Substituent and catalyst effects on GAC lactonization of γ-hydroxy esters

Elisabetta Brenna,† Francesco Distante, † Francesco G. Gatti*,† and Giuseppe Gatti‡

†Dipartimento di Chimica, Materiali ed Ingegneria Chimica "G. Natta", Politecnico di Milano, P.zza Leonardo da Vinci 32, 20133 Milano, Italy

‡ Dipartimento di Scienze Biomolecolari Scuola di Farmacia, Università degli Studi di Urbino, P.zza del Rinascimento 6, 61029 Urbino Italy

EXPERIMENTAL SUPPORTING INFORMATION

Index

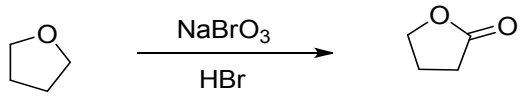
1. General Information

^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 or 500 DRX spectrometer in $CDCl_3$ solutions at room temperature. The residual $CHCl_3$ or TMS were used as internal reference for ^{1}H or ^{13}C. Chemical shifts are expressed in ppm and *J* values in Hz. GC–MS analyses were performed on an Agilent HP 6890 gas-chromatograph equipped with a 5973 mass detector and an Agilent HP-5 (30 m × 0.25 mm × 0.25 μm) column. Temperature program: 60 °C (1 min) / 6 °C min−1 / 150 °C (1 min) / 12 °C min−1 / 280 °C (5 min). Thin layer chromatography (TLC) analyses were performed on Merck Kieselgel 60 F254 plates, and column chromatographic separations were carried out on silica gel. All reagents and solvents were purchased from Sigma-Aldrich. The reagents were used without further purification, while where required the solvents were dried with molecular sieves (4 Å).

2. Synthesis

The hydroxyesters were prepared according to a slightly modified procedures described in literature.

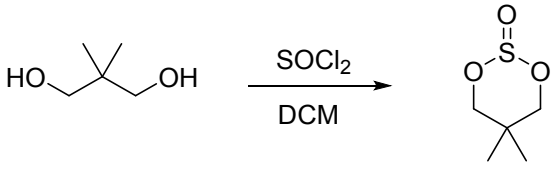
Dihydrofuran-2(3H)-one (2a)



2a

To a solution of THF (7.2 g, 100 mmol) in CH_2Cl_2 (100 mL) was added portion wise $NaBrO_3$ (15.1 g, 100 mmol) and an aqueous solution of HBr (47%, 15 mL) at room temperature. The reaction mixture was stirred overnight at room temperature, treated with a solution of $NaHCO_3$ (sat., 100 mL) and then with a solution of Na_2SO_3 (10% w/w, 100 mL) to remove the excess of Br_2. The reaction mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layer was dried over Na_2SO_4 and evaporated under *vacuum* to give a yellow liquid, which was distilled with a bulb-to-bulb apparatus (70°C, 5 mmHg), affording the product (8.6 g); 100% yield;[1] t_r=4.23 min 93% purity by GC; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 4.35 (t, *J* = 7.0 Hz, 2H), 2.49 (t, *J* = 7.0 Hz, 2H), 2.27 (m, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ (ppm) 177.75, 68.51, 27.72, 22.11; GC/MS: *m/z* (%) 86 (M^+, 100), 56 (50).

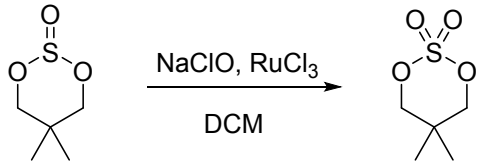
5,5-dimethyl-1,3,2-dioxathiane 2-oxide (3)



3

To a solution of 2,2-dimethylpropane-1,3-diol (10.0 g, 96 mmol) in CH_2Cl_2 (600 mL), was added portion wise $SOCl_2$ (9 ml, 124 mmol), over 30 minutes. The reaction mixture was heated at reflux for 2 hours and then cooled to r.t. Finally, the reaction was quenched with H_2O (500 mL). The aqueous phase was discarded, while the organic phase was washed with $NaHCO_3$ (sat., 1 x 50 mL), dried over Na_2SO_4 and evaporated under *vacuum*. The residue was distilled with a bulb-to-bulb apparatus (60°C, 10 mmHg) affording the product, as a colourless liquid (12.9 g); 90% yield; t_r=6.40 min 98% purity by GC; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 4.61 (d, *J* = 3.0 Hz, 2H), 3.41 (d, *J* = 3.0 Hz, 2H), 1.30 (s, 3H), 0.85 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ (ppm) 66.42, 31.61, 22.54, 22.43; GC/MS: *m/z* (%) 150 (M^+, 1), 71 (5), 56 (100).

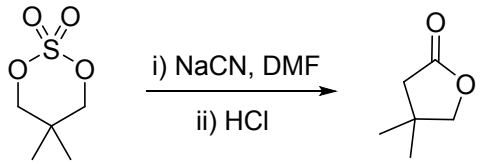
5,5-dimethyl-1,3,2-dioxathiane 2,2-dioxide (4)



3 **4**

To a mechanically stirred solution of **3** (7.0 g, 46 mmol) in CH_2Cl_2 (100 mL) and H_2O (50 mL) was added $RuCl_3$ (90% w/w, 15 mg) and then a solution of NaClO (7% w/w, 253 mL) was added portion wise over 20 minutes. The reaction mixture was stirred for 5 hours and mixed with *i*-PrOH (1 mL), then the aqueous phase was extracted with AcOEt (4 x 50 mL), and the combined organic phase was dried over Na_2SO_4, concentrated under *vacuum* giving an oil. The latter was triturated in hexane (25 mL) affording the sulfate **4** as a white solid (5.9 g); 78% yield; t_r=11.25 min 96% purity by GC; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 4.34 (s, 4H), 1.15 (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ (ppm) 81.73, 66.43, 20.90; GC/MS: *m/z* (%) 166 (M^+, 1), 86 (10), 68 (20), 56 (100).

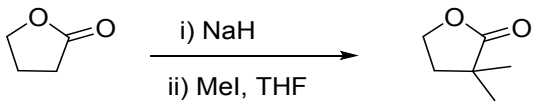
4,4-dimethyldihydrofuran-2(3H)-one (2b)



4 **2b**

To a solution of **4** (4.6 g, 28 mmol) in DMF (30 mL), NaCN (2.7 g, 56 mmol) was added and it was stirred for 6 hours at 80°C. Thus, the mixture was quenched with HCl (37%, 60 mL) for 4 hours. Finally, the reaction mixture was diluted with brine (sat., 10 mL) and washed with CH_2Cl_2 (4 x 20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure, affording the product (2.6 g);[2] 81% yield; t_r=5.20 min 99% purity by GC; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 3.98 (s, 2H), 2.33 (s, 2H), 1.20 (s, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ (ppm) 176.9, 79.6, 43.2, 36.5, 25.8; GC/MS: *m/z* (%) 114 (M^+, 15), 70 (40), 56 (100).

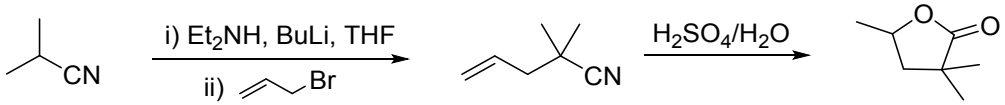
3,3-dimethyldihydrofuran-2(3H)-one (2c)



2a **2c**

To a well-stirred suspension of NaH (as dispersion mineral oil, 60% w/w, 2.76 g) in anhydrous THF (50 mL) was added a solution of **2a** (4.0 g, 46 mmol) in THF (10mL) and MeI (18.3 g) portion wise under a N_2 atmosphere and at reflux temperature. The mixture was stirred for 2h, then it was quenched with ice (30 g) and H_2O (30 mL) and treated with a solution of HCl (1M, 1 x 30 mL). Thus, the mixture was concentrated under reduced pressure and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). Finally, the combined organic phase was dried over Na_2SO_4, concentrated under reduced pressure affording a liquid. The latter was distilled with a bulb-to-bulb apparatus (65°C, 8 mmHg) affording the product as a colourless liquid (2.9 g); 55% yield; t_r=5.02 min 99% purity by GC; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 4.26 (t, 2H, *J* = 7 Hz), 2.11 (t, 2H, *J* = 7 Hz), 1.27 (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ (ppm) 182.31, 64.73, 37.12, 24.23; GC/MS: *m/z* (%) 114 (M^+, 10), 70 (45), 55 (100).

3,3,5-trimethyldihydrofuran-2(3H)-one (2e)

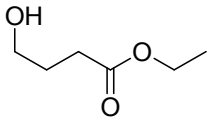


2e

To a well stirred solution of Et_2NH (12.5 mL, 121 mmol) in THF (50mL) a solution of BuLi in hexane (2.5 M, 52 mL, 127 mmol) was added portion wisely at 0°C under a N_2 atmosphere. The mixture was stirred for 1 hour, after which isobutyronitrile (10 mL, 110 mmol) was added. After 1 hour to the reaction mixture was added drop wise a solution of allylbromide (11 mL, 121 mmol) in THF (50 mL). Then, the reaction mixture was warmed to room temperature and after 12 h was quenched with a solution of NH_4Cl (sat., 70 mL), extracted with Et_2O (2 x 70 mL), washed with brine (sat.,1 x50 mL), dried over Na_2SO_4 and concentrated under *vacuum*. The resulting oil was distilled with a bulb-to-bulb apparatus (65°C, 5 mmHg) affording the intermediate 2,2-dimethylpent-4-enenitrile of sufficient purity for the next step.

A well stirred mixture of 2,2-dimethylpent-4-enenitrile (11.4 g, 104 mmol) and H_2SO_4/H_2O (50% v/v, 112 mL) was boiled for 6 hours. Then, the mixture was extracted with CH_2Cl_2 (2 x 100 mL), the combined organic phase was washed with brine (sat., 2 x 70 mL), with $NaHCO_3$ (sat., 2 x 70 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give the product as an oil (8.5 g);[3] 64% yield; t_r=6.69 min 97% purity by GC; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 4.57 (m, 1H), 2.21 (d, *J* = 6.0 Hz, 1H), 2.20 (d, *J* = 6.0 Hz, 1H), 1.42 (d, *J* = 7.0 Hz, 3H), 1.28 (d, *J* = 9.0 Hz, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ (ppm) 73.30, 45.16, 25.15, 24.37, 21.15; GC/MS: *m/z* (%) 113 (M^+-15, 10), 96 (1), 84 (40), 69 (100).

Ethyl 4-hydroxybutanoate (1a)



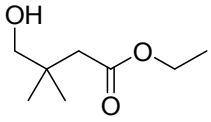
1a

To a solution of γ-butyrolactone (1.7 g, 20 mmol) in EtOH (20 mL) was added a catalytic amount of H_2SO_4 and the reaction was refluxed for 12 h. Then, the mixture was cooled to room temperature and $CaCO_3$ (0.2 g, 2 mmol) was added. After 30 minutes, the white solid was filtered out and the reaction mixture was concentrated under reduced pressure, in such a way to eliminate the excess of EtOH. Then, the remaining solution was diluted in CH_2Cl_2 (30 mL) and washed with an aqueous solution of $CaCO_3$ (5% w/w, 1 x 10 mL), with H_2O (1 x 10 mL) and with brine (sat., 1 x 10 mL). Finally, the organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give the product,[4] which was of sufficient purity[5] for the kinetic study (1.9 g); 75% yield; t_r=7.80 min; ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 4.14 (q, J = 7.0 Hz, 2H), 3.68 (t, J = 6.0 Hz, 2H), 2.42 (t, J = 7.0 Hz, 2H), 1.88 (m, 2H), 1.70(s, 1H), 1.25, (t, J = 7.0 Hz, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ (ppm) 173.97, 62.08, 60.50, 31.09, 27.72, 14.24; GC/MS: *m/z* (%) 102 (M^+-30, 60), 87 (100).

General procedure for the ring opening of lactone to give 4-hydroxyester (1b-f)

To an ice cooled and well stirred solution of lactone (17 mmol) in MeOH (30 mL) was added a solution of KOH (19 mmol) in H_2O (3 mL). The heterogeneous mixture was stirred for 5 hours at room temperature and then concentrated under *vacuum* to give a viscous oil. The latter was treated with Et_2O (4 x 10 mL) and concentrated under reduced pressure. This procedure was repeated at least 4 times in such a way to eliminate all traces of H_2O and MeOH. The crude material was left under high *vacuum* for 6 hours. Then, to a solution of the crude mixture in anhydrous DMF (45 mL) was added 2-iodopropane (5.8 g, 34 mmol) or ethylbromide (3.7 g, 34 mmol) under a N_2 atmosphere. After 14 hours, the reaction mixture was diluted with brine (sat., 70 mL) and then extracted with Et_2O (5 x 40 mL). The combined organic phase was washed with brine (sat., 50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the corresponding γ-hydroxyester,[5] which was of sufficient purity[6] for the kinetic study.

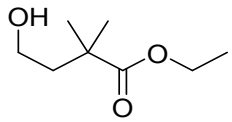
Ethyl 4-hydroxy-3,3-dimethylbutanoate (1b)



1b

73% yield; (2.0 g); t_r=9.05 min; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 4.15 (q, J = 7.0 Hz, 2H), 3.42 (d, J = 5.0 Hz, 2H), 2.30 (s, 2H), 1.57 (s, 1H), 1.27 (t, J = 7.0 Hz, 3H), 1.00 (s, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ (ppm) 176.91, 79.63, 43.22, 36.53, 25.81; GC/MS: *m/z* (%) 160 (M^+, 1), 142 (10), 130 (80), 115 (100), 87 (90), 59 (50).

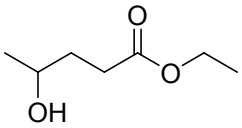
Ethyl 4-hydroxy-2,2-dimethylbutanoate (1c)



1c

(3.5 g); 87% yield; (2.4 g); t_r=5.01 min; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 4.14 (q, *J* = 7.0 Hz, 2H), 3.70 (m, 2H), 1.84 (t, *J* = 6.0 Hz, 2H), 1,26 (t, *J* = 7.0 Hz, 3H), 1.22 (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ (ppm) 178.42, 60.73, 59.78, 42.82, 40.79, 25.75, 14.13; GC/MS: *m/z* (%) 142 (M^+-18, 1), 133 (10), 114 (10), 70 (50), 56 (100).

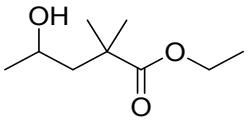
Ethyl 4-hydroxypentanoate (1d)



1d

71% yield; (1.7 g); t_r=10.65 min; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 4.13 (q, *J* =7.0 Hz, 2H), 3.86 (m, 1H), 2.44 (t, 2H), 1,93 (m, 1H), 1.82-1.74 (m, 2H), 1.26-1.21 (m, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ (ppm) 174.32, 67.50, 60.61, 34.03, 30.90, 23.74, 14.33; GC/MS: *m/z* (%) 146 (M^+, 10), 131 (15), 102 (85), 85 (100).

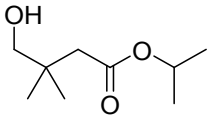
Ethyl 4-hydroxy-2,2-dimethylpentanoate (1e)



1e

64% yield; (1.9 g); t_r=9.59 min; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 4.12 (q, *J* =7.0 Hz, 2H), 3.93 (m, 1H), 2.00 (s, 1H), 1,94-1.88 (m, 1H), 1.52-1.40 (m, 1H), 1.27-1.22 (m, 12H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ (ppm) 179.06, 65.20, 60.63, 49.47, 41.09, 27,46, 24.92, 24.23, 14.09; GC/MS: *m/z* (%) 130 (M^+-44, 50), 115 (70), 87 (60), 69 (75), 57 (100).

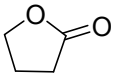
Isopropyl 4-hydroxy-3,3-dimethylbutanoate (1f)



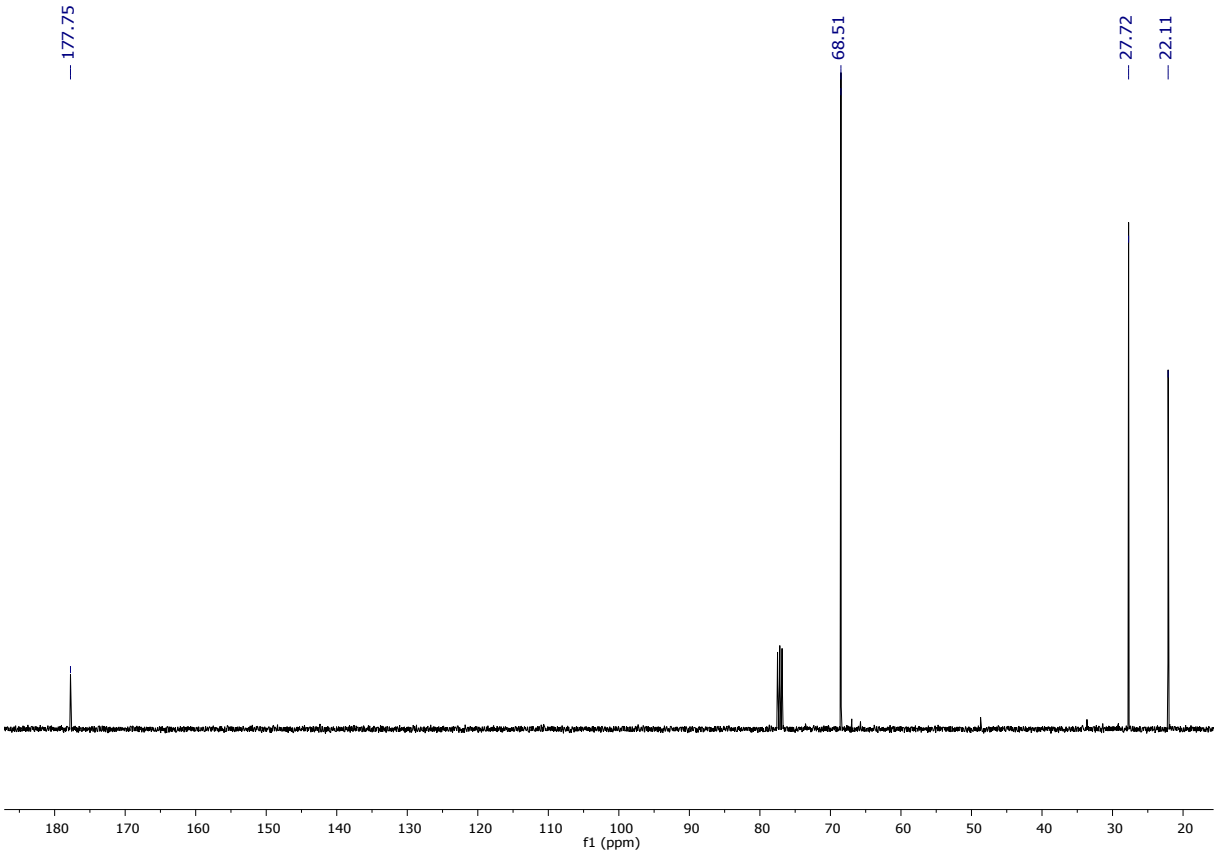
1f

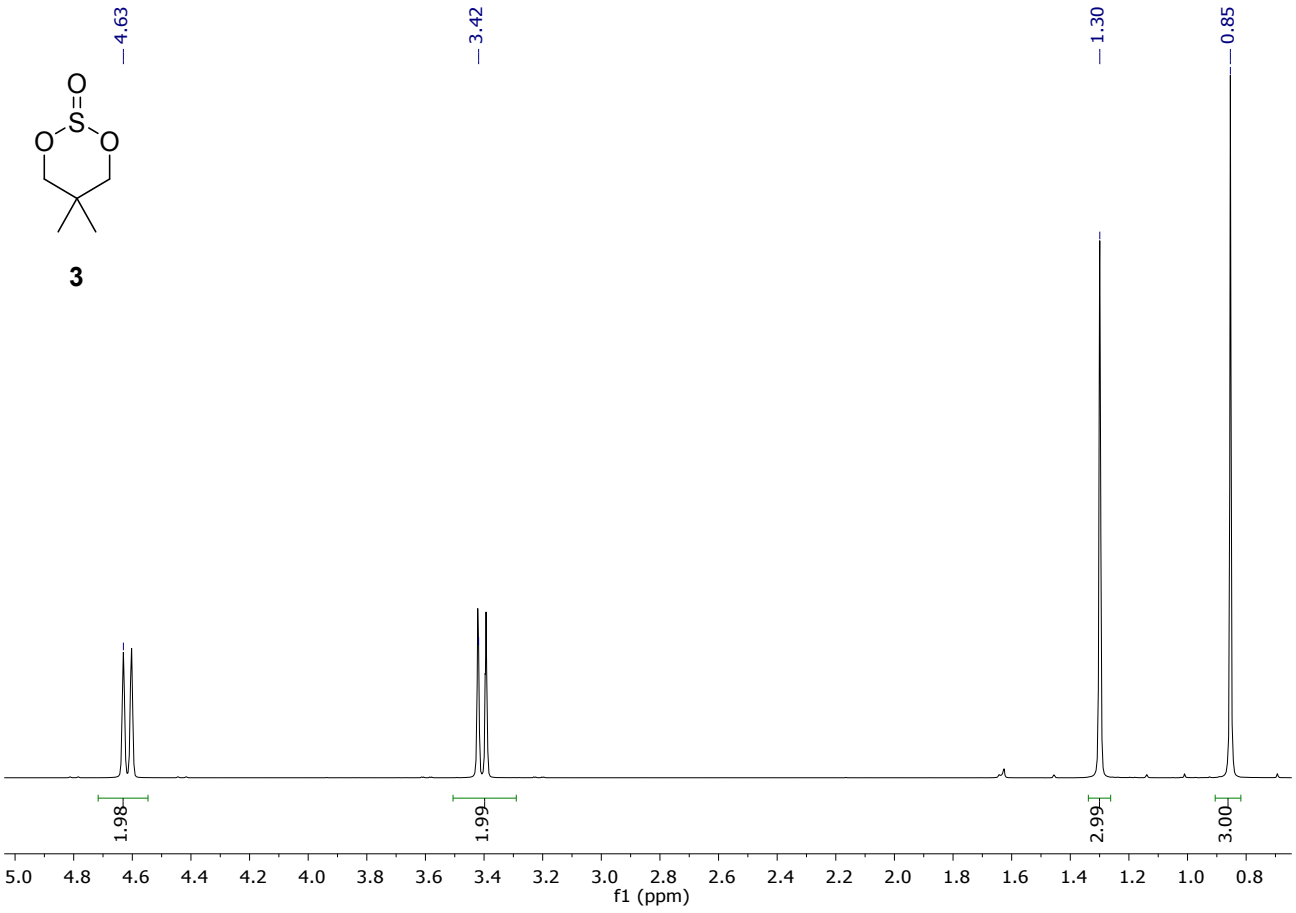
78% yield; (2.3 g); t_r=10.19 min; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 5.02 (m, 1H), 3.40 (s, 2H), 2.27 (s, 2H), 1.26 (d, *J* = 6.0 Hz, 6H), 0.99 (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ (ppm) 172.65, 71.39, 67.82, 44.21, 35.71, 24.72, 21.86; GC/MS: *m/z* (%) 144 (M^+-30, 20), 115 (40), 87 (40), 73 (40), 59 (100).

