Exploiting the vicinal disubstituent effect in the diastereoselective synthesis of γ and δ lactones

Elisabetta Brenna,[a] Francesco Dalla Santa,[a] Francesco G. Gatti,[*,a] Giuseppe Gatti[b] and Davide Tessaro[a]

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

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

SUPPORTING INFORMATION

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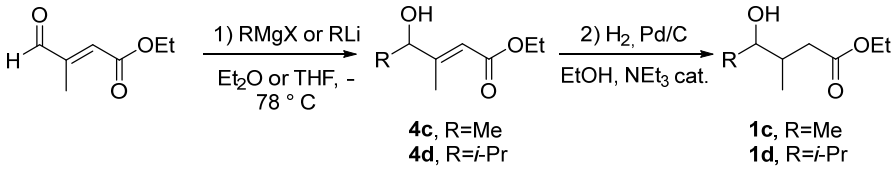
General remarks

^{1}H and ^{13}C NMR spectra were recorded on a 400 or 500 MHz spectrometers in $CDCl_3$ solutions at room temperature. The residual $CHCl_3$ or TMS were used as internal reference for ^{1}H or ^{13}C. High-resolution MS spectra were recorded with a Q-TOF mass spectrometer, equipped with an EI source. Chemical shifts are expressed in ppm and *J* values in Hz. GC–MS analyses were performed on a gas-chromatograph equipped with an HP-5973 mass detector and a 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 pre-coated silica gel 60 F254 plates, and column chromatographic separations were carried out on silica gel. The reagents were used without further purification, while where required, the solvents were dried over molecular sieves (4 Å).

Synthesis of γ-hydroxyesters 1c-d

The hydroxyesters **1c-d** were prepared by a two steps sequence according to the following scheme: *i*) addition of an organometallic reagent (MeLi or *i*-PrMgI) to the commercially available ethyl 4-oxo-3-methylcrotonate to give the corresponding allylic alcohol;[1] *ii*) catalytic hydrogenation of the C=C double bond.



General procedure for the organometallic addition

To a solution of the commercially available ethyl formylcrotonate (10 mmol) in anhydrous Et_2O (40 mL) at -78° C under a N_2 atmosphere, an organometallic solution (12 mmol) was dropwisely added. For the synthesis of **4c** was used a solution of the commercially available MeLi (1.6 M in THF), whereas for ethyl **4d**, *i*-PrMgBr was freshly prepared in Et_2O adopting a standard procedure.[1] After 2 hours, the reaction was quenched with a solution of NH_4Cl (sat., 50 mL). The reaction mixture was left to reach rt and washed with Et_2O (2 x 20 mL). The combined organic layers were washed with brine (sat., 30 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude material was submitted to column chromatography (Hexane/AcOEt, 8:2) affording the intermediate allylic alcohol as colourless liquid.

***Ethyl (E)-4-hydroxy-3-methylpent-2-enoate* (4c).** Yield = 54% (0.85 g); t_r=11.96 min 95% purity by GC; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.96 (m, *J* = 1.3, 1H), 4.27 (m, 1H), 4.17 (q, *J* = 7.1, 2H), 2.13 (t, *J* = 1.3, 3H), 1.67 (bd, 1H), 1.32 (d, *J* = 6.5, 3H), 1.28 (t, *J* = 7.1, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 166.94, 161.08, 114.10, 72.42, 59.75, 21.75, 14.89, 14.28; GC-MS: *m/z* (%) 158 (M^+, 2), 140 (M^+-18, 21), 129 (M^+-29, 5), 115 (M^+,100).[2]

***Ethyl (E)-4-hydroxy-3,5-dimethylhex-2-enoate* (4d).** Yield = 45% (0.84 g); t_r=14.73 min (*E*) 93% purity by GC; *E*/Z 88:12 by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.88 (m, *J* = 1.3, 1H), 4.17 (q, *J* = 7.1, 2H), 3.80 (d, *J*= 6.1, 1H), 2.11 (t, *J* = 1.3, 3H), 1.89 (m, 1H), 1.29 (t, *J* = 7.1, 3H), 1.28 (t, *J* = 7.1, 3H), 0.93-0.90 (m, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 166.71, 159.26, 116.20, 81.89, 59.72, 30.99, 19.60, 16.77, 14.78, 14.26; GC-MS: *m/z* (%) 186 (M^+, 2), 168 (3), 143 (M-43, 100), 125 (10); HRMS (ESI) calcd for $C_{10}H_{17}O_3^-$ $[M - H]^-$ 185.1183, found 185.1176.

General procedure for the hydrogenation of the allylic alcohols

To a solution of allylic alcohol (5 mmol) in EtOH (20 mL) and NEt_3 (10 mL) was added Pd/C (100 mg, 5 wt. %) and left to vigorous stirring under a H_2 atmosphere. After complete absorption of H_2 (around 110 mL) the reaction mixture was filtered on a Celite pad. The pad was washed with Et_2O (2x30 mL) and the solvent was removed under *vacuum* at 30 °C, affording a diastereomeric mixture of *syn* and *anti* hydroxyester as a slightly yellow liquid of sufficient purity for the kinetic study and the resolution. A small amount of pyridine or triethylamine was added to the NMR samples to neutralize the residual acidity of $CDCl_3$, which might catalyse the lactonization of hydroxyesters.

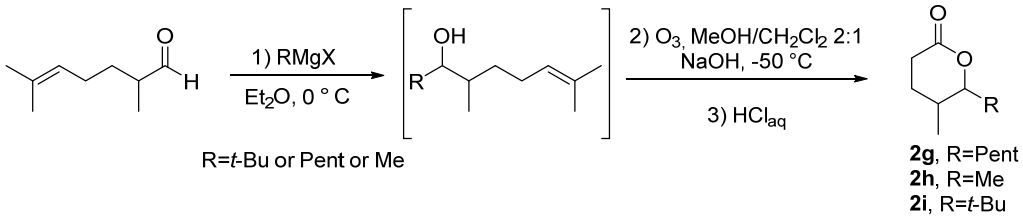
***Ethyl-4-hydroxy-3-methylpentanoate* (*syn*-1c + *anti*-1c).** Yield= 95% (0.76 g); 93% purity by ^{1}H-NMR; *syn*-**1c**/*anti*-**1c,** 56:44 by ^{1}H-NMR; GC (t_r *anti* =10.12 min and t_r *syn* = 10.32 min); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.14 (t, *J* = 7.1, 2H), 3.80 (m, 1H x 0.56), 3.60 (m, 1H x 0.44), 2.55-2.45 (m, 1H), 2.25-2.15 (m, 1H), 2.10-1.93 (m, 1H), 1.83-1.60 (bm, 1H), 1.26 (t,

J =.7.1, 3H), 1.19 (d, *J* = 6.3, *anti*-C*H*$_3$ 3H x 0.44), 1.15 (d, *J* = 6.3, *syn*-C*H*$_3$ 3H x 0.56); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.78, 173.67, 71.60, 70.43, 60.40, 60.37, 37.97, 37.76, 37.74, 36.68, 20.80, 19.57, 16.34, 14.38, 14.23; GC-MS: *m/z* (%) 145 (M^+-15, 15), 116 (100), 101 (52), 97 (23).[2]

***Ethyl-4-hydroxy-3,5-dimethylhexanoate* (*syn*-1d + *anti*-1d).** Yield= 95% (0.89 g); 94% purity by ^{1}H-NMR;[3] *syn*-**1d**/*anti*-**1d** 55:45 by ^{1}H-NMR; GC (t_r *anti* =11.80 min and t_r *syn* = 11.89 min; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.13 (t, *J* = 7.1, 2H), 3.11 (bm, 1H) 2.58 (dd, *J* = 15.0 and 4.8, *syn*-C*H*CO, 0.55H), 2.43 (dd, *J* = 15.0 and 4.8, *anti*-C*H*CO, 0.45H), 2.30-2.05 (m, 2H), 190-1.63 (m, 2H), 1.26 (t, *J*=7.1, 3H), 1.05-0.85 (m, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 174.20, 173.45, 80.31, 79.37, 60.22, 39.47, 37.65, 33.49, 32.44, 31.19, 30.08, 19.95, 19.14, 19.41, 17.16, 15.70, 14.16, 12.53; GC-MS: *m/z* (%) 170 (M^+-18, 2), 145 (M^+-43, 10), 116 (20), 99 (100); HRMS (ESI) calcd for $C_{10}H_{19}O_3^-$ [M – H]$^-$187.1340, found 187.1329.

Synthesis of *Aerangis* L. 2g and lactones 2h-i

The lactones **2g-2i** were prepared by modifying the Marshall's ozonolysis esterification[4]/lactonization[5] protocol in a multi steps sequence according to the following scheme: *i*) addition of Grignard reagent (PentMgBr, MeMgI or *t*-BuCl) to the cheap commercially available melonal to give the corresponding alcohol, which was submitted to next step without purification; *ii*) ozonolysis in presence of a NaOH solution in methanol followed by acid catalysed ring closure.



General procedure for the preparation of δ-lactones from 2,6-dimethylhept-5-enal (Melonal)

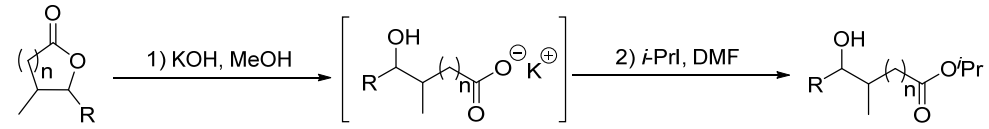
To an ice cooled suspension of a freshly prepared Grignard (0.23 mol) in Et_2O (100 mL) was slowly added a solution of 2,6-dimethylhept-5-enal (28.0, 0.2 mol) in Et_2O (75 mL) under a N_2 atmosphere. After complete consumption of 2,6-dimethylhept-5-enal, checked by TLC (*n*-hexane/AcOt, 9:1), the reaction mixture was quenched with a solution of HCl (80 mL, 1.0 M) in ice (200 g), and then diluted with Et_2O (200 mL). The organic phase was washed with brine (2 x 150 mL, sat.), dried over Na_2SO_4 and concentrated under reduced pressure to give the carbinol, sufficiently pure to be used for the next step. To a solution of the carbinol in CH_2Cl_2 (1.0 L) was added a solution of NaOH (1.9 mol, 76.0 g) in MeOH (1 L). To this mixture was bubbled O_3 at -50°C. After 6 hours, the reaction mixture was left to reach room temperature, and it was added H_2O (300 mL). The biphasic solution was concentrated to a fourth of its volume and left to stir for 12 hours. Then, the aqueous phase was first washed with CH_2Cl_2 (2x100 mL) and then acidified with a solution of HCl (5.0 M). The aqueous phase was extracted with Et_2O (4 x 100 mL). The combined organic phases were washed with brine (sat., 100 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a yellow liquid, which was submitted to the distillation procedure affording a colourless liquid.

5-Methyl-6-pentyltetrahydro-2H-pyran-2-one (*cis*-2g + *trans*-2g). Yield= 63% (23.2 g); B.p. 160-170 °C, 0.5 mmHg; 96% purity by GC-MS (t_R t*rans* = 18.59 min and t_R *cis* = 19.01 min); *cis*-**2g**/*trans*-**2g** 50:50 by GC-MS. For the ^{1}H-NMR and the ^{13}C-NMR chemical shifts see the single diastereoisomers. For the GC-MS fragmentation see the single diastereoisomers.

5,6-dimethylltetrahydro-2H-pyran-2-one (*cis*-2h + *trans*-2h). Yield= 54% (13.8 g); B.p. 120-130 °C, 0.5 mmHg; 93% purity by GC-MS (t_R *trans* = 10.61 min and t_R *cis* = 11.13 min); *cis*-**2h**/*trans*-**2h** 43:57 by GC-MS. For the ^{1}H-NMR and the ^{13}C-NMR chemical shifts see the single diastereoisomers. For the GC-MS fragmentation see the single diastereoisomers.
6-(*t*-Butyl)-5-methyltetrahydro-2H-pyran-2-one (*cis*-2i + *trans*-2i). Yield= 68% (23.1 g); B.p. 140-145 °C, 0.2 mmHg; 94% purity by GC-MS (t_R *trans* = 17.61 min and t_R *cis* = 18.13 min); *cis*-**2h**/*trans*-**2h** 79:21 by GC-MS. For the ^{1}H-NMR, the ^{13}C-NMR and the GC-MS see the single diastereoisomers.

Synthesis of γ-hydroxyesters 1e-f and δ-hydroxyesters 1g-1i

The hydroxyesters **1g-1i** were prepared starting from the corresponding lactones, by a two steps sequence according to the following scheme: *i*) hydrolysis of lactone to give the potassium carboxylate salt, which was submitted to next step without purification; *ii*) treatment with *i*-propyliodide to give the corresponding ester according to the procedure reported in the article.



2e, R= *n*-Bu, n=1, Whisky L.
2f, R= Pent, n=1, Cognac L
2g, R=Pent, n=2
2h, R=Me, n=2
2i, R=*t*-Bu, n=2

1e, R= *n*-Bu, n=1
1f, R= Pent, n=1
1g, R=Pent, n=2
1h, R=Me, n=2
1i, R=*t*-Bu., n=2

General procedure. To an ice cooled and well stirred solution of lactone **2** (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). 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 phases were washed with brine (sat., 50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the corresponding hydroxyester **1**,[6] which was of sufficient purity[7] for the next step.

***i*-Propyl-4-hydroxy-3-methyloctanoate (*syn*-1e + *anti*-1e).** Yield 92% (3.4 g) as a pale yellow liquid; 98% purity by ^{1}H-NMR;[3] GC (t_R *anti* = 17.45 min and t_R *syn* = 17.54 min); *syn*-**1e**/*anti*-**1e** 50:50 by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 5.02 (m, 1H), 3.56 (m, 0.5H), 3.39 (m, 0.5H), 2.45 (m, 1H), 2.19 (m, 1H), 2.12–1.94 (m, 1H), 1.79 – 1.26 (m, 6H), 1.23 (d, *J* = 6.3, 6H), 0.99 – 0.85 (m, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.4, 173.2, 75.1, 74.0, 67.4, 38.7, 37.6, 36.2, 35.4, 33.9, 33.7, 28.4.0, 27.9, 22.6 (d), 21.6 (d), 16.4 (d), 13.9, 13.4. MS: *m/z* (%) 172 $[M-44]^+$ (2), 157 $[M-59]^+$ (10), 139 (10), 130 (20), 117 (20), 99 (90), 88 (100).[8]

***i*-Propyl-4-hydroxy-3-methylononoate (*syn*-1f + *anti*-1f).** Yield 96% (3.8 g); purity 96% by ^{1}H NMR; GC (t_R *anti* = 19.46 min and t_R *syn* = 19.52 min); *syn*-**1f**/*anti*-**1f** 52:48 by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.02 (m, *J* = 6.2, 1H), 3.56 (m, 0.5H), 3.39 (m, 0.5H), 2.45 (m, 1H), 2.19 (m, 1H), 2.13–1.94 (m, 1H), 1.54–1.19 (m, 14H), 1.09 – 0.87 (m, 6H); ^{13}C-

NMR (101 MHz, $CDCl_3$): δ = 173.5, 173.2, 75.6, 74.5, 67.7, 39.0, 38.0, 36.4, 35.7, 34.6, 34.3, 32.0 (d), 26.0 (d), 25.6, 22.7, 21.9(d), 16.7, 14.0, 13.7. MS: *m/z* (%) 230 $[M]^+$ (1), 187 (1), 171 (15), 153 (15), 130 (30), 117 (25), 99 (70), 88 (100).[6]

***i-Propyl-5-hydroxy-4-methyldecanoate* (*syn*-1g + *anti*-1g).** Yield 98%; (4.1) g; purity 98% by ^{1}H NMR;[3] GC (t_R *anti* = 20.51 min and t_R *syn* = 20.57 min); *syn*-**1g**/*anti*-**1g** 58:42 by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.01 (m, *J* = 6.3, 1H), 3.50 (m, 0.6H), 3.42 (s, 0.4H), 2.44–2.18 (m, 2H), 1.90 – 1.73 (m, 1H), 1.65 – 1.27 (m, 10H), 1.23 (d, *J* = 6.2, 6H), 0.90 (d+d, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.7, 75.8, 74.4, 67.6, 38.5, 38.0, 34.5, 33.8, 32.8, 32.5, 32.0, 32.0, 28.6, 27.2, 26.0, 25.7, 22.7, 21.9, 15.4, 14.0, 13.4. MS: *m/z* (%) 244 $[M]^+$ (1), 201 (3), 185 (3), 153 (15), 113 (65), 99 (15); HRMS (ESI) calcd for $C_{14}H_{27}O_3^-$ $[M - H]^-$243.1967, found 243.1971.

***i-Propyl-5-hydroxy-4-methylhexanoate* (*syn*-1h + *anti*-1h).** Yield 95%; (3.0) g; purity 98% by ^{1}H-NMR;[3] GC (t_R *anti*= 14.02 min and t_R *syn*= 14.12 min);); *syn*-**1h**/*anti*-**1h** 50:50 by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.01 (m, *J* = 6.3, 1H), 3.72 (m, 0.5H), 3.63 (m, 0.5H), 2.43 – 2.18 (m, 2H), 1.83 (m, 1H), 1.54–1.37 (m, 3H), 1.29–1.08 (m, 9H), 0.97 – 0.78 (m, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.7, 71.4, 70.6, 67.6, 39.9, 39.5, 32.8, 32.5, 27.9, 27.7, 21.9, 20.2, 19.9, 14.8, 14.0. MS: *m/z* (%) 189 $[M+1]^+$ (1), 173 (2), 155 (1), 144 (20), 129 (25), 111 (35), 102 (95), 83 (35), 69 (25), 60 (100). HRMS (ESI) calcd for $C_{10}H_{19}O_3^-$ $[M - H]^-$187.1340, found 187.1343.

***i-Propyl-5-hydroxy-4,6,6-trimethylheptanoate* (*syn*-1i + *anti*-1i).** Yield 93%; (3.6) g; purity 94% by ^{1}H-NMR;[3] GC (t_R *anti*= 18.02 min and t_R *syn*= 18.12 min);); *syn*-**1i**/*anti*-**1i** 78:22 by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.98 (m, *J* = 6.3, 1H), 3.16 (m, 0.8H), 3.10 (m, 0.2H), 2.39–2.19 (m, 2H), 1.93 (m, 0.2H), !.80–1.53 (m, 3.6H), 1.42 – 1.32 (m, 1.2H), 1.37 (d+d, 6H), 0.97– 0.88(s+d, 12H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.5, 173.4, 83.9, 81.1, 67.4, 67.3, 35.8, 35.733.6, 33.2,32.5, 26.7, 26.4, 21.7, 19.9, 13.8; MS: MS: *m/z* (%) 230 $[M]^+$ (1), 213 (4), 198 (15), 153 (22), 130 (30), 117 (25), 99 (70), 88 (100). HRMS (ESI) calcd for $C_{13}H_{25}O_3^-$ $[M - H]^-$229.1809, found 229.1803.

Synthesis of *Trans* lactones

General procedure A. To a mixture of *syn*/*anti* hydroxyester **1** (23.4 mmol) in CH_2Cl_2 (60 mL) at – 35 °C was added a precooled solution of TFA (0.01 ÷ 0.1 eq) in CH_2Cl_2 (2 mL) under a N_2 atmosphere. After conversion of most of *anti*-**1** hydroxyester (checked by ^{1}H-NMR),[9] the reaction mixture was quenched with imidazole (2.0 eq) and left to reach r.t., then the solvent was removed under reduced pressure to give a crude material, which was left for at last 15 min under high *vacuum*.[10] To a solution of the crude material in CH_2Cl_2 (30 mL) was added Et_3SiCl (1.1 eq with respect to the *anti*-**1**) and a catalytic amount of DMAP. After 12 hours, the reaction mixture was concentrated under reduced pressure and submitted to column chromatography using a gradient elution (SiO_2, *n*-hexane/AcOt, 95:5->6:4) affording in order of elution the silyl derivative **3** and then *trans*-**2**, the latter was distilled with a bulb to bulb apparatus. Alternatively, the organic phase was diluted with CH_2Cl_2 (30 mL), washed with HCl (0.2 M, 2 x 30 mL) and brine (sat., 1 x 30 mL), dried over Na_2SO_4 and concentrated under *vacuum*. Finally, the lactone was isolated by distillation with a bulb to bulb apparatus.

***Trans*-4,5-dimethyldihydrofuran-2(3H)-one (*trans*-2c).** Yield= 80% (0.94 g as colourless liquid); B.p. 70-80 °C, 0.5 mmHg; purity 99% by GC (t_R = 6.58 min); *de* 94% by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.15 (tt, *J* = 7.1, 5.5, 3H), 2.76 – 2.57 (m, 1H), 2.27 – 2.08 (m, 2H), 1.41 (d, *J* = 6.2, 3H), 1.15 (d, *J* = 6.2, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 176.4, 83.5, 38.3, 37.4, 19.2, 16.9.[11] GC-MS: *m/z* (%) 114 $[M]^+$ (10), 99 (20), 70 (60), 55 (50), 42 (100).

***Trans*-5-butyl-4-methyldihydrofuran-2(3H)-one (*trans*-2e, *Whisky L.*).** Yield= 78% (1.40 g as colourless liquid); B.p. 100-108 °C, 0.5 mmHg; purity 99% by GC (t_R = 13.81 min); *de* 98% by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 4.01 (td, *J* = 7.7, 4.1, 1H), 2.74 – 2.59 (m, 1H), 2.29 – 2.11 (m, 2H), 1.75 – 1.29 (m, 6H), 1.14 (d, *J* = 6.5, 3H), 1.05 – 0.88 (t, *J* = 7.1, 3H). ^{13}C-

NMR (101 MHz, $CDCl_3$): δ = 176.4, 87.5, 37.2, 36.1, 33.8, 27.9, 22.5, 17.6, 13.9. MS: *m/z* (%) 156 $[M]^+$ (2), 138 (3), 128 (2), 114 (5), 99 (100).

***Trans-4-methyl-5-pentyldihydrofuran-2(3H)-one* (*trans*-2f, *Cognac L.*).** Yield= 75% (1.44 g as colourless liquid); B.p. 110-118 °C, 0.5 mmHg; purity 98% by GC (t_R = 16.20 min); *de* 96% by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.00 (td, *J* = 7.6, 4.1, 1H), 2.74 – 2.56 (m, 1H), 2.29 – 2.08 (m, 2H), 1.72 – 1.29 (m, 9H), 1.13 (d, *J* = 7.1, 3H), 0.90 (t, *J* = 7.1, 3H).^{13}C-NMR (101 MHz, $CDCl_3$): δ = 176.5, 87.5, 37.2, 36.1, 34.1, 31.7, 25.4, 22.5, 17.6, 14.0. MS: *m/z* (%) 170 $[M]^+$ (2), 152 (3), 142 (5), 128 (10), 110 (10), 99 (100).

***Trans-5-methyl-6-pentyltetrahydro-2H-pyran-2-one* (*trans*-2g, *Aerangis L.*).** Yield= 79% (1.43 g as colourless liquid); B.p. 160-170 °C, 0.5 mmHg;, 0.5 mmHg; purity 99% by GC (t_R = 18.62 min); *de* 94% by ^{1}H-NMR; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.93 (ddd, *J* = 9.8, 7.8, 3.0, 1H), 2.61 (ddd, *J* = 17.8, 6.8, 4.6, 1H), 2.46 (ddd, *J* = 17.8, 9.8, 7.1, 1H), 1.90 (ddt, *J* = 13.5, 7.1, 4.6, 1H), 1.76 – 1.66 (m, 2H), 1.63 –1.23 (m, 8H), 1.00 (d, *J* = 7.2, 3H),0.89 (d, *J* = 7.1 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 171.8, 85.8, 33.5, 32.2, 31.7, 29.5, 27.8, 24.2, 22.5, 17.4, 14.0. MS: *m/z* (%) 184 $[M]^+$ (1), 156 (3), 148 (3), 128 (10), 113 (65), 99 (15), 84 (70), 69 (10), 56 (100).

***Trans-5-methyl-6-methyltetrahydro-2H-pyran-2-one* (*trans*-2h).** Yield= 83% (1.24 g as colourless liquid, at T>15°C, as a colorless needle crystals); B.p. 120-130°C, 0.6 mmHg; purity 99% by GC (t_R = 9.77 min); *de* 92% by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.04 (dq, *J* = 9.4, 6.3, 1H), 2.62 (ddd, *J* = 17.7, 6.7, 4.3, 1H), 2.47 (ddd, *J* = 17.7, 9.7, 7.1, 1H), 1.90 (ddt, *J* = 13.2, 7.2, 4.2, 1H), 1.73 – 1.46 (m, 2H), 1.37 (d, *J* = 7.1, 3H), 1.01 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.6, 82.4, 34.7, 29.7, 28.0, 20.0, 17.4. MS: *m/z* (%) 128 $[M]^+$ (5), 113 (5), 99 (2), 84 (40), 69 (10), 56 (100).

***Trans-4 6-(t-butyl)-5-methyltetrahydro-2H-pyran-2-one* (*trans*-2i).** Yield= 90% (0.79 g as colourless liquid); B.p. 140-145 °C, 0.2 mmHg; purity 99% by GC (t_R = 17.61 min); *de* 92% by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.69 (d, *J* = 7.2, 1H), 2.47 (ddd, *J* = 17.0, 8.2, 4.3, 1H), 2.33 (ddd, *J* = 17.0, 8.2, 4.3, 1H), 2.02 (m, *J* = 6.2, 1H), 1.85 (m, 1H), 1.65 –153 (m, 1H), 1.13 (d, *J* = 6.6, 3H), 1.00 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.0, 92.6, 36.2, 28.7, 27.9, 27.8,, 26.0, 21.4. MS: *m/z* (%) 170 $[M]^+$ (5), 155 (8), 98 (40), 56 (100).

Synthesis of (*syn*)-silyl ethers

This procedure is similar to that of procedure A, unless a different amount of TFA (0.15 eq) was used, and the conversion of **1** into **2** was pushed until the consumption of most of *anti*-**1** (checked by ^{1}H-NMR),[9] the O-silylation was carried out at same conditions described for the procedure A.

***(syn)-Ethyl 3-methyl-4-((triethylsilyl)oxy)pentanoate* (3c).** Yield 78% (2.8 g as a colorless liquid); purity 98% by GC (t_R = 18.91 min); *de* 99% by ^{1}H NMR; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.14 (q, *J* = 7.1, 2H), 3.81 (qd, *J* = 6.3, 3.5, 1H), 2.59 – 2.46 (m, 1H), 2.14 – 2.00 (m, 2H), 1.27 (t, *J* = 7.2, 3H), 1.09 (d, *J* = 6.3, 3H), 1.04 – 0.86 (m, 15H), 0.60 (td, *J* = 8.3, 7.7, 7H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.7, 70.8, 60.1, 37.5, 37.4, 20.0, 14.7, 14.3, 6.9, 5.2. GC-MS: *m/z* (%) 273 $[M-1]^+$ (1), 259 (2), 245 (100); HRMS (quadrupole) calcd for $C_{12}H_{25}O_3Si^+$ $[M - Et]^+$ 245.1573, found 245.1572.

***(syn)-Isopropyl 3-methyl-4-((triethylsilyl)oxy)octanoate* (3e).** Yield 77% (3.0 g as a colorless liquid); purity 98% by GC (t_R = 23.01 min); *de* 99% by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.01 (m, *J* = 6.3, 1H), 3.60 (td, *J* = 6.1, 3.0, 1H), 2.51 – 2.41 (m, 1H), 2.15 – 1.97 (m, 2H), 1.56 – 1.15 (m, 15H), 1.06 – 0.79 (m, 16H), 0.60 (q, *J* = 7.9, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.3, 75.3, 67.4, 38.1, 35.4, 33.4, 28.4, 23.0, 22.0, 21.9, 14.3, 14.1, 7.0, 5.4. MS: *m/z* (%) 329 $[M-1]^+$ (1), 301 (10), 271 (13), 259 (100); HRMS (quadrupole) calcd for $C_{16}H_{33}O_3Si^+$ $[M - Et]^+$ 301.2204, found 301.2207.

***(syn)-Isopropyl 3-methyl-4-((triethylsilyl)oxy)nonanoate* (3f).** Yield 78% (3.3 as a colourless liquid); purity 94% by GC (t_R = 24.97 min); *de* 98% by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.00 (m, *J* = 6.2, 1H), 3.53 (td, *J* = 6.1, 3.3, 1H), 2.44 – 2.09 (m, 2H), 1.78 (dddd, *J* = 13.1, 10.3, 6.3, 4.3, 1H), 1.55 – 1.19 (m, 14H), 1.01 – 0.79 (m, 15H), 0.58 (q, *J* = 7.9, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.3, 75.3, 67.4, 38.1, 35.4, 33.7, 32.2, 25.8, 22.8, 22.0, 21.9, 14.3, 14.1, 7.0, 5.4. MS: *m/z* (%) 329 $[M-29]^+$ (15), 299 (15), 287 (20), 269 (100); HRMS (quadrupole) calcd for $C_{17}H_{35}O_3Si^+$ $[M - Et]^+$ 315.2361, found 315.2369.

***(syn)-Isopropyl 4-methyl-5-((triethylsilyl)oxy)decanoate* (3g).** Yield 78% (3.8 g as colourless liquid); purity 98% by GC (t_R = 24.97 min); *de* 98% by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.00 (m, *J* = 6.2, 1H), 3.53 (td, *J* = 6.1, 3.3, 1H), 2.44 – 2.09 (m, 2H), 1.78 (dddd, *J* = 13.1, 10.3, 6.3, 4.3, 1H), 1.55 – 1.19 (m, 16H), 1.01 – 0.79 (m, 16H), 0.58 (q, *J* = 7.9, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.5, 75.8, 67.3, 37.4, 33.6, 33.1, 32.0, 28.1, 25.6, 22.6, 21.8, 14.0, 13.9, 7.0, 5.2. MS: *m/z* (%) 329 $[M-29]^+$ (15), 299 (15), 287 (20), 269 (100).δ = 4; HRMS (quadrupole) calcd for $C_{18}H_{37}O_3Si^+$ $[M - Et]^+$ 329.2506, found 329.2514.

***(syn)-Isopropyl 4-methyl-5-((triethylsilyl)oxy)hexanoate* (3h).** Yield 82% (2.9 g as colourless liquid); purity 96% by GC (t_R = 21.82 min); *de* 97% by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.00 (m, *J* = 6.3, 1H), 3.72 (qd, *J* = 6.2, 3.8, 1H), 2.40 – 2.19 (m, 2H), 1.87 – 1.74 (m, 1H), 1.43 (tdd, *J* = 11.8, 5.7, 2.7 Hz, 2H), 1.23 (d, *J* = 6.3, 6H), 1.09 (d, *J* = 6.2, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.88 – 0.83 (m, 3H), 0.59 (q, *J* = 7.6, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.7, 71.7, 67.4, 40.1, 33.1, 28.0, 22.0, 20.5, 14.6, 7.0, 5.3. MS: *m/z* (%) 301 $[M-1]^+$ (1), 287 (1), 273 (10), 243 (15), 231 (20), 213 (100); HRMS (quadrupole) calcd for $C_{14}H_{29}O_3Si^+$ $[M - Et]^+$ 273.1880, found 273.1887.

Synthesis of (*syn*)-1i

This procedure is similar to that of procedure B, but, since the hydroxyester *syn*-**1i** is sufficiently stable at room temperature no *O*-silylation was carried out.

***(syn)-Isopropyl -5-hydroxy-4,6,6-trimethylheptanoate* (1i).** Yield 82% (3.7 g as colourless liquid); purity 96% by GC (t_R = 18.14 min); *de* 97% by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.98 (m, *J* = 6.3, 1H), 3.16 (m, 1H), 2.38 – 2.19 (m, 2H), 1.78 – 1.54 (m, 3H), 1.37 (m, 1H), 1.23 (d, *J* = 6.3, 6H), 0.91 (d+t, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.4, 81.1, 67.4, 35.8, 33.2, 32.3 (d), 26.7, 21.7, 13.8.

General procedure for the synthesis of *cis* lactones

To a solution of **3** or *syn*-**1i** (10.0 mmol) in CH_2Cl_2 (15 mL) was added TFA (1 g, 0.1 g for **1i**). After complete conversion of starting material into *cis*-**2**, checked by TLC, the reaction mixture was diluted with Et_2O (15 mL) and washed with a solution of $NaHCO_3$ (sat., 1 x 30 mL), brine (sat., 1 x 20 mL). The organic phase was dried over Na_2SO_4, concentrated under reduced pressure and the crud material was submitted to the bulb to bulb distillation apparatus affording the *cis*-lactone.

***Cis-4,5-dimethyldihydrofuran-2(3H)-one* (*cis*-2c).** Yield=89% (1.0 g as a colourless liquid); B.p. 73-81 °C, 0.5 mmHg; purity 98% by GC (t_R = 7.34 min); *de* 99% by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.65 (m, 1H), 2.75 – 2.52 (m, 2H), 2.21 (dd, *J* = 16.6, 5.1, 1H), 1.29 (d, *J* = 6.5, 3H), 1.03 (d, *J* = 6.9, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 176.8, 79.7, 37.0, 33.5, 15.5, 14.0. MS: *m/z* (%) 114 $[M]^+$ (10), 99 (20), 70 (60), 55 (50), 42 (100).[11]

***Cis-5-butyl-4-methyldihydrofuran-2(3H)-one* (*cis*-2e, *Whisky L*.).** Yield= 91% (1.4 g as a colourless liquid); B.p. 100-110°C, 0.5 mmHg; purity 99% by GC (t_R = 14.59 min); *de* 99% by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.42 (m, 1H), 2.68 (dd, *J* = 16.9, 7.8, 1H), 2.65 (m, 1H), 2.19 (dd, *J* = 16.9, 4.0, 1H), 1.72 – 1.31 (m, 6H), 1.01 (d, *J* = 7.0, 3H), 0.97 – 0.87

(t, *J* = 7.0, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 176.8, 83.8, 37.7, 33.2, 29.7, 28.2, 22.6, 14.0, 13.9. MS: *m/z* (%) 156 $[M]^+$ (2), 138 (3), 128 (2), 114 (5), 99 (100).

***Cis-4-methyl-5-pentyldihydrofuran-2(3H)-one* (*cis*-2f, *Cognac L.*).** Yield= 91% (1.6 g as a colourless liquid); B.p. 110-118°C, 0.5 mmHg; purity 98% by GC (t_R = 17.14 min); *de* 98% by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.42 (m, 1H), 2.68 (dd, *J* = 16.9, 7.8, 1H), 2.63 – 2.49 (m, 1H), 2.24 (dd, *J* = 16.9, 4.0, 1H), 1.71 – 131 (m, 7H), 1.01 (d, *J* = 7.0, 3H), 0.94 – 0.83 (t, *J* = 7.0, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 176.7, 83.6, 37.5, 33.0, 31.5, 29.8, 25.5, 22.4, 13.9, 13.8. MS: *m/z* (%) 170 $[M]^+$ (2), 152 (3), 142 (5), 128 (10), 110 (10), 99 (100).

