Merging singlet-oxygen induced furan oxidations with organocatalysis. Synthesis of enantiopure cyclopentanones and hydrindanes

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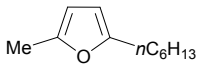
Part A: General methods and Experimental procedures.

General Methods:

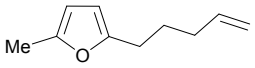
NMR data were obtained for ^{1}H at 500 MHz and for ^{13}C at 125 MHz. HRMS data was recorded on the Orbitrap analyzer of an LTQ Orbitrap XL, using an ESI ionization source. Enantiomeric excesses were determined by HPLC (UFLC) analysis using a chiral column and in comparison with the corresponding racemates. The columns used were a Daicel Chiralpak AD-H Column (250 × 4.6 mm), a Chiralpak AS-H Column (250 × 4.6 mm) or a Chiralcel OD Column (250 × 4.6 mm). Optical rotations were measured on an automatic polarimeter P3000 (A. Krüss Optronic). $[\alpha]_D^T$ values are quoted in g/100 mL concentration using a 50 mm polarimeter tube; D refers to the D-line of sodium (589 nm); temperatures (T) are given in degrees Celsius (°C).

The organocatalyst (cat. 1), as well as, the compounds 2,5-dimethyl furan **1a**, *trans*-cinnamaldehyde **2a**, *trans*-4-methoxycinnamaldehyde **2b**, *trans*-4-chlorocinnamaldehyde **2c**, and *trans*-2-methoxycinnamaldehyde **2e** are commercially available.

Synthesis of furan substrates 1b and 1c, as well as, enals 2d and 2f



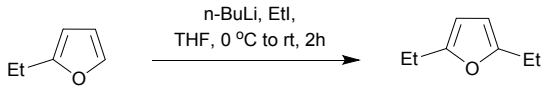
1b



1c

The furans **1b**[1] and **1c**[2] and the enals **2d**[3] and **2f**[3] were prepared according to previously reported methodologies.

Synthesis of 2,5-diethylfuran (1d)[4]



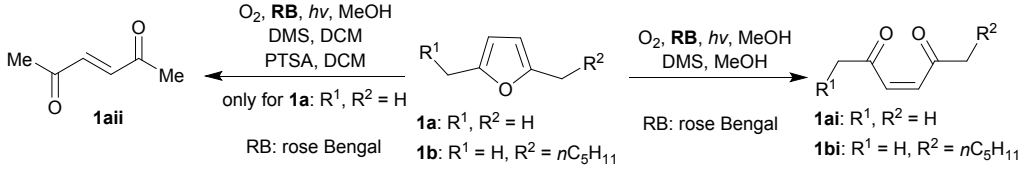
1d

To a solution of 2-ethylfuran (1.05 mL, 10.0 mmol) in anhydrous THF (35 mL), at 0 °C and under an argon atmosphere, was added dropwise a solution of *n*-BuLi (6.25 mL, 1.6 M in hexane, 10.0 mmol). The solution was stirred for 30 min at the same temperature, and, subsequently, a solution of iodoethane (1.20 mL, 15 mmol) in anhydrous THF (3 mL) was added. The reaction solution was warmed to room temperature and stirred for a further 2 hours. The reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and the resulting mixture was extracted

[1] G. I. Ioannou, T. Montagnon, D. Kalaitzakis, S. A. Pergantis and G. Vassilikogiannakis, *Org. Biomol. Chem.,* 2017, **15**, 10151.
[2] D. Kalaitzakis, M. Triantafyllakis, I. Alexopoulou, M. Sofiadis, and G. Vassilikogiannakis, *Angew.Chem. Int. Ed.,* 2014, **53**, 13201.
[3] M. Sofiadis, D. Kalaitzakis, J. Sarris, T. Montagnon and G. Vassilikogiannakis, *Angew.Chem. Int. Ed.,* 2019, **58**, 6742.
[4] C. Asta, J. Conrad, S. Mika and U. Beifuss, *Green Chem.,* 2011, **13**, 3066.

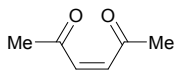
with Et_2O (20 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash column chromatography (silica gel, petroleum ether). Yield = 1.0 g (81%).
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86 (s, 2H), 2.61 (q, *J*=7.5 Hz, 4H), 1.22 (t, *J*=7.5 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9 (2C), 104.1 (2C), 21.3 (2C), 12.2 (2C) ppm.

Synthesis of enediones 1ai, 1aii and 1bi, 1bii



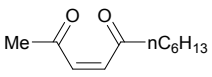
2,5-Disubstituted furans (0.2 mmol, 21.3 μL for **1a**, 33.2 mg for **1b**) were dissolved in methanol (4 mL, 50 mM) containing catalytic amounts of rose Bengal as photosensitizer (0.1 mM). The solutions were cooled using an ice bath. Oxygen was gently bubbled through the solutions while they were irradiated by a xenon Variac Eimac Cermax 300 W lamp (VIS 385-740 nm). The reactions were monitored by tlc. After completion of the reactions (3 min), the solutions were warmed to room temperature and Me_2S (58 μL, 0.8 mmol) was added. After completion of the reduction (45 min), the solutions were concentrated *in vacuo* and the residues were purified by flash column chromatography (silica gel, petroleum ether : EtOAc 10:1 → 4/1) to afford the corresponding cis-enediones **1ai** and **1bi**.
Towards to the synthesis of **1aii**, after the photooxygenation reaction the solvent (MeOH) was replaced by DCM (2 mL) and Me_2S (58 μL, 0.8 mmol) was added. After completion of the reduction (1 h), p-toluenesulfonic acid (PTSA·H_2O, 3.8 mg, 0.02 mmol) was added and the solution was stirred until completion of the isomerization (**1ai→1aii**) was observed by ^{1}H-NMR after 4 h. The solvent was removed under reduced pressure and the product was purified by flash column chromatography (silica gel, petroleum ether : EtOAc 6:1 → 5/1) to afford **1aii** as a white solid. Yield 80% (17.9 mg).

(Z)-Hex-3-ene-2,5-dione (1ai)[4]



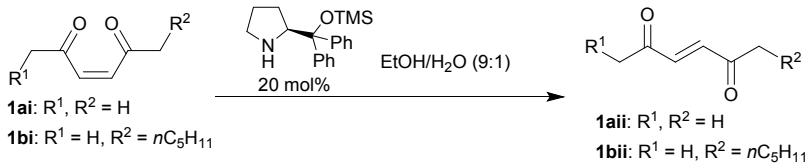
Yield = 15.7 mg (70%) of a slightly yellow oil. The *Z*-configuration was assigned by comparing the ^{1}H and ^{13}C NMR data with the corresponding known literature data.[4]
^{1}H NMR (500 MHz, $CDCl_3$): 6.28 (s, 2H), 2.27 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 200.5 (2C), 135.6 (2C), 29.7 (2C) ppm.

(Z)-Undec-3-ene-2,5-dione (1bi)



Yield = 30.9 mg (85%) of a yellow oil. The *Z*-configuration was assigned by the coupling constant *J* for the vinyl protons (*J*=11.9 Hz).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.31 (d, *J*=11.9 Hz, 1H) 6.28 (d, *J*=11.9 Hz, 1H), 2.53 (t, *J*=7.4 Hz, 2H), 2.29 (s, 3H), 1.62 (m, 2H), 1.32-1.25 (m, 6H), 0.87 (t, *J*=7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.8, 200.7, 136.1, 135.2, 42.6, 31.6, 29.7, 28.7, 23.4, 22.4, 14.0 ppm.

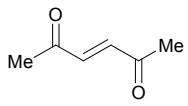


1ai: R^1, R^2 = H
1bi: R^1 = H, R^2 = nC_5H_{11}

1aii: R^1, R^2 = H
1bii: R^1 = H, R^2 = nC_5H_{11}

To the cis-enediones (0.1 mmol, 11.2 mg for **1ai** and 18.2 mg for **1bi**) in EtOH/H_2O (9/1 v/v, 1 mL) was added the organocatalyst (S)-2-(diphenyl ((trimethylsilyl) oxy) methyl) pyrrolidine (6.5 mg, 0.02 mmol, 20% mol) and the resulting solutions were stirred for 30 min until full consumption of the starting material was indicated by tlc analysis. The solvent was concentrated *in vacuo* and the corresponding trans-enediones **1aii** and **1bii** were purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 8:1 → 4:1).

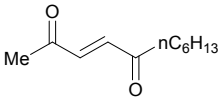
(E)-Hex-3-ene-2,5-dione (1aii)[4]



Yield = 8.7 mg (78%) of white solid. The *E*-configuration was assigned by comparing the ^{1}H and the ^{13}C NMR data with the corresponding known literature data.[4]

^{1}H NMR (500 MHz, $CDCl_3$): 6.79 (s, 2H), 2.38 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 198.5 (2C), 137.8 (2C), 28.0 (2C) ppm.

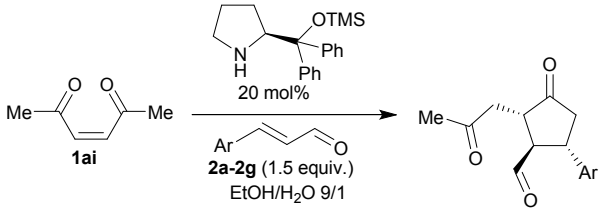
(E)-Undec-3-ene-2,5-dione (1bii)



Yield = 14.6 mg (80%) of white solid. The *E*-configuration was assigned by the coupling constant *J* for the vinyl protons (*J*=16.6 Hz).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.84 (d, *J*=16.6 Hz, 1H), 6.80 (d, *J*=16.6 Hz, 1H), 2.63 (t, *J*=7.3 Hz, 2H), 2.36 (s, 3H), 1.62 (m, 2H), 1.32-1.26 (m, 6H), 0.87 (t, *J*=6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.8, 198.5, 137.2, 136.8, 41.4, 31.5, 28.7, 28.1, 23.7, 22.4, 14.0 ppm.

General procedure for the organocatalysed synthesis of cyclopentanones of type 3 from 1ai

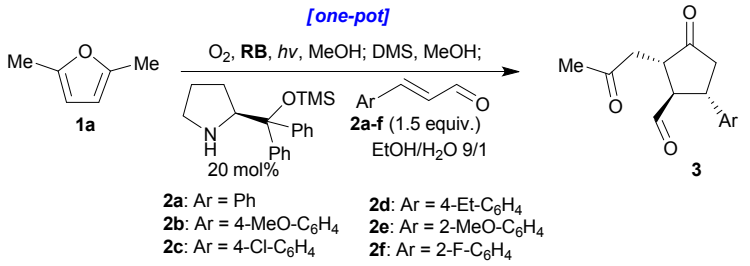


2a: Ar = Ph
2b: Ar = 4-MeO-C_6H_4
2c: Ar = 4-Cl-C_6H_4
2d: Ar = 4-Et-C_6H_4
2e: Ar = 2-MeO-C_6H_4
2f: Ar = 2-F-C_6H_4

To a solution of enedione **1ai** (11.2 mg, 0.1 mmol) in EtOH/H_2O (9/1 v/v, 1 mL) at room temperature, the organocatalyst (6.5 mg, 0.02 mmol, 20% mol) and the corresponding enal (0.15 mmol, 18.8 μL of **2a**, or 24.3 mg of **2b**, or 25 mg of **2c**, or 24 mg of **2d**, or 24.3 mg of **2e**, or 22.5 mg of **2f**) were added and the resulting solution stirred for 24 h at the same temperature. After completion of the reaction (as indicated by tlc analysis), the solution was concentrated *in vacuo* and the products of type **3** were purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 5:1 → 2:1 for all the products). Isolated yields: for **3a** = 22 mg (90%), for **3b** = 23 mg (84%), for **3c** = 22 mg (79%), for **3d** = 24 mg (88%), for **3e** = 26 mg (95%) and for **3f** = 23.6 mg (90%). All the dr values were calculated using the ^{1}H-NMR data of the crude reaction mixtures. Identical results were obtained when the reactions started from **1aii**.

Racemic mixtures of all the compounds of type **3** were prepared according to the general experimental procedure described above, in this case, using an equimolar mixture of (*S*)-(-)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (3.2 mg, 0.01 mmol) and (*R*)-(-)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (3.2 mg, 0.01 mmol) as organocatalyst.

General procedure for the one pot synthesis of cyclopentanones of type 3 from furan 1a

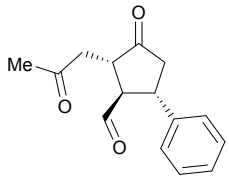


2,5-Dimethyl furan **1a** (10.7 μL, 0.1 mmol) was dissolved in methanol (2 mL, 50 mM) containing catalytic amounts of rose Bengal as photosensitizer (0.1 mM). The solution was cooled using an ice bath. Oxygen was gently bubbled through the solution while it was irradiated by a xenon Variac Eimac Cermax 300 W lamp (VIS 385-740 nm) for 2 min. Then the solution was warmed to room temperature and Me_2S (29 μL, 0.4 mmol) was added. After tlc analysis indicated completion of the reduction (45 min), the solvent was replaced by EtOH/H_2O (9/1 v/v, 1 mL). Then, the organocatalyst (6.5 mg, 0.02 mmol, 20 mol%) and the corresponding enal (0.15 mmol, 18.8 μL of **2a**, or 24.3 mg of **2b**, or 25 mg of **2c**, or 24 mg of **2d**, or 24.3 mg of **2e**, or 22.5 mg of **2f**) were added and the solution was stirred for 24 h at room temperature. After completion of the reaction (as indicated by ^{1}H-NMR of the crude reaction mixture), the solvent was concentrated *in vacuo* and the products of type **3** were purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 5:1 → 2:1 for all the products). All the dr values were calculated using the ^{1}H-NMR of the crude reaction mixture.

When the same protocol was scaled up to 1 mmol of furan **1a** with enal **2a** or **2c** (1.5 mmol) the results were identical.

In order to analyze the compounds by chiral HPLC and determine the ee values, the aldehyde group in products of type **3** was reduced using $NaBH_4$, because the two enantiomers of **3** were inseparable by chiral HPLC. The reductions were performed as follows: To each solution of pure compound of type **3** (0.06 mmol, 14.6 mg for **3a**, 16.4 mg for **3b**, 16.6 mg for **3c**, 16.3 mg for **3d**, 16.4 mg for **3e** and 15.7 mg for **3f**) in dry MeOH (2 mL) at 0 °C, a solution of $NaBH_4$ (0.7 mg, 0.0185 mmol) in dry MeOH (0.5 mL) was added dropwise. The resulting solution was stirred at the same temperature for 20 min. The reaction was then quenched by the addition of a saturated aqueous solution of NH_4Cl (1 mL) and the mixture was extracted with EtOAc (3× 3 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The reduced products were purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 5:1 → 1:1 for all the products). This reduction was performed to all the compounds of type **3**, derived either from pure enedione **1ai** or furan **1a** and the ee values were identical.

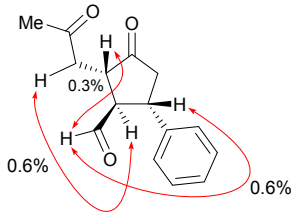
(1*R*,2*S*,5*S*)-3-oxo-2-(2-oxopropyl)-5-phenylcyclopentane-1-carbaldehyde (3a)



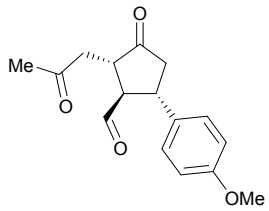
Yield = 15.9 mg (65%) of a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): 9.65 (d, *J*=2.2 Hz, 1H), 7.37 (m, 4H), 7.28 (m, 1H), 3.46 (td, J_1=11.6 Hz, J_2=8.2 Hz, 1H), 3.29 (td, J_1=11.2 Hz, J_2=2.2 Hz, 1H), 3.05 (dd, J_1=19.0 Hz, J_2=5.4 Hz, 1H), 2.91 (dd, J_1=19.0 Hz, J_2=3.6 Hz, 1H), 2.88 (ddd, J_1=18.6 Hz, J_2=8.4 Hz, J_3=1.1 Hz, 1H), 2.78 (dd, J_1=18.6 Hz, J_2=11.6 Hz, 1H), 2.75 (m, 1H), 2.16 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 214.2, 206.1, 201.2, 140.3, 129.1 (2C), 127.6, 127.3 (2C), 59.9, 46.0, 45.7, 42.5, 41.9, 29.7 ppm; $[\alpha]_D^{20}$= +40 (*c* 1.0, MeOH); HRMS (Orbitrap ESI): calcd for $C_{15}H_{17}O_3$: 245.1172 $[M+H]^+$; found 245.1171.

Representative NOEs



(1*R*,2*S*,5*S*)-5-(4-methoxyphenyl)-3-oxo-2-(2-oxopropyl)cyclopentane-1-carbaldehyde (3b)

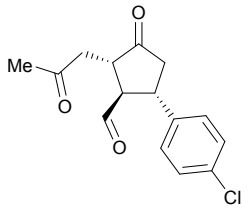


Yield = 16.4 mg (60%) of a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): 9.64 (d, *J*=2.2 Hz, 1H), 7.27 (d, *J*=8.8 Hz, 2H), 6.89 (d, *J*=8.8 Hz, 2H), 3.80 (s, 3H), 3.41 (td, J_1=11.6 Hz, J_2=8.3 Hz, 1H), 3.23 (td, J_1=11.2 Hz, J_2=2.2 Hz, 1H), 3.04 (dd, J_1=19.0 Hz, J_2=5.3 Hz, 1H), 2.90 (dd, J_1=19.0 Hz, J_2=3.6 Hz, 1H), 2.85 (dd, J_1=18.8 Hz, J_2=9.0 Hz, 1H), 2.73 (dd, J_1=18.5 Hz, J_2=12.0 Hz, 1H), 2.73 (m, 1H), 2.16 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 214.4, 206.1, 201.4, 158.9, 132.1, 128.3 (2C), 114.4 (2C), 60.1, 55.3,

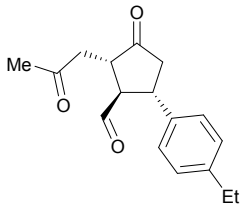
46.1, 45.8, 41.9, 41.8, 29.7 ppm; $[\alpha]_D^{20}$= +40 (*c* 0.5, MeOH); HRMS (Orbitrap ESI): calcd for $C_{16}H_{19}O_4$: 275.1278 $[M+H]^+$; found 275.1278.

(1*R*,2*S*,5*S*)-5-(4-chlorophenyl)-3-oxo-2-(2-oxopropyl)cyclopentane-1-carbaldehyde (3c)



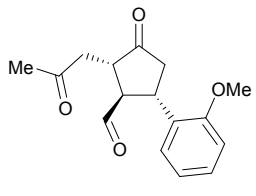
Yield = 16.4 mg (59%) of a yellow oil.
^{1}H NMR (500 MHz, $CDCl_3$): 9.64 (d, *J*=2.2 Hz, 1H), 7.34 (d, *J*=8.6 Hz, 2H), 7.30 (d, *J*=8.6 Hz, 2H), 3.45 (td, J_1=11.6 Hz, J_2=8.4 Hz, 1H), 3.25 (td, J_1=11.2 Hz, J_2=2.2 Hz, 1H), 3.07 (dd, J_1=19.1 Hz, J_2=5.3 Hz, 1H), 2.91 (dd, J_1=19.1 Hz, J_2=3.5 Hz, 1H), 2.87 (m, 1H), 2.73 (dd, J_1=18.6 Hz, J_2=12.0 Hz, 1H), 2.72 (m, 1H), 2.17 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 213.7, 206.2, 200.7, 138.9, 133.4, 129.2 (2C), 128.7 (2C), 59.9, 46.0, 45.6, 41.9, 41.7, 29.7 ppm; $[\alpha]_D^{20}$= +14 (*c* 1.0, MeOH); HRMS (Orbitrap ESI): calcd for $C_{15}H_{16}ClO_3$: 279.0782 $[M+H]^+$; found 279.0780.

(1*R*,2*S*,5*S*)-5-(4-ethylphenyl)-3-oxo-2-(2-oxopropyl)cyclopentane-1-carbaldehyde (3d)



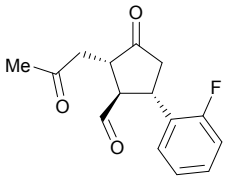
Yield = 16.9 mg (62%) of a yellow oil.
^{1}H NMR (500 MHz, $CDCl_3$): 9.65 (d, *J*=2.1 Hz, 1H), 7.27 (d, *J*=8.1 Hz, 2H), 7.19 (d, *J*=8.1 Hz, 2H), 3.43 (td, J_1=11.5 Hz, J_2=8.3 Hz, 1H), 3.26 (td, J_1=11.2 Hz, J_2=2.1 Hz, 1H), 3.04 (dd, J_1=19.0 Hz, J_2=5.4 Hz, 1H), 2.91 (dd, J_1=19.0 Hz, J_2=3.6 Hz, 1H), 2.86 (dd, J_1=18.6 Hz, J_2=8.3 Hz, 1H), 2.76 (dd, J_1=18.6 Hz, J_2=11.9 Hz, 1H), 2.75 (m, 1H), 2.64 (q, *J*=7.6 Hz, 2H), 2.16 (s, 3H), 1.23 (t, *J*=7.6 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 214.4, 206.1, 201.4, 143.6, 137.4, 128.5 (2C), 127.2 (2C), 60.0, 46.0, 45.8, 42.2, 41.9, 29.7, 28.4, 15.5 ppm; $[\alpha]_D^{20}$= +40 (*c* 1.0, MeOH); HRMS (Orbitrap ESI): calcd for $C_{17}H_{21}O_3$: 273.1485 $[M+H]^+$; found 273.1480.

(1*R*,2*S*,5*S*)-5-(2-methoxyphenyl)-3-oxo-2-(2-oxopropyl)cyclopentane-1-carbaldehyde (3e)



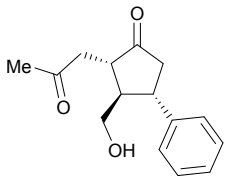
Yield = 17.3 mg (63%) of a yellow oil.
^{1}H NMR (500 MHz, $CDCl_3$): 9.60 (d, *J*=2.8 Hz, 1H), 7.32 (dd, J_1=7.5 Hz, J_2=1.5 Hz, 1H), 7.26 (m, 1H), 6.97 (td, J_1=7.5 Hz, J_2=1.0 Hz, 1H), 6.89 (d, *J*=8.2 Hz, 1H), 3.83 (m, 1H), 3.82 (s, 3H), 3.20 (td, J_1=11.0 Hz, J_2=2.8 Hz, 1H), 2.92 (m, 2H), 2.87-2.79 (m, 3H), 2.15 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 214.8, 205.9, 201.2, 157.0, 128.5, 127.9, 127.5, 121.0, 110.7, 59.0, 55.1, 46.0, 43.1, 41.8, 36.1, 29.8 ppm; $[\alpha]_D^{20}$= +20 (*c* 0.5, MeOH); HRMS (Orbitrap ESI): calcd for $C_{16}H_{19}O_4$: 275.1278 $[M+H]^+$; found 275.1277.

(1R,2S,5S)-5-(2-fluorophenyl)-3-oxo-2-(2-oxopropyl)cyclopentane-1-carbaldehyde (3f)



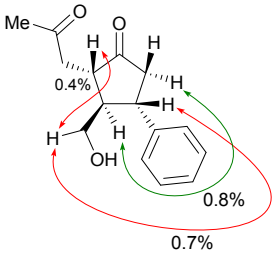
Yield = 17.0 mg (65%) of a yellow oil.
^{1}H NMR (500 MHz, $CDCl_3$): 9.64 (d, *J*=1.7 Hz, 1H), 7.40 (td, J_1=7.6 Hz, J_2=1.5 Hz, 1H), 7.27 (m, 1H), 7.16 (t, *J*=7.5 Hz, 1H), 7.10 (m, 1H), 3.78 (td, J_1=11.5 Hz, J_2=8.5 Hz, 1H), 3.27 (td, J_1=11.3 Hz, J_2=2.6 Hz, 1H), 3.00 (dd, J_1=19.0 Hz, J_2=5.5 Hz, 1H), 2.94 (dd, J_1=19.0 Hz, J_2=3.6 Hz, 1H), 2.87 (dd, J_1=18.6 Hz, J_2=8.5 Hz, 1H), 2.80 (m, 1H), 2.77 (dd, J_1=18.6 Hz, J_2=11.8 Hz, 1H), 2.16 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 213.7, 206.0, 200.6, 160.8 (d, *J*=245.0 Hz), 129.1 (d, *J*=8.7 Hz), 128.2 (d, *J*=5.0 Hz), 126.9 (d, *J*=12.5 Hz), 124.8 (d, *J*=2.5 Hz), 115.9 (d, *J*=22.5 Hz), 58.8, 46.0, 43.8, 41.9, 35.1 (d, *J*=1.2 Hz), 29.7 ppm; $[\alpha]_D^{20}$= +56 (*c* 1.75, MeOH); HRMS (Orbitrap ESI): calcd for $C_{15}H_{16}FO_3$: 263.1078 $[M+H]^+$; found 263.1080.

(2*S*,3*R*,4*S*)-3-(hydroxymethyl)-2-(2-oxopropyl)-4-phenylcyclopentan-1-one (7a)

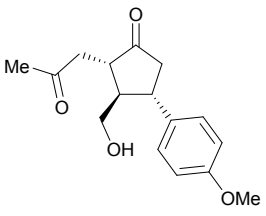


Yield = 9.9 mg (67%) of a yellow oil.
^{1}H NMR (500 MHz, $CDCl_3$): 7.35-7.23 (m, 5H), 3.51 (m, 2H), 3.30 (td, J_1=11.5 Hz, J_2=8.3 Hz, 1H), 3.24 (m, 1H), 2.84 (dd, J_1=19.0 Hz, J_2=8.3 Hz, 1H), 2.69 (m, 2H), 2.53 (dd, J_1=19.0 Hz, J_2=11.7 Hz, 1H), 2.50 (t, *J*=6.4 Hz, 1H), 2.23 (s, 3H), 2.04 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 216.6, 208.5, 141.5, 128.8 (2C), 127.6 (2C), 127.0, 59.9, 52.7, 46.8, 45.7, 42.5, 41.8, 29.9 ppm; $[\alpha]_D^{20}$= +20 (*c* 1.0, MeOH); HRMS (Orbitrap ESI): calcd for $C_{15}H_{19}O_3$: 247.1329 $[M+H]^+$; found 247.1326; HPLC (DAICEL Chiralpak AD-H, *n*-hexane/2-propanol = 90/10, flow = 0.8 mL/min, detection at 254 nm, retention time = 18.9 min, ee = >99%.

Representative NOEs



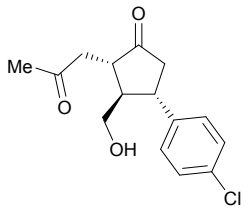
(2*S*,3*R*,4*S*)-3-(hydroxymethyl)-4-(4-methoxyphenyl)-2-(2-oxopropyl)cyclopentan-1-one (7b)



Yield = 10.4 mg (63%) of a yellow oil.
^{1}H NMR (500 MHz, $CDCl_3$): 7.20 (d, *J*=8.6 Hz, 2H), 6.87 (d, *J*=8.6 Hz, 2H), 3.80 (s, 3H), 3.50 (m, 2H), 3.25 (m, 2H), 2.81 (dd, J_1=19.0 Hz, J_2=8.3 Hz, 1H), 2.67 (m, 2H), 2.48 (m, 1H), 2.47 (dd, J_1=19.0 Hz, J_2=11.7 Hz, 1H), 2.23 (s, 3H), 1.98 (tt,

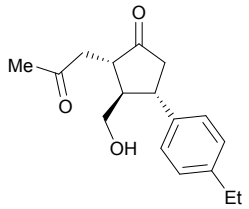
J_1=11.4 Hz, J_2=3.4 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 216.7, 208.5, 158.6, 133.3, 128.6 (2C), 114.1 (2C), 59.9, 55.3, 52.9, 46.8, 45.8, 42.5, 41.0, 29.9 ppm; $[\alpha]_D^{20}$= +28 (*c* 0.5, MeOH); HRMS (Orbitrap ESI): calcd for $C_{16}H_{21}O_4$: 277.1434 $[M+H]^+$; found 277.1431; HPLC (DAICEL Chiralpak AD-H, *n*-hexane/2-propanol = 90/10, flow = 0.8 mL/min, detection at 254 nm, retention time = 25.5 min (major), 32.7 min (minor), ee = 98%.

(2*S*,3*R*,4*S*)-4-(4-chlorophenyl)-3-(hydroxymethyl)-2-(2-oxopropyl)cyclopentan-1-one (7c)



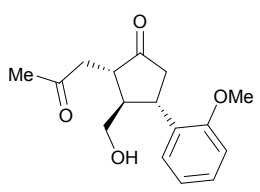
Yield = 10.9 mg (65%) of a yellow oil.
^{1}H NMR (500 MHz, $CDCl_3$): 7.31 (d, *J*=8.4 Hz, 2H), 7.22 (d, *J*=8.4 Hz, 2H), 3.48 (brs, 2H), 3.30 (td, J_1=11.5 Hz, J_2=8.4 Hz, 1H), 3.24 (m, 1H), 2.82 (dd, J_1=19.0 Hz, J_2=8.4 Hz, 1H), 2.69 (m, 2H), 2.48 (m, 1H), 2.47 (dd, J_1=19.0 Hz, J_2=11.8 Hz, 1H), 2.23 (s, 3H), 1.99 (tt, J_1=11.3 Hz, J_2=3.1 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 216.0, 208.4, 140.0, 132.7, 129.0 (2C), 128.9 (2C), 59.5, 52.6, 46.7, 45.6, 42.4, 41.1, 29.9 ppm; $[\alpha]_D^{20}$= +24 (*c* 0.5, MeOH); HRMS (Orbitrap ESI): calcd for $C_{15}H_{18}ClO_3$: 281.0939 $[M+H]^+$; found 281.0935; HPLC (DAICEL Chiralpak AD-H, *n*-hexane/2-propanol = 90/10, flow = 0.8 mL/min, detection at 254 nm, retention time = 20.4 min, ee = >99%.

(2*S*,3*R*,4*S*)-4-(4-ethylphenyl)-3-(hydroxymethyl)-2-(2-oxopropyl)cyclopentan-1-one (7d)



Yield = 10.0 mg (61%) of a yellow oil.
^{1}H NMR (500 MHz, $CDCl_3$): 7.20 (d, *J*=8.3 Hz, 2H), 7.17 (d, *J*=8.3 Hz, 2H), 3.51 (m, 2H), 3.26 (m, 2H), 2.82 (dd, J_1=19.1 Hz, J_2=8.2 Hz, 1H), 2.68 (m, 2H), 2.63 (q, *J*=7.6 Hz, 2H), 2.51 (dd, J_1=19.1 Hz, J_2=11.8 Hz, 1H), 2.48 (m, 1H), 2.23 (s, 3H), 2.01 (tt, J_1=11.5 Hz, J_2=3.3 Hz, 1H), 1.23 (t, *J*=7.6 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 216.7, 208.5, 143.0, 138.6, 128.2 (2C), 127.6 (2C), 60.0, 52.8, 46.9, 45.8, 42.5, 41.4, 29.9, 28.4, 15.5 ppm; $[\alpha]_D^{20}$= +28 (*c* 0.5, MeOH); HRMS (Orbitrap ESI): calcd for $C_{17}H_{23}O_3$: 275.1642 $[M+H]^+$; found 275.1641; HPLC (DAICEL Chiralpak AD-H, *n*-hexane/2-propanol = 90/10, flow = 0.8 mL/min, detection at 254 nm, retention time = 15.1 min, ee = >99%.

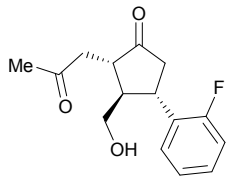
(2*S*,3*R*,4*S*)-3-(hydroxymethyl)-4-(2-methoxyphenyl)-2-(2-oxopropyl)cyclopentan-1-one (7e)



Yield = 10.4 mg (63%) of a yellow oil.
^{1}H NMR (500 MHz, $CDCl_3$): 7.27-7.22 (m, 2H), 6.96 (t, *J*=7.6 Hz, 1H), 6.90 (d, *J*=8.2 Hz, 1H), 3.84 (s, 3H), 3.62 (td, J_1=11.0 Hz, J_2=9.0 Hz, 1H), 3.50 (m, 2H), 3.13 (m, 1H), 2.77-2.64 (m, 4H), 2.58 (brt, *J*=6.2 Hz, 1H), 2.21 (s, 3H), 2.20 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 217.3, 208.1, 157.5, 129.2, 128.0, 127.9, 121.1, 110.8,

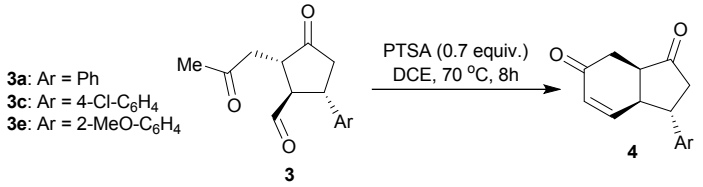
60.4, 55.4, 50.7, 46.8, 43.6, 42.2, 35.6, 30.0 ppm; $[\alpha]_D^{20}$= +54 (*c* 1.0, MeOH); HRMS (Orbitrap ESI): calcd for $C_{16}H_{21}O_4$: 277.1434 $[M+H]^+$; found 277.1431; HPLC (DAICEL Chiralpak AD-H, *n*-hexane/2-propanol = 90/10, flow = 0.8 mL/min, detection at 254 nm, retention time = 23.8 min, ee = >99%.

(2*S*,3*R*,4*S*)-4-(2-fluorophenyl)-3-(hydroxymethyl)-2-(2-oxopropyl)cyclopentan-1-one (7f)



Yield = 9.7 mg (61%) of a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): 7.31 (td, J_1=7.5 Hz, J_2=1.7 Hz, 1H), 7.23 (m, 1H), 7.13 (td, J_1=7.5 Hz, J_2=1.1 Hz, 1H), 7.05 (ddd, J_1=10.8 Hz, J_2=8.2 Hz, J_3=1.1 Hz, 1H), 3.56 (td, J_1=11.4 Hz, J_2=8.7 Hz, 1H), 3.52 (m, 2H), 3.23 (m, 1H), 2.81 (dd, J_1=19.0 Hz, J_2=8.7 Hz, 1H), 2.71 (m, 2H), 2.61 (dd, J_1=19.0 Hz, J_2=11.7 Hz, 1H), 2.52 (brt, *J*=6.4 Hz, 1H), 2.23 (s, 3H), 2.19 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 216.2, 208.4, 161.3 (d, *J*=243.7 Hz), 129.2 (d, *J*=5.0 Hz), 128.5 (d, *J*=8.7 Hz), 128.1 (d, *J*=12.5 Hz), 124.5 (d, *J*=3.7 Hz), 115.8 (d, *J*=22.5 Hz), 60.1, 50.9, 46.7, 43.9 (d, *J*=1.2 Hz), 42.4, 35.5, 29.9 ppm; $[\alpha]_D^{20}$= +40 (*c* 1.0, MeOH); HRMS (Orbitrap ESI): calcd for $C_{15}H_{18}FO_3$: 265.1234 $[M+H]^+$; found 265.1236; HPLC (DAICEL Chiralpak AD-H, *n*-hexane/2-propanol = 90/10, flow = 0.8 mL/min, detection at 254 nm, retention time = 18.1 min, ee = >99%.

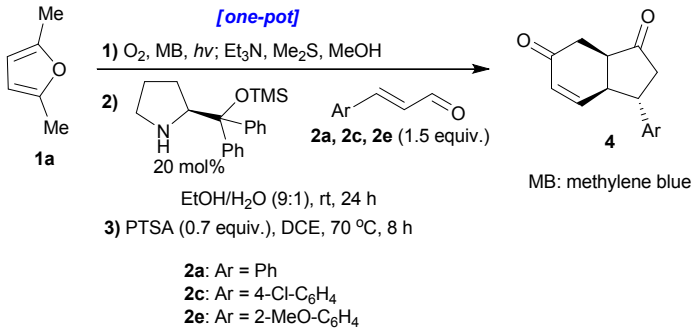
General procedure for the synthesis of products of type 4 from the corresponding compounds of type 3



Each compound of type **3** (0.1 mmol, 24.4 mg for **3a**, 27.8 mg for **3c**, 27.4 mg for **3e**) was dissolved in DCE (1 mL) and p-toluenesulfonic acid (PTSA·H_2O, 13.3 mg, 0.07 mmol) was added. The mixture was heated to 70 °C and stirred for 8 h. After tlc analysis indicated completion of the reaction, the solvent was removed under reduced pressure and the products of type **4** were purified by flash column chromatography (silica gel, petroleum ether:EtOAc). Isolated yields: for **4a** = 18.1 mg (80%), for **4c** = 20.8 mg (80%) and for **4e** = 21.5 mg (84%). All the dr values were measured using ^{1}H-NMR data for the crude reaction mixture.

Racemic mixtures of all the compounds of type **4** were prepared from the corresponding racemic mixtures of compounds of type **3** according to the general experimental procedure described above.

General procedure for the one pot synthesis of carbocycles of type 4 from furan 1a



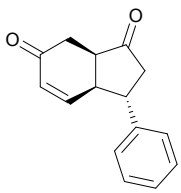
2a: Ar = Ph
2c: Ar = 4-Cl-C_6H_4
2e: Ar = 2-MeO-C_6H_4

2,5-Dimethyl furan **1a** (10.7 μL, 0.1 mmol) was dissolved in methanol (2 mL, 50 mM) containing catalytic amounts of methylene blue as photosensitizer (0.1 mM). The solution was cooled using an ice bath. Oxygen was gently bubbled through the solution while it was irradiated by a xenon Variac Eimac Cermax 300 W lamp (VIS 385-740 nm) for 2 min. The solution was then warmed to room temperature and a small amount of Et_3N (0.0035 mmol, 3.5% mol, 0.5 μL) was added, followed by Me_2S (29 μL, 0.4 mmol). After tlc analysis indicated completion of the reduction (45 min), the solvent was replaced with EtOH/H_2O (9/1 v/v, 1 mL). Then, the organocatalyst (6.5 mg, 0.02 mmol, 20 mol%) and the corresponding enal (0.15 mmol, 18.8 μL of **2a**, or 25 mg of **2c**, or 24.3 mg of **2e**) were added and the solution stirred for 24 h at room temperature. After completion of the reaction (as indicated by ^{1}H-NMR of the crude reaction mixture), the solvent was concentrated *in vacuo* and the products of type **3** were dissolved in DCE (1 mL). Then p-toluenesulfonic acid (PTSA·H_2O, 13.3 mg, 0.07 mmol) was added and the mixture was warmed to 70 °C and stirred for 8 h. After completion of the final step (as indicated by tlc analysis), the solvent was removed under reduced pressure and the products of type **4** were purified by flash column chromatography (silica gel, petroleum ether:EtOAc). All the dr values were measuterd using the ^{1}H-NMR data for the crude reaction mixture and the ee values were measured by chiral HPLC.

When the final aldol/dehydration step is included in our one pot sequences, without isolation and purification of the intermediates, we observed that isolated yields of the final products were a bit better when methylene blue was used instead of rose Bengal. For this reason, we decided to use methylene blue in these one pot protocols.

When the same protocol was scaled up to 1 mmol of furan **1a** with enal **2c** (1.5 mmol) the results were identical.

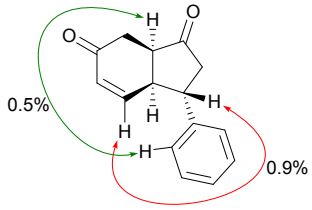
(3*S*,3a*R*,7a*R*)-3-phenyl-3,3a,7,7a-tetrahydro-1H-indene-1,6(2H)-dione (4a)



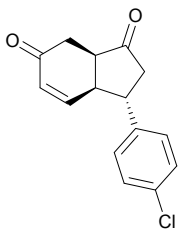
The product was prepared according to the general experimental procedure described above. The crude product was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 6:1) to furnish **4a** as a white solid (13.1 mg, 58%).

^{1}H NMR (500 MHz, $CDCl_3$): 7.38 (t, *J*=7.4 Hz, 2H), 7.30 (tt, J_1=7.4 Hz, J_2=1.9 Hz, 1H), 7.27 (m, 2H), 6.85 (dd, J_1=10.2 Hz, J_2=3.3 Hz, 1H), 6.07 (dd, J_1=10.2 Hz, J_2=2.0 Hz, 1H), 3.58 (m, 1H), 3.23 (m, 1H), 3.02 (q, *J*=7.2 Hz, 1H), 2.77 (dd, J_1=17.2 Hz, J_2=7.2 Hz, 1H), 2.73 (m, 2H), 2.54 (dd, J_1=17.2 Hz, J_2=7.1 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 215.5, 195.6, 149.1, 141.3, 130.5, 129.0 (2C), 127.4, 126.8 (2C), 45.0, 44.9, 44.5, 43.6, 34.1 ppm; $[\alpha]_D^{25}$=+30 (*c* 1.0, MeOH); HRMS (Orbitrap ESI): calcd for $C_{15}H_{15}O_2$: 227.1067 $[M+H]^+$; found 227.1068; HPLC (DAICEL Chiralpak AS-H, *n*-hexane/2-propanol = 50/50, flow = 0.5 mL/min, detection at 254 nm, retention time = 41.5 min, ee = >99%.

Representative NOEs



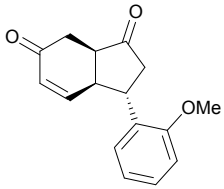
(3*S*,3a*R*,7a*R*)-3-(4-chlorophenyl)-3,3a,7,7a-tetrahydro-1H-indene-1,6(2H)-dione (4c)



The product was prepared according to the general experimental procedure described above. The crude product was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 6:1) to furnish **4c** as a white solid (13.8 mg, 53%).

^{1}H NMR (500 MHz, $CDCl_3$): 7.35 (m, 2H), 7.21 (d, *J*=8.5 Hz, 2H), 6.82 (dd, J_1=10.3 Hz, J_2=3.6 Hz, 1H), 6.08 (dd, J_1=10.3 Hz, J_2=2.0 Hz, 1H), 3.56 (m, 1H), 3.19 (m, 1H), 3.00 (q, *J*=7.3 Hz, 1H), 2.75 (m, 2H), 2.66 (dd, J_1=19.0 Hz, J_2=6.4 Hz, 1H), 2.55 (dd, J_1=17.2 Hz, J_2=7.1 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 214.9, 195.3, 148.5, 139.7, 133.3, 130.7, 129.2 (2C), 128.2 (2C), 45.0, 44.4 (2C), 43.6, 34.1 ppm; $[\alpha]_D^{25}$=+18 (*c* 1.0, MeOH); HRMS (Orbitrap ESI): calcd for $C_{15}H_{14}ClO_2$: 261.0677 $[M+H]^+$; found 261.0671; HPLC (DAICEL Chiralpak OD, *n*-hexane/2-propanol = 50/50, flow = 0.5 mL/min, detection at 254 nm, retention time = 28.4 min (major), 34.2 min (minor), ee = >99%.

(3*S*,3a*R*,7a*R*)-3-(2-methoxyphenyl)-3,3a,7,7a-tetrahydro-1H-indene-1,6(2H)-dione (4e)



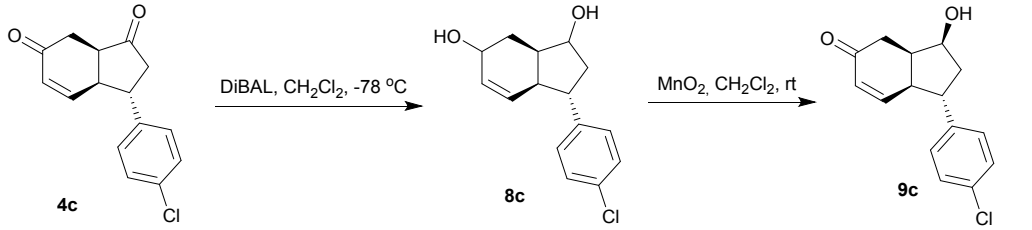
The product was prepared according to the general experimental procedure described above. The crude product was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 4:1) to furnish **4e** as a white solid (14.1 mg, 55%).

^{1}H NMR (500 MHz, $CDCl_3$): 7.29 (td, J_1=7.8 Hz, J_2=1.6 Hz, 1H), 7.08 (dd, J_1=7.8 Hz, J_2=1.4 Hz, 1H), 6.94 (m, 3H), 6.06 (dd, J_1=10.2 Hz, J_2=2.2 Hz, 1H), 3.89 (s, 3H), 3.87 (m, 1H), 3.30 (m, 1H), 2.92 (q, *J*=6.6 Hz, 1H), 2.85 (dd, J_1=17.2 Hz, J_2=5.4 Hz, 1H), 2.72 (dd, J_1=19.2 Hz, J_2=4.7 Hz, 1H), 2.63 (dd, J_1=19.2 Hz, J_2=8.6 Hz, 1H), 2.49 (dd, J_1=17.2 Hz, J_2=7.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz,

$CDCl_3$): 216.7, 195.9, 157.0, 150.5, 130.3, 129.8, 128.4, 126.5, 120.6, 110.7, 55.4, 44.6, 42.5, 41.5, 38.8, 34.3 ppm; $[\alpha]_D^{25}$=-66 (*c* 1.0, MeOH); HRMS (Orbitrap ESI): calcd for $C_{16}H_{17}O_3$: 257.1172 $[M+H]^+$; found 257.1174; HPLC (DAICEL Chiralpak AS-H, *n*-hexane/2-propanol = 60/40, flow = 0.5 mL/min, detection at 254 nm, retention time = 48.9 min (major), 66.6 min (minor), ee = >99%.

Synthetic procedure that contributed to the assignment of the absolute configuration of the products of type 4, and, consequently, also that of compounds of type 3 and 6

Synthesis of the carbocycle 9c

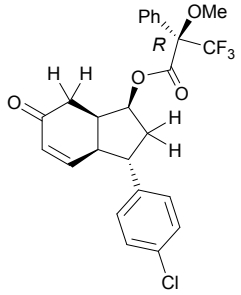


To a solution of diketone **4c** (31.2 mg, 0.12 mmol) in dry DCM (2 mL) at -78 °C, Dibal (264 μL, 1.0 M in Hexanes, 0.264 mmol) was added dropwise. The solution was stirred for 1 h at the same temperature. After the complete consumption of the starting material, as indicated by tlc analysis, the reaction was quenched with saturated aqueous Rochelle's salt (1 mL) and DCM (5 mL) was added. The biphasic suspension was stirred for 30 min at rt. The aqueous phase was separated and extracted with DCM (5× 2mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to afford a 4.3/1.3/1.1/1.0 mixture of 4 diastereoisomers of diol **8c** (determined by ^{1}H-NMR). Diol **8c** was used in the next step without further purification. A solution of the diol **8c** prepared above in dry DCM (2 mL) was added to a flame-dried flask containing activated MnO_2 (52.2 mg, 0.6 mmol). The suspension was stirred vigorously at rt for 4 h. After completion of the oxidation, (indicated by tlc analysis), the mixture was filtered through a pad of silica gel and the filtrate concentrated *in vacuo* to afford **9c** as a 2.4/1 mixture of diastereoisomers (separable). The product was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 2:1) to furnish the major diastereoisomer of **9c** as a yellow oil (12.6 mg, 40% over two steps).
^{1}H NMR (500 MHz, $CDCl_3$): 7.32 (d, *J*=8.4 Hz, 2H), 7.20 (d, *J*=8.4 Hz, 2H), 6.76 (dd, J_1=10.1 Hz, J_2=3.8 Hz, 1H), 6.00 (dd, J_1=10.1 Hz, J_2=1.1 Hz, 1H), 4.52 (m, 2H), 3.29 (dt, J_1=10.4 Hz, J_2=7.7 Hz, 1H), 2.85 (m, 2H), 2.64 (m, 2H), 2.20 (ddd, J_1=13.7 Hz, J_2=8.1 Hz, J_3=2.5 Hz, 1H), 2.00 (ddd, J_1=13.7 Hz, J_2=10.4 Hz, J_3=5.0 Hz, 1H), 1.77 (d, *J*=4.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 198.7, 150.2, 142.4, 132.4, 128.9 (2C), 128.5 (2C), 127.9, 76.1, 49.0, 45.7, 42.6, 42.4, 36.2 ppm; $[\alpha]_D^{20}$=+160 (*c* 0.5, MeOH); HRMS (Orbitrap ESI): calcd for $C_{15}H_{16}ClO_2$: 263.0833 $[M+H]^+$; found 263.0834.

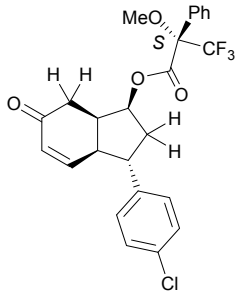
Mosher ester analysis applied to compound 9c

The absolute configuration of compound **9c** was determined using chiral MTPA derivatives.[5] The esterification of compound **9c** with *R*- and *S*-MTPA was performed as follows:

To a solution of **9c** (6.3 mg, 0.024 mmol) in dry CH_2Cl_2 at rt, DCC (10 mg, 0.048 mmol), the corresponding *R*- or *S*-MTPA (11.2 mg, 0.048 mmol) and a catalytic amount of 4-DMAP (0.3 mg, 10 mol%) were added and the solution was stirred for 24 h. After completion of the reaction, as indicated by tlc analysis, the mixture was filtered and the organic solvent was removed from the filtrate under reduced pressure. The residue was purified by flash column chromatography (silica gel, Hexane : EtOAc 3:1) to afford the corresponding *R*- or *S*-MTPA ester of **9c** as a slightly yellow oil in both cases. Yield for *R*-MTPA = 4.8 mg (42%) and for *S*-MTPA = 5.2 mg (45%).

