# An Acid/Per-acid Catalytic Cycle for the Baeyer-Villiger Oxidation

## Supporting Information

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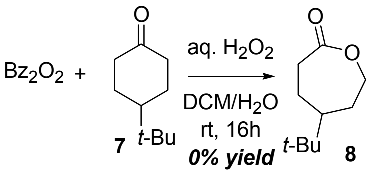
## **1.** General Experimental Procedures.

Proton NMR spectra were recorded on either Bruker 500 MHz or 400 MHz spectrometers. Proton chemical shifts are reported in ppm ($\delta$) relative to internal tetramethylsilane (TMS, $\delta$ 0.00 ppm) or residual $CHCl_3$ ($\delta$ 7.26 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), triplet (t), quartet (q), pentet (p) multiplet (m)], coupling constants [Hz], integration). Carbon NMR spectra were recorded on Bruker 500 MHz (125 MHz) or 400 MHz (100 MHz) spectrometers with complete proton decoupling. Carbon chemical shifts are reported in ppm with the respective solvent resonance as the internal standard ($CDCl_3$, $\delta$ 77.0 ppm). Unless otherwise noted, all NMR spectra were acquired at ambient temperature. Gas Chromatography was performed on a Hewlett-Packard 6890 GC system, equipped with chiral GC columns manufactured by Astec (B-DM and G-TA models). Infrared (IR) spectra were recorded on a Thermo Nicolet Avatar 210 spectrometer or a Thermo Nicolet Nexus 6700 FT-IR, $\upsilon_{max}$ ($cm^{-1}$) and are partially reported. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 Å F254 precoated plates (0.25 mm thickness). TLC $R_f$ values are reported. Visualization was accomplished by irradiation with a UV lamp and staining with $I_2$ on silica gel, or cerium ammonium molybdenate (CAM), or $KMnO_4$. Flash column chromatography was performed using Silica Gel 60 Å (32-63 micron) purchased from Silicycle, Quebec City, Canada. High resolution mass spectra were acquired in the Mass Spectrometry facility at the University of Illinois Urbana Champaign or at the Keck Center for Mass Spectroscopy at the School of Medicine at Yale University; the method of ionization is indicated in parentheses.

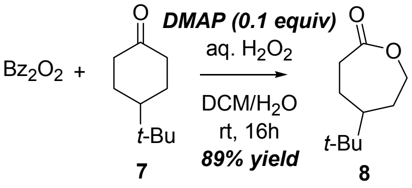
Reactions that required atmosphere and moisture control were carried out in a nitrogen atmosphere employing flame-dried glassware. Catalytic Baeyer-Villiger procedures were ***not*** performed under inert atmosphere. All solvents were dried using a Seca Solvent System® by Glass Contours. Chemicals were purchased from the commercial source indicated in the experimental procedures.

## **2.** Experimental Procedures.

### *Experiments in Endnote #7*

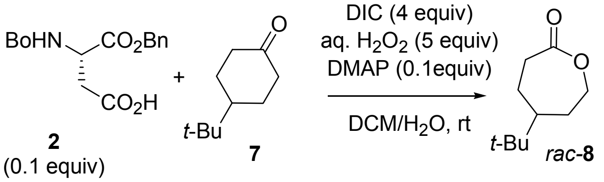


4-*t*-butyl cyclohexanone (Aldrich, 154.5 mg, 1.0 mmol, 1.0 equiv) and benzoyl peroxide (Aldrich, 484.4 mg, 2.0 mmol, 2.0 equiv) were dissolved in 2.0 mL of DCM (0.5 M). Then, aq. $H_2O_2$ (Aldrich, 0.57 mL of a 30% solution in $H_2O$ (~8.8 M), 5.0 mmol, 5.0 equiv) was added. The resulting biphasic mixture was stirred at rt for 16 h. Then, this was diluted with 50 mL $Et_2O$ and washed with 25 mL satd. aq. $Na_2SO_3$ and 25 mL satd. aq. $NaHCO_3$. The aqueous phase was then washed 1 X 30 mL $Et_2O$, the organic washes were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was dissolved in ~3 mL $CDCl_3$, and 87.3 μL of $CHBr_3$ (Aldrich, 1.0 mmol, 1.0 equiv) were added in to serve as an internal NMR standard ($CHBr_3$ displays a singlet at 6.82 ppm in $CDCl_3$). No signals corresponding to known lactone[1] **8** were detected in the crude NMR.



4-*t*-butyl cyclohexanone (Aldrich, 154.5 mg, 1.0 mmol, 1.0 equiv) and benzoyl peroxide (Aldrich, 484.4 mg, 2.0 mmol, 2.0 equiv) were dissolved in 2.0 mL of DCM (0.5 M). Then, aq. $H_2O_2$ (Aldrich, 0.57 mL of a 30% solution in $H_2O$ (~8.8 M), 5.0 mmol, 5.0 equiv) was added. The resulting biphasic mixture was stirred at rt for 16 h. Then, this was diluted with 50 mL $Et_2O$ and washed with 25 mL satd. aq. $Na_2SO_3$ and 25 mL satd. aq. $NaHCO_3$. The aqueous phase was then washed 1 X 30 mL $Et_2O$, the organic washes were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was dissolved in ~3 mL $CDCl_3$, and 87.3 μL of $CHBr_3$ (Aldrich, 1.0 mmol, 1.0 equiv) were added in to serve as an internal NMR. The yield of lactone was measured by comparing the relative ratio of the $CHBr_3$ signal at 6.82 ppm (1.00H) to that of one of the carboxylate protons of known[1] lactone **8** at 4.32 ppm (0.89H, ddd, *J* = 1.6, 5.7, 12.6) = 89% yield.

## *Experiments in Equation 1*



***Influence of rate of DIC addition on yield of lactone***

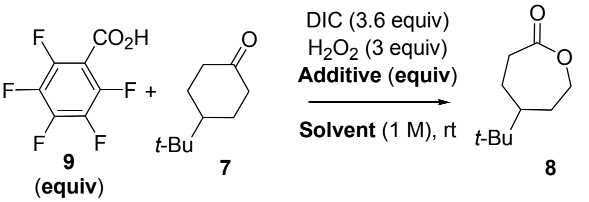
<u>*Two batch addition*</u>

4-*t*-butyl cyclohexanone (Aldrich, 154.5 mg, 1.0 mmol, 1.0 equiv), Boc-NH-Asp-$CO_2Bn$ (Nova Biochem, 32.3 mg, 0.1 mmol, 0.1 equiv) and DMAP (Aldrich, 12.2 mg, 0.1 mmol, 0.1 equiv) were dissolved in DCM (1 mL, 1 M); $H_2O_2$ (Aldrich, 0.28 mL of a 30% solution in $H_2O$ (~8.8 M), 2.5 mmol, 2.5 equiv) and DIC (Acros, 0.31 mL, 2.0 mmol, 2.0 equiv) were then added into the reaction flask. The resulting biphasic mixture was stirred at rt for 20 h. At this point, an aliquot from the reaction mixture was analyzed by GC and revealed the almost complete consumption of DIC (GC Assay conditions: BDM, 1.5 mL/min, 140 $^oC$ (12 min) then 5 $^oC$/min to 160 $^oC$); DIC elutes at 3.4 min, ketone **7** elutes at 10.2 min, and the two enantiomeric lactones **8** elute at 25.3 min and 26.2 min. Thus, 0.31 mL of DIC (2.0 mmol, 2.0 equiv) and 0.28 mL of $H_2O_2$ (2.5 mmol, 2.5 equiv) were added to the reaction mixture at this point. After 48 h, the reaction was diluted with 50 mL $Et_2O$ and washed sequentially with 50 mL satd. $Na_2SO_3$ and satd. $NaHCO_3$. The organic fraction was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was dissolved in ~3 mL $CDCl_3$, and 87.3 μL of $CHBr_3$ (Aldrich, 1.0 mmol, 1.0 equiv) were added in to serve as an internal NMR standard. The yield of lactone was measured by comparing the relative ratio of the $CHBr_3$ signal at 6.82 ppm (1.00H) to that of one of the carboxylate protons of known[1] lactone **8** at 4.33 ppm (0.13H, ddd, $J$ = 1.6, 6.0, 12.9): 13% yield.

*0.13 DIC equiv/h addition*

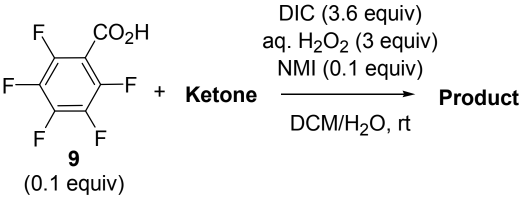
4-*t*-butyl cyclohexanone (Aldrich, 154.5 mg, 1.0 mmol, 1.0 equiv), Boc-NH-Asp-$CO_2Bn$ (Nova Biochem, 32.3 mg, 0.1 mmol, 0.1 equiv) and DMAP (Aldrich, 12.2 mg, 0.1 mmol, 0.1 equiv) were dissolved in DCM (1 mL, 1 M); $H_2O_2$ (Aldrich, 0.56 mL of a 30% solution in $H_2O$ (~8.8 M), 5.0 mmol, 5.0 equiv) was added to the reaction flask. Then, DIC (Acros, 0.62 mL, 4.0 mmol, 4.0 equiv) was added slowly with a syringe pump (KDScientific) at a rate of 0.02 mL/h (0.125 DIC equiv/h) until a total of 0.62 mL had been added into the reaction flask. This takes 32 h, and at this point, the reaction was diluted with 75 mL $Et_2O$ and washed sequentially with 50 mL satd. $Na_2SO_3$ and satd. $NaHCO_3$. The organic fraction was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was dissolved in ~3 mL $CDCl_3$, and 87.3 μL of $CHBr_3$ (Aldrich, 1.0 mmol, 1.0 equiv) were added in to serve as an internal NMR standard. The yield of lactone was measured by comparing the relative ratio of the $CHBr_3$ signal at 6.82 ppm (1.00H) to that of one of the carboxylate protons of known[1] lactone **8** at 4.17 ppm (0.76H, dd, $J$ = 10.4, 12.9): 76% yield.

## *Experiments in Table 1*



4-*t*-butyl cyclohexanone (Aldrich, 154.5 mg, 1.0 mmol, 1.0 equiv), the corresponding amount of $PhF_5CO_2H$ (**9**) (Acros, FW = 212.32 g/mol), and the corresponding nucleophile (0.1 equiv) were dissolved in 1.0 mL of solvent. Then, the peroxide source (3.0 equiv) was added and DIC (Acros, 0.56 mL, 3.6 mmol, 3.6 equiv) was added slowly with a syringe pump (KDScientific) at a rate of 0.19 mL/h (1.2 DIC equiv/h) until a total of 0.56 mL had been added into the reaction flask. This takes 3 h; at this point, the reaction was diluted with 50 mL $Et_2O$ and washed sequentially with 50 mL satd. $Na_2SO_3$ and 50 mL satd. $NaHCO_3$. The organic fraction was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was dissolved in ~3 mL $CDCl_3$, and 87.3 μL of $CHBr_3$ (Aldrich, 1.0 mmol, 1.0 equiv) were added in to serve as an internal NMR standard. The yield of lactone was measured by comparing the relative ratio of the $CHBr_3$ signal at 6.82 ppm to that of one of the carboxylate protons of known[1] lactone **8** at 4.33 or 4.17 ppm.

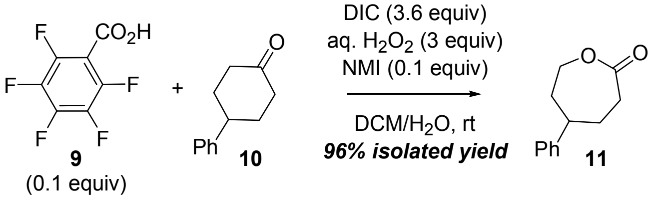
## *Experiments in Table 2*



***General procedures for Table 2***

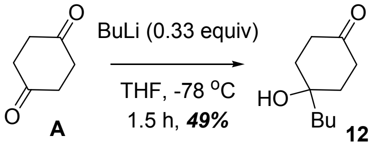
The corresponding ketone (1.0 mmol, 1.0 equiv), $PhF_5CO_2H$ (**9**) (Acros, 21.2 mg, 0.1 mmol, 0.1 equiv), and NMI (Aldrich, 8 μl, 0.1 mmol, 0.1 equiv) were dissolved in 1.0 mL of DCM (1 M). Then, $H_2O_2$ (Aldrich, 0.34 mL of a 30% solution in $H_2O$ (~8.8 M), 3.0 mmol, 3.0 equiv) was added and DIC (Acros, 0.56 mL, 3.6 mmol, 3.6 equiv) was added slowly with a syringe pump (KDScientific) at a rate of 0.19 mL/h (1.2 DIC equiv/h) until a total of 0.56 mL had been added into the reaction flask. This takes 3 h; at this point, the yield of lactone was determined by comparison to an internal NMR standard, or by isolation of the produced lactone by chromatography.