3. Copies of ^{1}H and ^{13}C NMR spectra

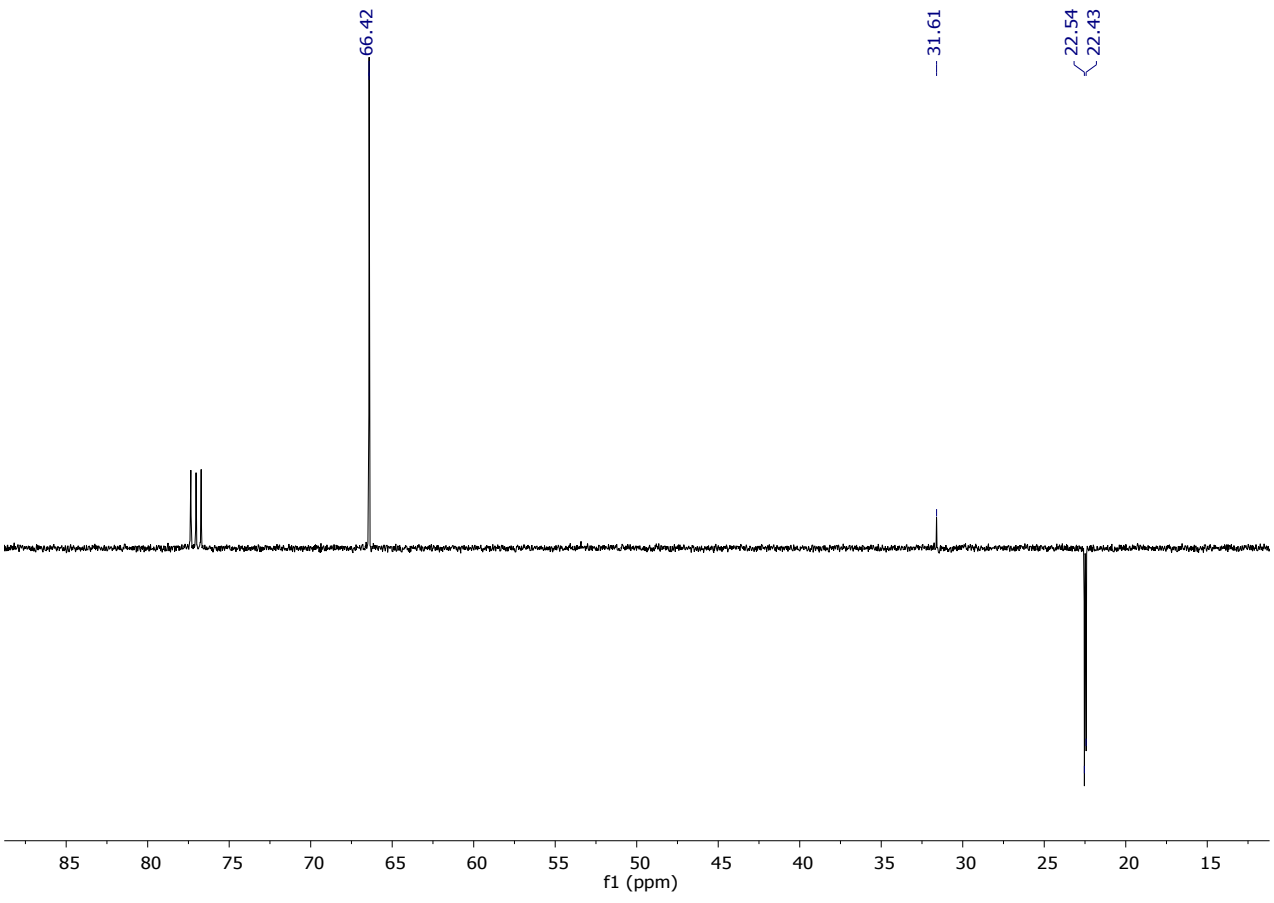


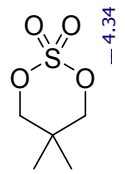
2a




4.63
3.42
1.30
0.85
1.98
1.99
2.99
3.00
f1 (ppm)

3

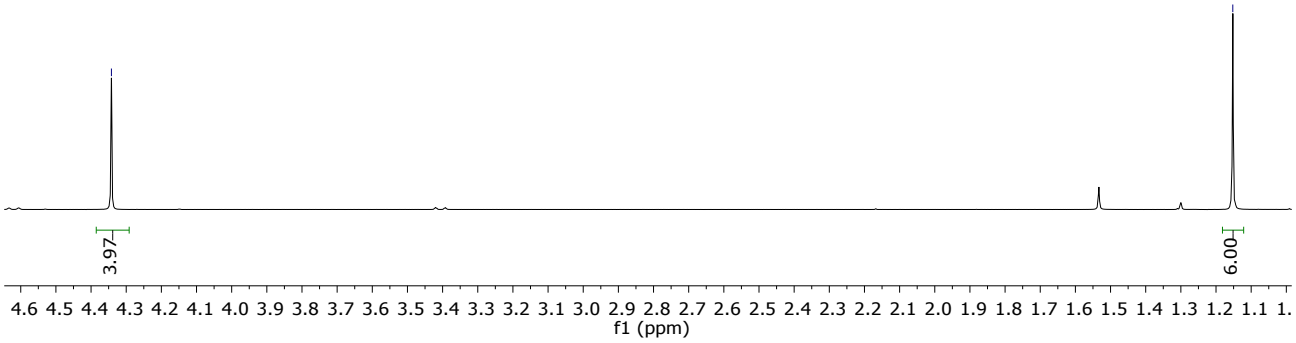

66.42
31.61
22.54
22.43
f1 (ppm)

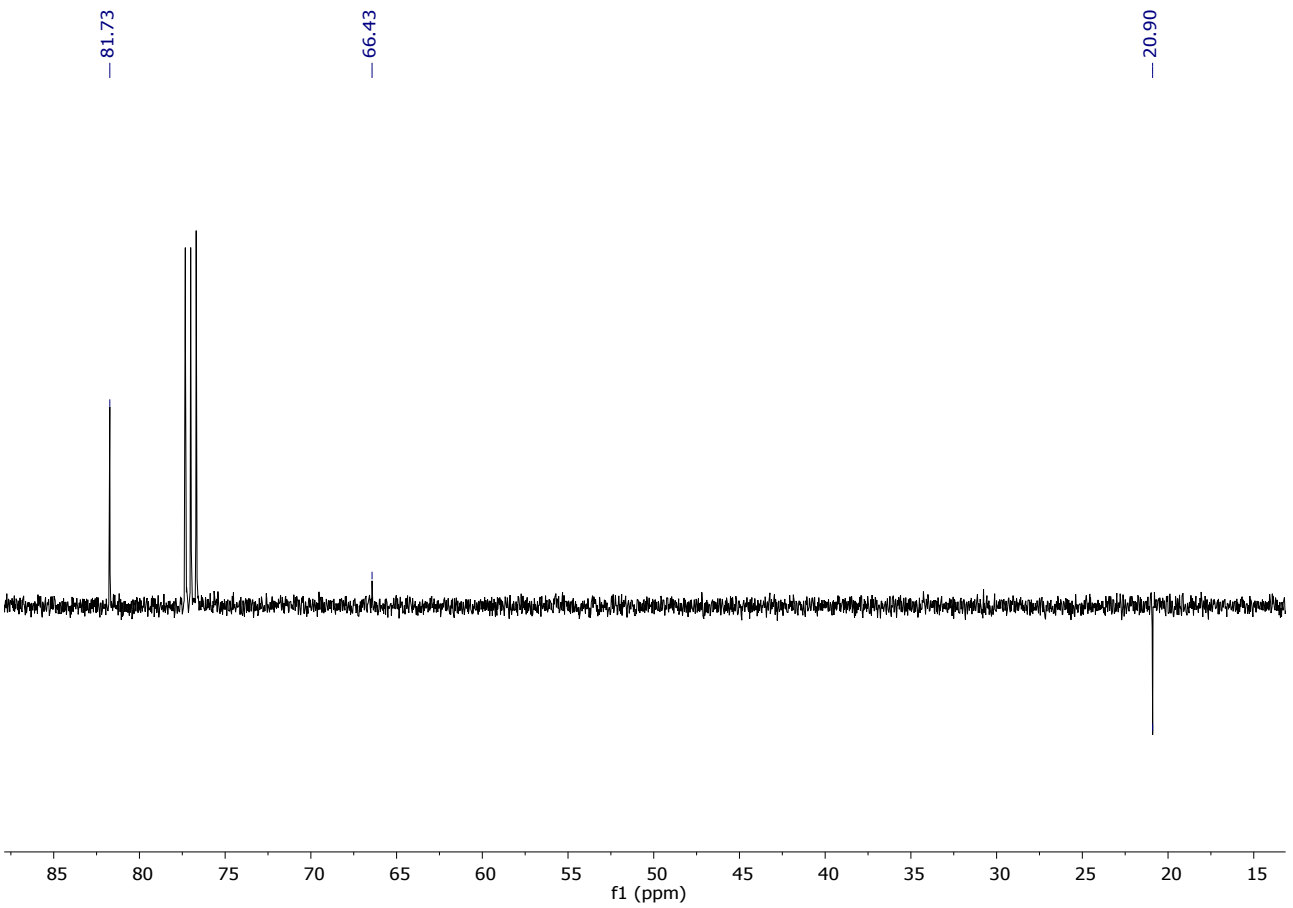

O
O
S
O
O

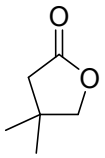
4.34

1.15

4

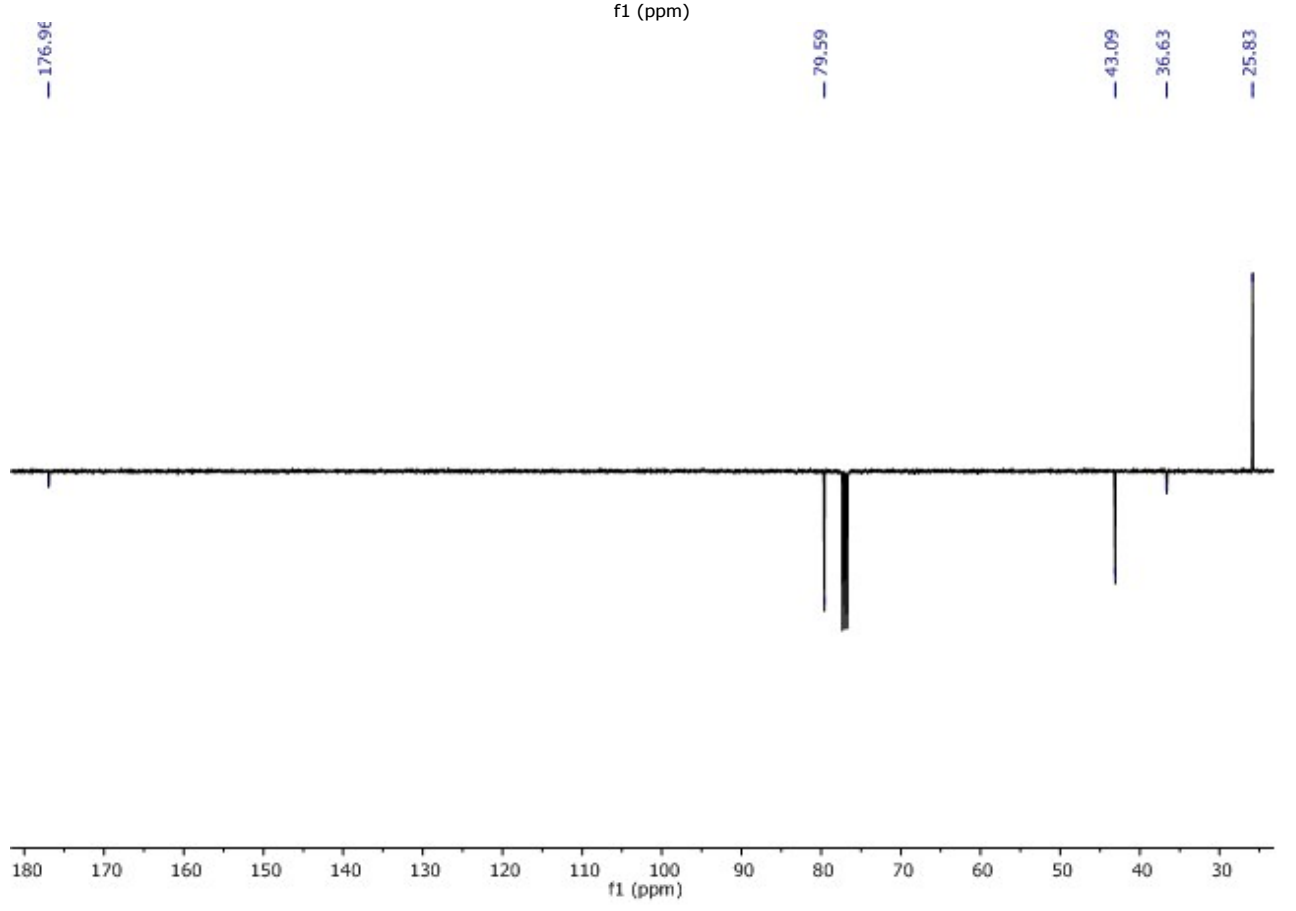

3.97
6.00
4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.
f1 (ppm)

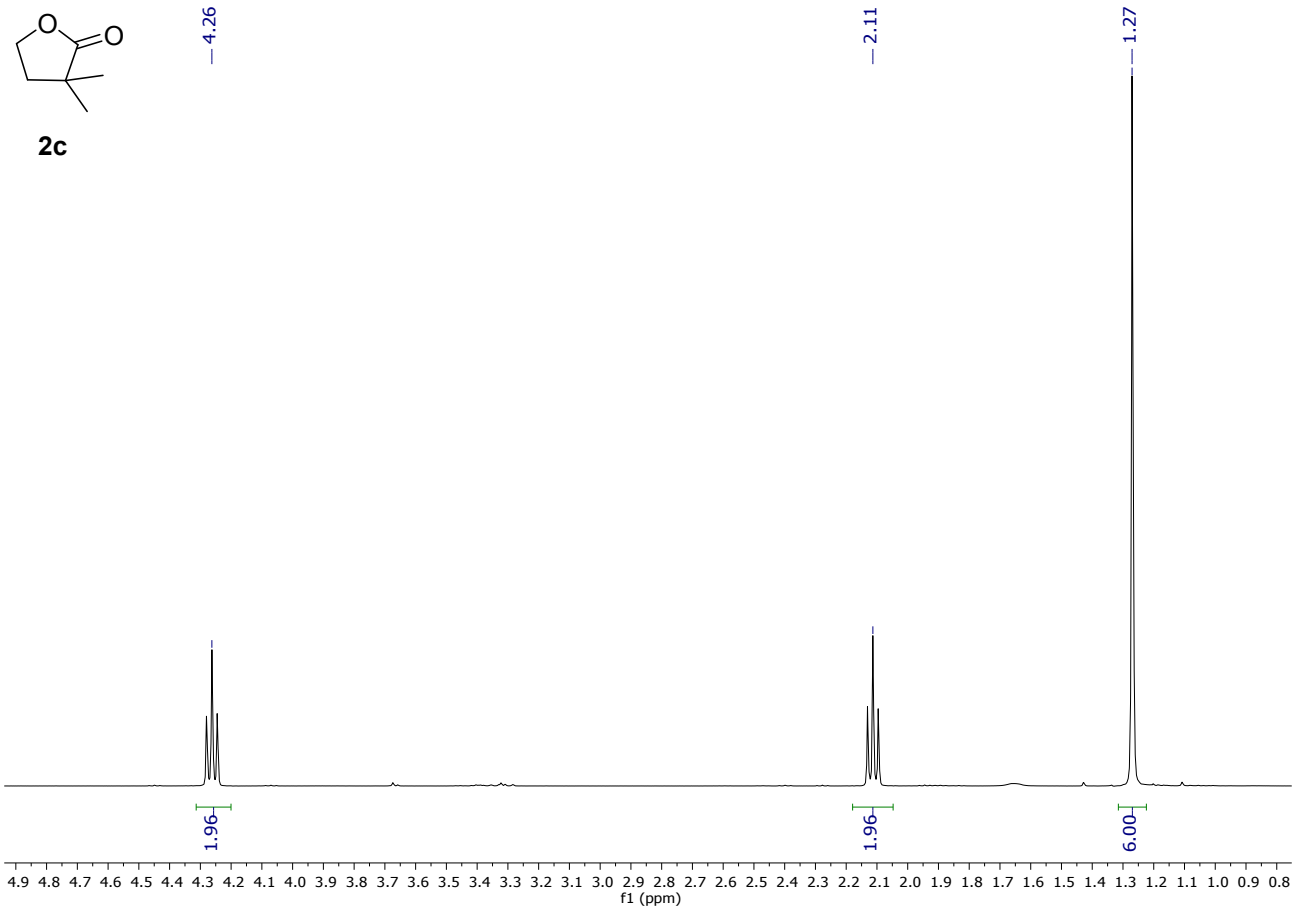

81.73
66.43
20.90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
f1 (ppm)



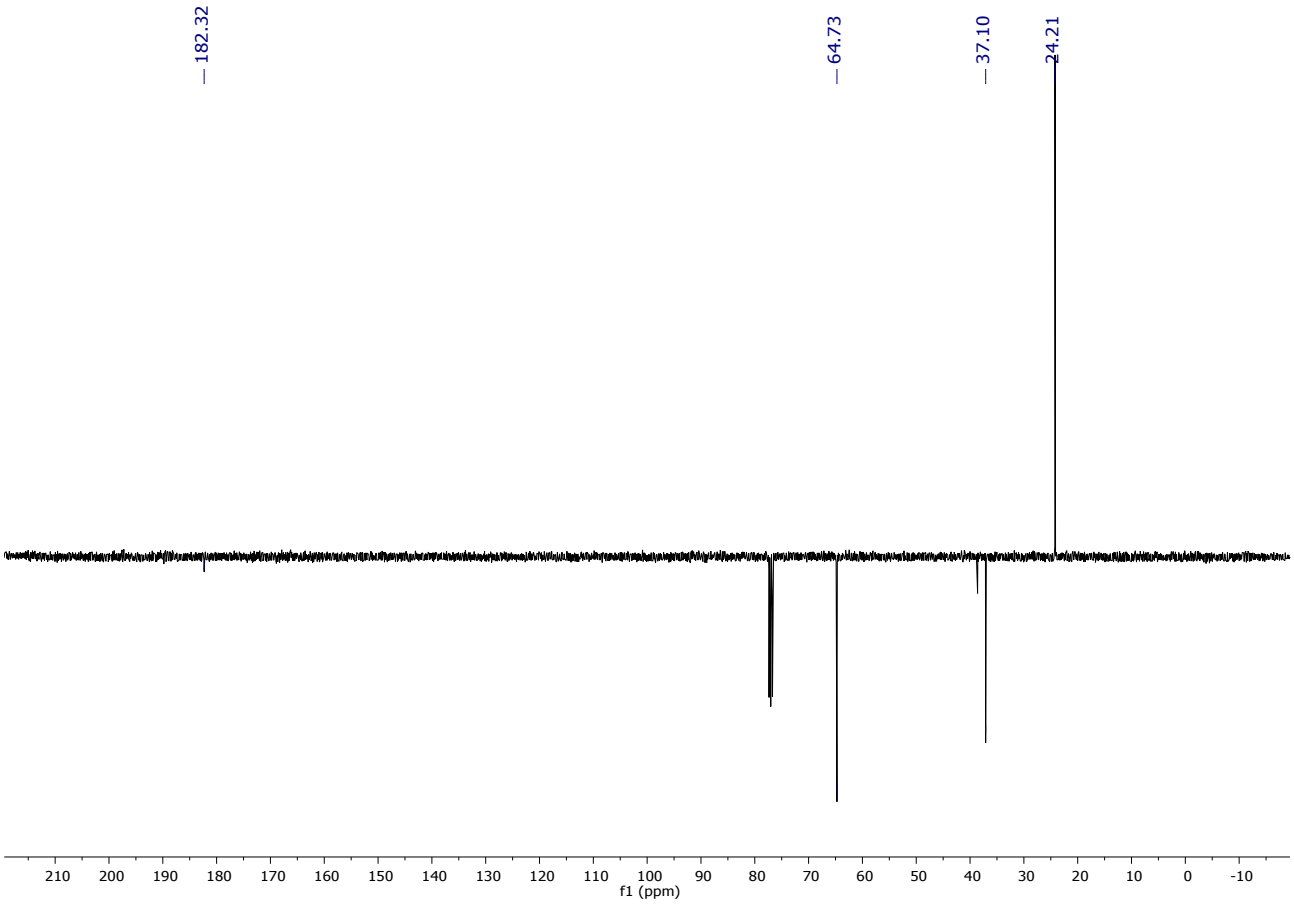
2b

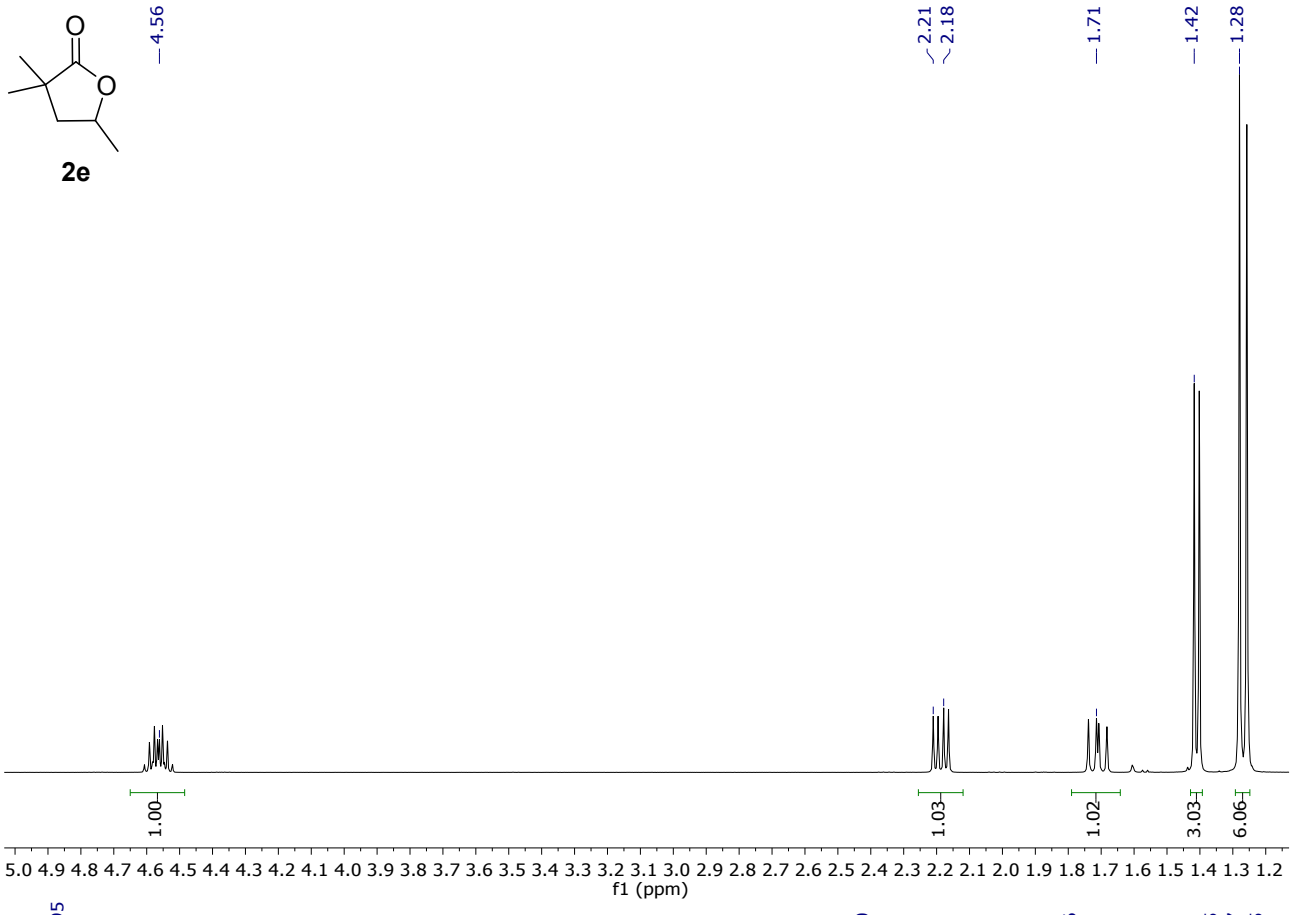
3.98
2.33
1.20
1.00
1.02
3.08
4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2
f1 (ppm)

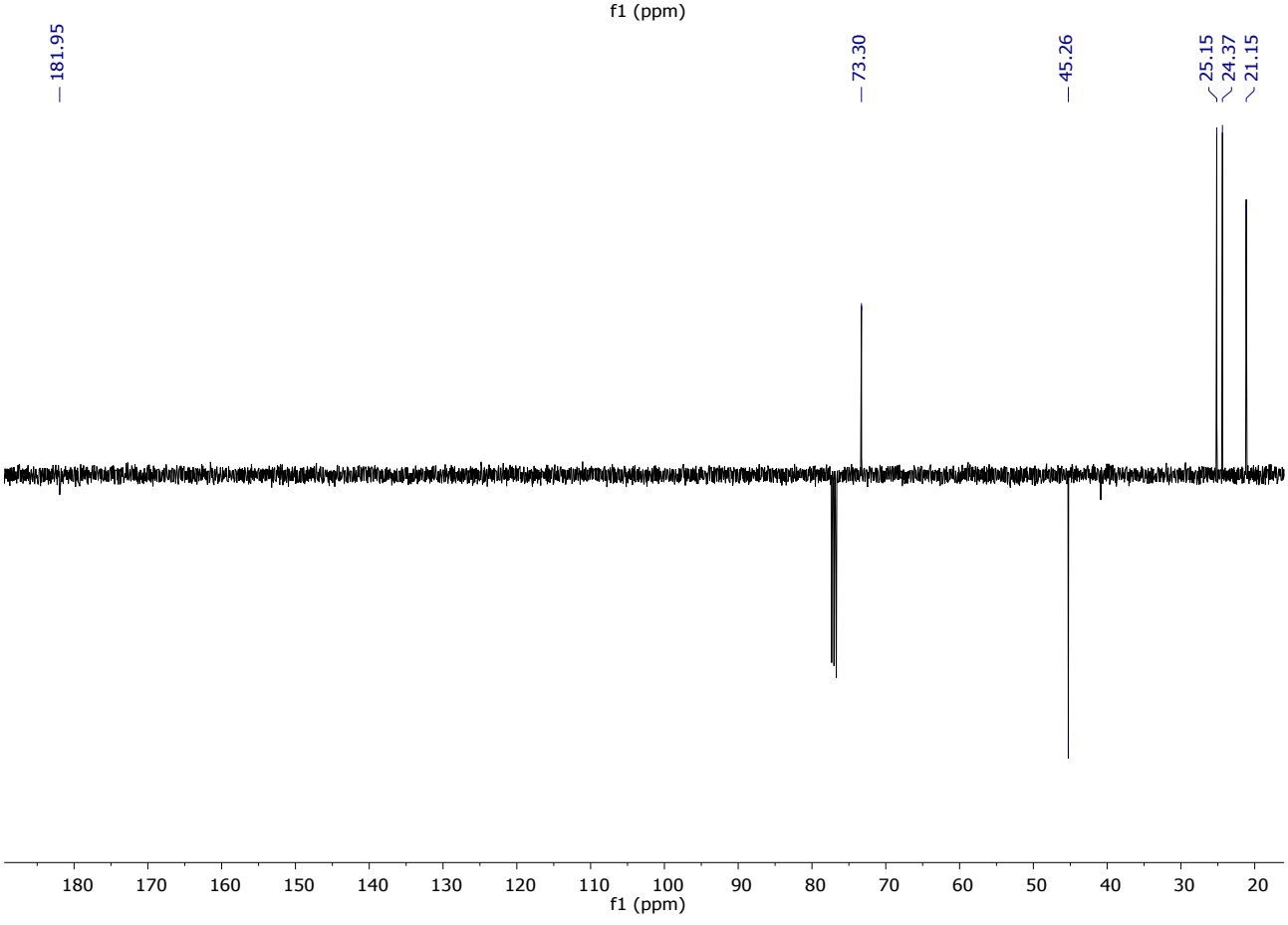

176.9
79.59
43.09
36.63
25.83
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30
f1 (ppm)

