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# Dynamic Kinetic Resolution of *Bis*-Aryl Succinic Anhydrides: Enantioselective Synthesis of densely functionalized *γ*-Butyrolactones

Romain Claveau, Brendan Twamley and Stephen J. Connon*

**Abstract:** *A new bifunctional organocatalyst promoted an efficient cycloaddition reaction for the construction of highly functionalized butyrolactones (paraconic acid derivatives) containing three contiguous stereocenters (including one quaternary) in a one pot reaction with excellent selectivity via a unique process involving the Dynamic Kinetic Resolution of a disubstituted anhydride.*

# Dynamic Kinetic Resolution of *Bis*-Aryl Succinic Anhydrides: Enantioselective Synthesis of densely functionalized $\gamma$-Butyrolactones

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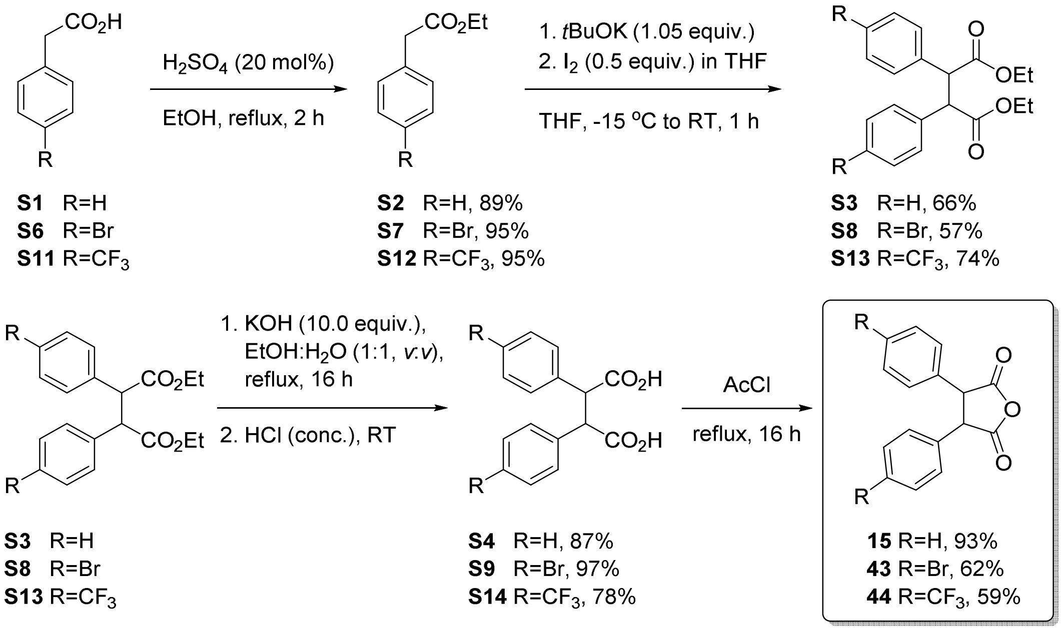
# 1. General

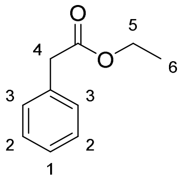
Proton Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker DPX 400 MHz and Bruker Avance II 600MHz spectrometers, using as solvent $CDCl_3$, DMSO-$d_6$ or $D_2O$ and referenced relative to residual $CHCl_3$ ($\delta = 7.26$ ppm) DMSO ($\delta = 2.50$ ppm) or $H_2O$ ($\delta = 4.79$ ppm). 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** **Synthetic route towards anhydrides 15 and 43-44.**

### Ethyl 2-phenylacetate (S2)



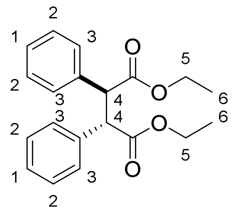
A 250 mL round-bottomed flask containing a stirring bar was charged with phenylacetic acid (**S1**) (10.00 g, 73.45 mmol). EtOH (100 mL) followed by conc. $H_2SO_4$ (0.8 mL) were added, the flask was fitted with a condenser and the resulting mixture was stirred under reflux for 2 h. The solution was 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]

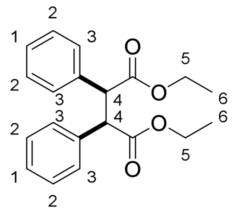
$\delta_H$ (400 MHz, $CDCl_3$): 7.36-7.25 (5 H, m, H-1, H-2 and H-3), 4.16 (2 H, q, *J* 7.1, H-5), 3.63 (2 H, s, H-4), 1.27 (3 H, t, *J* 7.1, H-6).

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

### Diethyl-2,3-diphenylsuccinate (*trans*-S3 and *cis*-S3)



*trans*-**S3**



*cis*-**S3**

A 250 mL oven dried round-bottomed flask containing a stirring bar was charged with potassium *tert*-butoxide (*tert*-BuOK, 5.47 g, 48.77 mmol). The flask was flushed with argon, then fitted with a septum and placed under an argon atmosphere. Dry THF (80 mL) was added *via* syringe and the resulting solution was cooled to -15 °C. To the resulting suspension, a solution of ethyl 2-phenylacetate (**S2**, 7.627 g, 46.45 mmol) in dry THF (20 mL) was slowly added and the resulting mixture stirred for 30 min. Immediately after the addition, a cooled solution of iodine (5.89 g, 23.22 mmol) in dry THF (50 mL) was slowly added *via* syringe over a 10 min period (exothermic reaction). After the addition, the flask was allowed to warm up to room temperature and the reaction was stirred for an additional 1 h. The mixture was treated with a saturated solution of sodium thiosulfate until the characteristic iodine colour has completely disappeared. THF was concentrated under reduced pressure and the remaining aqueous solution 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 vacuo* to allow the formation of a crude slightly yellow liquid. The crude product was purified by flash chromatography (eluting in gradient from 2% EtOAc in hexanes to 5% EtOAc in hexanes) to afford **S3** (4.99 g, 15.29 mmol, 66%, combined yield for both diastereoisomers). TLC (hexanes:EtOAc, 90:10 *v*/*v*): $R_f = 0.4$ (*cis*-**S3**) and $R_f = 0.34$ (*trans*-**S3**).

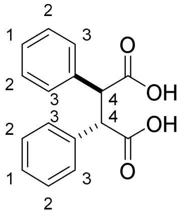
*trans*-**S3**:

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.14-7.01 (10 H, m, H-1, H-2 and H-3), 4.22 (2 H, s, H-4), 4.16 (4 H, q, *J* 7.1, H-5), 1.20 (6 H, t, *J* 7.1, H-6). |

*cis*-**S3**:

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.51-7.27 (10 H, m, H-1, H-2 and H-3), 4.36 (2 H, s, H-4), 3.85 (4 H, q, *J* 7.1, H-5), 0.92 (6 H, t, *J* 7.1, H-6). |
| HRMS (*m/z* - ESI): | Found: 327.1592 $(M+H)^+$ $C_{20}H_{23}O_4$ Requires: 327.1591. |

### 2,3-Diphenylsuccinic acid (*trans*-S4)



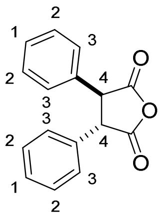
In a 500 mL round-bottomed flask containing a stirring bar, **S3** (4.00 g, 12.26 mmol) was dissolved in a solution of KOH (6.88 g, 122.55 mmol) in EtOH:$H_2O$ (200 mL, 50:50 *v*/*v*). The flask was fitted with a condenser and the solution was stirred under reflux for 16 h. The solution was allowed to cool down to room temperature. 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 layer was cooled down to 0 °C. Acidification with conc. HCl (added dropwise to the aqueous layer until pH 1) resulted in the precipitation of *trans*-**S4**. The solid was filtered and washed with a little warm water, then transferred to a 250 mL round-bottomed flask followed by an addition of $Et_2O$ (30 mL) to remove residual water. The solvent was removed *in vacuo* to afford *trans*-**S4** (2.9 g, 10.73 mmol, 87%). M.p. 210-212 °C (Lit.,[2] 212- 214 °C).

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

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.16-7.10 (10 H, m, H-1, H-2 and H-3), 4.27 (2 H, s, H-4). |

| | |
|---|---|
| $\nu_{max}$ (neat)/cm$^{-1}$: | 3031 (O-H), 1692 (C=O), 1536, 1420, 1290, 1251, 1178, 945, 731, 695. |
| HRMS (*m/z* - ESI): | Found: 269.0814 (M-H)$^-$ $C_{16}H_{13}O_4$ Requires: 269.0814. |

**2,3-Diphenyl-succinic anhydride (*trans*-15)**

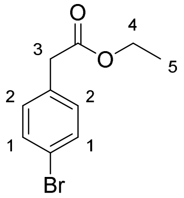


A 50 mL oven dried two-neck round-bottomed flask containing a stirring bar was charged with *trans*-**S4** (0.81 g, 6.80 mmol). The flask was then fitted with a condenser and a septum and flushed with argon. Freshly distilled acetyl chloride (10 mL) was added to the flask *via* syringe, the flask was flushed for an additional 2 min and then kept under an argon atmosphere. The reaction mixture was heated under reflux for 16 h, and then concentrated *in vacuo* to give an oil that solidified upon standing at room temperature. The crude product was purified by flash chromatography on a short plug of silica gel (eluting with 50 % EtOAc in hexanes) to afford *trans*-**15** (0.70 g, 2.78 mmol, 93%) as a pale yellow solid. M.p. 114-116 °C (Lit.,[3] 115-117 °C); TLC (hexanes:EtOAc, 80:20 *v*/*v*): $R_f = 0.46$.

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

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.3-7.07 (10 H, m, H-1, H-2 and H-3), 4.26 (2 H, s, H-4). |
| $\nu_{max}$ (neat)/cm$^{-1}$: | 2906, 1862, 1772 (C=O), 1498, 1455, 1241, 1218, 1050, 937, 912, 777, 763, 741, 695, 641, 624, 610. |
| HRMS (*m/z* - ESI): | Found: 251.0707 (M-H)$^-$ $C_{16}H_{11}O_3$ Requires: 251.0708. |

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

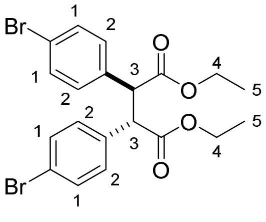


A 250 mL round-bottomed flask containing a stirring bar was charged with 4-Bromophenylacetic acid (**S6**, 12.5 g, 58.13 mmol). EtOH (50 mL) followed by conc. $H_2SO_4$ (0.11 mL) were added, the flask was fitted with a condenser and the resulting mixture was stirred under refluxed overnight. The solution 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*): $R_f = 0.44$.

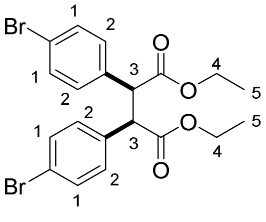
Spectral data for this compound were consistent with those in the literature.[4]

| | |
|---|---|
| $\delta_H$ (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. |

### 2,3-bis(4-bromophenyl)succinic acid (S8)



*trans*-**S8**



*cis*-**S8**

A 250 mL oven dried round-bottomed flask containing a stirring bar was charged with potassium *tert*-butoxide (*t*-BuOK, 2.91 g, 25.92 mmol). The flask was flushed with argon, then fitted with a septum and placed under an argon atmosphere. Dry THF (70 mL) was added *via* syringe and the resulting solution was cooled to 0 °C. To the resulting suspension, a solution of ethyl 2-(4-bromophenyl)acetate (**S7**, 6.0 g, 24.68 mmol) in dry THF (30 mL) was slowly added and the resulting mixture stirred for 30 min. After 30 min, iodine (3.13 g, 12.34 mmol) was added portion wise directly as a solid. The flask was allowed to warm up to room temperature and the reaction mixture was stirred overnight. The mixture was treated with a saturated solution of sodium thiosulfate until the characteristic iodine colour has completely disappeared. THF was concentrated under reduced pressure and the remaining aqueous solution 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 vacuo* to allow the formation of a crude solid that was purified by recrystallization from boiling ethanol. The recrystallized product was filtered from the mother liquor to afford **S8** (3.4 g, 57%, combined yield for both diastereomers) in a 19:81 (*cis*:*trans*) ratio. M.p. 114-116 °C; TLC (hexanes:EtOAc, 90:10 *v*/*v*): $R_f = 0.54$ (*cis*-**S8**) and $R_f = 0.32$ (*trans*-**S8**).

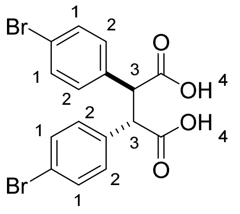
*trans*-**S8**:

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.29 (4 H, d, *J* 8.4, H-1), 6.90 (4 H, d, *J* 8.4, H-2), 4.23-4.05 (4 H, m, H-4), 4.14 (2 H, s, H-3), 1.20 (6 H, t, *J* 7.1, H-5). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 172.3 (C=O), 134.55 (q), 131.7, 129.9, 121.6 (q), 61.4, 54.1, 13.96. |

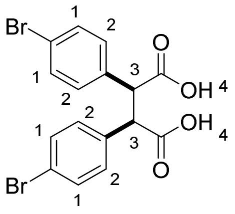
*cis*-**S8**:

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.47 (4 H, d, *J* 8.5, H-1), 7.35 (4 H, d, *J* 8.5, H-2), 4.26 (2 H, s, H-3), 3.94-3.81 (4 H, m, H-4), 0.97 (6 H, t, *J* 7.2, H-5). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 170.8 (C=O), 135.1 (q), 131.8, 130.1, 122.1 (q), 61.1, 54.4, 13.77. |
| $\nu_{max}$ (neat)/$cm^{-1}$: | 2988, 1709, 1488, 1170, 1069, 1025, 1011, 835, 757. |
| HRMS (*m/z* - ESI): | Found: 482.9797 $(M+H)^+$ $C_{20}H_{21}Br_2O_4$ Requires: 482.9801. |

## 2,3-bis(4-bromophenyl)succinic acid (S9)



*trans*-**S9**



*cis*-**S9**

In a 250 mL round-bottomed flask containing a stirring bar, **S8** (3.4 g, 7.02 mmol, 19:81 (*cis*:*trans*) ratio) was dissolved in a solution of KOH (6.8 g, 121.20 mmol) in EtOH:$H_2O$ (150 mL, 75:75 *v*/*v*). The flask was fitted with a condenser and the solution was stirred under reflux for 16 h. The solution was allowed to cool down to room temperature. 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 layer was cooled down to 0 °C. Acidification with conc. HCl (added dropwise to the aqueous layer until pH 1) resulted in the precipitation of **S9**. The solid was filtered and washed with a little warm water, then transferred to a 250 mL round-bottomed flask followed by an addition of $Et_2O$ (30 mL) to remove residual water. The solvent was removed *in vacuo* to afford **S9** (2.9 g, 97%, combined yield for both diastereomers) in a 13:87 (*cis*:*trans*) ratio. M.p. 264-266 °C.

*trans*-**S9**:

$\delta_H$ (400 MHz, DMSO-$d_6$): 12.62 (2 H, bs, H-4), 7.36 (4 H, d, *J* 8.2, H-1), 7.13 (4 H, d, *J* 8.2, H-2), 4.20 (2 H, s, H-3).

$\delta_C$ (100 MHz, DMSO-$d_6$): 173.9 (C=O), 136.3 (q), 131.7, 131.1, 120.8 (q), 53.2.

*cis*-**S9**:

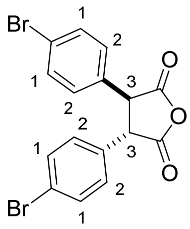
$\delta_H$ (400 MHz, DMSO-$d_6$): 12.62 (2 H, bs, H-4), 7.57 (4 H, d, *J* 8.2, H-1), 7.41 (4 H, d, *J* 8.2, H-2), 4.20 (2 H, s, H-3).

$\delta_C$ (100 MHz, DMSO-$d_6$): 172.4 (C=O), 137.0 (q), 131.9, 130.97, 121.4 (q), 54.1.

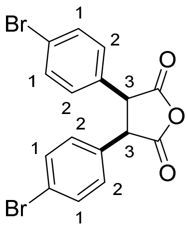
$\nu_{max}$ (neat)/cm$^{-1}$: 2898, 2571, 1701, 1488, 1404, 1281, 1074, 1011, 921, 806.

HRMS (*m/z* - ESI): Found: 424.9026 $(M-H)^-$ $C_{16}H_{11}Br_2O_4$ Requires: 424.9029.

## 3,4-bis(4-bromophenyl)succinic anhydride (43)



*trans*-**43**



*cis*-**43**

A 50 mL oven dried two-neck round-bottomed flask containing a stirring bar was charged with **S9** (1.0 g, 2.34 mmol, 13:87 (*cis*:*trans*) ratio). The flask was then fitted with a condenser and a septum and flushed with argon. Freshly distilled acetyl chloride (10 mL) was added to the flask *via* syringe, the flask was flushed for an additional 2 min and then kept under an argon atmosphere. The reaction mixture was heated under reflux for 16 h, and then concentrated *in vacuo* to give a crude solid. The crude product was purified by flash chromatography on a short plug of silica gel (eluting with 50 % EtOAc in hexanes) to afford **43** (592.0 mg, 62%, combined yield for both diastereomers) in a 36:64 (*cis*:*trans*) ratio. M.p. 180-182 °C; TLC (hexanes:EtOAc, 50:50 *v/v*): $R_f = 0.88$.

*trans*-**43**:

$\delta_H$ (400 MHz, $CDCl_3$): 7.54 (4 H, d, *J* 8.2, H-1), 7.08 (4 H, d, *J* 8.2, H-2), 4.31 (2 H, s, H-3).

$\delta_C$ (100 MHz, $CDCl_3$): 169.1 (C=O), 132.7, 131.9 (q), 129.4, 123.25 (q), 54.55.

*cis*-**43**:

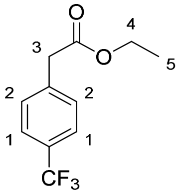
$\delta_H$ (400 MHz, $CDCl_3$): 7.32 (4 H, d, *J* 8.2, H-1), 7.76 (4 H, d, *J* 8.2, H-2), 4.68 (2 H, s, H-3).

$\delta_C$ (100 MHz, $CDCl_3$): 169.7 (C=O), 132.1, 130.3, 130.0 (q), 122.80 (q), 52.2.

$\nu_{max}$ (neat)/cm$^{-1}$: 1834, 1769, 1593, 1488, 1407, 1256, 1217, 1047, 1010, 935, 815, 761, 667.

HRMS (*m/z* - ESI): Found: 406.8917 $(M-H)^-$ $C_{16}H_9Br_2O_3$ Requires: 406.8923.

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

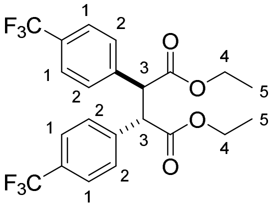


A 250 mL round-bottomed flask containing a stirring bar was charged with 4-Trifluoromethylphenylacetic acid (**S11**) (5.0 g, 24.49 mmol). EtOH (50 mL) followed by conc. $H_2SO_4$ (0.5 mL) were added, the flask was fitted with a condenser and the resulting mixture was stirred under refluxed overnight. 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*): $R_f = 0.51$.

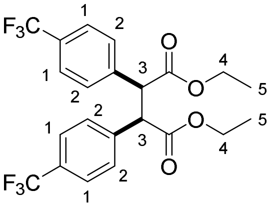
Spectral data for this compound were consistent with those in the literature.[5]

| | |
|---|---|
| $\delta_H$ (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. |

### Diethyl 2,3-bis(4-(trifluoromethyl)phenyl)succinate (S13)



*trans*-**S13**



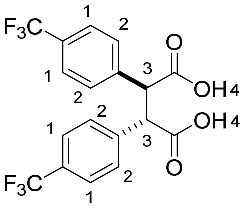
*cis*-**S13**

A 250 mL oven dried round-bottomed flask containing a stirring bar was charged with ethyl 2-(4-(trifluoromethyl)phenyl)acetate (**S12**, 3.82 g, 16.46 mmol). The flask was flushed with argon, then fitted with a septum and placed under an argon atmosphere.

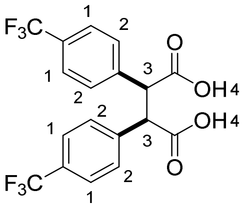
Dry THF (60 mL) was added *via* syringe and the resulting solution was cooled to 0 °C. Potassium *tert*-butoxide (*tert*-BuOK, 1.94 g, 17.28 mmol) was added portion wise directly as a solid. The solution turned red and was allowed to stir for 5 min. After 5 min, iodine (2.08 g, 8.23 mmol) was added portion wise directly as a solid, the solution was allowed to warm up to room temperature and the reaction mixture was stirred overnight. The mixture was treated with a saturated solution of sodium thiosulfate until the characteristic iodine colour has completely disappeared. THF was concentrated under reduced pressure and the remaining aqueous solution 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 vacuo* to allow the formation of a crude solid that was purified by recrystallisation from boiling ethanol. The recrystallised product was filtered from the mother liquor to afford **S13** (2.82 g, 74%, combined yield for both diastereomers) in a 1:99 (*cis*:*trans*) ratio. M.p. 134-136 °C; TLC (hexanes:EtOAc, 90:10 *v*/*v*): $R_f = 0.5$ (*trans*-**S13**).

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.64-7.60 (8 H, m, H-1 and H-2), 4.42 (2 H, s, H-3), 3.95-3.80 (4 H, m, H-4), 0.92 (6 H, t, *J* 7.1, H-5). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 170.4 (C=O), 139.9 (q) (q, $^5J_{C\text{-}F}$ 1.3 Hz), 130.4 (q) (q, $^2J_{C\text{-}F}$ 32.8 Hz), 128.9, 125.6 (q, $^3J_{C\text{-}F}$ 3.8 Hz), 123.9 (q) (q, $^1J_{C\text{-}F}$ 272.2 Hz), 61.3, 54.8, 13.6. |
| $\delta_F$ (376.5 MHz, $CDCl_3$): | -62.76. |
| $\nu_{max}$ (neat)/cm$^{-1}$: | 2988, 1159, 1615, 1327, 1216, 1159, 1104, 1071, 1019, 832. |
| HRMS (*m/z* - ESI): | Found: 461.1184 $(M-H)^-$ $C_{22}H_{19}F_6O_4$ Requires: 461.1193. |

## 2,3-bis(4-(trifluoromethyl)phenyl)succinic acid (S14)



*trans*-**S14**



*cis*-**S14**

In a 250 mL round-bottomed flask containing a stirring bar, **S13** (1.5 g, 3.24 mmol, 1:99 (*cis*:*trans*) ratio) was dissolved in a solution of KOH (3.0 g, 53.47 mmol) in EtOH:$H_2O$ (100 mL, 50:50 *v*/*v*). The flask was fitted with a condenser and the solution was stirred under reflux for 16 h. The solution was allowed to cool down to room temperature. 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 layer was cooled down to 0 °C. Acidification with conc. HCl (added dropwise to the aqueous layer until pH 1) resulted in the precipitation of **S14**. The solid was filtered and washed with a little warm water, then transferred to a 250 mL round-bottomed flask followed by an addition of $Et_2O$ (30 mL) to remove residual water. The solvent was removed *in vacuo* to afford **S14** (1.03 g, 78%, combined yield for both diastereomers) in a 13:87 (*cis*:*trans*) ratio. The mixture was further purified by recrystallisation from boiling water to afford analytically pure *trans*-**S14**. M.p. 194-200 °C.

$\delta_H$ (400 MHz, DMSO-$d_6$): 12.79 (2 H, bs, H-4), 7.52 (4 H, d, *J* 8.2, H-1), 7.44 (4 H, d, *J* 8.2, H-2), 4.44 (2 H, s, H-3).

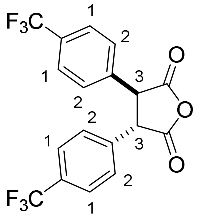
$\delta_C$ (100 MHz, DMSO-$d_6$): 173.6 (C=O), 141.5 (q), 129.80, 128.2 (q) (q, $^2J_{C\text{-F}}$ 31.9 Hz), 125.6 (q, $^3J_{C\text{-F}}$ 3.7 Hz), 124.5 (q) (q, $^1J_{C\text{-F}}$ 271.8 Hz), 53.5.

$\delta_F$ (376.5 MHz, DMSO-$d_6$):-61.1

$\nu_{max}$ (neat)/cm$^{-1}$: 2984, 1773, 1705, 1619, 1417, 1320, 1162, 1119, 1068, 1019, 925, 828.

HRMS (*m/z* - ESI): Found: 405.0567 $(M\text{-}H)^-$ $C_{18}H_{11}F_6O_4$ Requires: 405.0567.

### 2,3-bis(4-(trifluoromethyl)phenyl)succinic anhydride (44)



*trans*-**44**

A 50 mL oven dried two-neck round-bottomed flask containing a stirring bar was charged with *trans*-**S14** (220.0 mg, 0.541 mmol). The flask was then fitted with a condenser and a septum and flushed with argon. Freshly distilled acetyl chloride (10 mL) was added to the flask *via* syringe, the flask was flushed for an additional 2 min and then kept under an argon atmosphere. The reaction mixture was heated under reflux for 16 h, and then concentrated *in vacuo* to provide analytically pure *trans*-**44** (124.0 mg, 59%). The product was used without further purification. M.p. 140-142 °C.

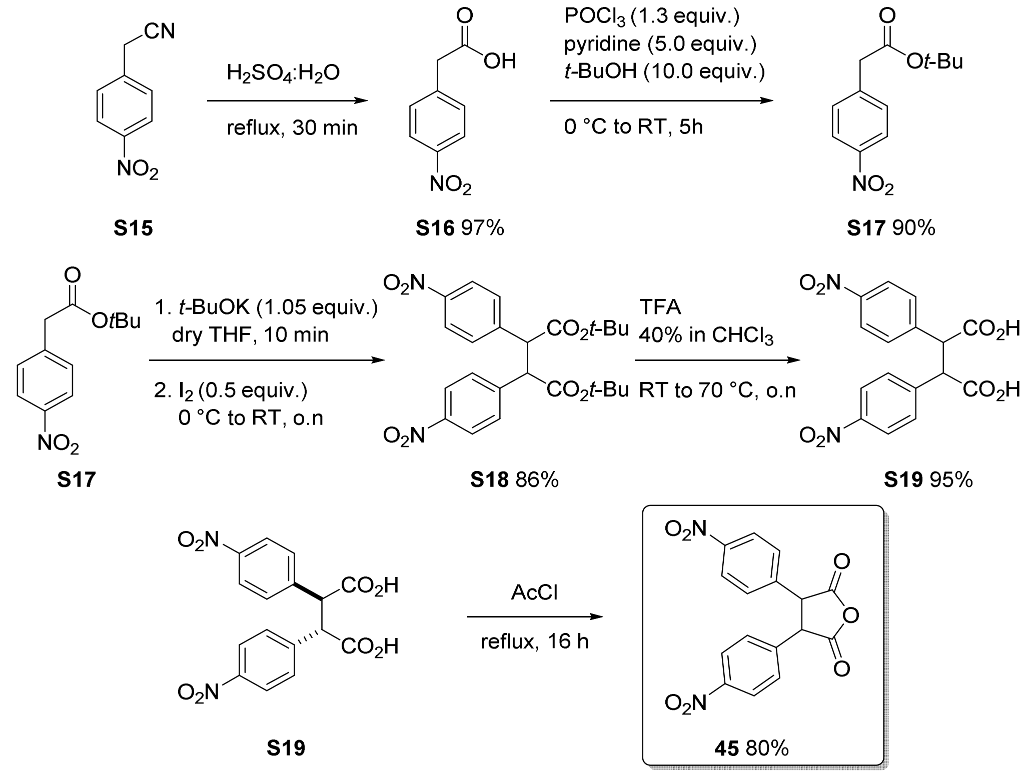
$\delta_H$ (400 MHz, $CDCl_3$): 7.69 (4 H, d, *J* 8.0, H-1), 7.36 (4 H, d, *J* 8.0, H-2), 4.49 (2 H, s, H-3).

$\delta_C$ (100 MHz, $CDCl_3$): 168.7 (C=O), 136.6 (q), 131.5 (q) (q, $^2J_{C\text{-}F}$ 33.0 Hz), 128.3, 126.6 (q, $^3J_{C\text{-}F}$ 3.7 Hz), 123.5 (q) (q, $^1J_{C\text{-}F}$ 272.5 Hz), 54.6.

$\delta_F$ (376.5 MHz, $CDCl_3$): -62.96.

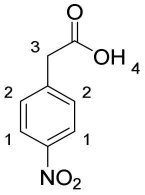
$\nu_{max}$ (neat)/cm$^{-1}$: 1846, 1774, 1622, 1422, 1322, 1259, 1224, 1165, 1109, 1044, 1020, 938, 832, 756, 659, 593.

HRMS (*m/z* - ESI): Found: 387.0467 $(M\text{-}H)^-$ $C_{18}H_9F_6O_3$ Requires: 387.0461.



**Scheme 2 Synthetic route towards anhydride 45.**

### 2-(4-nitrophenyl)acetic acid (S16)



In a 250 mL round-bottomed flask containing a stirring bar, concentrated sulfuric acid (20 mL) was added to deionised water (20 mL) followed by 4-nitrophenylacetonitrile (**S15**, 6.6 g, 40.70 mmol) added portion wise directly as a solid. The flask was fitted with a condenser and the resulting suspension was refluxed for 1 h, diluted with 20 mL of deionised water, cooled to 0 °C when colourless crystalline solid separated. The solid was filtered off, washed with ice-cold water to remove traces of acid and dried to yield **S16** as a light-yellow solid (7.18 g, 97%). M.p. 140-142 °C (lit.,[6] M.p. 153-155 °C).

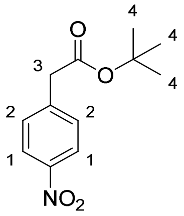
Spectral data for this compound were consistent with those in the literature.[6]

$\delta_H$ (400 MHz, DMSO-$d_6$): 10.06 (1 H, bs, H-4), 8.18 (2 H, d, *J* 8.7, H-1), 7.55 (2 H, d, *J* 8.7, H-2), 3.77 (2 H, s, H-3).

$\delta_C$ (100 MHz, DMSO-$d_6$): 172.2 (C=O), 146.8 (q), 143.5 (q), 131.2, 123.6, 40.6.

HRMS (*m/z* - ESI): Found: 180.0297 $(M-H)^-$ $C_8H_6NO_4$ Requires: 180.0302.

### ***tert*-butyl 2-(4-nitrophenyl)acetate (S17)**



To a solution of **S16** (5 g, 27.6 mmol) in 50 mL of $CHCl_3$, dry pyridine (11 mL, 138.0 mmol) and *t*-BuOH (25.9 mL, 276.0 mmol) were added followed by $POCl_3$ (3.3 mL, 35.88 mmol) dropwise over 2 mins. After 5 h, the reaction mixture was poured into a solution of ice containing 20 mL of $CH_2Cl_2$ and 10 mL of a HCl solution (2.0 N). The aqueous solution was extracted with $CH_2Cl_2$ (4 x 50 mL). The combined organic extracts were washed with brine, deionised water, dried over $MgSO_4$ and the solvent was removed *in vacuo* and the residue was purified by flash column chromatography, eluting in gradient from 100% hexanes to 10% EtOAc in hexanes to yield **S17** as a yellow liquid (5.9 g, 90%). TLC (hexanes:EtOAc, 9:1 *v/v*): $R_f = 0.38$.

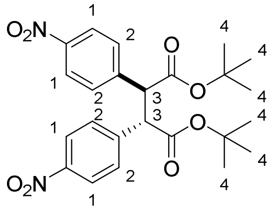
Spectral data for this compound were consistent with those in the literature.[7]

$\delta_H$ (400 MHz, $CDCl_3$): 8.18 (2 H, d, *J* 8.7, H-1), 7.44 (2 H, d, *J* 8.7, H-2), 3.63 (2 H, s, H-3), 1.44 (9 H, s, H-4).

$\delta_C$ (100 MHz, $CDCl_3$): 169.3 (C=O), 146.9 (q), 142.2 (q), 130.2, 123.4, 81.4 (q), 42.1, 27.8.

HRMS (*m/z* - ESI): Found: 236.0923 $(M-H)^-$ $C_{12}H_{14}NO_4$ Requires: 236.0928.

### Di-*tert*-butyl-2,3-bis(4-nitrophenyl)succinate (*trans*-S18)

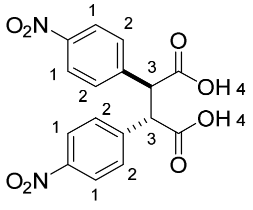


*trans*-**S18**

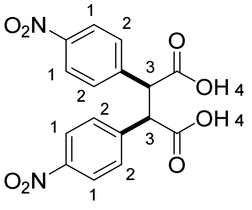
A 250 mL oven dried round-bottomed flask containing a stirring bar was charged with *tert*-butyl 2-(4-nitrophenyl)acetate (**S17**, 3.0 g, 12.6 mmol). The flask was flushed with argon, then fitted with a septum and placed under an argon atmosphere. Dry THF (50 mL) was added *via* syringe and the resulting solution was cooled to 0 °C. Potassium *tert*-butoxide (*tert*-BuOK, 1.48 g, 13.3 mmol) was added portion wise directly as a solid. The solution turned red and was allowed to stir for 5 min. After 5 min, iodine (1.59 g, 6.3 mmol) was added portion wise directly as a solid, the solution was allowed to warm up to room temperature and the reaction mixture was stirred overnight. The mixture was treated with a saturated solution of sodium thiosulfate until the characteristic iodine colour has completely disappeared. THF was concentrated under reduced pressure and the remaining aqueous solution 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 vacuo* to allow the formation of a crude solid that was triturated with cold $Et_2O$. The solid was filtered from $Et_2O$ to afford *trans*-**S18** (2.58 g, 86%) as a single diastereomer and analytically pure product. M.p. 156-158 °C; TLC (hexanes:EtOAc, 90:10 *v/v*): $R_f$ = 0.27 (*trans*-**S18**).

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 8.03 (4 H, d, *J* 8.8, H-1), 7.21 (4 H, d, *J* 8.8, H-2), 4.22 (2 H, s, H-3), 1.40 (18 H, s, H-4). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 170.4 (C=O), 147.3 (q), 143.0 (q), 128.98, 123.9, 82.5 (q), 55.4, 27.7. |
| $\nu_{max}$ (neat)/$cm^{-1}$: | 2980, 1721, 1517, 1346, 1147, 1109, 847, 785, 748, 696. |
| HRMS (*m/z* - ESI): | Found: 471.1470 $(M-H)^-$ $C_{24}H_{27}N_2O_8$ Requires: 471.1767. |

**2,3-bis(4-nitrophenyl)succinic acid (S19)**



*trans*-**S19**



*cis*-**S19**

A 250 mL round-bottomed flask containing a magnetic stirring bar was charged with **S18** (1.39 g, 2.94 mmol). HPLC grade $CHCl_3$ (40 mL), followed by trifluoracetic acid (TFA, 26 mL) were then added *via* syringe. The flask was fitted with a condenser and the reaction mixture was heated at reflux temperature for 24 h and then cooled to room temperature. The volatiles were removed *in vacuo* to afford **S19** as a white solid (1.0 g, 95%) in a 19:81 (*cis*:*trans*) ratio. M.p. 240-242 °C, decomposition.

*trans*-**S19**:

$\delta_H$ (400 MHz, DMSO-$d_6$):* 8.01 (4 H, d, *J* 8.6, H-1), 7.53 (4 H, d, *J* 8.6, H-2), 4.57 (2 H, s, H-3).

$\delta_C$ (100 MHz, DMSO-$d_6$): 177.9 (C=O), 152.3 (q), 151.8, 149.8 (q), 149.1, 58.0.

*cis*-**S19**:

$\delta_H$ (400 MHz, DMSO-$d_6$):* 8.25 (4 H, d, *J* 8.6, H-1), 7.78 (4 H, d, *J* 8.6, H-2), 4.55 (2 H, s, H-3).

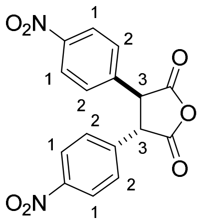
$\delta_C$ (100 MHz, DMSO-$d_6$): 176.4 (C=O), 135.1, 135.0 (q), 128.9 (q), 128.7, 58.96.

* The protic signal (H-4) is not visible in DMSO-$d_6$.

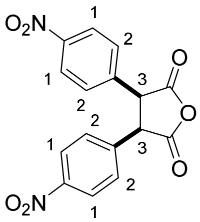
$\nu_{max}$ (neat)/cm$^{-1}$: 2860, 1710, 1604, 1519, 1424, 1348, 1301, 1110, 903, 856, 838, 735, 706, 692.

HRMS (*m/z* - ESI): Found: 359.0519 $(M-H)^-$ $C_{16}H_{11}N_2O_8$ Requires: 359.0515.

### 2,3-bis(4-nitrophenyl)succinic anhydride (45)



*trans*-**45**

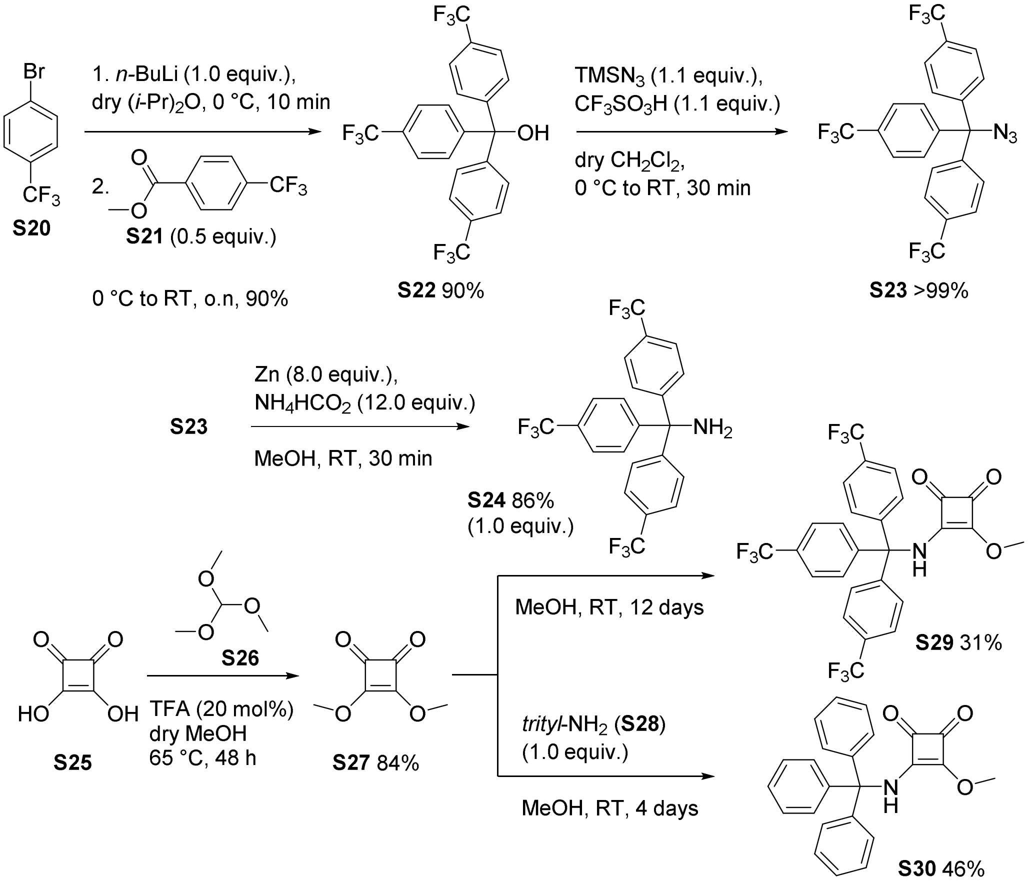


*cis*-**45**

A 25 mL oven dried two-neck round-bottomed flask containing a stirring bar was charged with **S19** (500.0 mg, 1.39 mmol, 19:81 (*cis*:*trans*) ratio). The flask was then fitted with a condenser and a septum and flushed with argon. Freshly distilled acetyl chloride (5 mL) was added to the flask *via* syringe, the flask was flushed for an additional 2 min and then kept under an argon atmosphere. The reaction mixture was heated under reflux for 16 h, and then concentrated *in vacuo*. The crude solid was triturated in dry $Et_2O$, filtered and dried under high vacuum to afford *trans*-**45** (381.1 mg, 80%) as a single diastereomer. M.p. 126-130 °C.

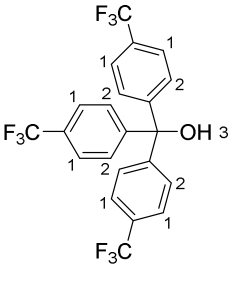
| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 8.27 (4 H, d, *J* 8.3, H-1), 7.45 (4 H, d, *J* 8.3, H-2), 4.61 (2 H, s, H-3). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 167.7 (C=O), 148.4 (q), 139.0 (q), 129.0, 124.8, 54.3. |
| $\nu_{max}$ (neat)/$cm^{-1}$: | 1863, 1782, 1604, 1517, 1345, 1206, 1045, 932, 692, 690, 769, 841. |
| HRMS (*m/z* - ESI): | Found: 341.0413 $(M-H)^-$ $C_{16}H_9N_2O_7$ Requires: 341.0410. |

## 3. Synthesis of catalysts: procedures



**Scheme 3 Synthesis of the catalyst precursors S29 and S30.**

**Tris(4-(trifluoromethyl)phenyl)methanol (S22)**

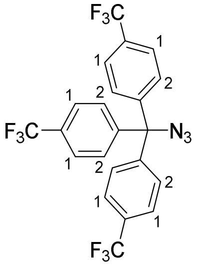


A 100 mL oven dried three-neck round-bottomed flask containing a stirring bar was charged with methyl 4-bromobenzotrifluoride (**S20**, 5.8 g, 25.72 mmol). Anhydrous diisopropyl ether (30 mL) was then added *via* syringe and the solution was cooled to -10 °C. A solution of *n*-butyl lithium (1.6 M in hexanes, 17.6 mL, 28.17 mmol) was added dropwise *via* syringe and the reaction was allowed to stir for 30 min. A solution of methyl 4-(trifluoromethyl)benzoate (**S21**, 2.5 g, 12.25 mmol) in dry diisopropyl ether (5 mL) was added dropwise *via* syringe at -10 °C and the resulting solution was allowed to come back to room temperature and stirred for 16 h. The reaction mixture was then quenched with cold water, acidified with aqueous HCl (2.0 N), and extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a residue that was purified by flash column chromatography (hexanes:EtOAc, 95:5 *v/v*) furnishing **S22** (5.34 g, 94%) as a light yellow solid. M.p. 88-90 °C (lit.,[8] M.p. 92-93 °C); TLC (hexanes:EtOAc, 95:5 *v/v*): $R_f = 0.19$.

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

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.62 (6 H, d, *J* 8.3, H-1), 7.42 (6 H, d, *J* 8.3, H-2), 2.87 (1 H, bs, H-3). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 149.1 (q), 130.3 (q) (q, $^2J_{C\text{-F}}$ 32.6 Hz), 128.1, 125.4 (q, $^3J_{C\text{-F}}$ 3.6 Hz), 123.8 (q) (q, $^1J_{C\text{-F}}$ 272.2 Hz), 81.3 (q). |
| $\delta_F$ (376.5 MHz, $CDCl_3$): | -62.7. |
| $\nu_{max}$ (neat)/cm$^{-1}$: | 3460, 2108, 1617, 1322, 1162, 1114, 1068, 1016, 832. |
| HRMS (*m/z* - ESI): | Found: 463.0745 $(M-H)^-$ $C_{22}H_{12}OF_9$ Requires: 463.0744. |

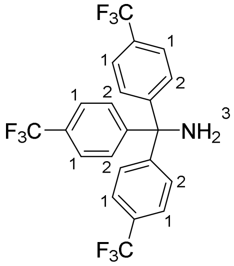
### 4,4',4''-(azidomethanetriyl)tris((trifluoromethyl)benzene) (S23)



A 250 mL oven dried three-neck round-bottomed flask containing a stirring bar was charged with **S22** (5.08 g, 10.94 mmol). Anhydrous $CH_2Cl_2$ (110 mL – 0.1 M) was then added *via* syringe and the solution was cooled to -10 °C. Triflic acid (1.06 mL, 12.03 mmol) was added *via* syringe and the reaction was allowed to stir for 15 min (***Caution: triflic acid is a highly corrosive liquid and should be handled very carefully***). Trimethylsilyl azide (1.6 mL, 12.03 mmol) was added dropwise *via* syringe at -10 °C and the resulting solution was allowed to come back to room temperature and stirred for 30 min. After complete disappearance of the starting material (monitored by TLC), the reaction mixture was poured in a large beaker containing crushed ice (≈ 200 g). The product was extracted with dichloromethane (4 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a residue that was purified by flash column chromatography eluting in gradient from 100% hexanes to 5% EtOAc in hexanes to isolate **S23** (5.20 g, 97%) as a white solid. M.p. 70-72 °C; TLC (hexanes:EtOAc, 95:5 *v/v*): $R_f = 0.89$.

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.66 (6 H, d, *J* 8.3, H-1), 7.43 (6 H, d, *J* 8.3, H-2). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 145.4 (q), 130.6 (q) (q, $^2J_{C\text{-F}}$ 32.8 Hz), 128.6, 125.7 (q, $^3J_{C\text{-F}}$ 3.7 Hz), 123.7 (q) (q, $^1J_{C\text{-F}}$ 272.8 Hz), 75.8 (q). |
| $\delta_F$ (376.5 MHz, $CDCl_3$): | -62.8. |
| $\nu_{max}$ (neat)/$cm^{-1}$: | 2106, 1615, 1412, 1321, 1253, 1164, 1112, 1068, 829, 600. |
| HRMS (*m/z* - APCI): | Found: 462.0898 $(M-N_2)^+$ $C_{22}H_{12}F_9N_3$ Requires: 462.0898. |

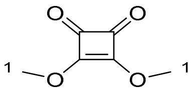
**tris(4-(trifluoromethyl)phenyl)methanamine (S24)**



A 100 mL oven dried round-bottomed flask containing a stirring bar was charged with **S23** (4.24 g, 8.92 mmol), activated zinc powder (2.33 g, 35.68 mmol) and ammonium formate (2.25 g, 35.68 mmol). Dry MeOH (35.7 mL - 0.25 M) was added *via* syringe and the reaction was allowed to stir at room temperature ($N_2$ gaz produced should be observable almost immediately), under argon until completion of the reaction (approx. 1 h, monitored by TLC). After the completion of the reaction, the reaction mixture was filtered through a celite pad, washed with $CH_2Cl_2$ and then the combined filtrates were evaporated under vacuum. The residue was taken into $CH_2Cl_2$, washed twice with a saturated brine solution and finally with deionised water. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a residue that was purified by flash column chromatography eluting in gradient from 100% hexanes to 30% EtOAc in hexanes to isolate **S24** (3.57 g, 86%) as a white solid. M.p. 82-84 °C; TLC (hexanes:EtOAc, 70:30 *v/v*): $R_f = 0.64$.

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.59 (6 H, d, *J* 8.3, H-1), 7.43 (6 H, d, *J* 8.3, H-2), 2.31 (2 H, bs, H-3). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 150.9 (q), 129.6 (q) (q, $^2J_{C\text{-}F}$ 32.6 Hz), 128.2, 125.3 (q, $^3J_{C\text{-}F}$ 3.7 Hz), 123.9 (q) (q, $^1J_{C\text{-}F}$ 272.0 Hz), 66.1 (q). |
| $\delta_F$ (376.5 MHz, $CDCl_3$): | -62.6. |
| $\nu_{max}$ (neat)/cm$^{-1}$: | 1616, 1408, 1322, 1159, 1113, 1068, 1014, 844, 823, 601. |
| HRMS (*m/z* - ESI): | Found: 462.0901 $(M\text{-}H)^-$ $C_{22}H_{13}NF_9$ Requires: 462.0904. |

**3,4-dimethoxycyclobut-3-ene-1,2-dione (S27)**

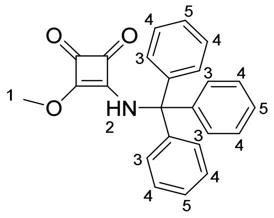


A 100 mL round-bottomed flask containing a magnetic stirring bar under argon atmosphere was charged with squaric acid (**S25**, 4.00 g, 35.07 mmol). Dry MeOH (40 mL), followed by trimethyl orthoformate (**S26**, 11.5 mL, 105.2 mmol) and TFA (536.8 µL, 7.01 mmol - 20 mol%), were then added *via* syringe. The flask was fitted with a condenser and the reaction mixture was heated at reflux temperature for 48 h and then cooled to room temperature. The volatiles were removed *in vacuo* and the residue obtained was purified by flash column chromatography (hexanes:EtOAc, 2:1 *v/v*) to give **S27** as a white solid (4.1 g, 84%). M.p. 52-54 °C (lit.,[9] M.p. 52-54 °C); TLC (hexanes:EtOAc, 2:1 *v/v*): $R_f = 0.21$.

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

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 4.36 (6 H, s, H-1). |

### 3-Methoxy-4-(tritylamino)cyclobut-3-ene-1,2-dione (S30)



A 25 mL sample vial containing a magnetic stirring bar was charged with 3,4-dimethoxycyclobut-3-ene-1,2-dione (**S27**, 1.02 g, 7.2 mmol) and tritylamine (**S28**, 1.87 g, 7.2 mmol). To the mixture of solids, dry MeOH (approx. 5 mL – the yield of the reaction is highly concentration dependant) was added *via* syringe. The resulting suspension was stirred at room temperature for 96 h. The reaction mixture was then cooled to 0 °C with an ice bath and the precipitate was filtered, washed with cold MeOH before being dried under high vacuum to yield **S30** as a white solid (1.21 g, 46%). M.p. 196-198 °C. TLC (hexanes:EtOAc, 2:1 *v*/*v*): $R_f$ = 0.3.

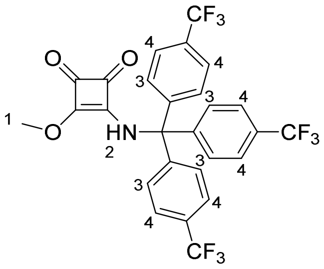
$\delta_H$ (400 MHz, $CDCl_3$): 7.35-7.31 (9 H, m, H-4 and H-5), 7.11-7.08 (6 H, m, H-3), 6.79 (1 H, bs, H-2), 3.79 (3 H, bs, H-1).

$\delta_C$ (100 MHz, $CDCl_3$): 189.2 (q), 184.5 (C=O), 178.1 (C=O), 172.4(q), ,143.7 (q), 128.7, 128.3, 127.9, 73.0 (q), 59.8.

$\nu_{max}$ (neat)/cm$^{-1}$: 3380, 3283, 3023, 2961, 1803, 1701, 1593, 1490, 1442, 1361, 1058, 1002, 899, 831, 752, 698.

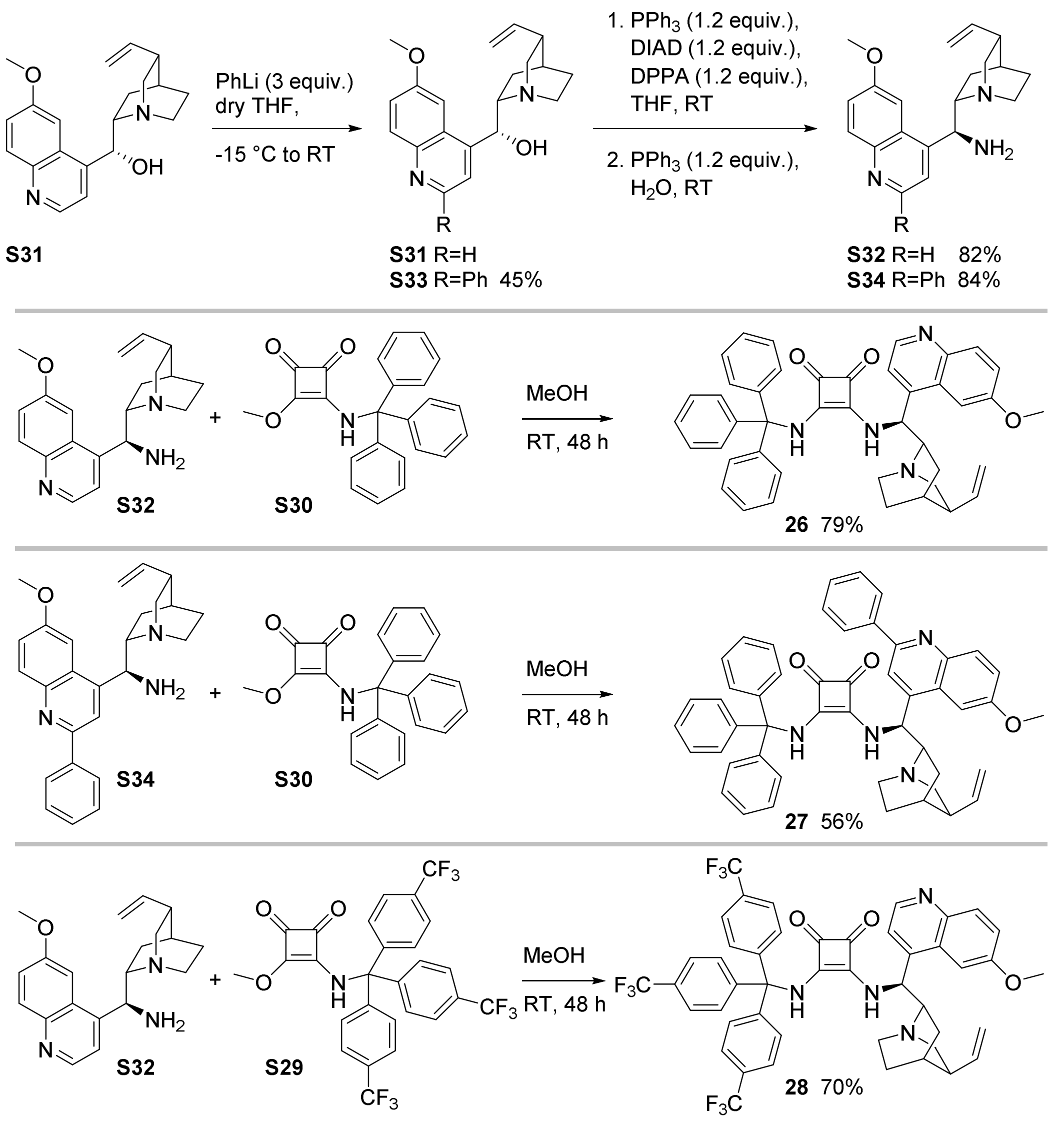
HRMS (*m/z* - ESI): Found: 392.1267 $(M+Na)^+$ $C_{24}H_{19}NO_3Na$ Requires: 392.1263.

## 3-methoxy-4-((tris(4-(trifluoromethyl)phenyl)methyl)amino)cyclobut-3-ene-1,2-dione (S29)



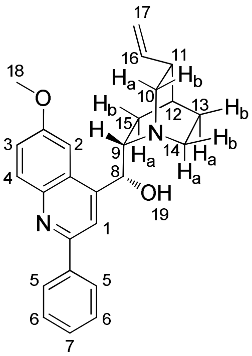
A 25 mL sample vial containing a magnetic stirring bar was charged with 3,4-dimethoxycyclobut-3-ene-1,2-dione (**S27**, 460.06 mg, 3.24 mmol) and the amine **S24** (1.50 g, 3.24 mmol). To the mixture of solids, dry MeOH (approx. 3-4 mL – the yield of the reaction is highly concentration dependant) was added *via* syringe. The resulting suspension was stirred at room temperature for 12 days. After 12 days, the solvent was removed under vacuum and the residue was purified by flash column chromatography eluting in gradient from 20% EtOAc in hexanes to 30% EtOAc in hexanes to isolate **S29** (572.2 mg, 31%) as a white solid. M.p. 94-98 °C; TLC (hexanes:EtOAc, 70:30 *v/v*): $R_f = 0.43$.

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.65 (6 H, d, *J* 8.3, H-4), 7.27 (6 H, d, *J* 8.3, H-3), 6.90 (1 H, bs, H-2), 3.85 (1 H, bs, H-1). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 184.4 (C=O), 178.4 (C=O), 146.2 (q), 130.9 (q) (q, $^2J_{C\text{-}F}$ 32.6 Hz), 129.0, 125.8 (q, $^3J_{C\text{-}F}$ 3.7 Hz), 123.6 (q) (q, $^1J_{C\text{-}F}$ 272.4 Hz), 72.1 (q), 60.1). |
| $\delta_F$ (376.5 MHz, $CDCl_3$): | -62.8. |
| $\nu_{max}$ (neat)/cm$^{-1}$: | 1804, 1708, 1591,1708, 1522, 1449, 1362, 1321, 1164, 1114, 1069, 1016, 834, 823, 612. |
| HRMS (*m/z* - ESI): | Found: 572.0912 $(M\text{-}H)^-$ $C_{27}H_{15}NO_3F_9$ Requires: 572.0908. |



**Scheme 4 Synthetic route towards catalysts 26-28.**

### (***R***)-(6-Methoxy-2-phenylquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanol - C-2 phenyl quinine (S33)



An oven dried 500 mL round-bottomed flask containing a magnetic stirring bar was charged with quinine **S31**, 6.48 g, 20.0 mmol) fitted with a septum and placed under an argon atmosphere. Anhydrous THF (120 mL) was added *via* syringe and the resulting suspension was cooled to -15 °C. A solution of phenyl lithium (1.8 M in THF, 33.3 mL, 59.9 mmol) was added *via* syringe to the vigorously stirred suspension and the reaction mixture was allowed to stir at -15 °C for 30 min then warmed to room temperature and allowed to stir for 3 h. Acetic acid (15 mL) was added dropwise *via* syringe to the reaction at 0 °C, followed by water (50 mL) and EtOAc (50 mL). The reaction was then allowed to warm to room temperature and iodine was added in several portions to the stirred mixture until the appearance of a persistent deep brown colouration. A solution of sodium thiosulfate ($Na_2S_2O_3$, 3.00 g) in water (50 mL), followed by a concentrated solution of aqueous ammonia (35%, 30 mL) were added and the mixture was allowed to stir for 10 min. The organic phase was then washed with brine and the aqueous phase extracted with dichloromethane (4 x 50 mL), the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude oily residue was purified by flash column chromatography (hexanes:EtOAc:MeOH:$Et_3N$, 8:1:0.5:0.5) to obtain **S33** (3.6 g, 45%) as a white solid. M.p. 134-136 °C (lit.,[10] M.p. 151 °C). TLC (hexanes:EtOAc:MeOH:$Et_3N$, 7:1:1.5:0.5): $R_f = 0.35$.

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

$\delta_H$ (400 MHz, $CDCl_3$):* 8.07 (2 H, d, *J* 7.7, H-5), 8.02 (1 H, d, *J* 8.6, H-4), 7.94 (1 H, s, H-1), 7.45 (2 H, app. T, H-6), 7.39 (1 H, app. T, H-7), 7.28 (1 H, app. D, *J* 8.6, H-3), 7.14 (1 H, app. D, H-2), 5.73-5.64 (2 H, m, H-8 and H-16), 4.96-4.89 (2 H, m, H-

17), 3.84 (3 H, s, H-18), 3.66-3.55 (1 H, m, H-14a), 3.16-3.10 (2 H, m, H-9 and H-10b), 2.78-2.67 (2 H, m, H-10a and H-14b), 2.36-2.27 (1 H, m, H-11), 1.86-1.73 (3 H, m, H-12, H-13b and H-15b), 1.58-1.46 (2 H, m, H-13a and H-15a).

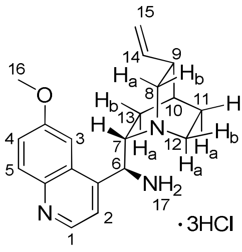
* The protic signal (H-19) is not visible in $CDCl_3$.

HRMS (*m/z* - ESI): Found: 401.2227 $(M+H)^+$ $C_{26}H_{29}N_2O_2$ Requires: 401.2229.

**General procedure I: General procedure for the preparation of 9-*epi*-amine-derivatives (3.HCl salts) of quinine (S32) and C-2 phenyl quinine (S34).**

A 500 mL oven-dried round bottom flask was charged with triphenylphosphine (1.2 equiv.) and the appropriate alkaloid (1 equiv.), placed under an argon atmosphere and fitted with a septum. Dry THF (150 mL) was added *via* syringe and the resulting solution was cooled to 0 °C. Diisopropyl azodicarboxylate (DIAD, 1.2 equiv.) was added dropwise *via* syringe followed by diphenylphosphoryl azide (DPPA, 1.2 equiv.) and the resulting mixture was allowed to warm up to room temperature. After stirring for 16 h, the solution was heated to 50 °C for 2 h. Triphenylphosphine (1.2 equiv.) was then added and heating was maintained for 2 h. After cooling the solution to ambient temperature, water (15 mL) was added and the mixture was stirred for 4 h. The reaction was then concentrated *in vacuo* and the residue dissolved in CH2Cl2 (60 mL) and HCl (2 N, 60 mL). The aqueous phase was separated and washed with CH2Cl2 (3 x 30 mL). The aqueous layer was then concentrated under reduced pressure and the crude product was recrystallised from EtOAc and MeOH or EtOH.

### (*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanamine·3HCl (S32)



Prepared according to general procedure I, using quinine (**S31**, 8.16 g, 9.25 mmol). The crude product was recrystallised from EtOH to obtain **3HCl·S32** (8.9 g, 82%) as a yellow solid. M.p. 216-218 °C, decomposition (lit.,[11] M.p. 220-222 °C).

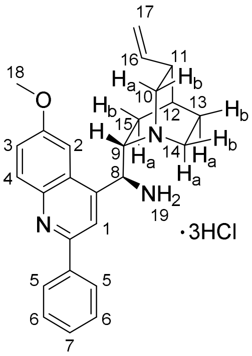
Spectral data for this compound were consistent with those in the literature.[11]

| | |
|---|---|
| $\delta_H$ (400 MHz, $D_2O$):* | 9.08 (1 H, d, *J* 5.8, H-1), 8.30 (1 H, d, *J* 9.4, H-5), 8.26 (1 H, d, *J* 5.8, H-2), 7.92 (1 H, dd, *J* 2.4, 9.4, H-4), 7.86 (1 H, bs, H-3), 5.88 (1 H, m, H-14), 5.8 (1 H, d, *J* 10.6, H-6), 5.28-5.20 (2 H, m, H-15), 4.50-4.41 (1 H, m, H-7), 4.12 (3 H, s, H-16), 4.08-3.97 (1 H, m, H-12a), 3.86 (1 H, dd, *J* 10.6, 13.4, H-8b), 3.65-3.48 (2 H, m, H-8a, H-12b), 2.98-2.89 (1 H, m, H-9), 2.14-2.03 (3 H, m, H-10, H-11a and H-11b), 1.91-1.85 (1 H, m, H-13b), 1.18-1.12 (1 H, m, H-13a). |

* The protic signal (H-17) is not visible in $D_2O$.

| | |
|---|---|
| HRMS (*m/z* - APCI): | Found: 324.2068 $(M+H)^+$ $C_{20}H_{26}N_3O$ Requires: 324.2070. |

### (S)-(6-methoxy-2-phenylquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methanamine 3HCl (S34)

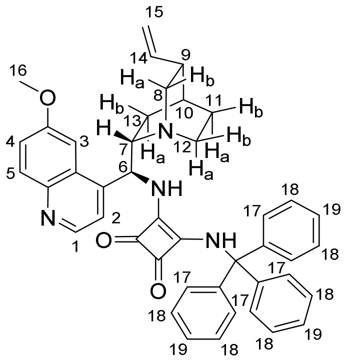


Prepared according to general procedure I, using C-2 phenyl quinine (**S33**, 2.9 g, 7.25 mmol). The crude product was recrystallised from EtOAc and MeOH to obtain **3HCl·S34** (3.1 g, 84%) as a yellow solid. M.p. 195-200 °C, decomposition.

Spectral data for this compound were consistent with those in the literature.[12]

| | |
|---|---|
| $\delta_H$ (600 MHz, DMSO-$d_6$): | 8.85 (1 H, s, H-1), 8.36 (2 H, d, *J* 7.3, H-5), 8.14 (1 H, d, *J* 9.1, H-4), 7.84 (1 H, d, *J* 2.4, H-3), 7.59-7.50 (4 H, m, H-4, H-6 and H-7), 5.90-5.84 (2 H, m, H-8 and H-16), 5.28 (1 H, d, *J* 17.3, H-17), 5.11 (1 H, d, *J* 10.5, H-17), 4.83-4.79 (1 H, m, H-9), 4.20-4.16 (1 H, m, H-14a), 4.01 (3 H, s, H-18), 3.76-3.72 (1 H, m, H-10b), 3.39-3.35 (2 H, m, H-10a and H-14b), 2.79-2.73 (1 H, m, H-11), 1.91-1.82 (3 H, m, H-12, H-13a and H-13b), 1.56-1.52 (1 H, m, H-15b), 0.94-0.90 (1 H, m, H-15a). |
| HRMS (*m/z* - ESI): | Found: 400.2391 $(M+H)^+$ $C_{26}H_{30}N_3O$ Requires: 400.2389. |

### 3-(((*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-4-(tritylamino)cyclobut-3-ene-1,2-dione (26)



A 25 mL oven dried round-bottomed flask containing a stirring bar was charged with **S32** (1.10 g, 3.42 mmol) and **S30** (1.26 g, 3.42 mmol). Dry MeOH (6.8 mL – 0.5 M) was added *via* syringe and the reaction mixture was placed under an argon atmosphere. The solution was allowed to stir at room temperature for 72 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (hexanes:EtOAc:MeOH:TEA, 70:20:5:5 *v/v*) furnishing **26** as a white solid (1.79 g, 79%). M.p. 160-162 °C. TLC ($CH_2Cl_2$:MeOH, 95:5 *v/v*): $R_f = 0.19$; $[\alpha]_D^{20} = +41.8$ ($c$ = 0.10, $CHCl_3$).

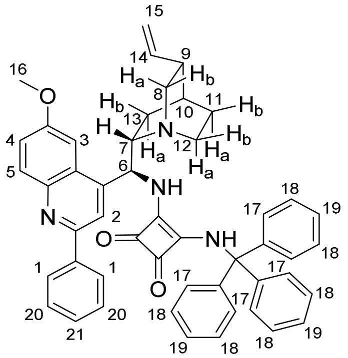
$\delta_H$ (400 MHz, $CDCl_3$): 8.62 (1 H, d, *J* 4.5, H-1), 8.01 (1 H, d, *J* 9.2, H-5), 7.57-7.49 (1 H, bs, H-3), 7.39 (1 H, dd, *J* 2.6, 9.2, H-4), 7.20-7.12 (9 H, m, H-18 and H-19), 7.03-6.98 (6 H, m, H-17), 6.56 (1 H, bs, H-2), 6.49 (1 H, bs, N-H), 5.88-5.75 (2 H, m, H-6 and H-14), 5.06-4.98 (2 H, m, H-15), 3.91 (3 H, s, H-16), 3.74 (1 H, bs, N-H), 3.31-3.17 (2 H, m, H-8b and H-12a), 2.65-2.57 (3 H, m, H-7, H-8a and H-12b), 2.28 (1 H, m, H-9), 1.67-1.61 (1 H, m, H-10), 1.56-1.42 (3 H, m, H-11a, H-11b and H-13b), 0.68-0.63 (1 H, m, H-13a).

$\delta_C$ (100 MHz, $CDCl_3$)*: 183.5 (C=O), 183.0 (C=O), 167.0 (q), 158.5 (q), 146.8, 144.8 (q), 144.1 (q), 142.8 (q), 141.8, 131.4, 128.6, 128.5, 128.2, 122.7, 117.9, 114.4, 101.2, 72.1 (q), 60.1, 56.5, 56.1, 52.5, 40.8, 39.7, 27.7, 27.5, 26.5.

| | |
|---|---|
| $\nu_{max}$ (neat)/cm$^{-1}$: | 2934, 1792, 1668, 1624, 1509, 1576, 1433, 1228, 1031, 844, 699, 631. |
| HRMS (*m/z* - APCI): | Found: 661.3176 $(M+H)^+$ $C_{43}H_{41}N_4O_3$ Requires: 661.3173. |

* The resonance of one carbon could not be identified in the spectrum.

### 3-(((S)-(6-methoxy-2-phenylquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-4-(tritylamino)cyclobut-3-ene-1,2-dione (27)



A 50x10 mm sample vial containing a magnetic stirring bar was charged with **S34** (64.89 mg, 0.162 mmol) and **S30** (60.0 mg, 0.162 mmol). To the resulting mixture, dry MeOH (0.8 mL) was added *via* syringe. The resulting suspension was stirred at room temperature for 96 h. The reaction mixture was then cooled to 0 °C with an ice bath and the precipitate was filtered, washed with cold MeOH before being dried under high vacuum to yield **27** as a white solid (67.0 mg, 56%). M.p. 152-156 °C. TLC ($CH_2Cl_2$:MeOH, 95:5 *v*/*v*): $R_f = 0.49$. $[\alpha]_D^{20} = -250.0$ (*c* = 0.064, $CHCl_3$).

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 8.09 (1 H, d, *J* 9.2, H-5), 8.01 (2 H, d, *J* 7.4, H-1), 7.59-7.53 (3 H, m, H-3 and H-20), 7.51-7.47 (1 H, app t, H-21), 7.40 (1 H, app. dd, *J* 2.6, 9.2, H-4), 7.14-7.05 (9 H, m, H-18 and H-19), 7.01-6.97 (6 H, m, H-17), 6.58 (1 H, bs, H-2), 5.96-5.79 (2 H, m, H-6 and H-14), 5.08-5.01 (2 H, m, H-15), 3.94 (3 H, s, H-16), 3.65 (1 H, bs, N-H), 3.38-3.20 (2 H, m, H-8b and H-12a), 2.73-2.58 (3 H, m, H-7, H-8a and H-12b), 2.30 (1 H, m, H-9), 1.60-1.46 (1 H, m, H-10 and H-13b), 1.15-0.99 (2 H, m, H-11a, H-11b), 0.76-0.68 (1 H, m, H-13a). |

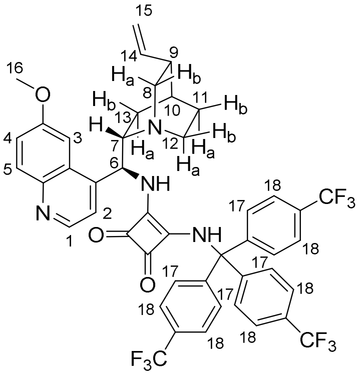
$\delta_C$ (100 MHz, $CDCl_3$)*: 183.5 (C=O), 183.0 (C=O), 166.8 (q), 158.6 (q), 154.2, 145.0 (q), 144.1 (q), 143.3 (q), 141.9 (q), 139.7 (q), 131.9, 129.2, 129.0, 128.6, 128.5, 128.3, 127.2, 123.0, 115.8, 114.4, 101.1, 72.2 (q), 63.1, 60.2, 56.6, 56.2, 52.6, 40.9, 39.8, 31.9, 29.7.

$\nu_{max}$ (neat)/cm$^{-1}$: 1789, 1666, 1624, 1575, 1508, 1441, 1351, 1233, 1033, 833, 767, 693, 633.

HRMS (*m/z* - ESI): Found: 737.3492 $(M+H)^+$ $C_{49}H_{45}N_4O_3$ Requires: 737.3492.