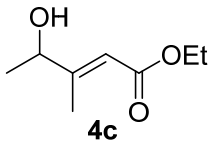
***Cis-5-methyl-6-pentyltetrahydro-2H-pyran-2-one* (*cis*-2g, *Aerangis L.*).** Yield= 90% (1.7 g as a colourless liquid); B.p. 160-170 °C, 0.5 mmHg; purity 98% by GC (t_R = 19.05 min); *de* 98% by ^{1}H-NMR; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.29 (m, 1H), 2.54 (dd, *J* = 7.9, 6.6, 2H), 2.11 – 1.94 (m, 2H), 1.77 – 1.22 (m, 9H), 0.97 (d, *J* = 6.9, 3H), 0.90 (t, *J* = 6.9, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.2, 83.1, 32.0, 31.7, 29.3, 26.8, 26.1, 25.3, 22.6, 14.0, 12.5. MS: *m/z* (%) 184 $[M]^+$ (1), 156 (3), 148 (3), 128 (10), 113 (65), 99 (15), 84 (70), 69 (10), 56 (100).

***Cis-5,6-dimethyltetrahydro-2H-pyran-2-one* (*cis*-2h).** Yield= 85% (1.1 g as a colourless liquid); B.p. 120-130°C, 0.5 mmHg; purity 98% by GC (t_R = 10.43 min); *de* 98% by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.52 (m, 1H), 2.63 – 2.42 (m, 2H), 2.11 – 1.90 (m, 2H), 1.76 – 1.62 (m, 1H), 1.30 (d, *J* = 6.6, 3H), 0.98 (d, *J* = 7.0, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.5, 79.0, 30.5, 27.1, 25.4, 17.2, 13.1. MS: *m/z* (%) 128 $[M]^+$ (5), 113 (5), 99 (2), 84 (40), 69 (10), 56 (100).

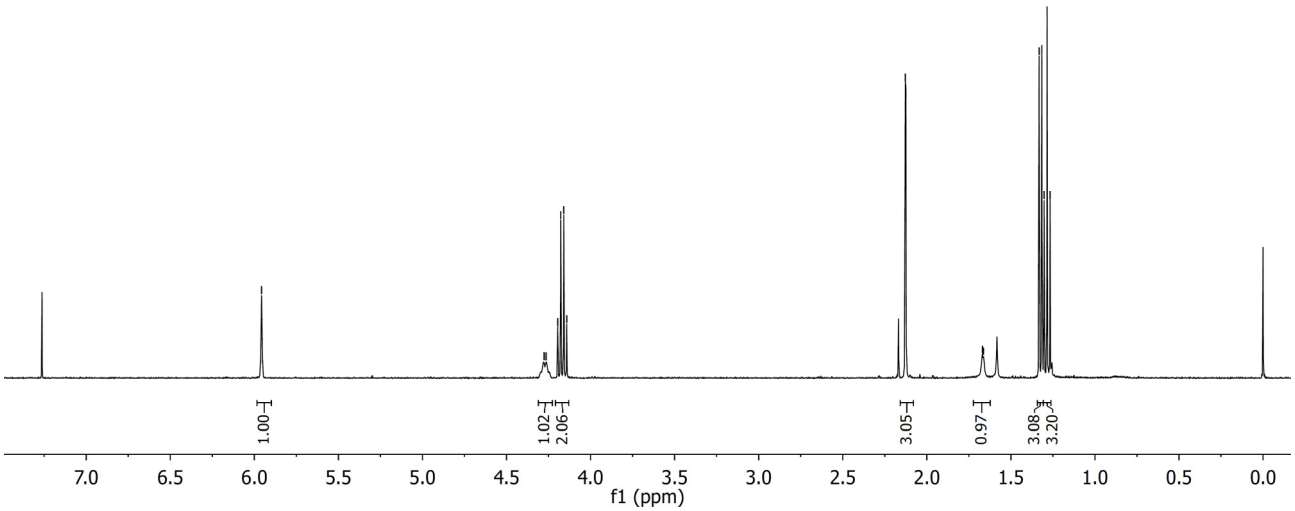
***Cis-4 6-(t-butyl)-5-methyltetrahydro-2H-pyran-2-one* (*cis*-2i).** Yield= 94% (1.6 g as a colourless liquid); purity 98% by GC (t_R = 18.13 min); *de* 98% by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.92 (d, *J* = 2.1, 1H), 2.55 – 2.48 (m, 2H), 2.24 (m, 2H), 2.01 (m, 2H), 1.62 (m, 1H), 0.98 (d+s, 12H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.2, 90.7, 34.6, 28.5, 27.5, 26.5, 25.8, 13.2. MS: *m/z* (%) 170 $[M]^+$ (5), 155 (8), 98 (40), 56 (100).

Copy of ^{1}H- and ^{13}C- NMR spectra

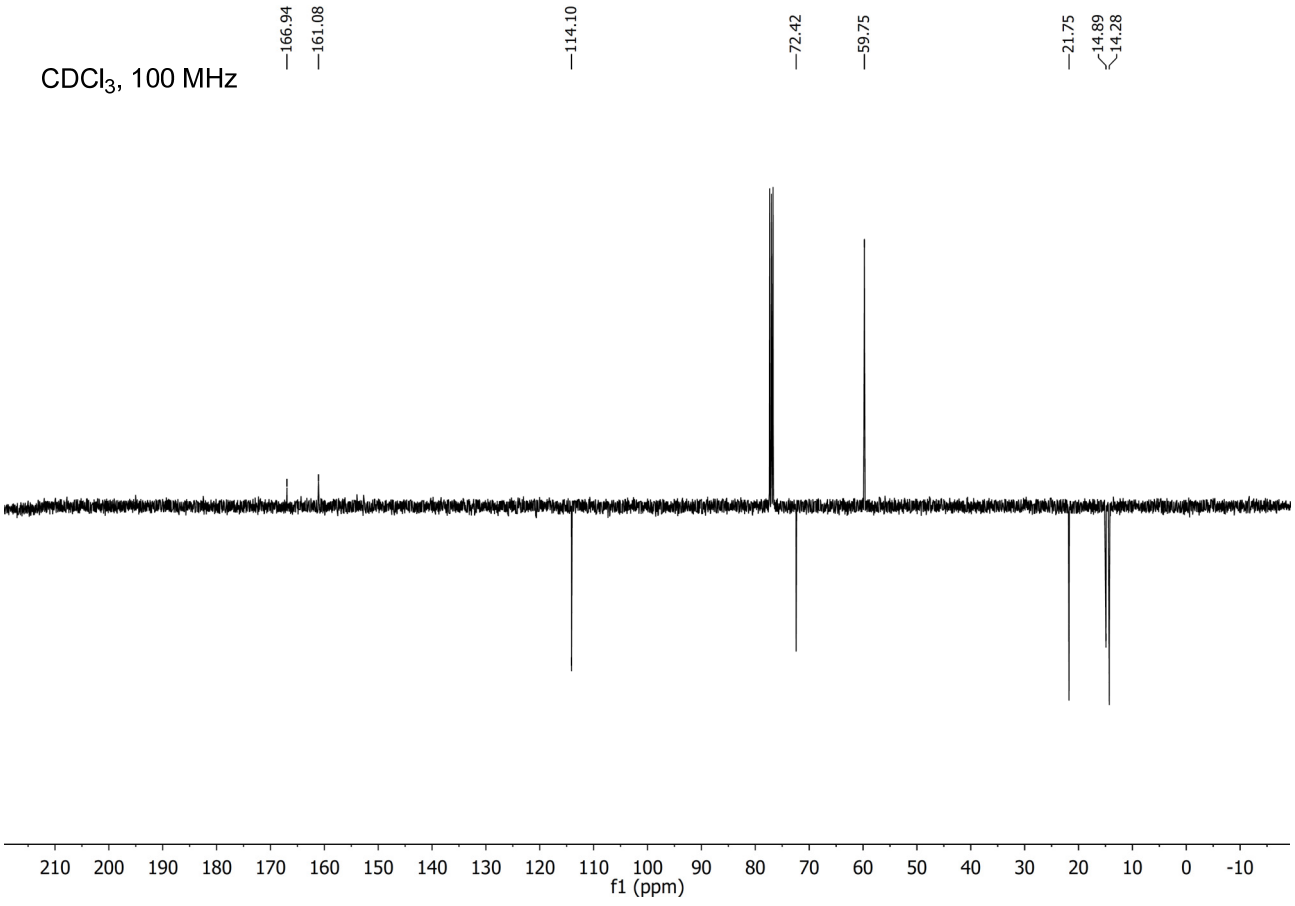
$CDCl_3$, 400 MHz



4c



$CDCl_3$, 100 MHz



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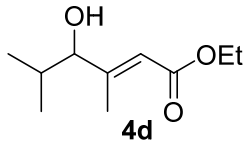
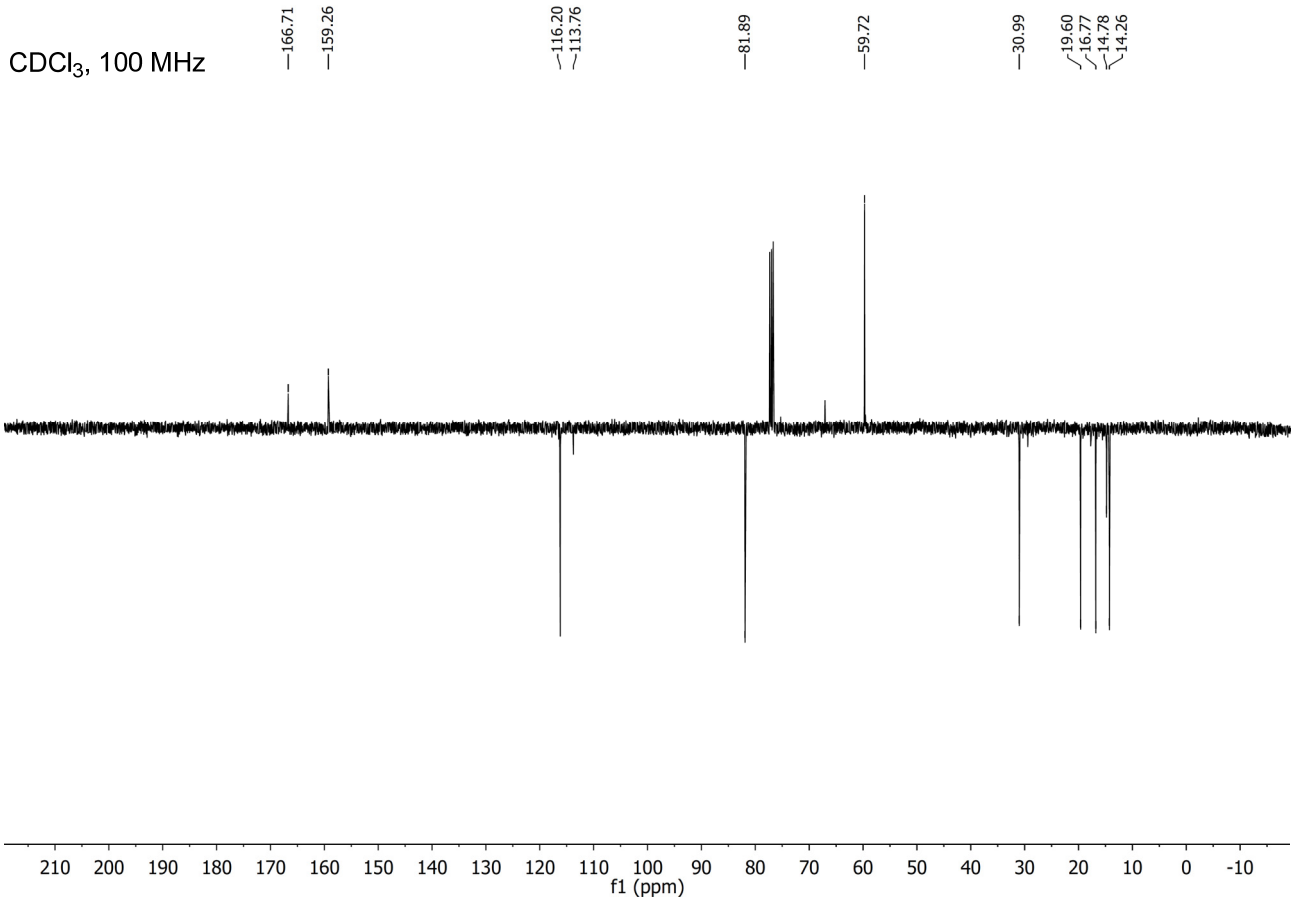
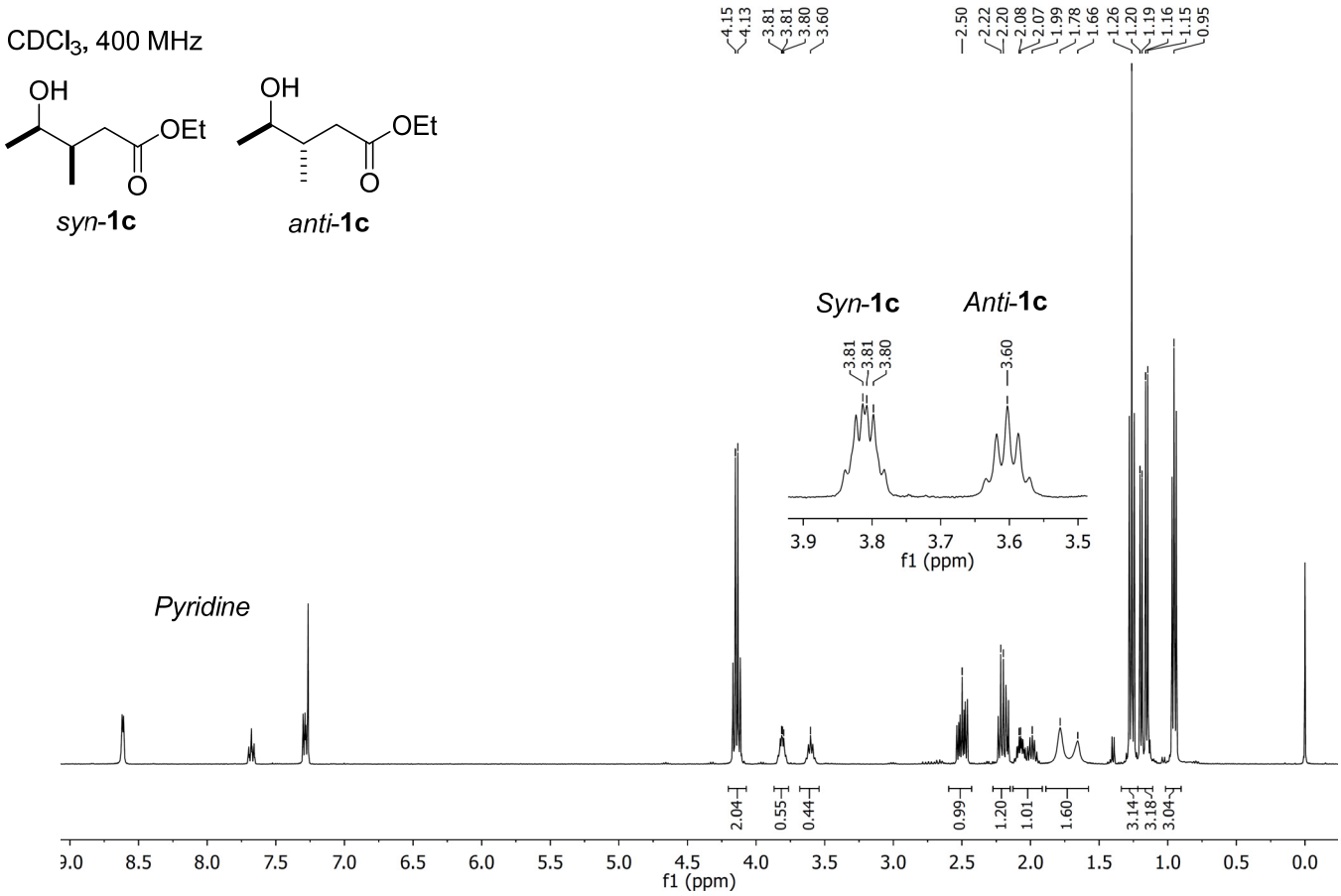


4d

$CDCl_3$, 100 MHz

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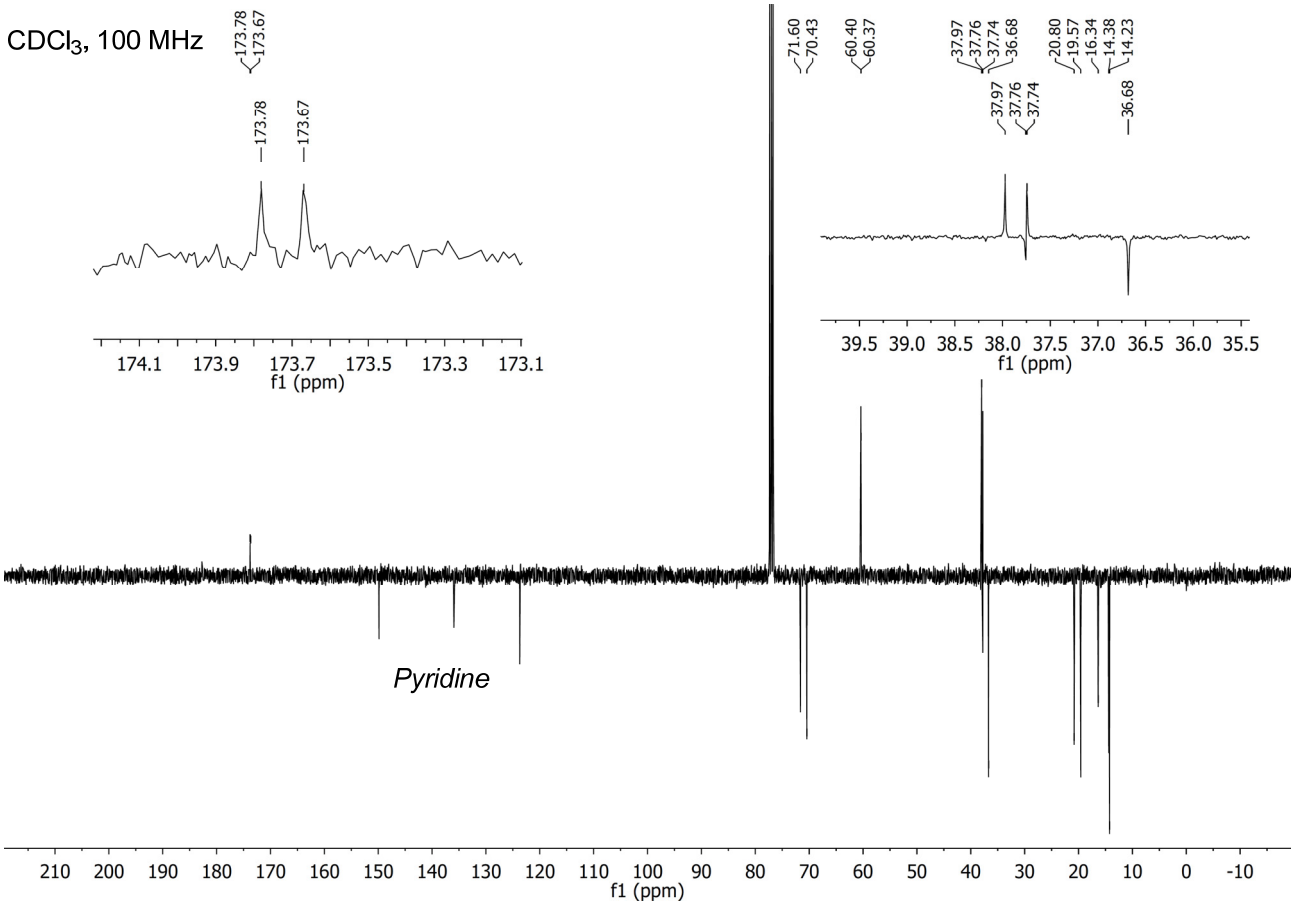
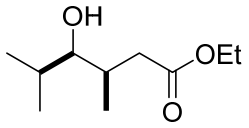
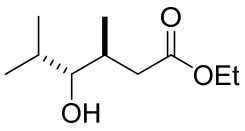
OH
OEt
O
anti-1c
Syn-1c
Anti-1c
Pyridine
f1 (ppm)


CDCl3, 100 MHz
Pyridine
f1 (ppm)

$CDCl_3$, 400 MHz



syn-**1d**



anti-**1d**

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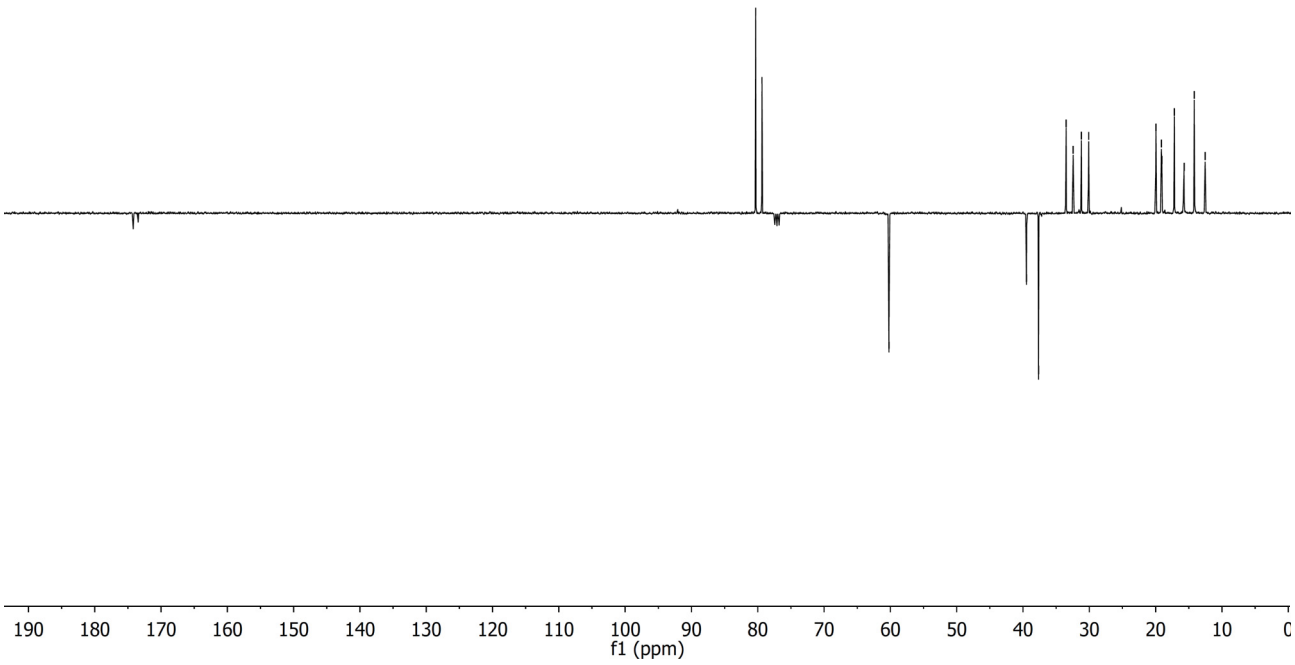

