A Photoenzyme for Challenging Lactam Radical Cyclizations

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EXPERIMENTAL PROCEDURES

General. Unless otherwise noted, all chemicals and reagents for chemical reactions were obtained from commercial suppliers and used as received (Sigma-Aldrich, Oakwood Chemical, Combi-Blocks, Chem-Impex, and Acros Chemicals). GDH-105 was purchased from Codexis as cell free lysate and used as received. KRED P103 was acquired though Merck Phramacuticals. Polymerases and restriction enzymes were purchased from New England BioLabs (NEB) and used as received. Silica gel chromatography purifications were carried out using AMD Silica Gel 60. ^{1}H- and ^{13}C- NMR spectra were recorded on a Bruker UltraShield Plus (500 and 125 MHz, respectively) instrument, and are internally referenced to residual proton signals in $CDCl_3$ (7.26 ppm). Data for ^{1}H-NMR are reported as follows: chemical shift (**δ** ppm), multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet), coupling constant (Hz), and integration. Data for ^{13}C NMR are reported in terms of chemical shift relative to $CDCl_3$ (77 ppm). High- resolution mass spectra were obtained on an Agilent 6220 LC/MS with an electrospray ionization time-of-flight (ESI-TOF) detector. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and peaks are reported in terms of frequency of absorption (cm^{-1}).

Chromatography. Analytical high-performance liquid chromatography (HPLC) was carried out using an Agilent 1260 Infinity LCMS System. Analytical chiral SFC was carried out using a JASCO.

Cloning. pET22b(+) and pET15b were used as cloning and expression vectors for all enzymes described in this study. Genes for the 'ene' reductase enzymes GluER were purchased as gBlocks from IDT and cloned using Gibson Cloning.[1] Genes for error prone-mutants were cloned between the NdeI and XhoI restriction sites and contained an N-terminal (GluER) 6xHis tag. Cloning was carried out using BL21 *E. coli*. .

Protein Expression and Purification. The 'ene'-reductase GluER used in purified protein experiments were expressed in BL21(DE3) *E. coli* cultures transformed with plasmid encoding GluER variants. Transformed glycerol stocks were used to initiate 10 mL overnight cultures (37 °C, 250 rpm). Expression cultures (500 mL of Turbo Broth with ampicillin (100 µg/ml final concentration) in a 2L flask) were inoculated with 1-2 ml of the overnight culture (37 °C, 250 rpm). For expression, GluER variants were expressed using the addition of 4% (v/v) auto inducing mix (sterile filtered mixture of 1.25% glucose, 5% lactose and 15% glycerol). The pellets were kept at -80 °C for at least 24 hrs before thawing for purification. For purification, frozen cells were thawed in ice-cold water and resuspended in buffer A (for GluER: 50 mM TEOA 25 mM imidazole pH 7.0). Lysozyme

(1 mg/mL), DNAse (0.1 mg/mL), FMN (1 mg/mL), and PMSF (1 mg/mL, added as a 35 mg/mL solution in absolute ethanol) were added to the resuspended cells, followed by shaking at room temperature for 30 minutes. The resuspended cells were disrupted by sonication (2 x 4 min, output control 5, 35% duty cycle; Sonicator QSonica Q500 Ultra Sonicator). To pellet insoluble material, lysates were centrifuged at 14,000 x g for 1.5 h at 4 °C. Proteins were purified using a nickel NTA column (5 mL HisTrap HP, GE Healthcare, Piscataway, NJ) using an AKTAStart purifier FPLC system (GE healthcare). The protein was eluted with 100 % buffer B (50 mM triethanolamine (TEOA), 250 mM imidazole pH 7.0) over 5 column volumes. Fractions containing enzyme were pooled, concentrated, and subjected to three exchanges with no-imidazole Buffer C (50 mM triethanolamine (TEOA), pH=7.0, for all other ERED) to remove excess salt and imidazole. Concentrated (1.0-1.5 mM) proteins were aliquoted, flash-frozen in liquid N_2, and stored at -80 °C until later use. Protein concentration was determined by A_{464} with calculated extinction coefficients. (GluER: 11.4×10^{-3} $M^{-1}cm^{-1}$ at 464 nm)

SEQUENCE INFORMATION

'Ene'-reductase from *Gluconobacter Oxydans* (GluER-T36A-W66A)
(GenBank Accession Code for WT sequence WP_011252080.1)

GluER T36A W66A

GluER T36A-W66A DNA sequence

ATGCCGACCCTTTTCGACCCCATCGATTTCGGACCTATCCACGCCAAGAATCGTATC
GTCATGTCCCCCCTGACTCGCGGTCGCGCTGACAAAGAGGCGGTTCCAGCCCCCA
TTATGGCTGAATACTACGCCCAACGCGCTTCGGCGGGTTTAATTATCACTGAAGCGA
CGGGGATTTCACGCGAAGGCTTAGGTGCCCCGTTTGCGCCGGGAATTTGGTCCGAT
GCACAGGTTGAGGCGTGGAAACCTATCGTCGCGGGTGTCCATGCAAAGGGCGGCA
AGATCGTATGTCAGCTTTGGCATATGGGCCGTATGGTACATTCTTCAGTTACAGGGA
CGCAGCCCGTAAGCAGTTCCGCCACTACTGCTCCAGGTGAGGTTCACACCTATGAG
GGCAAGAAGCCCTTCGAACAAGCGCGTGCAATCGATGCTGCAGACATCTCCCGCA
TCCTTAACGATTACGAAAATGCAGCACGTAATGCAATCCGCGCGGGTTTCGATGGA
GTGCAGATCCACGCAGCCAATGGCTACCTTATCGATGAGTTTTTGCGTAACGGAAC
CAATCATCGCACCGATGAGTATGGGGGGGTGCCGGAGAACCGTATTCGTTTCTTGA
AAGAGGTAACAGAACGCGTCATCGCGGCGATTGGCGCTGACCGTACGGGTGTGCG
TCTGAGTCCAAACGGTGACACACAGGGTTGTATCGACAGTGCTCCCGAAACCGTTT
TTGTTCCTGCCGCAAAGCTTTTGCAAGATTTANGGGTAGCGTGGCTTGAGCTGCGT
GAACCTGGTCCGAATGGTACGTTTGGAAAGACGGATCAACCAAAATTATCTCCACA
AATCCGTAANGTATTCCTTCGTCCATTGGTCTTAAATCAAGACTATACTTTTGAGGCC
GCACAGACGGCCCTGGCTGAGGGCAAGGNGGACGCTATTGCGTTTGGGCCGTAA
GTTCATTTCAAATCCAGACTTGCCTGAGCCTTTGCCCNGCTTTGCCCGTGGCATCGCAC
TGCAACCAGACGATATGAAAACATGGTACTCCCAAGGCCCAGAGGGTTACACAGACTATCC
ATCCGCAACTTCTGGGCCGAACTGA

GLUER T36A-W66A AMINO ACID SEQUENCE

MPTLFDPIDFGPIHAKNRIVMSPLTRGRADKEAVPAPIMAEYYAQRASAGLIITEATGISREGL
GAPFAPGIWSDAQVEAWKPIVAGVHAKGGKIVCQLWHMGRMVHSSVTGTQPVSSSATTA
PGEVHTYEGKKPFEQARAIDAADISRILNDYENAARNAIRAGFDGVQIHAANGYLIDEFLRN
GTNHRTDEYGGVPENRIRFLKEVTERVIAAIGADRTGVRLSPNGDTQGCIDSAPETVFVPAA
KLLQDLXVAWLELREPGPNGTFGKTDQPKLSPQIRXVFLRPLVLNQDYTFEAAQTALAEGK
XDAIAFGP

Primers for Site-Directed Mutagenesis

GluER-W66A

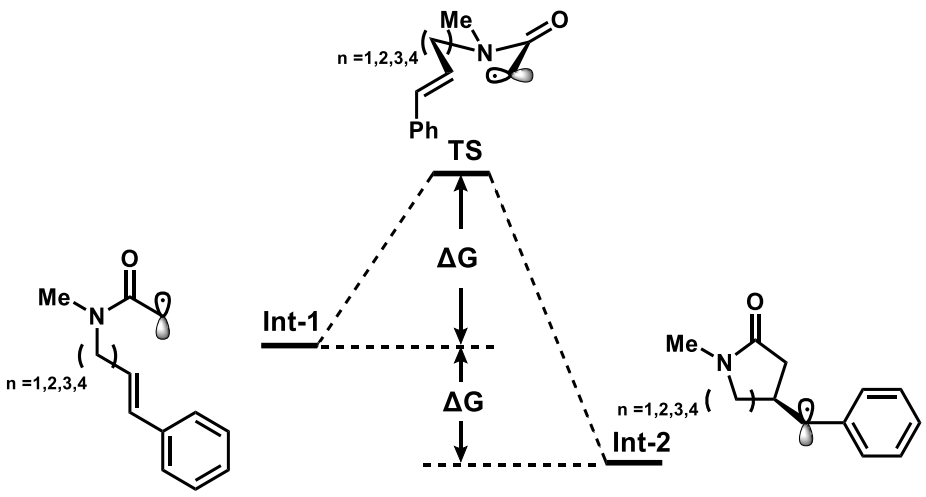
W66A Forward primer:
5′- TTTCACGCGAAGGCTTAGGTGCCCCGTTTGCGCCGGGAATTTG -3′
Reverse primer:
5′- ACCTAAGCCTTCGCGTGAAATCCCCGTCGCTTCAGTGATAA-3′

DENSITY FUNCTIONAL THEROY (DFT) CALCULATIONS

All DFT computations were carried out using the Gaussian 16, Revision C.01 program[2] and the and the **ω**B97XD functional.[3] Structures were optimized at the **ω**B97XD/ 6-31g(d,p) level of theory.[3] Higher level of theory single point calculations used SMD in acetonitrile with **ω**B97XD/def2TZVP.