* The resonance of two carbon could not be identified in the spectrum.

**3-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-4-((tris(4-(trifluoromethyl)phenyl)methyl)amino)cyclobut-3-ene-1,2-dione (28)**



A 5 mL oven dried round-bottomed flask containing a stirring bar was charged with **S32** (290.0 mg, 0.896 mmol) and **S29** (514.1 g, 0.896 mmol). Dry MeOH (2 mL) was added *via* syringe and the reaction mixture was placed under an argon atmosphere. The solution was allowed to stir at room temperature for 48 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography ($CH_2Cl_2$:MeOH, 95:5 *v/v*) furnishing **28** as a pale yellow solid (541 mg, 70%). M.p. 212-214 °C, decomposition. TLC (hexanes:EtOAc:MeOH:$Et_3N$, 7:2:0.5:0.5): $R_f$ = 0.25; $[\alpha]_D^{20}$ = -312.8 (*c* = 0.15, $CHCl_3$).

$\delta_H$ (600 MHz, $CDCl_3$): 8.56 (1 H, bs, N-H), 7.92 (1 H, d, *J* 9.0, H-5), 7.58-7.56 (7 H, m, H-1 and H-18), 7.52 (1 H, bs, H-3), 7.33 (1 H, d, *J*

9.0, H-4), 7.30-7.18 (6 H, m, H-2 and H-17), 6.43 (1 H, bs, N-H), 5.67-5.58 (2 H, m, H-6 and H-14), 4.96-4.92 (2 H, m, H-15), 3.92 (3 H, s, H-16), 3.03-2.98 (2 H, m, H-8b and H-12a), 2.45-2.42 (3 H, m, H-7, H-8a and H-12b), 2.27-2.19 (1 H, m, H-9), 1.64-1.58 (1 H, m, H-10), 1.57-1.49 (2 H, m, H-11a and H-13a), 1.29-1.23 (1 H, m, H-11b and H-13b).

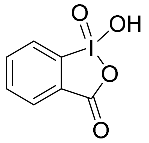
$\delta_C$ (150.9 MHz, $CDCl_3$): 167.7 (C=O), 167.3 (C=O), 158.4 (q), 147.2, 146.9 (q), 144.7 (q), 144.4 (q), 140.9, 131.6, 130.9 (q) (q, $^2J_{C\text{-F}}$ 32.4 Hz), 128.9, 127.9, 127.6, 125.9, 123.5 (q) (q, $^1J_{C\text{-F}}$ 272.5 Hz), 119.5, 117.8, 114.8, 101.5 (q), 71.3 (q), 61.7, 55.9, 55.8, 53.1, 40.7, 39.2, 27.7, 27.1, 26.9, 25.5.

$\delta_F$ (376.5 MHz, $CDCl_3$): -62.6.

$\nu_{max}$ (neat)/cm$^{-1}$: 2940, 1789, 1675, 1570, 1431, 1320, 1166, 1115, 1068, 1015, 919, 829.

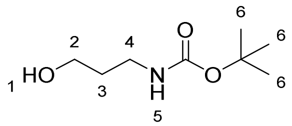
HRMS (*m/z* - ESI): Found: 863.2664 $(M-H)^-$ $C_{46}H_{36}N_4O_3F_9$ Requires: 863.2644.

**Acide 2-iodoxybenzoïque (IBX, S35)**



A 500 mL round-bottomed flask containing a magnetic stirring bar was charged with 2-iodobenzoic acid (15.0 g, 60.48 mmol), oxone (46.0 g, 302.40 mmol) and 250 mL of deionised water. The flask was fitted with a condenser and the resulting suspension was heated at 105 °C for 5h and then cooled to room temperature. The suspension was filtered, the solid washed several times with cold acetone, then allowed to dry on the bench overnight to afford IBX as a white solid (13.62 g, 80%).

### *tert*-butyl (3-hydroxypropyl)carbamate (S36)

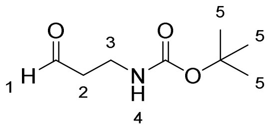


A 500 mL round-bottomed flask containing a magnetic stirring bar was charged with 3-amino-1-propanol (10.1 g, 134.5 mmol) and 70 mL of anhydrous $CH_2Cl_2$. The resulting solution was placed under an argon atmosphere and cooled to 0 °C. A solution of di-*tert*-butyl dicarbonate (32.3 g, 148.0 mmol) in anhydrous $CH_2Cl_2$ (100 mL) was added dropwise over 30 min. The reaction mixture was then allowed to come back to room temperature and stirred overnight. The reaction was quenched with 100 mL of a saturated sodium hydrogen carbonate solution. The organic layer was separated, washed with water and brine, dried over MgSO4, the solvent was then removed *in vacuo* to allow the formation of a crude oil that was purified by flash column chromatography (hexanes:EtOAc, 1:1 *v/v*) to obtain the pure product as a colorless oil (21.6 g, 92%). TLC (hexanes:EtOAc, 1:1 *v/v*): $R_f = 0.31$.

Spectral data for this compound were consistent with those in the literature.[13]

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 5.11 (1 H, bs, H-5), 3.59-3.56 (3H, m, H-1 and H-2), 3.20-3.16 (2 H, m, H-4), 1.61-1.58 (2 H, m, H-3), 1.36 (9 H, s, H-6). |
| HRMS (*m/z* - ESI): | Found: 198.1106 $(M+Na)^+$ $C_8H_{17}NNaO_3$ Requires: 198.1100. |

### *tert*-butyl (3-oxopropyl)carbamate (S37)



A 250 mL round-bottomed flask containing a magnetic stirring bar was charged with *tert*-butyl (3-hydroxypropyl)carbamate (**S36**, 1.5 g, 8.56 mmol), IBX (**S35**, 7.2 g, 25.7 mmol) and EtOAc (100 mL). The resulting suspension was stirred at 80 °C for 5 h, cooled to room temperature and filtered. The solvent was then removed *in vacuo* to afford a crude oil. The crude product was purified by flash column chromatography (hexanes:EtOAc, 2:1 *v/v*) to obtain pure **S37** as a colorless liquid (1.48 g, >99%). TLC (hexanes:EtOAc, 1:1 *v/v*): $R_f = 0.5$.

Spectral data for this compound were consistent with those in the literature.[14]

$\delta_H$ (400 MHz, $CDCl_3$): 9.80 (1 H, s, H-1), 4.88 (1 H, bs, H-4), 3.44-3.39 (2 H, m, H-3), 2.72-2.69 (2 H, t, *J* 5.8, H-2), 1.42 (9 H, s, H-5).

HRMS (*m/z* - ESI): Found: 196.0936 $(M+Na)^+$ $C_8H_{15}NNaO_3$ Requires: 196.0944.

# 4. Synthesis of racemic lactones

### Racemic preparation of lactones 31-42 and 46-52

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 the relevant freshly distilled or recrystallized 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 20 to 96 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 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. Catalyst evaluation (general procedures)

**General procedure II: Catalyst evaluation and reaction optimisation in the cycloaddition reaction between 2,3-diphenyl-succinic anhydride (15) and 4-Nitrobenzaldehyde (16).**

An oven-dried 5 mL reaction vessel containing a magnetic stirring bar under argon atmosphere was charged with 2,3-diphenyl-succinic anhydride (*trans*-**15**, 25.23 mg, 0.1 mmol), 4-Nitrobenzaldehyde (**16**, 15.11 mg, 0.1 mmol) and the relevant catalyst (**18-29**, 0.005 mmol - 5 mol%). Dry MTBE (1.0 mL, 0.1 M) was added *via* syringe and the reaction mixture was brought to the temperature indicated in Table 1 and Table 2. The resulting mixture was allowed to stir for the time indicated in Table 1 and Table 2. The yield and diastereomeric ratio of the products were determined by $^1$H NMR spectroscopic analysis using *p*-iodoanisole (11.7 mg, 50.0 μmol) as an internal standard. 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 15% EtOAc in hexanes to isolate both diastereomers combined.

The enantiomeric excess of the products was determined by CSP-HPLC using the conditions indicated.

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL. min$^{-1}$, RT, UV detection at 254 nm, retention times: **17d** 61.3 min (major enantiomer) and 74.1 min (minor enantiomer).

**General procedure III: Enantioselective preparation of lactones 31-42.**

A 10 mL oven dried two-neck round-bottomed flask containing a stirring bar was charged with 2,3-diphenyl-succinic anhydride (*trans*-**15**, 100.9 mg, 0.4 mmol) and catalyst **26** (13.2 mg, 0.02 mmol - 5 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). A mixture of MTBE:THF (4.0 mL, 0.1 M, 9:1 *v*:*v*) was added *via* syringe followed by the relevant freshly distilled or recrystallized aldehyde (0.4 mmol). The resulting mixture was allowed to stir for 10 days at room temperature. To the reaction mixture containing the corresponding crude carboxylic acids, anhydrous MeOH (809.1 μL, 20.0 mmol), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 240 μL, 0.48 mmol) were added *via* syringe and the reaction was allowed to stir for 15 min at 0 °C. The major diastereomer produced in the reaction was then purified using a flash chromatographic purification system (Biotage SP4) using a high performance prepacked silica cartridge (Biotage SNAP 10 g), eluting the mixture in gradient of EtOAc from 100% hexanes and slightly modifying the following general method.

Flow rate: 10 $\mathrm{mL.min^{-1}}$; Unit: CV = column volume.

Gradient: 100% hexanes for 3 CV; 100% hexanes to 20% EtOAc in hexanes over 40 CV.

The enantiomeric excess of the products was determined by CSP-HPLC using the conditions indicated for each case.

**<u>General procedure IV:</u> Enantioselective preparation of lactones 46-52.**

A 25 mL oven dried carousel tube containing a stirring bar was charged with the relevant anhydride (**43-45**, 0.4 mmol) and catalyst **26** (26.4 mg, 0.04 mmol - 10 mol%). The air was evacuated from the reaction vessel by flushing with a flow of argon before being placed under an argon atmosphere (balloon). A mixture of MTBE:THF (4.0 mL, 0.1 M, 9:1 *v*:*v*) was added *via* syringe and the flask was cooled to -15 °C. The relevant freshly distilled or recrystallized aldehyde (0.4 mmol) was added *via* syringe or directly as a solid. The resulting mixture was allowed to stir for the time indicate for each case and the temperature was maintained to -15 °C To the reaction mixture containing the corresponding crude carboxylic acids, anhydrous MeOH (809.1 μL, 20.0 mmol), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 240 μL, 0.48 mmol) were added *via* syringe and the reaction was allowed to stir for 15 min at -15 °C. The major diastereomer produced in the reaction was then purified using a flash chromatographic purification system (Biotage SP4) using a high performance prepacked silica cartridge (Biotage SNAP 10 g), eluting the mixture in gradient of EtOAc from 100% hexanes and slightly modifying the following general method.

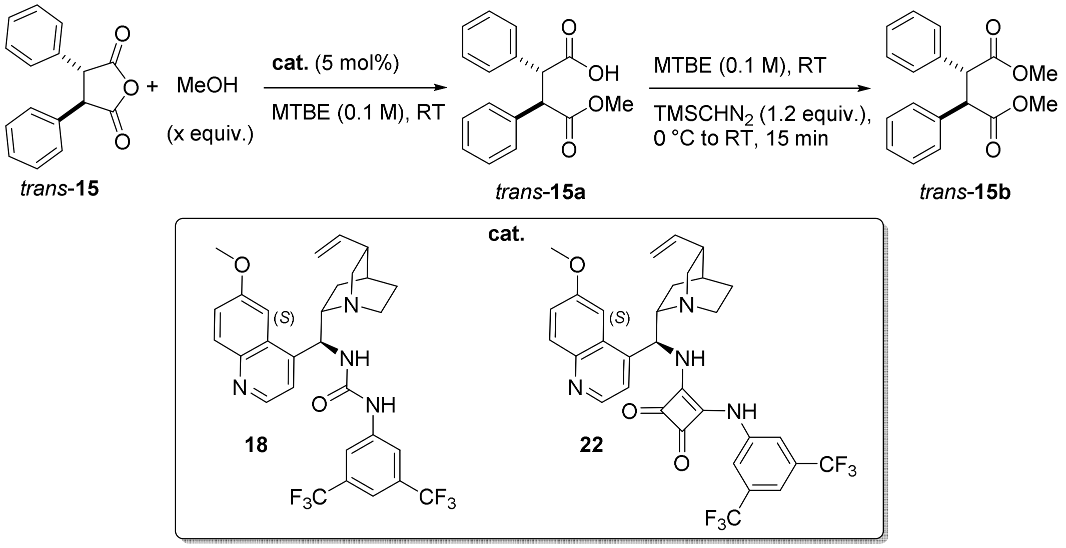
Flow rate: 10 mL.min$^{-1}$; Unit: CV = column volume.

Gradient: 100% hexanes for 3 CV; 100% hexanes to 20% EtOAc in hexanes over 40 CV.

The enantiomeric excess of the products was determined by CSP-HPLC using the conditions indicated for each case.

# 6. Full catalyst screening and optimization

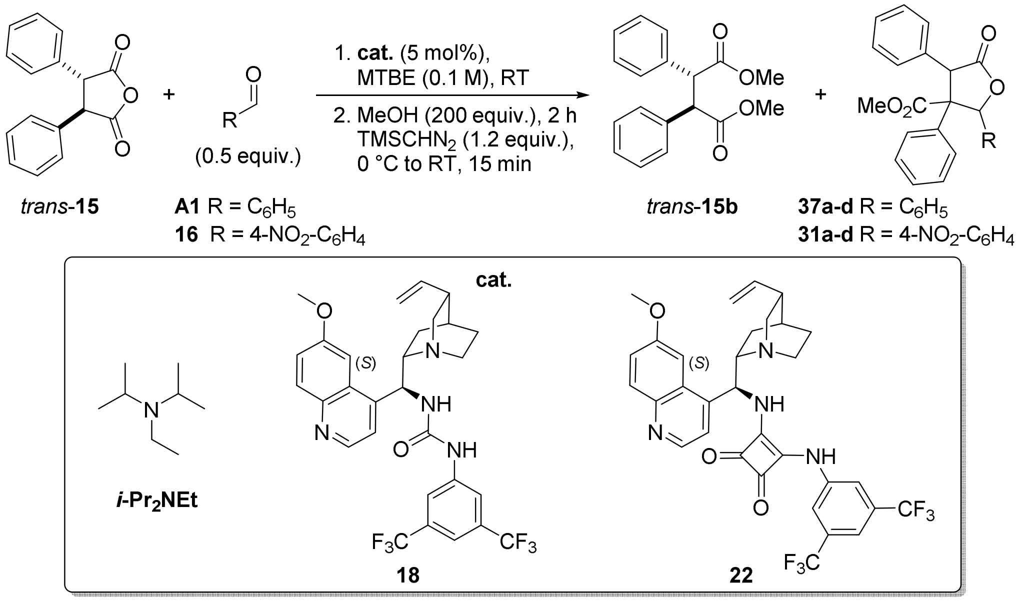
**Table 1** Proof of concept of the DKR - Optimization of the ring opening methanolysis.



| entry | cat. | time (min) | MeOH (x) | conv. (%)[a] | 15b *ee* (%)[b] |
|---|---|---|---|---|---|
| 1 | **18** | 30 | 150 | 93 | n.d.[c] |
| 2 | **18** | 120 | 200 | >99 | <3% |
| 3 | **22** | 120 | 200 | >99 | <3% |

[a] Conversion of starting material **15** determined by $^1$H NMR spectroscopic analysis using *p*-iodoanisole as the internal standard. [b] Determined by CSP-HPLC after derivatisation of the carboxylic acid product to the methyl esters by *in situ* esterification with TMSCHN$_2$. [c] Not determined.

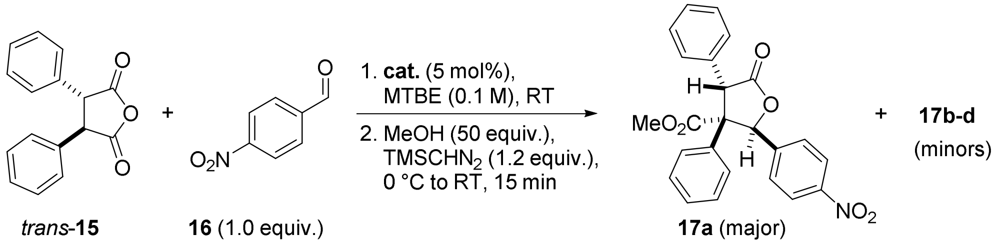
**Table 2** Proof of concept and preliminary experiments on the cycloaddition between *trans*-**15** and two aromatic aldehydes (**A1** and **16**).

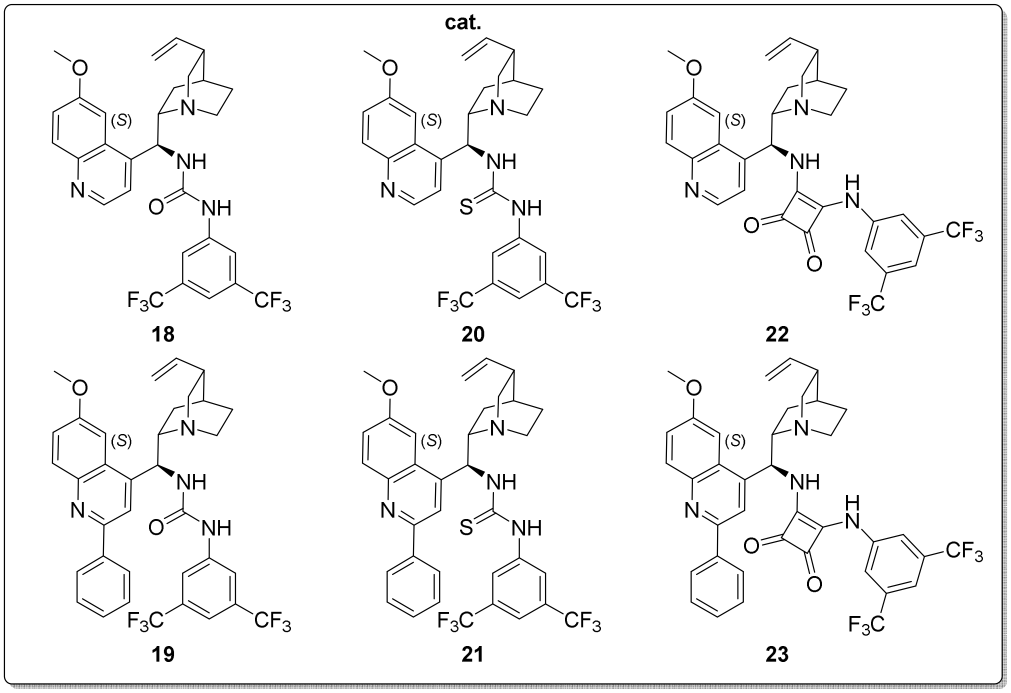


| entry | cat. | aldehyde | product | time (h) | conv. (%)[a] | *dr*[b] a:b:c:d | **15b** *ee* (%)[c] | **a** *ee* (%)[d] | **d** *ee* (%)[d] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **-** | **A1** | **37** | 24 | 0 | - | - | - | - |
| 2 | ***i*-Pr$_2$NEt**[e] | **A1**[f] | **37** | 24 | 87 | 81:14:4:1 | - | - | - |
| 3 | **18** | **A1** | **37** | 111 | 45 | 78:tr[g]:tr[g]:22 | 3 | 31 | 81 |
| 4 | **22** | **A1** | **37** | 111 | 46 | 82:tr[g]:tr[g]:18 | 4 | 46 | 82 |
| 5 | **22** | **16** | **31** | 24 | 50 | 75:tr[g]:tr[g]:25 | 2 | 39 | 79 |

[a] Conversion of starting material **15** determined by $^1$H NMR spectroscopic analysis using *p*-iodoanisole as the internal standard. [b] Diastereomeric ratio determined by $^1$H NMR spectroscopic analysis. [c] Determined by CSP-HPLC after derivatisation of the unreacted starting material **15** by ring opening alcoholysis with MeOH followed by *in situ* esterification with TMSCHN$_2$. [d] Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with TMSCHN$_2$. [e] 20 mol% was used. [f] (1.0 equiv.) of **A1** was used. [g] tr = traces (*i.e.* < 3%).

**Table 3** Catalyst screening – first experiments.

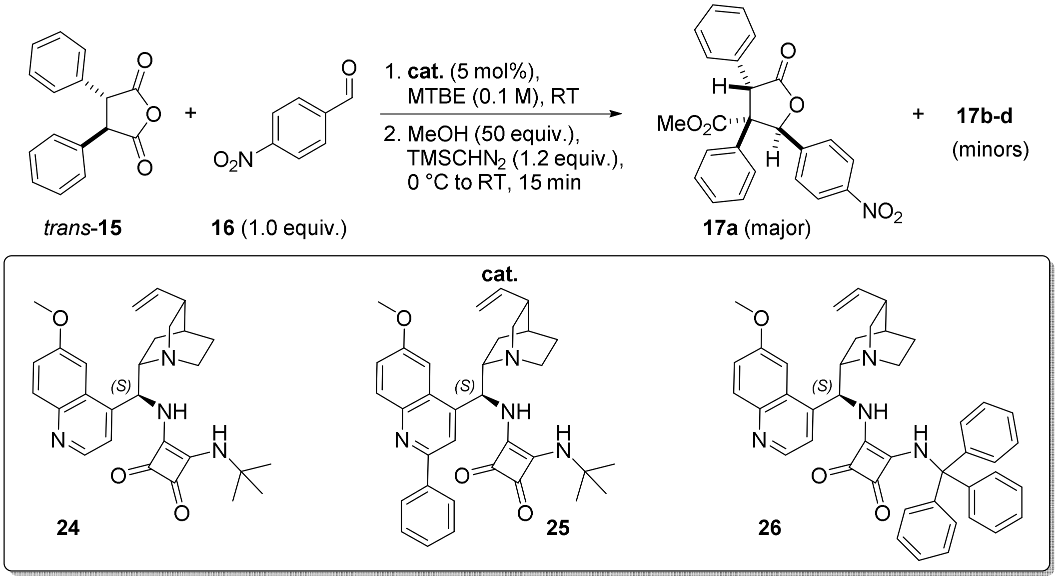




| entry | cat. | time (h) | conv. (%)[a] | 17 *dr*[b] a:b:c:d | 17a *ee* (%)[c] |
|---|---|---|---|---|---|
| 1 | **18** | 48 | 83 | 73:tr[d]:tr[d]:27 | 10 |
| 2 | **19** | 48 | 83 | 63:tr[d]:tr[d]:37 | 40 |
| 3 | **20** | 48 | 78 | 68:tr[d]:tr[d]:32 | 24 |
| 4 | **21** | 48 | 87 | 67:tr[d]:tr[d]:3 | 38 |
| 5 | **22** | 48 | 86 | 97:tr[d]:tr[d]:33 | 31 |
| 6 | **23** | 48 | 84 | 94:tr[d]:tr[d]:6 | 42 |

[a] Conversion of starting material **16** determined by $^1$H NMR spectroscopic analysis using *p*-iodoanisole as the internal standard. [b] Diastereomeric ratio determined by $^1$H NMR spectroscopic analysis. [c] Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$. [d] tr = traces (*i.e.* < 3%).

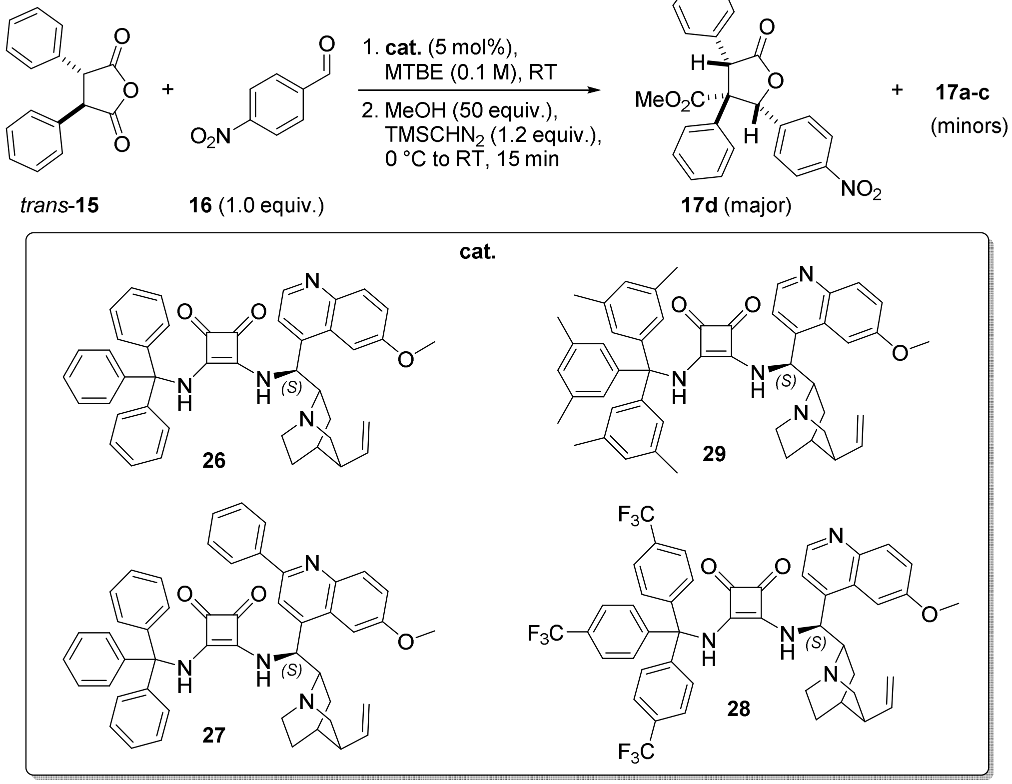
**Table 4** Catalyst screening – squaramide based.



| entry | cat. | time (h) | conv. (%)$^a$ | 17 *dr*$^b$ a:b:c:d | *ee* (%)$^c$ a:d |
|---|---|---|---|---|---|
| 1 | **24** | 48 | 84 | 70:tr$^d$:tr$^d$:30 | 8:n.d.$^e$ |
| 2 | **25** | 48 | 86 | 84:tr$^d$:tr$^d$:16 | 41:n.d.$^e$ |
| 3 | **26** | 144 | 81 | 35:tr$^d$:tr$^d$:65 | n.d.$^e$:95 |

[a] Conversion of starting material **16** determined by $^1$H NMR spectroscopic analysis using *p*-iodoanisole as the internal standard. [b] Diastereomeric ratio determined by $^1$H NMR spectroscopic analysis. [c] Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$. [d] tr = traces (*i.e.* < 3%). [e] Not determined.

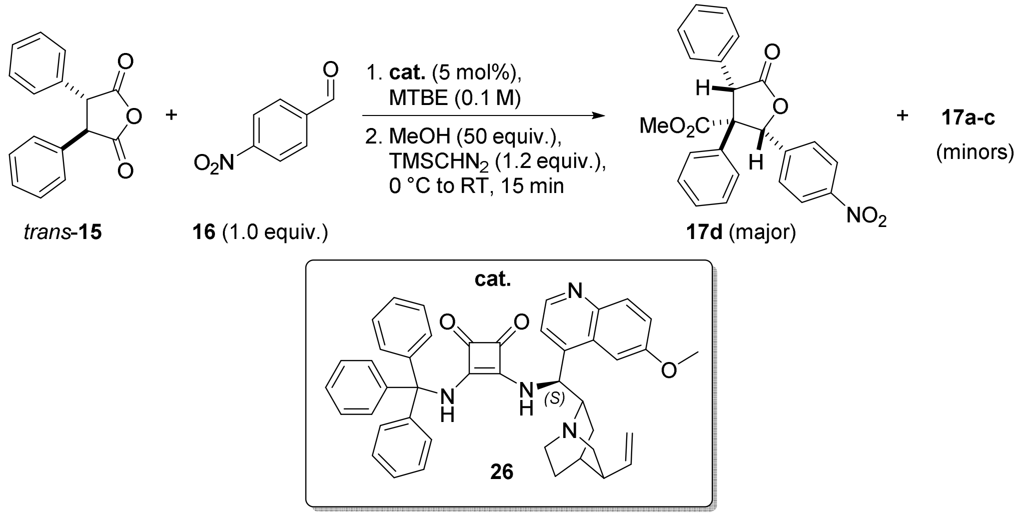
**Table 5** Catalyst screening – evaluation of different substitutions on the trityl moiety of the squaramide based catalyst.



| entry | cat. | time (h) | conv. (%)[a] | 17 dr[b] a:b:c:d | 17d ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **26** | 144 | 81 | 35:tr[d]:tr[d]:65 | 95 |
| 2 | **27** | 120 | 68 | 37:tr[d]:tr[d]:63 | 85 |
| 3 | **29** | 96 | 98 | 37:tr[d]:tr[d]:63 | 83 |
| 4 | **28** | 48 | 98 | 50:tr[d]:tr[d]:50 | 90 |

[a] Conversion of starting material **16** determined by $^1$H NMR spectroscopic analysis using *p*-iodoanisole as the internal standard. [b] Diastereomeric ratio determined by $^1$H NMR spectroscopic analysis. [c] Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$. [d] tr = traces (*i.e.* < 3%).

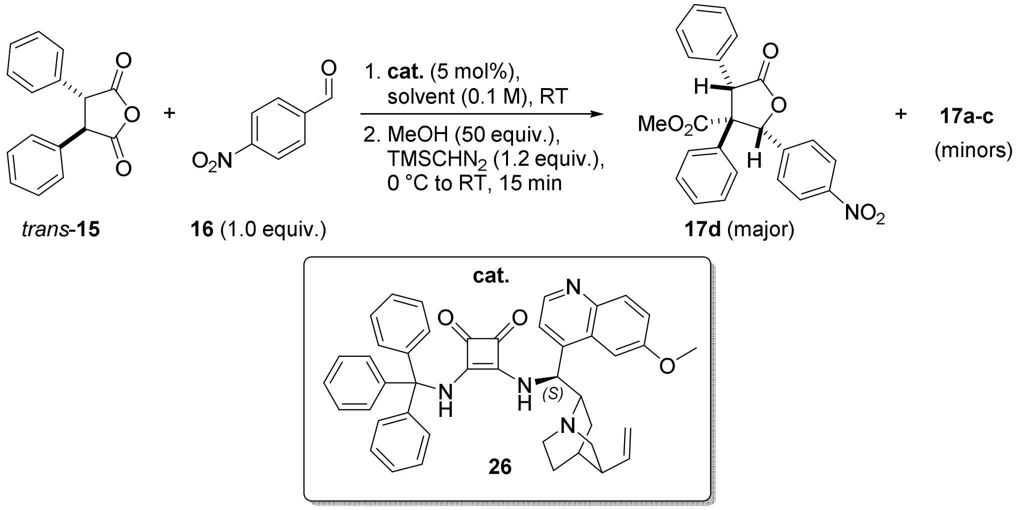
**Table 6** Influence of the temperature.



| entry | time<br>(d) | temp<br>(°C) | conv.<br>(%)[a] | *dr*[b]<br>17d:Σothers | 17d *ee*<br>(%)[c] |
|---|---|---|---|---|---|
| 1[d] | 17 | -30 | 55 | 1:3 | n.d.[e] |
| 2 | 7 | -15 | 60 | 1:2 | n.d.[e] |
| 3 | 7 | 0 | 80 | 1:1.4 | 89 |
| 4 | 6 | RT | 81 | 1.8:1 | 95 |
| 5 | 3 | 30 | 84 | 2.1:1 | 96 |
| 6 | 3 | 40 | >99 | n.d.[f] | 92 |

[a] Conversion of starting material **16** determined by $^1$H NMR spectroscopic analysis using *p*-iodoanisole as the internal standard. [b] Diastereomeric ratio determined by $^1$H NMR spectroscopic analysis. Here dr = (major diastereomer):(Σ other diastereomers). [c] Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$. [d] 20 mol% of the catalyst was used. [e] Not determined. [f] Not determined. Formation of 3 diastereomers. The concentration couldn't be maintained constant throughout the all reaction.

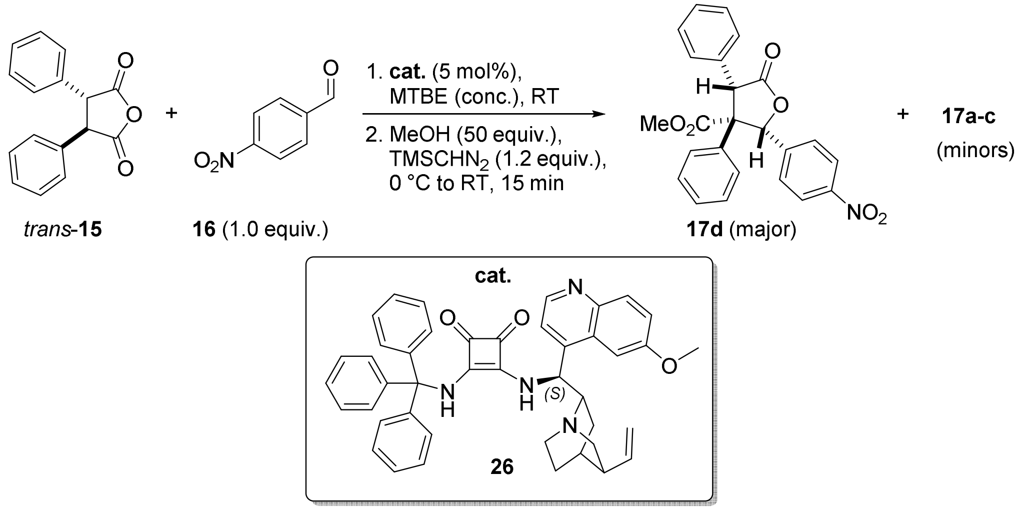
**Table 7** Influence of the solvent.



| entry | time<br>(d) | solvent | conv.<br>(%)[a] | *dr*[b]<br>17d:Σothers | 17d *ee*<br>(%)[c] |
|---|---|---|---|---|---|
| 1 | 6 | MTBE | 81 | 1.9:1 | 95 |
| 2 | 6 | THF | 89 | 1:1 | 89 |
| 3 | 6 | $Et_2O$ | 92 | 1.4:1 | 96 |
| 4[d] | 20 | (*i*-Pr)$_2$O | 62 | 1.4:1 | 89 |
| 5 | 4 | 2-Me-THF | 86 | 1:1 | 70 |
| 6 | 6 | MTBE:Me-THF (1:1, *v*:*v*) | 94 | 1:1 | 93 |
| 7 | 4 | MTBE:2-Me-THF (9:1, *v*:*v*) | 81 | 1.4:1 | 91 |

[a] Conversion of starting material **16** determined by $^1$H NMR spectroscopic analysis using *p*-iodoanisole as the internal standard. [b] Diastereomeric ratio determined by $^1$H NMR spectroscopic analysis. Here dr = (major diastereomer):(Σ other diastereomers). [c] Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with TMSCHN$_2$. [d] Catalyst insoluble.

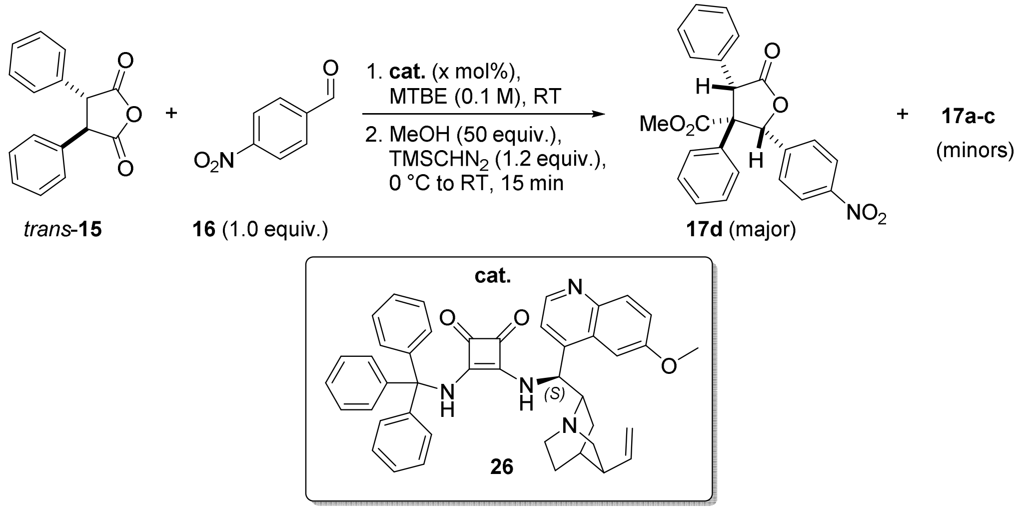
**Table 8** Influence of the concentration.



| entry | time<br>(d) | conc.<br>(M) | conv.<br>(%)[a] | *dr*[b]<br>17d:Σothers | 17d *ee*<br>(%)[c] |
|---|---|---|---|---|---|
| 1 | 4 | 0.05 | 88 | 2.2:1 | 91 |
| 2 | 6 | 0.1 | 81 | 1.8:1 | 95 |
| 3 | 4 | 0.2 | 95 | 2.1:1 | 90 |

[a] Conversion of starting material **16** determined by $^1$H NMR spectroscopic analysis using *p*-iodoanisole as the internal standard. [b] Diastereomeric ratio determined by $^1$H NMR spectroscopic analysis. Here dr = (major diastereomer):(Σ other diastereomers). [c] Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$.

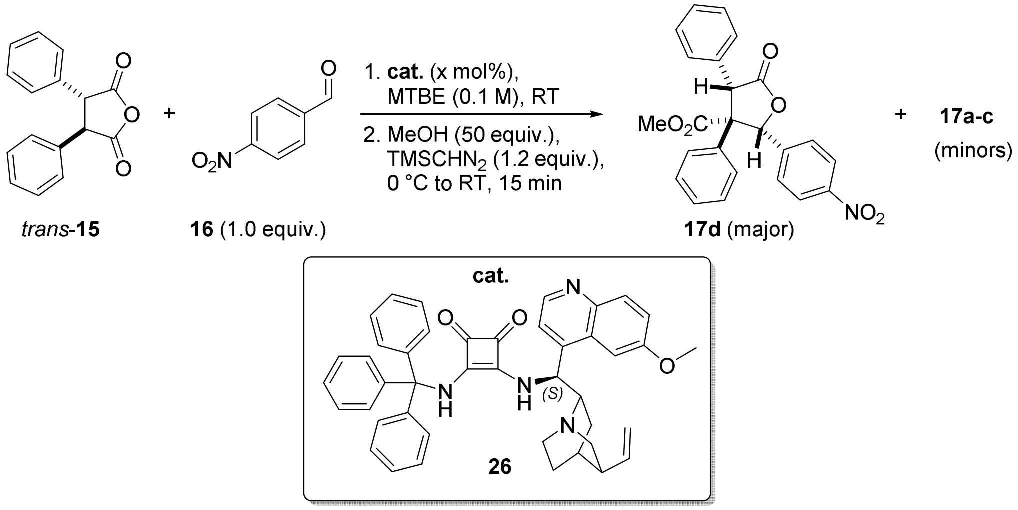
**Table 9** Influence of the catalyst loading.



| entry | time<br>(d) | cat. loading<br>(mol%) | conv.<br>(%)[a] | *dr*[b]<br>17d:Σothers | 17d *ee*<br>(%)[c] |
|---|---|---|---|---|---|
| 1 | 6 | 5 | 81 | 1.8:1 | 95 |
| 2 | 4 | 10 | 91 | 2.3:1 | 90 |
| 3 | 4 | 20 | 95 | 1.4:1 | 90 |

[a] Conversion of starting material **16** determined by $^1$H NMR spectroscopic analysis using *p*-iodoanisole as the internal standard. [b] Diastereomeric ratio determined by $^1$H NMR spectroscopic analysis. Here dr = (major diastereomer):(Σ other diastereomers). [c] Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$.

**Table 10** Refinement of the reaction conditions.

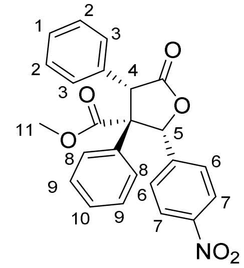


| entry | time (h) | temp (°C) | conc. (M) | cat. loading (mol%) | conv. (%)[a] | *dr*[b] 17d:Σothers | 17d *ee* (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | 23 | 40 | 0.05 | 5 | 92 | 1.8:1 | 95 |
| 2 | 23 | 50 | 0.05 | 5 | 92 | 1.3:1 | 94 |
| 3 | 23 | 40 | 0.05 | 1 | 90 | 2.1:1 | 93 |
| 4 | 26.5 | 40 | 0.025 | 1 | 76 | 2.0:1 | 92 |
| 5 | 26.5 | 40 | 0.02 | 1 | 64 | 1.9:1 | 84 |
| 6 | 26.5 | 40 | 0.05 | 1 | 90 | 2.3:1 | 92 |

[a] Conversion of starting material **16** determined by $^1$H NMR spectroscopic analysis using *p*-iodoanisole as the internal standard. [b] Diastereomeric ratio determined by $^1$H NMR spectroscopic analysis. Here dr = (major diastereomer):(Σ other diastereomers). [c] Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with TMSCHN$_2$.

# 7. Characterization data

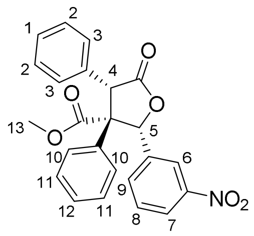
## Methyl (2R,3S,4S)-2-(4-nitrophenyl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (31)



Prepared according to general procedure III, using recrystallized 4-nitrobenzaldehyde (60.5 mg, 0.4 mmol). The reaction was allowed to stir for 10 days to give a diastereomeric mixture of carboxylic acids in a 1.5:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**31**) was isolated and purified by flash column chromatography to give a pale yellow solid (81.2 mg, 53%). M.p. 62-64 °C; TLC (hexanes:EtOAc, 8:2 *v/v*): $R_f = 0.26$; $[\alpha]_D^{20} = +50.4$ ($c = 0.442$, $CHCl_3$).

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 8.14 (2 H, d, *J* 8.8, H-7), 7.48 (2 H, d, *J* 8.8, H-6), 7.46-7.41 (3 H, m, H-9 and H-10), 7.37-7.33 (2 H, m, H-8), 7.27-7.22 (3 H, m, H-1 and H-2), 7.11-7.09 (2 H, m, H-3), 6.15 (1 H, s, H-5), 4.54 (1 H, s, H-4), 3.26 (3 H, s, H-11). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 172.1 (C=O), 168.7 (C=O), 148.1 (q), 141.4 (q), 134.4 (q), 130.5 (q), 130.3, 128.8, 128.7, 128.5, 128.4, 128.2, 127.6, 123.3, 82.0, 67.2 (q), 57.2, 52.0. |
| $\nu_{max}$ (neat)/$cm^{-1}$: | 3032, 2952, 1786 (C=O), 1726 (C=O), 1603, 1520 (N-O), 1497, 1448, 1434, 1347 (N-O), 1293, 1242, 1205, 1151, 1109, 1042, 1013, 863, 746, 697. |
| HRMS (*m/z* - APCI): | Found: 418.1293 $(M+H)^+$ $C_{24}H_{20}NO_6$ Requires: 418.1285. |

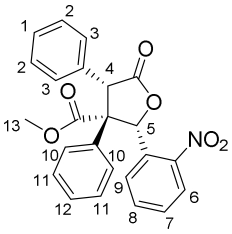
## Methyl (2R,3S,4S)-2-(3-nitrophenyl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (32)



Prepared according to general procedure III, using recrystallized 3-nitrobenzaldehyde (60.5 mg, 0.4 mmol). The reaction was allowed to stir for 10 days to give a diastereomeric mixture of carboxylic acids in a 2.3:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**32**) was isolated and purified by flash column chromatography to give a pale yellow solid (84.3 mg, 53%). M.p. 174-176 °C; TLC (hexanes:EtOAc, 8:2 *v/v*): $R_f = 0.23$; $[\alpha]_D^{20} = -26.0$ ($c = 0.905$, $CHCl_3$).

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 8.22 (1 H, s, H-6), 8.20 (1 H, d, *J* 8.2, H-7), 7.62 (1 H, d, *J* 7.8, H-9), 7.51 (1 H, app. T, *J* 8.0, H-8), 7.46-7.44 (3 H, m, H-11 and H-12), 7.36-7.34 (2 H, m, H-10), 7.29-7.26 (3 H, m, H-1 and H-2), 7.19-7.16 (2 H, m, H-3), 6.0 (1 H, s, H-5), 4.62 (1 H, s, H-4), 3.33 (3 H, s, H-13). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 172.2 (C=O), 168.7 (C=O), 148.0 (q), 136.3 (q), 134.2 (q), 132.8, 130.6 (q), 130.1, 129.2, 128.8, 128.7, 128.5, 128.33, 128.27, 123.9, 121.9, 82.3, 67.0 (q), 56.4, 52.0. |
| $\nu_{max}$ (neat)/$cm^{-1}$: | 3070, 1799 (C=O), 1721 (C=O), 1586, 1532 (N-O), 1493, 1445, 1433, 1352 (N-O), 1241, 1211, 1138, 1039, 957, 857. |
| HRMS (*m/z* - ESI): | Found: 456.0848 $(M+K)^+$ $C_{24}H_{19}KNO_6$ Requires: 456.0843. |

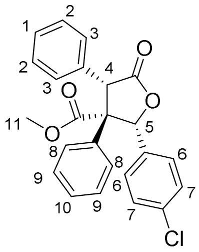
**Methyl (2R,3S,4S)-2-(2-nitrophenyl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (33)**



Prepared according to general procedure III, using recrystallized 2-nitrobenzaldehyde (60.5 mg, 0.4 mmol). The reaction was allowed to stir for 10 days to give a diastereomeric mixture of carboxylic acids in a 1:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**33**) was isolated and purified by flash column chromatography to give a pale yellow solid (54.0 mg, 34%). M.p. 54-56 °C; TLC (hexanes:EtOAc, 8:2 *v/v*): $R_f = 0.19$.

| | |
|---|---|
| $\delta_H$ (400 MHz, CDCl$_3$): | 7.88 (1 H, d, *J* 8.0, H-6), 7.82 (1 H, d, *J* 8.0, H-9), 7.65 (1 H, app. T, *J* 7.8, H-7), 7.65 (1 H, app. T, *J* 7.8, H-8), 7.38-7.32 (3 H, m, H-11 and H-12), 7.27-7.22 (5 H, m, H-1, H-2 and H-10), 7.18-7.15 (2 H, m, H-3), 6.89 (1 H, s, H-5), 4.73 (1 H, s, H-4), 3.31 (3 H, s, H-13). |
| $\delta_C$ (100 MHz, CDCl$_3$): | 172.2 (C=O), 169.0 (C=O), 149.0 (q), 133.6 (q), 132.6, 130.9 (q), 130.0, 129.7, 129.1, 128.8, 128.7, 128.20 (q), 128.17, 128.08, 128.05, 125.0, 78.6, 67.2 (q), 55.8, 52.0. |
| $\nu_{max}$ (neat)/cm$^{-1}$: | 3327, 2944, 1793 (C=O), 1719 (C=O), 1660, 1602, 1526 (N-O), 1433, 1351 (N-O), 1277, 1203, 1157, 1106, 1021, 966, 830, 743, 697. |
| HRMS (*m/z* - ESI): | Found: 416.1129 $(M-H)^-$ $C_{24}H_{18}NO_6$ Requires: 416.1139. |

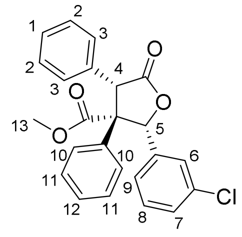
**Methyl (2R,3S,4S)-2-(4-chlorophenyl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (34)**



Prepared according to general procedure III, using recrystallized 4-chlorobenzaldehyde (56.2 mg, 0.4 mmol). The reaction was allowed to stir for 10 days to give a diastereomeric mixture of carboxylic acids in a 2.3:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**34**) was isolated and purified by flash column chromatography to give a white solid (84.2 mg, 52%). M.p. 52-54 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): $R_f = 0.1$; $[\alpha]_D^{20} = +319.9$ ($c = 0.27$, $CHCl_3$).

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.42-7.40 (3 H, m, H-9 and H-10), 7.34-7.31 (4 H, m, H-7 and H-8), 7.29-7.25 (5 H, m, H-1, H-2 and H-6), 7.17-7.14 (2 H, m, H-3), 6.0 (1 H, s, H-5), 4.49 (1 H, s, H-4), 3.32 (3 H, s, H-11). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 172.6 (C=O), 169.0 (C=O), 134.9 (q), 134.7 (q), 132.6 (q), 130.8 (q), 130.3, 128.64, 128.57, 128.51, 128.47, 128.22, 128.22, 128.1, 82.5, 66.9 (q), 56.9, 52.0. |
| $\nu_{max}$ (neat)/cm$^{-1}$: | 3046, 2951, 1785 (C=O), 1725 (C=O), 1599, 1493, 1448, 1433, 1240, 1202, 1153, 1091, 1013, 805, 761, 697. |
| HRMS (*m/z* - ESI): | Found: 405.0893 $(M-H)^-$ $C_{24}H_{18}ClO_4$ Requires: 405.0899. |

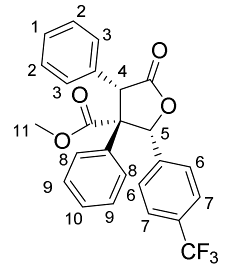
**Methyl (2R,3S,4S)-2-(3-chlorophenyl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (35)**



Prepared according to general procedure III, using freshly distilled 3-chlorobenzaldehyde (45.3 µL, 0.4 mmol). The reaction was allowed to stir for 10 days to give a diastereomeric mixture of carboxylic acids in a 3.5:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**35**) was isolated and purified by flash column chromatography to give a white solid (114.2 mg, 70%). M.p. 126-128 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): $R_f = 0.1$; $[\alpha]_D^{20} = +226.7$ ($c = 0.098$, $CHCl_3$).

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.42-7.40 (3 H, m, H-11 and H-12), 7.38-7.37 (1 H, m, H-7), 7.33-7.21 (7 H, m, H-1, H-2, H-6, H8 and H-10), 7.17-7.14 (3 H, m, H-3 and H-9), 6.03 (1 H, s, H-5), 4.48 (1 H, s, H-4), 3.34 (3 H, s, H-13). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 172.5 (C=O), 168.9 (C=O), 136.1 (q), 134.6 (q), 134.3 (q), 130.7 (q), 130.4, 129.4, 129.1, 128.6, 128.54, 128.47, 128.17, 128.15, 126.7, 124.9, 82.2, 66.9 (q), 56.9, 51.9. |
| $\nu_{max}$ (neat)/cm$^{-1}$: | 2948, 1785, 1725, 1599, 1571, 1202, 1156, 1033, 999, 757, 696. |
| HRMS (*m/z* - ESI): | Found: 429.0854 $(M+Na)^+$ $C_{24}H_{19}ClNaO_4$ Requires: 429.0864. |

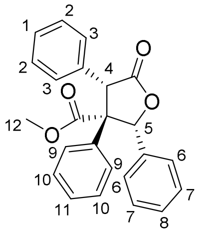
**Methyl (2R,3S,4S)-5-oxo-3,4-diphenyl-2-(4-(trifluoromethyl)phenyl) tetrahydrofuran-3-carboxylate (36)**



Prepared according to general procedure III, using freshly distilled *p*$CF_3$-benzaldehyde (69.7 μL, 0.4 mmol). The reaction was allowed to stir for 10 days to give a diastereomeric mixture of carboxylic acids in a 1.3:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**36**) was isolated and purified by flash column chromatography to give a white solid (81.3 mg, 46%). M.p. 52-54 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): $R_f = 0.1$; $[\alpha]_D^{20} = +309.6$ ($c = 0.431$, $CHCl_3$).

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.57 (2 H, app. d, *J* 8.2, H-7), 7.46-7.42 (5 H, m, H-6, H-9 and H-10), 7.37-7.32 (2 H, m, H-8), 7.29-7.24 (3 H, m, H-1 and H-2), 7.16-7.13 (2 H, m, H-3), 6.15 (1 H, s, H-5), 4.52 (1 H, s, H-4), 3.27 (3 H, s, H-11). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 172.5 (C=O), 168.9 (C=O), 138.2 (q), 134.6 (q), 131.0 (q) (q, $^2J_{C\text{-}F}$ 32.7 Hz), 130.7 (q), 130.4, 128.61, 128.59, 128.55, 128.25, 128.17, 126.98, 125.08 (q, $^3J_{C\text{-}F}$ 3.8 Hz), 123.81 (q) (q, $^1J_{C\text{-}F}$ 272.1 Hz), 82.2, 67.1 (q), 57.2, 51.9. |
| $\delta_F$ (376.5 MHz, $CDCl_3$): | -62.7. |
| $\nu_{max}$ (neat)/$cm^{-1}$: | 1786, 1725, 1324, 1167, 1123, 1113, 1068, 1015, 856, 758. |
| HRMS (*m/z* - ESI): | Found: 463.1133 $(M+Na)^+$ $C_{25}H_{19}F_3NaO_4$ Requires: 463.1127. |

### Methyl (2R,3S,4S)-5-oxo-2,3,4-triphenyltetrahydrofuran-3-carboxylate (37)



Prepared according to general procedure III, using freshly distilled benzaldehyde (40.8 µL, 0.4 mmol). The reaction was allowed to stir for 10 days to give a diastereomeric mixture of carboxylic acids in a 3.5:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**37**) was isolated and purified by flash column chromatography to give a white solid (90.4 mg, 61%). M.p. 158-160 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): $R_f$ = 0.15; $[\alpha]_D^{20}$ = +290.9 (*c* = 0.108, $CHCl_3$).

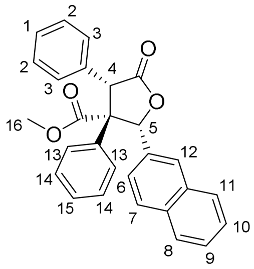
$\delta_H$ (400 MHz, $CDCl_3$): 7.34-7.08 (15 H, m, H-6, H-7, H-8, H-9, H-10 and H-11), 6.03 (1 H, s, H-5), 4.39 (1 H, H-4), 3.23 (3 H, s, H-12).

$\delta_C$ (100 MHz, $CDCl_3$): 172.8 (C=O), 169.1 (C=O), 135.0 (q), 134.0 (q), 130.9 (q), 130.4, 128.9, 128.7, 128.34, 128.32, 128.1, 128.2, 128.0, 126.5, 82.9, 66.8 (q), 57.1, 51.8.

$\nu_{max}$ (neat)/$cm^{-1}$: 3030, 1787 (C=O), 1714 (C=O), 1495, 1454, 1433, 1360, 1323, 1245, 1166, 1154, 1024, 1010, 965, 767, 756, 746, 692,671, 649, 592.

HRMS (*m/z* - ESI): Found: 371.1299 $(M-H)^-$ $C_{24}H_{19}O_4$ Requires: 371.1288.

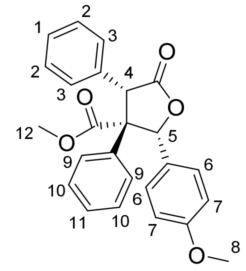
**Methyl (2R,3S,4S)-2-(naphthalen5-2-yl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (38)**



Prepared according to general procedure III, using recrystallized 2-Naphthaldehyde (62.53 mg, 0.4 mmol). The reaction was allowed to stir for 10 days to give a diastereomeric mixture of carboxylic acids in a 2.8:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**38**) was isolated and purified by flash column chromatography to give a white solid (94.7 mg, 56%). M.p. 50-52 °C; TLC (hexanes:EtOAc, 4:1 *v/v*): $R_f = 0.32$; $[\alpha]_D^{20} = +297.4$ ($c = 0.594$, $CHCl_3$).

| | |
|---|---|
| $\delta_H$ (600 MHz, $CDCl_3$): | 7.86 (1 H, bs, H-12), 7.82-7.78 (2 H, m, H-8 and H-11), 7.77 (1 H, app. d, H-7), 7.51-7.47 (2 H, m, H-8 and H-9), 7.44-7.40 (3 H, m, H-14 and H-15), 7.39-7.35 (3 H, m, H-6 and H-13), 7.30-7.27 (3 H, m, H-1, H-2 and H-3), 6.22 (1 H, s, H-5), 4.55 (1 H, s, H-4), 3.24 (3 H, s, H-16). |
| $\delta_C$ (150.9 MHz, $CDCl_3$): | 172.9 (C=O), 169.2 (C=O), 135.0 (q), 133.3 (q), 132.7 (q), 131.4 (q), 131.0 (q), 130.4, 128.8, 128.42, 128.38, 128.20, 128.1, 128.0, 127.9, 127.6, 126.6, 126.5, 126.2, 124.0, 83.3, 67.0 (q), 56.9, 51.9. |
| $\nu_{max}$ (neat)/cm$^{-1}$: | 3058, 2950, 1783, 1724, 1497, 1448, 1237, 1203, 1151, 1031, 956, 811, 745, 696, 647. |
| HRMS (*m/z* - APCI): | Found: 423.1590 $(M+H)^+$ $C_{28}H_{23}O_4$ Requires: 423.1590. |

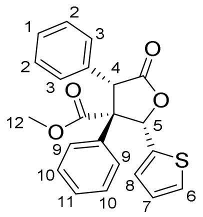
### Methyl (2R,3S,4S)-2-(4-methoxyphenyl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (39)



Prepared according to general procedure III, using freshly distilled 4-Methoxybenzaldehyde (48.7 µL, 0.4 mmol). The reaction was allowed to stir for 10 days to give a diastereomeric mixture of carboxylic acids in a 2.1:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**39**) was isolated and purified by flash column chromatography to give a white solid (47.0 mg, 29%). M.p. 48-50 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): $R_f = 0.14$; $[\alpha]_D^{20} = +84.9$ ($c = 0.727$, $CHCl_3$).

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.42-7.40 (3 H, m, H-10 and H-11), 7.34-7.26 (7 H, m, H-1, H-2, H-6 and H-9), 7.23-7.21 (2 H, m, H-3), 6.88-6.86 (2 H, app. d, *J* 8.9, H-7), 5.99 (1 H, s, H-5), 4.52 (1 H, s, H-4), 3.82 (3 H, s, H-8), 3.39 (3 H, s, H-12). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 173.0 (C=O), 169.4 (C=O), 160.1 (q), 135.1 (q), 131.2 (q), 130.3, 128.8, 128.34, 128.30, 128.18, 128.16, 128.0, 125.7 (q), 113.6, 83.4, 66.7 (q), 56.5, 55.3, 51.97. |
| $\nu_{max}$ (neat)/cm$^{-1}$: | 3031, 2952, 2926, 1784, 1741, 1724, 1612, 1514, 1451, 1299, 1250, 1204, 1154, 1025, 1009, 835, 810, 754, 697. |
| HRMS (*m/z* - APCI): | Found: 403.1534 $(M+H)^+$ $C_{25}H_{23}O_5$ Requires: 403.1540. |

### Methyl (2S,3S,4S)-5-oxo-3,4-diphenyl-2-(thiophen-2-yl)tetrahydrofuran-3-carboxylate (40)



Prepared according to general procedure III, using freshly distilled 2-Thiophenecarboxaldehyde (37.42 µL, 0.4 mmol). The reaction was allowed to stir for 10 days to give a diastereomeric mixture of carboxylic acids in a 10:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**40**) was isolated and purified by flash column chromatography to give a white solid (49.3 mg, 37%). M.p. 165-167 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): $R_f = 0.17$; $[\alpha]_D^{20} = +295.7$ ($c = 0.183$, $CHCl_3$).

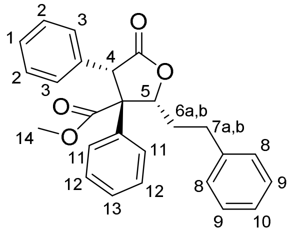
$\delta_H$ (400 MHz, $CDCl_3$): 7.39-7.34 (4 H, m, H-6, H-10 and H-11), 7.32-7.23 (7 H, m, H-1, H-2, H-3 and H-9), 7.04-7.02 (1 H, H-8), 7.03-6.97 (1 H, m, H-7), 6.11 (1 H, s, H-5), 4.52 (1 H, s, H-4), 3.50 (3 H, s, H-12).

$\delta_C$ (100 MHz, $CDCl_3$): 172.5 (C=O), 169.4 (C=O), 135.5 (q), 134.6 (q), 131.2 (q), 130.1, 128.5, 128.4, 128.32, 128.27, 128.20, 128.0, 127.0, 126.5, 80.9, 66.2 (q), 55.8, 52.3.

$\nu_{max}$ (neat)/cm$^{-1}$: 2951, 1783 (C=O), 1714 (C=O), 1496, 1435, 1338, 1256, 1154, 1079, 1013, 957, 816, 752, 698.

HRMS (*m/z* - ESI): Found: 377.0842 $(M-H)^-$ $C_{22}H_{17}O_4S$ Requires: 377.0853.

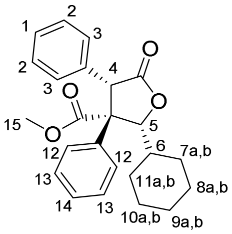
## Methyl (2R,3S,4S)-5-oxo-2-phenethyl-3,4-diphenyltetrahydrofuran-3-carboxylate (41)



Prepared according to general procedure III, using freshly distilled hydrocinnamaldehyde (52.72 μL, 0.4 mmol). The reaction was allowed to stir for 10 days to give a diastereomeric mixture of carboxylic acids in a 13:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**41**) was isolated and purified by flash column chromatography to give a white solid (124.5 mg, 78%). M.p. 172-174 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): $R_f = 0.15$; $[\alpha]_D^{20} = +306.7$ ($c = 1.0$, $CHCl_3$).

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.37-7.23 (11 H, m, H-1, H-2, H-8, H-9, H-10, H-12 and H-13), 7.19-7.15 (2 H, m, H-3), 8.86-6.84 (2 H, m, H-11), 4.90 (1 H, dd, *J* 1.8, 10.5, H-5), 4.10 (1 H, s, H-4), 3.64 (3 H, s, H-14), 3.11 (1 H, ddd, *J* 4.4, 8.3, 13.4, H-7a), 2.87 (1 H, ddd, *J* 8.41, 8.41, 13.8, H-7b), 2.18 (1 H, dddd, *J* 1.86, 8.28, 8.77, 14.24, H-6a), 2.07 (1 H, dddd, *J* 4.2, 7.9, 10.5, 14.5, H-6b). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 173.4 (C=O), 170.4 (C=O), 140.2 (q), 135.3 (q), 131.2 (q), 131.1, 128.8, 128.7, 128.3, 128.25, 128.20, 128.19, 127.8, 126.5, 80.7, 64.0 (q), 57.4, 52.2, 32.6, 31.7. |
| $\nu_{max}$ (neat)/$cm^{-1}$: | 3029, 2950, 1778, 1725, 1497, 1454, 1438, 1255, 1203, 1151, 1046, 959, 696, 651. |
| HRMS (*m/z* - APCI): | Found: 401.1744 $(M+H)^+$ $C_{26}H_{25}O_4$ Requires: 401.1747. |

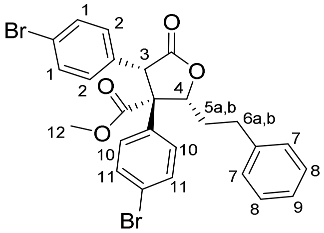
**Methyl (2R,3S,4S)-2-cyclohexyl-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (42)**



Prepared according to general procedure III, using freshly distilled cyclohexanecarboxaldehyde (48.5 µL, 0.4 mmol). The reaction was allowed to stir for 10 days to give a diastereomeric mixture of carboxylic acids in a 1.2:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**42**) was isolated and purified by flash column chromatography to give a white solid (66.0 mg, 44%). M.p. 139-141 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): $R_f = 0.19$; $[\alpha]_D^{20} = +178.1$ ($c = 0.232$, $CHCl_3$).

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.27-7.26 (3 H, m, H-1 and H-2), 7.19-7.12 (5 H, m, H-3, H-13 and H-14), 6.86-6-84 (2 H, app. d, H-12), 4.94-4.91 (1 H, d, *J* 9.5, H-5), 3.90 (1 H, s, H-4), 3.66 (3 H, s, H-15), 2.16-2.14 (1 H, m, H-6), 1.73-1.71 (1 H, m, H-7a), 1.57-1.54 (1 H, m, H-11a), 1.53-1.45 (3H, m, H-7b, H-9a and H-11b), 1.23-0.93 (4 H, m, H-8a, H-8b, H-10a and H-10b), 0.82-0.74 (1 H, m, H-9b). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 172.8 (C=O), 169.9 (C=O), 136.4 (q), 131.3, 130.6 (q), 128.2, 128.1, 128.0, 127.9, 127.8, 85.2 (q), 64.8 (q), 60.1, 52.0, 41.0, 30.6, 29.8, 26.1, 25.8, 25.6. |
| $\nu_{max}$ (neat)/$cm^{-1}$: | 2924, 2854, 1767, 1734, 1498, 1439, 1312, 1200, 1178, 1010, 924, 757, 695, 641. |
| HRMS (*m/z* - APCI): | Found: 379.1896 $(M+H)^+$ $C_{24}H_{27}O_4$ Requires: 379.1903. |

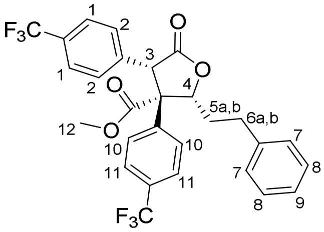
## Methyl (2R,3S,4S)-3,4-bis(4-bromophenyl)-5-oxo-2-phenethyltetrahydrofuran-3-carboxylate (46)



Prepared according to general procedure IV, using **43** (164.02 mg, 0.4 mmol) and freshly distilled hydrocinnamaldehyde (52.3 μL, 0.4 mmol). The reaction was allowed to stir for 8 days to give a diastereomeric mixture of carboxylic acids in a 34:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**46**) was isolated and purified by flash column chromatography to give a white solid (205.7 mg, 92%). M.p. 60-62 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): $R_f = 0.23$; $[\alpha]_D^{20} = -126.6$ ($c = 0.311$, $CHCl_3$).

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.34-7.32 (2 H, d, *J* 8.4, H-11), 7.28-7.26 (2 H, d, *J* 8.6, H-1), 7.28-7.13 (5 H, m, H-7, H-8 and H-9), 6.93-6.90 (2 H, d, *J* 8.4, H-10), 6.53-6.51 (2 H, d, *J* 8.6, H-2), 4.78-4.76 (1 H, app. d, H-4), 3.81 (1 H, s, H-3), 3.56 (3 H, s, H-12), 3.00-2.94 (1 H, m, H-6a), 2.78-2.70 (1 H, m, H-6b), 2.02-1.84 (2 H, m, H-5a and H-5b). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 172.4 (C=O), 169.8 (C=O), 139.9 (q), 134.0 (q), 132.9, 131.5, 131.4, 129.8 (q), 129.3, 128.79, 128.76, 126.6, 122.8 (q), 122.6 (q), 79.96, 63.5 (q), 57.0, 52.4, 32.3, 31.7. |
| $\nu_{max}$ (neat)/cm$^{-1}$: | 3028, 2951, 1781, 1730, 1491, 1208, 1160, 1076, 1009, 972, 810, 797, 749, 726, 700. |
| HRMS (*m/z* - ESI): | Found: 554.9813 $(M-H)^-$ $C_{26}H_{21}Br_2O_4$ Requires: 379.1903. |

## Methyl (2R,3S,4S)-5-oxo-2-phenethyl-3,4-bis(4-(trifluoromethyl)phenyl) tetrahydrofuran-3-carboxylate (47)



Prepared according to general procedure IV, using **44** (155.3 mg, 0.4 mmol) and freshly distilled hydrocinnamaldehyde (52.3 µL, 0.4 mmol). The reaction was allowed to stir for 5 days to give a diastereomeric mixture of carboxylic acids in a 11:1 (*major*:*others*) ratio. After esterification, the diastereomers (**47**) were isolated as a mixture and purified by flash column chromatography to afford a white solid (176.2 mg, 82%). M.p. 78-80 °C; TLC (hexanes:EtOAc, 4:1 *v/v*): $R_f = 0.47$; $[\alpha]_D^{20} = +51.8$ ($c = 1.18$, $CHCl_3$).

$\delta_H$ (400 MHz, $CDCl_3$): 7.38-7.36 (2 H, d, *J* 8.2, H-11), 7.34-7.24 (9 H, m, H-1, H-7, H-8, H-9 and H-10), 6.88-6.86 (2 H, d, *J* 8.2, H-10), 6.79-6.77 (2 H, d, *J* 8.2, H-2), 5.12 (1 H, dd, *J* 2.3, 11.6, H-4), 5.04 (1 H, s, H-3), 2.44 (3 H, s, H-12), 3.12-3.05 (1 H, m, H-6a), 2.91-2.84 (1 H, m, H-6b), 2.20-2.09 (1 H, m, H-5a), 1.95-1.87 (1 H, m, H-5b).

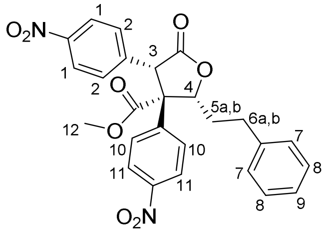
$\delta_C$ (100 MHz, $CDCl_3$): 173.3 (C=O), 170.9 (C=O), 140.0 (q), 139.8, 135.8, 131.7, 130.9, 128.8, 128.7, 128.67, 128.52, 128.1, 127.6, 126.6, 125.4, 124.7, 80.7, 64.5 (q), 50.08, 52.7, 33.2, 31.6.

$\delta_F$ (376.5 MHz, $CDCl_3$): Minor: -62.86, -62.89; Major: -62.92, -62.98.

$\nu_{max}$ (neat)/cm$^{-1}$: 2921, 1782, 1735, 1620, 1420, 1323, 1237, 1164, 1112, 1067, 1018, 850, 786, 749, 700.

HRMS (*m/z* - ESI): Found: 535.1340 $(M-H)^-$ $C_{28}H_{21}F_6O_4$ Requires: 535.1349.

## Methyl (2R,3S,4S)-3,4-bis(4-nitrophenyl)-5-oxo-2-phenethyltetrahydrofuran-3-carboxylate (48)



Prepared according to general procedure IV, using **45** (136.91 mg, 0.4 mmol) and freshly distilled hydrocinnamaldehyde (52.3 µL, 0.4 mmol). The reaction was allowed to stir for 3 days to give a diastereomeric mixture of carboxylic acids in a 5:1 (*major*:*others*) ratio. After esterification, the diastereomers (**48**) were isolated as a mixture and purified by flash column chromatography to afford a white solid (156.5 mg, 79%). M.p. 60-62 °C; TLC (hexanes:EtOAc, 70:30 *v/v*): $R_f$ = 0.47; $[\alpha]_D^{20}$ = -29.46 (*c* = 0.446, $CHCl_3$).

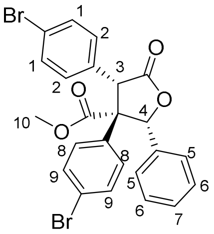
$\delta_H$ (400 MHz, $CDCl_3$): 8.01-7.99 (2 H, d, *J* 8.9, H-11), 7.96-7.94 (2 H, d, *J* 8.8, H-1), 7.39-7.22 (5 H, m, H-7, H-8 and H-9), 7.01-6.99 (2 H, d, *J* 8.9, H-10), 6.87-6.86 (2 H, d, *J* 8.8, H-2), 5.14-5.10 (1 H, dd, *J* 2.4, 8.96, H-4), 5.13 (1 H, s, H-3), 3.78 (3 H, s, H-12), 3.12-3.06 (1 H, m, H-6a), 2.92-2.84 (1 H, m, H-6b), 2.21-2.12 (1 H, m, H-5a), 1.96-1.88 (1 H, m, H-5b).

