Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Towards an asymmetric synthesis of the bacterial peptide deformylase (PDF) inhibitor Fumimycin

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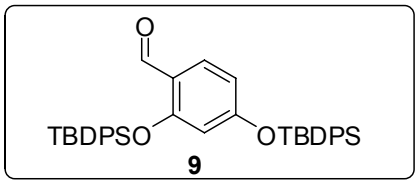
Supporting Information

General methods

All reactions utilizing air- or moisture-sensitive reagents were performed in dried glassware under an atmosphere of argon. Dichloromethane was distilled over CaH_2 and THF was distilled over sodium under an argon atmosphere. The other solvents and reagents were purchased and used without further purification. The microwave-assisted reactions were conducted using a focused microwave unit (Discover® Reactor from CEM Corporation). The instrument consists of a continuous focused microwave power delivery system with operator-selectable power output from 0–300 W. In all experiments, the microwave power was held constant to ensure reproducibility. Reactions were performed in 10 mL glass vessels, which were sealed with a septum and locked into a pressure device, which controlled the pressure in the reaction vessel (maximum 10 bar). The specified reaction time corresponds to the irradiation time. The temperature was monitored by an infrared temperature sensor positioned below the reaction vessel. The indicated temperature corresponds to the maximum temperature reached during each experiment.

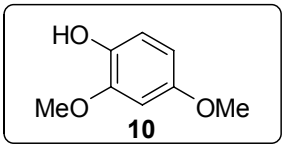
Thin layer chromatography (TLC) was performed on *Merck* precoated plates (silica gel 60, F_{254}, 0.25 mm) and compounds visualized by fluorescence under UV light. Column chromatography was performed on 60 (0.040-0.063 mm, 230-400 mesh ASTM) (Merck) Silica Gel. ^{1}H NMR spectra were recorded at 400 MHz on Bruker AM400, ^{13}C NMR spectra were recorded at 100 MHz, respectively. The chemical shifts are reported in ppm relative to the solvent residual peak. HPLC was performed on Agilent 1100 Series using Diacel Chiralpak AS (250 × 4.6 mm) or Diacel Chiracel OD (250 × 4.0 mm, 10 μm). Rotational values were determined on a Perkin Elmer 241 Polarimeter at λ = 589 nm (sodium D-line). The concentration c is given in [g/100 mL]. *Ee*'s were determined by comparison with the racemic products obtained by application of DL-proline as a catalyst.



9

2,4-Bis(*tert*-butyldiphenylsilyloxy)benzaldehyde (9)

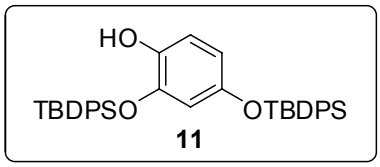
DIPEA (5.61 g, 43.4 mmol) and *tert*-butyldiphenylsilylchloride (11.9 g, 43.4 mmol) were added to a solution of 2,4-dihydroxybenzaldehyde (2.00 g, 14.5 mmol) in dichloromethane (40 mL). The reaction mixture was stirred for 20 h at rt. After this time water was added and the aqueous phase was extracted with dichloromethane. The organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica using *n*-pentane/diethyl ether 40:1 to afford 7.43 g (12.1 mmol) of **9** (83%) as a colourless solid. TLC (*n*-pentane/diethyl ether 40:1) R_f 0.05; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.53 (d, J = 0.7 Hz, 1 H), 7.62 (d, J = 8.6 Hz, 1 H), 7.52–7.49 (m, 4 H), 7.41–7.32 (m, 8 H), 7.28–7.18 (m, 8 H), 6.38 (ddd, J = 8.6 Hz, J = 2.2 Hz, J = 0.7 Hz, 1 H), 5.97 (d, J = 2.2 Hz, 1 H), 1.02 (s, 9 H), 0.88 (s, 9 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7, 161.9, 160.3, 135.2, 135.1, 131.7, 131.4, 130.8, 129.9, 129.5, 127.9, 127.7, 121.3, 114.4, 111.2, 26.5, 26.2, 19.6, 19.3 ppm; IR (KBr): v = 3343, 3073, 3051, 2959, 2859, 2757, 1958, 1897, 1820, 1596, 1391, 1361, 1277, 1197, 1114, 898, 848, 698 cm^{-1}; MS (FAB, 3-NBA): *m/z* (%) = 615 (29), 557 (100), 537 (63), 197 (49), 136 (63); HR-FABMS ($C_{39}H_{43}O_3Si_2$): calcd. 615.2751, found 615.2753.



10

2,4-Dimethoxyphenol (10)[i]

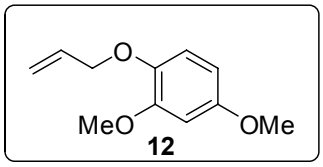
8 (10.0 g, 60.2 mmol) and H_2O_2 (6.60 mL, 78.3 mmol) were stirred in methanol (120 mL) in the presence of H_2SO_4 (1.20 mL) at room temperature for 16 h. After this time sodium sulphite was added and the aqueous phase was then extracted with dichloromethane. The organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica using cyclohexane/ethyl acetate 3:1 to afford 7.47 g of **10** (81%) as a colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 (d, J = 8.7 Hz, 1 H), 6.50 (d, J = 2.8 Hz, 1 H), 6.39 (dd, J = 8.7 Hz, J = 2.8 Hz, 1 H), 5.28–5.24 (m, 1 H), 3.86 (s, 3 H), 3.76 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 147.1, 139.8, 114.1, 104.2, 99.4, 55.9, 55.8 ppm.



11

2,4-Bis(*tert*-butyldiphenylsilyloxy)phenol (11)

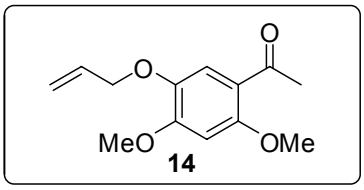
9 (7.43 g, 12.1 mmol) and H_2O_2 (1.3 mL, 15.7 mmol) were stirred in methanol (25 mL) in the presence of H_2SO_4 (0.30 mL) at room temperature for 16 h. After this time sodium sulphite was added and the aqueous phase was then extracted with dichloromethane. The organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica using *n*-pentane/diethyl ether 40:1 to afford 3.41 g of **11** (47%) as a colourless solid. TLC (*n*-pentane/diethyl ether 40:1) R_f 0.08; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66–7.64 (m, 8 H), 7.54–7.51 (m, 4 H), 7.35–7.28 (m, 8 H), 7.21–7.17 (m, 3 H), 5.60 (bs, 1 H), 1.08 (s, 9 H), 1.05 (s, 9 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 146.8, 141.2, 135.5, 135.3, 130.1, 129.7, 127.9, 127.6, 117.9, 110.5, 106.9, 26.7, 26.5, 19.4, 19.3 ppm; IR (KBr): ν = 3527, 3074, 2931, 2857, 2737, 2700, 1957, 1900, 1823, 1471, 1388, 1355, 1232, 1156, 1110 , 822, 800, 746, 505, 452 cm^{-1}; MS (FAB, 3-NBA): *m/z* (%) = 602 (22), 467 (59), 197 (36), 136 (79); HR-FABMS ($C_{38}H_{43}O_3Si_2$): calcd. 602.2673, found 602.2676



12

1-(Allyloxy)-2,4-dimethoxybenzene (12)[ii]

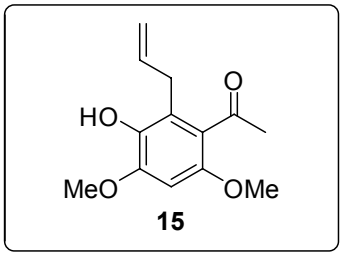
To a suspension of **10** (7.94 g, 52.0 mmol) and K_2CO_3 (14.2 g, 103 mmol) in acetone (90 mL) was added allylbromide (6.86 g, 57.0 mmol). The mixture was refluxed for 16 h, after which water was added. The aqueous phase was extracted three times with ethyl acetate and the organic phase was dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica using cyclohexane/ethyl acetate 3:1 to afford 8.35 g of **12** (70%) as a light yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 (d, J = 8.7 Hz, 1 H), 6.51 (d, J = 2.8 Hz, 1 H), 6.36 (dd, J = 8.7 Hz, J = 2.8 Hz, 1 H), 6.11–6.03 (m, 1 H), 5.39 (dd, J = 14.2 Hz, J = 1.4 Hz, 1 H), 5.25 (dd, J = 14.2 Hz, J = 1.4 Hz, 1 H), 4.53 (d, J = 5.5 Hz, 2 H), 3.84 (s, 3 H), 3.76 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6, 150.6, 142.2, 133.7, 117.6, 114.9, 102.9, 100.4, 70.8, 55.8, 55.5 ppm.



14

1-(5-(allyloxy)-2,4-dimethoxyphenyl)ethanone (14)[ii]

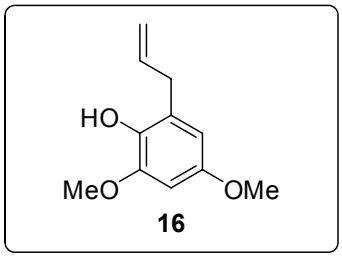
Trifluoroacetic acid anhydride (18.2 g, 86.8 mmol) and glacial acid (4.34 g, 72.3 mmol) were stirred for 10 min. Then in dichloromethane (42 mL) dissolved **12** (4.67 g, 24.1 mmol) was added at 0 °C. The reaction mixture was stirred for 1.5 h, then ethyl acetate was added. The organic phase was neutralized with a sat. sodium bicarbonate solution and the aqueous phase was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica using *n*-pentane/diethyl ether 2:1 to afford 4.21 g of **14** (74%) as a colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (s, 1 H), 6.49 (s, 1 H), 6.10–6.02 (m, 1 H), 5.40 (dt, J = 17.2 Hz, J = 1.3 Hz, 1 H), 5.27 (dt, J = 10.4 Hz, J = 1.3 Hz, 1 H), 4.58 (dt, J = 5.5 Hz, J = 1.4 Hz, 2 H), 3.94 (s, 3 H), 3.91 (s, 3 H), 2.58 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 155.7, 154.4, 141.8, 133.1, 119.1, 118.2, 114.9, 96.5, 70.3, 56.08, 56.05, 32.0 ppm; $C_{13}H_{16}O_4$ (236.10 g/mol): calcd. C 66.09, H 6.83, found C 65.90, H 6.82.



15

1-(2-Allyl-3-hydroxy-4,6-dimethoxyphenyl)ethanone (15)

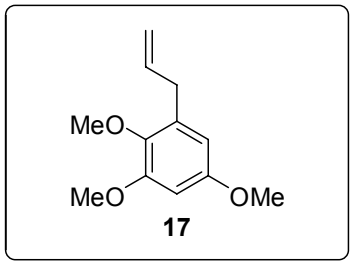
A solution of **14** (1.00 g, 4.23 mmol) in DMF (21.2 mL) was heated in the microwave (300 W, 180 °C) for 2 h, after which the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica using *n*-pentane/diethyl ether 1:1 to afford 0.59 g of **15** (59%) as a colourless solid. TLC (*n*-pentane/diethyl ether 1:1) R_f 0.20; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40 (s, 1 H), 5.97–5.87 (m, 1 H), 5.38 (bs, 1 H), 5.00–4.95 (m, 2 H), 3.91 (s, 3 H), 3.79 (s, 3 H), 3.39 (ddd, J = 6.2 Hz, J = 1.5 Hz, J = 1.5 Hz, 2 H), 2.46 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.7, 150.2, 147.3, 137.8, 136.2, 124.4, 123.3, 115.2, 94.4, 56.5, 56.1, 32.7, 30.3 ppm; IR (KBr): ν = 3373, 3084, 2962, 2843, 2034, 1844, 1682, 1488, 1443, 1353, 1263, 964, 917, 834, 818 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 236 (18), 221 (100), 189 (40), 43 (9); HR-EIMS (*m/z*): calcd. 236.1046, found 236.1049.



16

2-Allyl-4,6-dimethoxyphenol (16)

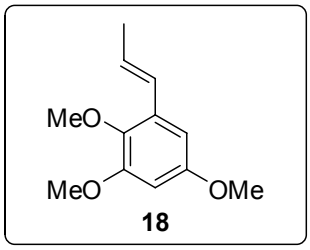
A solution of **12** (4.16 g, 21.4 mmol) in DMF (20 mL) was heated in the microwave (300 W, 180 °C) for 2 h, after which the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica using *n*-pentane/diethyl ether 9:1 to afford 3.33 g of **16** (80%) as a yellow liquid. TLC (*n*-pentane/diethyl ether 5:1) R_f 0.18; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 (d, J = 2.7 Hz, 1 H), 6.34 (d, J = 2.7 Hz, 1 H), 6.10–6.00 (m, 1 H), 5.53 (bs, 1 H), 5.17–5.09 (m, 2 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.45 (d, J = 6.6 Hz, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 146.8, 137.3, 136.4, 125.6, 115.4, 105.4, 97.1, 55.8, 55.5, 33.9 ppm; IR (KBr): ν = 3524, 3003, 2942, 2840, 1616, 1499, 1376, 1228, 1151, 832, 818 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 194 (100), 179 (34); HR-EIMS (*m/z*): calcd. 236.1046, found 236.1049; $C_{13}H_{14}O_3$ (194.09 g/mol): calcd. C 68.02, H 7.27, found C 67.73 H 7.09.



17

2,4-Aimethoxy-6-allylanisole (17)[iii]

To a solution of **15** (2.88 g, 14.9 mmol) and potassium carbonate (4.01 g, 29.7 mmol) in acetone (300 mL) was added dimethylsulfate (4.35 g, 34.5 mmol). The reaction mixture was refluxed for 16 h, then it was concentrated under reduced pressure und diethyl ether (100 mL) was added. The organic phase was washed with 10% aq. NaOH-solution and water, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica using *n*-pentane/diethyl ether 5:1 to afford 3.33 g of 2,4-dimethoxy-6-allylanisole (43%) as a colourless liquid. TLC (*n*-pentane/diethyl ether 4:1) R_f 0.37; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.38 (d, J = 2.9 Hz, 1 H), 6.29 (d, J = 2.9 Hz, 1 H), 5.97 (tdd, J = 16.9 Hz, J = 10.1 Hz, J = 6.6 Hz, 1 H), 5.11−5.05 (m, 2 H), 3.83 (s, 3 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.40 (d, J = 6.6 Hz, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 153.3, 141.0, 137.1, 133.9, 115.7, 104.9, 98.2, 60.8, 55.6, 55.4, 34.1 ppm.