Cyclization Reaction. We performed DFT calculations on cyclization reactions from 5-membered ring to 8-membered ring. The 8-member-ring cyclization has a much higher activation energy barrier compared to 5, 6, 7-membered ring. The reverse reaction's energy barrier of 8-member ring is 13.24 kcal/mol. Considering the reversable reaction's energy barrier is 20 kcal/mol at room temperature, it indicates the 8-member ring cyclization is a reversable reaction. These explain why 8-member ring cyclization has much more HDH.

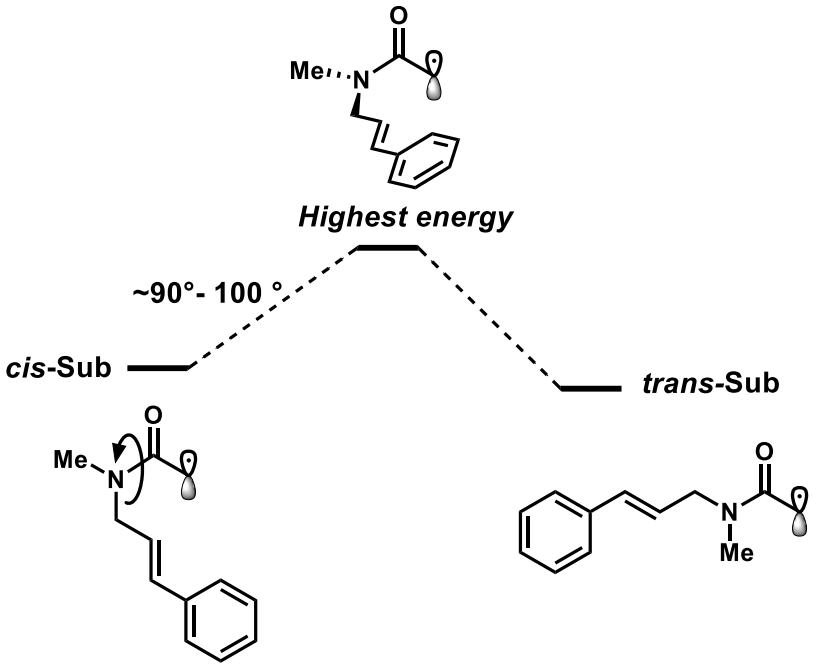
Cyclization for 5,6,7,8-member ring



Energy Form

Ring	$\Delta G^{\neq}$ (Kcal/mol)	ΔG (Kcal/mol)
5	8.16	-27.65
6	7.72	-25.85
7	9.07	-22.43
8	14.68	-13.24

Bond Rotation Energy. We performed relaxed scan on acyl radical's amide bond. The initial *cis*-substrate rotate the amide bond for 180° to get the *trans*- substrate. We picked the highest energy point to calculate the bond rotation energy barrier. The rotation energy barrier for all substrates is under 20 kcal/mol, which indicates in consistent ***cis/trans*** mixture in the reaction process.[4]



Energy Form

Ring	Initial Energy (Hartree)	Highest Energy (Hartree)	Rotation Energy (Kcal/mol)
5	-595.4383448	-595.4147151	14.83
6	-634.7450223	-634.7227519	13.97
7	-674.0517435	-674.0304544	13.36
8	-713.3557421	-713.3330032	14.27

Atomic coordinates

5-member ring Int-1

Electronic Energy: -595.6329337

Thermal correction to Gibbs Free Energy: 0.19086600

O	-4.17835400	0.27490100	1.38905300
N	-2.86729000	-0.29470700	-0.39129000
C	-3.55659000	-1.55901200	-0.55291700
H	-4.04261100	-1.61329800	-1.53413000
H	-2.85869700	-2.40061100	-0.46450300
H	-4.31217600	-1.63693100	0.22670600
C	-3.22890600	0.53547700	0.64836000
C	-1.77584900	-0.00687300	-1.31038100
H	-1.79822000	1.04687600	-1.60820500
H	-1.97255700	-0.58495300	-2.22117900
C	-0.42214100	-0.36988200	-0.76277800
H	-0.34156700	-1.36647100	-0.33190800
C	0.63365400	0.44622000	-0.79286100
H	0.51316200	1.42535100	-1.25966600
C	1.98514100	0.15761400	-0.28197700
C	2.23942700	-0.86622200	0.63962500
C	3.06085700	0.93627200	-0.72324900
C	3.53088600	-1.11430600	1.08569600
H	1.41813700	-1.46120100	1.02679200
C	4.35457300	0.68858600	-0.27801100
H	2.87928000	1.74124900	-1.43050700
C	4.59462900	-0.34053400	0.62662400
H	3.70766300	-1.90961800	1.80288600
H	5.17510900	1.30174000	-0.63681900
H	5.60241000	-0.53420700	0.97944200
C	-2.44426900	1.74338100	0.87238000

H -2.83458100 2.43122500 1.61082000

H -1.46595300 1.92026000 0.44382000

5-member ring TS

Electronic Energy: -595.6210563

Thermal correction to Gibbs Free Energy: 0.19199800

O 3.15262900 -1.01823300 1.65081500

N 2.81787500 0.33478600 -0.16170300

C 3.90233000 1.23163400 0.16258400

H 4.66534100 1.23711200 -0.62554200

H 3.53309700 2.25503300 0.29637800

H 4.35039000 0.88674200 1.09425000

C 2.58401900 -0.78582400 0.59100600

C 2.00768600 0.58448500 -1.34213000

H 2.44813000 0.11764600 -2.23483700

H 2.00830600 1.66631900 -1.52008300

C 0.58348600 0.09553600 -1.15401200

H 0.19812900 -0.59239100 -1.90090100

C -0.27406800 0.70539400 -0.29873400

H 0.11922400 1.49467700 0.34151900

C -1.68093000 0.36357700 -0.10023100

C -2.24869200 -0.82069900 -0.59575700

C -2.50422500 1.23993100 0.62170700

C -3.59348300 -1.10140900 -0.39633400

H -1.62727600 -1.53829700 -1.12240900

C -3.84992800 0.95899400 0.82078000

H -2.07854800 2.15506800 1.02438500

C -4.40168400 -0.21217000 0.30918600

H -4.01256900 -2.02446900 -0.78447000

H -4.46892000 1.65424600 1.37893800

H -5.45172500 -0.43612800 0.46671600

C 1.58055500 -1.70117400 0.00574500

H 0.91703800 -2.21330000 0.69208500

H 1.82284300 -2.20955800 -0.92348400

5-member ring Int-2

Electronic Energy: -595.682946

Thermal correction to Gibbs Free Energy: 0.19681700

O -3.08019400 -1.19558800 -1.55595000

N -2.84117200 0.38018500 0.10317600

C -4.08246800 1.07314300 -0.12604900

H -4.78860000 0.90947500 0.69786700

H -3.91206700 2.14984200 -0.23085500

H -4.51417800 0.68187700 -1.04830100

C -2.48372900 -0.73919300 -0.59955400

C -2.02588500 0.61397700 1.27616600

H -2.51847400 0.23419600 2.18388900

H -1.84413300 1.68506000 1.41893000

C -0.72703000 -0.15999500 0.96897300

C -1.23429000 -1.30670000 0.06188300

H -0.50997900 -1.63055900 -0.68640300

H -1.53388700 -2.18406600 0.64681200

H	-0.29549900	-0.55477500	1.89461700
C	0.27232600	0.70659300	0.26531000
H	-0.09559500	1.61503500	-0.20707800
C	1.63822100	0.38066100	0.09716600
C	2.21086300	-0.81411000	0.60788300
C	2.49714400	1.26368600	-0.60958800
C	3.55402400	-1.09566400	0.42362200
H	1.58833300	-1.52265100	1.14505100
C	3.83696700	0.97306400	-0.78669900
H	2.08249100	2.18277600	-1.01433900
C	4.37786100	-0.20829000	-0.27137700
H	3.96742600	-2.01702600	0.82211600
H	4.47060700	1.66659300	-1.33068100
H	5.42928900	-0.43539800	-0.41267300

6-member ring Int-1

Electronic Energy: -634.9505543

Thermal correction to Gibbs Free Energy: 0.21712500

C	2.00582200	-0.68100000	0.41461800
C	1.13410400	-0.32127800	-0.80135500
C	3.32079300	1.87093400	0.73028200
H	1.84512900	-1.73137400	0.68208300
H	1.29375700	0.73215400	-1.05760300
H	1.47455700	-0.91291500	-1.66049400
H	3.89101100	2.78125800	0.85948700
H	2.24967200	1.89416300	0.88675700

