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

Synthesis of Maculalactone A and Derivatives for Environmental Fate Tracking Studies

Electronic Supplementary Information

Samuel L. Bader,[a] Michael U. Luescher[a] and Karl Gademann[*a]

[a] Department of Chemistry, University of Basel, St. Johanns-Ring 19, 4056 Basel, Switzerland. E-mail: karl.gademann@unibas.ch

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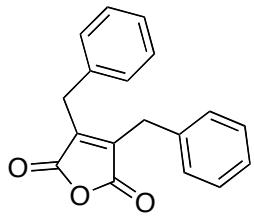
Synthetic Studies towards Maculalactone A

2,3-Dibenzylmaleic anhydride (6)



A solution of 2,3-dibromomaleic anhydride (**5**, 194 mg, 0.758 mmol, 1.00 eq.) in toluene (1.6 ml) was heated to reflux. Subsequently, di-*tert*-butyl peroxide (69.3 µl, 0.379 mmol, 0.500 eq.) was added in five portions over ten hours and the mixture was refluxed for another four hours. The reaction mixture was then cooled to room temperature and filtrated over basic aluminium oxide. The filtrate was concentrated and purified by column chromatography (SiO_2, pentane/EtOAc (10:1)) to give the title compound **6** (61 mg, 0.21 mmol, 28%) as pale yellow oil.

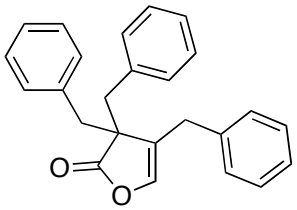
Rf (SiO_2, pentane/EtOAc (11:1)): 0.40.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.34 – 7.27 (m, 6 H), 7.17 – 7.10 (m, 4 H), 3.80 (s, 4 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 165.9, 143.1, 135.1, 129.2, 129.0, 127.6, 30.4.

The analytical data of product **6** match those reported in the literature.[1–3]

3,3,4-Tribenzylfuran-2(3H)-one (9)



To a solution of 3,4-dibenzylfuran-2(5H)-one (**7**, 29 mg, 0.11 mmol, 1.0 eq.) in toluene (5.4 ml) were added benzyl bromide (39 µl, 0.32 mmol, 3.0 eq.,) and *N*-anthrylated quinine chloride[4] (3 mg, 5 µmol, 0.05 eq.,) in one portion. The mixture was cooled to 0 °C and stirred for 10 minutes before a 50% aq. KOH solution (52.5 µl, 0.701 mmol, 6.50 eq.) was added within five minutes. After vigorous stirring for 30 minutes at 0 °C, the mixture was heated to room temperature and stirred for 72 hours. The resulting suspension was filtrated through a SiO_2 pad and the filtrate was concentrated. The crude mixture was purified by column chromatography (SiO_2, pentane/EtOAc (20:1)) to give the title compound **9** (21 mg, 0.059 mmol, 51%) as pale yellow solid.

Rf (SiO_2, pentane/EtOAc (5:1)): 0.43.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.41 (dd, *J* = 10.2, 4.6 Hz, 2 H), 7.35 – 7.19 (m, 11 H), 7.07 (d, *J* = 7.3 Hz, 2 H), 6.60 (t, *J* = 2.5 Hz, 1 H), 4.18 (d, *J* = 2.6 Hz, 2 H), 3.50 (d, *J* = 13.1 Hz, 2 H), 3.11 (d, *J* = 13.2 Hz, 2 H).

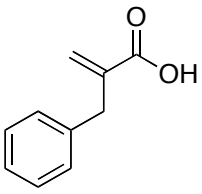
^{13}C-NMR (101 MHz, $CDCl_3$): 179.4, 137.0, 136.0, 135.7, 130.4, 129.0, 128.6, 128.5, 128.3, 128.3, 128.2, 128.1, 127.7, 127.2, 125.7, 70.2, 56.4, 45.6.

IR (neat): 3028, 2927, 1764, 1725, 1493, 1454, 1141, 1025, 698.

HRMS: Calculated for $C_{25}H_{23}O_2$ $[M+H]^+$: 355.1693, found: 355.1696.

Mp: 102 – 103 °C.

2-Benzylacrylic acid (11)



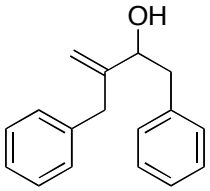
To a solution of 2-benzylacrylaldehyde (**10**, 500 mg, 3.42 mmol, 1.00 eq.) in *tert*-butanol (4 ml) was added 2-methyl-2-butene (1.09 ml, 10.3 mmol, 3.00 eq.). The reaction was cooled to 15 – 20 °C in a ice bath before a mixture of sodium chlorite (2.30 eq., 7.87 mmol, 889 mg) and monobasic sodium phosphate (821 mg, 6.84 mmol,

2.00 eq.,) in water (2.5 ml) was added dropwise within 30 minutes, maintaining the temperature below 20 °C. The reaction mixture was then slowly allowed to reach room temperature and stirred for two days. Subsequently, the mixture was concentrated, diluted with water and acidified to pH 3 with phosphoric acid. A white solid precipitated, which was collected by filtration to give the title compound **11** (197 mg, 1.2 mmol, 36%) as white solid. The filtrate was extracted three times with CH_2Cl_2. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated to give additional title compound **11** (358 mg, 2.2 mmol, 65%) as white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.30 (t, *J* = 7.3 Hz, 2 H), 7.22 (dd, *J* = 9.8, 7.8 Hz, 3 H), 6.38 (s, 1 H), 5.58 (d, *J* = 1.3 Hz, 1 H), 3.63 (s, 2 H).

The analytical data of product **11** match those reported in the literature.[5]

3-Benzyl-1-phenylbut-3-en-2-ol (12)



Pre-dried magnesium turnings (116 mg, 4.79 mmol, 1.40 eq.) were mixed with dry Et_2O (2 ml) and cooled to 0 °C. Then diisobutylaluminium hydride (1 M solution in hexane, 0.05 ml, 0.05 mmol, 0.015 eq.) was added and the mixture was stirred for 10 minutes. Subsequently, benzyl bromide (508 µl, 4.28 mmol, 1.25 eq.) in dry Et_2O (1 ml) was added dropwise. The resulting suspension was stirred for two hours at 0 °C. To the yellow suspension, a solution of 2-benzylacrylaldehyde (**10**, 500 mg, 3.42 mmol, 1.00 eq.,) in dry Et_2O (1 ml) was added dropwise. The mixture was stirred for three hours at room temperature before it was quenched with a sat. aq. NH_4Cl solution, stirred for another 30 minutes and filtrated over Celite. The layers were separated and the aq. layer was extracted three times with TBME. The org. layers were subsequently washed with water and brine, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (9:1)) to give the title compound **12** (460 mg, 1.9 mmol, 56%) as colorless oil.

Rf (SiO_2, pentane/EtOAc (9:1)): 0.29.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.33 – 7.27 (m, 4 H), 7.25 – 7.17 (m, 6 H), 5.17 (s, 1 H), 4.82 (d, *J* = 1.1 Hz, 1 H), 4.33 – 4.25 (m, 1 H), 3.52 (d, *J* = 15.5 Hz, 1 H), 3.39

(d, J = 15.5 Hz, 1 H), 2.95 (dd, J = 13.7, 4.1 Hz, 1 H), 2.76 (dd, J = 13.7, 8.9 Hz, 1 H), 1.58 (d, J = 3.5 Hz, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 150.7, 139.2, 138.3, 129.4, 129.2, 128.5, 128.4, 126.6, 126.3, 112.3, 75.0, 42.8, 39.4.

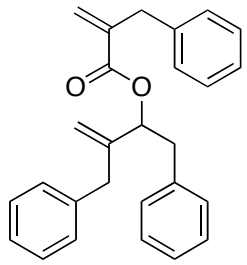
IR (neat): 3558, 3421, 3062, 3027, 2919, 1647, 1602, 1494, 1453, 1049, 1030, 906, 743, 697.

HRMS: Calculated for $C_{17}H_{18}NaO$ $[M+Na]^+$: 261.1250, found: 261.1254.

EI-MS (70 eV) m/z (%): 238 (3, $[M]^+$), 147 (63), 146 (78), 145 (15), 130 (10), 129 (100), 117 (25), 116 (24), 115 (13), 92 (61), 91 (88), 65 (12).

The analytical data of product **12** match those reported in the literature.[6]

3-Benzyl-1-phenylbut-3-en-2-yl 2-benzylacrylate (13)



To a solution of 3-benzyl-1-phenylbut-3-en-2-ol (**12**, 22 mg, 0.093 mmol, 1.0 eq.) and 2-benzylacrylic acid (**11**, 20 mg, 0.12 mmol, 1.3 eq.) in dry CH_2Cl_2 (2 ml) was added 4-dimethylaminopyridine (13 mg, 0.10 mmol, 1.1 eq.) at room temperature. Five minutes later, *N*,*N*'-dicyclohexylcarbodiimide (29 mg, 0.14 mmol, 1.5 eq.,) was added and the mixture was heated to reflux. After five hours at reflux, the reaction was cooled to room temperature and the precipitate was filtered off. After concentrating the filtrate, the crude product was purified by preparative TLC (SiO_2, pentane/EtOAc (15:1)) to give the title compound **13** (27 mg, 0.071 mmol, 76%) as pale yellow oil.

Rf (SiO_2, pentane/EtOAc (15:1)): 0.73.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.30 – 7.24 (m, 5 H), 7.24 – 7.18 (m, 4 H), 7.13 (dd, J = 6.9, 5.2 Hz, 4 H), 7.10 – 7.06 (m, 2 H), 6.16 (s, 1 H), 5.43 (dd, J = 7.9, 5.6 Hz, 1 H), 5.39 (d, J = 1.4 Hz, 1 H), 4.96 (s, 1 H), 4.71 (d, J = 1.0 Hz, 1 H), 3.54 (s, 2 H), 3.36 (d, J = 15.8 Hz, 1 H), 3.30 (d, J = 15.8 Hz, 1 H), 2.92 (dd, J = 13.9, 8.0 Hz, 1 H), 2.86 (dd, J = 14.0, 5.5 Hz, 1 H).

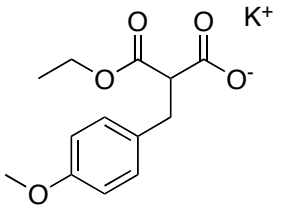
^{13}C-NMR (126 MHz, $CDCl_3$): 166.0, 146.8, 140.1, 138.8, 138.7, 137.4, 129.5, 129.5, 129.1, 128.6, 128.5, 128.4, 126.6, 126.5, 126.4, 114.4, 77.7, 40.4, 39.5, 38.1.

IR (neat): 3062, 3028, 2922, 1716, 1632, 1603, 1494, 1453, 1297, 1191, 1129, 1000, 908, 737, 697.

HRMS: Calculated for $C_{27}H_{26}NaO_2$ $[M+Na]^+$: 405.1825, found: 405.1825.

Synthesis of Maculalactone A Derivatives

Potassium 3-ethoxy-2-(4-methoxybenzyl)-3-oxopropanoate (19)



A solution of diethyl 2-(4-methoxybenzyl)malonate (**18**, 505 mg, 1.80 mmol, 1.00 eq.) in dry EtOH (2 ml) was cooled to -15 °C. A freshly filtrated solution of KOH (125 mg, 1.89 mmol, 1.05 eq.) in dry EtOH (2 ml) was added at -15 °C over 15 minutes. The resulting mixture was stirred for 17 hours at -15 °C before it was concentrated to give a white honey with some solid parts. This residue was suspended twice in Et_2O and again concentrated. The residue was triturated in Et_2O overnight. The precipitate was filtered off to give the title compound **19** (421 mg, 1.5 mmol, 81%) as white solid.

^{1}H-NMR (400 MHz, D_2O): 7.22 (d, J = 8.7 Hz, 2 H), 6.97 – 6.90 (m, 2 H), 4.09 (q, J = 7.1 Hz, 2 H), 3.80 (s, 3 H), 3.56 (dd, J = 8.9, 7.3 Hz, 1 H), 3.07 (s, 1 H), 3.05 (d, J = 2.9 Hz, 1 H), 1.15 (t, J = 7.1 Hz, 3 H).

^{13}C-NMR (101 MHz, D_2O): 176.0, 173.4, 157.4, 131.7, 129.9, 114.1, 62.0, 57.5, 55.4, 34.2, 13.2.

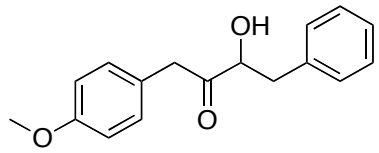
IR (neat): 3383, 1714, 1597, 1512, 1361, 1247, 1150, 1034, 818, 687.

FAB-MS (8 kV Xe) m/z (%): 291 (100, $[M+K]^+$), 281 (18), 253 (15), 252 (18), 242 (16), 121 (39), 39 (75).

HRMS: Calculated for $C_{13}H_{16}NaO_5$ $[M+Na]^+$: 275.0890, found: 275.0890.

Mp: 129 – 130 °C.

3-Hydroxy-1-(4-methoxyphenyl)-4-phenylbutan-2-one (21)



For the formation of the cyanohydrin, a published procedure[7] was modified as follows: To neat trimethylsilyl cyanide (2.67 ml, 20.0 mmol, 1.00 eq.) was added a crystal of ZnI_2 and the mixture was cooled to 0 °C. Then, freshly distilled phenylacetaldehyde (2.38 ml, 20.0 mmol, 1.00 eq.) was added over five minutes. The reaction was stirred and allowed to reach room temperature over three hours. The TMS protected cyanohydrin was isolated by Kugelrohr distillation at 80 to 110 °C and 0.5 mbar to give the intermediate TMS protected cyanohydrin (2.85 g, 13 mmol, 65%) as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.27 – 7.13 (m, 5 H), 4.41 (dd, *J* = 7.3, 6.4 Hz, 1 H), 2.98 (d, *J* = 6.4 Hz, 1 H), 2.97 (d, *J* = 7.3 Hz, 1 H), 0.00 (s, 9 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 199.6, 135.0, 129.8, 128.7, 127.6, 63.0, 42.9, -0.5.

The analytical data of the intermediate cyanohydrin match those reported in the literature.[7]

A solution of the TMS protected cyanohydrin (2.85 g, 13.0 mmol, 1.00 eq.) in dry Et_2O (20 ml) was added dropwise to a solution of (4-methoxybenzyl)magnesium chloride (19.5 mmol, 1.50 eq.) in dry Et_2O (60 ml) at reflux (important: the preparation of the Grignard reagent can be found at the end of this procedure). The mixture was stirred for five hours at reflux. A GC-MS analysis showed about 50% conversion. Therefore, another portion of (4-methoxybenzyl)magnesium chloride (19.5 mmol, 1.50 eq.) in dry Et_2O (70 ml) was added to the refluxing reaction. After another four hours at reflux, the reaction was cooled down and poured onto a mixture of 35% aq. HCl (60 ml) and ice (100 ml). The resulting mixture was allowed to reach room temperature overnight. The layers were separated and the aq. layer was extracted twice with TBME. The org. layers were washed with a sat. aq. Na_2CO_3 solution, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (5:1)) to give the title compound **21** (1.89 g, 7.0 mmol, 54%) as yellowish solid. Over both steps, a combined yield of 35% was achieved.

Rf (SiO_2, pentane/EtOAc (4:1)): 0.31.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.35 – 7.20 (m, 5 H), 7.09 – 7.04 (m, 2 H), 6.89 – 6.84 (m, 2 H), 4.55 – 4.47 (m, 1 H), 3.80 (s, 3 H), 3.75 (d, *J* = 16.0 Hz, 1 H), 3.69 (d, *J* = 16.0 Hz, 1 H), 3.22 (d, *J* = 5.6 Hz, 1 H), 3.15 (dd, *J* = 14.1, 4.7 Hz, 1 H), 2.89 (dd, *J* = 14.1, 7.4 Hz, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 209.5, 159.0, 136.6, 130.7 129.5, 128.8, 127.1, 125.0, 114.4, 76.7, 55.4, 45.0, 40.4.

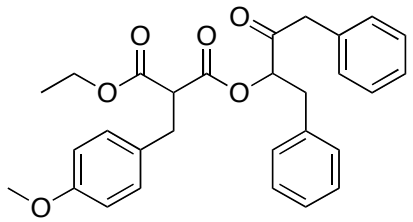
IR (neat): 3391, 2837, 1694, 1614, 1513, 1467, 1301, 1245, 1177, 1090, 1033, 798, 741.

HRMS: Calculated for $C_{17}H_{22}NO_3$ $[M+NH_4]^+$: 288.1594, found: 288.1592.

Mp: < 50 °C.

Crucial is the generation of the Grignard reagent as benzyl magnesium compounds are prone to reductive homo coupling. An efficient method was found to be as follows: Pre-dried magnesium turnings (1.60 eq., 20.8 mmol, 506 mg) were mixed with dry Et_2O (50 ml) and cooled to -20 °C. Then diisobutylaluminium hydride (1 M solution in hexane, 0.010 eq., 0.13 mmol, 0.13 ml) was added and the solution was stirred for 10 minutes. This was followed by the addition of a solution of 1-(chloromethyl)-4-methoxybenzene (1.50 eq., 19.5 mmol, 2.66 ml) in dry Et_2O (20 ml) over two hours at -20 °C. The reaction was stirred for 17 hours at -20 °C. According to GC-MS the resulting solution consists of starting material, Grignard reagent and dimerization product in a ration of 1 to 3 to 1.

1-Ethyl 3-(3-oxo-1,4-diphenylbutan-2-yl) 2-(4-methoxybenzyl)malonate (22)



To a suspension of potassium 3-ethoxy-2-(4-methoxybenzyl)-3-oxopropanoate (**19**, 386 mg, 1.33 mmol, 1.40 eq.,) in dry THF (6 ml) at 0 °C was added DMF (4 µl, 0.05 mmol, 0.05 eq.,) followed by the dropwise addition of pivaloyl chloride (201 µl, 1.61 mmol, 1.70 eq.) over five minutes. The reaction was then stirred for two hours at 0 °C and for 3.5 hours at room temperature. The resulting solution was concentrated and dried in high vacuum. Then, the residue was twice dissolved in dry CH_2Cl_2 (60 ml), concentrated and dried in high vacuum without exceeding a temperature of 25 °C. The residue was dissolved in dry CH_2Cl_2 (50 ml) and cooled to 0 °C. The addition of

4-dimethylaminopyridine (12 mg, 0.10 mmol, 0.10 eq.) was followed by the addition of a solution of 3-hydroxy-1,4-diphenylbutan-2-one (**16**, 228 mg, 0.95 mmol, 1.00 eq.) in dry CH_2Cl_2 (2 ml) over five minutes. The reaction was allowed to reach room temperature overnight before it was quenched with a mixture of water and a sat. aq. $NaHCO_3$ solution (1:1 v/v). The layers were separated and the aq. layer was extracted three times with CH_2Cl_2. The org. layers were washed with a sat. aq. NH_4Cl solution, combined, dried with Na_2SO_4 and concentrated. The crude was purified by column chromatography (SiO_2, pentane/EtOAc (6:1)) to give the title compound **22** (408 mg, 0.86 mmol, 91%) as yellowish oil, as a mixture of diastereoisomers.

Rf (SiO_2, pentane/EtOAc (8:1)): 0.42.

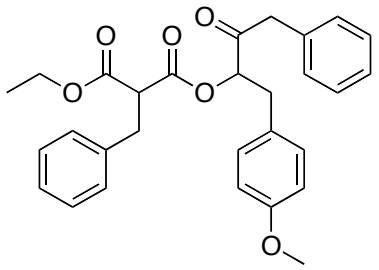
^{1}H-NMR (400 MHz, $CDCl_3$): 7.33 – 7.22 (m, 6 H), 7.16 – 7.07 (m, 2 H), 7.07 – 6.98 (m, 4 H), 6.83 – 6.73 (m, 2 H), 5.35 – 5.26 (m, 1 H), 4.17 – 4.05 (m, 2 H), 3.76 (s, 1.3 H), 3.71 – 3.64 (m, 2.6 H), 3.58 (s, 0.9 H), 3.47 (d, *J* = 17.1 Hz, 0.6 H), 3.34 (d, *J* = 17.1 Hz, 0.6 H), 3.22 – 3.07 (m, 2 H), 3.06 – 2.93 (m, 2 H), 1.20 – 1.13 (m, 3 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 204.4, 204.4, 168.6, 168.5, 168.4, 168.3, 158.6, 135.7, 135.6, 132.9, 132.9, 130.0, 130.0, 129.9, 129.9, 129.6, 129.6, 129.6, 129.5, 128.7, 128.7, 128.7, 127.2, 127.2, 127.2, 114.1, 79.6, 79.4, 61.8, 61.8, 55.3, 55.2, 54.1, 54.0, 46.4, 46.3, 37.1, 33.9, 33.9, 14.2, 14.1.

IR (neat): 3063, 3031, 2935, 1729, 1612, 1514, 1455, 1248, 1178, 1148, 1032, 700.

HRMS: Calculated for $C_{29}H_{30}NaO_6$ $[M+Na]^+$: 497.1935, found: 497.1938.

1-Ethyl 3-(1-(4-methoxyphenyl)-3-oxo-4-phenylbutan-2-yl) 2-benzylmalonate (23)



To a suspension of potassium 2-benzyl-3-ethoxy-3-oxopropanoate (**14**, 977 mg, 3.75 mmol, 1.40 eq.) in dry THF (20 ml) at 0 °C was added pivaloyl chloride (566 µl, 4.56 mmol, 1.70 eq.) dropwise over five minutes followed by the addition of DMF (10 µl, 0.13 mmol, 0.050 eq.). The reaction was then kept for 1.5 hours at 0 °C and for three hours at room temperature. The resulting solution was concentrated, dried in high vacuum and then twice dissolved in dry CH_2Cl_2 (20 ml), concentrated and dried in high vacuum without exceeding a temperature of 27 °C. The residue was dissolved in dry

CH_2Cl_2 (20 ml) and cooled to 0 °C. The addition of 4-dimethylaminopyridine (33 mg, 0.27 mmol, 0.10 eq.) to the reaction mixture was followed by the addition of a solution of 3-hydroxy-4-(4-methoxyphenyl)-1-phenylbutan-2-one (**20**, 724 mg, 2.68 mmol, 1.00 eq.) in dry CH_2Cl_2 (10 ml) over five minutes. The reaction was allowed to reach room temperature overnight before it was quenched with a mixture of water and a sat. aq. $NaHCO_3$ solution (1:1 v/v). The layers were separated and the aq. layer was extracted three times with CH_2Cl_2. The org. layers were washed with a sat. aq. NH_4Cl solution, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (6:1)) to give the title compound **23** (733 mg, 1.5 mmol, 58%) as yellowish liquid, as a mixture of diastereoisomers.