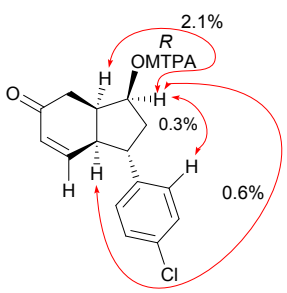


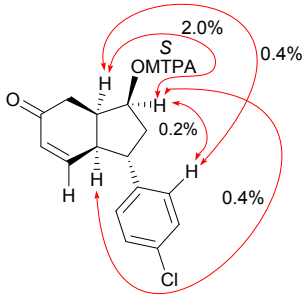
^{1}H NMR (500 MHz, $CDCl_3$): 7.50 (m, 2H), 7.43 (m, 3H), 7.33 (d, *J*=8.4 Hz, 2H), 7.17 (d, *J*=8.4 Hz, 2H), 6.64 (dd, J_1=10.2 Hz, J_2=4.5 Hz, 1H), 5.97 (dd, J_1=10.2 Hz, J_2=1.5 Hz, 1H), 5.61 (td, J_1=6.4 Hz, J_2=4.2 Hz, 1H), 3.51 (s, 3H), 3.19 (q, *J*=9.3 Hz, 1H), 3.13 (m, 1H), 2.82 (m, 1H), 2.47-2.30 (m, 4H) ppm.



^{1}H NMR (500 MHz, $CDCl_3$): 7.49 (m, 2H), 7.43 (m, 3H), 7.31 (d, *J*=8.4 Hz, 2H), 7.07 (d, *J*=8.4 Hz, 2H), 6.45 (dd, J_1=10.2 Hz, J_2=3.9 Hz, 1H), 5.86 (dd, J_1=10.2 Hz, J_2=1.9 Hz, 1H), 5.48 (td, J_1=5.4 Hz, J_2=2.9 Hz, 1H), 3.53 (d, *J*=1.1 Hz, 3H), 3.06 (m, 1H), 2.79 (tdd, J_1=8.5 Hz, J_2=3.9 Hz, J_3=1.9 Hz, 1H), 2.73 (m, 1H), 2.54 (dd, J_1=17.3 Hz, J_2=7.4 Hz, 1H), 2.50 (dd, J_1=17.3 Hz, J_2=6.4 Hz, 1H), 2.27 (ddd, J_1=14.6 Hz, J_2=8.1 Hz, J_3=2.9 Hz, 1H), 2.14 (ddd, J_1=15.6 Hz, J_2=10.2 Hz, J_3=5.4 Hz, 1H) ppm.

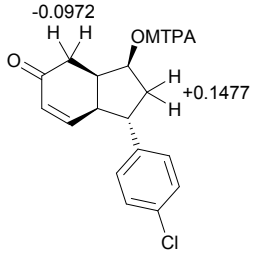
Representative NOEs of *R*- and *S*-MTPA ester of compound **9c**



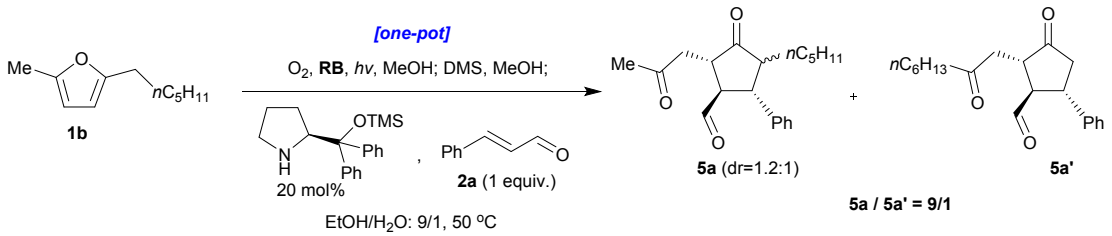


[5] J. M. Seco, E. Quiñoá, R. Riguera, *Chem. Rev.*, 2004, **104**, 17-117.

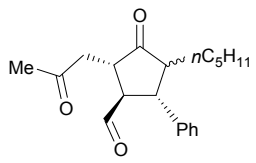
The absolute configuration was assigned after comparing the ^{1}H NMR spectra of the *R*- and *S*-MTPA esters of **9c**.[5] The corresponding differences in the chemicals shifts ($\Delta\delta^{RS}$ ppm) are reported below:



Synthesis of cyclopentanone 5a from furan 1b



Disubstituted furan **1b** (16.6 mg, 0.1 mmol) was dissolved in methanol (2 mL, 50 mM) containing catalytic amounts of rose Bengal as photosensitizer (0.1 mM). The solution was cooled using an ice bath. Oxygen was gently bubbled through the solution while it was irradiated by a xenon Variac Eimac Cermax 300 W lamp (VIS 385-740 nm) for 2 min. Then the solution was warmed to room temperature and Me_2S (29 μL, 0.4 mmol) was added. After tlc analysis indicated completion of the reduction (45 min), the solvent was replaced with EtOH/H_2O (9/1 v/v, 1 mL). Then, the organocatalyst (6.5 mg, 0.02 mmol, 20 mol%) and enal **2a** (12.6 μL, 0.1 mmol) were added and the solution was warmed to 50 ºC and stirred for 24 h. After completion of the reaction (as indicated by ^{1}H-NMR of the crude reaction mixture), the solution was concentrated *in vacuo* to afford a 9/1 mixture of products **5a** (dr 1.2/1) and **5a´** (determined by the ^{1}H-NMR of the crude reaction mixture). The product **5a** was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 10:1 → 5:1). The dr value of **5a** had increased to 1.7/1 after the chromatographic purification. Yield = 22 mg (70%) of a yellow oil.

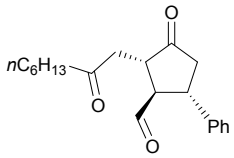


^{1}H NMR (500 MHz, $CDCl_3$): δ 9.71 (d, *J*=2.5 Hz, 1H for major), 9.60 (d, *J*=1.9 Hz, 1H for minor), 7.38-7.25 (m, 3H for major plus 5H for minor), 7.18 (d, *J*=7.5 Hz, 2H for major), 3.75 (t, *J*=9.2 Hz, 1H for major), 3.32 (td, J_1=9.8 Hz, J_2=2.5 Hz, 1H for major), 3.22 (td, J_1=11.2 Hz, J_2=1.9 Hz, 1H for minor), 3.06 (m, 1H for major plus 2H for minor), 2.95 (m, 1H for major plus 1H for minor), 2.78 (m, 1H for major plus 1H for minor), 2.67 (ddd, J_1=10.9 Hz, J_2=5.0 Hz, J_3=3.7 Hz, 1H for minor), 2.61 (q, *J*=7.7 Hz, 1H for major), 2.18 (s, 3H for major), 2.16 (s, 3H for minor), 1.64-1.43 (m, 2H for major plus 2H for minor), 1.19-1.02 (m, 6H for major plus 6H for minor), 0.77 (t, *J*=6.8 Hz, 3H for minor), 0.75 (t, *J*=7.0 Hz, 3H for

major) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 216.2 (1C for major plus 1C for minor), 206.3 (minor), 205.9 (major), 201.5 (minor), 201.1 (major), 140.2 (minor), 137.7 (major), 129.0 (2C for minor), 128.7 (2C for major), 128.3 (2C for major), 127.6 (3C for minor), 127.3 (major), 58.8 (minor), 55.9 (major), 55.5 (minor), 51.4 (major), 48.9 (minor), 45.4 (minor), 45.3 (major), 44.8 (major), 42.5 (major), 41.9 (minor), 31.7 (minor), 31.5 (major), 29.9 (major), 29.8 (minor), 28.3 (minor), 26.9 (major), 26.8 (major), 26.0 (minor), 22.3 (minor), 22.2 (major), 13.9 (1C for major plus 1C for minor) ppm.

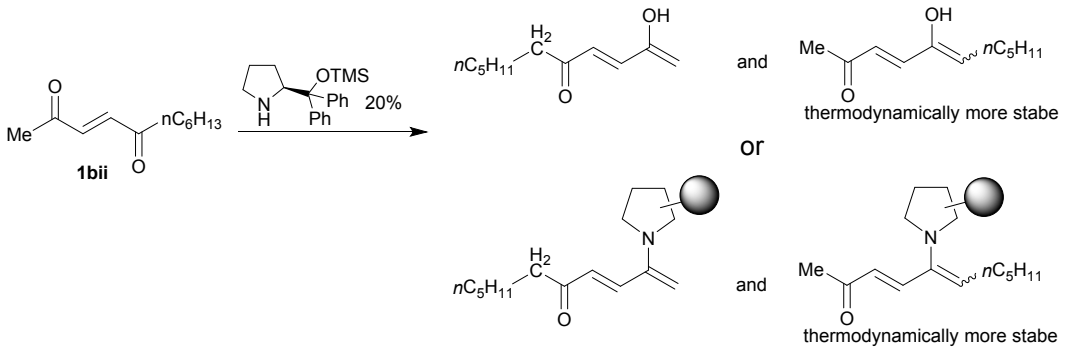
In order to investigate the source of the regioselectivity, we isolated the minor isomer **5a´**. This isomer was dissolved in EtOH/H_2O (9/1, 0.1 M) and the organocatalyst (20 mol%) added. The resulting solution was heated to 50 °C and stirred for 24 h. No formation of isomer **5a** was seen. This result suggests that it is not a reversible process that is responsible for the 9:1 final ratio of the organocatalytic reaction.

(1*R*,2*S*,5*S*)-3-oxo-2-(2-oxooctyl)-5-phenylcyclopentane-1-carbaldehyde (5a´)

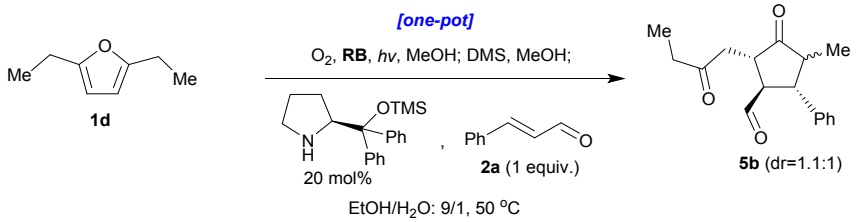


^{1}H NMR (500 MHz, $CDCl_3$): 9.65 (d, *J*=2.2 Hz, 1H), 7.39-7.28 (m, 5H), 3.46 (td, J_1=11.6 Hz, J_2=8.3 Hz, 1H), 3.30 (td, J_1=11.2 Hz, J_2=2.2 Hz, 1H), 3.03 (dd, J_1=18.9 Hz, J_2=5.3 Hz, 1H), 2.91-2.74 (m, 4H), 2.41 (m, 2H), 1.56 (m, 2H), 1.33-1.24 (m, 6H), 0.88 (t, *J*=6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 214.3, 208.8, 201.2, 140.3, 129.1 (2C), 127.6, 127.3 (2C), 60.0, 46.1, 45.7, 42.6 (2C), 40.9, 31.5, 28.7, 23.7, 22.4, 14.0 ppm.

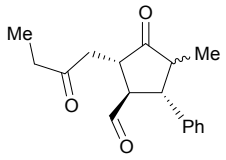
We propose that thermodynamic control explains the regioselectivity seen in the reaction of unsymmetrical enediones, with products of the more stable enolate (or enamine) of the enedione (such as, **1bii)** being favoured. The more thermodynamically stable enolate (or enamine) has a longer lifetime in which to react with the LUMO-lowered enals. Since the reaction conditions favor the thermodynamic outcome, the enediones predominantly react from the more highly substituted methylene position.



Synthesis of cyclopentanone 5b from furan 1d

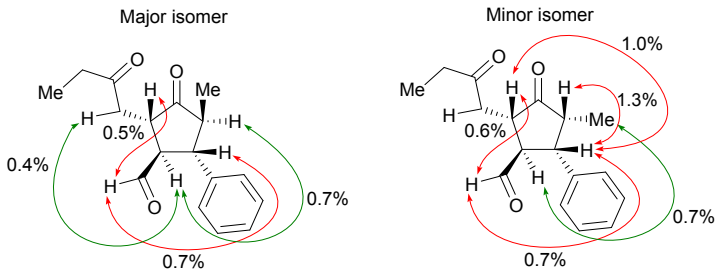


Disubstituted furan **1d** (12.4 mg, 0.1 mmol) was dissolved in methanol (2 mL, 50 mM) containing catalytic amounts of rose Bengal as photosensitizer (0.1 mM). The solution was cooled using an ice bath. Oxygen was gently bubbled through the solution while it was irradiated by a xenon Variac Eimac Cermax 300 W lamp (VIS 385-740 nm) for 2 min. Then the solution was warmed to room temperature and Me_2S (29 μL, 0.4 mmol) was added. After tlc analysis indicated completion of the reduction (45 min), the solvent was replaced with EtOH/H_2O (9/1 v/v, 1 mL). The organocatalyst (6.5 mg, 0.02 mmol, 20 mol%) and enal **2a** (12.6 μL, 0.1 mmol) were added and the solution was warmed to 50 °C and stirred for 24 h. After completion of the reaction (as indicated by ^{1}H-NMR of the crude reaction mixture), the solution was concentrated *in vacuo* to afford **5b** with dr 1.1/1 as determined by the ^{1}H-NMR of the crude reaction mixture. The product **5b** was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 10:1 → 5:1). The dr value for **5b** had changed to 1/2 after the chromatographic purification. Yield = 17.4 mg (64%) of a yellow oil.

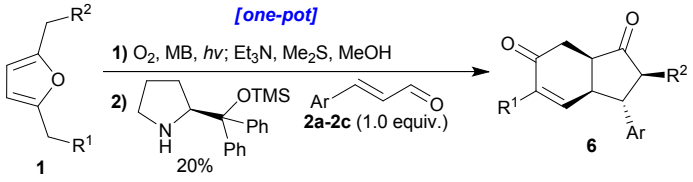


^{1}H NMR (500 MHz, $CDCl_3$): δ 9.68 (d, *J*=2.9 Hz, 1H for minor), 9.60 (d, *J*=2.2 Hz, 1H for major), 7.38-7.27 (m, 5H for major plus 3H for minor), 7.21 (d, *J*=7.2 Hz, 2H for minor), 3.73 (dd, J_1=11.2 Hz, J_2=8.8 Hz, 1H for minor), 3.45 (td, J_1=10.8 Hz, J_2=2.8 Hz, 1H for minor), 3.30 (td, J_1=11.1 Hz, J_2=2.2 Hz, 1H for major), 3.07 (dd, J_1=18.8 Hz, J_2=5.4 Hz, 1H for major), 2.96 (m, 2H for minor), 2.91-2.76 (m, 3H for major plus 2H for minor), 2.69 (ddd, J_1=11.0 Hz, J_2=5.4 Hz, J_3=3.5 Hz, 1H for major), 2.43 (m, 2H for major plus 2H for minor), 1.07 (d, *J*=6.8 Hz, 3H for major), 1.05 (t, *J*=7.3 Hz, 3H for minor), 1.04 (t, *J*=7.3 Hz, 3H for major), 0.84 (d, *J*=7.7 Hz, 3H for minor) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 216.8 (minor), 216.3 (major), 209.1 (major), 208.7 (minor), 201.4 (major), 201.3 (minor), 139.3 (major), 137.2 (minor), 129.0 (2C for major), 128.7 (2C for minor), 128.3 (2C for minor), 127.6 (3C for major), 127.3 (minor), 58.3 (major), 54.8 (minor), 51.3 (major), 51.2 (major), 46.2 (minor), 45.7 (minor), 45.6 (minor), 44.9 (major), 40.7 (major), 40.2 (minor), 35.9 (minor), 35.6 (major), 12.6 (minor), 12.4 (major), 7.6 (minor), 7.5 (major) ppm.

Representative NOEs of the isolated mixture of diastereoisomers



General procedure for the one-pot synthesis of carbocycles of type 6 from disubstituted furans of type 1



1b: R^1 = H, R^2 = nC_5H_{11}
1c: R^1 = H, R^2 = $CH_2CH_2CH{=}CH_2$
1d: R^1 = CH_3, R^2 = CH_3

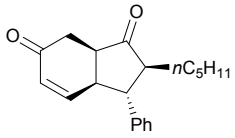
2a: Ar = Ph
2b: Ar = 4-MeO-C_6H_4
2c: Ar = 4-Cl-C_6H_4

Each disubstituted furan of type **1** (0.1 mmol, 16.6 mg for **1b**, 15 mg for **1c**, 12.4 mg for **1d**) was dissolved in methanol (2 mL, 50 mM) containing catalytic amounts of methylene blue as photosensitizer (0.1 mM). The solution was cooled using an ice bath. Oxygen was gently bubbled through the solution while it was irradiated by a xenon Variac Eimac Cermax 300 W lamp (VIS 385-740 nm) for 2 min. Then the solution was warmed to room temperature and a small amount of Et_3N (0.0035 mmol, 3.5% mol, 0.5 μL) followed by Me_2S (29 μL, 0.4 mmol) were added. After tlc analysis indicated completion of the reduction (45 min), the solvent was replaced with EtOH/H_2O (9/1 v/v, 1 mL). The organocatalyst (6.5 mg, 0.02 mmol, 20% mol) and the corresponding enal (0.1 mmol, 12.6 μL of **2a**, or 16.2 mg of **2b**, or 16.7 mg of **2c**) were added and the solution was warmed to 50 °C and stirred for 24 h. After completion of the reaction (as indicated by ^{1}H-NMR of the crude reaction mixture), the solvent was concentrated *in vacuo* and DCE (1 mL) was added. p-Toluenesulfonic acid (PTSA·H_2O, 13.3 mg, 0.07 mmol) was added, the mixture was then warmed to 70 °C and stirred for 8 h. After completion of the final step (as indicated by tlc analysis), the solvent was removed under reduced pressure and the products of type **6** were purified by flash column chromatography (silica gel, petroleum ether:EtOAc). All the dr values were measured using the ^{1}H-NMR data for the crude reaction mixture.

When the same protocol was scaled up to 1 mmol of furan **1b** and enal **2a** (1 mmol), the results were identical.

Racemic mixtures of all the compounds were prepared according to the general experimental procedure described above using a mixture of 10 mol% of (*S*)-(-)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (3.2 mg, 0.01 mmol) and 10 mol% of (*R*)-(-)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (3.2 mg, 0.01 mmol) as the organocatalyst.

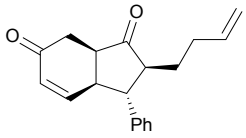
(2*S*,3*R*,3a*R*,7a*R*)-2-pentyl-3-phenyl-3,3a,7,7a-tetrahydro-1H-indene-1,6(2H)-dione (6a)



The product was prepared according to the general experimental procedure described above to furnish products with a dr 13/1 (separable). The crude residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 10:1 → 5:1) to furnish **6a** as a yellow oil (18.6 mg, 63%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (t, *J*=7.4 Hz, 2H), 7.33-7.28 (m, 3H), 6.67 (dd, J_1=10.2 Hz, J_2=4.5 Hz, 1H), 6.01 (d, *J*=10.2 Hz, 1H), 3.22-3.04 (m, 3H), 2.69 (m, 1H), 2.63 (dd, J_1=16.8 Hz, J_2=7.1 Hz, 1H), 2.46 (dd, J_1=16.8 Hz, J_2=12.6 Hz, 1H), 1.62 (m, 1H), 1.51 (m, 1H), 1.31-1.23 (m, 2H), 1.21-1.10 (m, 4H), 0.78 (t, *J*=6.9 Hz, 3H), ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 216.1, 195.8, 148.0, 140.1, 129.2, 129.0 (2C), 127.6, 127.2 (2C), 57.5, 51.8, 45.8, 42.6, 33.8, 31.7, 28.2, 26.3, 22.3, 13.9 ppm; HRMS (OrbitrapESI): calcd for $C_{20}H_{25}O_2$: 297.1849 $[M+H]^+$; found: 297.1848; $[a]_D^{25}$= +132 (*c* 1.0, MeOH); HPLC (DAICEL Chiralpak AS-H, *n*-hexane/2-propanol = 70/30, flow = 0.5 mL/min, detection at 254 nm, retention time = 26.3 min (major), 35.2 min (minor) ee = 99%.

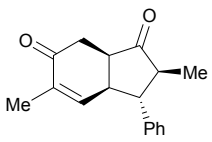
(2*S*,3*R*,3a*R*,7a*R*)-2-(but-3-en-1-yl)-3-phenyl-3,3a,7,7a-tetrahydro-1H-indene-1,6(2H)-dione (6b)



The product was prepared according to the general experimental procedure described above to furnish products with a dr 13/1 (separable). The crude residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 10:1 → 3:1) to furnish **6a** as a yellow oil (18.2 mg, 65%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (t, *J*=7.4 Hz, 2H), 7.34-7.29 (m, 3H), 6.66 (dd, J_1=10.3 Hz, J_2=4.4 Hz, 1H), 6.02 (d, *J*=10.3 Hz, 1H), 5.63 (ddt, J_1=17.1 Hz, J_2=10.4 Hz, J_3=6.5 Hz, 1H), 4.90 (m, 1H), 4.84 (dq, J_1=17.1 Hz, J_2=1.6 Hz, 1H), 3.20 (m, 1H), 3.14-3.04 (m, 2H), 2.72 (m, 1H), 2.65 (dd, J_1=16.9 Hz, J_2=7.2 Hz, 1H), 2.47 (dd, J_1=16.9 Hz, J_2=12.6 Hz, 1H), 1.99 (m, 2H), 1.80 (m, 1H), 1.59 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 215.9, 195.8, 147.8, 139.8, 137.6, 129.3, 129.1 (2C), 127.7, 127.2 (2C), 115.4, 56.5, 52.2, 45.7, 42.7, 34.0, 30.8, 27.7 ppm; HRMS (OrbitrapESI): calcd for $C_{19}H_{21}O_2$: 281.1536 $[M+H]^+$; found: 281.1535; $[a]_D^{25}$= +108 (*c* 0.5, MeOH); HPLC (DAICEL Chiralpak AS-H, *n*-hexane/2-propanol = 60/40, flow = 0.7 mL/min, detection at 254 nm, retention time = 20.9 min (major), 32 min (minor) ee = 99%.

(2*S*,3*R*,3a*R*,7a*R*)-2,5-dimethyl-3-phenyl-3,3a,7,7a-tetrahydro-1H-indene-1,6(2H)-dione (6c)

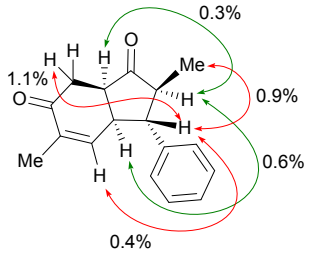


The product was prepared according to the general experimental procedure described above to furnish products with a dr 13/1 (separable). The crude residue was purified by flash column

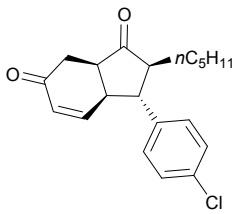
chromatography (silica gel, petroleum ether:EtOAc = 10:1 → 5:1) to furnish **6c** as a yellow oil (12.7 mg, 50%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (t, *J*=7.4 Hz, 2H), 7.34-7.29 (m, 3H), 6.42 (m, 1H), 3.22 (m, 1H), 3.11 (m, 1H), 2.93 (t, *J*=11.3 Hz, 1H), 2.68 (dd, J_1=16.6 Hz, J_2=7.3 Hz, 1H), 2.62 (m, 1H), 2.45 (dd, J_1=16.6 Hz, J_2=13.1 Hz, 1H), 1.76 (t, *J*=1.4 Hz, 3H), 1.09 (d *J*=6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 216.4, 196.2, 142.4, 139.6, 135.6, 129.1 (2C), 127.6, 127.3 (2C), 54.2, 53.3, 45.8, 42.2, 34.4, 16.1, 12.7 ppm; HRMS (OrbitrapESI): calcd for $C_{17}H_{19}O_2$: 255.1380 $[M+H]^+$; found: 255.1385; $[a]_D^{26}$= +112 (*c* 1.0, MeOH), HPLC (DAICEL Chiralpak AS-H, *n*-hexane/2-propanol = 60/40, flow = 0.5 mL/min, detection at 254 nm, retention time = 19.6 min (major), 21.7 min (minor) ee = 96%.

Representative NOEs



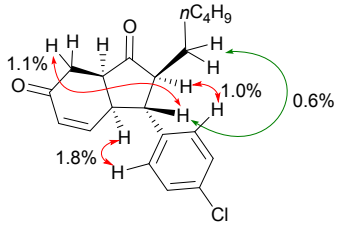
(2*S*,3*R*,3a*R*,7a*R*)-3-(4-chlorophenyl)-2-pentyl-3,3a,7,7a-tetrahydro-1H-indene-1,6(2H)-dione (6d)



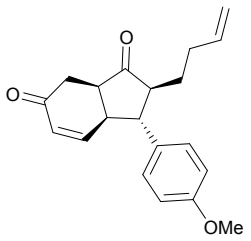
The product was prepared according to the general experimental procedure described above to furnish products with a dr 10/1 (separable). The crude residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 10:1 → 3:1) to furnish **6d** as a yellow oil (14.8 mg, 45%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, *J*=8.4 Hz, 2H), 7.24 (d, *J*=8.4 Hz, 2H), 6.64 (dd, J_1=10.2 Hz, J_2=4.7 Hz, 1H), 6.02 (dd, J_1=10.2 Hz, J_2=0.8 Hz, 1H), 3.19 (m, 1H), 3.10 (t, *J*=10.9 Hz, 1H), 3.01 (m, 1H), 2.64 (m, 2H), 2.44 (dd, J_1=16.8 Hz, J_2=12.8 Hz, 1H), 1.61 (m, 1H), 1.51 (m, 1H), 1.24-1.08 (m, 6H), 0.80 (t, *J*=7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 215.4, 195.5, 147.3, 138.6, 133.4, 129.5, 129.3 (2C), 128.5 (2C), 57.5, 51.3, 45.8, 42.6, 33.8, 31.7, 28.2, 26.4, 22.3, 13.9 ppm; HRMS (OrbitrapESI): calcd for $C_{20}H_{24}ClO_2$: 331.1459 $[M+H]^+$; found: 331.1457; $[a]_D^{26}$= +216 (*c* 0.5, MeOH), HPLC (DAICEL Chiralpak AS-H, *n*-hexane/2-propanol = 70/30, flow = 0.5 mL/min, detection at 254 nm, retention time = 27.9 min (major), 66.6 min (minor) ee = 99%.

Representative NOEs



(2*S*,3*R*,3a*R*,7a*R*)-2-(but-3-en-1-yl)-3-(4-methoxyphenyl)-3,3a,7,7a-tetrahydro-1H-indene-1,6(2H)-dione (6e)



The product was prepared according to the general experimental procedure described above to furnish products with a dr 13/1 (separable). The crude residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 10:1 → 3:1) to furnish **6e** as a yellow oil (13 mg, 42%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, *J*=8.4 Hz, 2H), 6.93 (d, *J*=8.4 Hz, 2H), 6.67 (dd, J_1=10.3 Hz, J_2=4.4 Hz, 1H), 6.01 (d, *J*=10.3 Hz, 1H), 5.64 (ddt, J_1=17.0 Hz, J_2=10.3 Hz, J_3=6.6 Hz, 1H), 4.90 (d, *J*=10.3 Hz, 1H), 4.86 (m, 1H), 3.83 (s, 3H), 3.18 (m, 1H), 3.05 (m, 2H), 2.65 (m, 2H), 2.44 (dd, J_1=16.8 Hz, J_2=12.8 Hz, 1H), 1.99 (m, 2H), 1.78 (m, 1H), 1.57 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 216.0, 195.8, 159.0, 148.0, 137.6, 131.6, 129.2, 128.2 (2C), 115.4, 114.4 (2C), 56.6, 55.3, 51.5, 45.7, 42.9, 34.0, 30.8, 27.6 ppm; HRMS (OrbitrapESI): calcd for $C_{20}H_{23}O_3$: 311.1642 $[M+H]^+$; found: 311.1642; $[a]_D^{26}$= +120 (*c* 0.2, MeOH); HPLC (Chiralcel OD, *n*-hexane/2-propanol = 70/30, flow = 0.6 mL/min, detection at 254 nm, retention time = 21.8 min (major), 27.7 min (minor) ee = 99%.

Reactor Set-up

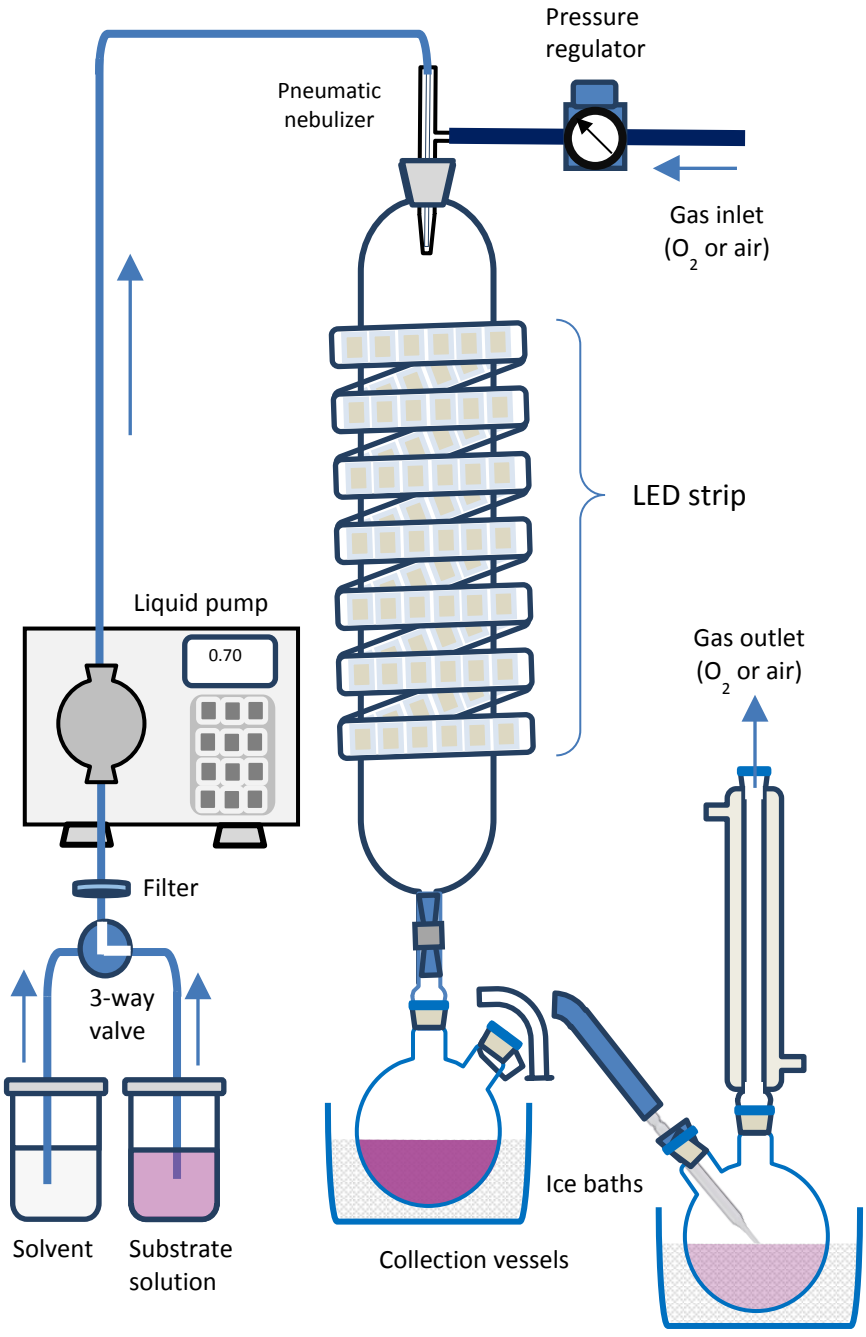
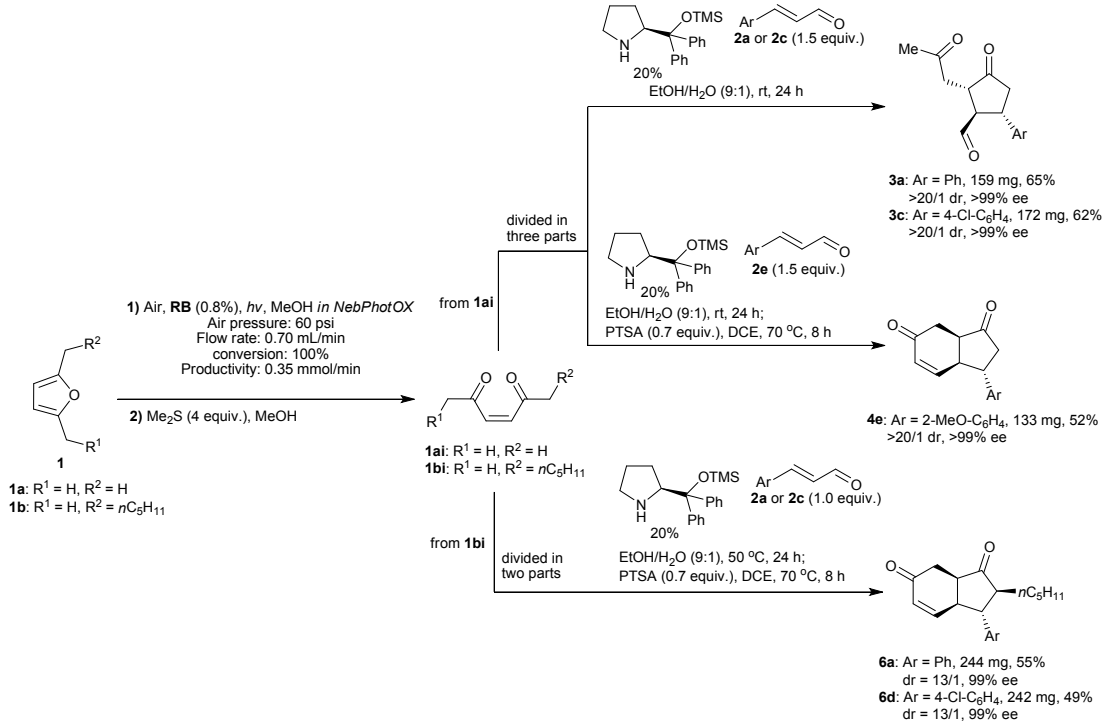


Figure 1. Schematic representation of NebPhotOX continuous flow reactor set-up. The vertical cylinder has 33 cm length and 6.7 cm diameter.

Figure 2. NebPhotOX in action.

SAFETY CAUTION: Measures were taken to eliminate all possible ignition sources from the fumehood area (sparks or flames; for example, the transformer for the LEDs was kept outside the fumehood) in which the NebPhotOX system was operated. The photoreactor operates at room temperature and pressure conditions without any significant heat input from the low power LEDs used. In addition, the fumehood was always adequately ventilated with a high air flow. System operating conditions prevented oxygen stagnation in the system. Additional cautions included the operator wearing safety glasses with side shields and flame resistant safety clothing. The two cooled collection flasks placed in series were prefilled with excess of Me_2S in MeOH (3 equiv in the first flask and 1 equiv in the second flask) for the fast reduction of the hydroperoxides. Even higher excesses of the reducing agent can be used.

General procedure for the synthesis of enantioenriched products of type 3, 4 and 6 from disubstituted furans of type 1 using a continuous flow photoreactor for the photoxygenation step.



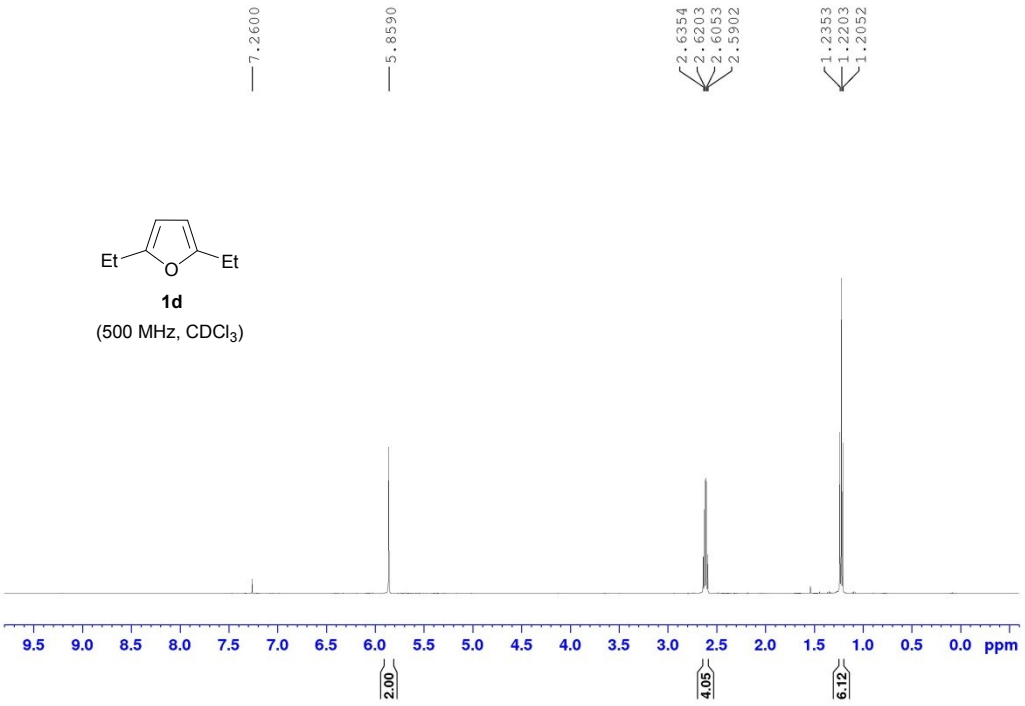
2-Substituted furans of type **1** (3 mmol, 324 μL for **1a**, 498 mg for **1b**) and rose Bengal (0.8 mol%, 24.4 mg) were dissolved in MeOH (total volume 6 mL, 0.5 M). The resulting solutions were transferred to the nebulizer via a liquid pump (flow rate set at 0.7 mL per min) and timing was initiated so that the exact flow rate could be calculated. The solutions were dispersed by the nebulizer into the reaction cylinder which was placed in vertical position using air as nebulizing gas (60 psi backpressure). The cylinder was irradiated by the LED jacket (natural white light 3800–4200 K, 10 W m^{-1}, 1050 Lm m^{-1}). When all the solution had been dispersed (8.6 min, flow rate: 0.70 mL per min, conversion 100%, productivity: 0.35 mmol per min), the timing was stopped and the three-way valve on the uptake line was switched to pure MeOH (3 mL) to flush out the system. The crude solutions were collected in the two cooled spherical flasks placed in series. The two flasks had been pre-charged with Me_2S (9 mmol, 656 μL for the first and 3 mmol, 219 μL for the second) for the rapid reduction of the hydroperoxides formed. The solutions from the two flasks were combined and stirred for a further 45 min, until tlc analysis indicated completion of the reduction. Then the crude solution was concentrated *in vacuo* for the measurement of the conversions by ^{1}H NMR.

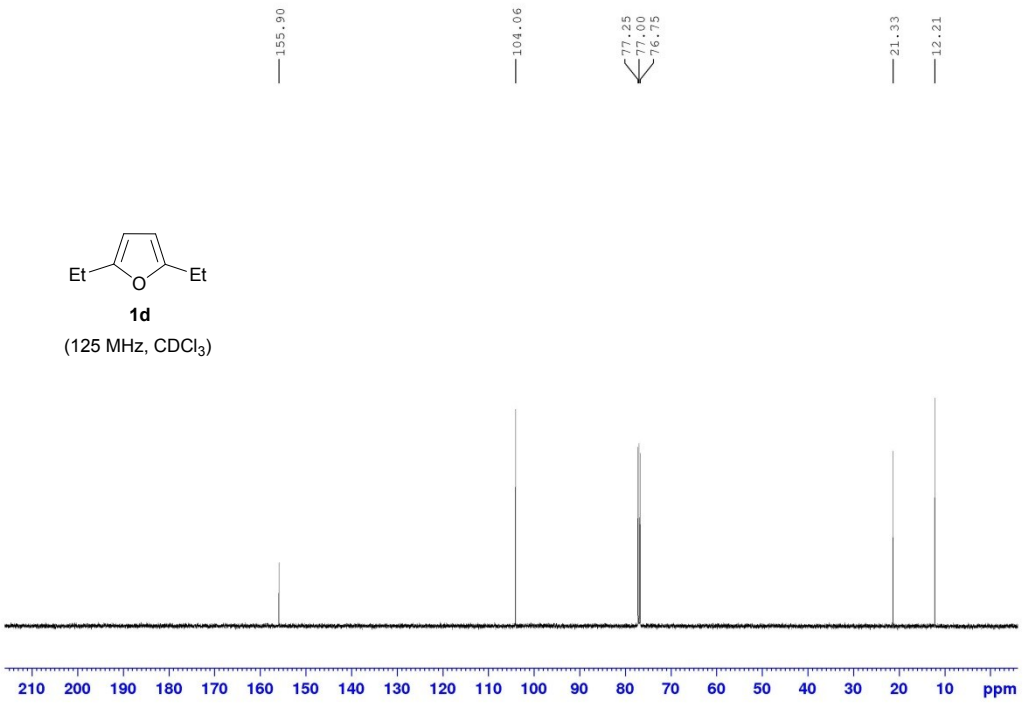
In the case of the cis-enedione **1ai**, the crude reaction mixture was dissolved in EtOH/H_2O (9/1 v/v, 30 mL) and the resulting solution was divided into three equal parts (10 mL each). In each part the corresponding enal (1.5 mmol, 189 μL for **2a**, 250 mg for **2c**, 243 mg for **2e**) followed by the organocatalyst (65 mg, 0.2 mmol) were added. The solution was stirred at room temperature for 24 h. In the synthesis of

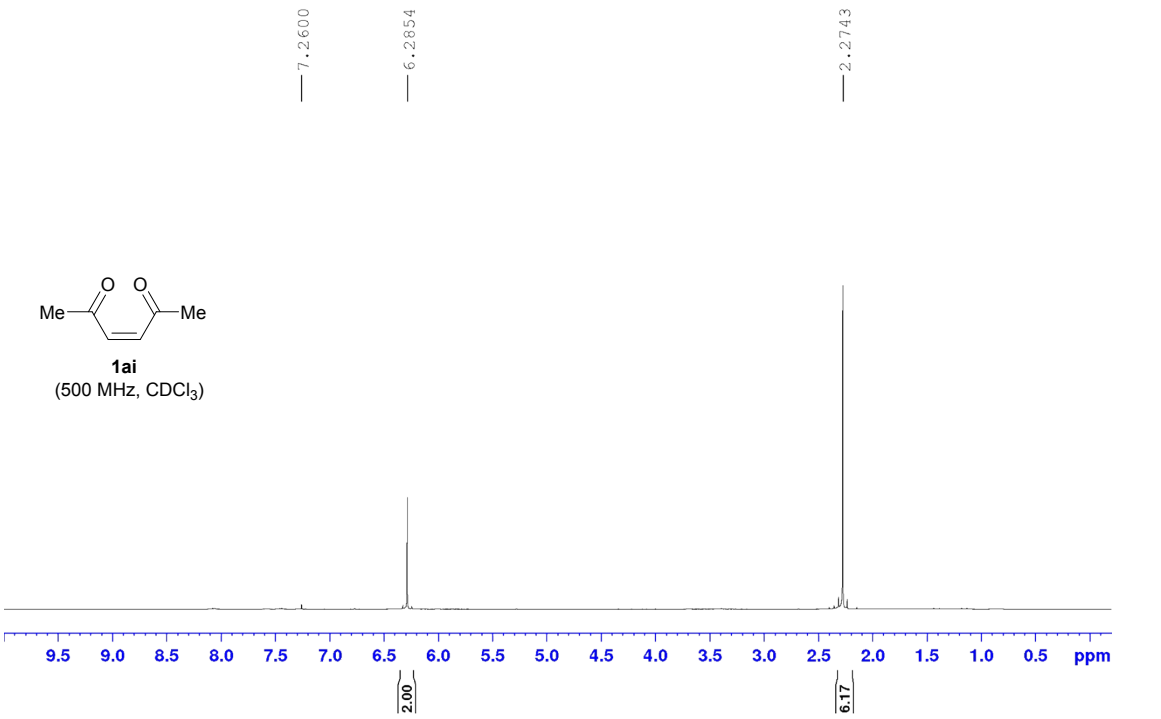
cyclopentanones **3a** and **3c**, the solution was concentrated *in vacuo* and the products were purified by flash column chromatography (silica gel, petroleum ether : EtOAc). Yield: for **3a** = 159 mg (65%) and for **3c** = 172 mg (62%). In the synthesis of carbocycle **4e**, after the formation of the intermediate **3e**, the solvent was replaced by DCE (10 mL) and p-toluenesulfonic acid (PTSA·H_2O, 133 mg, 0.7 mmol) was added. The mixture was warmed to 70 ^oC and stirred for 8 h. After the final step was complete (as indicated by tlc analysis), the solvent was removed under reduced pressure and the product **4e** was purified by flash column chromatography (silica gel, petroleum ether:EtOAc). Yield = 133 mg (52%).

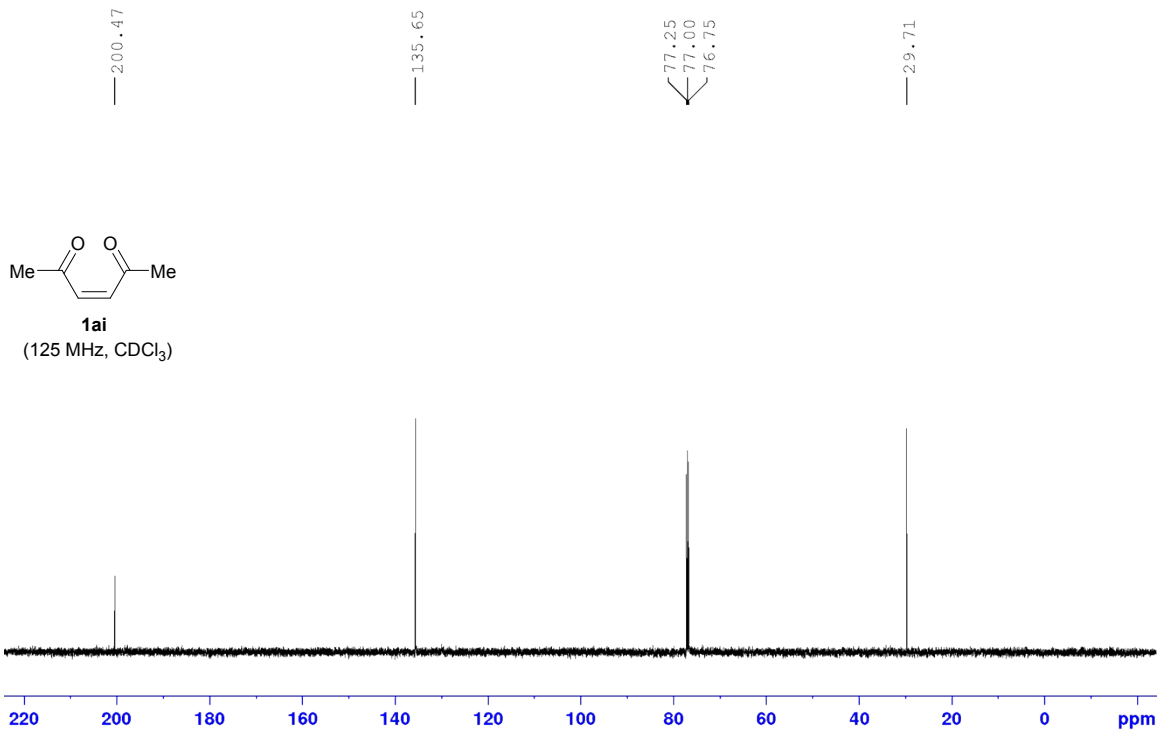
In case of the cis-enedione **1bi**, the crude reaction mixture was dissolved in EtOH/H_2O (9/1 v/v, 30 mL) and the resulting solution was divided into three equal parts (15 mL each). In each part the corresponding enal (1.5 mmol, 189 μL for **2a**, 250 mg for **2c**) followed by the organocatalyst (98 mg, 0.3 mmol) were added. The solution was warmed to 50 ^oC and stirred for 24 h. After that the solvent was replaced by DCE (15 mL) and p-toluenesulfonic acid (PTSA·H_2O, 200 mg, 0.7 mmol) was added. The mixture was warmed to 70 ^oC and stirred for 8 h. After the final step was complete (as indicated by tlc analysis), the solvent was removed under reduced pressure and the products of type **6** were purified by flash column chromatography (silica gel, petroleum ether:EtOAc).Yield: for **6a** = 244 mg (55%) and for **6d** = 242 mg (49%).