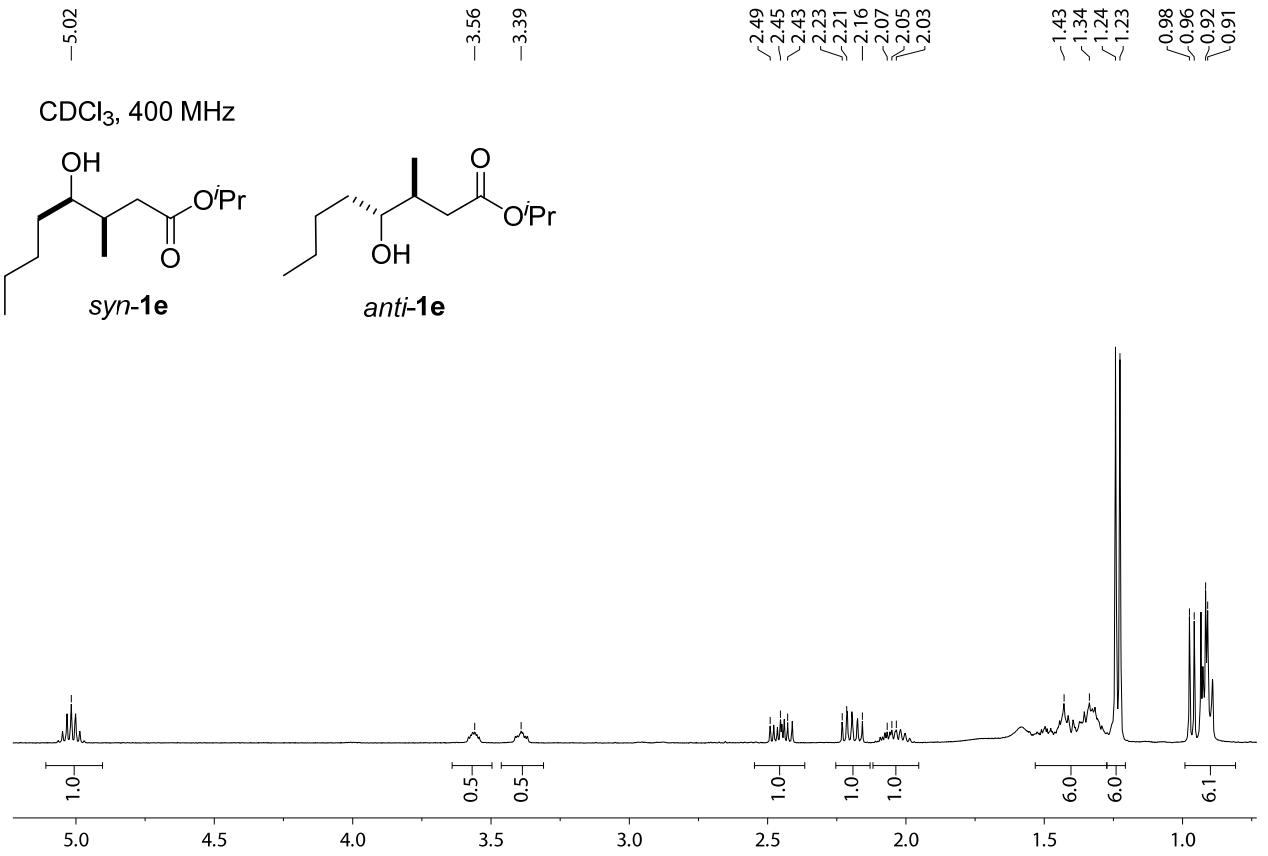
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1.34
1.24
1.23
0.98
0.96
0.92
0.91
CDCl3, 400 MHz
OH
OiPr
O
syn-1e
O
OiPr
OH
anti-1e
1.0
0.5
0.5
1.0
1.0
1.0
6.0
6.0
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3.0
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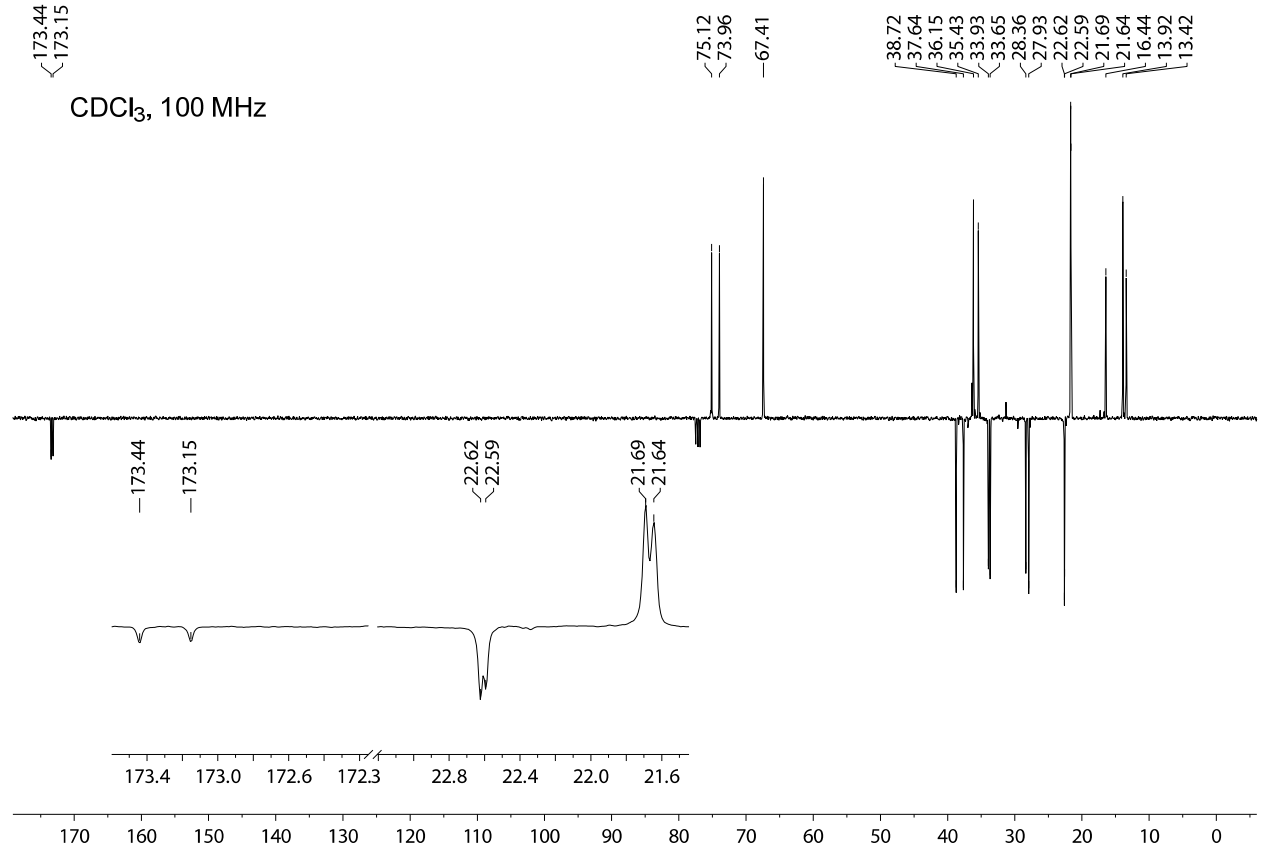
2.0
1.5
1.0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21.64
16.44
13.92
13.42
CDCl3, 100 MHz
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173.15
22.62
22.59
21.69
21.64
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172.6
172.3
22.8
22.4
22.0
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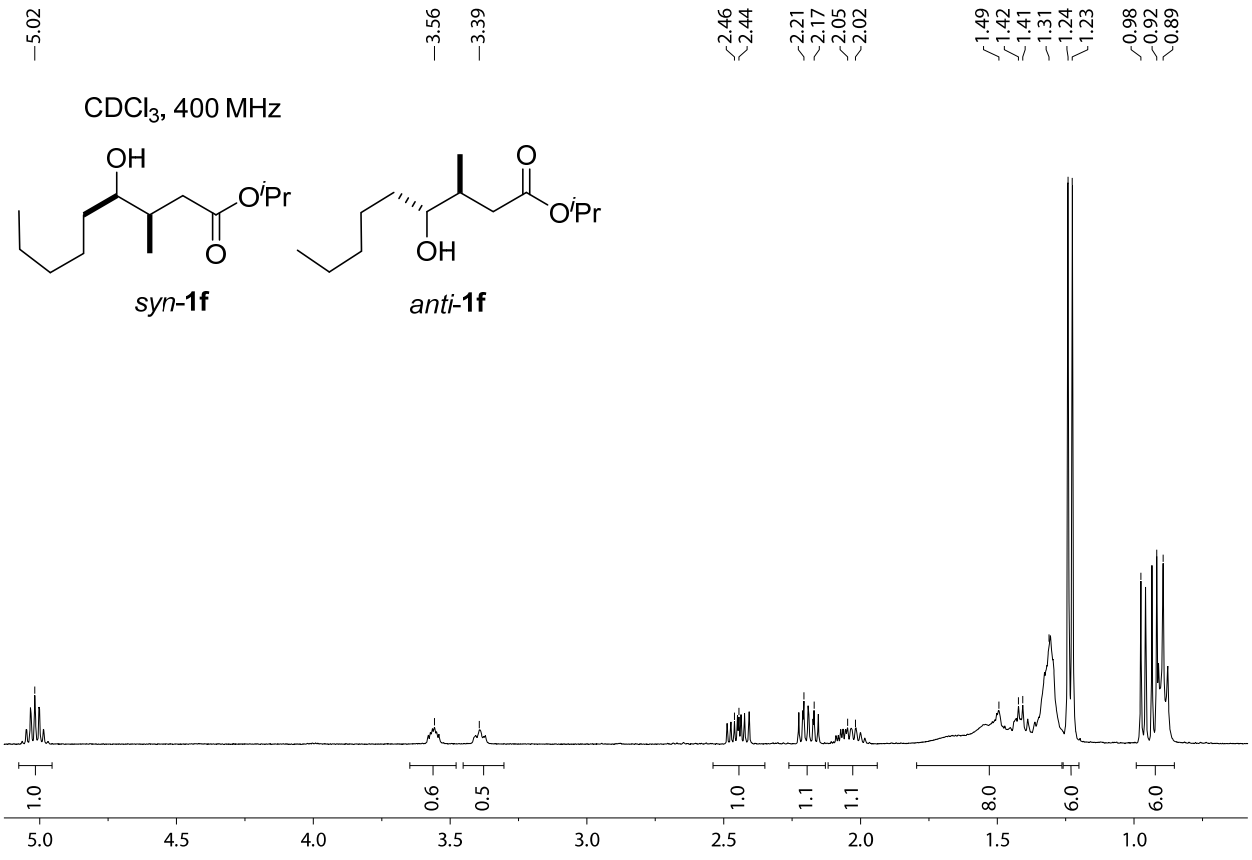
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0.92
0.89
CDCl3, 400 MHz
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O
OH
OiPr
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anti-1f
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0.5
1.0
1.1
1.1
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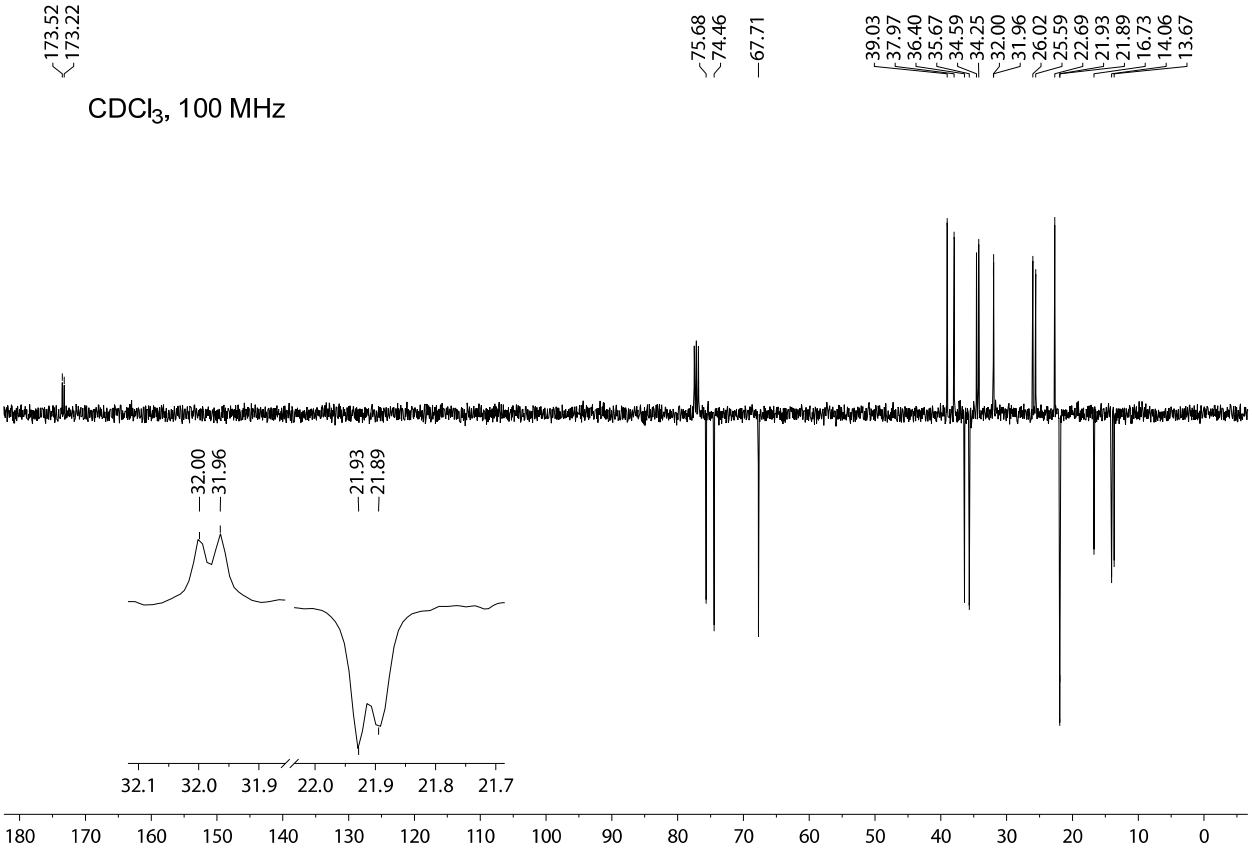
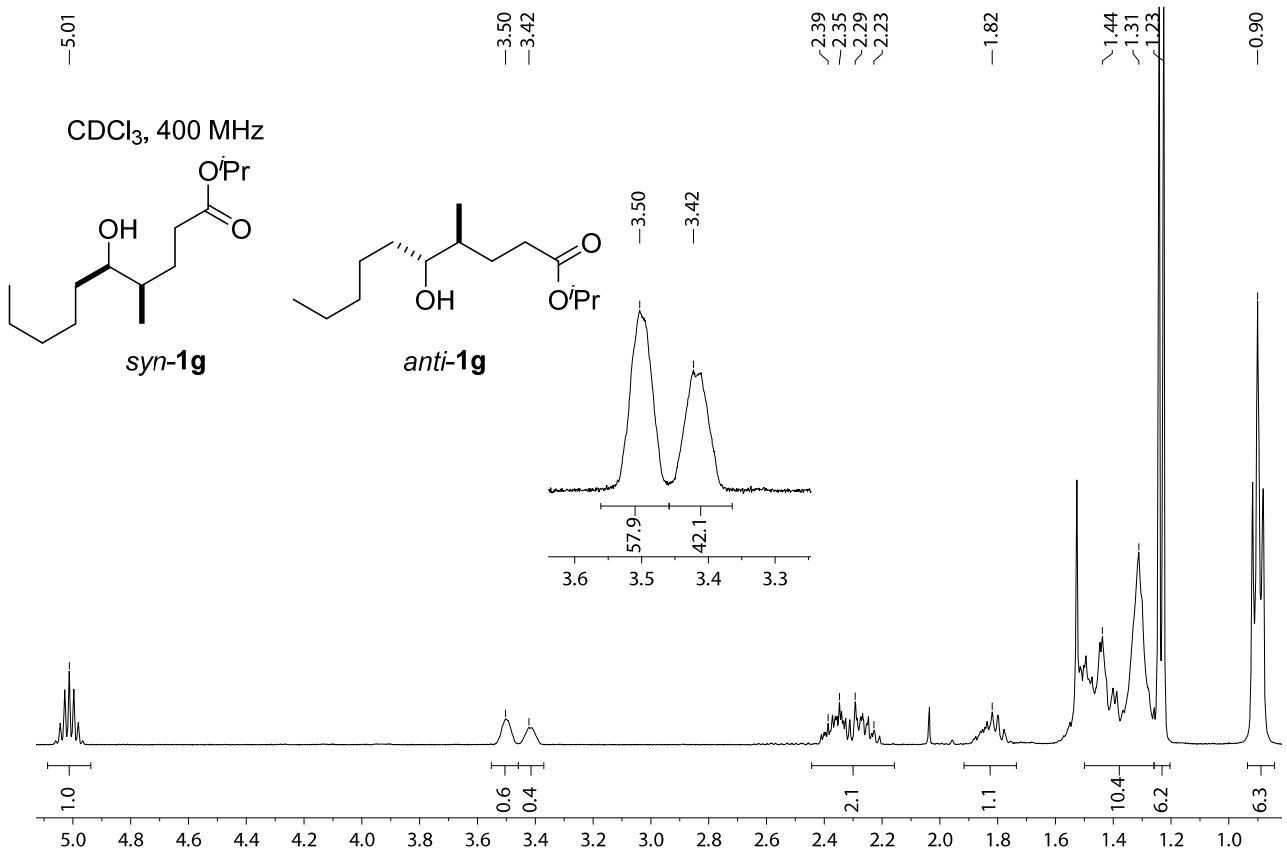
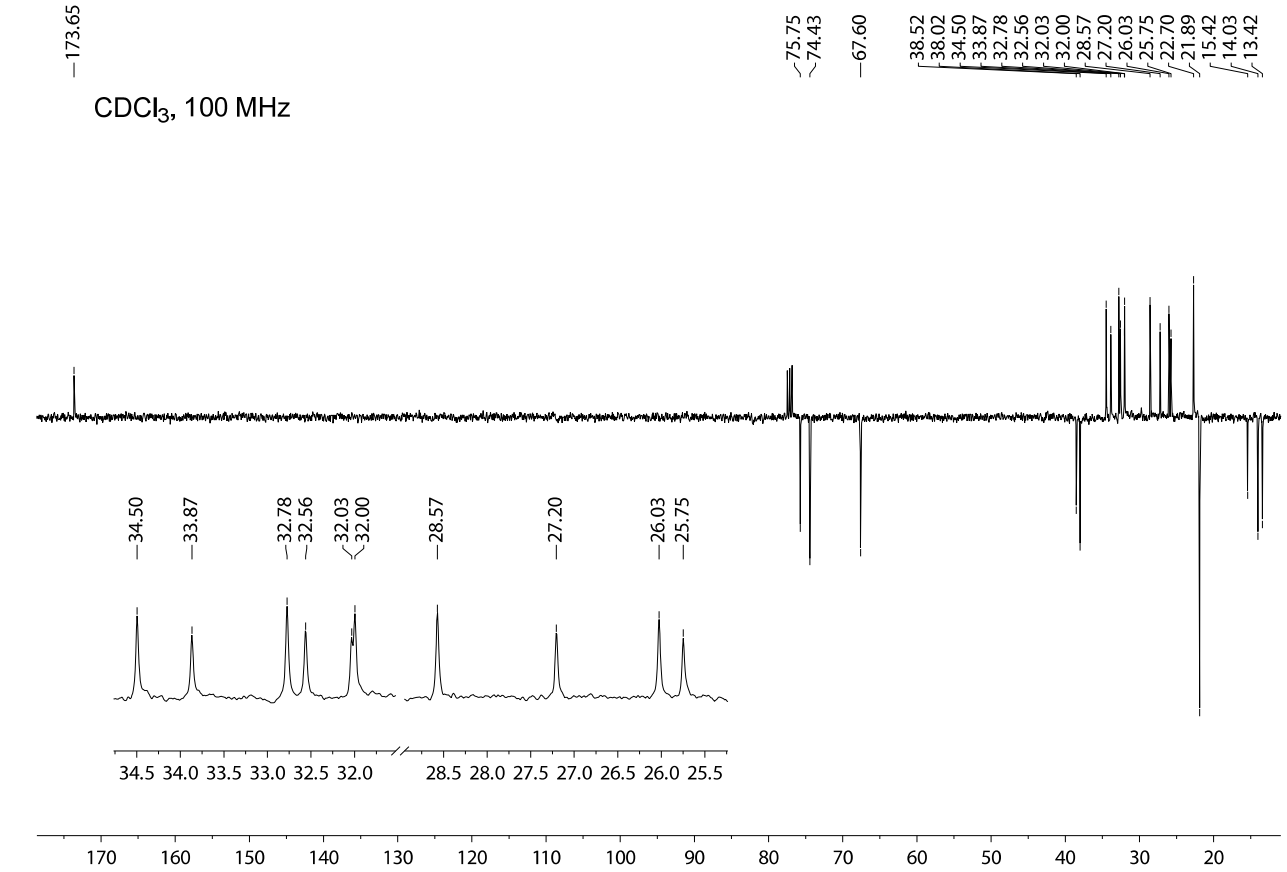
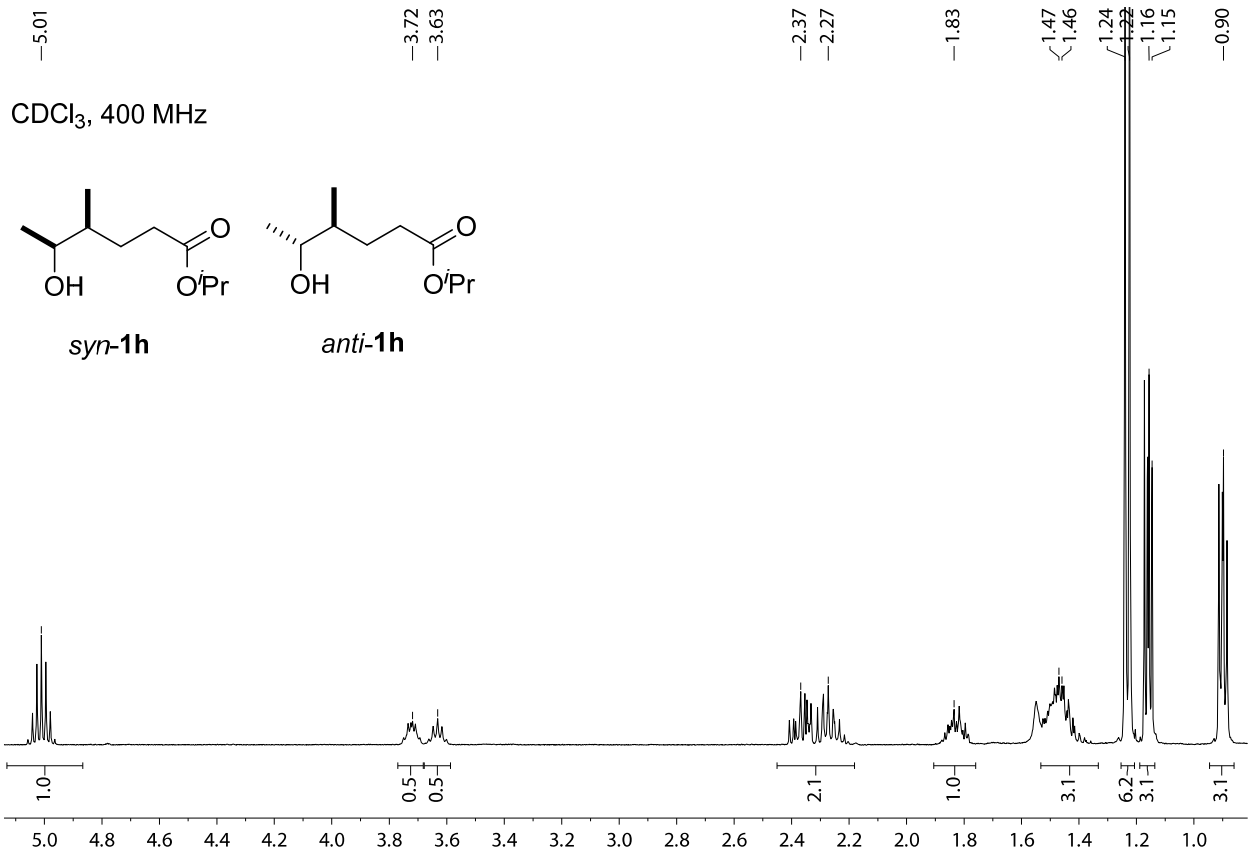
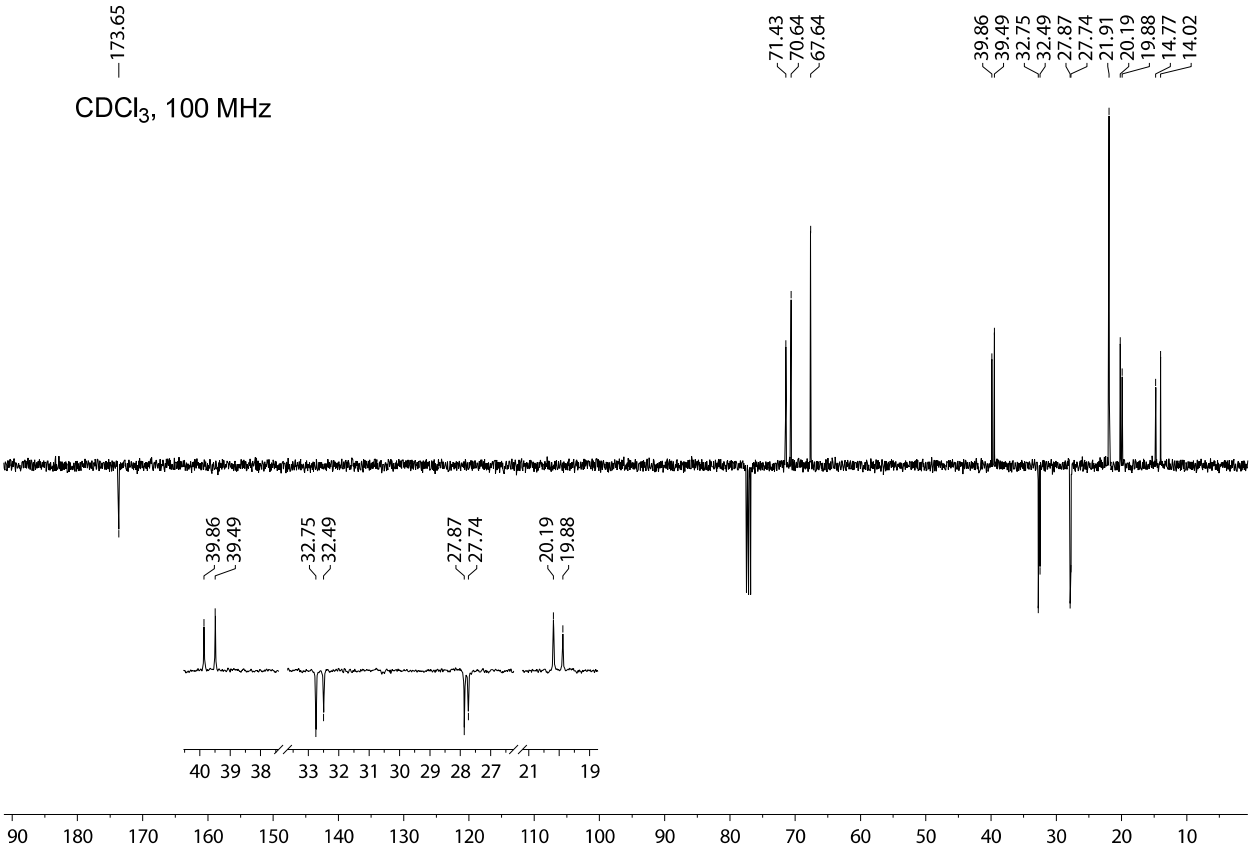
6.0
6.0
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

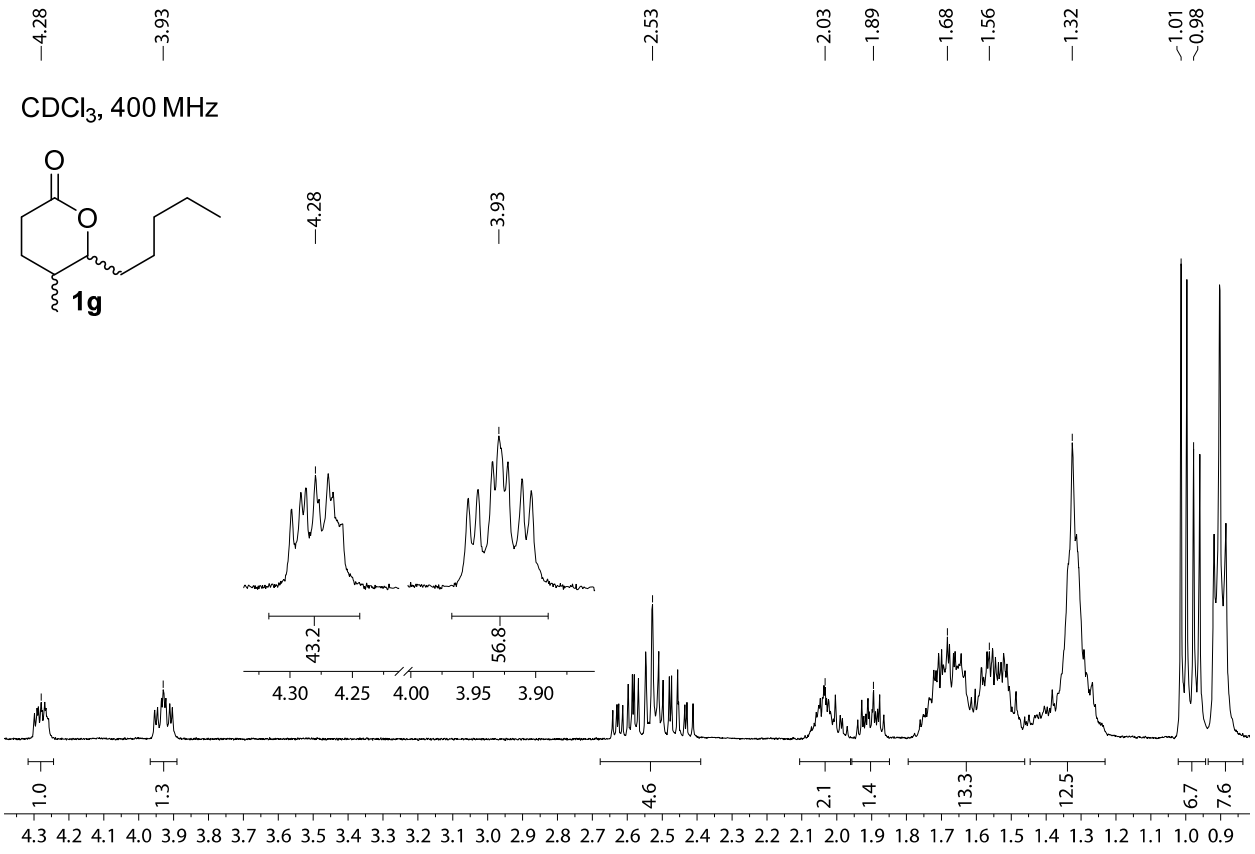

173.52
173.22
75.68
74.46
67.71
39.03
37.97
36.40
35.67
34.59
34.25
32.00
31.96
26.02
25.59
22.69
21.93
21.89
16.73
14.06
13.67
CDCl3, 100 MHz
32.00
31.96
21.93
21.89
32.1
32.0
31.9
22.0
21.9
21.8
21.7
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

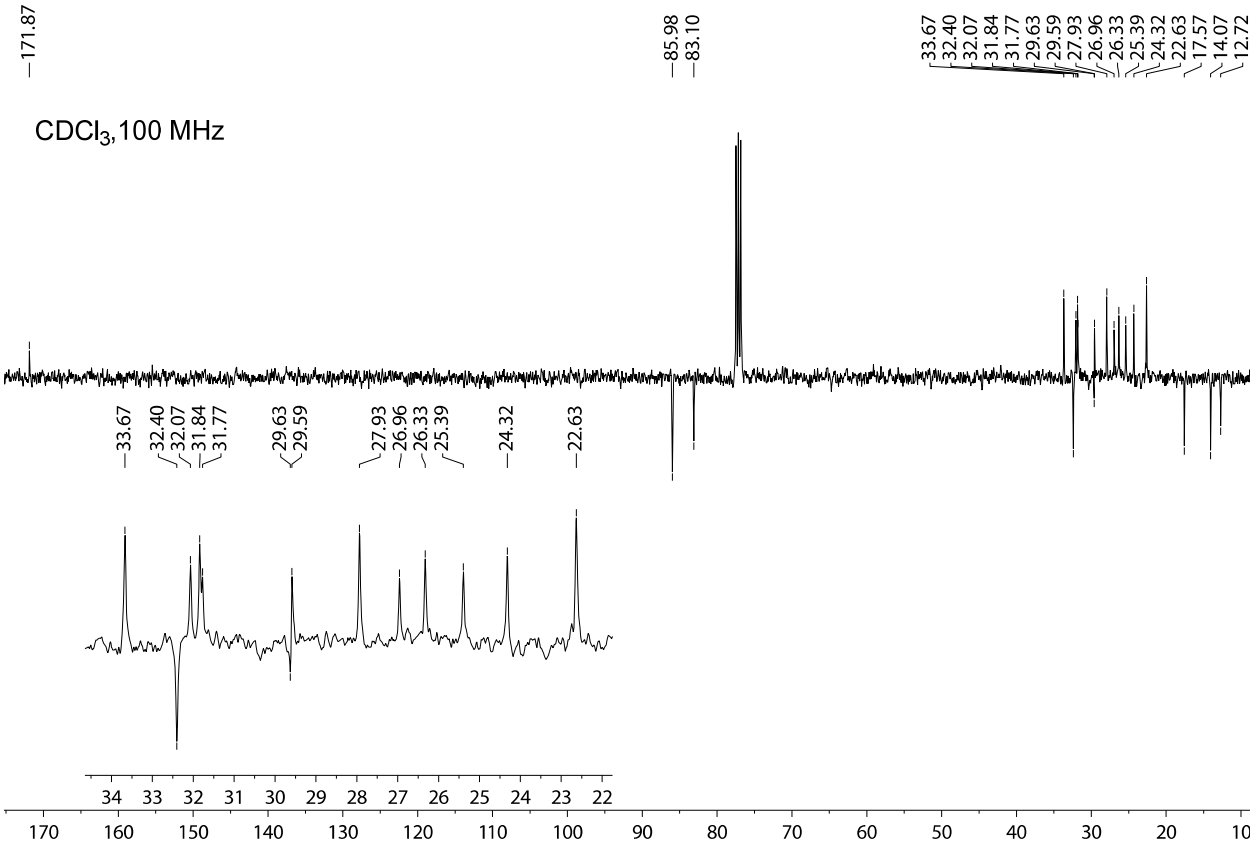

5.01
3.50
3.42
2.39
2.35
2.29
2.23
1.82
1.44
1.31
1.23
0.90
CDCl3, 400 MHz
OiPr
OH
O
syn-1g
anti-1g
57.9
42.1
1.0
0.6
0.4
2.1
1.1
10.4
6.2
6.3


173.65
75.75
74.43
67.60
38.52
38.02
34.50
33.87
32.78
32.56
32.03
32.00
28.57
27.20
26.03
25.75
22.70
21.89
15.42
14.03
13.42
CDCl3, 100 MHz


5.01
3.72
3.63
2.37
2.27
1.83
1.47
1.46
1.24
1.22
1.16
1.15
0.90
CDCl3, 400 MHz
OH
OiPr
syn-1h
anti-1h
1.0
0.5
0.5
2.1
1.0
3.1
6.2
3.1
3.1


173.65
71.43
70.64
67.64
39.86
39.49
32.75
32.49
27.87
27.74
21.91
20.19
19.88
14.77
14.02
CDCl3, 100 MHz


4.28
3.93
2.53
2.03
1.89
1.68
1.56
1.32
1.01
0.98
CDCl3, 400 MHz
1g
43.2
56.8
1.0
1.3
4.6
2.1
1.4
13.3
12.5
6.7
7.6


171.87
85.98
83.10
33.67
32.40
32.07
31.84
31.77
29.63
29.59
27.93
26.96
26.33
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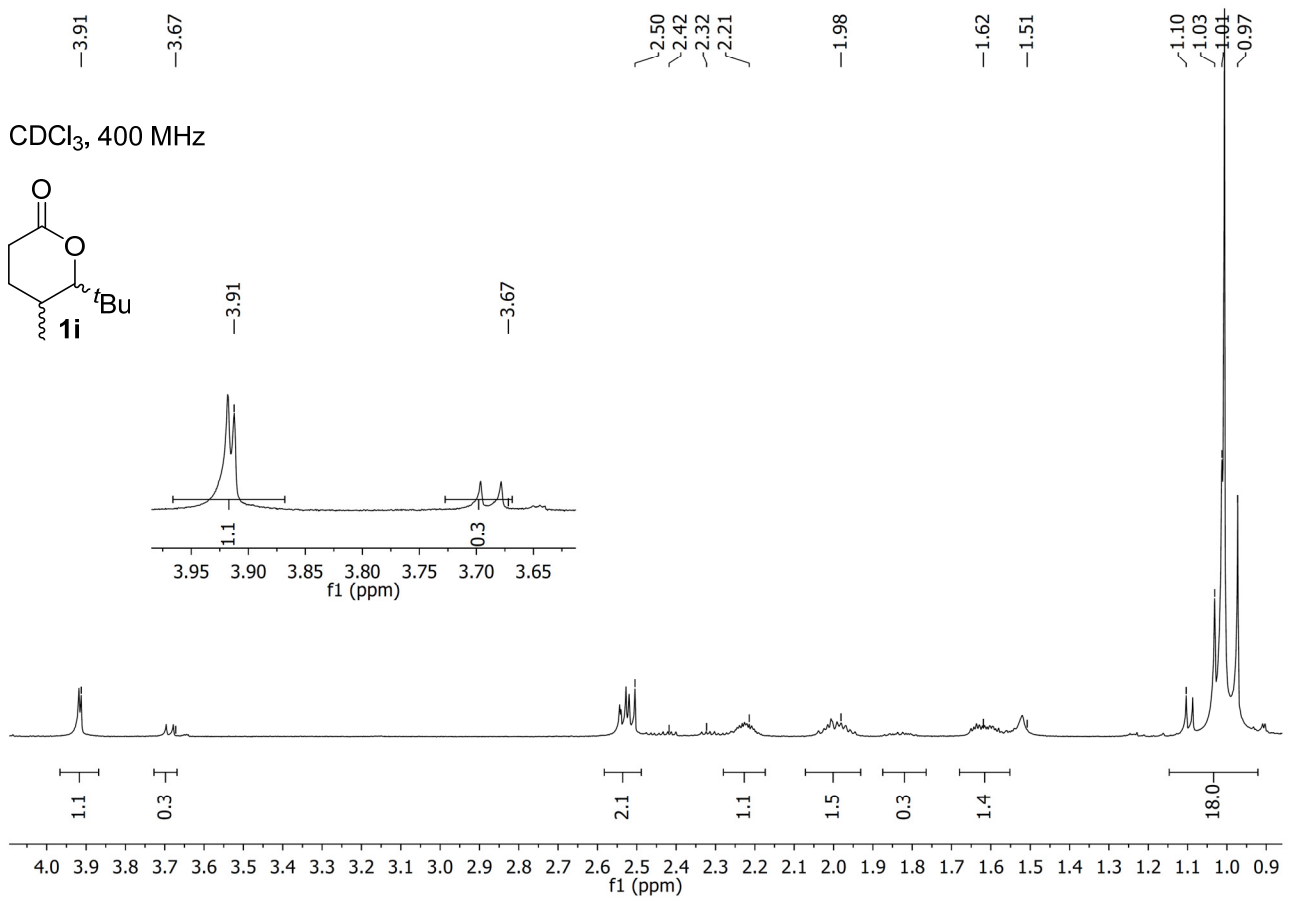
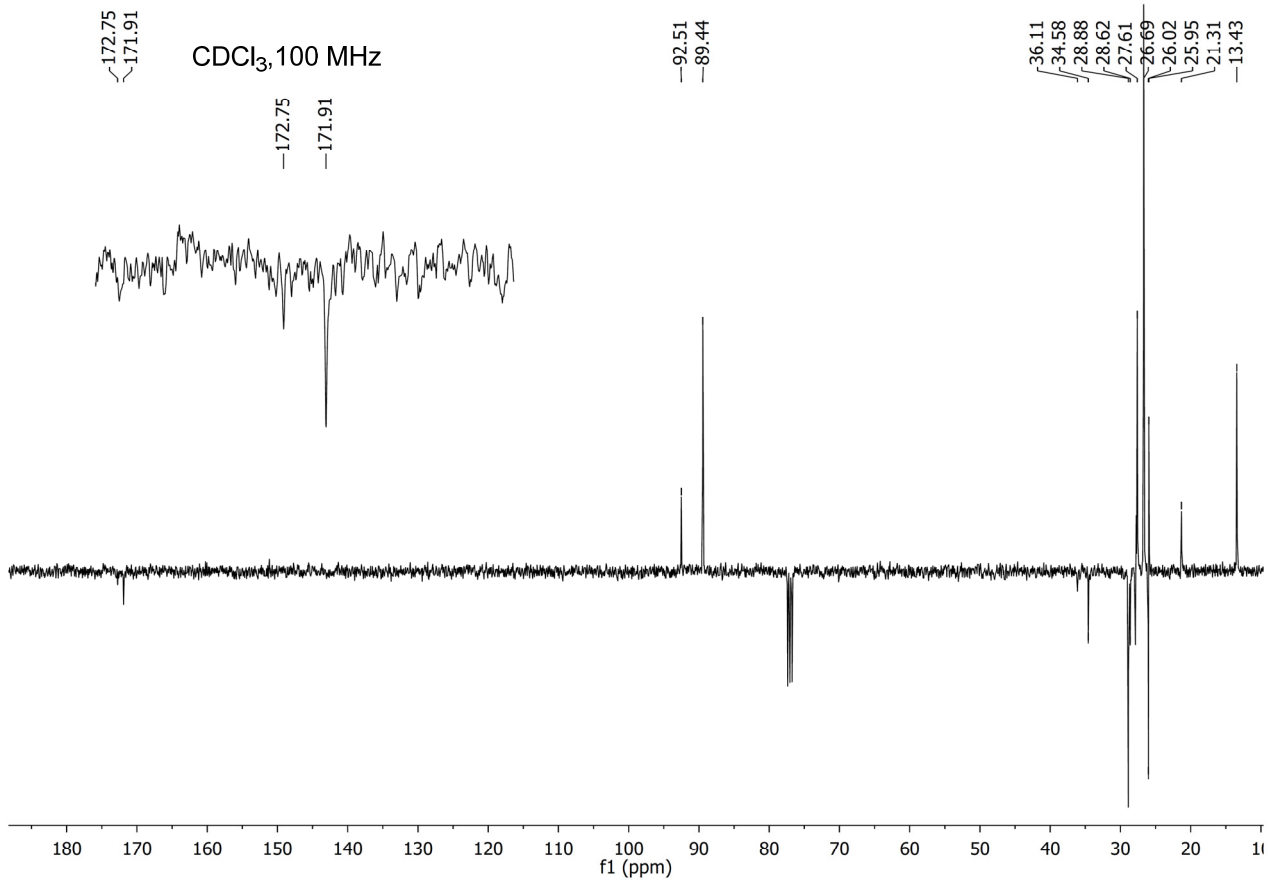
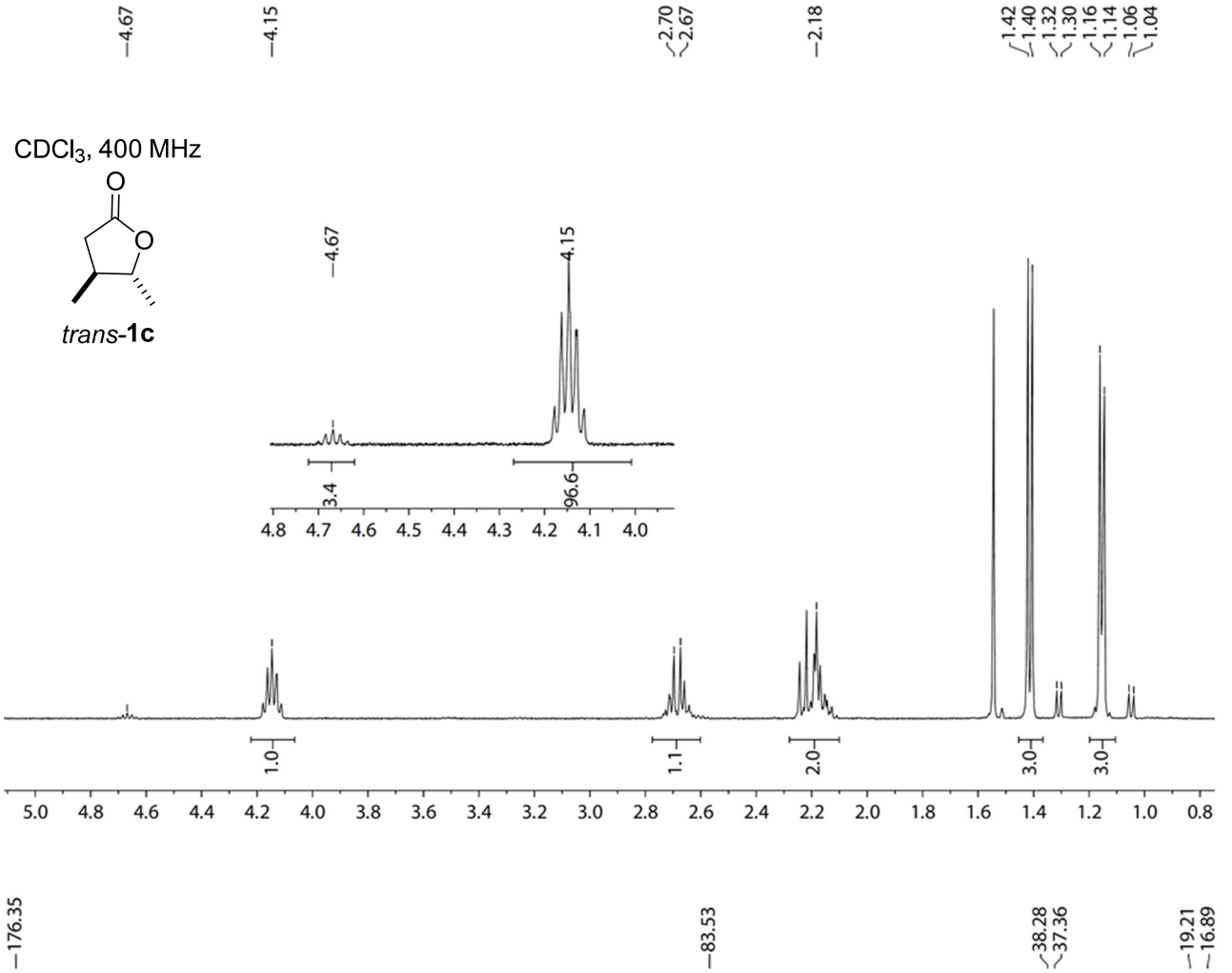
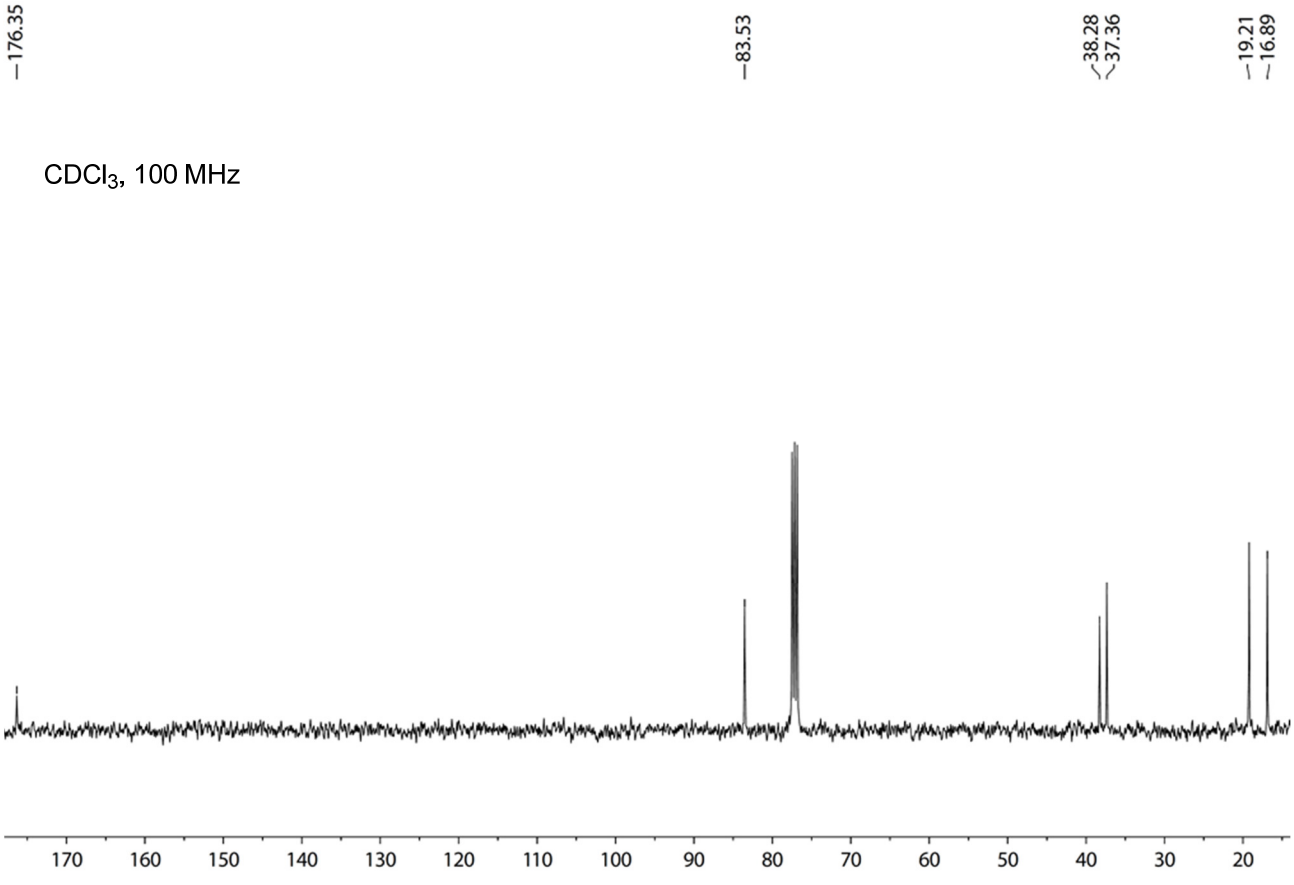
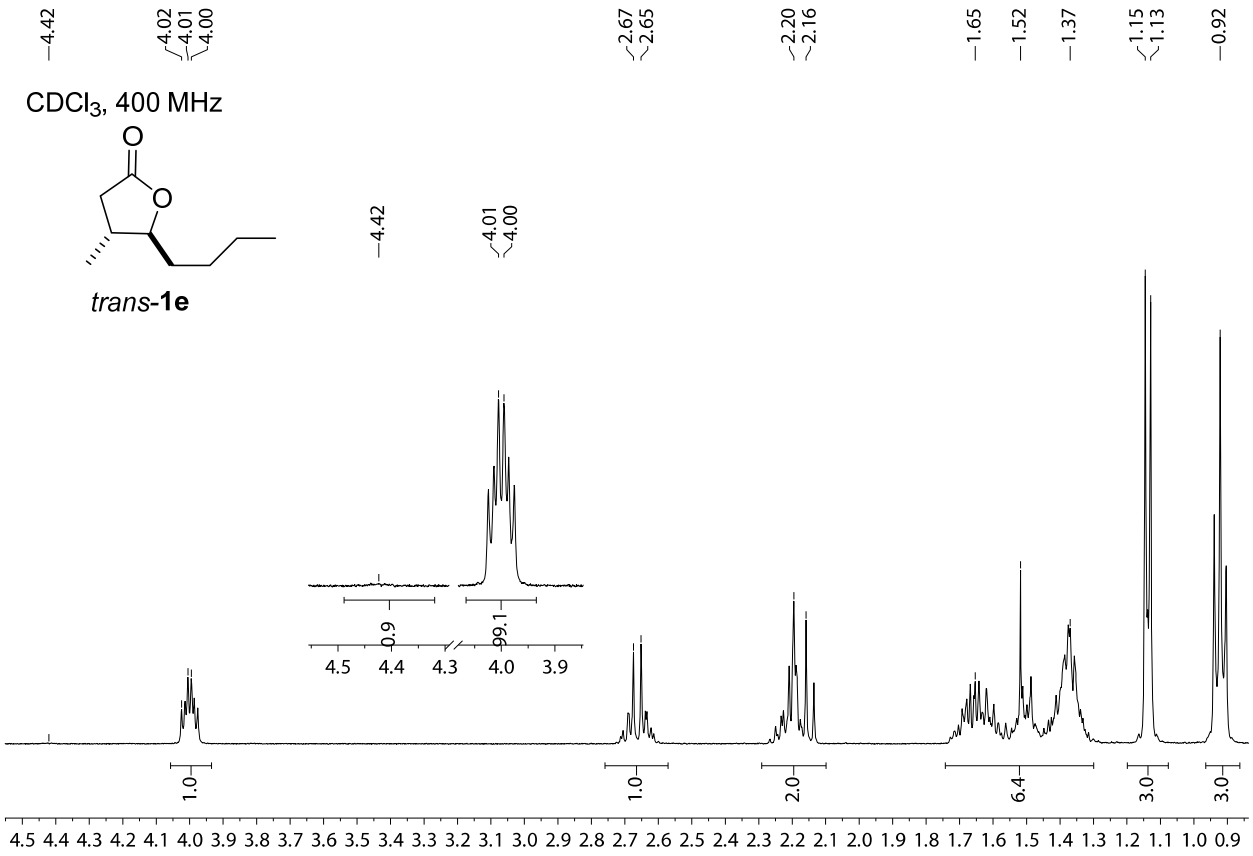
24.32
22.63
17.57
14.07
12.72
CDCl3,100 MHz