H	1.68781200	-0.09957900	1.28451000
N	3.42696900	-0.50414300	0.18199700
C	4.15205500	-1.63865300	-0.35566000
H	3.72351400	-1.96482200	-1.31134400
H	5.18627500	-1.33848200	-0.51359200
H	4.11957500	-2.48050300	0.34508200
O	5.27850200	0.82437800	0.03177300
C	4.08005200	0.70484100	0.29293600
C	-0.31854000	-0.57861100	-0.53695000
H	-0.60187500	-1.62167100	-0.39668700
C	-1.24612300	0.37790500	-0.44789400
H	-0.93957900	1.40893900	-0.62786900
C	-2.67925700	0.19099500	-0.16065700
C	-3.18805000	-0.97546000	0.42530500
C	-3.57603300	1.21814000	-0.47660100
C	-4.54897100	-1.11595200	0.66369400
H	-2.51165900	-1.77395600	0.71429600
C	-4.93874600	1.07972100	-0.23791200
H	-3.19761900	2.13400000	-0.92282700
C	-5.43119700	-0.09045500	0.33077600
H	-4.92297300	-2.02685000	1.12057500
H	-5.61608800	1.88776300	-0.49560000
H	-6.49376900	-0.20090100	0.52157000

6-member ring TS

Electronic Energy: -634.9425597

Thermal correction to Gibbs Free Energy: 0.22143100

C	2.93975400	-1.23636500	0.31772600
C	1.72054900	-1.74138500	-0.47174600
C	1.09579000	0.52489800	1.38470100
H	3.84189000	-1.73761600	-0.04253400
H	1.83650800	-1.43886300	-1.51875700
H	1.72681900	-2.83861800	-0.45199500
H	0.20597500	1.13246600	1.49346700
H	1.37019100	-0.10524900	2.22460000
H	2.83942400	-1.50625000	1.37541100
N	3.14509300	0.19394000	0.16753700
C	4.12598800	0.62632200	-0.80932100
H	3.87826000	0.27361300	-1.82005000
H	4.13923600	1.71478900	-0.81988900
H	5.11641700	0.24787400	-0.53918300
O	2.09328800	2.22436800	0.08337200
C	2.13209000	1.07239600	0.50395000
C	0.39347400	-1.25585200	0.05502500
H	0.07110800	-1.70396300	0.99225500
C	-0.53997600	-0.67280600	-0.75447500
H	-0.23118800	-0.38610300	-1.75869300
C	-1.90192600	-0.30975700	-0.38425300
C	-2.40253700	-0.44744500	0.92157100
C	-2.75793000	0.21674400	-1.36465400
C	-3.70712500	-0.08415400	1.22576700
H	-1.76364100	-0.83218400	1.71028000

C -4.06346800 0.57779000 -1.06024000

H -2.38621500 0.34121700 -2.37805400

C -4.54543000 0.42777700 0.23742800

H -4.07206000 -0.19616300 2.24196200

H -4.70594700 0.98108200 -1.83652500

H -5.56426100 0.71247200 0.47909900

6-member ring Int-2

Electronic Energy: -634.999605

Thermal correction to Gibbs Free Energy: 0.22498500

C 0.83909700 -0.70545300 -0.99925600

C 2.09804000 -1.42516900 -0.54323400

C 1.56195300 1.35863500 0.15804100

C 0.42461200 0.34314100 0.04579100

H 1.85436200 -2.11175500 0.28343500

H 2.49193300 -2.04317900 -1.35892200

H 1.01472400 -0.20511100 -1.95893200

H 0.04201600 -1.43834800 -1.15493800

H 1.41973300 2.03807900 1.00111300

H 1.58632100 1.98250500 -0.74538600

H 0.33065100 -0.17474800 1.01212400

C 2.95655800 0.76984800 0.31026300

O 3.86355200 1.45482000 0.76070500

C 4.45939200 -1.11833000 0.06058400

H 4.82026700 -1.53186100 -0.88768100

H 5.14583800 -0.34994000 0.41125900

H	4.41486900	-1.92956200	0.79830700
N	3.15355800	-0.51623000	-0.11967800
C	-0.87713500	1.00045800	-0.28824000
H	-0.83564700	1.96754400	-0.78603900
C	-2.15407800	0.43138400	-0.07071300
C	-2.33914700	-0.83655900	0.54190700
C	-3.32102800	1.13357600	-0.47440800
C	-3.60735500	-1.35828600	0.73271500
H	-1.47569200	-1.40741000	0.86870700
C	-4.58272000	0.60370800	-0.27834200
H	-3.20787800	2.10637700	-0.94496700
C	-4.73787300	-0.64694500	0.32613200
H	-3.72126700	-2.32970900	1.20394500
H	-5.45670900	1.16362500	-0.59626300
H	-5.72873800	-1.06150100	0.47890800

7-member ring Int-1

Electronic Energy: -674.2674138

Thermal correction to Gibbs Free Energy: 0.24473400

C	1.61684900	2.10297100	-0.34918300
C	-0.06285600	-0.87825900	0.53698600
C	1.92400200	-1.93197200	-0.62969200
C	1.14047300	-1.76530900	0.68305700
H	1.17035200	1.90546700	-1.31592500
H	0.12671400	0.19423500	0.56660300
H	2.79498400	-2.57265400	-0.44991300

H	1.28442200	2.96445400	0.21531800
H	1.29567900	-2.45185800	-1.36192400
H	1.80703700	-1.34994900	1.44835400
H	0.83266000	-2.75709800	1.03143300
C	2.37355400	-0.60985500	-1.26317600
H	1.49001200	-0.05151100	-1.57198800
H	2.95149800	-0.82418500	-2.17172800
N	3.17784300	0.21293800	-0.37490000
C	2.77974800	1.40295200	0.19196000
O	3.41477100	1.91624000	1.11462300
C	4.40819200	-0.37748000	0.11717600
H	4.88902300	-0.93284100	-0.69391300
H	5.06785900	0.41566300	0.46527200
H	4.23222200	-1.06450300	0.95472900
C	-2.51040000	-0.49025600	0.14961000
C	-3.77378000	-1.08094800	0.26633400
C	-2.44553700	0.87464500	-0.16249500
C	-4.93483500	-0.33471800	0.09646700
H	-3.84377600	-2.13997000	0.50034800
C	-3.60353600	1.62199100	-0.33048300
H	-1.47950300	1.35534400	-0.28612700
C	-4.85427300	1.02172100	-0.20027200
H	-5.90347100	-0.81441100	0.19597800
H	-3.53096000	2.67793900	-0.57176900
H	-5.75794000	1.60719900	-0.33554900
C	-1.30880300	-1.31969900	0.34905500

H -1.48267800 -2.39651000 0.35604000

7-member ring TS

Electronic Energy: -674.2589881

Thermal correction to Gibbs Free Energy: 0.25076700

C 0.93759800 -0.23599900 1.45892700

C 0.27630200 1.15692100 -0.29826200

C 2.79474100 1.63822300 -0.64311900

C 1.40276200 2.16787000 -0.27614200

H 1.40974500 0.53257800 2.05769900

H 0.40312900 0.30887400 -0.96796300

H 2.76689100 1.19856800 -1.64813100

H -0.01755800 -0.61332500 1.79926300

H 3.47162000 2.49822500 -0.70396500

H 1.15503500 2.96141100 -0.99326100

H 1.44125300 2.65468000 0.70667700

C 3.42036400 0.61784300 0.31988000

H 3.30415700 0.95328200 1.35546800

H 4.49907200 0.58073800 0.13896600

N 2.93166500 -0.74492800 0.17059800

C 1.69094700 -1.15405600 0.60986100

O 1.20120100 -2.22916600 0.25514100

C 3.63156000 -1.58055100 -0.78558200

H 4.67722300 -1.70503100 -0.48465800

H 3.13943600 -2.55080100 -0.81468500

H 3.60983900 -1.14484400 -1.79345800

C -2.15693400 0.60556900 -0.01828100

C -3.43712800 1.15339000 0.15940100

C -2.05164900 -0.76924600 -0.29411000

C -4.57556500 0.36807900 0.03737300

H -3.53325400 2.21199900 0.38658000

C -3.19349600 -1.55155500 -0.41080400

H -1.07698600 -1.24194600 -0.38146700

C -4.45817500 -0.98916600 -0.25226000

H -5.55607000 0.81425900 0.17142700

H -3.09211600 -2.61254500 -0.61587800

H -5.34597000 -1.60690600 -0.34280600

C -0.98785300 1.47014200 0.10714700

H -1.14756700 2.42383100 0.61070800

7-member ring Int-2

Electronic Energy: -674.3124547

Thermal correction to Gibbs Free Energy: 0.25402300

C 0.80972400 -0.08045600 1.00683700

C 0.32601300 0.87407300 -0.12349100

C 2.71576300 1.69316800 -0.70548800

C 1.28098400 2.05948100 -0.31920100

H 1.20846000 0.50814700 1.84064500

H 0.31461500 0.28778700 -1.05483600

H 2.73070400 1.20683500 -1.68885800

H -0.02503600 -0.66911600 1.38650500

H 3.29302200 2.61963600 -0.80371000

H	0.86586400	2.72161600	-1.08731500
H	1.30149200	2.64182300	0.61340000
C	3.43285900	0.78001900	0.29587700
H	3.26962900	1.14044900	1.31894300
H	4.51112000	0.83001200	0.12472500
N	3.06437500	-0.62673500	0.18948600
C	1.81080800	-1.09106500	0.47730300
O	1.47284100	-2.24996300	0.26931100
C	4.01018900	-1.51320700	-0.46265900
H	4.94741300	-1.55708700	0.10227900
H	3.56722000	-2.50640600	-0.50978200
H	4.23082600	-1.16941500	-1.48072800
C	-2.22810400	0.55343600	0.01453800
C	-3.50756500	1.11329600	0.27121000
C	-2.17721500	-0.81551800	-0.36439800
C	-4.65954200	0.35878000	0.14860100
H	-3.57127600	2.15749400	0.56548700
C	-3.33874000	-1.56084400	-0.48034200
H	-1.22061800	-1.29613700	-0.54652100
C	-4.58541400	-0.98469200	-0.22945100
H	-5.62507400	0.81337900	0.34805500
H	-3.27374400	-2.60603500	-0.76615200
H	-5.48997000	-1.57658100	-0.32340000
C	-1.06836000	1.35587000	0.13970300
H	-1.19639700	2.38640600	0.46612500