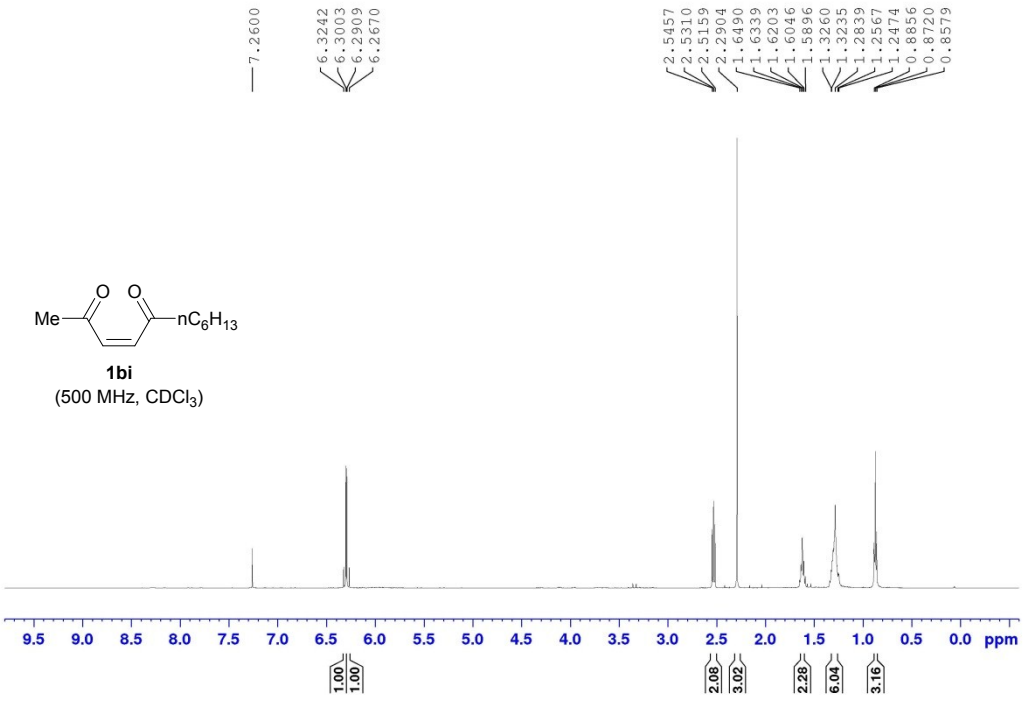
Part B: Copies of ^{1}H-NMR, ^{13}C-NMR, COSY, HMBC and NOE spectra

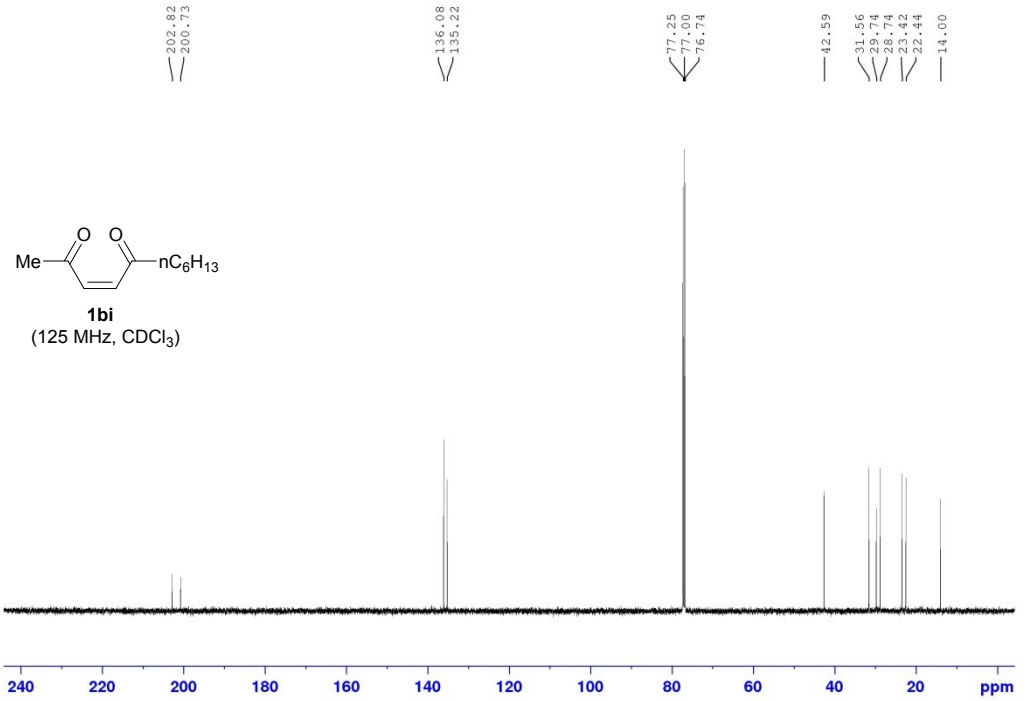


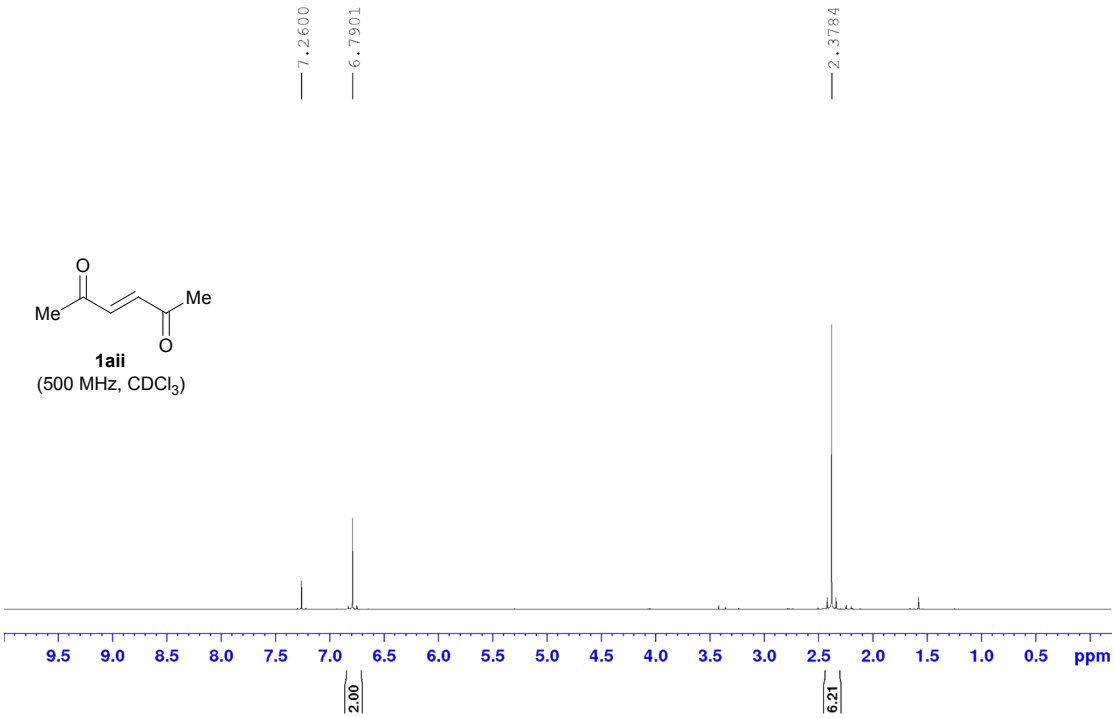


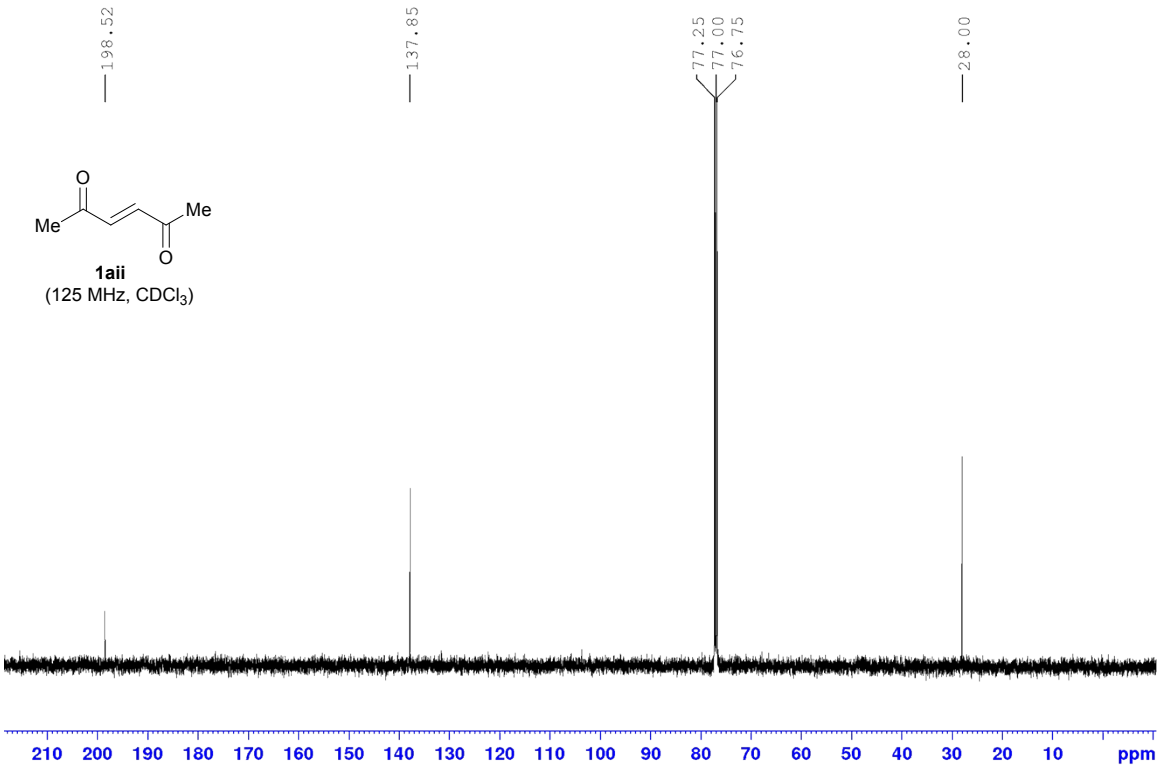

7.2600
6.2854
2.2743
Me
O
O
Me
1ai
(500 MHz, CDCl3)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.00
6.17

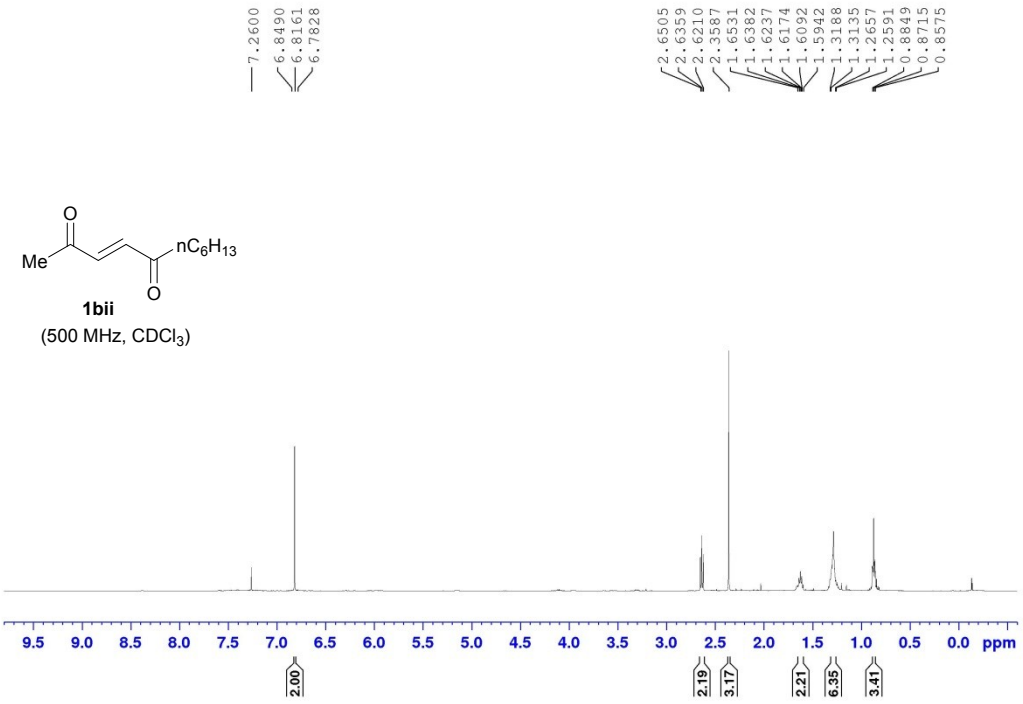

200.47
135.65
77.25
77.00
76.75
29.71
Me
O
O
Me
1ai
(125 MHz, CDCl3)
220 200 180 160 140 120 100 80 60 40 20 0 ppm


7.2600
6.3242
6.3003
6.2909
6.2670
2.5457
2.5310
2.5159
2.2904
1.6490
1.6339
1.6203
1.6046
1.5896
1.3260
1.3235
1.2839
1.2567
1.2474
0.8856
0.8720
0.8579
Me
nC6H13
1bi
(500 MHz, CDCl3)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00
1.00
2.08
3.02
2.28
6.04
3.16

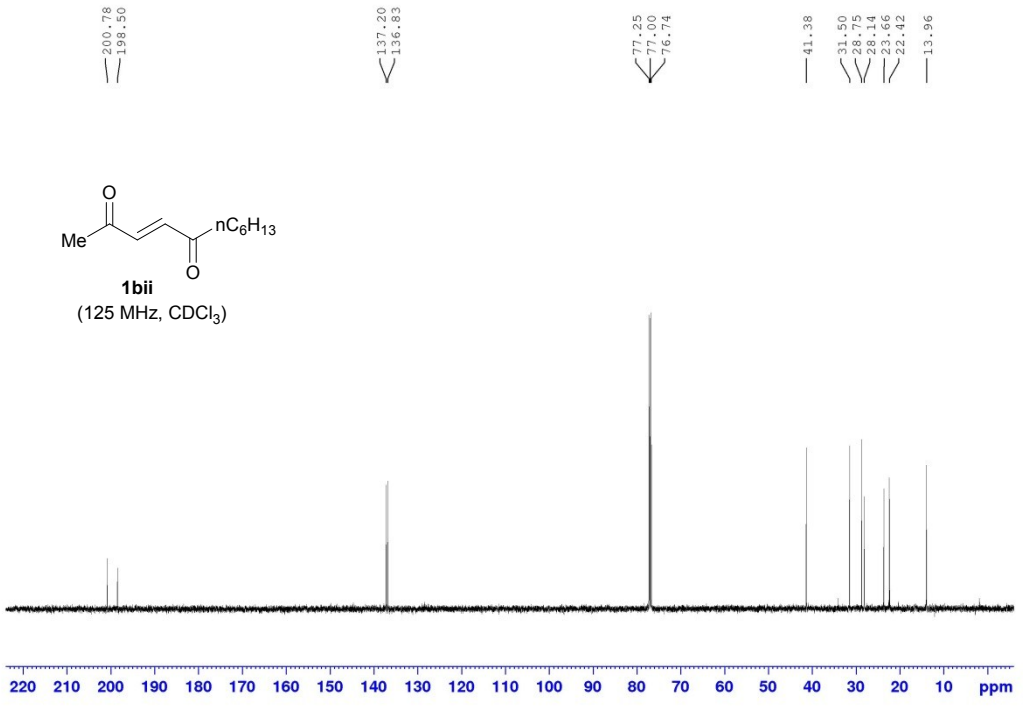

202.82
200.73
136.08
135.22
77.25
77.00
76.74
42.59
31.56
29.74
28.74
23.42
22.44
14.00
Me
nC6H13
1bi
(125 MHz, CDCl3)
240 220 200 180 160 140 120 100 80 60 40 20 ppm


7.2600
6.7901
2.3784
O
Me
Me
O
1aii
(500 MHz, CDCl3)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.00
6.21

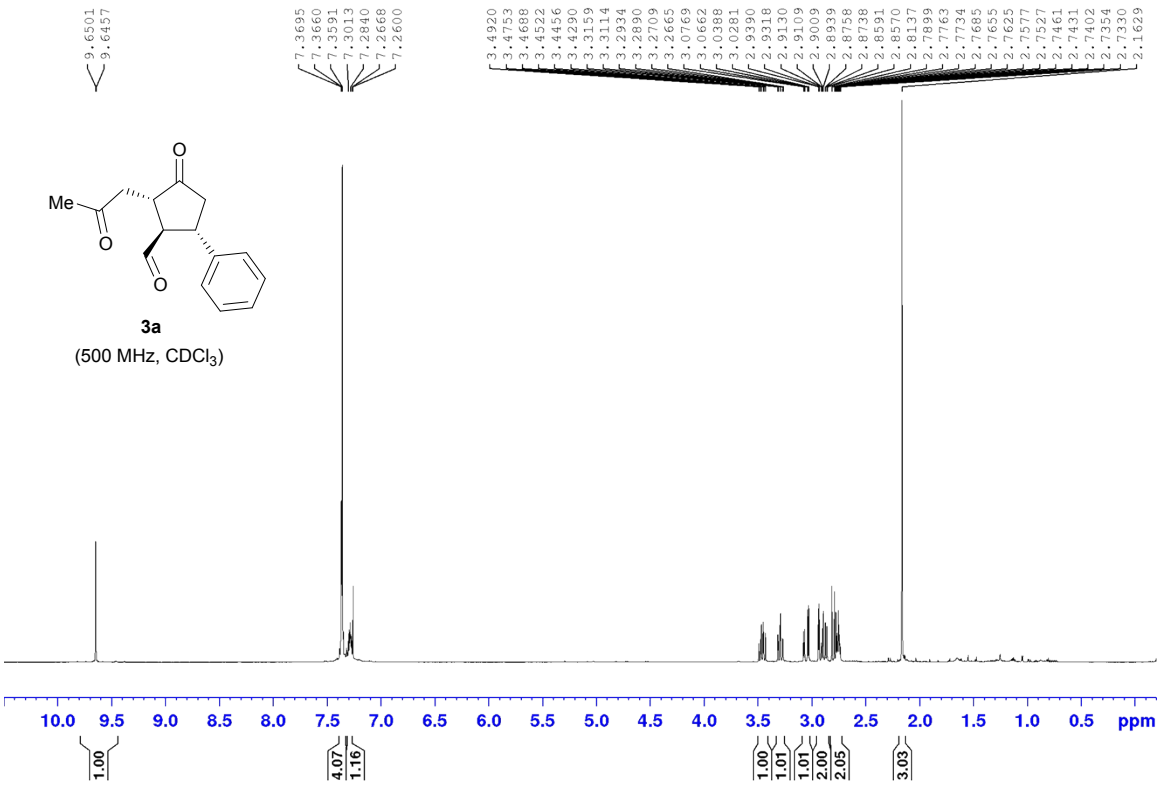

198.52
137.85
77.25
77.00
76.75
28.00
O
Me
Me
O
1aii
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

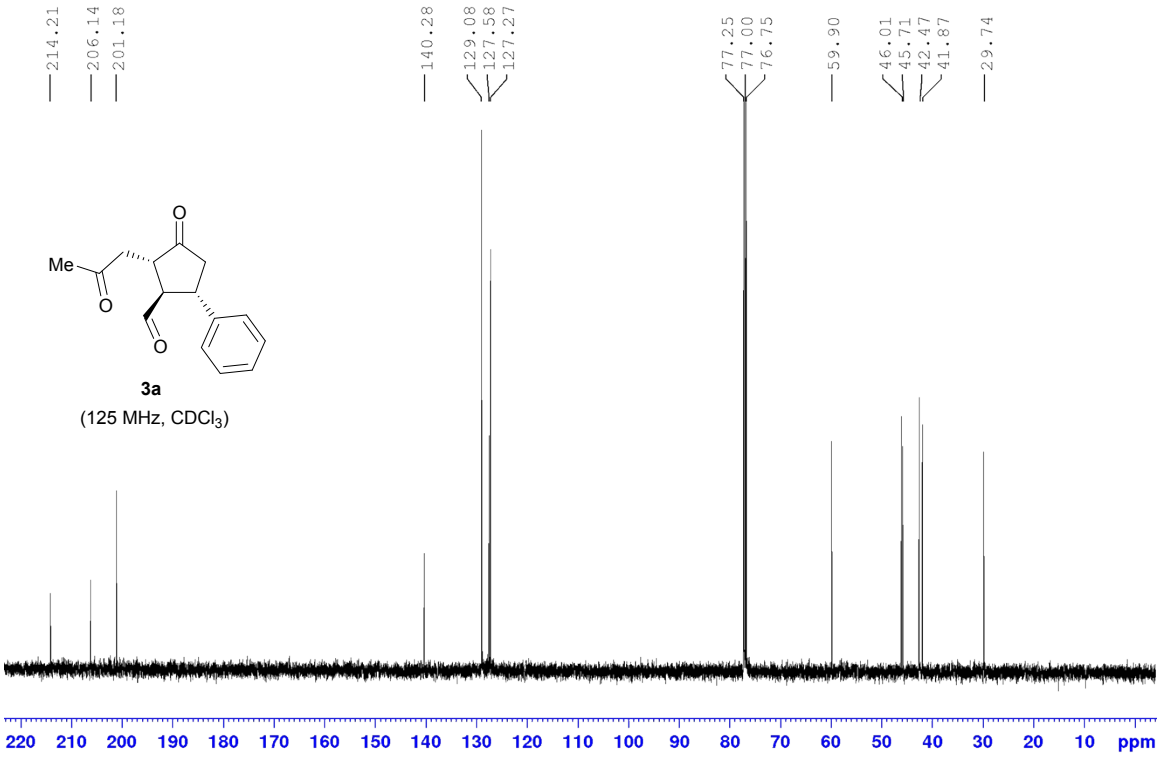


1bii
(500 MHz, $CDCl_3$)

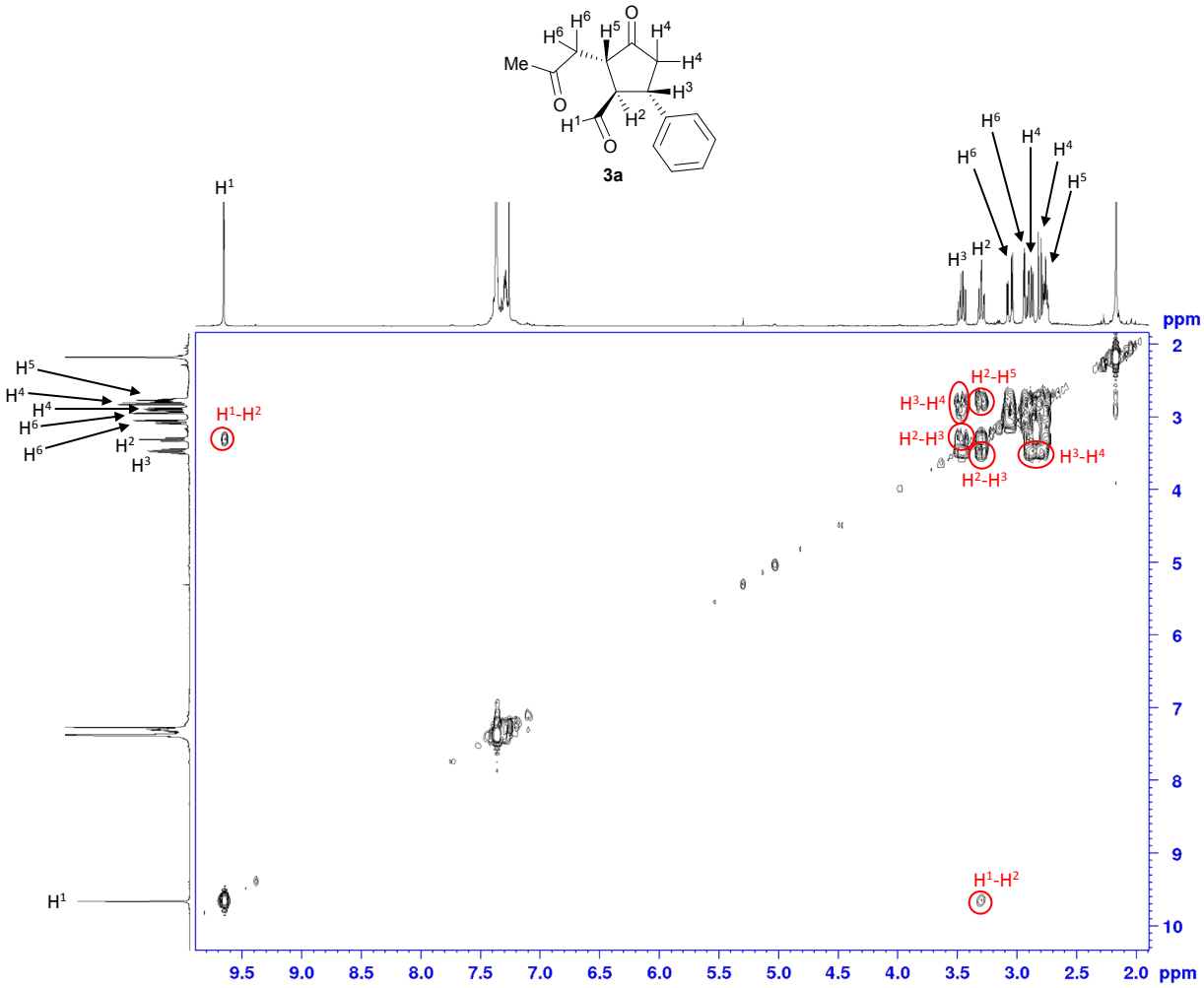


1bii
(125 MHz, $CDCl_3$)

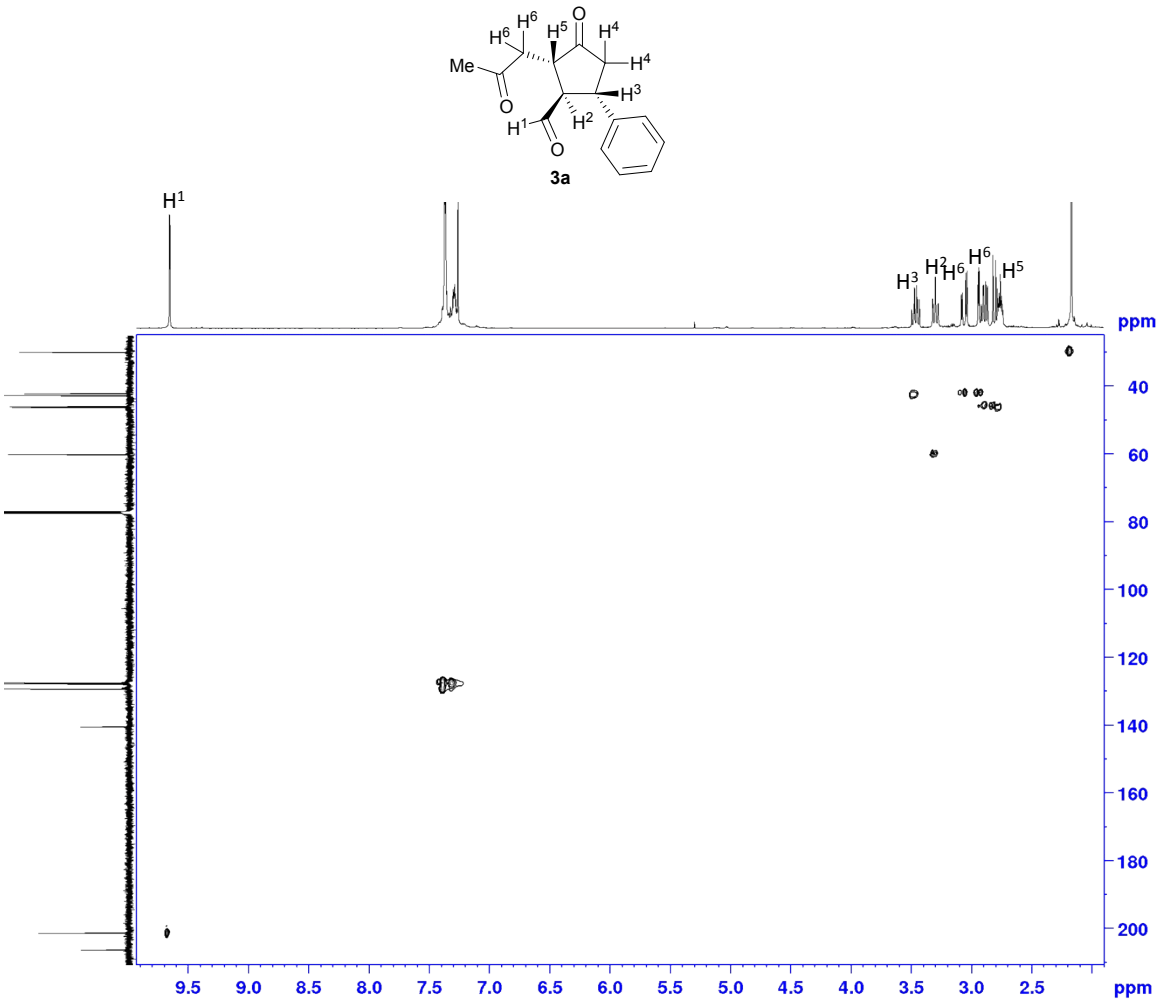

9.6501
9.6457
7.3695
7.3660
7.3591
7.3013
7.2840
7.2668
7.2600
3.4920
3.4753
3.4688
3.4522
3.4456
3.4290
3.3159
3.3114
3.2934
3.2890
3.2709
3.2665
3.0769
3.0662
3.0388
3.0281
2.9390
2.9318
2.9130
2.9109
2.9009
2.8939
2.8758
2.8738
2.8591
2.8570
2.8137
2.7899
2.7763
2.7734
2.7685
2.7655
2.7625
2.7577
2.7527
2.7461
2.7431
2.7402
2.7354
2.7330
2.1629
Me
O
O
O
3a
(500 MHz, CDCl3)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
4.07
1.16
1.00
1.01
1.01
2.00
2.05
3.03


214.21
206.14
201.18
140.28
129.08
127.58
127.27
77.25
77.00
76.75
59.90
46.01
45.71
42.47
41.87
29.74
Me
O
O
O
3a
(125 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

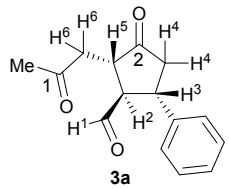
COSY correlations of compound 3a



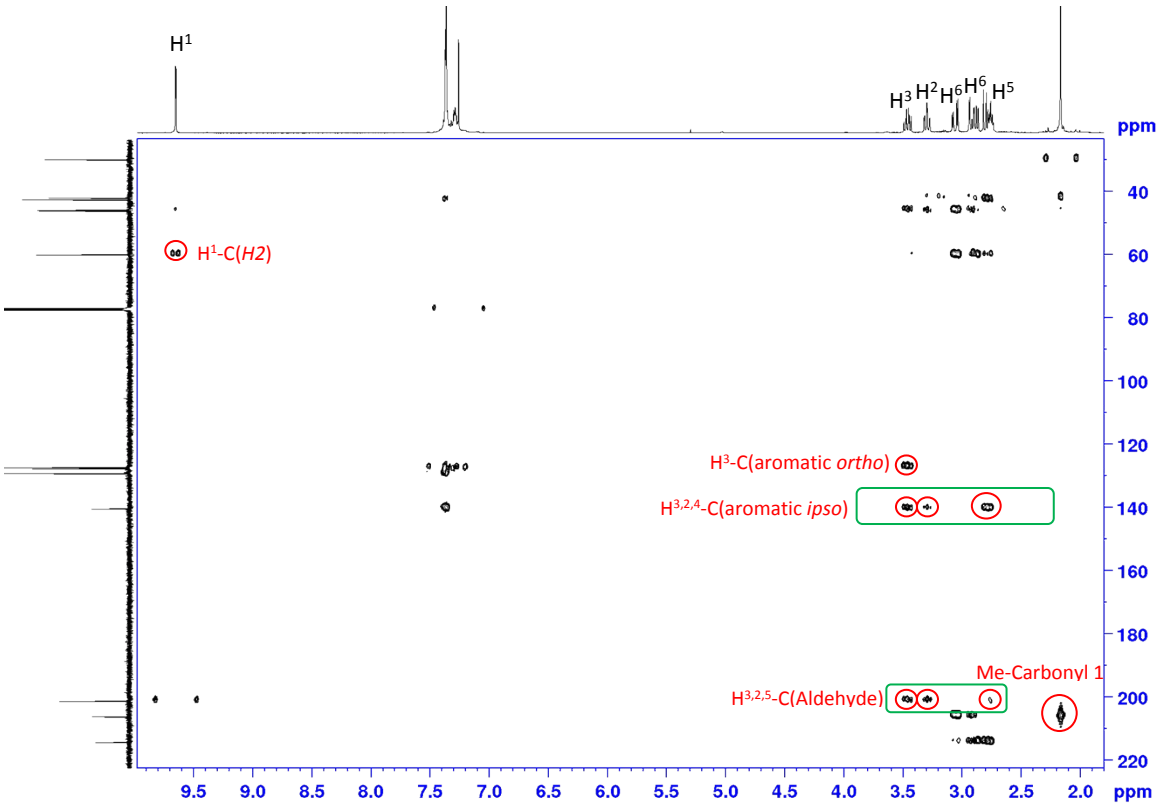
HSQC correlations of compound 3a



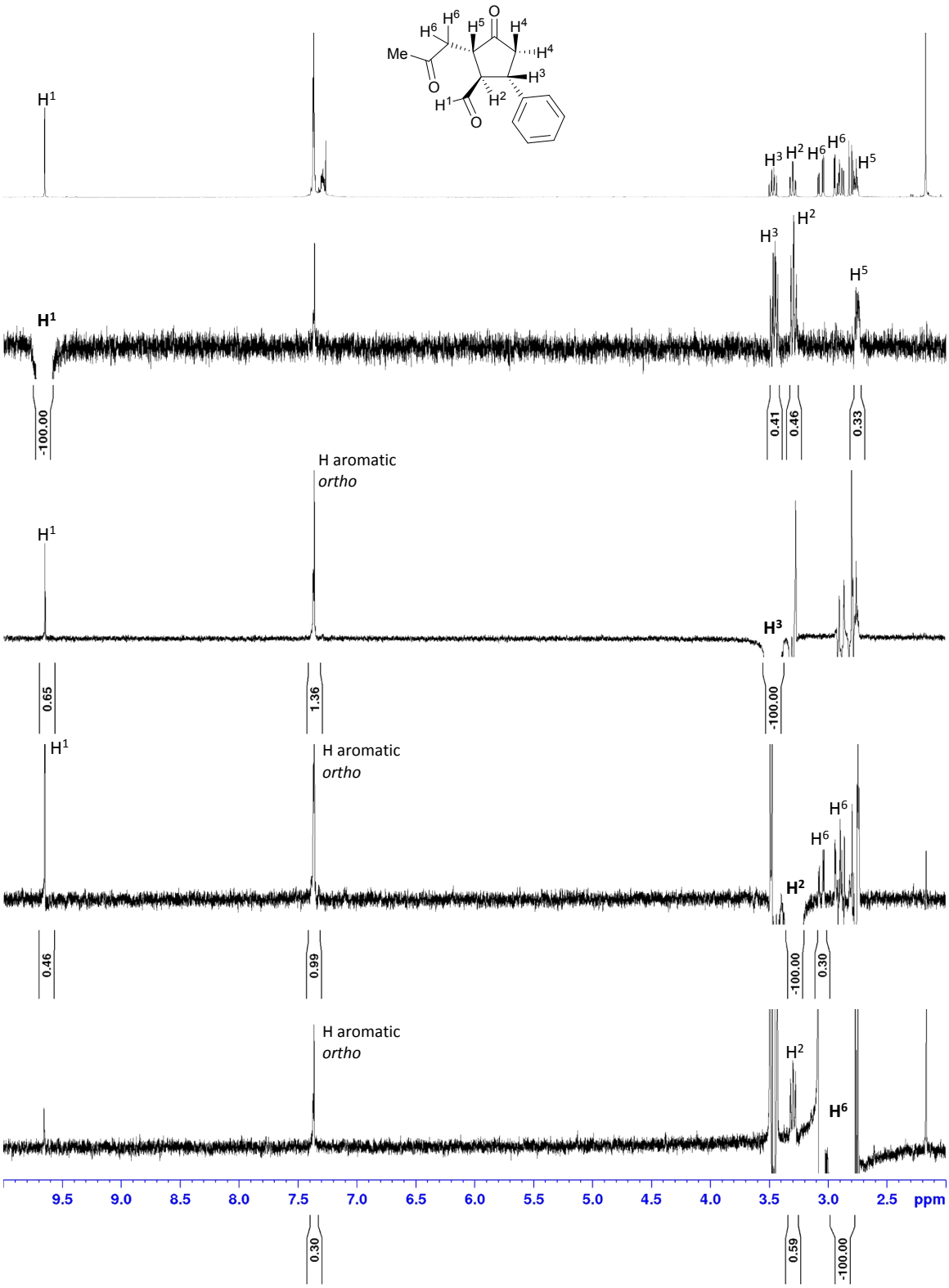
HMBC correlations of compound 3a

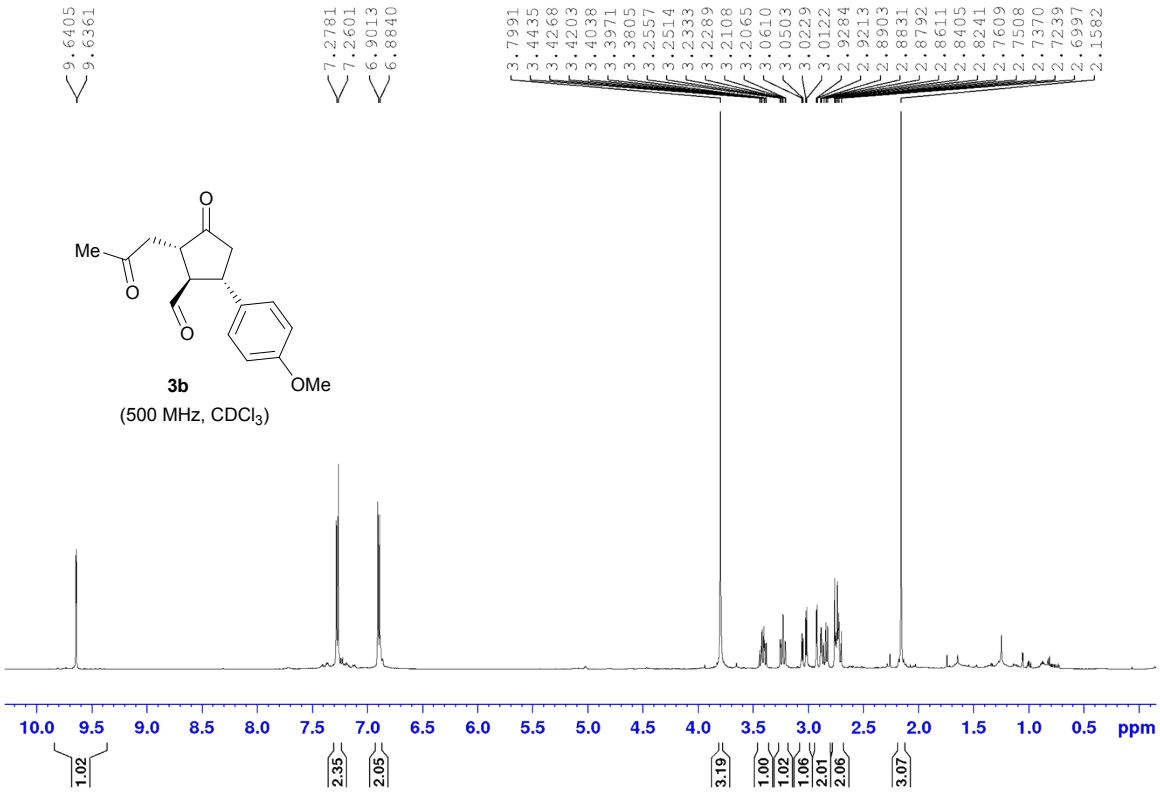


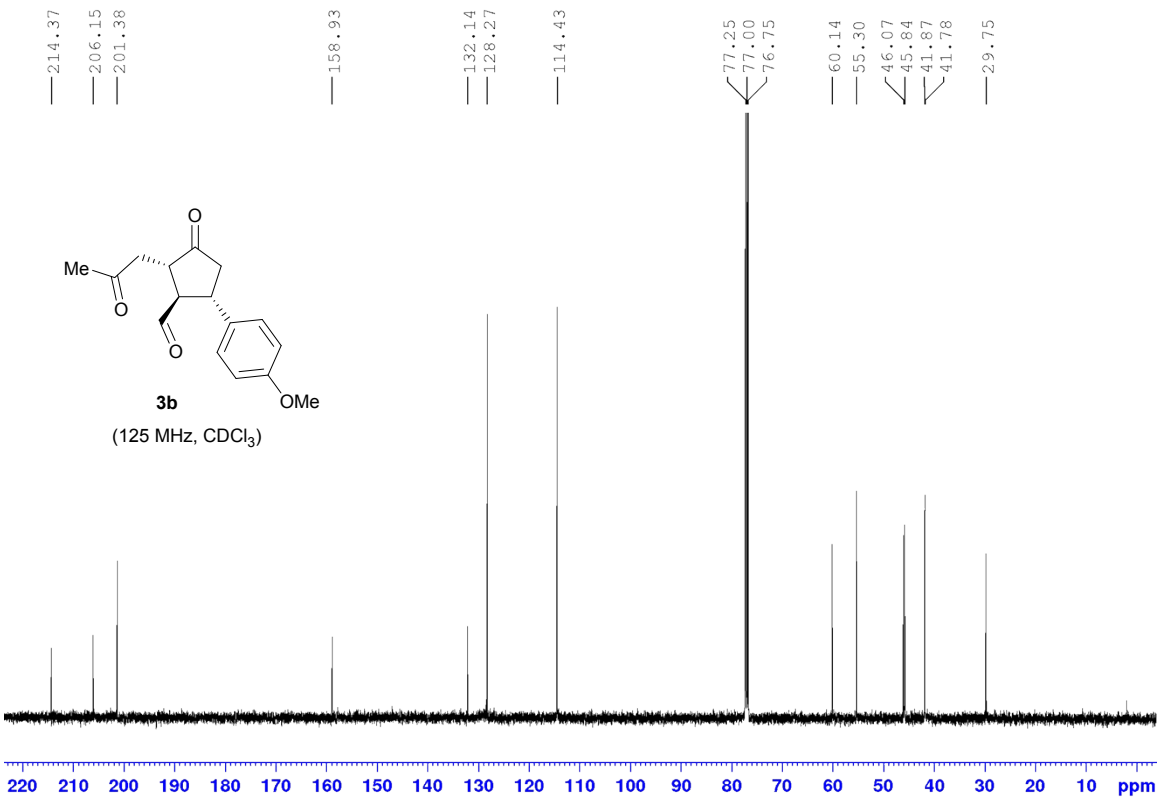
3a

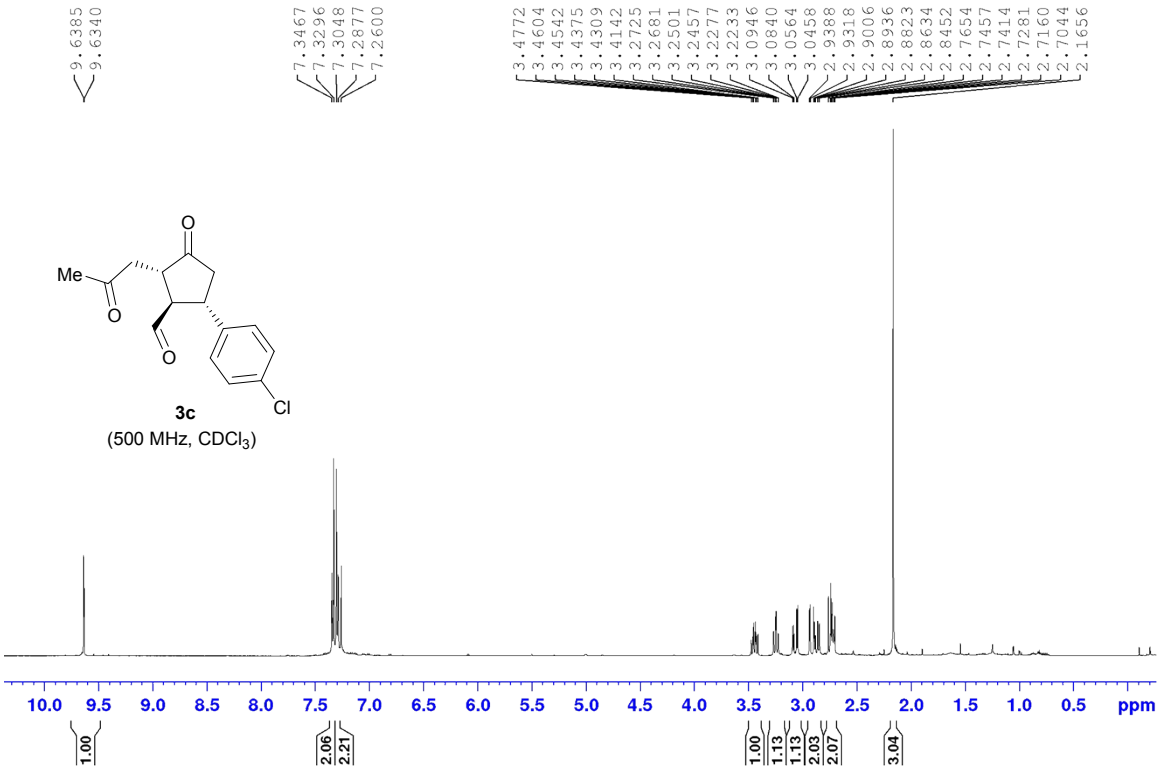


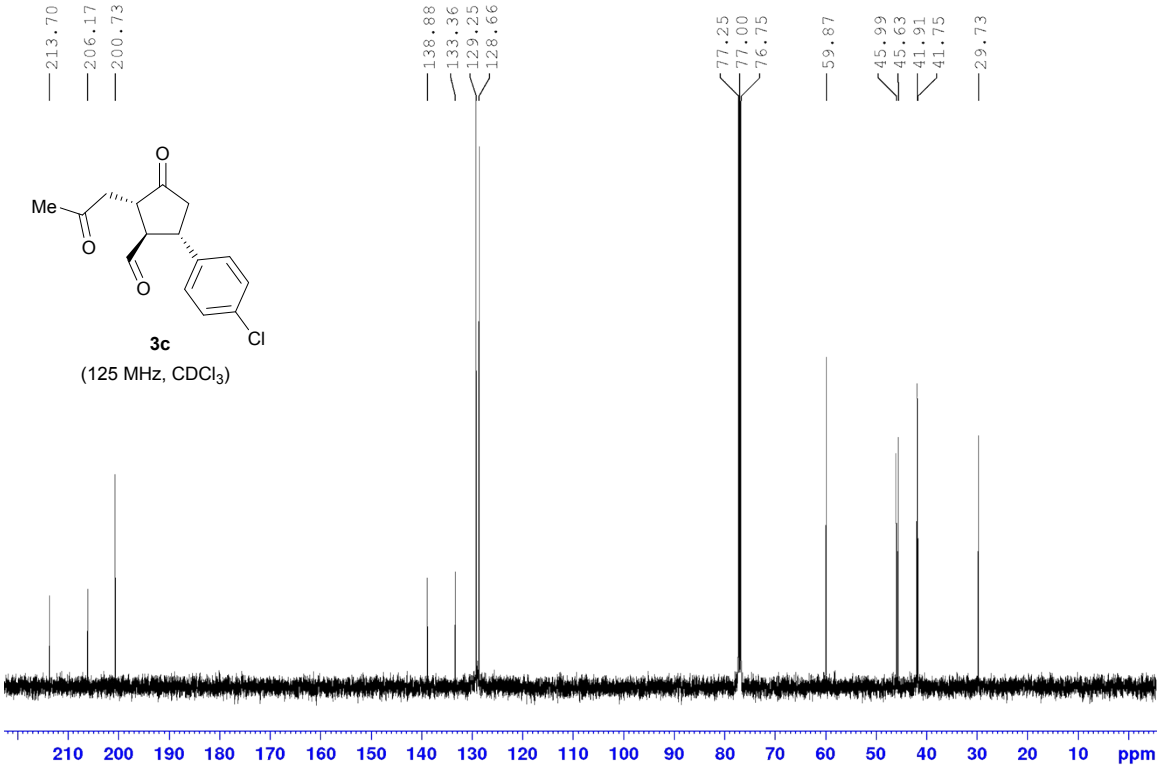
Representative NOEs of compound 3a

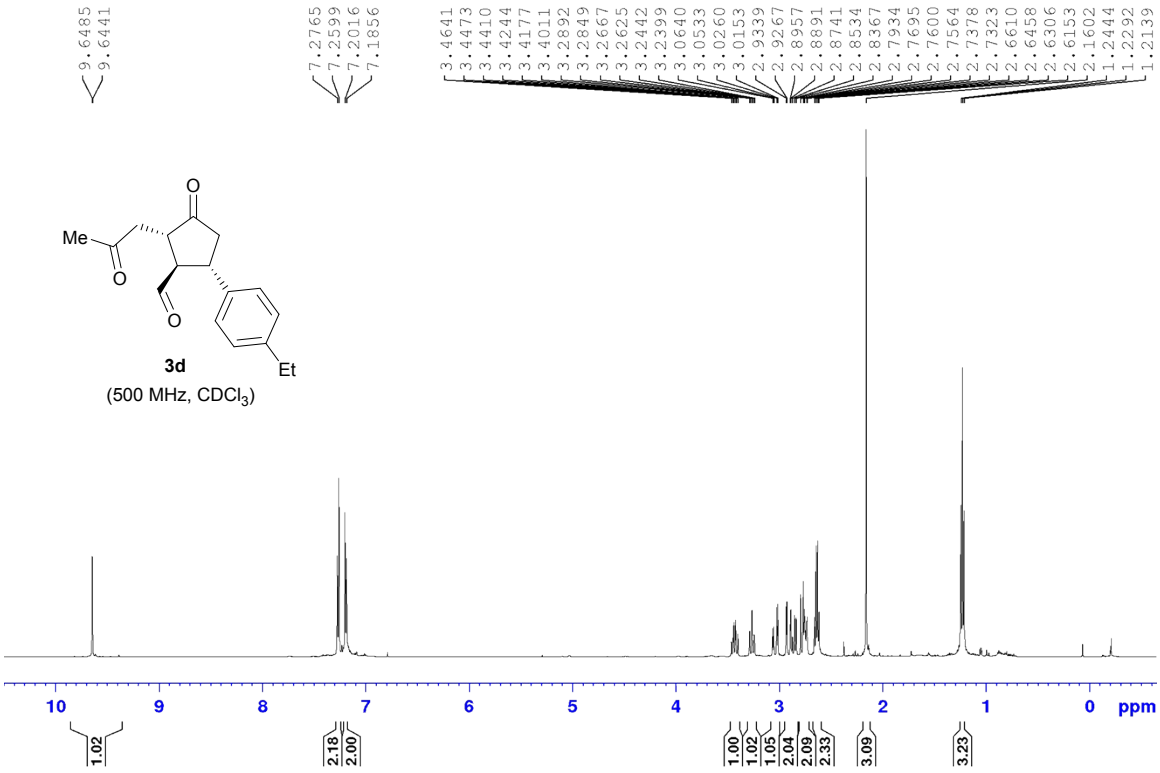


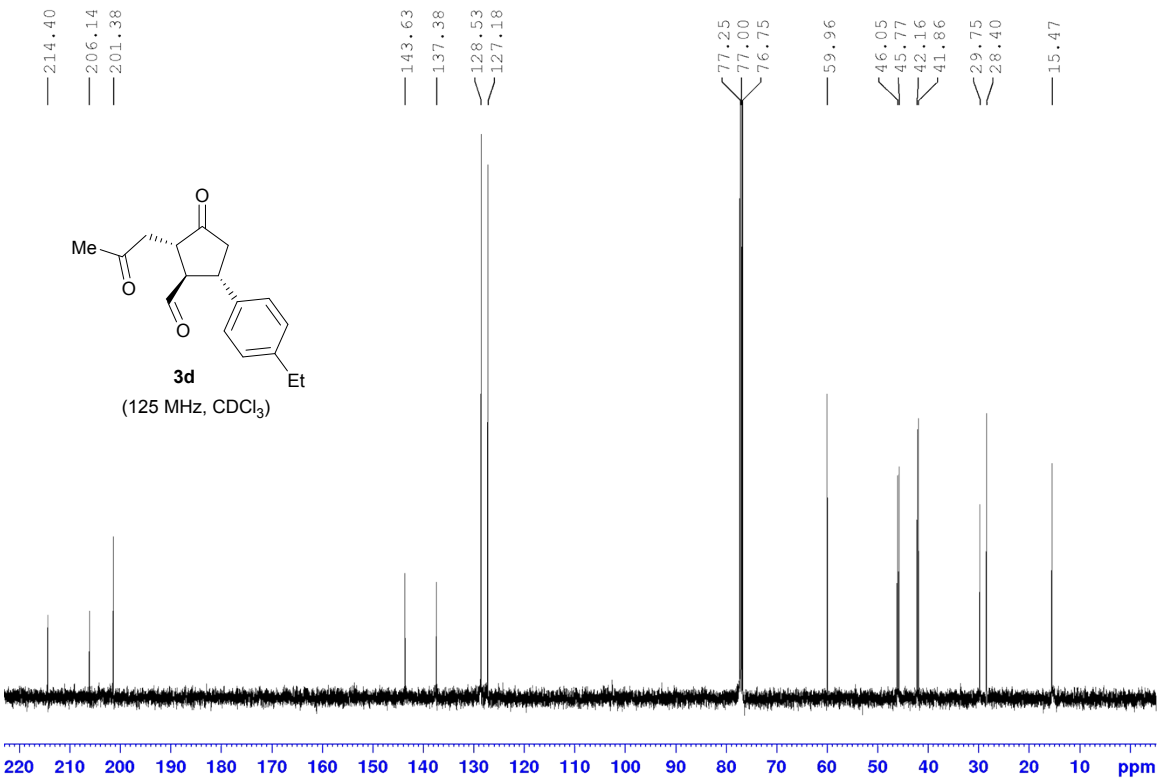

9.6405
9.6361
7.2781
7.2601
6.9013
6.8840
3.7991
3.4435
3.4268
3.4203
3.4038
3.3971
3.3805
3.2557
3.2514
3.2333
3.2289
3.2108
3.2065
3.0610
3.0503
3.0229
3.0122
2.9284
2.9213
2.8903
2.8831
2.8792
2.8611
2.8405
2.8241
2.7609
2.7508
2.7370
2.7239
2.6997
2.1582
Me
O
O
O
OMe
3b
(500 MHz, CDCl3)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.02
2.35
2.05
3.19
1.00
1.02
1.06
2.01
2.06
3.07

