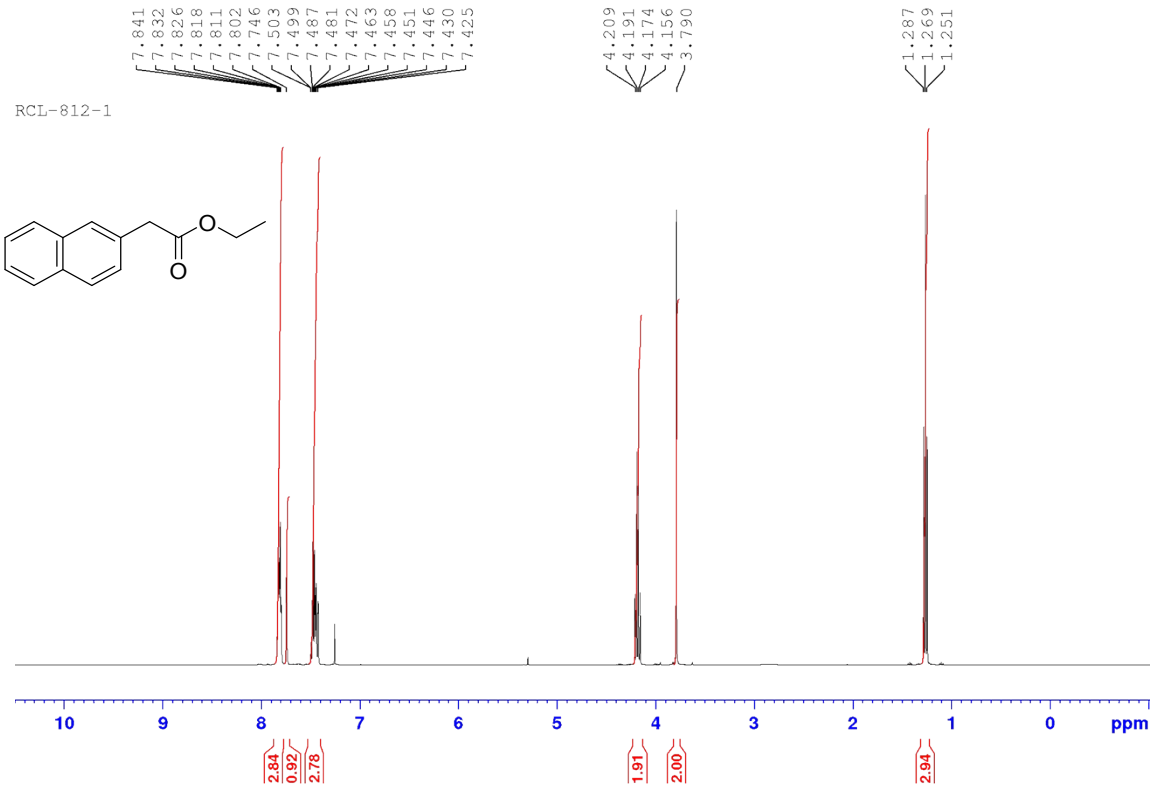


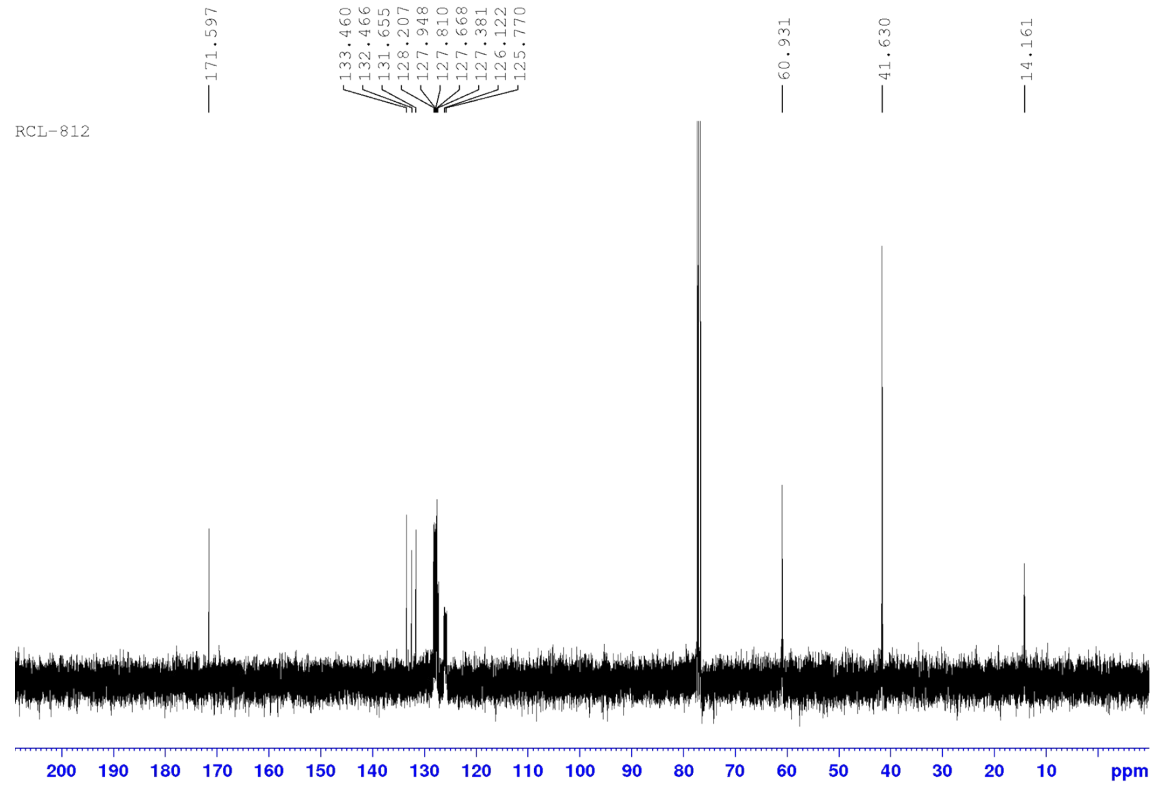
(S28): selectives TOCSY experiments



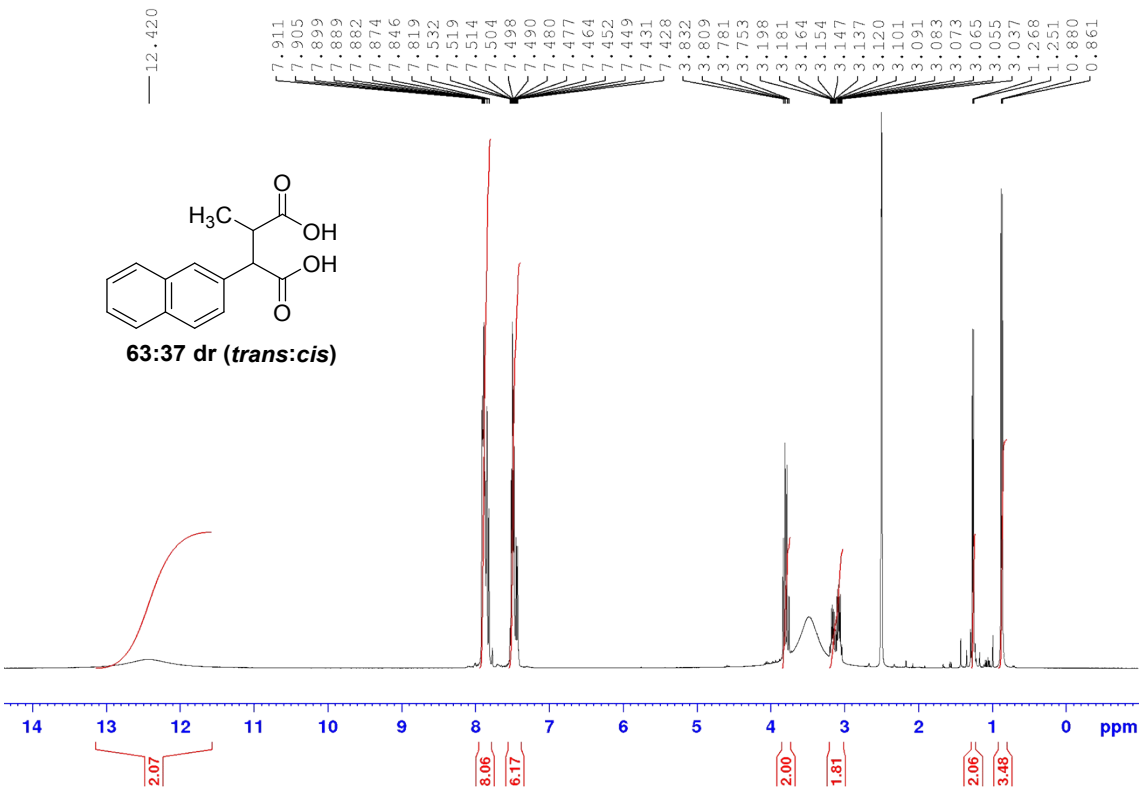


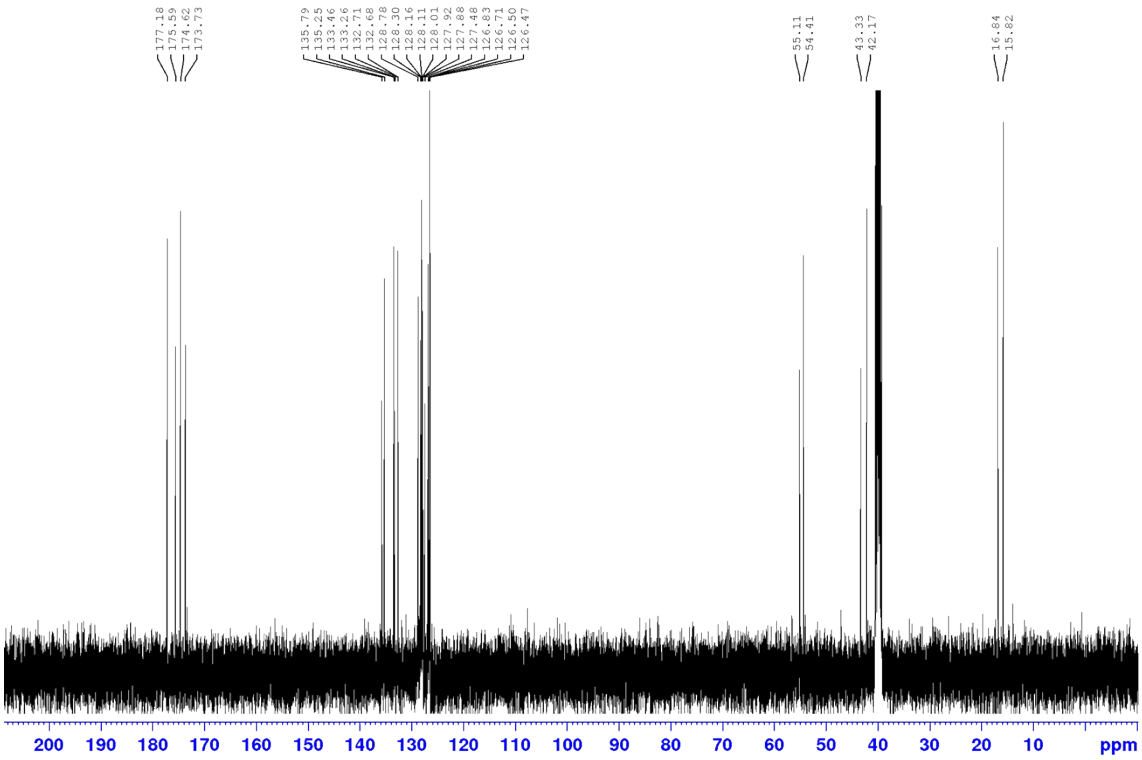
Ethyl 2-(naphthalen-2-yl)acetate (S30)



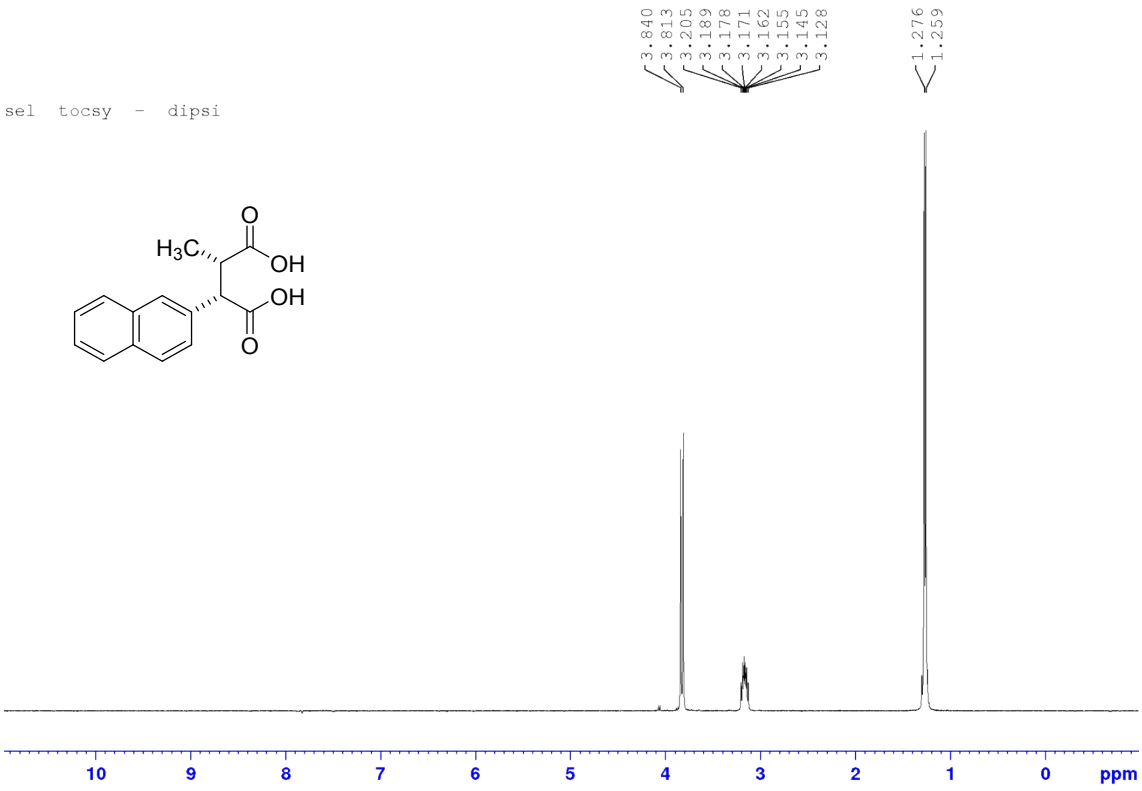


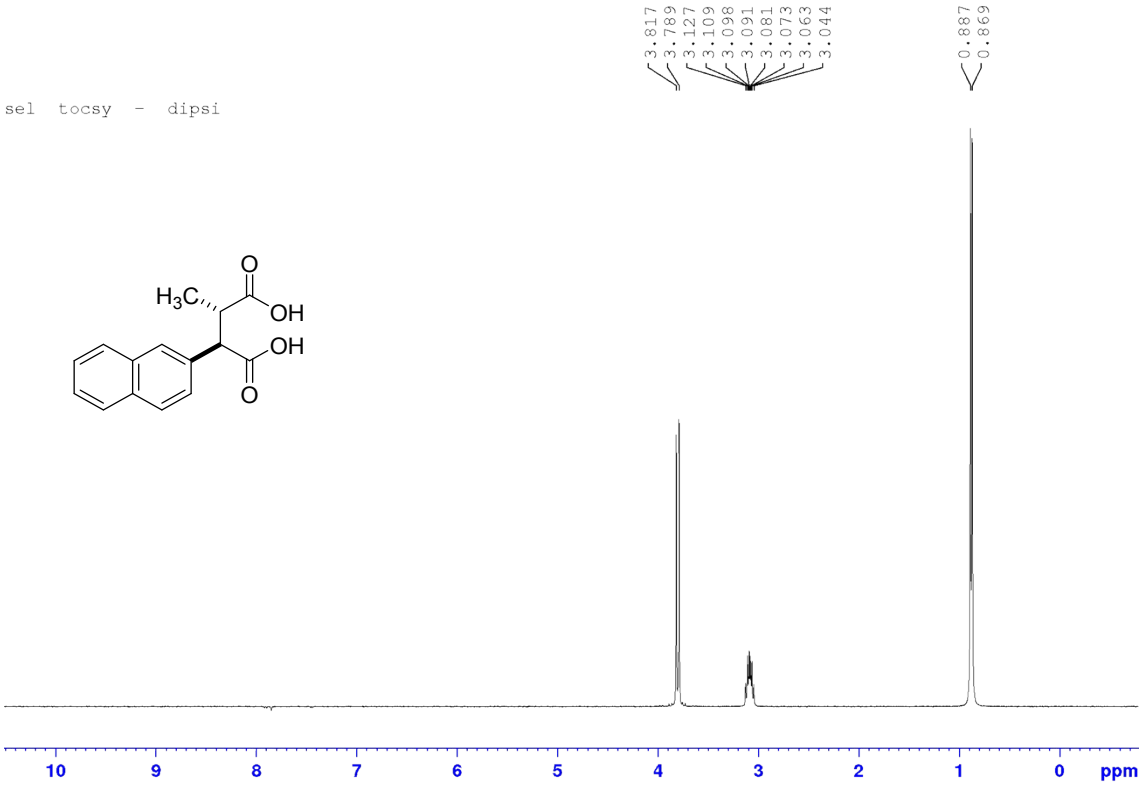
2-Methyl-3-(naphthalen-2-yl)succinic acid (S32)



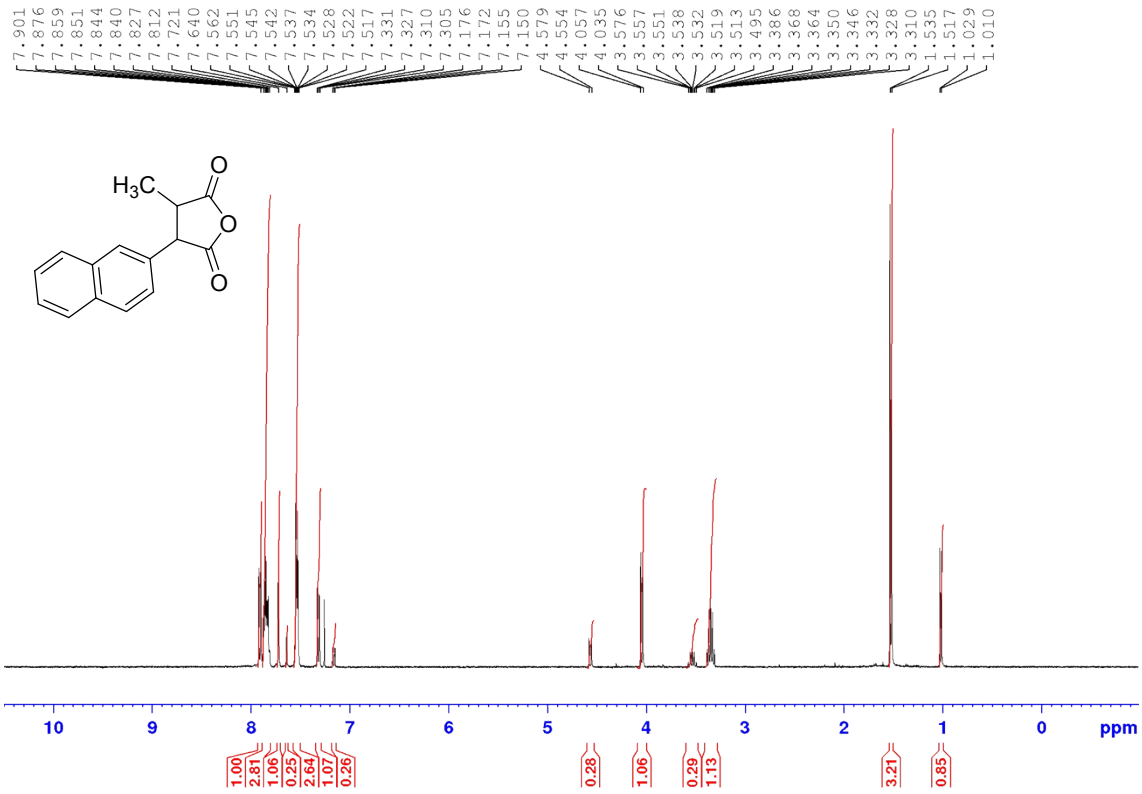


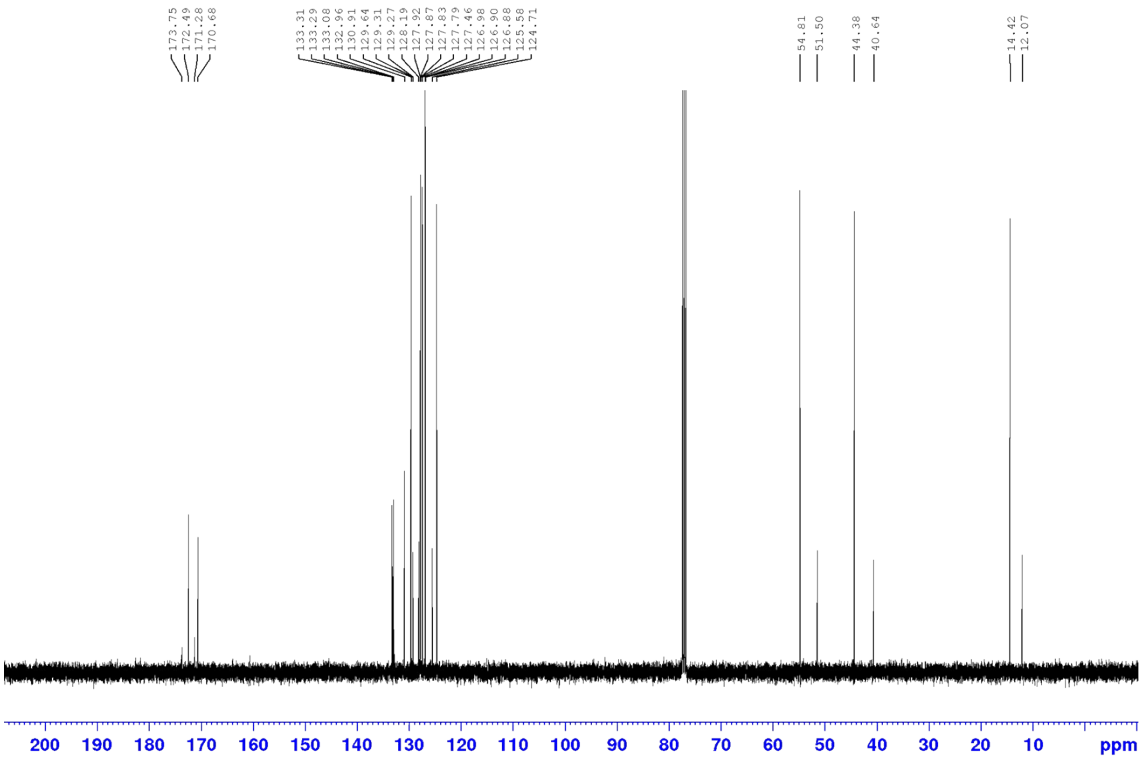
(S32): selectives TOCSY experiments





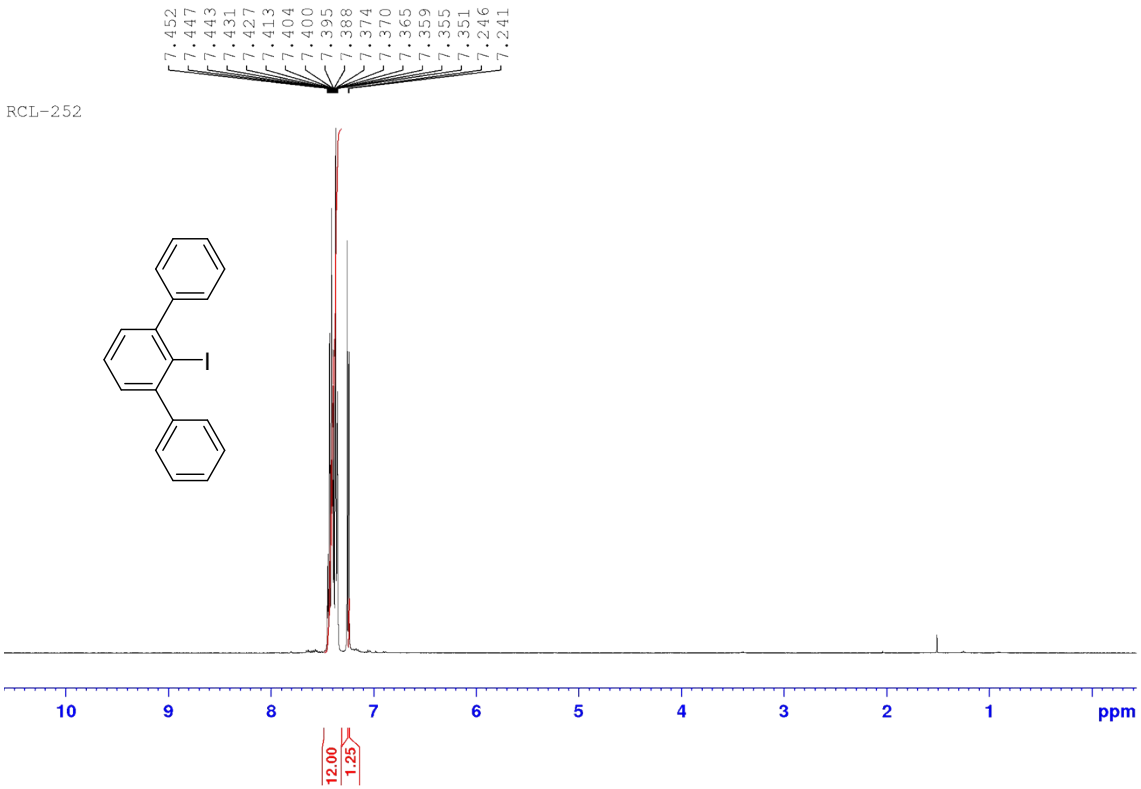
3-Methyl-4-(naphthalen-2-yl)dihydrofuran-2,5-dione (S33)

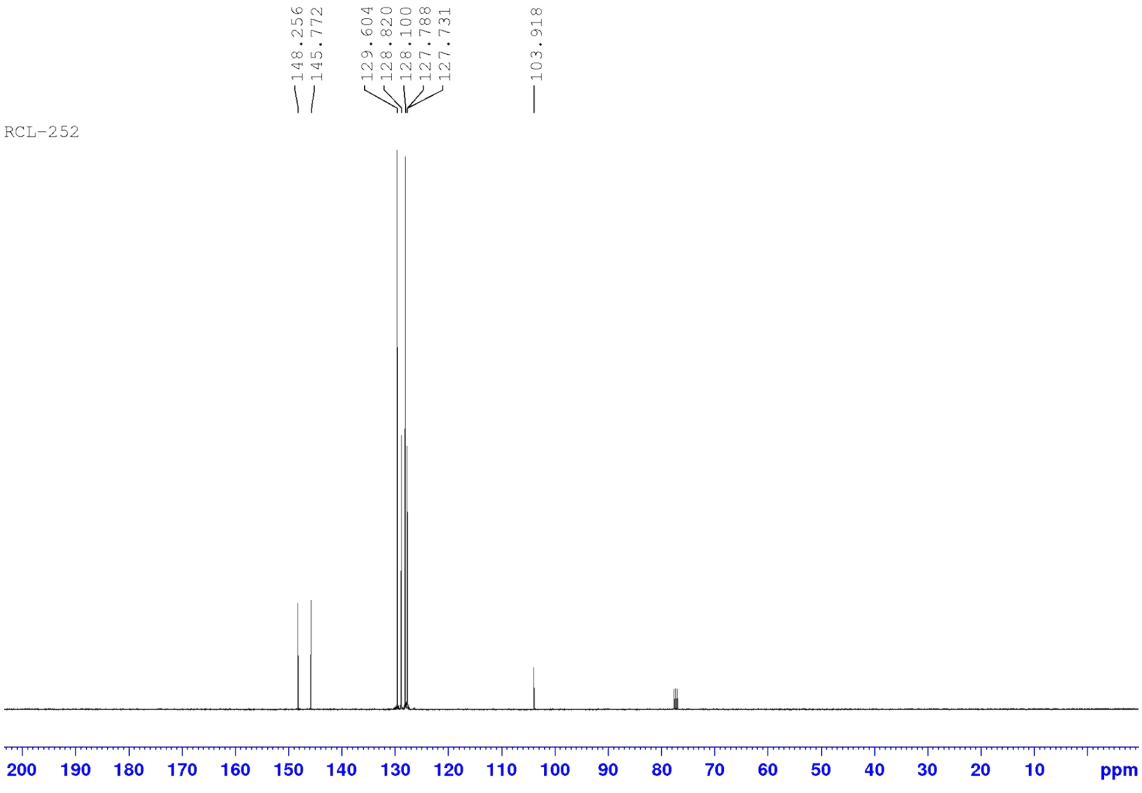




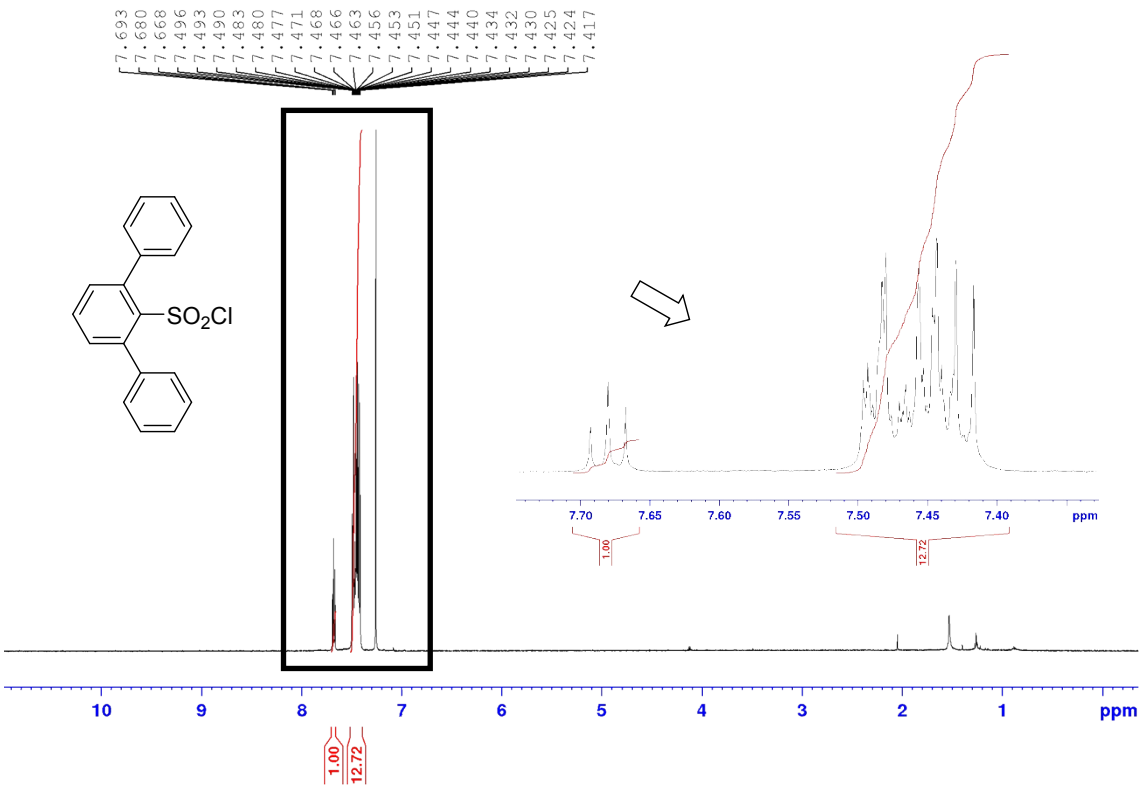
8. NMR spectra: ^{1}H and ^{13}C (catalysts)

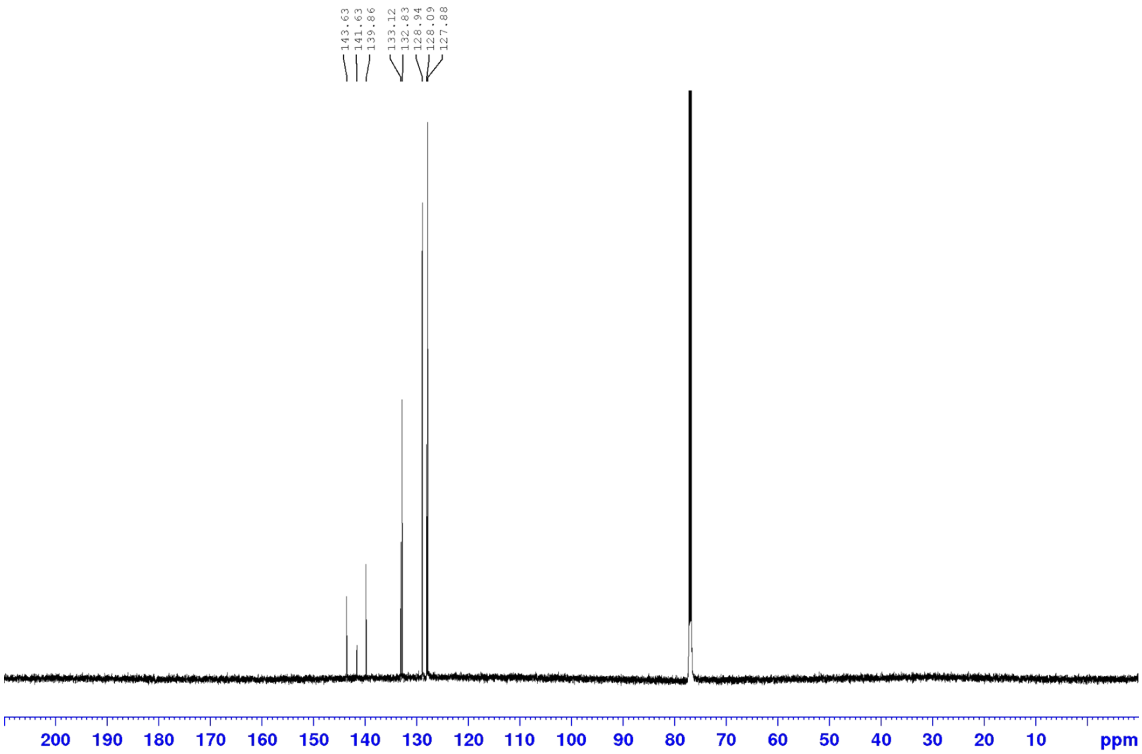
2'-Iodo-1,1':3',1''-terphenyl (S34)



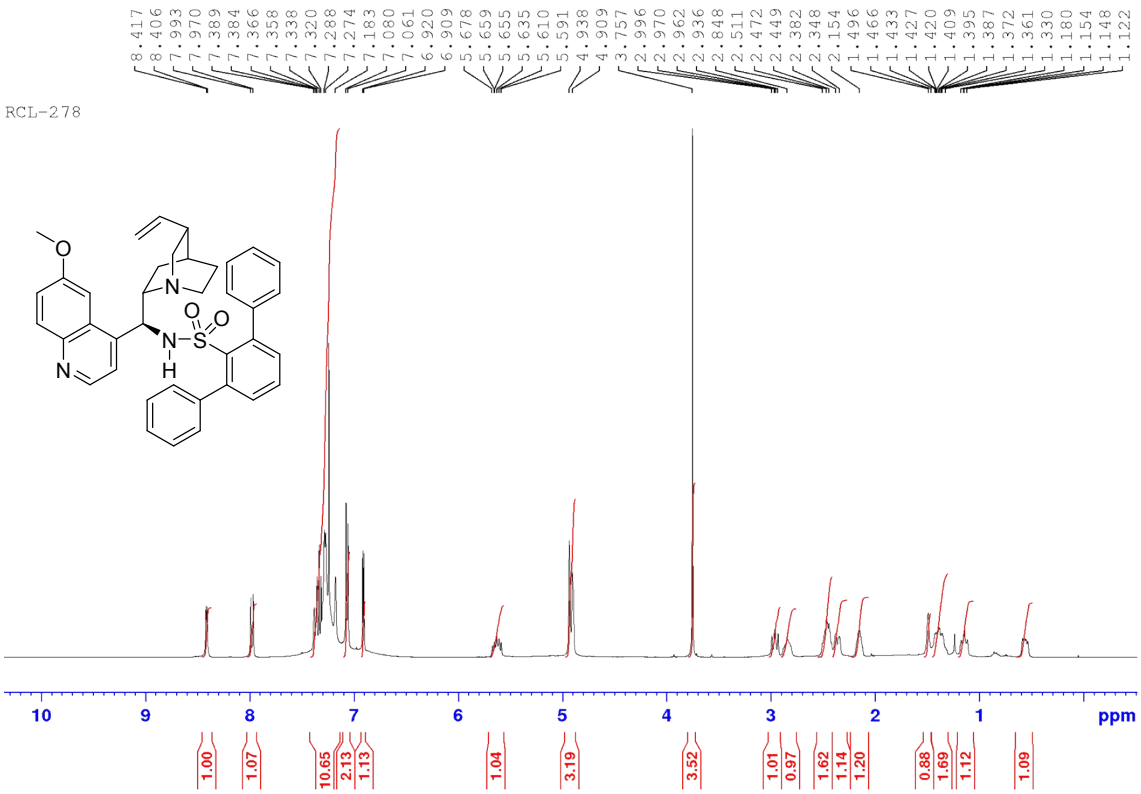


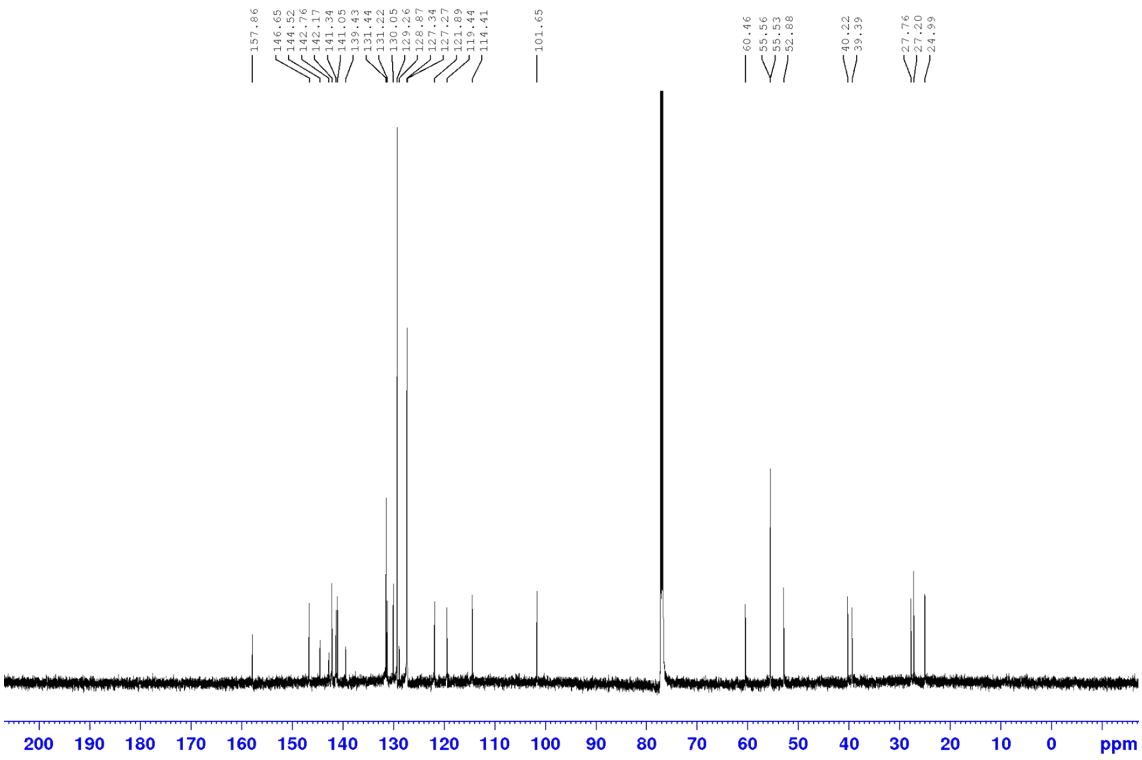
[1,1':3',1''-Terphenyl]-2'-sulfonyl chloride (S35)



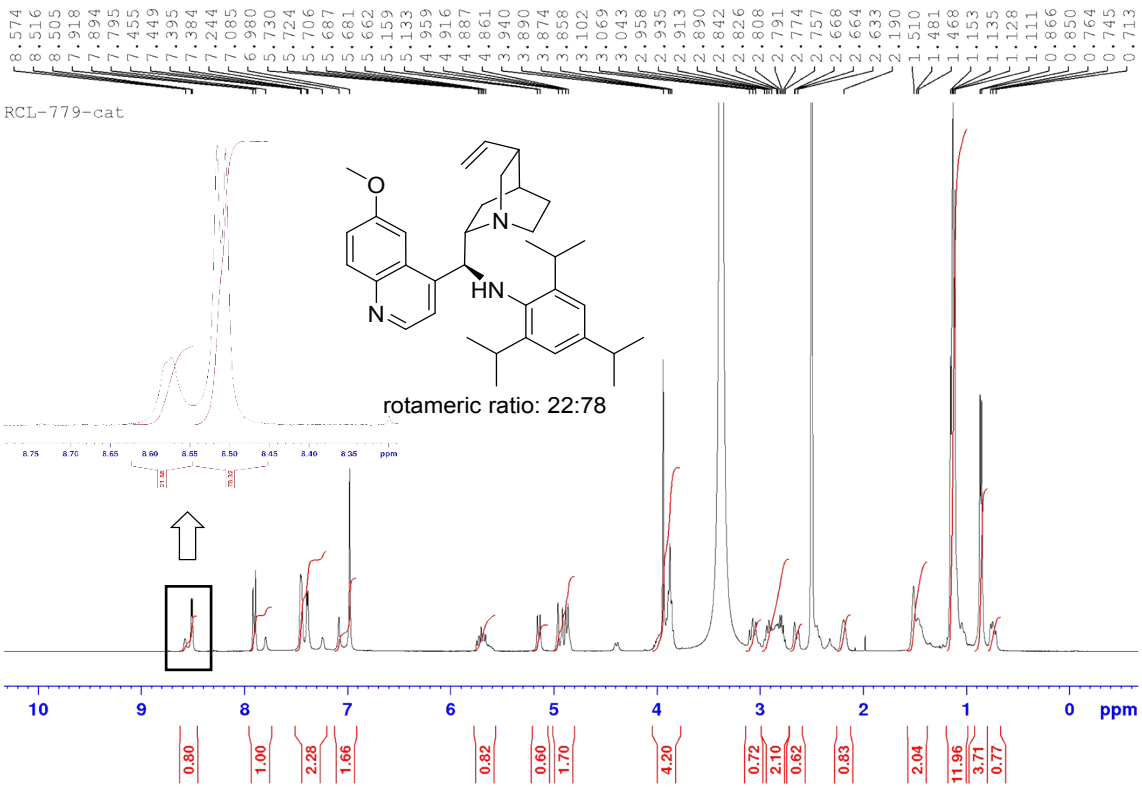


_N_-((_S_)-(6-methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)-[1,1':3',1''-terphenyl]-2'-sulfonamide (44)

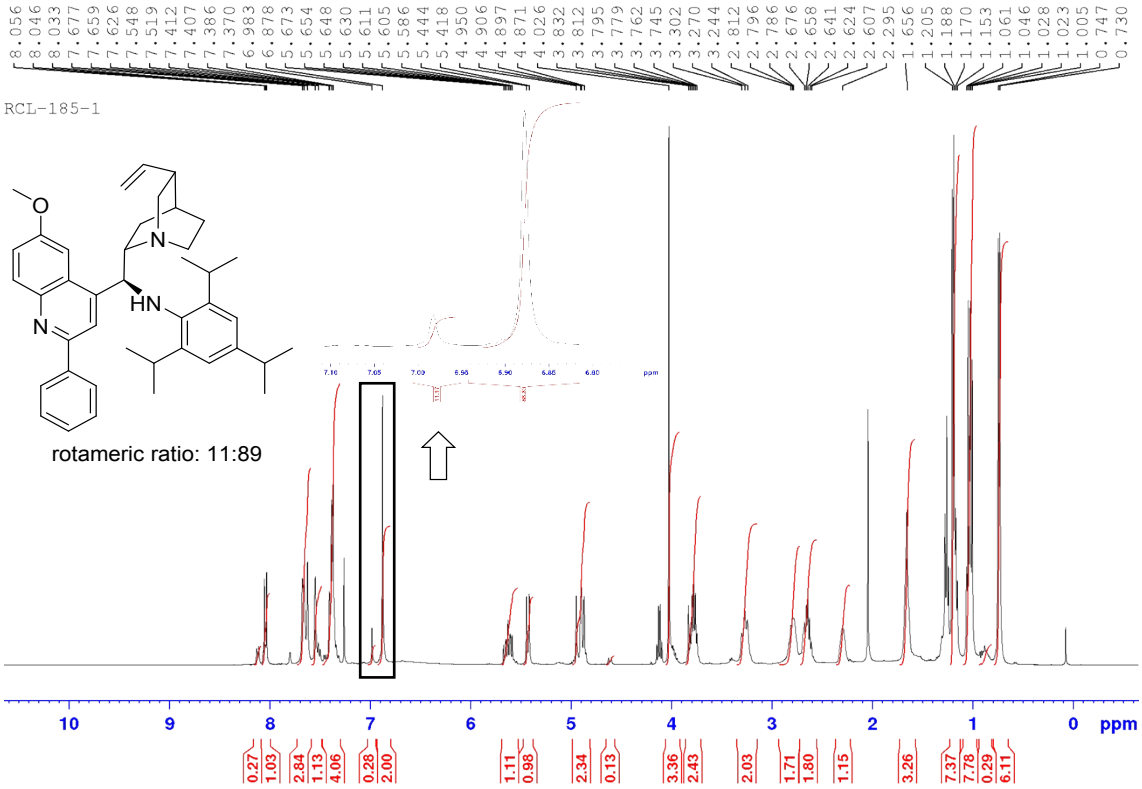


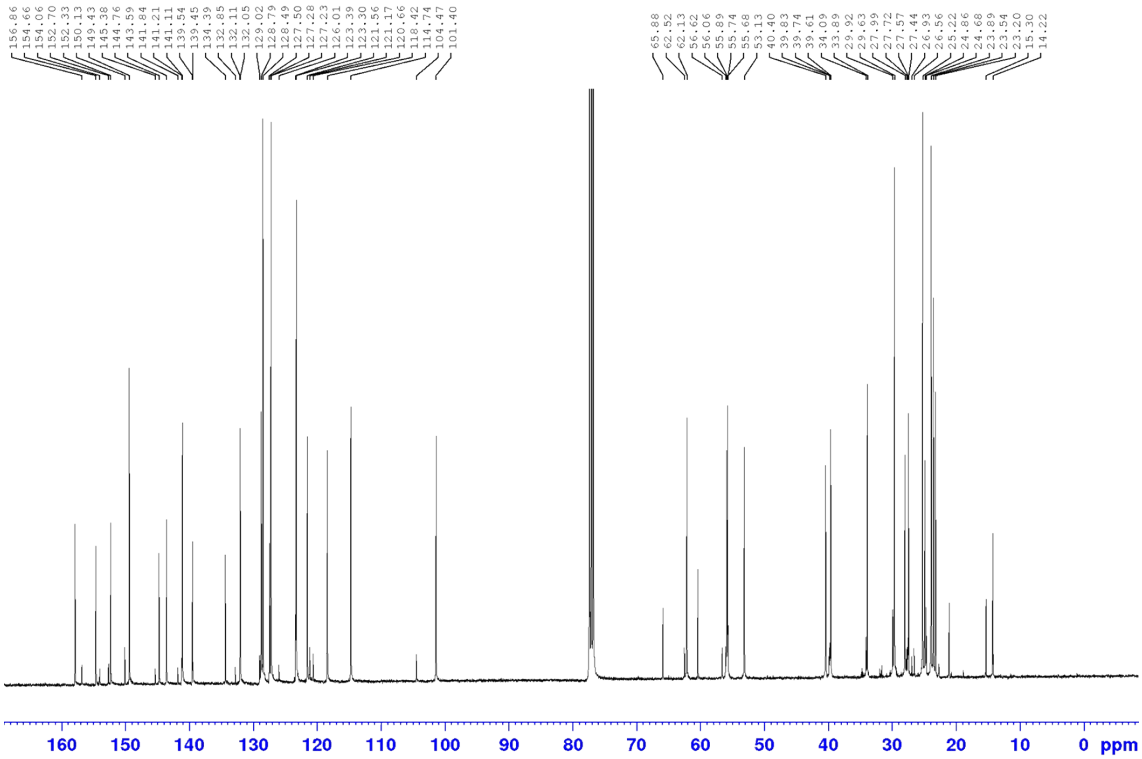


2,4,6-Triisopropyl-*N*-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)benzenesulfonamide (42)