8-member ring Int-1

Electronic Energy: -713.582719

Thermal correction to Gibbs Free Energy: 0.27038700

C	4.32930000	-1.56446100	1.19213400
C	2.32320500	-0.04288200	-1.19228900
C	-1.43515400	-0.63134900	-0.35882800
C	0.80078500	0.07420200	-1.28650800
C	0.05023000	-0.64141000	-0.15242600
H	3.25637900	-1.69568800	1.12654400
H	-1.78927600	-1.11802200	-1.26778400
H	2.61361300	-1.10108000	-1.16587800
H	0.47277600	-0.34419300	-2.24536500
H	4.92532300	-2.33381800	1.66479300
H	2.77873500	0.37844900	-2.09558300
H	0.50622300	1.13124800	-1.29824900
H	0.28410200	-0.18078400	0.81429600
H	0.40547600	-1.68109300	-0.10113100
C	2.91802300	0.66703900	0.02810500
H	2.50356800	0.26564000	0.95679800
H	2.63321700	1.72562300	0.00757500
N	4.36834200	0.60654400	0.08235200
C	5.07351900	-0.44951700	0.61563600
O	6.30571800	-0.48060000	0.61223700
C	5.09849700	1.66256400	-0.59026500
H	4.83079300	1.71226400	-1.65268600
H	4.87922400	2.63335600	-0.13124600

H	6.16250300	1.45177100	-0.49955000
C	-3.77275700	0.00516500	0.30138000
C	-4.50419500	0.95143600	1.02869800
C	-4.47277500	-0.85822200	-0.55165400
C	-5.88454000	1.05054100	0.89464300
H	-3.97915300	1.62278300	1.70311200
C	-5.85144200	-0.76014400	-0.68778800
H	-3.93706100	-1.62628900	-1.10078300
C	-6.56394900	0.19623200	0.03226100
H	-6.42971600	1.79533400	1.46585800
H	-6.37494300	-1.44035200	-1.35241200
H	-7.64169100	0.26809700	-0.07274100
C	-2.30909400	-0.04752400	0.46436400
H	-1.92214700	0.46573200	1.34528800

8-member ring TS

Electronic Energy: -713.5678403

Thermal correction to Gibbs Free Energy: 0.27891000

C	0.74729600	-0.35595800	1.46224800
C	2.98536400	0.96470000	-0.98390100
C	0.08134200	1.28284000	-0.02083100
C	2.31738100	2.32988700	-0.77088300
C	1.13309600	2.35297700	0.20689400
H	1.28185000	0.29455700	2.14427700
H	0.27517100	0.54795500	-0.79750000
H	2.31689300	0.32350300	-1.56898000

H	1.98423800	2.69613800	-1.74878900
H	-0.23542600	-0.68233600	1.77713000
H	3.87159800	1.11003900	-1.61023800
H	3.06210700	3.05099200	-0.41345400
H	0.65574000	3.33718400	0.13840500
H	1.50953900	2.29172900	1.23418000
C	3.36388100	0.19715300	0.30746600
H	3.05805200	0.75667600	1.19354500
H	4.44977900	0.08888400	0.38496300
N	2.79160800	-1.14037000	0.36167100
C	1.45238000	-1.34558200	0.64271700
O	0.86169100	-2.34167600	0.21913900
C	3.43195700	-2.12677400	-0.49034200
H	3.26981900	-1.92368800	-1.55812700
H	4.50768700	-2.12442300	-0.29326000
H	3.01799900	-3.10896500	-0.27054800
C	-2.34227300	0.59503400	0.06820400
C	-3.65182400	1.06393200	0.26666000
C	-2.16818400	-0.72807800	-0.37609000
C	-4.74967200	0.25632400	0.00545600
H	-3.80164200	2.08012800	0.62221900
C	-3.27044400	-1.53401800	-0.63073200
H	-1.17355100	-1.15046900	-0.48557600
C	-4.56296300	-1.04760400	-0.44834900
H	-5.75267500	0.64206200	0.15902600
H	-3.11522300	-2.55557300	-0.96271900

