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Effective stereoselective approach to substituted 1,4-dioxane-2,5-diones as prospective substrates for ring-opening polymerization

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S1. Synthetic procedures

S1.1. General

All of the synthetic experiments were conducted under an argon atmosphere. 1,4-Dioxane, diethyl ether, THF and diisopropylethylamine (DIPEA) were refluxed with Na/benzophenone/dibenzo-18-crown-6 and distilled prior to use. DMF was distilled under reduced pressure. MeCN was distilled over P_2O_5. DCC, L-valine, L-leucine, L-phenylalanine, L-serine, L-tyrosine (Sigma-Aldrich) were used as purchased. (L)-3,6-Dimethyl-1,4-dioxane-2,5-dione (Sigma-Aldrich, 99%) was purified prior to use by sublimation and subsequent recrystallizations from dry toluene followed by drying *in vacuo*.

$CDCl_3$ (Cambridge Isotope Laboratories, Inc., D 99.8 %) was used as purchased. DMSO-d_6 (Aldrich, ≥99.5 atom % ^2H) was distilled over CaH_2 and stored over molecular sieves. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 spectrometer (400 MHz) at 20 °C. The chemical shifts are reported in ppm relative to the solvent residual peaks.

Elemental analysis (C, H) was performed on a Perkin Elmer Series II CHNS/O Analyzer 2400.

S1.2. Common synthetic procedures

2-Bromoacetic acid anhydride and (RS)-2-bromopropanoic acid anhydride. DCC (50 mmol) was added with stirring to the solution of carboxylic acid (100 mmol) in CH_2Cl_2 (100 ml). After 1 h of stirring, the solution was filtered and evaporated. The residue was dissolved in ether (50 ml), filtered, the precipitate was washed by ether (10 ml), the combined filtrates were evaporated and dried *in vacuo*. The product was used for acylation without further purification.

L-Amino acid diazotization.[1,2] Solution of $NaNO_2$ (1.38 g in 10 ml of H_2O) was added with stirring at 0 °C to the solution of α-amino acid (10 mmol) in 2*M* H_2SO_4 (10 ml). After 12 h of stirring, the mixture was extracted with ethyl acetate (4×10 ml). The combined extracts were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was recrystallized from *i*-PrOH.

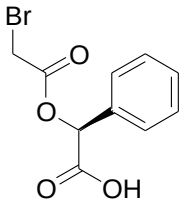
Acylation of α-hydroxy acids using α-bromocarboxylic acid bromoanhydride (typical method A). α-Hydroxy acid (10 mmol) was added to α-bromocarboxylic acid bromoanhydride (10 mmol). The mixture was stirred at 90 °C for 3-6 h, conversion of α-hydroxy acid was controlled by ^{1}H NMR. After cooling to room temperature, the mixture was dissolved in ethyl acetate (20 ml) and stirred with equivalent of aq. $NaHCO_3$ within 30 min. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The product **1** or **3** was used for cyclization without further purification.

Acylation of α-hydroxy acids using α-bromocarboxylic acid anhydride (typical method B). α-Bromocarboxylic acid anhydride (10–12 mmol) dissolved in CH_2Cl_2 (25 ml) was added to α-hydroxy acid (10 mmol). The mixture was refluxed for 5-8 h, conversion of α-hydroxy acid was controlled by ^{1}H NMR. After cooling to room temperature, the mixture was stirred with equivalent of aq. $NaHCO_3$ within 30 min. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The product **1** or **3** was used for cyclization without further purification.

Cyclization (general method C). DIPEA (10 mmol) was dissolved in MeCN (5 ml). The solution was heated to 60 °C, acylated α-hydroxy acid **1** or **3** (10 mmol) dissolved in MeCN (25 ml) was added. After 30 min of stirring, the mixture was cooled, THF (20 ml) was added, DIPEA hydrochloride was filtered off. The filtrate was evaporated under reduced pressure, the residue was purified using column chromatography (silica 40-200, benzene). Recrystallization from ^{i}PrOH was used for additional purification.

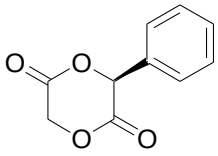
S2. Preparation details and NMR spectra

S2.1. Products yields and characteristics



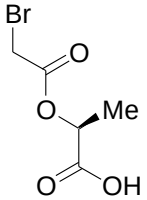
1a

Compound **1a** was prepared using typicl method A by the reaction of (*R*)-mandelic acid (4.56 g, 30 mmol) and bromoacetyl bromide (6.06 g, 30 mmol). The yield was 8.03 g (98%). The product was used for the synthesis of **2a** without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.05 (broad, 2H); 7.40-7.52 (m, 5H); 6.00 (s, 1H); 3.97 (s, 2H).



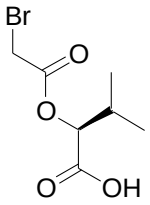
2a

Compound **2a** was prepared using general method C by the reaction of **1a** (8.03 g, 29 mmol) and DIPEA (3.74 g, 29 mmol). The product (5.07 g, 86%) was obtained by recrystallization from *i*-PrOH. Colorless crystals. M. p. 119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.50 (m, 5H); 6.06 (s, 1H); 4.88 (d, ^{3}J = 16.7 Hz, 1H); 4.68 (d, ^{3}J = 16.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.21; 164.08; 131.17; 130.15; 129.67; 125.86; 77.69; 65.39.



1b

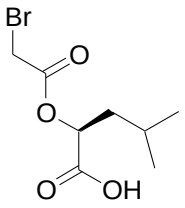
Compound **1b** was prepared using typical method A by the reaction of (*S*)-lactic acid (45 g, 500 mmol) and bromoacetyl bromide (101 g, 500 mmol) at 60 °C (3 h). The product (76 g, 72%) was obtained by distillation under reduced pressure. Colorless liquid, B.p. 126 °C (0.6 Torr). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.45 (bs, 1H); 5.17 (q, ^{3}J = 7.34 Hz, 1H); 3.91 (s, 2H); 1.57 (d, ^{3}J = 7.34 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.14. 166.70. 69.52. 40.39. 25.04. 16.52.



1c

(S)-2-Hydroxy-3-methylbutanoic acid was prepared by diazotization of L-valine (yield 88%, M. p. 89 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.16 (d, ^3J = 3.42 Hz, 1H); 2.16 (dd, ^3J = 6.85 & 3.42 Hz, 1H); 1.07 (d, ^3J = 6.85 Hz, 3H); 0.93 (d, ^3J = 6.85 Hz, 3H).

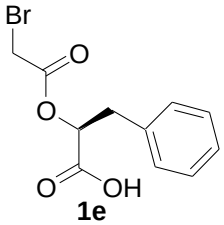
Compound **1c** was prepared using typical method A by the reaction of (S)-2-hydroxy-3-methylbutanoic acid (3.54 g, 30 mmol) and bromoacetyl bromide (6.06 g, 30 mmol). The yield was 6.88 g (96%). The product was used for the synthesis of **2c** without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.02 (bs, 1H); 4.95 (d, ^3J = 3.9 Hz, 1H); 3.96 (d, ^2J = 12.7 Hz, 1H); 3.91 (d, ^2J = 12.7 Hz, 1H); 2.32 (dd. ^3J = 6.8 and 3.9 Hz, 1H); 1.06 (d, ^3J = 6.8 Hz, 3H); 1.03 (d, ^3J = 6.8 Hz, 3H).



1d

(*S*)-2-Hydroxy-4-methylpentanoic acid was prepared by diazotization of L-leucine (yield 86%, M. p. 83 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 1H); 4.30 (dd, ^3J = 7.34, 5.87 Hz, 1H); 2.16 (d, ^3J = 6.85 Hz, 1H); 1,57-1,68 (m, 2H); 0.96 (d, ^3J = 6,36 Hz, 6H).

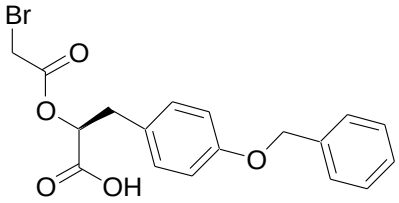
Compound **1d** was prepared using common method A by the reaction of (*S*)-2-hydroxy-4-methylpentanoic acid (3.96 g, 30 mmol) and bromoacetyl bromide (6.06 g, 30 mmol). The yield was 7.44 g (98%). The product was used for the synthesis of **2d** without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.00 (s, 1H); 5.09-5.11 (m, 1H); 3.93 (d, ^2J = 12.6 Hz, 1H); 3.89 (d, ^2J = 12.6 Hz, 1H); 1.68-1.90 (m, 3H); 0.97 (d, ^3J = 6.3 Hz, 3H); 0.95 (d, ^3J = 6.3 Hz, 3H).



1e

(*S*)-2-Hydroxy-4-phenylpropanoic acid was prepared by diazotization of L-phenylalanine (yield 78%, M. p. 112 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.15-7.31 (m, 5H); 5.31 (s, 1H); 4.16 (dd, ^3J = 8.31 & 4.40 Hz, 1H); 3.75 (s, 1H); 2.97 (dd, ^2J = 13.69 Hz, ^3J = 4.40 Hz, 1H); 2.79 (dd, ^2J = 13.69, ^3J = 8.43 Hz, 1H).

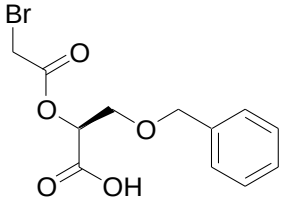
Compound **6** was prepared using typical method A by the reaction of (S)-2-hydroxy-3-phenylpropanoic acid (4.99 g, 30 mmol) and bromoacetyl bromide (6.06 g, 30 mmol). The yield was 8.52 g (99%). The product was used for the synthesis of **2e** without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.16 (bs, 1H); 7.26-7.36 (m, 5H); 5.33 (dd, ^{3}J = 9.0 and. 4.0 Hz, 1H); 3.87 (s, 2H); 3.30 (dd, ^{2}J = 14.5 Hz, ^{3}J = 3.9 Hz, 1H); 3.18 (dd, ^{2}J = 14.4 Hz, ^{3}J = 8.9 Hz, 1H).



1f

(S)-3-(4-Benzyloxybenzyl)-2-hydroxypropanoic acid was prepared from L-tyrosine using published method (yield 48%, M. p. 96 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.47 (bs, 1H); 7.30-7.46 (m, 5H); 7.14 (d, ^{3}J = 8.31 Hz, 2H); 6.90 (d, ^{3}J = 8.31 Hz, 2H); 5.25 (s, 1H); 5.06 (s, 2H); 4.09 (dd, ^{3}J = 7.82 & 4.40 Hz, 1H); 2.89 (dd, ^{2}J = 14.18, ^{3}J = 4.40 Hz, 1H); 2.71 (dd, ^{2}J = 14.18, ^{3}J = 7.82 Hz, 1H).

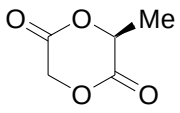
Compound **1f** was prepared using typical method B by the reaction of (S)-3-(4-benzyloxyphenyl)-2-hydroxypropanoic acid (2.72 g, 10 mmol) and bromoacetic acid anhydride (2.6 g, 10 mmol) in CH_2Cl_2 (25 ml). The yield was 3.93 g (>99%). The product was used for the synthesis of **2f** without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.47 (s, 1H); 7.31-7.44 (m, 5H); 7.18 (d, ^{3}J = 8.6 Hz, 2H); 6.93 (d, ^{3}J = 8.6 Hz, 2H); 5.26 (dd, ^{3}J = 8.6 and 4.0 Hz, 1H); 5.05 (s, 2H); 3.9 (s, 2H); 3.22 (dd, ^{2}J = 14.5 Hz, ^{3}J = 3.8 Hz, 1H); 3.11 (dd, ^{2}J = 14.5 Hz, ^{3}J = 8.6 Hz, 1H).



1g

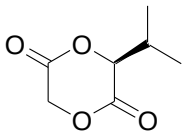
Compound **1g** was prepared using typical method B by the reaction of (S)-3-benzyloxy-2-hydroxypropanoic acid (5.89 g, 30 mmol) and bromoacetic acid anhydride (7.8 g, 30 mmol). The yield was 9.03 g (95%). The product was used for the synthesis of **2g** without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.05 (bs, 1H); 7.29-7.40 (m, 5H); 5.35 (dd, ^{3}J = 5.1 and 2.5 Hz, 1H); 4.62 (d, ^{2}J = 12.4 Hz, 2H); 3.93-3.98 (m, 3H); 3.86 (dd, ^{2}J = 11.1 Hz, ^{4}J = 2.5 Hz, 1H).



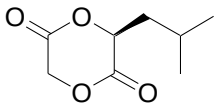
2b

Compound **2b** was prepared using general method C by the reaction of **1b** (30 g, 140 mmol) and DIPEA (18.34 g, 140 mmol). The product was isolated by column chromatography. The yield was 11.83 g (67%), colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.03 (q, ^{3}J = 6.9 Hz, 1H); 4.98 (d, ^{2}J = 16.1 Hz, 1H); 4.85 (d, ^{2}J = 16.1 Hz, 1H); 1.64 (d, ^{3}J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.60. 164.81. 72.14. 65.67. 16.36.



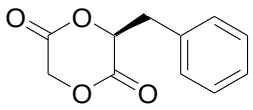
2c

Compound **2c** was prepared using general method C by the reaction of **1c** (6.88 g, 29 mmol) and DIPEA (3.74 g, 29 mmol). The product was purified by recrystallization from *i*-PrOH. The yield was 4.21 g (90%). Colourless crystals, M. p. 63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.92 (d, ^{2}J = 16.7 Hz, 1H); 4.87 (d, ^{2}J = 16.7 Hz, 1H); 4.72 (d, ^{3}J = 4.6 Hz, 1H); 2.45 (dd, ^{3}J = 6.8 and 4.3 Hz, 1H); 1.14 (d, ^{3}J = 6.8 Hz, 3H); 1.07 (d, ^{3}J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.99. 164.43. 80.22. 65.27. 30.62. 18.49. 16.53.



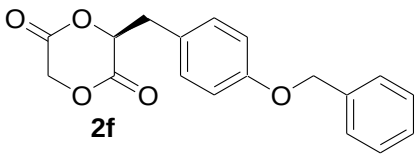
2d

Compound 2d was prepared using general method C by the reaction of **1d** (7.44 g, 29 mmol) and DIPEA (3.74 g, 29 mmol). The product was purified by recrystallization from *i*-PrOH. The yield was 4.44 g (87%). Colourless crystals, m.p. 78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.86-4.97 (m, 3H); 1.87-2.00 (m, 3H); 1.00 (d, ^{3}J = 5.9 Hz, 3H); 0.98 (d, ^{3}J = 5.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.17; 164.46; 74.35; 65.41; 39.46; 24.05; 22.96; 21.40.



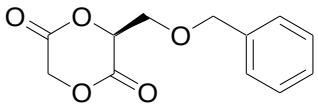
2e

Compound **2e** was prepared using general method C by the reaction of **1e** (8.52 g, 29 mmol) and DIPEA (3.74 g, 29 mmol). The product was purified by recrystallization from *i*-PrOH. The yield was 5.32 g (86%). Colourless crystals, M. p. 108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.38 (m, 5H); 5.25 (t, ^{3}J = 4.89 Hz, 1H); 4.62 (d, ^{2}J = 16.6 Hz); 3.82 (d, ^{2}J = 16.6); 3.42 (dd, ^{2}J = 14.7 Hz, ^{3}J = 4.9 Hz); 3.36 (dd, ^{2}J = 14.7 Hz, ^{3}J = 4.9 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.71; 163.80; 136.34; 128.81; 128.47; 127.89; 74.06; 70.89; 65.60; 42.04.



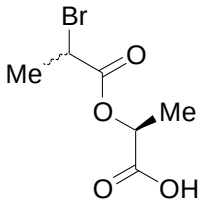
2f

Compound **2f** was prepared using common method C by the reaction of **1f** (3.93 g, 10 mmol) and DIPEA (1.29 g,10 mmol). The product was purified by recrystallization from hexane / ethyl acetate. The yield was 2.3 g (74%). Colourless crystals, M. p. 122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.43 (m, 5H); 7.18 (d, ^{3}J = 8.8 Hz, 2H); 6.96 (d, ^{3}J = 8.8 Hz, 2H); 5.21 (t, ^{3}J = 4.4 Hz, 1H); 5.06 (s, 2H); 4.56 (d, ^{2}J = 17.1 Hz, 1H); 3.70 (d, ^{2}J = 17.1 Hz, 1H); 3.31 (d, ^{3}J = 4.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.10; 163.31; 158.79; 136.67; 131.36; 128.76; 128.24; 127.65; 125.66; 115.75; 70.17; 64.82; 37.75.



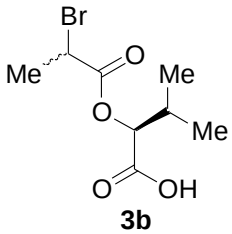
2g

Compound **2g** was prepared using general method C by the reaction of **1g** (9.03 g, 28.5 mmol) and DIPEA (3.67 g, 28.5 mmol). The product was isolated by column chromatography. The yield was 5.32 g (86%), colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.41 (m, 5H); 5.04-5.08 (m, 2H); 4.81 (d, ^{2}J = 16.6 Hz, 1H); 4.58 (s, 2H); 4.08 (dd, ^{2}J = 10.8 Hz, ^{4}J = 2.0 Hz, 1H); 3.95 (dd, ^{2}J = 10.3 Hz, ^{4}J = 2.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.71; 163.80; 136.34; 128.81; 128.47; 127.89; 76.54; 74.06; 70.89; 65.60; 42.04.



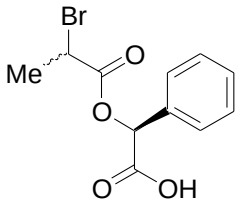
3a

Compound **3a** was prepared using typical method A. Both diastereomers were detected in the reaction mixture (see Fig. S22).



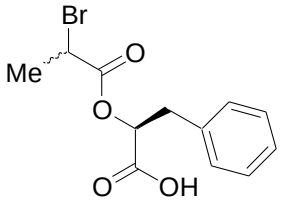
3b

Compound **3b** was prepared using typical method A and obtained as a mixture of diastereomers (1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ for (3*R*,6*S*) 10.08 (bs, 1H); 4.93 (d, ^{3}J = 4.0 Hz, 1H); 4.49 (q, ^{3}J = 6.9 Hz, 1H); 2.30-2.40 (m, 1H); 1.86-1.90 (m, 3H); 1.03 (dd, ^{3}J = 6.9 Hz, ^{4}J = 2.1 Hz, 6H). δ for (3*S*,6*S*) 10.08 (bs, 1H); 4.91 (d, ^{3}J = 4.0 Hz, 1H); 4.44 (q, ^{3}J = 7.0 Hz, 1H); 2.30-2.40 (m, 1H); 1.82-1.86 (m, 3H); 1.06 (dd, ^{3}J = 7.0 Hz, ^{4}J = 2.1 Hz, 6H).



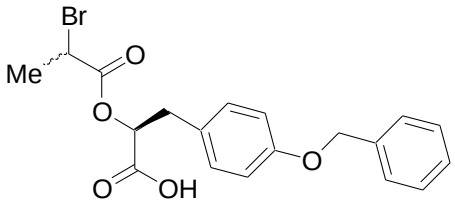
3c

Compound **3c** was prepared using typical method A by the reaction of (*S*)-mandelic acid (4.56 g, 30 mmol) and 2-bromopropionyl chloride (5.14 g, 30 mmol). The yield was 8.18 g (95%). The product was used for the synthesis of **4c** without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ for (3*R*,6*S*): δ 10.74 (bs, 1H); 7.40-7.51 (m, 5H); 5.98 (s, 1H); 4.51 (q, ^{3}J = 6.82 Hz, 1H); 1.88 (d, ^{3}J = 6.8 Hz, 3H). For (3*S*,6*S*) 10.74 (bs, 1H); 7.36-7.54 (m, 5H); 5.97 (s, 1H); 4.47 (q, ^{3}J = 6.8 Hz, 1H); 1.86 (d, ^{3}J = 6.8 Hz, 3H).



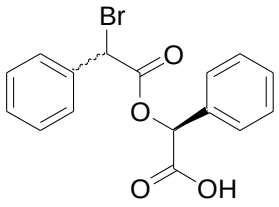
3d

Compound **3d** was prepared using typical method A and obtained as a mixture of diastereomers (1:1) and used for the synthesis of **4d** without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ for (3R, 6S): δ 9.71 (bs, 1H); 7.19-7.33 (m, 5H); 5.27-5.33 (m, 1H); 4.41 (q, ^{3}J = 6.8 Hz, 1H); 3.12-3.31 (m, 2H); 1.78 (d, ^{3}J = 4.8 Hz, 3H). For (3S, 6S) δ 9.71 (bs, 1H); 7.19-7.33 (m, 5H); 5.27-5.33 (m, 1H); 4.41 (q, ^{3}J = 6.9 Hz, 1H); 3.12-3.31 (m, 2H); 1.76 (d, ^{3}J = 4.9 Hz, 3H).



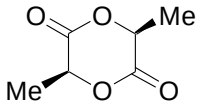
3e

Compound **3e** was prepared using typical method A by the reaction of (*S*)-3-(4-benzyloxybenzyl)-2-hydroxypropanoic acid (2.72 g, 10 mmol) and 2-bromopropanoic anhydride (2.286 g, 10 mmol). The product, 1:1 mixture of diastereomers, was used for the synthesis of **4e** without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ for (3*R*,6*S*) 9.16 (bs, 1H); 7.31-7.44 (m, 5H); 7.19 (d, ^{3}J = 8.6 Hz, 2H); 6.92 (d, ^{3}J = 8.6 Hz, 2H); 5.21-5.28 (m, 1H); 5.04 (s, 2H); 4.41 (q, ^{3}J = 6.8 Hz, 1H); 3.08-3.26 (m, 2H); 1.77 (d, ^{3}J = 6.8. 3H). For (3*S*,6*S*): δ 9.16 (bs, 1H); 7.28-7.43 (m, 5H); 7.18 (m, ^{3}J = 8.6 Hz, 2H); 6.92 (m, ^{3}J = 8.6 Hz, 2H); 5.21-5.28 (m, 1H); 5.04 (s, 2H); 4.37 (q, ^{3}J = 7.1 Hz, 1H); 3.08-3.26 (m, 2H);1.79 (d, ^{3}J = 7.1 Hz, 3H).



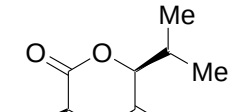
3f

Compound **3f** was prepared using typical method A by the reaction of (*R*)-mandelic acid (4.56 g, 30 mmol) and 2-bromo-2-phenylacetyl chloride (7.0 g, 30 mmol). The yield was 9.22 g (88%). The product, 1:1 mixture of diastereomers, was used for the synthesis of **4f** without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ for (3*R*,6*S*) 10.57 (bs, 1H); 7.30-7.59 (m, 10H); 5.98 (s, 1H); 5.49 (s, 1H). For (3S, 6S) 10.57 (bs, 1H); 7.30-7.59 (m, 10H); 5.96 (s, 1H); 5.49 (s, 1H).



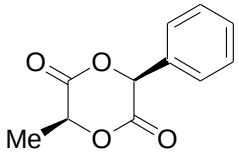
4a

Compound **4a** was prepared using general method C. ^{1}H NMR spectrum of **4a** (Fig. S28 is identical to the spectrum of commercial L-lactide.



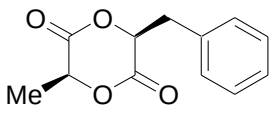
4b

Compound **4b** was prepared using general method C. Colourless crystals, M. p. 60 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.99 (q, ^{3}J = 6.6 Hz, 1H); 4.75 (d, ^{3}J = 3.2 Hz, 1H); 2.49 (sept d, ^{3}J =7.0 Hz, 3.2 Hz, 1H); 1.65 (d, ^{3}J = 6.6 Hz, 3H); 1.15 (d, ^{3}J =7.0 Hz, 3H); 1.05 (d, ^{3}J =7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.75; 166.33; 79.97; 72.25; 29.39; 18.67; 16.01; 15.94.



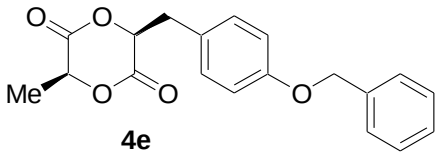
4c

Compound **4c** was prepared using common method C starting from **17** (8.18 g, 28.5 mmol) and DIPEA (3.67 g, 28.5 mmol). The product was purified by recrystallization from *i*-PrOH. The yield was 2.47 g (42%). Colourless crystals, M. p. 144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.46 (m, 5H); 5.93 (s, 1H); 5.18 (q, ^{3}J = 6.85 Hz, 1H); 1.64 (d, ^{3}J = 6.85 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.10; 165.78; 131.50; 130.09; 129.05; 127.64; 77.90; 72.91; 16.51.



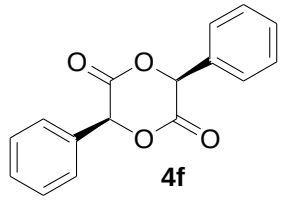
4d

Compound **4d** was prepared using general method C. M. p. 155 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.24-7.36 (m, 5H); 5.64 (dd, ^{3}J = 9.0 Hz, 3.7 Hz, 1H); 5.44 (q, ^{3}J = 6.7 Hz, 1H); 3.38 (dd, ^{2}J = 15.0 Hz, ^{3}J = 6.7 Hz, 1H); 3.07 (dd, ^{2}J = 15.0 Hz, ^{3}J = 9.0 Hz, 1H); 1.64 (d, ^{3}J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.30; 167.51; 135.90; 129.56; 128.32; 126.81; 75.88; 72.20; 35.07; 15.14.



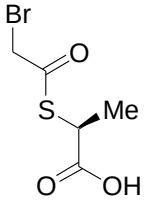
4e

Compound **4e** was prepared using general method C starting from **3e** (4.07 g, 10 mmol) and DIPEA (1.29 g, 10 mmol) and purified by recrystallization from hexane / ethyl acetate. The yield was 1.27 g (39%). Colourless crystals, M. p. 166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.43 (m, 5H); 7.23 (d, ^{3}J = 8.80 Hz, 2H); 6.93 (d, ^{3}J = 8.80 Hz, 2H); 5.01-5.08 (m, 3H); 4.93 (q, ^{3}J = 6.9 Hz, 1H); 3.39 (dd, ^{2}J = 14.7 Hz, ^{3}J = 3.9 Hz, 1H); 3.11 (dd, ^{2}J = 14.7 Hz, ^{3}J = 8.7 Hz, 1H); 1.52 (d, ^{3}J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.90; 166.26; 158.30; 136.99; 131.19; 128.73; 128.13; 127.57; 126.93; 115.15; 77.16; 72.54; 70.10; 35.66; 16.18.