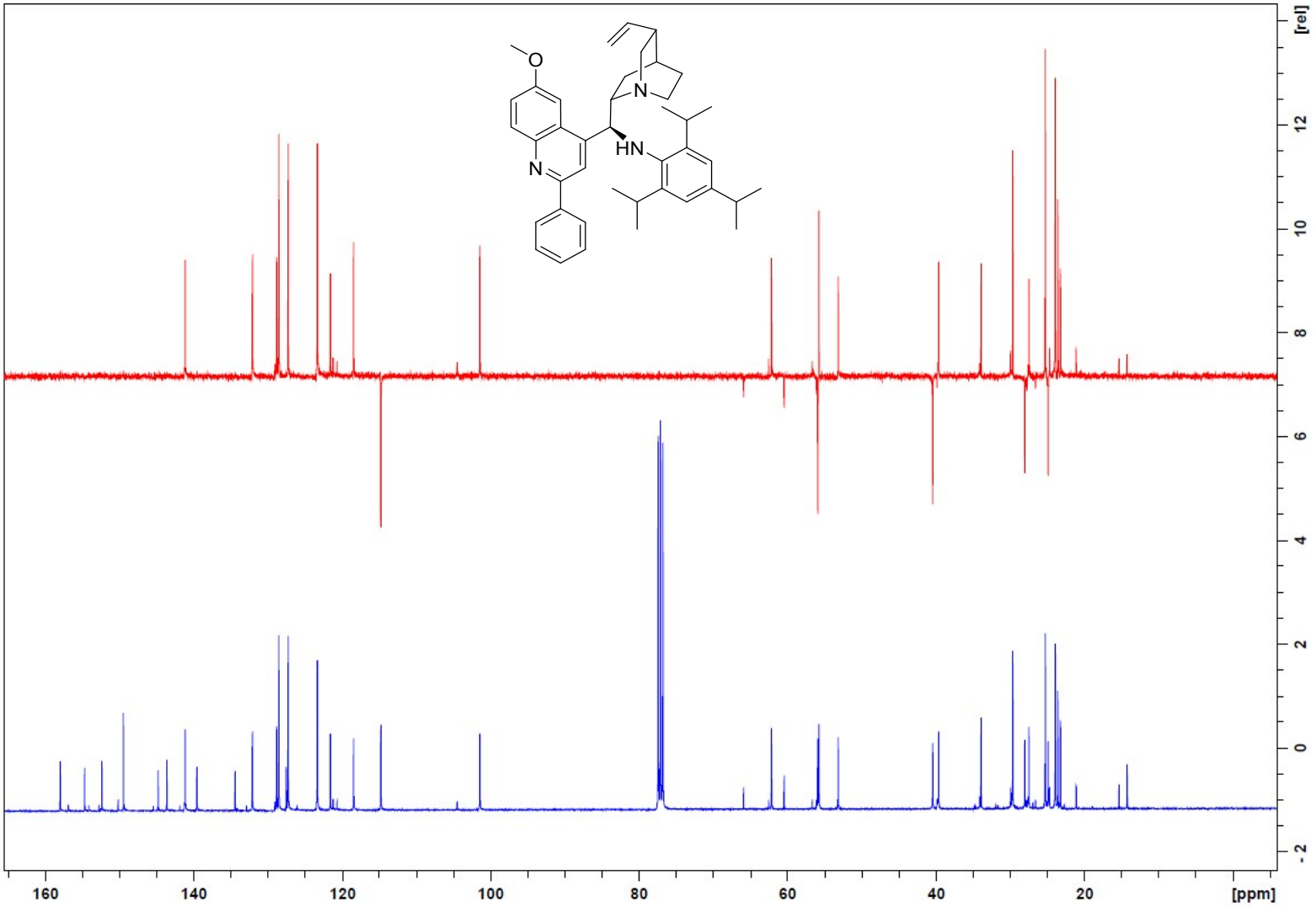


2,4,6-Triisopropyl-*N*-((*S*)-(6-methoxy-2-phenylquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)benzenesulfonamide (43)

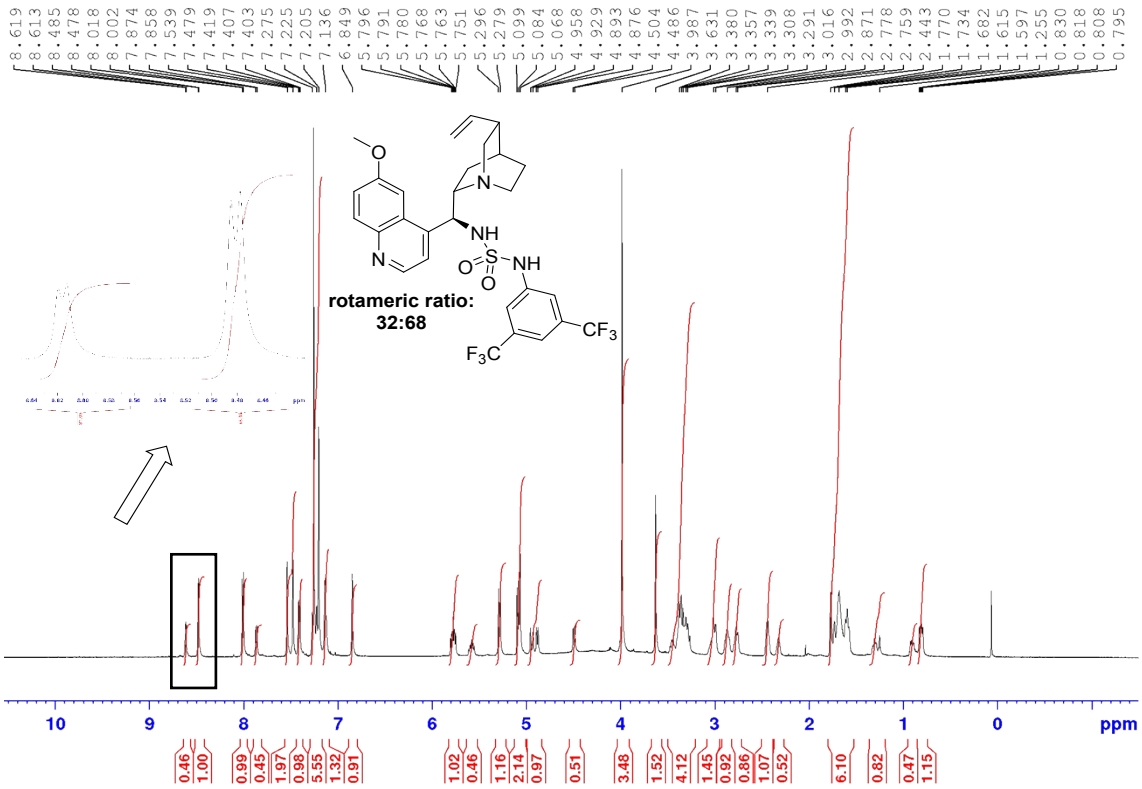


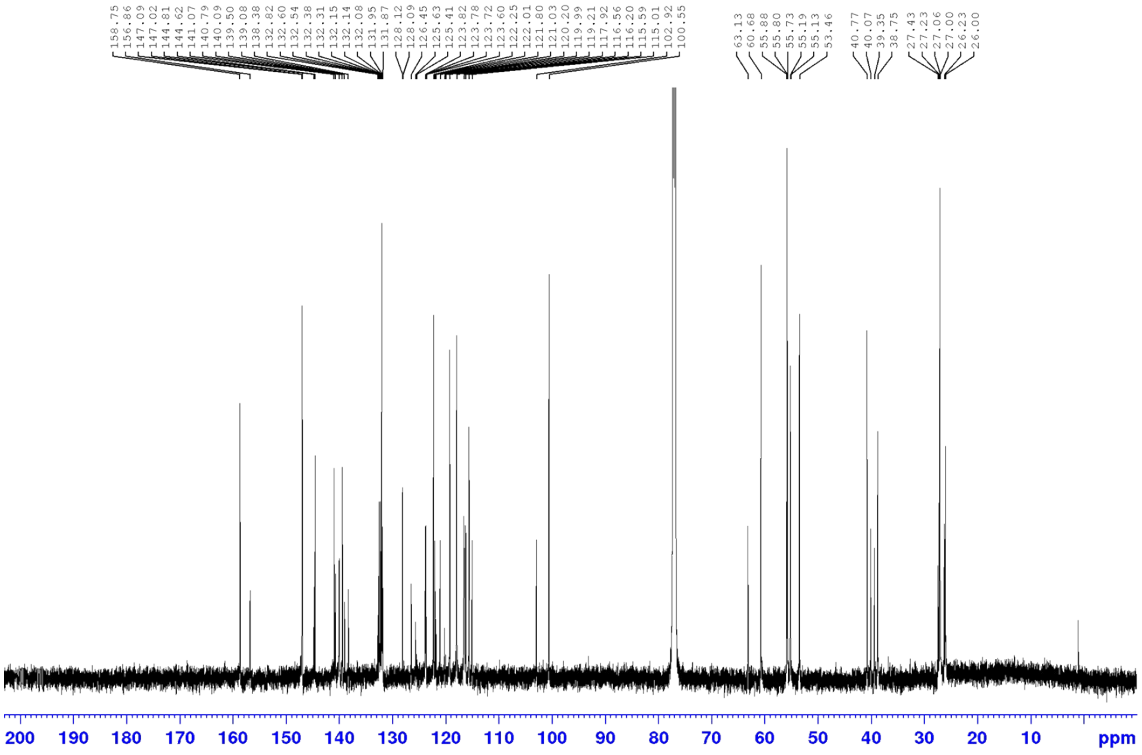


(43) ^{13}C + DEPT 135

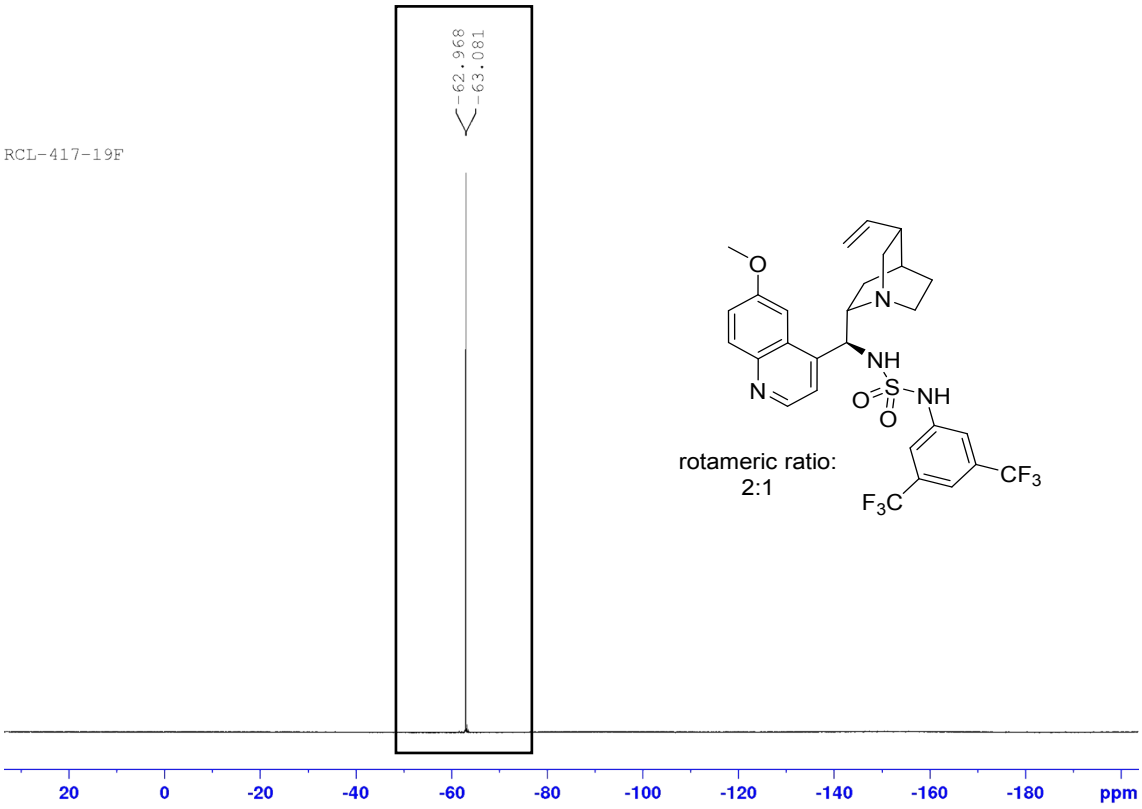


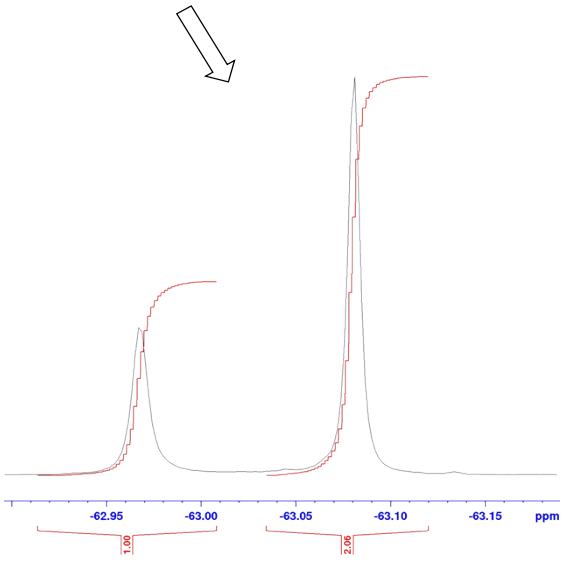
_N_-((_S_)-(6-methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)-3,5-bis(trifluoromethyl)benzenesulfamide (45)



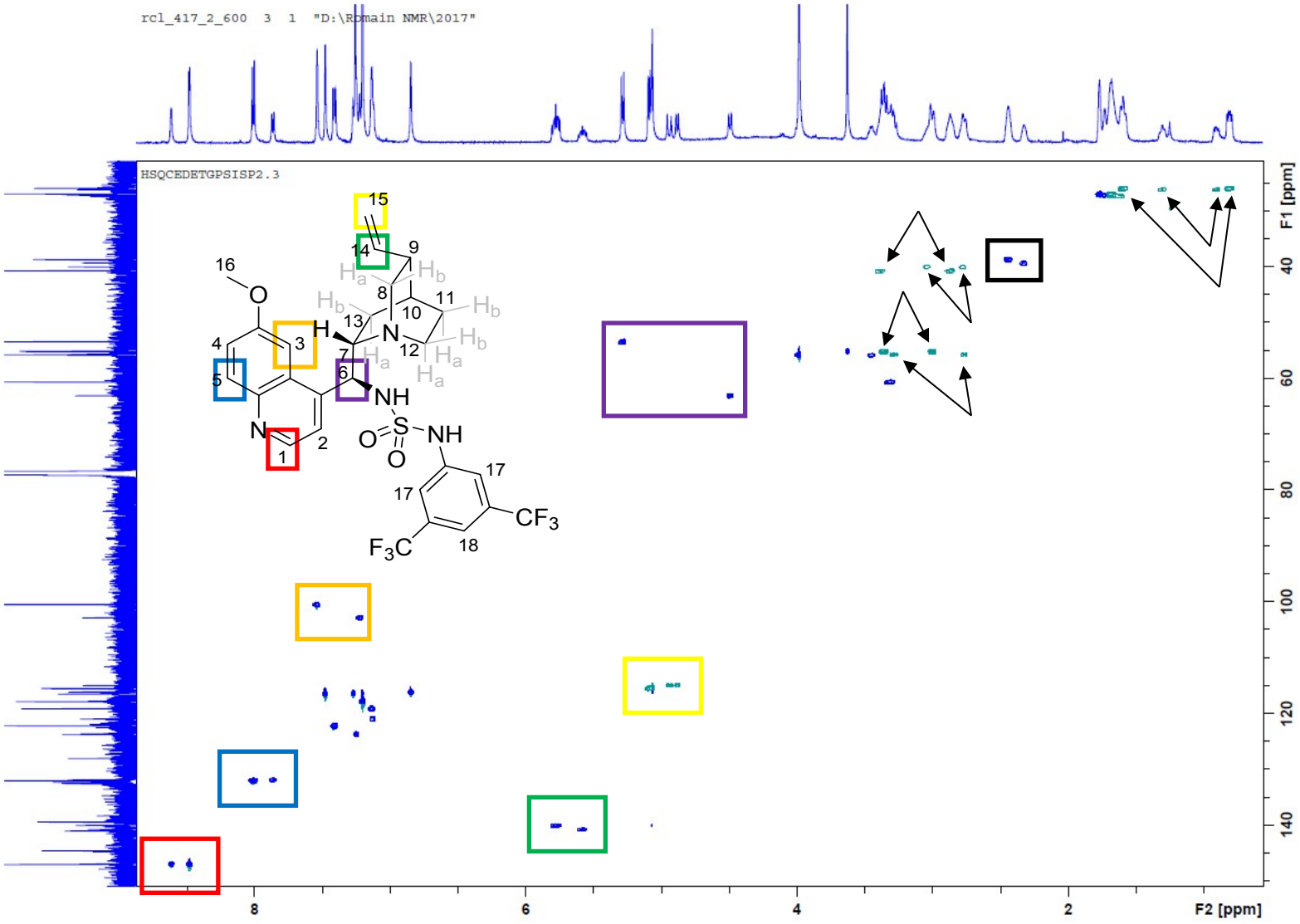


_N_-((_S_)-(6-methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)-3,5-bis(trifluoromethyl)benzenesulfamide (45)

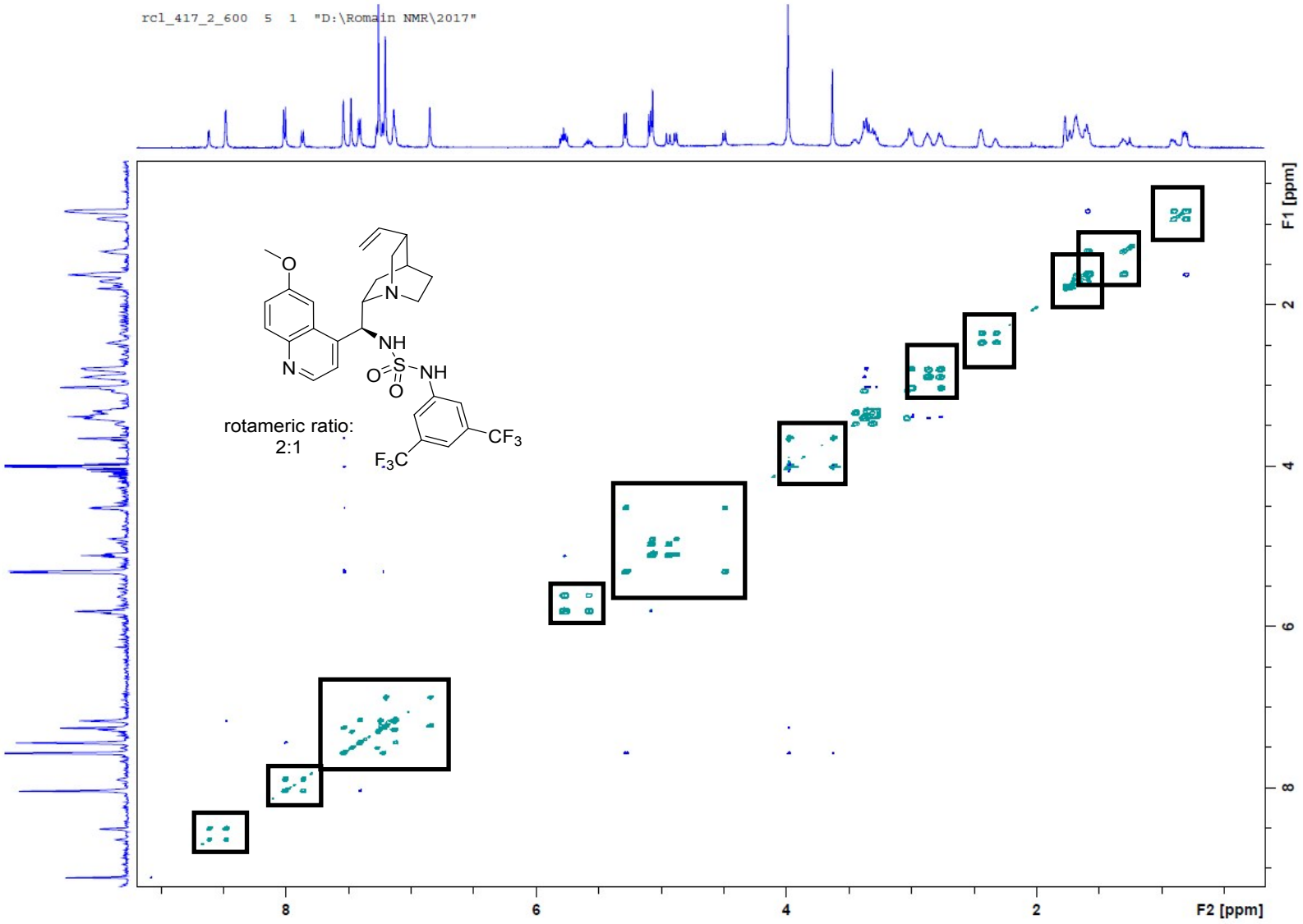




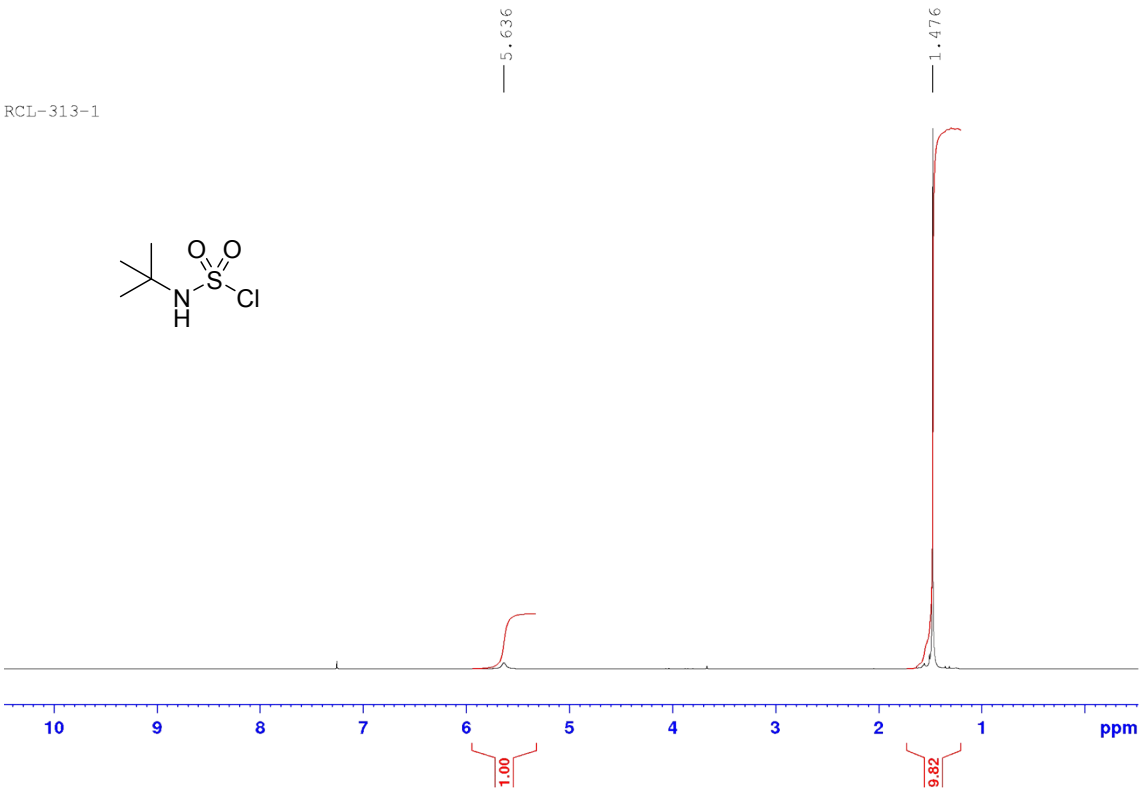
(45) HSQC – rotamers patterns identification

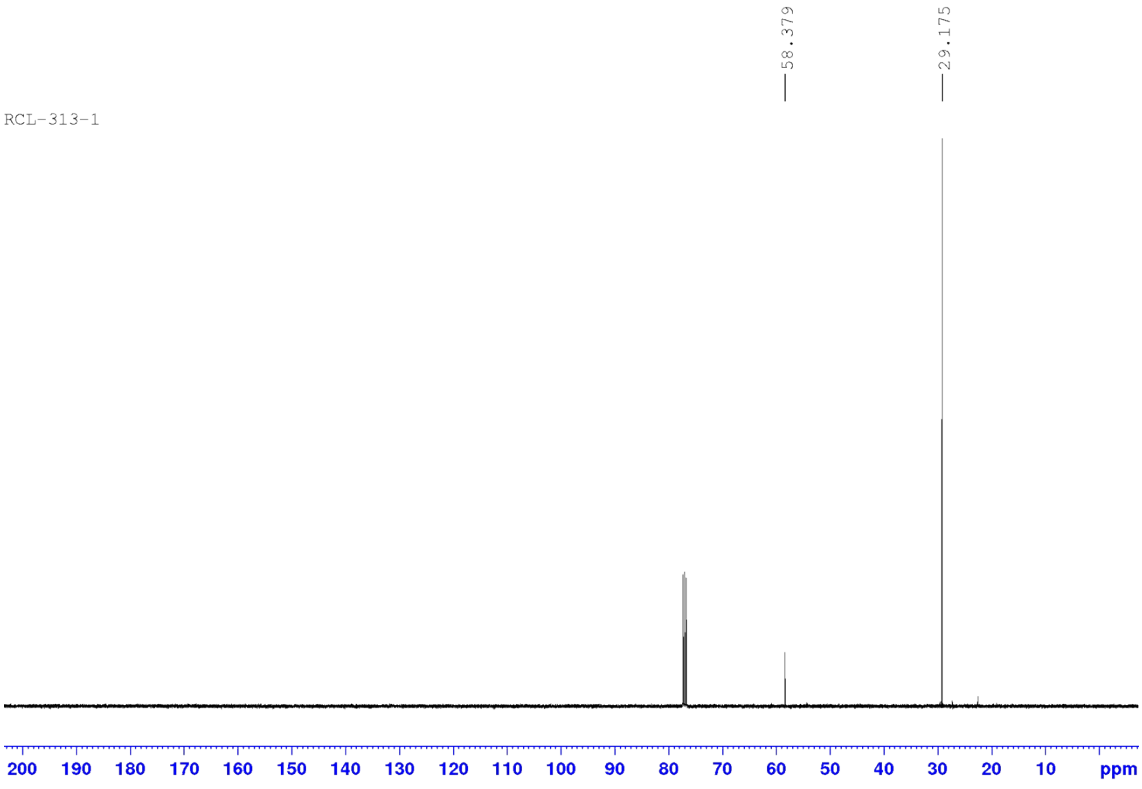


(45) NOESY

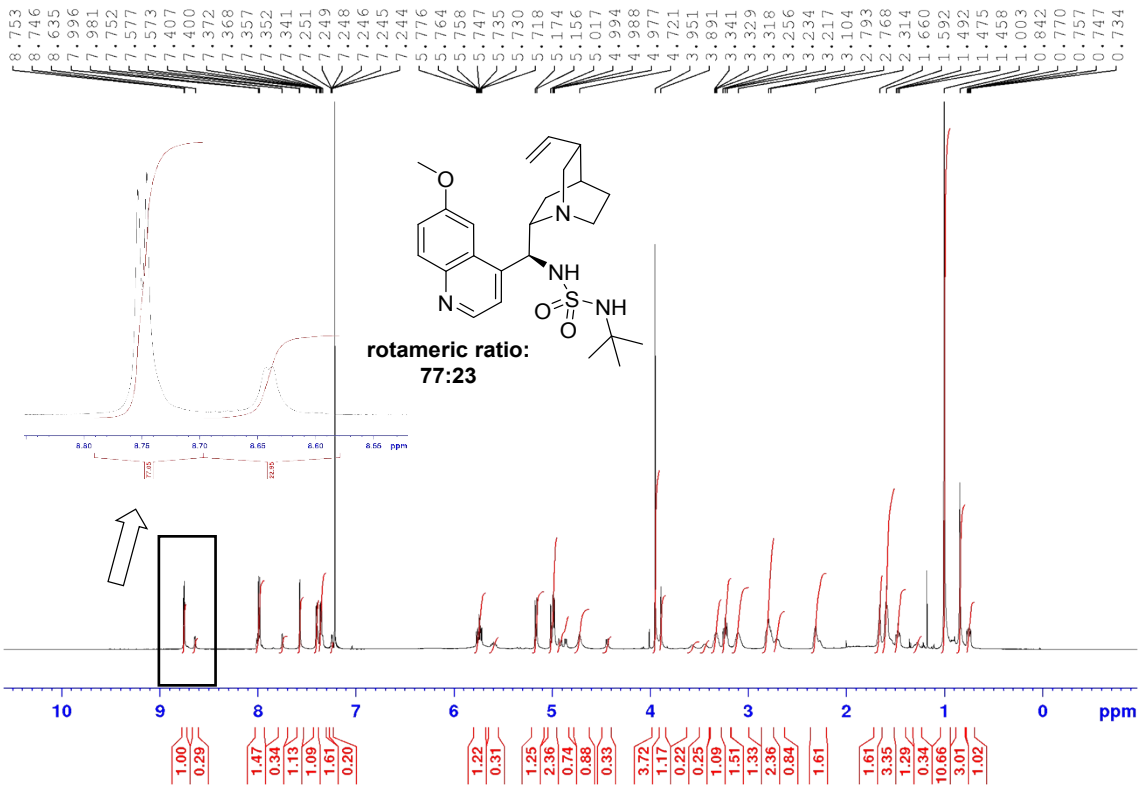

rcl_417_2_600 5 1 "D:\Romain NMR\2017"
rotameric ratio:
2:1
F1 [ppm]
F2 [ppm]
2
4
6
8

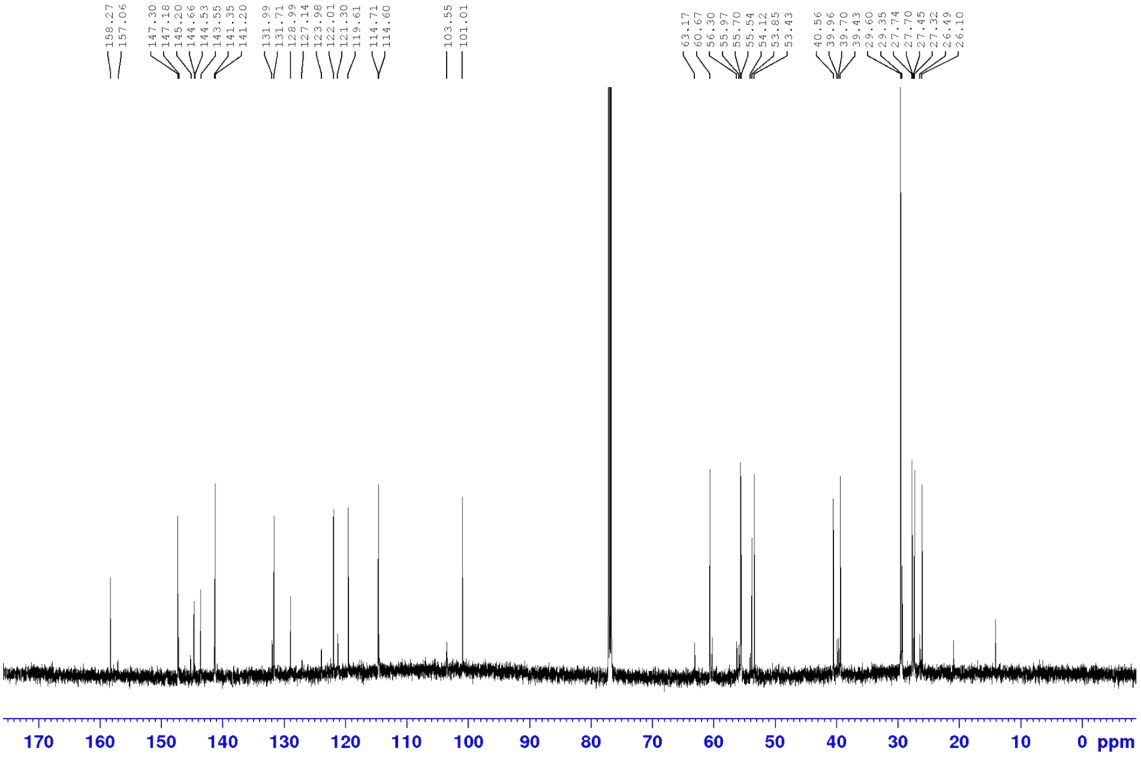
tert-Butylsulfamoyl chloride (S36)



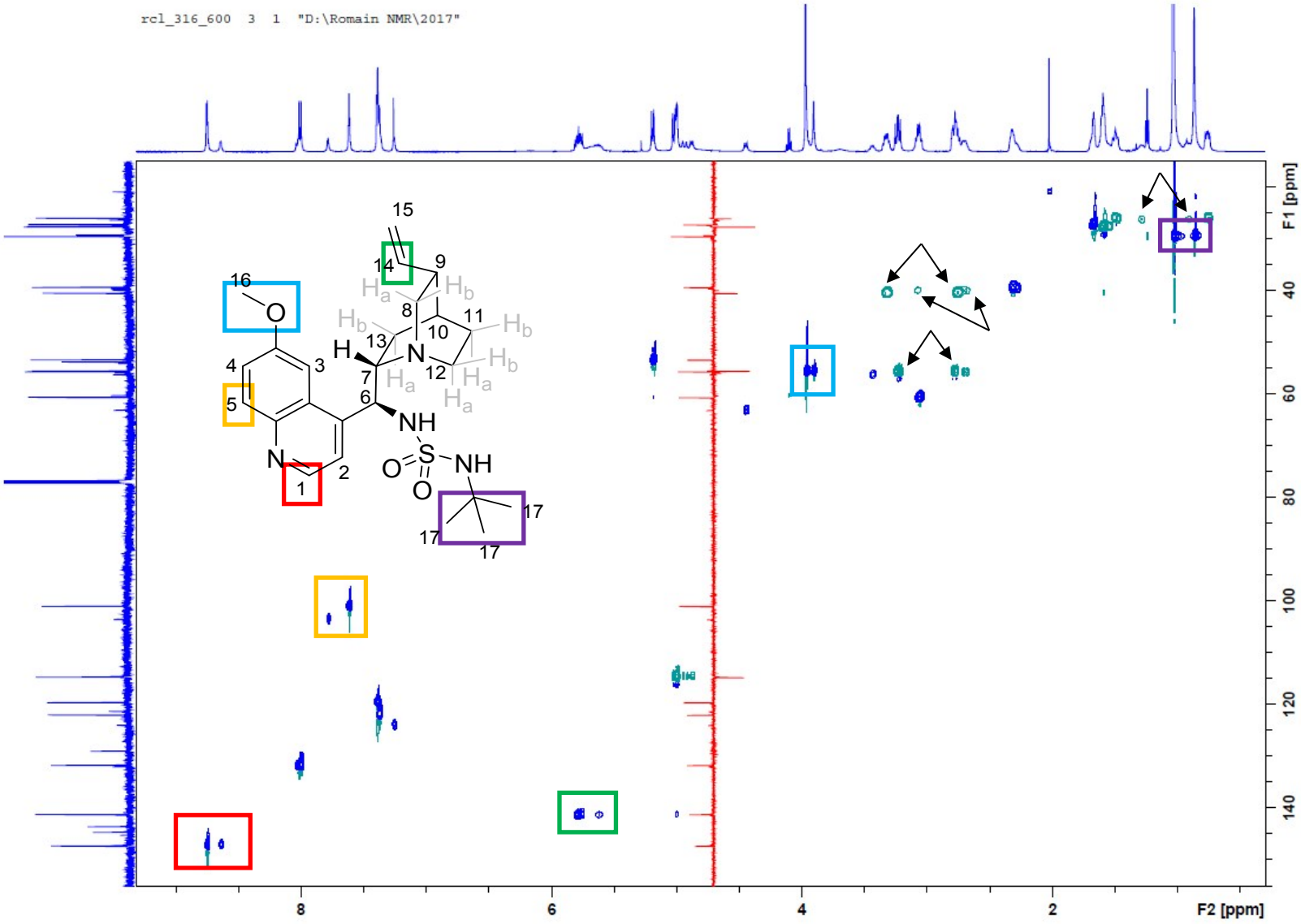


_N_-((_S_)-(6-methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)-2-methylpropane-2-sulfamide (46)

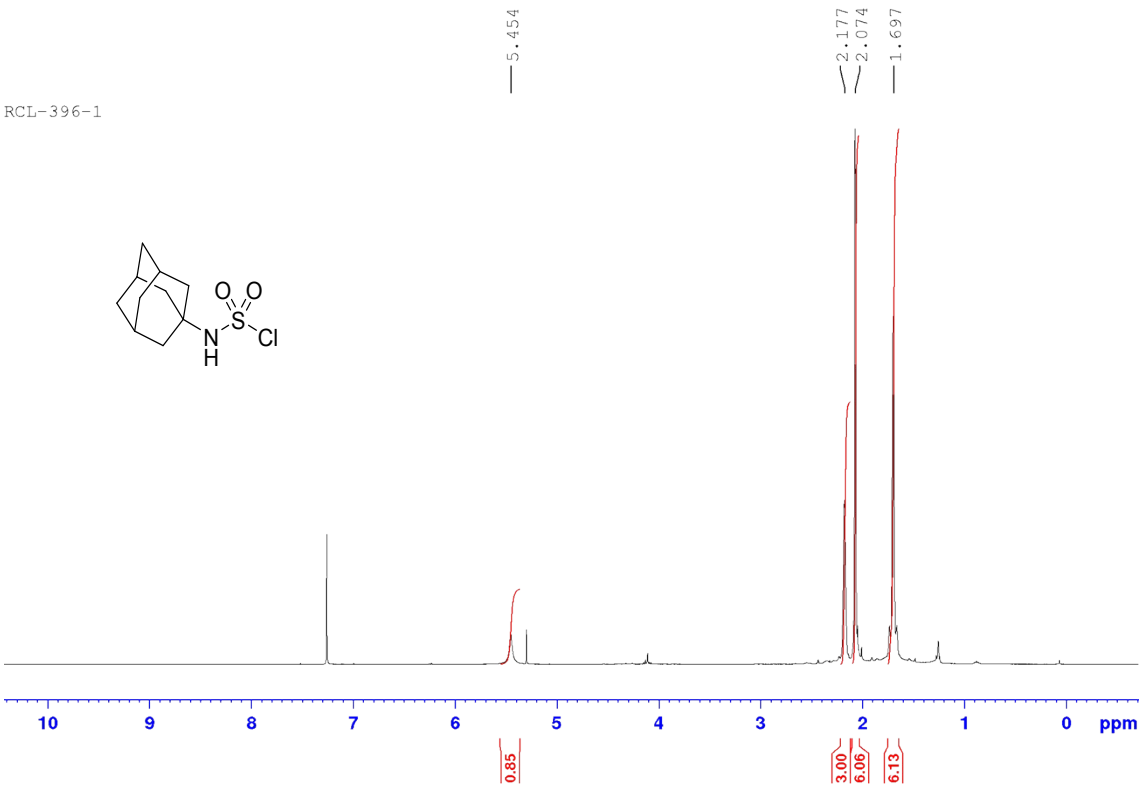


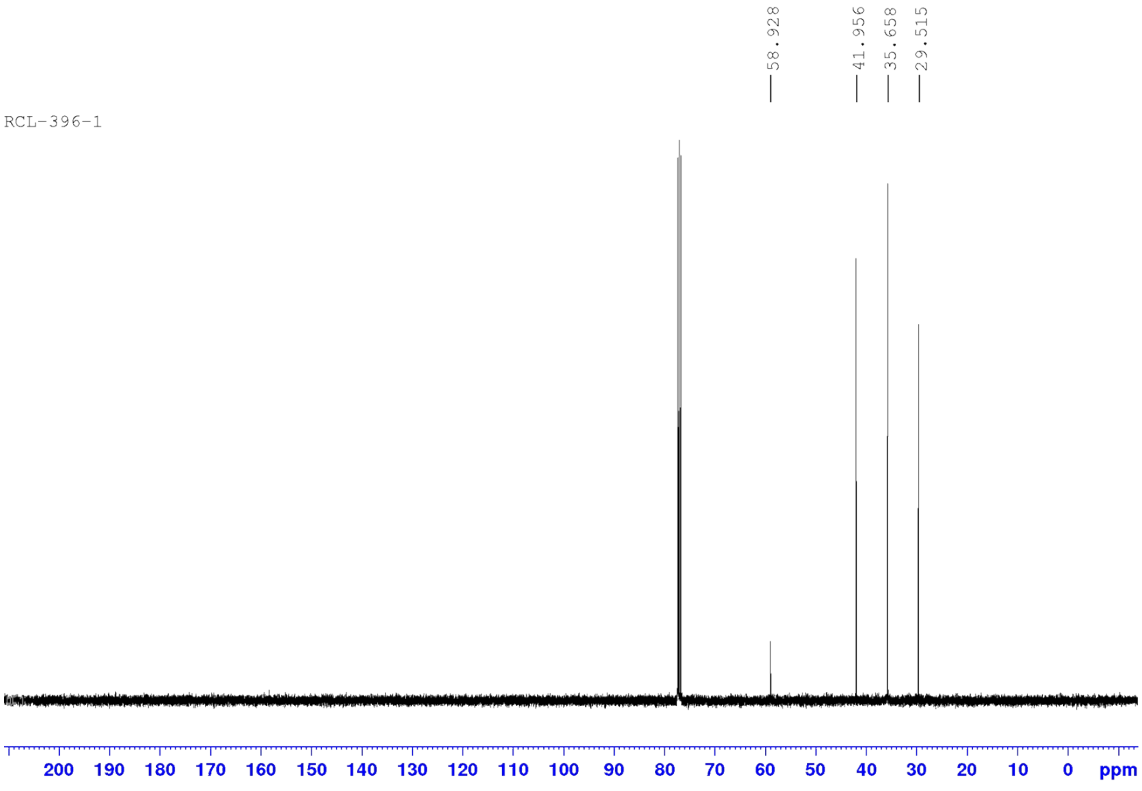


(46) Combination of HSQC and DEPT 135 to help the assignment of rotameric species