$\delta_C$ (100 MHz, $CDCl_3$): 172.4 (C=O), 170.4 (C=O), 142.8 (q), 139.5 (q), 138.7 (q), 131.5, 129.2 (q), 128.8, 128.5, 128.2, 126.7, 124.0 (q), 123.7, 123.1, 80.7, 64.6 (q), 53.4, 52.8, 33.2, 31.6.

$\nu_{max}$ (neat)/cm$^{-1}$: 2953, 1781, 1735, 1605, 1519, 1346, 1238, 1109, 1018, 851,736, 700.1.

HRMS (*m/z* - ESI): Found: 489.1308 $(M-H)^-$ $C_{26}H_{21}N_2O_8$ Requires: 489.1303.

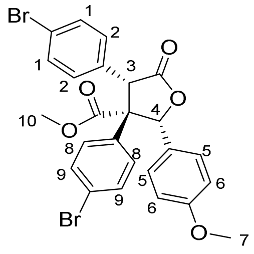
### Methyl (2R,3S,4S)-3,4-bis(4-bromophenyl)-5-oxo-2-phenyltetrahydrofuran-3-carboxylate (49)



Prepared according to general procedure IV, using **43** (164.02 mg, 0.4 mmol) and freshly distilled benzaldehyde (40.8 µL, 0.4 mmol). The reaction was allowed to stir for 7 days to give a diastereomeric mixture of carboxylic acids in a 4.4:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**49**) was isolated and purified by flash column chromatography to give a white solid (145.6 mg, 69%). M.p. 78-80 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): $R_f = 0.15$; $[\alpha]_D^{20} = +43.8$ ($c = 0.504$, $CHCl_3$).

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.55-7.53 (2 H, d, *J* 8.6, H-9), 7.42-7.40 (2 H, d, *J* 8.5, H-1), 7.34-7.27 (5 H, m, H-5, H-6 and H-7), 7.20-7.18 (2 H, d, *J* 8.6, H-8), 7.04-7.02 (2 H, d, *J* 8.5, H-2), 6.05 (1 H, s, H-4), 4.32 (1 H, s, H-3), 3.29 (3 H, s, H-10). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 171.9 (C=O), 168.6 (C=O), 133.8 (q), 133.5 (q), 132.0, 131.6, 131.4, 130.3, 129.7 (q), 129.2, 128.4, 126.3, 122.9 (q), 122.6 (q), 82.8, 66.3 (q), 56.5, 52.1. |
| $\nu_{max}$ (neat)/cm$^{-1}$: | 2950, 1778, 1727, 1489, 1238, 1205, 1157, 1074, 1009, 974, 798, 753, 698, 627. |
| HRMS (*m/z* - ESI): | Found: 526.9480 $(M-H)^-$ $C_{24}H_{17}Br_2O_4$ Requires: 526.9499. |

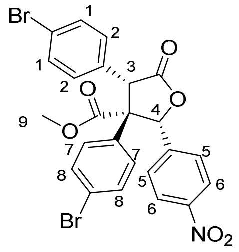
## Methyl (2R,3S,4S)-3,4-bis(4-bromophenyl)-2-(4-methoxyphenyl)-5-oxotetrahydrofuran-3-carboxylate (50)



Prepared according to general procedure IV, using **43** (164.02 mg, 0.4 mmol) and freshly distilled 4-Methoxybenzaldehyde (48.7 μL, 0.4 mmol). The reaction was allowed to stir for 10 days to give a diastereomeric mixture of carboxylic acids in a 10:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**50**) was isolated and purified by flash column chromatography to give a white solid (115.06 mg, 51%). M.p. 60-62 °C; TLC (hexanes:EtOAc, 4:1 *v/v*): $R_f = 0.29$; $[\alpha]_D^{20} = +88.7$ ($c = 0.08$, $CHCl_3$).

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.54-7.52 (2 H, d, *J* 8.7, H-9), 7.43-7.41 (2 H, d, *J* 8.5, H-1), 7.21-7.19 (2 H, d, *J* 8.8, H-6), 7.17-7.15 (2 H, d, *J* 8.7, H-8), 7.07-7.05 (2 H, d, *J* 8.5, H-2), 6.87-6.84 (2 H, d, *J* 8.8, H-5), 5.90 (1 H, s, H-4), 4.35 (1 H, s, H-3), 3.80 (3 H, s, H-7), 3.59 (3 H, s, H-10). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 172.1 (C=O), 168.8 (C=O), 160.3 (q), 133.8 (q), 131.8, 131.5, 131.4, 130.3, 129.9 (q), 127.9, 125.1 (q), 122.8 (q), 122.6 (q), 113.8, 83.2, 66.1 (q), 55.8, 55.3, 52.2. |
| $\nu_{max}$ (neat)/$cm^{-1}$: | 2927, 2850, 1785, 1728, 1612, 1515, 1491, 1299, 1251, 1206, 1161, 1075, 1028, 1008, 836, 809. |
| HRMS (*m/z* - APCI): | Found: 558.9760 $(M+H)^+$ $C_{25}H_{21}Br_2O_5$ Requires: 558.9750. |

### Methyl (2R,3S,4S)-3,4-bis(4-bromophenyl)-2-(4-nitrophenyl)-5-oxotetrahydrofuran-3-carboxylate (51)



Prepared according to general procedure IV, using **43** (164.02 mg, 0.4 mmol) and freshly recrystallised 4-nitrobenzaldehyde (60.44 µL, 0.4 mmol). The reaction was allowed to stir for 6 days to give a diastereomeric mixture of carboxylic acids in a 4:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**51**) was isolated and purified by flash column chromatography to give a white solid (150.7 mg, 66%). M.p. 88-90 °C; TLC (hexanes:EtOAc, 4:1 *v/v*): $R_f = 0.20$; $[\alpha]_D^{20} = +25.4$ ($c = 0.306$, $CHCl_3$).

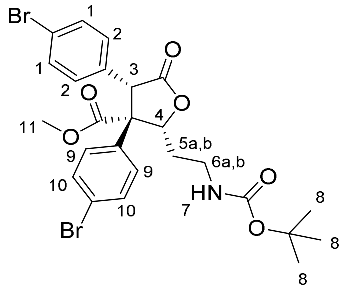
$\delta_H$ (400 MHz, $CDCl_3$): 8.20-8.18 (2 H, d, *J* 8.6, H-6), 7.61-7.59 (2 H, d, *J* 8.5, H-8), 7.49-7.47 (2 H, d, *J* 8.6, H-5), 7.43-7.41 (2 H, d, *J* 8.4, H-1), 7.24-7.22 (2 H, d, *J* 8.5, H-7), 7.00-6.98 (2 H, d, *J* 8.4, H-2), 6.14 (1 H, s, H-4), 4.37 (1 H, s, H-3), 3.27 (3 H, s, H-9).

$\delta_C$ (100 MHz, $CDCl_3$): 171.1 (C=O), 168.1 (C=O), 148.3 (q), 140.8 (q), 133.2 (q), 132.0, 131.97, 131.5, 130.0, 129.0 (q), 127.3, 123.5, 123.3 (q), 123.0 (q), 81.6, 66.6 (q), 56.8, 52.3.

$\nu_{max}$ (neat)/cm$^{-1}$: 2952, 1789, 1730, 1606, 1522, 1491, 1346, 1258, 1207, 1155, 1075, 1041, 1009, 799, 749, 686.

HRMS (*m/z* - APCI): Found: 571.9338 $(M-H)^-$ $C_{24}H_{16}Br_2NO_4$ Requires: 571.9349.

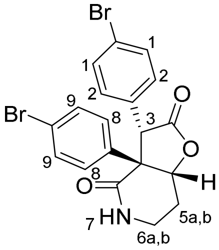
**Methyl (2R,3S,4S)-3,4-bis(4-bromophenyl)-2-(2-((*tert*-butoxycarbonyl)amino) ethyl)-5-oxotetrahydrofuran-3-carboxylate (52)**



Prepared according to general procedure IV, using **43** (164.02 mg, 0.4 mmol) and *tert*-butyl (3-oxopropyl)carbamate (**S37**, 67.9 µL, 0.4 mmol). The reaction was allowed to stir for 12 days to give a diastereomeric mixture of carboxylic acids in a 19:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**52**) was isolated and purified by flash column chromatography to give a white solid (139.5 mg, 58%). M.p. 62-64 °C; TLC (hexanes:EtOAc, 70:30 *v/v*): $R_f = 0.34$; $[\alpha]_D^{20} = +40.0$ ($c = 0.05$, $CHCl_3$).

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.46-7.42 (4 H, m (app. t), H-1 and H-10), 7.05-7.03 (2 H, d, *J* 8.5, H-9), 6.93-6.91 (2 H, d, *J* 8.6, H-2), 5.06 (1 H, app. d, H-4), 4.92 (1 H, bs, H-7 (NH)), 4.02 (1 H, s, H-3), 3.62 (3 H, s, H-11), 3.45-3.35 (2 H, m, H-6a and H-6b), 2.27-2.15 (1 H, m, H-5a), 1.75-1.66 (1 H, m, H-5b), 1.45 (9 H, s, H-8). |
| $\delta_C$ (100 MHz, $CDCl_3$): | Mixture of diastereomers: 173.5 (C=O), 172.2 (C=O), 171.1 (C=O), 169.8 (C=O), 156.2 (C=O), 156.0 (C=O), 134.9 (q), 133.9 (q), 132.8, 132.2, 131.68, 131.66, 131.44, 131.08, 130.7 (q), 129.8 (q), 129.3, 128.8, 79.8, 79.7, 63.8 (q), 63.6 (q), 56.6, 53.0, 52.7, 52.5, 38.0 (q), 37.3 (q), 30.26, 30.20, 28.4, 28.3. |
| $\nu_{max}$ (neat)/$cm^{-1}$: | 3405, 2977, 1774, 1729, 1690, 1523, 1491, 1365, 1238, 1165, 1075, 1010, 987, 835, 777, 746. |
| HRMS (*m/z* - APCI): | Found: 594.0151 $(M-H)^-$ $C_{25}H_{26}Br_2NO_6$ Requires: 594.0132. |

**3,3a-bis(4-bromophenyl)hexahydrofuro[3,2-c]pyridine-2,4-dione (54a)**

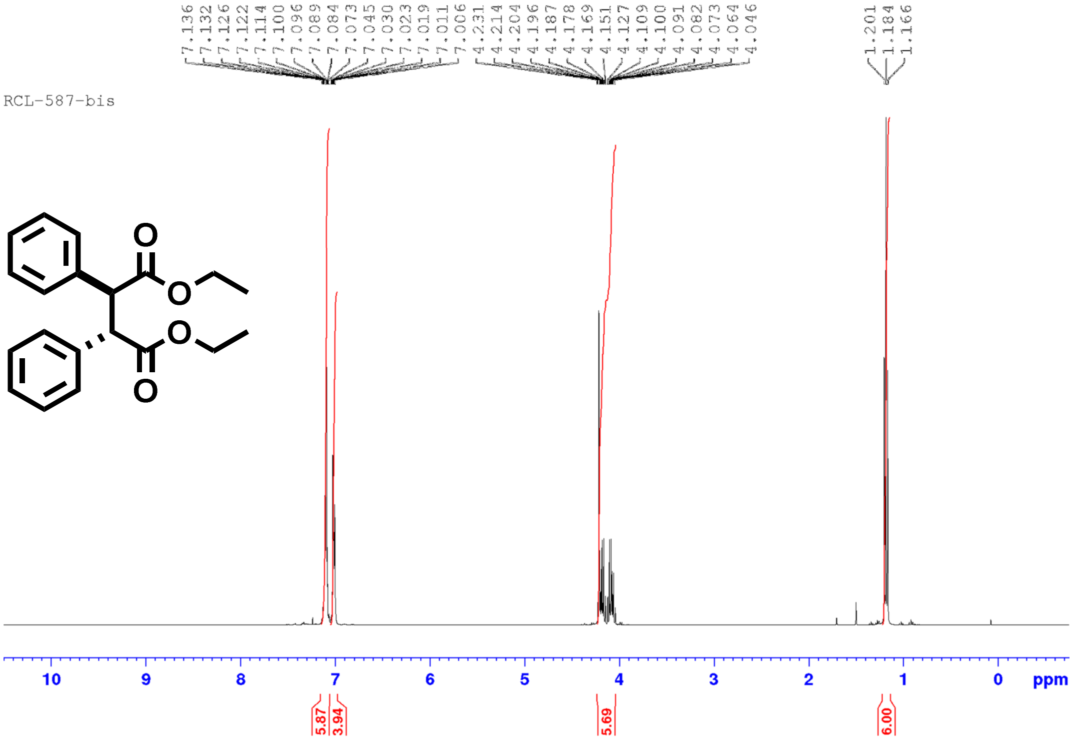


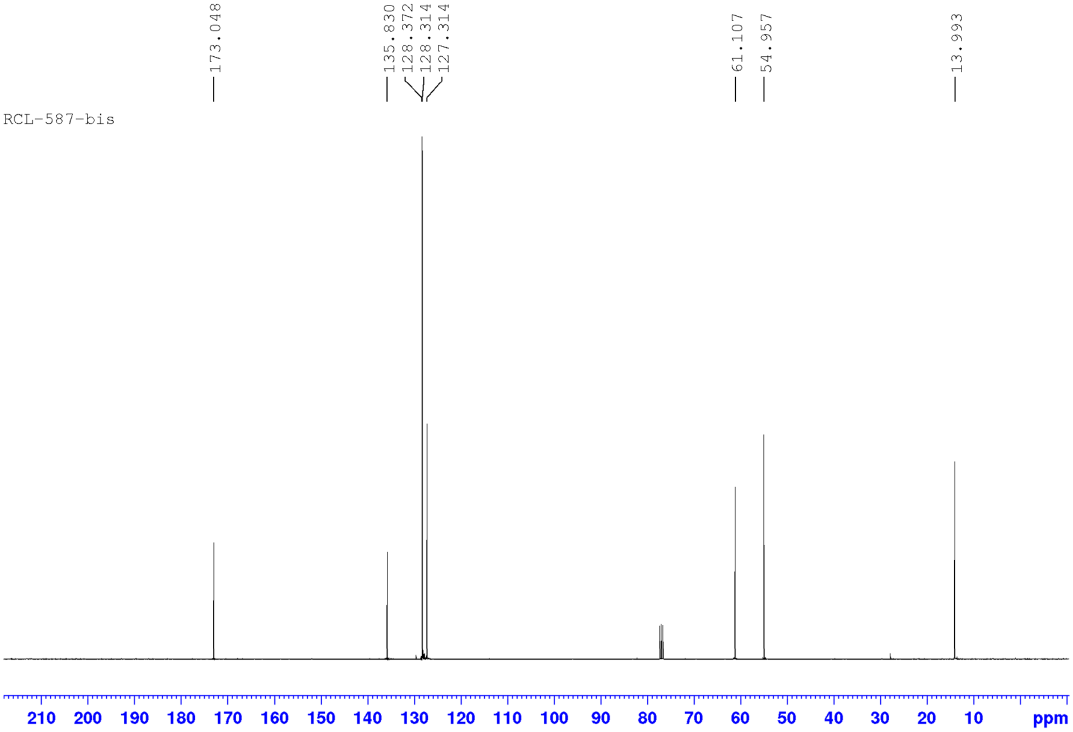
A 10 mL oven-dried round-bottomed flask containing a stirring bar was charged with **53** (97.5 mg, 0.168 mmol, 86:14 dr) and placed under an Argon atmosphere. Dry $CH_2Cl_2$ (1.7 mL) was added *via* syringe and the resulting solution was cooled to 0 °C. A 2M solution of trimethylaluminium in hexanes (168.5 μL, 0.337 mmol) was then added dropwise *via* syringe. The resulting solution was allowed to come back slowly to room temperature and stirred for 5 h. After 5 h, the reaction mixture was quenched by adding dropwise cold MeOH *via* syringe followed by cold deionised water. The resulting biphasic mixture was then diluted with water (20 mL) and extracted with $CH_2Cl_2$ (3 x 20 mL), the combined organic fractions were washed with water, brine, dried over $MgSO_4$ and the solvent was removed *in vacuo* to afford the crude product. Purification by flash column chromatography eluting in gradient from hexanes to 50% of EtOAc in hexanes furnished the desired product **54a** in quantitative yield (74 mg, 81%). M.p. 80-82 °C; TLC (hexanes:EtOAc, 1:1 *v/v*): $R_f = 0.29$; $[\alpha]_D^{20} = +244.7$ ($c = 0.146$, $CHCl_3$).

| | |
|---|---|
| $\delta_H$ (400 MHz, $CDCl_3$): | 7.30-7.28 (4 H, app. bd, H-1 and H-9), 7.01 (2 H, d, *J* 8.6, H-8), 6.77 (2 H, d, *J* 8.4, H-2), 6.02 (1 H, bs, H-7 (NH)), 5.39 (1 H, app. dd, H-4), 4.77 (1 H, s, H-3), 3.63-3.56 (1 H, m, H-6a), 3.30-3.24 (1 H, m, H-6b), 2.45-2.38 (1 H, m, H-5a), 2.28-2.20 (1 H, m, H-5b). |
| $\delta_C$ (100 MHz, $CDCl_3$): | 174.2 (C=O), 170.8 (C=O), 132.4 (q), 131.78, 131.75 (q), 131.6, 130.9, 129.3, 122.5 (q), 122.2 (q), 77.9, 58.3 (q), 55.6, 37.4, 23.5. |
| $\nu_{max}$ (neat)/cm$^{-1}$: | 3216, 2926, 1769, 1665, 1489, 1398, 1317, 1223, 1171, 1074, 1009, 961, 909, 812. |
| HRMS (*m/z* - APCI): | Found: 463.9503 $(M+H)^+$ $C_{19}H_{16}Br_2NO_3$ Requires: 463.9491. |

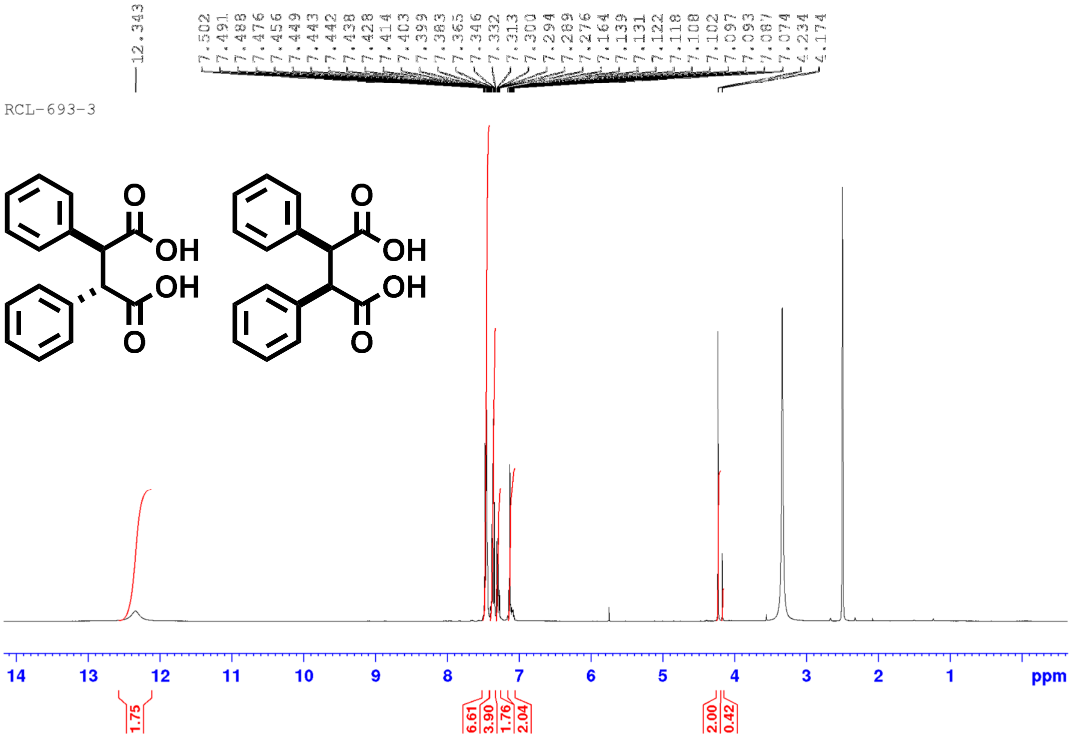
# 8. NMR spectra: $^1$H and $^{13}$C

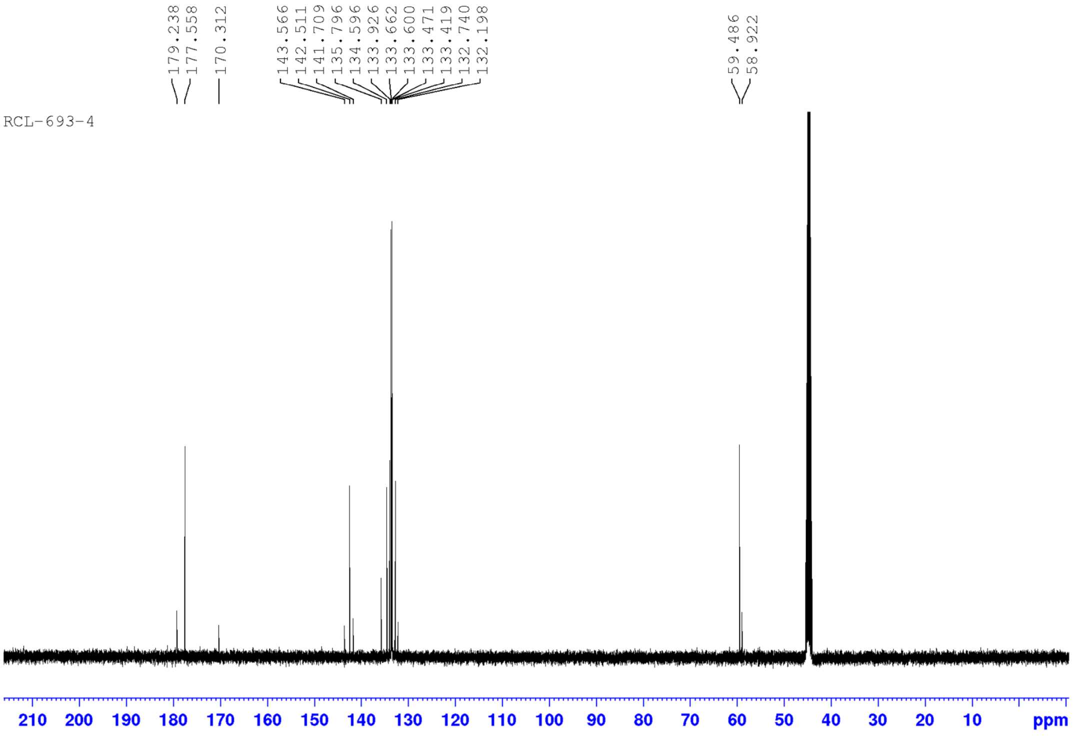
## Diethyl-2,3-diphenylsuccinate (S3)



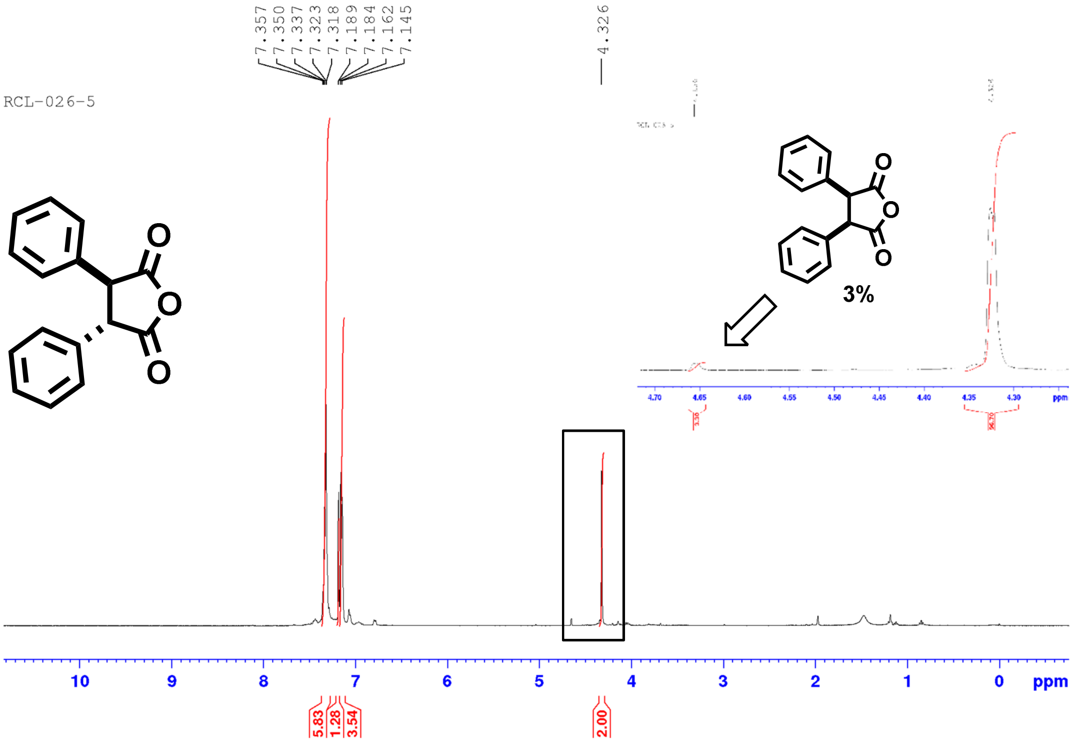


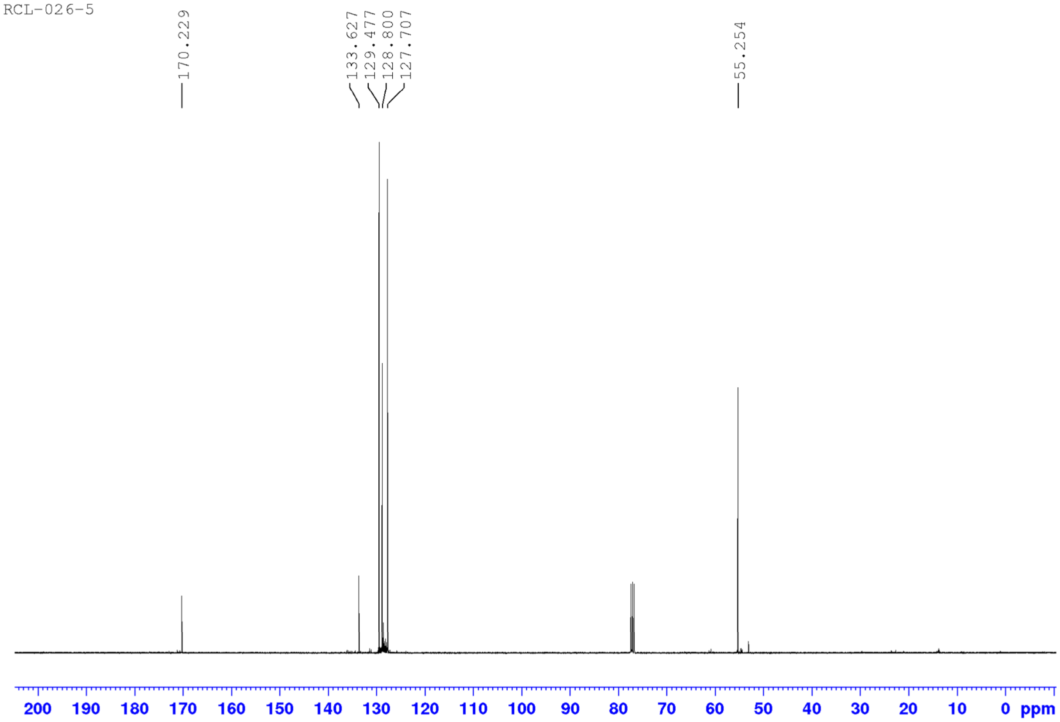
## 2,3-diphenylsuccinic acid (S4)



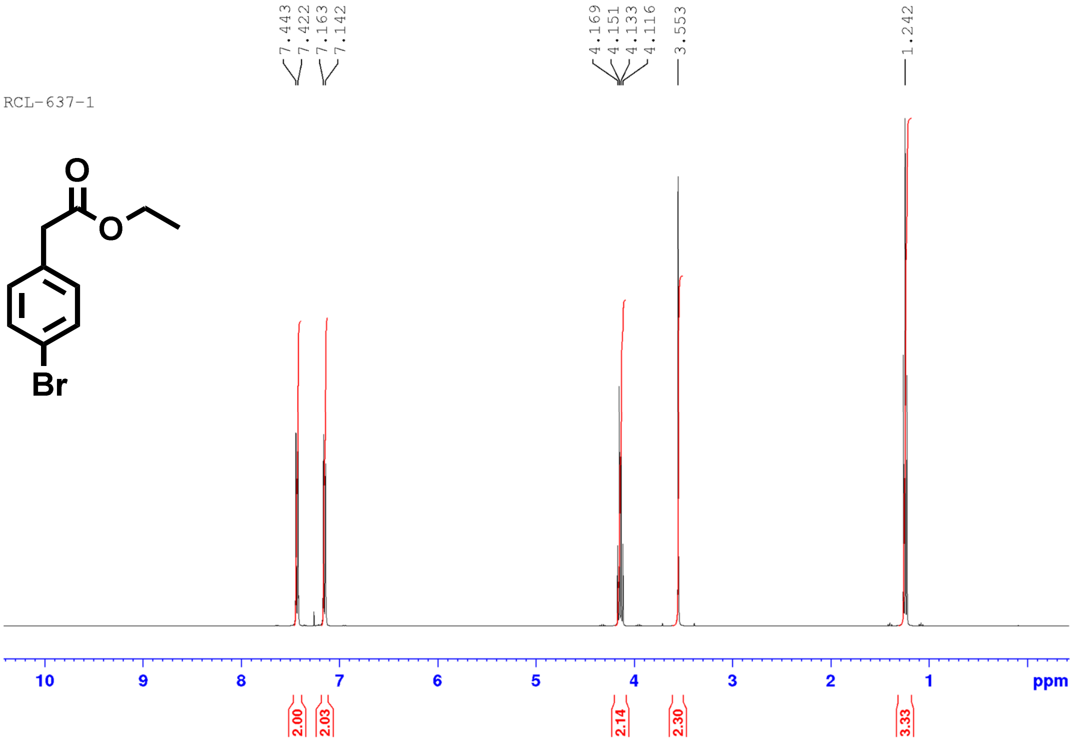


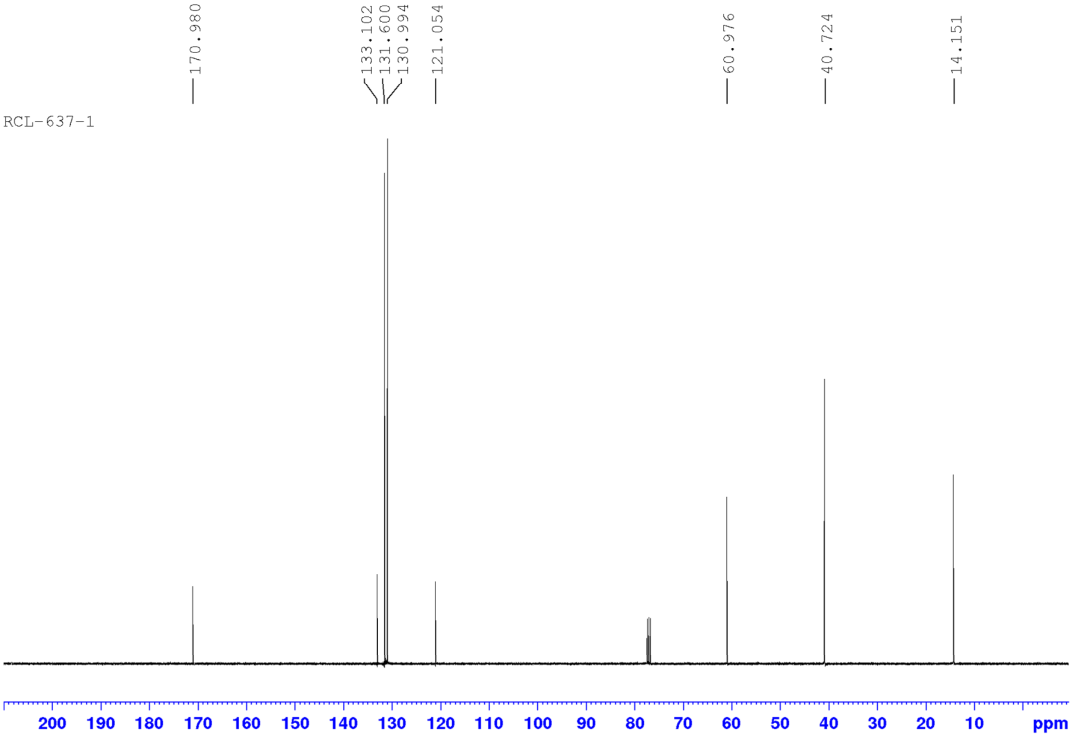
## 2,3-Diphenyl-succinic anhydride (*trans*-15)



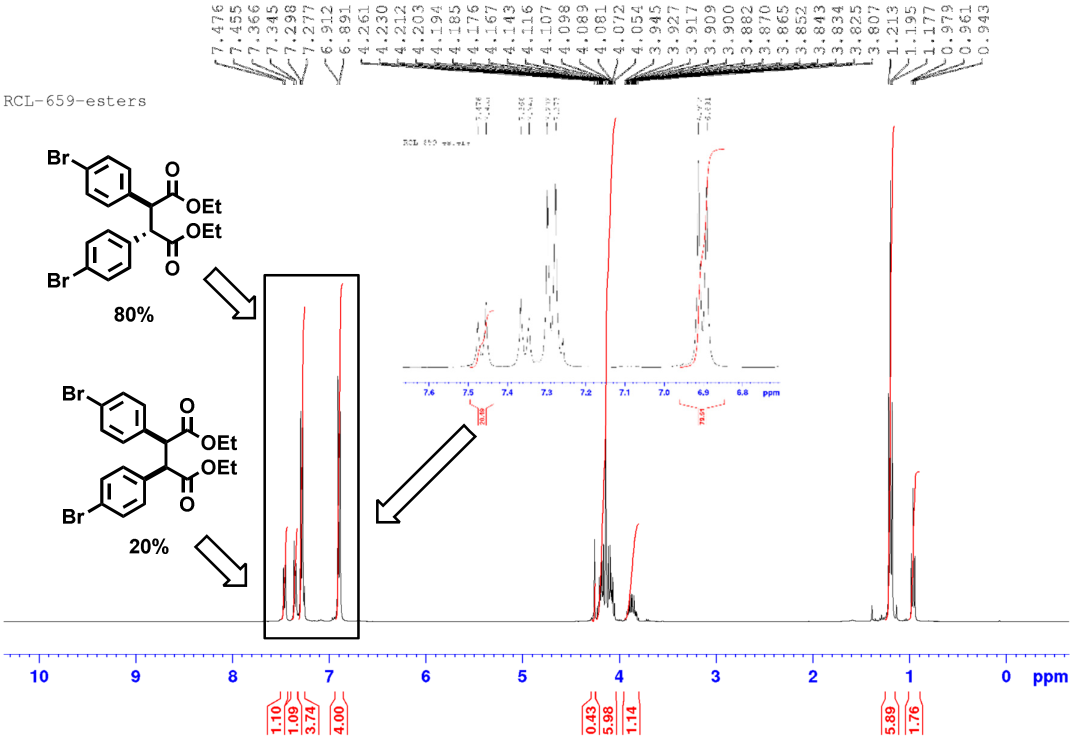


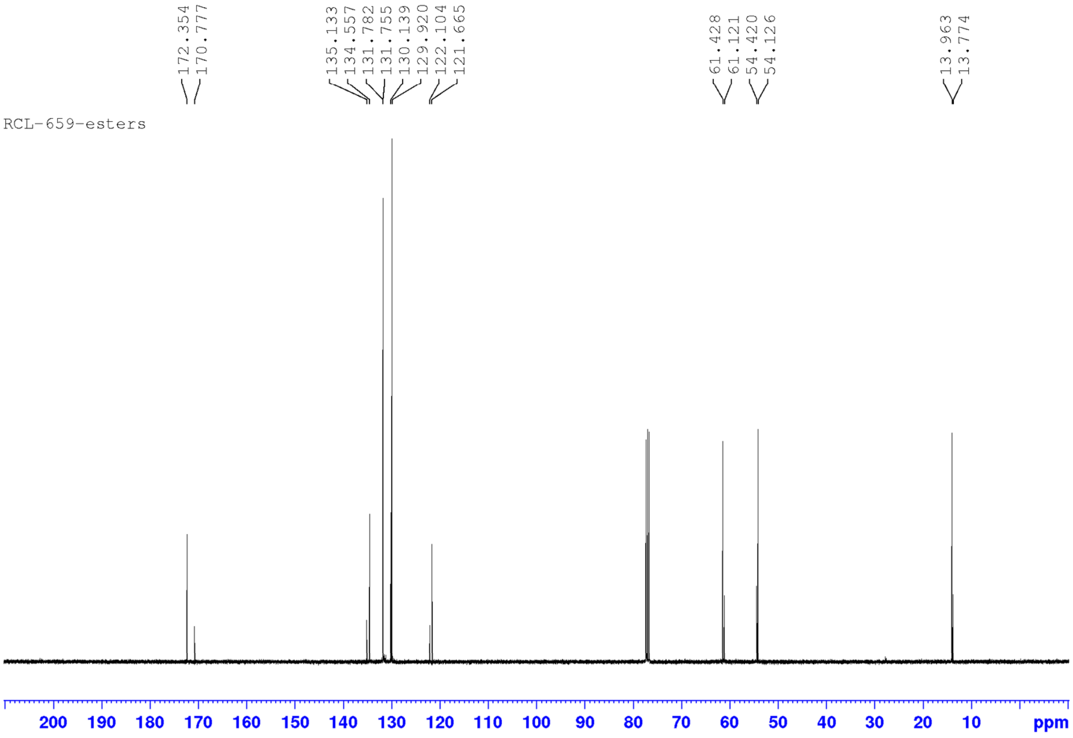
## Ethyl 2-(4-bromophenyl)acetate (S7)



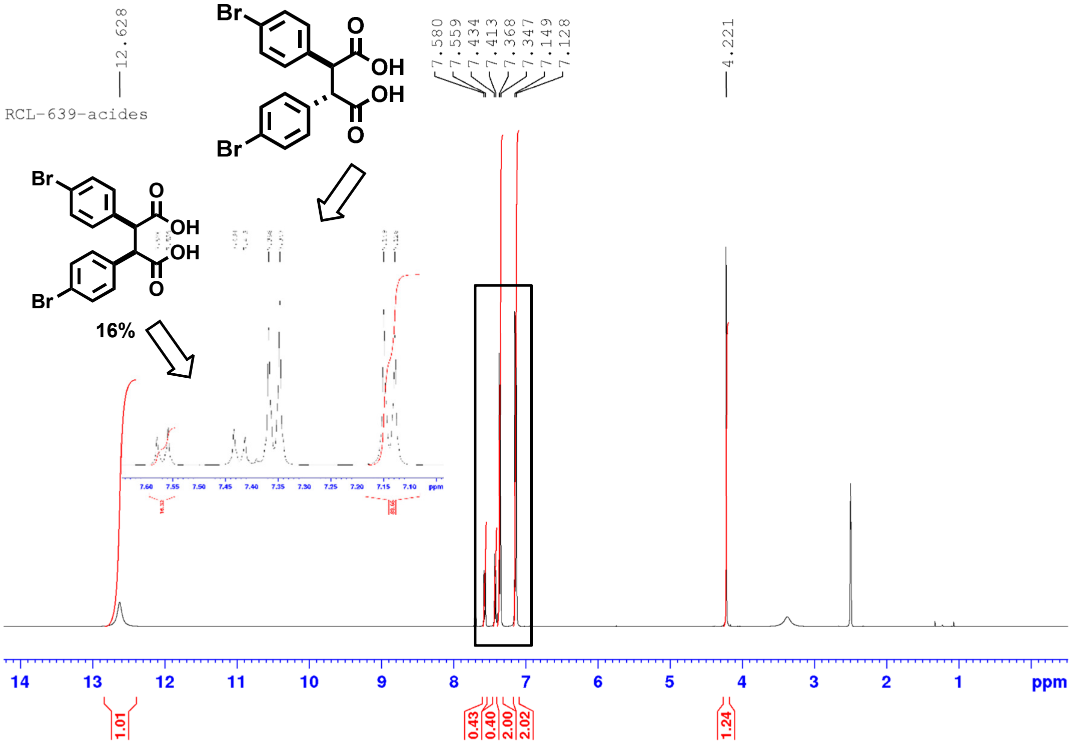


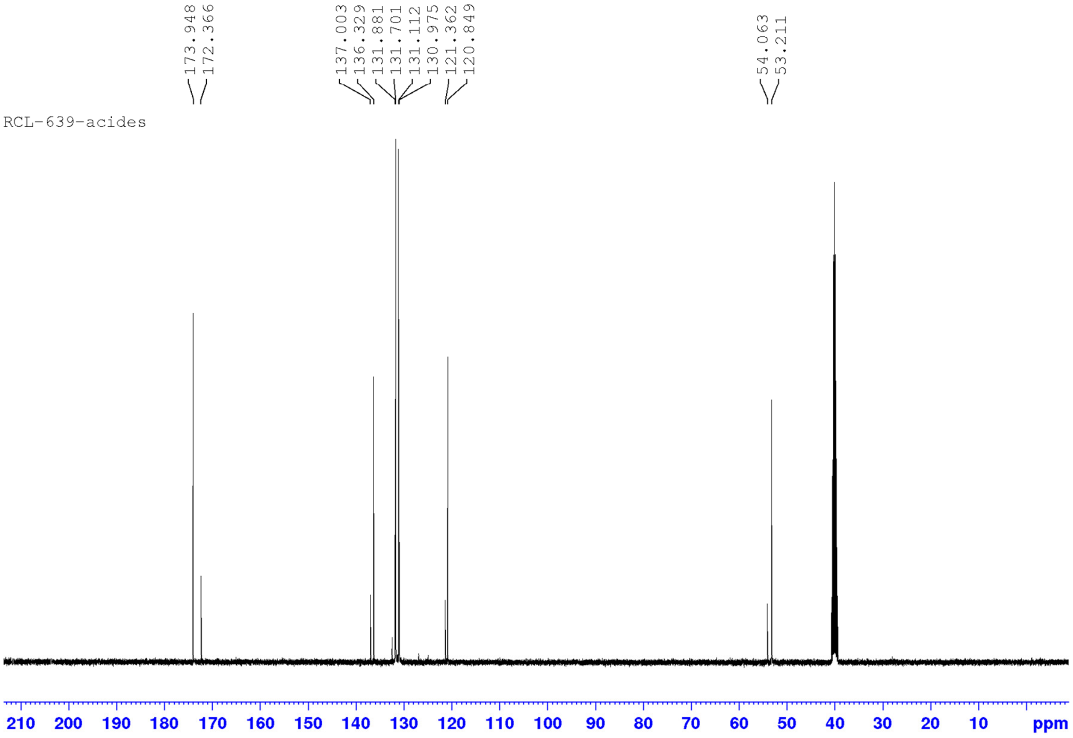
## Diethyl 2,3-bis(4-bromophenyl)succinate (S8)



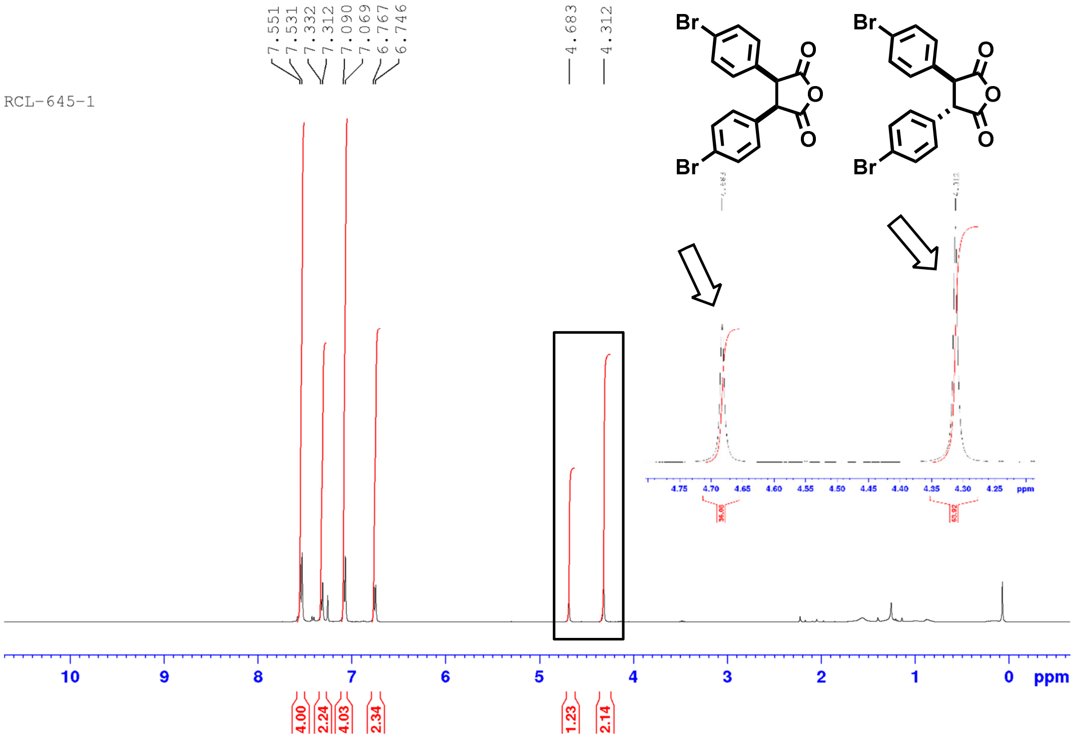


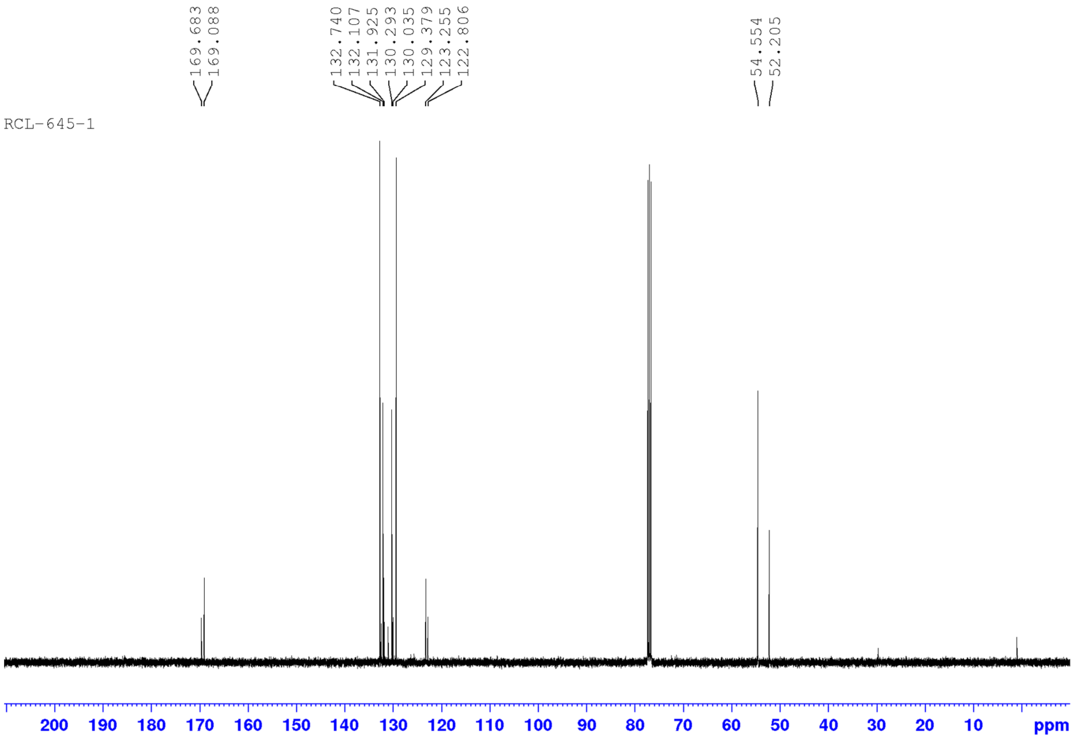
## 2,3-bis(4-bromophenyl)succinic acid (S9)



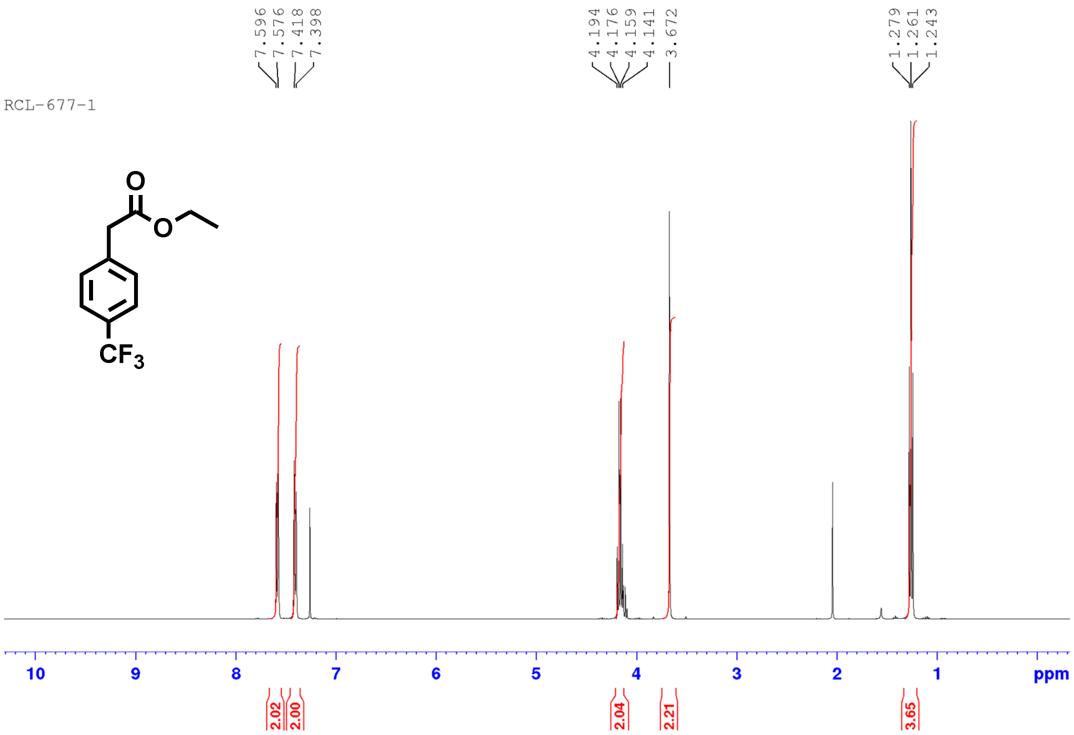


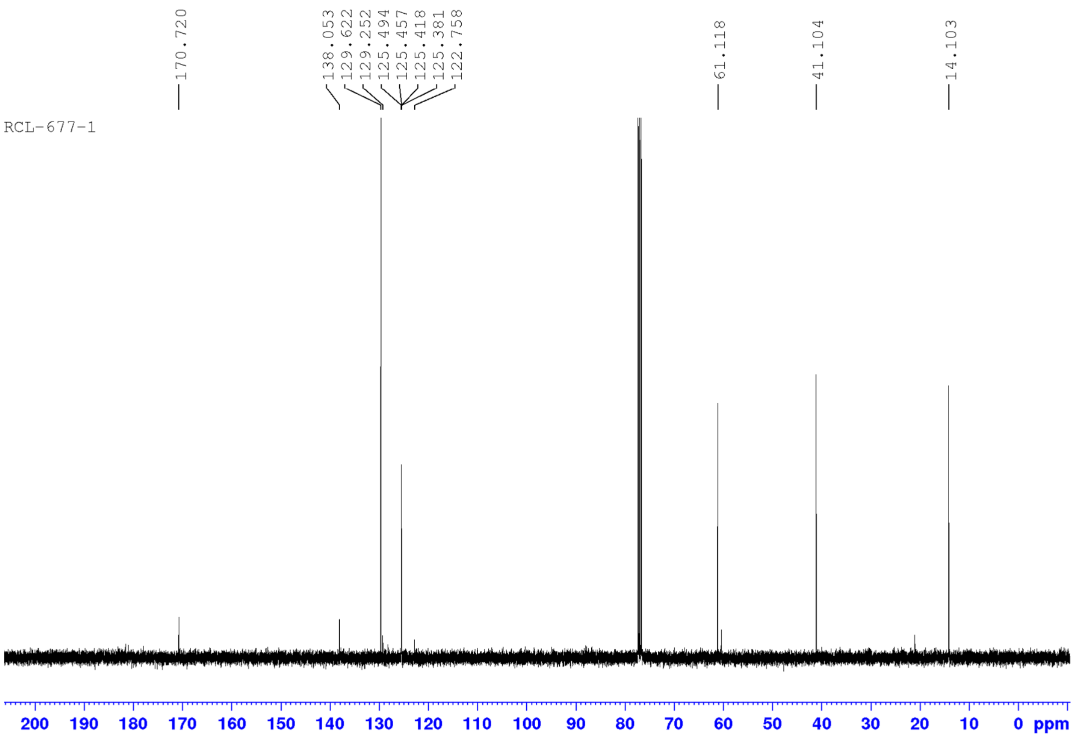
## 3,4-bis(4-bromophenyl)dihydrofuran-2,5-dione (43)



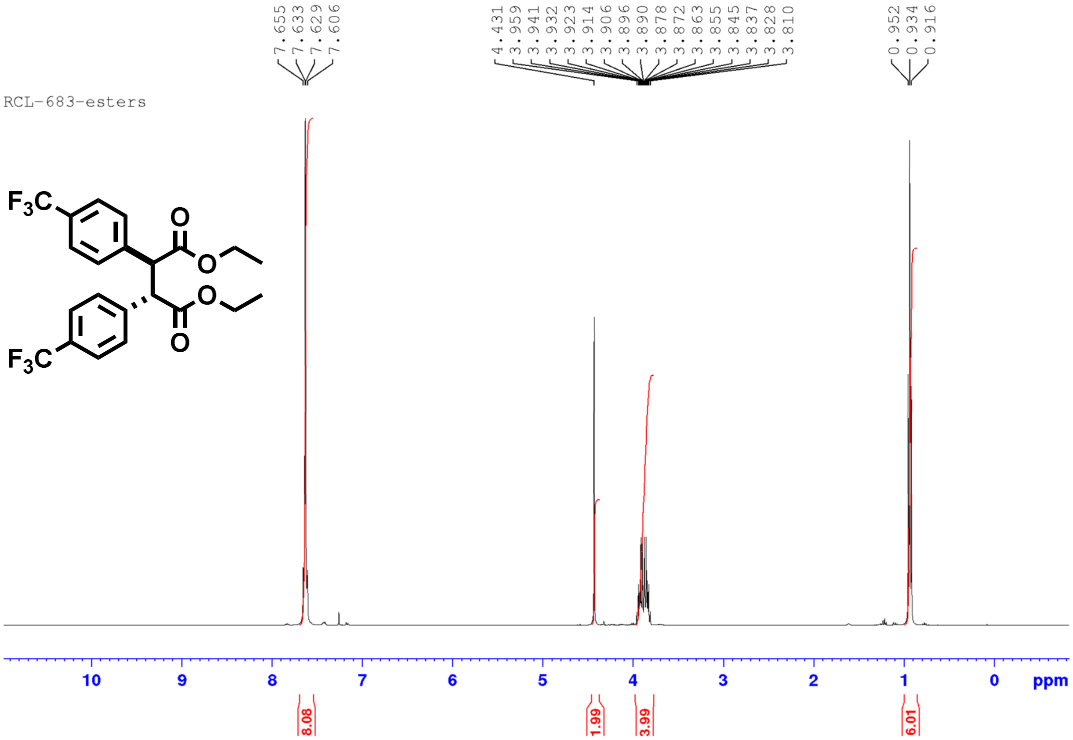


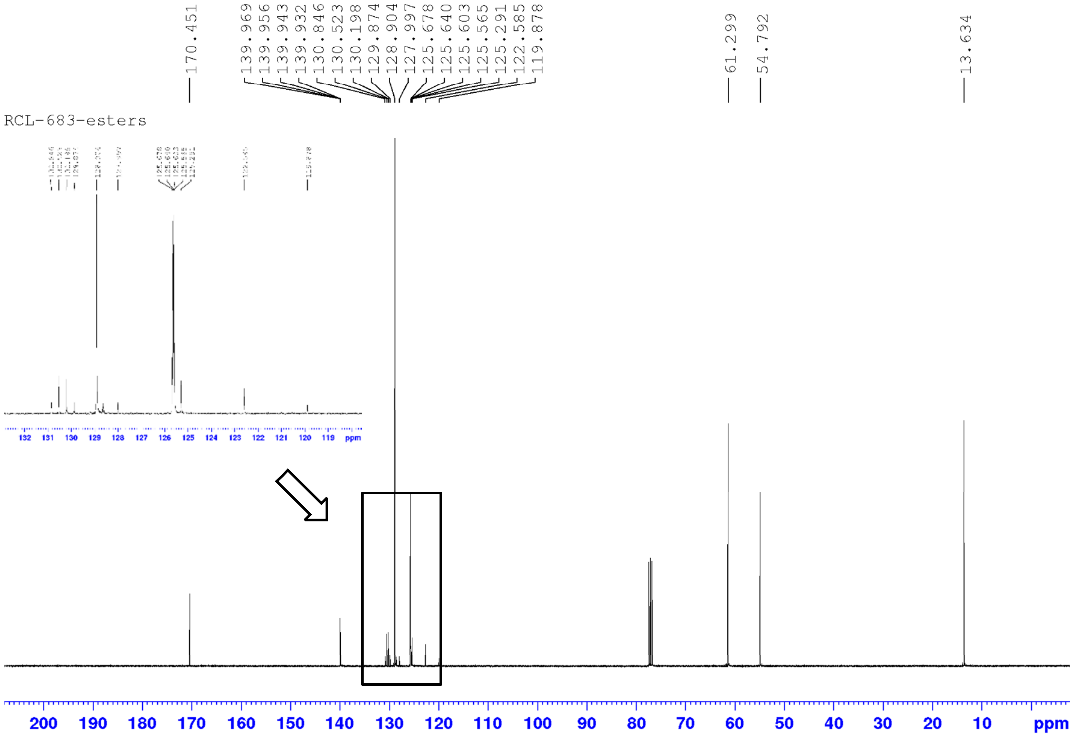
## Ethyl 2-(4-(trifluoromethyl)phenyl)acetate (S12)



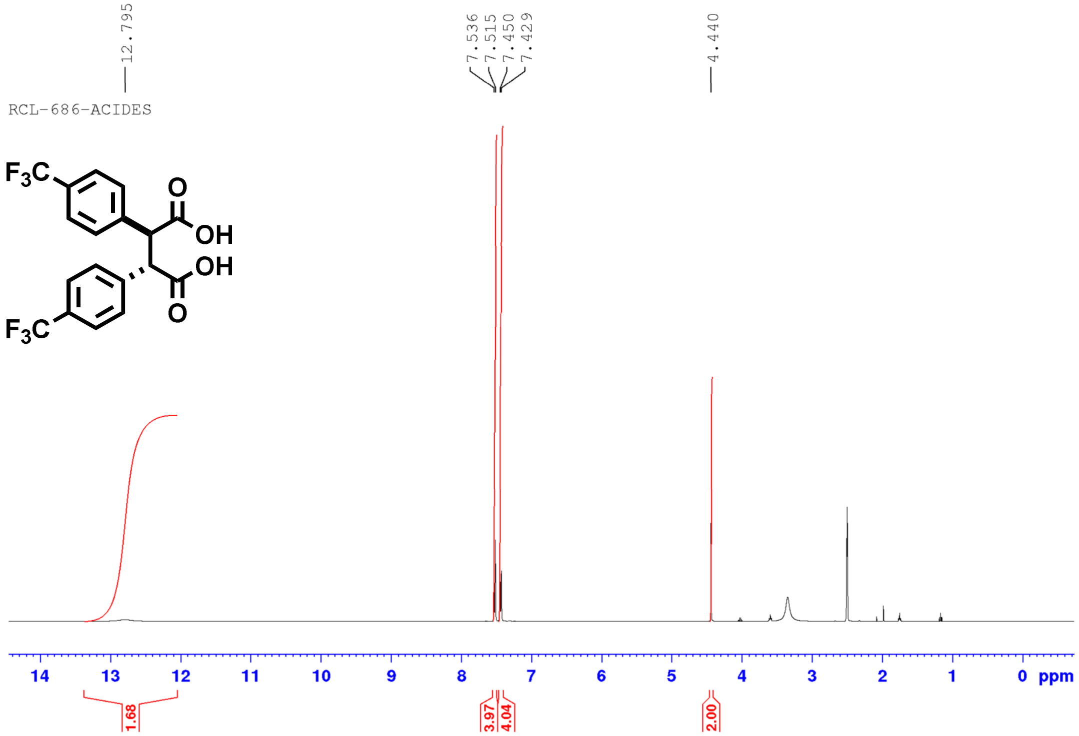


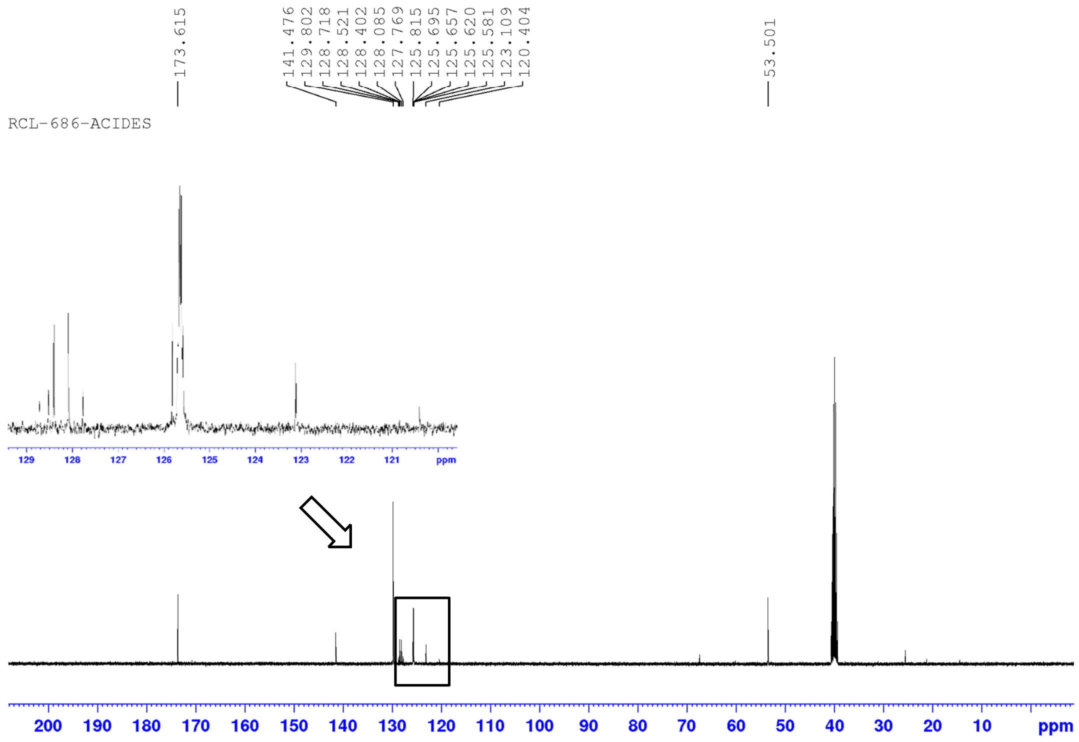
## Diethyl 2,3-bis(4-(trifluoromethyl)phenyl)succinate (S13)



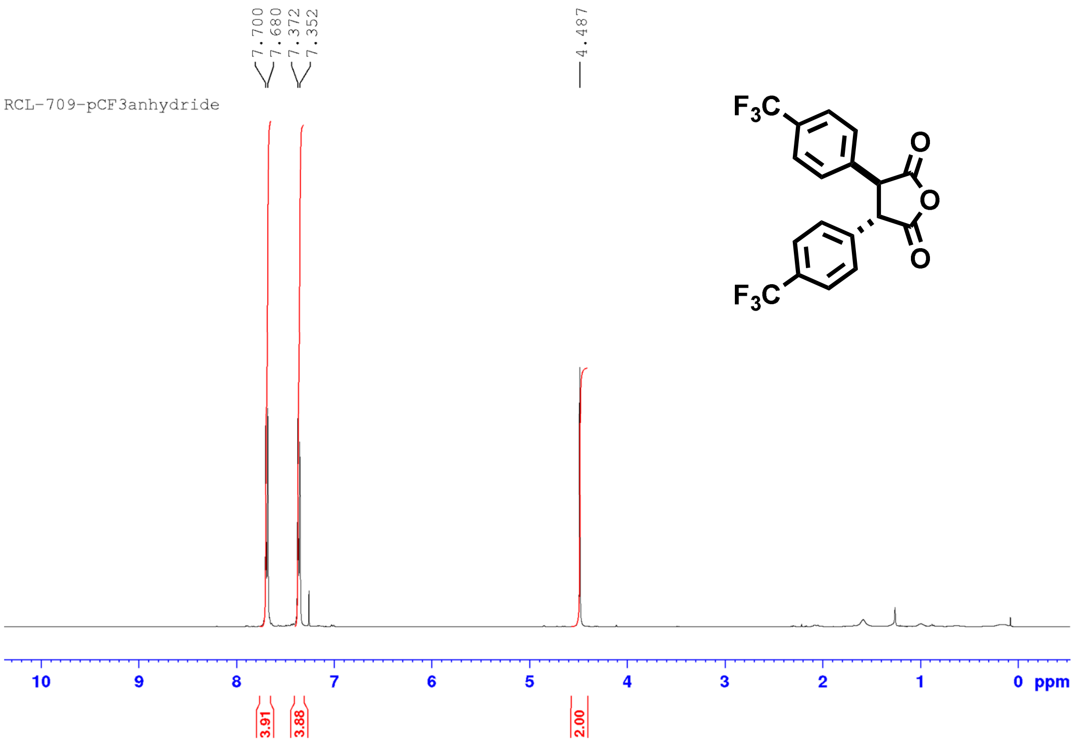


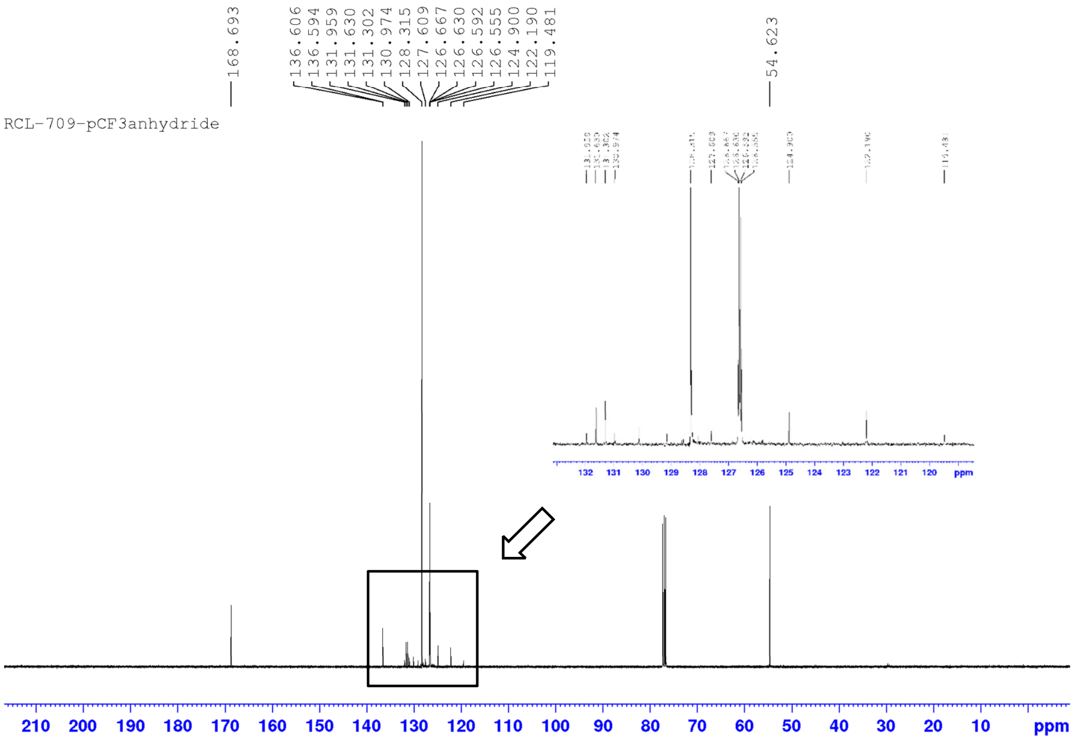
## 2,3-bis(4-(trifluoromethyl)phenyl)succinic acid (S14)