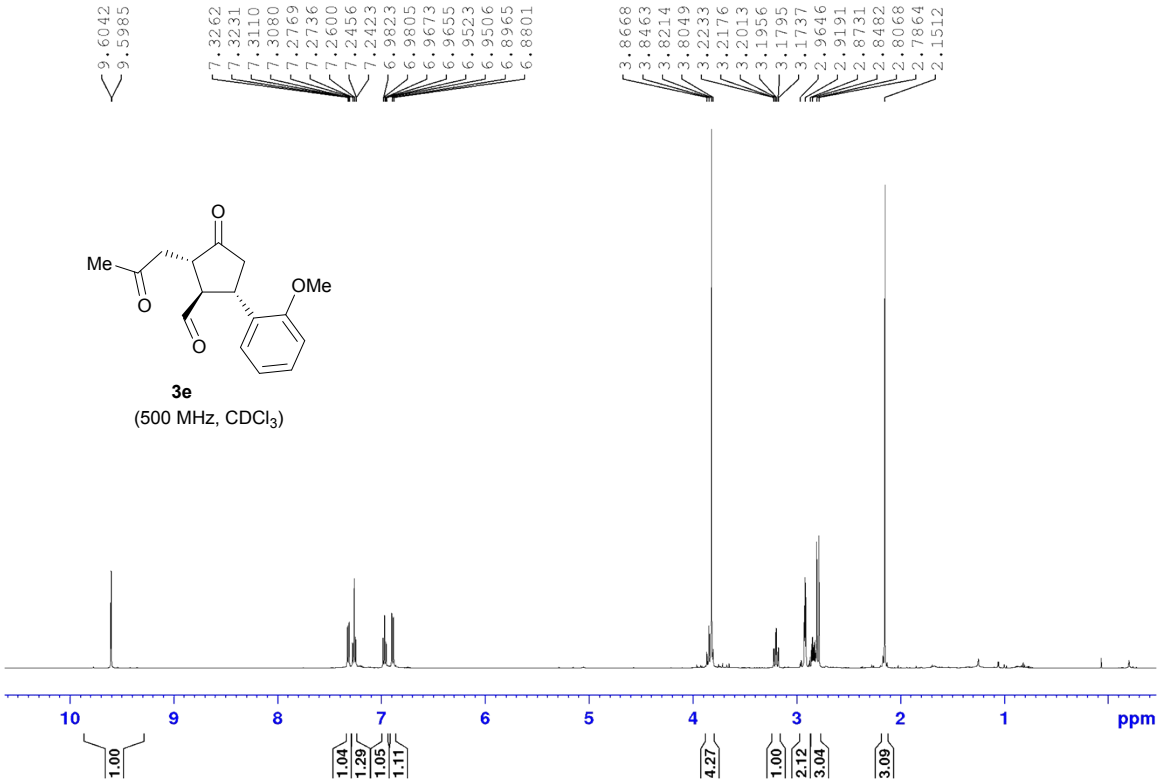

214.37
206.15
201.38
158.93
132.14
128.27
114.43
77.25
77.00
76.75
60.14
55.30
46.07
45.84
41.87
41.78
29.75
Me
O
O
O
OMe
3b
(125 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


9.6385
9.6340
7.3467
7.3296
7.3048
7.2877
7.2600
3.4772
3.4604
3.4542
3.4375
3.4309
3.4142
3.2725
3.2681
3.2501
3.2457
3.2277
3.2233
3.0946
3.0840
3.0564
3.0458
2.9388
2.9318
2.9006
2.8936
2.8823
2.8634
2.8452
2.7654
2.7457
2.7414
2.7281
2.7160
2.7044
2.1656
Me
O
O
O
Cl
3c
(500 MHz, CDCl3)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
2.06
2.21
1.00
1.13
1.13
2.03
2.07
3.04

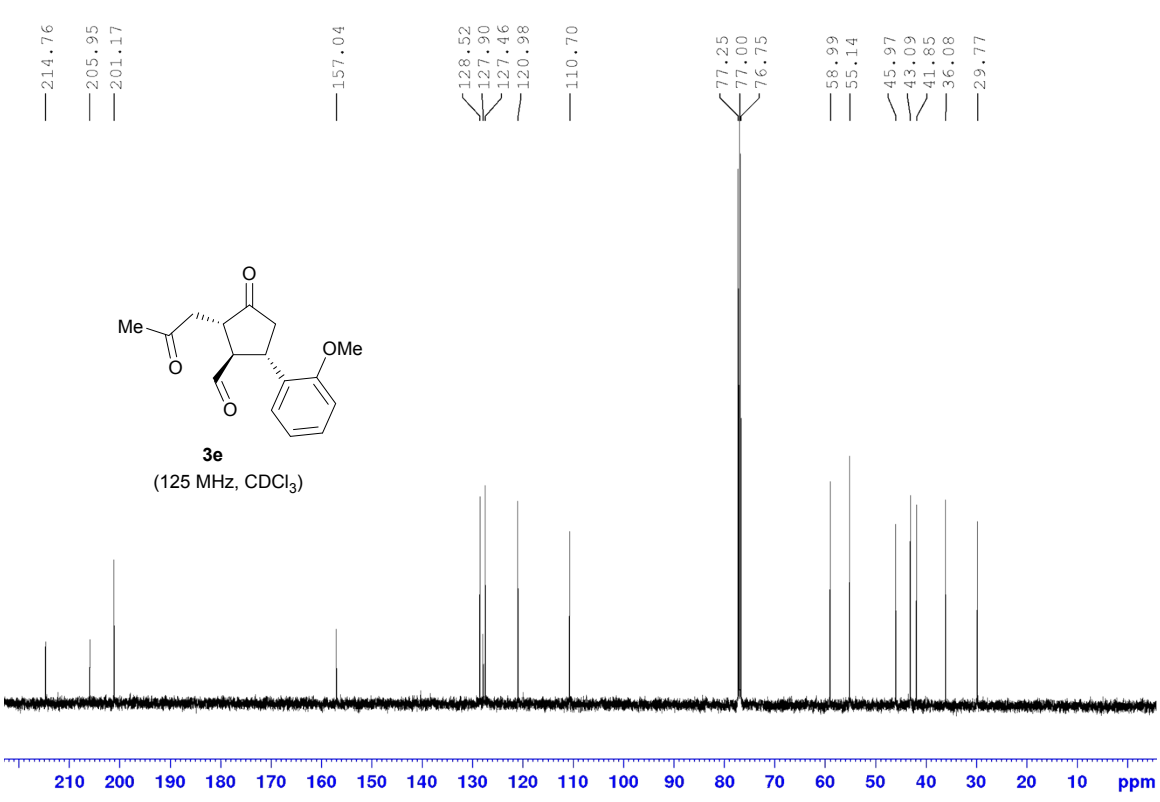

213.70
206.17
200.73
138.88
133.36
129.25
128.66
77.25
77.00
76.75
59.87
45.99
45.63
41.91
41.75
29.73
Me
O
O
O
Cl
3c
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


9.6485
9.6441
7.2765
7.2599
7.2016
7.1856
3.4641
3.4473
3.4410
3.4244
3.4177
3.4011
3.2892
3.2849
3.2667
3.2625
3.2442
3.2399
3.0640
3.0533
3.0260
3.0153
2.9339
2.9267
2.8957
2.8891
2.8741
2.8534
2.8367
2.7934
2.7695
2.7600
2.7564
2.7378
2.7323
2.6610
2.6458
2.6306
2.6153
2.1602
2.2444
2.2292
2.2139
Me
O
O
O
Et
3d
(500 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
0
ppm
1.02
2.18
2.00
1.00
1.02
1.05
2.04
2.09
2.33
3.09
3.23

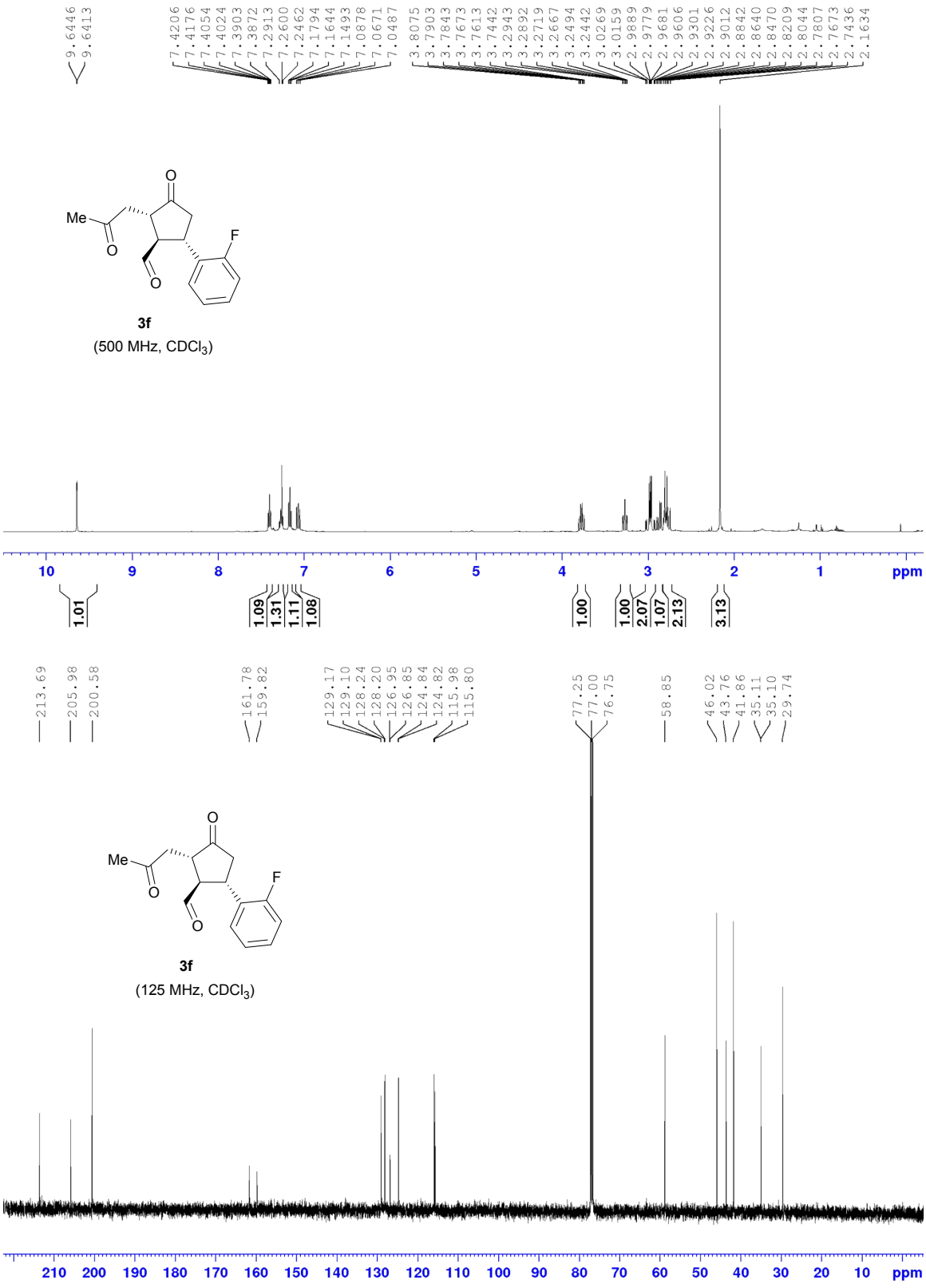

214.40
206.14
201.38
143.63
137.38
128.53
127.18
77.25
77.00
76.75
59.96
46.05
45.77
42.16
41.86
29.75
28.40
15.47
Me
O
O
O
Et
3d
(125 MHz, CDCl3)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

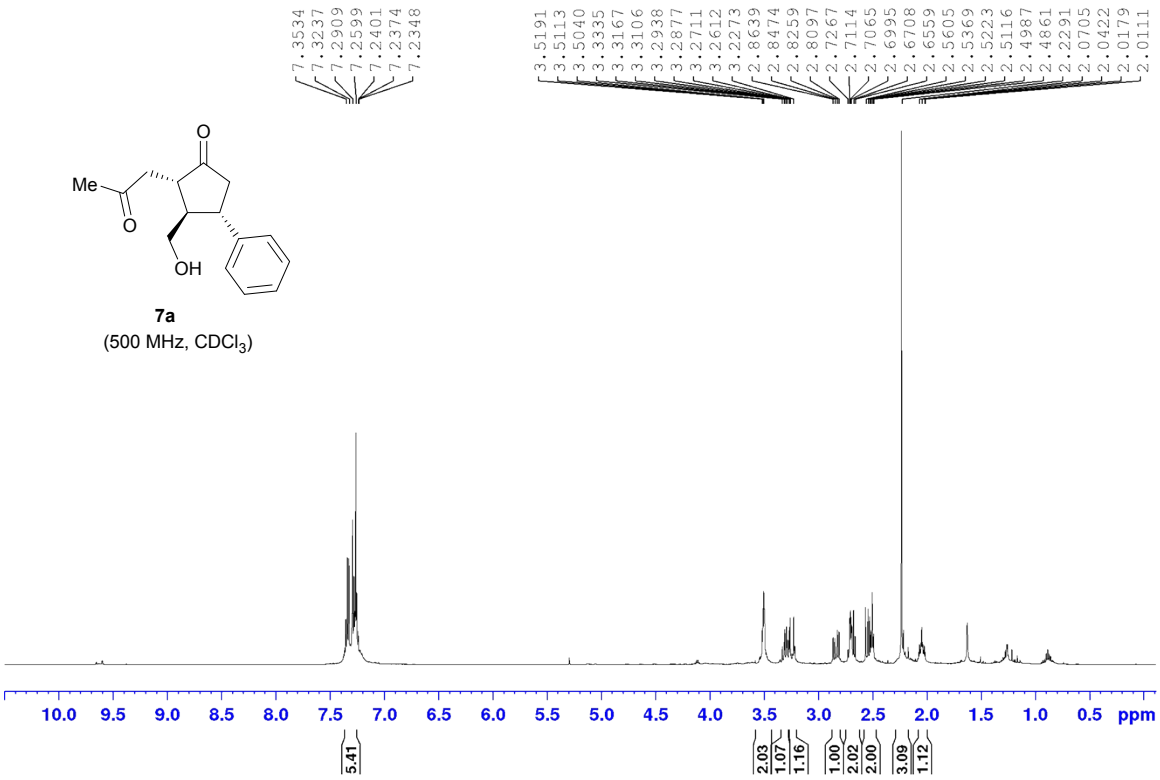


3e
(500 MHz, $CDCl_3$)

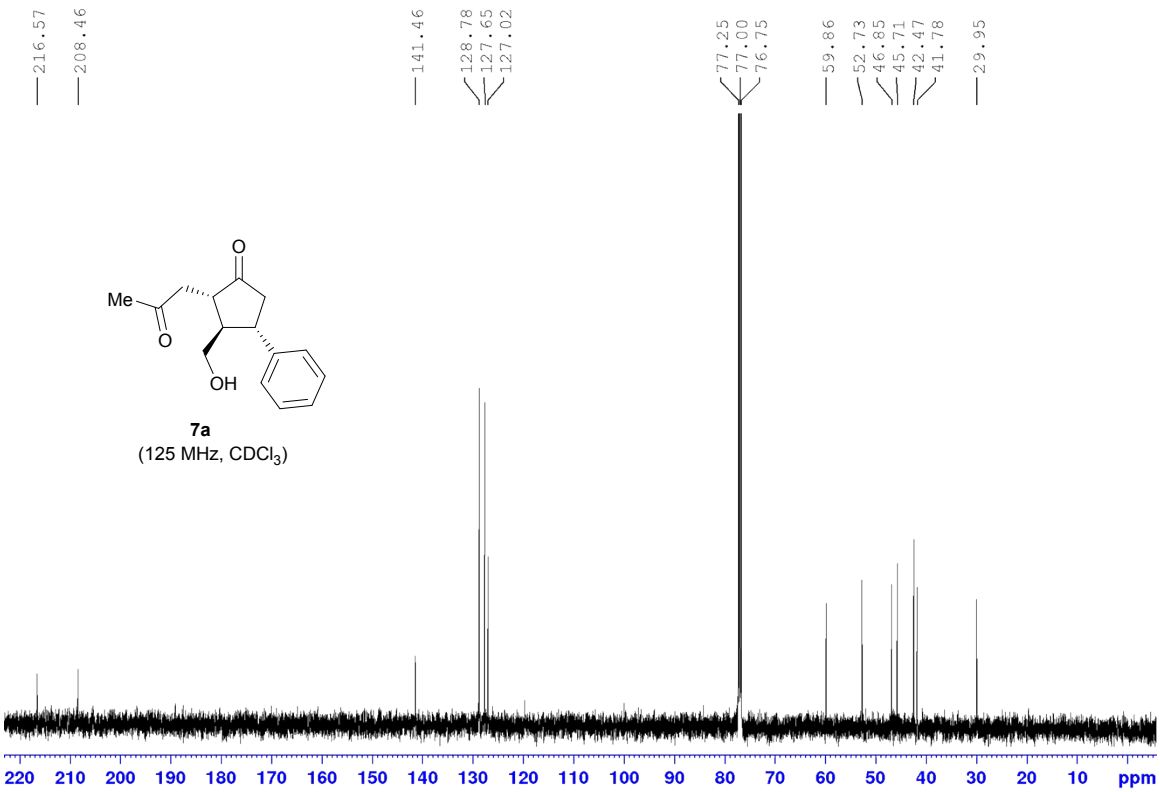


3e
(125 MHz, $CDCl_3$)


9.6446
9.6413
7.4206
7.4176
7.4054
7.4024
7.3903
7.3872
7.2913
7.2600
7.2462
7.1794
7.1644
7.1493
7.0878
7.0671
7.0487
3.8075
3.7903
3.7843
3.7673
3.7613
3.7442
3.2943
3.2892
3.2719
3.2667
3.2494
3.2442
3.0269
3.0159
2.9889
2.9779
2.9681
2.9606
2.9301
2.9226
2.9012
2.8842
2.8640
2.8470
2.8209
2.8044
2.7807
2.7673
2.7436
2.1634
Me
O
O
O
F
3f
(500 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
1.01
1.09
1.31
1.11
1.08
1.00
1.00
2.07
1.07
2.13
3.13
213.69
205.98
200.58
161.78
159.82
129.17
129.10
128.24
128.20
126.95
126.85
124.84
124.82
115.98
115.80
77.25
77.00
76.75
58.85
46.02
43.76
41.86
35.11
35.10
29.74
Me
O
O
O
F
3f
(125 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

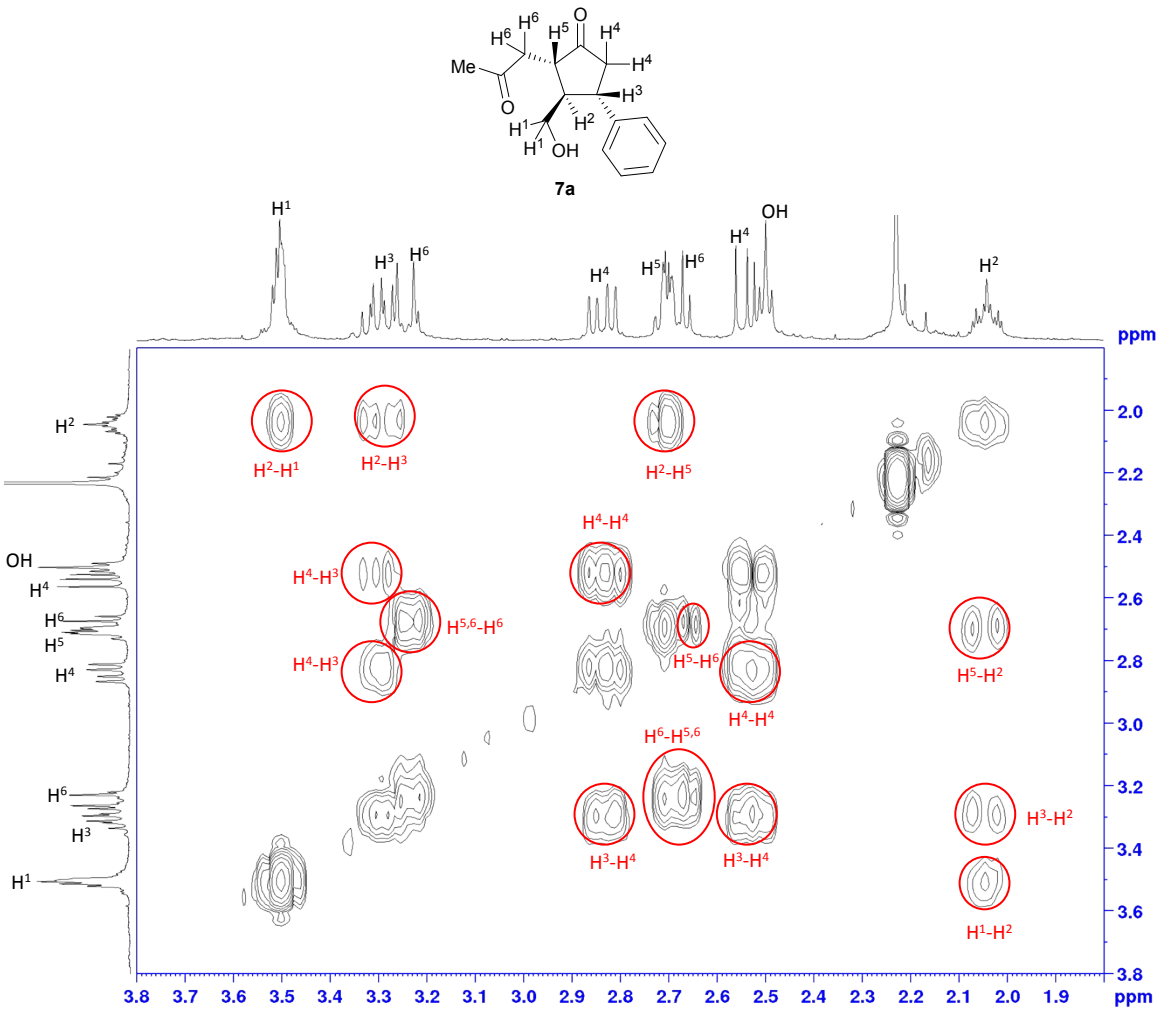


7a
(500 MHz, $CDCl_3$)

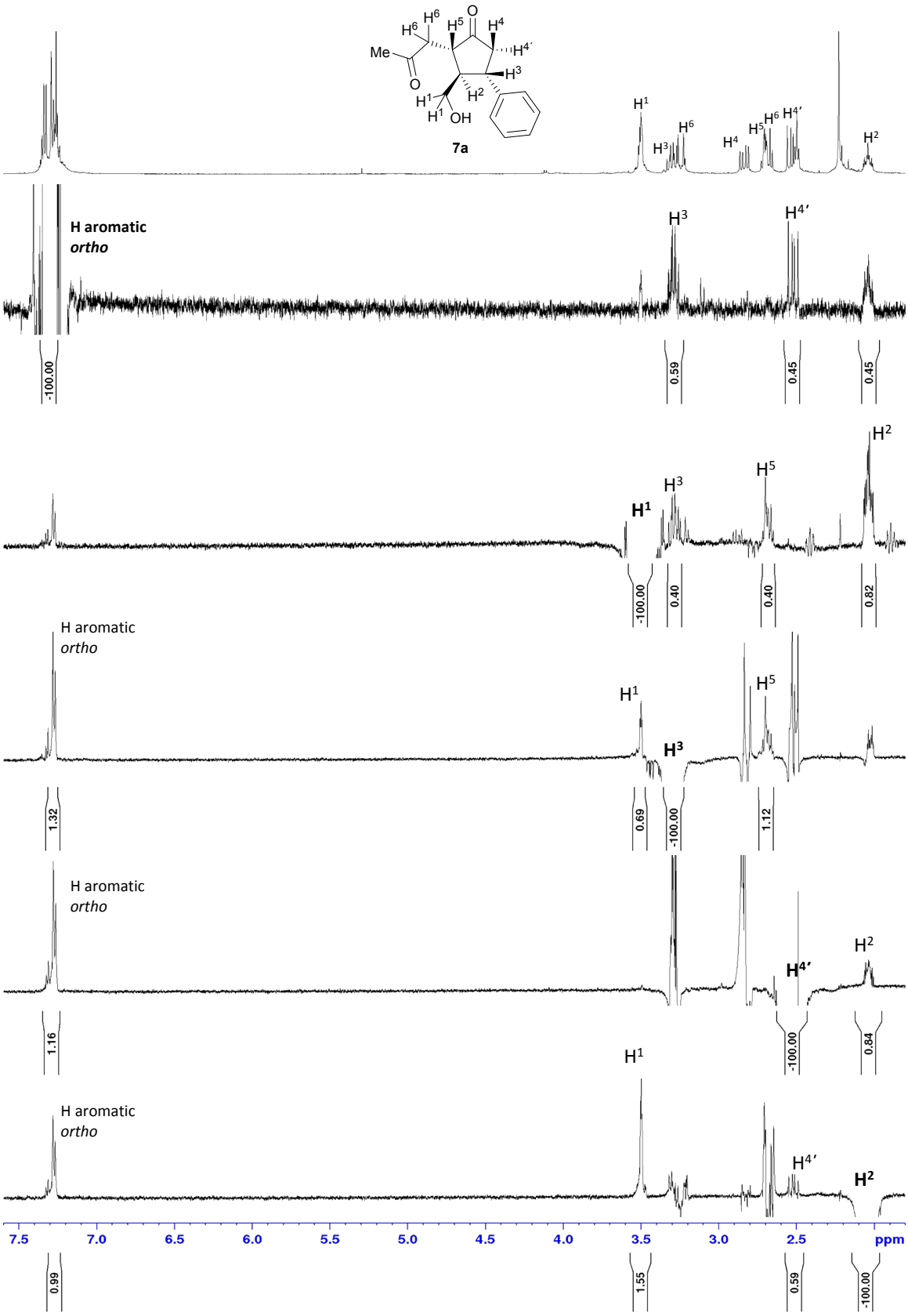


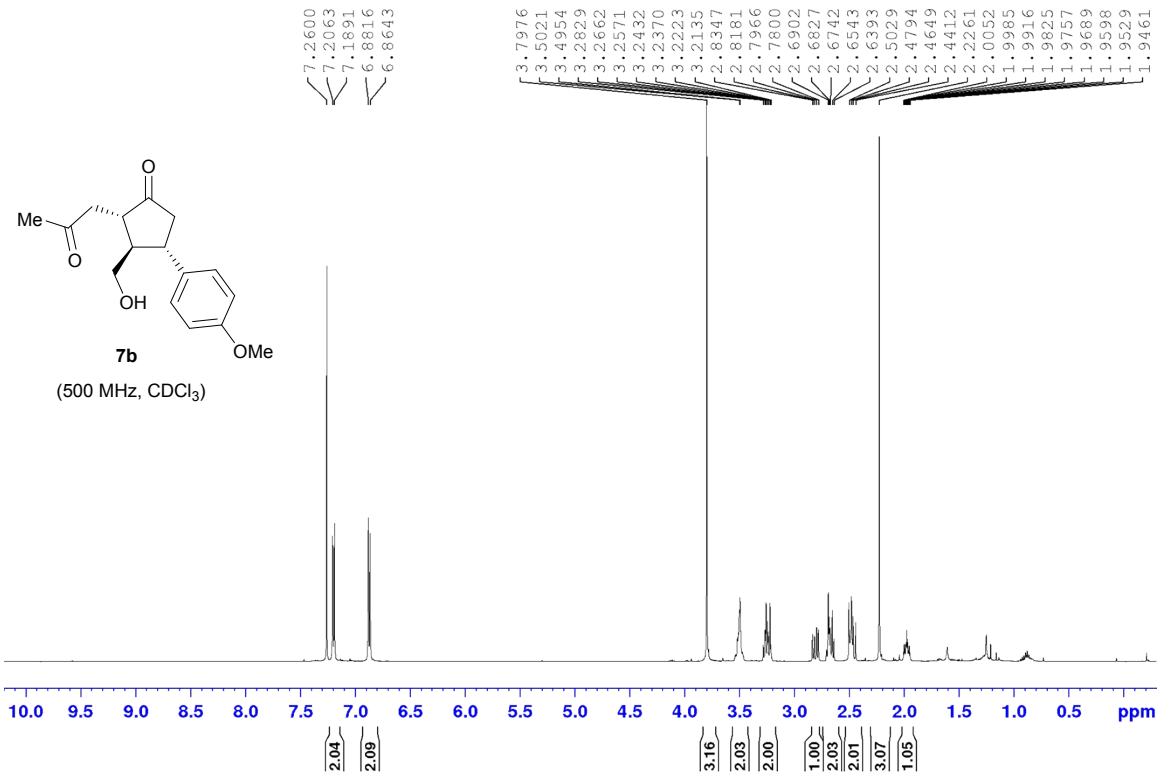
7a
(125 MHz, $CDCl_3$)

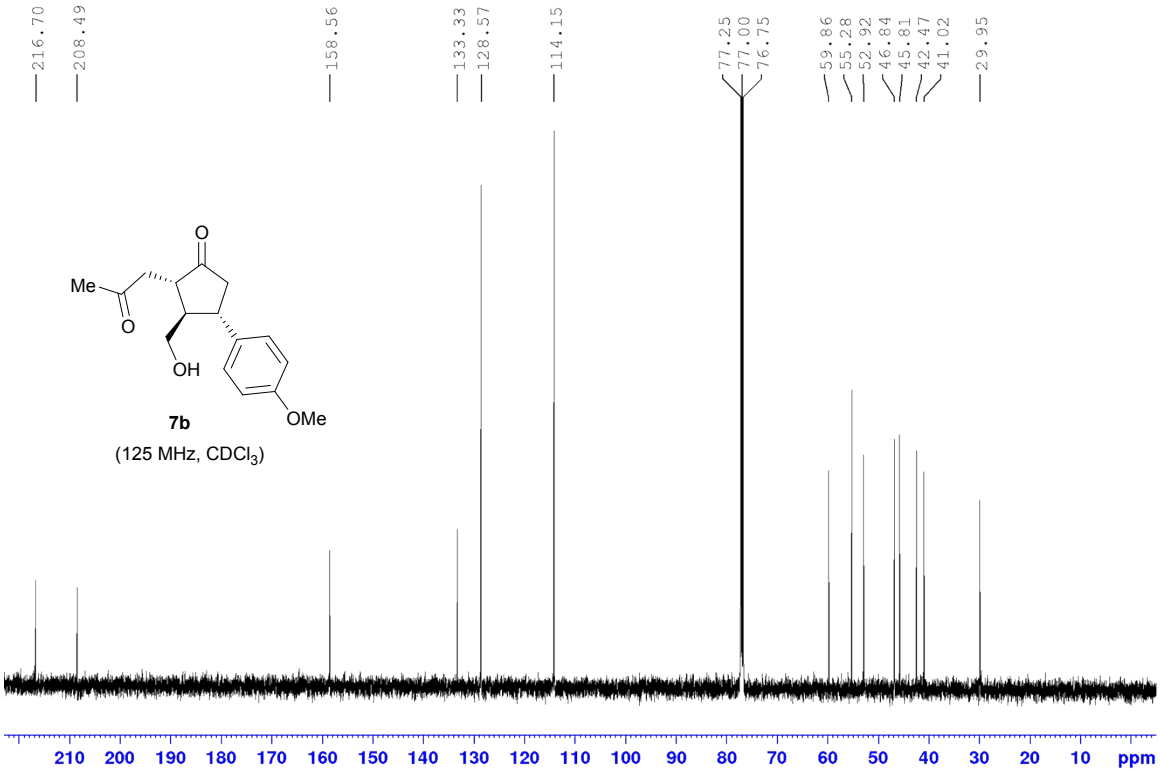
COSY correlations of compound 7a

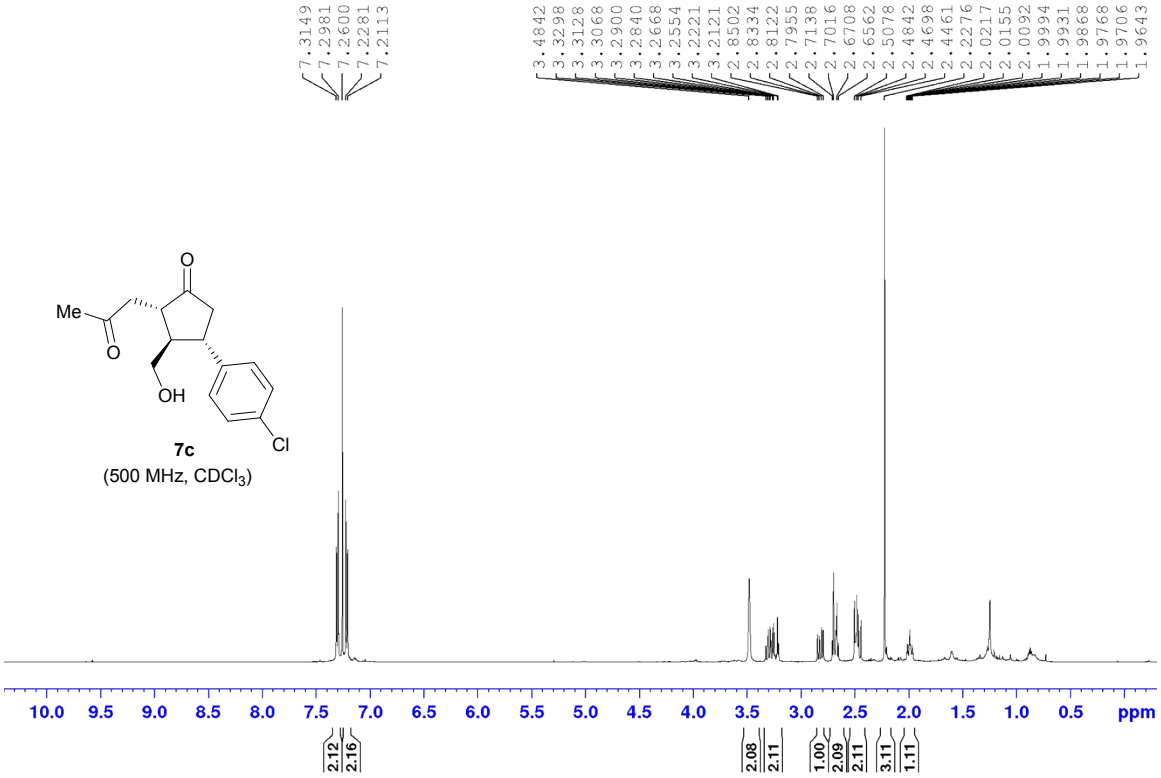


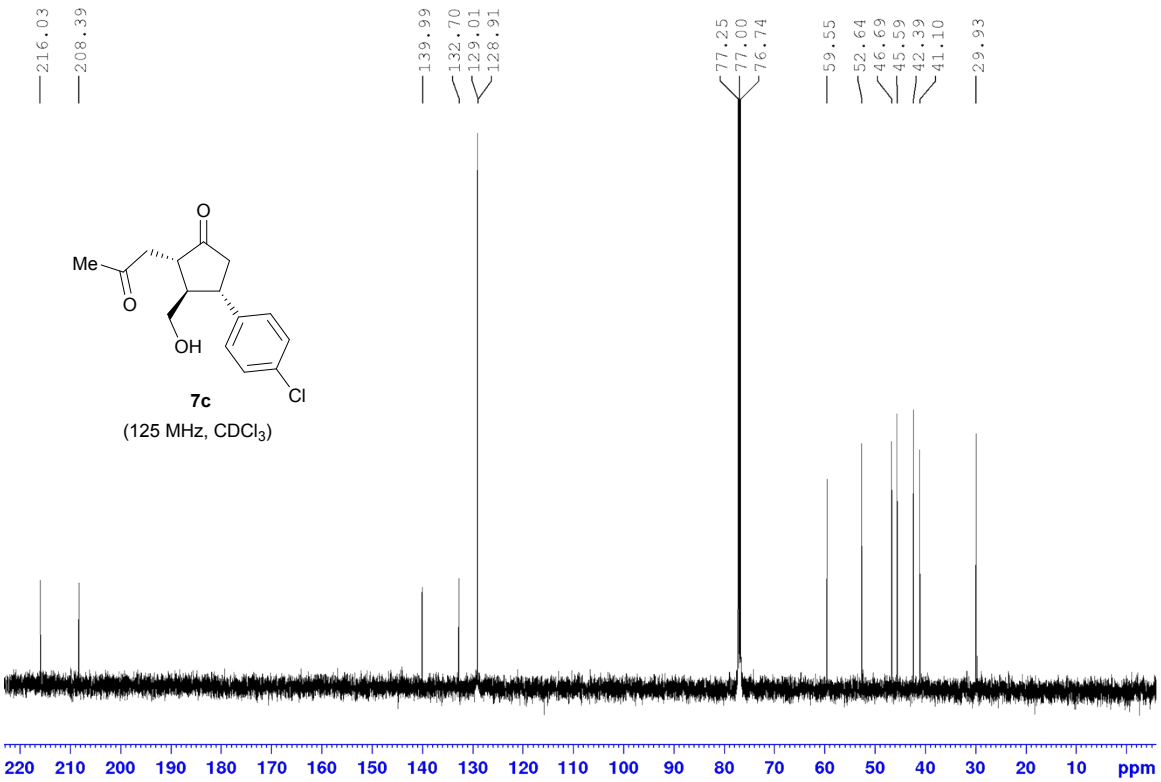
Representative NOEs of compound 7a

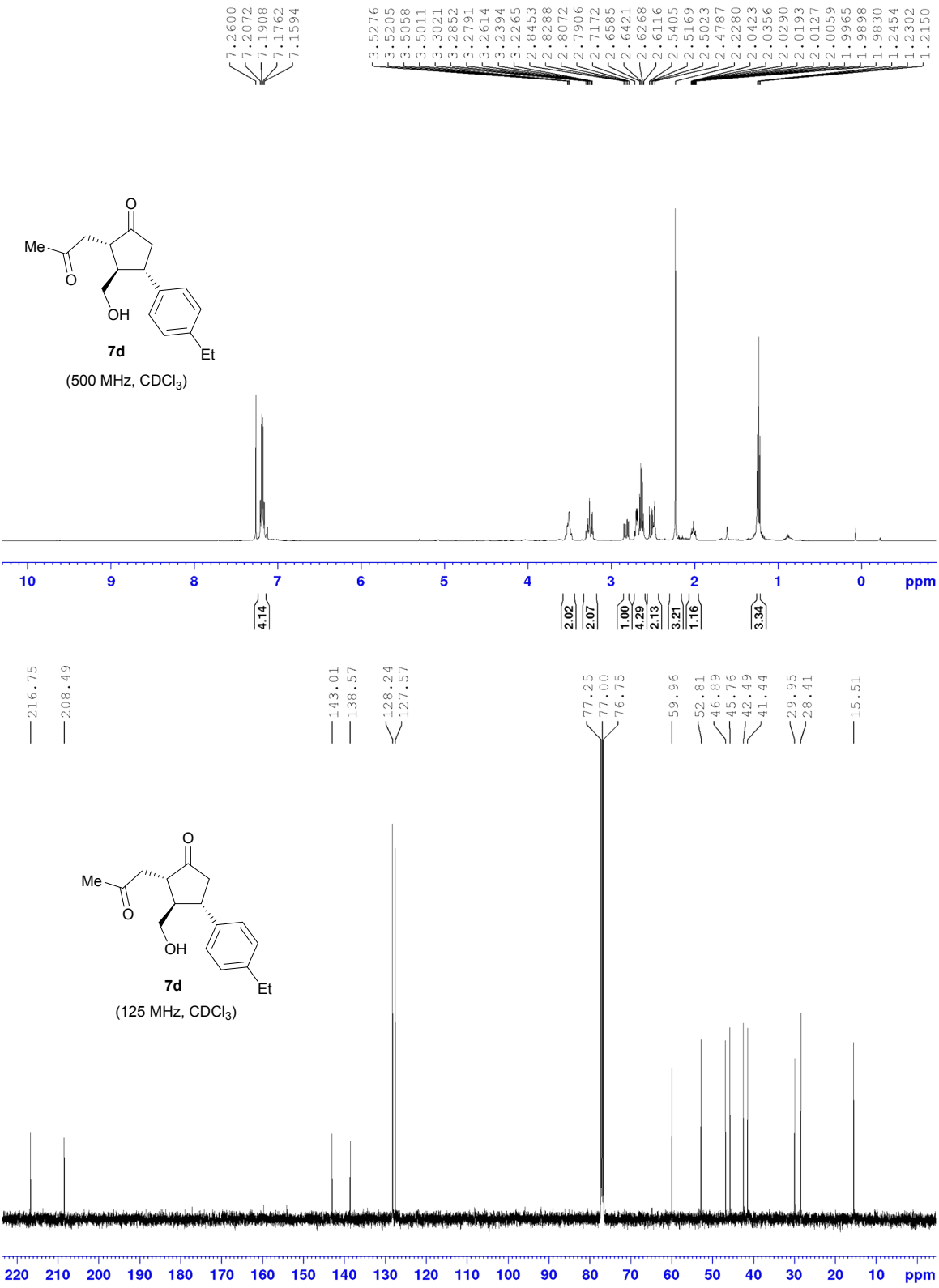


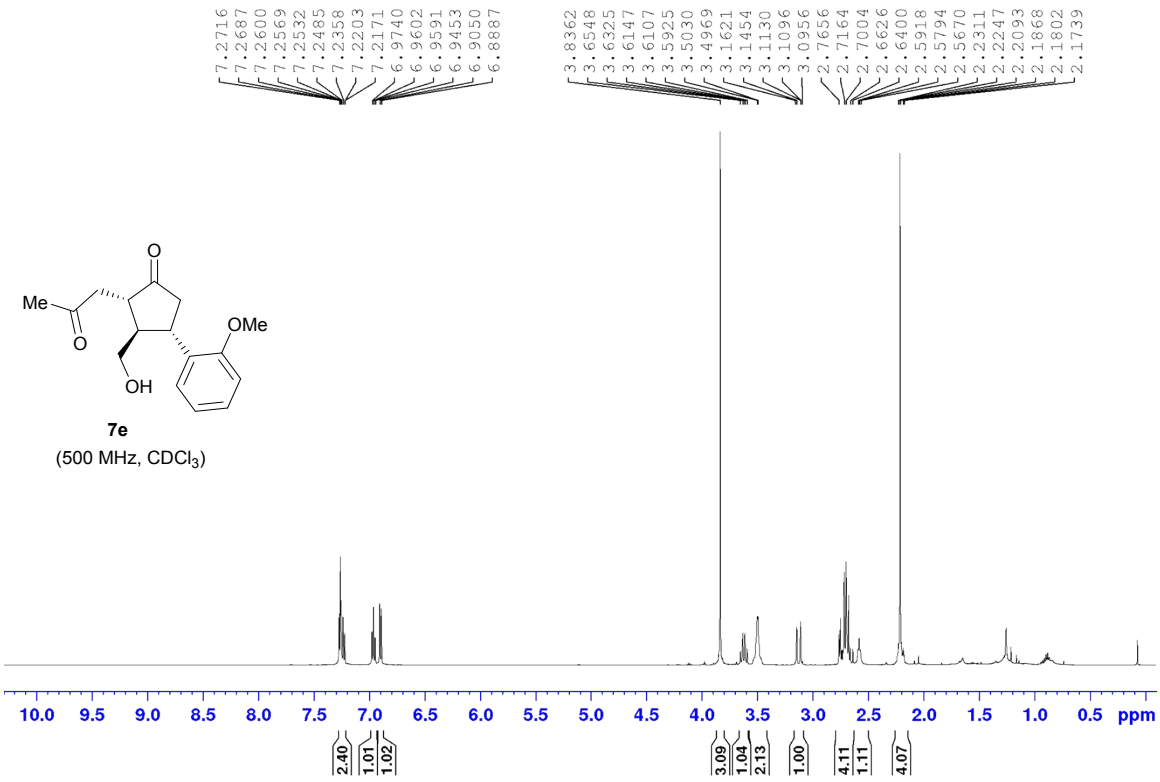

7.2600
7.2063
7.1891
6.8816
6.8643
3.7976
3.5021
3.4954
3.2829
3.2662
3.2571
3.2432
3.2370
3.2223
3.2135
2.8347
2.8181
2.7966
2.7800
2.6902
2.6827
2.6742
2.6543
2.6393
2.5029
2.4794
2.4649
2.4412
2.2261
2.0052
1.9985
1.9916
1.9825
1.9757
1.9689
1.9598
1.9529
1.9461
Me
O
O
OH
OMe
7b
(500 MHz, CDCl3)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.04
2.09
3.16
2.03
2.00
1.00
2.03
2.01
3.07
1.05