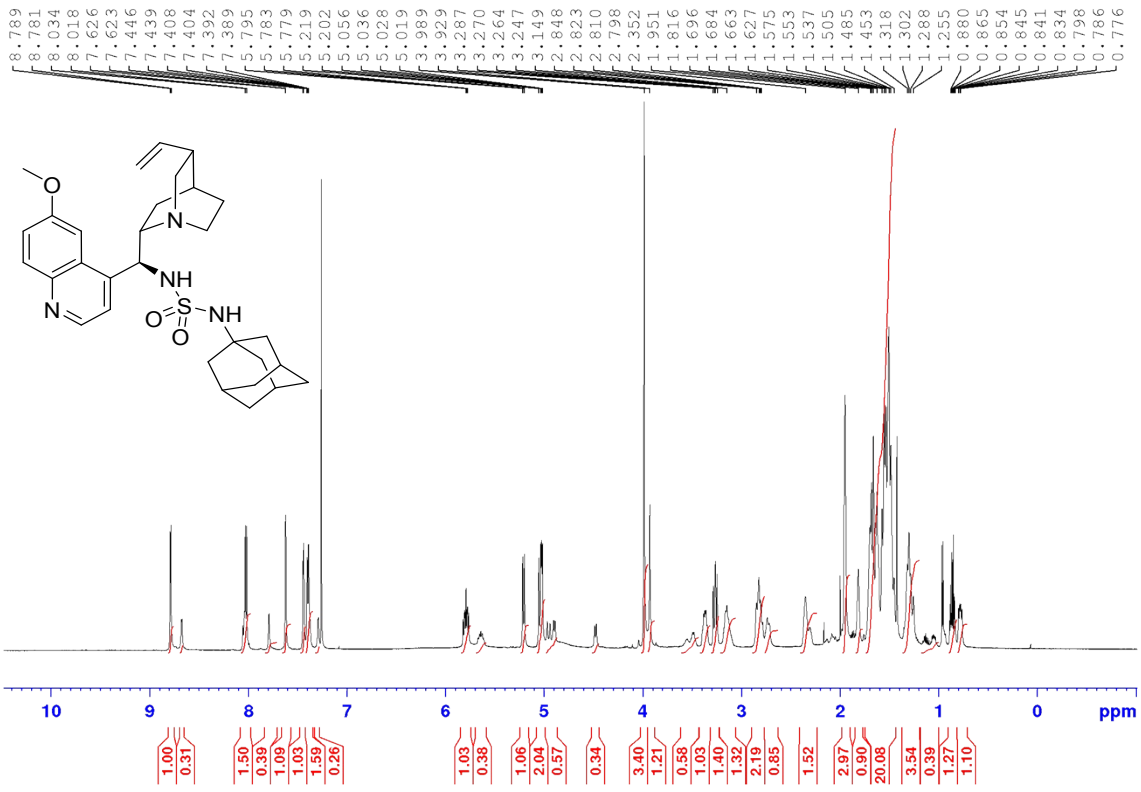


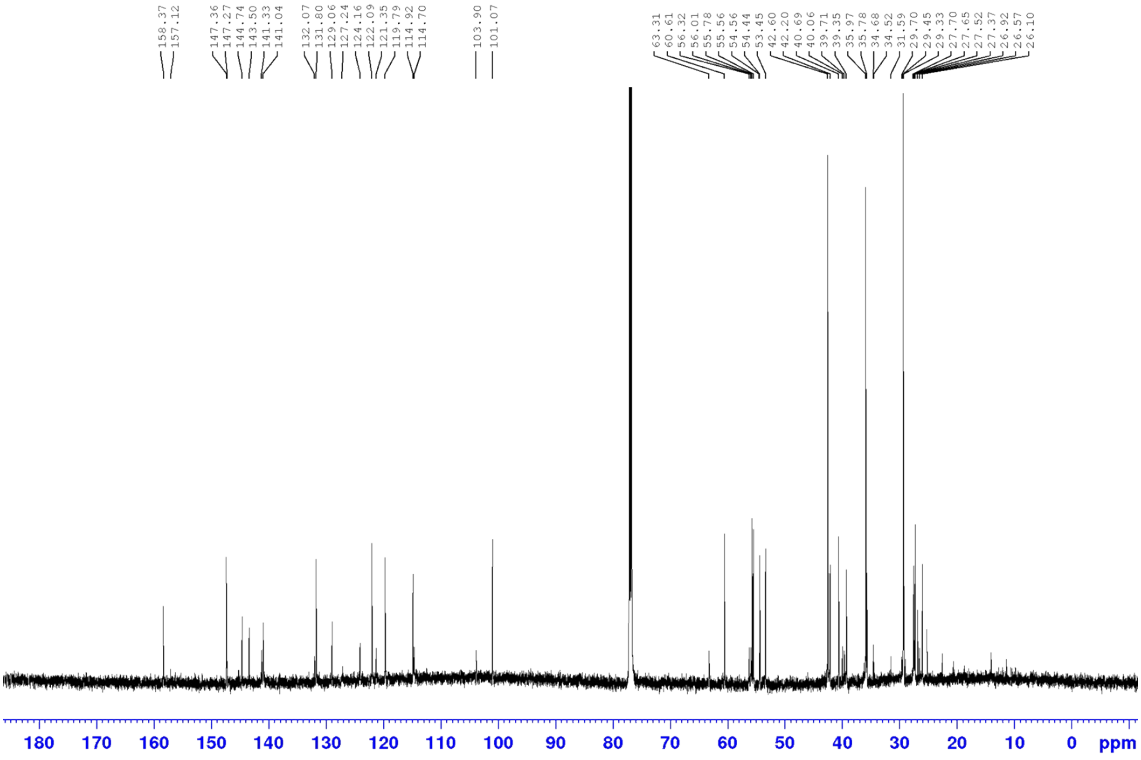
(Adamantan-1-yl)sulfamoyl chloride (S37)



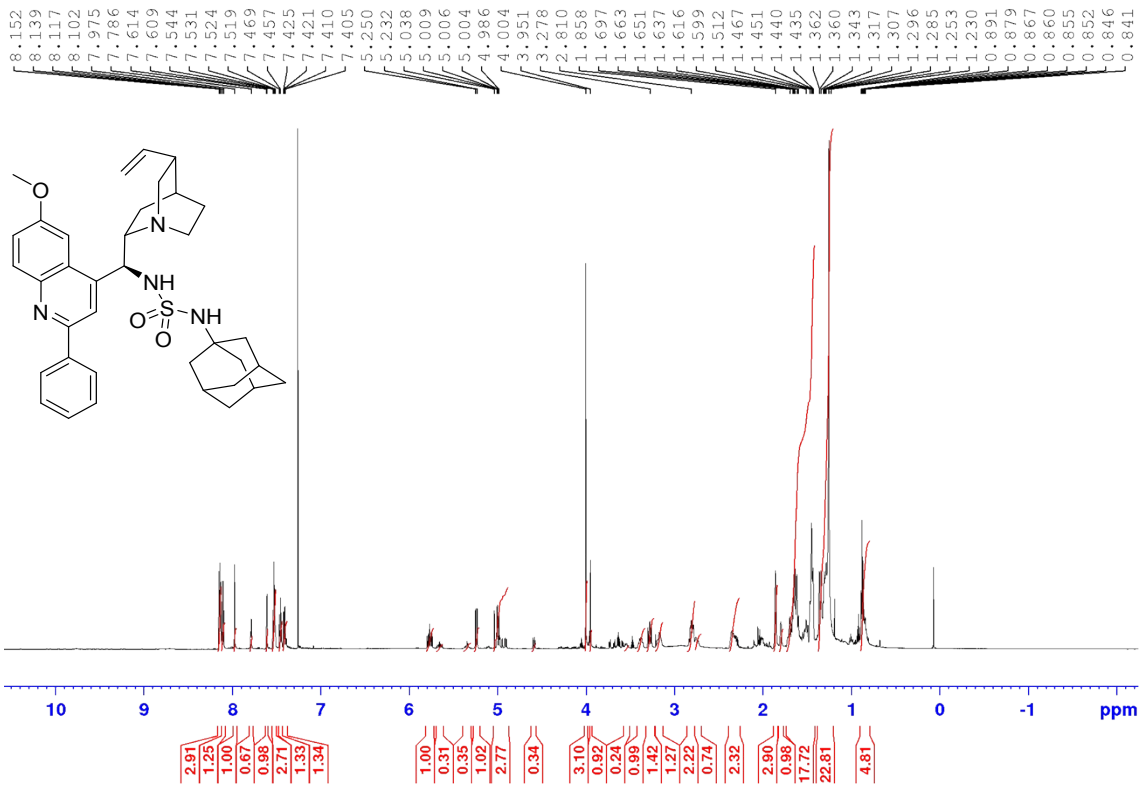


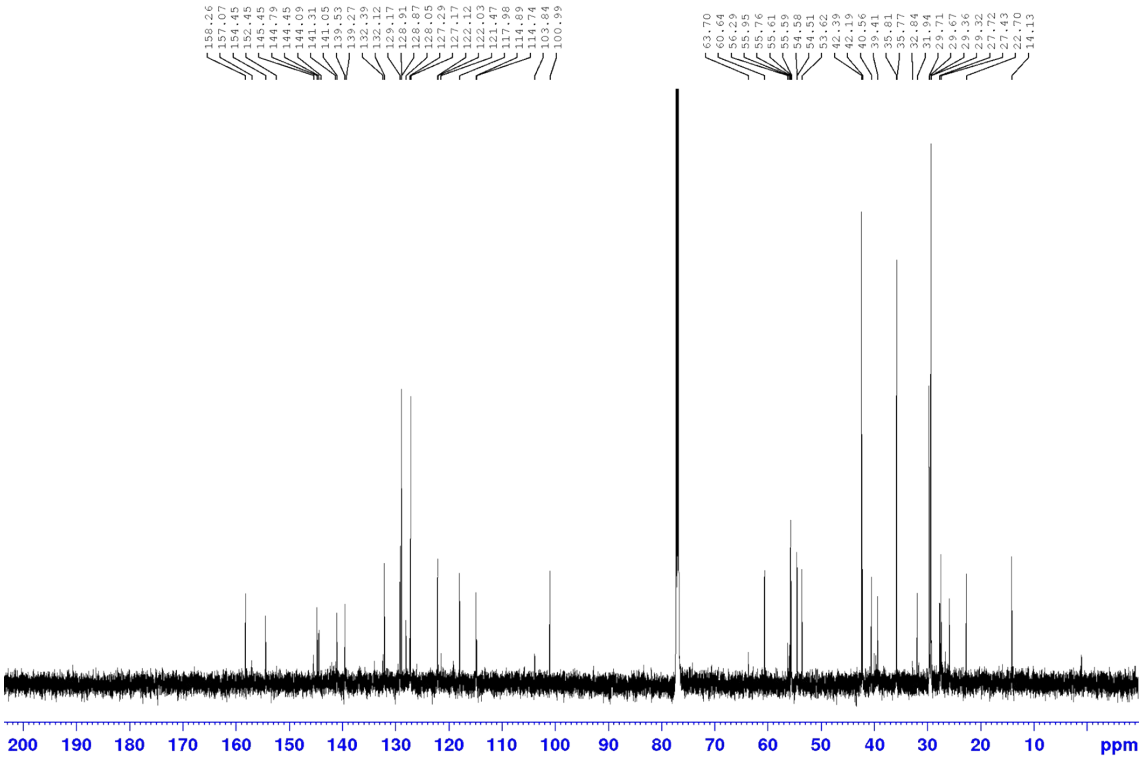
(3*R*,5*R*,7*R*)-*N*-((*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)adamantane-1-sulfamide (20)



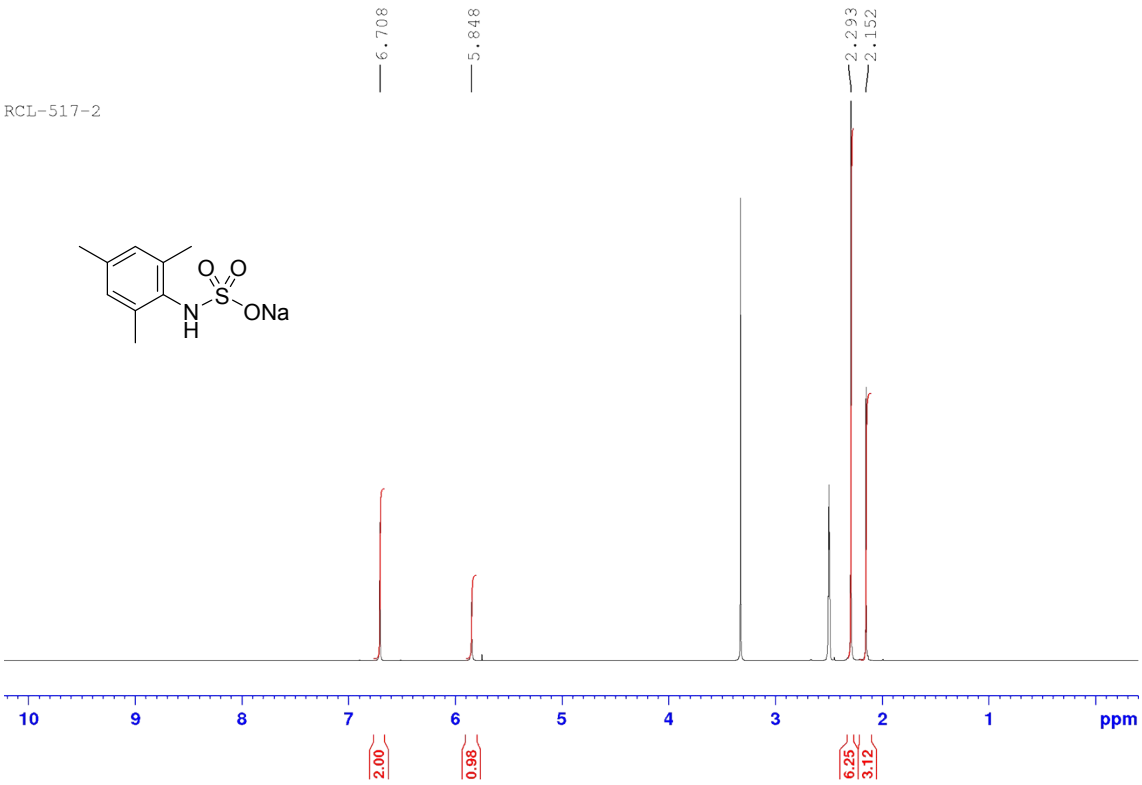


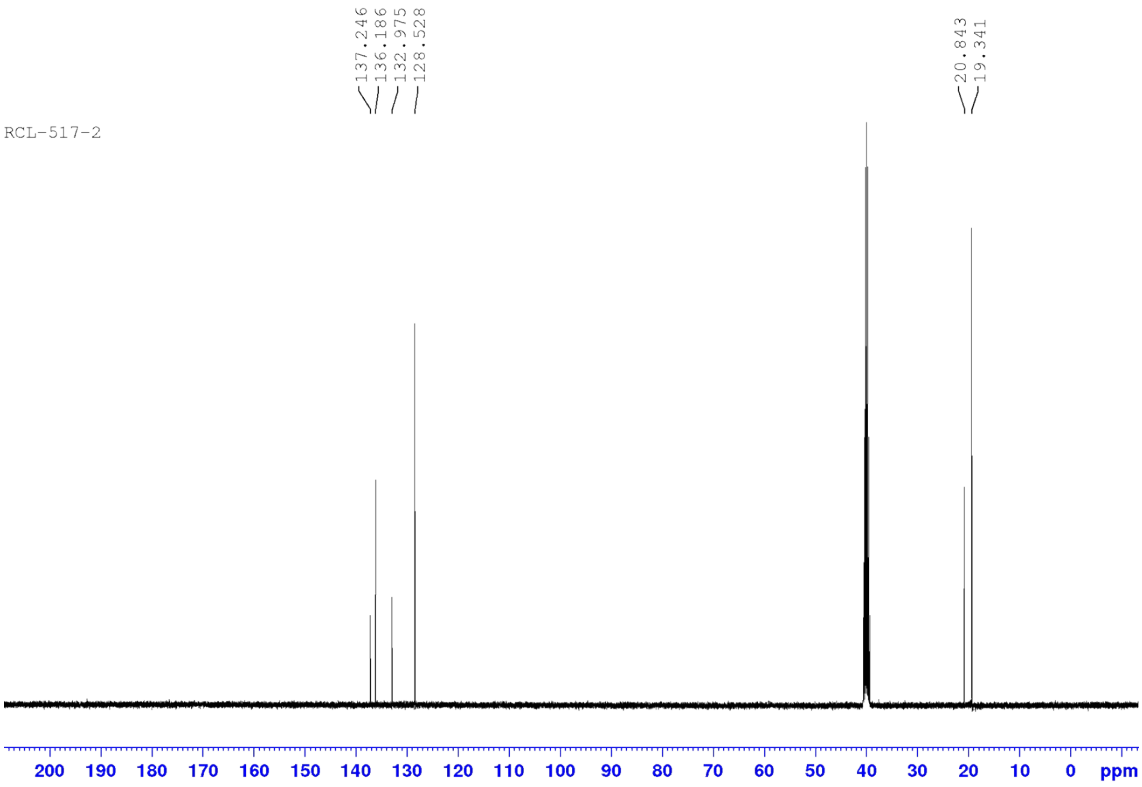
(3*R*,5*R*,7*R*)-*N*-((*S*)-(6-methoxy-2-phenylquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)adamantane-1-sulfonamide (48)



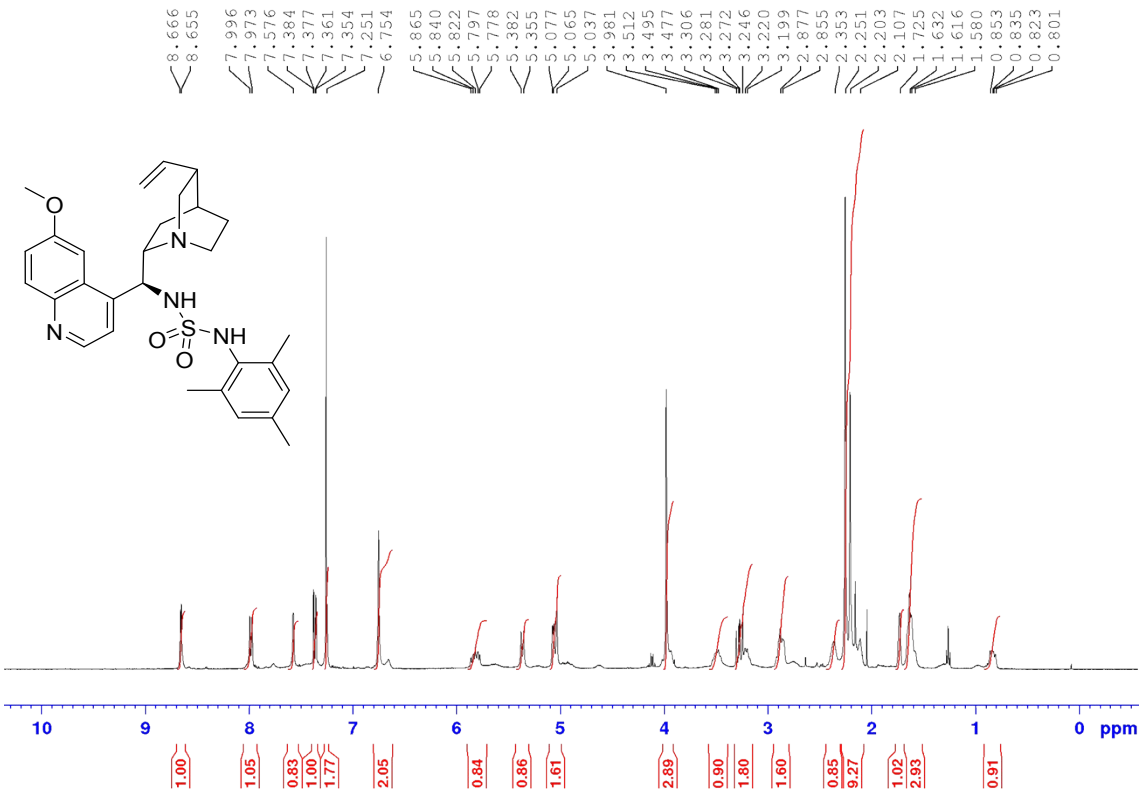


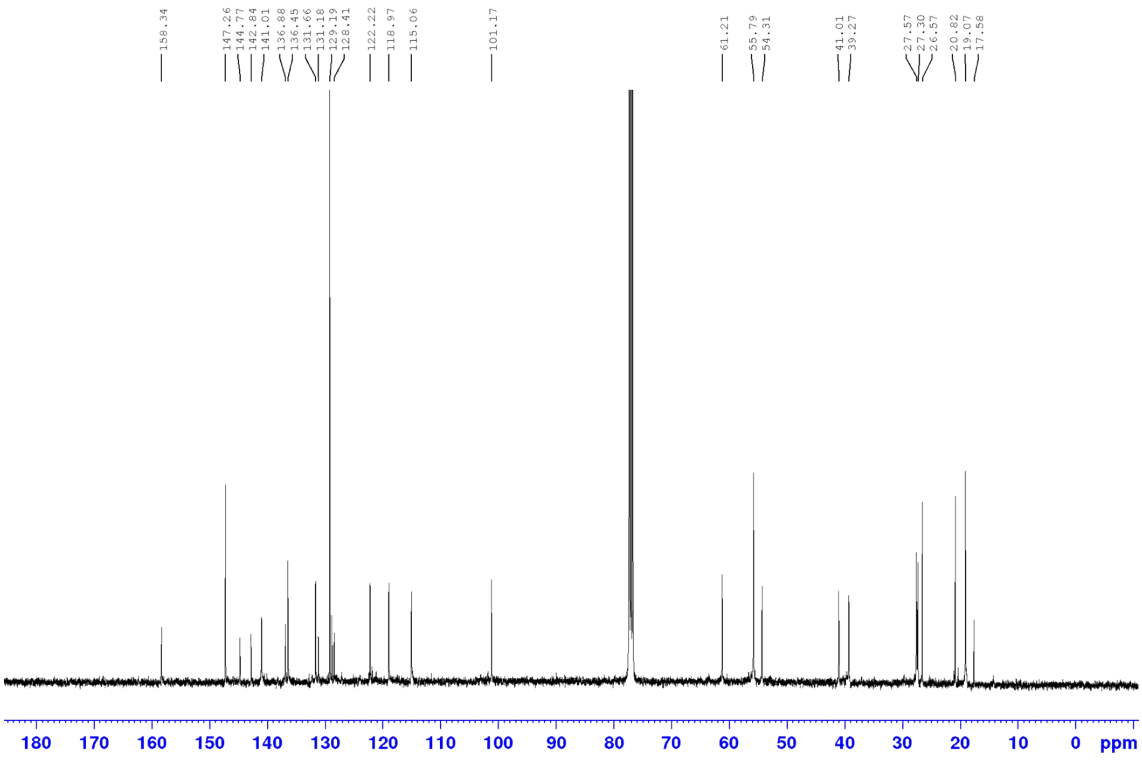
Sodium mesitylsulfamate (S39)





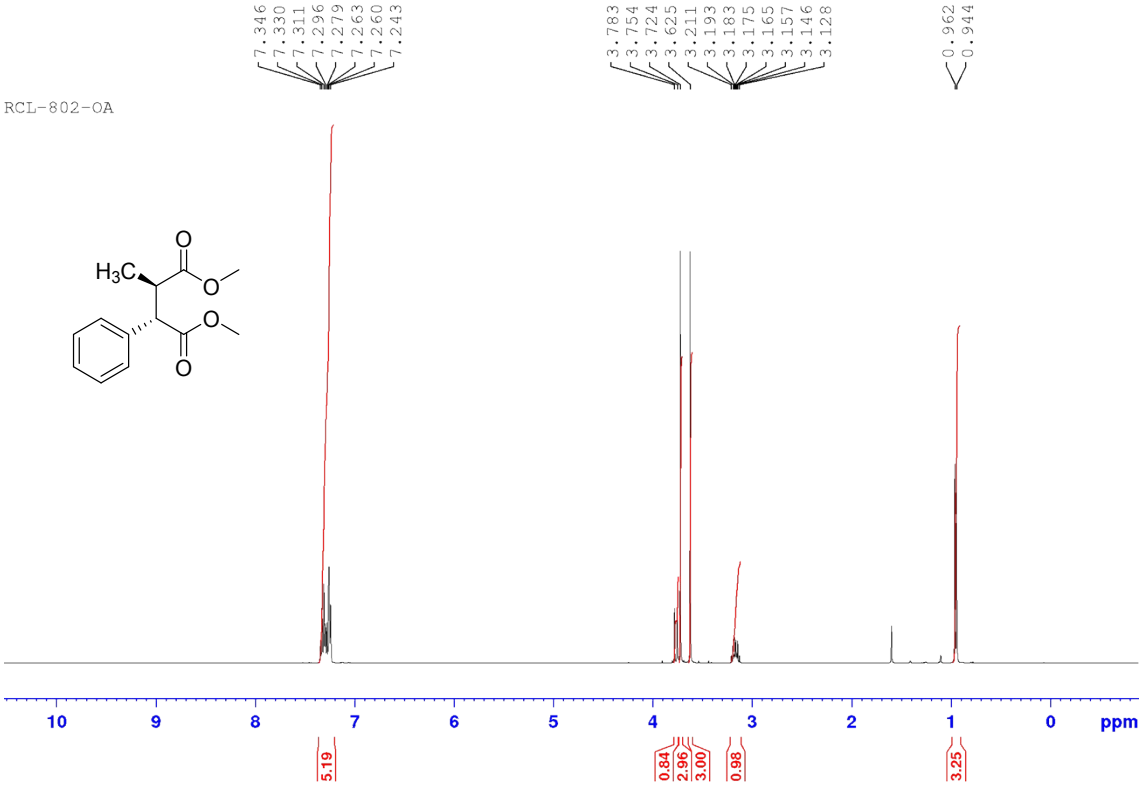
_N_-((_S_)-(6-Methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)-2,4,6-trimethylbenzenesulfonamide (47)

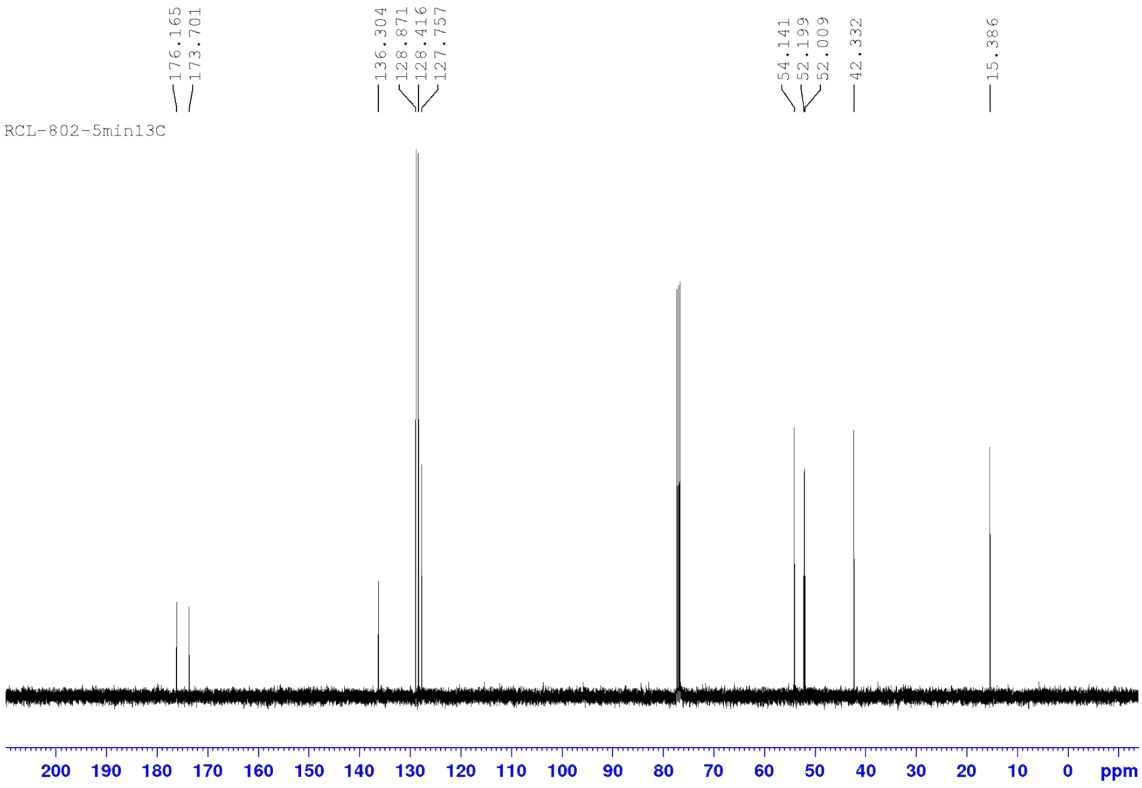




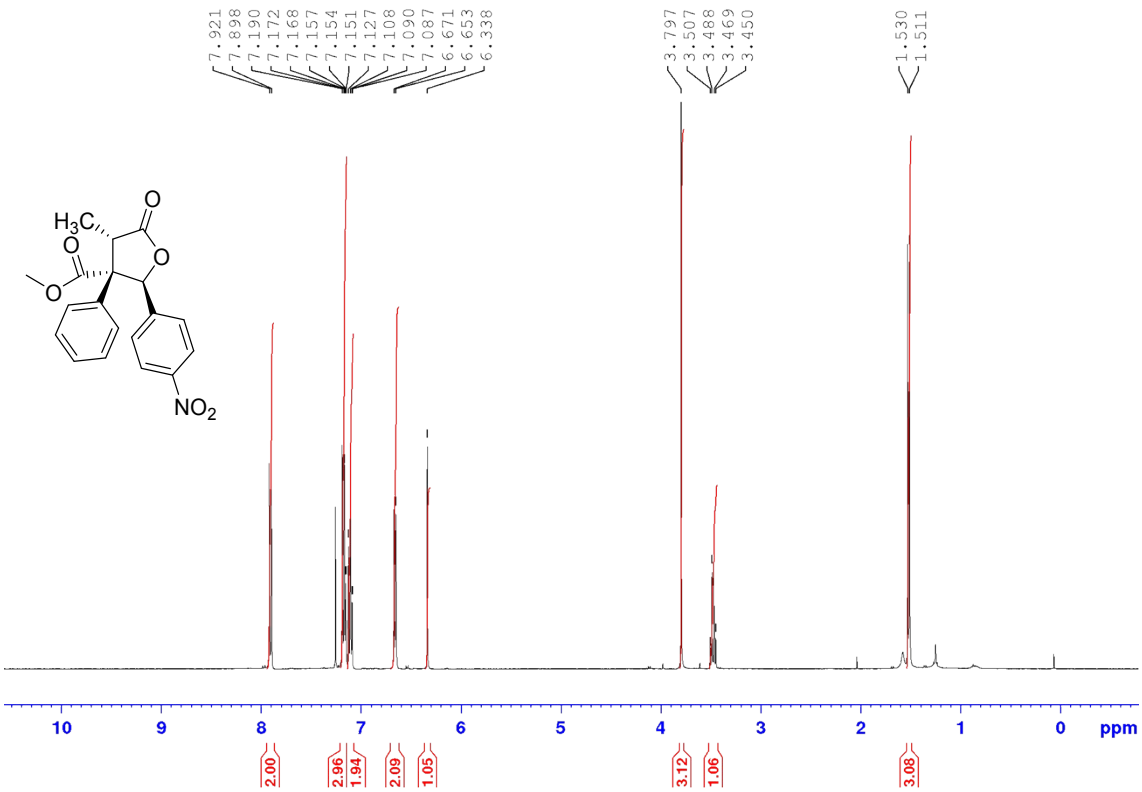
9. NMR spectra: ^{1}H and ^{13}C (open anhydrides and lactones)

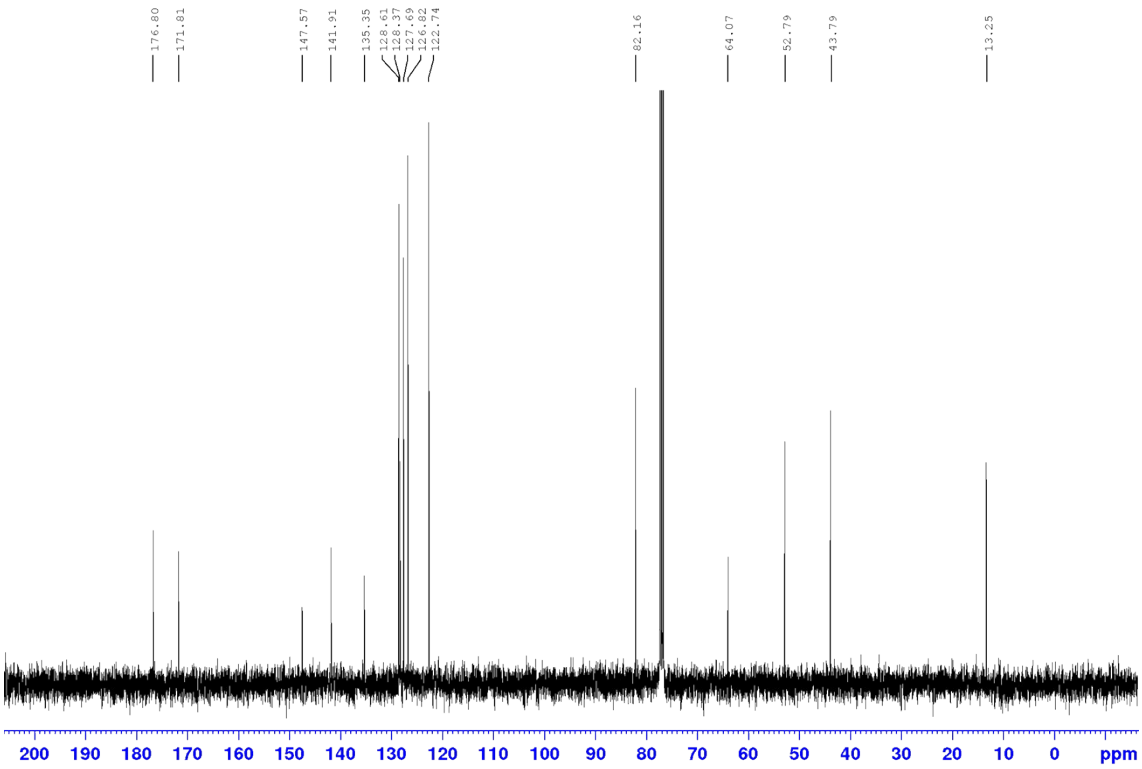
Dimethyl (2*R*,3*S*)-2-methyl-3-phenylsuccinate (49)



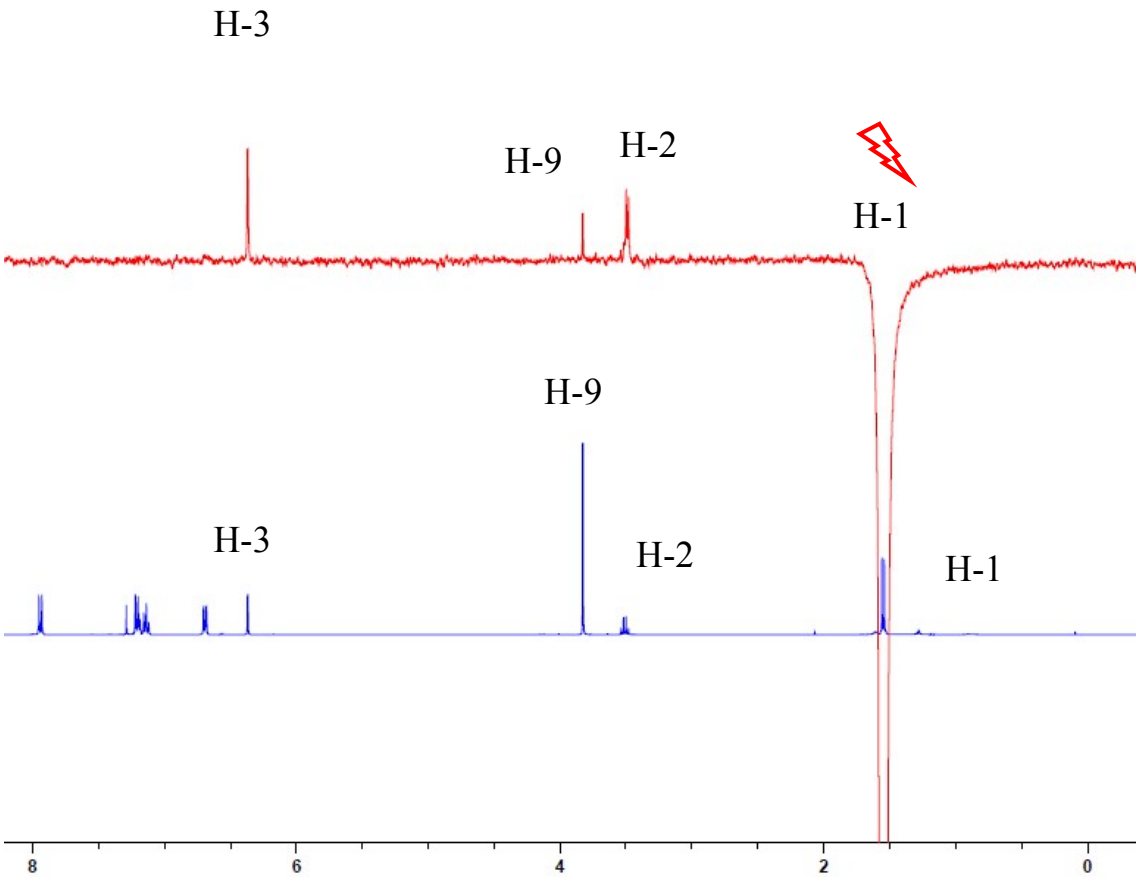


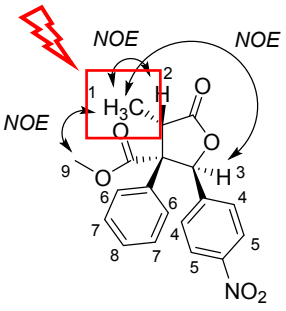
Methyl 4-methyl-2-(4-nitrophenyl)-5-oxo-3-phenyltetrahydrofuran-3-carboxylate (57)



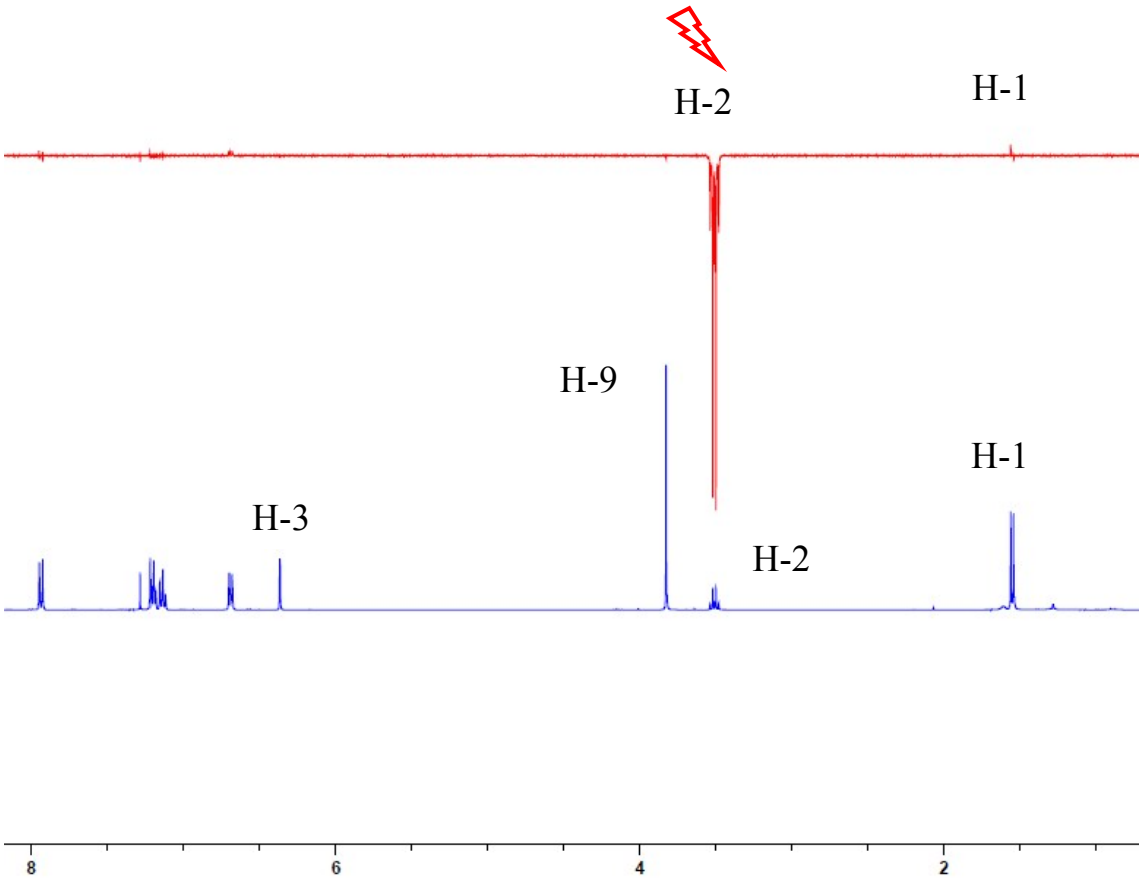


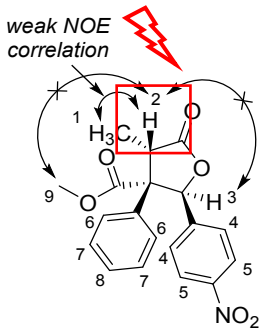
(57): NOE experiments – Irradiation H-1



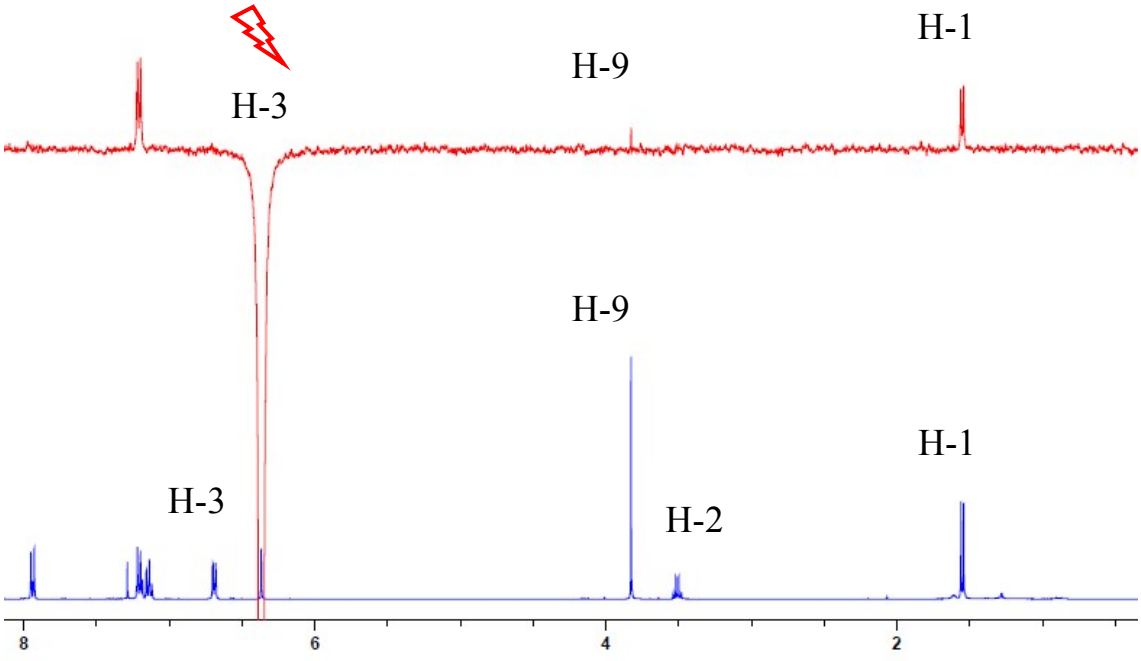


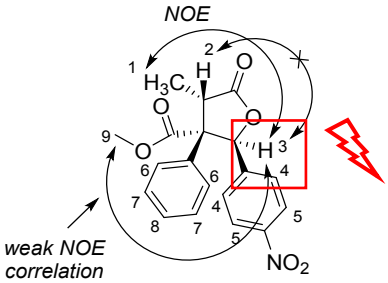
(57): NOE experiments – Irradiation H-2



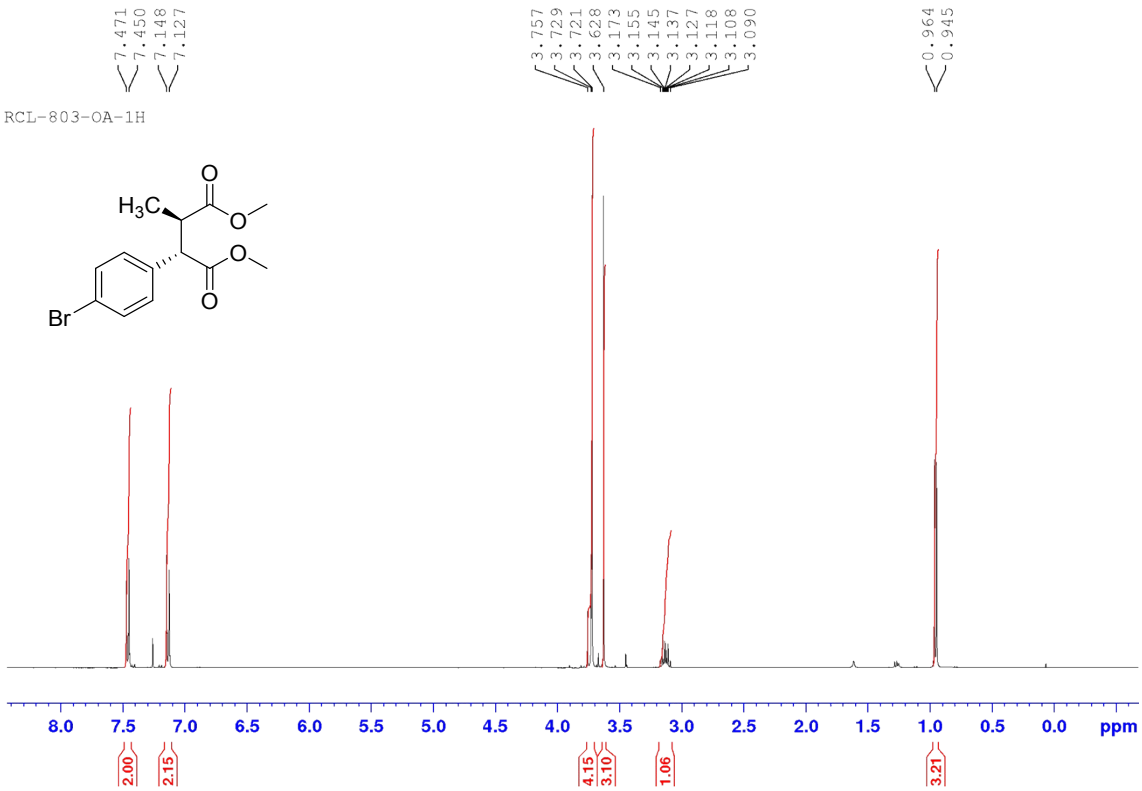


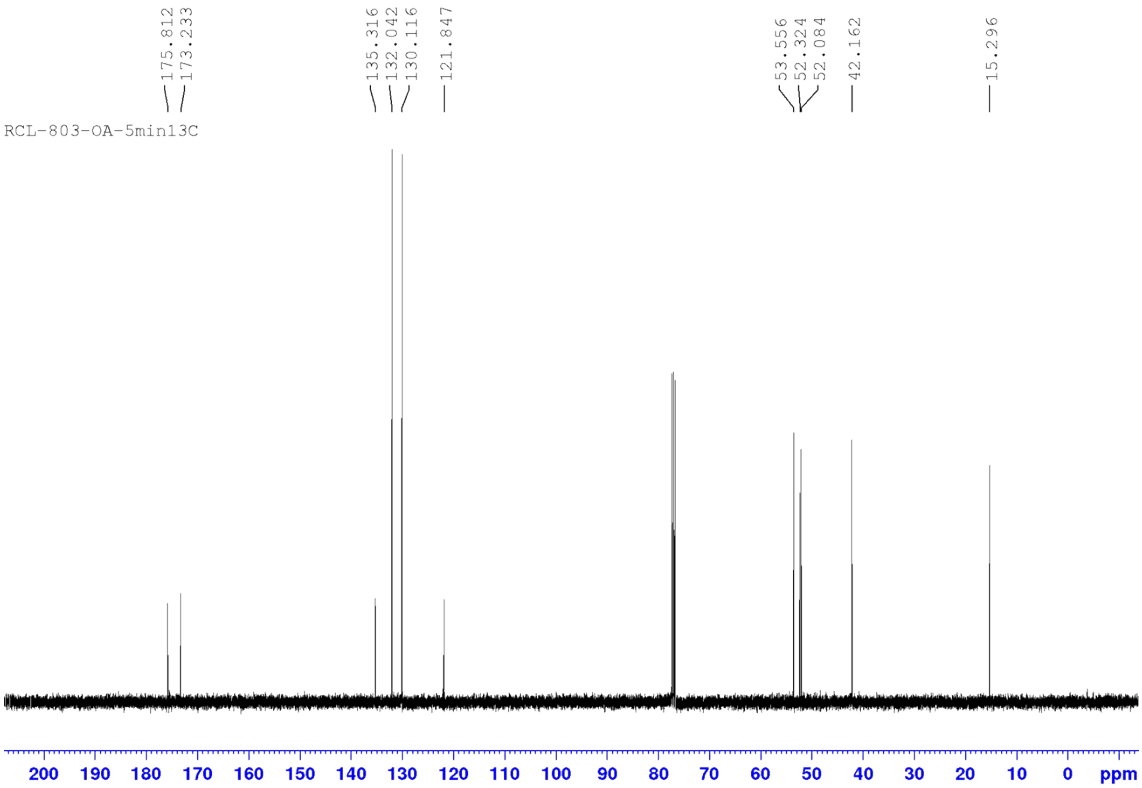
(57): NOE experiments – Irradiation H-3



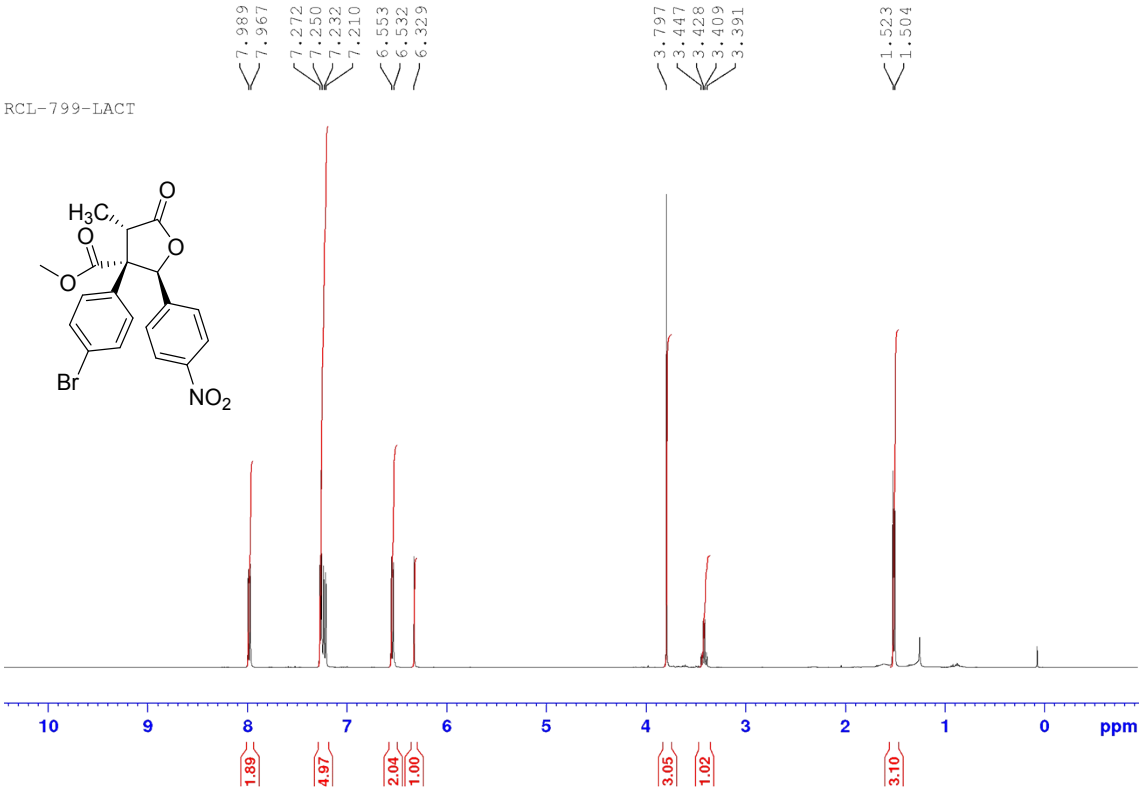


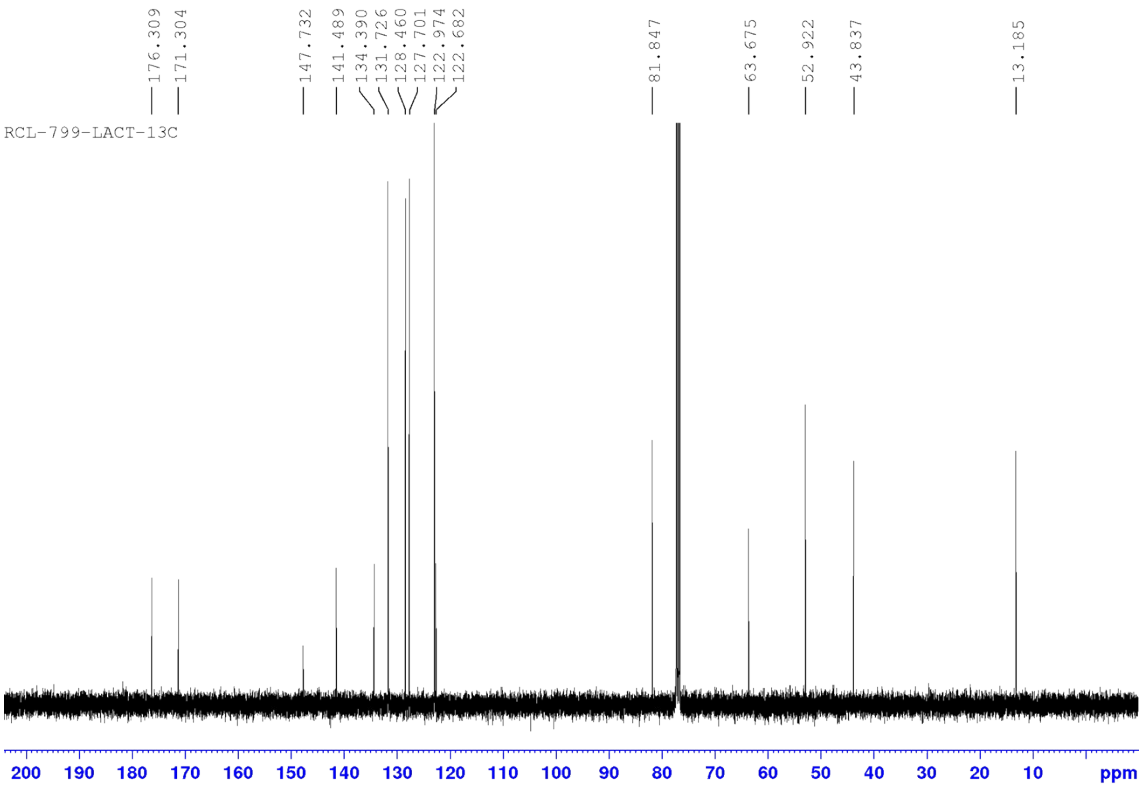
Dimethyl (2*S*,3*R*)-2-(4-bromophenyl)-3-methylsuccinate (50)