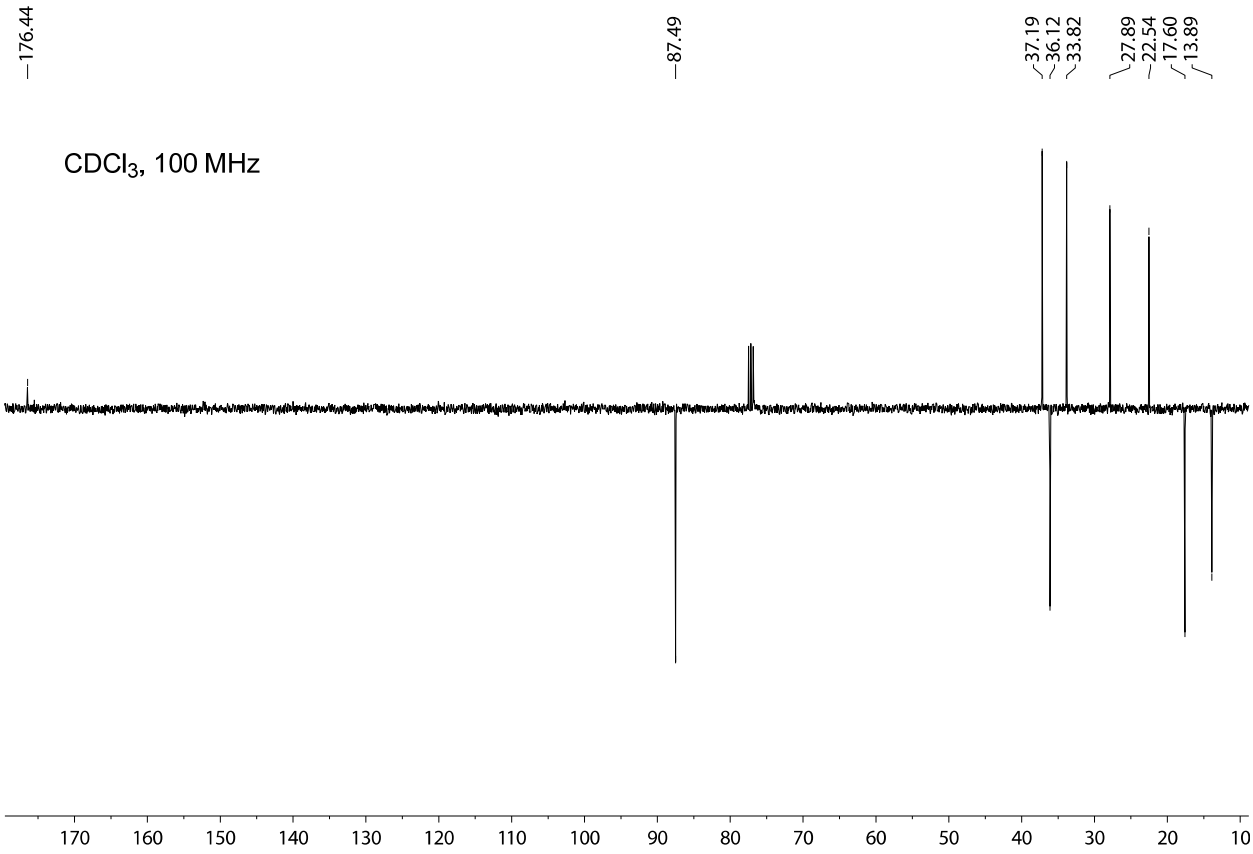

CDCl3, 400 MHz
1i
f1 (ppm)

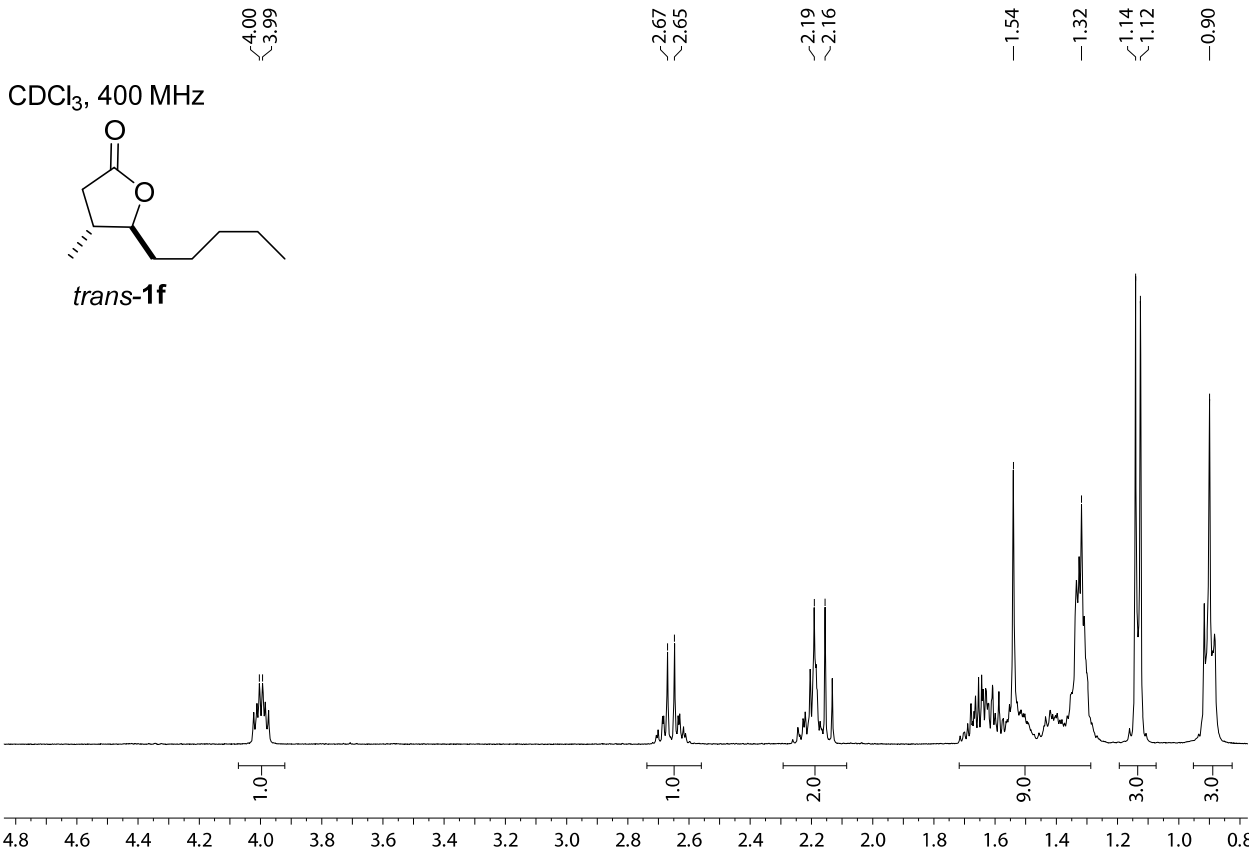

CDCl3,100 MHz
f1 (ppm)

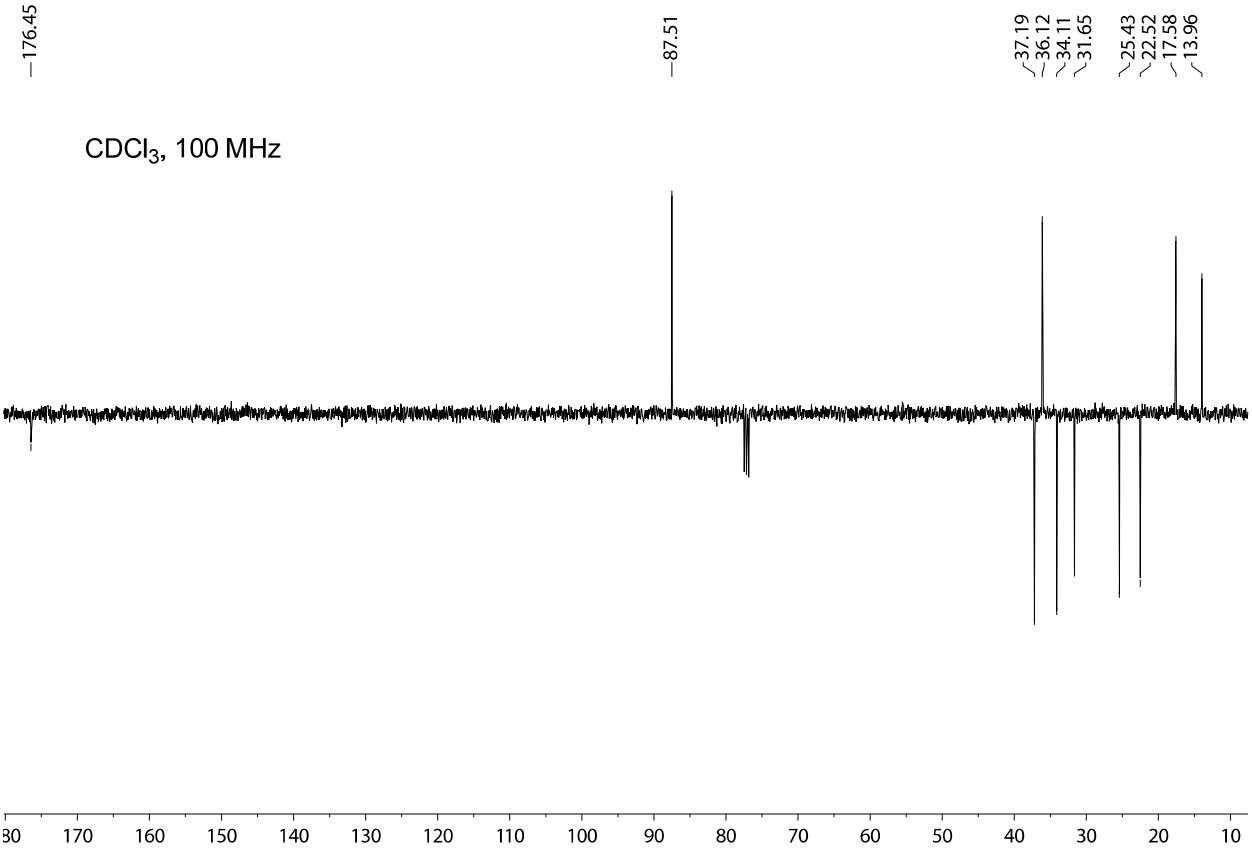

4.67
4.15
2.70
2.67
2.18
1.42
1.40
1.32
1.30
1.16
1.14
1.06
1.04
CDCl3, 400 MHz
trans-1c
3.4
96.6
1.0
1.1
2.0
3.0
3.0

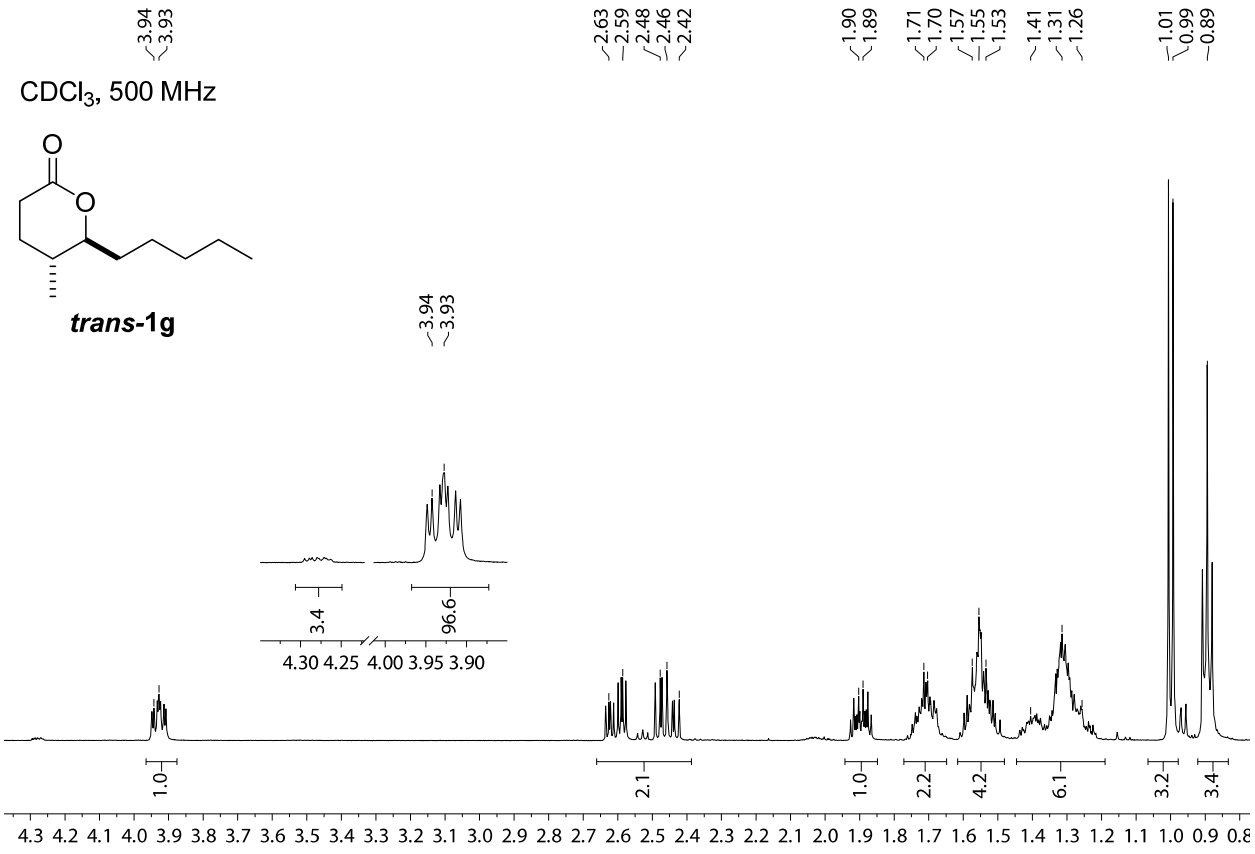

176.35
83.53
38.28
37.36
19.21
16.89
CDCl3, 100 MHz

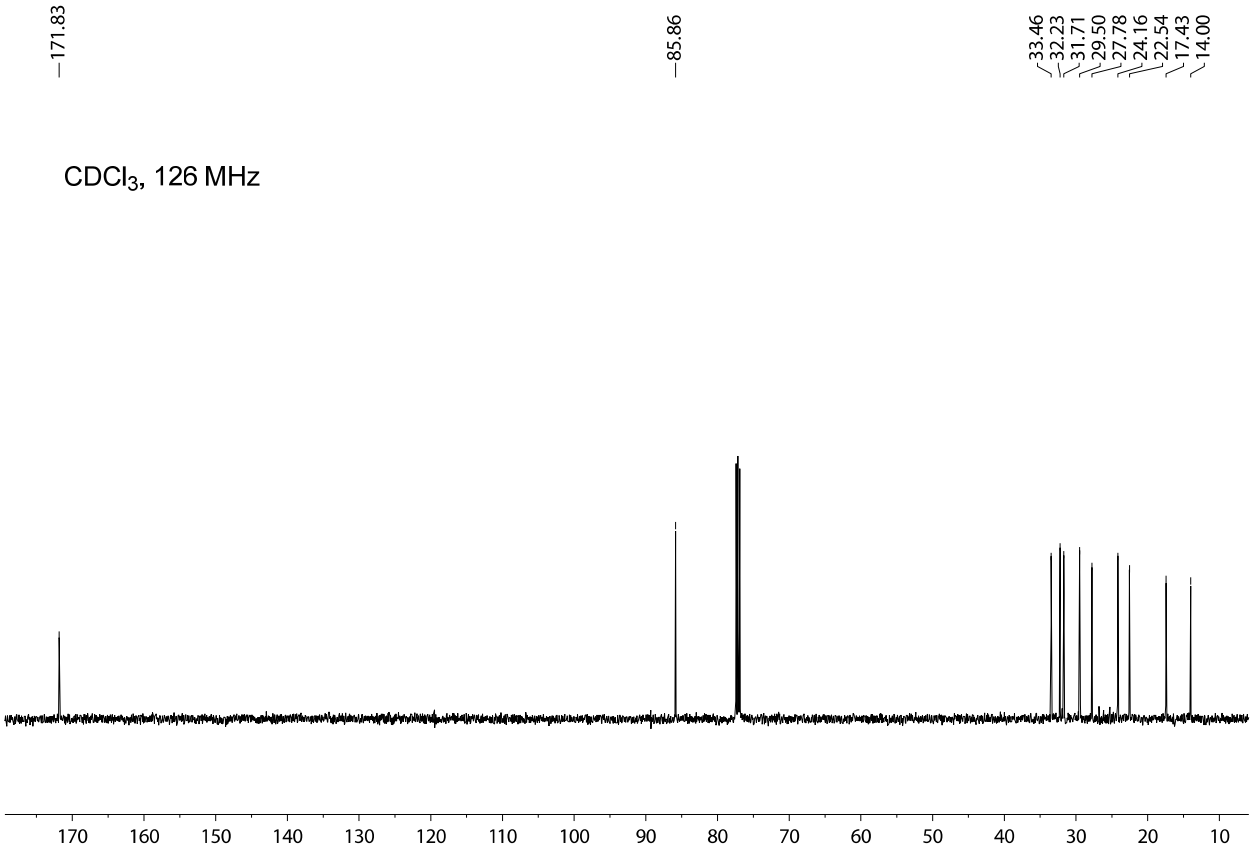

4.42
4.02
4.01
4.00
2.67
2.65
2.20
2.16
1.65
1.52
1.37
1.15
1.13
0.92
CDCl3, 400 MHz
O
O
trans-1e
4.42
4.01
4.00
0.9
99.1
4.5 4.4 4.3 4.0 3.9
1.0
1.0
2.0
6.4
3.0
3.0
4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9

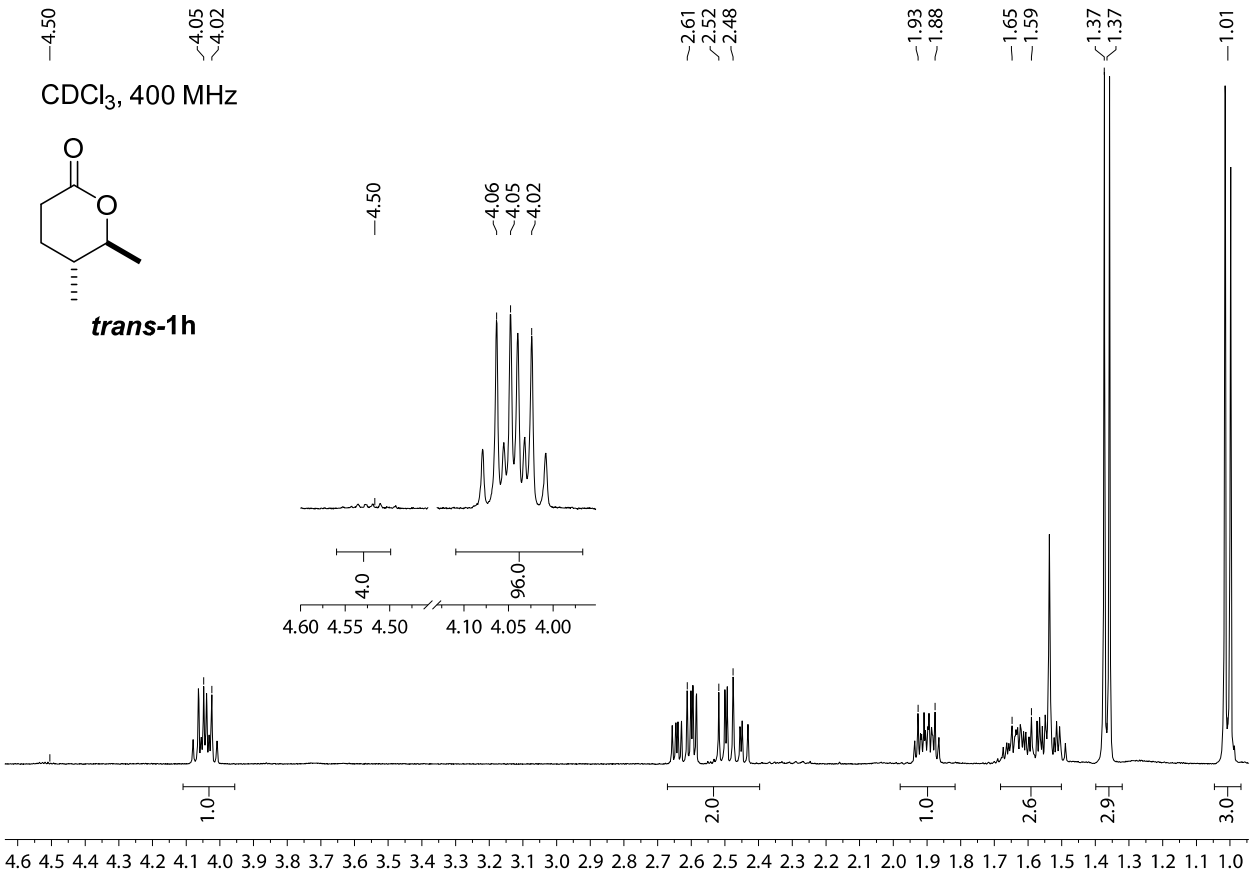

176.44
87.49
37.19
36.12
33.82
27.89
22.54
17.60
13.89
CDCl3, 100 MHz
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

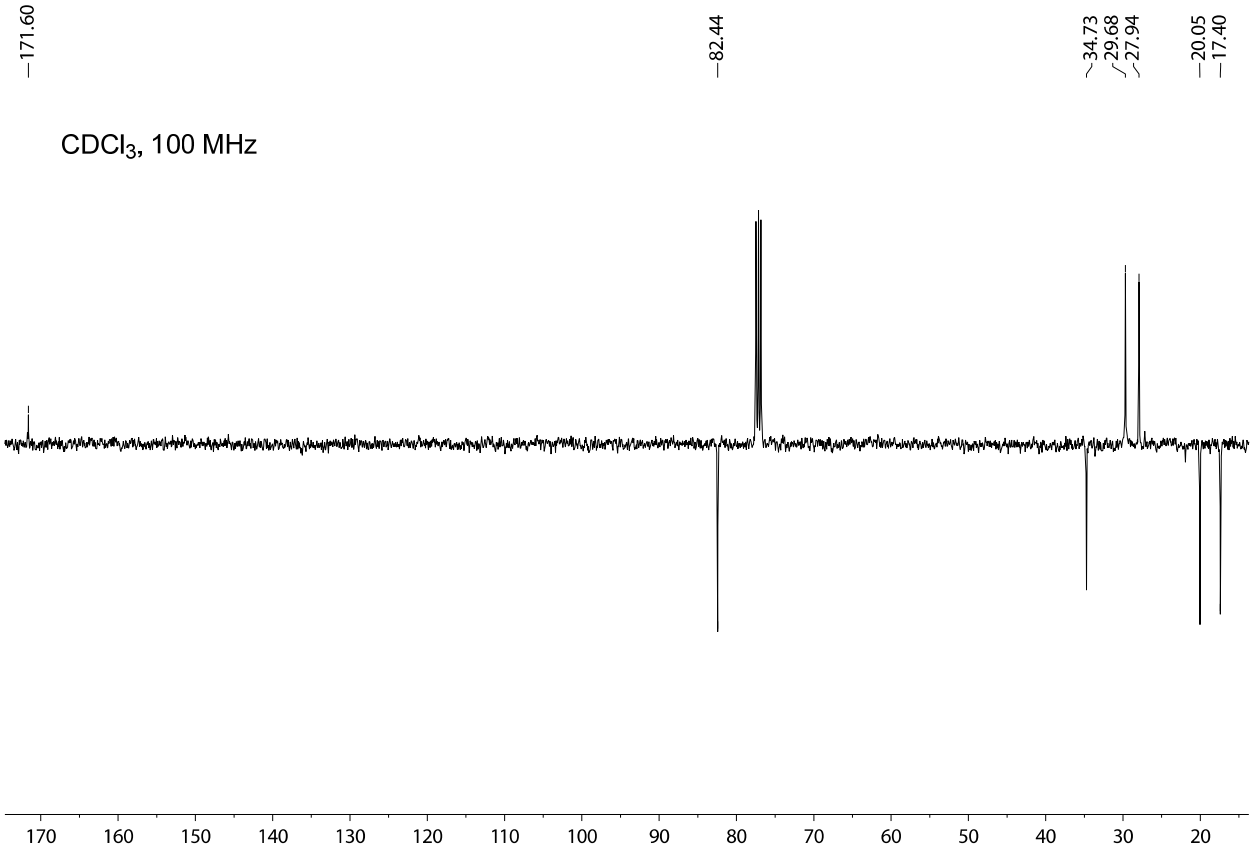

4.00
3.99
2.67
2.65
2.19
2.16
1.54
1.32
1.14
1.12
0.90
CDCl3, 400 MHz
O
O
trans-1f
1.0
1.0
2.0
9.0
3.0
3.0
4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0

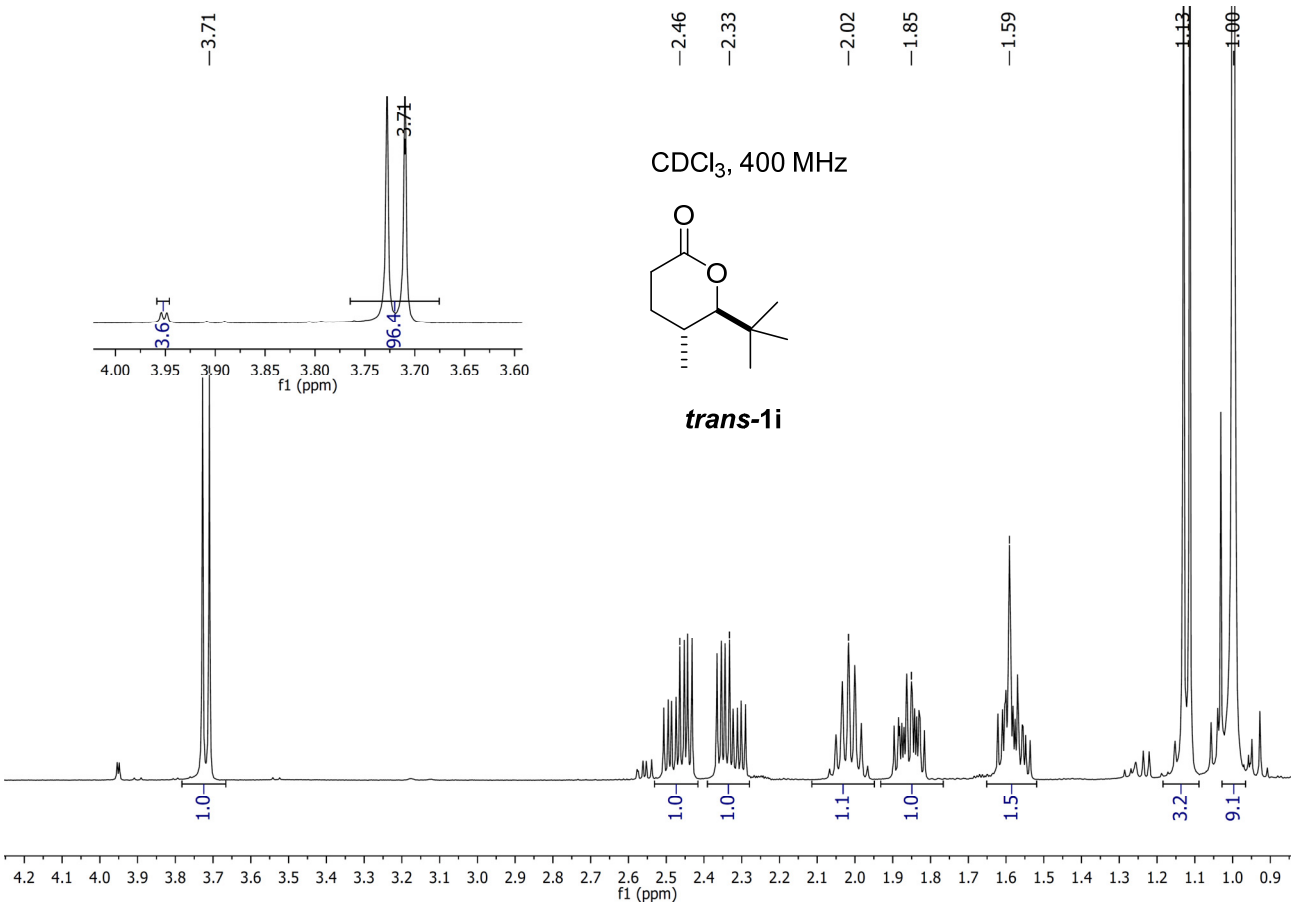

176.45
87.51
37.19
36.12
34.11
31.65
25.43
22.52
17.58
13.96
CDCl3, 100 MHz
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