216.70
208.49
158.56
133.33
128.57
114.15
77.25
77.00
76.75
59.86
55.28
52.92
46.84
45.81
42.47
41.02
29.95
Me
O
O
OH
OMe
7b
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.3149
7.2981
7.2600
7.2281
7.2113
3.4842
3.3298
3.3128
3.3068
3.2900
3.2840
3.2668
3.2554
3.2221
3.2121
2.8502
2.8334
2.8122
2.7955
2.7138
2.7016
2.6708
2.6562
2.5078
2.4842
2.4698
2.4461
2.2276
2.0217
2.0155
2.0092
1.9994
1.9931
1.9868
1.9768
1.9706
1.9643
O
Me
O
OH
Cl
7c
(500 MHz, CDCl3)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.12
2.16
2.08
2.11
1.00
2.09
2.11
3.11
1.11

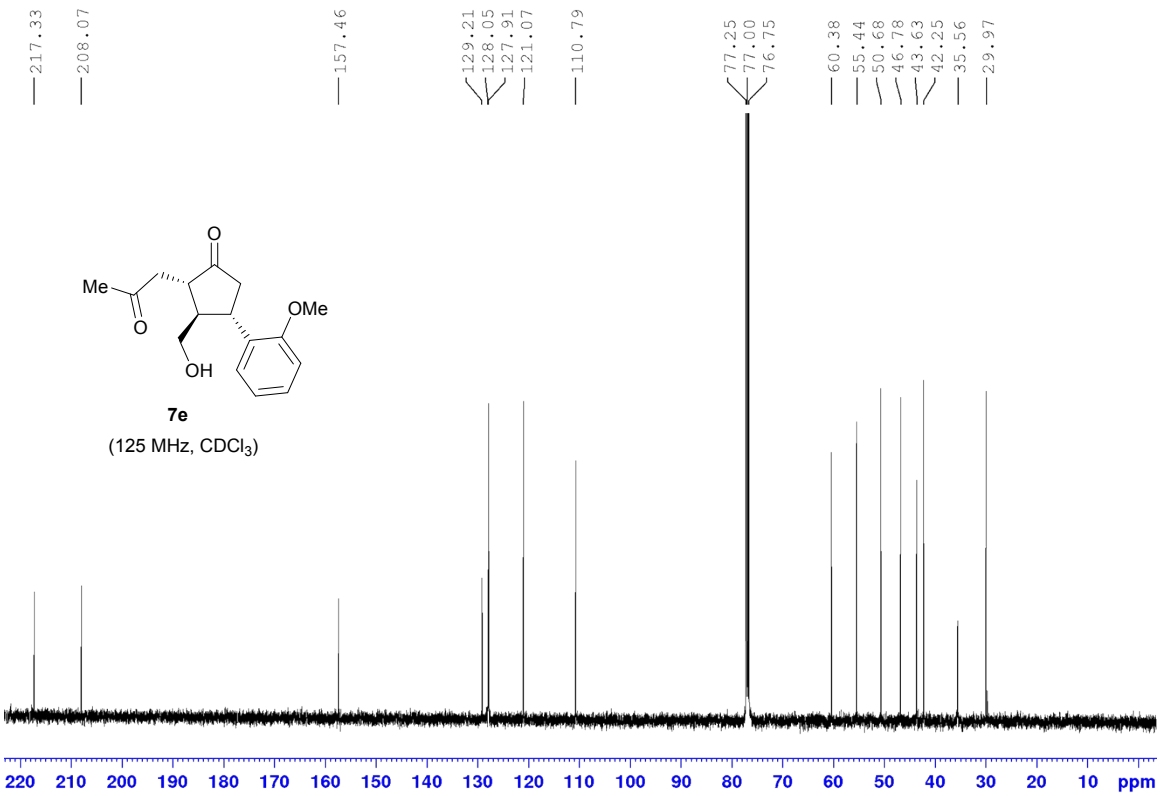

216.03
208.39
139.99
132.70
129.01
128.91
77.25
77.00
76.74
59.55
52.64
46.69
45.59
42.39
41.10
29.93
O
Me
O
OH
Cl
7c
(125 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.2600
7.2072
7.1908
7.1762
7.1594
3.5276
3.5205
3.5058
3.5011
3.3021
3.2852
3.2791
3.2614
3.2394
3.2265
2.8453
2.8288
2.8072
2.7906
2.7172
2.6585
2.6421
2.6268
2.6116
2.5405
2.5169
2.5023
2.4787
2.2280
2.0423
2.0356
2.0290
2.0193
2.0127
2.0059
1.9965
1.9898
1.9830
1.2454
1.2302
1.2150
Me
O
O
OH
Et
7d
(500 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
0
ppm
4.14
2.02
2.07
1.00
4.29
2.13
3.21
1.16
3.34
216.75
208.49
143.01
138.57
128.24
127.57
77.25
77.00
76.75
59.96
52.81
46.89
45.76
42.49
41.44
29.95
28.41
15.51
Me
O
O
OH
Et
7d
(125 MHz, CDCl3)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



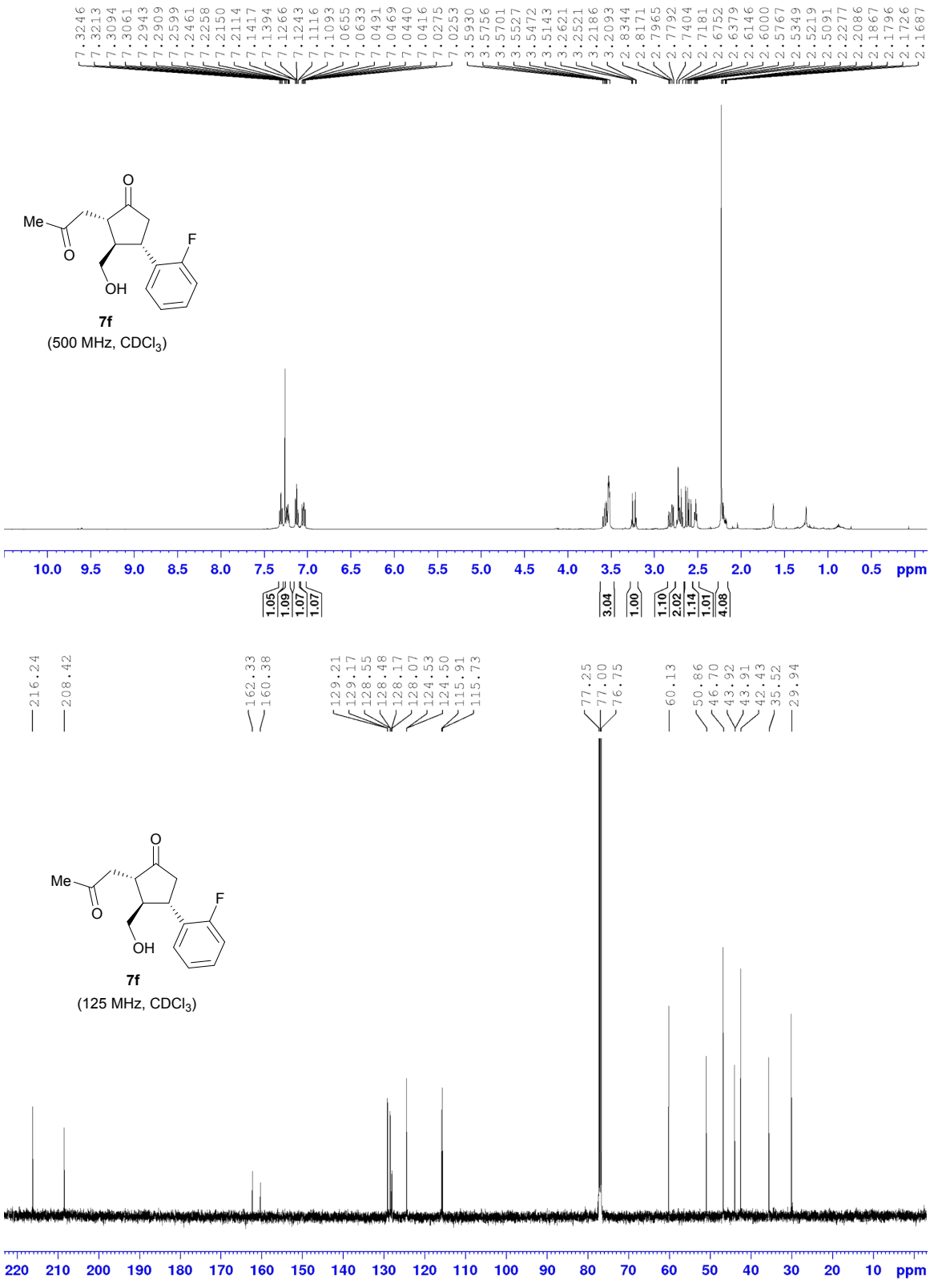
7e

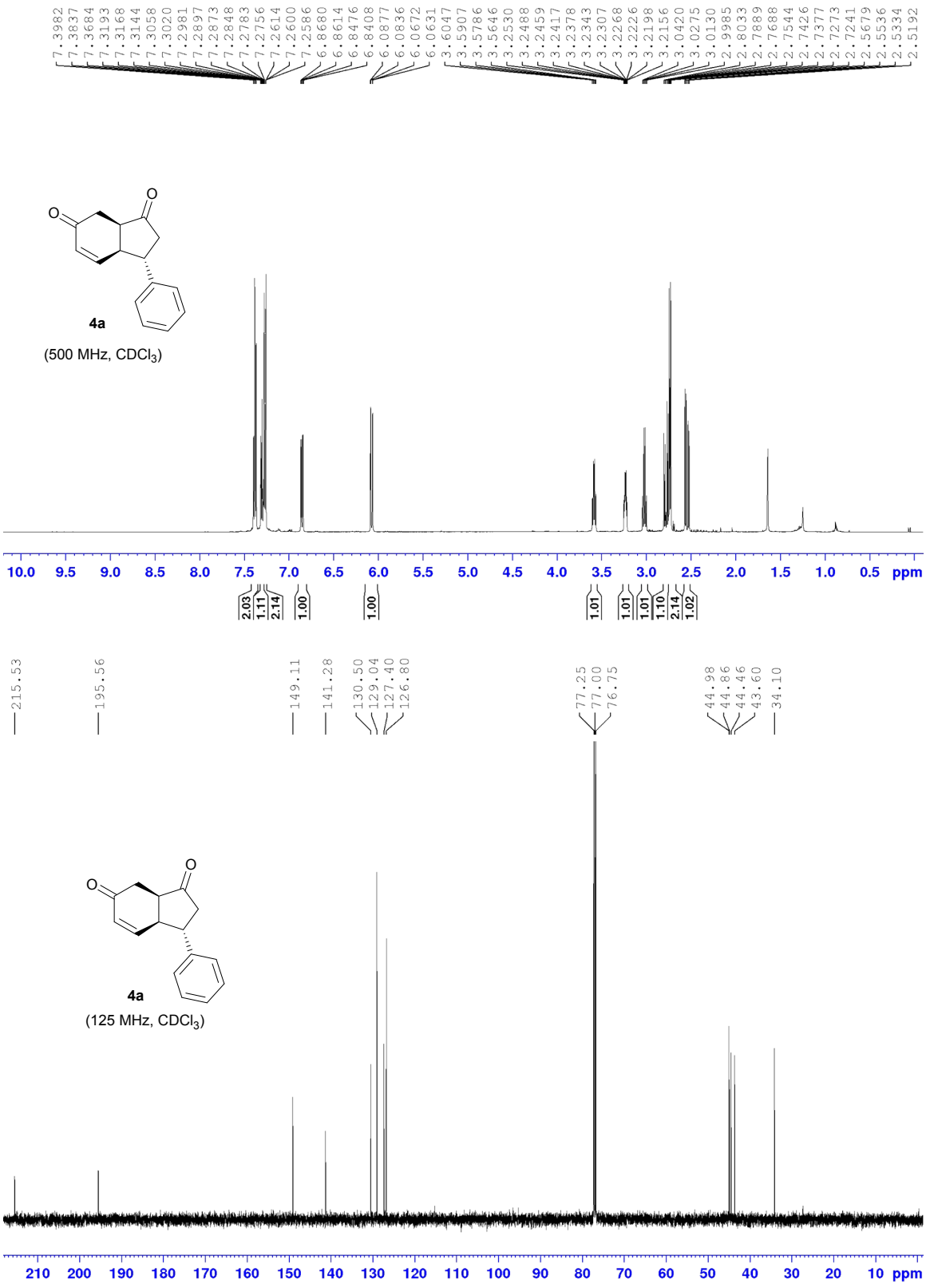
(500 MHz, $CDCl_3$)



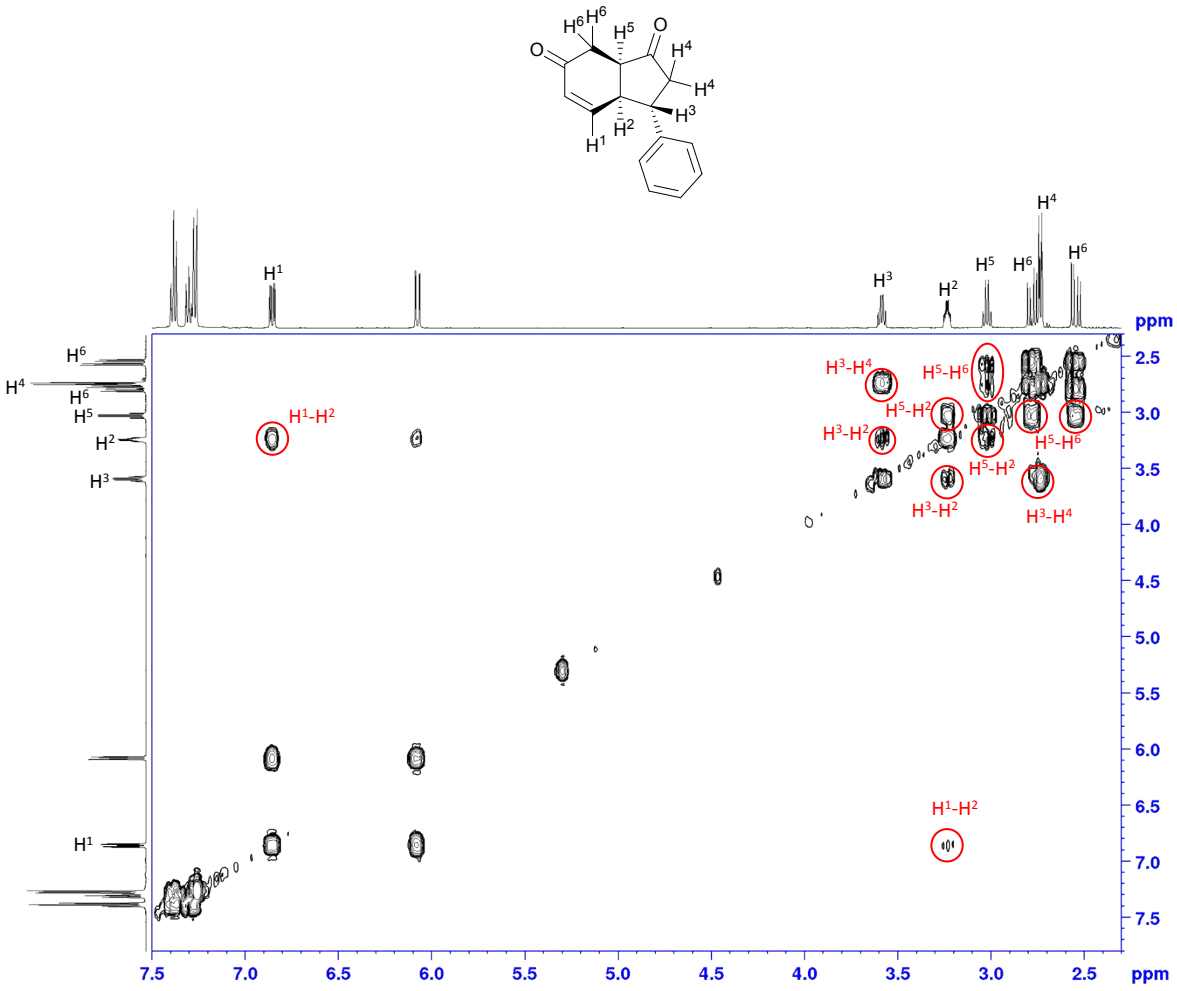
7e

(125 MHz, $CDCl_3$)

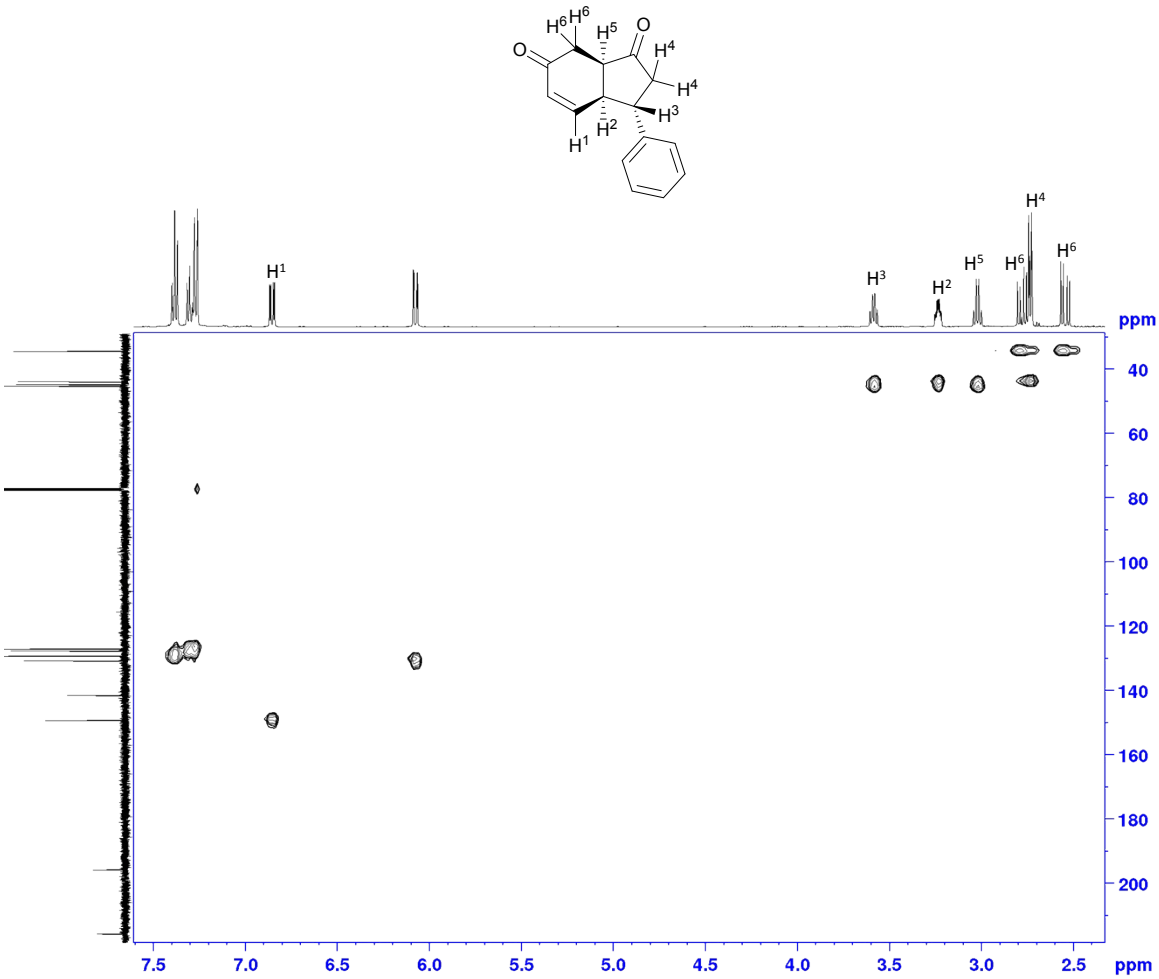

7.3246
7.3213
7.3094
7.3061
7.2943
7.2909
7.2599
7.2461
7.2258
7.2150
7.2114
7.1417
7.1394
7.1266
7.1243
7.1116
7.1093
7.0655
7.0633
7.0491
7.0469
7.0440
7.0416
7.0275
7.0253
3.5930
3.5756
3.5701
3.5527
3.5472
3.5143
3.2621
3.2521
3.2186
3.2093
2.8344
2.8171
2.7965
2.7792
2.7404
2.7181
2.6752
2.6379
2.6146
2.6000
2.5767
2.5349
2.5219
2.5091
2.2277
2.2086
2.1867
2.1796
2.1726
2.1687
Me
O
O
F
OH
7f
(500 MHz, CDCl3)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.05
1.09
1.07
1.07
3.04
1.00
1.10
2.02
1.14
1.01
4.08
216.24
208.42
162.33
160.38
129.21
129.17
128.55
128.48
128.17
128.07
124.53
124.50
115.91
115.73
77.25
77.00
76.75
60.13
50.86
46.70
43.92
43.91
42.43
35.52
29.94
Me
O
O
F
OH
7f
(125 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.3982
7.3837
7.3684
7.3193
7.3168
7.3144
7.3058
7.3020
7.2981
7.2897
7.2873
7.2848
7.2783
7.2756
7.2614
7.2600
7.2586
6.8680
6.8614
6.8476
6.8408
6.0877
6.0836
6.0672
6.0631
3.6047
3.5907
3.5786
3.5646
3.2530
3.2488
3.2459
3.2417
3.2378
3.2343
3.2307
3.2268
3.2226
3.2198
3.2156
3.0420
3.0275
3.0130
2.9985
2.8033
2.7889
2.7688
2.7544
2.7426
2.7377
2.7273
2.7241
2.5679
2.5536
2.5334
2.5192
4a
(500 MHz, CDCl3)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.03
1.11
2.14
1.00
1.00
1.01
1.01
1.01
1.10
2.14
1.02
215.53
195.56
149.11
141.28
130.50
129.04
127.40
126.80
77.25
77.00
76.75
44.98
44.86
44.46
43.60
34.10
4a
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

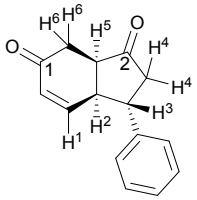
COSY correlations of compound 4a

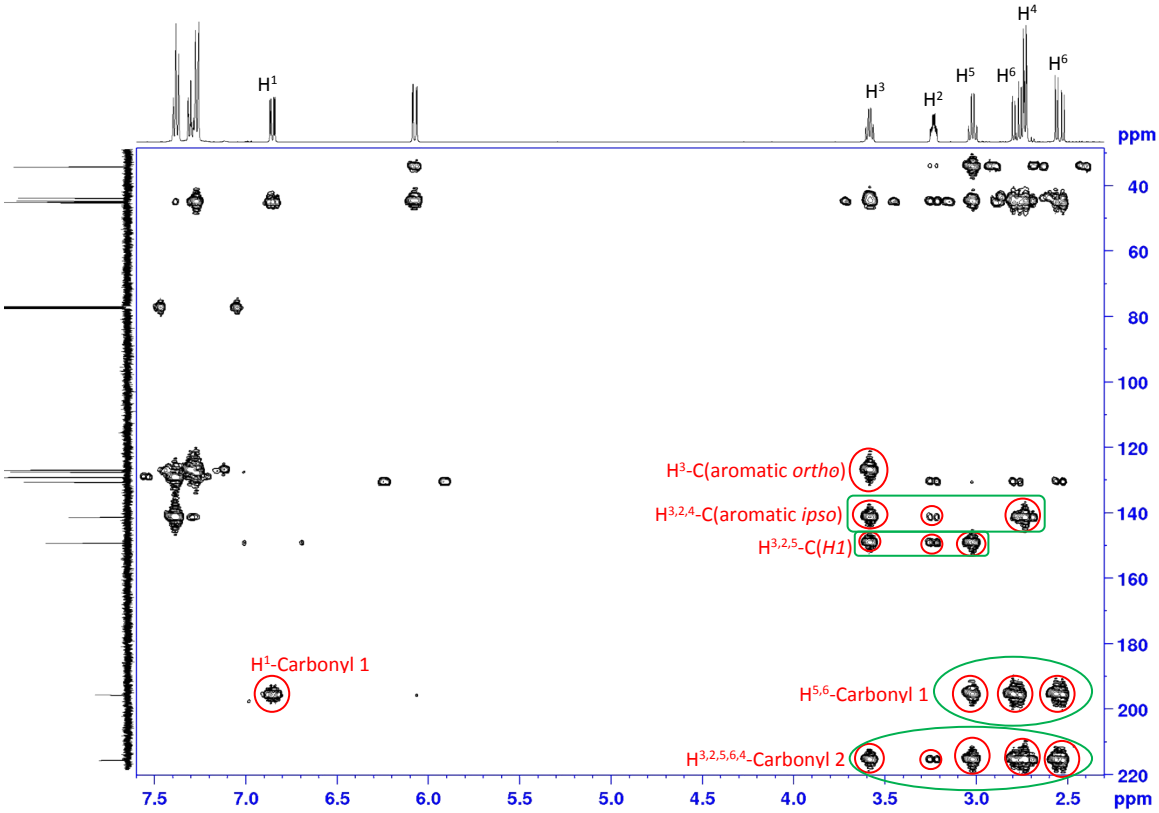


HSQC correlations of compound 4a

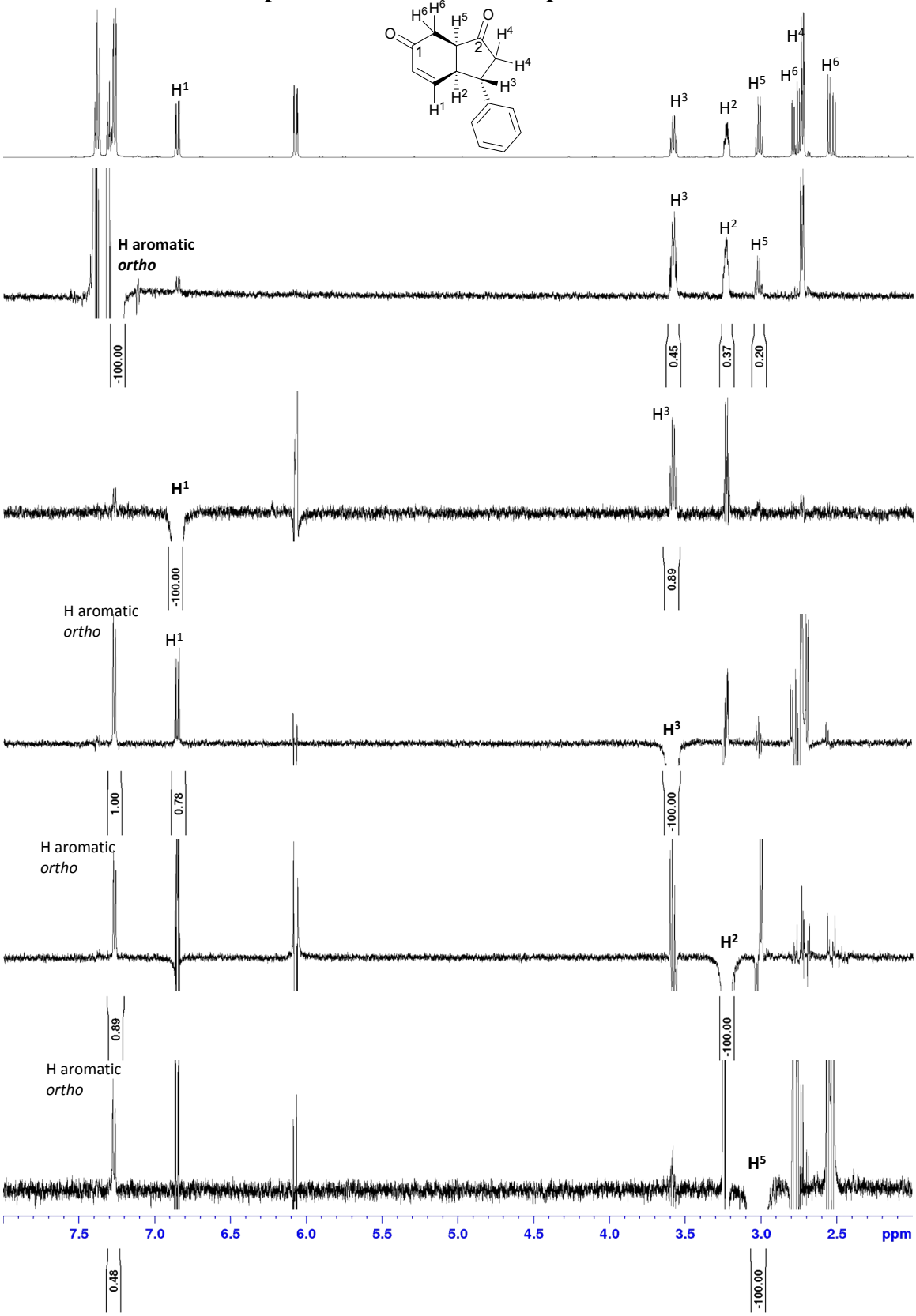


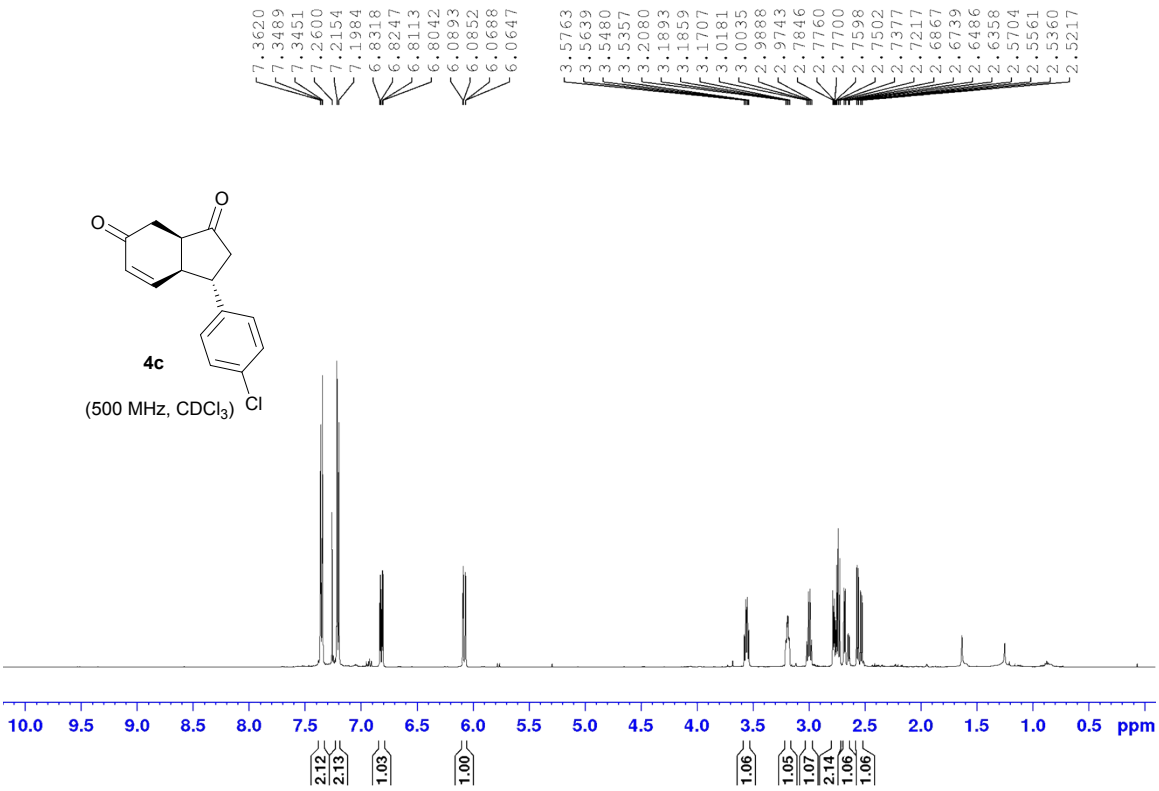
HMBC correlations of compound 4a

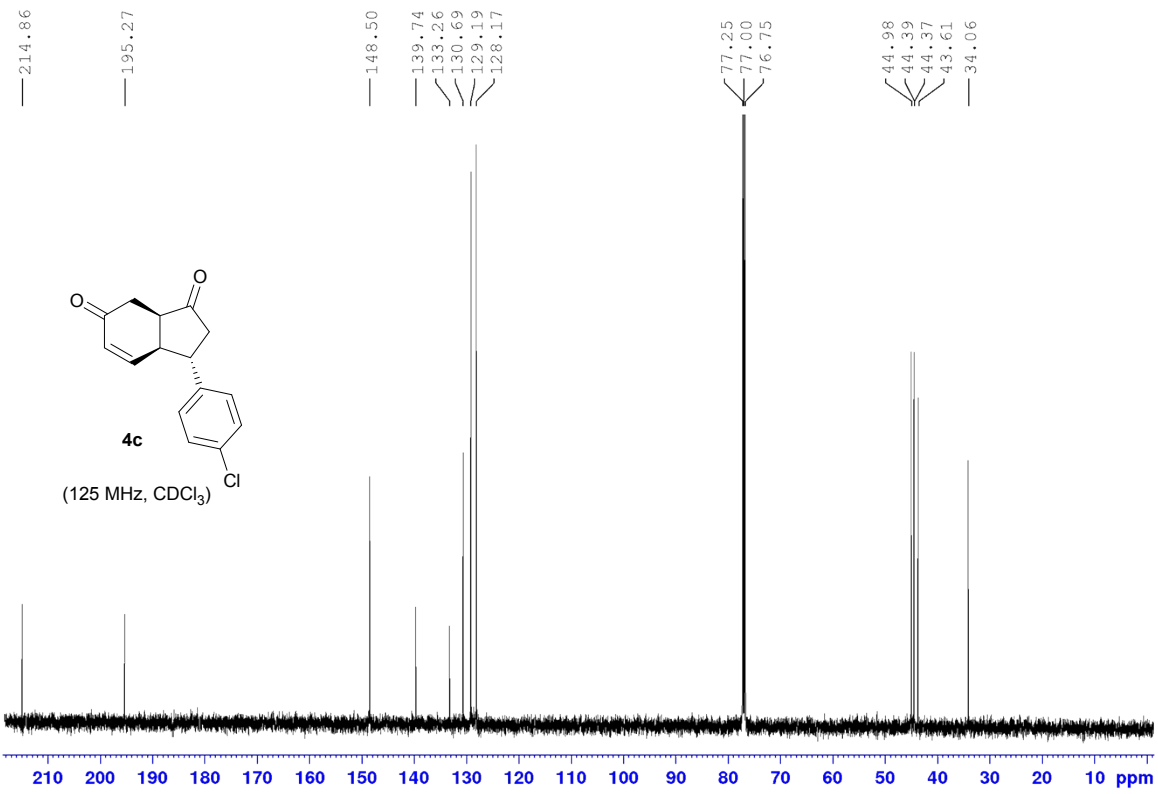


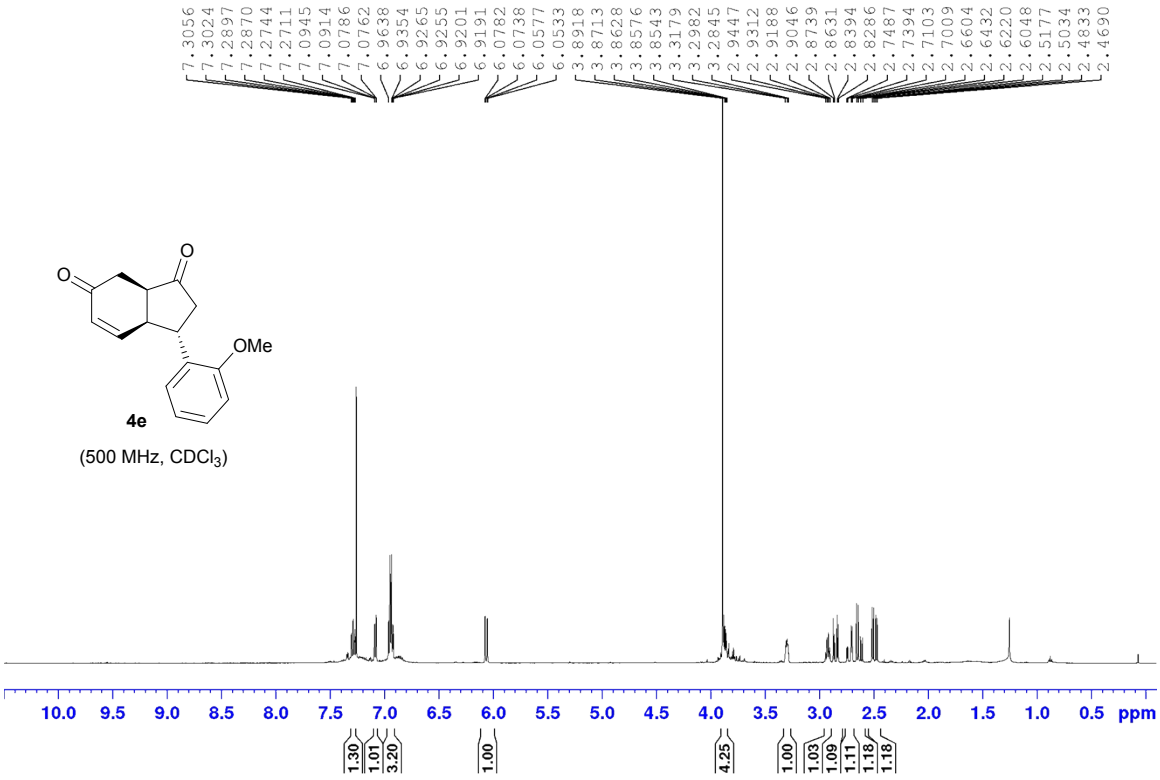


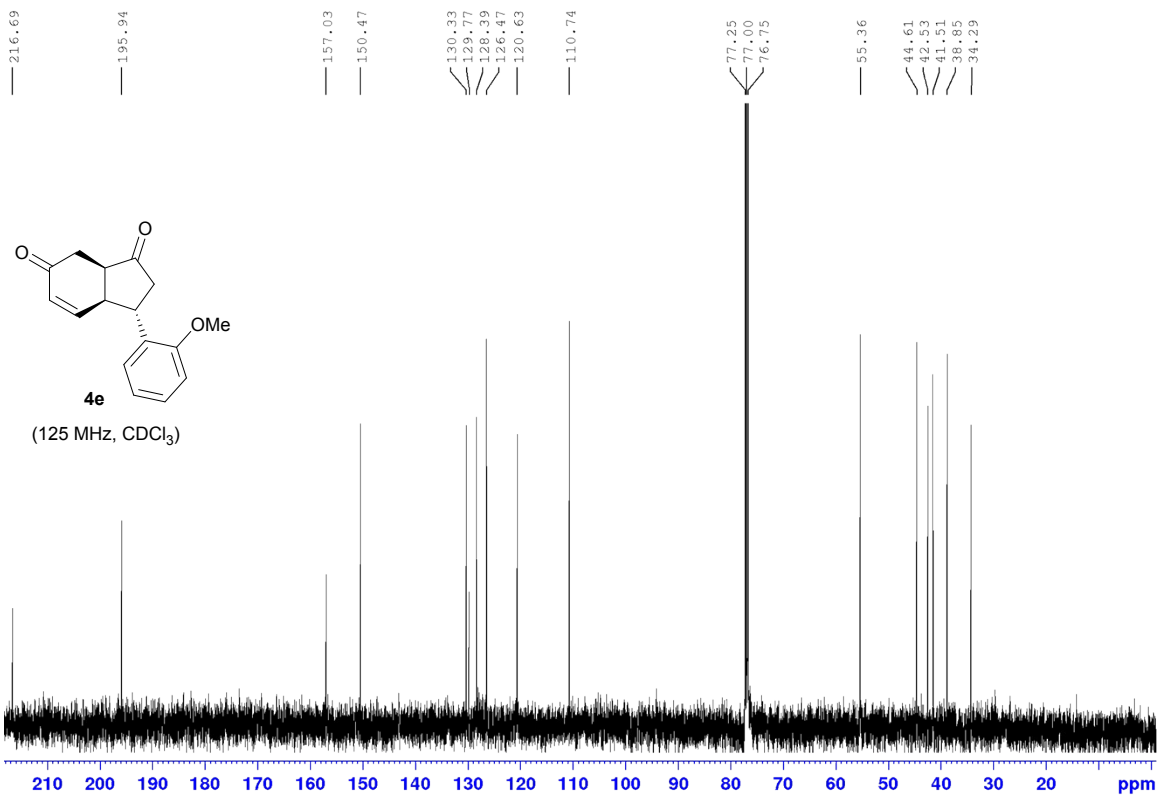
Representative NOEs of compound 4a

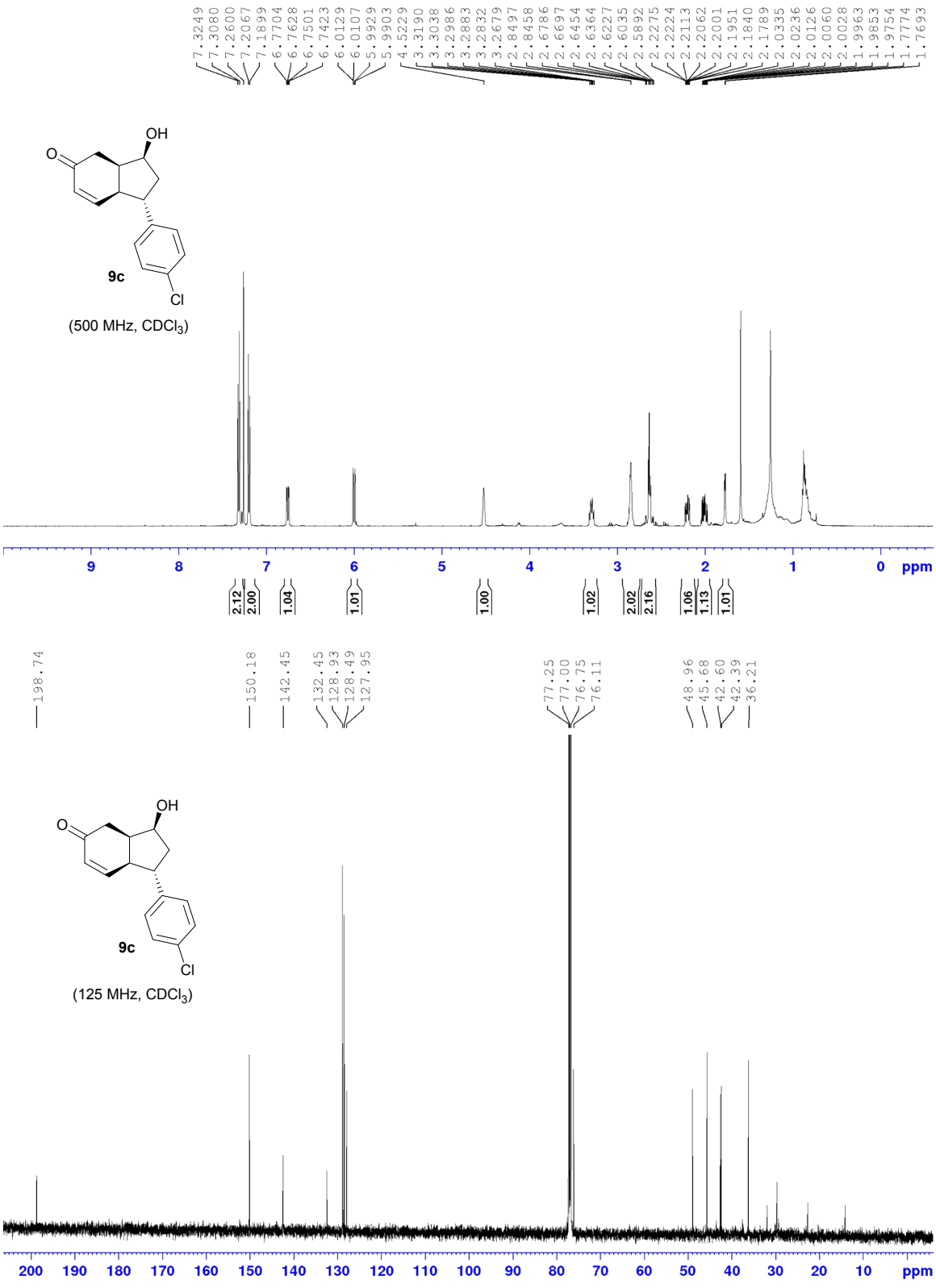


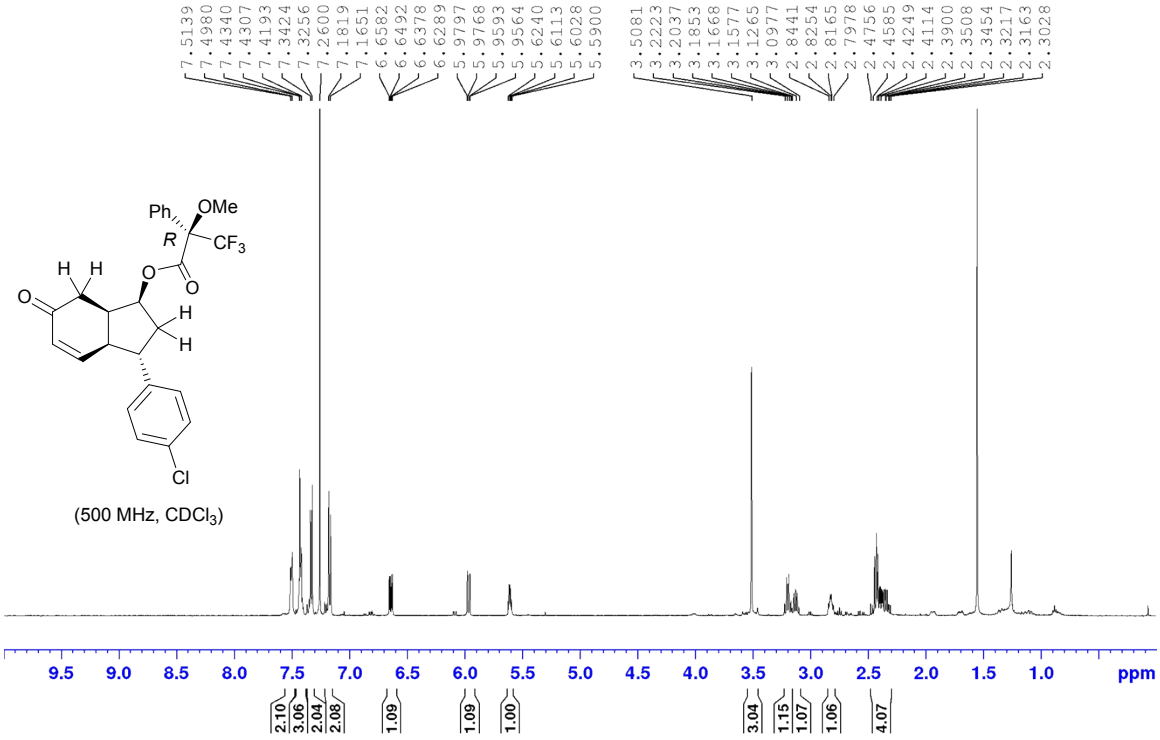

7.3620
7.3489
7.3451
7.2600
7.2154
7.1984
6.8318
6.8247
6.8113
6.8042
6.0893
6.0852
6.0688
6.0647
3.5763
3.5639
3.5480
3.5357
3.2080
3.1893
3.1859
3.1707
3.0181
3.0035
2.9888
2.9743
2.7846
2.7760
2.7700
2.7598
2.7502
2.7377
2.7217
2.6867
2.6739
2.6486
2.6358
2.5704
2.5561
2.5360
2.5217
O
O
4c
(500 MHz, CDCl3)
Cl
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.12
2.13
1.03
1.00
1.06
1.05
1.07
2.14
1.06
1.06