Rf (SiO_2, pentane/EtOAc (6:1)): 0.35.

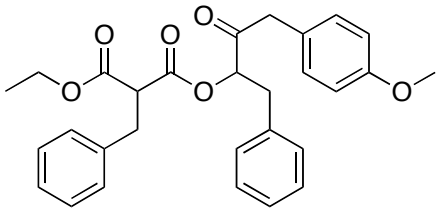
^{1}H-NMR (400 MHz, $CDCl_3$): 7.33 – 7.21 (m, 6 H), 7.20 – 7.16 (m, 1 H), 7.15 – 7.10 (m, 1 H), 7.07 – 6.98 (m, 3 H), 6.94 – 6.90 (m, 1 H), 6.84 – 6.75 (m, 2 H), 5.30 – 5.22 (m, 1 H), 4.16 – 4.08 (m, 2 H), 3.78 (s, 1.5 H), 3.78 (s, 1.5 H), 3.74 – 3.70 (m, 1 H), 3.58 (s, 1 H), 3.49 (d, *J* = 16.9 Hz, 0.5 H), 3.37 (d, *J* = 16.9 Hz, 0.5 H), 3.28 – 3.11 (m, 2 H), 3.00 – 2.89 (m, 2 H), 1.19 – 1.13 (m, 3 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 204.4, 204.3, 168.4, 168.1, 168.2, 168.2, 158.7, 158.7, 137.5, 137.5, 132.8, 132.8, 130.5, 130.5, 129.8, 129.7, 128.8, 128.8, 128.6, 128.6, 127.4, 127.3, 127.1, 126.9, 126.9, 114.0, 113.9, 79.7, 79.5, 61.8, 61.7, 55.3, 53.7, 53.6, 46.4, 46.3, 36.1, 34.6, 34.6, 14.0, 14.0.

IR (neat): 1727, 1612, 1514, 1455, 1246, 1177, 1146, 1030, 832, 752, 698.

HRMS: Calculated for $C_{29}H_{30}NaO_6$ $[M+Na]^+$: 497.1935, found: 497.1943.

1-Ethyl 3-(4-(4-methoxyphenyl)-3-oxo-1-phenylbutan-2-yl) 2-benzylmalonate (24)



To a suspension of potassium 2-benzyl-3-ethoxy-3-oxopropanoate (**14**, 2.37 g, 2.37 g, 1.40 eq.) in dry THF (40 ml) at 0 °C was added DMF (25 µl, 0.32 mmol, 0.050 eq.) followed by the dropwise addition of pivaloyl chloride (1.37 ml, 11.1 mmol, 1.70 eq.) over five minutes. The reaction was then kept for 1.5 hour at 0 °C and for 2.5 hours at room temperature. The resulting solution was concentrated, dried in high vacuum and then twice dissolved in dry CH_2Cl_2 (40 ml), concentrated and dried in high vacuum

without exceeding a temperature of 27 °C. The residue was dissolved in dry CH_2Cl_2 (40 ml) and cooled to 0 °C. The addition of 4-dimethylaminopyridine (79 mg, 0.65 mmol, 0.10 eq.) to the reaction mixture was followed by the addition of a solution of 3-hydroxy-1-(4-methoxyphenyl)-4-phenylbutan-2-one (**21**, 1.76 g, 6.50 mmol, 1.00 eq.) in dry CH_2Cl_2 (10 ml) over five minutes. The reaction was allowed to reach room temperature overnight before it was quenched with a mixture of water and a sat. aq. $NaHCO_3$ solution (1:1 v/v). The layers were separated and the aq. layer was extracted three times with CH_2Cl_2. The org. layers were washed with a sat. aq. NH_4Cl solution, combined, dried with Na_2SO_4 and concentrated to give the title compound **24** (3.33 g, 6.5 mmol, quantitative) as a yellow liquid (mixture of diastereoisomers), which started to crystallize upon prolonged standing.

Rf (SiO_2, pentane/EtOAc (4:1)): 0.59.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.30 – 7.20 (m, 6 H), 7.20 – 7.15 (m, 2 H), 7.14 – 7.10 (m, 2 H), 7.04 – 7.00 (m, 1 H), 6.98 – 6.90 (m, 2 H), 6.86 – 6.81 (m, 2 H), 5.34 – 5.25 (m, 1 H), 4.17 – 4.05 (m, 2 H), 3.79 (s, 1.5 H), 3.79 (s, 1.5 H), 3.75 – 3.69 (m, 1 H), 3.52 (s, 1 H), 3.44 (d, *J* = 17.0 Hz, 0.5 H), 3.33 (d, *J* = 17.0 Hz, 0.5 H), 3.27 – 3.11 (m, 2 H), 3.06 – 2.91 (m, 2 H), 1.19 – 1.11 (m, 3 H).

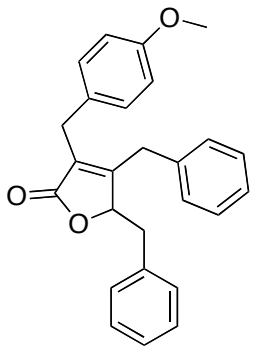
^{13}C-NMR (101 MHz, $CDCl_3$): 204.7, 204.7, 168.5, 168.4, 168.4, 168.3, 158.9, 137.7, 137.6, 135.7, 135.6, 130.9, 130.9, 129.6, 129.6, 129.0, 129.0, 128.7, 128.7, 128.7, 127.2, 127.2, 127.1, 124.8, 124.8, 114.2, 79.6, 79.4, 62.0, 61.8, 55.4, 53.8, 53.7, 45.6, 45.6, 37.1, 34.7, 34.7, 14.1, 14.1.

IR (neat): 3982, 2936, 1728, 1612, 1513, 1247, 1177, 1147, 1030, 737, 699.

HRMS: Calculated for $C_{29}H_{30}NaO_6$ $[M+Na]^+$: 497.1935, found: 497.1934.

Mp: < 50 °C.

4,5-Dibenzyl-3-(4-methoxybenzyl)furan-2(5H)-one (25)



A two neck round bottom flask was equipped with a condenser and a device to run the condensed solvent over a bed of 4 Å molecular sieves. In the flask, a mixture of

cesium carbonate (56 mg, 0.17 mmol, 0.20 eq.) and THF (60 ml) was heated until the suspension was strongly refluxing. After refluxing for 30 minutes, a solution of 1-ethyl 3-(3-oxo-1,4-diphenylbutan-2-yl) 2-(4-methoxybenzyl)malonate (**22**, 408 mg, 0.860 mmol, 1.00 eq.,) in THF (8 ml) was added over five minutes. The reaction was further stirred under reflux. After four hours, a TLC showed only little conversion and additional cesium carbonate (56 mg, 0.17 mmol, 0.20 eq.) was added. After another four hours, the mixture was cooled down and filtrated over a bed of SiO_2. The filtrate was concentrated and purified by column chromatography (SiO_2, pentane/EtOAc (6:1)) to give the title compound **25** (252 mg, 0.66 mmol, 76%) as pale yellow oil.

Rf (SiO_2, pentane/EtOAc (6:1)): 0.36.

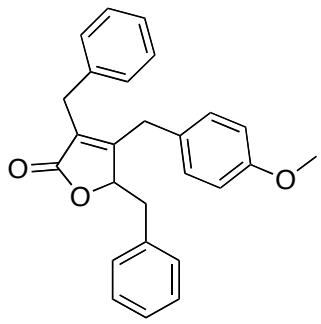
^{1}H-NMR (500 MHz, C_6D_6): 7.06 – 7.01 (m, 6 H), 6.98 – 6.95 (m, 2 H), 6.87 – 6.83 (m, 2 H), 6.73 – 6.67 (m, 4 H), 4.56 – 4.52 (m, 1 H), 3.47 (dd, *J* = 15.2, 3.8 Hz, 2 H), 3.32 (s, 3 H), 2.97 (d, *J* = 15.7 Hz, 1 H), 2.77 (dd, *J* = 14.5, 3.9 Hz, 1 H), 2.33 (dd, *J* = 14.5, 6.4 Hz, 1 H).

^{13}C-NMR (126 MHz, C_6D_6): 172.9, 160.1, 158.8, 136.7, 135.6, 130.5, 129.8, 129.7, 129.7, 129.1, 128.9, 128.7, 128.4, 128.2, 128.0, 127.2, 127.2, 114.4, 81.2, 54.8, 38.2, 33.0, 28.9.

IR (neat): 3028, 2910, 2836, 1729, 1510, 1246, 1049, 1032, 702.

HRMS: Calculated for $C_{26}H_{24}NaO_3$ $[M+Na]^+$: 407.1618, found: 407.1618.

3,5-Dibenzyl-4-(4-methoxybenzyl)furan-2(5H)-one (26)



A two neck round bottom flask was equipped with a condenser and a device to run the condensed solvent over a bed of 4 Å molecular sieves. In the flask, a mixture of cesium carbonate (69 mg, 0.21 mmol, 0.20 eq.) and THF (75 ml) was heated until the suspension was strongly refluxing. After refluxing for 30 minutes, a solution of 1-ethyl 3-(4-(4-methoxyphenyl)-3-oxo-1-phenylbutan-2-yl) 2-benzylmalonate (**23**, 498 mg, 1.05 mmol, 1.00 eq.) in THF (25 ml) was added over five minutes. The reaction was further stirred under reflux. After 3.5 hours, the finished reaction was cooled to room

temperature. The mixture was filtrated over a bed of SiO_2 and the filtrate was concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (6:1)) to give the title compound **26** (241 mg, 0.63 mmol, 60%) as yellowish solid.

Rf (SiO_2, pentane/EtOAc (5:1)): 0.31.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.27 – 7.23 (m, 3 H), 7.21 – 7.13 (m, 5 H), 6.95 – 6.86 (m, 4 H), 6.84 – 6.80 (m, 2 H), 4.97 – 4.90 (m, 1 H), 3.86 (d, *J* = 15.6 Hz, 1 H), 3.79 (s, 3 H), 3.62 (d, *J* = 15.3 Hz, 1 H), 3.56 (d, *J* = 15.3 Hz, 1 H), 3.42 (d, *J* = 15.7 Hz, 1 H), 3.22 (dd, *J* = 14.6, 4.0 Hz, 1 H), 2.81 (dd, *J* = 14.6, 6.2 Hz, 1 H).

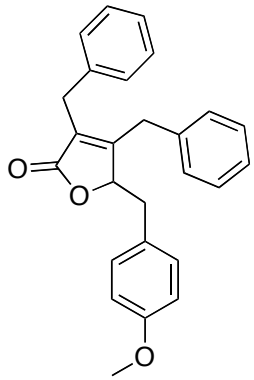
^{13}C-NMR (101 MHz, $CDCl_3$): 173.7, 162.3, 158.9, 137.9, 135.0, 129.8, 129.6, 128.8, 128.7, 128.6, 128.3, 127.9, 127.3, 126.5, 114.6, 81.7, 55.5, 38.1, 32.5, 29.4.

IR (neat): 3029, 2838, 1747, 1511, 1249, 1177, 1024, 836, 725, 698, 655.

HRMS: Calculated for $C_{26}H_{25}O_3$ $[M+H]^+$: 385.1798, found: 385.1797.

Mp: 62 – 63 °C.

3,4-Dibenzyl-5-(4-methoxybenzyl)furan-2(5H)-one (27)



A two neck round bottom flask was equipped with a condenser and a device to run the condensed solvent over a bed of 4 Å molecular sieves. In the flask, a mixture of cesium carbonate (55 mg, 0.17 mmol, 0.20 eq.,) and THF (60 ml) was heated until the suspension was strongly refluxing. After refluxing for 30 minutes, a solution of 1-ethyl 3-(1-(4-methoxyphenyl)-3-oxo-4-phenylbutan-2-yl) 2-benzylmalonate (**24**, 403 mg, 1.00 eq., 0.850 mmol) in THF (20 ml) was added over five minutes. The reaction was further stirred under reflux. After 7.5 hours, the finished reaction was cooled to room temperature. The mixture was filtrated over a bed of SiO_2 and the filtrate was concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (6:1)) to give the title compound **27** (230 mg, 0.60 mmol, 70%) as yellowish solid.

Rf (SiO_2, pentane/EtOAc (6:1)): 0.25.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.34 – 7.24 (m, 4 H), 7.19 – 7.15 (m, 3 H), 7.09 – 7.03 (m, 4 H), 6.87 – 6.83 (m, 2 H), 6.80 – 6.75 (m, 2 H), 4.92 (t, *J* = 4.7 Hz, 1 H), 3.92 (d, *J* = 15.6 Hz, 1 H), 3.79 (s, 3 H), 3.63 (d, *J* = 15.4 Hz, 1 H), 3.56 (d, *J* = 15.3 Hz, 1 H), 3.46 (d, *J* = 15.6 Hz, 1 H), 3.20 (dd, *J* = 14.7, 4.0 Hz, 1 H), 2.80 (dd, *J* = 14.7, 5.6 Hz, 1 H).

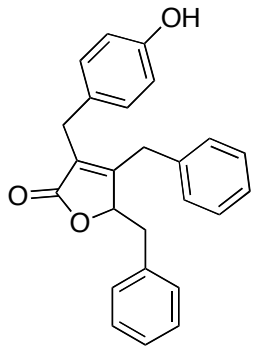
^{13}C-NMR (101 MHz, $CDCl_3$): 173.7, 161.8, 158.9, 137.8, 136.1, 130.7, 129.2, 128.8, 128.8, 128.6, 128.3, 127.4, 126.7, 126.5, 114.1, 81.8, 55.3, 37.0, 33.4, 29.5.

IR (neat): 2932, 1735, 1676, 1612, 1454, 1332, 1244, 1178, 1132, 1099, 1033, 1006, 836, 706, 658.

HRMS: Calculated for $C_{26}H_{24}NaO_3$ $[M+Na]^+$: 407.1618, found: 407.1618.

Mp: 101 – 102 °C.

4,5-Dibenzyl-3-(4-hydroxybenzyl)furan-2(5H)-one (28)



To a solution of 4,5-dibenzyl-3-(4-methoxybenzyl)furan-2(5H)-one (**25**, 252 mg, 0.655 mmol, 1.00 eq.) in dry CH_2Cl_2 (15 ml) at -78 °C was added BBr_3 (1 M solution in CH_2Cl_2, 3.3 ml, 3.3 mmol, 5.0 eq.) over 15 minutes. The reaction was allowed to reach room temperature overnight. Subsequently, the reaction mixture was cooled to 0 °C and poured on ice. The layers were separated and the aq. layer was extracted two times with CH_2Cl_2. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated to give the title compound **28** (258 mg, 0.66 mmol, quantitative) as brownish foam.

Rf (SiO_2, pentane/EtOAc (3:1)): 0.31.

^{1}H-NMR (500 MHz, C_6D_6): 7.07 – 6.99 (m, 6 H), 6.95 (dd, *J* = 7.4, 1.8 Hz, 2 H), 6.74 – 6.66 (m, 4 H), 6.55 – 6.49 (m, 2 H), 4.78 (s, 1 H), 4.57 – 4.47 (m, 1 H), 3.48 – 3.36 (m, 2 H), 3.28 (d, *J* = 15.0 Hz, 1 H), 2.95 (d, *J* = 15.7 Hz, 1 H), 2.75 (dd, *J* = 14.5, 3.9 Hz, 1 H), 2.31 (dd, *J* = 14.5, 6.2 Hz, 1 H).

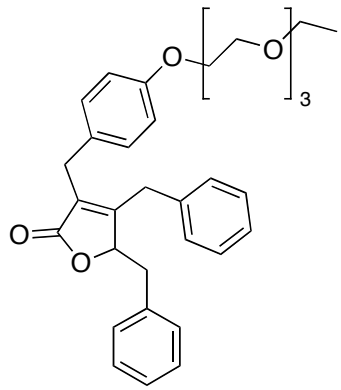
^{13}C-NMR (101 MHz, C_6D_6): 173.4, 160.5, 155.3, 136.6, 135.5, 129.8, 129.8, 129.8, 129.7, 129.1, 128.9, 128.8, 128.2, 127.9, 127.2, 115.8, 81.5, 38.1, 33.0, 28.8.

IR (neat): 3357, 3029, 2922, 1723, 1512, 1452, 1341, 1225, 1051, 831, 748, 699.

HRMS: Calculated for $C_{25}H_{22}NaO_3$ $[M+Na]^+$: 393.1461, found: 393.1460.

EI-MS (70 eV) m/z (%): 280 (7), 279 (35, $[M]^+$), 276 (18), 107 (45), 91 (100).

4,5-Dibenzyl-3-(4-(2-(2-(2-ethoxyethoxy)ethoxy)ethoxy)benzyl)furan-2(5H)-one (29)



To a solution of 4,5-dibenzyl-3-(4-hydroxybenzyl)furan-2(5H)-one (**28**, 50 mg, 0.14 mmol, 1.0 eq.) and potassium carbonate (37 mg, 0.27 mmol, 2.0 eq.) in acetone (1 ml) was added triethylene glycol monoethyl ether *p*-tosylate[8,9] (54 mg, 0.15 mmol, 1.1 eq.). The reaction mixture was stirred for 50 hours at reflux before it was concentrated. The crude product was first purified by column chromatography (SiO_2, pentane/EtOAc (3:2)) and then by preparative HPLC chromatography (Gemini-NX 10u C18 250x21.2 mm, CH_3CN/water (95:5 to 0:100)) to give the title compound **29** (31 mg, 0.058 mmol, 43%) as pale yellow oil.

Rf (SiO_2, pentane/EtOAc (1:1)): 0.47.

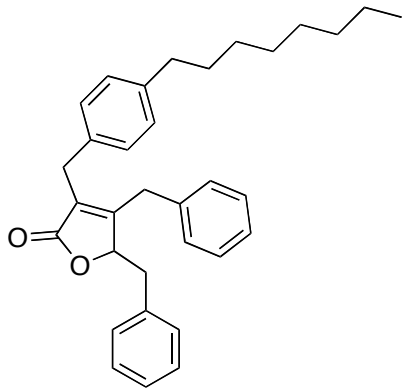
^{1}H-NMR (400 MHz, $CDCl_3$): 7.34 – 7.23 (m, 6 H), 7.17 – 7.12 (m, 2 H), 7.07 – 7.02 (m, 2 H), 6.81 – 6.76 (m, 2 H), 6.76 – 6.70 (m, 2 H), 4.97 – 4.89 (m, 1 H), 4.14 – 4.06 (m, 2 H), 3.91 (d, *J* = 15.6 Hz, 1 H), 3.87 – 3.82 (m, 2 H), 3.77 – 3.72 (m, 2 H), 3.72 – 3.64 (m, 4 H), 3.60 (dt, *J* = 4.4, 1.6 Hz, 2 H), 3.57 – 3.49 (m, 4 H), 3.46 (d, *J* = 15.4 Hz, 1 H), 3.22 (dd, *J* = 14.5, 4.0 Hz, 1 H), 2.81 (dd, *J* = 14.5, 6.2 Hz, 1 H), 1.21 (t, *J* = 7.0 Hz, 3 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 173.7, 161.5, 157.5, 136.1, 135.0, 130.1, 129.6, 129.3, 129.2, 129.0, 128.8, 128.7, 127.4, 127.3, 114.9, 81.7, 71.0, 70.9, 70.8, 70.0, 69.9, 67.6, 66.8, 38.1, 33.3, 28.7, 15.3.

IR (neat): 2870, 1750, 1609, 1510, 1454, 1245, 1107, 1049, 830, 749, 702.

HRMS: Calculated for $C_{33}H_{42}NO_6$ $[M+NH_4]^+$: 548.3007, found: 548.3003.

4,5-Dibenzyl-3-(4-octylbenzyl)furan-2(5H)-one (30)



A solution of 4,5-dibenzyl-3-(4-hydroxybenzyl)furan-2(5H)-one (**28**, 50 mg, 0.14 mmol, 1.0 eq.) in a mixture of dry CH_2Cl_2 (3 ml) and dry pyridine (1 ml) was cooled to 0 °C. To the cooled solution was added trifluoromethansulfonic anhydride (28 µl, 0.16 mmol, 1.2 eq.) over five minutes. The reaction mixture was stirred for 30 minutes at 0 °C and 30 minutes at room temperature. Since a TLC shows only little conversion, additional trifluoromethansulfonic anhydride (28 µl, 0.16 mmol, 1.2 eq.) was added at 0 °C. After stirring for 15 minutes at 0 °C and 45 minutes at room temperature a TLC confirmed complete conversion. The reaction was cooled to 0 °C and quenched with a 1 M aq. HCl solution. The layers were separated and the aq. layer was extracted twice with CH_2Cl_2. The org. layers were subsequently washed with a 1 M aq. HCl solution and a sat. aq. $NaHCO_3$ solution, combined, dried with Na_2SO_4 and concentrated to give the activated intermediate (59 mg, 0.12 mmol, 87%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.39 – 7.23 (m, 6 H), 7.19 – 7.12 (m, 2 H), 7.08 – 7.01 (m, 4 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 5.02 (t, *J* = 4.6 Hz, 1 H), 3.89 (d, *J* = 15.7 Hz, 1 H), 3.67 – 3.47 (m, 3 H), 3.30 (dd, *J* = 14.6, 4.1 Hz, 1 H), 2.88 (dd, *J* = 14.6, 5.4 Hz, 1 H).

^{19}F-NMR (376 MHz, $CDCl_3$, no ^{19}F reference): -72.86 (s).