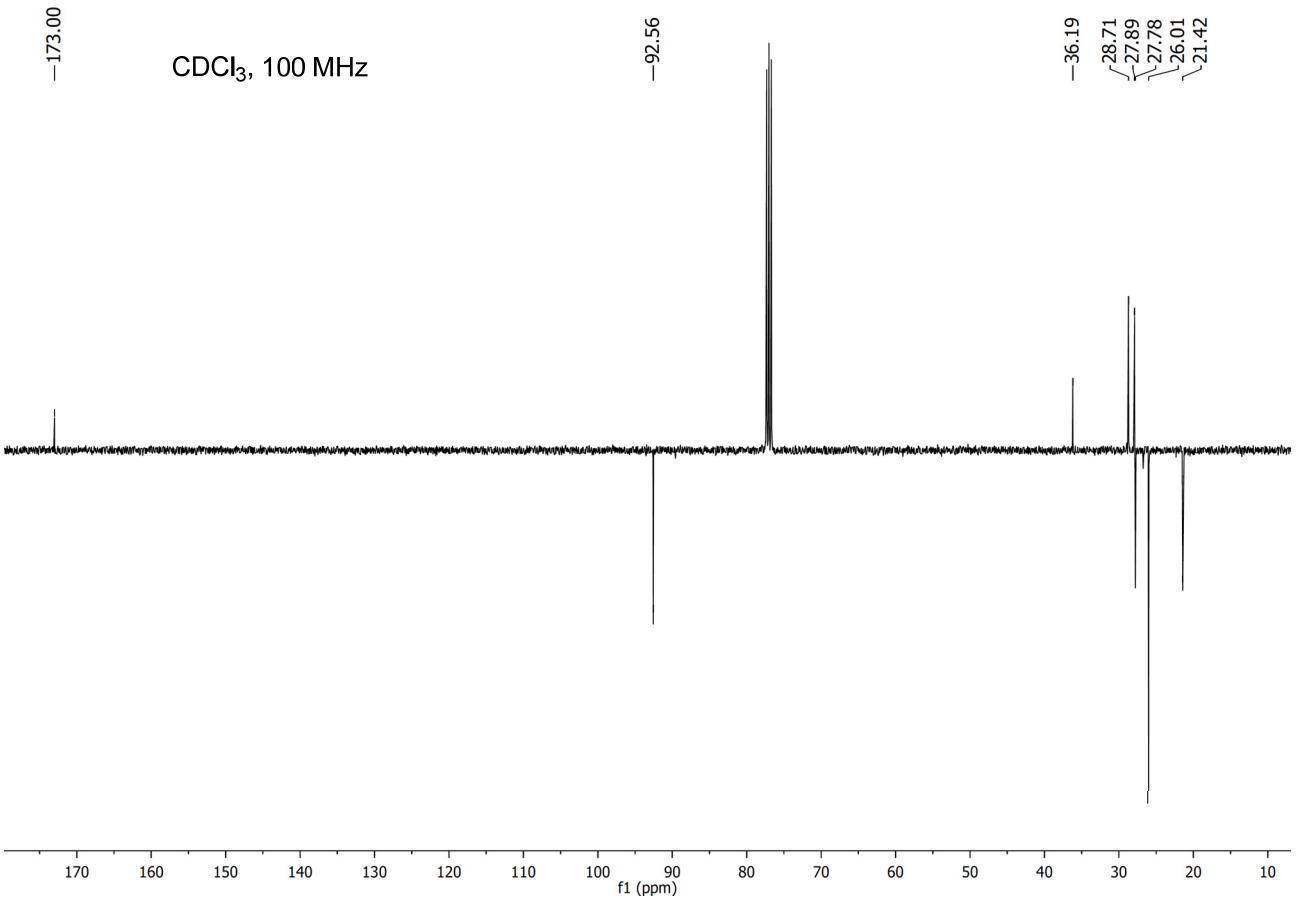

3.94
3.93
2.63
2.59
2.48
2.46
2.42
1.90
1.89
1.71
1.70
1.57
1.55
1.53
1.41
1.31
1.26
1.01
0.99
0.89
CDCl3, 500 MHz
trans-1g
3.4
96.6
4.30 4.25 4.00 3.95 3.90
1.0
2.1
1.0
2.2
4.2
6.1
3.2
3.4
4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9

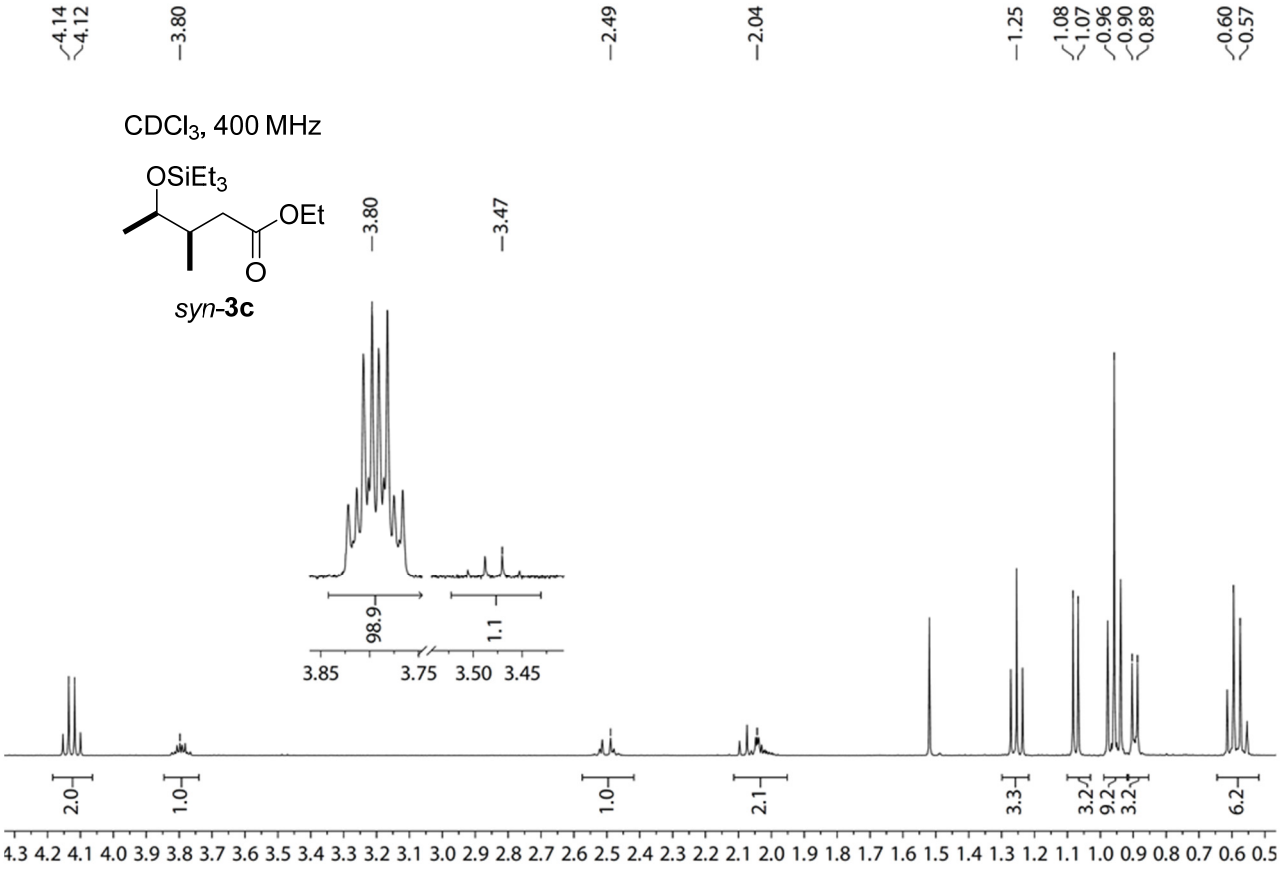

171.83
85.86
33.46
32.23
31.71
29.50
27.78
24.16
22.54
17.43
14.00
CDCl3, 126 MHz
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

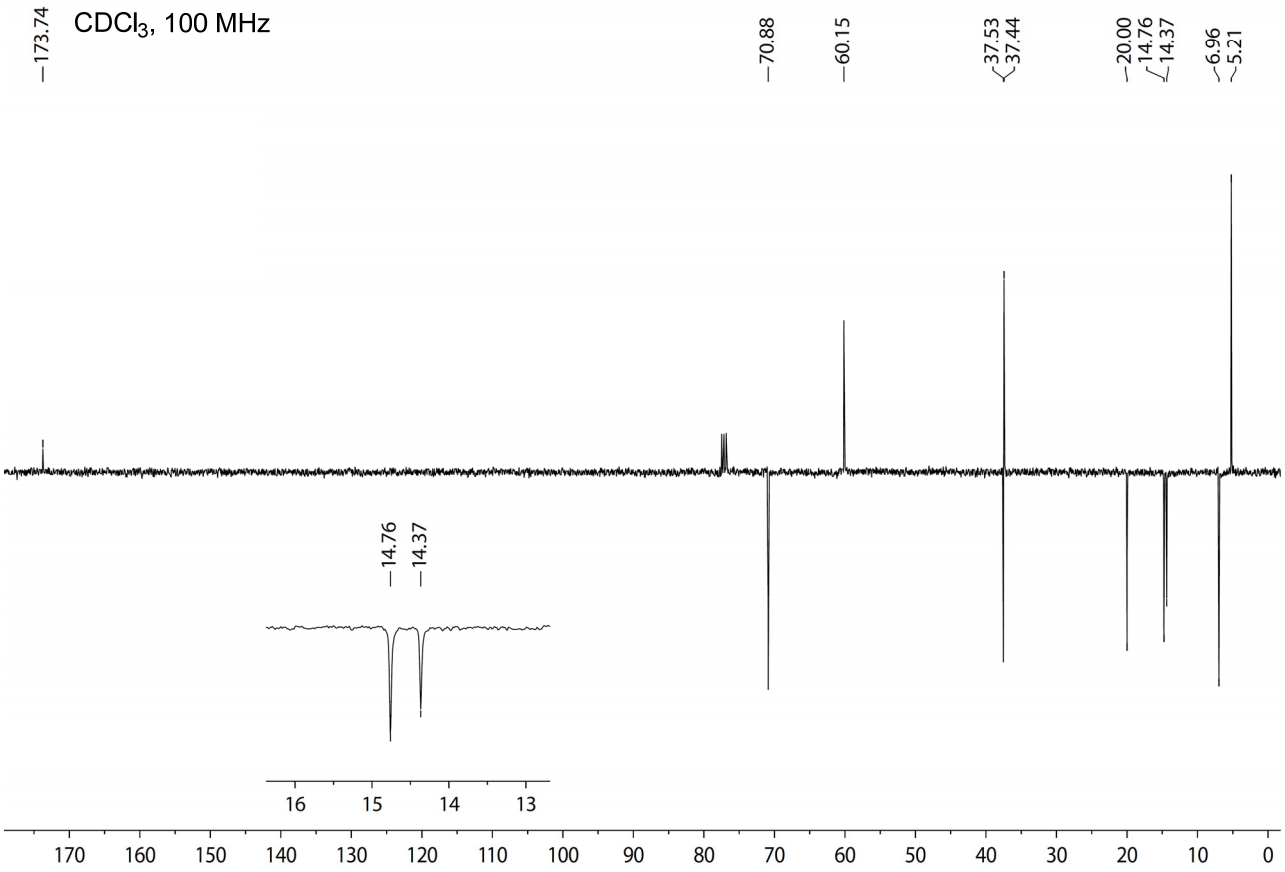

4.50
4.05
4.02
2.61
2.52
2.48
1.93
1.88
1.65
1.59
1.37
1.37
1.01
CDCl3, 400 MHz
trans-1h
4.50
4.06
4.05
4.02
4.0
96.0
4.60 4.55 4.50
4.10 4.05 4.00
1.0
2.0
1.0
2.6
2.9
3.0
4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0

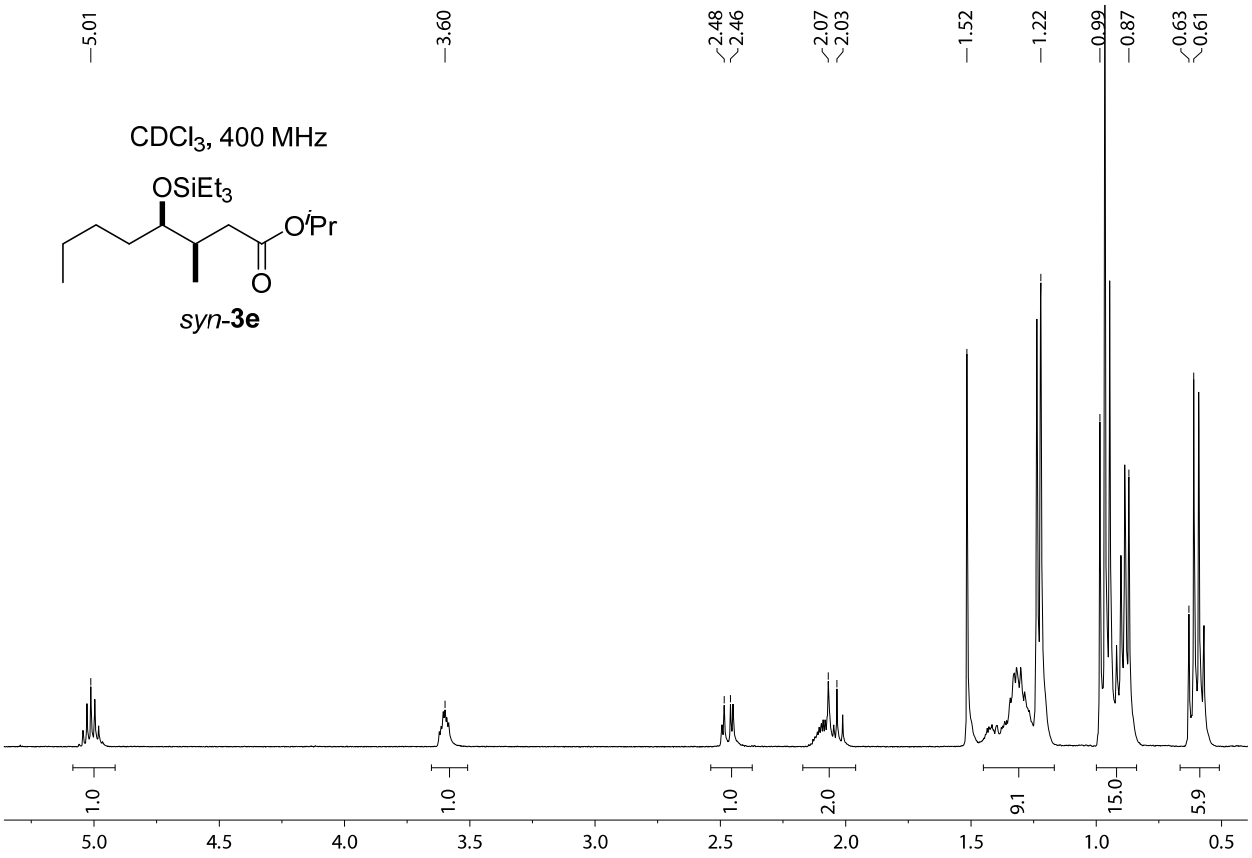

171.60
82.44
34.73
29.68
27.94
20.05
17.40
CDCl3, 100 MHz
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20

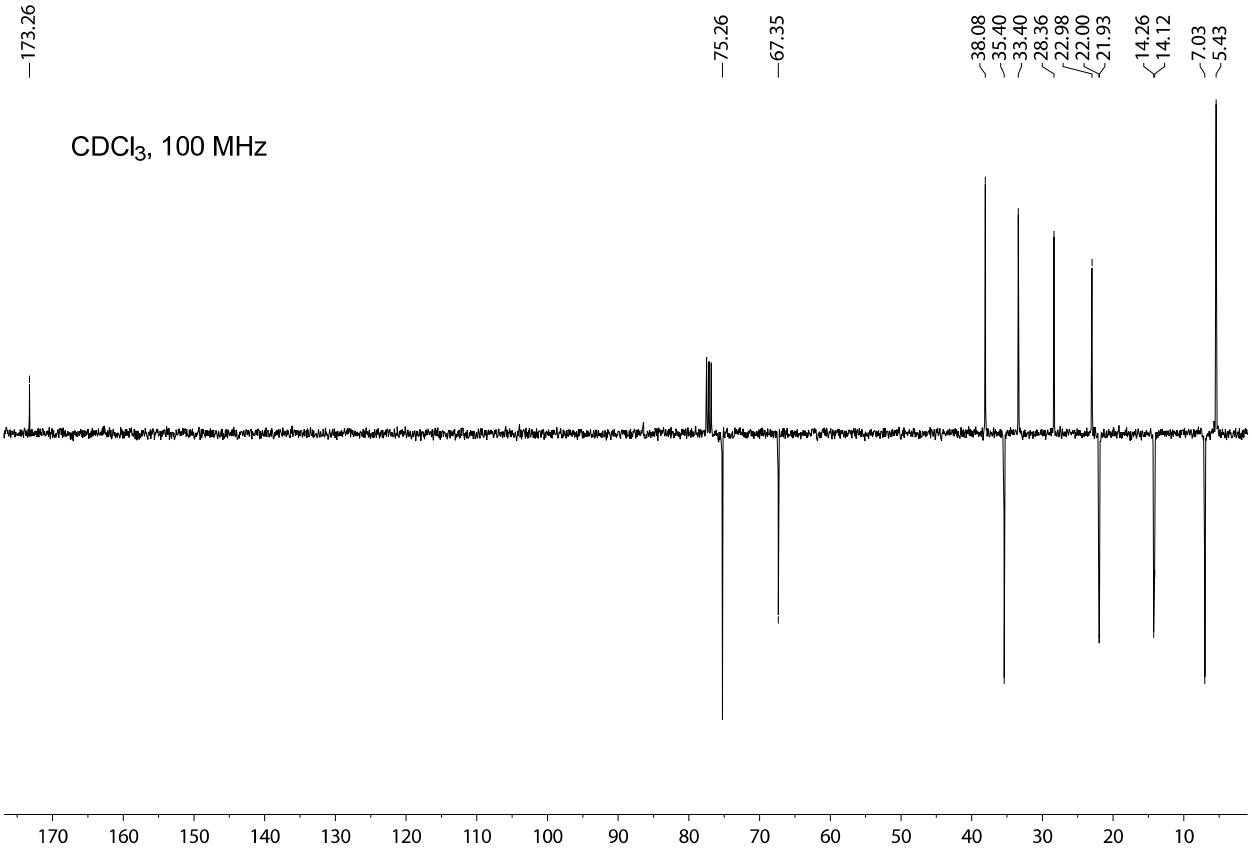

3.71
2.46
2.33
2.02
1.85
1.59
1.13
1.00
CDCl3, 400 MHz
O
O
trans-1i
3.6
96.4
f1 (ppm)
1.0
1.0
1.0
1.1
1.0
1.5
3.2
9.1
f1 (ppm)

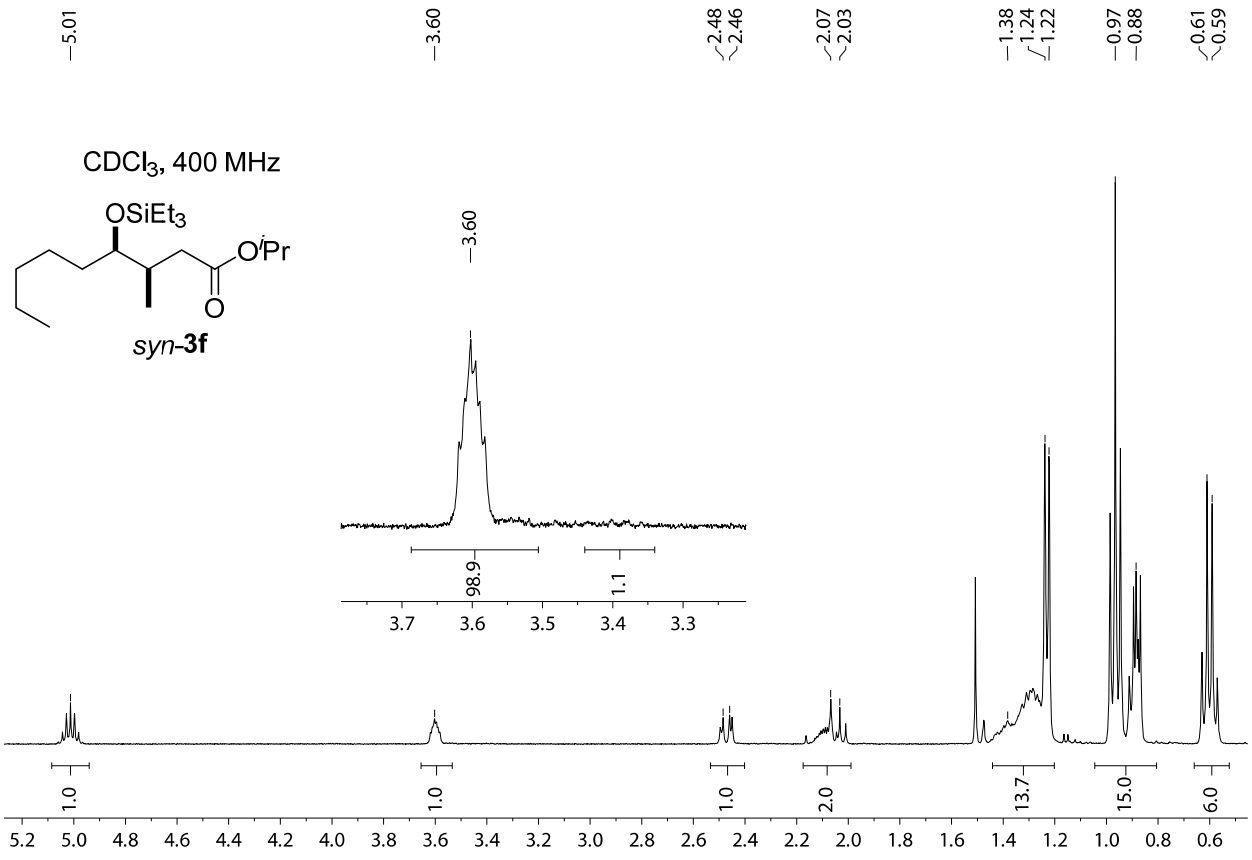

173.00
CDCl3, 100 MHz
92.56
36.19
28.71
27.89
27.78
26.01
21.42
f1 (ppm)

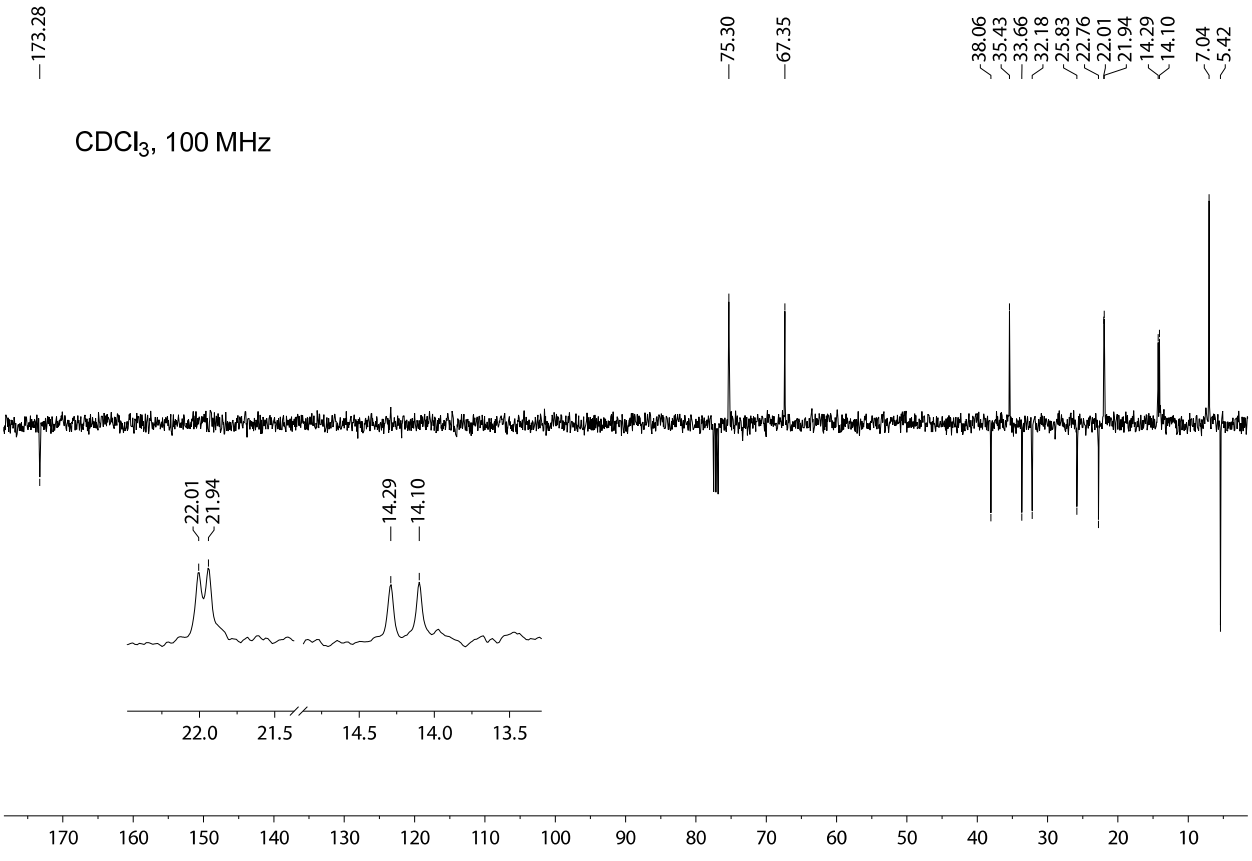

4.14
4.12
3.80
2.49
2.04
1.25
1.08
1.07
0.96
0.90
0.89
0.60
0.57
CDCl3, 400 MHz
OSiEt3
OEt
O
syn-3c
3.80
3.47
98.9
1.1
3.85
3.75
3.50
3.45
2.0
1.0
1.0
2.1
3.3
3.2
9.2
3.2
6.2
4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7 0.6 0.5

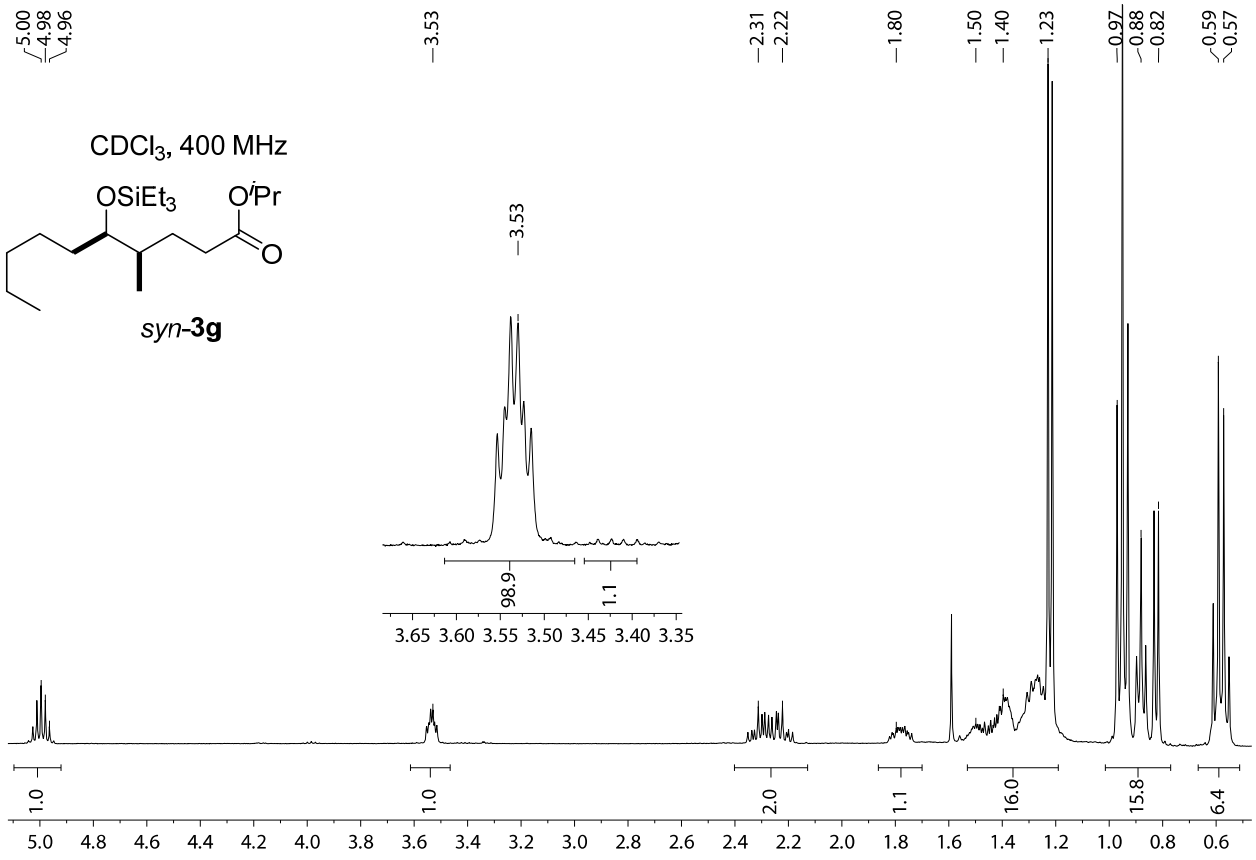

173.74
CDCl3, 100 MHz
70.88
60.15
37.53
37.44
20.00
14.76
14.37
6.96
5.21
14.76
14.37
16
15
14
13
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

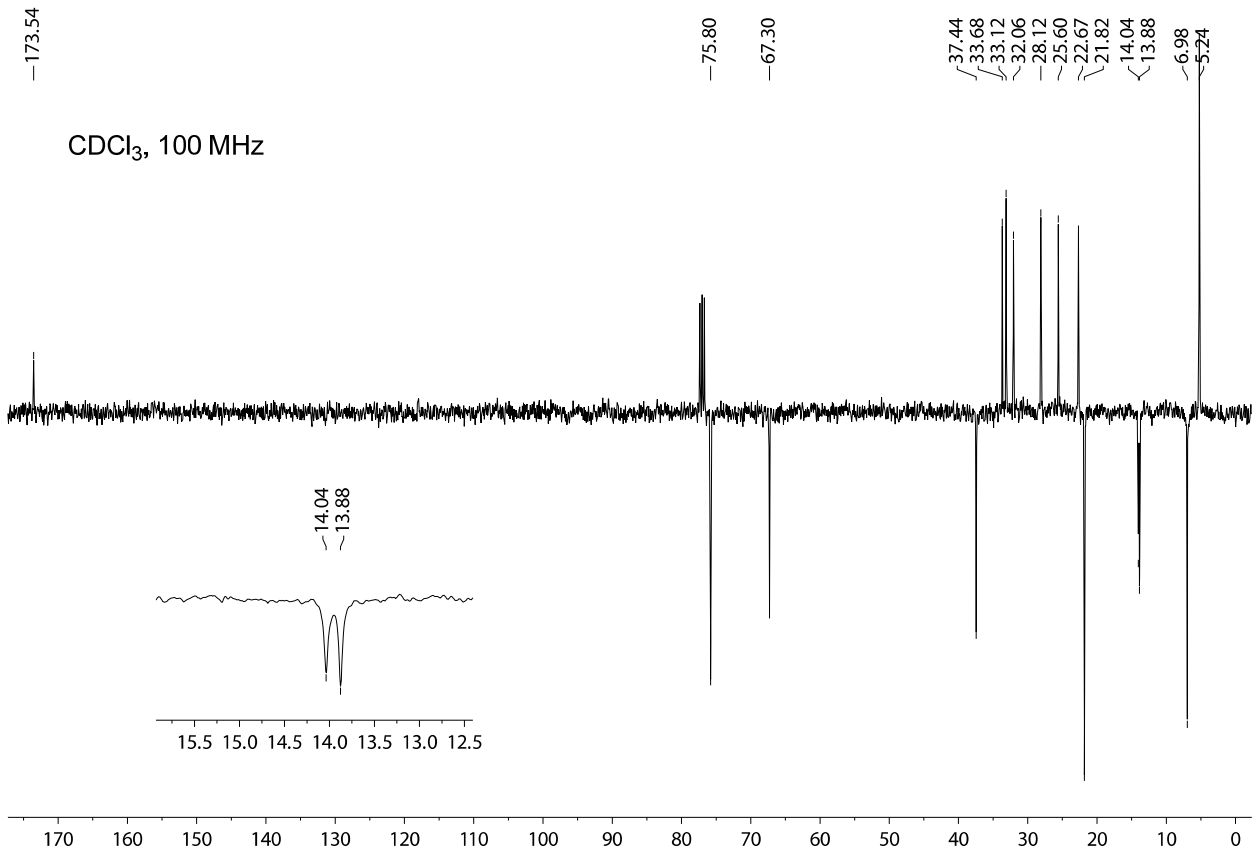

5.01
3.60
2.48
2.46
2.07
2.03
1.52
1.22
0.99
0.87
0.63
0.61
CDCl3, 400 MHz
OSiEt3
OiPr
O
syn-3e
1.0
1.0
1.0
2.0
9.1
15.0
5.9
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