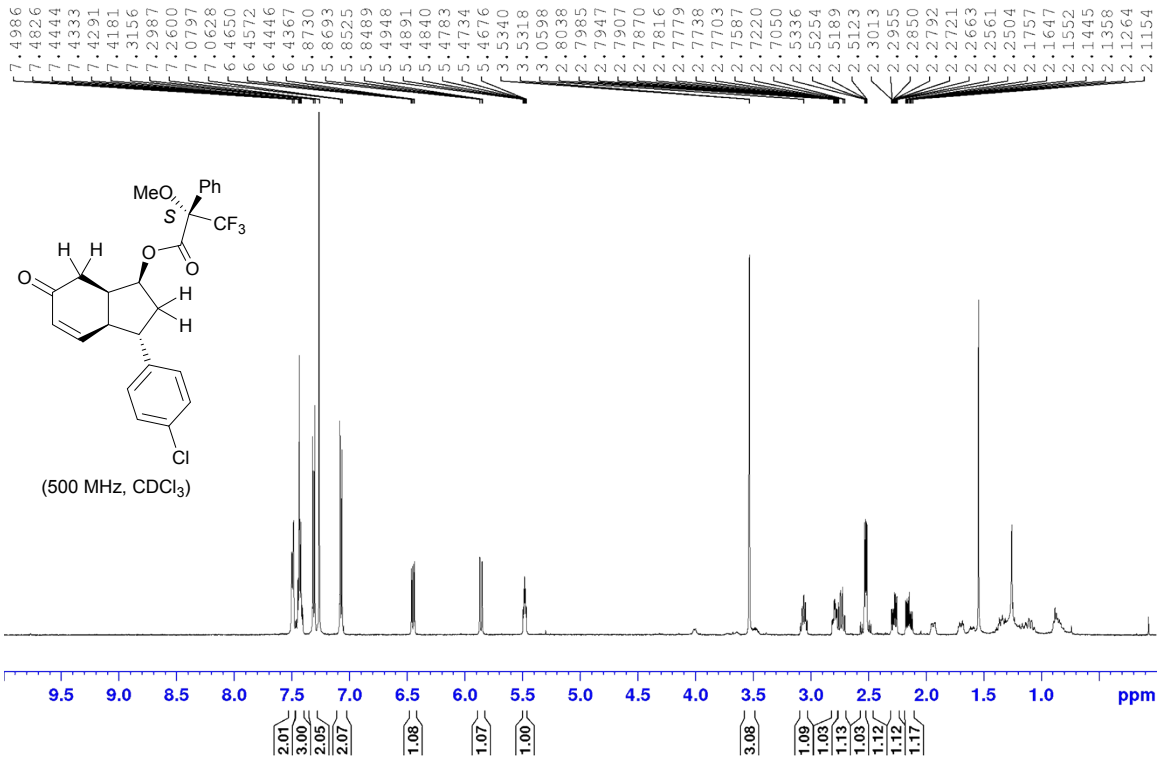

214.86
195.27
148.50
139.74
133.26
130.69
129.19
128.17
77.25
77.00
76.75
44.98
44.39
44.37
43.61
34.06
O
O
4c
(125 MHz, CDCl3)
Cl
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.3056
7.3024
7.2897
7.2870
7.2744
7.2711
7.0945
7.0914
7.0786
7.0762
6.9638
6.9354
6.9265
6.9255
6.9201
6.9191
6.0782
6.0738
6.0577
6.0533
3.8918
3.8713
3.8628
3.8576
3.8543
3.3179
3.2982
3.2845
2.9447
2.9312
2.9188
2.9046
2.8739
2.8631
2.8394
2.8286
2.7487
2.7394
2.7103
2.7009
2.6604
2.6432
2.6220
2.6048
2.5177
2.5034
2.4833
2.4690
O
O
OMe
4e
(500 MHz, CDCl3)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.30
1.01
3.20
1.00
4.25
1.00
1.03
1.09
1.11
1.18
1.18

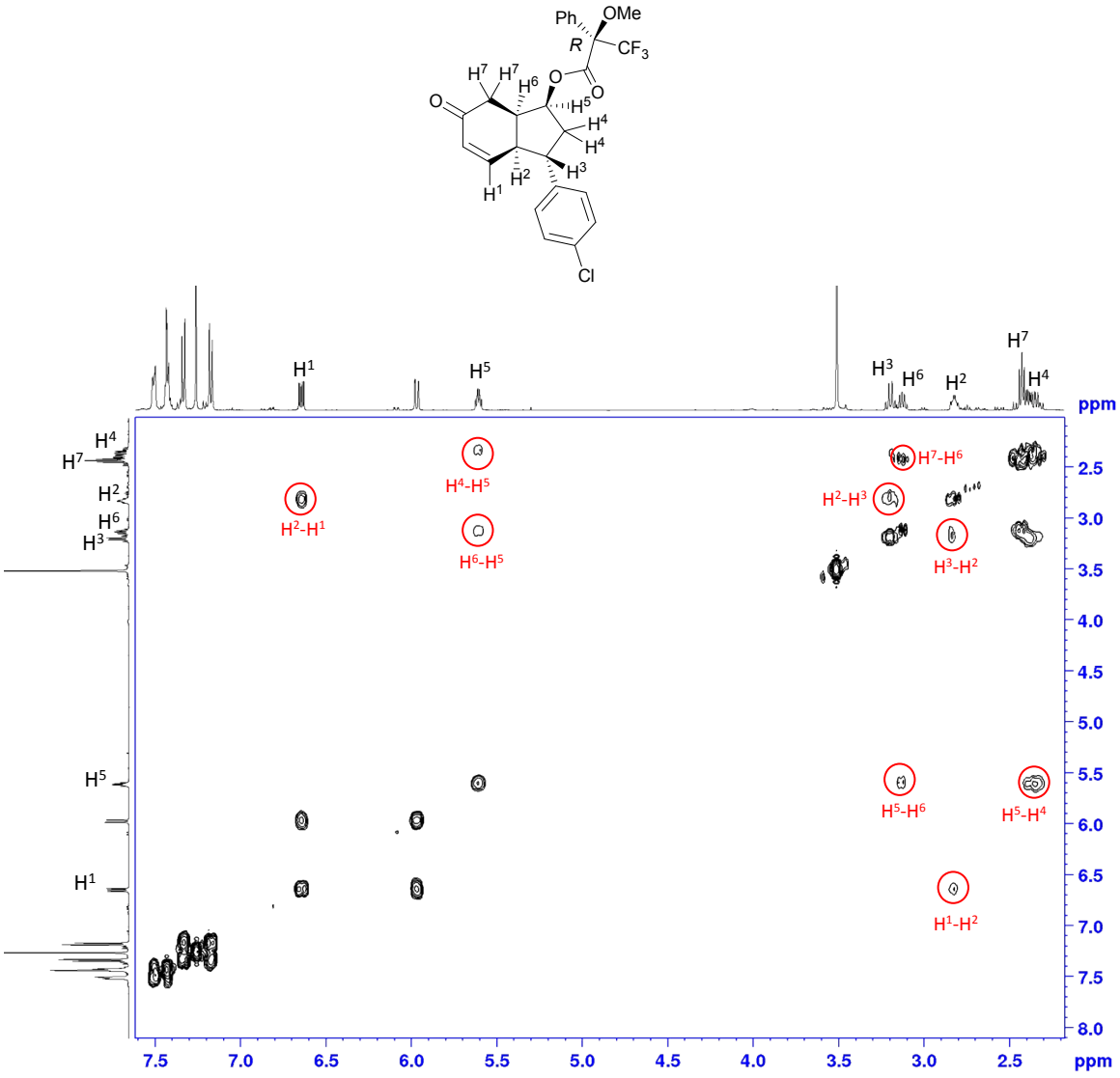

216.69
195.94
157.03
150.47
130.33
129.77
128.39
126.47
120.63
110.74
77.25
77.00
76.75
55.36
44.61
42.53
41.51
38.85
34.29
O
O
OMe
4e
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


7.3249
7.3080
7.2600
7.2067
7.1899
6.7704
6.7628
6.7501
6.7423
6.0129
6.0107
5.9929
5.9903
4.5229
3.3190
3.3038
3.2986
3.2883
3.2832
3.2679
2.8497
2.8458
2.6786
2.6697
2.6454
2.6364
2.6227
2.6035
2.5892
2.2275
2.2224
2.2113
2.2062
2.2001
2.1951
2.1840
2.1789
2.0335
2.0236
2.0126
2.0060
2.0028
1.9963
1.9853
1.9754
1.7774
1.7693
OH
O
9c
Cl
(500 MHz, CDCl3)
9
8
7
6
5
4
3
2
1
0
ppm
2.12
2.00
1.04
1.01
1.00
1.02
2.02
2.16
1.06
1.13
1.01
198.74
150.18
142.45
132.45
128.93
128.49
127.95
77.25
77.00
76.75
76.11
48.96
45.68
42.60
42.39
36.21
OH
O
9c
Cl
(125 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

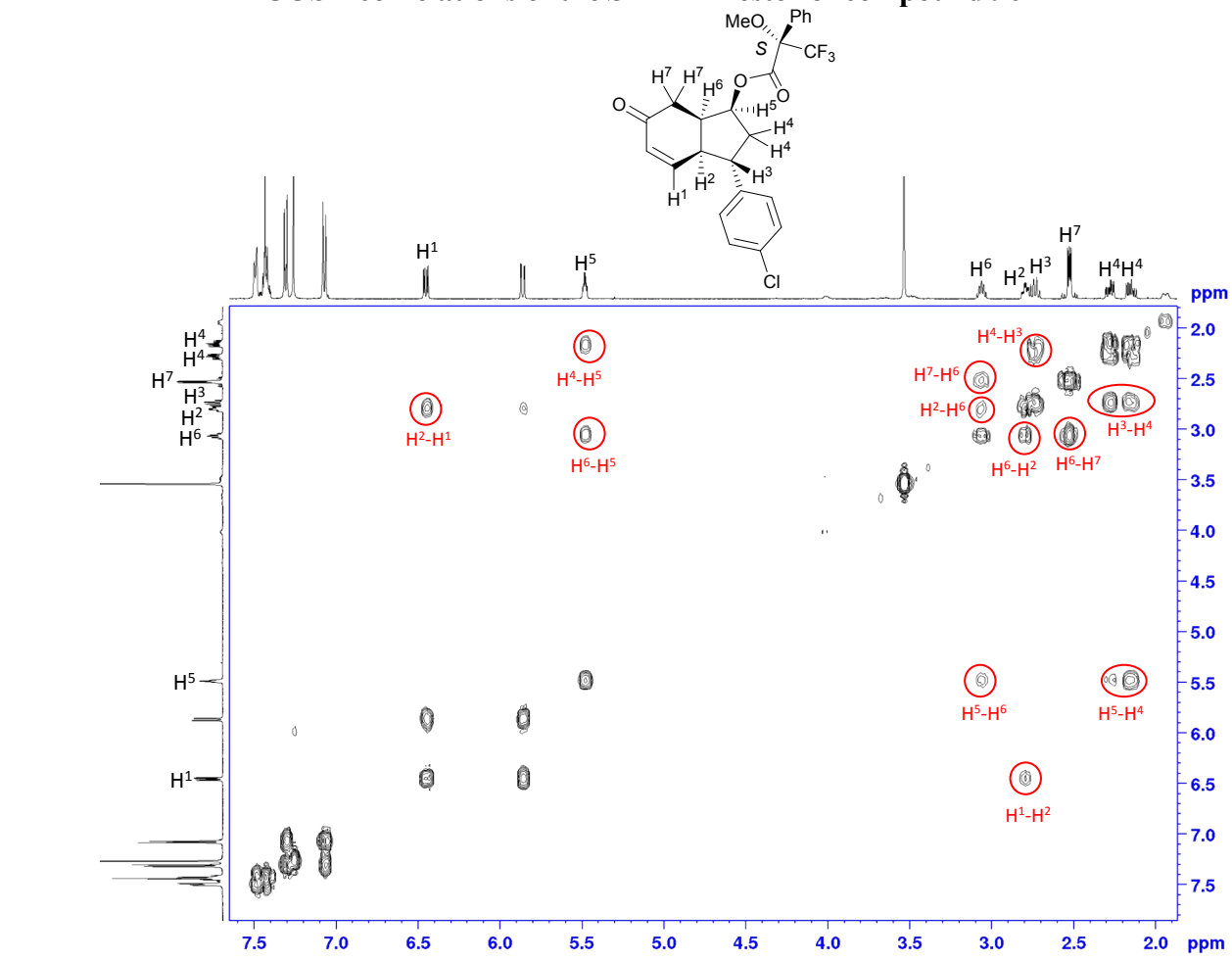

Ph
OMe
R
CF3
H H
O
O
O
O
H
H
Cl
(500 MHz, CDCl3)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm


MeO
Ph
S
CF3
H H
O
O
O
O
H
H
Cl
(500 MHz, CDCl3)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

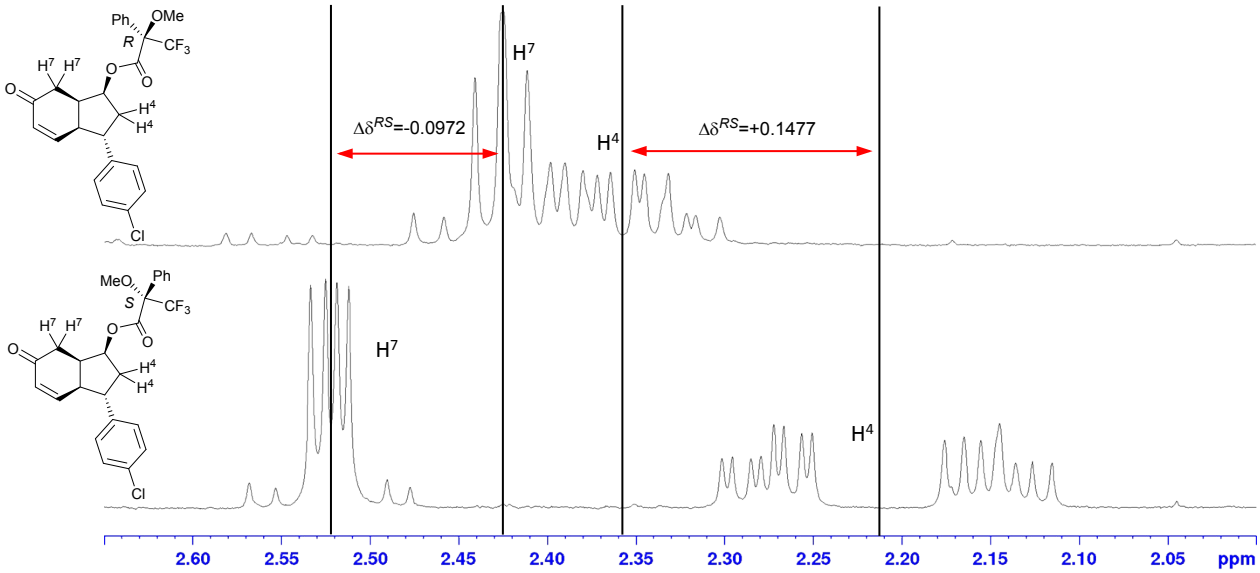
COSY correlations of the *R*-MTPA ester of compound 9c



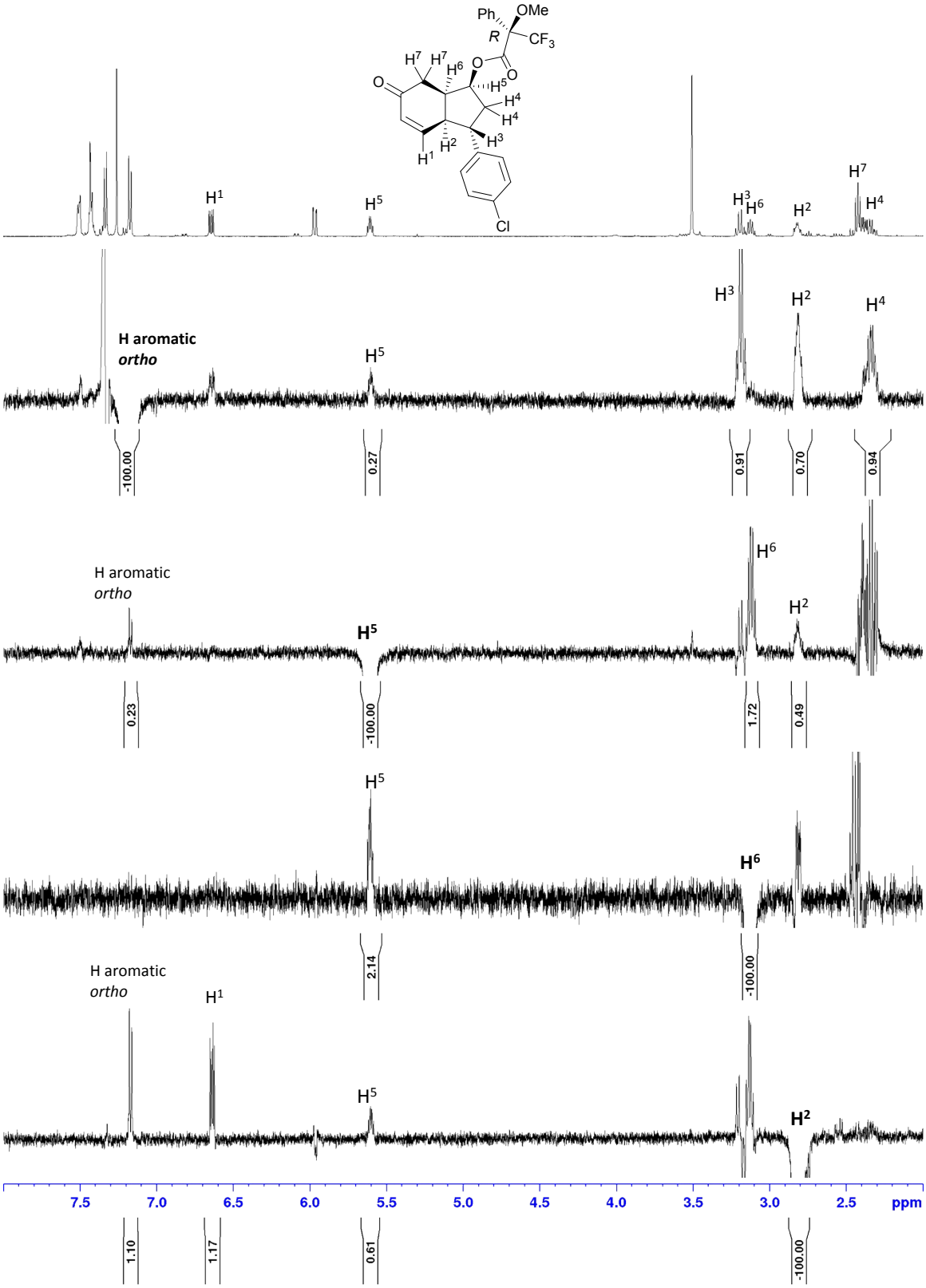
COSY correlations of the *S*-MTPA ester of compound 9c



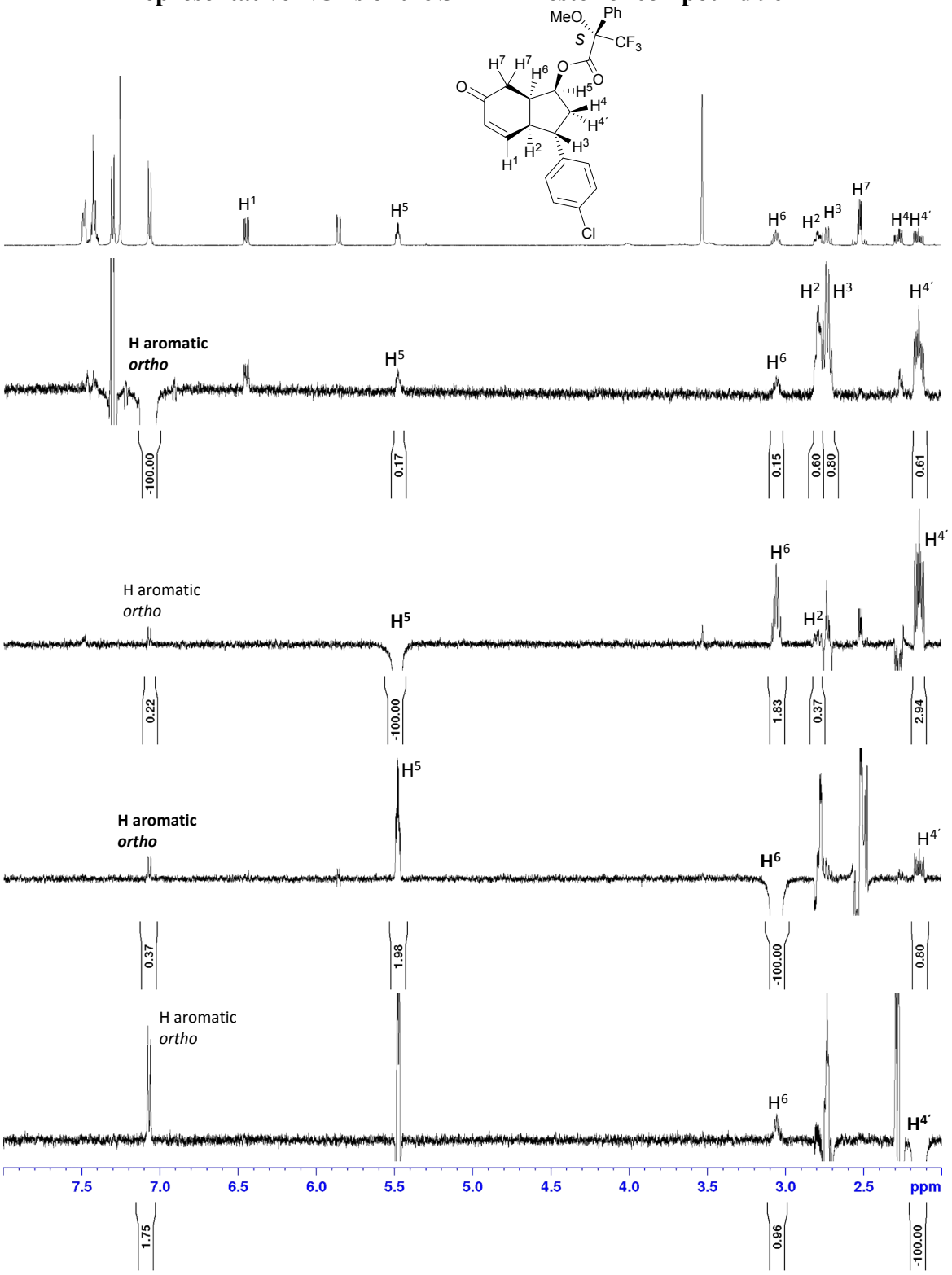
Comparison of the ^{1}H NMR spectrum of the *R* and *S*-MTPA ester of 9c

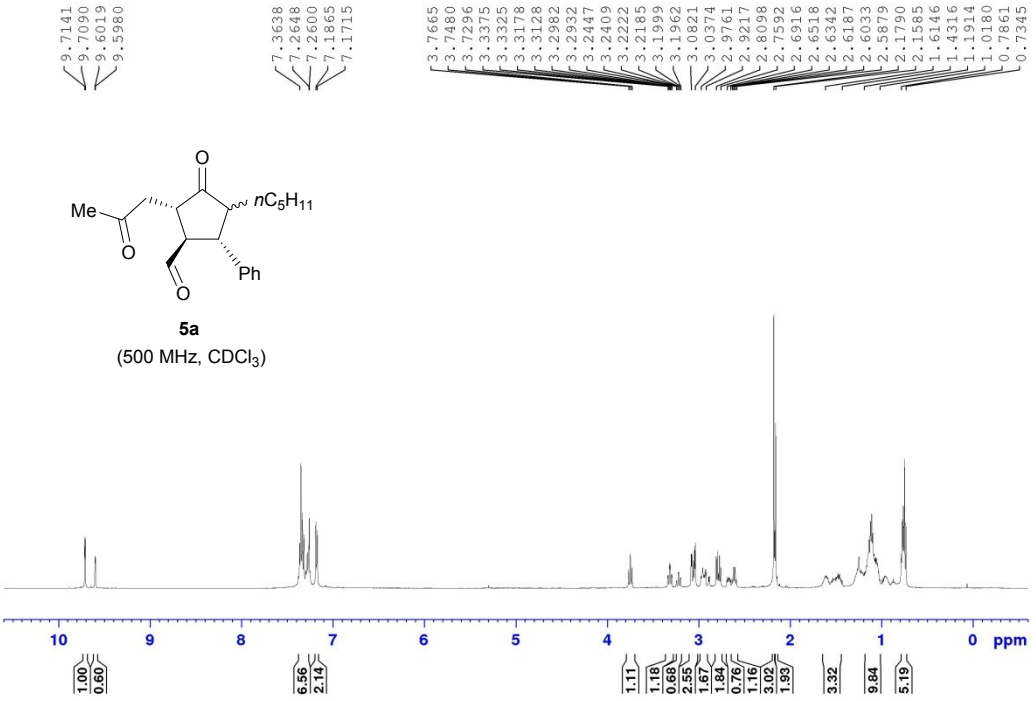


Representative NOEs of the *R*-MTPA ester of compound 9c



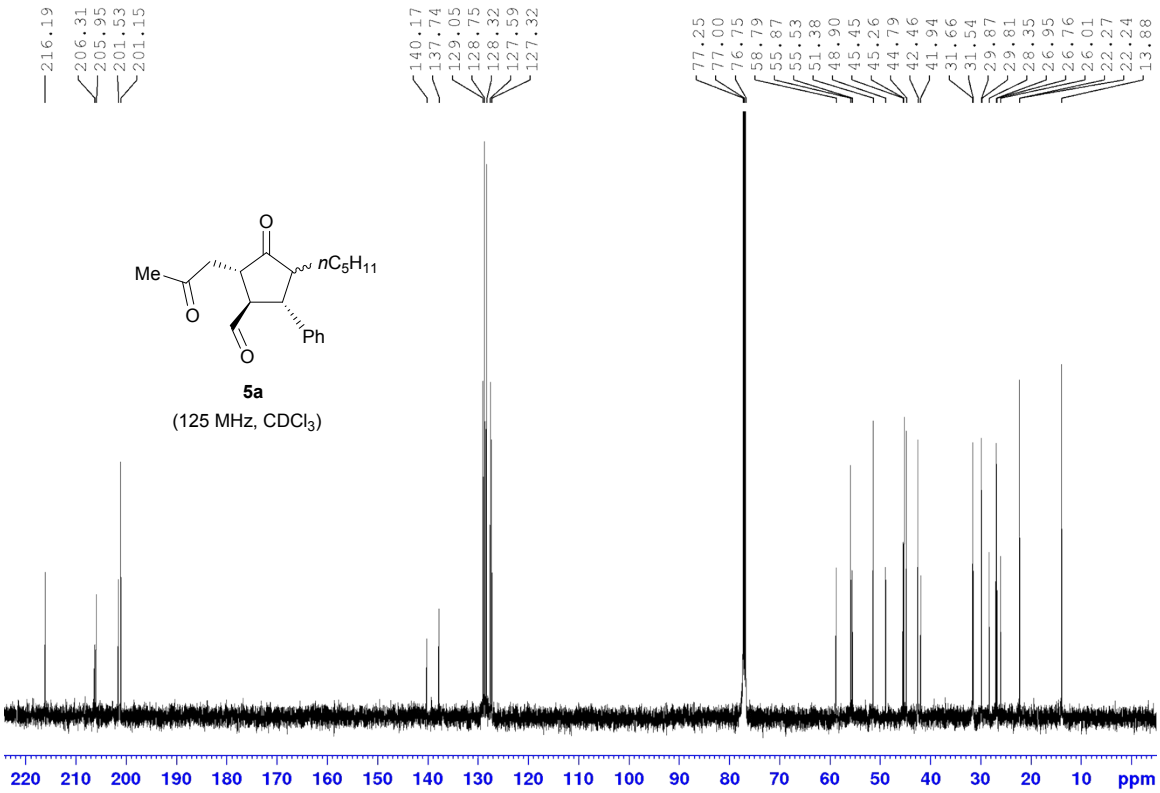
Representative NOEs of the *S*-MTPA ester of compound 9c





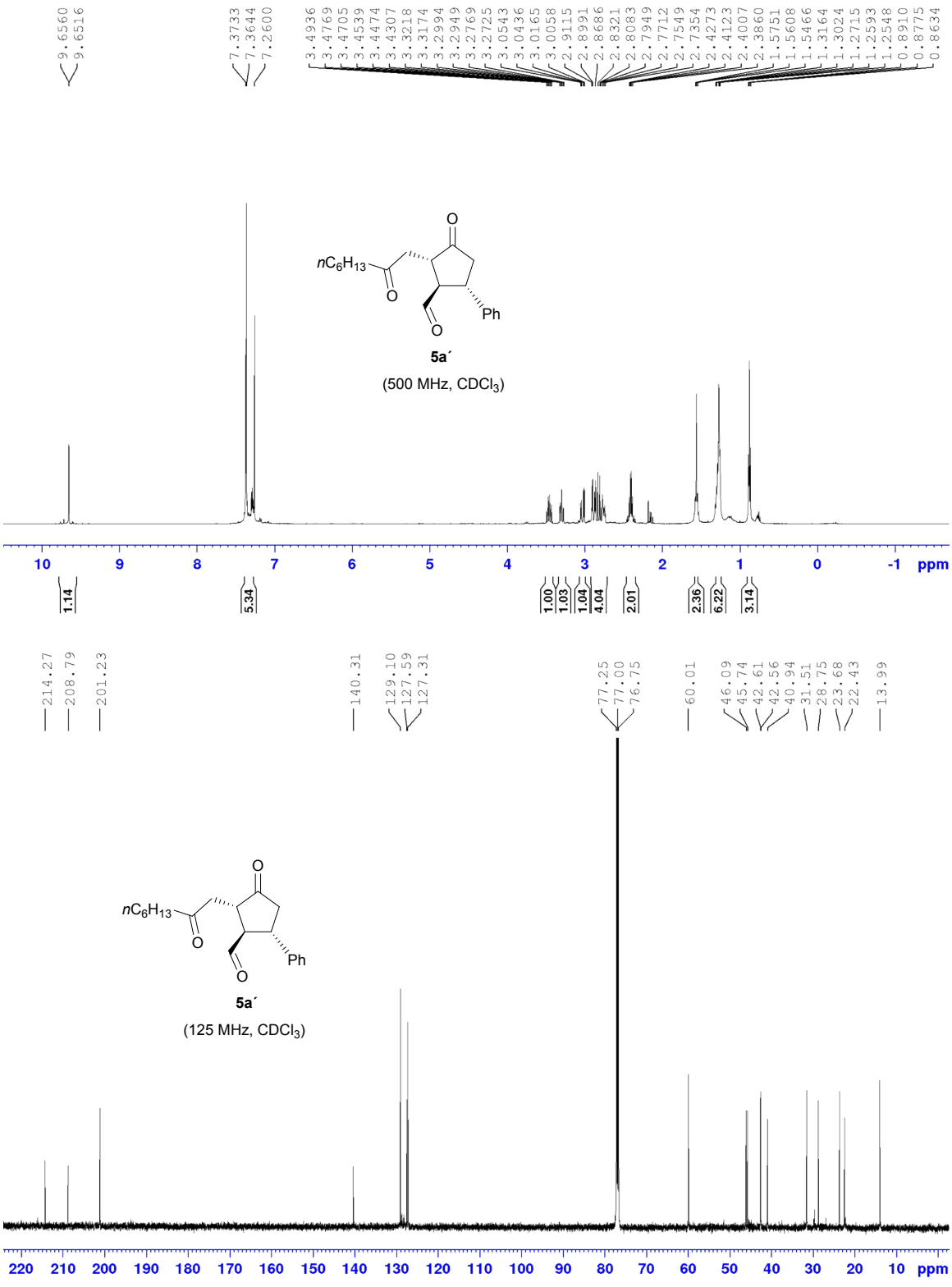
5a

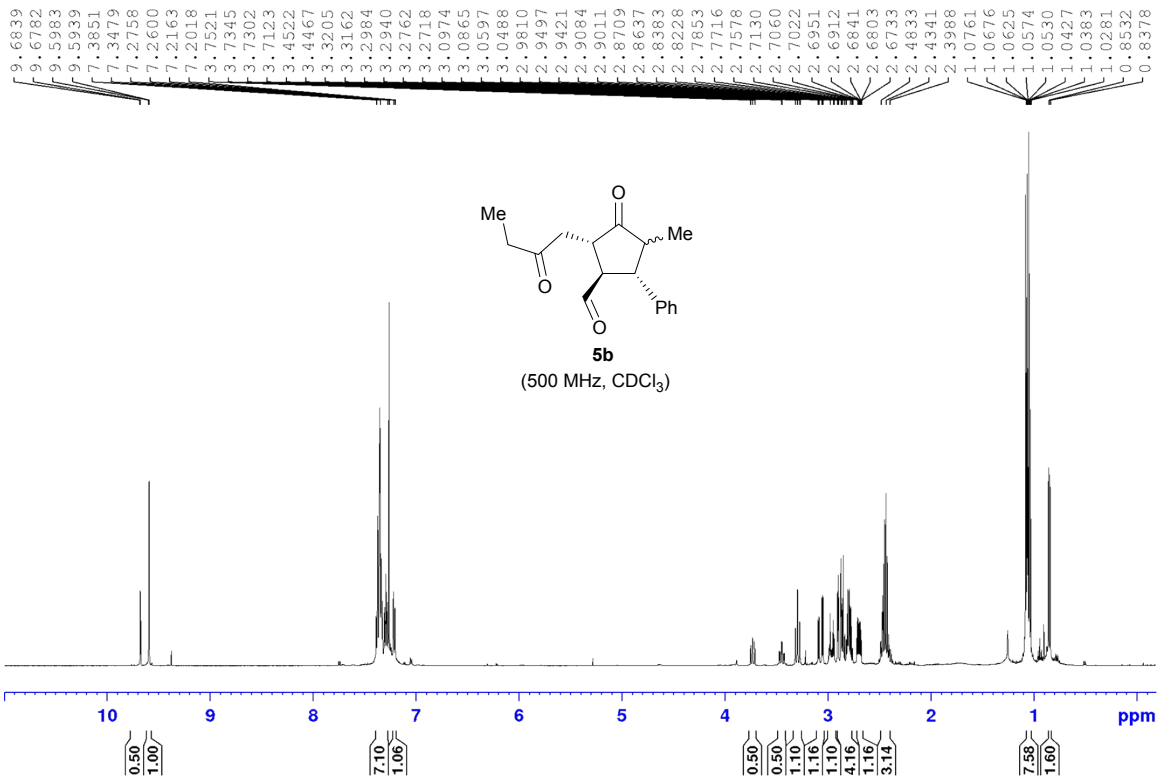
(500 MHz, $CDCl_3$)

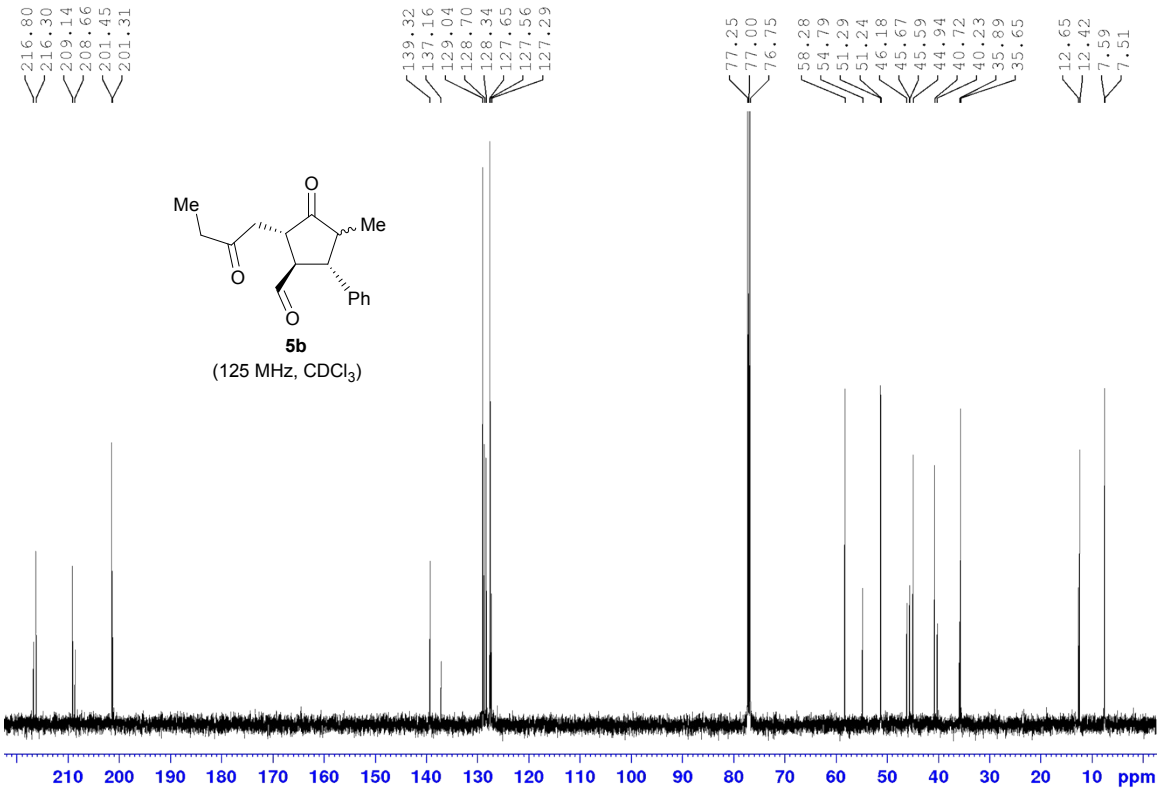


5a

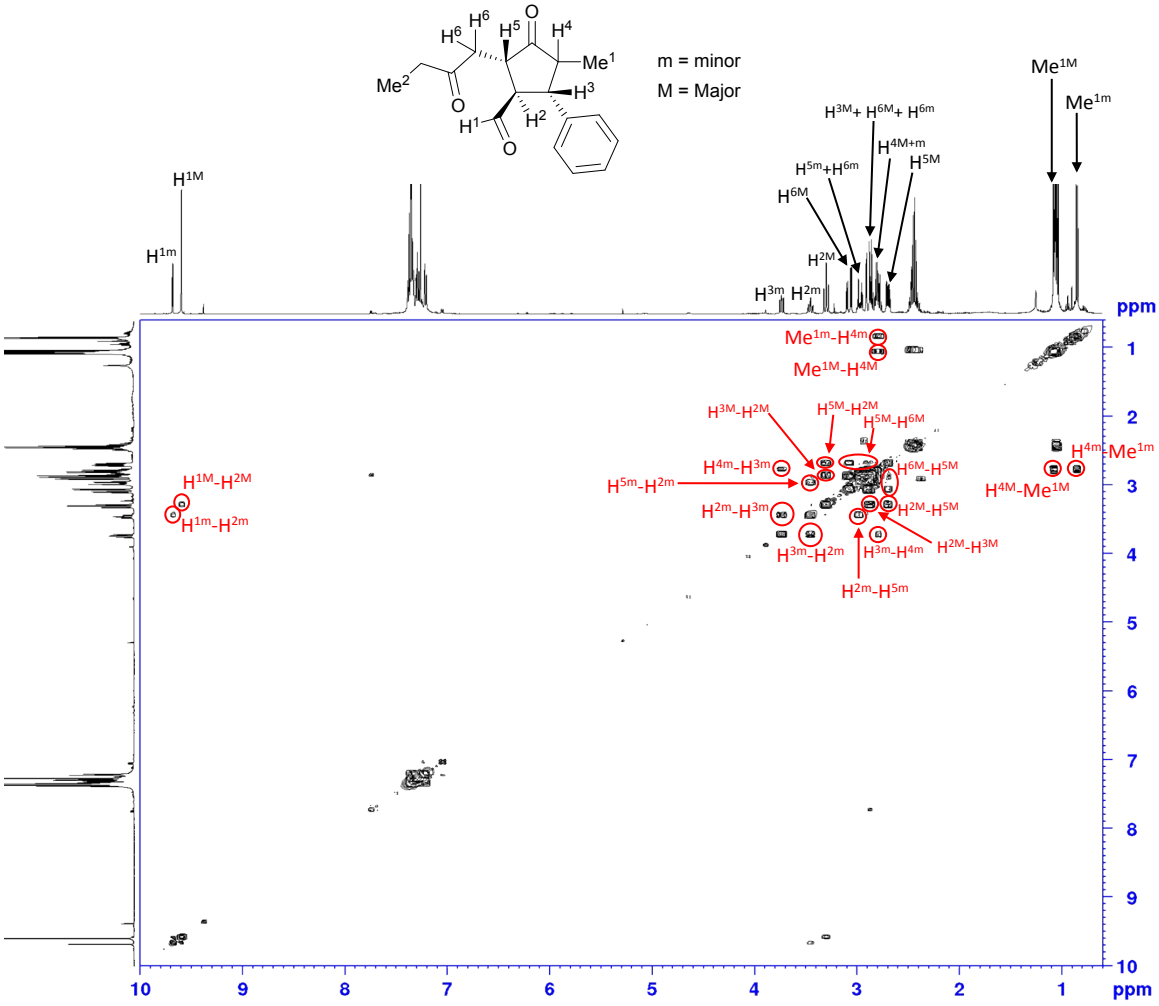
(125 MHz, $CDCl_3$)


9.6560
9.6516
7.3733
7.3644
7.2600
3.4936
3.4769
3.4705
3.4539
3.4474
3.4307
3.3218
3.3174
3.2994
3.2949
3.2769
3.2725
3.0543
3.0436
3.0165
3.0058
2.9115
2.8991
2.8686
2.8321
2.8083
2.7949
2.7712
2.7549
2.7354
2.4273
2.4123
2.4007
2.3860
1.5751
1.5608
1.5466
1.3164
1.3024
1.2715
1.2593
1.2548
0.8910
0.8775
0.8634
nC6H13
O
O
O
Ph
5a´
(500 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.14
5.34
1.00
1.03
1.04
4.04
2.01
2.36
6.22
3.14
214.27
208.79
201.23
140.31
129.10
127.59
127.31
77.25
77.00
76.75
60.01
46.09
45.74
42.61
42.56
40.94
31.51
28.75
23.68
22.43
13.99
nC6H13
O
O
O
Ph
5a´
(125 MHz, CDCl3)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

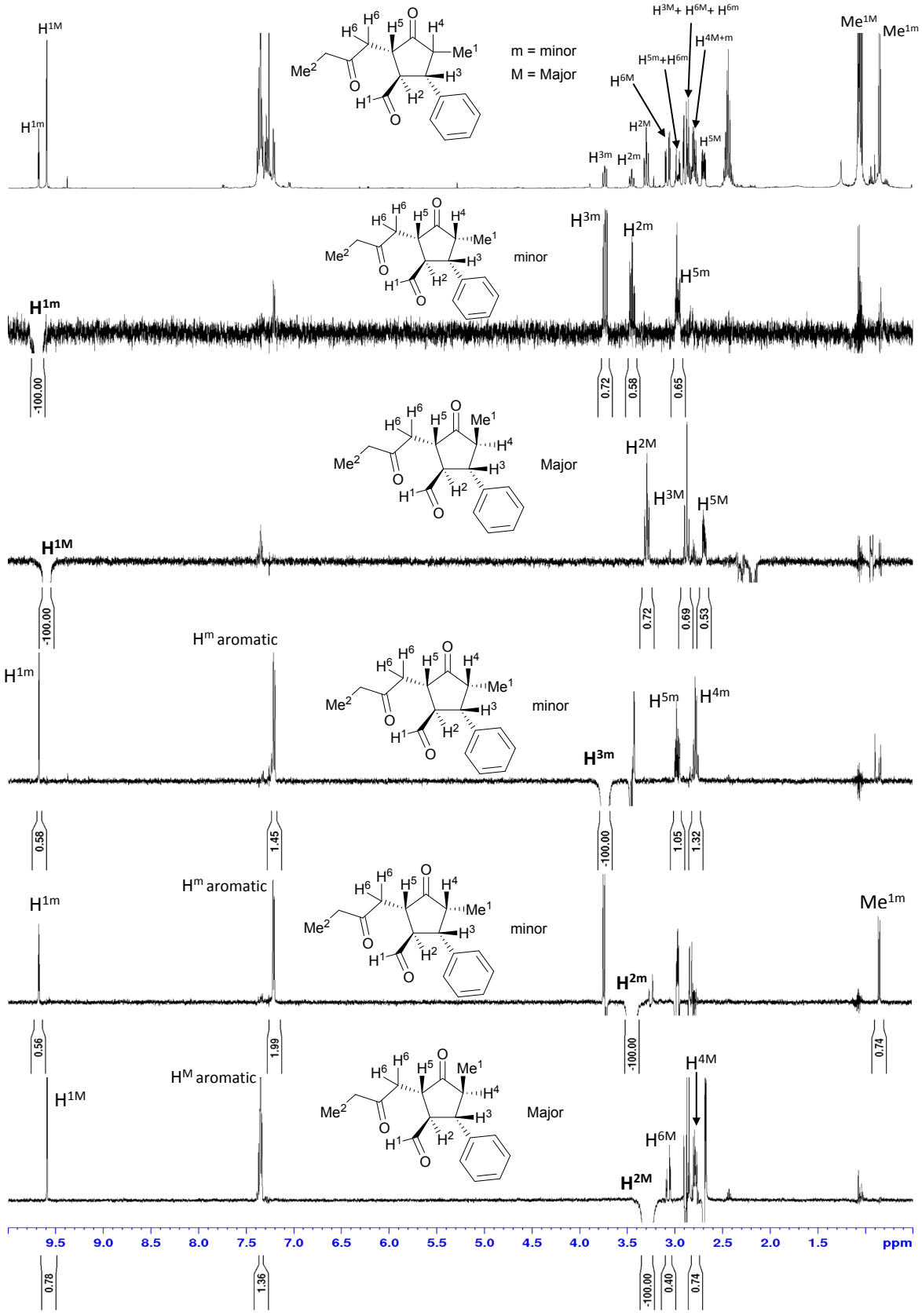

Me
O
Me
O
Ph
O
5b
(500 MHz, CDCl3)
ppm

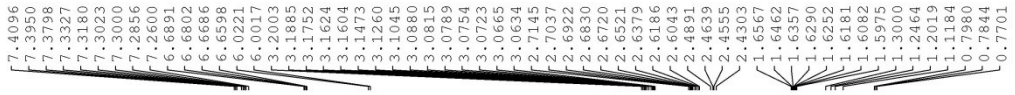

Me
O
Me
O
Ph
O
5b
(125 MHz, CDCl3)
ppm

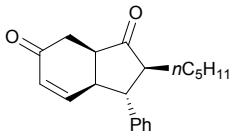
COSY correlations of compound 5b



Representative NOEs of compound 5b

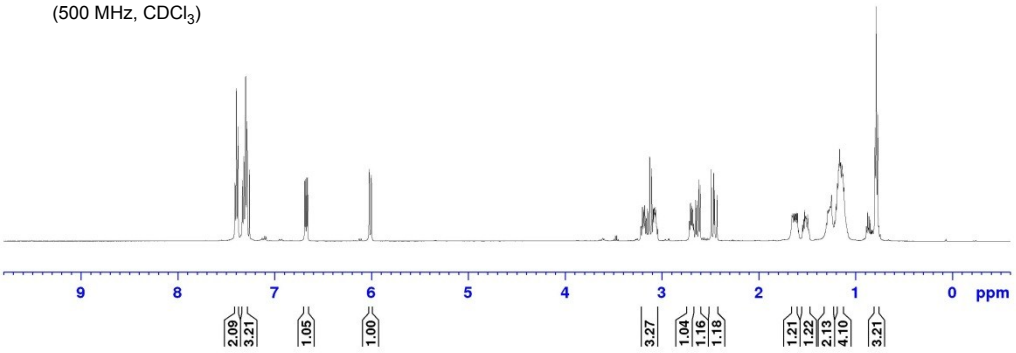


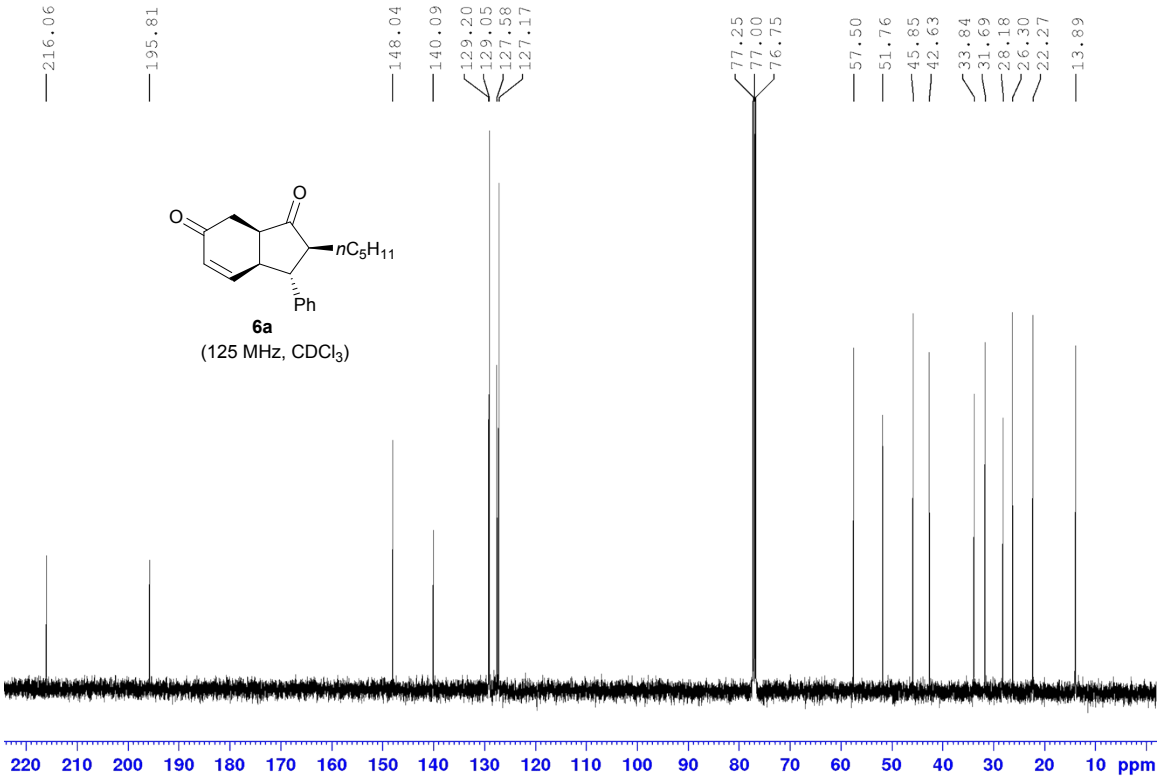




6a

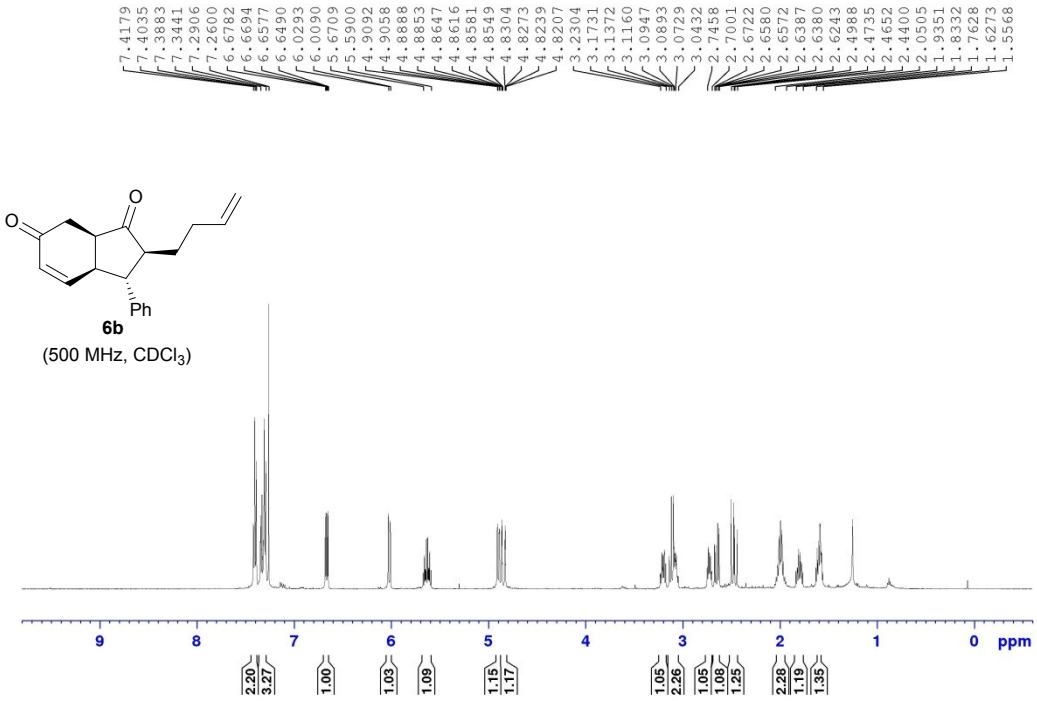
(500 MHz, $CDCl_3$)

