Supporting Information

Polymer-assisted Synthesis of Single and Fused Diketomorpholines

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Content

General Information

Solvents and chemicals were purchased from Sigma-Aldrich (Milwaukee, WI, www.sigmaaldrich.com) and Acros (Geel, Belgium, www.across.cz). The Wang resin (100-200 mesh, 1% DVB, 0.9 mmol/g) was obtained from AAPPTec (Louisville, KY, www.aapptec.com).

The synthesis was carried out in plastic reaction vessels (syringes, each equipped with a porous disk) using a manually operated synthesizer (Torviq, Niles, MI, www.torviq.com). All reactions were carried out at ambient temperature (25 ˚C) unless stated otherwise. The volume of wash solvent was 10 mL per 1 g of resin. For washing, resin slurry was shaken with the fresh solvent for at least 1 min before changing the solvent. Resin-bound intermediates were dried by a stream of nitrogen for prolonged storage and/or quantitative analysis. For the LC/MS analysis, a sample of resin (~5 mg) was treated with TFA in DCM, the cleavage cocktail was evaporated under a stream of nitrogen, and cleaved compounds extracted into MeCN (1 mL).

The LC/MS analyses were carried out on UHPLC-MS system consisting of UHPLC chromatograph Acquity with photodiode array detector and single quadrupole mass spectrometer (Waters), using X-Select C18 column at 30 °C and flow rate of 600 μL/min. The mobile phase was (A) 10 mM ammonium acetate in H_2O, and (B) MeCN, linearly programmed from 20% to 80% B over 2.5 min, kept for 1.5 min. The column was re-equilibrated with 20% of solution B for 1 min. The ESI source operated at discharge current of 5 μA, vaporizer temperature of 350 °C and capillary temperature of 200 ˚C.

Purification was carried out on C18 reverse phase column (YMC Pack ODS-A, 20 × 100 mm, 5 μm particles), the gradient was formed from 10 mM aqueous ammonium acetate and MeCN, flow rate 15 mL/min.

For lyophilization of residual solvents (H_2O, ammonium acetate buffer, DMSO) the ScanVac Coolsafe 110-4 working at -110 °C was used.

All 1D and 2D NMR experiments were performed with using ECA400II or ECX500 spectrometer (JEOL RESONANCE, Tokyo, Japan) at magnetic field strength of 9.39 T or 11.75 T corresponding to ^{1}H and ^{13}C resonance frequencies of 399.78 MHz or 500.16 MHz and 100.53 MHz or 125.77 MHz at 27 ºC. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) are reported in Hertz (Hz). The signal of MeCN-d_3 was set at 1.94 ppm in ^{1}H NMR spectra and at 118.26 ppm in ^{13}C NMR spectra. The signal of MeOH-d_4 was set at 3.31 ppm in ^{1}H NMR spectra and at 49.15 ppm in ^{13}C NMR spectra.

HRMS analysis was performed using LC-MS (Dionex Ultimate 3000) with Orbitrap Elite high-resolution mass spectrometer (Thermo Exactive plus, MA, USA) operating at positive full scan mode (120 000 FWMH) in the range of 100-1000 m/z. The settings for electrospray

ionization were as follows: oven temperature of 150 °C and the source voltage of 3.6 kV. The acquired data were internally calibrated with phthalate as a contaminant in MeOH (m/z 297.15909). Samples were diluted to a final concentration of 0.1 mg/mL in MeCN. Before HPLC separation (column Phenomenex Gemini, 50 × 2.00 mm, 3 *μ*m particles, C18), the samples were injected using direct infusion into the mass spectrometer using autosampler. The mobile phase was isocratic MeCN/10 mM ammonium acetate (80:20) and flow 0.3 mL/min.

The supercritical fluid chromatography system UPC^2 (Waters, Milford, MA, USA) utilized two columns (100 × 4.6 mm) with different stationary phases with particle size 3 *μ*m CHIRALPAK® IC-3 (Daicel, Illkirch Cedex, France). Column IC-3 was used for all analyses. Isocratic elution was performed using CO_2 (>99,995%, SIAD, Czech Republic) with 25% MeOH, 1% H_2O, 0.1% TFA and 0.1% DEA for purified compounds **4**{*1,1*}, **5**{R^1,R^2} and **5^R**{*1,2*}. Second, with 20% MeOH, 1% H_2O and 0.1% TFA for purified compound **7**{*1,1*} and with 10% MeOH, 1% H_2O, 0.1% TFA and 0.1% DEA for reaction mixture **5**{*1,2*} and **5^R**{*1,2*} originating from reaction kinetic. Flow rate was set at 2.2 mL/min, the temperature at 38 °C, ABPR 2000 psi, the temperature of autosampler was set to 10 °C. All samples were dissolved in MeCN (1 mL). Injected volume was 2 *μ*L.

Experimental Procedures

Synthesis of α-acylamino ketones **1**{R^1} was performed according to previously reported procedure (Králová, P.; Fülöpová, V.; Maloň, M.; Volná, T.; Popa, I.; Soural, M. Stereoselective Polymer-Supported Synthesis of Morpholine- and Thiomorpholine-3-Carboxylic Acid Derivatives. *ACS Comb. Sci.* **2017**, *19* (3), 173–180).

1. Acylation: 2{R^1,R^2}

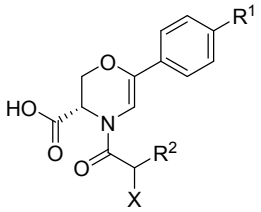
Carboxylic acids: 2-iodoacetic acid (560 mg, 3.0 mmol), (S)-(-)-α-bromopropionic acid (459 mg, 3.0 mmol) or α-bromophenylacetic acid (645 mg, 3.0 mmol) was dissolved in DCM (10 mL) and DIC (232 *μ*L, 1.5 mmol) was added. The reaction mixture was shaken for 30 min at room temperature, the precipitated diisopropylurea was filtered and the remaining solution was added to resin **1**{R^1} (1 g). After shaking for 24 h at room temperature the resulting resins **2**{R^1,R^2} were washed three times with DCM, DMF and DCM.

Acyl bromides: Solution of 2-bromopropionyl bromide (310 *μ*L, 1.5 mmol) and DIEA (350 *μ*L, 1.5 mmol) in DCM (10 mL) was added to the resin **1**{R^1} (1 g) and shaken for 24 h at room temperature. The resulting resin **2**{*R^1,2*} was washed three times with DCM, DMF and DCM.

2. Cyclization to oxazines: 3{*R¹,R²*}

The resin **2**{*R¹,R²*} (500 mg) was washed three times with DCM and solution of trifluoroacetic acid (TFA) in DCM (50%, 5 mL) was added. The suspension was shaken for 1 h (or 4 h for derivatives **2**{*R¹,3*}) at room temperature. The cleavage cocktail was isolated, and the resin was further washed three times with the fresh cleavage cocktail (5 mL). The combined washes were evaporated using a stream of nitrogen.

Table 1. Crude purities of *N*-acyl-3,4-dihydro-2*H*-1,4-oxazine-3-carboxylic acids **3**{*R¹,R²*}



3{*R¹,R²*}

cmpd	R¹	R²	crude purity [%][a]
3{*1,1*}	H	H	97
3{*1,2*}	H	Me	94
3*R*{*1,2*}	H	Me	96
3{*1,3*}	H	Ph	91
3{*2,2*}	MeO	Me	94
3{*2,3*}	MeO	Ph	56
3{*3,1*}	Br	H	94
3{*3,2*}	Br	Me	85
3{*3,3*}	Br	Ph	79
3{*1,1*}	H	H	90

[a]Determined from the HPLC-UV traces (205-400 nm).

3. Cyclization to diketomorpholines: 4{*R¹,R²*}, 5{*R¹,R²*}

To the crude intermediates **3**{*R¹,R²*} (cleaved from 500 mg resin), a solution of DIEA (435 *μ*L, 2.5 mmol) in DMSO was added. The reaction mixture was stirred either for 20 min at room temperature (derivatives **4**{*R¹,1*}), for 20 h at room temperature (derivatives **5**{*R¹,1*} and **5**{*R¹,3*}) or for 1 h at 80 °C (derivatives **5**{*R¹,2*}). The reaction mixture was freeze-dried and residual material was purified by semi-preparative HPLC chromatography.

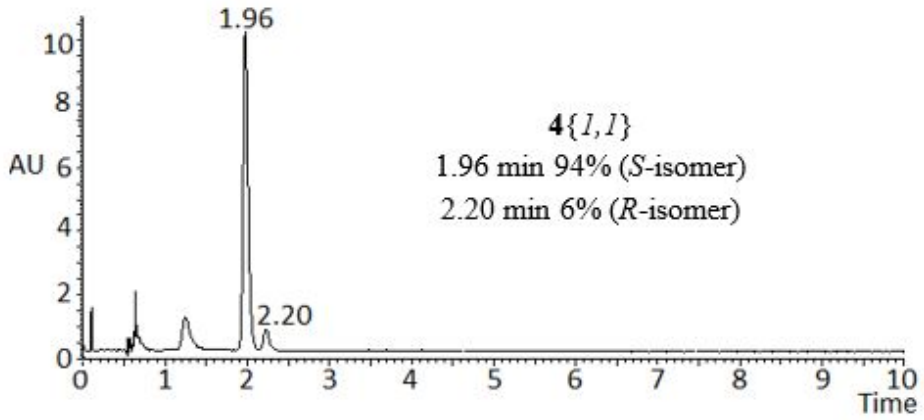
4. TES reduction: 6{*R¹,R²*} and 7{*R¹,R²*}

To the crude intermediates **4**{*R¹,R²*} and **5**{*R¹,R²*} a solution of TFA/TES/DCM (2:1:2, 3.75 mL) was added and the reaction mixture was stirred for 8 h at room temperature. Solvents were

evaporated using a stream of nitrogen and the residual material was purified by semipreparative HPLC chromatography.