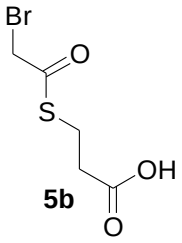
4f

Compound **4f** was prepared using general method C starting from **3f** (9.22 g, 26.5 mmol) and DIPEA (3.4 g, 26.5 mmol). The yield was 2.33 g (29%). Colourless crystals, M. p. 220 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.47-7.52 (m, 10H); 6.61 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 166.84; 132.47; 129.49; 128.56 (double intensity); 77.66.



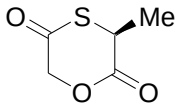
5a

Compound **5a** was prepared using typical method A. B. p.115-118 °C (0.5 Torr). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.36 (bs, 1H); 4.25 (q, ^{3}J = 7.4 Hz, 1H); 4.06 (s, 2H); 1.57 (d, ^{3}J = 7.4 Hz, 3H).



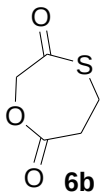
5b

Compound **5b** was prepared using typical method A. M. p. 106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.49 (bs, 1H); 4.03 (s, 2H); 3.16 (t, ^{3}J = 6.9 Hz, 2H); 2.72 (t, ^{3}J = 6.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.71; 177.86; 33.82; 33.47; 24.78.



6a

Compound **6a** was prepared using general method C. B. p. 106 °C (0.5 Torr). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.94 (d, ^{2}J = 15.2 Hz, 1H); 4.71 (d, ^{2}J = 15.2 Hz, 1H); 4.22 (q, ^{3}J = 6.8 Hz, 1H); 1.59 (d, ^{3}J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.61; 164.81; 72.14; 65.67; 16.36.



6b

Compound **6b** was prepared using general method C. M. p. 126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ δ 4.03 (s, 2H); 3.26 (m, 2H); 2.78 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 195.84; 171.43; 68.30; 34.42; 23.30.

S2.2. NMR spectra

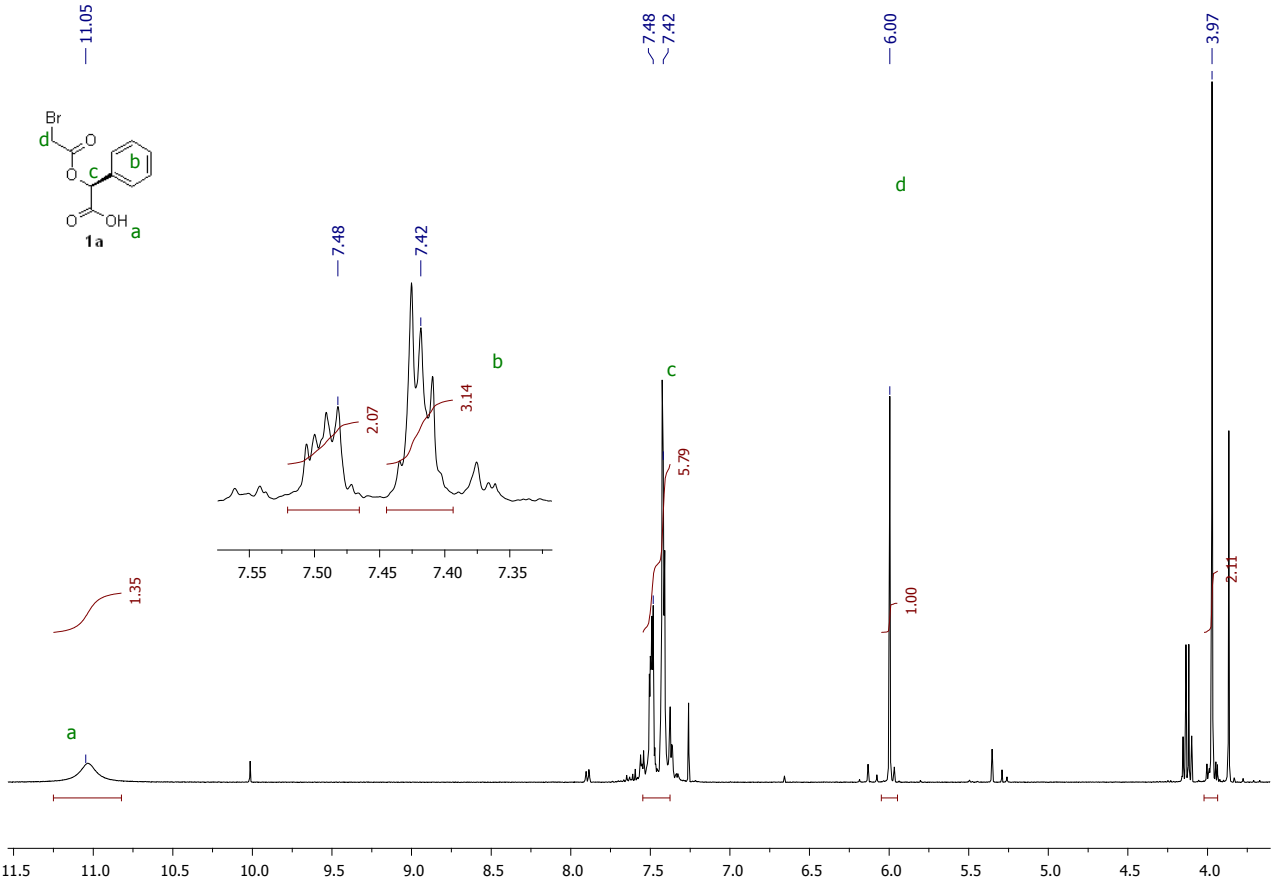


Fig. S1. [1]H NMR spectrum of **1a**.

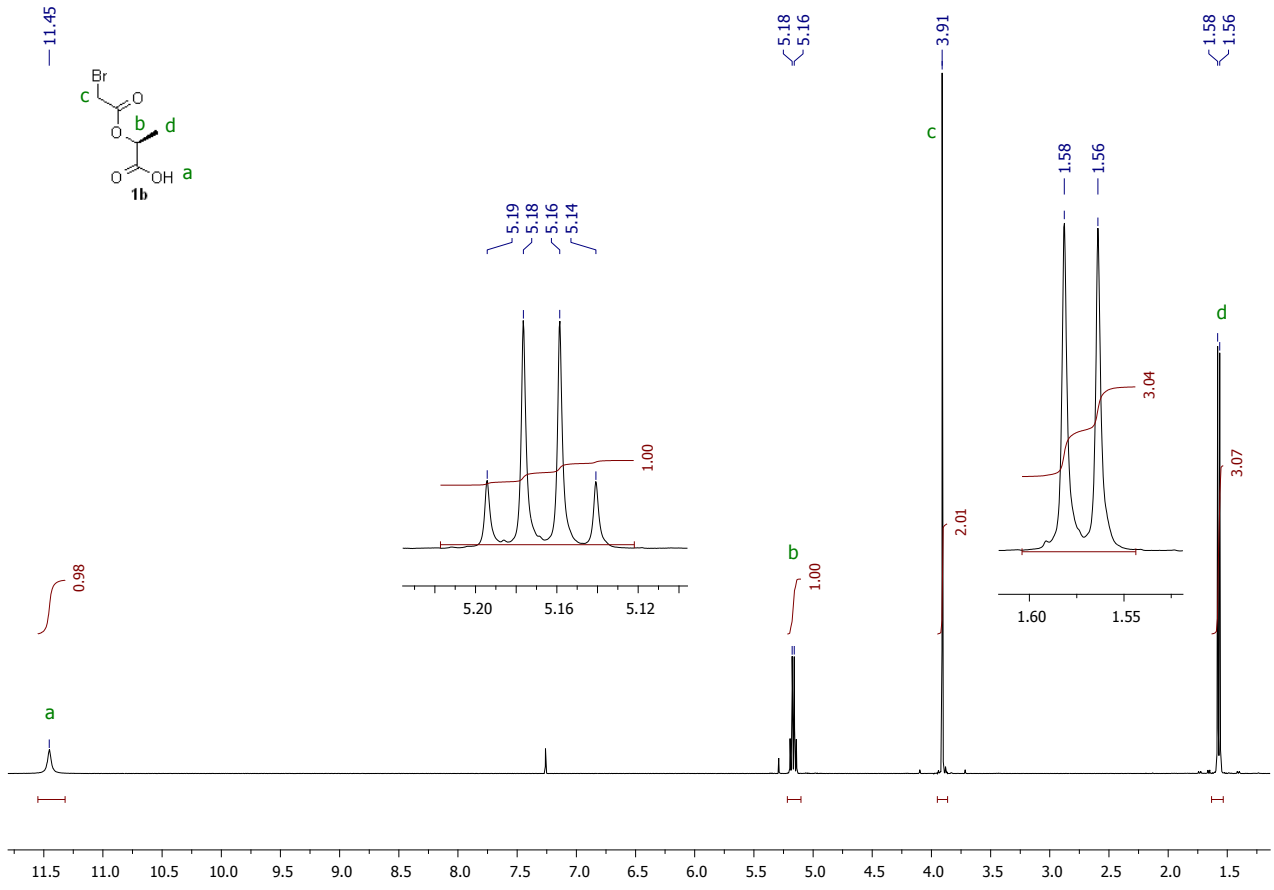


Fig. S2. [1]H NMR spectrum of **1b**.

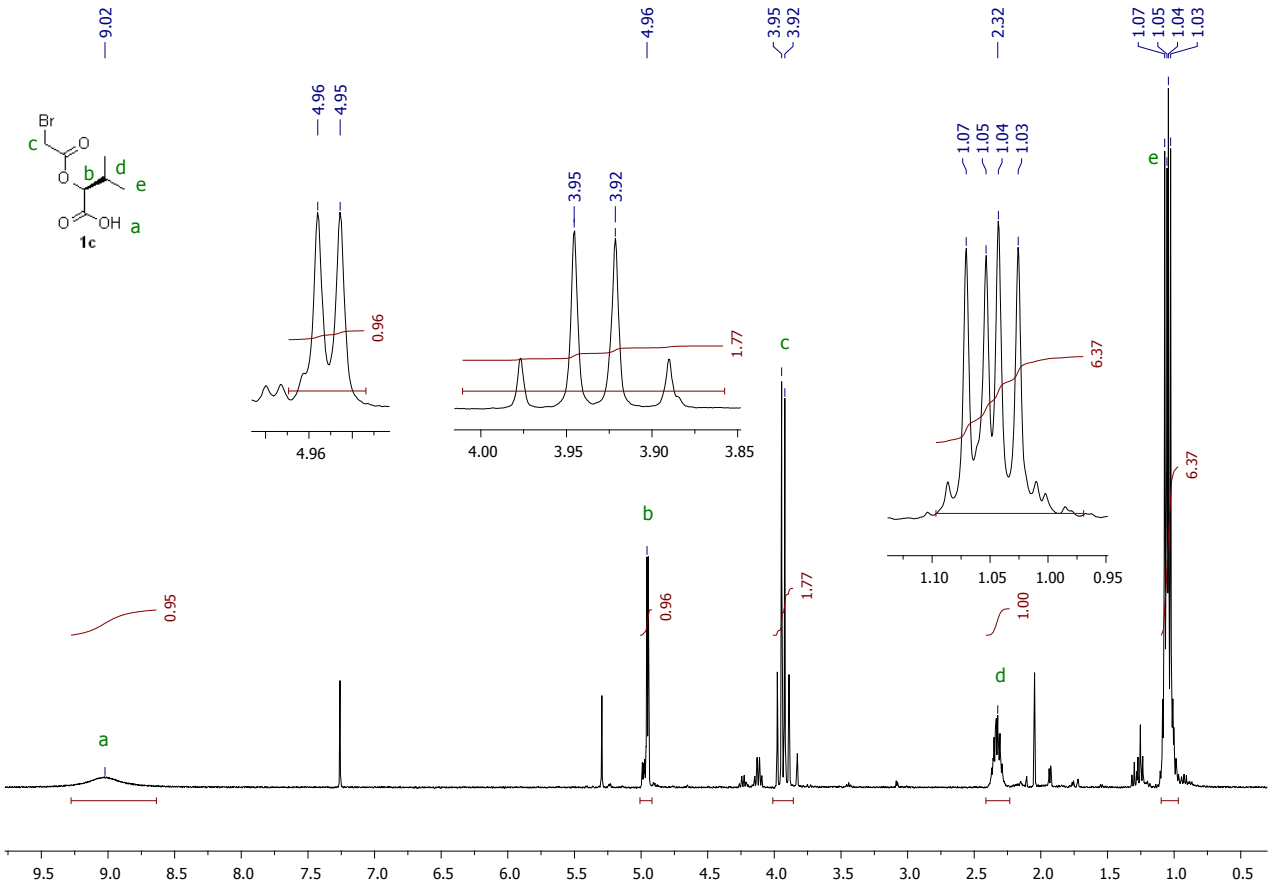


Fig. S3. ^{1}H NMR spectrum of **1c**.

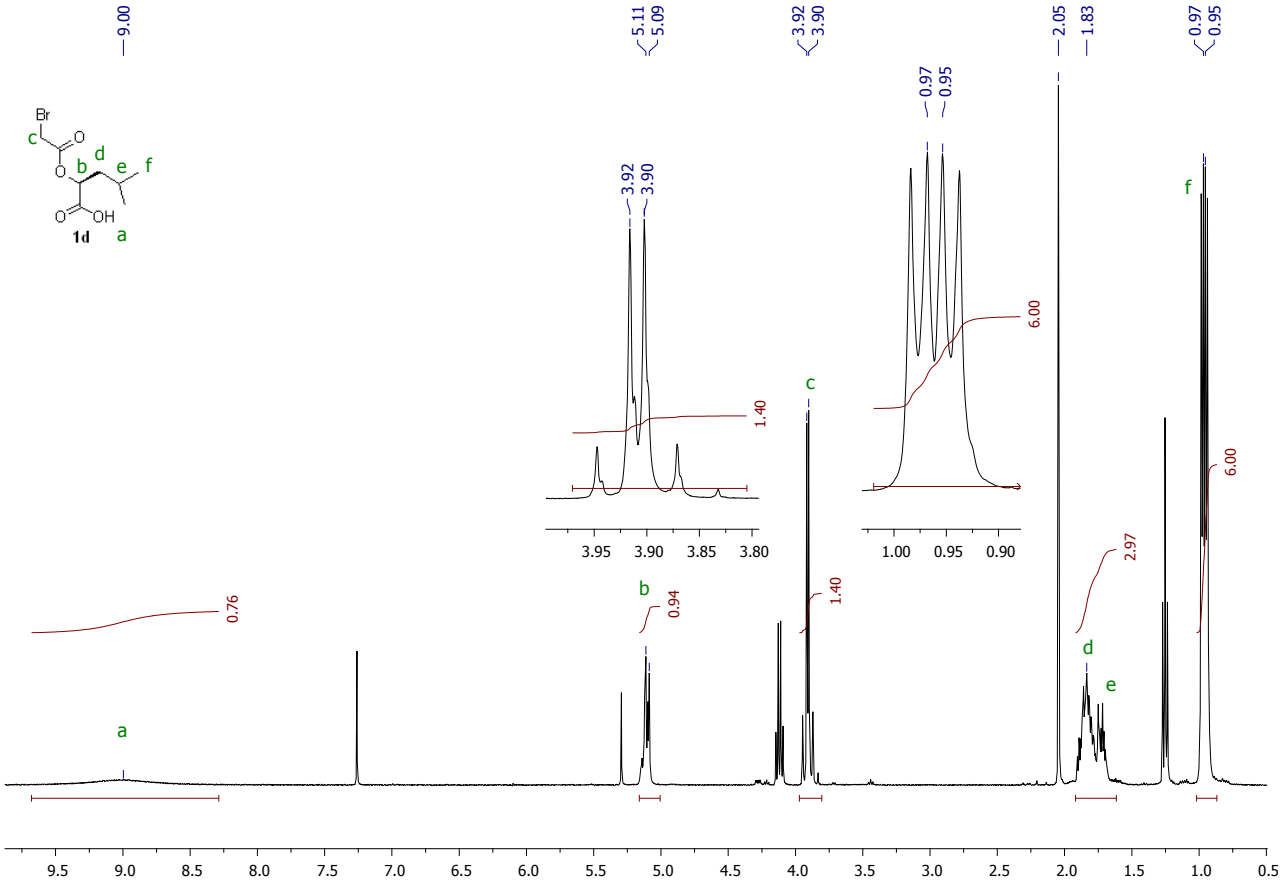


Fig. S4. ^{1}H NMR spectrum of **1d**.

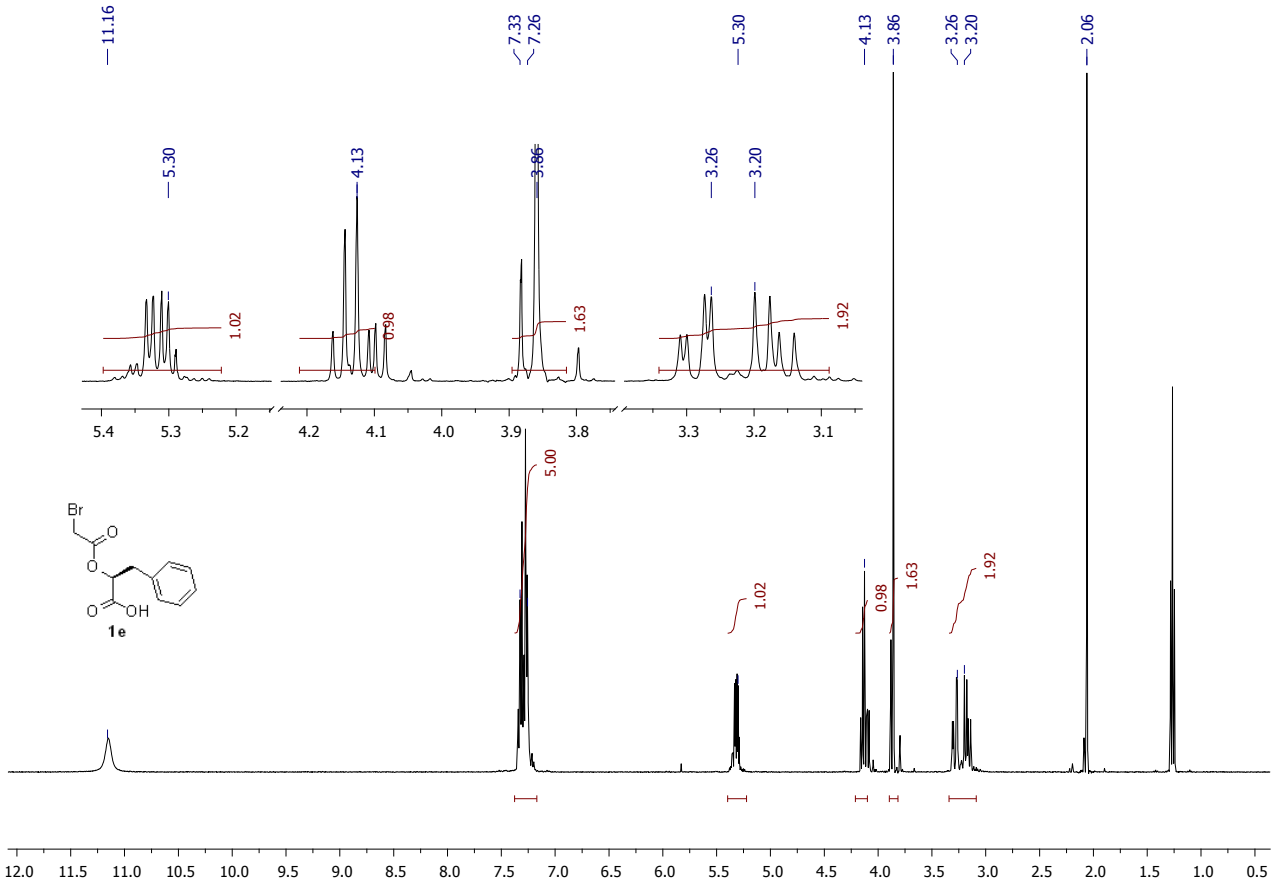


Fig. S5. ^{1}H NMR spectrum of **1e**.

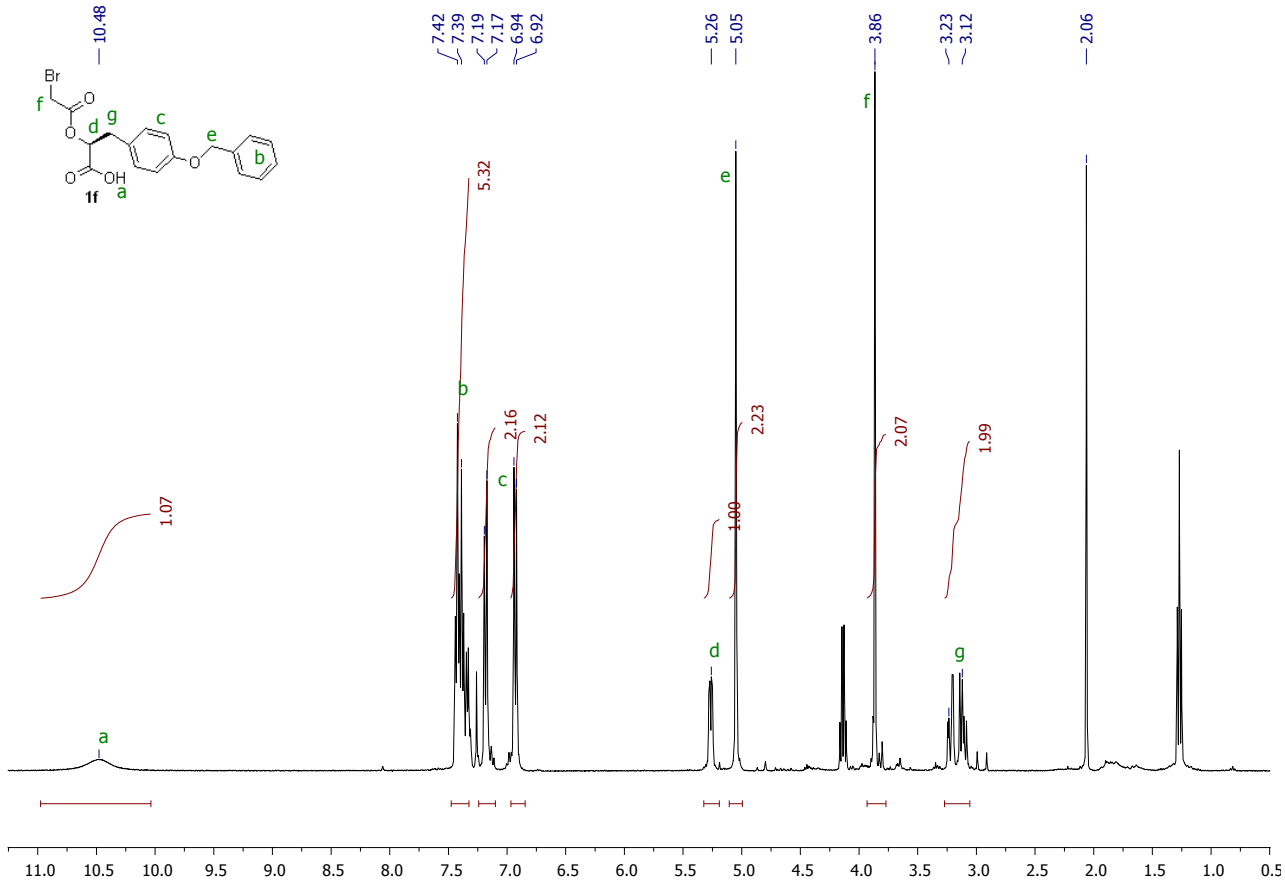


Fig. S6. ^{1}H NMR spectrum of **1f**.

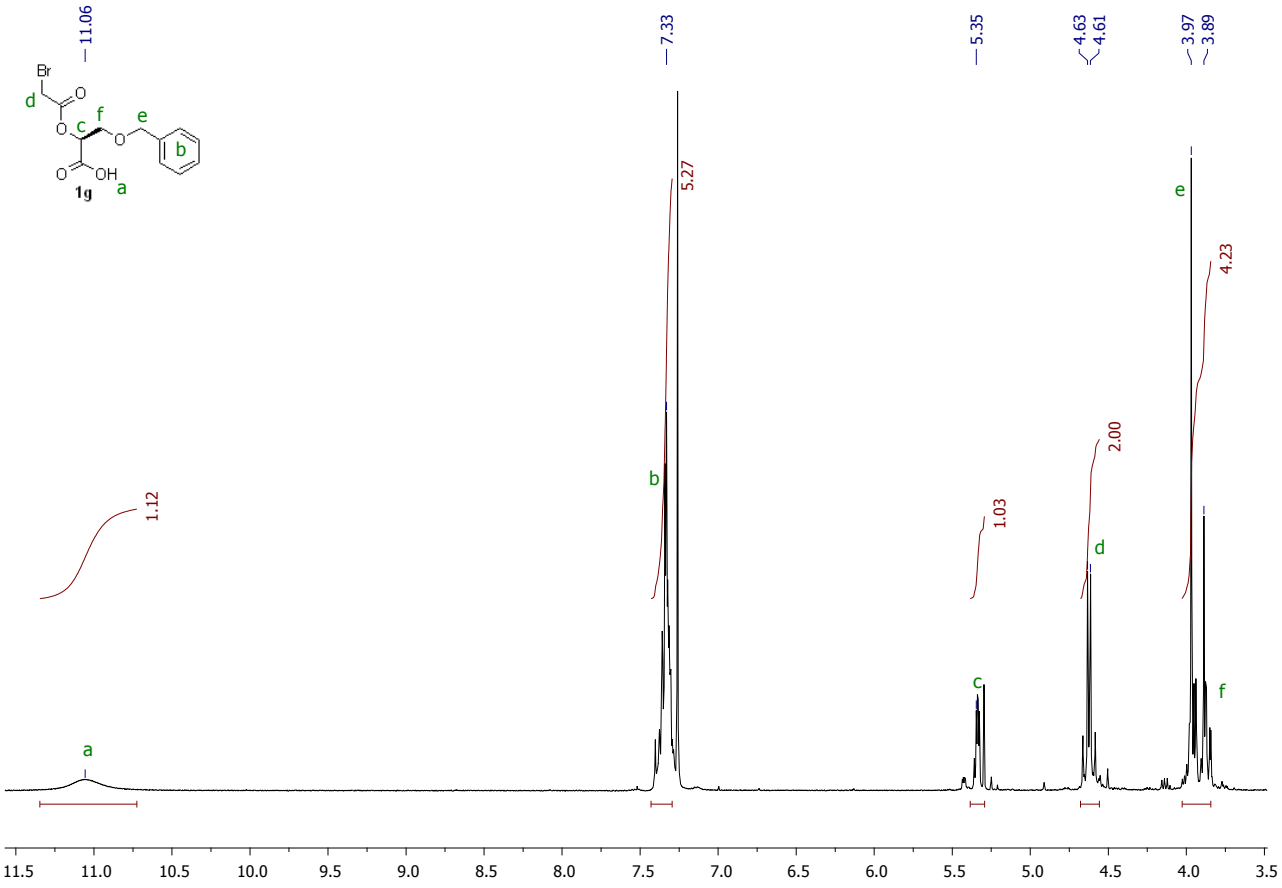


Fig. S7. ^{1}H NMR spectrum of **1g**.

