Rapid Assembly of Complex Cyclopentanes Employing Chiral, α,β-Unsaturated Acylammonium Intermediates.

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Supporting Information

General Procedures

All non-aqueous reactions were performed under a nitrogen atmosphere in oven-dried glassware. Dichloromethane (CH_2Cl_2) was dried by passing through activated molecular sieves or alumina (solvent purification system). Tetrahydrofuran (THF) was distilled over sodium and benzophenone. Diisopropylethylamine $EtN(^iPr)_2$ was distilled from potassium hydroxide prior to use. Other solvents and reagents were used as received from commercially available sources. Deuterated solvents were purchased from either Aldrich or Cambridge Isotopes and used as received. ^1H NMR spectra were measured at 500 MHz and 300 MHz and referenced relative to residual chloroform (7.26 ppm) or benzene (7.16 ppm) and were reported in parts per million. Coupling constants (*J*) were reported in Hertz (Hz), with multiplicity reported following usual convention: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dddd, doublet of doublet of doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; ddq, doublet of doublet of quartets; ddddt, doublet of doublet of doublet of doublet of triplets; qq, quartet of quartets; qdd, quartet of doublet of doublets; m, multiplet; bs, broad singlet. ^{13}C NMR spectra were measured at 125 MHz and 75 MHz and referenced relative to residual chloroform (77.23 ppm) or benzene (128.06 ppm) and were reported in parts per million (ppm). Flash column chromatography was performed with 60Å Silica Gel (230-400 mesh) as stationary phase using a gradient solvent system or on an automated flash chromatography system (EtOAc/hexanes as eluent unless indicated otherwise). High resolution mass spectra (ESI) were obtained through the Laboratory for Biological Mass Spectrometry (Texas A&M University). Thin Layer Chromatography (TLC) was performed using glass-backed silica gel F254 (Silicycle, 250 μm thickness). Visualization of developed plates was performed by fluorescence quenching or by staining with phosphomolybdic acid (PMA), potassium permanganate ($KMnO_4$), *p*-anisaldehyde or cerium sulfate. *Fourier* Transform Infrared (FTIR) spectra were recorded as thin films on NaCl plates. Optical rotations were recorded on a polarimeter at 589 nm employing a 25 mm cell. High Performance Liquid Chromatography (HPLC) was performed on a chromatographic system using various chiral columns (25 cm) as noted. Gas Chromatography (GC) was performed on a gas chromatographic

system using a chiral column as noted. X-ray diffraction was obtained by the X-ray Diffraction Laboratory at Texas A&M University.

Hazard Warning:
Ozonides produced from the oxidative cleavage were reduced using excess dimethyl sulfide. Stirring for at least 9 h at room temperature prior to work-up ensured complete ozonide reduction.

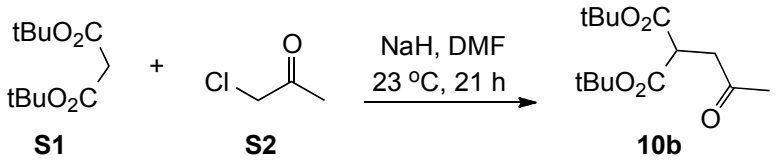
(*S*)-(+)-HBTM was synthesized according to the literature procedure.[1] (–)-BTM was purchased from TCI chemicals and used as received. All unsaturated acid chlorides were purchased from Sigma-Aldrich and used as received without further purification.

Abbreviation list

4-PPY	=	4-Pyrrolidinopyridine
9-AJ	=	9-azajulolidine
DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	=	4-(Dimethylamino)pyridine
DMS	=	dimethyl sulfide
$EtN(^{i}Pr)_2$	=	*N*,*N*-diisopropylethylamine
HBTM	=	homobenzotetramisole
BTM	=	benzotetramisole
LDA	=	lithium bis(trimethylsilyl)amide
LiHMDS	=	lithium bis(trimethylsilyl)amide
TsCl	=	4-toluenesulfonyl chloride

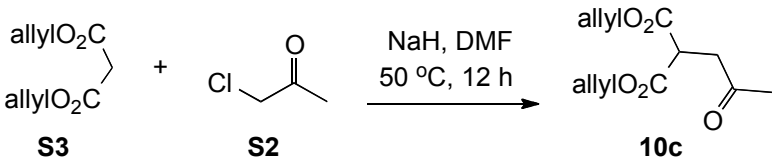
[1] Birman, V. B. & Li, X. Homobenzotetramisole: an effective catalyst for kinetic resolution of aryl-cycloalkanols. *Org. Lett.* **10**, 1115-1118 (2008).

Experimental Procedures



S1 **S2** **10b**

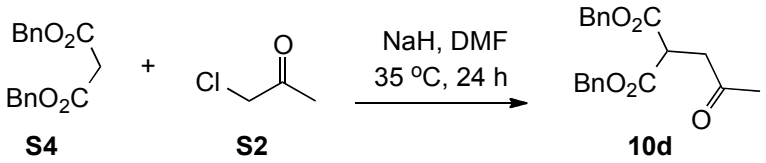
Di-*tert*-butyl 2-(2-oxopropyl)malonate (10b). To an oven dried, round-bottomed flask was added NaH 60% in mineral oil (0.49 g, 9.83 mmol, 1.25 equiv.) and 20 mL anhydrous DMF. The flask was then cooled to 0 °C with an ice bath and di-*tert*-butyl malonate (**S1**, 2.0 mL, 8.94 mmol, 1.00 equiv.) was added dropwise. After 25 min, chloroacetone (**S2**, 1.08 mL, 13.40 mmol, 1.50 equiv.) was added dropwise and the ice bath removed and allowed to warm up to ambient temperature (23 °C). After 21 h the reaction mixture was cooled to 0 °C with an ice bath and 10 mL of sat. NH_4Cl was added slowly. The mixture was warmed to ambient temperature (23 °C), extracted with EtOAc (4 x 15 mL), and the combined organic extracts were then washed with water (15 mL) and brine (15 mL). The organic layer was collected and dried over $MgSO_4$, filtered, concentrated by rotary evaporation, and purified by flash column chromatography (gradient SiO_2, 20 → 60% EtOAc/hexanes) to afford keto diester **10b** (1.46 g, 60%) as a colorless oil: TLC (EtOAc:hexanes, 5:5 *v/v)*: R_f = 0.80; ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.68 (t, *J* = 7.2 Hz, 1H), 2.95 (d, *J* = 7.2 H, 2H), 2.20 (s, 3H), 1.45 (s, 18H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 205.1, 168.1(2), 81.7(2), 49.0, 42.0, 29.8, 27.8(6); IR (thin film): 2982, 2928, 1726 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{14}H_{24}LiO_5$ $[M+Li]^+$: 279.1784; found 279.1781.



S3 **S2** **10c**

Diallyl 2-(2-oxopropyl)malonate (10c). To an oven dried, round-bottomed flask was added NaH 60% in mineral oil (1.16 g, 28.97 mmol, 1.06 equiv.) and then 50 mL

anhydrous DMF followed by dropwise addition of diallyl malonate[2] (**S3**, 5.00 g, 27.14 mmol, 1.00 equiv.) at ambient temperature (23 °C). After 25 min, chloroacetone (**S2**, 6.55 mL, 81.41 mmol, 3.00 equiv.) was added dropwise and the reaction mixture was heated to 50 °C for 12 h, after which time it was allowed to cool to ambient temperature (23 °C) and 15 mL of sat. NH_4Cl was added. The mixture was extracted with EtOAc (4 x 20 mL) and then washed with water (20 mL) and brine (20 mL). The organic layers were combined and dried over $MgSO_4$, filtered, concentrated by rotary evaporation, and purified by flash column chromatography (gradient SiO_2, 20 → 60% EtOAc/hexanes) to afford keto diester **10c** (4.24 g, 65%) as a colorless oil: TLC (EtOAc:hexanes, 1:9 *v/v)*: R_f = 0.75; ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.93-5.86 (m, 2H), 5.35 (q, *J* = 1.5 Hz, 1H), 5.31 (q, *J* = 1.5 Hz, 1H), 5.26 (q, *J* = 1.3 Hz, 1H), 5.24 (q, *J* = 1.3 Hz, 1H), 4.65 (m, 2H), 4.63 (m, 2H), 3.94 (t, *J* = 7.1 Hz, 1H), 3.09 (d, *J* = 7.2 Hz, 2H), 2.21 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 205.0, 168.7(2), 131.6(2), 119.0(2), 66.5(2), 47.1, 42.3, 30.0; IR (thin film): 3081, 2951, 1741 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{12}H_{16}LiO_5$ $[M+Li]^+$: 247.1158; found 247.1149.

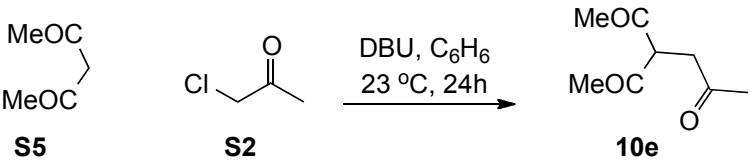


S4 **S2** **10d**

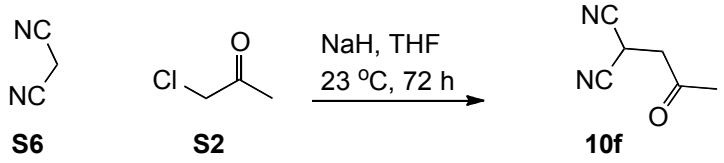
Dibenzyl 2-(2-oxopropyl)malonate (10d). To an oven dried, round-bottomed flask containing dibenzyl malonate (**S4**, 2.50 mL, 11.96 mmol, 1.00 equiv.) in 24 mL of anhydrous DMF at 0 °C was slowly added NaH 60% in mineral oil (0.51 g, 12.75 mmol, 1.07 equiv.). After 5 min at 0 °C chloroacetone (**S2**, 2.88 mL, 35.88 mmol, 3.00 equiv.) was added dropwise and the reaction mixture was heated at 35 °C for 24 h, after which time it was allowed to cool to ambient temperature (23 °C) and 15 mL of sat. NH_4Cl was added. The mixture was extracted with EtOAc (4 x 20 mL) and then washed with water (20 mL) and brine (20 mL). The organic layers were combined and dried over $MgSO_4$, filtered, concentrated by rotary evaporation, and purified by flash

[2] Jana, R., Trivedi, R. & Tunge, J. A. Mild decarboxylative allylation of coumarins. *Org. Lett*. **11**, 3434-3436 (2009).

column chromatography (SiO_2, 10 → 60% EtOAc/hexanes) to afford keto diester **10d** (1.90 g, 47%) as a colorless oil: TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.45; ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.31-7.27 (m, 5H), 7.26-7.24 (m, 5H), 5.17 (s, 2H), 5.11 (s, 2H), 3.96 (t, *J* = 7.1 Hz, 1H), 3.06 (d, *J* = 7.1 Hz, 2H), 2.13 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 204.9, 168.7, 135.3, 128.7, 128.5, 128.3, 67.6, 47.1, 42.1, 29.8; IR (thin film): 1753, 1726, 1270, 1226, 1152 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{20}H_{20}LiO_5$ $[M+Li]^+$: 347.1471; found 347.1476.



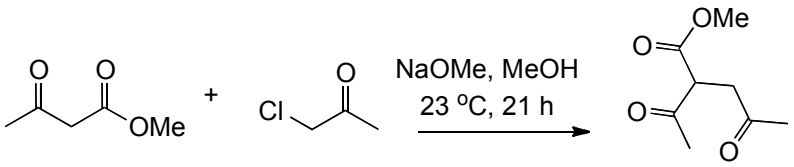
3-Acetylhexane-2,5-dione (10e). In an oven dried, 250 mL round-bottomed flask was added acetylacetone (**S5**, 5.0 g, 49.98 mmol, 1.00 equiv.) dissolved in 100 mL of spectra grade benzene. DBU (7.5 mL, 49.98 mmol, 1.00 equiv.) was slowly added to the solution. Upon completion of the addition, chloroacetone (**S2**, 5.23 mL, 64.97 mmol, 1.30 equiv.) was added dropwise and the reaction mixture was stirred for 24 h at ambient temperature (23 ºC). The reaction mixture was then diluted with CH_2Cl_2 (40 mL), washed with brine (50 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. Flash column chromatography (SiO_2, 10 → 40% EtOAc/hexanes) afforded triketone **10e** (2.34 g, 30%) as a yellow oil. All characterization data was in accordance with previously reported data for this compound.[3]



2-(2-Oxopropyl)malononitrile (10f). In an oven dried 250 mL round-bottomed flask, malononitrile (**S6**, 3.0 g, 45.41 mmol) was dissolved in 45 mL of dry THF and cooled

[3] St. Clair, M. B. G., Amarnath, V., Moody, M. A., Anthony, D. C., Anderson, C. W. & Graham, D. G. Pyrrole oxidation and protein cross-linking as necessary steps in the development of γ-diketone neuropathy. *Chem. Res. Toxicol.* **1**, 179-185 (1988).

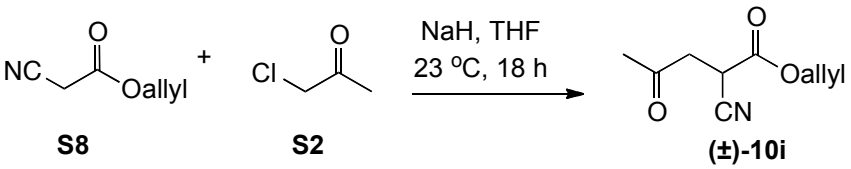
to 0 ºC. NaH 60% in mineral oil (2.04 g, 55.64 mmol, 1.22 equiv.) was slowly added to the cooled solution and stirred for 30 min at 0 ºC before adding chloroacetone (**S2**, 4.75 mL, 59.02 mmol, 1.30 equiv.) dropwise. After stirring at ambient temperature (23 ºC) for 72 h, the reaction mixture was cooled to 0 ºC with an ice bath and carefully quenched with sat. NH_4Cl (10 mL), extracted with EtOAc (3 x 15 mL), then washed with water (35 mL) and brine (35 mL). The organic layer was dried over $NaSO_4$, filtered, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 10 → 50% EtOAc/hexanes) to afford keto dinitrile **10f** (0.598 g, 11% unoptimized) as a white solid: TLC (EtOAc:hexanes, 4.5:5.5 *v/v)*: R_f = 0.41; ^{1}H NMR (500 MHz; $CDCl_3$): δ 4.20 (t, *J* = 6.5 Hz, 1H), 3.23 (d, *J* = 6.5 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 200.01, 112.26 (2), 43.49, 29.43, 17.49; IR (thin film): 2978, 2949, 2915, 1716 cm^{-1}; HRMS (ESI-) *m/z* calcd. for $C_6H_5N_2O$ $[M-H]^-$: 121.0407; found, 121.0401.



S7 **S2** **(±)-10g**

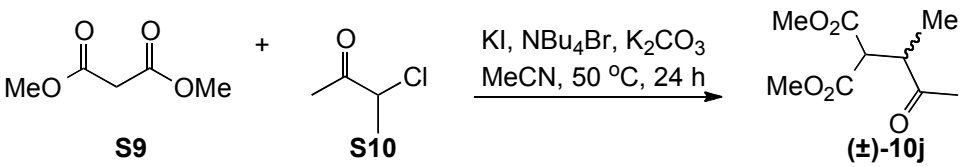
Methyl 2-acetyl-4-oxopentanoate ((±)-10g). An oven dried, 500 mL round-bottomed flask was charged with 500 mL of HPLC grade MeOH under a nitrogen atmosphere and then cooled to 0 °C with an ice bath prior to the addition of methylacetoacetone (**S7**, 10.0 mL, 92.66 mmol, 1.0 equiv.) followed by NaOMe (5.51 g, 102.00 mmol, 1.10 equiv.). After 25 min at 0 °C, chloroacetone (**S2**, 10.4 mL, 129.73 mmol, 1.40 equiv.) was added dropwise. After the addition, the ice bath was removed and the reaction was stirred at ambient temperature (23 °C) for 21 h. The reaction was again cooled to 0 °C and 100 mL of sat. NH_4Cl was added. The reaction mixture was then extracted with EtOAc (4 x 100 mL), then washed with water (2 x 25 mL) and brine (1 x 50 mL). The organic layer was collected and dried over $MgSO_4$, filtered, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 20 → 60% EtOAc/hexanes) to afford diketo ester **(±)-10g** (6.86 g, 43%) as a pale yellow oil: TLC (EtOAc:hexanes, 5:5 *v/v)*: R_f = 0.50; ^{1}H NMR (500 MHz;

$CDCl_3$): δ 4.02 (dd, *J* = 8.3, 5.7 Hz, 1H), 3.73 (s, 3H), 3.15 (dd, *J* = 18.5, 8.3 Hz, 1H), 2.95 (dd, *J* = 18.5, 5.6 Hz, 1H), 2.35 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 205.8, 202.3, 169.5, 53.6, 52.9, 41.8, 30.3, 29.9; IR (thin film): 3002, 2955, 2928, 1759, 1700 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_8H_{12}LiO_4$ $[M+Li]^+$: 179.0896; found 179.0898.



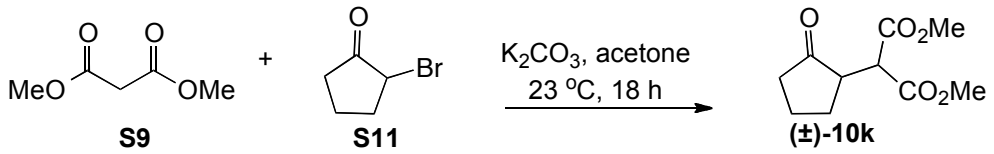
S8 **S2** **(±)-10i**

Allyl 2-cyano-4-oxopentanoate ((±)-10i). The allyl cyanoacetate (**S8**, 5.0g, 39.96 mmol, 1.00 equiv.) was dissolved in 80 mL of dry THF and cooled to 0 ºC. Then NaH 60% in mineral oil (1.79 g, 44.75 mmol, 1.12 equiv.) was slowly added through an addition funnel and stirred for an hour before adding chloroacetone (**S2**, 4.81g, 51.95 mmol, 1.30 equiv.). The reaction was allowed to stir for 18 h at room temperature (23 ºC) then cooled to 0 ºC and then quenched with sat. NH_4Cl. EtOAc was added and extracted 3 times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The filtrate was then concentrated by rotary evaporation and purified by flash column chromatography (SiO_2, 10 → 100% EtOAc/hexanes) to afford allyl cyanoacetate **(±)-10i** as a as a yellow oil (5.56 g, 77%): TLC (EtOAc:hexanes, 3.5:6.5 v/v): R_f = 0.48; ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.95-5.88 (m, 1H), 5.39 (dd, *J* = 17.0, 1Hz, 1H), 5.31 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.70-4.69 (m, 2H), 3.98 (dd, *J* = 7.0, 5.5 Hz, 1H), 3.21 (dd, *J* = 18.0, 7.5 Hz, 1H), 3.02 (dd, *J* = 18.0, 5.5 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 202.59, 165.16, 130.77, 119.77, 116.10, 67.68, 42.19, 31.66, 29.64; IR (thin film): 2916, 2256, 1753, 1714 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_9H_{12}NO_3$ $[M+H]^+$: 182.0817; found 182.0820.



S9 **S10** **(±)-10j**

Dimethyl 2-(3-oxobutan-2-yl)malonate ((±)-10j). To a 250 mL, round-bottomed flask were added dimethyl malonate (**S9**, 1.81 mL, 15.84 mmol, 1.0 equiv.), 3-chlorobutan-2-one (**S10**, 2.0 mL, 19.80 mmol, 1.25 equiv.), KI (0.132 g, 0.79 mmol, 0.05 equiv.), K_2CO_3 (2.63 g, 19.00 mmol, 1.20 equiv.), NBu_4Br (0.102 g, 0.32 mmol, 0.02 equiv.) and MeCN (25 mL). The reaction was heated to 50 ^oC for 12 h. Stirring was continued for another 12 h at ambient temperature (23 ^oC). After which time, the reaction was concentrated under reduced pressure by rotary evaporation, diluted with 20 mL of CH_2Cl_2, and filtered to remove solids. The filtrate was then concentrated by rotary evaporation and purified by flash column chromatography (SiO_2, 20 → 60% EtOAc/hexanes) to afford keto diester **(±)-10j** (3.17 g, 99%) as a colorless oil. ^{13}C NMR (125 MHz; $CDCl_3$): δ 209.6, 169.1, 169.0, 54.1, 52.9, 52.8 45.9, 28.8, 14.6. All other characterization data was in accordance with previously reported data for this compound.[4]

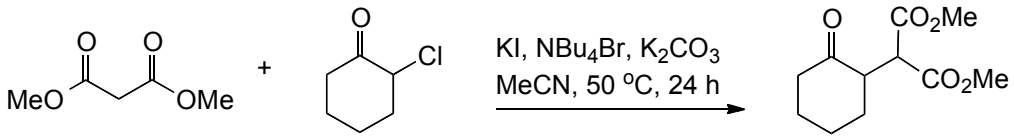


S9 **S11** **(±)-10k**

2-(2-Oxocyclopentyl)malonate ((±)-10k). To 2-bromocyclopentanone (**S11**, prepared and purified immediately prior to use[5], 3.42 g, 20.98 mmol, 1.50 equiv.) was added dimethyl malonate (**S9**, 1.60 mL, 13.98 mmol, 1.00 equiv.), K_2CO_3 (2.50 g, 18.09 mmol, 1.30 equiv.) and acetone (30 mL), which was allowed to react for 18 h at ambient temperature (23 ^oC). After which time, the reaction was concentrated under reduced pressure by rotary evaporation, diluted with 20 mL of CH_2Cl_2 and then filtered to remove the solids. The filtrate was then concentrated by rotary evaporation and purified by flash column chromatography (SiO_2, 20 → 60% EtOAc/hexanes) to afford

[4] L'Esperance, R. P., Ford, T. M. & Jones Jr, M. Reaction of dicarbomethoxy carbene with acetaldehyde and simple ketones. *J. Am. Chem. Soc.* **110**, 209-213 (1998).
[5] Tanemura, K., Suzuki, T., Nishida, Y., Satsumabayashi, K. & Horaguchi, T. A mild and efficient procedure for α-bromination of ketones using N-bromosuccinimide catalysed by ammonium acetate. *Chem. Commun*. **4**, 470-471 (2004).

cyclopentanone diester **(±)-10k** as a colorless oil (720.0 mg, 24%)[6]: TLC (EtOAc:hexanes, 5:5 *v/v)*: R_f = 0.53; ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.83 (d, *J* = 5.7 Hz, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 2.73-2.69 (m, 1H), 2.36 (dd, *J* = 18.8, 8.4 Hz, 1H), 2.28-2.20 (m, 2H), 2.12-2.08 (m, 1H), 1.90-1.78 (m, 2H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 217.1, 169.0, 168.4, 52.7, 52.6, 51.0, 48.6, 37.4, 26.6, 20.6; IR (thin film): 2956, 2880, 1738 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{10}H_{14}LiO_5$ $[M+Li]^+$: 221.1001; found 221.1002.



S9 **S12** **(±)-10l**

Dimethyl 2-(2-oxocyclohexyl)malonate ((±)-10l). To a 250 mL round-bottomed flask were added 2-chlorocyclohexanone (**S12**, 5.0 mL, 43.78 mmol, 1.25 equiv.), dimethyl malonate (**S9**, 4.0 mL, 34.94 mmol, 1.0 equiv.), KI (0.30 g, 1.81 mmol), K_2CO_3 (5.87g, 42.47 mmol, 1.22 equiv.), NBu_4Br (0.23 g, 0.71 mmol, 0.02 equiv.) and MeCN (50 mL). The reaction mixture was heated to 50 °C for 12 h and then stirred at ambient temperature (23 °C) for an additional 12 h. The reaction was then concentrated under reduced pressure by rotary evaporation, diluted with 50 mL of CH_2Cl_2 and filtered to remove the solids. The filtrate was then concentrated by rotary evaporation and purified by flash column chromatography (SiO_2, 20 → 60% EtOAc/hexanes) to afford cyclohexanone diester **(±)-10l** (966.8 mg, 12% unoptimized) as a pale yellow oil: TLC (EtOAc:hexanes, 5:5 *v/v)*:R_f = 0.65; ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.58 (s, 3H), 3.57 (s, 3H), 3.51 (d, *J* = 9.5 Hz, 1H), 3.07-3.01 (m, 1H), 2.29-2.26 (m, 2H), 2.00-1.96 (m, 1H), 1.90-1.85 (m, 1H), 1.79-1.75 (m, 1H), 1.63-1.45 (m, 2H), 1.44-1.35 (m, 1H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 209.9, 169.1, 169.0, 52.9, 52.8, 52.1, 50.6, 42.1, 31.4, 27.9, 25.2; IR (thin film): 2955, 2863, 1738, 1706 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{11}H_{16}LiO_5$ $[M+Li]^+$: 235.1158; found 235.1154.

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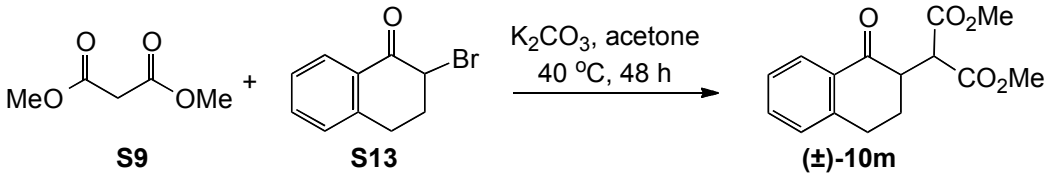
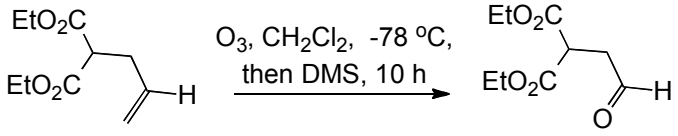
[6] Saitoh, F., Mori, M., Okamura, K. & Date, T. Synthesis and X-ray crystal structures of tricyclic ketone containing trans-fused bicyclo[3.3.0]octane unit. *Tetrahedron* **51**, 4439-4446 (1995).



S9 **S13** **(±)-10m**

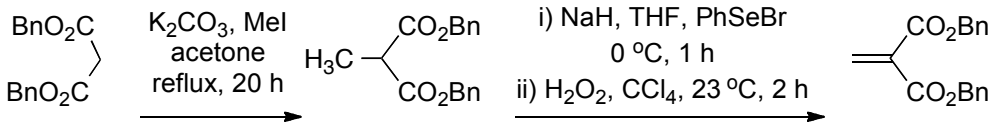
Dimethyl 2-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)malonate ((±)-10m). To a 50 mL, round-bottomed flask were added dimethyl malonate (**S9**, 1.45 mL, 12.66 mmol, 1.00 equiv.), K_2CO_3 (4.39 g, 31.74 mmol, 2.51 equiv.) and acetone (8 mL). The reaction was heated to 40 °C, then **S13** (4.0 g, 17.77 mmol, 1.40 equiv.) which was freshly prepared and used immediately without purification[7], was added dropwise over ~4 min and the reaction was maintained at 40 °C for 48 h. After 48 h, the reaction was allowed to cool to ambient temperature (23 °C) and EtOAc (20 mL) and water (20 mL) were added and the reaction was stirred for an additional 10 min. The organic layer was collected, washed with brine 2 x 10mL, dried over $MgSO_4$, filtered, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 5 → 30% EtOAc/hexanes) to afford aromatic keto diester **(±)-10m** (3.50 g, 56%) as a yellow/orange solid: TLC (EtOAc:hexanes, 2:8 *v/v)*: R_f = 0.48; ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.00 (d, *J* = 7.9 Hz, 1H), 7.48 (td, *J* = 7.5, 1.3 Hz, 1H), 7.31-7.28 (m, 1H), 7.26-7.23 (m, 1H), 4.02 (d, *J* = 7.1 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.38-3.33 (m, 1H), 3.12 (dt, *J* = 16.4, 8.5 Hz, 1H), 3.00 (dt, *J* = 16.7, 3.4 Hz, 1H), 2.20-2.15 (m, 2H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 196.9, 169.3, 169.0, 143.9, 133.9, 132.2, 128.9, 127.8, 127.0, 52.9, 52.8, 52.2, 48.5, 29.6, 26.8; IR (thin film): 2952, 1735, 1676, 1270, 1217, 1155, 764, 749 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{15}H_{16}LiO_5$ $[M+Li]^+$: 283.1158; found 283.1172.



S14 **10o**

[7] Prokopowicz, M.; Mlynarz, P.; Kafarski, P. Synthesis of phosphonate derivatives of 2,3-dihydroindene. *Tetrahedron Lett.* **50,** 7314-7317 (2009).

Diethyl 2-(2-oxoethyl)malonate (10o). Ozone was bubbled through a 100 mL round-bottomed flask with diethyl 2-(2-methylallyl)malonate (**S14**, 1.04 mL, 5.30 mmol, 1.00 equiv.) and CH_2Cl_2 (29 mL) at -78°C until it turned a deep blue color. Then oxygen was bubbled through until the color dissipated at which time dimethyl sulfide (1.00 mL, 13.4 mmol, 2.53 equiv.) was added and the reaction was allowed to stir overnight (10 h) while warming to ambient temperature (23 °C). The reaction mixture was concentrated under reduced pressure by rotary evaporation, and purified by flash column chromatography (SiO_2, 20 → 60% EtOAc/hexanes) to afford aldehyde diester **10o** (0.72 g, 67%) as a colorless oil. All characterization data was in accordance with previously reported data for this compound.[8]



S4 **S15** **22**

Dibenzyl 2-methylenemalonate (22). Dibenzyl 2-methylmalonate **S15** was prepared by modified reported procedure.[9] In an oven-dried, 250-mL round-bottomed flask, dibenzyl malonate (**S4**,14.2 g, 50.0 mmol, 1.0 equiv) and anhydrous K_2CO_3 (8.3 g, 60.0 mmol, 1.2 equiv) were dissolved in anhydrous acetone (50 mL) and stirred at ambient temperature (23 °C) for 5 minutes, then iodomethane (3.73 mL, 60.0 mmol, 1.2 equiv) was added dropwise. The reaction mixture was refluxed (60-65 °C) for 20 h. Upon completion (as judged by TLC), the reaction mixture was diluted with Et_2O (50 mL) and filtered through a pad of celite (Et_2O wash). The filtrate was concentrated by rotary evaporation, and purified by an automated flash chromatography system

[8] Groth, T., Meldal, M. Synthesis of aldehyde building blocks and protected as acid labile *N*-Boc *N,O*-Acetals: towards combinatorial solid phase synthesis of novel peptide isosteres. *J. Comb. Chem.* **3,** 33-44 (2001).

[9] Kalaitzakis, D., Kambourakis, S., Rozzell, D. J. & Smonou, I. Stereoselective chemoenzymatic synthesis of sitophilate: a natural pheromone. *Tetrahedron: Asymmetry* **18**, 2418-2426 (2007).

(gradient of EtOAc/hexanes) to obtain dibenzyl 2-methylmalonate **S15** (12.6 g, 85% yield) as clear liquid. Spectral data matched that previously reported.[10]

Dibenzyl 2-methylenemalonate **22** was prepared by a modified published procedure.[11] Into an oven-dried, 250-mL round-bottomed flask containing NaH (60% suspension in mineral oil, 1.40 g, 35.0 mmol, 1.5 equiv) in THF (80 mL) at 0 °C was added slowly a solution of dibenzyl 2-methylmalonate **S15** (6.90 g, 23.3 mmol, 1.0 equiv) in THF (10 mL). After gas evolution had ceased, a solution of PhSeBr (6.61 g, 28.0 mmol, 1.2 equiv) in THF (20 mL) was quickly added at 0 °C, resulting in a bright yellow solution. After 30 min, the reaction mixture was diluted with Et_2O (20 mL) and quenched with saturated $NaHCO_3$ (50 mL). The organic layer was separated and washed with 10% $NaHSO_3$ (2 × 50 mL), H_2O (3 × 50 mL) and dried over anhydrous Na_2SO_4. The filtrate was concentrated by rotary evaporation, and purified by an automated flash chromatography system (gradient of EtOAc/hexanes) to afford dibenzyl 2-methyl-2-(phenylselanyl)malonate which was carried on directly.

An oven-dried, 100-mL round-bottomed flask was charged with a solution of dibenzyl 2-methyl-2-(phenylselanyl)malonate in anhydrous CCl_4 (30 mL), followed by an addition of H_2O_2 (35% in H_2O, 20.0 mL, 233 mmol, 10.0 equiv). The reaction temperature was maintained at ambient temperature (23 °C) using a water bath. After 2 h, H_2O (10 mL) was added to dissolve the white precipitate. Then the organic layer was separated, washed with anhydrous CCl_4 (3 × 10 mL), and dried over anhydrous Na_2SO_4. The filtrate was concentrated by rotary evaporation to afford pure dibenzyl 2-methylenemalonate **22** (5.67 g, 83% yield over two steps) as light yellow liquid. Pure compound **22** was stored as a frozen solution in anhydrous benzene (1.0 M) at –20 °C to prevent decomposition. TLC (EtOAc:hexanes, 2:8 *v/v)*: R_f = 0.80; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.35 (m, 10H), 6.65 (s, 2H), 5.31 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.7 (2), 135.6 (2), 135.4, 134.5, 128.6 (4), 128.4 (2), 128.3 (4), 67.3 (2);

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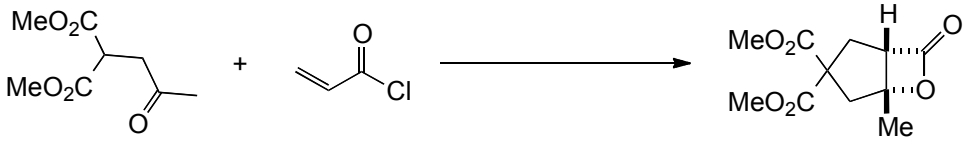
[10] Ton, T. M. U., Tejo, C., Tiong, D. L. Y. & Chan, P. W. H. Copper(II) triflate catalyzed amination and aziridination of 2-alkyl substituted 1,3-dicarbonyl compounds. *J. Am. Chem. Soc.* **134**, 7344-7350 (2012).

[11] Trend, R. M., Ramtohul, Y. K. & Stoltz, B. M. Oxidative cyclizations in a nonpolar solvent using molecular oxygen and studies on the stereochemistry of oxypalladation. *J. Am. Chem. Soc.* **127**, 17778-17788 (2005).

IR (thin film): 3066, 3034, 2956, 1735, 1498, 1456, 1385, 1324, 1223, 1123 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{18}H_{16}NaO_4$ $[M+Na]^+$: 319.0941; found 319.0929.

Table 1: Optimization of the nucleophile-catalyzed Michael-aldol-β-lactonization (NMCAL) process.



10a **1a** **(±)-14a**

Entry 1 of Table 1: Same procedure as described for **Entry 3 of Table 1**, except that no DBU was added. No β-lactone **(±)-14a** was detected by FT-IR, ^{1}H NMR, or TLC analysis.

Entry 2 of Table 1: Same procedure as described for **Entry 3 of Table 1**, except that no $LiClO_4$ was added. No β-lactone **(±)-14a** was detected by FT-IR, ^{1}H NMR, or TLC analysis.

Entry 3 of Table 1: A mixture of dimethyl 2-(2-oxopropyl) malonate (**10a**,[12] 33 mg, 0.18 mmol, 1.00 equiv.), $LiClO_4$ (19 mg, 0.18 mmol, 1.00 equiv.), DBU (27 mg, 0.18 mmol, 1.00 equiv.), DMAP (4.4 mg, 0.036 mmol, 0.20 equiv.), and $EtN(^iPr)_2$ (63 μL, 0.36 mmol, 2.0 equiv.) in CH_2Cl_2 (0.5 mL) was stirred at 23 ^oC for 0.5 h. The reaction mixture was then cooled to 0 ^oC, and acryloyl chloride (**1a**, 27 uL, 0.36 mmol, 2.0 equiv.) was added. The reaction mixture was warmed to 23 ^oC and stirred for 4 h. The reaction was then diluted with CH_2Cl_2 (2 mL) and then 30% EtOAc in hexanes (4 mL), and passed through a pad of silica gel to remove solids. The filtrate was concentrated under reduced pressure by rotary evaporation and the residue was purified by flash column chromatography (SiO_2, eluting with 20 → 50% EtOAc:hexanes) to afford β-

[12] Millán, A. et al. Ti/Pd bimetallic systems for the efficient allylation of carbonyl compounds and homocoupling reactions. *Chem. Eur. J.* **17**, 3985-3994 (2011).

lactone **(±)-14a** as a solid (29.6 mg, 68%). Spectral data matched that previously reported.[13]

Entry 4 of Table 1

A solution of dimethyl 2-(2-oxopropyl) malonate (**10a**, 33 mg, 0.18 mmol, 1.00 equiv.) in THF (0.5 mL) was cooled to -78 ^{o}C and then LDA (180 μL, 1.0 M solution in THF, 0.18 mmol, 1.00 equiv.) was then added dropwise. The reaction was stirred for 10 min at -78 ^{o}C and then warmed to 0 ^{o}C. Subsequently, CH_2Cl_2 (1 mL), DMAP (23 μL, 1.6 M solution in CH_2Cl_2, 0.037 mmol, 0.20 equiv.), and $EtN(^{i}Pr)_2$ (60 μL, 0.32 mmol, 2.00 equiv.) were added. The reaction was allowed to stir for an additional 10 min at 0 ^{o}C before acryloyl chloride (**1a**, 230 μL of a 1.6 M solution in CH_2Cl_2, 0.36 mmol, 2.00 equiv.) was added. The reaction was warmed to 23 ^{o}C and stirred for 4 h. The reaction was diluted with CH_2Cl_2 (2 mL) and then 30% EtOAc in hexanes (4 mL), and passed through a pad of silica gel. The filtrate was concentrated under reduced pressure by rotary evaporation and the residue was purified by flash column chromatography (SiO_2, eluting 20 → 50% EtOAc:hexanes) to afford β-lactone **(±)-14a** (31.8 mg, 73%).

Entry 5 of Table 1: Same procedure as described for **Entry 4 of Table 1**, except that *t*-BuLi (72 μL, 2.5 M solution in hexane, 0.18 mmol, 1.00 equiv.) was used as base. β-lactone **(±)-14a** (32.7 mg, 75%) was obtained after flash column chromatography.

Entry 6 of Table 1: Same procedure as described for **Entry 4 of Table 1**, except that LiHMDS (180 μL, 1.0 M solution in THF, 0.18 mmol, 1.00 equiv.) was used as base. β-lactone **(±)-14a** (34.0 mg, 78%) was obtained after flash column chromatography.

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[13] Leverett, C. A., Purohit, V. C. & Romo, D. Enantioselective, organocatalyzed, intramolecular aldol lactonizations with keto acids leading to bi- and tricyclic β-lactones and topology-morphing transformations. *Angew. Chem. Int. Ed*. **49**, 9479-9483 (2010).

Entry 7 of Table 1: Same procedure as described for **Entry 4 of Table 1**, except that NaHMDS (180 μL, 1.0 M solution in THF, 0.18 mmol, 1.00 equiv.) was used as base. β-lactone **(±)-14a** (10.0 mg, 23%) was obtained after flash column chromatography.

Entry 8 of Table 1: Same procedure as described for **Entry 4 of Table 1**, except that KHMDS (180 μL, 1.0 M solution in THF, 0.18 mmol, 1.00 equiv.) was used as base. No β-lactone **(±)-14a** was detected by FT-IR, ^{1}H NMR, or TLC analysis.

Entry 9 of Table 1: Same procedure as described for **Entry 4 of Table 1**, except that isopropyl magnesium chloride (90 μL, 2.0 M solution in THF, 0.18 mmol, 1.00 equiv.) was used as base. β-Lactone **(±)-14a** (32.5 mg, 75%) was obtained after flash column chromatography.

Entry 10 of Table 1:

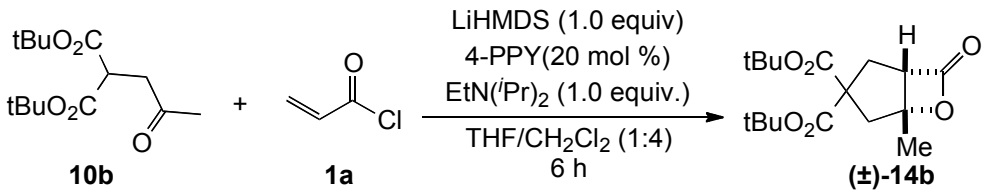
A solution of dimethyl 2-(2-oxopropyl) malonate (**10a,** 33 mg, 0.18 mmol, 1.00 equiv.) in THF (0.5 mL) was cooled to -78 ^{o}C and then LiHMDS (180 μL, 1.0 M solution in THF, 0.18 mmol, 1.00 equiv.) was added dropwise. The reaction was stirred for 10 min at -78 ^{o}C and then warmed up to 0 ^{o}C. Subsequently, CH_2Cl_2 (1 mL), 4-PPY (36 μL, 1.0 M solution in CH_2Cl_2, 0.036 mmol, 0.20 equiv.), and EtN(^{i}Pr)$_2$ (60 μL, 0.32 mmol, 2.00 equiv.) were added. The reaction was allowed to stir for an additional 10 min at 0 ^{o}C before acryloyl chloride (**1a**, 230 μL of a 1.6 M solution in CH_2Cl_2, 0.36 mmol, 1.77 equiv.) was added dropwise. The reaction was then warmed to 23 ^{o}C and stirred for 4 h. The reaction was diluted with CH_2Cl_2 (2 mL) and then 30% EtOAc in hexanes (4 mL), and passed through a pad of silica gel. The filtrate was concentrated under reduced pressure by rotary evaporation and the residue was purified by flash column chromatography (SiO_2, eluting with 20 → 50% EtOAc in hexanes) to afford β-lactone **(±)-14a** as a solid (36.6 mg, 84%).

Entry 11 of Table 1: Same procedure as described for **Entry 10 of Table 1**, except that 9-azajulolidine (36 μL, 1.0 M solution in CH_2Cl_2, 0.036 mmol, 2.00 equiv.) was

added as the nucleophile. β-Lactone **(±)-14a** (33.6 mg, 77%) was obtained after flash column chromatography.

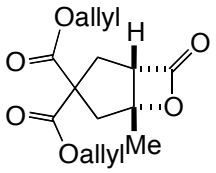
Entry 12 of Table 1: Same procedure as described for **Entry 10 of Table 1**, except that no nucleophile was added. No β-lactone **(±)-14a** was detected by FT-IR, ^{1}H NMR, or TLC analysis.

Representative procedure for the racemic the nucleophile-catalyzed Michael-aldol-β-lactonization (NMCAL) process as described for β-lactone (±)-14b.



Di-*tert*-butyl 5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((±)-14b). To an oven-dried, 25 mL round-bottomed flask equipped with a magnetic stir bar were added Michael donor **10b** (88 mg, 0.32 mmol, 1.00 equiv.) and THF (1 mL). The mixture was cooled to -78 ^{o}C with vigorous stirring and LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.) was added dropwise via microliter syringe over ~ 4 min. After the addition, the reaction was stirred for 10 min at -78 ^{o}C and then warmed to 0 ^{o}C by switching the dry ice/acetone bath to an ice/water bath. Stirring was continued for an additional 10 min at this temperature, and then CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.) and EtN(^{i}Pr)$_2$ (60 μL, 0.32 mmol, 1.00 equiv.) were added via microliter syringe, sequentially. The reaction was allowed to stir for an additional 10 min at 0 ^{o}C before acryloyl chloride (**1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.) was added via microliter syringe dropwise over ~ 2 min. After the addition, the ice bath was removed and the reaction was stirred for 6 h at ambient temperature (23 ^{o}C). At this time, the reaction was cooled to 0 ^{o}C and silica gel (2 mL) was added and the reaction was stirred at 0 ^{o}C for 10 min. The ice/water bath was removed and the reaction stirred at ambient temperature (23 ^{o}C) for 20 min. The mixture was then diluted with hexanes (4.0 mL), filtered through a short silica gel pad (~2 mL of silica gel), and rinsed with EtOAc (3 x

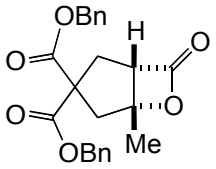
4 mL). The filtrate was then concentrated by rotary evaporation and following ^{1}H NMR analysis of the crude reaction mixture, it was purified by flash column chromatography (SiO_2, 10 → 30% EtOAc/hexanes) to afford bicyclic-β-lactone **(±)-14b** (105 mg, 73%) as colorless needles: m.p. 73.2 – 75.2 °C (recrystallized from hexanes:CH_2Cl_2 (1:1); TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.66; ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.46 (d, *J* = 9.0 Hz, 1H), 2.99 (d, *J* = 14.1 Hz, 1H), 2.87 (d, *J* = 15.4 Hz, 1H), 2.34 (d, *J* = 15.4 Hz, 1H), 2.07 (dd, *J* = 14.1, 9.1 Hz, 1H), 1.63 (s, 3H), 1.46 (s, 9H), 1.43 (s, 9H); ^{13}C NMR(125 MHz; $CDCl_3$): δ 169.6, 169.2, 168.9, 87.0, 82.7, 82.6, 62.2, 58.8, 43.3, 34.3, 27.8(3), 27.5(3), 21.6; IR (thin film): 2981, 2928, 1833, 1732 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{17}H_{26}LiO_6$ $[M + Li]^+$: 333.1889; found 333.1902.