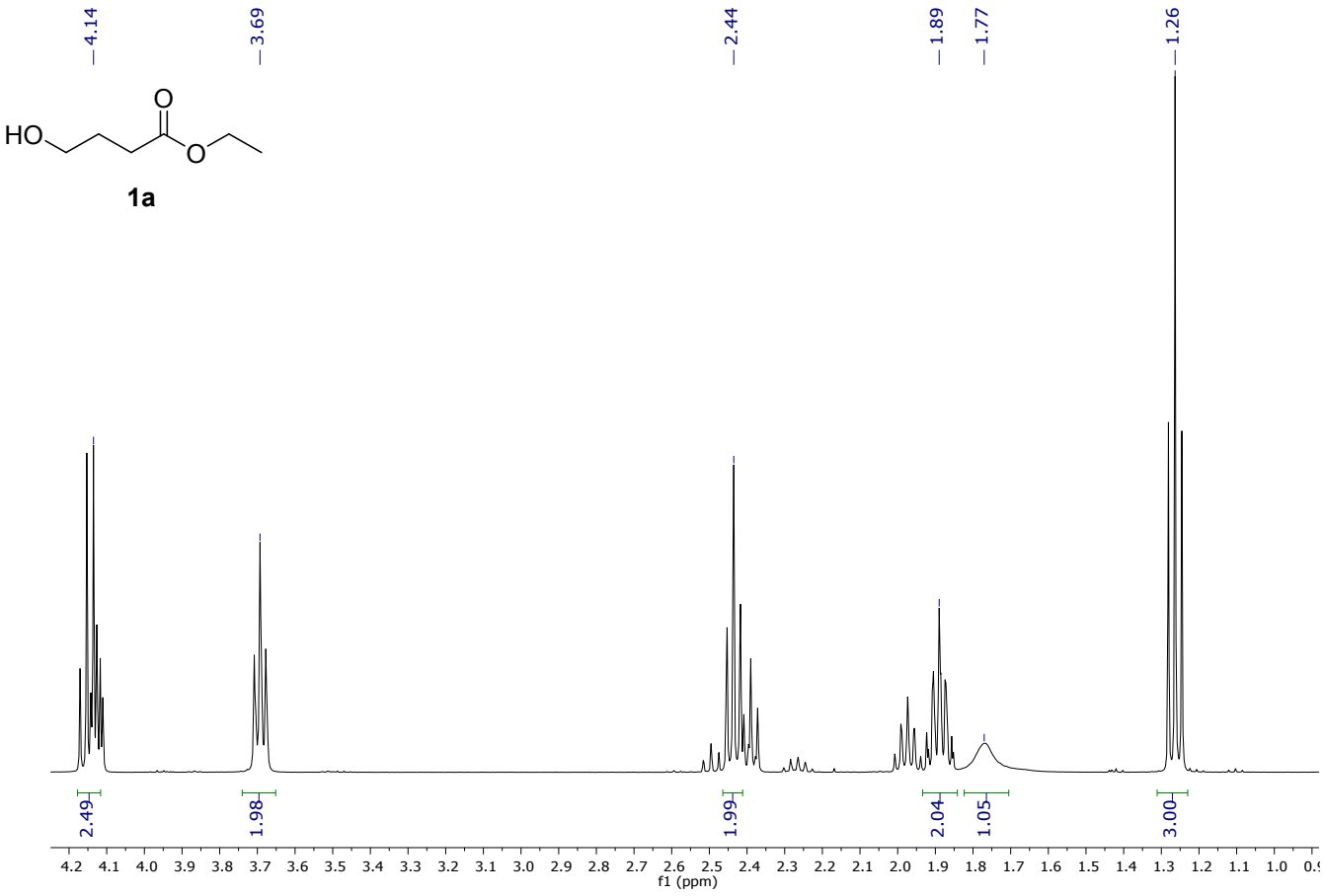

4.26
2.11
1.27
1.96
1.96
6.00
4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8
f1 (ppm)

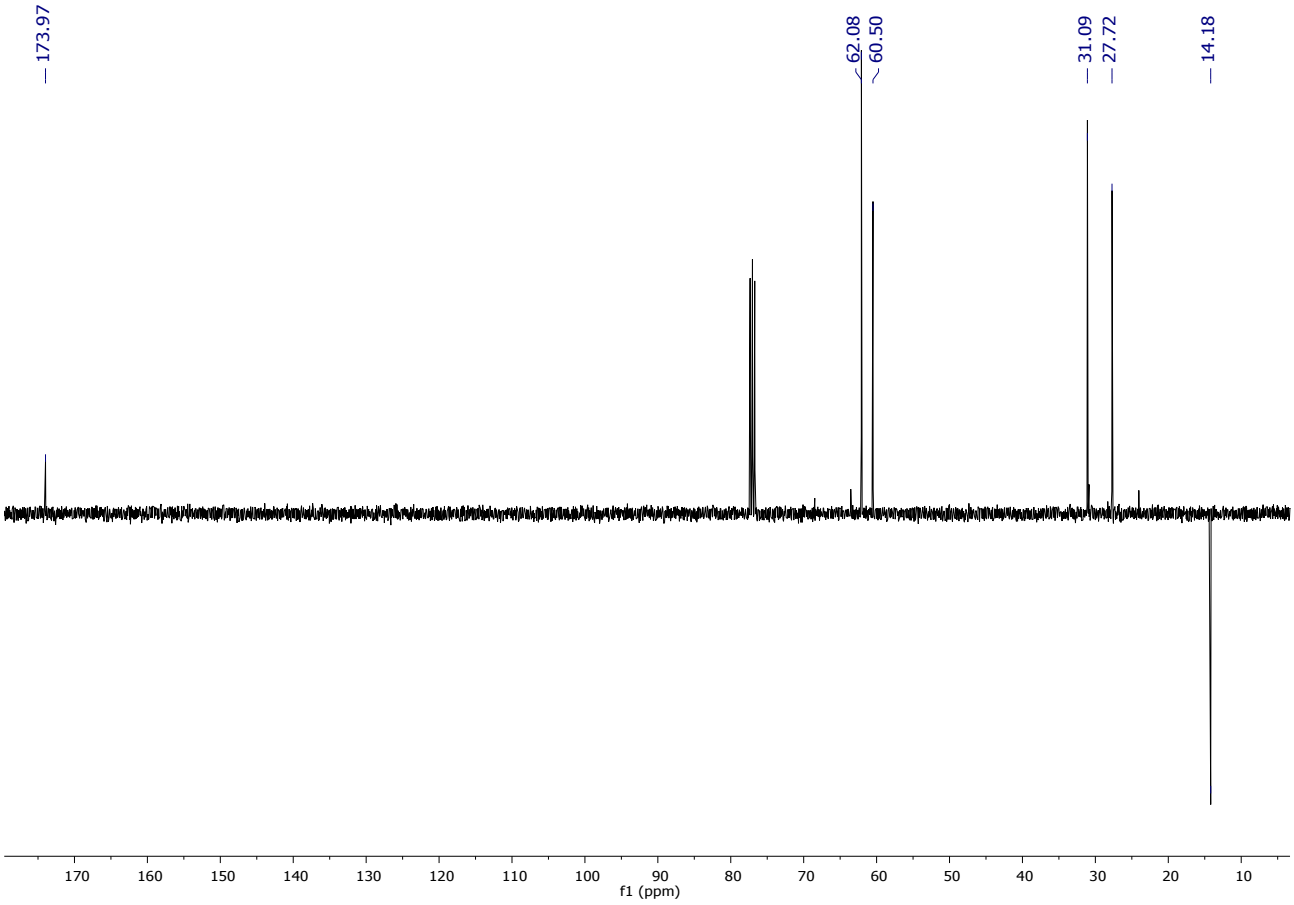
2c

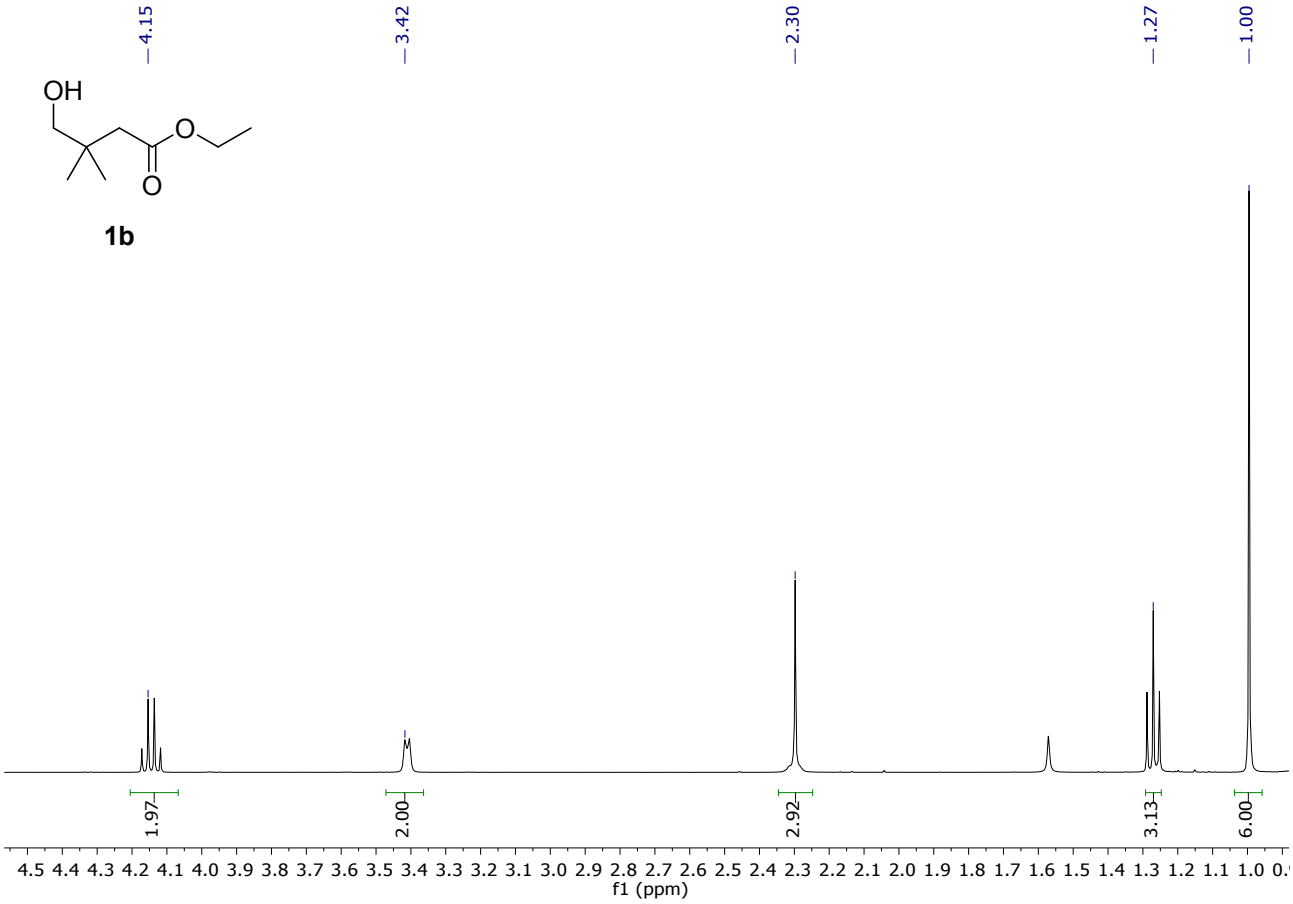

182.32
64.73
37.10
24.21
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

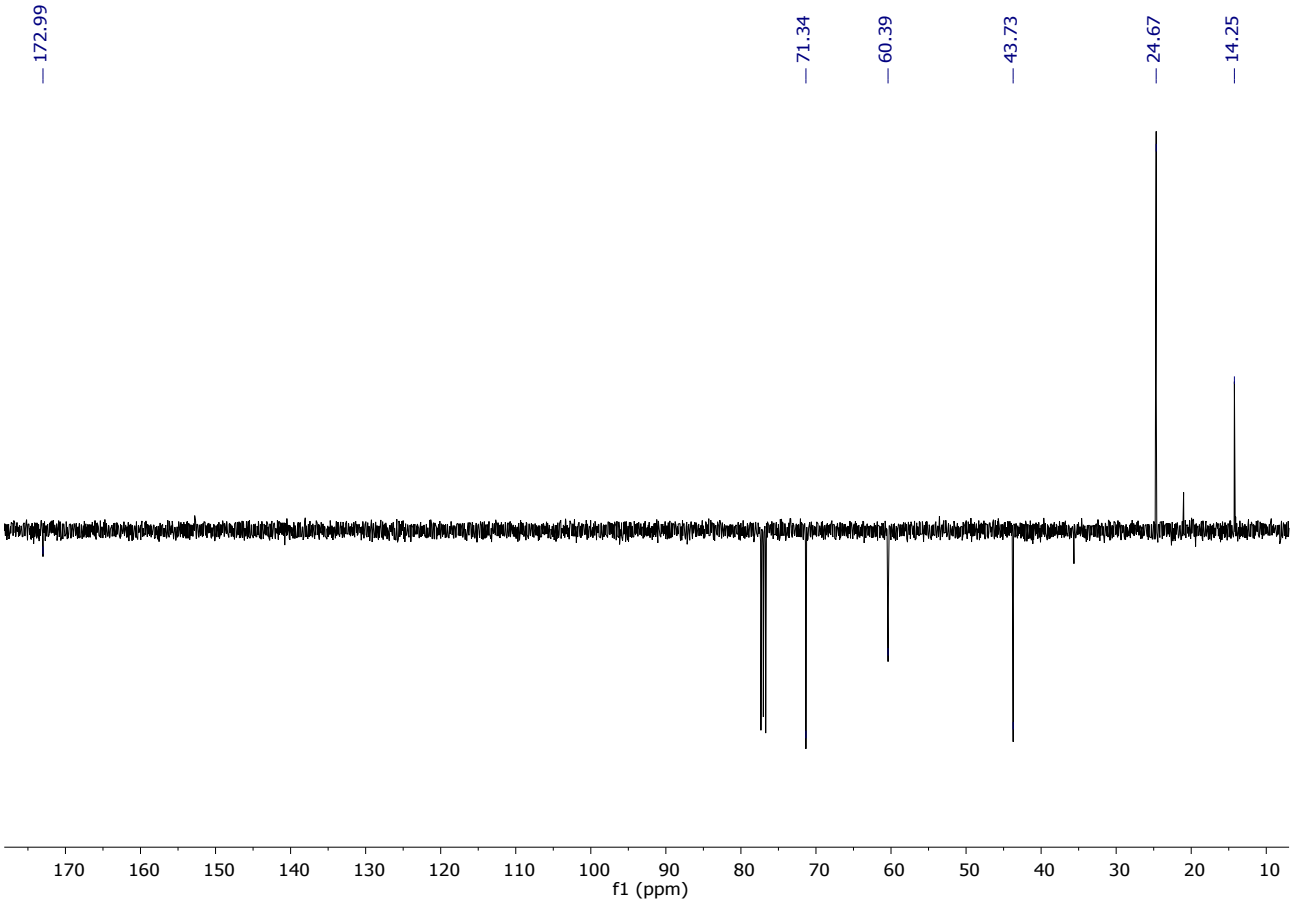

2e
4.56
2.21
2.18
1.71
1.42
1.28
1.00
1.03
1.02
3.03
6.06
f1 (ppm)

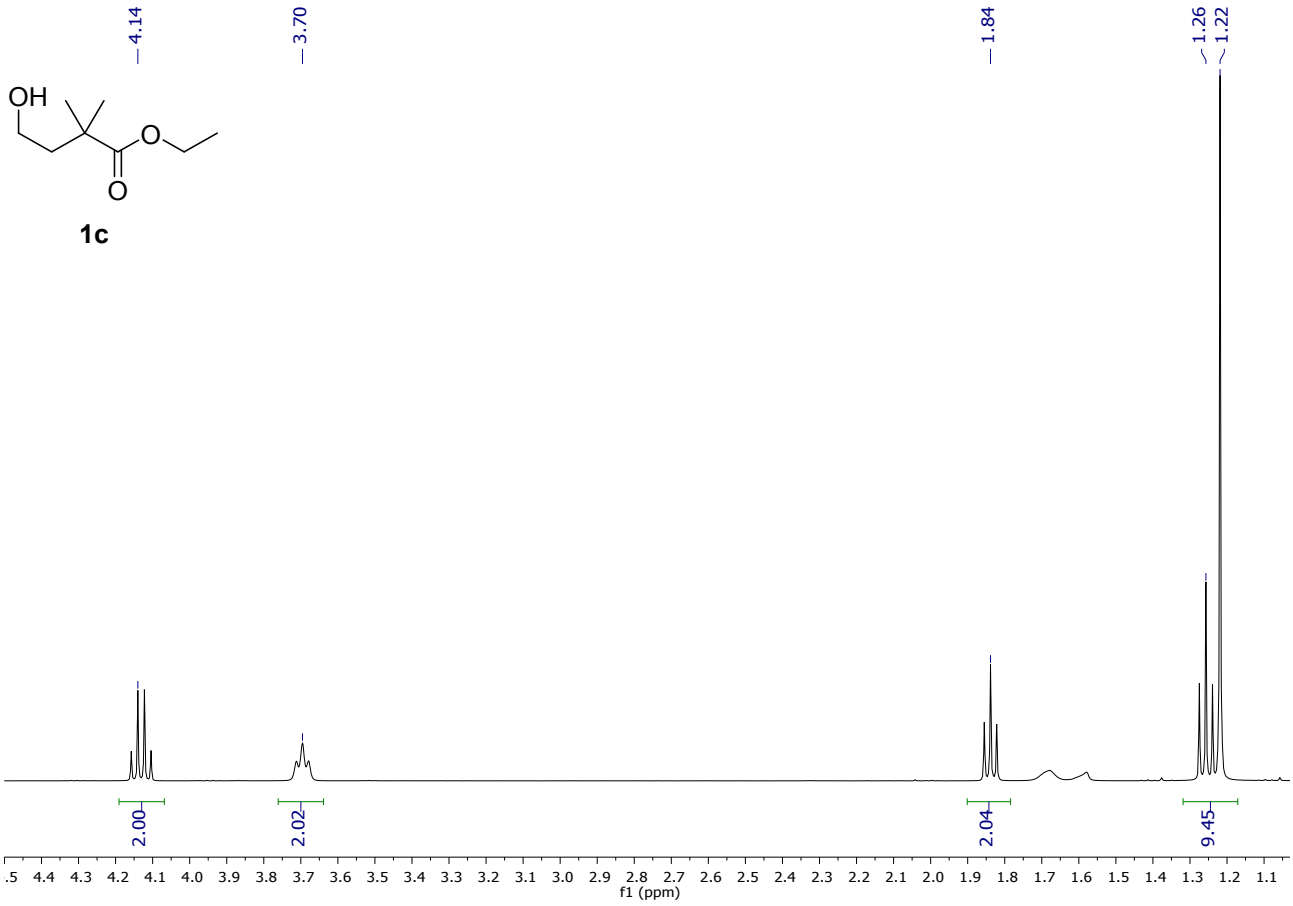

181.95
73.30
45.26
25.15
24.37
21.15
f1 (ppm)

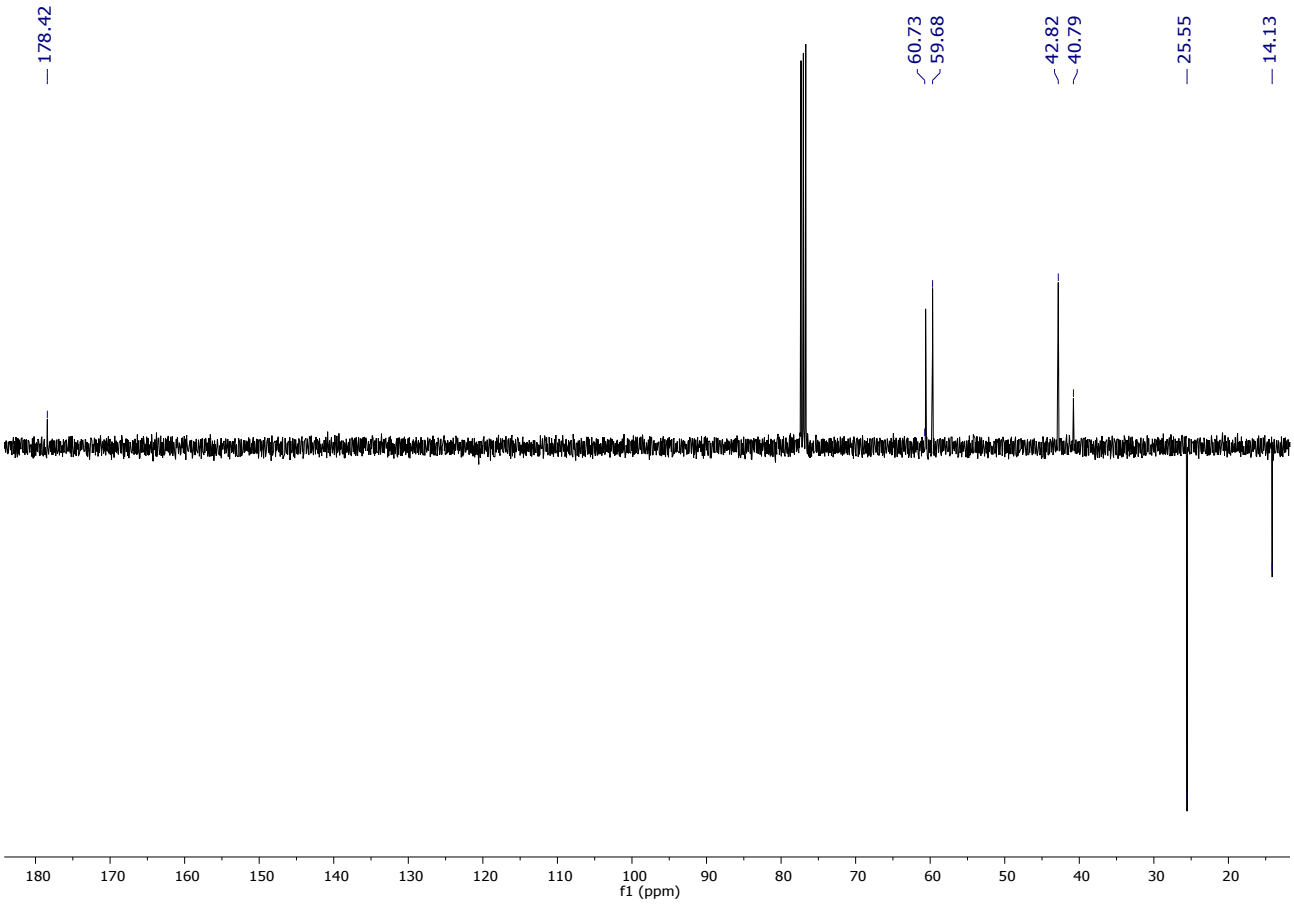

4.14
3.69
2.44
1.89
1.77
1.26
HO
O
O
1a
2.49
1.98
1.99
2.04
1.05
3.00
f1 (ppm)

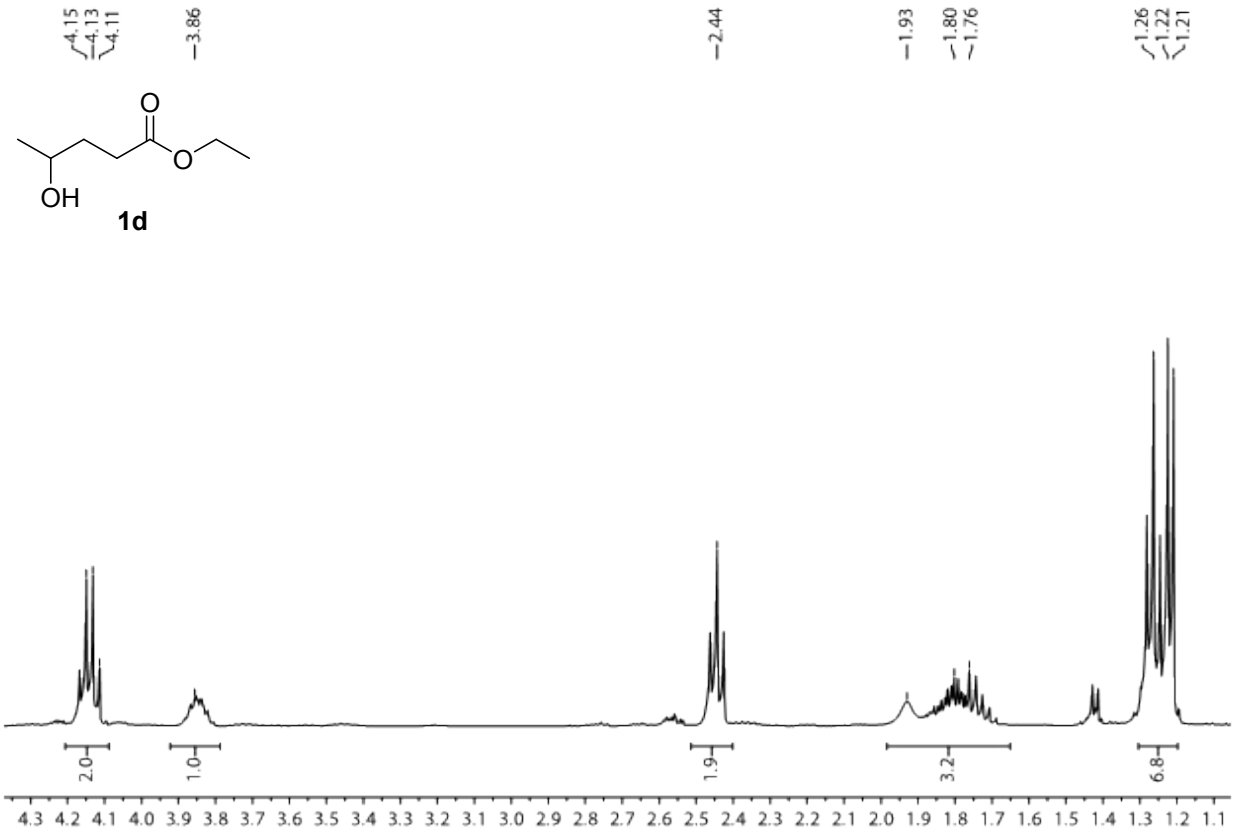

173.97
62.08
60.50
31.09
27.72
14.18
f1 (ppm)


4.15
3.42
2.30
1.27
1.00
OH
O
O
1b
1.97
2.00
2.92
3.13
6.00
4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0
f1 (ppm)

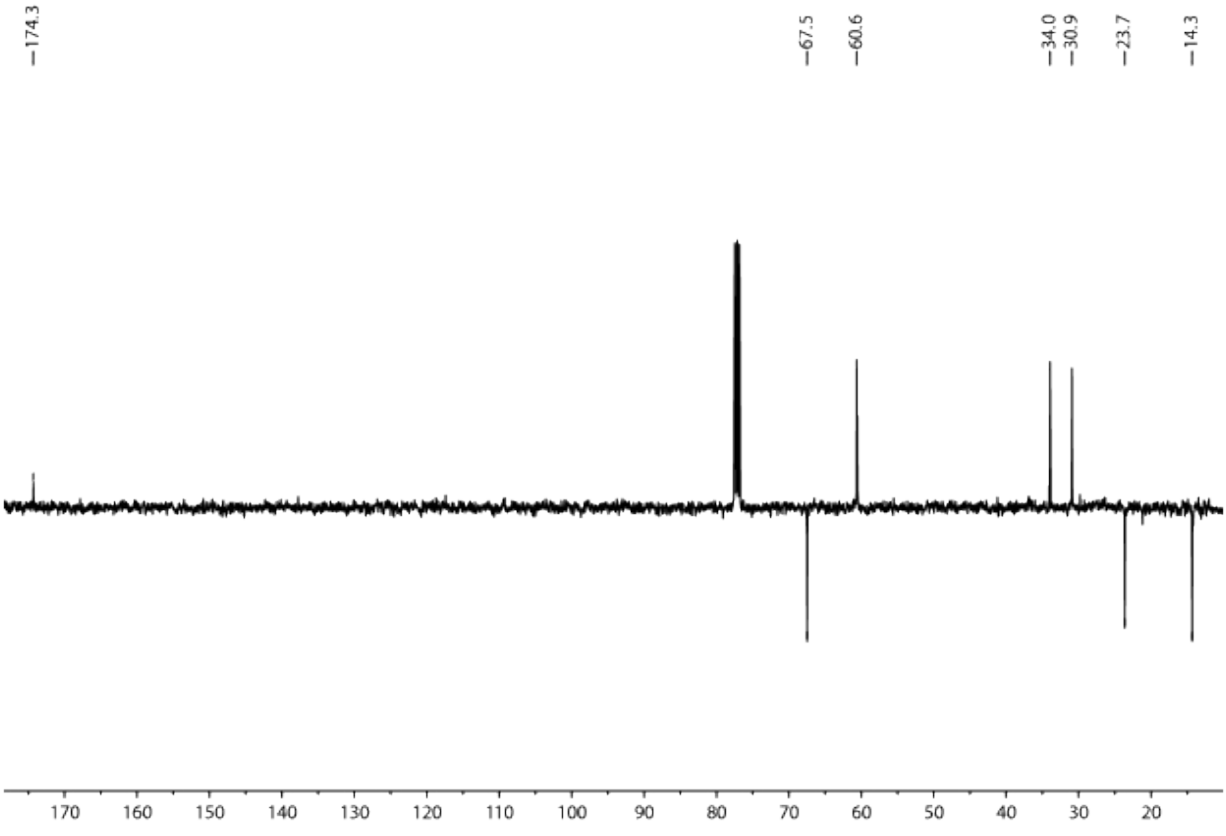

172.99
71.34
60.39
43.73
24.67
14.25
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