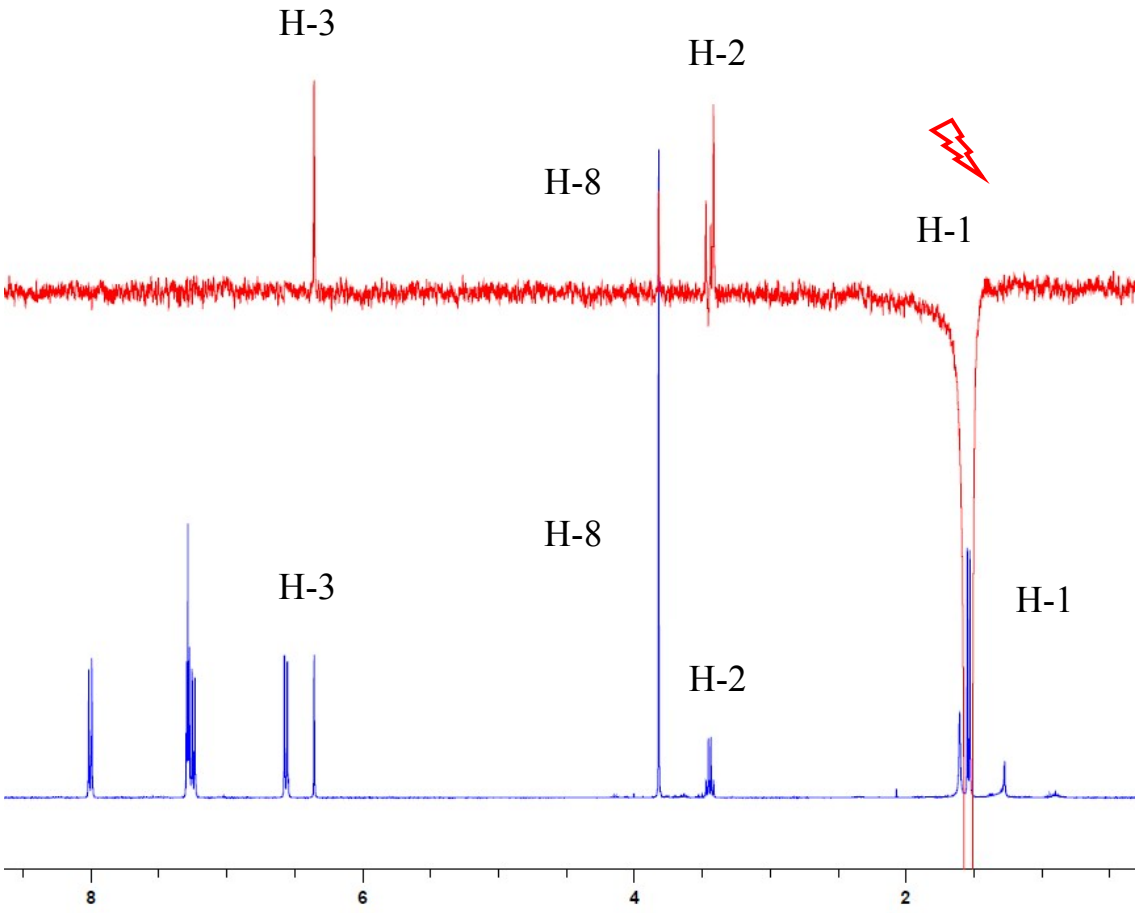


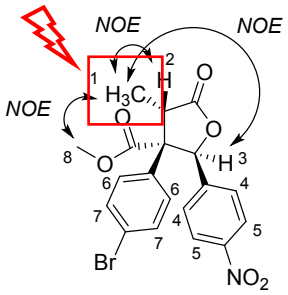
Methyl 3-(4-bromophenyl)-4-methyl-2-(4-nitrophenyl)-5-oxotetrahydrofuran-3-carboxylate (58)



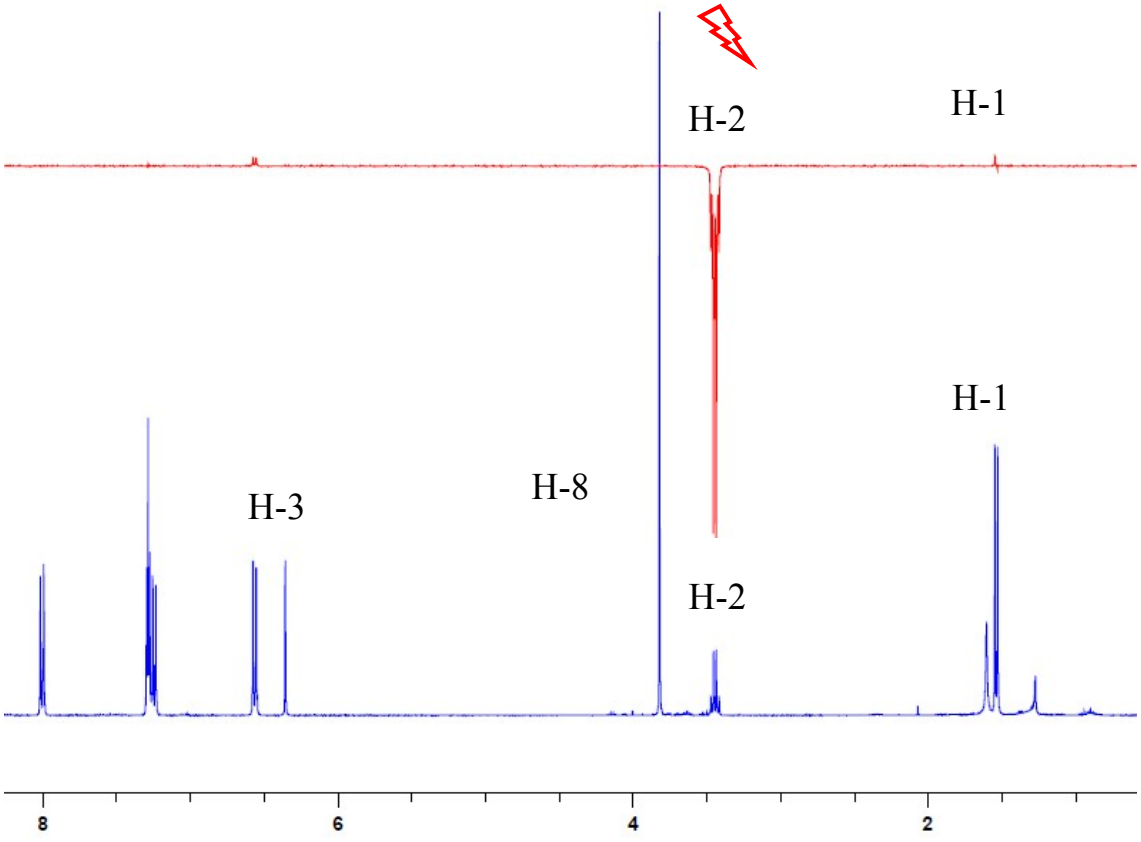


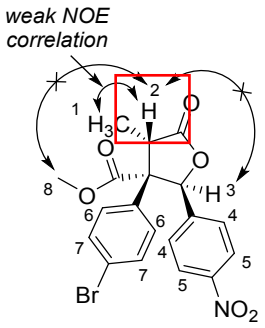
(58): NOE experiments – Irradiation H-1



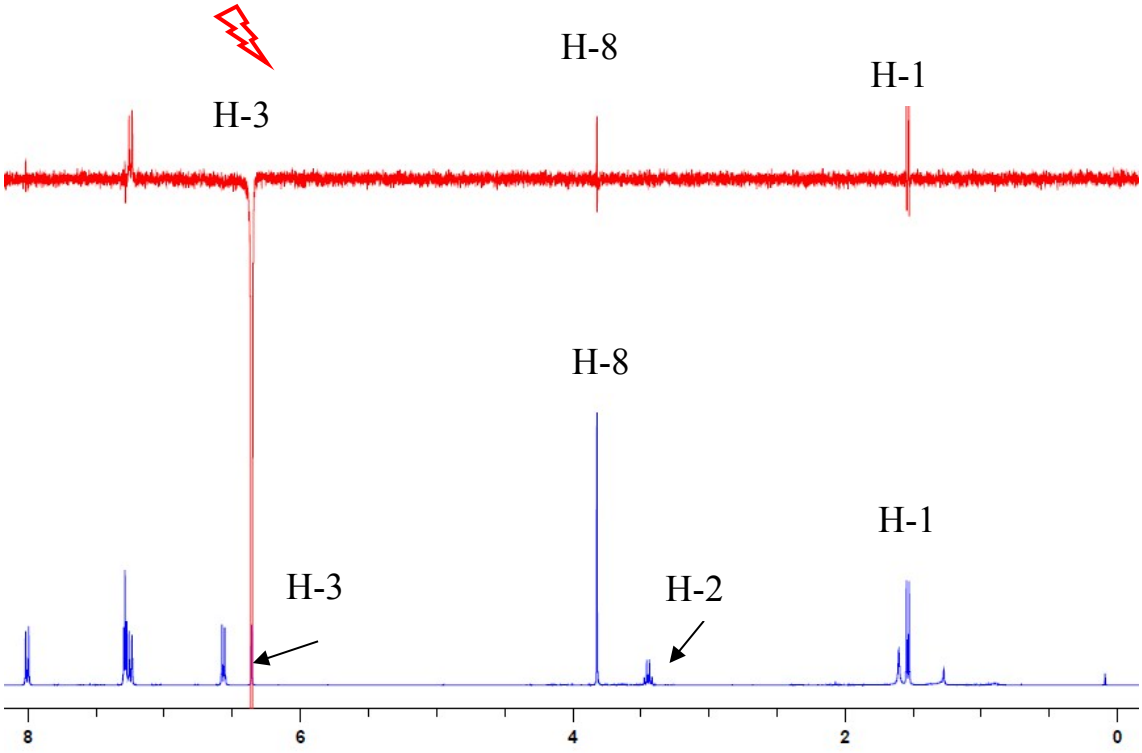


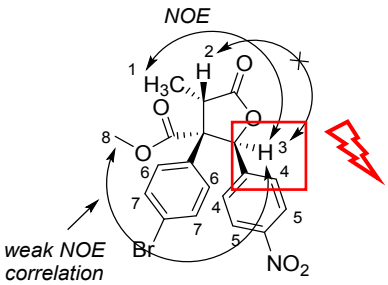
(58): NOE experiments – Irradiation H-2



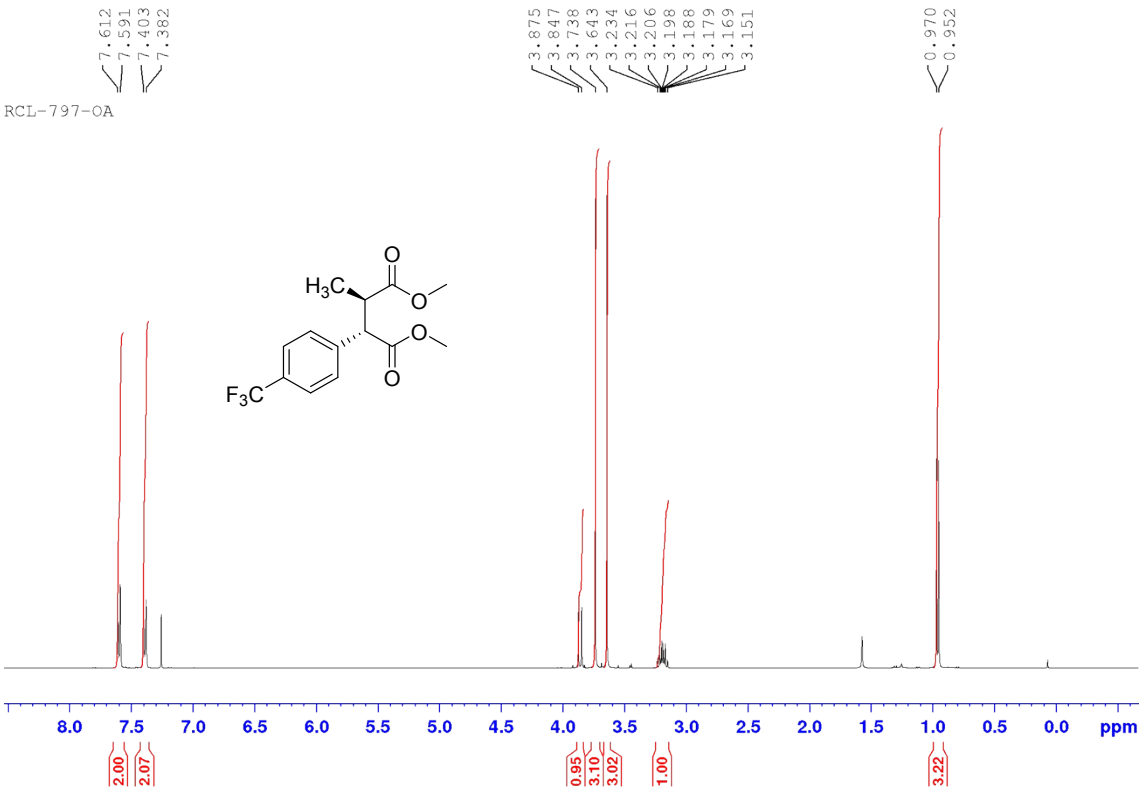


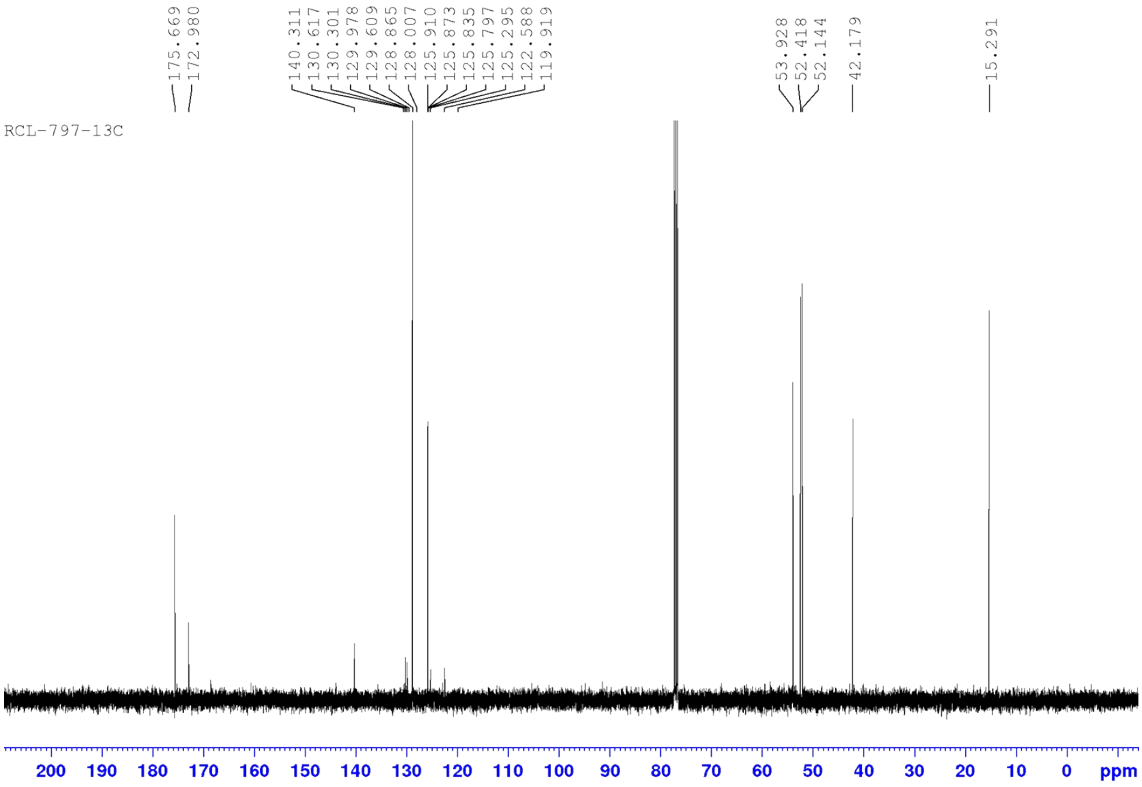
(58): NOE experiments – Irradiation H-3



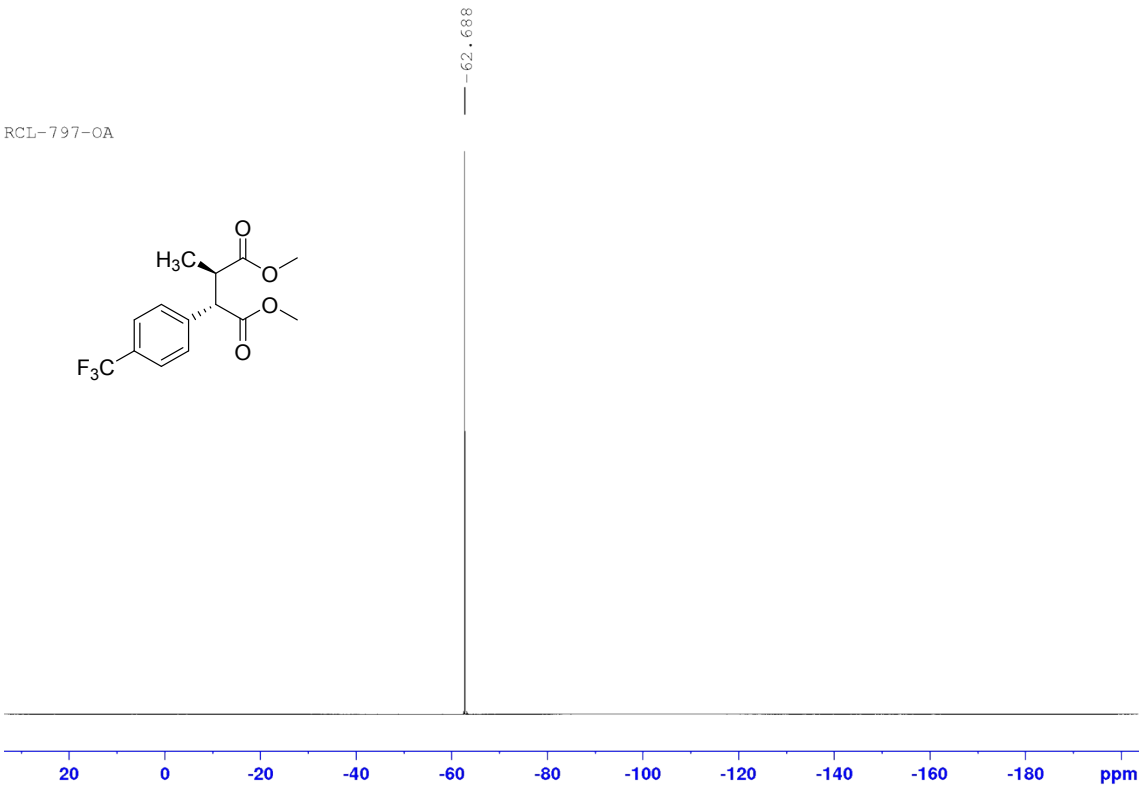


Dimethyl (2*R*,3*S*)-2-methyl-3-(4-(trifluoromethyl)phenyl)succinate (51)

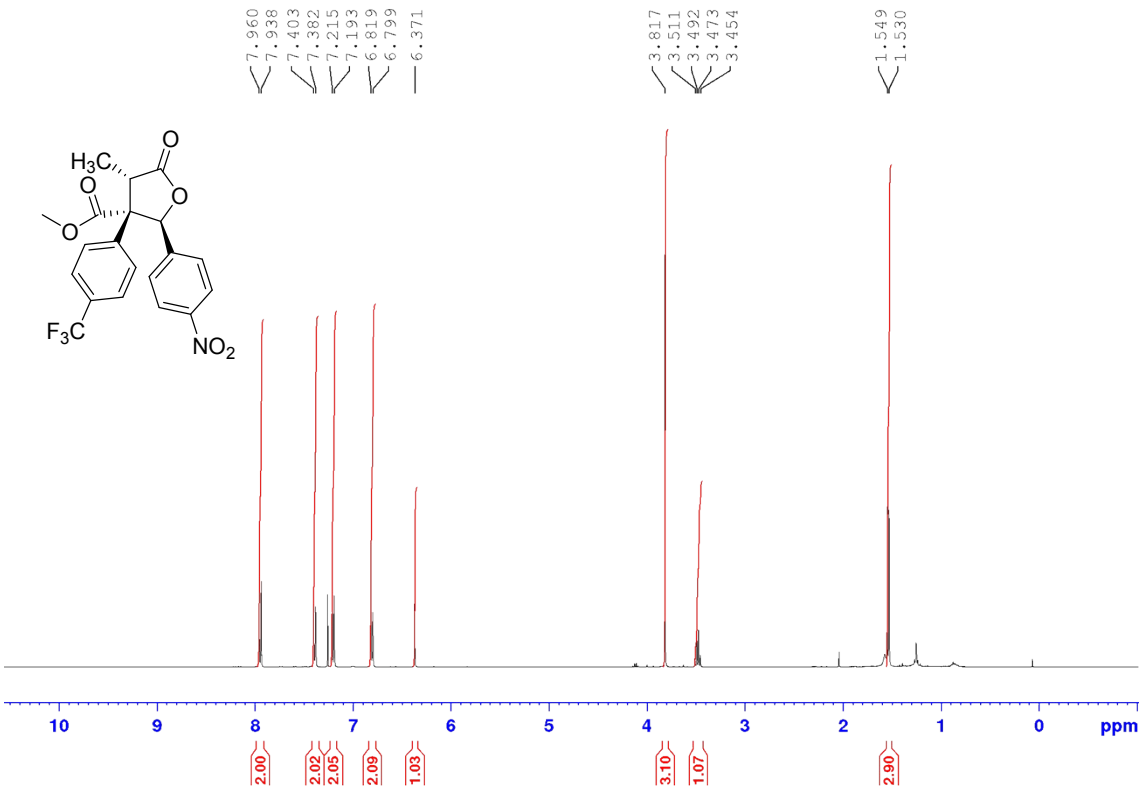


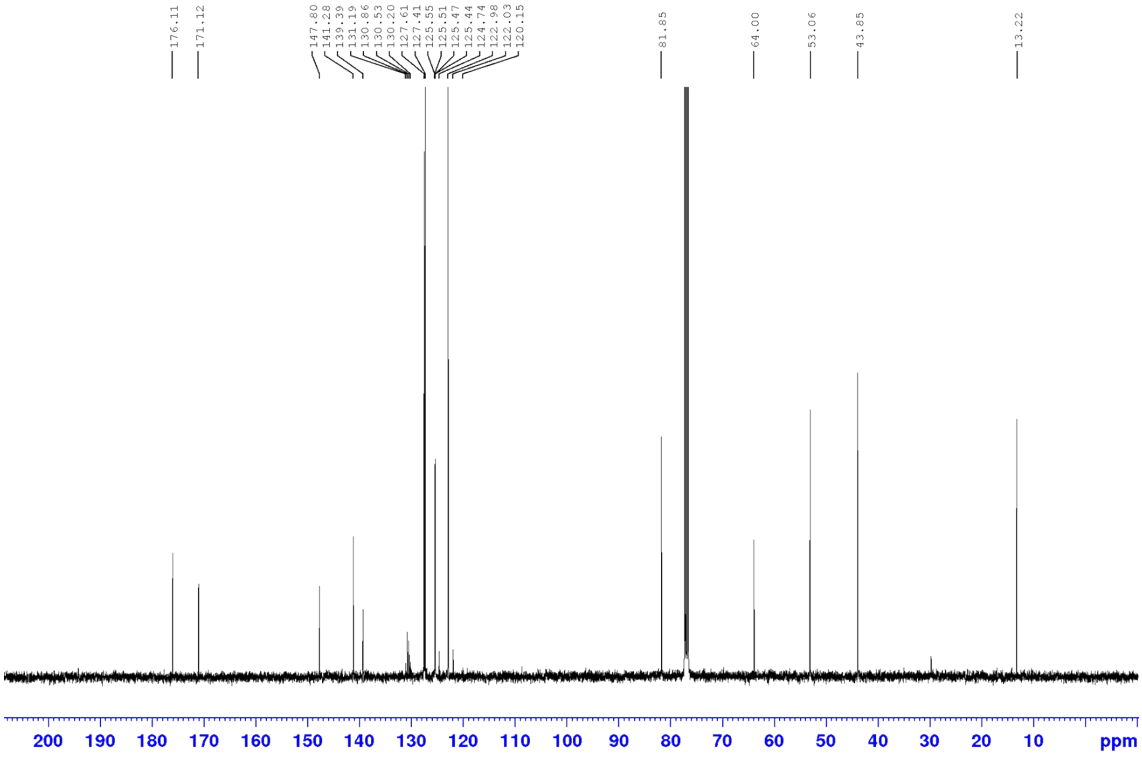


Dimethyl (2*R*,3*S*)-2-methyl-3-(4-(trifluoromethyl)phenyl)succinate (51)

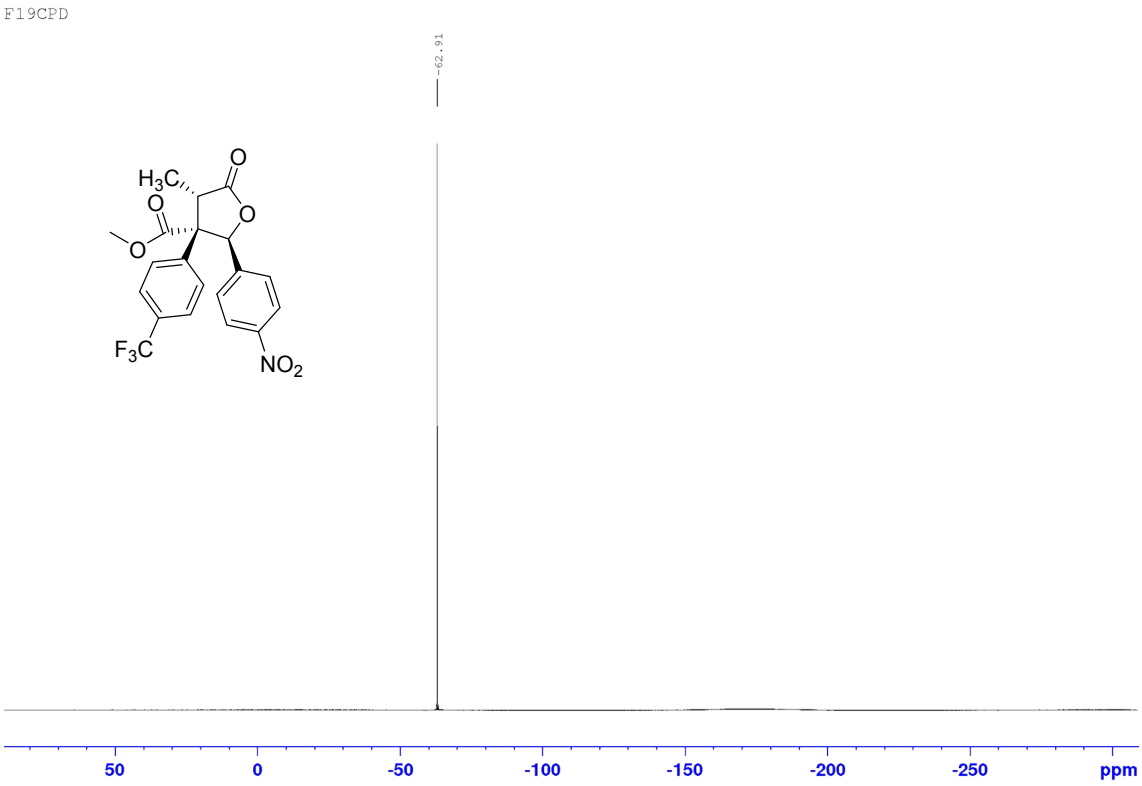


Methyl 4-methyl-2-(4-nitrophenyl)-5-oxo-3-(4-(trifluoromethyl)phenyl) tetrahydrofuran-3-carboxylate (59)

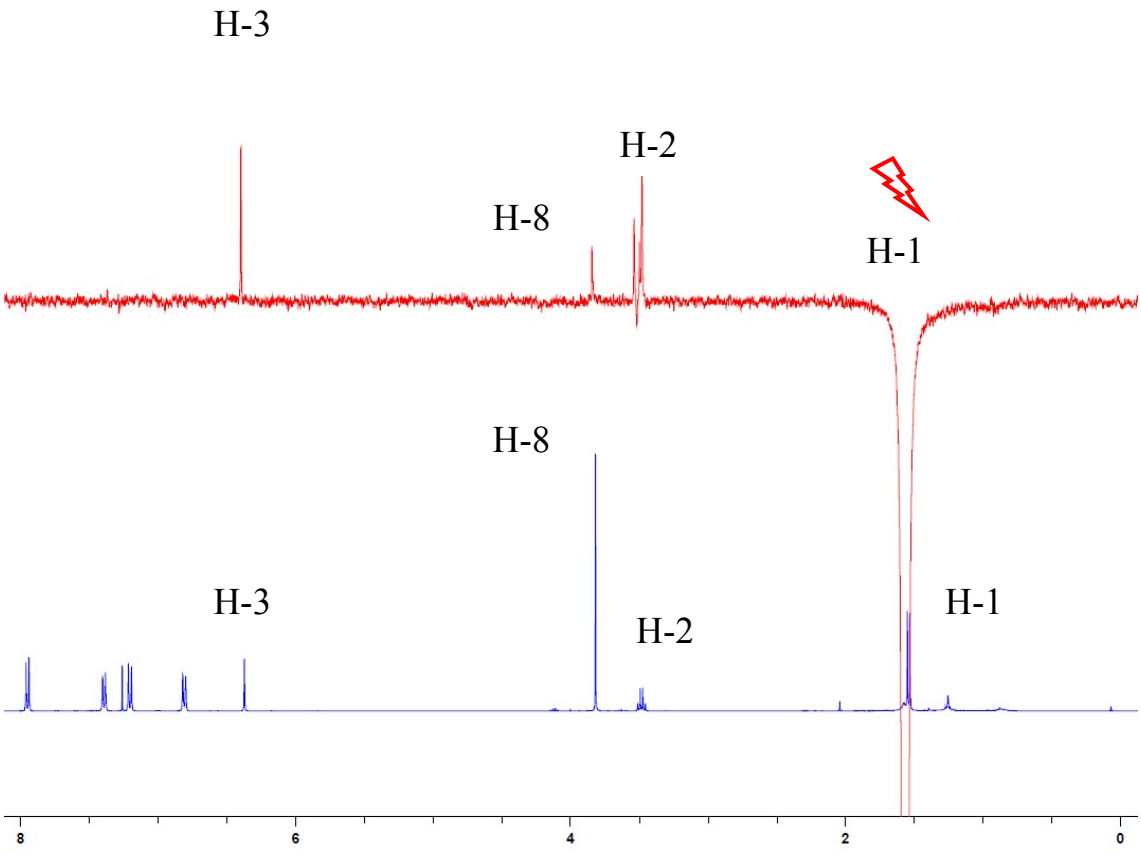


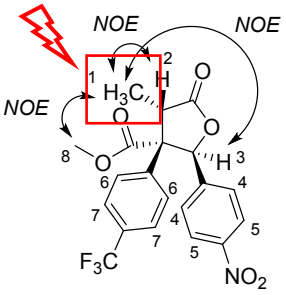


Methyl 4-methyl-2-(4-nitrophenyl)-5-oxo-3-(4-(trifluoromethyl)phenyl) tetrahydrofuran-3-carboxylate (59)