A solution of 9-borabicyclo[3.3.1]nonane (0.5 M solution in THF, 320 µl, 0.16 mmol, 1.4 eq.) was cooled to 0 °C before 1-octene (26 µl, 0.16 mmol, 1.4 eq.) was added. The mixture was stirred for 30 minutes at 0 °C, giving solution A. To a second solution of the triflate intermediate (58 mg, 0.12 mmol, 1.0 eq.) and 1,1'-bis(diphenylphosphino)ferrocene-paladium(II) dichloride*CH_2Cl_2 (5 mg, 6 µmol, 0.05 eq.) in dry THF (1 ml) was added a 3 M aq. NaOH solution (0.12 ml). This was followed by the addition of solution A. The reaction mixture was stirred at reflux

overnight and concentrated forming a black residue. The residue was mixed with water and extracted three times with TBME. The org layers were combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (10:1)) and subsequently by preparative TLC (SiO_2, pentane/EtOAc (9:1)) to give the title compound **30** (14 mg, 0.030 mmol, 26%) as pale yellow oil. Over both steps, a yield of 23% was achieved.

Rf (SiO_2, pentane/EtOAc (9:1)): 0.45.

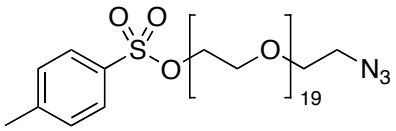
^{1}H-NMR (500 MHz, $CDCl_3$): 7.32 – 7.23 (m, 6 H), 7.17 – 7.12 (m, 2 H), 7.04 – 6.97 (m, 4 H), 6.82 (d, *J* = 7.9 Hz, 2 H), 4.96 – 4.88 (m, 1 H), 3.94 (d, *J* = 15.5 Hz, 1 H), 3.58 (d, *J* = 5.3 Hz, 2 H), 3.47 (d, *J* = 15.5 Hz, 1 H), 3.22 (dd, *J* = 14.5, 4.0 Hz, 1 H), 2.81 (dd, *J* = 14.6, 6.3 Hz, 1 H), 2.59 – 2.50 (m, 2 H), 1.60 – 1.55 (m, 3 H), 1.33 – 1.24 (m, 10 H), 0.88 (t, *J* = 6.9 Hz, 3 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 173.7, 161.6, 141.1, 136.2, 135.1, 135.0, 129.6, 129.2, 128.9, 128.8, 128.8, 128.7, 128.2, 127.4, 127.2, 81.7, 38.2, 35.7, 33.3, 32.1, 31.7, 29.7, 29.5, 29.4, 29.1, 22.8, 14.3.

IR (neat): 2925, 2854, 1752, 1512, 1495, 1454, 1337, 1078, 1049, 1008, 750, 700.

HRMS: Calculated for $C_{33}H_{38}NaO_2$ $[M+Na]^+$: 489.2760, found: 489.2763.

***O*-(2-Azidoethyl)-*O*'-tosylnonadecaethylene glycol (31)**



To a solution of *O*-(2-azidoethyl)nonadecaethylene (19 mg, 0.020 mmol, 1.0 eq.) in dry THF (0.5 ml) and NEt_3 (0.2 ml) at 0 °C was added *p*-toluenesulfonyl chloride (11 mg, 0.060 mmol, 3.0 eq.). The reaction was allowed to reach room temperature overnight. An ESI-MS measurement showed still starting material in the reaction mixture. Additional *p*-toluenesulfonyl chloride (15 mg, 0.082 mmol, 4.1 eq.) was added and the reaction was stirred overnight. The finished reaction was poured on a mixture of ice and a 37% aq. HCl solution. The resulting mixture was once extracted with Et_2O. The aq. layer was saturated with NaCl and extracted four times with EtOAc. The org. layers were washed with a sat. aq. $NaHCO_3$ solution, combined, dried with Na_2SO_4 and concentrated to give the title compound **31** (19 mg, 0.018 mmol, 88%) as clear oil.

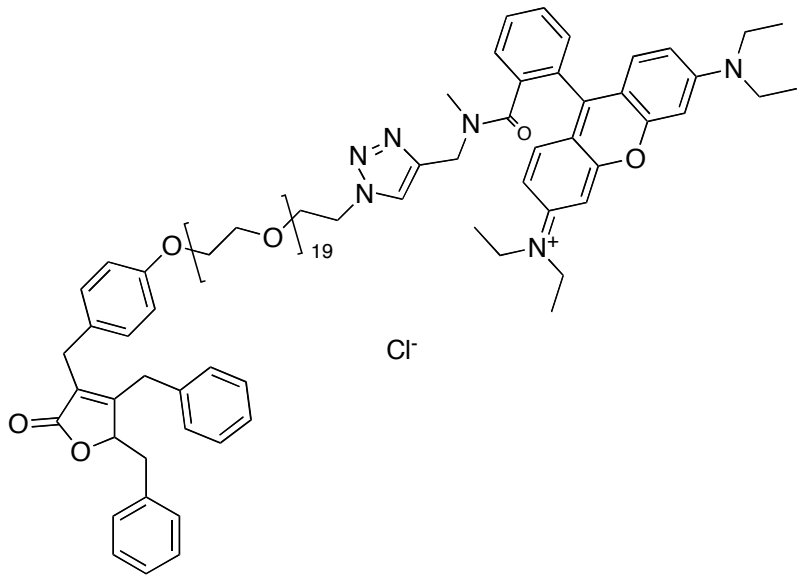
^{1}H-NMR (400 MHz, $CDCl_3$): 7.81 – 7.76 (m, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 4.14 (dd, *J* = 5.4, 4.3 Hz, 2 H), 3.69 – 3.59 (m, 72 H), 3.57 (s, 4 H), 3.41 – 3.34 (m, 2 H), 2.43 (s, 3 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 144.9, 133.1, 129.9, 128.1, 70.9, 70.8, 70.8, 70.7, 70.7, 70.6, 70.1, 69.4, 68.8, 50.8, 21.8.

IR (neat): 2921, 2858, 2108, 1457, 1351, 1293, 1248, 1177, 1095, 1037, 923, 849, 818, 778, 664, 555.

HRMS: Calculated for $C_{47}H_{87}N_3Na_2O_{22}S$ $[M+2Na]^{2+}$ 561.7645, found: 561.7643.

Rhodamine B maculalactone A hybrid (33)



To a solution of *O*-(2-Azidoethyl)-*O*'-tosylnonadecaethylene glycol (**31**, 76 mg, 0.065 mmol, 1.0 eq.) in acetone (2 ml) was first added 4,5-dibenzyl-3-(4-hydroxybenzyl)furan-2(5H)-one (**28**, 48 mg, 0.13 mmol, 2.0 eq.) followed by potassium carbonate (20 mg, 0.14 mmol, 2.2 eq.). The mixture was heated to reflux for 24 hours. The reaction was filtrated and concentrated to give 220 mg crude product. To a solution of the crude product and *N*-(6-(diethylamino)-9-(2-(methyl(prop-2-yn-1-yl)carbamoyl)phenyl)-3*H*-xanthen-3-ylidene)-*N*-ethylethanaminium chloride (**32**, 35 mg, 0.065 mmol, 1.0 eq.) in CH_2Cl_2 (5 ml) and water (5 ml) was added copper(II) sulfate (2 mg, 0.01 mmol, 0.2 eq.) and L-ascorbic acid (3 mg, 0.01 mmol, 0.2 eq.). The mixture was vigorously stirred at room temperature. After four days, *t*BuOH (5 ml) and after seven days, additional L-ascorbic acid (3 mg, 0.01 mmol, 0.2 eq.) was added. After 10 days, the reaction was concentrated and separated by preparative HPLC (Phenomenex Gemini C18, CH_3CN/water (1:4 to 3:2)) and (Phenomenex Gemini C18,

CH_3CN/water + 0.1% HCO_2H (2:3 to 3:2)) to give the title compound **33** (26 mg, 0.014 mmol, 22%) as purple oil.

^{1}H-NMR (500 MHz, MeOD): 7.95 (d, *J* = 14.0 Hz, 0.4 H), 7.75 (t, *J* = 5.7 Hz, 2 H), 7.69 (d, *J* = 7.0 Hz, 0.6 H), 7.53 – 7.42 (m, 2 H), 7.33 – 7.13 (m, 12 H), 7.06 (d, *J* = 8.8 Hz, 0.4 H), 7.02 – 6.92 (m, 3.6 H), 6.73 (s, 4 H), 5.01 (t, *J* = 4.5 Hz, 1 H), 4.59 – 4.52 (m, 0.6 H), 4.48 – 4.39 (m, 3 H), 4.10 – 4.04 (m, 2 H), 3.96 (d, *J* = 15.5 Hz, 1 H), 3.88 (s, 0.4 H), 3.85 – 3.77 (m, 4 H), 3.73 – 3.48 (m, 81.4 H), 3.46 (s, 2 H), 3.28 (dd, *J* = 14.7, 3.9 Hz, 1 H), 2.99 (s, 2 H), 2.90 (dd, *J* = 14.6, 5.7 Hz, 1 H), 2.67 (s, 0.6 H), 1.32 (t, *J* = 6.3 Hz, 12 H).

^{13}C-NMR (126 MHz, MeOD): 175.8, 170.2, 164.3, 159.3, 159.1, 158.7, 157.2, 157.1, 156.8, 137.8, 137.0, 136.4, 133.1, 132.1, 131.7, 131.4, 131.3, 131.1, 130.8, 130.3, 130.1, 129.5, 129.5, 128.6, 128.2, 128.1, 125.4, 115.7, 115.4, 115.2, 114.8, 97.3, 83.6, 71.7, 71.6, 71.5, 71.4, 70.9, 70.3, 68.6, 51.5, 46.9, 42.8, 38.5, 38.5, 33.9, 29.1, 13.0.

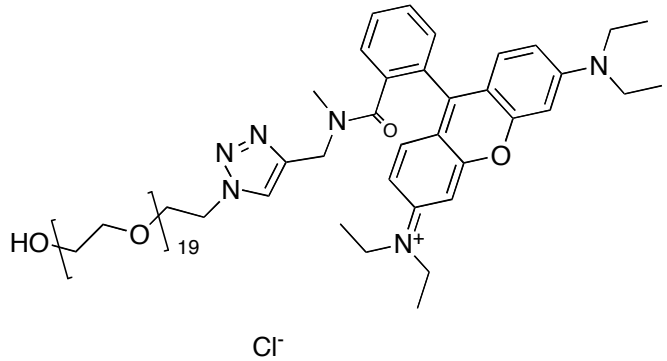
IR (neat): 3398, 2907, 2871, 2359, 2332, 1750, 1634, 1589, 1470, 1414, 1346, 1276, 1249, 1182, 1133, 1105, 684.

HRMS: Calculated for $C_{97}H_{137}N_6Na_2O_{24}$ $[M+2Na]^{3+}$ 605.3154, found: 605.3163.

HPLC (Phenomenex Gemini C18, CH_3CN/water (5 min 2:3, in 25 min to 3:2), 1 ml/min, 540 nm): single peak at 14.5 minutes retention time.

UV/VIS: λ_{max} (H_2O) = 568 nm.

Rhodamine B with linker (34)



To a solution of *O*-(2-Azidoethyl)nonadecaethylene (54 mg, 0.055 mmol, 1.0 eq.) and *N*-(6-(diethylamino)-9-(2-(methyl(prop-2-yn-1-yl)carbamoyl)phenyl)-3*H*-xanthen-3-ylidene)-*N*-ethylethanaminium chloride (**32**, 29 mg, 0.055 mmol, 1.0 eq.) in *t*BuOH (4 ml) and water (4 ml) was added copper(II) sulfate (4 mg, 0.03 mmol, 0.5 eq.) and L-ascorbic acid (11 mg, 0.055 mmol, 1.0 eq.). The mixture was vigorously stirred at

room temperature. After five and again after six days, additional L-ascorbic acid (11 mg, 0.055 mmol, 1.0 eq.) was added. After 13 days, the reaction was concentrated and separated by preparative HPLC (Phenomenex Gemini C18, CH_3CN/water + 0.1% HCO_2H (1:17 to 9:11)) and (Phenomenex Synergi Hydro-RP, CH_3CN/water + 0.1% HCO_2H (1:19 to 4:1)) giving 19 mg of product, which still contained impurities. Subsequently, the mixture was purified by preparative TLC (SiO_2, CH_2Cl_2/MeOH (4:1)) giving 10 mg still impure product. This was again separated by semi-preparative HPLC (Phenomenex Synergi Hydro-RP, CH_3CN/water + 0.1% HCO_2H (2 min 1:19, in 3 min to 3:7, in 25 min to 4:1)) to give the title compound **34** (2 mg, 1.2 µmol, 3%) as purple oil.

^{1}H-NMR (400 MHz, MeOD): 8.55 (s, 1 H), 8.10 (s, 0.4 H), 7.80 – 7.67 (m, 1.6 H), 7.51 – 7.42 (m, 0.6 H), 7.35 – 7.29 (m, 0.4 H), 7.27 – 7.18 (m, 2 H), 7.04 – 6.93 (m, 2 H), 6.42 – 6.33 (m, 2 H), 4.64 – 4.51 (m, 2 H), 4.49 – 4.39 (m, 2 H), 3.80 (t, J = 5.0 Hz, 1 H), 3.75 – 3.47 (m, 83 H), 3.42 – 3.33 (m, 4 H), 3.05 (s, 1 H), 3.00 (s, 1 H), 1.33 (t, J = 7.1 Hz, 6 H), 1.19 – 1.10 (m, 6 H).

IR (neat): 3485, 2871, 1618, 1590, 1512, 1468, 1414, 1349, 1276, 1249, 1181 ,1112, 949, 824, 779, 646, 609.

HRMS: Calculated for $C_{72}H_{119}N_6O_{22}$ $[M+2H]^{3+}$ 473.2787, found: 473.2793.

HPLC (Phenomenex Synergi Hydro-RP, CH_3CN/water + 0.1% HCO_2H (2 min 1:19, in 3 min to 3:7, in 25 min to 4:1), 1 ml/min, 540 nm): single peak at 14.8 minutes retention time.

UV/VIS: λ_{max} (H_2O) = 563 nm.

SAR Studies and Visualization of Maculalactone A in *Artemia salina*

Assay with *Thamnocephalus platyurus*

The assay "Thamnotoxkit F^{TM}" was purchased from MicrobioTest Inc., Kleimoer 15, 9030 Mariakerke (Gent), Belgium. The assay was conducted as described in the standard operating procedure.

The standard freshwater (SFW) was prepared as described and oxygenated prior use by bubbling air for 30 minutes through it. Diluted standard freshwater (DFW) was prepared by mixing SFW (2.5 ml) with deionized water (17.5 ml). The *T. platyurus* cysts were hydrated in DFW (0.2 ml) for 30 minutes before they were added to DFW

(10 ml) and incubated in a Petri dish for 24 hours at 25 °C under continuous light (8 W fluorescent tube lamp).

Dilutions of the test substances with concentrations of 50, 12.5, 5 and 0.5 mM in methanol were prepared. In a 24 well plate, four repetitions of each concentration were prepared by mixing 2 µl of the substance solution with 998 µl SFW giving aqueous solutions with concentrations of 100, 25, 10 and 1 µM. A blank from 2 µl methanol and 998 µl SFW was prepared. About 40 larvae were added to the first vial of each dilution by a pipette. From there, 10 larvae were transported to each of the remaining three vials of each concentration. Only these three vials were counted. The plate was covered with parafilm and incubated for 24 hours at 25 °C in the dark.

The mortality was determined by counting the dead larvae. Death was defined as no movement within 10 seconds. The remaining larvae were killed by adding CO_2 containing water (dry ice in water) and the total amount of individuals in each vial was determined.

Test Substance	0 µM Dead/ Total	1 µM Dead/ Total	10 µM Dead/ Total	25 µM Dead/ Total	100 µM Dead/ Total
1	1/10	1/10	3/10	2/10	5/10
	0/10	0/10	2/11	4/10	5/11
	0/10	0/10	5/9	3/10	7/10
25	0/10	0/10	2/8	8/14	7/10
	0/10	0/9	3/10	1/10	3/10
	0/8	0/8	6/10	3/9	5/10
26	0/9	0/10	5/12	2/9	1/10
	0/11	0/10	1/10	2/10	3/10
	0/11	0/11		1/10	2/10
27	0/10	0/10	0/10	0/11	0/10
	0/10	0/10	2/10	0/10	2/10
	0/10	0/10	1/10	0/11	4/10

Table 1: Raw Data of Assay with *Thamnocephalus platyurus*. Cysts Lot: TP070512, SFW Lot: EPA200912.

Assay with *Artemia franciscana*

The assay "Artoxkit M™" was purchased from MicrobioTest Inc., Kleimoer 15, 9030 Mariakerke (Gent), Belgium. The assay was conducted as described in the standard operating procedure.

The standard seawater (SSW) was prepared as described and oxygenated prior use by bubbling air for 30 minutes trough it. The *A. franciscana* cysts were added to SSW (10 ml) and incubated in a Petri dish for 30 to 32 hours at 25 °C under continuous light (8 W fluorescent tube lamp).

Dilutions of the test substances with concentrations of 50, 12.5, 5 and 0.5 mM in methanol were prepared. In a 24 well plate, four repetitions of each concentration were prepared by mixing 2 µl of the substance solution with 998 µl SSW giving aqueous solutions with concentrations of 100, 25, 10 and 1 µM. A blank from 2 µl methanol and 998 µl SSW was prepared. About 40 larvae were added to the first vial of each dilution by a pipette. From there, 10 larvae were transported to each of the remaining three vials of each concentration. Only these three vials were counted. The plate was covered with parafilm and incubated for 33 hours at 25 °C in the dark.

The mortality was determined by counting the dead larvae. Dead was defined as no movement within 10 seconds. The remaining larvae were killed by adding CO_2 containing water (dry ice in water) and the total amount of individuals in each vial was determined.

Test Substance	0 μM Dead/ Total	1 μM Dead/ Total	10 μM Dead/ Total	25 μM Dead/ Total	100 μM Dead/ Total
1	0/9	0/11	1/9	2/10	5/10
	1/10	0/11	0/11	1/11	0/10
	0/10	0/10	0/10	1/10	4/9
25	1/11	0/9	0/10	3/9	10/11
	0/10	0/10	1/10	7/10	9/10
	0/9	0/10	0/9	7/11	9/12
26	0/10	0/10	0/11	0/10	0/11
	0/9	0/10	0/10	0/11	1/10
	1/10	1/9	0/9	0/10	0/10
27	1/10	0/9	0/10	0/10	2/10
	0/10	0/8	0/11	0/11	3/10
	0/10	1/12	0/10	0/10	2/10
29	0/10	0/10	0/11	0/9	0/10
	0/9	0/7	0/11	0/10	0/9
	0/8	0/8	0/10	1/10	0/10
33	0/10	1/10	0/10	1/10	4/9
	0/11	1/8	0/12	0/11	4/11
	0/11	1/10	0/10	0/10	4/10

Table 2: Raw Data of Assay with *Artemia franciscana*. Cysts Lot: AF/F2006, SFW Lot: ASPM060712.

Staining experiments with *Artemia salina*

The *A. salina* cysts were purchased from OOO Biotrade, Peschanaya Str. 96V of 29, Barnaul, 656049, Russia. The standard seawater (SSW) was prepared by dissolving 1.4 g "Artemia Salz" (Artemia-sal. JBL GmBH & co. KG, D-67141 Neuhofen) in tab water. The SSW was oxygenated prior use by bubbling air for 30 minutes through it. 20 mg *A. salina* cysts were added to SSW (20 ml) in a Petri and illuminated for 30 minutes trough a 3 mm layer of water (20 W energy-saver lamp). The cysts were

then incubated for 48 hours at 25 °C under continuous light (8 W fluorescent tube lamp).

Solutions with a concentration of 0.5 mM of rhodamine B, **33** and **34** in DMSO were prepared. In a 24 well plate, 2 µl of this solutions were diluted with 998 µl SSW giving a concentration of 1 µM. A blank from 2 µl DMSO and 998 µl SSW was prepared. With a pipette, about 25 larvae were added to each solution. The plate was covered with parafilm and incubated for 25 hours at 25 °C in the dark.

After incubation, some individuals were investigated under the fluorescence microscope (Figure 1).

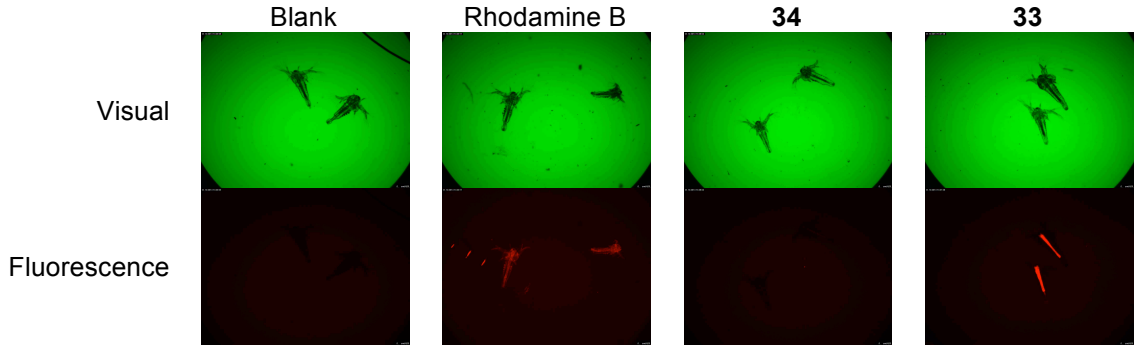


Fig 1: Pictures taken before washing. **33** results in a specific staining while **34** is inactive and rhodamine B colors the complete organism.

The remaining nauplia were transferred in a mixture of 2 µl DMSO and 998 µl SSW and incubated for three hours at 25 °C in the dark. The transfer was repeated and they were again incubated for three hours under the same conditions.

The larvae were transported in a mixture of formalin 10% and a standard PBS puffer (1:1 v/v). The larvae were fixed at 4 °C in the dark. A comparison of the different markers after washing can be found in figure 2. Further micrographs from *A. salina* stained with **33** taken by bifocal microscope are displayed in figure 3 and 4.