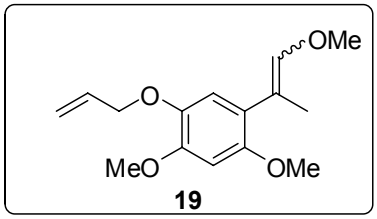


18

(*E*)-1-(3,4,6-Trimethoxy-2-(prop-1-enyl)phenyl)ethanone (18)

To a suspension of KO*t*Bu (5.46 g, 48.7 mmol) in THF (52 mL) was added 2,4-dimethoxy-6-allylanisole and the reaction was stirred at reflux for 16 h. The reaction mixture was extracted with ethyl acetate and the organic phases were washed with water and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica using *n*-pentane/diethyl ether 5:1 to afford 0.96 g of (*E*)-1-(3,4,6-trimethoxy-2-(prop-1-enyl)phenyl)ethanone (66%) as a colourless liquid. TLC (cyclohexane/ ethyl acetate 6:1) R_f 0.32; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.70 (qd, J = 15.9 Hz, J = 1.7 Hz, 1 H), 6.54 (d, J = 2.8 Hz, 1 H), 6.38 (d, J = 2.8 Hz, 1 H), 6.24 (qd, J = 15.9 Hz, J = 6.6 Hz, 1 H), 3.82 (s, 3 H), 3.79 (s, 3 H), 3.74 (s, 3 H), 1.91 (dd, J = 6.6 Hz,

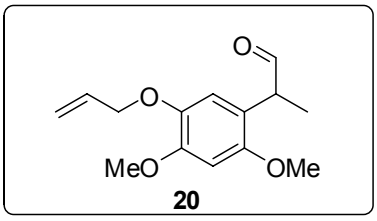
J = 1.7 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0, 153.5, 140.3, 131.8, 127.1, 125.2, 100.2, 98.9, 61.0, 55.7, 55.4, 18.7 ppm; IR (KBr): *v* = 3450, 2998, 2937, 2837, 2007, 1485, 1467, 1377, 1338, 1220, 1202, 1151 , 1057, 939, 910 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 208 (100), 193 (91), 165 (27), 150 (18), 135 (12), 105 (10), 91 (11), 58 (10), 43 (84); HR-EIMS ($C_{12}H_{17}O_3$): calcd. 208.1099, found 208.1098.



19

1-(Allyloxy)-2,4-dimethoxy-5-(1-methoxyprop-1-en-2-yl-)benzene (**19**)

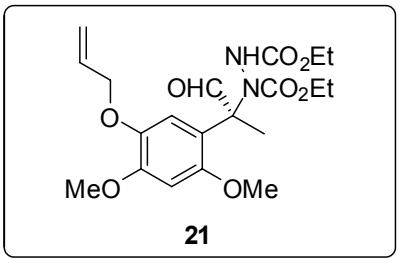
Methoxymethyltriphenylphosphoniumchloride (4.39 g, 12.8 mmol) was dissolved in dry THF (34 mL) and *n*-butyllithium (5.14 mL, 2.5 M in hexane, 19.2 mmol) was added at 0 °C. After 30 min. **14** (2.00 g, 8.56 mmol) dissolved in dry THF (10 mL) was added and the mixture was stirred for another 30 min. Then 30 mL water was added and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica using *n*-pentane/diethyl ether 3:1 to afford 1.36 g of **16** (60%) as a colourless solid. TLC (*n*-pentane/diethyl ether 2:1) R_f 0.20; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (s, 1 H), 6.71 (s, 1 H), 6.48 (s, 1 H), 6.06–5.95 (m, 1 H), 5.31 (dd, *J* = 13.8 Hz, *J* = 1.4 Hz, 1 H), 5.18 (dd, *J* = 13.8 Hz, *J* = 1.4 Hz, 1 H), 4.47 (ddd, *J* = 5.5 Hz, *J* = 1.4 Hz, 2 H), 3.80 (s, 3 H), 3.74 (s, 3 H), 3.48 (s, 3 H), 1.78 (d, *J* = 1.4 Hz, 2 H), 1.29–1.11 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4, 149.1, 143.3, 141.7, 133.9, 119.8, 117.7, 117.3, 111.0, 98.6, 70.9, 59.6, 56.6, 56.2, 18.6 ppm; IR (KBr): *v* = 3082, 3005, 2935, 2834, 1609, 1519, 1460, 1426, 1406, 1365, 1353, 1321, 1281, 1241, 1204, 1163, 1138, 1036, 928, 860, 850, 809 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 264 (22), 223 (35), 195 (9), 58 (38), 43 (100); HR-EIMS ($C_{15}H_{20}O_4$): calcd. 264.1362, found 264.1364; $C_{15}H_{20}O_4$ (279.16 g/mol): calcd. C 68.16, H 7.63; found C 68.15, H 7.55.



20

2-(5-Allyloxy)-2,4-dimethoxyphenyl)propanal (20)

19 (582 mg, 2.20 mmol), sodium iodide (330 mg, 2.20 mmol) and acetonitrile (22.0 mL) were put together in a flask. Then chlorotrimethylsilane (239 mg, 2.20 mmol) was added and the reaction mixture was stirred for five minutes at rt, after which the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica using *n*-pentane/diethyl ether 2:1 to afford 453 mg of **20** (82%) as a colourless oil. TLC (*n*-pentane/diethyl ether 2:1) R_f 0.18; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (d, *J* = 0.5 Hz, 1 H), 6.66 (s, 1 H, CH), 6.55 (s, 1 H), 6.09–6.00 (m, 1 H), 5.38 (dddd, *J* = 3.2 Hz, *J* = 17.3 Hz, *J* = 1.4, 1.4 Hz, 1 H), 5.25 (dddd, *J* = 2.7 Hz, *J* = 10.4 Hz, *J* = 1.4, 1.4 Hz, 1 H), 4.52 (ddd, *J* = 5.5 Hz, *J* = 1.4 Hz, 2 H), 3.88 (s, 3 H), 3.793 (s, 3 H), 3.787 (q, *J* = 7.1 Hz, 1 H), 1.34 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.9, 151.9, 149.8, 142.0, 133.6, 117.9, 117.8, 116.0, 97.7, 71.2, 56.2, 56.1, 46.6, 13.5 ppm; IR (KBr): *v* = 3082, 2975, 2937, 2838, 1724, 1647, 1610, 1510, 1463, 1404, 1366, 1318, 1248, 1205, 1135, 1034, 928, 872, 819 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 250 (37), 221 (25), 209 (100), 181 (22), 153 (18); HR-EIMS ($C_{14}H_{18}O_4$): calcd. 250.1205, found 250.1204; $C_{14}H_{18}O_4$ (250.12 g/mol): calcd. C 67.18, H 7.25; found C 67.50, H 7.10.

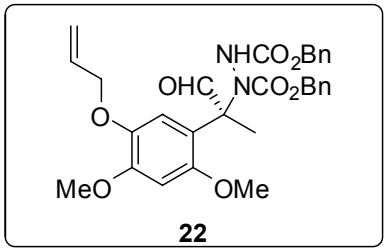


21

Diethyl 1-(2-(5-(allyloxy)-2,4-dimethoxyphenyl)-1-oxopropane-2-yl)hydrazine-1,2-dicarboxylate (21)

20 (125 mg, 0.50 mmol), diethyl azodicarboxylate (131 mg, 0.75 mmol), L-proline (115 mg, 1.00 mmol) and acetonitrile (2.00 mL) were heated to 60 °C for 16 h. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography on silica using *n*-pentane/diethyl ether 1:1, then 1:5 to afford 170 mg of **21** (80%) as a colourless solid with 47% *ee*. TLC (diethyl ether) R_f 0.33; $[\alpha]_D$ = –16.77° (c = 1.55, $CHCl_3$); HPLC (Chiralpak IA, heptane/*iso*propanol 90:10, 1.0 mL/min): R_t(maj) = 17.4 min, R_t (min) = 23.9 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86, 9.82 (2 × bs, 1 H), 6.94, 6.87 (2 × s, 1 H), 6.60–6.45 (m, 2 H), 6.11–5.96 (m, 1 H), 5.44–5.21 (m, 2 H), 4.62, 4.52 (2 × d, *J* = 5.6 Hz, 2 H), 4.28–3.97 (m, 4 H), 3.88 (s, 3 H), 3.81, 3.79 (2 × s, 3 H), 1.89, 1.66 (2 × s, 3 H), 1.26, 1.16 (2 × t, *J* = 7.1 Hz, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 156.0, 155.6, 151.6, 150.8, 142.1, 133.6, 133.4, 118.1, 116.9, 115.7, 97.8, 97.6, 72.5,

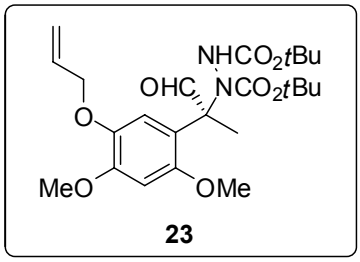
72.3, 71.3, 71.1, 62.8, 62.7, 62.2, 61.9, 56.3, 56.1, 18.8, 14.42, 14.36 ppm; IR (KBr): ν = 3311, 2982, 1728, 1610, 1513, 1466, 1401, 1378, 1342, 1316, 1207, 1095, 1067, 1029, 92, 818 cm^{-1}; MS (FAB, 3-NBA): *m/z* (%) = 424 (19), 395 (15), 323 (26), 249 (100), 221 (34); HRMS ($C_{20}H_{30}N_2O_8$): calcd. 425.1924, found 425.1920; $C_{20}H_{29}N_2O_8$ (424.18 g/mol): calcd. C 56.59, H 6.65, N 6.60; found C 56.49, H 6.63, N 6.53.



22

Dibenzyl (1-(2-(5-(allyloxy)-2,4-dimethoxyphenyl)-1-oxopropane-2-yl)hydrazine-1,2-dicarboxylate (22)

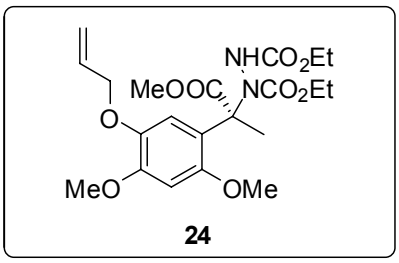
20 (1.50 g, 6.00 mmol), dibenzyl azodicarboxylate (2.68 g, 9.00 mmol), L-proline (1.38 g, 12.0 mmol) and acetonitrile (20.0 mL) were heated to 60 °C for 16 h. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography on silica using *n*-pentane/diethyl ether 1:1 to afford 2.67 g of **22** (80%) as a colourless solid with 23% *ee*. TLC (cyclohexane/ethyl acetate 2:1) R_f 0.21; HPLC (Chiralpak IA, heptane/*iso*propanol 90:10, 1.0 mL/min): R_t(maj) = 16.8 min, R_t (min) = 23.5 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.83, 9.72 (2 × bs, 1 H), 7.25–7.01 (m, 11 H), 6.86, 6.54 (2 × bs, 1 H), 6.34, 6.33 (2 × s, 1 H), 5.01–5.91 (m, 1 H), 5.32–4.89 (m, 6 H), 4.41, 4.35 (2 × d, J = 5.3 Hz, 2 H), 3.80 (s, 3 H), 3.67 (s, 3 H), 2.10, 1.83 (2 × s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.0, 155.8, 155.6, 151.5, 150.9, 142.2, 135.6, 133.5, 128.6, 128.5, 128.4, 128.3, 128.03, 127.95, 118.1, 115.5, 97.5, 72.8, 71.0, 68.4, 67.6, 56.3, 56.1, 15.3 ppm; IR (KBr): ν = 3317, 3065, 2951, 2724, 1958, 1728, 1610, 1514, 1454, 1401, 1347, 1208, 1028, 920, 820 cm^{-1}; MS (FAB, 3-NBA): *m/z* (%) = 548 (24), 475 (32), 249 (100), 221 (49), 207 (50), 154 (33), 147 (36), 132 (50), 91 (97); HR-FABMS ($C_{30}H_{33}N_2O_8$): calcd. 548.2159, found 548.2161; $C_{30}H_{32}N_2O_8$ (548.22 g/mol): calcd. C 65.68, H 5.88, N 5.11; found C 65.13, H 5.85, N 5.11.



23

di-*tert*-Butyl (1-(2-(5-(allyloxy)-2,4-dimethoxyphenyl)-1-oxopropane-2-yl)hydrazine-1,2-dicarboxylate (23)

20 (500 mg, 2.00 mmol), di-*tert*-butyl azodicarboxylate (691 mg, 3.00 mmol), L-proline (460 mg, 2.00 mmol) and acetonitrile (6.00 mL) were heated to 60 °C for 16 h. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography on silica using *n*-pentane/diethyl ether 1:1 to afford 685 mg of **23** (71%) as a colourless oil in 60% *ee*. TLC (cyclohexane/ethyl acetate 1:1) R_f 0.19; $[\alpha]_D$ = –5.0° (c = 4.0, $CHCl_3$). HPLC (Chiralcel OD, heptane/*iso*propanol 95:5, 0.3 mL/min): R_t(maj) = 28.5 min, R_t (min) = 32.9 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69, 9.60 (2 × s, 1 H), 6.76, 6.68 (2 × bs, 1 H, NH), 6.34–6.28 (m, 2 H), 5.90–5.81 (m, 1 H), 5.21–5.06 (m, 2 H), 4.33 (d, *J* = 5.6 Hz, 2 H), 3.70 (s, 3 H), 3.63 (s, 3 H), 1.28–1.07 (m, 21 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 155.4, 155.1, 154.6, 154.5, 150.9, 150.5, 149.8, 149.4, 142.0, 131.9, 131.7, 118.0, 117.9, 115.7, 115.6, 114.3, 114.2, 97.8, 81.5, 80.9, 72.0, 71.4, 71.1, 56.4, 56.1, 55.5, 28.1, 28.0 ppm; IR (KBr): *v* = 3330, 2979, 2933, 1725, 1611, 1511, 1460, 1384, 1368, 1248, 1206, 1154, 1030, 922, 761, 734 cm^{-1}; MS (FAB, 3-NBA): *m/z* (%) = 480 (8), 351 (10), 295 (77), 249 (55), 133 (100); HR-FABMS ($C_{24}H_{36}N_2O_8$): calcd. 480.2472, found 480.2473.