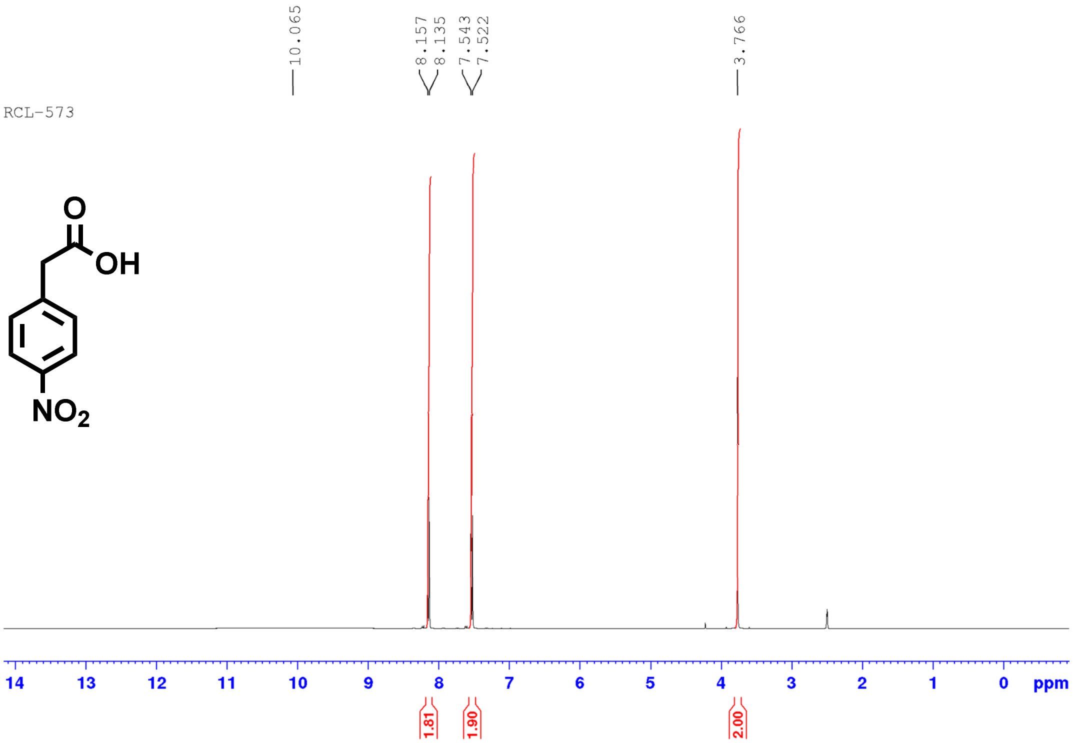


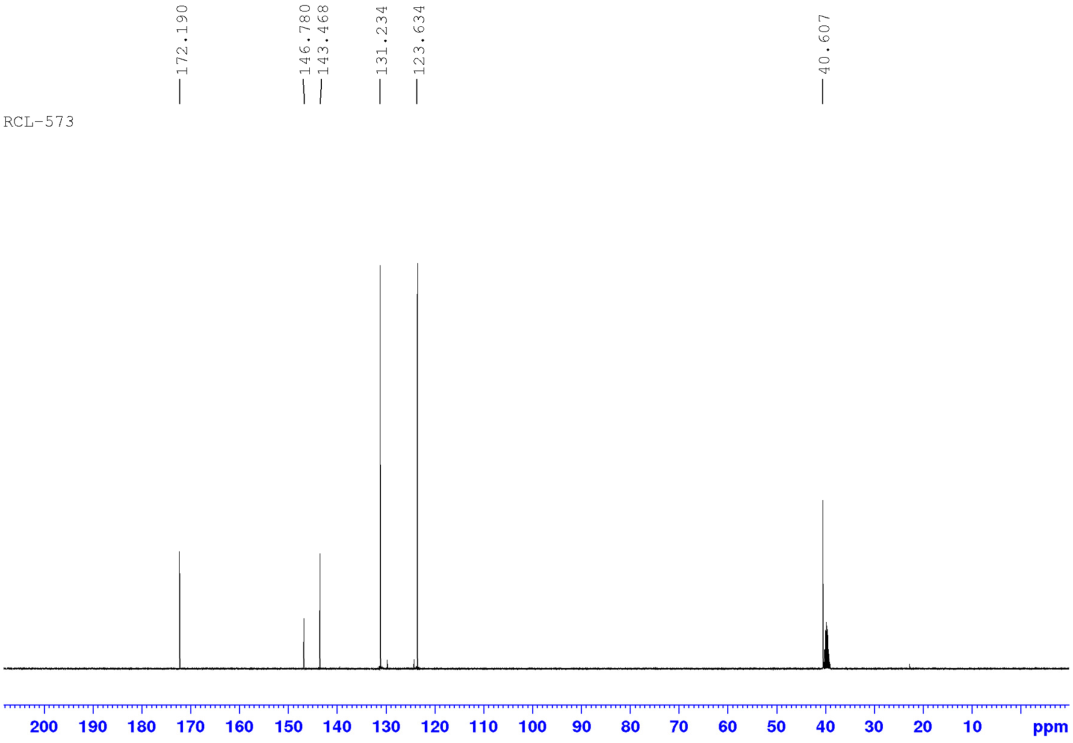
## 3,4-bis(4-(trifluoromethyl)phenyl)dihydrofuran-2,5-dione (44)



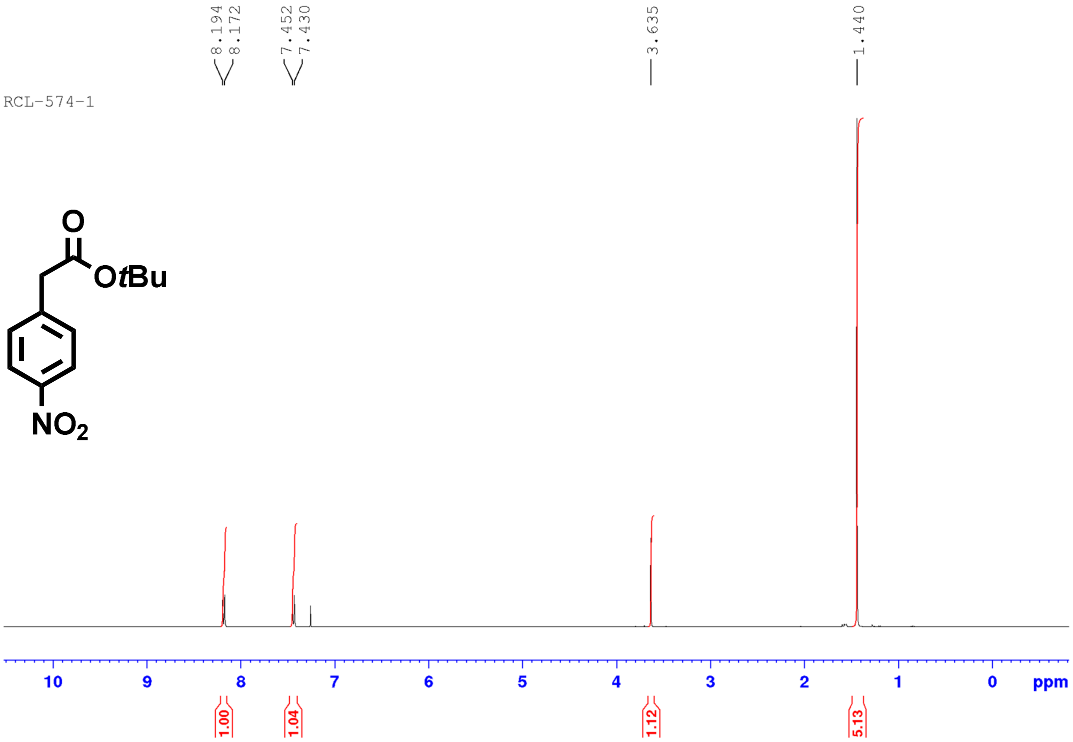


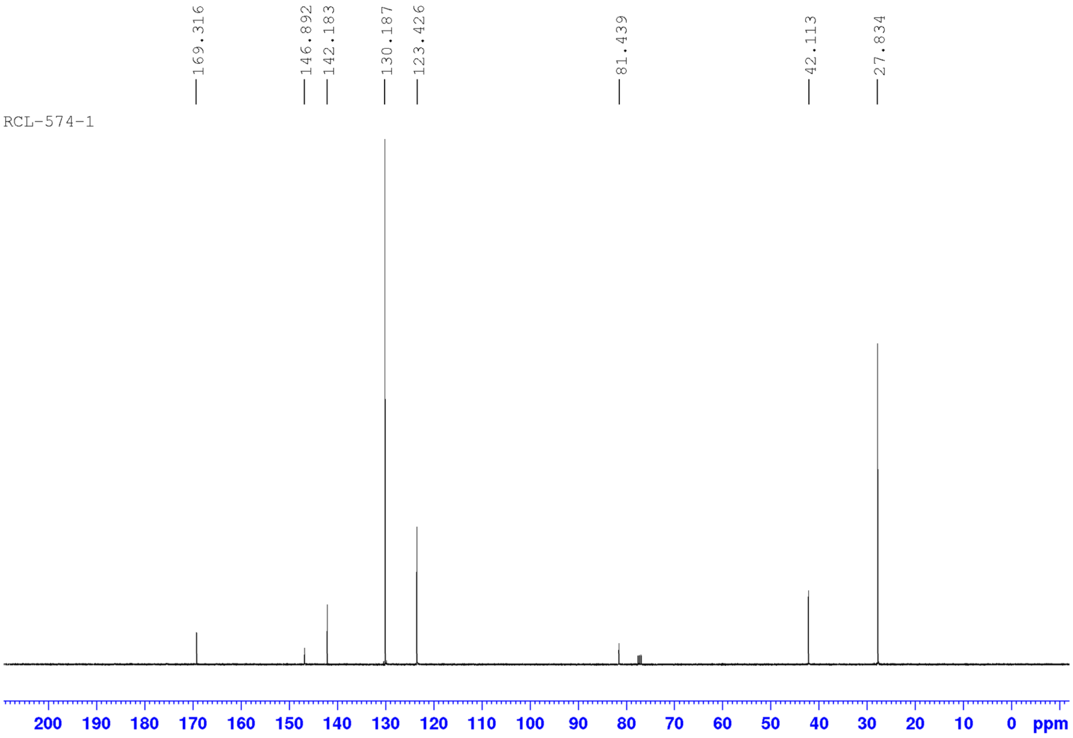
## 2-(4-nitrophenyl)acetic acid (S16)



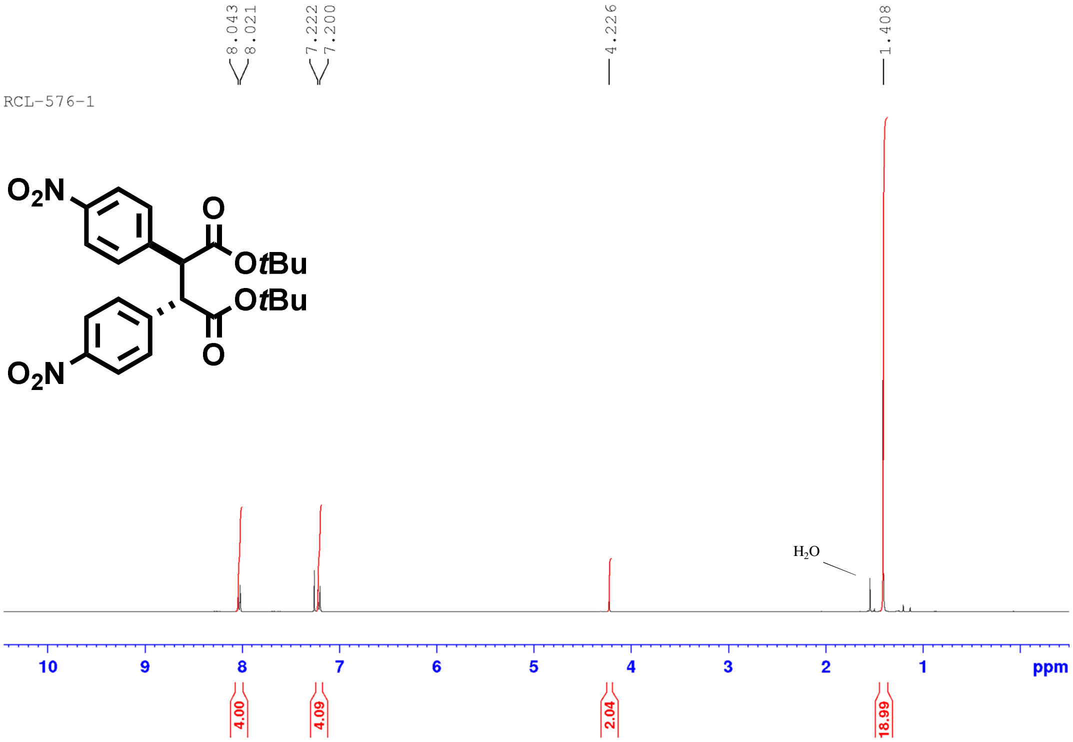


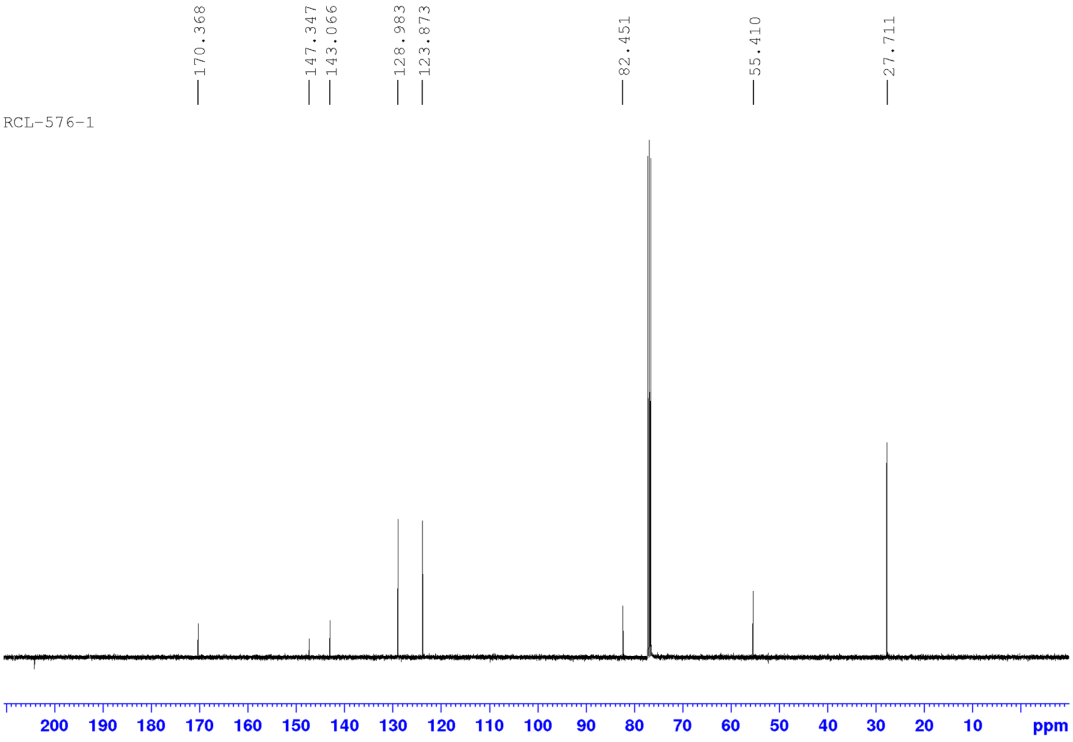
## *tert*-butyl 2-(4-nitrophenyl)acetate (S17)



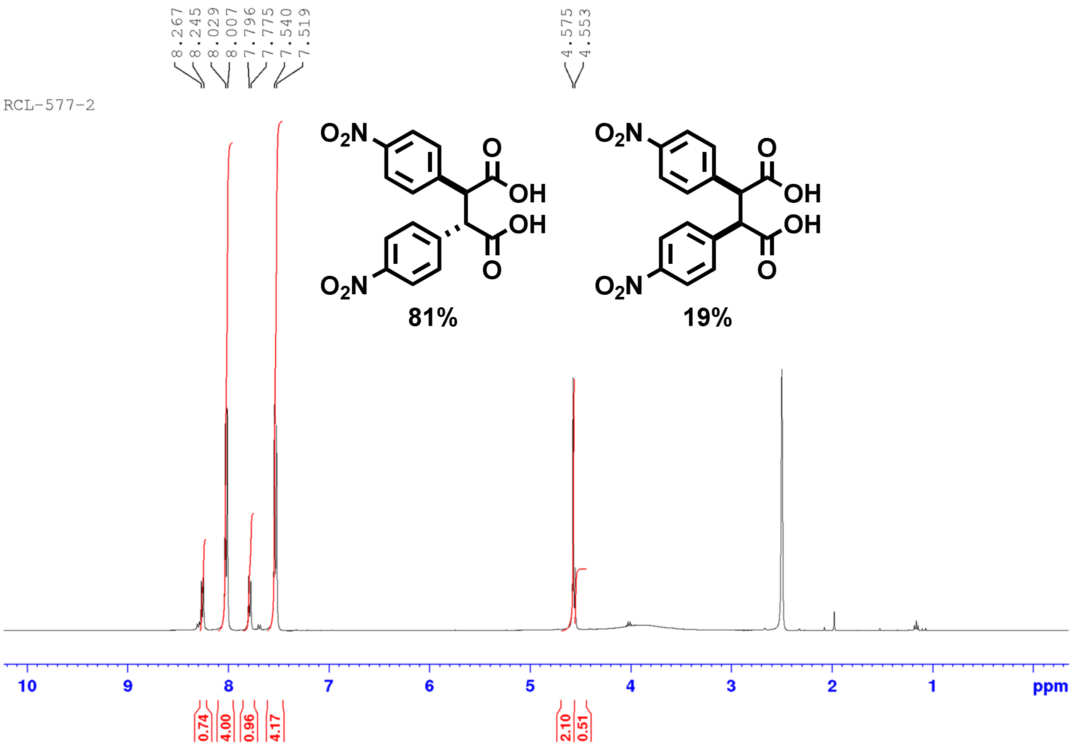


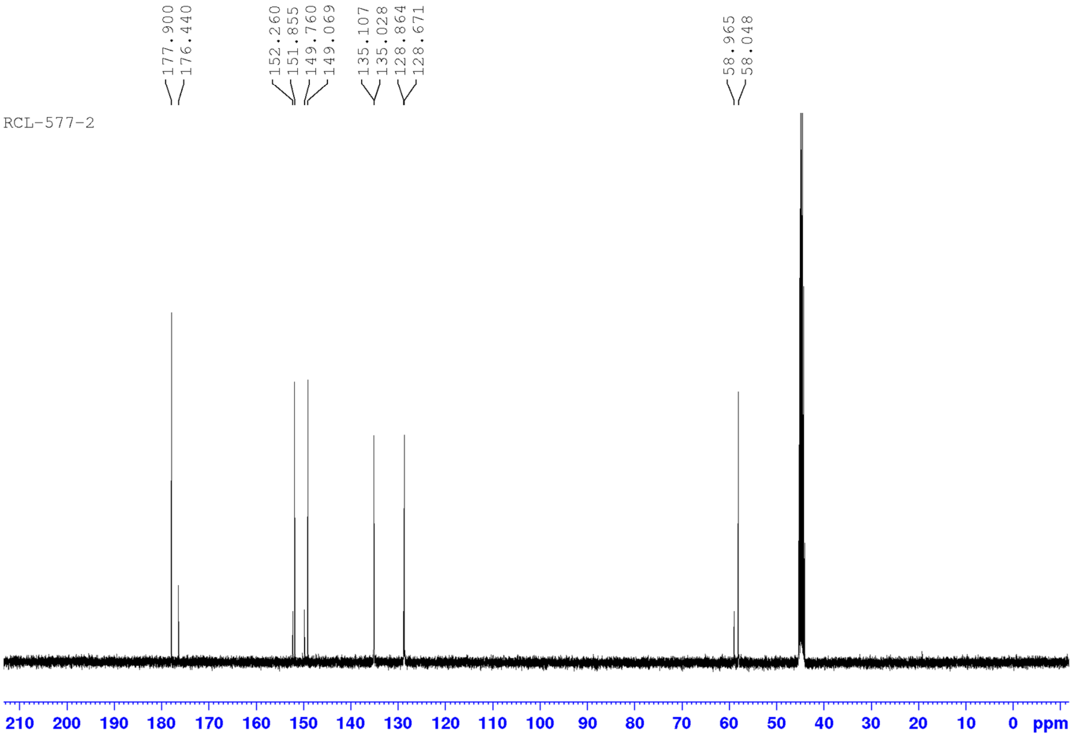
## di-*tert*-butyl 2,3-bis(4-nitrophenyl)succinate (S18)



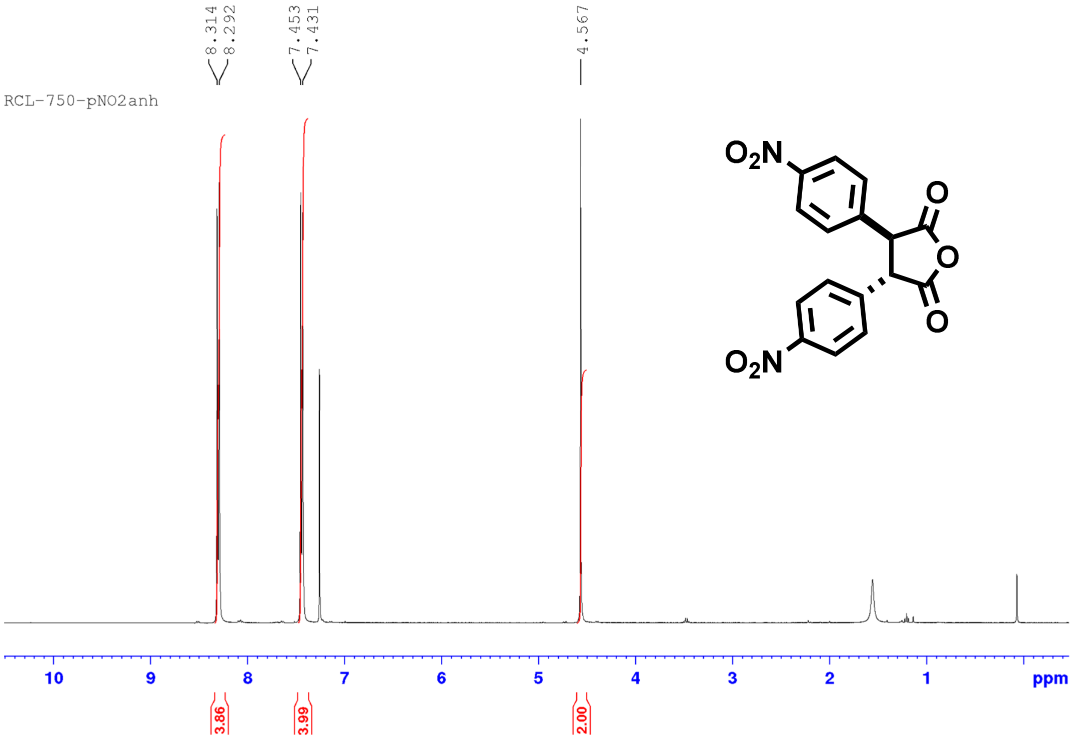


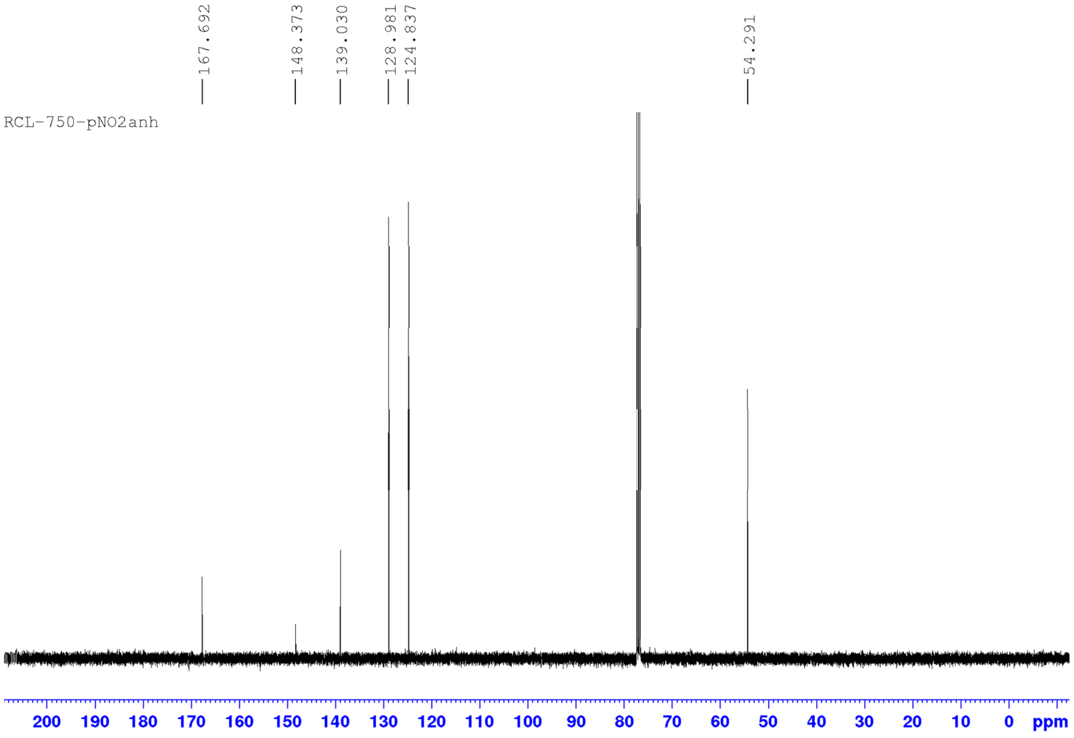
## 2,3-bis(4-nitrophenyl)succinic acid (S19)



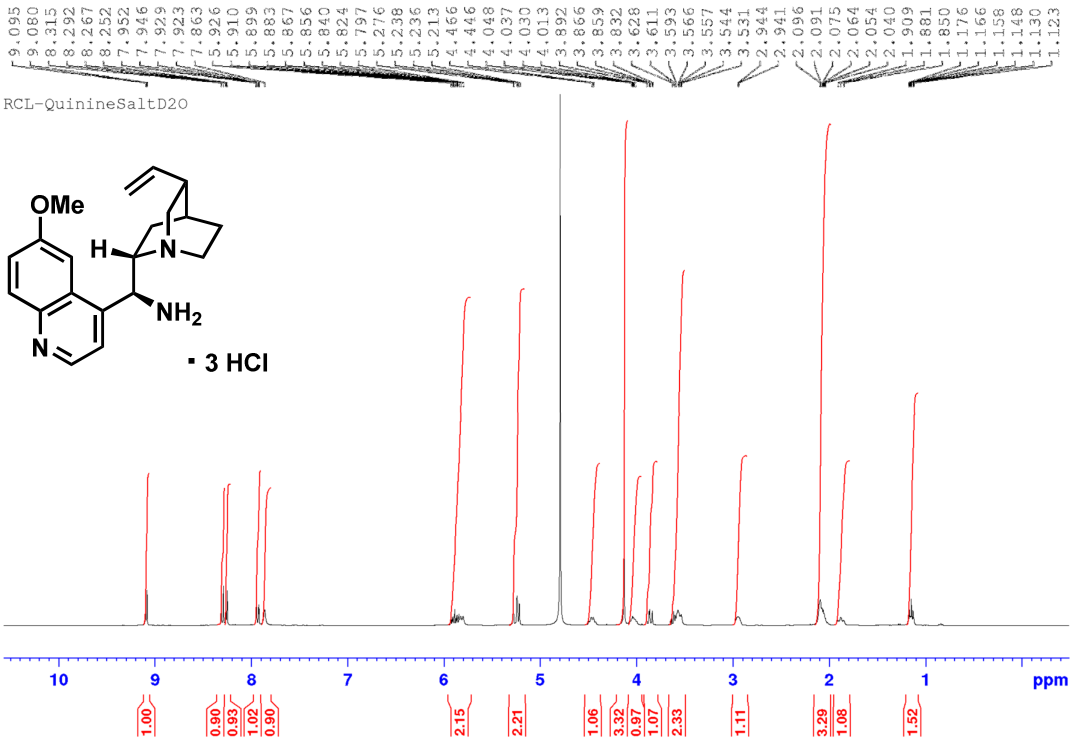


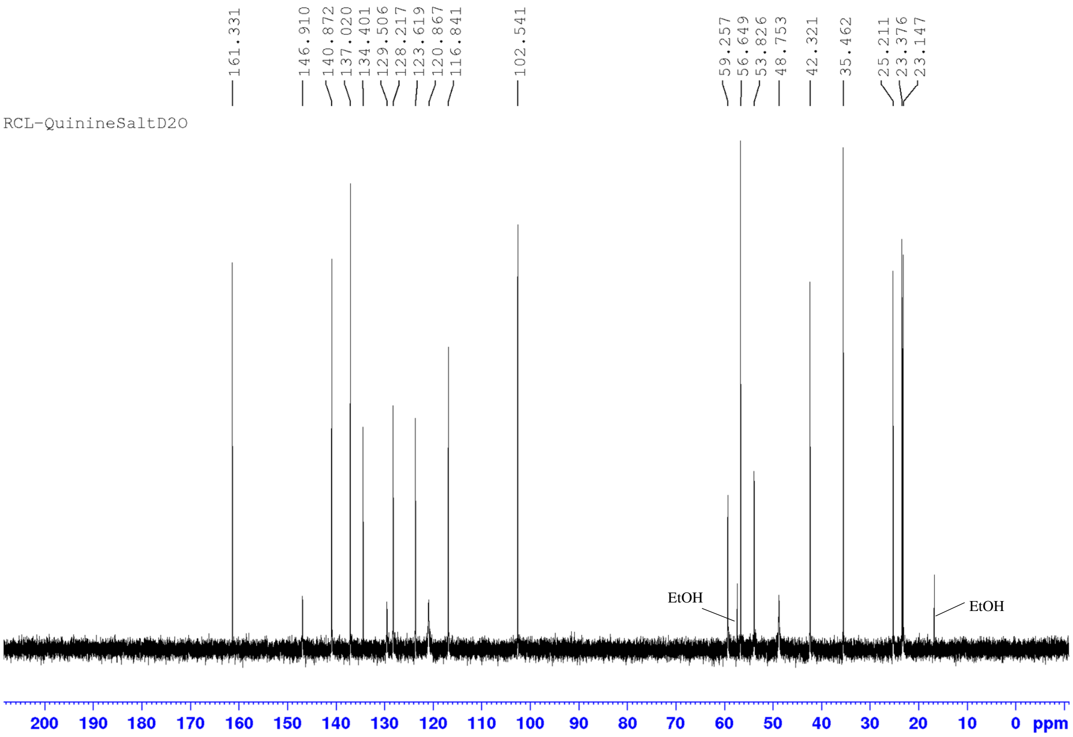
## 3,4-bis(4-nitrophenyl)dihydrofuran-2,5-dione (45)



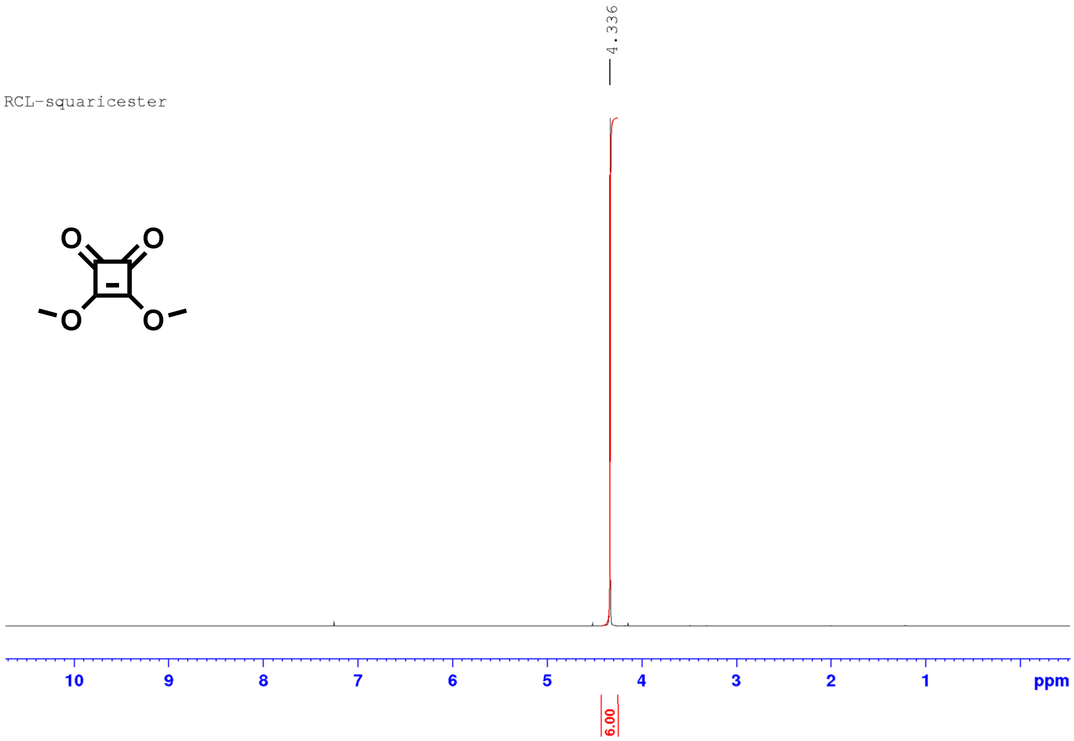


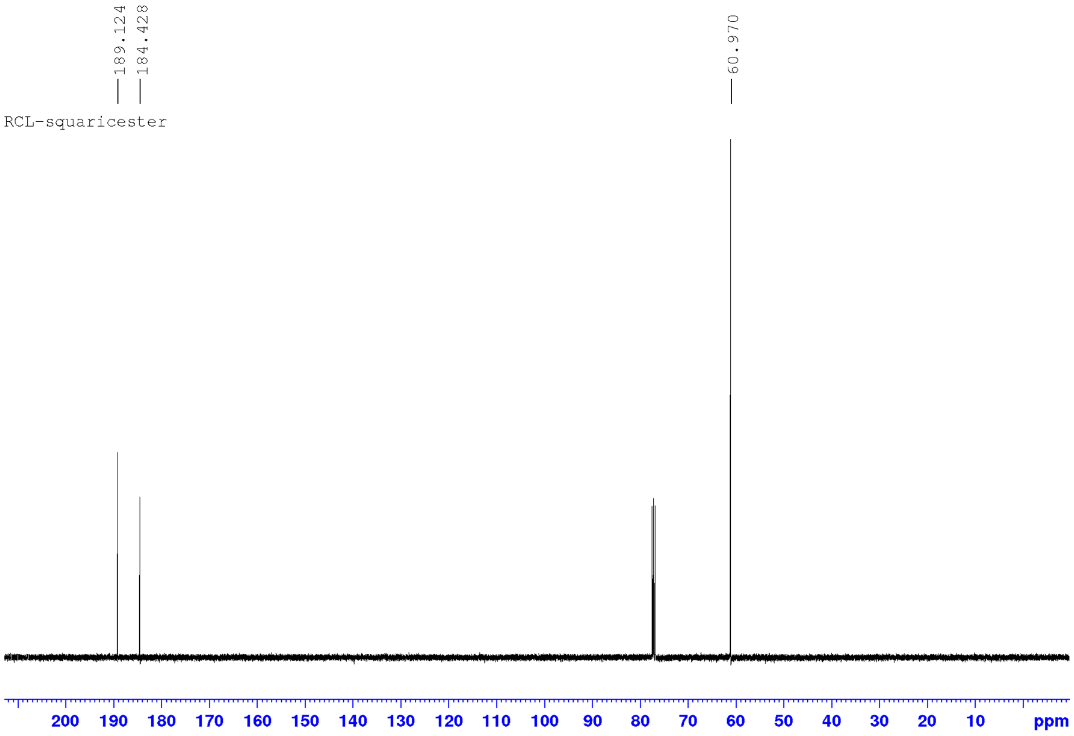
## (*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanamine·3HCl (S32)



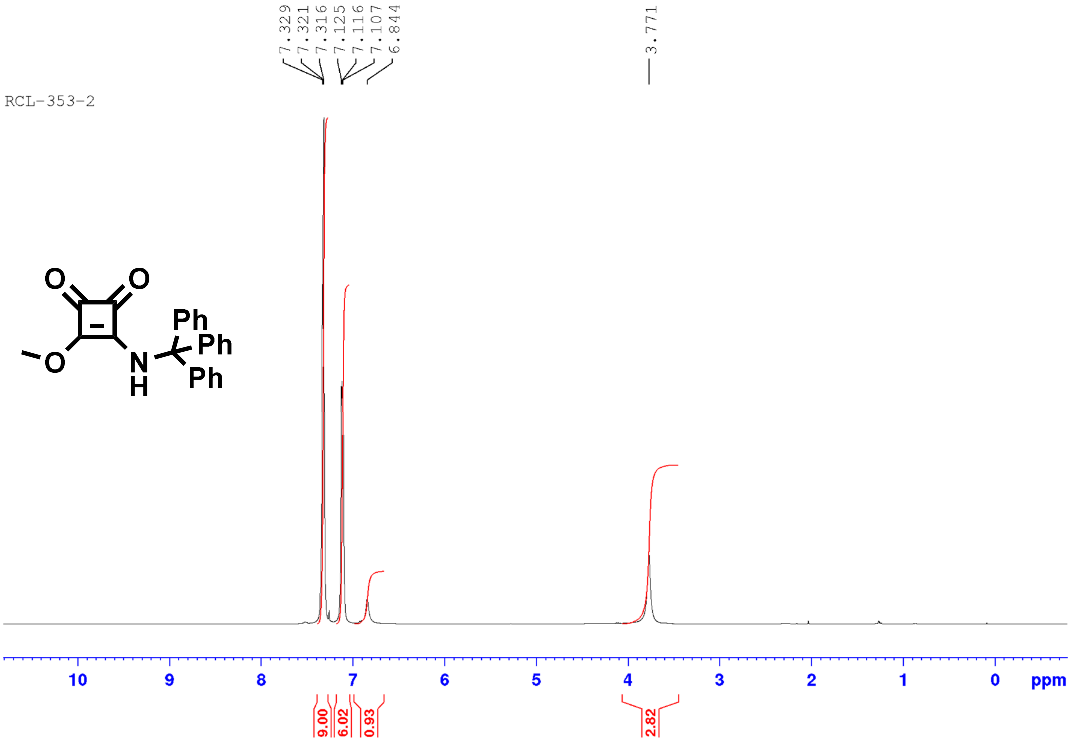


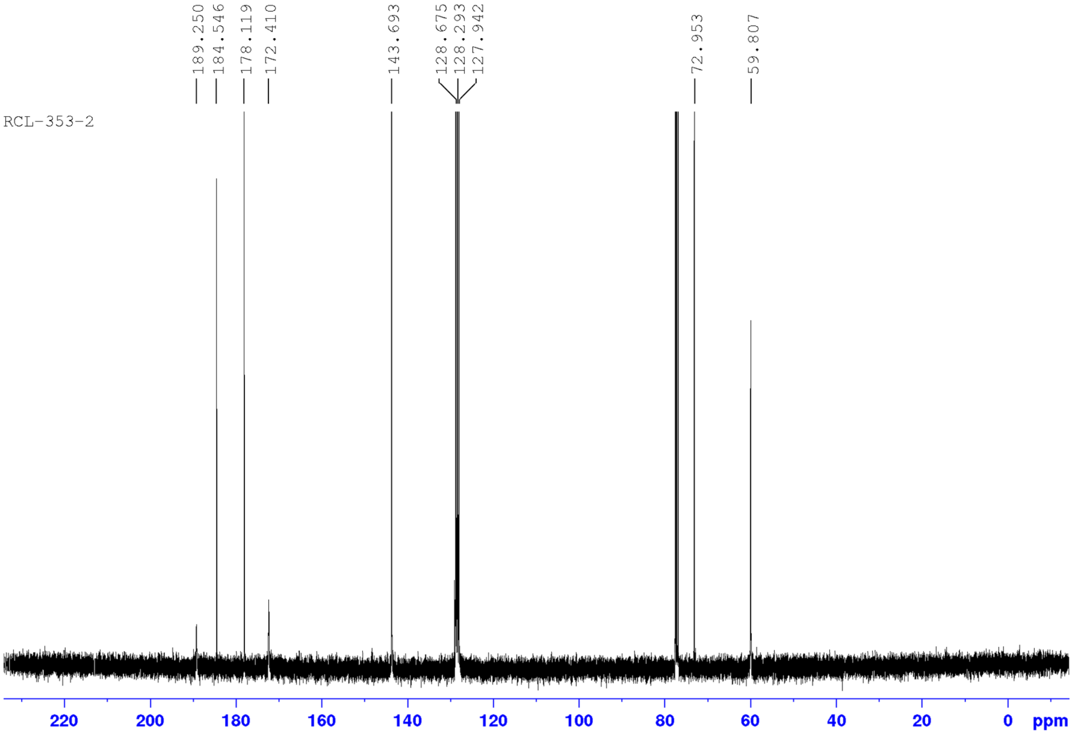
## 3,4-dimethoxycyclobut-3-ene-1,2-dione (S27)



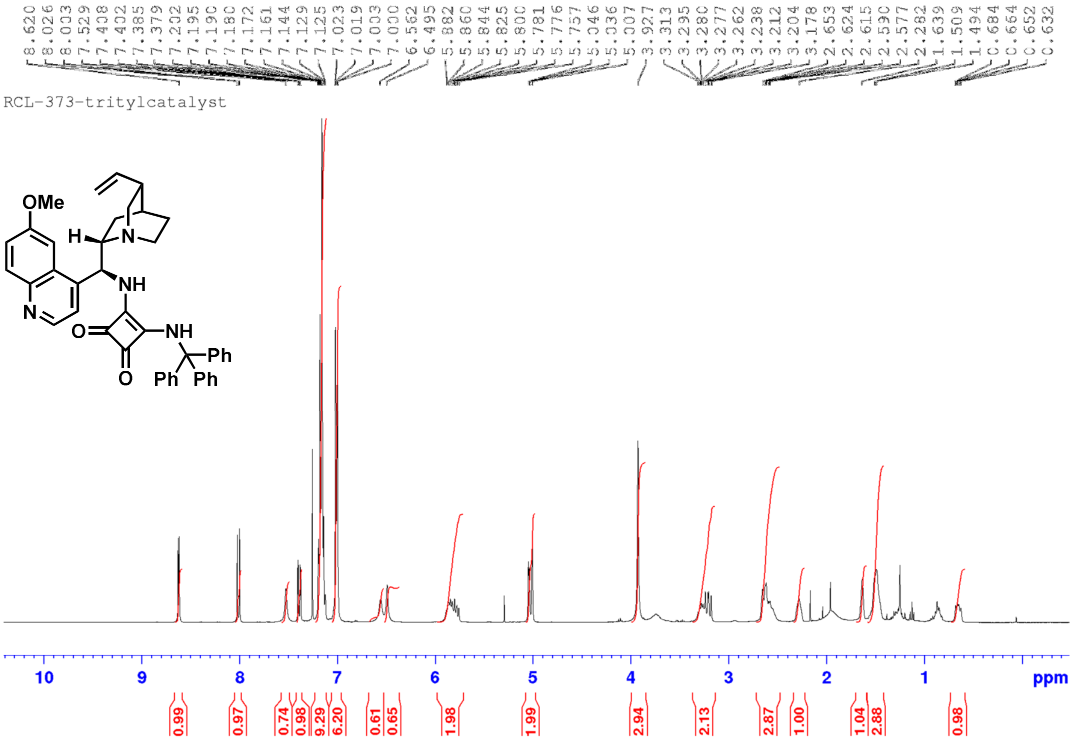


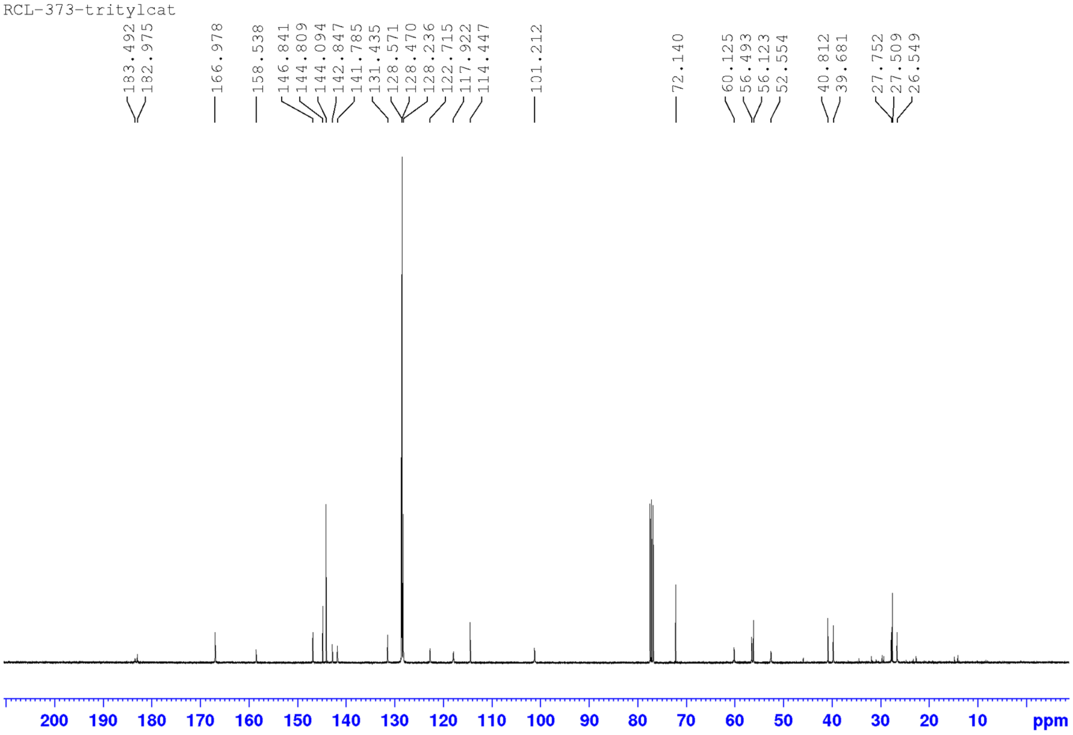
## 3-Methoxy-4-(tritylamino)cyclobut-3-ene-1,2-dione (S30)



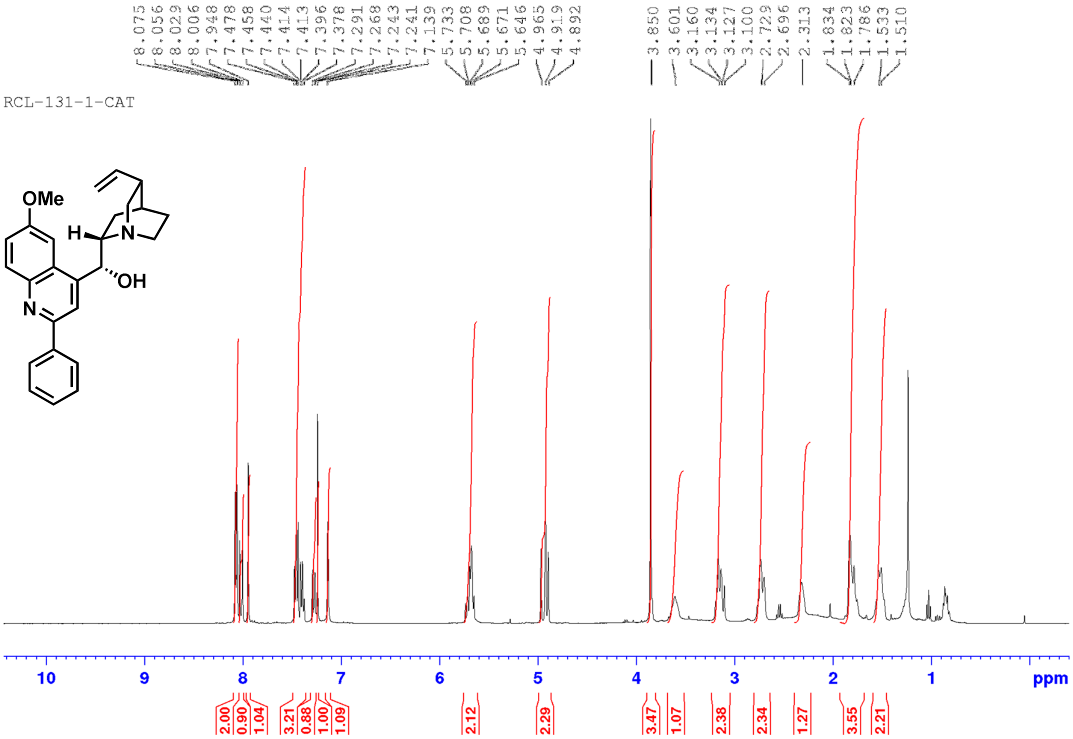


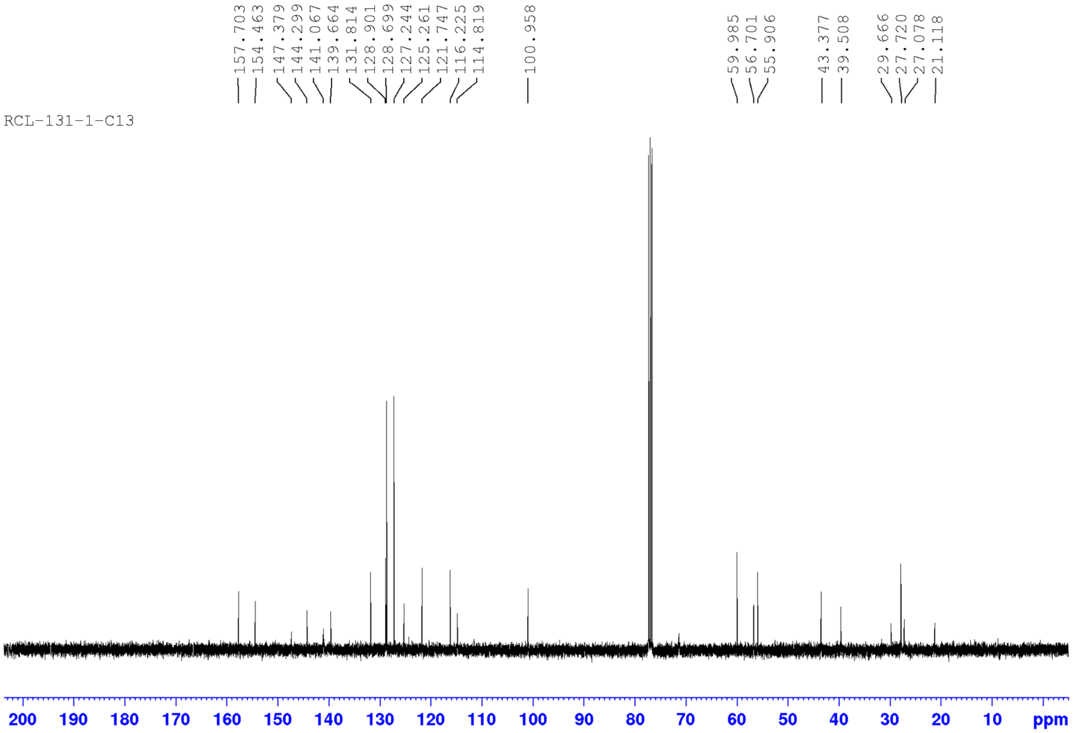
## 3-(((*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-4-(tritylamino)cyclobut-3-ene-1,2-dione (26)



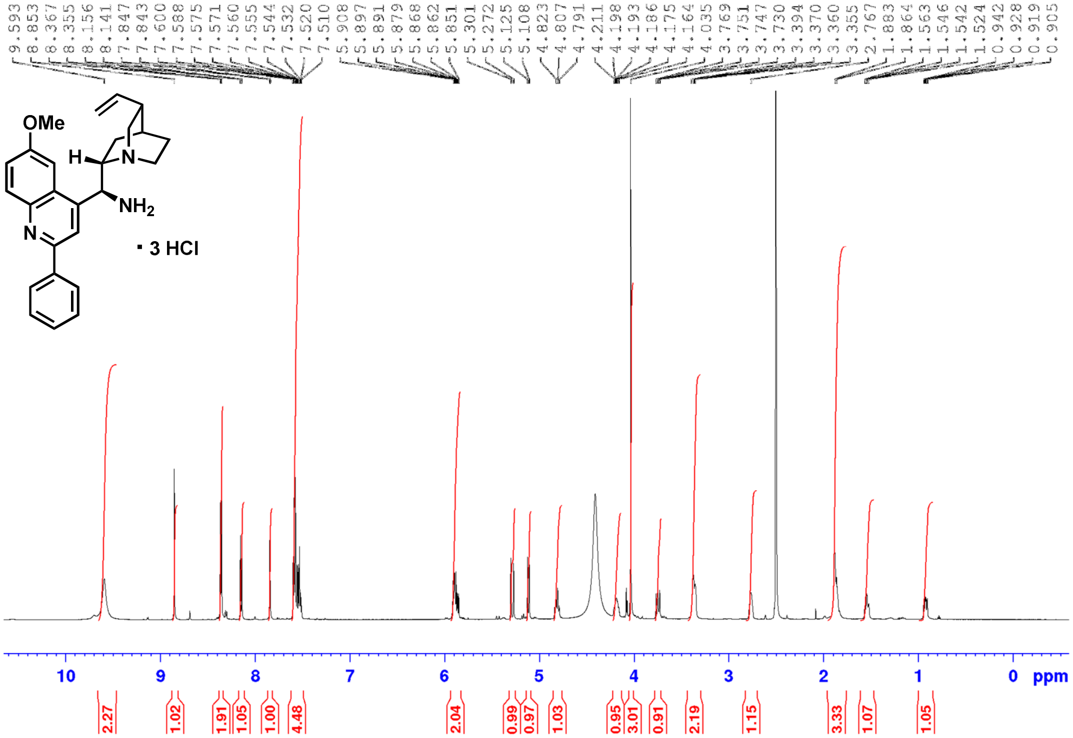


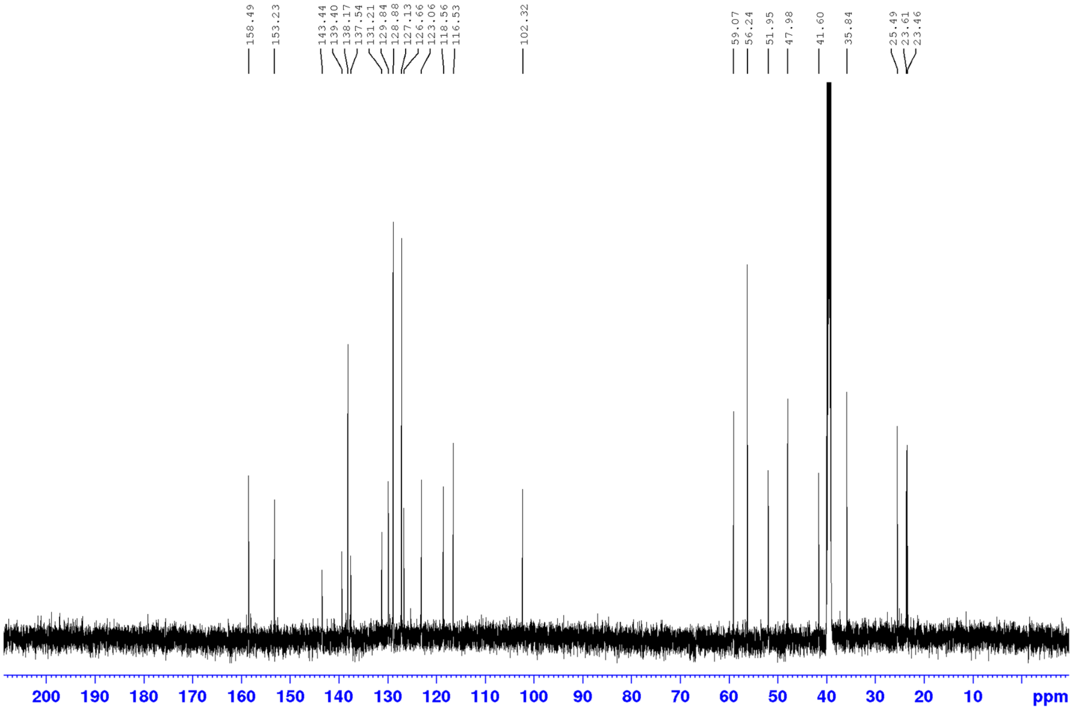
## (*R*)-(6-Methoxy-2-phenylquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanol (S33)



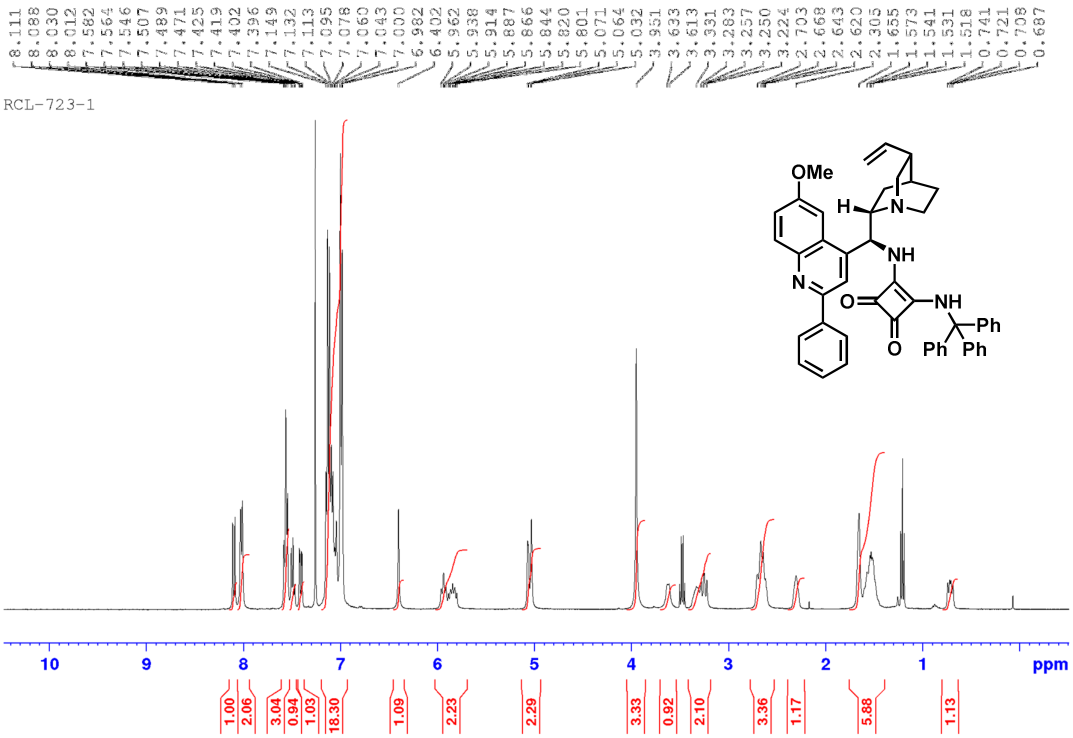


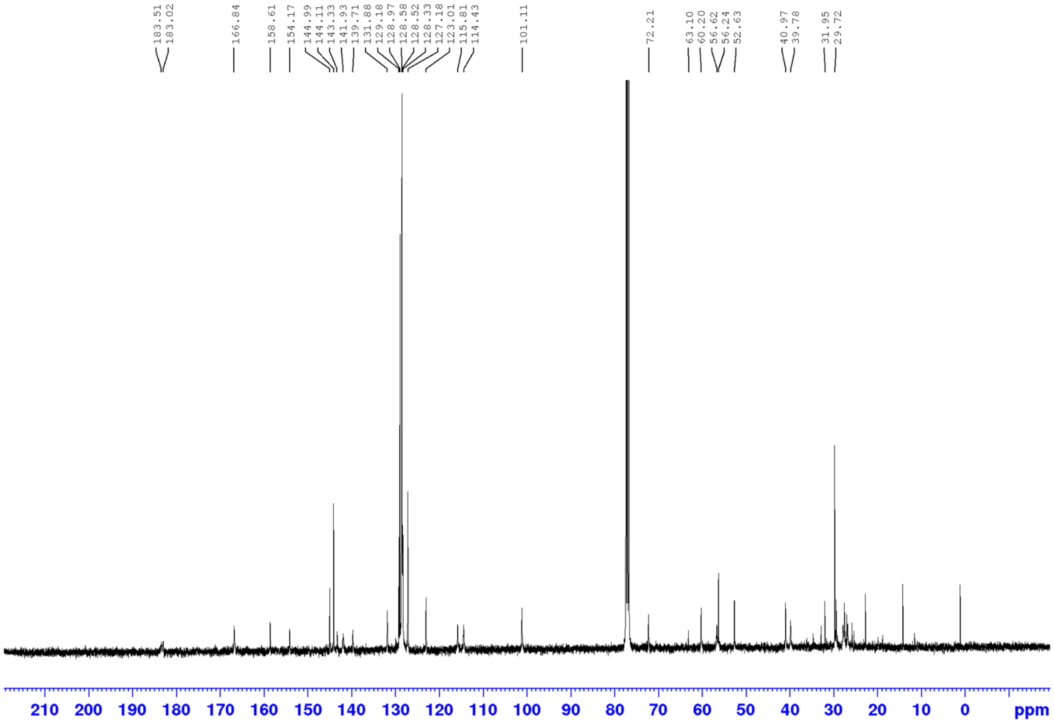
## (S)-(6-methoxy-2-phenylquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methanamine 3HCl (S34)



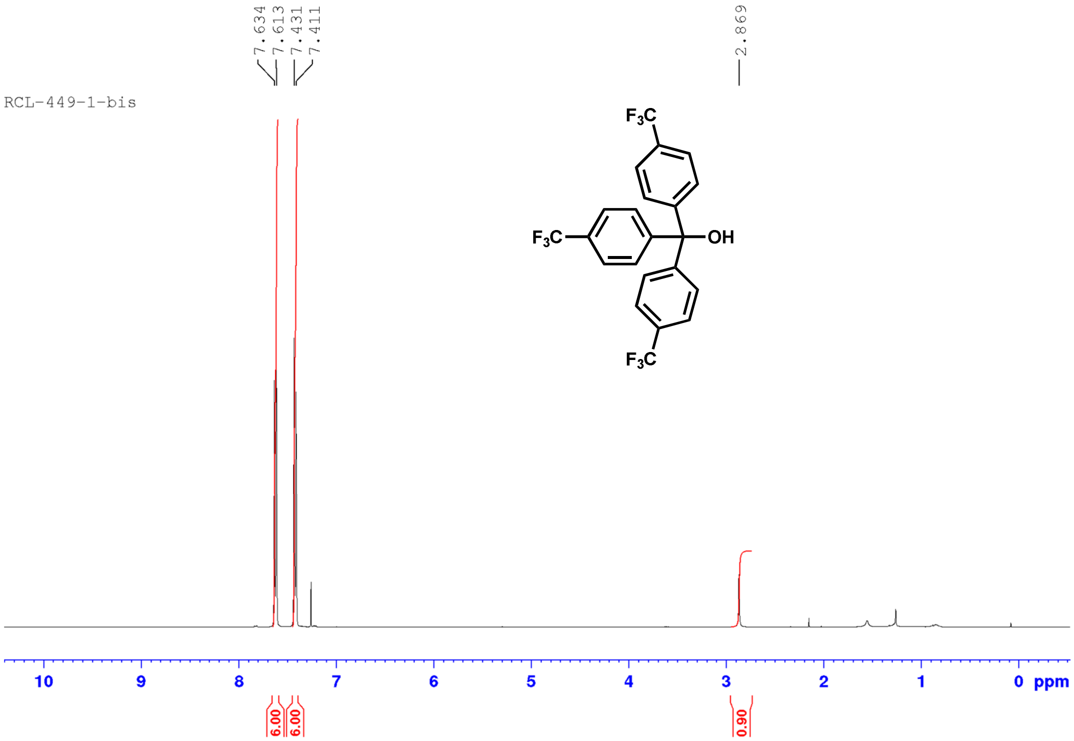


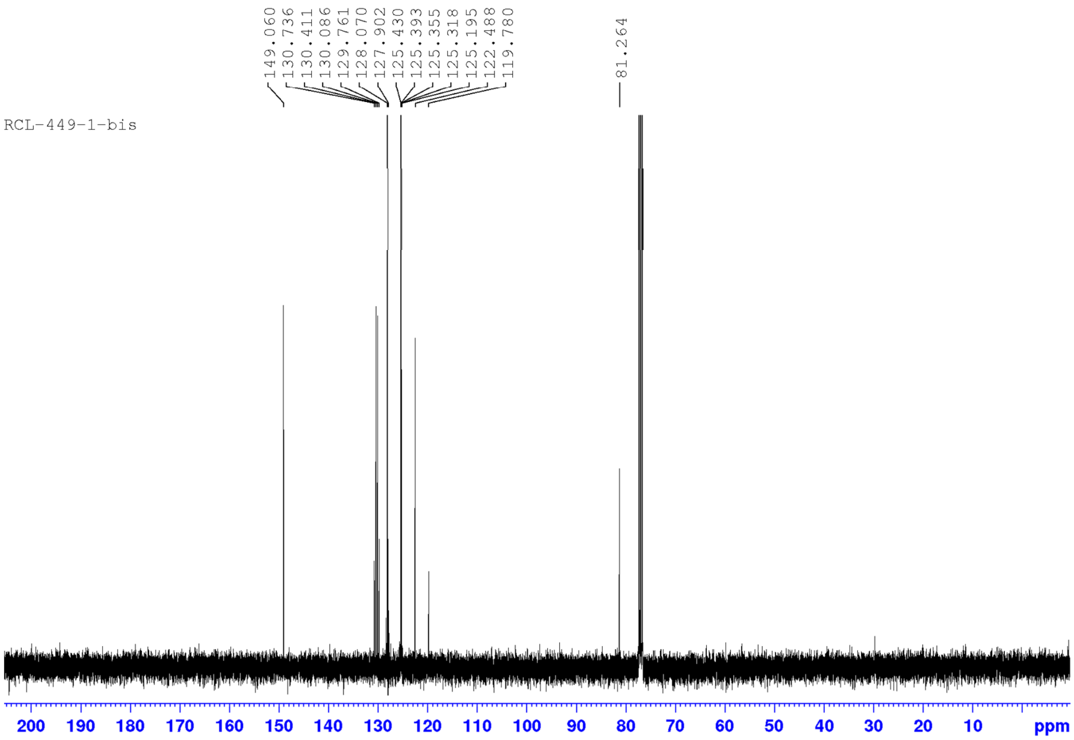
## 3-(((S)-(6-methoxy-2-phenylquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-4-(tritylamino)cyclobut-3-ene-1,2-dione (27)



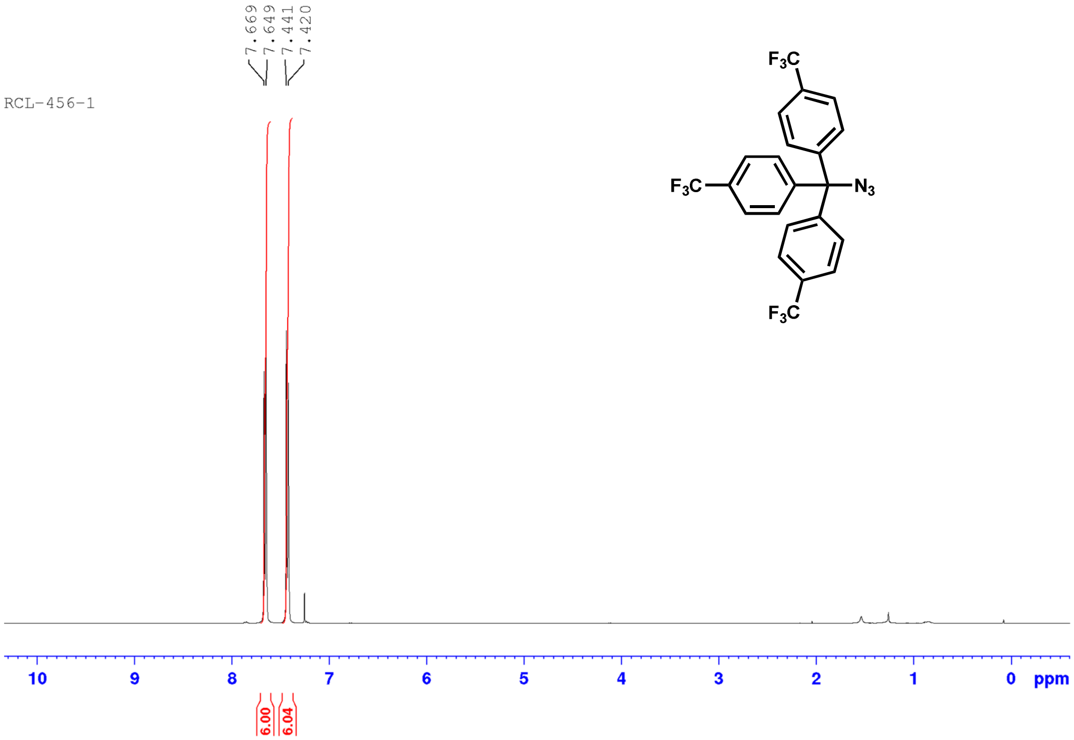


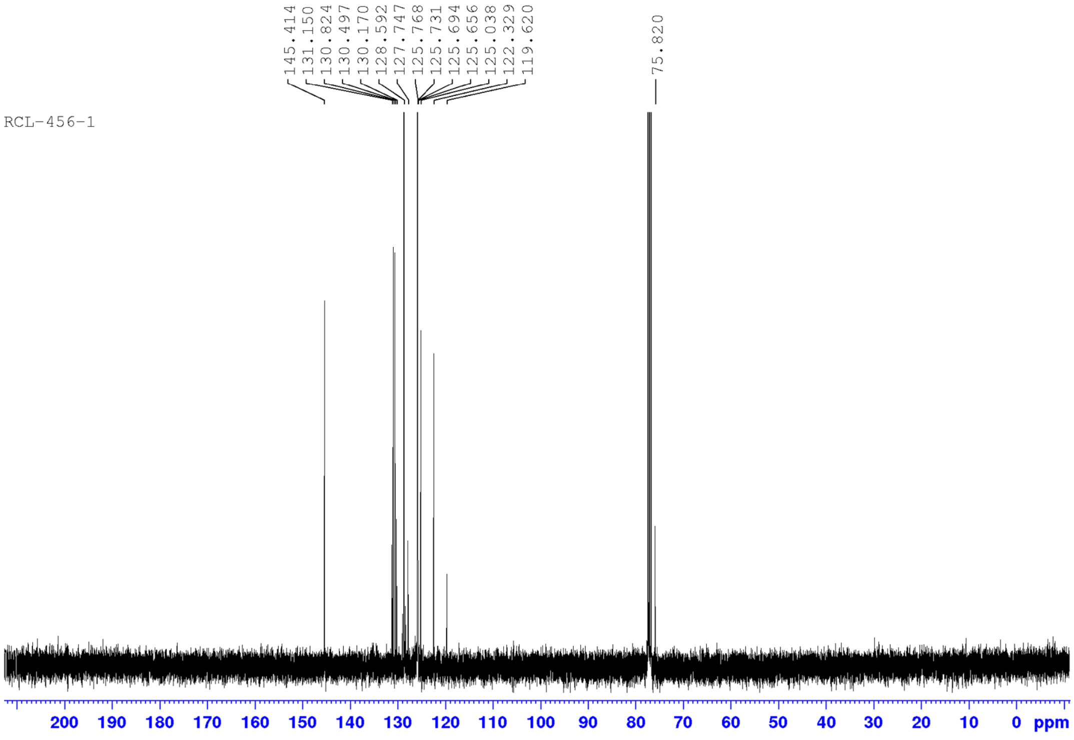
## Tris(4-(trifluoromethyl)phenyl)methanol (S22)



