Catalytic formal cycloadditions between anhydrides and ketones: excellent enantio and diastereocontrol, controllable decarboxylation and the formation of adjacent quaternary stereocentres

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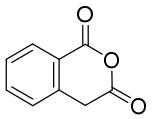
1.0 General

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 CD_3OD and referenced relative to residual $CHCl_3$ (δ = 7.26 ppm) DMSO (δ = 2.50 ppm) or CH_3OH (δ = 3.31 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 and Fluorine NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer (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. A Waters micromass LCT-tof mass spectrometer was used in ESI positive and ESI negative modes for electrospray ionization mass spectrometry. 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}. Anhydrous acetonitrile, toluene and methylene chloride (CH_2Cl_2) were obtained by distillation over calcium hydride and stored under argon. Anhydrous tetrahydrofuran (THF) and diethyl ether were obtained by distillation over sodium-benzophenone and stored under argon. Anhydrous methanol (MeOH) and isopropyl alcohol (^{i}PrOH) were obtained using 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, OJ-H, IA, or Chiralcel OD-H (4.6 mm x 25 cm) columns. The data for the crystal structures collected on a Bruker Smart Apex2 CCD diffractometer. For each dataset, a suitable crystal was selected and mounted using inert oil on a 0.3mm MiTeGen loop and placed on the goniometer head in a 100K N2 gas stream. The datasets were collected using Bruker APEX2 v2011.8-0 software. Data integrations, reductions and corrections for absorption and polarization effects were all performed using APEX2 v2011.8-0 software. Space group determination, structure solution and refinement were obtained using Bruker Shelxtl* Ver. 6.14 software. The structures were solved with Direct Methods using the SHELXTL program and refined against IF^2I with the program XL from SHELX-97 using all data. Non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were placed into geometrically calculated positions and refined using a riding model. (*Software Reference Manual, version 5.625; Bruker Analytical X-Ray Systems Inc.: Madison, WI, 2001. Sheldrick, G. M. SHELXTL, An Integrated System for Data Collection, Processing, Structure Solution and Refinement; Bruker

Analytical X-Ray Systems Inc.: Madison, WI, 2001.). Absolute configurations have been assigned by analogy with the structures unambiguously identified by X-ray crystallographic analysis.

2.0 Synthesis of anhydrides

2.1 Homophthalic anhydride (8)

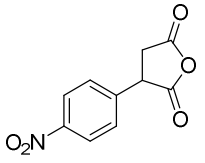


8

Homophthalic anhydride (**8**) was synthesised according to the reported literature procedure.[1] The isolated compound exhibited identical spectroscopic data to those reported in the literature.[1]

M.p. 140-144 °C (lit.,[2] m.p. 140-145 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.05 (1 H, d, *J* 8.2), 7.75 (1 H, app. t), 7.52 (1 H, app. t), 7.44 (1 H, d, *J* 7.8), 4.27 (2 H, s).

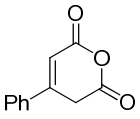
2.2 3-(4-Nitrophenyl)dihydrofuran-2,5-dione (*p*-nitrophenyl succinic anhydride) (53)



p-Nitrophenyl succinic anhydride (**55**) was synthesised according to the reported literature procedure.[3] The isolated compound exhibited identical spectroscopic data to those reported in the literature.[3]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (2 H, d, *J* 8.9), 7.51 (2 H, d, *J* 8.9), 4.49 (1 H, dd, *J* 7.2, 10.4), 3.55 (1 H, dd, *J* 10.4, 18.8), 3.17 (1 H, dd, *J* 7.2, 18.8); HRMS (*m/z* -ESI): [M-H] found 220.0243. $C_{10}H_6NO_5$ Requires 220.0240.

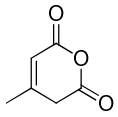
2.3 4-Phenyl-2*H*-pyran-2,6(3*H*)-dione (phenyl glutaconic anhydride) (55)



Phenyl glutaconic anhydride (**55**) was synthesised according to the reported literature procedure.[4] The isolated compound exhibited identical spectroscopic data to those reported in the literature.[4]

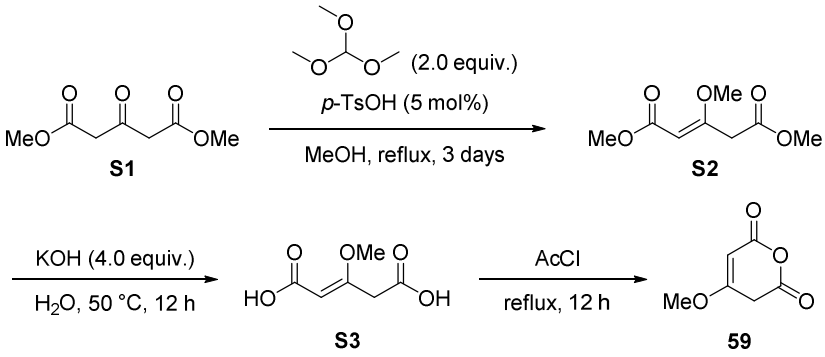
M.p. 197-199°C; (lit.[4] m.p. 198-201 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.81 (2 H, d, *J* 7.2), 7.59-7.43 (3 H, m), 6.80 (1 H, s), 4.16 (2 H, s).

2.4 **4-Methyl-2*H*-pyran-2,6(3*H*)-dione** (methyl glutaconic anhydride) (**57**)

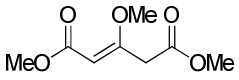


Methyl glutaconic anhydride (**57**) was synthesised according to the reported literature procedure.[4] The isolated compound exhibited identical spectroscopic data to those reported in the literature.[4] M.p. 79-81 °C; (lit.[4] m.p. 78-82 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.09 (1 H, s), 3.63 (2 H, s), 1.97 (3 H, s).

2.5 **4-Methoxy-2*H*-pyran-2,6(3*H*)-dione** (methoxy glutaconic anhydride) (**59**)



(*Z*)-Dimethyl 3-methoxypent-2-enedioate (**S2**)

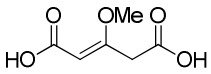


An oven dried 50 mL round-bottomed flask containing a stirring bar was charged with **S1** (2.00 g, 11.48 mmol). Methanol (25.0 mL) was added followed by trimethyl orthoformate (2.5 mL, 22.96 mmol) and *p*-toluenesulfonic acid (98.2 mg, 0.57 mmol). The flask was fitted with a condenser and a septum and the reaction mixture was heated at reflux temperature under an argon atmosphere for 3 days. Volatiles were then removed *in vacuo* to obtain a yellow oil that was purified by column chromatography on silica gel eluting from 100% hexane to 20% EtOAc in hexane, to give **S2** as a pale yellow oil (1.79 g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.19 (1 H, s), 3.84 (2 H, s), 3.71 (3 H, s), 3.69 (3 H, s), 3.68 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 168.1, 167.7, 92.9, 55.9, 52.1, 51.0, 38.1; IR (neat):

3000, 2953, 2844, 1742, 1709, 1628, 1436, 1377, 1327, 1252, 1134, 1052, 930, 824 cm^{-1}; HRMS (*m/z* -EI): $[M+Na]^+$ found 211.0582. $C_8H_{12}O_5Na$ Requires 211.0582.

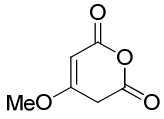
(*Z*)-3-Methoxypent-2-enedioic acid (**S3**)



A 50 mL round-bottomed flask containing a stirring bar was charged with **S2** (1.50 g, 7.97 mmol). Water (25.0 mL), followed by KOH (1.79 g, 31.88 mmol) were added, the flask was fitted with a condenser and the reaction mixture was heated at 50 °C for 12 h. The pH of the solution was then adjusted to pH = 2 by the dropwise addition of concentrated HCl. The reaction was then extracted with Et_2O (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to furnish **S3** as an off white solid that was used in the next step without any further purification (1.25 g, 98%).

M.p. deg. 180 °C; ^1H NMR (400 MHz, DMSO-d_6): δ = 12.05 (2 H, s), 5.12 (1 H, s), 3.68 (2 H, s), 3.61 (3 H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.2, 168.3, 168.2, 93.3, 55.9, 37.9; IR (neat): 2991, 2899, 2609, 1660, 1702, 1590, 1392, 1321, 1272, 1213, 1196, 1156, 1040, 918, 832, 731, 711 cm^{-1}; HRMS (*m/z* -EI): $[M-H]^-$ found 159.0292. $C_6H_7O_5$ Requires 159.0293.

4-Methoxy-2*H*-pyran-2,6(3*H*)-dione (methoxy glutaconic anhydride) (**59**)

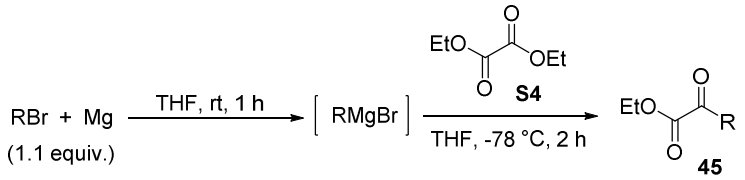


An oven dried 25 mL round-bottomed flask containing a stirring bar was charged with **S3** (500.0 mg, 3.12 mmol). Freshly distilled acetyl chloride (8.0 mL) was added, the flask was fitted with a condenser and a septum and the reaction mixture was heated at reflux temperature under an argon atmosphere for 16 h. The acetyl chloride was then removed *in vacuo* to obtain a brown oil that was purified using a plug of silica eluting with hexane:EtOAc 1:1 *v/v* to obtain methoxy glutaconic anhydride (**59**) as an off white solid (301.6 mg, 68%).

M.p. 85-87 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.38 (1 H, s), 3.83 (3 H, s), 3.52 (2 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 163.6, 161.1, 89.0, 57.1, 34.2 cm^{-1}; HRMS (*m/z* -EI): $[M+H]^+$ found 143.0338. $C_6H_7O_4$ Requires 143.0344.

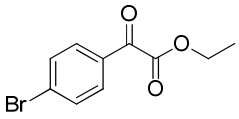
3.0 Synthesis of α-ketoesters substrates (45) and *N*-benzyl isatin (51)

3.1 Procedure A: general protocol for the synthesis of ethyl α-ketoesters (45) by addition of Grignard reagents to diethyl oxalate (S4)



An oven dried 25 mL round-bottomed flask containing a stirring bar was charged with freshly ground magnesium (1.2 equiv.) and anhydrous THF (2 mL), it was then fitted with a condenser and kept under an argon atmosphere. The relevant aryl bromide (1.1 equiv.) was added dropwise *via* syringe down the condenser and the reaction mixture was then heated at reflux temperature for 1 h. The resulting solution of Grignard reagent was taken up with a syringe and added dropwise over 1 h using a syringe pump to a solution of diethyl oxalate (**S4**) (680 μL, 5.05 mmol, 1.0 equiv.) in dry THF (10 mL) at -78 °C. Upon completion of the addition, the reaction mixture was stirred at -78 °C for 1 h, then warmed to room temperature. A 2 M aqueous solution of HCl (10 mL) and H_2O (10 mL) were added and the solution was extracted with Et_2O (4 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, the solvent was removed *in vacuo* and the residue was purified either by column chromatography or by distillation at reduced pressure to afford the corresponding ethyl α-ketoester.

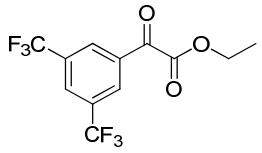
3.1.1 Ethyl 2-(4-bromophenyl)-2-oxoacetate (S5)



Prepared according to general procedure A using 1,4-dibromobenzene (1.30 mg, 5.51 mmol), magnesium (145.8 mg, 6.00 mmol), diethyl oxalate (**S4**, 680 μL, 5.05 mmol) and THF (15 mL). The crude product was purified by Kugelrohr distillation to yield α-ketoester **S5** (324.6 mg, 25%) as a colourless oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.[5]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (2 H, d, *J* 8.6), 7.66 (2 H, d, *J* 8.6), 4.45 (2 H, q, *J* 7.2), 1.42 (3 H, t, *J* 7.2); HRMS (*m/z* -EI): [M] found 255.9728. $C_{10}H_9O_3Br$ Requires 255.9735.

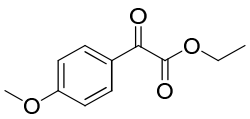
3.1.2 Ethyl 2-(3,5-bis(trifluoromethyl)phenyl)-2-oxoacetate (S6)



Prepared according to general procedure A using the commercially available 3,5-*bis*(trifluoromethyl)phenylmagnesium bromide (0.5 M in THF, 6.0 mL, 3.00 mmol), diethyl oxalate (**S4**, 370 μL, 2.73 mmol) and THF (10 mL). The crude product was purified by column chromatography (hexane:EtOAc 20:1) to yield α-ketoester **S6** (437.4 mg, 51%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (2 H, s), 8.15 (1 H, s), 4.50 (2 H, q, *J* 7.2), 1.46 (3 H, t, *J* 7.2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.9, 161.9, 134.6, 132.9 (q, $J_{C\text{-}F}$ 34.2), 130.4 (q, $J_{C\text{-}F}$ 3.8), 128.0 (sept., $J_{C\text{-}F}$ 3.5), 122.9 (q, $J_{C\text{-}F}$ 272.4), 63.5, 14.3; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -63.13; IR (neat): 3096, 2991, 1735, 1705, 1276, 1171, 1130, 1033, 913, 847, 698, 681 cm^{-1}; HRMS (*m/z* -EI): [M-$C_2H_5O_2$] found 241.0080. $C_9H_3OF_6$ Requires 241.0088.

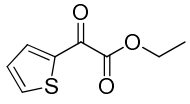
3.1.3 Ethyl 2-(4-methoxyphenyl)-2-oxoacetate (S7)



Prepared according to general procedure A using 4-bromoanisole (1.3 mL, 10.36 mmol), magnesium (274.6 mg, 11.30 mmol), diethyl oxalate (**S4**, 1.3 mL, 9.57 mmol) and THF (25 mL). The crude product was purified by column chromatography (hexane:EtOAc 20:1) to yield α-ketoester **S7** (1.23 g, 62%) as a colourless oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.[5]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (2 H, d, *J* 8.9), 6.98 (2 H, d, *J* 8.9), 4.44 (2 H, q, *J* 7.1), 3.90 (3 H, s), 1.42 (3 H, t, *J* 7.1); HRMS (*m/z* -EI): [M] found 208.0732. $C_{11}H_{12}O_4$ Requires 208.0736.

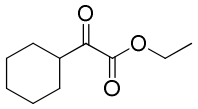
3.1.4 Ethyl 2-oxo-2-(thiophen-2-yl)acetate (S8)



Prepared according to general procedure A using 2-bromothiophene (1.7 mL, 10.86 mmol), magnesium (287.8 mg, 11.84 mmol), diethyl oxalate (**S4**, 1.3 mL, 9.57 mmol) and THF (25 mL). The crude product was purified by distillation at reduced pressure to yield α-ketoester **S8** (951.9 mg, 54%) as a dark yellow oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.[6]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (1 H, d, *J* 3.8), 7.82 (1 H, d, *J* 4.9), 7.20 (1 H, app. t), 4.44 (2 H, q, *J* 7.2), 1.43 (3 H, t, *J* 7.2); HRMS (*m/z* -EI): [M] found 184.0188. $C_8H_8O_3S$ Requires 184.0194.

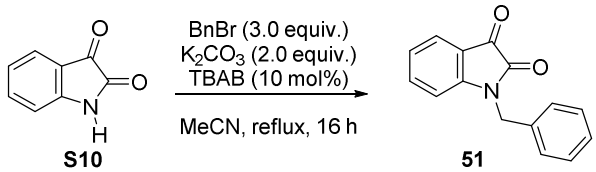
3.1.5 Ethyl 2-cyclohexyl-2-oxoacetate (S9)



Prepared according to general procedure A using the commercially available cyclohexylmagnesium chloride (2.0 M in Et_2O, 3.0 mL, 6.00 mmol), diethyl oxalate (**S4**, 740 μL, 5.45 mmol) and THF (15 mL). The crude product was purified by column chromatography (hexane:EtOAc 20:1) to yield α-ketoester **S9** (682.8 mg, 68%) as a colourless oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.[5]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.31 (2 H, q, *J* 7.1), 3.10-2.96 (1 H, m), 1.99-1.58 (6 H, m), 1.45-1.06 (7 H, m); HRMS (*m/z* -ESI): $[M+H]^+$ found 185.1178. $C_{10}H_{17}O_3$ Requires 185.1178.

3.2 *N*-Benzyl isatin (51)



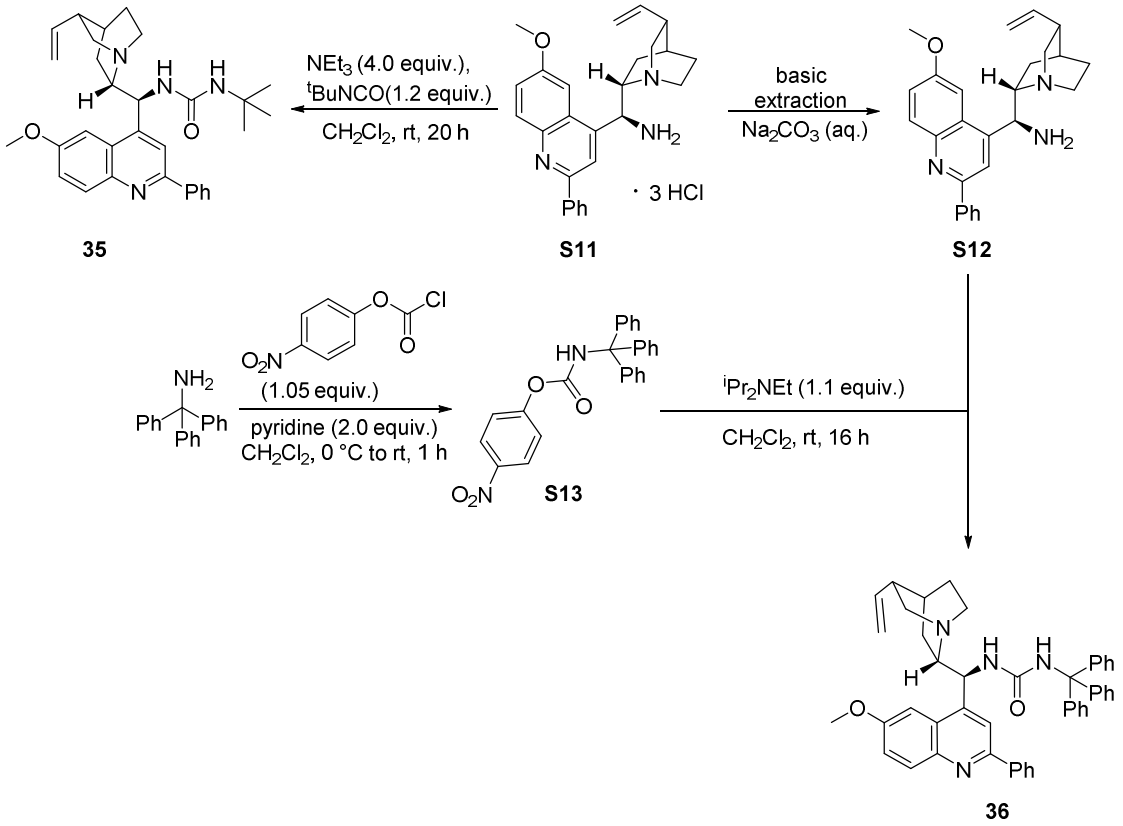
A 50 mL round-bottomed flask containing a stirring bar was charged with isatin (**S10**, 1.00 g, 6.80 mmol), K_2CO_3 (1.88 g, 13.59 mmol), TBAB (219.2 mg, 0.68 mmol) and MeCN (25 mL). Benzyl bromide (2.5 mL, 20.61 mmol) was added *via* syringe, the apparatus was fitted with a condenser and the reaction mixture was heated at reflux temperature for 16 h. The solvent was then removed in vacuo and the residue was recrystallised from EtOH to afford pure **51** (1.35 g, 84%) as orange

needles. The isolated compound exhibited identical spectroscopic data to those reported in the literature.[7]

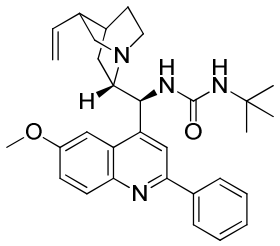
M.p. 128-130 °C (lit.,[8] 129-131 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (1 H, d, *J* 7.3), 7.46 (1 H, app. t), 7.38-7.28 (5 H, m), 7.07 (1 H, app. t), 6.77 (1 H, d, *J* 7.8), 4.93, (2 H, s); HRMS (*m/z* - ESI): $[M+H]^+$ found 238.0860. $C_{15}H_{12}NO_2$ Requires 238.0868.

4.0 Catalysts synthesis and characterisation

4.1 Synthesis of C-2'-phenyl-substituted catalysts 35 and 36



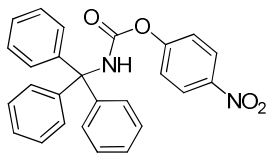
5.1.1 1-*tert*-Butyl-3-((*S*)-(6-methoxy-2-phenylquinolin-4-yl)((2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)urea (35)



An oven dried 25 mL reaction vessel containing a stirring bar under argon atmosphere was charged with **S11**[1] (500.0 mg, 0.98 mmol). Anhydrous CH_2Cl_2 (10 mL) was added *via* syringe and the reaction was cooled to 0 °C. Freshly distilled triethylamine (685.0 μL, 4,91 mmol) was added *via* syringe and, when the solid had dissolved *tert*-butyl isocyanate (125.0 μL, 1.09 mmol) was added. The resulting solution was warmed to room temperature and stirred for 20 h. The mixture was then transferred into a separating funnel, washed with water (2 x 10 mL), the organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (100% EtOAc) to obtain urea **35** (254.1 mg, 52% yield) as an amorphous white solid.

M.p. 131-134 °C; $[\alpha]_D^{20}$ = -16.5° (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16-8.06 (3 H, m), 7.84 (1 H, s), 7.76 (1 H, *J* 1.9), 7.52 (2 H, app. t), 7.48-7.36 (2 H, m), 6.27 (1 H, bs), 5.70 (1 H, ddd, *J* 7.2, 10.2, 16.6), 5.42 (1 H, bs), 5.11-5.02 (2 H, m), 4.88 (1 H, bs), 4.02 (3 H, s), 3.66-3.48 (2 H, m), 3.46 (1 H, dd, *J* 10.5, 13.6), 3.08-2.87 (2 H, m), 2.57-2.44 (1 H, m), 1.97-1.72 (3 H, m), 1.64 (1 H, app. t), 1.26 (9 H, s), 1.24-1.14 (1 H, m); ^{13}C NMR (100 MHz, $CDCl_3$)*: δ = 158.1, 157.2, 154.8, 145.2, 139.7, 139.3, 132.3, 129.1, 128.9, 127.5, 127.2, 122.1, 117.9, 116.1, 102.1, 60.2, 56.0, 55.2, 50.6, 41.1, 38.4, 29.5, 27.3, 26.5, 25.6 (* the resonance of 2 quaternary C could not be identified in the spectrum); IR (neat): 3311, 2962, 1667, 1621, 1545, 1500, 1353, 1221, 1029, 916, 829, 771, 694 cm^{-1}; HRMS (*m/z* -ESI): [M-H] found 497.2928. $C_{31}H_{37}N_4O_2$ Requires 497.2917.

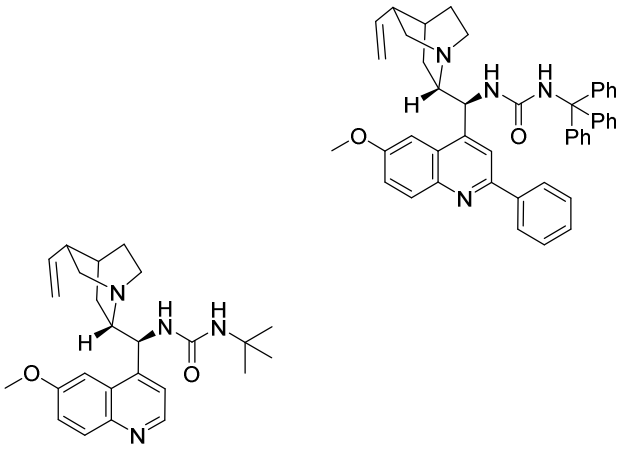
5.1.2 4-Nitrophenyl tritylcarbamate (S13)



A 50 mL oven dried round-bottomed flask containing a stirring bar was charged with triphenylmethylamine (1.50 g, 5.78 mmol) and anhydrous CH_2Cl_2 (5 mL), then it was fitted with a septum, kept under an argon atmosphere (balloon) and cooled to 0 °C. A solution of 4-nitrophenyl chloroformate (1.22 g, 6.07 mmol) in anhydrous CH_2Cl_2 (20 mL) was added *via* syringe at 0 °C, immediately followed by freshly distilled pyridine (935.0 µL, 11.57 mmol). The resulting solution was stirred for 16 h at room temperature, then concentrated *in vacuo*. The residue was purified by column chromatography (6:4 CH_2Cl_2:hexane) to afford **S13** (1.85 g, 75%) as a white solid.

M.p. 140-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (2 H, d, *J* 8.4), 7.44-7.16 (17 H, m), 6.43 (1 H, bs); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 151.5, 144.1, 144.1, 128.7, 128.3, 127.6, 125.1, 121.9; IR (neat): 3310, 3058, 1726, 1514, 1481, 1243, 1207, 1101, 1008, 858, 699 cm^{-1}

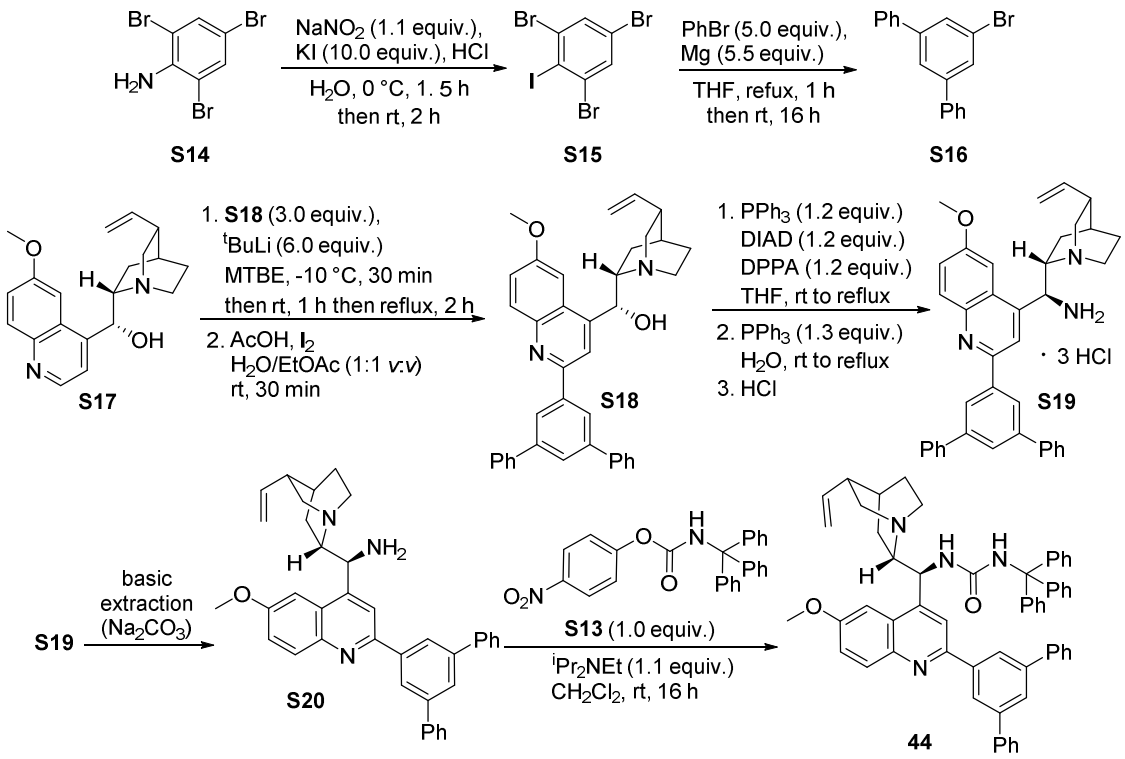
5.1.3 1-Trityl-3-((*S*)-(6-methoxy-2-phenylquinolin-4-yl)((2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)urea (36)



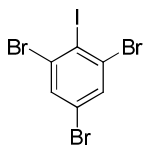
A 50 mL oven dried round-bottomed flask containing a stirring bar was charged with the free amine **S12**[1] (936.5 mg, 2.35 mmol) and anhydrous CH_2Cl_2 (10 mL), then it was fitted with a septum and kept under an argon atmosphere (balloon) and cooled to 0 °C. A solution of **S13** (1.00 g, 2.36 mmol) in anhydrous CH_2Cl_2 (20 mL) was added *via* syringe, immediately followed by anhydrous diisopropylethylamine (450.0 µL, 2.59 mmol and the reaction mixture was stirred at room temperature for 20 h. The yellow solution was transferred to a separating funnel, and washed with a 2 M aqueous solution of NaOH (6 x 30 mL) until the aqueous washings were almost colourless. The organic extracts were then washed with brine, dried over $MgSO_4$ filtered and the solvent was removed *in vacuo* to afford a residue which was purified by column chromatography eluting in gradient from 10% hexane in EtOAc to 100% EtOAc to yield **36** (901.3 mg, 56%) as an amorphous white solid. Alternatively **36** could also be purified by recrystallisation from CH_2Cl_2.

M.p. 126-130 °C; $[\alpha]_D^{20}$ = -23.0° (*c* 0.20, $CHCl_3$); ^{1}H NMR (600 MHz, CD_3OD)*: δ = 8.04 (2 H, d, *J* 7.8), 8.02 (1 H, d, *J* 9.3), 7.81 (1 H, bs) 7.66 (1 H, bs), 7.54 (2 H, app. t), 7.48 (1 H, t, *J* 7.4), 7.39 (1 H, dd, J 2.0, 9.1), 7.23-7.03 (15 H, m), 5.93-5.77 (1 H, m), 5.41 (1 H, app. bs), 5.02 (1 H, app. d), 4.96 (1 H, app. d), 3.75 (3 H, s), 3.45-3.21 (3 H, m), 2.89-2.66 (2 H, m), 2.42-2.27 (1 H, m), 1.74-1.43 (4 H, m), 0.97-0.77 (1 H, m) (* the two protic signals (N-H) are not visible in CD_3OD); ^{13}C NMR (150 MHz, CD_3OD)*: 158.4, 158.0, 155.4, 148.1, 145.8, 144.6, 141.6, 139.9, 130.8, 129.2, 128.9, 128.8, 127.6, 126.7, 122.6, 113.9, 102.3, 69.8, 65.9, 59.8, 55.8, 55.3, 41.2, 39.7, 27.9, 27.5, 26.3, 26.2 (* the resonance of 2 quaternary C belonging to the quinoline unit could not be identified in the spectrum); IR (neat): 3311, 3059, 2924, 1621, 1596, 1494, 1444, 1348, 1230, 1028, 910, 826, 696 cm^{-1}; HRMS (*m/z* -ESI): $[M+H]^+$ found 685.3557. $C_{46}H_{45}N_4O_2$ Requires 685.3543.

4.2 Synthesis of the C-2'-*m*-terphenyl-substituted catalyst 44



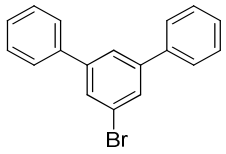
5.2.1 1,3,5-Tribromo-2-iodobenzene (S15)



A 250 mL three neck round-bottomed flask containing a stirring bar and fitted with a thermometer was charged with 2,4,6-tribromoaniline (**S14**, 10.00 g, 30.32 mmol) and concentrated aqueous HCl (20 mL) and the suspension was cooled to 0 °C. A solution of $NaNO_2$ (2.30 g, 33.35 mmol) in water (10 mL) was added dropwise to the reaction mixture while keeping its temperature below 10 °C and upon completion of the addition the reaction was stirred at 0 °C for 30 min. A solution of KI (50.33 g, 303.20 mmol) in H_2O (75 mL) was added dropwise to the vigorously stirred reaction mixture at 0 °C, then it was warmed to room temperature and stirred for 2 h. An aqueous 0.5 M solution of Na_2SO_3 (20 mL) and CH_2Cl_2 (50 mL) were added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with a 2 M aqueous solution of NaOH (50 mL), H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and the solvent was removed *in vacuo.* The solid residue obtained was recrystallised from CH_2Cl_2/hexane to yield **S15** (10.82 g, 81%) as pale yellow needles. The isolated compound exhibited identical spectroscopic data to those reported in the literature.[9]

M.p. 105-109 °C (lit.,[9] 101-103 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (2 H, s).

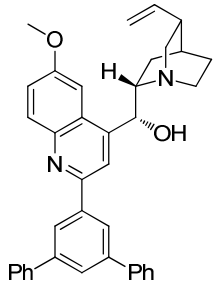
5.2.2 1-Bromo-3,5-diphenylbenzene (S16)



An oven dried 250 mL round-bottomed flask equipped with a stirring bar was charged with freshly ground magnesium (2.74 g, 112.76 mmol) and anhydrous THF (20 mL), then it was fitted with a condenser and placed under an argon atmosphere. Bromobenzene (11.8 mL, 112.76 mmol) was added *via* syringe in two portions at room temperature, then the reaction mixture was heated at reflux temperature for 1 h. The reaction was cooled to room temperature, then a solution of **S15** (9.92 g, 22.51 mmol) in anhydrous THF (70 mL) was added *via* syringe and the reaction mixture was heated at reflux for 1 h, then stirred at room temperature for 16 h. A 2 M aqueous solution of HCl (50 ml) was added slowly to the reaction, followed by CH_2Cl_2 (50 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue was purified by flash chromatography (100% hexane) to yield **S16** (5.92 g, 85%) as a white solid. The isolated compound exhibited identical spectroscopic data to those reported in the literature.[10]

M.p. 113-114 °C (lit.,[10] 107-109 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (3 H, bs), 7.61 (4 H, d, *J* 7.8), 7.47 (4 H, app. t), 7.40 (2 H, t, *J* 7.7).

5.2.3 (*R*)-(6-Methoxy-2-*m*-terphenylquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methanol (S18)

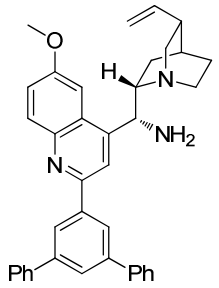


An oven dried 250 mL round-bottomed flask containing a large stirring bar was charged with **S16** (4.63 g, 14.98 mmol) fitted with a septum and placed under an argon atmosphere. Anhydrous diethyl ether (10 mL) was added *via* syringe and the suspension was cooled to -10 °C. A solution of *tert*-butyl lithium (1.7 M in pentane, 17.0 mL, 28.90 mmol) was added *via* syringe in one portion and the reaction mixture was stirred at -10 °C for 30 min then warmed to room temperature and stirred for 1 h. The reaction was cooled to 0 °C, then anhydrous MTBE (30 mL) was added *via* syringe followed by quinine (**S17**, 1.62 g, 4.99 mmol) and the reaction mixture was stirred at 0 °C for 30 min, then at room temperature for 1 h, then heated at reflux temperature for 2 h. Acetic acid (5 mL) is added dropwise *via* syringe to the reaction at 0 °C, followed by H_2O (20 mL) and EtOAc (20 mL). The reaction is allowed to room temperature, then solid iodine is added in several portions to the vigorously stirred mixture until the appearance of a persistent deep brown coloration. A solution of sodium thiosulfate ($Na_2S_2O_3$, 1.00 g) in water (20 mL) is added, followed by a concentrated solution of aqueous ammonia (35%, 20 mL) and the mixture is stirred vigorously for 10 min. The organic phase is then washed with brine and the aqueous phase is extracted with CH_2Cl_2 (3 x 20 mL), the combined organic extracts are then dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude oily residue is purified by column chromatography eluting in gradient from 100% EtOAc to 2% MeOH in AcOEt to EtOAc:MeOH:NEt_3 95:5:1 to obtain **S218** (2.07 g, 75%) as an off-white amorphous solid.

M.p 126-128 °C; $[\alpha]_D^{20}$ = + 11.0 (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (2 H, s), 8.11 (1 H, d, *J* 9.1), 8.06 (1 H, s), 7.83 (1 H, s), 7.73 (4 H, d, *J* 7.8), 7.49 (4 H, app. t), 7.44-7.33 (3 H, m), 7.20 (1 H, d, *J* 2.3), 5.74 (1 H, ddd, *J* 7.7, 10.3, 17.2), 5.61 (1 H, bs), 4.96 (1 H, d, *J* 17.2), 4.91 (1 H, d, *J* 10.3), 3.91 (3 H, s), 3.57-3.44 (1 H, m), 3.25-3.07 (2 H, m), 2.79-2.65 (2 H, m),

2.37-2.22 (1 H, m), 1.89-1.76 (3 H, m), 1.65-1.42 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 154.5, 148.2, 144.6, 142.4, 141.8, 141.3, 140.9, 132.1, 129.0, 127.7, 127.6, 127.0, 125.8, 125.3, 122.0, 116.5, 114.7, 101.3, 72.3, 60.3, 57.2, 56.0, 43.6, 40.1, 28.1, 27.7, 21.8; IR (neat): 3256, 3062, 2932, 2865, 1620, 1595, 1500, 1361, 1231, 1029, 878, 827, 758, 696 cm^{-1}; HRMS (*m/z* -ESI): $[M+H]^+$ found 553.2863. $C_{38}H_{37}N_2O_2$ Requires 553.2855.

5.3.2 (*S*)-[6-Methoxy-2-*m*-terphenylquinolin-4-yl][(2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl]methanamine (S20)

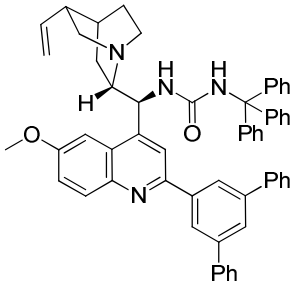


An oven dried 100 mL round-bottomed flask containing a stirring bar was charged with triphenylphospine (1.05 g, 4.00 mmol) and **S18** (1.84 g, 3.33 mmol), fitted with a septum and placed under an argon atmosphere. Anhydrous THF (25 mL) was added *via* syringe and the resulting solution was cooled to 0 °C. Diisopropyl azodicarboxylate (790 μL, 4.00 mmol) was added dropwise *via* syringe followed by diphenylphosphoryl azide (870 μL, 4.04 mmol), the resulting mixture was allowed to warm up to room temperature and stirred for 16 h, then heated at reflux temperature for 2 h. The reaction mixture was cooled to room temperature, then triphenylphospine (1.13 g, 4.33 mmol) was added and the solution was heated at reflux temperature for 5 hours. After cooling the reaction to room temperature, deionised H_2O (10 mL) was added and the reaction was stirred at room temperature for 20 h, it was then concentrated *in vacuo* and the residue was taken up in CH_2Cl_2 (10 mL) and Et_2O (10 mL). Concentrated HCl was added and the precipitate formed was filtered and dried to obtain the hydrochloride salt **S19** (1.39 g) as a pale yellow solid which was used without further purification. The free amino group at C-9 could be generated by dissolving the relative hydrochloride salt in a mixture of CH_2Cl_2 (20 mL) and a saturated aqueous solution of Na_2CO_3. The basic aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL), the organic extracts were dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to obtain compound **S20** as a tan solid.

M.p. 124-126 °C; $[\alpha]_D^{20}$ = + 31.2° (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *: δ= 8.35 (2 H, s), 8.15 (1 H, d, *J* 9.3), 8.08 (1 H, bs), 7.89 (1 H, s), 7.77 (4 H, d, *J* 7.6), 7.53-7.49 (5 H, m), 7.46-7.40

(3 H, m), 5.82-5.75 (1 H, m), 5.02-4.93 (2 H, m), 4.69 (1 H, bs), 3.98 (3 H, s), 3.32-3.25 (3 H, m), 2.88-2.82 (2 H, m), 2.30 (1 H, m), 1.65-1.47 (4 H, m), 0.91-0.88 (1 H, m); (* The protic signals are not visible in $CDCl_3$) ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 154.6, 147.6, 144.9, 142.4, 141.6, 141.2, 140.9, 132.2, 128.8, 128.8, 127.8, 127.6, 127.5, 126.8, 125.3, 121.4, 118.1, 114.4, 101.8, 77.3, 56.1, 55.6, 41.0, 39.7, 28.1, 27.6, 26.0; IR (neat): 2933, 2098, 1620, 1595, 1480, 1230, 1031, 907, 829, 759, 696 cm^{-1}; HRMS (*m/z* -ESI) :[M+H] found 552.3009. $C_{38}H_{38}N_3O$ Requires 552.3015.

5.3.3 1-Trityl-3-((*S*)-(6-methoxy-2-*m*-terphenylquinolin-4-yl)((2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)urea (44)



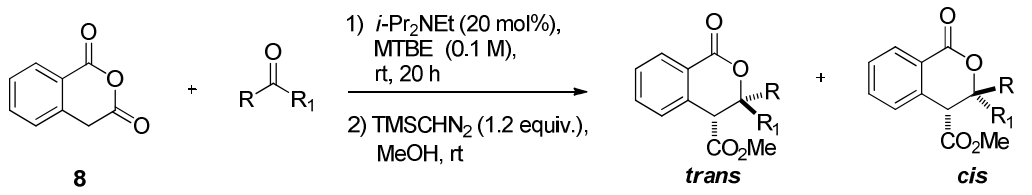
A 100 mL oven dried round-bottomed flask containing a stirring bar was charged with the free amine **S20** (1.14 g, 2.06 mmol) and anhydrous CH_2Cl_2 (15 mL), then it was fitted with a septum and kept under an argon atmosphere (balloon) and cooled to 0 °C. A solution of **S13** (876.2 mg, 2.06 mmol) in anhydrous CH_2Cl_2 (10 mL) was added *via* syringe, immediately followed by anhydrous diisopropylethylamine (395.0 µL, 2.27 mmol and the reaction mixture was stirred at room temperature for 20 h. The yellow solution was transferred to a separating funnel, and washed with a 2 M aqueous solution of NaOH (6 x 30 mL) until the aqueous washings were almost colourless. The organic extracts were then washed with brine, dried over $MgSO_4$ filtered and the solvent was removed *in vacuo* to afford a residue which was purified by column chromatography eluting in gradient from 10% hexane in EtOAc to 100% EtOAc to yield **44** (948.4 mg, 55%) as an amorphous tan solid.

M.p. 98-102 °C; $[\alpha]_D^{20}$ = +17.5° (*c* 0.20, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ = 8.33 (2 H, d, *J* 1.6), 8.17 (1 H, d, *J* 9.3), 7.94-7.82 (2 H, m), 7.81-7.70 (6 H, m),7.63-7.33 (12 H m), 7.26-6.94 (9 H, m) 5.75 (1 H, ddd, *J* 7.0, 9.9, 17.4), 5.07 (1 H, d, *J* 11.2), 5.04-4.89 (2 H, m), 3.99 (3 H, s), 3.52-3.17 (3 H, m), 2.99-2.79 (2 H, m), 2.20-2.35 (1 H, m), 1.75-1.36 (4 H, m), 0.92-0.76 (3 H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.1, 158.0, 154.2, 145.1, 142.4, 141.3, 141.1, 140.9, 140.2, 132.5, 132.4, 128.9, 128.7, 128.6, 128.5, 127.8, 127.5, 127.4, 127.3, 126.9, 126.5, 125.3, 125.1, 122.0,

114.4, 101.6, 69.6, 55.9, 55.6, 40.9, 39.3, 27.9, 27.1, 26.1; IR (neat): 3315, 3058, 2928, 2861, 2095, 1621, 1593, 1493, 1360, 1230, 1028, 914, 757, 696 cm^{-1}; HRMS (*m/z* -ESI): $[M+H]^+$ found 837.4157. $C_{58}H_{53}N_4O_2$ Requires 837.4169.

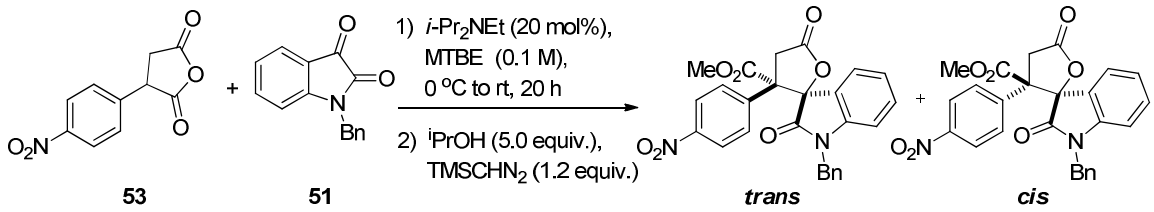
5.0 Synthesis of racemic products

5.1 Procedure B: general protocol for the preparation of racemic dihydroisocoumarins by annulation reactions between anhydride 8 and ketones (*i.e.* trifluoromethyl ketones, α-ketoesters, 1,2-diketones and α-ketoamides)



An oven dried 10 mL round-bottomed flask containing a stirring bar under argon atmosphere was charged with the relevant ketone (0.25 mmol) and anhydrous MTBE (2.5 mL, 0.1 M). Anhydride **8** (39.9 mg, 0.25 mmol) was then added to the reaction followed by *N*,*N*-diisopropylethylamine (8.7 μL, 0.05 mmol, 20 mol%) and the resulting mixture was stirred for 20 h at room temperature. To the reaction mixture containing the corresponding carboxylic acids, anhydrous MeOH (750.0 μL), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150.0 μL, 0.30 mmol) were added *via* syringe and the reaction was allowed to stir for 30 min at room temperature. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash chromatography to isolate the racemic major diastereomer.

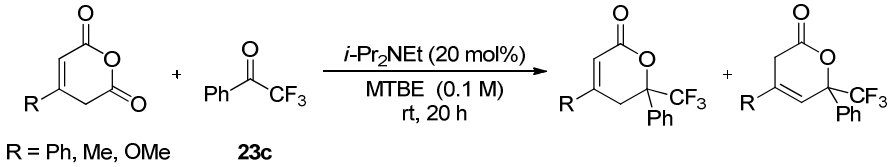
5.2 Preparation of racemic *trans*-54 by annulation reaction between anhydride 53 and *N*-benzyl isatin (51)



A oven-dried 10 mL reaction vessel containing a stirring bar under argon atmosphere was charged with anhydride **53** (1.0 equiv.). Anhydrous MTBE (0.1 M) was added *via* syringe and the reaction mixture was then cooled to 0 °C. *N*-benzyl isatin (**51**) (1.0 equiv.) was added to the reaction mixture followed by *N*,*N*-diisopropylethylamine (20 mol%) and the resulting mixture was allowed to warm to room temperature and stirred for 20 h. To the reaction mixture containing the corresponding

carboxylic acids, anhydrous isopropyl alcohol (5.0 equiv.), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 1.2 equiv.) were added *via* syringe at 0 ^{o}C and the reaction was allowed to stir for 1 h at room temperature. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash chromatography to isolate the racemic ***trans*-54**.

5.3 Procedure C: general protocol for the preparation of racemic δ-lactones by annulation reactions between glutaconic anhydrides and 2,2,2-trifluoromethyl acetophenone at room temperature



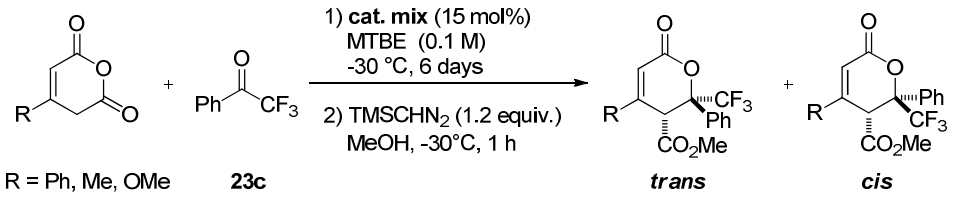
An oven dried 10 mL round-bottomed flask containing a stirring bar under argon atmosphere was charged with the relevant anhydride (0.25 mmol) and anhydrous MTBE (2.5 mL, 0.1 M). To the solution 2,2,2-trifluoromethyl acetophenone (**23c**, 34.1 μL, 0.25 mmol) was then added followed by *N*,*N*-diisopropylethylamine (8.7 μL, 0.05 mmol, 20 mol%) and the resulting mixture was stirred for 20 h at room temperature. The reaction mixture was directly loaded onto the silica column and the mixture containing the two isomeric products was isolated by flash chromatography.

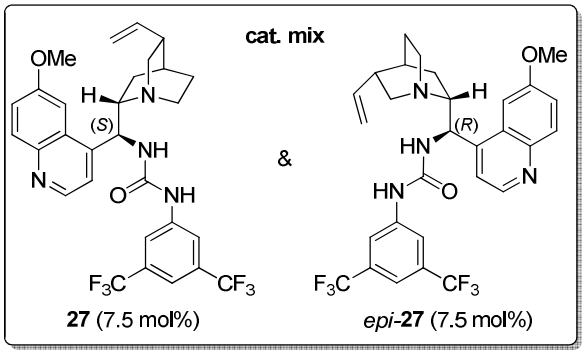
5.4 Synthesis of racemic δ-lactones by annulation reactions between glutaconic anhydrides and trifluoromethyl ketones at low temperatures

Due to the failure of the previously employed protocols involving the use of *N*,*N*-diisopropylethylamine (DIPEA) as the achiral catalyst to promote the synthesis of racemic δ-lactones from the reaction between glutaconic anhydrides and trifluoromethyl ketones at low temperatures (Table 4 and Scheme 8), an alternative protocol was developed. This consisted in the simultaneous use of a catalysts mixture containing equimolar amounts of catalyst **27**[11] and its epimeric form *epi*-**27**[11] as outlined in 5.4.1 and 5.5.1 Even if this protocol did not lead to the strictly racemic synthesis of the desired products (since the two catalysts **27** and *epi*-**27** employed simultaneously are epimers and not enantiomers), the relative abundance of both enantiomeric

products formed in the reactions was enough to unequivocally assign their retention times using CSP-HPLC analysis.

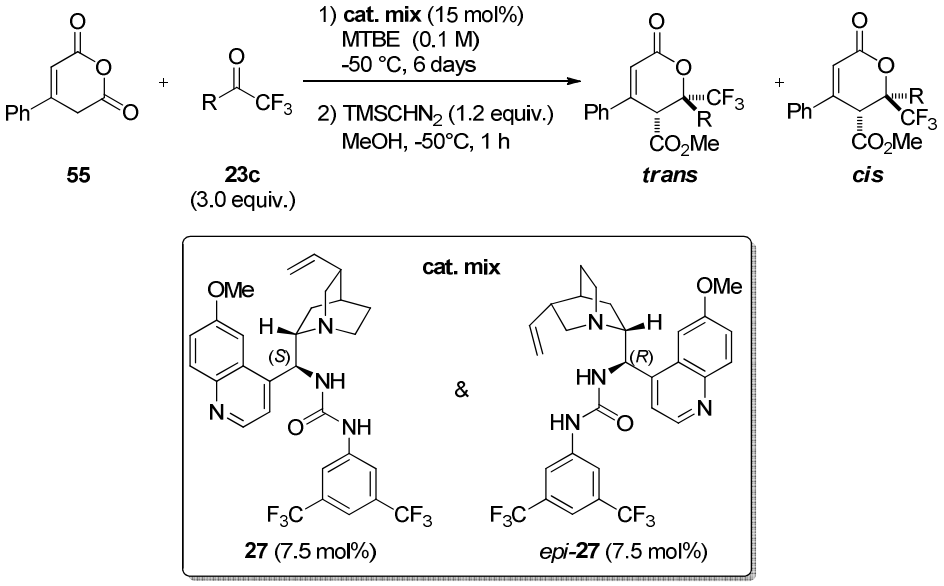
5.4.1 Procedure D: general protocol for the preparation of racemic δ-lactones by annulation reactions between glutaconic anhydrides and 2,2,2-trifluoromethyl acetophenone at -30 °C





An oven dried 5 mL round-bottomed flask containing a stirring bar under argon atmosphere was charged with the relevant anhydride (0.20 mmol) and anhydrous MTBE (2.0 mL, 0.1 M). The reaction was cooled at -30 °C and 2,2,2-trifluoromethyl acetophenone (**23c**, 27.2 μL, 0.20 mmol) followed by equimolar amounts of catalyst **27** (8.7 mg, 0.015mmol, 7.5 mol%) and catalyst *epi*-**27** (8.7 mg, 0.015 mmol, 7.5 mol%) were added to the solution. The reaction was stirred for 6 days at -30 °C, then anhydrous MeOH (610 μL), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 120 μL, 0.24 mmol) were added *via* syringe and the reaction was allowed to stir for 1 h at -30 °C. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash chromatography to isolate the mixture of diastereomeric products combined.