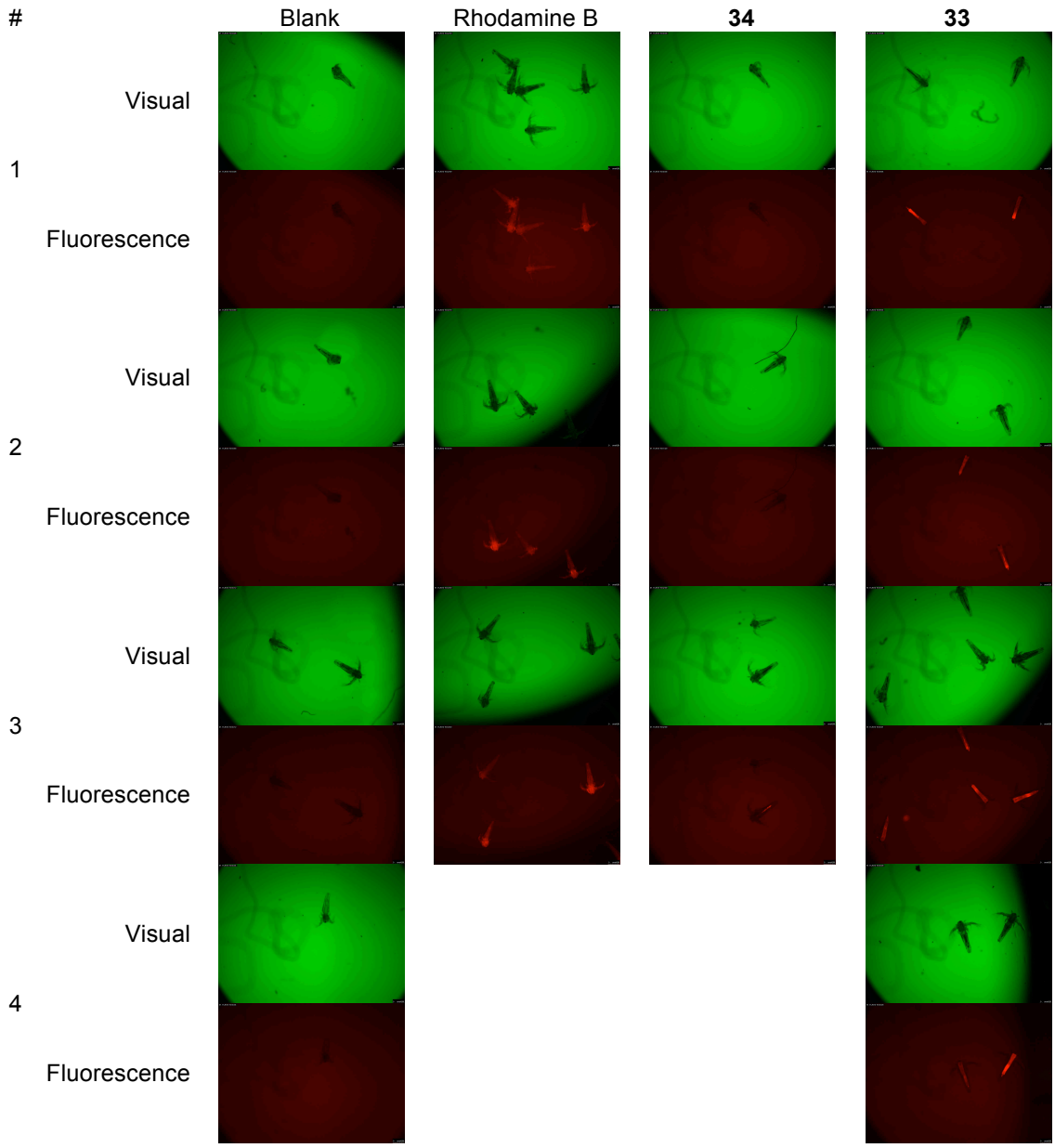


Fig 2: Pictures series taken after washing. While the blank and **34** shows no fluorescence, rhodamine B marks the complete organism and **33** stains only specific parts.

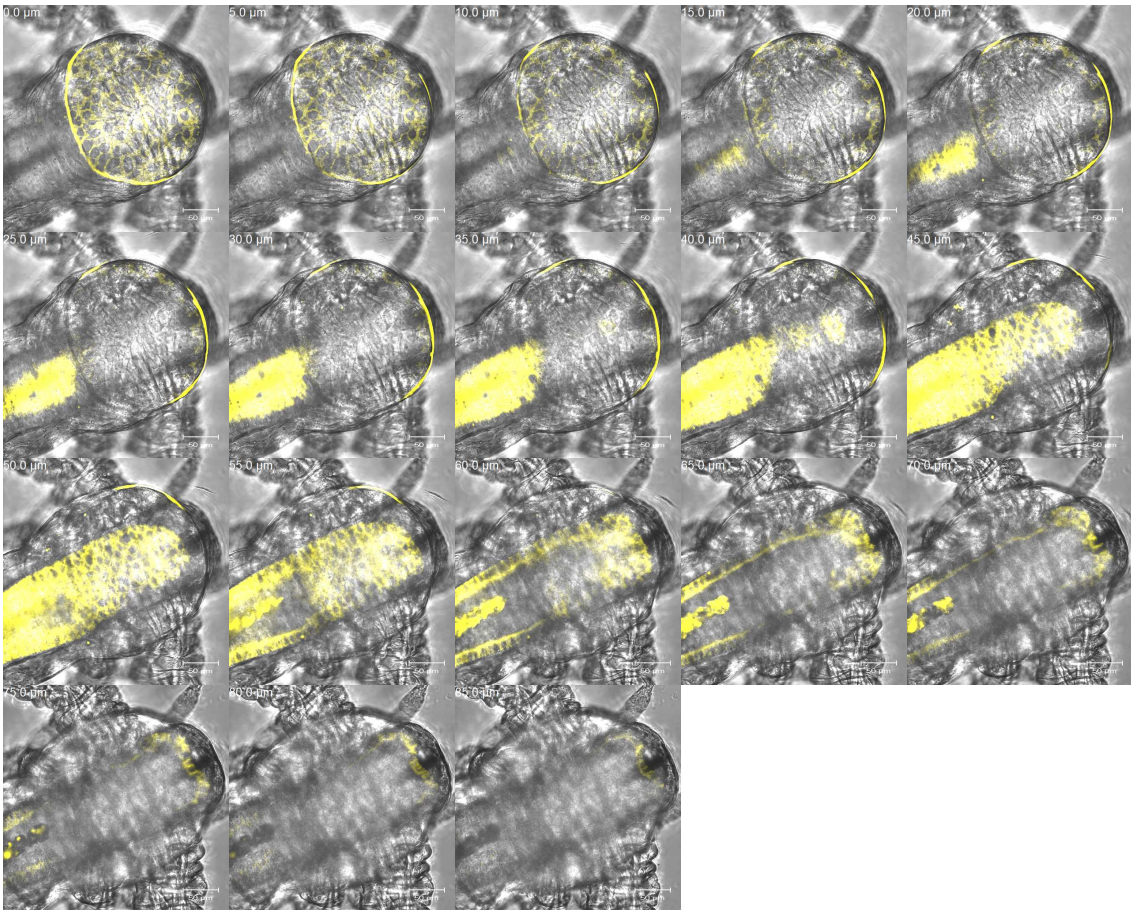


Fig 3: Head region of *Artemia salina* nauplia stained with compound **33**. Visual and fluorescence images, 10 µm slides in the y-axis, scale bar = 50 µm.

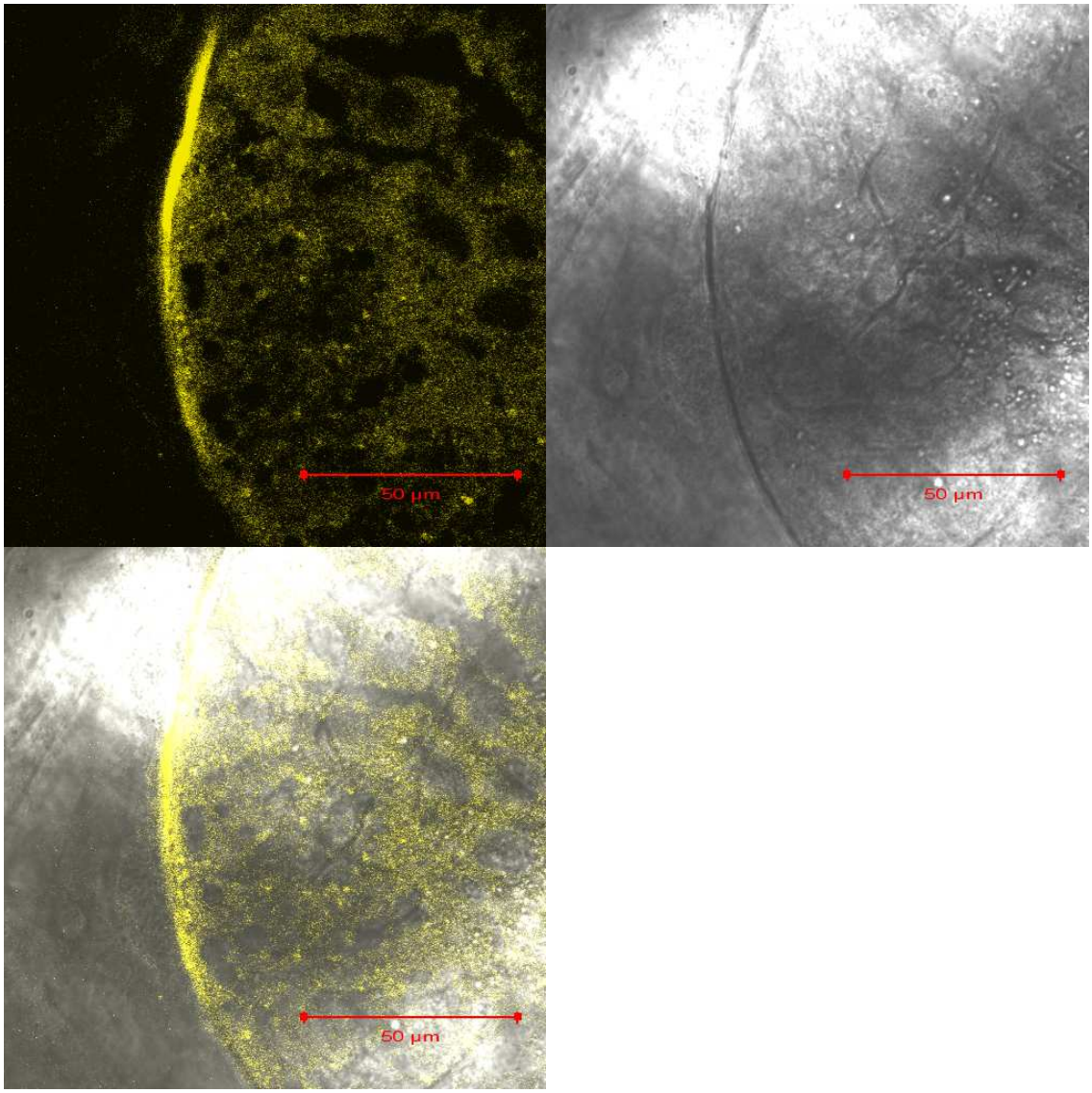
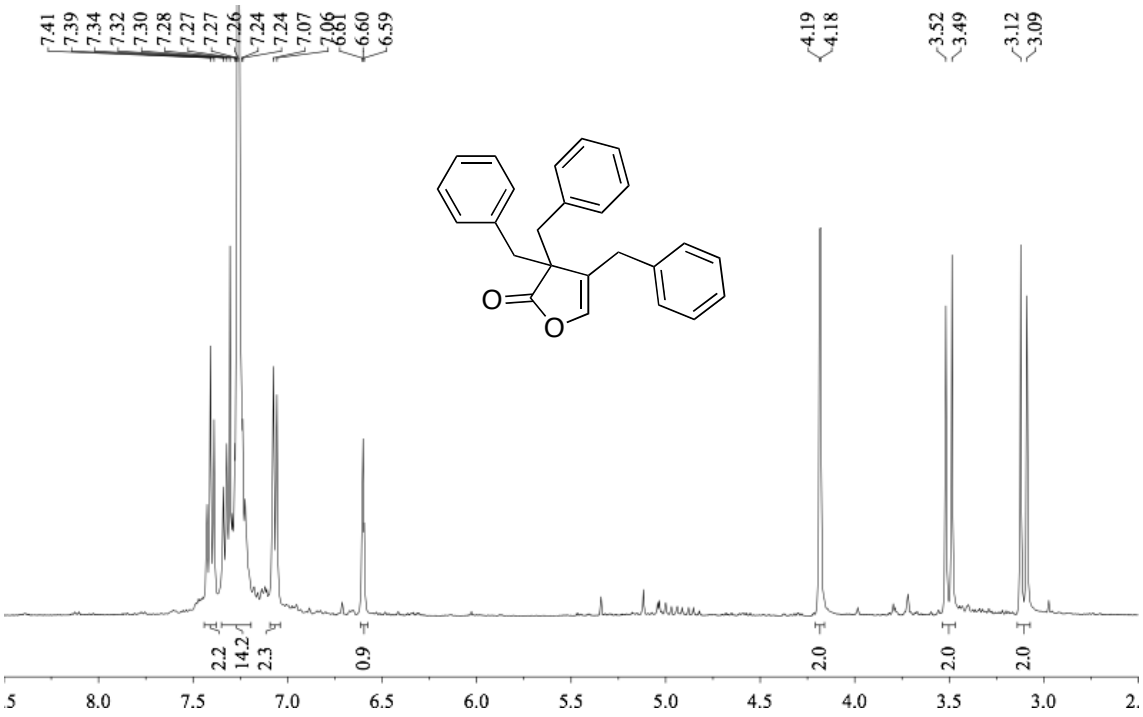


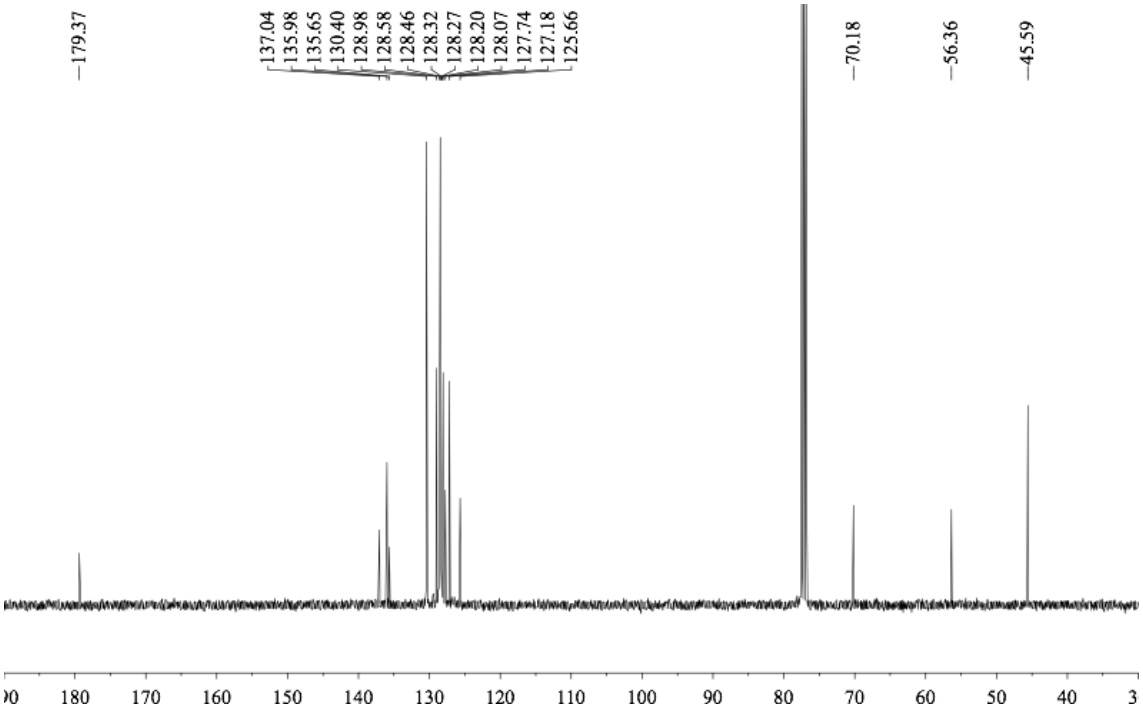
Fig 4: Close up of the circular area in the head accumulating the maculalactone A marker **33** in *Artemia salina* nauplia. Visual, fluorescence and combination images, scale bar = 50 µm.

^{1}H and ^{13}C NMR spectra

3,3,4-Tribenzylfuran-2(3H)-one (9)

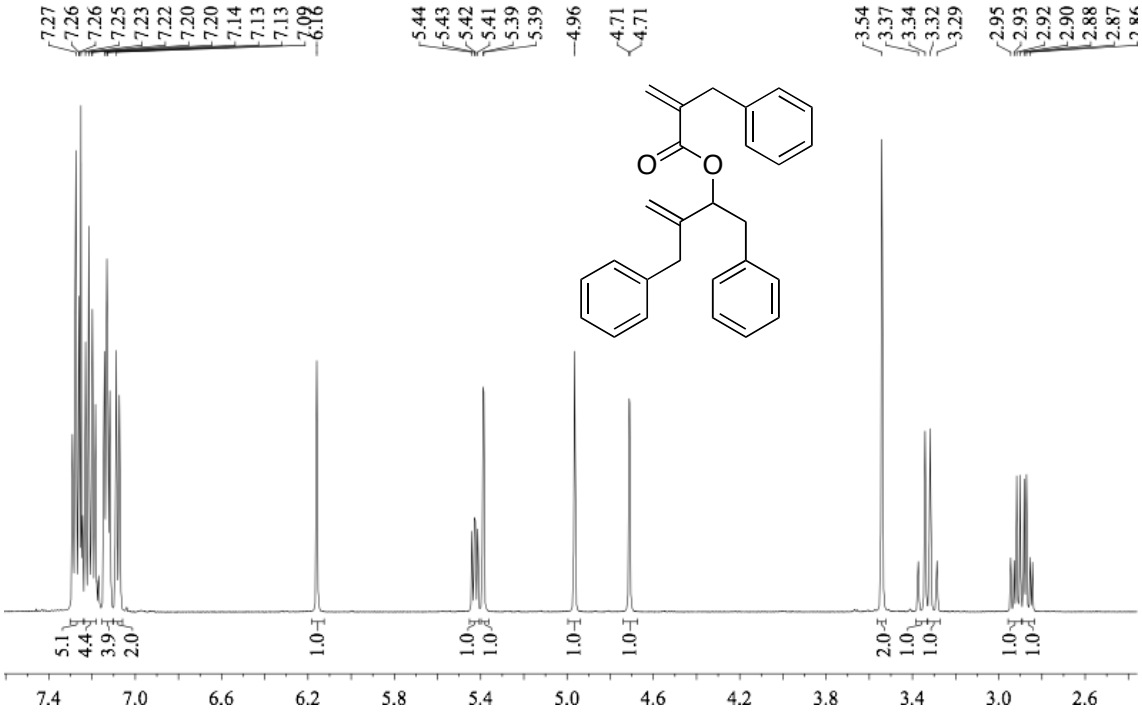


400 MHz ^{1}H-NMR in $CDCl_3$

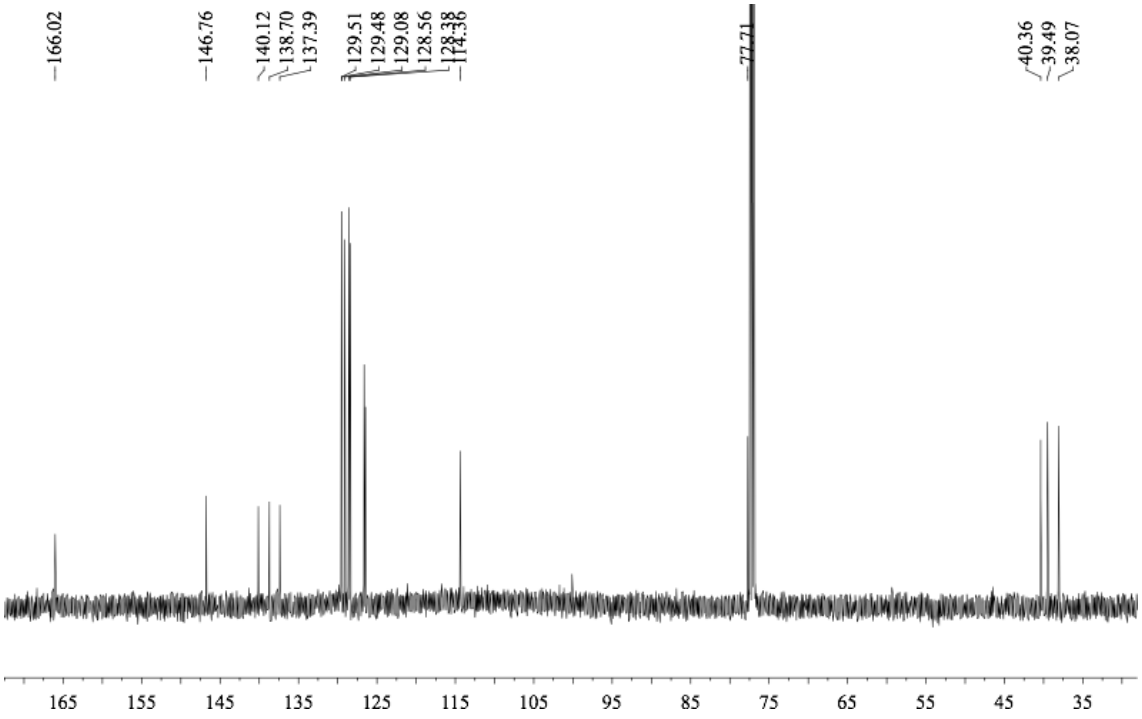


101 MHz ^{13}C-NMR in $CDCl_3$

3-Benzyl-1-phenylbut-3-en-2-yl 2-benzylacrylate (13)