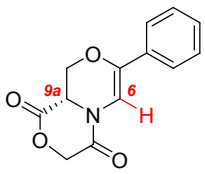
Analytical Data of Final Compounds

SFC chromatogram of crude intermediate 4{*1,1*}

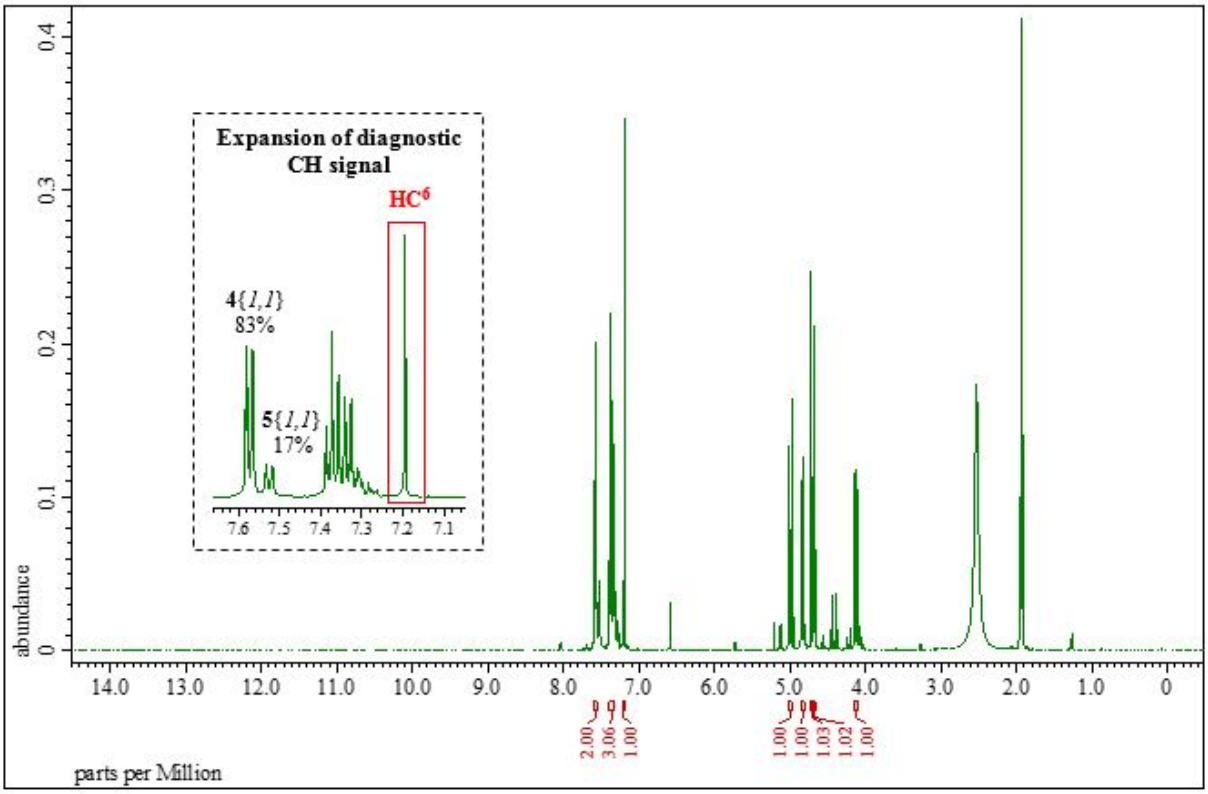


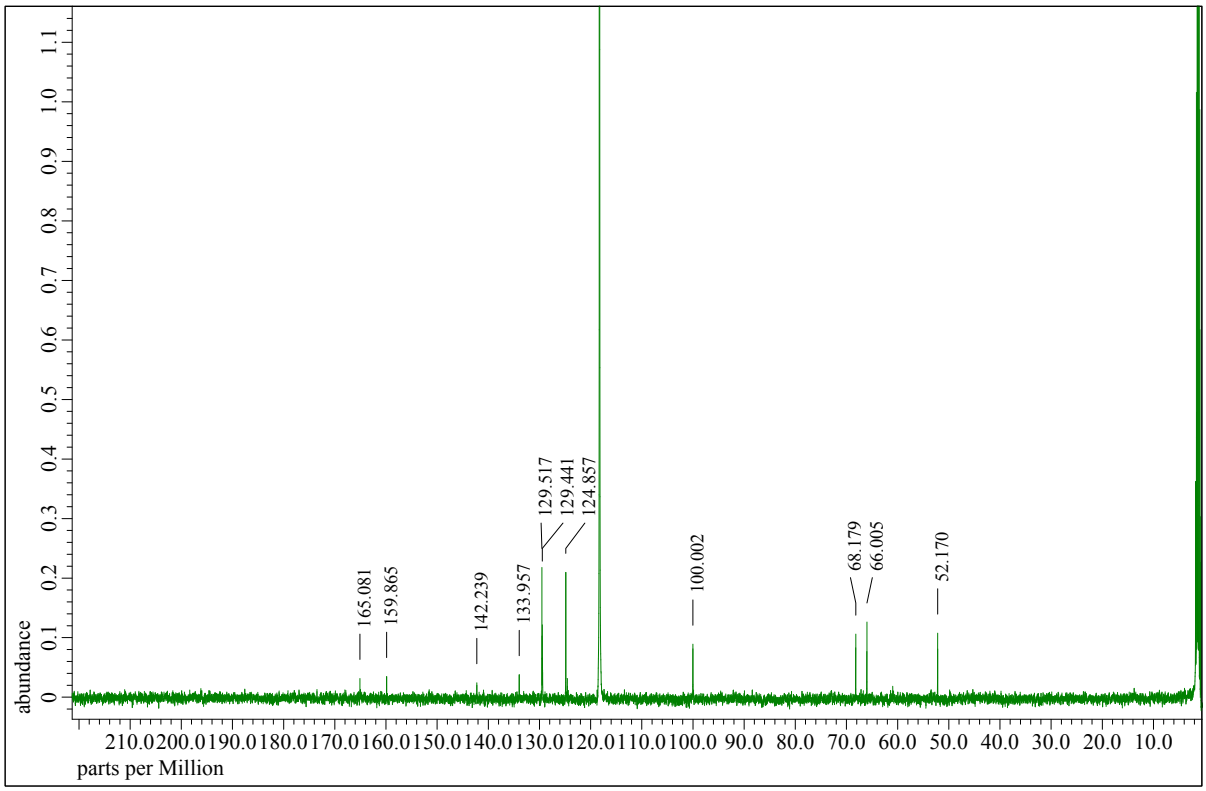
General method for calculation of yields using ^{1}H NMR: ^{1}H NMR spectra of external standard at three different concentration were measured. In each spectrum, solvent signal was integrated followed by the integration of selected H^{Ar} signal of external standard. Ratios of solvent/standard signal areas along with known quantity of standard were used to construct a calibration curve. Then, ^{1}H NMR spectra of studied sample was measured and the ratio of solvent/sample (selected H^{Ar} signal) areas was determined. Using the calibration curve, the quantity of compound in a sample was calculated.

(*9aS*)-7-phenyl-9,*9a*-dihydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine-1,4-(3*H*)-dione 4{*1,1*}

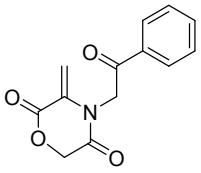


Creme amorphous solid, 11.6 mg (45%, 0.047 mmol). Cleaved from 347 mg of resin **2**{*1,1*} (0.37 mmol/g, 0.128 mmol of substrate). HPLC purity 98%. ^{1}H NMR (500 MHz, MeCN-d_3): dissolving the sample led to partial conversion to **5**{*1,1*} (17%, see the zoomed proton spectrum below), the following NMR data were extracted for **4**{*1,1*}: δ = 7.56-7.58 (m, 2H), 7.40-7.32 (m, 3H), 7.19 (s, 1H), 5.00 (d, *J* = 15.9 Hz, 1H), 4.84 (dd, *J* = 11.1, 4.0 Hz, 1H), 4.70 (d, *J* = 15.9 Hz, 1H), 4.68 (dd, *J* = 9.6, 4.0 Hz, 1H), 4.12 (dd, *J* = 11.1, 9.6 Hz, 1H). ^{13}C NMR (126 MHz, MeCN-d_3): δ = 165.08, 159.87, 142.24, 133.96, 129.52, 129.44, 124.86, 100.00, 68.18, 66.00, 52.17. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{13}H_{12}NO_4$ $[M+H]^+$ 246.0761, found 246.0760.