## ***Entry 1***

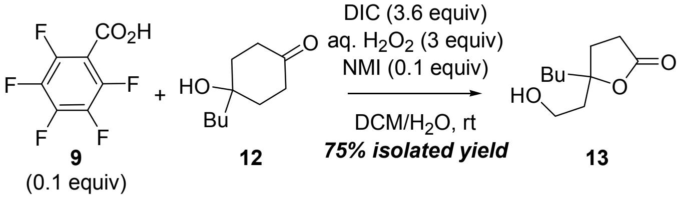


Experiment run as described above with commercially available ketone **10** (Aldrich, 174.2 mg, 1.0 mmole, 1.0 equiv). After 3 h, the crude mixture was concentrated to ~0.5 mL solvent and directly loaded on top of an $SiO_2$ column (2 X 18 cm, eluting with 9:1 hexanes:acetone); 183.2 mg of known lactone[2] **11** were obtained as a white powder (96% isolated yield).

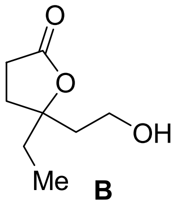
## ***Entry 2***



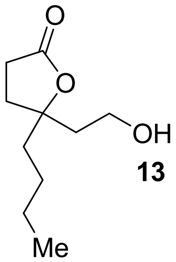
Diketone **A** (Aldrich, 3.36 g, 30 mmol, 3.0 equiv) was dissolved in THF (150 mL) in a flame dried round bottom flask and the resulting solution was cooled to -78 °C. BuLi (Aldrich, 6.2 mL of a 1.6 M solution in hexanes, 9.92 mmol, 1.0 equiv) was syringed in and the resulting solution stirred at -78 °C for 1.5 h before adding 100 mL satd. aq. $NH_4Cl$ to the cold solution. This mixture was then warmed to rt, the layers were separated, and the aqueous phase extracted 2 X 100 mL $Et_2O$. The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting yellow oil was purified by chromatography (3 X 21 cm, 9:1 hexanes:acetone) to yield 630 mg of ketone **12** as a light yellow oil. Ketone (**12**) Characterization data: **Rf**: 0.61, 6:4 hexanes:acetone. **MS**: (ES) Molecular ion calculated for $NaC_{10}H_{18}O_2^+$: 193.1199; found m/z = 193.1200, error = 0.5 ppm. **IR**: (neat, $cm^{-1}$) 3461, 2935, 1702. **$^1$H NMR**: (400 MHz, $CDCl_3$, ppm) δ 7.50 (2H, d, *J* = 7.9 Hz) 2.27-2.21 (2H, m) 2.00-1.93 (2H, m) 1.80 (2H, td, *J* = 13.4, 5.0 Hz) 1.67 (1H, br s) 1.59-1.54 (2H, m) 1.43-1.33 (4H, m) 0.93 (3H, t, *J* = 7.3 Hz). **$^{13}$C NMR**: (125 MHz, $CDCl_3$) δ 212.23, 70.30, 42.37, 37.04, 36.88, 25.61, 23.19, 14.05.



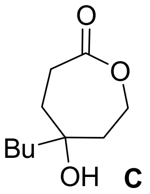
Experiment run as described in the general procedures with ketone **12** prepared as described above (174.2 mg, 1.0 mmol, 1.0 equiv). After 3 h, the crude mixture was concentrated to ~0.5 mL solvent and directly loaded on top of an $SiO_2$ column (2 X 18 cm, eluting with 8:2 hexanes:acetone); lactone **13** was obtained contaminated with a substantial amount of diisopropyl urea (DIU). To remove the urea, the mixture of **13** and DIU was washed 6 X 80 mL hexanes to extract lactone **13** (solubility of **13** in hexanes is about 30 mg/ 80 mL). The hexanes washes were combined and concentrated under reduced pressure to yield 140 mg of **13** as a clear colorless oil with observable but minimal DIU contamination (75% yield). Lactone (**13**) <u>Characterization data</u>: **Rf**: 0.26, 7:3 hexanes:acetone. **MS**: (ES) Molecular ion calculated for $NaC_{10}H_{18}O_3^+$: 209.1148; found m/z = 209.1146, error = 1 ppm. **IR**: (neat, $cm^{-1}$) 3413, 2922, 1772. **$^1$H NMR**: (500 MHz, $CDCl_3$, ppm) $\delta$ 3.84-3.73 (2H, m) 2.65-2.55 (2H, m) 2.20-1.93 (5H, m) 1.74-1.63 (2H, m) 1.37-1.26 (4H, m) 0.92 (3H, t, *J* = 6.9 Hz). **$^{13}$C NMR**: (125 MHz, $CDCl_3$) $\delta$ 176.96, 88.29, 58.20, 40.60, 38.67, 31.16, 28.85, 25.56, 22.83, 13.85. **GC Assay**: (BDM, 140 °C for 12 min, then ramp 5 °C/min to 160 °C, 1.5 mL/min) 42.1 min, 44.6 min. <u>Note</u>: we based our structural assignment of lactone **13** as a five-membered lactone and not a 7-membered lactone (as in **C**, see below) on the very similar $^{13}$C NMR of **13** and the known lactone[3] **B** (see below). It is specially telling that in **13** the signal at 88.29 ppm is far smaller in intensity than that at 58.20 ppm; this points to a carboxylate carbon (88.29 ppm) with less protons than the hydroxyl carbon (58.20 ppm), and this is exactly what would be expected for the 5-membered isomer **13**, and opposite of what would be expected for the 7-membered isomeric lactone **C**.



**B**

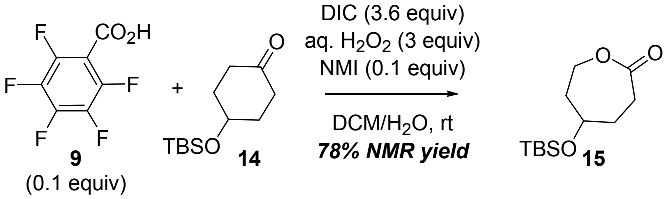


**13**



**C**

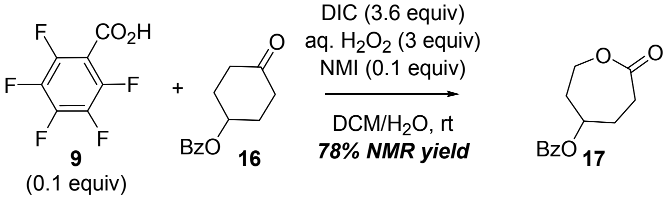
***<u>Entry 3</u>***



Experiment run as described above with known ketone[4] **14** (228.5 mg, 1.0 mmole, 1.0 equiv). This takes 3 h; at this point, the reaction was diluted with 40 mL $Et_2O$ and washed sequentially with 20 mL satd. $Na_2SO_3$ and 20 mL satd. $NaHCO_3$. The aqueous phase was washed 1 X 30 mL $Et_2O$. The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was dissolved in ~3 mL $CDCl_3$, and 87.3 µL of $CHBr_3$ (Aldrich, 1.0 mmol, 1.0 equiv) were added in to serve as an internal NMR standard. The yield of lactone was measured by comparing the relative ratio of the $CHBr_3$ signal at 6.82 ppm (1.00H) to that of one of the carboxylate protons of lactone **15** at 4.53 ppm (0.78H, dd, *J* = 12.9, 10.1 Hz) = 78% yield. Lactone (**15**) <u>Characterization data</u>: **Rf**: 0.38, 1:1 hexanes:$Et_2O$. **MS**: (ES) Molecular ion calculated for $C_{12}H_{24}O_3Si^+$: 245.1567; found m/z = 245.1568, error = 0.1 ppm. **IR**: (neat, $cm^{-1}$) 2950, 2931, 1738. **$^1$H NMR**: (500 MHz, $CDCl_3$, ppm) $\delta$ 4.51 (1H, dd, *J* = 12.6, 9.8 Hz) 4.07 (1H, br s) 3.98 (1H, ddd, *J* = 12.9, 5.7, 1.9 Hz) 3.05-2.99 (1H, m) 2.33

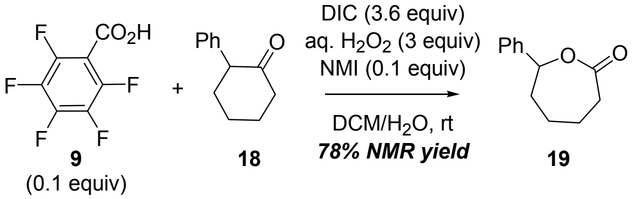
(1H, ddd, $J$ = 14.2, 5.7, 3.8 Hz) 1.90-1.75 (4H, m) 0.83 (9H, s) 0.00 (3H, s) -0.01 (3H, s). **$^{13}$C NMR**: (125 MHz, $CDCl_3$) δ 176.18, 66.65, 62.78, 37.21, 30.96, 27.30, 25.61, 17.86, -4.96, -4.99.

***Entry 4***



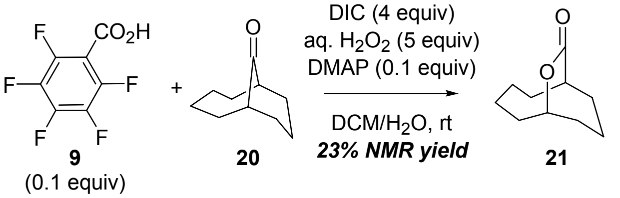
Experiment run as described above with known ketone[5] **16** (218.3 mg, 1.0 mmole, 1.0 equiv). This takes 3 h; at this point, the reaction was diluted with 40 mL $Et_2O$ and washed sequentially with 20 mL satd. $Na_2SO_3$ and 20 mL satd. $NaHCO_3$. The aqueous phase was washed 1 X 30 mL $Et_2O$. The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was dissolved in ~3 mL $CDCl_3$, and 87.3 μL of $CHBr_3$ (Aldrich, 1.0 mmol, 1.0 equiv) were added in to serve as an internal NMR standard. The yield of lactone was measured by comparing the relative ratio of the $CHBr_3$ signal at 6.82 ppm (1.00H) to that of one of the carboxylate protons of lactone **17** at 4.20-4.16 ppm (0.48H, m) = 48% yield. Lactone (**17**) Characterization data: **Rf**: 0.07, 1:1 hexanes:$Et_2O$. **MS**: (ES) Molecular ion calculated for $C_{13}H_{15}O_4^+$: 235.0965; found m/z = 235.0965, error = 0.2 ppm. **IR**: (neat, $cm^{-1}$) 2950, 2931, 1738. **$^{1}$H NMR**: (500 MHz, $CDCl_3$, ppm) δ 8.03 (2H, apparent d, $J$ = 7.2 Hz) 7.59 (1H, apparent t, $J$ = 7.2 Hz) 7.46 (2H, apparent t, $J$ = 7.2 Hz) 5.40-5.36 (1H, m) 4.57-4.52 (1H, m) 4.23-4.19 (1H, m) 3.04-2.99 (1H, m) 2.63-2.58 (1H, m) 2.25-2.07 (4H, m). **$^{13}$C NMR**: (125 MHz, $CDCl_3$) δ 174.85, 165.23, 133.27, 129.82, 129.45, 128.44, 70.41, 63.49, 34.47, 28.47, 27.59.