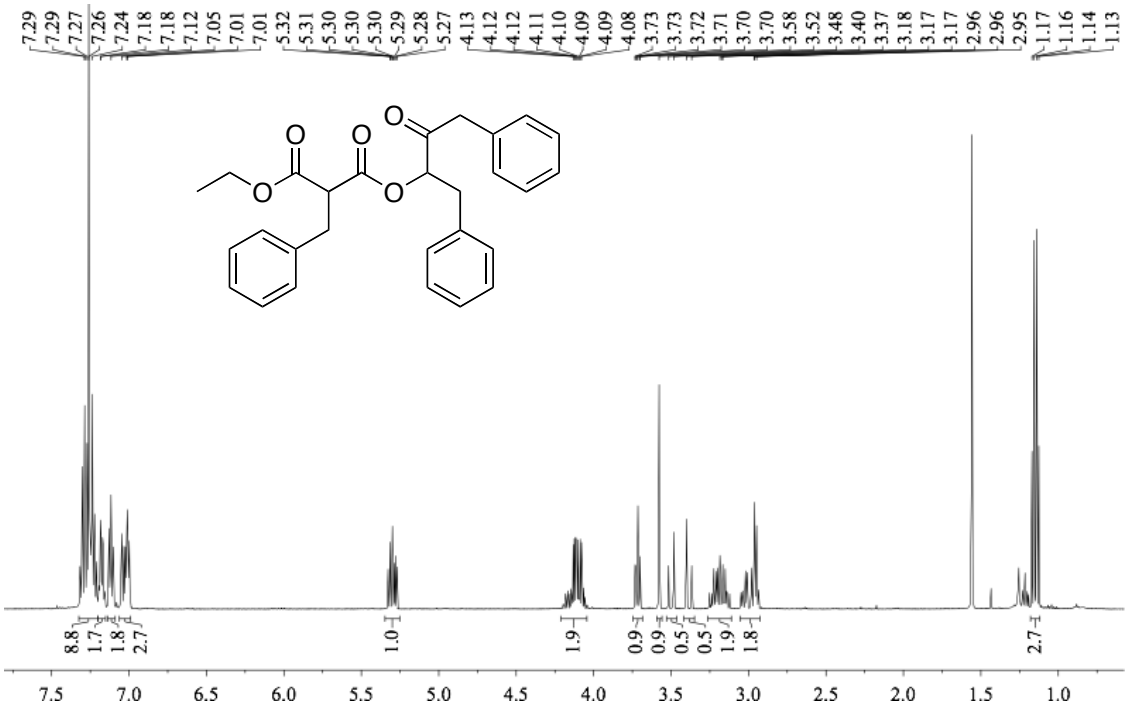


500 MHz ^{1}H-NMR in $CDCl_3$

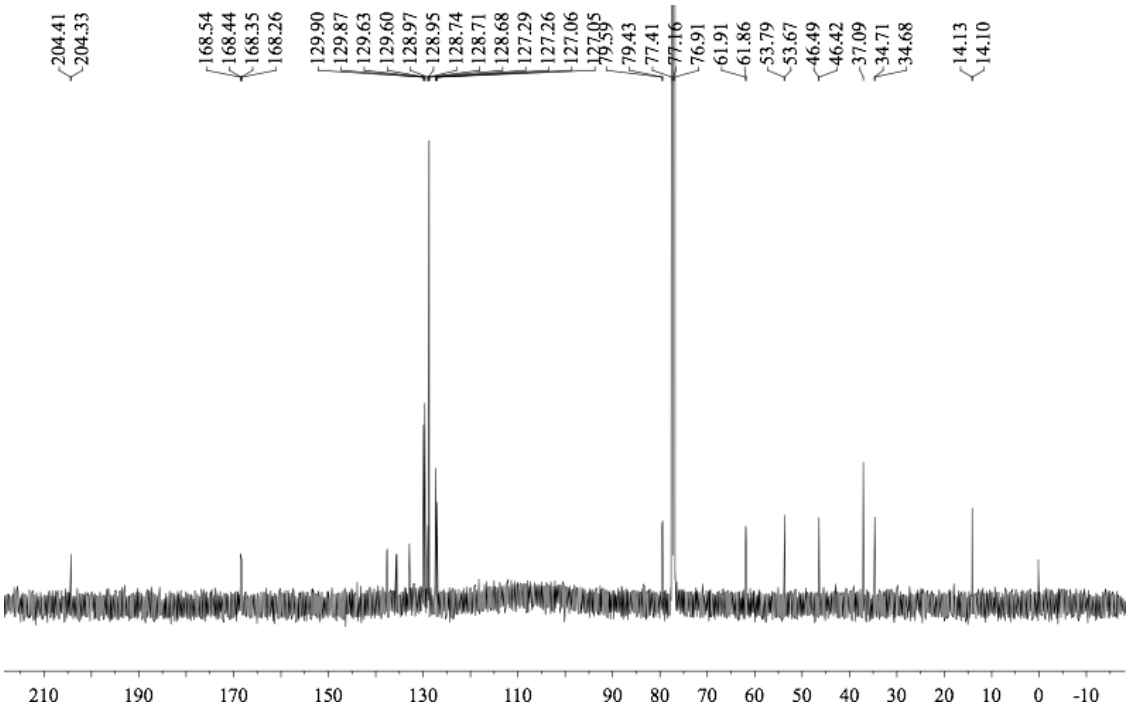


126 MHz ^{13}C-NMR in $CDCl_3$

1-Ethyl 3-(3-oxo-1,4-diphenylbutan-2-yl) 2-benzylmalonate (17) as a mixture of diastereomers

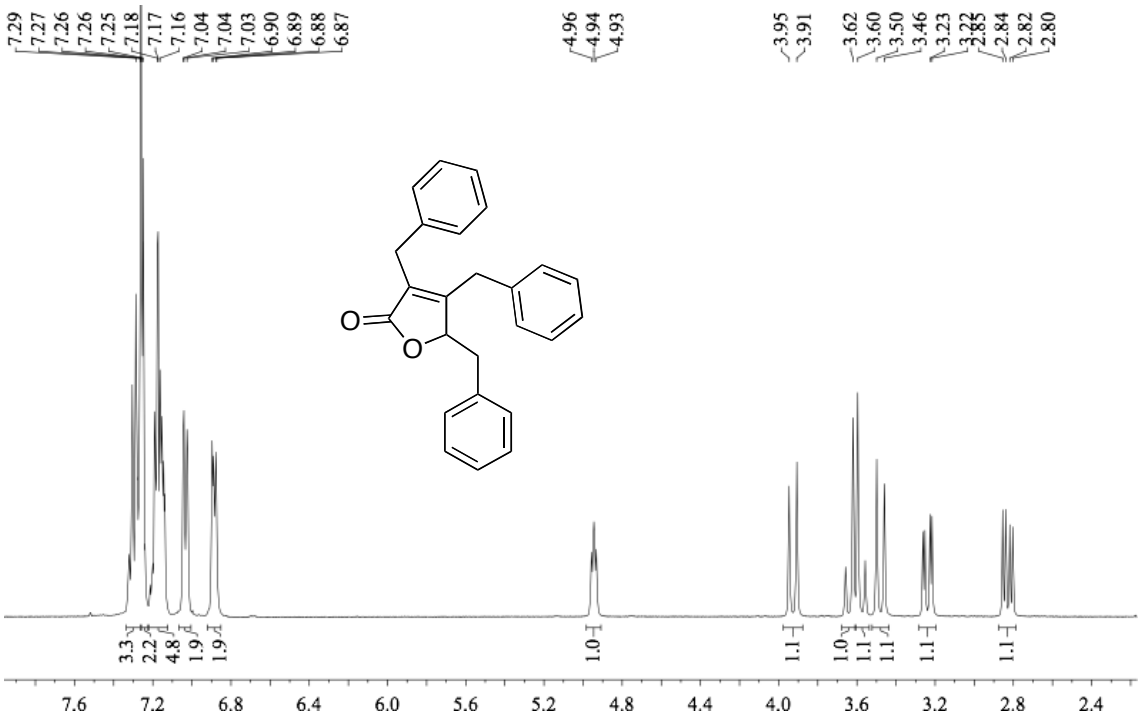


500 MHz ^{1}H-NMR in $CDCl_3$

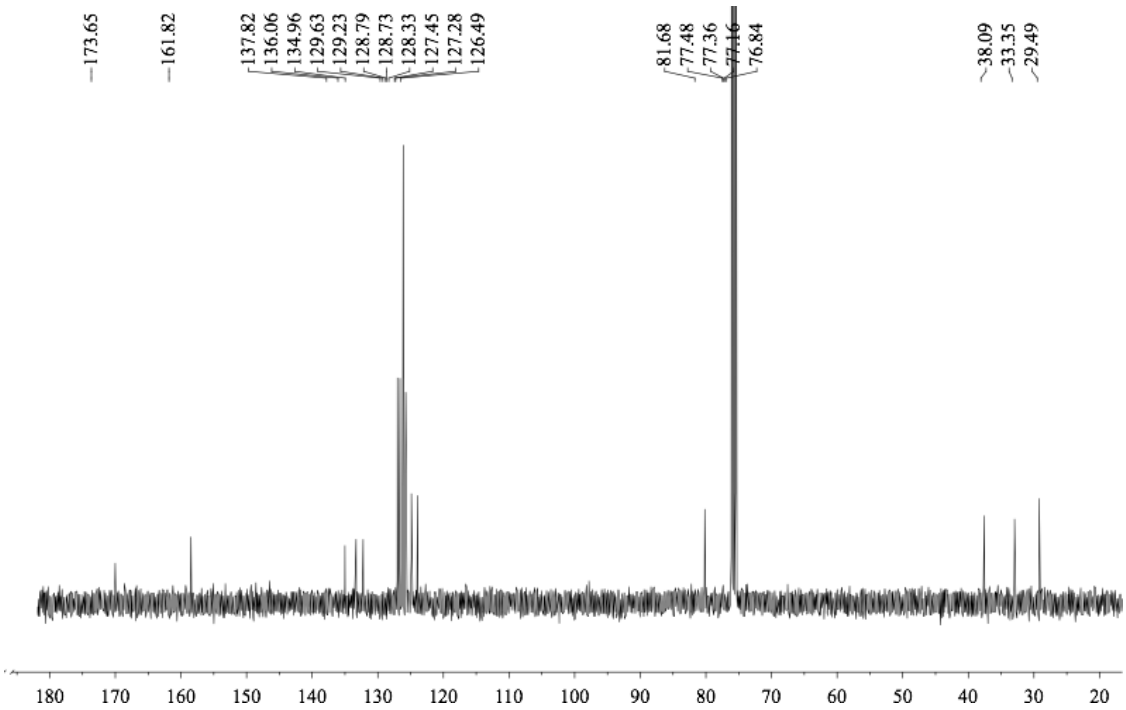


126 MHz ^{13}C-NMR in $CDCl_3$

Maculalactone A (1)

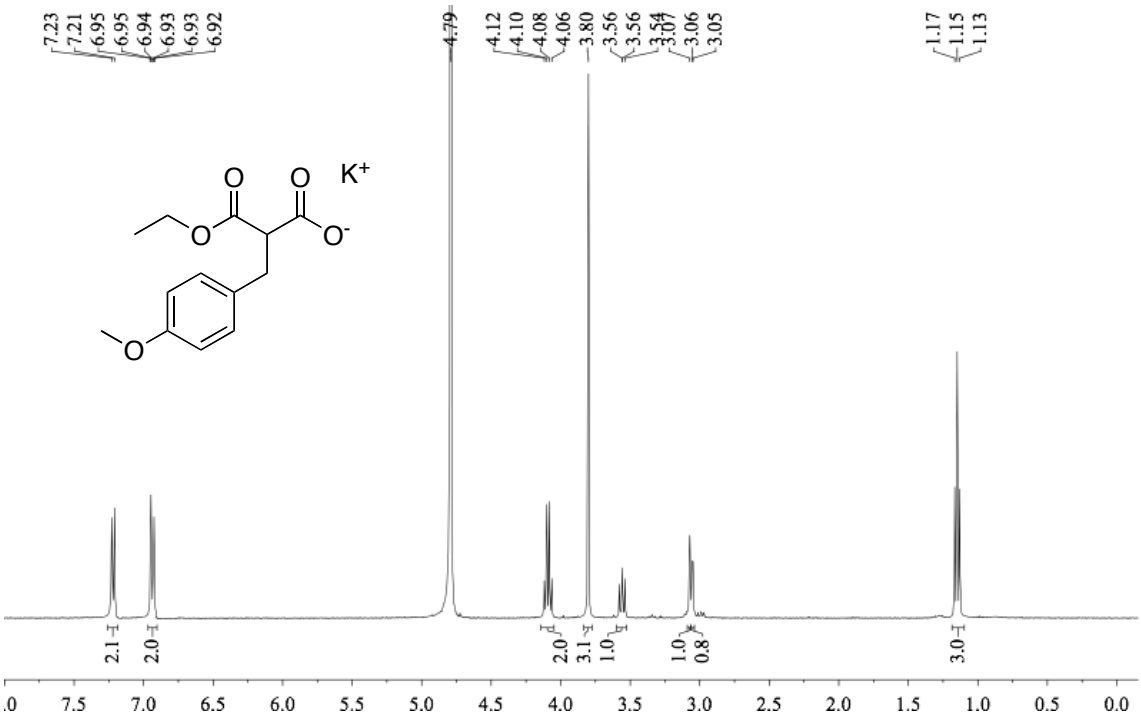


400 MHz ^{1}H-NMR in $CDCl_3$

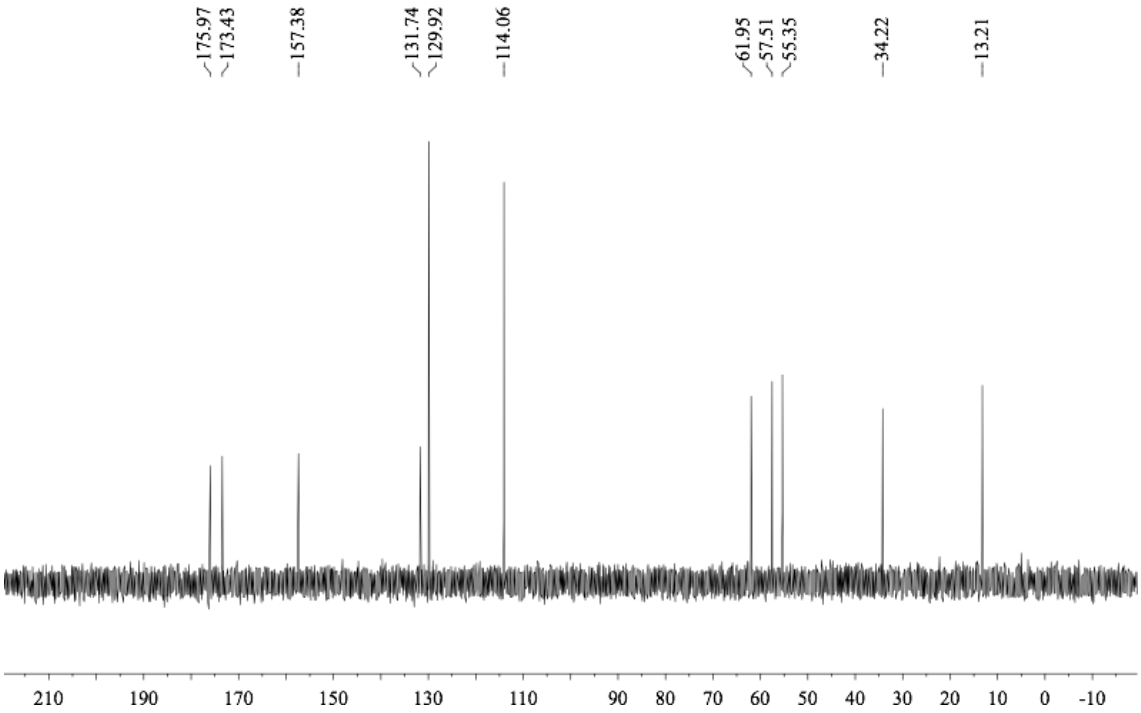


101 MHz ^{13}C-NMR in $CDCl_3$

Potassium 3-ethoxy-2-(4-methoxybenzyl)-3-oxopropanoate (18)

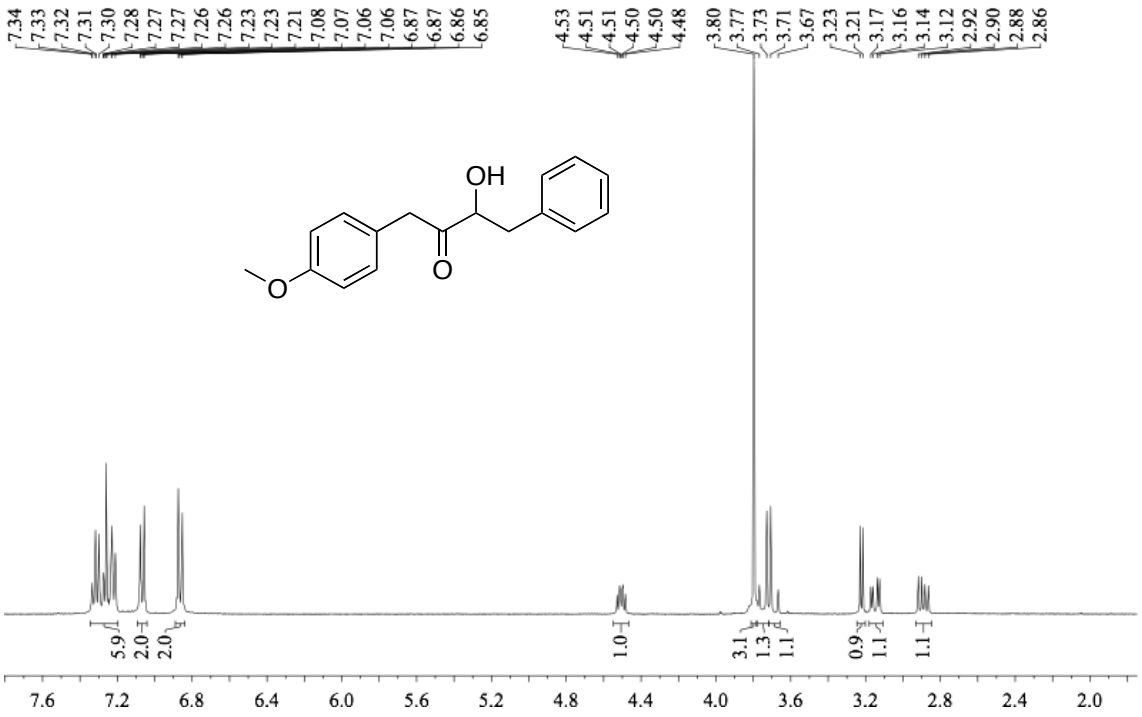


400 MHz ^{1}H-NMR in D_2O

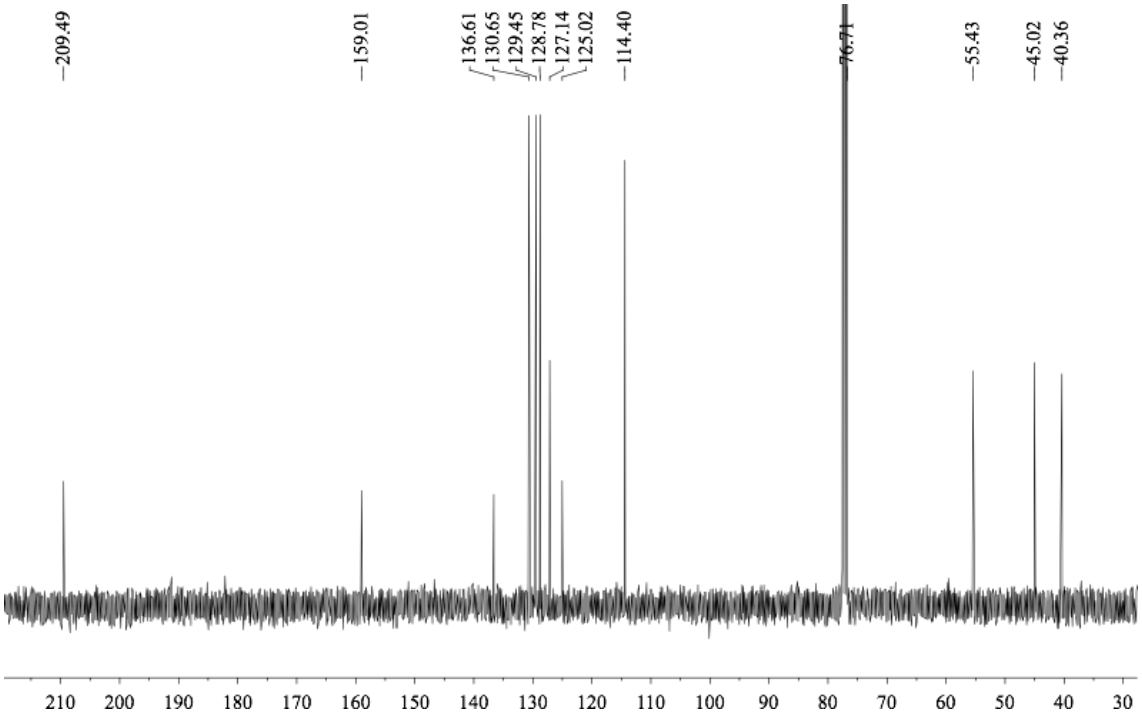


101 MHz ^{13}C-NMR in D_2O

3-Hydroxy-1-(4-methoxyphenyl)-4-phenylbutan-2-one (21)