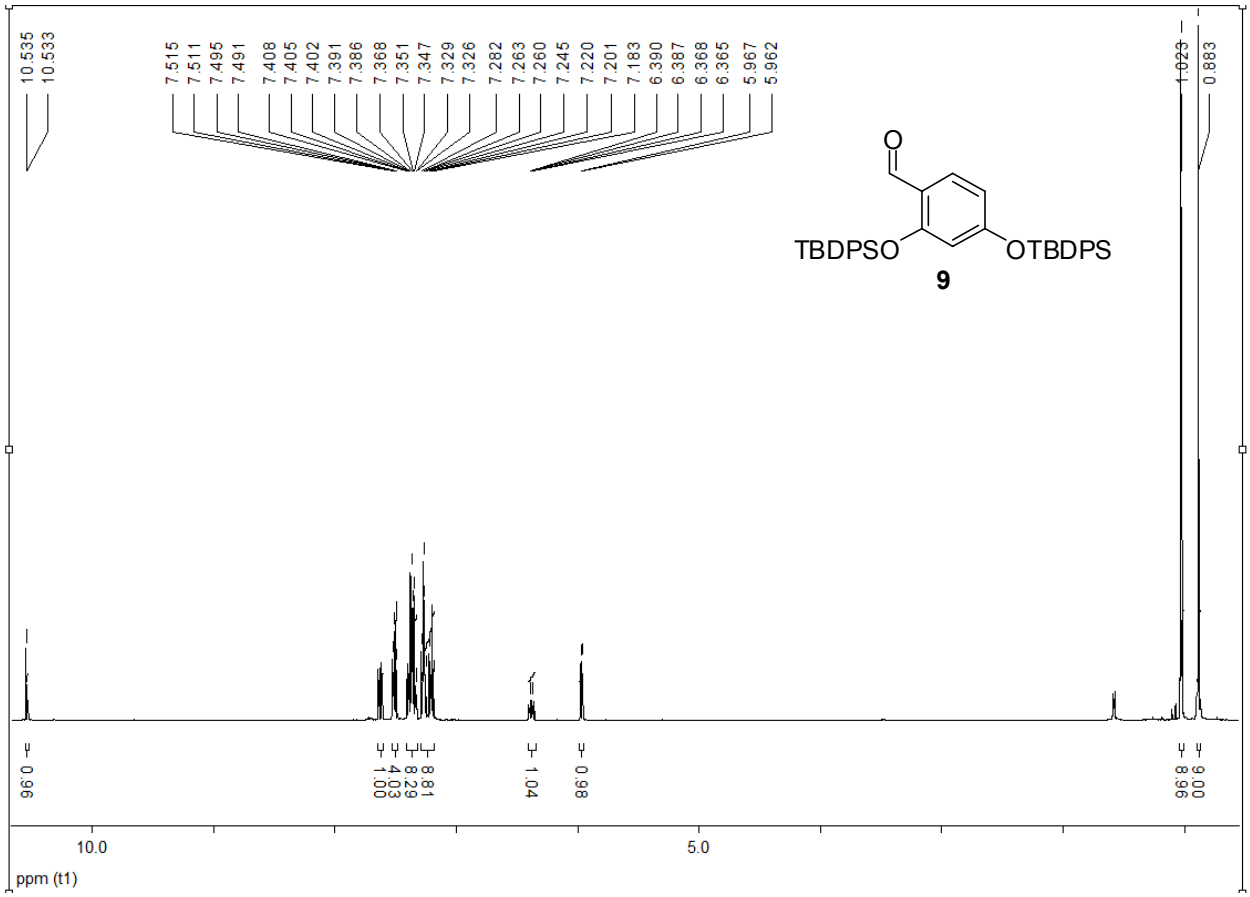


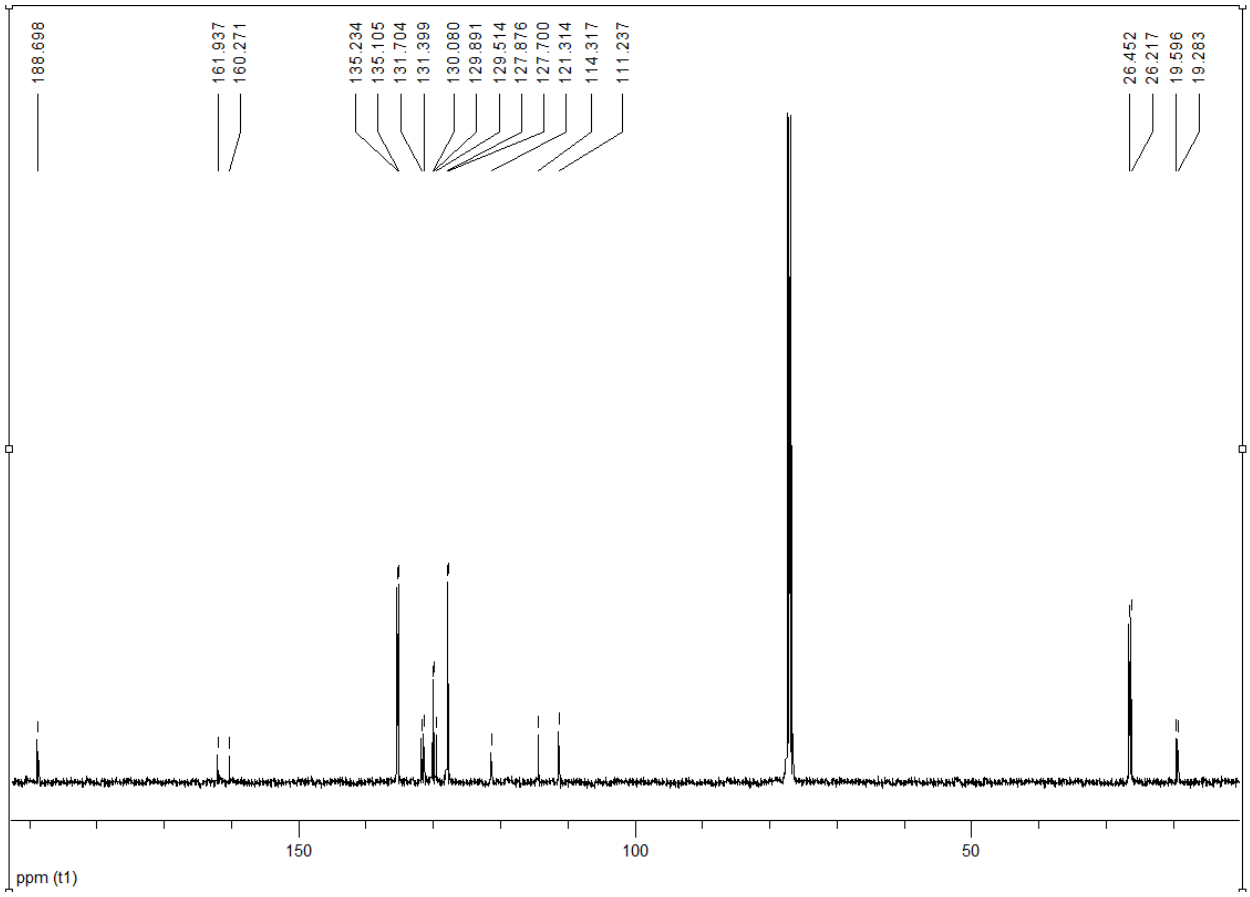
24

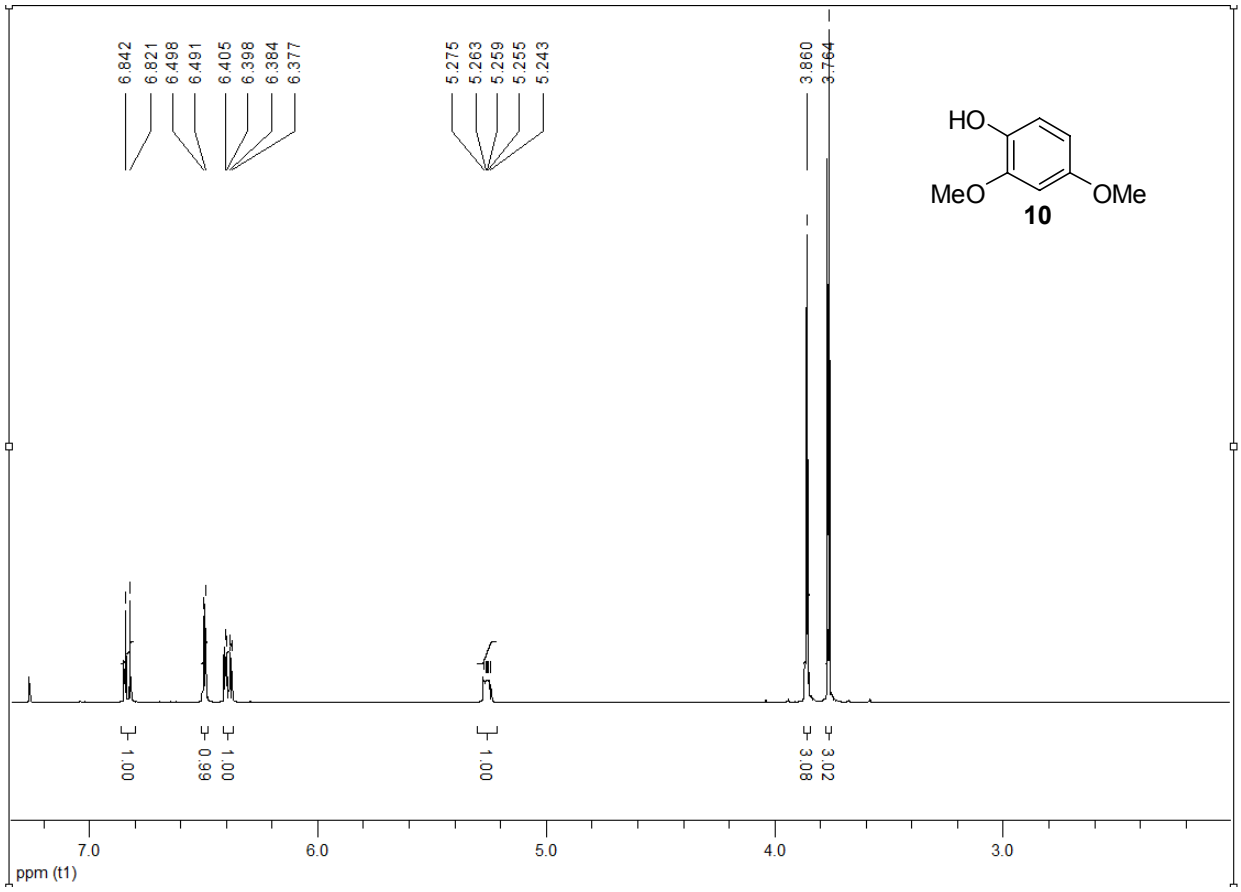
Diethyl 1-(2-(5-(allyloxy)-2,4-dimethoxyphenyl)-1-methoxy-1-oxopropane-2-yl)hydrazine-1,2-dicarboxylate (24)

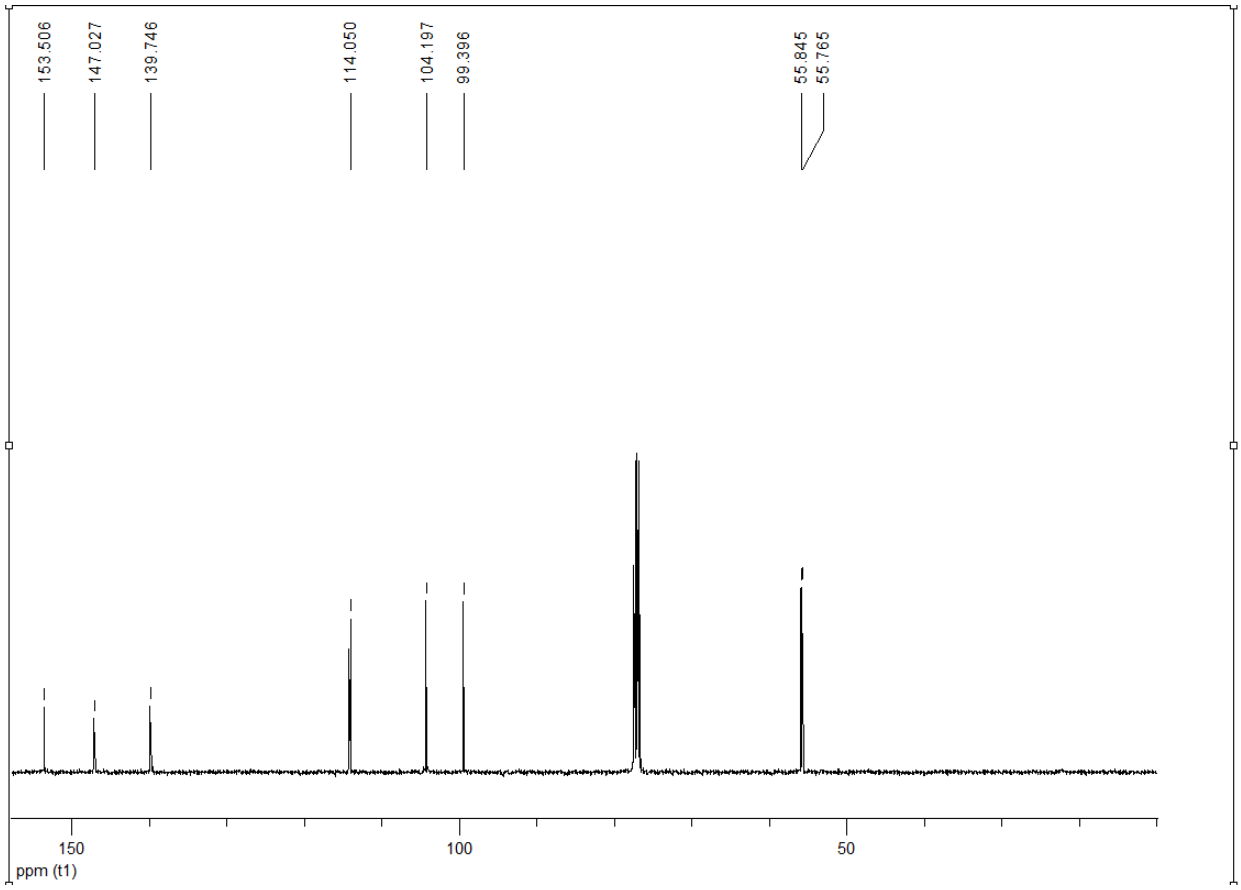
NaH_2PO_4 (1.77 g, 14.8 mmol) was dissolved in water (8.40 mL) and mixted with a solution of **21** (3.14 g, 7.39 mmol) in DMSO (113 mL). This was cooled to 0 °C and a solution of $NaClO_2$ (1.34 g, 14.9 mmol) in water (13.8 mL) was added, then the reaction was stirred at for 16 h at r.t. Then the solution was brought to pH 2-3, extracted with dichloromethan and