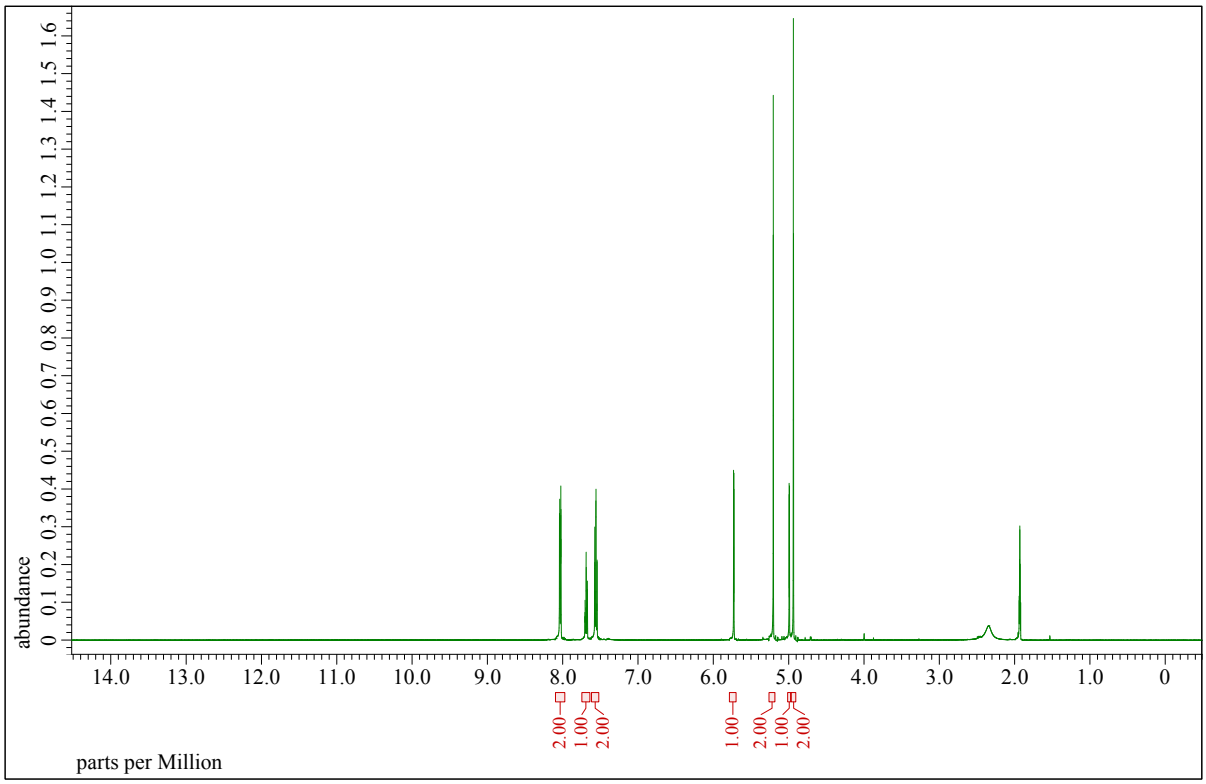




3-methylene-4-(2-oxo-2-phenylethyl)morpholine-2,5-dione 5{*1,1*}



Creme amorphous solid, 18.3 mg (46%, 0.075 mmol). Cleaved from 415 mg of resin **2**{*1,1*} (0.39 mmol/g, 0.162 mmol of substrate). HPLC purity 99%. ^{1}H NMR (500 MHz, MeCN-d_3): δ = 8.02-8.05 (m, 2H), 7.67-7.71 (m, 1H), 7.54-7.58 (m, 2H), 5.73 (d, J = 2.4 Hz, 1H), 5.20 (s, 2H), 4.99 (d, J = 2.4 Hz, 1H), 4.94 (s, 2H). ^{13}C NMR (126 MHz, MeCN-d_3): δ = 192.57, 163.27, 160.13, 135.60, 135.11, 134.32, 129.90, 129.08, 107.38, 67.88, 50.75. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{13}H_{12}NO_4$ $[M+H]^+$ 246.0761, found 246.0761.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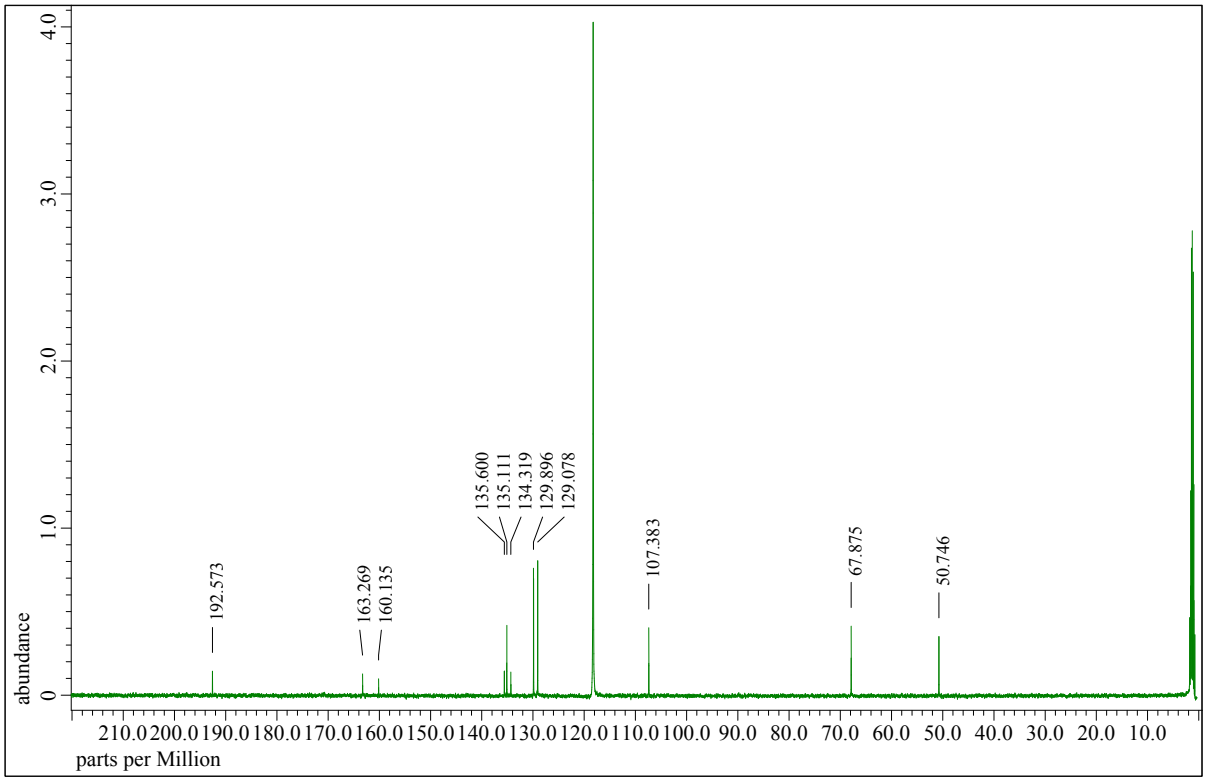
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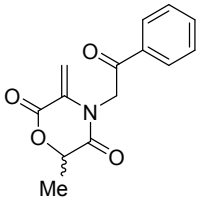
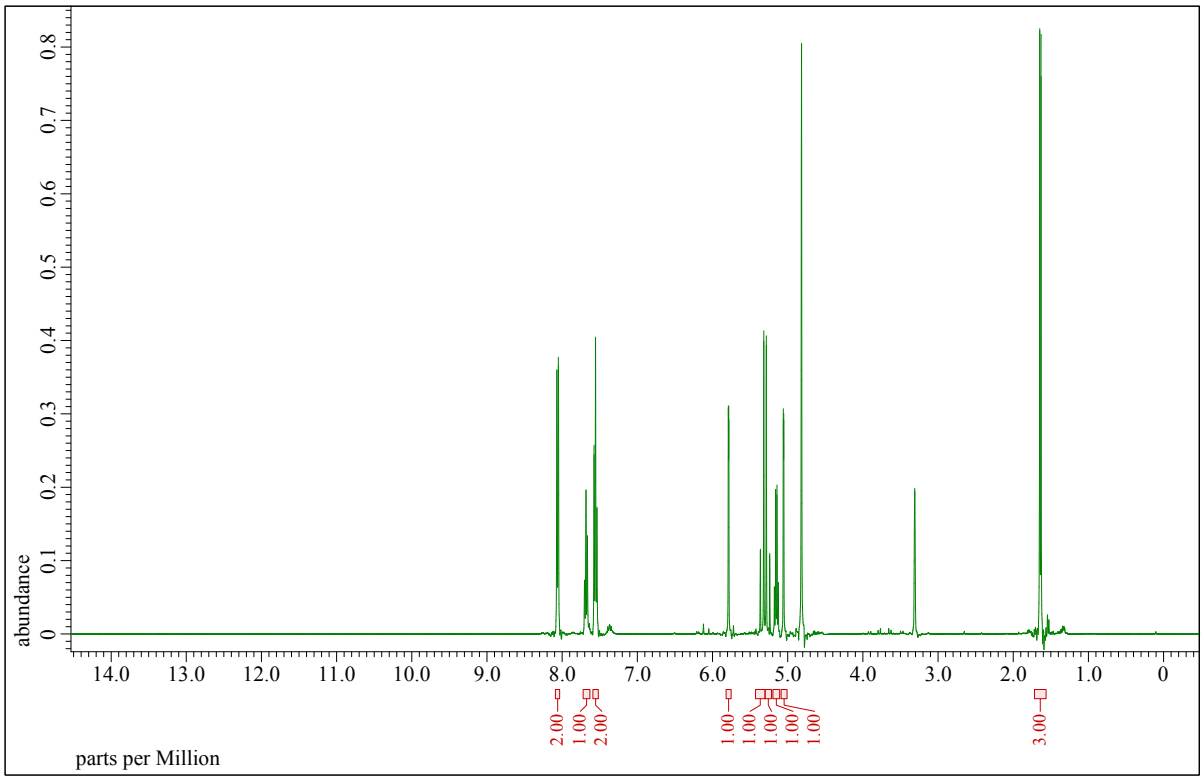
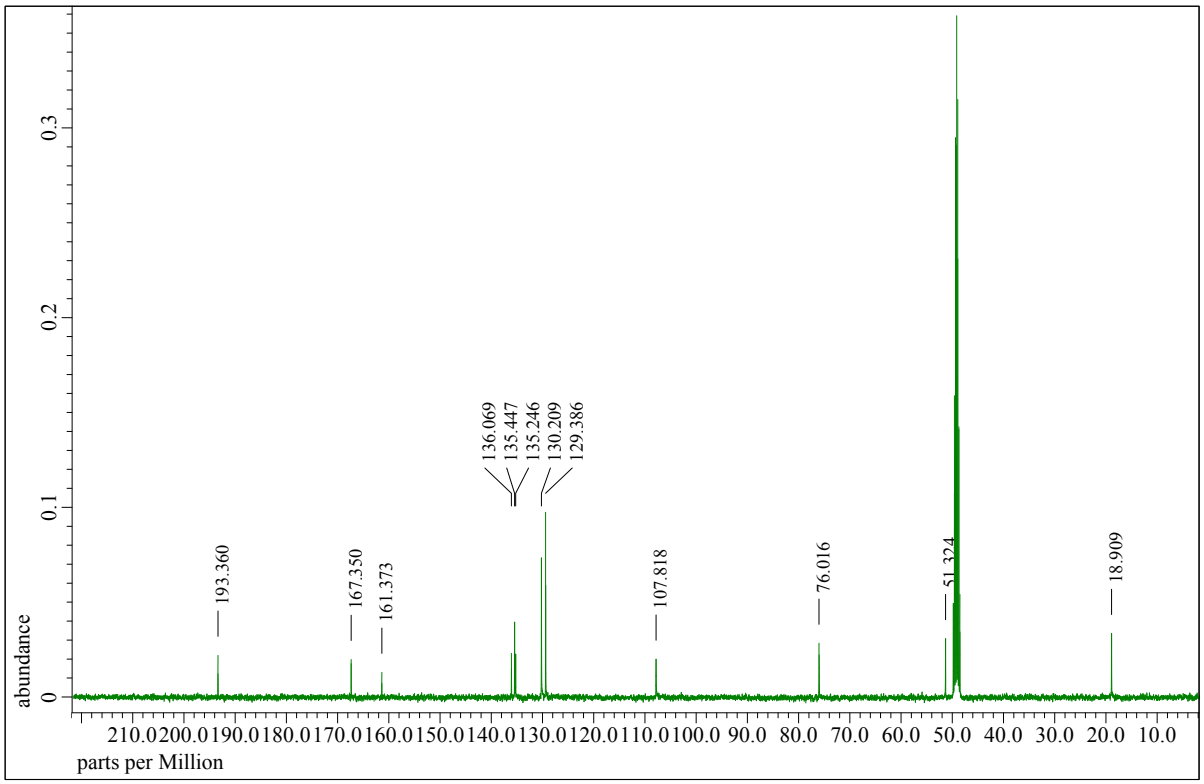
6-methyl-3-methylene-4-(2-oxo-2-phenylethyl)morpholine-2,5-dione 5{*1,2*}

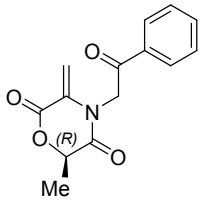


SFC: Mixture of enantiomers in ratio 90:10 (*R:S*). Creme amorphous solid, 21.5 mg (48%, 0.083 mmol). Cleaved from 473 mg of resin **2**{*1,2*} (0.37 mmol/g, 0.175 mmol of substrate). HPLC purity 99%. ^{1}H NMR (400 MHz, MeOH-d_4): δ = 8.05-8.07 (m, 2H), 7.66-7.68 (m, 1H), 7.54-7.58 (m, 2H), 5.79 (d, *J* = 2.3 Hz, 1H), 5.34 (d, *J* = 18.0 Hz, 1H), 5.26 (d, *J* = 18.0 Hz, 1H), 5.15 (q, *J* = 7.0 Hz, 1H), 5.06 (d, *J* = 2.3 Hz, 1H), 1.64 (dd, *J* = 7.0, 0.6 Hz, 3H). ^{13}C NMR (101 MHz, MeOH-d_4): δ = 193.36, 167.35, 161.37, 136.07, 135.45, 135.25, 130.21, 129.39, 107.82, 76.02, 51.32, 18.91. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{14}H_{14}NO_4$ $[M+H]^+$ 260.0917, found 260.0918.

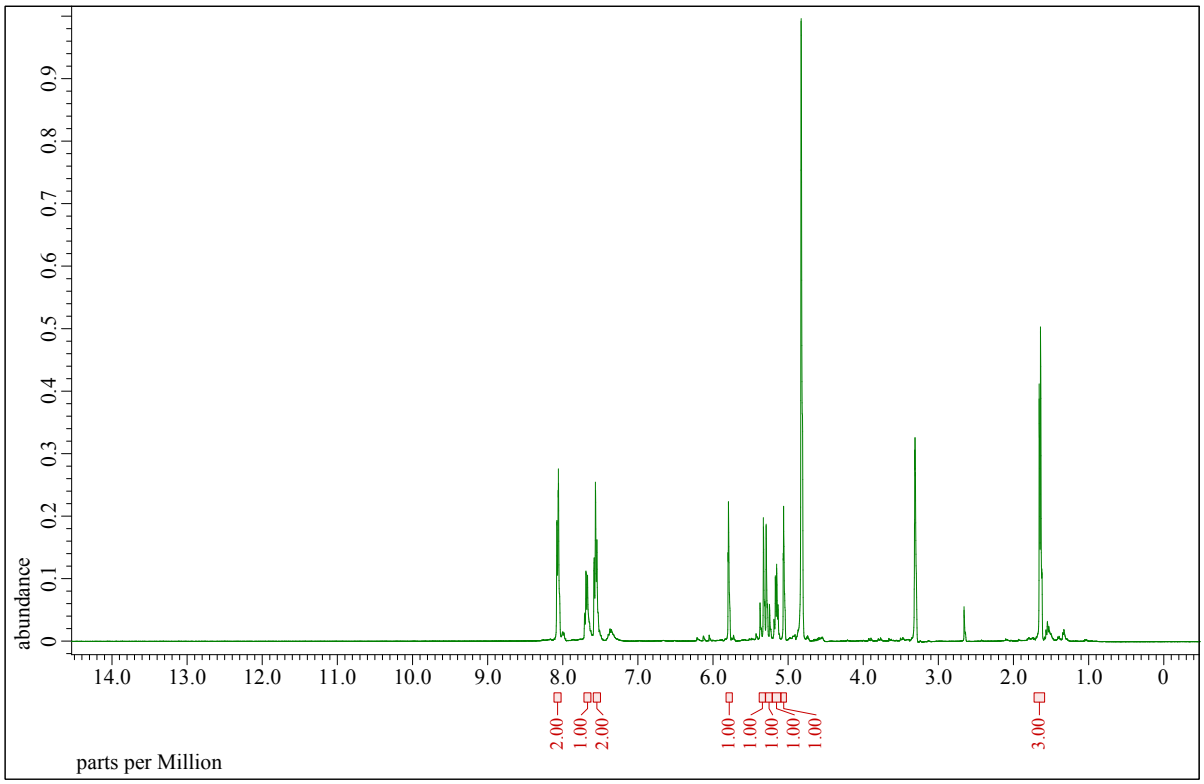




(6*R*)-methyl-3-methylene-4-(2-oxo-2-phenylethyl)morpholine-2,5-dione 5^{R}{*1,2*}