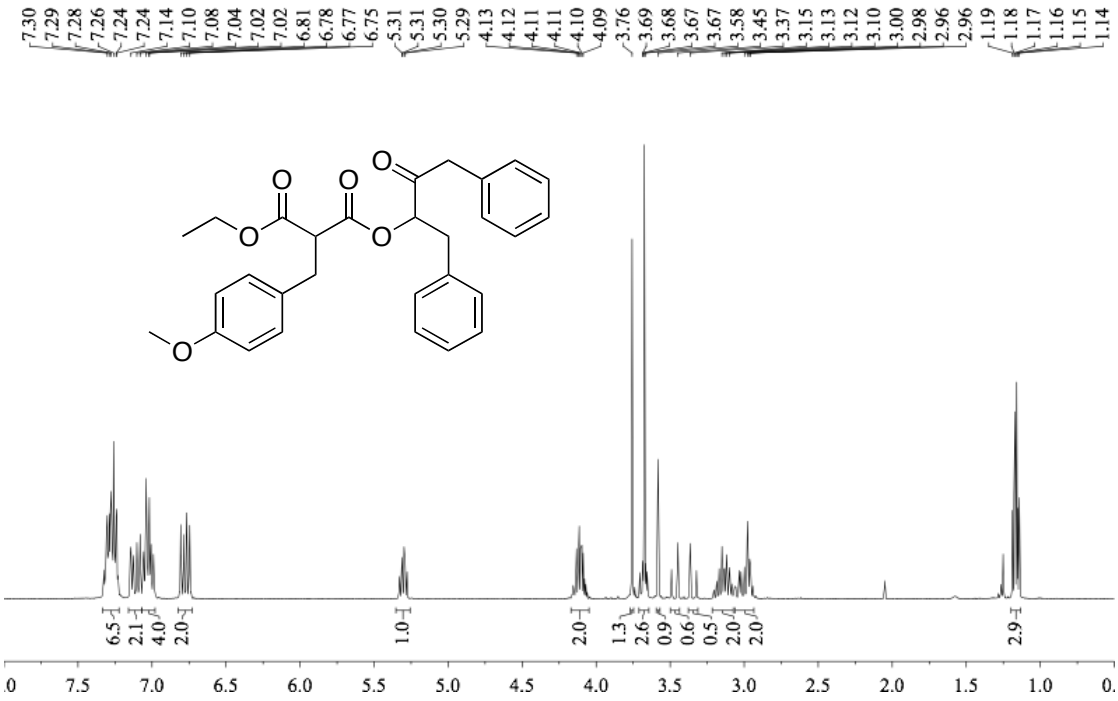


400 MHz ^{1}H-NMR in $CDCl_3$

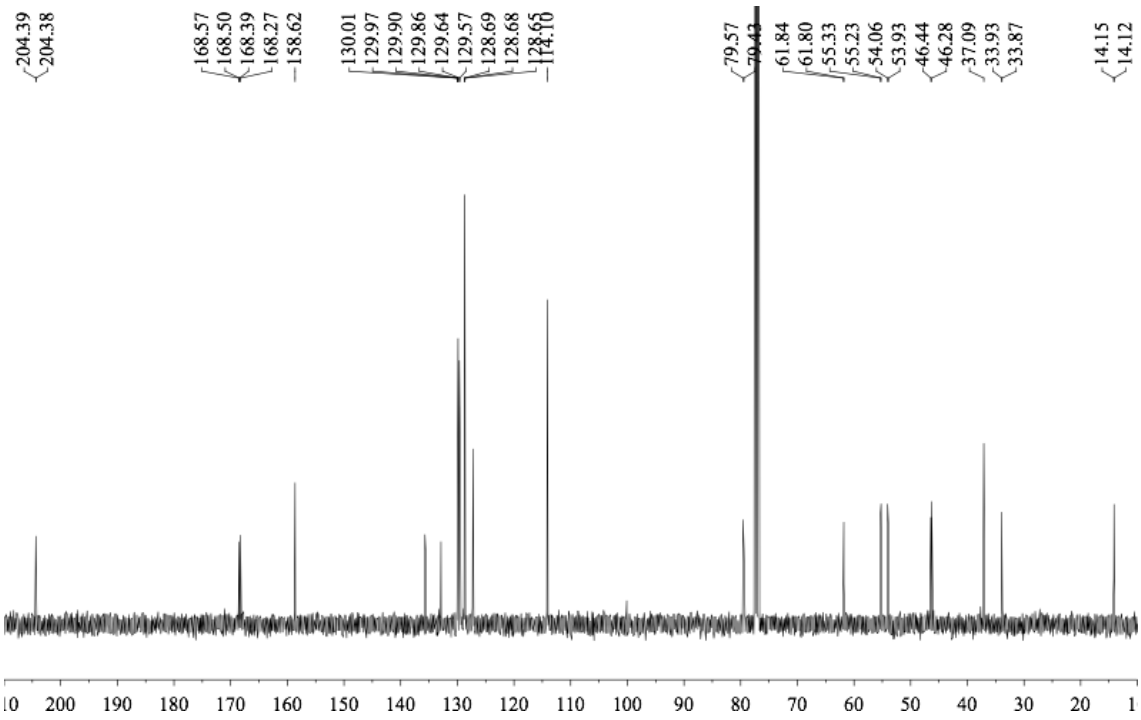


101 MHz ^{13}C-NMR in $CDCl_3$

1-Ethyl 3-(3-oxo-1,4-diphenylbutan-2-yl) 2-(4-methoxybenzyl)malonate (22) as a mixture of diastereomers

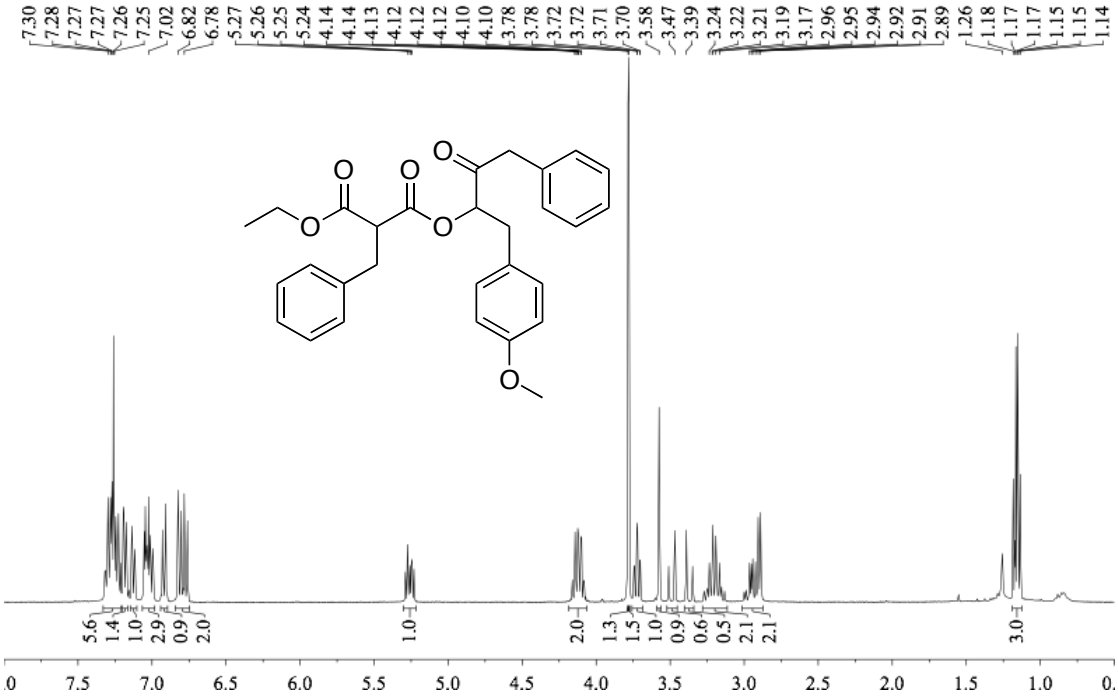


400 MHz ^{1}H-NMR in $CDCl_3$

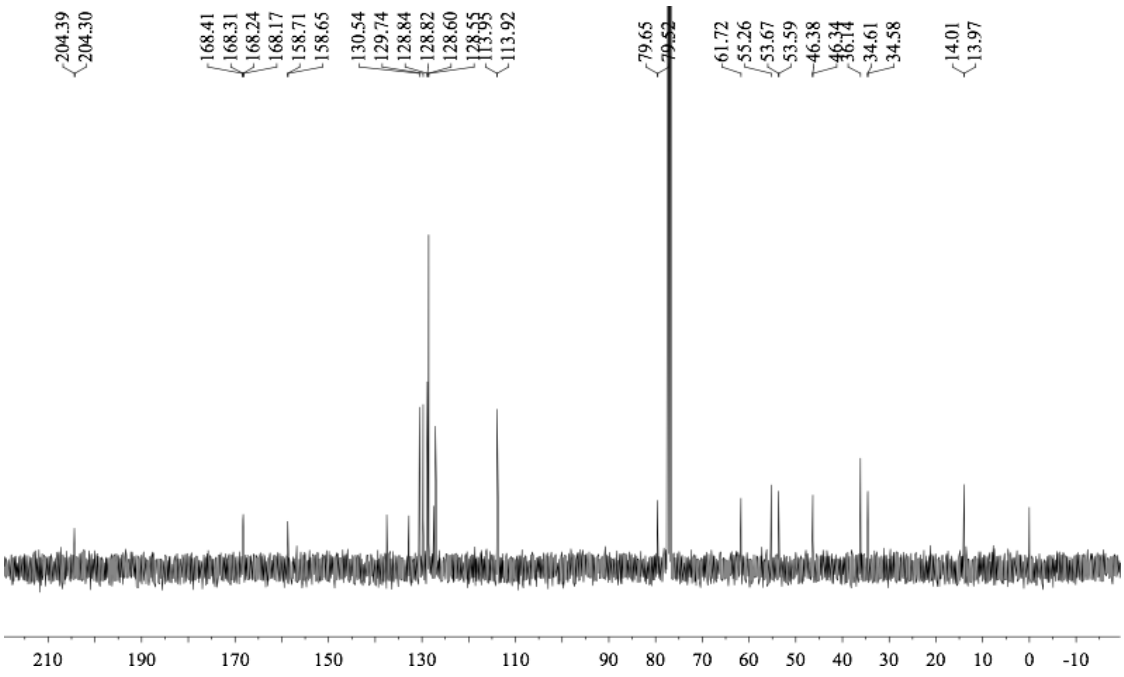


101 MHz ^{13}C-NMR in $CDCl_3$

1-Ethyl 3-(1-(4-methoxyphenyl)-3-oxo-4-phenylbutan-2-yl) 2-benzylmalonate (23) as a mixture of diastereomers

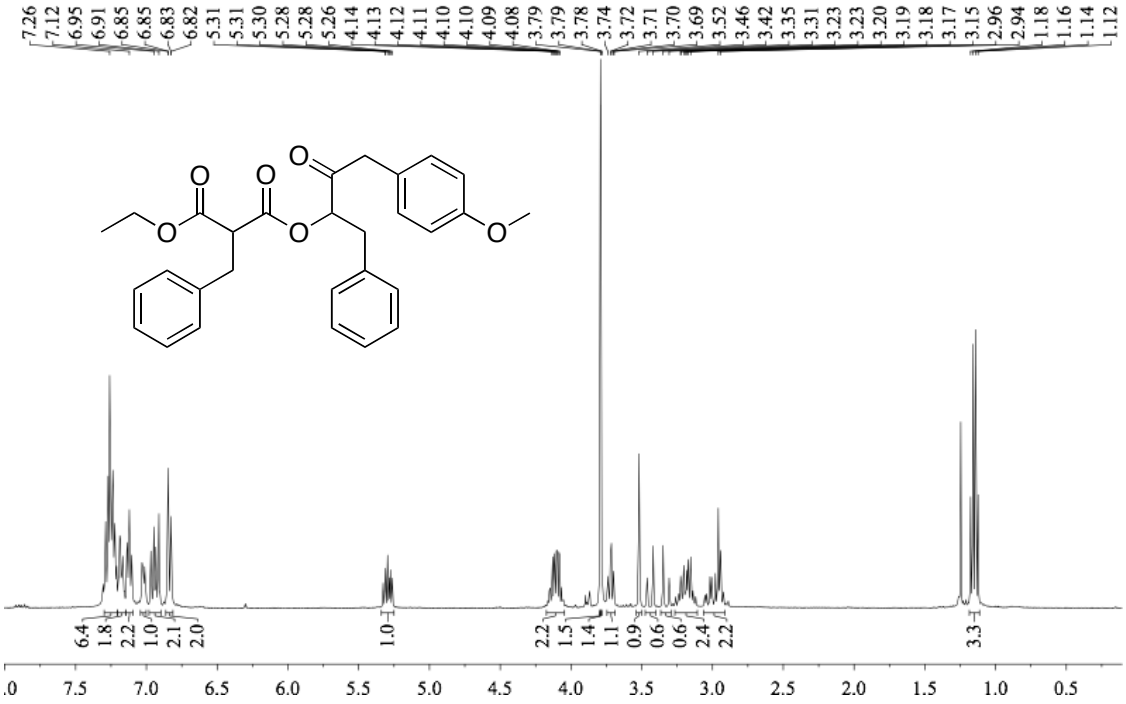


400 MHz ^{1}H-NMR in $CDCl_3$

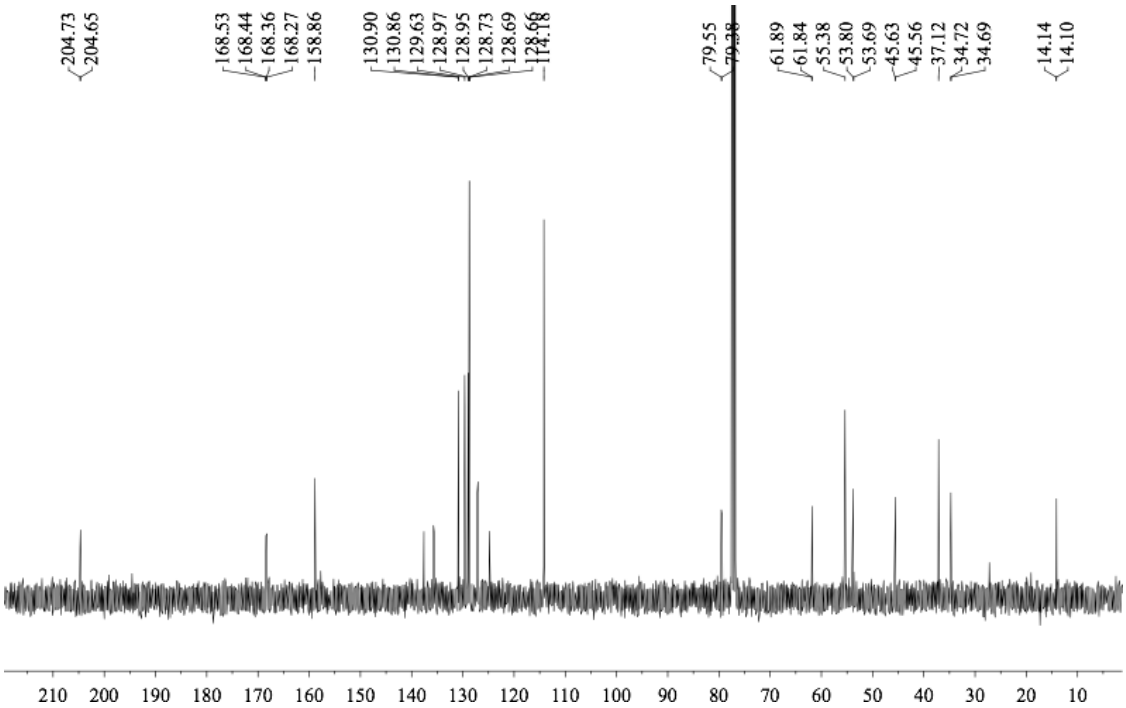


101 MHz ^{13}C-NMR in $CDCl_3$

1-Ethyl 3-(4-(4-methoxyphenyl)-3-oxo-1-phenylbutan-2-yl) 2-benzylmalonate (24) as a mixture of diastereomers

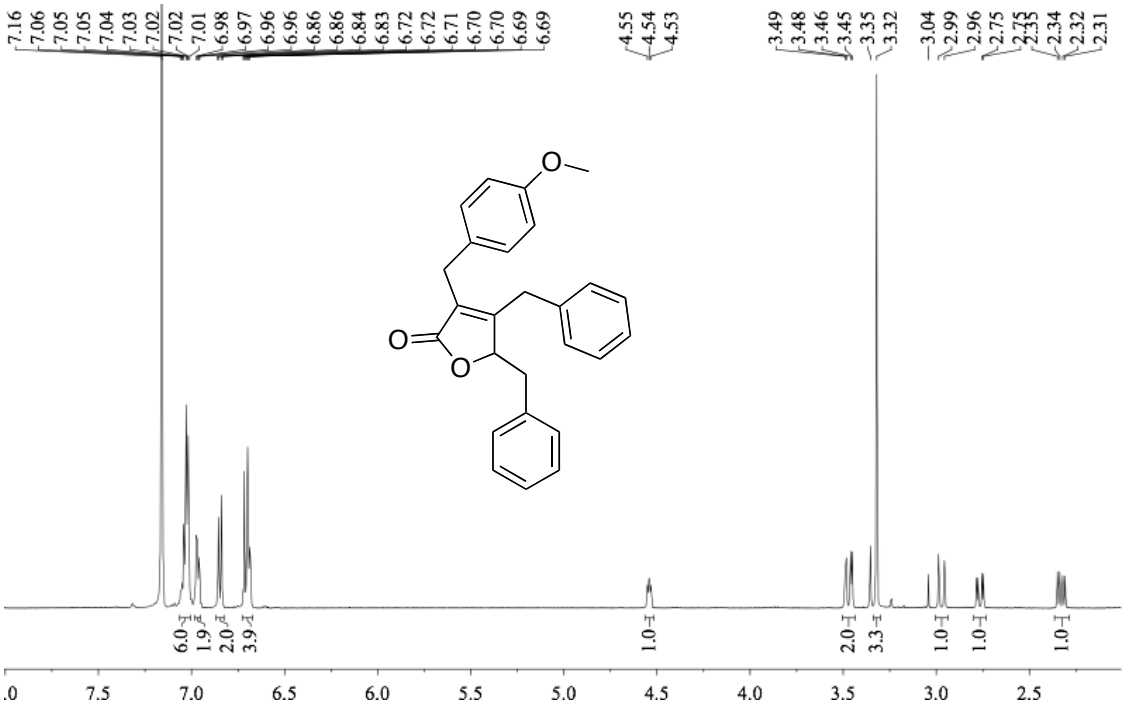


400 MHz ^{1}H-NMR in $CDCl_3$

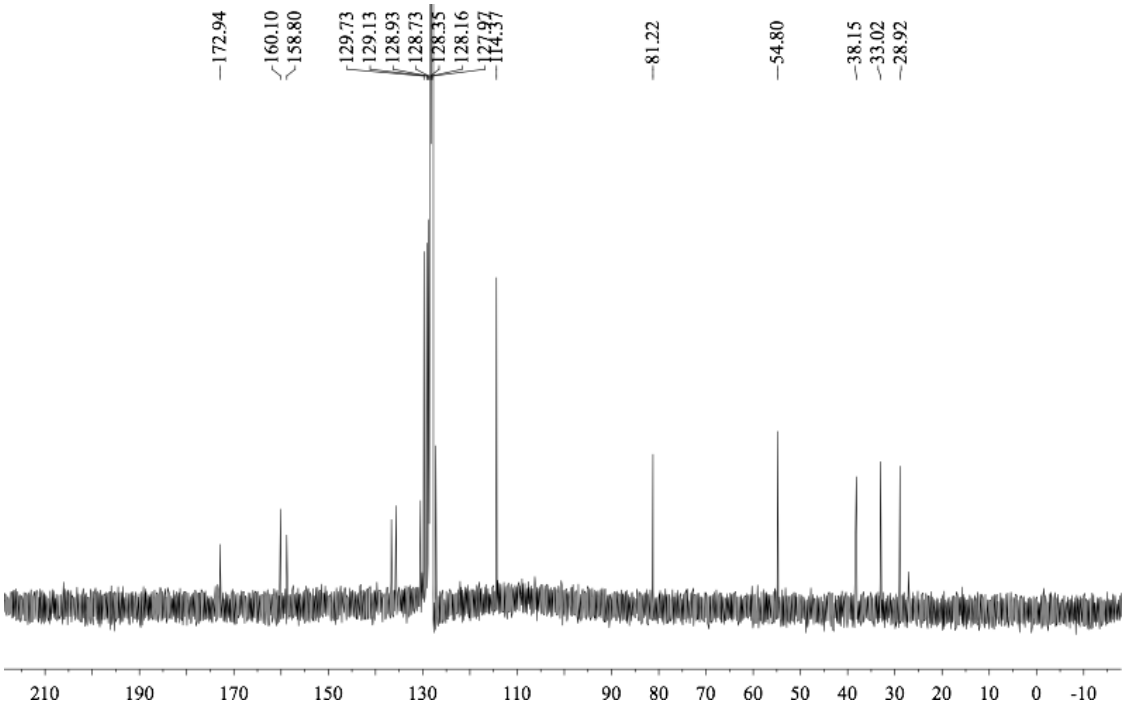


101 MHz ^{13}C-NMR in $CDCl_3$

4,5-Dibenzyl-3-(4-methoxybenzyl)furan-2(5H)-one (25)