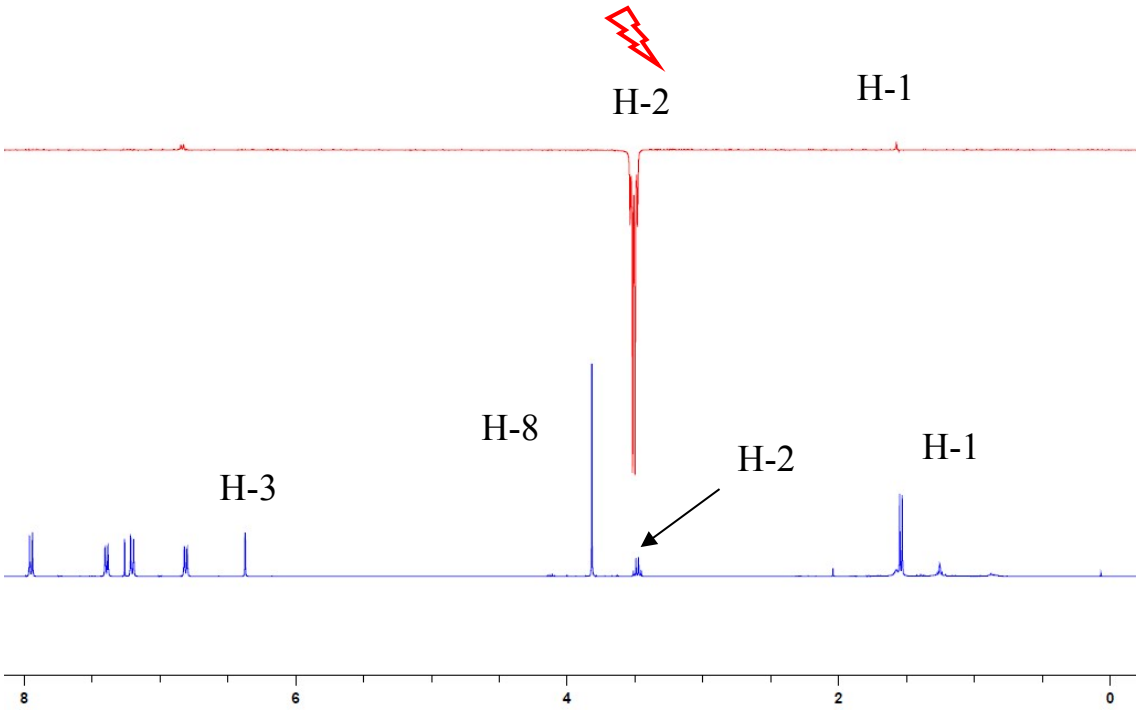


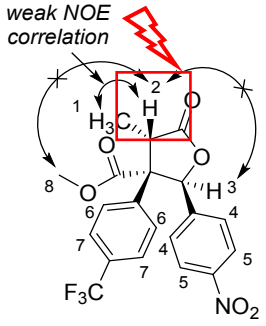
(59): NOE experiments – Irradiation H-1



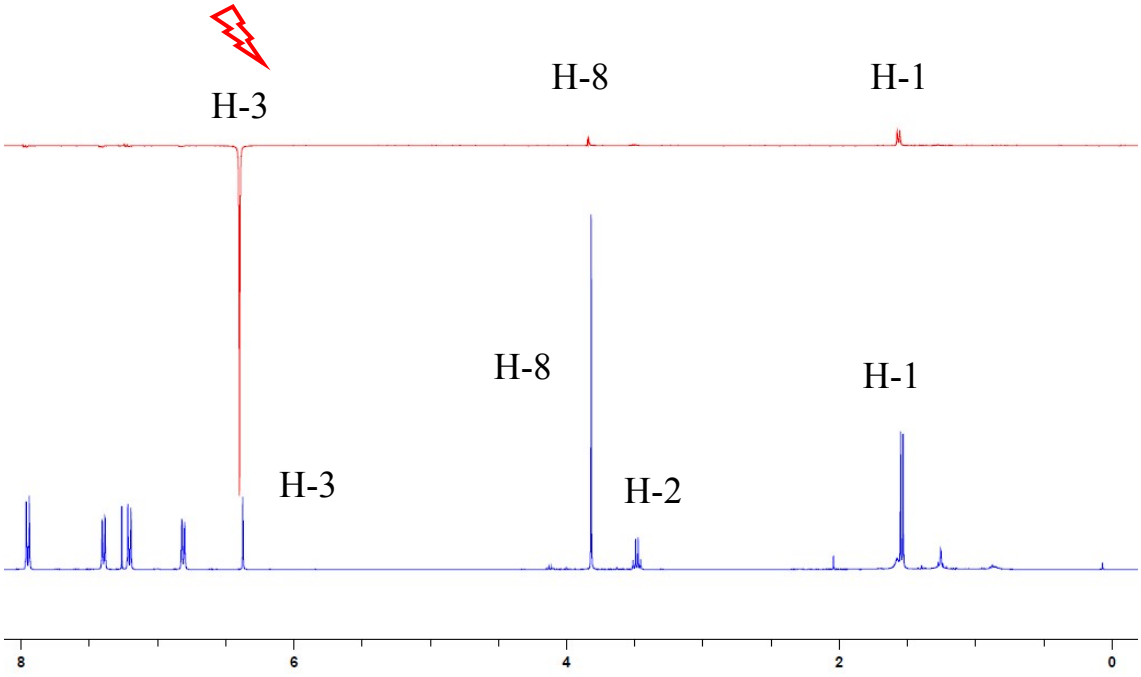


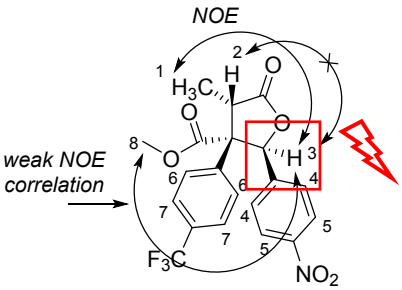
(59): NOE experiments – Irradiation H-2



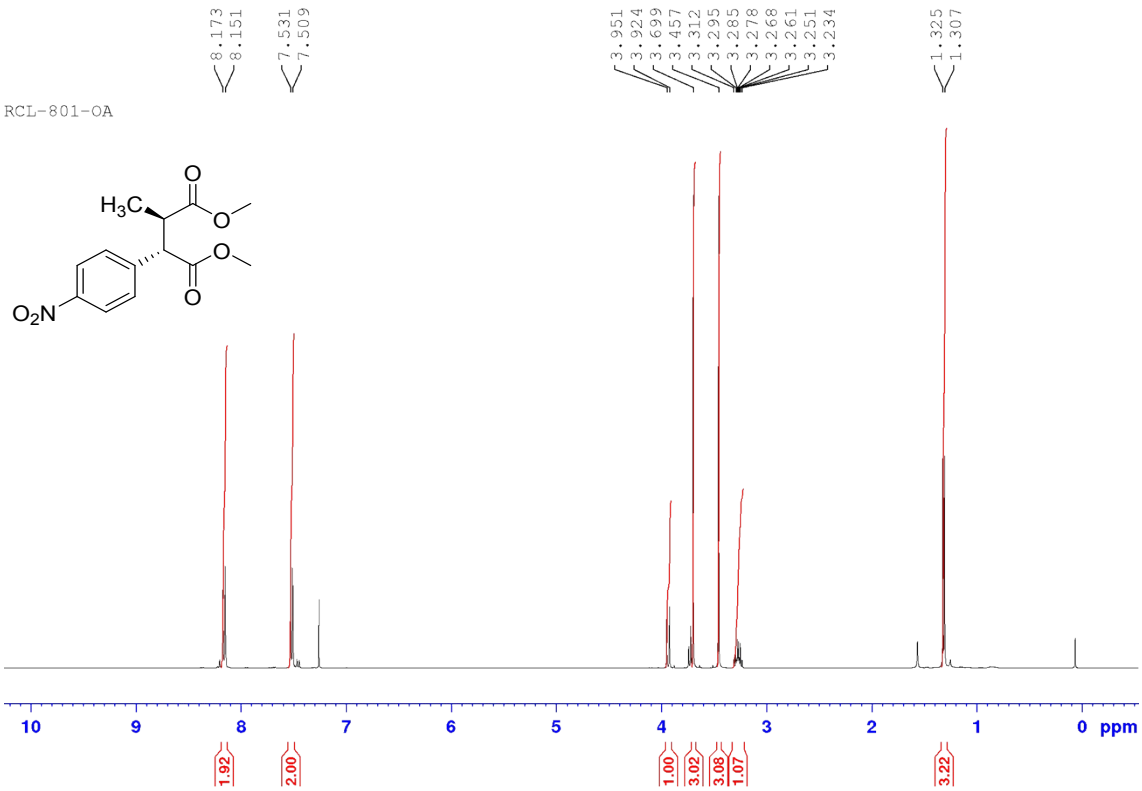


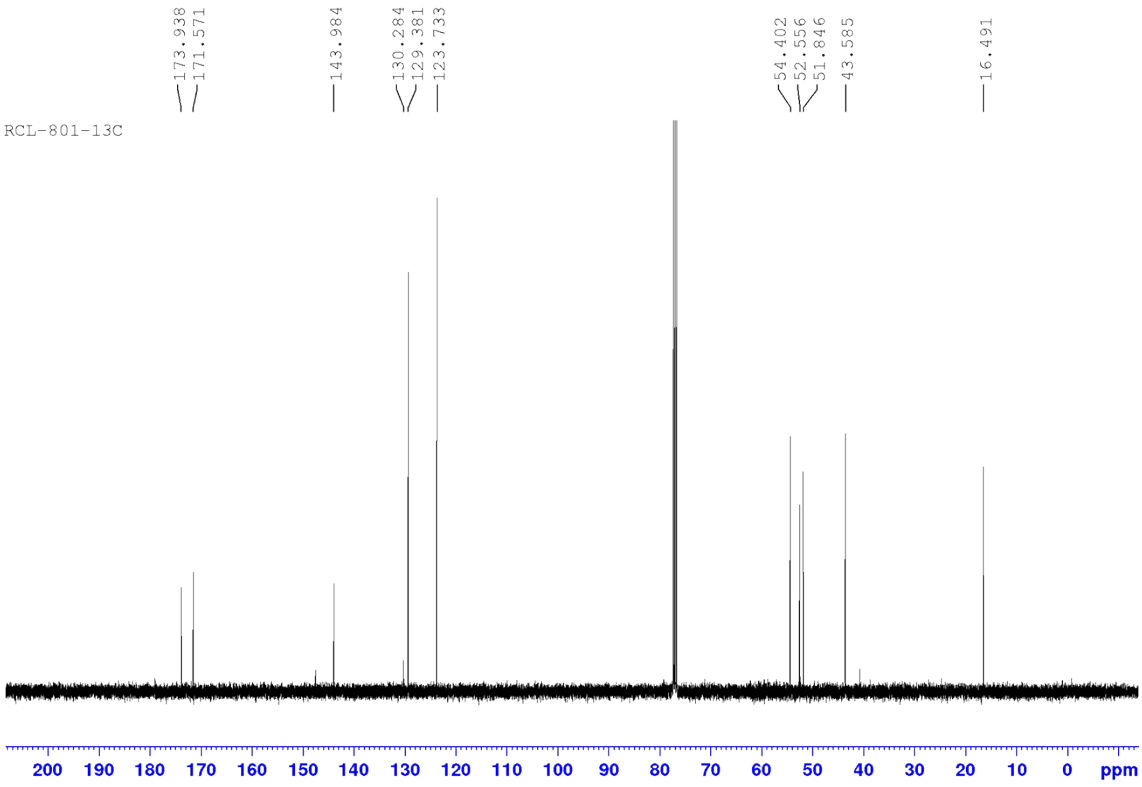
(59): NOE experiments – Irradiation H-3



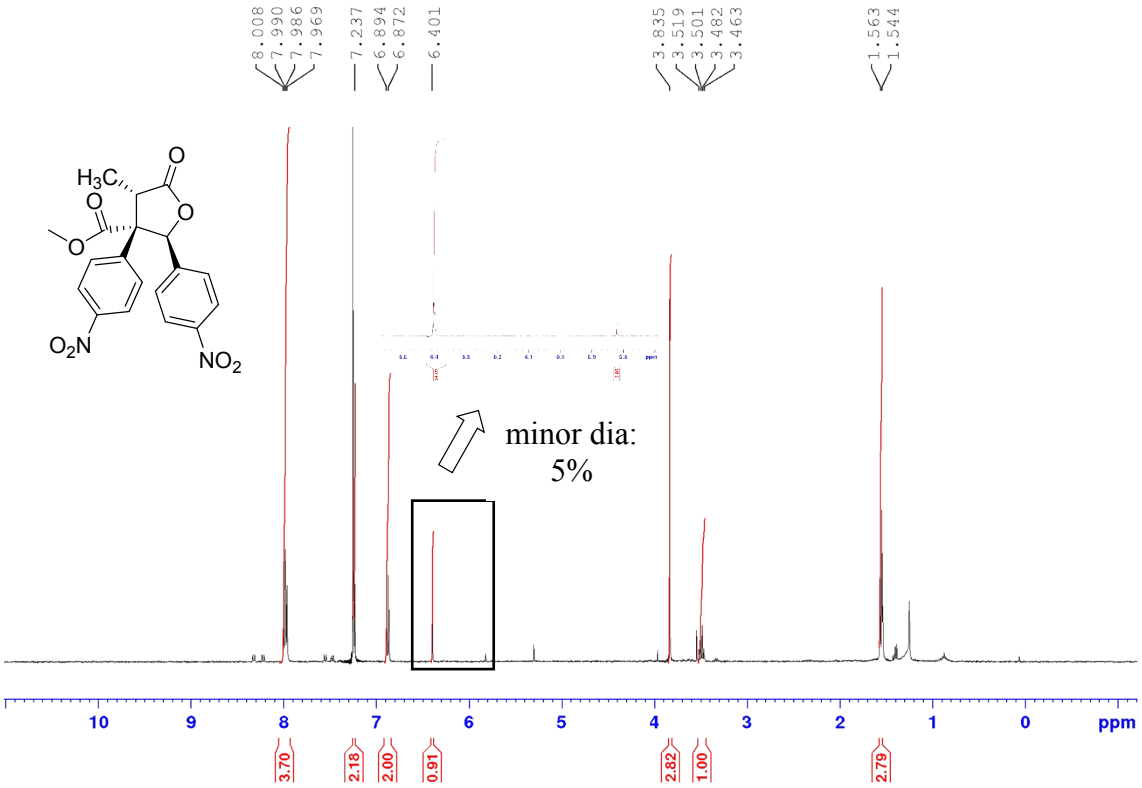


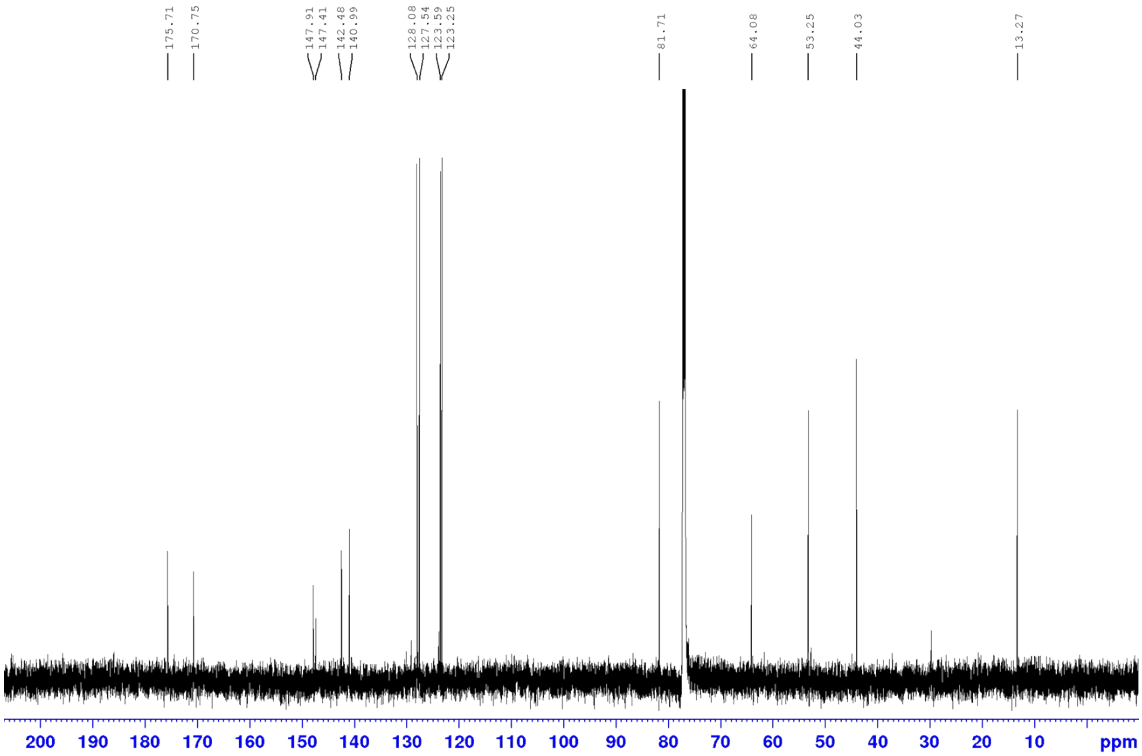
Dimethyl (2*R*,3*S*)-2-methyl-3-(4-nitrophenyl)succinate (52)



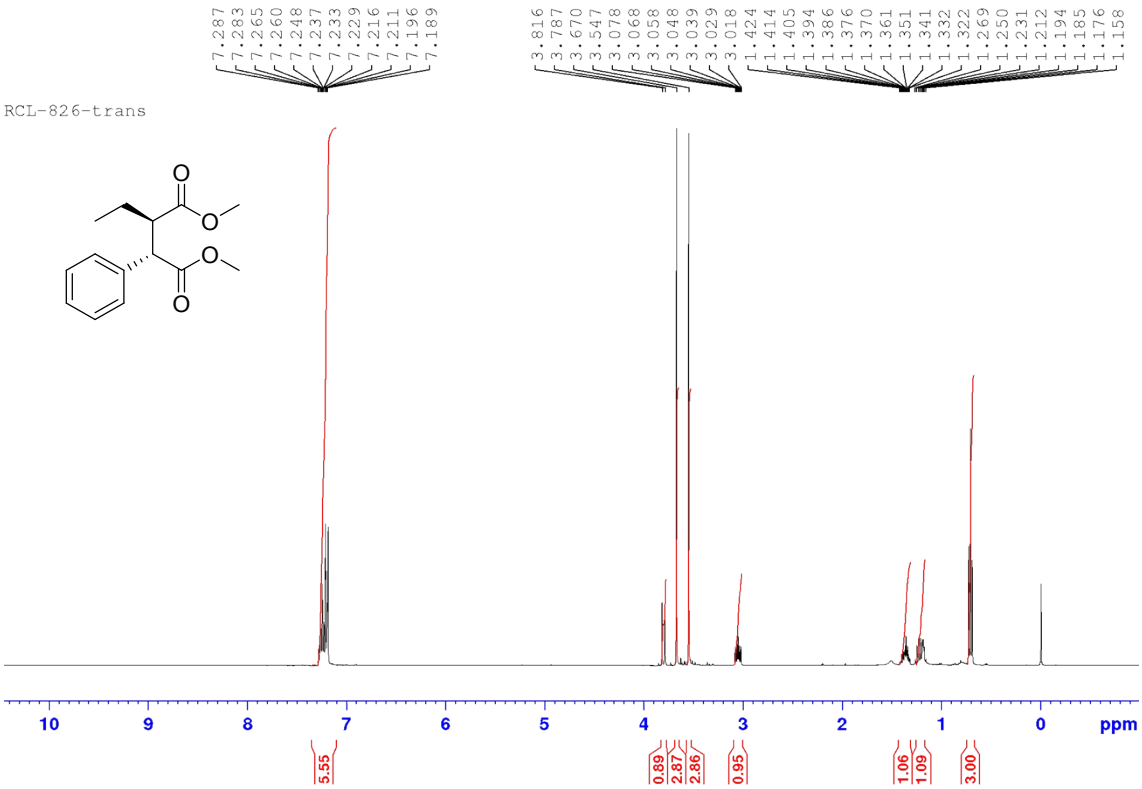


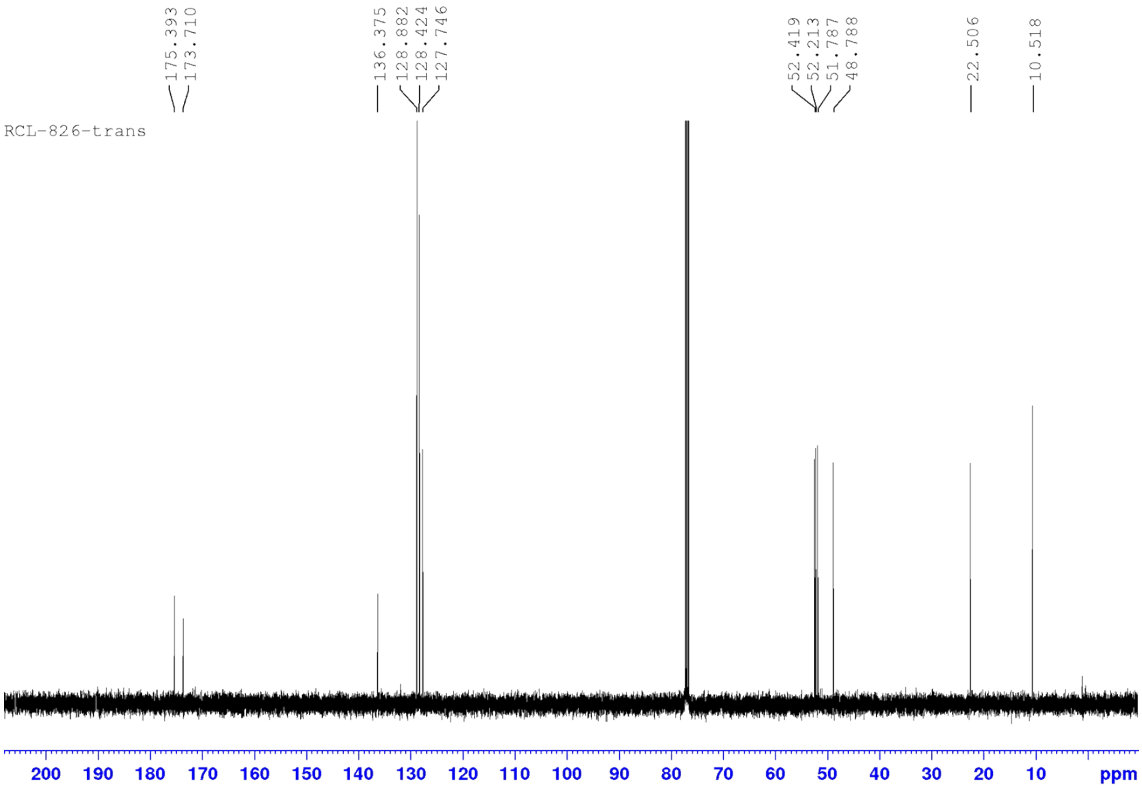
Methyl 4-methyl-2,3-bis(4-nitrophenyl)-5-oxotetrahydrofuran-3-carboxylate (60)



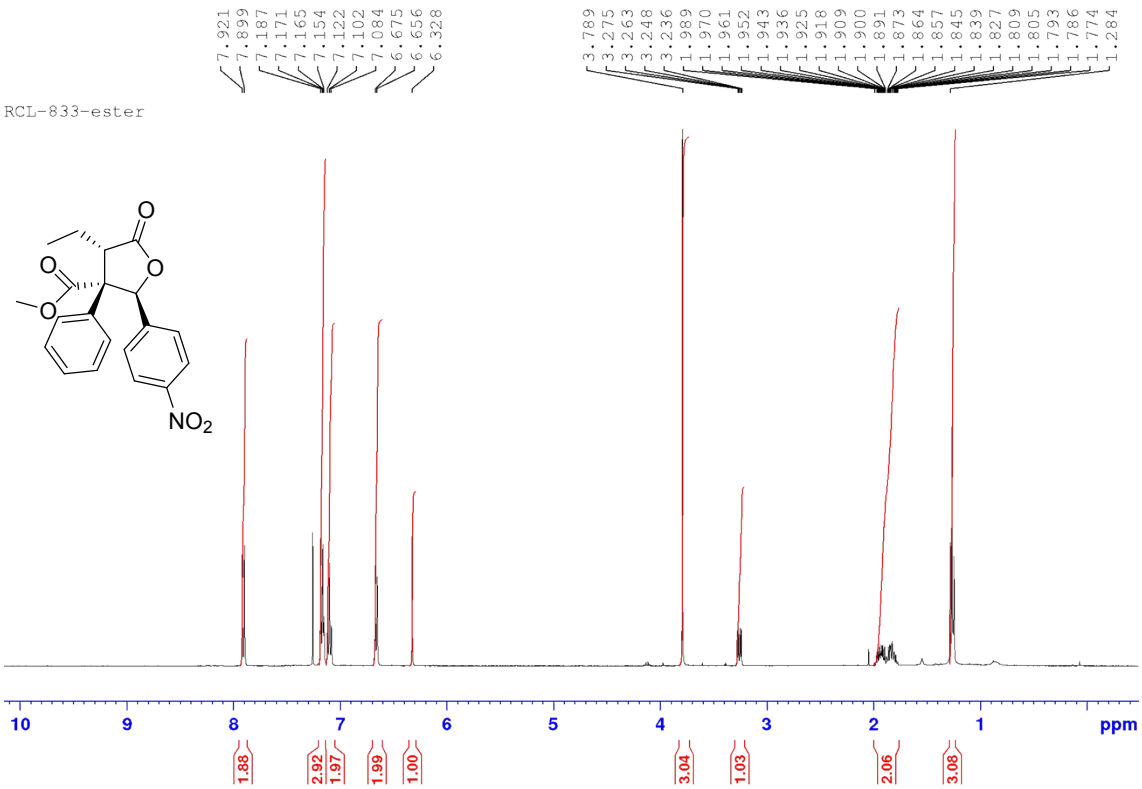


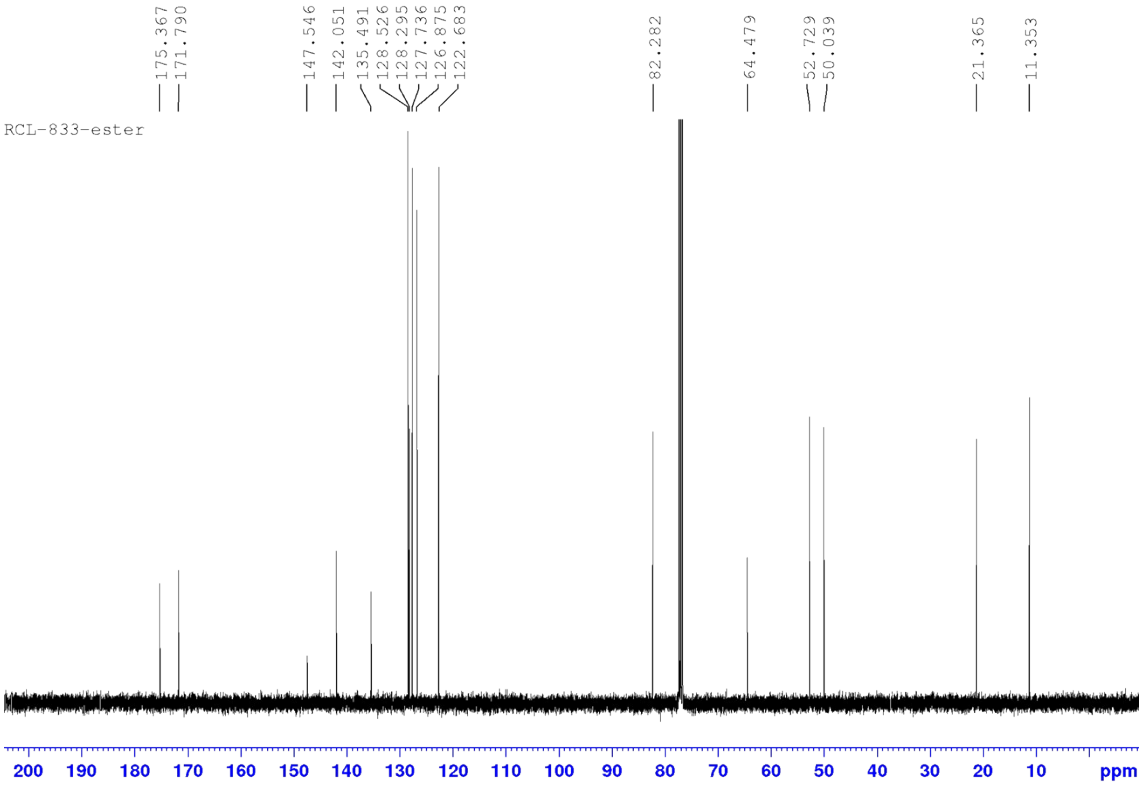
Dimethyl 2-ethyl-3-phenylsuccinate (54)



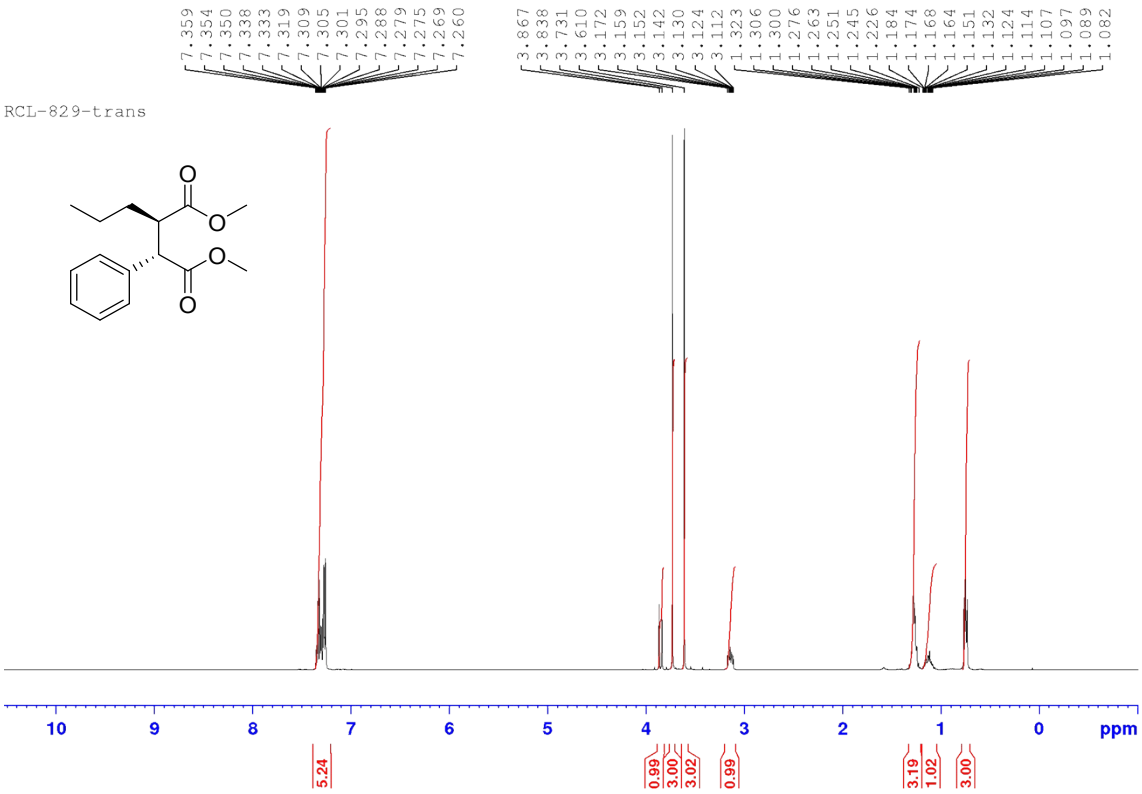


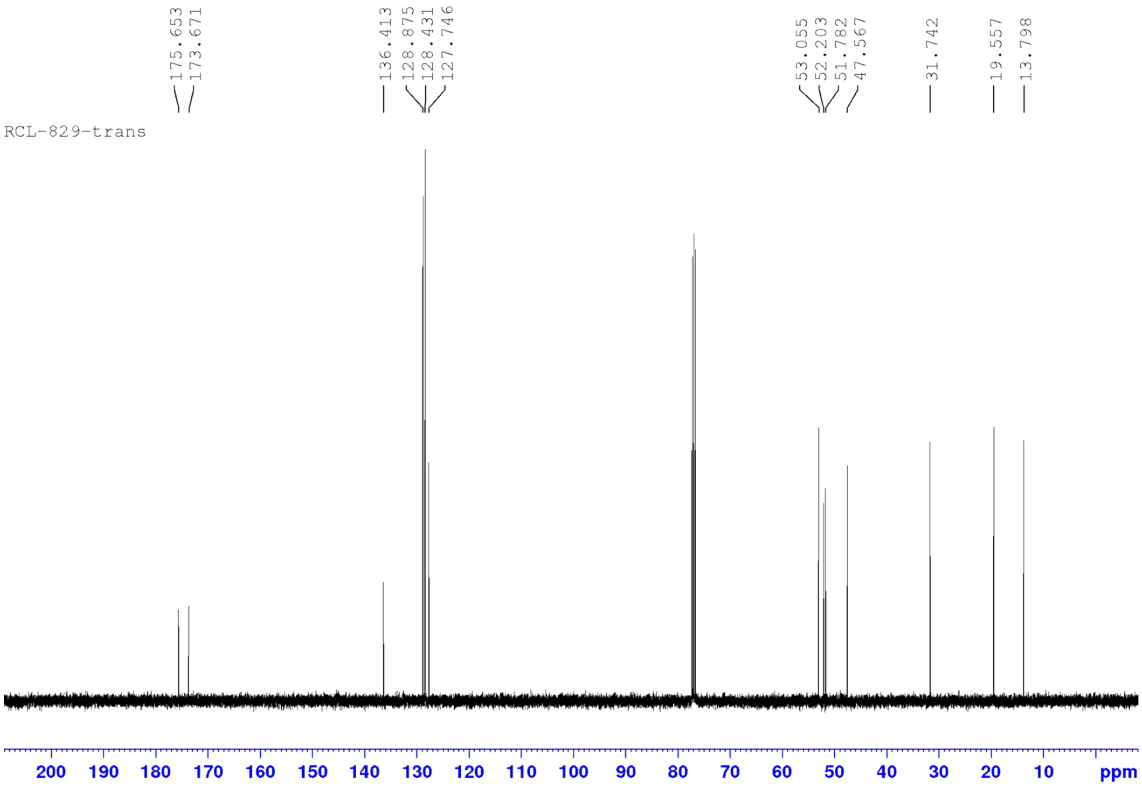
Methyl 4-ethyl-2-(4-nitrophenyl)-5-oxo-3-phenyltetrahydrofuran-3-carboxylate (62)



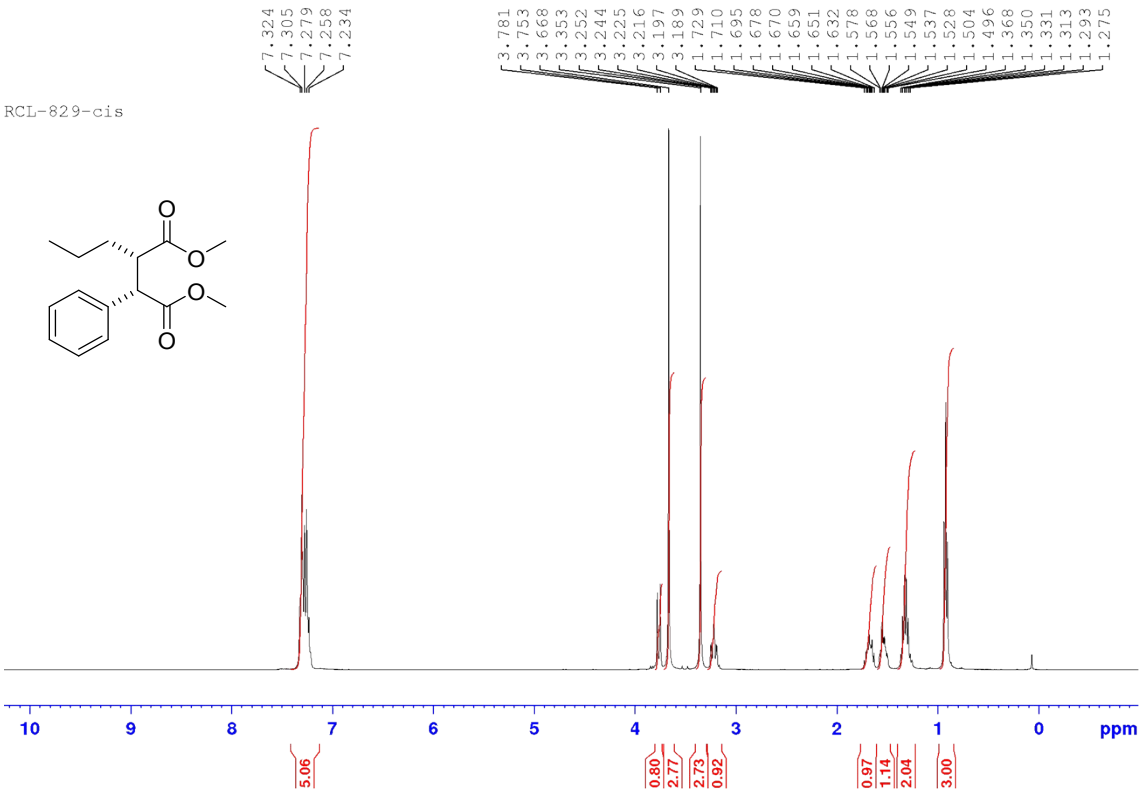


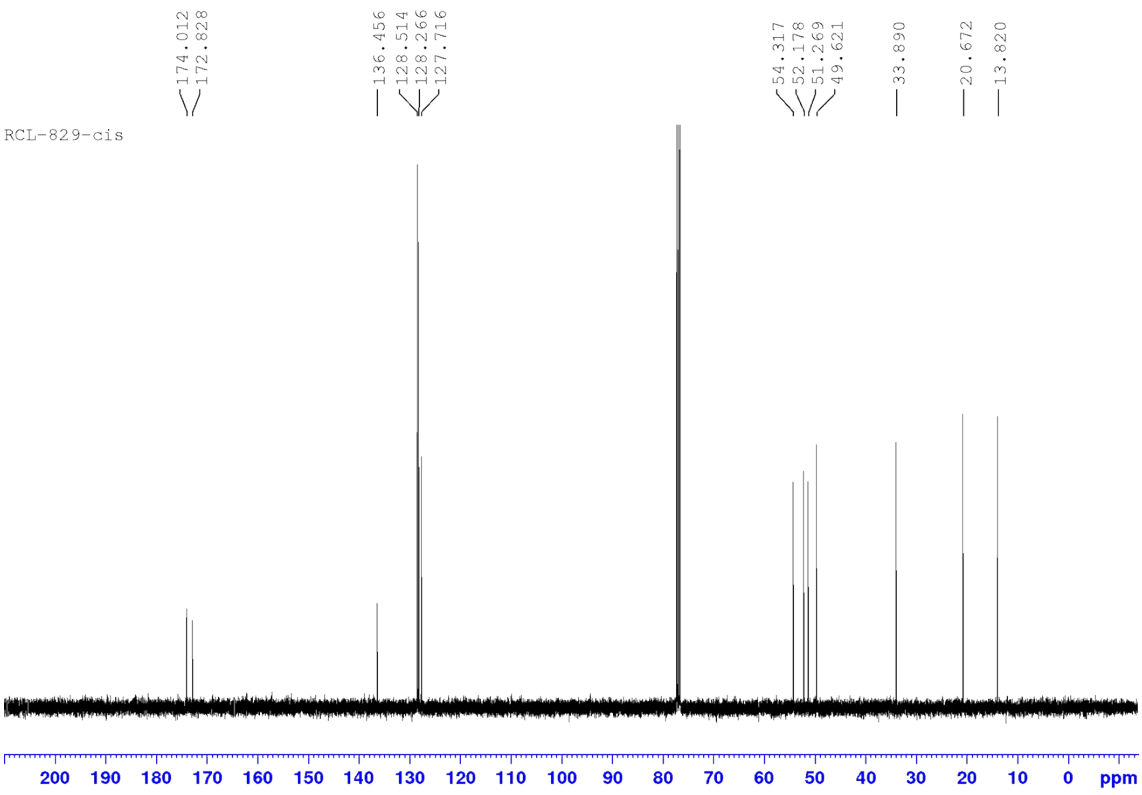
Dimethyl 2-phenyl-3-propylsuccinate (*trans*-55)



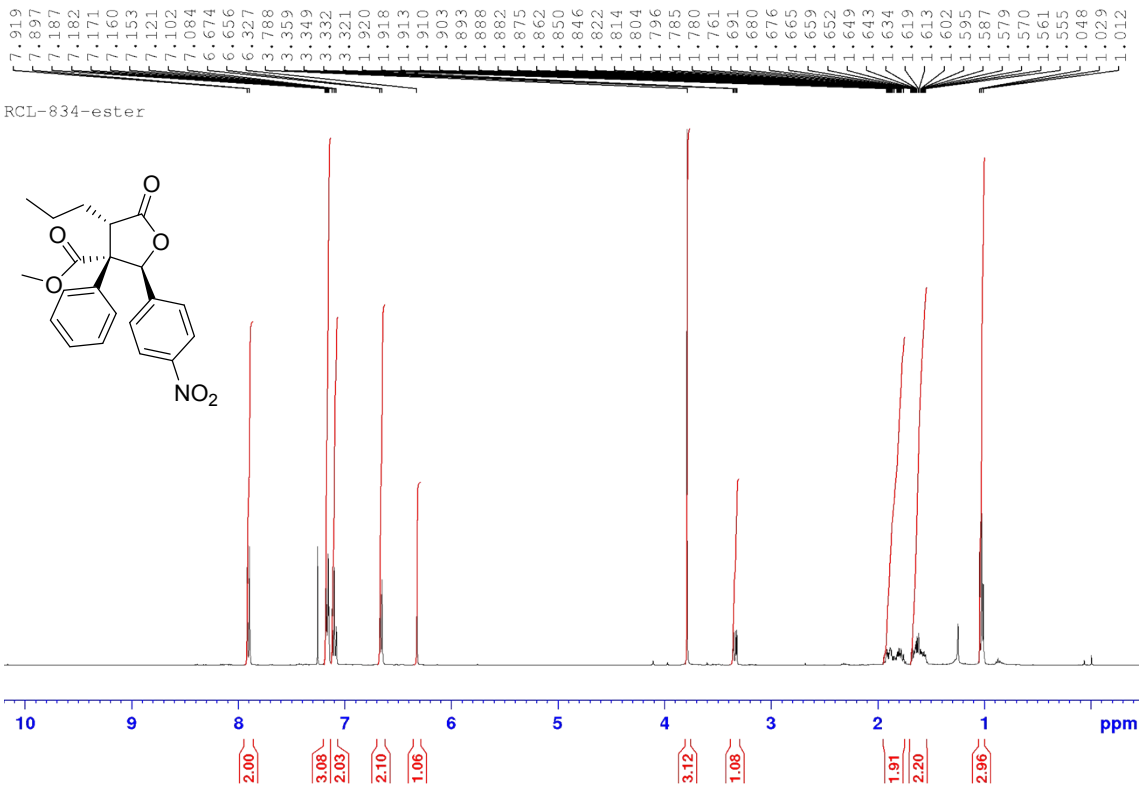


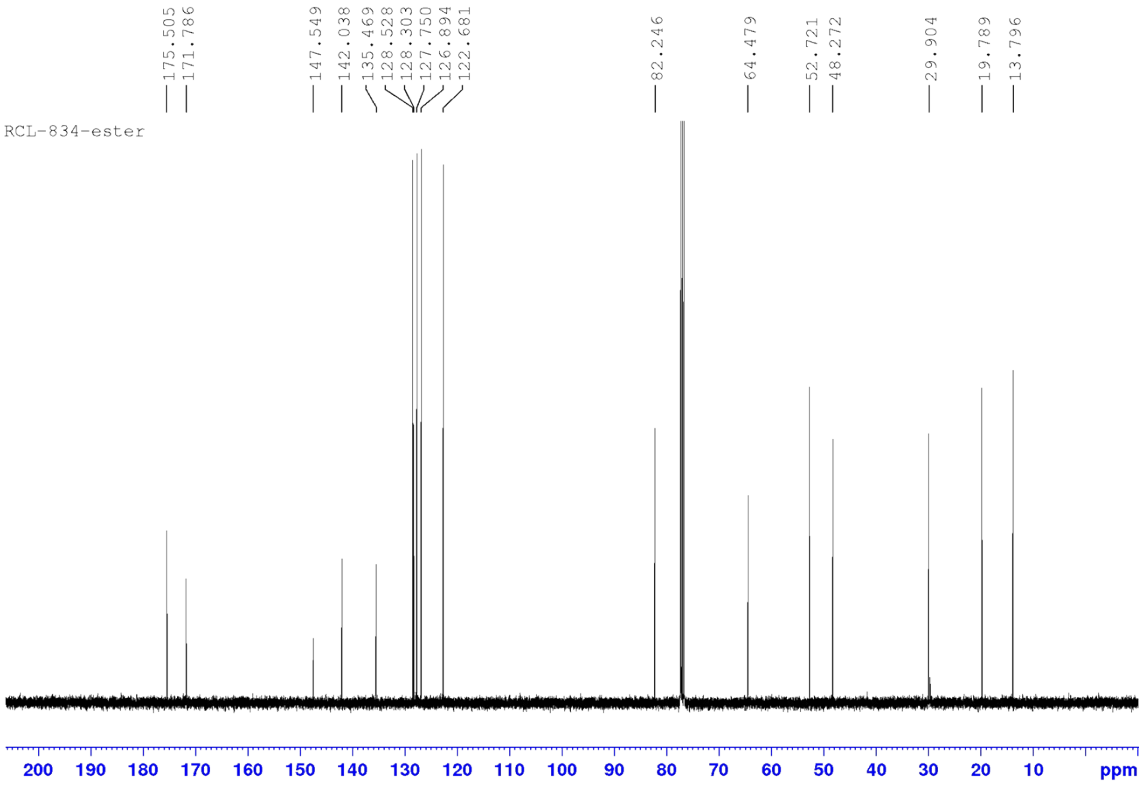
Dimethyl 2-phenyl-3-propylsuccinate (*cis*-55)



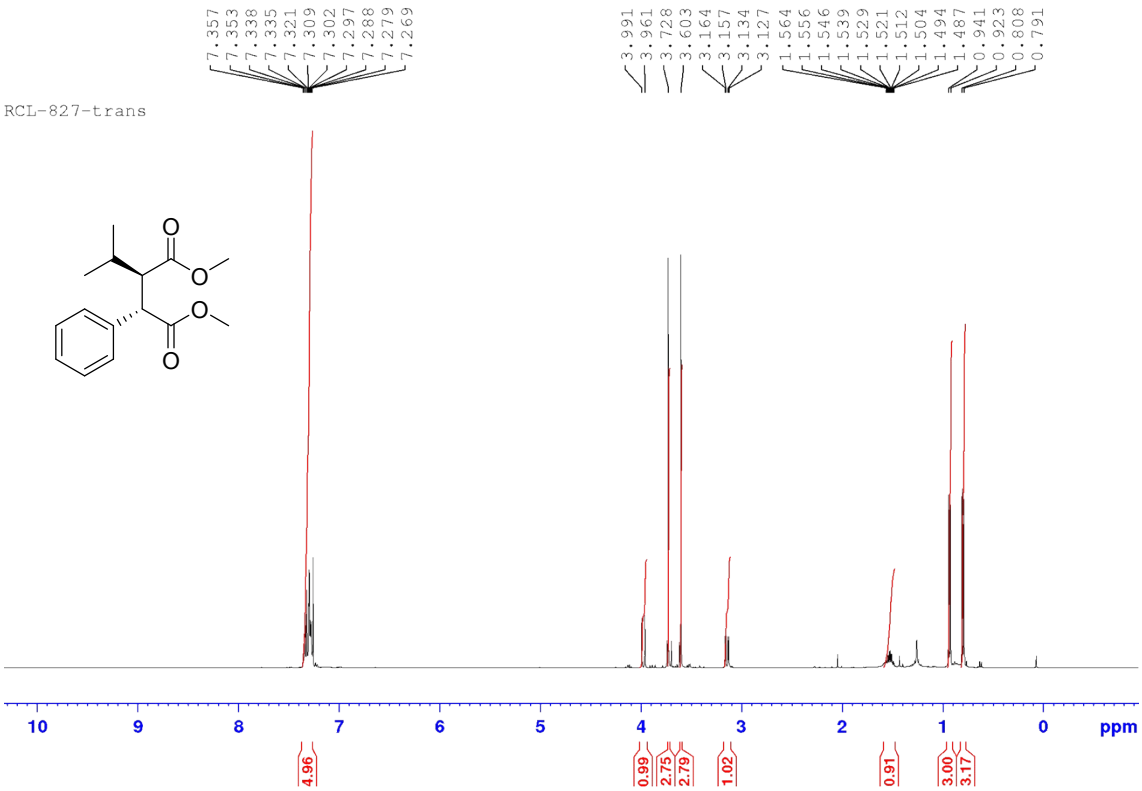


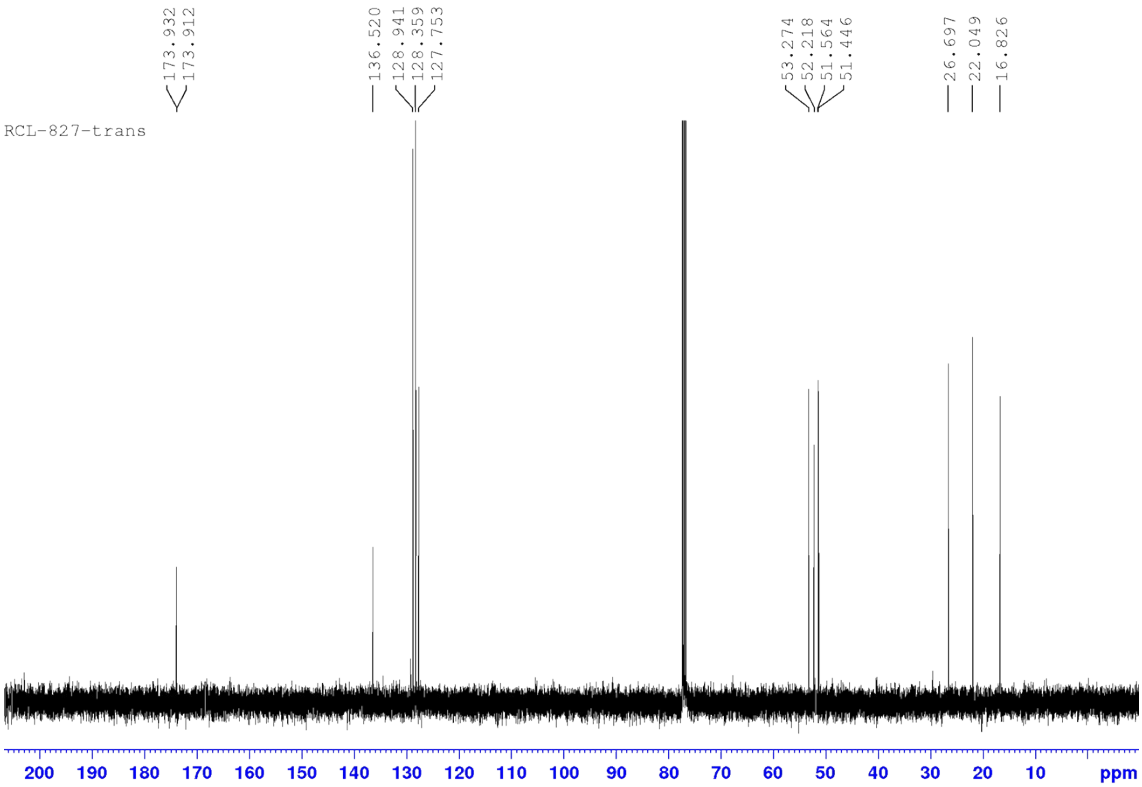
Methyl 2-(4-nitrophenyl)-5-oxo-3-phenyl-4-propyltetrahydrofuran-3-carboxylate (63)



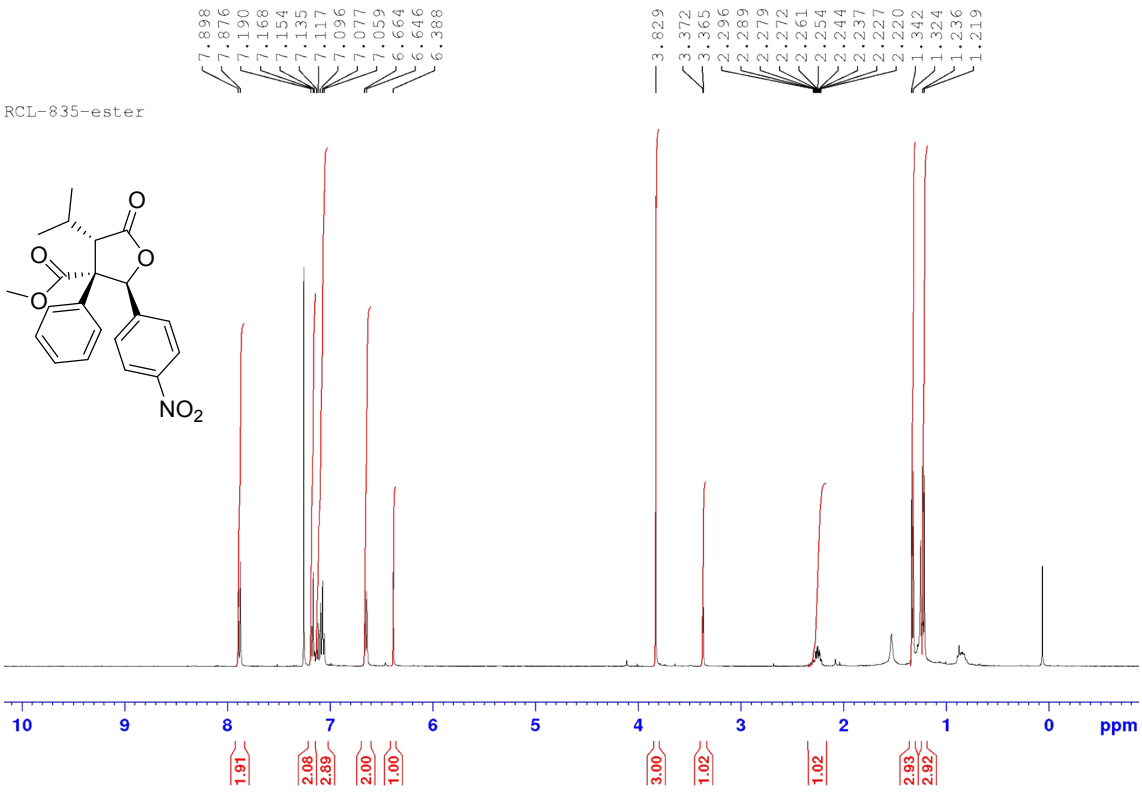


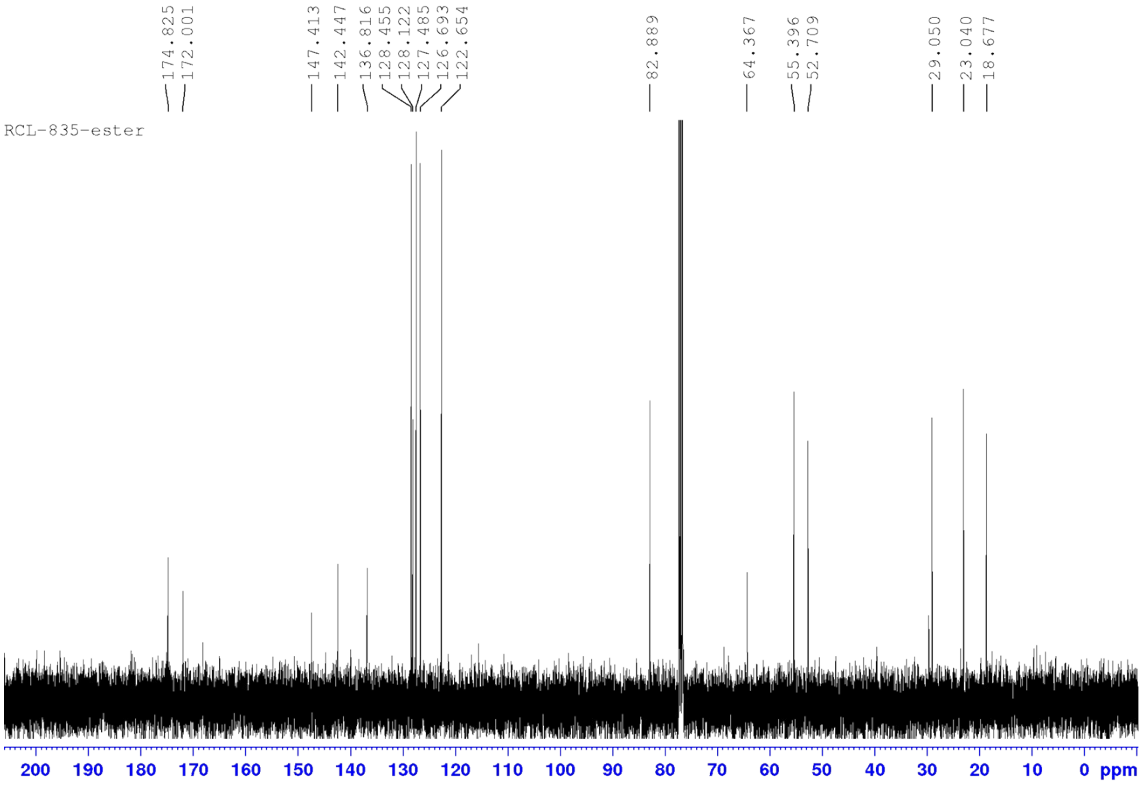
Dimethyl 2-isopropyl-3-phenylsuccinate (56)