***Entry 5***



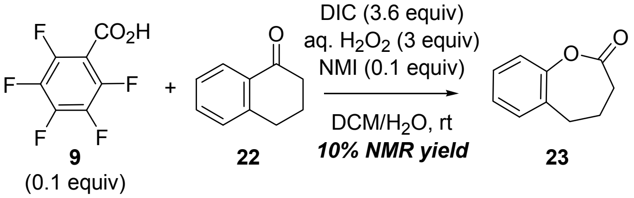
Experiment run as described above with commercially available ketone **18** (Aldrich, 174.2 mg, 1.0 mmole, 1.0 equiv). This takes 3 h; at this point, the reaction was diluted with 40 mL $Et_2O$ and washed sequentially with 20 mL satd. $Na_2SO_3$ and 20 mL satd. $NaHCO_3$. The aqueous phase was washed 1 X 30 mL $Et_2O$. The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was dissolved in ~3 mL $CDCl_3$, and 87.3 μL of $CHBr_3$ (Aldrich, 1.0 mmol, 1.0 equiv) were added in to serve as an internal NMR standard. The yield of lactone was measured by comparing the relative ratio of the $CHBr_3$ signal at 6.82 ppm (1.00H) to that of the carboxylate proton of known lactone[6] **19** at 5.30 ppm (0.78H, d, $J$ = 9.6 Hz) = 78% yield.

***Entry 6***



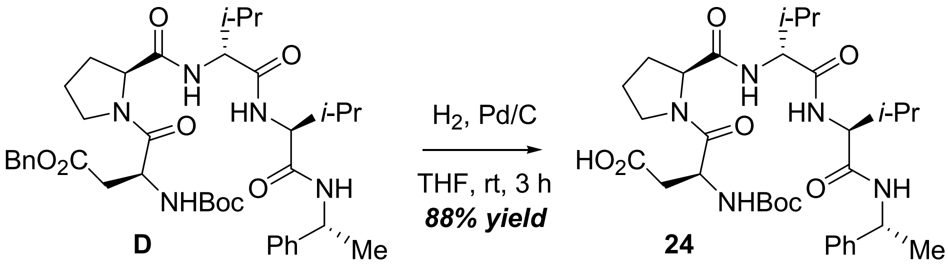
Known ketone[7] **20** (152.2 mg, 1.0 mmol, 1.0 equiv), catalyst **9** (Acros, 21.2 mg, 0.1 mmol, 0.1 equiv) and DMAP (Aldrich, 12.2 mg, 0.1 mmol, 0.1 equiv) were dissolved in 1 mL DCM (1 M). Aq. $H_2O_2$ (Aldrich, 0.56 mL of a 30% solution in $H_2O$ (~8.8 M), 5.0 mmol, 5.0 equiv) was added and DIC (Acros, 0. 62 mL, 4.0 mmol, 4.0 equiv) was added slowly with a syringe pump (KDScientific) at a rate of 0.08 mL/h (0.5 DIC equiv/h) until a total of 0.62 mL had been added into the reaction flask. This takes 8 h; at this point, the reaction was diluted with 75 mL $Et_2O$ and washed sequentially with 50 mL satd. $Na_2SO_3$ and 50 mL satd. $NaHCO_3$. The organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was dissolved in ~3 mL $CDCl_3$, and 87.3 μL of $CHBr_3$ (Aldrich, 1.0 mmol, 1.0 equiv) were added in to serve as an internal NMR standard. The yield of lactone was measured by comparing the relative ratio of the $CHBr_3$ signal at 6.82 ppm (1.00H) to that of the carboxylate bridgehead proton of lactone **21** at 4.71-4.66 ppm (0.23H, m) = 23% yield. Lactone (**21**) Characterization data: **Rf**: 0.14, 6:4 hexanes:$Et_2O$. **MS**: (ES) Molecular ion calculated for $C_{10}H_{17}O_3^+$: 169.1223; found m/z = 169.1223, error = 0 ppm. **IR**: (neat, $cm^{-1}$) 2925, 1703. **$^1$H NMR**: (500 MHz, $CDCl_3$, ppm) $\delta$ 4.68-4.65 (1H, m) 3.30-3.28 (1H, m) 2.25-1.91 (6H, m) 1.82-1.55 (8H, m). **$^{13}$C NMR**: (125 MHz, $CDCl_3$) $\delta$ 178.53, 78.04, 45.38, 34.36, 34.28, 31.84, 29.50, 25.71, 23.99, 22.03. **GC Assay**: (G-TA, 140 °C for 12 min, then ramp 5 °C/min to 160 °C, 1.5 mL/min) 34.8 min, 37.4 min.

***Entry 7***



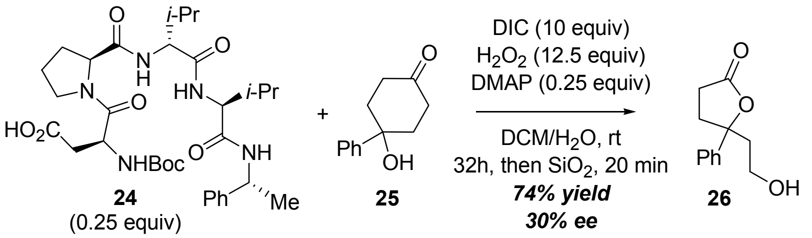
Experiment run as described above with commercially available ketone **22** (Aldrich, 0.13 mL, 1.0 mmole, 1.0 equiv). DIC was added at a rate of 0.09 mL/h (0.6 DIC equiv/h) until a total of 0.55 mL had been added into the reaction flask. This takes 6 h; at this point, the reaction was diluted with 40 mL $Et_2O$ and washed sequentially with 20 mL satd. $Na_2SO_3$ and 20 mL satd. $NaHCO_3$. The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was dissolved in ~3 mL $CDCl_3$, and 87.3 μL of $CHBr_3$ (Aldrich, 1.0 mmol, 1.0 equiv) were added in to serve as an internal NMR standard. The yield of lactone was measured by comparing the relative ratio of the $CHBr_3$ signal at 6.82 ppm (1.00H) to that of the two protons α to lactone carbonyl of known lactone[8] **23** at 2.80 ppm (0.19H, t, $J$ = 7.3 Hz) = 10% yield.

## *Experiments in Scheme 3*



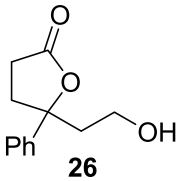
Peptide **D** was prepared by using solution phase peptide assembly techniques described elsewhere.[9] Peptide (**D**) Characterization data: **$^1$H NMR**: (400 MHz, $CDCl_3$, ppm) $\delta$ 7.38-7.19 (10H, m) 6.79 (1H, d, *J* = 8.6 Hz) 6.59 (1H, d, *J* = 8.8 Hz) 5.18-5.01 (5H, m) 4.84-4.78 (1H, m) 4.58-4.56 (1H, m) 4.18 (1H, dd, *J* = 8.6, 6.8 Hz) 4.00 (1H, t, *J* = 7.1 Hz) 3.73-3.68 (2H, m) 2.96 (1H, dd, *J* = 16.2, 8.8 Hz) 2.71 (1H, dd, *J* = 16.4, 4.8 Hz) 2.34-2.29 (2H, m) 2.16-1.91 (4H, m) 1.46-1.38 (12H, m) 0.94 (3H, d, *J* = 6.8 Hz) 0.91 (3H, d, *J* = 6.8 Hz) 0.84 (3H, d, *J* = 6.8 Hz) 0.77 (3H, d, *J* = 6.8 Hz).

The deprotection of the benzyl ester in **B** was performed by dissolving **B** (489 mg, 0.677 mmol, 1.0 equiv) in THF (2.2 mL, 0.3 M), flushing the reaction flask with $N_2$ for ~10 minutes, charging the reaction flask with Pd/C (Strem, 10% Pd on graphite, 150 mg) and exposing this suspension to a balloon charged with $H_2$. The resulting suspension was stirred at rt for 3 h until no **D** could be detected by TLC ($R_f$ **D** = 0.43, 6:4 hexanes:acetone; $R_f$ **24** = 0.26 (streak), 1:1 hexanes:acetone). The resulting suspension was then diluted with 100 mL EtOAc and filtered through celite to remove the Pd catalyst. The celite pad was generously washed with EtOAC (~200 mL) and the filtrate concentrated under reduced pressure to yield 378 mg of pure **24** as a white powder (88% yield). Peptide (**24**) Characterization data: **Rf**: 0.26 (streak), 1:1 hexanes:acetone. **MS**: (ES) Molecular ion calculated for $C_{32}H_{50}N_5O_8^+$: 632.3654; found m/z = 632.3649, error = 0.7 ppm. **IR**: (neat, $cm^{-1}$) 3306, 2969, 1712, 1685, 1632. **$^1$H NMR**: (500 MHz, $CDCl_3$, ppm) $\delta$ 7.50 (2H, d, *J* = 7.9 Hz) 7.65 (1H, d, *J* = 8.1 Hz) 7.56-7.51 (2H, m) 7.24-7.15 (5H, m) 5.10-5.01 (2H, m) 4.84-4.77 (1H, m) 4.73 (1H, d, *J* = 7.1 Hz) 4.22 (1H, dd, *J* = 7.3, 3.8 Hz) 4.09 (1H, dd, *J* = 10.6, 8.8 Hz) 3.98 (1H, t, *J* = 8.8 Hz) 3.88 (1H, dd, *J* = 17.4, 9.6 Hz) 2.97 (1H, dd, *J* = 17.4, 11.1 Hz) 2.81 (1H, dd, *J* = 17.7, 4.5 Hz) 2.62 (1H, dd, *J* = 11.6, 6.1 Hz) 2.31-2.21 (1H, m) 2.15-1.98 (2H, m) 1.97-1.75 (2H, m) 1.48 (3H, d, *J* = 7.1 Hz) 1.42 (9H, s) 0.94 (3H, d, *J* = 6.8 Hz) 0.88 (3H, d, *J* = 6.8 Hz) 0.85 (3H, d, *J* = 6.8 Hz) 0.43 (3H, d, *J* = 6.8 Hz) . **$^{13}$C NMR**: (125 MHz, $CDCl_3$) $\delta$ 175.03, 172.47, 171.996, 171.33, 142.47, 128.35, 126.95, 125.82, 80.23, 77.20, 60.06, 59.94, 59.87, 49.16, 47.60, 37.42, 30.94, 28.98, 28.24, 26.77, 24.096, 21.96, 19.54, 19.36, 18.65, 16.18. **$[\alpha]_D$** = -55 (c = 1.26, $CHCl_3$).

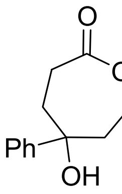


Known ketone[10] **25** (39.4 mg, 0.21 mmol, 1.0 equiv), catalyst **24** (32.7 mg, 0.052 mmol, 0.25 equiv) and DMAP (Aldrich, 6.3 mg, 0.052 mmol, 0.25 equiv) were dissolved in 0.52 mL DCM (0.4 M). Aq. $H_2O_2$ (Aldrich, 0.29 mL of a 30% solution in $H_2O$ (~8.8 M), 2.6 mmol, 12.5 equiv) was added and DIC (Acros, 0.32 mL, 2.1 mmol, 10.0 equiv) was added slowly with a syringe pump (KDScientific) at a rate of 10 μL/h (0.12 DIC equiv/h) until a total of 0.32 mL had been added into the reaction flask. This takes 32 h; at this point, the reaction was diluted with 5 mL $Et_2O$ and ~ 50 mg of $SiO_2$ were added to the reaction mixture. This was stirred for ~ 20 minutes. The silica treatment speeds up the rearrangement of the kinetically produced 7-membered lactone **E** (see below) to the more stable lactone **26**. The intermediacy of the 7-membered lactone **E** can be followed by GC (G-TA, 170 °C, 1.5 mL/min: 31.6 min (**E** enantiomer), 32.7 min (**E** enantiomer)). After 20 min, the resulting reaction mixture was diluted with 50 ml of $Et_2O$ and washed sequentially with 50 mL satd. $Na_2SO_3$ and 50 mL satd. $NaHCO_3$. The aqueous phase was washed 1 X 50 mL $Et_2O$ and the organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was dissolved in $CDCl_3$, and 18.1 μL of $CHBr_3$ (Aldrich, 0.21 mmol, 1.0 equiv) were added in to serve as an internal NMR standard. The yield of lactone was measured by comparing the relative ratio of the $CHBr_3$ signal at 6.82 ppm (1.00H) to that of one of the carboxylate protons of lactone **26** at 3.65-3.60 ppm (0.74H, m) = 74% yield. Lactone (**26**) Characterization data: **Rf**: 0.13, 7:3 $Et_2O$:hexanes. **MS**: (ES) Molecular ion calculated for $NaC_{12}H_{14}O_3^+$: 229.0835; found m/z = 229.0835, error = 0 ppm. **IR**: (neat, $cm^{-1}$) 3420, 2945, 1769. **$^1$H NMR**: (400 MHz, $CDCl_3$, ppm) δ 7.41-7.30 (5H, m) 3.69-3.63 (1H, m) 3.53-3.47 (1H, m) 2.63-2.41 (4H, m) 2.31-2.22 (2H, m) 1.74 (1H, br s). **$^{13}$C NMR**: (125 MHz, $CDCl_3$) δ176.24, 142.20, 128.73, 127.84, 124.44, 88.50, 58.57, 44.33, 35.74, 28.16. **GC Assay**: (G-TA, 170 °C, 1.5 mL/min) 35.2 min (35%), 41.2 min (65%) = ***30% ee*** = ***65:35 er***.