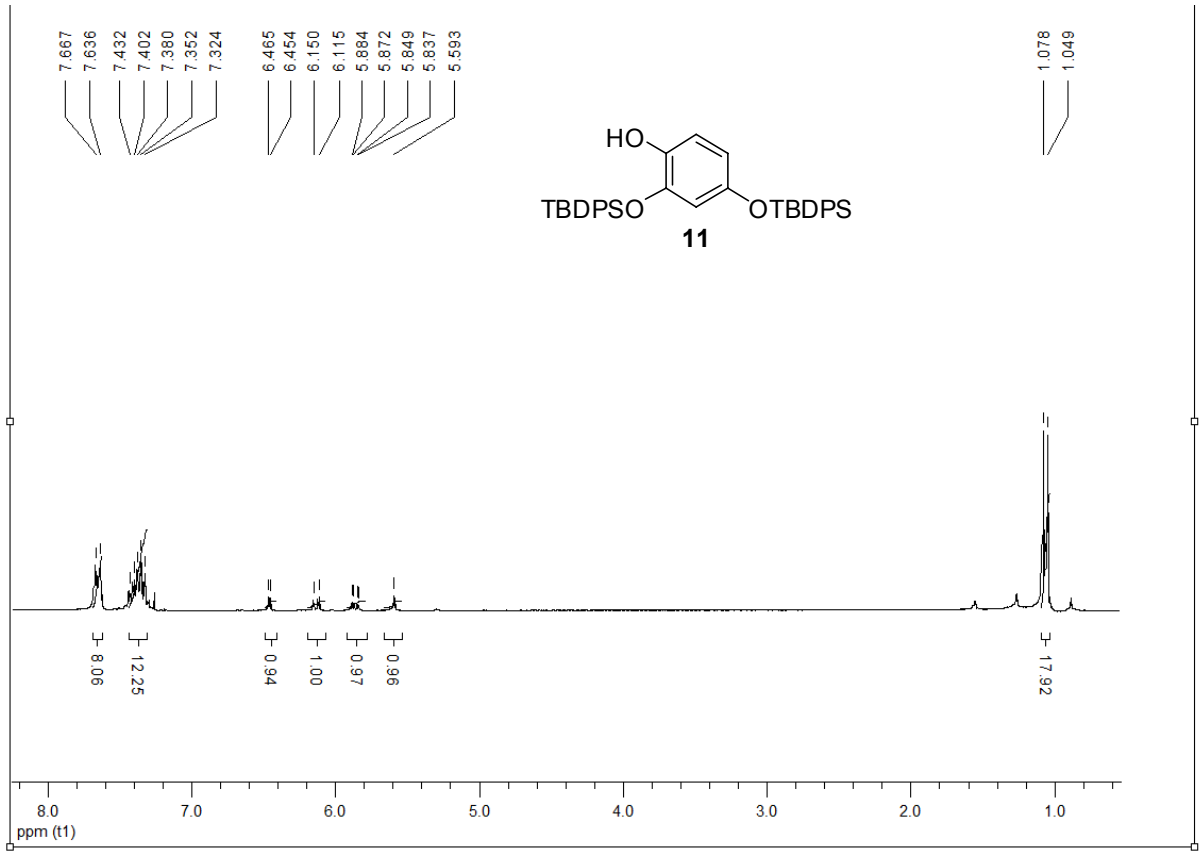
the organic phases were extracted with 1 M NaOH. To precipitate the product the aqueous phase was acidified another time with 1 M HCl and extracted with diethyl ether. The ether phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. To esterify the free carboxlic acid, DBU (1.13 g, 7.39 mmol) and dimethylcarbonate (24.0 mL) were added and the reaction mixture was refluxed for 9 h. After hydrolysis the aqueous phase was extracted with dichloromethane, the combined organic phases were dried Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica using cyclohexane/ethyl acetate 1:3, then 1:5 to afford 705 mg of **24** (21% over two steps) as a colourless oil. TLC (cyclohexane/ethyl acetate 1:3) R_f 0.36; $[\alpha]_D = -25.51°$ (c = 4.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00, 6.95 (2 × s, 1 H), 6.54, 6.42, (2 × bs, 1 H), 6.39, 6.35 (2 × s, 1 H), 6.05–5.95 (m, 1 H), 5.35–5.16 (m, 2 H), 4.49, 4.46 (2 × d, *J* = 5.3 Hz, 2 H), 4.11, 4.05 (2 × q, *J* = 7.2 Hz, 2 H), 3.97–3.84 (m, 2 H), 3.80 (s, 3 H), 3.71–3.67 (m, 6 H), 2.10, 1.97 (2 × s, 3 H), 1.18, 0.99 (2 × t, *J* = 7.1 Hz, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 156.5, 155.6, 151.5, 150.4, 141.9, 133.6, 119.4, 117.9, 115.8, 97.9, 70.9, 69.2, 62.4, 61.4, 56.8, 56.1, 52.5, 25.5, 14.42, 14.35 ppm; IR (KBr): ν = 3310, 3081, 2983, 2952, 2849, 1720, 1647, 1613, 1515, 1465, 1397, 1375, 1317, 1210, 1138, 1099, 1064, 1029, 919, 872, 781, 733 cm^{-1}; MS (FAB, 3-NBA): *m/z* (%) = 454 (21), 279 (100), 219 (25); HR-FABMS ($C_{21}H_{30}N_2O_9$): calcd. 454.1951, found 454.1950.