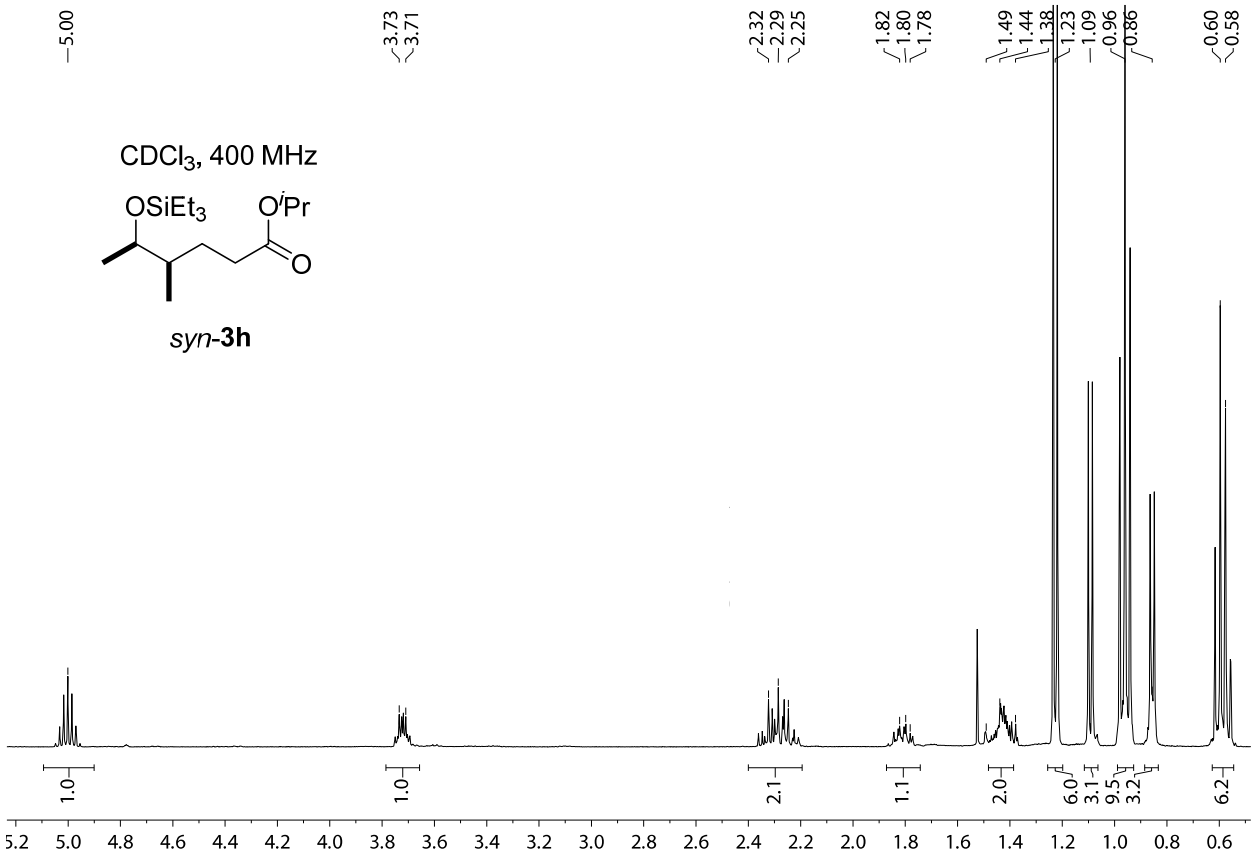

173.26
75.26
67.35
38.08
35.40
33.40
28.36
22.98
22.00
21.93
14.26
14.12
7.03
5.43
CDCl3, 100 MHz
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

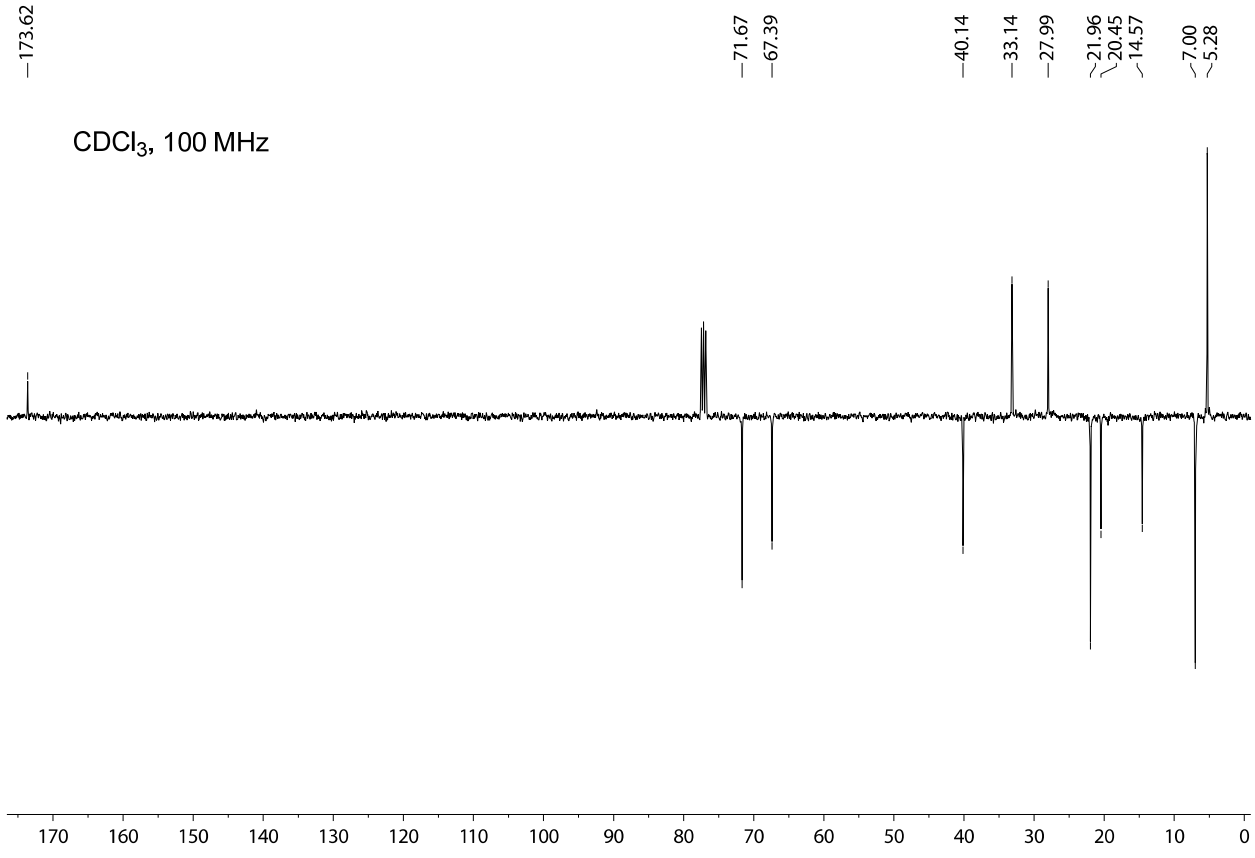

5.01
3.60
2.48
2.46
2.07
2.03
1.38
1.24
1.22
0.97
0.88
0.61
0.59
CDCl3, 400 MHz
OSiEt3
OiPr
O
syn-3f
98.9
1.1
1.0
1.0
1.0
2.0
13.7
15.0
6.0

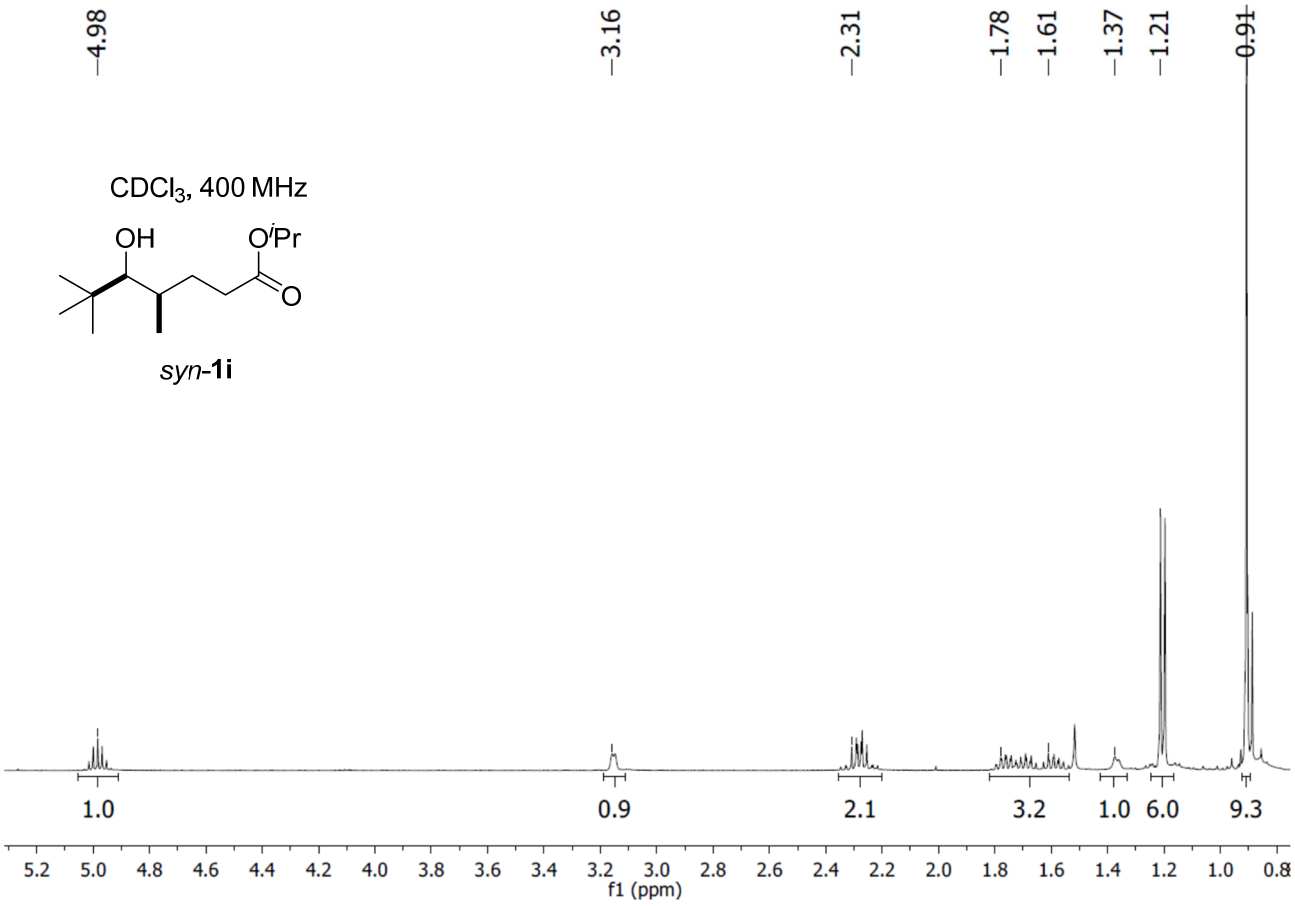

173.28
75.30
67.35
38.06
35.43
33.66
32.18
25.83
22.76
22.01
21.94
14.29
14.10
7.04
5.42
CDCl3, 100 MHz


5.00
4.98
4.96
3.53
2.31
2.22
1.80
1.50
1.40
1.23
0.97
0.88
0.82
0.59
0.57
CDCl3, 400 MHz
OSiEt3
OiPr
O
syn-3g
98.9
1.1
1.0
1.0
2.0
1.1
16.0
15.8
6.4


173.54
75.80
67.30
37.44
33.68
33.12
32.06
28.12
25.60
22.67
21.82
14.04
13.88
6.98
5.24
CDCl3, 100 MHz
14.04
13.88


5.00
3.73
3.71
2.32
2.29
2.25
1.82
1.80
1.78
1.49
1.44
1.38
1.23
1.09
0.96
0.86
0.60
0.58
CDCl3, 400 MHz
OSiEt3
OiPr
O
syn-3h
1.0
1.0
2.1
1.1
2.0
6.0
3.1
9.5
3.2
6.2
5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6


173.62
71.67
67.39
40.14
33.14
27.99
21.96
20.45
14.57
7.00
5.28
CDCl3, 100 MHz
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0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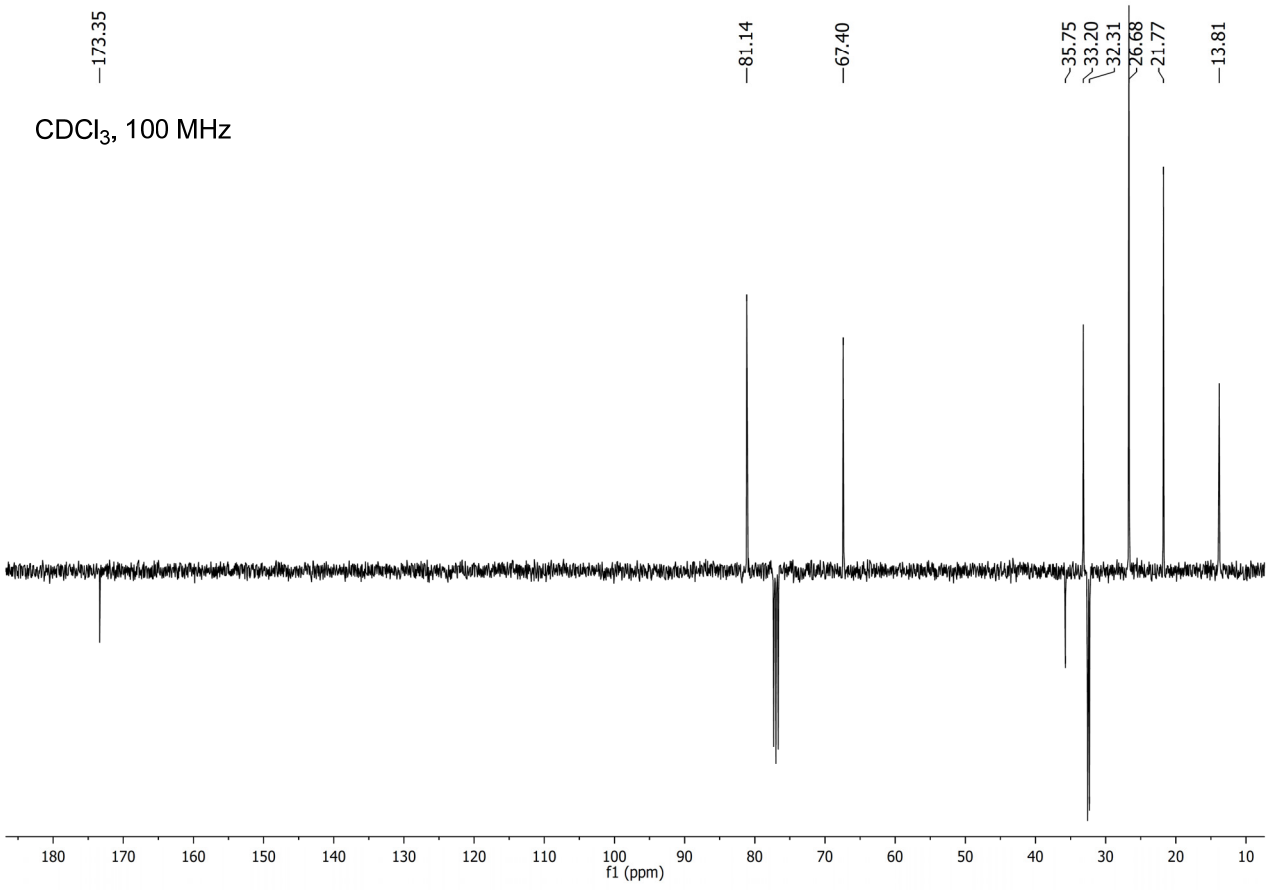
2.31
1.78
1.61
1.37
1.21
0.91
CDCl3, 400 MHz
OH
OiPr
O
1.0
0.9
2.1
3.2
1.0
6.0
9.3
5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f1 (ppm)

syn-**1i**


173.35
81.14
67.40
35.75
33.20
32.31
26.68
21.77
13.81
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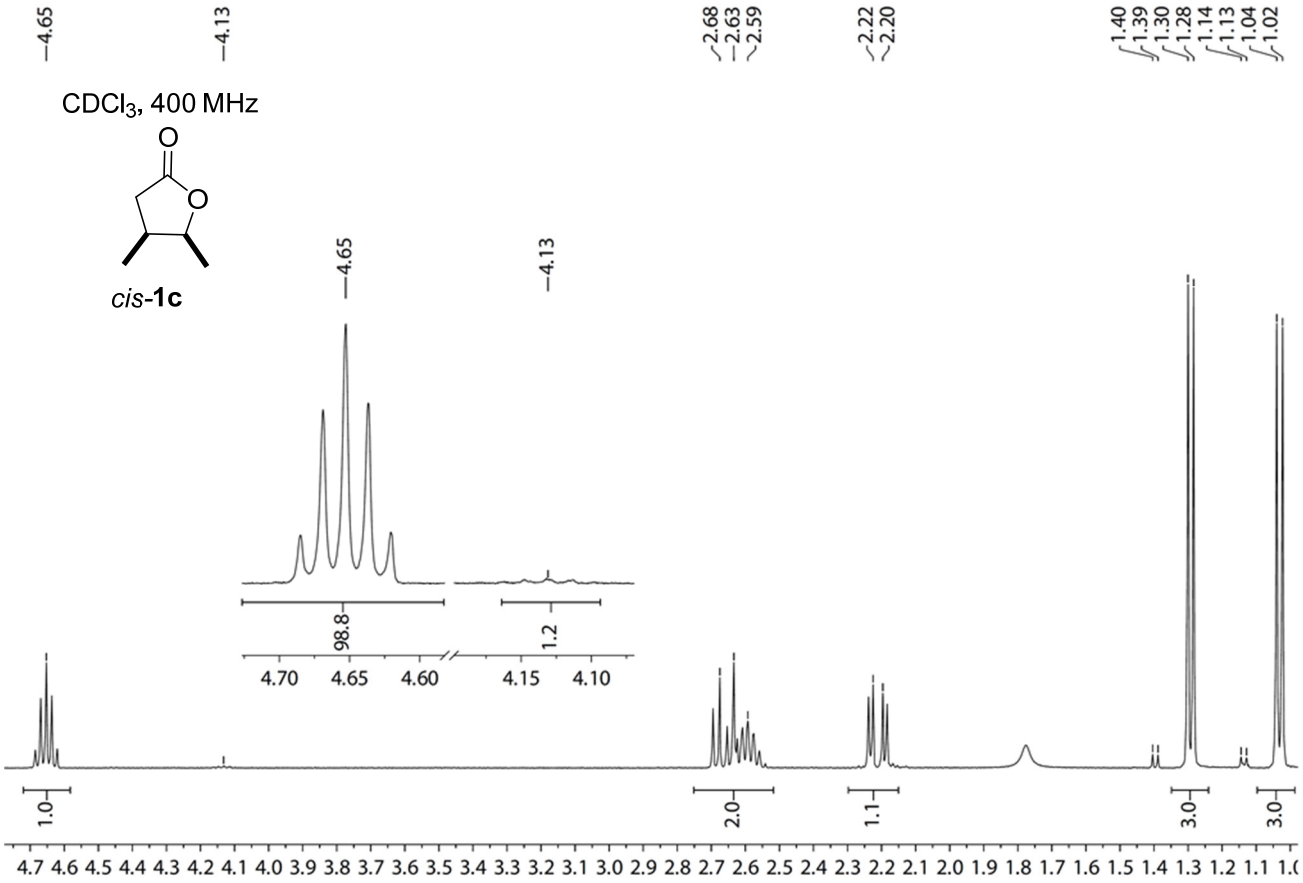
f1 (ppm)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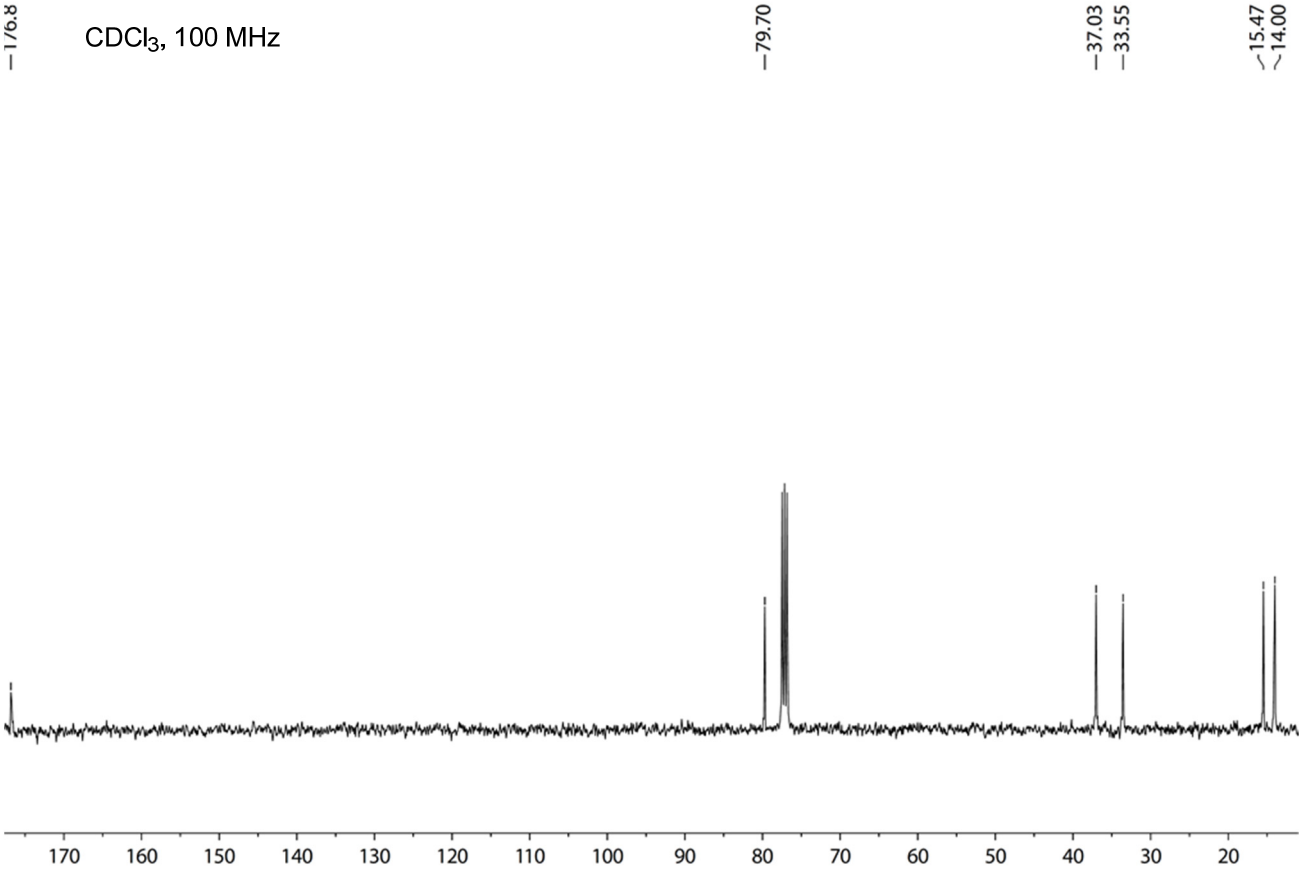
4.13
2.68
2.63
2.59
2.22
2.20
1.40
1.39
1.30
1.28
1.14
1.13
1.04
1.02
CDCl3, 400 MHz
cis-1c
98.8
1.2
1.0
2.0
1.1
3.0
3.0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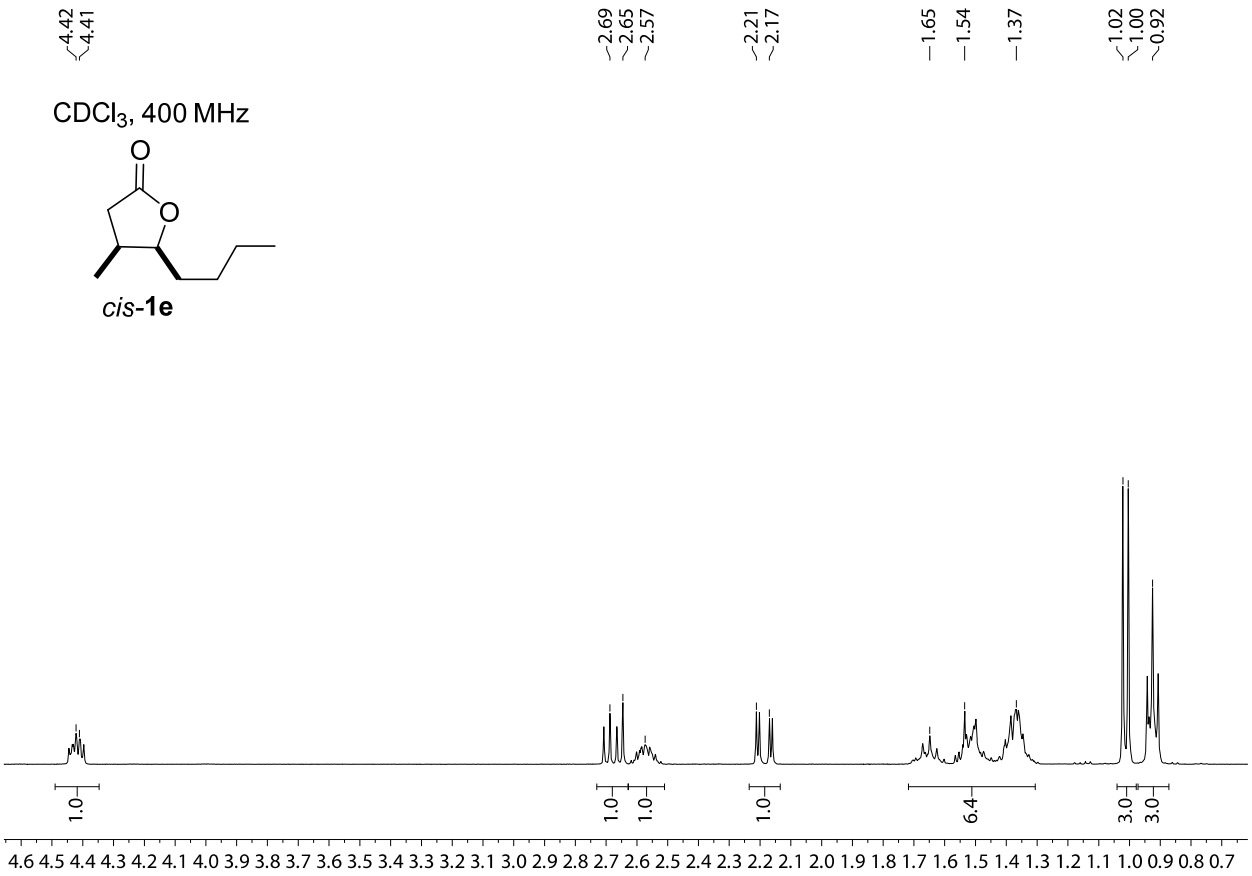
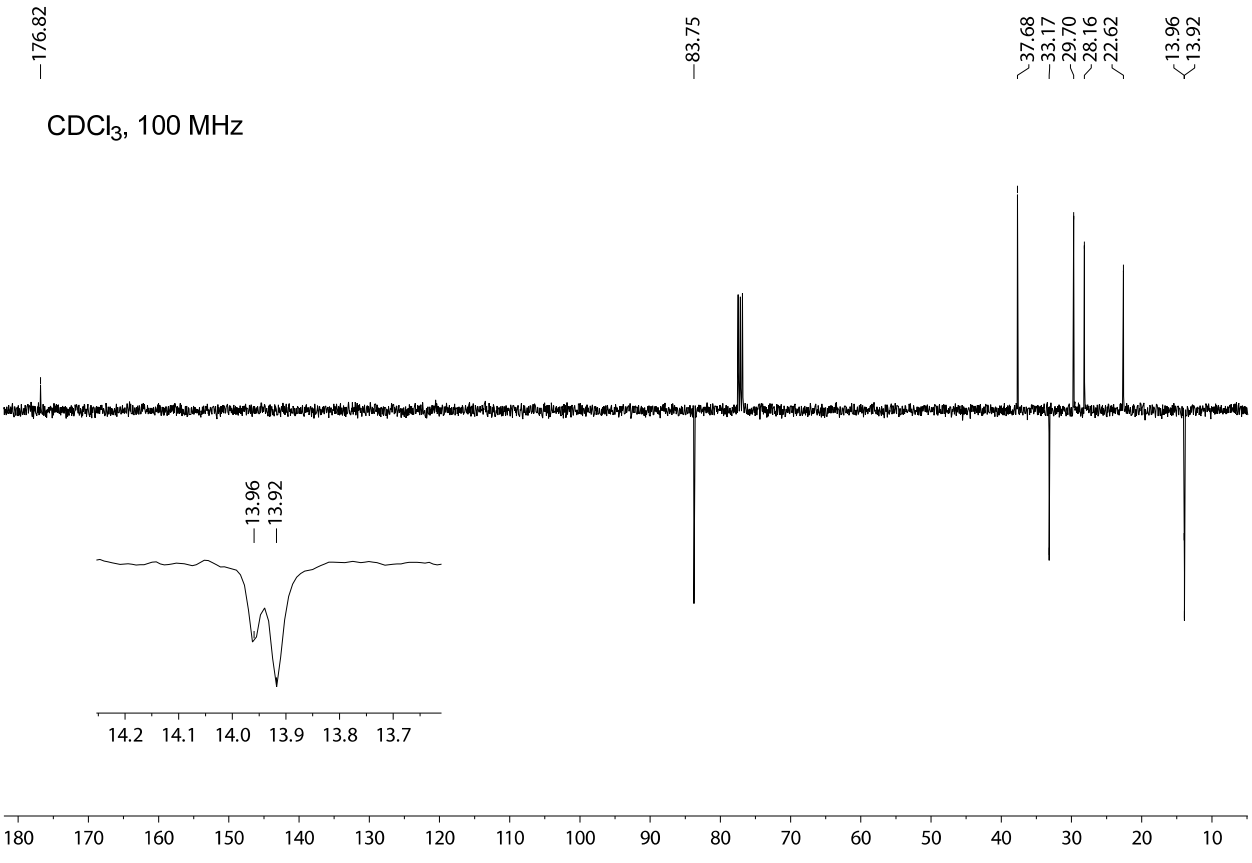
33.55
15.47
14.00