5.4.2 Procedure E: general protocol for the preparation of racemic δ-lactones by annulation reactions between anhydride 55 and trifluoromethyl ketones at -50 °C



An oven dried 5 mL round-bottomed flask containing a stirring bar under argon atmosphere was charged with anhydride **55** (30.1 mg, 0.16 mmol) and anhydrous MTBE (1.6 mL, 0.1 M). The reaction was cooled at -50 °C and the relevant trifluoromethyl ketone (0.48 mmol) followed by equimolar amounts of catalyst **27** (6.9 mg, 0.012 mmol, 7.5 mol%) and catalyst *epi*-**27** (6.9 mg, 0.012 mmol, 7.5 mol%) were added to the solution. The reaction was stirred for 6 days at -50 °C, then anhydrous MeOH (490 μL), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 96 μL, 0.192 mmol) were added *via* syringe and the reaction was allowed to stir for 1 h at -50 °C. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash chromatography to isolate the major diastereomer except in the case of compound **65** (Table 4, entry 6) where the diastereomeric products ***trans*-65** and ***cis*-65** could not be separated and where therefore isolated as a mixture.

6.0 Catalyst evaluation at low temperature (general procedures)

6.1 Procedure F: general protocol for asymmetric cycloaddition reactions between anhydride 8 and trifluoromethyl ketones (Table 1 and Table 2)

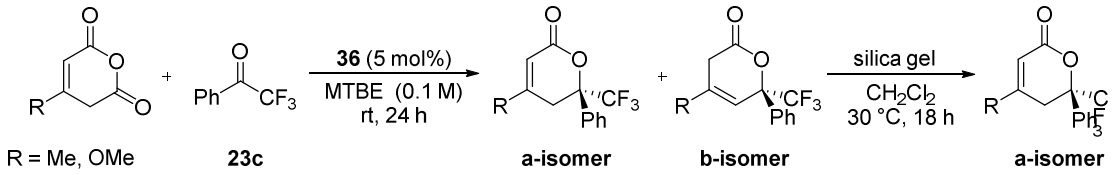
An oven dried 10 mL reaction vessel containing a stirring bar under argon atmosphere was charged with anhydride **8** (0.25 mmol, 1.0 equiv.) and the cinchona-based catalyst (5 mol%). Anhydrous MTBE (0.1 M) was added *via* syringe and the suspension was then cooled to -30 °C. The relevant trifluoromethyl ketone (1.0 equiv.) was added *via* syringe and the reaction mixture was stirred under

argon atmosphere for the time indicated in Table 1 or Table 2. The yield was monitored by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole (0.5 equiv.) as an internal standard. The reaction was then diluted with EtOAc (15 mL) and extracted with an aqueous solution of $NaHCO_3$ (10% *w*/*v*, 3 x 10 mL). The combined aqueous extracts were acidified with HCl (2.0 M) and the mixture was then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo* to yield the diastereomeric mixture of carboxylic acids. The diastereomeric ratio of the products was determined *via* ^{1}H NMR spectroscopic analysis of the crude mixture, the carboxylic acids were then suspended in anhydrous MTBE (0.1 M). Dry MeOH (750.0 μL), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 1.2 equiv.) were added *via* syringe and the reaction was allowed to stir for 30 min at room temperature. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash chromatography to isolate the major diastereomer. The enantiomeric excess of the products was determined by CSP-HPLC using the conditions indicated for each case.

6.2 Procedure G: general protocol for asymmetric cycloaddition reactions between anhydride 8 and α-ketoesters (Table 3)

An oven dried 20 mL reaction vessel containing a stirring bar under argon atmosphere was charged with the relevant α-ketoester (0.246 mmol, 1.0 equiv.). Anhydrous MTBE (0.02 M) was added *via* syringe and the solution was cooled to -15 °C. Anhydride **8** (1.0 equiv.) was added to the reaction immediately followed by catalyst **44** (5 mol%) and the reaction mixture was stirred under argon atmosphere for the time indicated in Table 3. The yield was monitored by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole (0.5 equiv.) as an internal standard. The reaction was then diluted with EtOAc (15 mL) and extracted with an aqueous solution of $NaHCO_3$ (10% *w*/*v*, 3 x 10 mL). The combined aqueous extracts were acidified with HCl (2.0 M) and the mixture was then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo* to yield the diastereomeric mixture of carboxylic acids. The diastereomeric ratio of the products was determined via ^{1}H NMR spectroscopic analysis of the crude mixture, the carboxylic acids were then suspended in anhydrous MTBE (0.1 M). Dry MeOH (750.0 μL), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 1.2 equiv.) were added *via* syringe and the reaction was allowed to stir for 30 min at room temperature. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash chromatography to isolate the major diastereomer. The enantiomeric excess of the products was determined by CSP-HPLC using the conditions indicated for each case.

6.3 Procedure H general protocol for asymmetric cycloaddition reactions between glutaconic anhydrides 57 and 59 with 2,2,2-trifluoromethyl acetophenone (23c) at room temperature and silica gel-promoted isomerisations (Scheme 5)



An oven dried 10 mL round-bottomed flask containing a stirring bar under argon atmosphere was charged with catalyst **36** (8.4 mg, 0.0123 mmol, 5 mol%) and anhydrous MTBE (2.5 mL, 0.1 M). 2,2,2-Trifluoromethyl acetophenone (**23c**, 33.5 μL, 0.246 mmol) was then added to the solution *via* syringe followed by the relevant anhydride (0.246 mmol) and the resulting mixture was stirred for 24 h at room temperature. The reaction mixture was then directly loaded onto a silica column and the two isomeric products (*i.e.* **a-isomer** and **b-isomer**) were isolated combined by flash chromatography. The two isomers combined were then dissolved in CH_2Cl_2 (5.0 mL) and added to a 25 mL round-bottomed flask containing a stirring bar. Silica gel (pore size 60 Å, 220-440 mesh, particle size 40-63 μm - approx. 500 mg) was added to the solution and the mixture was stirred at 30 °C for the time indicated in Scheme 5 in order to convert **b-isomer** into **a-isomer**. The conversion was followed by TLC analysis (hexane:EtOAc 8:2) monitoring the disappearance of **b-isomer**. Once the reaction was deemed complete, **a-isomer** was purified by flash chromatography and the enantiomeric excess of the product was determined by CSP-HPLC using the conditions indicated for each case.

6.4 Procedure I: general protocol for asymmetric cycloaddition reactions between anhydride 55 and trifluoromethyl ketones at -50 °C (Table 4)

An oven dried 5 mL round-bottomed flask containing a stirring bar under argon atmosphere was charged with catalyst **36** (16.4 mg, 0.024 mmol, 15 mol%) and anhydrous MTBE (1.6 mL, 0.1 M). The solution was cooled to -50 °C and then the relevant trifluoromethyl ketone (0.48 mmol) was added *via* syringe followed by anhydride **55** (30.1 mg, 0.16 mmol). The resulting mixture was left stirring at -50 °C for the time indicated in Table 4. To the reaction mixture, anhydrous MeOH (490 μL), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 96 μL, 0.192 mmol) were then added *via* syringe and the reaction was allowed to stir for 1 h at -50 °C. The *dr* of the

products was measured by ^{1}H-NMR. The solvent was removed in vacuo and the crude mixture of diastereomeric esters was purified by flash chromatography eluting in gradient from 100% hexanes to 15% EtOAc in hexane to isolate the major diastereomer except in the case of compound **65** (Table 4, entry 6) where the diastereomeric products ***trans*-65** and ***cis*-65** could not be separated and where therefore isolated as a mixture. The enantiomeric excess of the products was determined by CSP-HPLC using the conditions indicated for each case.

6.5 Procedure J: general protocol for asymmetric cycloaddition reactions between glutaconic anhydrides and 2,2,2-trifluoromethyl acetophenone at -30 °C (Scheme 8)

An oven dried 5 mL round-bottomed flask containing a stirring bar under argon atmosphere was charged with catalyst **36** (20.5 mg, 0.030 mmol, 15 mol%) and anhydrous MTBE (2.0 mL, 0.1 M). The solution was cooled to -30 °C and then 2,2,2-trifluoromethyl acetophenone (**23c**, 27.2 μL, 0.20 mmol) was added *via* syringe followed by the relevant anhydride (0.20 mmol). The resulting mixture was left stirring for at -30 °C for 6 days, then anhydrous MeOH (610 μL), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 120 μL, 0.24 mmol) were added *via* syringe and the reaction was allowed to stir for 1 h at -30 °C. The *dr* of the products was measured by ^{1}H-NMR. The reaction mixture was then directly loaded onto a silica gel column and the diastereomeric products were separated pure by flash chromatography except in the case of compound **60c** where both diastereomeric products ***trans*-60c** and ***cis*-60c** could not be separated and where therefore isolated as a mixture. The enantiomeric excess of the products was determined by CSP-HPLC using the conditions indicated for each case.

7.0 ^{1}H-NMR spectra for the determination of the relative stereochemical configuration of lactone products *cis*-37 and *cis*-43

The *dr* of the crude carboxylic acids obtained after the work-up of cycloaddition reactions between homophthalic anhydride and ketones was determined by ^{1}H NMR spectroscopy using the chemical shift of proton $\mathbf{H_a}$.

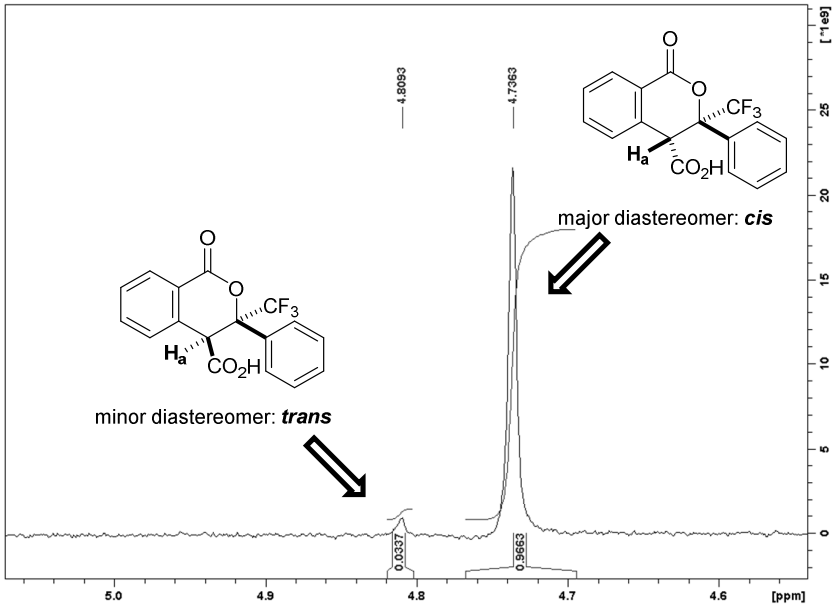


Figure: ^{1}H NMR spectrum of the crude mixture of carboxylic acid products prior to their esterification highlighting the chemical shifts resonance of proton H_a in both *trans*- and *cis*-isomers. The product ***cis*-43** (Table 2, entry 1) was isolated from this reaction.

The *cis*- stereochemistry for the major diastereomer was established using ^{1}H NMR NOE experiments on ***cis*-37** and ***cis*-43.** The resonances associated with proton $\mathbf{H_a}$ and the *o*-protons on the aromatic ring pendant from the lactone ring ($\mathbf{H_b}$) showed a NOE contact indicating their close proximity to each other.

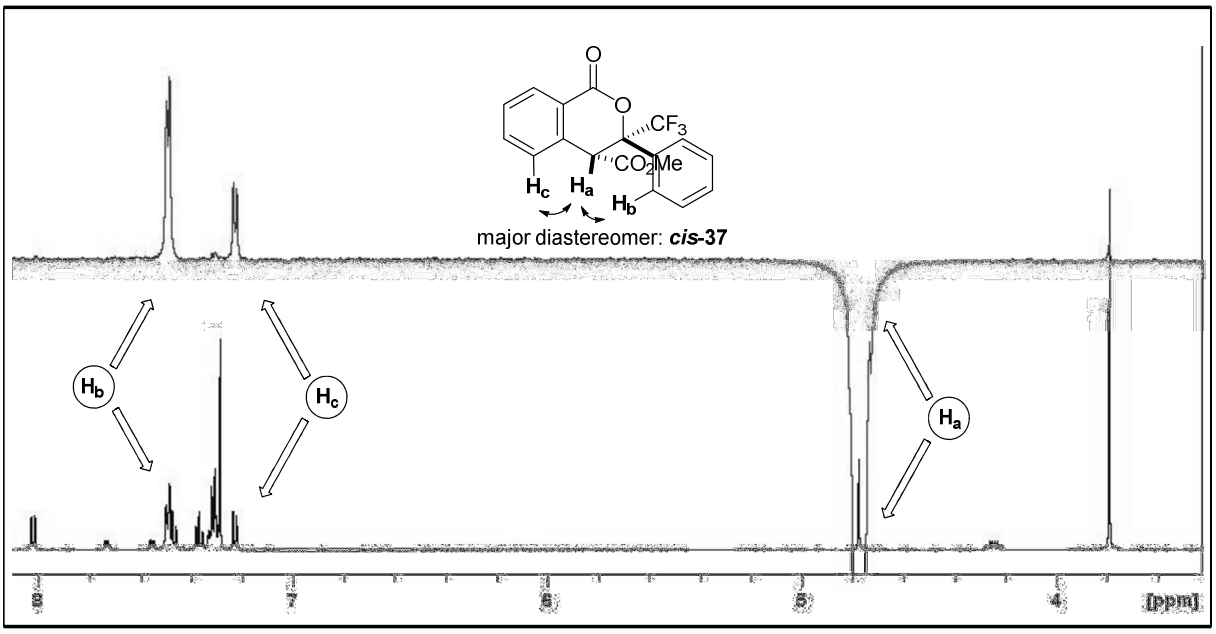


Figure: ^{1}H NMR spectrum of ***cis*-37** and ^{1}H NMR NOE experiment proving the proximity of proton H_a, H_b and H_c.

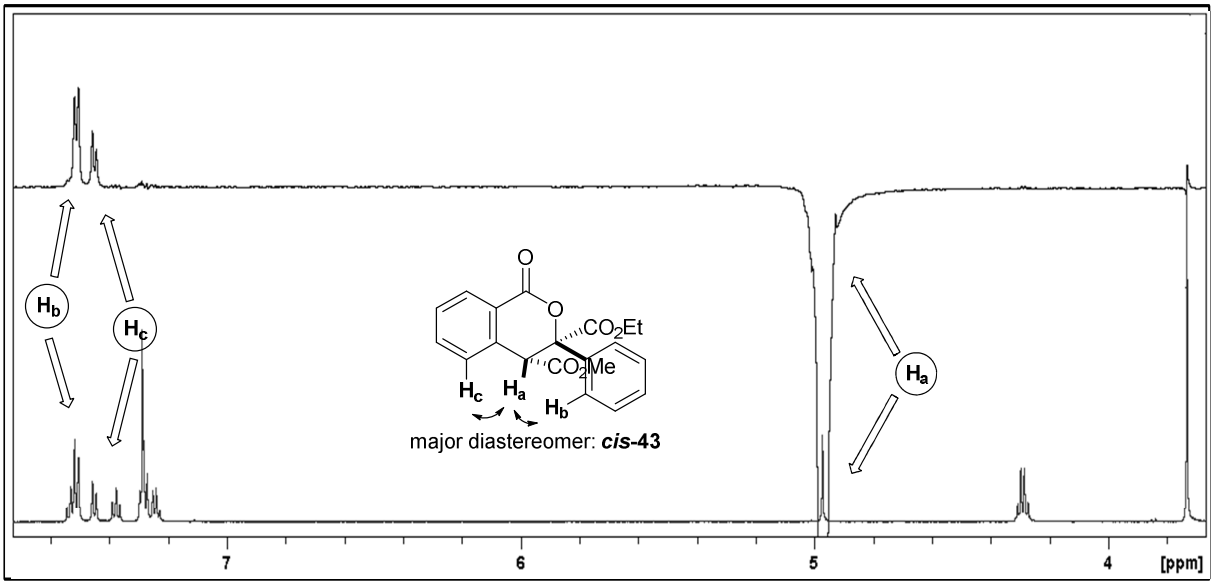
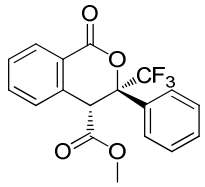


Figure: ^{1}H NMR spectrum of ***cis*-43** and ^{1}H NMR NOE experiment proving the proximity of proton H_a, H_b and H_c.

8.0 Characterisation data

(3*R*,4*R*)-Methyl 1-oxo-3-phenyl-3-(trifluoromethyl)isochroman-4-carboxylate (***cis*-37**, Table 2, entry 1)

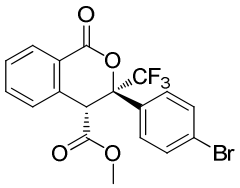


Prepared according to general procedure F using anhydride **8** (30.0 mg, 0.18 mmol), anhydrous MTBE (1.2 mL), 2,2,2-trifluoroacetophenone (17.3 μL, 0.12 mmol) and catalyst **36** (4.2 mg, 0.0061 mmol, 5 mol%). The reaction was stirred for 64 h at -30 °C to give a diastereomeric mixture of carboxylic acids in a 97:3 ratio (*cis*:*trans*). After esterification, the major diastereomer (***cis*-37**) was purified by flash chromatography eluting in gradient from 100% hexane to 5% EtOAc in hexane and isolated as a white solid (39.1 mg, 93%, 92% *ee*).

CSP-HPLC analysis. Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 85/15, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: 27.2 min (major enantiomer) and 37.7 min (minor enantiomer).

M.p. 138-140 °C; $[\alpha]_D^{20}$ = -170.0 (*c* 0.15, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (1 H, d, *J* 7.5), 7.50-7.41 (3 H, m), 7.36-7.23 (4 H, m), 7.20 (1 H, d, *J* 7.5), 4.75 (1 H, s), 3.76 (3 H, s); ^{1}H NMR (100 MHz, $CDCl_3$): δ = 168.3, 162.0, 134.5, 134.1, 133.7, 130.8, 129.9, 129.5, 129.0, 127.4, 126.6 (q, $J_{C\text{-}F}$ 0.8), 125.3, 122.6 (q, $J_{C\text{-}F}$ 284.6), 84.2 (q, $J_{C\text{-}F}$ 30.2), 53.5, 47.9; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -76.87; IR (neat): 2959, 1744, 1733, 1328, 1228, 1178, 1106, 1076, 1033, 961, 711, 647 cm^{-1}; HRMS (*m/z* - ESI): $[M+H]^+$ found 351.0852. $C_{18}H_{14}O_4F_3$ Requires 351.0844.

(3*R*,4*R*)-Methyl 3-(4-bromophenyl)-1-oxo-3-(trifluoromethyl)isochroman-4-carboxylate (***cis*-38**, Table 2, entry 2)

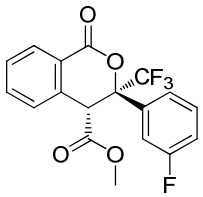


Prepared according to general procedure C using anhydride **8** (60.0 mg, 0.37 mmol), anhydrous MTBE (3.7 mL), 4'-bromo-2,2,2-trifluoroacetophenone (56.0 μL, 0.37 mmol) and catalyst **36** (12.6 mg, 0.018 mmol, 5 mol%). The reaction was stirred at -30 °C for 61 h to give a diastereomeric mixture of carboxylic acids in a 98:2 ratio (*cis*:*trans*). After esterification, the major diastereomer (***cis*-38**) was purified by column chromatography eluting in gradient from 100% hexane to 10% EtOAc in hexane and isolated as a white solid (134.0 mg, 85%, 95% ee).

CSP-HPLC analysis. Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: 28.8 min (minor enantiomer) and 30.9 min (major enantiomer).

M.p. 58-60 °C; $[\alpha]_D^{20}$ = -166.4 (*c* 0.28, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (1 H, d, *J* 7.7), 7.50-7.33 (6 H, m), 7.20 (1 H, d, *J* 7.6), 4.68 (1 H, s), 3.76 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 161.6, 134.8, 133.8, 132.9, 132.3, 131.0, 129.7, 128.3, 127.4, 125.1, 124.5, 122.3 (q, $J_{C\text{-}F}$ 283.8), 83.9 (q, $J_{C\text{-}F}$ 30.7), 53.6, 47.7; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -76.93; IR (neat): 2958, 2924, 2852, 1741, 1600, 1460, 1330, 1245, 1179, 1103, 1070, 961, 819, 723 cm^{-1}; HRMS (*m/z* - ESI): $[M-H]^-$ found 426.9803. $C_{18}H_{11}O_4F_3Br$ Requires 426.9793.

(3*R*,4*R*)-Methyl 3-(3-fluorophenyl)-1-oxo-3-(trifluoromethyl)isochroman-4-carboxylate (***cis*-39**, Table 2, entry 3)



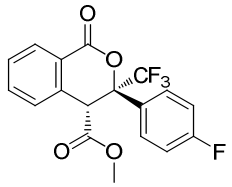
Prepared according to general procedure C using anhydride **8** (39.9 mg, 0.25 mmol), anhydrous MTBE (2.5 mL), 2,2,2,3'-tetrafluoroacetophenone (34.5 μL, 0.25 mmol) and catalyst **36** (8.4 mg, 0.012 mmol, 5 mol%). The reaction was stirred at -30 °C for 95 h to give a diastereomeric mixture of carboxylic acids in a 97:3 ratio (*cis*:*trans*). After esterification, the major diastereomer (***cis*-39**) was purified by column chromatography eluting in gradient from 100% hexane to 5% EtOAc in hexane and isolated as a white solid (80.6 mg, 89%, 92% *ee*).

CSP-HPLC analysis. Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 98/2, 0.7 mL min^{-1}, RT, UV detection at 254 nm, retention times: 29.7 min (minor enantiomer) and 31.6 min (major enantiomer).

M.p.125-127 °C; $[\alpha]_D^{20}$ = -176.6 (*c* 0.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (1 H, d, *J* 7.6), 7.48 (1 H, app. t), 7.37 (1 H, app. t), 7.32-7.13 (4 H, m), 7.02-6.94 (1 H, m), 4.68 (1 H, s), 3.76

(3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 162.7 (d, $J_{C\text{-}F}$ 248.5), 161.4, 136.1 (d, $J_{C\text{-}F}$ 6.9), 134.5, 133.5, 130.7, 130.6 (d, $J_{C\text{-}F}$ 8.3), 129.5, 127.3, 124.9, 122.2 (q, $J_{C\text{-}F}$ 284.4), 122.2 (d, $J_{C\text{-}F}$ 2.2), 117.0 (d, $J_{C\text{-}F}$ 20.9), 114.1 (d, $J_{C\text{-}F}$ 24.4), 83.6 (q, $J_{C\text{-}F}$ 30.9), 53.4, 47.7; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -76.79, -110.61; IR (neat): 2953, 2920, 1748, 1595, 1438, 1331, 1215, 1185, 1153, 1116, 1061, 1024, 828, 784, 707 cm^{-1}; HRMS (*m/z* - ESI): $[M\text{-}H]^-$ found 367.0602. $C_{18}H_{11}O_4F_4$ Requires 367.0593.

(3*R*,4*R*)-Methyl 3-(4-fluorophenyl)-1-oxo-3-(trifluoromethyl)isochroman-4-carboxylate (***cis*-40**, Table 2, entry 4)

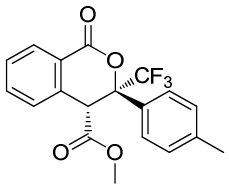


Prepared according to general procedure C using anhydride **8** (39.9 mg, 0.25 mmol), anhydrous MTBE (2.5 mL), 2,2,2,4'-tetrafluoroacetophenone (34.5 μL, 0.25 mmol) and catalyst **36** (8.4 mg, 0.012 mmol, 5 mol%). The reaction was stirred at -30 °C for 94 h to give a diastereomeric mixture of carboxylic acids in a 97:3 ratio (*cis*:*trans*). After esterification, the major diastereomer (***cis*-40**) was purified by column chromatography eluting in gradient from 100% hexane to 5% EtOAc in hexane and isolated as a white solid (71.6 mg, 79%, 92% *ee*).

CSP-HPLC analysis. Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 13.0 min. (minor enantiomer) and 15.8 min. (major enantiomer).

M.p. 77-79 °C; $[\alpha]_D^{20}$ = -200.0 (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (1 H, d, *J* 7.7), 7.51-7.42 (3 H, m), 7.37 (1 H, app. t), 7.21 (1 H, d, *J* 7.6), 7.03-6.94 (2 H, m), 4.70 (1 H, s), 3.76 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 163.3 (d $J_{C\text{-}F}$ 250.9), 161.7, 134.7, 133.9, 130.9, 129.63, 129.62, 128.8 (d, $J_{C\text{-}F}$ 8.7), 127.4, 125.1, 122.5 (q $J_{C\text{-}F}$ 284.1), 116.2 (d, $J_{C\text{-}F}$ 21.3), 83.9 (q, $J_{C\text{-}F}$ 32.7), 53.6, 47.9; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -77.08, -110.91; IR (neat): 2958, 2928, 1791, 1605, 1512, 1460, 1332, 1223, 1173, 1096, 1070, 964, 834, 725, 703 cm^{-1}; HRMS (*m/z* - ESI): $[M\text{-}H]^-$ found 367.0598. $C_{18}H_{11}O_4F_4$ Requires 367.0593.

(3*R*,4*R*)-Methyl 1-oxo-3-p-tolyl-3-(trifluoromethyl)isochroman-4-carboxylate (***cis*-41**, Table 2, entry 5)

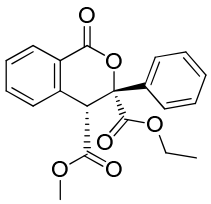


Prepared according to general procedure C using anhydride **8** (30.0 mg, 0.18 mmol), anhydrous MTBE (1.2 mL), 4'-methyl-2,2,2-trifluoroacetophenone (18.7 μL, 0.12 mmol) and catalyst **36** (4.2 mg, 0.0061 mmol, 5 mol%). The reaction was stirred at -30 °C for 94 h to give a diastereomeric mixture of carboxylic acids in a 88:12 ratio (*cis*:*trans*). After esterification, the major diastereomer (***cis*-41**) was purified by column chromatography eluting in gradient from 100% hexane to 5% EtOAc in hexane and isolated as a white solid (26.7 mg, 61%, 91% *ee*).

CSP-HPLC analysis. Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 19.4 min (major enantiomer) and 29.6 min (minor enantiomer).

M.p. 112-114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (1 H, d, *J* 7.7), 7.45 (1 H, dd, *J* 1.2, 7.7), 7.38-7.30 (3 H, m), 7.20 (1 H, d, *J* 7.5), 7.08 (2 H, d, *J* 8.3), 4.73 (1 H, s), 3.75 (3 H, s), 2.24 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 162.1, 140.0, 134.5, 134.2, 130.8, 130.7, 129.8, 129.4, 127.4, 126.5, 125.3, 122.7 (q, $J_{C\text{-}F}$ 284.9), 84.2 (q, $J_{C\text{-}F}$ 31.2), 53.5, 47.9, 21.1; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -81.77; IR (neat): 2926, 2852, 1737, 1433, 1331, 1277, 1233, 1187, 1177, 1103, 1074, 962, 810, 723 cm^{-1}; HRMS (*m/z* - ESI): $[M\text{-}H]^-$ found 363.0847. $C_{19}H_{14}O_4F_3$ Requires 363.0844.

(3*R*,4*R*)-3-Ethyl 4-methyl 1-oxo-3-phenylisochroman-3,4-dicarboxylate (***cis*-43**, Table 3, entry 1)



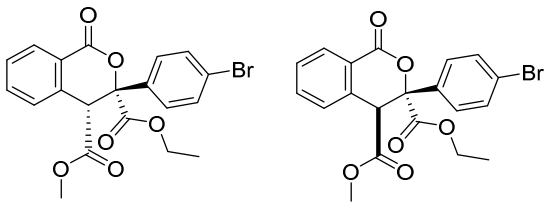
Prepared according to general procedure D using anhydride **8** (39.9 mg, 0.25 mmol), anhydrous MTBE (12.0 mL), α-ketoester **42** (39.1 μL, 0.25 mmol) and catalyst **44** (10.2 mg, 0.012 mmol, 5 mol%). The reaction was stirred at -15 °C for 36 h to give a diastereomeric mixture of carboxylic acids in a 93:7 ratio (*cis*:*trans*). After esterification, the major diastereomer (***cis*-43**) was purified by

column chromatography eluting in gradient from 100% hexane to 10% EtOAc in hexane and isolated as a white solid (77.5 mg, 89%, 92% *ee*).

CSP-HPLC analysis. Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 39.1 min (minor enantiomer) and 48.5 min (major enantiomer).

M.p. 132-134 °C; $[\alpha]_D^{20}$ = -82.0 (*c* 0.10, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.00 (1 H, d, *J* 7.7), 7.54-7.45 (3 H, m), 7.42 (1 H, d, *J* 7.5), 7.35 (1 H, app. t), 7.30-7.18 (3 H, m), 4.95 (1 H, s), 4.26 (2 H, q, *J* 7.2), 3.70 (3 H, s), 1.26 (3 H, t, *J* 7.2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 168.9, 163.0, 136.9, 134.6, 133.8, 130.5, 129.2, 129.1, 129.03, 129.01, 125.6, 124.5, 84.3, 62.8, 53.1, 50.4, 14.0; IR (neat): 2949, 2924, 2852, 1759, 1738, 1722, 1460, 1276, 1259, 1218, 1147, 1084, 1048, 721, 690 cm^{-1}; HRMS (*m/z* - ESI): $[M+Na]^+$ found 377.0996. $C_{20}H_{18}O_6Na$ Requires 377.1001.

3-Ethyl 4-methyl 3-(4-bromophenyl)-1-oxoisochroman-3,4-dicarboxylate (***cis*-46** – ***trans*-46**, Table 3, entry 2)



Prepared according to general procedure D using anhydride **8** (40.9 mg, 0.25 mmol), anhydrous MTBE (12.0 mL), α-ketoester **S5** (64.9 mg, 0.25 mmol) and catalyst **44** (10.2 mg, 0.012 mmol, 5 mol%). The reaction was stirred at -15 °C for 41 h to give a diastereomeric mixture of carboxylic acids in a 97:3 ratio (*cis*:*trans*). After esterification, both diastereomers (***cis*-46** and ***trans*-46**) were purified by column chromatography eluting in gradient from 100% hexane to 10% EtOAc in hexane and isolated as a pale yellow solid (99.0 mg, 94%, combined yield for both diastereoisomers, ***cis*-46**: 95% *ee*, ***trans*-46**: 91% *ee*.

CSP-HPLC analysis. Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 75/25, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: ***cis*-46** - 28.9 min (major enantiomer), 44.9 min (minor enantiomer) and ***trans*-46** 26.1 min (major enantiomer) and 53.0 min (minor enantiomer).

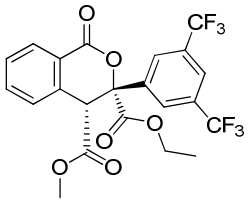
M.p. 145-147 °C.

Major diastereomer assigned for ^1H NMR and ^{13}C NMR; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.00 (1 H, d, *J* 7.7), 7.53 (1 H, app. t), 7.45-7.31 (6 H, m), 4.88 (1 H, s), 4.26 (2 H, q, *J* 7.1), 3.70 (3 H, s),

1.26 (3 H, t, *J* 7.1); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 168.6, 162.7, 136.1, 134.8, 133.5, 132.2, 130.6, 129.4, 129.1, 127.4, 124.3, 123.5, 83.9, 63.0, 53.2, 50.2, 14.0.; IR (neat): 2991, 2953, 2926, 2852, 1758, 1735, 1724, 1602, 1457, 1273, 1222, 1119, 1041, 1005, 971, 786, 728 cm^{-1}; HRMS (*m/z* - ESI): $[M-H]^-$ found 431.0115. $C_{20}H_{16}O_6Br$ Requires 431.0130.

***[α]$^{20}_D$ referred to a mixture of *cis*-46:*trans*-46 in a 97:3 ratio**

(3*R*,4*R*)-3-Ethyl 4-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-1-oxoisochroman-3,4-dicarboxylate (***cis*-47**, Table 3, entry 3)

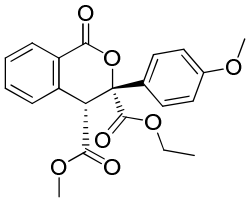


Prepared according to general procedure D using anhydride **8** (43.6 mg, 0.27 mmol), anhydrous MTBE (13.5 mL,), α-ketoester **S6** (84.4 mg, 0.27 mmol) and catalyst **44** (11.2 mg, 0.017 mmol, 5 mol%). The reaction was stirred at -50 °C for 94 h to give a diastereomeric mixture of carboxylic acids in a 97:3 ratio (*cis*:*trans*). After esterification, the major diastereomer (***cis*-47**) was purified by column chromatography eluting in gradient from 100% hexane to 20% EtOAc in hexane and isolated as a white solid (121.8 mg, 92%, 85% *ee*).

CSP-HPLC analysis. Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.3 mL min^{-1}, RT, UV detection at 254 nm, retention times: 20.7 min (minor enantiomer) and 36.4 min (major enantiomer).

M.p. 147-149 °C; $[\alpha]_D^{20}$ = -64.4 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (1 H, dd, *J* 1.0, 7.7), 7.95 (2 H, s), 7.76 (1 H, s), 7.57 (1 H, app. t), 7.46 (1 H, d, *J* 7.6), 7.41 (1 H, app. t), 4.93 (1 H, s), 4.31 (2 H, app. q), 3.73 (3 H, s), 1.29 (3 H, t, *J* 7.1); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 167.9, 161.9, 140.1, 135.2, 132.9, 132.6 (q, $J_{C\text{-}F}$ 33.8), 130.8, 129.9, 129.0, 126.1 (m), 124.0, 122.8 (q, $J_{C\text{-}F}$ 273.6), 83.4, 63.6, 53.4, 50.2, 14.0; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -63.00; IR (neat): 2966, 2924, 1761, 1734, 1375, 1276, 1227, 1169, 1127, 1072, 899, 681 cm^{-1}; HRMS (*m/z* - ESI): $[M\text{-}H]^-$ found 489.0773. $C_{22}H_{15}O_6F_6$ Requires 489.0773.

(3*R*,4*R*)-3-Ethyl 4-methyl 3-(4-methoxyphenyl)-1-oxoisochroman-3,4-dicarboxylate (***cis*-48**, Table 3, entry 4)



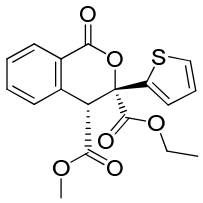
Prepared according to general procedure D using anhydride **8** (27.6 mg, 0.17 mmol), anhydrous MTBE (0.02 M, 8.5 mL), α-ketoester **S7** (35.4 mg, 0.17 mmol) and catalyst **44** (14.2 mg, 0.017

mmol, 10 mol%). The reaction was stirred at -15 °C for 72 h to give a diastereomeric mixture of carboxylic acids in a 81:19 ratio (*cis*:*trans*). After esterification, the major diastereomer (***cis*-48**) was purified by column chromatography eluting in gradient from 100% hexane to 20% EtOAc in hexane and isolated as a white solid (39.9 mg, 61%, 87% *ee*).

CSP-HPLC analysis. Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 80/20, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 25.0 min. (major enantiomer) and 44.7 min. (minor enantiomer).

M.p. 132-134 °C; $[\alpha]_D^{20}$ = -93.3 (*c* 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (1 H, d, *J* 7.6), 7.50 (1 H, app. t), 7.45-7.30 (4 H, m), 6.74 (2 H, d, *J* 8.9), 4.90 (1 H, s), 4.24 (2 H, q, *J* 7.1), 3.69 (3 H, s), 3.68 (3 H, s), 1.24 (3 H, t, *J* 7.1); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 169.2, 163.2, 160.0, 134.7, 134.1, 130.6, 129.3, 129.2, 128.8, 127.2, 124.7, 114.4, 84.1, 62.8, 55.4, 53.2, 50.3, 14.2; IR (neat): 2966, 2924, 2853, 1742, 1723, 1604, 1510, 1246, 1225, 1188, 1114, 1089, 1022, 853, 730 cm^-; HRMS (*m/z* - ESI): $[M-H]^-$ found 383.1129. $C_{21}H_{19}O_7$ Requires 383.1131.

(3*S*,4*R*)-3-Ethyl 4-methyl 1-oxo-3-(thiophen-2-yl)isochroman-3,4-dicarboxylate (***trans*-49**, Table 3, entry 5)



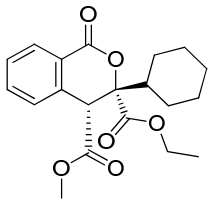
Prepared according to general procedure D using anhydride **8** (39.0 mg, 0.24 mmol), anhydrous MTBE (0.02 M, 12.0 mL,), α-ketoester **S8** (44.0 mg, 0.24 mmol) and catalyst **44** (10.0 mg, 0.012 mmol, 10 mol%). The reaction was stirred at -15 °C for 86 h to give a diastereomeric mixture of carboxylic acids in a 94:6 ratio (*trans*:*cis*). After esterification, the major diastereomer (***trans*-49**) was purified by column chromatography eluting in gradient from 100% hexane to 10% EtOAc in hexane and isolated as a white solid (64.9 mg, 75%, 88% *ee*).

CSP-HPLC analysis. Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 32.3 min (major enantiomer) and 55.0 min. (minor enantiomer).

M.p. 108-112 °C; $[\alpha]_D^{20}$ = -105.2 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (1 H, d, *J* 7.8), 7.56 (1 H, app. t), 7.49 (1 H, d, *J* 7.6), 7.40 (1 H, app. t), 7.17 (1 H, d, *J* 4.8), 7.09 (1 H, d, *J* 3.4), 6.83 (1 H, app. t), 4.87 (1 H, s), 4.39-4.24 (2 H, m), 3.69 (3 H, s), 1.30 (3 H, app. t); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0, 168.2, 162.3, 140.4, 134.7, 133.7, 130.6, 129.3, 129.2, 127.2,

127.00, 126.98, 124.1, 82.7, 63.0, 53.1, 51.3, 14.0; IR (neat): 3105, 2962, 2924, 1734,1601, 1459, 1432, 1254, 1218, 1112, 1078, 727 cm^{-1}; HRMS (*m/z* - ESI): $[M-H]^-$ found 359.0585. $C_{18}H_{15}O_6S$ Requires 359.0589.

(3*S*,4*R*)-3-Ethyl 4-methyl 3-cyclohexyl-1-oxoisochroman-3,4-dicarboxylate (***cis*-50**, Table 3, entry 6)

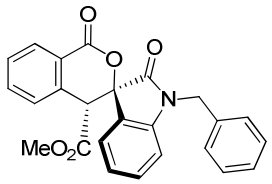


Prepared according to general procedure D using anhydride **8** (23.1 mg, 0.14 mmol), anhydrous MTBE (7.4 mL,), α-ketoester **S9** (26.3 mg, 0.14 mmol) and catalyst **44** (10.0 mg, 0.012 mmol). The reaction was stirred at -15 °C for 72 h to give a diastereomeric mixture of carboxylic acids in a 90:10 ratio (*cis*:*trans*). After esterification, the major diastereomer (***cis*-50**) was purified by column chromatography eluting in gradient from 100% hexane to 10% EtOAc in hexane and isolated as a white solid (42.9 mg, 85%, 66% *ee*).

CSP-HPLC analysis. Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.7 mL min^{-1}, RT, UV detection at 254 nm, retention times: 20.3 min (major enantiomer) and 32.9 min (minor enantiomer).

M.p. 99-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (1 H, d, *J* 7.6), 7.50 (1 H, app. t), 7.42 (1 H, app. t), 7.26 (1 H, d, *J* 7.6), 4.50 (1 H, s), 4.04-3.88 (2 H, m), 3.66 (3 H, s), 2.34-2.23 (1 H, m), 2.10-1.90 (2 H, m), 1.88-1.72 (2 H, m), 1.73-1.61 (1 H, m), 1.40-1.05 (1 H, m), 0.92 (3 H, app t), 0.88-0.74 (3 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 168.8, 163.7, 134.7, 133.7, 130.1, 129.2, 127.6, 125.6, 87.7, 61.9, 52.8, 48.3, 44.1, 29.7, 27.4, 26.9, 26.3, 26.1, 25.9; IR (neat): 2929, 2853, 1730, 1605, 1466, 1224, 1189, 1167, 1074, 1018, 998, 730, 696 cm^{-1}; HRMS (*m/z* - ESI): $[M-H]^-$ found 359.1495. $C_{20}H_{23}O_6$ Requires 359.1495.

(3*R*,4'*R*)-Methyl 1-benzyl-1',2-dioxospiro[indoline-3,3'-isochroman]-4'-carboxylate (*cis*-52, Scheme 4**)**

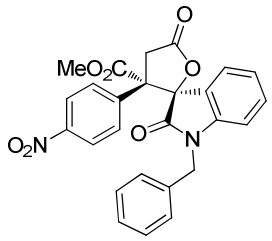


An oven dried 20 mL reaction vessel containing a stirring bar under argon atmosphere was charged with anhydride **8** (20.0 mg, 0.12 mol) and catalyst **36** (16.7 mg, 0.024 mmol, 20 mol%). Anhydrous MTBE (12.0 mL) was added *via* syringe and the solution was cooled to -15 °C. *N*-Benzyl isatin (**51**) (29.2 mg, 0.12 mmol) was added to the reaction and the mixture was stirred at -15 °C for 39 h. The reaction was then diluted with EtOAc (15 mL) and extracted with an aqueous solution of $NaHCO_3$ (10% *w*/*v*, 3 x 10 mL). The combined aqueous extracts were acidified with HCl (2.0 N) and the mixture was then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo* to yield the diastereomeric mixture of carboxylic acids. ^{1}H NMR spectroscopic analysis of the crude mixture allowed to establish the *dr* of the products to be 91:9 (*cis*:*trans*). The carboxylic acids were suspended in anhydrous MTBE (0.1 M). Dry MeOH (350.0 μL), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 75.0 μL) were added *via* syringe and the reaction was allowed to stir for 5 min at room temperature. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash chromatography eluting in gradient from 100% hexane to 25% EtOAc in hexane. The major diastereomer ***cis*-52** was isolated pure (42.2 mg, 85%, 80% *ee*) as an off-white solid.

CSP-HPLC analysis. Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 66.8 min (minor enantiomer) and 83.8 min (major enantiomer).

M.p. 140-142 °C; $[\alpha]_D^{20}$ = -52.0 (*c* 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (1 H, d, *J* 7.1), 7.65 (1 H, app. t), 7.57 (1 H, app. t), 7.40-7.20 (7 H, m, H-4), 6.97-6.89 (2 H, m), 6.73 (1 H, d, *J* 7.9), 4.92 (1 H, *J* 15.7), 4.82, (1 H, *J* 15.7), 4.54 (1 H, s), 3.67 (3 H, s); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.1, 168.4, 163.3, 143.2, 135.1, 134.5, 133.7, 131.6, 130.5, 129.4, 129.0, 128.0, 127.7, 126.7, 125.9, 125.4, 124.3, 123.4, 110.1, 80.4, 53.0, 50.5, 44.4; IR (neat): 2928, 2852, 1739, 1662, 1597, 1447, 1254, 1216, 1156, 1118, 1080, 834, 754, 728, 685 cm^{-1}; HRMS (*m/z* - ESI): $[M+Na]^+$ found 436.1158. $C_{25}H_{19}NO_5Na$ Requires 436.1161.

(2*R*,3*S*)-Methyl 1'-benzyl-3-(4-nitrophenyl)-2',5-dioxo-4,5-dihydro-3H-spiro[furan-2,3'-indoline]-3-carboxylate (*trans*-54, Scheme 4**)**

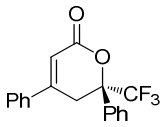


An oven dried 10 mL reaction vessel containing a stirring bar under argon atmosphere was charged with anhydride **53** (37.2 mg, 0.17 mmol). Anhydrous MTBE (17.0 mL) was added *via* syringe and the solution was cooled to -15 °C. Catalyst **36** (23.0 mg, 0.033 mmol, 20 mol%) was added to the reaction, immediately followed by *N*-benzyl isatin (**51**) (39.9 mg, 0.17 mmol) and the reaction mixture was stirred at -15 °C for 21 h. The reaction was then diluted with EtOAc (15 mL) and extracted with an aqueous solution of $NaHCO_3$ (10% *w*/*v*, 3 x 10 mL). The combined aqueous extracts were acidified with HCl (2.0 N) and the mixture was then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo* to obtain a diastereomeric mixture of carboxylic acids which was suspended in anhydrous MTBE (0.1 M). Dry ^{i}PrOH (64.0 μL), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150.0 μL) were added to the suspension *via* syringe and the reaction was allowed to stir for 30 min at room temperature. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash chromatography eluting in gradient from 100% hexane to 20% EtOAc in hexane. The major diastereomer ***trans*-54** was isolated pure (72.9 mg, 91%, 98% *ee*) as an off-white solid.

CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 75/25, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 22.3 min (minor enantiomer) and 53.7 min (major enantiomer).

M.p. 191-193 °C; $[\alpha]_D^{20}$ = +41.6 (*c* 0.18, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.87 (2 H, d, *J* 8.9), 7.75 (1 H, app. t), 7.60-7.35 (5H, m) 7.32-7.13 (5 H, m), 4.8 (1 H, *J* 14.9), 4.30 (2 H, app. t), 3.82 (3 H, s), 3.33 (1 H, d, *J* 14.9). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.4, 171.6, 169.8, 147.6, 144.3, 141.8, 140.8, 134.2, 132.5, 128.7, 128.3, 128.0, 125.9, 124.0, 123.3, 122.3, 110.2, 85.3, 60.3, 53.6, 44.3, 36.6; IR (neat): 3021, 2958, 2924, 2857, 1808, 1723, 1608, 1520, 1467, 1350, 1259, 1171, 997, 865, 759, 745 cm^{-1}; HRMS (*m/z* - ESI): $[M+H]^+$ found 473.1341. $C_{26}H_{21}N_2O_7$ Requires 473.1349.

(*R*)-4,6-Diphenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (**56a**, Scheme 5)



An oven dried 10 mL reaction vessel containing a stirring bar under argon atmosphere was charged with anhydride **55** (46.3 mg, 0.246 mmol) and catalyst **29**[12] (8.3 mg, 0.0197 mmol, 8 mol%). Anhydrous MTBE (2.5 mL) was added *via* syringe followed by 2,2,2-trifluoroacetophenone (35.0 µL, 0.246 mmol) and the reaction mixture was stirred at room temperature for 24 h. The solvent was removed in *vacuo* and **56a** was purified by column chromatography eluting in gradient from 100% hexanes to 10% EtOAc in hexane, to give a white solid (75.0 mg, 92%, 62% *ee*).

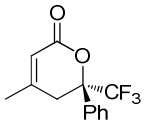
CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.75 mL min^{-1}, RT, UV detection at 254 nm, retention times: 10.3 min (minor enantiomer) and 11.4 min (major enantiomer).

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

M.p. 122-124 ^{o}C; $[\alpha]_D^{20}$ = -22.7 (c 0.12, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54-7.39 (10 H, m), 6.25 (1 H, s), 3.62 (1 H, d, *J* 17.7), 3.52 (1 H, dd, *J* 17.7, 2.3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.7, 151.9, 135.5, 133.7, 131.1, 129.7, 129.1, 128.8, 126.5, 126.0, 121.8 (q, $J_{C\text{-}F}$ 280.4), 114.9, 82.5 (q, $J_{C\text{-}F}$ 32.3), 29.6; HRMS (*m/z* - ESI): $[M+H]^+$ found 319.1020. $C_{18}H_{14}F_3O_2$ Requires 319.1024.

M.p., $[\alpha]^{20}_D$ ^{1}H NMR, ^{13}C NMR and HRMS are referred to 56a synthesised in 76% *ee* as described in Scheme 7

(*R*)-4-Methyl-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (**58a**, Scheme 5)

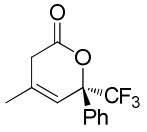


Prepared according to general procedure H using catalyst **36** (8.4 mg, 0.0123 mmol, 5 mol%) and anhydride **57** (31.0 mg, 0.246 mmol). The silica gel-promoted isomerisation reaction lasted for 3 days at room temperature. A mixture (55:45) of the two isomers (**58a**:**58b**) was obtained. Upon purification by column chromatography eluting in gradient from 10% EtOAc in hexane to 30% EtOAc in hexane, **58a** was isolated as a white solid (33.4 mg, 53%, 49% *ee*).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 98/2, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: 21.7 min (major enantiomer) and 23.0 min (minor enantiomer).

M.p. 94-96 °C; $[\alpha]_D^{20}$ = -25.4 (*c* 0.32, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57-7.46 (2 H, m), 7.45-7.34 (3 H, m), 5.75 (1 H, s), 3.17 (1 H, d, *J* 17.6), 2.99 (1 H, d, *J* 17.6), 1.96 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.4, 154.2, 134.2, 129.8, 128.9, 126.5, 123.3 (q, $J_{C\text{-}F}$ 283.6), 116.8, 82.4 (q, $J_{C\text{-}F}$ 30.7), 32.6, 23.5; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -80.25; IR (neat): 2979, 2924, 2857, 1726, 1646, 1438, 1309, 1236, 1172, 1034, 977, 940, 849, 763 cm^{-1}; HRMS (*m/z* - ESI): $[M+H]^+$ found 257.0787. $C_{13}H_{12}O_2F_3$ Requires 257.0789.

(*R*)-4-Methyl-6-phenyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-2-one (**58b**, Scheme 5)

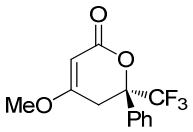


Prepared according to general procedure H using catalyst **36** (8.4 mg, 0.0123 mmol, 5 mol%) and anhydride **57** (31.0 mg, 0.246 mmol). The silica gel-promoted isomerisation reaction lasted for 3 days at room temperature. A mixture (55:45) of the two isomers (**58a**:**58b**) was obtained. Upon purification by column chromatography eluting in gradient from 20% EtOAc in hexanes to 30% EtOAc in hexane, **58b** was isolated as colourless oil (26.6 mg, 42%, 57% *ee*).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 98/2, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: 14.3 min (major enantiomer) and 16.5 min (minor enantiomer).

$[\alpha]_D^{20}$ = +41.1 (*c* 0.47, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67-7.52 (2 H, m), 7.50-7.34 (3 H, m), 6.12 (1 H, s), 3.12 (1 H, d, *J* 21.6), 2.92 (1 H, d, *J* 21.6), 1.90 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 135.5, 135.1, 129.6, 128.8, 126.5, 123.6 (q, $J_{C\text{-}F}$ 284.9), 116.5, 80.0 (q, $J_{C\text{-}F}$ 30.9), 34.1, 22.0; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -79.64; IR (neat): 3071, 2916, 1763, 1697, 1449, 1230, 1168, 1042, 940, 824, 761, 714 cm^{-1}; HRMS (*m/z* - ESI): $[M+H]^+$ found 257.0786. $C_{13}H_{12}O_2F_3$ Requires 257.0789.

(*R*)-4-Methoxy-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (**60a**, Scheme 5)

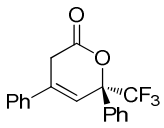


Prepared according to general procedure H using catalyst **36** (8.4 mg, 0.0123 mmol, 5 mol%) and anhydride **59** (35.0 mg, 0.246 mmol). The silica gel-promoted isomerisation reaction lasted for 18 h and afforded the single isomer **60a** which was purified by column chromatography eluting in gradient from 10% EtOAc in hexane to 30% EtOAc in hexane. Product **60a** was obtained as a white solid (64.1 mg, 96%, 46% *ee*).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: 21.6 min (major enantiomer) and 23.9 min (minor enantiomer).

M.p. 98-100 °C; $[\alpha]_D^{20}$ = -14.2 (*c* 0.53, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59-7.47 (2 H, m), 7.46-7.34 (3 H, m), 5.06 (1 H, s), 3.66 (3 H, s), 3.31 (1 H, d, *J* 17.1), 3.10 (1 H, d, *J* 17.1); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 163.5, 133.7, 129.9, 128.9, 126.6, 123.3 (q, $J_{C\text{-}F}$ 283.4), 90.6, 81.2 (q, $J_{C\text{-}F}$ 30.7), 56.5, 31.2; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -80.32; IR (neat): 3075, 2999, 2949, 2919, 2857, 1716, 1625, 1445, 1388, 1313, 1232, 1168, 1045, 994, 884, 819, 759, 714 cm^{-1}; HRMS (*m/z* - ESI): $[M-H]^-$ found 271.0594. $C_{13}H_{10}O_3F_3$ Requires 271.0582.