SFC: Mixture of enantiomers in ratio 85:15 (*R:S*). Creme amorphous solid, 11.6 mg (24%, 0.045 mmol). Cleaved from 464 mg of resin $\mathbf{2}^{S}${*1,2*} (0.40 mmol/g, 0.186 mmol of substrate) prepared from (*S*)-(-)-2-bromopropionic. HPLC purity 99%. ^{1}H NMR (400 MHz, MeOH-d_4): δ = 8.06-8.08 (m, 2H), 7.67-7.71 (m, 1H), 7.55-7.58 (m, 2H), 5.79 (d, *J* = 2.3 Hz, 1H), 5.34 (d, *J* = 18.0 Hz, 1H), 5.26 (d, *J* = 18.0 Hz, 1H), 5.16 (q, *J* = 7.0 Hz, 1H), 5.06 (d, *J* = 2.3 Hz, 1H), 1.64 (dd, *J* = 7.0, 0.6 Hz, 3H). ^{13}C NMR (101 MHz, MeOH-d_4): δ= 193.37, 167.38, 161.38, 136.09, 135.45, 135.27, 130.21, 129.39, 107.81, 76.03, 51.33, 18.91. HRMS (ESI-TOF, neg.): *m/z* calcd for $C_{14}H_{12}NO_4$ $[M-H]^-$ 258.0761, found 258.0758.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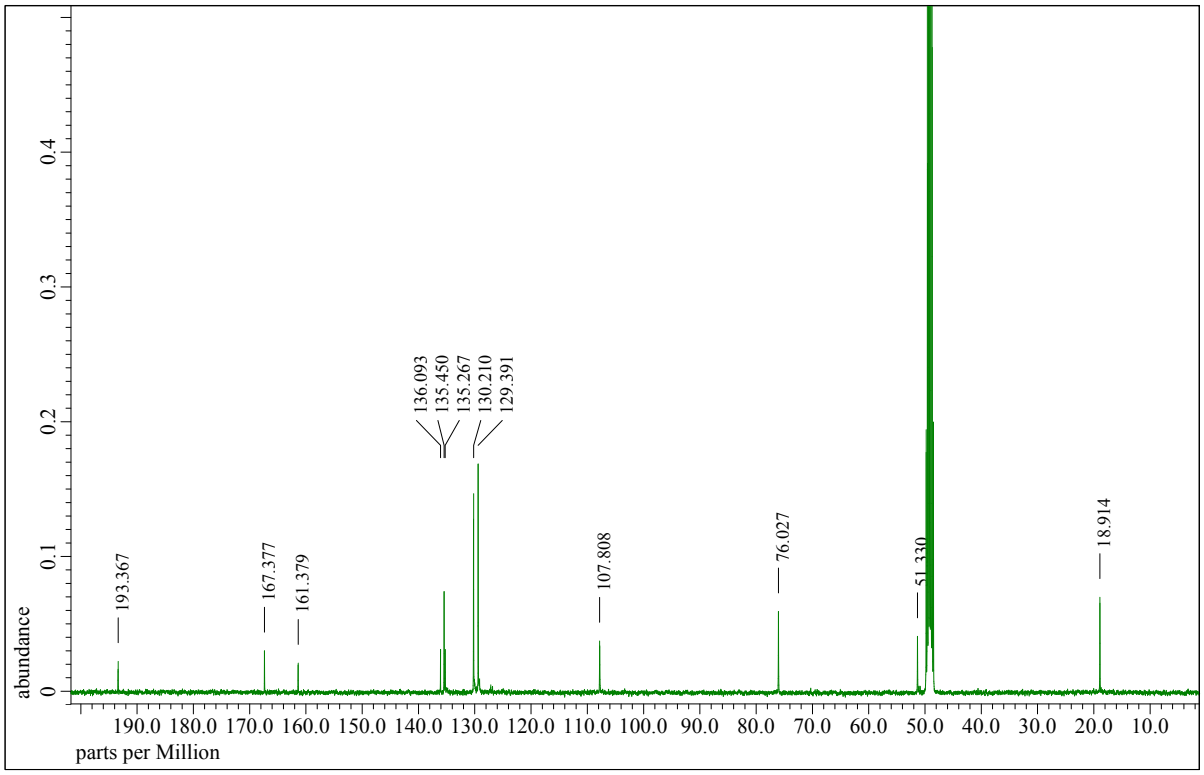
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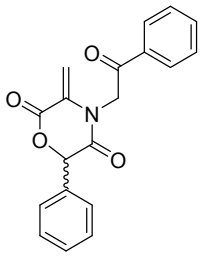
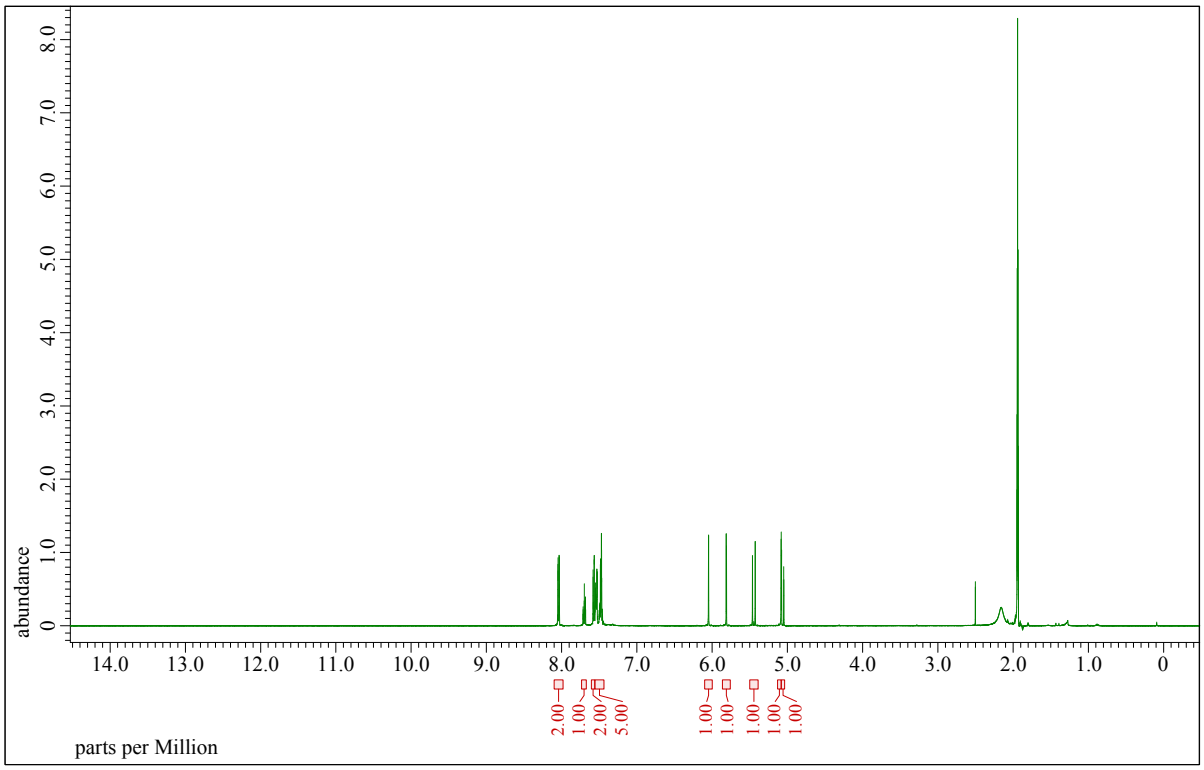
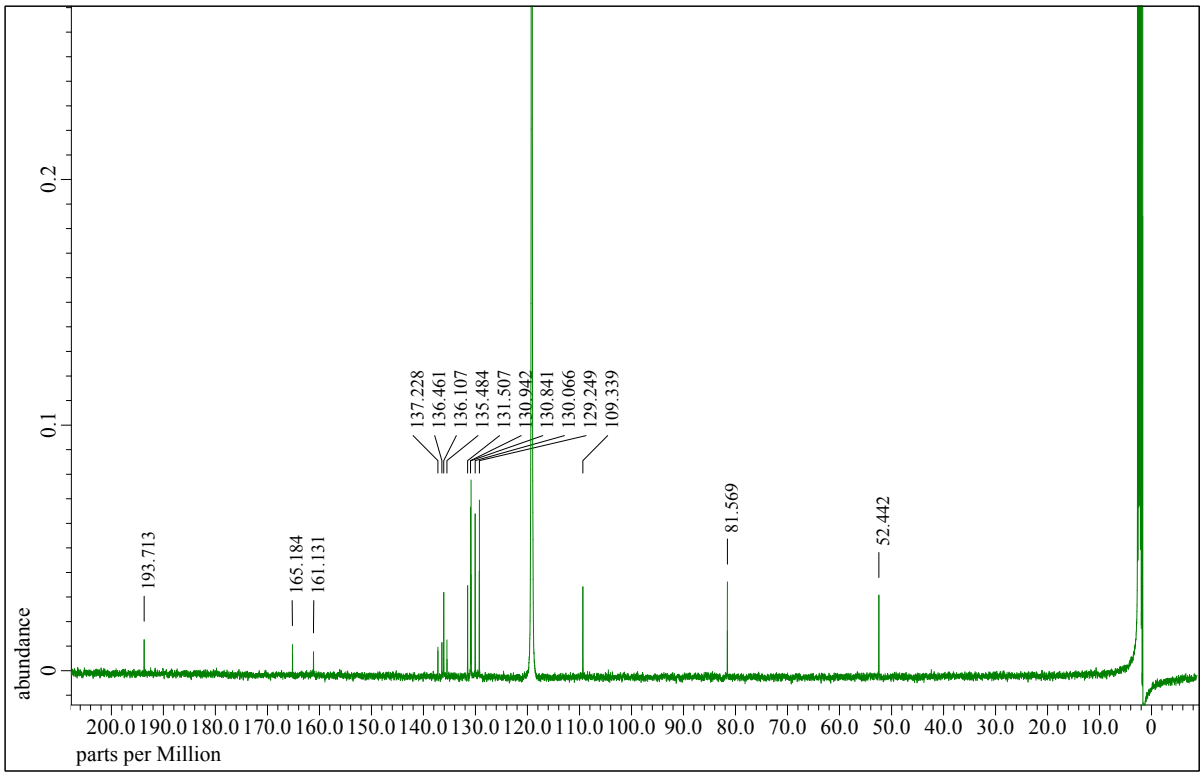
3-methylene-4-(2-oxo-2-phenylethyl)-6-phenylmorpholine-2,5-dione 5{*1,3*}

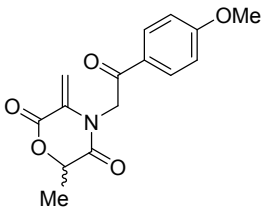


SFC: 100% *R*-isomer. Creme amorphous solid, 7.6 mg (27%, 0.024 mmol). Cleaved from 222 mg of resin **2**{*1,2*} (0.39 mmol/g, 0.087 mmol of substrate). HPLC purity 98%. ^{1}H NMR (500 MHz, MeCN-d_3): δ = 8.03-8.05 (m, 2H), 7.68-7.72 (m, 1H), 7.57-7.58 (m, 2H), 7.47-7.55 (m, 5H), 6.05 (s, 1H), 5.81 (d, J = 2.3 Hz, 1H), 5.45 (d, J = 18.0 Hz, 1H), 5.08 (d, J = 2.3 Hz, 1H), 5.06 (d, J = 18.0 Hz, 1H). ^{13}C NMR (126 MHz, MeCN-d_3): δ= 192.79, 164.26, 160.21, 136.31, 135.54, 135.19, 134.56, 130.59, 130.02, 129.92, 129.15, 128.33, 108.42, 80.65, 51.52. HRMS (ESI-TOF, neg.): *m/z* calcd for $C_{19}H_{14}NO_4$ $[M-H]^-$ 320.0917, found 320.0912.