4.42
4.41
2.69
2.65
2.57
2.21
2.17
1.65
1.54
1.37
1.02
1.00
0.92
CDCl3, 400 MHz
O
O
cis-1e
1.0
1.0
1.0
1.0
6.4
3.0
3.0
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 0.7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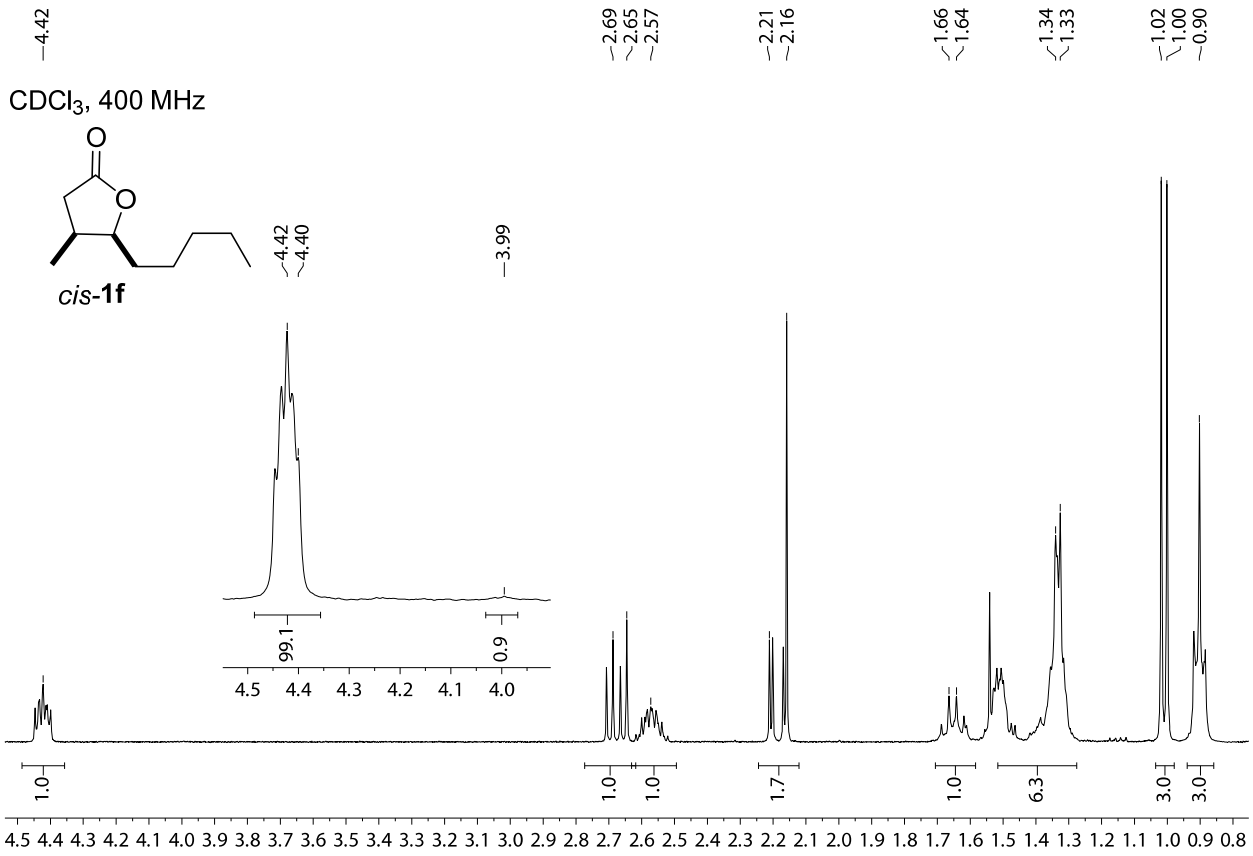
83.75
37.68
33.17
29.70
28.16
22.62
13.96
13.92
CDCl3, 100 MHz
13.96
13.92
14.2 14.1 14.0 13.9 13.8 13.7
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10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2.69
2.65
2.57
2.21
2.16
1.66
1.64
1.34
1.33
1.02
1.00
0.90
CDCl3, 400 MHz
cis-1f
4.42
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1.0
1.7
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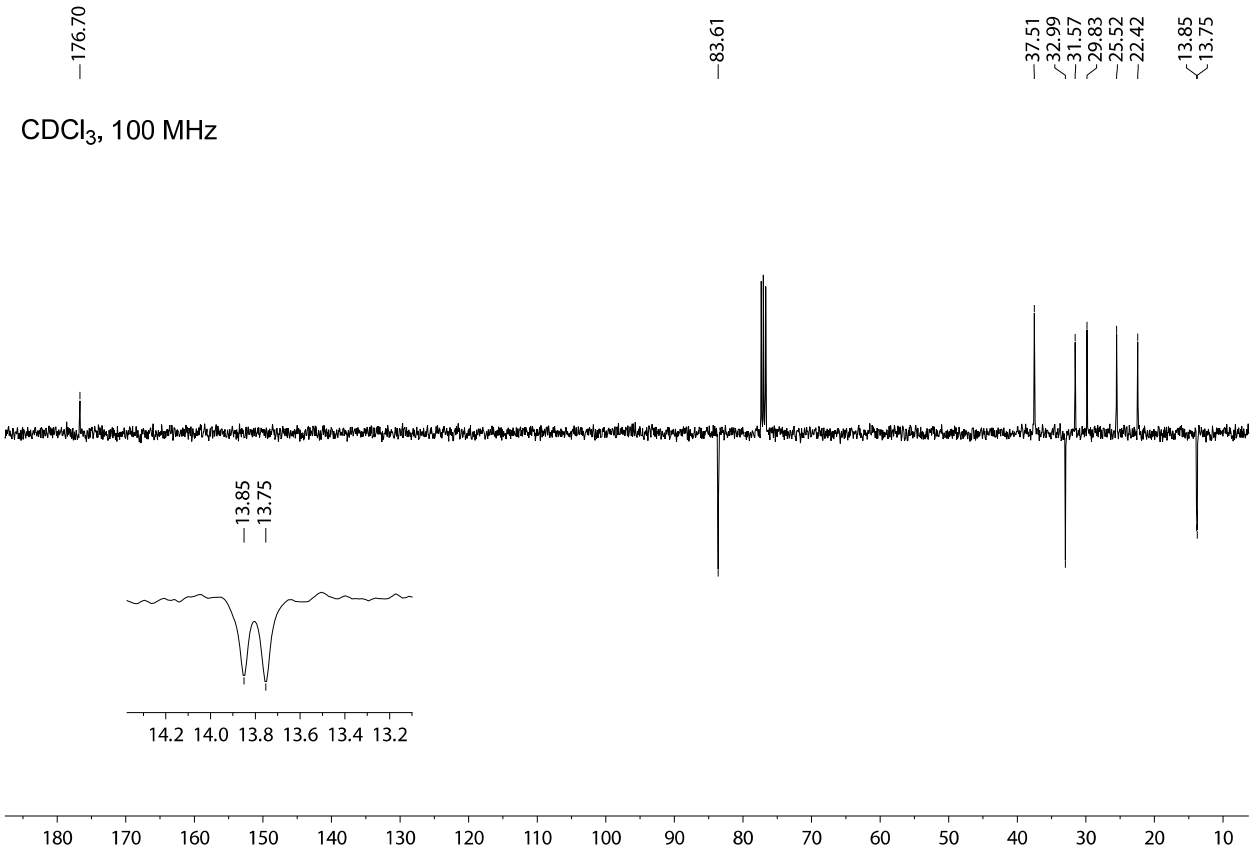
6.3
3.0
3.0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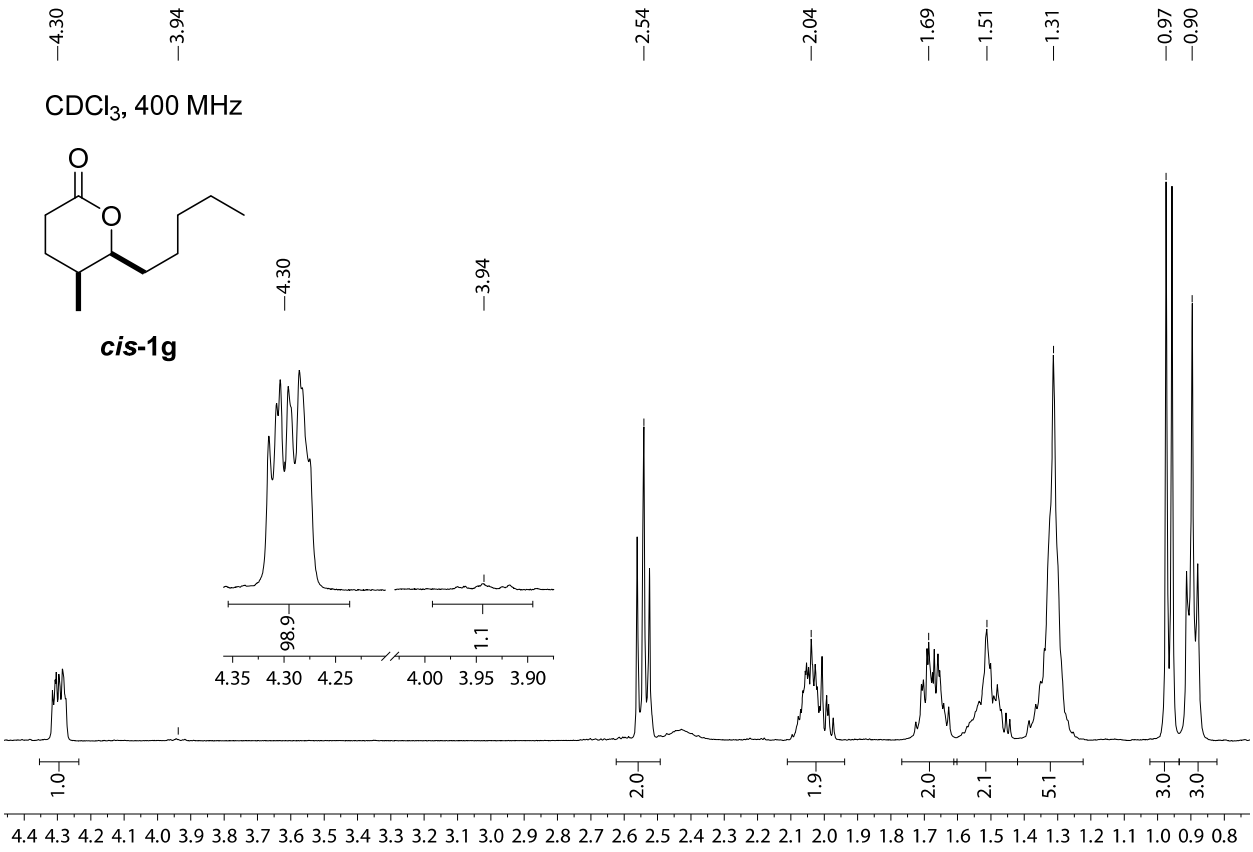
25.52
22.42
13.85
13.75
CDCl3, 100 MHz
13.85
13.75


4.30
3.94
2.54
2.04
1.69
1.51
1.31
0.97
0.90
CDCl3, 400 MHz
cis-1g
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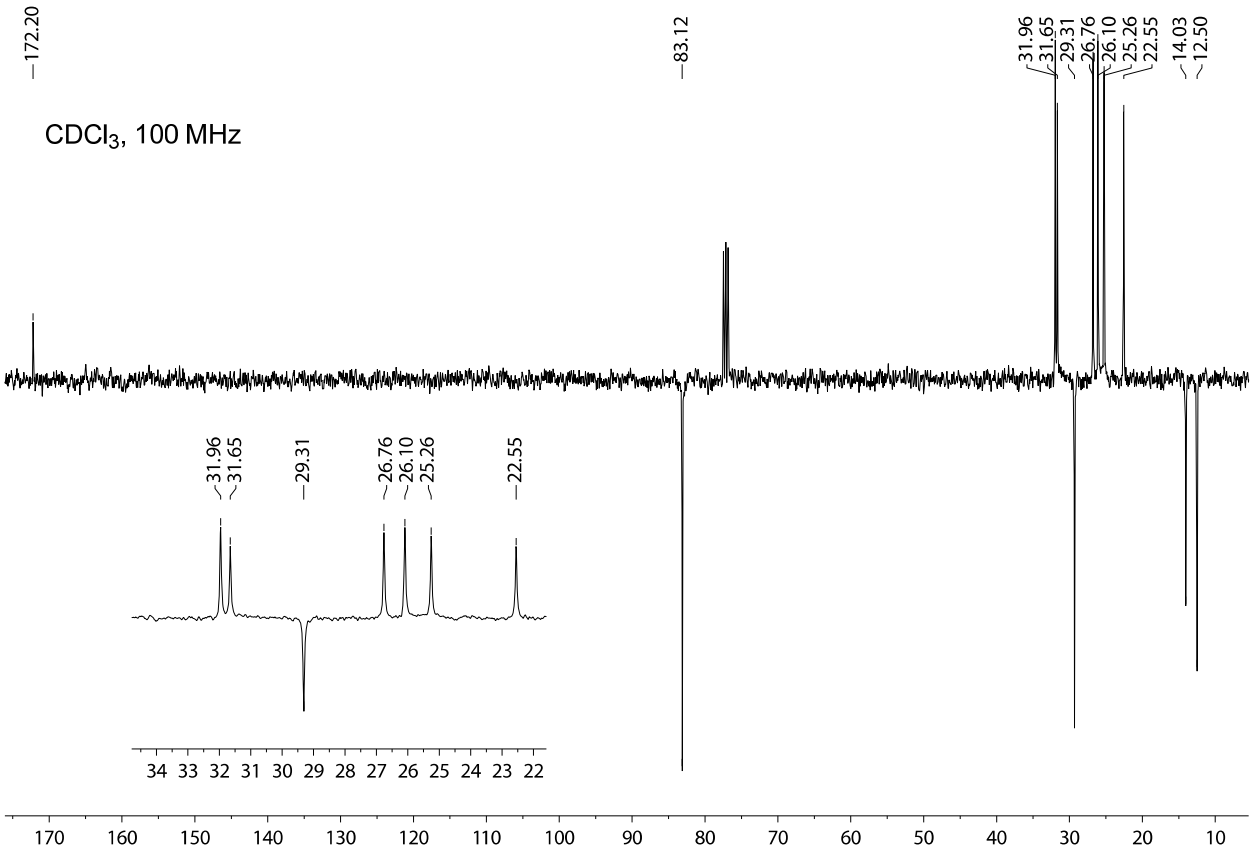
1.1
1.0
2.0
1.9
2.0
2.1
5.1
3.0
3.0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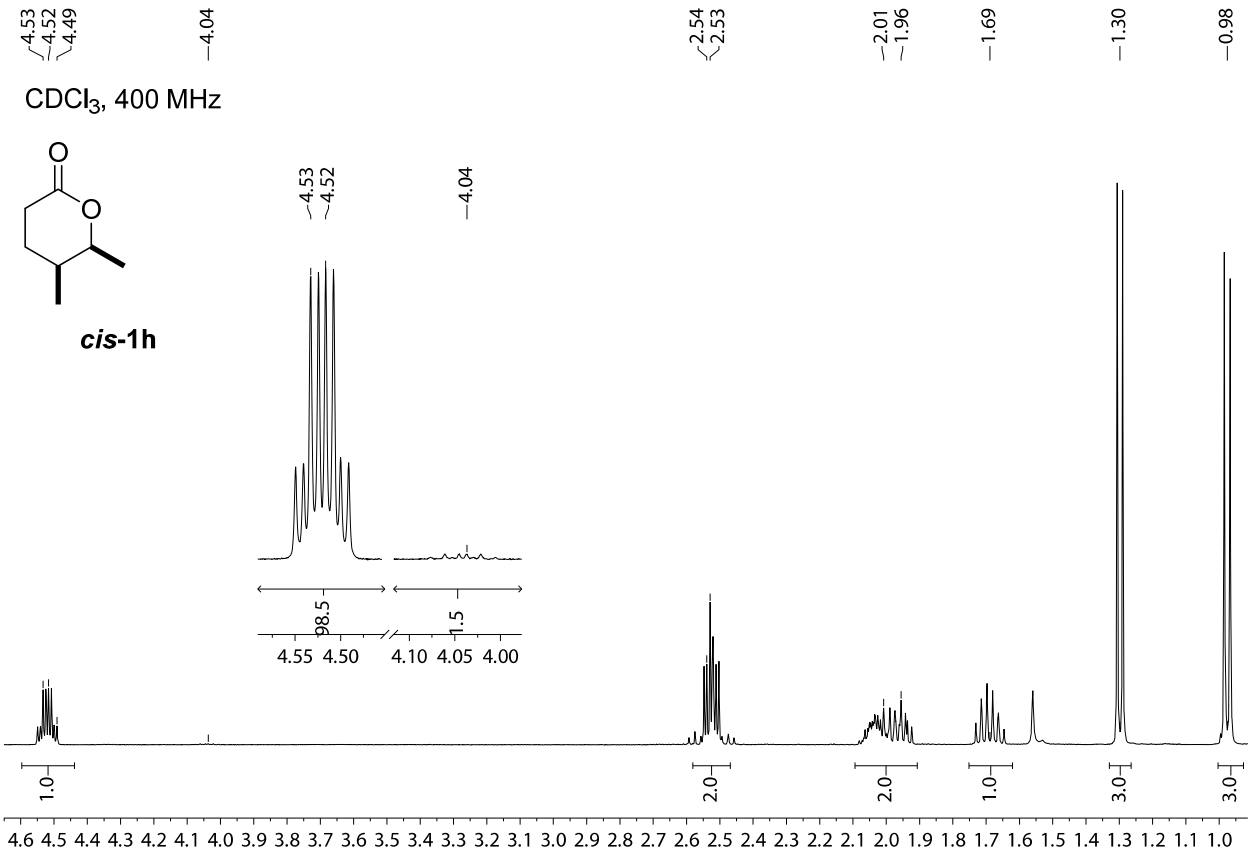
29.31
26.76
26.10
25.26
22.55
14.03
12.50
CDCl3, 100 MHz


4.53
4.52
4.49
4.04
2.54
2.53
2.01
1.96
1.69
1.30
0.98
CDCl3, 400 MHz
cis-1h
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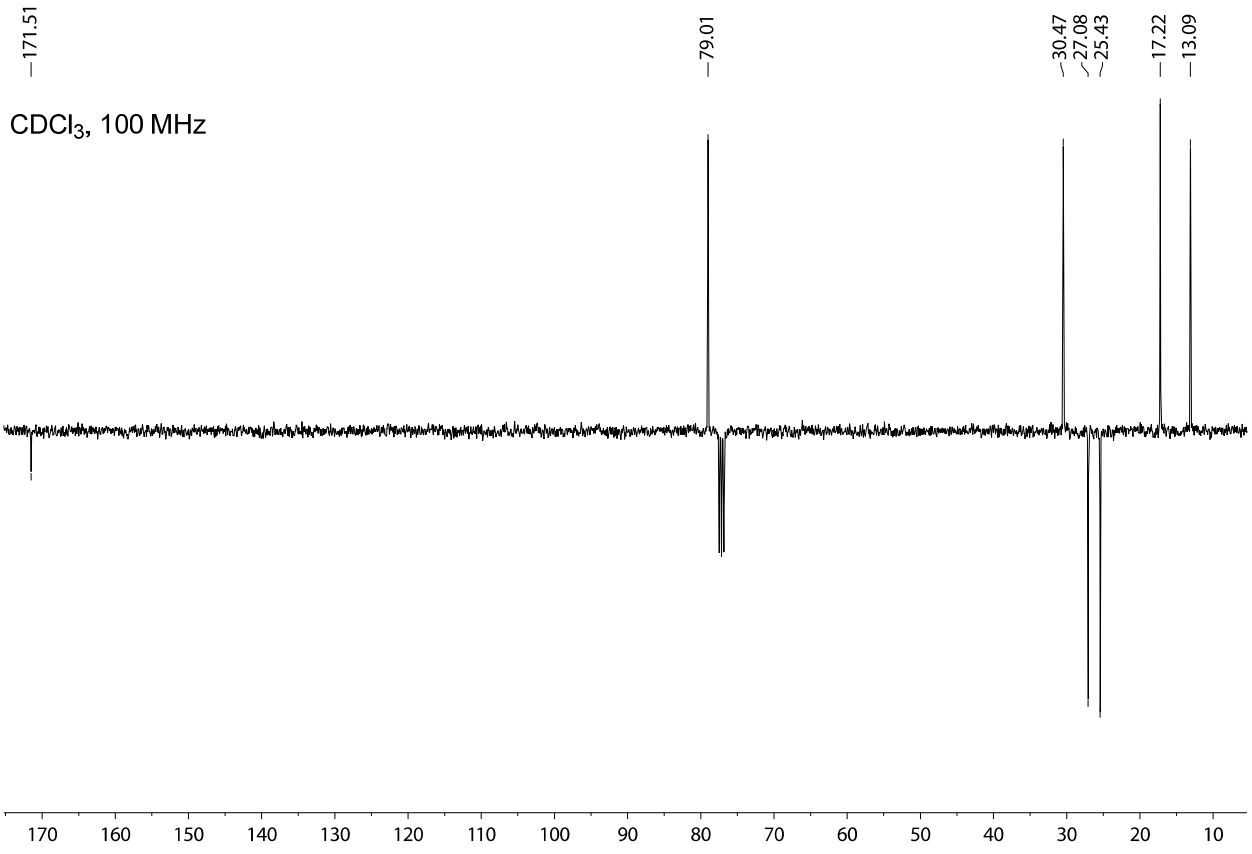
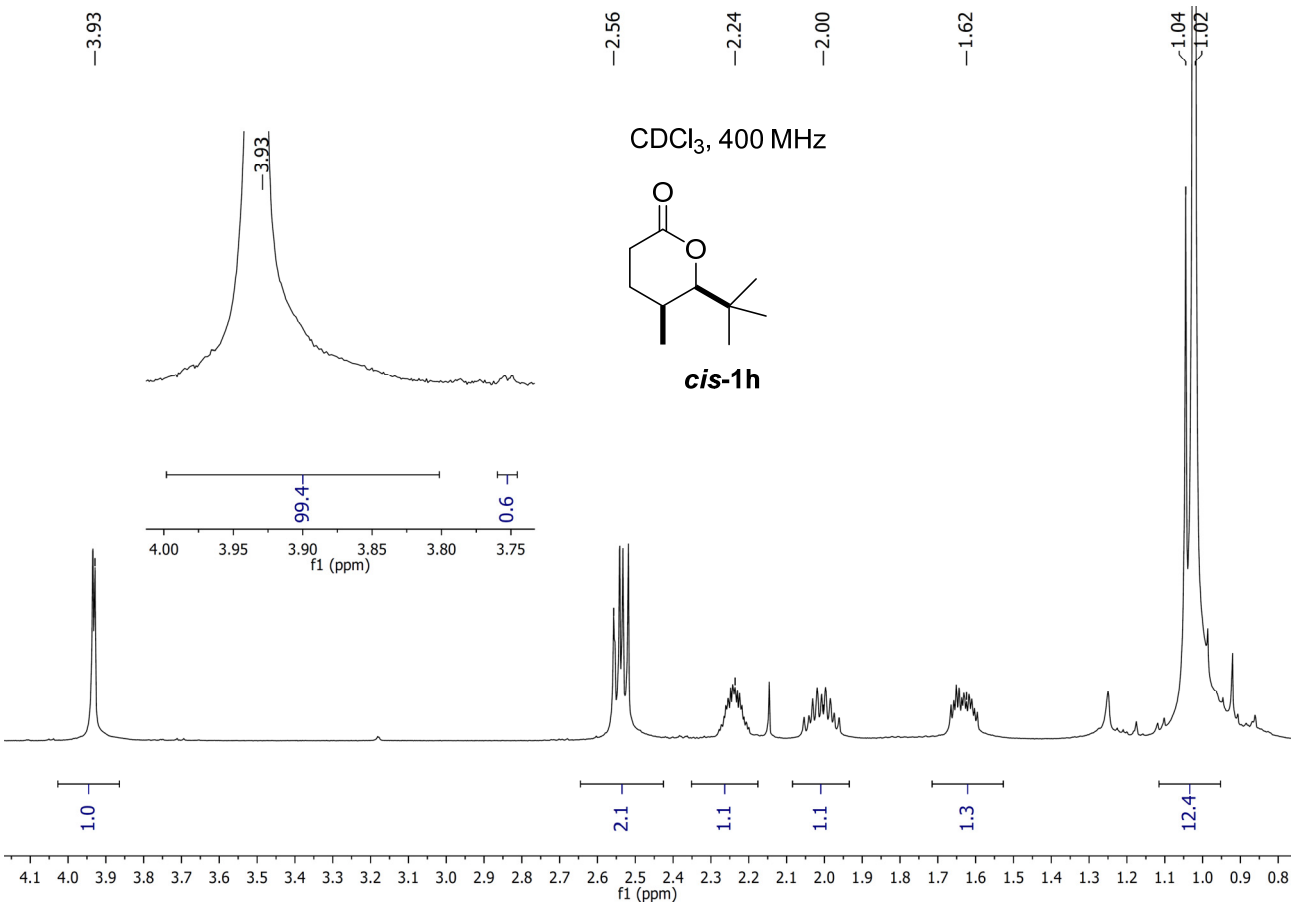
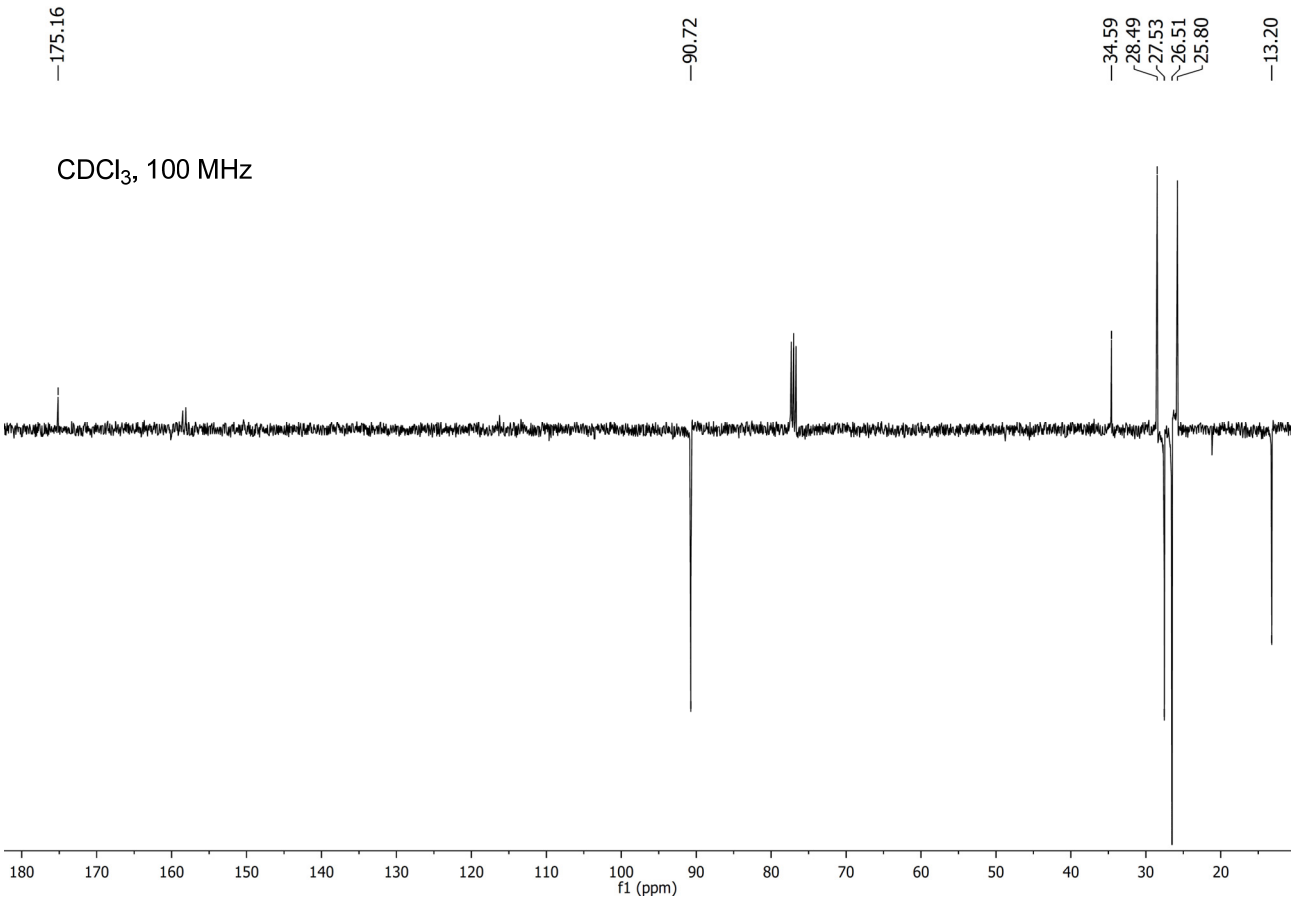
1.0
2.0
2.0
1.0
3.0
3.0


171.51
79.01
30.47
27.08
25.43
17.22
13.09
CDCl3, 100 MHz


3.93
2.56
2.24
2.00
1.62
1.04
1.02
CDCl3, 400 MHz
O
O
cis-1h
99.4
0.6
4.00 3.95 3.90 3.85 3.80 3.75
f1 (ppm)
1.0
2.1
1.1
1.1
1.3
12.4
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)


175.16
90.72
34.59
28.49
27.53
26.51
25.80
13.20
CDCl3, 100 MHz
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)

Kinetic study

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

$$-\frac{d[\mathrm{E}]}{dt}=k_2[\mathrm{AH}][\mathrm{E}]=k_{obs}[\mathrm{E}]$$

where $k_{obs} = k_2$ [TFA] is the experimental *pseudo* first-order rate constant, and k_2 is the true second-order catalytic rate constant.

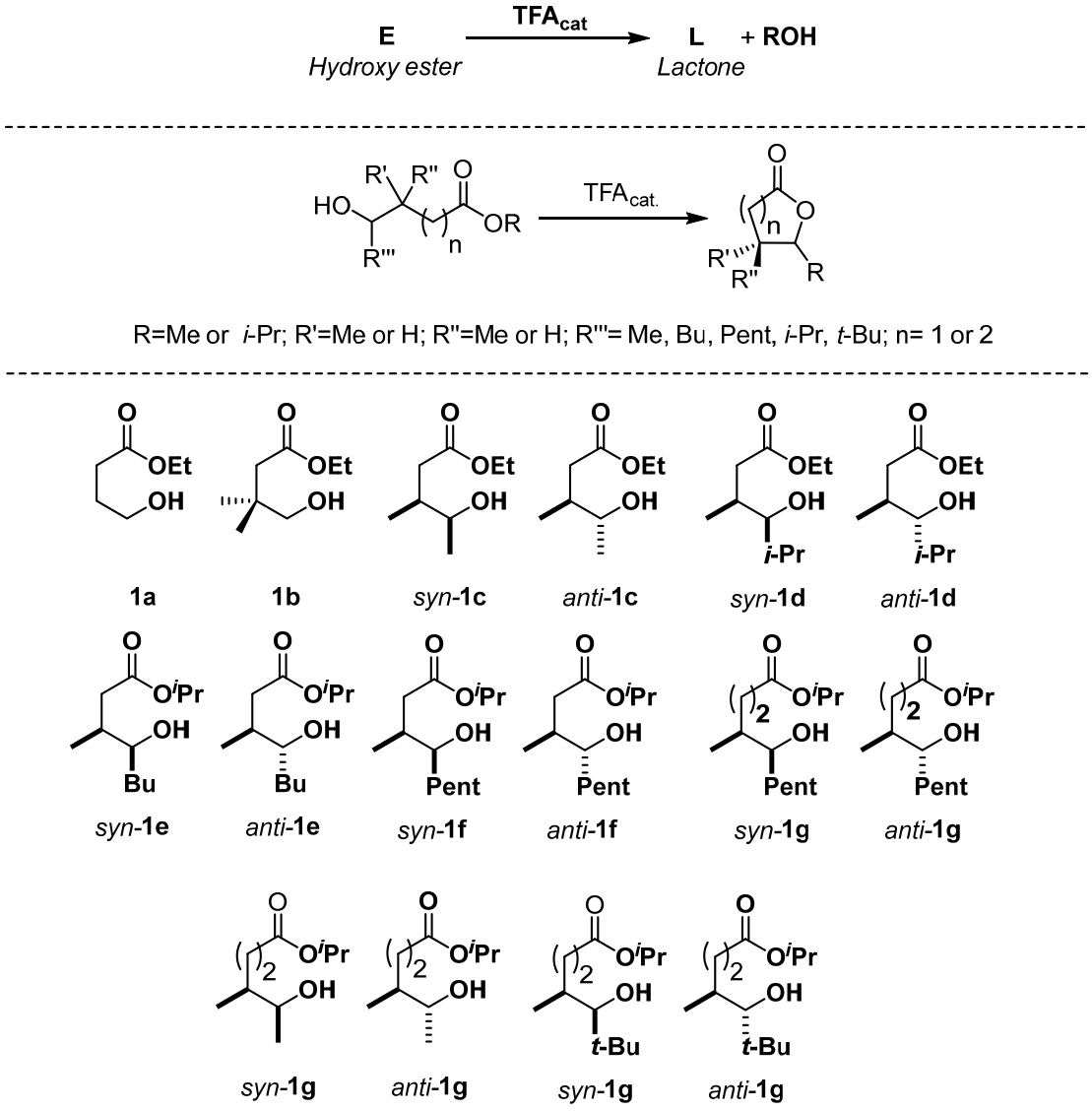


Figure SI.1 Kinetic scheme and hydroxyesters studied.

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

The rate constants k_2 of compounds **1a-b** have been previously measured.[12] The relative rate constants k_r were calculated with respect to **1a**, where $k_r = k_{2,(1i)}/k_{2,(1a)}$ (with *i*=**c-d**).The relative Gibbs energy barriers ($\delta\Delta G_r^{\ddagger}$) were calculated with respect to **1a** by the following equation:

$$\delta\Delta G_r^{\ddagger} = -RT \ln k_r \quad \text{where } RT = 0.602 \text{ kcal·mol}^{-1}$$

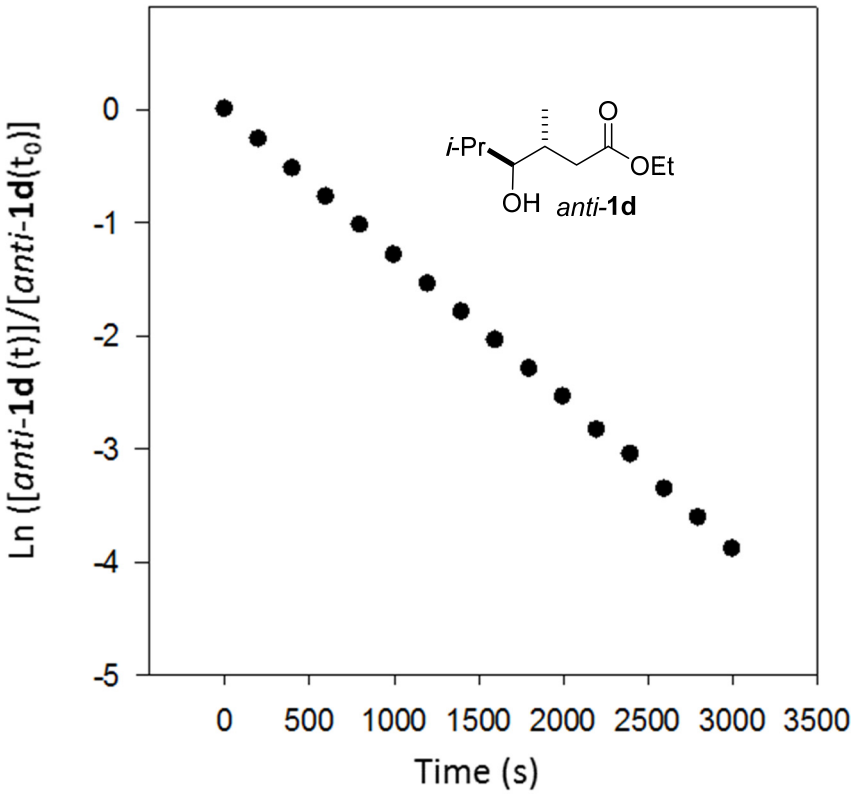
The selectivity *s* between the fastest and the slowest diastereoisomer (*anti vs. syn*) of **1c** in different solvents were calculated by the equation: $s = k_{obs,(anti\text{-}\mathbf{1c})}/k_{obs,(syn\text{-}\mathbf{1c})}$.