(±)-14c

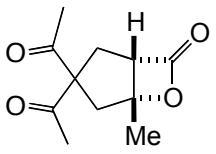
Diallyl 5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((±)-14c). Prepared according to the representative procedure using Michael donor **10c** (76.8 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.) and $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and acryloyl chloride (**1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After addition of acryloyl chloride, the reaction was allowed to react for 6 h at ambient temperature (23 ^{o}C). Purification by flash column chromatography (SiO_2, 10 → 30% EtOAc/hexanes) afforded bicyclic-β-lactone **(±)-14c** (79.1 mg, 84%) as a colorless oil: TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.45; ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.92-5.80 (m, 2H), 5.34-5.22 (m, 4H), 4.69-4.57 (m, 4H), 3.54-3.53 (m, 1H), 3.12 (d, *J* = 14.2 Hz, 1H), 3.01 (dd, *J* = 15.3, 0.9 Hz, 1H), 2.44 (d, *J* = 15.3 Hz, 1H), 2.21 (dd, *J* = 14.2, 9.0 Hz, 1H) 1.7 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ170.1, 169.6, 169.0, 131.6, 131.2, 119.24, 119.22, 87.0, 77.2, 67.1, 66.8, 59.0, 43.8, 34.7, 21.6; IR (thin

film): 2362, 2339, 1824, 1729 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{15}H_{19}O_6$ $[M + H]^+$ 295.1182; found 295.1177.



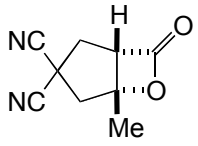
(±)-14d

Dibenzyl 5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((±)-14d). Prepared according to the representative procedure using Michael donor **10d** (108.9 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.) and $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and acryloyl chloride (**1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After addition of acryloyl chloride, the reaction was allowed to react for 6 h at ambient temperature (23 ^oC). Purification by flash column chromatography (SiO_2, 10 → 50% EtOAc/hexanes) afforded bicyclic-β-lactone **(±)-14d** (48 mg, 63%) as a white solid: TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.32; ^1H NMR (500 MHz; $CDCl_3$): δ 7.23 (dt, *J* = 7.3, 3.4 Hz, 6H), 7.18 (dd, *J* = 6.1, 3.4 Hz, 2H), 7.13 (dd, *J* = 6.5, 2.7 Hz, 2H), 5.12 (d, *J* = 12.2 Hz, 1H), 5.05-4.99 (m, 3H), 3.45 (d, *J* = 8.9 Hz, 1H), 3.07 (d, *J* = 14.1 Hz, 1H), 2.96 (d, *J* = 15.3 Hz, 1H), 2.36 (d, *J* = 15.3 Hz, 1H), 2.12 (dd, *J* = 14.2, 9.0 Hz, 1H), 1.62 (s, 3H).; ^{13}C NMR (125 MHz; $CDCl_3$): δ 170.1, 169.7, 169.0, 135.2, 135.0, 128.8(2), 128.7(2), 128.65, 128.63(2), 128.5, 128.1(2), 86.9, 68.2, 67.9, 60.9, 59.0, 43.7, 34.6, 29.6 (grease peak), 21.6; IR (thin film): 1829, 1735, 1264 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{23}H_{22}LiO_6$ $[M + Li]^+$: 401.1576; found 401.1560.



(±)-14e

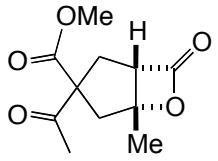
Methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-diyldiethanone ((±)-14e). Prepared according to the representative procedure using Michael donor **10e** (49.8 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and acryloyl chloride (**1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After the addition of acryloyl chloride, the reaction was allowed to react for 6 h at ambient temperature (23 °C). Purification by flash column chromatography (SiO_2, 10 → 50% EtOAc/hexanes) afforded bicyclic-β-lactone **(±)-14e** as a white solid (42.8 mg, 64%): m.p. 97.0 – 101.3 ºC (recrystallized from hexanes:CH_2Cl_2 (1:1)); TLC (EtOAc:hexanes, 4.5:5.5 *v/v)*: R_f = 0.25; ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.47 (d, *J* = 8.5 Hz, 1H), 3.26 (d, *J* = 14 Hz, 1H), 2.94 (d, *J* = 15.5 Hz, 1H), 2.35 (d, *J* = 15.5 Hz, 1H), 2.22 (s, 3H), 2.10 (s, 3H), 1.99 (dd, *J* = 14, 8.5 Hz, 1H), 1.69 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 203.37, 202.70, 168.96, 86.60, 76.56, 58.42, 41.35, 32.18, 26.63, 26.47, 21.73; IR (thin film): 2977, 2932, 1820, 1719, 1698 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{11}H_{14}LiO_4$ $[M+Li]^+$: 217.1052; found 217.1058.



(±)-14f

Methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarbonitrile ((±)-14f). To an oven-dried, 25 mL round-bottomed flask equipped with a magnetic stir bar was added Michael donor **10f** (19.5 mg, 0.16 mmol, 1.00 equiv.) and THF (0.5 mL). The mixture was cooled to -78 °C and with vigorous stirring, LiHMDS (160 μL of a 1.0 M solution in THF, 0.16 mmol, 1.00 equiv.) was added dropwise via microliter syringe over ~ 4 min. After the addition, the reaction was stirred for 10 min at -78 °C and then warmed to 0 °C by switching the dry ice/acetone bath to an ice/water bath. Stirring was continued for an additional 10 min at this temperature, and then CH_2Cl_2 (2 mL), 4-PPY (40 μL of a 0.82 M solution in CH_2Cl_2, 0.032 mmol, 0.20 equiv.) and $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 2.00 equiv.) were added via microliter syringe sequentially. The reaction

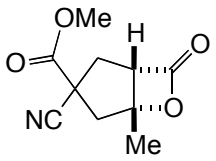
was allowed to stir for an additional 10 min at 0 °C before the acryloyl chloride (**1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.32 mmol, 2.00 equiv.) was added via microliter syringe dropwise over ~2 min. After the addition, the reaction was stirred for 3 h at 0 °C. At this time, silica gel (~2 g) was added and the reaction was stirred at 0 °C for 10 min. The ice/water bath was removed and the reaction stirred at ambient temperature (23 °C) for 20 min. The mixture was then diluted with hexanes (1.0 mL), filtered through a short silica gel pad (~2 g of silica gel), and rinsed with EtOAc (3 x 3 mL). The filtrate was then concentrated by rotary evaporation and following ^{1}H NMR analysis of the crude reaction mixture, it was purified by flash column chromatography (SiO_2, 10 → 50% EtOAc/hexanes) to afford bicyclic-β-lactone **(±)-14f** (16.9 mg, 60%) as a white solid: m.p. 120.2 – 123.0 °C (recrystallized from hexanes:CH_2Cl_2 (1:1)); TLC (EtOAc:hexanes, 4.5:5.5 *v/v)*: R_f = 0.24; ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.84 (d, *J* = 8.5 Hz, 1H), 3.19 (d, *J* = 15 Hz, 1H), 3.10 (d, *J* = 14.5 Hz, 1H), 2.62 (dd, *J* = 14.5, 8.5 Hz, 1H), 2.44 (d, *J* = 15 Hz, 1H), 1.82 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 166.2, 114.4, 114.3, 85.5, 59.1, 46.6, 38.4, 33.5, 21.4; IR (thin film): 2958, 2255, 1822 cm^{-1}; HRMS (ESI-) *m/z* calcd. for $C_9H_7N_2O_2$ [M-H]$^-$: 175.0508; found 175.0501.



(±)-14g

Methyl 3-acetyl-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3-carboxylate ((±)-14g). Prepared according to the representative procedure using Michael donor **10g** (55.1 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.), EtN(^{i}Pr)$_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and acryloyl chloride (**1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After addition of acryloyl chloride, the reaction was allowed to react for 8 h at ambient temperature (23 °C) as opposed to the standard 6 h. Purification by flash column chromatography (SiO_2, 25 → 55% EtOAc/hexanes) afforded a mixture of

diastereomers (1:1) of bicyclic-β-lactone **(±)-14g** (52.9 mg, 73%) as a pale yellow oil: TLC (EtOAc:hexanes, 5:5 *v/v)*: R_f = 0.31; (NMR data is provided for the 1:1 mixture of diastereomers) ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.76 (s, 3H), 3.72 (s, 3H), 3.51 (d, *J* = 8.5 Hz, 1H), 3.48 (d, *J* = 8.5 Hz, 1H), 3.14 (d, *J* = 14.2 Hz, 1H), 3.04 (d, *J* = 14.0 Hz, 1H), 2.93 (d, *J* = 15.6 Hz, 1H), 2.87 (d, *J* = 15.3 Hz, 1H), 2.44 (d, *J* = 15.6 Hz, 1H), 2.3 (m, 1H), 2.25 (s, 3H), 2.18 (s, 3H), 2.17 - 2.11 (m, 1H), 2.04 (dd, *J*= 14.0, 8.9 Hz, 1H), 1.68 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 201.6, 201.5, 171.6, 171.2, 169.2, 168.9, 87.0, 86.7, 67.8, 67.1, 59.0, 58.8, 53.5 (2), 43.0, 42.5, 33.6, 33.2, 26.9 26.5, 21.8, 21.7; IR (thin film):1827, 1711 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{11}H_{15}O_5$ $[M+H]^+$: 227.0919; found 227.0923.



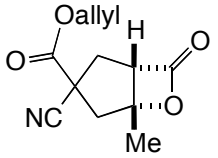
(±)-14h

Methyl 3-cyano-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3-carboxylate ((±)-14h).

Prepared according to the representative procedure using known Michael donor **10h**[14] (50.0 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.), $EtN(^iPr)_2$ (92 μL, 0.48 mmol, 1.50 equiv.), acryloyl chloride (**1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After the addition of acryloyl chloride, the reaction was allowed to react at ambient temperature (23 ^{o}C) for 6 h. Purification by flash column chromatography (SiO_2, 10 → 40% EtOAc/hexanes) afforded a mixture of diastereomers (1.7:1) of bicyclic-β-lactone **(±)-14h** (43.5 mg, 65%) as a yellow oil: TLC (EtOAc:hexanes, 3.5:6.5 *v/v)*: R_f = 0.38 and 0.12; (NMR data is provided for the 1.7:1 mixture of diastereomers) ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.89 (s, 3H), 3.86 (s, 3H), 3.74 (d, *J* =

[14] Kim, C. H., Jang, K. D., Choi, S. Y., Chung, Y. K. & Lee, E. A carbonyl ylide cycloaddition approach to platensimycin. *Angew. Chem. Int. Ed.* **47***,* 4009-4011 (2008).

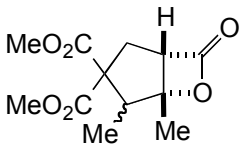
5 Hz, 1H), 3.65 (d, *J* = 5.0 Hz, 1H), 3.25-3.21 (m, 2H), 2.91 (d, *J* = 15.1 Hz, 1H), 2.82 (d, *J* = 15.1 Hz, 1H), 2.53 (dd, *J* = 14.4, 8.5 Hz, 1H), 2.45-2.35 (m, 4H), 1.77 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ168.1, 167.7, 167.6, 166.9, 118.3, 118.2, 86.3, 86.0, 59.4, 59.2, 54.7, 54.6, 47.2, 46.9, 46.1, 45.4, 37.0, 35.5, 21.6 (2).; IR (thin film): 2357, 1824, 1747 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{10}H_{11}LiNO_4$ $[M+Li]^+$: 216.0848; found 216.0839.



(±)-14i

Allyl 3-cyano-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3-carboxylate ((±)-14i). Prepared according to the representative procedure using known Michael donor **10i**[15] (57.98 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), acryloyl chloride (**1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After addition of acryloyl chloride, the reaction was allowed to react at ambient temperature (23 ºC) for 24 h. Purification by flash column chromatography (SiO_2, 10 → 50% EtOAc/hexanes) afforded a mixture of diastereomers (1.16:1) of bicyclic-β-lactone **(±)-14i** (40.7 mg, 60%) as a yellow oil: TLC (EtOAc:hexanes, 3.5:6.5 *v/v)*: R_f = 0.39; (NMR data is provided for the 1.16:1 mixture of diastereomers) ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.97-5.89 (m, 2H), 5.44-5.38 (m, 2H), 5.35-5.32 (m, 2H), 4.75-4.71 (m, 4H), 3.74 (d, *J* = 8.0 Hz, 1H), 3.63 (dd, *J* = 9.0, 1 Hz, 1H), 3.25 (dd, *J* = 14.5, 7.5 Hz, 2H), 2.92 (dd, *J* = 15.0, 1.0 Hz, 1H), 2.82 (d, *J* = 14.5 Hz, 1H), 2.53 (dd, J = 14.5, 8.5 Hz, 1H), 2.45-2.40 (m, 2H), 2.38 (d, *J* = 2.5 Hz, 1H), 1.77 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 167.75, 167.53, 167.28, 166.08, 130.58, 130.47, 120.50, 120.39, 118.23, 118.20, 86.34, 86.04, 68.48, 68.23, 59.35, 59.19, 47.37, 47.12, 46.05, 45.33, 36.92, 35.52, 21.57 (2); IR (thin film): 2937, 2246, 1822,

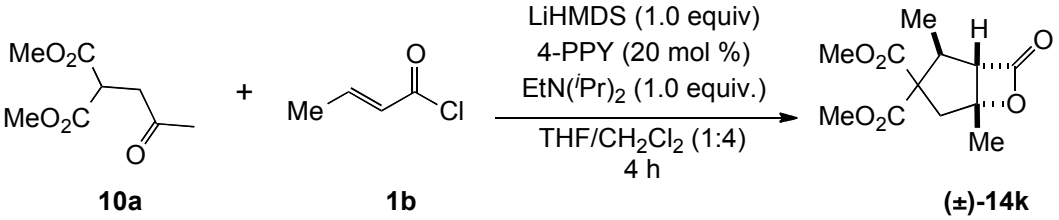
1745 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{12}H_{14}NO_4$ $[M+H]^+$: 236.0923; found 236.1220



(±)-14j

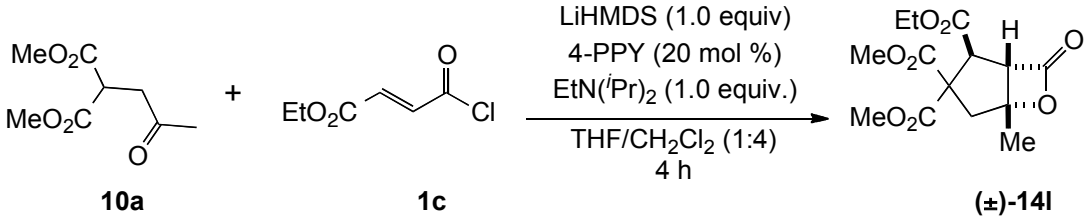
Dimethyl 4,5-dimethyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((±)-14j). Prepared according to the representative procedure using Michael donor **10j** (65.4 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and acryloyl chloride (**1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After the addition of acryloyl chloride, the reaction was allowed to react for 9 h at ambient temperature (23 ^oC) as opposed to the standard 6 h. Purification by flash column chromatography (SiO_2, 15 → 50% EtOAc/hexanes) afforded a mixture of diastereomers (2:1) of bicyclic-β-lactone **(±)-14j** (69.3 mg, 84%) as a pale yellow oil: TLC (EtOAc:hexanes, 4:6 *v/v)*: R_f = 0.33 and 0.42; (NMR data is provided for the 2:1 mixture of diastereomers) ^1H NMR (500 MHz; $CDCl_3$): δ 3.72 (brs, 6H), 3.71 (s, 6H), 3.52-3.48 (m, 2H), 3.36 (d, *J* = 7.6 Hz, 1H), 2.95 (d, *J* = 14.3 Hz, 1H), 2.81 (d, *J* = 14.6 Hz, 1H), 2.70-2.61 (m, 2H), 2.00 (dd, *J* = 14.3, 9.1 Hz, 1H), 1.60 (s, 3H), 1.59 (s, 3H), 1.19 (d, *J* = 7.1 Hz, 3H), 0.90 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 171.1, 170.0, 169.9, 169.8, 169.31, 169.27, 89.12, 87.9, 65.5, 63.1, 58.4, 57.9, 53.4, 53.23, 53.20, 52.6, 47.7, 45.8, 33.6, 31.0, 20.5, 19.6, 13.0, 9.8; IR (thin film): 2961, 1824, 1735 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{12}H_{16}OLiO_6$ $[M+Li]^+$: 263.1107; found 263.1115.

Representative procedure for the racemic nucleophile-catalyzed Michael-aldol-β-lactonization (NMCAL) process when varying the Michael acceptors as described for β-lactone (±)-14k.

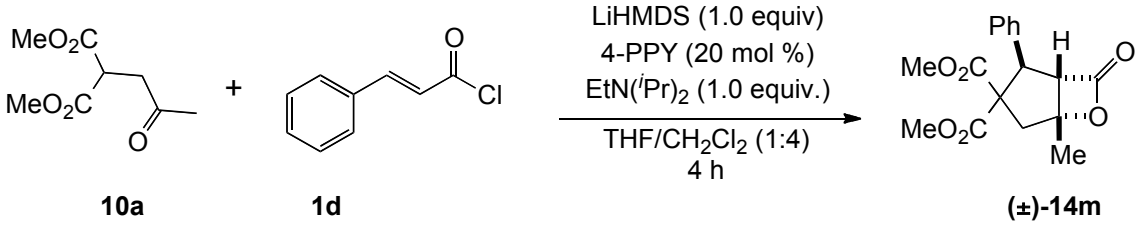


Dimethyl 2,5-dimethyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((±)-14k). To an oven-dried, 25 mL round-bottomed flask equipped with a magnetic stir bar was added dimethyl 2-(2-oxopropyl) malonate (**10a**, 61.0 mg, 0.32 mmol, 1.00 equiv.) along with THF (1 mL) and the mixture was cooled to -78 ^{o}C. With vigorous stirring, LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.) was added dropwise via microliter syringe. After complete addition, the reaction was stirred for 10 min at -78 ^{o}C and then warmed to 0 ^{o}C by switching the dry ice/acetone bath to an ice/water bath. Stirring was continued for an additional 10 min at this temperature, and then CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.) and EtN(^{i}Pr)$_2$ (60 μL, 0.32 mmol, 1.00 equiv.) were added via microliter syringe, sequentially. The reaction was allowed to stir for an additional 10 min at 0 ^{o}C before (*E*)-but-2-enoyl chloride (**1b**, 260 μL of a 1.6 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.) was added via microliter syringe dropwise over ~2 min. After complete addition, the ice bath was removed and the reaction was stirred for 4 h at ambient temperature (23 ^{o}C). The reaction was then cooled to 0 ^{o}C and silica gel (2 g) was added and stirred at 0 ^{o}C for 10 min. Then the ice/water bath was removed and the reaction stirred at ambient temperature (23 ^{o}C) for 20 min. The mixture was then diluted with hexanes (4.0 mL), filtered through a short silica gel pad (~2 g of silica gel), and rinsed with EtOAc (3 x 4 mL). The filtrate was then concentrated by rotary evaporation, analyzed by ^{1}H NMR. Purification by flash column chromatography (SiO_2, 10 → 40% EtOAc/hexanes) afforded a single diastereomer of bicyclic-β-lactone **(±)-14k** (77.1 mg, 94%) as a white solid: TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.25; ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.71 (s, 3H), 3.70 (s, 3H), 3.42 (q, *J* = 7.5 Hz, 1H), 3.17 (s, 1H), 2.82 (d, *J* = 16.5 Hz, 1H), 2.63 (d, *J* = 16.5 Hz, 1H), 1.66 (s, 3H), 0.86 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 170.6, 168.8, 168.3, 86.0, 65.9, 64.5, 53.2,

53.0, 40.9, 39.6, 22.2, 17.0; IR (thin film): 2996, 2927, 1835, 1735, 1730 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{12}H_{17}O_6$ $[M+H]^+$: 257.1025; found 257.1038.

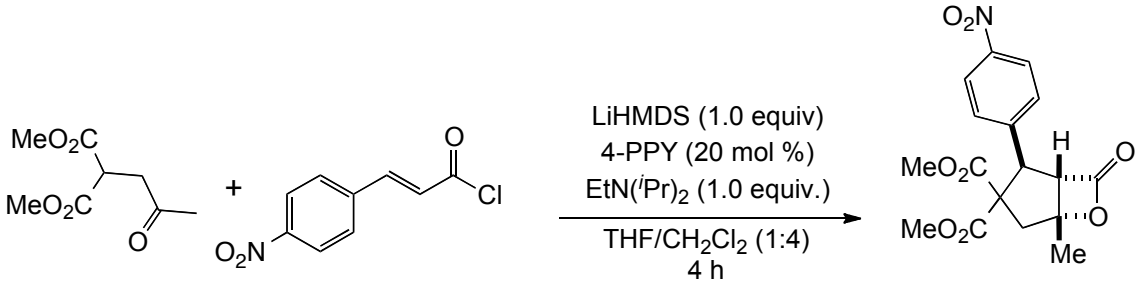


2-Ethyl 3,3-dimethyl 5-methyl-7-oxo-6-oxabicyclo[3.2.0] heptane-2,3,3-tricarboxylate ((±)-14l). Prepared according to the representative procedure for **(±)-14k**, except that ethyl fumaroyl chloride (**1c**, 68.2 *u*L, 0.42 mmol, 1.30 equiv.) was added as the Michael acceptor to afford a single diastereomer of bicyclic-β-lactone **(±)-14l** (91.5 mg, 91%) as a white solid: TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.35; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.23 (s, 1H), 4.18-4.06 (m, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 3.71 (s, 1H), 2.97 (d, *J* = 15.5 Hz, 1H), 2.78 (d, *J* = 15.5 Hz, 1H), 1.74 (s, 3H), 1.25 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 169.4, 168.4, 167.1, 87.17, 64.1, 62.2, 62.1, 53.8, 53.5, 50.7, 42.6, 21.6, 14.2; IR (thin film) 2985, 2958, 1832, 1740 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{14}H_{19}O_8$ $[M+H]^+$ 315.1080; found 315.1097.



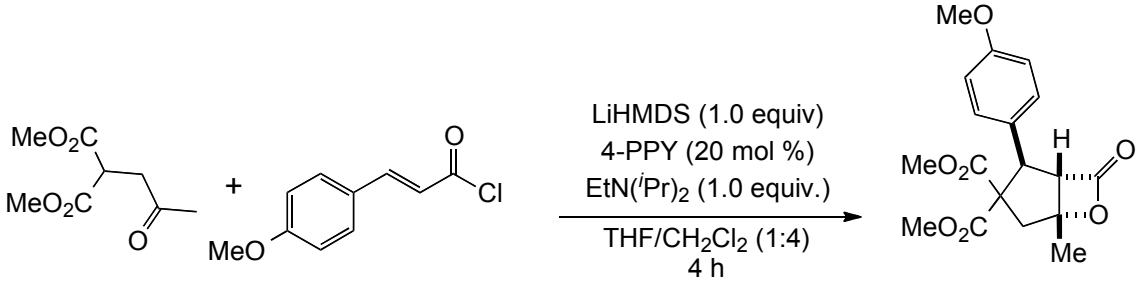
Dimethyl 5-methyl-7-oxo-2-phenyl-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((±)-14m). Prepared according to the representative procedure for **(±)-14k**, except that cinnamoyl chloride (**1d**, 70 mg, 0.42 mmol, 1.30 equiv.) was added as the Michael acceptor to afford a single diastereomer of bicyclic-β-lactone **(±)-14m** (91.6 mg, 90%) as a white solid: TLC (EtOAc:hexanes, 2:8 *v/v)*: R_f = 0.15; ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.27 (m, 3H), 6.95 (d, *J* = 7.0 Hz, 2H), 4.62 (s, 1H), 3.78 (s, 3H), 3.68 (s, 1H), 3.30 (s, 3H), 2.90 (s, 2H), 1.89 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 170.6,

167.9, 167.6, 138.2, 128.7 (2), 128.0, 127.9(2), 87.3, 66.8, 65.4, 53.5, 52.63, 51.0, 41.9, 21.4; IR (thin film): 2967, 2935, 1829, 1732, 1728 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{17}H_{19}O_6$ $[M+H]^+$: 319.1182; found 319.1149.



10a **1e** **(±)-14n**

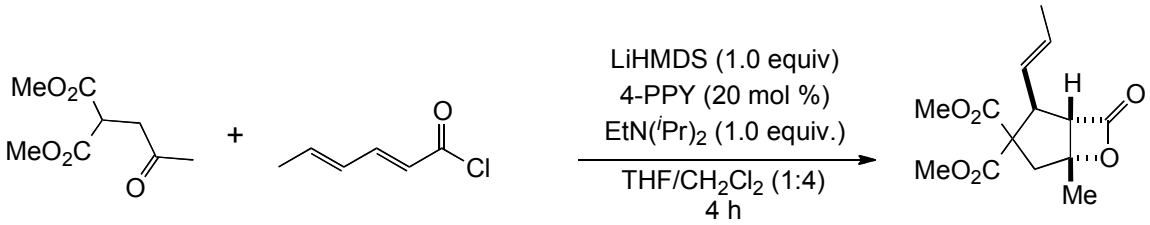
Dimethyl 5-methyl-2-(4-nitrophenyl)-7-oxo-6-oxabicyclo [3.2.0]heptane-3,3-dicarboxylate ((±)-14n). Prepared according to the representative procedure for **(±)-14k**, except that *trans*-4-nitrocinnamoyl chloride (**1e**, 89 mg, 0.42 mmol, 1.30 equiv.) was added as the Michael acceptor to afford a single diastereomer of bicyclic-β-lactone **(±)-14n** (96.5 mg, 83%) as a white solid: TLC (EtOAc:hexanes, 2:8 *v/v)*: R_f = 0.25; ^1H NMR (500 MHz; $CDCl_3$): δ 8.17 (d, *J* = 9.0 Hz, 2H), 7.15 (d, *J* = 9.0 Hz, 2H), 4.77 (s, 1H), 3.82 (s, 3H), 3.69 (s, 1H), 3.36 (s, 3H), 2.98 (d, *J* = 16 Hz, 1H), 2.88 (d, *J* = 16 Hz, 1H), 1.94 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 170.1, 167.3, 166.9, 147.6, 145.7, 129.0(2), 124.0(2), 87.2, 66.8, 65.2, 53.9, 53.0, 50.7, 42.2, 21.6; IR (thin film): 2986, 2945, 1831, 1736, 1729 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{17}H_{18}NO_8$ $[M + H]^+$: 364.1032; found 364.1059.



10a **1f** **(±)-14o**

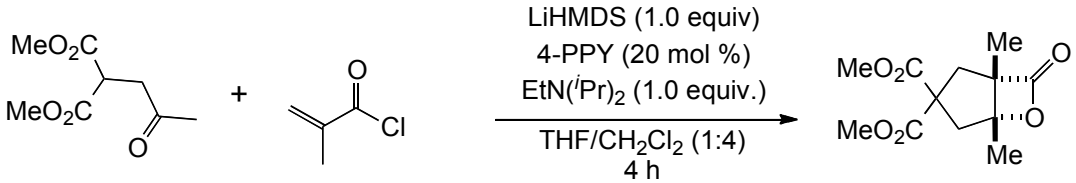
Dimethyl 2-(4-methoxyphenyl)-5-methyl-7-oxo-6-oxabicyclo [3.2.0]heptane-3,3-dicarboxylate ((±)-14o). Prepared according to the representative procedure for **(±)-14k**, except that (*E*)-3-(4-methoxyphenyl)acryloyl chloride (**1f**, 82 mg, 0.42 mmol,

1.30 equiv.) was added as the Michael acceptor to afford a single diastereomer of bicyclic-β-lactone **(±)-14o** (97.0 mg, 87%) as a white solid: TLC (EtOAc:hexanes, 2:8 *v/v)*: R_f = 0.20; ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.86 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 4.57 (s, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.63 (s, 1H), 3.33 (s, 3H), 2.87 (s, *2*H), 1.88 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 170.7, 168.0, 167.7, 159.1, 130.2, 129.0(2), 114.0(2), 87.2, 66.8, 65.6, 55.2, 53.4, 52.6, 50.3, 41.9, 21.5; IR (thin film): 2993, 2946, 1828, 1728, 1725 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{18}H_{21}O_7$ $[M + H]^+$: 349.1287; found 349.1299.



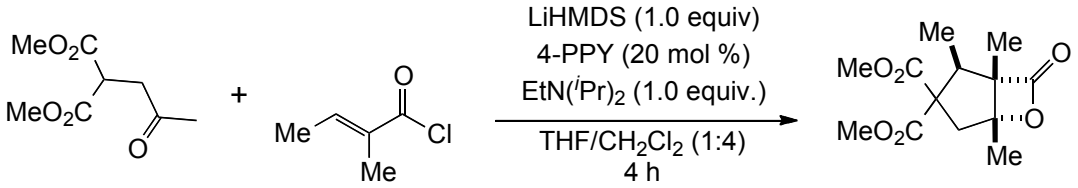
10a **1g** **(±)-14p**

Dimethyl 5-methyl-7-oxo-2-((E)-prop-1-en-1-yl)-6-oxabicyclo [3.2.0]heptane-3,3-dicarboxylate ((±)-14p). Prepared according to the representative procedure for **(±)-14k**, except that sorbic chloride (**1g**, 51.4 *u*L, 0.42 mmol, 1.3 equiv) was added as the Michael acceptor to afford a single diastereomer of bicyclic-β-lactone **(±)-14p** (58.0 mg, 64%) as a white solid: TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.50; ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.59 (m, 1H), 5.09 (m, 1H), 3.90 (d, *J* = 10 Hz, 1H), 3.75 (s, 3H), 3.63 (s, 3H), 3.33 (s, 1H), 2.82 (d, *J* = 16 Hz, 1H), 2.65 (d, *J* = 16 Hz, 1H), 1.71 (s, 3H), 1.64 (dd, *J* = 6.5, 1.5 Hz, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): 170.5, 168.4, 168.0, 130.0, 126.4, 86.4, 65.3, 64.5, 53.3, 53.0, 48.6, 41.5, 22.0, 18.0; IR (thin film): 2977, 2963, 1829, 1732, 1729 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{14}H_{19}O_6$ $[M+H]^+$: 283.1182; found 283.1203.



10a **1h** **(±)-14q**

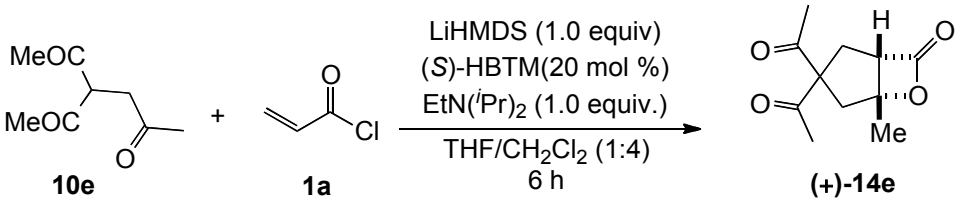
Dimethyl 1,5-dimethyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((±)-14q). Prepared according to the representative procedure for **(±)-14k**, except that methacryloyl chloride (**1h**, 41 μL, 0.42 mmol, 1.30 equiv.) was added as the Michael acceptor to afford a single diastereomer of bicyclic-β-lactone **(±)-14q** (64.1 mg, 78%) as a white solid: TLC (EtOAc:hexanes, 2.5:7.5 *v/v)*: R_f = 0.45; ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.73 (s, 3H), 3.71 (s, 3H), 3.15 (d, *J* = 14 Hz, 1H), 2.98 (d, *J* = 15 Hz, 1H), 2.40 (d, *J* = 15 Hz, 1H), 1.85 (d, *J* = 14 Hz, 1H), 1.52 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): 172.4, 170.9, 170.3, 89.3, 62.3, 58.4, 53.4, 53.2, 44.1, 42.1, 18.7, 14.1; IR (thin film): 2986, 2937, 1829, 1739, 1725 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{12}H_{17}O_6$ $[M+H]^+$: 257.1025; found 257.1058.



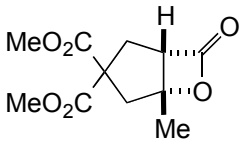
10a **1i** **(±)-14r**

Dimethyl 1,2,5-trimethyl-7-oxo-6-oxabicyclo [3.2.0]heptane-3,3-dicarboxylate ((±)-14r). Prepared according to the representative procedure for **(±)-14k**, except that (*E*)-2-methylbut-2-enoyl chloride (**1i**, 50 mg, 0.42 mmol, 1.30 equiv.) was added as the Michael acceptor, to afford a single diastereomer of bicyclic-β-lactone **(±)-14r** (29.2 mg, 60%) as a white solid: TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.20; ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.75 (s, 3H), 3.74 (s, 3H), 3.38 (q, *J* = 8.0 Hz, 1H), 2.86 (d, *J* = 15.5 Hz, 1H), 2.58 (d, *J* = 15.5 Hz, 1H), 1.52 (s, 3H), 1.21 (s, 3H), 0.78 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 173.0, 170.7, 169.2, 88.8, 64.5, 63.3, 53.3, 53.1, 42.1, 41.7, 19.2, 12.3, 11.4; IR (thin film): 2995, 2928, 1832, 1732, 1728 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{13}H_{19}O_6$ $[M+H]^+$: 271.1182; found 271.1159.

Representative procedure for the enantioselective nucleophile-catalyzed Michael-aldol-β-lactonization (NMCAL) process as described for β-lactone (+)-14e.

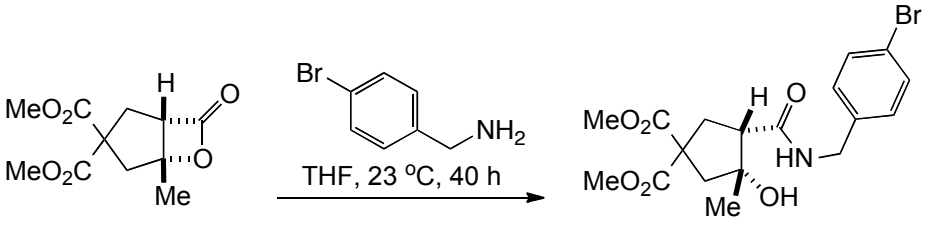


Methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-diyldiethanone ((+)-14e). To an oven-dried, 25 mL round-bottomed flask equipped with a magnetic stir bar was added Michael donor **10e** (49.8 mg, 0.32 mmol, 1.00 equiv.) along with THF (1 mL) and cooled to -78 ^{o}C. With vigorous stirring, LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.) was added dropwise via microliter syringe over ~4 min. After the addition the reaction was stirred for 10 min at -78 ^{o}C and then warmed to 0 ^{o}C by switching the dry ice/acetone bath to an ice/water bath. Stirring was continued for an additional 10 min at this temperature, and then CH_2Cl_2 (3 mL), (*S*)-HBTM (17 mg, 0.064 mmol, dissolved in 1.1 mL CH_2Cl_2, 0.20 equiv.) and $EtN(^{i}Pr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.) were added via microliter syringe sequentially. The reaction was allowed to stir for an additional 10 min at 0 ^{o}C before acryloyl chloride (**1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.) was added via microliter syringe dropwise over ~4 min. After the addition, the ice bath was removed and the reaction stirred for 6 h at ambient temperature (23 ^{o}C). At this time, the reaction was cooled to 0 ^{o}C and silica gel (2 g) was added and stirred at 0 ^{o}C for 10 min. Then the ice/water bath was removed and the reaction stirred at ambient temperature (23 ^{o}C) for 20 min. The mixture was then diluted with hexanes (4.0 mL), filtered through a short silica gel pad (~2 g of silica gel), and rinsed with EtOAc (3 x 4 mL). This process removes polar impurities including (*S*)-HBTM. The filtrate was concentrated by rotary evaporation, and following ^{1}H NMR analysis of the reaction mixture, it was purified by flash column chromatography (SiO_2, 10 → 50% EtOAc/hexanes) to afford bicyclic-β-lactone **(+)-14e** (41.2 mg, 61%) as a white solid: $[\alpha]_D^{21}$ = +167.34 (*c* = 1.00, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel AD-H column: hexanes:*i*PrOH = 95:05, flow rate 0.5 mL/min, λ = 210 nm: t_{minor} = 52.0 min, t_{major} = 67.4 min; 95% *ee*. Spectral data matched that reported above for the racemic compound.



(+)-14a

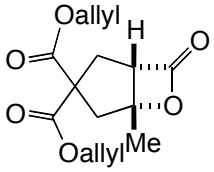
(**1*S*,5*R*)-Dimethyl 5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((+)-14a).** Prepared according to the representative procedure using Michael donor **10a** (60.0 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (3 mL), (*S*)-HBTM (17 mg, 0.064 mmol, dissolved in 1.1 mL CH_2Cl_2, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and acryloyl chloride (**1a**, 34 μL, 0.42 mmol, dissolved in 260 μL CH_2Cl_2, 1.30 equiv.). After the addition of acryloyl chloride, the reaction was allowed to react for 6 h at ambient temperature (23 ºC). After ^{1}H NMR analysis of the reaction mixture, it was purified by flash column chromatography (SiO_2, 20 → 50% EtOAc/hexanes) to afford bicyclic-β-lactone **(+)-14a** (55.8 mg, 72% yield) as a colorless oil: $[\alpha]_D^{21}$ = +67.25 (*c* = 1.00, $CHCl_3$). Enantiomeric excess was determined by chiral GC analysis in comparison with authentic racemic material; t_{minor} = 253.1 min, t_{major} = 263.4 min; 97% *ee*. Spectral data matched that previously reported[16] and absolute stereochemistry was assigned by derivatization below.



(+)-14a **(+)-S16**

(3*R*,4*S*)-Dimethyl4-((4-bromobenzyl)carbamoyl)-3-hydroxy-3-methylcyclo-pentane 1,1-dicarboxylate ((+)-S16). To a oven-dried, 5 mL round-bottomed flask was added β-lactone **(+)-14a** (48.5 mg, 0.20 mmol, 1.00 equiv) and *p*-

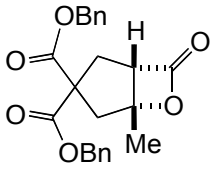
bromobenzylamine (0.10 mL, 0.80 mmol, 4.00 equiv), in THF (2 mL). The reaction was allowed to stir at ambient temperature (23 °C) for 40 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and purified by flash column chromatography (SiO_2, 20 → 60% EtOAc/hexanes) to afford amide **(+)-S16** (85.5 mg, 65%) as a colorless crystalline solid: m.p. 118–121 °C (recrystallized from $CDCl_3$); TLC (EtOAc:hexanes, 5:5 *v/v*): R_f = 0.35; $[\alpha]_D^{21}$ = +8.00 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.46 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 6.38 (brs, 1H), 4.45-4.37 (m, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 2.80 (t, *J* = 12.7 Hz, 1H), 2.67-2.58 (m, 2H), 2.52 (dd, *J* = 12.1, 7.9 Hz, 1H), 2.13 (d, *J* = 14.3 Hz, 1H), 1.37 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 173.3, 173.1, 172.7, 137.1, 132.1(2), 129.6(2), 121.8, 80.0, 58.0, 53.8, 53.4, 53.3, 48.5, 43.0, 37.5, 25.7; IR (thin film): 3336, 2960, 2922, 1732, 1637 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{18}H_{23}BrNO_6$ $[M+H]^+$: 428.0709; found 428.0692.



(+)-14c

(1*R*,5*S*)-Diallyl 5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((+)-14c). Prepared according to the representative procedure using Michael donor **10c** (76.8 mg, 0.32 mmol), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (3 mL), (*S*)-HBTM (17 mg, 0.064 mmol, dissolved in 1.1 mL CH_2Cl_2, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and acryloyl chloride (**1a**, 34 μL, 0.42 mmol, dissolved in 260 μL CH_2Cl_2, 1.30 equiv.). After the addition of acryloyl chloride the reaction was allowed to react for 6 h at ambient temperature (23 ºC). Purification by flash column chromatography afforded bicyclic-β-lactone **(+)-14c** (69 mg, 73%) as a colorless oil: $[\alpha]_D^{21}$ = +39.8 (*c* = 0.200, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel IA column: hexanes:*i*PrOH = 92:08, flow rate 0.5 mL/min, λ = 210 nm: t_{major} = 17.3 min, t_{minor} = 21.3 min; 95% *ee*. Spectral data matched

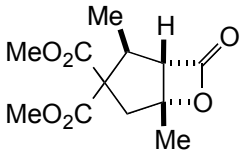
that reported above for the racemic compound that reported above for the racemic compound.



(+)-14d

(1*S*,5*R*)-Dibenzyl 5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((+)-14d). Prepared according to the representative procedure using Michael donor **10d** (11.78 mg, 0.35 mmol, 1.0 equiv.), THF (1 mL), LiHMDS (256 μL of a 1.0 M solution in THF, 0.26 mmol, 0.74 equiv.), CH_2Cl_2 (3 mL), (*S*)-HBTM (10.4 mg, 0.033 mmol, dissolved in 1.1 mL CH_2Cl_2, 0.10 equiv.), $EtN(^iPr)_2$ (48 μL, 0.28 mmol, 0.92 equiv.), and acryloyl chloride (**1a**, 34 μL, 0.42 mmol, dissolved in 227 μL CH_2Cl_2, 1.20 equiv.). After the addition of acryloyl chloride, the reaction was allowed to react for 6 h at ambient temperature (23 ºC). Purification by flash column chromatography afforded bicyclic-β-lactone **(+)-14d** (59.2 mg, 59%) as a colorless oil: $[\alpha]_D^{21}$ = +41.3 (*c* = 0.36, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel OD-H column: hexanes:*i*PrOH = 95:05, flow rate 1.0 mL/min, λ = 210 nm: t_{major} = 36.6 min, t_{minor} = 45.6 min; 98% *ee*. Spectral data matched

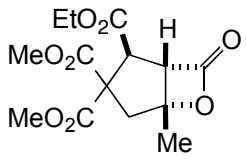
that reported above for the racemic compound.



(+)-14k

(1*S*,2*S*,5*R*)-Dimethyl 2,5-dimethyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((+)-14k). Prepared according to the representative procedure using Michael donor **10a** (60.0 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), (*S*)-HBTM (17

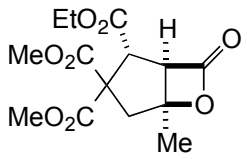
mg, 0.064 mmol, dissolved in 1.1 mL CH_2Cl_2, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and (*E*)-but-2-enoyl chloride (**1b**, 40 μL, 0.42 mmol, dissolved in 2 mL CH_2Cl_2, 1.30 equiv.). The solution of (*E*)-but-2-enoyl chloride was added by syringe pump over 2 h at 0 °C. After the addition of (*E*)-but-2-enoyl chloride, the reaction was allowed to react for 16 h at room temperature (23 °C) as opposed to the standard 6 h. Purification by flash column chromatography afforded a single diastereomer of bicyclic-β-lactone **(+)-14k** (64.5 mg, 80%) a colorless solid: $[\alpha]_D^{21}$ = +116.51 (*c* = 1.00, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel OD-H column: hexanes:*i*PrOH = 90:10, flow rate 0.5 mL/min, λ = 210 nm: t_{major} = 22.4 min, t_{minor} = 29.1 min 94% *ee*. Spectral data matched that reported above for the racemic compound.