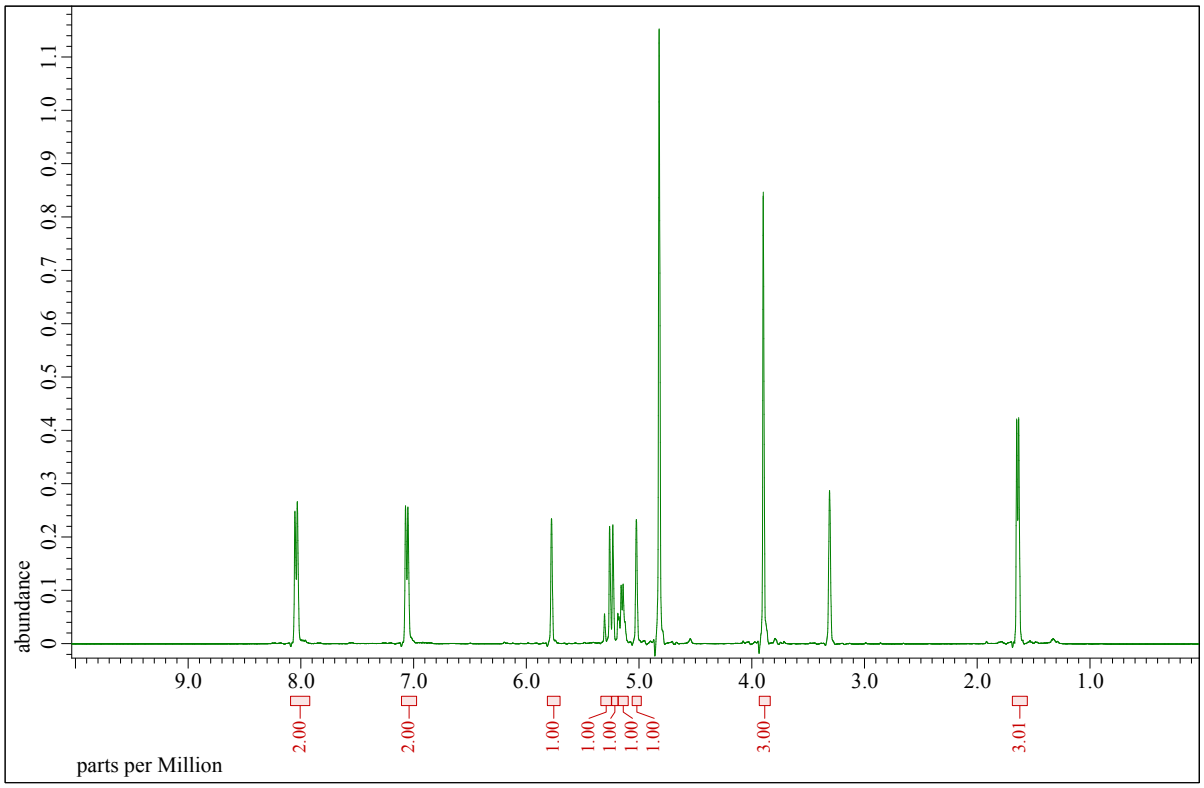




4-(2-(4-methoxyphenyl)-2-oxoethyl)-6-methyl-3-methylenemorpholine-2,5-dione 5{*2,2*}



SFC: Mixture of enantiomers in ratio 91:9 (*R:S*). Yellow-brown amorphous solid, 15.4 mg (35%, 0.053 mmol). Cleaved from 411 mg of resin **2**{*2,2*} (0.37 mmol/g, 0.152 mmol of substrate). HPLC purity 99%. ^{1}H NMR (400 MHz, MeOH-d_4): δ = 8.04 (br. d, J = 8.4 Hz, 2H), 7.06 (br. d, J = 8.4 Hz, 2H), 5.78 (s, 1H), 5.28 (d, J = 18.0 Hz, 1H), 5.21 (d, J = 18.0 Hz, 1H), 5.15 (q, J = 7.0 Hz, 1H), 5.02 (s, 1H), 3.90 (s, 3H), 1.64 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, MeOH-d_4): δ = 191.80, 167.38, 166.18, 161.39, 135.31, 131.82, 128.90, 115.39, 107.74, 76.03, 56.31, 50.94, 18.92. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{15}H_{16}NO_5$ $[M+H]^+$ 290.1023, found 290.1020.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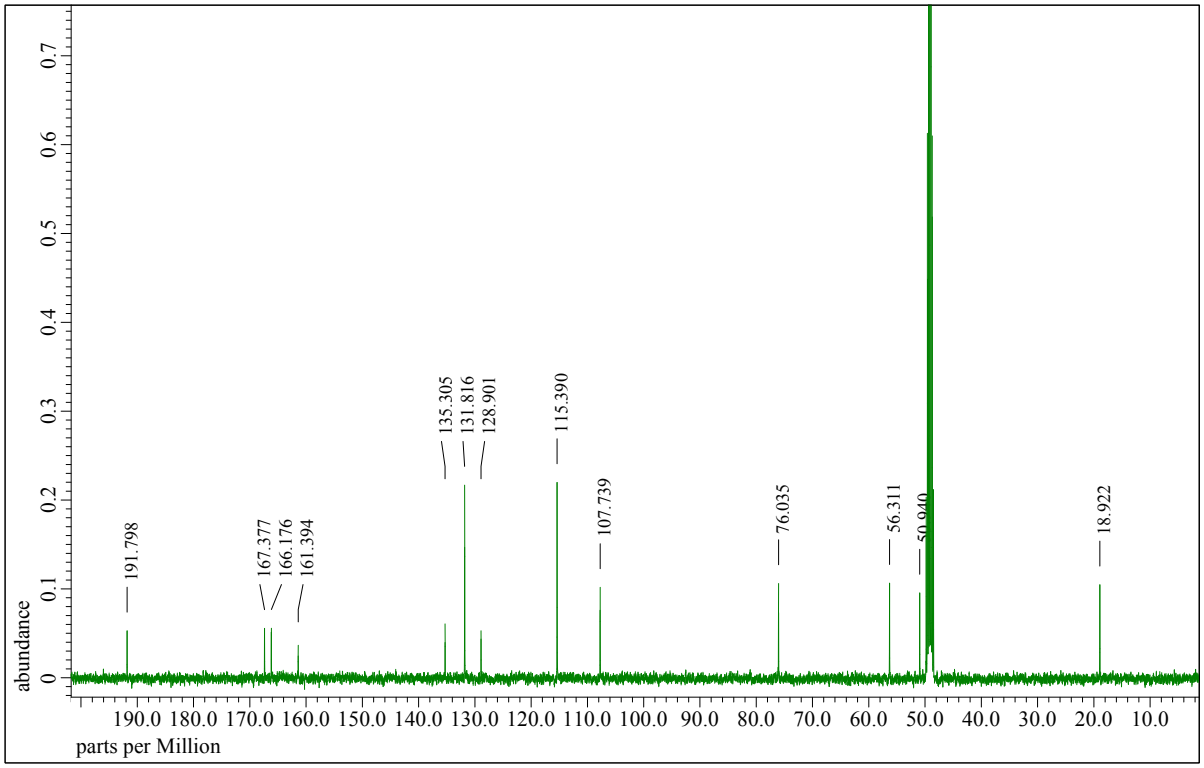
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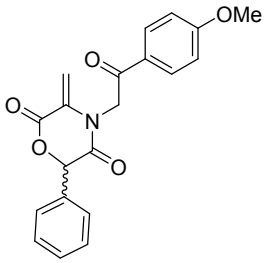
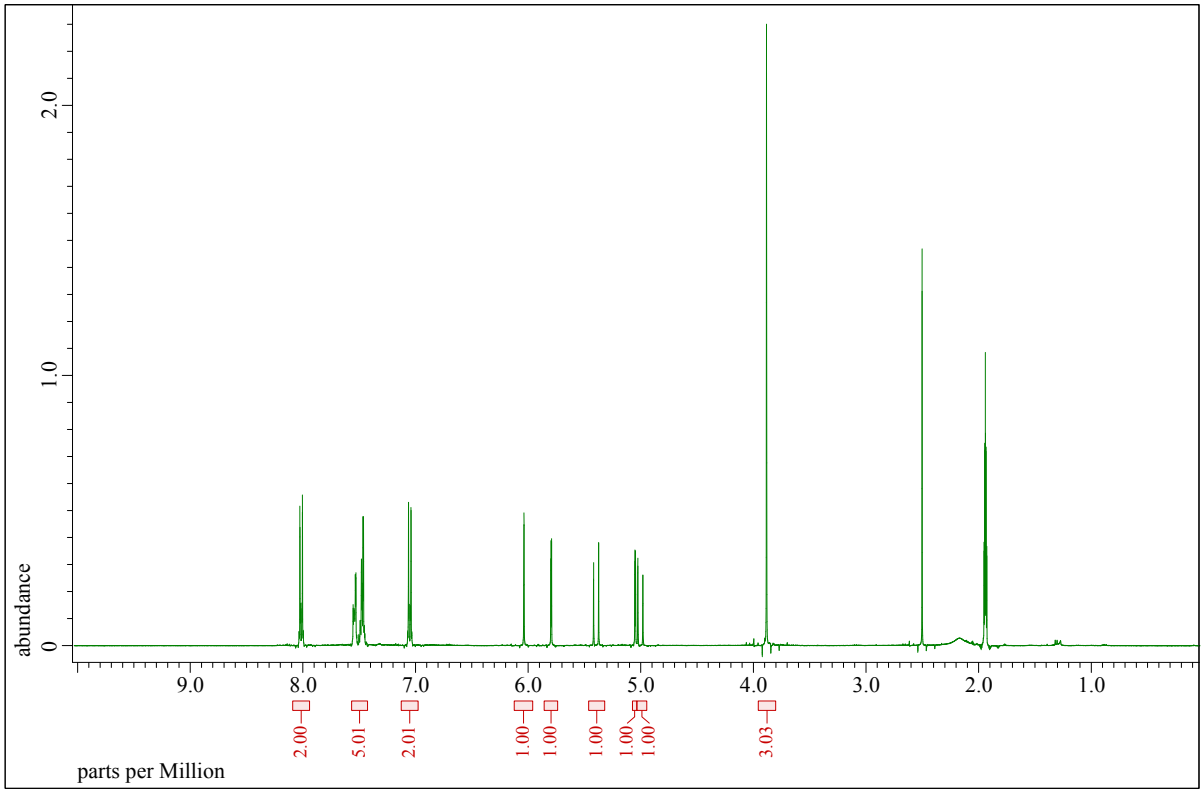
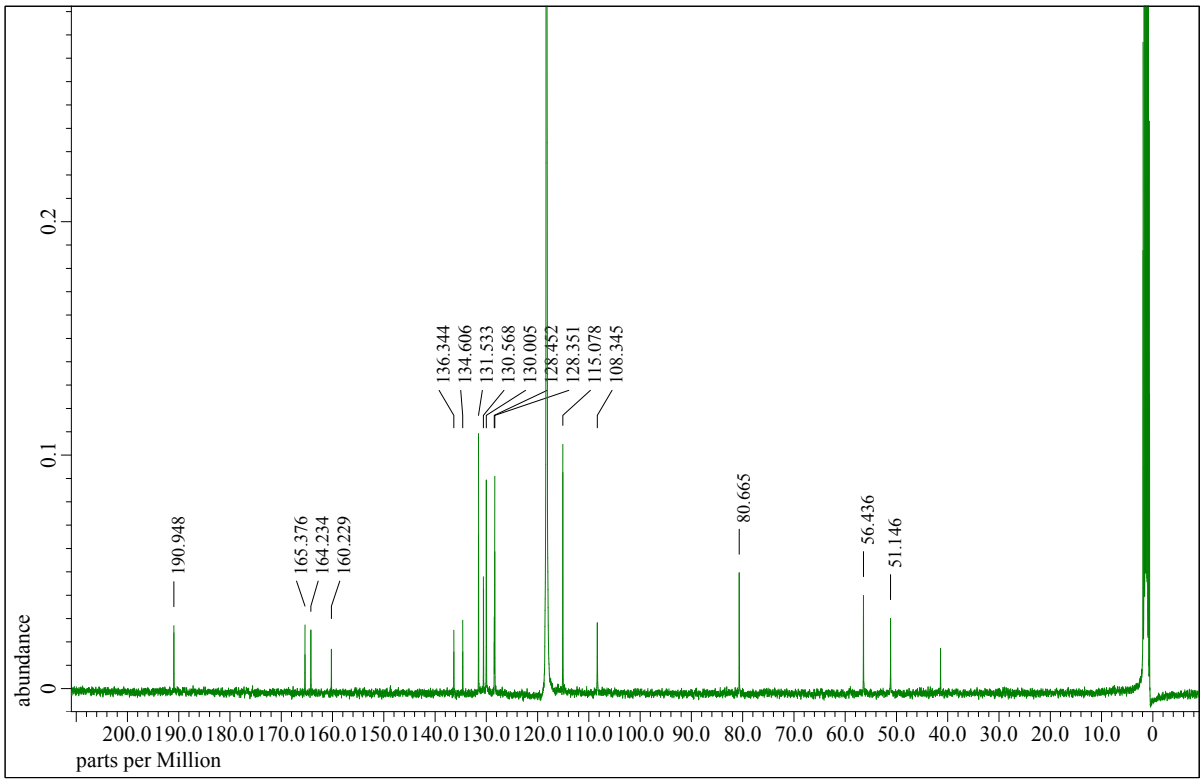
4-(2-(4-methoxyphenyl)-2-oxoethyl)-3-methylene-6-phenylmorpholine-2,5-dione 5{*2,3*}

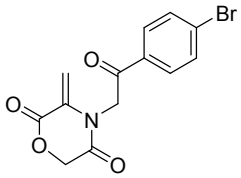


SFC: 100% *R*-isomer. Yellow-brown amorphous solid, 9.1 mg (14%, 0.026 mmol). Cleaved from 511 mg of resin **2**{*2,2*} (0.37 mmol/g, 0.189 mmol of substrate). HPLC purity 99%. ^{1}H NMR (400 MHz, MeCN-d_3): δ = 8.01 (br. d, *J* = 9.0 Hz, 2H), 7.46-7.53 (m, 5H), 7.05 (br. d, *J* = 9.0 Hz, 2H), 6.04 (s, 1H), 5.80 (d, *J* = 2.4 Hz, 1H), 5.40 (d, *J* = 17.9 Hz, 1H), 5.05 (d, *J* = 2.4 Hz, 1H), 5.00 (d, *J* = 17.9 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, MeCN-d_3): δ = 190.95, 165.38, 164.23, 160.23, 136.34, 134.61, 131.53, 130.57, 130.01, 128.45, 128.35, 115.08, 108.34, 80.66, 56.44, 51.15. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{20}H_{18}NO_5$ $[M+H]^+$ 352.1179, found 352.1180.