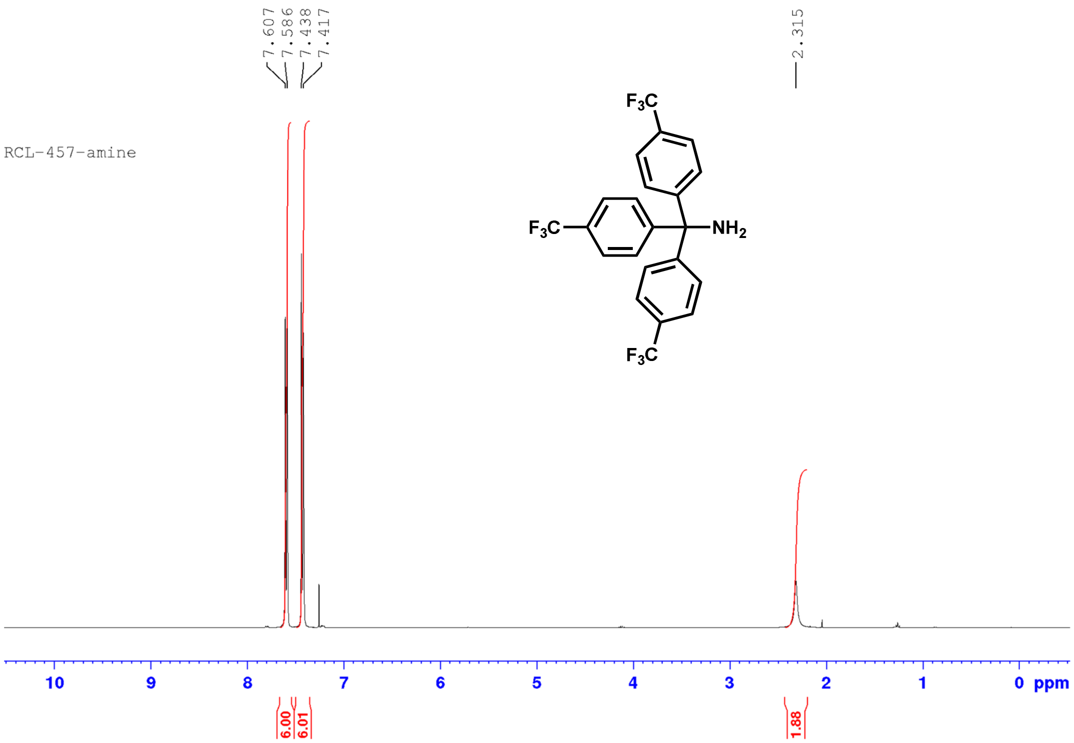


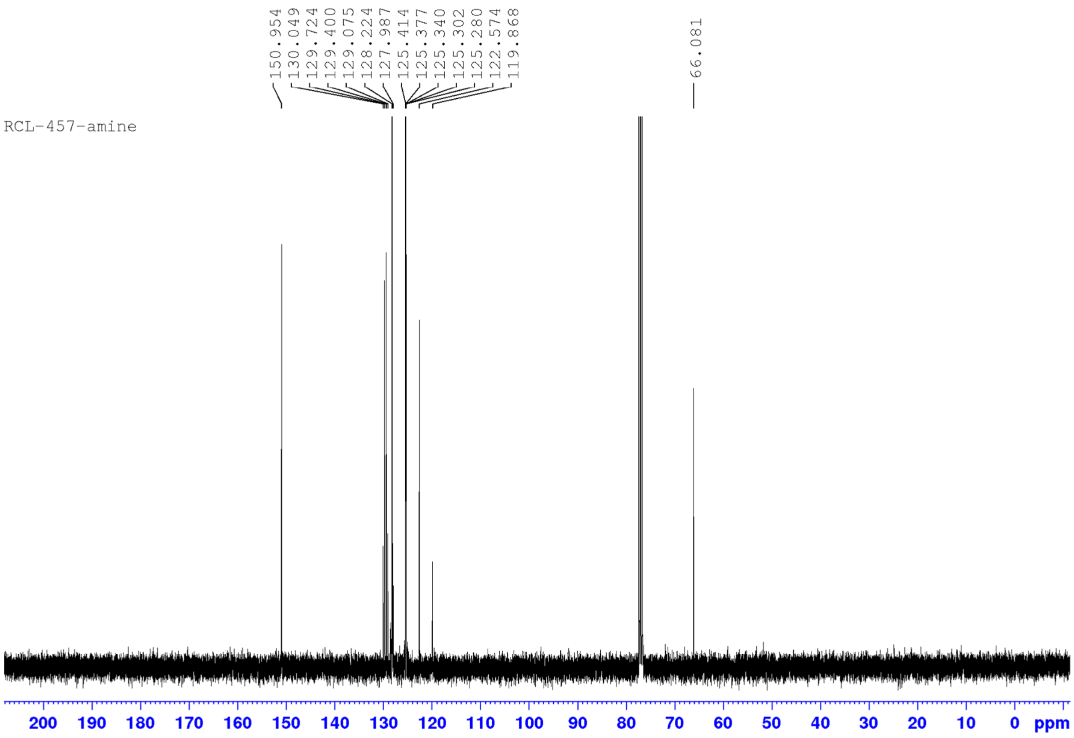
## 4,4',4''-(azidomethanetriyl)tris((trifluoromethyl)benzene) (S23)



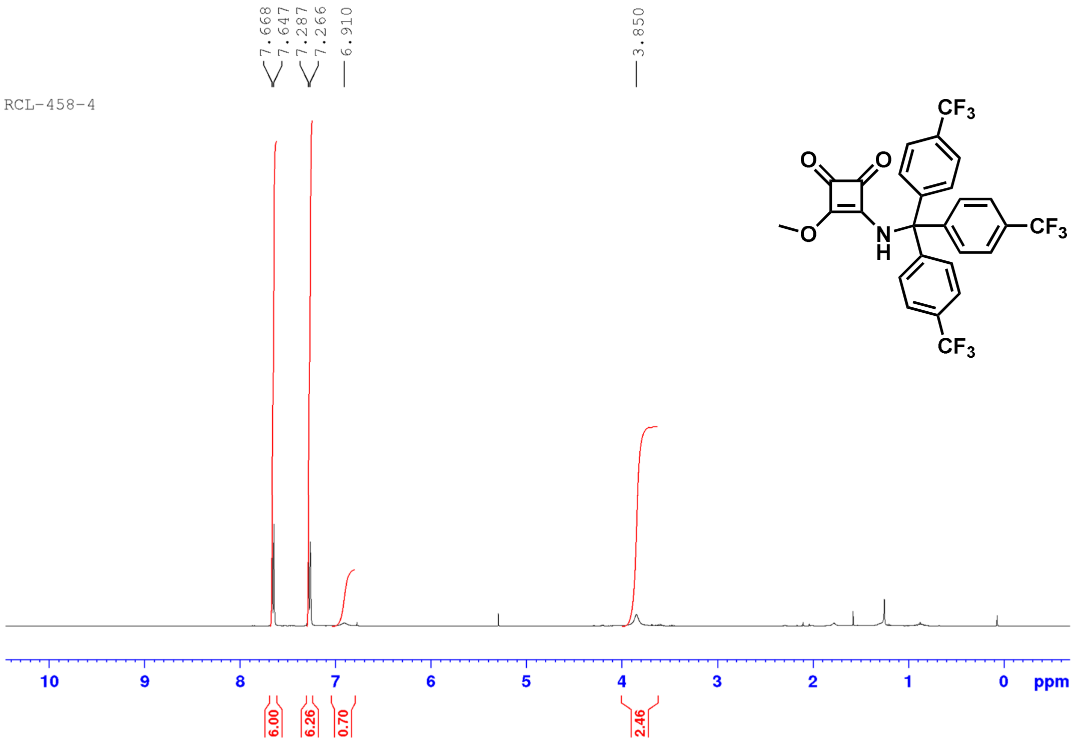


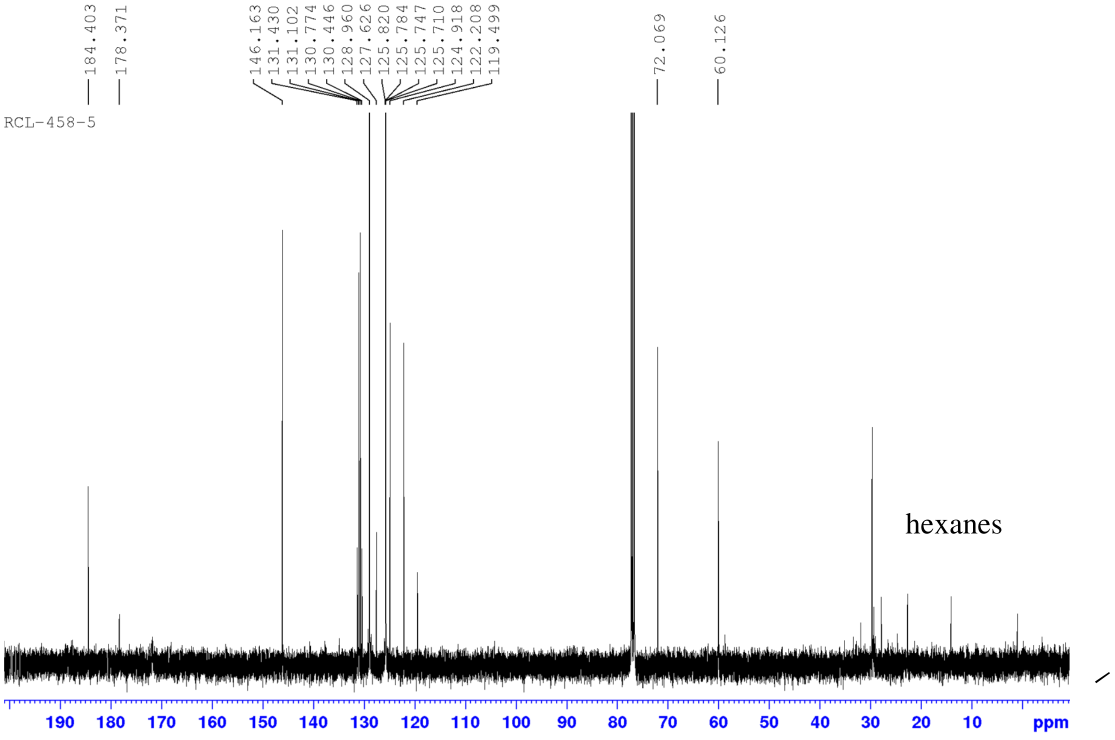
## tris(4-(trifluoromethyl)phenyl)methanamine (S24)



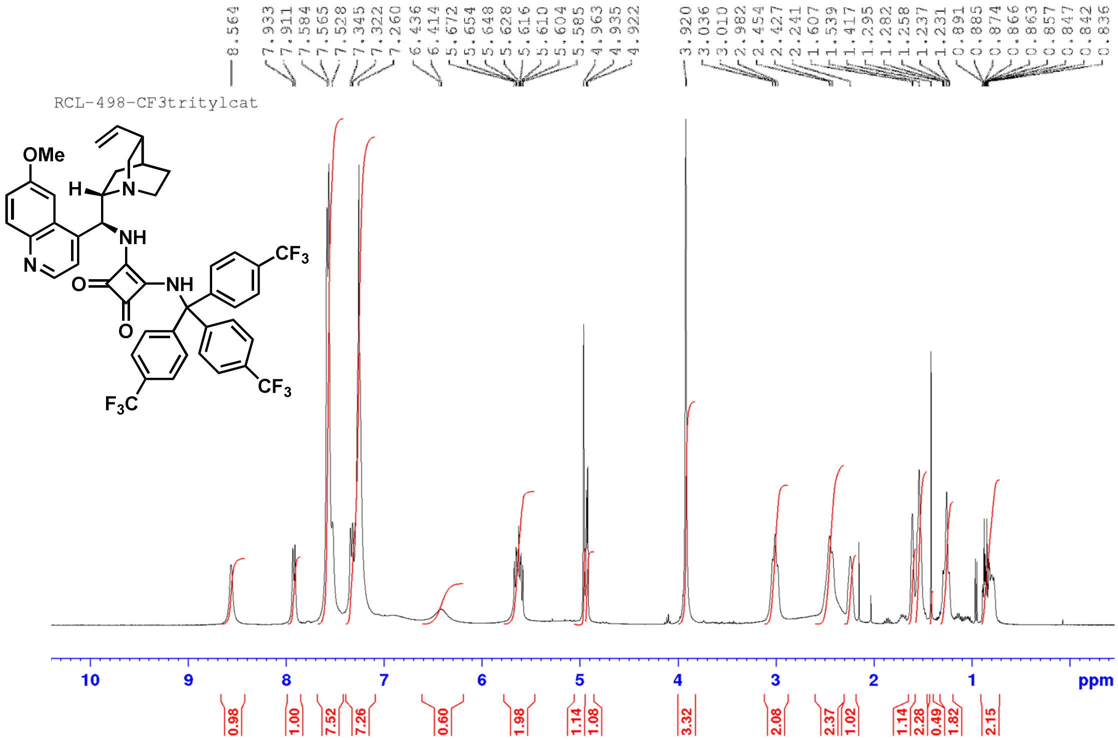


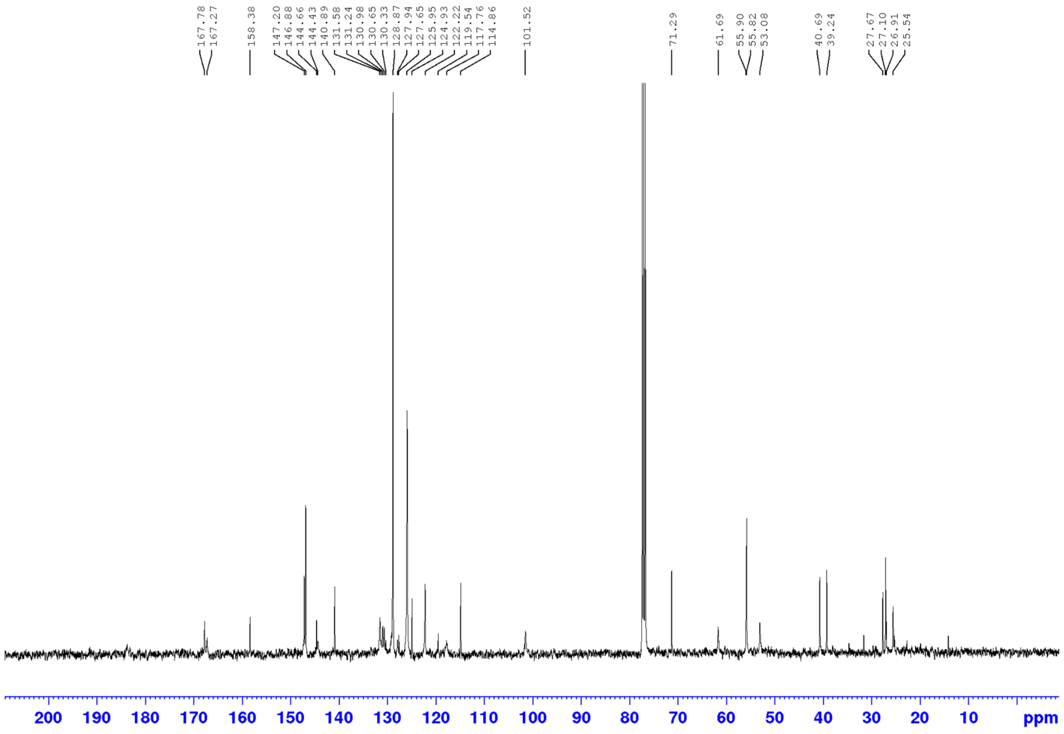
## 3-methoxy-4-((tris(4-(trifluoromethyl)phenyl)methyl)amino)cyclobut-3-ene-1,2-dione (S29)



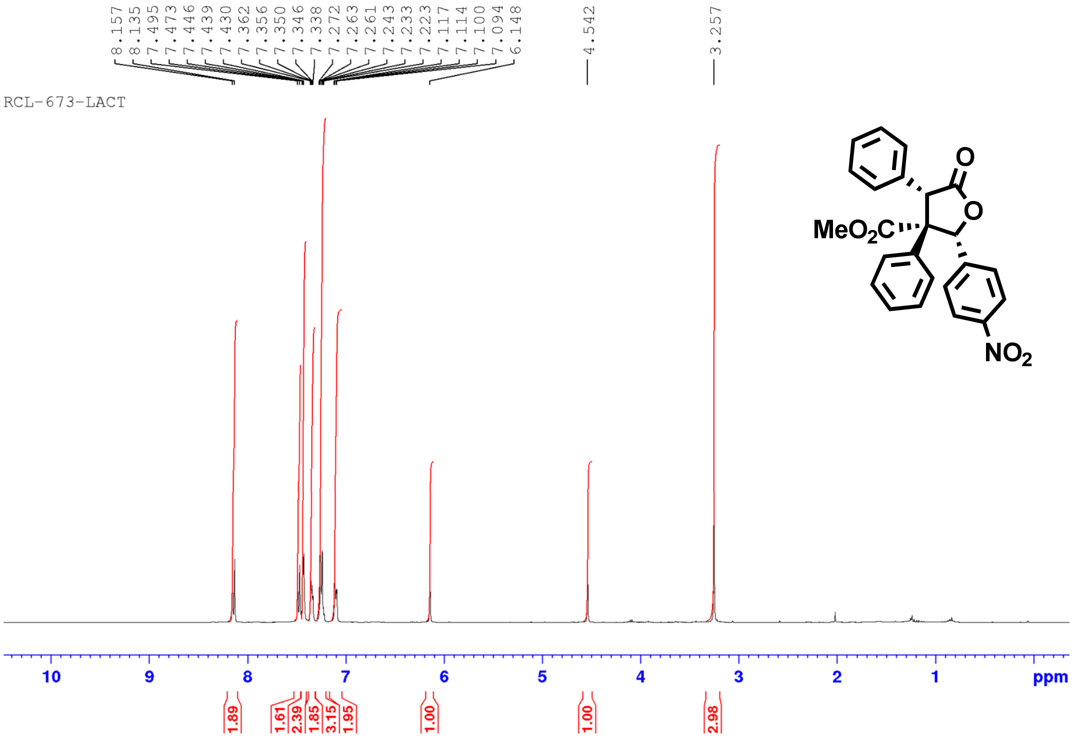


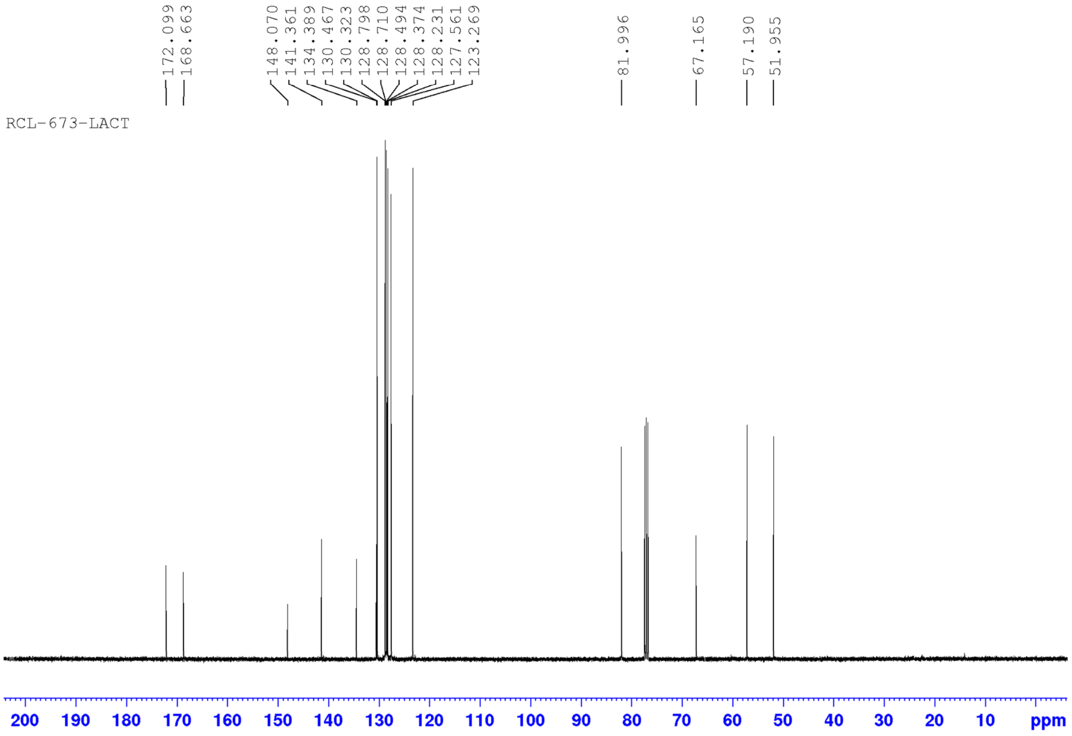
## 3-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-4-((tris(4-(trifluoromethyl)phenyl)methyl)amino)cyclobut-3-ene-1,2-dione (28)



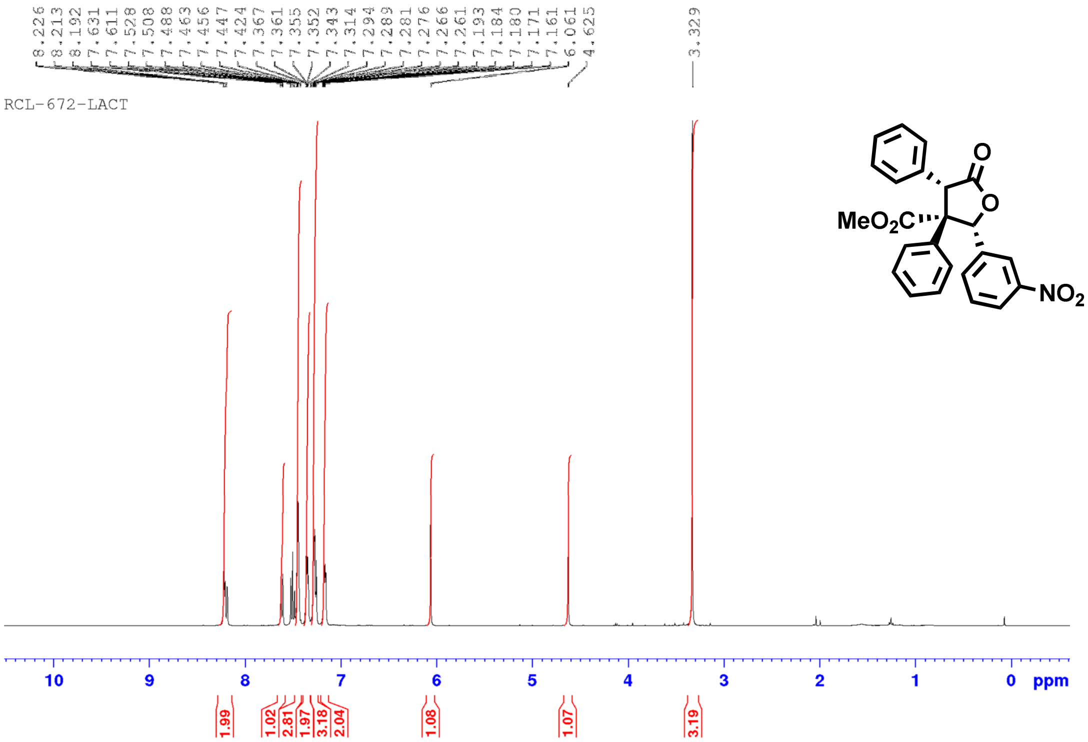


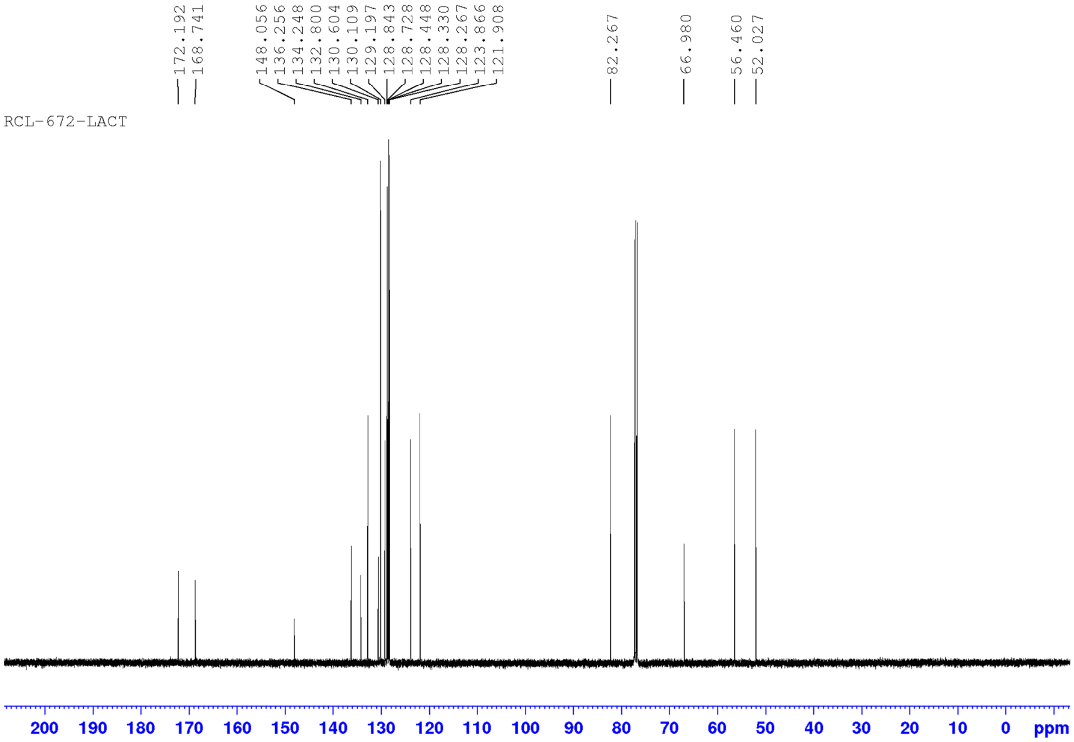
## Methyl (2R,3S,4S)-2-(4-nitrophenyl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (31)



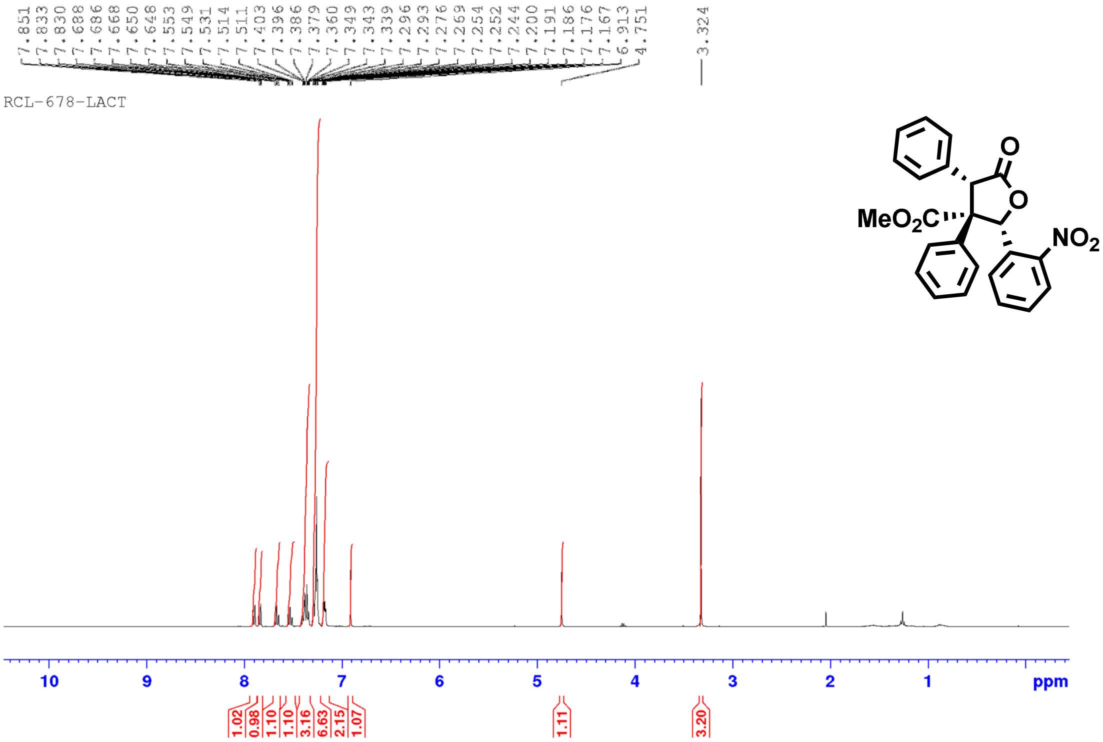


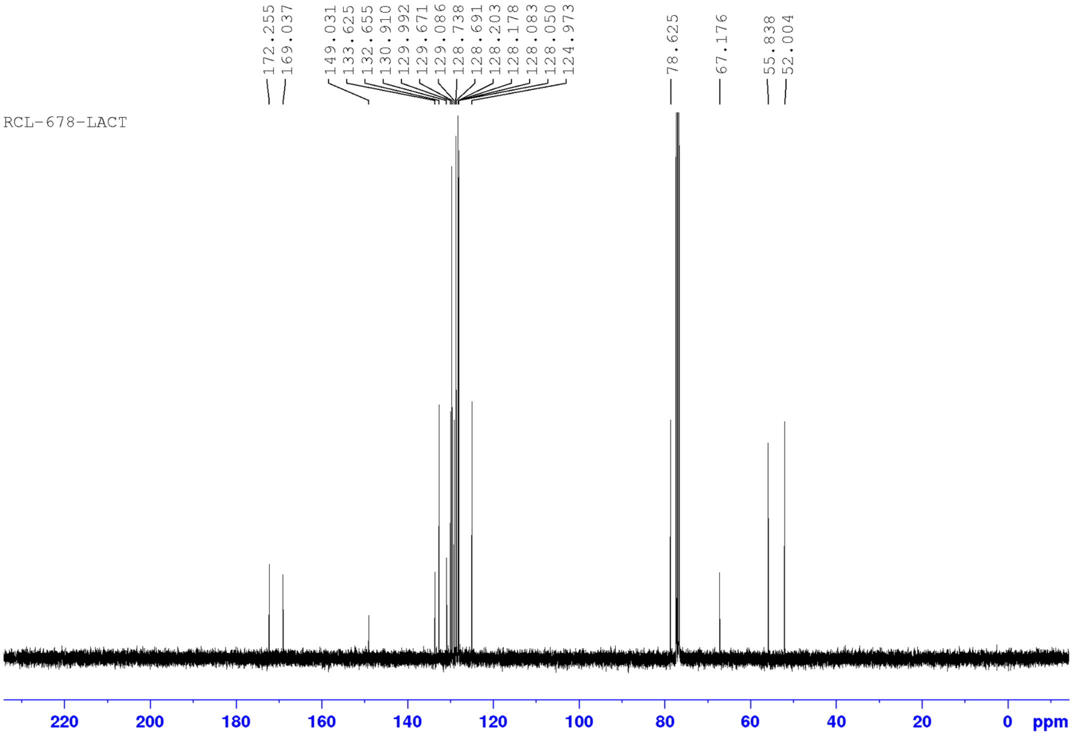
## Methyl (2R,3S,4S)-2-(3-nitrophenyl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (32)



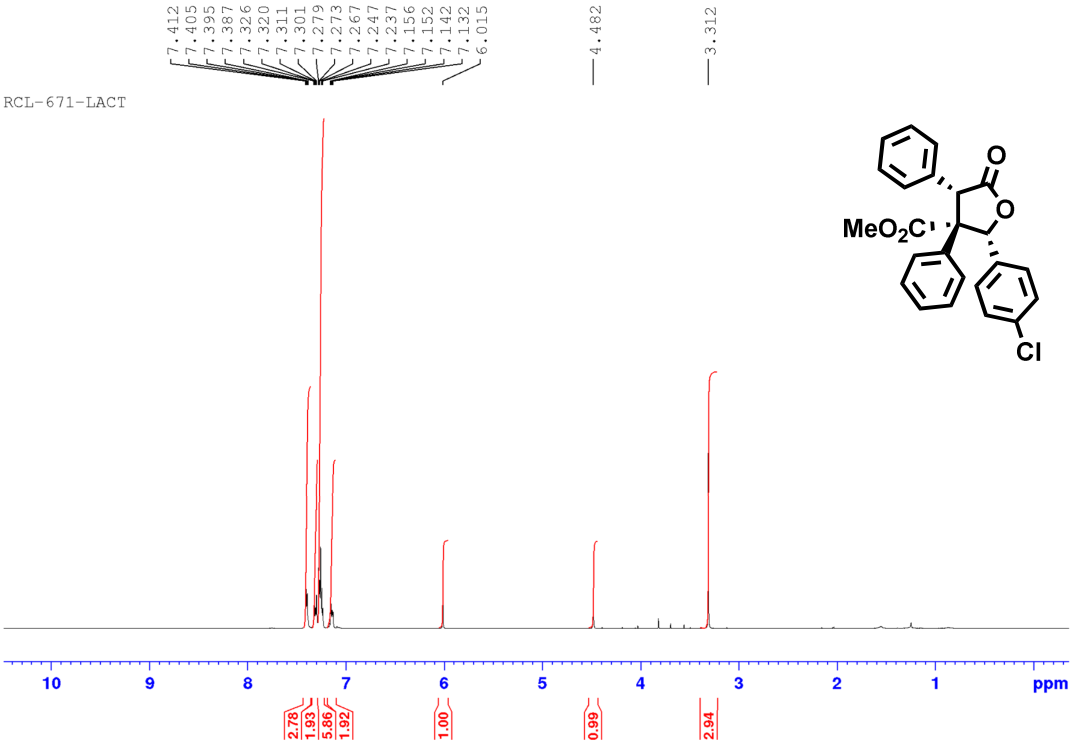


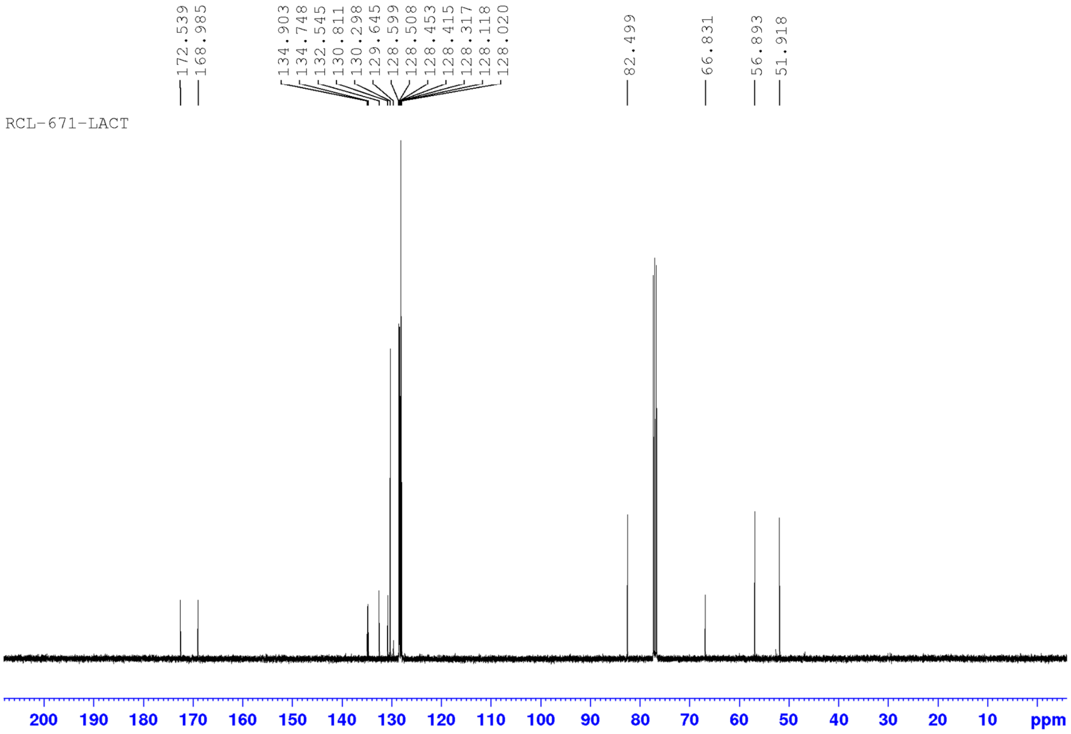
## Methyl (2R,3S,4S)-2-(2-nitrophenyl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (33)



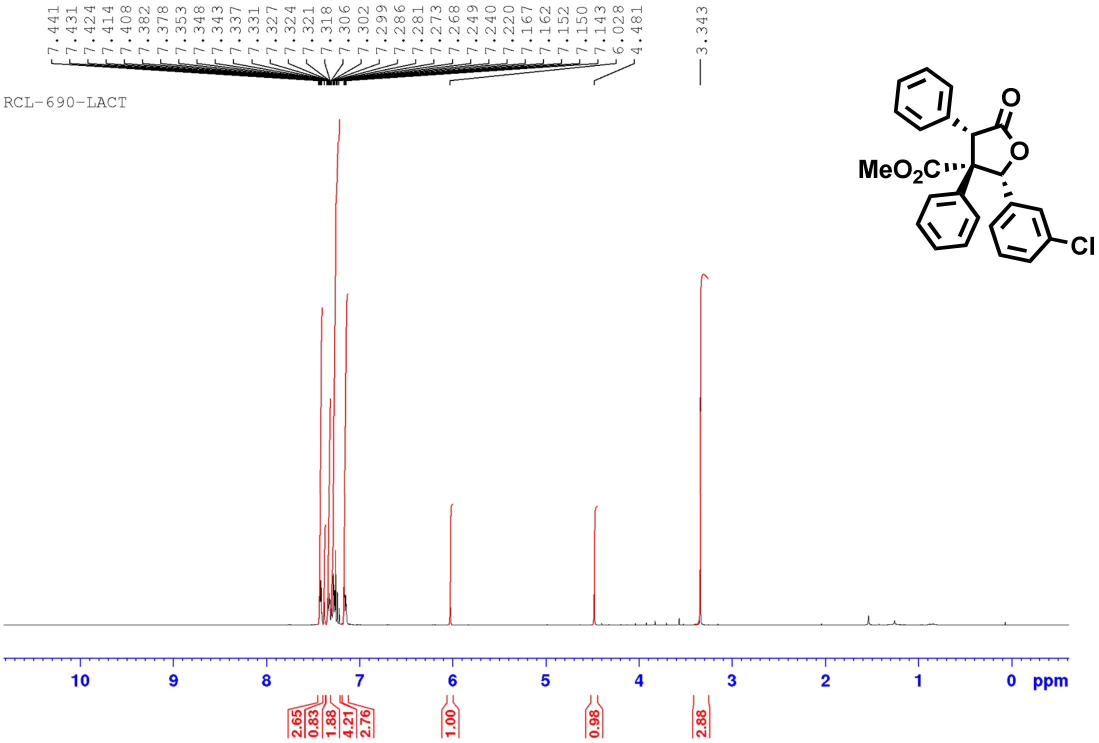


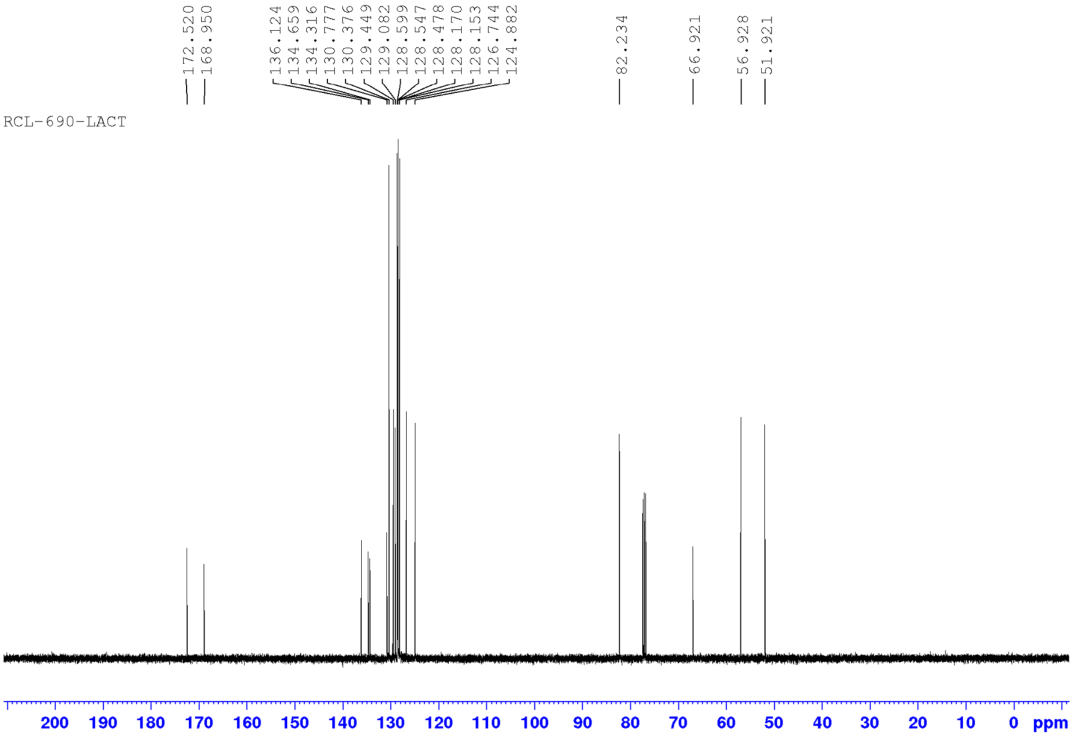
## Methyl (2R,3S,4S)-2-(4-chlorophenyl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (34)



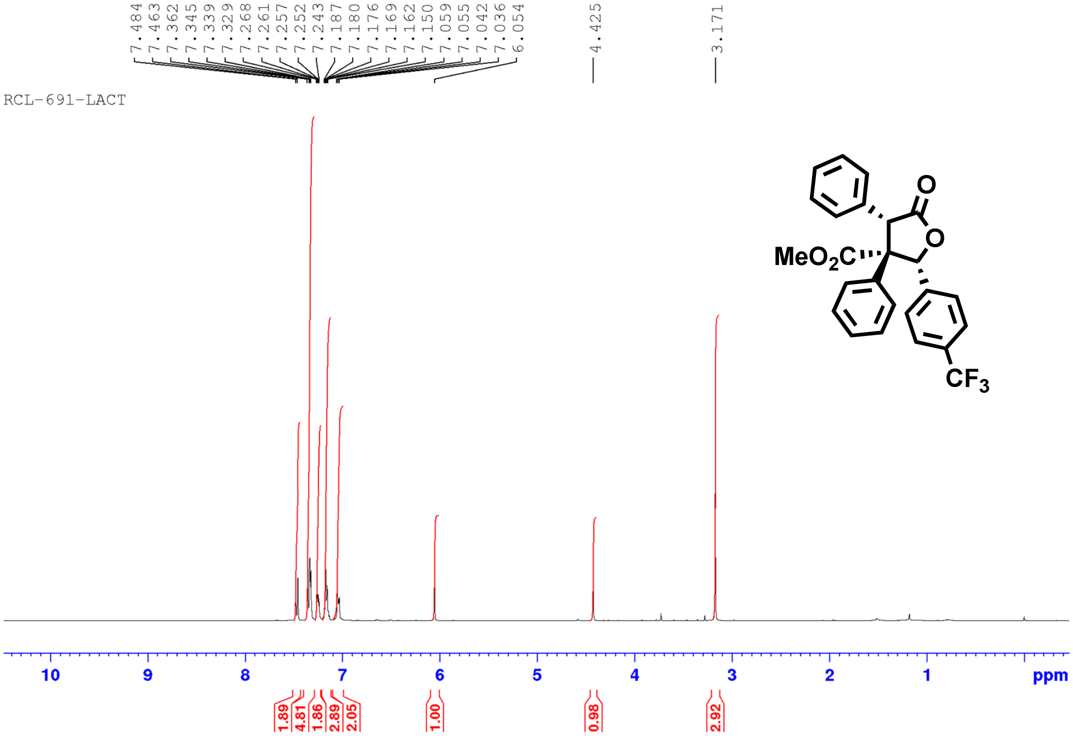


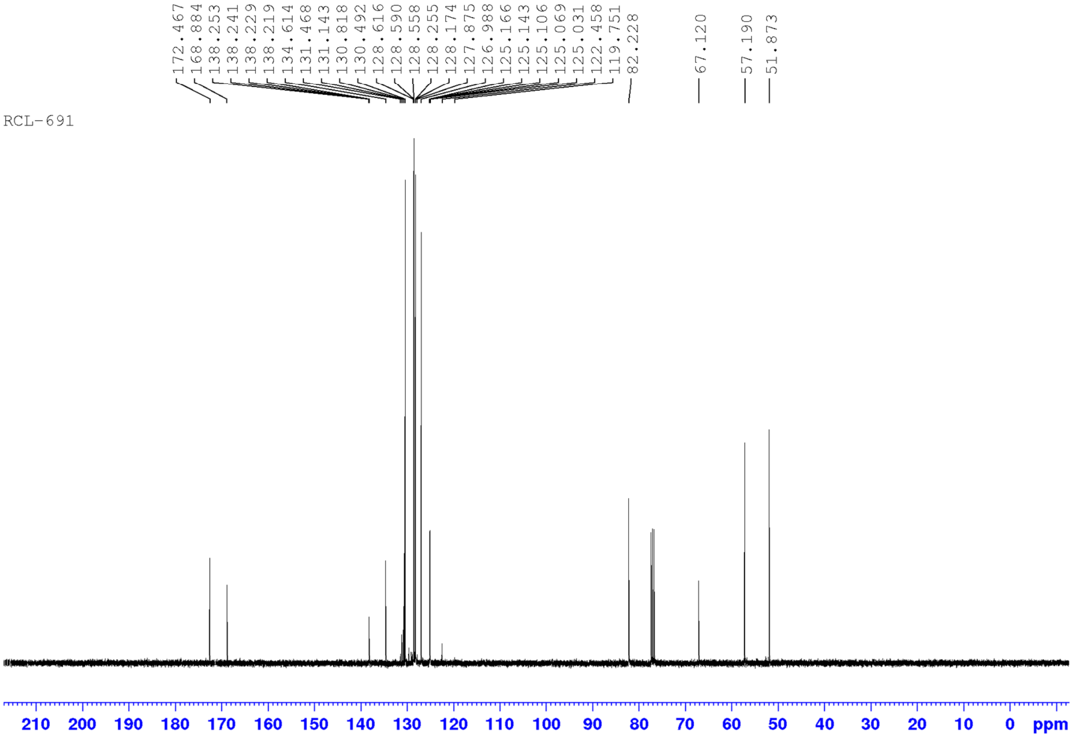
## Methyl (2R,3S,4S)-2-(3-chlorophenyl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (35)



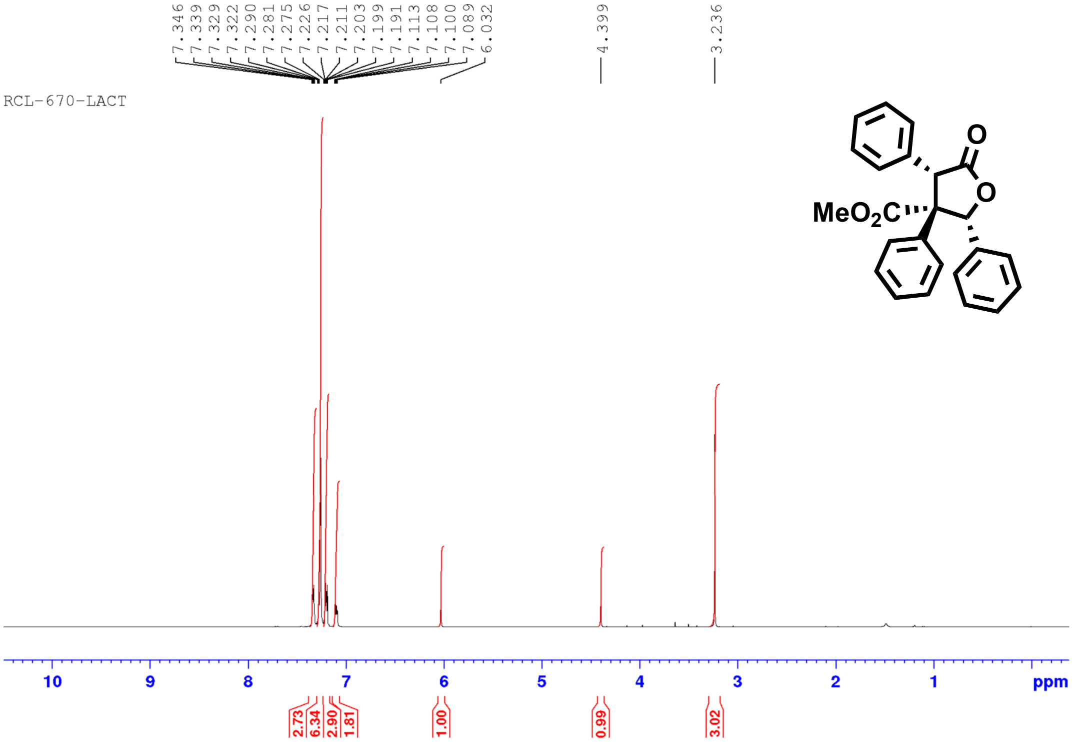


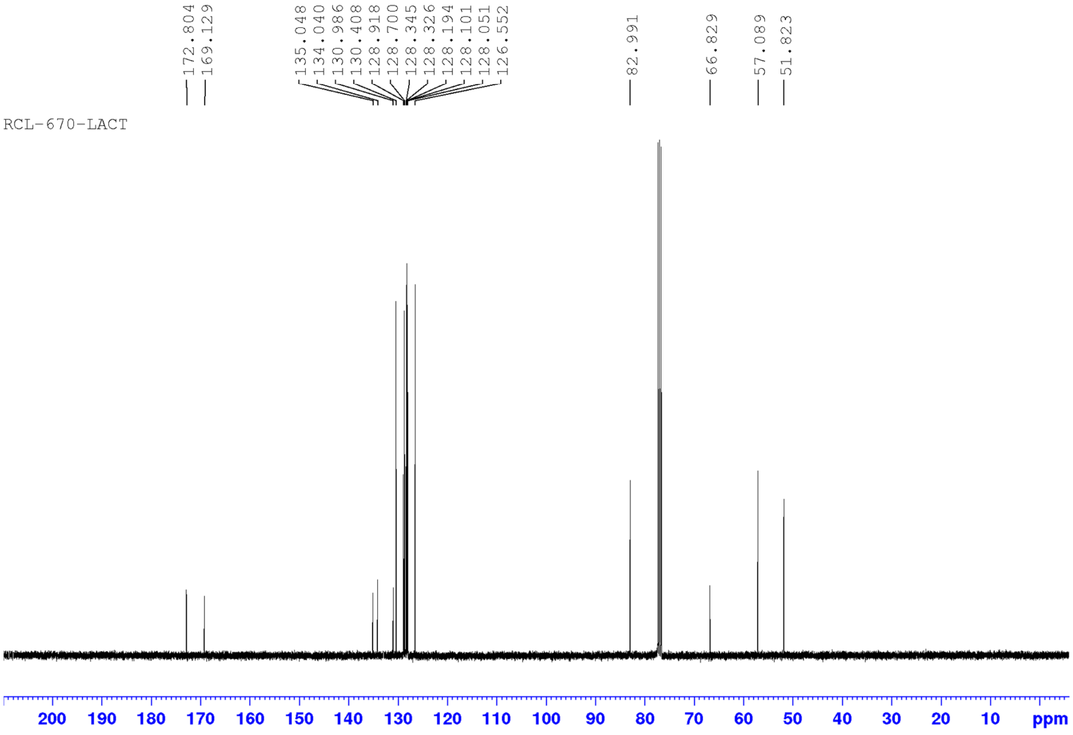
## Methyl (2R,3S,4S)-5-oxo-3,4-diphenyl-2-(4-(trifluoromethyl)phenyl) tetrahydrofuran-3-carboxylate (36)



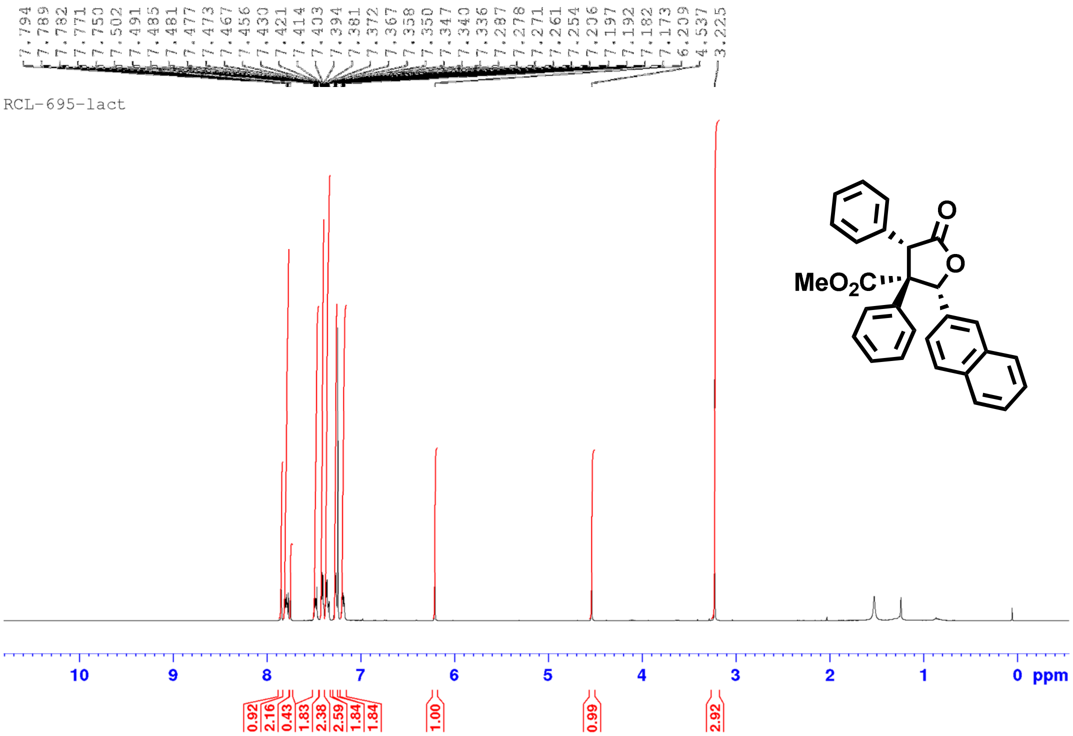


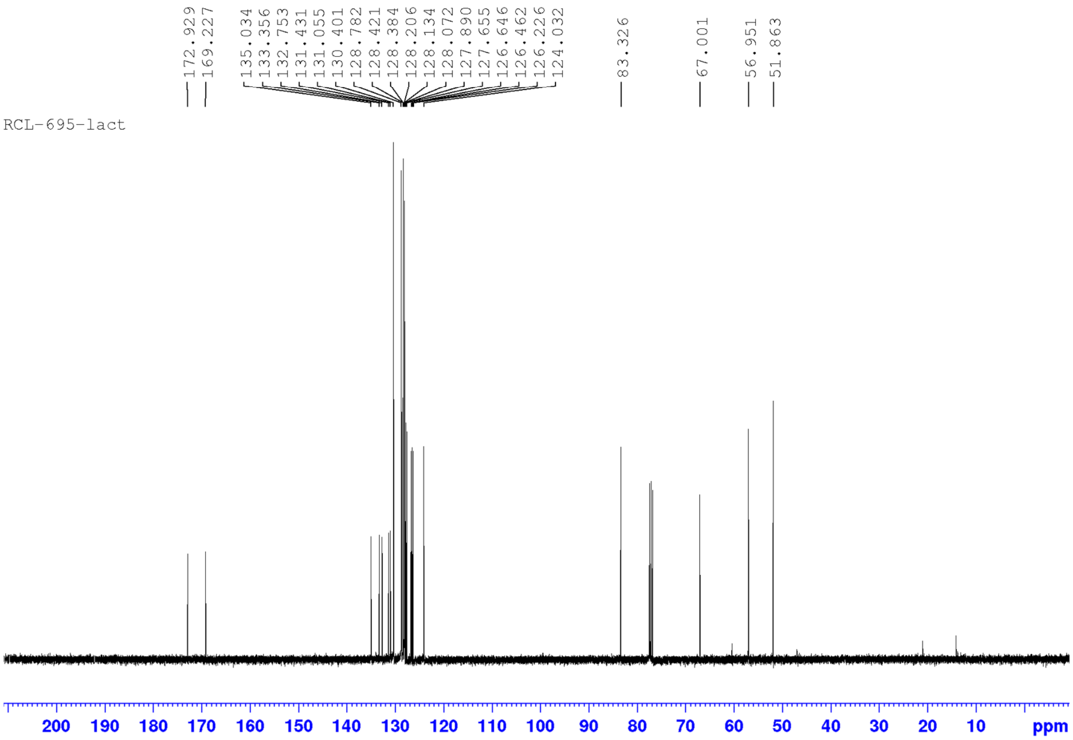
## Methyl (2R,3S,4S)-5-oxo-2,3,4-triphenyltetrahydrofuran-3-carboxylate (37)



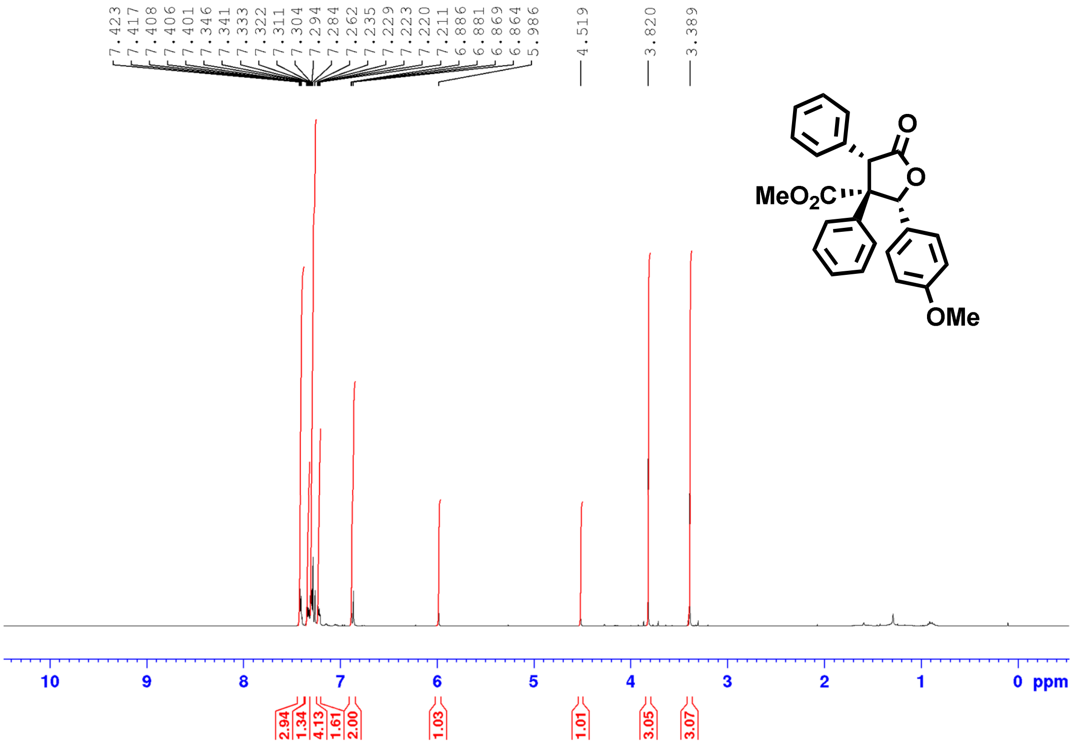


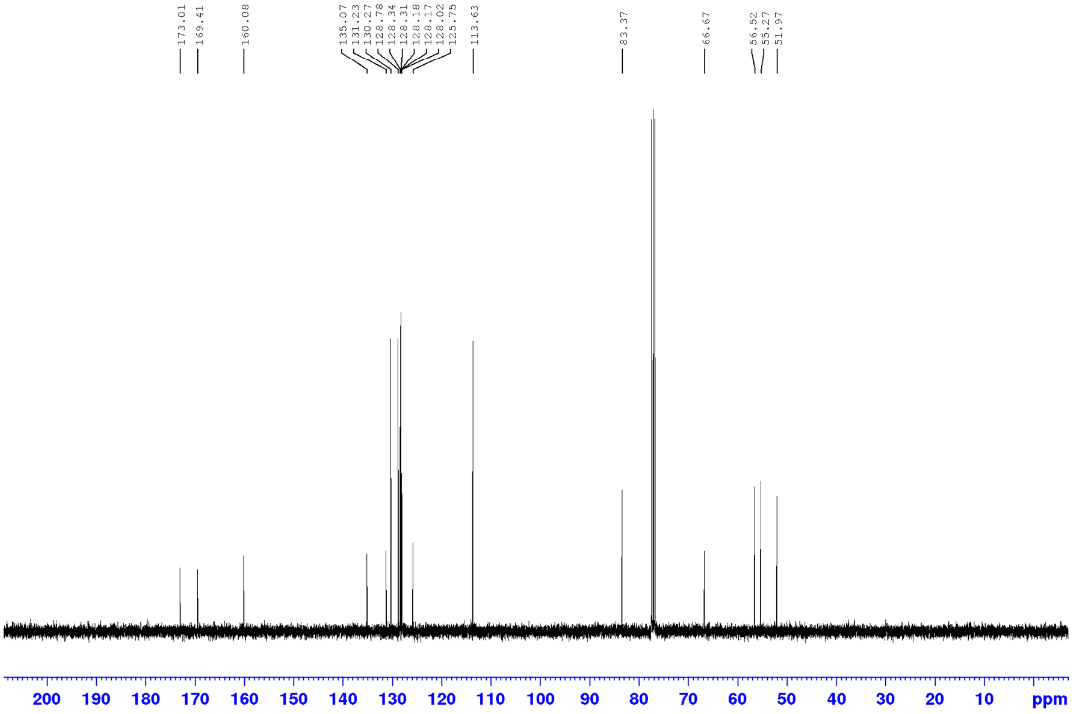
## Methyl (2R,3S,4S)-2-(naphthalen-2-yl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (38)



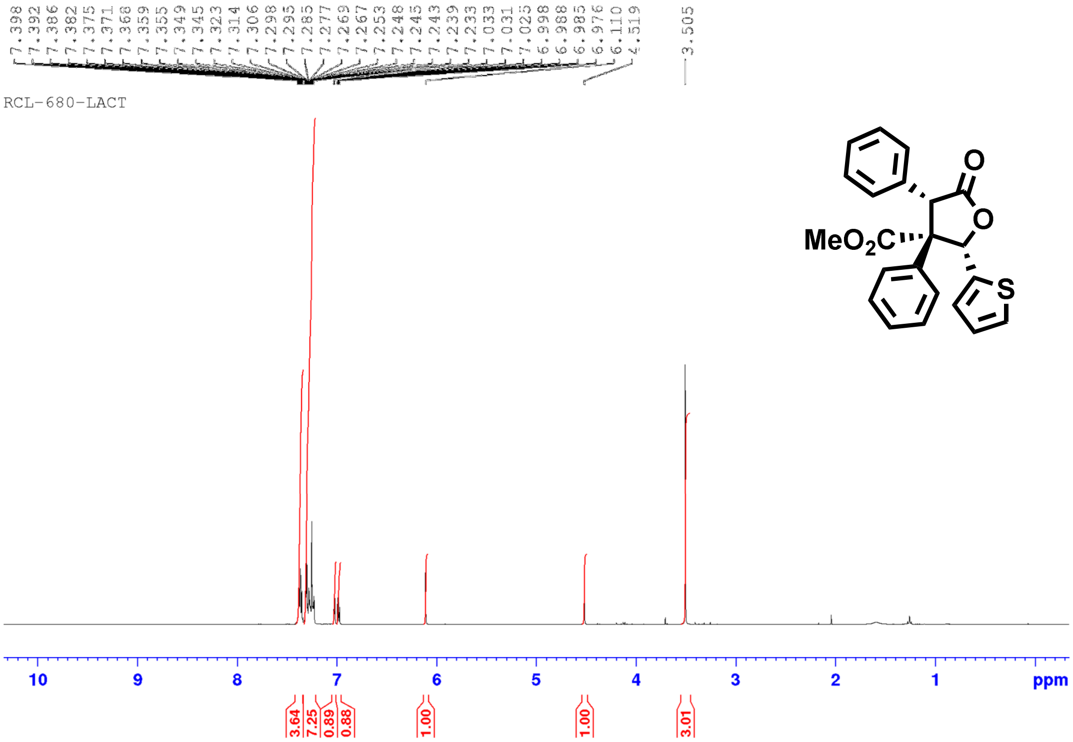


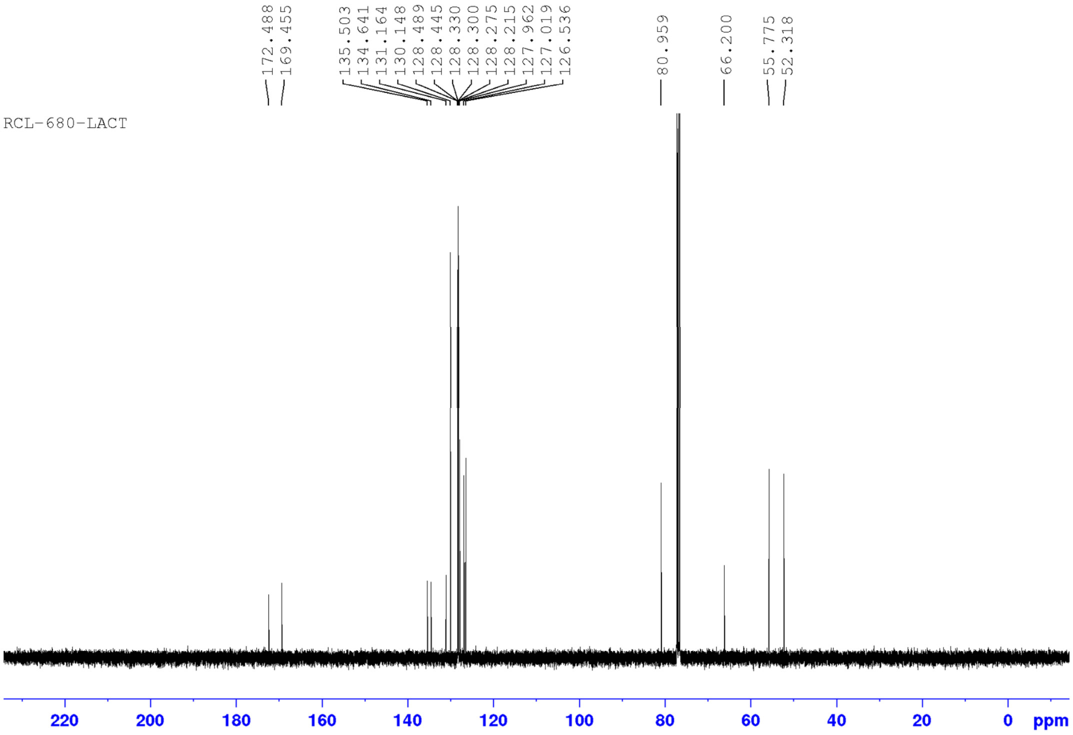
## Methyl (2R,3S,4S)-2-(4-methoxyphenyl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (39)



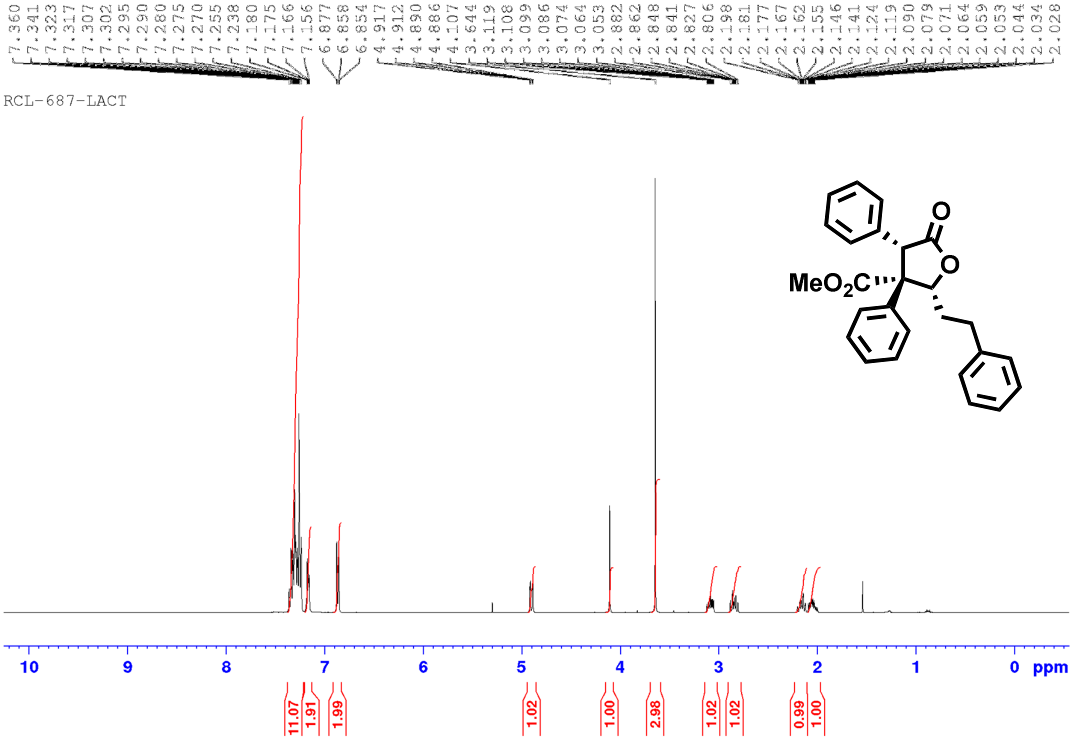


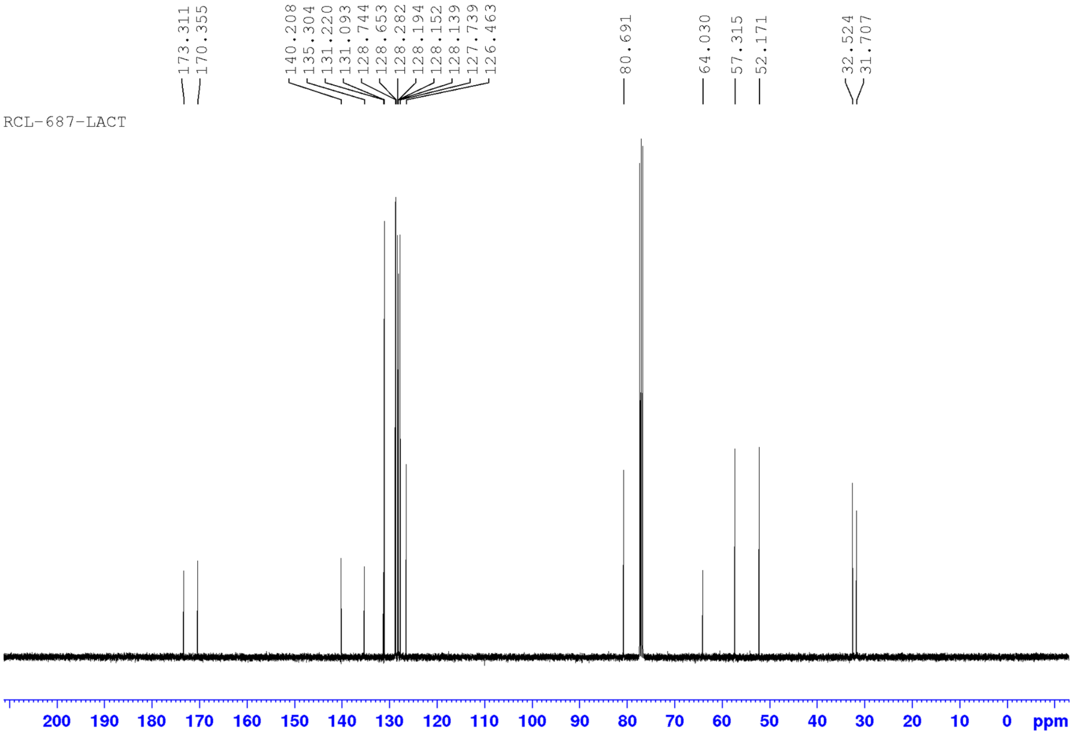
## Methyl (2S,3S,4S)-5-oxo-3,4-diphenyl-2-(thiophen-2-yl)tetrahydrofuran-3-carboxylate (40)