(+)-14l

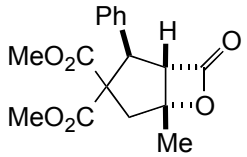
(1*R*,2*R*,5*S*)-2-Ethyl 3,3-dimethyl 5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,3,3-tricarboxylate ((+)-14l). Prepared according to the representative procedure using Michael donor **10a** (60.0 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (3 mL), (*S*)-HBTM (17 mg, 0.064 mmol, dissolved in 1.1 mL CH_2Cl_2, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol), and ethyl fumaroyl chloride (**1c**, 68.2 μL, 0.42 mmol, dissolved in 260 μL CH_2Cl_2, 1.30 equiv.). After the addition of ethyl fumaroyl chloride, the reaction was allowed to react for 24 h at room temperature (23 °C) as opposed to the standard 6 h. Purification by an automated flash chromatography system (gradient of EtOAc/hexanes) afforded a single diastereomer of bicyclic-β-lactone **(+)-14l** (95.2 mg, 95%) a yellow oil: $[\alpha]_D^{21}$ = +109.5 (*c* = 1.00, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel AD-H column: hexanes:*i*PrOH = 88:12, flow rate 0.9 mL/min, λ = 230 nm:

t_{major} = 9.2 min, t_{minor} = 16.2 min; 90% *ee*. Spectral data matched that reported above for the racemic compound.



(–)-14l

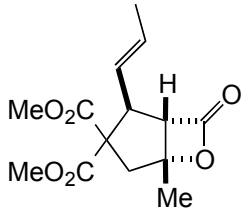
(1*S*,2*S*,5*R*)-2-Ethyl 3,3-dimethyl 5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,3,3-tricarboxylate ((-)-14l). Prepared according to the representative procedure using Michael donor **10a** (60.0 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (3 mL), (*R*)-HBTM (17 mg, 0.064 mmol, dissolved in 1.1 mL CH_2Cl_2, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and ethyl fumaroyl chloride (**1c**, 68.2 mg, 0.42 mmol, dissolved in 260 μL CH_2Cl_2, 1.30 equiv.). After complete addition, the reaction was allowed to react for 24 h at room temperature (23 ^oC) as opposed to the standard 6 h. Purification by an automated flash chromatography system (gradient of EtOAc/hexanes) afforded a single diastereomer of bicyclic-β-lactone **(-)-14l** (90.6 mg, 90%) as a yellow oil: $[\alpha]_D^{21}$ = -109.9 (*c* = 1.00, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel AD-H column: hexanes:*i*PrOH = 88:12, flow rate 0.9 mL/min, λ = 230 nm: t_{minor} = 9.2 min, t_{major} = 15.8 min; 89% *ee*. Spectral data matched that reported above for the racemic compound.



(+)-14m

(1*S*,2*R*,5*R*)-Dimethyl 5-methyl-7-oxo-2-phenyl-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((+)-14m). Prepared according to the representative procedure using

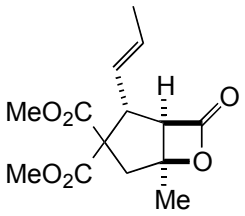
Michael donor **10a** (60.8 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (3 mL), (*S*)-HBTM (17 mg, 0.064 mmol, dissolved in 400 μL CH_2Cl_2, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and cinnamoyl chloride (**1d**, 67.7 mg, 0.35 mmol, dissolved in 2.6 mL CH_2Cl_2, 1.10 equiv.). The solution of cinnamoyl chloride was added by syringe pump over 2 h at 0 °C. After the addition of cinnamoyl chloride, the reaction was allowed to react for 18 h at room temperature (23 °C) as opposed to the standard 6 h. Purification by flash column chromatography afforded a single diastereomer of bicyclic-β-lactone **(+)-14m** (82.3 mg, 80%) as a white solid: $[\alpha]_D^{21}$ = +188.23 (*c* = 0.17, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel AD-H column: hexanes:*i*PrOH = 70:30, flow rate 0.5 mL/min, λ = 210 nm: t_{major} = 12.0 min, t_{minor} = 13.1 min; 99% *ee*. Spectral data matched that reported above for the racemic compound.



(+)-14p

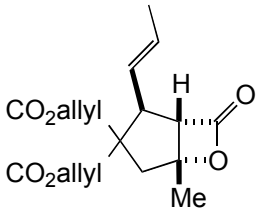
(1*S*,2*S*,5*R*)-Dimethyl-5-methyl-7-oxo-2-((*E*)-prop-1-en-1-yl)-6-oxabicyclo[3.2.0] heptane-3,3-dicarboxylate ((+)-14p). Prepared according to the representative procedure using Michael donor **10a** (60.0 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), (*S*)-HBTM (17 mg, 0.064 mmol, dissolved in 1 mL CH_2Cl_2, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and sorbic chloride (**1g**, 51.4 μL, 0.42 mmol, dissolved in 2 mL CH_2Cl_2, 1.3 equiv.). The solution of sorbic chloride was added by syringe pump over 2 h at 0 °C. After the addition of sorbic chloride, the reaction was allowed to react for 16 h at room temperature (23 °C) as opposed to the standard 6 h. Purification by flash column chromatography afforded a single diastereomer of bicyclic-β-lactone **(+)-14p** (56.0 mg, 62%) a white crystalline solid:

m.p. 98–102 °C (recrystallized from $CDCl_3$); $[\alpha]_D^{21}$ = +140.00 (*c* = 1.00, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel AD-H column: hexanes:*i*PrOH = 70:30, flow rate 0.5 mL/min, λ = 210 nm: t_{major} = 22.2 min, t_{minor} = 27.1 min; 99% *ee*. Spectral data matched that reported above for the racemic compound.



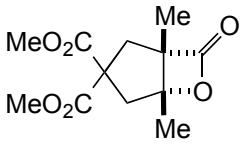
(–)-14p

(1*R*,2*R*,5*S*)-Dimethyl5-methyl-7-oxo-2-((*E*)-prop-1-en-1-yl)-6-oxabicyclo[3.2.0] heptane-3,3-dicarboxylate ((-)-14p). Prepared according to the representative procedure using Michael donor **10a** (60.0 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (3 mL), (*R*)-HBTM (17 mg, 0.064 mmol, dissolved in 1 mL CH_2Cl_2, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and sorbic chloride (**1g**, 51.4 μL, 0.42 mmol, dissolved in 2 mL CH_2Cl_2, 1.30 equiv.). The solution of sorbic chloride was added by syringe pump over 2 h at 0 °C. After the addition of sorbic chloride, the reaction was allowed to react for 21 h at room temperature (23 °C) as opposed to the standard 6 h. Purification by flash column chromatography afforded a single diastereomer of bicyclic-β-lactone **(-)-14p** (54.2 mg, 60%) a colorless solid: $[\alpha]_D^{21}$ = -138.00 (*c* = 1.00, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel AD-H column: hexanes:*i*PrOH = 70:30, flow rate 0.5 mL/min, λ = 210 nm: t_{minor} = 22.2 min, t_{major} = 27.2 min; 99% *ee*. Spectral data matched that reported above for the racemic compound.



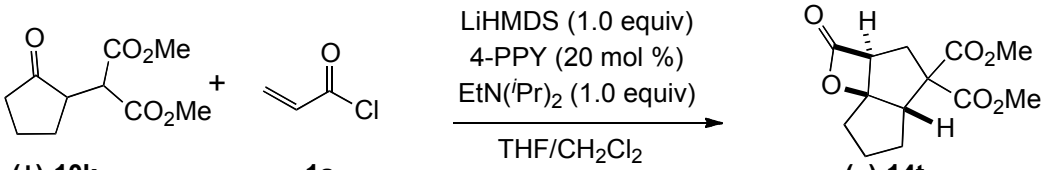
(+)-14s

(1*S*,2*S*,5*R*)-Diallyl1,5-dimethyl-7-oxo-2-((*E*)-prop-1-en-1-yl)-6-oxabicyclo[3.2.0] heptane-3,3-dicarboxylate ((+)-14s). Prepared according to the representative procedure using Michael donor **10c** (60.0 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (3 mL), (*S*)-HBTM (17 mg, 0.064 mmol, dissolved in 1 mL CH_2Cl_2, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and sorbic chloride (**1g**, 51.4 μL, 0.42 mmol, dissolved in 2 mL CH_2Cl_2, 1.30 equiv.). The solution of sorbic chloride was added by syringe pump over 2 h at 0 °C. After the addition of sorbic chloride, the reaction was allowed to react for 21 h at room temperature (23 °C) as opposed to the standard 6 h. Purification by flash column chromatography afforded a single diastereomer of bicyclic-β-lactone **(+)-14s** (58.8 mg, 55%) a colorless oil: TLC (EtOAc:hexanes, 2:8 *v/v)*: R_f = 0.64; $[\alpha]_D^{21}$ = +76.8 (*c* = 0.53, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel AD-H column: hexanes:*i*PrOH = 95:05, flow rate 0.5 mL/min, λ = 210 nm: t_{major} = 17.7 min, t_{minor} = 25.5 min; 94% *ee*. ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.91-5.77 (m, 2H), 5.62-5.57 (m, 1H), 5.34-5.21 (m, 4H), 5.14-5.08 (m, 1H), 4.69-4.61 (m, 2H), 4.58-4.50 (m, 2H), 3.95 (d, *J* = 10.0 Hz, 1H), 3.35 (s, 1H), 2.87 (d, *J* = 15.7 Hz, 1H), 2.69 (d, *J* = 15.7 Hz, 1H), 1.73 (s, 3H), 1.63 (dd, *J* = 6.5, 1.7 Hz, 3H);^{13}C NMR (125 MHz; $CDCl_3$): δ 169.7, 168.1, 167.7, 131.5, 131.4, 130.3, 126.5, 119.3, 119.1, 86.5, 67.1, 66.7, 65.5, 64.7, 48.7, 41.7, 22.2, 18.0; IR (thin film): 2940, 2857, 1835, 1741, 1270, 1149 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{18}H_{22}LiO_6$ $[M+Li]^+$: 341.1576; found 341.1562.



(+)-14q

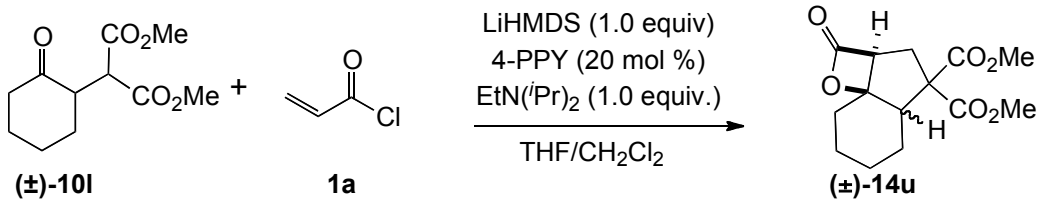
(1*S*,5*R*)-Dimethyl 1,5-dimethyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((+)-14q). Prepared according to the representative procedure using Michael donor **10a** (60.0 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (3 mL), (*S*)-HBTM (17 mg, 0.064 mmol, dissolved in 1 mL CH_2Cl_2, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and methacryloyl chloride (**1h**, 41.0 μL, 0.42 mmol, dissolved in 2 mL CH_2Cl_2, 1.30 equiv.). The solution of methacryloyl chloride was added by syringe pump over 2 h at 0 °C. After the addition of methacryloyl chloride the reaction was allowed to react for 18 h at room temperature (23 °C) as opposed to the standard 6 h. Purification by flash column chromatography afforded a single diastereomer of bicyclic-β-lactone **(+)-14q** (65.4 mg, 80%) as colorless solid: $[\alpha]_D^{21}$ = +83.3 (*c* = 0.24, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel OD-H column: hexanes:*i*PrOH = 92:08, flow rate 1.0 mL/min, λ = 210 nm: t_{minor} = 12.3 min, t_{major} = 15.2 min; 99% *ee*. Spectral data matched that reported above for the racemic compound.



(±)-10k **1a** **(±)-14t**

Dimethyl 2-oxohexahydropentaleno[6a,1-*b*]oxete-4,4(2*H*)-dicarboxylate ((±)-14t). Prepared according to the representative procedure for **(±)-14a**, except that Michael donor **(±)-10k** (68.0 mg, 0.32 mmol, 1.00 equiv.) was used, along with THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and acryloyl chloride (**1a**, 261 μL of a

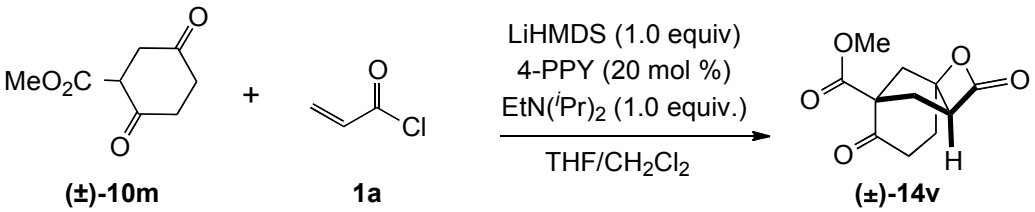
1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After addition of acryloyl chloride, the reaction was allowed to react for 24 h at ambient temperature (23 ^oC) as opposed to the standard 6 h. The mixture was then diluted with hexanes (4.0 mL), filtered through a short silica gel pad (~2 g of silica gel), and rinsed with EtOAc (3 x 4 mL). The filtrate was then concentrated by rotary evaporation the resulting oil was of sufficient purity to warrant no further purification affording a single diastereomer of tricyclic-β-lactone **(±)-14t** (77.7 mg, 91%): as a colorless oil: TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.43; ^1H NMR (500 MHz; $CDCl_3$): δ 3.74 (s, 3H), 3.71 (s, 3H), 3.60-3.58 (m, 1H), 3.50 (dd, *J* = 11.1, 8.2 Hz, 1H), 2.84 (d, *J* = 15.0 Hz, 1H), 2.64 (dd, *J* = 15.0, 9.0 Hz, 1H), 2.32-2.27 (m, 1H), 2.15 (m, 1H), 1.92-1.82 (m, 2H), 1.75 (m, 1H), 1.30-1.23 (m, 1H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 170.4, 169.5 (2), 95.7, 63.4, 59.4, 53.5, 53.2, 52.0, 31.7, 31.5, 27.3, 23.3; IR (thin film): 2363, 2340, 1824, 1732 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{13}H_{16}O_6Li$ $[M+Li]^+$: 275.1107; found 275.1106.



(±)-10l **1a** **(±)-14u**

Dimethyl 2-oxohexahydro-2H-indeno[7a,1-b]oxete-4,4(4aH)-dicarboxylate ((±)-14u). Prepared according to the representative procedure for **(±)-14a**, except that Michael donor **(±)-10l** (73.1 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol), and acryloyl chloride (**1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After addition of acryloyl chloride, the reaction was allowed to react for 24 h at ambient temperature (23 ^oC) as opposed to the standard 6 h. Purification by flash column chromatography (SiO_2, 10 → 30% EtOAc/hexanes) afforded a mixture of diastereomers (1:1) of bicyclic-β-lactone **(±)-14u** (61.0 mg, 70%) as a colorless oil: TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.41; (NMR data is provided for the 1:1 mixture of diastereomers); ^1H NMR (500 MHz; $CDCl_3$): δ 3.77-3.69 (m, 12H), 3.44 (dd, *J* = 11.3, 8.9 Hz, 2H), 3.17 (dd, *J* = 12.9, 5.8 Hz, 1H), 3.04 (d, *J* = 14.0 Hz, 1H), 2.96 (d, *J*

= 14.8 Hz, 1H), 2.70 (dd, *J* = 14.8, 9.1 Hz, 1H), 2.42 (dd, *J* = 12.5, 3.7 Hz, 1H), 2.13-2.09 (m, 2H), 2.05-1.87 (m, 5H), 1.79-1.72 (m, 4H), 1.67-1.51 (m, 2H), 1.40-1.11 (m, 3H), 0.92 (m, 1H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 171.0, 169.91, 169.86, 169.5, 169.2, 168.7, 88.9, 88.6, 64.7, 61.1, 55.6, 55.2, 53.4, 53.3, 53.2, 52.6, 51.9, 47.6, 34.1, 32.8, 31.7, 31.0, 26.6, 25.5, 24.4, 24.1, 23.7, 22.1; IR (thin film): 2958, 2863, 1830, 1735 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{14}H_{18}O_6Li$ $[M+Li]^+$: 289.1263; found 289.1277.

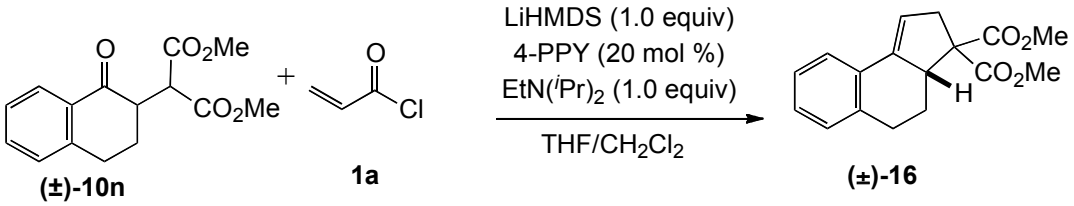


(±)-10m **1a** **(±)-14v**

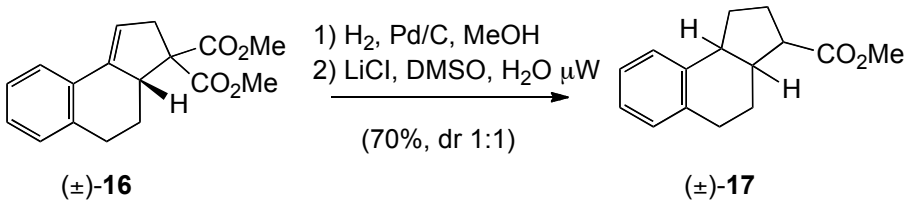
Methyl 3,7-dioxo-2-oxatricyclo[4.3.1.01,4]decane-6-carboxylate ((±)-14v). Prepared according to the representative procedure using methyl 2,5-dioxocyclohexanecarboxylate[17] (**(±)-10m**, 27 mg, 0.16 mmol, 1.00 equiv.) as the Michael donor**,** THF (0.5 mL), LiHMDS (160 μL of a 1.0 M solution in THF, 0.16 mmol, 1.00 equiv.), CH_2Cl_2 (2 mL), 4-PPY (40 μL of a 0.82 M solution in CH_2Cl_2, 0.032 mmol, 0.20 equiv.), $EtN(^iPr)_2$ (30 μL, 0.16 mmol, 1.00 equiv.), and acryloyl chloride (**1a**, 130 μL of a 1.6 M solution in CH_2Cl_2, 0.21 mmol, 1.30 equiv.). After addition of acryloyl chloride, the reaction was allowed to react for 8 h at ambient temperature (23 ^{o}C). Purification by flash column chromatography (SiO_2, 10 → 50% EtOAc/hexanes) afforded a single diastereomer of bicyclic-β-lactone **(±)-14v** (9.0 mg, 25%) as a white solid: TLC (EtOAc:hexanes, 5:5 *v/v)*: R_f = 0.55; ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.74 (s, 3H), 3.68 (dd, *J* = 8.5, 7.0 Hz, 1H), 3.93 (m, 1H), 2.77 (dd, *J* = 12.0, 1.0 Hz, 1H), 2.65 (m, 3H), 2.29 (m, 2H), 2.16(m, 1H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 205.6, 168.6, 168.3, 82.9, 69.9, 57.5, 52.8, 42.3, 37.0, 32.0, 28.3; IR (thin film): 2963, 2874, 1829, 1742, 1735 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{11}H_{13}O_5$ $[M+H]^+$:

[17] Tan, B., Lu, Y., Zeng, X.; Chua, P. J., Zhong, G. Facile domino access to chiral bicyclo[3.2.1]octanes and discovery of a new catalytic activation mode. *Org. Lett.* **12,** 2682-2685 (2010).

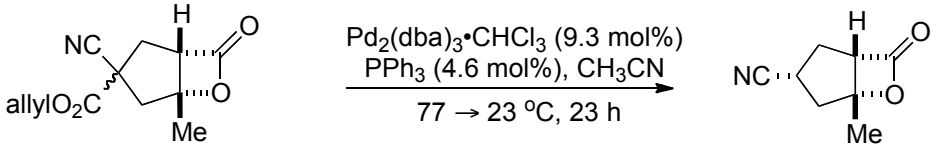
225.0763; found 225.0798.



Dimethyl 4,5-dihydro-2*H*-cyclopenta[*a*]naphthalene-3,3(3a*H*)-dicarboxylate ((±)-16). Prepared according to the representative procedure using Michael donor **(±)-10n** (88.4 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and acryloyl chloride (**1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After addition of acryloyl chloride, the reaction was allowed to react for 12 h at ambient temperature (23 ^oC) as opposed to the standard 6 h. Purification by flash column chromatography (SiO_2, 5 → 30% EtOAc/hexanes) afforded tricyclic compound **(±)-16** as a white solid (50 mg, 55%): TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.69; ^1H NMR (500 MHz; $CDCl_3$): δ 7.54 (t, *J* = 4.5 Hz, 1H), 7.12-7.07 (m, 3H), 6.00 (q, *J* = 2.6 Hz, 1H), 3.76 (s, 3H), 3.69-3.67 (m, 1H), 3.67 (s, 3H), 3.28 (dt, *J* = 17.4, 2.5 Hz, 1H), 2.97-2.93 (m, 1H), 2.85 (ddd, *J* = 16.6, 4.4, 2.4 Hz, 1H), 2.78 (dt, *J* = 17.4, 2.4 Hz, 1H), 2.21-2.17 (m, 1H), 1.33 (qd, *J* = 12.7, 4.6 Hz, 1H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 172.6, 171.2, 139.1, 136.6, 131.3, 129.1, 127.7, 126.3, 124.9, 118.2, 63.2, 52.9, 52.4, 50.1, 40.7, 30.8, 26.1; IR (thin film): 1735, 1270, 1243 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{17}H_{18}LiO_4$ $[M+Li]^+$: 293.1365; found 293.1375.



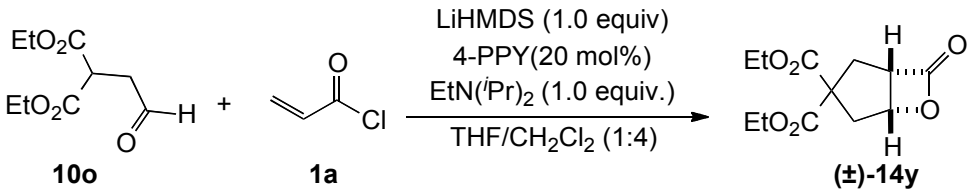
Methyl 2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalene-3-carboxylate ((±)-17). To an oven dried, round-bottomed flask containing **(±)-16** (39.0 mg, 0.14 mmol, 1.0 equiv.) and 20% Pd/C (12.0 mg, 0.2 equiv.) was added MeOH (15 mL). The reaction was then purged with H_2 gas, and stirred at ambient temperature (23 ^oC) under a H_2 atmosphere (1 atm, balloon) for 2 h. The H_2 balloon was removed and the reaction was filtered through celite to remove the Pd. This was of sufficient purity to warrant no further purification affording a single diastereomer, which was immediately carried on by dissolving in DMSO (0.60mL) and H_2O (60 μL) in a microwave reaction tube. To this mixture was added LiCl (60.0 mg, 1.4 mmol, 10.0 equiv) and the reaction was placed in a microwave reactor and heated to 180 ^oC for 20 min. Then $NaHCO_3$ (4 mL) was added to the reaction mixture and it was extracted with Et_2O (3 x 4 mL). The organic layer was washed with brine (2 x 4 mL), collected and dried over $MgSO_4$, filtered, concentrated by rotary evaporation, and purified by flash column chromatography (gradient SiO_2, 0 → 15% EtOAc/hexanes) afforded a mixture of diastereomers (1:1) of monoester **(±)-17** (22.57 mg, 70%) as a colorless oil: TLC (EtOAc:hexanes, 1:9 *v/v)*: R_f = 0.67; (NMR data is provided for the 1:1 mixture of diastereomers)^{1}H NMR (500 MHz; $CDCl_3$): δ 7.15-7.08 (m, 8H), 3.72 (s, 3H), 3.71 (s, 3H), 3.29-3.12 (m, 3H), 2.77-2.53 (m, 8H), 2.23-2.18 (m, 4H), 2.05-1.99 (m, 1H), 1.92-1.86 (m, 4H), 1.61-1.44 (m, 4H);^{13}C NMR (125 MHz; $CDCl_3$): δ 177.0, 174.8, 139.9(2), 137.1, 136.0, 129.2, 129.1, 128.9, 128.7, 126.2, 126.1, 125.8, 125.6, 52.0, 51.7, 50.2, 49.0, 43.4, 42.2, 41.9(2), 35.2, 33.1, 29.9, 29.7 (grease), 29.3, 28.9, 27.5, 24.9, 21.4; IR (thin film): 2919, 2854, 1741, 1459, 1430, 1205, 906, 737 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{15}H_{18}LiO_2$ $[M+Li]^+$: 237.1467; found 237.1471.



(±)-**14i** (dr 1.16:1) (±)-**14x**

5-Methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3-carbonitrile ((±)-14x). To an oven-dried, 10 mL round-bottomed flask equipped with a magnetic stir bar was added $Pd_2(dba)_3$-$CHCl_3$ (47 mg, 0.045 mmol, 0.092 equiv.), triphenylphosphine (6 mg, 0.023

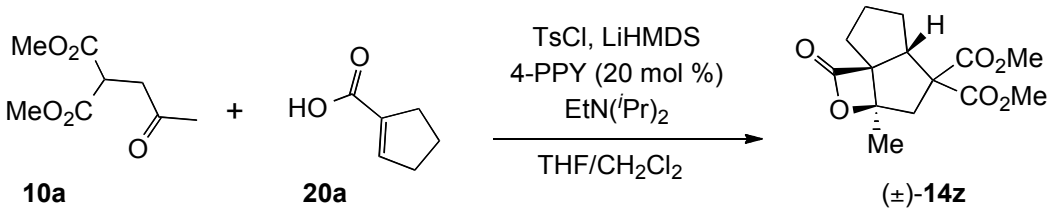
mmol, 0.047 equiv.), bicyclic-β-lactone **(±)-14i** (115 mg, 0.489 mmol, 1.00 equiv., as a 1.16:1 mixture of diastereomers) along with CH_3CN (6 mL). After addition, the flask was equipped with a reflux condenser and the reaction mixture was heated to 77 °C using an oil bath. With vigorous stirring the reaction remained at 77 °C for 6 h. After which the oil bath was removed and the reaction stirred at ambient temperature (23 °C) for 17 h. The mixture was then diluted with hexanes (4.0 mL), filtered through a short silica gel pad (~2 mL of silica gel), and rinsed with EtOAc (3 x 4 mL). The filtrate was concentrated by rotary evaporation and purified by flash column chromatography (gradient SiO_2, 20 → 100% EtOAc/hexanes) afforded a single diastereomer of bicyclic-β-lactone **(±)-14x** (738 mg, 75% yield) a colorless solid: m.p. 101-103 °C (recrystallized from $CDCl_3$); TLC (EtOAc:hexanes, 5:5 v/v): R_f = 0.25; ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.64 (d, *J* = 8.3 Hz, 1H), 3.35 (t, *J* = 8.0 Hz, 1H), 2.66 (d, *J* = 15.1 Hz, 1H), 2.58 (d, *J* = 14.4 Hz, 1H), 2.20 (dt, *J* = 14.4, 8.1 Hz, 1H), 2.00 (dd, *J* = 15.1, 8.2 Hz, 1H), 1.73 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): 168.8, 120.9, 86.9, 59.2, 40.0, 31.5, 28.2, 21.5; IR (thin film): 2360, 2339, 2235, 1807 cm^{-1}; HRMS (ESI-) *m/z* calcd for $C_8H_8NO_2$ [M - H]$^-$: 150.0555; found 150.0562.



Diethyl 7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((±)-14y).

Prepared according to the representative procedure using Michael donor **10o** (64.7 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL, 0.064 mmol of a 0.82 M solution in CH_2Cl_2, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and acryloyl chloride (**1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After addition of acryloyl chloride, the reaction was allowed to react for 12 h at ambient temperature (23 ^oC) as opposed to the standard 6 h. Purification by flash column chromatography (SiO_2, 5 → 30% EtOAc/hexanes) afforded bicyclic β-lactone **(±)-14y** as a colorless oil (49 mg, 60%): TLC (EtOAc:hexanes, 3:9 *v/v)*: R_f = 0.38; ^{1}H

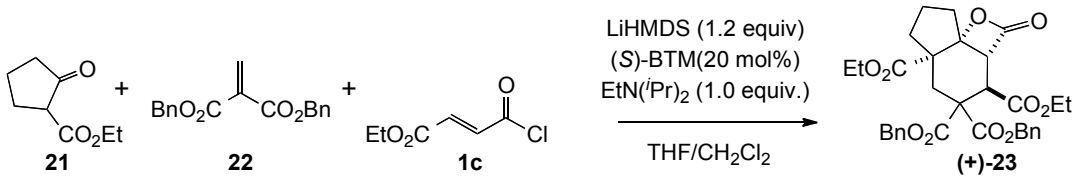
NMR (500 MHz; $CDCl_3$): δ 5.10 (t, *J* = 4.1 Hz, 1H), 4.33-4.23 (m, 4H), 4.04 (dd, *J* = 9.1, 3.9 Hz, 1H), 3.23 (d, *J* = 14.2 Hz, 1H), 3.08 (d, *J* = 15.6 Hz, 1H), 2.52 (dd, *J* = 16.2, 4.8 Hz, 1H), 2.15 (dd, *J* = 14.4, 9.1 Hz, 1H), 1.35-1.30 (m, 6H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 170.5, 170.1, 169.2, 62.5, 60.1, 56.1, 45.1, 39.1, 34.1, 29.8, 14.1, 14.0; IR (thin film): 2925, 2854, 1838, 1735 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{12}H_{17}O_6$ $[M+H]^+$: 257.1025; found 257.1034.



Dimethyl 2a-methyl-1-oxohexahydropentaleno[1,6a-*b*]oxete-4,4(1*H*)-dicarboxylate ((±)-14z). To an oven-dried, 10 mL round-bottomed flask equipped with a magnetic stir bar were added cyclopent-1-enecarboxylic acid (**20a**, 58.50 mg, 0.52 mmol, 1.63 equiv.) TsCl (103 mg, 0.54 mmol, 1.69 equiv.), $EtN(^iPr)_2$ (97 μL, 0.55 mmol, 1.72 equiv.) and CH_2Cl_2 (3 mL). This mixture was allowed to react at ambient temperature (23 °C) for 30 min. To an oven-dried, 25 mL round-bottomed flask equipped with a magnetic stir bar was added Michael donor **10a** (61.40 mg, 0.32 mmol, 1.00 equiv.) along with THF (1 mL) and the mixture was cooled to -78 °C. With vigorous stirring, LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.) was added dropwise via microliter syringe. After complete addition, the reaction was stirred for 10 min at -78 °C and then warmed to 0 °C by switching the dry ice/acetone bath to an ice/water bath. Stirring was continued for an additional 10 min at this temperature, and then CH_2Cl_2 (3 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.) and $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.) were added via microliter syringe, sequentially. The reaction was allowed to stir for an additional 10 min at 0 °C the previous solution of **18a,** TsCl, $EtN(^iPr)_2$, in CH_2Cl_2 was added by syringe pump over 2 h at 0 °C. After the addition was complete, the reaction was allowed to react for 16 h at room temperature (23 °C). The reaction was then cooled to 0 °C and silica gel (2 g) was added and stirred at 0 °C for 10 min. Then the ice/water bath was removed and the reaction stirred at ambient temperature (23 °C) for

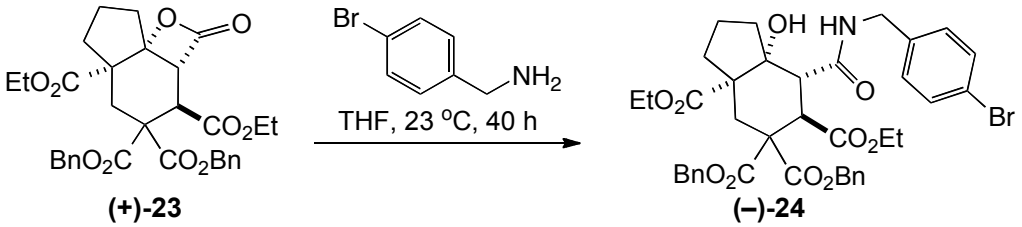
20 min. The mixture was then diluted with hexanes (4.0 mL), filtered through a short silica gel pad (~2 mL of silica gel), and rinsed with EtOAc (3 x 4 mL). The filtrate was then concentrated by rotary evaporation, analyzed by ^{1}H NMR. Purification by flash column chromatography (SiO_2, 10 → 40% EtOAc/hexanes) afforded a single diastereomer of bicyclic-β-lactone **(±)-14z** (59.4 mg, 66%) as a white solid: TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.14; ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.78 (s, 3H), 3.74 (s, 3H), 3.62 (dd, *J* = 11.6, 7.1 Hz, 1H), 2.87 (d, *J* = 15.8 Hz, 1H), 2.64 (d, *J* = 15.8 Hz, 1H), 2.22 (m, 1H), 1.88-1.68 (m, 4H), 1.53 (s, 3H), 1.14 (m, *J* = 7.4 Hz, 1H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 172.7, 171.1, 169.5, 89.7, 72.9, 61.5, 53.8, 53.4, 53.2, 41.8, 28.9, 26.3, 25.8, 20.1; IR (thin film): 2958, 2928, 2857, 1833, 1738 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{14}H_{20}O_6$ $[M+H]^+$: 283.1182; found 283.1168.

Representative procedure for Michael-Michael-aldol-lactonization:



(2a*R*,3*R*,5a*S*,8a*R*)-4,4-Dibenzyl 3,5a-diethyl 2-oxohexahydro-2*H*-indeno[3a,4-*b*]oxete-3,4,4,5a(5*H*)-tetracarboxylate ((+)-23). An oven-dried, 100-mL round-bottomed flask was charged with a solution of LiHMDS (1.80 mL of 1.0 M solution in THF, 1.80 mmol, 1.2 equiv) in THF (2.5 mL) at -78 °C, followed by slow addition of a solution of cyclopentanone **21** (234 mg, 1.50 mmol, 1.0 equiv) in THF (2.5 mL). The resulting mixture was warmed to -20 °C and stirred for 30 min, then a solution of diester **22** (1.80 mL of 1.0 M solution in benzene, 1.80 mmol, 1.2 equiv) in THF (2.5 mL) was added dropwise. After 1 h at -20 °C, a solution of (*S*)-BTM (75.7 mg, 0.30 mmol, 20 mol%) and EtN(^{i}Pr)$_2$ (194 mg, 1.50 mmol, 1.0 equiv) in CH_2Cl_2 (2.5 mL) was added. Then a solution of acid chloride **1c** (366 mg, 2.25 mmol, 1.5 equiv) in CH_2Cl_2 (5.0 mL) was added at -20 °C over 5 h by a syringe pump. The reaction temperature was maintained at -20 °C throughout the addition of **1c** and then the reaction was stirred at this temperature for 15 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and the product was purified by an

automated flash chromatography system (gradient of EtOAc/hexanes) to afford a single diastereomer of tricyclic-β-lactone **(+)-23** (457 mg, 53% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 2:8 *v/v*): R_f = 0.40; $[\alpha]_{.}^{17}$ = +3.49 (*c* = 1.0, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AS-H column: hexanes:*i*PrOH = 90:10, flow rate 1.0 mL/min, λ = 210 nm: t_{major} = 12.3 min, t_{minor} = 19.1 min; 93% ee. Absolute stereochemistry was assigned by derivatization below. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.28 (m, 10H), 5.21-5.13 (m, 4H), 4.18-4.02 (m, 5H), 3.82 (d, *J* = 9.6 Hz, 1H), 3.08 (d, *J* = 15.1 Hz, 1H), 2.69-2.64 (m, 1H), 2.43 (d, *J* = 15.1 Hz, 1H), 2.21-2.017 (m, 1H), 1.81-1.56 (m, 4H), 1.23-1.16 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5, 170.3, 170.2, 169.3, 168.1, 135.0, 134.3, 129.1 (2), 128.9, 128.7 (2), 128.6 (2), 128.4, 128.2 (2), 85.7, 68.3, 68.1, 61.91, 61.90, 55.9, 52.7, 52.2, 43.3, 39.7, 39.3, 39.2, 23.3, 13.9, 13.8; IR (thin film): 2978, 1836, 1737, 1453, 1370, 1269, 1027 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{32}H_{35}O_{10}$ $[M+H]^+$: 579.2230, found: 579.2251.



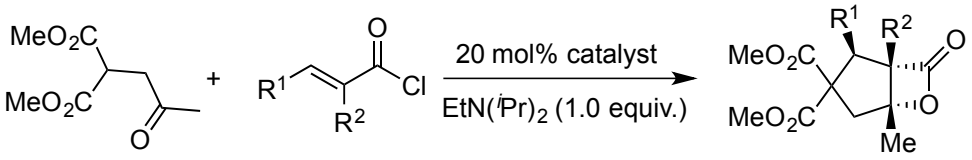
(+)-23 **(–)-24**

(3a*S*,6*R*,7*R*,7a*R*)-5,5-dibenzyl 3a,6-diethyl 7-(benzylcarbamoyl)-7a-hydroxyhexahydro-1*H*-indene-3a,5,5,6(6*H*)-tetracarboxylate ((-)-24). Into an oven-dried, 25-mL round-bottomed flask containing a solution of β-lactone **(+)-23** (400 mg, 0.69 mmol, 1.0 equiv) in THF (7 mL), was added dropwise *p*-bromobenzylamine (0.35 mL, 2.8 mmol, 4.0 equiv). The reaction was allowed to stir at ambient temperature (23 °C) for 40 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and purified by an automated flash chromatography system (gradient of EtOAc/hexanes) to afford bicyclic amide **(–)-24** (300 mg, 57% yield) as a colorless solid: TLC (EtOAc:hexanes, 2:8 *v/v*): R_f = 0.35; $[\alpha]_{.}^{20}$ = -24.15 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6): δ 7.21 (d, *J* = 8.3 Hz, 2H), 7.16-7.08 (m, 5H), 7.08-6.96 (m, 6H), 6.93 (d, *J* = 8.3 Hz, 2H), 6.61 (t, *J* = 6.0 Hz, 1H), 5.74 (s, 1H), 5.07-

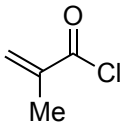
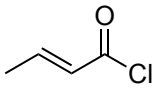
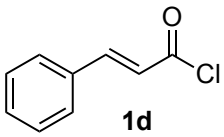
5.01 (m, 4H), 4.36 (d, J = 11.8 Hz, 1H), 4.22 (dd, J = 15.0, 6.0 Hz, 1H), 4.08 (dd, J = 15.0, 6.0 Hz, 1H), 3.98-3.88 (m, 2H), 3.84-3.71 (m, 2H), 3.45 (d, J = 14.9 Hz, 1H), 2.91 (d, J = 11.8 Hz, 1H), 2.68 (d, J = 14.9 Hz, 1H), 2.17-2.08 (m, 2H), 1.94-1.84 (m, 2H), 1.49-1.39 (m, 2H), 0.92 (t, J = 7.1 Hz, 3H), 0.83 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz; C_6D_6): δ 174.9, 172.9, 172.2, 170.7, 170.6, 137.8, 135.6, 135.1, 131.4 (2), 129.6 (2), 128.35 (2), 128.28 (2), 128.23 (2), 128.13, 128.07 (2), 127.95, 120.9, 80.8, 67.55, 67.46, 60.85, 60.83, 57.1, 54.7, 48.7, 44.9, 42.6, 36.9, 34.1, 33.6, 20.7, 13.7, 13.5; IR (thin film): 3357, 2959, 1741, 1645, 1547, 1489, 1261 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{39}H_{43}BrNO_{10}$ $[M+H]^+$: 764.2065; found 764.2055.

NCMAL Optimization Studies for β-Substituted, Unsaturated Acid Chlorides

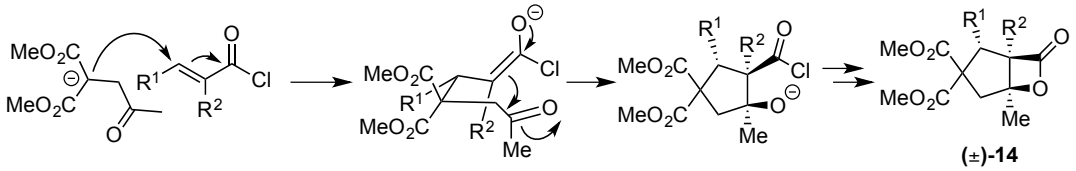
Table S1. Optimization of the tandem Michael-aldol-β-lactonization process for α- and β-substituted acid chlorides.