(*R*)-4,6-Diphenyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-2-one (**56b**, Scheme 6)



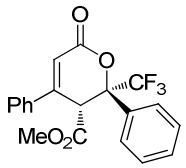
An oven dried 10 mL reaction vessel containing a stirring bar under argon atmosphere was charged with anhydride **55** (46.3 mg, 0.246 mmol) and catalyst **29**[12] (8.3 mg, 0.0197 mmol, 8 mol%). Anhydrous MTBE (2.5 mL) was added *via* syringe and the suspension was then cooled to -10 °C. 2,2,2-Trifluoroacetophenone (35.0 µL, 0.246 mmol) was added *via* syringe and the reaction mixture was stirred at -10 °C for 48 h. The crude reaction mixture was directly loaded onto a silica gel column and product **56b** was purified by flash chromatography eluting in gradient from 100% hexanes to 10% EtOAc in hexane to obtain a colourless oil (64.5 mg, 80%, 66% *ee*).

CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 10.0 min (minor enantiomer) and 11.1 min (major enantiomer).

$[\alpha]_D^{20}$ = -43.7 (*c* 0.10, acetone); IR (neat): 3056, 2921, 1756, 1640, 1463, 1230, 1188, 1040, 1026, 980, 776, 690 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3): δ = 7.65 (2 H, m), 7.48-7.27 (8 H, m), 6.70 (1 H, s), 3.66-3.32 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 136.9, 136.1, 134.7, 129.7, 129.5, 128.9, 128.8, 125.9, 125.4, 122.9 (q, $J_{C\text{-}F}$ 281.4), 117.0, 84.2 (q, $J_{C\text{-}F}$ 31.2), 31.8; ^{19}F NMR (376.5 MHz, $CDCl_3$): -73.6; HRMS (*m/z* - ESI): $[M+H]^+$ found 319.1020. $C_{18}H_{14}F_3O_2$ Requires 319.1024.

$[\alpha]^{20}_D$ ^{1}H NMR, ^{13}C NMR and HRMS are referred to 56b synthesised in 79% *ee* as described in Scheme 7

(2*R*,3*R*)-Methyl 6-oxo-2,4-diphenyl-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate (***cis*-56c**, Table 4, entry 1)

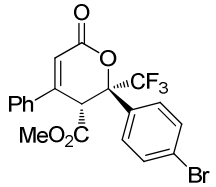


Prepared according to general procedure I using 2,2,2-trifluoroacetophenone (67.0 µL, 0.48 mmol). The reaction was stirred at -50 °C for 6 days. After esterification and purification by flash chromatography eluting in gradient from 100% hexanes to 15% EtOAc in hexane, lactone ***cis*-56c** was obtained as a white solid (55.0 mg, 92%, 98% *ee*).

CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 12.0 min (major enantiomer) and 13.3 min (minor enantiomer).

M.p. 178-180 °C; $[\alpha]_D^{20}$ = -2.68 (*c* = 0.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50-7.40 (2 H, m), 7.40-7.38 (5 H, m), 7.38-7.30 (3 H, m), 6.33 (1 H, s), 4.73 (1 H, s), 3.80 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 161.6, 149.8, 134.2, 134.1, 131.5, 130.0, 129.5, 129.2, 126.15, 126.13, 122.6 (q, $J_{C\text{-}F}$ 283.9), 117.2, 84.2 (q, $J_{C\text{-}F}$ 30.8 Hz), 53.9, 46.7; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -76.55; IR (neat): 1750, 1733, 1626, 1450, 1428, 1321, 1231, 1167, 1037, 1039, 961, 883, 776, 720 cm^{-1}; HRMS (*m/z* - EI): $[M]^+$ found 376.0912. $C_{20}H_{15}F_3O_4$ Requires 376.0922.

(2*R*,3*R*)-Methyl-2-(4-bromophenyl)-2-(trifluoromethyl)-3,6-dihydro-6-oxo-4-phenyl-2*H*-pyran-3-carboxylate (***cis*-61**, Table 4, entry 2)

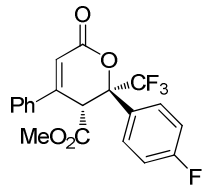


Prepared according to general procedure I using 4'-bromo-2,2,2-trifluoroacetophenone (121.0 mg, 0.48 mmol). The reaction was stirred at -50 °C for 6 days. After esterification and purification by flash chromatography eluting in gradient from 100% hexanes to 15% EtOAc in hexane, lactone ***cis*-61** was obtained as a white solid (66.0 mg, 90%, 99% *ee*).

CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 10.3 min (minor enantiomer) and 11.7 min (major enantiomer).

M.p. 58-60 °C; $[\alpha]_D^{20}$ = -2.45 (*c* = 0.46, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50 (2 H, d, *J* 8.8), 7.48-7.38 (5 H, m), 7.36 (2 H, d, *J* 8.8), 6.36 (1 H, s), 4.68 (1 H, s), 3.82 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 161.0, 149.7, 134.0, 133.3, 132.6, 131.8, 129.7, 128.0, 126.6, 126.2, 122.4 (q, $J_{C\text{-}F}$ 284.6), 117.0, 84.0 (q, $J_{C\text{-}F}$ 29.6), 54.0, 46.5; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -77.10; IR (neat): 1733, 1626, 1493, 1445, 1321, 1222, 1180, 1042, 1009, 960, 870, 771, 728 cm^{-1}; HRMS (*m/z* - EI): $[M]^+$ found 454.0038. $C_{20}H_{14}BrF_3O_4$ Requires 454.0028.

(2*R*,3*R*)-Methyl-2-(trifluoromethyl)-2-(4-fluorophenyl)-3,6-dihydro-6-oxo-4-phenyl-2*H*-pyran-3-carboxylate (***cis*-62**, Table 4, entry 3)

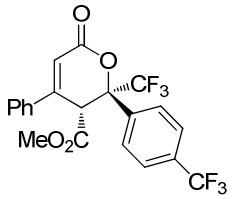


Prepared according to general procedure I using 4',2,2,2-tetrafluoroacetophenone (92.0 mg, 0.48 mmol). The reaction was stirred at -50 °C for 6 days. After esterification and purification by flash chromatography eluting in gradient from 100% hexanes to 15% EtOAc in hexane, lactone ***cis*-62** was obtained as a white solid (58.0 mg, 92%, 96% *ee*).

CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 97/3, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 21.3 min (minor enantiomer) and 23.2 min (major enantiomer).

M.p. 54-56 °C; $[\alpha]_D^{20}$ = -2.17 (*c* = 0.34, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.58-7.36 (7 H, m), 7.06 (2 H, app. t), 6.36 (1 H, s), 4.69 (1 H, s), 3.82 (3 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 163.5 (d, $J_{C\text{-}F}$ 248.1), 161.1, 149.8, 134.1, 131.7, 129.7 (d, $J_{C\text{-}F}$ 3.7), 129.6, 128.3 (d, $J_{C\text{-}F}$ 8.3), 126.1, 125.3 (q, $J_{C\text{-}F}$ 280.8), 117.1, 116.4 (d, $J_{C\text{-}F}$ 21.1), 83.9 (q, $J_{C\text{-}F}$ 30.8), 54.0, 46.7; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -77.23, -111.3; IR (neat): 1733, 1626, 1604, 1514, 1450, 1227, 1171, 1093, 1042, 1016, 964, 870, 828, 772, 713 cm^{-1}; HRMS (*m/z* - EI): $[M\text{-}H]^-$ found 393.0323. $C_{20}H_{13}F_4O_4$ Requires 393.0750.

(2*R*,3*R*)-Methyl-2-(trifluoromethyl)-2-(4-(trifluoromethyl)phenyl)-3,6-dihydro-6-oxo-4-phenyl-2*H*-pyran-3-carboxylate (***cis*-63**, Table 4, entry 4)

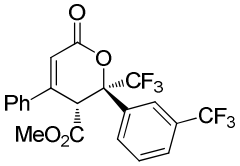


Prepared according to general procedure I using 2,2,2-trifluoro-4′-(trifluoromethyl)acetophenone (81.0 μL, 0.48 mmol). The reaction was stirred at -50 °C for 6 days. After esterification and purification by flash chromatography eluting in gradient from 100% hexanes to 15% EtOAc in hexane, lactone ***cis*-63** was obtained as a white solid (63.0 mg, 89%, 96% *ee*).

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: 7.0 min (major enantiomer) and 8.4 min. (minor enantiomer).

M.p. 55-57 °C; $[\alpha]_D^{20}$ = -2.02 (*c* = 0.09, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (4 H, app. s), 7.54-7.34 (5 H, m), 6.37 (1 H, s), 4.74 (1 H, s), 3.83 (3 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 160.6, 149.5, 137.9, 133.6, 132.3 (q, $J_{C\text{-}F}$ 32.8), 131.7, 129.5, 126.6, 126.1 (q, $J_{C\text{-}F}$ 3.7), 126.0, 123.4 (q, $J_{C\text{-}F}$ 272.8), 122.2 (q, $J_{C\text{-}F}$ 284.0), 116.8, 83.7 (q, $J_{C\text{-}F}$ 30.9), 53.9, 46.3; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -63.6, -76.9; IR (neat): 1738, 1622, 1450, 1416, 1325, 1171, 1128, 1102, 1042, 1016, 964, 870, 827, 771, 720 cm^{-1}; HRMS (*m/z* - EI): $[M+H]^+$ found 445.0877. $C_{21}H_{15}F_6O_4$ Requires 445.0869.

(2*R*,3*R*)-Methyl-2-(trifluoromethyl)-2-(3-(trifluoromethyl)phenyl)-3,6-dihydro-6-oxo-4-phenyl-2*H*-pyran-3-carboxylate (***cis*-64**, Table 4, entry 5)



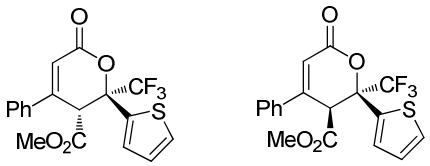
Prepared according to general procedure I using 2,2,2-trifluoro-3′-(trifluoromethyl)acetophenone (82.0 μL, 0.48 mmol). The reaction was stirred at -50 °C for 6 days. After esterification and purification by flash chromatography eluting in gradient from 100% hexanes to 15% EtOAc in hexane, lactone ***cis*-64** was obtained as a white solid (68.0 mg, 96%, 96% *ee*).

CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min-1, RT, UV detection at 254 nm, retention times: 7.3 min (minor enantiomer) and 8.2 min (major enantiomer).

M.p. 52-54 °C; $[\alpha]_D^{20}$ = -2.12 (*c* = 0.29, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78-7.69 (2 H, m), 7.68-7.62 (1 H, d, *J* 8.0), 7.53 (1 H, app. t), 7.49-7.39 (5 H, m), 6.36 (1 H, s), 4.75 (1 H, s), 3.83 (3 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 160.7, 149.8, 135.5, 133.9, 131.9, 131.8 (q, $J_{C\text{-}F}$ 33.1), 130.0, 129.6, 127.1 (q, $J_{C\text{-}F}$ 3.7), 126.6, 126.1, 123.5 (q, $J_{C\text{-}F}$ 272.5), 123.1 (q, $J_{C\text{-}F}$ 4.3), 122.3

(q, $J_{C\text{-}F}$ 284.5), 117.1, 83.8 (q, $J_{C\text{-}F}$ 31.0), 54.1, 46.6; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -63.4, -80.0; IR (neat): 1739, 1624, 1449, 1415, 1325, 1295, 1172, 1129, 1073, 1039, 962, 830, 774, 715 cm^{-1}; HRMS (*m/z* - EI): $[M]^+$ found 454.0804. $C_{21}H_{14}F_6O_4$ Requires 444.0796.

(2*S*,3*R*)-Methyl 6-oxo-4-phenyl-2-(thiophen-2-yl)-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate & (2*S*,3*S*)-Methyl 6-oxo-4-phenyl-2-(thiophen-2-yl)-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate (***trans*-65** + ***cis*-65**, Table 4, entry 6)



***trans*-65** ***cis*-65**

Prepared according to general procedure I using 2-(trifluoroacetyl)thiophene (62.0 µL, 0.48 mmol). The reaction was stirred at -50 ^{o}C for 7 days to give a diastereomeric mixture of carboxylic acids in 17:83 (*cis*:*trans*) ratio. After esterification and purification by flash chromatography eluting in gradient from 100% hexanes to 15% EtOAc in hexane, lactones ***trans*-65** and ***cis*-65** were isolated combined as a colourless yellow oil (52.0 mg, 85%, ***trans*-65**: 82% *ee*, ***cis*-65**: 32% *ee*).

CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: ***cis*-65** 8.2 min (major enantiomer) and 10.3 min (minor enantiomer); ***trans*-65** 11.7 min (major enantiomer) and 14.7 min (minor enantiomer).

***trans*-65**:

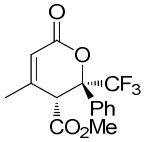
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54-7.39 (5 H, m), 7.33 (1 H, d, *J* 5.0), 7.21 (1 H, d, *J* 3.6), 6.98 (1 H, app. t), 6.41 (1 H, s), 4.62 (1 H, s), 3.79 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 160.7, 149.8, 137.3, 134.0, 131.7, 129.5, 128.3, 127.7, 127.6, 126.3, 122.1 (q, $J_{C\text{-}F}$ 284.4), 116.7, 83.1 (q, $J_{C\text{-}F}$ = 32.0), 53.9, 48.1; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -77.28;

***cis*-65**:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67-7.60 (2 H, m), 7.54-7.39 (4 H, m), 7.28 (1 H, d, *J* 3.2), 7.01 (1 H, app. t), 6.59 (1 H, s), 4.67 (1 H, s), 3.37 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 160.4, 148.6, 135.6, 134.0, 131.7, 129.5, 128.2, 127.2, 126.7, 126.6, 123.5 (q, $J_{C\text{-}F}$ 288.4), 115.8, 82.5 (q, $J_{C\text{-}F}$ = 30.6), 53.3, 48.0; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -76.48 (for minor isomer);

IR (neat): 1738, 1626, 1445, 1433, 1188, 1167, 1110, 1038, 874, 776, 724, 711 cm^{-1}; HRMS (*m/z* - EI): $[M]^+$ found 382.0482. $C_{18}H_{13}F_3O_4S$ Requires 382.0487.

(2*R*,3*R*)-Methyl 4-methyl-6-oxo-2-phenyl-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate (***cis*-58c**, Scheme 8).

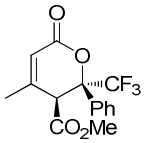


Prepared according to general procedure J using anhydride **57** (25.2 mg, 0.20 mmol), 2,2,2-trifluoromethyl acetophenone (**23c**, 27.2 μL, 0.20 mmol) and catalyst **36** (20.5 mg, 0.030 mmol, 15 mol%). The reaction was left stirring for at -30 °C for 6 days to give a diastereomeric mixture of carboxylic acids in a 88:12 (*cis*:*trans*) ratio. After esterification, the major diastereomer (***cis*-58c**) was purified by column chromatography eluting in gradient from 20% EtOAc in hexanes to 40% EtOAc in hexane and isolated as a white solid (53.4 mg, 85%, 98% *ee*).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: 17.4 min (major enantiomer) and 19.8 min (minor enantiomer).

M.p. 114-116 °C; $[\alpha]_D^{20}$ = -255.6 (*c* 0.25, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52-7.34 (5 H, m), 5.83 (1 H, s), 4.04 (1 H, s), 3.83 (3 H, s), 1.85 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 160.7, 151.1, 134.3, 130.1, 129.2, 126.0, 122.4 (q, $J_{C\text{-}F}$ 284.5), 119.4, 83.9 (q, $J_{C\text{-}F}$ 30.7), 53.8, 49.6, 22.6; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -77.25; IR (neat): 2983, 2953, 1756, 1734, 1436, 1297, 1236, 1177, 1037, 964, 873, 765, 719 cm^{-1}; HRMS (*m/z* - ESI): $[M+Na]^+$ found 337.0655. $C_{15}H_{13}O_4F_3Na$ Requires 337.0664.

(2*R*,3*S*)-Methyl 4-methyl-6-oxo-2-phenyl-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate (***trans*-58c**, Scheme 8).

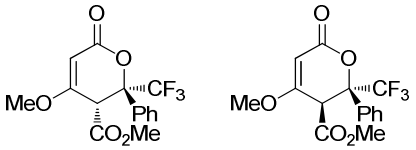


Prepared according to general procedure J using anhydride **57** (25.2 mg, 0.20 mmol), 2,2,2-trifluoromethyl acetophenone (**23c**, 27.2 μL, 0.20 mmol) and catalyst **36** (20.5 mg, 0.030 mmol, 15 mol%). The reaction was left stirring for at -30 °C for 6 days t to give a diastereomeric mixture of carboxylic acids in a 88:12 (*cis*:*trans*) ratio. After esterification, the minor diastereomer (***trans*-58c**) was purified by column chromatography eluting in gradient from 20% EtOAc in hexanes to 40% EtOAc in hexane and isolated as a colourless oil (7.1 mg, 11%, 68% *ee*).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: 13.3 min (minor enantiomer) and 14.4 min (major enantiomer).

$[\alpha]_D^{20}$ = -221.2 (*c* 0.05, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.68-7.56 (2 H, m), 7.47-7.34 (3 H, m), 6.08 (1 H, s), 4.08 (1 H, s), 3.29 (3 H, s), 2.09 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 160.3, 149.5, 133.7, 129.7, 128.7, 125.9, 124.0 (q, $J_{C\text{-}F}$ 288.3), 118.1, 82.3 (q, $J_{C\text{-}F}$ 28.7), 53.0, 50.2, 22.0; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -76.20; IR (neat): 2958, 2930, 2853, 1741, 1440, 1266, 1232, 1172, 1132, 1025, 969, 861, 739, 700 cm^{-1}; HRMS (*m/z* - ESI): $[M+Na]^+$ found 337.0655. $C_{15}H_{13}O_4F_3Na$ Requires 337.0664.

(2*R*,3*R*)-Methyl 4-methoxy-6-oxo-2-phenyl-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate & (2*R*,3*S*)-methyl 4-methoxy-6-oxo-2-phenyl-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate (***cis*-60c** and ***trans*-60c**, Scheme 8)



***cis*-60c** ***trans*-60c**

Prepared according to general procedure J using anhydride **59** (28.4 mg, 0.20 mmol), 2,2,2-trifluoromethyl acetophenone (**23c**, 27.2 μL, 0.20 mmol) and catalyst **36** (20.5 mg, 0.030 mmol, 15 mol%). The reaction was left stirring for at -30 °C for 6 days t to give a diastereomeric mixture of carboxylic acids in a 69:31 (*cis*:*trans*) ratio. After esterification, the two inseparable diastereomers were purified by column chromatography eluting in gradient from 20% EtOAc in hexanes to 40% EtOAc in hexane and isolated combined to furnish a pale yellow oil (61.0 mg, 92%, ***cis*-60c**: 95% *ee*, ***trans*-60c**: 90% *ee*).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: ***cis*-60c** 16.9 min (minor enantiomer) and 25.2 min (major enantiomer); ***trans*-60c** 14.6 min (major enantiomer) and 19.3 min (minor enantiomer).

A small amount of the major diastereomer (***cis*-60c**) was isolated in racemic form to allow characterisation of the compound. The NMR resonances associated with the minor diastereoisomer (***trans*-60c**) were then identified by comparing the spectra associated with both isomers.

***cis*-60c**:

M.p. 106-108 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.56-7.46 (2 H, m), 7.45-7.37 (3 H, m), 5.16 (1 H, s), 4.13 (1 H, s), 3.84 (3 H, s), 3.62 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 166.2, 162.8, 134.0, 130.1, 129.1, 126.2, 122.4 (q, $J_{C\text{-}F}$ 284.3), 93.0, 83.0 (q, $J_{C\text{-}F}$ 30.9), 57.0, 53.8, 48.7;

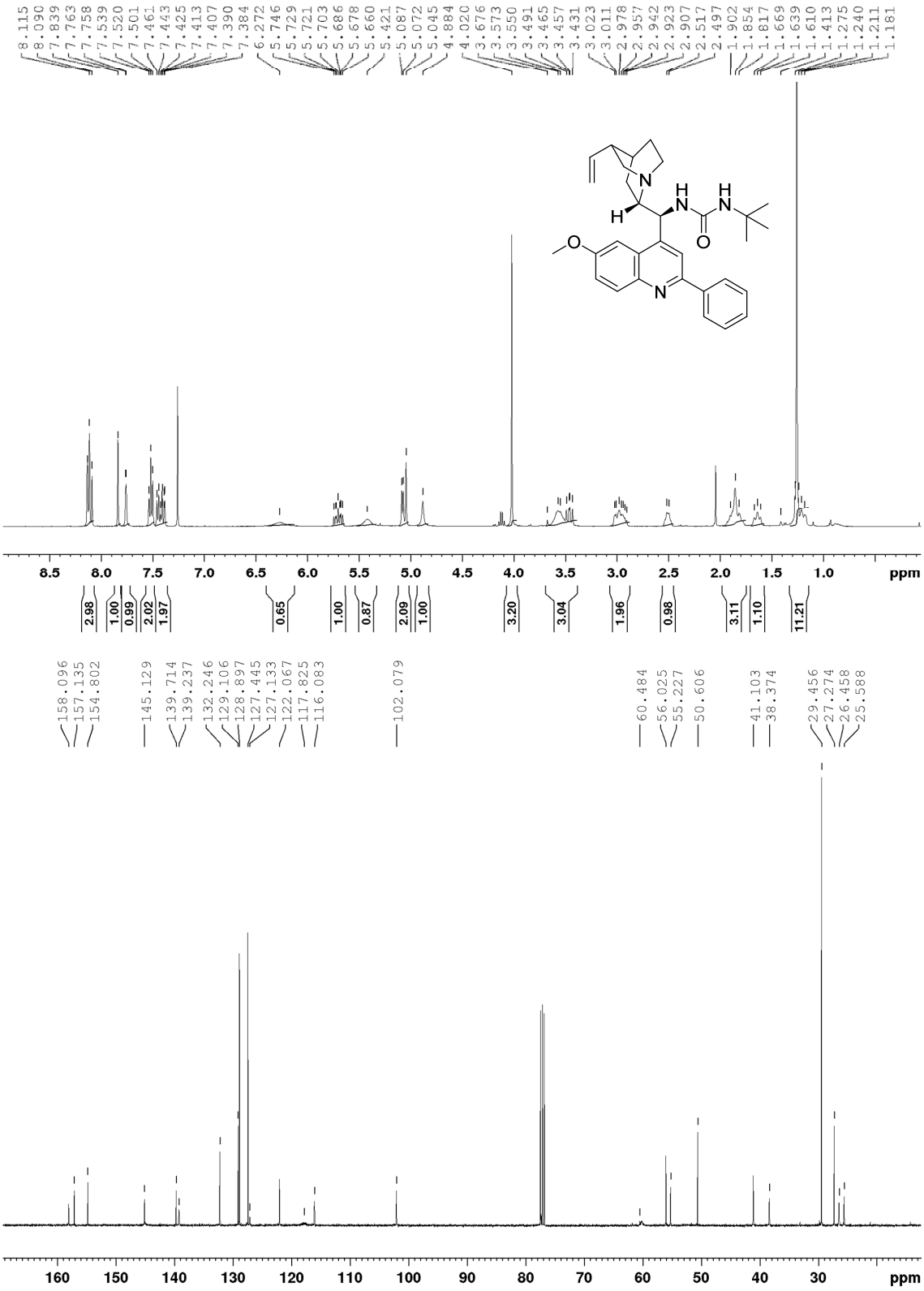
^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -77.11; IR (neat): 2958, 2924, 2848, 1743, 1638, 1439, 1361, 1318, 1236, 1170, 1033, 986, 825, 769 cm^{-1}; HRMS (*m/z* - ESI): $[M+Na]^+$ found 353.0600. $C_{15}H_{13}O_5F_3Na$ Requires 353.0613.

***trans*-60c**:

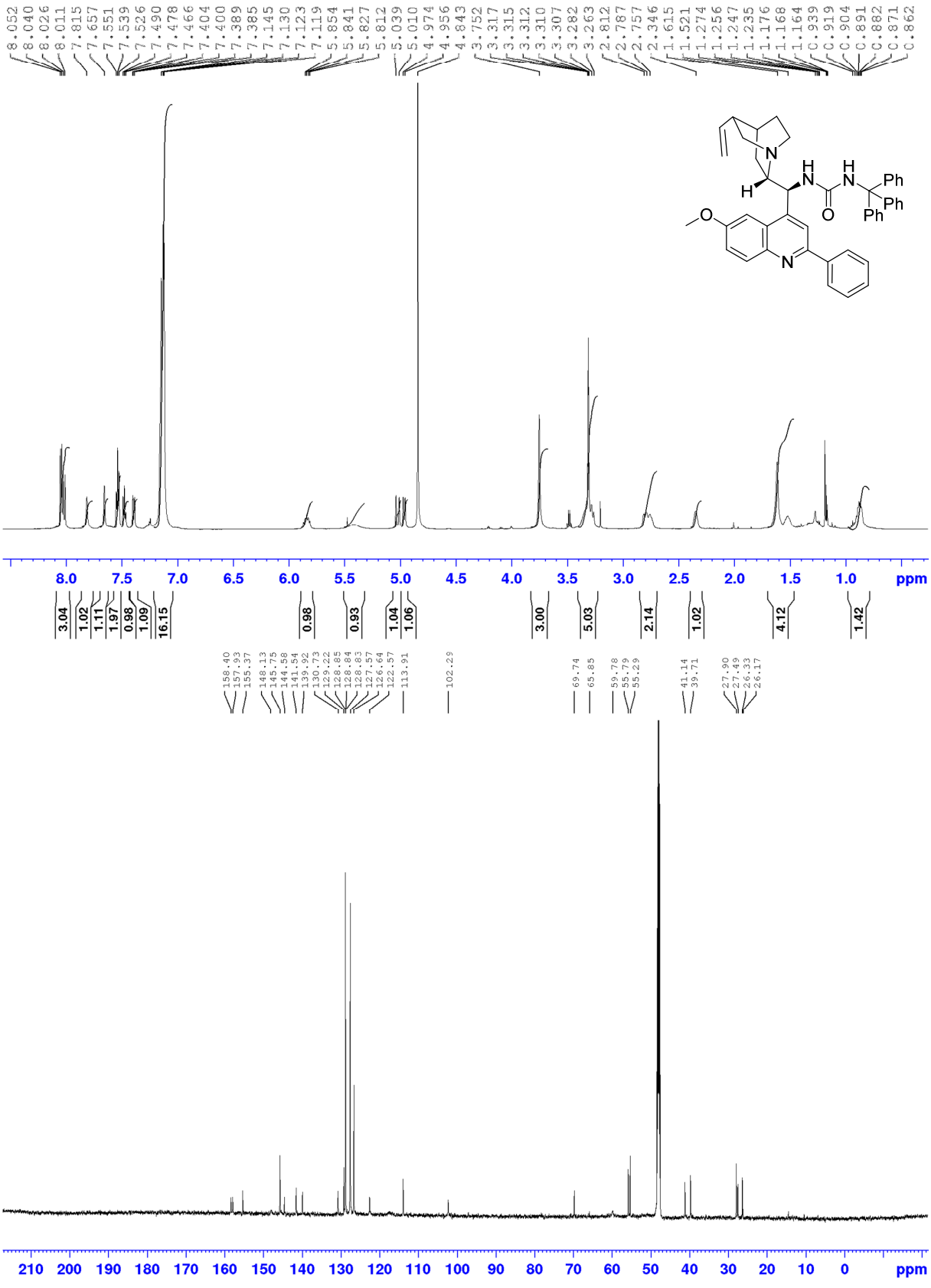
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67-7.58 (2 H, m), 7.45-7.37 (3 H, m), 5.43 (1 H, s), 4.18 (1 H, s), 3.82 (3 H, s), 3.28 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 166.1, 162.5, 132.9, 129.8, 128.5, 126.1, 123.9 (q, $J_{C\text{-}F}$ 288.7), 91.6, 81.4 (q, $J_{C\text{-}F}$ 29.1), 57.1, 53.1, 48.4; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -76.35.

9.0 NMR Spectra

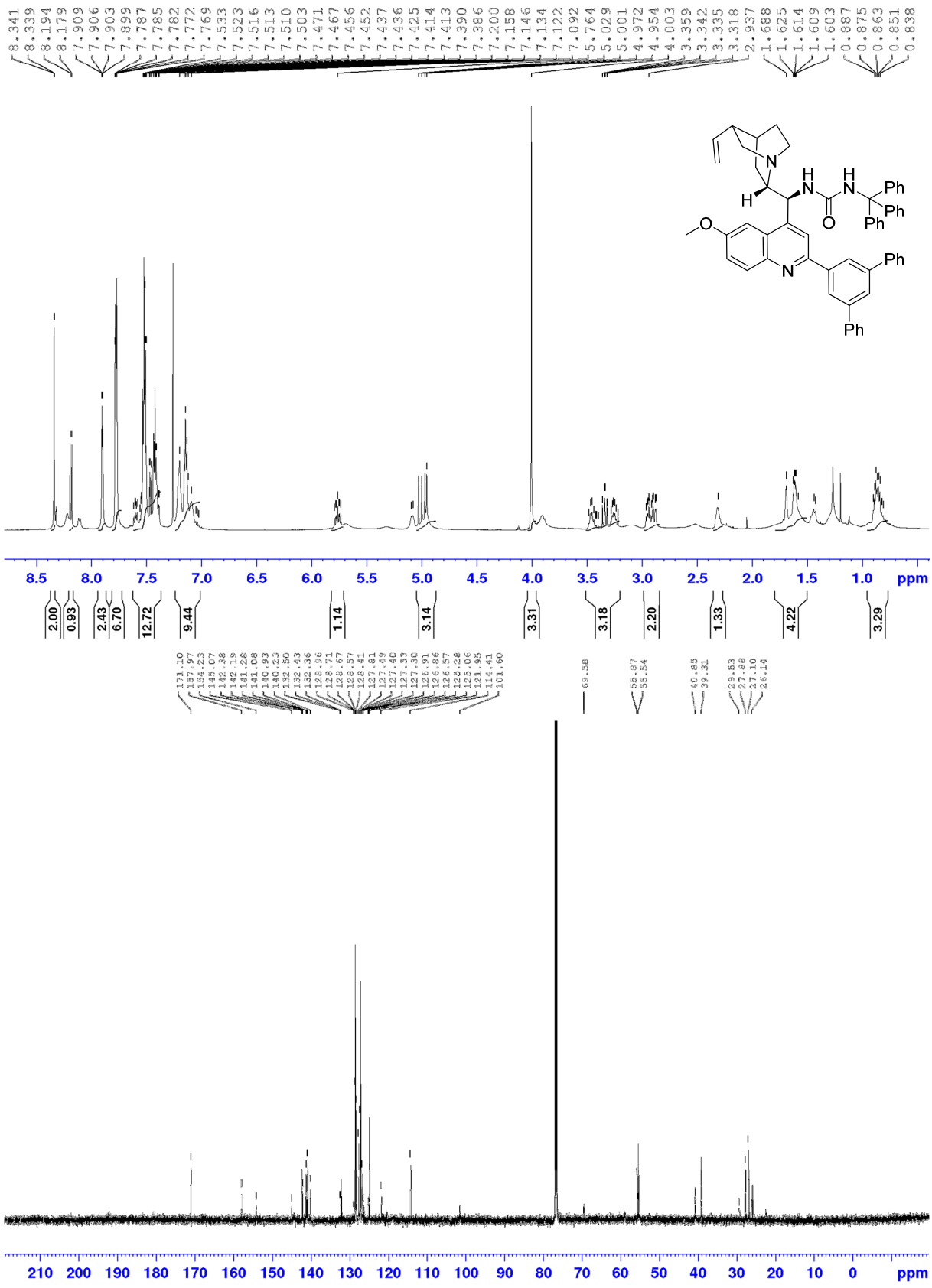
1-*tert*-Butyl-3-((*S*)-(6-methoxy-2-phenylquinolin-4-yl)((2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)urea (35)



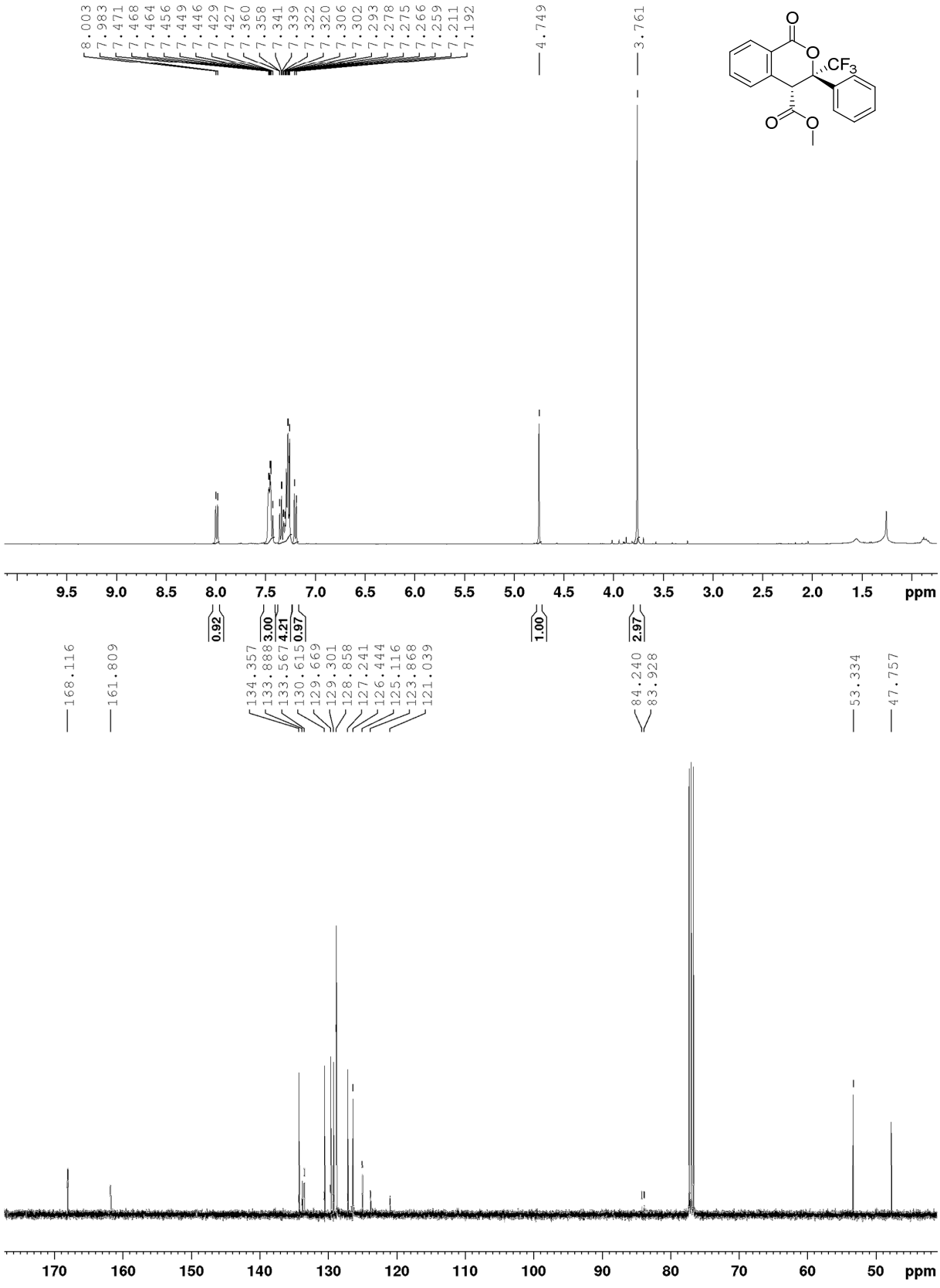
1-Trityl-3-((*S*)-(6-methoxy-2-phenylquinolin-4-yl)((2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)urea (36)

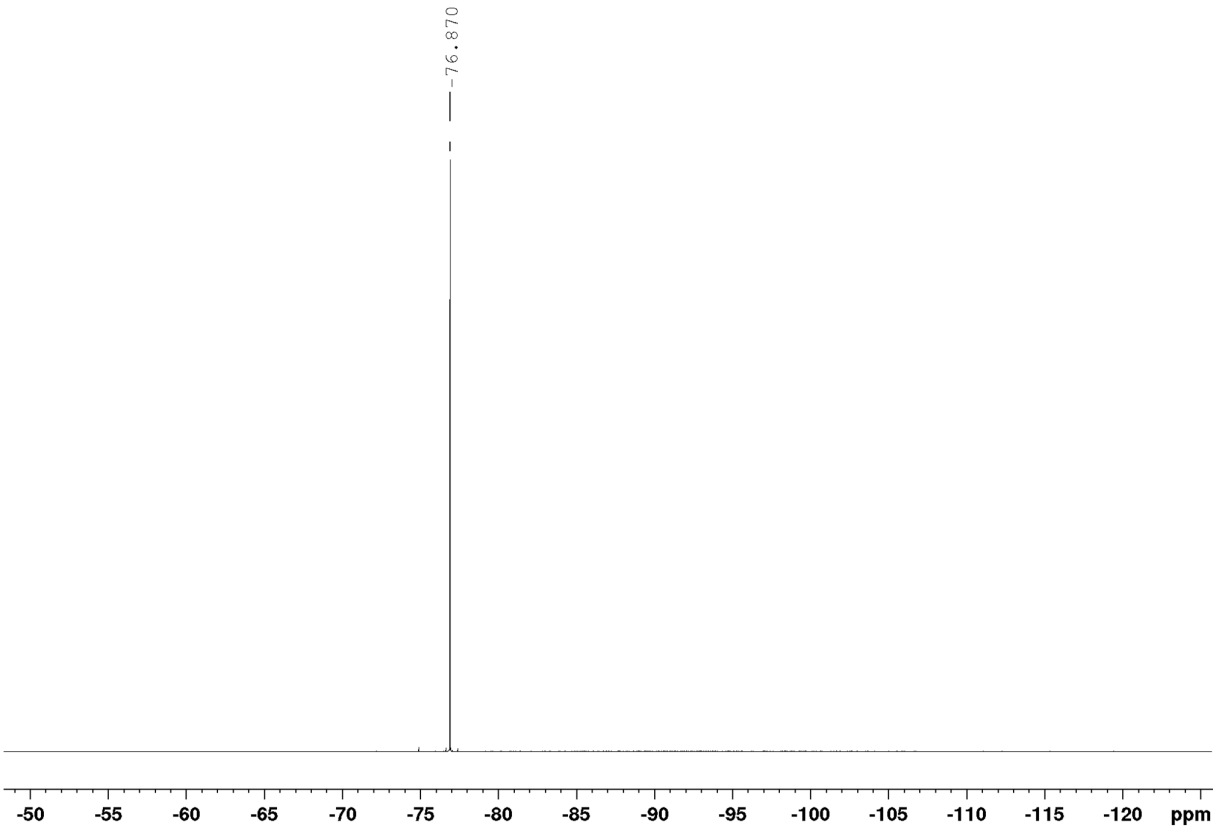


1-Trityl-3-((*S*)-(6-methoxy-2-*m*-terphenylquinolin-4-yl)((2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)urea (44)

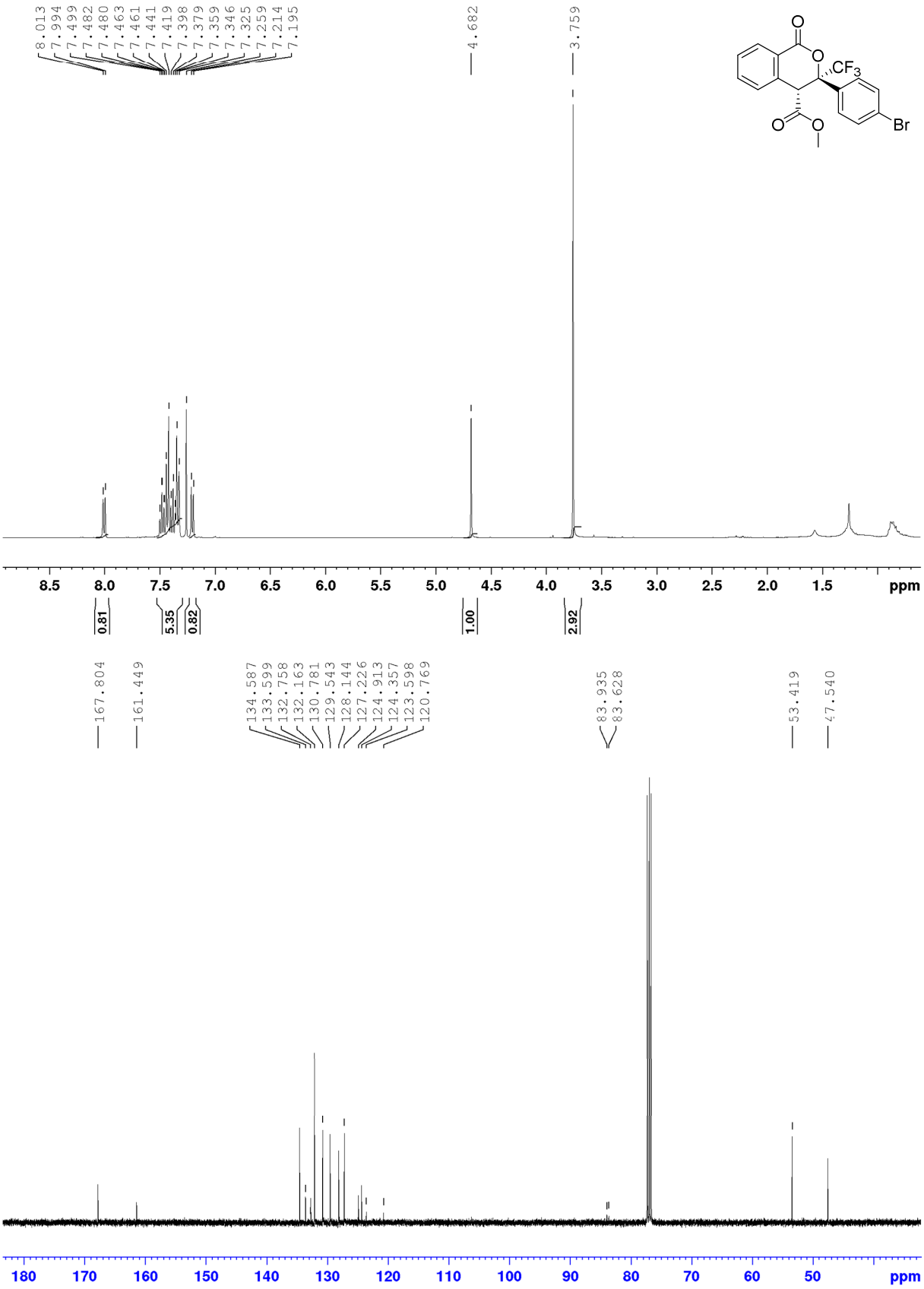


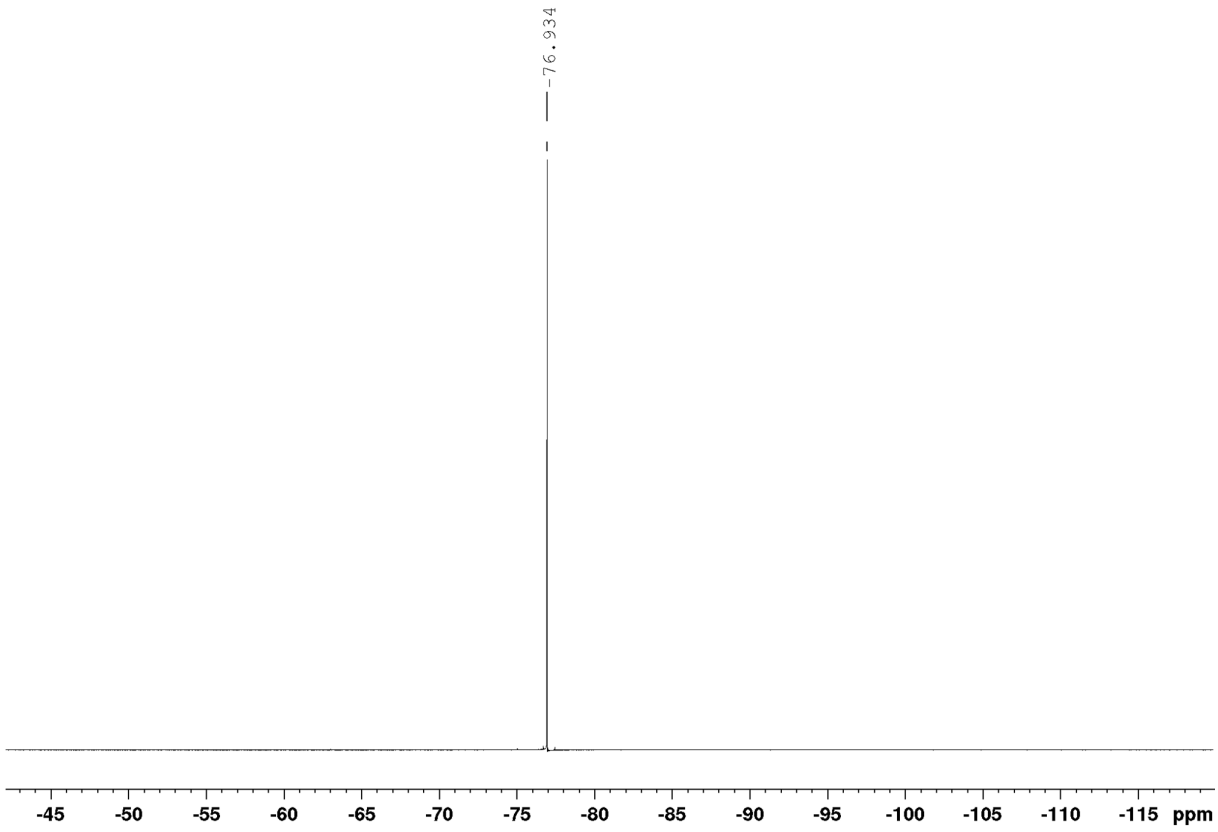
(3*R*,4*R*)-Methyl 1-oxo-3-phenyl-3-(trifluoromethyl)isochroman-4-carboxylate (*cis*-37)



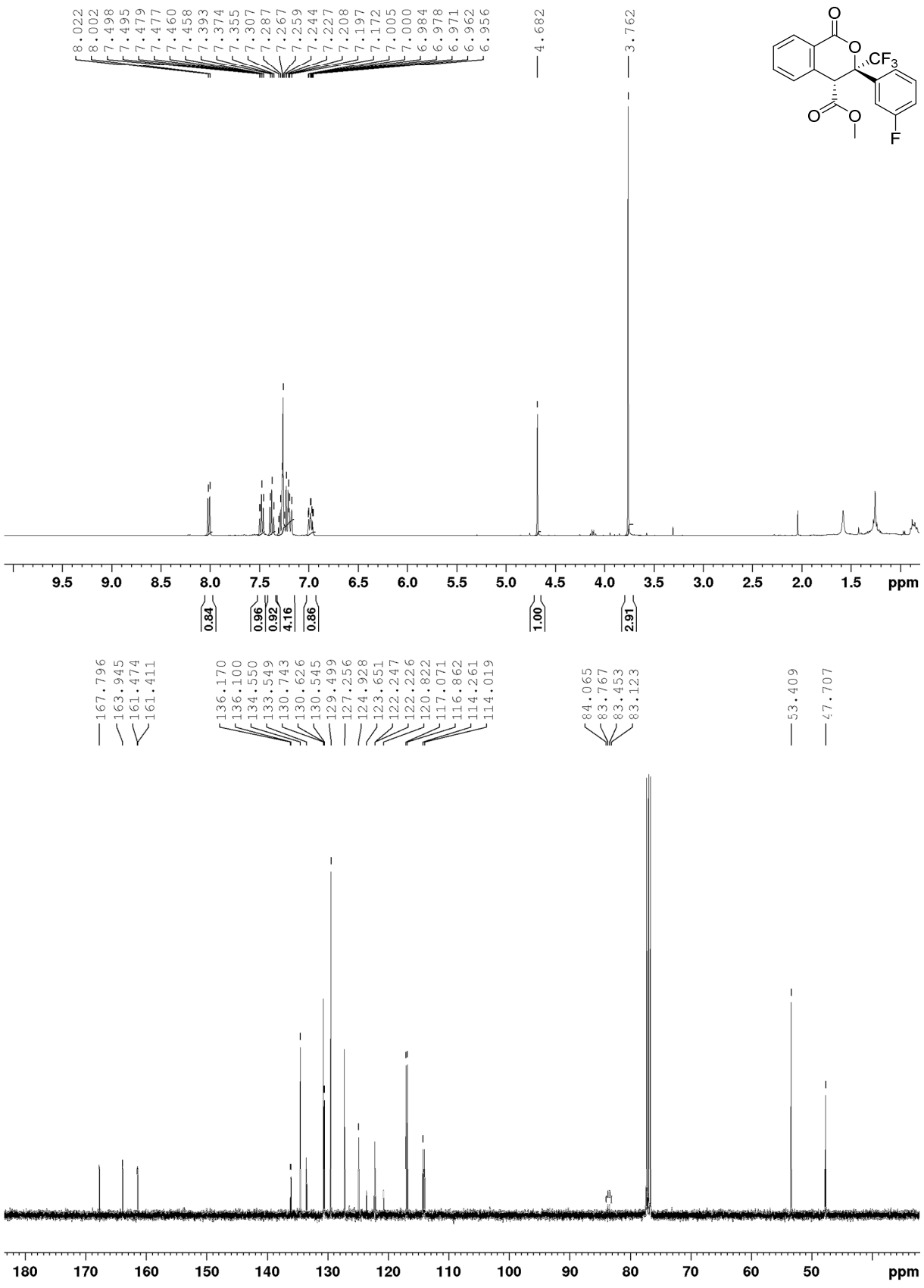

-76.870
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
ppm

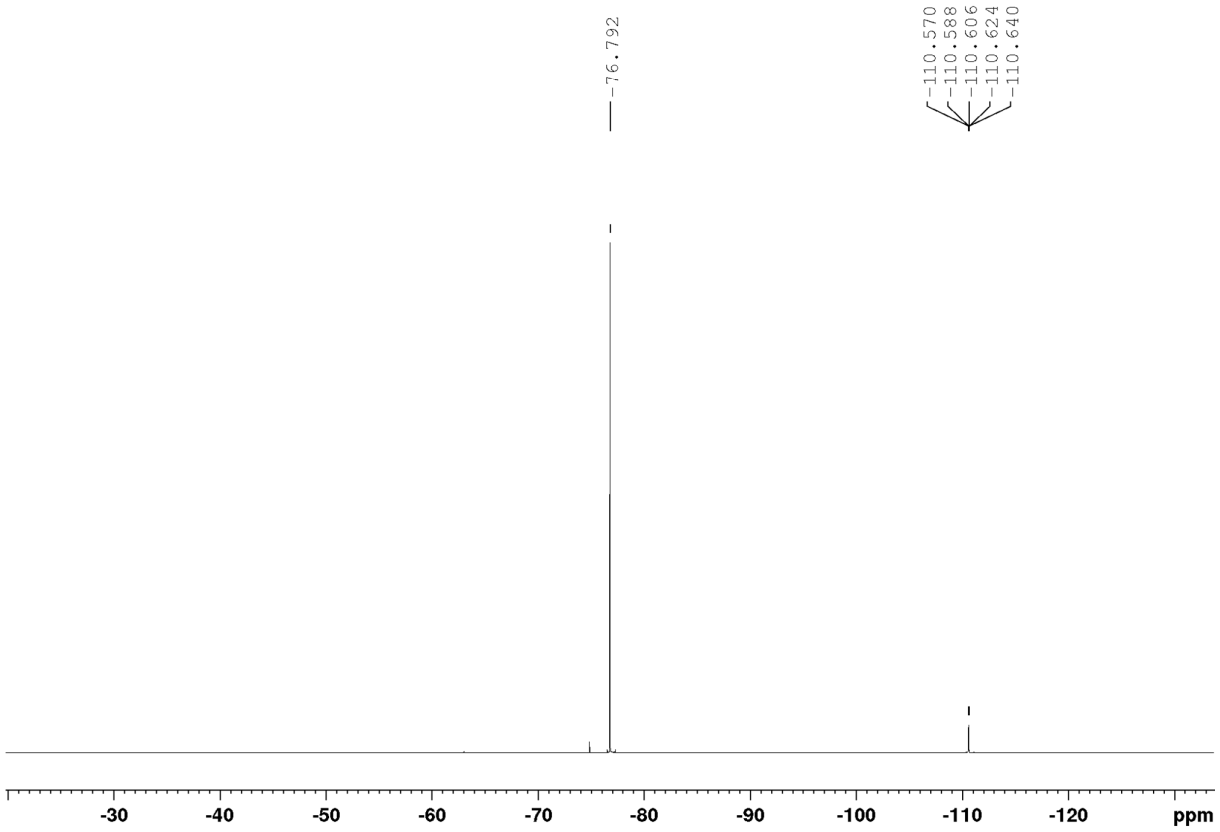
(3*R*,4*R*)-Methyl 3-(4-bromophenyl)-1-oxo-3-(trifluoromethyl)isochroman-4-carboxylate (*cis*-38)