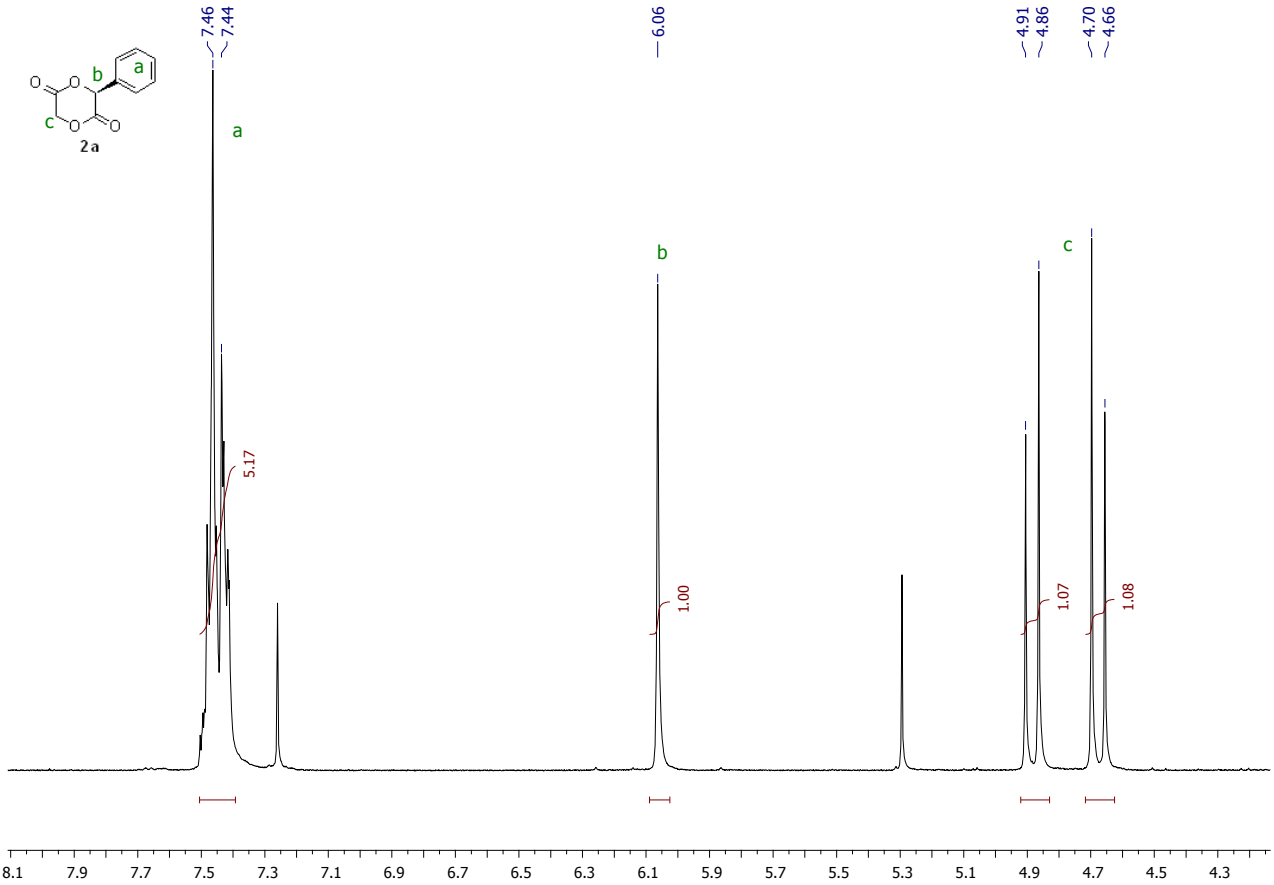


Fig. S8. ^{1}H NMR spectrum of **2a**.

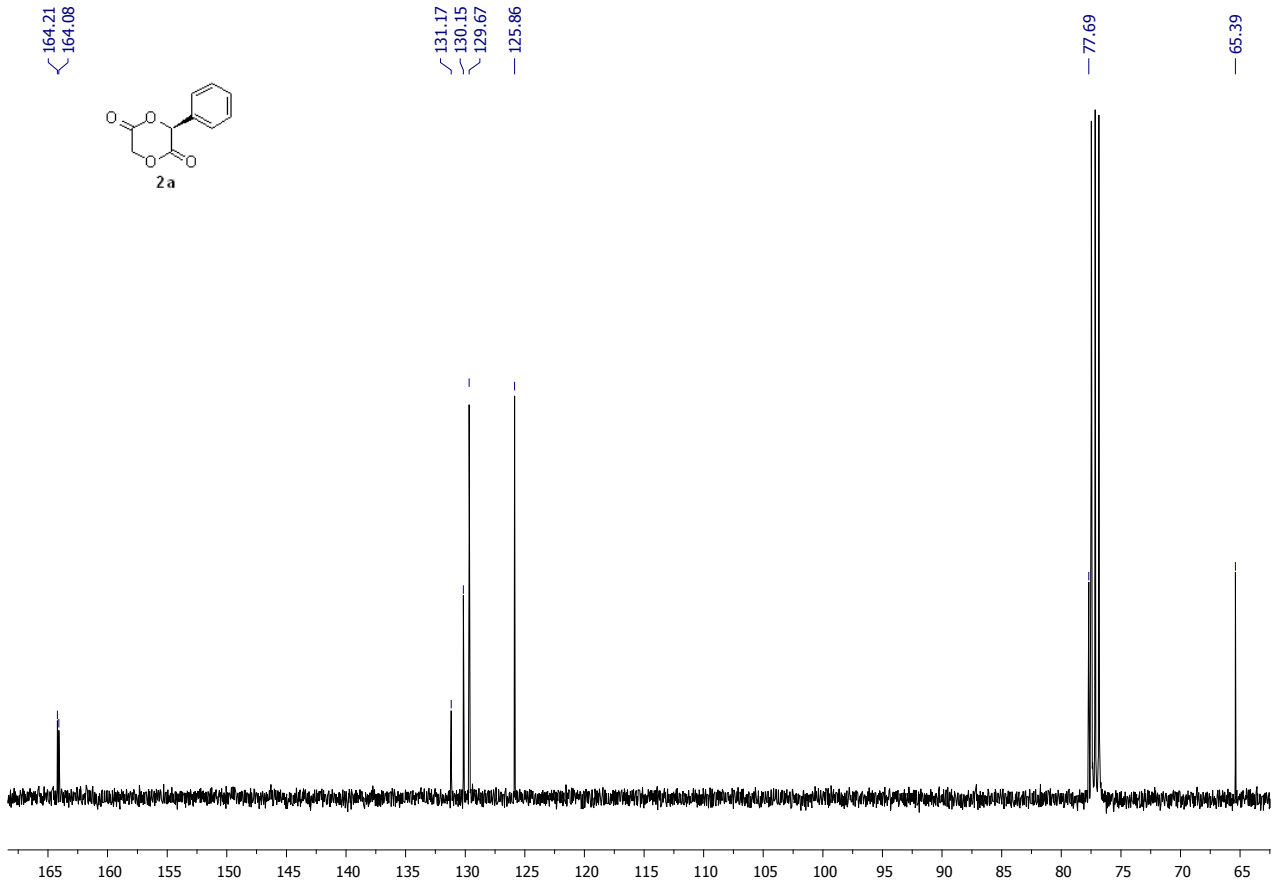


Fig. S9. ^{13}C NMR spectrum of **2a**.

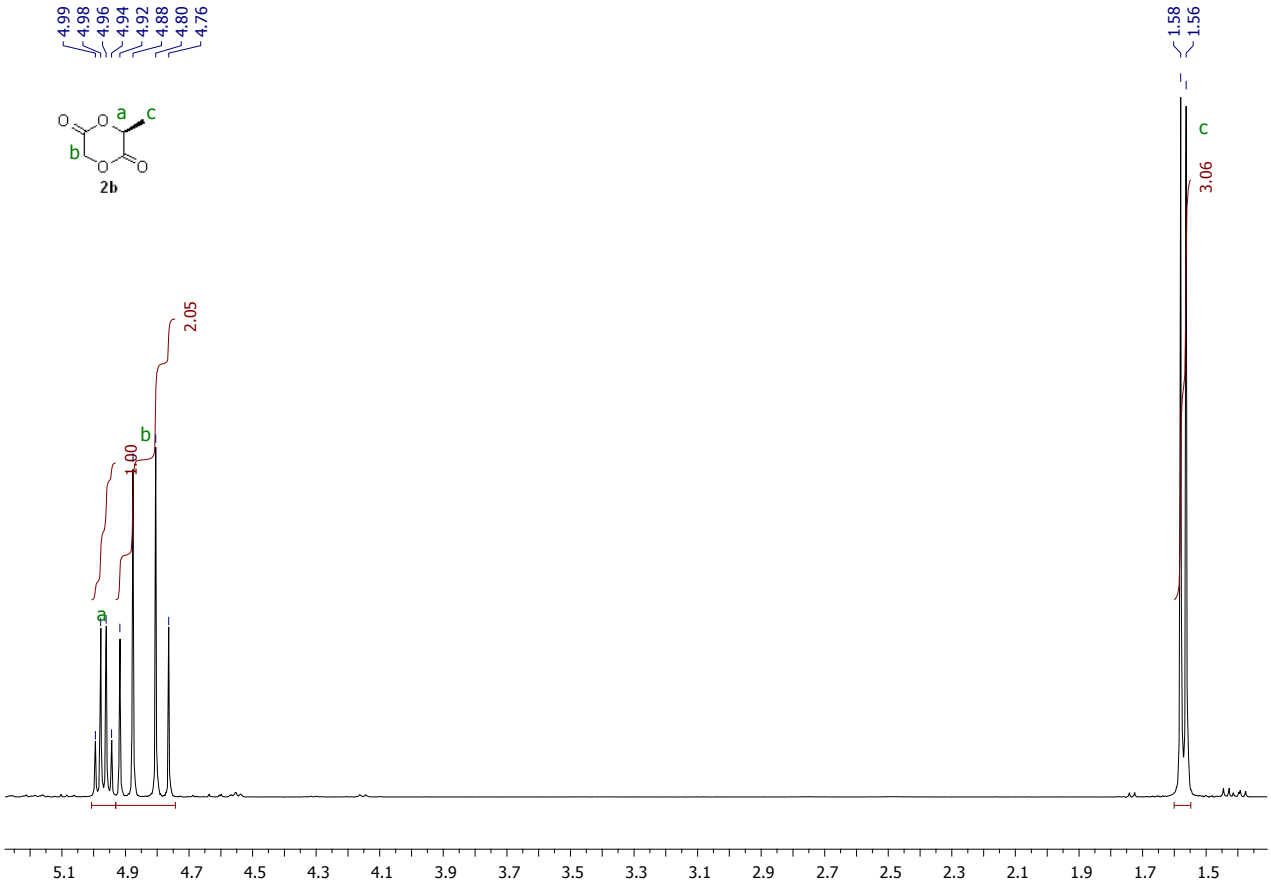


Fig. S10. ^{1}H NMR spectrum of **2b**.

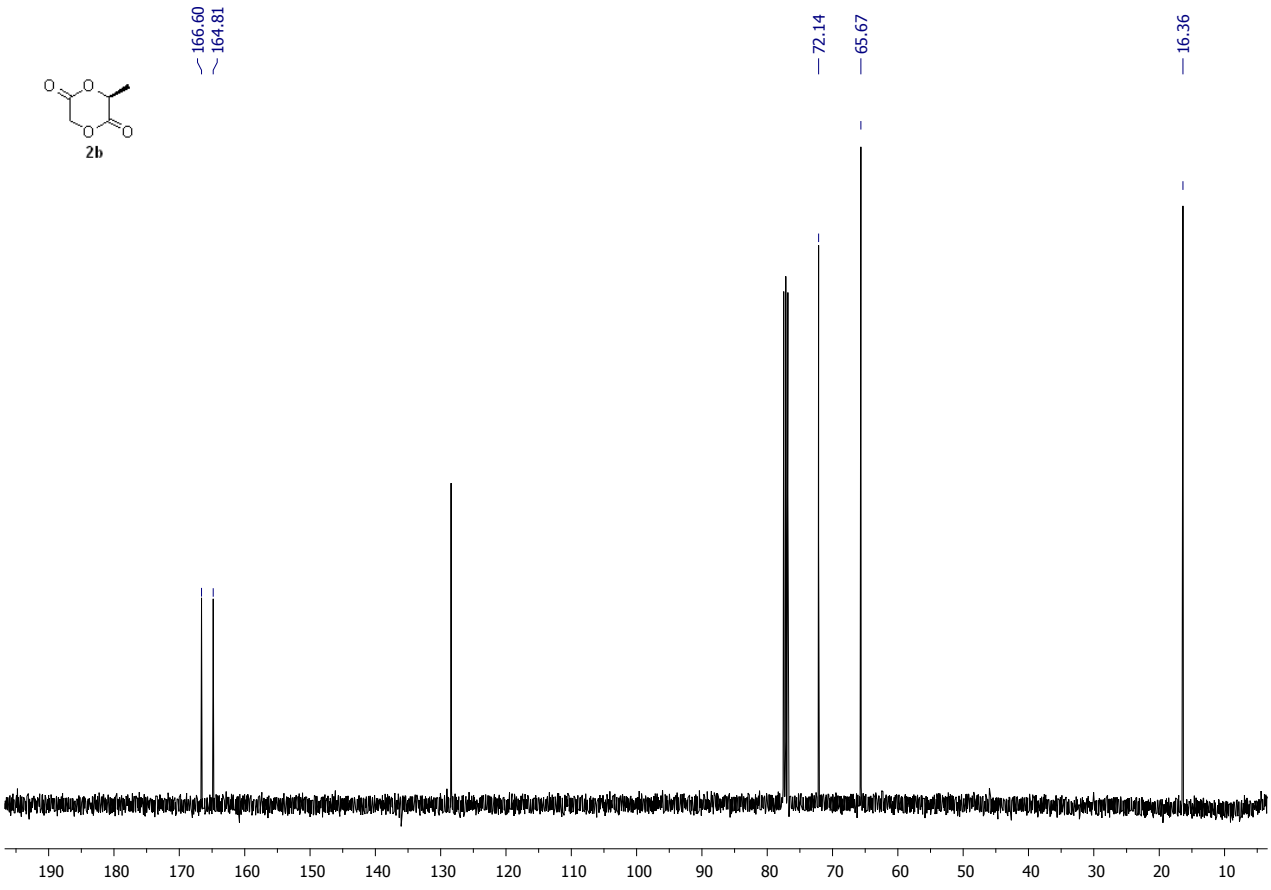


Fig. S11. ^{13}C NMR spectrum of **2b**.

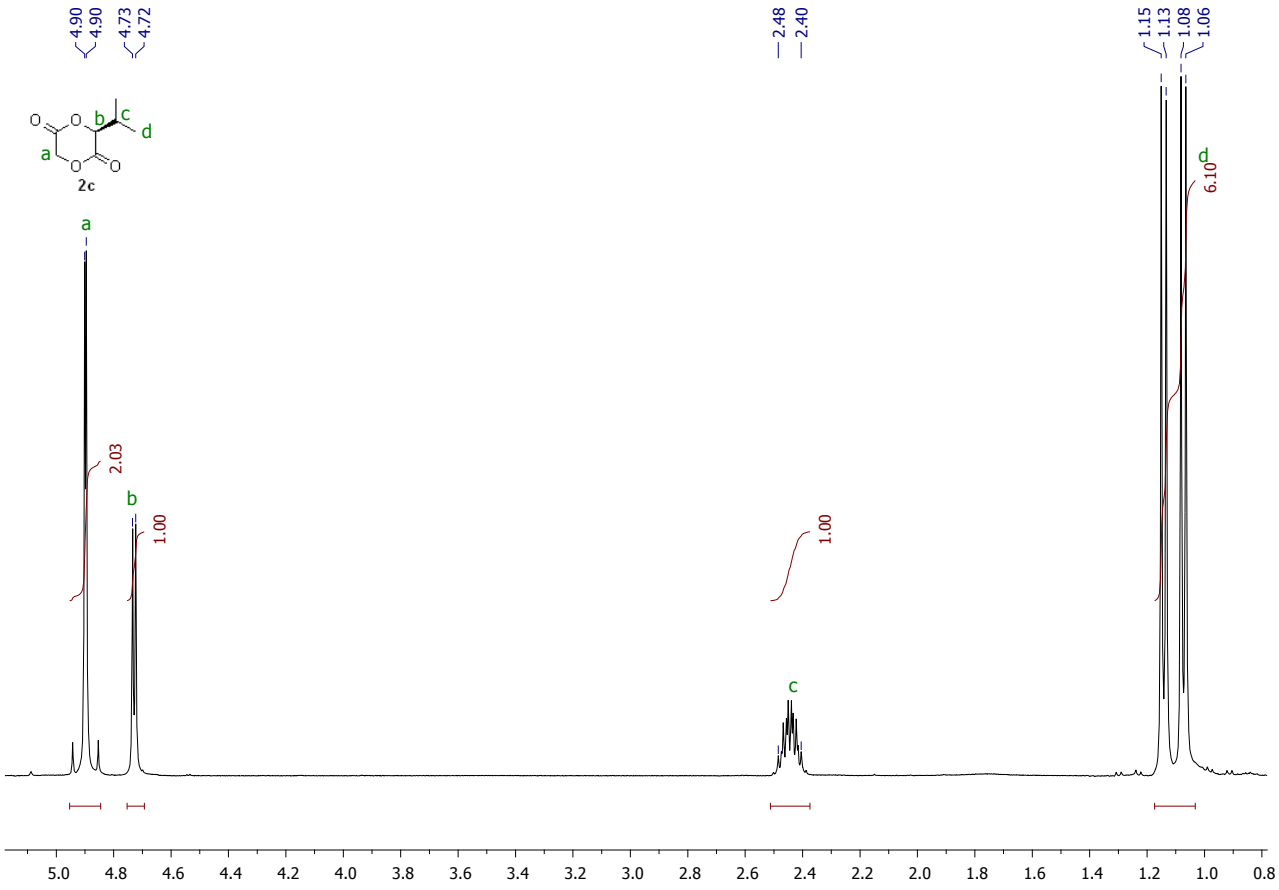


Fig. S12. ^{1}H NMR spectrum of **2c**.

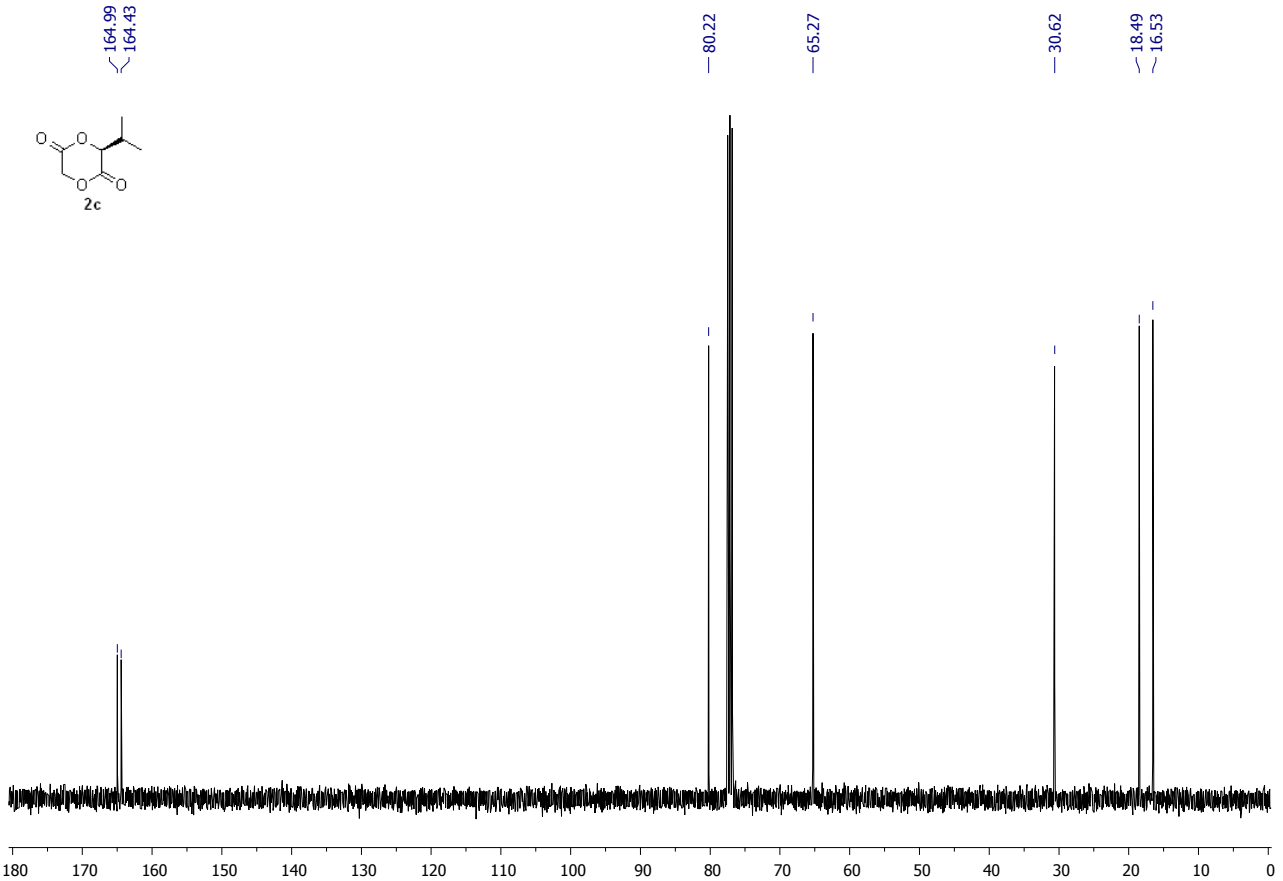


Fig. S13. ^{13}C NMR spectrum of **2c**.

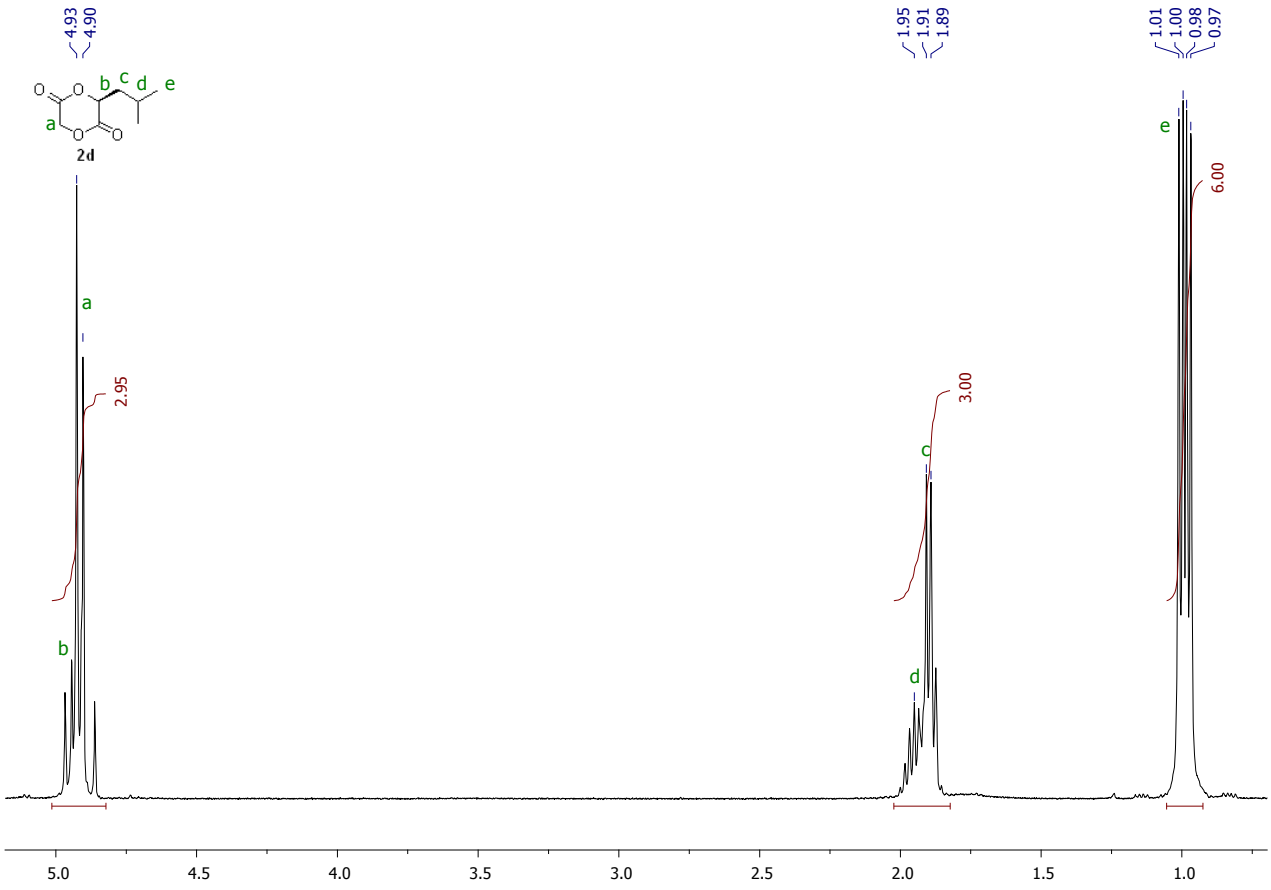


Fig. S14. ^{1}H NMR spectrum of **2d**.