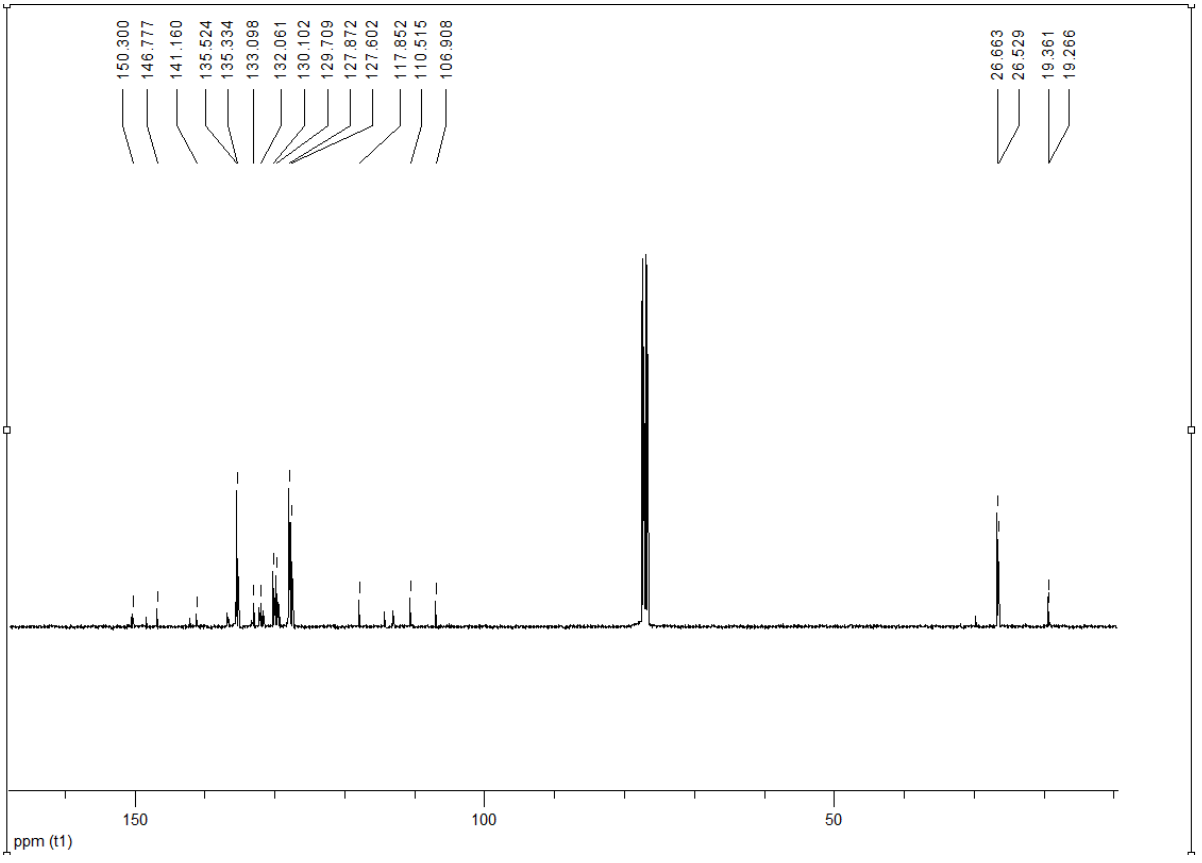


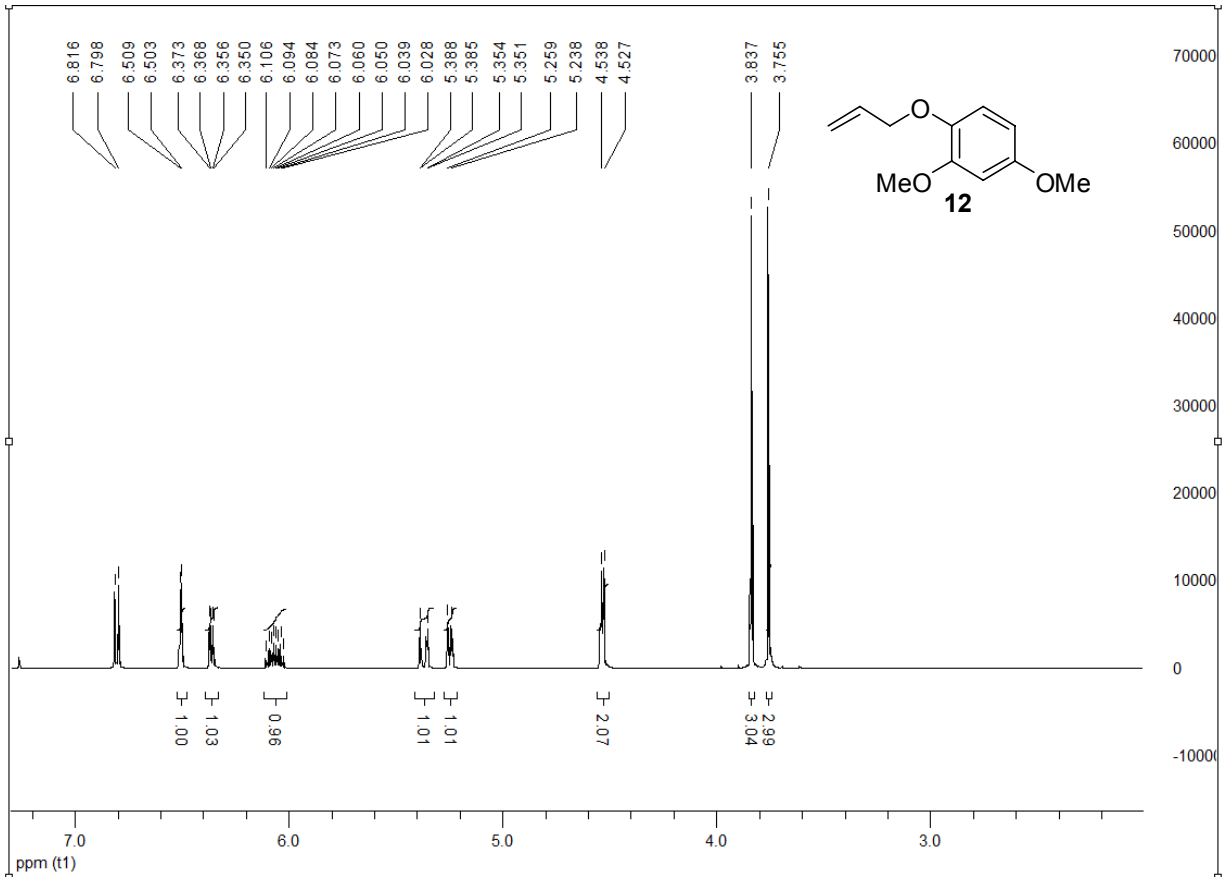


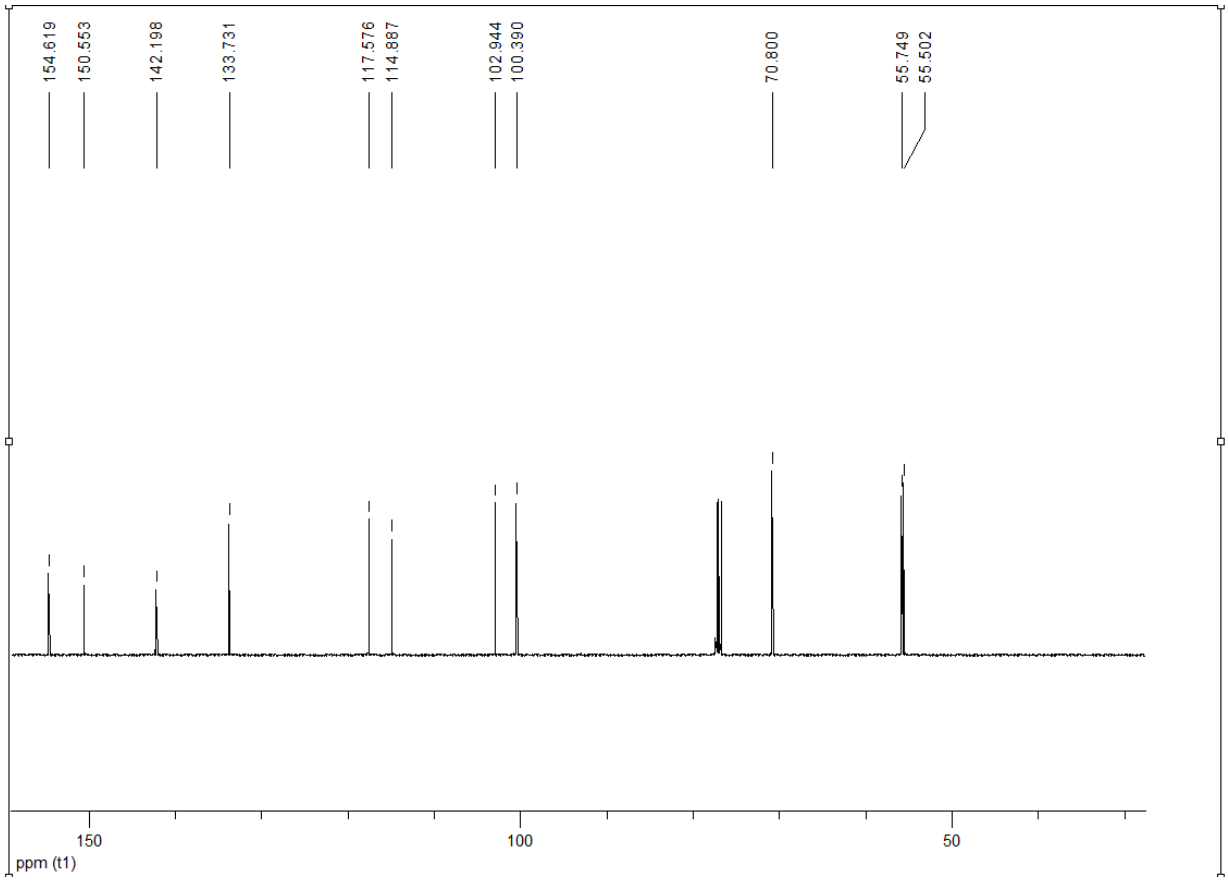


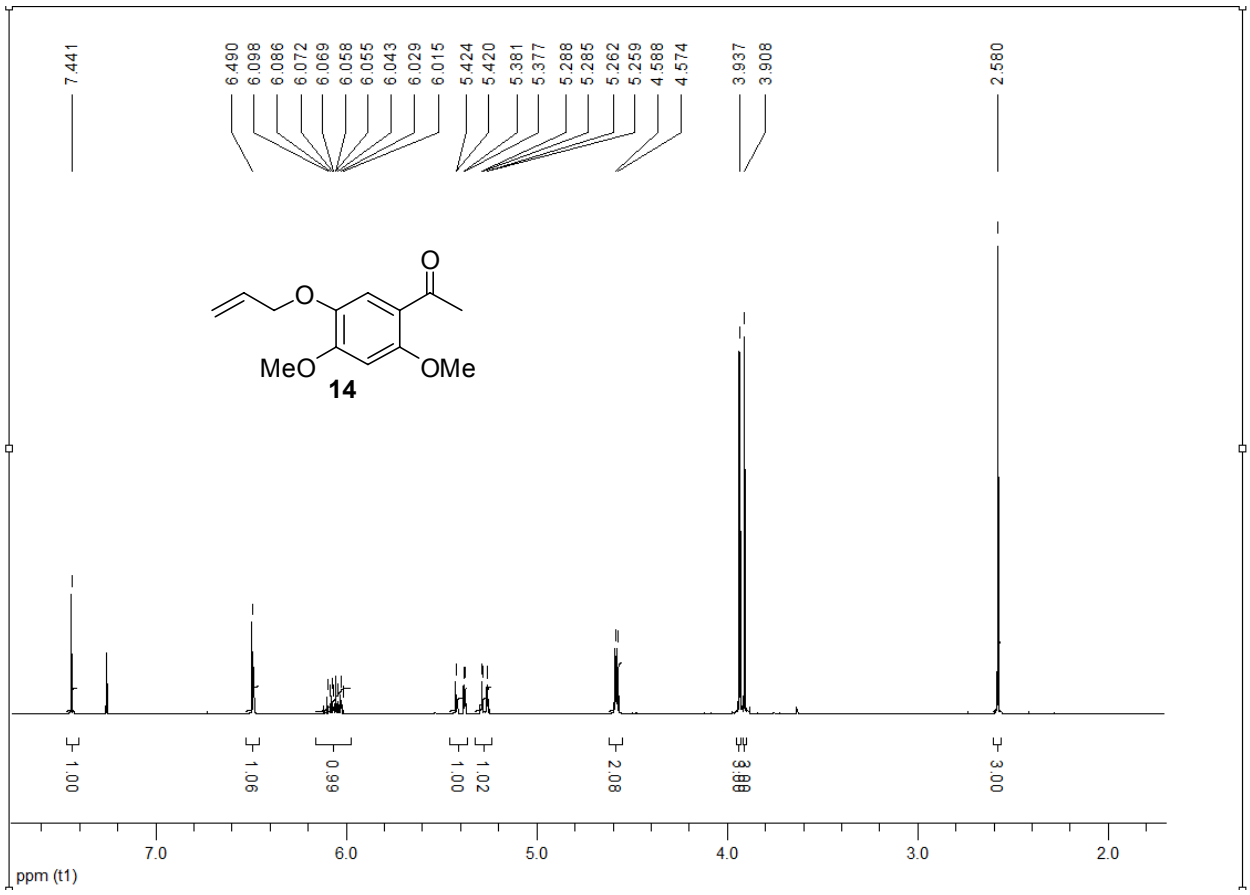


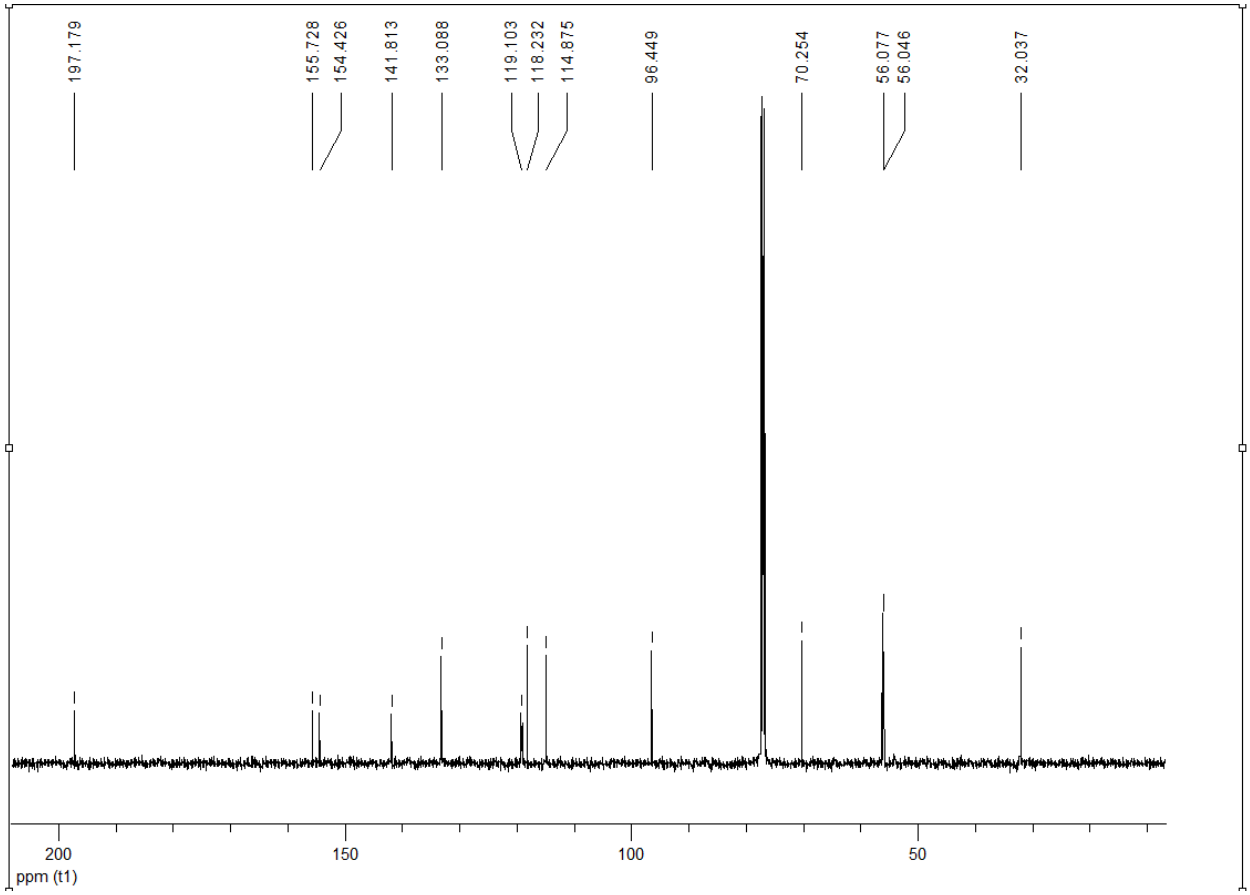


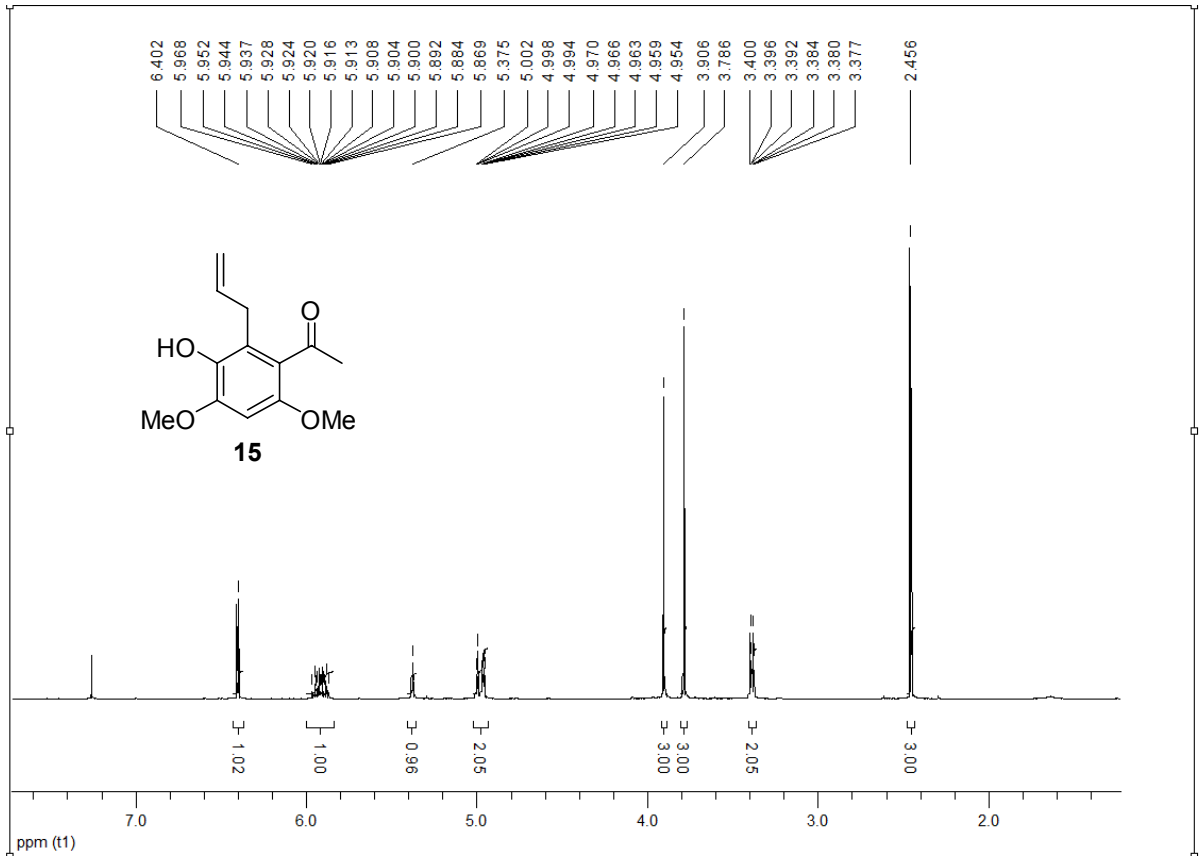


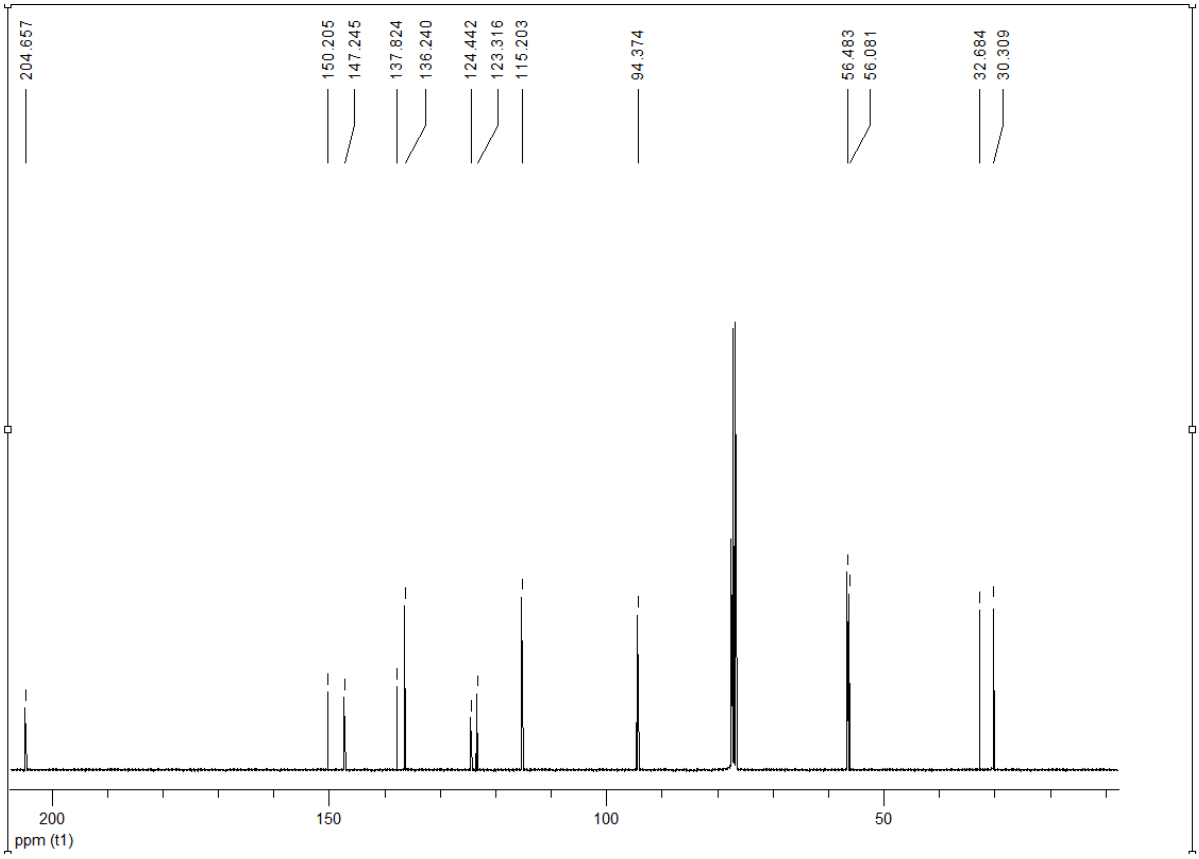


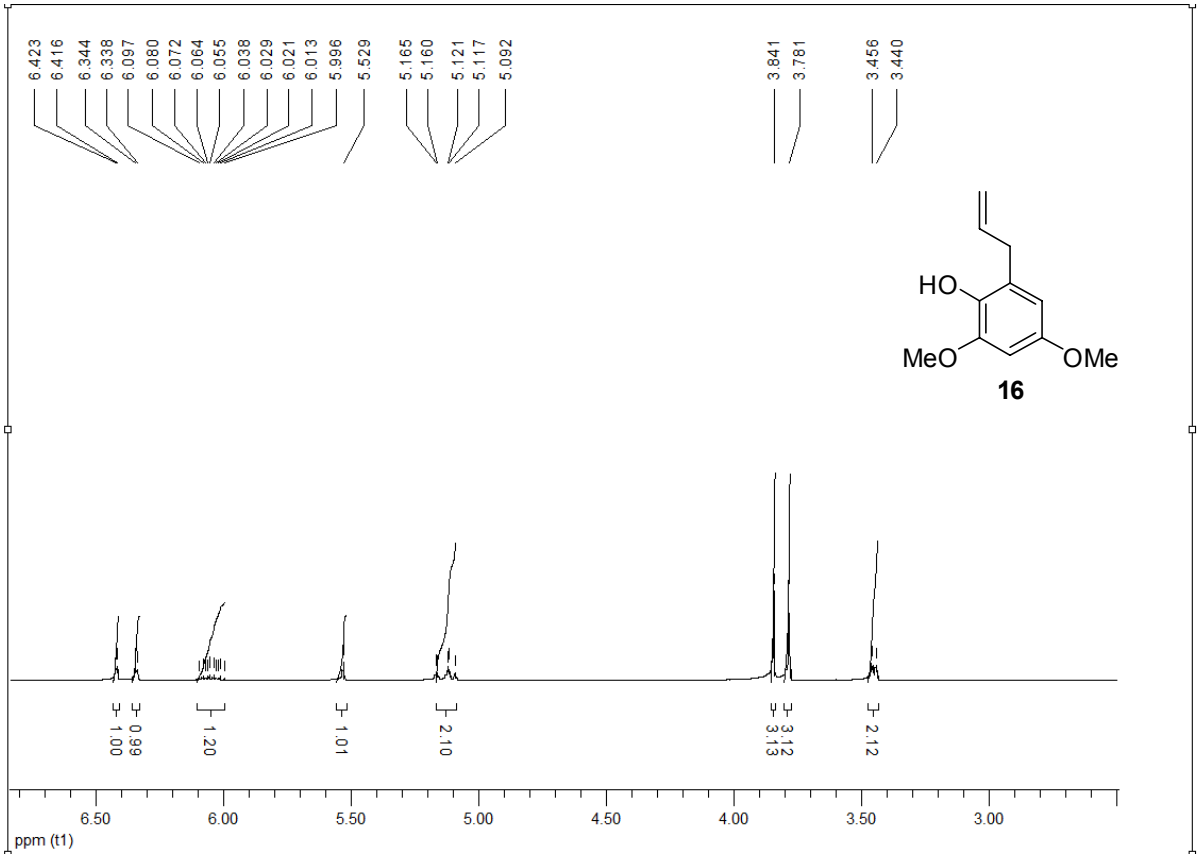


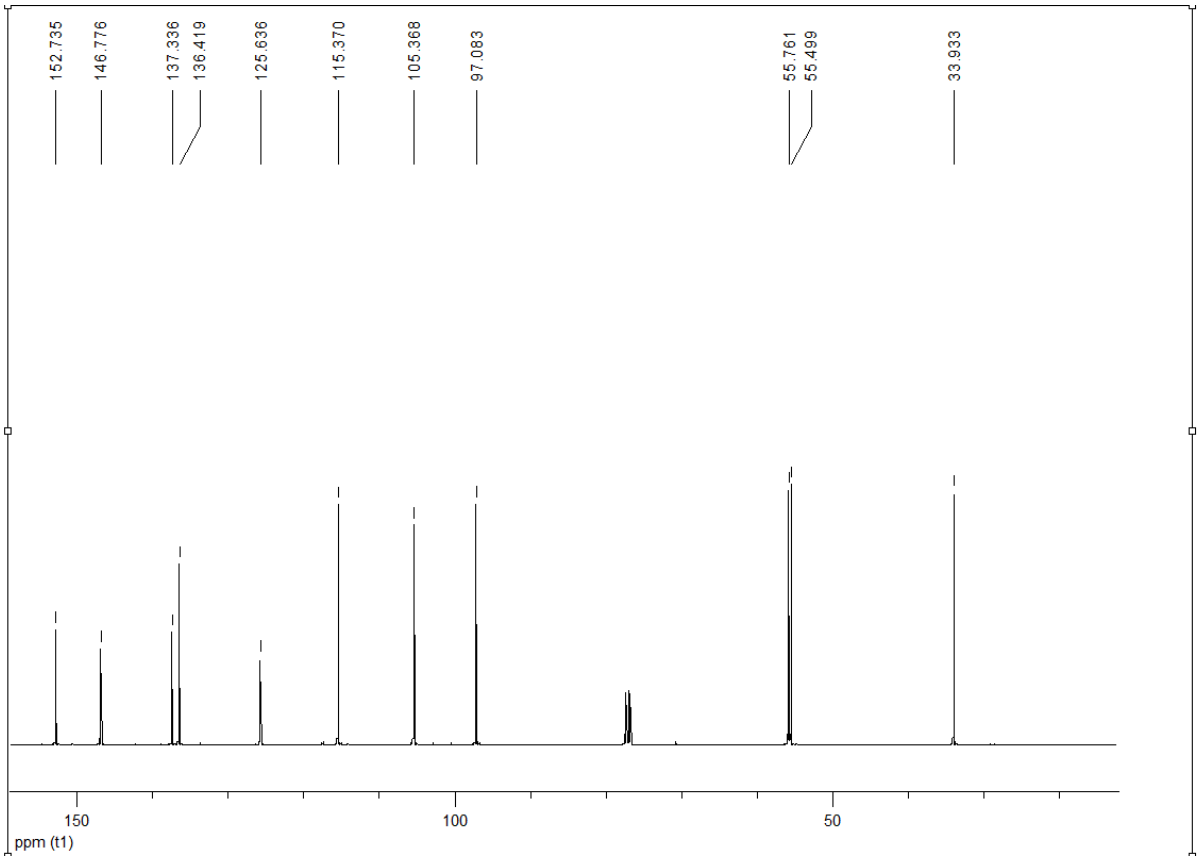