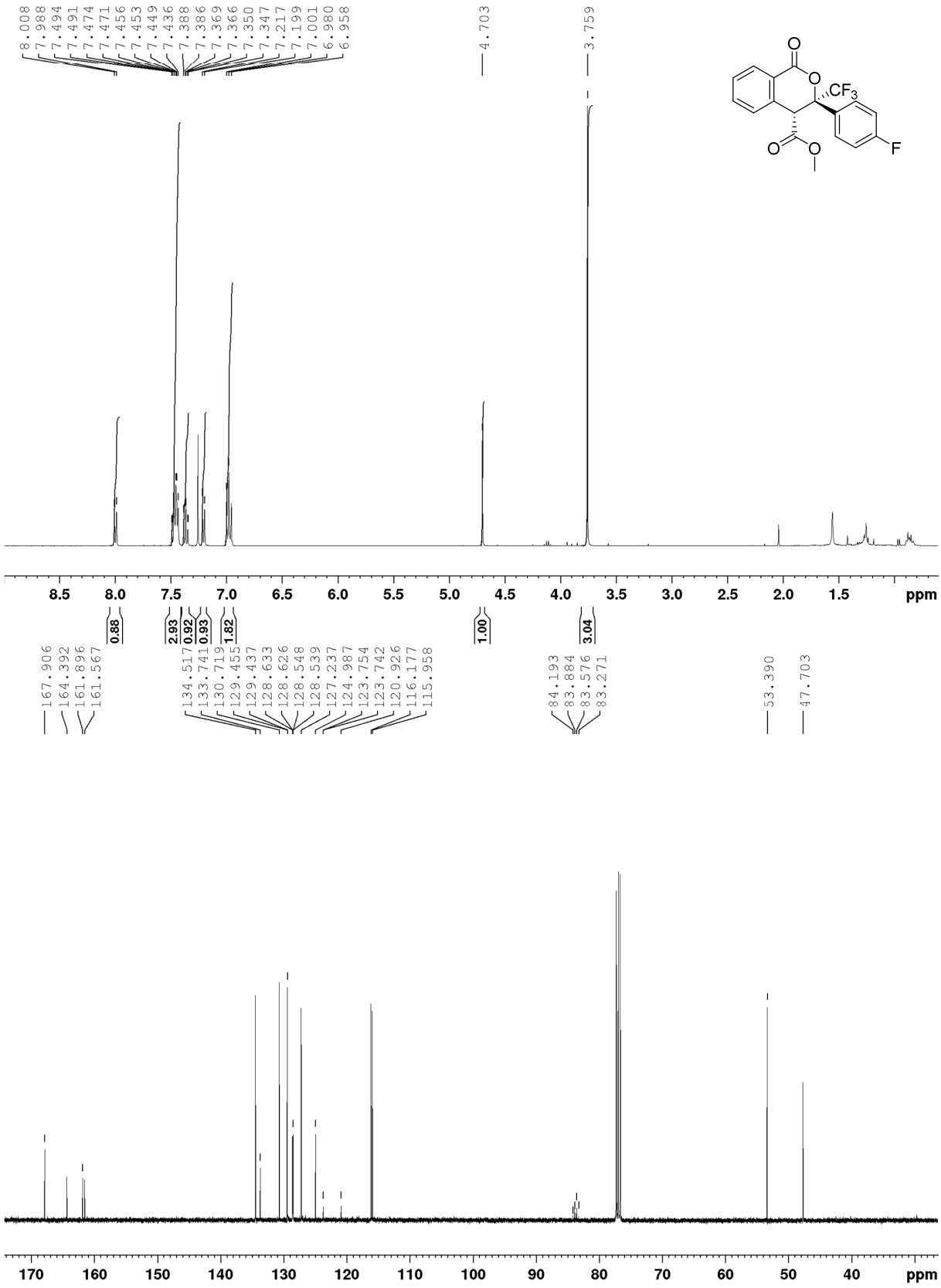

-76.934
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
ppm

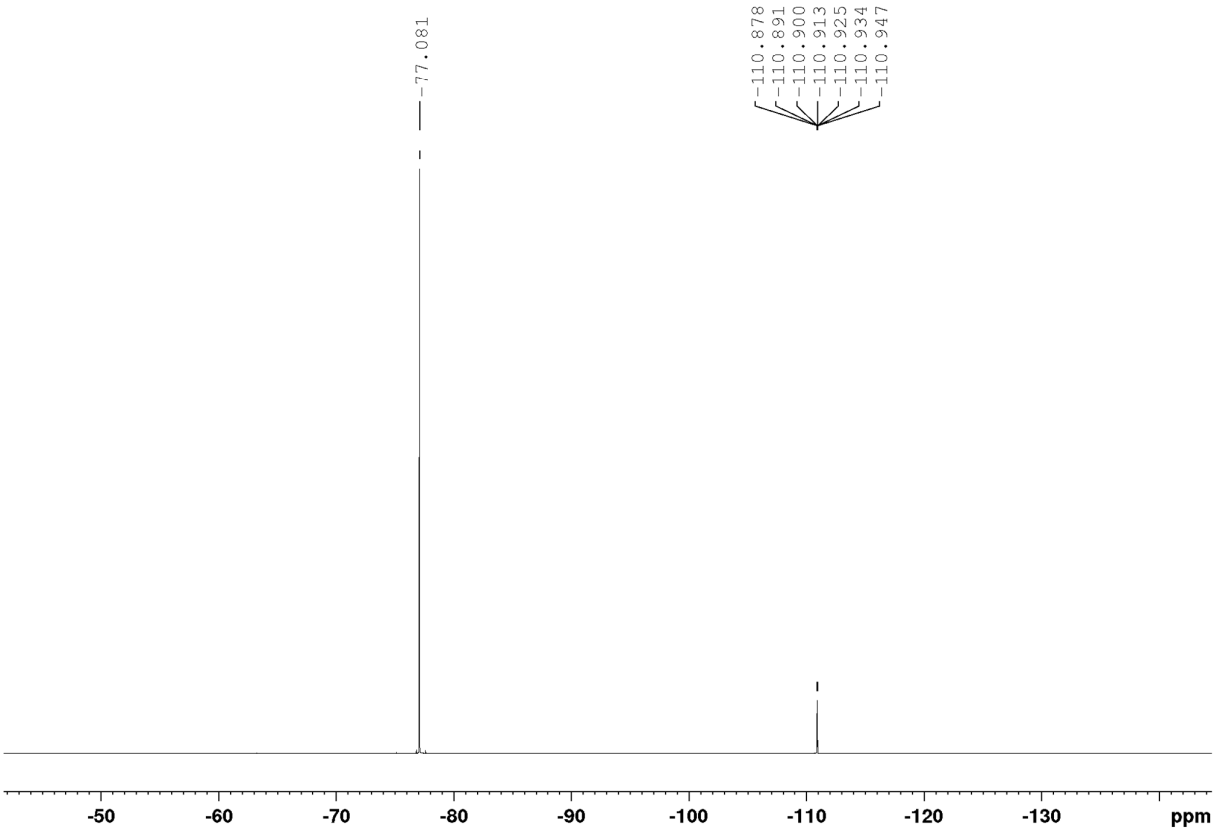
(3*R*,4*R*)-Methyl 3-(3-fluorophenyl)-1-oxo-3-(trifluoromethyl)isochroman-4-carboxylate (*cis*-39)



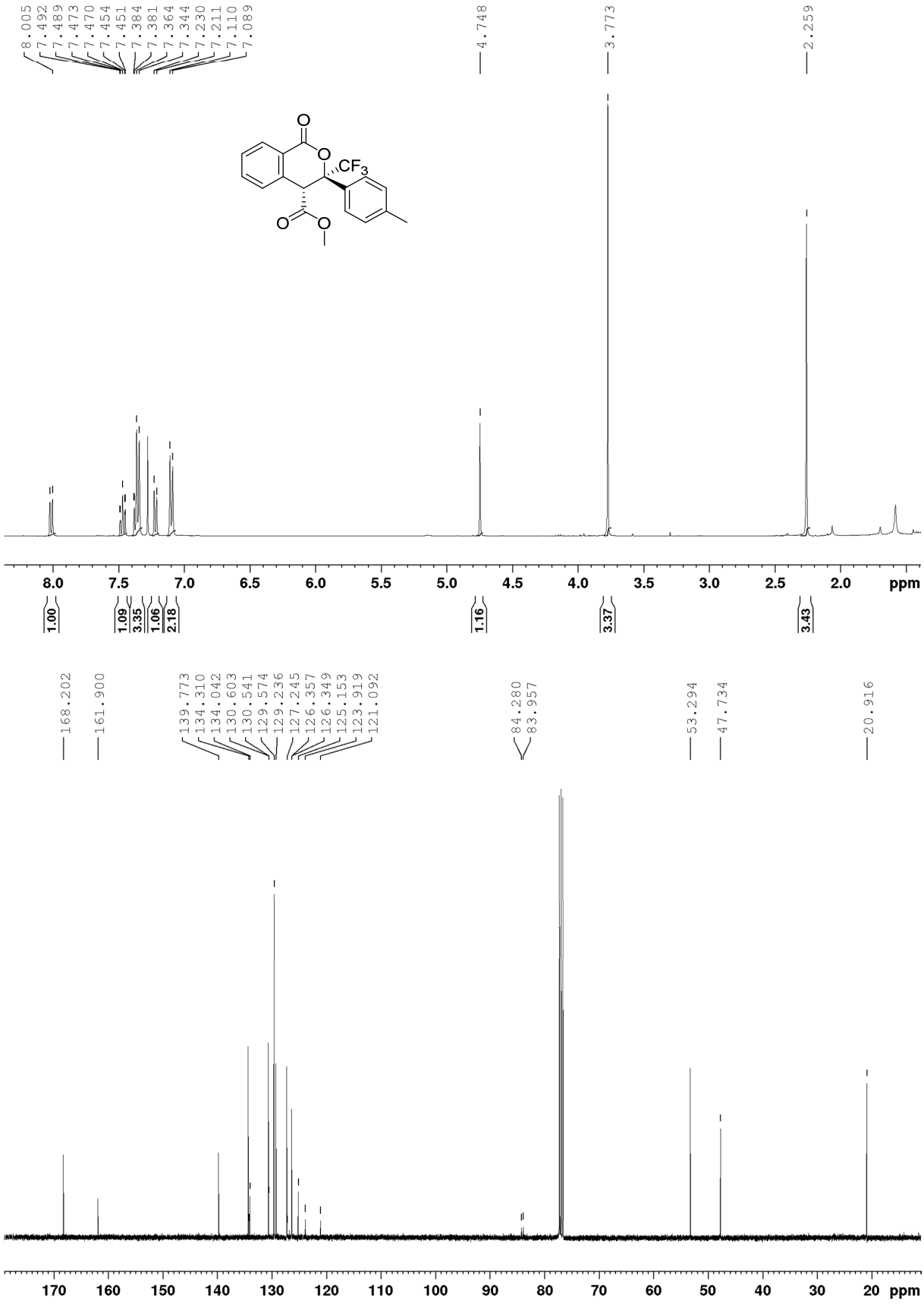

-76.792
-110.570
-110.588
-110.606
-110.624
-110.640
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm

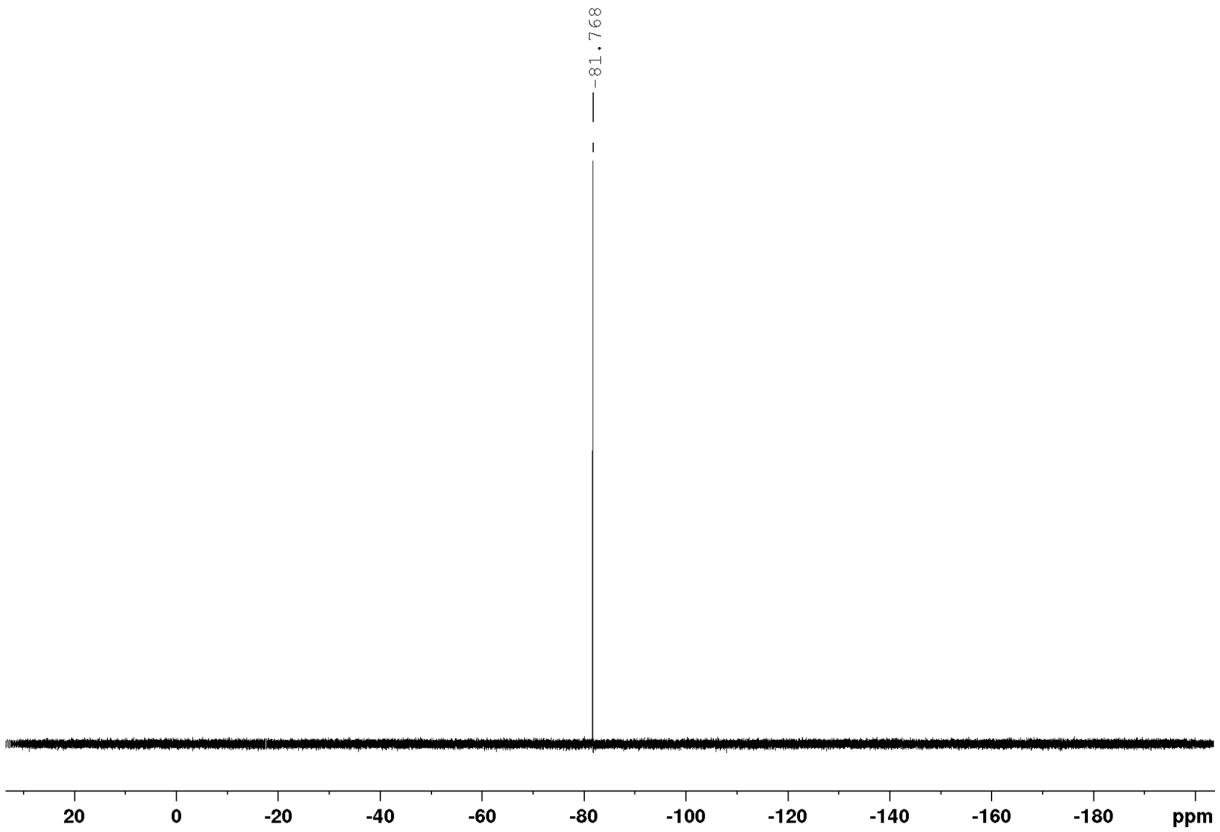
(3*R*,4*R*)-Methyl 3-(4-fluorophenyl)-1-oxo-3-(trifluoromethyl)isochroman-4-carboxylate (*cis*-40)



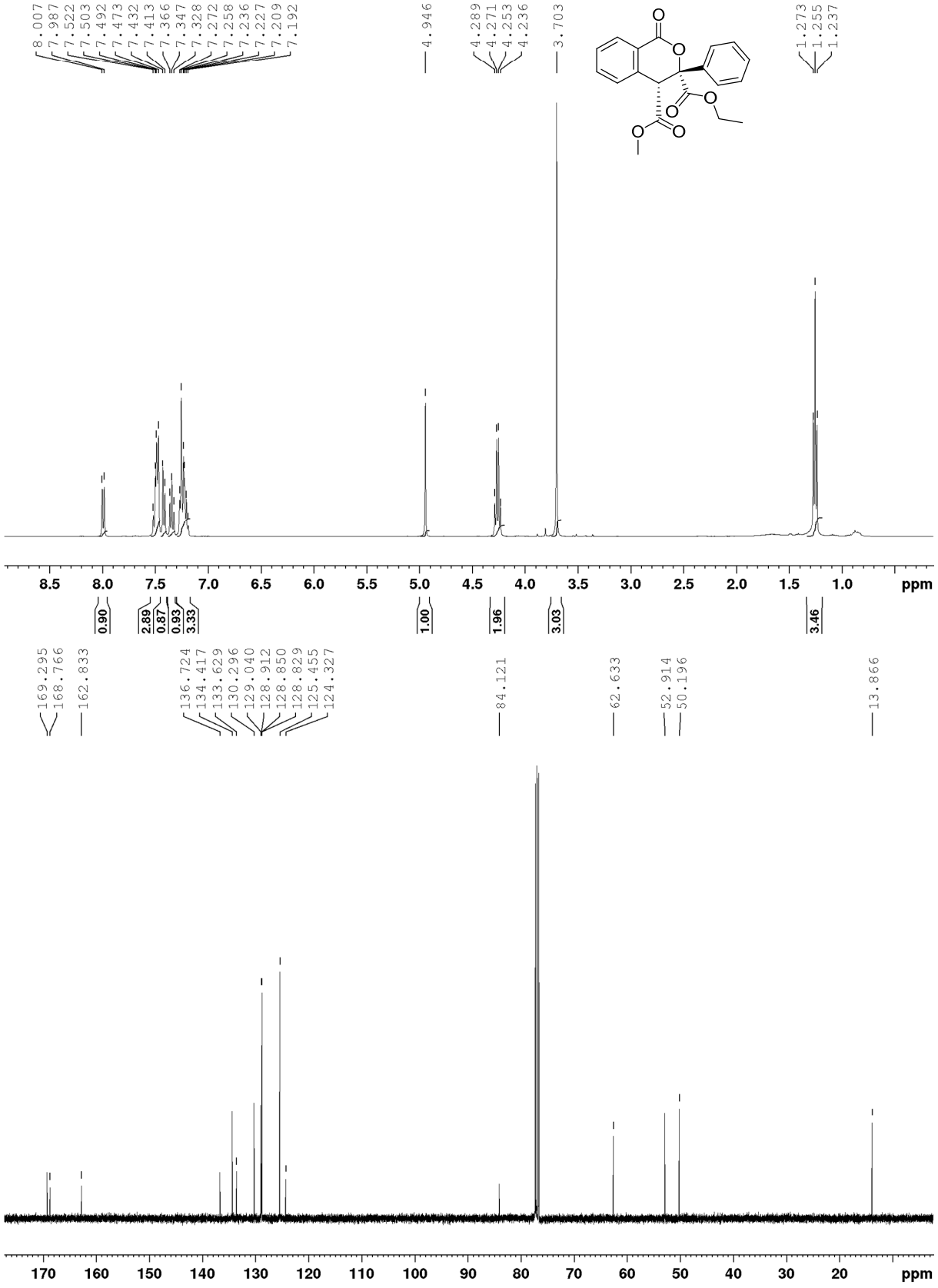

-77.081
-110.878
-110.891
-110.900
-110.913
-110.925
-110.934
-110.947
-50
-60
-70
-80
-90
-100
-110
-120
-130
ppm

(3*R*,4*R*)-Methyl 1-oxo-3-p-tolyl-3-(trifluoromethyl)isochroman-4-carboxylate (*cis*-41)

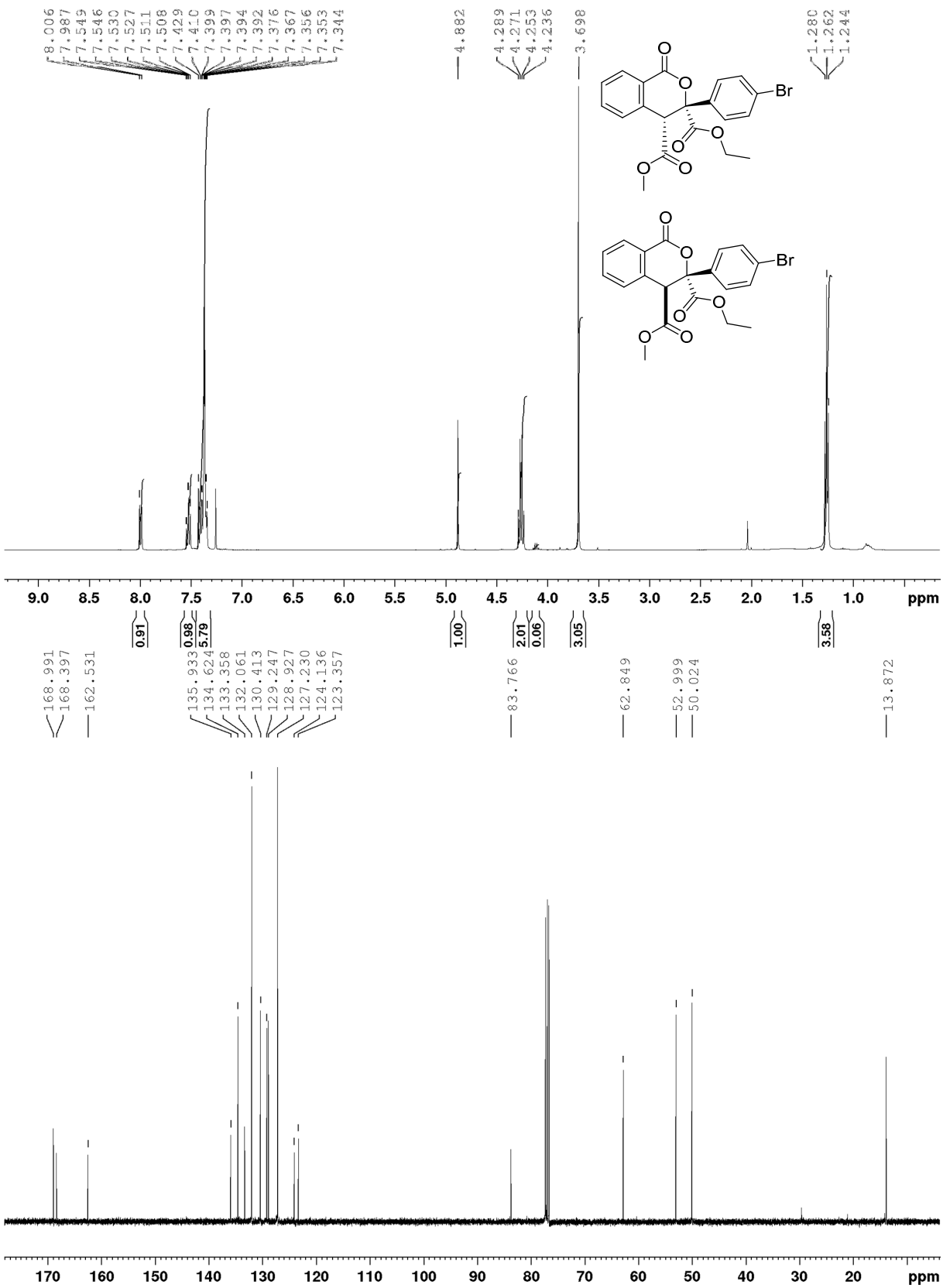



-81.768
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
ppm

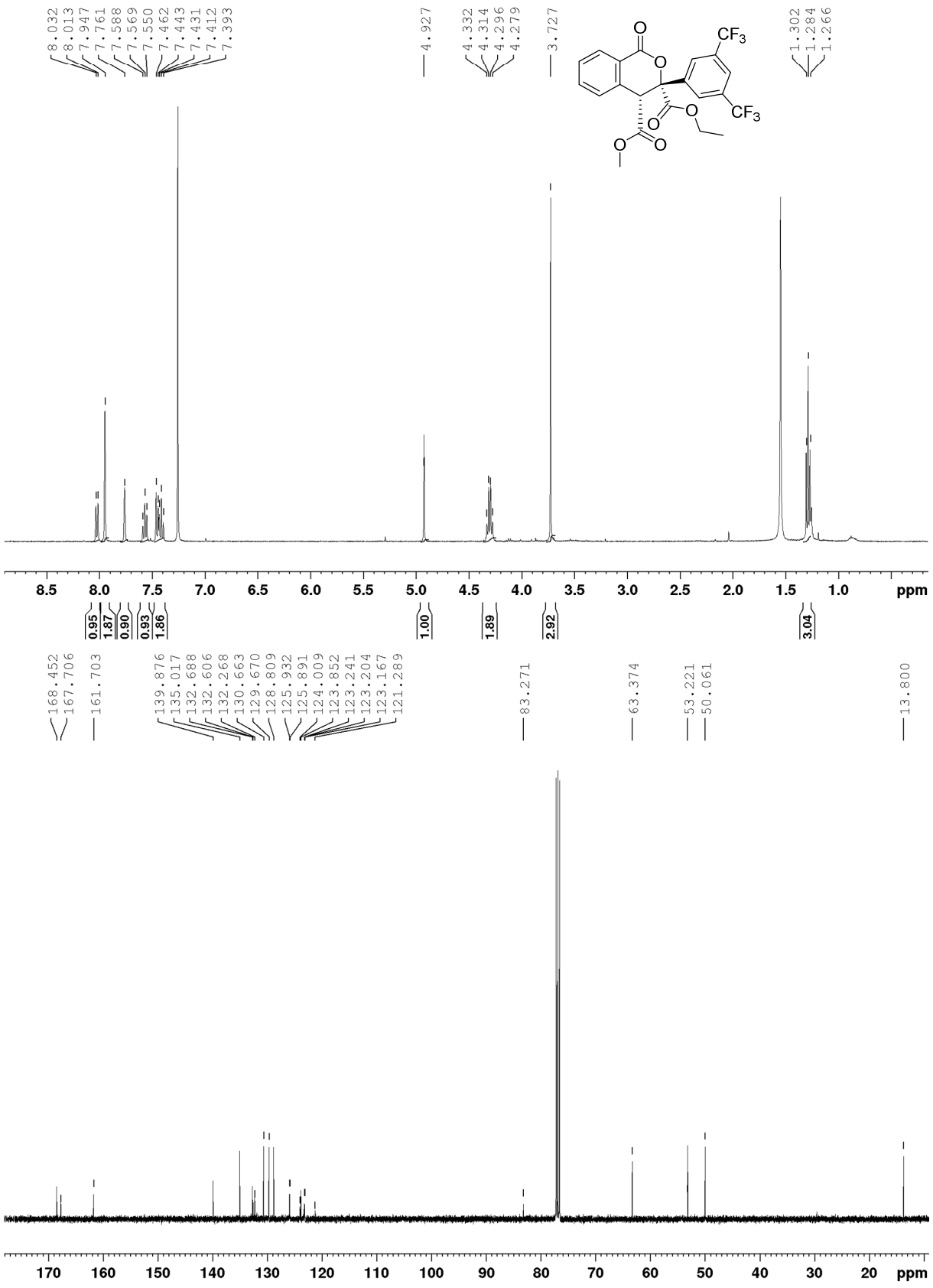
(3*R*,4*R*)-3-Ethyl 4-methyl 1-oxo-3-phenylisochroman-3,4-dicarboxylate (*cis*-43)

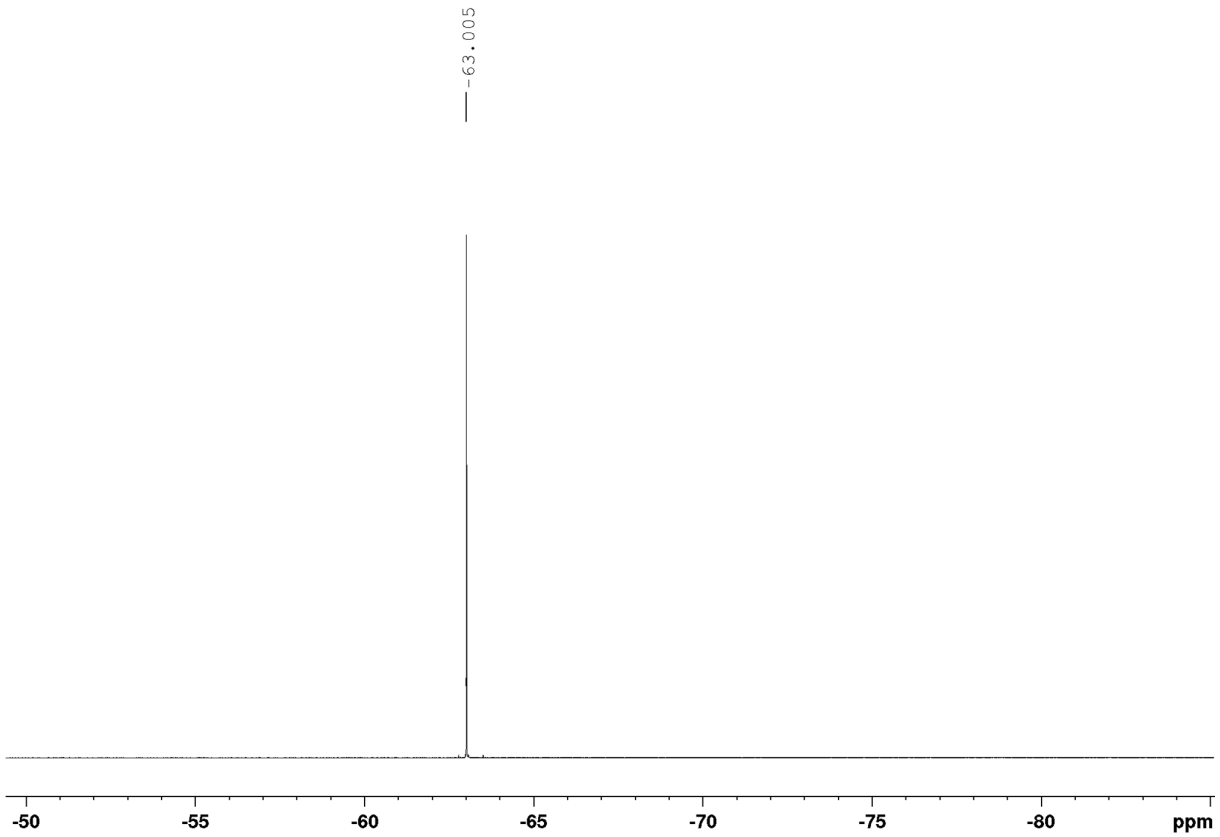


3-Ethyl 4-methyl 3-(4-bromophenyl)-1-oxoisochroman-3,4-dicarboxylate (*cis*-46 – *trans*-46)

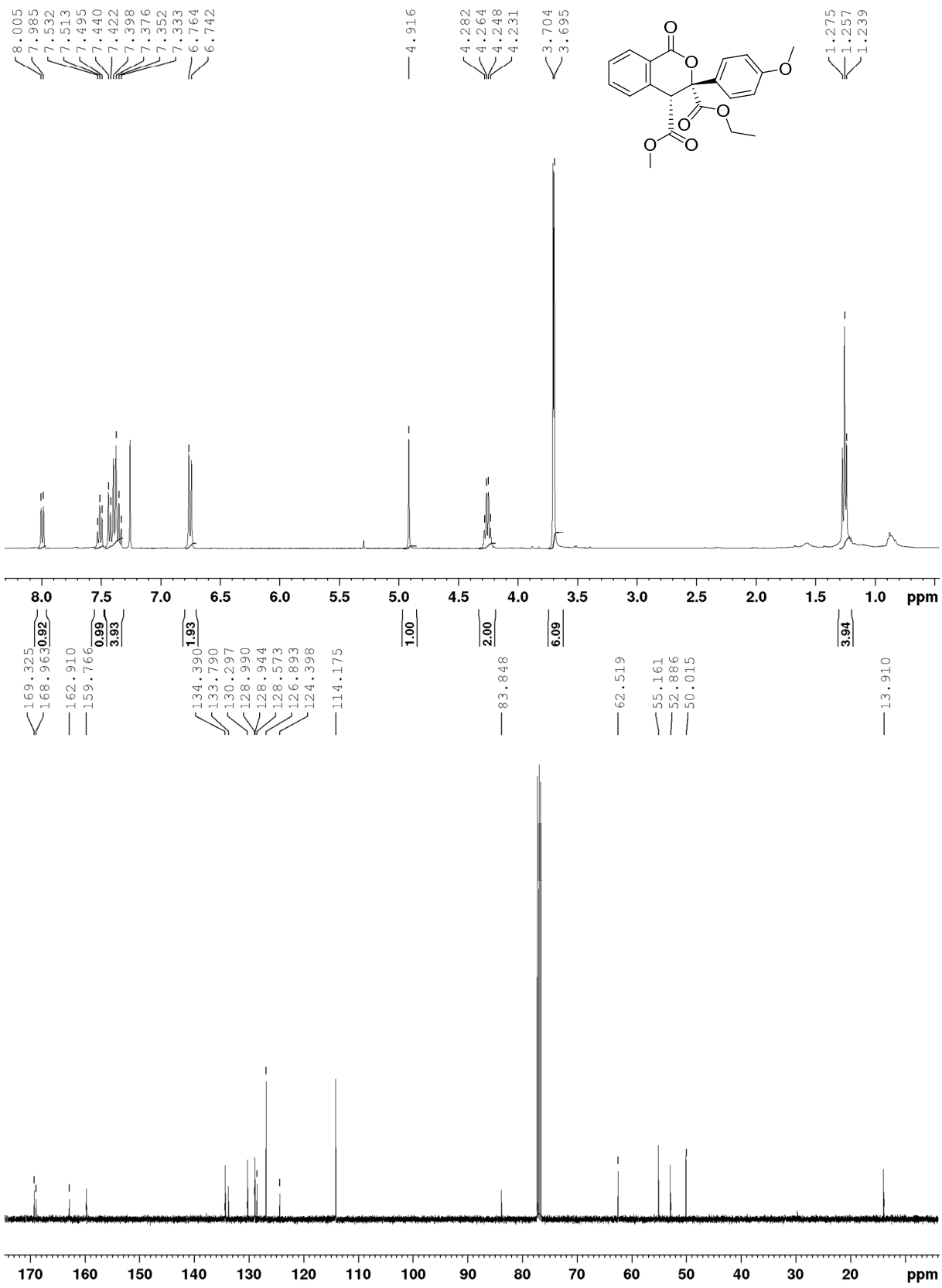


(3*R*,4*R*)-3-Ethyl 4-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-1-oxoisochroman-3,4-dicarboxylate (*cis*-47)

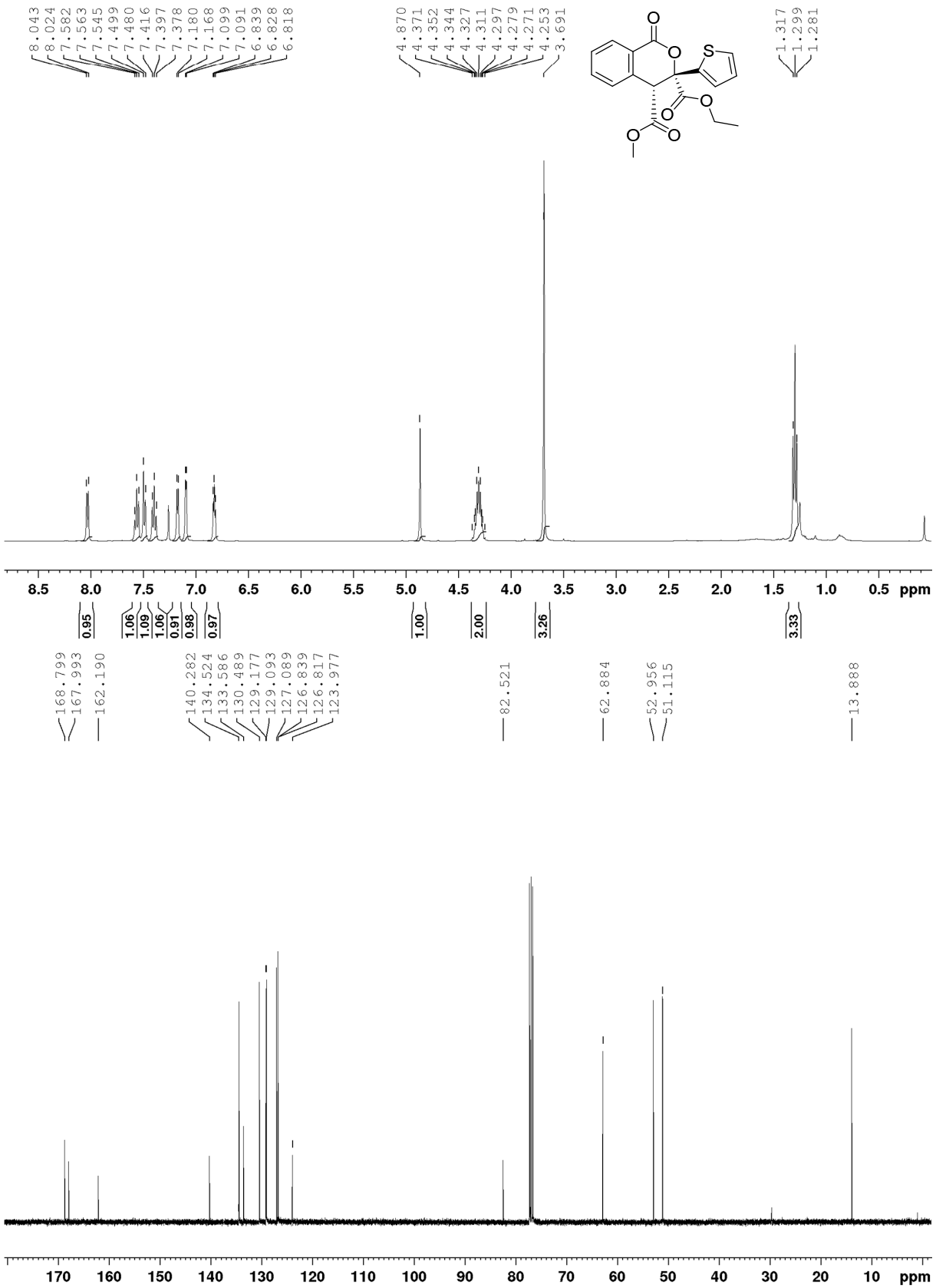



-63.005
-50
-55
-60
-65
-70
-75
-80
ppm

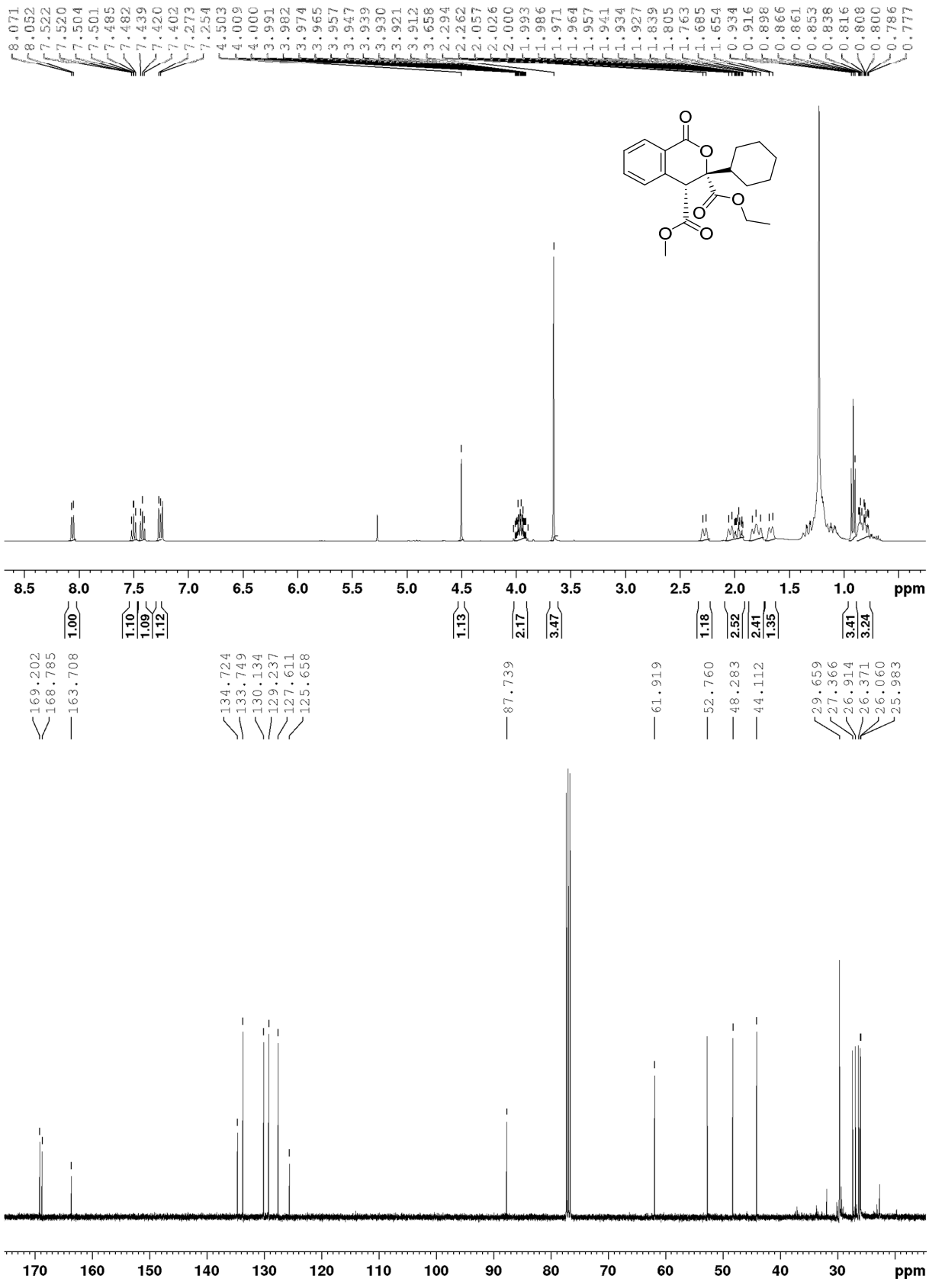
(3*R*,4*R*)-3-Ethyl 4-methyl 3-(4-methoxyphenyl)-1-oxoisochroman-3,4-dicarboxylate (*cis*-48)



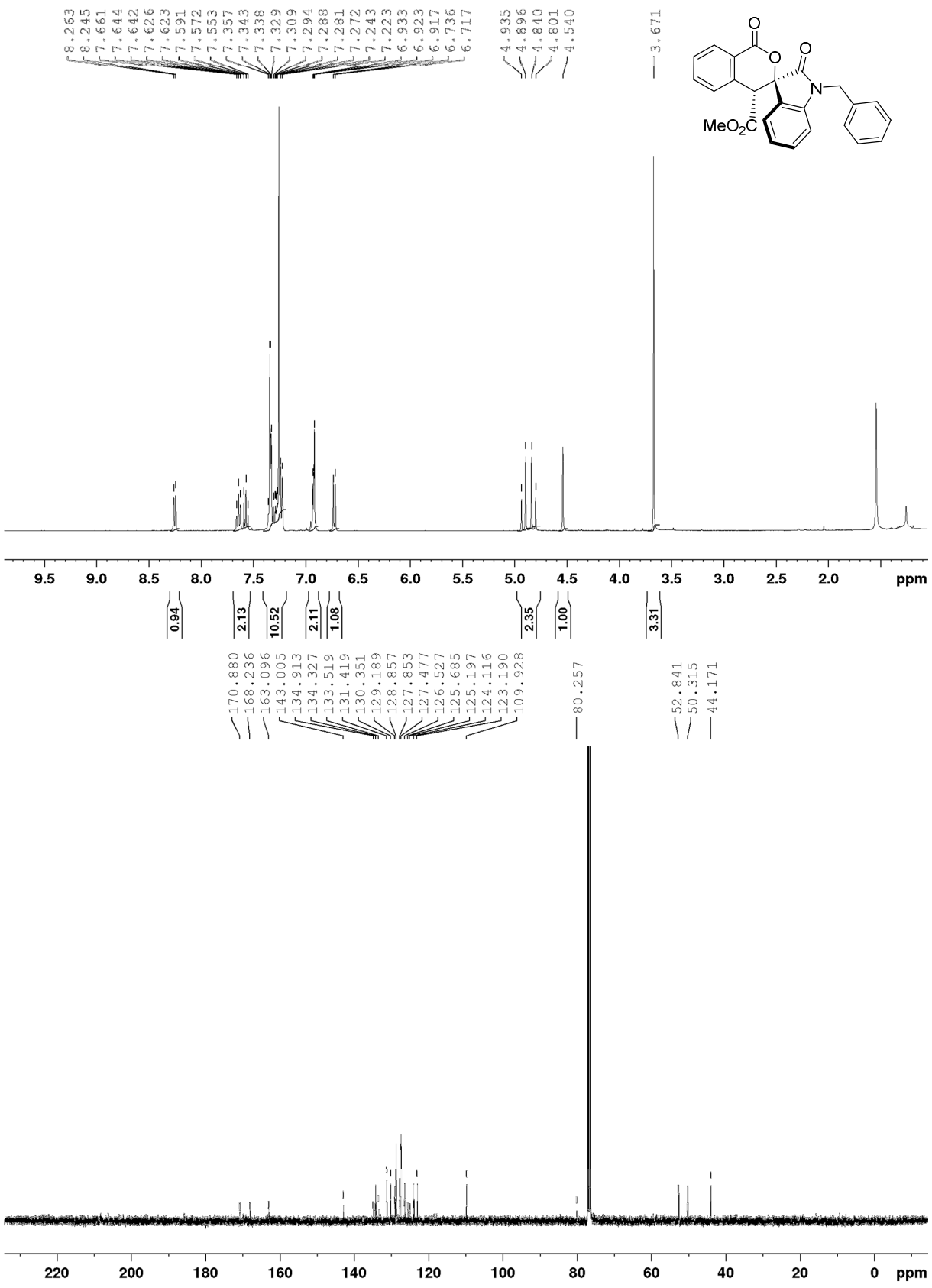
(3*S*,4*R*)-3-Ethyl 4-methyl 1-oxo-3-(thiophen-2-yl)isochroman-3,4-dicarboxylate (*trans*-49)



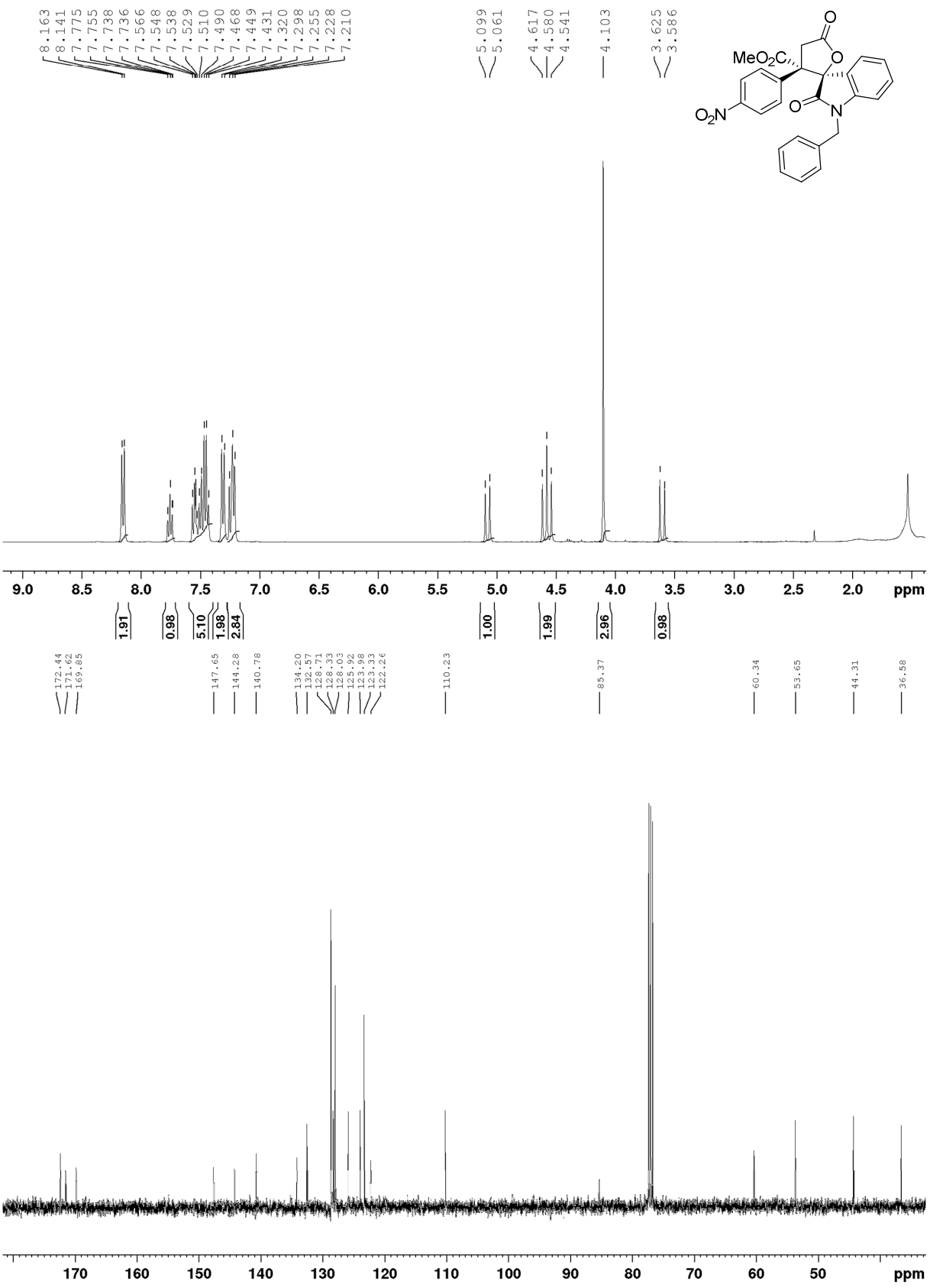
3*S*,4*R*)-3-Ethyl 4-methyl 3-cyclohexyl-1-oxoisochroman-3,4-dicarboxylate (*cis*-50)



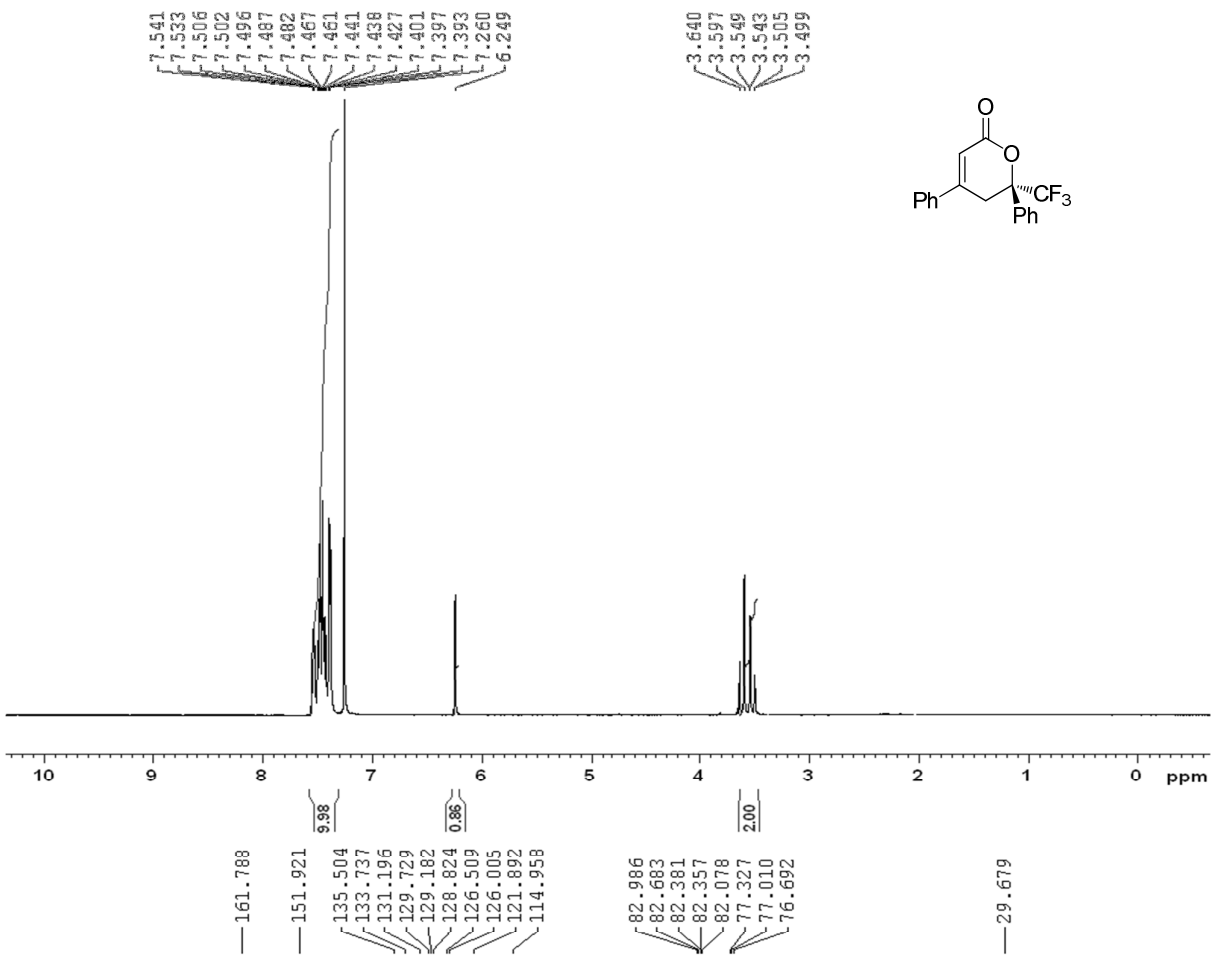
(3*R*,4'*R*)-Methyl 1-benzyl-1',2-dioxospiro[indoline-3,3'-isochroman]-4'-carboxylate (*cis*-52)