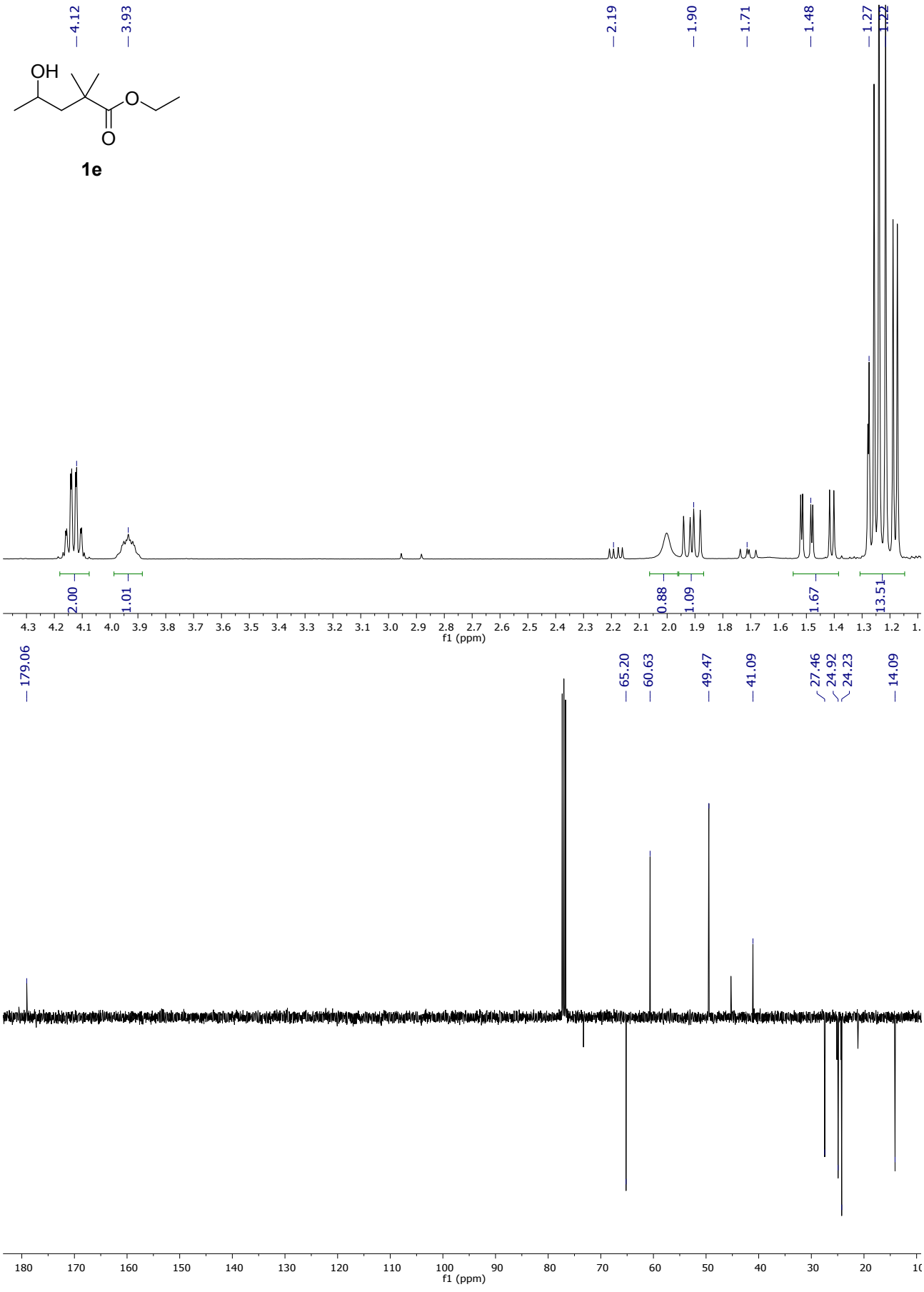

4.14
3.70
1.84
1.26
1.22
OH
O
O
1c
2.00
2.02
2.04
9.45
f1 (ppm)

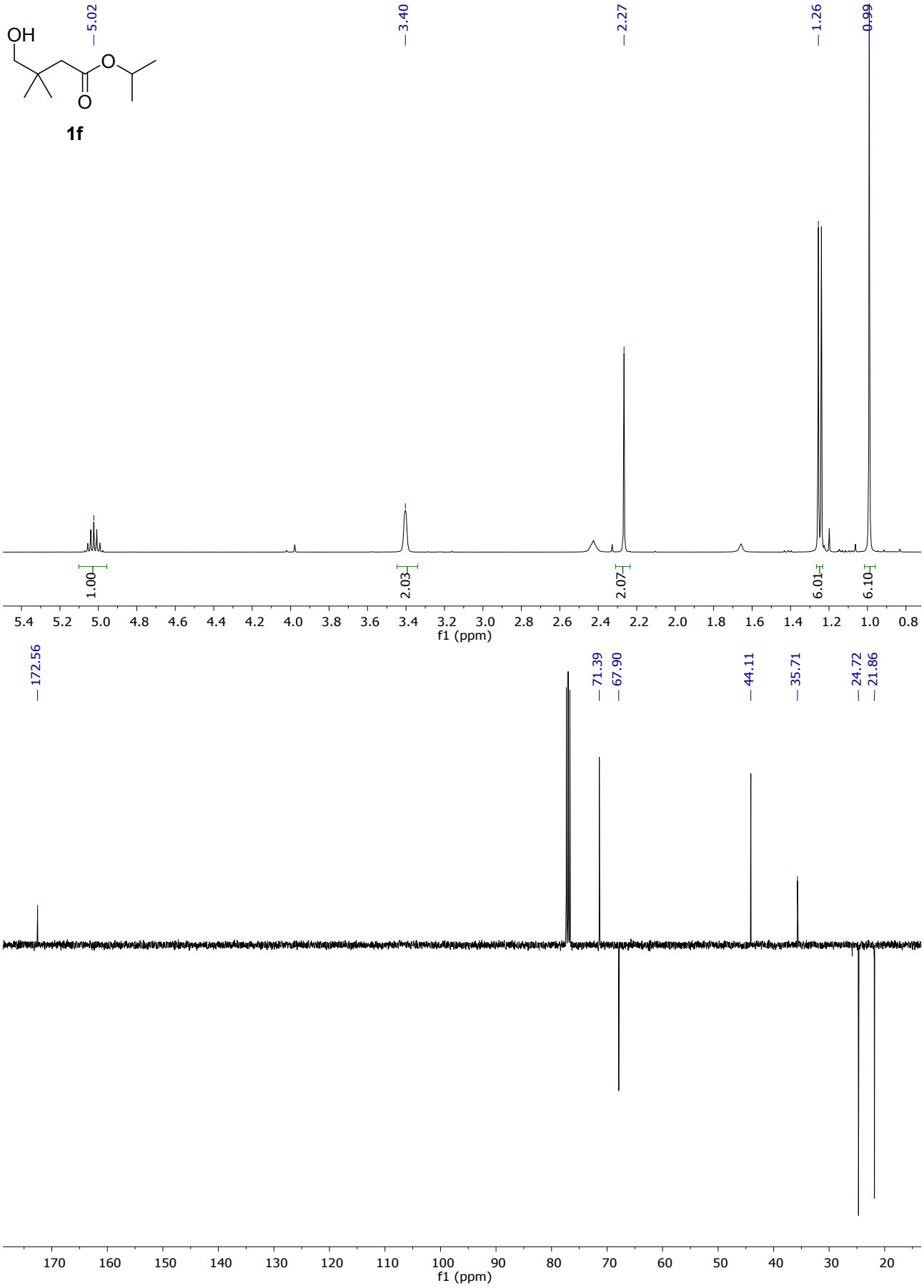

178.42
60.73
59.68
42.82
40.79
25.55
14.13
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)


4.15
4.13
4.11
3.86
2.44
1.93
1.80
1.76
1.26
1.22
1.21
O
O
OH
2.0
1.0
1.9
3.2
6.8
4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1

1d


174.3
67.5
60.6
34.0
30.9
23.7
14.3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20


4.12
3.93
2.19
1.90
1.71
1.48
1.27
1.22
OH
O
O
1e
2.00
1.01
0.88
1.09
1.67
13.51
f1 (ppm)
179.06
65.20
60.63
49.47
41.09
27.46
24.92
24.23
14.09
f1 (ppm)


OH
O
O
1f
5.02
3.40
2.27
1.26
0.99
1.00
2.03
2.07
6.01
6.10
f1 (ppm)
172.56
71.39
67.90
44.11
35.71
24.72
21.86
f1 (ppm)

4. Kinetic Experiments

The rate low of cyclization of hydroxyesters **E** (**1**) to give the lactone **L** (**2**) (shown in Figure S.1) can be written as:

$$-\frac{d[\mathrm{E}]}{d\mathrm{t}} = k_1[\mathrm{AH}][\mathrm{E}] = k_{\mathrm{obs}}[\mathrm{E}]$$

where k_{obs} = k_1 [AH] is the experimental *pseudo* first-order rate constant, and k_1 is the true catalytic rate constant.

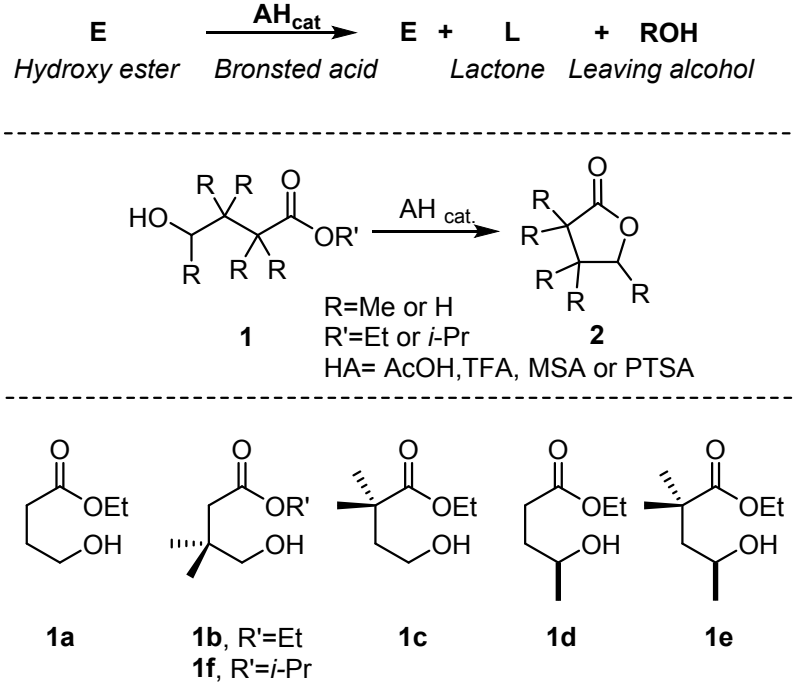


Figure S.1

The reaction progress was monitored by measuring a series of H^1-NMR (500 MHz) spectra recorded as pseudo 2D at 303 K of a sample of hydroxyesters in $CDCl_3$ at 303 K allowing a fixed time delay between successive spectra. Pulse width of 30° and relaxation delay of 2 sec. were used in order to avoid errors due to the relaxation. Exponential filter was applied to FID for optimization of signal-to-noise ratio. Baseline correction was applied to spectra before integration. Bias and slope of integrals were carefully adjusted.

The sample was prepared by adding directly, with a gastight Hamilton syringe, a solution of AH in CH_2Cl_2 (20÷60 μL, 10^{-2}M) to a solution of couples of hydroxyesters (≈ 8-10 mg each) in $CDCl_3$ (500.0 μL) into a NMR tube.

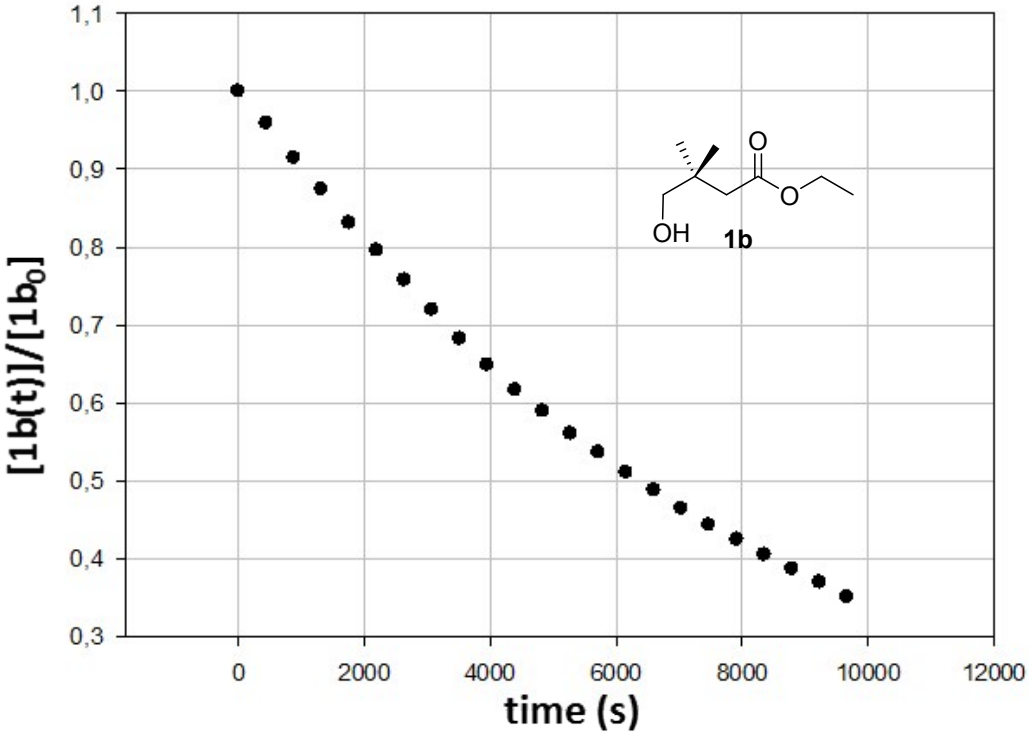
The observed reaction rate constant k_{obs} of the *pseudo* first-order was obtained by linear regression of $\ln[E]/[E]_0$ or of $\ln[1 - [L]/[L]_{eq}]$ *versus* time. The data were analyzed using *Sigmaplot* softwere.

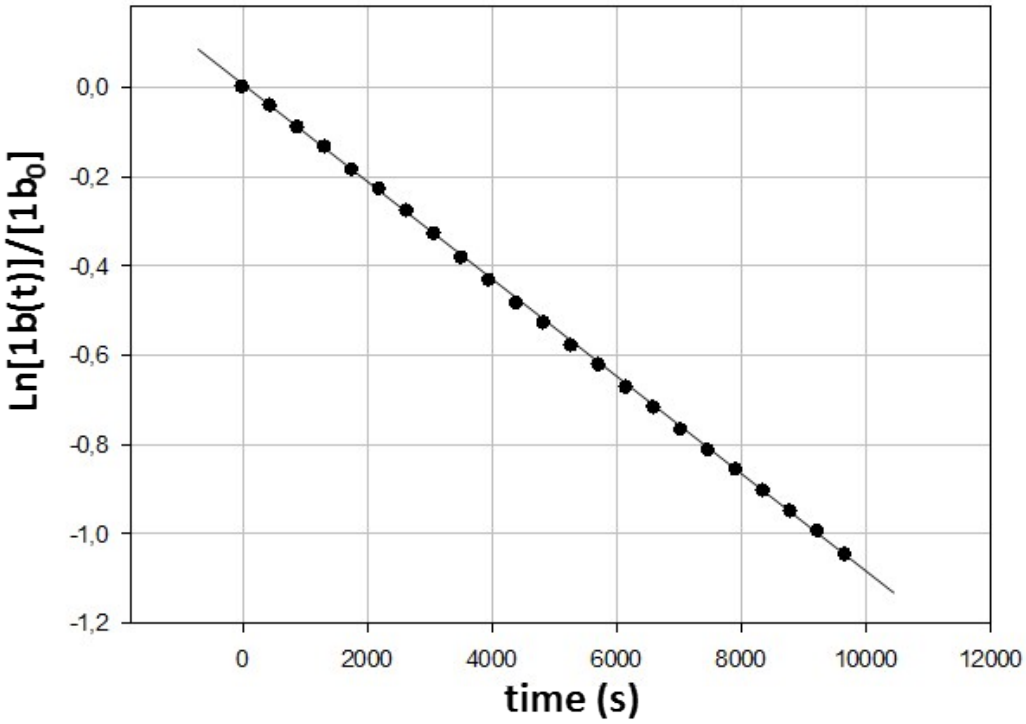
The relative rate constant k_r were calculated with respect to **1a**, where $k_r = k_{obs,1i}/k_{obs,1a}$ (with *i*=b-f).[7] The relative Gibbs energy barriers ($\delta\Delta G_r^{\ddagger}$) were calculated with respect to **1a** by the following equation:

$$\delta\Delta G_r^{\ddagger} = -RT\ ln\ k_r$$ where *R*T = 0.602 kcal·mol^{-1} at 303 K

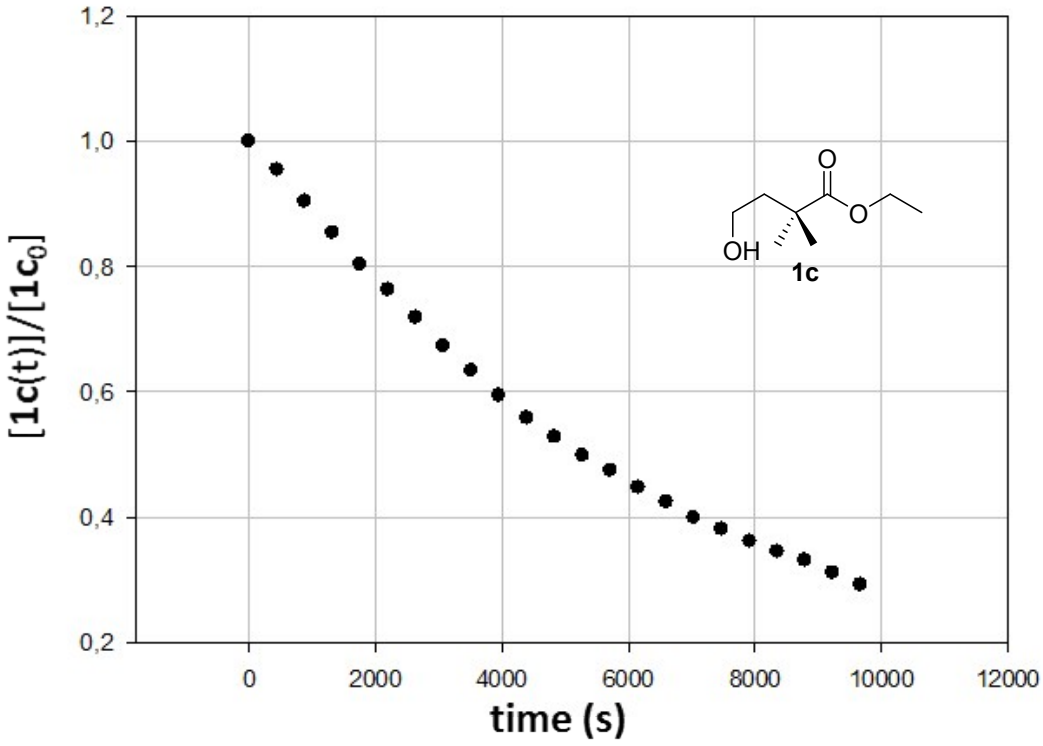
Cyclization of 1b *vs* 1c with TFA

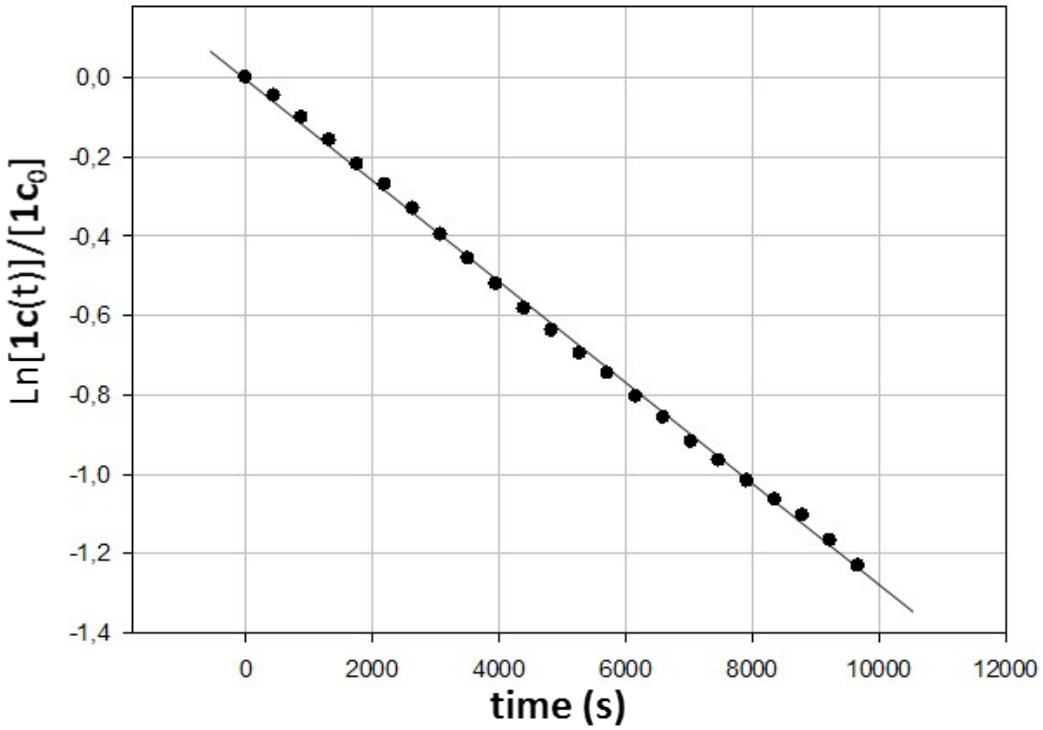
k_{obs}=(1.090±0.004)x10^{-4}, r^2= 0.9998, [TFA]= (1.71±0.10)x10^{-3}M, k_1= 6.37x10^{-2} s^{-1} M^{-1}





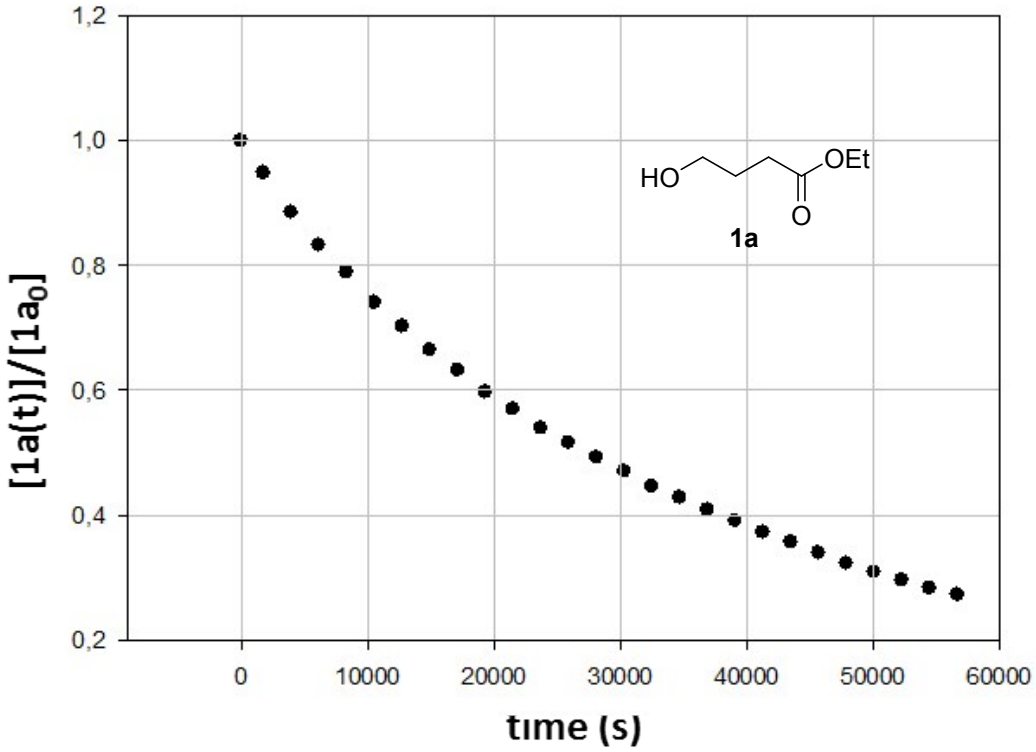
k_{obs}=(1.287±0.009)x10^{-4}, r^2= 0.9989, [TFA]= (1.71±0.10)x10^{-3}M, k_1= 7.53x10^{-2} s^{-1} M^{-1}