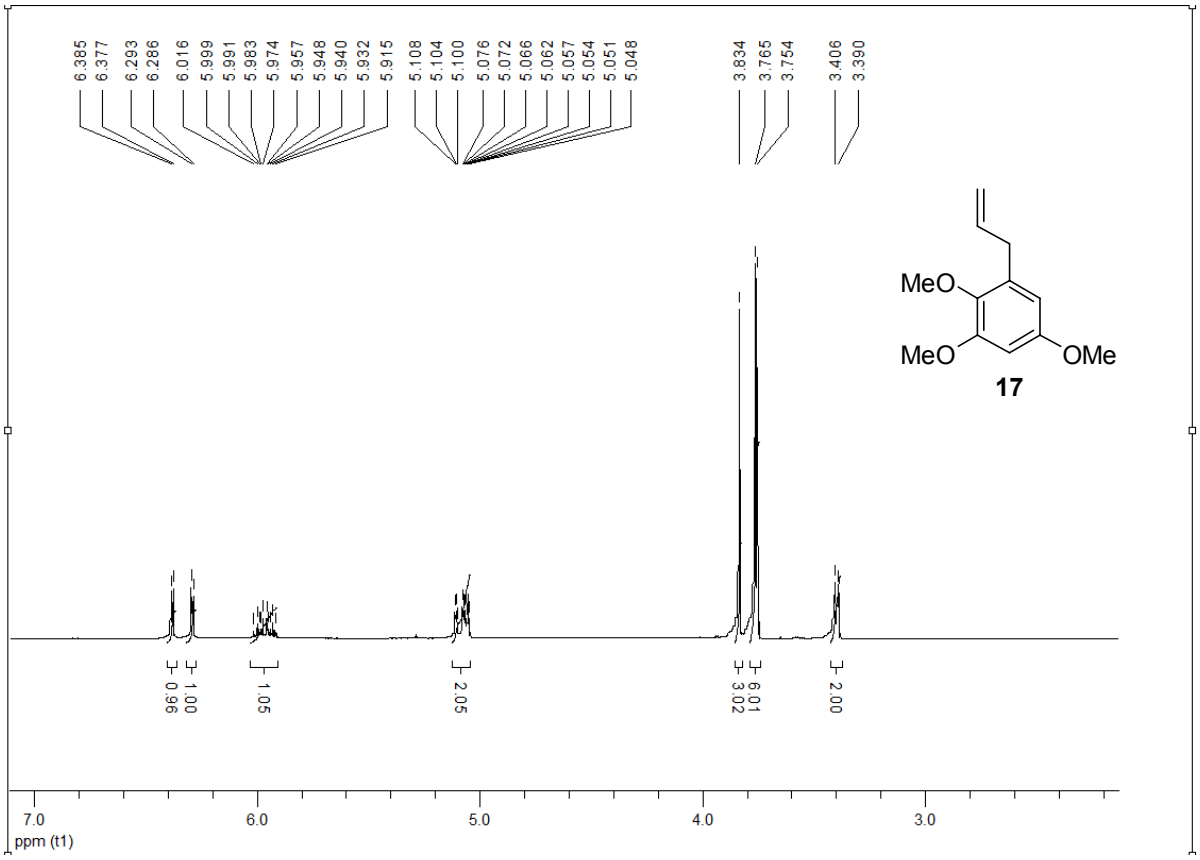


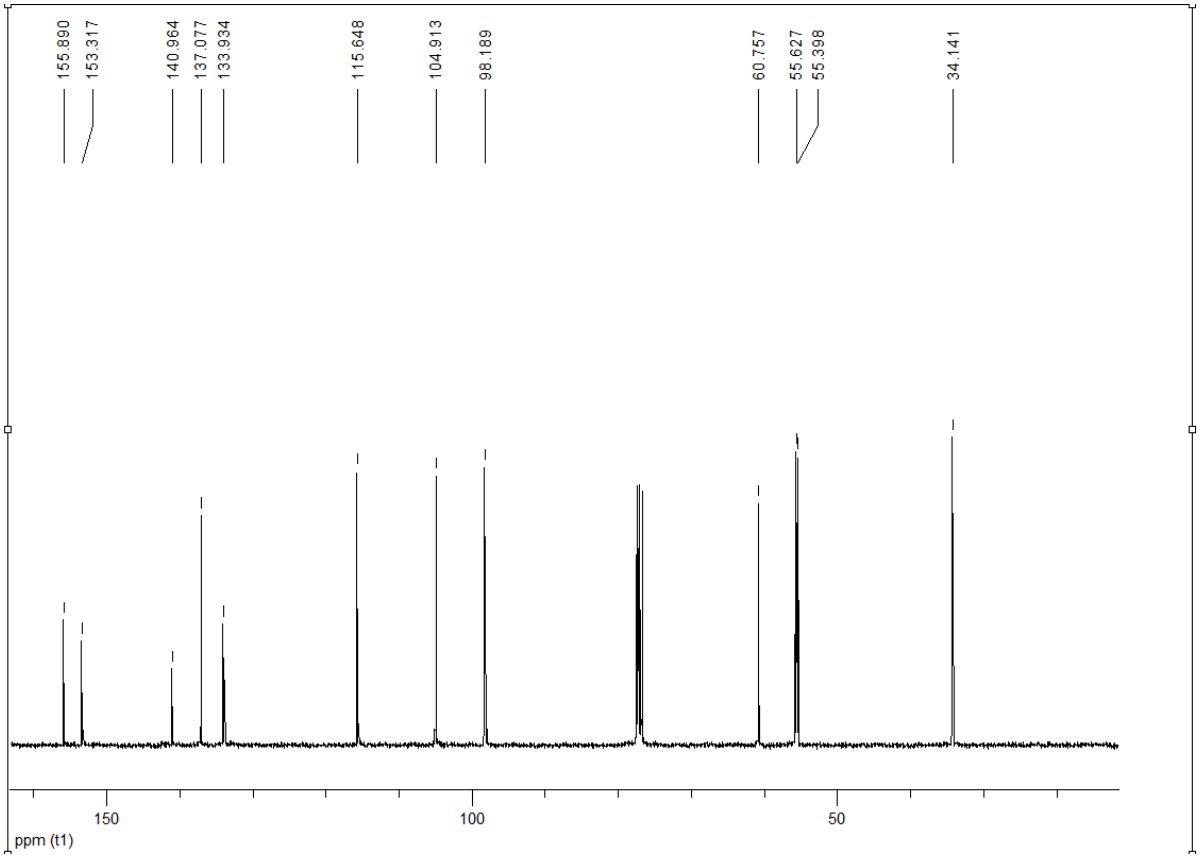


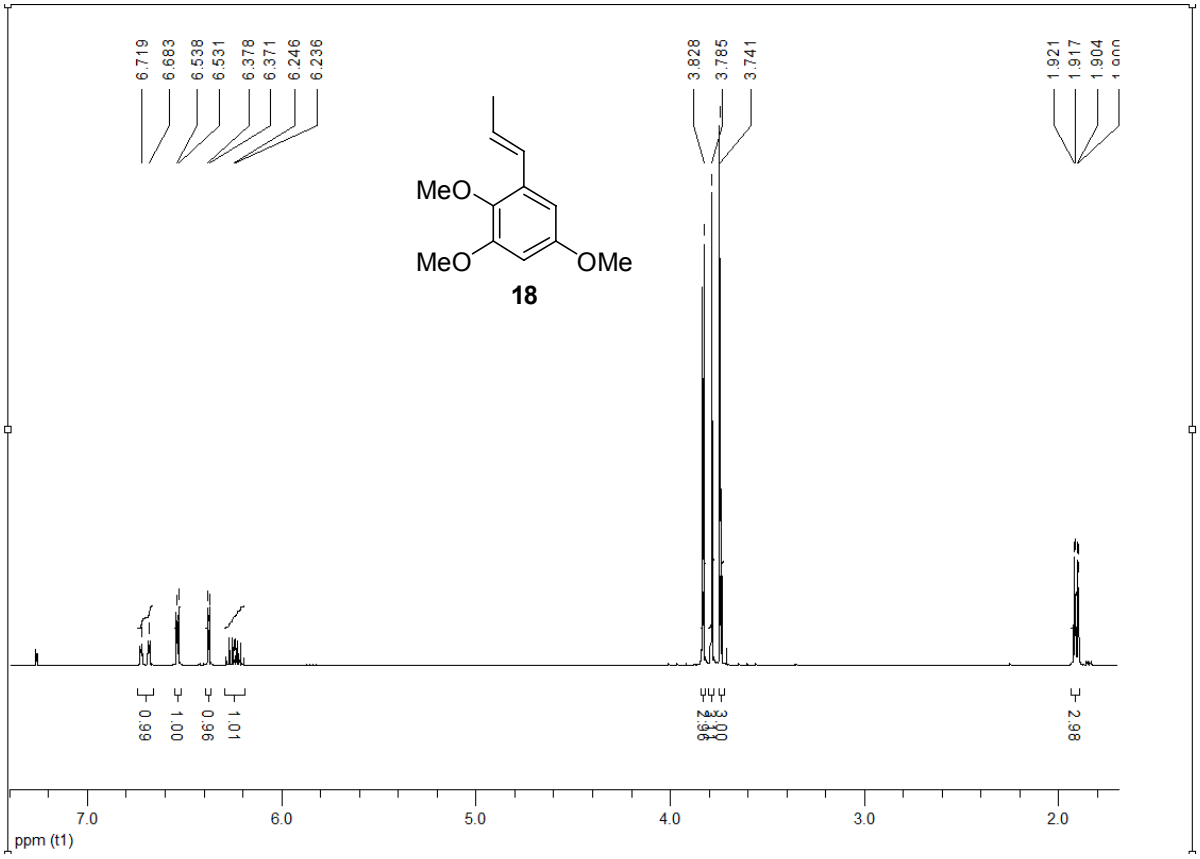


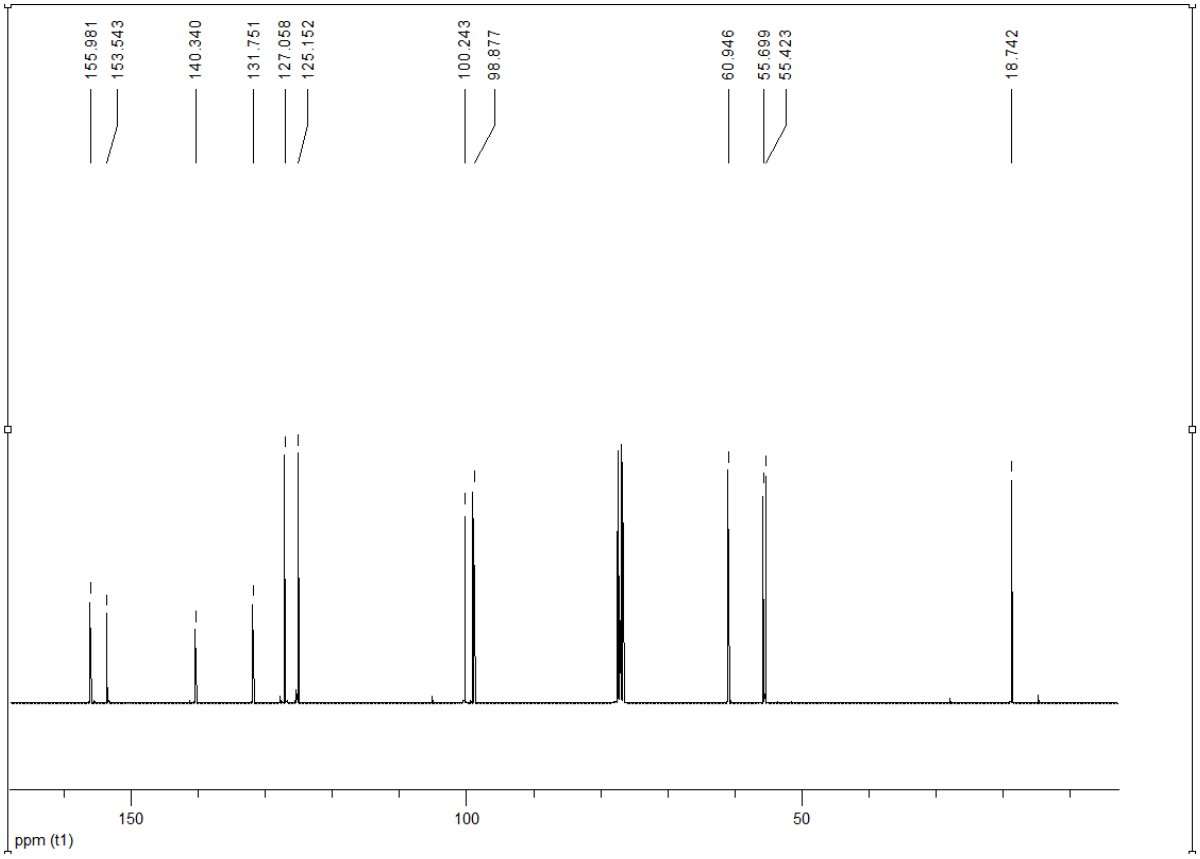


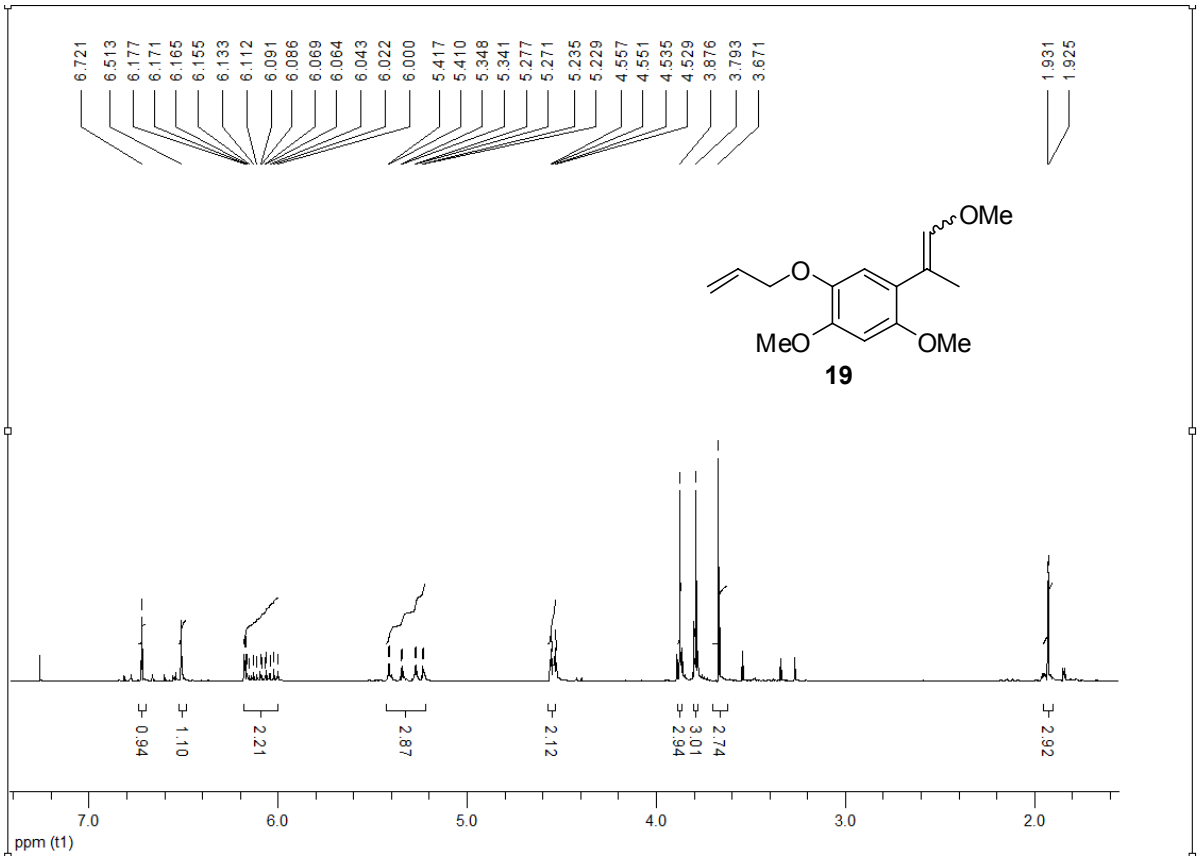


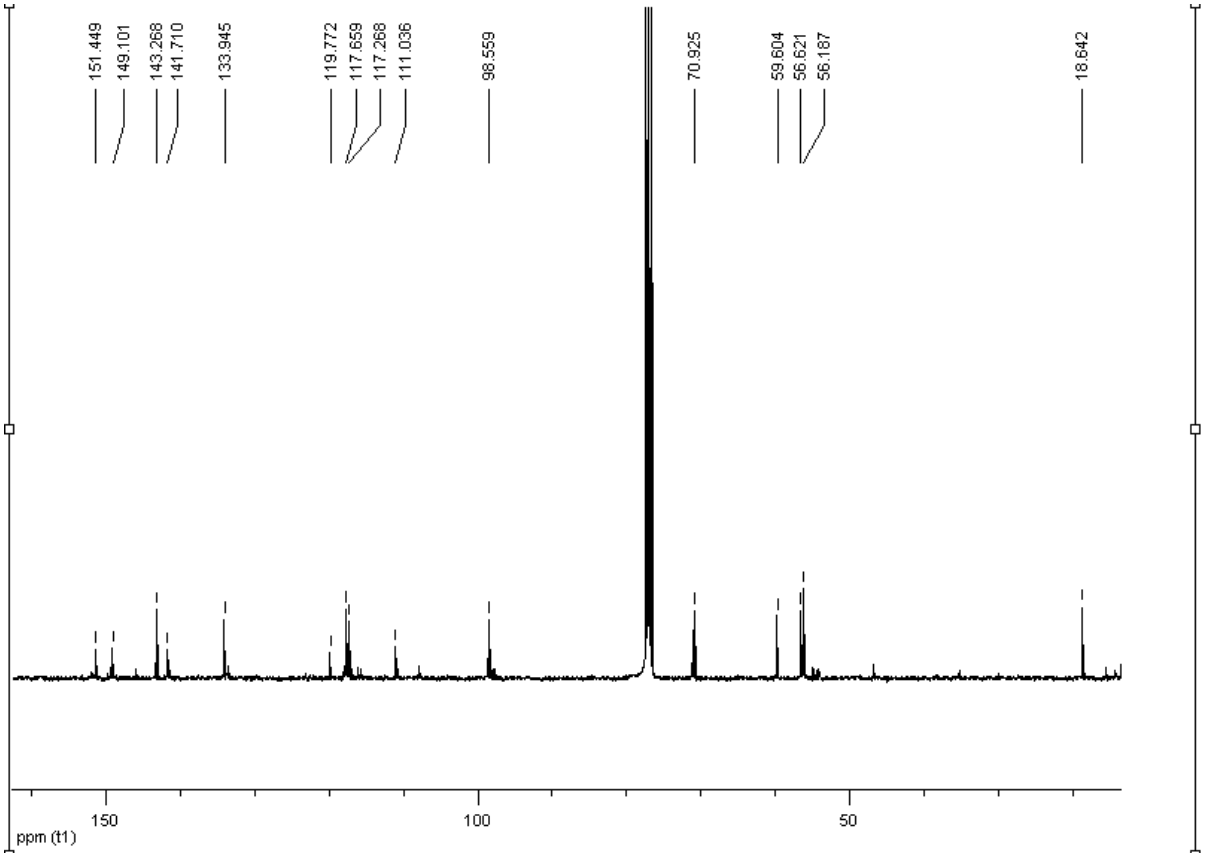


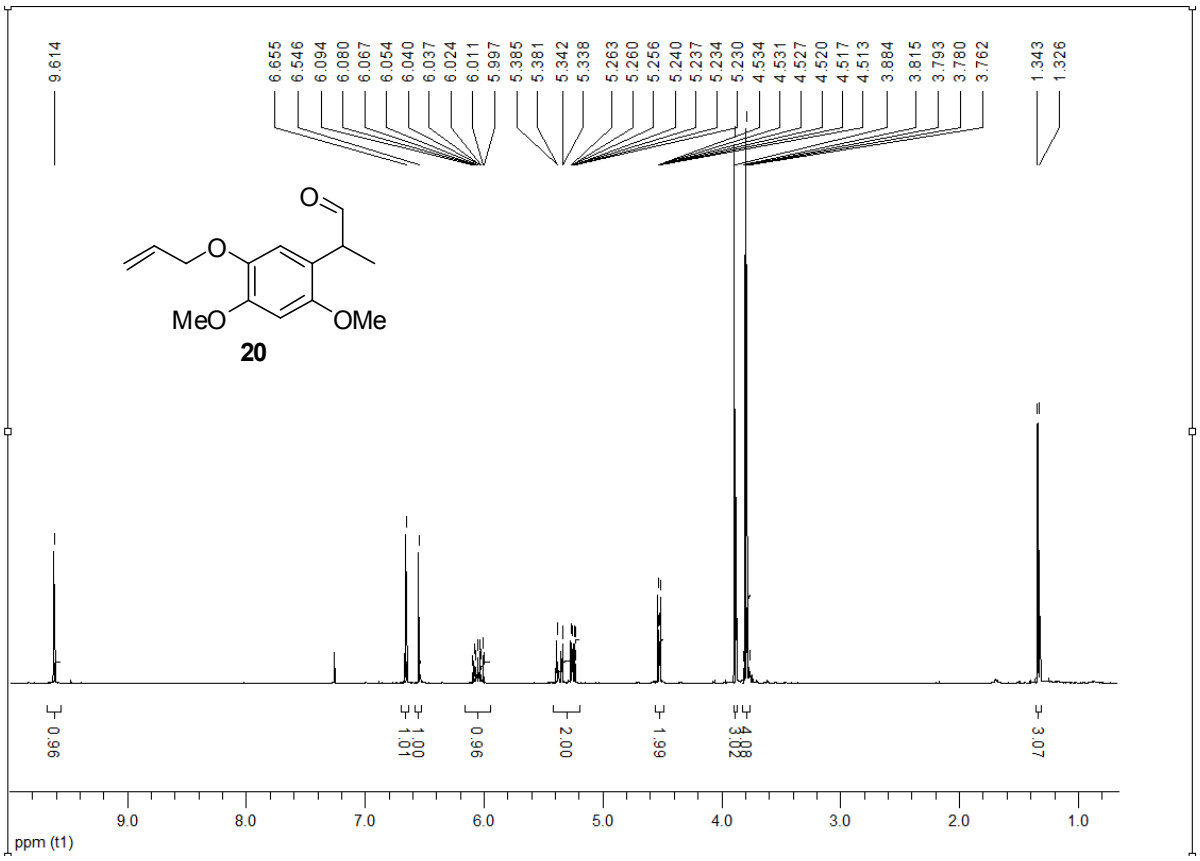


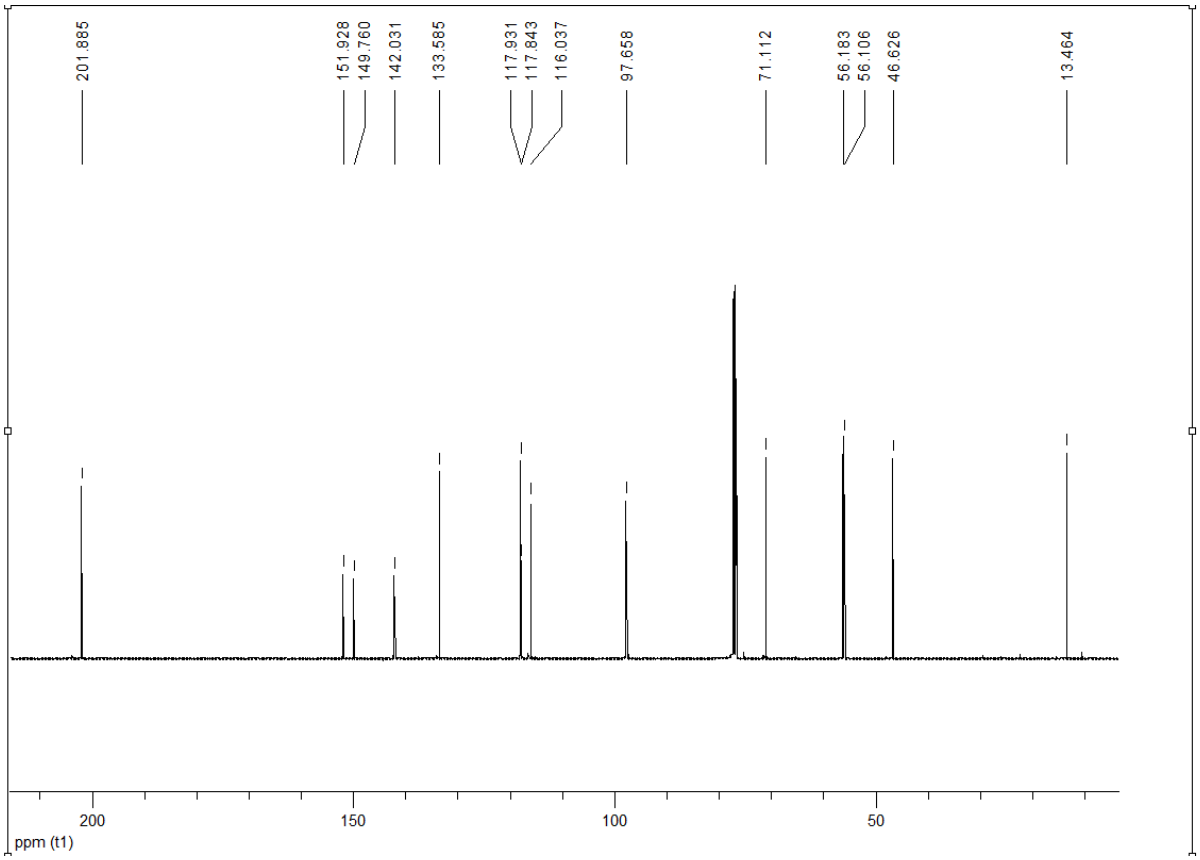


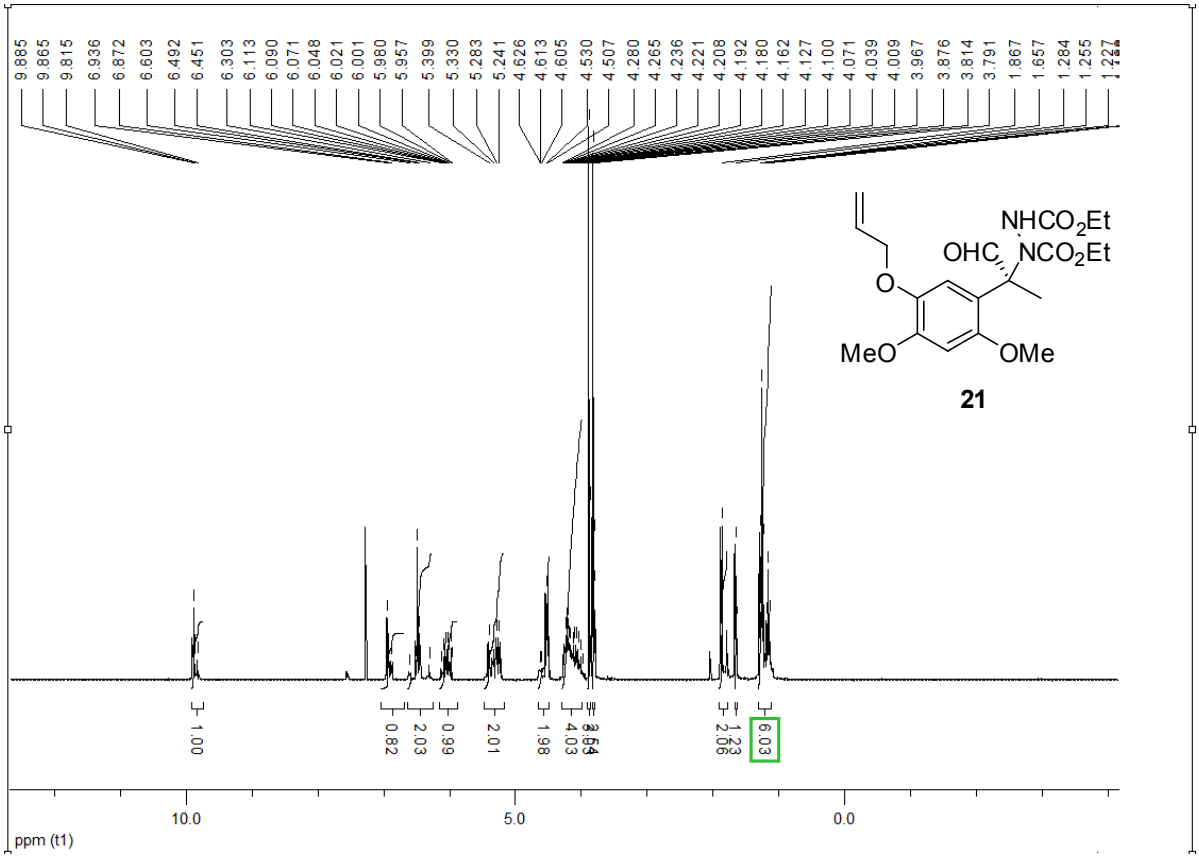


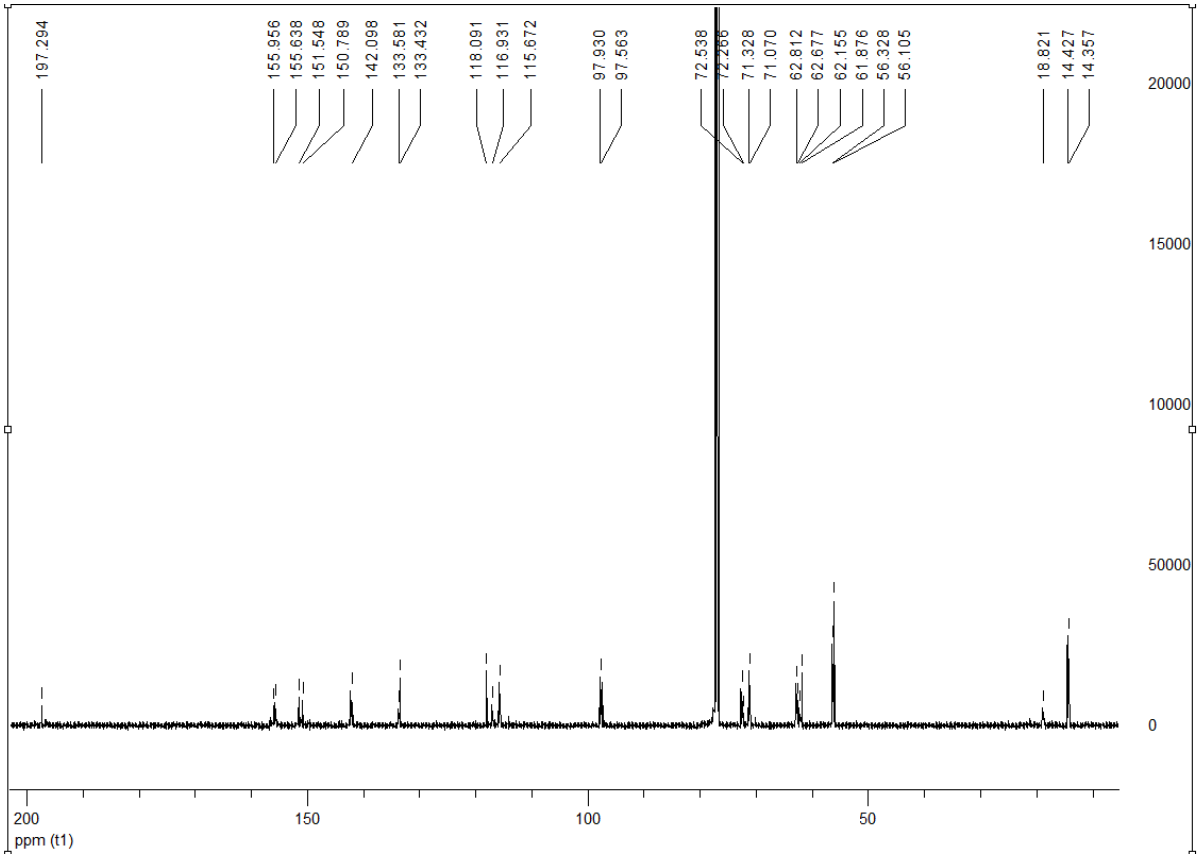