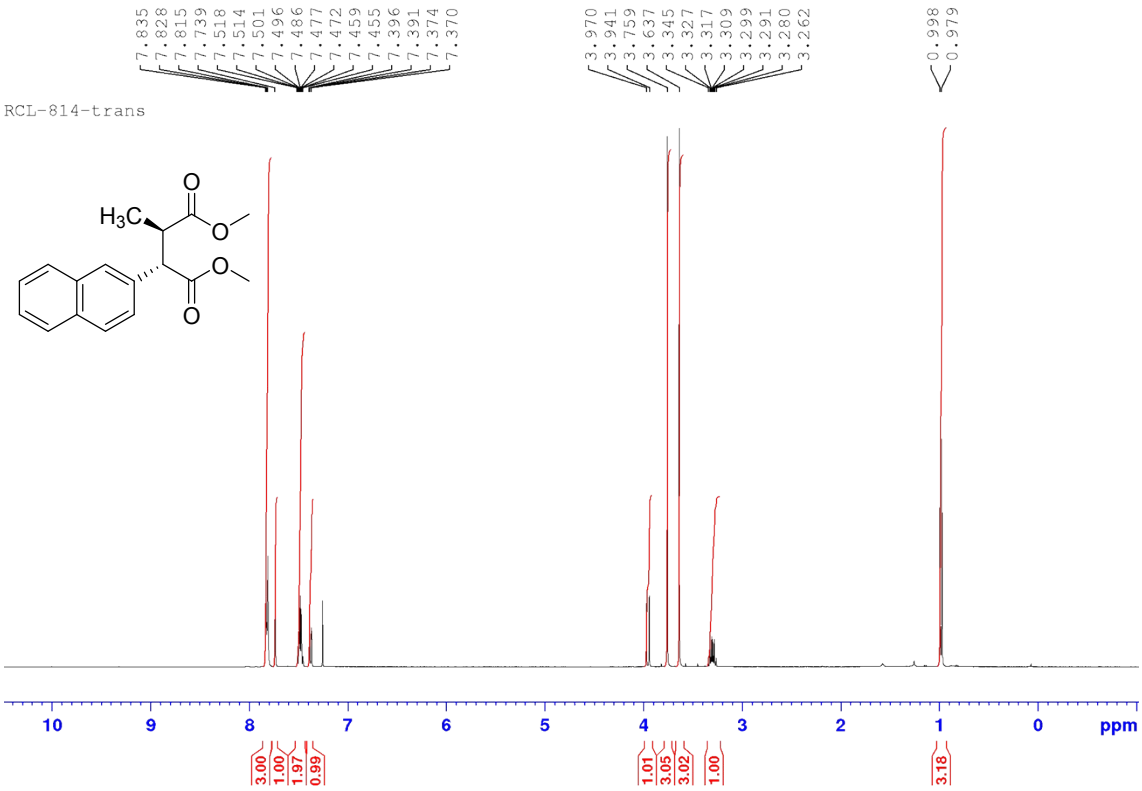


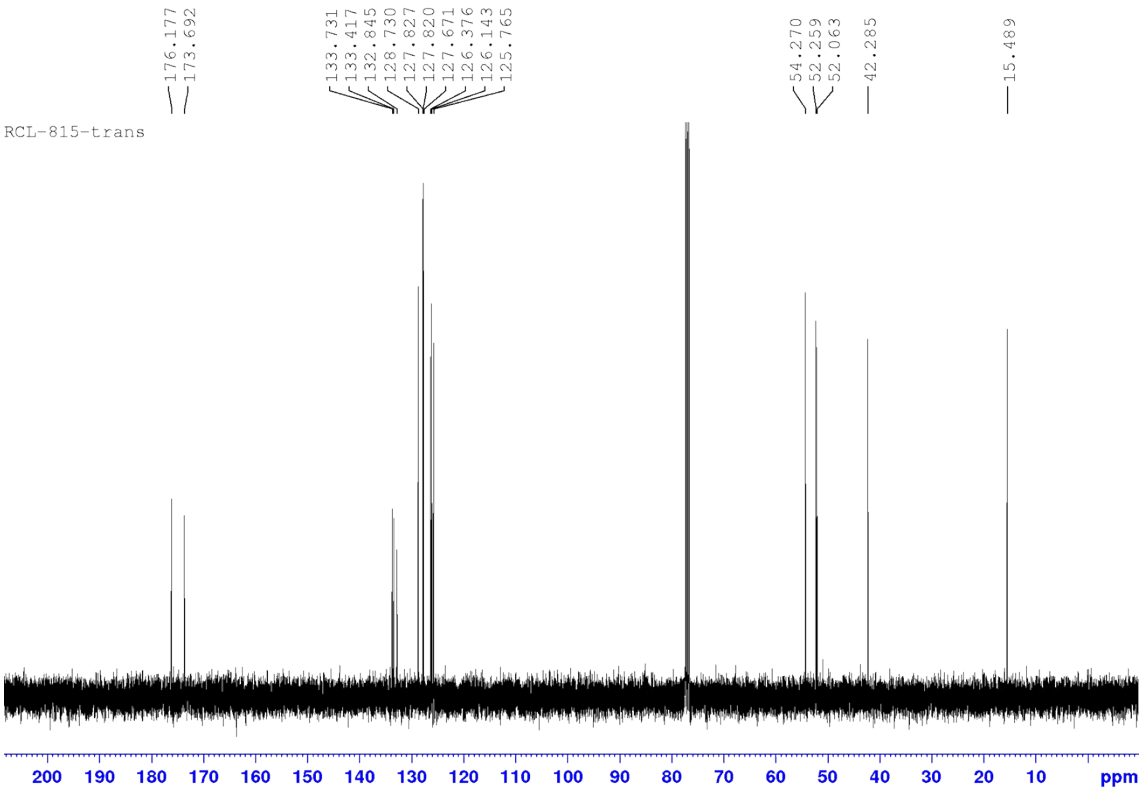
Methyl 4-isopropyl-2-(4-nitrophenyl)-5-oxo-3-phenyltetrahydrofuran-3-carboxylate (64)



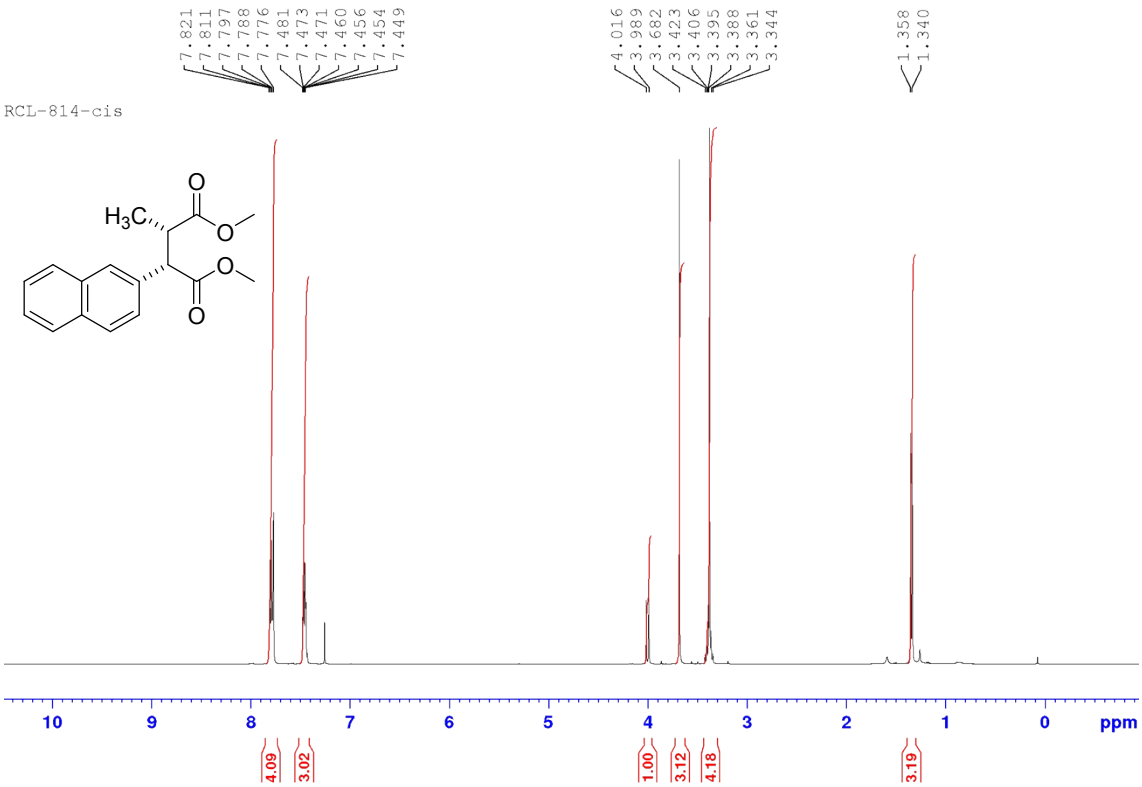


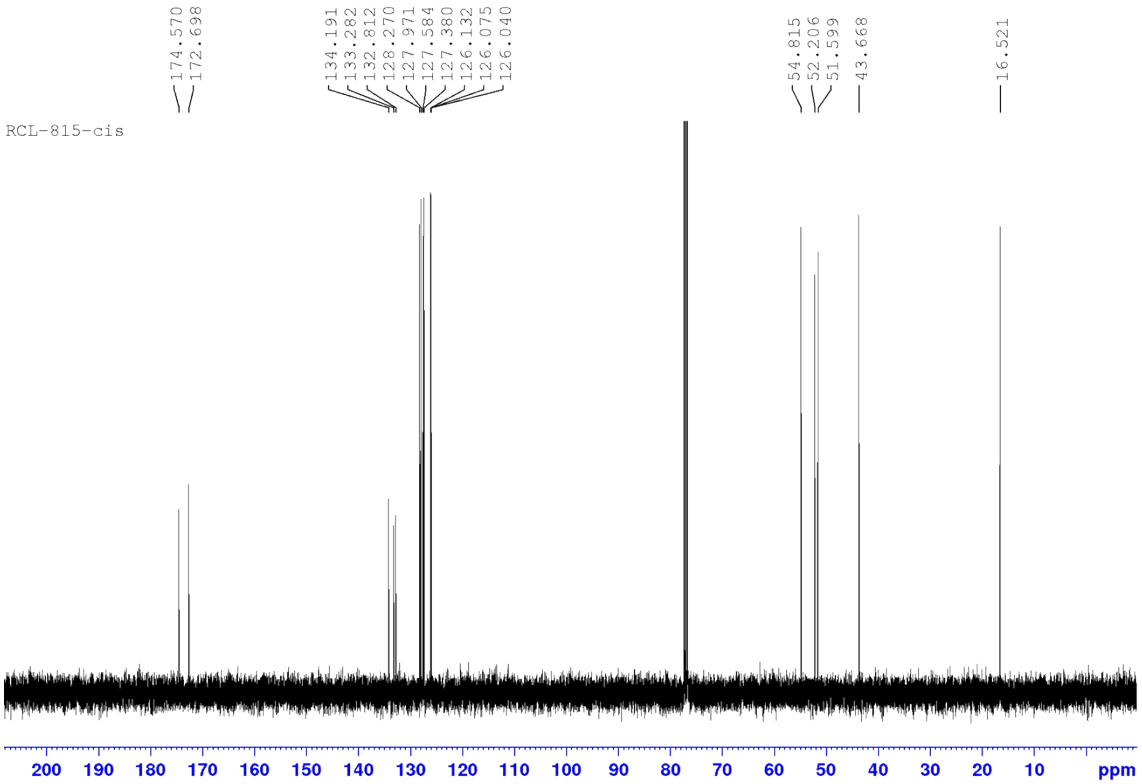
Dimethyl 2-methyl-3-(naphthalen-2-yl)succinate (*trans*-53)



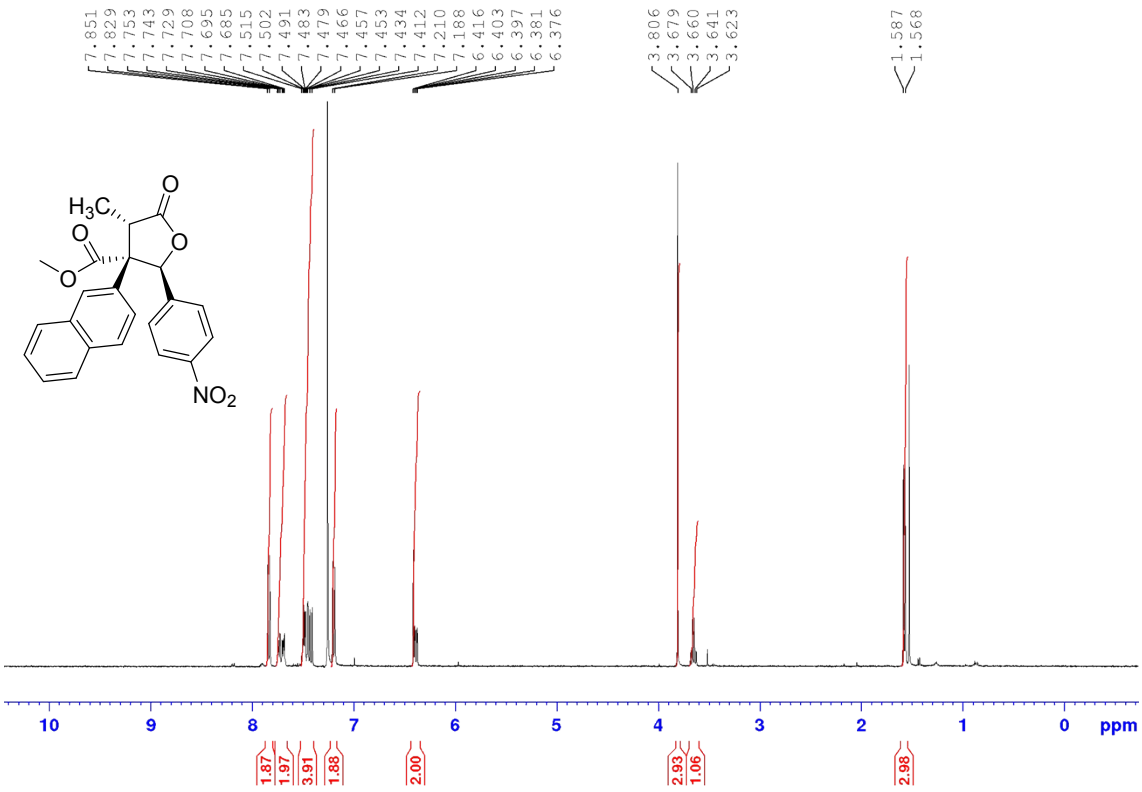


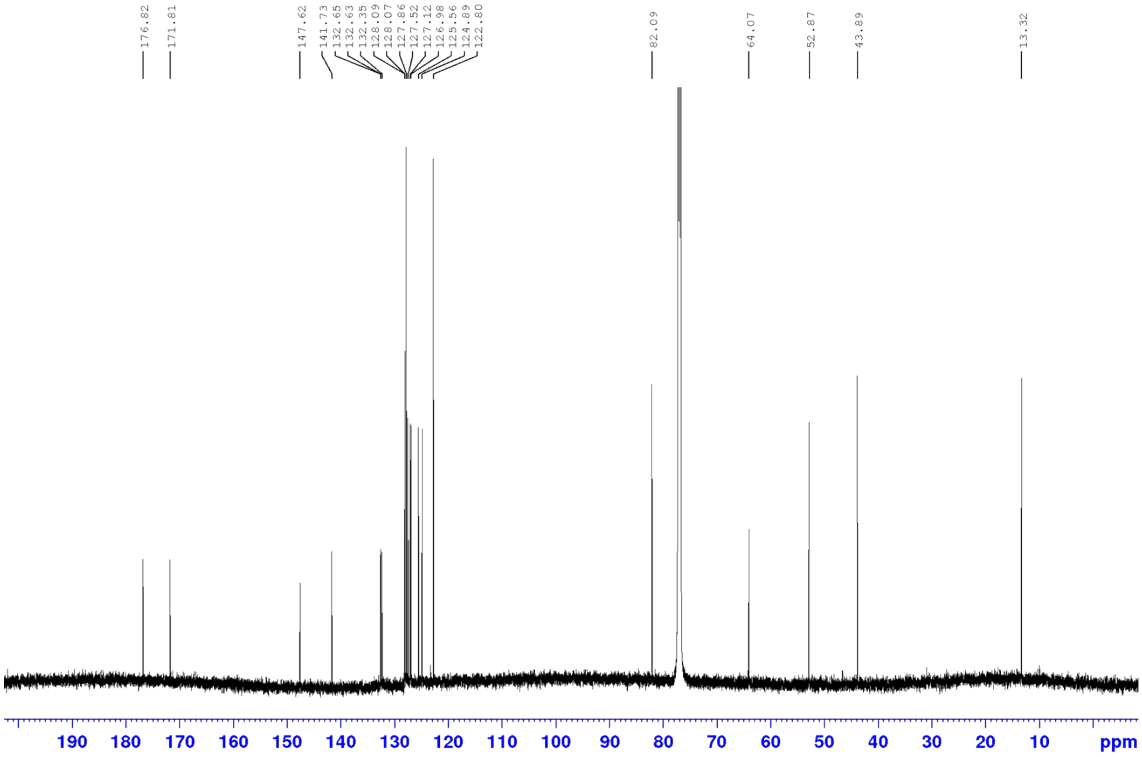
Dimethyl 2-methyl-3-(naphthalen-2-yl)succinate (*cis*-53)





Methyl 4-methyl-3-(naphthalen-2-yl)-2-(4-nitrophenyl)-5-oxotetrahydrofuran-3-carboxylate (61)





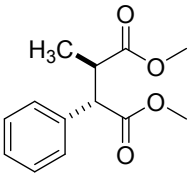
10. HPLC chromatograms

Racemic preparation of lactones 57-64

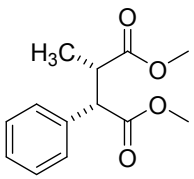
An oven-dried 5 mL reaction vessel containing a magnetic stirring bar under argon atmosphere was charged with the relevant anhydride (0.1 mmol). Anhydrous MTBE or THF (1.0 mL, 0.1 M) was added *via* syringe followed by recrystallized 4-nitro-benzaldehyde aldehyde (0.1 mmol). *N*,*N*-Diisopropylethylamine (3.6 μL, 20.0 μmol - 20 mol%) was added *via* syringe and the resulting mixture was allowed to stir for 48 h at room temperature. To the reaction mixture containing the corresponding crude carboxylic acids, anhydrous MeOH (202.3 μL, 5.0 mmol), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 60 μL, 0.12 mmol) were added *via* syringe and the reaction was allowed to stir for 15 min at 0 °C. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash column chromatography, eluting in gradient from 100% hexanes to 30% EtOAc in hexanes to isolate all of the 4 diastereomers combined. A sample of the purified diastereomer, isolated after column chromatography, was then re-purified by preparative TLC chromatography to produce racemic material for HPLC traces analysis.

Product 49

Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 95:5, 0.5 mL min^{-1}, RT, UV detection at 254 nm

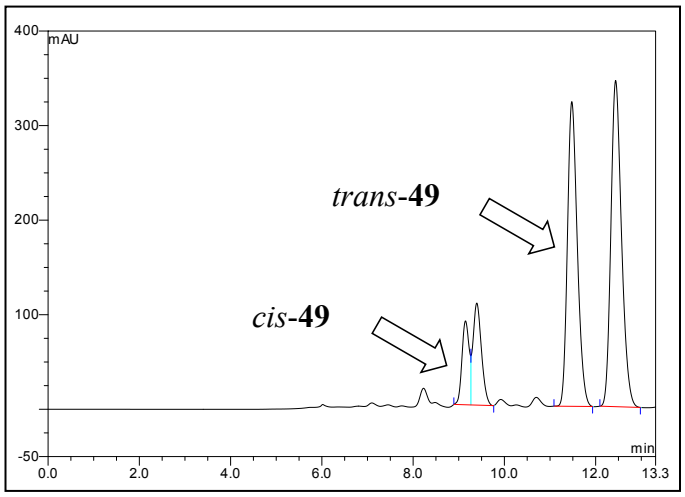


trans-**49**

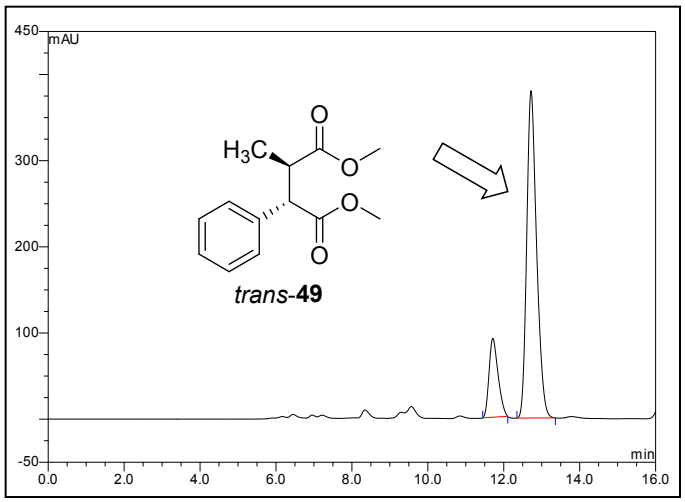


cis-**49**

No.	Ret. Time Min	Rel. Area %
1	11.48	49.38
2	12.44	50.62
Total		100.00

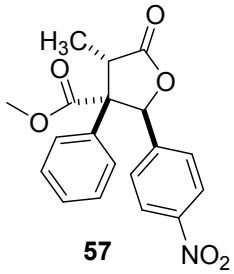


No.	Ret. Time Min	Rel. Area %
1	11.71	18.06
2	12.72	81.94
Total		100.00



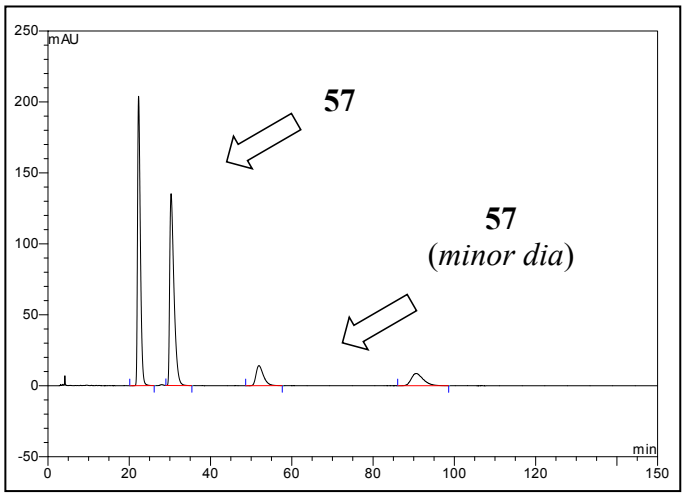
Product 57

Chiralcel ODH (4.6 mm x 25 cm), hexane/IPA: 90:10, 1 mL min^{-1}, RT, UV detection at 254 nm

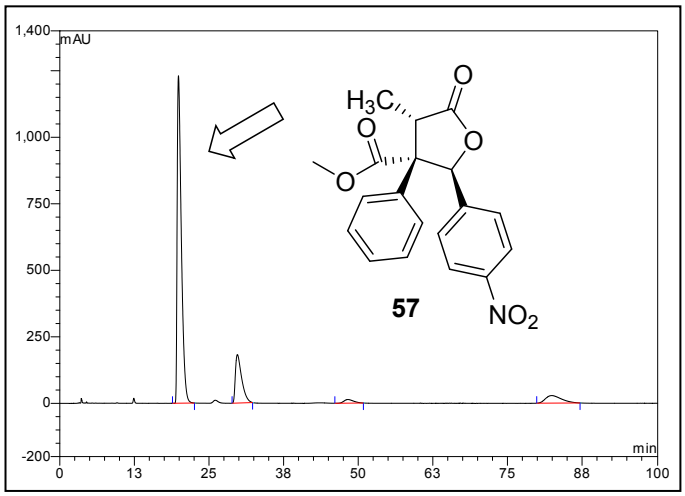


57

No.	Ret. Time Min	Rel. Area %
1	22.3	49.92
2	30.3	50.08
Total		100.00



No.	Ret. Time Min	Rel. Area %
1	19.88	81.64
2	29.75	18.36
Total		100.00



Product 57 (after crystallisation from $CHCl_3$)

Study Conditions

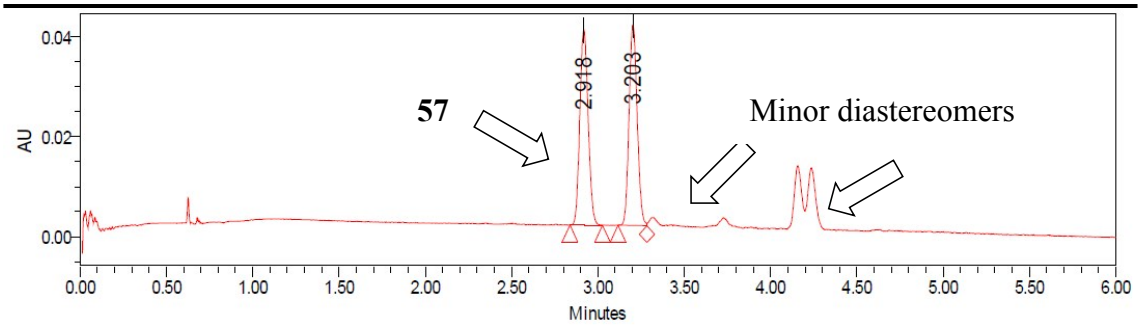
Instrument: ACQUITY UPC^2
Chiral Stationary Phase: ACQUITY UPC^2 Trefoil CEL2, 2.5µm 3.0 x 150mm Column
Detection: UV 230 nm with PDA detector
Mobile Phase: A = CO_2, B = Ethanol/ACN (1:1, *v*:*v*)
Column Temperature: 30 °C

Gradient Table

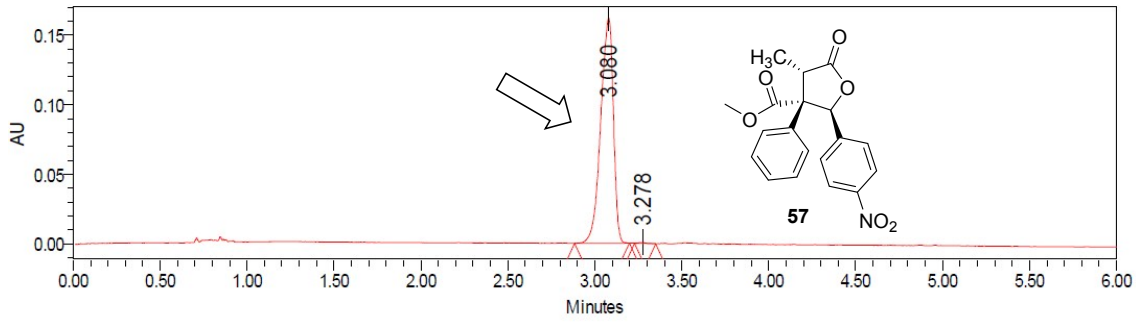
	Time (min)	FR (mL/min)	A (%)	B (%)	Curve
1	Initial	1.200	97.0	3.0	Initial
2	8.50	1.200	40.0	60.0	6
3	10.00	1.200	40.0	60.0	6
4	10.10	1.200	97.0	3.0	6

Inlet Pressure: 1500 (psi)

Racemic:



Chiral: 99% *ee*



Peak Results: Racemic

	Ret. Time (min)	Rel. Area (%)
1	2.918	49.93
2	3.203	50.07
Total:		100.00

Peak Results: Chiral

	Ret. Time (min)	Rel. Area (%)
1	3.080	99.78
2	3.278	0.22
Total:		100.00

Product 50

Study Conditions

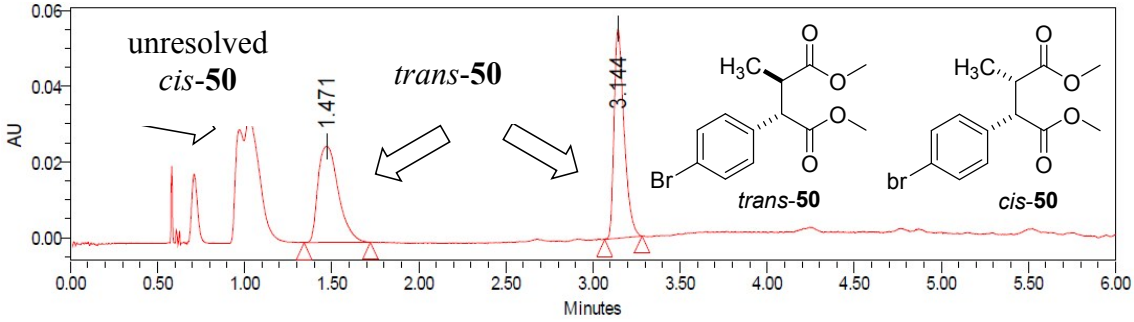
Instrument: ACQUITY UPC^2
Chiral Stationary Phase: ACQUITY UPC^2 Trefoil CEL2, 2.5µm 3.0 x 150mm Column
Detection: UV 230 nm with PDA detector
Mobile Phase: A = CO_2, B = Ethanol/ACN (1:1, *v*:*v*)
Column Temperature: 30 °C

Gradient Table

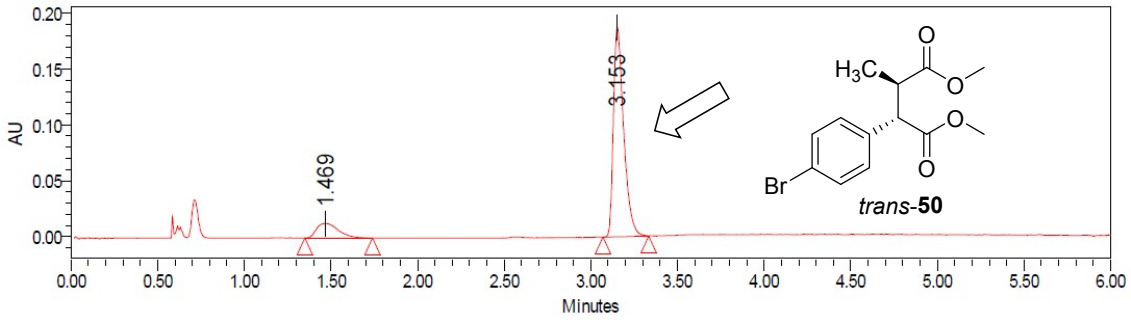
	Time (min)	FR (mL/min)	A (%)	B (%)	Curve
1	Initial	1.200	97.0	3.0	Initial
2	8.50	1.200	40.0	60.0	6
3	10.00	1.200	40.0	60.0	6
4	10.10	1.200	97.0	3.0	6

Inlet Pressure: 1500 (psi)

Racemic:



Chiral: 75% *ee*



Peak Results: Racemic

	Ret. Time (min)	Rel. Area (%)
1	1.471	49.44
2	3.144	50.56
Total:		100.00

Peak Results: Chiral

	Ret. Time (min)	Rel. Area (%)
1	1.469	12.75
2	3.153	87.25
Total:		100.00

Product 58

Study Conditions

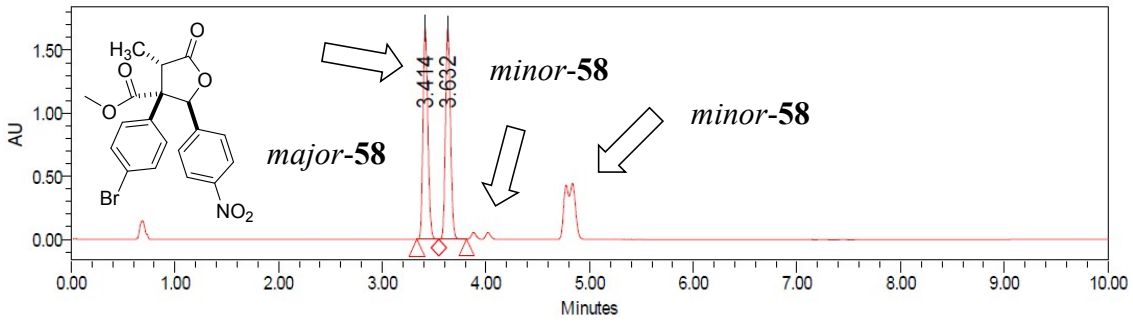
Instrument: ACQUITY UPC^2
Chiral Stationary Phase: ACQUITY UPC^2 Trefoil CEL2, 2.5µm 3.0 x 150mm Column
Detection: UV 230 nm with PDA detector
Mobile Phase: A = CO_2, B = Ethanol/ACN (1:1, *v*:*v*)
Column Temperature: 30 °C

Gradient Table

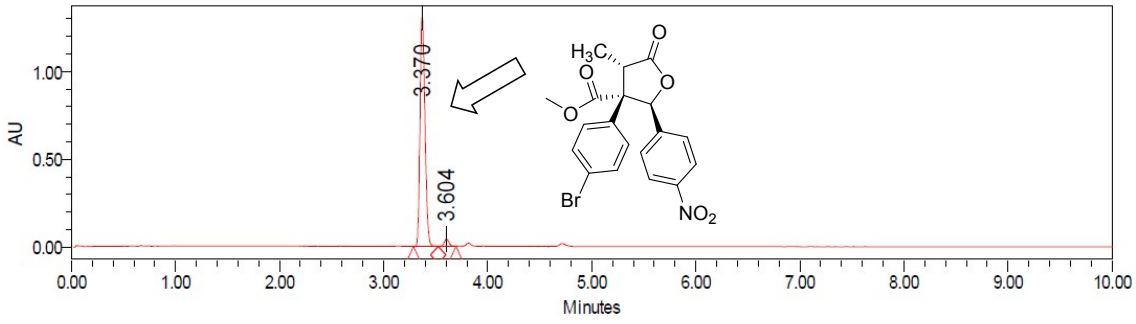
	Time (min)	FR (mL/min)	A (%)	B (%)	Curve
1	Initial	1.200	97.0	3.0	Initial
2	8.50	1.200	40.0	60.0	6
3	10.00	1.200	40.0	60.0	6
4	10.10	1.200	97.0	3.0	6

Inlet Pressure: 1500 (psi)

Racemic:



Chiral: 94% *ee*



Peak Results: Racemic

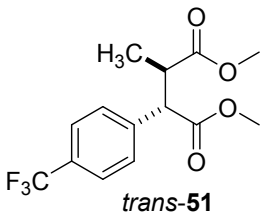
	Ret. Time (min)	Rel. Area (%)
1	3.414	49.5
2	3.632	50.5
Total:		100.00

Peak Results: Chiral

	Ret. Time (min)	Rel. Area (%)
1	3.370	97.1
2	3.604	2.9
Total:		100.00

Product 51

Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 95:5, 0.5 mL min^{-1}, RT, UV detection at 254 nm



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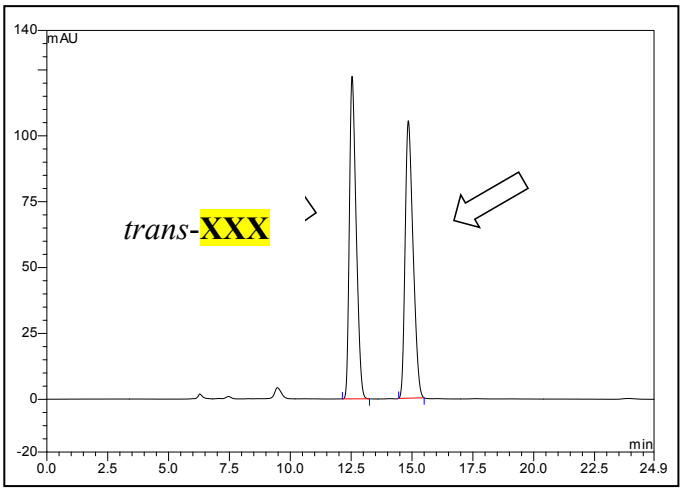
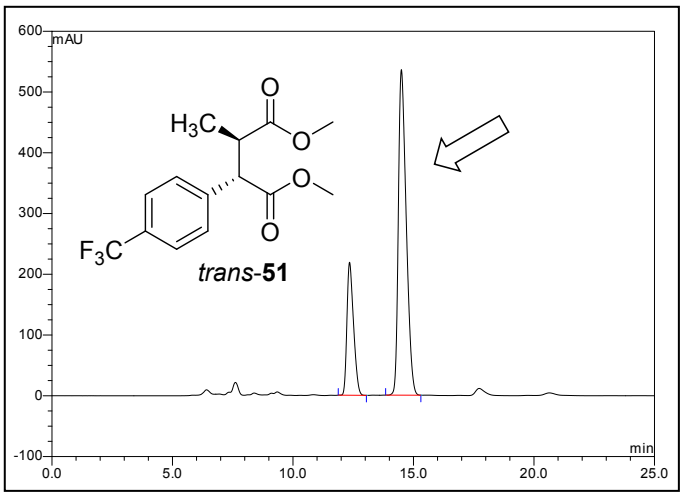
No.	Ret. Time Min	Rel. Area %
1	12.54	49.89
2	14.85	50.11
Total		100.00



No.	Ret. Time Min	Rel. Area %
1	12.35	25.46
2	14.50	74.54
Total		100.00



Product 59

Study Conditions

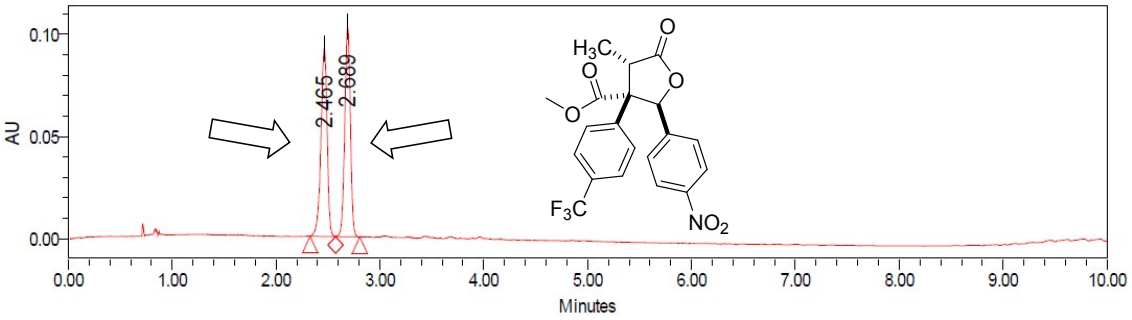
Instrument: ACQUITY UPC^2
Chiral Stationary Phase: ACQUITY UPC^2 Trefoil CEL2, 2.5µm 3.0 x 150mm Column
Detection: UV 254 nm with PDA detector
Mobile Phase: A = CO_2, B = Ethanol/ACN (1:1, *v*:*v*)
Column Temperature: 30 °C

Gradient Table

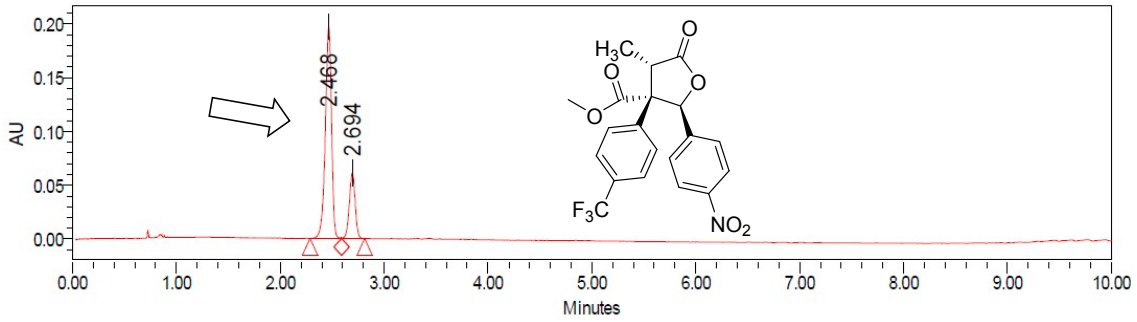
	Time (min)	FR (mL/min)	A (%)	B (%)	Curve
1	Initial	1.200	97.0	3.0	Initial
2	8.50	1.200	40.0	60.0	6
3	10.00	1.200	40.0	60.0	6
4	10.10	1.200	97.0	3.0	6

Inlet Pressure: 1500 (psi)

Racemic:



Chiral: 55% *ee*



Peak Results: Racemic

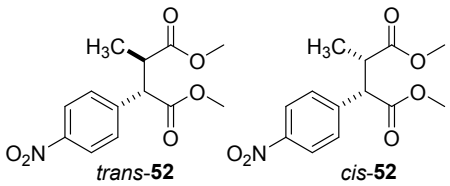
	Ret. Time (min)	Rel. Area (%)
1	2.465	49.66
2	2.689	50.34
Total:		100.00

Peak Results: Chiral

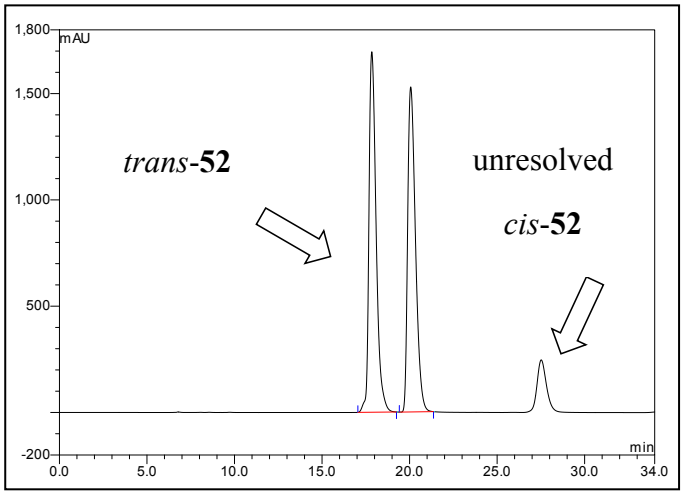
	Ret. Time (min)	Rel. Area (%)
1	2.468	77.43
2	2.694	22.57
Total:		100.00

Product 52

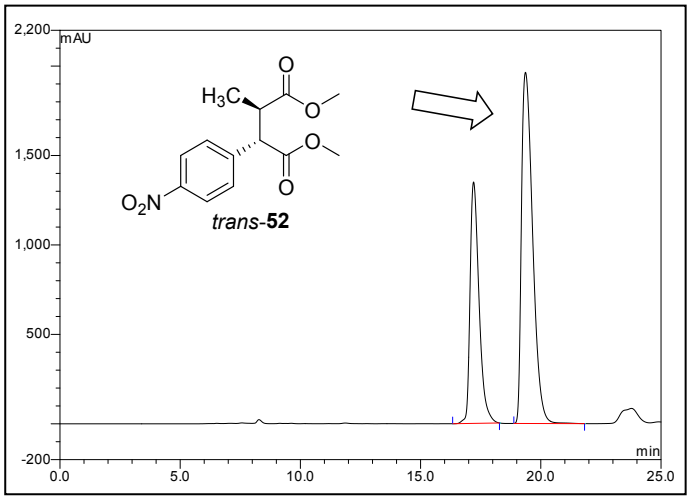
Chiralcel ODH (4.6 mm x 25 cm), hexane/IPA: 90:10, 1 mL min^{-1}, RT, UV detection at 254 nm



No.	Ret. Time Min	Rel. Area %
1	17.84	50.54
2	20.07	49.46
Total		100.00



No.	Ret. Time Min	Rel. Area %
1	17.21	35.58
2	19.36	64.42
Total		100.00



Product 60

Study Conditions

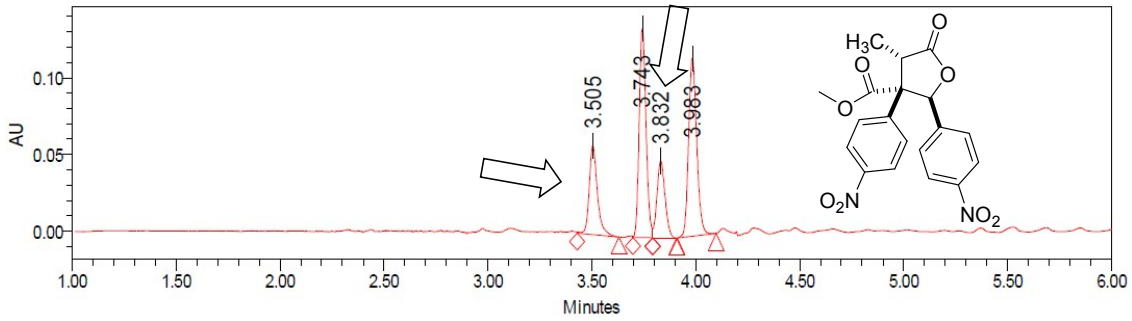
Instrument: ACQUITY UPC^2
Chiral Stationary Phase: ACQUITY UPC^2 Trefoil CEL1, 2.5µm 3.0 x 150mm Column
Detection: UV 254 nm with PDA detector
Mobile Phase: A = CO_2, B = Methanol/IPA (1:1, *v*:*v*)
Column Temperature: 30 °C