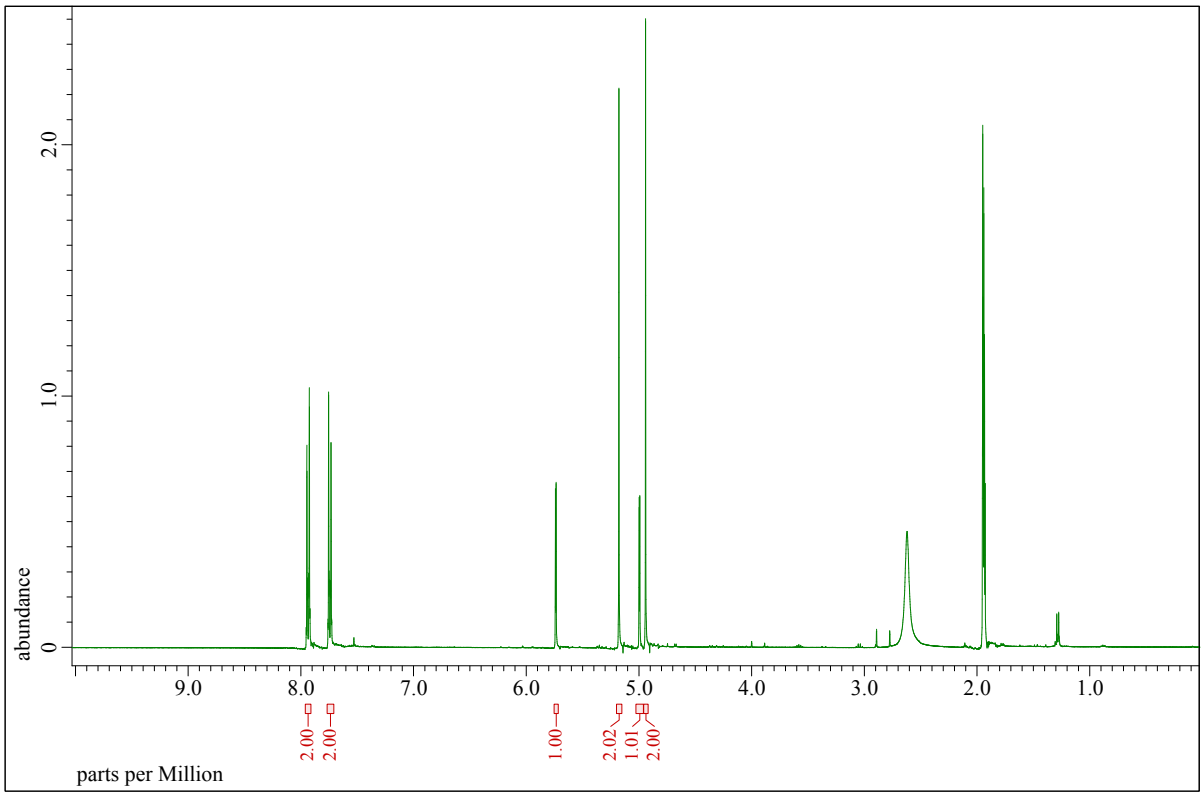


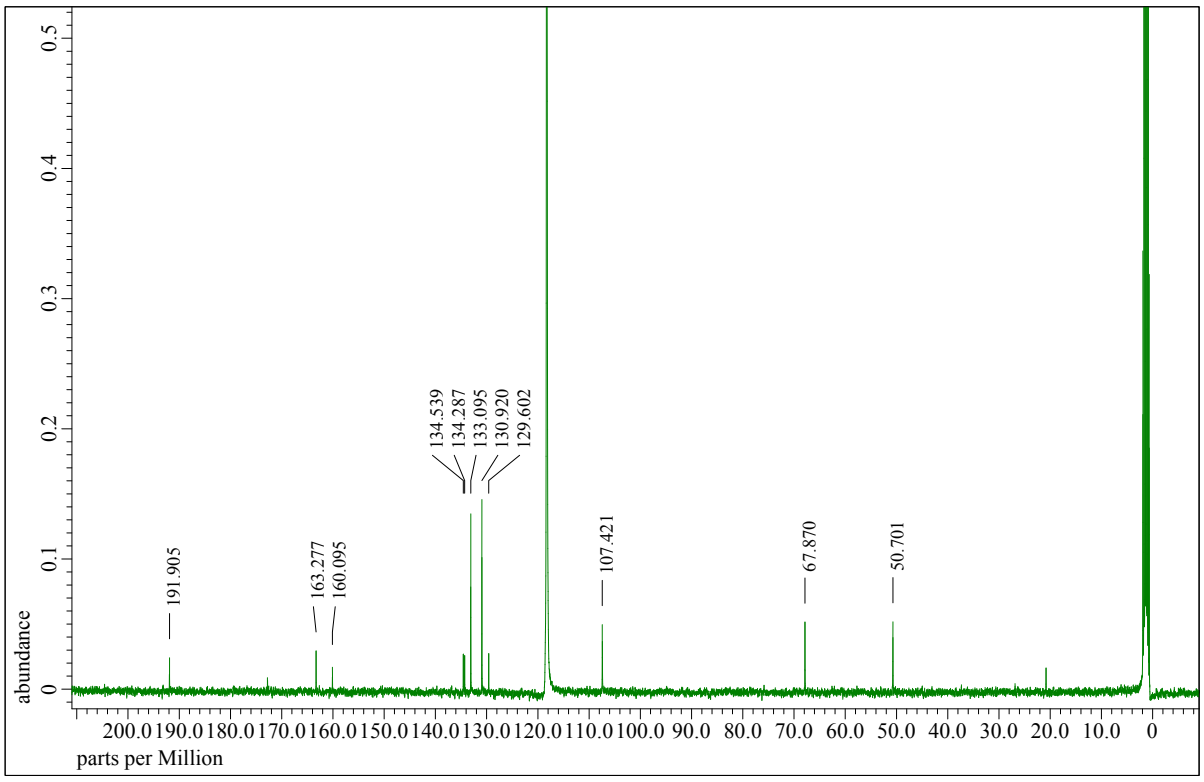


4-(2-(4-bromophenyl)-2-oxoethyl)-3-methylenemorpholine-2,5-dione 5{*3,1*}



Creme amorphous solid, 16.6 mg (30%, 0.052 mmol). Cleaved from 466 mg of resin **2**{*2,1*} (0.37 mmol/g, 0.172 mmol of substrate). HPLC purity 98%. ^{1}H NMR (400 MHz, MeCN-d_3): δ = 7.94 (br. d, *J* = 8.6 Hz, 2H), 7.74 (br. d, *J* = 8.6 Hz, 2H), 5.74 (d, *J* = 2.4 Hz, 1H), 5.18 (s, 2H), 5.00 (d, *J* = 2.4 Hz, 1H), 4.94 (s, 2H). ^{13}C NMR (101 MHz, MeCN-d_3): δ = 191.91, 163.28, 160.09, 134.54, 134.29, 133.09, 130.92, 129.60, 107.42, 67.87, 50.70. HRMS (ESI-TOF, neg.): *m/z* calcd for $C_{13}H_9BrNO_4$ $[M-H]^-$ 321.9709, found 321.9711.