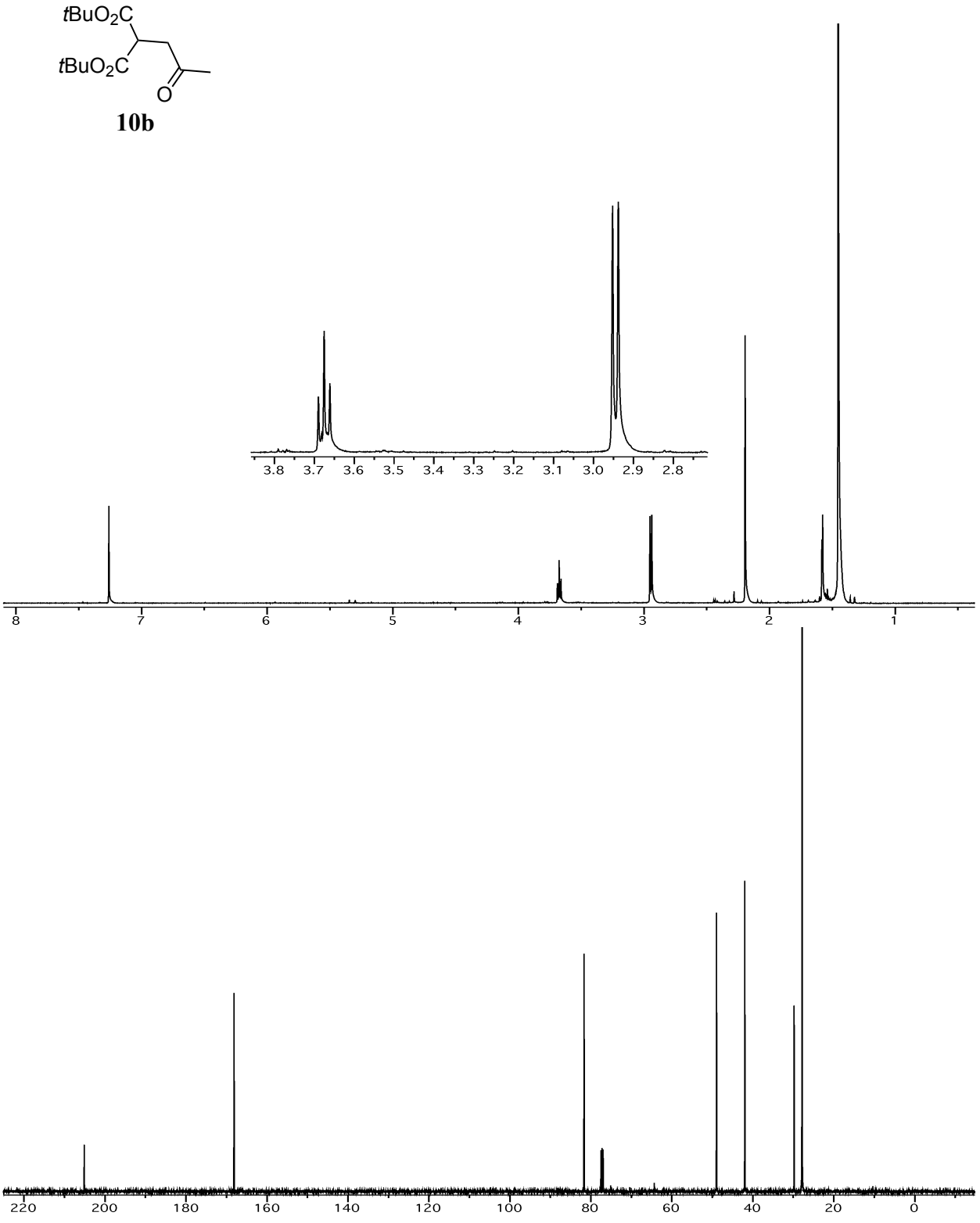
10a (1.0 equiv.) **1b,d,h** (2.0 equiv.) **14k,m,q**

entry	catalyst	**1a**	acid chloride addn. time	yield %	ee
1	(S)-HBTM	 **1h**	4 min	78	30
2	(S)-HBTM		2 h	80	99
3	none		--	80	0
4	(S)-HBTM	 **1b**	4 min	60	80
5	(S)-HBTM		2 h	80	93
6	(S)-HBTM	 **1d**	4 min	72	80
7	(S)-HBTM		2 h	80	99

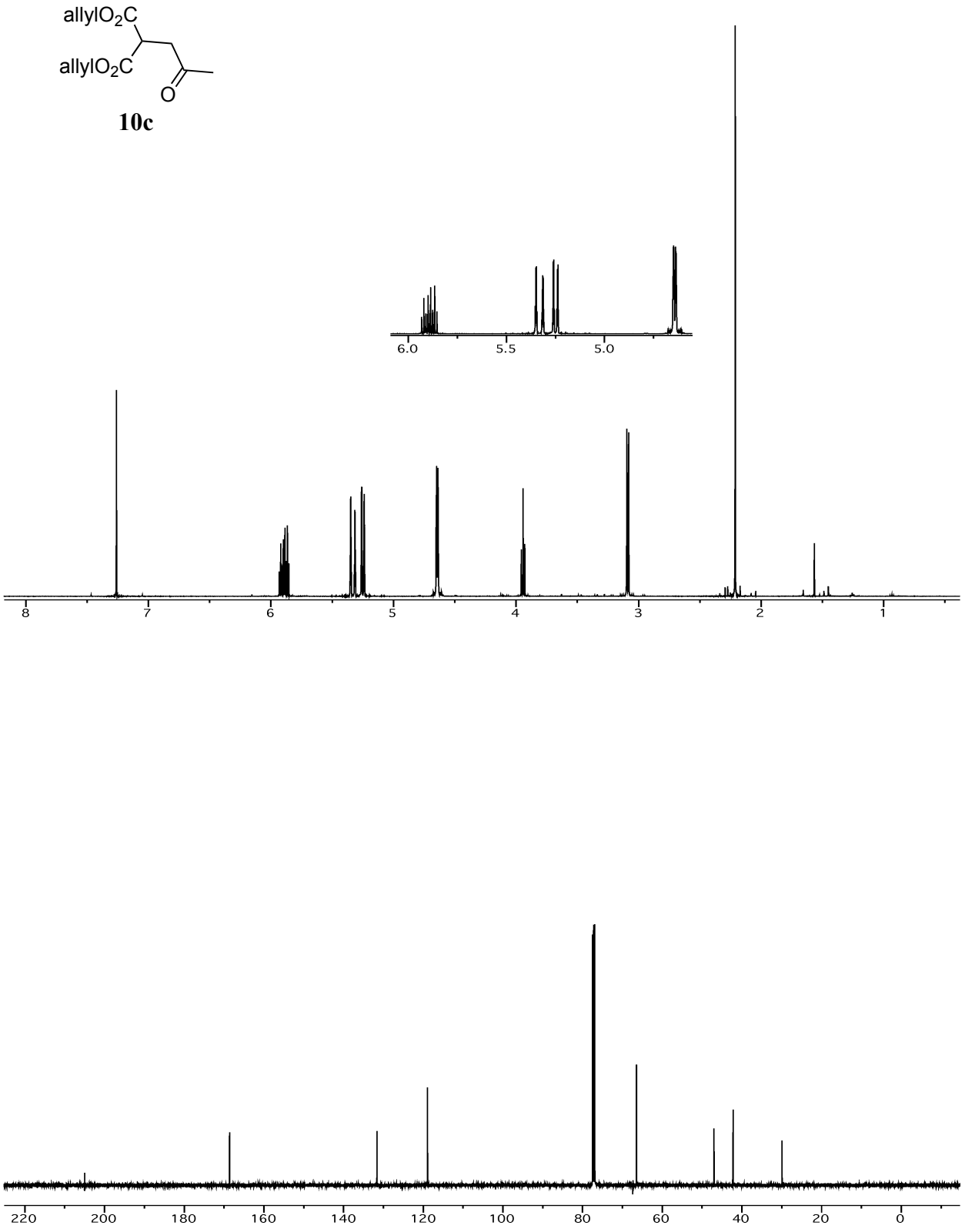
When the optimized racemic conditions were initially applied to both α-substituted and β-substituted unsaturated acid chlorides, a significant decrease in enantioselectivity was observed, however the yield remained relatively constant. For instance, adding α-methacrolyl chloride (**1h**) with the usual 4 minute addition time gave cyclopentane **14q** in 30% ee in 78% yield (Table S1, entry 1). Likewise, β-methacroloyl choride gave reduced enantioselectivity (80% ee) in 60% yield of cyclopentane **14k** (Table S1, entry 4) and β-phenyl acryloyl choride (Table S1, entry 6) led to cyclopentane **14m** in 72% yield and 80% ee. These results are suggestive of a potential background racemic pathway that is in operation with substituted acid chlorides likely due to slower formation of the chiral unsaturated acylammonium intermediate in these cases. To explore this possibility, the same reaction conditions were applied without a nucleophilic catalyst (Table S1, entry 1) and this indeed delivered racemic cyclopentane **14q** in 80% yield. One possible mechanism for this racemic background pathway is a direct Michael addition of the malonate anion to the unsaturated acid chloride as shown in the Scheme below.



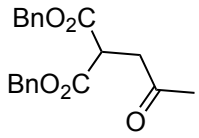
Building on this hypothesis, acid chloride **1h** was added over an extended period of time (2 h, syringe pump) and this led to a dramatic improvement in the enantioselectivity from 30 to >99%. This trend also held for acid chlorides **1b** and **1d** leading to increased enantioselectivity achievable with longer addition times of the unsaturated acid chlorides (Table S1, entries 5 and 7).



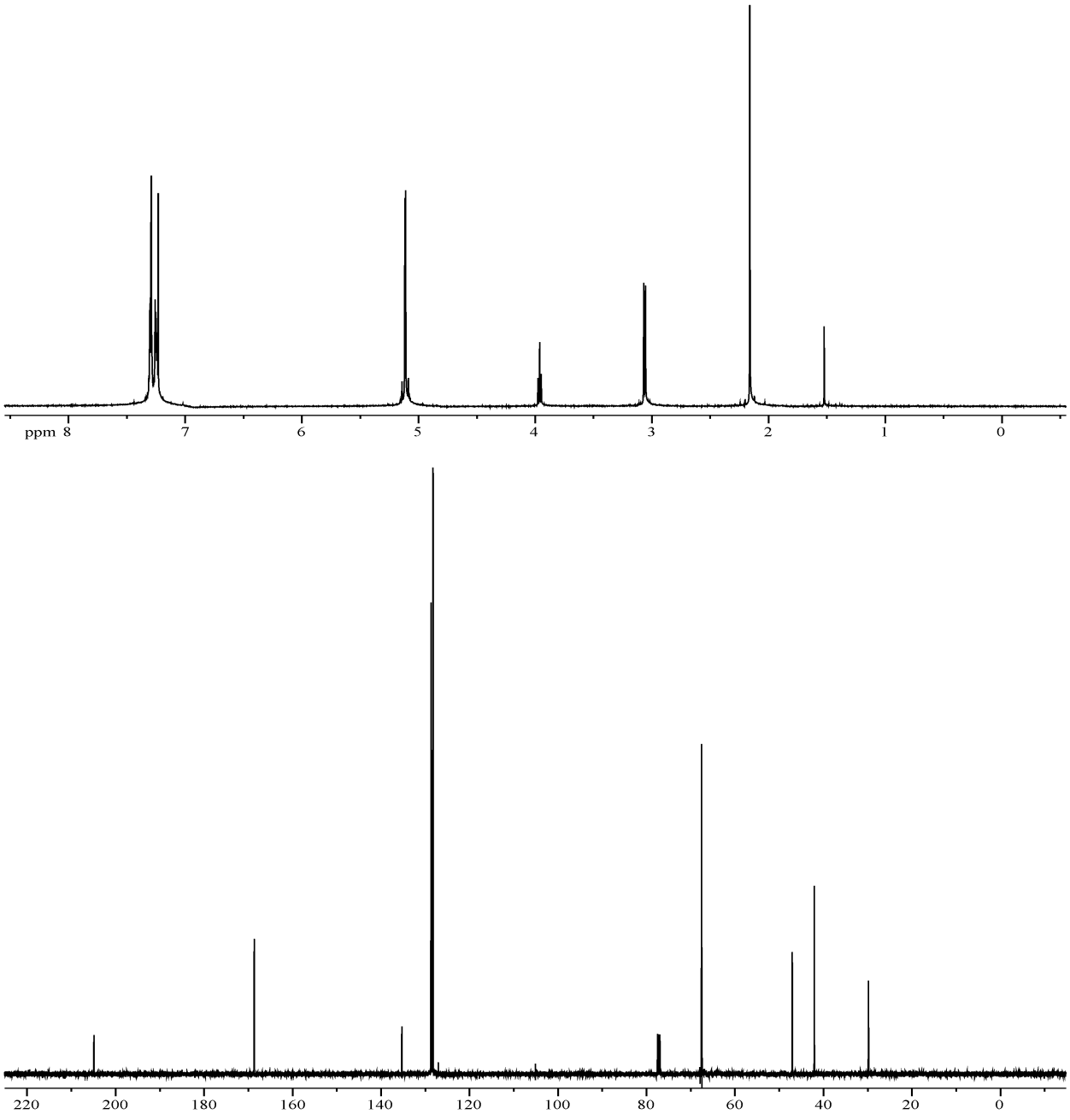
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **10b** in $CDCl_3$



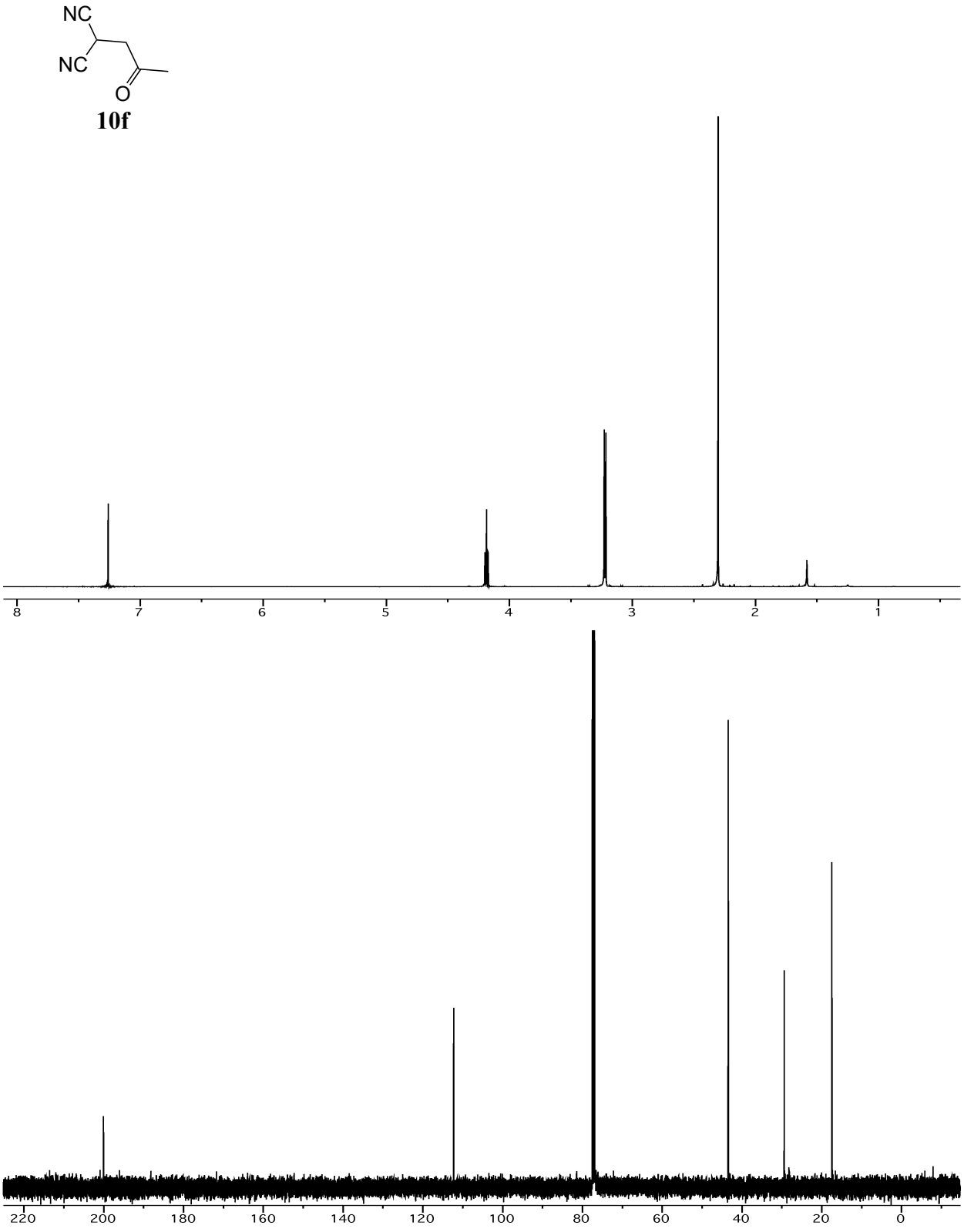
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **10c** in $CDCl_3$



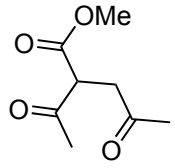
10d



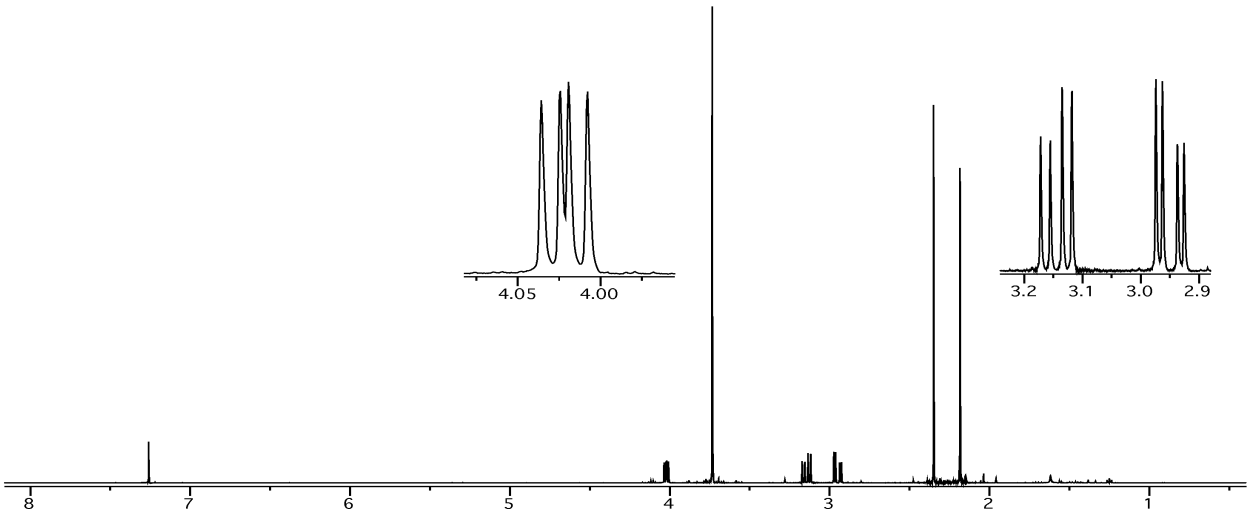
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **10d** in $CDCl_3$

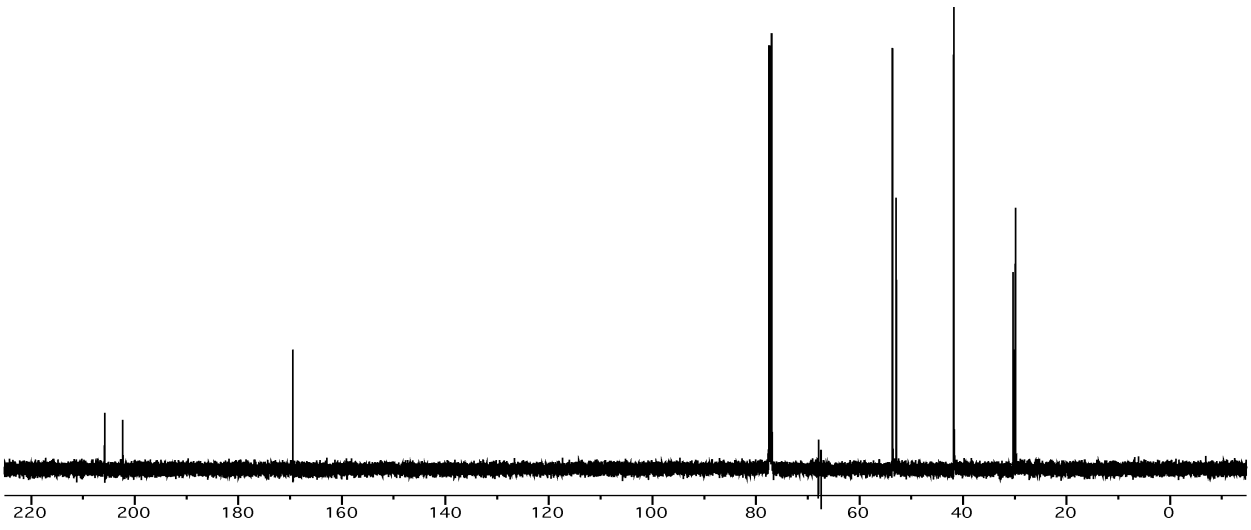


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **10f** in $CDCl_3$

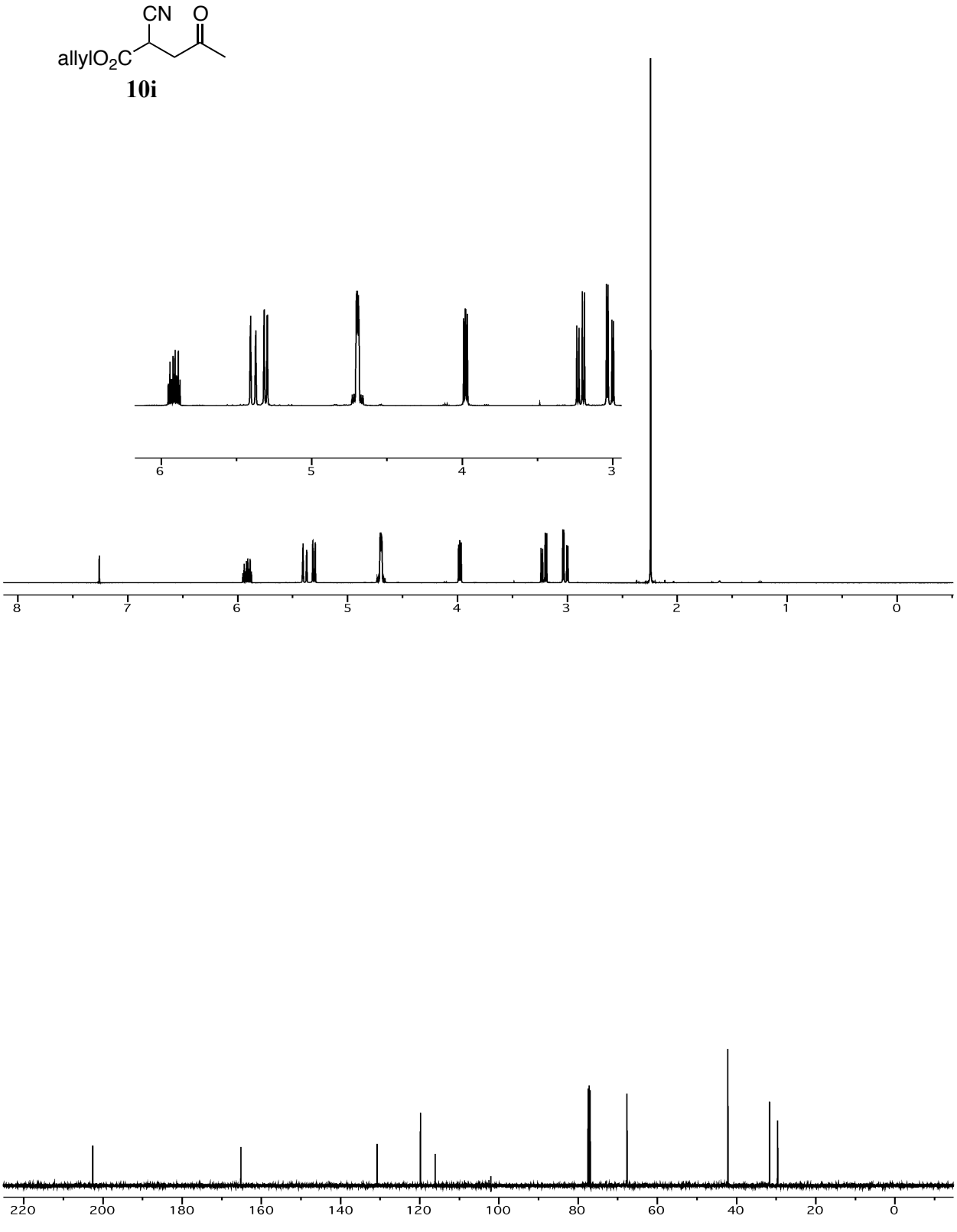


10g

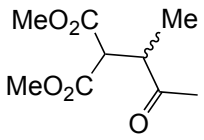




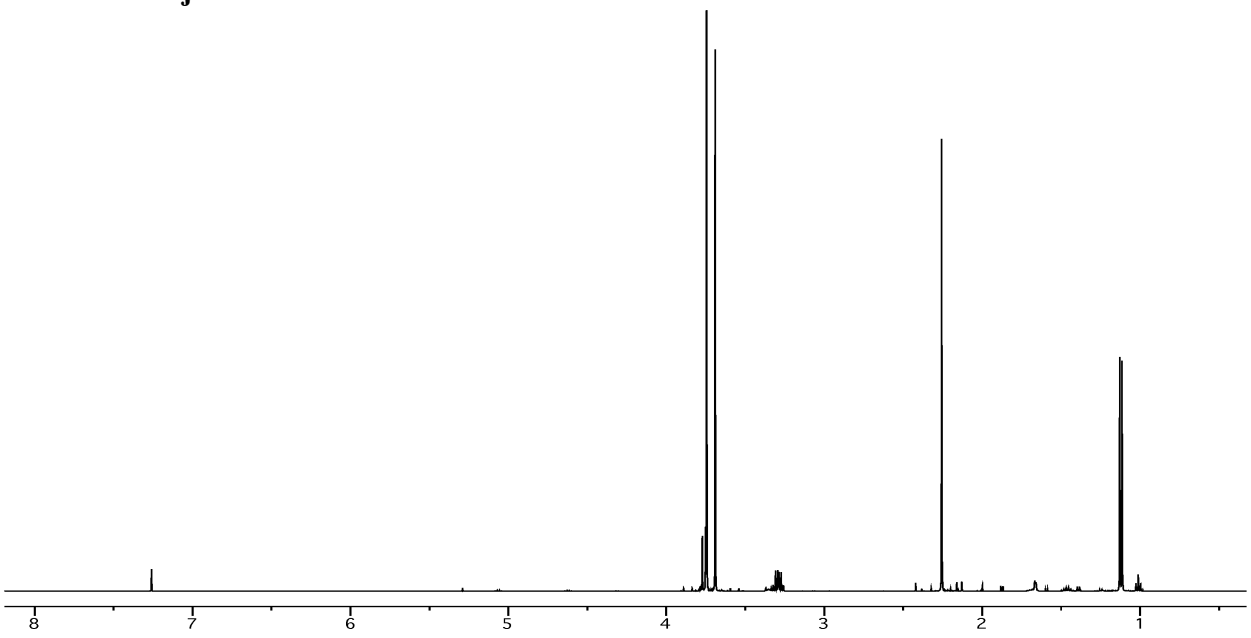
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **10g** in $CDCl_3$

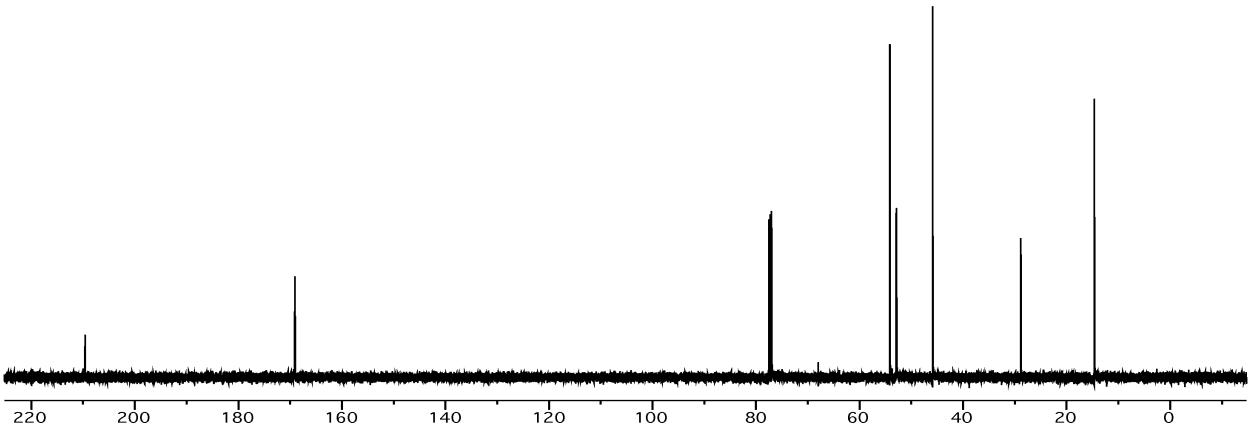


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **10i** in $CDCl_3$

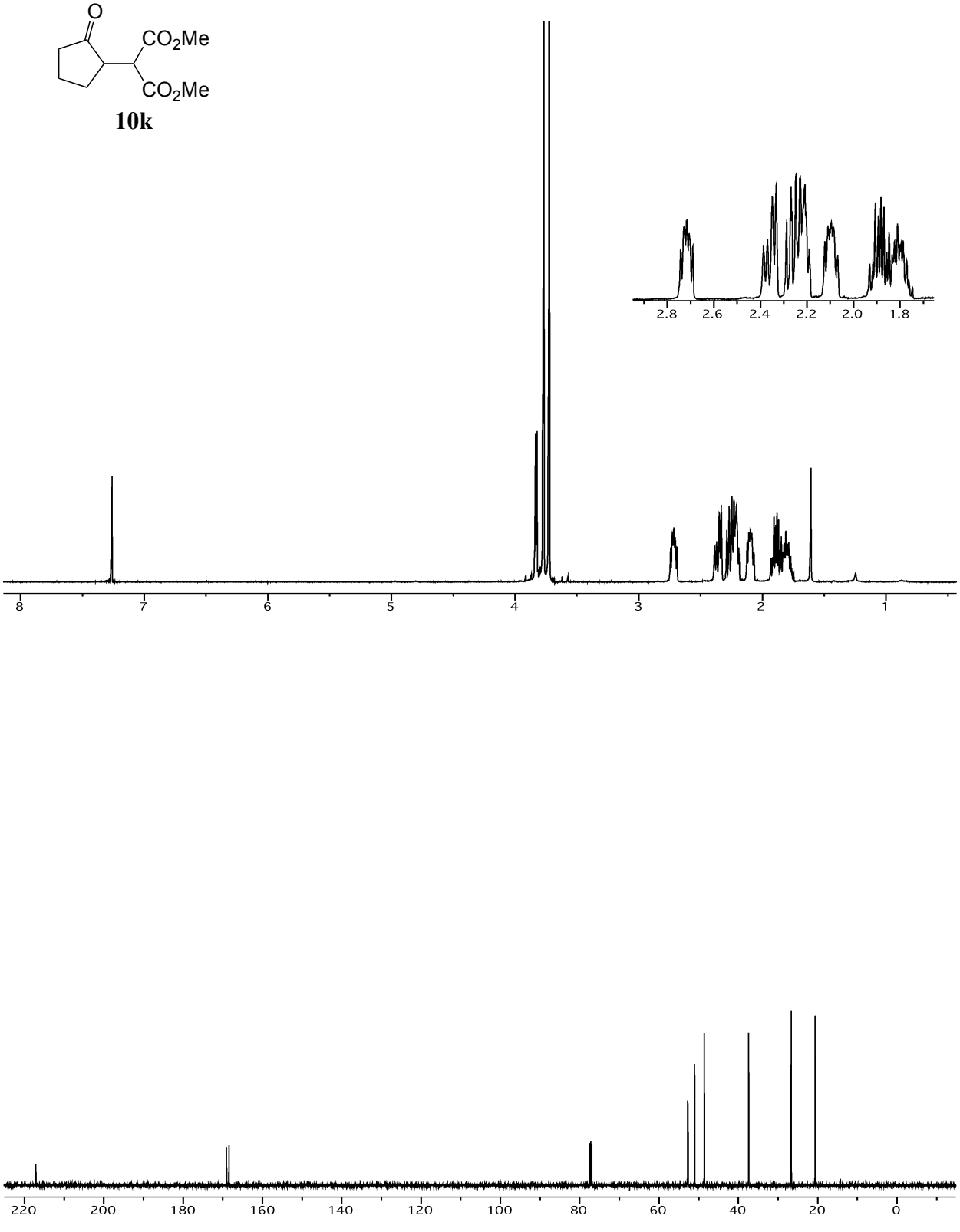


10j

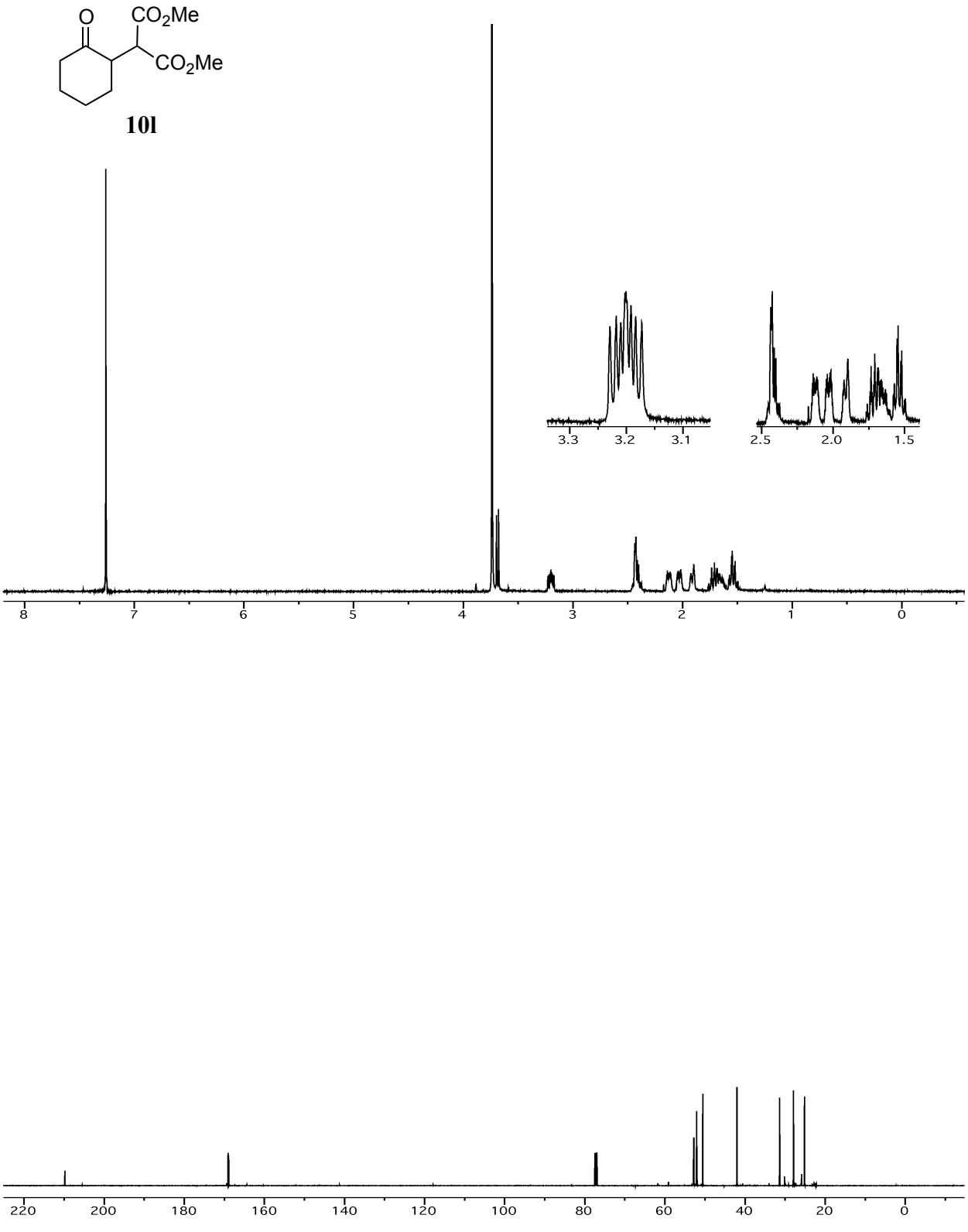




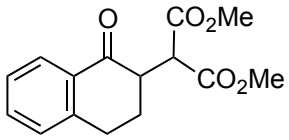
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **10j** in $CDCl_3$



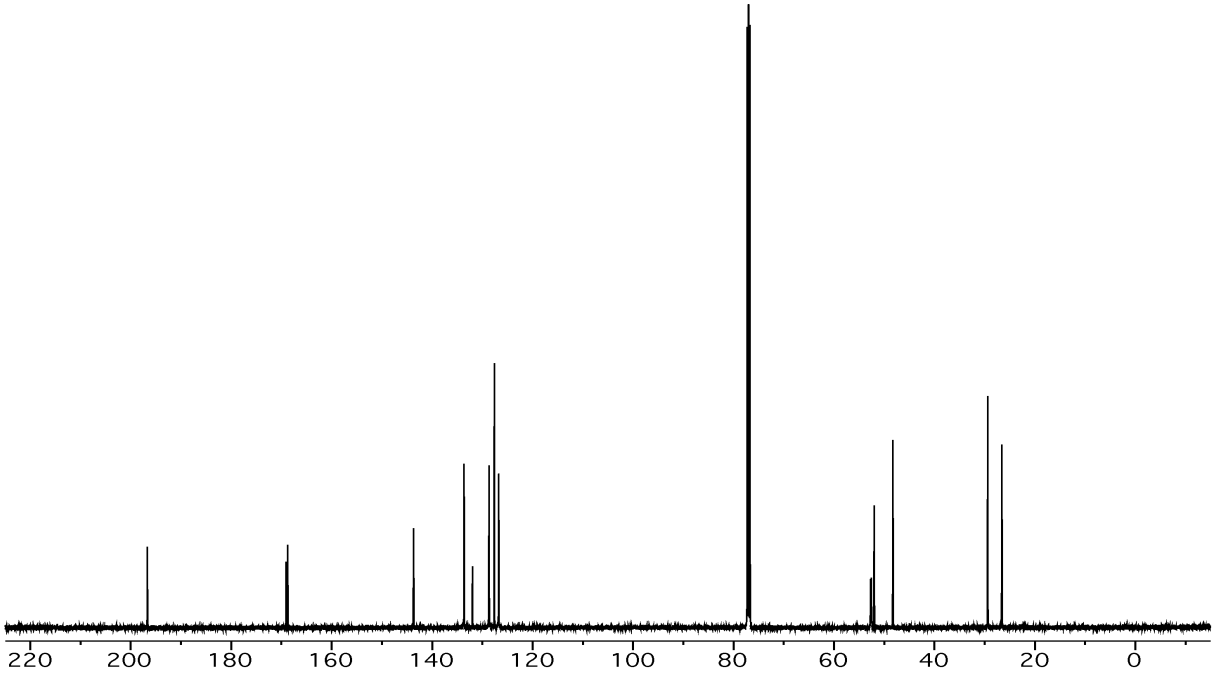
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **10k** in $CDCl_3$



^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **10l** in $CDCl_3$



10n



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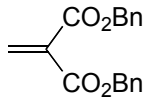
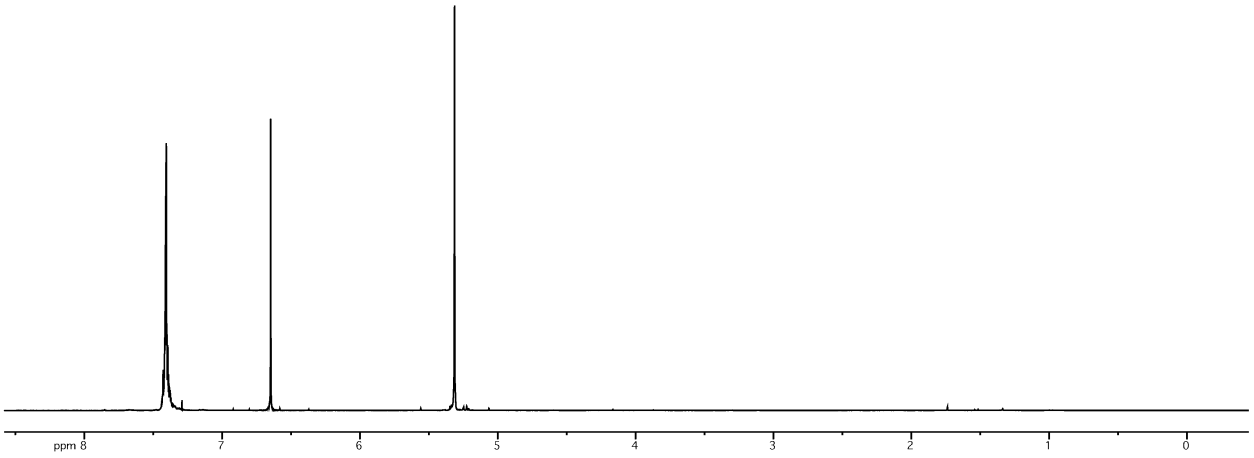
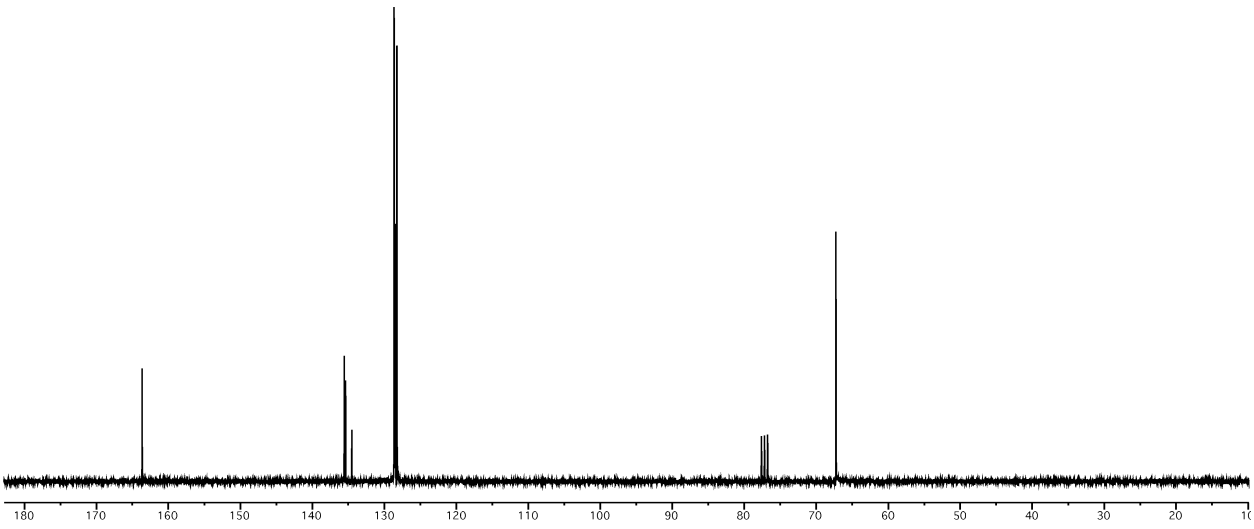
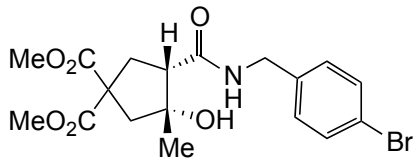