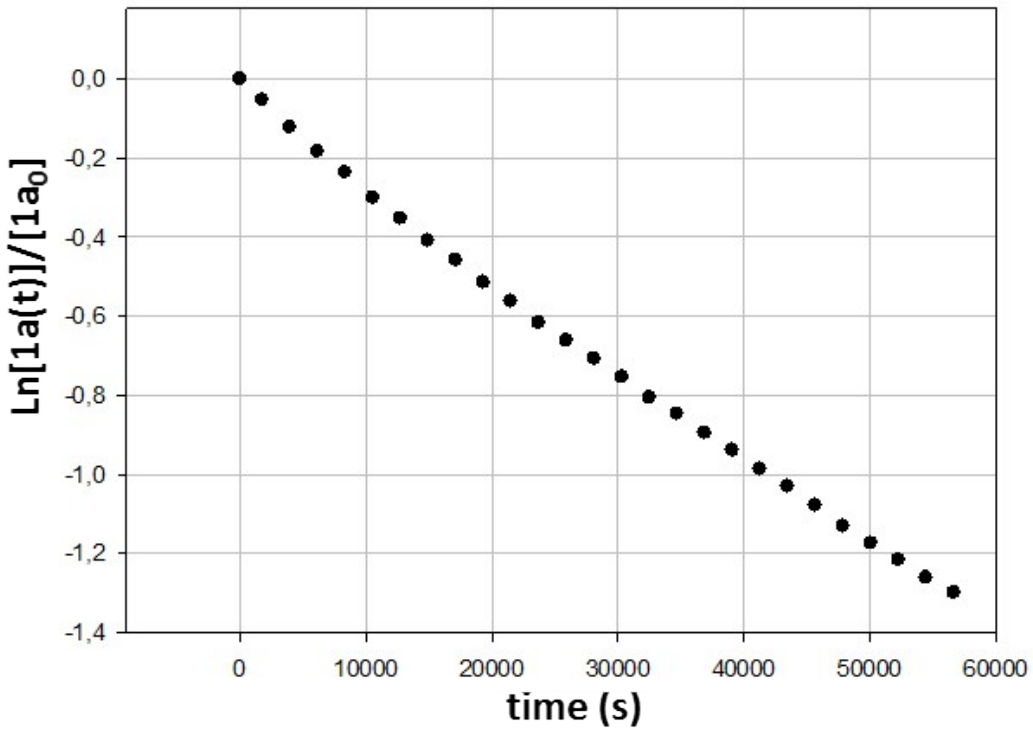




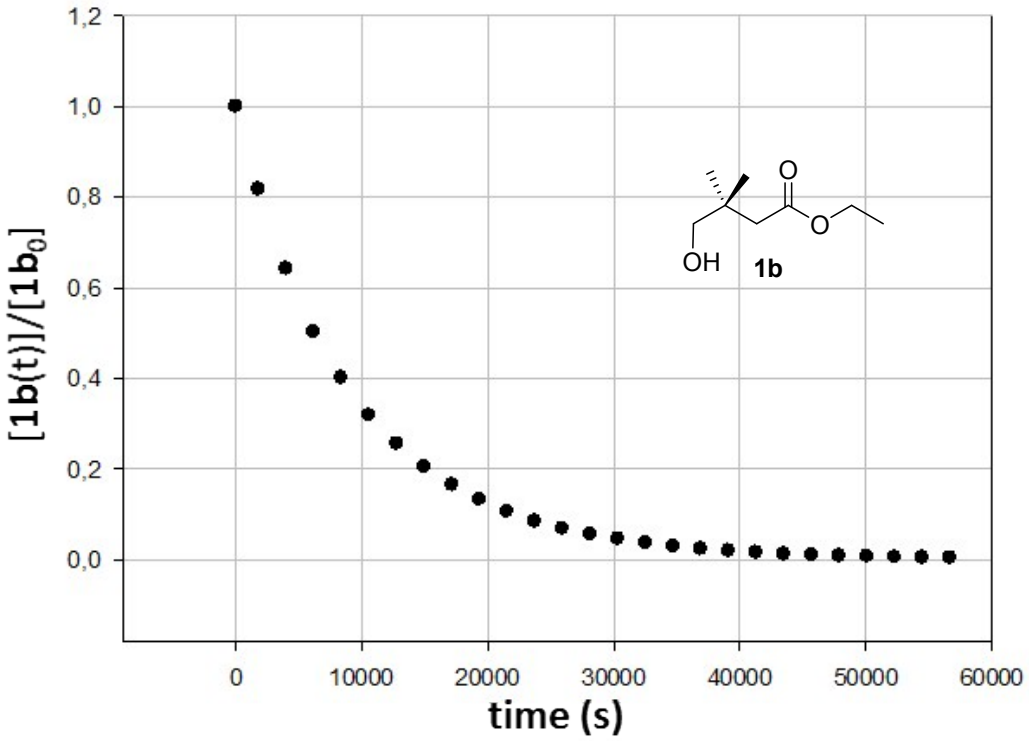
Cyclization of 1a *vs* 1b with TFA

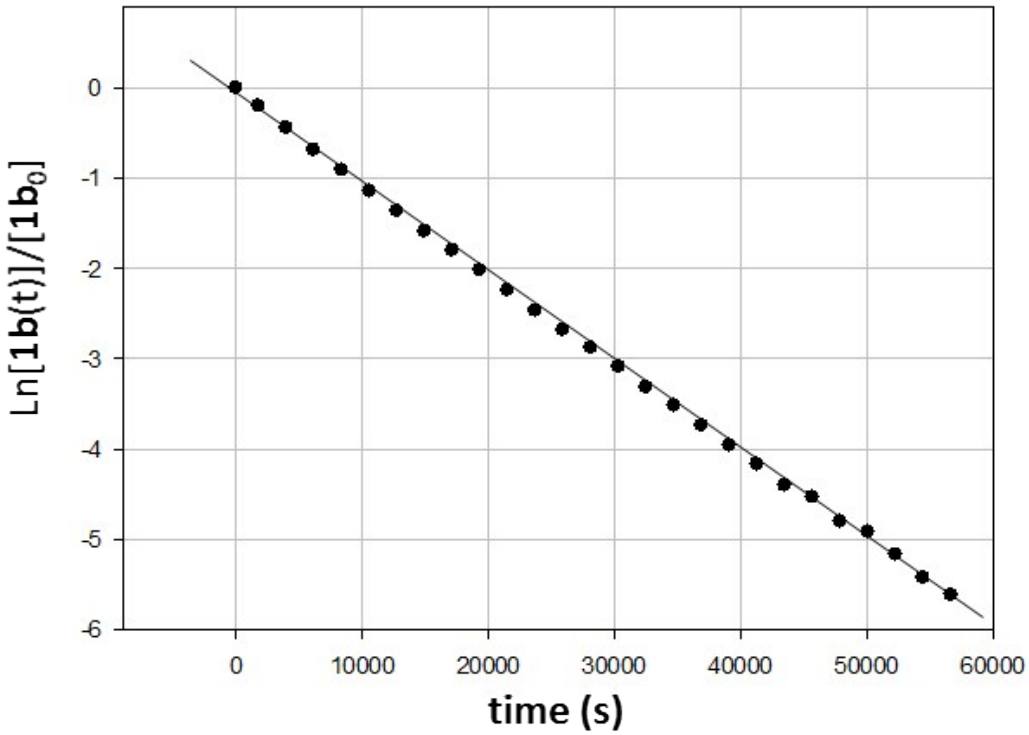
k_{obs}=(2.2580±0.002)x10^{-5}, r^2=0.9971, [TFA]=(1.54±0.05)x10^{-3} M, k_1=1.466x10^{-2} s^{-1} M^{-1}





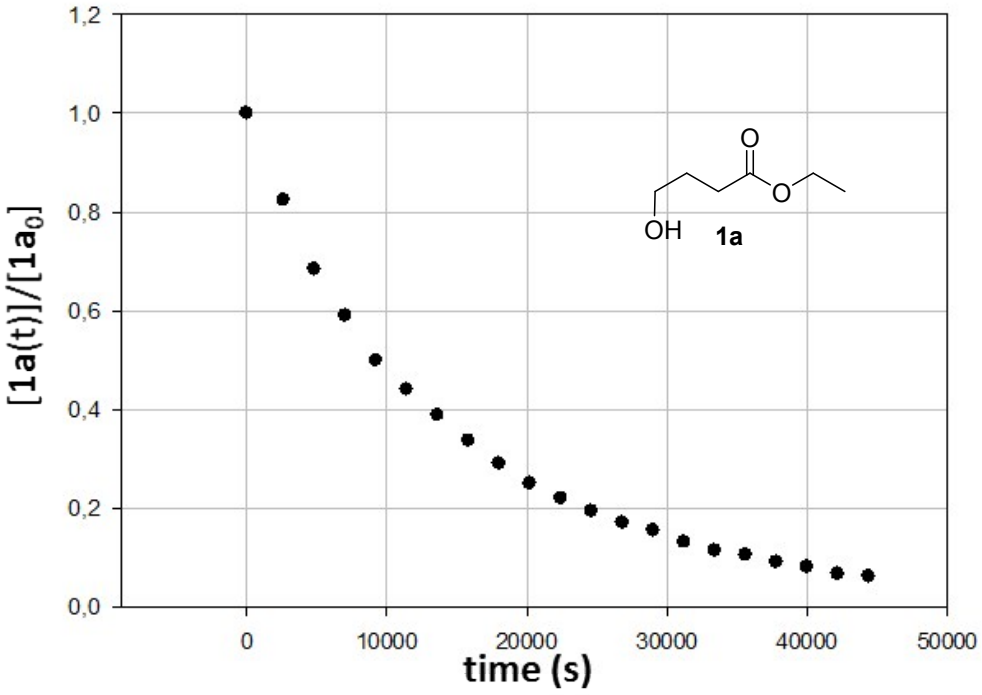
k_{obs}=(9.8140±0.005)x10^{-5}, r^2= 0.9994, 1.54±0.05)x10^{-3} M, k_1= 6.373x10^{-2} s^{-1} M^{-1}

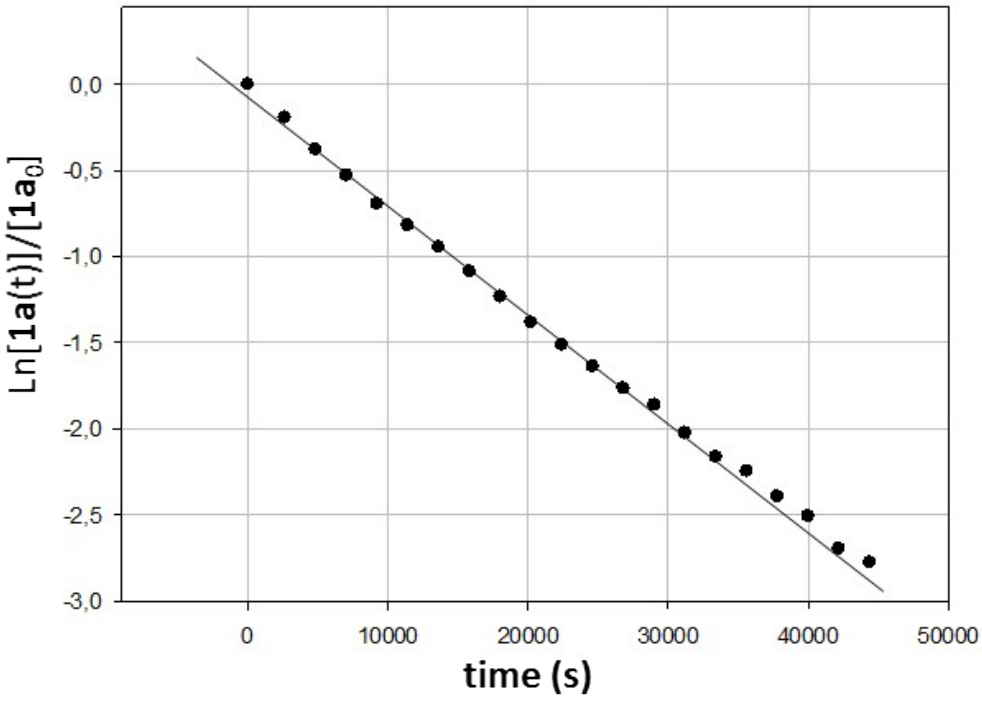




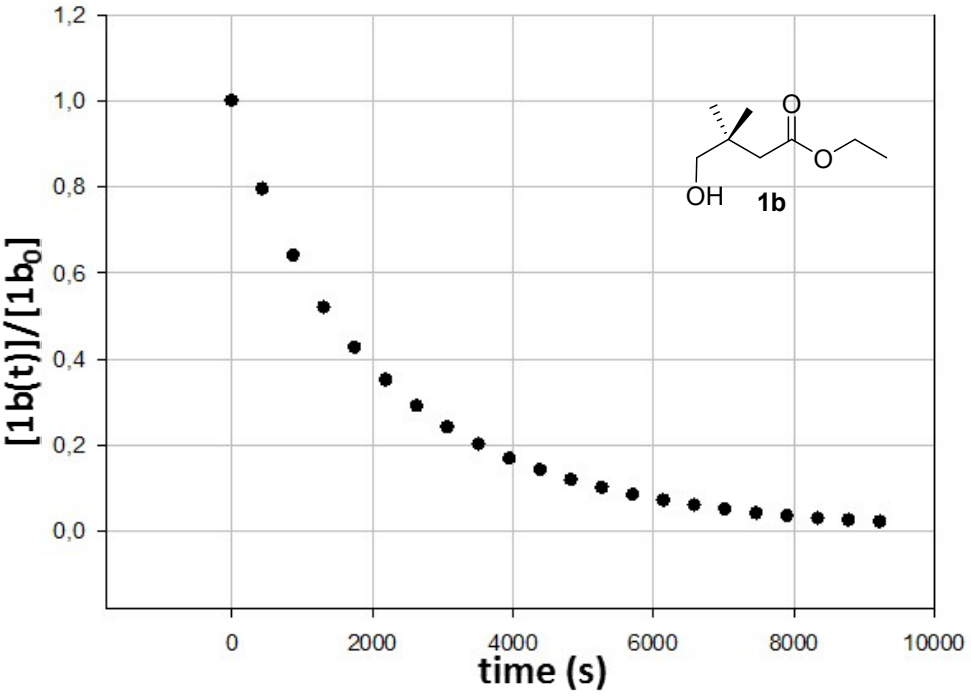
Cyclization of 1a *vs* 1b with MSA

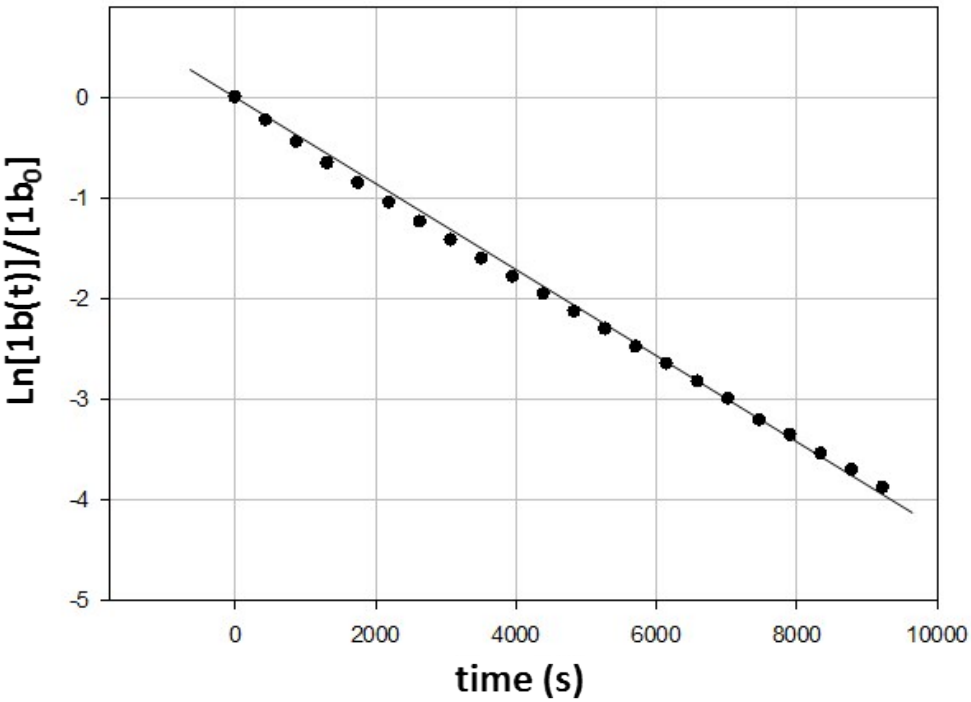
k_{obs}=(6.1885±0.063)x10^{-5}, r^2= 0.9980, [MSA]= (2.82±0.10)x10^{-4}M, k_1= 2.2x10^{-1} s^{-1} M^{-1}





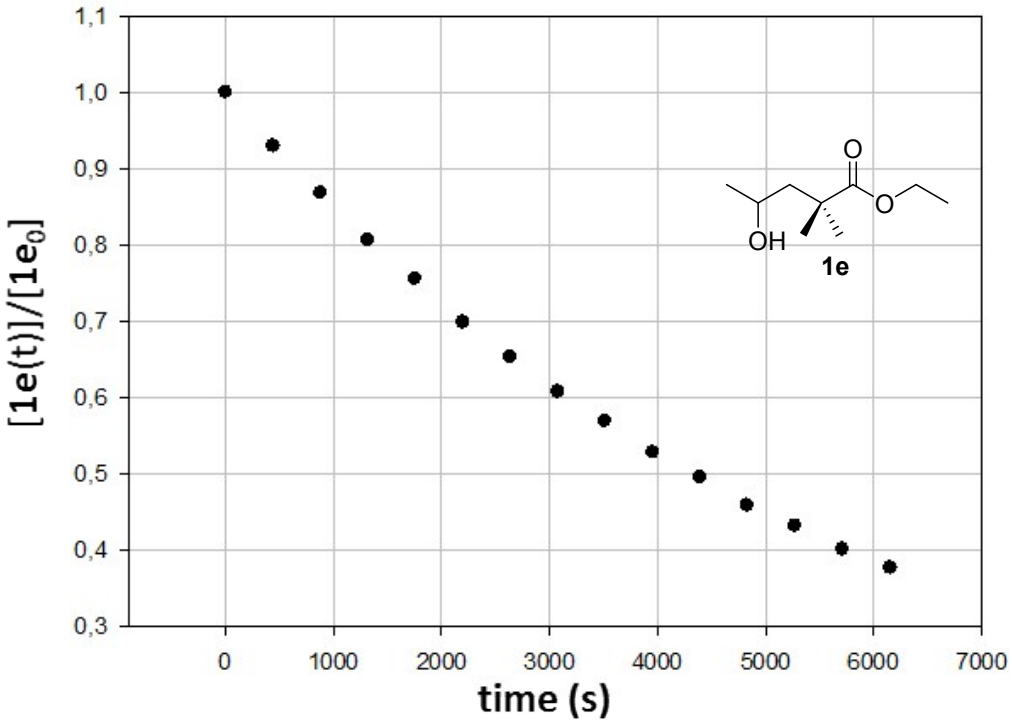
k_{obs}=(4.1406±0.063)x10^{-4}, r^2= 0.9980, [MSA]= (2.82±0.10)x10^{-4}M, k_1= 1.468 s^{-1} M^{-1}

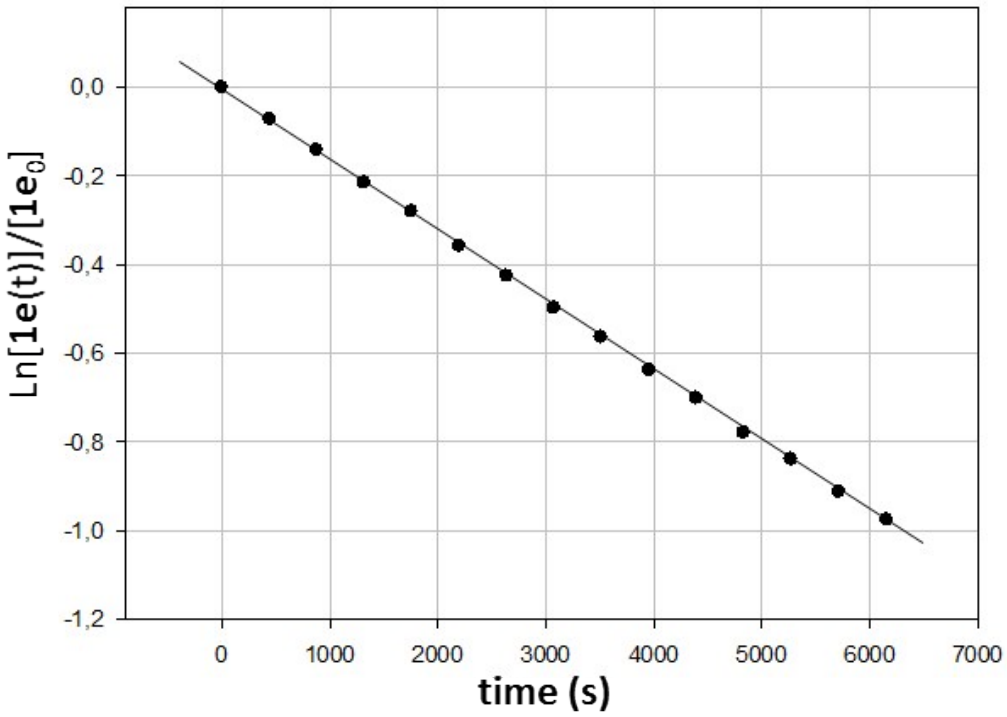




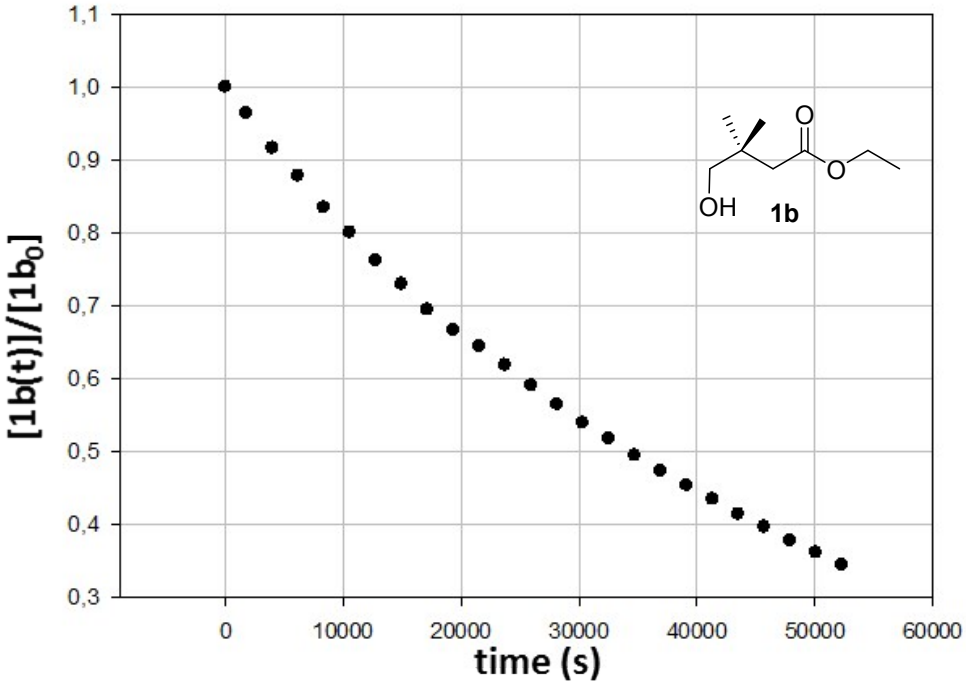
Cyclization of 1b *vs* 1e with TFA

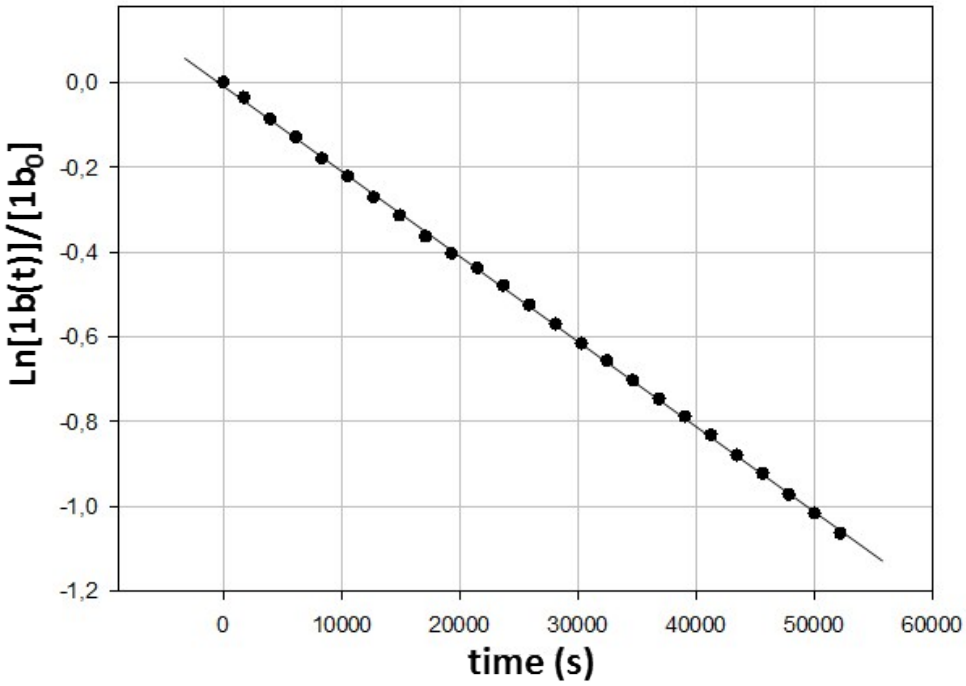
k_{obs}=(1.593±0.006)x10^{-4}, r^2= 0.9998, [TFA]= (3.17±0.10)x10^{-4} M, k_1= 5.0310^{-1} s^{-1} M^{-1}





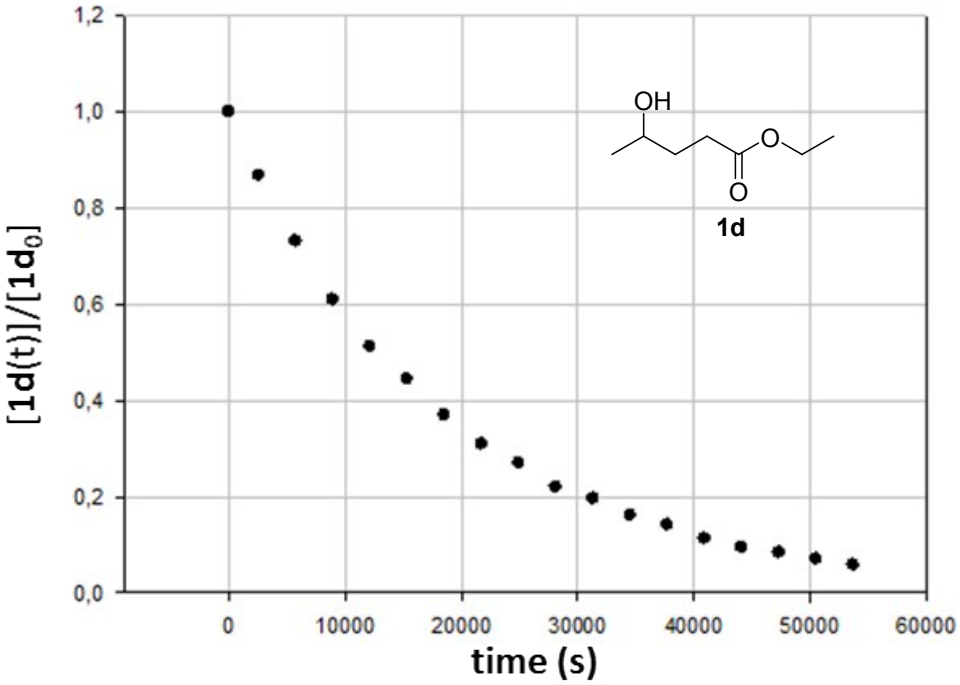
k_{obs}=(2.011±0.007)x10^{-5}, r^2= 0.9997, [TFA]= (3.17±0.10)x10^{-4}M, k_1= 6.34x10^{-2} s^{-1} M^{-1}