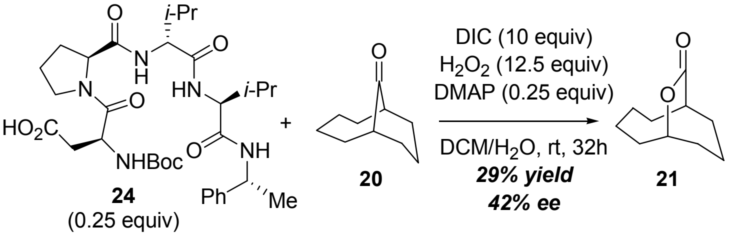
***NOTE:*** The assignment of **26** as a five-membered lactone follows the logic behind the assignment of lactone **13.**



**26**



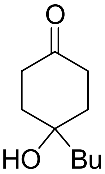
**E**



Known ketone[7] **20** (30 mg, 0.19 mmol, 1.0 equiv), catalyst **24** (31.1 mg, 0.049 mmol, 0.25 equiv) and DMAP (Aldrich, 6.0 mg, 0.052 mmol, 0.25 equiv) were dissolved in 0.5 mL DCM (0.4 M). Aq. $H_2O_2$ (Aldrich, 0.28 mL of a 30% solution in $H_2O$ (~8.8 M), 2.5 mmol, 12.5 equiv) was added and DIC (Acros, 0.30 mL, 1.9 mmol, 10.0 equiv) was added slowly with a syringe pump (KDScientific) at a rate of 10 μL/h (0.13 DIC equiv/h) until a total of 0.30 mL had been added into the reaction flask. This takes 30 h. At this point, the reaction mixture was diluted with 30 ml of $Et_2O$ and washed sequentially with 30 mL satd. $Na_2SO_3$ and 30 mL satd. $NaHCO_3$. The aqueous phase was washed 1 X 30 mL $Et_2O$ and the organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was dissolved in $CDCl_3$, and 17.2 μL of $CHBr_3$ (Aldrich, 0.19 mmol, 1.0 equiv) were added in to serve as an internal NMR standard. The yield of lactone was measured by comparing the relative ratio of the $CHBr_3$ signal at 6.82 ppm (1.00H) to that of the carboxylate bridgehead proton of lactone **21** at 4.71-4.67

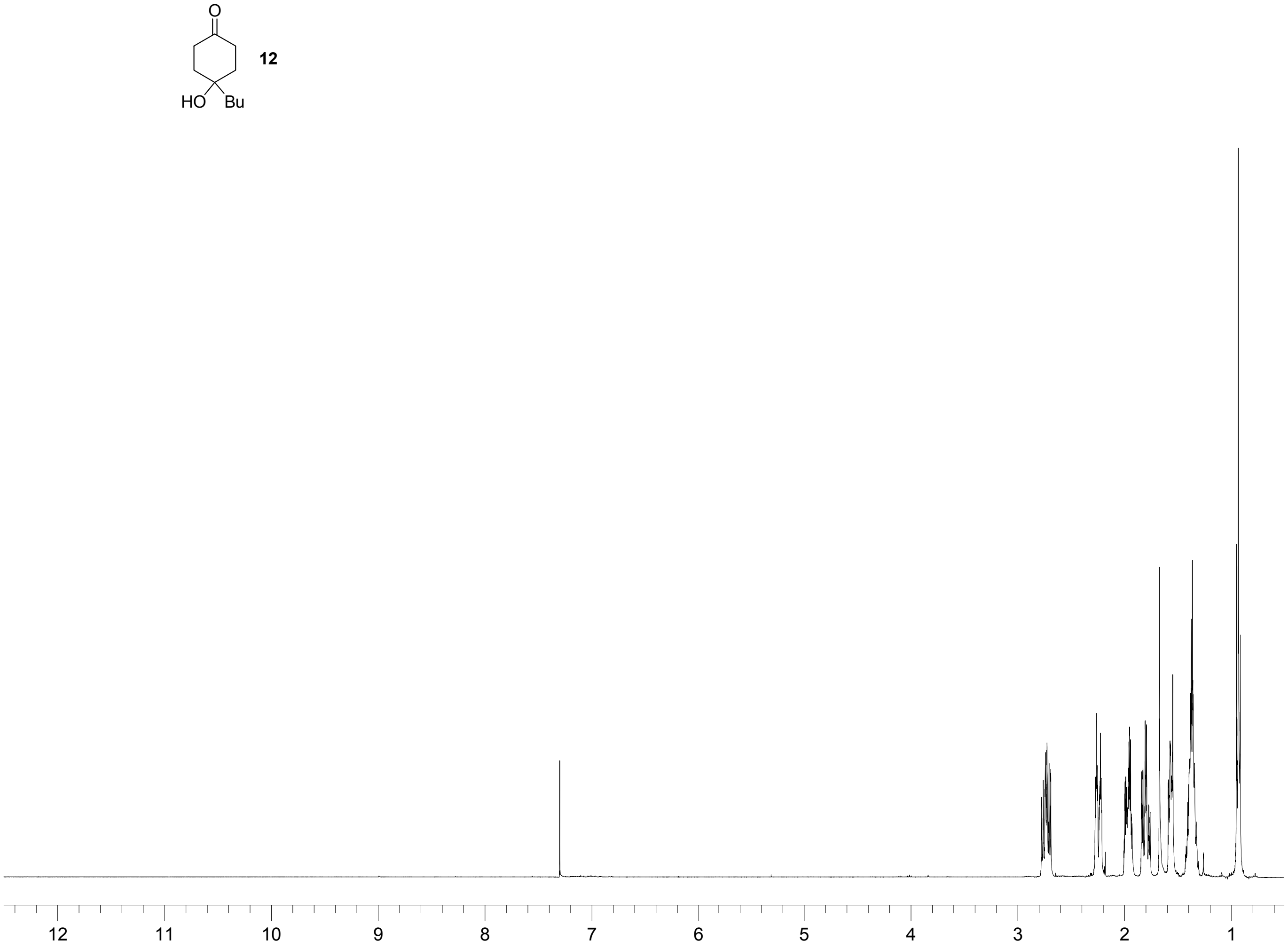
ppm (0.30H, m) = 30% yield. **GC Assay**: (G-TA, 140 $^{o}$C for 12 min, then ramp 5 $^{o}$C/min to 160 $^{o}$C, 1.5 mL/min) 34.8 min (71%), 37.4 min (29%) = ***42% ee*** = ***71:29 er***.