abundance
parts per Million
2.00
2.00
1.00
2.02
1.01
2.00


abundance
parts per Million
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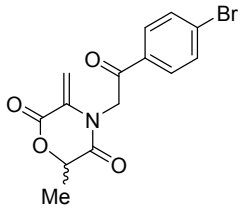
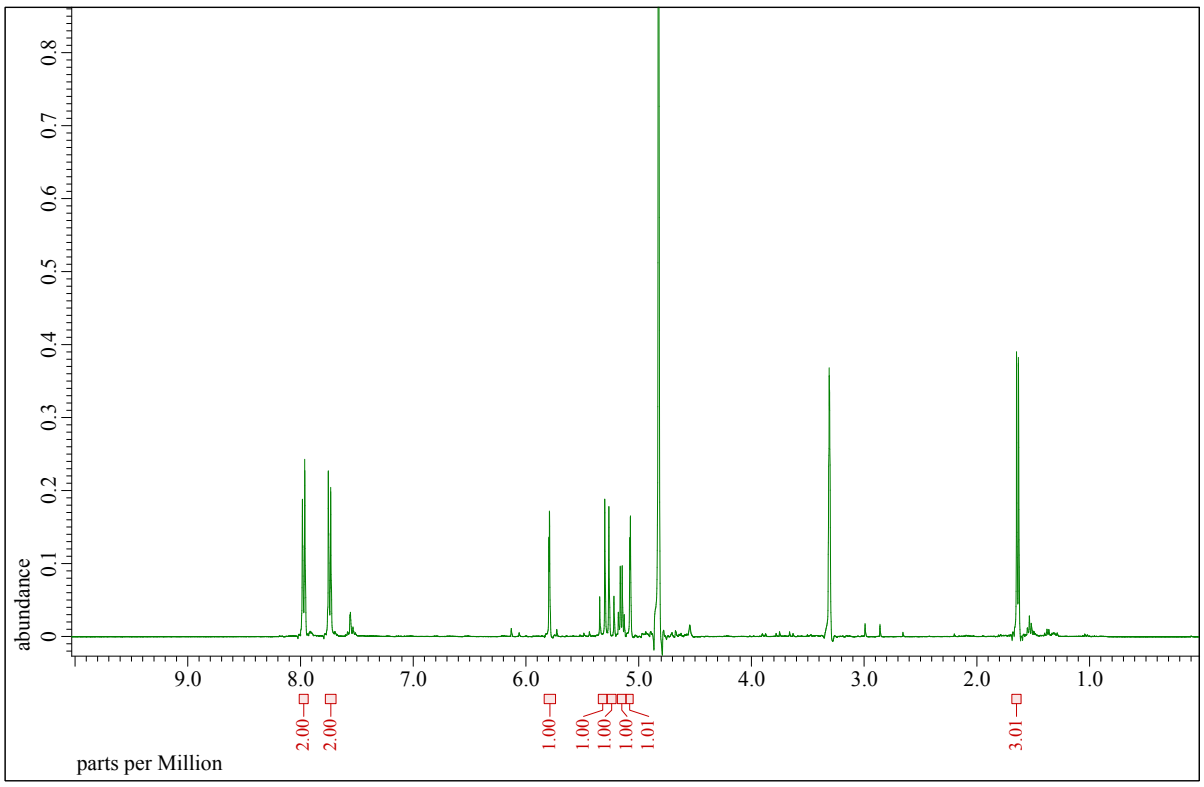
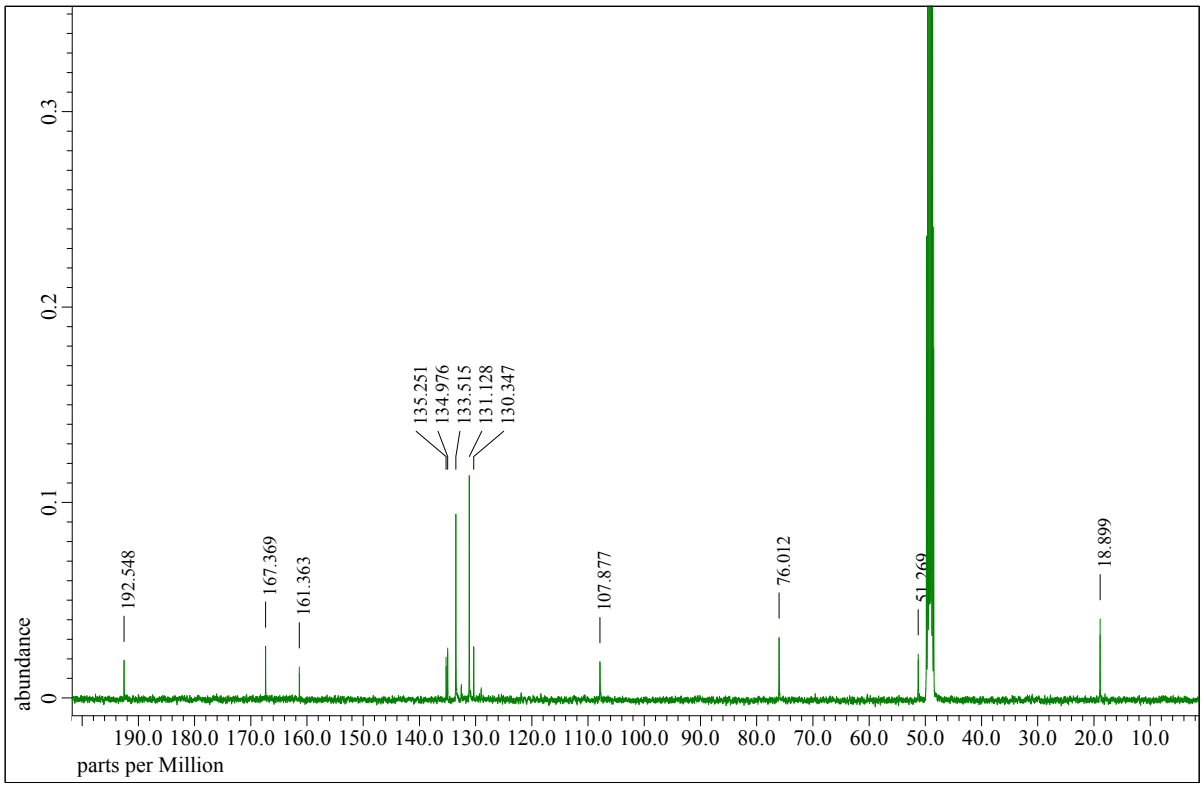
163.277
160.095
134.539
134.287
133.095
130.920
129.602
107.421
67.870
50.701

4-(2-(4-bromophenyl)-2-oxoethyl)-6-methyl-3-methylenemorpholine-2,5-dione 5{*3,2*}

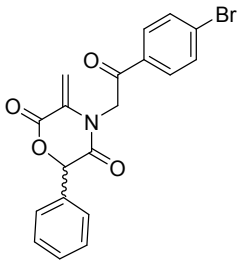


SFC: Mixture of enantiomers in ratio 87:13 (*R*:*S*). Creme amorphous solid, 9.1 mg (22%, 0.027 mmol). Cleaved from 339 mg of resin **2**{*3,2*} (0.37 mmol/g, 0.125 mmol of substrate). HPLC purity 96%. ^{1}H NMR (400 MHz, MeOH-d_4): δ = 7.97 (br. d, *J* = 8.3 Hz, 2H), 7.74 (br. d, *J* = 8.3 Hz, 2H), 5.79 (d, *J* = 2.3 Hz, 1H), 5.32 (d, *J* = 18.1 Hz, 1H), 5.24 (d, *J* = 18.1 Hz, 1H), 5.15 (q, *J* = 6.9 Hz, 1H), 5.08 (d, *J* = 2.3 Hz, 1H), 1.64 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, MeOH-d_4): δ = 192.55, 167.37, 161.36, 135.25, 134.98, 133.51, 131.13, 130.35, 107.88, 76.01, 51.27, 18.90. HRMS (ESI-TOF, neg.): *m/z* calcd for $C_{14}H_{11}BrNO_4$ $[M-H]^-$ 335.9866, found 335.9870.

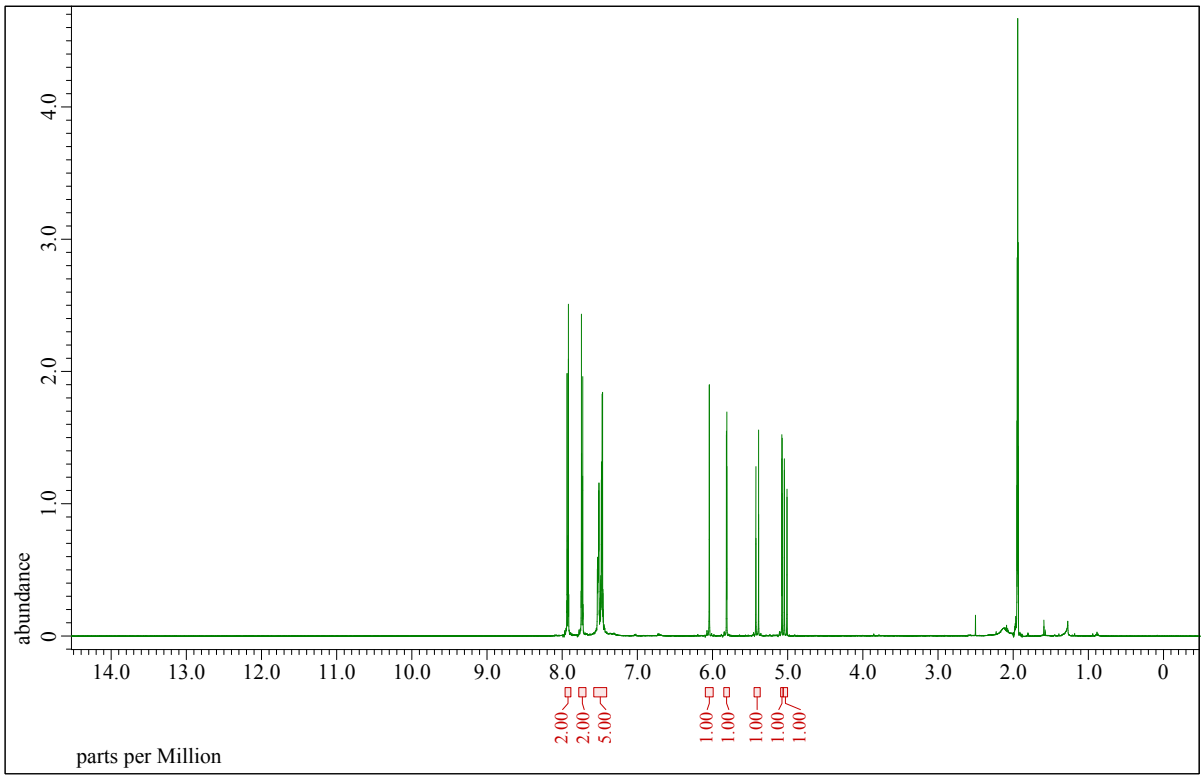




4-(2-(4-bromophenyl)-2-oxoethyl)-3-methylene-6-phenyl-morpholine-2,5-dione 5{*3,3*}



SFC: Mixture of enantiomers in ratio 50:50 (*R:S*). Creme amorphous solid, 9.8 mg (18%, 0.025 mmol). Cleaved from 359 mg of resin **2**{*3,2*} (0.37 mmol/g, 0.132 mmol of substrate). HPLC purity 99%. ^{1}H NMR (500 MHz, MeCN-d_3): δ = 7.93 (d, *J* = 8.9 Hz, 2H), 7.73 (d, *J* = 8.9 Hz, 2H), 7.46-7.53 (m, 5H), 6.04 (s, 1H), 5.81 (d, *J* = 2.6 Hz, 1H), 5.40 (d, *J* = 18.0 Hz, 1H), 5.07 (d, J = 2.6 Hz, 1H), 5.03 (d, *J* = 18.0 Hz, 1H). ^{13}C NMR (126 MHz, MeCN-d_3): δ = 192.14, 164.25, 160.16, 136.26, 134.50, 134.48, 133.11, 130.96, 130.59, 130.02, 129.68, 128.29, 108.46, 80.62, 51.46. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{19}H_{15}BrNO_4$ $[M+H]^+$ 400.0179, found 400.0179.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parts per Million
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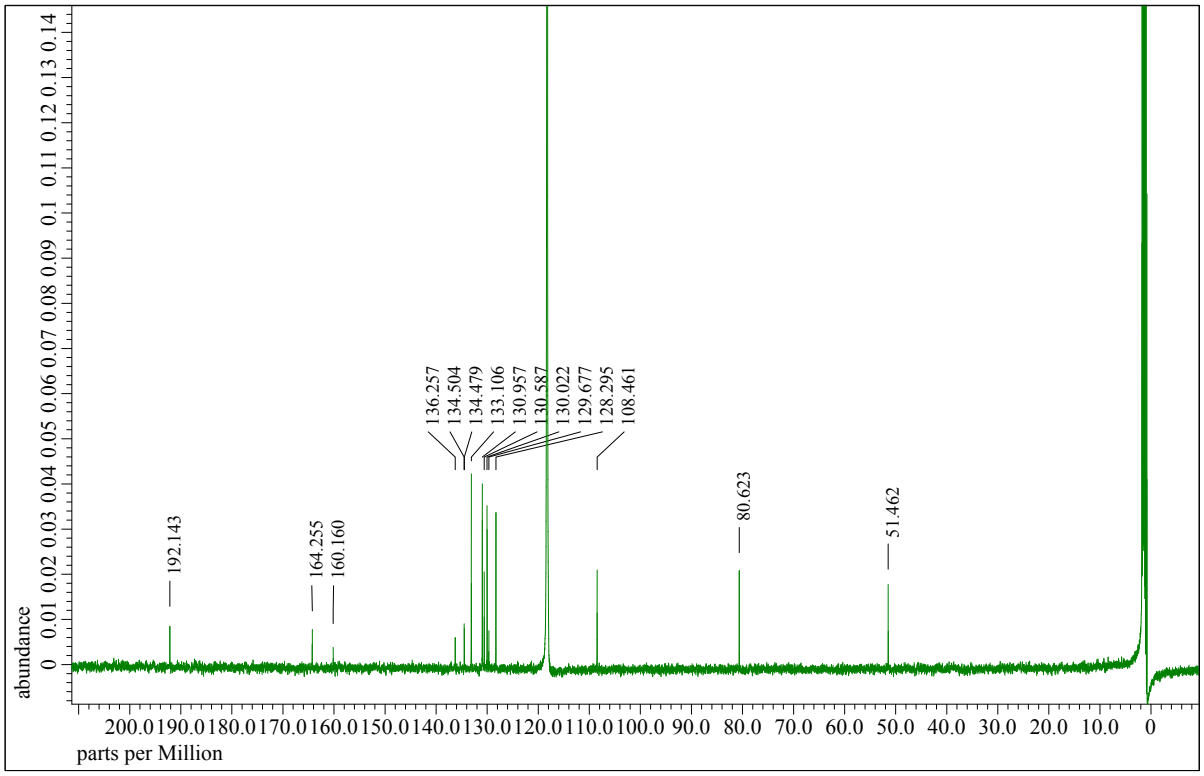
2.00
5.00
1.00
1.00
1.00
1.00
1.00