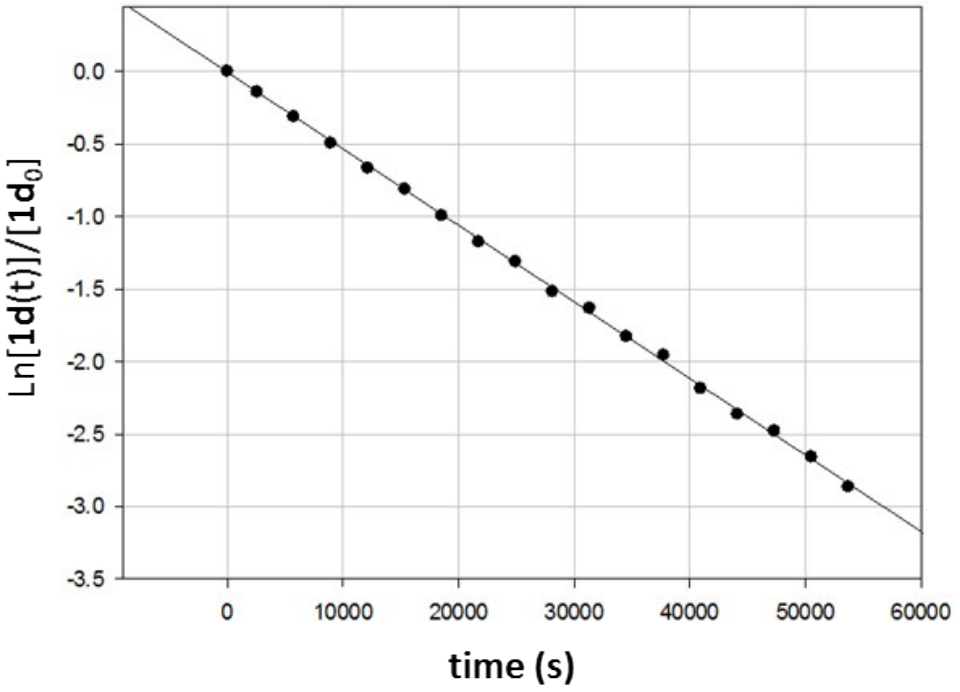




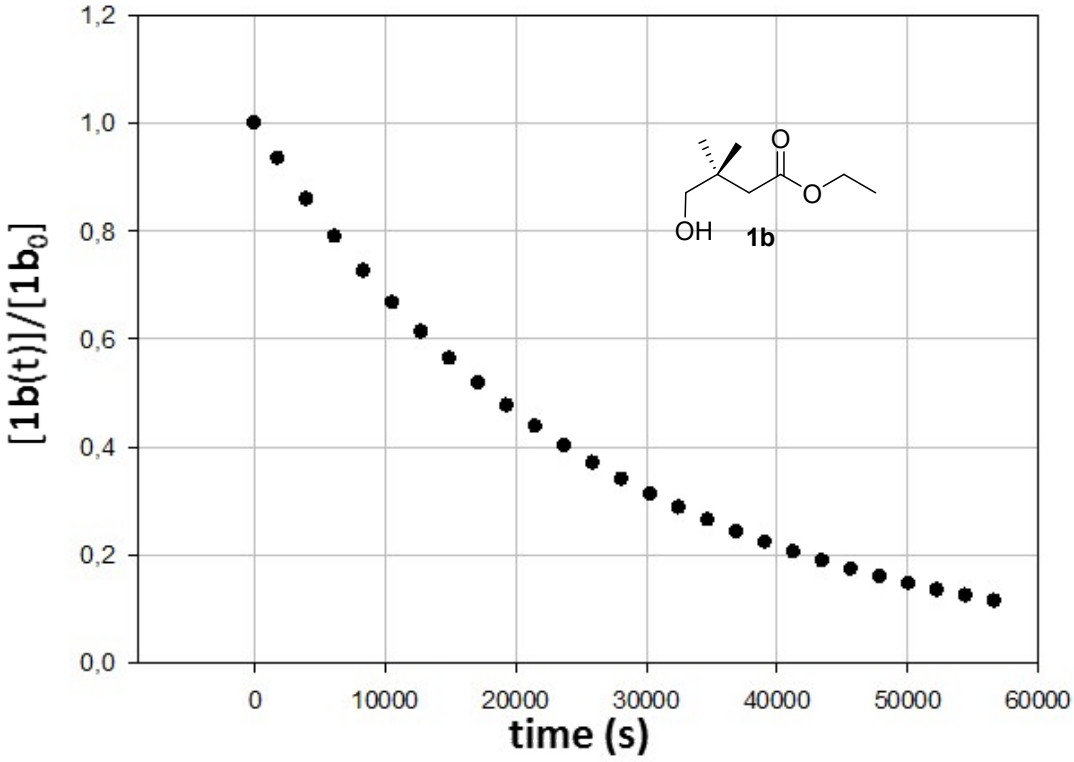
Cyclization of 1b *vs* 1d with TFA

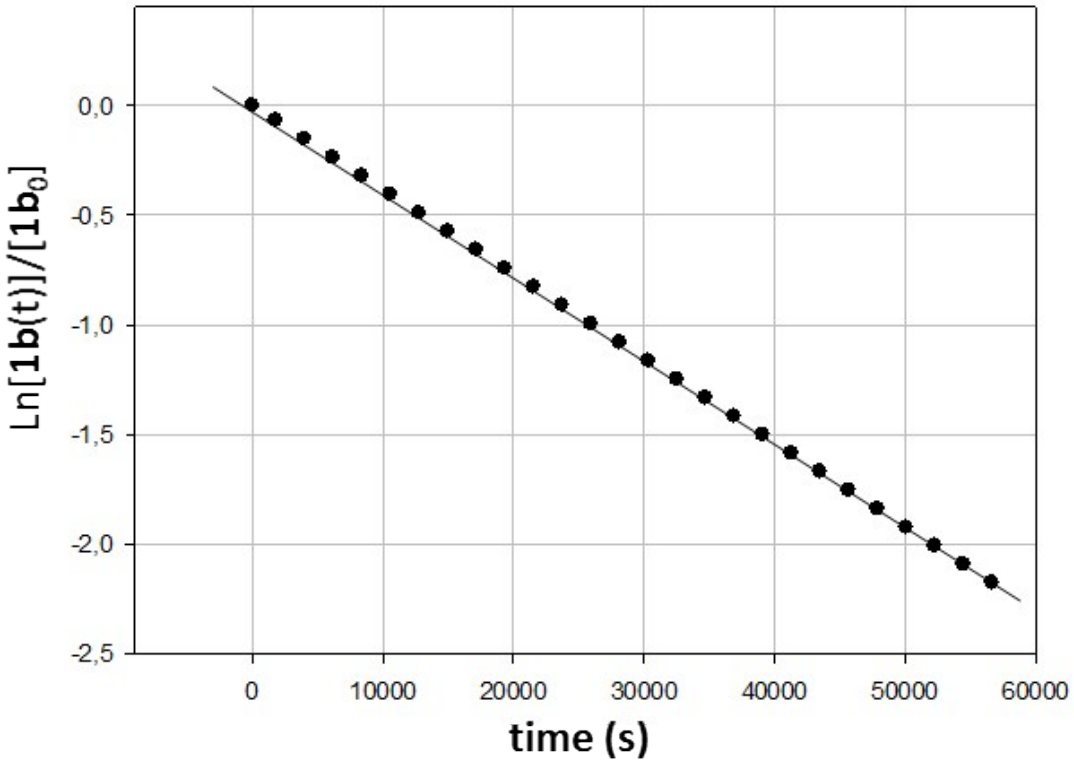
k_{obs}=(5.27±0.03)x10^{-5}, r^2= 0.999, [TFA]= (6.2±0.10)x10^{-4}M, k_1= 0.086 s^{-1} M^{-1}





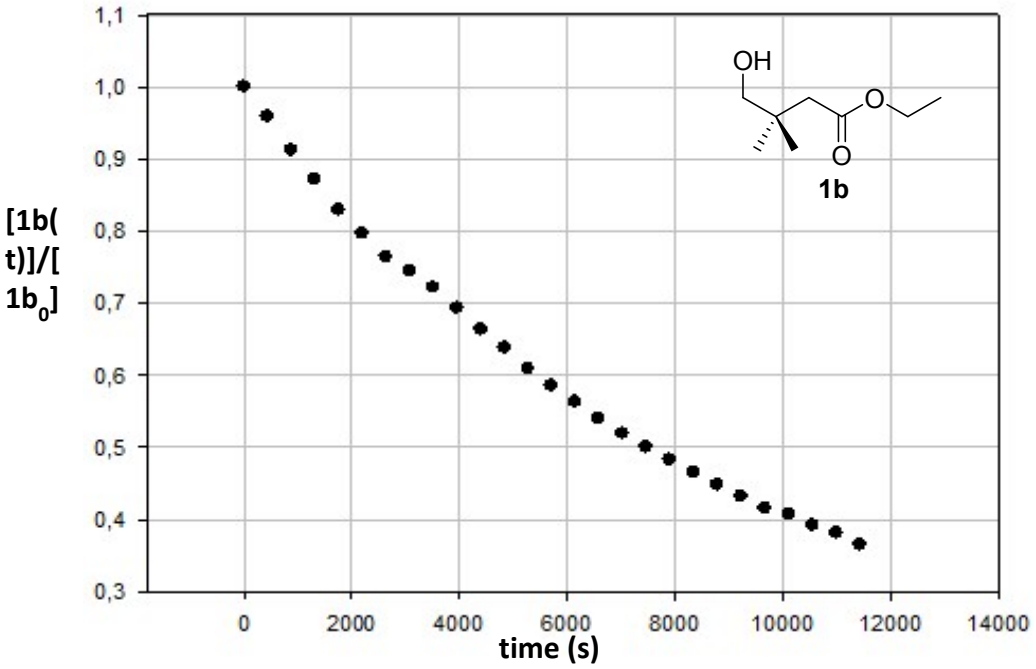
k_{obs}=(3.84±0.03)x10^{-5}, r^2= 0.999, [TFA]= (6.20±0.10)x10^{-4}M, k_1= 0.062

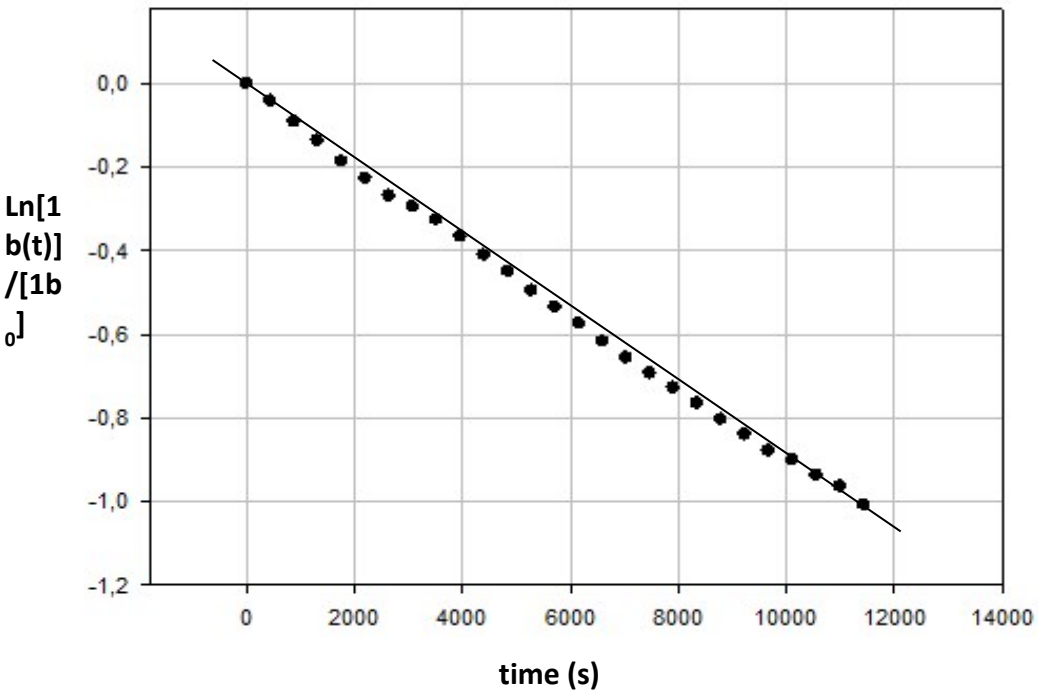




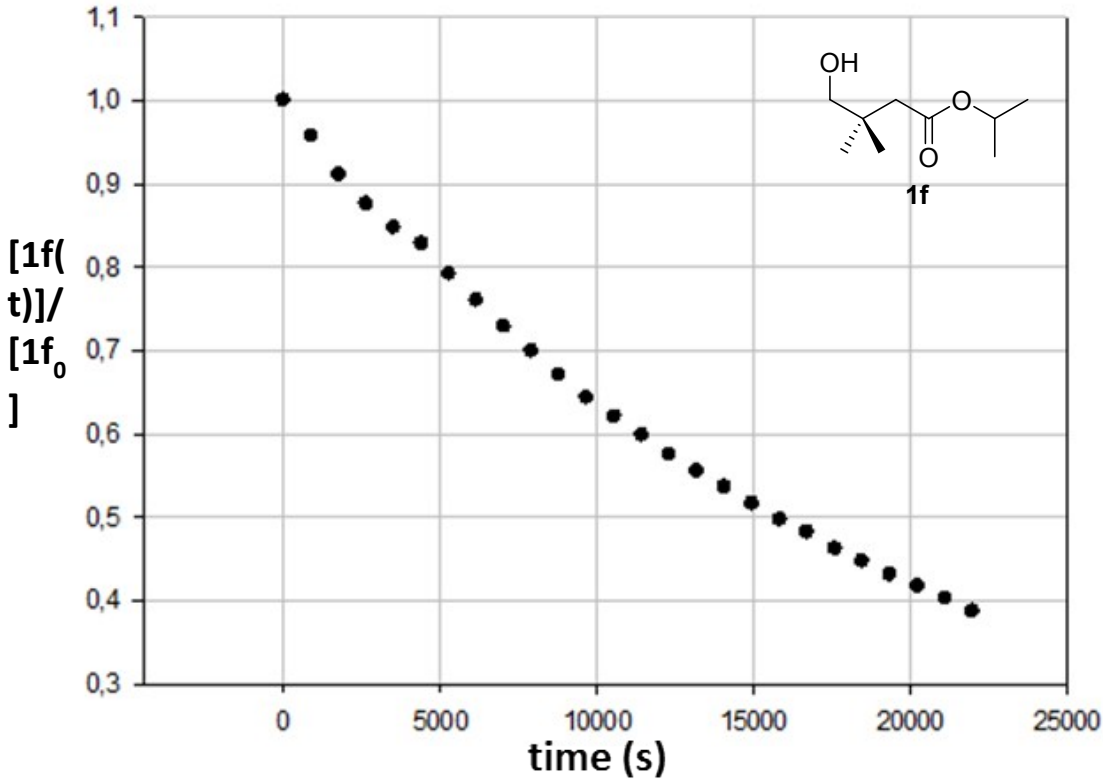
Cyclization of 1b *vs* 1f with TFA

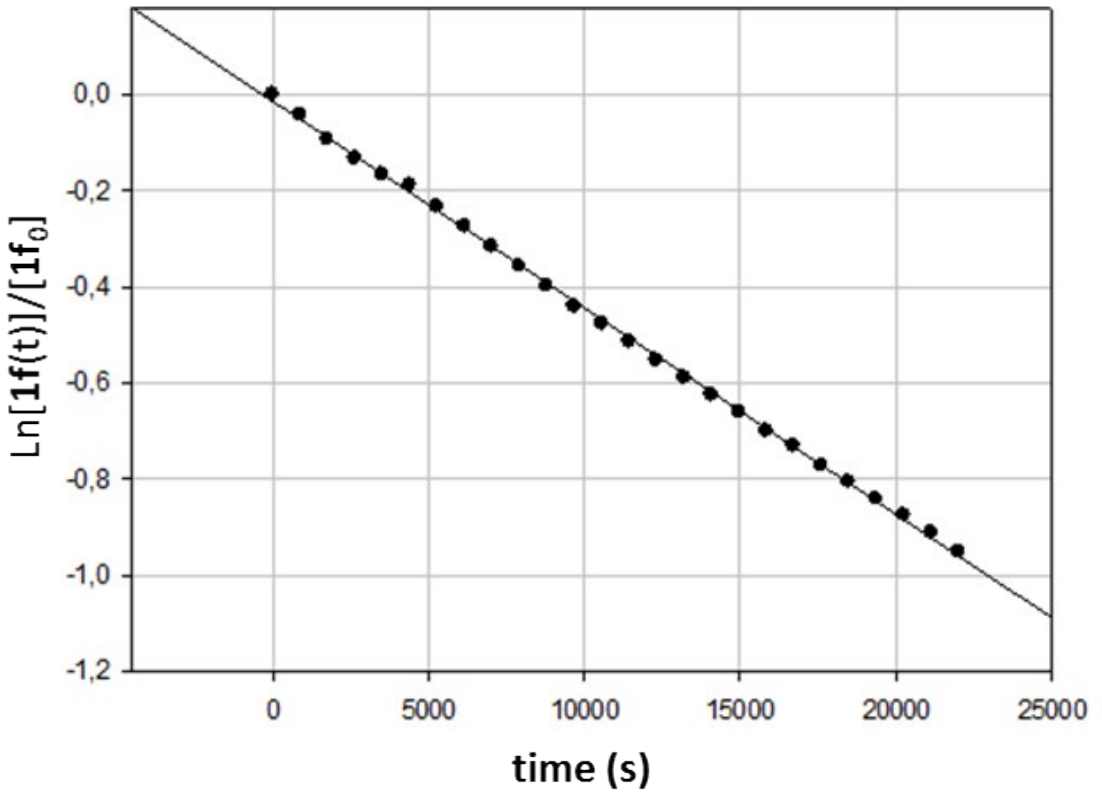
K_{obs}= (8.780±0.071)x10^{-5} s^{-1}, r^2= 0.998, [TFA]= (1.40±0.10)x10^{-3}M, k_1= 6.27x10^{-2}M s^{-1}M^{-1}





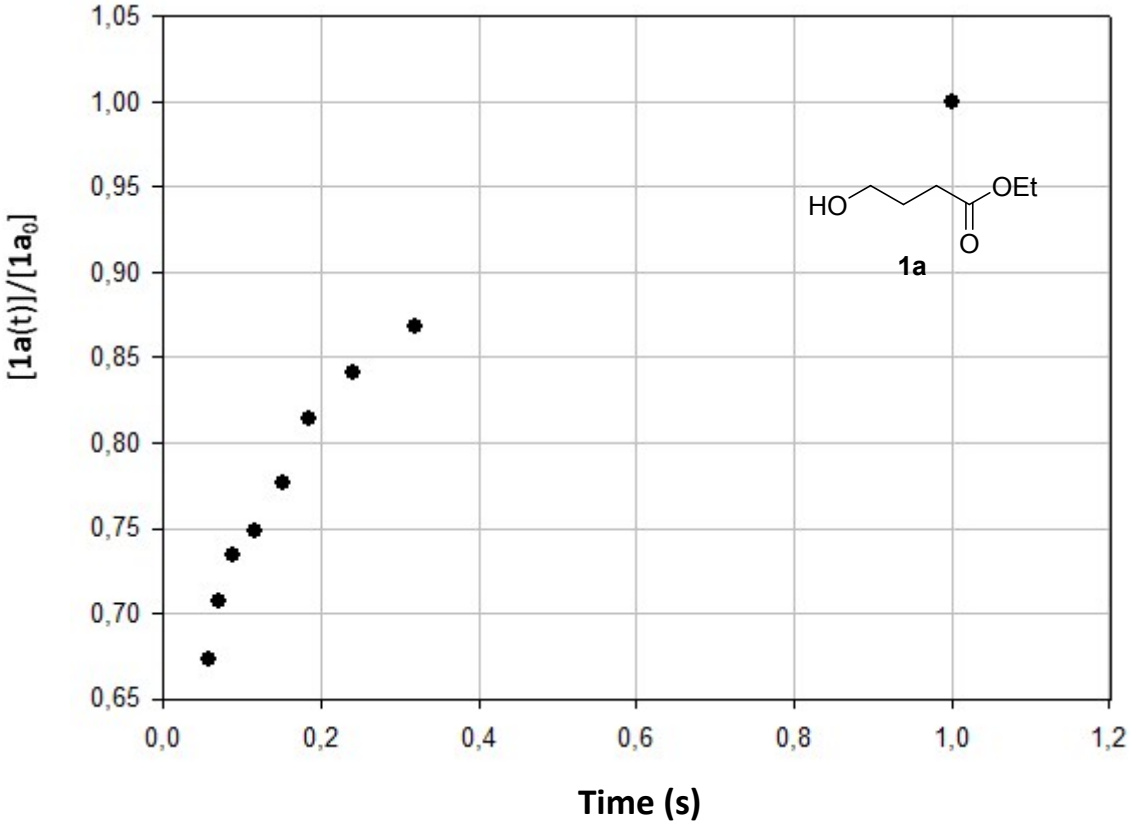
k_{obs}= (4.30±0.023)x10^{-5} s^{-1}, r^2= 0.999, , [TFA]= (1.40±0.10)x10^{-3}M, k_1= 3.07x10^{-2}M s^{-1}M^{-1}

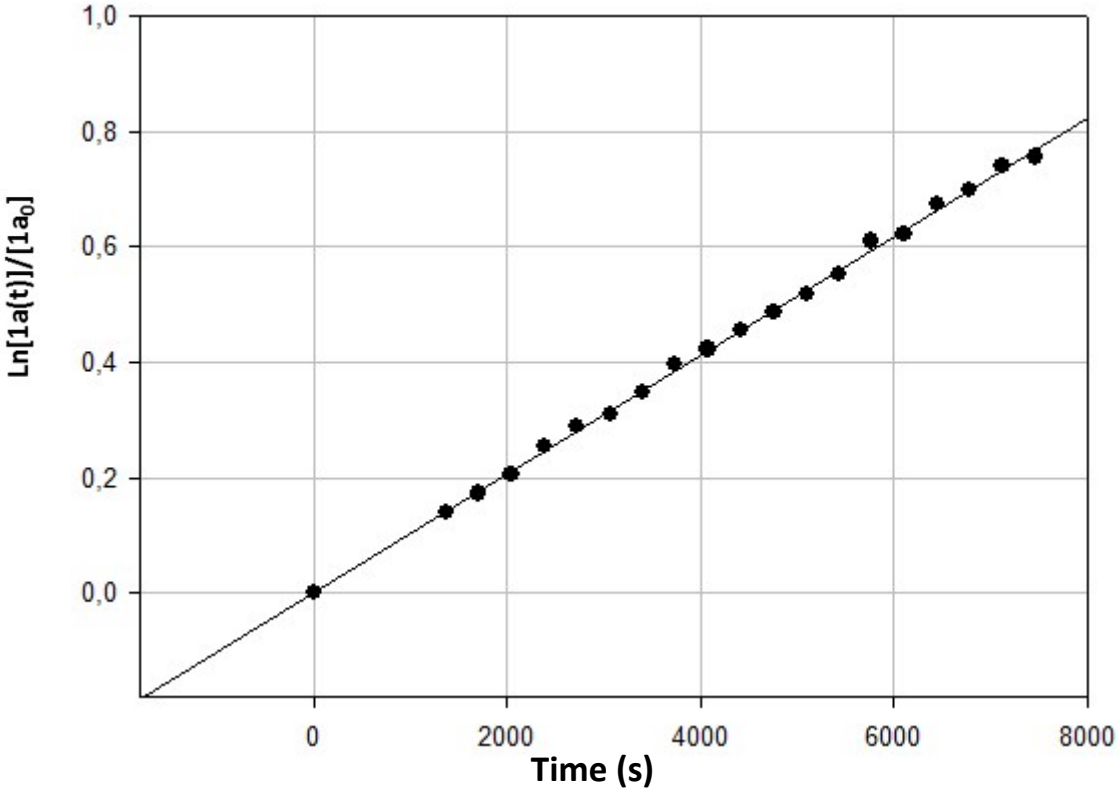




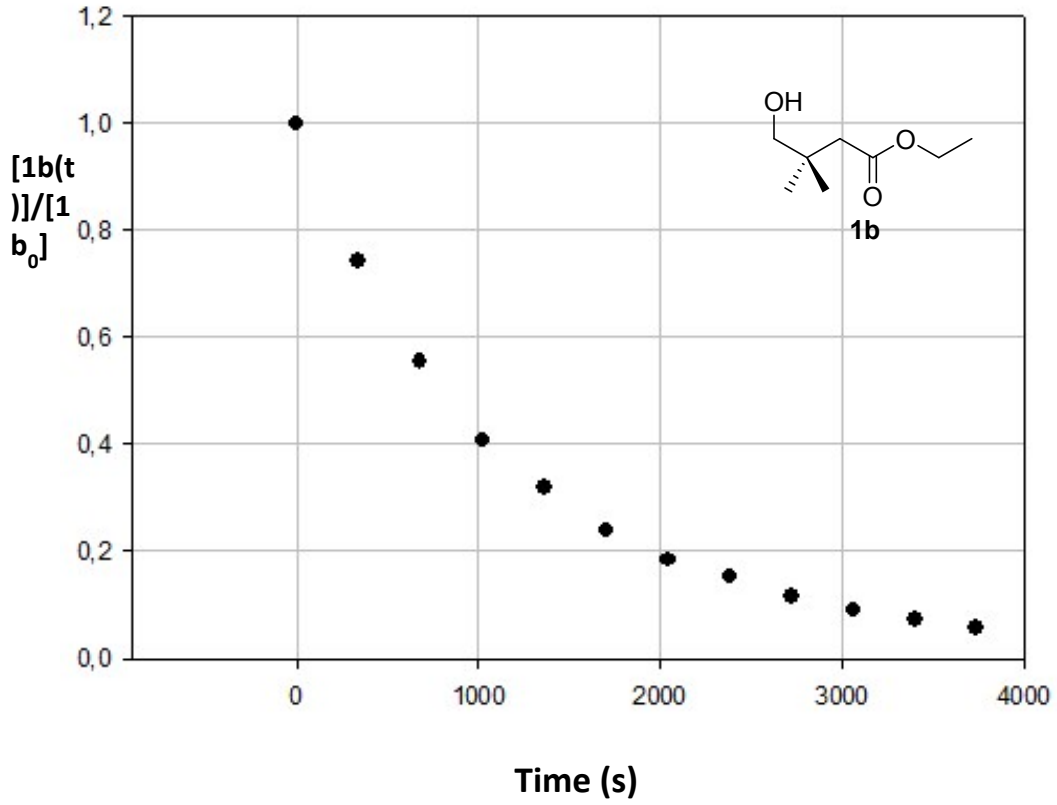
Cyclization of 1a *vs* 1b with PTSA

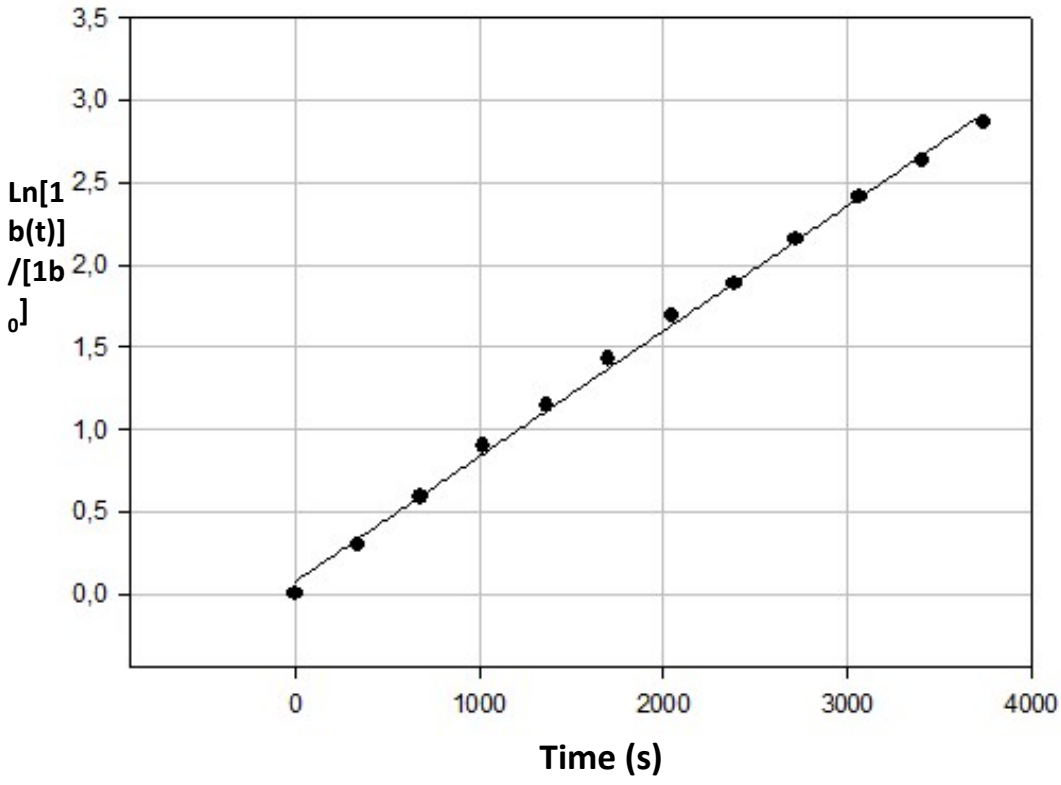
k_{obs}= (1.028±0.008)x10^{-4} s^{-1}, r^2= 0.999, [PTSA]= (2.56±0.10)x10^{-4}M,[8] k_1= 4.016x10^{-1}M s^{-1}M^{-1}