## 3. $^{1}$H, $^{13}$C Spectra

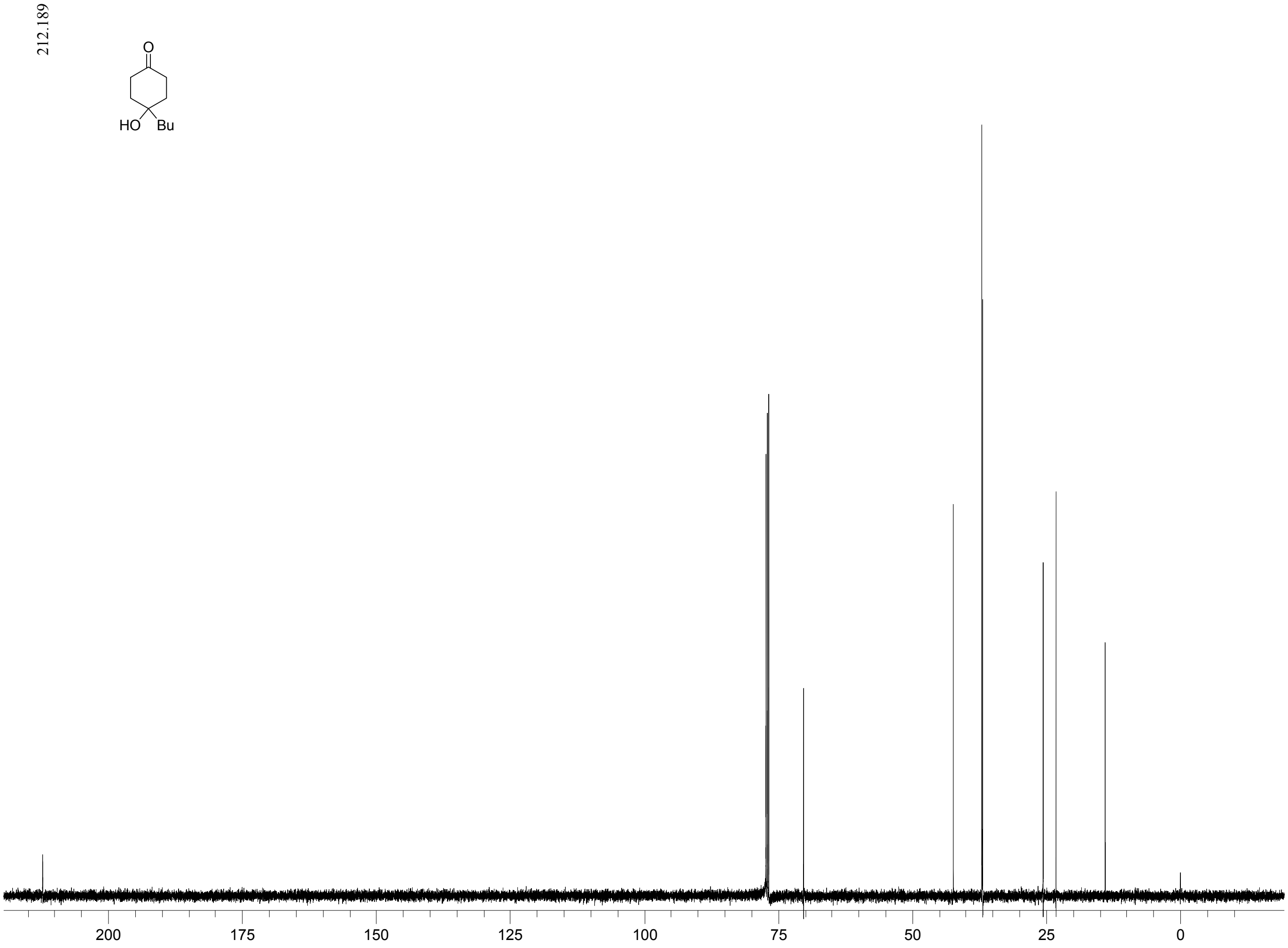


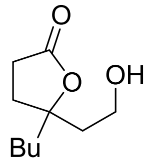
**12**

**$^{1}$H NMR**



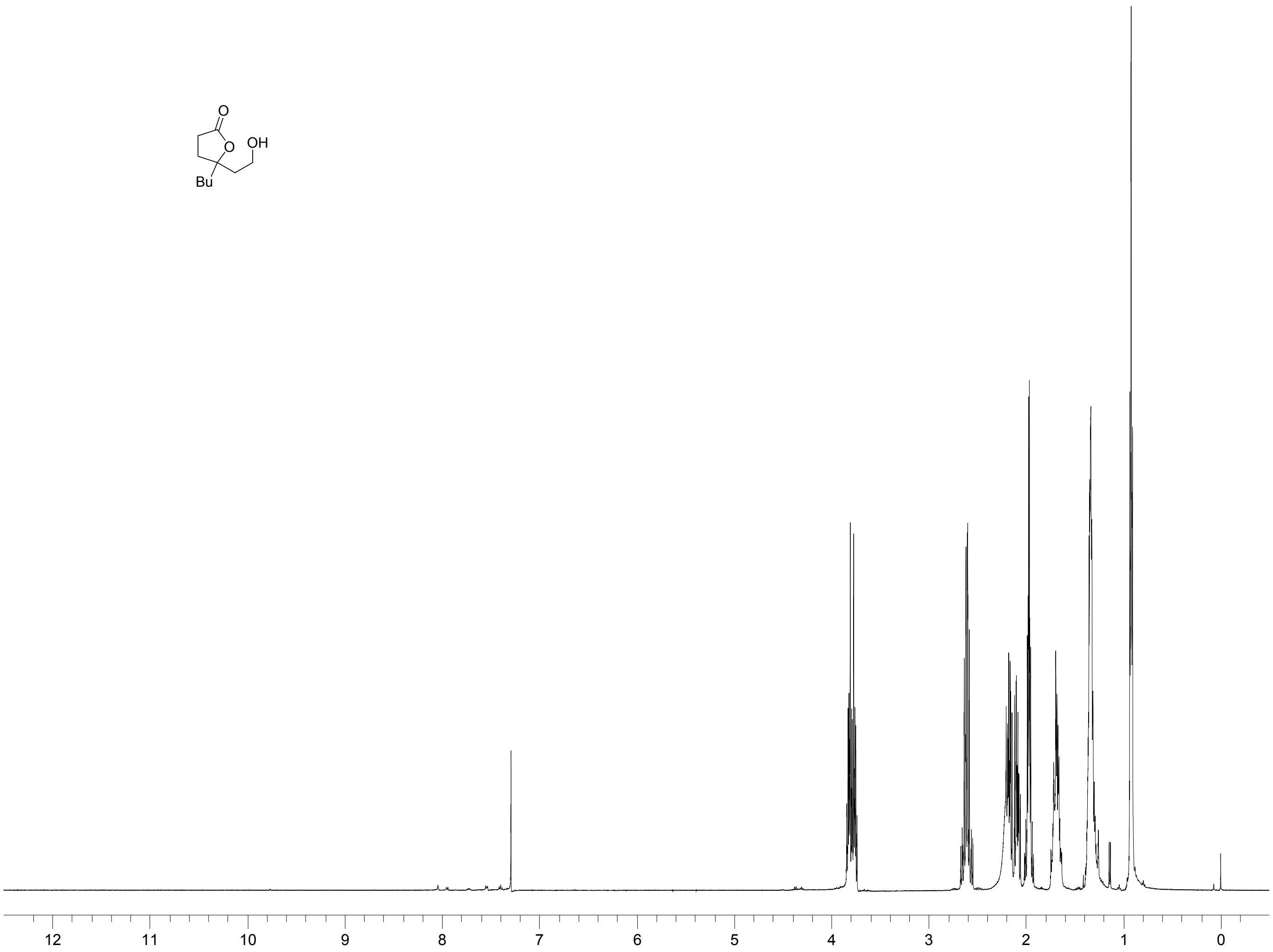
## $^{13}$C NMR





**13**

**$^1$H NMR**



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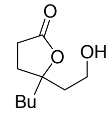
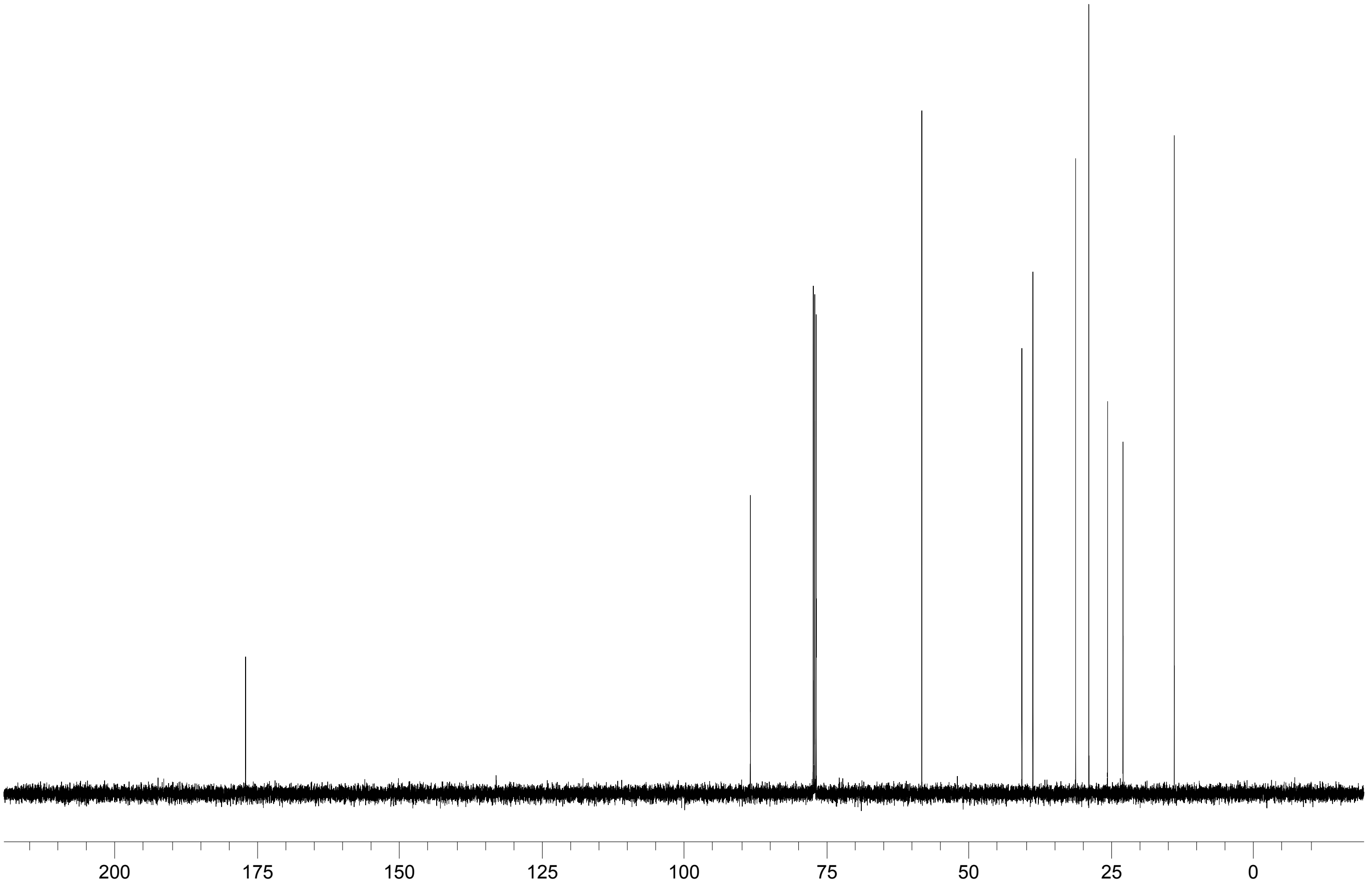
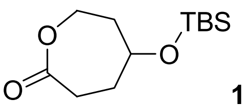