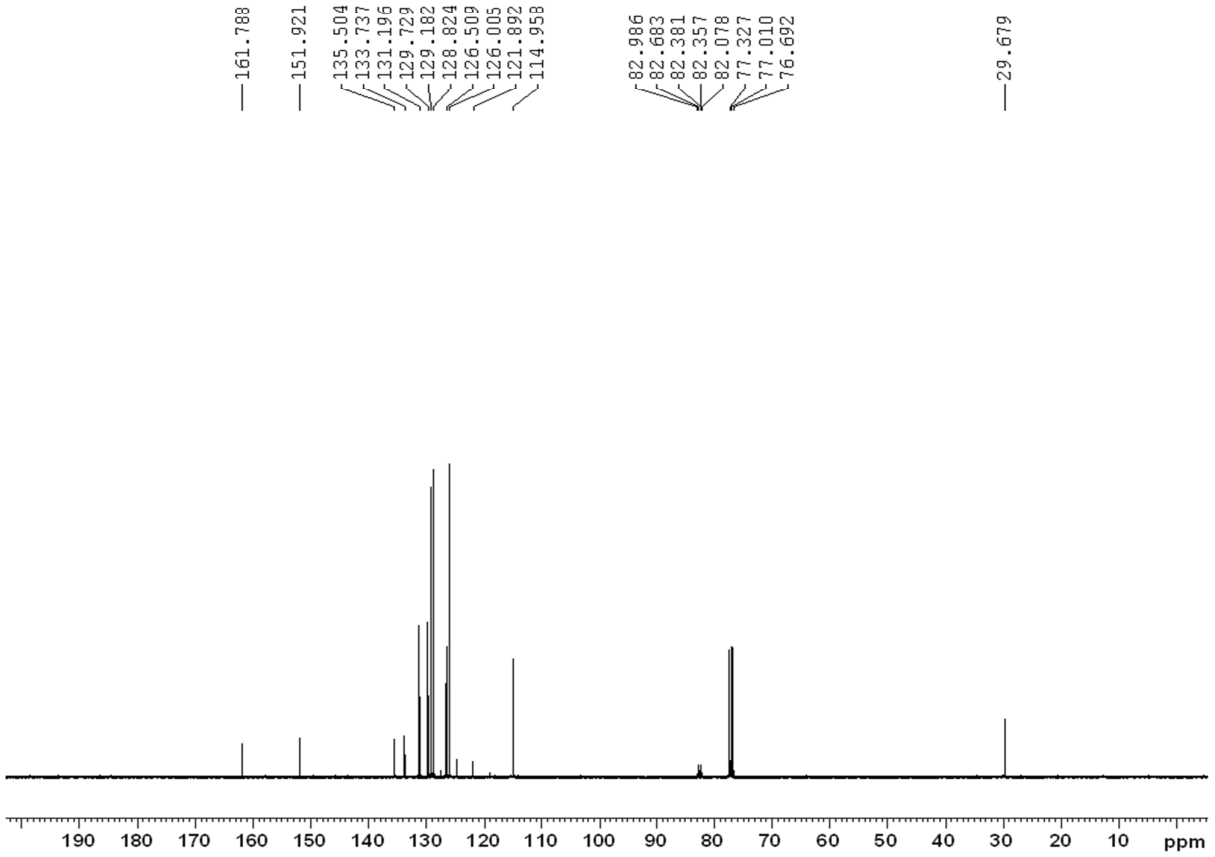


(2*R*,3*S*)-Methyl 1'-benzyl-3-(4-nitrophenyl)-2',5-dioxo-4,5-dihydro-3H-spiro[furan-2,3'-indoline]-3-carboxylate (*trans*-54)

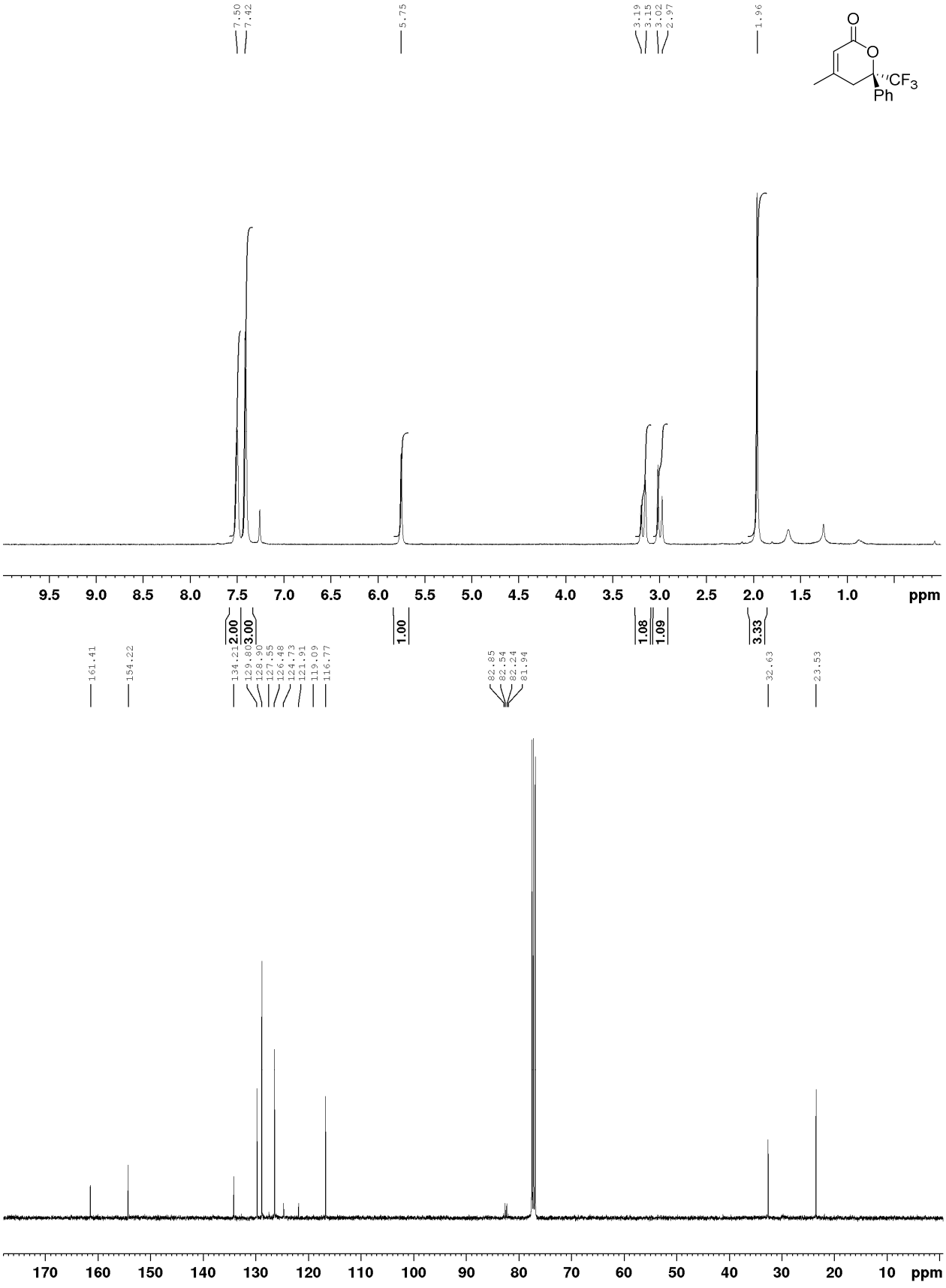


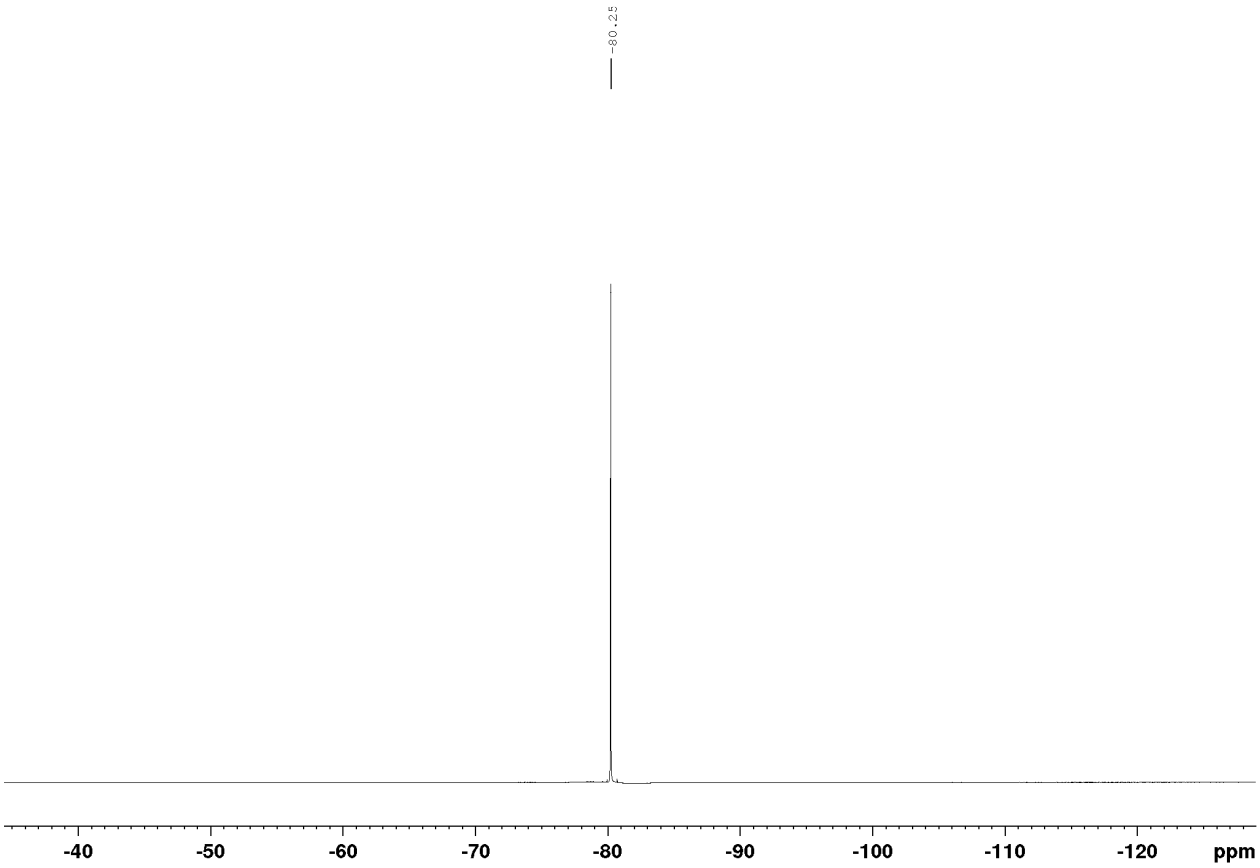
(*R*)-4,6-Diphenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (56a)



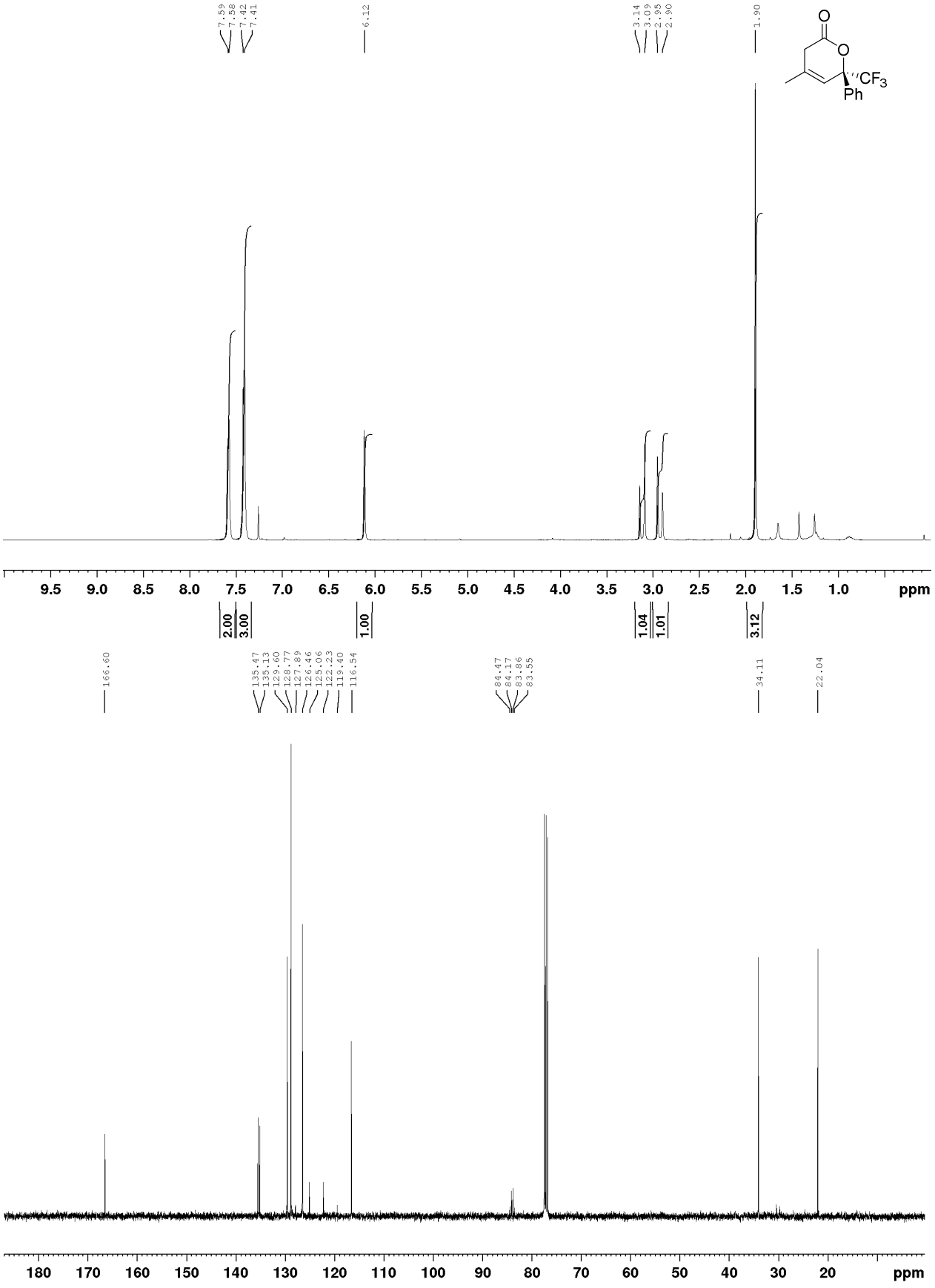


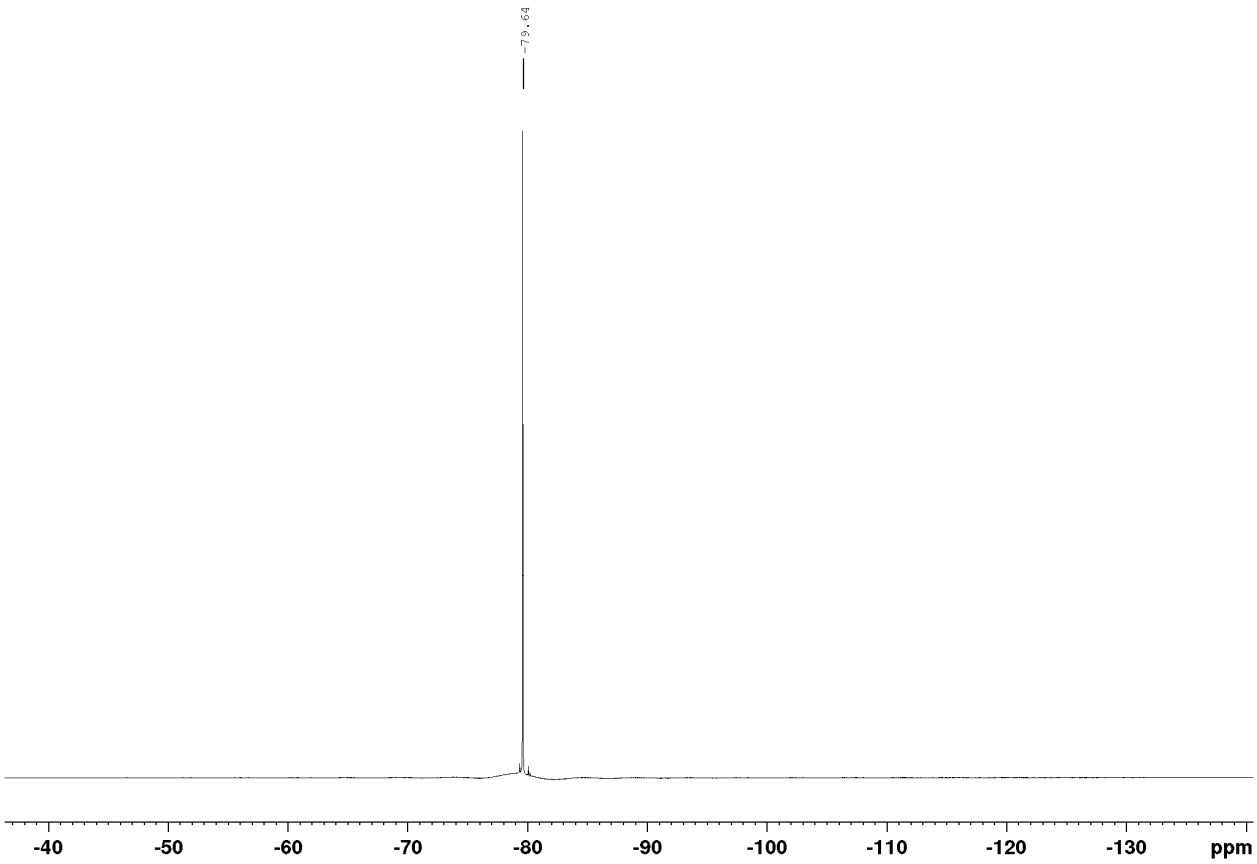
(*R*)-4-Methyl-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (58a)



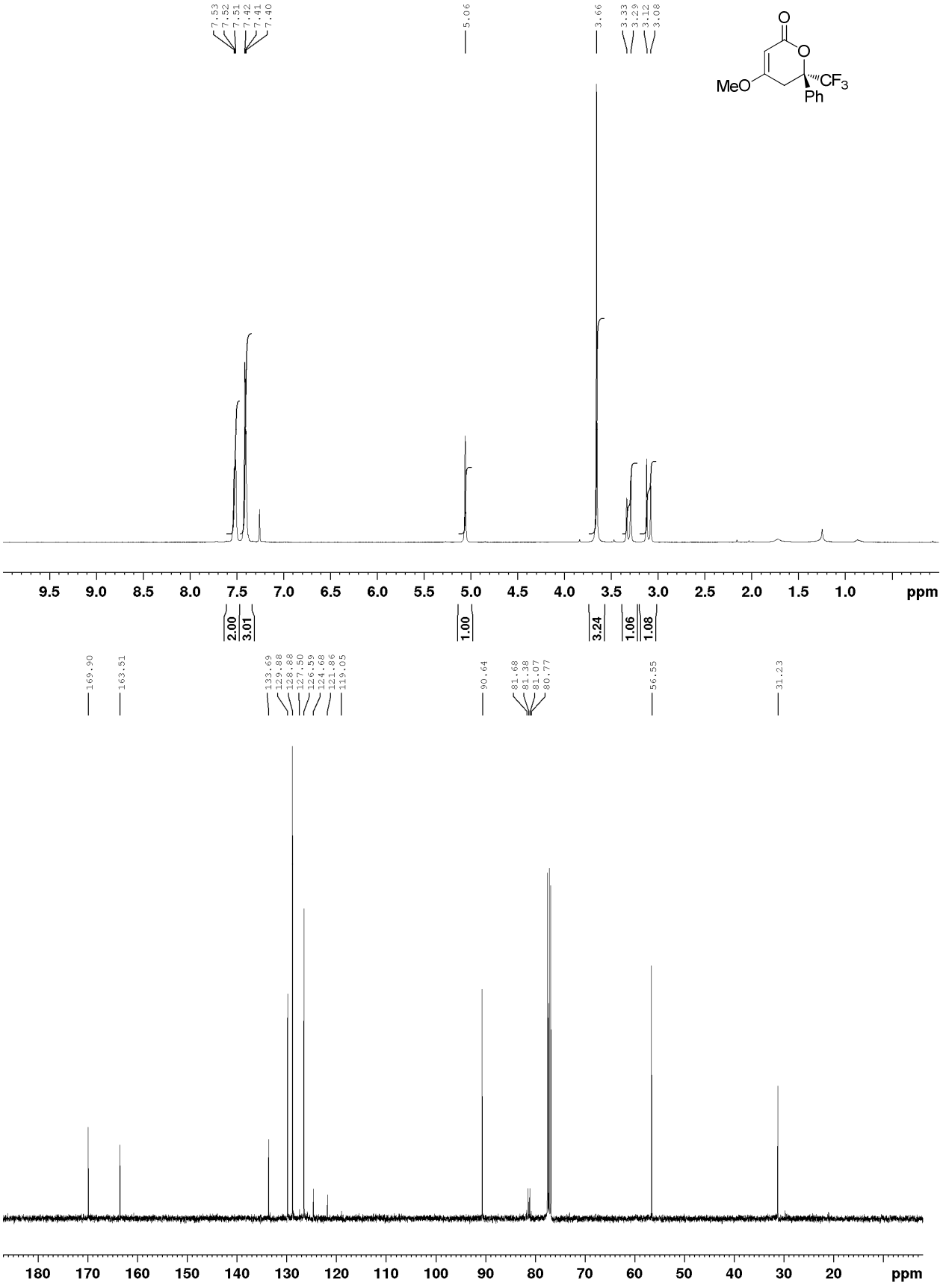

-80.25
-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm

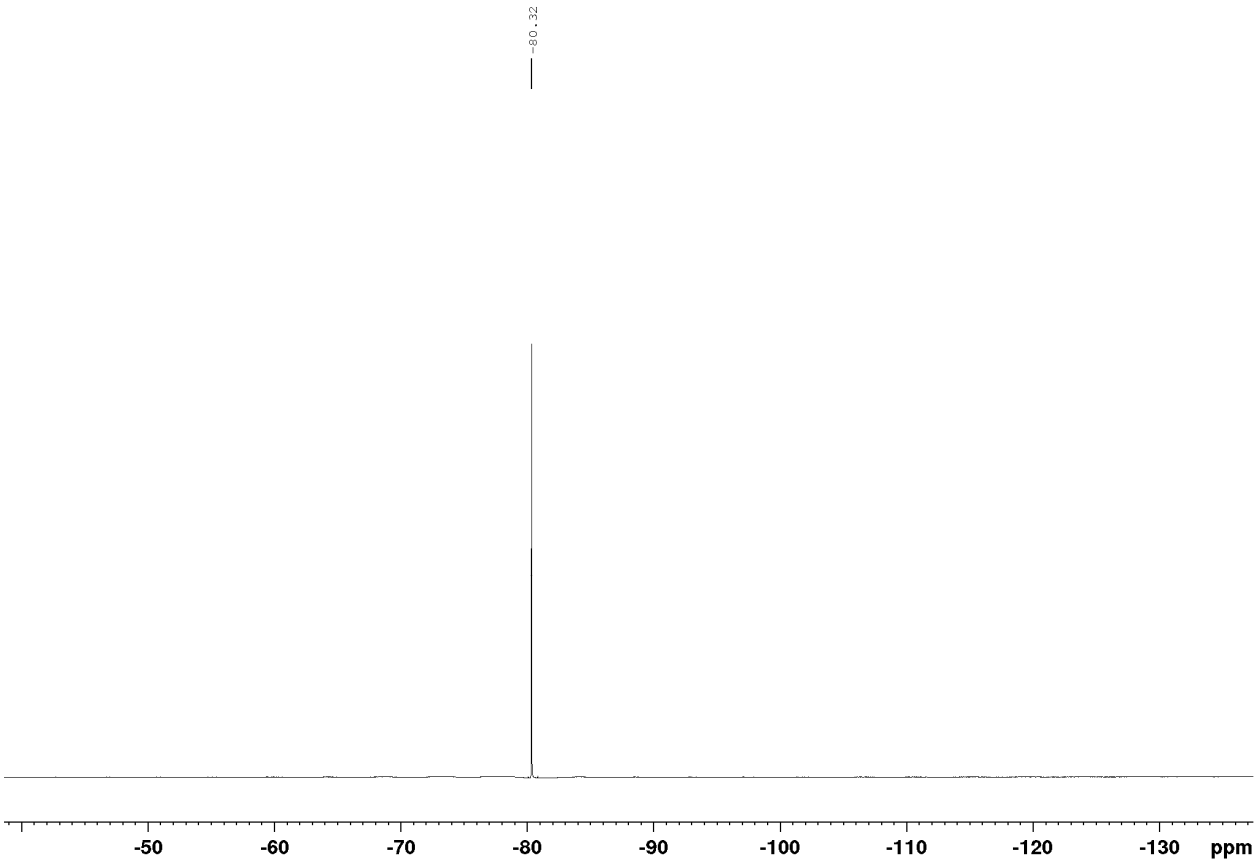
(*R*)-4-Methyl-6-phenyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-2-one (58b)



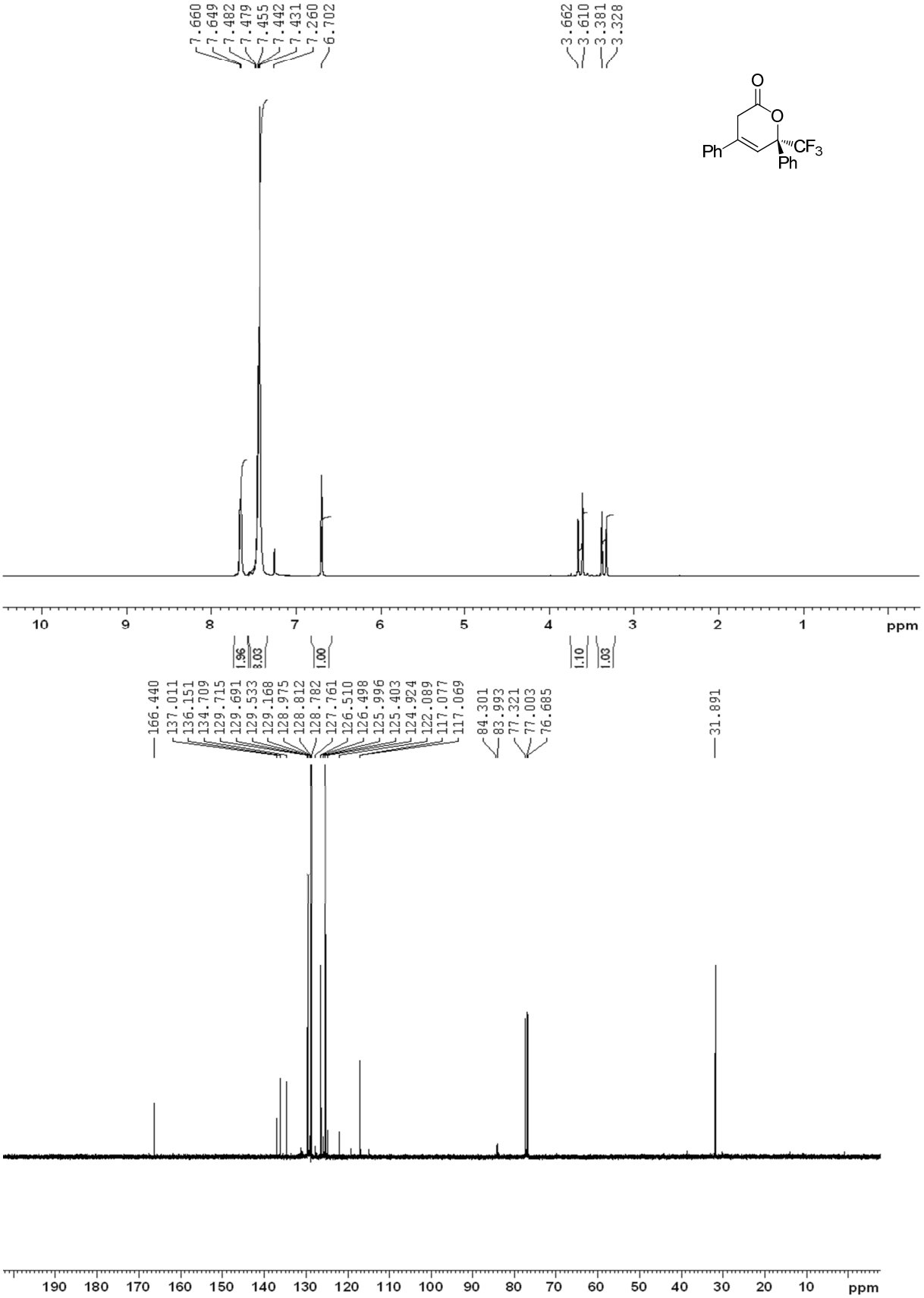

-79.64
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
ppm

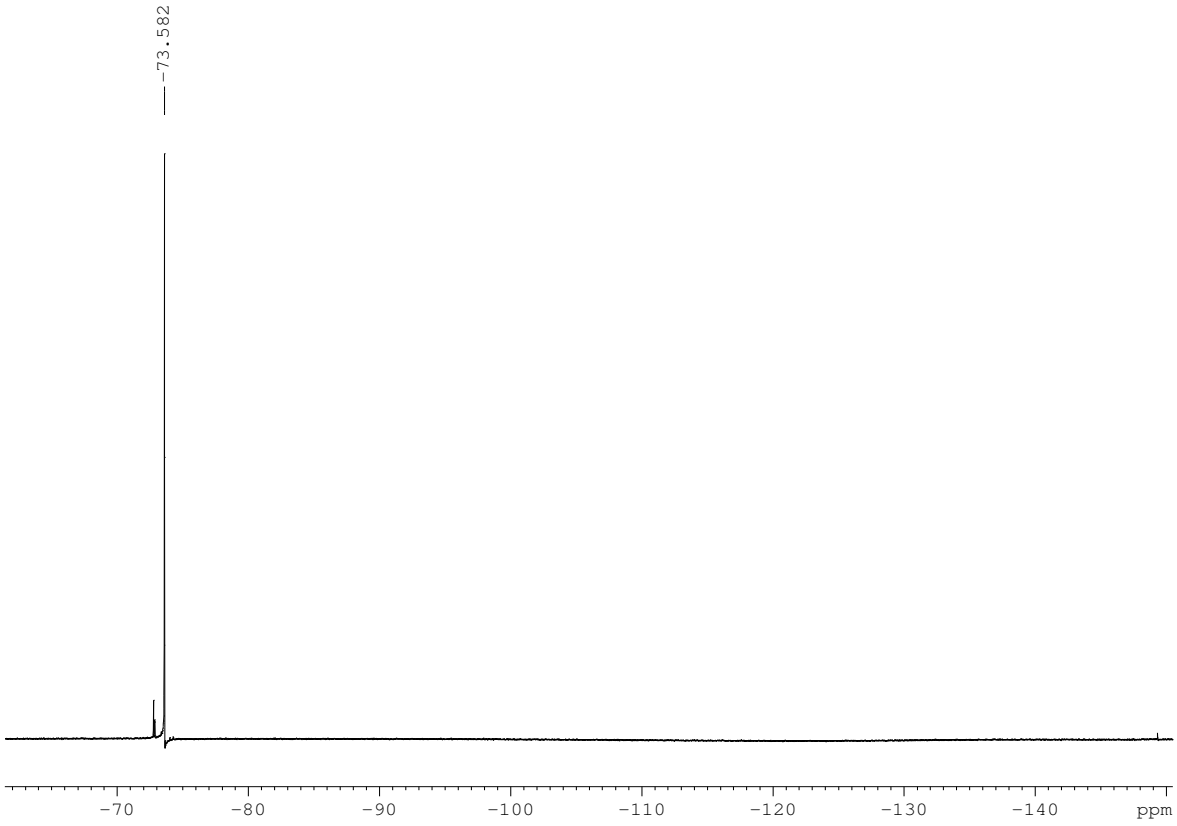
(*R*)-4-Methoxy-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (60a)



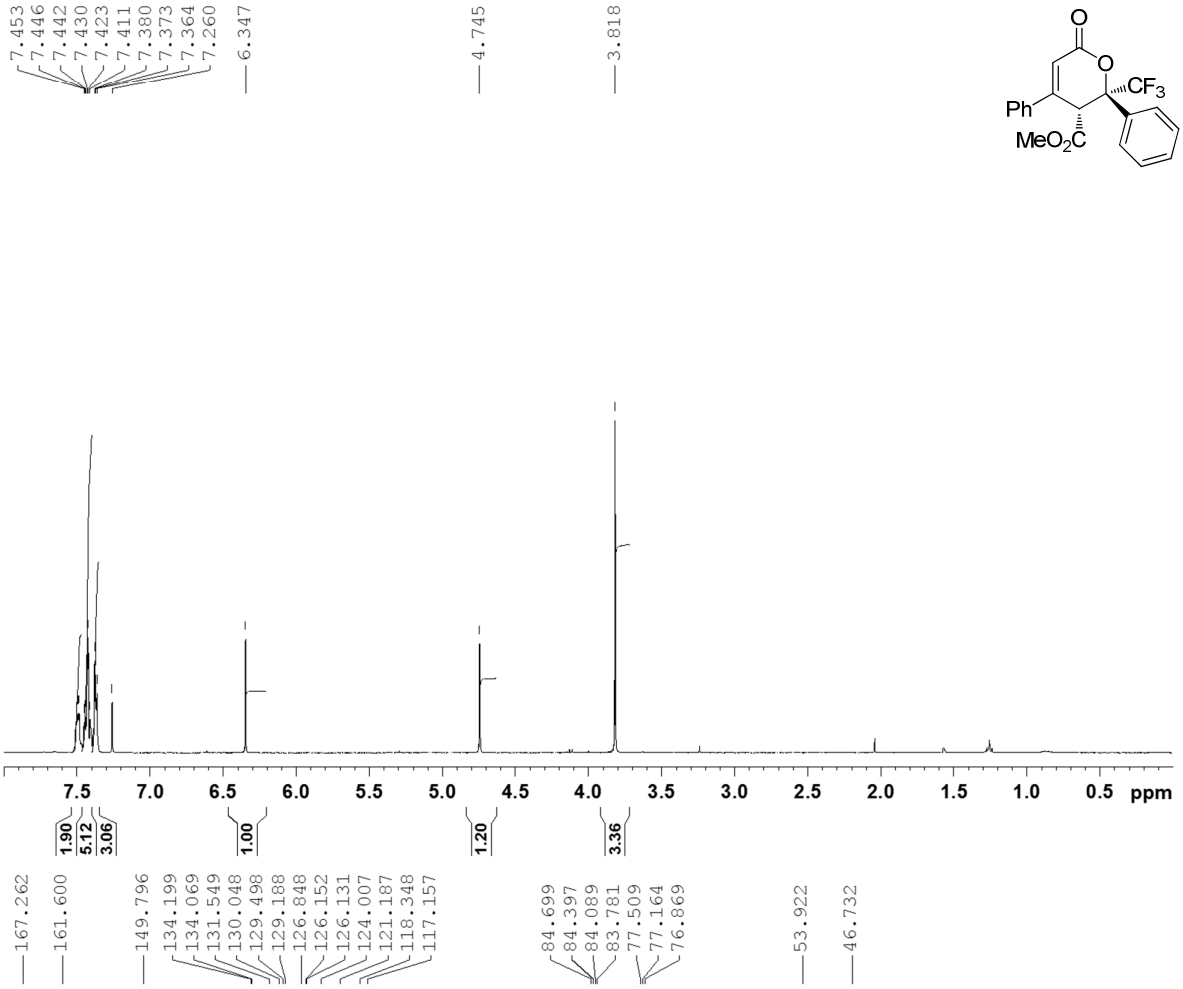

-80.32
-50
-60
-70
-80
-90
-100
-110
-120
-130
ppm

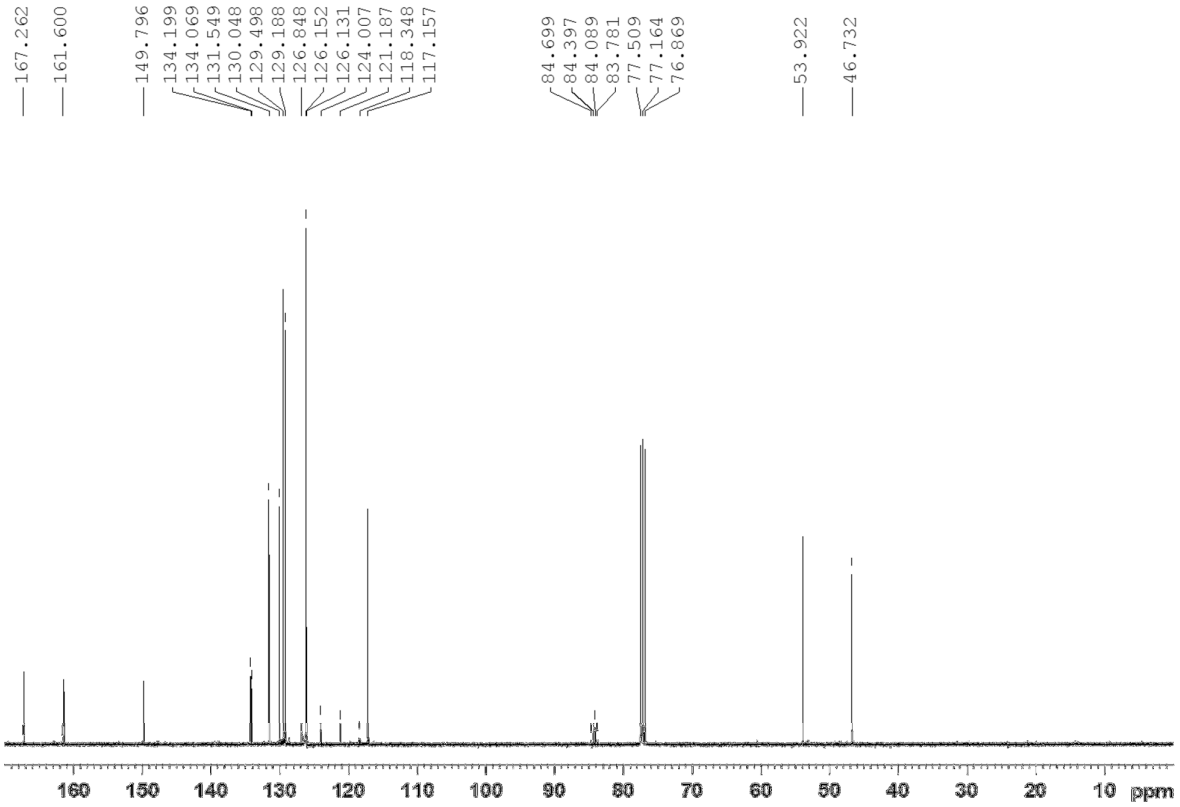
(*R*)-4,6-Diphenyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-2-one (56b)

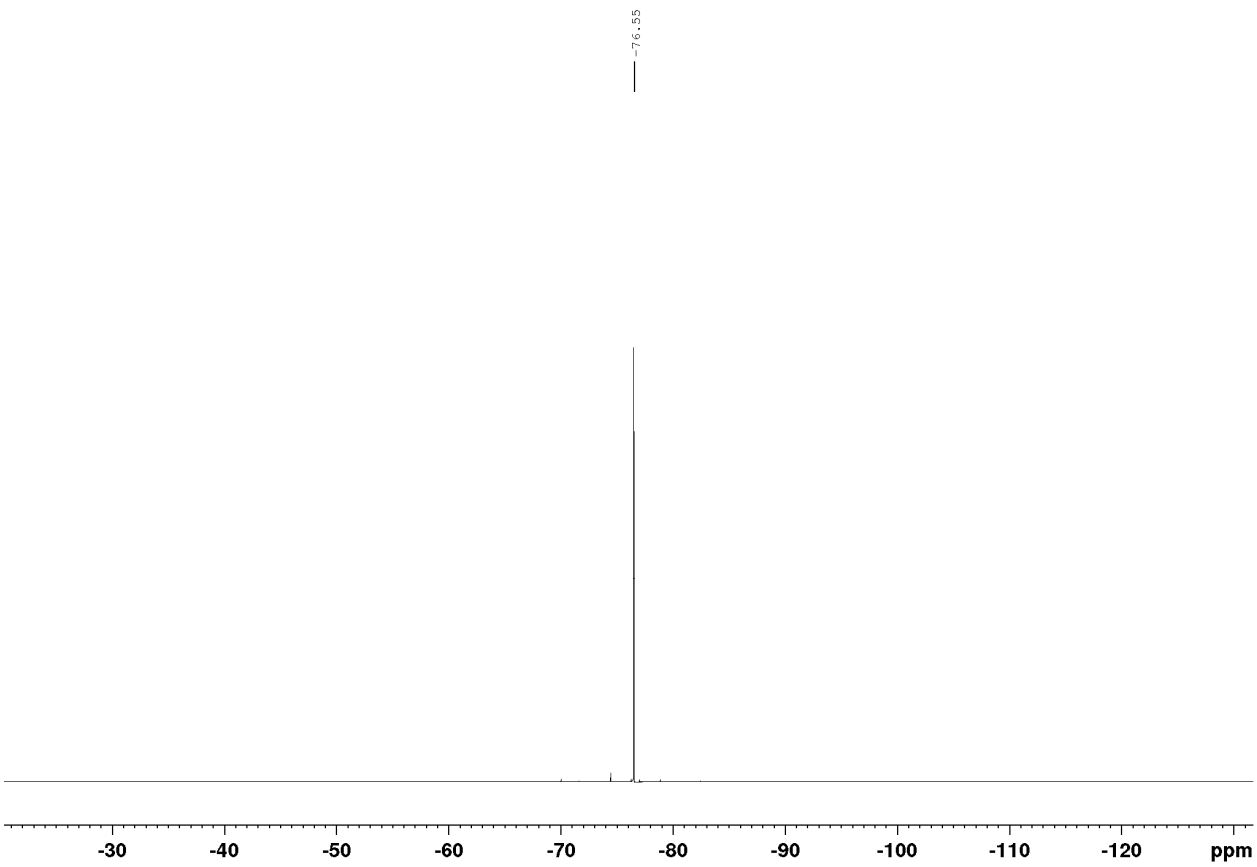



-73.582
-70
-80
-90
-100
-110
-120
-130
-140
ppm

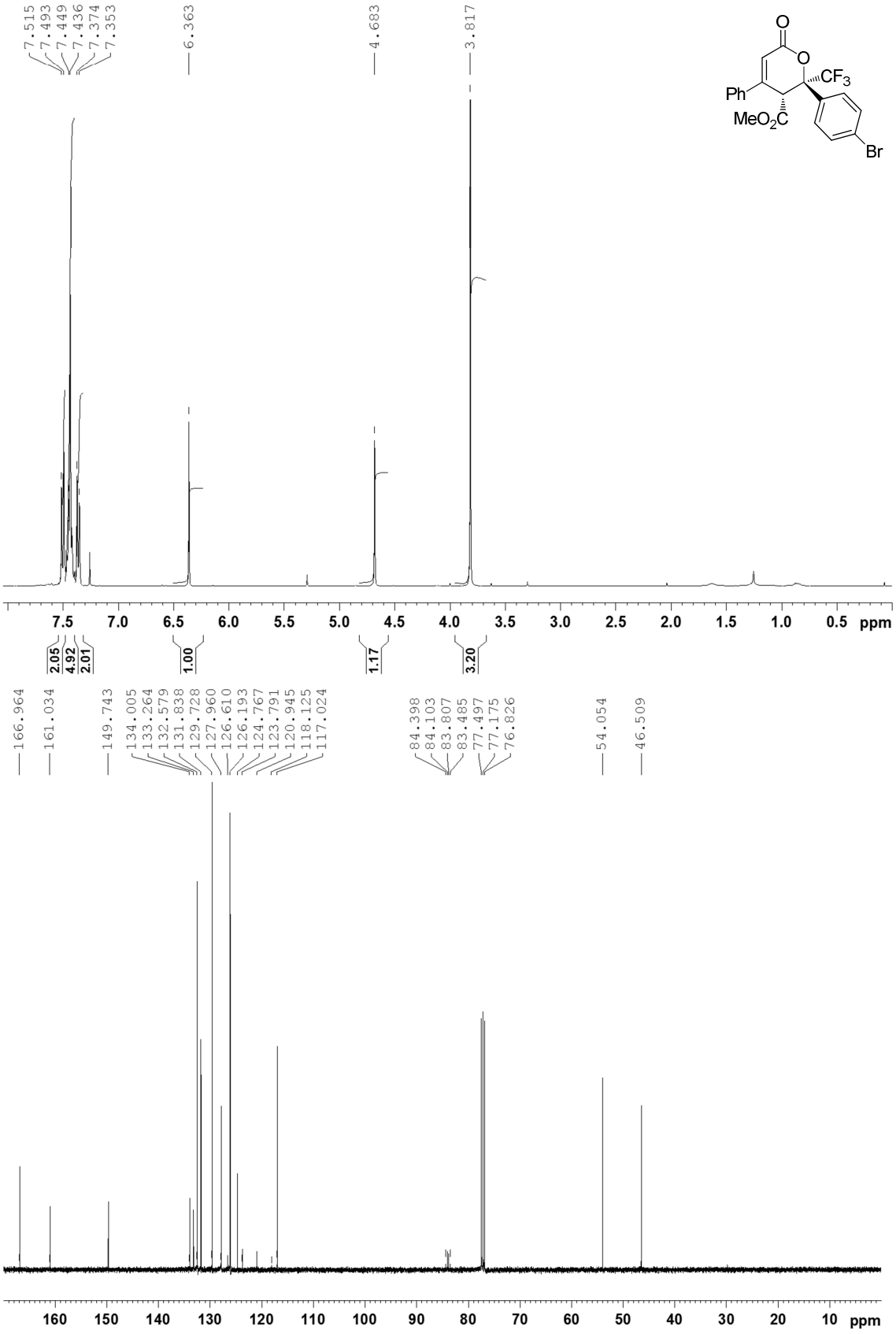
(2*R*,3*R*)-Methyl 6-oxo-2,4-diphenyl-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate (*cis*-56c)

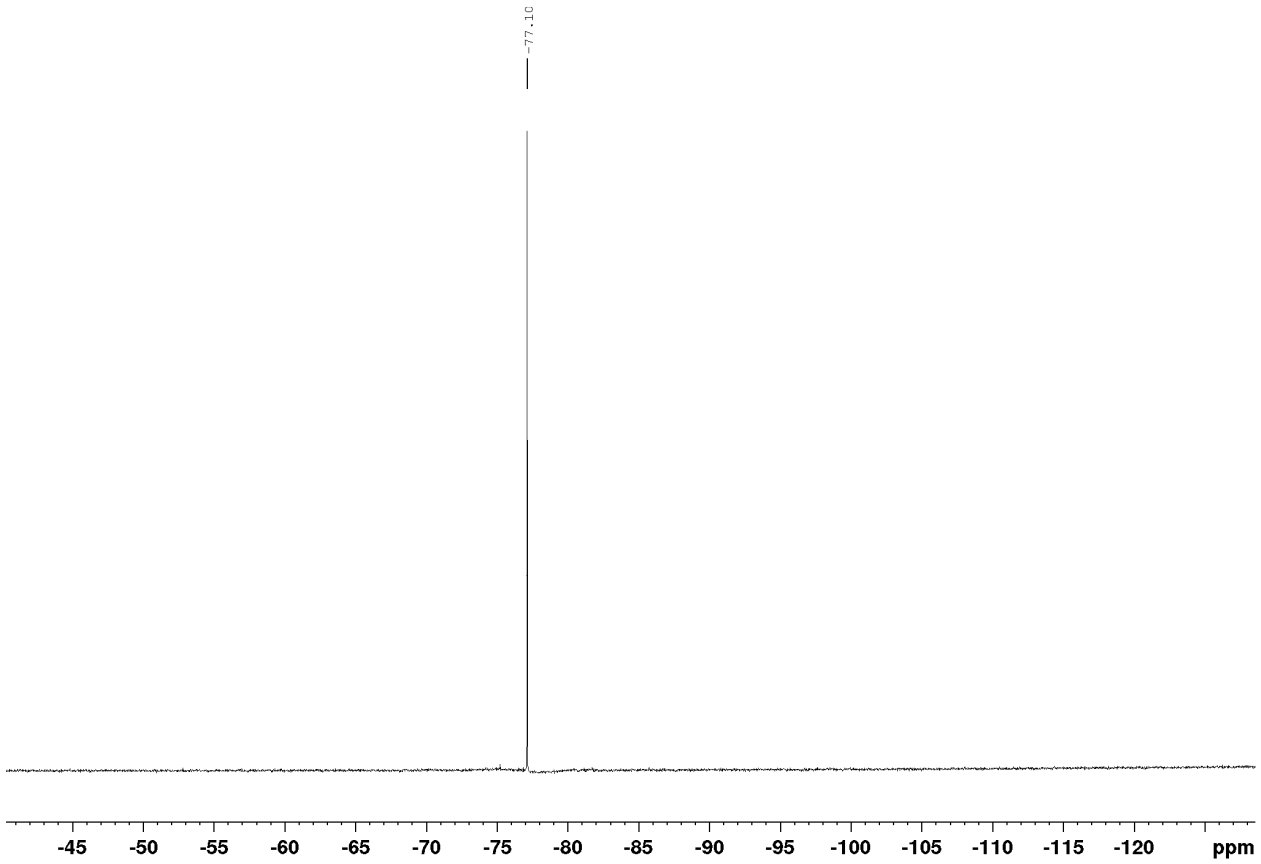




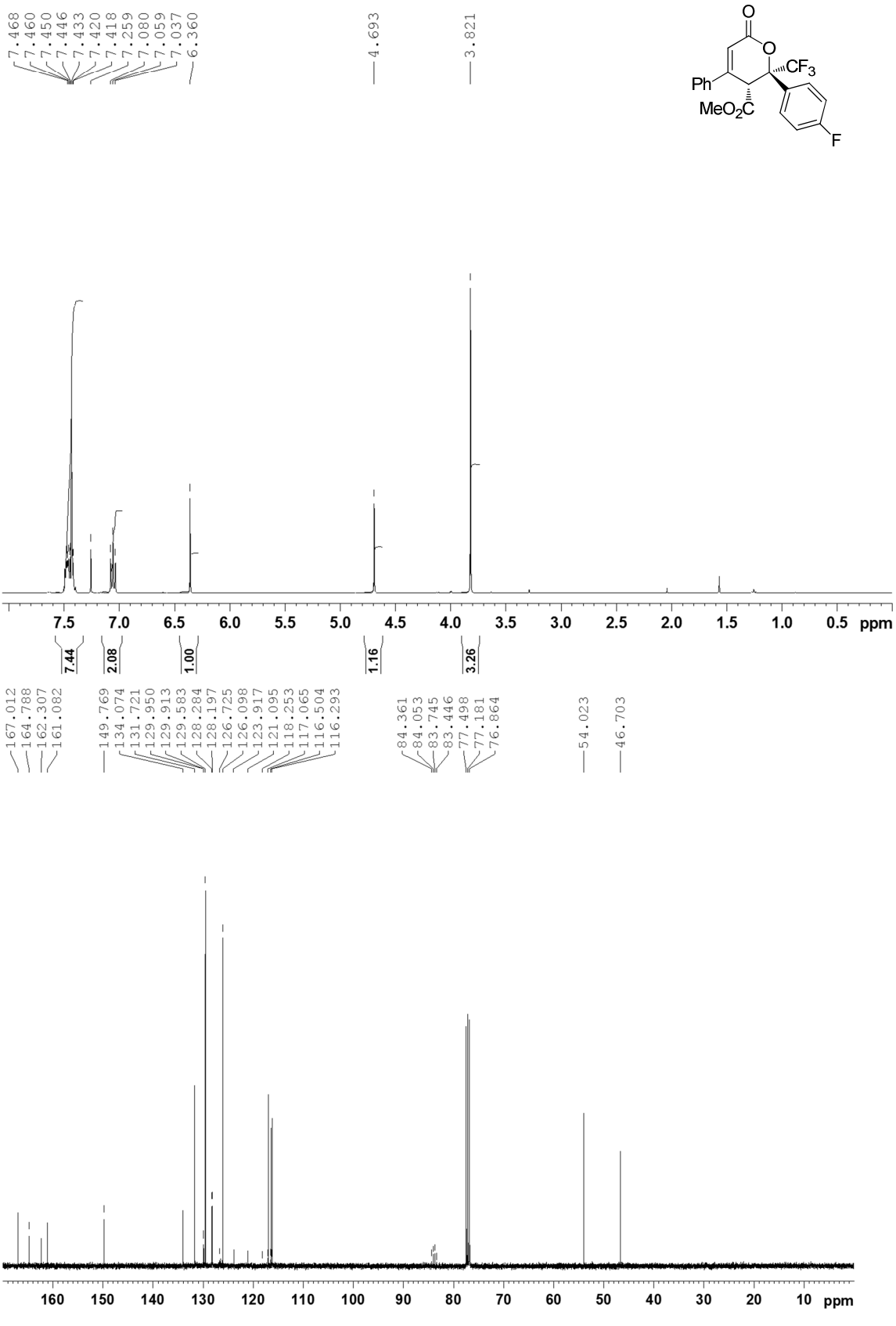

-76.55
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm

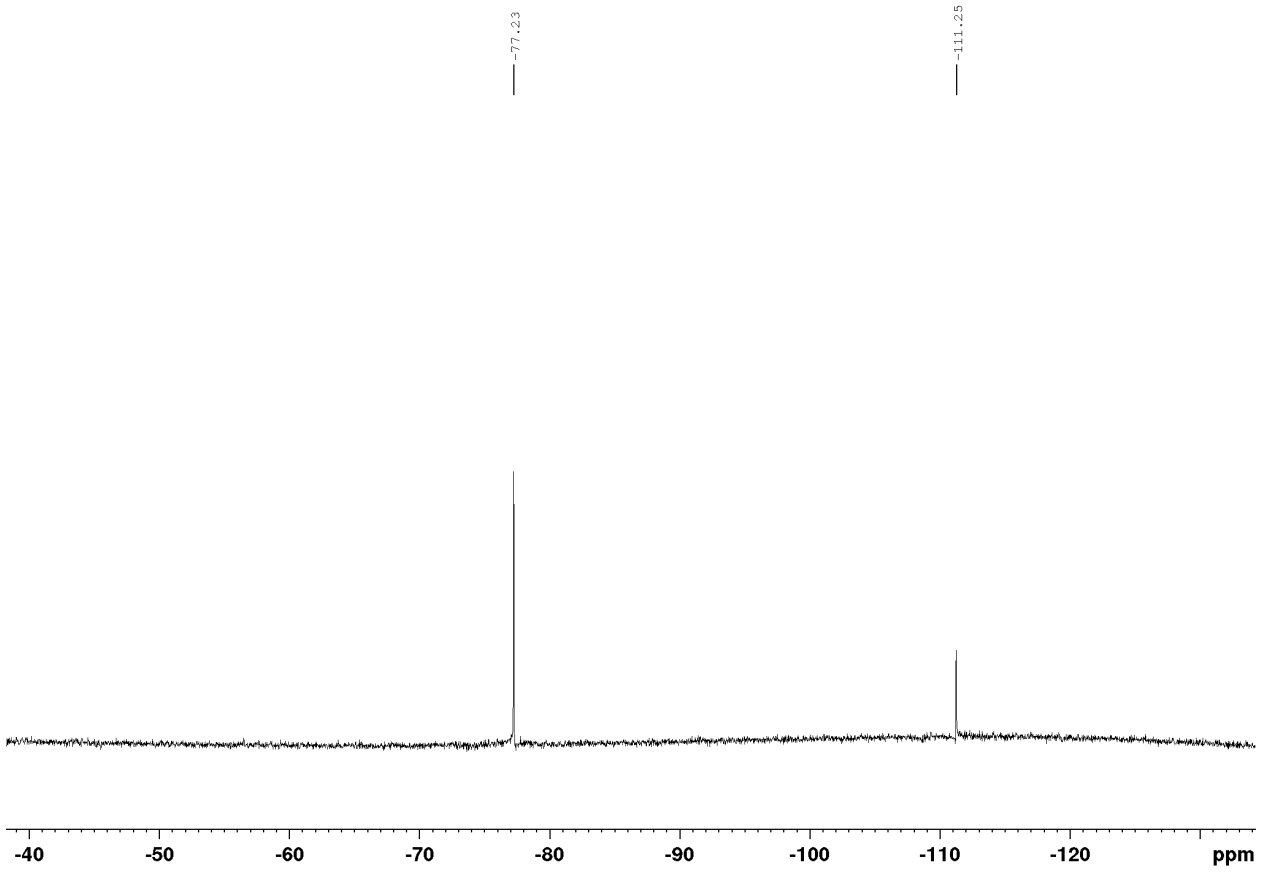
(2*R*,3*R*)-Methyl-2-(4-bromophenyl)-2-(trifluoromethyl)-3,6-dihydro-6-oxo-4-phenyl-2*H*-pyran-3-carboxylate (*cis*-61)