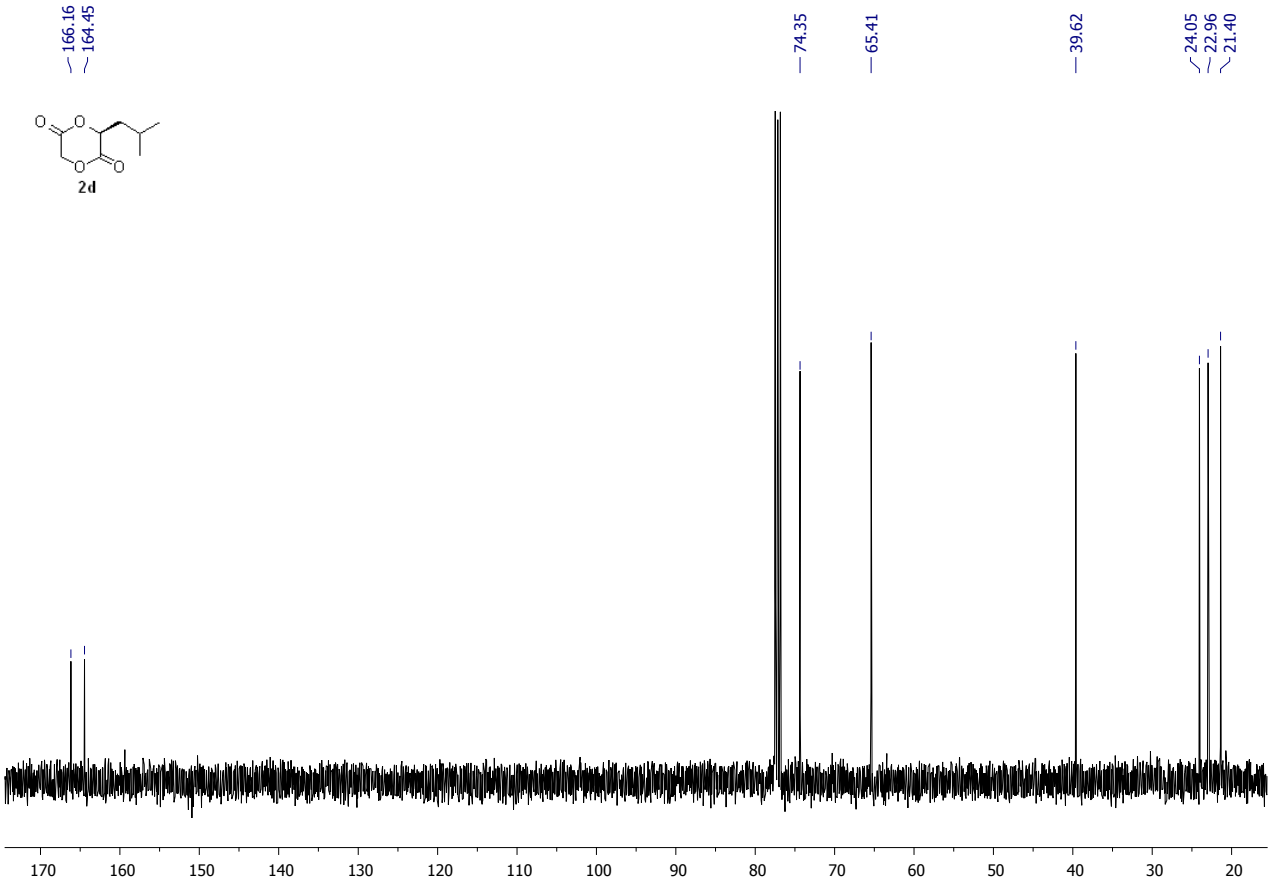


Fig. S15. ^{13}C NMR spectrum of **2d**.

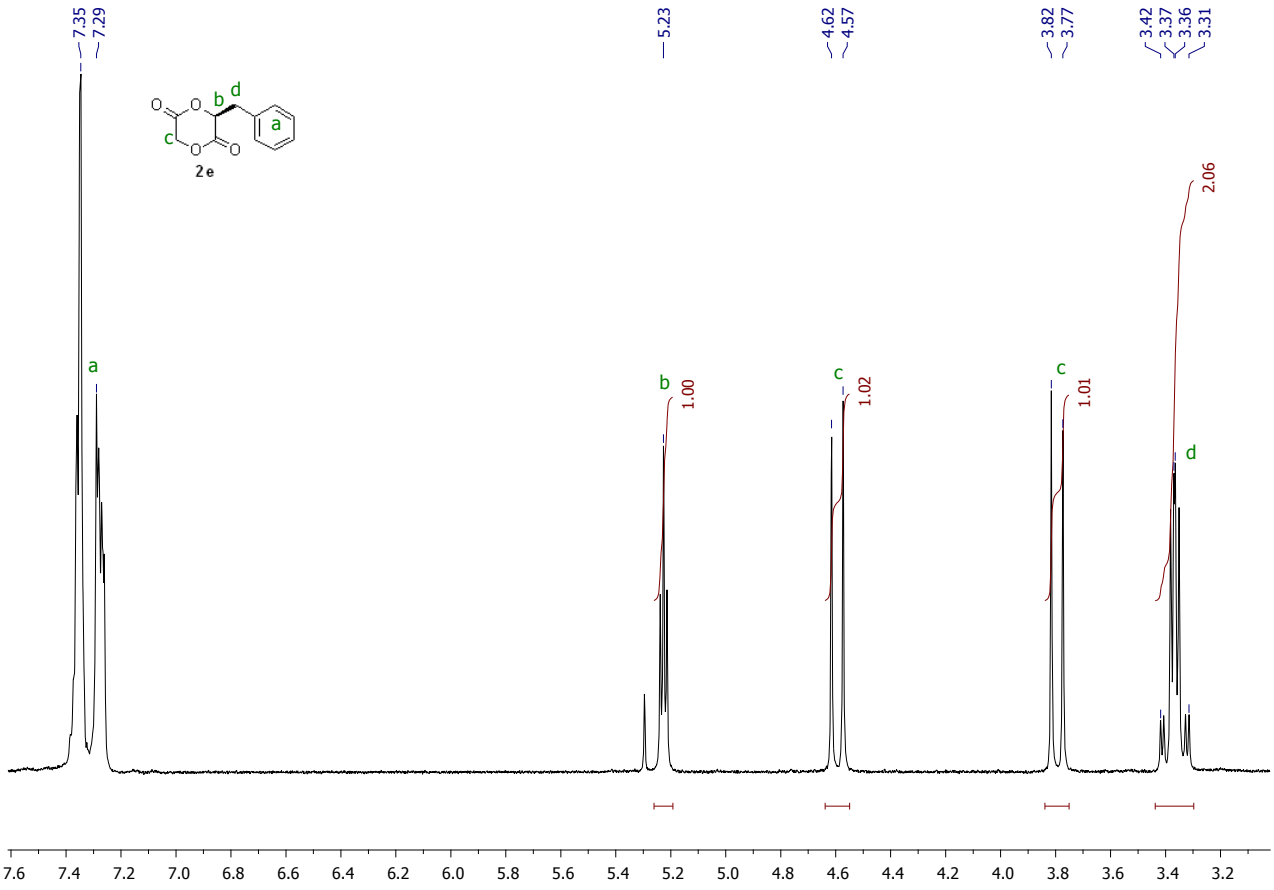


Fig. S16. ^{1}H NMR spectrum of **2e**.

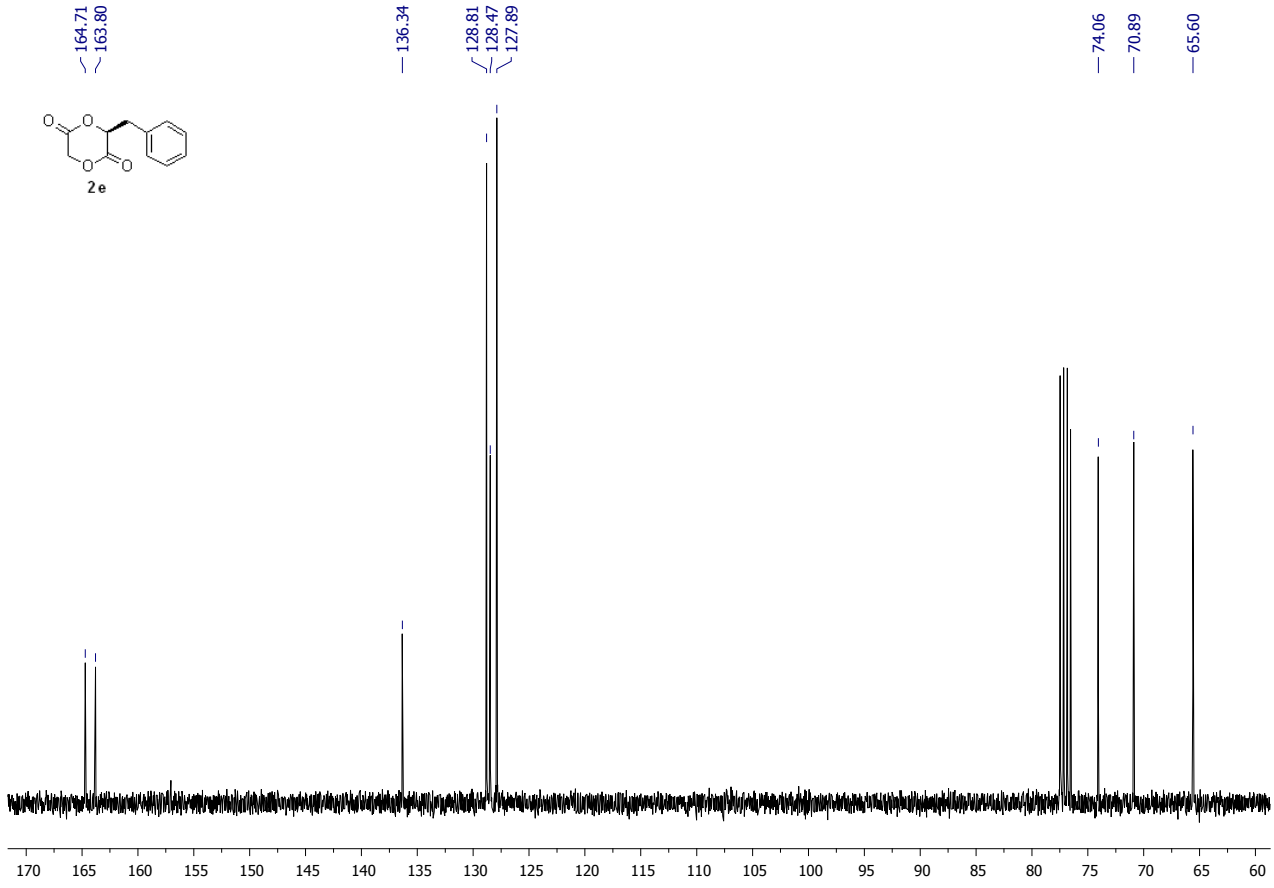


Fig. S17. ^{13}C NMR spectrum of **2e**.

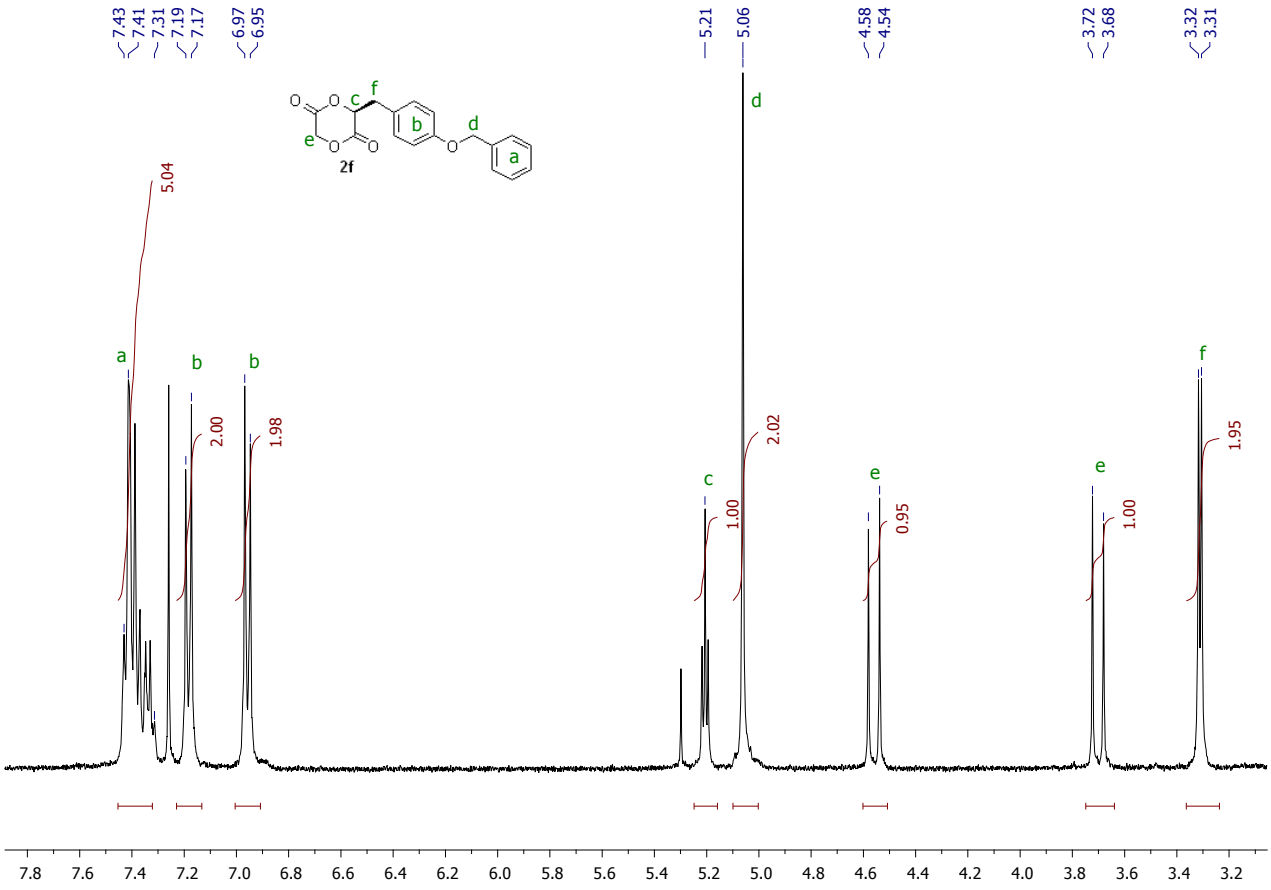


Fig. S18. ^{1}H NMR spectrum of **2f**.

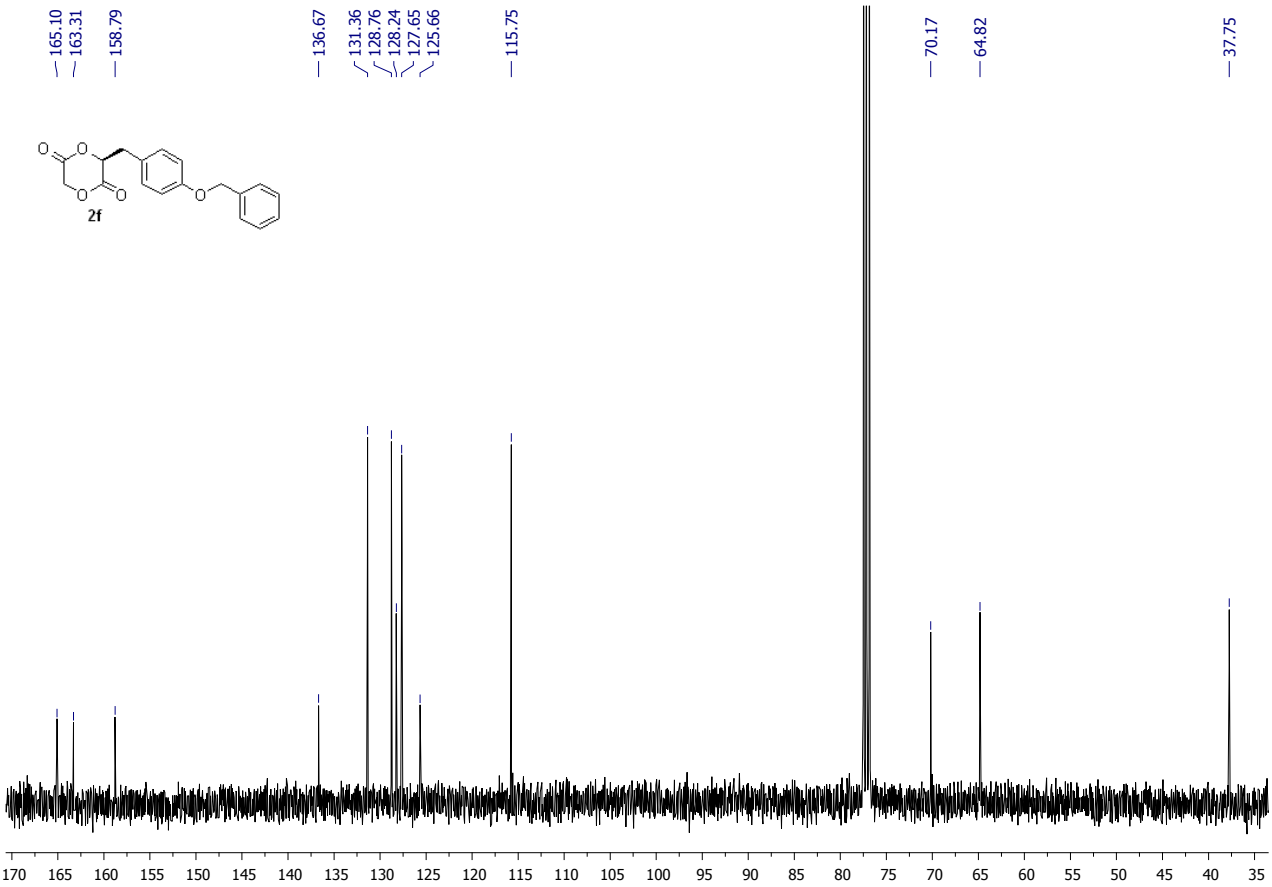


Fig. S19. ^{13}C NMR spectrum of **2f**.

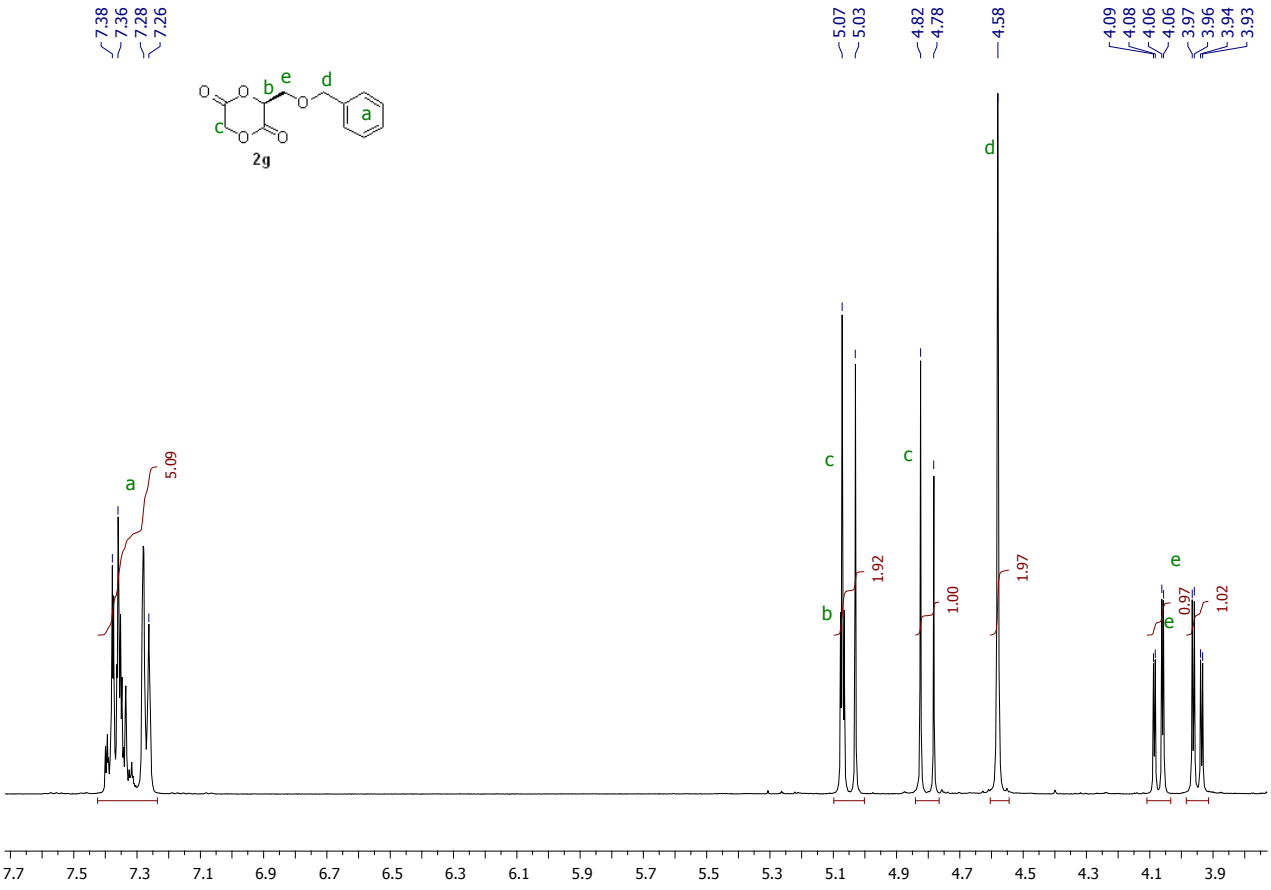


Fig. S20. ^{1}H NMR spectrum of **2g**.

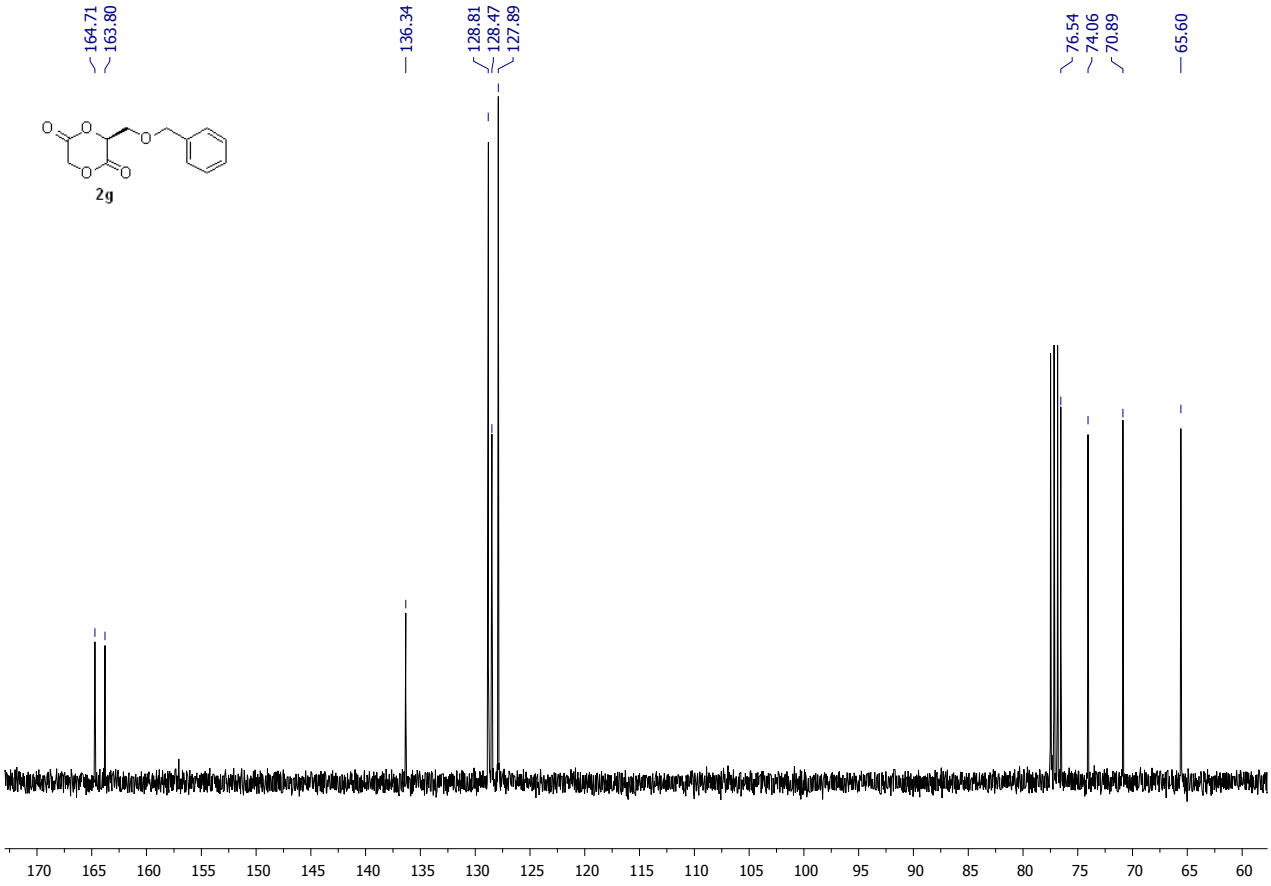


Fig. S21. ^{13}C NMR spectrum of **2g**.

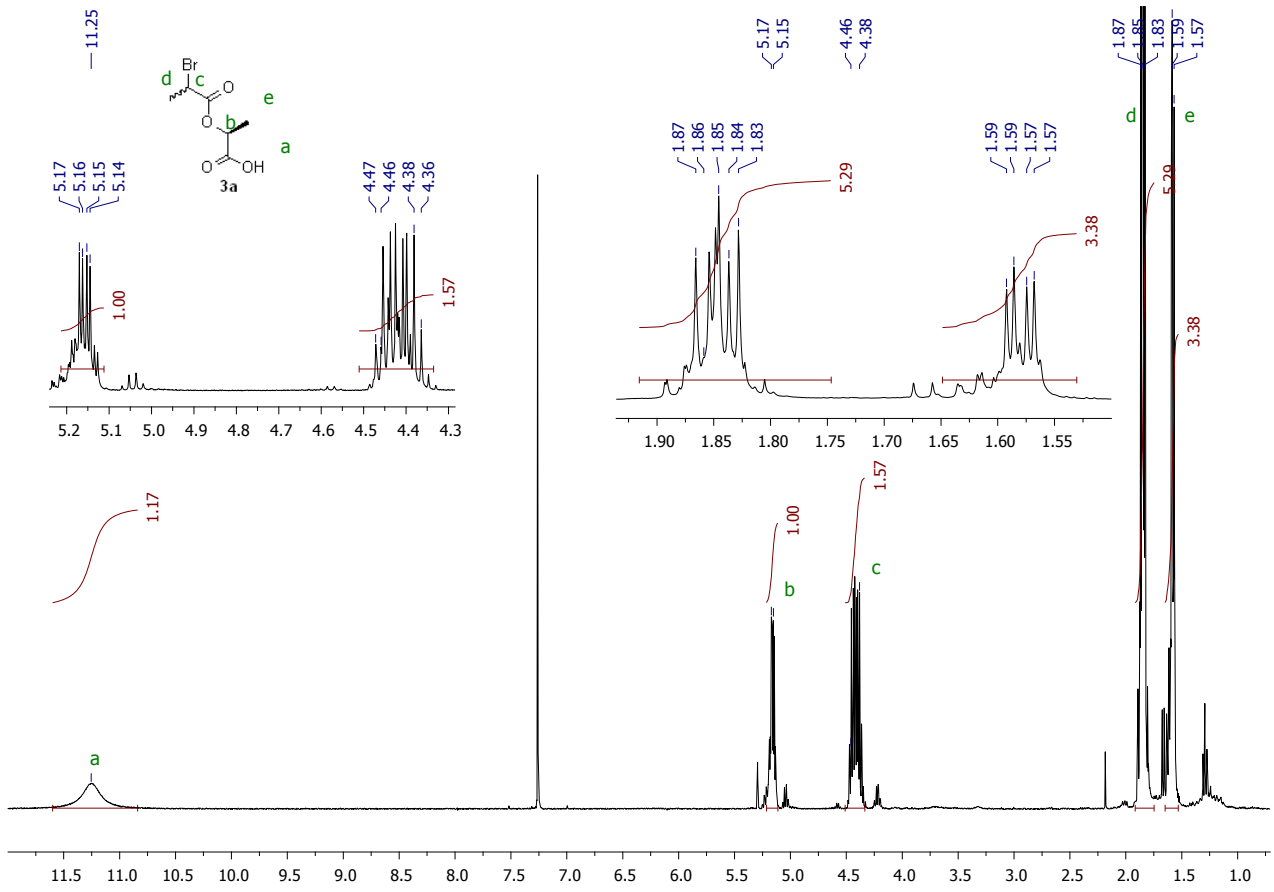


Fig. S22. ^{1}H NMR spectrum of **3a**.