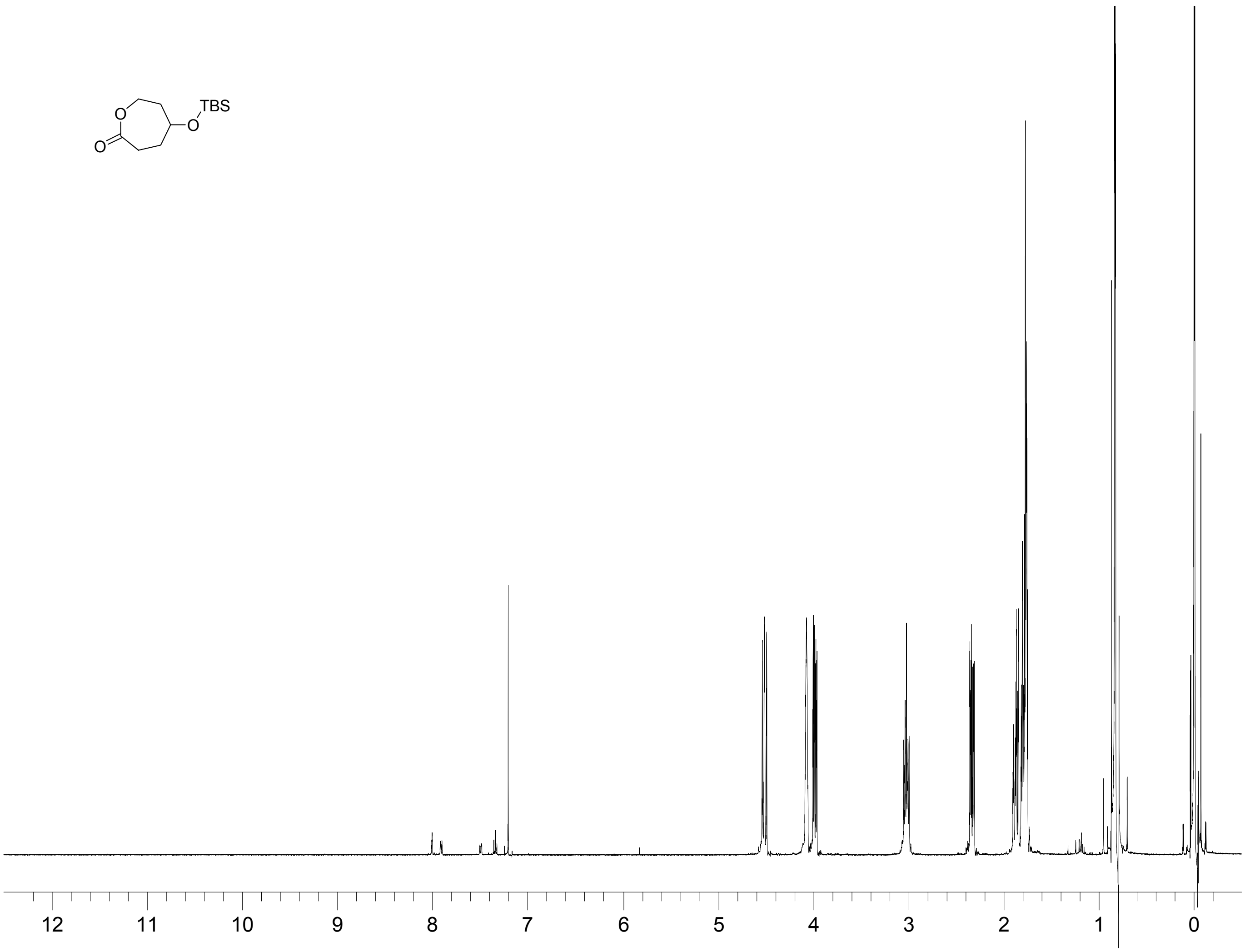
**13**





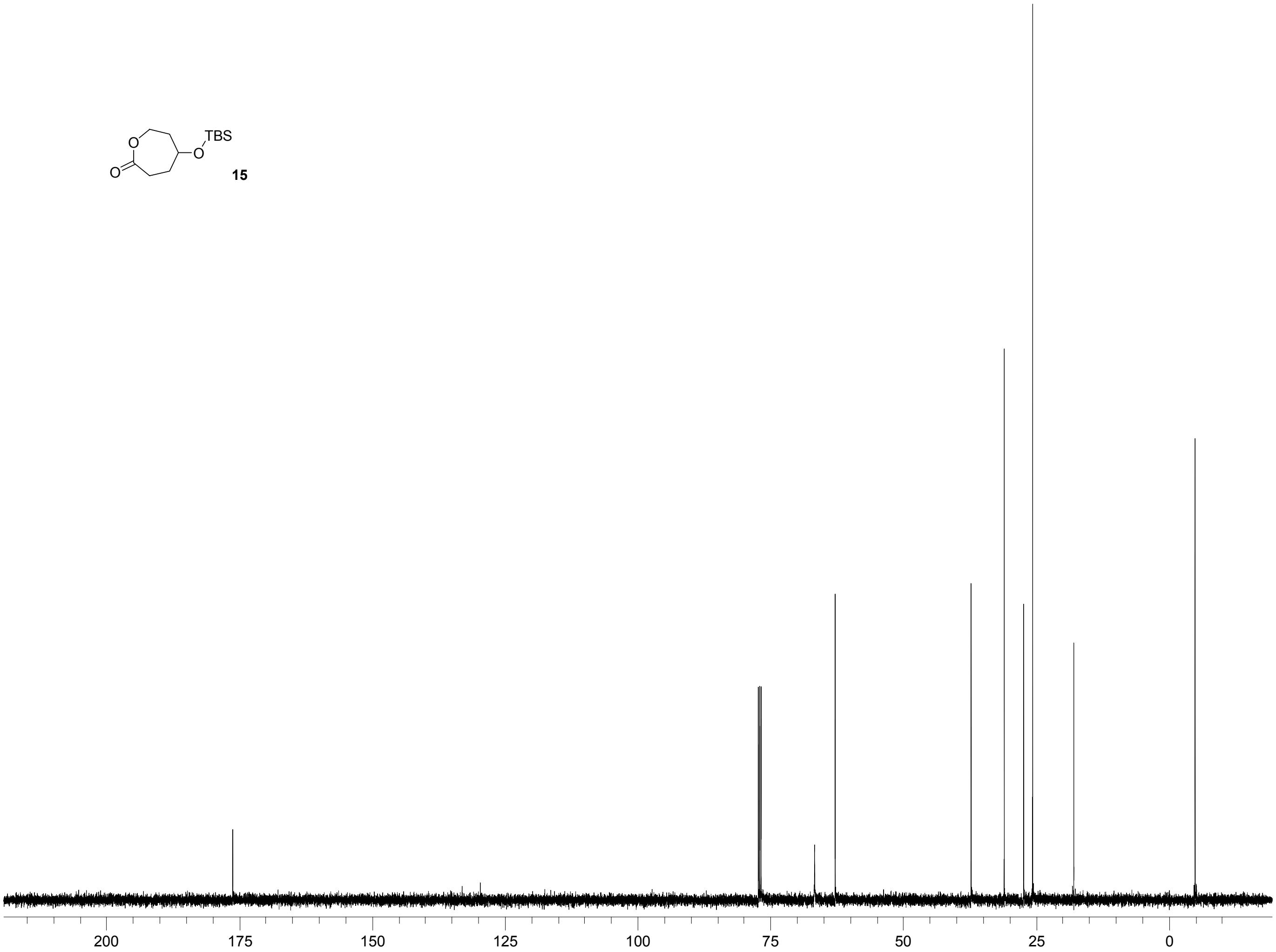
**15**

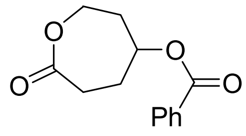
**$^1$H NMR**



## $^{13}$C NMR

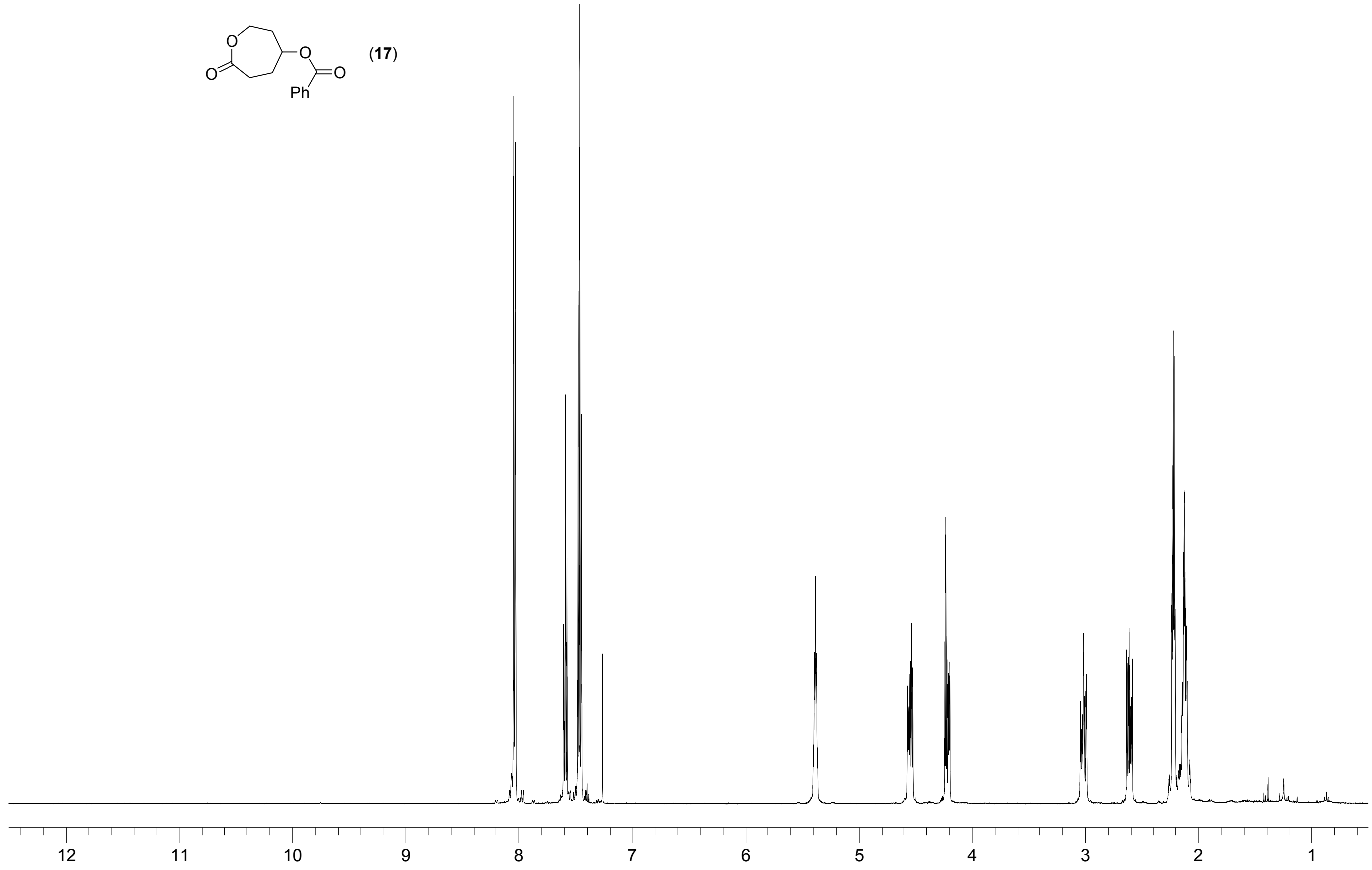
**15**



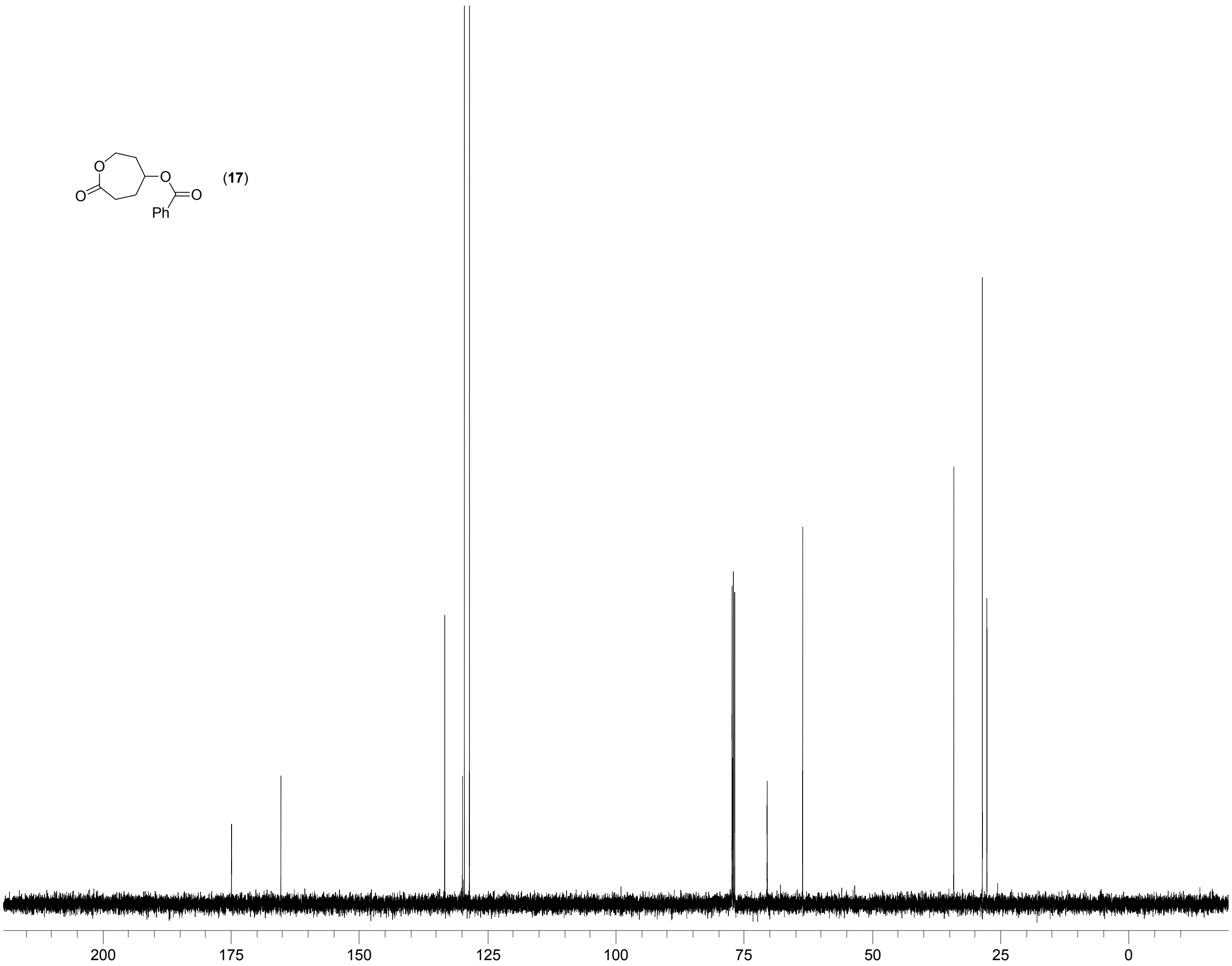


(**17**)

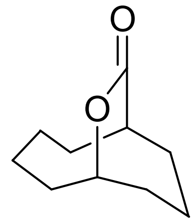
**$^1$H NMR**



## $^{13}$C NMR

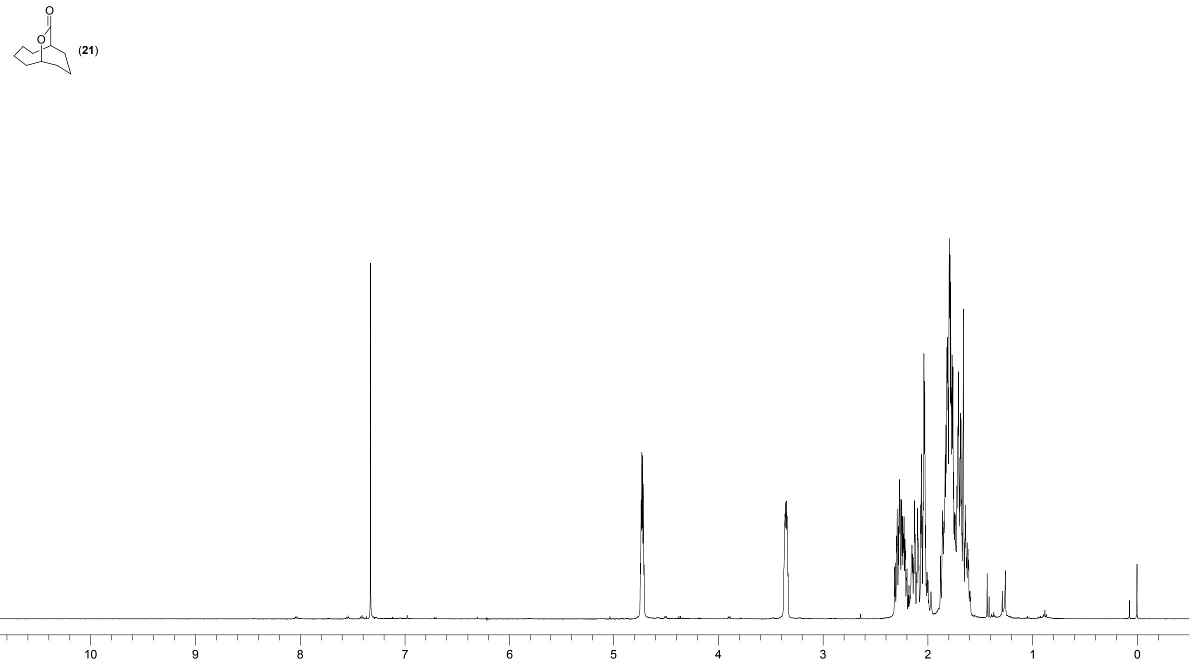


(**17**)