abundance
parts per Million
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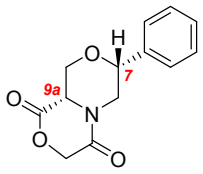
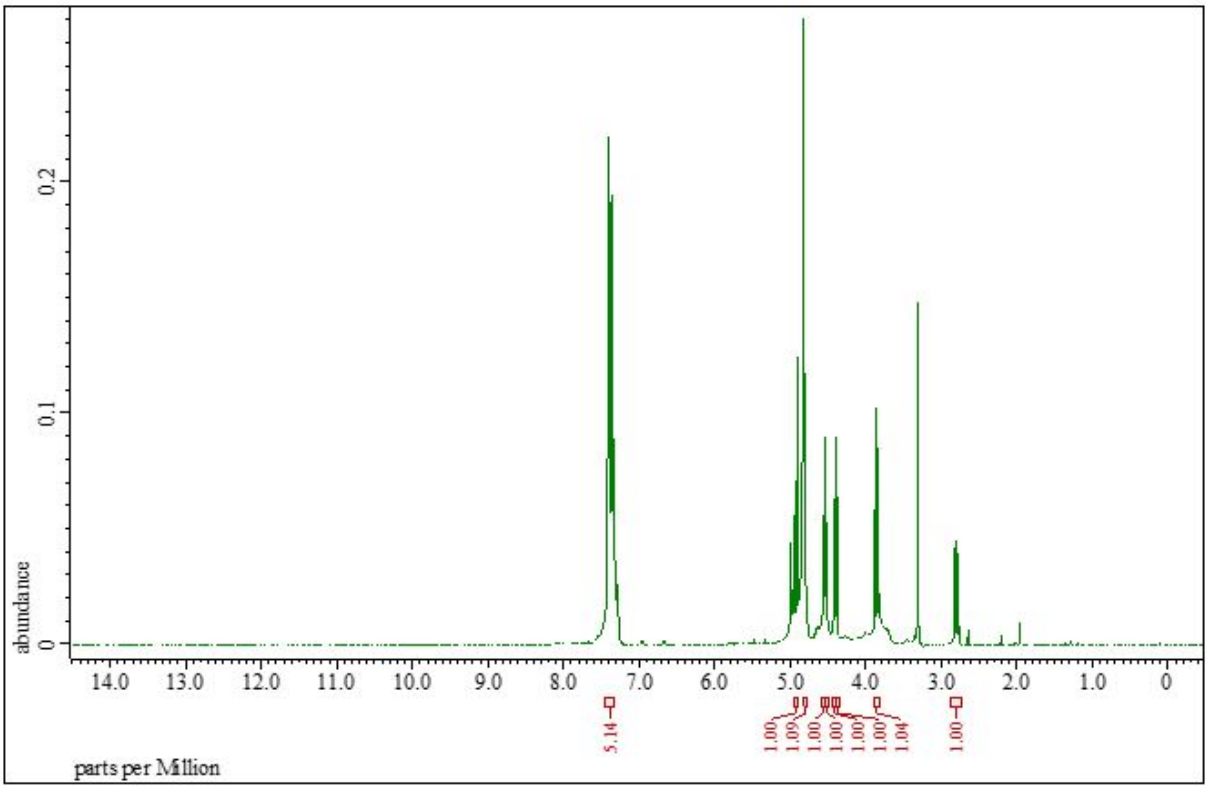
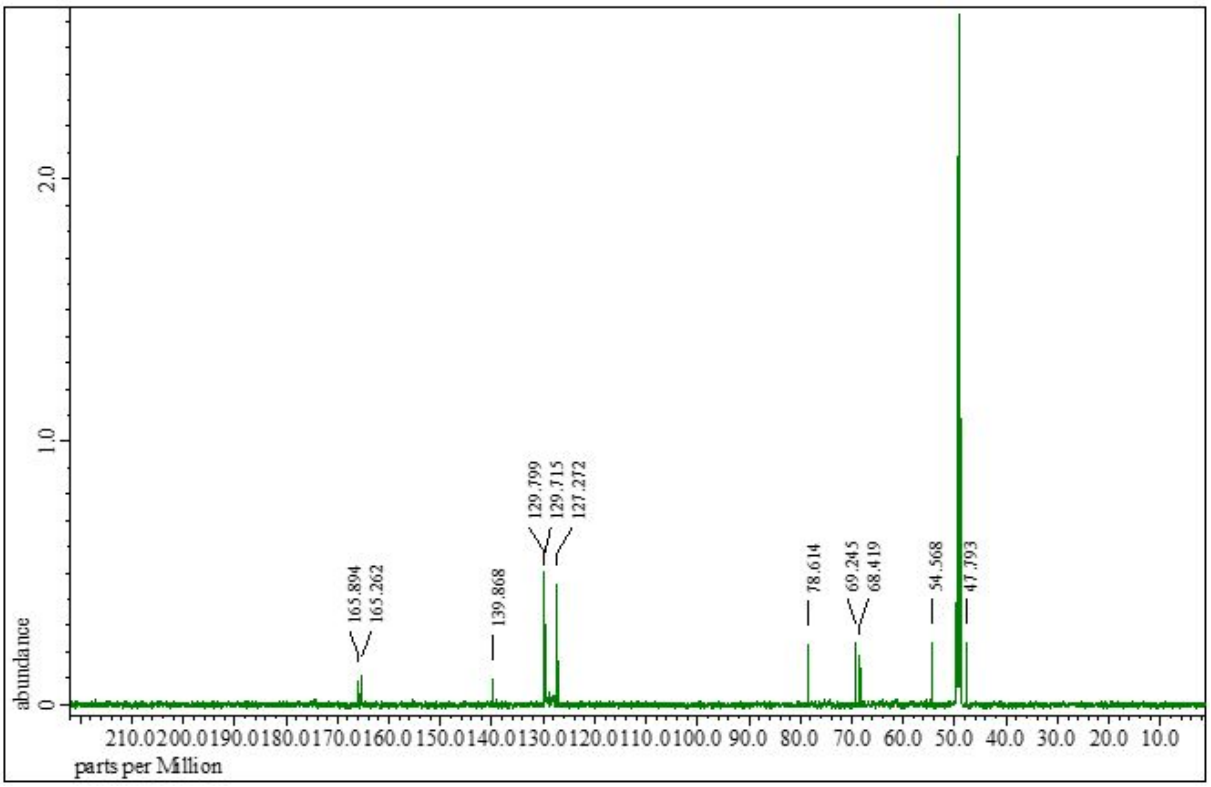
160.160
136.257
134.504
134.479
133.106
130.957
130.587
130.022
129.677
128.295
108.461
80.623
51.462

(*7R,9aS*)-7-phenyltetrahydro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazine-1,4(3*H*)-dione 6{*1,1*}

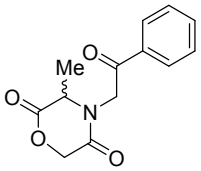


Creme amorphous solid, 24.6 mg (54%, 0.010 mmol). Cleaved from 471 mg of resin **2**{*1,1*} (0.39 mmol/g, 0.184 mmol of substrate), prepared to reduce the crude compound **4**{*1,1*}. HPLC purity 98%. ^{1}H NMR (500 MHz, MeOH-d_4): δ = 7.28-7.41 (m, 5H), 4.92 (d, *J* = 16.3 Hz, 1H), 4.80 (d, *J* = 16.3 Hz, 1H), 4.56 (dd, *J* = 11.5, 2.9 Hz, 1H), 4.53 (dd, *J* = 10.8, 4.4 Hz, 1H), 4.41 (dd, *J* = 11.5, 4.4 Hz, 1H), 4.39 (dd, *J* = 13.5, 2.9 Hz, 1H), 3.85 (dd, *J* = 11.5, 10.8 Hz, 1H, overlap with methyl of MeOH-d_4), 2.80 (dd, *J* = 13.5, 11.5 Hz, 1H). ^{13}C NMR (126 MHz, MeOH-d_4): δ = 165.89, 165.26, 139.87, 129.80, 129.71, 127.27, 78.61, 69.24, 68.42, 54.57, 47.79. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{13}H_{14}NO_4$ $[M+H]^+$ 248.0917, found 248.0918.

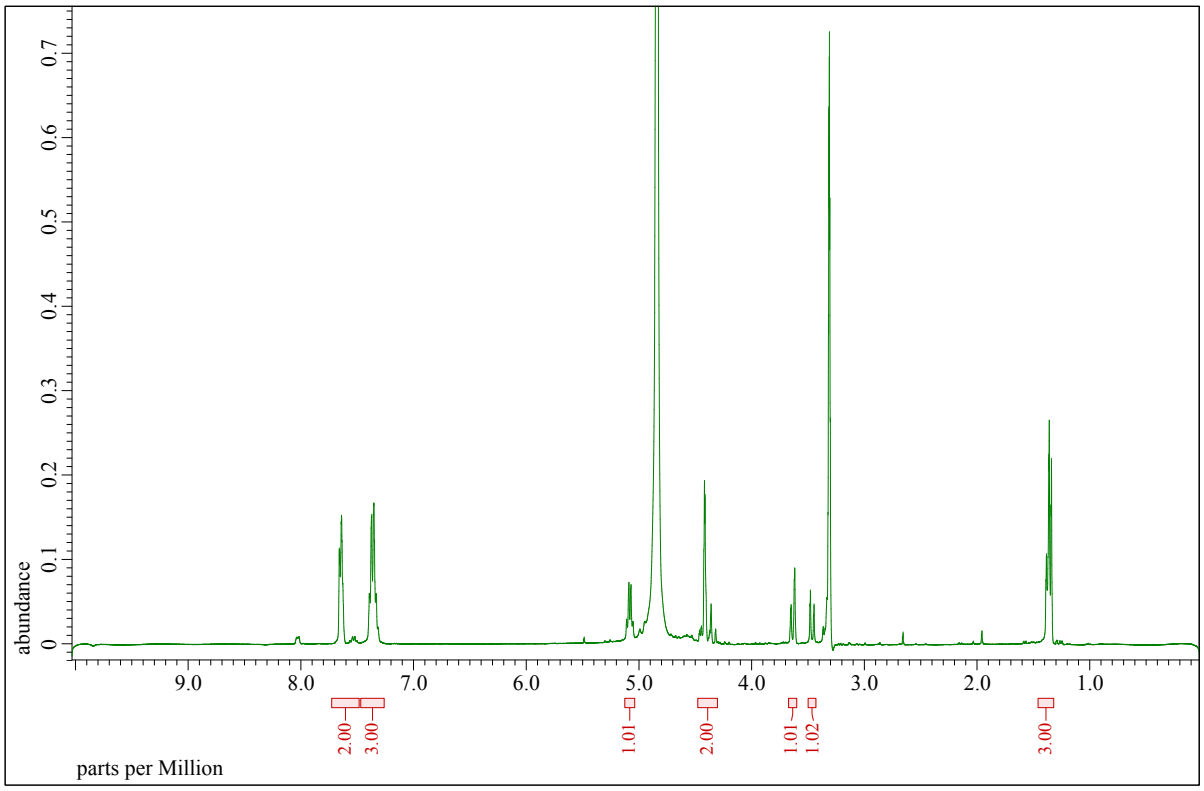




3-methyl-4-(2-oxo-2-phenylethyl)morpholine-2,5-dione 7{*1,1*}



SFC: Mixture of enantiomers in ratio 80:20 (*R:S*). Yellow-brown amorphous solid, 3.1 mg (12%, 0.013 mmol). Cleaved from 279 mg of resin **2**{*1,1*} (0.37 mmol/g, 0.103 mmol of substrate), prepared to reduce the compound **5**{*1,1*}. HPLC purity 97%. ^{1}H NMR (400 MHz, MeOH-d_4): δ = 7.62-7.66 (m, 2H), 7.33-7.39 (m, 3H), 5.08 (q, *J* = 7.5 Hz, 1H), 4.36-4.42 (m, 2H), 3.64 (d, *J* = 12.7 Hz, 1H), 3.46 (d, *J* = 12.7 Hz, 1H), 1.36 (td, *J* = 10.5, 1.9 Hz, 3H). HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{13}H_{14}NO_4$ $[M+H]^+$ 248.0917, found 248.0918.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0.3
0.4
0.5
0.6
0.7
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
2.00
3.00
1.01
2.00
1.01
1.02
3.00
parts per Million