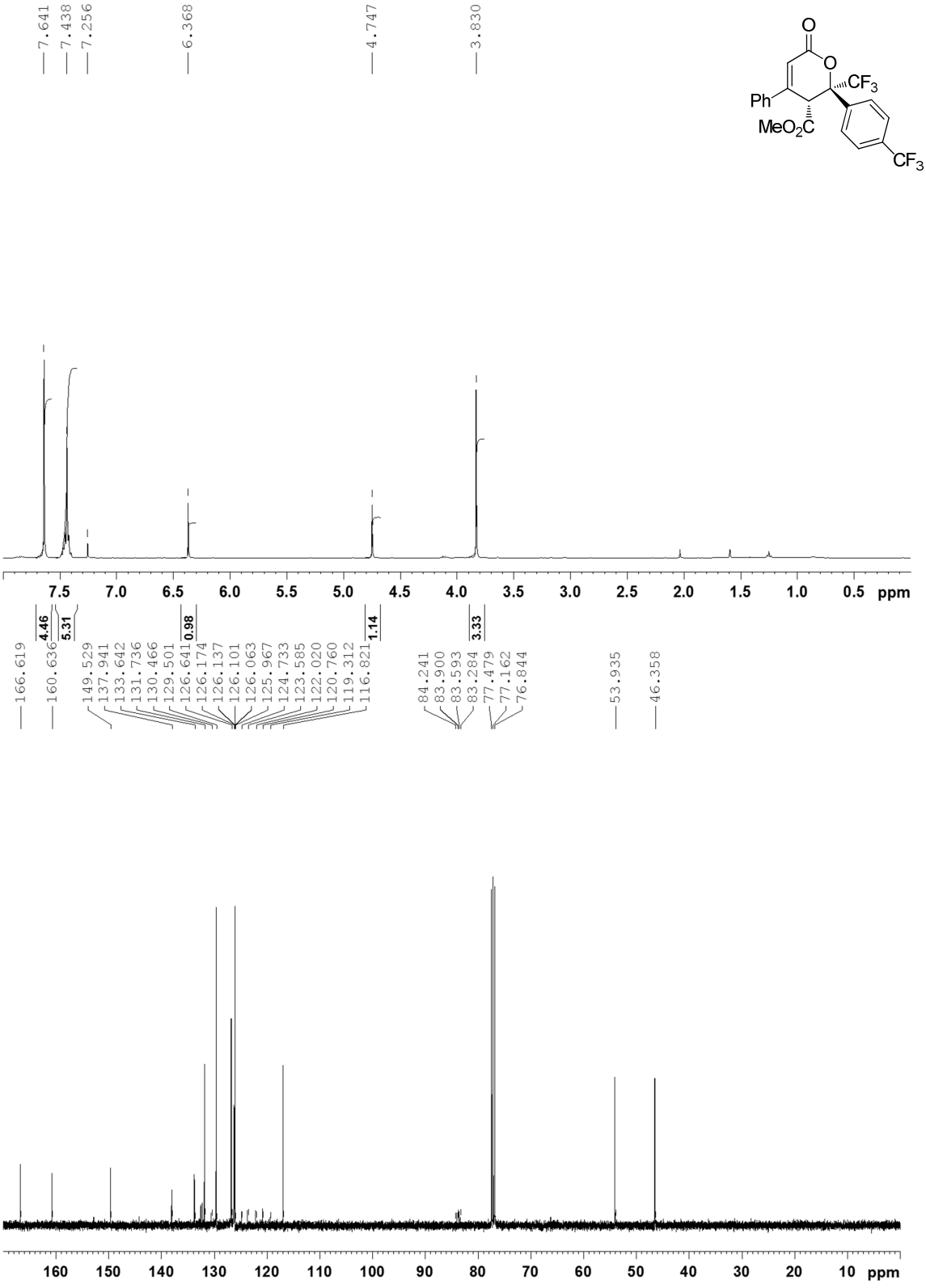

-77.10
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
ppm

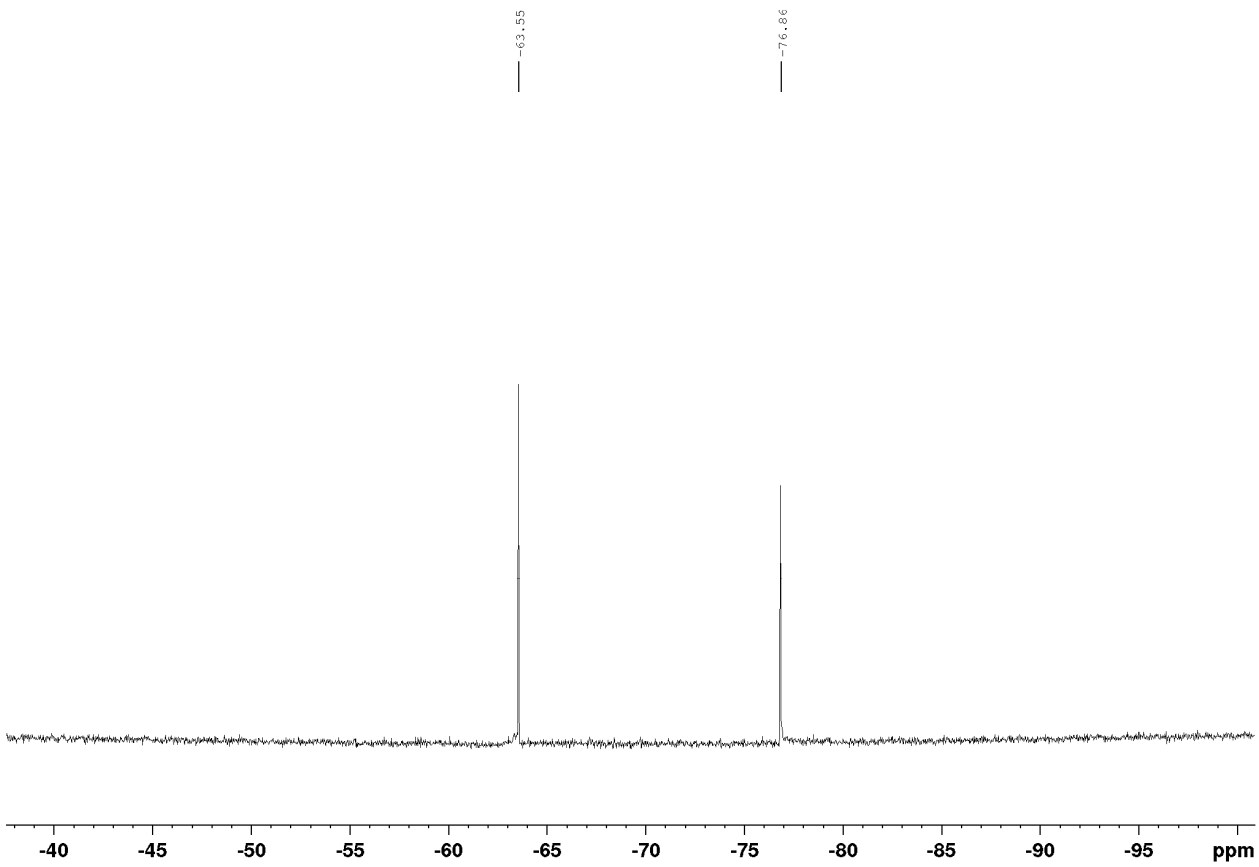
(2*R*,3*R*)-Methyl-2-(trifluoromethyl)-2-(4-fluorophenyl)-3,6-dihydro-6-oxo-4-phenyl-2*H*-pyran-3-carboxylate (*cis*-62)



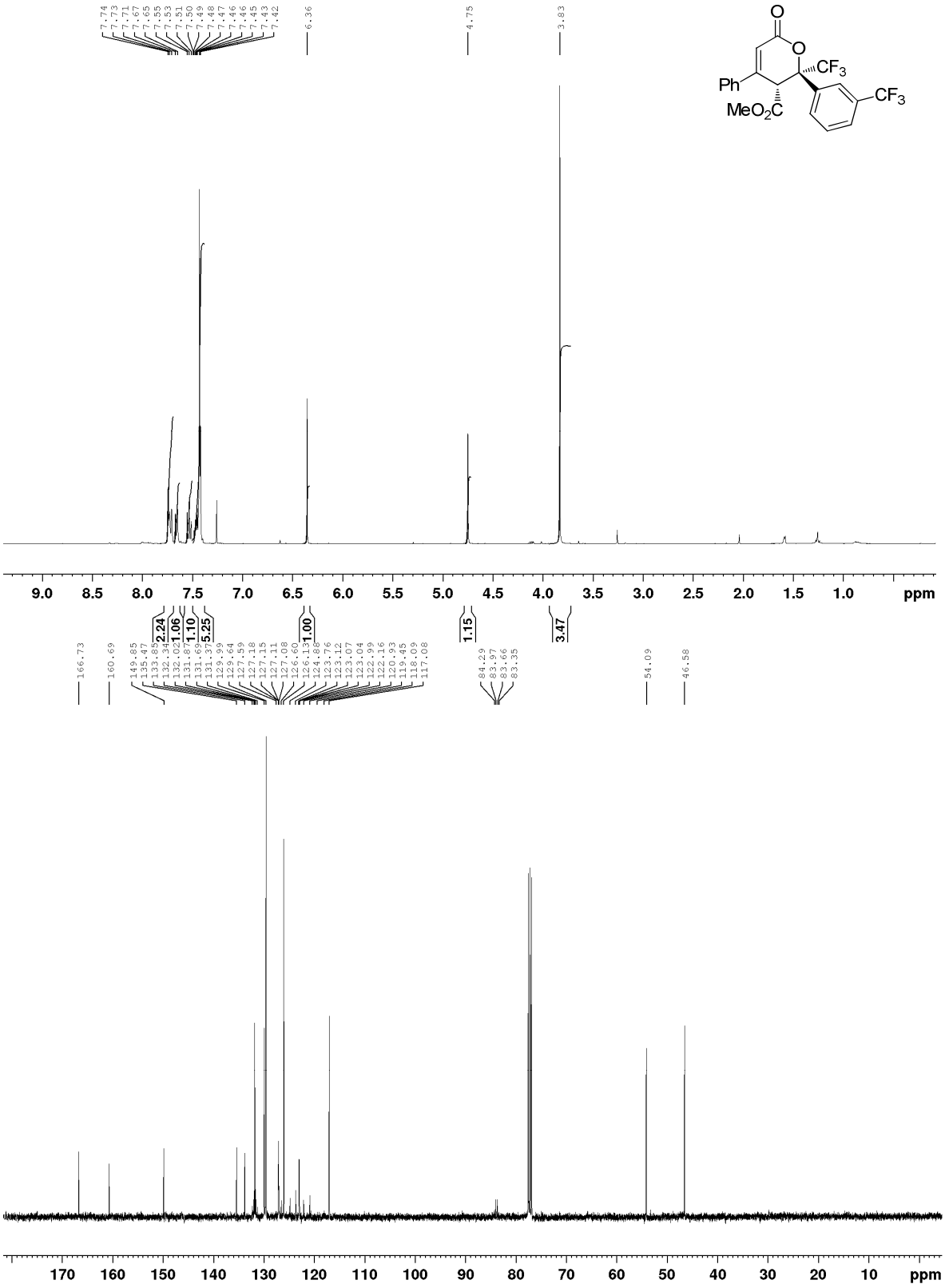

-77.23
-111.25
-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm

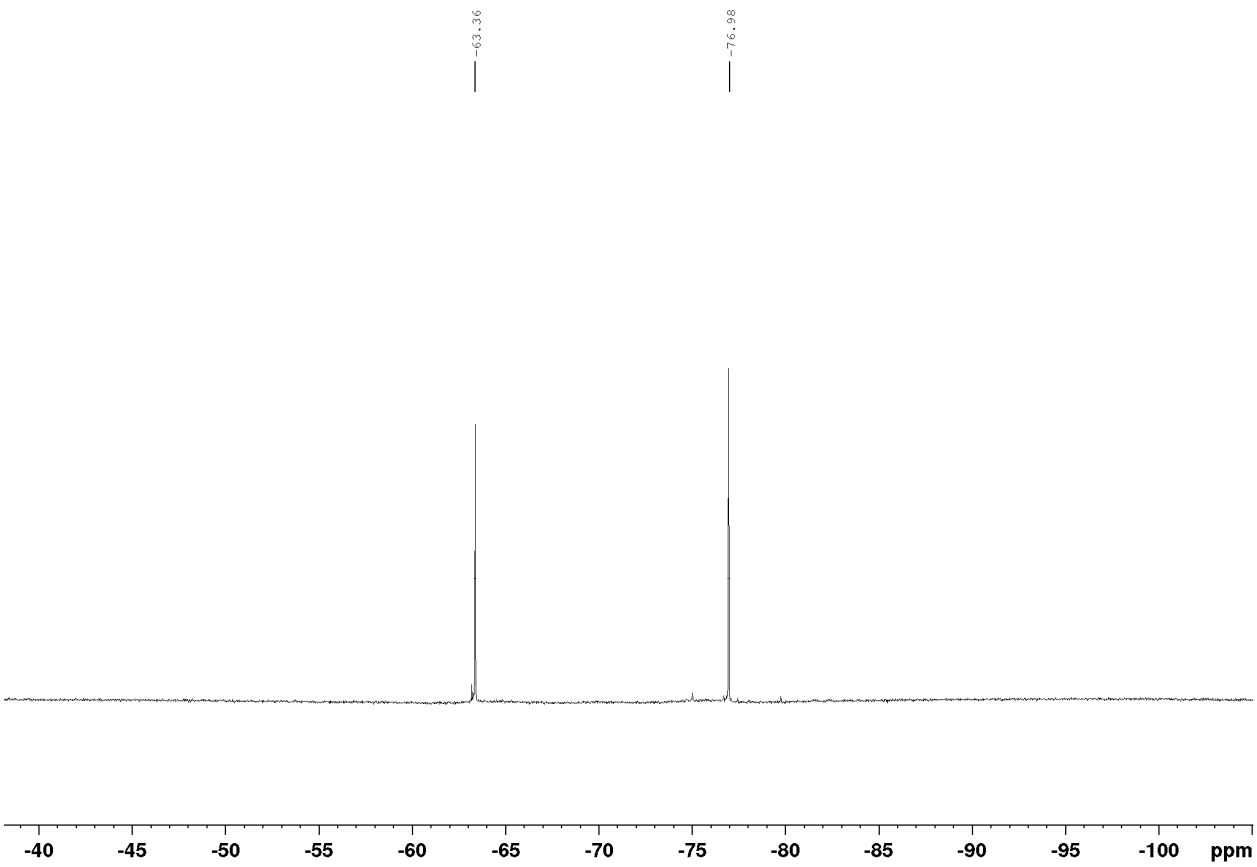
(2*R*,3*R*)-Methyl-2-(trifluoromethyl)-2-(4-(trifluoromethyl)phenyl)-3,6-dihydro-6-oxo-4-phenyl-2*H*-pyran-3-carboxylate (***cis*-63**)



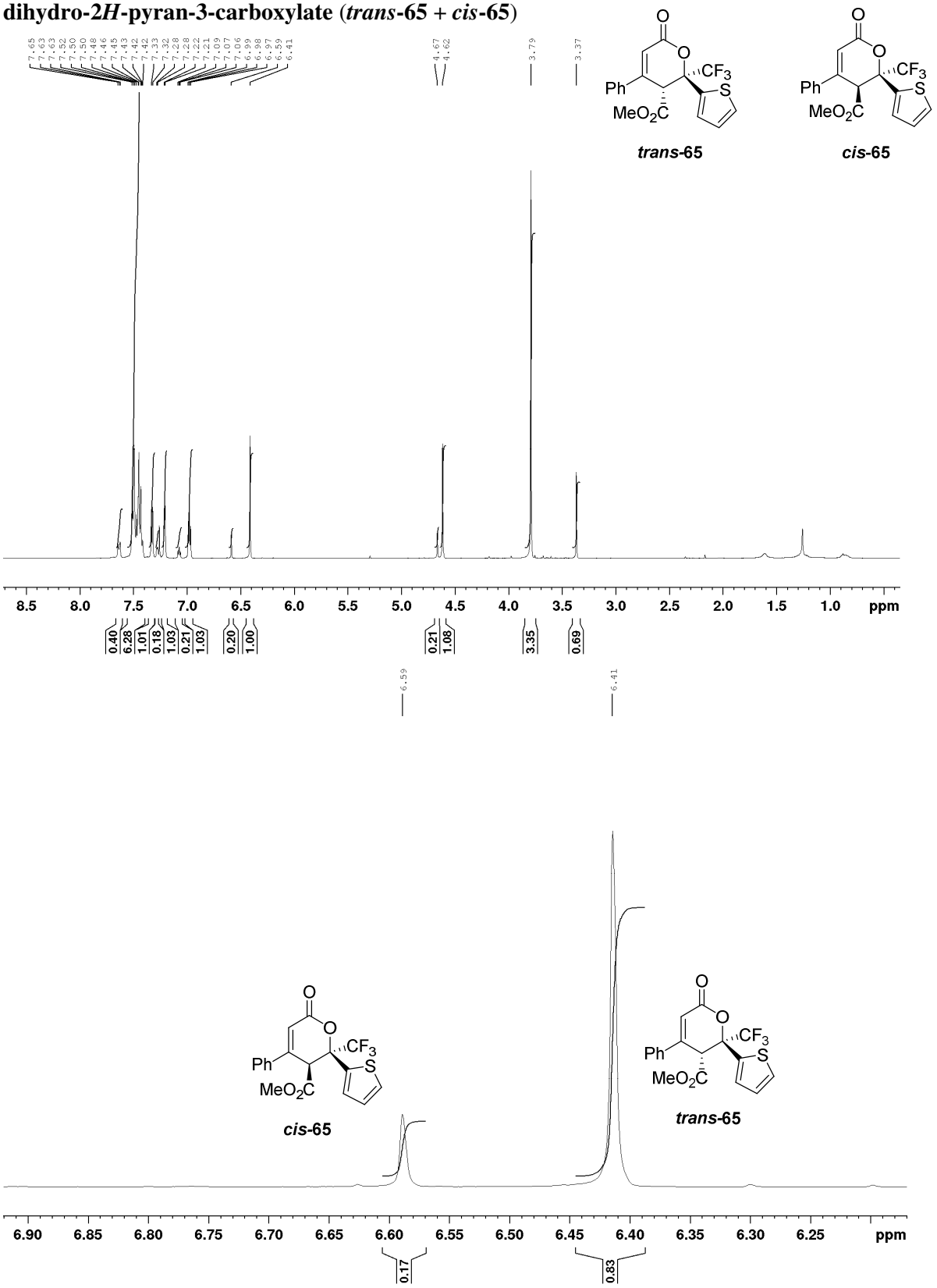

-63.55
-76.86
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
ppm

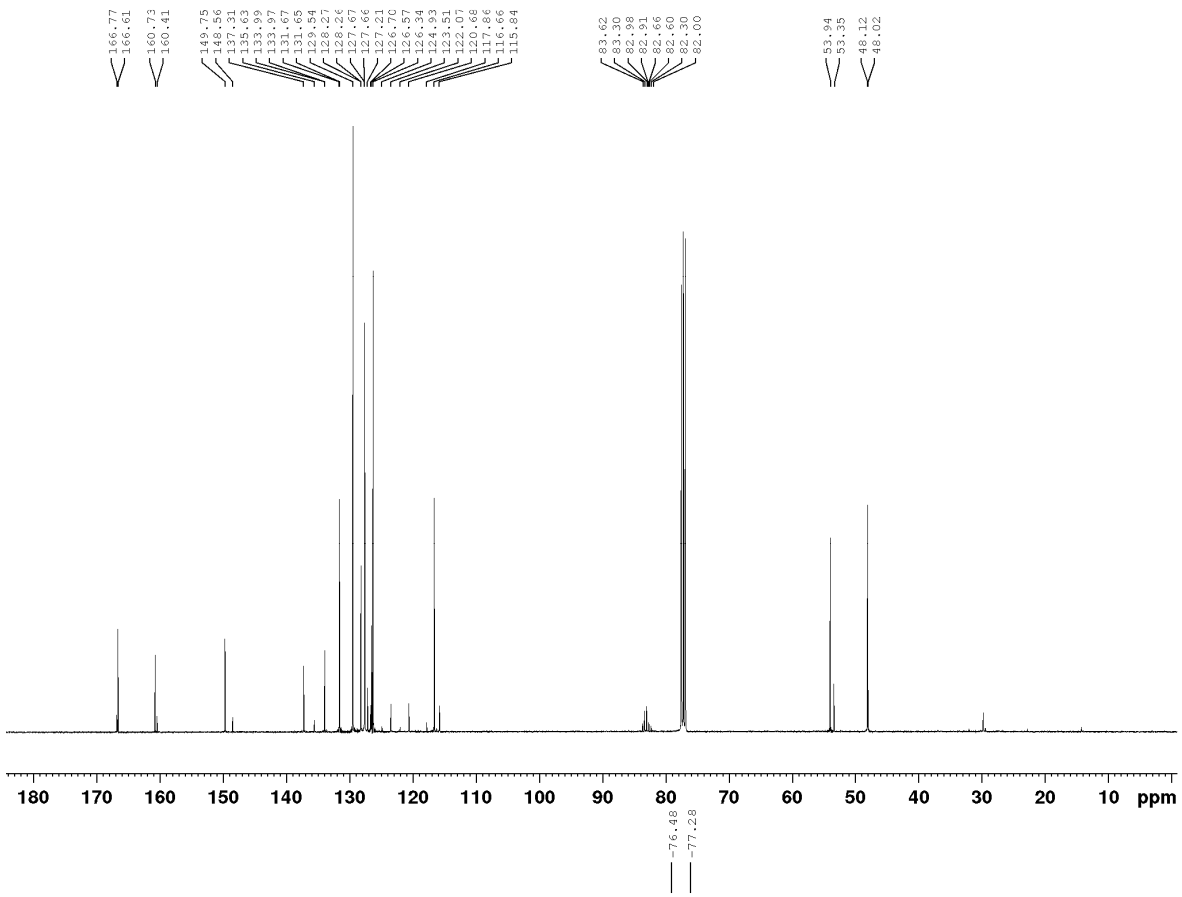
(2*R*,3*R*)-Methyl-2-(trifluoromethyl)-2-(3-(trifluoromethyl)phenyl)-3,6-dihydro-6-oxo-4-phenyl-2*H*-pyran-3-carboxylate (*cis*-64)

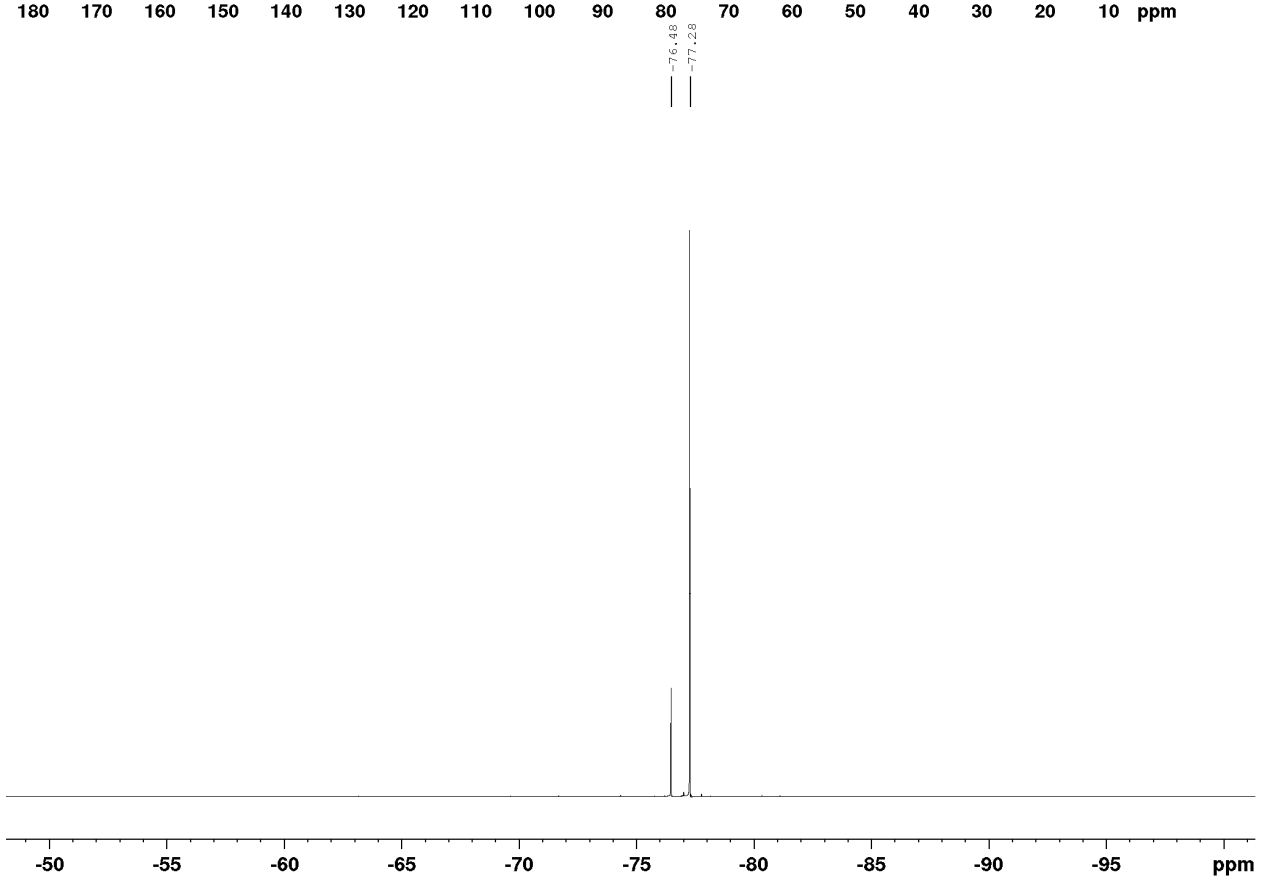



-63.36
-76.98
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
ppm

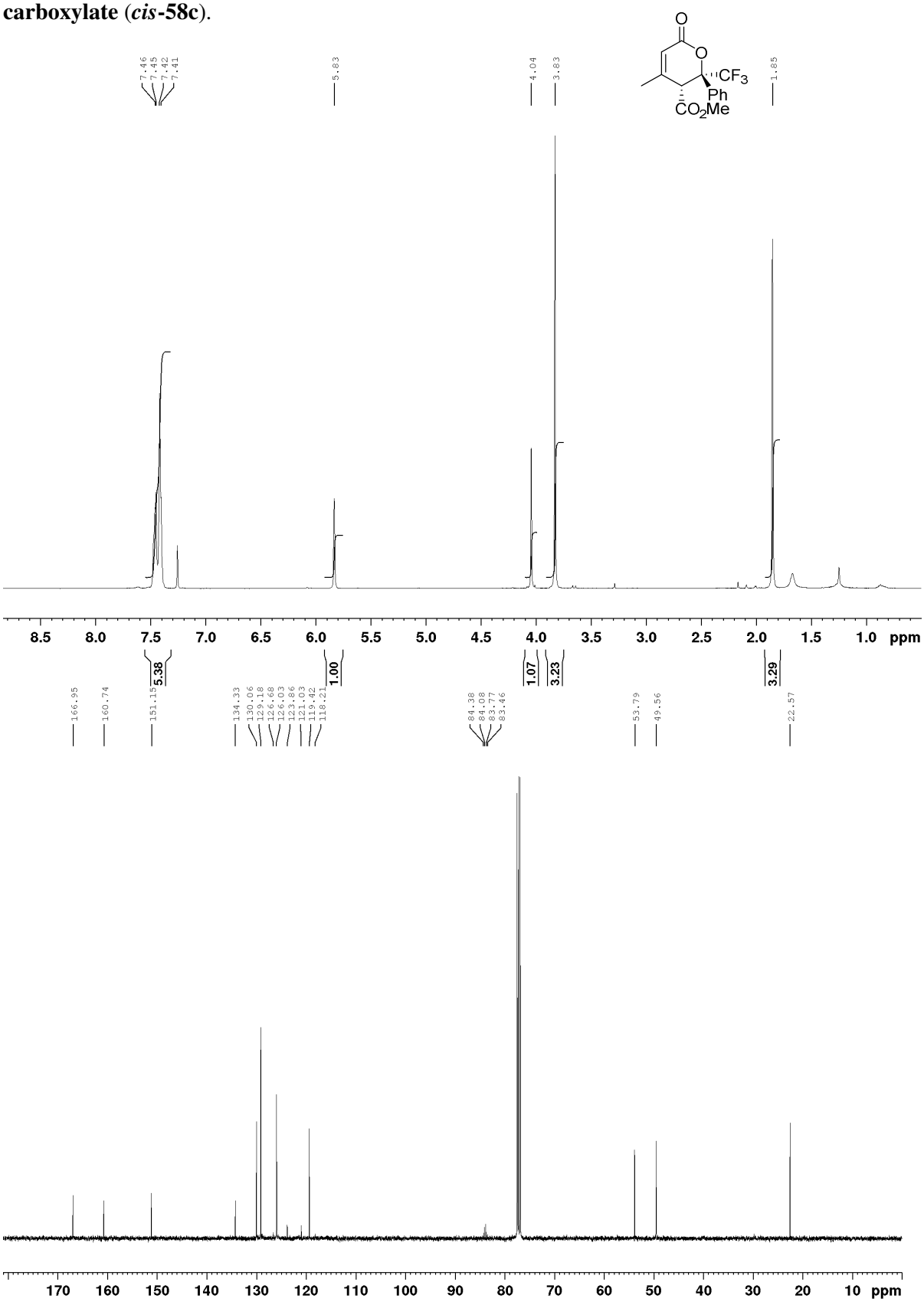
(2*S*,3*R*)-Methyl 6-oxo-4-phenyl-2-(thiophen-2-yl)-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate & (2*S*,3*S*)-Methyl 6-oxo-4-phenyl-2-(thiophen-2-yl)-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate (*trans*-65 + *cis*-65)

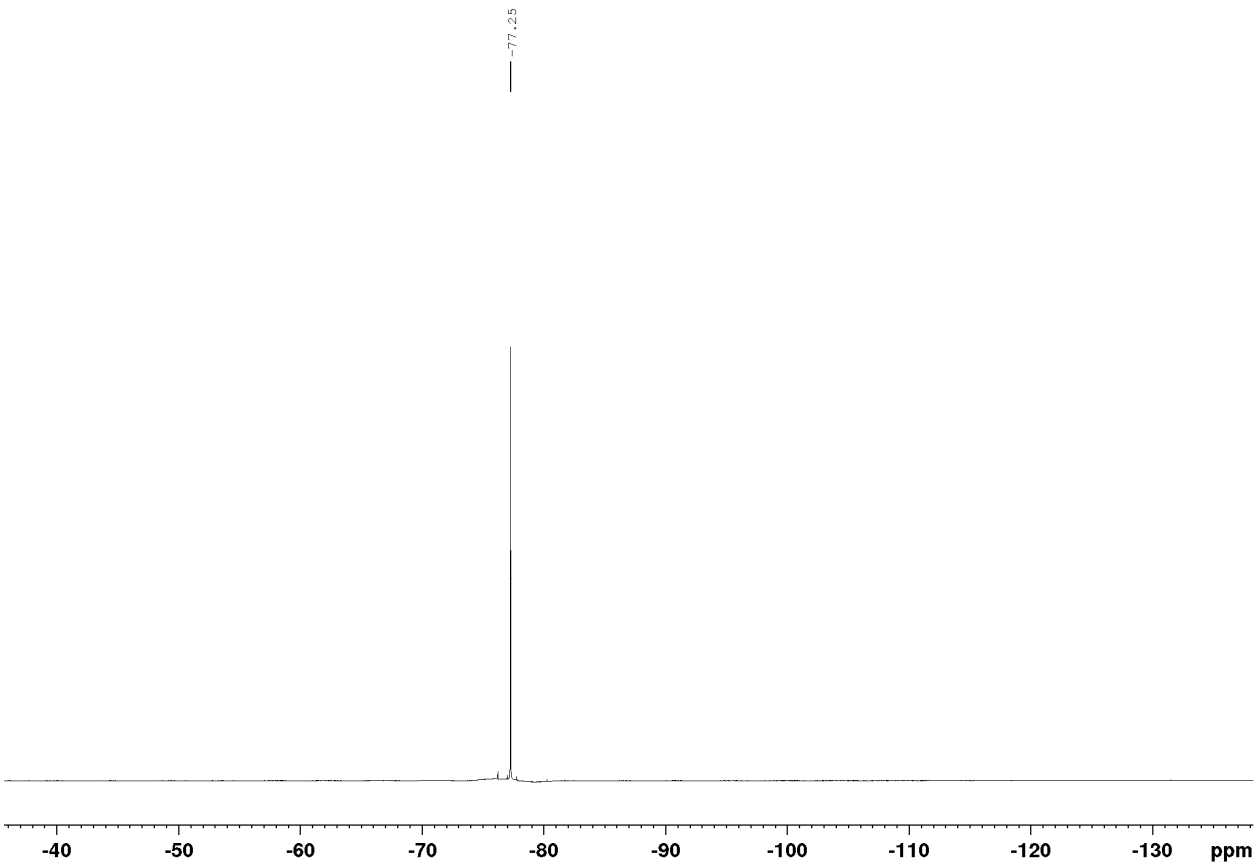



166.77
166.61
160.73
160.41
149.75
148.56
137.31
135.63
133.99
133.97
131.67
131.65
129.54
128.27
128.26
127.67
127.66
127.21
126.76
126.57
126.34
124.93
123.51
122.07
120.68
117.86
116.66
115.84
83.62
83.30
82.98
82.91
82.66
82.60
82.30
82.00
53.94
53.35
48.12
48.02
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

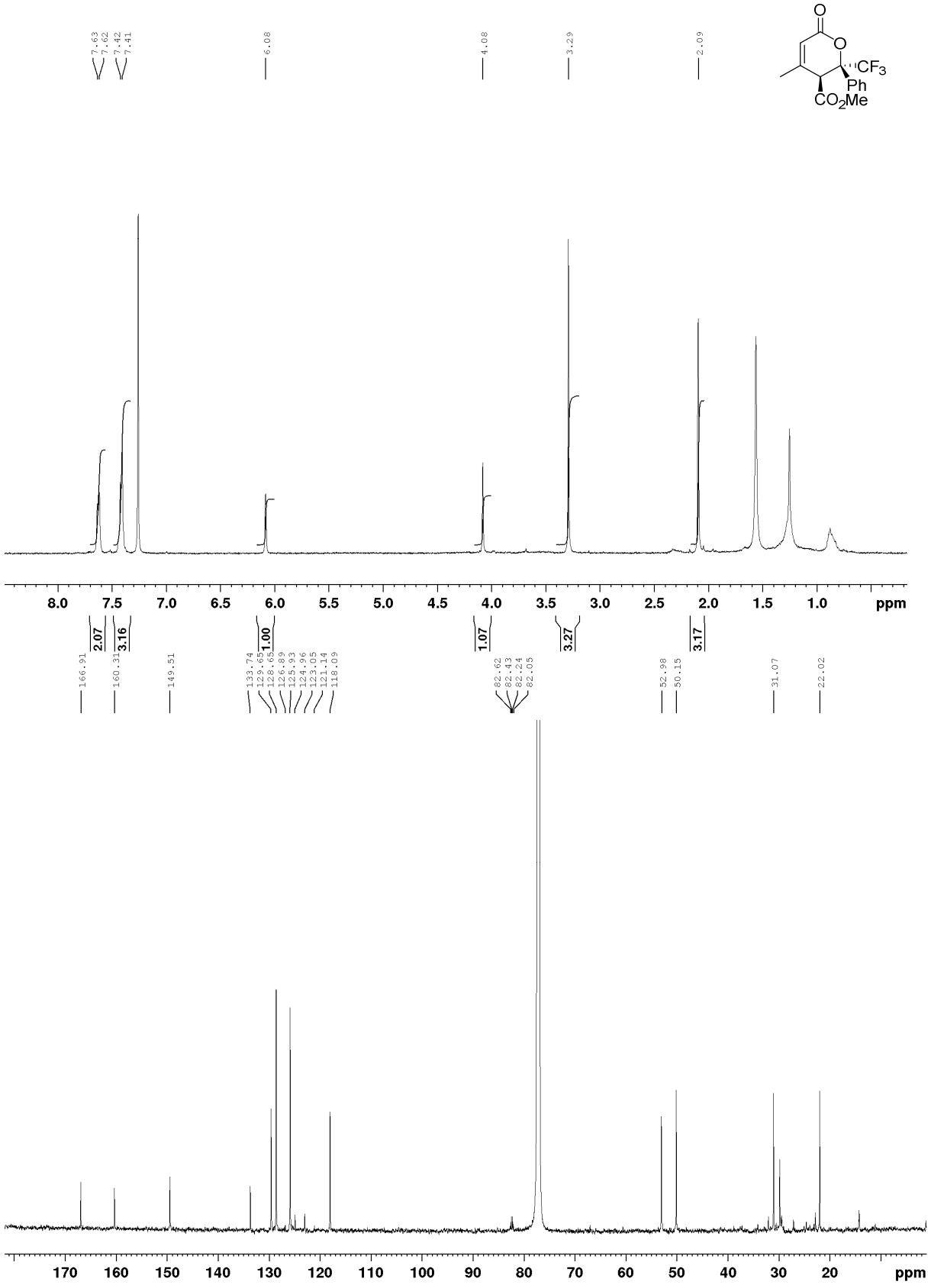

-76.48
-77.28
-50 -55 -60 -65 -70 -75 -80 -85 -90 -95 ppm

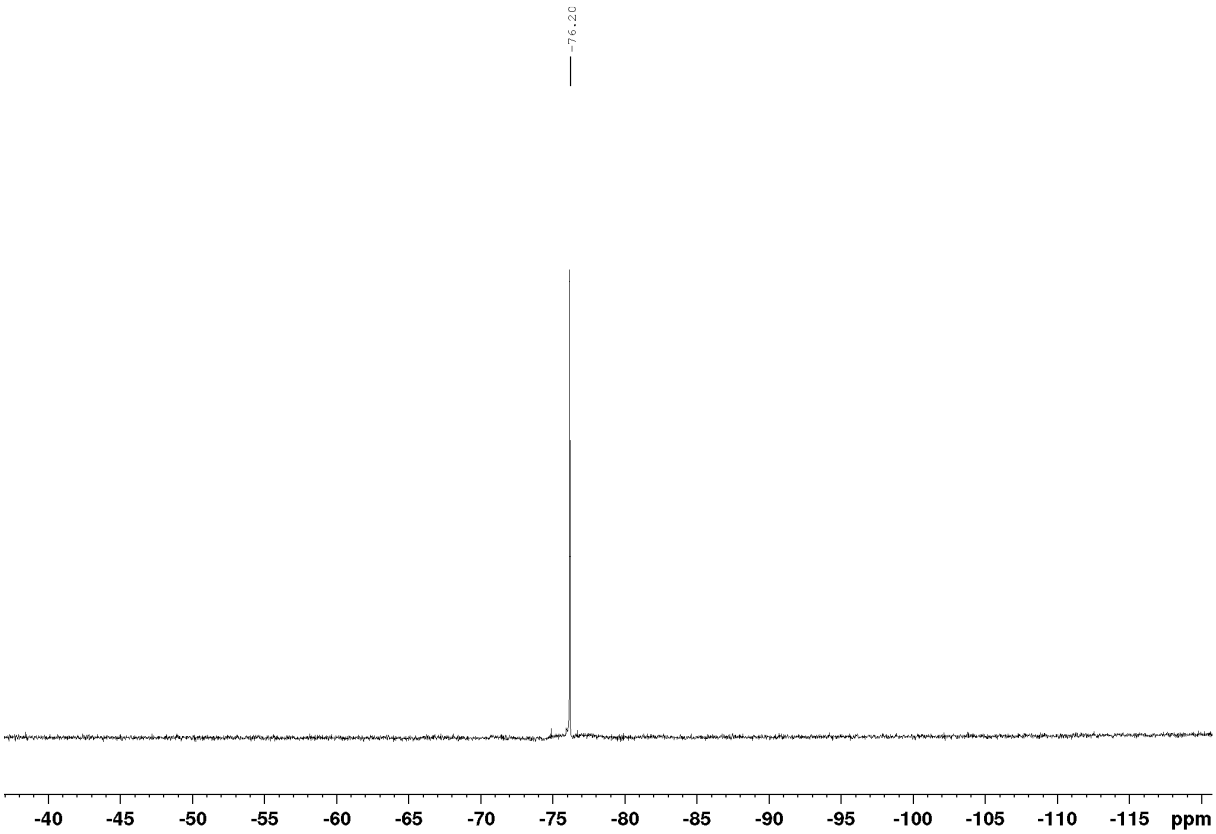
(2*R*,3*R*)-Methyl 4-methyl-6-oxo-2-phenyl-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate (***cis*-58c**).



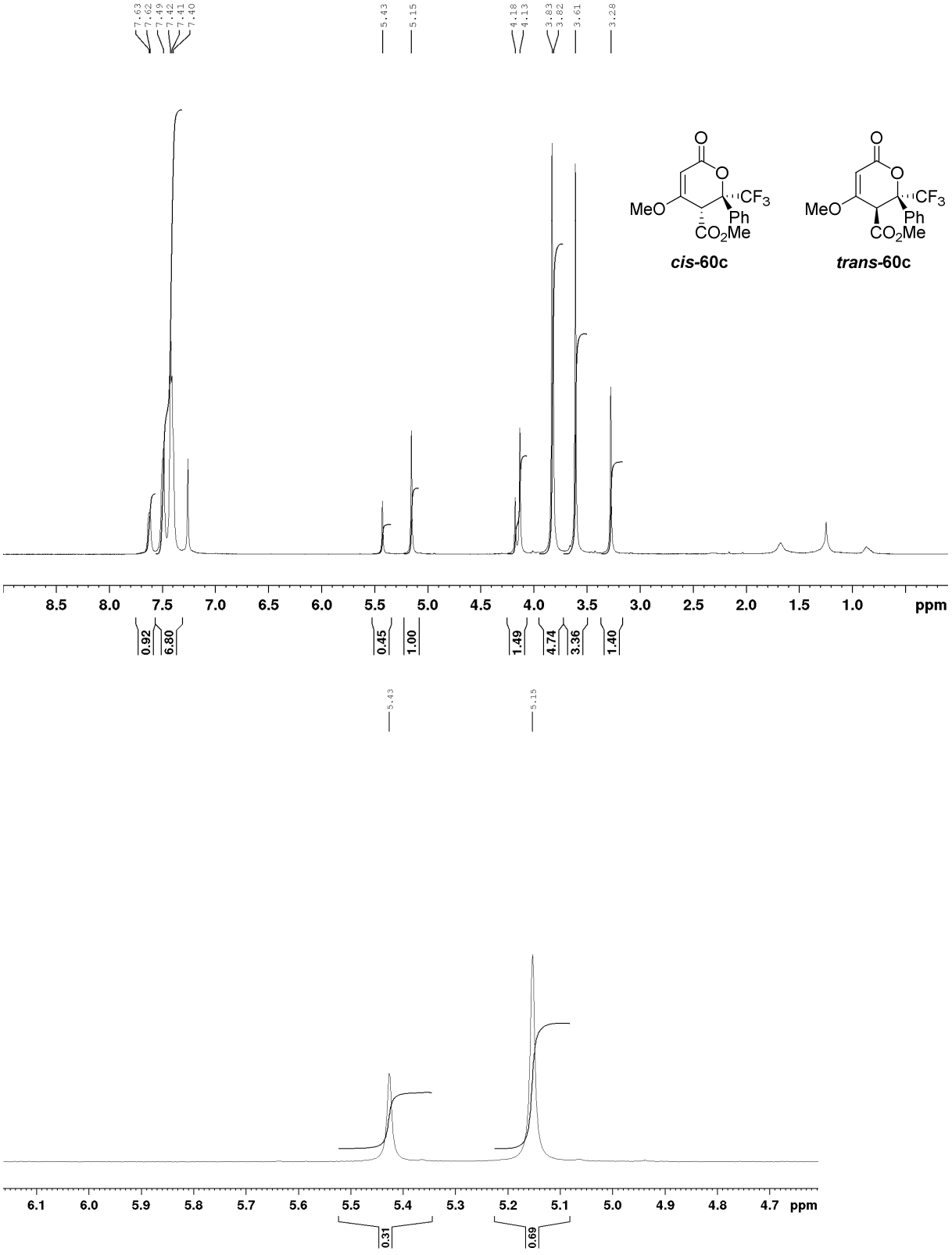

-77.25
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
ppm

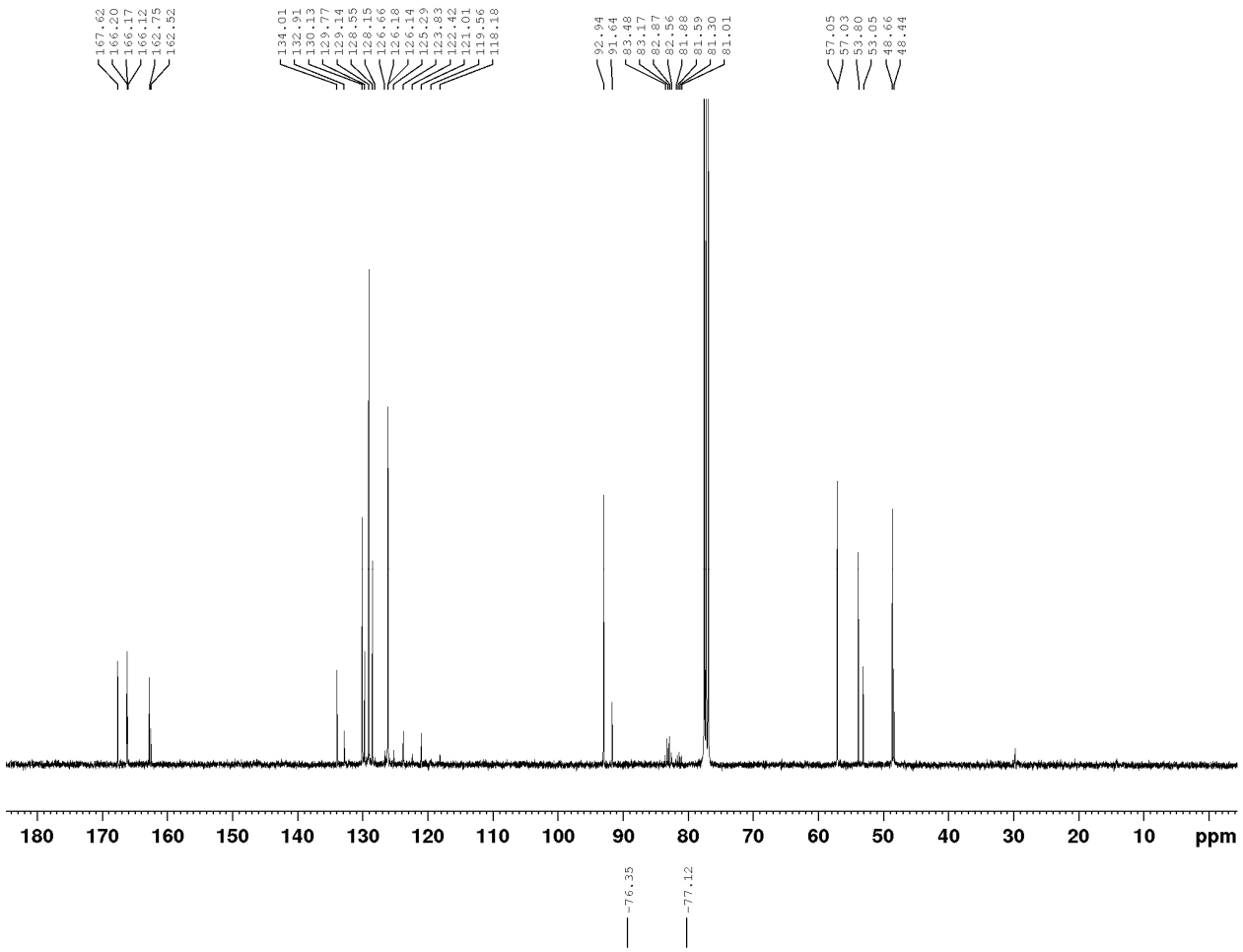
(2*R*,3*S*)-Methyl 4-methyl-6-oxo-2-phenyl-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate (*trans*-58c).