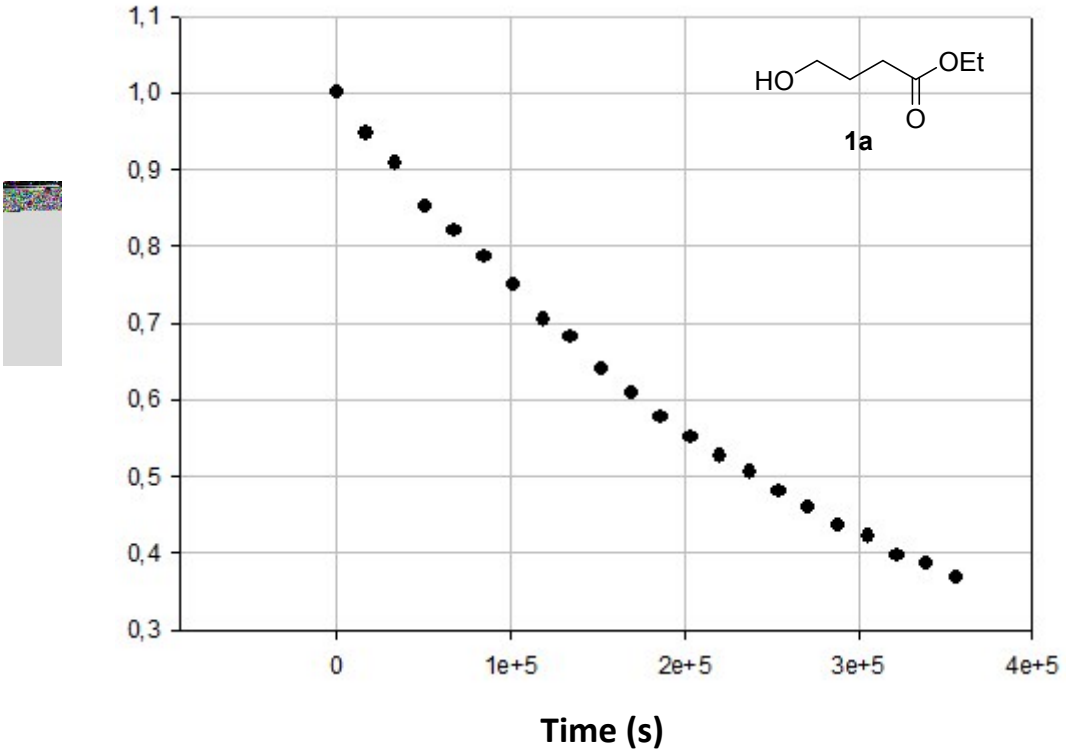
k_{obs}= (7.5±0.1)x10^{-4} s^{-1}, r^2= 0.998, [PTSA]= (2.56±0.10)x10^{-4} M, k_1= 2.93 s^{-1}M^{-1}

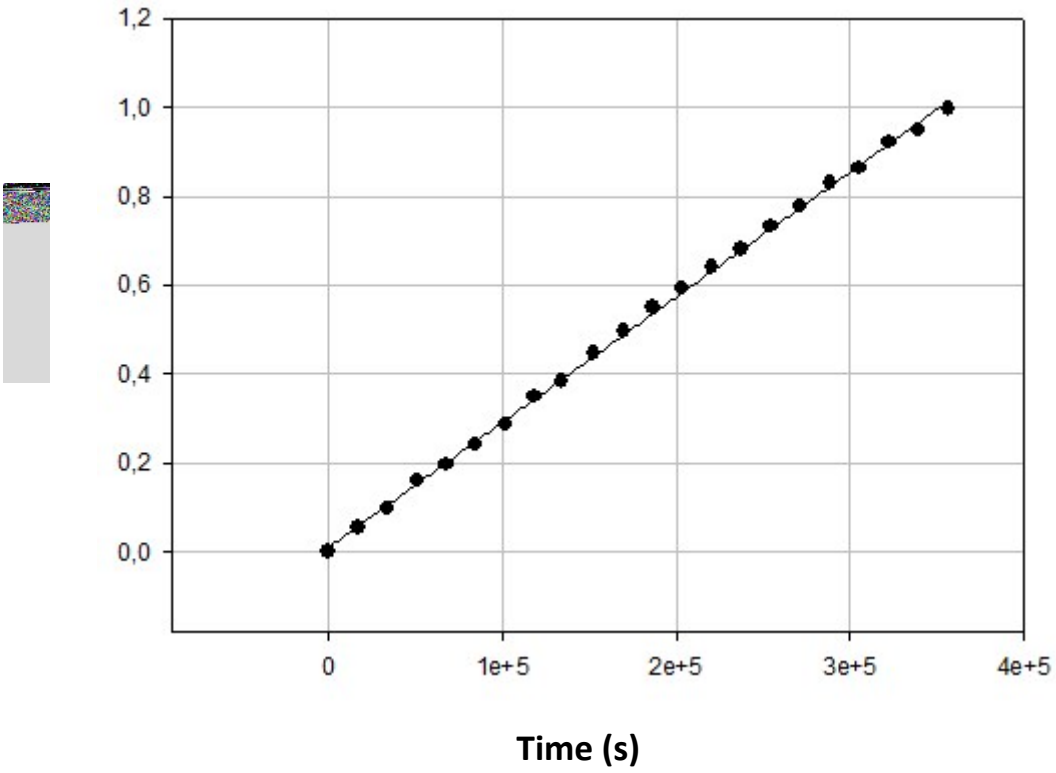




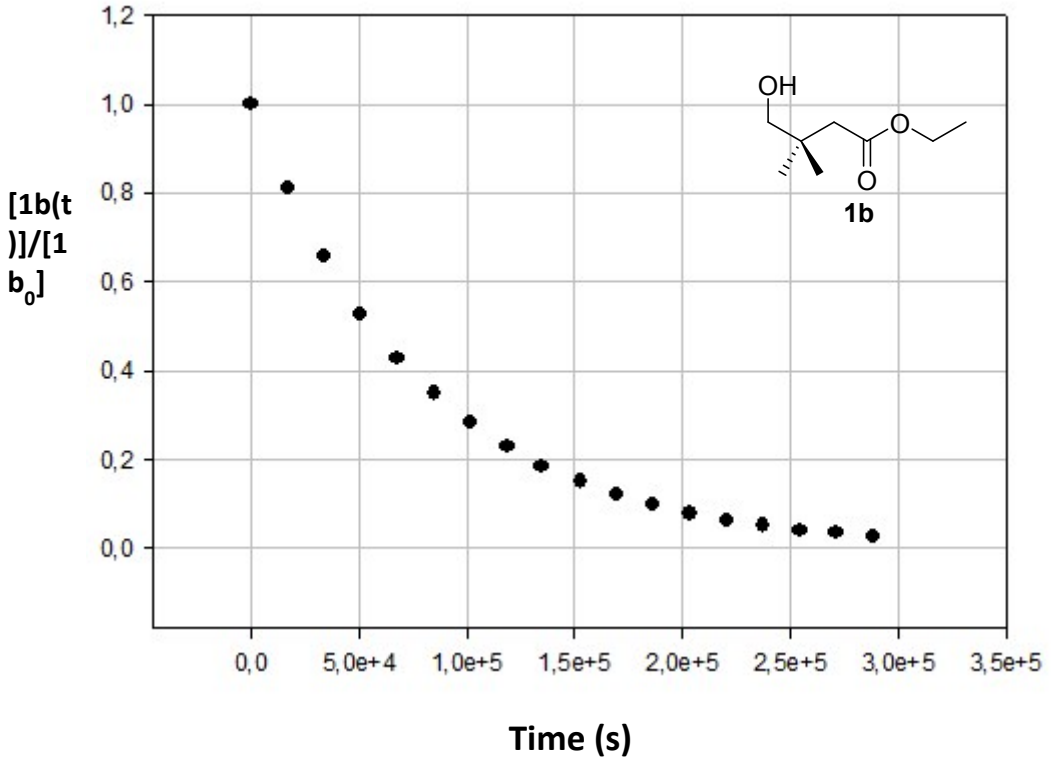
Cyclization of 1a *vs* 1b with AcOH

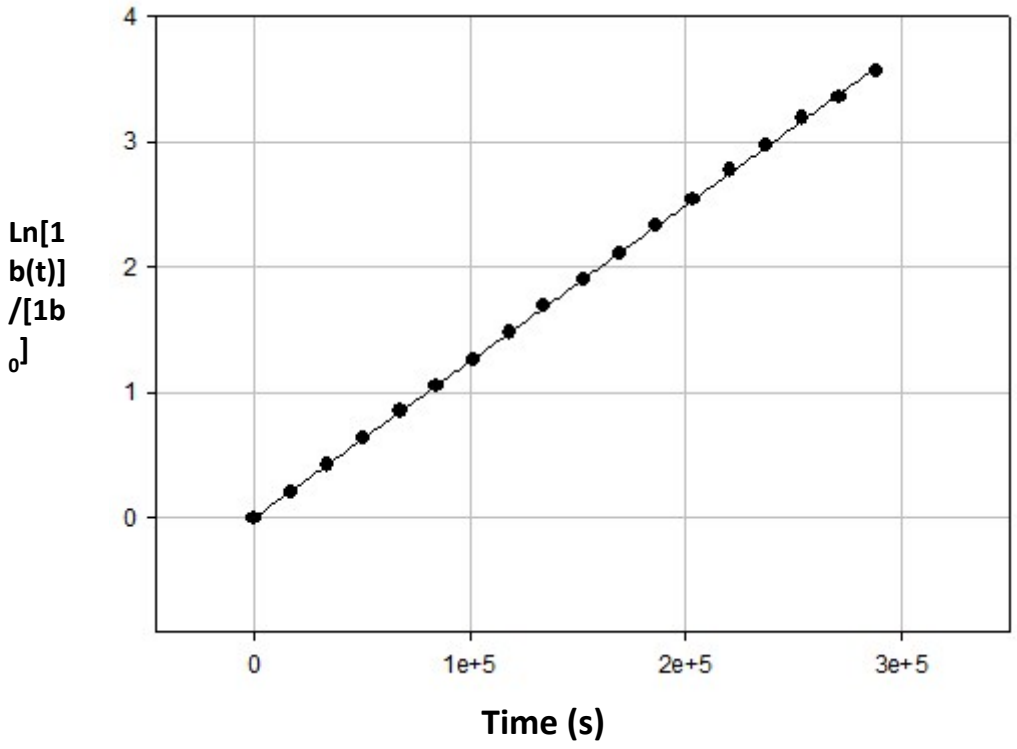
k_{obs}= (3.54±0.02)x10^{-6} s^{-1}, r^2= 0.999, [AcOH]= 2.41±0.10 M, k_1= 1.47x10^{-6} Ms^{-1}M^{-1}





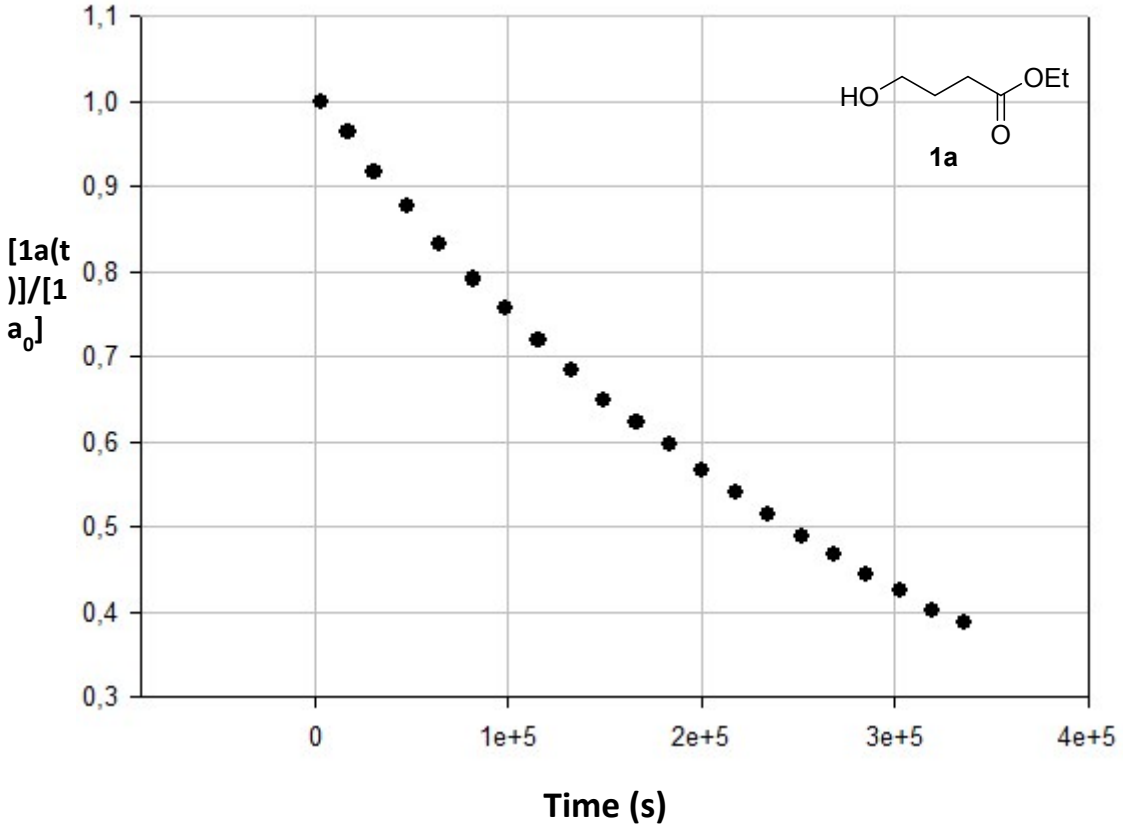
k_{obs}= (1.687±0.003)x10^{-5} s^{-1}, r^2= 0.999, [AcOH]= 2.41±0.10 M, k_1= 7.00x10^{-6} s^{-1}M^{-1}

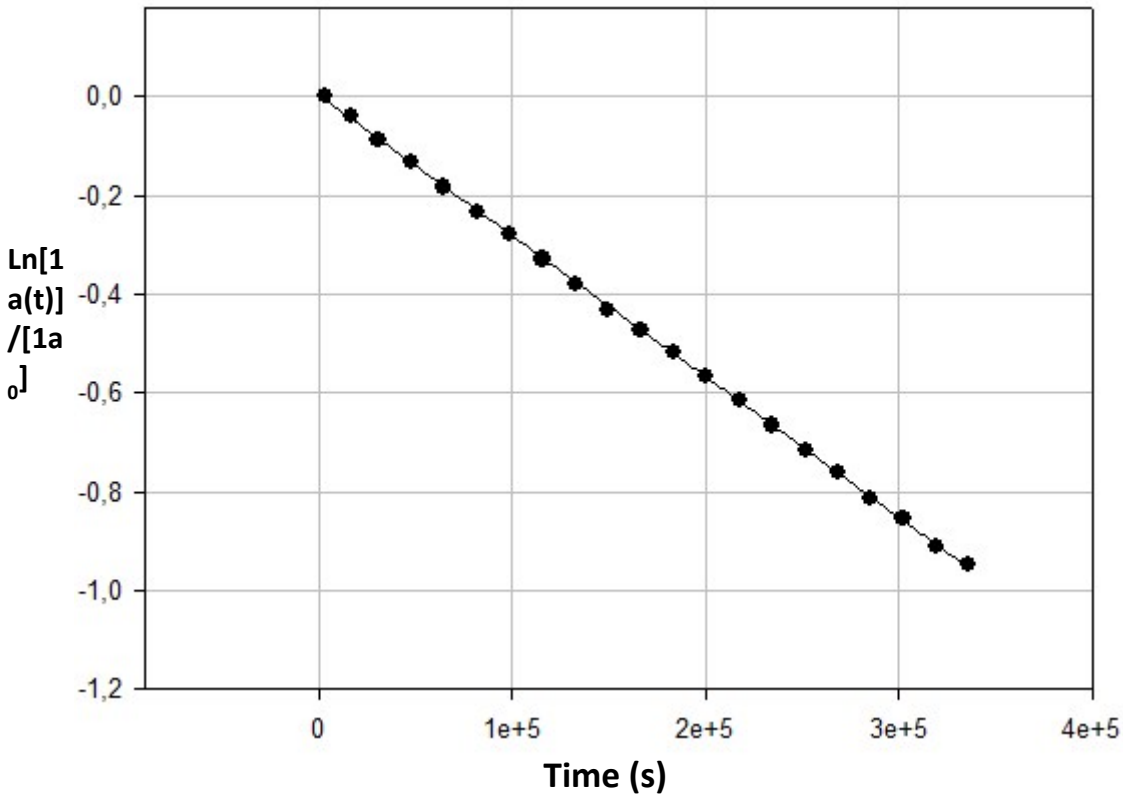




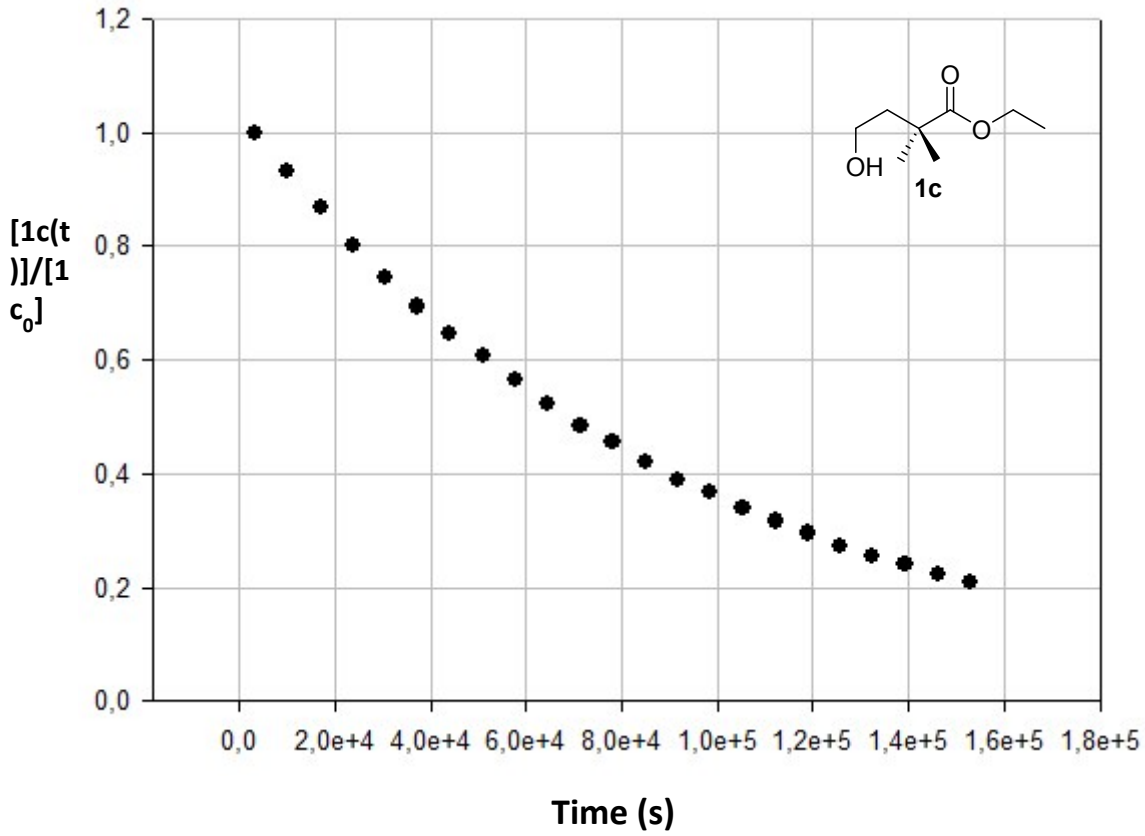
Cyclization of 1a *vs* 1c with AcOH

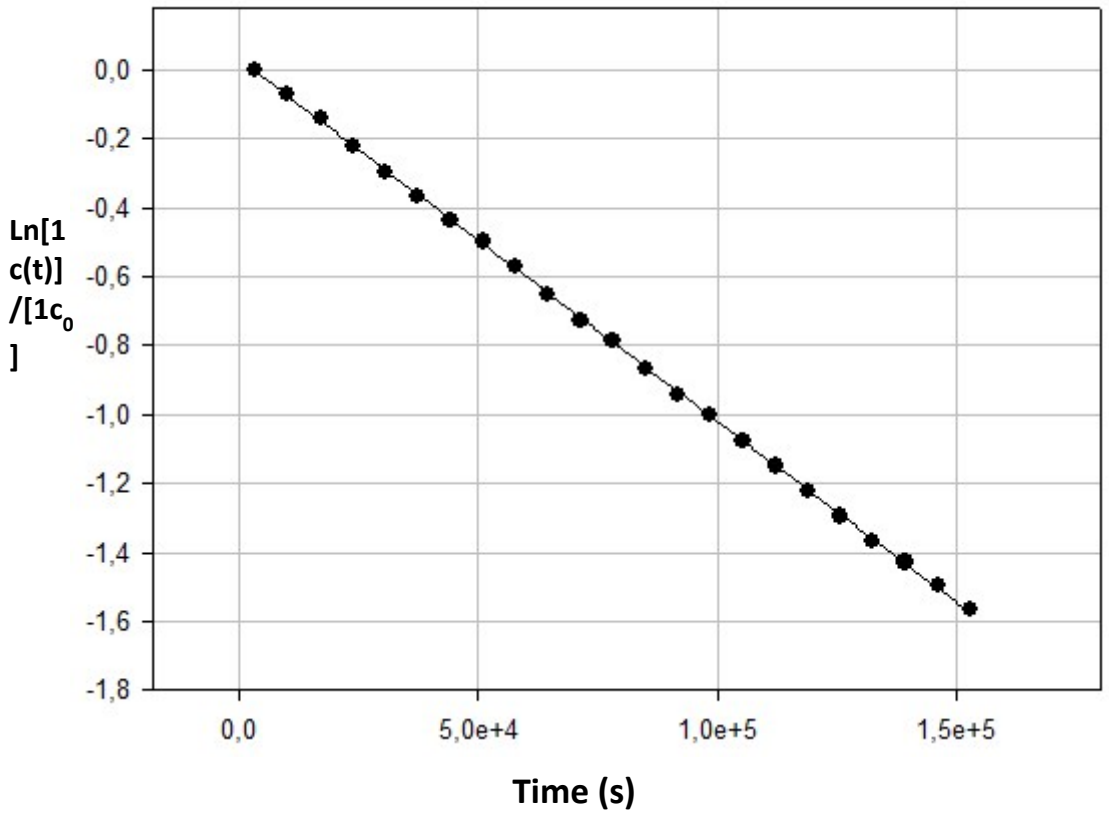
k_{obs}= (3.35±0.02)x10^{-6} s^{-1}, r^2= 0.999, [AcOH]= 1.78±0.10 M, k_1= 5.96x10^{-6} Ms^{-1}M^{-1}