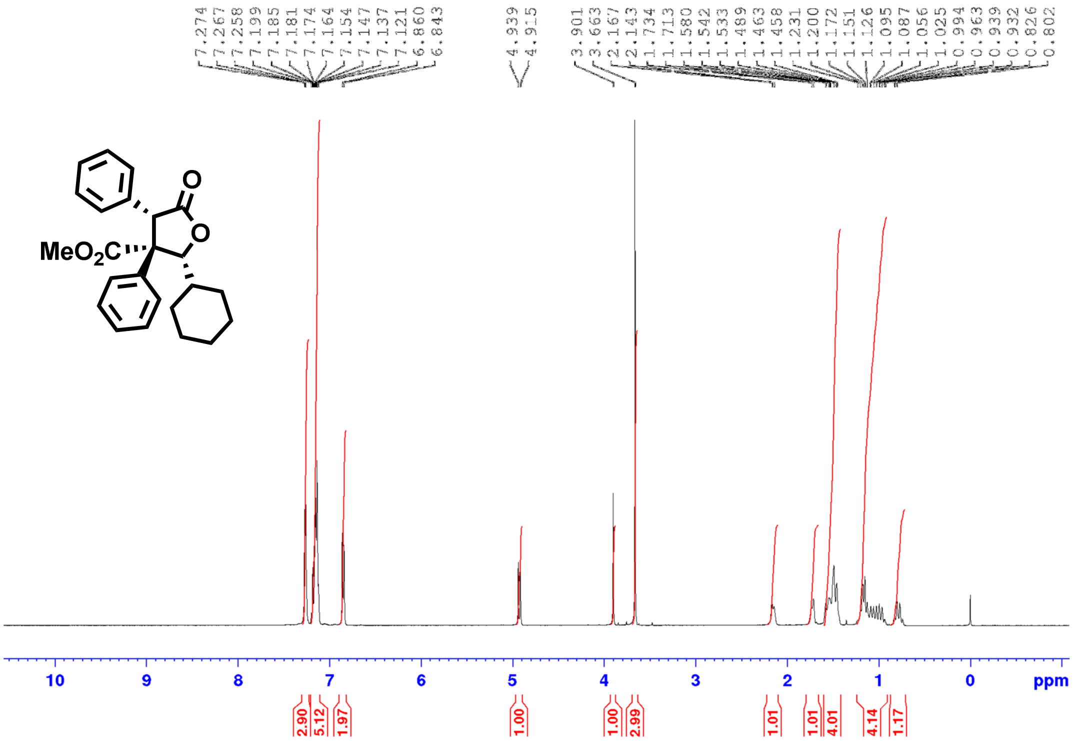


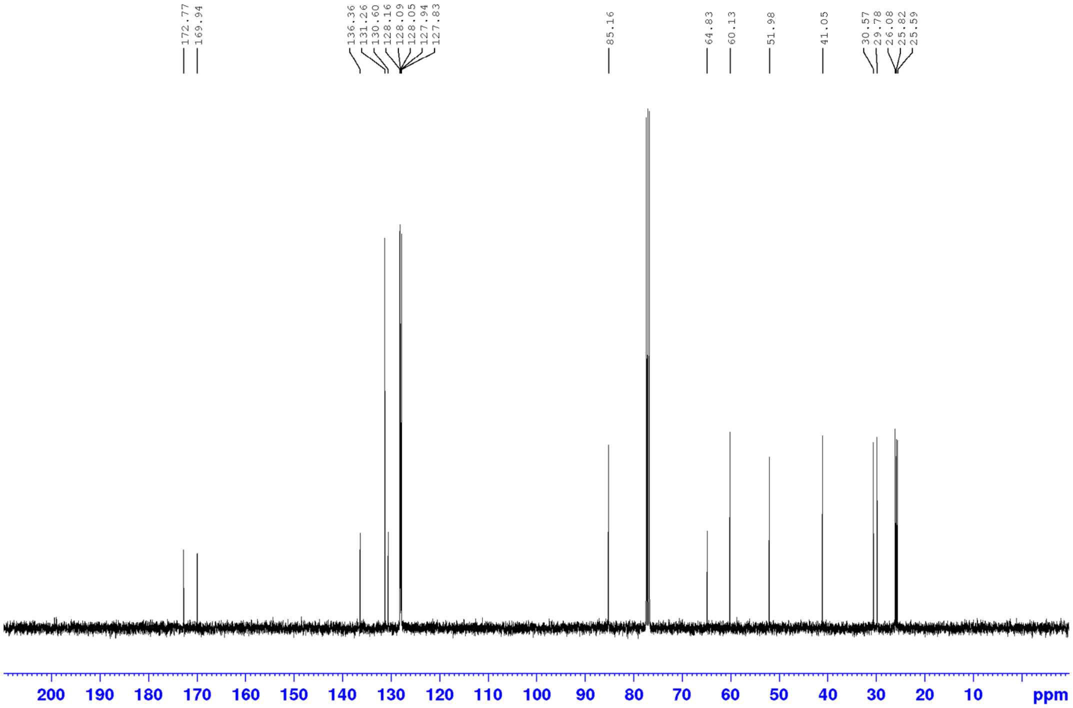
## Methyl (2R,3S,4S)-5-oxo-2-phenethyl-3,4-diphenyltetrahydrofuran-3-carboxylate (41)



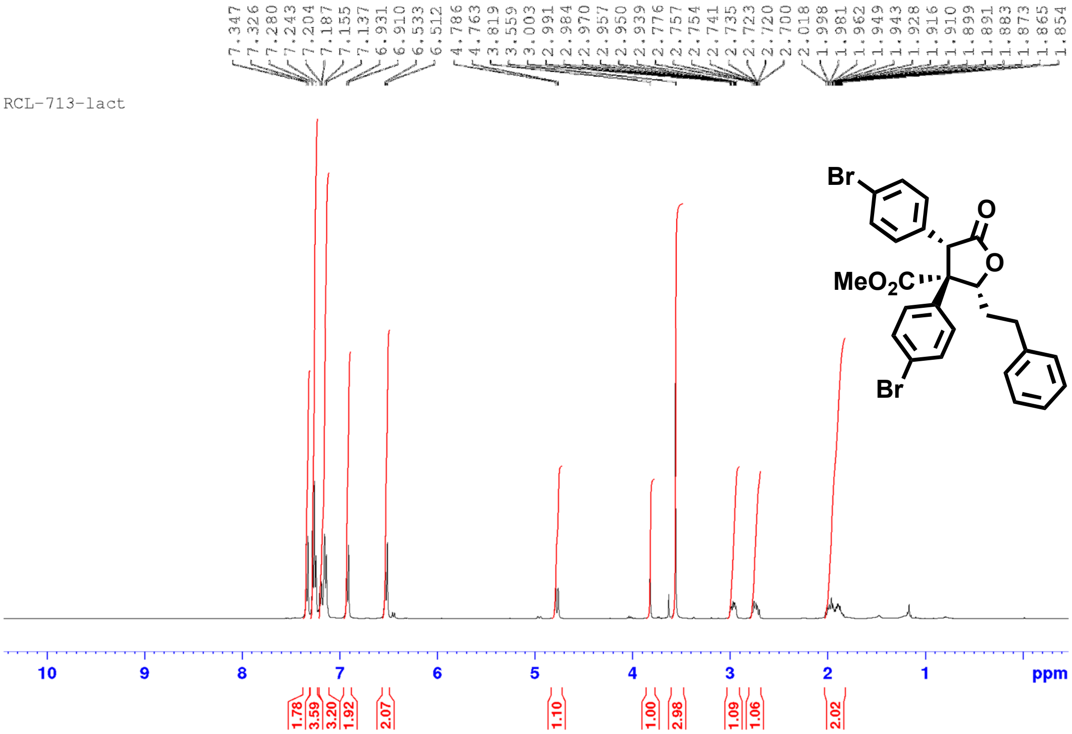


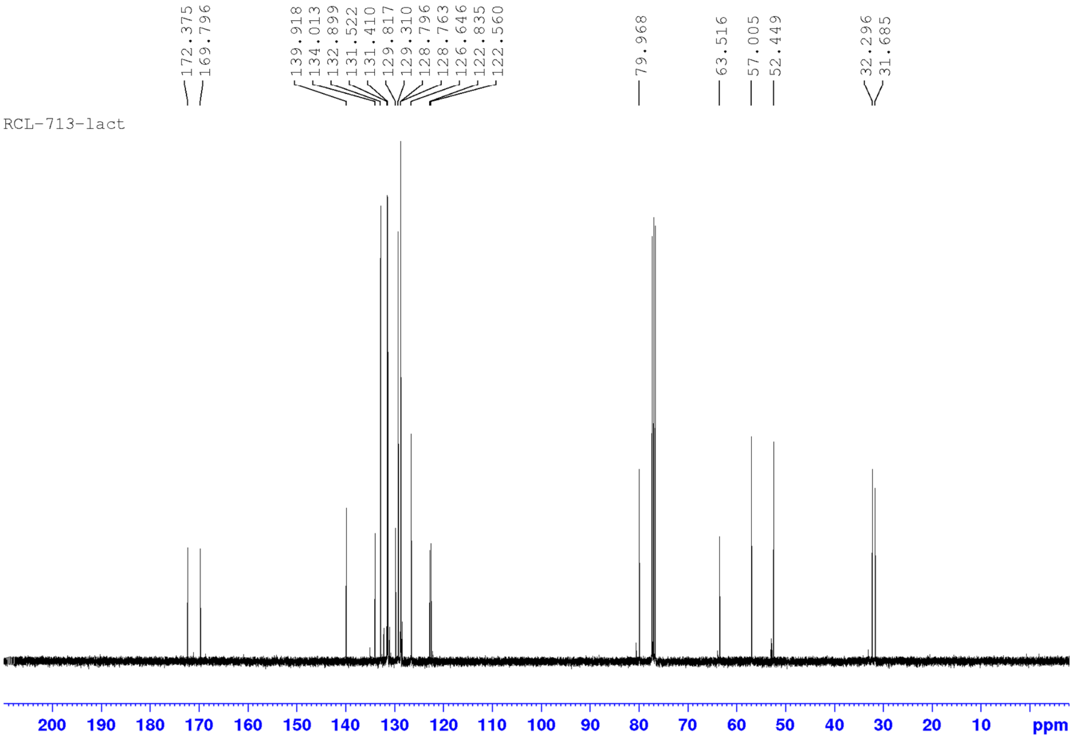
## Methyl (2R,3S,4S)-2-cyclohexyl-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (42)



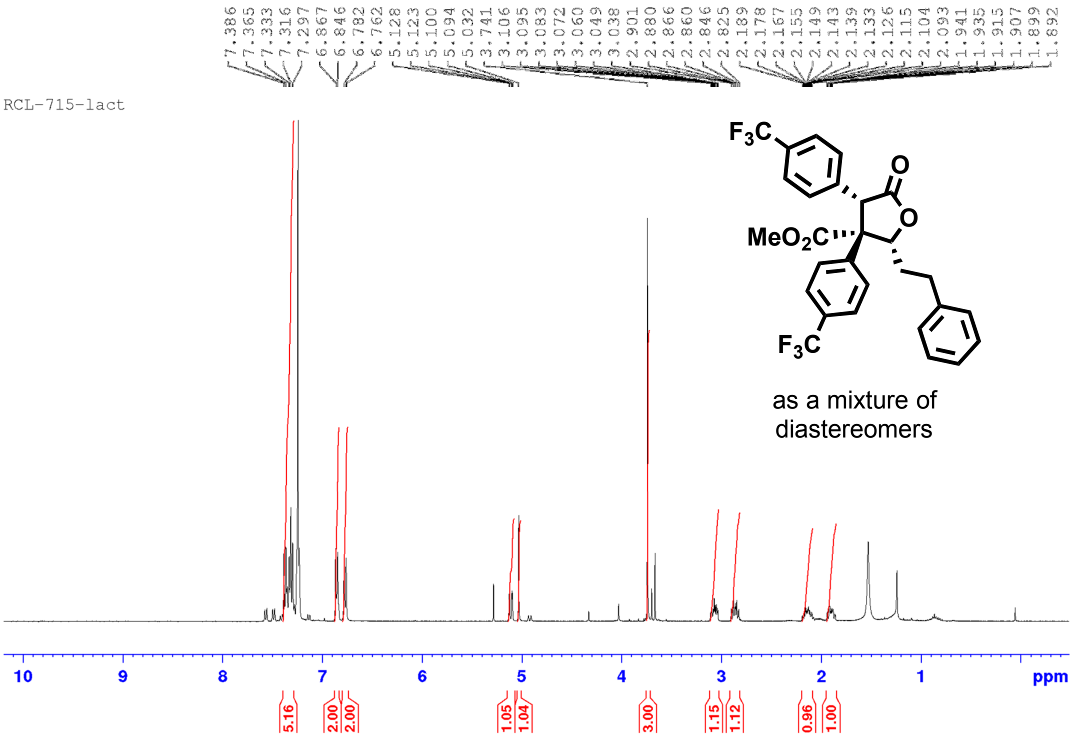


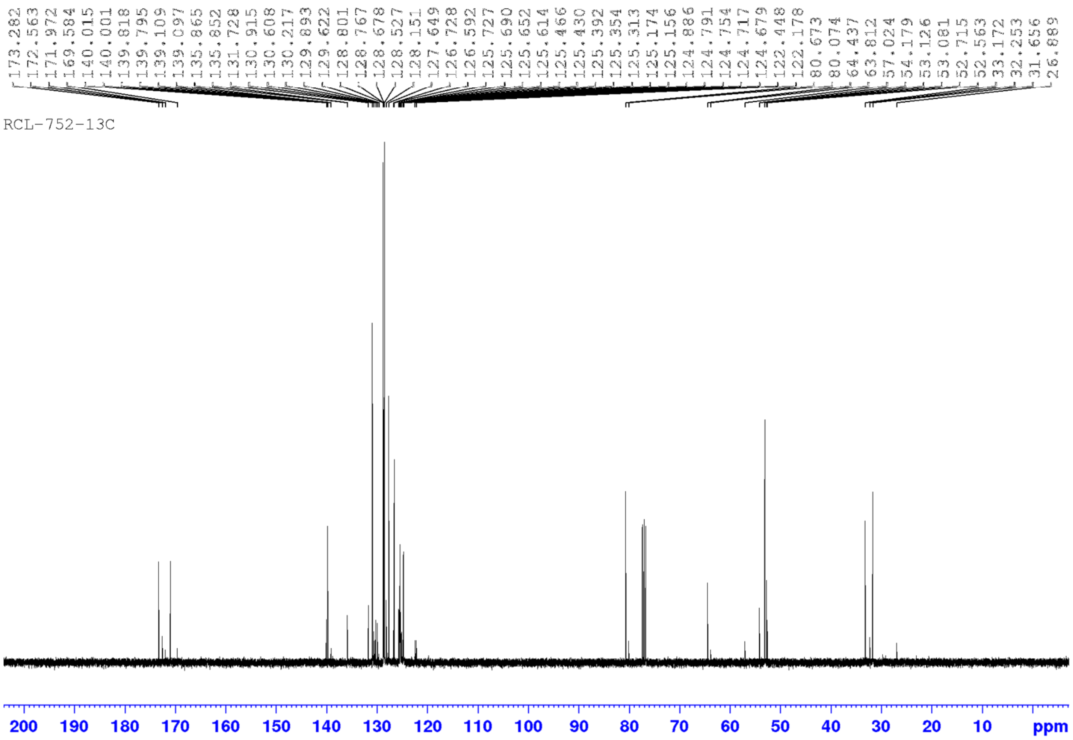
## Methyl (2R,3S,4S)-3,4-bis(4-bromophenyl)-5-oxo-2-phenethyltetrahydrofuran-3-carboxylate (46)



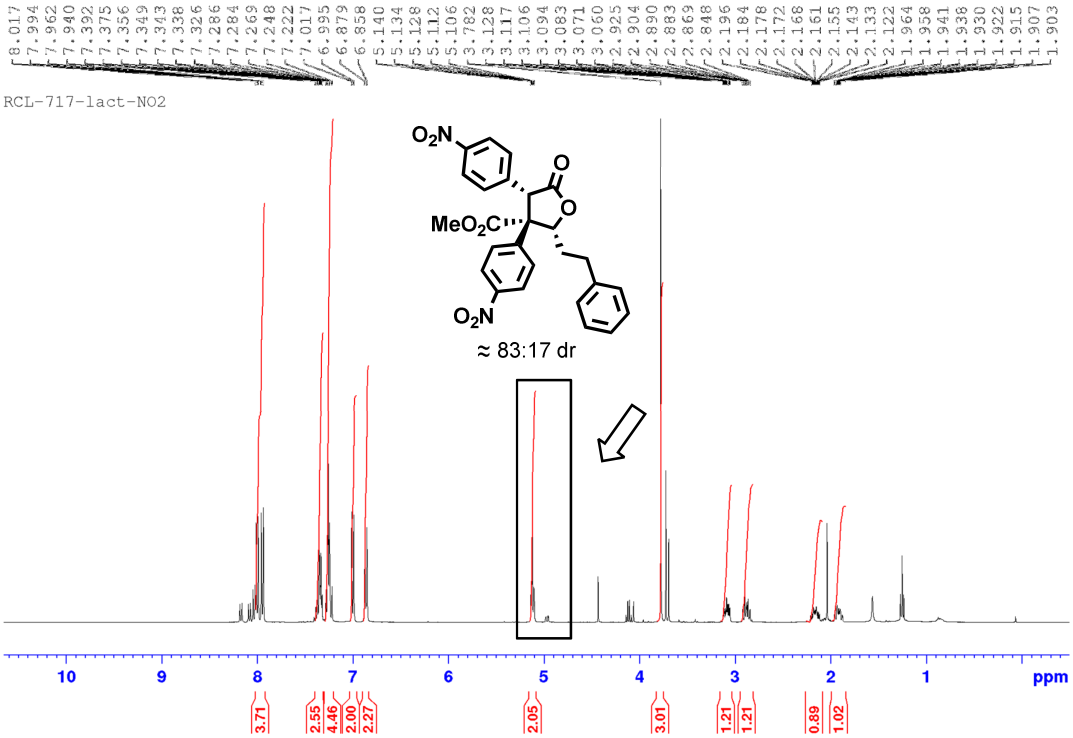


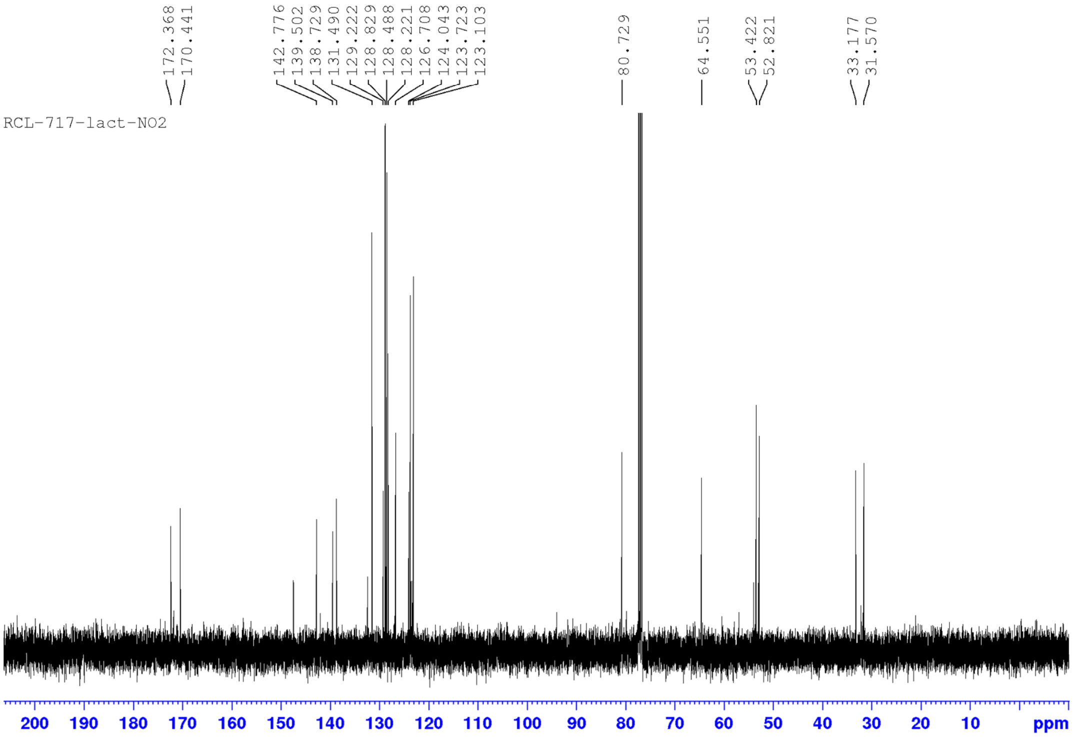
## Methyl (2R,3S,4S)-5-oxo-2-phenethyl-3,4-bis(4-(trifluoromethyl)phenyl) tetrahydrofuran-3-carboxylate (47)



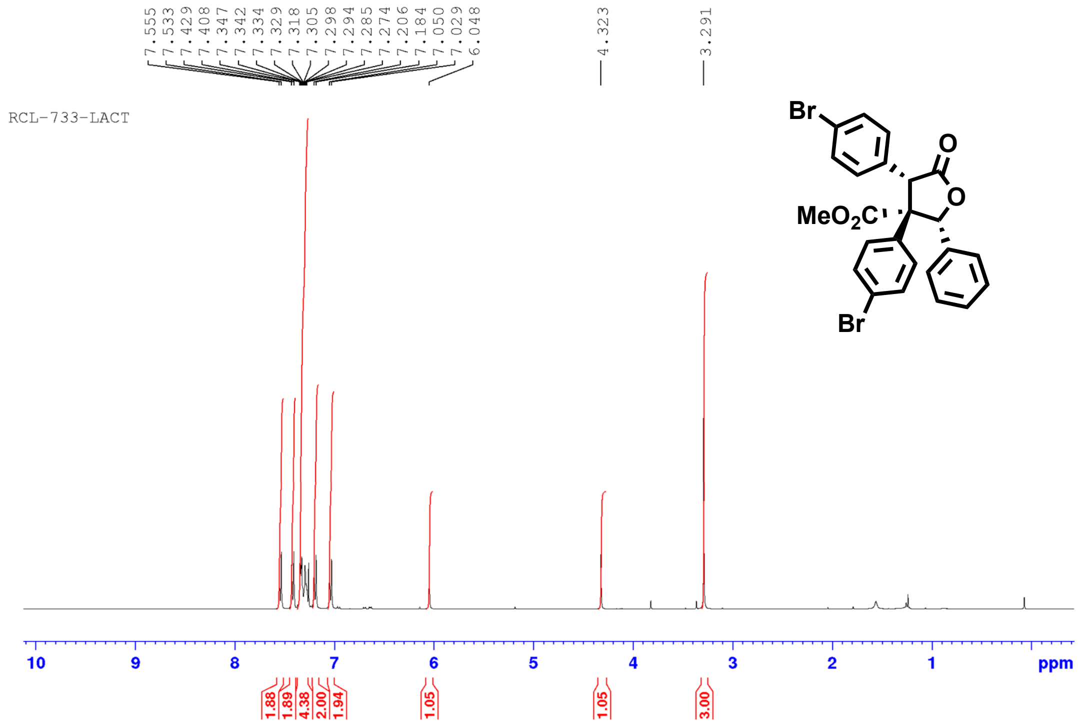


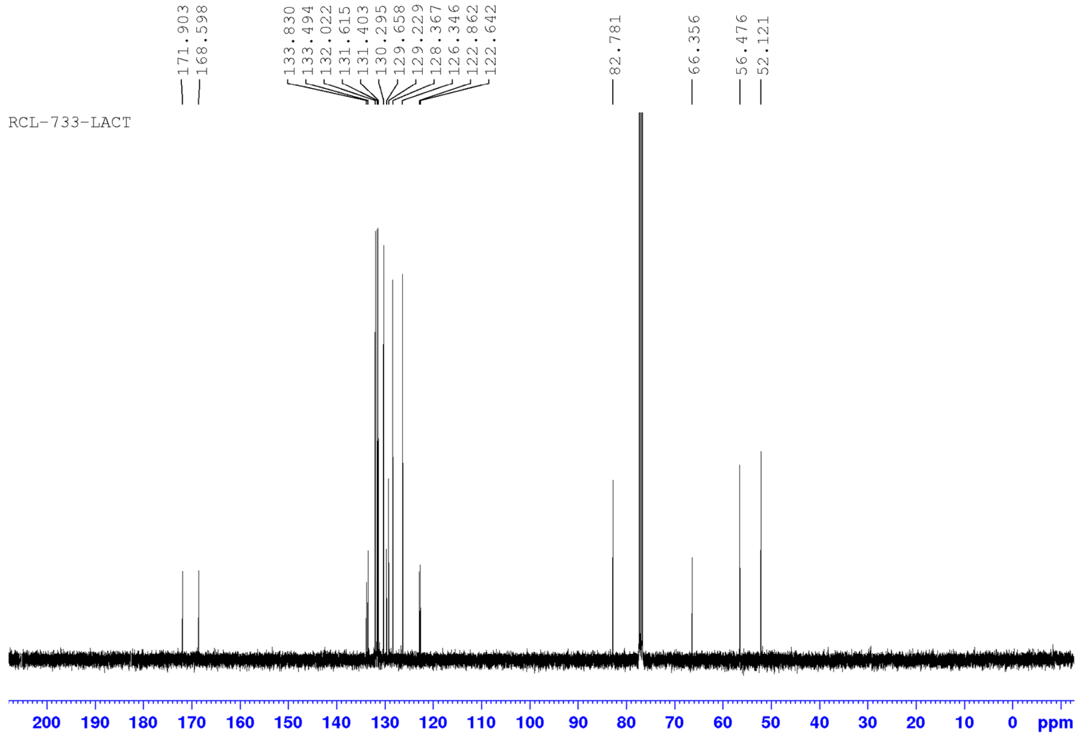
# Methyl (2R,3S,4S)-3,4-bis(4-nitrophenyl)-5-oxo-2-phenethyltetrahydrofuran-3-carboxylate (48)



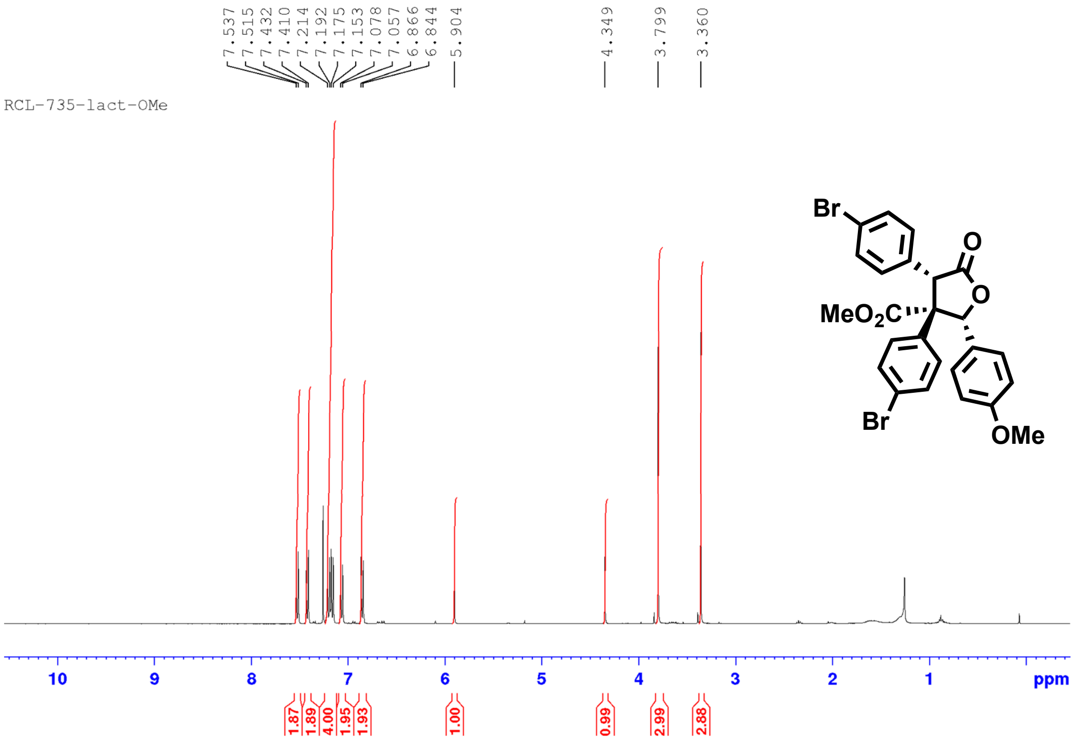


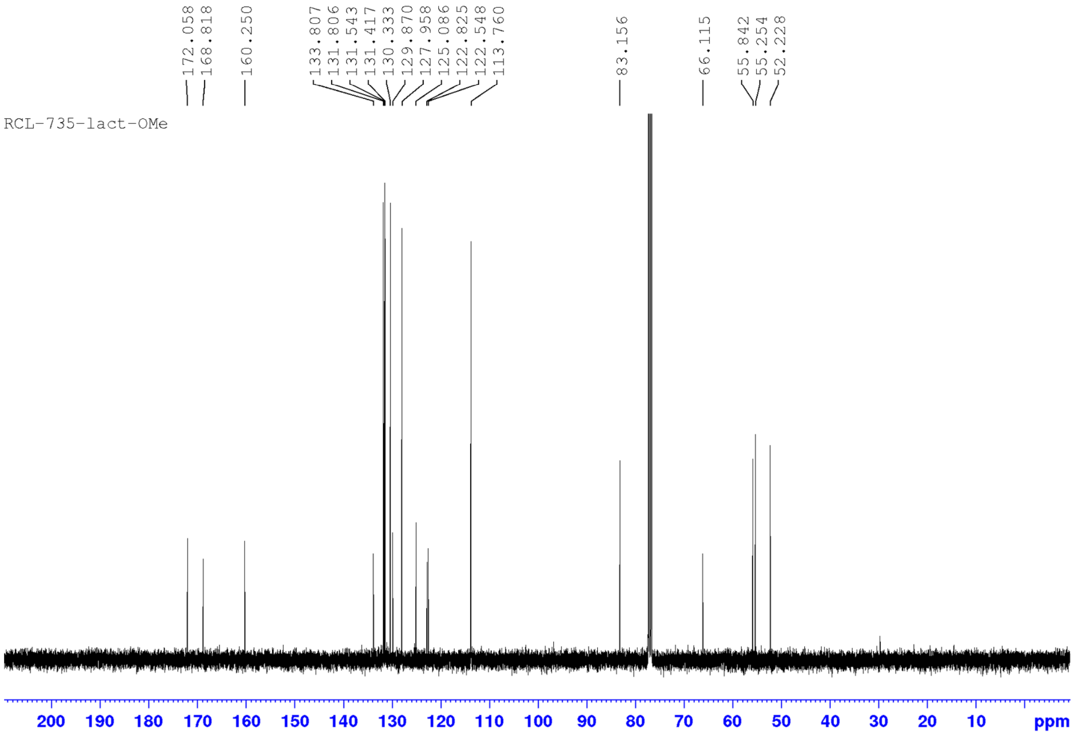
## Methyl (2R,3S,4S)-3,4-bis(4-bromophenyl)-5-oxo-2-phenyltetrahydrofuran-3-carboxylate (49)



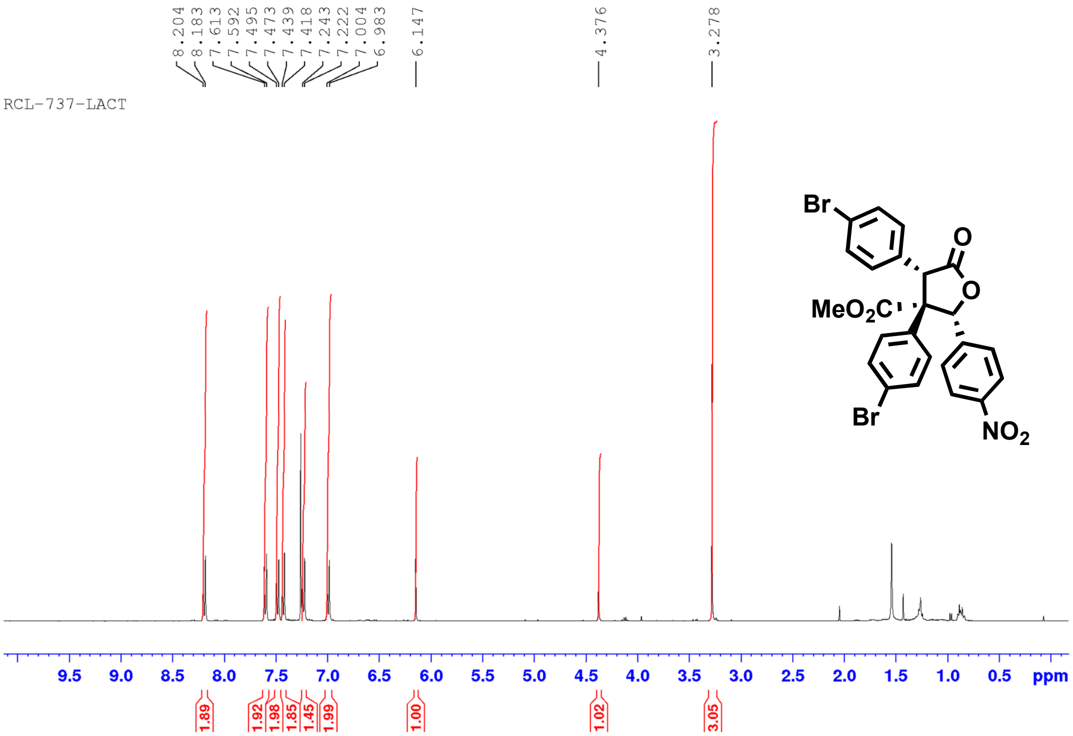


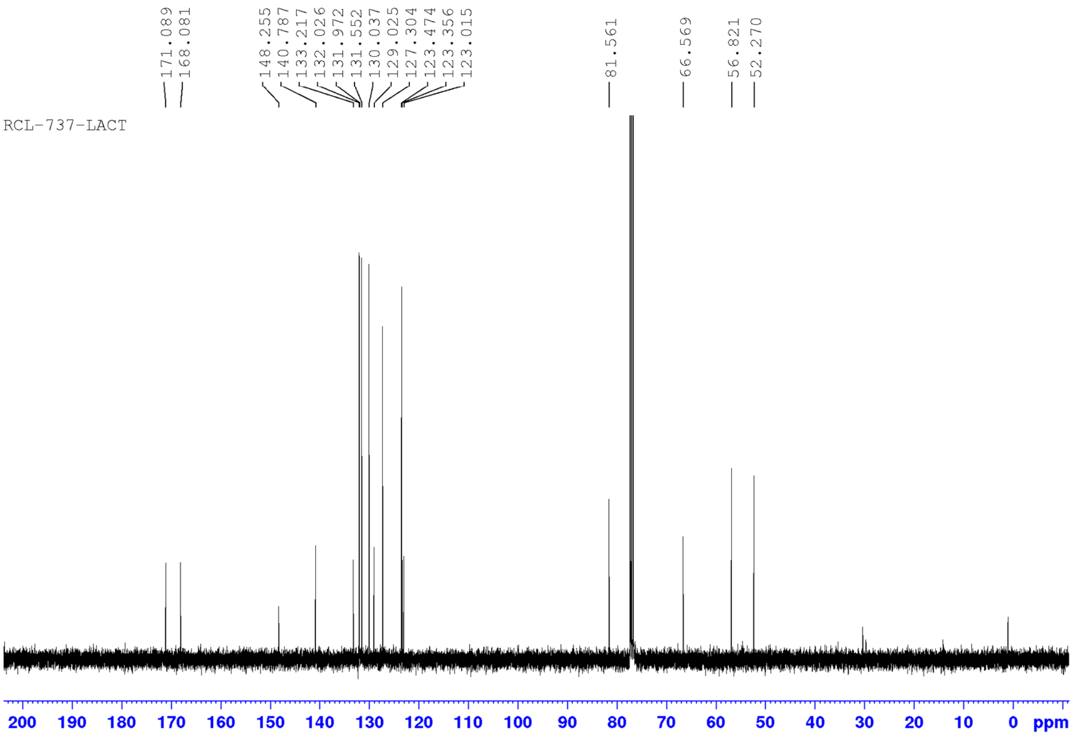
## Methyl (2R,3S,4S)-3,4-bis(4-bromophenyl)-2-(4-methoxyphenyl)-5-oxotetrahydrofuran-3-carboxylate (50)



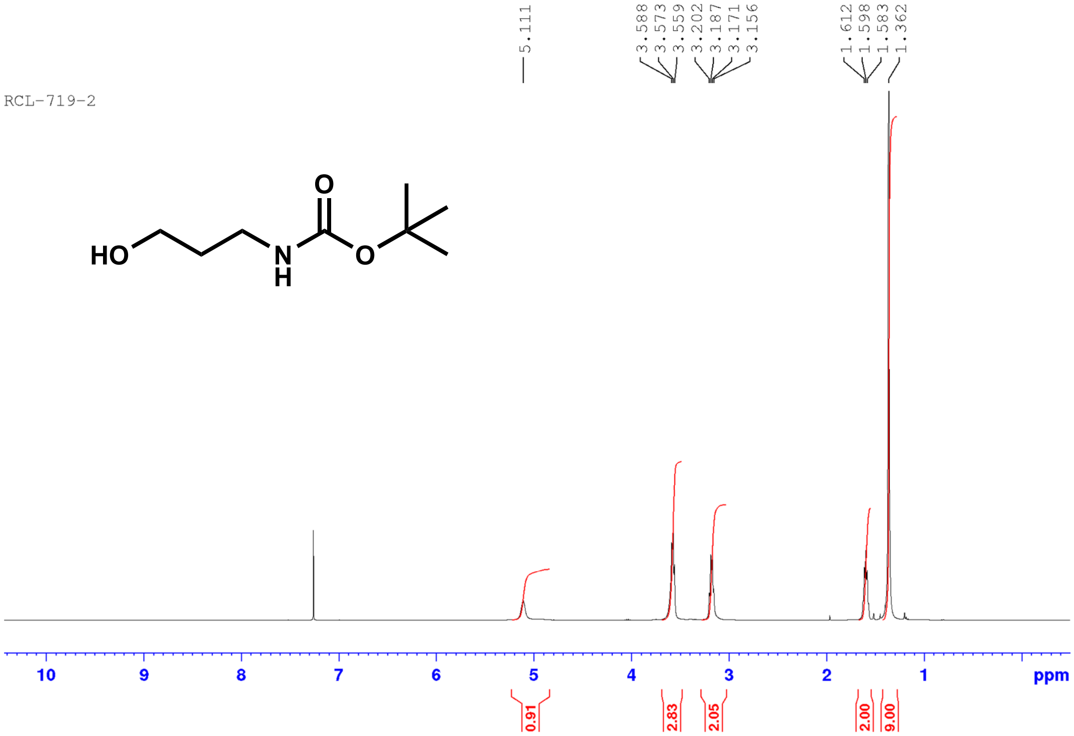


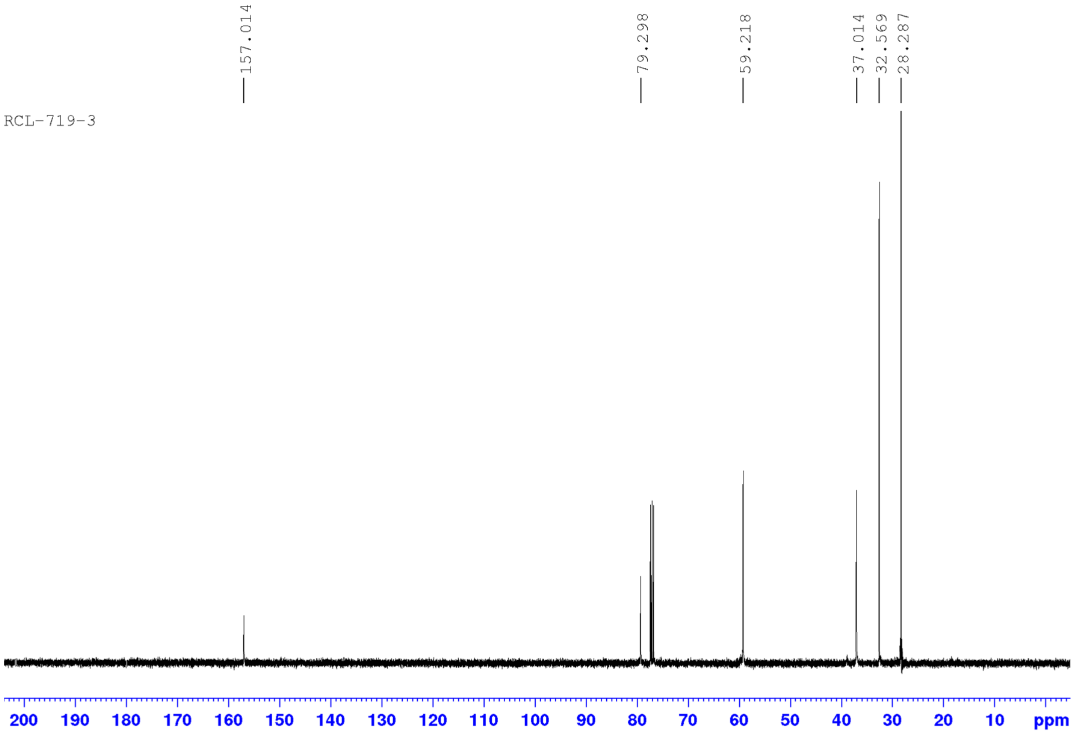
## Methyl (2R,3S,4S)-3,4-bis(4-bromophenyl)-2-(4-nitrophenyl)-5-oxotetrahydrofuran-3-carboxylate (51)



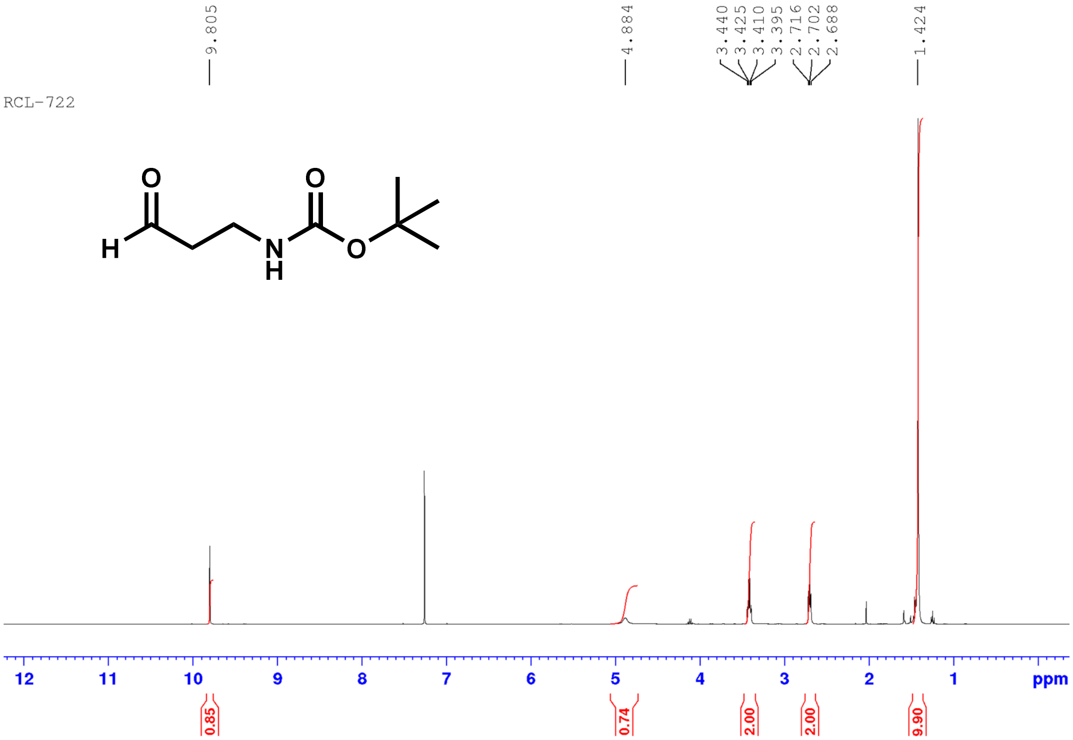


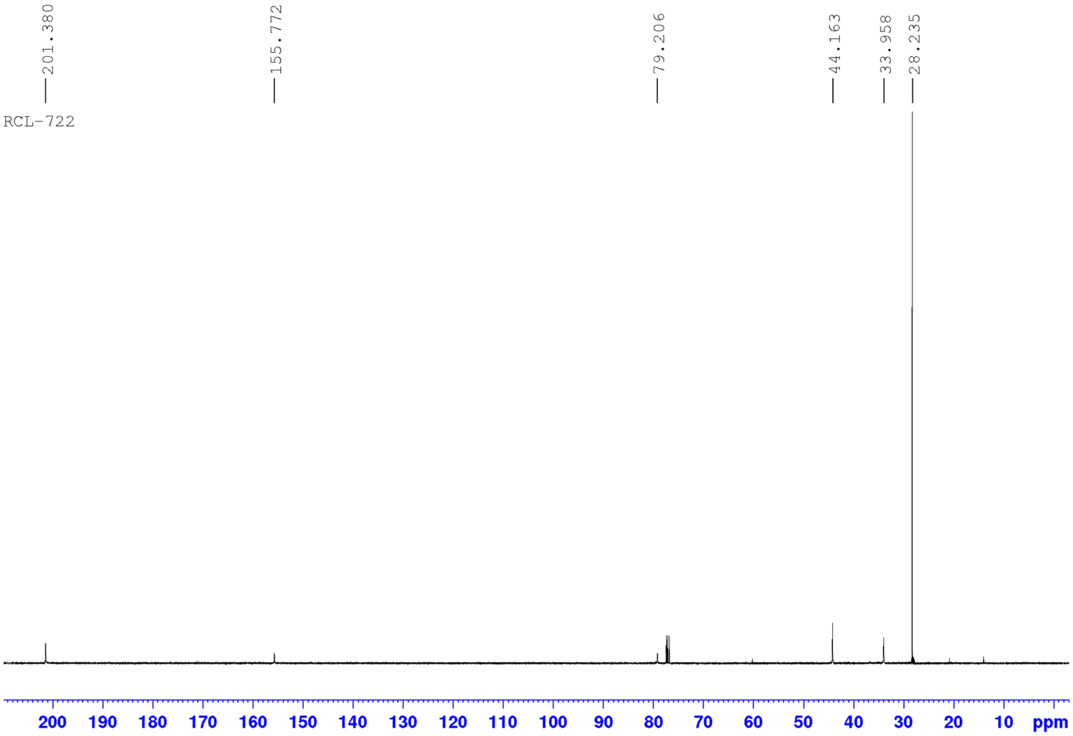
## ***tert*-butyl (3-hydroxypropyl)carbamate (S36)**



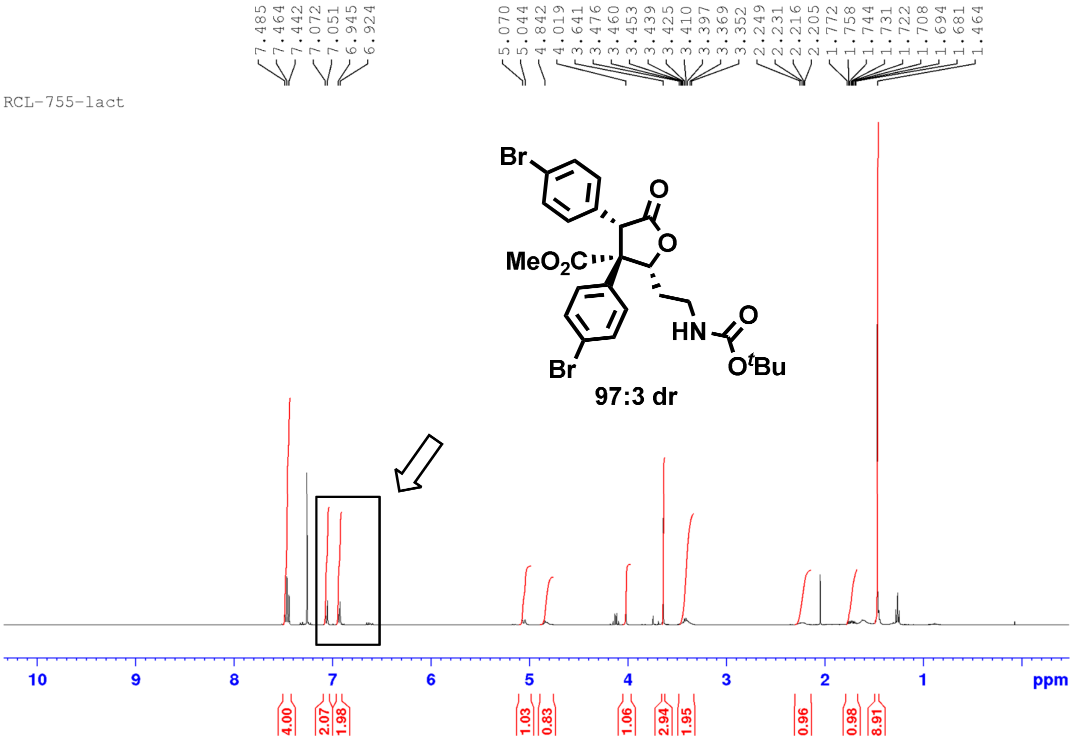


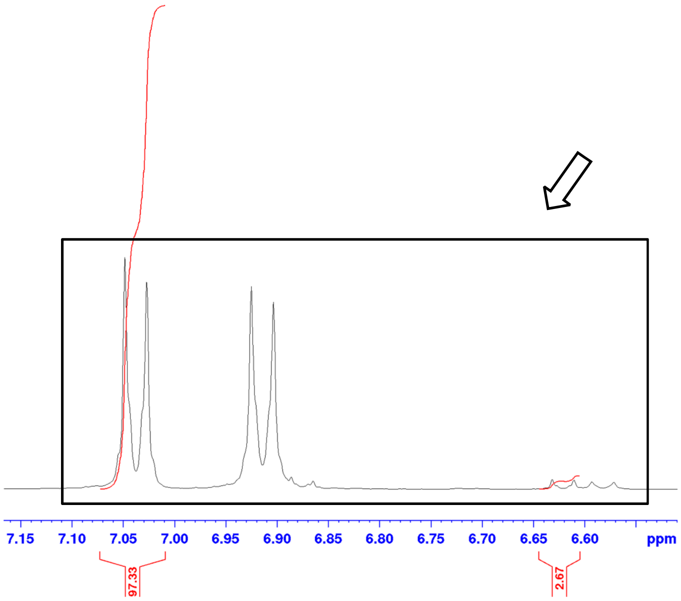
## ***tert*-butyl (3-oxopropyl)carbamate (S37)**



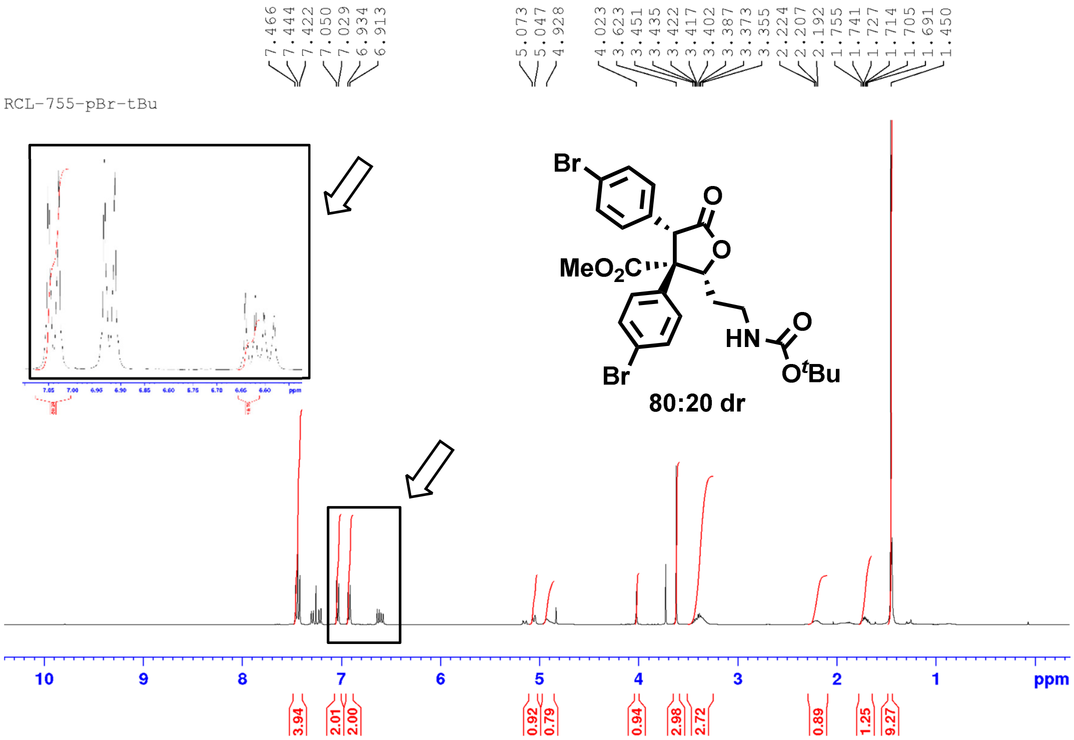


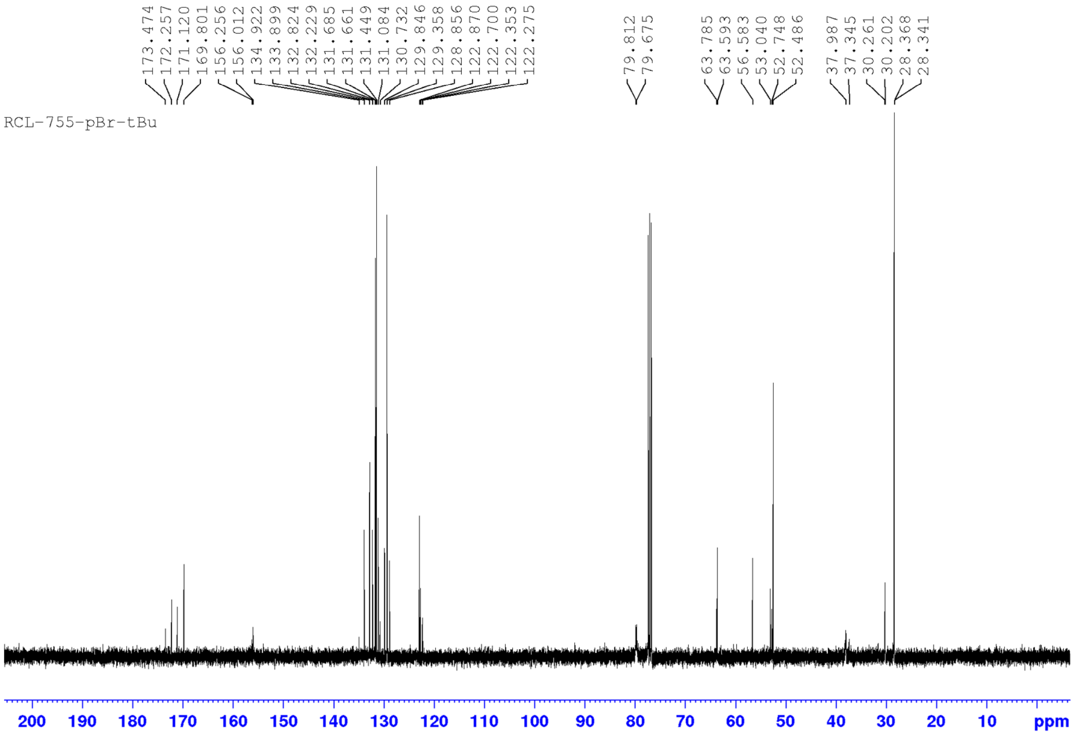
## Methyl (2R,3S,4S)-3,4-bis(4-bromophenyl)-2-(2-((*tert*-butoxycarbonyl)amino)ethyl)-5-oxotetrahydrofuran-3-carboxylate (52)



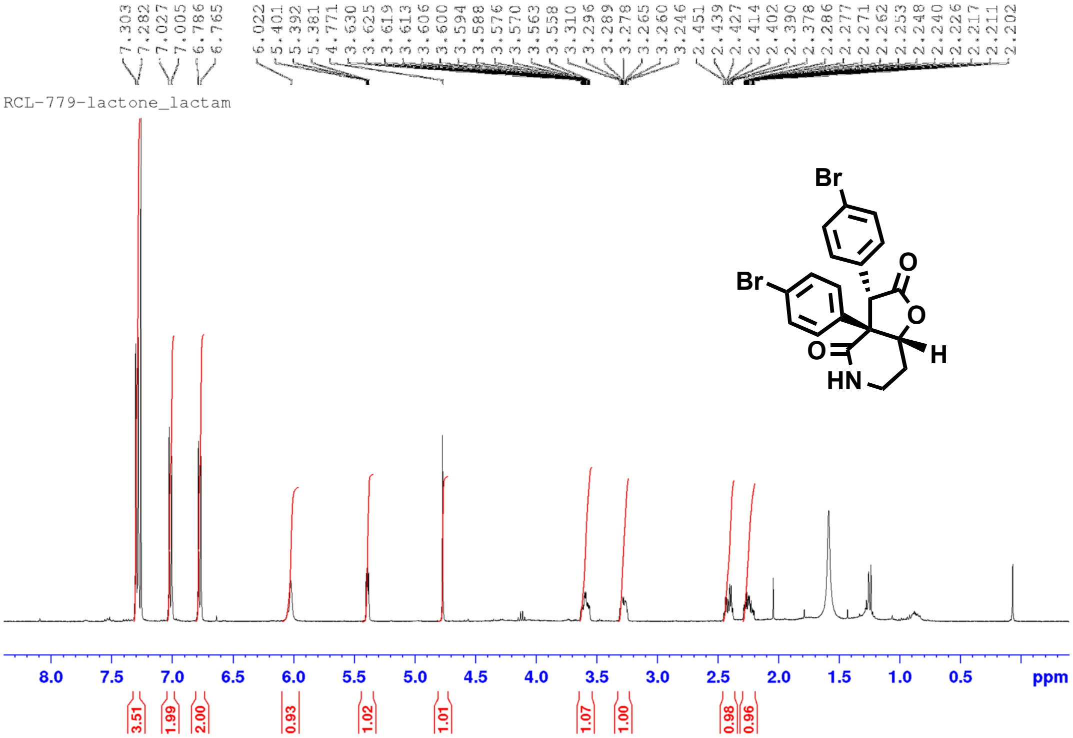


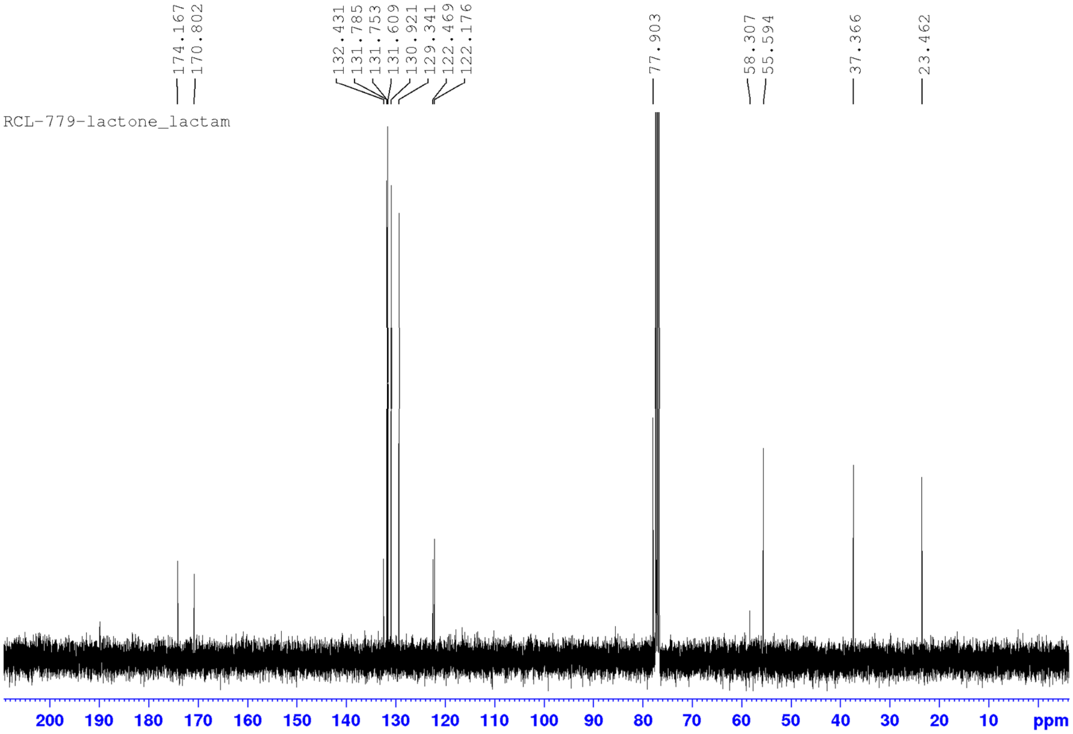
## Methyl (2R,3S,4S)-3,4-bis(4-bromophenyl)-2-(2-((*tert*-butoxycarbonyl)amino)ethyl)-5-oxotetrahydrofuran-3-carboxylate (52)





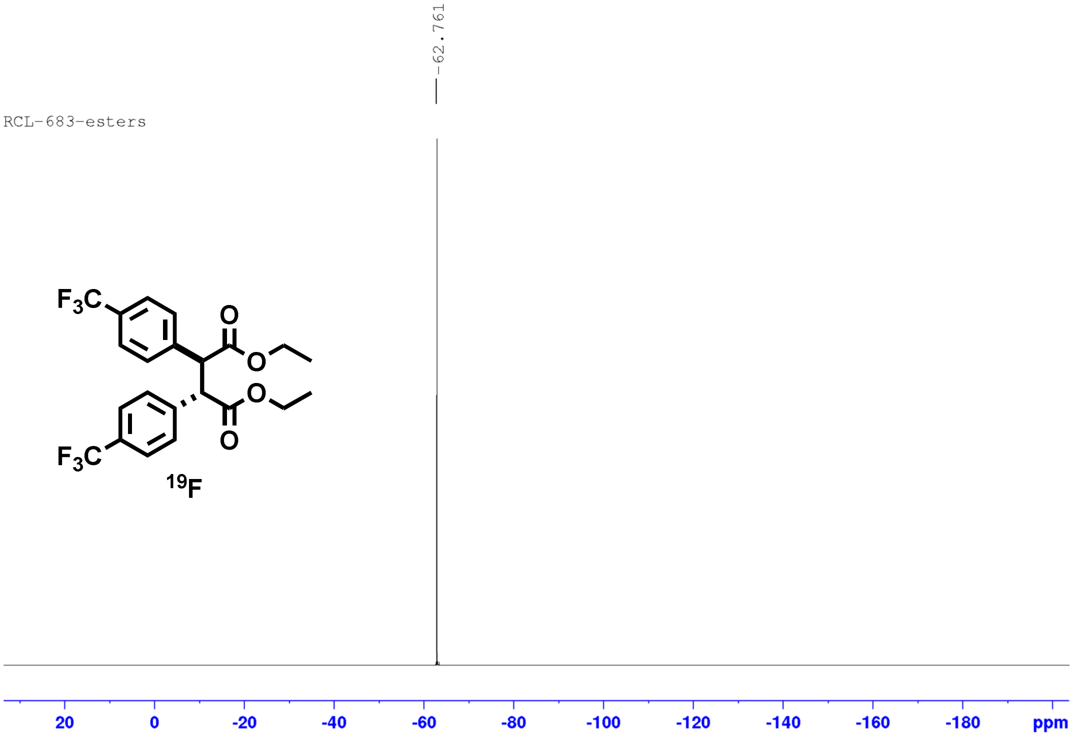
## 3,3a-bis(4-bromophenyl)hexahydrofuro[3,2-c]pyridine-2,4-dione (54b)





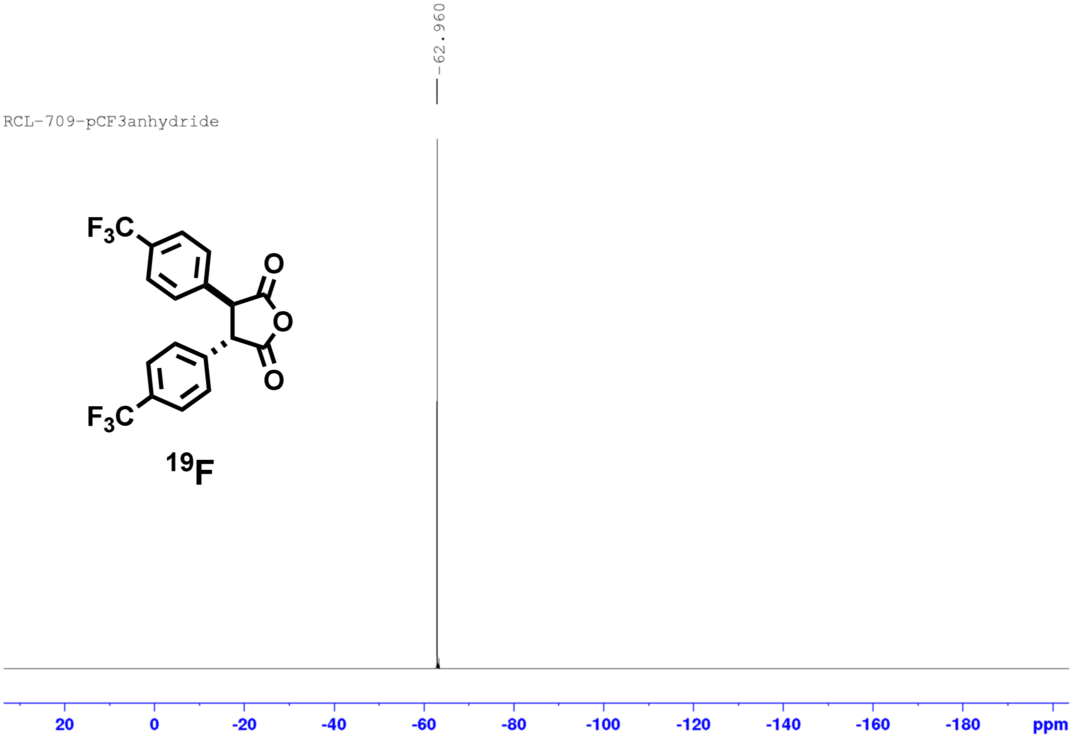
## 9. NMR spectra: $^{19}F$

### Diethyl 2,3-bis(4-(trifluoromethyl)phenyl)succinate (S13)

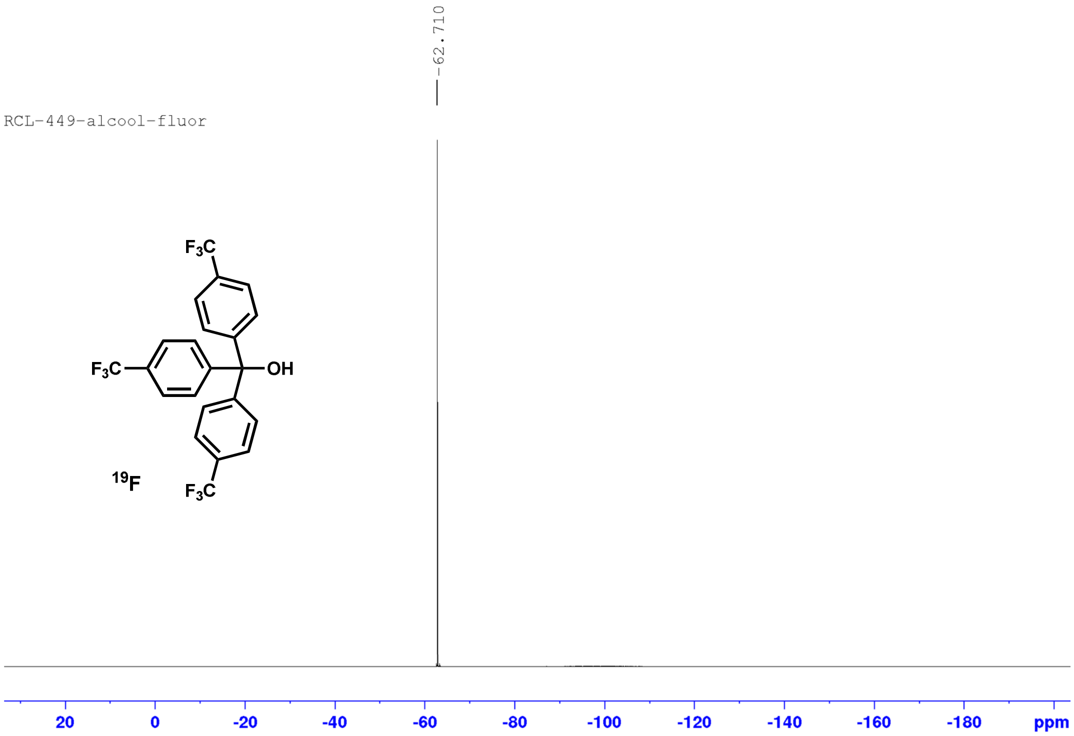


## 2,3-bis(4-(trifluoromethyl)phenyl)succinic acid (S14)

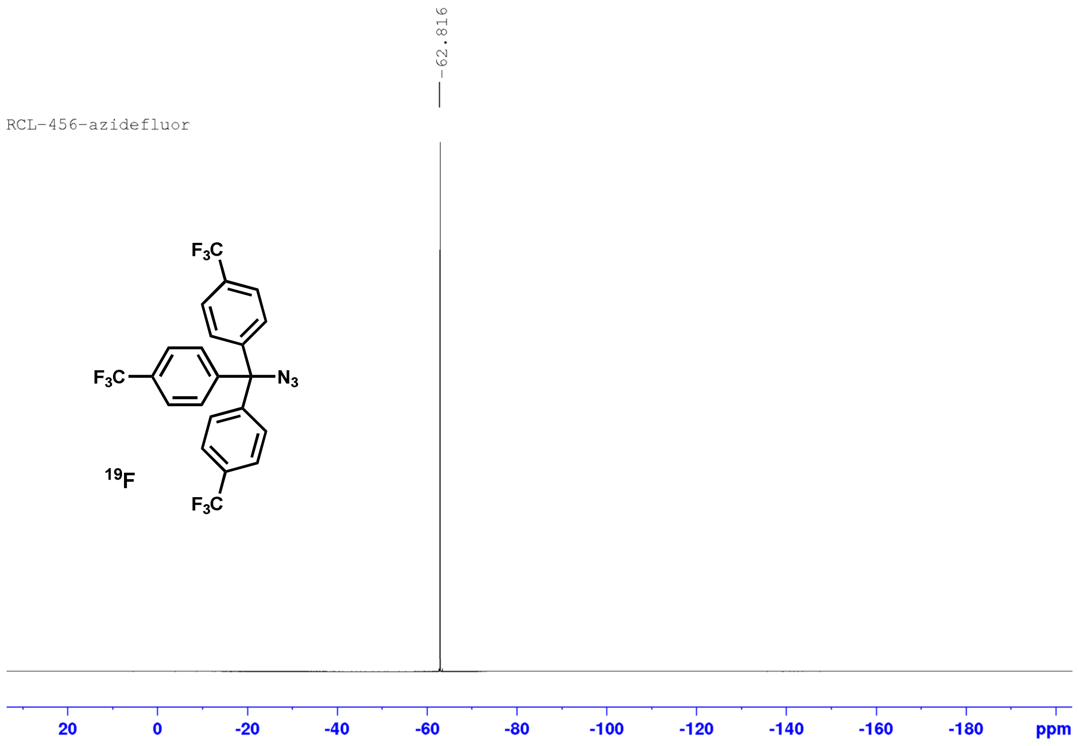
## 3,4-bis(4-(trifluoromethyl)phenyl)dihydrofuran-2,5-dione (44)