H -5.41928600 -1.68390800 -0.64789400

C -1.22388700 1.48682500 0.34301300

H -1.45816900 2.37556800 0.92934500

8-member ring Int-2

Electronic Energy: -713.6156856

Thermal correction to Gibbs Free Energy: 0.28225200

C -0.64208900 -0.11588700 -1.11414100

C -3.11766200 0.97308600 0.95824300

C -0.18488700 0.98688500 -0.09600700

C -2.29650800 2.26290100 0.83329500

C -1.09052900 2.23892700 -0.12048900

H -1.14926100 0.35450000 -1.96177600

H -0.22022300 0.54304400 0.91018300

H -2.57786500 0.26571900 1.59828300

H -1.94837700 2.52920100 1.83801300

H 0.23994000 -0.62264500 -1.50657300

H -4.04550100 1.20512600 1.49107800

H -2.95145300 3.08350100 0.51655700

H -0.48036900 3.11417500 0.12724600

H -1.42414700 2.40339500 -1.15294600

C -3.42498700 0.24989700 -0.37339100

H -3.07951500 0.83944400 -1.22616100

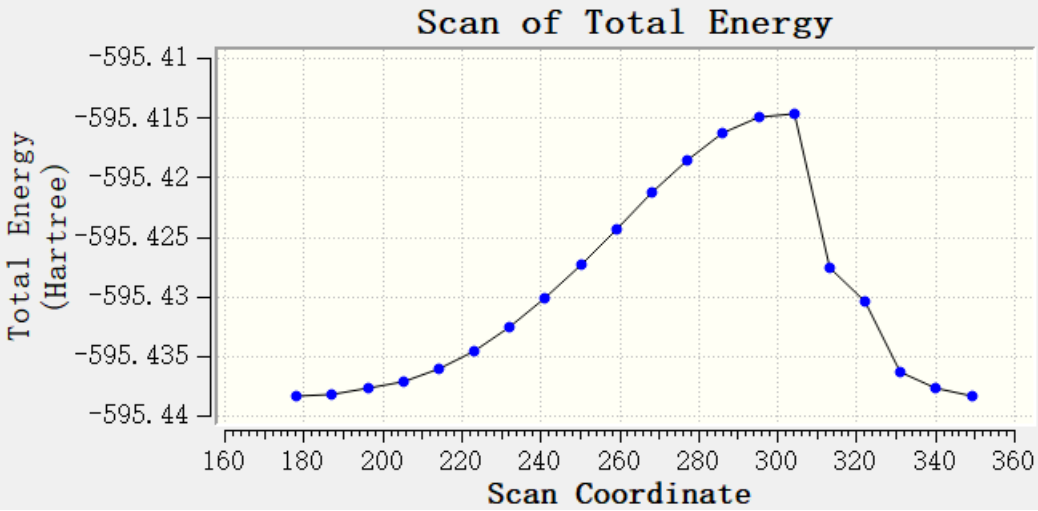
H -4.50183700 0.12393200 -0.51170200

N -2.82926600 -1.07951200 -0.42982300

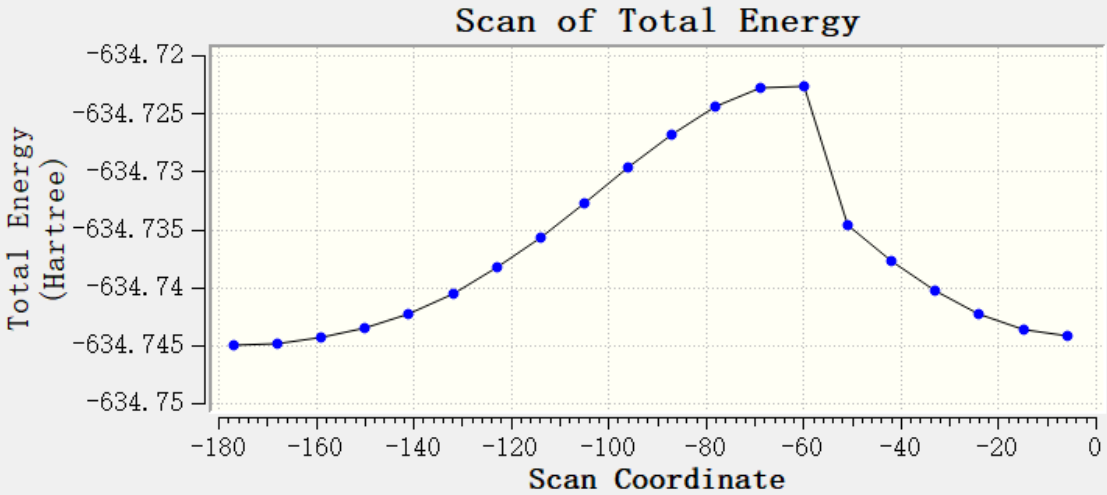
C -1.46821500 -1.23881300 -0.50669800

O	-0.91612600	-2.26172600	-0.11827800
C	-3.58161800	-2.13417100	0.22911700
H	-3.65716200	-1.96776800	1.31229800
H	-4.59014900	-2.17430500	-0.19131000
H	-3.07377400	-3.08263100	0.06617900
C	2.36678100	0.55492300	-0.10540500
C	3.67220200	1.05060000	-0.36454600
C	2.25755500	-0.76120500	0.41890500
C	4.79523700	0.28784100	-0.10375500
H	3.77958200	2.05311600	-0.77035300
C	3.39166400	-1.51579800	0.67143300
H	1.28108600	-1.20241700	0.59488000
C	4.66468500	-1.00183900	0.41907400
H	5.78150500	0.69360300	-0.30725500
H	3.28262100	-2.52168500	1.06480100
H	5.54646800	-1.60104600	0.62154500
C	1.24148400	1.37368000	-0.36892100
H	1.42361500	2.34797400	-0.81828600

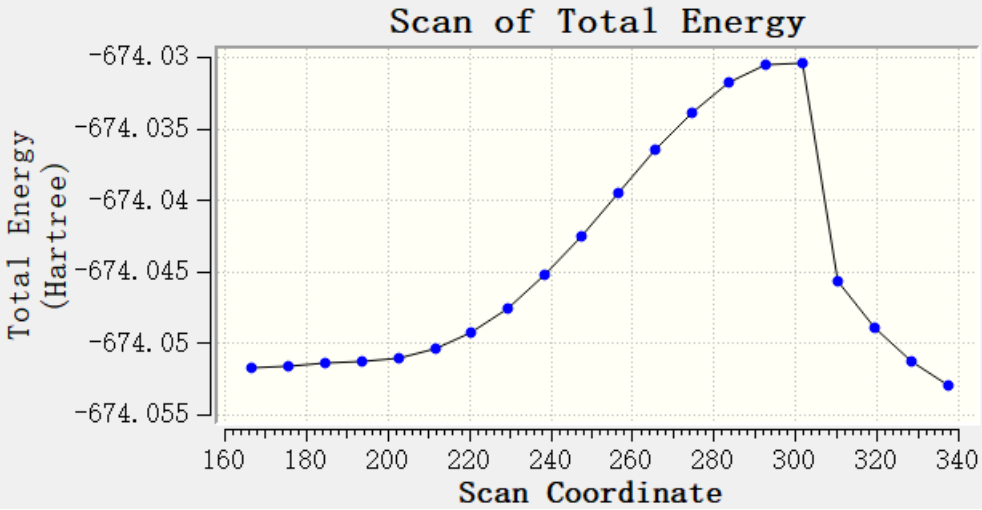
Relaxed Scan Energy Curve
5-member ring



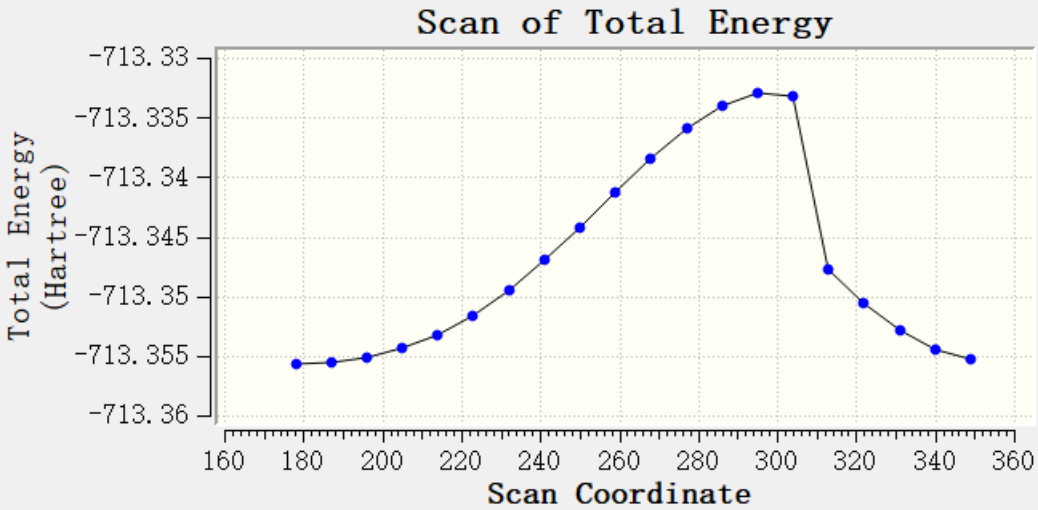
6-member ring



7-member ring



8-member ring



GENERAL SYNTHESIS PROCEDURES

The 5,6,7,8-*exo*-trig cyclization substrates were synthesized using the General Procedure adapted from *Biegasiewicz et al.*[8] Chloroamide starting material and afforded lactam for the 5, 6, and 7 membered cyclization have all been previously characterized in *Biegasiewicz et al* – as well as the hydrodehalogenation product for the 5 membered amide. Here we characterize the substrate and products of the 8 membered lactamization (cycloadduct and hydrodehalogenation product). Additionally, the previously uncharacterized 6 and 7 membered hydrodehalogenation product

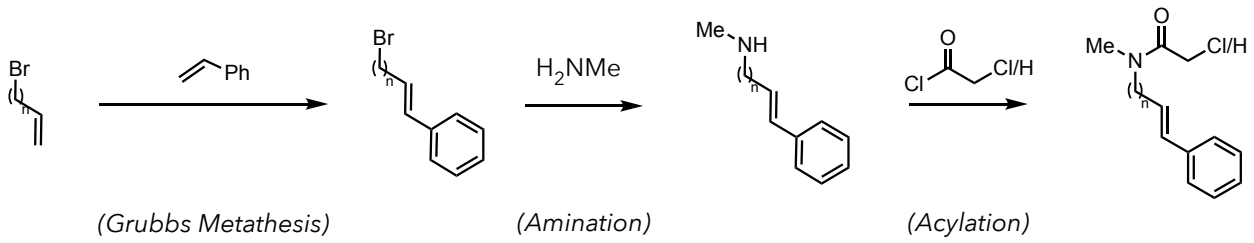
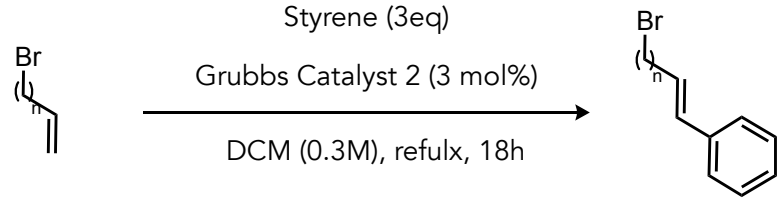
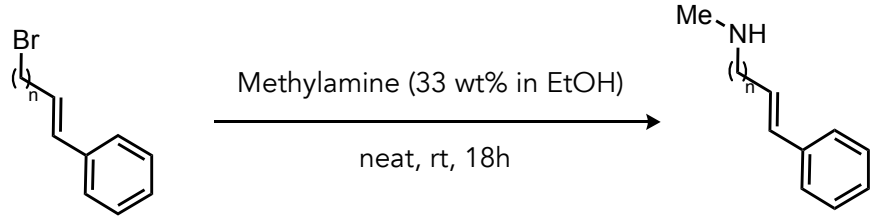


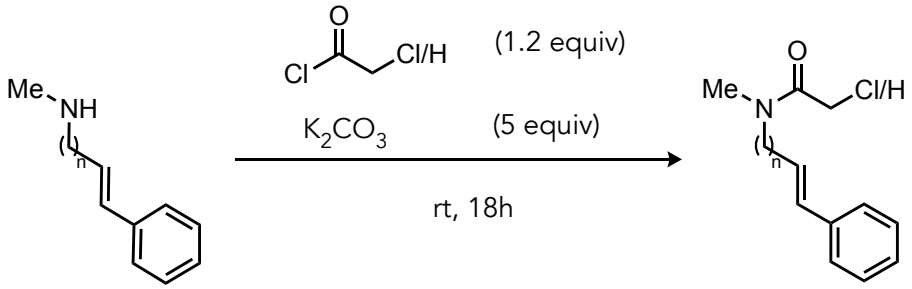
Figure S1. Synthetic scheme for the synthesis of adapted from *Biegasiewicz et al.*[3]



Grubbs Metathesis. Allylic bromide (1 equiv) and styrene (3 equiv) are added to a flame-dried round bottom flask with a magnetic stir bar under nitrogen atmosphere. Dry, degassed DCM (0.3 M) is added with Grubbs Catalyst 2 (0.3 mol%) and heated under reflux for 18h. The reaction is then concentrated under reduced pressure and purified by silica gel chromatography (mobile phase gradient: 100% hexanes). See Substrates Characterization for Yields.