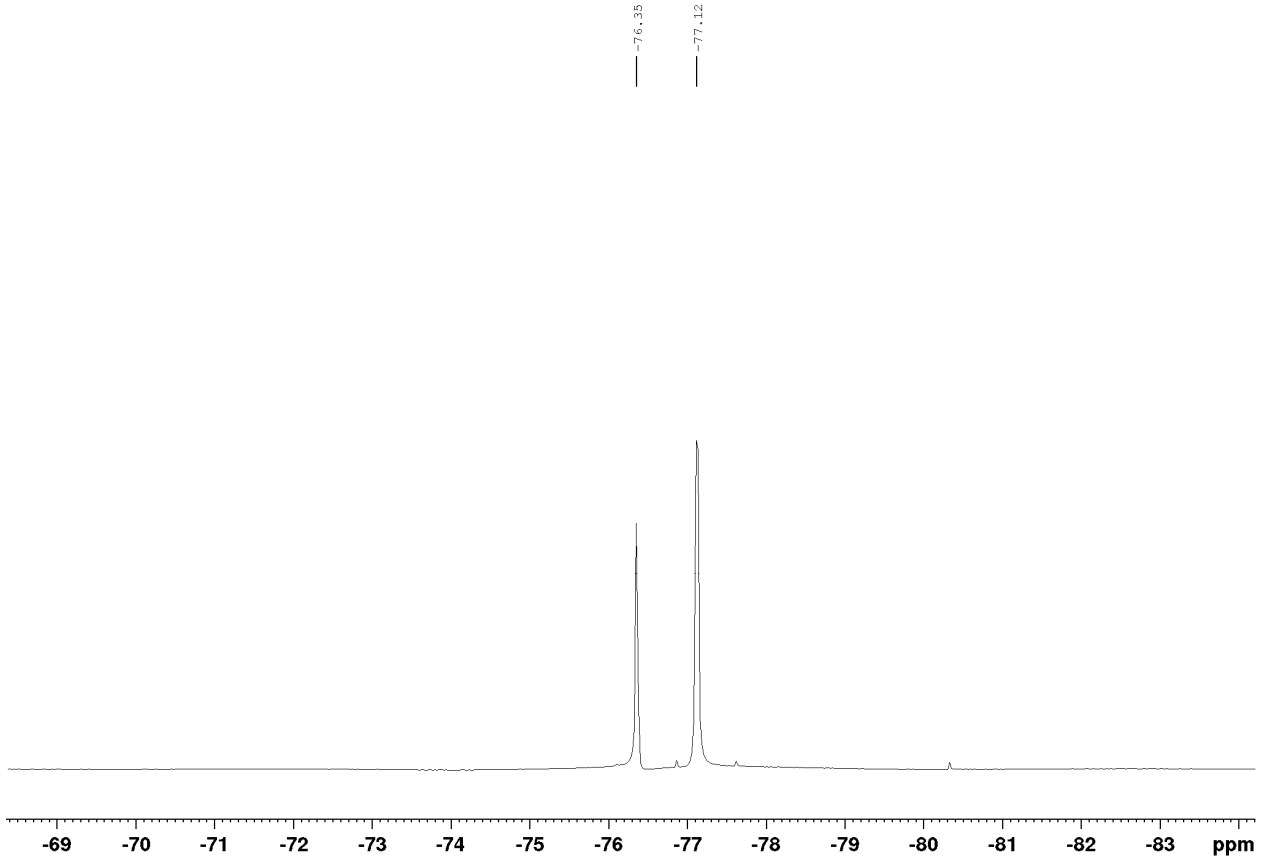


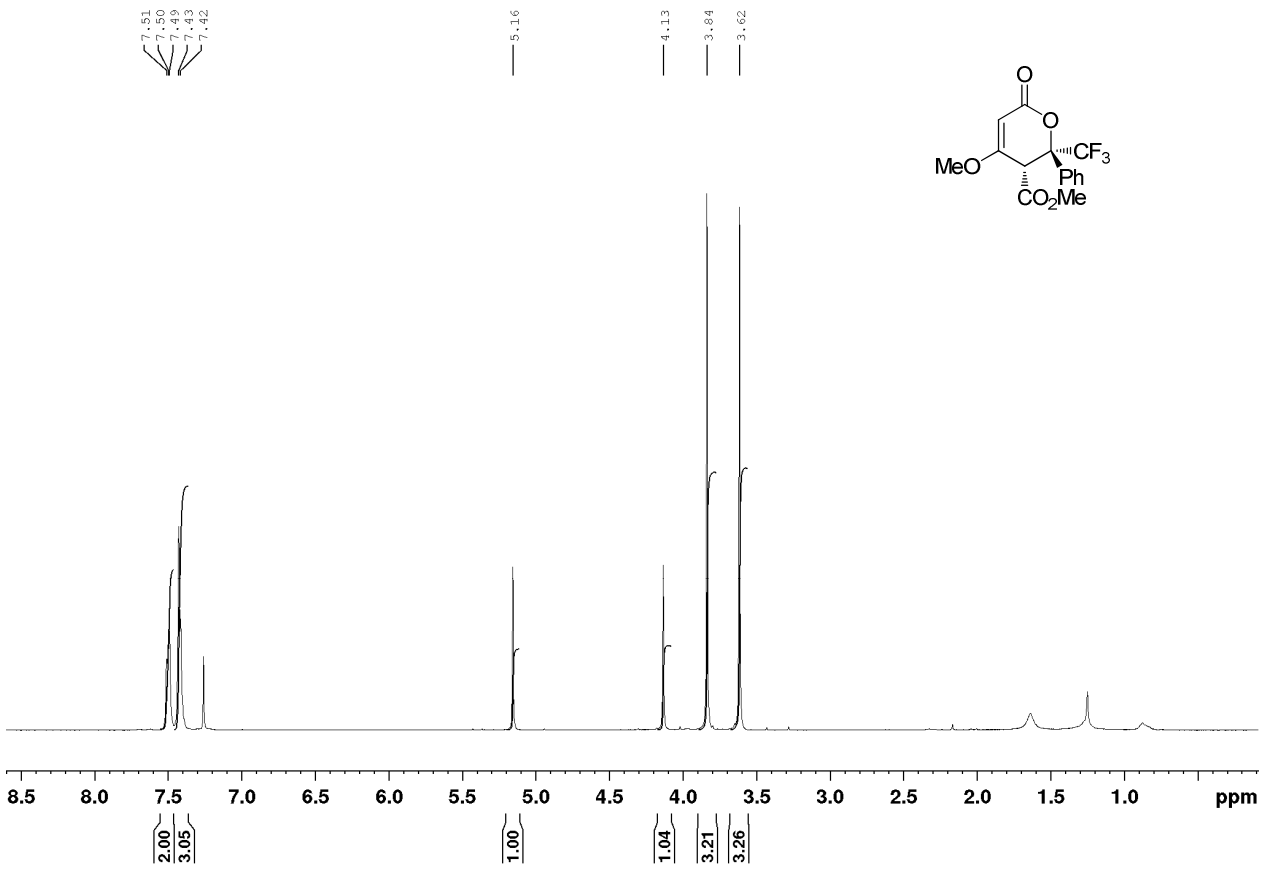

-76.20
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
ppm

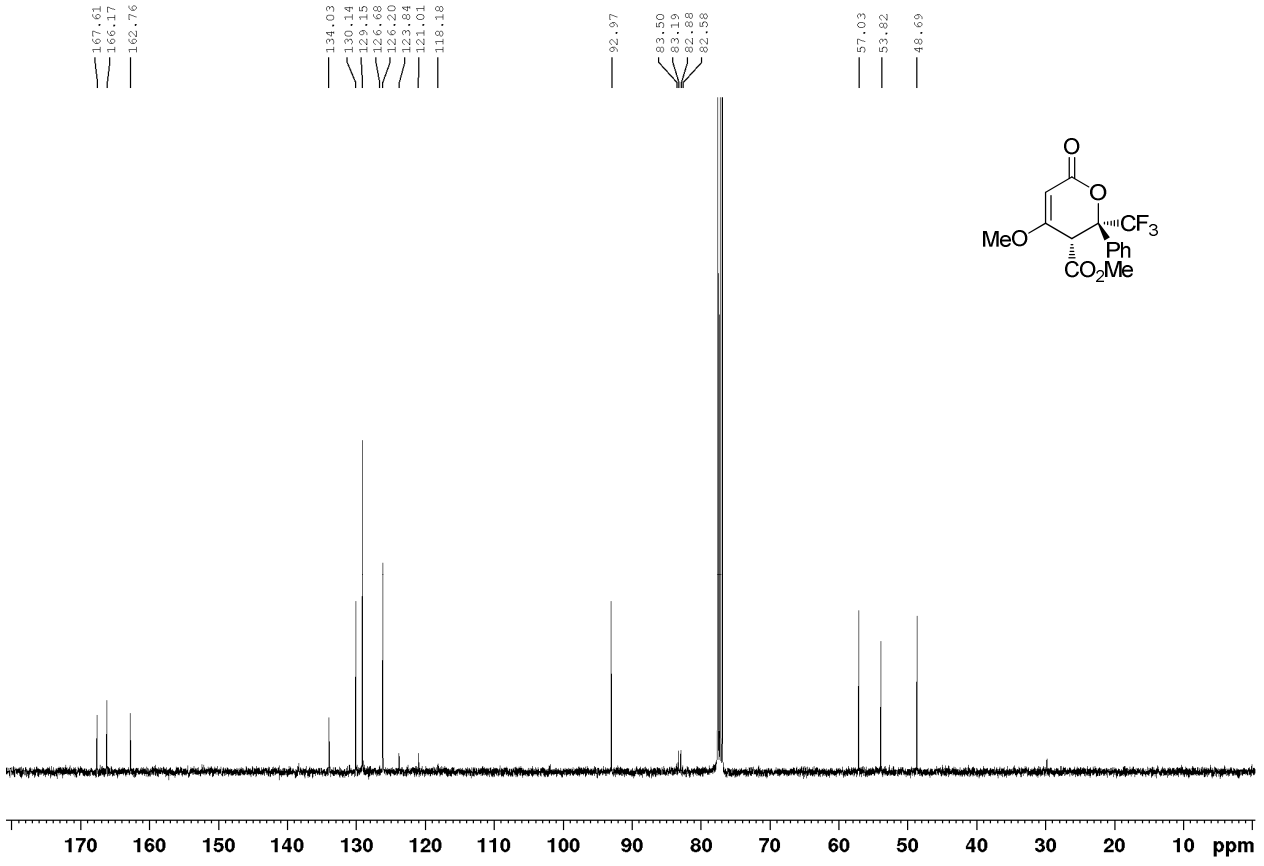
(2*R*,3*R*)-Methyl 4-methoxy-6-oxo-2-phenyl-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate & (2*R*,3*S*)-methyl 4-methoxy-6-oxo-2-phenyl-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate (***cis*-60c** and ***trans*-60c**)

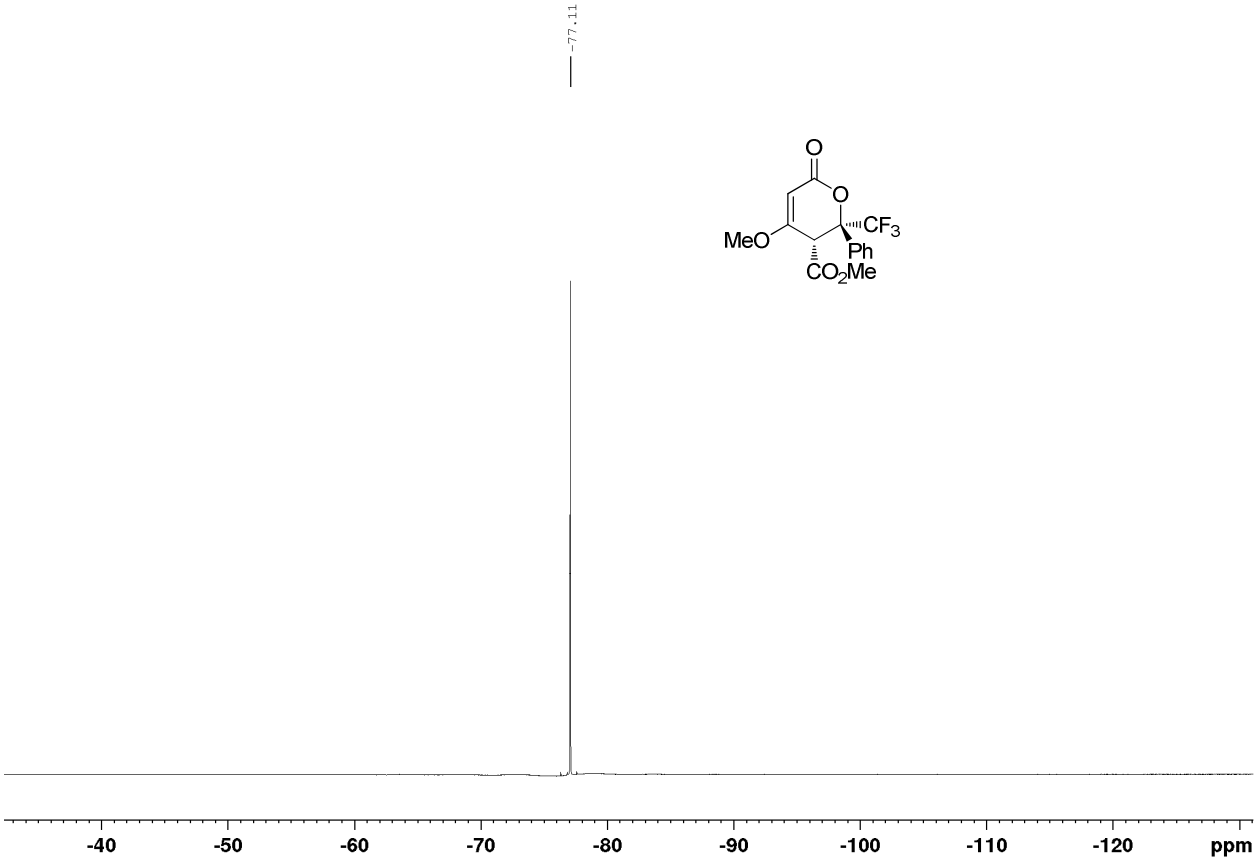



167.62
166.20
166.17
166.12
162.75
162.52
134.01
132.91
130.13
129.77
129.14
128.55
128.15
126.66
126.18
126.14
125.29
123.83
122.42
121.01
119.56
118.18
92.94
91.64
83.48
83.17
82.87
82.56
81.88
81.59
81.30
81.01
57.05
57.03
53.80
53.05
48.66
48.44
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


-76.35
-77.12
-69 -70 -71 -72 -73 -74 -75 -76 -77 -78 -79 -80 -81 -82 -83 ppm


7.51
7.50
7.49
7.43
7.42
5.16
4.13
3.84
3.62
O
O
CF3
MeO
Ph
CO2Me
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.00
3.05
1.00
1.04
3.21
3.26


167.61
166.17
162.76
134.03
130.14
129.15
126.68
126.20
123.84
121.01
118.18
92.97
83.50
83.19
82.88
82.58
57.03
53.82
48.69
O
O
CF3
MeO
Ph
CO2Me
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

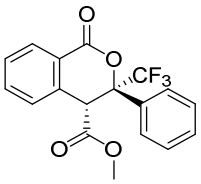

-77.11
O
O
CF3
MeO
Ph
CO2Me
-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm

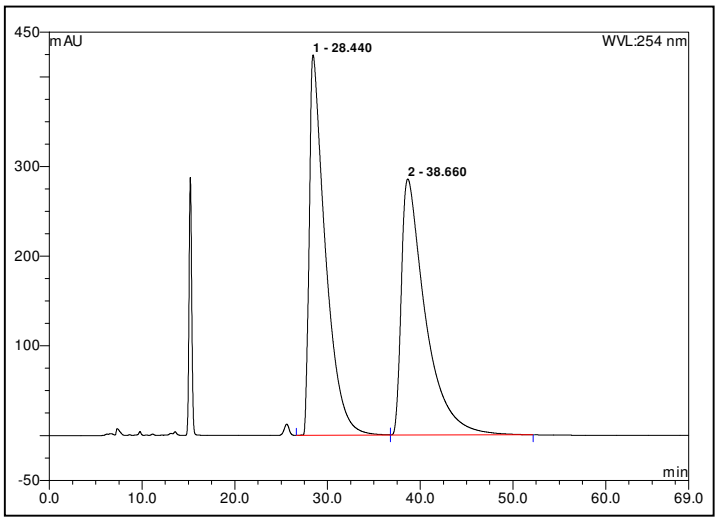
10.0 HPLC chromatograms

(3*R*,4*R*)-Methyl 1-oxo-3-phenyl-3-(trifluoromethyl)isochroman-4-carboxylate (***cis*-37**, Table 2, entry 1)

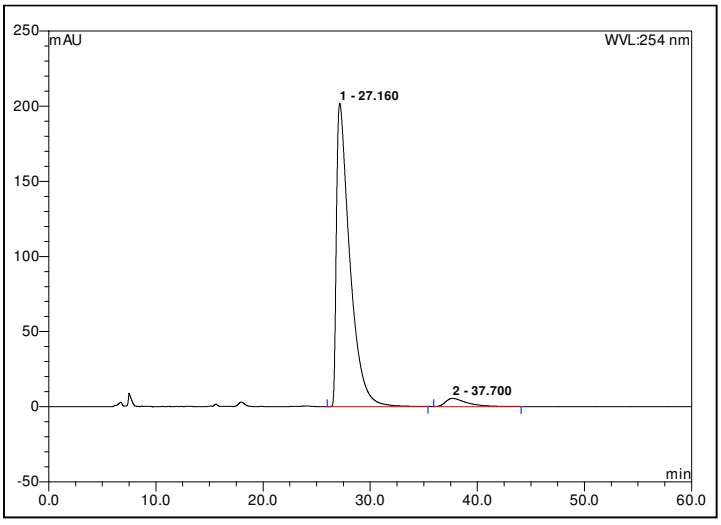
Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 85/15, 0.5 mL min^{-1}, RT, UV detection at 254 nm.

No.	Ret.Time min	Rel.Area %
1	28.4	50.0
2	38.7	50.0
Total:		100.00





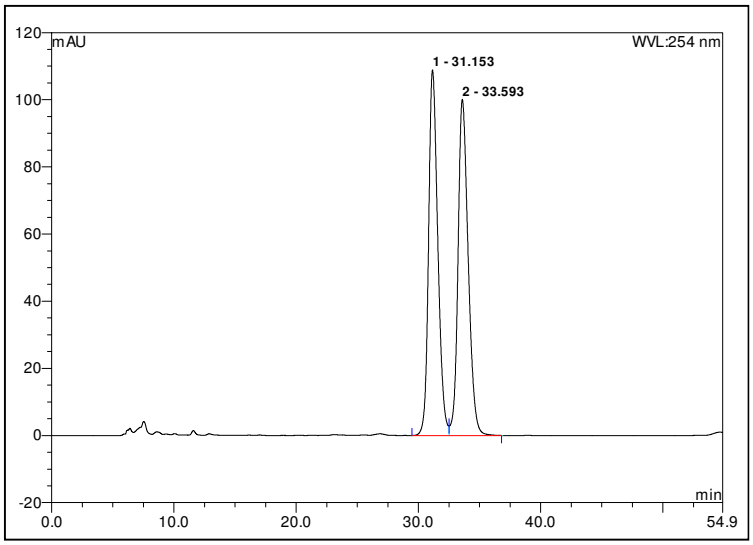
No.	Ret.Time min	Rel.Area %
1	27.2	95.9
2	37.7	4.1
Total:		100.00

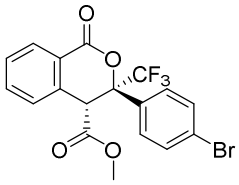


(3*R*,4*R*)-Methyl 3-(4-bromophenyl)-1-oxo-3-(trifluoromethyl)isochroman-4-carboxylate (***cis*-38**, Table 2, entry 2)

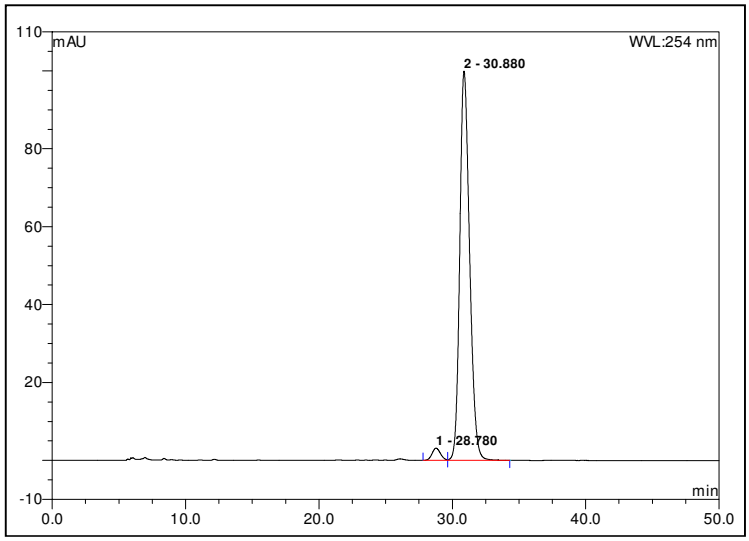
Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.5 mL min^{-1}, RT, UV detection at 254 nm.

No.	Ret.Time min	Rel.Area %
1	31.1	49.7
2	33.6	50.3
Total:		100.00





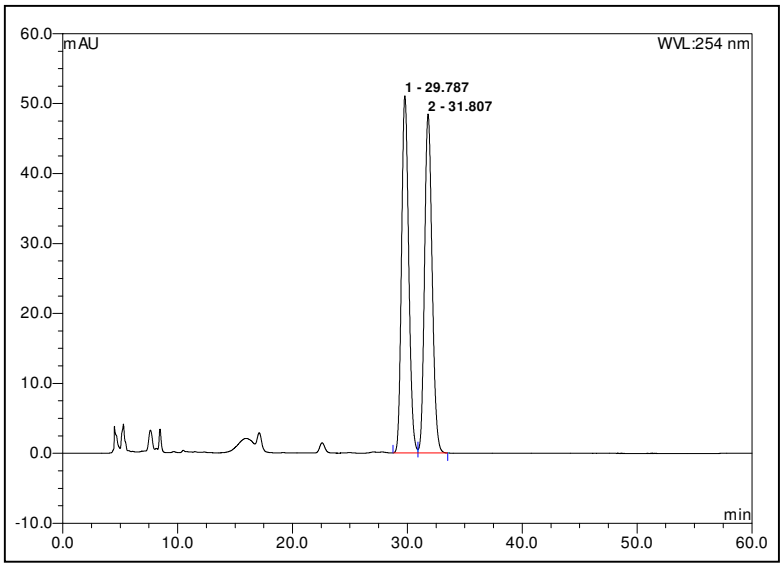
No.	Ret.Time min	Rel.Area %
1	28.8	2.6
2	30.9	97.4
Total:		100.00

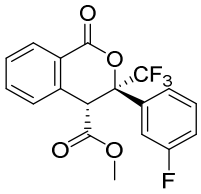


(3*R*,4*R*)-Methyl 3-(3-fluorophenyl)-1-oxo-3-(trifluoromethyl)isochroman-4-carboxylate (***cis*-39**, Table 2, entry 3)

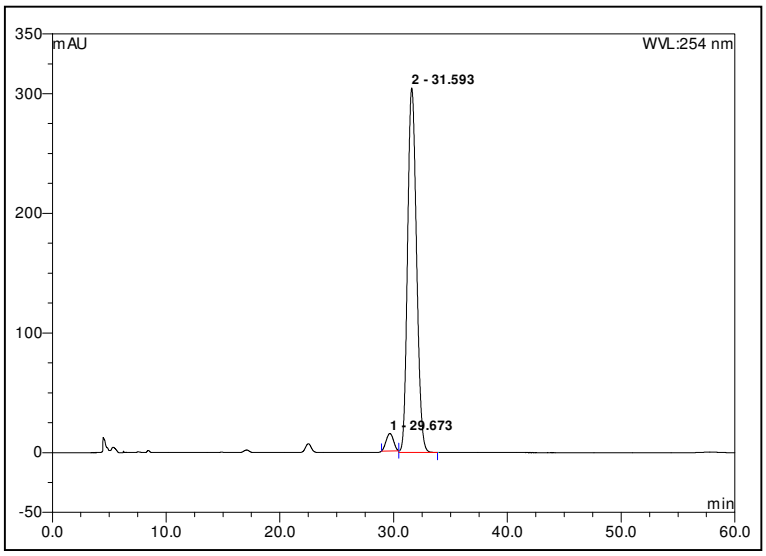
Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 98/2, 0.7 mL min^{-1}, RT, UV detection at 254 nm.

No.	Ret.Time Min	Rel.Area %
1	29.8	50.0
2	31.8	50.0
Total:		100.00





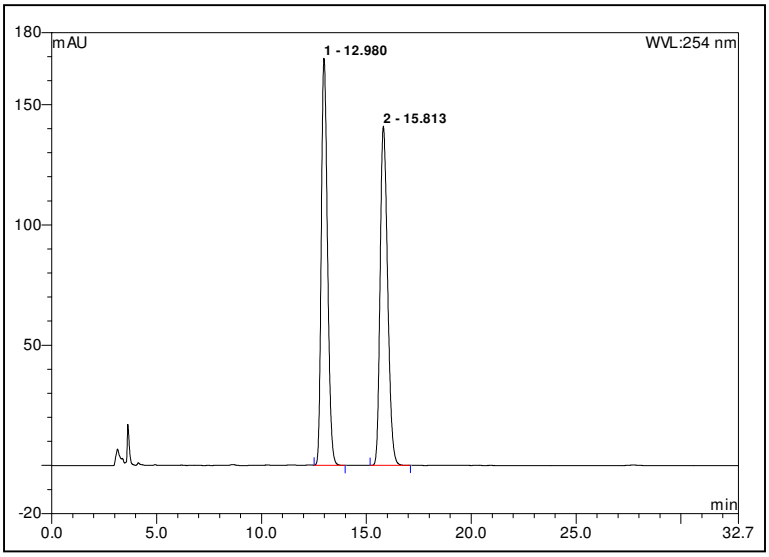
No.	Ret.Time min	Rel.Area %
1	29.7	3.8
2	31.6	96.2
Total:		100.00

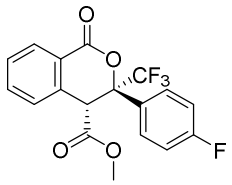


(3*R*,4*R*)-Methyl 3-(4-fluorophenyl)-1-oxo-3-(trifluoromethyl)isochroman-4-carboxylate (***cis*-40**, Table 2, entry 4)

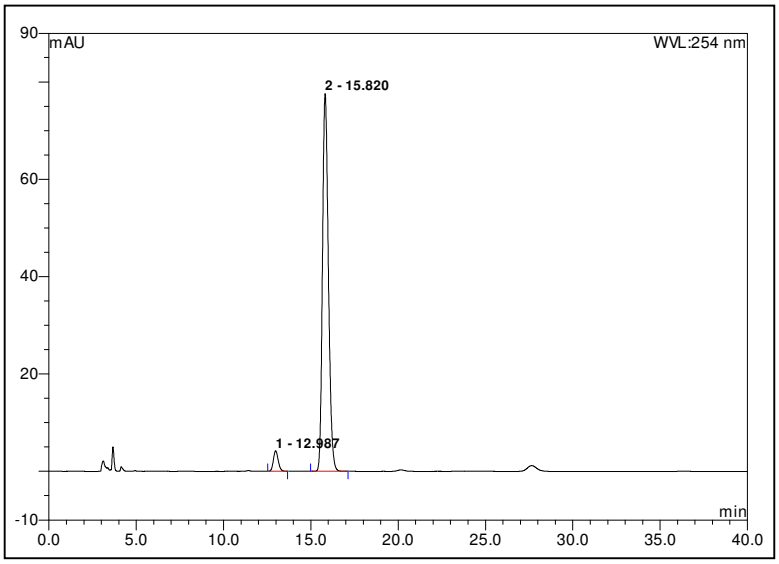
Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 1.0 mL min^{-1}, RT, UV detection at 254 nm.

No.	Ret.Time min	Rel.Area %
1	13.0	49.9
2	15.8	50.1
Total:		100.00





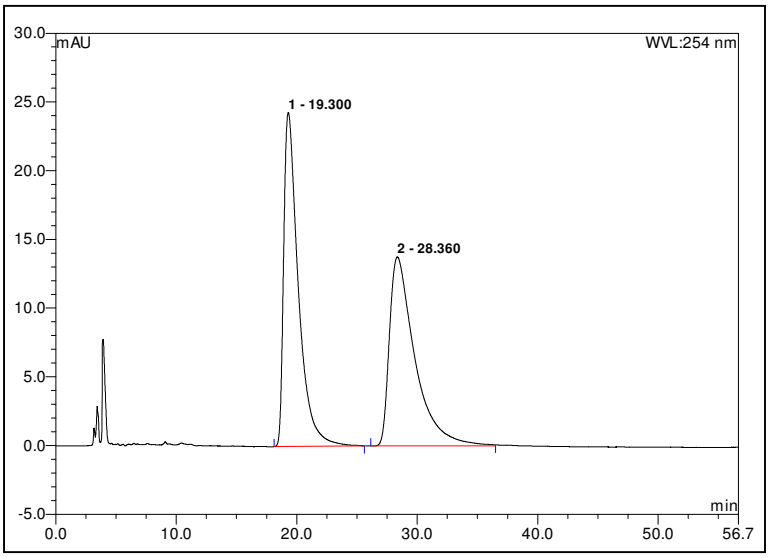
No.	Ret.Time min	Rel.Area %
1	13.0	4.2
2	15.8	95.8
Total:		100.00

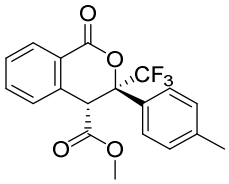


(3*R*,4*R*)-Methyl 1-oxo-3-p-tolyl-3-(trifluoromethyl)isochroman-4-carboxylate (***cis*-41**, Table 2, entry 5)

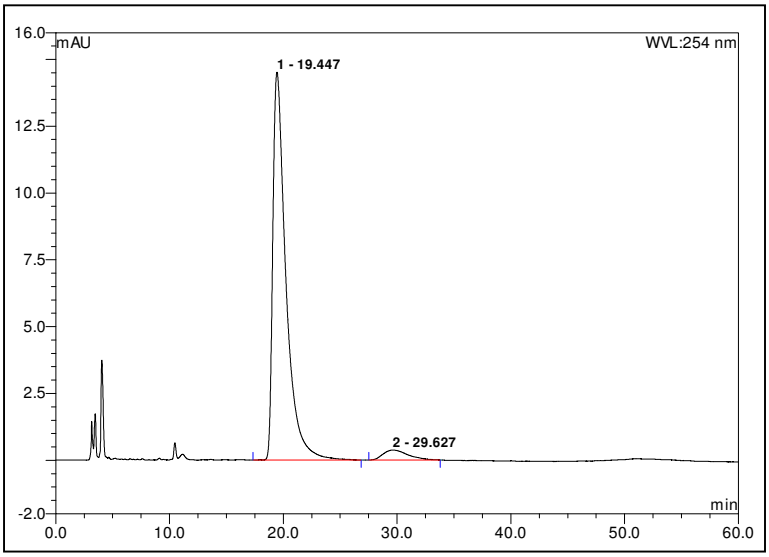
Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 1.0 mL min^{-1}, RT, UV detection at 254 nm.

No.	Ret.Time min	Rel.Area %
1	19.3	50.4
2	28.4	49.6
Total:		100.00





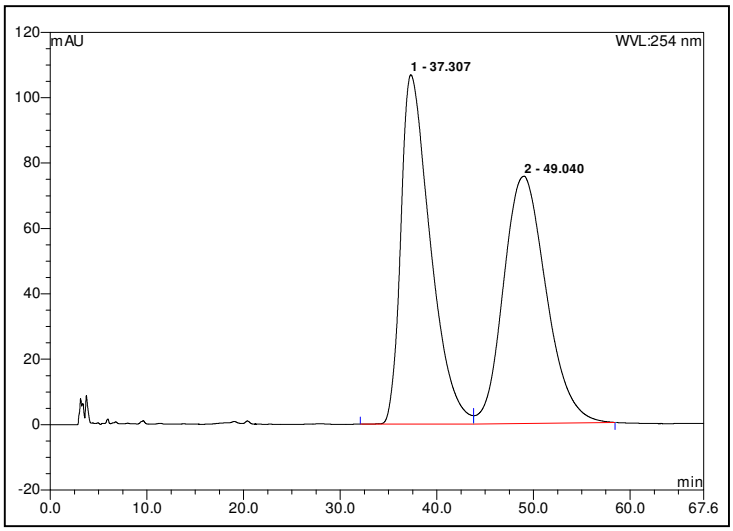
No.	Ret.Time min	Rel.Area %
1	19.4	95.4
2	29.6	4.6
Total:		100.00

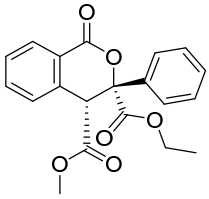


(3*R*,4*R*)-3-Ethyl 4-methyl 1-oxo-3-phenylisochroman-3,4-dicarboxylate (***cis*-43**, Table 3, entry 1)

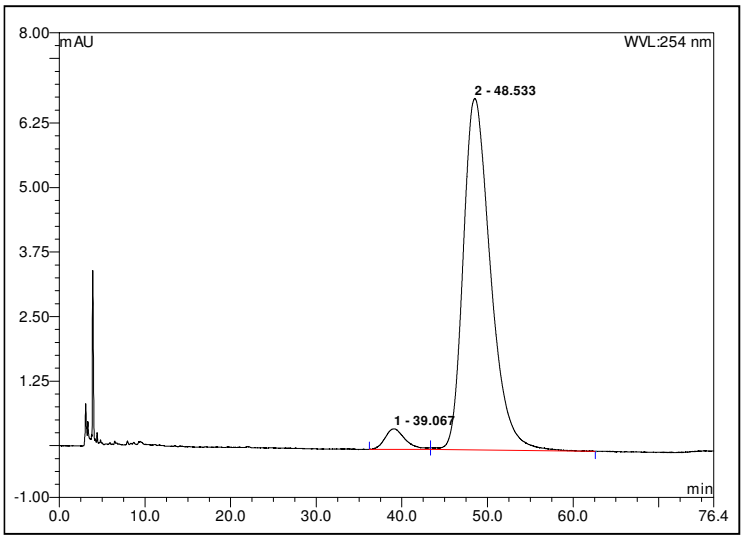
Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm

No.	Ret.Time min	Rel.Area %
1	37.3	49.4
2	49.0	50.6
Total:		100.00





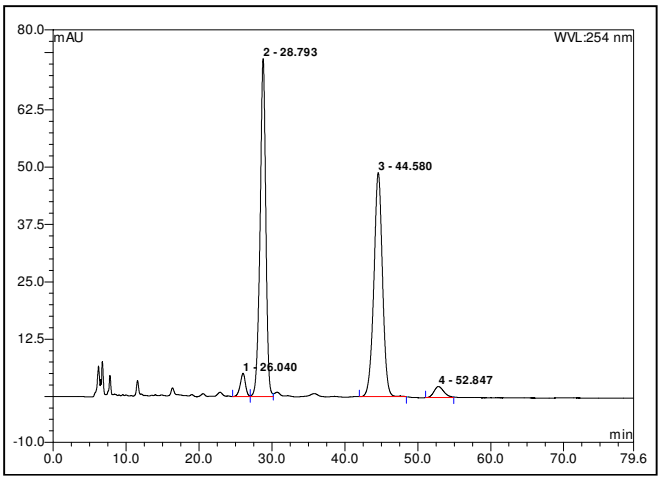
No.	Ret.Time min	Rel.Area %
1	39.1	4.1
2	48.5	95.9
Total:		100.00

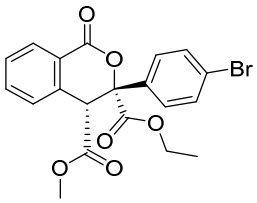


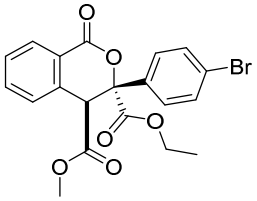
3-Ethyl 4-methyl 3-(4-bromophenyl)-1-oxoisochroman-3,4-dicarboxylate (***cis*-46** – ***trans*-46**, Table 3, entry 2)

Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm.

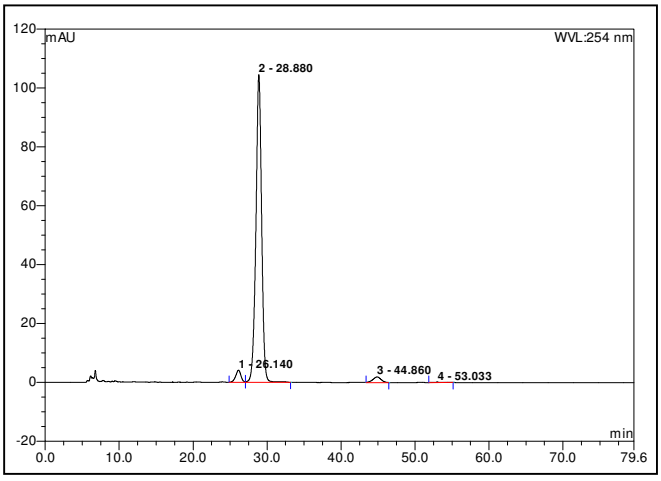
No.	Ret.Time min	Rel.Area %	Prod.
1	26.0	3.0	***trans*-46**
2	28.8	47.3	***cis*-46**
3	44.6	47.0	***cis*-60c**
4	52.9	2.7	***trans*-46**
Total:		100.00	







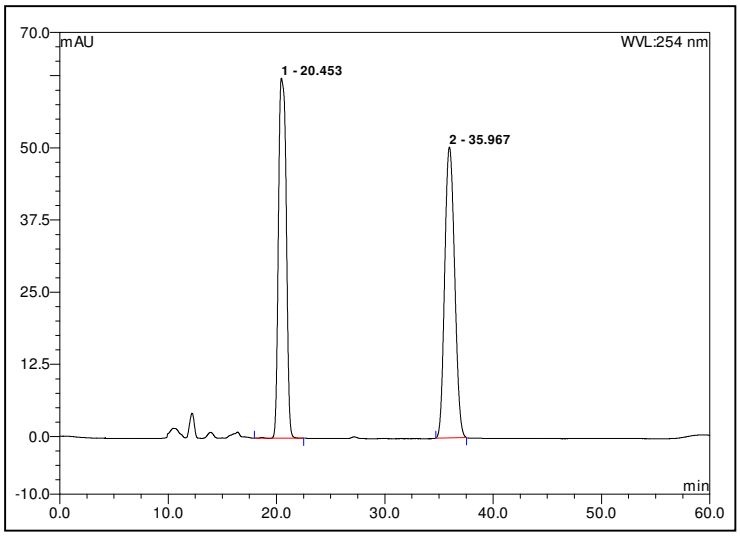
No.	Ret.Time min	Rel.Area %	Prod.
1	26.1	3.33	***trans*-46**
2	28.9	94.0	***cis*-46**
3	44.9	2.4	***cis*-60c**
4	53.0	0.16	***trans*-46**
Total:		100.00	

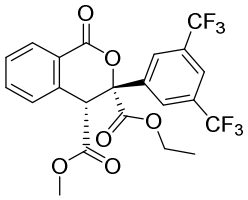


(3*R*,4*R*)-3-Ethyl 4-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-1-oxoisochroman-3,4-dicarboxylate (***cis*-47**, Table 3, entry 3)

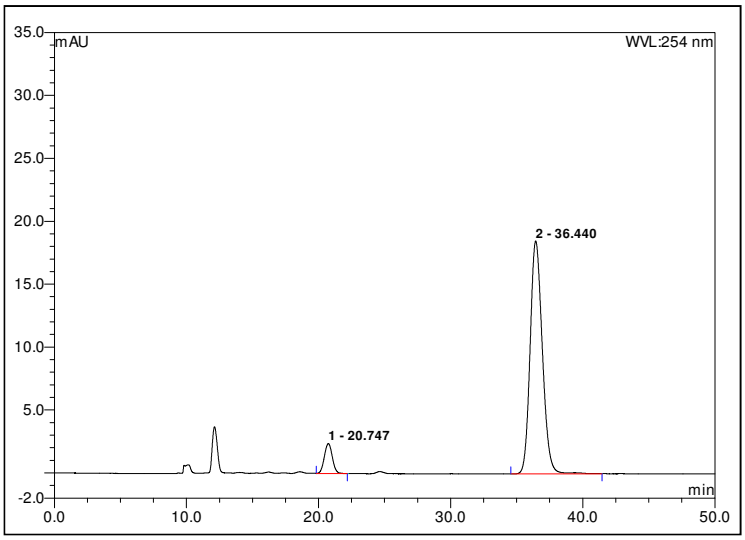
Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.3 mL min^{-1}, RT, UV detection at 254 nm.

No.	Ret.Time min	Rel.Area %
1	20.4	49.2
2	36.0	50.8
Total:		100.00





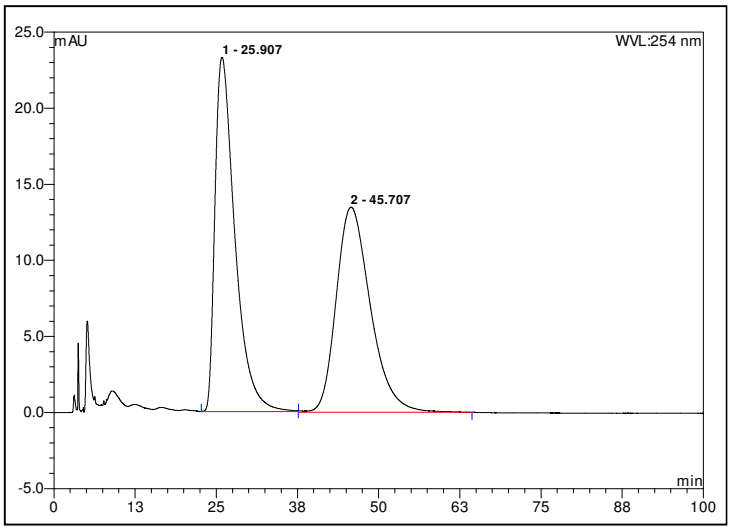
No.	Ret.Time min	Rel.Area %
1	20.7	7.6
2	36.4	92.4
Total:		100.00

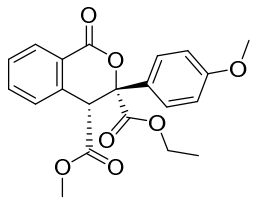


(3*R*,4*R*)-3-Ethyl 4-methyl 3-(4-methoxyphenyl)-1-oxoisochroman-3,4-dicarboxylate (***cis*-48**, Table 3, entry 4)

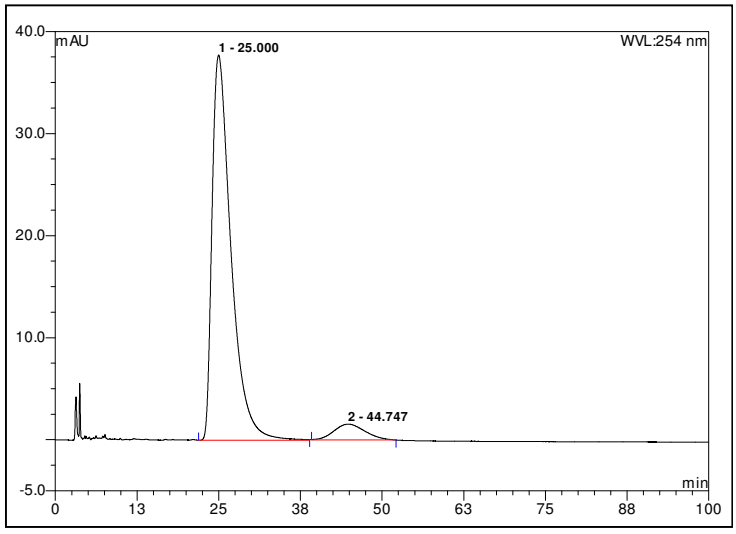
Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 80/20, 1.0 mL min^{-1}, RT, UV detection at 254 nm

No.	Ret.Time min	Rel.Area %
1	25.9	50.2
2	45.7	49.8
Total:		100.00





No.	Ret.Time min	Rel.Area %
1	25.0	93.6
2	44.7	6.4
Total:		100.00

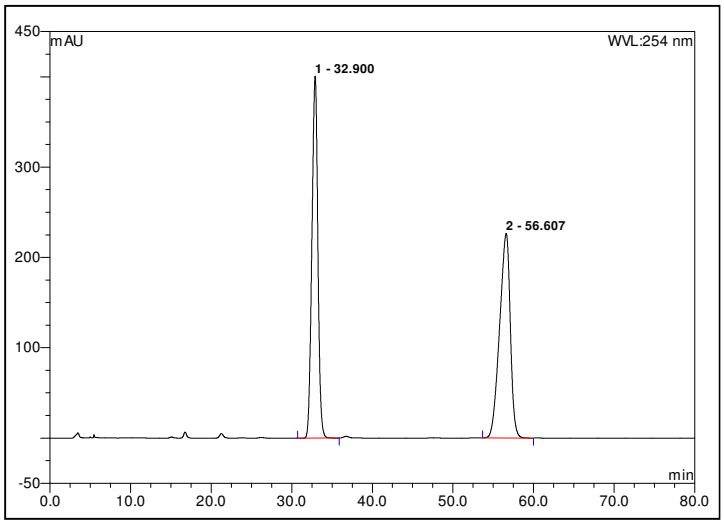


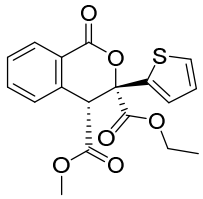
(3*S*,4*R*)-3-Ethyl 4-methyl 1-oxo-3-(thiophen-2-yl)isochroman-3,4-dicarboxylate (*trans*-49,

Table 3, entry 5)

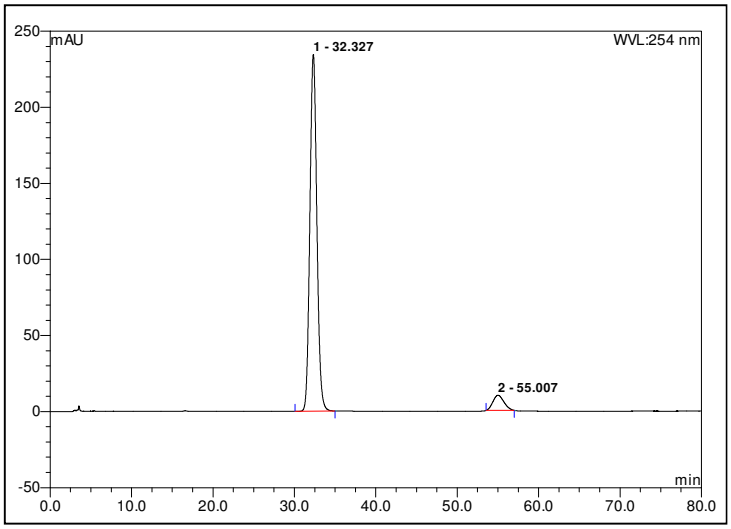
Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm

No.	Ret.Time min	Rel.Area %
1	32.9	49.7
2	56.6	50.3
Total:		100.00





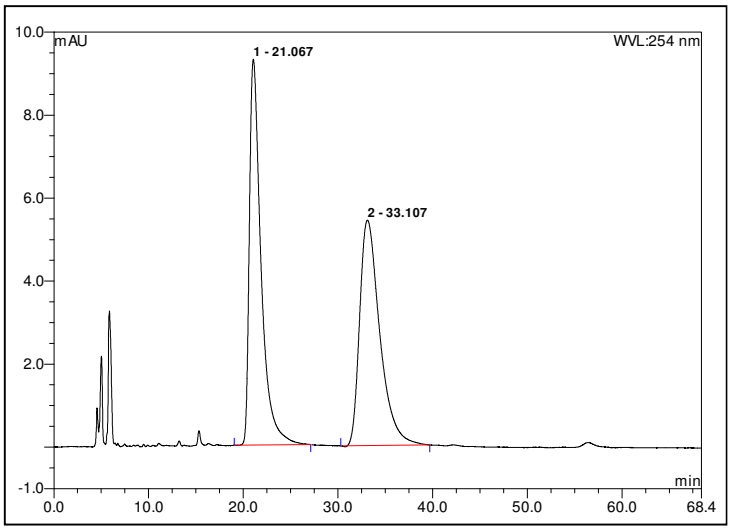
No.	Ret.Time min	Rel.Area %
1	32.3	93.8
2	55.0	6.2
Total:		100.00

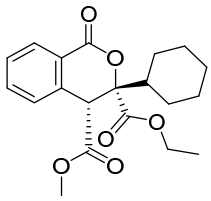


(3*S*,4*R*)-3-Ethyl 4-methyl 3-cyclohexyl-1-oxoisochroman-3,4-dicarboxylate (***cis*-50**, Table 3, entry 6)

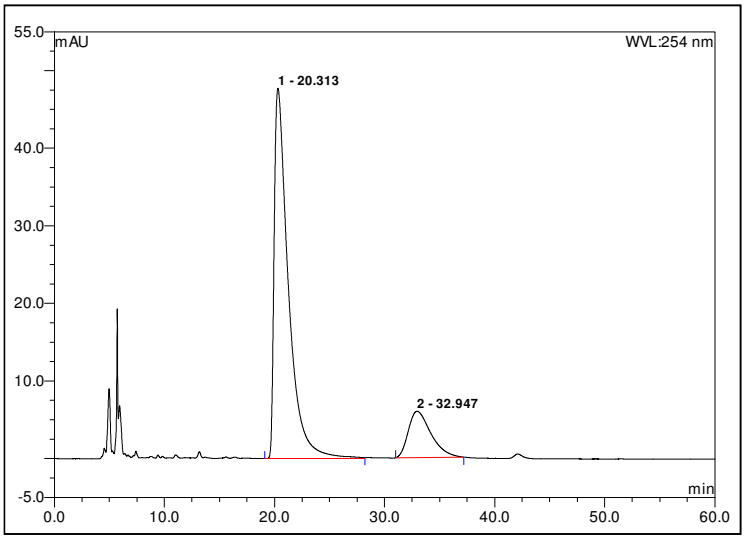
Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.7 mL min^{-1}, RT, UV detection at 254 nm

No.	Ret.Time min	Rel.Area %
1	21.1	49.9
2	33.1	50.1
Total:		100.00





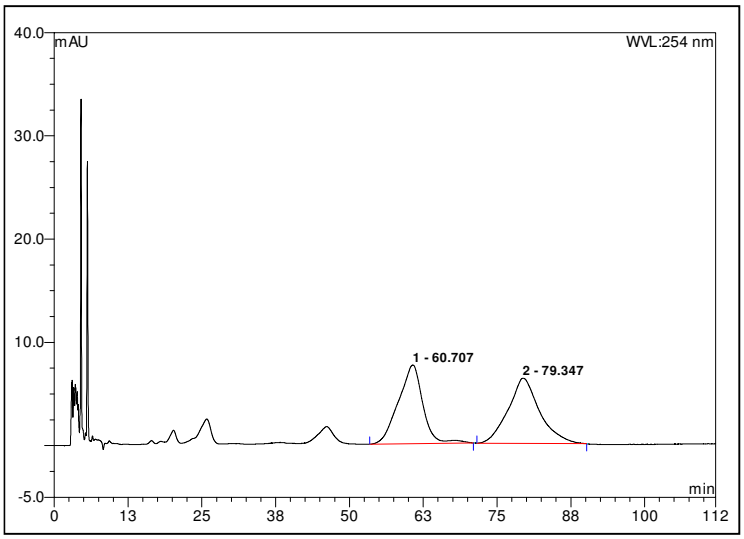
No.	Ret.Time min	Rel.Area %
1	20.3	83.4
2	32.9	16.6
Total:		100.00

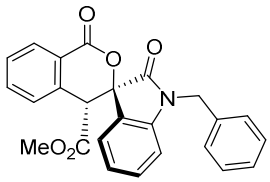


(3*R*,4'*R*)-Methyl 1-benzyl-1',2-dioxospiro[indoline-3,3'-isochroman]-4'-carboxylate (*cis*-52, Scheme 4)

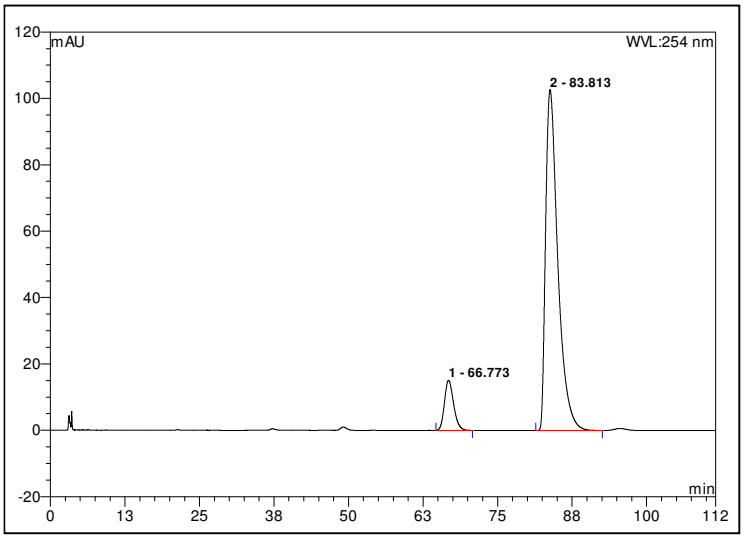
Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm.