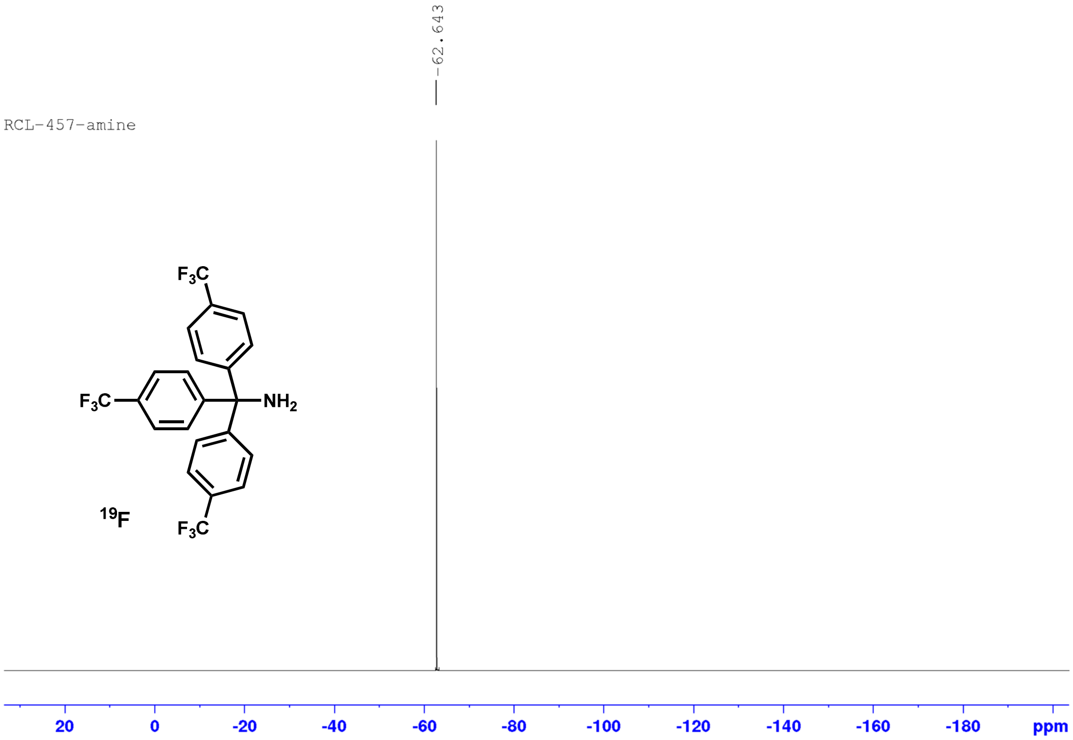
## Tris(4-(trifluoromethyl)phenyl)methanol (S22)



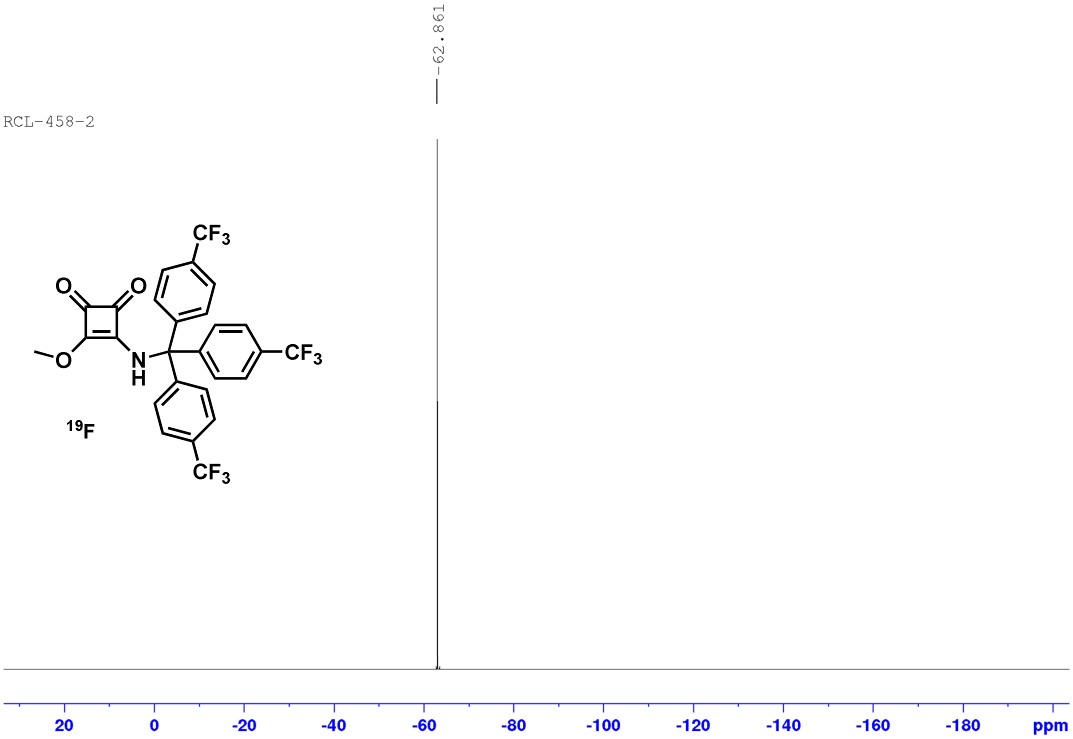
## 4,4',4''-(azidomethanetriyl)tris((trifluoromethyl)benzene) (S23)



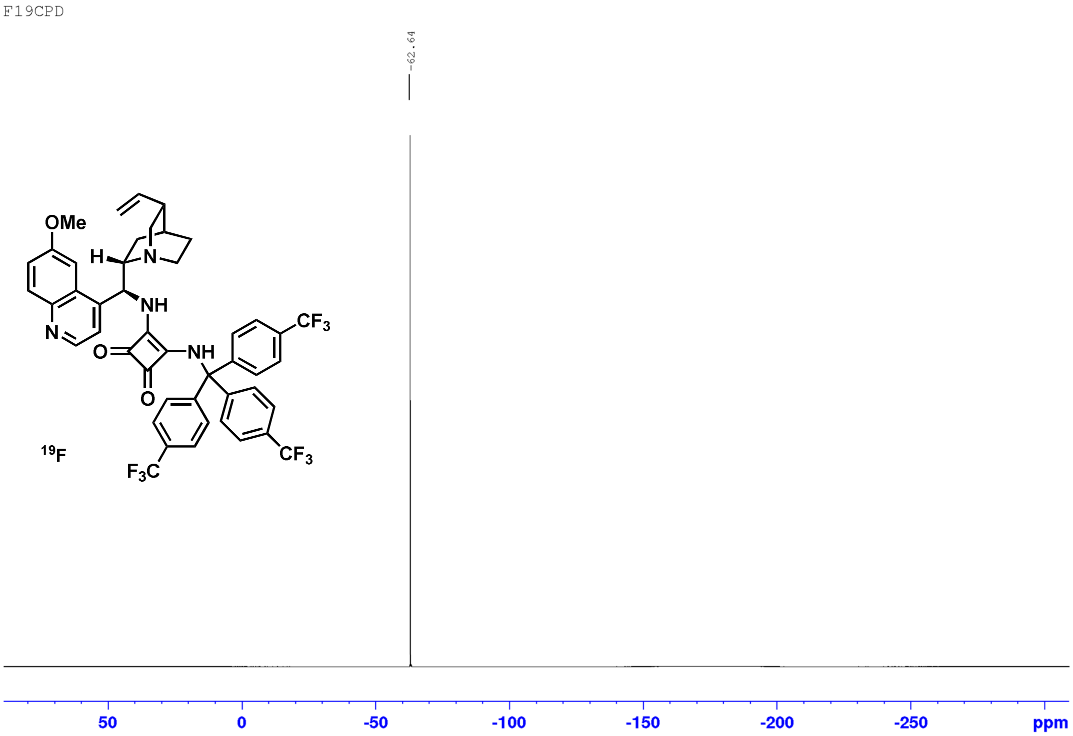
## tris(4-(trifluoromethyl)phenyl)methanamine (S24)



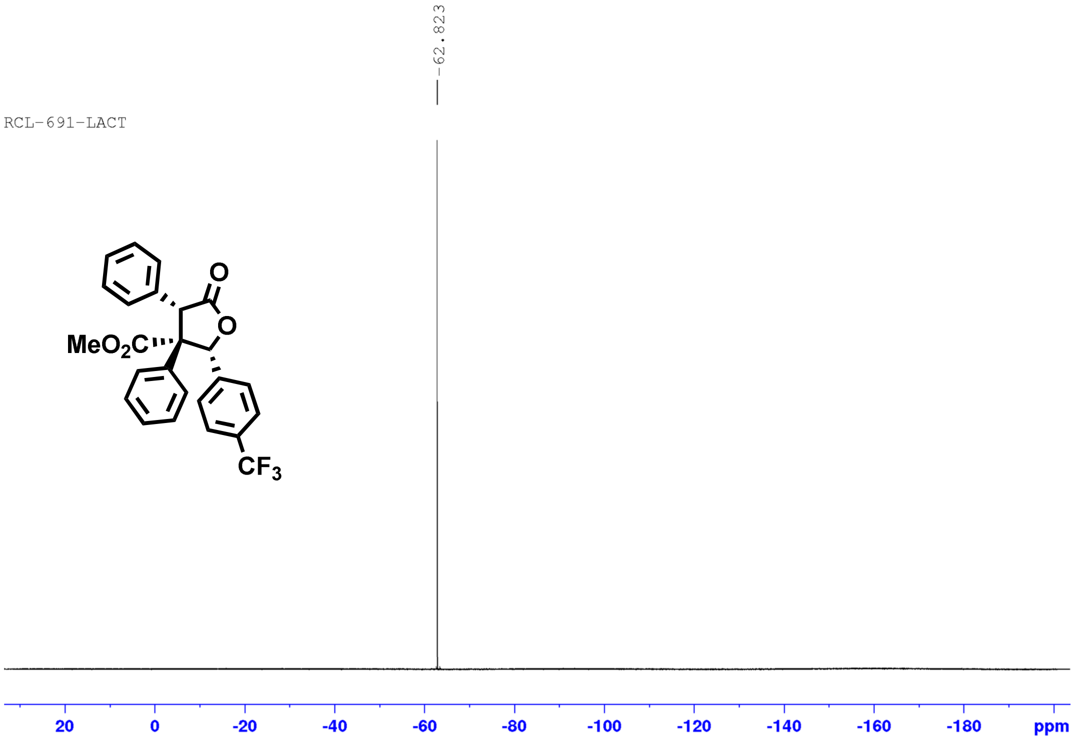
## 3-methoxy-4-((tris(4-(trifluoromethyl)phenyl)methyl)amino)cyclobut-3-ene-1,2-dione (S29)



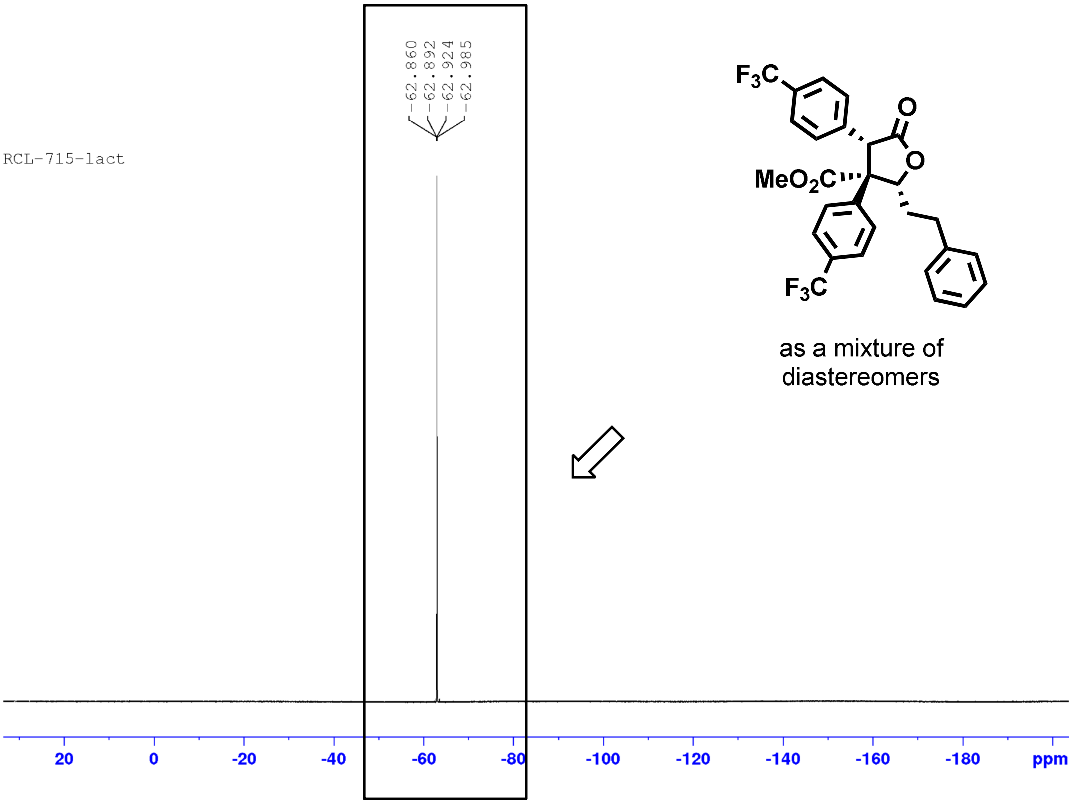
## 3-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-4-((tris(4-(trifluoromethyl)phenyl)methyl)amino)cyclobut-3-ene-1,2-dione (28)



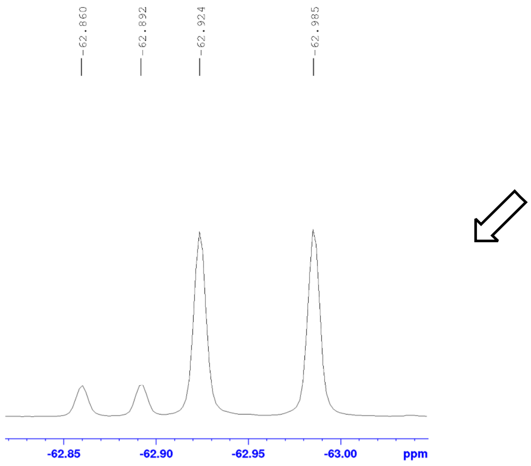
## Methyl (2R,3S,4S)-5-oxo-3,4-diphenyl-2-(4-(trifluoromethyl)phenyl) tetrahydrofuran-3-carboxylate (36)



## Methyl (2R,3S,4S)-5-oxo-2-phenethyl-3,4-bis(4-(trifluoromethyl)phenyl) tetrahydrofuran-3-carboxylate (47)



as a mixture of diastereomers



# 10. HPLC chromatograms

## Racemic preparation of lactones 31-42 and 46-52

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 the relevant freshly distilled or recrystallized 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 20 to 96 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 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 31

### 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*)

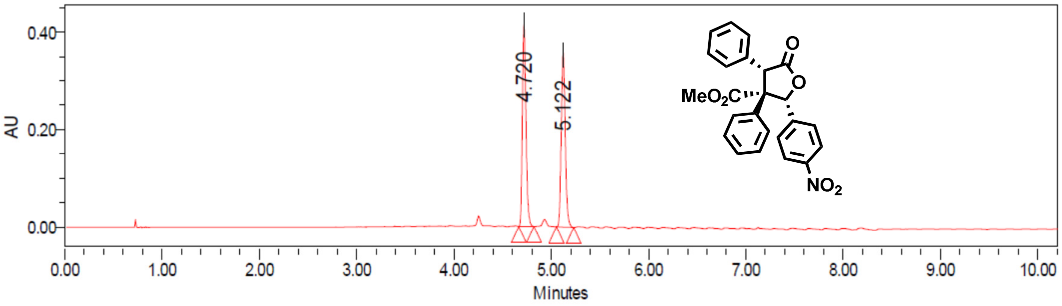
**Column Temperature:** 30 °C

### Gradient Table

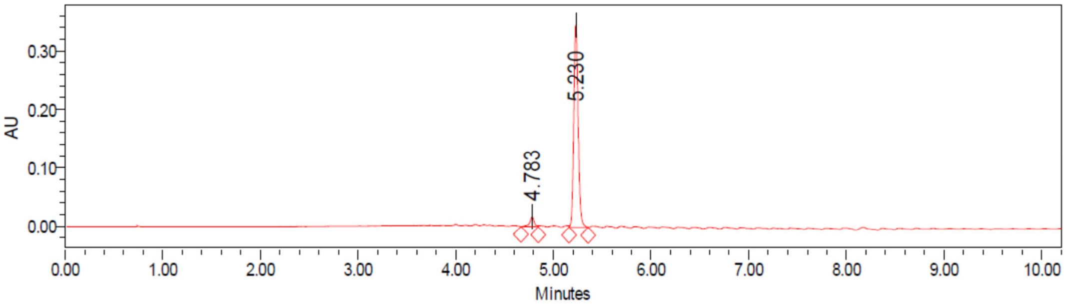
| | Time (min) | FR (mL/min) | A (%) | B (%) | Curve |
|---|---|---|---|---|---|
| **1** | Initial | 1.200 | 97.0 | 3.0 | Initial |
| **2** | 8.50 | 1.200 | 40.0 | 60.0 | 6 |
| **3** | 10.00 | 1.200 | 40.0 | 60.0 | 6 |
| **4** | 10.10 | 1.200 | 97.0 | 3.0 | 6 |

**Inlet Pressure:** 1500 (psi)

### Racemic:



### Chiral: 90% *ee*



### Peak Results: Racemic

| | Ret. Time (min) | Rel. Area (%) |
|---|---|---|
| **1** | 4.720 | 50.96 |
| **2** | 5.122 | 49.04 |
| **Total:** | | 100.00 |

### Peak Results: Chiral

| | Ret. Time (min) | Rel. Area (%) |
|---|---|---|
| **1** | 4.783 | 4.87 |
| **2** | 5.230 | 95.13 |
| **Total:** | | 100.00 |

## Product 32

**Study Conditions**

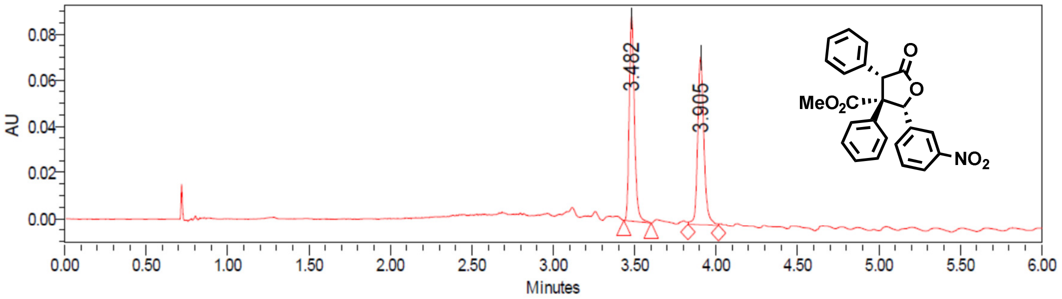
| |
|---|
| **Instrument:** ACQUITY UPC$^2$ |
| **Chiral Stationary Phase:**<br>ACQUITY UPC$^2$ Trefoil CEL1, 2.5μm<br>3.0 x 150mm Column |
| **Detection:** UV 254 nm with PDA detector |
| **Mobile Phase:**<br>A = $CO_2$, B = Methanol/IPA (1:1, *v*:*v*) |
| **Column Temperature:** 30 °C |

**Gradient Table**

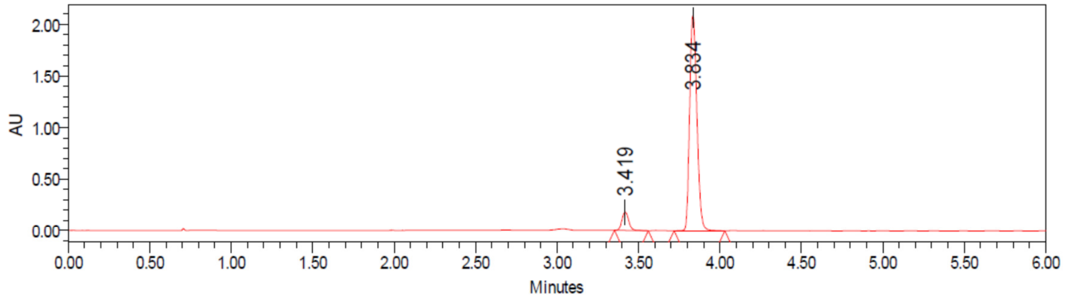
| | **Time** (min) | **FR** (mL/min) | **A** (%) | **B** (%) | **Curve** |
|---|---|---|---|---|---|
| **1** | Initial | 1.200 | 97.0 | 3.0 | Initial |
| **2** | 8.50 | 1.200 | 40.0 | 60.0 | 6 |
| **3** | 10.00 | 1.200 | 40.0 | 60.0 | 6 |
| **4** | 10.10 | 1.200 | 97.0 | 3.0 | 6 |

| |
|---|
| **Inlet Pressure:** 1500 (psi) |

**Racemic:**



**Chiral: 85% *ee***



**Peak Results: Racemic**

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 3.482 | 50.40 |
| **2** | 3.905 | 49.60 |
| **Total:** | | 100.00 |

**Peak Results: Chiral**

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 3.419 | 7.52 |
| **2** | 3.834 | 92.48 |
| **Total:** | | 100.00 |

**Product 33**

**Study Conditions**

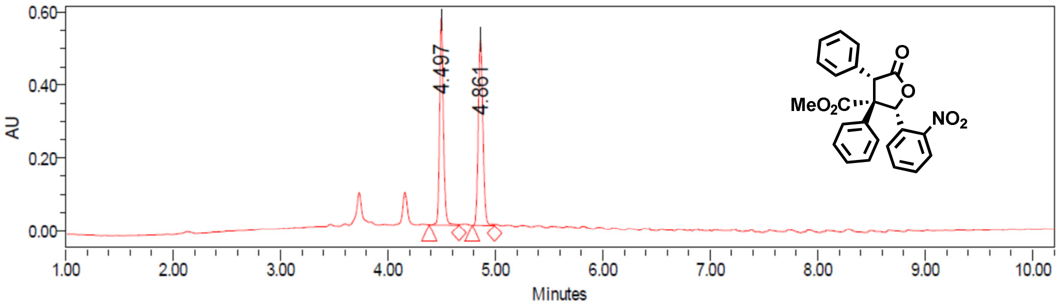
| |
|---|
| **Instrument:** ACQUITY UPC$^2$ |
| **Chiral Stationary Phase:**<br>ACQUITY UPC$^2$ Trefoil CEL1, 2.5µm<br>3.0 x 150mm Column |
| **Detection:** UV 254 nm with PDA detector |
| **Mobile Phase:**<br>A = $CO_2$, B = Methanol/IPA (1:1, *v*:*v*) |
| **Column Temperature:** 30 °C |

**Gradient Table**

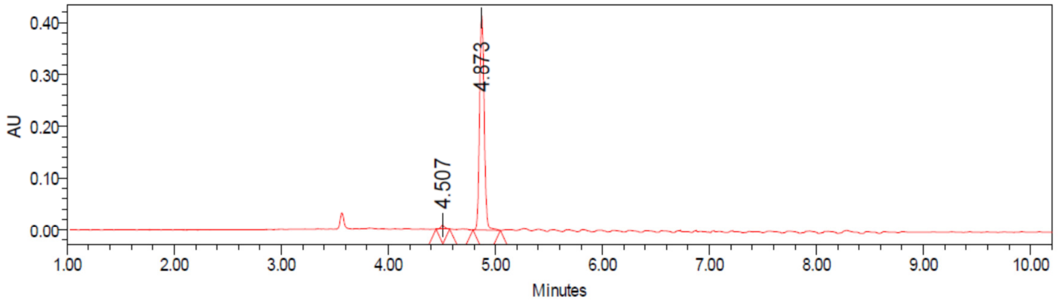
| | **Time** (min) | **FR** (mL/min) | **A** (%) | **B** (%) | **Curve** |
|---|---|---|---|---|---|
| **1** | Initial | 1.200 | 97.0 | 3.0 | Initial |
| **2** | 8.50 | 1.200 | 40.0 | 60.0 | 6 |
| **3** | 10.00 | 1.200 | 40.0 | 60.0 | 6 |
| **4** | 10.10 | 1.200 | 97.0 | 3.0 | 6 |

**Inlet Pressure:** 1500 (psi)

**Racemic:**



**Chiral: 97% *ee***



**Peak Results: Racemic**

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 4.497 | 48.68 |
| **2** | 4.861 | 51.32 |
| **Total:** | | 100.00 |

**Peak Results: Chiral**

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 4.507 | 1.71 |
| **2** | 4.873 | 98.29 |
| **Total:** | | 100.00 |

## Product 34

### Study Conditions

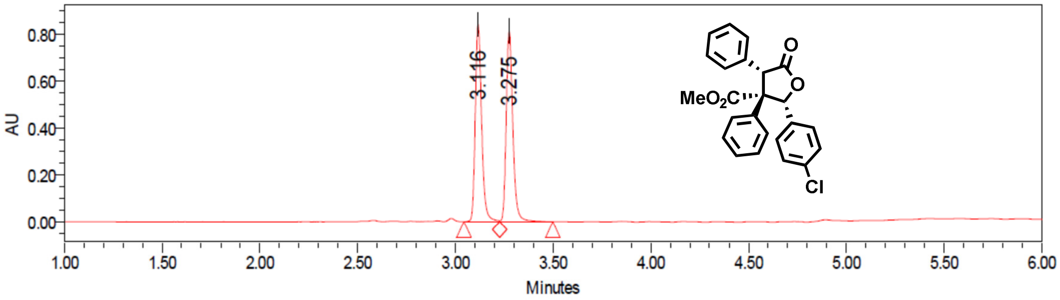
| | |
|---|---|
| **Instrument:** ACQUITY UPC$^2$ | |
| **Chiral Stationary Phase:**<br>ACQUITY UPC$^2$ Trefoil CEL2, 2.5µm<br>3.0 x 150mm Column | |
| **Detection:** UV 254 nm with PDA detector | |
| **Mobile Phase:**<br>A = $CO_2$, B = Ethanol/ACN (1:1, *v*:*v*) | |
| **Column Temperature:** 30 °C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

### Gradient Table

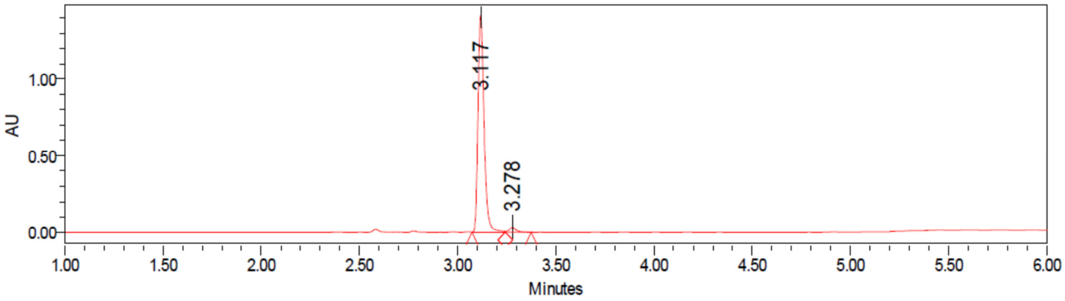
| | **Time** (min) | **FR** (mL/min) | **A** (%) | **B** (%) | **Curve** |
|---|---|---|---|---|---|
| **1** | Initial | 1.200 | 97.0 | 3.0 | Initial |
| **2** | 4.50 | 1.200 | 40.0 | 60.0 | 6 |
| **3** | 6.00 | 1.200 | 40.0 | 60.0 | 6 |
| **4** | 6.10 | 1.200 | 97.0 | 3.0 | 6 |

**Inlet Pressure:** 1500 (psi)

**Racemic:**



**Chiral: 95% *ee***



### Peak Results: Racemic

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 3.116 | 49.96 |
| **2** | 3.275 | 50.04 |
| **Total:** | | 100.00 |

### Peak Results: Chiral

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 3.117 | 97.55 |
| **2** | 3.278 | 2.45 |
| **Total:** | | 100.00 |

## Product 35

### Study Conditions

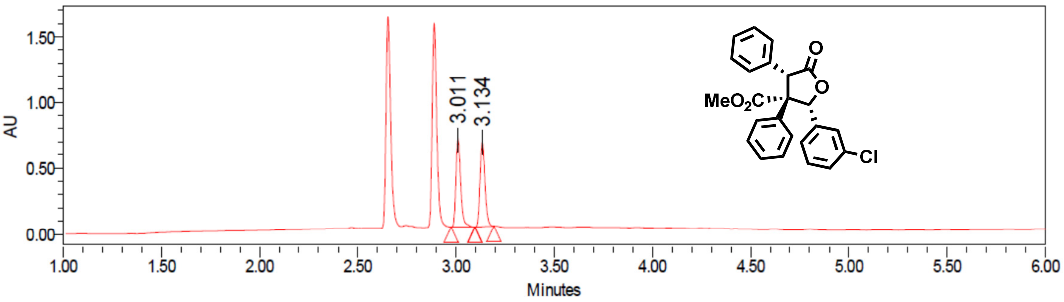
| | |
|---|---|
| **Instrument:** ACQUITY UPC$^2$ | |
| **Chiral Stationary Phase:**<br>ACQUITY UPC$^2$ Trefoil CEL1, 2.5µm<br>3.0 x 150mm Column | |
| **Detection:** UV 230 nm with PDA detector | |
| **Mobile Phase:**<br>A = $CO_2$, B = Methanol/IPA (1:1, *v*:*v*) | |
| **Column Temperature:** 30 °C | |

### Gradient Table

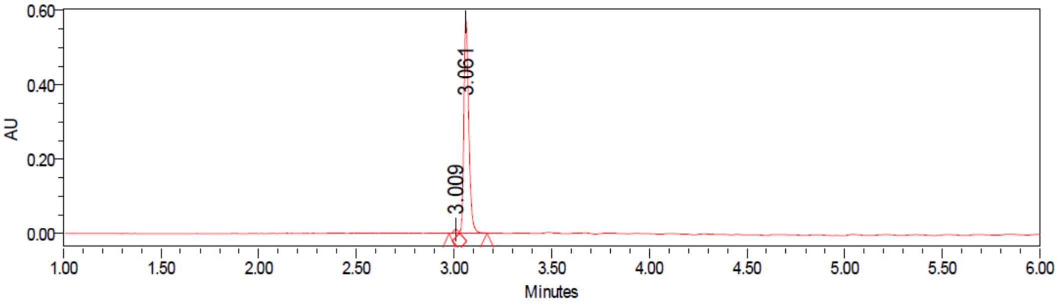
| | Time (min) | FR (mL/min) | A (%) | B (%) | Curve |
|---|---|---|---|---|---|
| **1** | Initial | 1.200 | 97.0 | 3.0 | Initial |
| **2** | 4.50 | 1.200 | 40.0 | 60.0 | 6 |
| **3** | 6.00 | 1.200 | 40.0 | 60.0 | 6 |
| **4** | 6.10 | 1.200 | 97.0 | 3.0 | 6 |

**Inlet Pressure:** 1500 (psi)

### Racemic:



### Chiral: 97% *ee*



### Peak Results: Racemic

| | Ret. Time (min) | Rel. Area (%) |
|---|---|---|
| **1** | 3.011 | 50.04 |
| **2** | 3.134 | 49.96 |
| **Total:** | | 100.00 |

### Peak Results: Chiral

| | Ret. Time (min) | Rel. Area (%) |
|---|---|---|
| **1** | 3.009 | 1.55 |
| **2** | 3.061 | 98.45 |
| **Total:** | | 100.00 |

## Product 36

### Study Conditions

**Instrument:** ACQUITY UPC$^2$

**Chiral Stationary Phase:**

ACQUITY UPC$^2$ Trefoil CEL1, 2.5μm

3.0 x 150mm Column

**Detection:** UV 212 nm with PDA detector

**Mobile Phase:**

A = $CO_2$, B = Methanol/IPA (1:1, *v*:*v*)

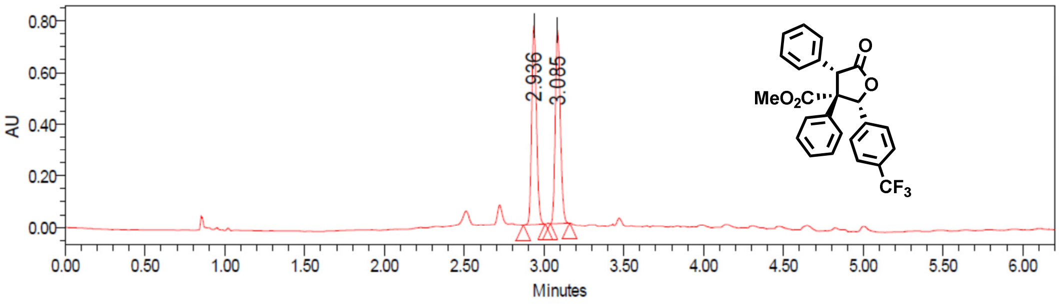
**Column Temperature:** 30 °C

### Gradient Table

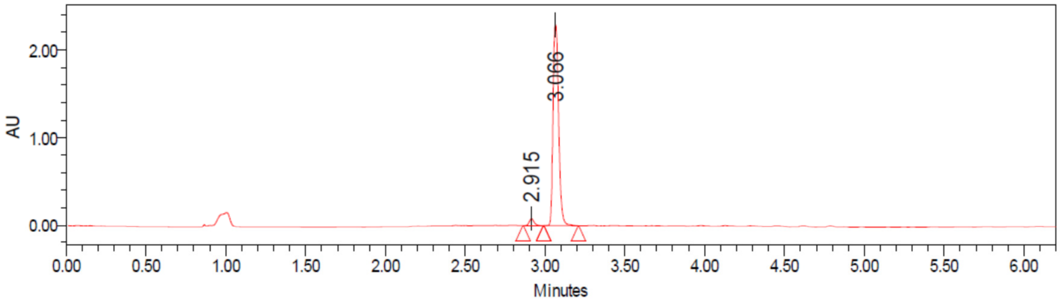
| | Time (min) | FR (mL/min) | A (%) | B (%) | Curve |
|---|---|---|---|---|---|
| **1** | Initial | 1.200 | 97.0 | 3.0 | Initial |
| **2** | 4.50 | 1.200 | 40.0 | 60.0 | 6 |
| **3** | 6.00 | 1.200 | 40.0 | 60.0 | 6 |
| **4** | 6.10 | 1.200 | 97.0 | 3.0 | 6 |

**Inlet Pressure:** 1500 (psi)

### Racemic:



### Chiral: 94% *ee*



### Peak Results: Racemic

| | Ret. Time (min) | Rel. Area (%) |
|---|---|---|
| **1** | 2.936 | 49.63 |
| **2** | 3.085 | 50.37 |
| **Total:** | | 100.00 |

### Peak Results: Chiral

| | Ret. Time (min) | Rel. Area (%) |
|---|---|---|
| **1** | 2.915 | 2.96 |
| **2** | 3.066 | 97.04 |
| **Total:** | | 100.00 |

## Product 37

### Study Conditions

**Instrument:** ACQUITY UPC$^2$

**Chiral Stationary Phase:**

ACQUITY UPC$^2$ Trefoil CEL1, 2.5µm
3.0 x 150mm Column

**Detection:** UV 212 nm with PDA detector

**Mobile Phase:**

A = $CO_2$, B = Methanol/IPA (1:1, *v*:*v*)

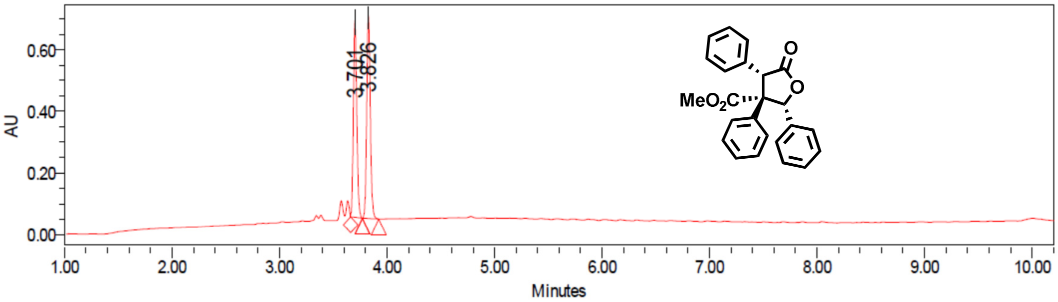
**Column Temperature:** 30 °C

### Gradient Table

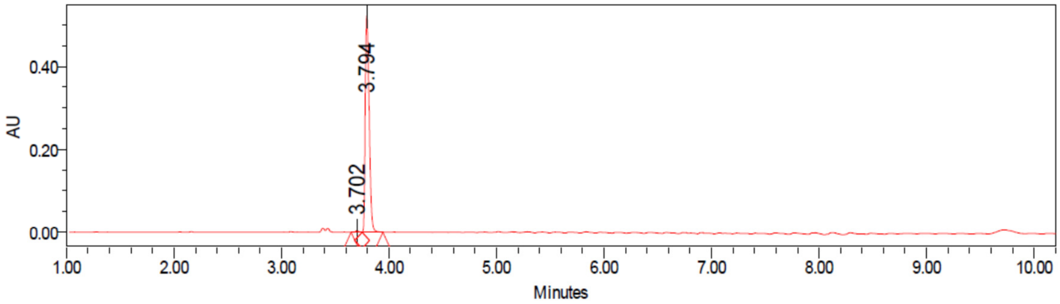
| | Time (min) | FR (mL/min) | A (%) | B (%) | Curve |
|---|---|---|---|---|---|
| **1** | Initial | 1.200 | 97.0 | 3.0 | Initial |
| **2** | 8.50 | 1.200 | 40.0 | 60.0 | 6 |
| **3** | 10.00 | 1.200 | 40.0 | 60.0 | 6 |
| **4** | 10.10 | 1.200 | 97.0 | 3.0 | 6 |

**Inlet Pressure:** 1500 (psi)

**Racemic:**



**Chiral: 99% *ee***



### Peak Results: Racemic

| | Ret. Time (min) | Rel. Area (%) |
|---|---|---|
| **1** | 3.701 | 48.84 |
| **2** | 3.826 | 51.16 |
| **Total:** | | 100.00 |

### Peak Results: Chiral

| | Ret. Time (min) | Rel. Area (%) |
|---|---|---|
| **1** | 3.702 | 0.57 |
| **2** | 3.794 | 99.43 |
| **Total:** | | 100.00 |

**Product 38**

**Study Conditions**

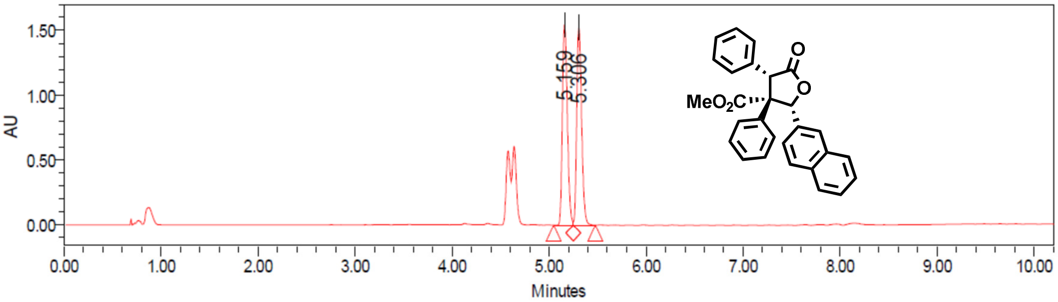
| |
|---|
| **Instrument:** ACQUITY UPC$^2$ |
| **Chiral Stationary Phase:**<br>ACQUITY UPC$^2$ Trefoil AMY1, 2.5µm<br>3.0 x 150mm Column |
| **Detection:** UV 254 nm with PDA detector |
| **Mobile Phase:**<br>A = $CO_2$, B = Ethanol/ACN (1:1, *v*:*v*) |
| **Column Temperature:** 30 °C |

**Gradient Table**

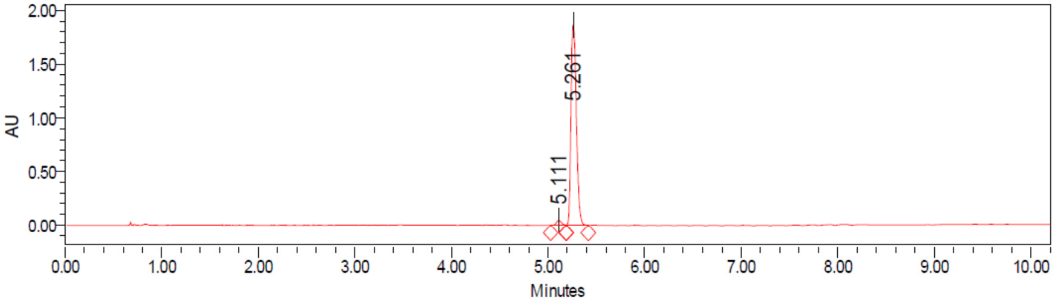
| | **Time** (min) | **FR** (mL/min) | **A** (%) | **B** (%) | **Curve** |
|---|---|---|---|---|---|
| **1** | Initial | 1.200 | 97.0 | 3.0 | Initial |
| **2** | 8.50 | 1.200 | 40.0 | 60.0 | 6 |
| **3** | 10.00 | 1.200 | 40.0 | 60.0 | 6 |
| **4** | 10.10 | 1.200 | 97.0 | 3.0 | 6 |

| |
|---|
| **Inlet Pressure:** 1500 (psi) |

**Racemic:**



**Chiral: 96% *ee***



**Peak Results: Racemic**

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 5.159 | 50.50 |
| **2** | 5.306 | 49.50 |
| **Total:** | | 100.00 |

**Peak Results: Chiral**

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 5.111 | 2.24 |
| **2** | 5.261 | 97.76 |
| **Total:** | | 100.00 |

## Product 39

**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*)

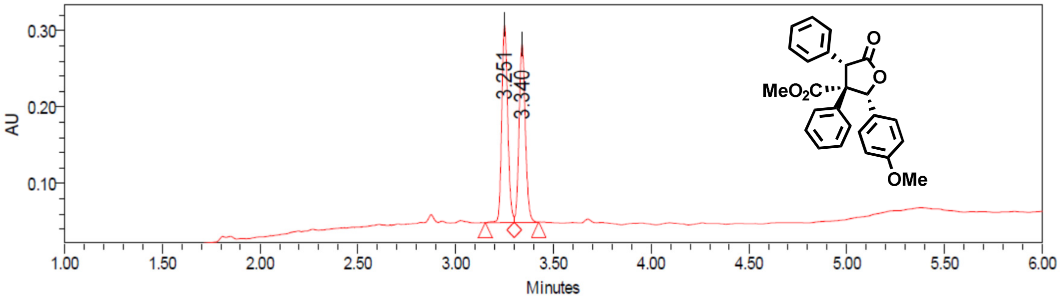
**Column Temperature:** 30 °C

**Gradient Table**

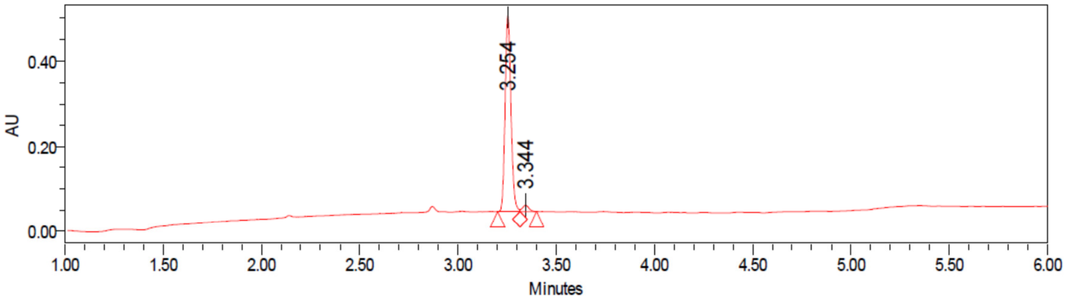
| | **Time** (min) | **FR** (mL/min) | **A** (%) | **B** (%) | **Curve** |
|---|---|---|---|---|---|
| **1** | Initial | 1.200 | 97.0 | 3.0 | Initial |
| **2** | 4.50 | 1.200 | 40.0 | 60.0 | 6 |
| **3** | 6.00 | 1.200 | 40.0 | 60.0 | 6 |
| **4** | 6.10 | 1.200 | 97.0 | 3.0 | 6 |

**Inlet Pressure:** 1500 (psi)

**Racemic:**



**Chiral: 93% *ee***



**Peak Results: Racemic**

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 3.251 | 50.15 |
| **2** | 3.340 | 49.85 |
| **Total:** | | 100.00 |

**Peak Results: Chiral**

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 3.254 | 96.67 |
| **2** | 3.344 | 3.33 |
| **Total:** | | 100.00 |

## Product 40

### Study Conditions

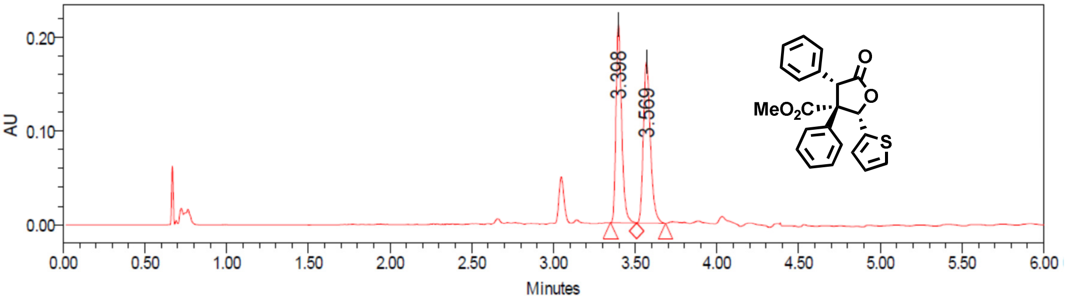
| |
|---|
| **Instrument:** ACQUITY UPC$^2$ |
| **Chiral Stationary Phase:**<br>ACQUITY UPC$^2$ Trefoil AMY1, 2.5µm<br>3.0 x 150mm Column |
| **Detection:** UV 254 nm with PDA detector |
| **Mobile Phase:**<br>A = CO2, B = Ethanol/IPA (1:1, *v*:*v*) |
| **Column Temperature:** 30 °C |

### Gradient Table

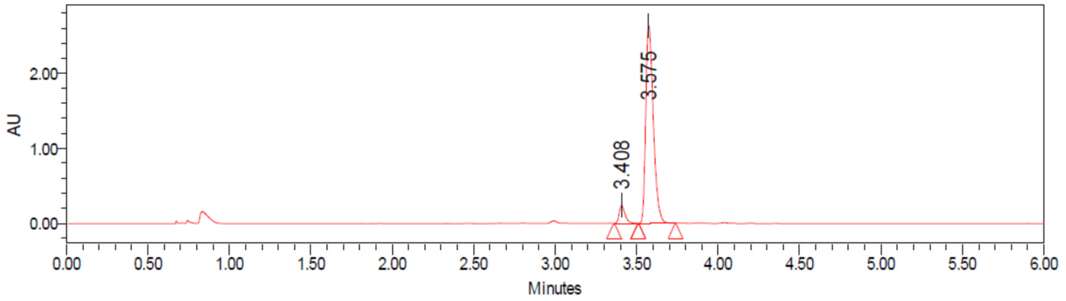
| | Time (min) | FR (mL/min) | A (%) | B (%) | Curve |
|---|---|---|---|---|---|
| **1** | Initial | 1.200 | 97.0 | 3.0 | Initial |
| **2** | 4.50 | 1.200 | 40.0 | 60.0 | 6 |
| **3** | 6.00 | 1.200 | 40.0 | 60.0 | 6 |
| **4** | 6.10 | 1.200 | 97.0 | 3.0 | 6 |

**Inlet Pressure:** 1500 (psi)

### Racemic:



### Chiral: 87% *ee*



### Peak Results: Racemic

| | Ret. Time (min) | Rel. Area (%) |
|---|---|---|
| **1** | 3.398 | 49.77 |
| **2** | 3.569 | 50.23 |
| **Total:** | | 100.00 |

### Peak Results: Chiral

| | Ret. Time (min) | Rel. Area (%) |
|---|---|---|
| **1** | 3.408 | 6.55 |
| **2** | 3.575 | 93.45 |
| **Total:** | | 100.00 |

**Product 41**

### 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*)

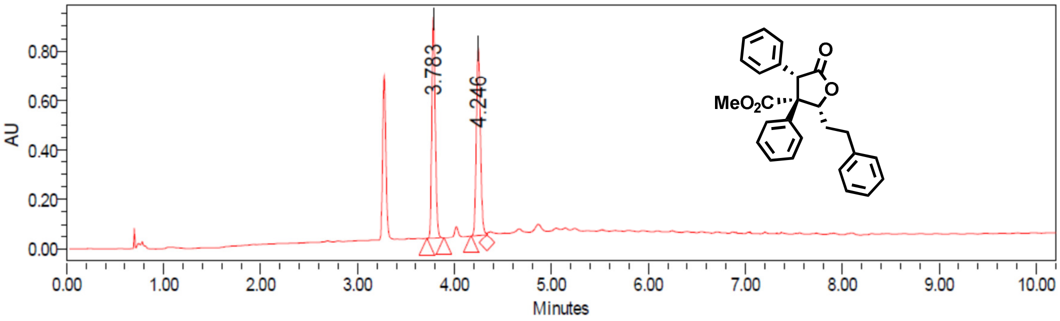
**Column Temperature:** 30 °C

### Gradient Table

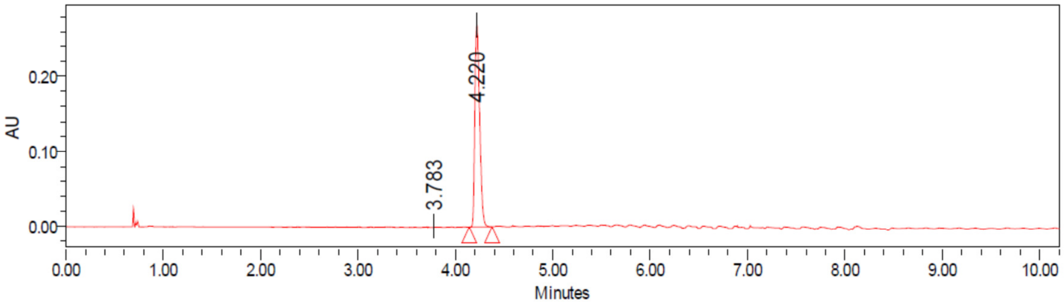
| | Time (min) | FR (mL/min) | A (%) | B (%) | Curve |
|---|---|---|---|---|---|
| **1** | Initial | 1.200 | 97.0 | 3.0 | Initial |
| **2** | 8.50 | 1.200 | 40.0 | 60.0 | 6 |
| **3** | 10.00 | 1.200 | 40.0 | 60.0 | 6 |
| **4** | 10.10 | 1.200 | 97.0 | 3.0 | 6 |

**Inlet Pressure:** 1500 (psi)

**Racemic:**



**Chiral: >99% *ee***



**Peak Results: Racemic**

| | Ret. Time (min) | Rel. Area (%) |
|---|---|---|
| **1** | 3.783 | 50.17 |
| **2** | 4.246 | 49.83 |
| **Total:** | | 100.00 |

**Peak Results: Chiral**

| | Ret. Time (min) | Rel. Area (%) |
|---|---|---|
| **1** | 3.783 | 0.02 |
| **2** | 4.220 | 99.98 |
| **Total:** | | 100.00 |

**Product 42**

**Study Conditions**

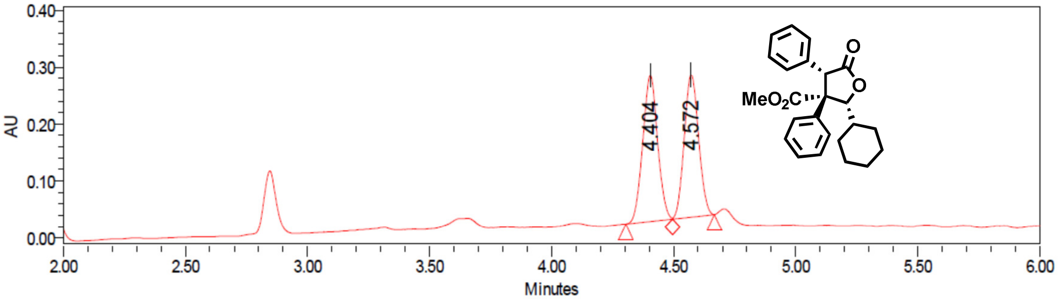
| | |
|---|---|
| **Instrument:** ACQUITY UPC$^2$ | |
| **Chiral Stationary Phase:**<br>ACQUITY UPC$^2$ Trefoil AMY1, 2.5μm<br>3.0 x 150mm Column | |
| **Detection:** UV 212 nm with PDA detector | |
| **Mobile Phase:**<br>A = $CO_2$, B = Ethanol/ACN/IPA (1:1:1, *v*:*v*:*v*) | |
| **Column Temperature:**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

**Gradient Table**

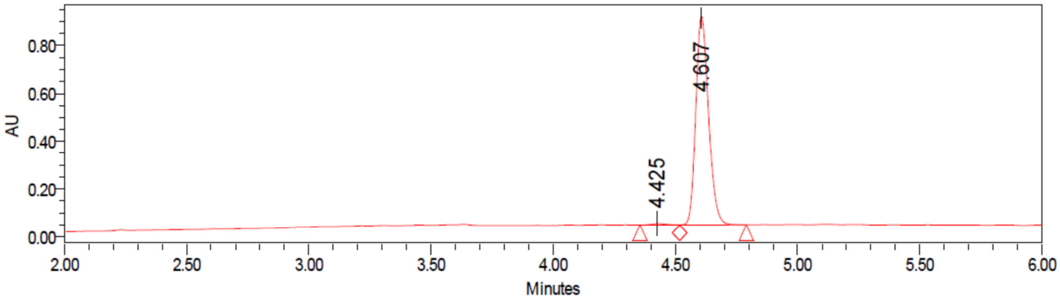
| | **Time** (min) | **FR** (mL/min) | **A** (%) | **B** (%) | **Curve** |
|---|---|---|---|---|---|
| **1** | Initial | 1.200 | 97.0 | 3.0 | Initial |
| **2** | 8.50 | 1.200 | 40.0 | 60.0 | 6 |
| **3** | 10.00 | 1.200 | 40.0 | 60.0 | 6 |
| **4** | 10.10 | 1.200 | 97.0 | 3.0 | 6 |

**Inlet Pressure:** 1500 (psi)

**Racemic:**



**Chiral: 99% *ee***



**Peak Results: Racemic**

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 4.404 | 51.52 |
| **2** | 4.572 | 48.48 |
| **Total:** | | 100.00 |

**Peak Results: Chiral**

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 4.425 | 0.77 |
| **2** | 4.607 | 99.23 |
| **Total:** | | 100.00 |

## Product 46

### Study Conditions

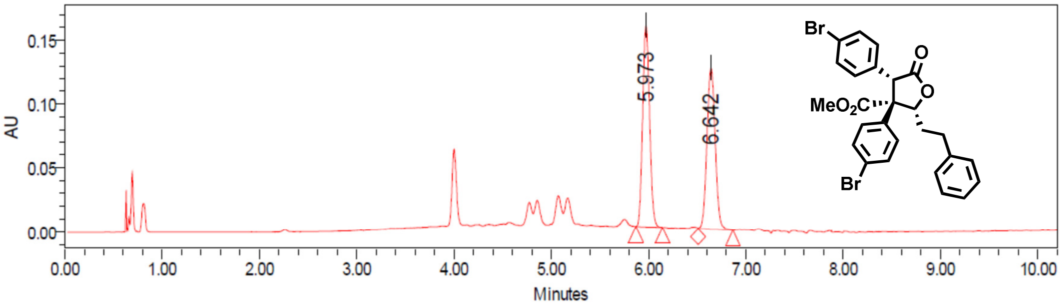
| | |
|---|---|
| **Instrument:** ACQUITY UPC$^2$ | |
| **Chiral Stationary Phase:** | ACQUITY UPC$^2$ Trefoil AMY1, 2.5μm<br>3.0 x 150mm Column |
| **Detection:** UV 230 nm with PDA detector | |
| **Mobile Phase:** | A = $CO_2$, B = Ethanol/IPA (1:1, *v*:*v*) |
| **Column Temperature:** 30 °C | |

### Gradient Table

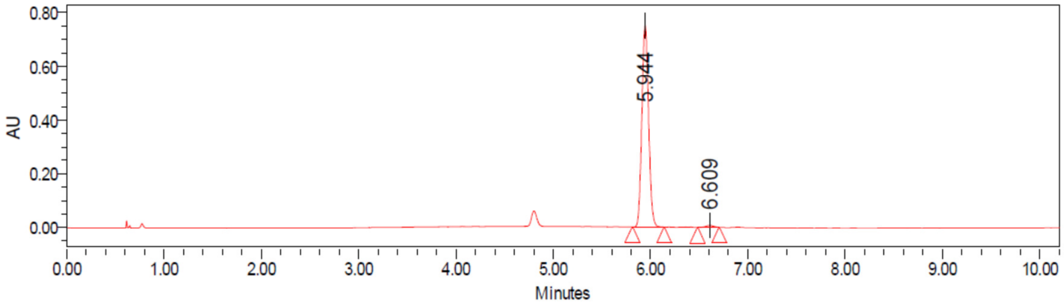
| | **Time** (min) | **FR** (mL/min) | **A** (%) | **B** (%) | **Curve** |
|---|---|---|---|---|---|
| **1** | Initial | 1.200 | 97.0 | 3.0 | Initial |
| **2** | 8.50 | 1.200 | 40.0 | 60.0 | 6 |
| **3** | 10.00 | 1.200 | 40.0 | 60.0 | 6 |
| **4** | 10.10 | 1.200 | 97.0 | 3.0 | 6 |

**Inlet Pressure:** 1500 (psi)

**Racemic:**



**Chiral: 98% *ee***



**Peak Results: Racemic**

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 5.973 | 50.06 |
| **2** | 6.642 | 49.94 |
| **Total:** | | 100.00 |

**Peak Results: Chiral**

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 5.944 | 98.82 |
| **2** | 6.609 | 1.18 |
| **Total:** | | 100.00 |

**Product 47**

### Study Conditions

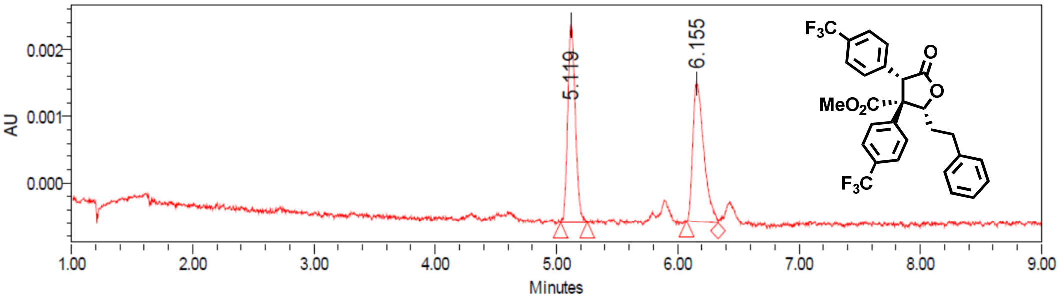
| | |
|---|---|
| **Instrument:** ACQUITY UPC$^2$ | |
| **Chiral Stationary Phase:** | ACQUITY UPC$^2$ Trefoil CEL1, 2.5µm<br>3.0 x 150mm Column |
| **Detection:** UV 230 nm with PDA detector | |
| **Mobile Phase:** | A = $CO_2$, B = Mehanol/IPA (1:1, *v*:*v*) |
| **Column Temperature:** 30 °C | |

### Gradient Table

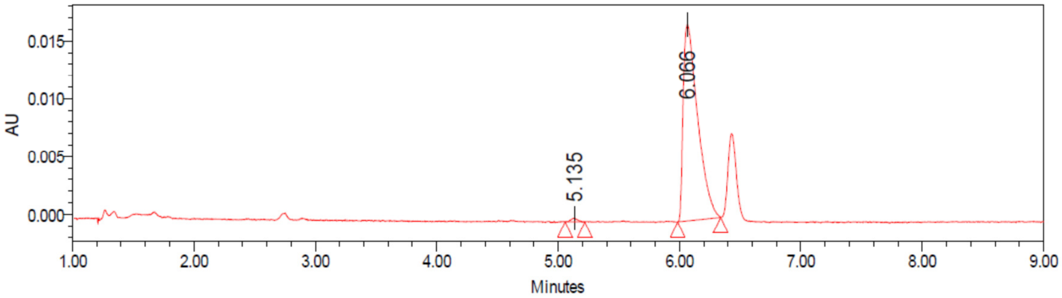
| | Time (min) | FR (mL/min) | A (%) | B (%) | Curve |
|---|---|---|---|---|---|
| **1** | Initial | 1.200 | 99.0 | 1.0 | Initial |
| **2** | 8.50 | 1.200 | 92.0 | 8.0 | 6 |
| **3** | 10.00 | 1.200 | 40.0 | 60.0 | 6 |
| **4** | 10.10 | 1.200 | 97.0 | 3.0 | 6 |

**Inlet Pressure:** 1500 (psi)

**Racemic:**



**Chiral: 98% *ee***



### Peak Results: Racemic

| | Ret. Time (min) | Rel. Area (%) |
|---|---|---|
| **1** | 5.119 | 49.53 |
| **2** | 6.155 | 50.47 |
| **Total:** | | 100.00 |

### Peak Results: Chiral

| | Ret. Time (min) | Rel. Area (%) |
|---|---|---|
| **1** | 5.135 | 0.89 |
| **2** | 6.066 | 99.11 |
| **Total:** | | 100.00 |

## Product 48

### 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*)

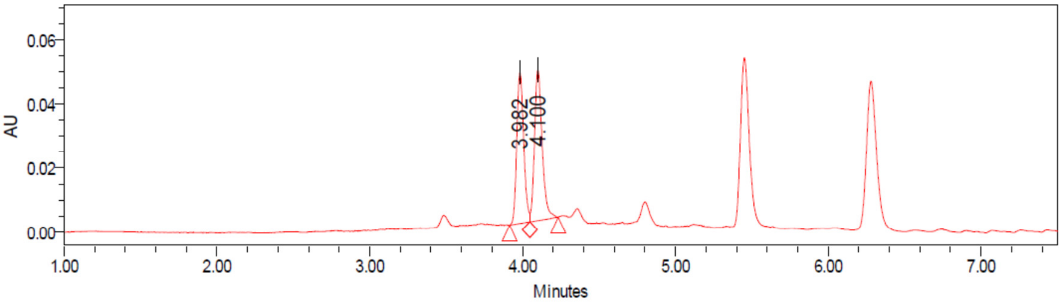
**Column Temperature:** 30 °C

### Gradient Table

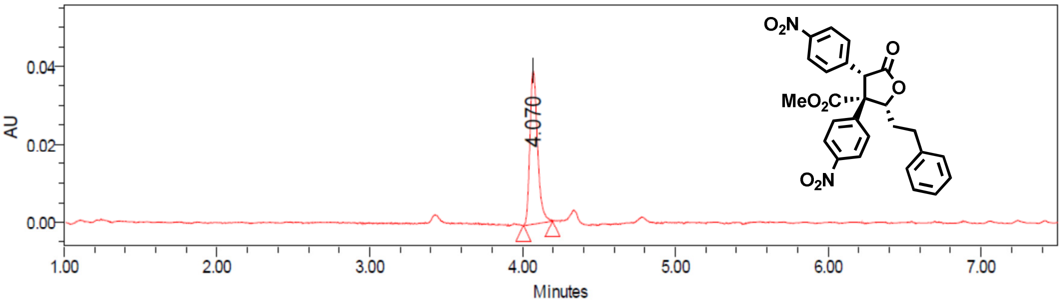
| | **Time** (min) | **FR** (mL/min) | **A** (%) | **B** (%) | **Curve** |
|---|---|---|---|---|---|
| **1** | Initial | 1.200 | 97.0 | 3.0 | Initial |
| **2** | 8.50 | 1.200 | 40.0 | 60.0 | 6 |
| **3** | 10.00 | 1.200 | 40.0 | 60.0 | 6 |
| **4** | 10.10 | 1.200 | 97.0 | 3.0 | 6 |

**Inlet Pressure:** 1500 (psi)

**Racemic:**



**Chiral: >99% *ee***



### Peak Results: Racemic

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 3.982 | 49.54 |
| **2** | 4.100 | 50.46 |
| **Total:** | | 100.00 |

### Peak Results: Chiral

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | - | not detected |
| **2** | 4.070 | 100.00 |
| **Total:** | | 100.00 |

## Product 49

### Study Conditions

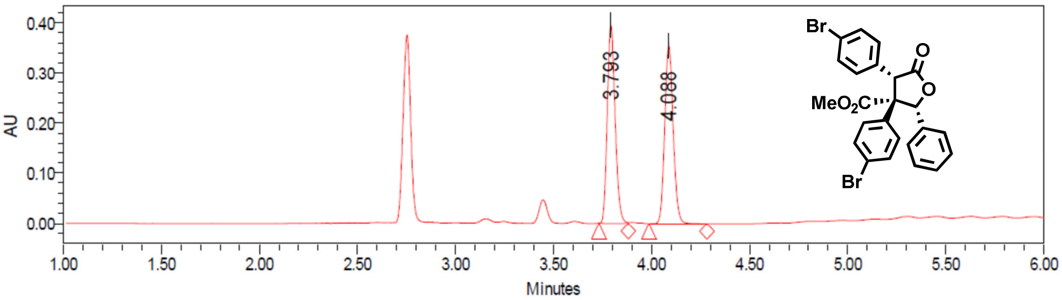
| | |
|---|---|
| **Instrument:** ACQUITY UPC$^2$ | |
| **Chiral Stationary Phase:** | ACQUITY UPC$^2$ Trefoil AMY1, 2.5µm<br>3.0 x 150mm Column |
| **Detection:** UV 230 nm with PDA detector | |
| **Mobile Phase:** | A = $CO_2$, B = Ethanol/ACN/IPA (1:1:1, *v*:*v*:*v*) |
| **Column Temperature:** 30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

### Gradient Table

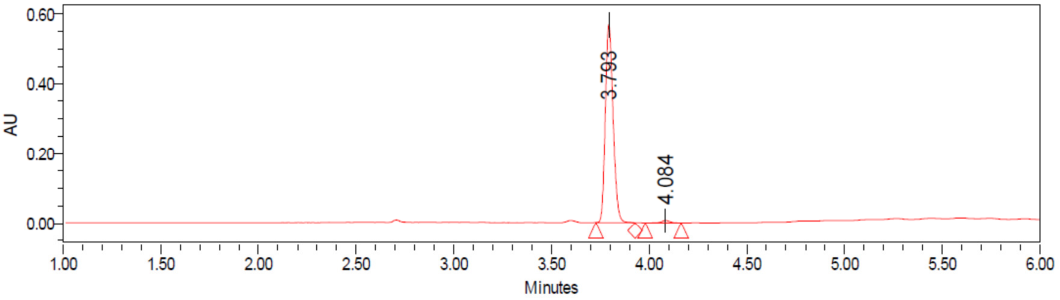
| | **Time** (min) | **FR** (mL/min) | **A** (%) | **B** (%) | **Curve** |
|---|---|---|---|---|---|
| **1** | Initial | 1.200 | 97.0 | 3.0 | Initial |
| **2** | 4.50 | 1.200 | 40.0 | 60.0 | 6 |
| **3** | 6.00 | 1.200 | 40.0 | 60.0 | 6 |
| **4** | 6.10 | 1.200 | 97.0 | 3.0 | 6 |

**Inlet Pressure:** 1500 (psi)

**Racemic:**



**Chiral: 97% *ee***



### Peak Results: Racemic

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 3.793 | 50.57 |
| **2** | 4.088 | 49.43 |
| **Total:** | | 100.00 |

### Peak Results: Chiral

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 3.793 | 98.57 |
| **2** | 4.084 | 1.43 |
| **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*)

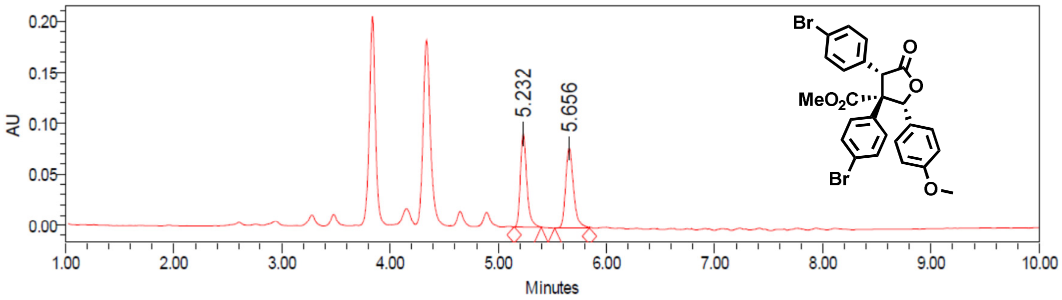
**Column Temperature:** 30 °C

### Gradient Table

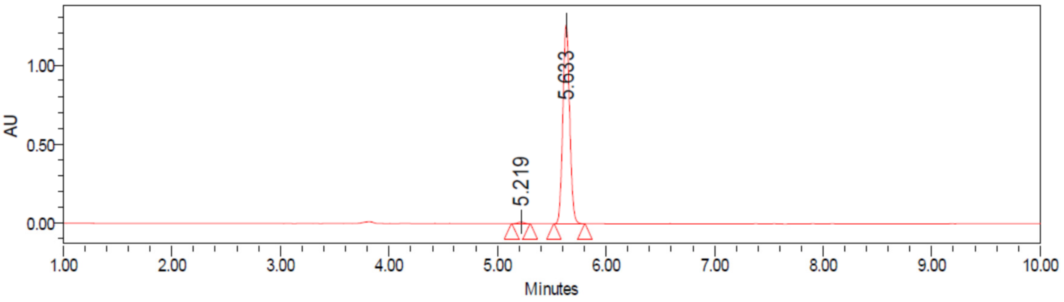
| | Time (min) | FR (mL/min) | A (%) | B (%) | Curve |
|---|---|---|---|---|---|
| 1 | Initial | 1.200 | 97.0 | 3.0 | Initial |
| 2 | 8.50 | 1.200 | 40.0 | 60.0 | 6 |
| 3 | 10.00 | 1.200 | 40.0 | 60.0 | 6 |
| 4 | 10.10 | 1.200 | 97.0 | 3.0 | 6 |

**Inlet Pressure:** 1500 (psi)

**Racemic:**



**Chiral: 99% *ee***



**Peak Results: Racemic**

| | Ret. Time (min) | Rel. Area (%) |
|---|---|---|
| **1** | 5.232 | 49.37 |
| **2** | 5.656 | 50.63 |
| **Total:** | | 100.00 |

**Peak Results: Chiral**

| | Ret. Time (min) | Rel. Area (%) |
|---|---|---|
| **1** | 5.219 | 0.66 |
| **2** | 5.633 | 99.34 |
| **Total:** | | 100.00 |