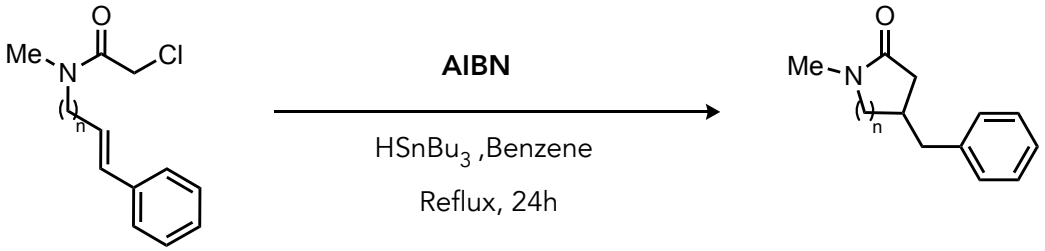


Amination. Allylic bromide from Grubbs Metathesis is added with to a flask with stir bar. Methylamine solution (33 % wt. in ethanol, 10 equiv) is added directly and in one portion. Sodium Iodide (0.1 equiv) is added, and reaction mixture is equid with a reflux condenser and heated to 40 °C and allowed to procced overnight. A solution of 1 M sodium hydroxide is added, and the mixture is transferred to a separatory funnel containing 1 M HCl and diethyl ether. After extraction, the aqueous layer is basified using 1 M sodium hydroxide and the product is extracted of the aqueous layer with diethyl ether. The combined ethereal extracts are dried using sodium sulfate and concentrated under reduced pressure to afford amine which is acylated without further purification. See Substrates Characterization for Crude Yields.

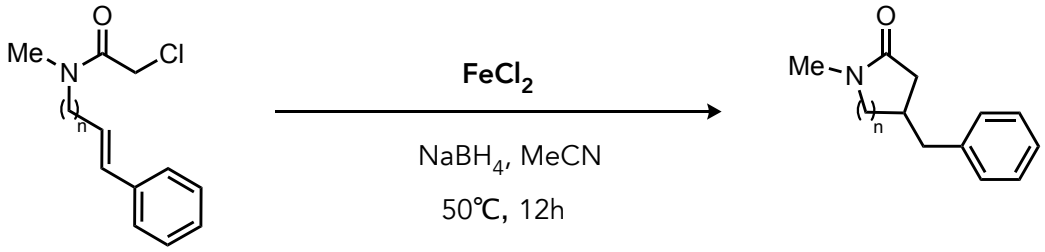


Acylation. The secondary amine (1 equiv.) is added to a flame dried flask under nitrogen pressure containing dry DCM and postassium carbonate (5 equiv.) for a final concentration of 0.25 M for the secondary amine. The chloroacetylchloride (for substrate) or acetylchloride (HDH Standards) (3 equivalents) is added dropwise to the stirred solution at room temperature. The solution is stirred overnight and then poured into a separatory funnel containing a 1:1 solution of 10% HCl and DCM. The aqueous layer is extracted with DCM. The organic layers are collected, washed with brine, dried with anhydrous sodium sulfate and concentrated *in vacuo* to yield a crude amide as an oil. The crude oil is purified via silica gel flash chromatography in a gradient of 12 % EtOAc/Hexanes to 60% EtoAC/Hexanes. See Substrates Characterization for Yields.

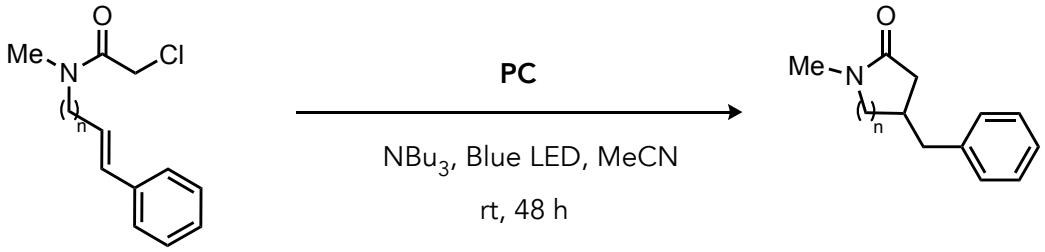
LACTAMIZATION PRODECURES



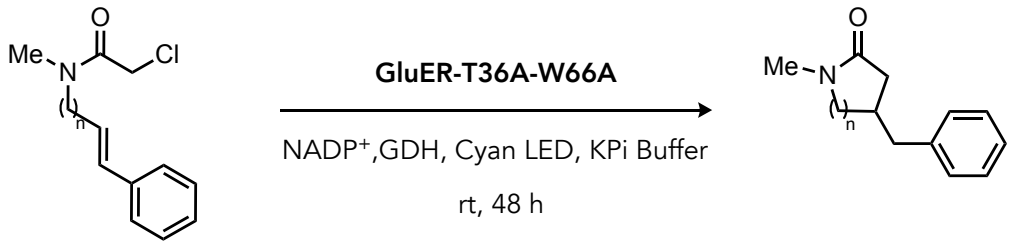
Organotin Method. Procedure adapted from Sato *et al*.[5] and detailed below. The chloroamide starting material (0.224 mmol) was dissolved in dry benzene (4 ml). To this was added a solution of Bu_3SnH (1 equiv.) and AIBN (9 mol%) in dry benzene (6 ml) via a syringe during 40 min under reflux and the mixture was further refluxed for 12 h. After cooling, the solvent was evaporated off and the residue was chromatographed on silica gel. The crude residue is purified using automated silica gel chromatography* (SNAP KP-Sil 10 g column) with the following biotage gradient (CV =column volume): equilibration10% EtOAc/90% hexanes → 25% EtOAc/75% hexanes, 5 CV | gradient-25% EtOAc/75% hexanes, 1 CV | 25% EtOAc/75% hexanes → 100% EtOAc, 4 CV | 100% EtOAc, 18 CV. The product reliably elutes during the 100% ethyl acetate phase of the gradient and can be collected in fractions 8-15. TLC analysis using potassium permanganate stain often may also be used to visualize the product containing fractions, which appear on the plate after heating as temporary white spots, which disappear again over time. LCMS analysis of small aliquots (~15 µL) of suspected product-containing fractions may also be performed. Fractions containing product are combined and concentrated and weighed for isolated yield determination. Yield defined as a mixture of HDH and Lactam Products



Iron Hydride Method. Adapted From Kyne *et al.* and detailed below.[6] The $FeCl_2$ (10 mol%) and $NaBH_4$ (2 equiv) were added to a screw cap tube in a glovebox. Acetonitrile (0.375 mL) was added under argon, and the mixture stirred for 15 min at room temperature. A solution of chloroamide (0.224 mmol) in acetonitrile (0.125 mL) was added under argon. The reaction was sealed, removed from the glovebox, heated to 50°C and allowed to procced overnight. The reaction was cooled to room temperature, quenched with water and the aqueous phase extracted with DCM. The combined organic phase was washed with brine, dried with sodium sulfate, and the solvent removed in vacuo. The crude residue is purified using automated silica gel chromatography* (SNAP KP-Sil 10 g column) with the following biotage gradient (CV =column volume): equilibration10% EtOAc/90% hexanes → 25% EtOAc/75% hexanes, 5 CV | gradient- 25% EtOAc/75% hexanes, 1 CV | 25% EtOAc/75% hexanes → 100% EtOAc, 4 CV | 100% EtOAc, 18 CV. The product reliably elutes during the 100% ethyl acetate phase of the gradient and can be collected in fractions 8-15. TLC analysis using potassium permanganate stain often may also be used to visualize the product containing fractions, which appear on the plate after heating as temporary white spots, which disappear again over time. LCMS analysis of small aliquots (~15 µL) of suspected product-containing fractions may also be performed. Fractions containing product are combined and concentrated and weighed for isolated yield determination. Yield defined as a mixture of HDH and Lactam Products



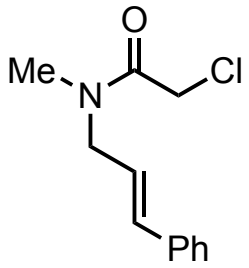
Photoredox Method. Adapted from Fava *et al* and detailed below.[7] An 8 dram vial was charged with chloroamide (0.25 mmol 1 equiv.), $Ir(ppy)_2(dtb\text{-}bpy)PF_6$ (**PC**, 1 mol%) and NBu_3 (2 equiv.) under nitrogen in a glovebox. Degassed acetonitrile (12.5 ml, 0.02M) was added and the reaction sealed. The reaction was then irradiated with a 450 nm Kessil Lamp for 48 hrs. After this period, the mixture was diluted with Et_2O and the organic phase was extracted three times with brine, dried over MgSO4, filtered and evaporated under reduce pressure. The crude residue is purified using automated silica gel chromatography* (SNAP KP-Sil 10 g column) with the following biotage gradient (CV =column volume): equilibration10% EtOAc/90% hexanes → 25% EtOAc/75% hexanes, 5 CV | gradient- 25% EtOAc/75% hexanes, 1 CV | 25% EtOAc/75% hexanes → 100% EtOAc, 4 CV | 100% EtOAc, 18 CV. The product reliably elutes during the 100% ethyl acetate phase of the gradient and can be collected in fractions 8-15. TLC analysis using potassium permanganate stain often may also be used to visualize the product containing fractions, which appear on the plate after heating as temporary white spots, which disappear again over time. LCMS analysis of small aliquots (~15 µL) of suspected product-containing fractions may also be performed. Fractions containing product are combined and concentrated and weighed for isolated yield determination. Yield defined as a mixture of HDH and Lactam Products