22

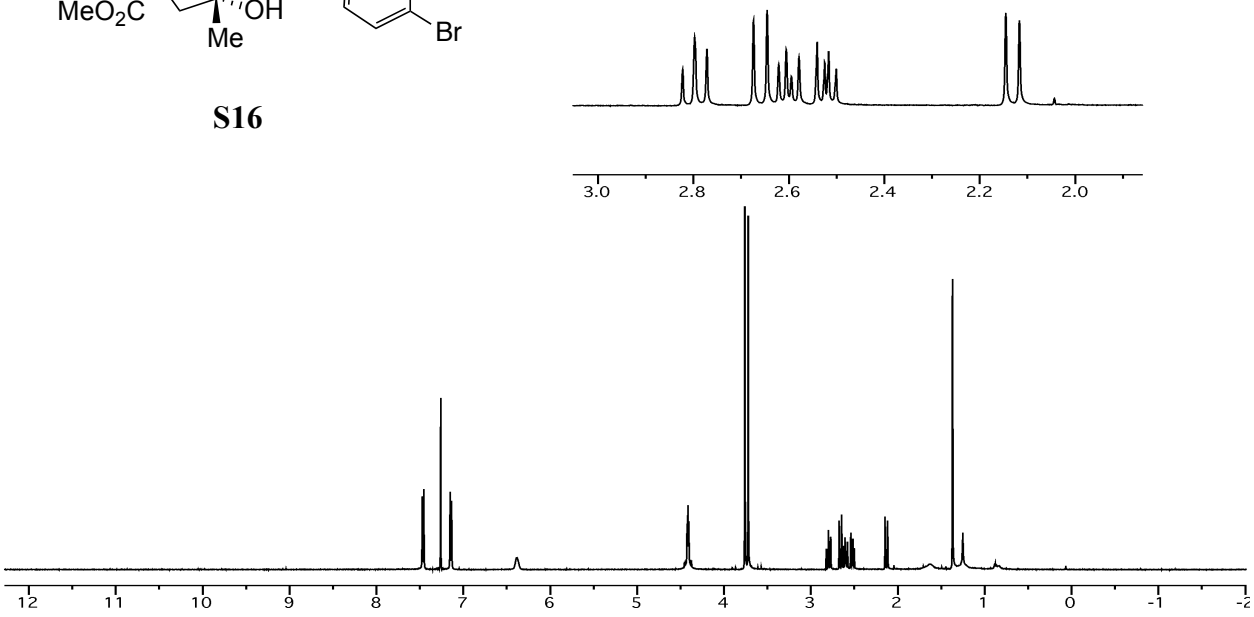


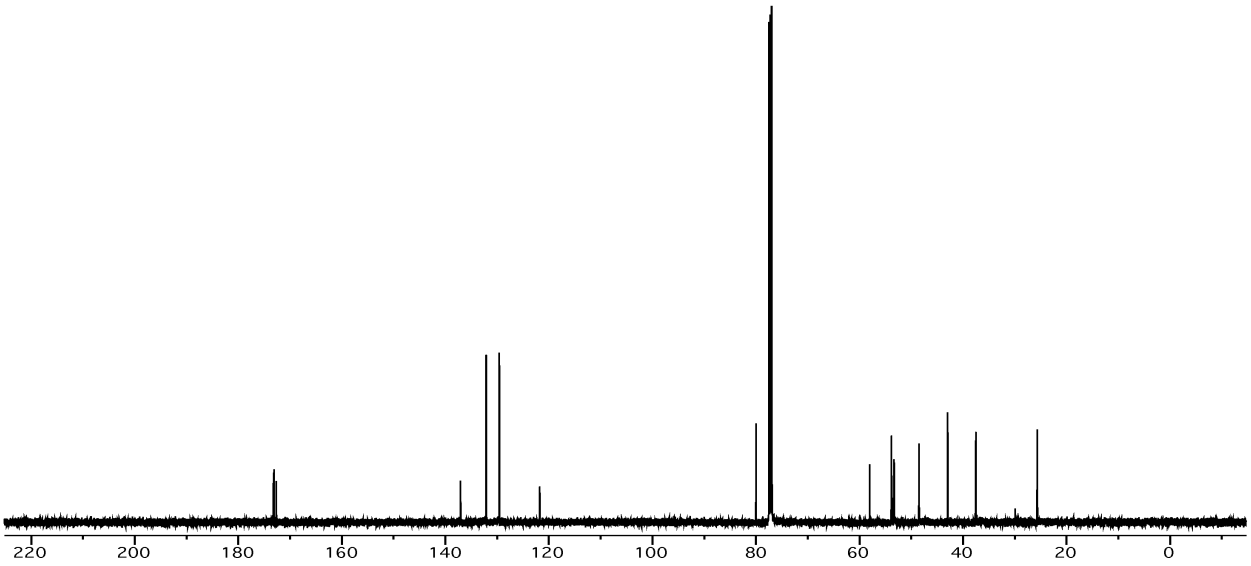


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of enone **22** in $CDCl_3$

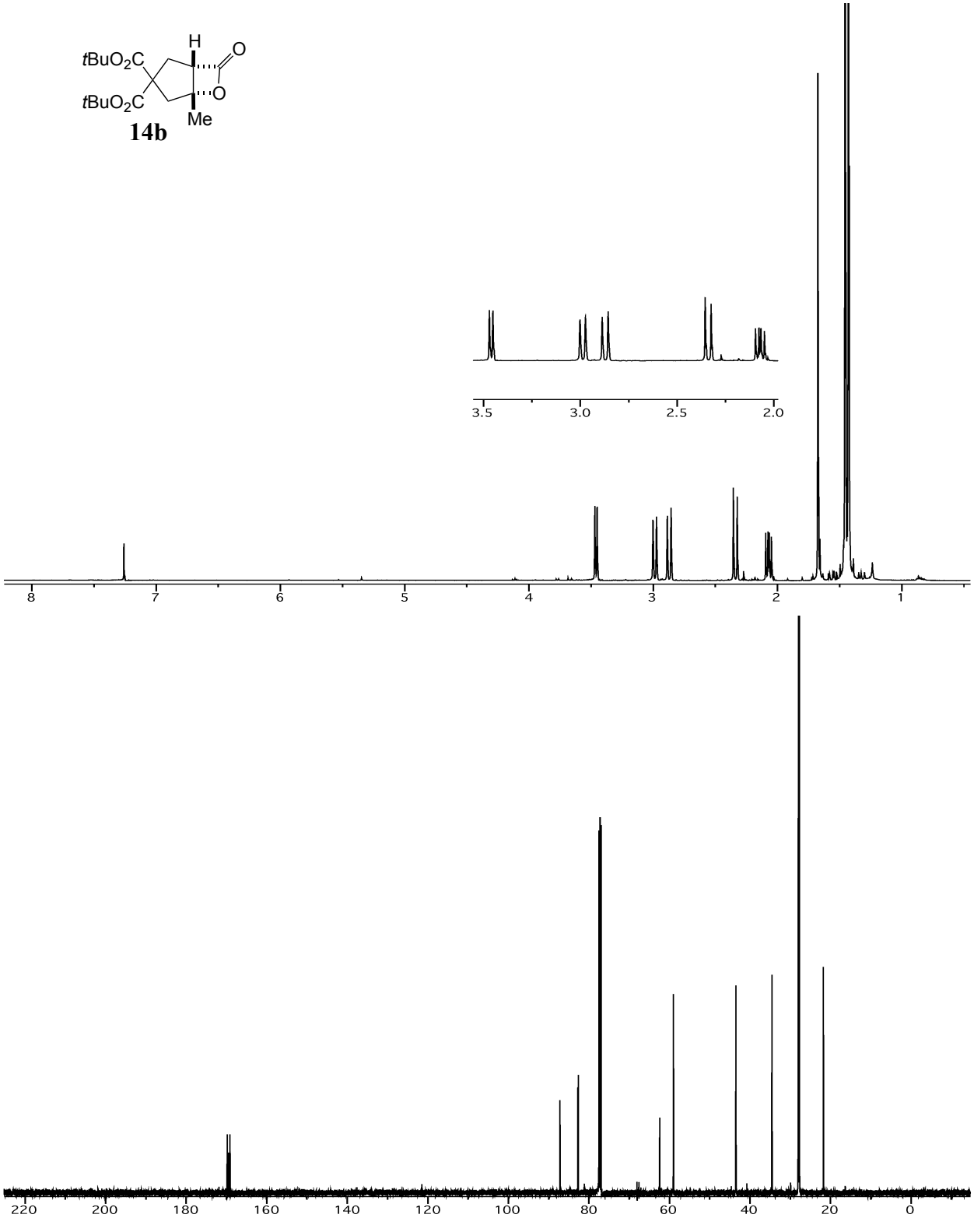


S16

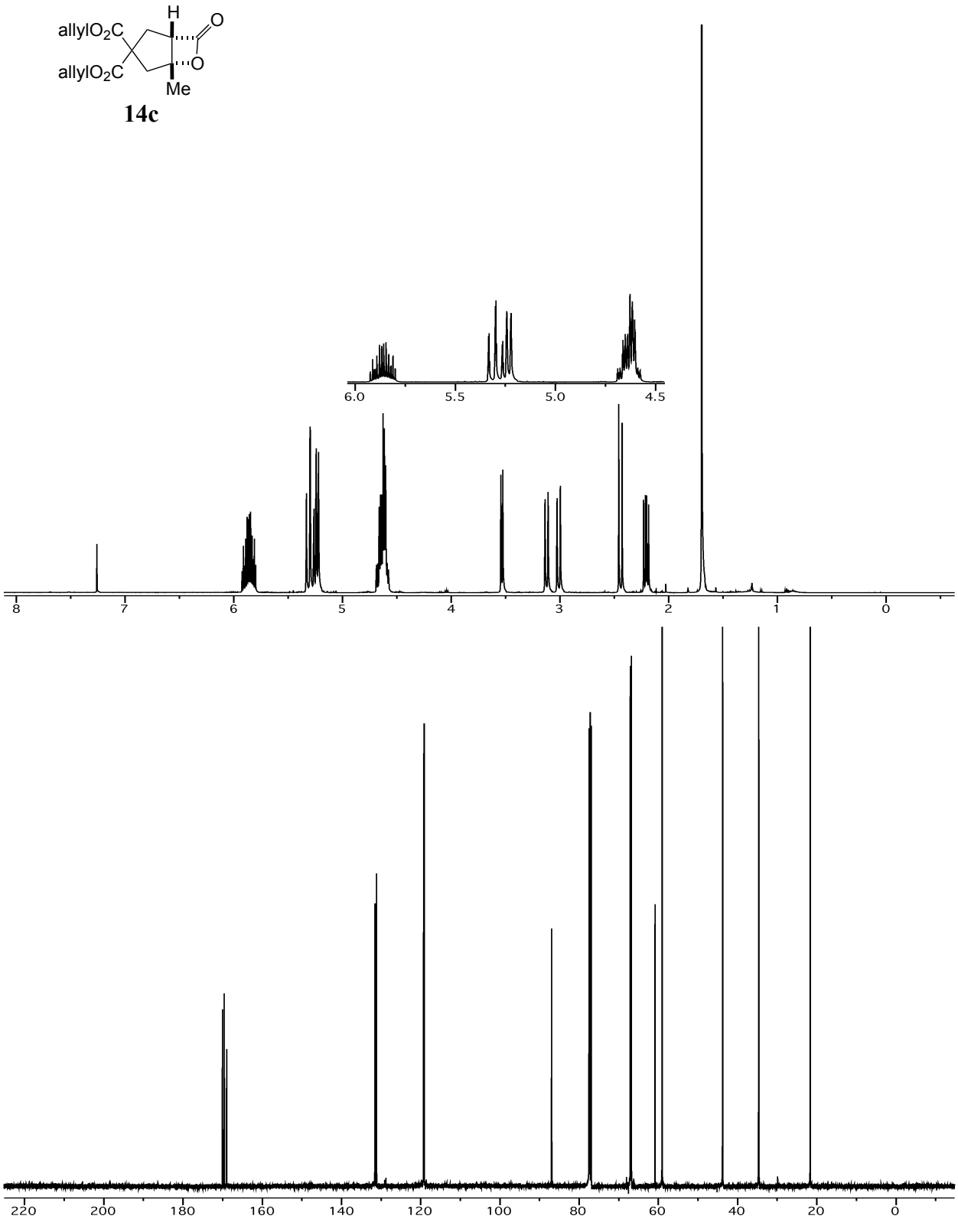




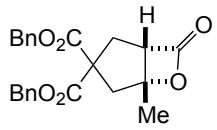
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of amide **S16** in $CDCl_3$



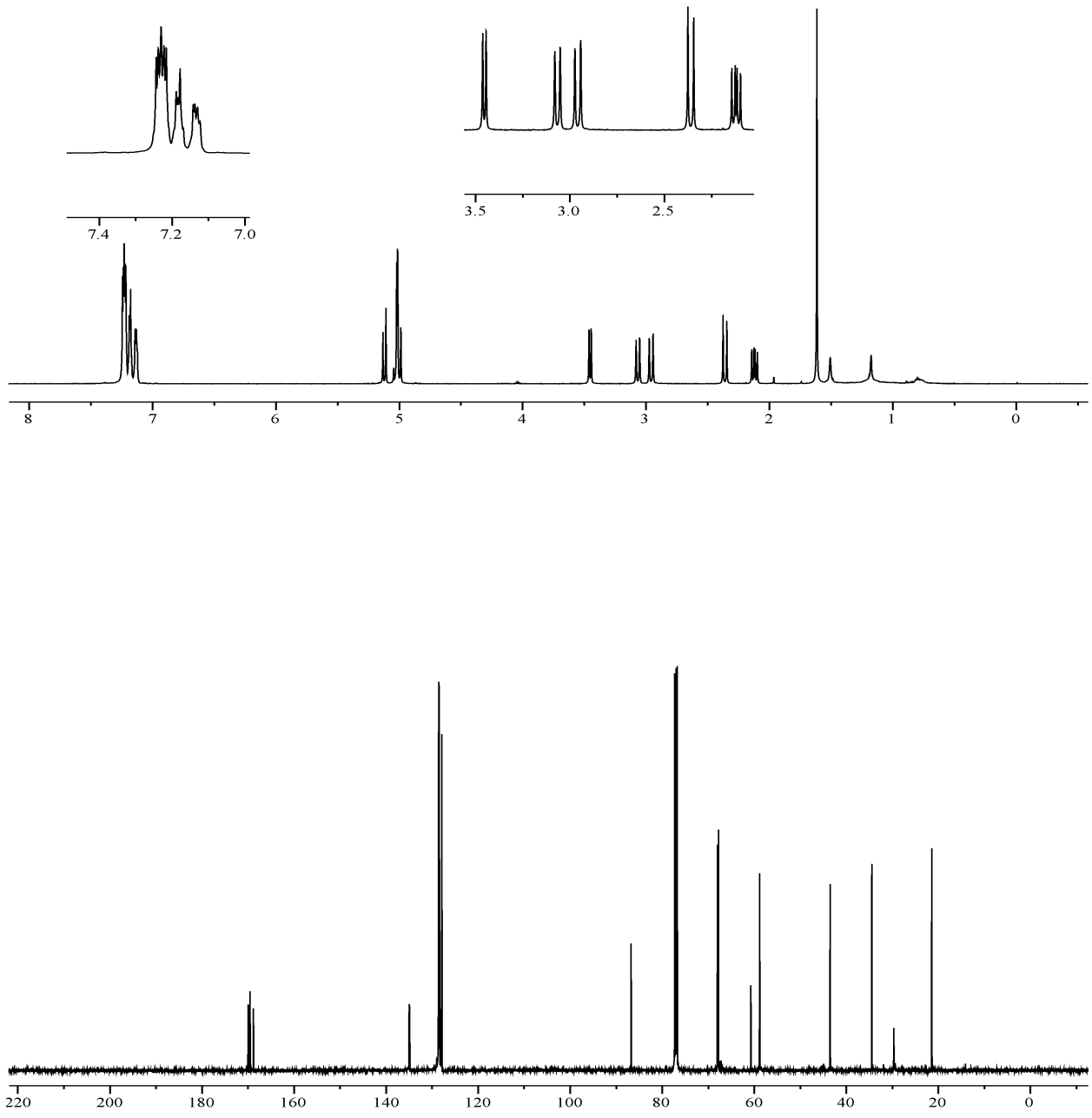
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14b** in $CDCl_3$



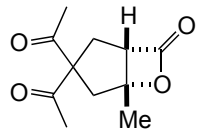
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14c** in $CDCl_3$



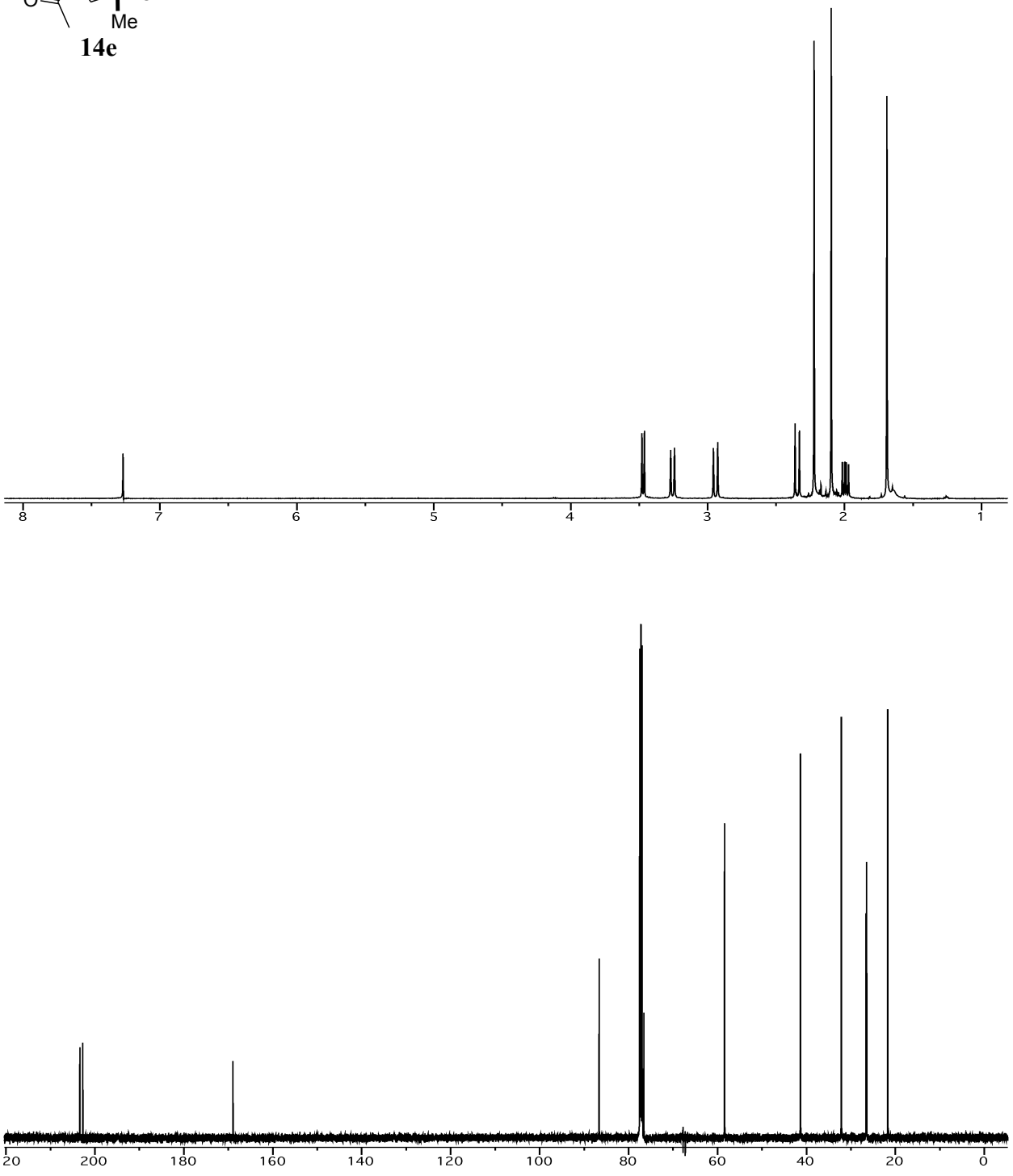
14d



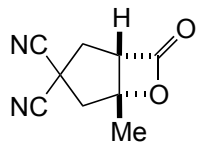
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14d** in $CDCl_3$



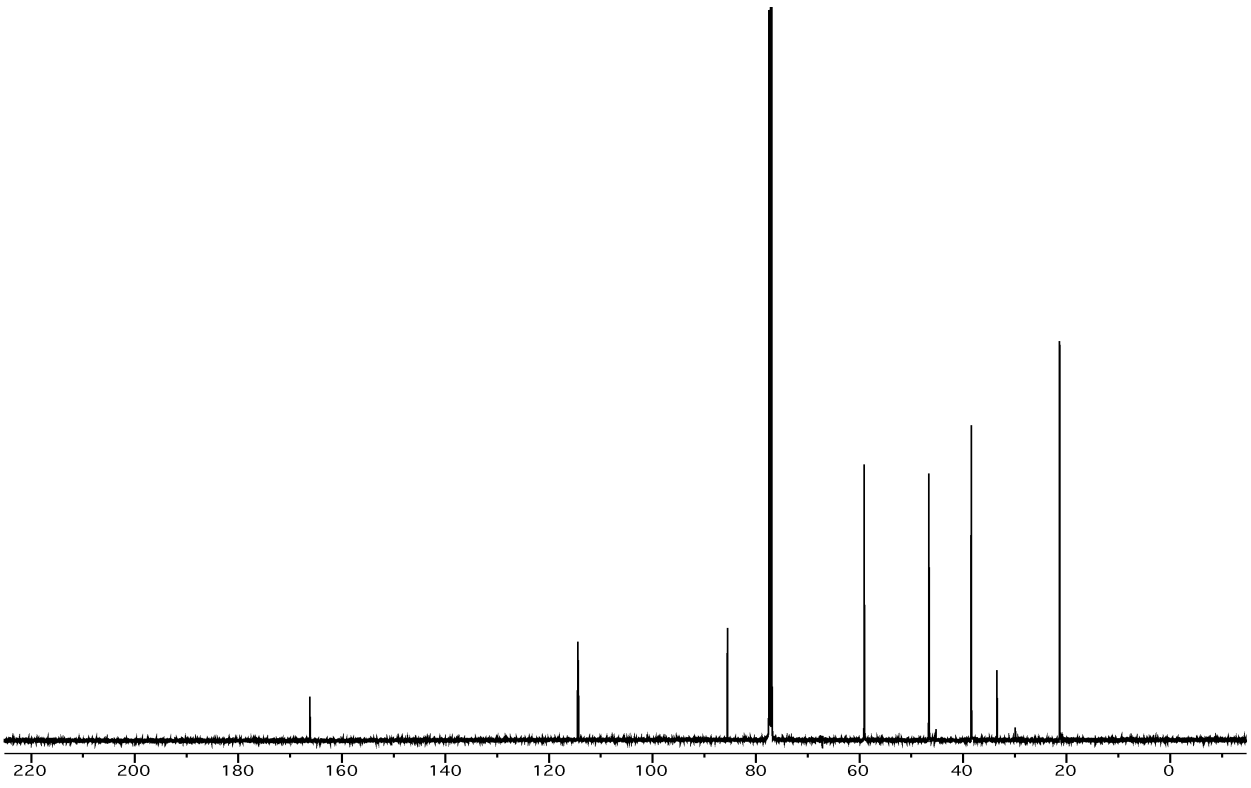
14e



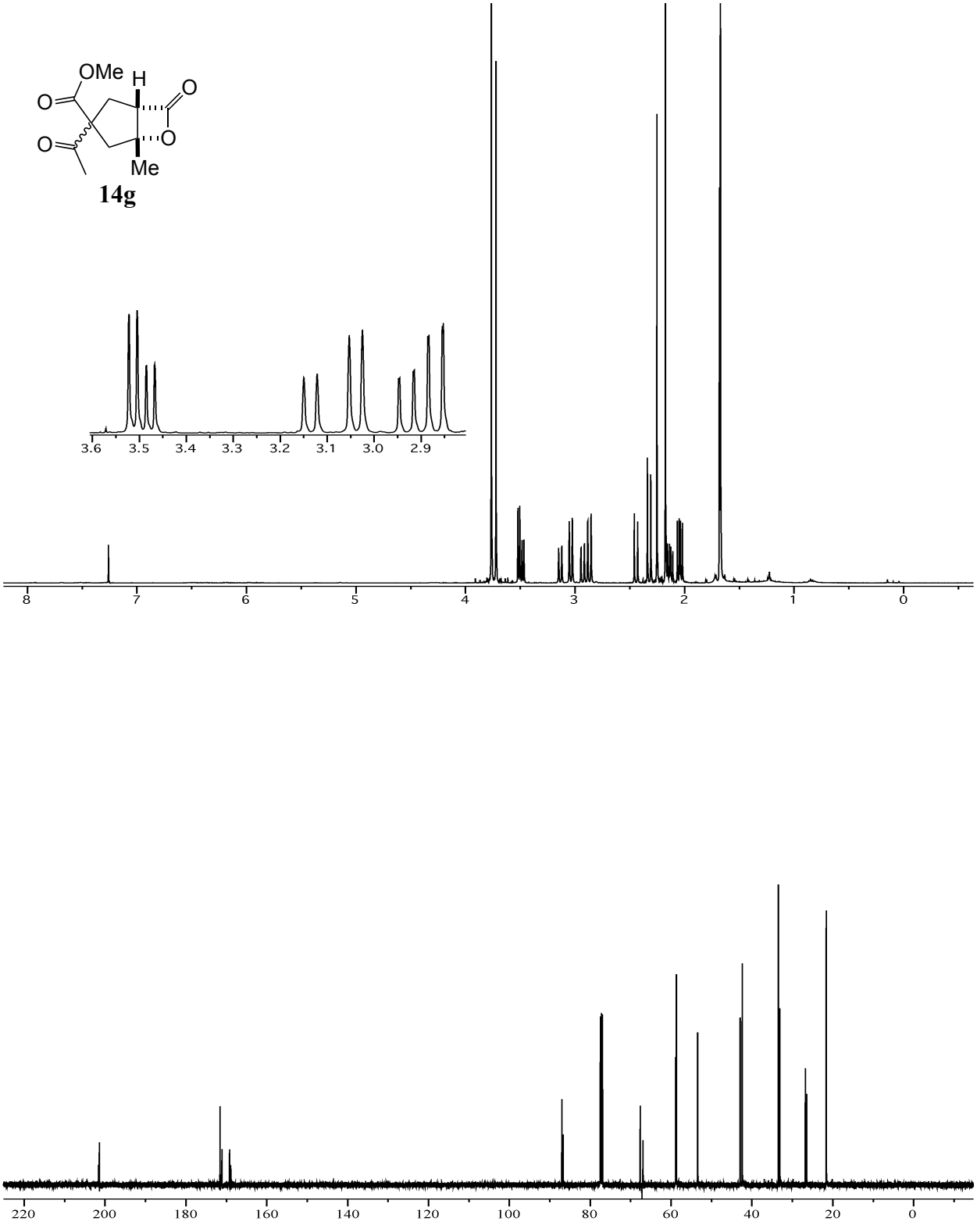
^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of β-lactone **14e** in $CDCl_3$



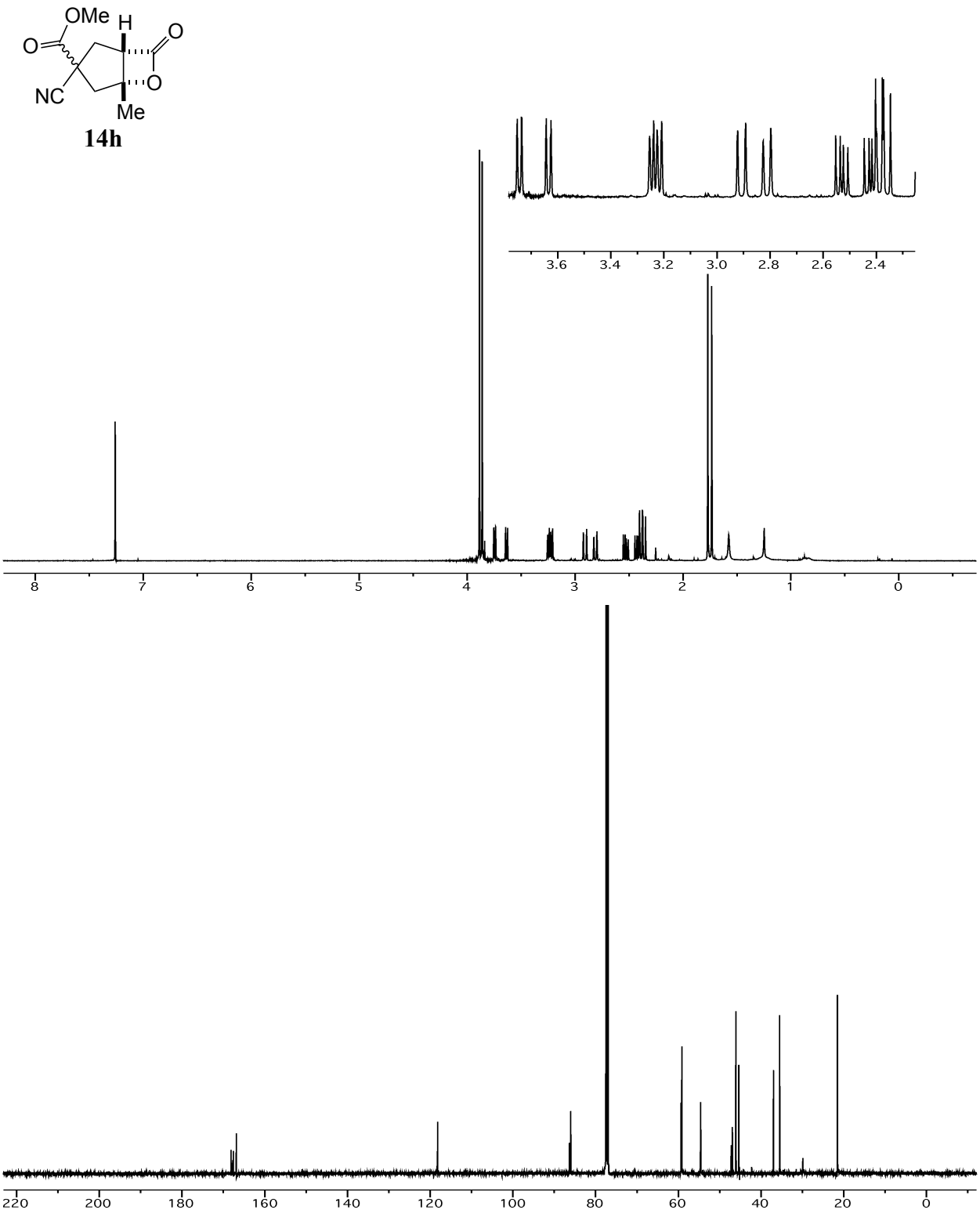
14f



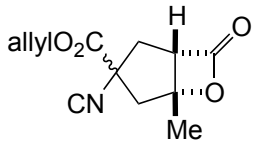
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14f** in $CDCl_3$



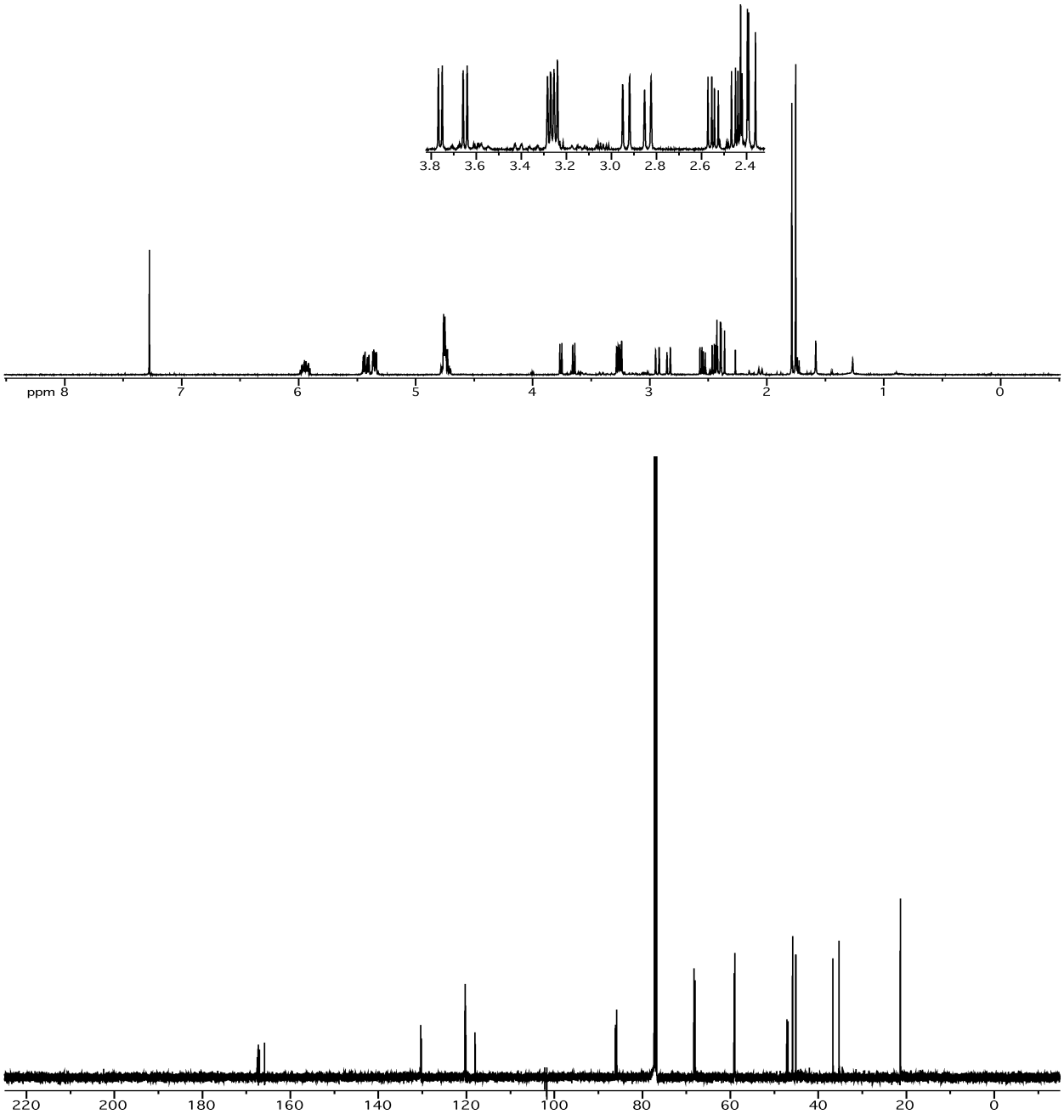
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14g** in $CDCl_3$



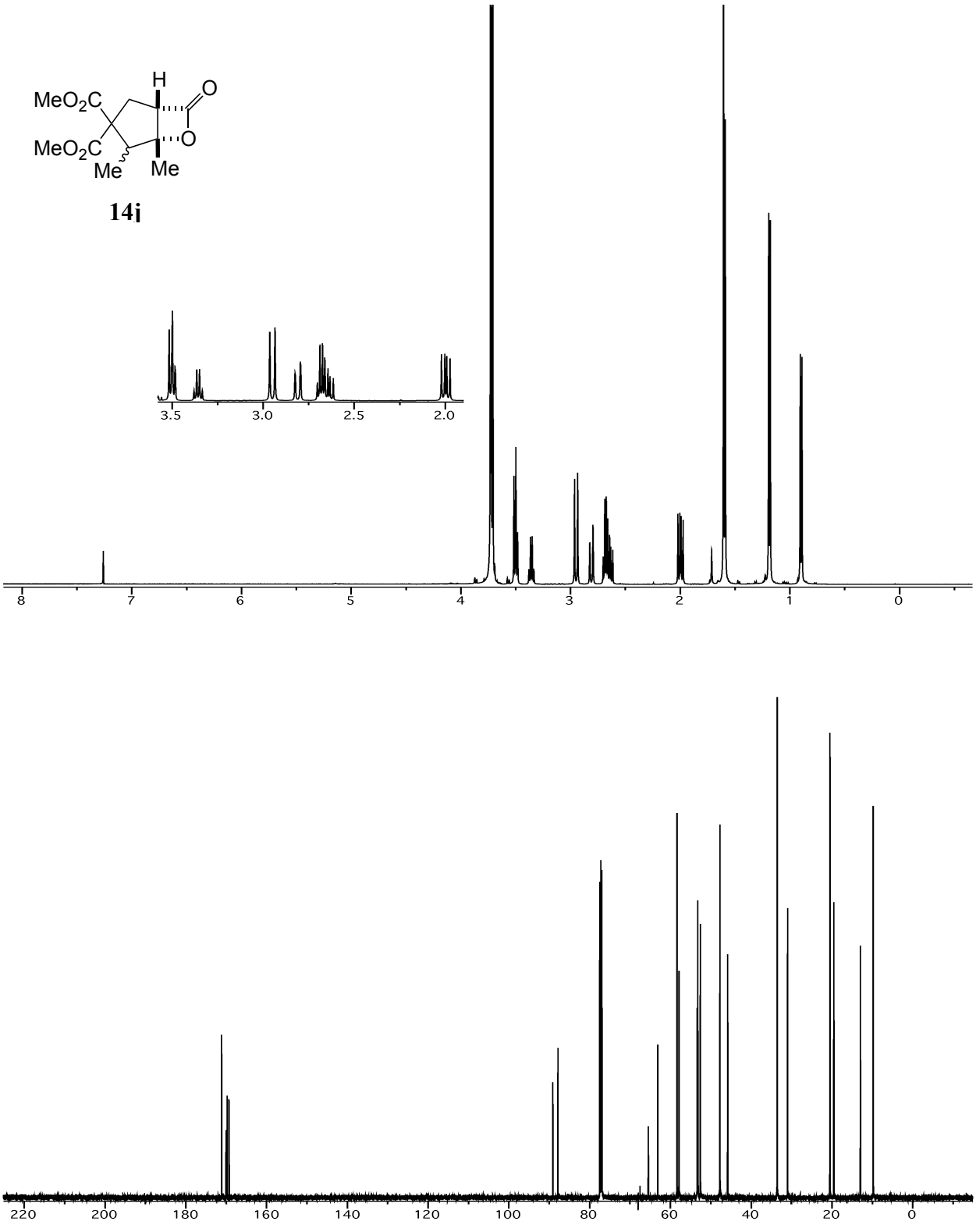
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14h** in $CDCl_3$



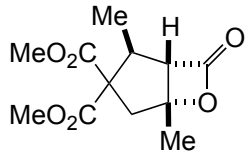
14i



^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14i** in $CDCl_3$

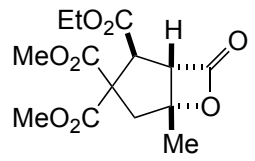


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14j** in $CDCl_3$

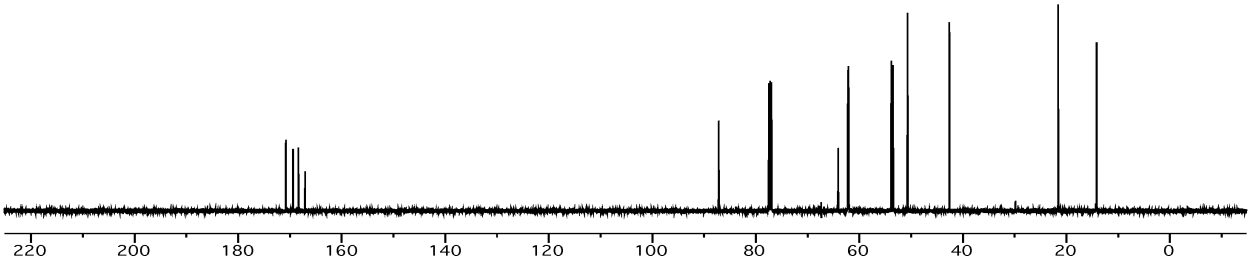


14k

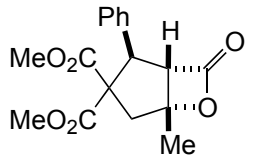
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14k** in $CDCl_3$



14l

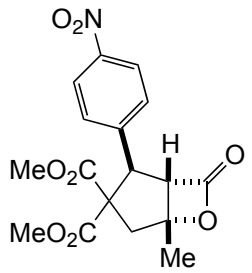


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14l** in $CDCl_3$

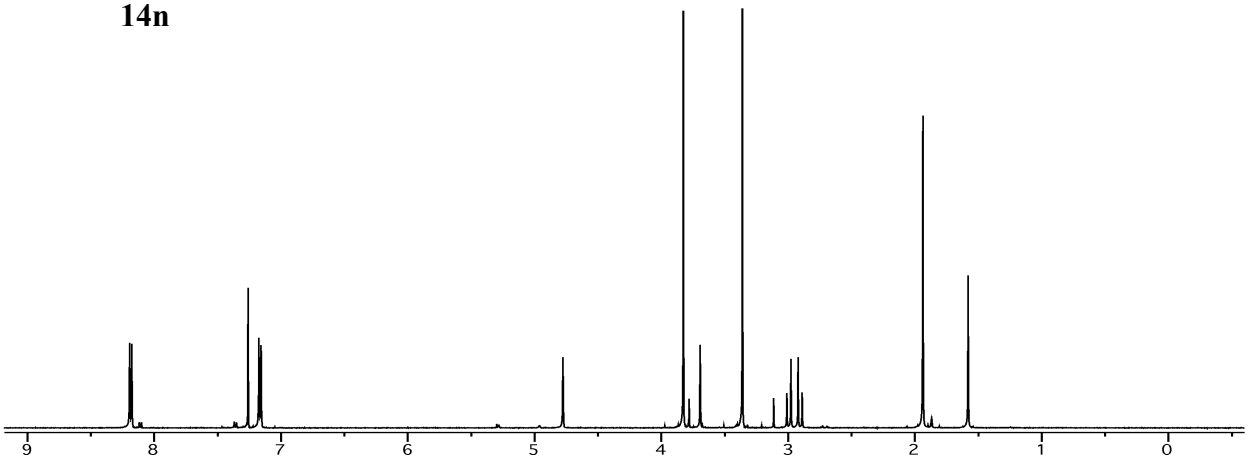


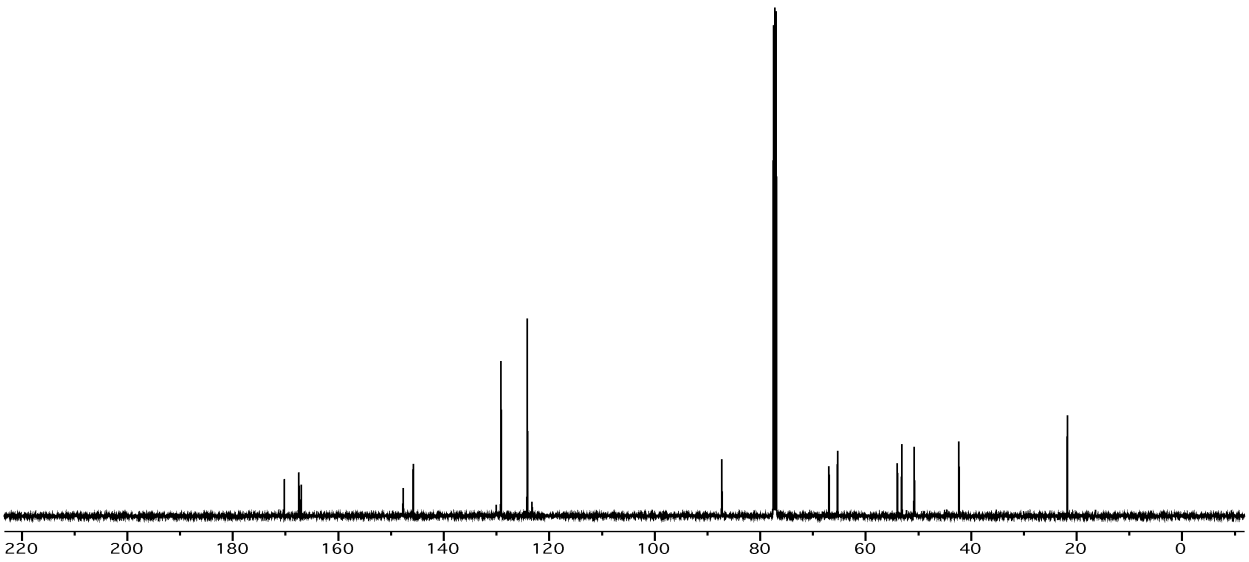
14m

^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14m** in $CDCl_3$

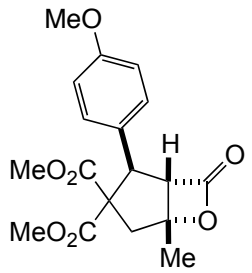


14n

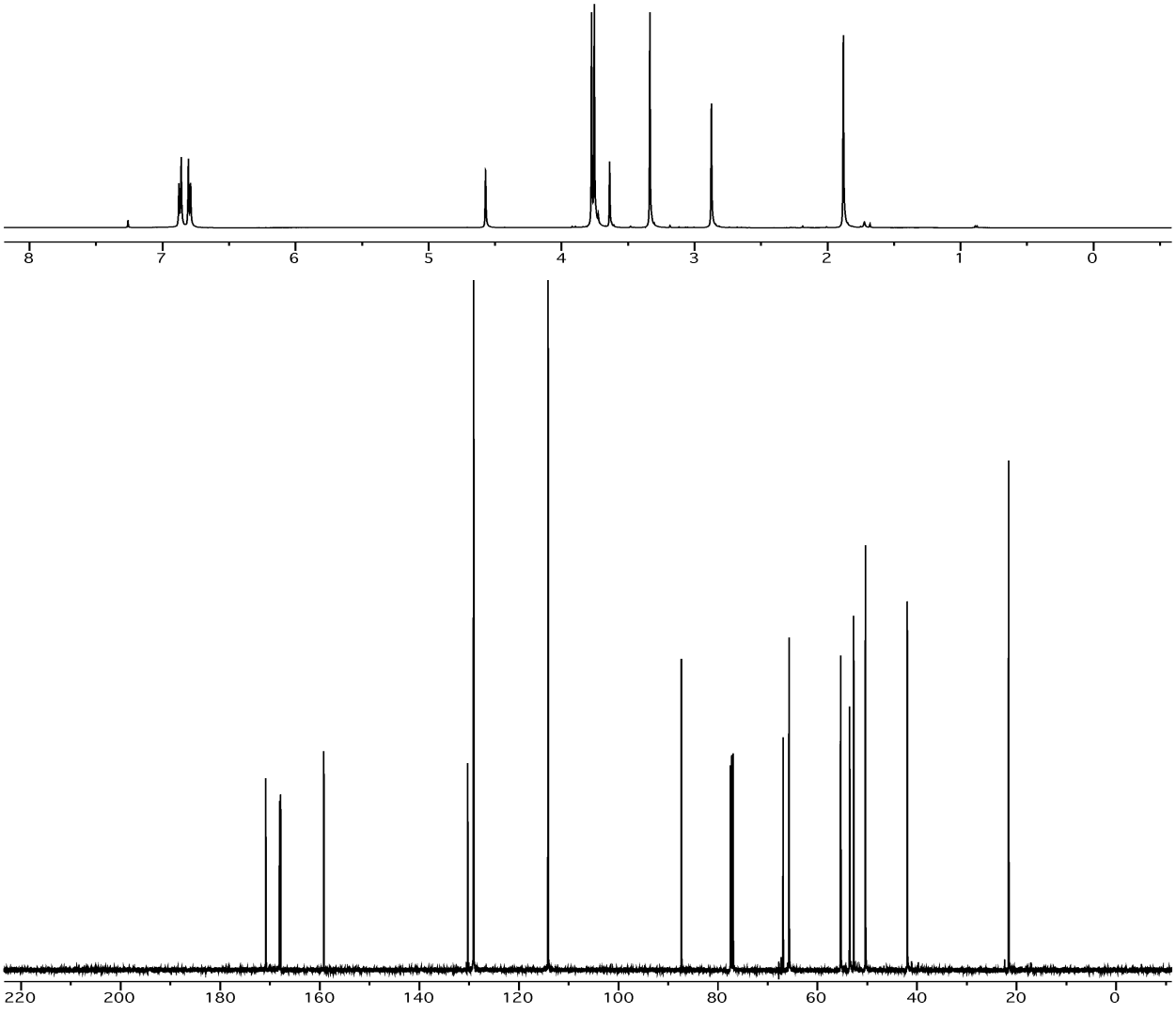




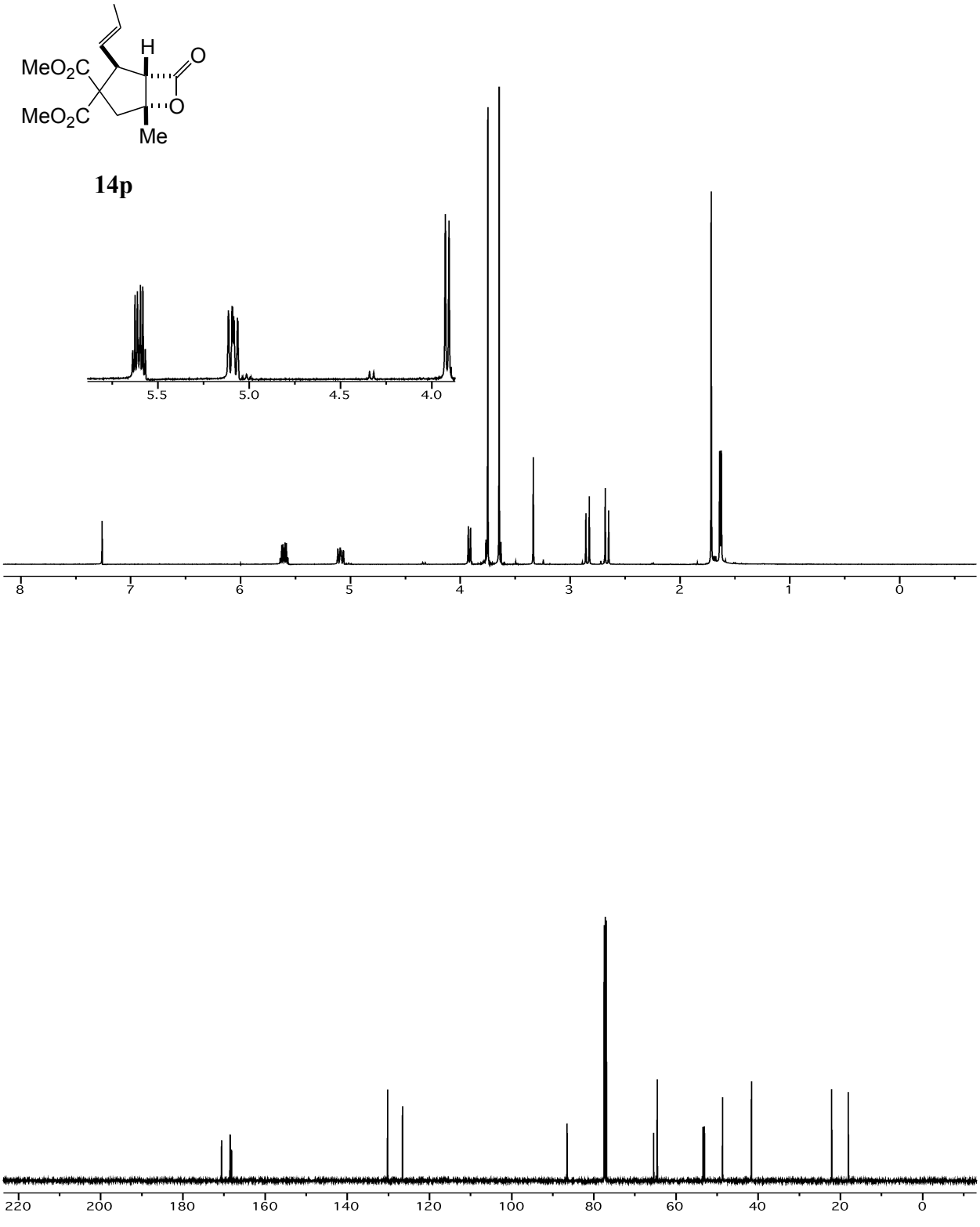
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14n** in $CDCl_3$