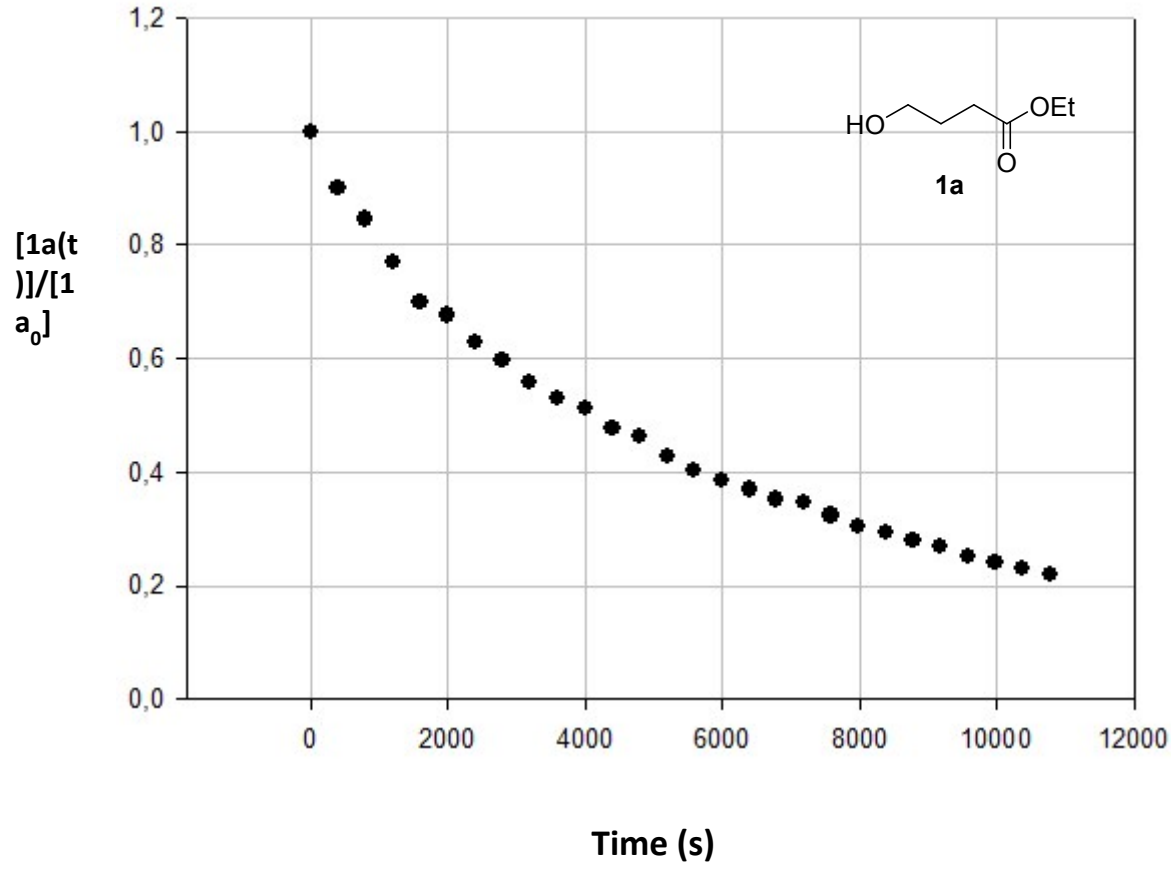
k_{obs}= (8.480±0.002)x10^{-7} s^{-1}, r^2= 0.999, [AcOH]= 1.78±0.10 M, k_1=1.51x10^{-6} Ms^{-1}M^{-1}

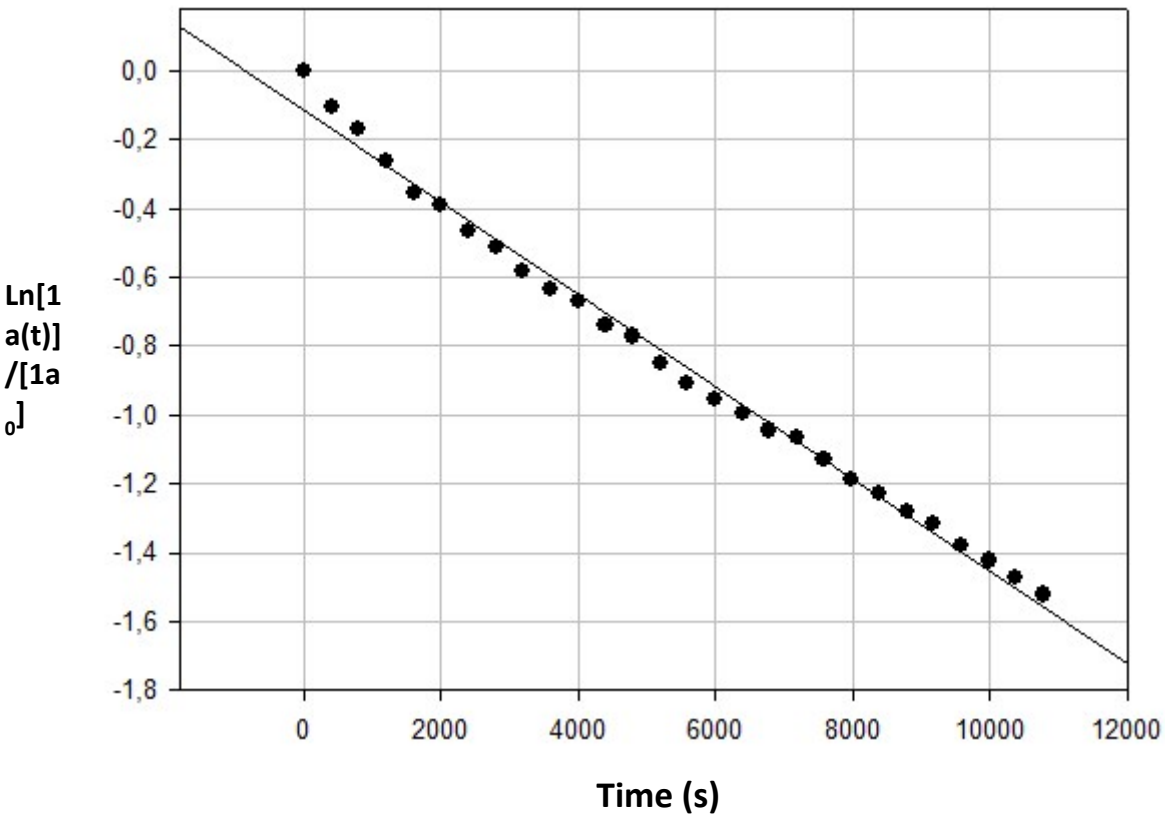




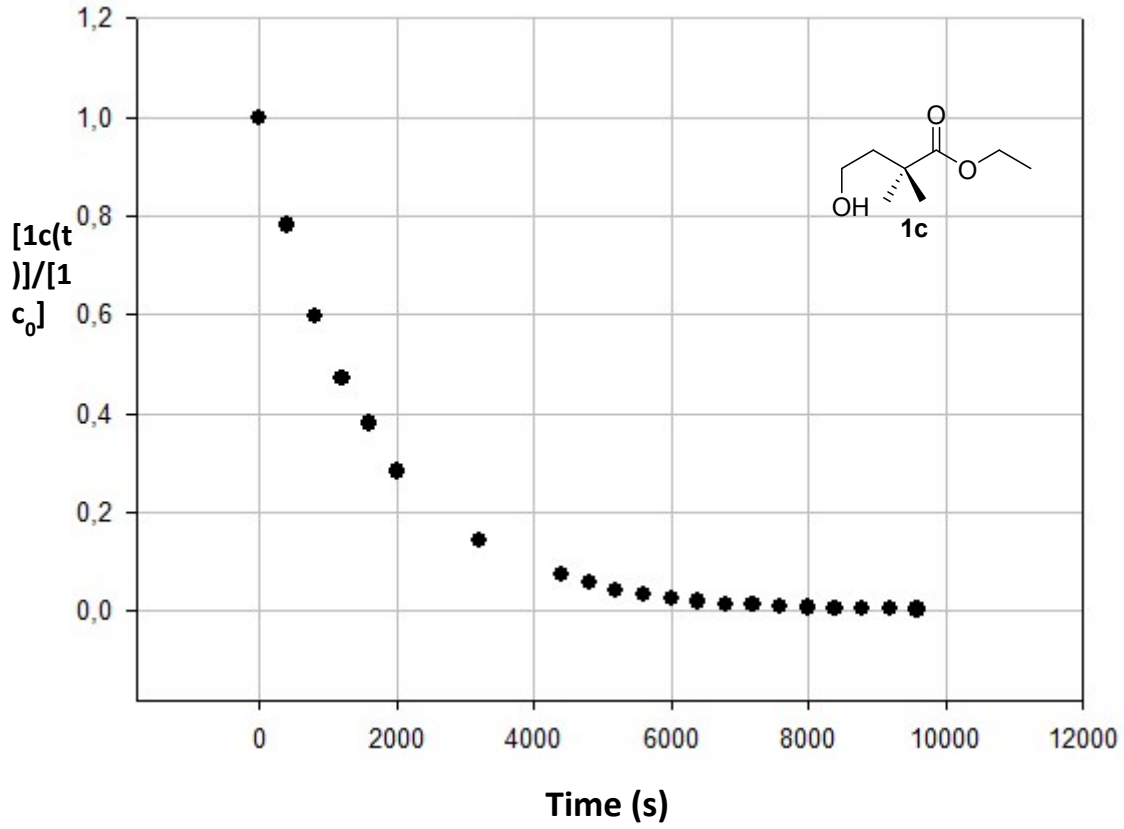
Cyclization of 1a *vs* 1c with MSA

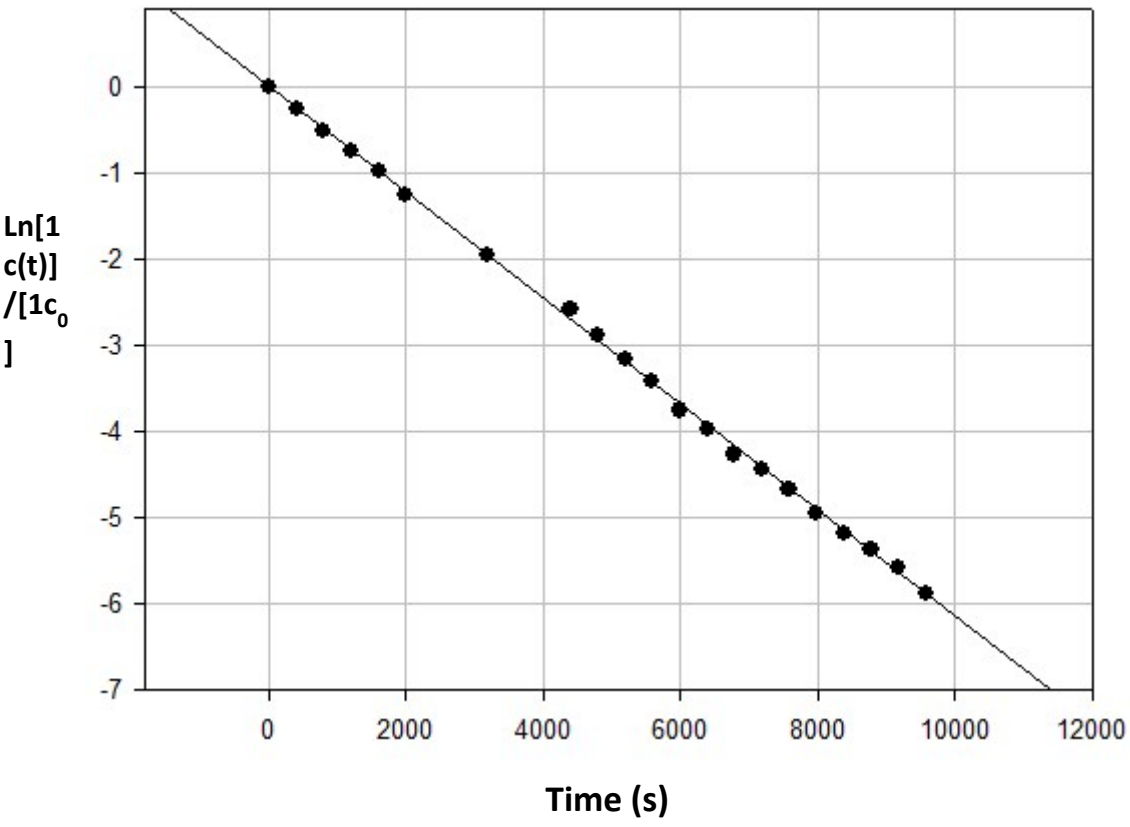
k_{obs}= (3.340±0.01)x10^{-4} s^{-1}, r^2= 0.993, [MSA]= 6.0x10^{-4}±0.10x10^{-4} M, k_1= 2.23x10^{-1} Ms^{-1}M^{-1}





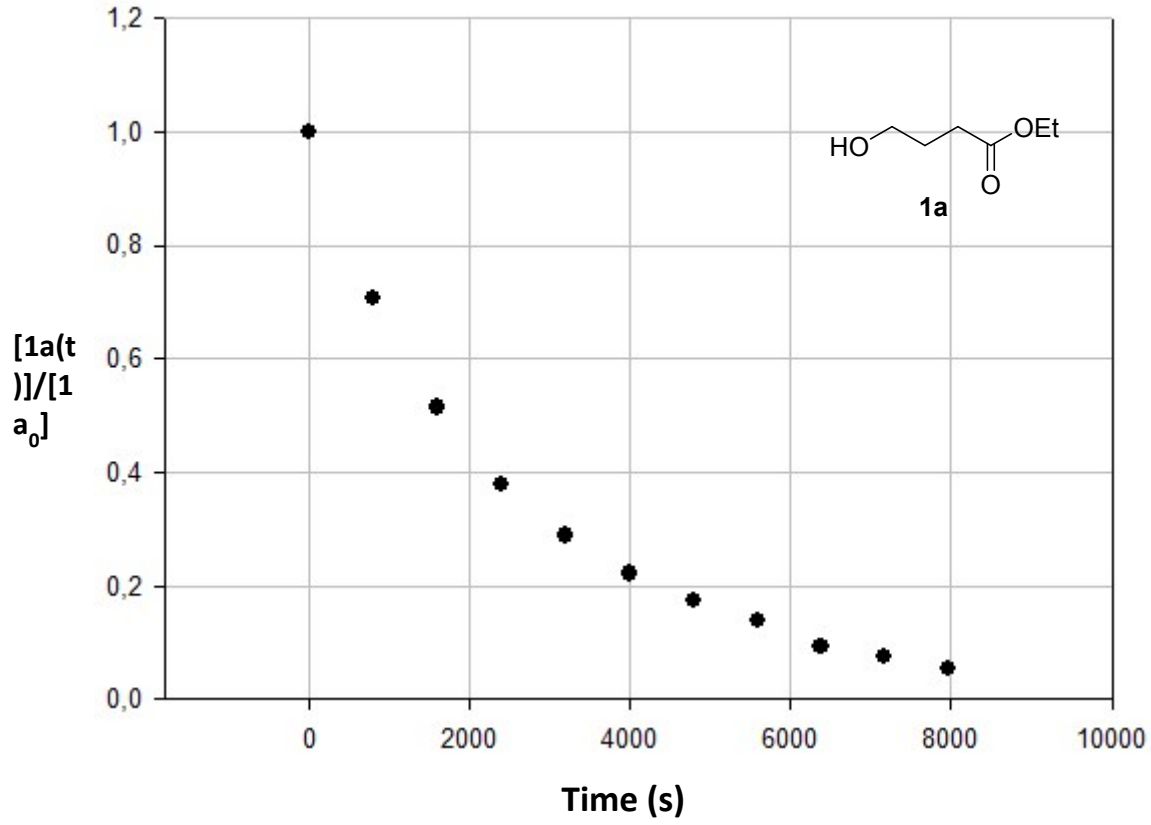
k_{obs}= (6.140±0.02)x10^{-4} s^{-1}, r^2= 0.999, [MSA]= (6.0x10^{-4}±0.10) x10^{-4} M, k_1= 9,70x10^{-1} Ms^{-1}M^{-1}

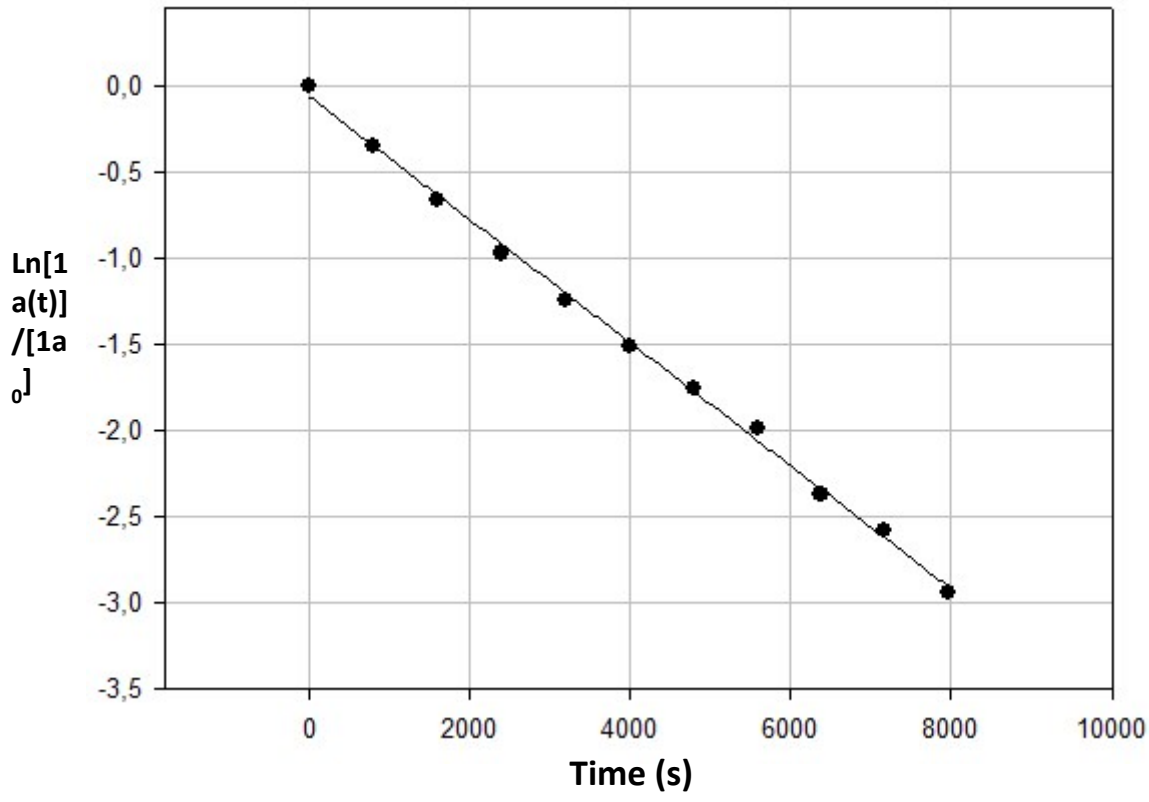




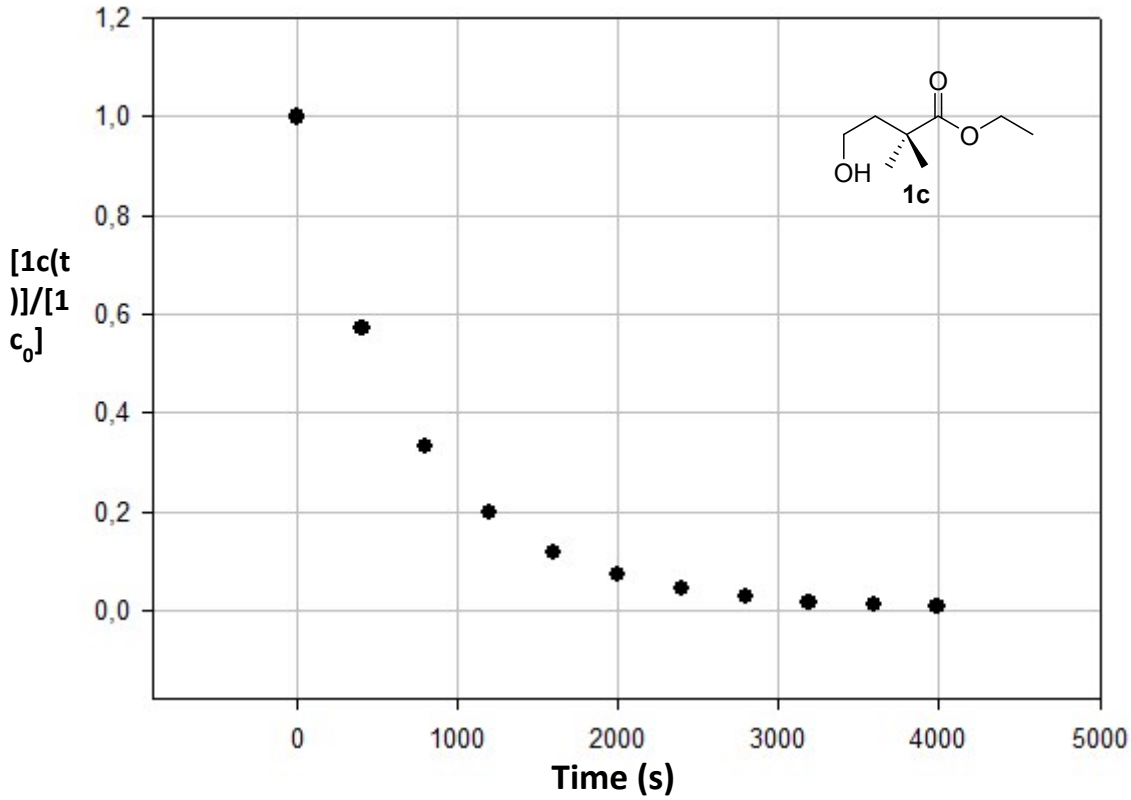
Cyclization of 1a *vs* 1c with PTSA

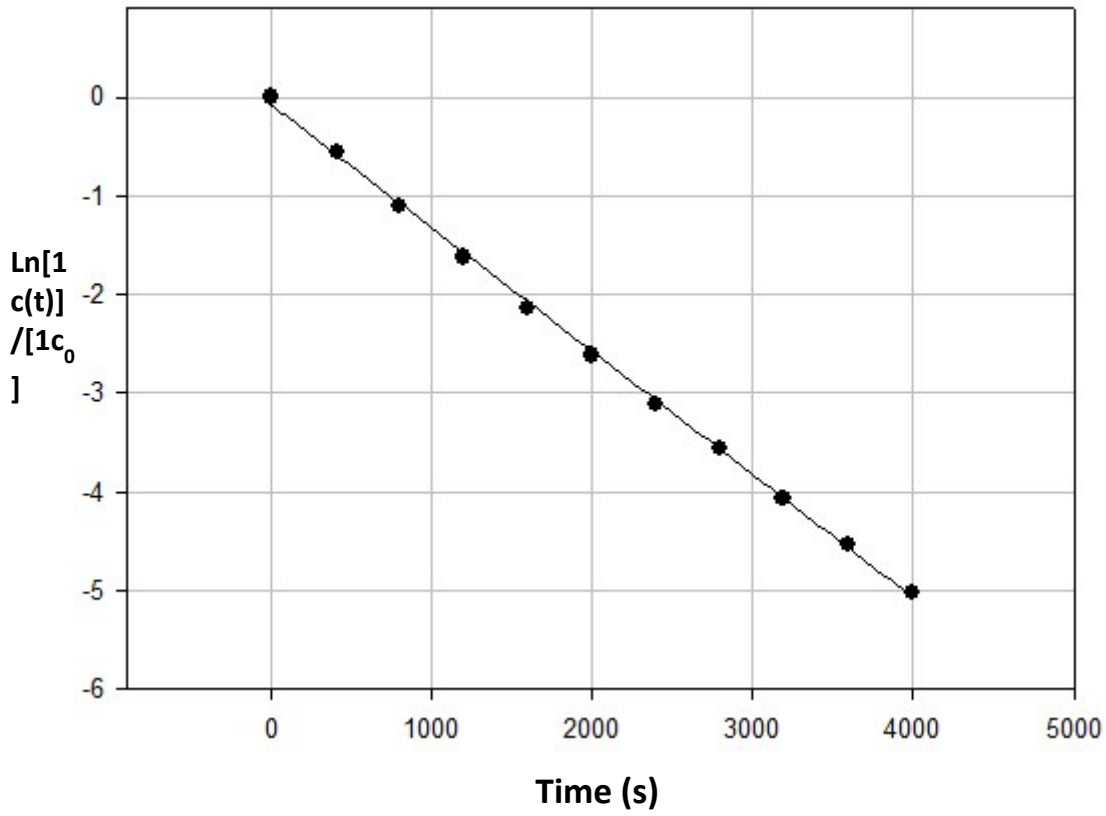
k_{obs}= (3.566±0.02)x10^{-4} s^{-1}, r^2= 0.998, [PTSA]=(8.7x10^{-4}±0.10) x10^{-4} M, k_1= 4.10x10^{-1} Ms^{-1}M^{-1}





k_{obs}= (1.248±0.03)x10^{-3} s^{-1}, r^2= 0.999, [PTSA]= (8.7x10^{-4}± 0.1)x10^{-4}M, k_1= 1.43 Ms^{-1}M^{-1}





5. References and Notes

[1] Amati, A; Dosualdo, G.; Zhao, L.; Bravo, A.; Fontana, F.; Minisci, F.; Bjorsvik, H. *Org. Process Res. Dev.* **1998**, *2*, 261 – 269.
[2] Sund, C.; Belda, O.; Borkakoti, N.; Lindberg, J.; Derbyshire, D.; Vrang, L.; Hamelink, E.; Hgren, C.; Woestenenk, E.; Wikstroem, K.; Eneroth, A.; Lindstroem, E.; Kalayanov, G. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6721 – 6727.
[3] Tiecco, M.; Tingoli, M.; Testaferri, L.; Bartoli, D. *Synt. Commun.* **1989**, *19*, 2817 – 2824.
[4] Brown, H. C.; Keblys, A., K. *J. Org. Chem.*, **1966**, *31*, 485.
[5] The hydroxyesters can be stored at -20°C for several months, in presence of a small amount of NEt_3, otherwise at rt are prone to undergo to spontaneous cyclization.
[6] The purity of hydroxyesters cannot be detected by GC-MS, because the esters close partially into the GC-injector.
[7] The standard deviation Δk_r was calculated as following

$$\Delta k_r = k_r \sqrt{\frac{(\Delta k_{obs,1a})^2}{(k_{obs,1a})^2} + \frac{(\Delta k_{obs,1i})^2}{(k_{obs,1i})^2}}$$

[8] For solubility reasons, the acid was dissolved in a mixed solvent system of $CHCl_3$/MeOH, 99:1.