Photoenzymatic Method. Procedure adapted from Biegasiewicz *et al* and detailed below.[8] All reactions are run with 0.224 mmol of chloroamide starting material. Solid (D)-glucose (6 equiv.) and GDH-105 lyophilized lysate (0.2 mg lysate/ mg of starting material) are weighed out into a 25 mL round bottom flask equipped with a magnetic stir bar. This, along with thoroughly degassed reaction buffer (100 mM KPi, pH = 8, 10% v:v glycerol) and the weighed out starting material are taken into a Coy® anaerobic chamber. Reaction buffer, NADP+ (made as a 5 mg/mL solution in reaction buffer, 1 mol%), and purified GluER T36A W66A solution (1 mol%) are added such that the final liquid volume added (12.5 mL) creates a reaction mixture with a starting material concentration of 17.92 mM. Starting material is dissolved in degassed THF cosolvent (2 µL/ mg of starting material). This solution is taken up and pipetted directly into the reaction flask. The reaction flask is capped and sealed with a rubber septum and taken out of the anaerobic chamber where it is placed to stir at 400rpm with fan cooling the reaction setup under nitrogen atmosphere irradiated with cyan light (50 W Chanzon high power LED chip, **λ**max= 490 nm, measured photon flux = 12,000 mM/m2 s) for 36 h. Workup is performed as follows: the contents of the reaction flask are poured into a 125 mL Erlenmeyer flask containing 50 mL of 1 M aqueous hydrochloric acid and 50 mL of dichloromethane. This is stirred vigorously for 45 minutes, after which time the biphasic mixture is filtered through a thick pad of Celite® to remove precipitated material. The filtrate is poured into a separatory funnel and the dichloromethane layer is collected. The aqueous layer is extracted with dichloromethane (2 x 50 mL) (without any emulsion-related difficulties), and the combined organic layers are dried with anhydrous sodium sulfate and concentrated. The crude residue is purified using automated silica gel chromatography* (SNAP KP-Sil 10 g column) with the following biotage gradient (CV =column volume): equilibration10% EtOAc/90% hexanes → 25% EtOAc/75% hexanes, 5 CV | gradient- 25% EtOAc/75% hexanes, 1 CV | 25% EtOAc/75% hexanes → 100% EtOAc, 4 CV | 100% EtOAc, 18 CV. The product reliably elutes during the 100% ethyl acetate phase of the gradient and can be collected in fractions 8-15. TLC analysis using potassium permanganate stain often may also be used to visualize the product containing fractions, which appear on the plate after heating as temporary white spots, which disappear again over time. LCMS analysis of small aliquots (~15 µL) of suspected product-containing fractions may also be performed. Fractions containing product are

combined and concentrated and weighed for isolated yield determination. Yield defined as a mixture of HDH and Lactam Products

SUBSTRATE CHARACTERIZATION

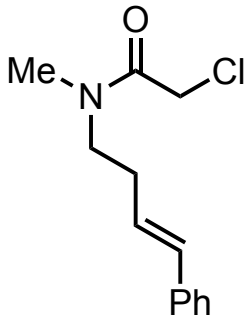


5-exo Substrate (*E*)- 2-chloro-N-cinnamyl-N-methylacetamide (reported by Biegasiewicz *et al.*[8])

Grubbs Metathesis: (Cinnamyl Bromide was purchased)
Amination: (1.7g, 78%)
Acylation (Chloroacytal Chloride) : (835.7 mg, 55%)

^{1}H-NMR (500 MHz, CDCl3) **δ** 7.38 – 7.28 (m, 5H), 6.51 (t, J = 13 Hz, 1H), 6.10-6.18 (m, 1H), 4.17-4.14 (m, 2H), 4.11 (s, 2H), 3.04 (d, J = 30 Hz, 3H).

^{13}C-NMR (126 MHz, CDCl3) **δ** 166.73, 166.39, 152.98, 136.35, 135.83, 133.50, 132.63, 128.64, 127.90, 126.50, 123.45, 123.30, 52.20, 50.10, 41.43, 41.03, 35.02, 34.05.

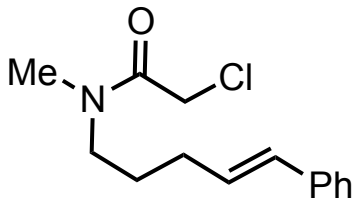


6-exo Substrate (*E*)-2-chloro-N-methyl-N-(4-phenylbut-3-en-1-yl)acetamide (reported by Biegasiewicz *et al*.[8])

Grubbs Metathesis: (773 mg, 11%)
Amination: (159 mg, 34%)
Acylation (Chloroacytal Chloride) : (191 mg, 81%)

^{1}H-NMR 500 MHz, CDCl3) **δ** 7.34 – 7.27 (m, 4H), 7.24 – 7.18 (m, 1H), 6.40 (t, J = 15 Hz 1H), 6.14 (m, 1H), 4.07 (d, J = 11 Hz, 2H), 3.51 (m, 2H), 3.05 (d, J = 35 Hz, 3H), 2.45 (m, 2H).

^{13}C-NMR (126 MHz, CDCl3) **δ** 166.41, 137.28, 136.75, 133.30, 132.32, 128.63, 128.55, 127.66, 127.26, 126.53, 126.11, 125.00, 50.28, 48.25, 41.46, 40.94, 36.16, 33.84, 32.06, 30.90.

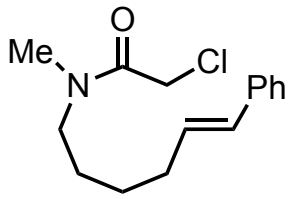


7-exo Substrate (*E*)-2-chloro-N-methyl-N-(5-phenylpent-4-en-1-yl)acetamide (reported by Biegasiewicz *et al*.[8])

Grubbs Metathesis: (1.12, 22.8%)
Amination: (990 mg, 40%)
Acylation (Chloroacytal Chloride) : (434 mg, 55%)

^{1}H-NMR 500 MHz, CDCl3) **δ** 7.36-7.36 (m, 4H), 7.25 – 7.17 (m, 1H), 6.39 (t, J = 14 Hz, 1H), 6.19 (m, 1H), 4.07 (d, J = 6.2 Hz, 2H), 3.41 (dt, J= 24, 6 Hz, 2H), 3.03 (d, J = 53.3 Hz, 3H), 2.26 (m, 2H), 1.87 – 1.66 (m, 2H).

^{13}C-NMR (126 MHz, CDCl3) **δ** 166.44, 137.55, 137.17, 131.37, 130.58, 129.52, 128.52, 127.32, 127.03, 125.99, 49.80, 48.04, 41.49, 40.93, 35.72, 33.72, 27.94, 26.59.



8-exo Substrate : (*E*)-2-chloro-N-methyl-N-(6-phenylhex-5-en-1-yl)acetamide

Grubbs Metathesis: (2.2g, 18.7%)
Amination: (1.45 g, 69%)
Acylation (Chloroacytal Chloride): (342 mg, 45%)

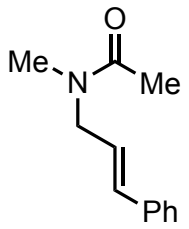
^{1}H-NMR 400 MHz, CDCl3) **δ** 7.1 (m, 4H), 7.20 (m, 1H) , 6.38 (m 1H) , 6.19 (m, 1H) , 4.06 (s 2H), 3.37 (dt, *J* = 8 and 25 Hz, 2H), 3.01 (dd, *J* = 9 and 43 Hz, 3H) , 2.26 (p, *J* = 7 Hz, 2H) , 1.57 (m, 4H).

^{13}C-NMR (126 MHz, CDCl3) **δ** 169.48, 166.71, 137.43, 131.40, 130.77, 130.32, 129.61, 128.51, 127.04, 126.93, 125.71, 50.35, 48.23, 41.35, 40.77, 35.65, 33.81, 32.56, 27.89, 26.34.