Gradient Table

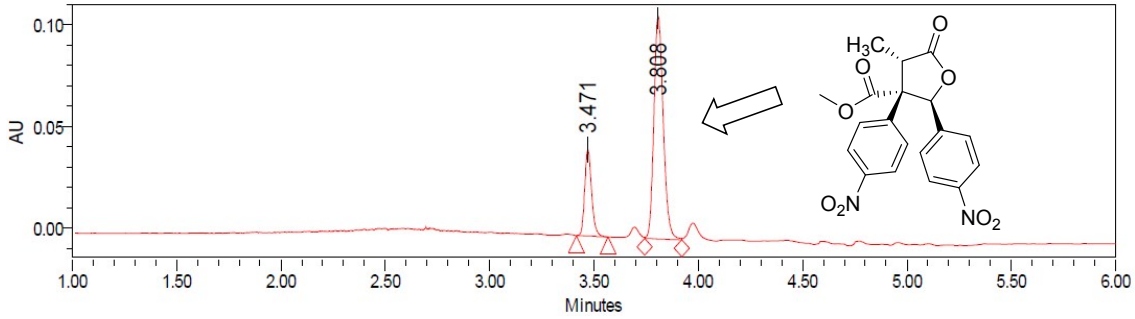
	Time (min)	FR (mL/min)	A (%)	B (%)	Curve
1	Initial	1.200	97.0	3.0	Initial
2	4.50	1.200	40.0	60.0	6
3	6.00	1.200	40.0	60.0	6
4	6.10	1.200	97.0	3.0	6

Inlet Pressure: 1500 (psi)

Racemic:



Chiral: 55% *ee*



Peak Results: Racemic

	Ret. Time (min)	Rel. Area (%)
1	3.505	50.76
2	3.832	49.24
Total:		100.00

Peak Results: Chiral

	Ret. Time (min)	Rel. Area (%)
1	3.471	22.24
2	3.808	77.76
Total:		100.00

Product 54

Study Conditions

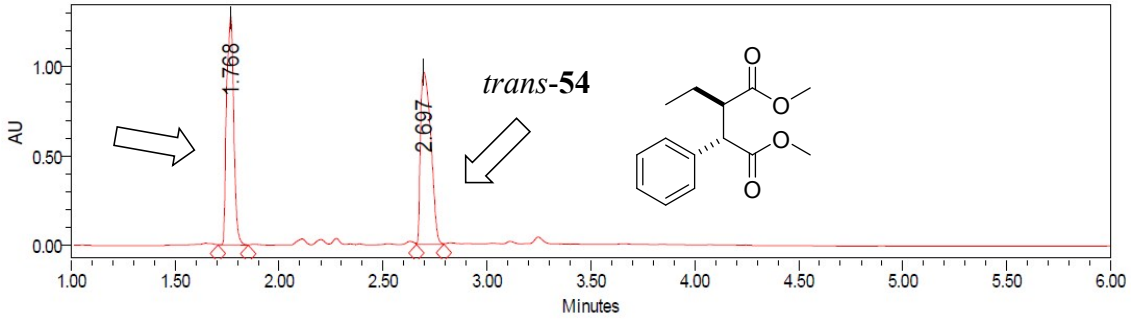
Instrument: ACQUITY UPC^2
Chiral Stationary Phase: ACQUITY UPC^2 Trefoil AMY1, 2.5µm 3.0 x 150mm Column
Detection: UV 230 nm with PDA detector
Mobile Phase: A = CO_2, B = Ethanol/IPA (1:1, *v*:*v*)
Column Temperature: 30 °C

Gradient Table

	Time (min)	FR (mL/min)	A (%)	B (%)	Curve
1	Initial	1.200	99.0	1.0	Initial
2	4.50	1.200	40.0	60.0	6
3	8.10	1.200	40.0	60.0	6
4	8.20	1.200	97.0	3.0	6

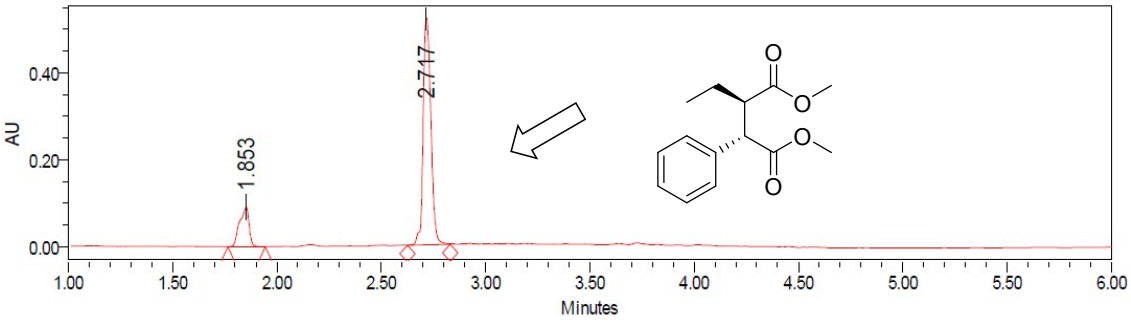
Inlet Pressure: 1500 (psi)

Racemic:



trans-**54**

Chiral: 65% *ee*



Peak Results: Racemic

	Ret. Time (min)	Rel. Area (%)
1	1.768	49.82
2	2.697	50.18
Total:		100.00

Peak Results: Chiral

	Ret. Time (min)	Rel. Area (%)
1	1.853	17.47
2	2.717	82.53
Total:		100.00

Product 62

Study Conditions

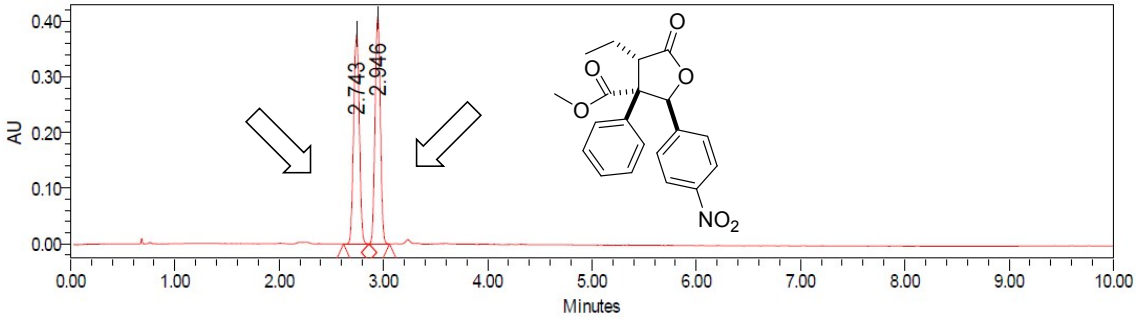
Instrument: ACQUITY UPC^2
Chiral Stationary Phase: ACQUITY UPC^2 Trefoil CEL2, 2.5µm 3.0 x 150mm Column
Detection: UV 230 nm with PDA detector
Mobile Phase: A = CO_2, B = Ethanol/ACN (1:1, *v*:*v*)
Column Temperature: 30 °C

Gradient Table

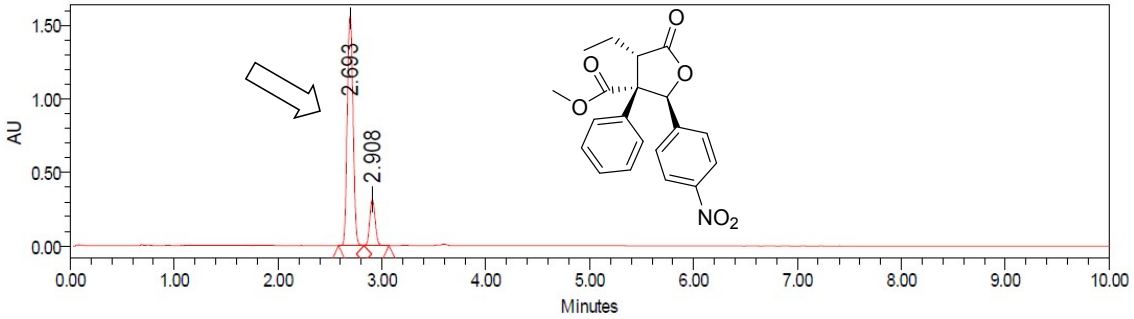
	Time (min)	FR (mL/min)	A (%)	B (%)	Curve
1	Initial	1.200	97.0	3.0	Initial
2	8.50	1.200	40.0	60.0	6
3	10.00	1.200	40.0	60.0	6
4	10.10	1.200	97.0	3.0	6

Inlet Pressure: 1500 (psi)

Racemic:



Chiral: 69% *ee*



Peak Results: Racemic

	Ret. Time (min)	Rel. Area (%)
1	2.743	50.01
2	2.946	49.99
Total:		100.00

Peak Results: Chiral

	Ret. Time (min)	Rel. Area (%)
1	2.693	84.34
2	2.908	15.66
Total:		100.00

Product 55

Study Conditions

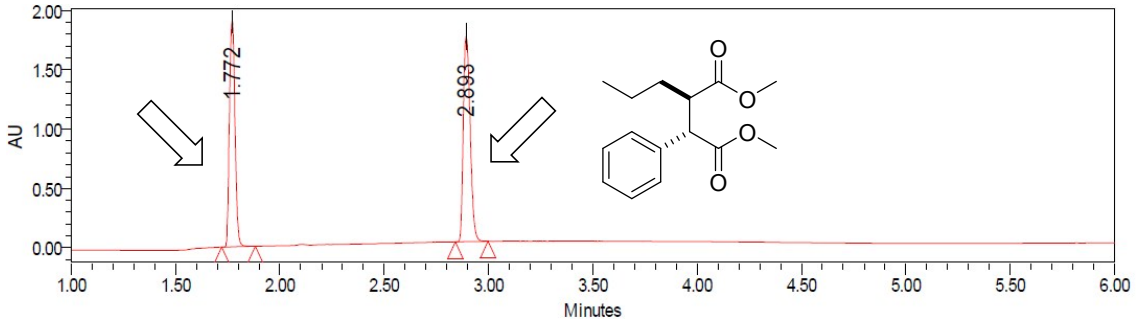
Instrument: ACQUITY UPC^2
Chiral Stationary Phase: ACQUITY UPC^2 Trefoil AMY1, 2.5µm 3.0 x 150mm Column
Detection: UV 212 nm with PDA detector
Mobile Phase: A = CO_2, B = Ethanol/IPA (1:1, *v*:*v*)
Column Temperature: 30 °C

Gradient Table

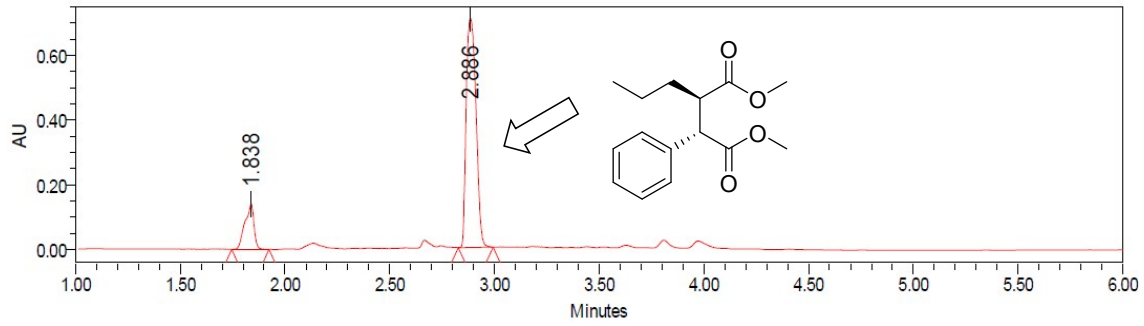
	Time (min)	FR (mL/min)	A (%)	B (%)	Curve
1	Initial	1.200	99.0	1.0	Initial
2	4.50	1.200	40.0	60.0	6
3	8.10	1.200	40.0	60.0	6
4	8.20	1.200	97.0	3.0	6

Inlet Pressure: 1500 (psi)

Racemic:



Chiral: 69% *ee*



Peak Results: Racemic

	Ret. Time (min)	Rel. Area (%)
1	1.772	49.10
2	2.893	50.90
Total:		100.00

Peak Results: Chiral

	Ret. Time (min)	Rel. Area (%)
1	1.838	15.40
2	2.886	84.60
Total:		100.00

Product 63

Study Conditions

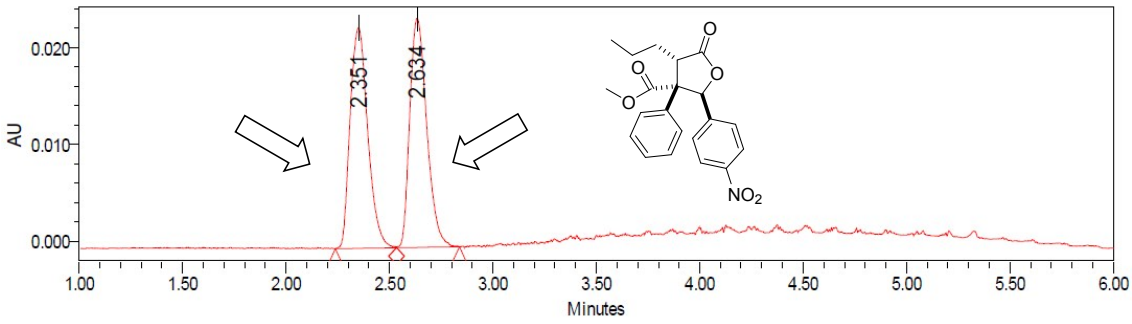
Instrument: ACQUITY UPC^2
Chiral Stationary Phase: ACQUITY UPC^2 Trefoil AMY1, 2.5µm 3.0 x 150mm Column
Detection: UV 254 nm with PDA detector
Mobile Phase: A = CO_2, B = Ethanol/IPA (1:1, *v*:*v*)
Column Temperature: 30 °C

Gradient Table

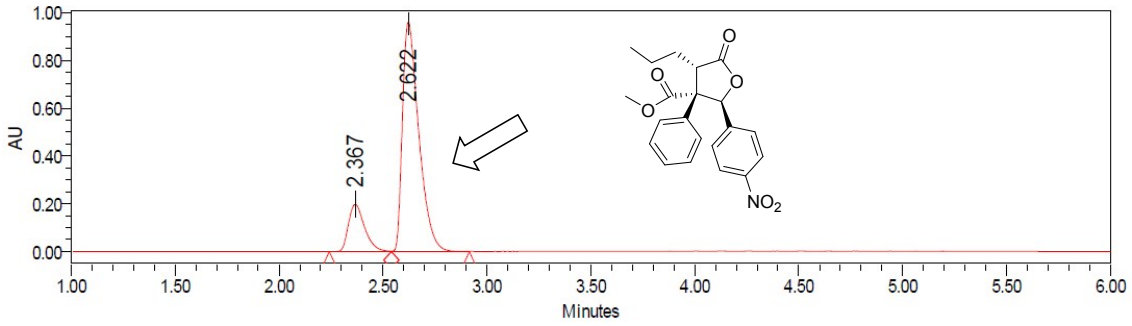
	Time (min)	FR (mL/min)	A (%)	B (%)	Curve
1	Initial	1.200	97.0	3.0	Initial
2	8.50	1.200	40.0	60.0	6
3	10.00	1.200	40.0	60.0	6
4	10.10	1.200	97.0	3.0	6

Inlet Pressure: 1500 (psi)

Racemic:



Chiral: 66% *ee*



Peak Results: Racemic

	Ret. Time (min)	Rel. Area (%)
1	2.351	50.02
2	2.634	49.98
Total:		100.00

Peak Results: Chiral

	Ret. Time (min)	Rel. Area (%)
1	2.367	17.0
2	2.622	83.0
Total:		100.00

Product 56

Study Conditions

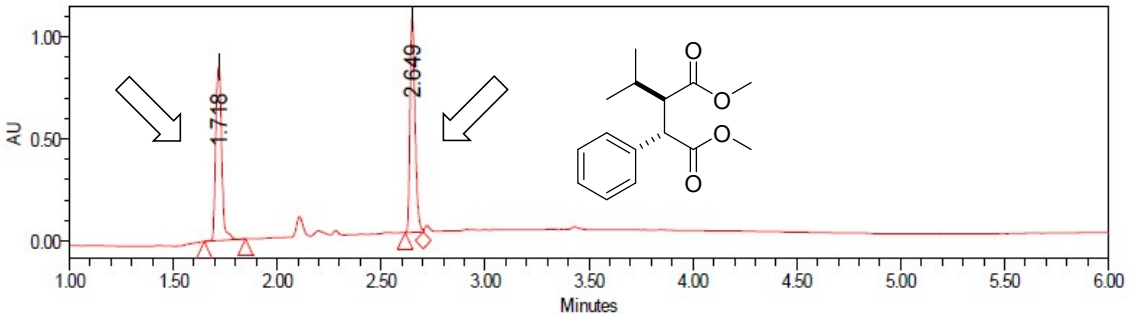
Instrument: ACQUITY UPC^2
Chiral Stationary Phase: ACQUITY UPC^2 Trefoil AMY1, 2.5µm 3.0 x 150mm Column
Detection: UV 212 nm with PDA detector
Mobile Phase: A = CO_2, B = Ethanol/IPA (1:1, *v*:*v*)
Column Temperature: 30 °C

Gradient Table

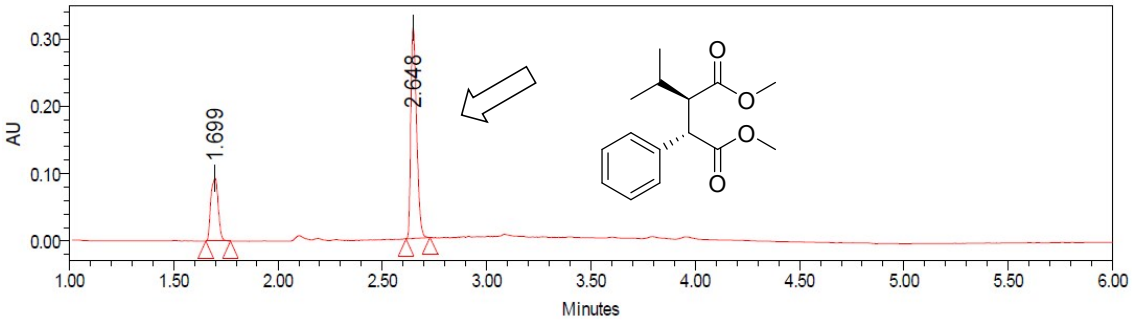
	Time (min)	FR (mL/min)	A (%)	B (%)	Curve
1	Initial	1.200	99.0	1.0	Initial
2	4.50	1.200	40.0	60.0	6
3	8.10	1.200	40.0	60.0	6
4	8.20	1.200	97.0	3.0	6

Inlet Pressure: 1500 (psi)

Racemic:



Chiral: 45% *ee*



Peak Results: Racemic

	Ret. Time (min)	Rel. Area (%)
1	1.718	49.96
2	2.649	50.04
Total:		100.00

Peak Results: Chiral

	Ret. Time (min)	Rel. Area (%)
1	1.699	27.57
2	2.648	72.43
Total:		100.00

Product 64

Study Conditions

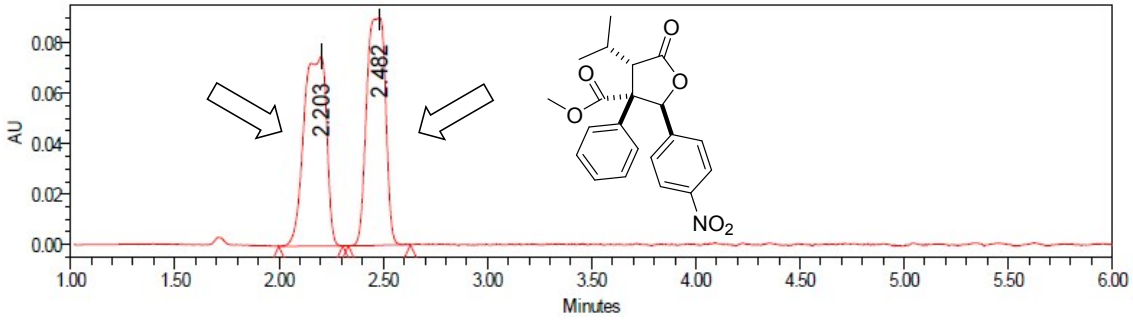
Instrument: ACQUITY UPC^2
Chiral Stationary Phase: ACQUITY UPC^2 Trefoil CEL1, 2.5µm 3.0 x 150mm Column
Detection: UV 254 nm with PDA detector
Mobile Phase: A = CO_2, B = Methanol/IPA (1:1, *v*:*v*)
Column Temperature: 30 °C

Gradient Table

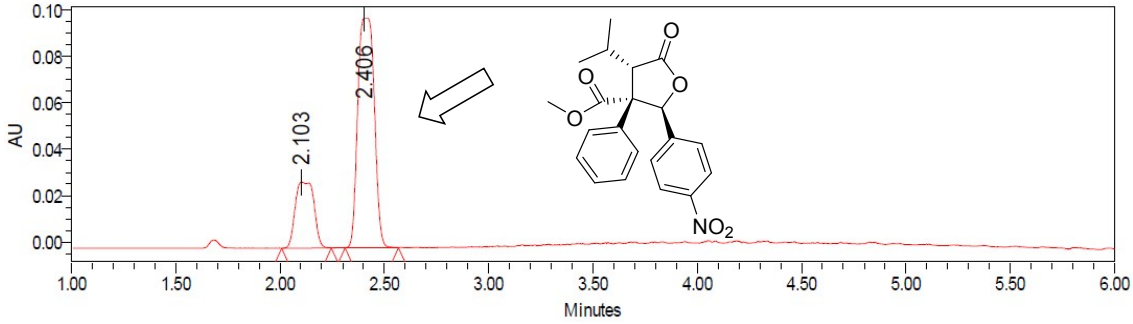
	Time (min)	FR (mL/min)	A (%)	B (%)	Curve
1	Initial	1.200	97.0	3.0	Initial
2	8.50	1.200	40.0	60.0	6
3	10.00	1.200	40.0	60.0	6
4	10.10	1.200	97.0	3.0	6

Inlet Pressure: 1500 (psi)

Racemic:



Chiral: 51% *ee*



Peak Results: Racemic

	Ret. Time (min)	Rel. Area (%)
1	2.203	49.90
2	2.482	50.10
Total:		100.00

Peak Results: Chiral

	Ret. Time (min)	Rel. Area (%)
1	2.103	24.69
2	2.406	75.31
Total:		100.00

Product 53

Study Conditions

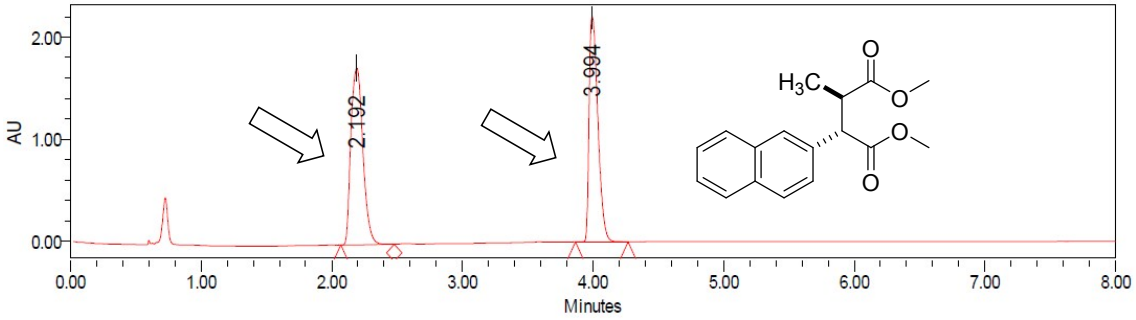
Instrument: ACQUITY UPC^2
Chiral Stationary Phase: ACQUITY UPC^2 Trefoil AMY1, 2.5µm 3.0 x 150mm Column
Detection: UV 254 nm with PDA detector
Mobile Phase: A = CO_2, B = Ethanol/ACN/IPA (1:1:1, *v*:*v*:*v*)
Column Temperature: 30 °C

Gradient Table

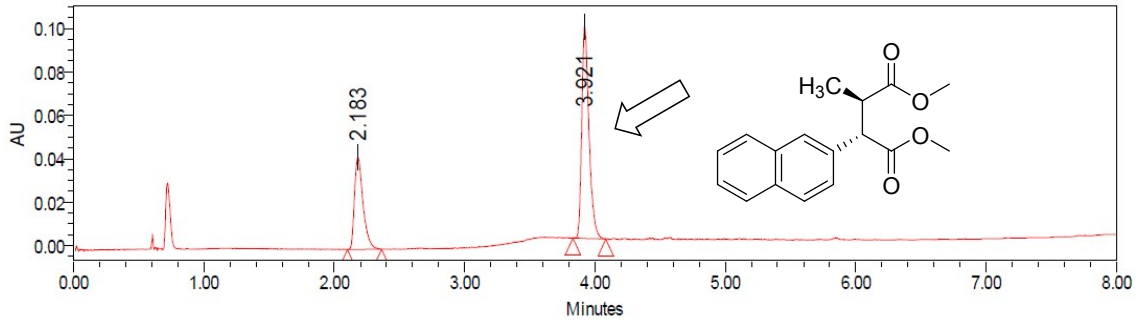
	Time (min)	FR (mL/min)	A (%)	B (%)	Curve
1	Initial	1.200	97.0	3.0	Initial
2	8.50	1.200	40.0	60.0	6
3	10.00	1.200	40.0	60.0	6
4	10.10	1.200	97.0	3.0	6

Inlet Pressure: 1500 (psi)

Racemic:



Chiral: 32% *ee*



Peak Results: Racemic

	Ret. Time (min)	Rel. Area (%)
1	2.192	50.75
2	3.994	49.25
Total:		100.00

Peak Results: Chiral

	Ret. Time (min)	Rel. Area (%)
1	2.183	33.96
2	3.921	66.04
Total:		100.00

Product 61

Study Conditions

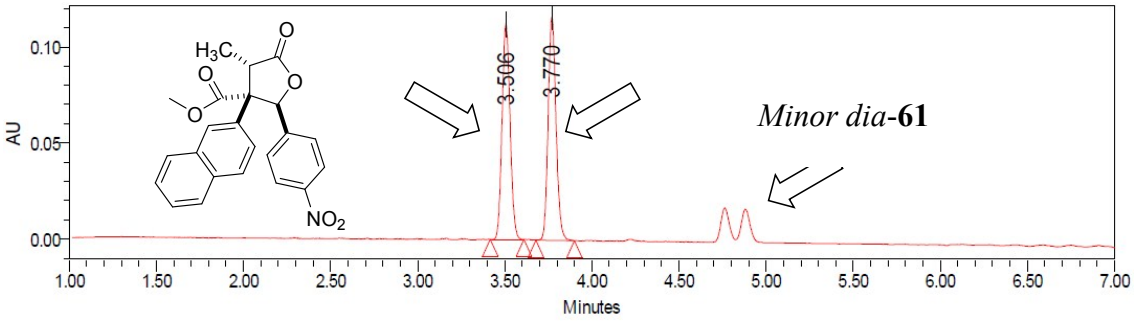
Instrument: ACQUITY UPC^2
Chiral Stationary Phase: ACQUITY UPC^2 Trefoil CEL2, 2.5µm 3.0 x 150mm Column
Detection: UV 254 nm with PDA detector
Mobile Phase: A = CO_2, B = Ethanol/ACN (1:1, *v*:*v*)
Column Temperature: 30 °C

Gradient Table

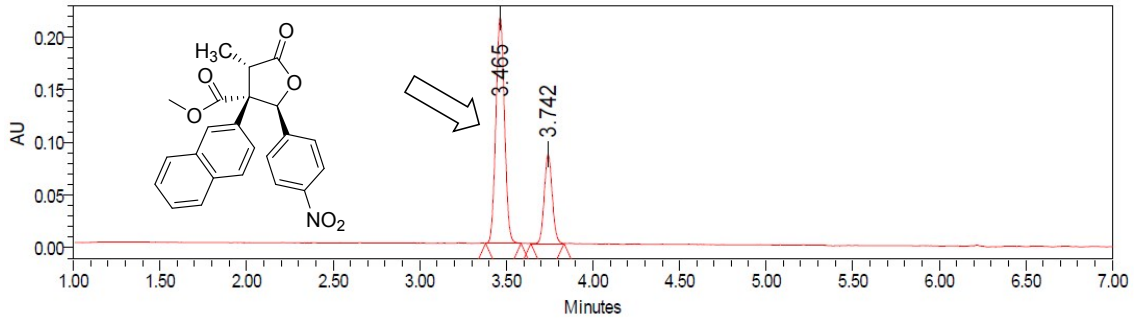
	Time (min)	FR (mL/min)	A (%)	B (%)	Curve
1	Initial	1.200	97.0	3.0	Initial
2	8.50	1.200	40.0	60.0	6
3	10.00	1.200	40.0	60.0	6
4	10.10	1.200	97.0	3.0	6

Inlet Pressure: 1500 (psi)

Racemic:



Chiral: 47% *ee*



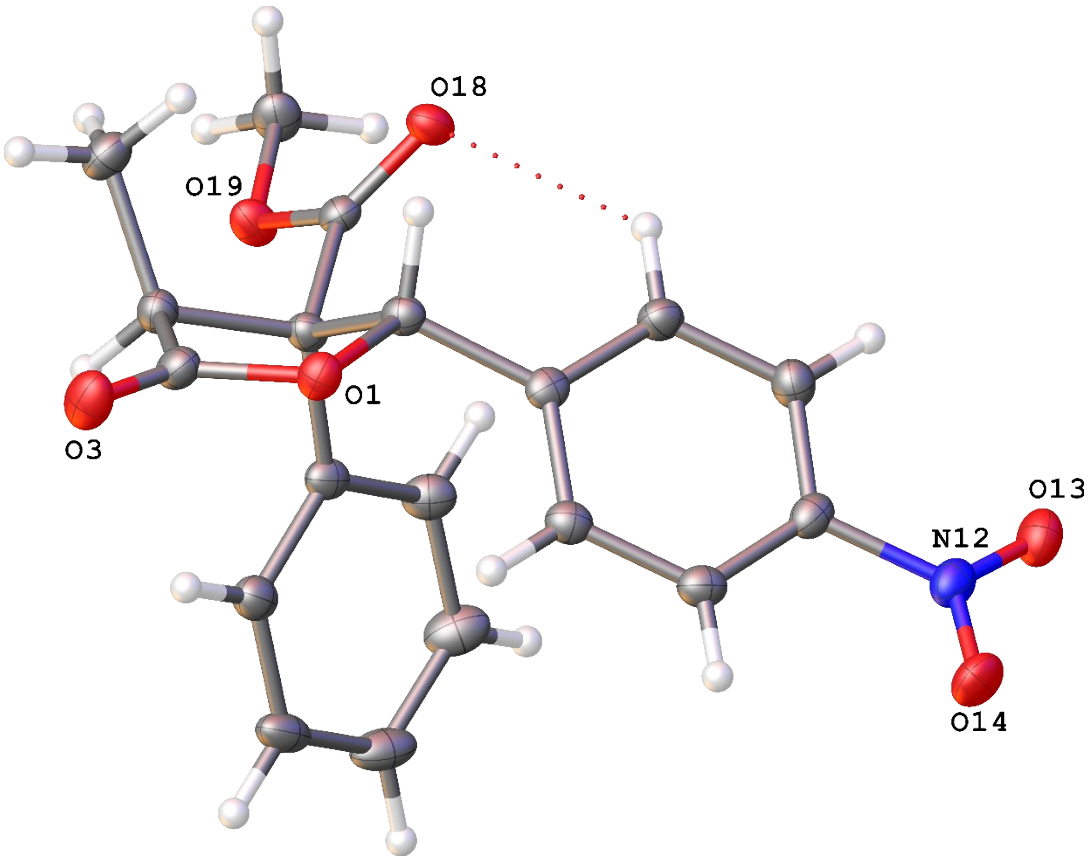
Peak Results: Racemic

	Ret. Time (min)	Rel. Area (%)
1	3.506	49.59
2	3.770	50.41
Total:		100.00

Peak Results: Chiral

	Ret. Time (min)	Rel. Area (%)
1	3.465	73.31
2	3.742	26.69
Total:		100.00

11. X-ray crystallography data for 57 - CCDC 1866834



A clear colourless fragment-like specimen of $C_{19}H_{17}NO_6$, approximate dimensions 0.110 mm x 0.260 mm x 0.500 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 100(2)K on a Bruker D8 Quest ECO with an Oxford Cryostream low temperature device using a MiTeGen micromount. See Table 1 for collection parameters and exposure time. Bruker APEX software was used to correct for Lorentz and polarization effects.

A total of 7382 frames were collected. The total exposure time was 14.35 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a hexagonal unit cell yielded a total of 41115 reflections to a maximum θ angle of 69.94° (0.82Å resolution), of which 3197 were independent (average redundancy 12.860, completeness = 99.6%, R_{int} = 3.69%, R_{sig} = 1.49%) and 3194 (99.91%) were greater than $2\sigma(F^2)$. The final cell constants of a = 9.3038(3) Å, b = 9.3038(3) Å, c = 33.9408(13) Å, volume = 2544.33(19) $Å^3$, are

based upon the refinement of the XYZ-centroids of 9971 reflections above 20 σ(I) with 10.42° < 2θ < 139.8°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.890. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.6704 and 0.7533.

The structure was solved with the XT structure solution program using Intrinsic Phasing and refined with the XL refinement package using Least Squares minimisation with Olex2, using the space group $P6_1$, with Z = 6 for the formula unit, $C_{19}H_{17}NO_6$. The final anisotropic full-matrix least-squares refinement on F^2 with 237 variables converged at R1 = 2.56%, for the observed data and wR2 = 6.61% for all data. The goodness-of-fit was 1.060. The largest peak in the final difference electron density synthesis was 0.181 $e^-/Å^3$ and the largest hole was -0.188 $e^-/Å^3$ with an RMS deviation of 0.037 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.391 g/cm^3 and F(000), 1116 e^-.

Refinement Note: Flack parameter refined. Chiral Centres: C4: S, C6: S, C7: S.

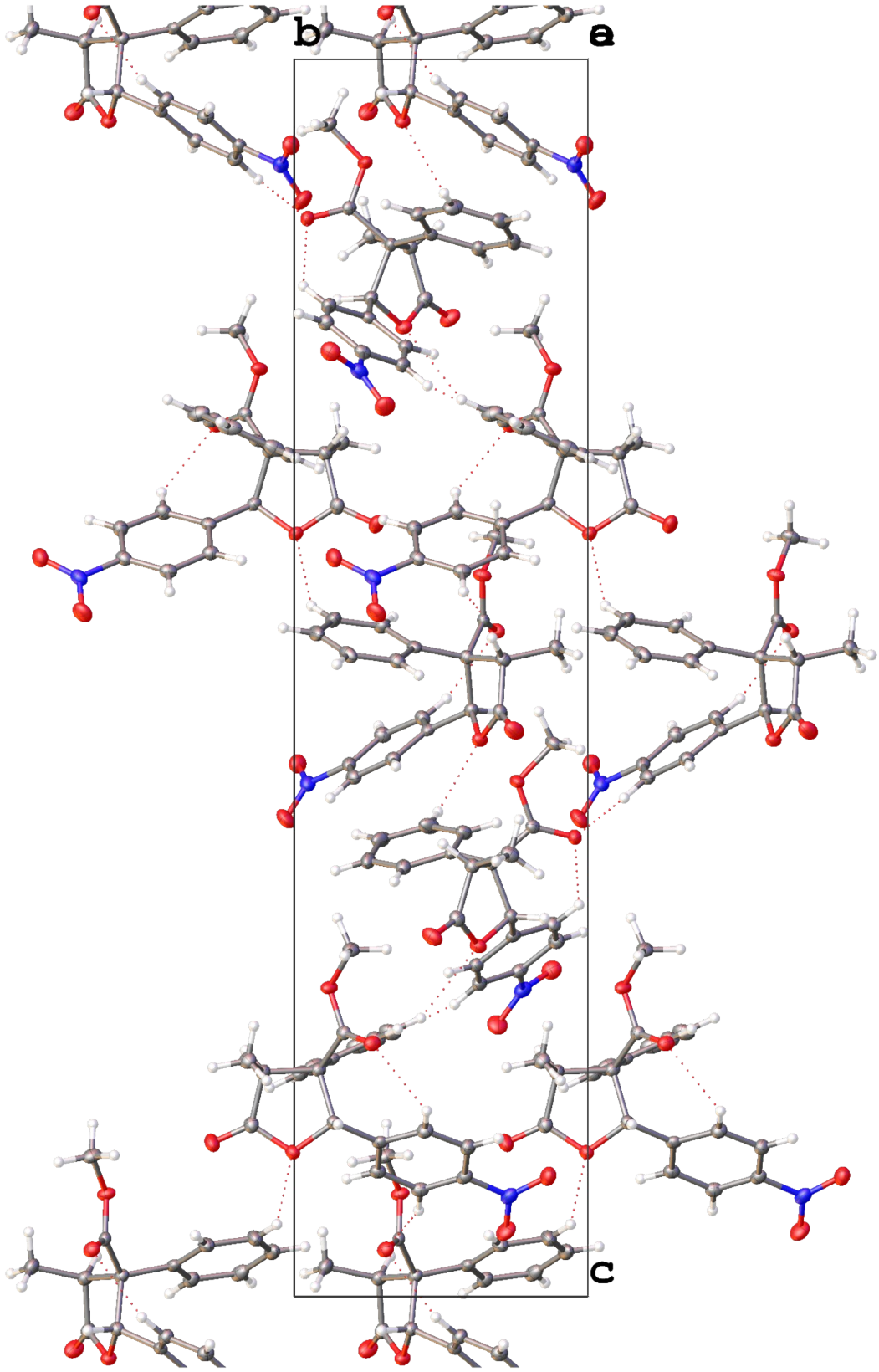


Figure: Packing diagram of **57** viewed normal to the a-axis. Dotted lines indicate hydrogen bonds.

Table 1. Data collection details for 57

Axis	dx/mm	2θ/°	ω/°	φ/°	χ/°	Width/°	Frames	Time/s	Wavelength/Å	Voltage/kV	Current/mA	Temperature/K
Omega	50.004	108.90	95.60	168.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	48.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Omega	50.004	-49.30	298.82	32.00	-64.50	0.70	166	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	120.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Phi	50.004	-47.74	343.92	252.00	23.00	0.70	309	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	0.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	72.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	192.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Omega	50.004	-49.30	298.82	256.00	-64.50	0.70	166	7.00	1.54184	45	0.6	100
Phi	50.004	79.30	65.73	360.00	-57.00	0.70	514	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	96.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	24.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	144.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Omega	50.004	-49.30	298.82	96.00	-64.50	0.70	166	7.00	1.54184	45	0.6	100
Phi	50.004	-7.14	24.51	296.58	23.00	0.70	284	7.00	1.54184	45	0.6	100
Phi	50.004	109.30	95.73	360.00	-57.00	0.70	514	7.00	1.54184	45	0.6	100
Phi	50.004	-49.30	73.15	0.00	-57.00	0.70	514	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	216.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Phi	50.004	94.30	80.73	360.00	-57.00	0.70	514	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	342.10	216.00	64.50	0.70	199	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	264.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Phi	50.004	-47.74	325.81	360.00	57.00	0.70	514	7.00	1.54184	45	0.6	100
Omega	55.004	-55.62	289.02	160.00	-64.50	0.70	180	7.00	1.54184	45	0.6	100
Omega	55.004	-55.62	178.62	32.00	54.74	0.70	205	7.00	1.54184	45	0.6	100
Omega	55.004	110.58	93.09	168.00	-54.74	0.70	205	7.00	1.54184	45	0.6	100
Omega	55.004	110.58	93.09	120.00	-54.74	0.70	205	7.00	1.54184	45	0.6	100
Omega	55.004	-55.62	178.62	96.00	54.74	0.70	205	7.00	1.54184	45	0.6	100
Omega	55.004	110.58	93.09	192.00	-54.74	0.70	205	7.00	1.54184	45	0.6	100
Omega	55.004	110.58	93.09	72.00	-54.74	0.70	205	7.00	1.54184	45	0.6	100

Table 2. Crystal data and structure refinement for 57.		
Identification code	tcd893	
Empirical formula	$C_{19}H_{17}F_6NO_6$	
Formula weight	355.33	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Hexagonal	
Space group	$P6_1$	
Unit cell dimensions	a = 9.3038(3) Å	α = 90°
	b = 9.3038(4) Å	β = 90°
	c = 33.9408(13) Å	γ = 120°
Volume	2544.33(19) Å^3	
Z	6	
Density (calculated)	1.391 Mg/m^3	
Absorption coefficient	0.876 mm^{-1}	
F(000)	1116	
Crystal size	0.5 x 0.26 x 0.11 mm^3	
Theta range for data collection	5.490 to 69.943°.	
Index ranges	-11≤h≤11, -10≤k≤11, -40≤l≤41	
Reflections collected	41115	
Independent reflections	3197 [R(int) = 0.0369]	
Completeness to theta = 67.679°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7533 and 0.6704	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3197 / 1 / 237	
Goodness-of-fit on F^2	1.060	
Final R indices [I>2σ(I)]	R1 = 0.0256, wR2 = 0.0661	
R indices (all data)	R1 = 0.0256, wR2 = 0.0661	
Absolute structure parameter	0.03(3)	
Largest diff. peak and hole	0.181 and -0.188 e.Å^{-3}	

Table 3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for 57.

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	3738(2)	3686(2)	5501(1)	19(1)
C(2)	4447(2)	2987(2)	5279(1)	20(1)
O(3)	5305(2)	2509(2)	5425(1)	28(1)
C(4)	3941(2)	2886(2)	4852(1)	19(1)
C(5)	2651(2)	1070(2)	4760(1)	24(1)
C(6)	3288(2)	4125(2)	4834(1)	16(1)
C(7)	2612(2)	3971(2)	5262(1)	17(1)
C(8)	2537(2)	5453(2)	5421(1)	17(1)
C(9)	1177(2)	5633(2)	5327(1)	20(1)
C(10)	1076(2)	6988(2)	5461(1)	22(1)
C(11)	2334(2)	8131(2)	5700(1)	20(1)
N(12)	2216(2)	9542(2)	5855(1)	23(1)

O(13)	1239(2)	9883(2)	5696(1)	28(1)
O(14)	3087(2)	10294(2)	6139(1)	31(1)
C(15)	3695(2)	7980(2)	5804(1)	20(1)
C(16)	3799(2)	6644(2)	5656(1)	19(1)
C(17)	1873(2)	3560(2)	4537(1)	16(1)
O(18)	450(2)	3105(2)	4621(1)	20(1)
O(19)	2413(2)	3603(2)	4171(1)	21(1)
C(20)	1168(2)	3110(2)	3864(1)	23(1)
C(21)	4650(2)	5906(2)	4750(1)	18(1)
C(22)	4227(2)	7015(2)	4584(1)	22(1)
C(23)	5414(3)	8668(2)	4531(1)	29(1)
C(24)	7051(3)	9246(2)	4640(1)	29(1)
C(25)	7480(2)	8157(2)	4811(1)	26(1)
C(26)	6285(2)	6494(2)	4864(1)	21(1)

Table 4. Bond lengths [Å] and angles [°] for 57.