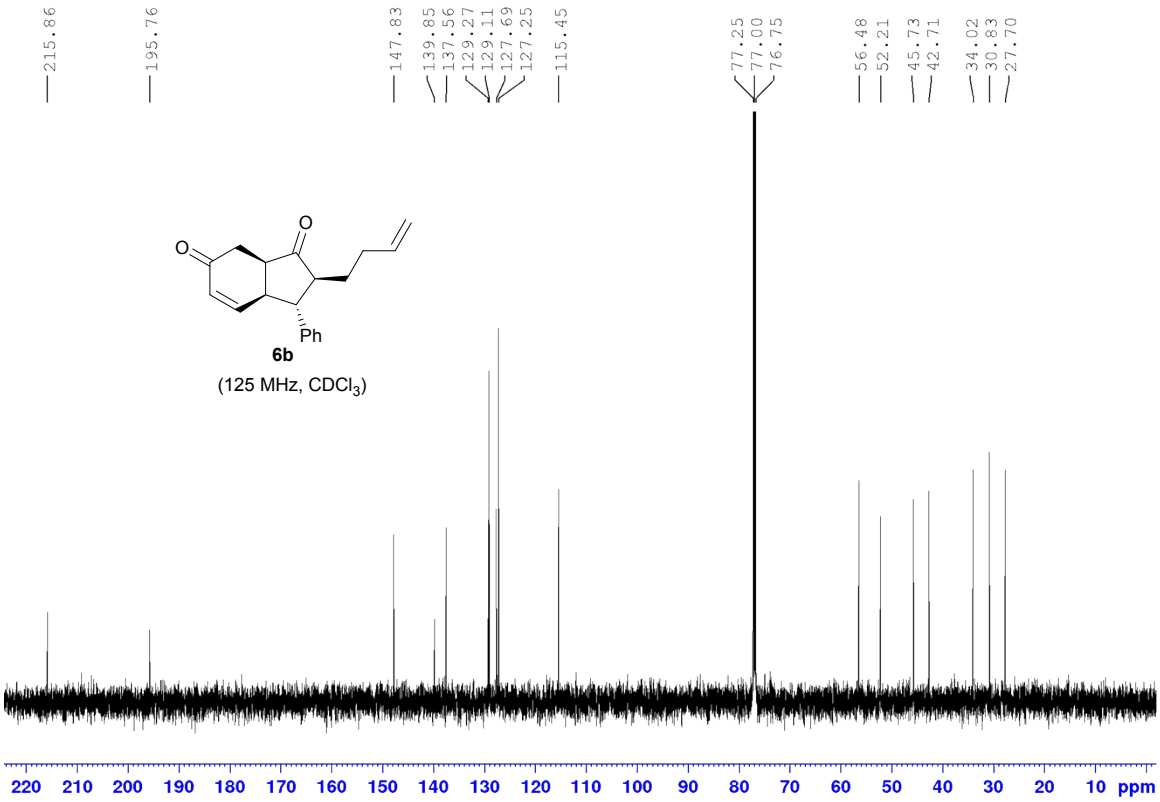


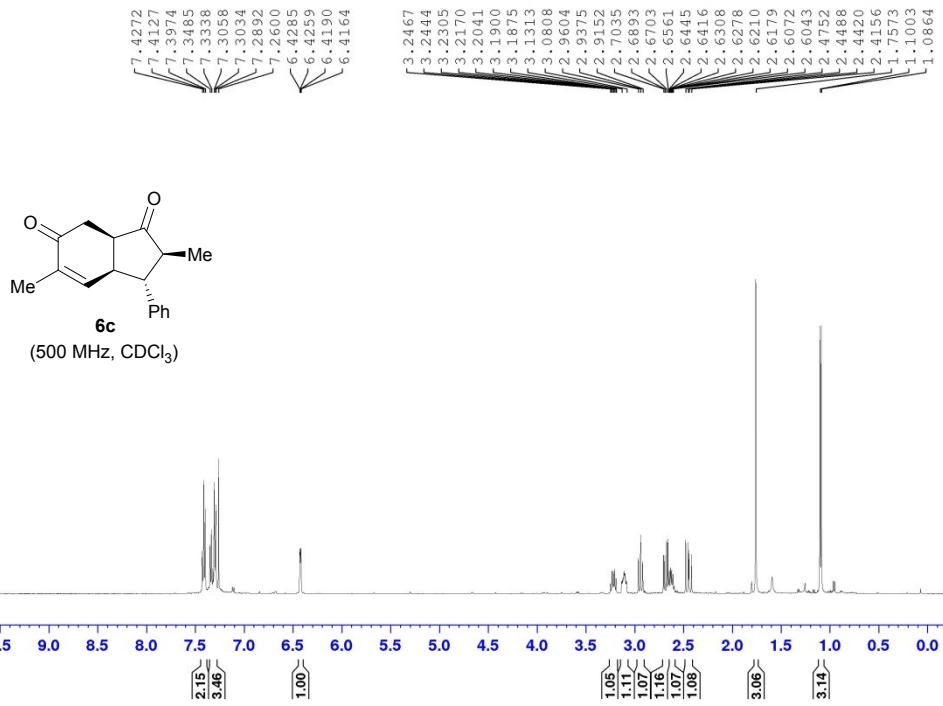


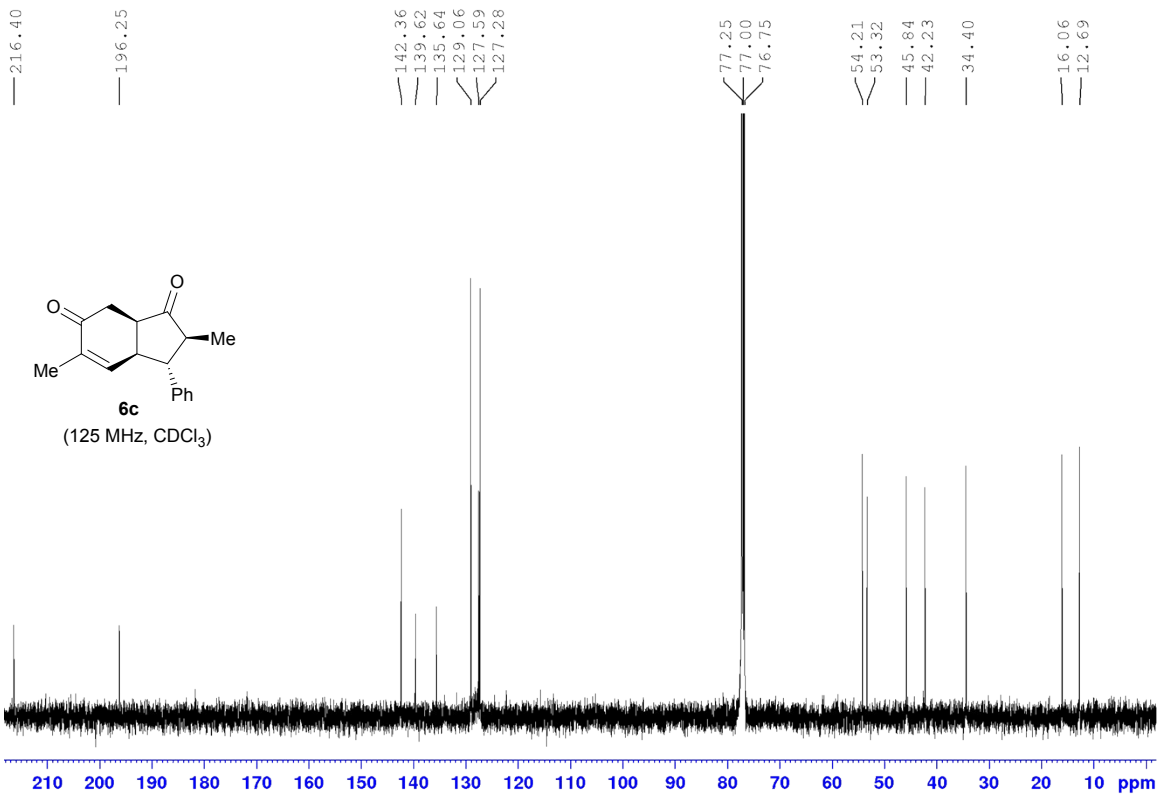
6a

(125 MHz, $CDCl_3$)

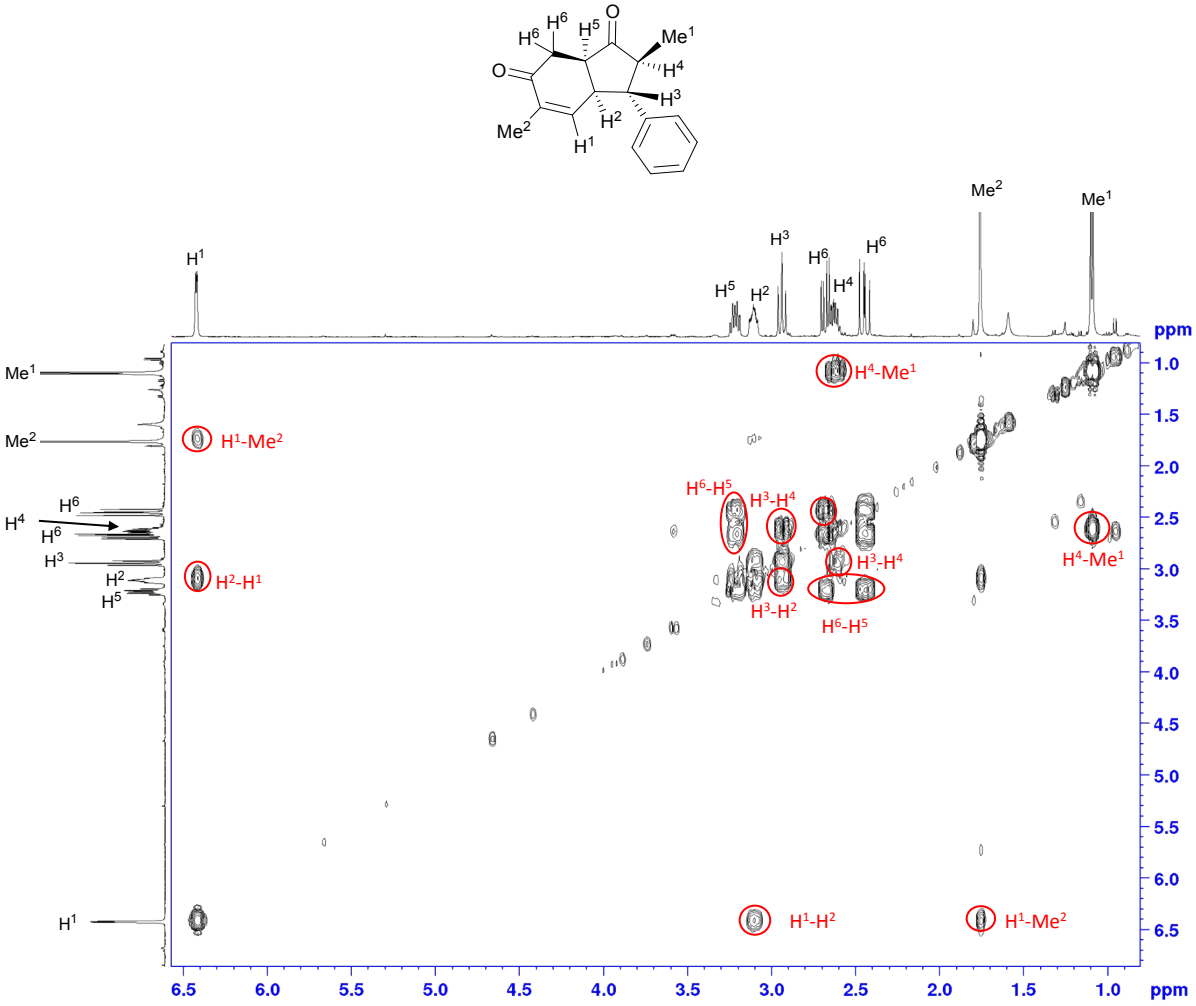

7.4179
7.4035
7.3883
7.3441
7.2906
7.2600
6.6782
6.6694
6.6577
6.6490
6.0293
6.0090
5.6709
5.5900
4.9092
4.9058
4.8888
4.8853
4.8647
4.8616
4.8581
4.8549
4.8304
4.8273
4.8239
4.8207
3.2304
3.1731
3.1372
3.1160
3.0947
3.0893
3.0729
3.0432
2.7458
2.7001
2.6722
2.6580
2.6572
2.6387
2.6380
2.6243
2.4988
2.4735
2.4652
2.4400
2.0505
1.9351
1.8332
1.7628
1.6273
1.5568
O
O
Ph
6b
(500 MHz, CDCl3)
9
8
7
6
5
4
3
2
1
0
ppm
2.20
3.27
1.00
1.03
1.09
1.15
1.17
1.05
2.26
1.05
1.08
1.25
2.28
1.19
1.35


215.86
195.76
147.83
139.85
137.56
129.27
129.11
127.69
127.25
115.45
77.25
77.00
76.75
56.48
52.21
45.73
42.71
34.02
30.83
27.70
O
O
Ph
6b
(125 MHz, CDCl3)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

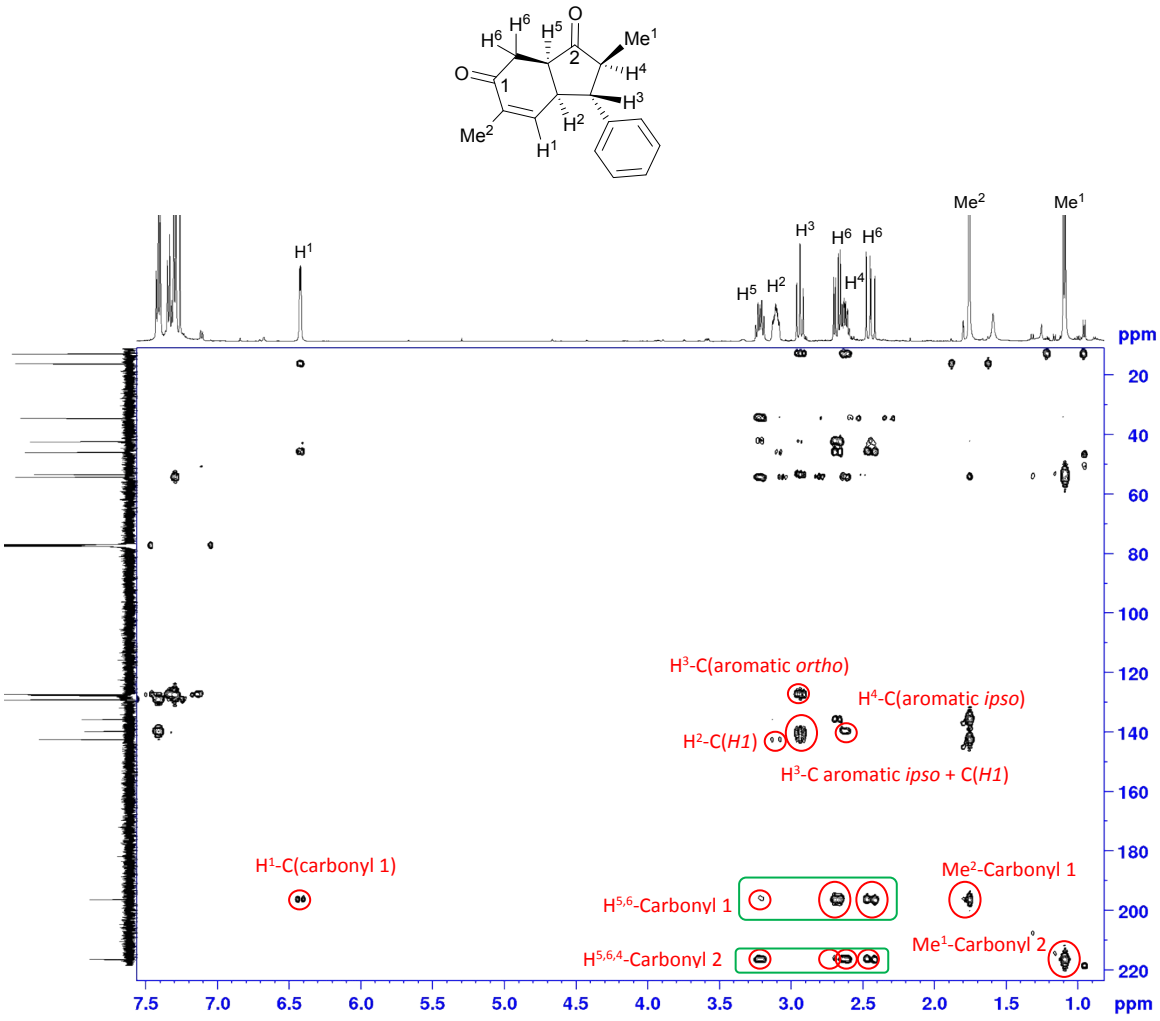

7.4272
7.4127
7.3974
7.3485
7.3338
7.3058
7.3034
7.2892
7.2600
6.4285
6.4259
6.4190
6.4164
3.2467
3.2444
3.2305
3.2170
3.2041
3.1900
3.1875
3.1313
3.0808
2.9604
2.9375
2.9152
2.7035
2.6893
2.6703
2.6561
2.6445
2.6416
2.6308
2.6278
2.6210
2.6179
2.6072
2.6043
2.4752
2.4488
2.4420
2.4156
1.7573
1.1003
1.0864
O
O
Me
Me
Ph
6c
(500 MHz, CDCl3)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.15
3.46
1.00
1.05
1.11
1.07
1.16
1.07
1.08
3.06
3.14


216.40
196.25
142.36
139.62
135.64
129.06
127.59
127.28
77.25
77.00
76.75
54.21
53.32
45.84
42.23
34.40
16.06
12.69
O
O
Me
Me
Ph
6c
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

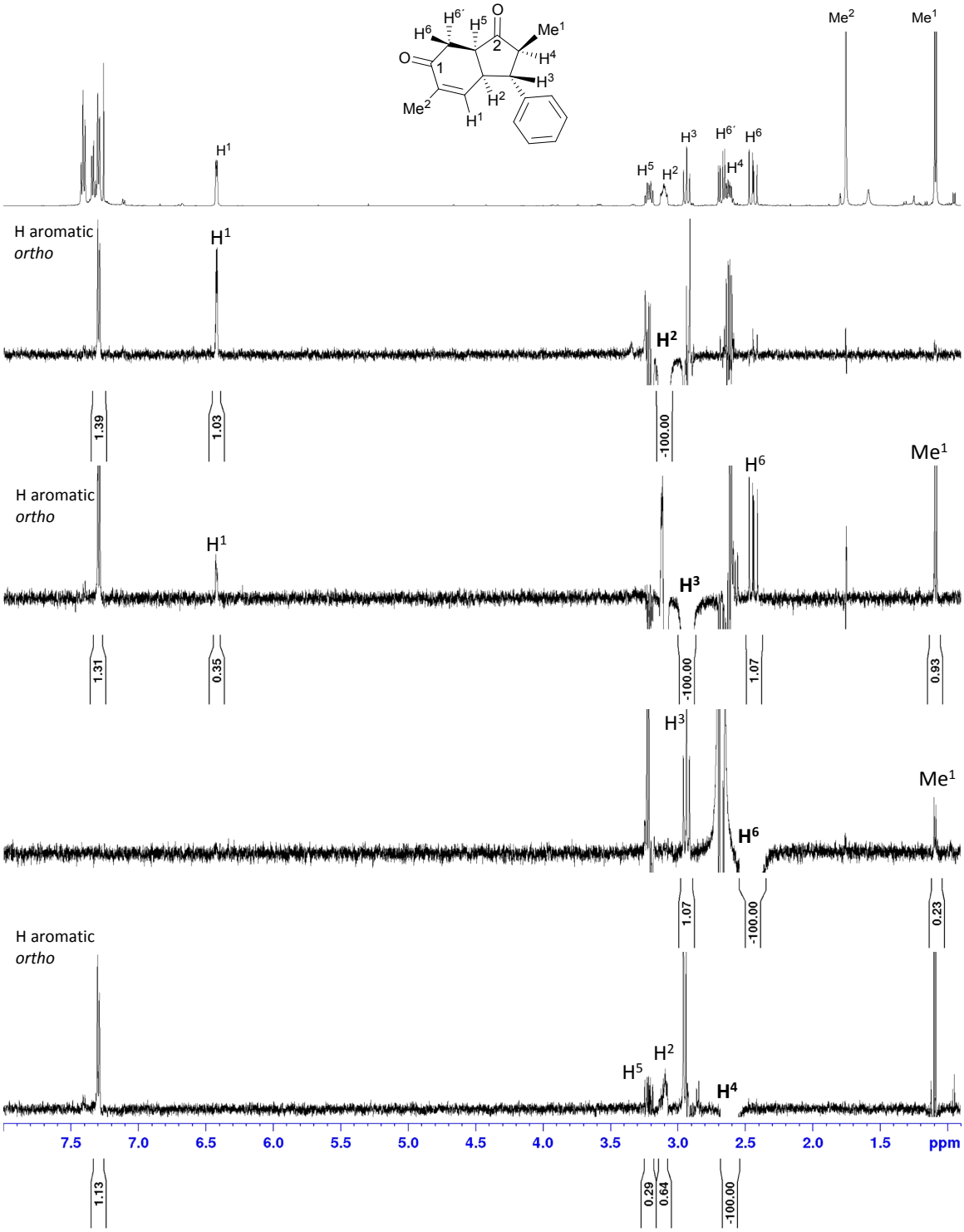
COSY correlations of compound 6c

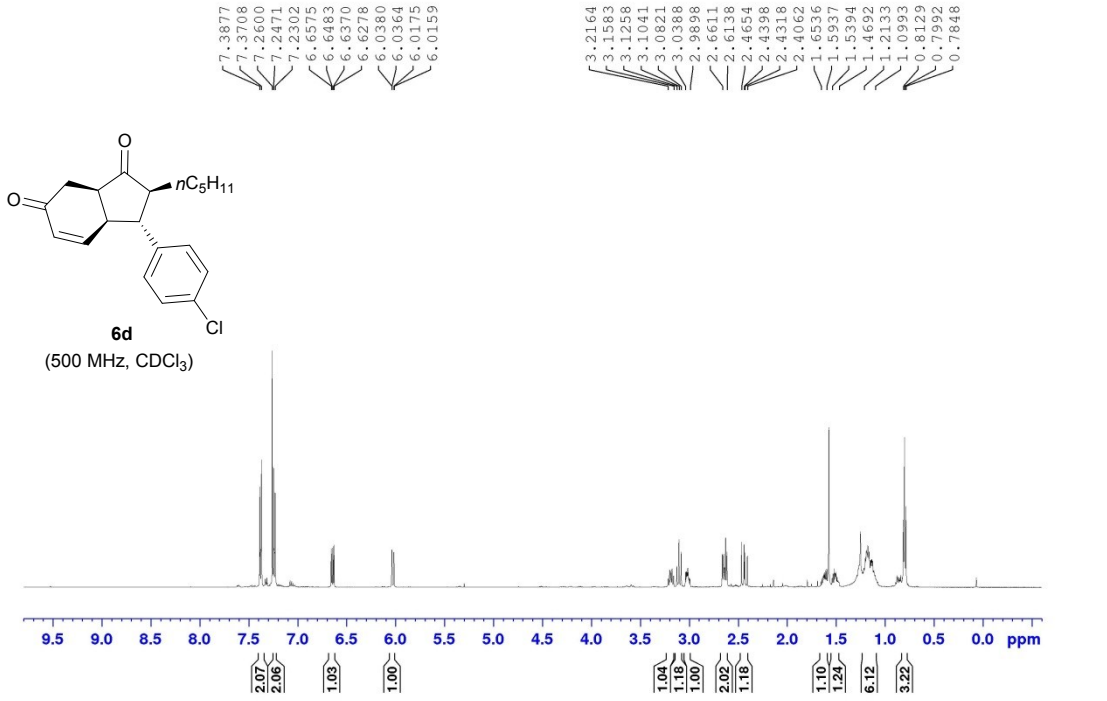


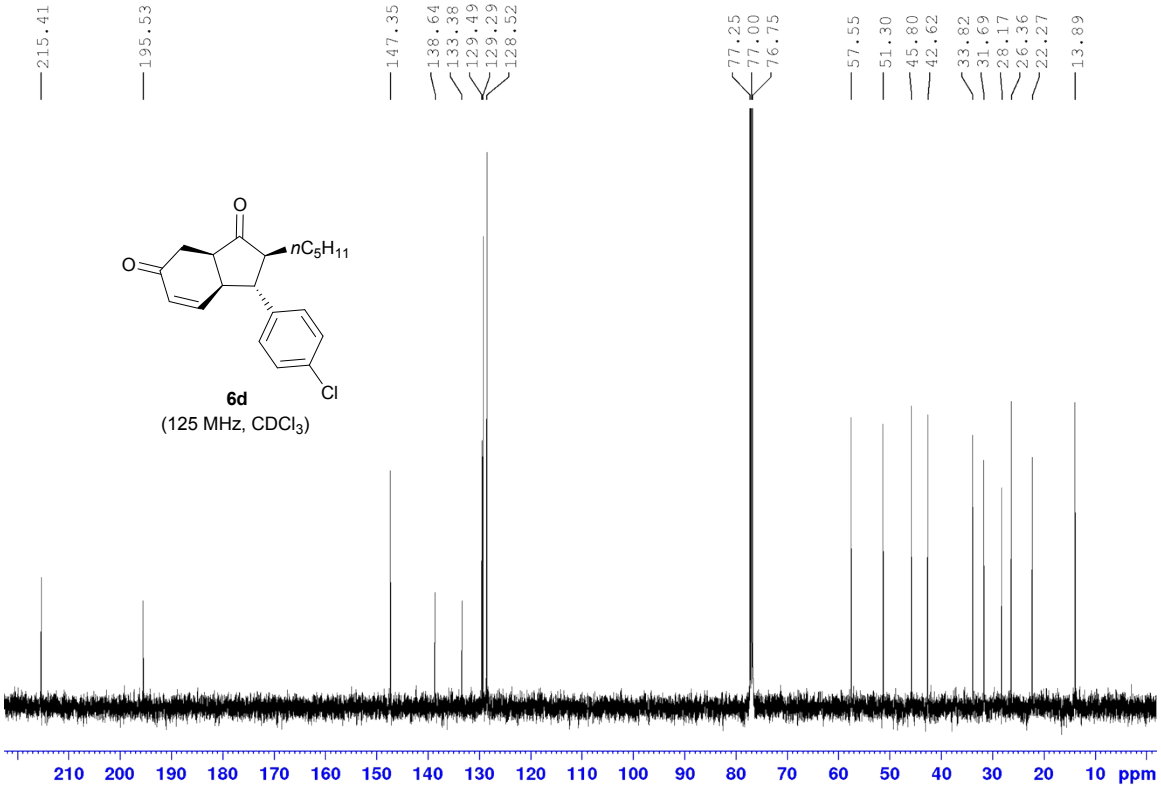
HMBC correlations of compound 6c



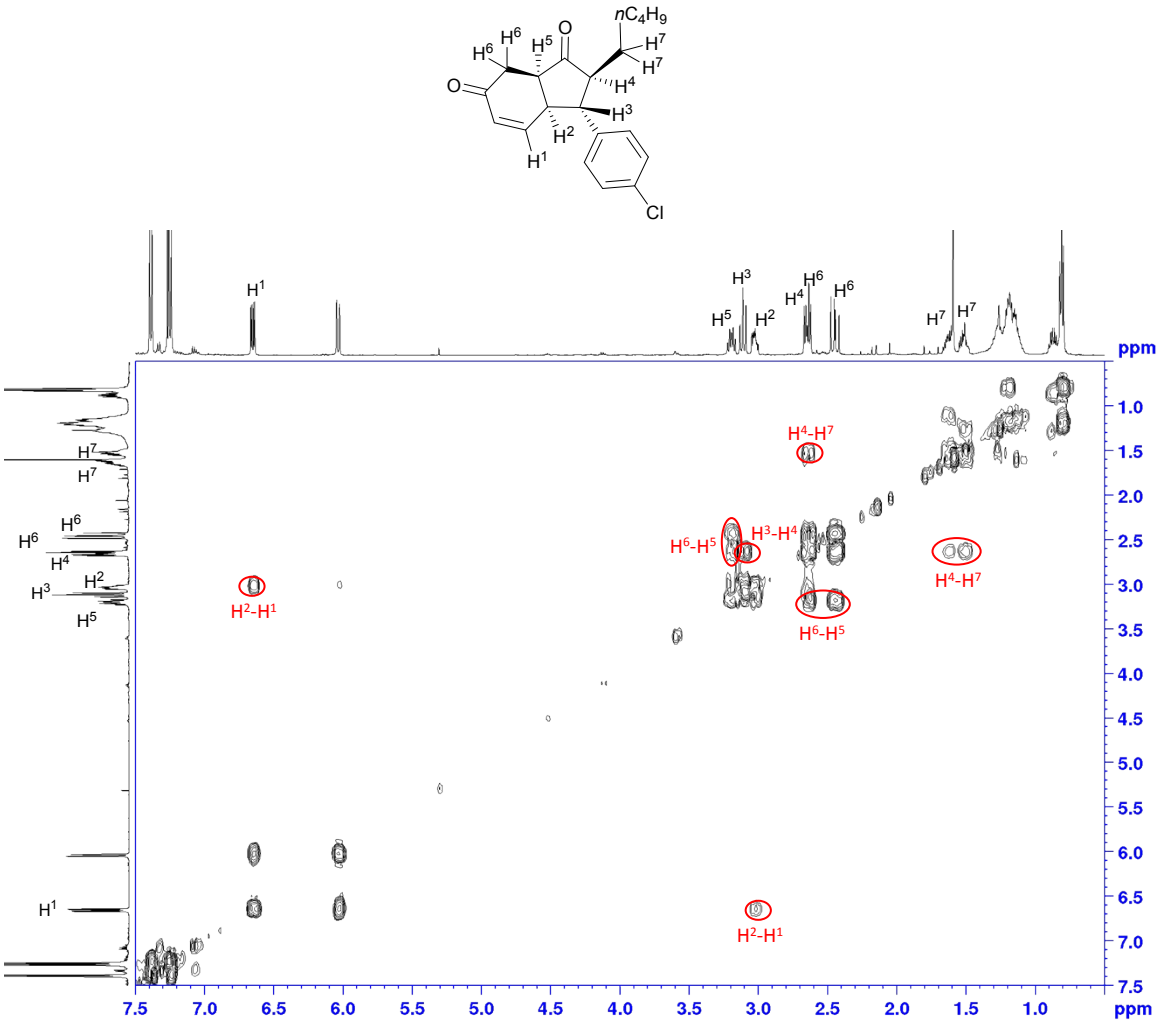
Representative NOEs of compound 6c



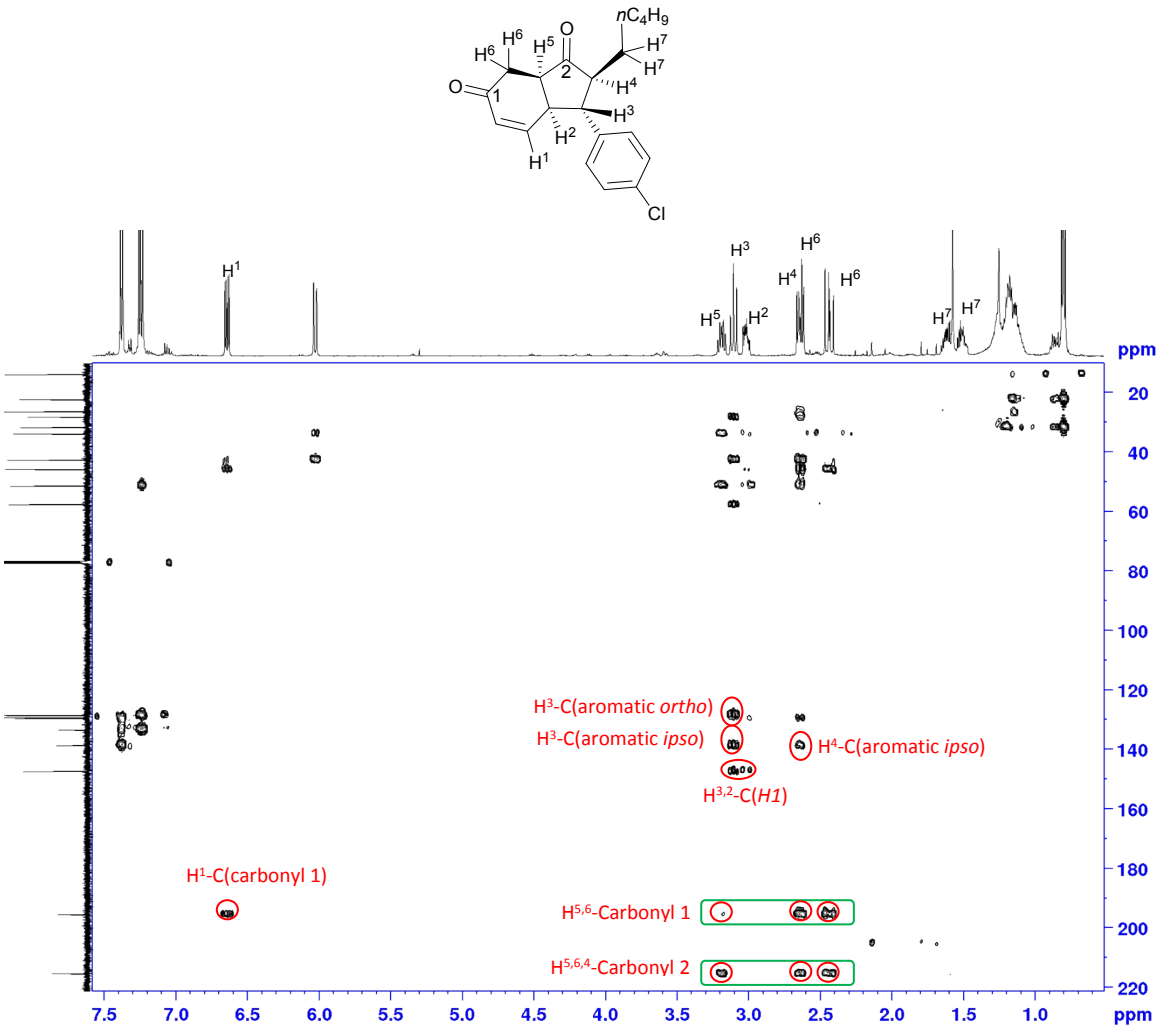

7.3877
7.3708
7.2600
7.2471
7.2302
6.6575
6.6483
6.6370
6.6278
6.0380
6.0364
6.0175
6.0159
3.2164
3.1583
3.1258
3.1041
3.0821
3.0388
2.9898
2.6611
2.6138
2.4654
2.4398
2.4318
2.4062
1.6536
1.5937
1.5394
1.4692
1.2133
1.0993
0.8129
0.7992
0.7848
O
O
nC5H11
Cl
6d
(500 MHz, CDCl3)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.07
2.06
1.03
1.00
1.04
1.18
1.00
2.02
1.18
1.10
1.24
6.12
3.22


215.41
195.53
147.35
138.64
133.38
129.49
129.29
128.52
77.25
77.00
76.75
57.55
51.30
45.80
42.62
33.82
31.69
28.17
26.36
22.27
13.89
O
O
nC5H11
Cl
6d
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

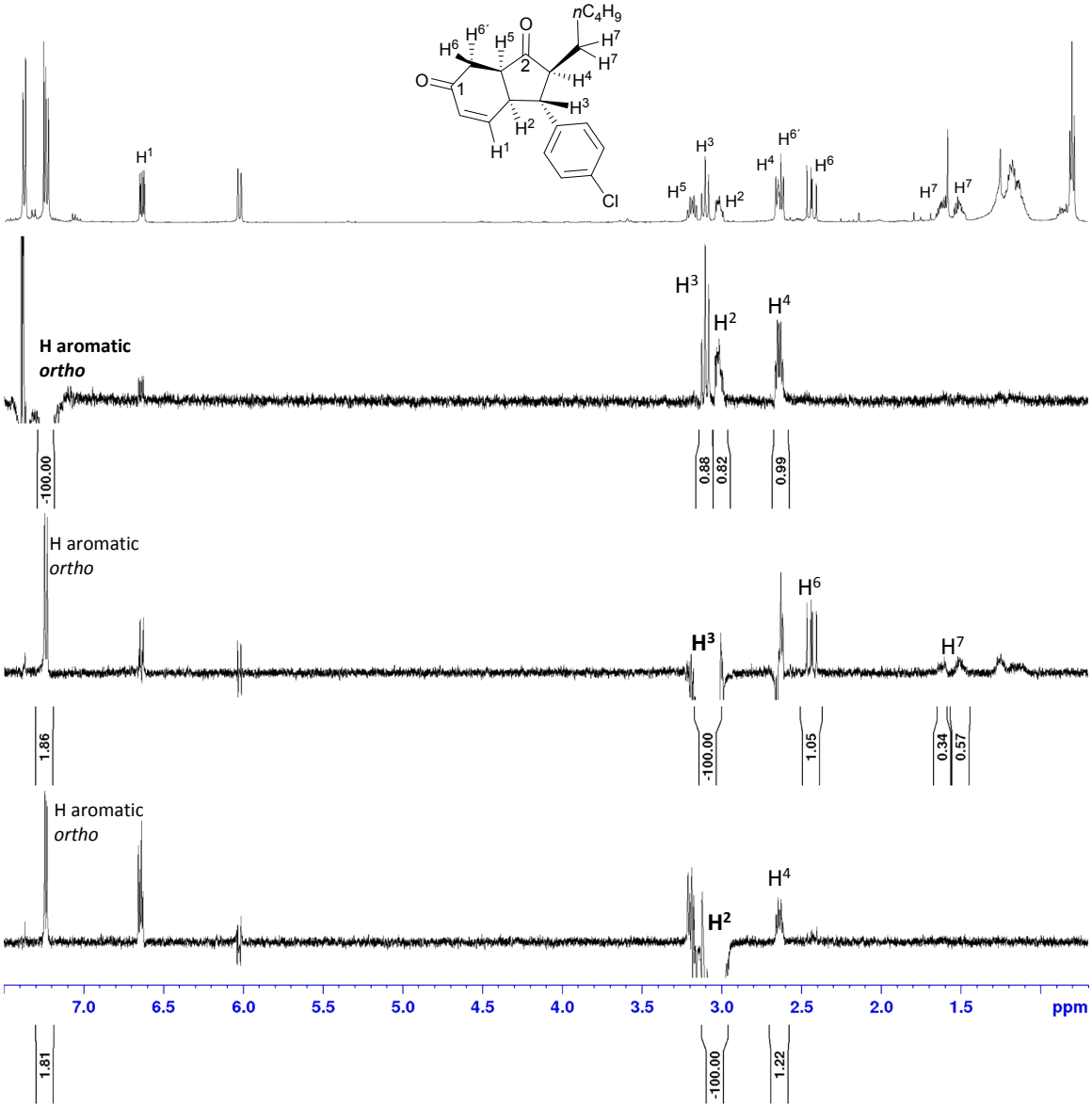
COSY correlations of compound 6d

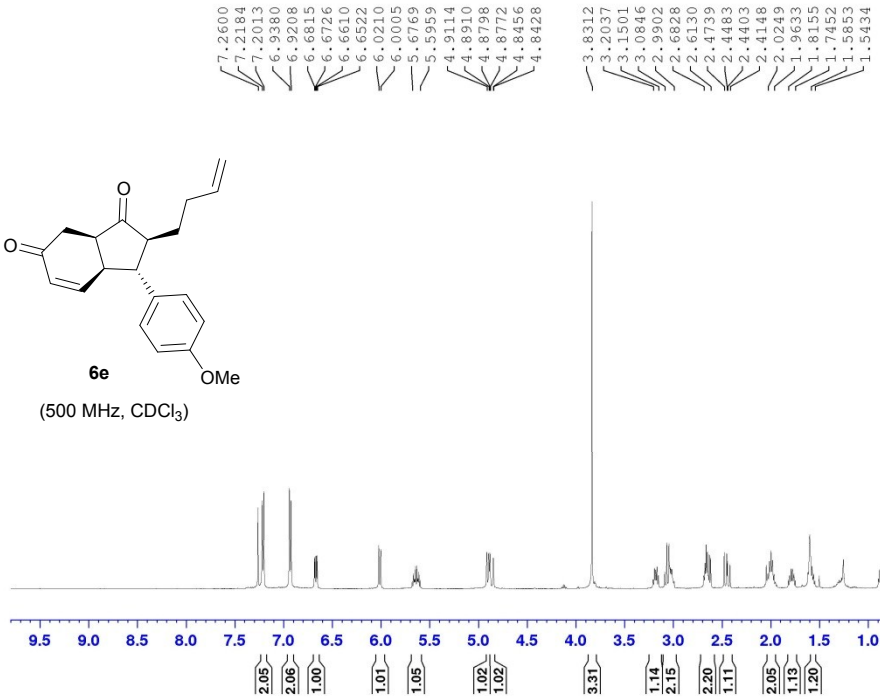


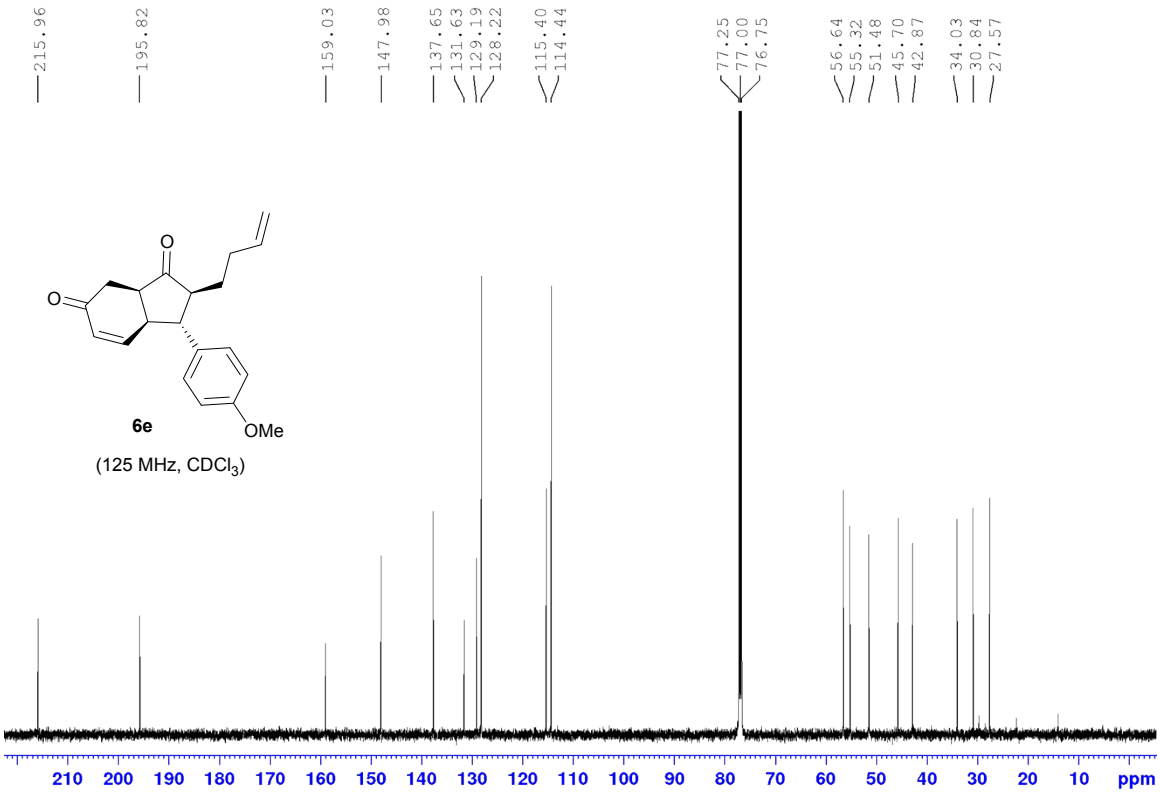
HMBC correlations of compound 6d



Representative NOEs of compound 6d

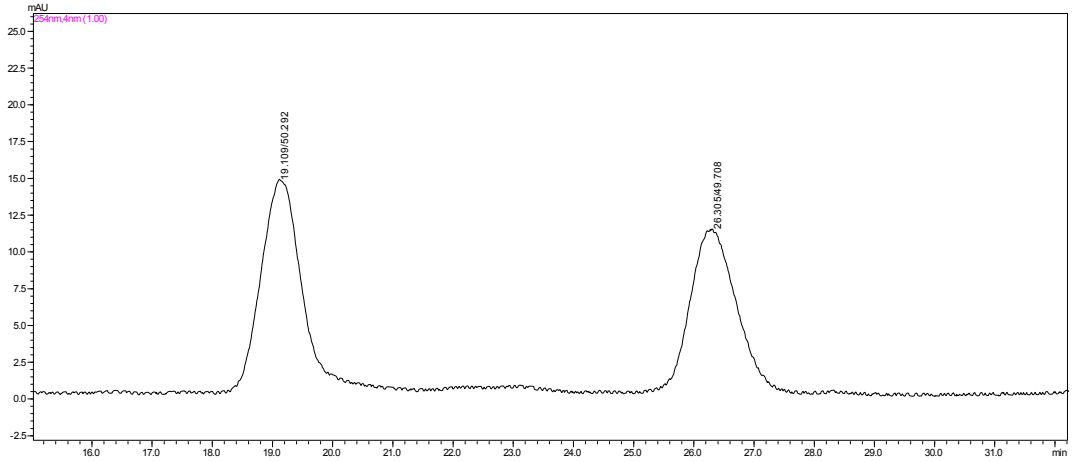



7.2600
7.2184
7.2013
6.9380
6.9208
6.6815
6.6726
6.6610
6.6522
6.0210
6.0005
5.6769
5.5959
4.9114
4.8910
4.8798
4.8772
4.8456
4.8428
3.8312
3.2037
3.1501
3.0846
2.9902
2.6828
2.6130
2.4739
2.4483
2.4403
2.4148
2.0249
1.9633
1.8155
1.7452
1.5853
1.5434
O
O
6e
OMe
(500 MHz, CDCl3)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.05
2.06
1.00
1.01
1.05
1.02
1.02
3.31
1.14
2.15
2.20
1.11
2.05
1.13
1.20