No.	Ret.Time min	Rel.Area %
1	60.7	49.4
2	79.3	50.6
Total:		100.00





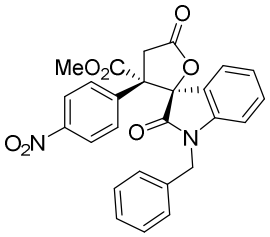
No.	Ret.Time min	Rel.Area %
1	66.8	9.9
2	83.8	90.1
Total:		100.00

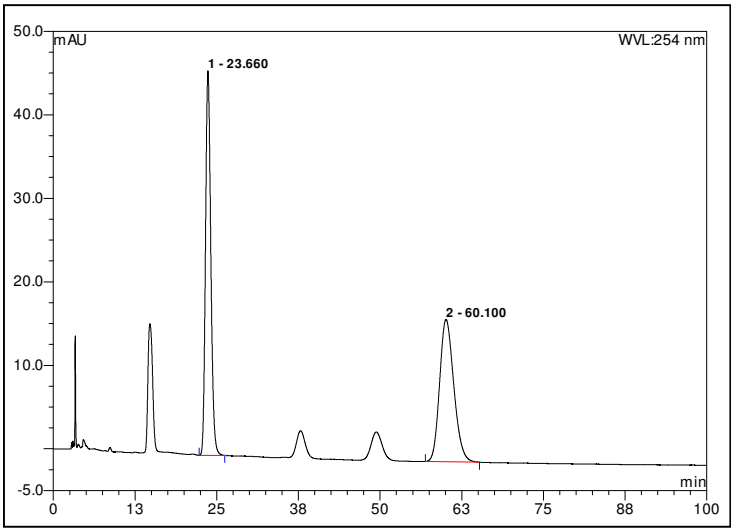


(2*R*,3*S*)-Methyl 1'-benzyl-3-(4-nitrophenyl)-2',5-dioxo-4,5-dihydro-3H-spiro[furan-2,3'-indoline]-3-carboxylate (*trans*-54, Scheme 4**)**

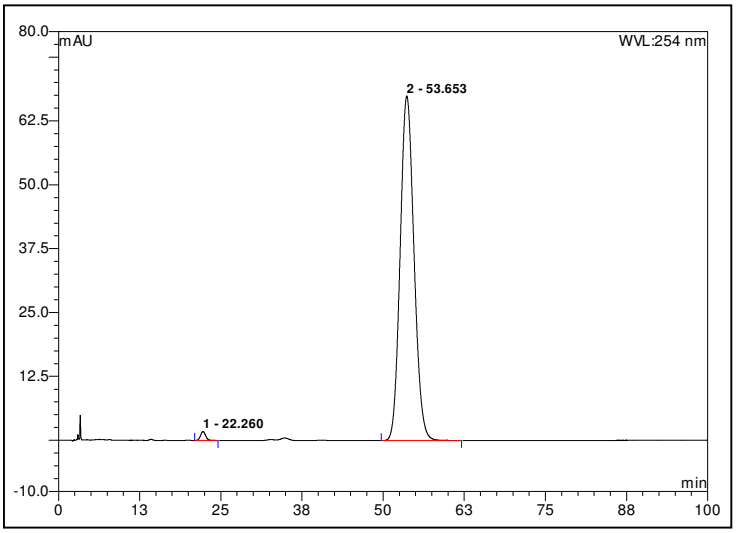
Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 75/25, 1.0 mL min^{-1}, RT, UV detection at 254 nm.

No.	Ret.Time min	Rel.Area %
1	23.7	50.3
2	60.1	49.7
Total:		100.00





No.	Ret.Time min	Rel.Area %
1	22.3	1.0
2	53.7	99.0
Total:		100.00

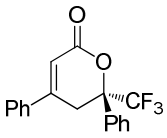


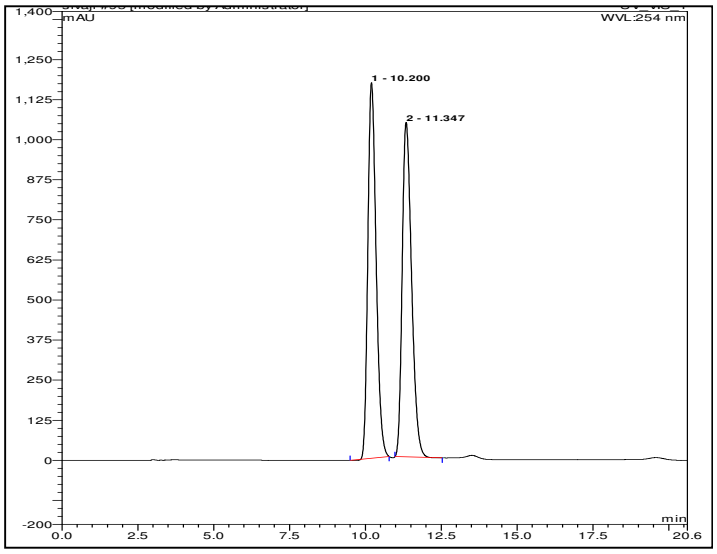
(*R*)-4,6-Diphenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (56a)

Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.75 mL min^{-1}, RT, UV detection at 254 nm.

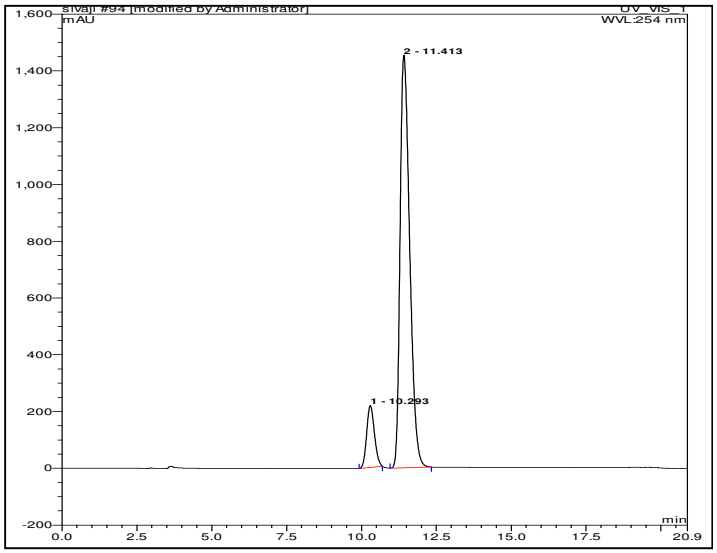
CSP-HPLC trace refers to 56a synthesised in 76% *ee* as decribed in Scheme 7

No.	Ret.Time min	Rel.Area %
1	10.3	50.3
2	11.3	49.7
Total:		100.00





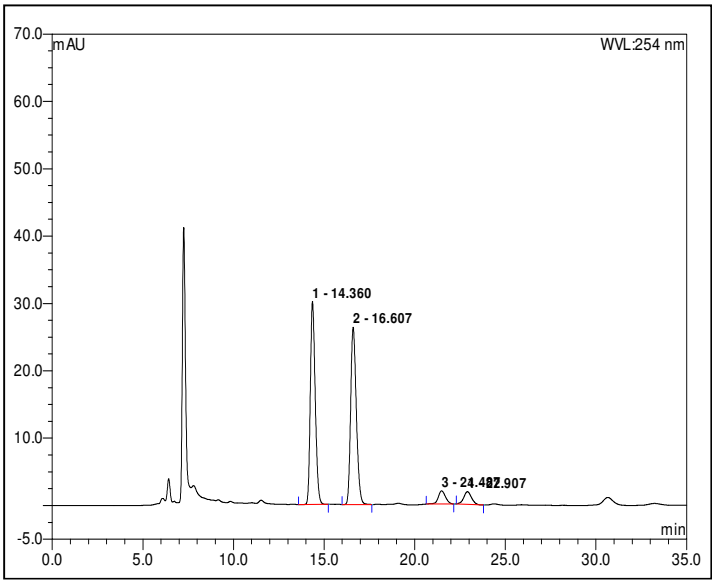
No.	Ret.Time min	Rel.Area %
1	10.3	11.82
2	11.4	88.18
Total:		100.00

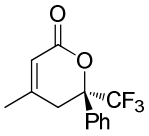


(*R*)-4-Methyl-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (**58a**, Scheme 5)

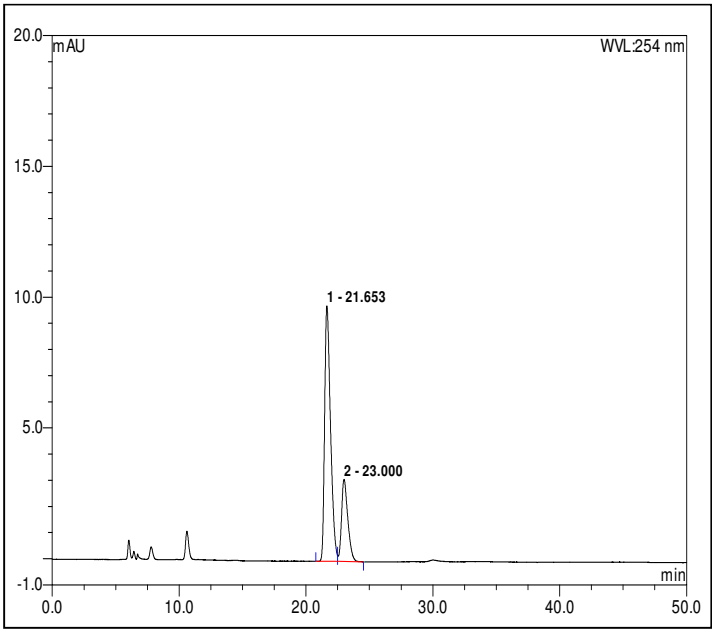
Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 98/2, 0.5 mL min^{-1}, RT, UV detection at 254 nm.

No.	Ret.Time Min	Rel.Area %
1	14.4	45.5
2	16.6	45.6
3	21.5	4.5
4	22.9	4.5
Total:		100.00





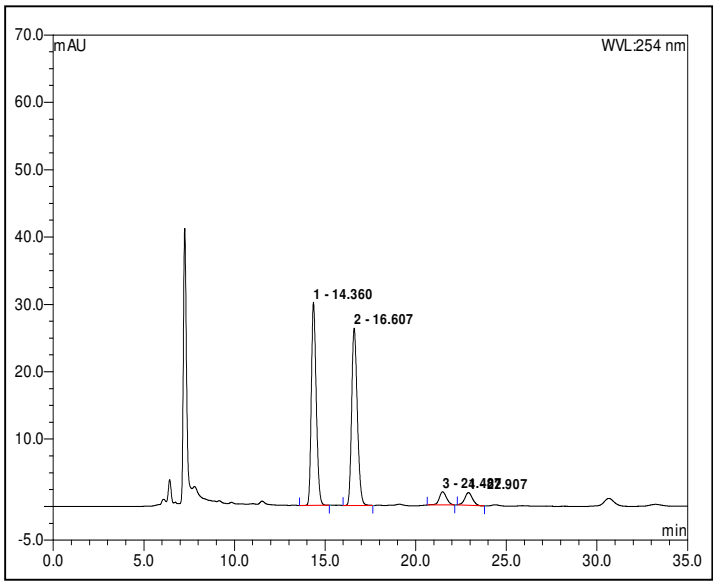
No.	Ret.Time Min	Rel.Area %
1	21.7	74.6
2	23.0	25.4
Total:		100.00

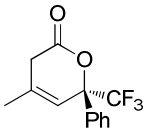


(*R*)-4-Methyl-6-phenyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-2-one (58b, Scheme 5)

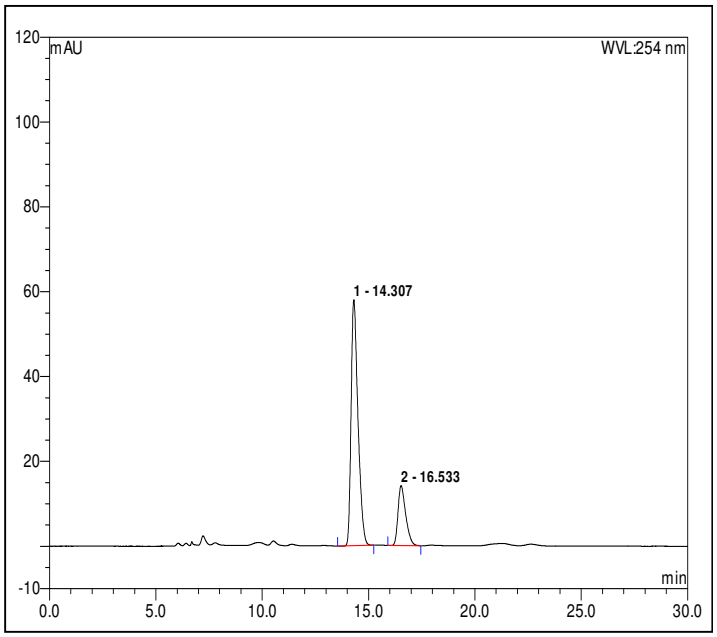
Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 98/2, 0.5 mL min^{-1}, RT, UV detection at 254 nm.

No.	Ret.Time min	Rel.Area %
1	14.4	45.5
2	16.6	45.6
3	21.5	4.5
4	22.9	4.5
Total:		100.00





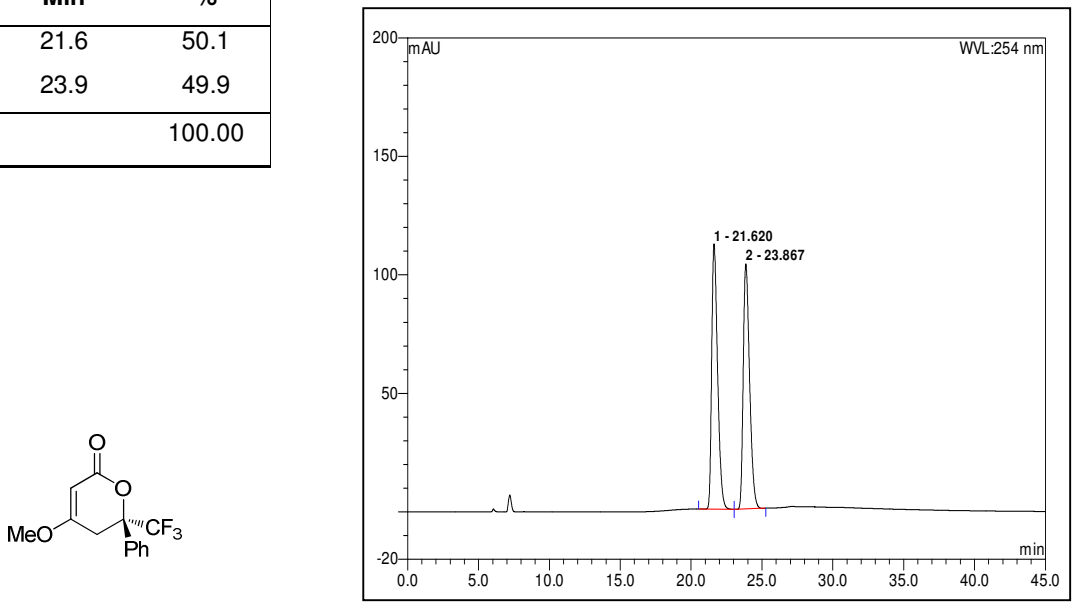
No.	Ret.Time min	Rel.Area %
1	14.3	78.7
2	16.5	21.3
Total:		100.00



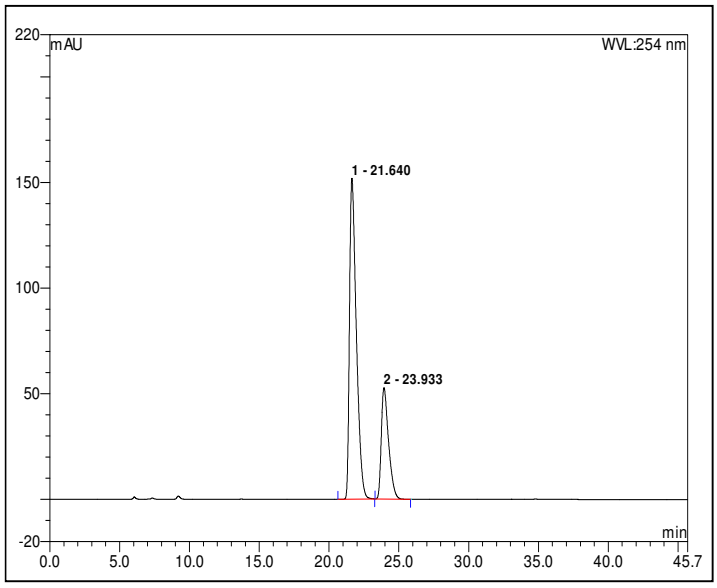
(*R*)-4-Methoxy-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (60a, Scheme 5)

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

No.	Ret.Time Min	Rel.Area %
1	21.6	50.1
2	23.9	49.9
Total:		100.00



No.	Ret.Time Min	Rel.Area %
1	21.6	73.1
2	23.9	26.9
Total:		100.00

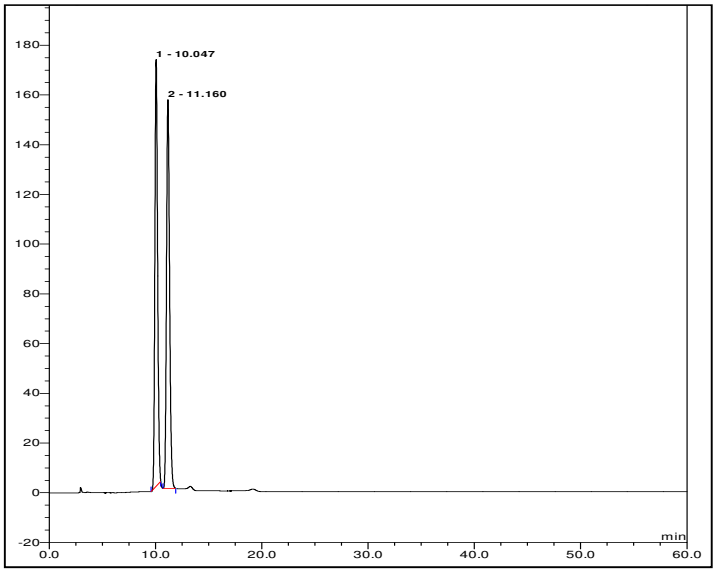


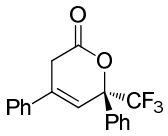
(*R*)-4,6-Diphenyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-2-one (56b)

Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm.

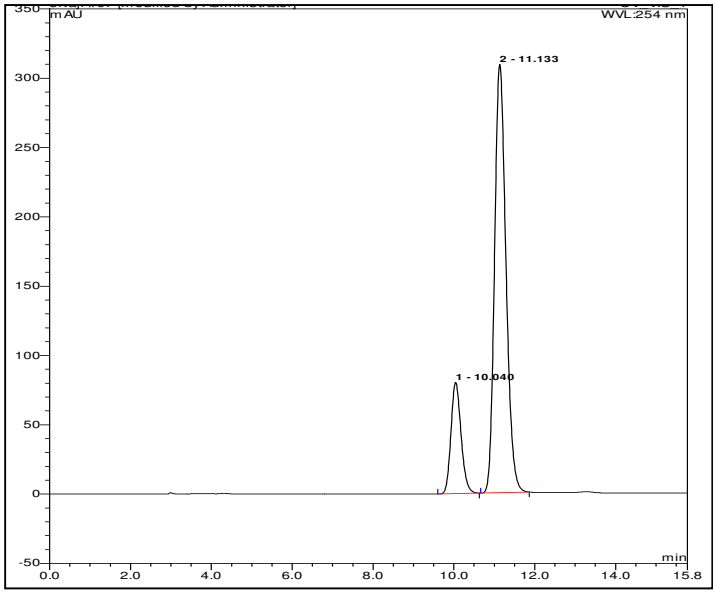
CSP-HPLC trace refers to 56b synthesised in 79% *ee* as decribed in Scheme 7

No.	Ret.Time min	Rel.Area %
1	10.0	52.1
2	11.2	47.9
Total:		100.00





No.	Ret.Time min	Rel.Area %
1	10.0	89.8
2	11.1	10.3
Total:		100.00

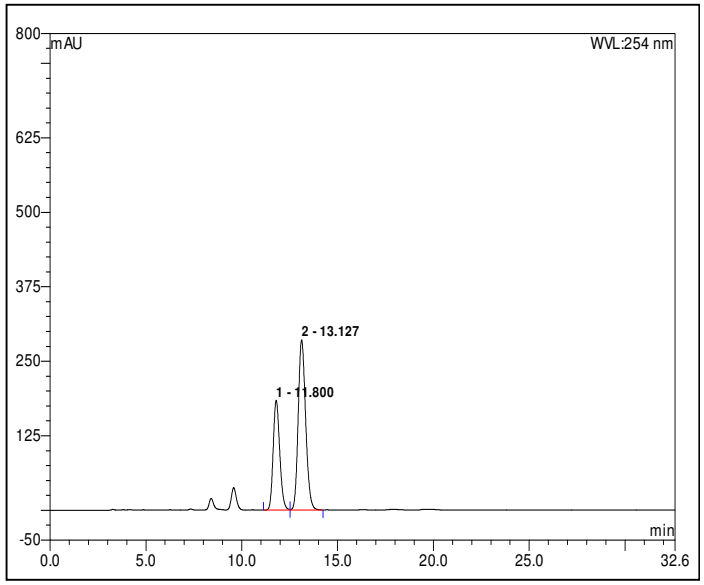


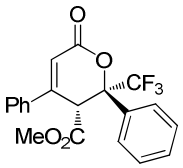
(2*R*,3*R*)-Methyl 6-oxo-2,4-diphenyl-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate

(***cis*-56c**, Table 4, entry 1)

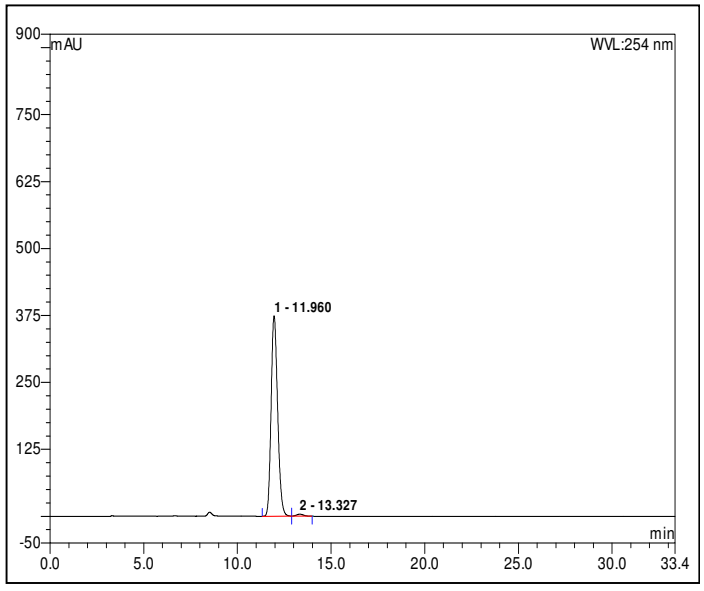
Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm.

No.	Ret.Time Min	Rel.Area %
1	11.8	36.3
2	13.1	63.7
Total:		100.00





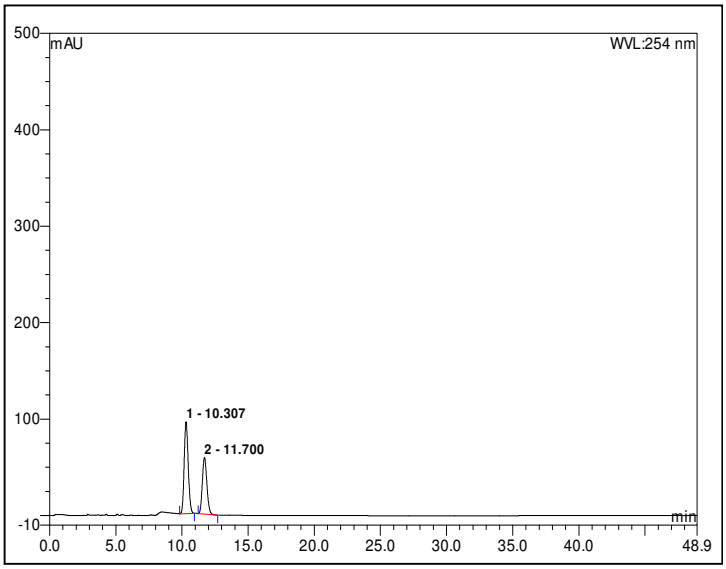
No.	Ret.Time min	Rel.Area %
1	12.0	99.0
2	13.3	1.0
Total:		100.00

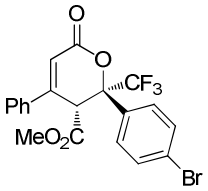


(2*R*,3*R*)-Methyl-2-(4-bromophenyl)-2-(trifluoromethyl)-3,6-dihydro-6-oxo-4-phenyl-2*H*-pyran-3-carboxylate (***cis*-61**, Table 4, entry 2)

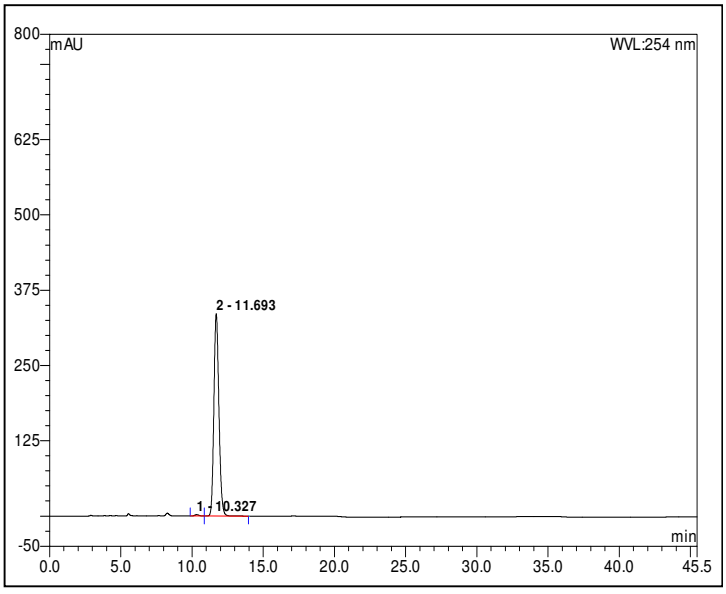
Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm.

No.	Ret.Time min	Rel.Area %
1	10.3	59.0
2	11.7	41.0
Total:		100.00





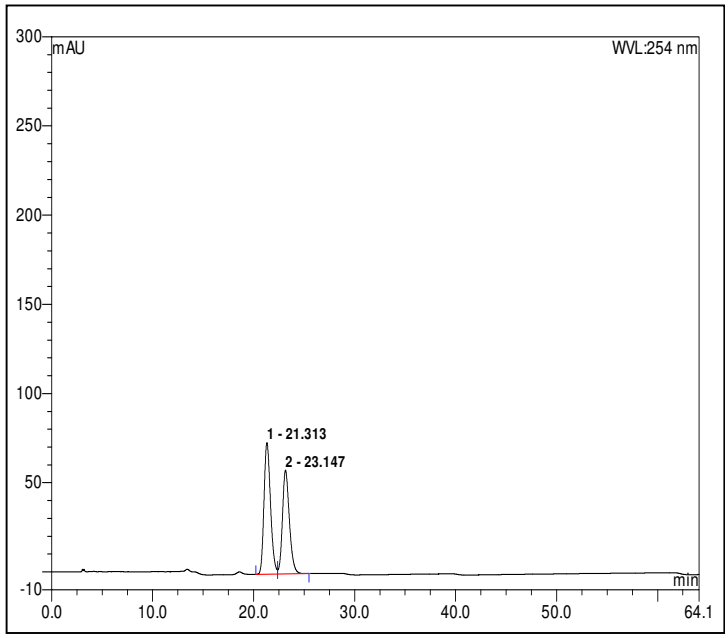
No.	Ret.Time min	Rel.Area %
1	10.3	0.5
2	11.7	99.5
Total:		100.00

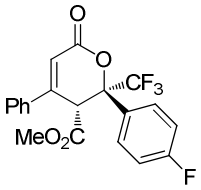


(2*R*,3*R*)-Methyl-2-(trifluoromethyl)-2-(4-fluorophenyl)-3,6-dihydro-6-oxo-4-phenyl-2*H*-pyran-3-carboxylate (***cis*-62**, Table 4, entry 3)

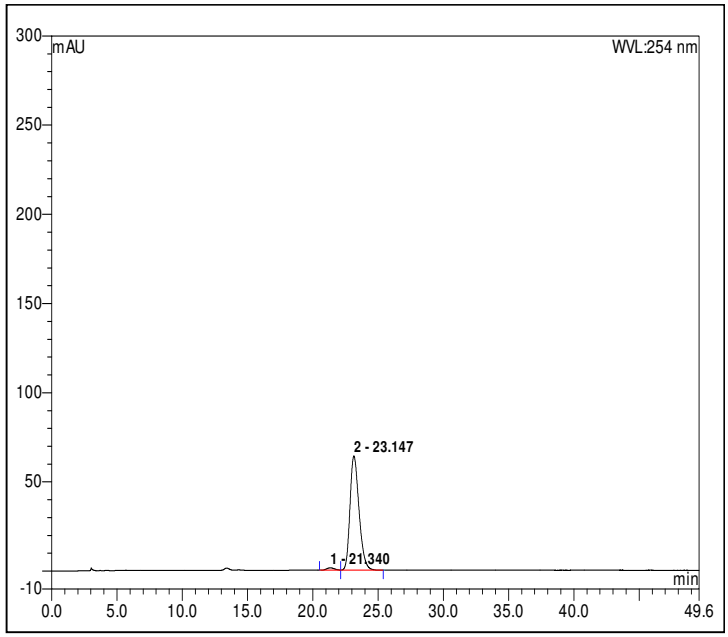
Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 97/3, 1.0 mL min^{-1}, RT, UV detection at 254 nm.

No.	Ret.Time min	Rel.Area %
1	21.3	54.3
2	23.2	45.7
Total:		100.00





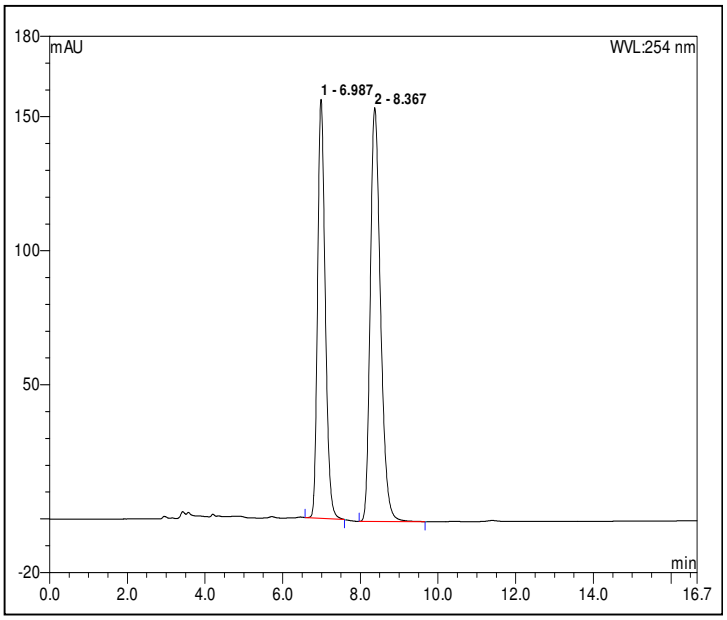
No.	Ret.Time min	Rel.Area %
1	21.3	1.9
2	23.2	98.1
Total:		100.00

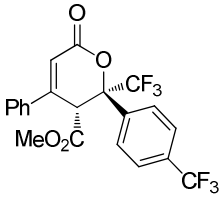


(2*R*,3*R*)-Methyl-2-(trifluoromethyl)-2-(4-(trifluoromethyl)phenyl)-3,6-dihydro-6-oxo-4-phenyl-2*H*-pyran-3-carboxylate (***cis*-63**, Table 4, entry 4)

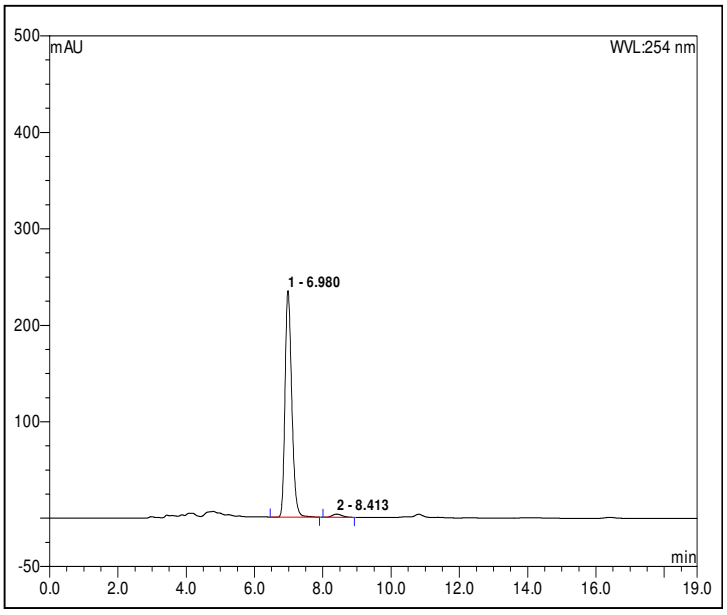
Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm.

No.	Ret.Time min	Rel.Area %
1	7.0	43.0
2	8.4	57.0
Total:		100.00





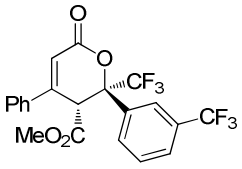
No.	Ret.Time min	Rel.Area %
1	7.0	98.0
2	8.4	2.0
Total:		100.00

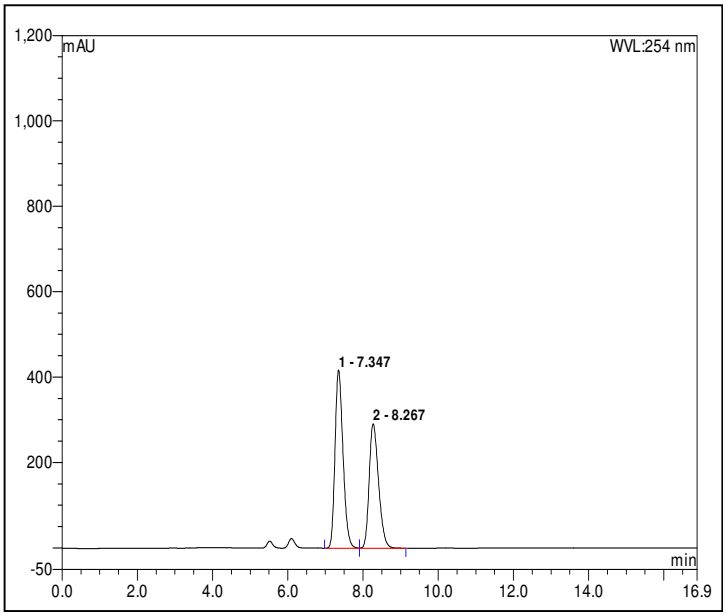


(2*R*,3*R*)-Methyl-2-(trifluoromethyl)-2-(3-(trifluoromethyl)phenyl)-3,6-dihydro-6-oxo-4-phenyl-2*H*-pyran-3-carboxylate (***cis*-64**, Table 4, entry 5)

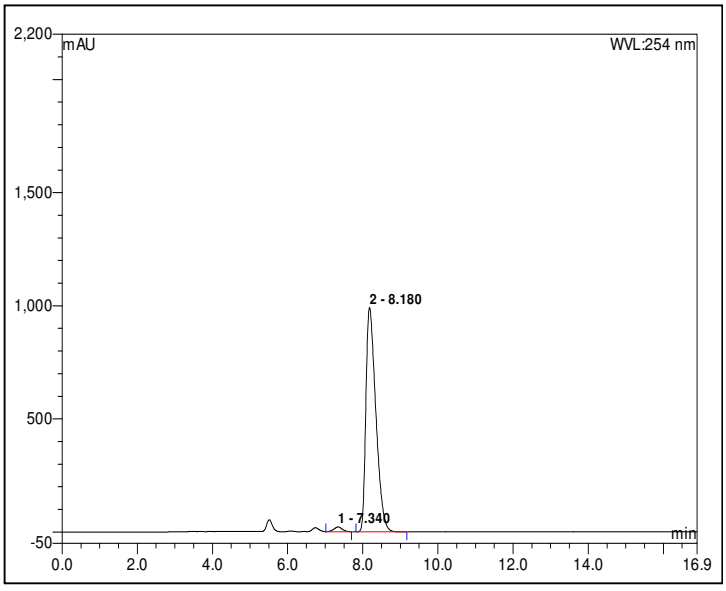
Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min-1, RT, UV detection at 254 nm.

No.	Ret.Time min	Rel.Area %
1	7.4	55.0
2	8.3	45.0
Total:		100.00





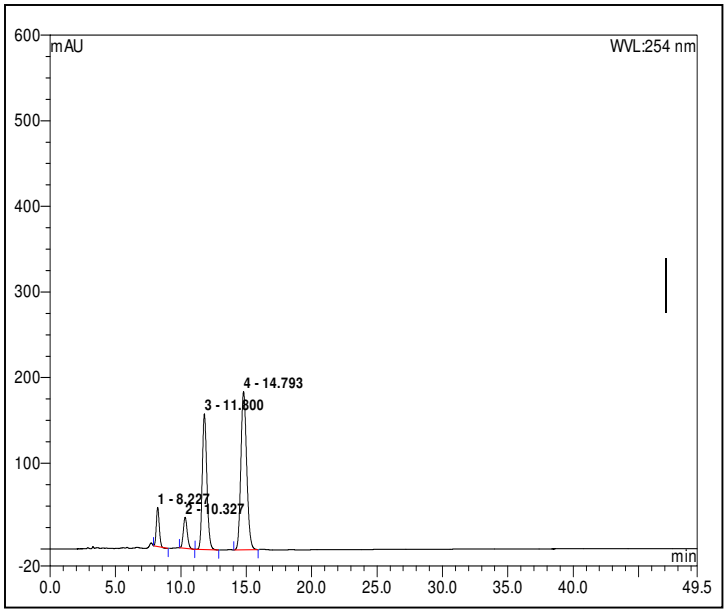
No.	Ret.Time min	Rel.Area %
1	7.3	1.8
2	8.2	98.2
Total:		100.00

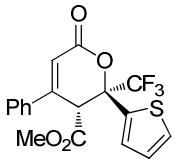


(2*S*,3*R*)-Methyl 6-oxo-4-phenyl-2-(thiophen-2-yl)-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate & (2*S*,3*S*)-Methyl 6-oxo-4-phenyl-2-(thiophen-2-yl)-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate (***trans*-65 + *cis*-65**, Table 4, entry 6)

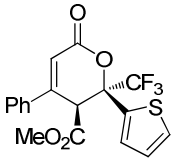
Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm.

No.	Ret.Time min	Rel.Area %
1	8.2	6.4
2	10.3	6.8
3	11.8	35.1
4	14.8	51.7
Total:		100.00



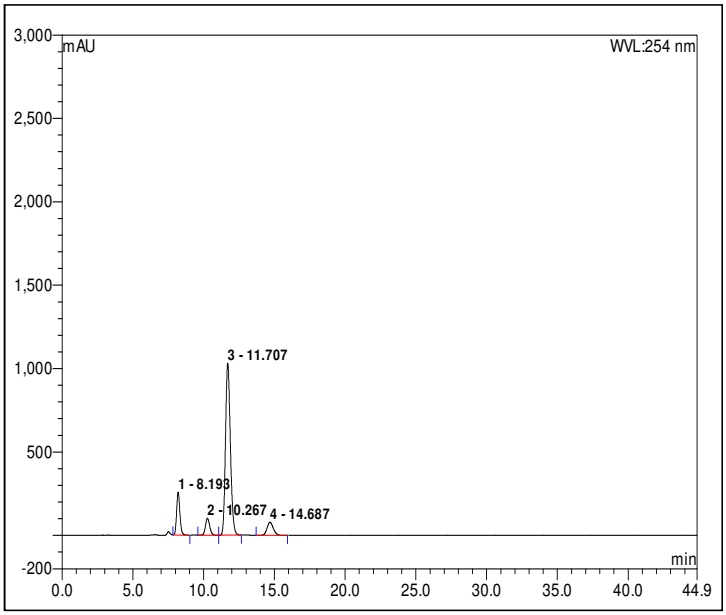


***trans*-65**



***cis*-65**

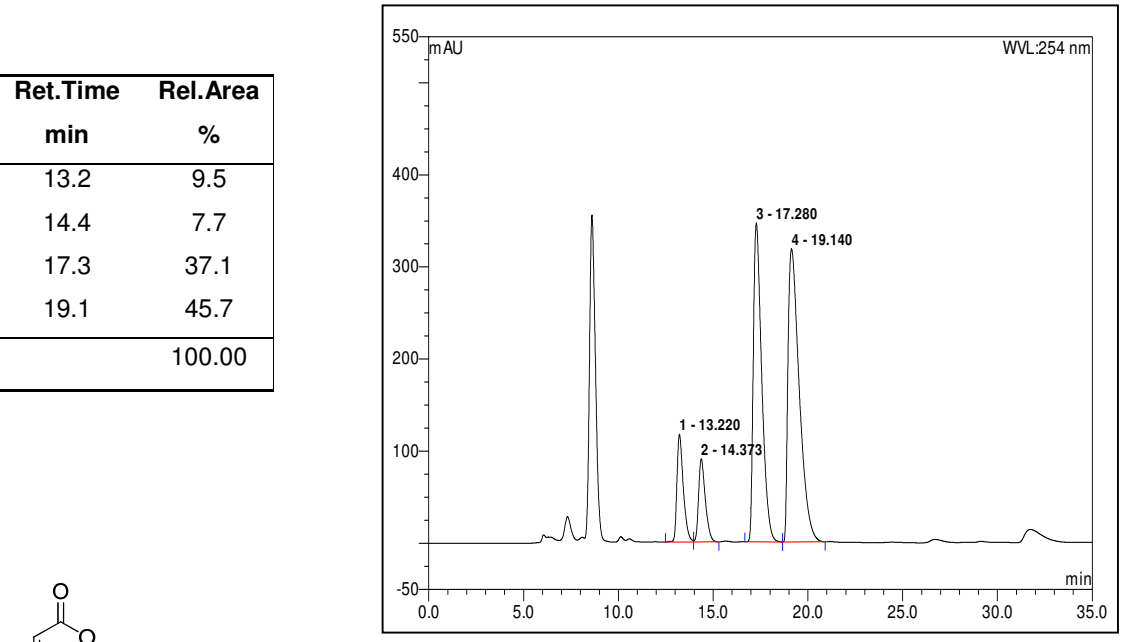
No.	Ret.Time min	Rel.Area %
1	8.2	12.3
2	10.3	6.3
3	11.7	74.2
4	14.7	7.2
Total:		100.00

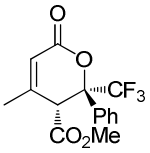


(2*R*,3*R*)-Methyl 4-methyl-6-oxo-2-phenyl-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate (***cis*-58c**, Scheme 8).

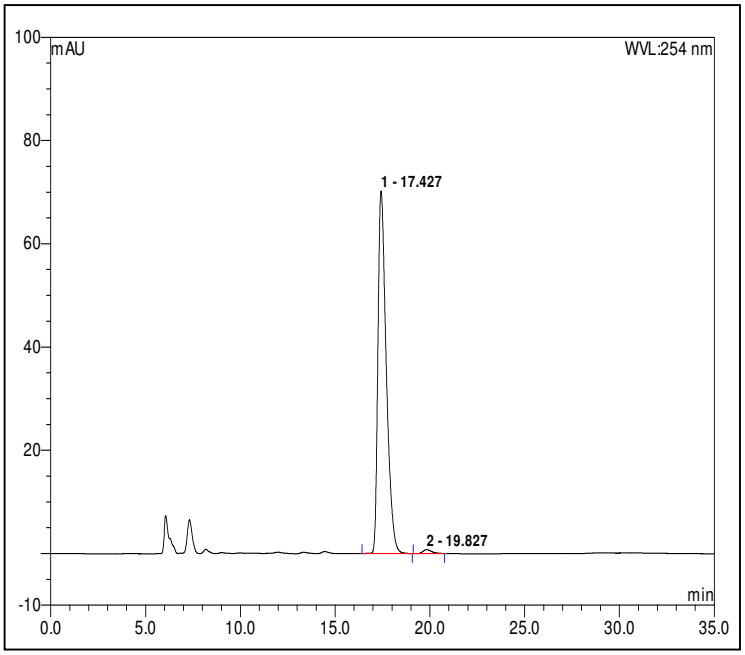
Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.5 mL min^{-1}, RT, UV detection at 254 nm.

No.	Ret.Time min	Rel.Area %
1	13.2	9.5
2	14.4	7.7
3	17.3	37.1
4	19.1	45.7
Total:		100.00





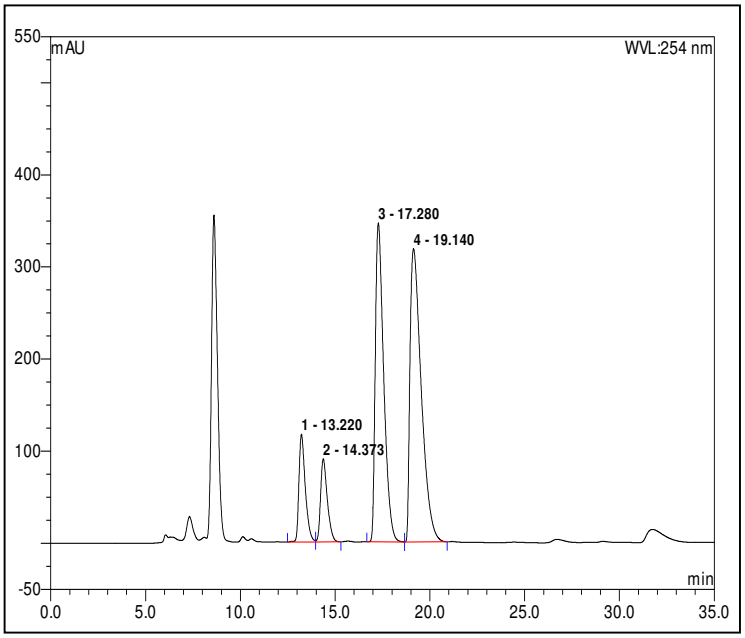
No.	Ret.Time min	Rel.Area %
1	17.4	98.9
2	19.8	1.1
Total:		100.00

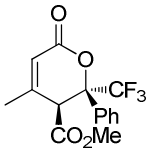


(2*R*,3*S*)-Methyl 4-methyl-6-oxo-2-phenyl-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate (***trans*-58c**, Scheme 8).

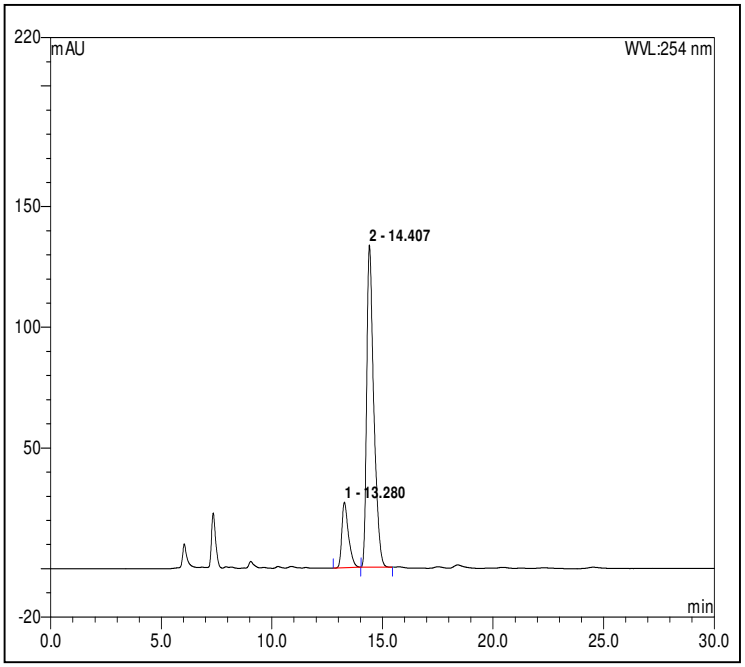
Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.5 mL min^{-1}, RT, UV detection at 254 nm.

No.	Ret.Time min	Rel.Area %
1	13.2	9.5
2	14.4	7.7
3	17.3	37.1
4	19.1	45.7
Total:		100.00





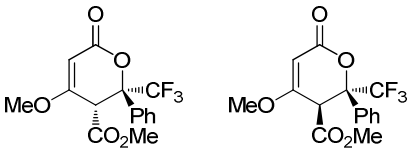
No.	Ret.Time min	Rel.Area %
1	13.3	16.0
2	14.4	84.0
Total:		100.00



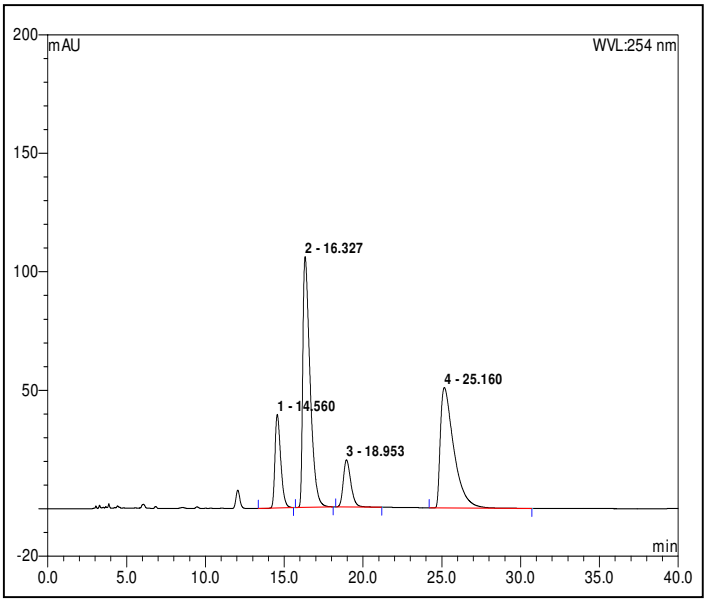
(2*R*,3*R*)-Methyl 4-methoxy-6-oxo-2-phenyl-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate & (2*R*,3*S*)-methyl 4-methoxy-6-oxo-2-phenyl-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-3-carboxylate (***cis*-60c** and ***trans*-60c**, Scheme 8)

Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 1.0 mL min^{-1}, RT, UV detection at 254 nm.

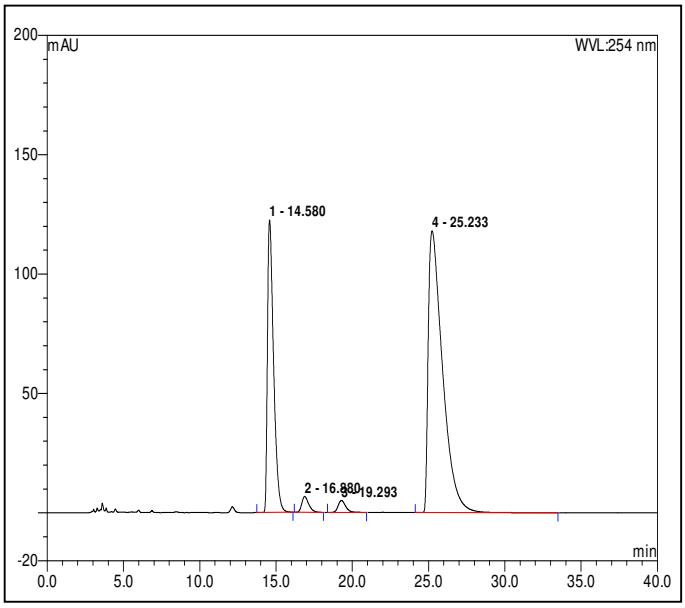
No.	Ret.Time min	Rel.Area %	Prod.
1	14.6	12.3	***trans*-60c**
2	16.3	42.2	***cis*-60c**
3	19.0	8.2	***trans*-60c**
4	25.2	37.3	***cis*-60c**
Total:		100.00	



***cis*-60c** ***trans*-60c**



No.	Ret.Time min	Rel.Area %	Prod.
1	14.6	29.7	***trans*-60c**
2	16.9	1.8	***cis*-60c**
3	19.3	1.5	***trans*-60c**
4	25.2	67.0	***cis*-60c**
Total:		100.00	



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