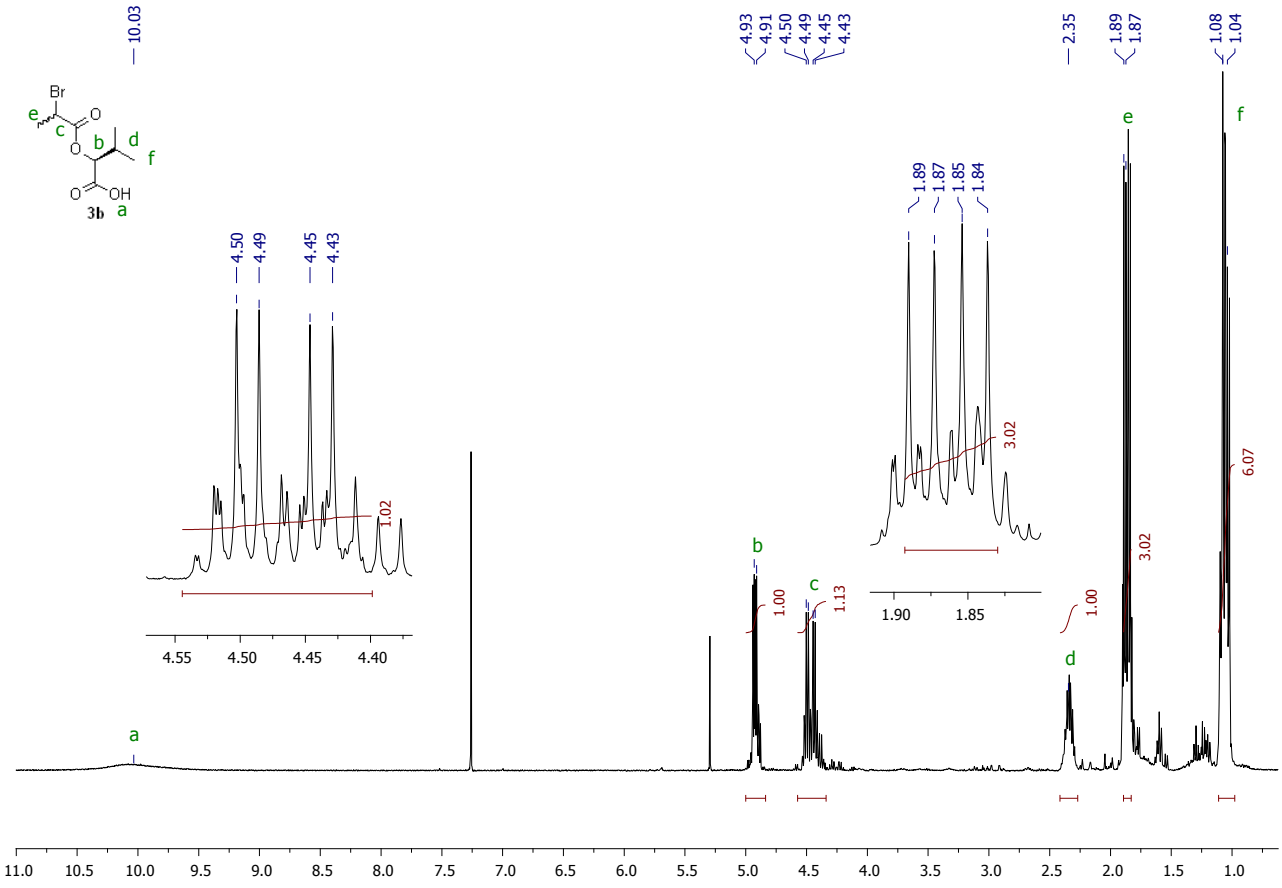


Fig. S23. ^{1}H NMR spectrum of **3b**.

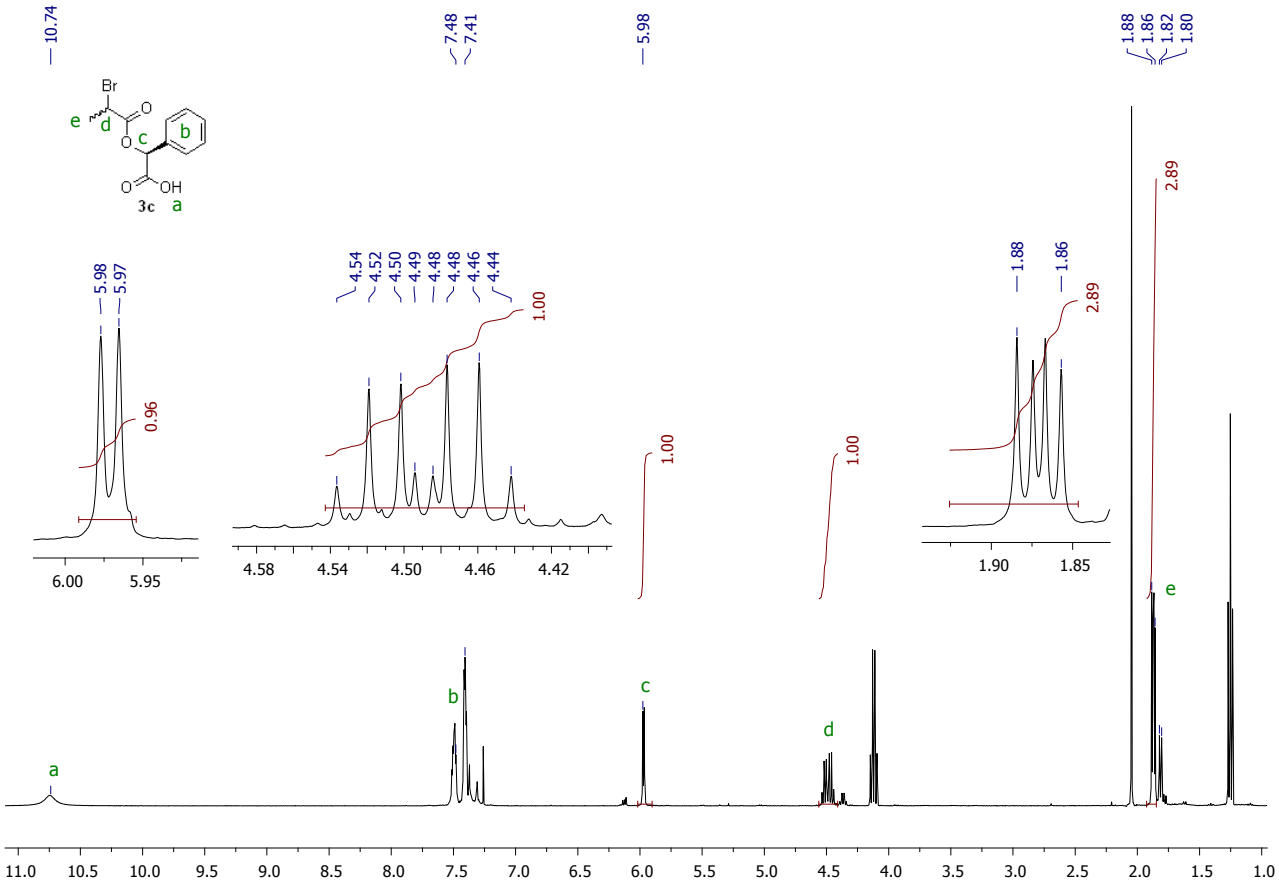


Fig. S24. [1]H NMR spectrum of **3c**.

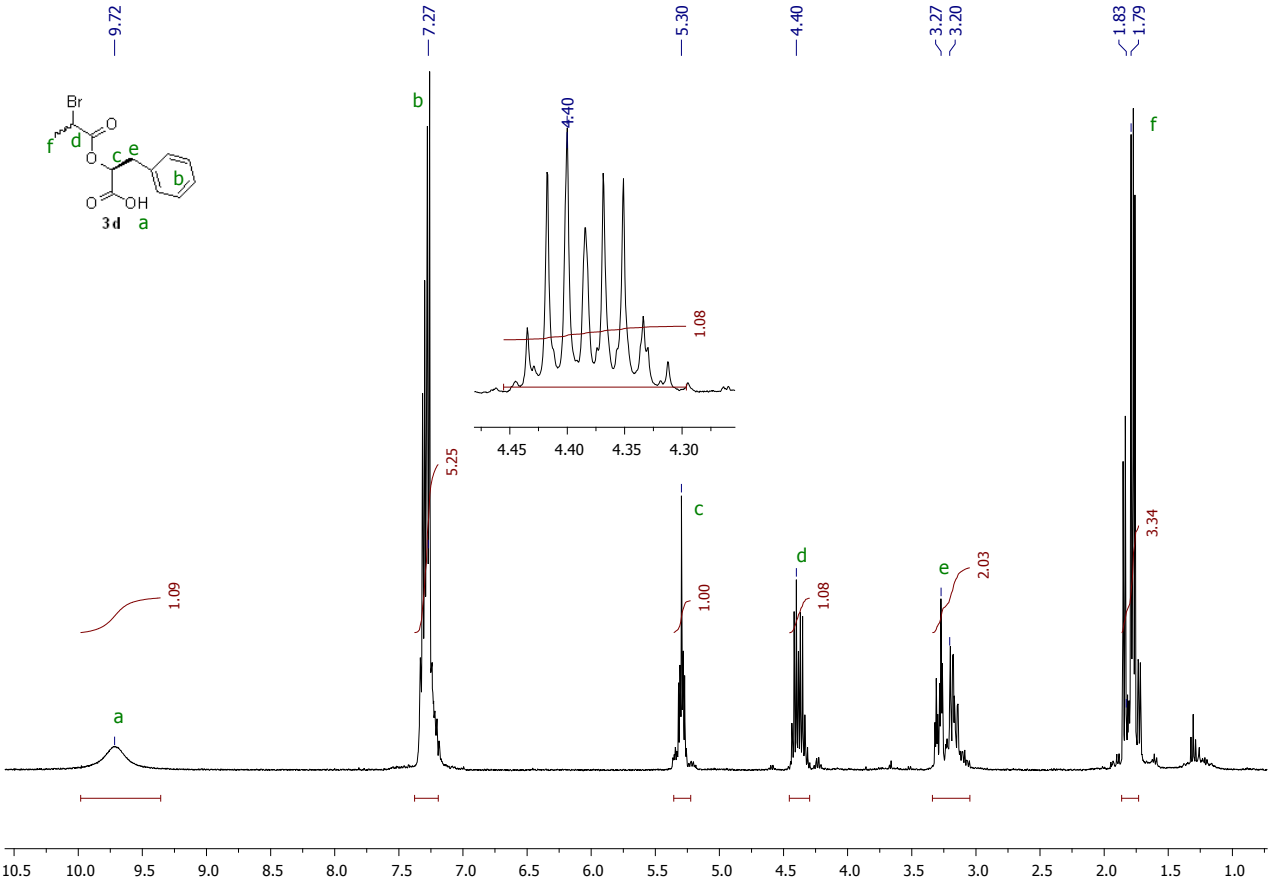


Fig. S25. [1]H NMR spectrum of **3d**.

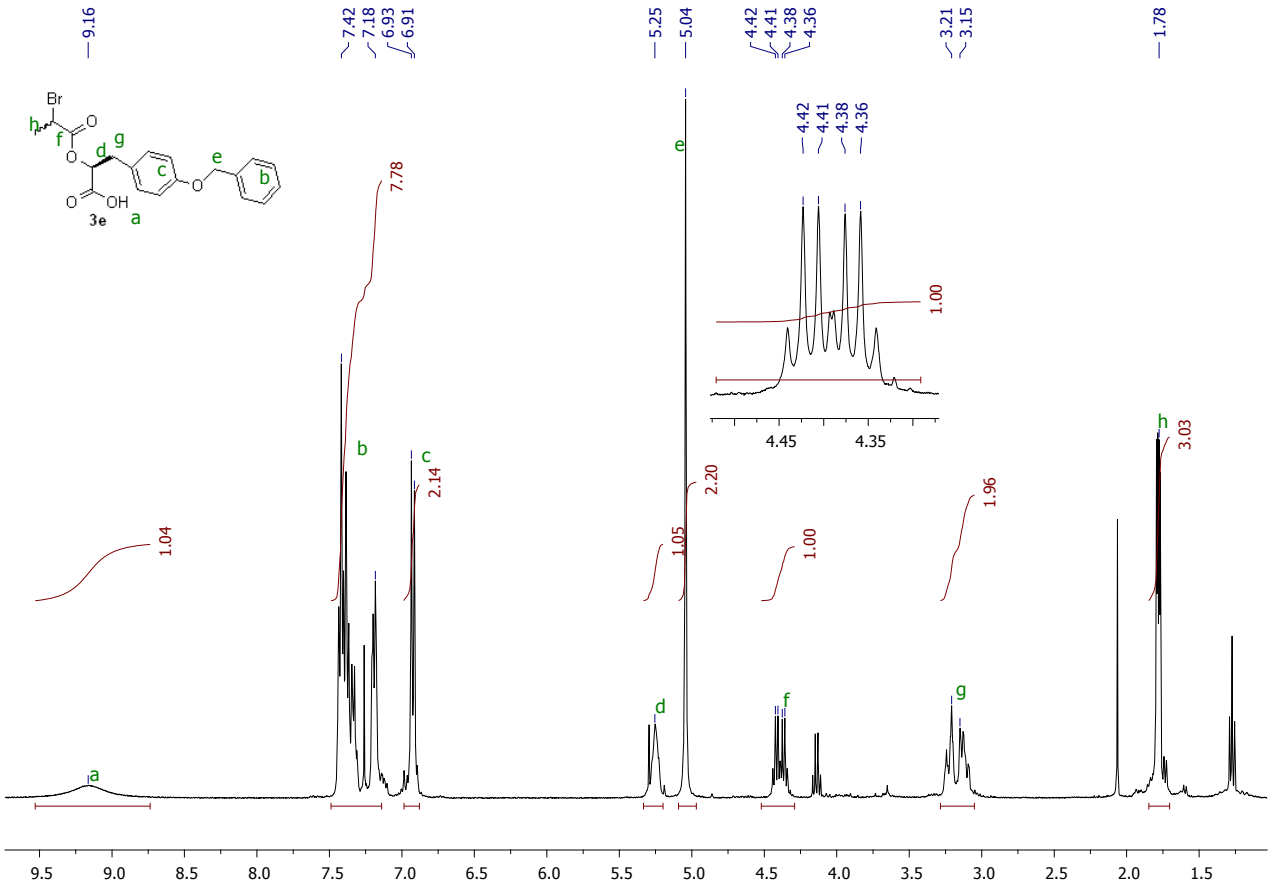


Fig. S26. [1]H NMR spectrum of **3f**.

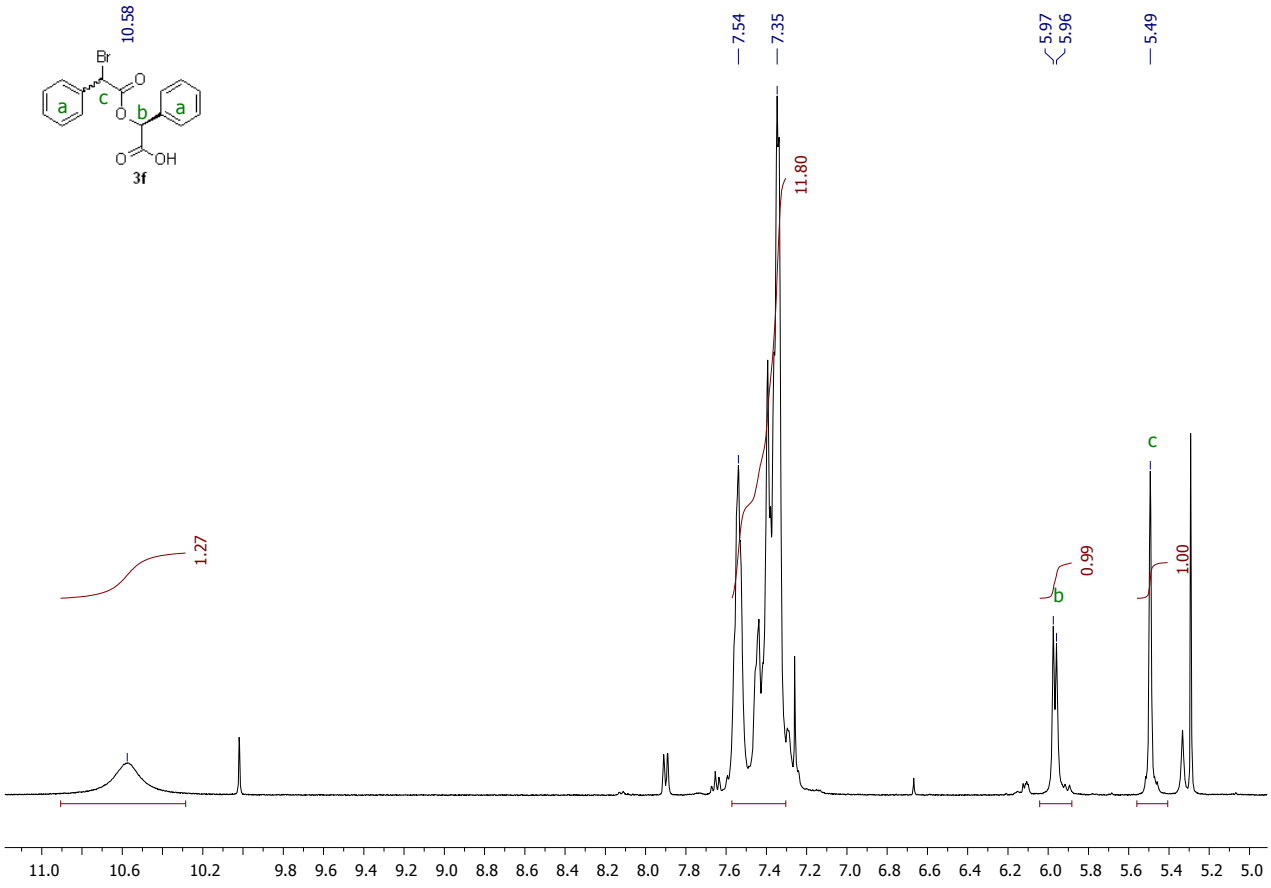


Fig. S27. [1]H NMR spectrum of **3g**.

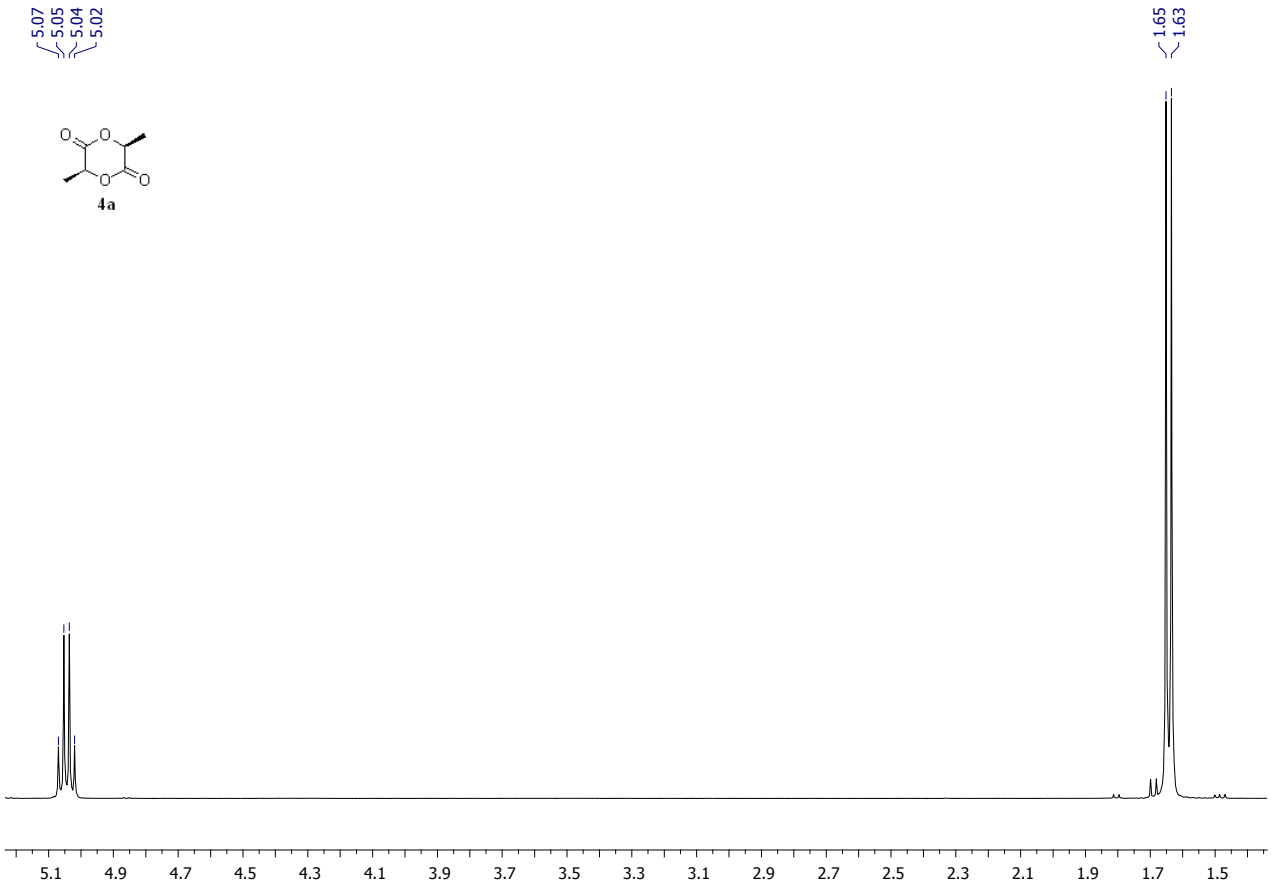


Fig. S28. ^{1}H NMR spectrum of **4a**.

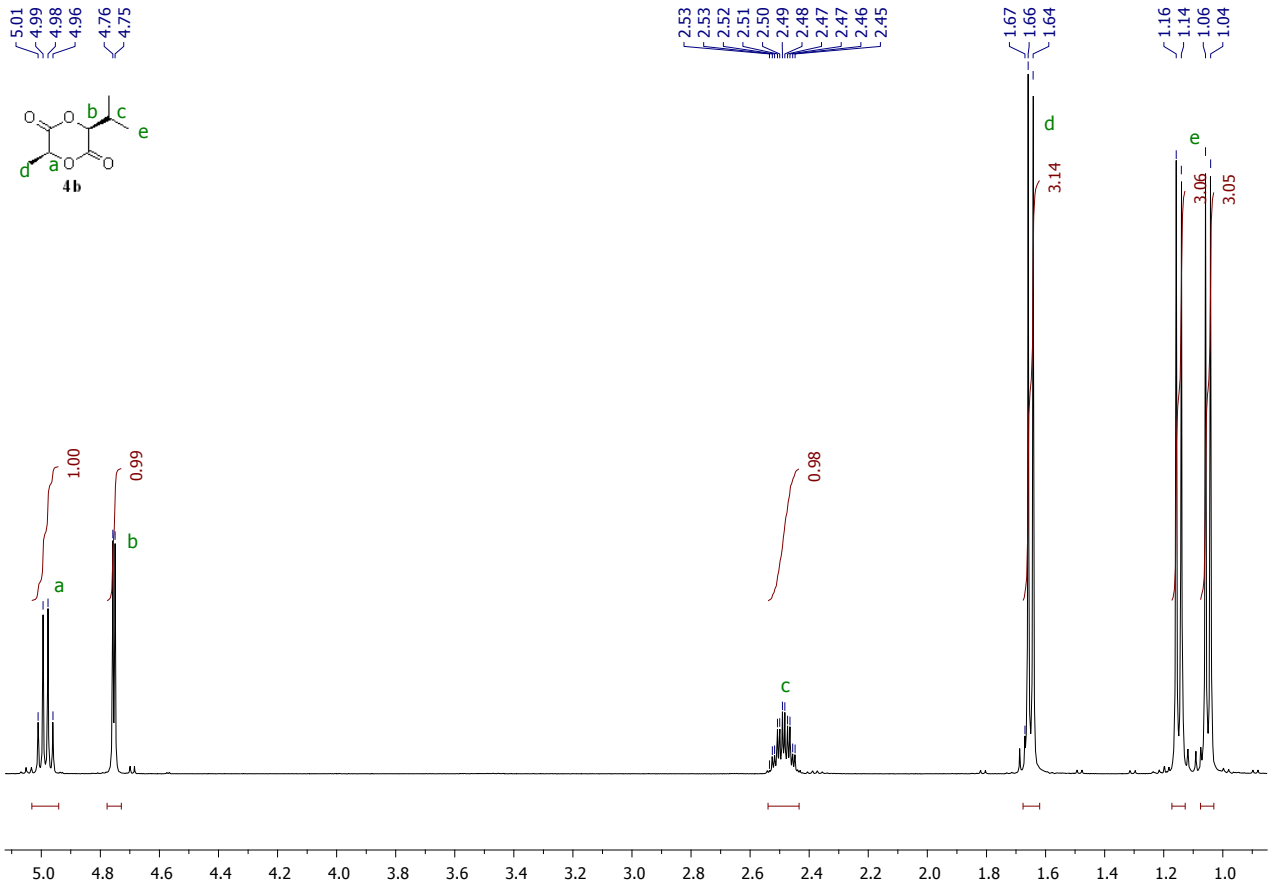


Fig. S29. ^{1}H NMR spectrum of **4b**.