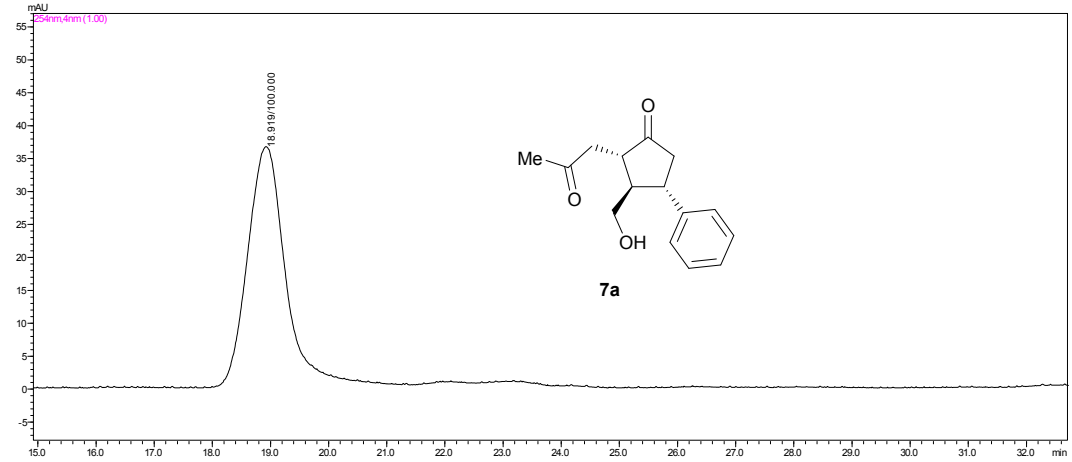

215.96
195.82
159.03
147.98
137.65
131.63
129.19
128.22
115.40
114.44
77.25
77.00
76.75
56.64
55.32
51.48
45.70
42.87
34.03
30.84
27.57
O
O
6e
OMe
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

Part C: Copies of HPLC chromatograms

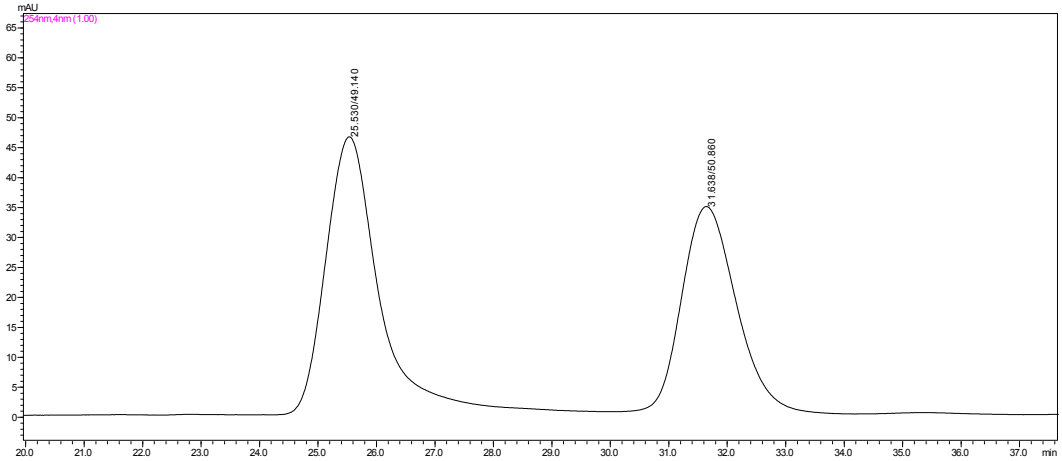
Racemic mixture of 7a



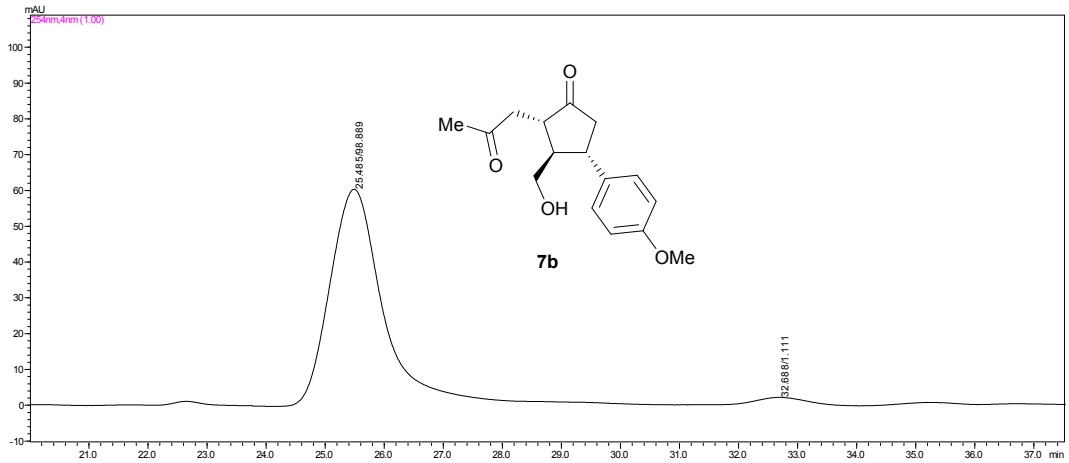
(2*S*,3*R*,4*S*)-3-(hydroxymethyl)-2-(2-oxopropyl)-4-phenylcyclopentan-1-one (7a)



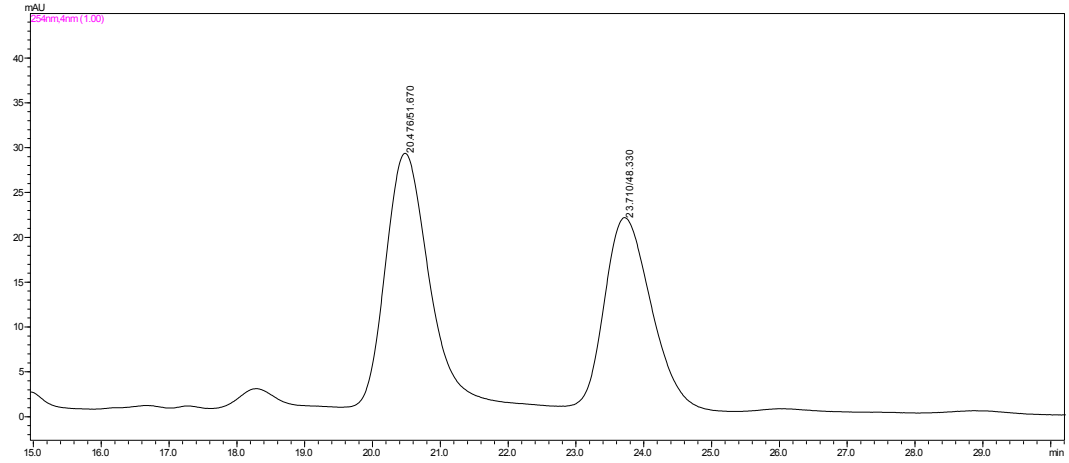
Racemic mixture of 7b



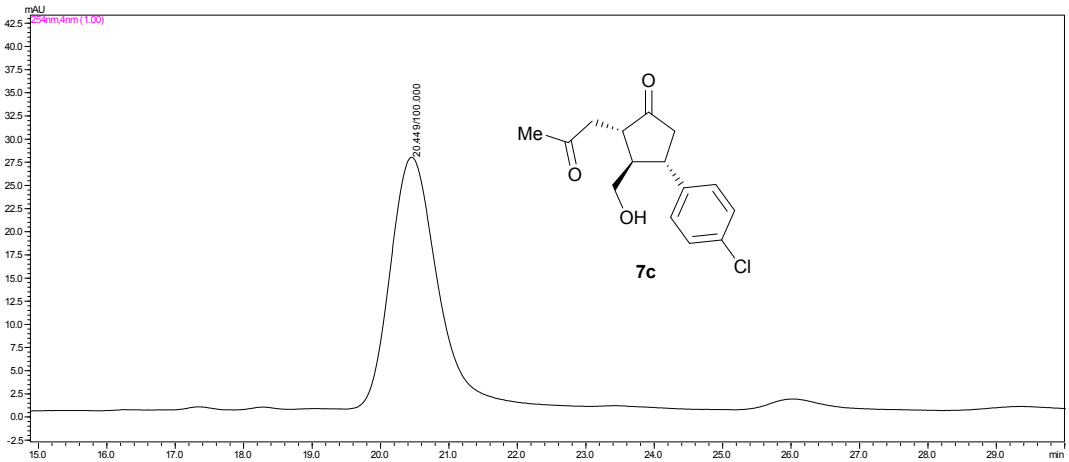
(2*S*,3*R*,4*S*)-3-(hydroxymethyl)-4-(4-methoxyphenyl)-2-(2-oxopropyl)cyclopentan-1-one (7b)



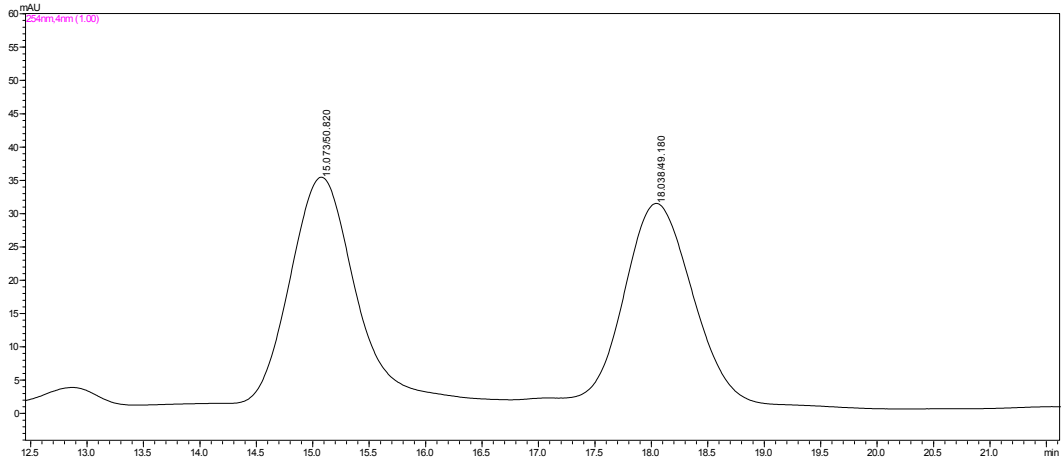
Racemic mixture of 7c



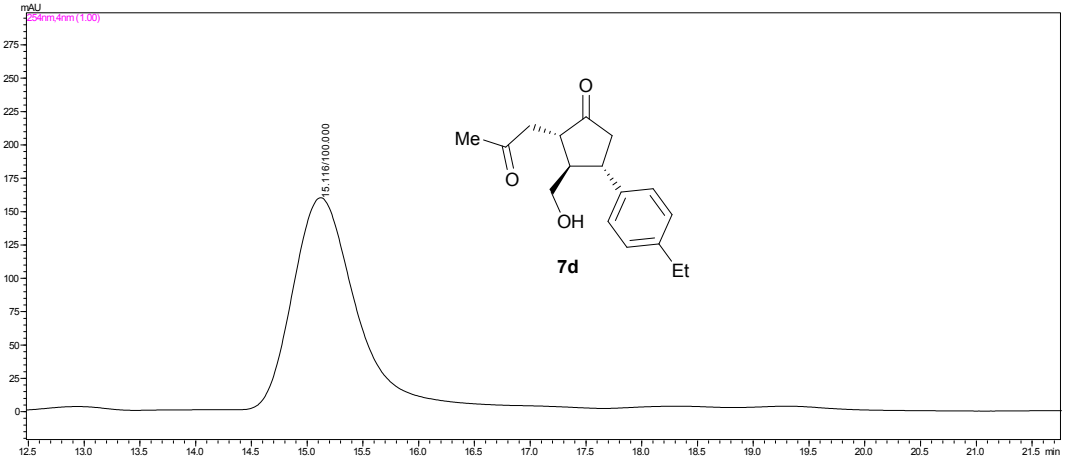
(2*S*,3*R*,4*S*)-4-(4-chlorophenyl)-3-(hydroxymethyl)-2-(2-oxopropyl)cyclopentan-1-one (7c)



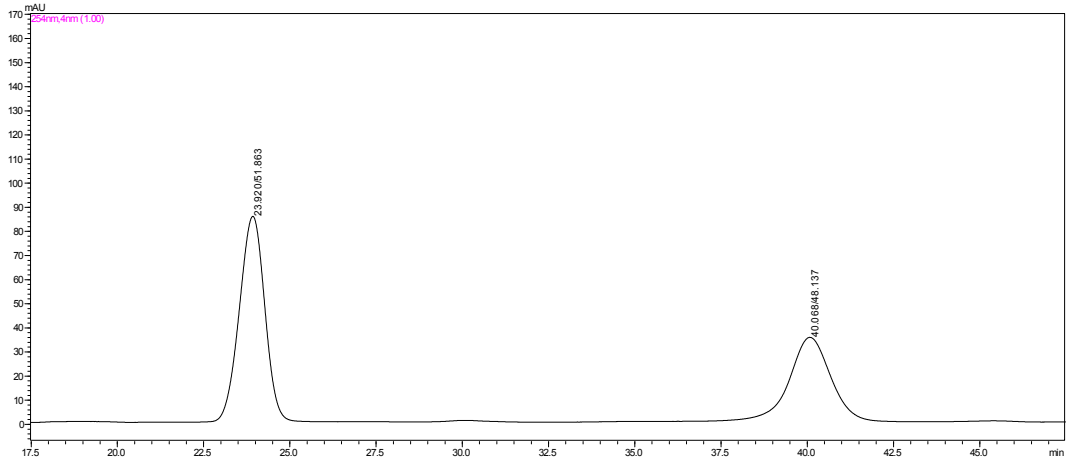
Racemic mixture of 7d



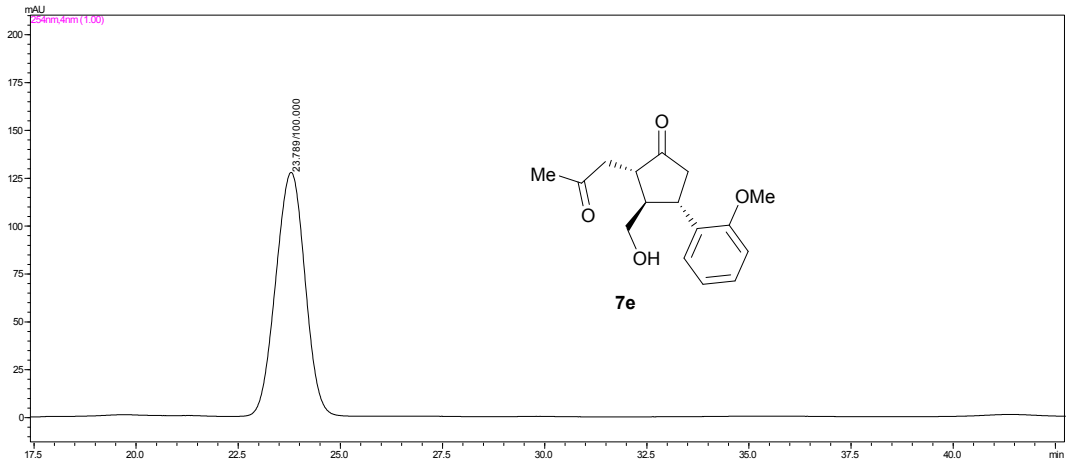
(2*S*,3*R*,4*S*)-4-(4-ethylphenyl)-3-(hydroxymethyl)-2-(2-oxopropyl)cyclopentan-1-one (7d)



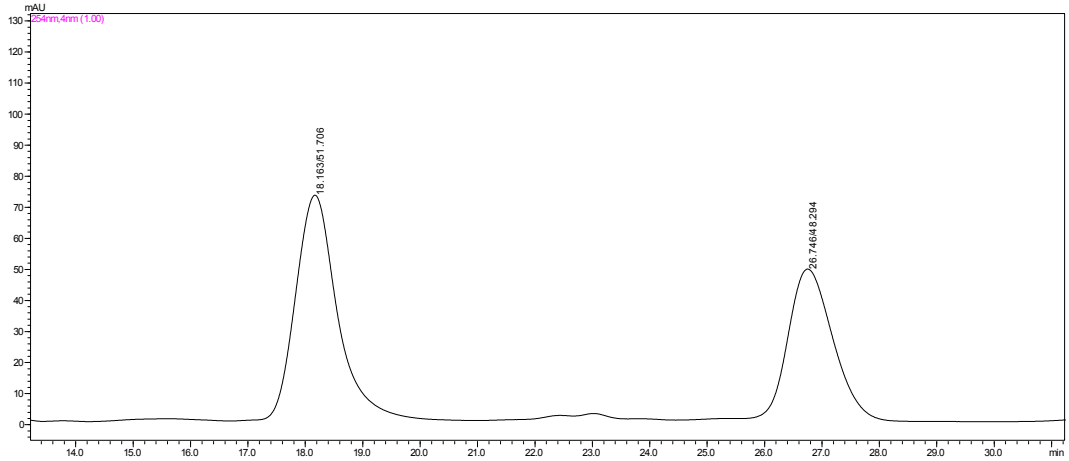
Racemic mixture of 7e



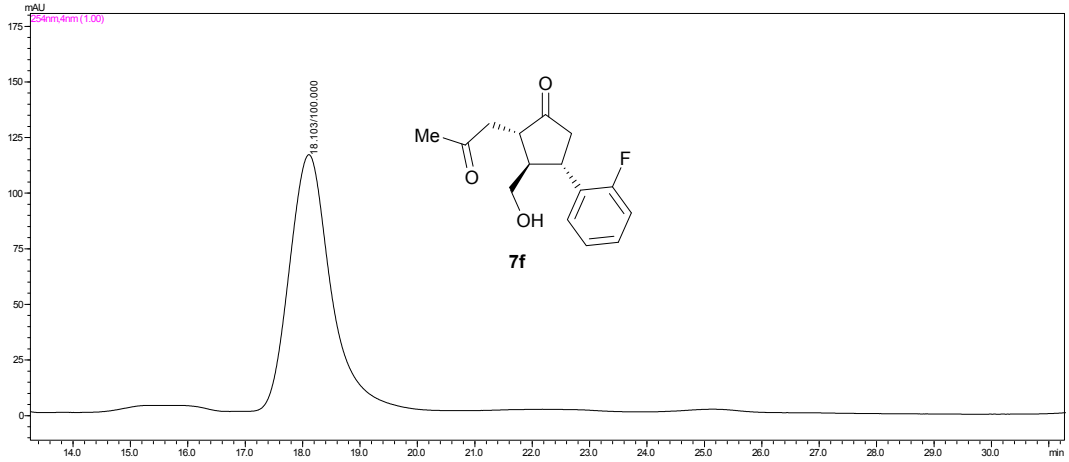
(2*S*,3*R*,4*S*)-3-(hydroxymethyl)-4-(2-methoxyphenyl)-2-(2-oxopropyl)cyclopentan-1-one (7e)



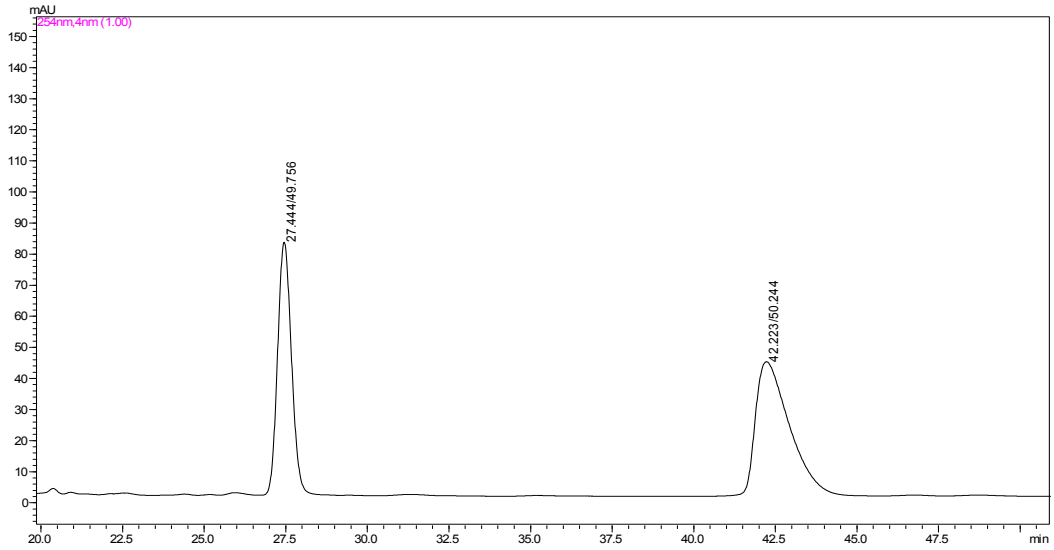
Racemic mixture of 7f



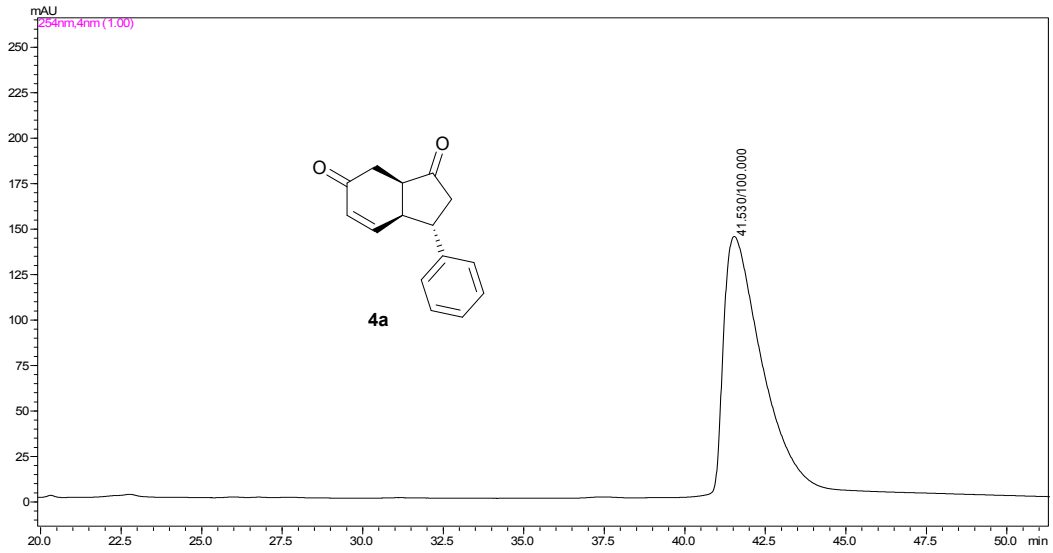
(2*S*,3*R*,4*S*)-4-(2-fluorophenyl)-3-(hydroxymethyl)-2-(2-oxopropyl)cyclopentan-1-one (7f)



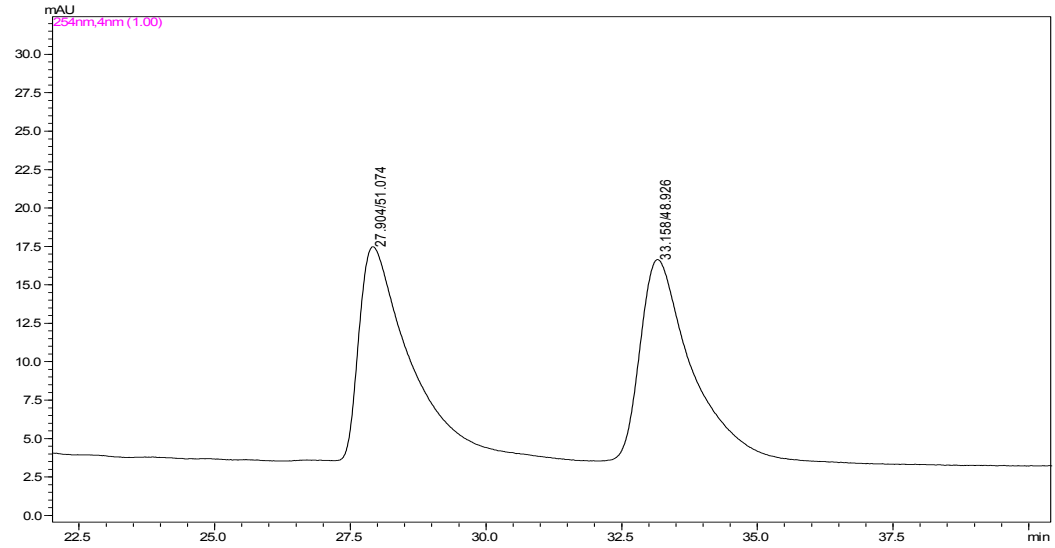
Racemic mixture of 4a



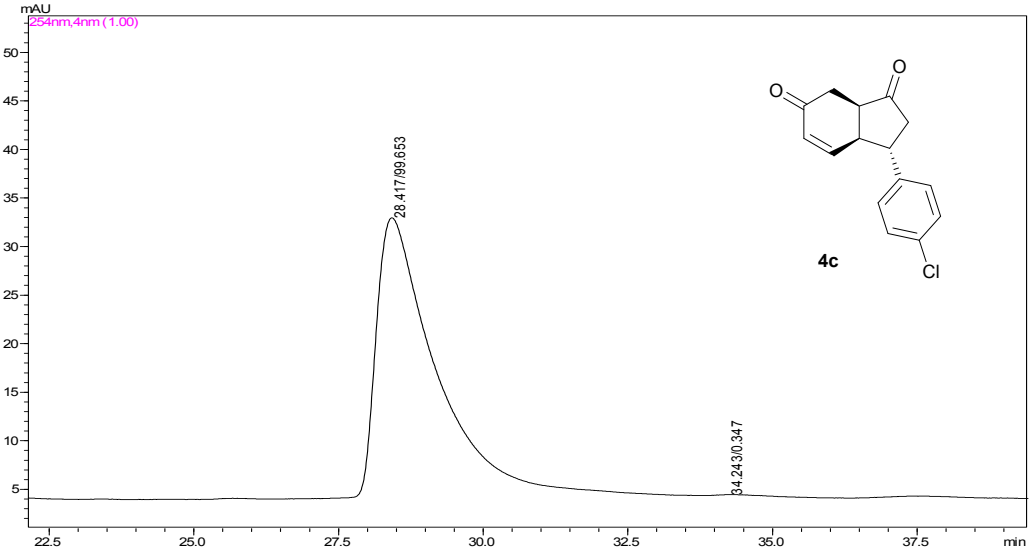
(3*S*,3a*R*,7a*R*)-3-phenyl-3,3a,7,7a-tetrahydro-1H-indene-1,6(2H)-dione (4a)



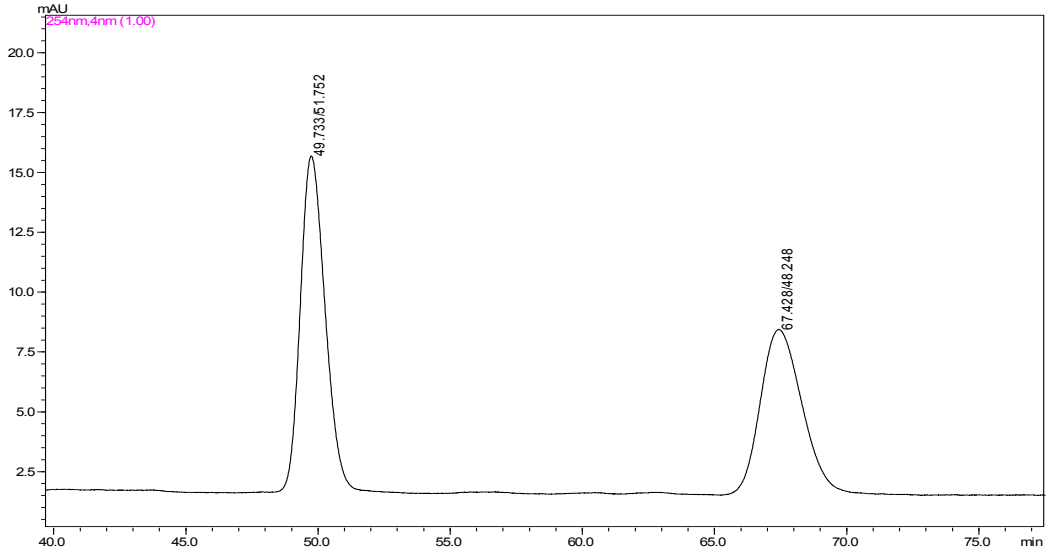
Racemic mixture of 4c



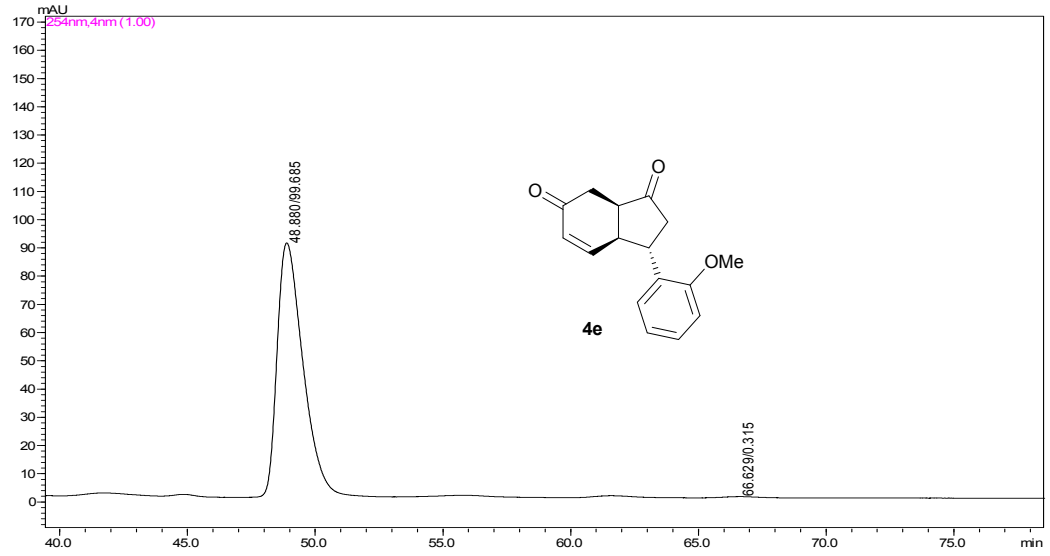
(3*S*,3a*R*,7a*R*)-3-(4-chlorophenyl)-3,3a,7,7a-tetrahydro-1H-indene-1,6(2H)-dione (4c)



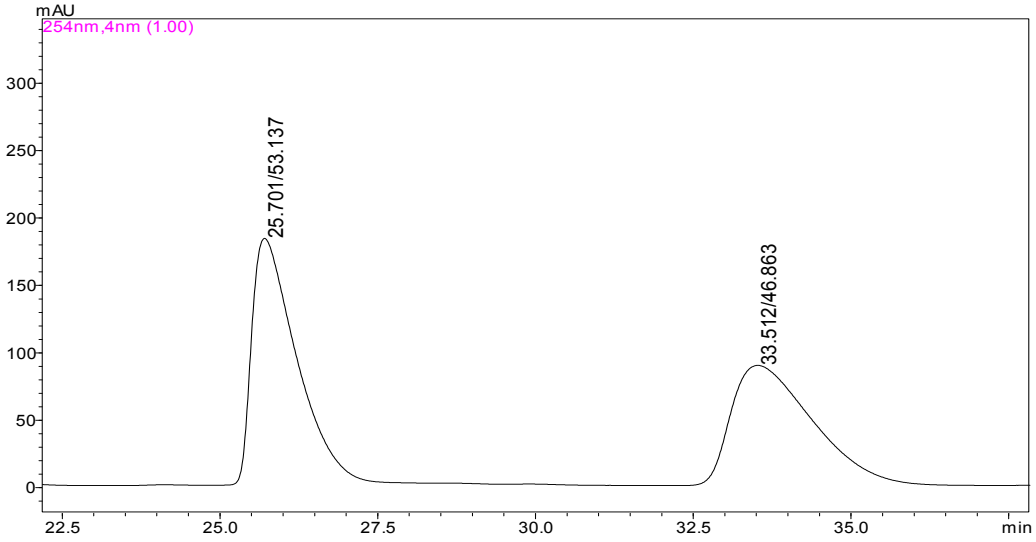
Racemic mixture of 4e



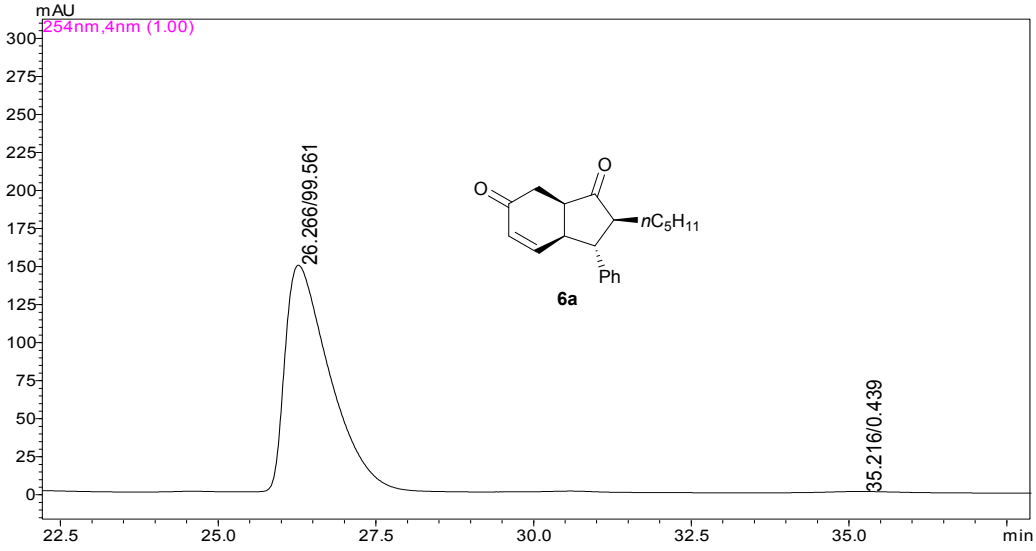
(3*S*,3a*R*,7a*R*)-3-(2-methoxyphenyl)-3,3a,7,7a-tetrahydro-1H-indene-1,6(2H)-dione (4e)



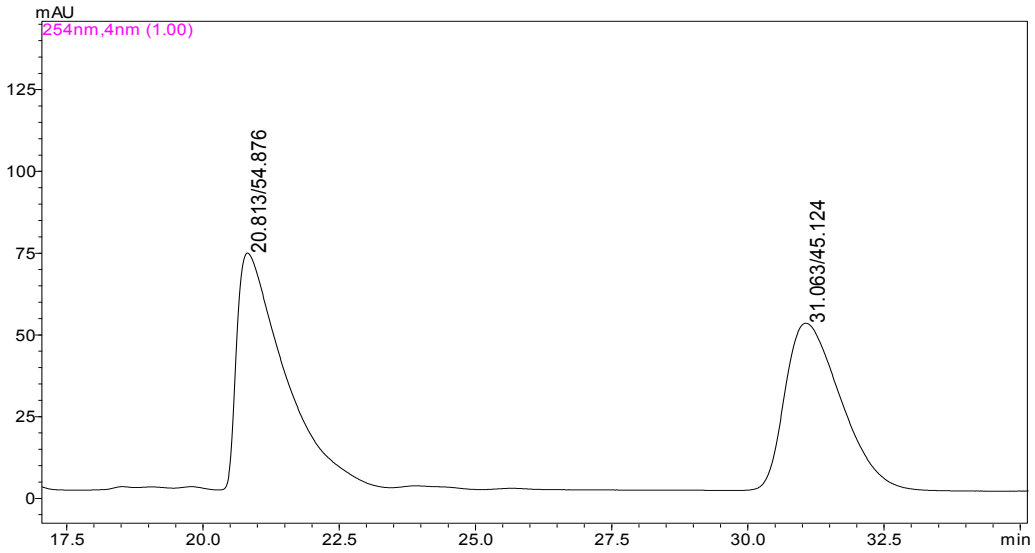
Racemic mixture of 6a



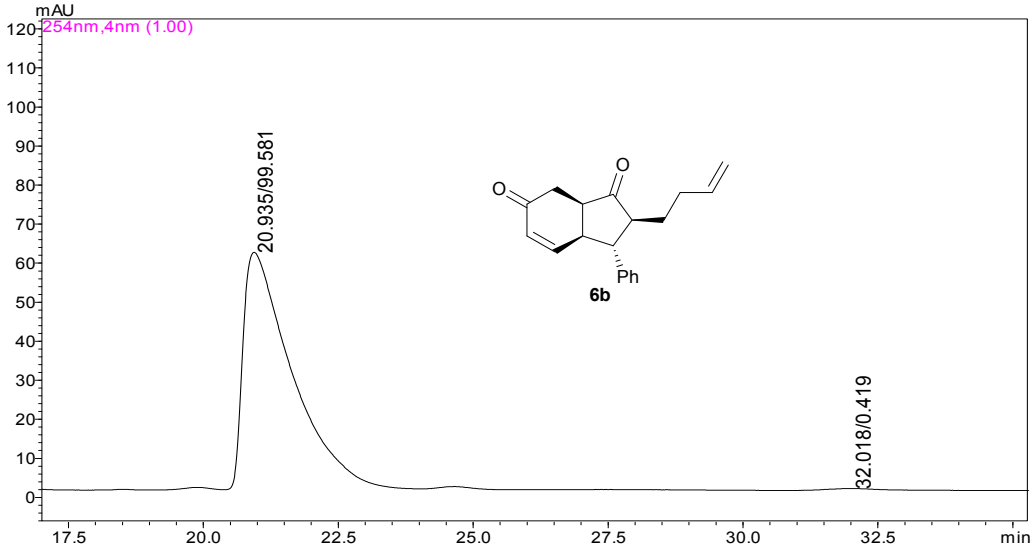
(2*S*,3*R*,3a*R*,7a*R*)-2-pentyl-3-phenyl-3,3a,7,7a-tetrahydro-1H-indene-1,6(2H)-dione (6a)



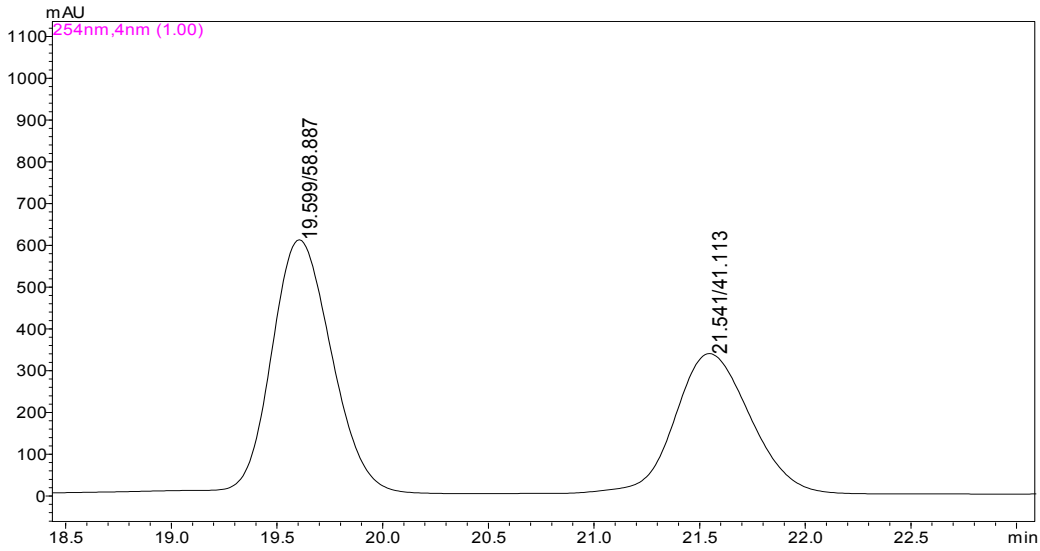
Racemic mixture of 6b



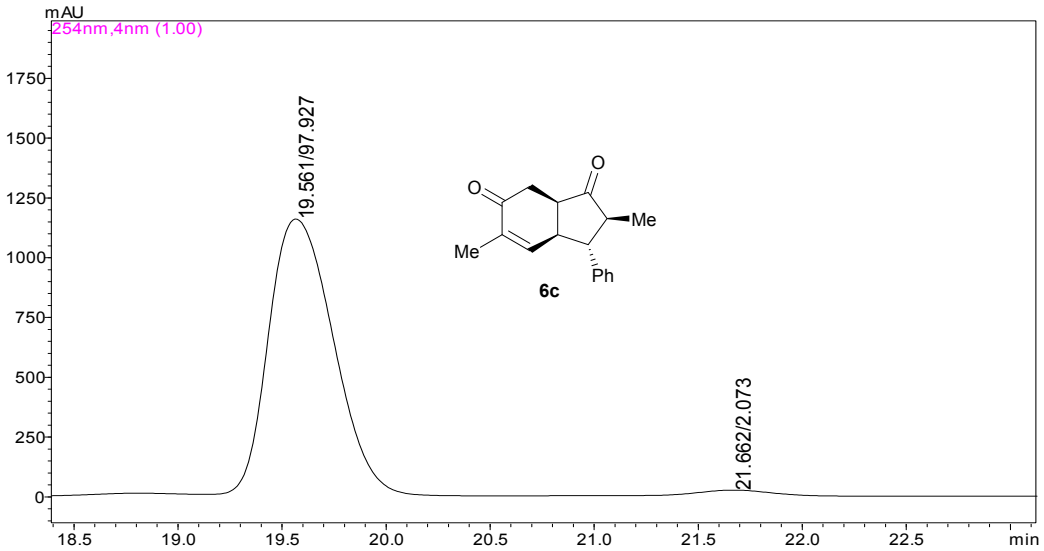
(2*S*,3*R*,3a*R*,7a*R*)-2-(but-3-en-1-yl)-3-phenyl-3,3a,7,7a-tetrahydro-1H-indene-1,6(2H)-dione (6b)



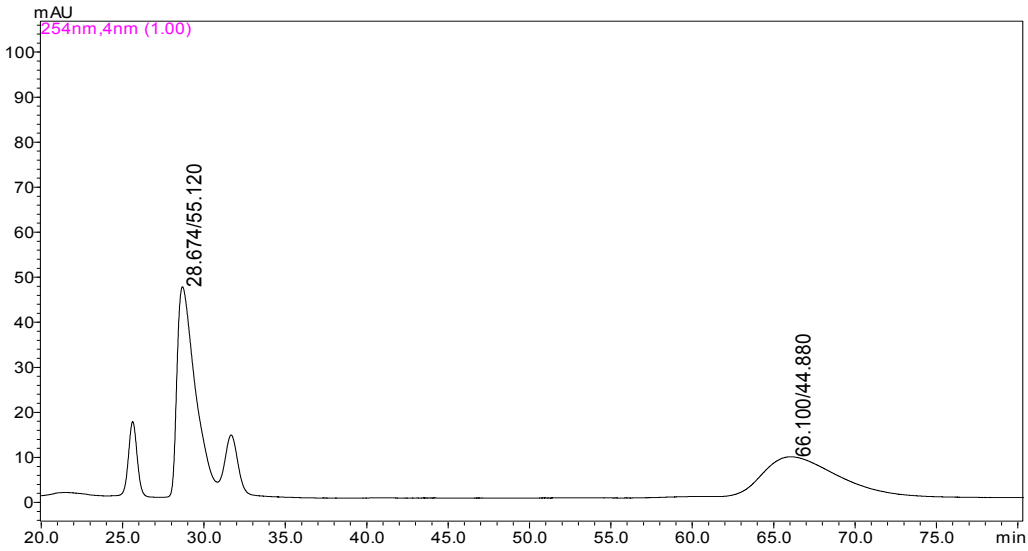
Racemic mixture of 6c



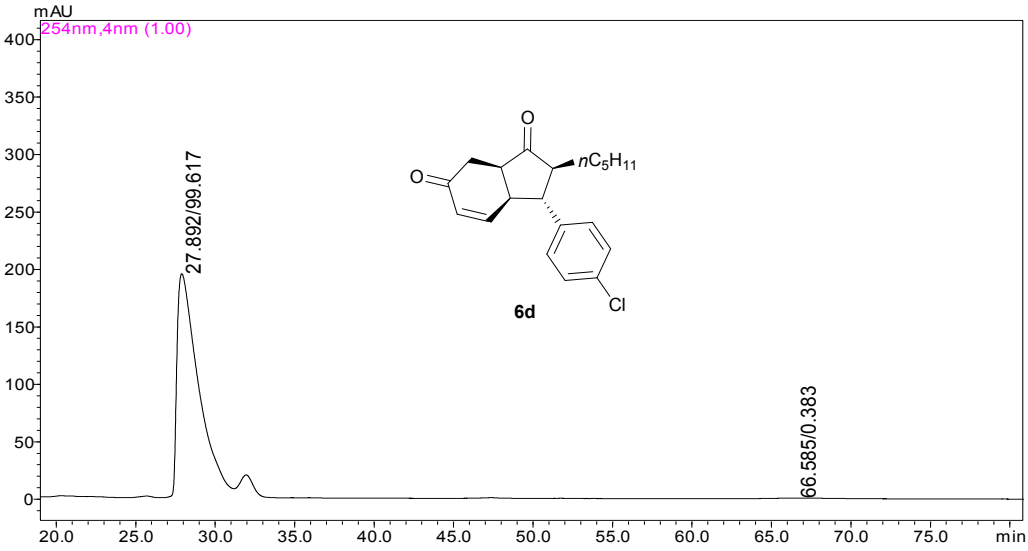
(2*S*,3*R*,3a*R*,7a*R*)-2,5-dimethyl-3-phenyl-3,3a,7,7a-tetrahydro-1H-indene-1,6(2H)-dione (6c)



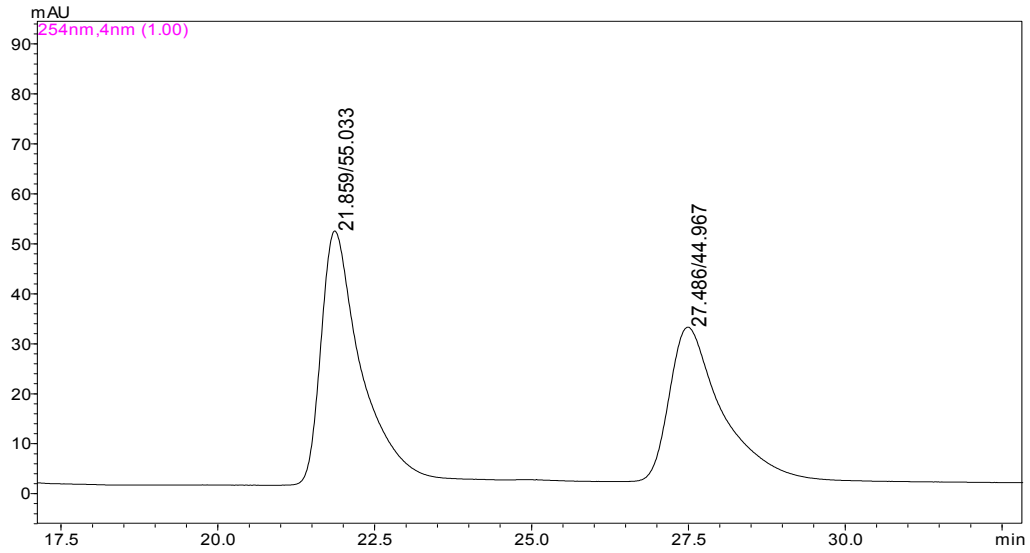
Racemic mixture of 6d



(2*S*,3*R*,3a*R*,7a*R*)-3-(4-chlorophenyl)-2-pentyl-3,3a,7,7a-tetrahydro-1H-indene-1,6(2H)-dione (6d)



Racemic mixture of 6e



(2*S*,3*R*,3a*R*,7a*R*)-2-(but-3-en-1-yl)-3-(4-methoxyphenyl)-3,3a,7,7a-tetrahydro-1H-indene-1,6(2H)-dione (6e)