**Product 51**

### 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*)

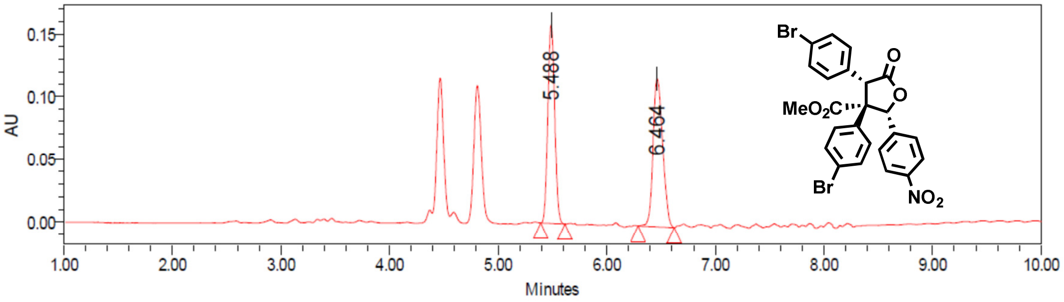
**Column Temperature:** 30 °C

### Gradient Table

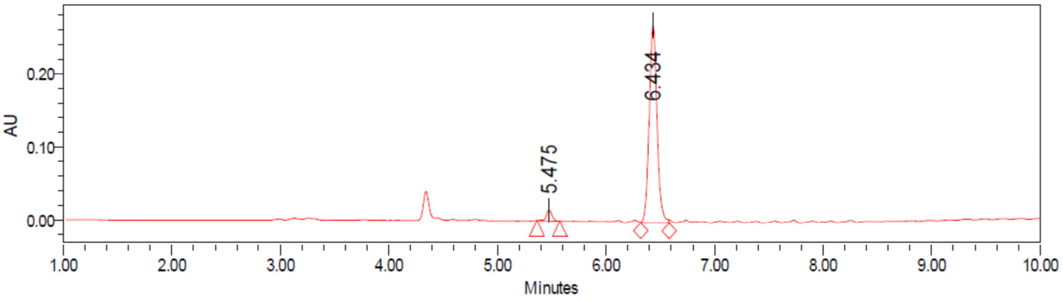
| | **Time** (min) | **FR** (mL/min) | **A** (%) | **B** (%) | **Curve** |
|---|---|---|---|---|---|
| **1** | Initial | 1.200 | 97.0 | 3.0 | Initial |
| **2** | 8.50 | 1.200 | 40.0 | 60.0 | 6 |
| **3** | 10.00 | 1.200 | 40.0 | 60.0 | 6 |
| **4** | 10.10 | 1.200 | 97.0 | 3.0 | 6 |

**Inlet Pressure:** 1500 (psi)

**Racemic:**



**Chiral: 92% *ee***



### Peak Results: Racemic

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 5.488 | 49.94 |
| **2** | 6.464 | 50.06 |
| **Total:** | | 100.00 |

### Peak Results: Chiral

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 5.475 | 4.02 |
| **2** | 6.434 | 95.96 |
| **Total:** | | 100.00 |

## Product 52

### Study Conditions

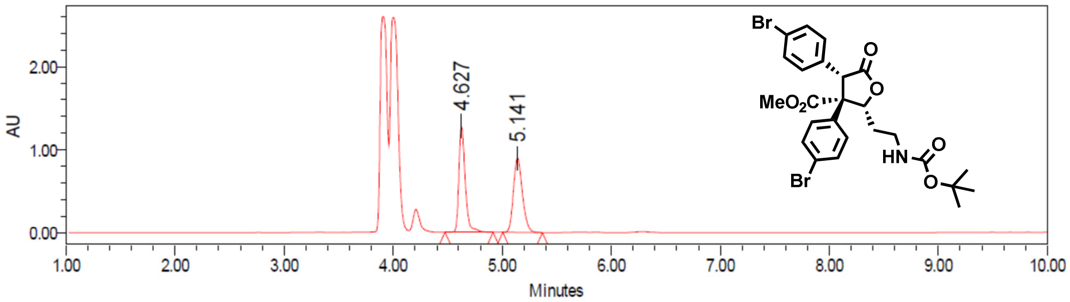
| |
|---|
| **Instrument:** ACQUITY UPC$^2$ |
| **Chiral Stationary Phase:**<br>ACQUITY UPC$^2$ Trefoil AMY1, 2.5µm<br>3.0 x 150mm Column |
| **Detection:** UV 230 nm with PDA detector |
| **Mobile Phase:**<br>A = $CO_2$, B = Ethanol/ACN/IPA (1:1:1, *v*:*v*:*v*) |
| **Column Temperature:** 30 °C |

### Gradient Table

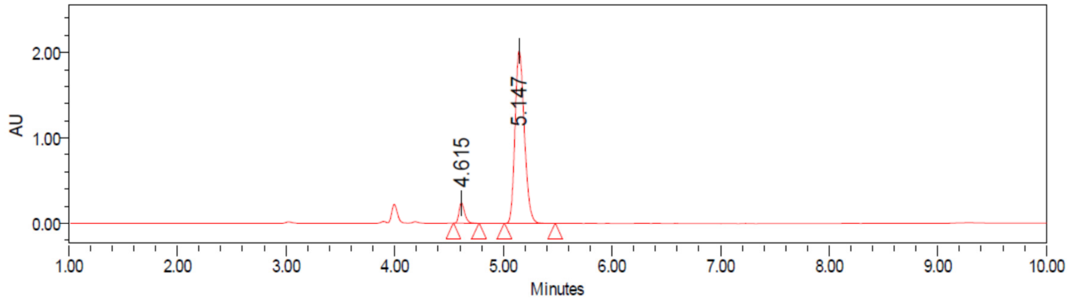
| | **Time** (min) | **FR** (mL/min) | **A** (%) | **B** (%) | **Curve** |
|---|---|---|---|---|---|
| **1** | Initial | 1.200 | 97.0 | 3.0 | Initial |
| **2** | 8.50 | 1.200 | 40.0 | 60.0 | 6 |
| **3** | 10.00 | 1.200 | 40.0 | 60.0 | 6 |
| **4** | 10.10 | 1.200 | 97.0 | 3.0 | 6 |

**Inlet Pressure:** 1500 (psi)

**Racemic:**



**Chiral: 90% *ee***



### Peak Results: Racemic

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 4.627 | 50.08 |
| **2** | 5.141 | 49.92 |
| **Total:** | | 100.00 |

### Peak Results: Chiral

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 4.615 | 4.87 |
| **2** | 5.147 | 95.13 |
| **Total:** | | 100.00 |

## Product 54a

### Study Conditions

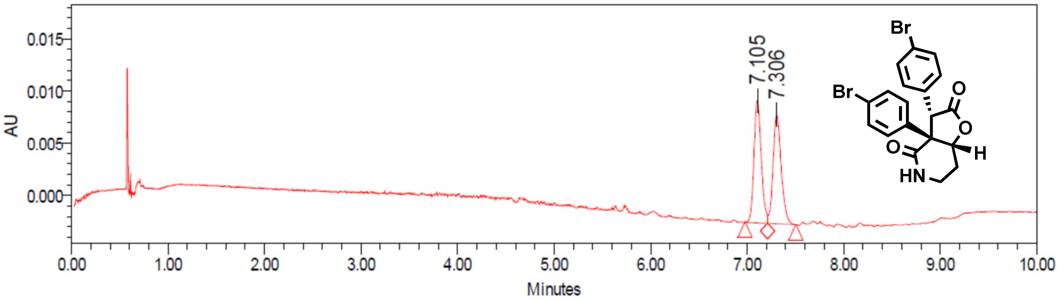
| |
|---|
| **Instrument:** ACQUITY UPC$^2$ |
| **Chiral Stationary Phase:**<br>ACQUITY UPC$^2$ Trefoil AMY1, 2.5µm<br>3.0 x 150mm Column |
| **Detection:** UV 254 nm with PDA detector |
| **Mobile Phase:**<br>A = $CO_2$, B = Ethanol/ACN/IPA (1:1:1, *v*:*v*:*v*) |
| **Column Temperature:** 30 °C |

### Gradient Table

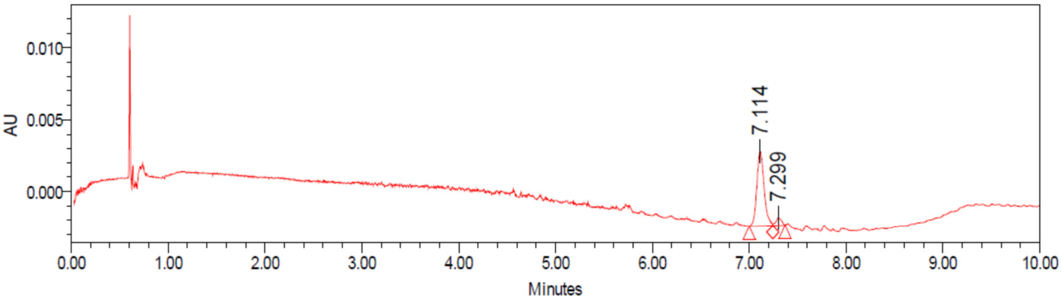
| | **Time** (min) | **FR** (mL/min) | **A** (%) | **B** (%) | **Curve** |
|---|---|---|---|---|---|
| **1** | Initial | 1.200 | 97.0 | 3.0 | Initial |
| **2** | 8.50 | 1.200 | 40.0 | 60.0 | 6 |
| **3** | 10.00 | 1.200 | 40.0 | 60.0 | 6 |
| **4** | 10.10 | 1.200 | 97.0 | 3.0 | 6 |

**Inlet Pressure:** 1500 (psi)

**Racemic:**



**Chiral: 86% *ee***



### Peak Results: Racemic

| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 7.105 | 49.89 |
| **2** | 7.306 | 50.11 |
| **Total:** | | 100.00 |

### Peak Results: Chiral

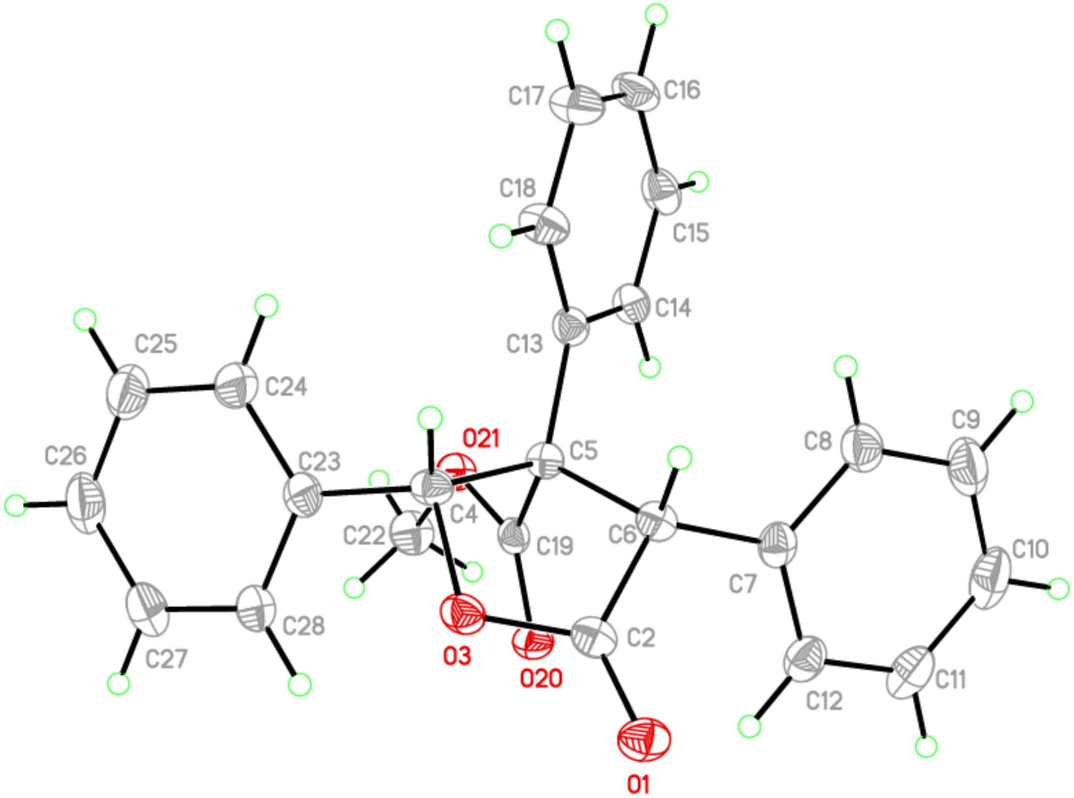
| | **Ret. Time** (min) | **Rel. Area** (%) |
|---|---|---|
| **1** | 7.114 | 92.79 |
| **2** | 7.299 | 7.21 |
| **Total:** | | 100.00 |

## X-ray diffraction measurements

X-ray structural analyses for crystals of **37** and **41** were performed on a Bruker SMART APEX Duo CCD at 100(2) K with an Oxford Cobra cryostat, with samples mounted on a MiTeGen microloop using Cu Kα radiation (λ = 1.54178 Å). Bruker APEX[15] software was used to collect and reduce data and determine the space group. Absorption corrections were applied using SADABS.[16] The structure was solved with the XT structure solution program[17] using Intrinsic Phasing and refined with the XL refinement package[18] using Least Squares minimisation in Olex2.[19] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned to calculated positions using a riding model with appropriately fixed isotropic thermal parameters.

Crystallographic data, CCDC 1578091 and 1578092, can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

## 11. X-ray crystallographic data data for lactone 37.



A specimen of $C_{24}H_{20}O_4$, (**37**) approximate dimensions 0.010 mm x 0.250 mm x 0.450 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 100(2)K using an Oxford Cryosystems 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 4462 frames were collected. The total exposure time was 13.63 hours. The integration of the data using an orthorhombic unit cell yielded a total of 26460 reflections to a maximum θ angle of 68.40° (0.83 Å resolution), of which 3533 were independent (average redundancy 7.489, completeness = 99.6%, $R_{int}$ = 3.42%, $R_{sig}$ = 1.82%) and 3525 (99.77%) were greater than $2\sigma(F^2)$. The final cell constants of $\underline{a}$ = 9.3600(4) Å, $\underline{b}$ = 10.9241(4) Å, $\underline{c}$ = 18.8533(7) Å, volume = 1927.74(13) 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 0.843. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.6347 and 0.7531.

The structure was solved using the Bruker APEX Software Package and refined with XL in Olex2, using the space group $P2_12_12_1$, with Z = 4 for the formula unit, $C_{24}H_{20}O_4$. The final anisotropic full-matrix least-squares refinement on $F^2$ with 254 variables converged at R1 = 3.10%, for the observed data and wR2 = 7.72% for all data. The goodness-of-fit was 1.080. The largest peak in the final difference electron density synthesis was 0.152 $e^-/Å^3$ and the largest hole was -0.328 $e^-/Å^3$ with an RMS deviation of 0.063 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.283 g/cm$^3$ and F(000), 784 $e^-$.

**Refinement Note:** Chirality assignment:

C4 = R

C5 = S

C6 = S

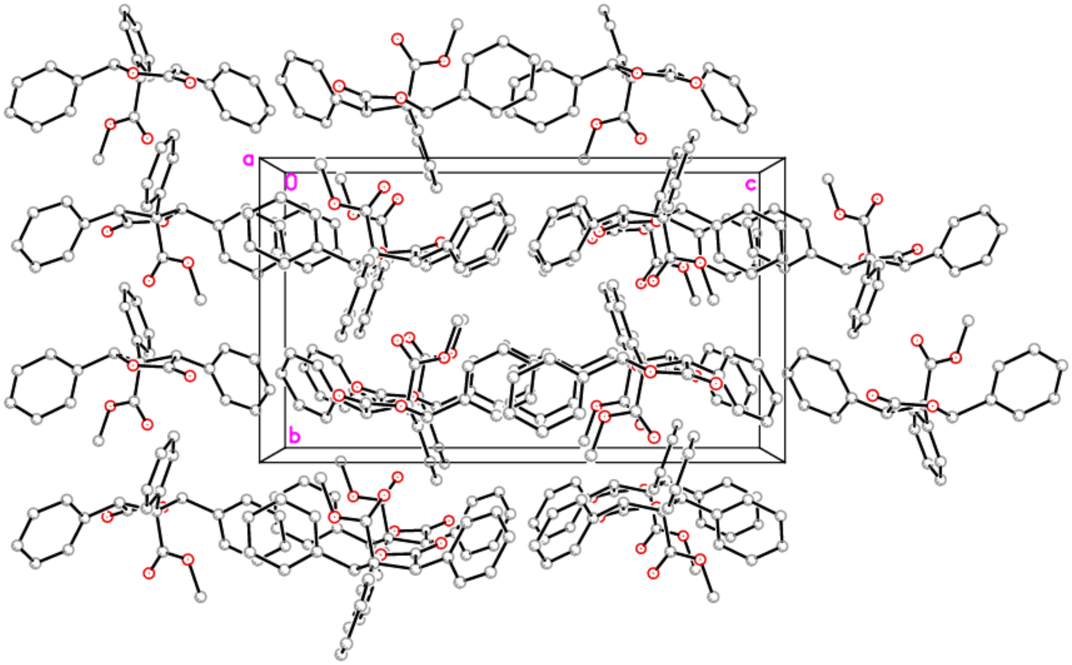


**Figure: Packing of diagram of 37 viewed to the a-axis.**

**Table 11. Data collection details for 37.**

| Axis | dx/mm | 2θ/° | ω/° | φ/° | χ/° | Width/° | Frames | Time/s | Wavelength/Å | Voltage/kV | Current/mA | Temperature/K |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Omega | 45.000 | 104.23 | 94.63 | 324.00 | -54.74 | 0.80 | 157 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 45.000 | 104.23 | 342.74 | 0.00 | 64.50 | 0.80 | 163 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 45.000 | 104.23 | 94.63 | 135.00 | -54.74 | 0.80 | 157 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 45.000 | 90.14 | 352.61 | 59.39 | 82.71 | 0.80 | 91 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Phi | 45.000 | -41.42 | 341.01 | 238.61 | 23.00 | 0.80 | 314 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 45.000 | 104.23 | 94.63 | 0.00 | -54.74 | 0.80 | 157 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 45.000 | 104.23 | 94.63 | 189.00 | -54.74 | 0.80 | 157 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 45.000 | -39.23 | 312.62 | 160.00 | -64.50 | 0.80 | 128 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 45.000 | 104.23 | 94.63 | 297.00 | -54.74 | 0.80 | 157 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 45.000 | 104.23 | 342.74 | 216.00 | 64.50 | 0.80 | 163 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 45.000 | -39.23 | 205.13 | 120.00 | 54.74 | 0.80 | 157 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 45.000 | 104.23 | 94.63 | 162.00 | -54.74 | 0.80 | 157 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 45.000 | 104.23 | 342.74 | 81.00 | 64.50 | 0.80 | 163 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 45.000 | 104.23 | 342.74 | 270.00 | 64.50 | 0.80 | 163 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 45.000 | -39.23 | 312.62 | 0.00 | -64.50 | 0.80 | 128 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 45.000 | 104.23 | 94.63 | 54.00 | -54.74 | 0.80 | 157 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 45.000 | 104.23 | 342.74 | 135.00 | 64.50 | 0.80 | 163 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 55.000 | 110.58 | 93.39 | 120.00 | -54.74 | 0.80 | 179 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 55.000 | 94.75 | 352.44 | 168.66 | 80.84 | 0.80 | 92 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 55.000 | 110.58 | 338.50 | 192.00 | 64.50 | 0.80 | 185 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 55.000 | 110.58 | 338.50 | 24.00 | 64.50 | 0.80 | 185 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 55.000 | 110.58 | 93.39 | 96.00 | -54.74 | 0.80 | 179 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 55.000 | 110.58 | 93.39 | 168.00 | -54.74 | 0.80 | 179 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 55.000 | -0.33 | 234.22 | 360.00 | 54.74 | 0.80 | 179 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Phi | 55.000 | -53.29 | 323.96 | 235.29 | 57.00 | 0.80 | 322 | 11.00 | 1.54184 | 45 | 0.6 | 100 |
| Phi | 55.000 | 110.89 | 0.81 | 292.00 | 23.00 | 0.80 | 230 | 11.00 | 1.54184 | 45 | 0.6 | 100 |

**Table 12. Crystal data and structure refinement for 37.**

| | | |
|---|---|---|
| **Identification code** | tcd698 | |
| **Empirical formula** | $C_{24}H_{20}O_4$ | |
| **Formula weight** | 372.40 | |
| **Temperature** | 100(2) K | |
| **Wavelength** | 1.54178 Å | |
| **Crystal system** | Orthorhombic | |
| **Space group** | $P2_12_12_1$ | |
| **Unit cell dimensions** | a = 9.3600(4) Å | α = 90° |
| | b = 10.9241(4) Å | β = 90° |
| | c = 18.8533(7) Å | γ = 90° |
| **Volume** | 1927.74(13) $Å^3$ | |
| **Z** | 4 | |
| **Density (calculated)** | 1.283 $Mg/m^3$ | |
| **Absorption coefficient** | 0.703 $mm^{-1}$ | |
| **F(000)** | 784 | |
| **Crystal size** | 0.45 x 0.25 x 0.01 $mm^3$ | |
| **Theta range for data collection** | 4.678 to 68.398°. | |
| **Index ranges** | $-11 \leq h \leq 11$, $-11 \leq k \leq 12$, $-22 \leq l \leq 22$ | |
| **Reflections collected** | 26460 | |
| **Independent reflections** | 3533 [R(int) = 0.0342] | |
| **Completeness to theta = 67.679°** | 99.8 % | |
| **Absorption correction** | Semi-empirical from equivalents | |
| **Max. and min. transmission** | 0.7531 and 0.6347 | |
| **Refinement method** | Full-matrix least-squares on $F^2$ | |
| **Data / restraints / parameters** | 3533 / 0 / 254 | |
| **Goodness-of-fit on F2** | 1.080 | |
| **Final R indices [I>2σ(I)]** | R1 = 0.0310, wR2 = 0.0772 | |
| **R indices (all data)** | R1 = 0.0311, wR2 = 0.0772 | |
| **Absolute structure parameter** | -0.01(3) | |
| **Largest diff. peak and hole** | 0.152 and -0.328 e.$Å^{-3}$ | |

**Table 13. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$ x $10^3$) for 37.**

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

| | **x** | **y** | **z** | **U(eq)** |
|---|---|---|---|---|
| O(1) | 6359(1) | 7245(1) | 8433(1) | 23(1) |
| O(3) | 6032(1) | 6888(1) | 7280(1) | 20(1) |
| O(20) | 3923(1) | 8997(1) | 7401(1) | 20(1) |
| O(21) | 2442(1) | 8399(1) | 6527(1) | 19(1) |
| C(2) | 5571(2) | 6960(1) | 7960(1) | 18(1) |
| C(4) | 4892(2) | 6490(1) | 6812(1) | 18(1) |

| | | | | |
|---|---|---|---|---|
| C(5) | 3482(2) | 6836(1) | 7223(1) | 16(1) |
| C(6) | 4015(2) | 6590(1) | 7992(1) | 17(1) |
| C(7) | 3149(2) | 7055(2) | 8611(1) | 20(1) |
| C(8) | 1996(2) | 6362(2) | 8851(1) | 26(1) |
| C(9) | 1168(2) | 6760(2) | 9419(1) | 35(1) |
| C(10) | 1482(2) | 7848(2) | 9757(1) | 37(1) |
| C(11) | 2628(2) | 8542(2) | 9524(1) | 33(1) |
| C(12) | 3459(2) | 8155(2) | 8958(1) | 24(1) |
| C(13) | 2157(2) | 6084(2) | 7050(1) | 18(1) |
| C(14) | 806(2) | 6559(2) | 7206(1) | 20(1) |
| C(15) | -418(2) | 5869(2) | 7103(1) | 24(1) |
| C(16) | -319(2) | 4682(2) | 6846(1) | 27(1) |
| C(17) | 1010(2) | 4193(2) | 6702(1) | 29(1) |
| C(18) | 2240(2) | 4880(2) | 6808(1) | 24(1) |
| C(19) | 3291(2) | 8205(2) | 7082(1) | 16(1) |
| C(22) | 2349(2) | 9645(2) | 6274(1) | 26(1) |
| C(23) | 5100(2) | 7071(2) | 6093(1) | 21(1) |
| C(24) | 4497(2) | 6525(2) | 5499(1) | 28(1) |
| C(25) | 4606(2) | 7090(2) | 4840(1) | 37(1) |
| C(26) | 5326(2) | 8190(2) | 4770(1) | 36(1) |
| C(27) | 5941(2) | 8728(2) | 5358(1) | 32(1) |
| C(28) | 5838(2) | 8171(2) | 6019(1) | 24(1) |

**Table 14. Bond lengths [Å] and angles [°] for 37.**

| | | | |
|---|---|---|---|
| O(1)-C(2) | 1.197(2) | C(18)-H(18) | 0.9500 |
| O(3)-C(2) | 1.356(2) | C(22)-H(22A) | 0.9800 |
| O(3)-C(4) | 1.4507(19) | C(22)-H(22B) | 0.9800 |
| O(20)-C(19) | 1.208(2) | C(22)-H(22C) | 0.9800 |
| O(21)-C(19) | 1.3310(19) | C(23)-C(24) | 1.389(3) |
| O(21)-C(22) | 1.4453(19) | C(23)-C(28) | 1.393(2) |
| C(2)-C(6) | 1.513(2) | C(24)-H(24) | 0.9500 |
| C(4)-H(4) | 1.0000 | C(24)-C(25) | 1.390(3) |
| C(4)-C(5) | 1.577(2) | C(25)-H(25) | 0.9500 |
| C(4)-C(23) | 1.508(2) | C(25)-C(26) | 1.385(3) |
| C(5)-C(6) | 1.558(2) | C(26)-H(26) | 0.9500 |
| C(5)-C(13) | 1.523(2) | C(26)-C(27) | 1.381(3) |
| C(5)-C(19) | 1.529(2) | C(27)-H(27) | 0.9500 |
| C(6)-H(6) | 1.0000 | C(27)-C(28) | 1.390(3) |
| C(6)-C(7) | 1.509(2) | C(28)-H(28) | 0.9500 |
| C(7)-C(8) | 1.393(3) | | |
| C(7)-C(12) | 1.398(3) | C(2)-O(3)-C(4) | 111.07(12) |
| C(8)-H(8) | 0.9500 | C(19)-O(21)-C(22) | 116.47(13) |

| | | | |
|---|---|---|---|
| C(8)-C(9) | 1.391(3) | O(1)-C(2)-O(3) | 121.56(15) |
| C(9)-H(9) | 0.9500 | O(1)-C(2)-C(6) | 129.22(15) |
| C(9)-C(10) | 1.381(3) | O(3)-C(2)-C(6) | 109.17(13) |
| C(10)-H(10) | 0.9500 | O(3)-C(4)-H(4) | 108.9 |
| C(10)-C(11) | 1.385(3) | O(3)-C(4)-C(5) | 104.16(12) |
| C(11)-H(11) | 0.9500 | O(3)-C(4)-C(23) | 109.01(13) |
| C(11)-C(12) | 1.387(3) | C(5)-C(4)-H(4) | 108.9 |
| C(12)-H(12) | 0.9500 | C(23)-C(4)-H(4) | 108.9 |
| C(13)-C(14) | 1.398(2) | C(23)-C(4)-C(5) | 116.65(13) |
| C(13)-C(18) | 1.394(2) | C(6)-C(5)-C(4) | 98.55(12) |
| C(14)-H(14) | 0.9500 | C(13)-C(5)-C(19) | 113.29(12) |
| C(14)-C(15) | 1.386(2) | C(13)-C(5)-C(4) | 116.59(13) |
| C(15)-H(15) | 0.9500 | C(13)-C(5)-C(6) | 111.49(12) |
| C(15)-C(16) | 1.387(3) | C(19)-C(5)-C(4) | 104.30(12) |
| C(16)-H(16) | 0.9500 | C(19)-C(5)-C(6) | 111.59(12) |
| C(16)-C(17) | 1.381(3) | C(2)-C(6)-C(5) | 102.97(12) |
| C(17)-H(17) | 0.9500 | C(2)-C(6)-H(6) | 105.3 |
| C(17)-C(18) | 1.388(2) | C(5)-C(6)-H(6) | 105.3 |
| C(7)-C(6)-C(2) | 117.24(13) | C(16)-C(17)-H(17) | 119.7 |
| C(7)-C(6)-C(5) | 119.37(13) | C(16)-C(17)-C(18) | 120.64(16) |
| C(7)-C(6)-H(6) | 105.3 | C(18)-C(17)-H(17) | 119.7 |
| C(8)-C(7)-C(6) | 118.88(15) | C(13)-C(18)-H(18) | 119.6 |
| C(8)-C(7)-C(12) | 118.43(16) | C(17)-C(18)-C(13) | 120.73(16) |
| C(12)-C(7)-C(6) | 122.68(15) | C(17)-C(18)-H(18) | 119.6 |
| C(7)-C(8)-H(8) | 119.6 | O(20)-C(19)-O(21) | 124.73(14) |
| C(9)-C(8)-C(7) | 120.74(18) | O(20)-C(19)-C(5) | 123.80(14) |
| C(9)-C(8)-H(8) | 119.6 | O(21)-C(19)-C(5) | 111.23(13) |
| C(8)-C(9)-H(9) | 119.8 | O(21)-C(22)-H(22A) | 109.5 |
| C(10)-C(9)-C(8) | 120.36(18) | O(21)-C(22)-H(22B) | 109.5 |
| C(10)-C(9)-H(9) | 119.8 | O(21)-C(22)-H(22C) | 109.5 |
| C(9)-C(10)-H(10) | 120.3 | H(22A)-C(22)-H(22B) | 109.5 |
| C(9)-C(10)-C(11) | 119.35(18) | H(22A)-C(22)-H(22C) | 109.5 |
| C(11)-C(10)-H(10) | 120.3 | H(22B)-C(22)-H(22C) | 109.5 |
| C(10)-C(11)-H(11) | 119.6 | C(24)-C(23)-C(4) | 119.47(15) |
| C(10)-C(11)-C(12) | 120.72(19) | C(24)-C(23)-C(28) | 119.38(17) |
| C(12)-C(11)-H(11) | 119.6 | C(28)-C(23)-C(4) | 121.10(15) |
| C(7)-C(12)-H(12) | 119.8 | C(23)-C(24)-H(24) | 120.0 |
| C(11)-C(12)-C(7) | 120.39(17) | C(23)-C(24)-C(25) | 120.07(18) |
| C(11)-C(12)-H(12) | 119.8 | C(25)-C(24)-H(24) | 120.0 |
| C(14)-C(13)-C(5) | 119.41(14) | C(24)-C(25)-H(25) | 119.8 |
| C(18)-C(13)-C(5) | 122.27(14) | C(26)-C(25)-C(24) | 120.33(18) |
| C(18)-C(13)-C(14) | 117.99(15) | C(26)-C(25)-H(25) | 119.8 |
| C(13)-C(14)-H(14) | 119.5 | C(25)-C(26)-H(26) | 120.1 |

| | | | |
|---|---|---|---|
| C(15)-C(14)-C(13) | 121.09(15) | C(27)-C(26)-C(25) | 119.78(18) |
| C(15)-C(14)-H(14) | 119.5 | C(27)-C(26)-H(26) | 120.1 |
| C(14)-C(15)-H(15) | 119.9 | C(26)-C(27)-H(27) | 119.8 |
| C(14)-C(15)-C(16) | 120.15(16) | C(26)-C(27)-C(28) | 120.31(19) |
| C(16)-C(15)-H(15) | 119.9 | C(28)-C(27)-H(27) | 119.8 |
| C(15)-C(16)-H(16) | 120.3 | C(23)-C(28)-H(28) | 119.9 |
| C(17)-C(16)-C(15) | 119.37(16) | C(27)-C(28)-C(23) | 120.10(17) |
| C(17)-C(16)-H(16) | 120.3 | C(27)-C(28)-H(28) | 119.9 |

**Table 15. Anisotropic displacement parameters (Å$^2$x 10$^3$) for 37.**

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) | 19(1) | 24(1) | 26(1) | 2(1) | -6(1) | 0(1) |
| O(3) | 14(1) | 22(1) | 23(1) | -1(1) | 0(1) | -1(1) |
| O(20) | 22(1) | 16(1) | 21(1) | -2(1) | -1(1) | -3(1) |
| O(21) | 21(1) | 17(1) | 20(1) | 3(1) | -3(1) | 0(1) |
| C(2) | 18(1) | 13(1) | 23(1) | 2(1) | -1(1) | 1(1) |
| C(4) | 14(1) | 17(1) | 23(1) | -3(1) | 0(1) | 0(1) |
| C(5) | 15(1) | 15(1) | 17(1) | -1(1) | 0(1) | 1(1) |
| C(6) | 17(1) | 15(1) | 20(1) | 3(1) | -2(1) | 1(1) |
| C(7) | 19(1) | 24(1) | 17(1) | 4(1) | -2(1) | 3(1) |
| C(8) | 25(1) | 32(1) | 22(1) | 5(1) | -1(1) | -2(1) |
| C(9) | 28(1) | 52(1) | 26(1) | 7(1) | 7(1) | -3(1) |
| C(10) | 34(1) | 58(1) | 19(1) | -2(1) | 4(1) | 7(1) |
| C(11) | 34(1) | 43(1) | 22(1) | -7(1) | -4(1) | 5(1) |
| C(12) | 23(1) | 30(1) | 19(1) | -1(1) | -3(1) | 2(1) |
| C(13) | 17(1) | 19(1) | 16(1) | 2(1) | -1(1) | -1(1) |
| C(14) | 20(1) | 19(1) | 20(1) | 2(1) | 1(1) | 1(1) |
| C(15) | 16(1) | 31(1) | 25(1) | 6(1) | 2(1) | 0(1) |
| C(16) | 20(1) | 29(1) | 31(1) | 4(1) | -3(1) | -10(1) |
| C(17) | 29(1) | 21(1) | 37(1) | -3(1) | -1(1) | -6(1) |
| C(18) | 18(1) | 19(1) | 33(1) | -1(1) | 1(1) | 0(1) |
| C(19) | 13(1) | 19(1) | 15(1) | 0(1) | 2(1) | 1(1) |
| C(22) | 31(1) | 20(1) | 27(1) | 7(1) | -3(1) | 2(1) |
| C(23) | 14(1) | 25(1) | 22(1) | -3(1) | 5(1) | 3(1) |
| C(24) | 24(1) | 36(1) | 26(1) | -7(1) | 3(1) | -4(1) |
| C(25) | 32(1) | 58(1) | 21(1) | -5(1) | 2(1) | -6(1) |
| C(26) | 32(1) | 55(1) | 23(1) | 7(1) | 6(1) | -1(1) |
| C(27) | 29(1) | 37(1) | 30(1) | 6(1) | 8(1) | -3(1) |
| C(28) | 22(1) | 28(1) | 23(1) | -2(1) | 5(1) | -1(1) |

**Table 16. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters (Å$^2$x $10^3$) for 37.**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(4) | 4941 | 5580 | 6760 | 21 |
| H(6) | 4021 | 5679 | 8044 | 21 |
| H(8) | 1773 | 5610 | 8623 | 31 |
| H(9) | 382 | 6280 | 9574 | 42 |
| H(10) | 918 | 8118 | 10146 | 44 |
| H(11) | 2847 | 9292 | 9755 | 39 |
| H(12) | 4243 | 8640 | 8805 | 29 |
| H(14) | 727 | 7369 | 7386 | 23 |
| H(15) | -1328 | 6210 | 7208 | 29 |
| H(16) | -1157 | 4210 | 6771 | 32 |
| H(17) | 1084 | 3379 | 6530 | 35 |
| H(18) | 3147 | 4526 | 6714 | 28 |
| H(22A) | 1662 | 9688 | 5882 | 39 |
| H(22B) | 3290 | 9913 | 6107 | 39 |
| H(22C) | 2032 | 10179 | 6661 | 39 |
| H(24) | 4011 | 5766 | 5542 | 34 |
| H(25) | 4183 | 6718 | 4435 | 45 |
| H(26) | 5398 | 8573 | 4319 | 44 |
| H(27) | 6436 | 9483 | 5311 | 38 |
| H(28) | 6272 | 8541 | 6421 | 29 |

**Table 17. Torsion angles [°] for 37.**

| | | | |
|---|---|---|---|
| O(1)-C(2)-C(6)-C(5) | 158.70(16) | C(6)-C(7)-C(8)-C(9) | -179.83(16) |
| O(1)-C(2)-C(6)-C(7) | 25.5(2) | C(6)-C(7)-C(12)-C(11) | 179.93(16) |
| O(3)-C(2)-C(6)-C(5) | -23.60(15) | C(7)-C(8)-C(9)-C(10) | -0.3(3) |
| O(3)-C(2)-C(6)-C(7) | -156.81(13) | C(8)-C(7)-C(12)-C(11) | -0.3(2) |
| O(3)-C(4)-C(5)-C(6) | -34.89(14) | C(8)-C(9)-C(10)-C(11) | 0.2(3) |
| O(3)-C(4)-C(5)-C(13) | -154.19(12) | C(9)-C(10)-C(11)-C(12) | -0.1(3) |
| O(3)-C(4)-C(5)-C(19) | 80.09(14) | C(10)-C(11)-C(12)-C(7) | 0.1(3) |
| O(3)-C(4)-C(23)-C(24) | 156.97(15) | C(12)-C(7)-C(8)-C(9) | 0.4(3) |
| O(3)-C(4)-C(23)-C(28) | -25.6(2) | C(13)-C(5)-C(6)-C(2) | 157.47(12) |
| C(2)-O(3)-C(4)-C(5) | 22.93(16) | C(13)-C(5)-C(6)-C(7) | -70.57(17) |
| C(2)-O(3)-C(4)-C(23) | 148.12(13) | C(13)-C(5)-C(19)-O(20) | 151.58(15) |
| C(2)-C(6)-C(7)-C(8) | -151.32(15) | C(13)-C(5)-C(19)-O(21) | -33.83(18) |
| C(2)-C(6)-C(7)-C(12) | 28.5(2) | C(13)-C(14)-C(15)-C(16) | 0.5(2) |
| C(4)-O(3)-C(2)-O(1) | 178.22(14) | C(14)-C(13)-C(18)-C(17) | 2.1(3) |
| C(4)-O(3)-C(2)-C(6) | 0.31(16) | C(14)-C(15)-C(16)-C(17) | 0.6(3) |
| C(4)-C(5)-C(6)-C(2) | 34.41(14) | C(15)-C(16)-C(17)-C(18) | -0.4(3) |
| C(4)-C(5)-C(6)-C(7) | 166.37(13) | C(16)-C(17)-C(18)-C(13) | -1.0(3) |

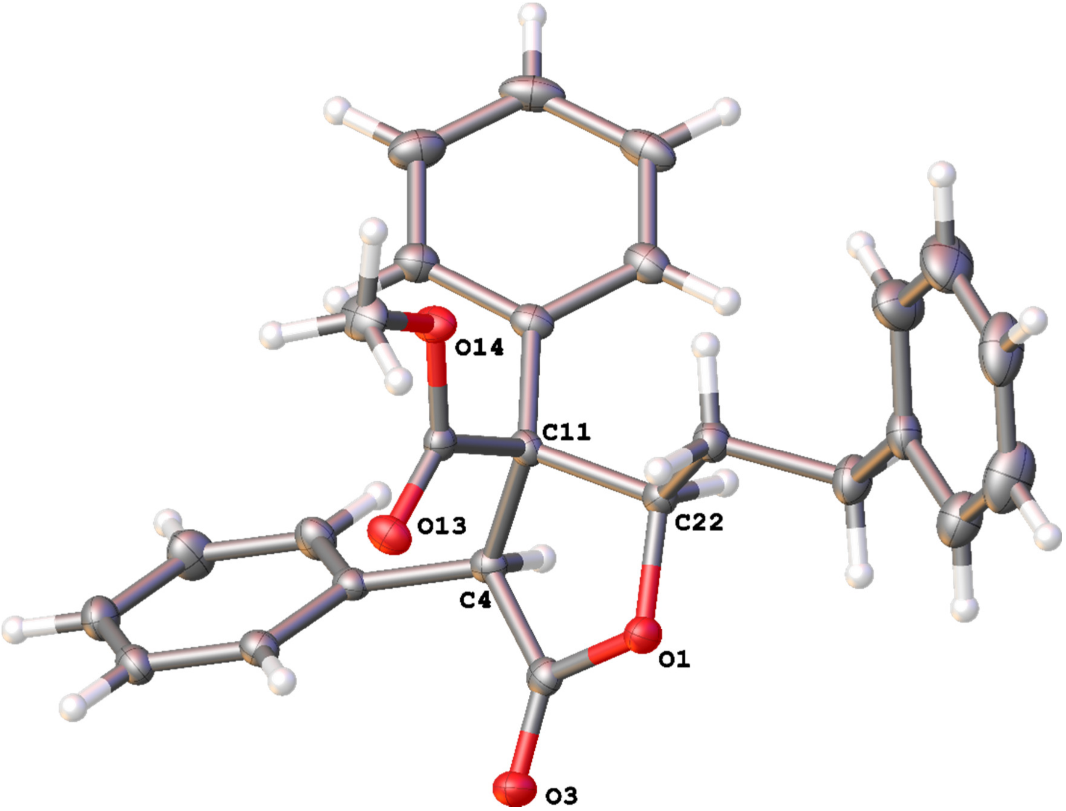
| | | | |
|---|---|---|---|
| C(4)-C(5)-C(13)-C(14) | -159.49(14) | C(18)-C(13)-C(14)-C(15) | -1.9(2) |
| C(4)-C(5)-C(13)-C(18) | 27.2(2) | C(19)-C(5)-C(6)-C(2) | -74.74(15) |
| C(4)-C(5)-C(19)-O(20) | -80.65(17) | C(19)-C(5)-C(6)-C(7) | 57.22(18) |
| C(4)-C(5)-C(19)-O(21) | 93.95(14) | C(19)-C(5)-C(13)-C(14) | -38.4(2) |
| C(4)-C(23)-C(24)-C(25) | 176.05(17) | C(19)-C(5)-C(13)-C(18) | 148.30(15) |
| C(4)-C(23)-C(28)-C(27) | -176.01(16) | C(22)-O(21)-C(19)-O(20) | 3.6(2) |
| C(5)-C(4)-C(23)-C(24) | -85.48(19) | C(22)-O(21)-C(19)-C(5) | -170.96(13) |
| C(5)-C(4)-C(23)-C(28) | 91.94(18) | C(23)-C(4)-C(5)-C(6) | -155.05(13) |
| C(5)-C(6)-C(7)-C(8) | 83.27(19) | C(23)-C(4)-C(5)-C(13) | 85.65(17) |
| C(5)-C(6)-C(7)-C(12) | -96.93(18) | C(23)-C(4)-C(5)-C(19) | -40.07(17) |
| C(5)-C(13)-C(14)-C(15) | -175.48(15) | C(23)-C(24)-C(25)-C(26) | 0.7(3) |
| C(5)-C(13)-C(18)-C(17) | 175.51(16) | C(24)-C(23)-C(28)-C(27) | 1.4(3) |
| C(6)-C(5)-C(13)-C(14) | 88.45(17) | C(24)-C(25)-C(26)-C(27) | 0.0(3) |
| C(6)-C(5)-C(13)-C(18) | -84.83(18) | C(25)-C(26)-C(27)-C(28) | 0.0(3) |
| C(6)-C(5)-C(19)-O(20) | 24.8(2) | C(26)-C(27)-C(28)-C(23) | -0.7(3) |
| C(6)-C(5)-C(19)-O(21) | -160.64(12) | C(28)-C(23)-C(24)-C(25) | -1.4(3) |

**Table 18. Hydrogen bonds for 37 (Å$^2$ and °).**

Symmetry transformations used to generate equivalent atoms: #1 -x+1,y-1/2,-z+3/2

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| C(4)-H(4)...O(20)#1 | 1.00 | 2.57 | 3.2942(19) | 129 |

## 12. X-ray crystallography data for lactone 41.



A clear colourless block fragment-like specimen of $C_{26}H_{24}O_4$ (**41**), approximate dimensions 0.100 mm x 0.260 mm x 0.360 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 100(2)K with an Oxford Cryosystems 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 4075 frames were collected. The total exposure time was 14.80 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using an orthorhombic unit cell yielded a total of 24619 reflections to a maximum θ angle of 69.83° (0.82 Å resolution), of which 3890 were independent (average redundancy 6.329, completeness = 99.5%, $R_{int}$ = 3.62%, $R_{sig}$ = 2.01%) and 3867 (99.41%) were greater than $2\sigma(F^2)$. The final cell constants of a = 9.3111(3) Å, b = 14.0732(5) Å, c = 15.7875(6) Å, volume = 2068.75(13) $Å^3$, are based upon the refinement of the XYZ-centroids of 9982 reflections above 20 σ(I) with 6.280° < 2θ < 139.6°. Data were corrected for absorption effects using the Multi-Scan method

(SADABS). The ratio of minimum to maximum apparent transmission was 0.851. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.6413 and 0.7533.

Using Olex2, the structure was solved with the XT structure solution program using Intrinsic Phasing and refined with the XL refinement package using Least Squares minimisation, using the space group $P2_12_12_1$, with Z = 4 for the formula unit, $C_{26}H_{24}O_4$.The final anisotropic full-matrix least-squares refinement on $F^2$ with 272 variables converged at R1 = 3.00%, for the observed data and wR2 = 7.73% for all data. The goodness-of-fit was 1.048. The largest peak in the final difference electron density synthesis was 0.168 $e^-/Å^3$ and the largest hole was -0.225 $e^-/Å^3$ with an RMS deviation of 0.044 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.286 $g/cm^3$ and F(000), 848 $e^-$.

**Refinement Note:** The Model has Chirality at C4= S, C11= S, and C22= R.

**Table 19. Data collection details for 41.**

| Axis | dx/mm | 2θ/° | ω/° | φ/° | χ/° | Width/° | Frames | Time/s | Wavelength/Å | Voltage/kV | Current/mA | Temperature/K |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Omega | 50.043 | 108.90 | 95.00 | 264.00 | -54.74 | 0.90 | 150 | 15.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | 108.90 | 95.00 | 144.00 | -54.74 | 0.90 | 150 | 15.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | -49.30 | 189.65 | 128.00 | 54.74 | 0.90 | 150 | 9.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | 108.90 | 95.00 | 48.00 | -54.74 | 0.90 | 150 | 15.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | -49.30 | 189.65 | 224.00 | 54.74 | 0.90 | 150 | 9.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | 108.90 | 341.90 | 168.00 | 64.50 | 0.90 | 155 | 15.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | -49.30 | 298.92 | 192.00 | -64.50 | 0.90 | 129 | 9.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | 108.90 | 341.90 | 120.00 | 64.50 | 0.90 | 155 | 15.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | 108.90 | 95.00 | 240.00 | -54.74 | 0.90 | 150 | 15.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | -49.30 | 298.92 | 0.00 | -64.50 | 0.90 | 129 | 9.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | 108.90 | 95.00 | 168.00 | -54.74 | 0.90 | 150 | 15.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | 108.90 | 95.00 | 24.00 | -54.74 | 0.90 | 150 | 15.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | -49.30 | 189.66 | 160.00 | 54.74 | 0.90 | 150 | 9.00 | 1.54184 | 45 | 0.6 | 100 |
| Phi | 50.043 | 109.30 | 95.73 | 215.75 | -57.00 | 0.90 | 276 | 15.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | -11.30 | 227.66 | 204.00 | 54.74 | 0.90 | 150 | 9.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | -49.30 | 189.65 | 32.00 | 54.74 | 0.90 | 150 | 9.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | 108.90 | 95.00 | 72.00 | -54.74 | 0.90 | 150 | 15.00 | 1.54184 | 45 | 0.6 | 100 |
| Phi | 50.043 | 94.30 | 80.73 | 0.00 | -57.00 | 0.90 | 400 | 15.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | 108.90 | 95.00 | 288.00 | -54.74 | 0.90 | 150 | 15.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | 108.90 | 95.00 | 120.00 | -54.74 | 0.90 | 150 | 15.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | 108.90 | 341.90 | 72.00 | 64.50 | 0.90 | 155 | 15.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | -49.30 | 189.65 | 288.00 | 54.74 | 0.90 | 150 | 9.00 | 1.54184 | 45 | 0.6 | 100 |
| Omega | 50.043 | -11.30 | 227.66 | 102.00 | 54.74 | 0.90 | 150 | 9.00 | 1.54184 | 45 | 0.6 | 100 |
| Phi | 55.043 | 110.89 | 93.65 | 215.75 | -57.00 | 0.90 | 276 | 15.00 | 1.54184 | 45 | 0.6 | 100 |

**Table 20. Crystal data and structure refinement for 41.**

| | | |
|---|---|---|
| **Identification code** | tcd810 | |
| **Empirical formula** | $C_{26}H_{24}O_4$ | |
| **Formula weight** | 400.45 | |
| **Temperature** | 100.0 K | |
| **Wavelength** | 1.54178 Å | |
| **Crystal system** | Orthorhombic | |
| **Space group** | $P2_12_12_1$ | |
| **Unit cell dimensions** | a = 9.3111(3) Å | α = 90° |
| | b = 14.0732(5) Å | β = 90° |
| | c = 15.7875(6) Å | γ = 90° |
| **Volume** | 2068.75(13) $Å^3$ | |
| **Z** | 4 | |
| **Density (calculated)** | 1.286 $Mg/m^3$ | |
| **Absorption coefficient** | 0.690 $mm^{-1}$ | |
| **F(000)** | 848 | |
| **Crystal size** | 0.36 x 0.26 x 0.1 $mm^3$ | |
| **Theta range for data collection** | 4.208 to 69.831°. | |
| **Index ranges** | $-11\leq h\leq 11$, $-17\leq k\leq 16$, $-19\leq l\leq 19$ | |
| **Reflections collected** | 24619 | |
| **Independent reflections** | 3890 [R(int) = 0.0362] | |
| **Completeness to theta = 67.679°** | 100.0 % | |
| **Absorption correction** | Semi-empirical from equivalents | |
| **Max. and min. transmission** | 0.7533 and 0.6413 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| **Data / restraints / parameters** | 3890 / 0 / 272 | |
| **Goodness-of-fit on F2** | 1.048 | |
| **Final R indices [I>2σ(I)]** | R1 = 0.0300, wR2 = 0.0771 | |
| **R indices (all data)** | R1 = 0.0301, wR2 = 0.0773 | |
| **Absolute structure parameter** | -0.08(3) | |
| **Largest diff. peak and hole** | 0.168 and -0.225 $e.Å^{-3}$ | |

**Table 21. Atomic coordinates (x $10^4$) and equivalent isotropic displacement parameters ($Å^2$ x $10^3$) for 41.**

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

| | **x** | **y** | **z** | **U(eq)** |
|---|---|---|---|---|
| O(1) | 6582(1) | 4392(1) | 4697(1) | 18(1) |
| O(3) | 8109(1) | 3205(1) | 4458(1) | 22(1) |
| O(13) | 8113(1) | 4397(1) | 6386(1) | 19(1) |
| O(14) | 6339(1) | 4961(1) | 7204(1) | 19(1) |
| C(2) | 7131(2) | 3522(1) | 4863(1) | 17(1) |
| C(4) | 6299(2) | 3063(1) | 5581(1) | 16(1) |
| C(5) | 7096(2) | 2294(1) | 6060(1) | 16(1) |

| | | | | |
|---|---|---|---|---|
| C(6) | 6348(2) | 1490(1) | 6332(1) | 21(1) |
| C(7) | 7046(2) | 761(1) | 6763(1) | 26(1) |
| C(8) | 8509(2) | 825(1) | 6922(1) | 23(1) |
| C(9) | 9266(2) | 1618(1) | 6651(1) | 20(1) |
| C(10) | 8571(2) | 2345(1) | 6220(1) | 17(1) |
| C(11) | 5676(2) | 3949(1) | 6055(1) | 15(1) |
| C(12) | 6860(2) | 4436(1) | 6567(1) | 15(1) |
| C(15) | 7415(2) | 5510(1) | 7652(1) | 25(1) |
| C(16) | 4339(2) | 3729(1) | 6573(1) | 17(1) |
| C(17) | 4489(2) | 3233(1) | 7336(1) | 21(1) |
| C(18) | 3301(2) | 2996(1) | 7821(1) | 27(1) |
| C(19) | 1939(2) | 3250(1) | 7552(1) | 28(1) |
| C(20) | 1772(2) | 3748(1) | 6800(1) | 26(1) |
| C(21) | 2961(2) | 3986(1) | 6316(1) | 21(1) |
| C(22) | 5396(2) | 4594(1) | 5270(1) | 17(1) |
| C(23) | 5330(2) | 5661(1) | 5419(1) | 20(1) |
| C(24) | 4797(2) | 6196(1) | 4632(1) | 24(1) |
| C(25) | 4832(2) | 7268(1) | 4736(1) | 23(1) |
| C(26) | 5538(2) | 7841(1) | 4153(1) | 29(1) |
| C(27) | 5548(3) | 8825(1) | 4242(1) | 39(1) |
| C(28) | 4873(2) | 9250(1) | 4921(1) | 39(1) |
| C(29) | 4163(3) | 8692(1) | 5503(2) | 41(1) |
| C(30) | 4142(2) | 7707(1) | 5412(1) | 34(1) |

**Table 22. Bond lengths [Å] and angles [°] for 41.**

| | | | |
|---|---|---|---|
| O(1)-C(2) | 1.352(2) | C(20)-C(21) | 1.387(2) |
| O(1)-C(22) | 1.4545(18) | C(21)-H(21) | 0.9500 |
| O(3)-C(2) | 1.199(2) | C(22)-H(22) | 1.0000 |
| O(13)-C(12) | 1.2025(19) | C(22)-C(23) | 1.521(2) |
| O(14)-C(12) | 1.3386(19) | C(23)-H(23A) | 0.9900 |
| O(14)-C(15) | 1.450(2) | C(23)-H(23B) | 0.9900 |
| C(2)-C(4) | 1.518(2) | C(23)-C(24) | 1.536(2) |
| C(4)-H(4) | 1.0000 | C(24)-H(24A) | 0.9900 |
| C(4)-C(5) | 1.515(2) | C(24)-H(24B) | 0.9900 |
| C(4)-C(11) | 1.565(2) | C(24)-C(25) | 1.517(2) |
| C(5)-C(6) | 1.396(2) | C(25)-C(26) | 1.388(3) |
| C(5)-C(10) | 1.399(2) | C(25)-C(30) | 1.390(3) |
| C(6)-H(6) | 0.9500 | C(26)-H(26) | 0.9500 |
| C(6)-C(7) | 1.392(2) | C(26)-C(27) | 1.392(3) |
| C(7)-H(7) | 0.9500 | C(27)-H(27) | 0.9500 |
| C(7)-C(8) | 1.389(2) | C(27)-C(28) | 1.379(3) |
| C(8)-H(8) | 0.9500 | C(28)-H(28) | 0.9500 |
| C(8)-C(9) | 1.386(2) | C(28)-C(29) | 1.379(3) |

| | | | |
|---|---|---|---|
| C(9)-H(9) | 0.9500 | C(29)-H(29) | 0.9500 |
| C(9)-C(10) | 1.389(2) | C(29)-C(30) | 1.395(3) |
| C(10)-H(10) | 0.9500 | C(30)-H(30) | 0.9500 |
| C(11)-C(12) | 1.529(2) | | |
| C(11)-C(16) | 1.521(2) | C(2)-O(1)-C(22) | 110.08(12) |
| C(11)-C(22) | 1.559(2) | C(12)-O(14)-C(15) | 114.23(12) |
| C(15)-H(15A) | 0.9800 | O(1)-C(2)-C(4) | 109.71(13) |
| C(15)-H(15B) | 0.9800 | O(3)-C(2)-O(1) | 121.44(14) |
| C(15)-H(15C) | 0.9800 | O(3)-C(2)-C(4) | 128.83(15) |
| C(16)-C(17) | 1.399(2) | C(2)-C(4)-H(4) | 105.9 |
| C(16)-C(21) | 1.393(2) | C(2)-C(4)-C(11) | 101.94(12) |
| C(17)-H(17) | 0.9500 | C(5)-C(4)-C(2) | 115.27(12) |
| C(17)-C(18) | 1.386(2) | C(5)-C(4)-H(4) | 105.9 |
| C(18)-H(18) | 0.9500 | C(5)-C(4)-C(11) | 120.82(12) |
| C(18)-C(19) | 1.384(3) | C(11)-C(4)-H(4) | 105.9 |
| C(19)-H(19) | 0.9500 | C(6)-C(5)-C(4) | 119.22(13) |
| C(19)-C(20) | 1.386(3) | C(6)-C(5)-C(10) | 118.43(14) |
| C(20)-H(20) | 0.9500 | C(10)-C(5)-C(4) | 122.32(14) |
| C(5)-C(6)-H(6) | 119.5 | C(19)-C(18)-H(18) | 120.0 |
| C(7)-C(6)-C(5) | 120.99(15) | C(18)-C(19)-H(19) | 120.1 |
| C(7)-C(6)-H(6) | 119.5 | C(18)-C(19)-C(20) | 119.71(16) |
| C(6)-C(7)-H(7) | 120.0 | C(20)-C(19)-H(19) | 120.1 |
| C(8)-C(7)-C(6) | 119.91(16) | C(19)-C(20)-H(20) | 119.9 |
| C(8)-C(7)-H(7) | 120.0 | C(19)-C(20)-C(21) | 120.26(17) |
| C(7)-C(8)-H(8) | 120.2 | C(21)-C(20)-H(20) | 119.9 |
| C(9)-C(8)-C(7) | 119.64(16) | C(16)-C(21)-H(21) | 119.6 |
| C(9)-C(8)-H(8) | 120.2 | C(20)-C(21)-C(16) | 120.84(16) |
| C(8)-C(9)-H(9) | 119.7 | C(20)-C(21)-H(21) | 119.6 |
| C(8)-C(9)-C(10) | 120.51(15) | O(1)-C(22)-C(11) | 104.71(12) |
| C(10)-C(9)-H(9) | 119.7 | O(1)-C(22)-H(22) | 108.6 |
| C(5)-C(10)-H(10) | 119.7 | O(1)-C(22)-C(23) | 108.66(12) |
| C(9)-C(10)-C(5) | 120.51(14) | C(11)-C(22)-H(22) | 108.6 |
| C(9)-C(10)-H(10) | 119.7 | C(23)-C(22)-C(11) | 117.31(13) |
| C(12)-C(11)-C(4) | 110.02(12) | C(23)-C(22)-H(22) | 108.6 |
| C(12)-C(11)-C(22) | 106.23(12) | C(22)-C(23)-H(23A) | 109.3 |
| C(16)-C(11)-C(4) | 113.49(12) | C(22)-C(23)-H(23B) | 109.3 |
| C(16)-C(11)-C(12) | 113.37(12) | C(22)-C(23)-C(24) | 111.83(13) |
| C(16)-C(11)-C(22) | 114.17(12) | H(23A)-C(23)-H(23B) | 107.9 |
| C(22)-C(11)-C(4) | 98.39(11) | C(24)-C(23)-H(23A) | 109.3 |
| O(13)-C(12)-O(14) | 123.67(14) | C(24)-C(23)-H(23B) | 109.3 |
| O(13)-C(12)-C(11) | 123.63(14) | C(23)-C(24)-H(24A) | 108.9 |
| O(14)-C(12)-C(11) | 112.54(12) | C(23)-C(24)-H(24B) | 108.9 |
| O(14)-C(15)-H(15A) | 109.5 | H(24A)-C(24)-H(24B) | 107.8 |
| O(14)-C(15)-H(15B) | 109.5 | C(25)-C(24)-C(23) | 113.17(14) |

| | | | |
|---|---|---|---|
| O(14)-C(15)-H(15C) | 109.5 | C(25)-C(24)-H(24A) | 108.9 |
| H(15A)-C(15)-H(15B) | 109.5 | C(25)-C(24)-H(24B) | 108.9 |
| H(15A)-C(15)-H(15C) | 109.5 | C(26)-C(25)-C(24) | 121.05(16) |
| H(15B)-C(15)-H(15C) | 109.5 | C(26)-C(25)-C(30) | 118.02(16) |
| C(17)-C(16)-C(11) | 118.86(14) | C(30)-C(25)-C(24) | 120.92(16) |
| C(21)-C(16)-C(11) | 123.00(14) | C(25)-C(26)-H(26) | 119.5 |
| C(21)-C(16)-C(17) | 118.13(15) | C(25)-C(26)-C(27) | 120.93(19) |
| C(16)-C(17)-H(17) | 119.5 | C(27)-C(26)-H(26) | 119.5 |
| C(18)-C(17)-C(16) | 121.05(17) | C(26)-C(27)-H(27) | 119.8 |
| C(18)-C(17)-H(17) | 119.5 | C(28)-C(27)-C(26) | 120.47(19) |
| C(17)-C(18)-H(18) | 120.0 | C(28)-C(27)-H(27) | 119.8 |
| C(19)-C(18)-C(17) | 120.00(16) | C(27)-C(28)-H(28) | 120.3 |
| C(29)-C(28)-C(27) | 119.34(18) | C(30)-C(29)-H(29) | 119.9 |
| C(29)-C(28)-H(28) | 120.3 | C(25)-C(30)-C(29) | 120.96(19) |
| C(28)-C(29)-H(29) | 119.9 | C(25)-C(30)-H(30) | 119.5 |
| C(28)-C(29)-C(30) | 120.3(2) | C(29)-C(30)-H(30) | 119.5 |

**Table 23. Anisotropic displacement parameters (Å$^2$x 10$^3$) for 41.**

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

| | **$U_{11}$** | **$U_{22}$** | **$U_{33}$** | **$U_{23}$** | **$U_{13}$** | **$U_{12}$** |
|---|---|---|---|---|---|---|
| O(1) | 20(1) | 18(1) | 17(1) | 2(1) | 2(1) | 2(1) |
| O(3) | 21(1) | 24(1) | 20(1) | 1(1) | 5(1) | 4(1) |
| O(13) | 14(1) | 19(1) | 25(1) | -3(1) | 1(1) | -1(1) |
| O(14) | 17(1) | 22(1) | 18(1) | -6(1) | 0(1) | -1(1) |
| C(2) | 16(1) | 18(1) | 16(1) | -2(1) | -3(1) | -1(1) |
| C(4) | 14(1) | 16(1) | 16(1) | -1(1) | 0(1) | -1(1) |
| C(5) | 15(1) | 16(1) | 15(1) | -2(1) | 1(1) | 2(1) |
| C(6) | 16(1) | 21(1) | 26(1) | 2(1) | 0(1) | -1(1) |
| C(7) | 26(1) | 19(1) | 33(1) | 6(1) | 2(1) | -3(1) |
| C(8) | 25(1) | 22(1) | 23(1) | 3(1) | -1(1) | 5(1) |
| C(9) | 18(1) | 21(1) | 21(1) | -3(1) | -2(1) | 4(1) |
| C(10) | 16(1) | 16(1) | 18(1) | -2(1) | 1(1) | 0(1) |
| C(11) | 14(1) | 14(1) | 17(1) | -1(1) | -2(1) | 0(1) |
| C(12) | 16(1) | 14(1) | 15(1) | 2(1) | -1(1) | 1(1) |
| C(15) | 23(1) | 29(1) | 24(1) | -9(1) | -5(1) | -4(1) |
| C(16) | 16(1) | 14(1) | 21(1) | -4(1) | 2(1) | -1(1) |
| C(17) | 21(1) | 19(1) | 23(1) | -1(1) | 3(1) | 0(1) |
| C(18) | 32(1) | 23(1) | 26(1) | -2(1) | 10(1) | -5(1) |
| C(19) | 24(1) | 24(1) | 36(1) | -10(1) | 14(1) | -8(1) |
| C(20) | 14(1) | 26(1) | 38(1) | -13(1) | 2(1) | -3(1) |
| C(21) | 18(1) | 18(1) | 26(1) | -6(1) | 0(1) | -1(1) |
| C(22) | 14(1) | 19(1) | 16(1) | 0(1) | 0(1) | 1(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C(23) | 21(1) | 18(1) | 20(1) | 0(1) | -2(1) | 2(1) |
| C(24) | 31(1) | 20(1) | 23(1) | 2(1) | -5(1) | 2(1) |
| C(25) | 24(1) | 20(1) | 25(1) | 3(1) | -7(1) | 3(1) |
| C(26) | 35(1) | 26(1) | 25(1) | 3(1) | -6(1) | -4(1) |
| C(27) | 54(1) | 26(1) | 37(1) | 8(1) | -12(1) | -12(1) |
| C(28) | 56(1) | 19(1) | 42(1) | 0(1) | -21(1) | 3(1) |
| C(29) | 52(1) | 29(1) | 42(1) | -5(1) | -5(1) | 15(1) |
| C(30) | 39(1) | 25(1) | 37(1) | 4(1) | 4(1) | 8(1) |

**Table 24. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for 41.**

| | **x** | **y** | **z** | **U(eq)** |
|---|---|---|---|---|
| H(4) | 5457 | 2742 | 5311 | 19 |
| H(6) | 5348 | 1440 | 6221 | 25 |
| H(7) | 6521 | 221 | 6948 | 31 |
| H(8) | 8990 | 329 | 7216 | 28 |
| H(9) | 10266 | 1663 | 6761 | 24 |
| H(10) | 9103 | 2881 | 6032 | 20 |
| H(15A) | 7968 | 5889 | 7245 | 38 |
| H(15B) | 8062 | 5079 | 7955 | 38 |
| H(15C) | 6943 | 5934 | 8058 | 38 |
| H(17) | 5420 | 3056 | 7525 | 25 |
| H(18) | 3421 | 2659 | 8337 | 32 |
| H(19) | 1122 | 3085 | 7881 | 33 |
| H(20) | 838 | 3926 | 6616 | 31 |
| H(21) | 2835 | 4329 | 5803 | 25 |
| H(22) | 4481 | 4388 | 4994 | 20 |
| H(23A) | 6298 | 5895 | 5573 | 23 |
| H(23B) | 4678 | 5793 | 5900 | 23 |
| H(24A) | 5402 | 6018 | 4141 | 29 |
| H(24B) | 3800 | 5996 | 4507 | 29 |
| H(26) | 6020 | 7557 | 3687 | 35 |
| H(27) | 6024 | 9206 | 3832 | 47 |
| H(28) | 4897 | 9921 | 4986 | 47 |
| H(29) | 3685 | 8980 | 5969 | 49 |
| H(30) | 3649 | 7329 | 5817 | 40 |

**Table 25. Torsion angles [°] for 41.**

| | | | |
|---|---|---|---|
| O(1)-C(2)-C(4)-C(5) | -157.25(12) | C(12)-C(11)-C(16)-C(17) | -52.01(18) |
| O(1)-C(2)-C(4)-C(11) | -24.49(15) | C(12)-C(11)-C(16)-C(21) | 129.10(15) |
| O(1)-C(22)-C(23)-C(24) | 71.37(16) | C(12)-C(11)-C(22)-O(1) | 77.45(14) |
| O(3)-C(2)-C(4)-C(5) | 24.6(2) | C(12)-C(11)-C(22)-C(23) | -43.07(17) |
| O(3)-C(2)-C(4)-C(11) | 157.36(16) | C(15)-O(14)-C(12)-O(13) | 1.6(2) |
| C(2)-O(1)-C(22)-C(11) | 23.67(15) | C(15)-O(14)-C(12)-C(11) | -174.11(13) |

| | | | |
|---|---|---|---|
| C(2)-O(1)-C(22)-C(23) | 149.78(12) | C(16)-C(11)-C(12)-O(13) | 155.04(14) |
| C(2)-C(4)-C(5)-C(6) | -141.92(14) | C(16)-C(11)-C(12)-O(14) | -29.24(17) |
| C(2)-C(4)-C(5)-C(10) | 36.2(2) | C(16)-C(11)-C(22)-O(1) | -156.86(12) |
| C(2)-C(4)-C(11)-C(12) | -75.19(14) | C(16)-C(11)-C(22)-C(23) | 82.62(17) |
| C(2)-C(4)-C(11)-C(16) | 156.60(13) | C(16)-C(17)-C(18)-C(19) | 0.0(3) |
| C(2)-C(4)-C(11)-C(22) | 35.57(13) | C(17)-C(16)-C(21)-C(20) | -0.6(2) |
| C(4)-C(5)-C(6)-C(7) | 179.09(15) | C(17)-C(18)-C(19)-C(20) | -0.4(3) |
| C(4)-C(5)-C(10)-C(9) | -179.10(14) | C(18)-C(19)-C(20)-C(21) | 0.3(2) |
| C(4)-C(11)-C(12)-O(13) | 26.8(2) | C(19)-C(20)-C(21)-C(16) | 0.2(2) |
| C(4)-C(11)-C(12)-O(14) | -157.52(12) | C(21)-C(16)-C(17)-C(18) | 0.5(2) |
| C(4)-C(11)-C(16)-C(17) | 74.46(18) | C(22)-O(1)-C(2)-O(3) | 179.07(14) |
| C(4)-C(11)-C(16)-C(21) | -104.43(17) | C(22)-O(1)-C(2)-C(4) | 0.76(16) |
| C(4)-C(11)-C(22)-O(1) | -36.34(13) | C(22)-C(11)-C(12)-O(13) | -78.78(18) |
| C(4)-C(11)-C(22)-C(23) | -156.85(13) | C(22)-C(11)-C(12)-O(14) | 96.94(14) |
| C(5)-C(4)-C(11)-C(12) | 54.18(17) | C(22)-C(11)-C(16)-C(17) | -173.85(13) |
| C(5)-C(4)-C(11)-C(16) | -74.04(17) | C(22)-C(11)-C(16)-C(21) | 7.3(2) |
| C(5)-C(4)-C(11)-C(22) | 164.93(13) | C(22)-C(23)-C(24)-C(25) | -175.37(15) |
| C(5)-C(6)-C(7)-C(8) | -0.5(3) | C(23)-C(24)-C(25)-C(26) | 126.20(18) |
| C(6)-C(5)-C(10)-C(9) | -1.0(2) | C(23)-C(24)-C(25)-C(30) | -54.6(2) |
| C(6)-C(7)-C(8)-C(9) | 0.1(3) | C(24)-C(25)-C(26)-C(27) | 178.94(18) |
| C(7)-C(8)-C(9)-C(10) | -0.2(3) | C(24)-C(25)-C(30)-C(29) | -179.43(19) |
| C(8)-C(9)-C(10)-C(5) | 0.6(2) | C(25)-C(26)-C(27)-C(28) | 1.0(3) |
| C(10)-C(5)-C(6)-C(7) | 0.9(2) | C(26)-C(25)-C(30)-C(29) | -0.2(3) |
| C(11)-C(4)-C(5)-C(6) | 94.85(17) | C(26)-C(27)-C(28)-C(29) | -1.2(3) |
| C(11)-C(4)-C(5)-C(10) | -87.06(18) | C(27)-C(28)-C(29)-C(30) | 0.7(3) |
| C(11)-C(16)-C(17)-C(18) | -178.42(15) | C(28)-C(29)-C(30)-C(25) | 0.0(3) |
| C(11)-C(16)-C(21)-C(20) | 178.27(14) | C(30)-C(25)-C(26)-C(27) | -0.3(3) |
| C(11)-C(22)-C(23)-C(24) | -170.21(13) | | |

**Table 26. Hydrogen bonds for 41 (Å$^2$ and °).**

Symmetry transformations used to generate equivalent atoms:
#1 x-1/2,-y+1/2,-z+1 #2 -x+3/2,-y+1,z+1/2

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| C(4)-H(4)...O(3)#1 | 1.00 | 2.59 | 3.4647(18) | 147 |
| C(15)-H(15C)...O(3)#2 | 0.98 | 2.52 | 3.413(2) | 151 |

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