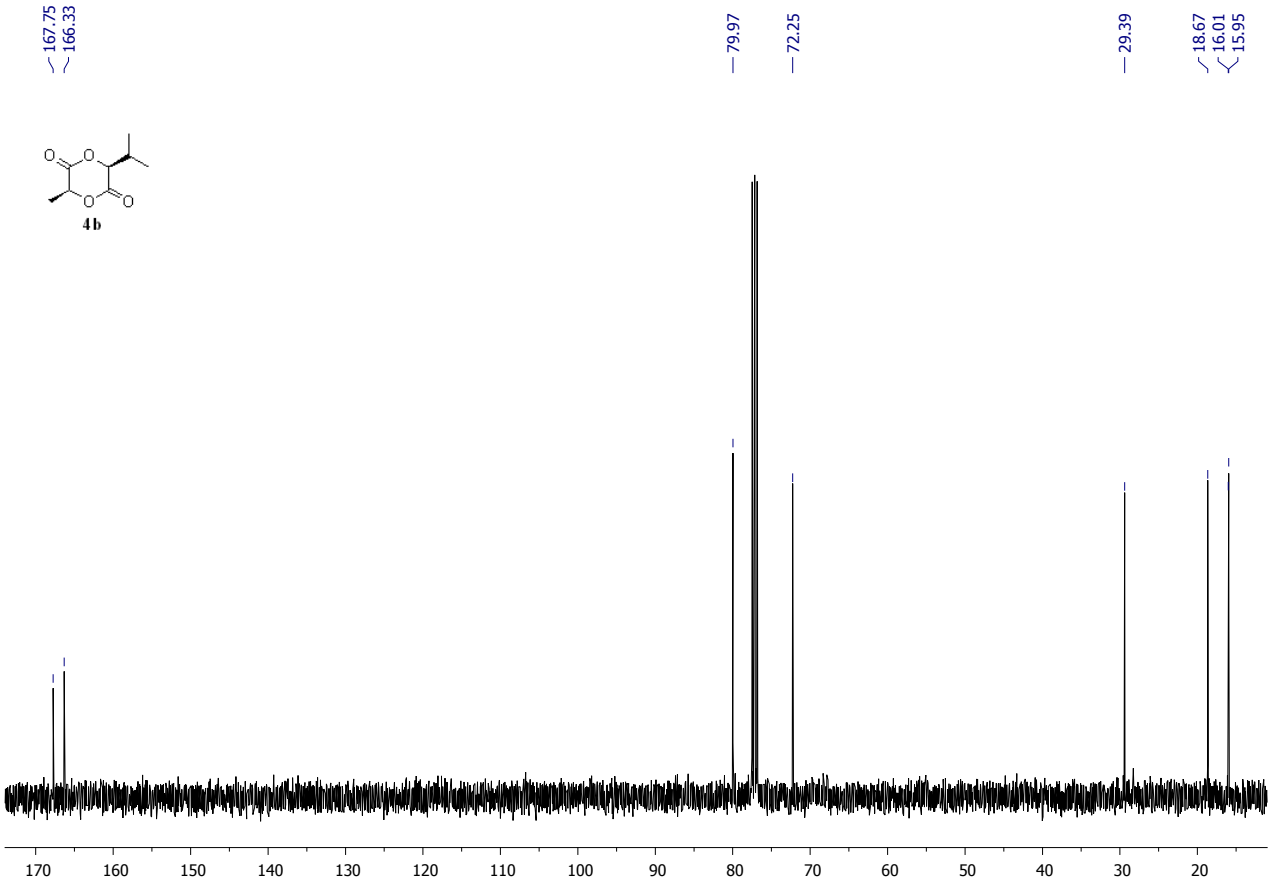


Fig. S30. ^{13}C NMR spectrum of **4b**.

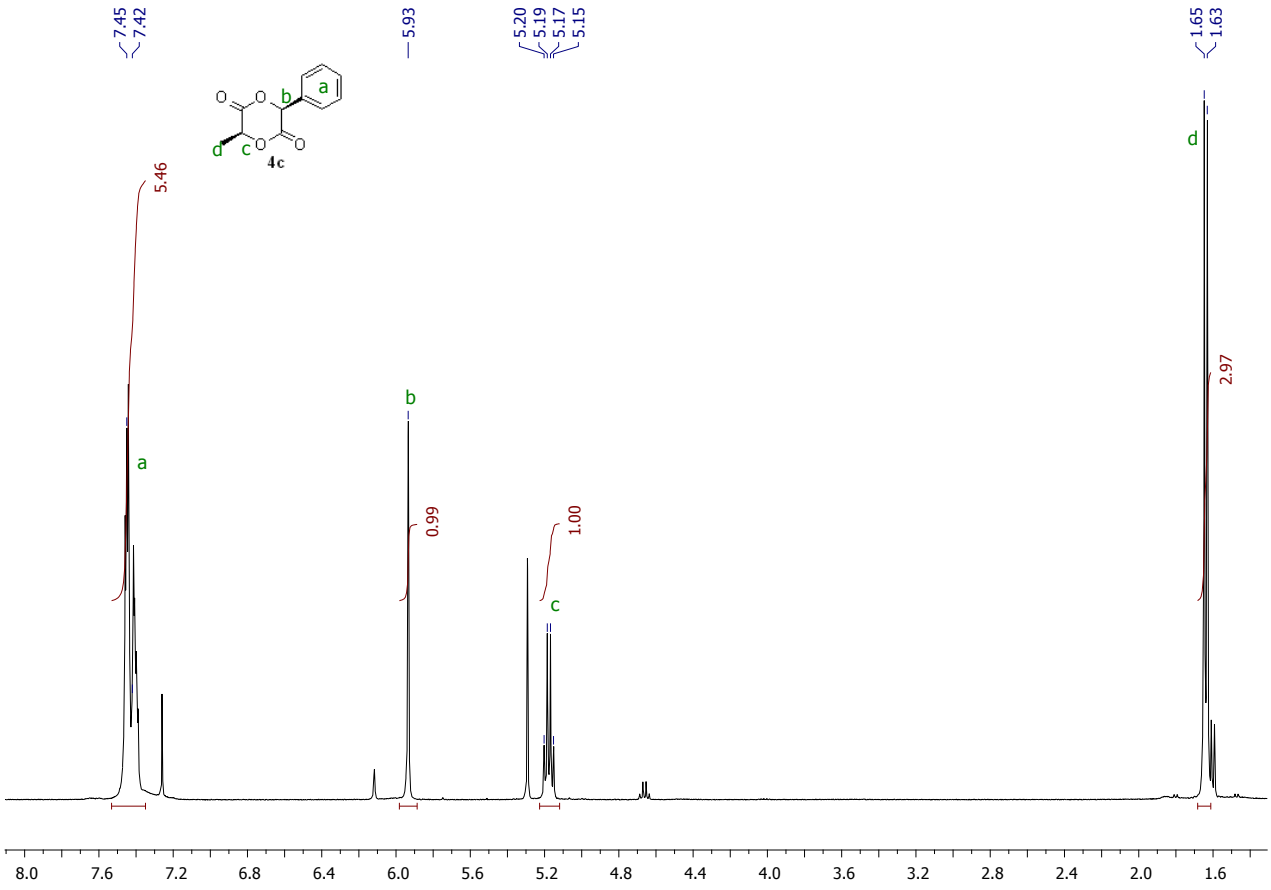


Fig. S31. ^{1}H NMR spectrum of **4c**.

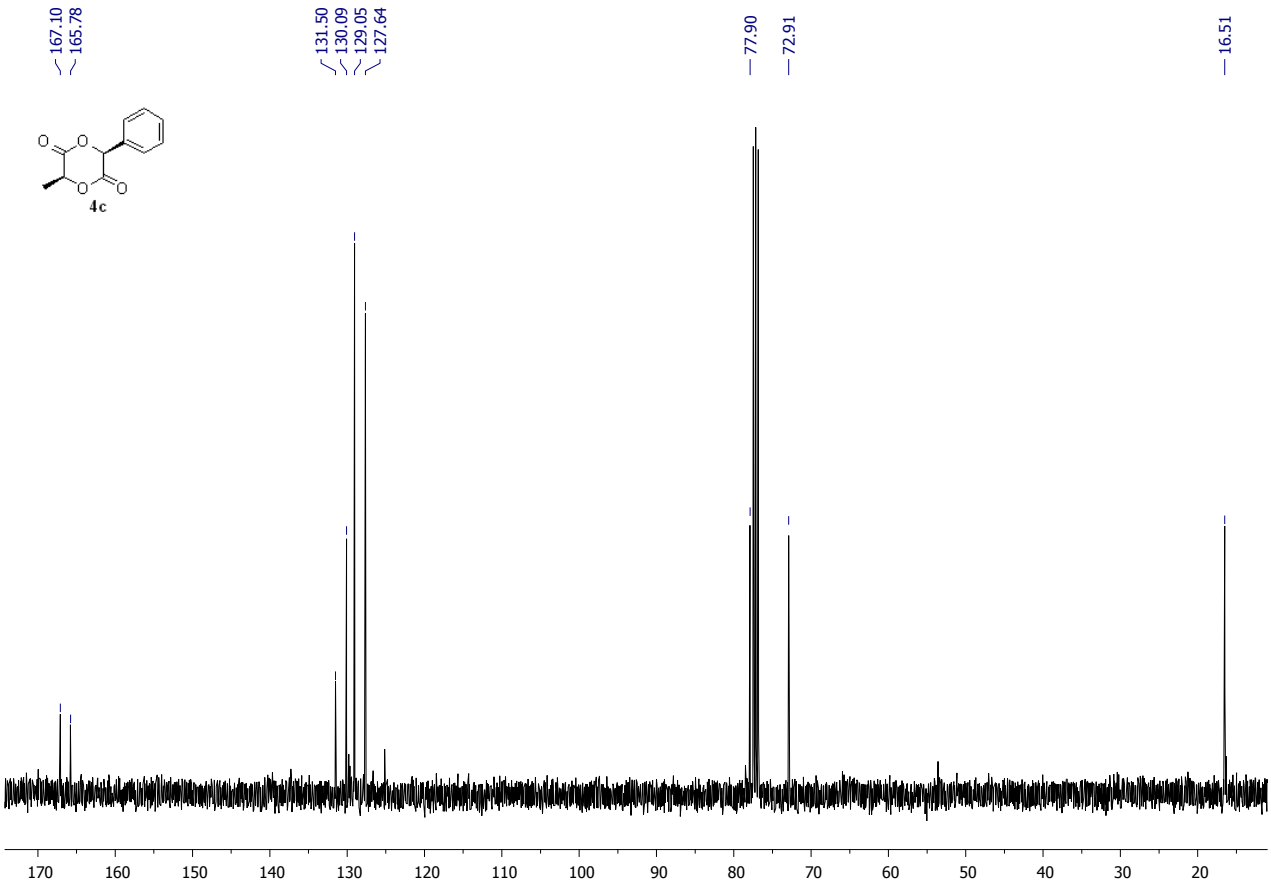


Fig. S32. ^{13}C NMR spectrum of **4c**.

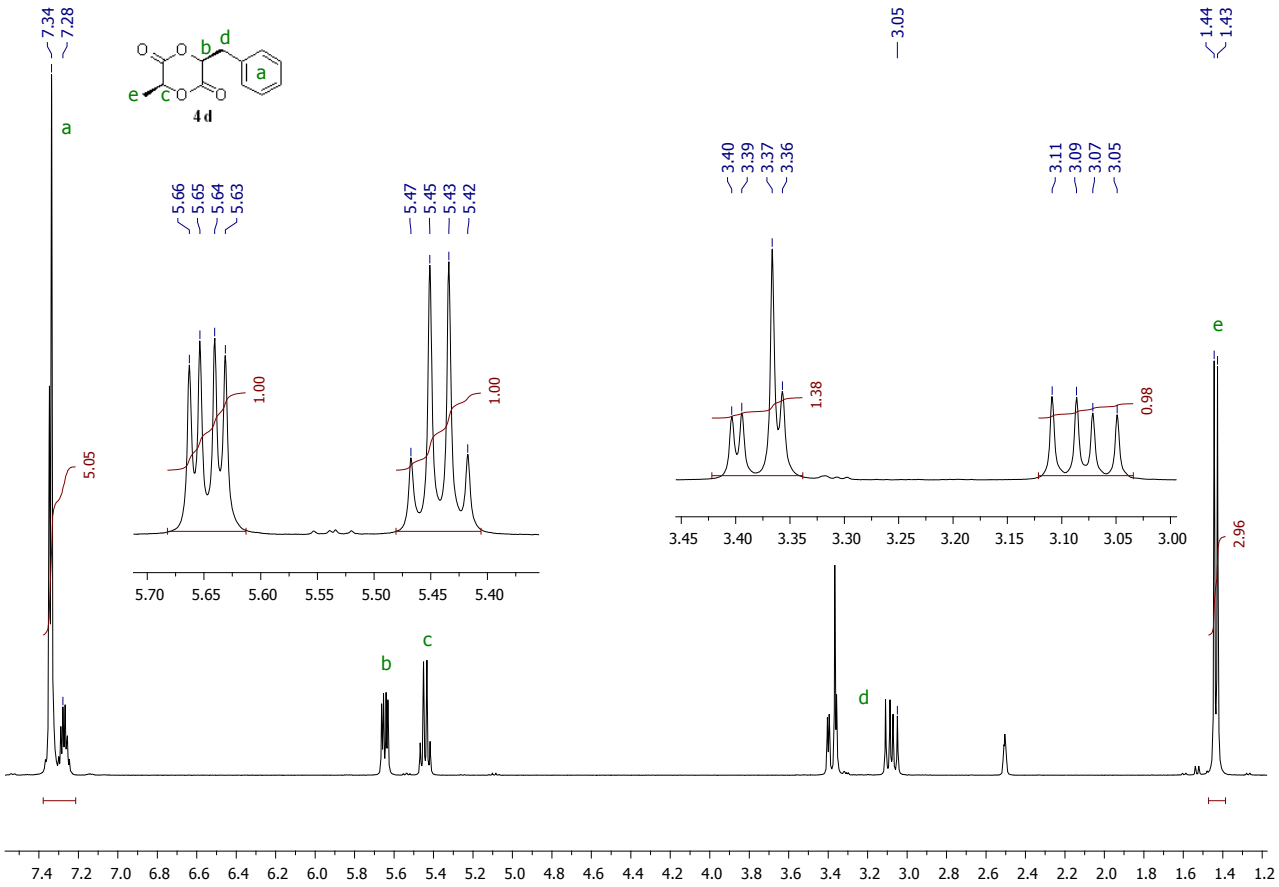


Fig. S33. ^{1}H NMR spectrum of **4d**.

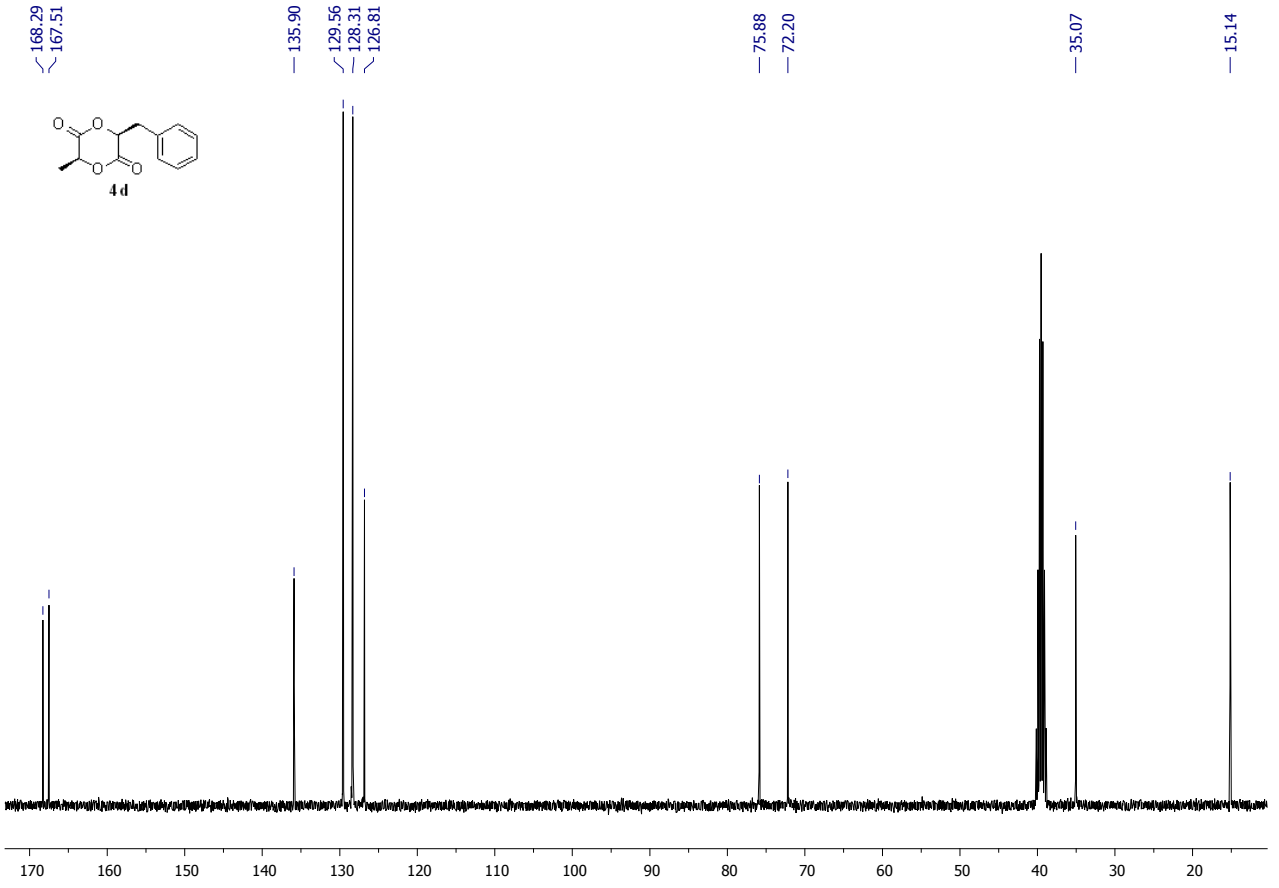


Fig. S34. ^{13}C NMR spectrum of **4d**.

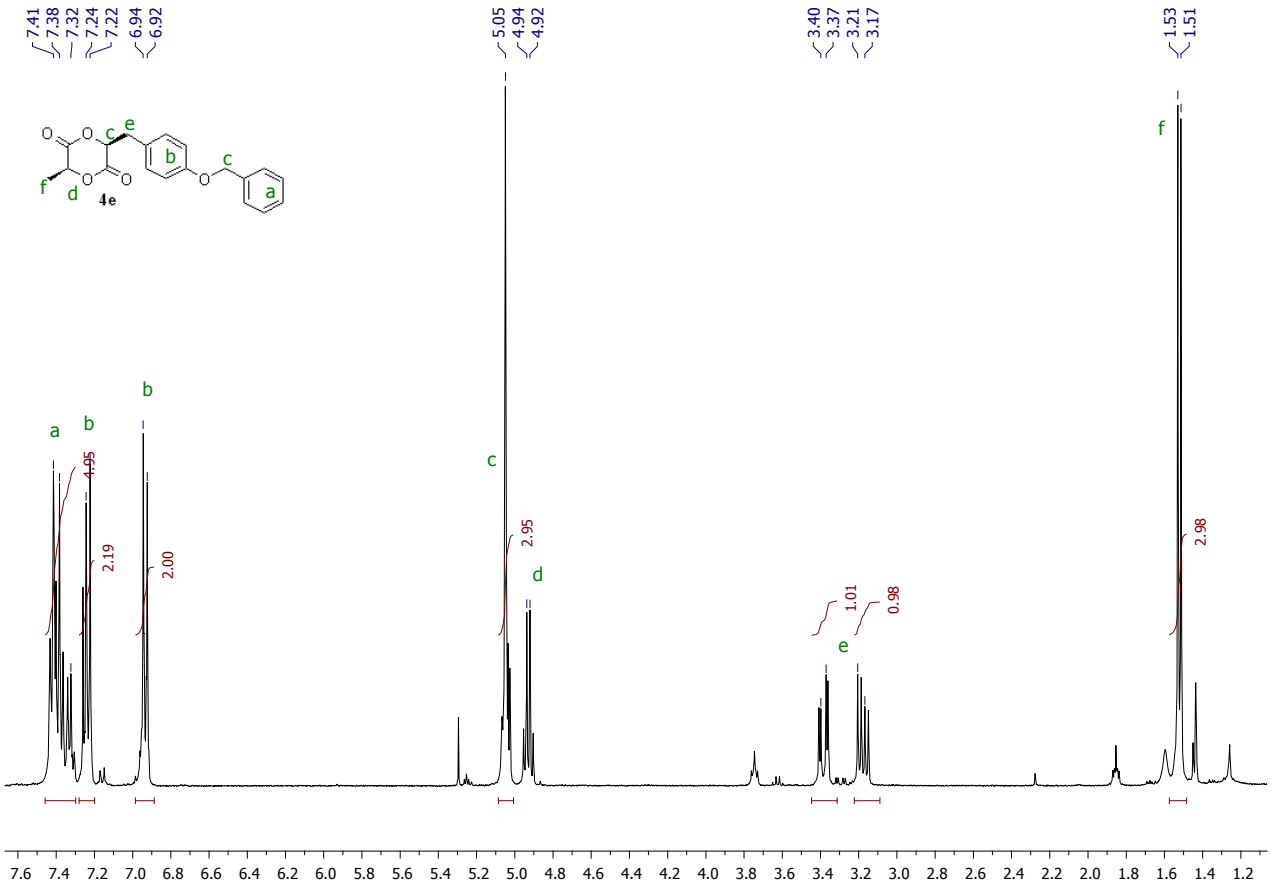


Fig. S35. ^{1}H NMR spectrum of **4e**.

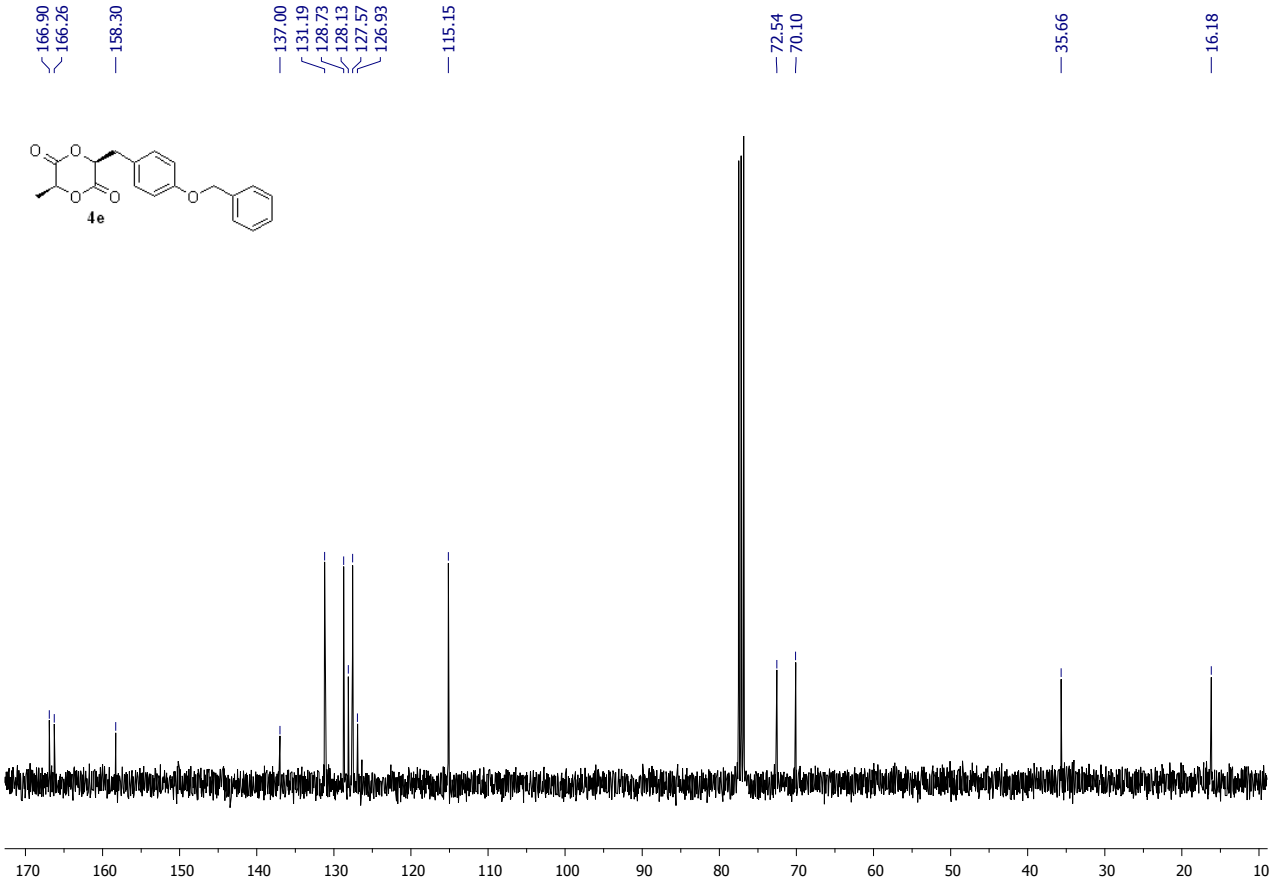


Fig. S36. ^{13}C NMR spectrum of **4e**.