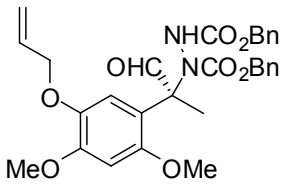












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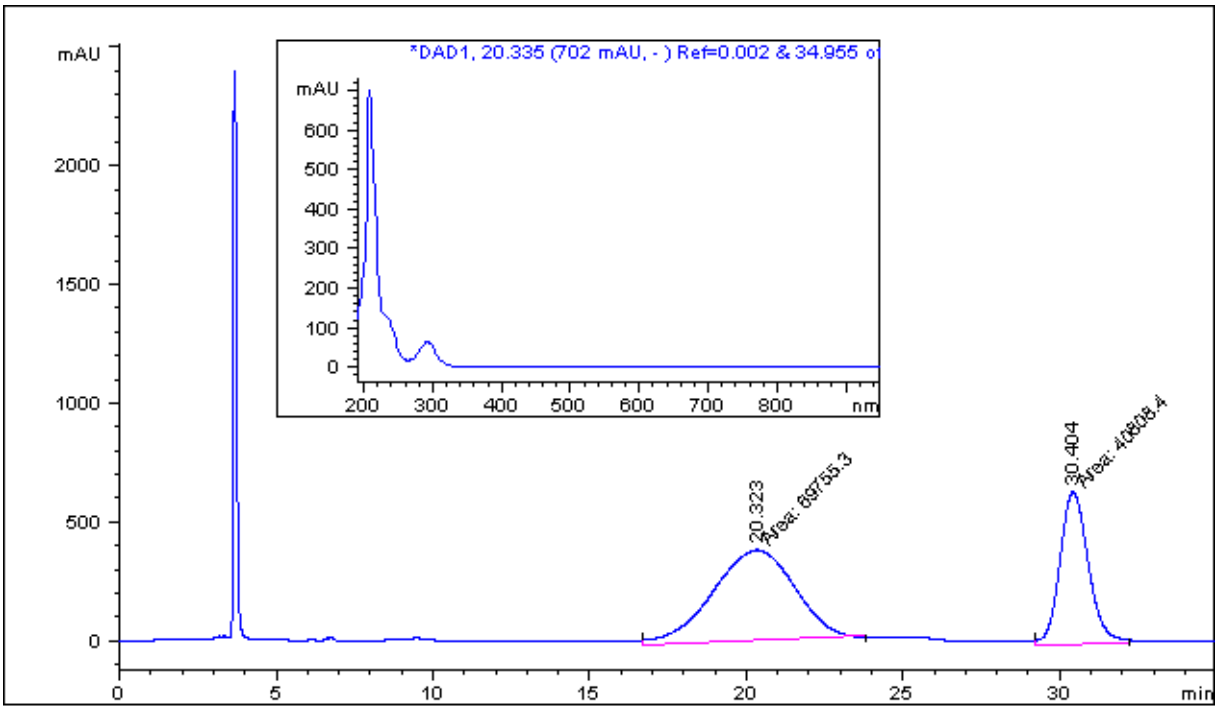
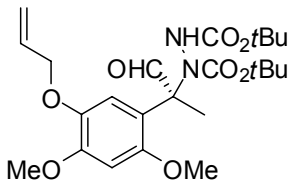


At around 4 min: solvent



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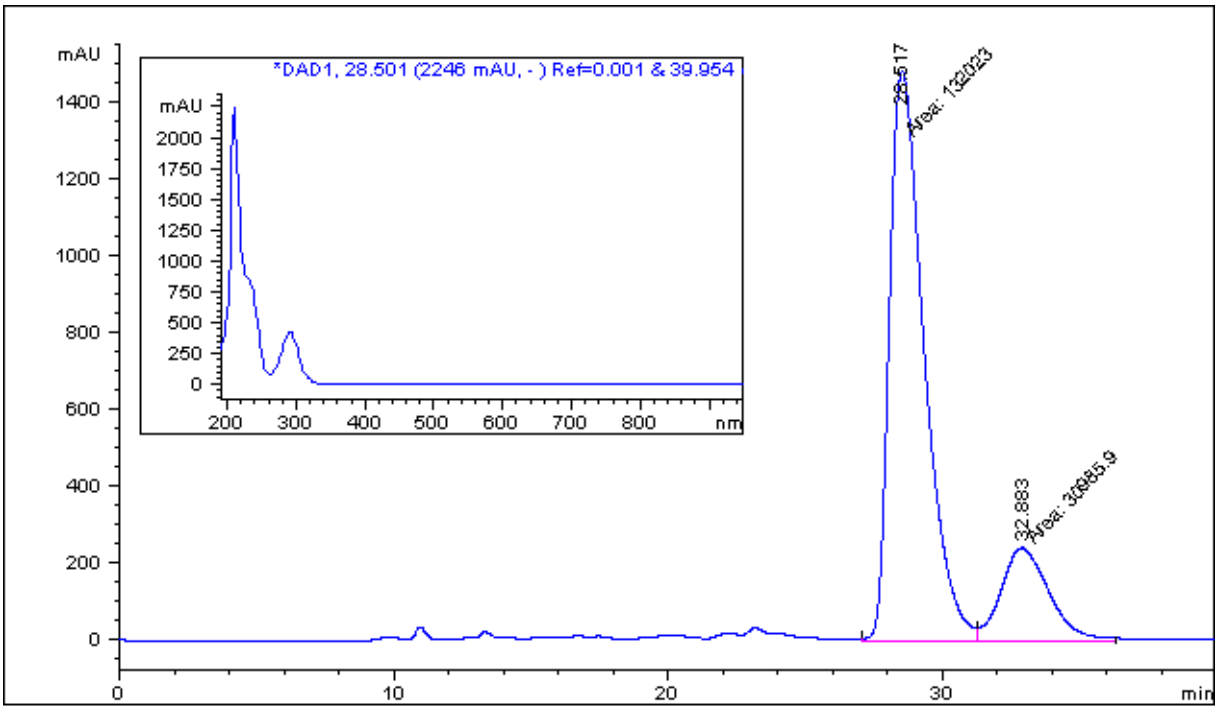

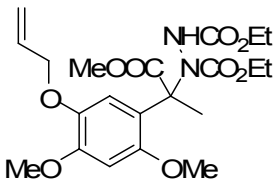