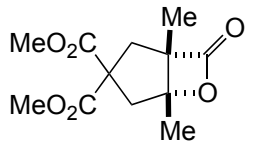
14o



^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14o** in $CDCl_3$

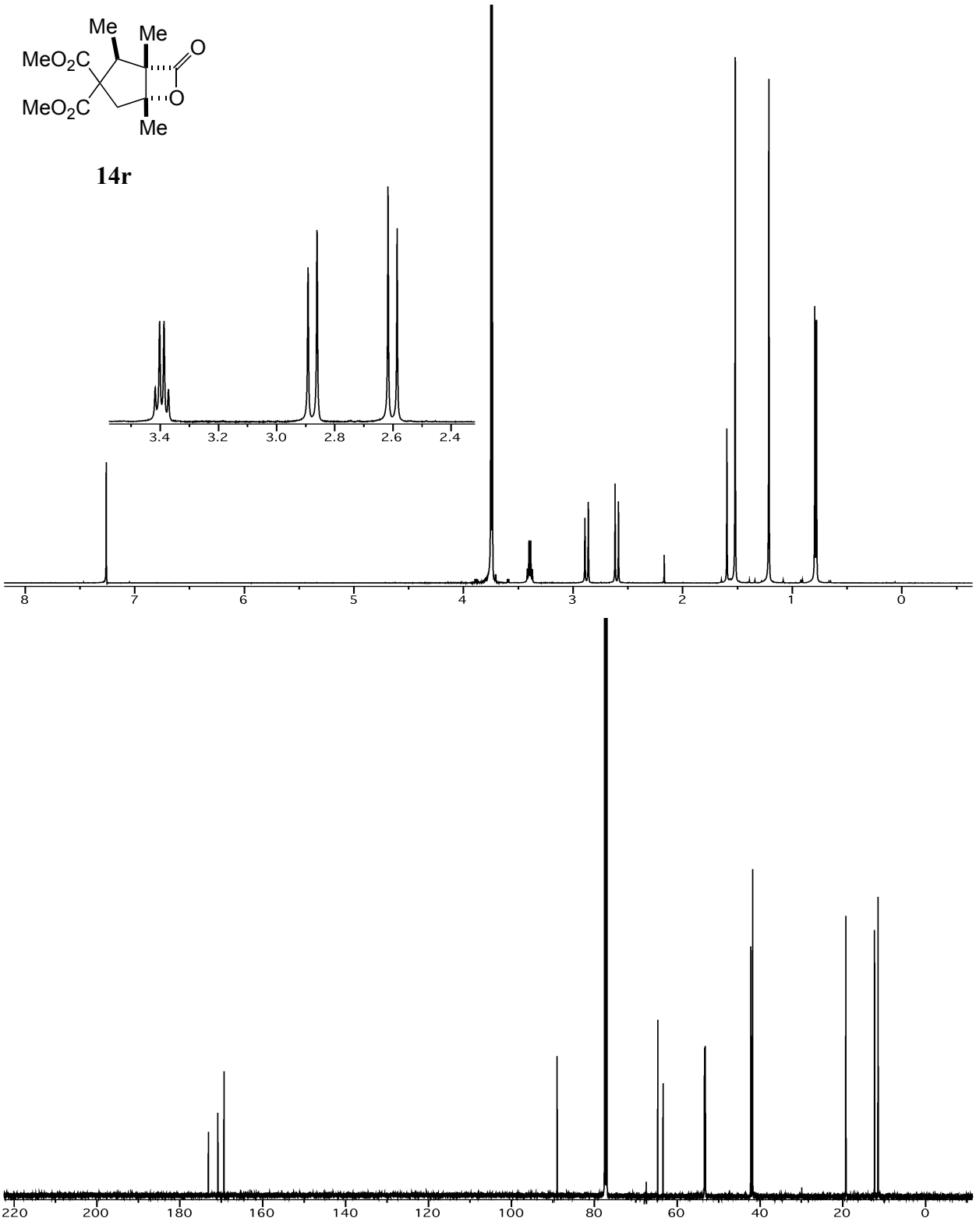


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14p** in $CDCl_3$

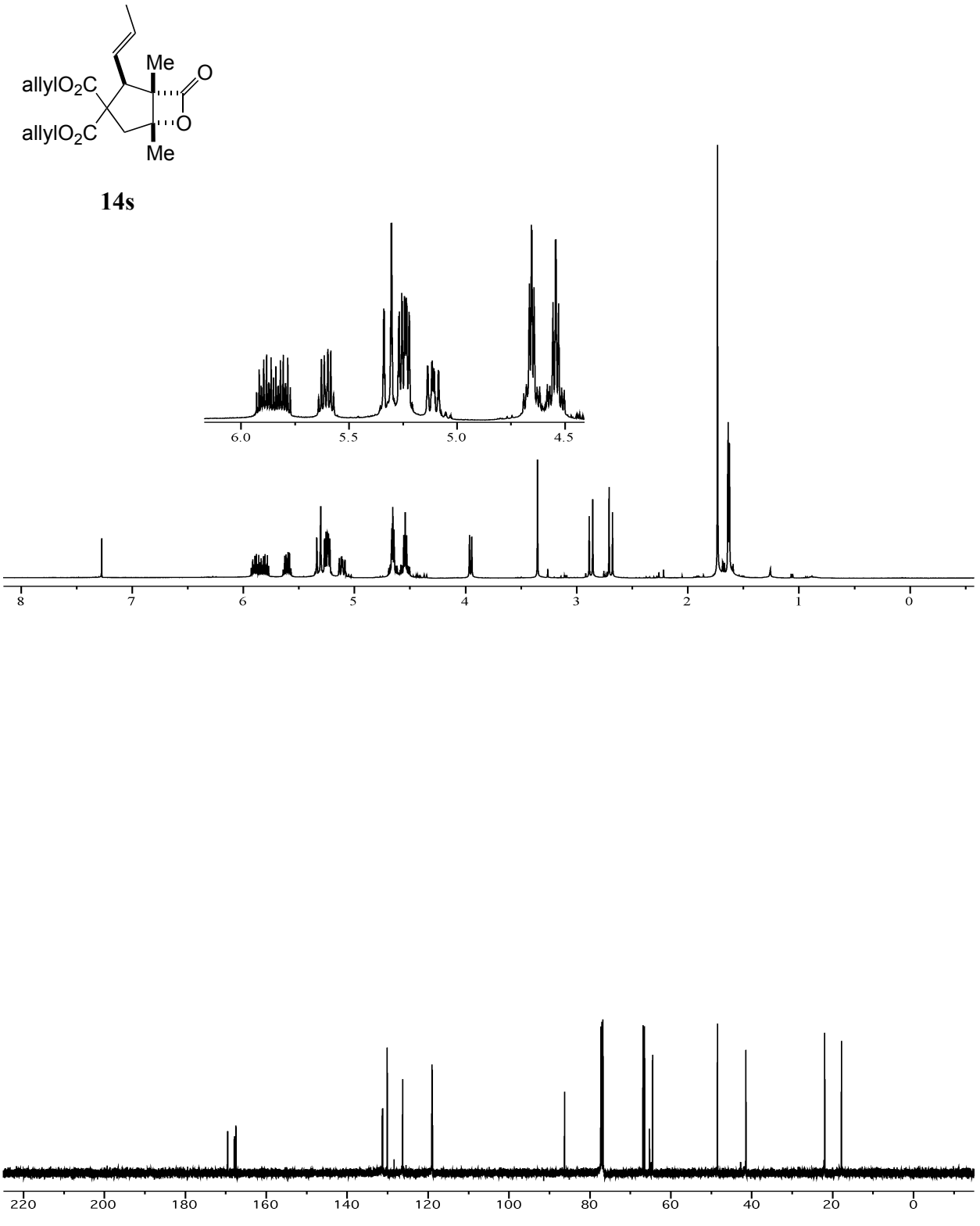


14q

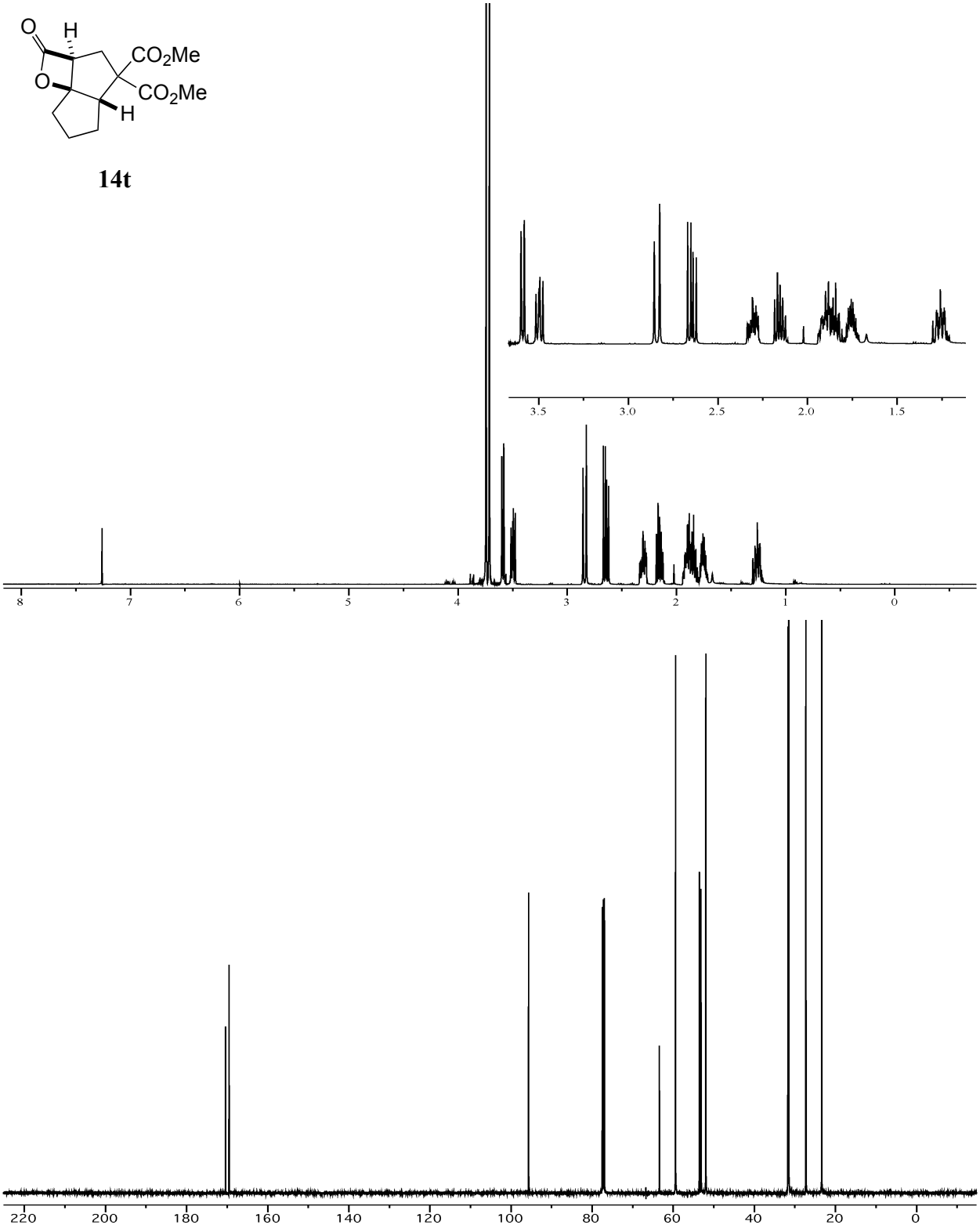
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14q** in $CDCl_3$



^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14r** in $CDCl_3$

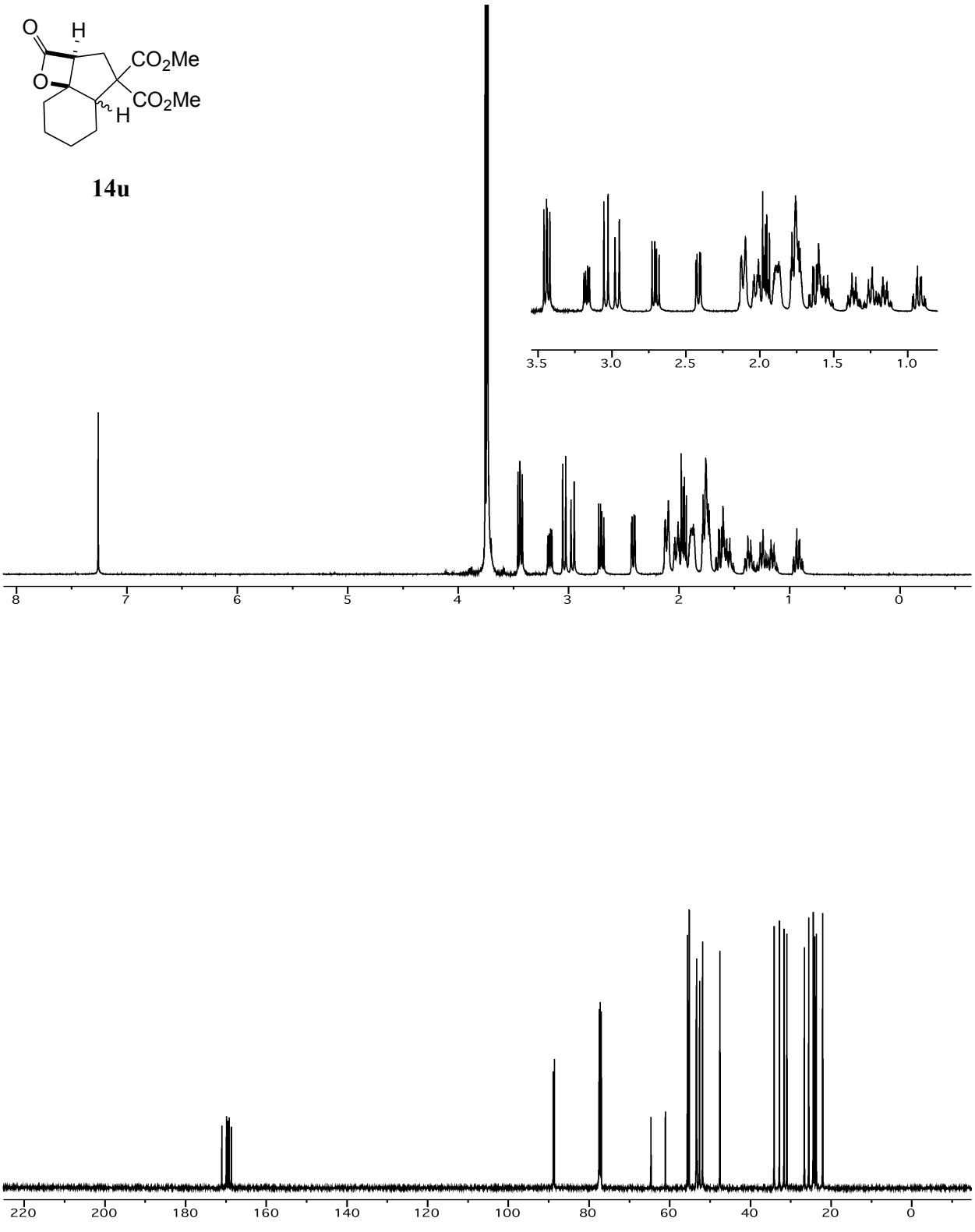


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14s** in $CDCl_3$

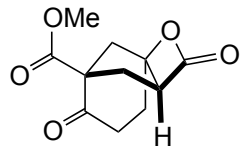


14t

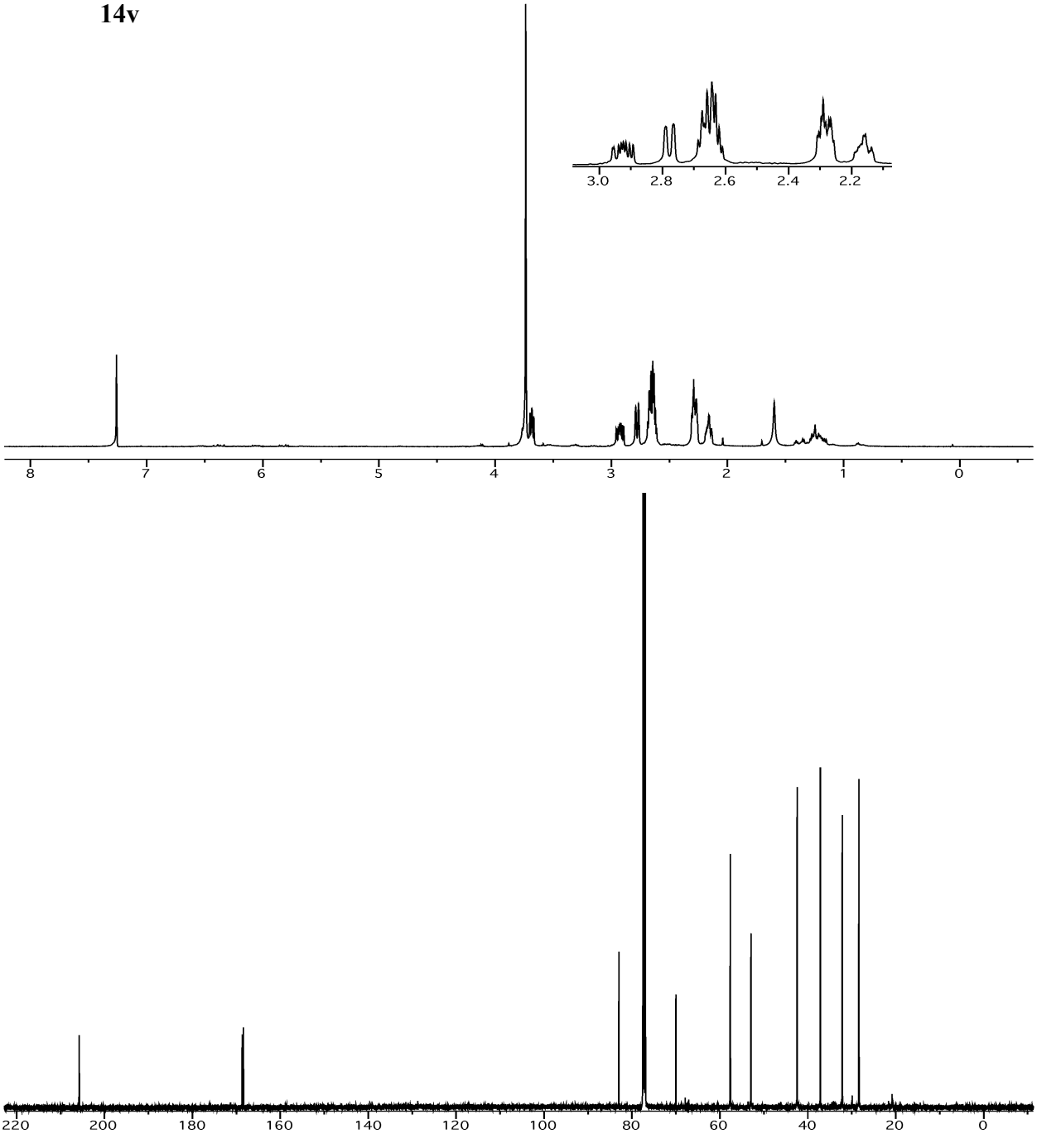
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of tricyclic β-lactone **14t** in $CDCl_3$



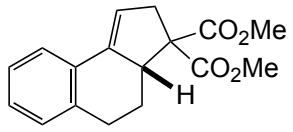
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of tricyclic β-lactone **14u** in $CDCl_3$



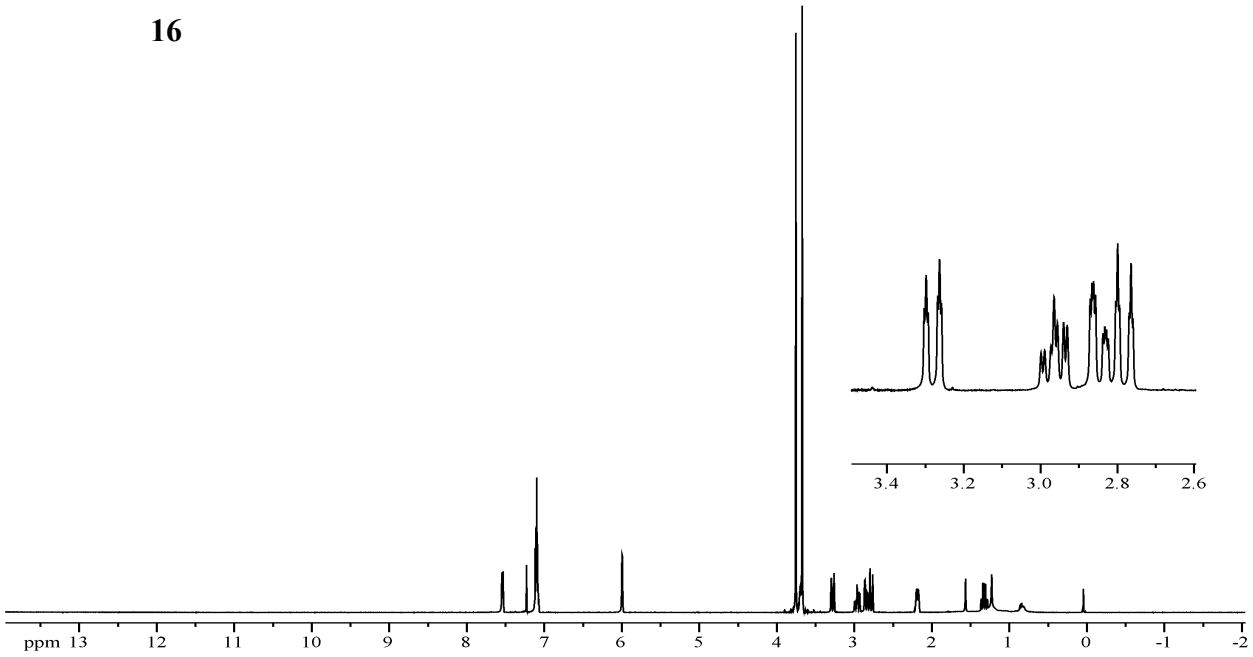
14v

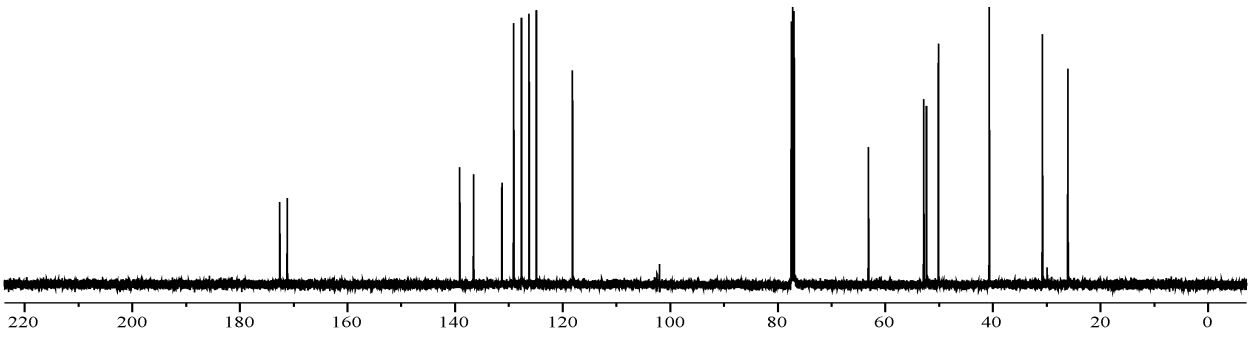


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of bridged β-lactone **14v** in $CDCl_3$

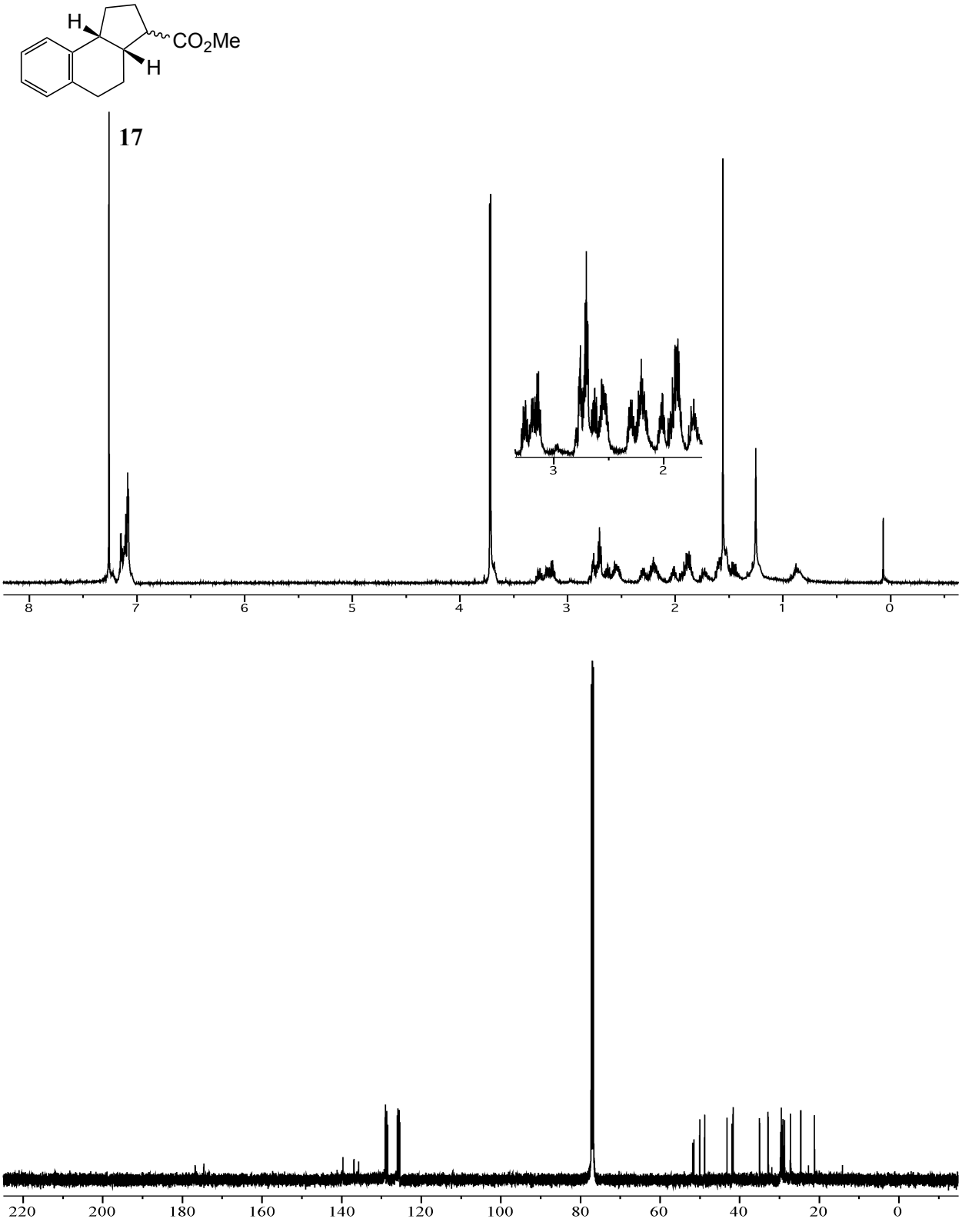


16

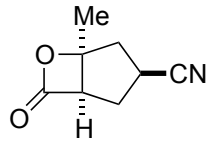




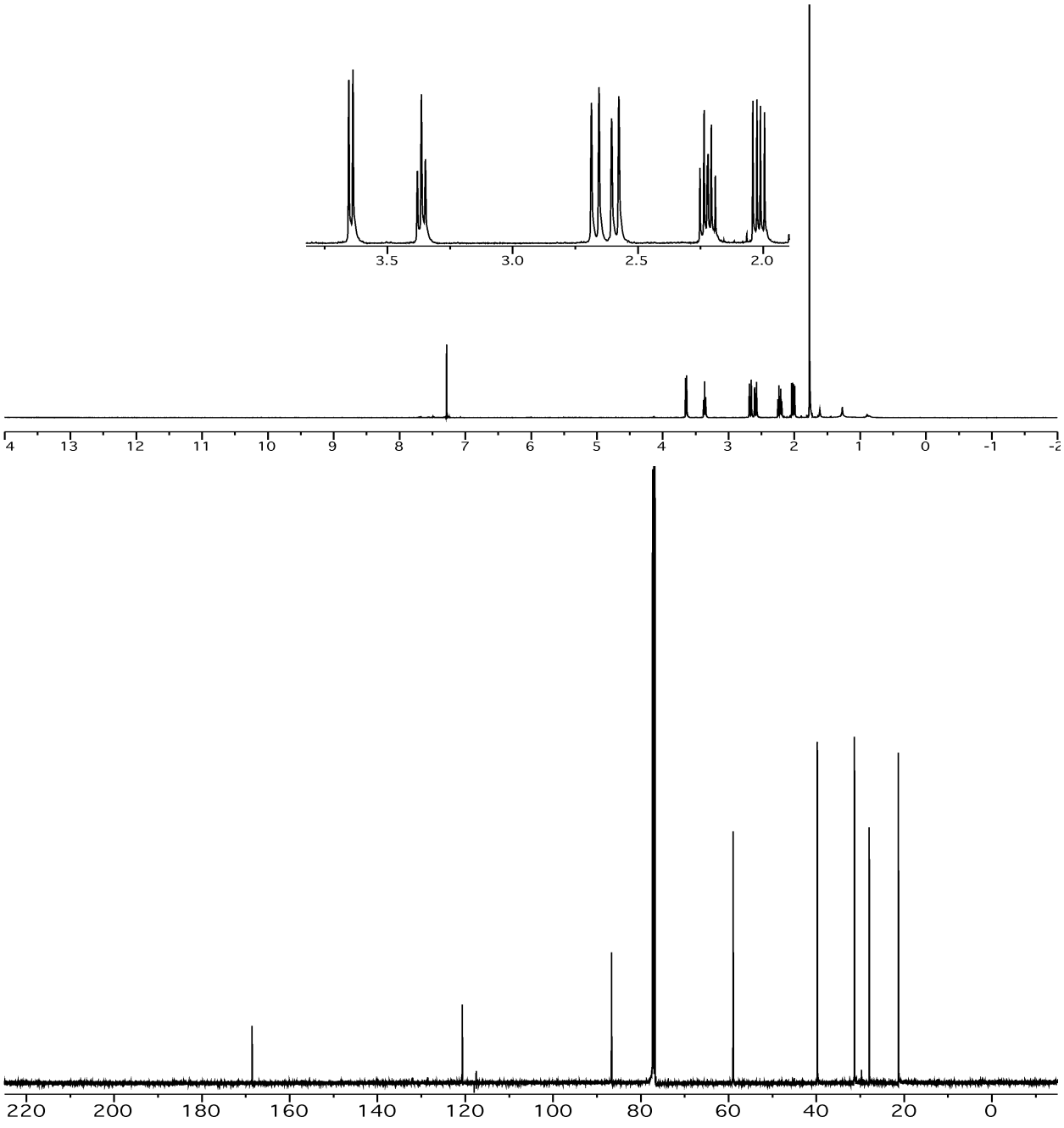
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of cyclopentene **16** in $CDCl_3$



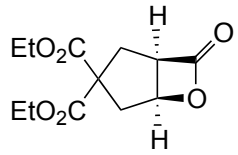
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of cyclopentane **17** in $CDCl_3$



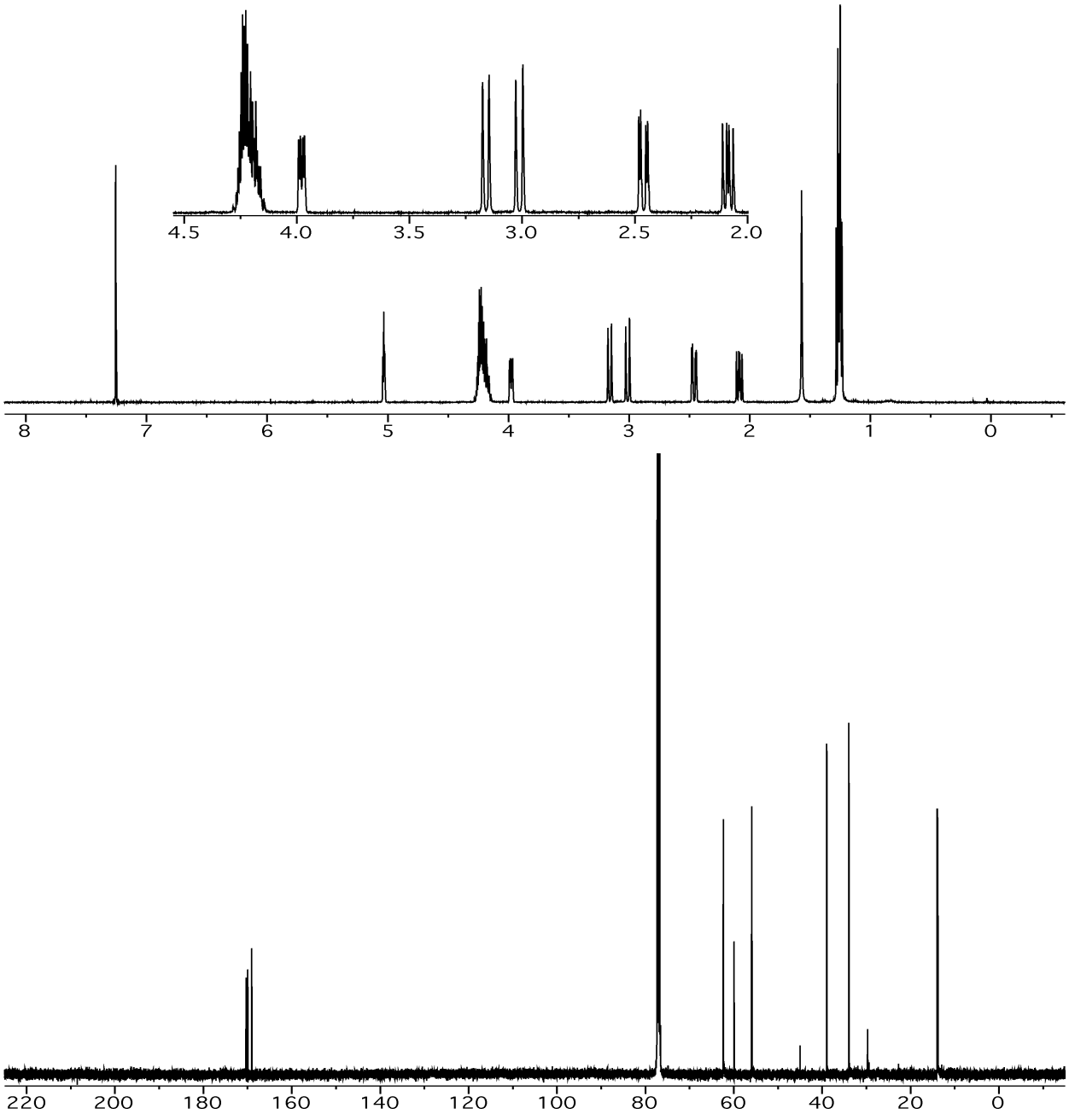
14x



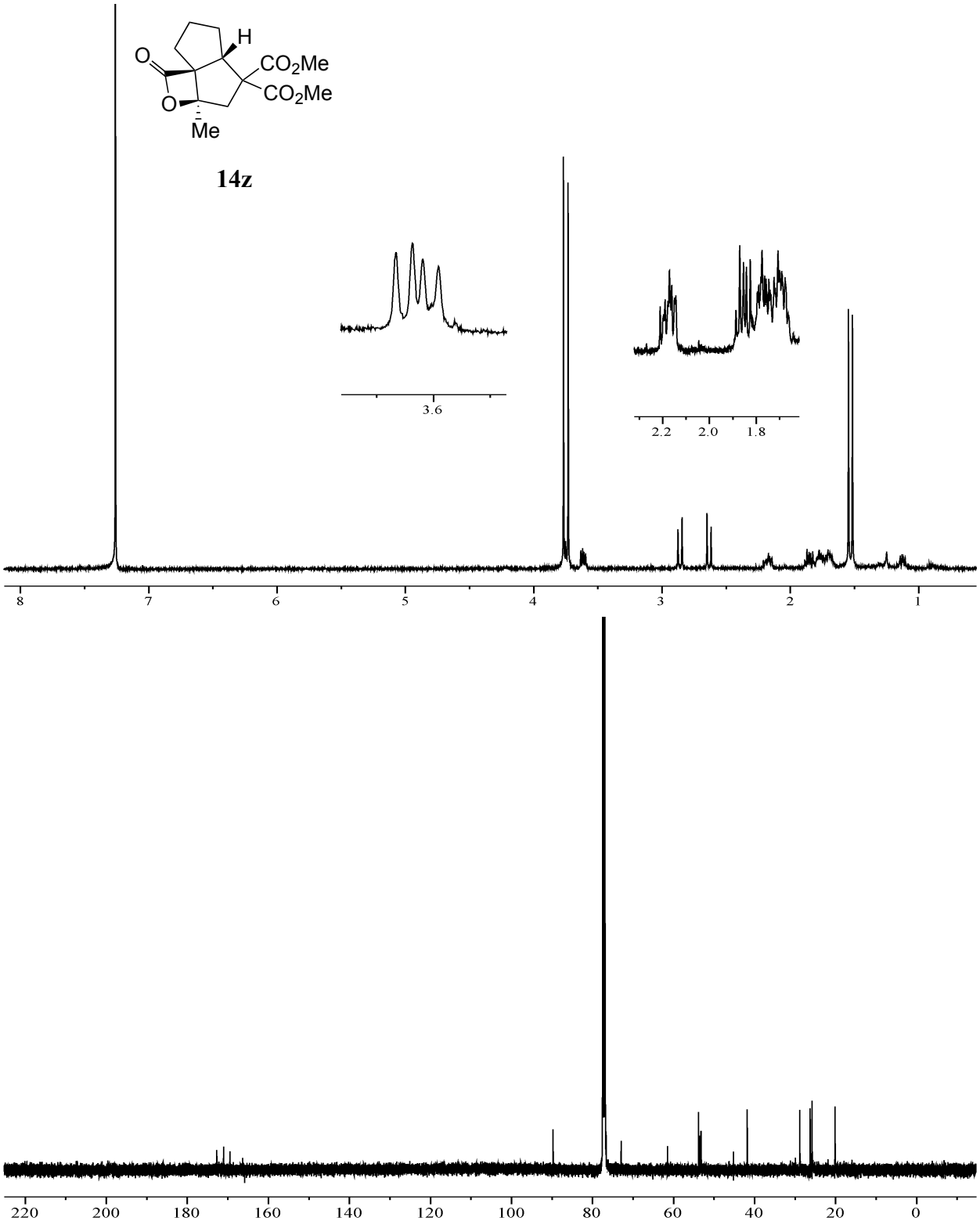
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14x** in $CDCl_3$



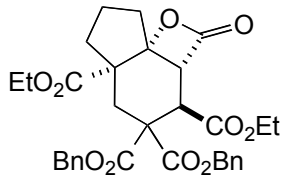
14y



^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14y** in $CDCl_3$

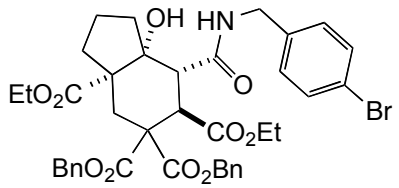


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of tricyclic β-lactone **14z** in $CDCl_3$

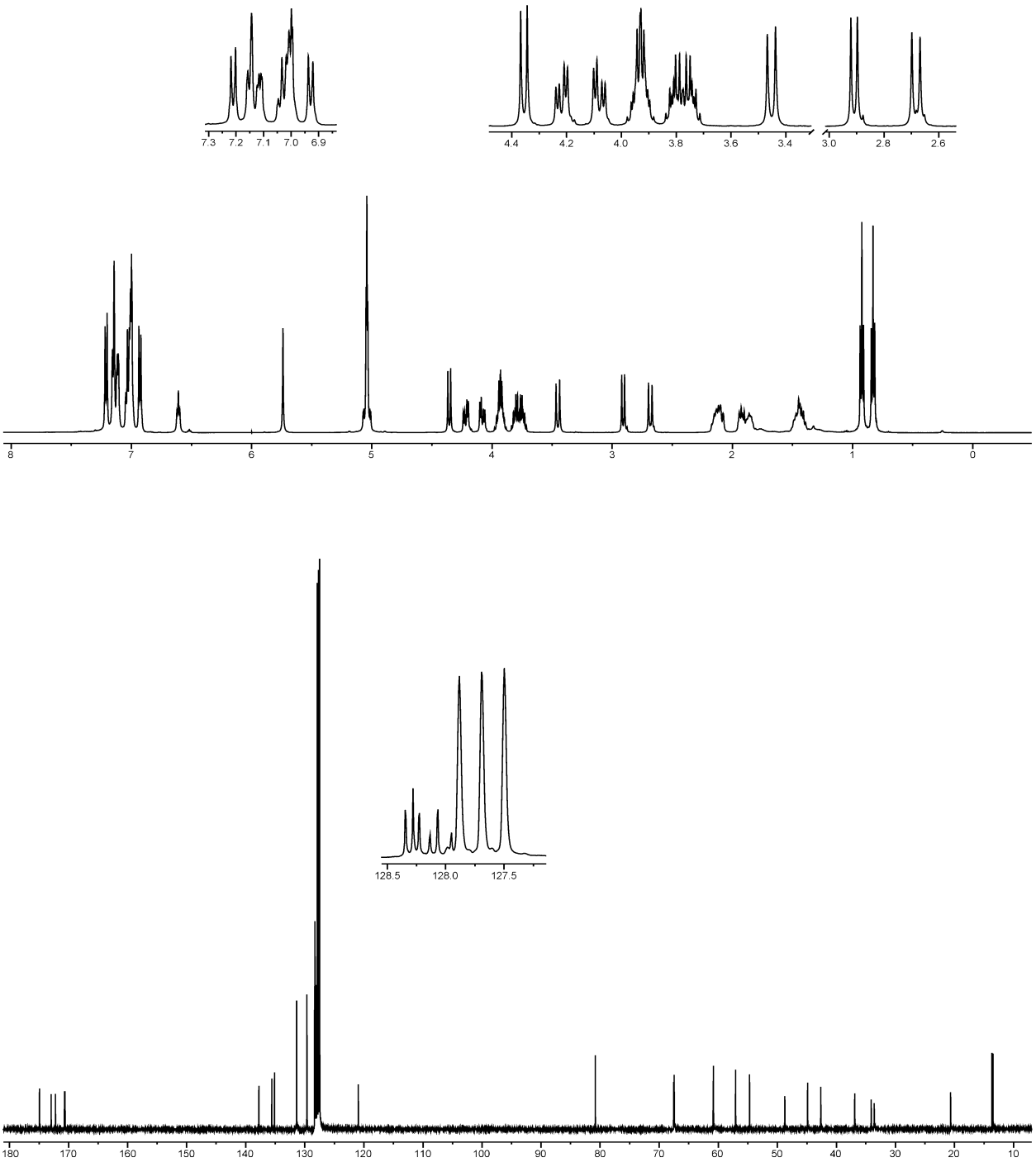


(+)-23

^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone (+)-**23** in $CDCl_3$



(–)-**24**



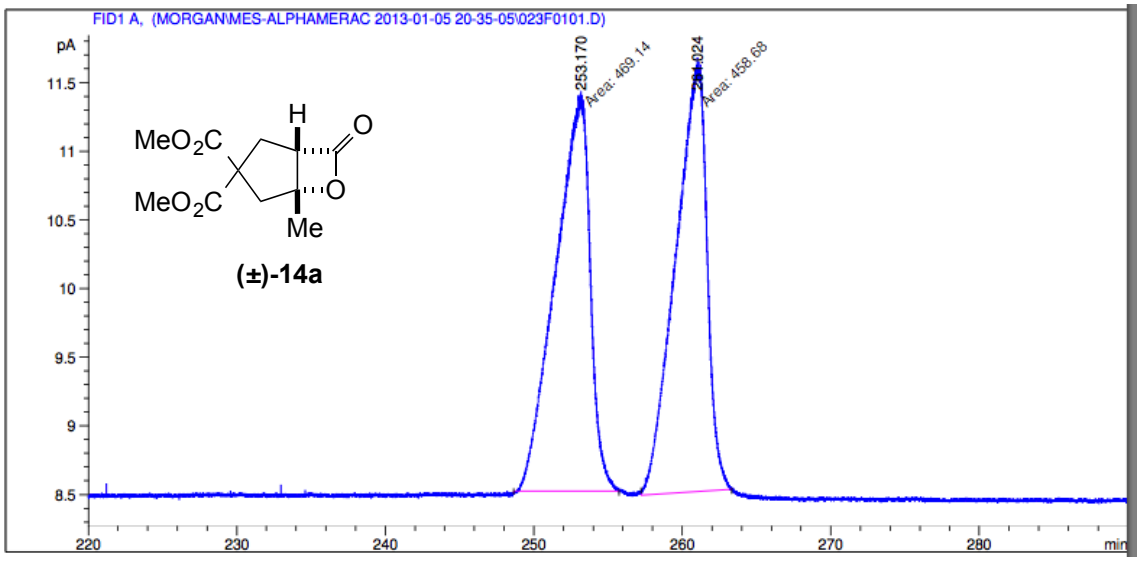
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of amide (–)-**24** in C_6D_6

Figure S1. Chiral GC determination of enantiomeric excess.