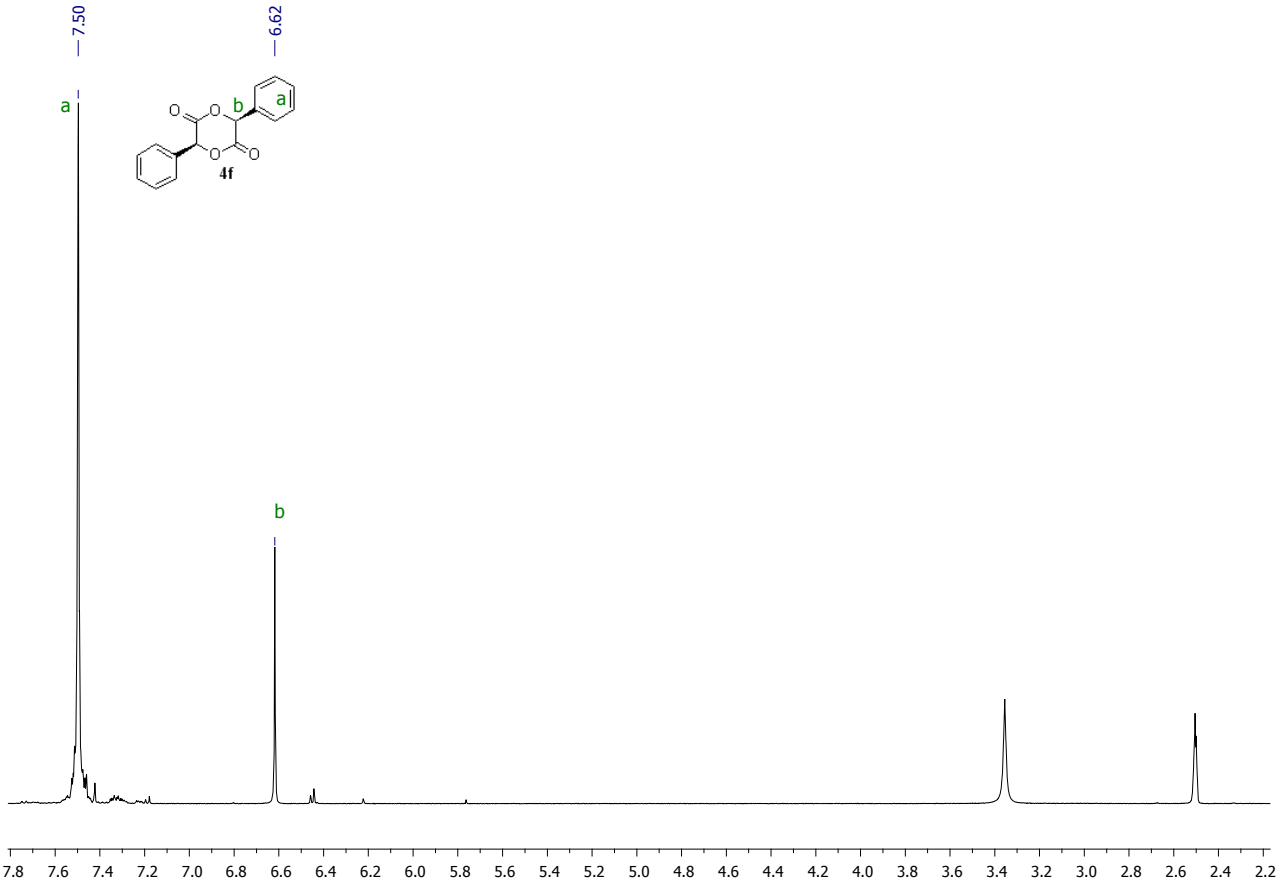


Fig. S37. ^{1}H NMR spectrum of **4f**.

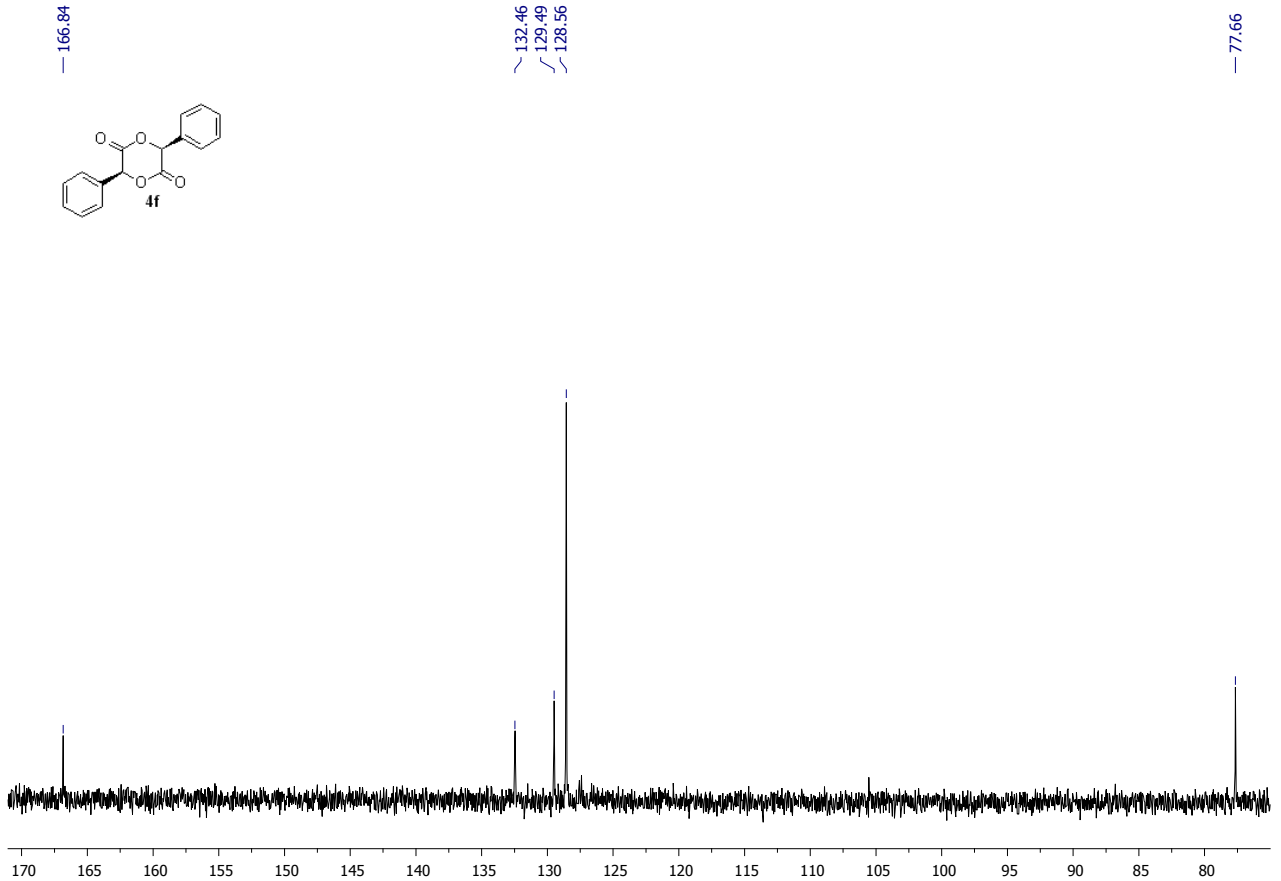


Fig. S38. ^{13}C NMR spectrum of **4f**.

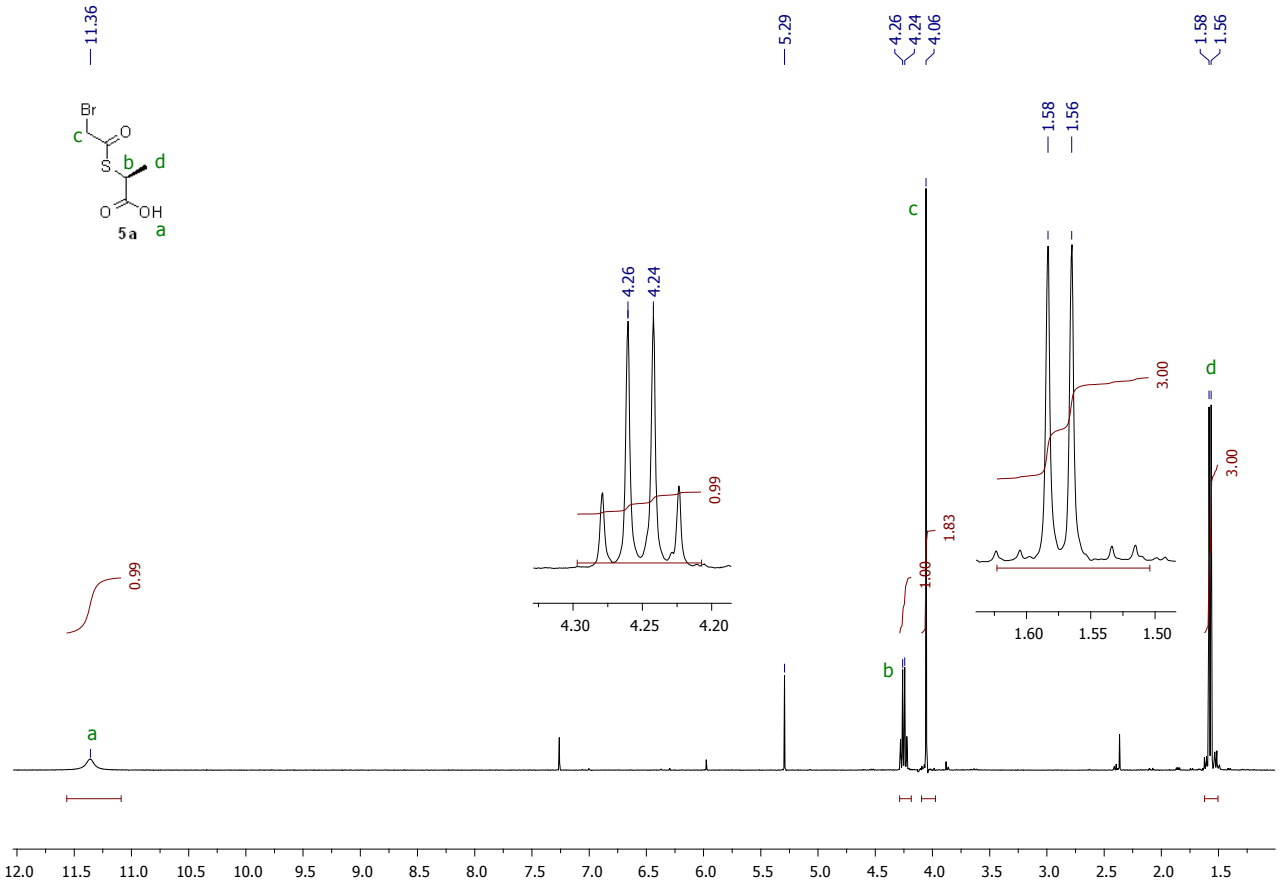


Fig. S31. ^{1}H NMR spectrum of **5a**.

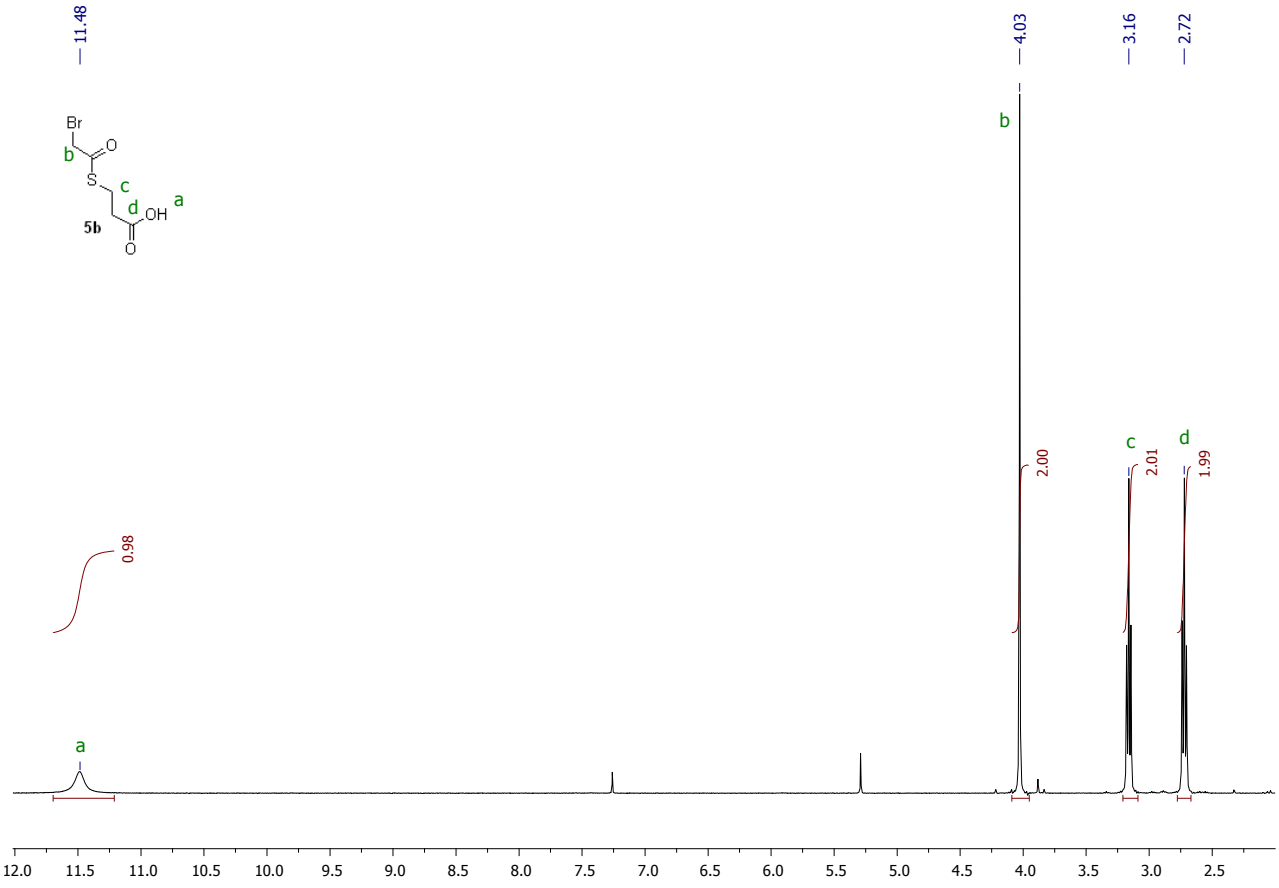


Fig. S32. ^{1}H NMR spectrum of **5b**.

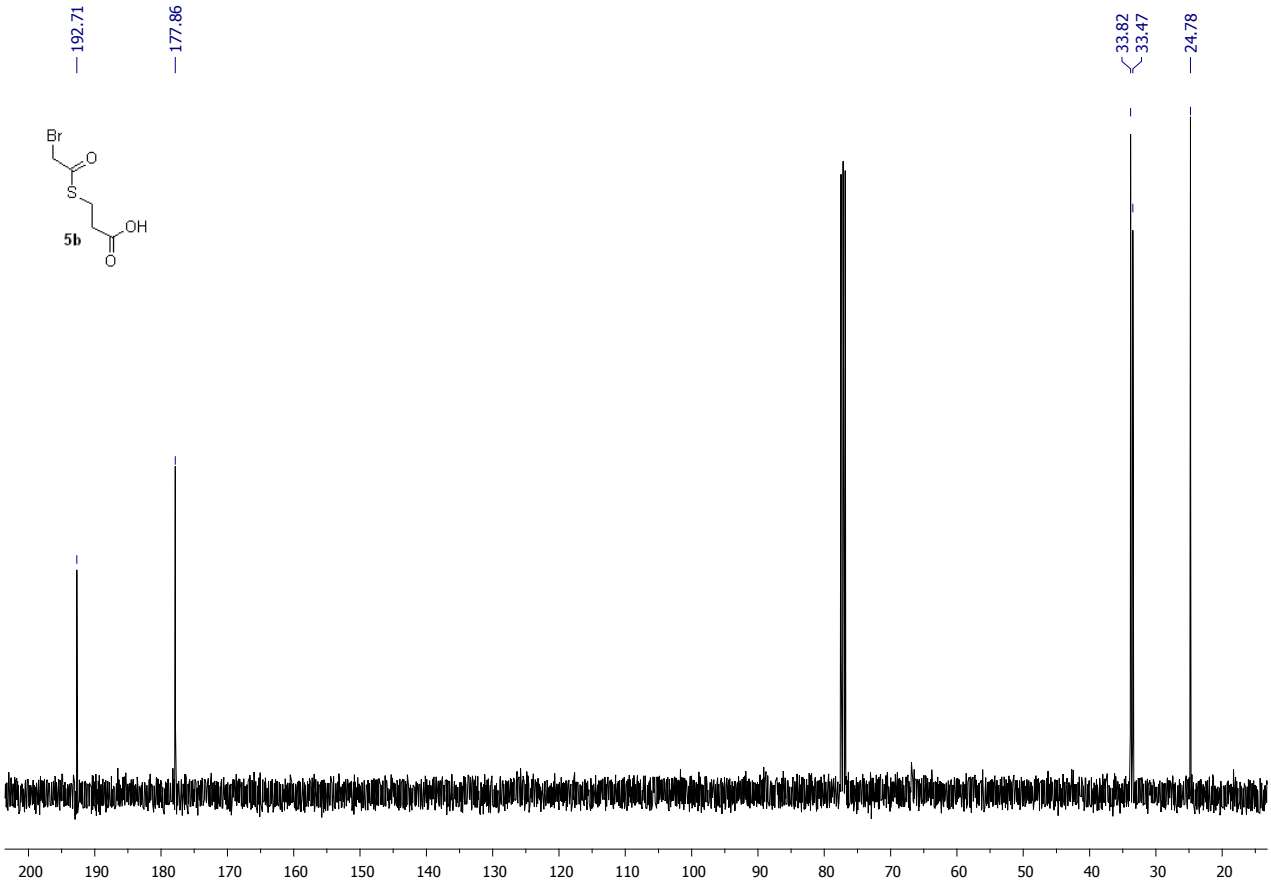


Fig. S33. ^{13}C NMR spectrum of **5b**.

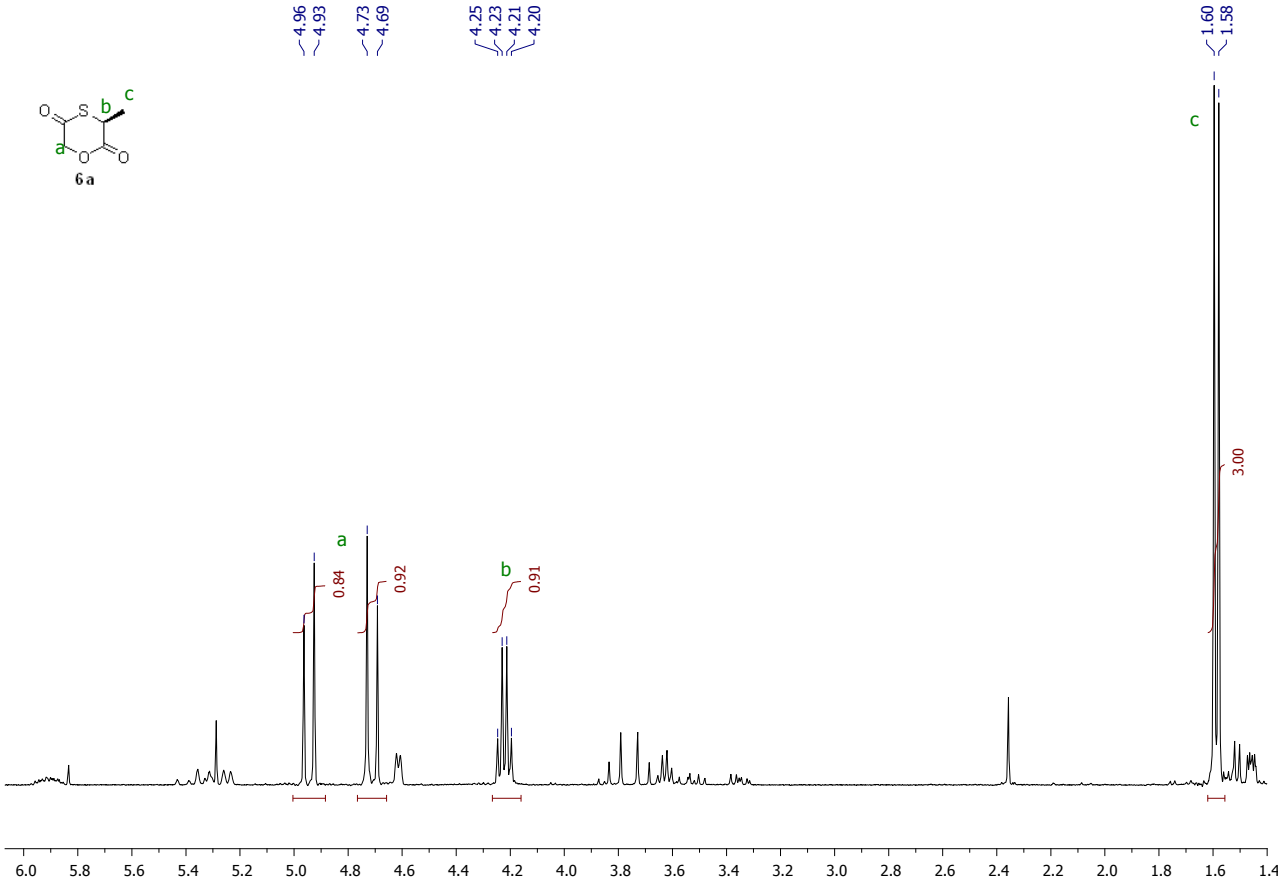


Fig. S34. ^{1}H NMR spectrum of **6a**.

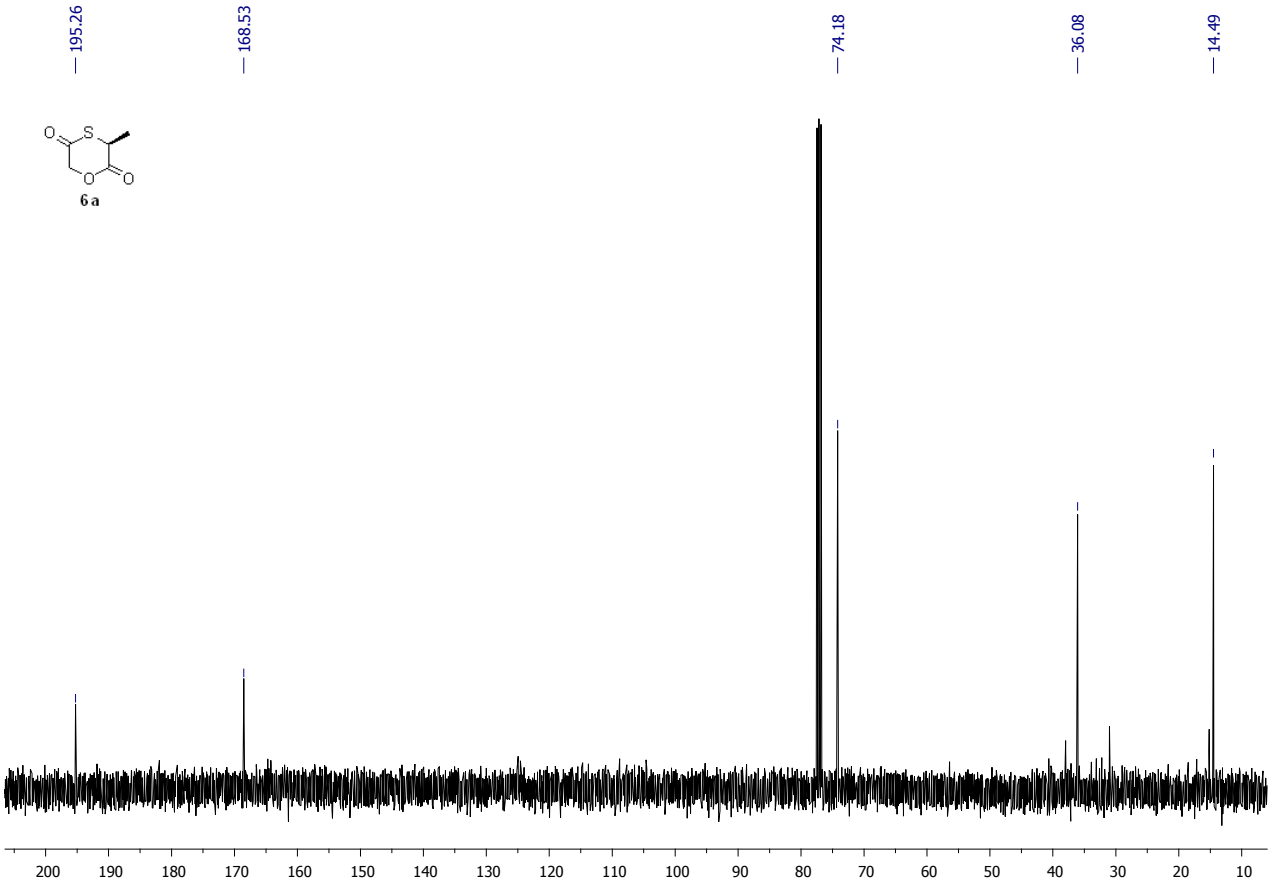


Fig. S35. ^{13}C NMR spectrum of **6a**.

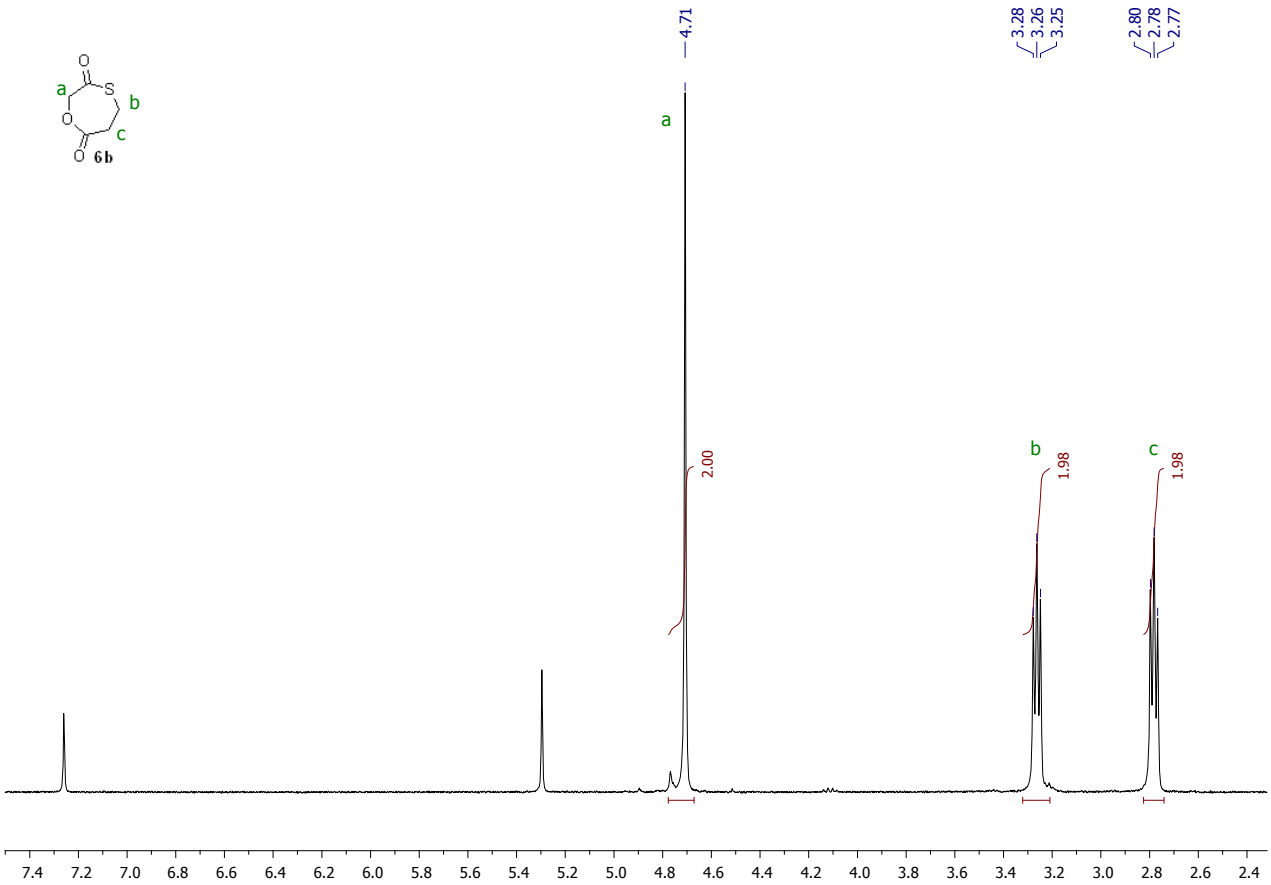


Fig. S36. ^{1}H NMR spectrum of **6b**.