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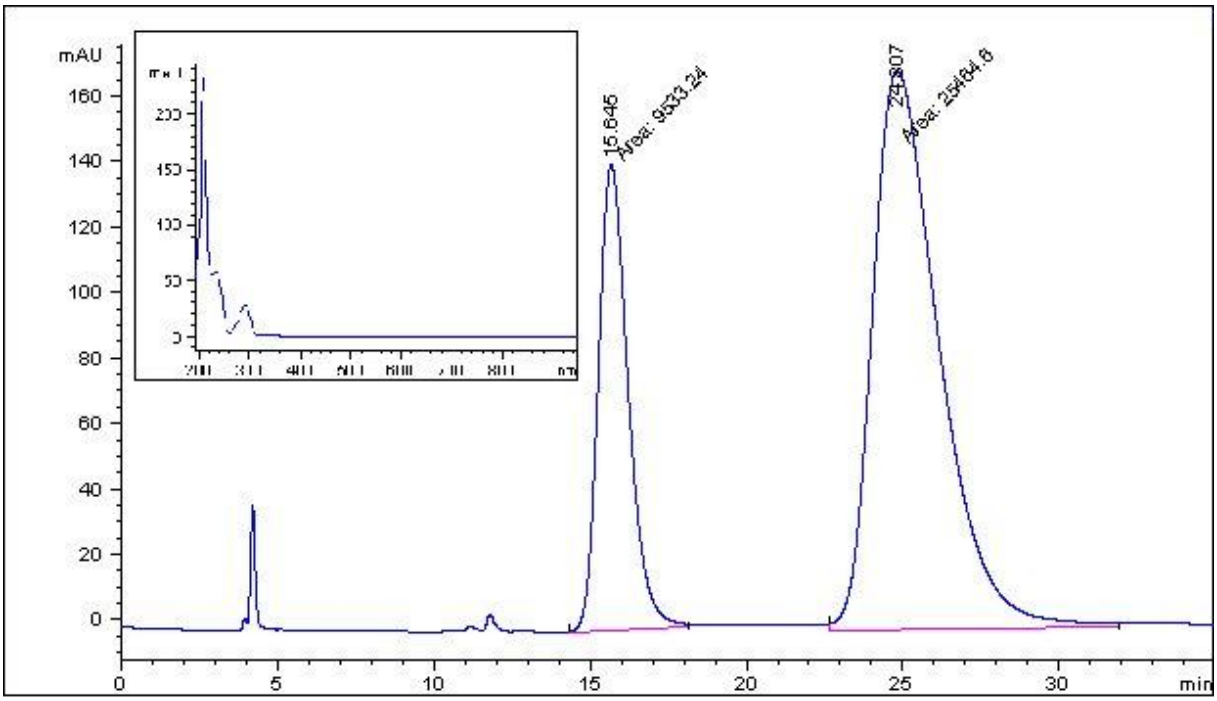

At around 4.5 min: solvent

[i] F. Michel, F. Thomas, S. Hamman, E. Saint-Aman, C. Bucher, J.-L. Pierre, *Chem. Eur. J.*, 2004, **10**, 4115-4125.

[ii] C. B. de Koning, J. P. Michael, W. A. L. van Otterlo, *J. Chem. Soc., Perkin Trans. 1*, 2000, 799-811.

[iii] I. R. Green, C. B. de Koning, V. I. Hugo, *S.-Afr. Tydskr. Chem.*, 1999, **52**, 112-119.