O(1)-C(2)	1.361(2)	C(23)-H(23)	0.9500
O(1)-C(7)	1.450(2)	C(23)-C(24)	1.389(3)
C(2)-O(3)	1.198(2)	C(24)-H(24)	0.9500
C(2)-C(4)	1.511(2)	C(24)-C(25)	1.388(3)
C(4)-H(4)	1.0000	C(25)-H(25)	0.9500
C(4)-C(5)	1.538(2)	C(25)-C(26)	1.394(3)
C(4)-C(6)	1.551(2)	C(26)-H(26)	0.9500
C(5)-H(5A)	0.9800		
C(5)-H(5B)	0.9800	C(2)-O(1)-C(7)	110.18(13)
C(5)-H(5C)	0.9800	O(1)-C(2)-C(4)	110.43(14)
C(6)-C(7)	1.560(2)	O(3)-C(2)-O(1)	121.37(17)
C(6)-C(17)	1.528(2)	O(3)-C(2)-C(4)	128.17(17)
C(6)-C(21)	1.527(2)	C(2)-C(4)-H(4)	110.2
C(7)-H(7)	1.0000	C(2)-C(4)-C(5)	108.18(15)
C(7)-C(8)	1.514(2)	C(2)-C(4)-C(6)	102.59(13)
C(8)-C(9)	1.394(3)	C(5)-C(4)-H(4)	110.2
C(8)-C(16)	1.394(2)	C(5)-C(4)-C(6)	115.29(15)
C(9)-H(9)	0.9500	C(6)-C(4)-H(4)	110.2
C(9)-C(10)	1.387(3)	C(4)-C(5)-H(5A)	109.5
C(10)-H(10)	0.9500	C(4)-C(5)-H(5B)	109.5
C(10)-C(11)	1.384(3)	C(4)-C(5)-H(5C)	109.5
C(11)-N(12)	1.468(2)	H(5A)-C(5)-H(5B)	109.5
C(11)-C(15)	1.388(3)	H(5A)-C(5)-H(5C)	109.5
N(12)-O(13)	1.229(2)	H(5B)-C(5)-H(5C)	109.5
N(12)-O(14)	1.227(2)	C(4)-C(6)-C(7)	100.61(13)
C(15)-H(15)	0.9500	C(17)-C(6)-C(4)	111.18(13)
C(15)-C(16)	1.388(3)	C(17)-C(6)-C(7)	110.20(13)
C(16)-H(16)	0.9500	C(21)-C(6)-C(4)	113.13(14)
C(17)-O(18)	1.206(2)	C(21)-C(6)-C(7)	110.51(14)
C(17)-O(19)	1.331(2)	C(21)-C(6)-C(17)	110.80(14)

O(19)-C(20)	1.452(2)	O(1)-C(7)-C(6)	104.06(13)
C(20)-H(20A)	0.9800	O(1)-C(7)-H(7)	108.8
C(20)-H(20B)	0.9800	O(1)-C(7)-C(8)	109.45(13)
C(20)-H(20C)	0.9800	C(6)-C(7)-H(7)	108.8
C(21)-C(22)	1.395(3)	C(8)-C(7)-C(6)	116.64(14)
C(21)-C(26)	1.389(3)	C(8)-C(7)-H(7)	108.8
C(22)-H(22)	0.9500	C(9)-C(8)-C(7)	119.03(15)
C(22)-C(23)	1.385(3)	C(9)-C(8)-C(16)	119.35(16)
C(16)-C(8)-C(7)	121.61(16)	O(19)-C(20)-H(20B)	109.5
C(8)-C(9)-H(9)	119.6	O(19)-C(20)-H(20C)	109.5
C(10)-C(9)-C(8)	120.78(17)	H(20A)-C(20)-H(20B)	109.5
C(10)-C(9)-H(9)	119.6	H(20A)-C(20)-H(20C)	109.5
C(9)-C(10)-H(10)	120.8	H(20B)-C(20)-H(20C)	109.5
C(11)-C(10)-C(9)	118.41(17)	C(22)-C(21)-C(6)	119.34(15)
C(11)-C(10)-H(10)	120.8	C(26)-C(21)-C(6)	121.83(16)
C(10)-C(11)-N(12)	119.02(17)	C(26)-C(21)-C(22)	118.62(17)
C(10)-C(11)-C(15)	122.31(17)	C(21)-C(22)-H(22)	119.6
C(15)-C(11)-N(12)	118.67(16)	C(23)-C(22)-C(21)	120.75(18)
O(13)-N(12)-C(11)	117.96(16)	C(23)-C(22)-H(22)	119.6
O(14)-N(12)-C(11)	117.91(16)	C(22)-C(23)-H(23)	119.8
O(14)-N(12)-O(13)	124.13(16)	C(22)-C(23)-C(24)	120.41(19)
C(11)-C(15)-H(15)	120.8	C(24)-C(23)-H(23)	119.8
C(16)-C(15)-C(11)	118.37(16)	C(23)-C(24)-H(24)	120.4
C(16)-C(15)-H(15)	120.8	C(25)-C(24)-C(23)	119.29(18)
C(8)-C(16)-H(16)	119.6	C(25)-C(24)-H(24)	120.4
C(15)-C(16)-C(8)	120.72(16)	C(24)-C(25)-H(25)	119.9
C(15)-C(16)-H(16)	119.6	C(24)-C(25)-C(26)	120.21(18)
O(18)-C(17)-C(6)	124.67(15)	C(26)-C(25)-H(25)	119.9
O(18)-C(17)-O(19)	124.31(16)	C(21)-C(26)-C(25)	120.71(18)
O(19)-C(17)-C(6)	111.02(14)	C(21)-C(26)-H(26)	119.6
C(17)-O(19)-C(20)	115.55(13)	C(25)-C(26)-H(26)	119.6
O(19)-C(20)-H(20A)	109.5		

Table 5. Anisotropic displacement parameters (Å^{2}x 10^3) for 57.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	23(1)	21(1)	16(1)	-1(1)	-3(1)	13(1)
C(2)	21(1)	17(1)	22(1)	-2(1)	-2(1)	9(1)
O(3)	34(1)	32(1)	27(1)	-6(1)	-10(1)	23(1)
C(4)	19(1)	20(1)	19(1)	-2(1)	0(1)	10(1)
C(5)	28(1)	20(1)	23(1)	-4(1)	-4(1)	12(1)
C(6)	14(1)	18(1)	16(1)	-2(1)	-1(1)	7(1)
C(7)	17(1)	17(1)	17(1)	0(1)	-2(1)	8(1)
C(8)	19(1)	17(1)	13(1)	2(1)	3(1)	7(1)
C(9)	19(1)	20(1)	20(1)	-3(1)	-2(1)	8(1)
C(10)	22(1)	24(1)	21(1)	-1(1)	0(1)	13(1)
C(11)	23(1)	16(1)	18(1)	1(1)	4(1)	9(1)
N(12)	26(1)	20(1)	22(1)	0(1)	6(1)	10(1)
O(13)	33(1)	25(1)	30(1)	0(1)	3(1)	19(1)
O(14)	34(1)	27(1)	31(1)	-12(1)	-3(1)	15(1)
C(15)	19(1)	20(1)	18(1)	-1(1)	0(1)	6(1)
C(16)	18(1)	20(1)	17(1)	1(1)	1(1)	8(1)
C(17)	18(1)	13(1)	17(1)	-1(1)	-1(1)	6(1)
O(18)	16(1)	22(1)	19(1)	-2(1)	-1(1)	7(1)
O(19)	19(1)	28(1)	14(1)	-3(1)	-2(1)	12(1)
C(20)	24(1)	30(1)	18(1)	-5(1)	-6(1)	15(1)
C(21)	18(1)	19(1)	13(1)	-2(1)	2(1)	7(1)
C(22)	23(1)	22(1)	18(1)	1(1)	-3(1)	8(1)
C(23)	36(1)	22(1)	22(1)	4(1)	-2(1)	9(1)
C(24)	29(1)	21(1)	21(1)	-1(1)	4(1)	0(1)
C(25)	16(1)	28(1)	24(1)	-7(1)	1(1)	4(1)
C(26)	20(1)	23(1)	20(1)	-4(1)	1(1)	10(1)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for 57.

	x	y	z	U(eq)
H(4)	4931	3269	4678	22
H(5A)	3124	359	4817	36
H(5B)	2344	969	4481	36
H(5C)	1662	726	4923	36
H(7)	1479	2970	5277	21
H(9)	309	4817	5169	24
H(10)	166	7129	5390	26
H(15)	4535	8772	5972	25
H(16)	4740	6540	5716	23
H(20A)	1672	3143	3608	35
H(20B)	731	3875	3861	35
H(20C)	262	1980	3915	35
H(22)	3112	6633	4507	27
H(23)	5106	9410	4418	35

	x	y	z	U(eq)
H(24)	7868	10375	4599	35
H(25)	8593	8546	4892	31
H(26)	6591	5756	4979	26

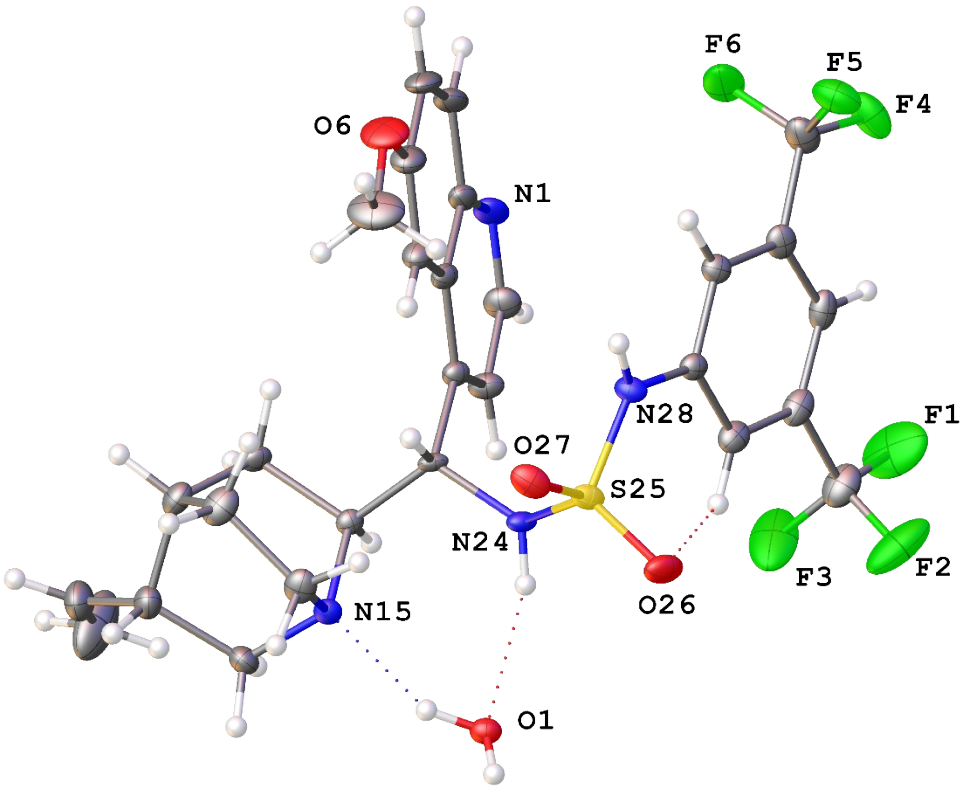
Table 7. Torsion angles [°] for 57.

O(1)-C(2)-C(4)-C(5)	-104.99(17)	C(7)-C(6)-C(21)-C(26)	83.1(2)
O(1)-C(2)-C(4)-C(6)	17.30(18)	C(7)-C(8)-C(9)-C(10)	-178.84(16)
O(1)-C(7)-C(8)-C(9)	-159.14(15)	C(7)-C(8)-C(16)-C(15)	-179.06(16)
O(1)-C(7)-C(8)-C(16)	21.3(2)	C(8)-C(9)-C(10)-C(11)	-2.0(3)
C(2)-O(1)-C(7)-C(6)	-25.26(17)	C(9)-C(8)-C(16)-C(15)	1.4(3)
C(2)-O(1)-C(7)-C(8)	-150.62(14)	C(9)-C(10)-C(11)-N(12)	-177.99(16)
C(2)-C(4)-C(6)-C(7)	-30.33(16)	C(9)-C(10)-C(11)-C(15)	1.2(3)
C(2)-C(4)-C(6)-C(17)	-147.04(14)	C(10)-C(11)-N(12)-O(13)	-17.1(2)
C(2)-C(4)-C(6)-C(21)	87.54(17)	C(10)-C(11)-N(12)-O(14)	162.05(17)
O(3)-C(2)-C(4)-C(5)	73.2(2)	C(10)-C(11)-C(15)-C(16)	0.9(3)
O(3)-C(2)-C(4)-C(6)	-164.55(19)	C(11)-C(15)-C(16)-C(8)	-2.2(3)
C(4)-C(6)-C(7)-O(1)	33.96(15)	N(12)-C(11)-C(15)-C(16)	-179.95(15)
C(4)-C(6)-C(7)-C(8)	154.61(14)	C(15)-C(11)-N(12)-O(13)	163.69(16)
C(4)-C(6)-C(17)-O(18)	112.54(19)	C(15)-C(11)-N(12)-O(14)	-17.1(2)
C(4)-C(6)-C(17)-O(19)	-66.18(18)	C(16)-C(8)-C(9)-C(10)	0.7(3)
C(4)-C(6)-C(21)-C(22)	156.48(16)	C(17)-C(6)-C(7)-O(1)	151.39(13)
C(4)-C(6)-C(21)-C(26)	-28.8(2)	C(17)-C(6)-C(7)-C(8)	-87.97(17)
C(5)-C(4)-C(6)-C(7)	87.00(17)	C(17)-C(6)-C(21)-C(22)	30.9(2)
C(5)-C(4)-C(6)-C(17)	-29.7(2)	C(17)-C(6)-C(21)-C(26)	-154.45(16)
C(5)-C(4)-C(6)-C(21)	-155.12(15)	O(18)-C(17)-O(19)-C(20)	2.1(2)
C(6)-C(7)-C(8)-C(9)	83.1(2)	C(21)-C(6)-C(7)-O(1)	-85.82(16)
C(6)-C(7)-C(8)-C(16)	-96.42(19)	C(21)-C(6)-C(7)-C(8)	34.83(19)
C(6)-C(17)-O(19)-C(20)	-179.19(14)	C(21)-C(6)-C(17)-O(18)	-120.75(18)
C(6)-C(21)-C(22)-C(23)	175.36(18)	C(21)-C(6)-C(17)-O(19)	60.53(18)
C(6)-C(21)-C(26)-C(25)	-175.13(17)	C(21)-C(22)-C(23)-C(24)	0.3(3)
C(7)-O(1)-C(2)-O(3)	-173.23(17)	C(22)-C(21)-C(26)-C(25)	-0.4(3)
C(7)-O(1)-C(2)-C(4)	5.07(19)	C(22)-C(23)-C(24)-C(25)	-1.1(3)
C(7)-C(6)-C(17)-O(18)	1.9(2)	C(23)-C(24)-C(25)-C(26)	1.2(3)
C(7)-C(6)-C(17)-O(19)	-176.84(14)	C(24)-C(25)-C(26)-C(21)	-0.5(3)
C(7)-C(6)-C(21)-C(22)	-91.59(19)	C(26)-C(21)-C(22)-C(23)	0.5(3)

Table 8. Hydrogen bonds for 57 (Å and °).

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(9)-H(9)...O(18)	0.95	2.49	3.183(2)	129

12. X-ray crystallography data for catalyst 20 - CCDC 1866833



A specimen of $C_{28}H_{30}F_6N_4O_4S$, approximate dimensions 0.110 mm x 0.290 mm x 0.380 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 100(2)K on a Bruker D8 Quest ECO with an Oxford Cryostream low temperature device using a MiTeGen micromount. See Table 1 for collection parameters and exposure time. Bruker APEX software was used to correct for Lorentz and polarization effects.

A total of 1002 frames were collected. The total exposure time was 2.53 hours. The integration of the data using an orthorhombic unit cell yielded a total of 39589 reflections to a maximum θ angle of 28.43° (0.75 Å resolution), of which 7137 were independent (average redundancy 5.547, completeness = 99.1%, R_{int} = 5.03%, R_{sig} = 3.43%) and 6559 (91.90%) were greater than $2\sigma(F^2)$. The final cell constants of $\underline{a}$ = 10.0847(3) Å, $\underline{b}$ = 12.3157(4) Å, $\underline{c}$ = 23.0056(7) Å, volume = 2857.30(15) $Å^3$, are based upon the refinement of the XYZ-centroids of reflections above 20 σ(I). Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of

minimum to maximum apparent transmission was 0.879. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.6554 and 0.7457.

The structure was solved with the XT structure solution program using Intrinsic Phasing and refined with the XL refinement package using Least Squares minimisation with Olex2, using the space group $P2_12_12_1$, with Z = 4 for the formula unit, $C_{28}H_{30}F_6N_4O_4S$. The final anisotropic full-matrix least-squares refinement on F^2 with 405 variables converged at R1 = 4.58%, for the observed data and wR2 = 11.44% for all data. The goodness-of-fit was 1.103. The largest peak in the final difference electron density synthesis was 0.530 $e^-/Å^3$ and the largest hole was -0.343 $e^-/Å^3$ with an RMS deviation of 0.064 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.471 g/cm^3 and F(000), 1312 e^-.

Refinement Note: Donor hydrogen atoms (O1, N24, N28) were located and refined with restraints (DFIX). The vinyl carbons (C22, C23) were refined with restraints (SIMU). Chirality at C14, S; C18, S; C21, R.

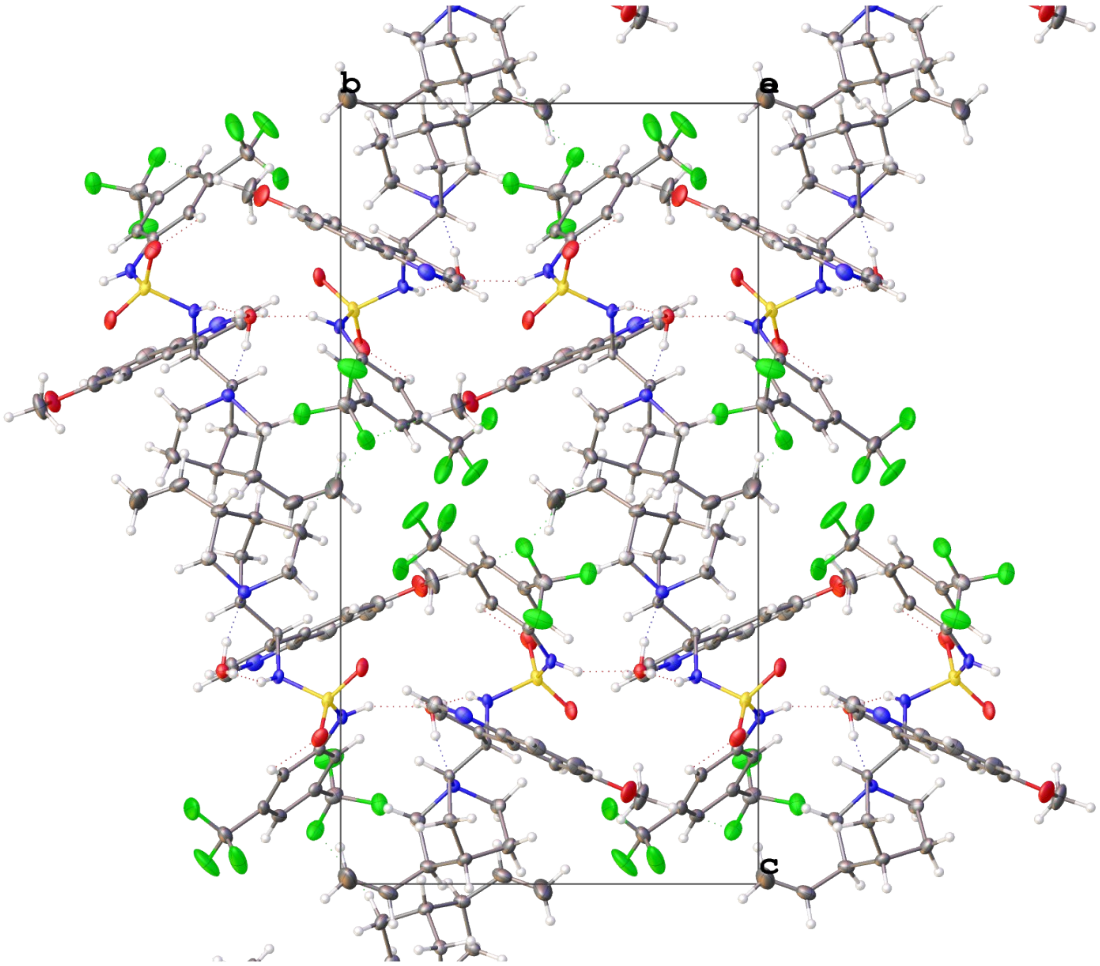


Figure: Packing diagram of **20** viewed normal to the a-axis. Dotted lines indicate hydrogen bonds.

Table 1. Data collection details for 20

Axis	dx/mm	2θ/°	ω/°	φ/°	χ/°	Width/°	Frames	Time/s	Wavelength/Å	Voltage/kV	Current/mA	Temperature/K
Phi	41.320	8.00	0.00	0.00	54.76	1.00	180	5.00	0.71073	50	20.0	100
Omega	41.320	34.33	216.97	0.00	54.76	0.80	212	10.00	0.71073	50	20.0	100
Phi	41.320	34.33	27.26	260.49	54.76	0.80	199	10.00	0.71073	50	20.0	100
Omega	41.320	-23.04	159.61	80.00	54.76	0.80	212	10.00	0.71073	50	20.0	100
Phi	41.320	34.33	216.32	172.49	54.76	0.80	199	10.00	0.71073	50	20.0	100

Crystal Data for $C_{28}H_{30}F_6N_4O_4S$ (M =632.62 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 10.0847(3) Å, b = 12.3157(4) Å, c = 23.0056(7) Å, V = 2857.30(15) Å^3, Z = 4, T = 100(2) K, μ(MoKα) = 0.195 mm^{-1}, Dcalc = 1.471 g/cm^3, 39589 reflections measured (5.22° ≤ 2Θ ≤ 56.86°), 7137 unique (R_{int} = 0.0503, R_{sigma} = 0.0343) which were used in all calculations. The final R_1 was 0.0458 (I > 2σ(I)) and wR_2 was 0.1144 (all data).

Table 2. Crystal data and structure refinement for 20.		
Identification code	tcd698	
Empirical formula	$C_{28}H_{30}F_6N_4O_4S$	
Formula weight	632.62	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 10.0847(3) Å	α = 90°
	b = 12.3157(4) Å	β = 90°
	c = 23.0056(7) Å	γ = 90°
Volume	2857.30(15) $Å^3$	
Z	4	
Density (calculated)	1.471 Mg/m^3	
Absorption coefficient	0.195 mm^{-1}	
F(000)	1312	
Crystal size	0.38 x 0.29 x 0.11 mm^3	
Theta range for data collection	2.610 to 28.430°.	
Index ranges	-13≤h≤13, -16≤k≤16, -30≤l≤30	
Reflections collected	39589	
Independent reflections	7137 [R(int) = 0.0503]	
Completeness to theta = 25.242°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7457 and 0.6554	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7137 / 12 / 405	
Goodness-of-fit on F^2	1.103	
Final R indices [I>2σ(I)]	R1 = 0.0458, wR2 = 0.1113	
R indices (all data)	R1 = 0.0517, wR2 = 0.1144	
Absolute structure parameter	0.02(3)	
Largest diff. peak and hole	0.530 and -0.343 $e.Å^{-3}$	

Table 3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 20.

U(eq) is defined as one third of the trace of the orthogonalised U_{ij} tensor.

	x	y	z	U(eq)
F(1)	2263(3)	1790(3)	275(1)	65(1)
N(1)	-69(3)	2947(2)	2839(1)	23(1)
O(1)	7295(2)	2165(2)	2730(1)	17(1)
C(2)	338(3)	3896(3)	3091(1)	21(1)
F(2)	4163(3)	2542(2)	305(1)	58(1)
C(3)	-640(3)	4673(3)	3241(2)	27(1)
F(3)	3572(4)	1438(2)	963(1)	66(1)
C(4)	-292(4)	5635(3)	3489(2)	30(1)
F(4)	-1171(2)	4392(2)	689(1)	34(1)
F(5)	-480(2)	5925(2)	1022(1)	34(1)
C(5)	1044(4)	5884(3)	3590(2)	25(1)
O(6)	1290(3)	6892(2)	3818(1)	37(1)

F(6)	-1255(2)	4721(3)	1604(1)	46(1)
C(7)	2646(4)	7191(3)	3884(2)	42(1)
C(8)	2024(3)	5150(3)	3456(1)	21(1)
C(9)	1690(3)	4130(2)	3208(1)	16(1)
C(10)	2653(3)	3327(2)	3059(1)	15(1)
C(11)	2233(3)	2394(3)	2797(1)	20(1)
C(12)	869(3)	2242(3)	2699(2)	24(1)
C(13)	4121(3)	3489(2)	3197(1)	13(1)
C(14)	4596(3)	2597(2)	3614(1)	14(1)
N(15)	6036(2)	2696(2)	3742(1)	16(1)
C(16)	6342(3)	3770(3)	4000(1)	21(1)
C(17)	5403(4)	4025(3)	4514(2)	26(1)
C(18)	4707(3)	2964(3)	4688(1)	21(1)
C(19)	3786(3)	2617(3)	4191(1)	18(1)
C(20)	6371(3)	1842(3)	4170(1)	21(1)
C(21)	5790(3)	2097(3)	4778(1)	23(1)
C(22)	5281(4)	1134(3)	5111(2)	32(1)
N(24)	4905(2)	3511(2)	2657(1)	14(1)
S(25)	5151(1)	4687(1)	2360(1)	17(1)
O(26)	6015(2)	4497(2)	1878(1)	26(1)
O(27)	5492(2)	5512(2)	2775(1)	23(1)
N(28)	3678(2)	5034(2)	2145(1)	16(1)
C(29)	2924(3)	4493(2)	1726(1)	15(1)
C(30)	3397(3)	3621(3)	1400(1)	20(1)
C(31)	2583(3)	3158(2)	979(1)	22(1)
C(32)	3144(4)	2237(3)	629(2)	31(1)
C(33)	1304(3)	3528(3)	876(1)	22(1)
C(34)	857(3)	4392(2)	1209(1)	19(1)
C(35)	-507(3)	4841(3)	1133(2)	26(1)
C(36)	1641(3)	4867(2)	1633(1)	16(1)
C(23)	5037(7)	162(4)	4926(2)	65(2)

Table 4. Bond lengths [Å] and angles [°] for 20.

F(1)-C(32)	1.324(5)	N(15)-C(16)	1.481(4)
N(1)-C(2)	1.368(5)	N(15)-C(20)	1.479(4)
N(1)-C(12)	1.323(4)	C(16)-H(16A)	0.9900
O(1)-H(1A)	0.867(14)	C(16)-H(16B)	0.9900
O(1)-H(1B)	0.874(14)	C(16)-C(17)	1.548(5)
C(2)-C(3)	1.417(4)	C(17)-H(17A)	0.9900
C(2)-C(9)	1.419(4)	C(17)-H(17B)	0.9900
F(2)-C(32)	1.323(4)	C(17)-C(18)	1.536(5)
C(3)-H(3)	0.9500	C(18)-H(18)	1.0000
C(3)-C(4)	1.361(6)	C(18)-C(19)	1.533(4)
F(3)-C(32)	1.322(5)	C(18)-C(21)	1.541(5)
C(4)-H(4)	0.9500	C(19)-H(19A)	0.9900
C(4)-C(5)	1.401(5)	C(19)-H(19B)	0.9900
F(4)-C(35)	1.340(4)	C(20)-H(20A)	0.9900
F(5)-C(35)	1.359(4)	C(20)-H(20B)	0.9900

C(5)-O(6)	1.370(4)	C(20)-C(21)	1.547(4)
C(5)-C(8)	1.376(4)	C(21)-H(21)	1.0000
O(6)-C(7)	1.424(5)	C(21)-C(22)	1.503(5)
F(6)-C(35)	1.330(4)	C(22)-H(22)	0.9500
C(7)-H(7A)	0.9800	C(22)-C(23)	1.294(7)
C(7)-H(7B)	0.9800	N(24)-H(24)	0.878(13)
C(7)-H(7C)	0.9800	N(24)-S(25)	1.622(2)
C(8)-H(8)	0.9500	S(25)-O(26)	1.428(2)
C(8)-C(9)	1.420(4)	S(25)-O(27)	1.436(2)
C(9)-C(10)	1.428(4)	S(25)-N(28)	1.623(3)
C(10)-C(11)	1.365(4)	N(28)-H(28)	0.887(13)
C(10)-C(13)	1.527(4)	N(28)-C(29)	1.396(4)
C(11)-H(11)	0.9500	C(29)-C(30)	1.394(4)
C(11)-C(12)	1.407(4)	C(29)-C(36)	1.390(4)
C(12)-H(12)	0.9500	C(30)-H(30)	0.9500
C(13)-H(13)	1.0000	C(30)-C(31)	1.392(5)
C(13)-C(14)	1.536(4)	C(31)-C(32)	1.501(5)
C(13)-N(24)	1.472(3)	C(31)-C(33)	1.388(5)
C(14)-H(14)	1.0000	C(33)-H(33)	0.9500
C(14)-N(15)	1.486(4)	C(33)-C(34)	1.387(5)
C(14)-C(19)	1.559(4)	C(34)-C(35)	1.493(5)
C(34)-C(36)	1.385(4)	N(1)-C(12)-C(11)	125.0(3)
C(36)-H(36)	0.9500	N(1)-C(12)-H(12)	117.5
C(23)-H(23A)	0.9500	C(11)-C(12)-H(12)	117.5
C(23)-H(23B)	0.9500	C(10)-C(13)-H(13)	108.2
		C(10)-C(13)-C(14)	109.8(2)
C(12)-N(1)-C(2)	116.7(3)	C(14)-C(13)-H(13)	108.2
H(1A)-O(1)-H(1B)	103(5)	N(24)-C(13)-C(10)	110.3(2)
N(1)-C(2)-C(3)	118.1(3)	N(24)-C(13)-H(13)	108.2
N(1)-C(2)-C(9)	122.8(3)	N(24)-C(13)-C(14)	111.9(2)
C(3)-C(2)-C(9)	119.1(3)	C(13)-C(14)-H(14)	108.0
C(2)-C(3)-H(3)	119.7	C(13)-C(14)-C(19)	110.9(2)
C(4)-C(3)-C(2)	120.7(3)	N(15)-C(14)-C(13)	111.7(2)
C(4)-C(3)-H(3)	119.7	N(15)-C(14)-H(14)	108.0
C(3)-C(4)-H(4)	119.7	N(15)-C(14)-C(19)	110.0(2)
C(3)-C(4)-C(5)	120.6(3)	C(19)-C(14)-H(14)	108.0
C(5)-C(4)-H(4)	119.7	C(16)-N(15)-C(14)	110.9(2)
O(6)-C(5)-C(4)	115.9(3)	C(20)-N(15)-C(14)	107.2(2)
O(6)-C(5)-C(8)	123.5(3)	C(20)-N(15)-C(16)	108.7(2)
C(8)-C(5)-C(4)	120.6(3)	N(15)-C(16)-H(16A)	109.4
C(5)-O(6)-C(7)	116.7(3)	N(15)-C(16)-H(16B)	109.4
O(6)-C(7)-H(7A)	109.5	N(15)-C(16)-C(17)	111.1(2)
O(6)-C(7)-H(7B)	109.5	H(16A)-C(16)-H(16B)	108.0
O(6)-C(7)-H(7C)	109.5	C(17)-C(16)-H(16A)	109.4
H(7A)-C(7)-H(7B)	109.5	C(17)-C(16)-H(16B)	109.4
H(7A)-C(7)-H(7C)	109.5	C(16)-C(17)-H(17A)	110.2
H(7B)-C(7)-H(7C)	109.5	C(16)-C(17)-H(17B)	110.2
C(5)-C(8)-H(8)	119.9	H(17A)-C(17)-H(17B)	108.5
C(5)-C(8)-C(9)	120.1(3)	C(18)-C(17)-C(16)	107.8(3)

C(9)-C(8)-H(8)	119.9	C(18)-C(17)-H(17A)	110.2
C(2)-C(9)-C(8)	118.9(3)	C(18)-C(17)-H(17B)	110.2
C(2)-C(9)-C(10)	117.9(3)	C(17)-C(18)-H(18)	110.3
C(8)-C(9)-C(10)	123.2(3)	C(17)-C(18)-C(21)	107.5(3)
C(9)-C(10)-C(13)	121.2(3)	C(19)-C(18)-C(17)	108.7(3)
C(11)-C(10)-C(9)	118.6(3)	C(19)-C(18)-H(18)	110.3
C(11)-C(10)-C(13)	120.2(3)	C(19)-C(18)-C(21)	109.7(3)
C(10)-C(11)-H(11)	120.5	C(21)-C(18)-H(18)	110.3
C(10)-C(11)-C(12)	119.1(3)	C(14)-C(19)-H(19A)	109.9
C(12)-C(11)-H(11)	120.5	C(14)-C(19)-H(19B)	109.9
C(18)-C(19)-C(14)	108.7(2)	C(36)-C(29)-N(28)	117.1(3)
C(18)-C(19)-H(19A)	109.9	C(36)-C(29)-C(30)	119.4(3)
C(18)-C(19)-H(19B)	109.9	C(29)-C(30)-H(30)	120.4
H(19A)-C(19)-H(19B)	108.3	C(31)-C(30)-C(29)	119.2(3)
N(15)-C(20)-H(20A)	109.3	C(31)-C(30)-H(30)	120.4
N(15)-C(20)-H(20B)	109.3	C(30)-C(31)-C(32)	117.5(3)
N(15)-C(20)-C(21)	111.7(3)	C(33)-C(31)-C(30)	122.1(3)
H(20A)-C(20)-H(20B)	107.9	C(33)-C(31)-C(32)	120.4(3)
C(21)-C(20)-H(20A)	109.3	F(1)-C(32)-C(31)	113.0(3)
C(21)-C(20)-H(20B)	109.3	F(2)-C(32)-F(1)	107.1(3)
C(18)-C(21)-C(20)	106.7(2)	F(2)-C(32)-C(31)	112.3(3)
C(18)-C(21)-H(21)	107.5	F(3)-C(32)-F(1)	105.6(3)
C(20)-C(21)-H(21)	107.5	F(3)-C(32)-F(2)	106.5(4)
C(22)-C(21)-C(18)	111.9(3)	F(3)-C(32)-C(31)	111.9(3)
C(22)-C(21)-C(20)	115.5(3)	C(31)-C(33)-H(33)	121.3
C(22)-C(21)-H(21)	107.5	C(34)-C(33)-C(31)	117.4(3)
C(21)-C(22)-H(22)	115.5	C(34)-C(33)-H(33)	121.3
C(23)-C(22)-C(21)	128.9(4)	C(33)-C(34)-C(35)	121.3(3)
C(23)-C(22)-H(22)	115.5	C(36)-C(34)-C(33)	121.8(3)
C(13)-N(24)-H(24)	124(3)	C(36)-C(34)-C(35)	116.9(3)
C(13)-N(24)-S(25)	117.05(18)	F(4)-C(35)-F(5)	105.9(3)
S(25)-N(24)-H(24)	109(3)	F(4)-C(35)-C(34)	113.4(3)
N(24)-S(25)-N(28)	102.89(12)	F(5)-C(35)-C(34)	111.6(3)
O(26)-S(25)-N(24)	105.95(13)	F(6)-C(35)-F(4)	107.0(3)
O(26)-S(25)-O(27)	119.05(14)	F(6)-C(35)-F(5)	105.8(3)
O(26)-S(25)-N(28)	111.42(14)	F(6)-C(35)-C(34)	112.7(3)
O(27)-S(25)-N(24)	112.78(13)	C(29)-C(36)-H(36)	120.0
O(27)-S(25)-N(28)	103.65(13)	C(34)-C(36)-C(29)	120.0(3)
S(25)-N(28)-H(28)	115(3)	C(34)-C(36)-H(36)	120.0
C(29)-N(28)-H(28)	119(3)	C(22)-C(23)-H(23A)	120.0
C(29)-N(28)-S(25)	125.7(2)	C(22)-C(23)-H(23B)	120.0
C(30)-C(29)-N(28)	123.5(3)	H(23A)-C(23)-H(23B)	120.0

Table 5. Anisotropic displacement parameters ($Å^2$x 10^3) for 20.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
F(1)	62(2)	64(2)	70(2)	-50(2)	2(2)	-10(2)

N(1)	10(1)	31(1)	28(1)	5(1)	1(1)	-1(1)
O(1)	14(1)	15(1)	21(1)	-1(1)	0(1)	0(1)
C(2)	13(1)	29(2)	20(1)	7(1)	3(1)	2(1)
F(2)	69(2)	34(1)	73(2)	-21(1)	46(2)	-13(1)
C(3)	14(1)	39(2)	28(2)	10(2)	4(1)	8(1)
F(3)	124(3)	26(1)	49(2)	-3(1)	16(2)	29(2)
C(4)	24(2)	35(2)	31(2)	5(1)	9(1)	18(2)
F(4)	32(1)	31(1)	39(1)	7(1)	-18(1)	-11(1)
F(5)	26(1)	27(1)	48(1)	-3(1)	-11(1)	2(1)
C(5)	26(2)	23(2)	27(2)	0(1)	3(1)	11(1)
O(6)	39(2)	25(1)	46(2)	-11(1)	4(1)	16(1)
F(6)	14(1)	85(2)	40(1)	16(1)	2(1)	-2(1)
C(7)	41(2)	22(2)	64(3)	-18(2)	-1(2)	7(2)
C(8)	22(1)	19(2)	22(1)	1(1)	4(1)	6(1)
C(9)	15(1)	17(1)	17(1)	4(1)	4(1)	2(1)
C(10)	13(1)	15(1)	17(1)	2(1)	3(1)	0(1)
C(11)	14(1)	17(1)	27(2)	-2(1)	2(1)	0(1)
C(12)	17(1)	25(2)	29(2)	-2(1)	-2(1)	-4(1)
C(13)	8(1)	10(1)	20(1)	-1(1)	3(1)	1(1)
C(14)	13(1)	12(1)	16(1)	0(1)	2(1)	-2(1)
N(15)	12(1)	18(1)	17(1)	0(1)	-1(1)	-1(1)
C(16)	18(1)	24(2)	22(2)	-2(1)	-1(1)	-7(1)
C(17)	31(2)	20(2)	26(2)	-7(1)	5(1)	-6(1)
C(18)	22(2)	23(2)	17(1)	-4(1)	4(1)	-2(1)
C(19)	12(1)	19(1)	21(1)	2(1)	4(1)	-1(1)
C(20)	18(1)	24(2)	20(1)	4(1)	-2(1)	4(1)
C(21)	23(2)	29(2)	16(1)	1(1)	0(1)	1(1)
C(22)	38(2)	38(2)	21(2)	9(1)	2(2)	6(2)
N(24)	11(1)	12(1)	20(1)	2(1)	3(1)	3(1)
S(25)	11(1)	14(1)	25(1)	4(1)	1(1)	-2(1)
O(26)	17(1)	27(1)	34(1)	10(1)	10(1)	2(1)
O(27)	18(1)	15(1)	35(1)	3(1)	-6(1)	-6(1)
N(28)	15(1)	11(1)	22(1)	-2(1)	-2(1)	0(1)
C(29)	14(1)	14(1)	17(1)	2(1)	2(1)	-2(1)
C(30)	24(2)	14(1)	22(1)	1(1)	4(1)	-1(1)
C(31)	31(2)	14(1)	21(2)	-1(1)	6(1)	-4(1)
C(32)	41(2)	22(2)	29(2)	-8(1)	6(2)	-4(2)
C(33)	28(2)	23(2)	16(1)	0(1)	1(1)	-11(1)
C(34)	18(1)	19(2)	20(1)	3(1)	1(1)	-7(1)
C(35)	18(1)	33(2)	28(2)	5(1)	-5(1)	-7(1)
C(36)	17(1)	14(1)	19(1)	2(1)	1(1)	-2(1)
C(23)	116(5)	34(2)	46(2)	10(2)	32(3)	-5(3)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for 20.

	x	y	z	U(eq)
H(1A)	8090(30)	2430(50)	2700(30)	72(19)
H(1B)	7120(40)	2270(30)	3099(6)	40(13)

	x	y	z	U(eq)
H(3)	-1549	4521	3168	32
H(4)	-960	6142	3594	36
H(7A)	3101	7122	3510	63
H(7B)	3068	6712	4170	63
H(7C)	2701	7944	4019	63
H(28)	3390(40)	5667(18)	2277(17)	24(10)
H(8)	2926	5325	3529	25
H(11)	2854	1854	2682	23
H(12)	600	1583	2519	28
H(13)	4225	4206	3396	15
H(14)	4445	1879	3423	17
H(16A)	6248	4339	3699	25
H(16B)	7271	3776	4138	25
H(17A)	5915	4315	4847	31
H(17B)	4739	4575	4397	31
H(18)	4189	3070	5054	25
H(19A)	3039	3135	4157	21
H(19B)	3418	1887	4272	21
H(20A)	7347	1777	4200	25
H(20B)	6018	1137	4033	25
H(21)	6513	2435	5014	27
H(22)	5115	1256	5512	39
H(24)	5600(30)	3100(30)	2590(17)	41(13)
H(30)	4266	3347	1464	24
H(33)	757	3202	588	27
H(36)	1302	5448	1860	20
H(23A)	5180	-17	4530	78
H(23B)	4714	-374	5188	78

Table 7. Torsion angles [°] for 20.

N(1)-C(2)-C(3)-C(4)	-179.5(3)	C(13)-N(24)-S(25)-O(27)	43.5(2)
N(1)-C(2)-C(9)-C(8)	178.2(3)	C(13)-N(24)-S(25)-N(28)	-67.6(2)
N(1)-C(2)-C(9)-C(10)	-0.6(4)	C(14)-C(13)-N(24)-S(25)	-146.1(2)
C(2)-N(1)-C(12)-C(11)	0.8(5)	C(14)-N(15)-C(16)-C(17)	50.2(3)
C(2)-C(3)-C(4)-C(5)	1.2(5)	C(14)-N(15)-C(20)-C(21)	-71.4(3)
C(2)-C(9)-C(10)-C(11)	1.9(4)	N(15)-C(14)-C(19)-C(18)	11.4(3)
C(2)-C(9)-C(10)-C(13)	-177.0(3)	N(15)-C(16)-C(17)-C(18)	14.5(4)
C(3)-C(2)-C(9)-C(8)	-2.0(4)	N(15)-C(20)-C(21)-C(18)	17.3(4)
C(3)-C(2)-C(9)-C(10)	179.2(3)	N(15)-C(20)-C(21)-C(22)	142.3(3)
C(3)-C(4)-C(5)-O(6)	177.3(3)	C(16)-N(15)-C(20)-C(21)	48.5(3)
C(3)-C(4)-C(5)-C(8)	-1.8(5)	C(16)-C(17)-C(18)-C(19)	-67.0(3)
C(4)-C(5)-O(6)-C(7)	-175.6(4)	C(16)-C(17)-C(18)-C(21)	51.7(3)
C(4)-C(5)-C(8)-C(9)	0.4(5)	C(17)-C(18)-C(19)-C(14)	52.2(3)
C(5)-C(8)-C(9)-C(2)	1.4(5)	C(17)-C(18)-C(21)-C(20)	-69.4(3)
C(5)-C(8)-C(9)-C(10)	-179.8(3)	C(17)-C(18)-C(21)-C(22)	163.4(3)
O(6)-C(5)-C(8)-C(9)	-178.5(3)	C(18)-C(21)-C(22)-C(23)	108.4(6)
C(8)-C(5)-O(6)-C(7)	3.5(5)	C(19)-C(14)-N(15)-C(16)	-65.3(3)

C(8)-C(9)-C(10)-C(11)	-176.8(3)	C(19)-C(14)-N(15)-C(20)	53.3(3)
C(8)-C(9)-C(10)-C(13)	4.2(4)	C(19)-C(18)-C(21)-C(20)	48.6(3)
C(9)-C(2)-C(3)-C(4)	0.7(5)	C(19)-C(18)-C(21)-C(22)	-78.6(3)
C(9)-C(10)-C(11)-C(12)	-1.9(4)	C(20)-N(15)-C(16)-C(17)	-67.4(3)
C(9)-C(10)-C(13)-C(14)	118.3(3)	C(20)-C(21)-C(22)-C(23)	-13.9(7)
C(9)-C(10)-C(13)-N(24)	-117.9(3)	C(21)-C(18)-C(19)-C(14)	-65.1(3)
C(10)-C(11)-C(12)-N(1)	0.5(5)	N(24)-C(13)-C(14)-N(15)	54.8(3)
C(10)-C(13)-C(14)-N(15)	177.7(2)	N(24)-C(13)-C(14)-C(19)	178.0(2)
C(10)-C(13)-C(14)-C(19)	-59.2(3)	N(24)-S(25)-N(28)-C(29)	-64.0(3)
C(10)-C(13)-N(24)-S(25)	91.4(2)	S(25)-N(28)-C(29)-C(30)	-5.5(4)
C(11)-C(10)-C(13)-C(14)	-60.6(3)	S(25)-N(28)-C(29)-C(36)	175.2(2)
C(11)-C(10)-C(13)-N(24)	63.2(3)	O(26)-S(25)-N(28)-C(29)	49.2(3)
C(12)-N(1)-C(2)-C(3)	179.5(3)	O(27)-S(25)-N(28)-C(29)	178.4(2)
C(12)-N(1)-C(2)-C(9)	-0.8(5)	N(28)-C(29)-C(30)-C(31)	-178.0(3)
C(13)-C(10)-C(11)-C(12)	177.1(3)	N(28)-C(29)-C(36)-C(34)	177.7(3)
C(13)-C(14)-N(15)-C(16)	58.4(3)	C(29)-C(30)-C(31)-C(32)	178.7(3)
C(13)-C(14)-N(15)-C(20)	176.9(2)	C(29)-C(30)-C(31)-C(33)	-0.6(5)
C(13)-C(14)-C(19)-C(18)	-112.7(3)	C(30)-C(29)-C(36)-C(34)	-1.6(4)
C(13)-N(24)-S(25)-O(26)	175.4(2)	C(30)-C(31)-C(32)-F(1)	174.6(3)
C(30)-C(31)-C(32)-F(2)	-64.1(4)	C(33)-C(34)-C(35)-F(4)	-5.3(4)
C(30)-C(31)-C(32)-F(3)	55.6(4)	C(33)-C(34)-C(35)-F(5)	-124.8(3)
C(30)-C(31)-C(33)-C(34)	0.3(5)	C(33)-C(34)-C(35)-F(6)	116.4(4)
C(31)-C(33)-C(34)-C(35)	-179.5(3)	C(33)-C(34)-C(36)-C(29)	1.3(4)
C(31)-C(33)-C(34)-C(36)	-0.6(4)	C(35)-C(34)-C(36)-C(29)	-179.7(3)
C(32)-C(31)-C(33)-C(34)	-179.0(3)	C(36)-C(29)-C(30)-C(31)	1.3(4)
C(33)-C(31)-C(32)-F(1)	-6.0(5)	C(36)-C(34)-C(35)-F(4)	175.6(3)
C(33)-C(31)-C(32)-F(2)	115.3(4)	C(36)-C(34)-C(35)-F(5)	56.2(4)
C(33)-C(31)-C(32)-F(3)	-125.0(4)	C(36)-C(34)-C(35)-F(6)	-62.6(4)

Table 8. Hydrogen bonds for 20 (Å and °).

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1A)...N(1)#1	0.867(14)	1.99(2)	2.838(3)	165(6)
O(1)-H(1B)...N(15)	0.874(14)	1.918(19)	2.732(3)	154(3)
C(7)-H(7C)...F(4)#2	0.98	2.45	3.243(4)	138
N(28)-H(28)...O(1)#3	0.887(13)	1.969(19)	2.817(3)	159(4)
C(17)-H(17A)...F(4)#4	0.99	2.52	3.422(4)	151
N(24)-H(24)...O(1)	0.878(13)	2.087(17)	2.930(3)	161(4)
C(30)-H(30)...O(26)	0.95	2.45	3.057(4)	121

Symmetry transformations used to generate equivalent atoms:

#1 x+1,y,z

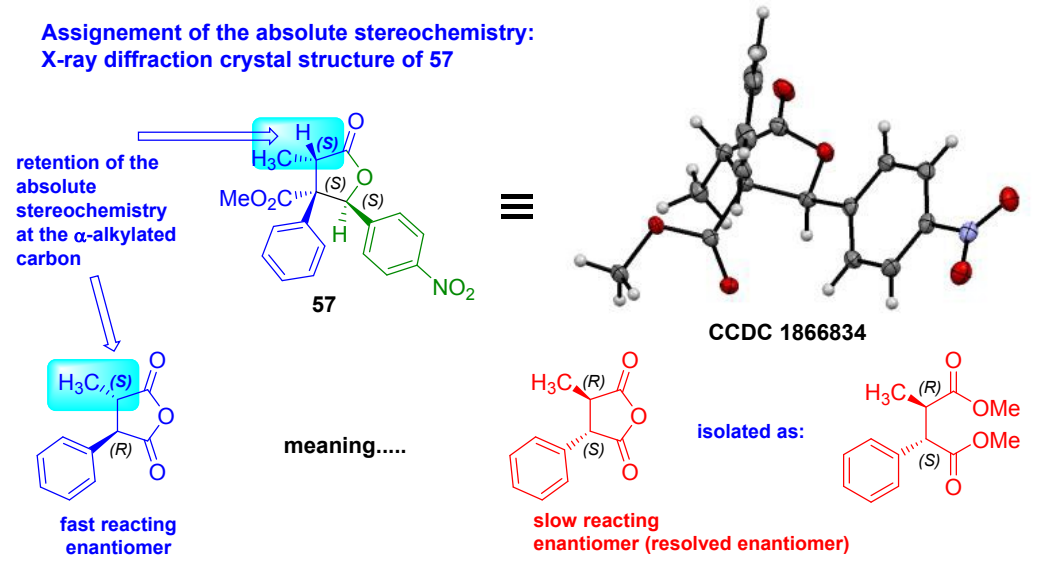
#2 -x,y+1/2,-z+1/2

#3 -x+1,y+1/2,-z+1/2

#4 -x+1/2,-y+1,z+1/2

13. Assignment of *bis*-ester absolute stereochemistry

In conjunction with ^{1}H NMR spectroscopic NOE experiments to assign relative stereochemistry we assigned absolute stereochemistry of the ring opened hemiesters by analogy with the stereochemistry from the lactone product (*vide supra*).



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