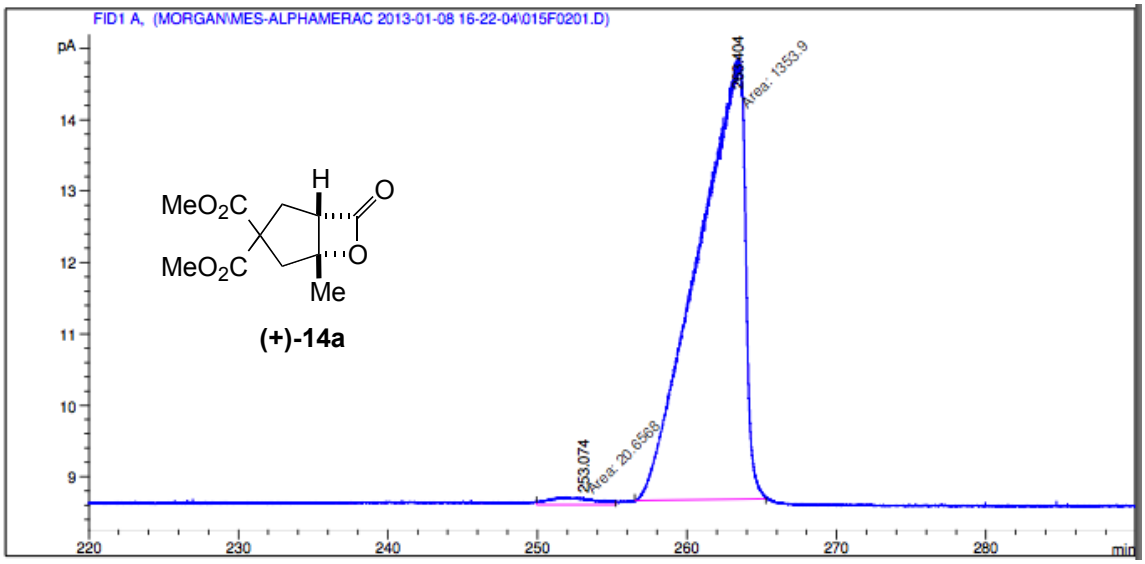
Determination of enantiomeric excess of β-lactone (+)-14a:

Analysis of β-lactone 14a: Method: CHIRALDEX-BDM GC column, 13.85 psi, 70-160 °C oven temperature

Temp (°C)	Rate (°C/min)	Hold time (min)	Total time (min)
70	0.00	2.00	2.00
80	6.00	5.00	8.67
94	0.05	3.00	291.67
160	40.0	1.00	294.32

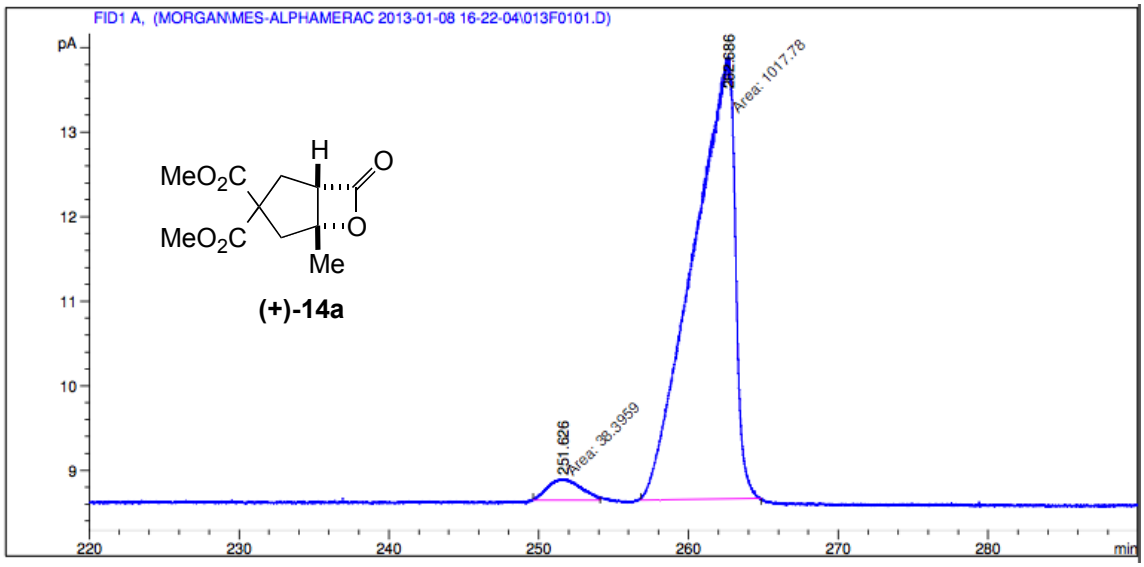


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	253.170	MM	2.6883	469.14023	2.90851	50.56371
2	261.024	MM	2.4268	458.67972	3.15007	49.43629
Totals :				927.81995	6.05858	



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	253.074	MM	3.0844	20.65680	1.11619e-1	1.50280
2	263.404	MM	3.6433	1353.90149	6.19348	98.49720
Totals :				1374.55829	6.30510	

For 1 gram scale reaction:

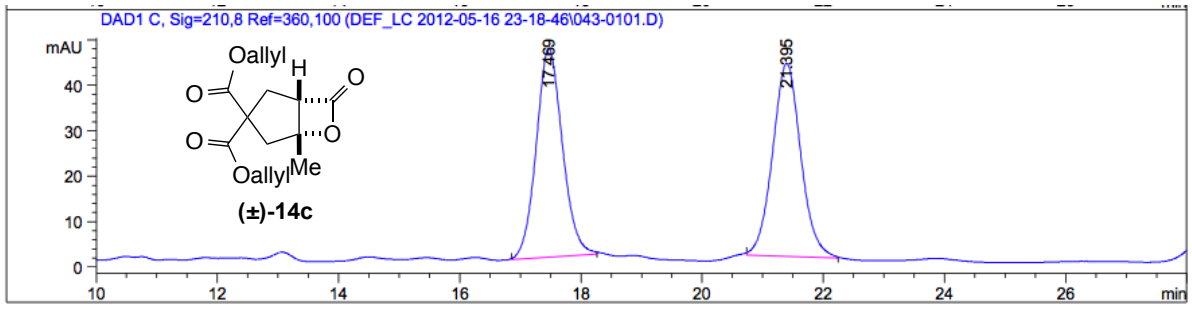


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	251.626	MM	2.4909	38.39586	2.56910e-1	3.63537
2	262.686	MM	3.2436	1017.77905	5.22972	96.36463
Totals :				1056.17491	5.48663	

Figure S2. Chiral HPLC determinations of enantiomeric excess.

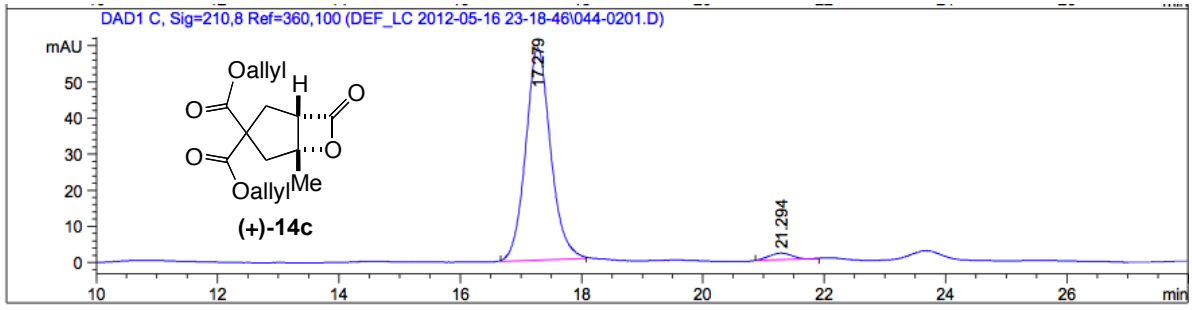
Determination of enantiomeric excess of β-lactone 14c:

Chiral HPLC Analysis of β-lactone (+)-14c: Chiralcel IA column: hexanes:*i*PrOH = 92:08, flow rate 0.5 mL/min, λ = 210 nm: t_{major} = 17.28 min, t_{minor} = 21.29 min; 95% *ee*.



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.469	BB	0.4584	1380.03906	45.94238	50.0339
2	21.395	BB	0.4922	1378.16772	42.51847	49.9661
Totals :				2758.20679	88.46085	

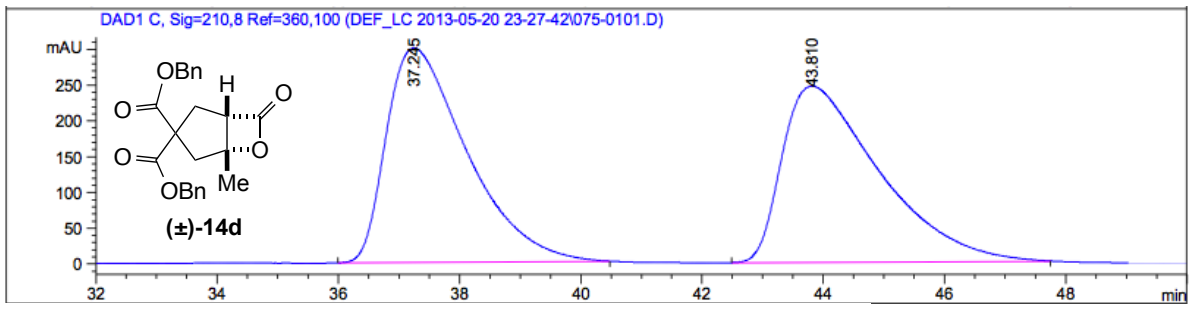


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.279	BB	0.4330	1679.59167	58.83675	97.3688
2	21.294	BB	0.3267	45.38679	1.80935	2.6312
Totals :				1724.97847	60.64610	

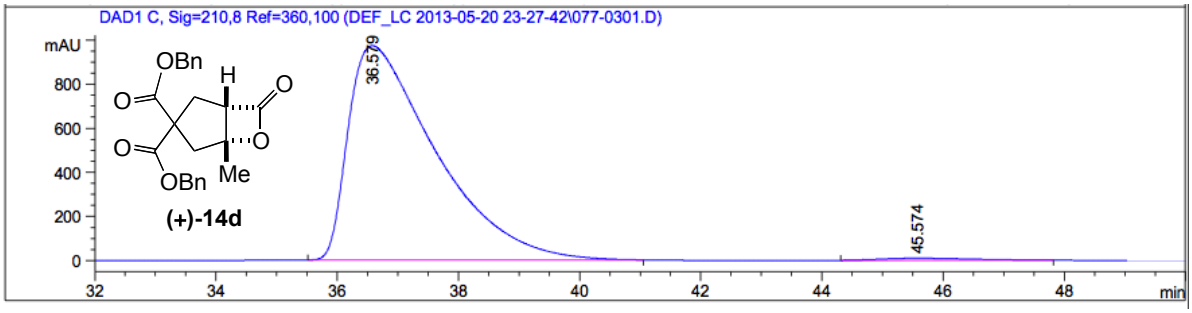
Determination of enantiomeric excess of β-lactone (+)-14d:

Chiral HPLC Analysis of β-lactone (+)-14d: Chiralcel OD-H column: hexanes:*i*PrOH = 95:05, flow rate 1.0 mL/min, λ = 210 nm: t_{major} = 36.58 min, t_{minor} = 45.57 min,; 98% *ee*.



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.245	BB	1.3899	2.77147e4	299.96042	50.2328
2	43.810	BB	1.6070	2.74579e4	246.23305	49.7672
Totals :				5.51726e4	546.19347	

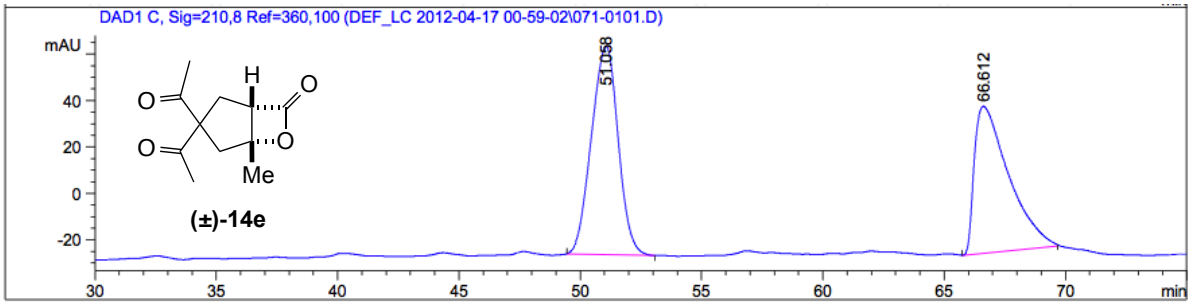


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.579	BB	1.4738	9.74570e4	971.97943	98.9620
2	45.574	BB	1.2386	1022.21277	9.75475	1.0380
Totals :				9.84792e4	981.73418	

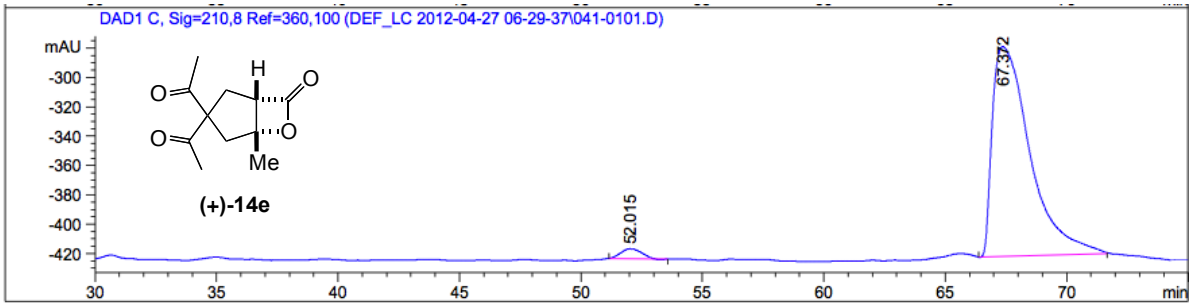
Determination of enantiomeric excess of β-lactone (+)-14e:

Chiral HPLC Analysis of β-lactone 14e: Chiralcel AD-H column: hexanes:*i*PrOH = 95:05, flow rate 0.5 mL/min, λ = 210 nm: t_{minor} = 52.02 min, t_{major} = 67.37 min; 95% *ee*.



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	51.058	BB	1.1917	6904.16602	89.93245	52.5774
2	66.612	BB	1.3835	6227.27295	63.31452	47.4226
Totals :				1.31314e4	153.24697	

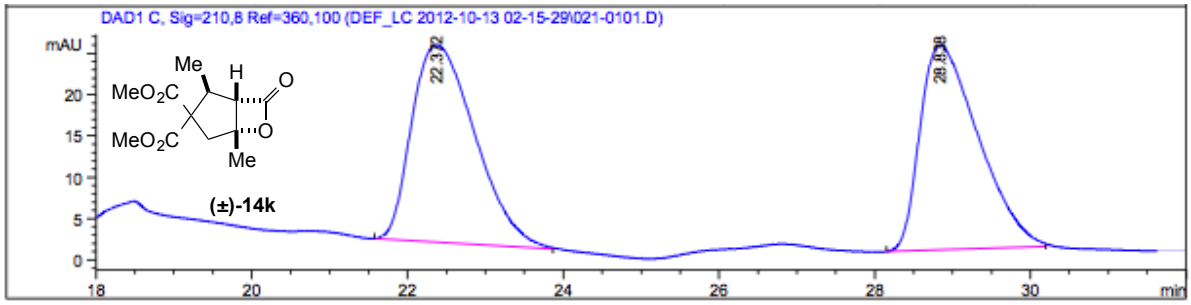


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	52.015	BB	0.7163	397.05292	6.74918	2.5066
2	67.372	BB	1.6573	1.54434e4	143.07353	97.4934
Totals :				1.58405e4	149.82271	

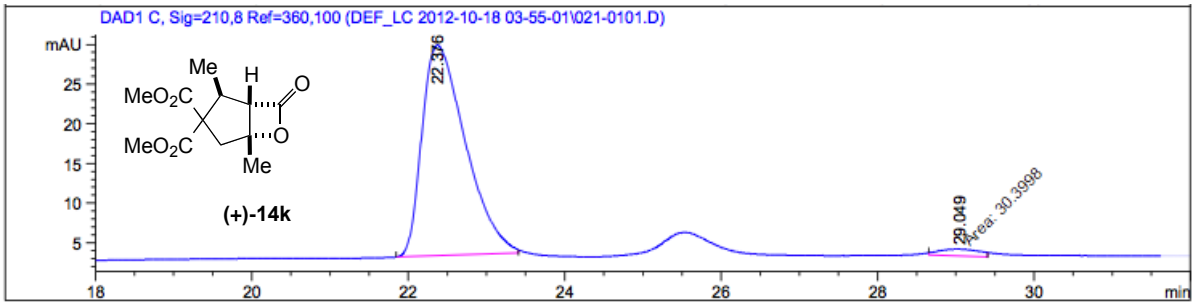
Determination of enantiomeric excess of β-lactone (+)-14k:

Chiral HPLCAnalysis of β-lactone 14k: Chiralcel OD-H column: hexanes:*i*PrOH = 90:10, flow rate 0.5 mL/min, λ = 210 nm: t_{major} = 22.38 min, t_{minor} = 29.05 min; 94% *ee.*



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.372	BB	0.8831	1347.21545	23.84849	51.0730
2	28.838	BB	0.7853	1290.60730	24.71064	48.9270
Totals :				2637.82275	48.55913	

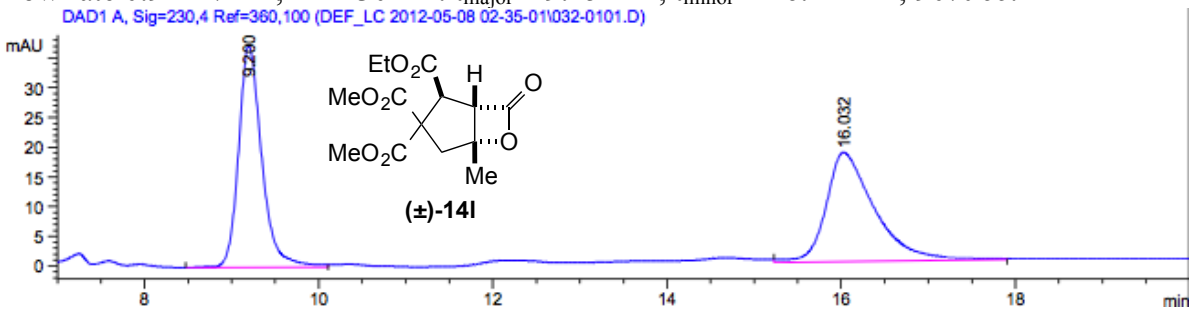


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.376	BB	0.5900	1023.85535	26.54196	97.1165
2	29.049	MM	0.5977	30.39977	8.47750e-1	2.8835
Totals :				1054.25512	27.38971	

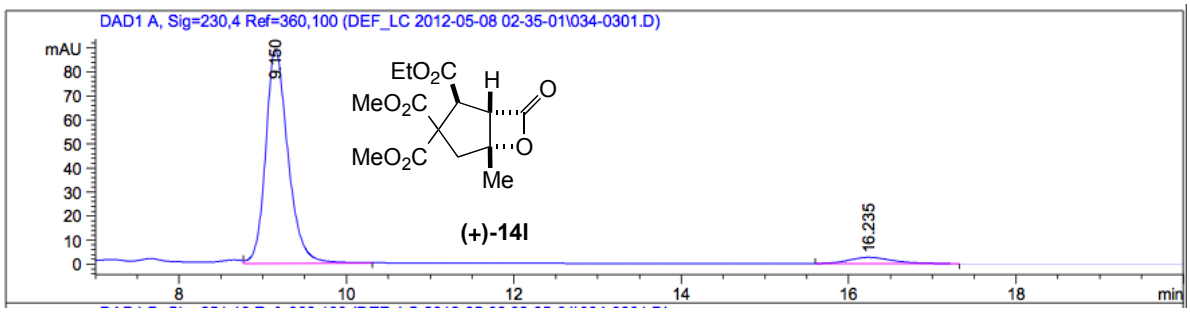
Determination of enantiomeric excess of β-lactone (+)-14l:

Chiral HPLC Analysis of β-lactone (+)-14l: Chiralcel AD-H column: hexanes:*i*PrOH = 88:12, flow rate 0.9 mL/min, λ = 230 nm: t_{major} = 9.15 min, t_{minor} = 16.24 min; 90% *ee*.



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.200	VV	0.2818	693.80536	37.16629	49.2484
2	16.032	VB	0.5660	714.98303	18.37302	50.7516
Totals :				1408.78839	55.53931	

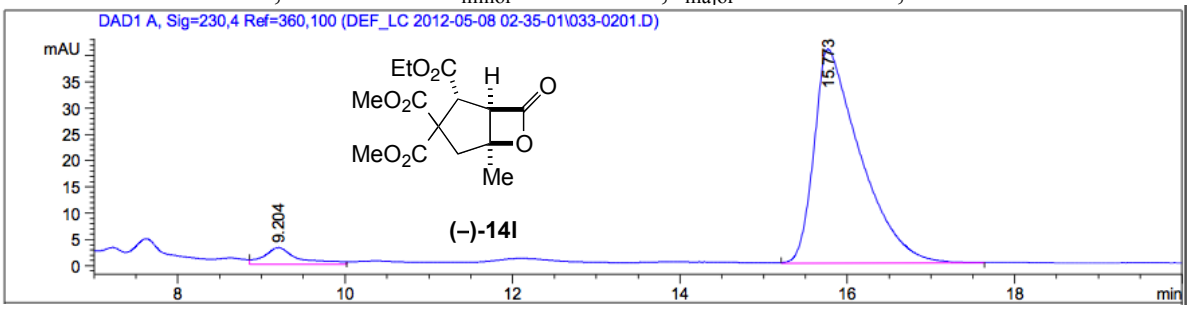


Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.150	VB	0.2819	1657.60339	88.73829	94.8448
2	16.235	BB	0.5305	90.09774	2.56041	5.1552
Totals :				1747.70113	91.29870	

Determination of enantiomeric excess of β-lactone (–) −14l derived from use of (*R*)-HBTM:

Chiral HPLC Analysis of β-lactone (–)-14l: Chiralcel AD-H column: hexanes:*i*PrOH = 88:12, flow rate 0.9 mL/min, λ = 230 nm: t_{minor} = 9.20 min, t_{major} = 15.77 min; 89% *ee*.

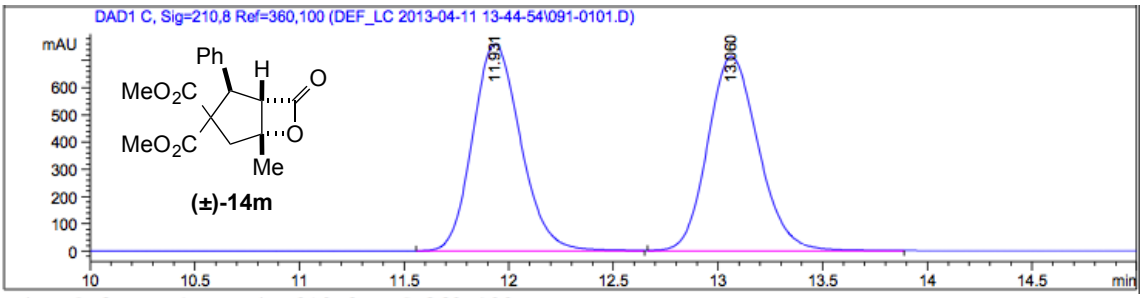


Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.204	VV	0.3967	90.00094	3.15648	5.4064
2	15.773	BB	0.5552	1574.70947	40.72122	94.5936
Totals :				1664.71041	43.87770	

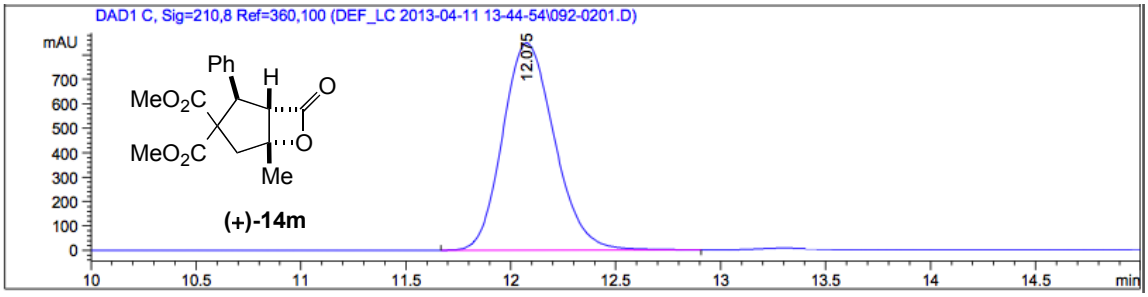
Determination of enantiomeric excess of β-lactone (+)-14m:

Chiral HPLC Analysis of (+)-β-lactone 14m: Chiralcel AD-H column: hexanes:*i*PrOH = 70:30, flow rate 0.5 mL/min, λ = 210 nm: t_{major} = 12.0 min, t_{minor} = 13.1 min; 99% *ee*.



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.931	BB	0.2474	1.20770e4	760.01733	50.0964
2	13.060	BB	0.2606	1.20305e4	713.89355	49.9036
Totals :				2.41075e4	1473.91089	

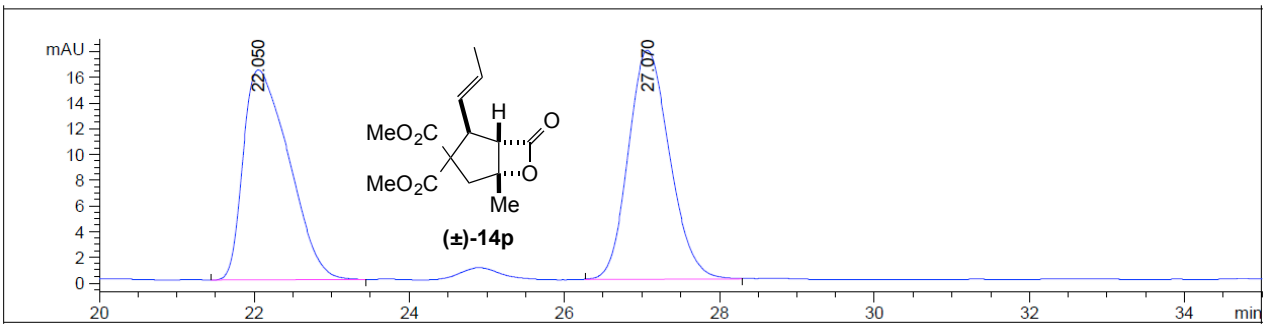


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.075	BB	0.2685	1.45686e4	847.91510	100.0000
Totals :				1.45686e4	847.91510	

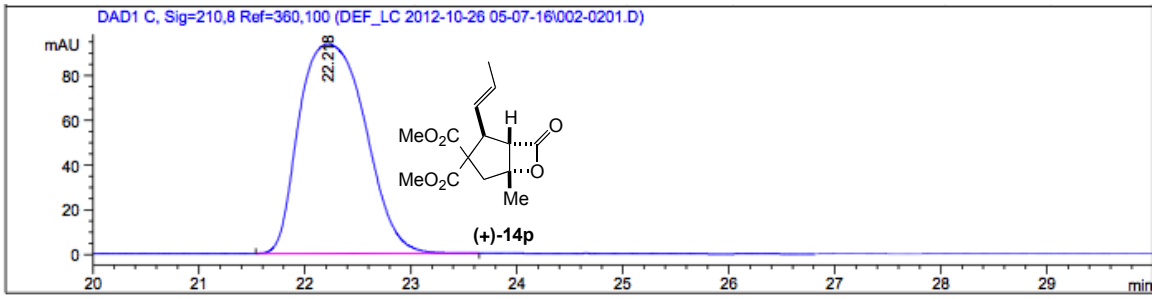
Determination of enantiomeric excess of β-lactone (+)-14p:

Chiral HPLC Analysis of β-lactone 14p: Chiralcel AD-H column: hexanes:*i*PrOH = 70:30, flow rate 0.5 mL/min, λ = 210 nm: t_{major} = 22.22 min, t_{minor} = 27.07 min; 99% *ee*.



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

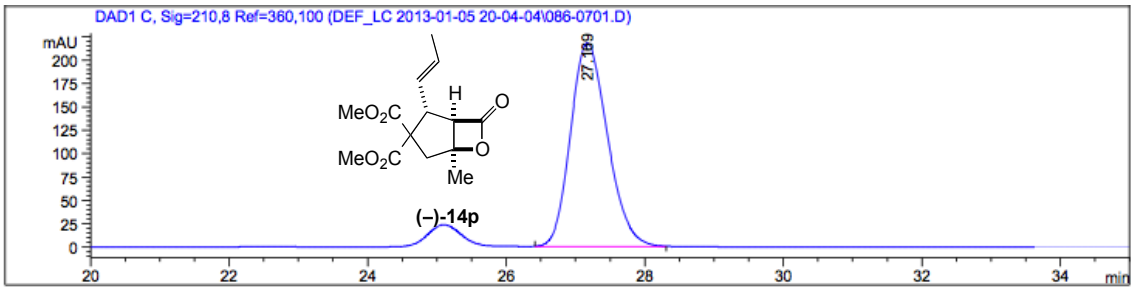
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.050	BB	0.6828	2204.23926	53.93431	50.5226
2	27.070	BB	0.5737	2158.63965	58.60735	49.4774
Totals :				4362.87891	112.54166	



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.218	BB	0.7221	4071.58838	93.48624	100.0000
Totals :				4071.58838	93.48624	

Chiral HPLC Analysis of β-lactone (−) −14p derived from use of (*R*)-HBTM: Chiralcel AD-H column: hexanes:*i*PrOH = 70:30, flow rate 0.5 mL/min, λ = 210 nm: t_{minor} = 22.2 min, t_{major} = 27.2 min; 99% *ee*.

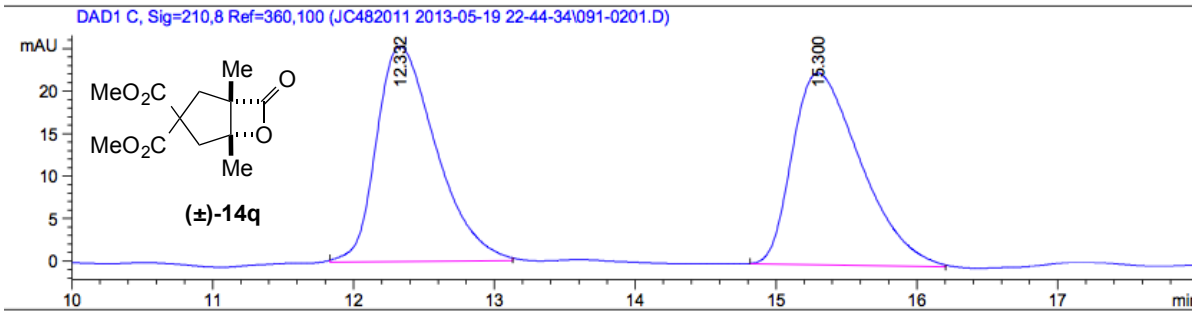


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.169	BB	0.5773	8080.22998	217.58018	100.0000
Totals :				8080.22998	217.58018	

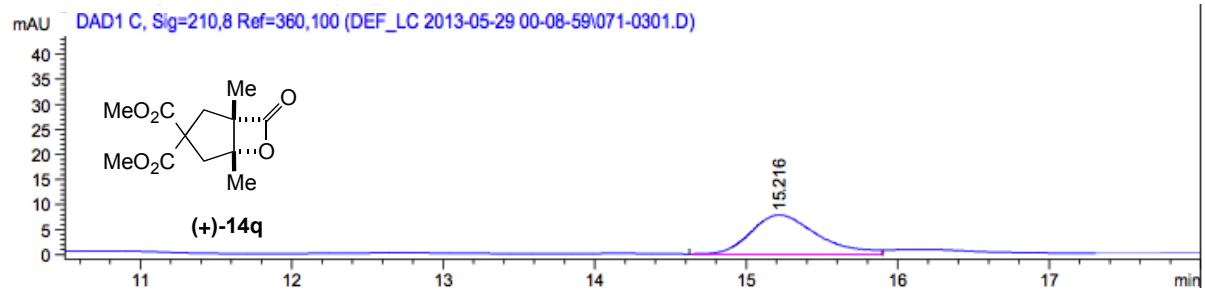
Determination of enantiomeric excess of β-lactone (+)-14q:

Chiral HPLC Analysis of β-lactone (+)-14q: Chiralcel OD-H column: hexanes:*i*PrOH = 92:08, flow rate 1.0 mL/min, λ = 210 nm: t_{minor} = 12.33 min, t_{major} = 15.22 min; 99% *ee*.



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.332	BB	0.4513	745.72705	25.34275	49.4180
2	15.300	BB	0.5243	763.29059	22.58295	50.5820
Totals :				1509.01764	47.92570	

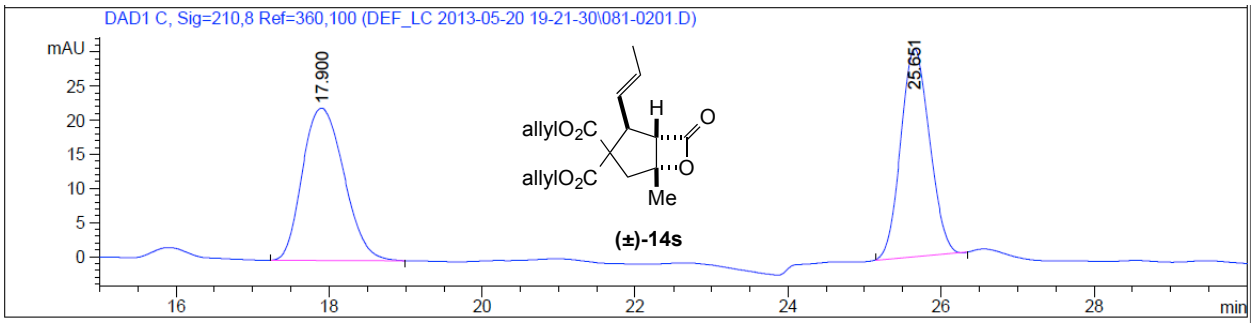


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.214	BB	0.4135	218.03964	7.91135	100.0000
Totals :				218.03964	7.91135	

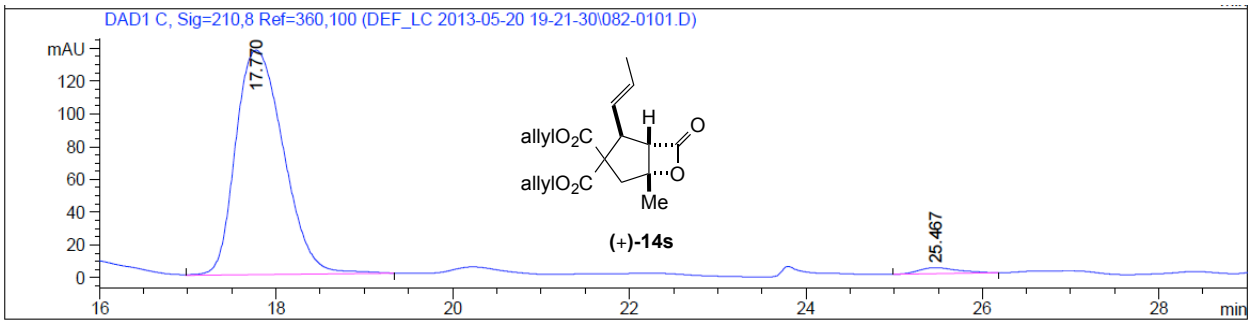
Determination of enantiomeric excess of β-lactone (+)-14s:

Chiral HPLC Analysis of β-lactone (+)-14s: Chiralcel AD-H column: hexanes:*i*PrOH = 95:05, flow rate 0.5 mL/min, λ = 210 nm: t_{major} = 17.7 min, t_{minor} = 25.5 min; 94% *ee*.



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.900	BB	0.6046	842.74713	22.31680	51.3632
2	25.651	BB	0.4075	798.01489	30.47148	48.6368
Totals :				1640.76202	52.78828	

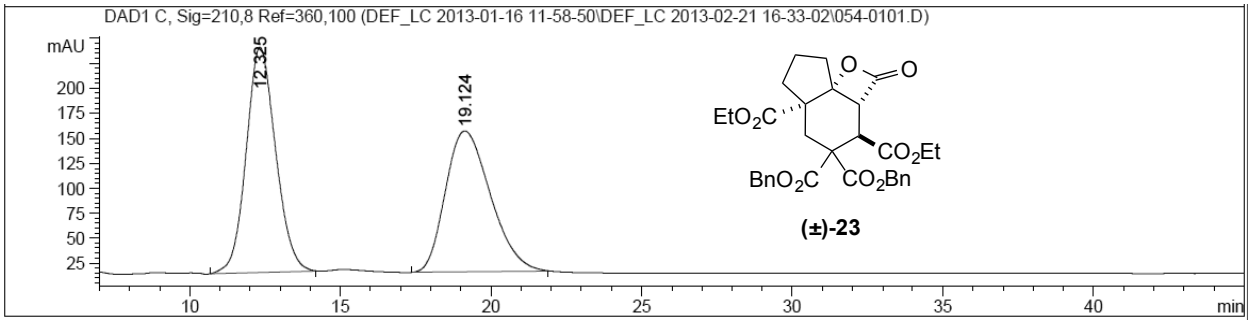


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.770	VB	0.6057	5172.05908	137.21623	97.8567
2	25.467	BB	0.4594	113.28335	3.65705	2.1433
Totals :				5285.34243	140.87328	

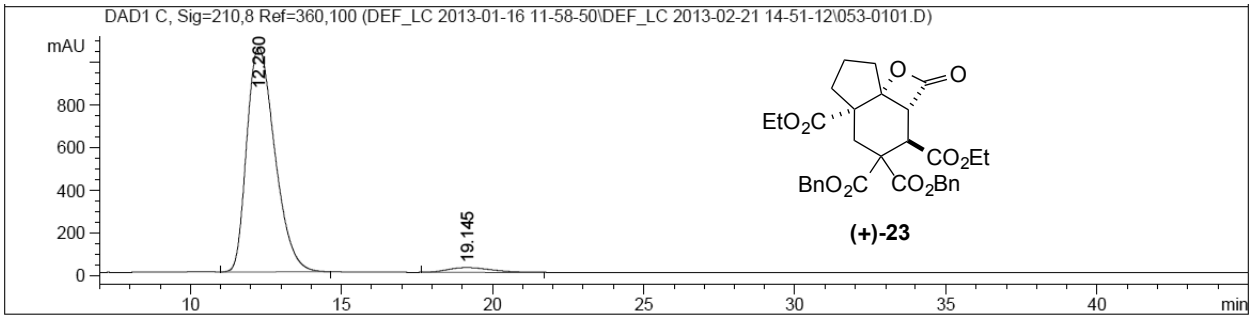
Determination of enantiomeric excess of β-lactone (+)-23:

Chiral HPLC Analysis of β-lactone(+)-23: Chiracel AS-H column: hexanes:*i*PrOH = 90:10, flow rate 1.0 mL/min, λ = 210 nm: t_{major} = 12.26 min, t_{minor} = 19.15 min; 93% *ee*.