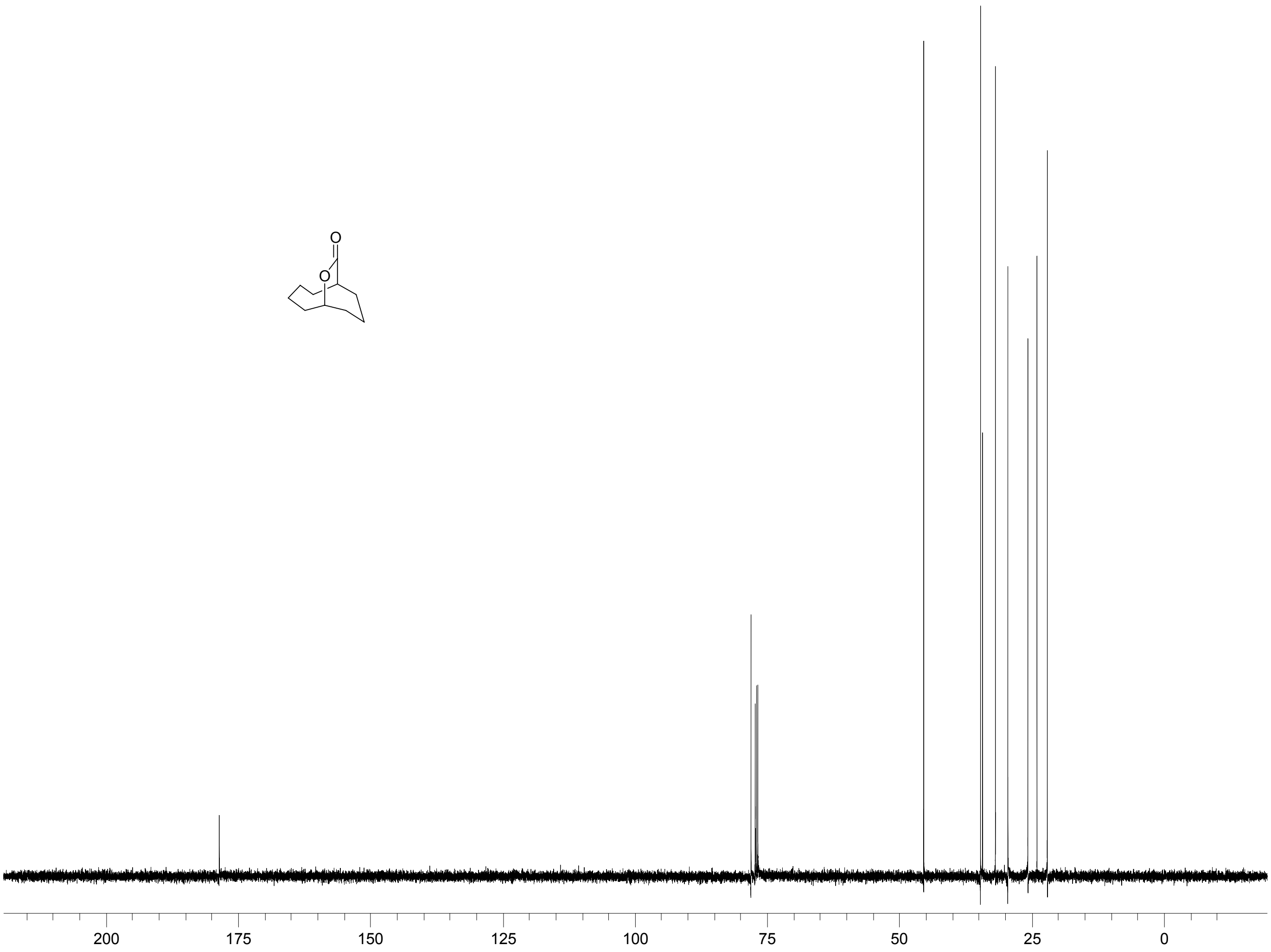


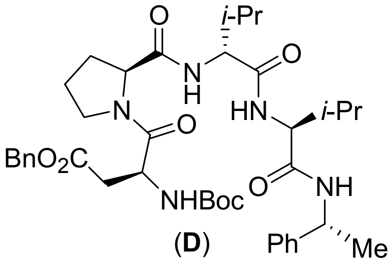
(**21**)

**$^1$H NMR**



### $^{13}$C NMR

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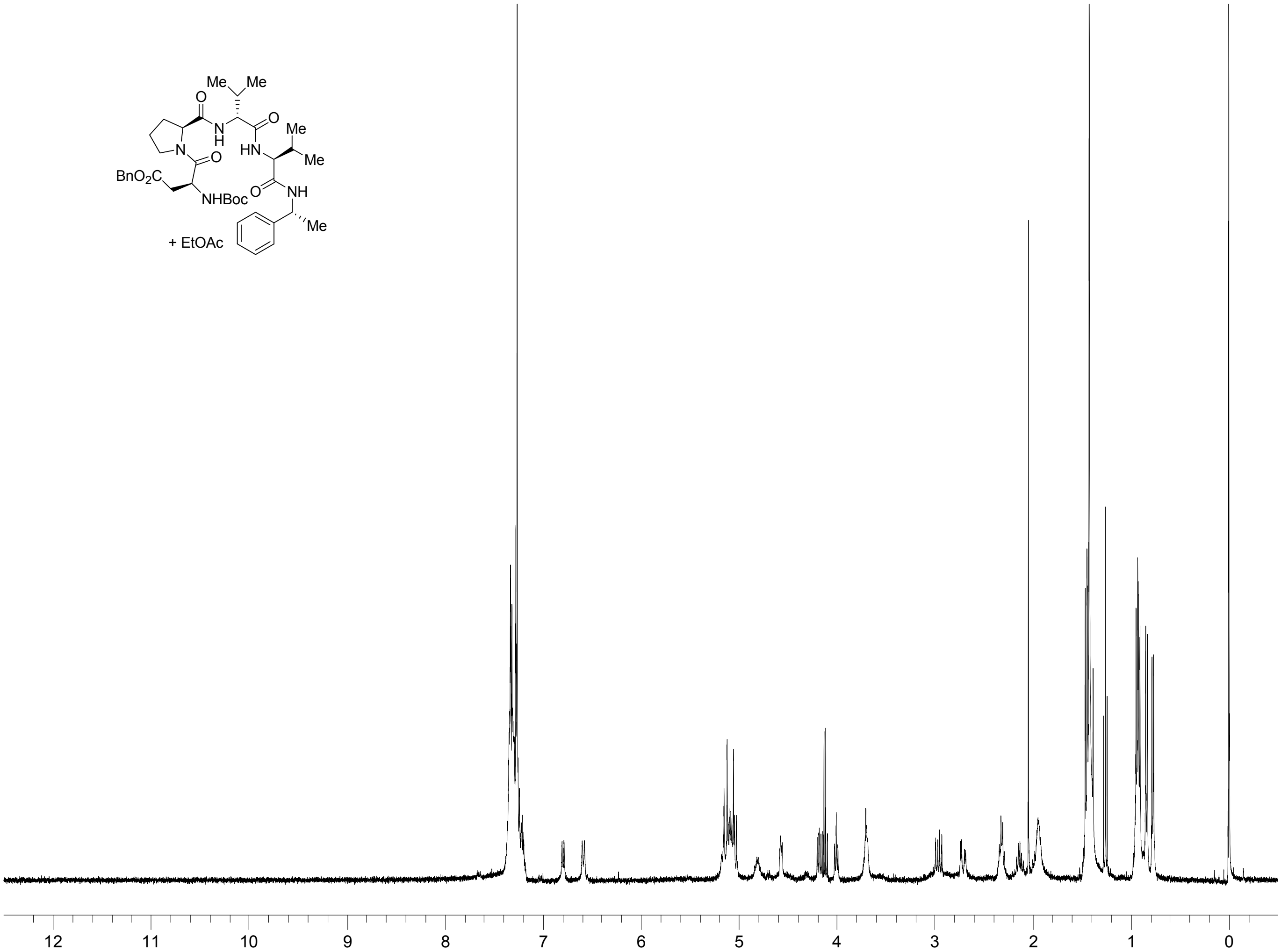
H
O
HN
i-Pr
N
O
BnO2C
NHBoc
O
NH
Ph
Me

(**D**)

**$^1$H NMR**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N
H
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Me
N
HN
O
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NHBoc
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NH
Me
+ EtOAc
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7
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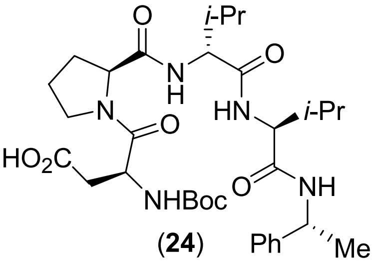
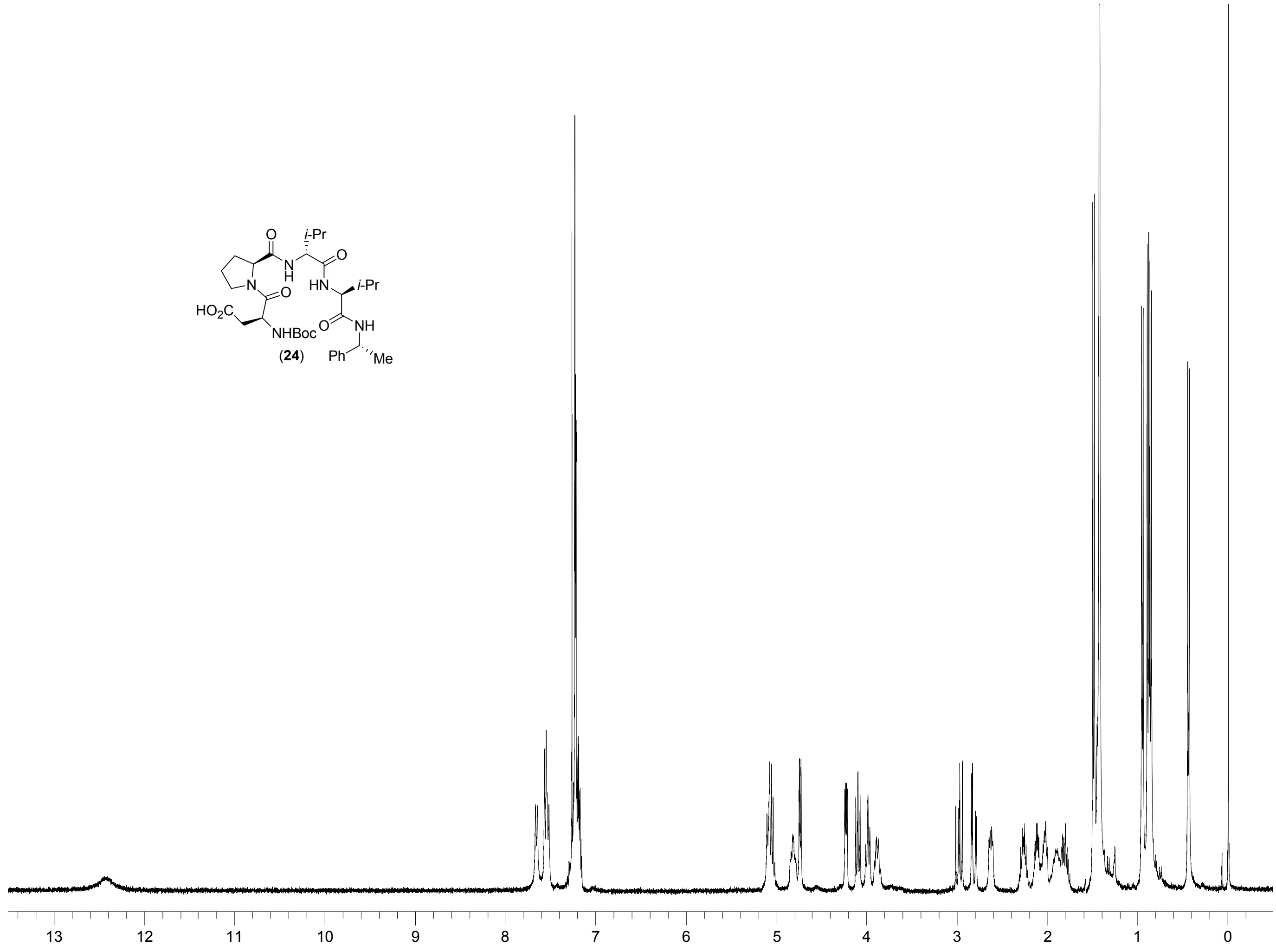
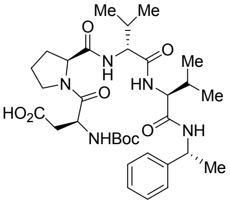
4
3
2
1
0