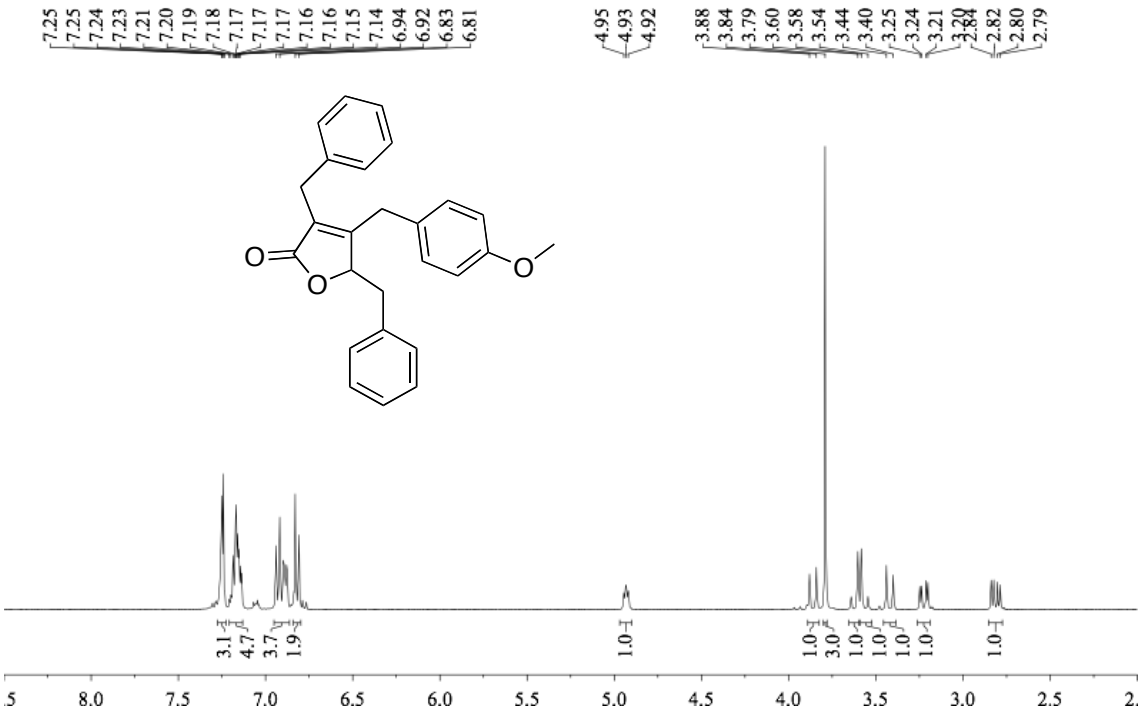


500 MHz ^{1}H-NMR in C_6D_6

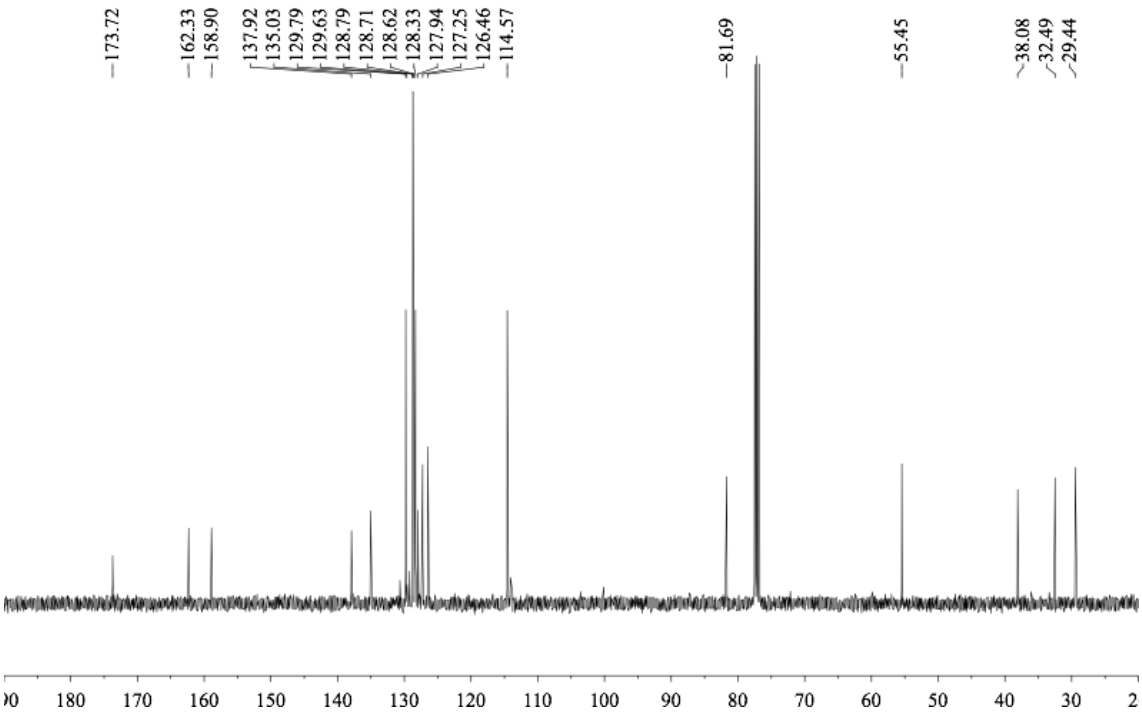


126 MHz ^{13}C-NMR in C_6D_6

3,5-Dibenzyl-4-(4-methoxybenzyl)furan-2(5H)-one (26)

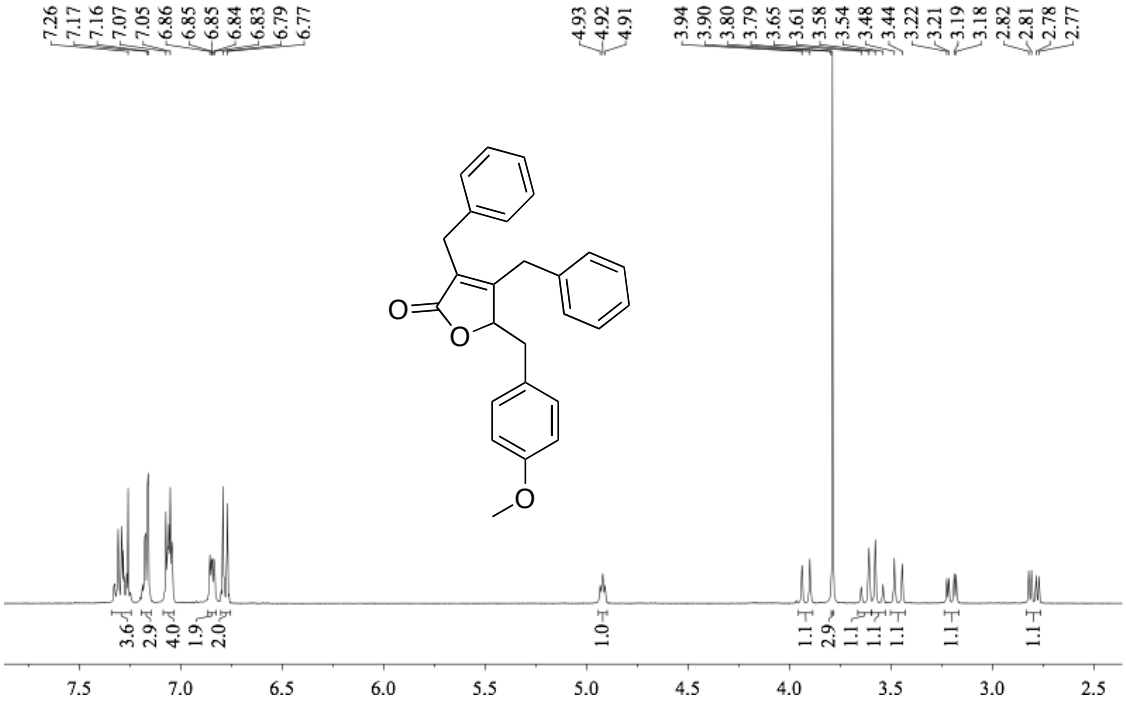


400 MHz ^{1}H-NMR in $CDCl_3$

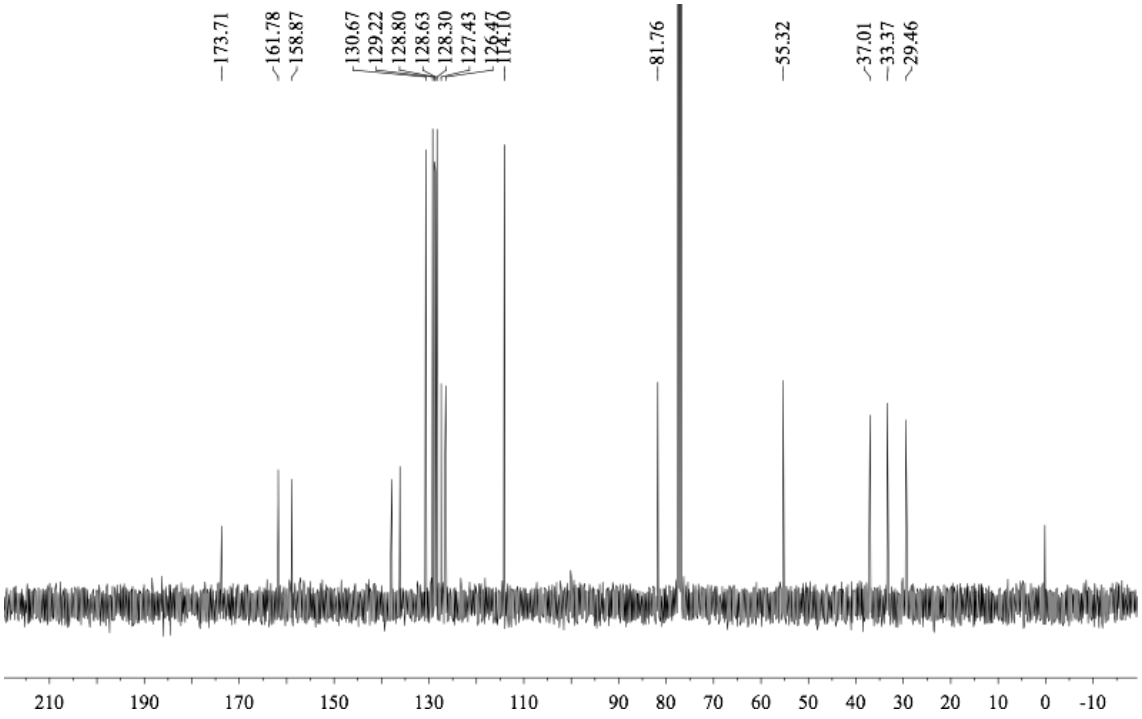


101 MHz ^{13}C-NMR in $CDCl_3$

3,4-Dibenzyl-5-(4-methoxybenzyl)furan-2(5H)-one (27)

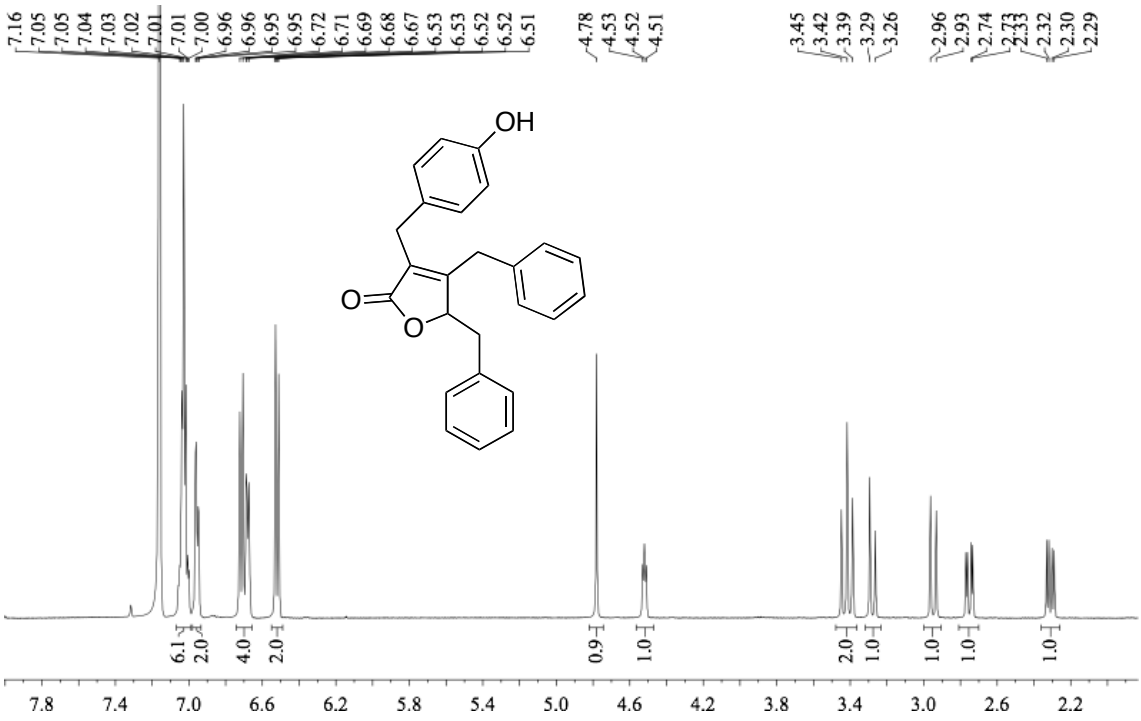


400 MHz ^{1}H-NMR in $CDCl_3$

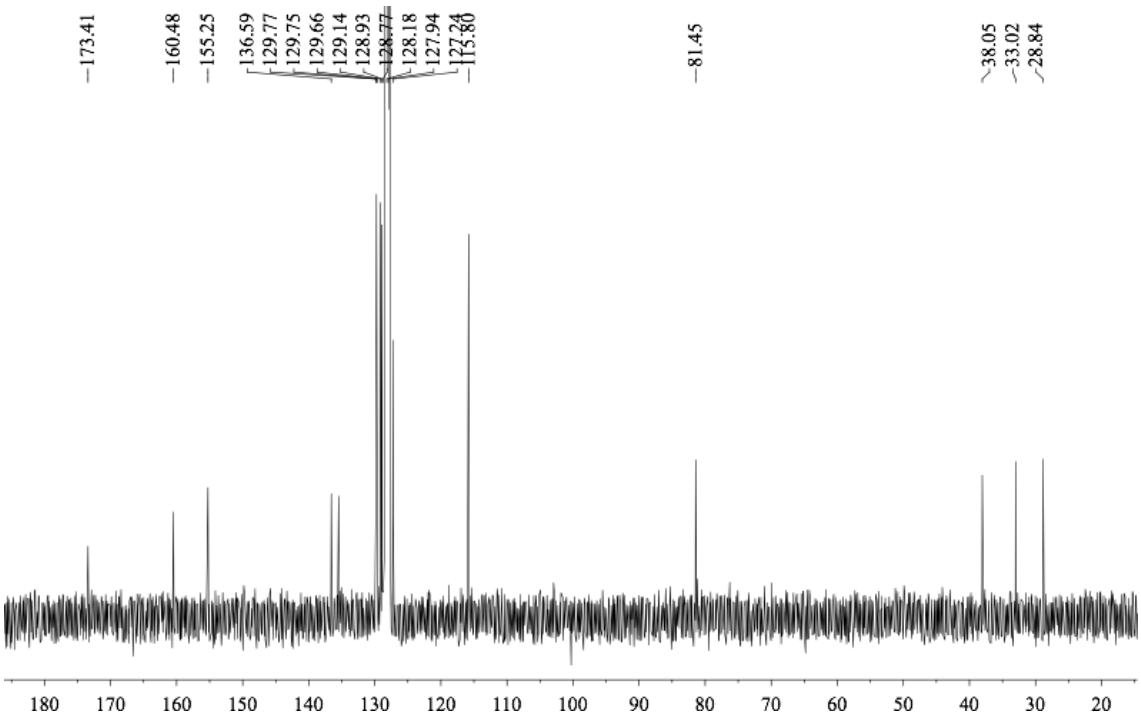


101 MHz ^{13}C-NMR in $CDCl_3$

4,5-Dibenzyl-3-(4-hydroxybenzyl)furan-2(5H)-one (28)

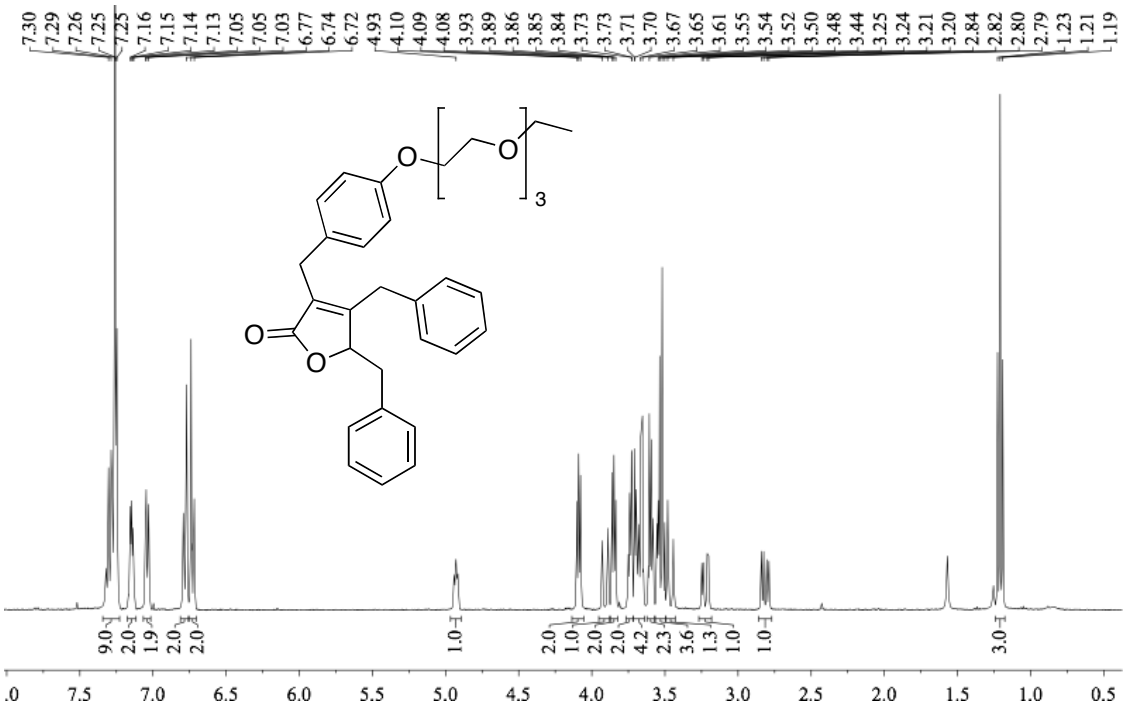


500 MHz ^{1}H-NMR in C_6D_6

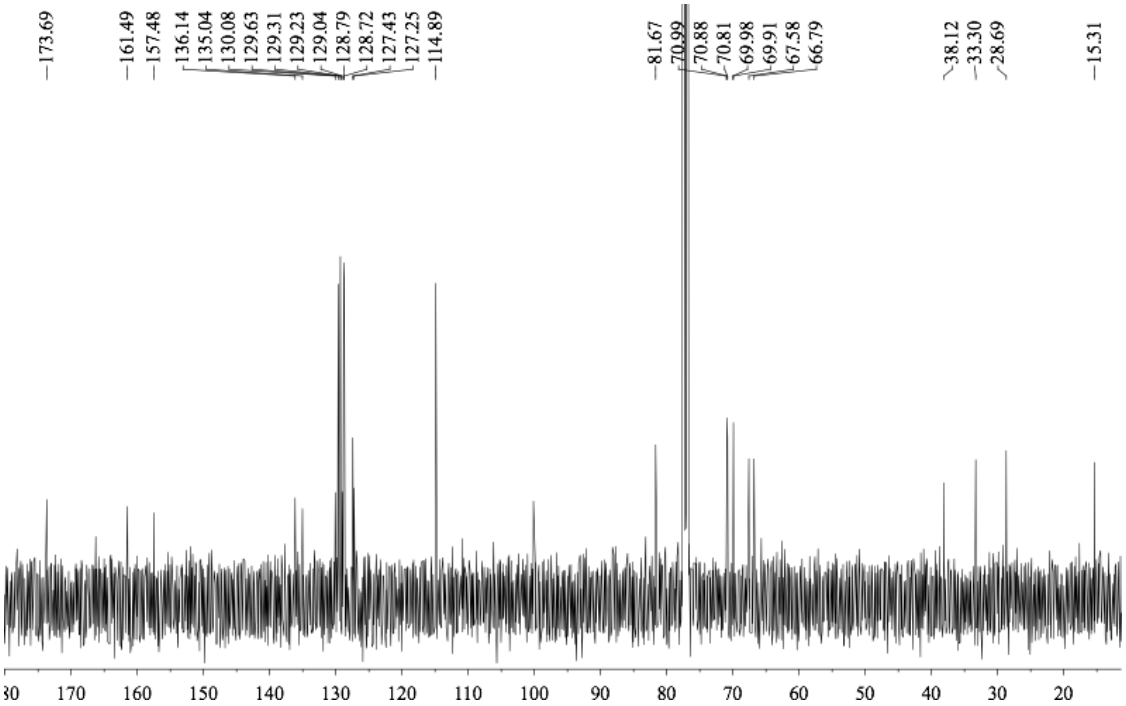


101 MHz ^{13}C-NMR in C_6D_6

4,5-Dibenzyl-3-(4-(2-(2-(2-ethoxyethoxy)ethoxy)ethoxy)benzyl)furan-2(5H)-one (29)