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.325	BB	1.0386	1.53574e4	225.48831	51.1229
2	19.124	BB	1.5974	1.46827e4	141.17160	48.8771



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.260	VB	1.0057	6.78546e4	1053.12708	96.7046
2	19.145	BB	1.4121	2312.24585	22.55283	3.2954

Figure S3. Single crystal X-ray structure (ORTEP) of amide (+)-**S16**. The crystals were grown from a concentrated solution of amide (+)-**S16** in $CDCl_3$, using a slow evaporation method (probability ellipsoids are shown at the 50% level). X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under accession code CCDC 927699.

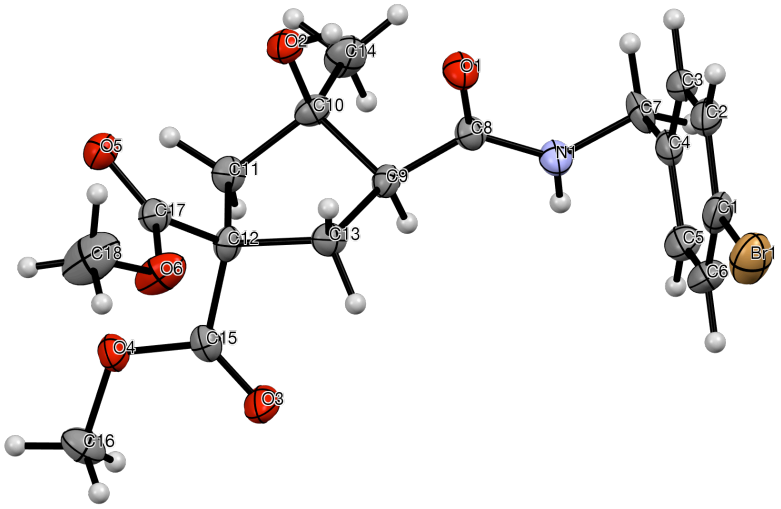


Table 1.Crystal data and structure refinement for DRB_MS_121026_A1_306.

Identification code	drb	
Empirical formula	C18 H22 Br N O6	
Formula weight	428.28	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 25.835(5) Å	a= 90°.
	b = 10.3517(19) Å	b= 102.657(2)°.
	c = 7.2252(13) Å	g = 90°.
Volume	1885.3(6) $Å^3$	
Z	4	
Density (calculated)	1.509 Mg/m^3	
Absorption coefficient	2.214 mm^{-1}	
F(000)	880	
Crystal size	0.14 x 0.09 x 0.02 mm^3	
Theta range for data collection	2.13 to 24.99°.	
Index ranges	-30<=h<=30, -12<=k<=12, -8<=l<=8	
Reflections collected	8634	
Independent reflections	3250 [R(int) = 0.0389]	
Completeness to theta = 24.99°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9571 and 0.7469	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	3250 / 1 / 239
Goodness-of-fit on F^2	1.043
Final R indices [I>2sigma(I)]	R1 = 0.0332, wR2 = 0.0734
R indices (all data)	R1 = 0.0412, wR2 = 0.0760
Absolute structure parameter	0.024(8)
Largest diff. peak and hole	0.338 and -0.217 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for DRB_MS_121026_A1_306. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	685(1)	-33(1)	9099(1)	48(1)
O(1)	713(1)	5887(2)	4818(3)	29(1)
O(2)	1086(1)	7405(2)	2361(3)	27(1)
O(3)	2953(1)	7004(3)	6603(3)	44(1)
O(4)	3083(1)	7706(2)	3812(3)	28(1)
O(5)	2044(1)	6847(2)	442(3)	27(1)
O(6)	2447(1)	5245(2)	2257(3)	40(1)
N(1)	956(1)	6502(3)	7883(4)	26(1)
C(1)	619(1)	1805(4)	8885(5)	33(1)
C(2)	183(1)	2324(3)	7673(5)	30(1)
C(3)	142(1)	3657(3)	7526(4)	27(1)
C(4)	531(1)	4459(4)	8572(5)	26(1)
C(5)	956(1)	3896(4)	9789(5)	34(1)
C(6)	1008(2)	2576(4)	9959(5)	36(1)
C(7)	489(1)	5917(4)	8371(6)	29(1)
C(8)	1032(1)	6437(3)	6107(4)	23(1)
C(9)	1515(1)	7101(3)	5697(5)	21(1)
C(10)	1376(1)	8053(3)	4015(4)	24(1)
C(11)	1923(1)	8349(3)	3638(5)	24(1)
C(12)	2217(1)	7037(3)	3886(4)	21(1)
C(13)	1908(1)	6180(3)	5063(5)	24(1)
C(14)	1079(2)	9251(3)	4446(5)	37(1)
C(15)	2787(1)	7219(3)	4968(5)	24(1)
C(16)	3644(1)	7911(4)	4675(6)	34(1)
C(17)	2219(1)	6402(3)	1974(5)	25(1)
C(18)	2506(2)	4556(4)	551(5)	58(1)

Figure S4. Single crystal X-ray structure (ORTEP) of bicyclic-β-lactone (±)-**14k**. The crystals were grown from a concentrated solution of β-lactone (±)-**14k** in diethyl ether, using a slow evaporation method (probability ellipsoids are shown at the 50% level). X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under accession code CCDC 940574.

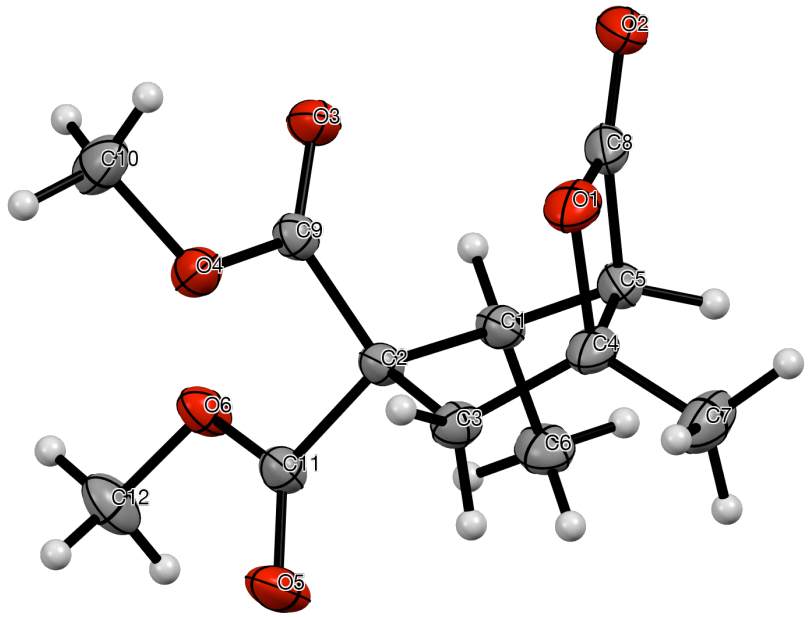


Table 1. Crystal data and structure refinement for DRB_GL_120307_A3_40_2.

Identification code	drb	
Empirical formula	C12 H16 O6	
Formula weight	256.25	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.891(4) Å	a= 102.611(7)°.
	b = 9.592(6) Å	b= 90.215(7)°.
	c = 10.273(7) Å	g = 106.979(7)°.
Volume	632.1(7) $Å^3$	
Z	2	
Density (calculated)	1.346 Mg/m^3	
Absorption coefficient	0.109 mm^{-1}	
F(000)	272	
Crystal size	0.58 x 0.35 x 0.13 mm^3	
Theta range for data collection	2.69 to 27.50°.	
Index ranges	-8<=h<=8, -12<=k<=12, -13<=l<=13	
Reflections collected	7210	
Independent reflections	2858 [R(int) = 0.0265]	
Completeness to theta = 27.50°	98.6 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9860 and 0.9397
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2858 / 0 / 167
Goodness-of-fit on F^2	1.060
Final R indices [I>2sigma(I)]	R1 = 0.0371, wR2 = 0.0938
R indices (all data)	R1 = 0.0436, wR2 = 0.0978
Largest diff. peak and hole	0.289 and -0.209 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for DRB_GL_120307_A3_40_2. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	9081(2)	986(1)	6833(1)	23(1)
C(2)	9825(2)	2678(1)	6776(1)	20(1)
C(3)	8776(2)	3456(1)	7913(1)	24(1)
C(4)	8610(2)	2586(2)	8994(1)	28(1)
C(5)	8844(2)	1042(1)	8333(1)	27(1)
C(6)	7033(2)	147(1)	6050(1)	31(1)
C(7)	6997(2)	2708(2)	9949(1)	41(1)
C(8)	10784(2)	1557(2)	9241(1)	31(1)
C(9)	12149(2)	3297(1)	6973(1)	22(1)
C(10)	14893(2)	5476(2)	7018(2)	36(1)
C(11)	9186(2)	2891(1)	5420(1)	24(1)
C(12)	9766(2)	2488(2)	3125(1)	35(1)
O(1)	10653(1)	2965(1)	9760(1)	33(1)
O(2)	12054(1)	1044(1)	9540(1)	42(1)
O(3)	13292(1)	2600(1)	7126(1)	29(1)
O(4)	12726(1)	4745(1)	6936(1)	28(1)
O(5)	7849(2)	3398(1)	5223(1)	39(1)
O(6)	10308(1)	2399(1)	4465(1)	27(1)

Figure S5. Single crystal X-ray structure (ORTEP) of bicyclic-β-lactone (±)-**14m**. The crystals were grown from a concentrated solution of β-lactone (±)-**14m** in diethyl ether, using a slow evaporation method (probability ellipsoids are shown at the 50% level). X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under accession code CCDC 940572.

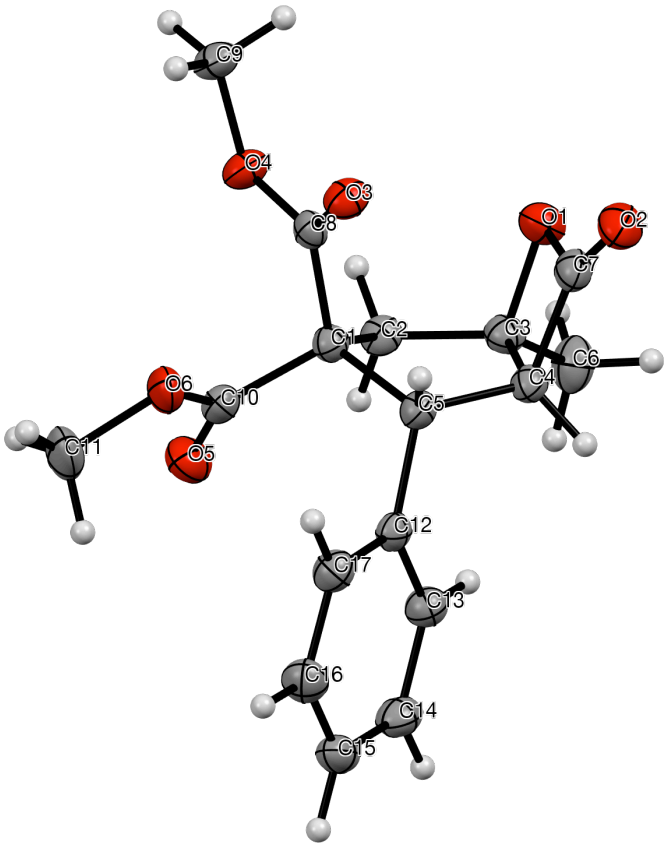


Table 1. Crystal data and structure refinement for DRB_GL_120307_A3_40_3.

Identification code	drb	
Empirical formula	C17 H18 O6	
Formula weight	318.31	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 9.695(2) Å	a= 90°.
	b = 13.257(3) Å	b= 106.298(3)°.
	c = 12.556(3) Å	g = 90°.
Volume	1549.0(6) $Å^3$	
Z	4	
Density (calculated)	1.365 Mg/m^3	
Absorption coefficient	0.104 mm^{-1}	
F(000)	672	

Crystal size	0.45 x 0.15 x 0.10 mm^3
Theta range for data collection	2.67 to 24.19°.
Index ranges	-11<=h<=11, -9<=k<=15, -11<=l<=14
Reflections collected	6067
Independent reflections	2469 [R(int) = 0.0174]
Completeness to theta = 24.19°	99.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9897 and 0.9548
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2469 / 0 / 211
Goodness-of-fit on F^2	1.032
Final R indices [I>2sigma(I)]	R1 = 0.0323, wR2 = 0.0810
R indices (all data)	R1 = 0.0382, wR2 = 0.0870
Largest diff. peak and hole	0.225 and -0.201 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DRB_GL_120307_A3_40_3. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8317(2)	6000(1)	1963(1)	22(1)
C(2)	7746(2)	5370(1)	899(1)	25(1)
C(3)	7040(2)	6103(1)	-9(1)	25(1)
C(4)	7651(2)	7158(1)	368(1)	23(1)
C(5)	8688(2)	7067(1)	1549(1)	22(1)
C(6)	6834(2)	5747(1)	-1180(1)	36(1)
C(7)	6131(2)	7410(1)	352(1)	26(1)
C(8)	7202(2)	6112(1)	2609(1)	21(1)
C(9)	5758(2)	5217(1)	3522(1)	30(1)
C(10)	9652(2)	5513(1)	2733(1)	26(1)
C(11)	11293(2)	5597(2)	4519(2)	45(1)
C(12)	10252(2)	7175(1)	1583(1)	22(1)
C(13)	10799(2)	6845(1)	730(1)	27(1)
C(14)	12243(2)	6939(1)	821(1)	31(1)
C(15)	13172(2)	7352(1)	1762(1)	31(1)
C(16)	12644(2)	7685(1)	2614(1)	32(1)
C(17)	11195(2)	7608(1)	2519(1)	28(1)
O(1)	5614(1)	6452(1)	122(1)	31(1)
O(2)	5465(1)	8138(1)	474(1)	35(1)
O(3)	6774(1)	6901(1)	2872(1)	28(1)
O(4)	6777(1)	5208(1)	2863(1)	28(1)
O(5)	10359(1)	4868(1)	2469(1)	37(1)
O(6)	9958(1)	5929(1)	3748(1)	32(1)

Figure S6. Single crystal X-ray structure (ORTEP) of bicyclic-β-lactone (+)-**14p**. The crystals were grown from a concentrated solution of amide β-lactone (+)-**14p** in $CDCl_3$, using a slow evaporation method (probability ellipsoids are shown at the 50% level). X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under accession code CCDC 927698.

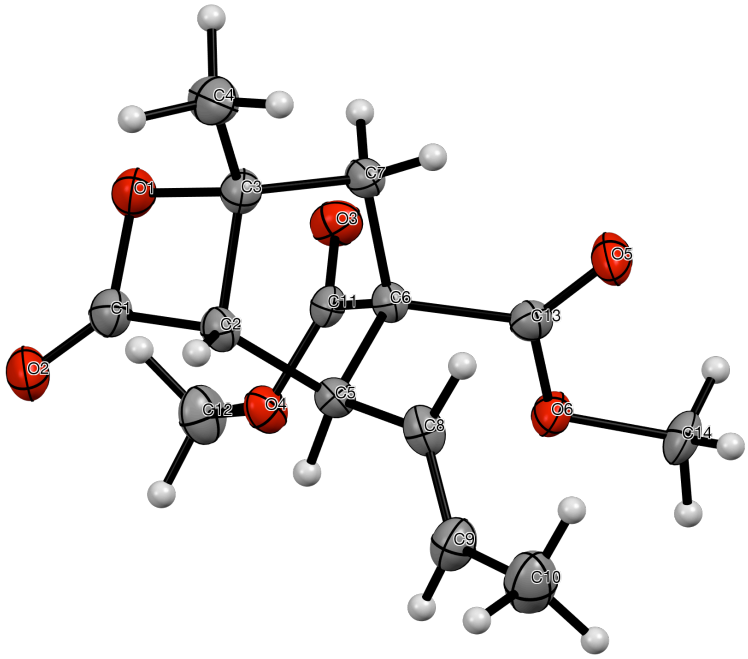


Table 1. Crystal data and structure refinement for DRB_MS_121001_G_290A.

Identification code	drb	
Empirical formula	C14 H18 O6	
Formula weight	282.28	
Temperature	110(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.9133(3) Å	α= 90°.
	b = 12.1780(5) Å	β= 90°.
	c = 12.9803(5) Å	γ = 90°.
Volume	1408.96(9) $Å^3$	
Z	4	
Density (calculated)	1.331 Mg/m^3	
Absorption coefficient	0.878 mm^{-1}	
F(000)	600	
Crystal size	0.22 x 0.09 x 0.02 mm^3	
Theta range for data collection	4.98 to 60.00°.	
Index ranges	-10<=h<=10, -13<=k<=12, -14<=l<=14	
Reflections collected	28220	
Independent reflections	2069 [R(int) = 0.0521]	

Completeness to theta = 60.00°	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9826 and 0.8302
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2069 / 0 / 185
Goodness-of-fit on F^2	1.082
Final R indices [I>2sigma(I)]	R1 = 0.0309, wR2 = 0.0823
R indices (all data)	R1 = 0.0335, wR2 = 0.0833
Absolute structure parameter [Hooft]	-0.2(2) [-0.17(8)]
Largest diff. peak and hole	0.354 and -0.198 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for DRB_MS_121001_G_290A. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	9124(2)	-236(2)	3096(2)	28(1)
C(2)	9367(2)	773(2)	2425(2)	22(1)
C(3)	10333(2)	1184(2)	3330(2)	24(1)
C(4)	12006(3)	1254(2)	3248(2)	34(1)
C(5)	7993(2)	1542(2)	2327(1)	21(1)
C(6)	7898(2)	2068(1)	3429(1)	20(1)
C(7)	9541(2)	2173(2)	3776(2)	22(1)
C(8)	8260(2)	2364(2)	1486(2)	25(1)
C(9)	7444(3)	2434(2)	634(2)	31(1)
C(10)	7747(3)	3153(2)	-266(2)	44(1)
C(11)	7020(2)	1369(2)	4210(2)	21(1)
C(12)	5329(3)	-75(2)	4489(2)	32(1)
C(13)	7142(2)	3197(2)	3406(1)	22(1)
C(14)	4819(2)	4115(2)	3334(2)	28(1)
O(1)	9897(2)	159(1)	3923(1)	30(1)
O(2)	8513(2)	-1106(1)	3034(1)	34(1)
O(3)	7127(2)	1509(1)	5125(1)	28(1)
O(4)	6140(2)	622(1)	3771(1)	24(1)
O(5)	7794(2)	4054(1)	3458(1)	33(1)
O(6)	5661(1)	3095(1)	3329(1)	25(1)

Figure S7. Single crystal X-ray structure (ORTEP) of bicyclic-β-lactone (±)-**14q**. The crystals were grown from a concentrated solution of β-lactone (±)-**14q** in diethyl ether, using a slow evaporation method (probability ellipsoids are shown at the 50% level). X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under accession code CCDC 940574.

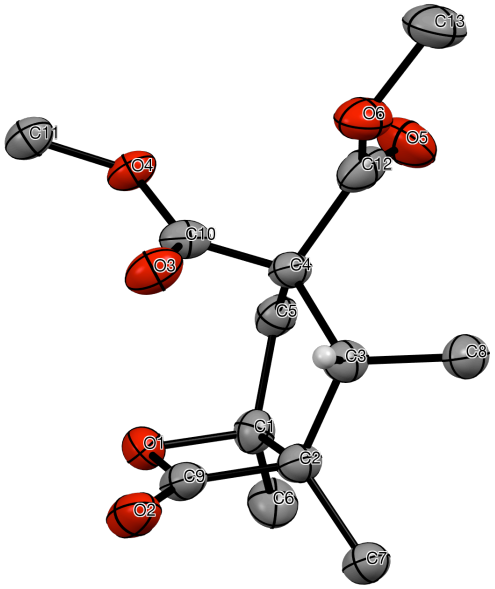


Table 1. Crystal data and structure refinement for DRB_GL_120405_G_53_3.

Identification code	drb	
Empirical formula	C13 H18 O6	
Formula weight	270.27	
Temperature	110(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 6.8942(16) Å	a= 90°.
	b = 8.0356(18) Å	b= 90.741(11)°.
	c = 23.889(5) Å	g = 90°.
Volume	1323.3(5) $Å^3$	
Z	4	
Density (calculated)	1.357 Mg/m^3	
Absorption coefficient	0.908 mm^{-1}	
F(000)	576	
Crystal size	0.07 x 0.05 x 0.05 mm^3	
Theta range for data collection	3.70 to 59.98°.	
Index ranges	-7<=h<=7, -9<=k<=9, -26<=l<=26	
Reflections collected	15678	
Independent reflections	1921 [R(int) = 0.0490]	
Completeness to theta = 59.98°	98.5 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.9560 and 0.9392
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1921 / 0 / 178
Goodness-of-fit on F^2	1.103
Final R indices [I>2sigma(I)]	R1 = 0.0776, wR2 = 0.2129
R indices (all data)	R1 = 0.0901, wR2 = 0.2188
Extinction coefficient	0.0086(16)
Largest diff. peak and hole	0.618 and -0.262 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for DRB_GL_120405_G_53_3. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	-2923(6)	4934(6)	3149(2)	30(1)
C(2)	-2111(6)	6288(5)	3553(2)	31(1)
C(3)	-1737(7)	5419(5)	4122(2)	33(1)
C(4)	-1626(6)	3528(5)	3969(2)	30(1)
C(5)	-3060(6)	3346(5)	3475(2)	30(1)
C(6)	-4600(7)	5348(6)	2758(2)	40(1)
C(7)	-3086(7)	7991(6)	3572(2)	38(1)
C(8)	-3320(8)	5783(6)	4541(2)	43(1)
C(9)	-370(6)	6253(5)	3172(2)	33(1)
C(10)	454(6)	3042(5)	3824(2)	31(1)
C(11)	2385(6)	891(6)	3455(2)	34(1)
C(12)	-2361(8)	2376(6)	4450(2)	41(1)
O(5)	-3851(6)	1678(5)	4454(2)	54(1)
O(6)	-1002(5)	2318(4)	4856(1)	48(1)
C(13)	-1655(9)	1330(7)	5337(2)	56(2)
O(1)	-1036(4)	5003(4)	2835(1)	34(1)
O(2)	1109(5)	7004(4)	3123(2)	47(1)
O(3)	1844(5)	3904(4)	3875(1)	41(1)
O(4)	499(4)	1479(3)	3624(1)	32(1)

Figure S8. Single crystal X-ray structure (ORTEP) of tricyclic-β-lactone (±)-**14t**. The crystals were grown from a concentrated solution of β-lactone (±)-**14t** in $CDCl_3$, using a slow evaporation method (probability ellipsoids are shown at the 50% level). X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under accession code CCDC 927698.

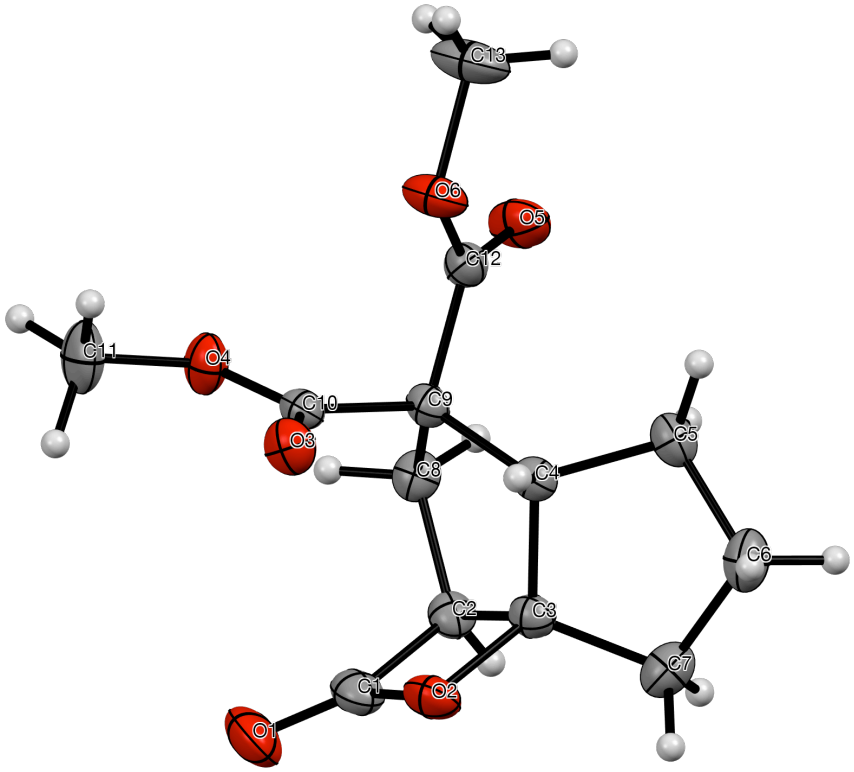


Table 1. Crystal data and structure refinement for DRB_MS_120913_A3_SS4BL.

Identification code	drb	
Empirical formula	C13 H16 O6	
Formula weight	268.26	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 7.7457(16) Å	a= 90°.
	b = 12.057(3) Å	b= 98.045(2)°.
	c = 14.063(3) Å	g = 90°.
Volume	1300.4(5) $Å^3$	
Z	4	
Density (calculated)	1.370 Mg/m^3	
Absorption coefficient	0.109 mm^{-1}	
F(000)	568	

Crystal size	0.18 x 0.17 x 0.11 mm^3
Theta range for data collection	2.23 to 27.49°.
Index ranges	-9<=h<=9, -15<=k<=15, -18<=l<=18
Reflections collected	13565
Independent reflections	2950 [R(int) = 0.0252]
Completeness to theta = 27.49°	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9881 and 0.9806
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2950 / 0 / 174
Goodness-of-fit on F^2	1.050
Final R indices [I>2sigma(I)]	R1 = 0.0360, wR2 = 0.0952
R indices (all data)	R1 = 0.0420, wR2 = 0.1003
Largest diff. peak and hole	0.329 and -0.174 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DRB_MS_120913_A3_SS4BL. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2877(2)	4445(1)	1736(1)	32(1)
C(2)	3301(2)	4346(1)	2819(1)	25(1)
C(3)	1821(2)	5195(1)	2823(1)	24(1)
C(4)	2657(1)	6276(1)	3221(1)	21(1)
C(5)	2043(2)	6336(1)	4208(1)	27(1)
C(6)	131(2)	5990(1)	3970(1)	32(1)
C(7)	210(2)	4989(1)	3305(1)	33(1)
C(8)	4981(2)	4892(1)	3286(1)	24(1)
C(9)	4642(1)	6153(1)	3192(1)	21(1)
C(10)	5127(2)	6620(1)	2250(1)	22(1)
C(11)	7411(2)	6797(1)	1318(1)	41(1)
C(12)	5673(2)	6792(1)	4024(1)	24(1)
C(13)	6744(2)	8558(1)	4535(1)	47(1)
O(1)	3415(2)	4100(1)	1042(1)	48(1)
O(2)	1518(1)	5163(1)	1754(1)	32(1)
O(3)	4187(1)	7150(1)	1671(1)	30(1)
O(4)	6772(1)	6359(1)	2161(1)	31(1)
O(5)	6208(1)	6396(1)	4790(1)	37(1)
O(6)	5840(1)	7850(1)	3791(1)	34(1)

Figure S9. Single crystal X-ray structure (ORTEP) of tricyclic-β-lactone (±)-**14v**. The crystals were grown from a concentrated solution of β-lactone (±)-**14v** in diethyl ether, using a slow evaporation method (probability ellipsoids are shown at the 50% level). X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under accession code CCDC 875803.

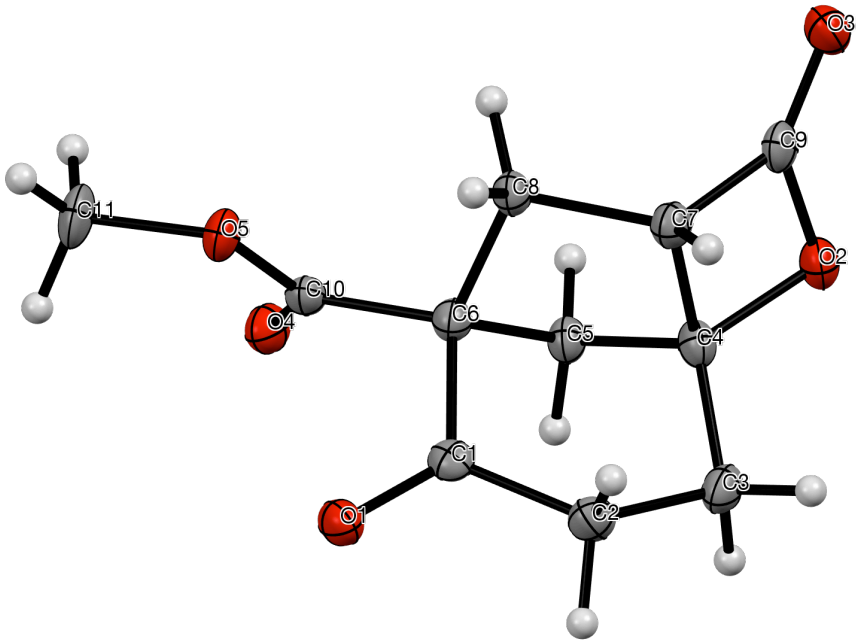


Table 1. Crystal data and structure refinement for DRB_GL_120305_G_5038.

Identification code	drb	
Empirical formula	C11 H12 O5	
Formula weight	224.21	
Temperature	110(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.1277(8) Å	a= 91.291(9)°.
	b = 7.5181(9) Å	b= 98.594(9)°.
	c = 10.9862(14) Å	g = 91.918(10)°.
Volume	499.96(11) $Å^3$	
Z	2	
Density (calculated)	1.489 Mg/m^3	
Absorption coefficient	1.007 mm^{-1}	
F(000)	236	
Crystal size	0.11 x 0.08 x 0.05 mm^3	
Theta range for data collection	4.07 to 60.00°.	
Index ranges	-6<=h<=6, -8<=k<=8, -12<=l<=12	
Reflections collected	11342	
Independent reflections	1450 [R(int) = 0.0623]	

Completeness to theta = 60.00°	97.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9514 and 0.8973
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1450 / 0 / 147
Goodness-of-fit on F^2	1.034
Final R indices [I>2sigma(I)]	R1 = 0.0340, wR2 = 0.0922
R indices (all data)	R1 = 0.0404, wR2 = 0.0943
Extinction coefficient	0.022(2)
Largest diff. peak and hole	0.191 and -0.205 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for DRB_GL_120305_G_5038. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	-176(3)	3959(2)	6390(2)	17(1)
C(2)	471(3)	2164(2)	5921(2)	21(1)
C(3)	2986(3)	1854(2)	6035(2)	21(1)
C(4)	3985(3)	2806(2)	7212(2)	18(1)
C(5)	3703(3)	4810(2)	7149(2)	18(1)
C(6)	1355(3)	4887(2)	7487(2)	17(1)
C(7)	3054(3)	2279(2)	8374(2)	18(1)
C(8)	1546(3)	3763(2)	8677(2)	17(1)
C(9)	5465(3)	2175(2)	8914(2)	19(1)
C(10)	580(3)	6740(2)	7652(2)	17(1)
C(11)	-2029(3)	8464(2)	8446(2)	27(1)
O(1)	-1821(2)	4669(2)	5906(1)	22(1)
O(2)	6235(2)	2332(2)	7806(1)	22(1)
O(3)	6573(2)	2012(2)	9896(1)	25(1)
O(4)	1328(2)	8054(2)	7227(1)	22(1)
O(5)	-1084(2)	6751(2)	8313(1)	20(1)

Figure S10. Single crystal X-ray structure (ORTEP) of bicyclic-β-lactone (±)-**14x**. The crystals were grown from a concentrated solution of β-lactone (±)-**14x** in $CDCl_3$, using a slow evaporation method (probability ellipsoids are shown at the 50% level). X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under accession code CCDC 940570.

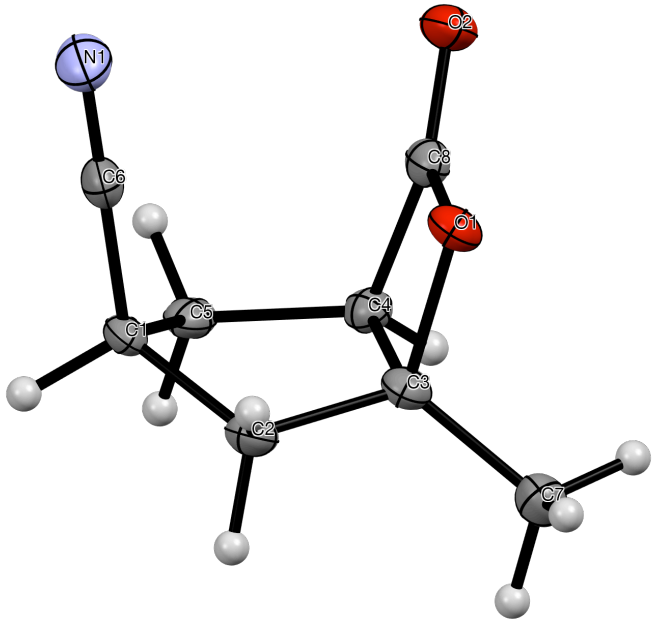


Table 1. Crystal data and structure refinement for DRB_MS_130218_G_RB1.

Identification code	drb	
Empirical formula	C8 H9 N O2	
Formula weight	151.16	
Temperature	110(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 5.6893(5) Å	a= 90°.
	b = 10.7024(11) Å	b= 95.454(6)°.
	c = 12.4002(12) Å	g = 90°.
Volume	751.62(12) $Å^3$	
Z	4	
Density (calculated)	1.336 Mg/m^3	
Absorption coefficient	0.802 mm^{-1}	
F(000)	320	
Crystal size	0.06 x 0.05 x 0.03 mm^3	
Theta range for data collection	5.47 to 60.00°.	
Index ranges	-6<=h<=6, 0<=k<=12, 0<=l<=13	
Reflections collected	1110	

Independent reflections	1110 [R(int) = 0.0000]
Completeness to theta = 60.00°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9764 and 0.9535
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1110 / 0 / 101
Goodness-of-fit on F^2	1.013
Final R indices [I>2sigma(I)]	R1 = 0.0460, wR2 = 0.1087
R indices (all data)	R1 = 0.0600, wR2 = 0.1126
Largest diff. peak and hole	0.226 and -0.279 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for DRB_MS_130218_G_RB1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	26(3)	3346(1)	3528(1)	20(1)
O(2)	-1888(3)	5167(2)	3834(1)	25(1)
N(1)	-2187(4)	4260(2)	910(2)	29(1)
C(1)	2299(4)	4353(2)	1607(2)	17(1)
C(2)	3130(4)	3186(2)	2264(2)	19(1)
C(3)	2655(4)	3448(2)	3422(2)	18(1)
C(4)	2415(4)	4876(2)	3522(2)	17(1)
C(5)	2834(4)	5426(2)	2420(2)	20(1)
C(6)	-227(4)	4286(2)	1214(2)	20(1)
C(7)	3996(4)	2697(2)	4296(2)	24(1)
C(8)	-138(4)	4594(2)	3664(2)	19(1)

Figure S11. Single crystal X-ray structure (ORTEP) of amide (–)-24. The crystals were grown from a concentrated solution of amide (–)-**24** in Et_2O/pentane (1:1 *v/v*, 0.5 mL), using a slow evaporation method (probability ellipsoids are shown at the 50% level). X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under accession code CCDC 927697.

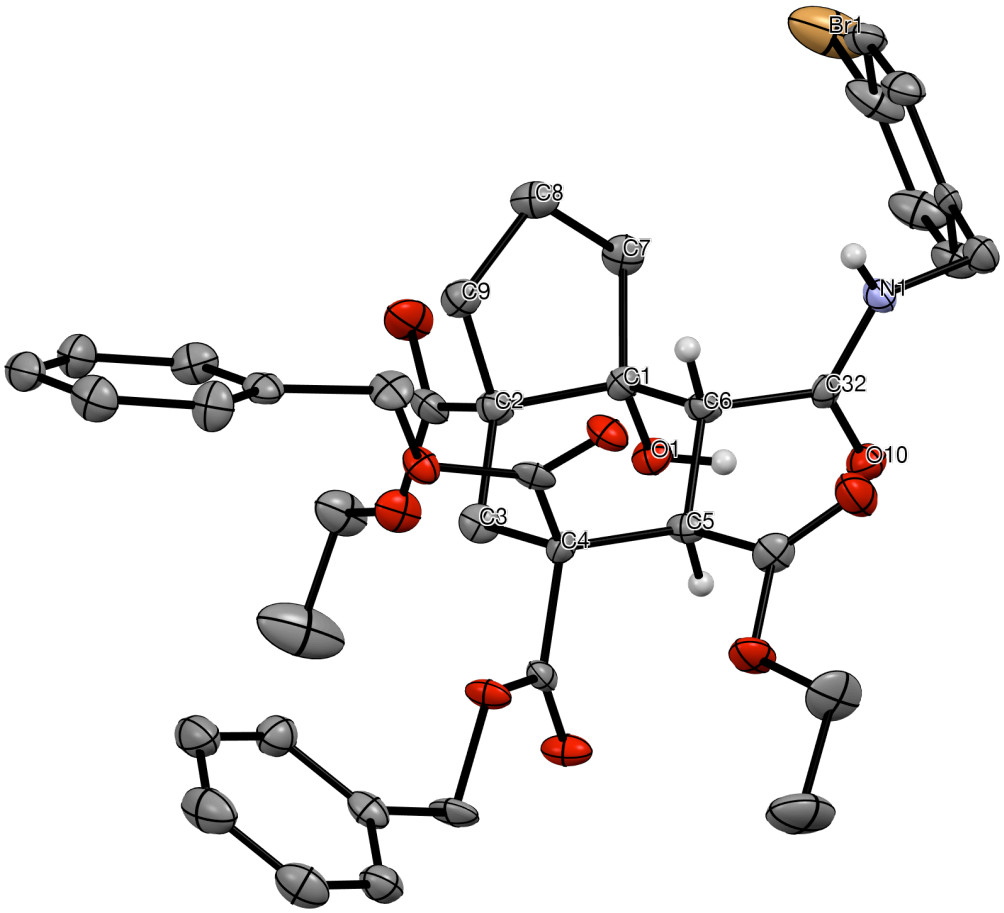


Table 1. Crystal data and structure refinement for DRB_KV_130207_G_94.

Identification code	drb	
Empirical formula	C39 H42 Br N O10	
Formula weight	764.65	
Temperature	110(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 8.0123(4) Å	α= 76.698(4)°.
	b = 9.5367(5) Å	β= 83.324(4)°.
	c = 12.5723(7) Å	γ = 77.616(4)°.
Volume	910.87(8) $Å^3$	
Z	1	
Density (calculated)	1.394 Mg/m^3	

Absorption coefficient	2.036 mm^{-1}
F(000)	398
Crystal size	0.36 x 0.06 x 0.04 mm^3
Theta range for data collection	3.62 to 59.99°.
Index ranges	-8<=h<=8, -10<=k<=10, -14<=l<=14
Reflections collected	10251
Independent reflections	4623 [R(int) = 0.0470]
Completeness to theta = 59.99°	94.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9230 and 0.5277
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4623 / 3 / 464
Goodness-of-fit on F^2	1.072
Final R indices [I>2sigma(I)]	R1 = 0.0401, wR2 = 0.0962
R indices (all data)	R1 = 0.0465, wR2 = 0.1031
Absolute structure parameter [Flack / Hooft]	[0.03(2) / 0.04(1)]
Extinction coefficient	0.0281(12)
Largest diff. peak and hole	0.342 and -0.611 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DRB_KV_130207_G_94. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	1413(4)	1827(3)	11000(2)	20(1)
O(2)	-138(4)	5371(4)	10656(3)	32(1)
O(3)	2720(4)	4695(3)	10515(3)	25(1)
O(4)	1481(4)	2017(3)	6731(2)	22(1)
O(5)	2309(4)	4176(3)	6591(2)	19(1)
O(6)	6103(3)	1405(3)	8573(2)	23(1)
O(7)	5556(3)	2419(3)	6822(2)	19(1)
O(8)	1823(4)	-1155(4)	8247(3)	31(1)
O(9)	4431(4)	-591(3)	7747(3)	27(1)
O(10)	1120(4)	-871(3)	10821(3)	22(1)
N(1)	-1298(5)	-441(4)	9920(3)	18(1)
C(1)	458(5)	2384(5)	10047(3)	18(1)
C(2)	1102(5)	3801(5)	9400(4)	19(1)
C(3)	2888(5)	3451(5)	8826(4)	18(1)
C(4)	3154(5)	2265(4)	8130(4)	16(1)
C(5)	2582(5)	874(5)	8823(3)	16(1)
C(6)	734(5)	1216(5)	9324(4)	18(1)
C(7)	-1458(6)	2946(5)	10309(4)	22(1)
C(8)	-2038(6)	4156(6)	9302(4)	28(1)
C(9)	-398(6)	4595(5)	8682(4)	22(1)

C(10)	1136(6)	4706(5)	10255(4)	24(1)
C(11)	2788(6)	5484(6)	11376(5)	33(1)
C(12)	4597(8)	5506(9)	11477(6)	64(2)
C(13)	2222(5)	2789(5)	7082(4)	17(1)
C(14)	1334(6)	4749(5)	5615(4)	22(1)
C(15)	1567(5)	6296(5)	5169(4)	20(1)
C(16)	1276(6)	7320(5)	5816(4)	25(1)
C(17)	1415(6)	8756(6)	5368(5)	29(1)
C(18)	1826(6)	9214(6)	4246(4)	27(1)
C(19)	2148(6)	8174(6)	3597(4)	29(1)
C(20)	2013(6)	6726(6)	4056(4)	27(1)
C(21)	5104(5)	1944(5)	7871(4)	16(1)
C(22)	7392(5)	2319(6)	6527(4)	24(1)
C(23)	7597(5)	3272(5)	5399(4)	21(1)
C(24)	6689(6)	4689(5)	5150(4)	25(1)
C(25)	6921(6)	5554(6)	4125(4)	34(1)
C(26)	8055(7)	5017(7)	3354(5)	39(2)
C(27)	8978(6)	3582(6)	3582(4)	32(1)
C(28)	8729(6)	2720(5)	4615(4)	26(1)
C(29)	2834(6)	-374(5)	8246(4)	21(1)
C(30)	4920(7)	-1819(6)	7213(5)	37(1)
C(31)	6754(6)	-1940(7)	6845(6)	48(2)
C(32)	203(5)	-153(5)	10070(4)	15(1)
C(33)	-2153(6)	-1436(5)	10754(4)	22(1)
Br(1)	-5455(1)	1769(1)	14453(1)	55(1)
C(34)	-2984(5)	-700(5)	11682(4)	18(1)
C(35)	-2182(6)	-935(6)	12653(4)	26(1)
C(36)	-2913(6)	-193(6)	13465(4)	32(1)
C(37)	-4435(6)	786(6)	13320(4)	34(1)
C(38)	-5253(6)	1058(5)	12357(4)	23(1)
C(39)	-4535(5)	302(5)	11565(4)	25(1)