(**24**)

**$^1$H NMR**



## $^{13}$C NMR



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Me
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NH
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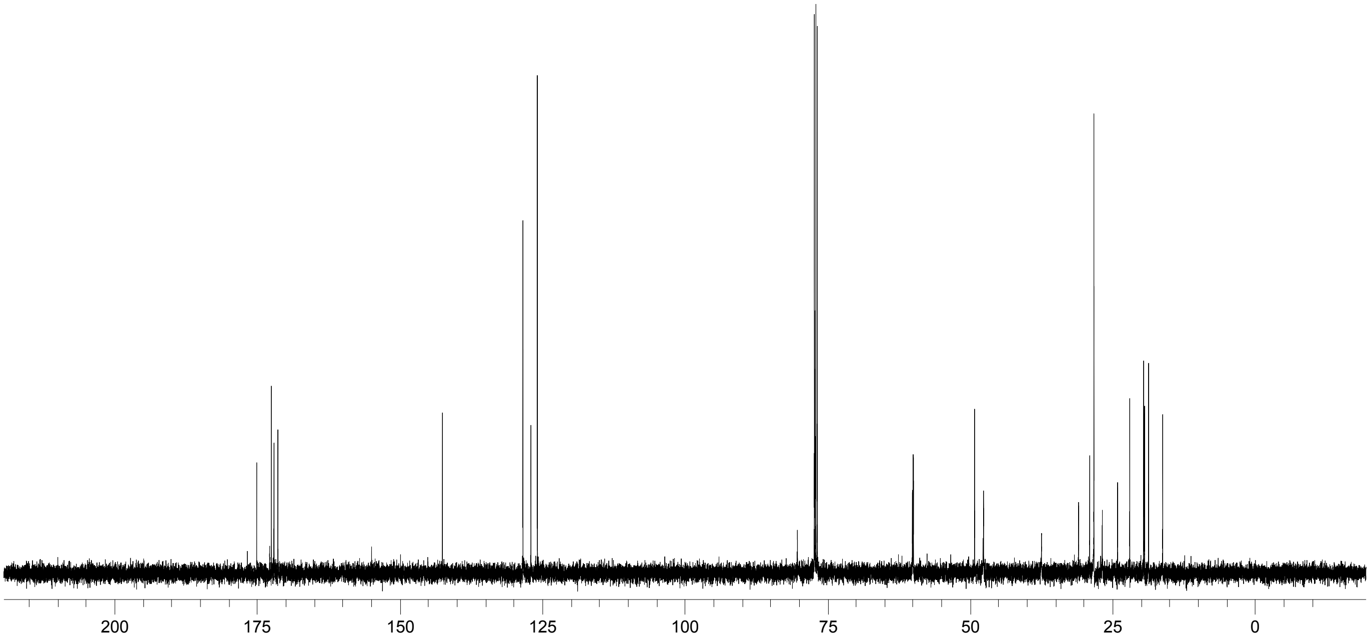

200
175
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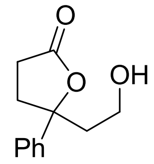
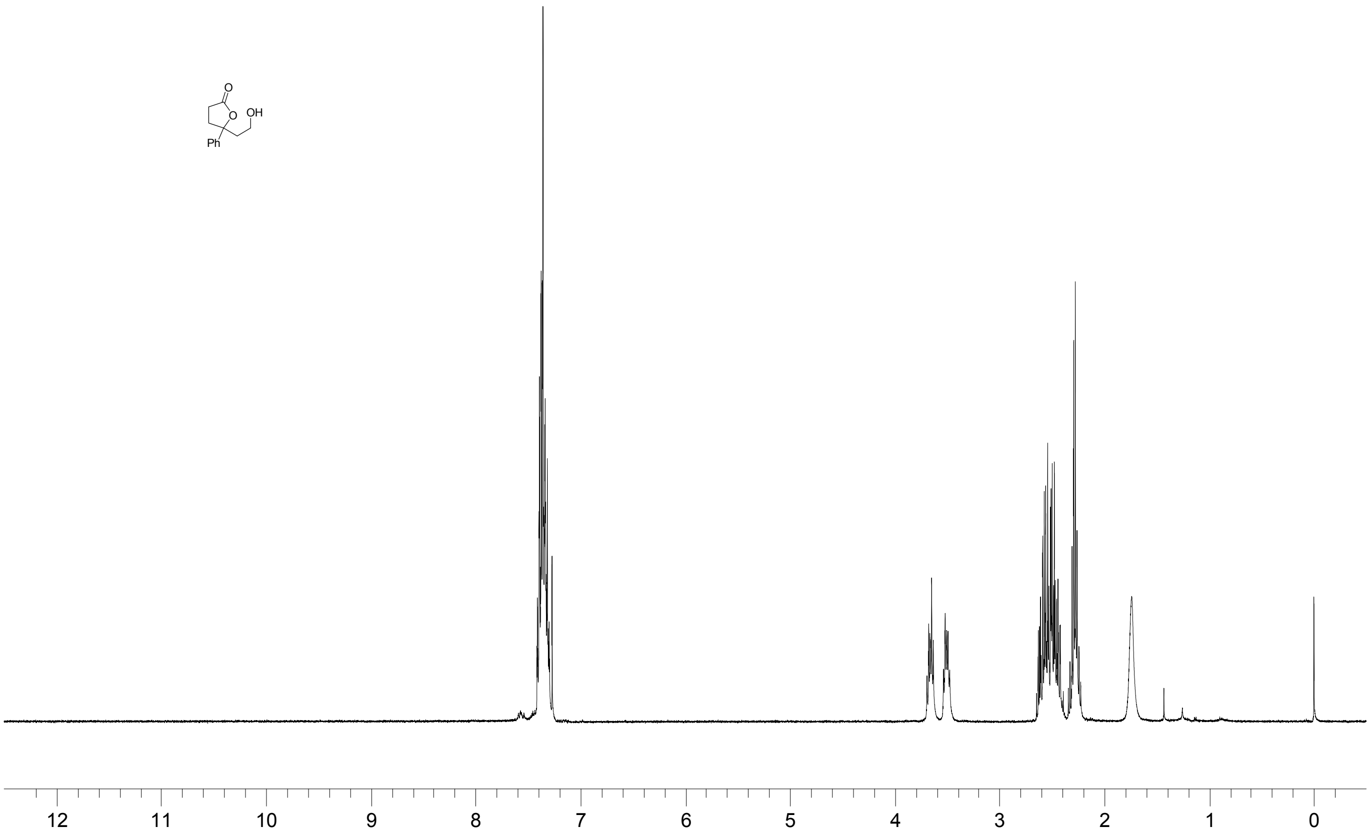
125
100
75
50
25
0

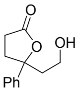


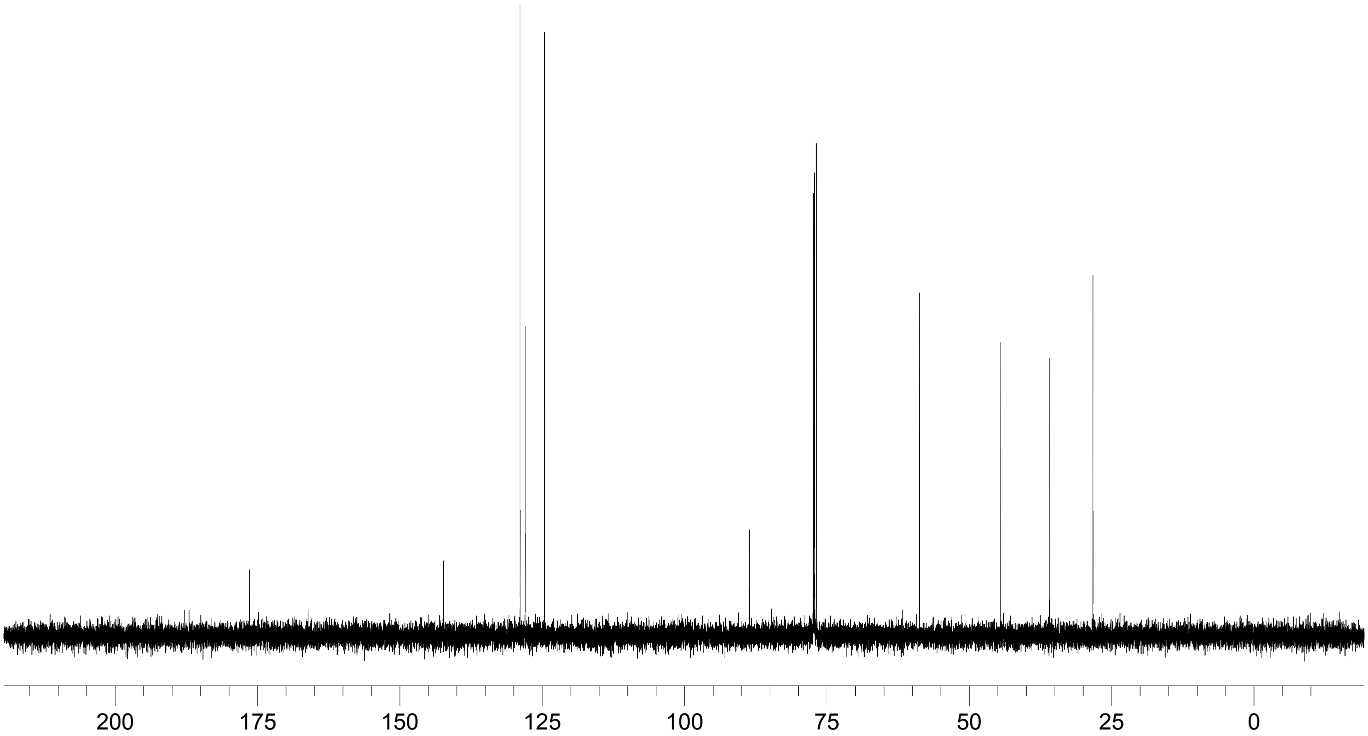
(**26**)

**$^{1}$H NMR**



$^{13}$C NMR





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## **4.** References.

[1] Žmitek, K.; Stavber, S.; Zupan, M.; Bonnet-Delpon, D.; Iskra, J. *Tetrahedron* **2006**, *62*, 1479.
[2] Keck, G. E, Dougherty, S. M.; Savin, K. A. *J. Am. Chem. Soc.* **1995**, *117*, 6210.
[3] Kayser, M. M.; Clouthier, C. M. *J. Org. Chem.* **2006**, *71*, 8424.
[4] Malapelle, A.; Coslovi, A.; Doisneau, G.; B. J. –M. *Eur. J. Org. Chem.* **2007**, 3145.
[5] Awasthis, K. K.; Chakrabarty, R.; Saxena, A. K. *Med. Chem. Res.* **2004**, *13*, 758.
[6] Dohi, T.; Takenaga, N.; Goto, A.; Maruyama, A.; Kita, Y. *Org. Lett.* **2007**, *9*, 3129.
[7] Winkler, J. D.; Hong, B. C.; Hey, J. P.; Williard, P. G. *J. Am Chem. Soc.* **1991**, *113*, 8839.
[8] Youssefyeh, R. D.; Campbell, H. F.; Klein, S.; Airey, J. E.; Darkes, P.; Powers, M.; Schnapper, M. Neuenschwander, K. .; Fitzpatrick, L. R.; Pendley, C. E.; Martin, G. E. *J. Med. Chem.* **1992**, *35*, 895.
[9] Peris, G.; Jakobsche, C. E.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 8710.
[10] Singh, C.; Malik, H. *Org. Lett.* **2005**, *7*, 5673.