The difference between the Gibbs energy barriers ($\delta\Delta G_{r,syn/anti}^{\ddagger}$) of the slow and the fastest isomer was calculate by the following equation:

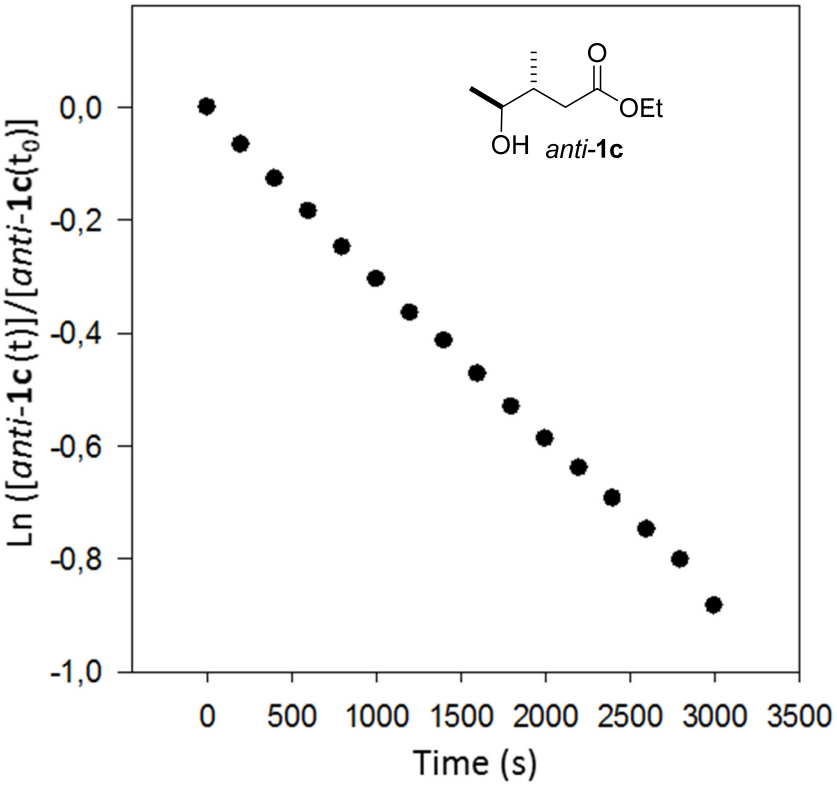
$$\delta\Delta G_{r,anti/syn}^{\ddagger} = -RT \ln k_{r,syn/anti}$$ where RT = 0.602 kcal·mol^{-1}

Linear regression plots of TFA catalyzed ring closure in $CDCl_3$ at 303 K

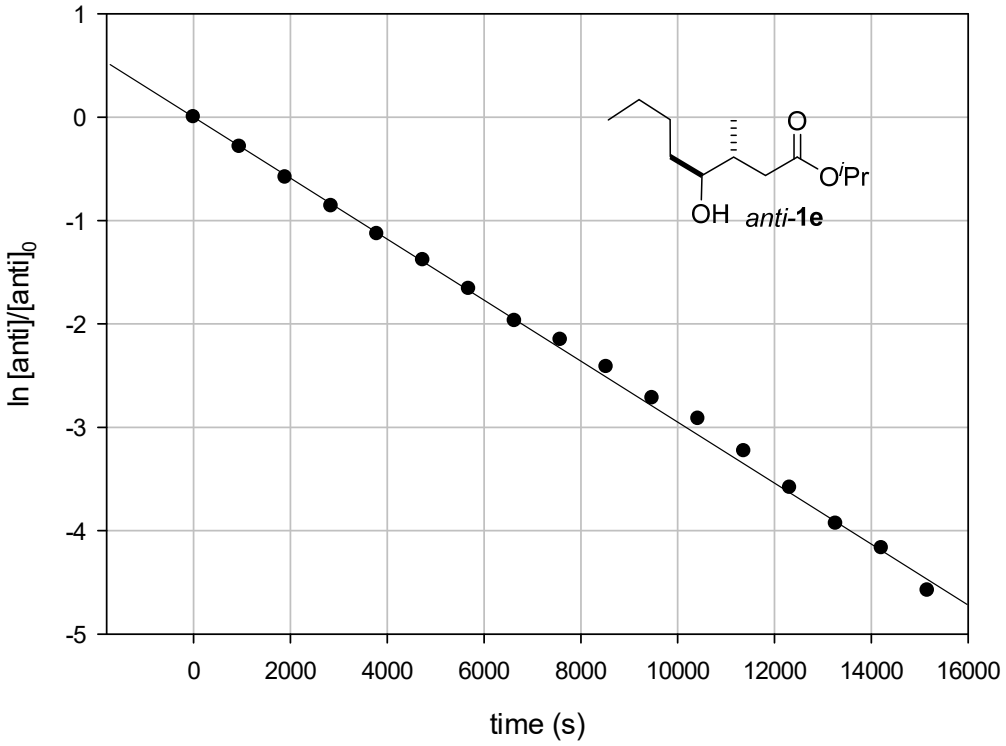
Anti-**1d** k_{obs}=(1.285±0.005)x10^{-3} s^{-1}, r^2= 0.9998, [TFA]= (2.11±0.10)x10^{-4} M



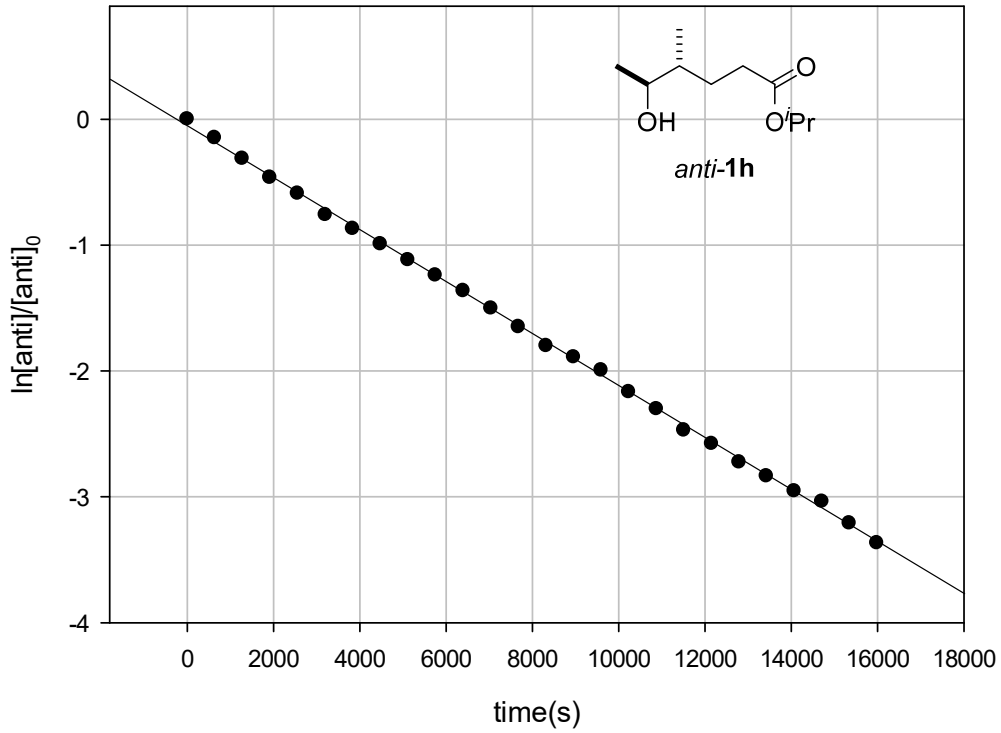
Anti-**1c** k_{obs}=(3.071±0.005)x10^{-4} s^{-1}, r^2= 0.9993, [TFA]= (2.11±0.10)x10^{-4} M



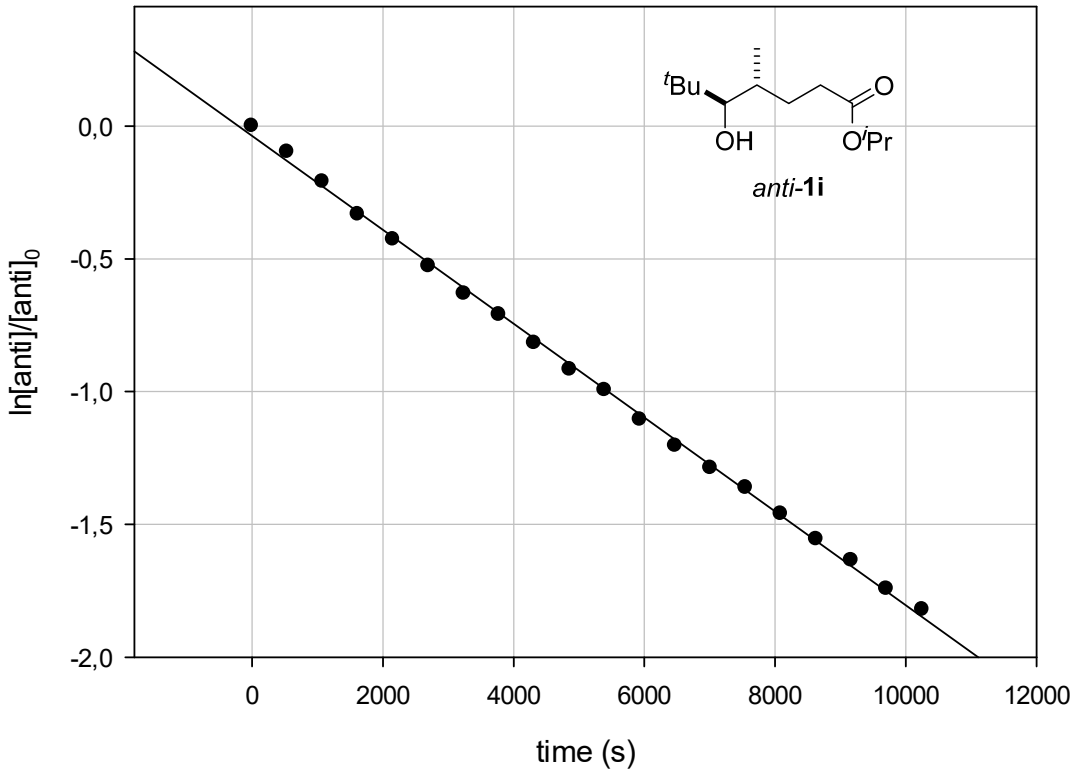
Anti-**1e** k_{obs}=(2.93±0.04)x$10^{-4}s^{-1}$, r^2= 0.9990



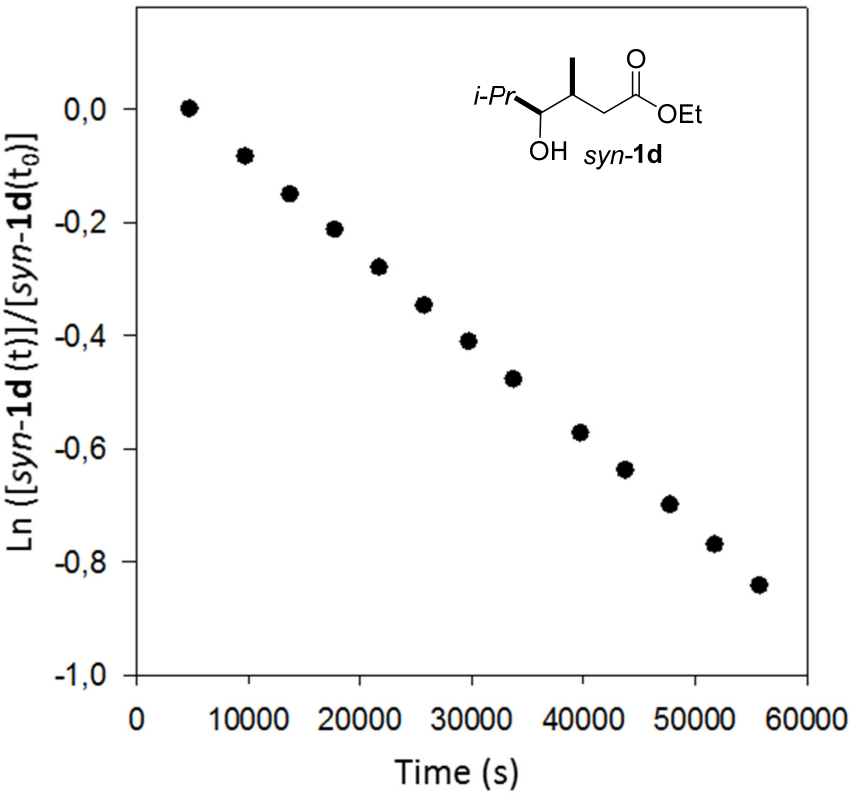
Anti-**1h** k_{obs}=(3.75±0.04)x$10^{-5}s^{-1}$, r^2= 0.9995



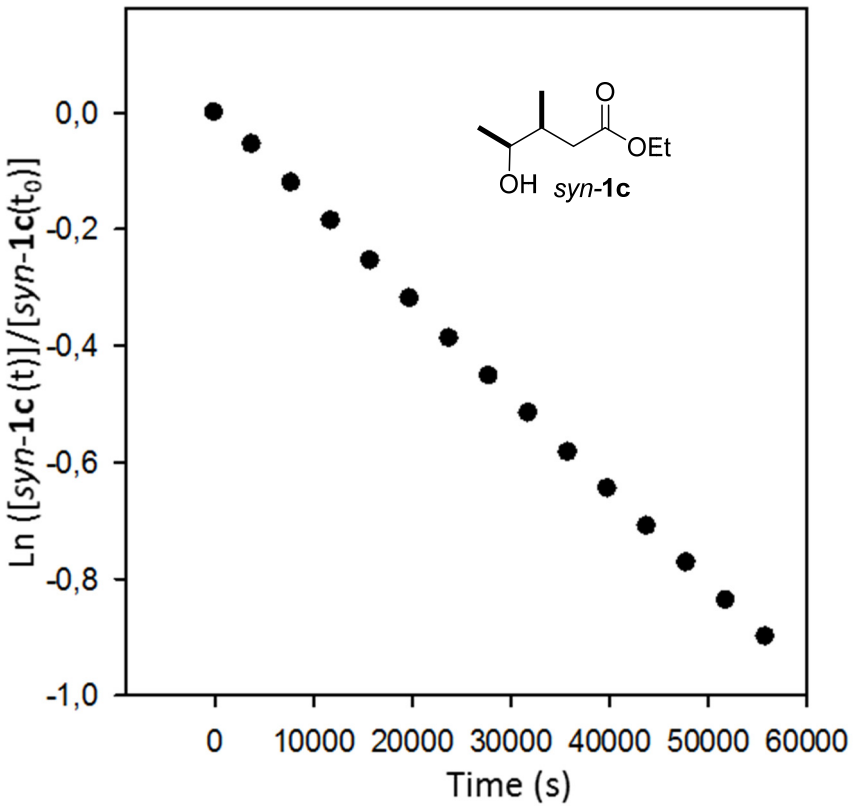
Anti-**1i** k_{obs}=(17.6742±0.04)x$10^{-4}s^{-1}$, r^2= 0.9990



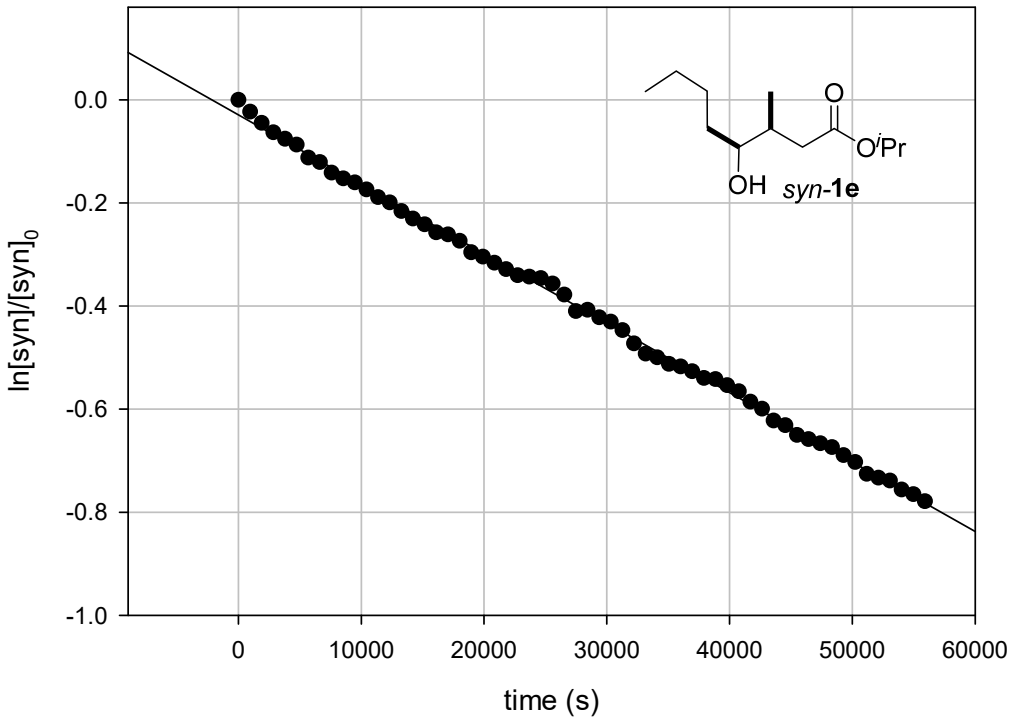
Syn-**1d** k_{obs}=(1.639±0.005)x10^{-5} s^{-1}, r^2= 0.9999, [TFA]= (2.11±0.10)x10^{-4} M



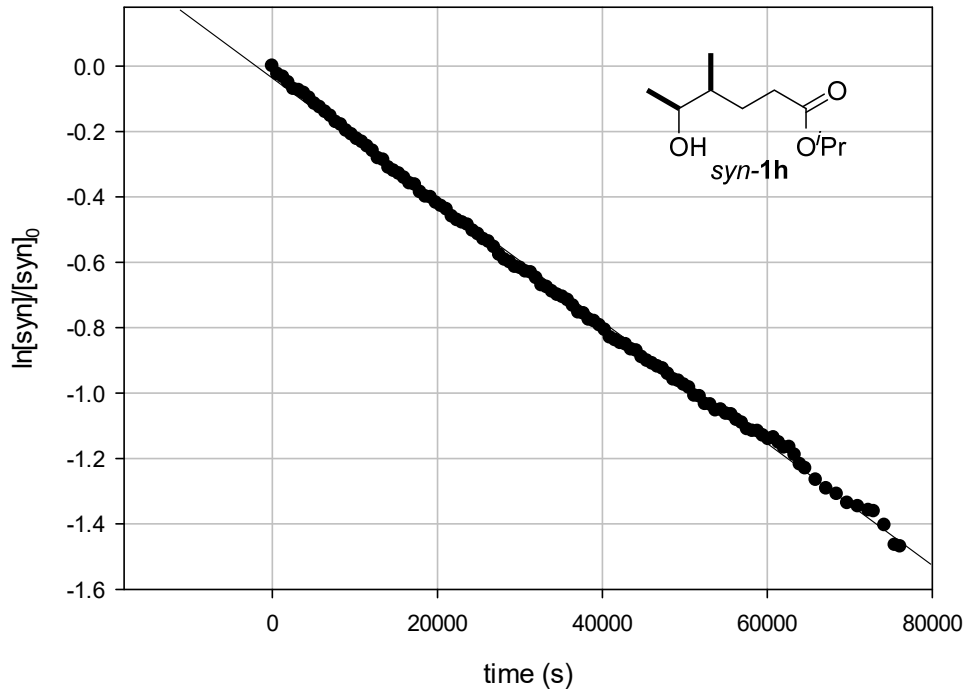
Syn-**1c** k_{obs}=(1.625±0.005)x10^{-5} s^{-1}, r^2= 0.9999, [TFA]= (2.11±0.10)x10^{-4} M



Syn-**1e** k_{obs}=(1.35±0.01)x$10^{-5}s^{-1}$, r^2= 0.999



Syn-**1h** k_{obs}=(2.31±0.01)x$10^{-6}s^{-1}$, r^2= 0.996



Syn-**1i** k_{obs}=(1.238 ±0.04)x$10^{-5}s^{-1}$, r^2= 0.9988

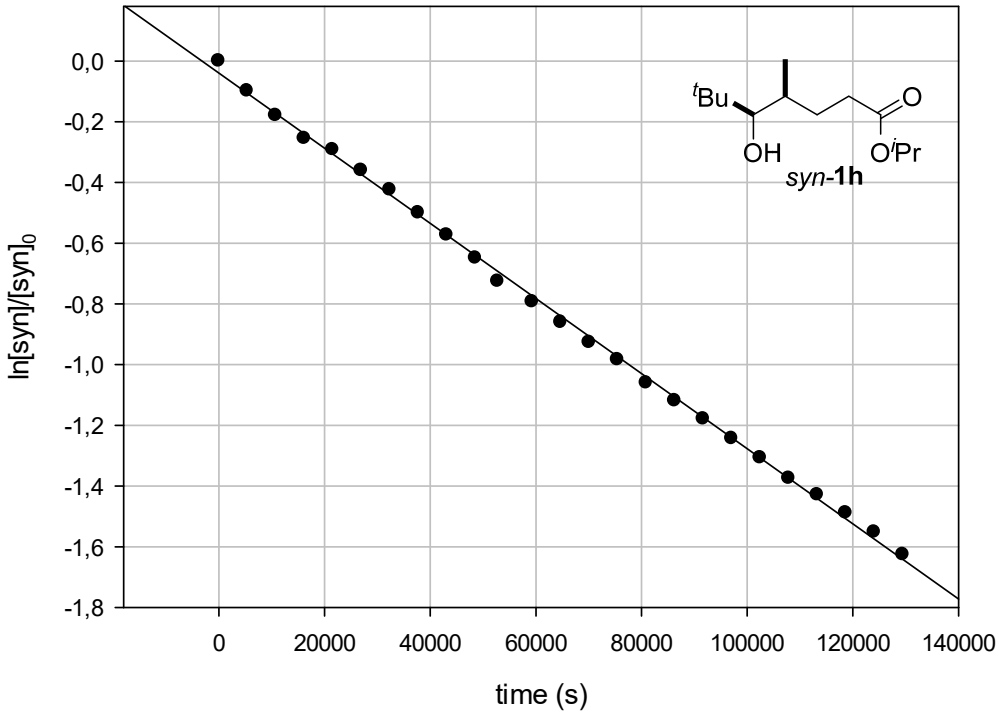


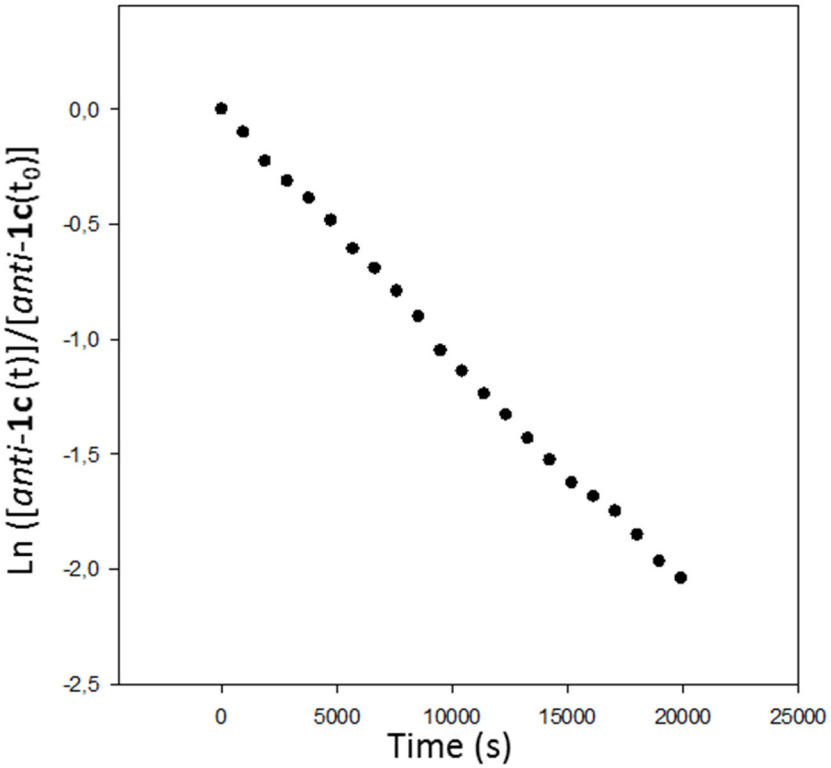
Table SI-1. Summary of kinetic data in $CDCl_3$ at 303 K.

Hydroxyester	k_2 (s^{-1} M^{-1})	$\Delta G^{\pm}$ (kcal mol^{-1})	$\delta\Delta G^{\pm}$ (kcal mol^{-1})	$k_{rel,\ 1a}$	*Selectivity* $s=k_{anti}/k_{syn}$
1a	1.466 x 10^{-2} (a)	20.29	0	1	
1b	6.373 x 10^{-2} (a)	19.41	-0.88	4.34	
***Syn*-1c**	7.701 x 10^{-2}	19.29	-1.00	5.26	18.88
***Anti*-1c**	1.456	17.52	-2.77	99.4	
***Syn*-1d**	7.771 x 10^{-2}	19.29	-1.00	5.30	78.40
***Anti*-1d**	6.090	16.66	-3.63	415.0	

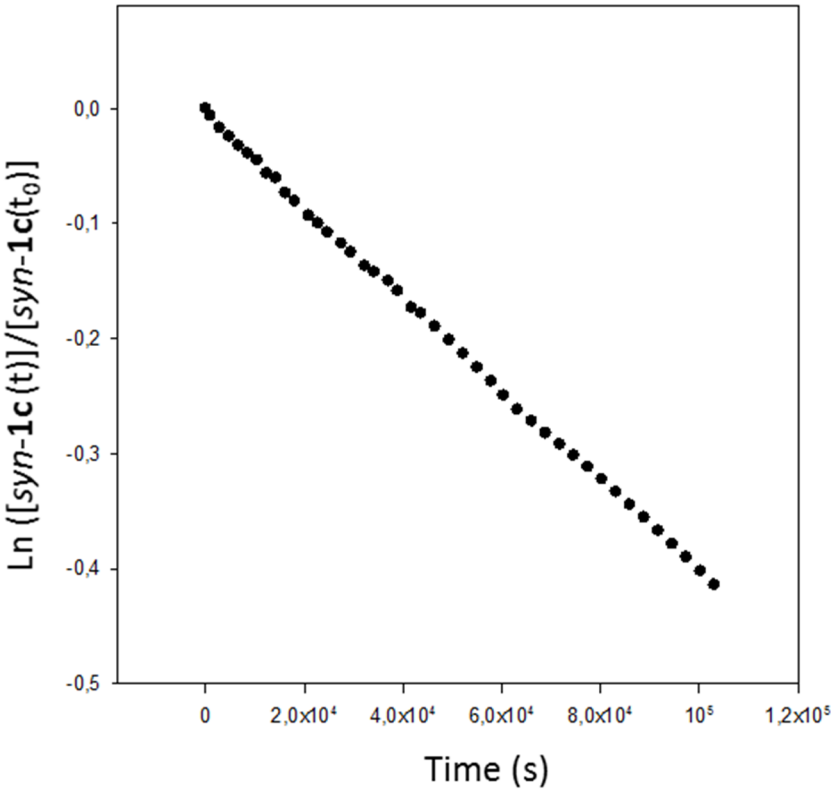
(a) Ref. 12

Solvent effect for 1c in C_6D_6

Anti-**1c** k_{obs}=(1.036±0.010)x10^{-4} s^{-1}, r^2= 0.9980

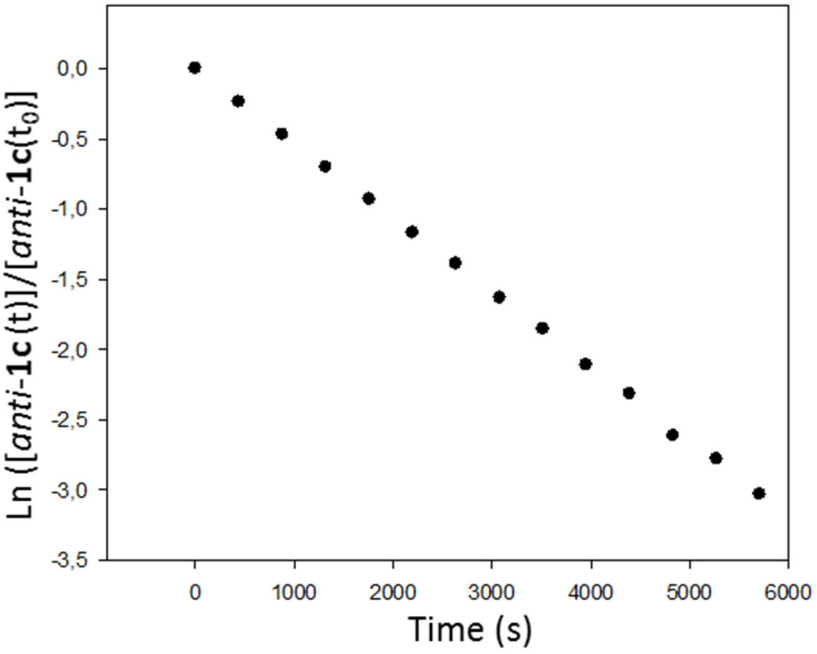


Syn-**1c** k_{obs}=(3.953±0.001)x10^{-6} s^{-1}, r^2= 0.9996

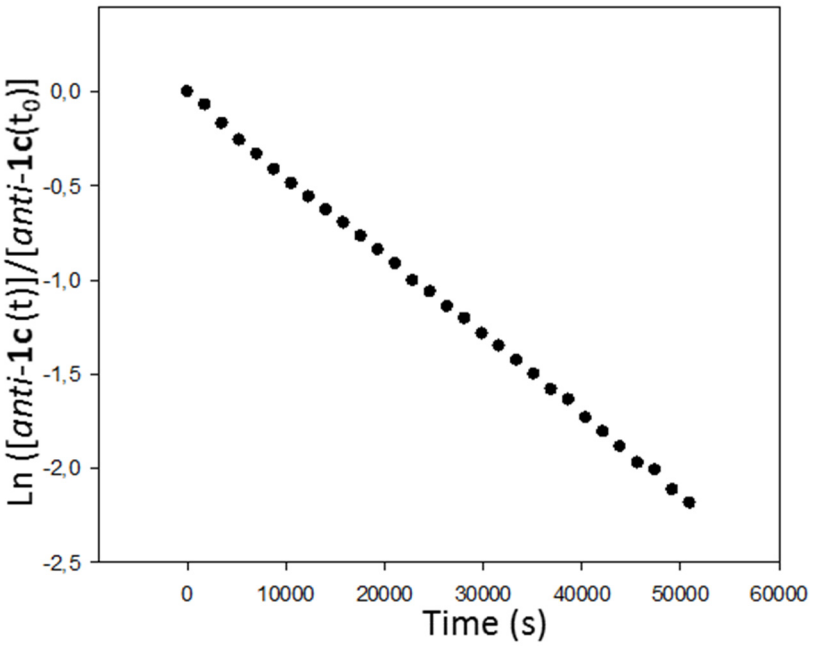


Solvent effect for 1c in CD_3CN

Anti-**1c** k_{obs}=(5.310±0.003)x10^{-4} s^{-1}, r^2= 0.9997

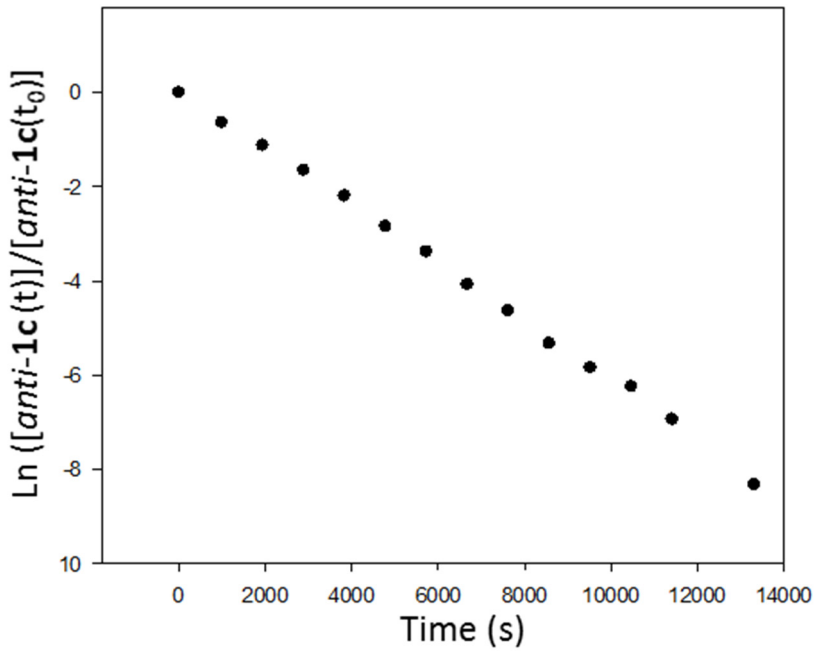


Syn-**1c** k_{obs}=(4.226±0.002)x10^{-5} s^{-1}, r^2= 0.9996



Solvent effect for 1c in D_2O

Anti-**1c** k_{obs}=(6.186±0.006)x10^{-4} s^{-1}, r^2= 0.9988



Syn-**1c** k_{obs}=(5.913±0.008)x10^{-5} s^{-1}, r^2= 0.9970

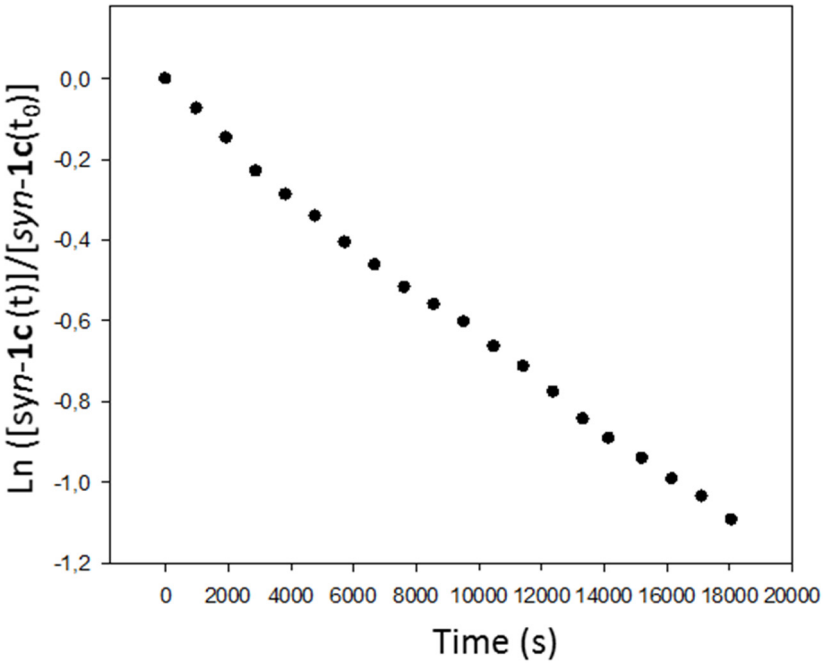


Table SI-2. Summary of kinetic data of **1c** in different solvents at 303 K.

Solvent	$K_{obs,anti}$	$K_{obs,syn}$	***Selectivity*** $k_{r,\ anti/syn}$	$\delta\Delta G^{\ddagger}$ (kcal mol^{-1})
C_6D_6	1.036 x 10^{-4}	3.953 x 10^{-6}	26.2	-1.97
$CDCl_3$	3.071 x 10^{-4}	1.625 x 10^{-5}	18.9	-1.77
CD_3CN	5.310 x 10^{-4}	4.226 x 0^{-5}	12.6	-1.52
D_2O	6.186 x 10^{-4}	5.913 x 10^{-5}	10.5	-1.41
d6-DMSO	-	-	-	-

References and Notes

[1] S. E. Denmark and D. C. Forbes *Tetrahedron Lett.* 1992, **33**, 5037-5040.
[2] E. Brenna, F. G. Gatti, D. Monti, F. Parmeggiani, A. Sacchetti and J. Valoti *J. Mol. Catal. B.: Enzym.* 2015, **114**, 77-85.
[3] The purity of hydroxyesters cannot be determined by GC, since, these esters partially close into the GC injector.
[4] J. A. Marshall and A. W. Garofalo *J. Org. Chem.*, 1993, **58**, 3675-3680.
[5] J. Swatschek, L. Grothues, J. O. Bauer, C. Strohmann and M. Christmann *J. Org. Chem.*, 2014, **79**, 976-3983.
[6] The hydroxyesters can be stored at -20 °C for several months, in presence of a small amount of NEt_3, otherwise at rt undergo to spontaneous cyclization.
[7] The purity of hydroxyesters cannot be detected by GC-MS, because the esters close partially into the GC-injector.
[8] T. Ebata, K. Matsumoto, H. Yoshikoshi, K. Koseki, H. Kawakami, K. O. and H. Matsushita *Heterocycle*, 1993, **36**, 1071-1026.
[9] The reaction progress was monitored by ^{1}H-NMR analysis. A sample (0.1 mL) was quickly added to a precooled solution of NEt_3 (50 mg) in CH_2Cl_2 (0.5 mL), then the solvent was removed under reduced pressure and submitted to the ^{1}H-NMR analysis.
[10] It is important to remove the alcohol (*i*-PrOH or EtOH) before the O-silylation.
[11]E. Brenna, F. G. Gatti, D. Monti, F. Parmeggiani, A. Sacchetti and J. Valoti *J. Mol. Catal. B.: Enzym*. 2015, **114**, 77-85.
[12] E. Brenna, F. Distante, F. G. Gatti and G. Gatti *Catal. Sci. Technol.*, 2017, **7**, 1497-1507.