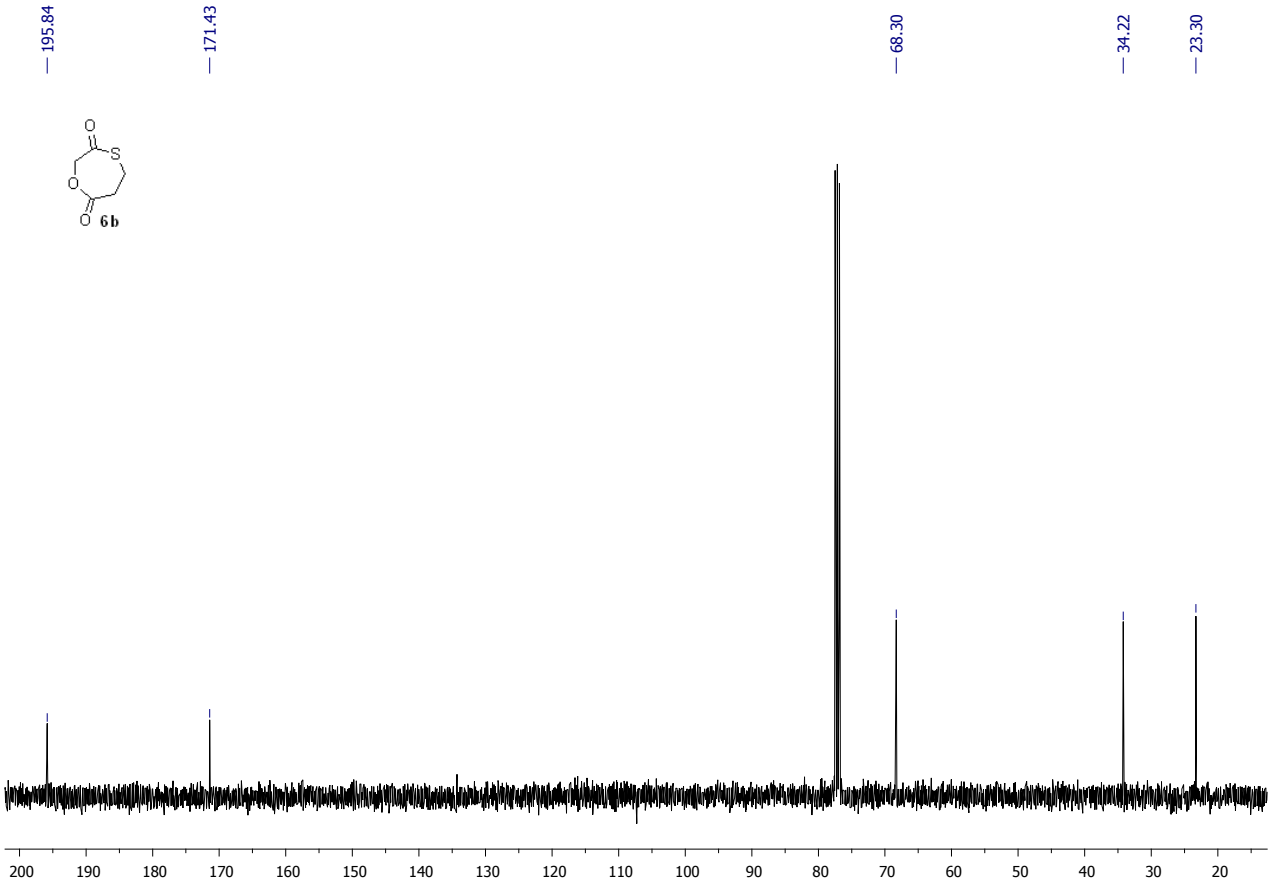


Fig. S37. ^{13}C NMR spectrum of **6b**.

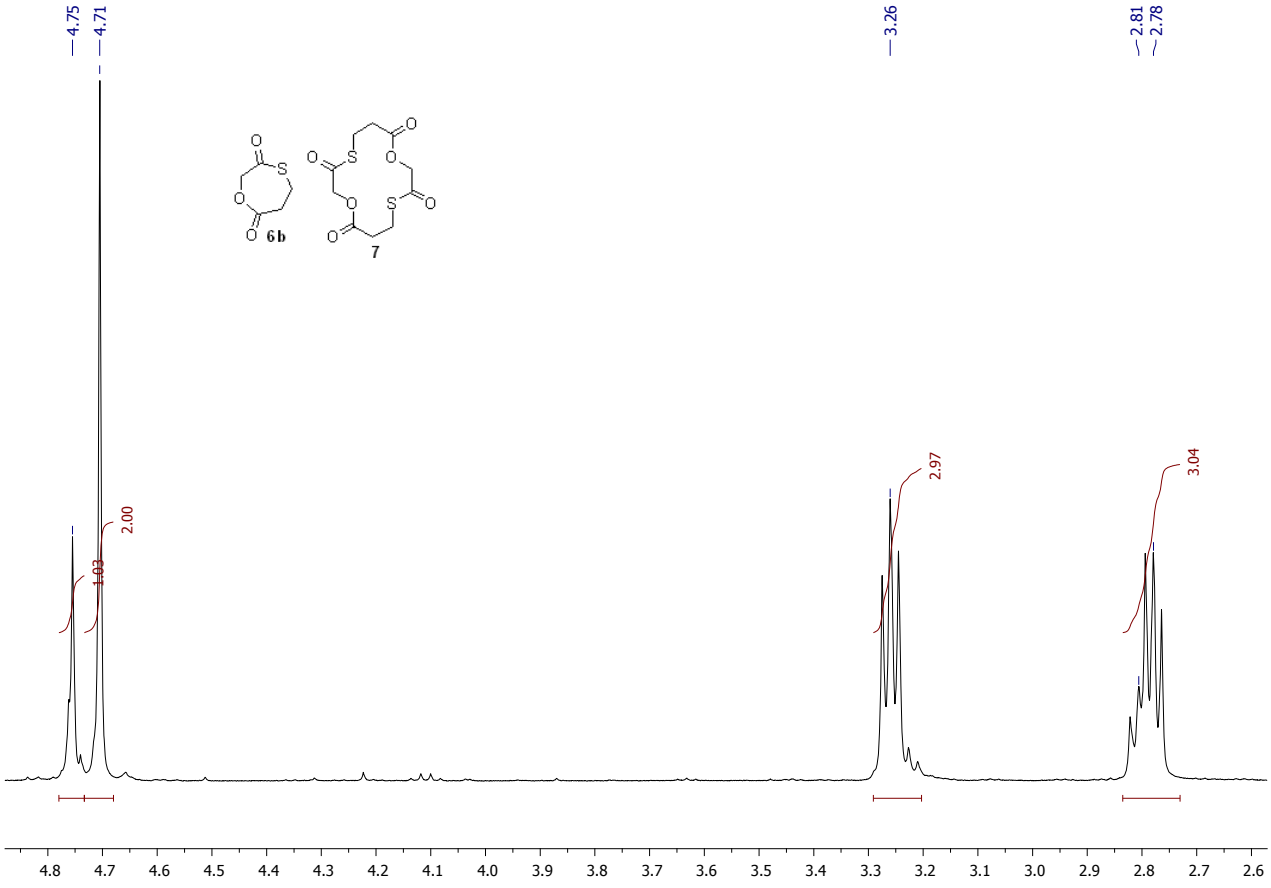
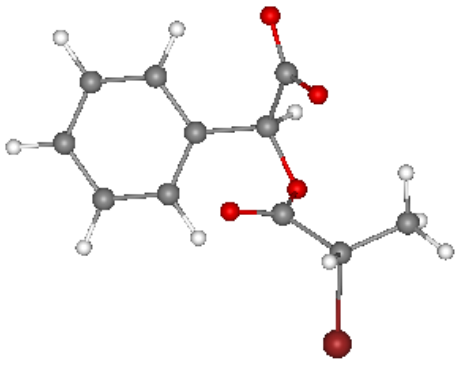


Fig. S38. ^{1}H NMR spectrum of the mixture of **6b** and **7**.

S3. Computational details

Stationary points and transition states were found by DFT method using Priroda-06 program. Molecular structures and free energies were refined by Gaussian-09 package (B3PW91/DGTZVP level of theory). Data for stable conformations of carboxylate anions **I1_SN2** derived from **3c** and **3f** and transition states of intramolecular cyclization **TS_SN2** are given below.

I1_SN2_PhMe__SR

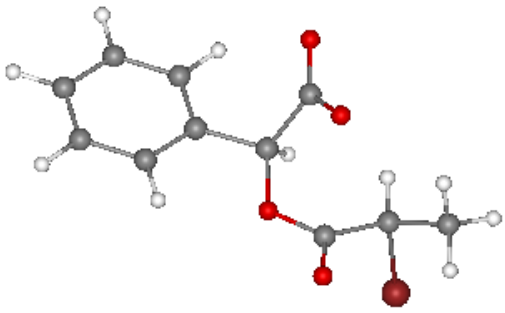


Sum of electronic and thermal G = -3299.502421

cartesian

8	1.05827308	0.25610000	0.62052310
6	-0.30062687	0.74430001	0.66042310
6	1.63117313	0.14199999	-0.59307688
6	-0.37972689	2.15810013	-0.05387693
1	-0.43812692	0.97099996	1.72312307
6	3.13077307	0.41100001	-0.53177691
8	0.67757314	2.54519987	-0.60387689
8	1.08747315	-0.21620001	-1.61527693
8	-1.47982693	2.73710012	0.09592307
35	4.03597307	-1.28400004	0.04702307
1	3.47057319	0.52600002	-1.55907691
6	3.55317307	1.55770004	0.35632306
6	-1.32672691	-0.31060001	0.28992307
6	-2.66352677	0.04040000	0.04862308
6	-3.61772704	-0.94180000	-0.22077692
1	-4.64742661	-0.64530003	-0.41437694
6	-3.26502681	-2.29269981	-0.24747694
6	-1.93762684	-2.64900017	-0.00287693
1	-1.63992691	-3.69589996	-0.02507693
6	-0.98182690	-1.66900003	0.26602307
1	-4.01162720	-3.05620003	-0.45897692
1	-2.92362690	1.09490001	0.06302307
1	0.04787314	-1.96169996	0.44772306
1	4.62817287	1.74179995	0.26742306
1	2.98707318	2.44029999	0.04052307
1	3.30527306	1.35650003	1.39992309

I1_SN2_PhMe__SS

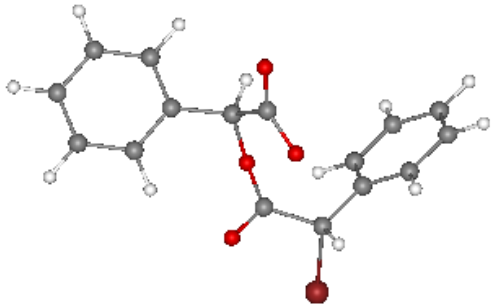


Sum of electronic and thermal G = -3299.507115

cartesian

8	0.77746165	-0.58879614	-0.73336923
6	0.05036163	0.02880386	0.33513078
6	2.03286171	-0.20179616	-1.03796923
6	0.20486164	1.60720384	0.33093077
1	0.45076165	-0.32109615	1.29553080
6	2.94856167	0.28200382	0.08403078
8	0.98426163	2.05310392	-0.54926926
8	2.47056150	-0.41109616	-2.15166903
8	-0.42003834	2.18790388	1.23973072
6	4.00966167	1.23990381	-0.39956921
6	-1.38573837	-0.42049617	0.22373077
6	-2.26913834	-0.18289615	1.28723073
6	-3.60413837	-0.57399619	1.20313072
1	-4.27473831	-0.37559617	2.03723073
6	-4.08563852	-1.21039617	0.05553078
6	-3.21273851	-1.44529617	-1.00726926
1	-3.57283831	-1.93699610	-1.90916932
6	-1.87413836	-1.05439615	-0.92526925
1	-5.12803841	-1.51659620	-0.00886922
1	-1.90223837	0.34190387	2.16383100
1	-1.19683838	-1.23959613	-1.75236928
35	3.82256174	-1.37959611	0.83493078
1	2.41756153	0.66740382	0.94633079
1	4.69686174	1.49830389	0.41043079
1	4.56706142	0.80970383	-1.23336923
1	3.49286175	2.14240408	-0.73956925

I1_SN2_Ph2__SR

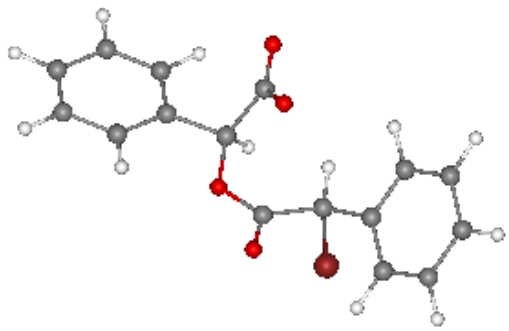


Sum of electronic and thermal G = -3491.118873

cartesian

8	0.04524547	-0.78058499	0.35049999
6	-0.93905449	0.20801502	0.06679998
6	0.61244547	-1.41098499	-0.75209999
6	-0.60705459	0.87941498	-1.30569994
1	-0.79155457	0.98881501	0.82160002
6	2.13524532	-1.21968508	-0.83270001
8	0.35694546	0.31131500	-1.91110003
8	0.06654546	-2.32418489	-1.33990002
8	-1.26415455	1.87811518	-1.63440001
35	3.00494528	-2.88358498	-0.08650002
1	2.38544559	-1.28128505	-1.88839996
6	2.76164532	-0.01498497	-0.19510001
6	3.40894556	0.92221504	-1.00709999
6	4.00534534	2.05701518	-0.45590001
1	4.49344540	2.77951503	-1.10640001
6	3.96304560	2.27011514	0.92159998
6	3.31514549	1.34061503	1.74029994
1	3.27124548	1.50061512	2.81559992
6	2.72024536	0.20911503	1.18770003
1	4.42434549	3.15521502	1.35479999
1	3.41824532	0.77581495	-2.08400011
1	2.21734548	-0.50958502	1.82700002
6	-2.36235476	-0.29638499	0.18069999
6	-3.42225456	0.62261504	0.16139998
6	-4.74135447	0.18791503	0.28579998
1	-5.55145454	0.91461498	0.26169997
6	-5.02605438	-1.17228508	0.43559998
6	-3.97465420	-2.08998489	0.44989997
1	-4.18175459	-3.15348482	0.55449998
6	-2.65275431	-1.65698504	0.32260001
1	-6.05545425	-1.51178503	0.53439999
1	-3.19985437	1.67601514	0.01689999
1	-1.83605444	-2.37128496	0.30989999

I1_SN2_Ph2__SS

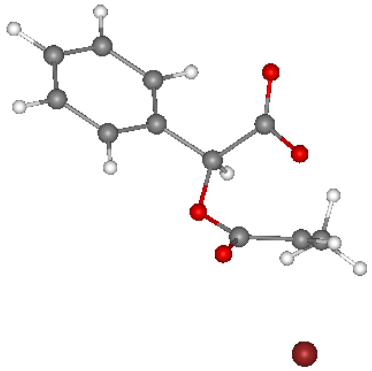


Sum of electronic and thermal G = -3491.124521

cartesian

6	-2.90088177	0.09316969	0.11335152
6	-3.88678193	0.71286970	-0.66384852
6	-5.12328196	0.09926972	-0.85174847
1	-5.88238192	0.59146971	-1.45584846
6	-5.38838196	-1.14443028	-0.27174848
6	-4.40288162	-1.77273035	0.48945153
1	-4.59138203	-2.74903035	0.93035150
6	-3.16388178	-1.15883029	0.68045151
1	-6.35508204	-1.62203026	-0.41894847
1	-3.67918181	1.67636979	-1.11814845
1	-2.37798190	-1.66763020	1.23175156
8	0.66081816	0.81286967	-0.77014852
6	1.32441819	0.26466972	0.37915152
6	-0.67248183	0.78616971	-0.91684854
6	0.83571815	-1.20363021	0.72965151
1	1.09591818	0.88666970	1.25365150
6	-1.54748189	0.69876969	0.33755153
8	-0.07148184	-1.65253019	-0.01214847
8	-1.16058183	0.98056972	-2.01124835
8	1.37851810	-1.68533015	1.74495149
35	-1.70418179	2.60426974	0.99765152
1	-1.04928184	0.21346970	1.16665149
6	2.80801821	0.33786970	0.11435153
6	3.32071805	0.59676969	-1.16264844
6	4.70011806	0.64126968	-1.37934852
1	5.07861805	0.84336972	-2.37974834
6	5.59001827	0.42896971	-0.32624847
6	5.08321810	0.16586971	0.94965148
1	5.76431799	-0.01043031	1.78015149
6	3.70771813	0.12026972	1.16865146
1	6.66441822	0.46496969	-0.49604851
1	2.63211823	0.76436973	-1.98414838
1	3.31291819	-0.11773029	2.15145159

TS_SN2_PhMe__SR

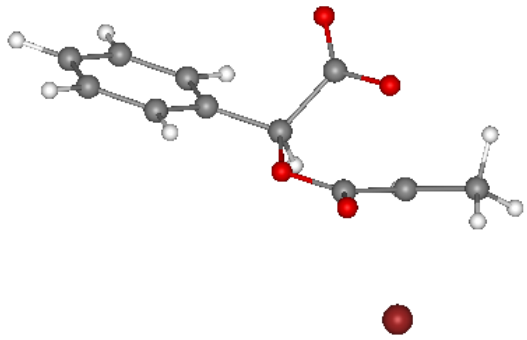


Sum of electronic and thermal G = -3299.476102

cartesian

8	1.02739227	-0.86672312	-0.14943846
6	0.14599228	0.21467693	0.15516154
6	2.18759227	-0.65252310	-0.85453844
6	0.33669227	1.44147694	-0.78813845
1	0.36649227	0.58787692	1.16406155
6	2.95749235	0.57727689	-0.48843843
8	1.48409224	1.51087689	-1.38013852
8	2.49649239	-1.43402314	-1.71943855
8	-0.56620765	2.27247691	-0.86843842
35	5.03579235	-0.77992308	0.27046156
1	3.62179232	0.92087686	-1.26573849
6	2.93679237	1.30617690	0.83506155
6	-1.27070773	-0.31922308	0.14966156
6	-2.29280758	0.41287690	0.76596159
6	-3.60480785	-0.05792308	0.76156157
1	-4.38770771	0.52577692	1.24136150
6	-3.91560793	-1.27062309	0.14166154
6	-2.90030766	-2.00342298	-0.47343844
1	-3.12900782	-2.95002317	-0.95873845
6	-1.58570778	-1.53212309	-0.47013843
1	-4.93920803	-1.63982308	0.13946156
1	-2.06060791	1.36577690	1.23286152
1	-0.79250765	-2.10432315	-0.94063842
1	3.93659210	1.68577695	1.04236150
1	2.24509239	2.15347695	0.80556154
1	2.66689229	0.63527691	1.65206146

TS_SN2_PhMe__SS

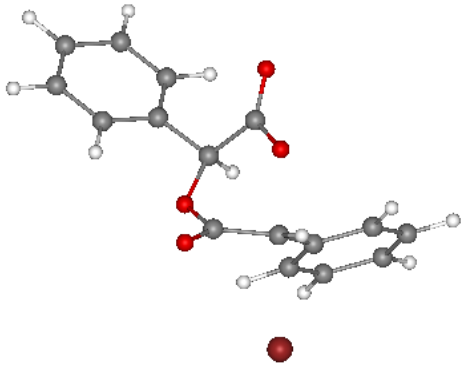


Sum of electronic and thermal G = -3299.489472

cartesian

6	3.92569971	1.45085001	-0.24390769
8	0.76879990	-0.51094997	-0.84210771
6	0.04579991	0.00155002	0.27829230
6	2.03270006	-0.07614999	-1.07930768
6	0.19289988	1.55765009	0.37699232
1	0.47189990	-0.41434997	1.20259225
6	2.73889995	0.58985001	0.05689231
8	1.32339990	2.00184989	-0.05970770
8	2.50439978	-0.19884998	-2.18810749
8	-0.71180010	2.22374988	0.87879229
35	3.99230003	-1.53734994	0.66939229
1	2.42329979	0.44875002	1.07429230
6	-1.38490021	-0.46704996	0.16729231
6	-1.88530004	-1.02314997	-1.01380777
6	-3.21510029	-1.44315004	-1.09030771
1	-3.58780003	-1.87654996	-2.01620770
6	-4.06180000	-1.31355000	0.01059230
6	-3.56570005	-0.75814998	1.19269228
1	-4.21550035	-0.64804995	2.05839229
6	-2.23909998	-0.33884996	1.26939225
1	-5.09710026	-1.64284992	-0.04960770
1	-1.22500002	-1.13205004	-1.86780775
1	-1.86500013	0.10855001	2.18579245
1	4.57109976	1.52845001	0.63139230
1	4.48999977	1.02335000	-1.07310772
1	3.57289982	2.44645000	-0.52880770

TS_SN2_Ph2__SR

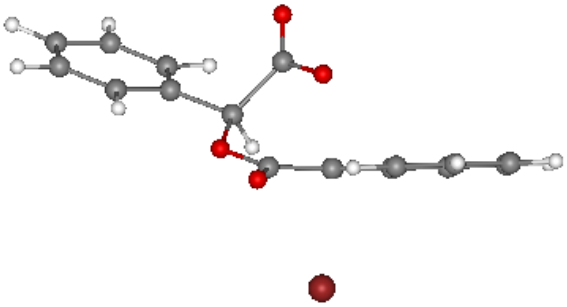


Sum of electronic and thermal G = -3491.097493

cartesian

8	0.07413638	-1.59590316	0.20895150
6	-0.61666358	-0.39870304	-0.16634852
6	1.17643642	-2.04460311	-0.47404850
6	-0.34416366	0.02759695	-1.63544858
1	-0.24516356	0.43429697	0.44385150
6	2.15413642	-0.99820304	-0.91814852
8	0.76033640	-0.42010304	-2.14294863
8	1.27963638	-3.22380304	-0.70014852
8	-1.13896358	0.77309698	-2.20124865
35	4.21083641	-2.07830310	0.29155150
1	2.73763657	-1.27800298	-1.77994859
6	2.43913651	0.30169696	-0.26574850
6	2.98203659	1.33199692	-1.04554856
6	3.26193619	2.57619691	-0.48544851
1	3.68413639	3.36329699	-1.10624850
6	2.99663639	2.81499696	0.86405146
6	2.45183635	1.79369712	1.64725149
1	2.25283623	1.96359706	2.70305157
6	2.17703629	0.54829699	1.09025145
1	3.21563625	3.78589702	1.30325150
1	3.17213631	1.15309691	-2.10004854
1	1.79793644	-0.25560305	1.71405149
6	-2.08676338	-0.59570307	0.13075149
6	-2.92426348	0.52059692	0.24195150
6	-4.28506327	0.36369693	0.49945149
1	-4.92276335	1.24159694	0.57895148
6	-4.82986355	-0.91370308	0.65135145
6	-3.99866343	-2.02900314	0.54195148
1	-4.41086340	-3.02900290	0.65945148
6	-2.63526344	-1.87260294	0.28335148
1	-5.89166355	-1.03730297	0.85425144
1	-2.50886345	1.51539707	0.10715149
1	-1.98546350	-2.73850298	0.20645151

TS_SN2_Ph2__SS



Sum of electronic and thermal G = -3491.108772

cartesian

6	-2.80907869	-0.09017271	-0.01636668
6	-3.44067860	-0.52327275	1.16043329
6	-4.70877838	-1.09177268	1.12323332
1	-5.18297815	-1.41937268	2.04563332
6	-5.37147856	-1.23957276	-0.09836668
6	-4.74987841	-0.81377268	-1.27346671
1	-5.26077843	-0.92427266	-2.22756672
6	-3.47797871	-0.24527270	-1.23946667
1	-6.36517859	-1.68147278	-0.13236667
1	-2.92957854	-0.40117270	2.11183333
1	-2.99937868	0.09662730	-2.14916682
8	0.71512139	0.99692732	-0.81896669
6	1.30052137	0.31092727	0.28793335
6	-0.61857855	0.91052729	-1.05396664
6	0.74612141	-1.14827275	0.40793332
1	1.02852142	0.83032727	1.21813333
6	-1.44957864	0.45482728	0.10083333
8	-0.45657858	-1.29187274	-0.03796667
8	-1.03257859	1.16832733	-2.16316676
8	1.44052136	-2.01717281	0.93373334
35	-2.03497863	2.89912724	0.69023335
1	-1.05877864	0.54962730	1.09773338
6	2.80182147	0.37522730	0.13693333
6	3.40242147	0.76712728	-1.06316662
6	4.79392147	0.80942726	-1.17686665
1	5.24542141	1.11922729	-2.11706686
6	5.60252142	0.46182728	-0.09486668
6	5.00602150	0.06992730	1.10623336
1	5.62432146	-0.20707273	1.95743334
6	3.61792135	0.02742729	1.22033334
1	6.68632174	0.49682730	-0.18416668
1	2.77442145	1.04612732	-1.90276670
1	3.16092134	-0.29587269	2.15113330

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2. H. Matsuda, T. Okino, M. Murakami and K. Yamaguchi, *Tetrahedron*, 1996, **52**, 14501.