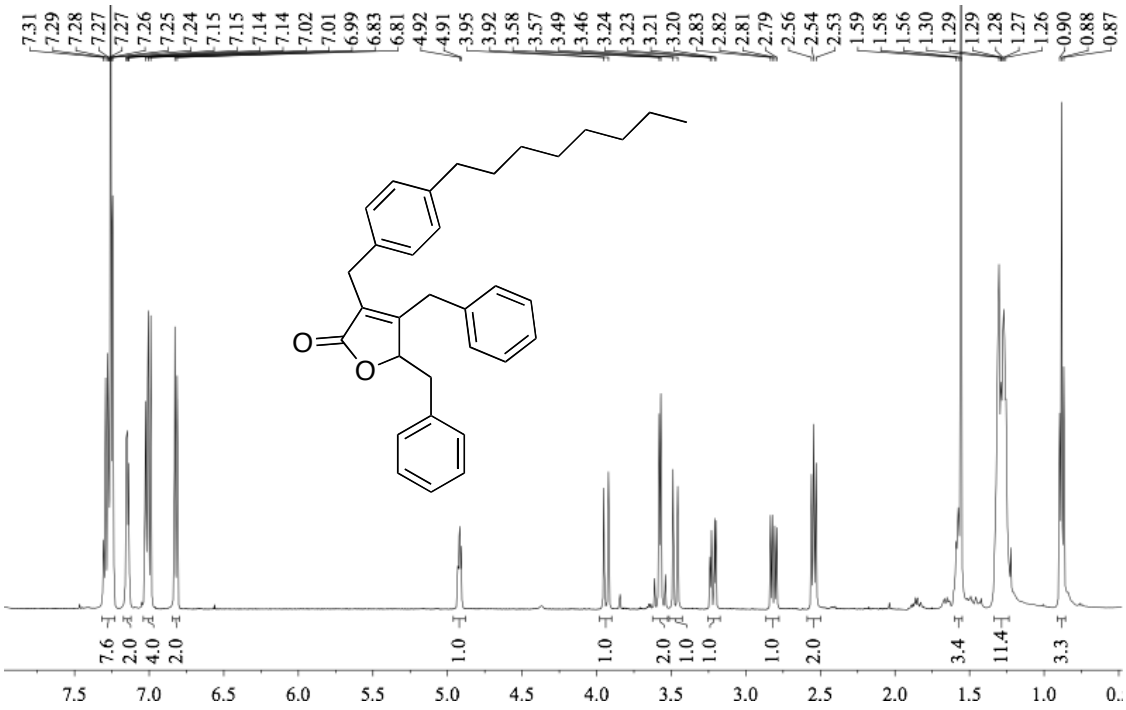


400 MHz ^{1}H-NMR in $CDCl_3$

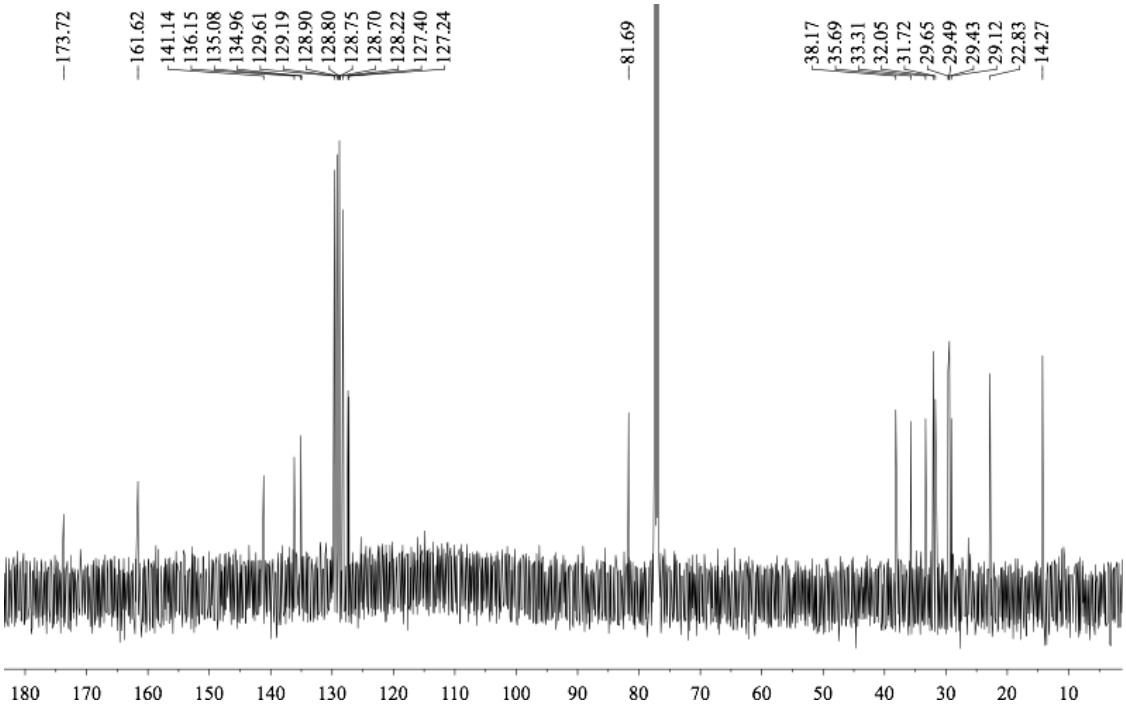


101 MHz ^{13}C-NMR in $CDCl_3$

4,5-Dibenzyl-3-(4-octylbenzyl)furan-2(5H)-one (30)

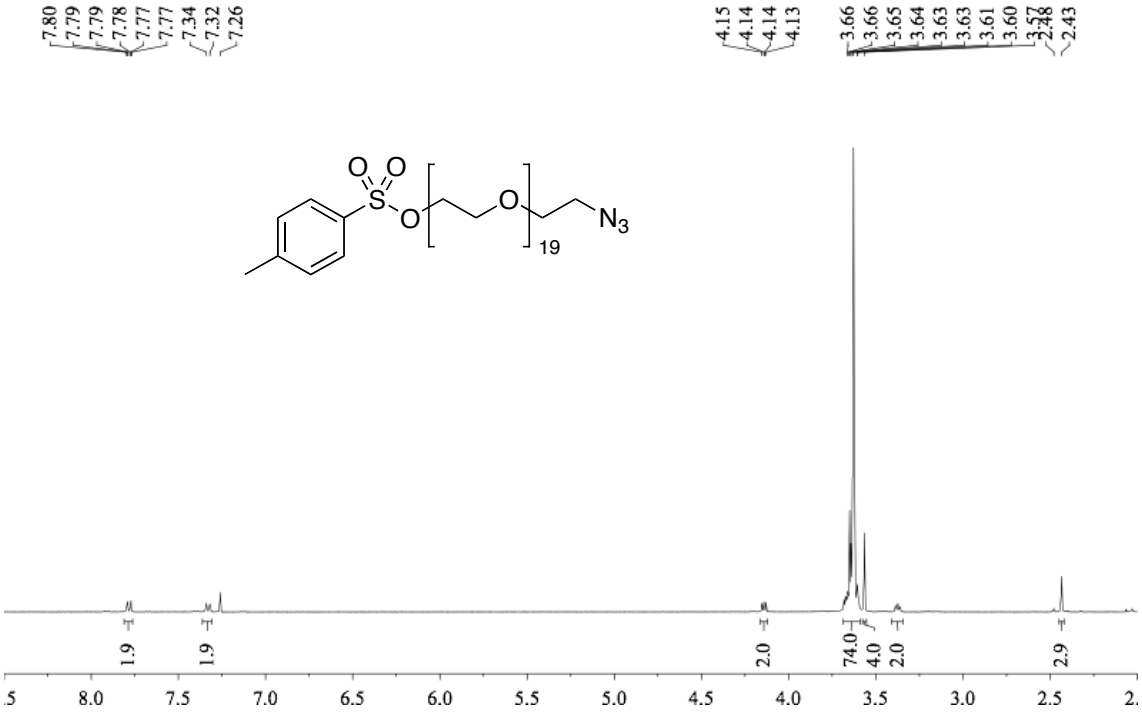


500 MHz ^{1}H-NMR in $CDCl_3$

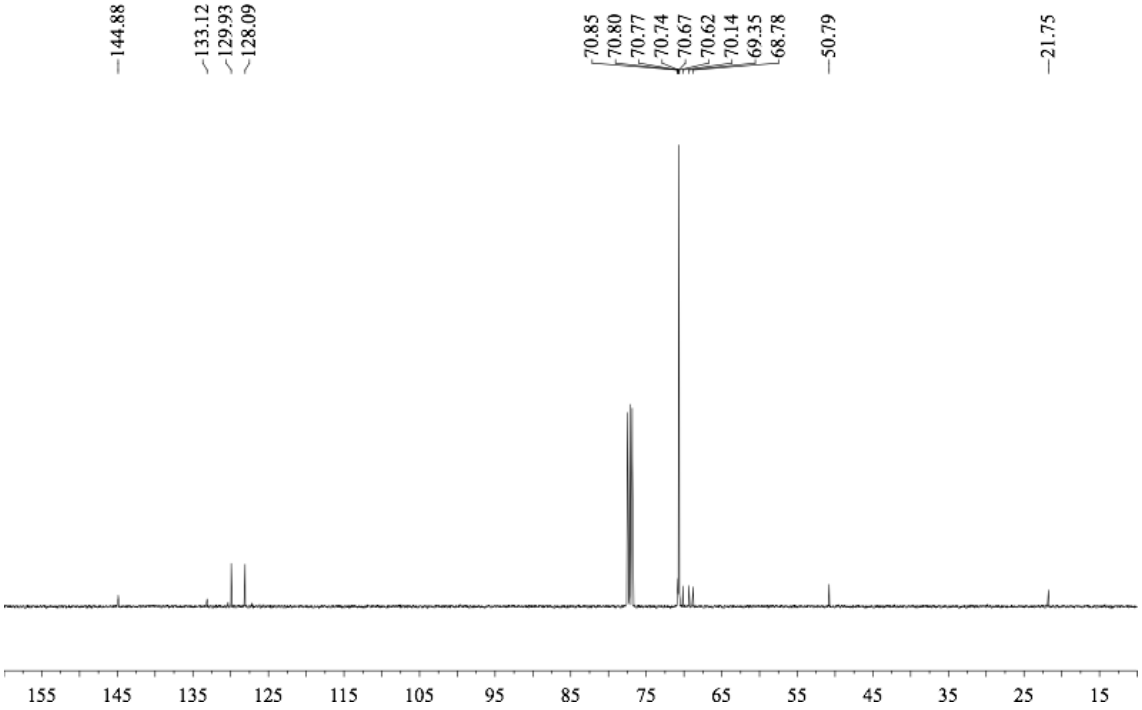


126 MHz ^{13}C-NMR in $CDCl_3$

***O*-(2-Azidoethyl)-*O*'-tosylnonadecaethylene glycol (31)**

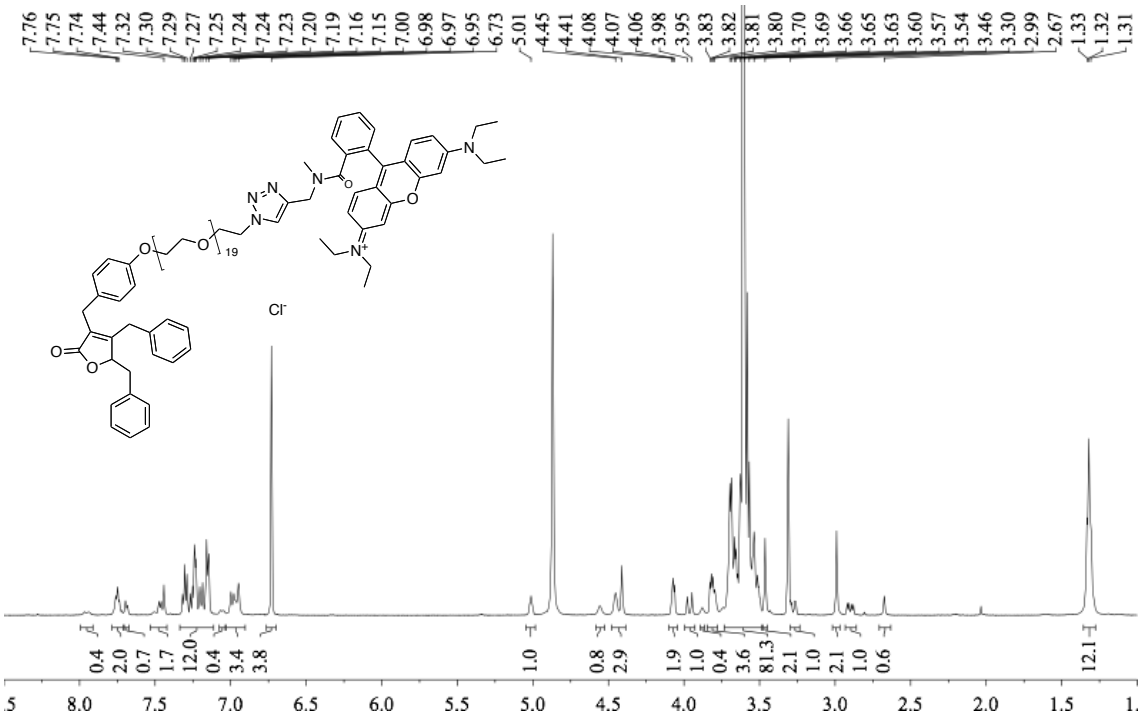


400 MHz ^{1}H-NMR in $CDCl_3$

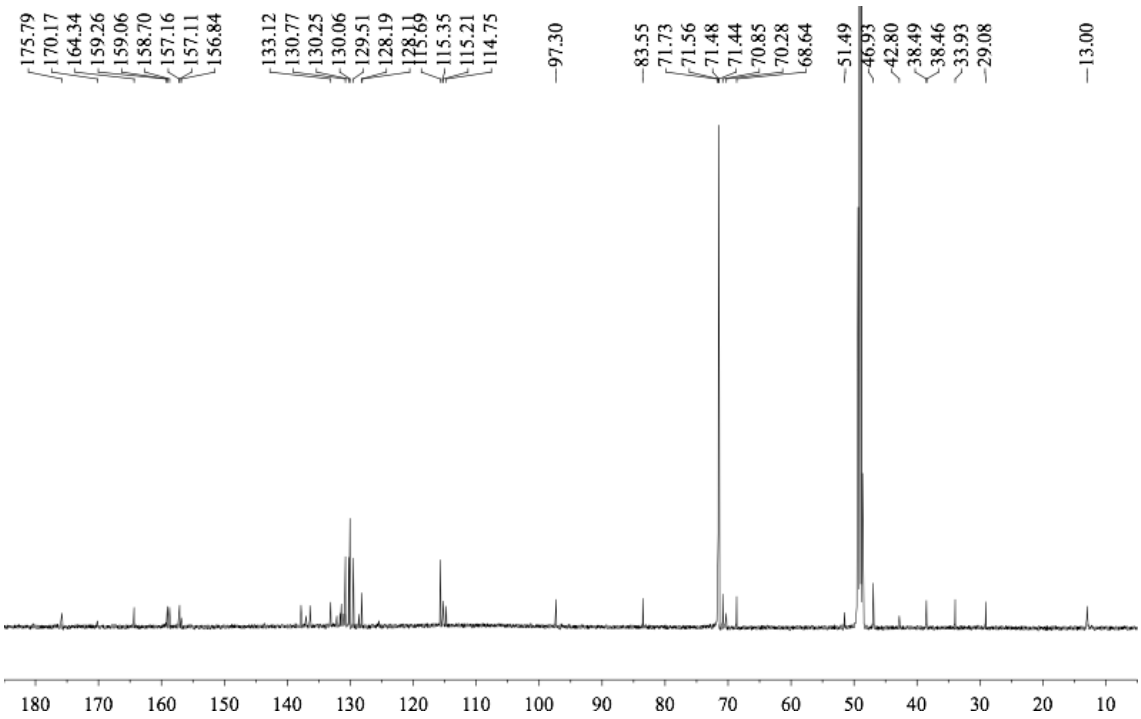


101 MHz ^{13}C-NMR in $CDCl_3$

Rhodamine B maculalactone A hybrid (33)

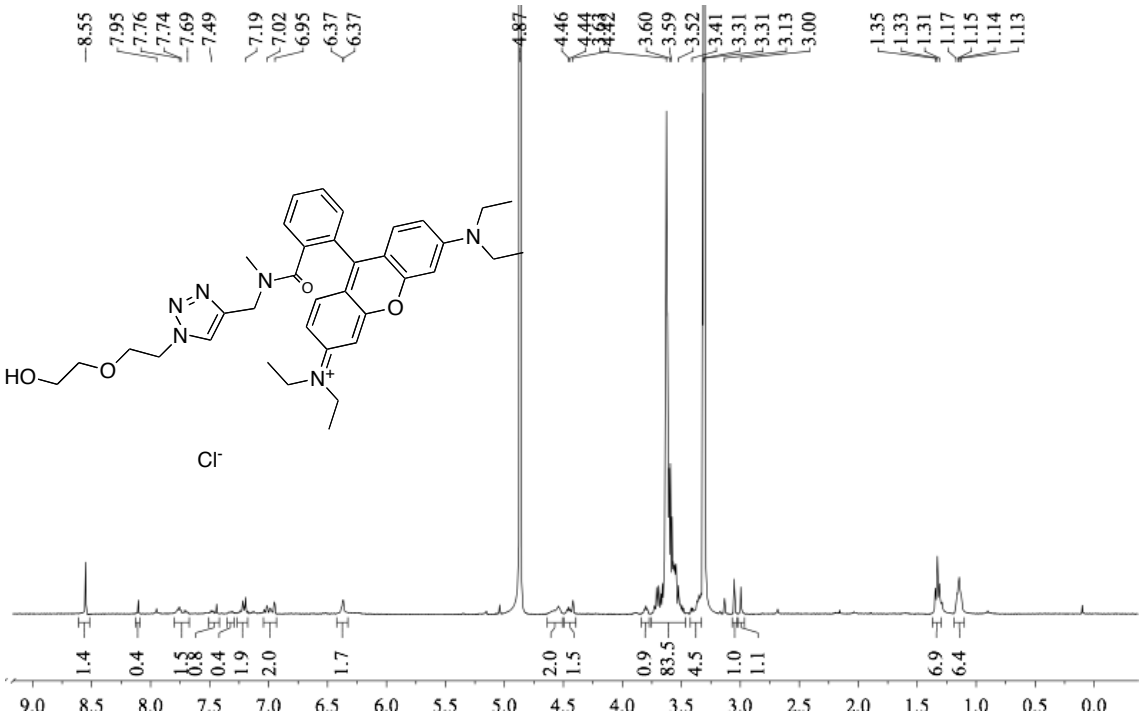


500 MHz ^{1}H-NMR in MeOD

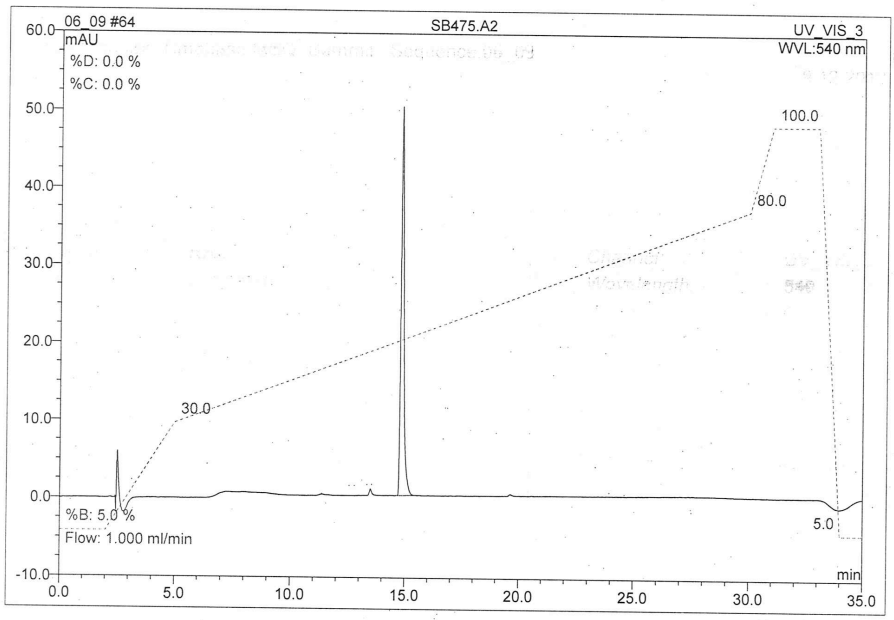


126 MHz ^{13}C-NMR in MeOD

Rhodamine B with linker (34)



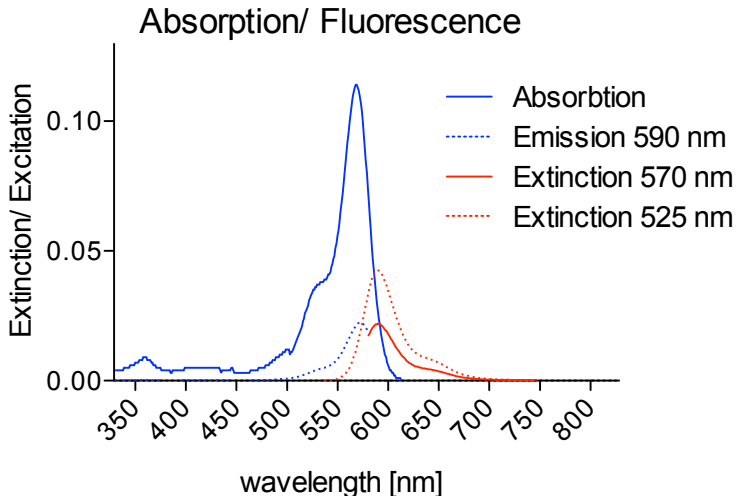
400 MHz ^{1}H-NMR in MeOD



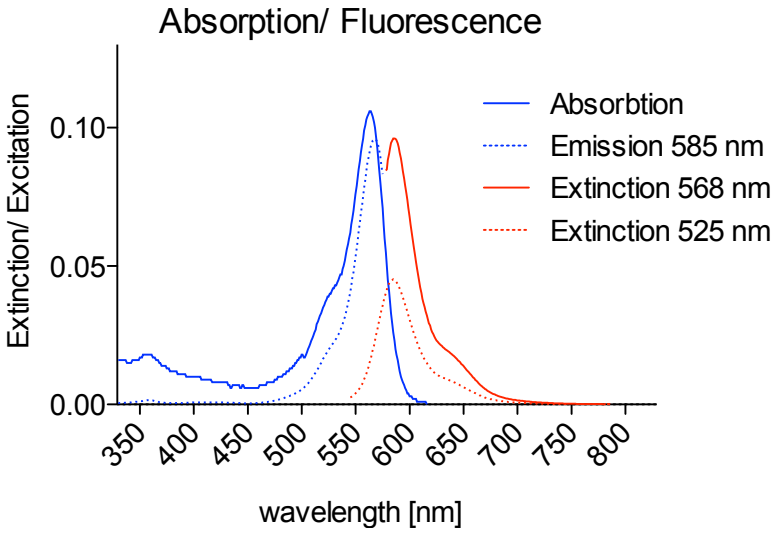
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.82	n.a.	50.153	7.663	100.00	n.a.	BMB
Total:			50.153	7.663	100.00	0.000	

HPLC (Phenomenex Synergi Hydro-RP, ACN/water + 0.1% HCO_2H (2 min 1:19, in 3 min to 3:7, in 25 min to 4:1), 1 ml/min, 540 nm)

Absorption and Fluorescence Spectra



Spectra of compound **33** with emission at 590 nm under varying extinction and extinction at 525 and 570 nm and varying emission. The absolute values vary due to differences in the extinction energy. λ_{max} = 568 nm.



Spectra of compound **34** with emission at 585 nm under varying extinction and extinction at 525 and 568 nm and varying emission. The absolute values vary due to differences in the extinction energy: λ_{max} = 563 nm.

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