IR: (cm^{-1}) 2931, 1742, 1648, 1617, 1446, 1405, 965, 744, 693

HR-MS[M+1]: calculated 266.1306, found 266.1299

PRODUCT CHARACTERIZATION

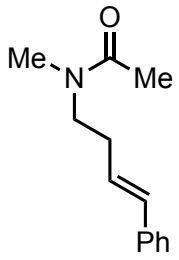


5 exo HDH: (*E*) - N-cinnamyl-N-methylacetamide (reported by Biegasiewicz *et al*.[8])

Acylation (Acetyl Chloride): (129 mg, 89%)

^{1}H-NMR 400 MHz, CDCl3) **δ** 7.38 – 7.19 (m, 5H), 7.34 – 7.21 (m, 3H), 6.48 (t, J = 10 Hz, 1H), 6.17 – 6.10 (m, 1H), 4.07 (dd, J = 44, 4 Hz, 2H), 2.99 (s, 3H), 2.14 (s, 3H).

^{13}C-NMR (126 MHz, CDCl3) **δ** 170.50, 132.84, 131.76, 129.95, 128.72, 127.70, 126.41, 124.59, 123.69, 52.65, 49.33, 35.47, 33.53, 21.86, 21.34.



6 exo HDH: (*E*)-N-methyl-N-(4-phenylbut-3-en-1-yl)acetamide

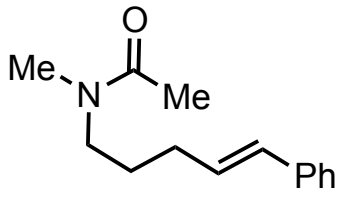
Acylation (Acetyl Chloride): (98 mg, 71%)

^{1}H-NMR (400 MHz, CDCl3) **δ** 7.28 (m, 4H), 7.12 (m,1H), 6.38 (dd, J= 15, 11, 1H), 6.09 (m, 1H), 3.40 (dt, J = 33, 9 Hz, 2H), 2.90 (d, J = 19 Hz, 3H), 2.40 (m, 2H), 2.00 (d, J=16 Hz, 3H) .

^{13}C-NMR (126 MHz, CDCl3) **δ** 171.14, 137.43, 136.96, 132.78, 131.85, 128.62, 128.53, 127.49, 127.15, 126.06, 125.63, 50.73, 47.42, 36.56, 33.40, 32.77, 32.06, 31.25, 21.88, 21.39.

IR: (cm^{-1}) 3024, 2931, 1621, 1492, 1400, 1359, 1260, 1198, 1030, 966, 743, 589

HR-MS[M+1]: calculated 204.1382, found 204.1381



7exo HDH : (*E*)-N-methyl-N-(5-phenylpent-4-en-1-yl)acetamide

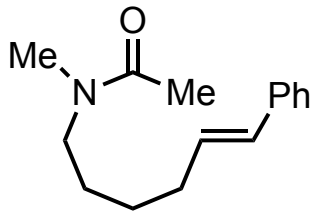
Acylation (Acetyl Chloride): (83 mg, 62%)

^{1}H- NMR (400 MHz, CDCl3) **δ** 7.30(m 4H), 7.21(m 1H), 6.40 (m, 1H), 6.20 (m, 1H), 3.36 (dt *J*= 8 and 40 Hz, 2H) , 2.97 (d, *J* = 24, 3H), 2.23 (p, *J* = 7 Hz, 2H), 2.08 (d, J = 7 Hz, 3H), 1.73 (m, 2H).

^{13}C-NMR (126 MHz, CDCl3) 170.50, 137.66, 137.29, 131.12, 130.34, 129.86, 128.89, 128.60, 128.50, 127.24, 126.95, 125.99, 50.27, 47.21, 36.20, 33.23, 30.36, 30.00, 27.90, 27.00, 21.99, 21.30.

IR: (cm^{-1}) 2928, 1637, 1490, 1433, 1397, 1012, 964, 743, 692, 601

HR-MS[M+1]: calculated 218.1539, found 218.1537



8 exo HDH : (*E*)-N-methyl-N-(6-phenylhex-5-en-1-yl)acetamide

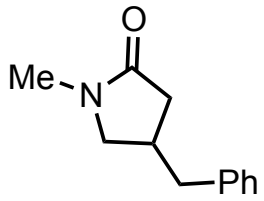
Acylation (Acetyl Chloride): (101 mg, 77%)

^{1}H-NMR (400 MHz, CDCl3) **δ** 7.33 (m, 4H), 7.19 (m, 1H), 6.38 (dd, *J* = 6 and 16 Hz, 1H), 6.20 (m, 1H), 3.34 (dt, *J* = 8 and 40 Hz, 2H), 2.93 (dd, *J* = 8 and 24 Hz, 3H), 2.25 (p, *J* = 7 Hz, 2H), 2.09 (d, *J* = 6 Hz, 3H), 1.49 (m, 4H).

^{13}C- NMR (126 MHz, CDCl3) **δ** 170.40, 137.66, 137.29, 131.12, 130.34, 128.50, 126.95, 125.98, 50.26, 47.21, 36.20, 33.23, 30.36, 30.00, 27.90, 26.93, 21.99, 21.29.

IR: (cm^{-1}) : 3023, 2829, 2856, 1637, 1491, 1433, 1397, 1184, 964, 743, 602, 468

HR-MS [M+1]: calculated 232.1695, found 232.1689

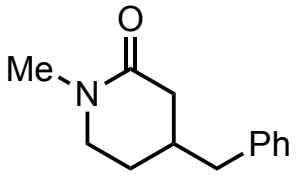


5 exo Lactam: 4-benzyl-1-methylpyrrolidin-2-one (reported by Biegasiewicz *et al.*[8])

Photoenzymatic Method : (39 mg, 82.4%)

^{1}H-NMR 500 MHz, CDCl3) **δ** 7.29 (t, J= 7 Hz, 2H), 7.22 (t, J= 7 Hz, 1H), 7.16 (d, J= 7 Hz, 2H), 3.36 (dd, J= 10, 7 Hz, 1H), 3.08 (dd, J = 10, 5 Hz, 1H), 2.80 (s, 3H), 2.80 – 2.75 (m, 1H), 2.72 – 2.59 (m, 2H), 2.53 – 2.44 (dd, J = 15, 8 Hz, 1H), 2.16 (dd, J = 17, 7 Hz, 1H).

^{13}C-NMR (126 MHz, CDCl3) **δ** 174.20, 139.26, 128.93, 126.69, 54.65, 40.67, 37.24, 32.92, 29.71.

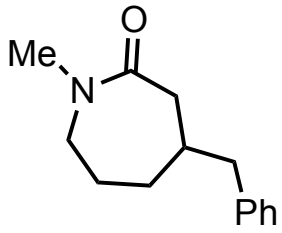


6 exo Lactam : 4-benzyl-1-methylpiperidin-2-one (reported by Biegasiewicz *et al.*[8])

Photoenzymatic Method : (37 mg, 72.8%)

^{1}H-NMR 500 MHz, CDCl3) **δ** 7.28 (t, J=7 Hz, 2H), 7.20 (t, J=7 Hz, 1H), 7.13 (d, 2H), 3.27 – 3.23 (m, 2H), 2.92 (s, 3H), 2.62 (dd, J = 13, 6 Hz, 1H), 2.59 (dd, J = 13, 6 Hz, 1H), 2.46 (m, 1H), 2.06 (m, 2H), 1.86 (m, 1H), 1.48 (m, 1H).

^{13}C-NMR (126 MHz, CDCl3) **δ** 169.55, 139.18, 128.89, 128.53, 126.30, 49.10, 42.02, 38.47, 35.24, 34.41, 28.56.

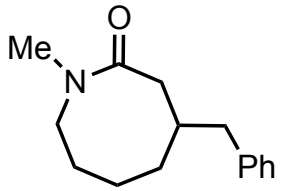


7 exo Lactam: 4-benzyl-1-methylazepan-2-one (reported by Biegasiewicz *et al*.[8])

Photoenzymatic Method : (40 mg, 73.6%)

^{1}H-NMR 500 MHz, CDCl3) **δ**7.27 (t, J=7 Hz, 2H), 7.19 (t, J= 7 Hz, 1H), 7.15 (d, J= 7 Hz, 2H), 3.46 (dd, J = 14, 11 Hz, 1H), 3.20 (dd, J = 15, 6 Hz, 1H), 2.97 (s, 3H), 2.72 (dd, J = 13, 5 Hz, 1H), 2.56 – 2.44 (m, 3H), 1.93 (m, 1H), 1.79 (m, 2H), 1.46 (m, 1H), 1.28 (m, 1H).

^{13}C-NMR (126 MHz, CDCl3) **δ** 174.38, 139.91, 129.41, 128.29, 125.86, 51.24, 43.12, 36.19, 35.25, 26.93.



8 exo Lactam : 4-benzyl-1-methylazepan-2-one

Photoenzymatic Method : (36 mg, 66%)
After HPLC purification : (5 mg, 9%)

^{1}H-NMR (400 MHz, CDCl3) **δ** 7.29 (m 2H) , 7.22 (m, 3H), 3.68 (m, 1H) , 3.29 (dt, *J* = 4 , 48 Hz, 1H), 2.94 (s, 3H) , 2.75 (dd, *J* = 7 and 13 Hz, 1H) , 2.50 (m, 3H), 2.16 (m, 1H), 1.75 (m, 3H), 1.51 (m, 1H), 1.18 (m, 2H).

^{13}C-NMR (126 MHz, CDCl3) **δ** 174.09, 161.27, 140.32, 129.33, 128.29, 126.03, 49.17, 43.14, 41.36, 38.92, 33.28, 28.41, 21.88.

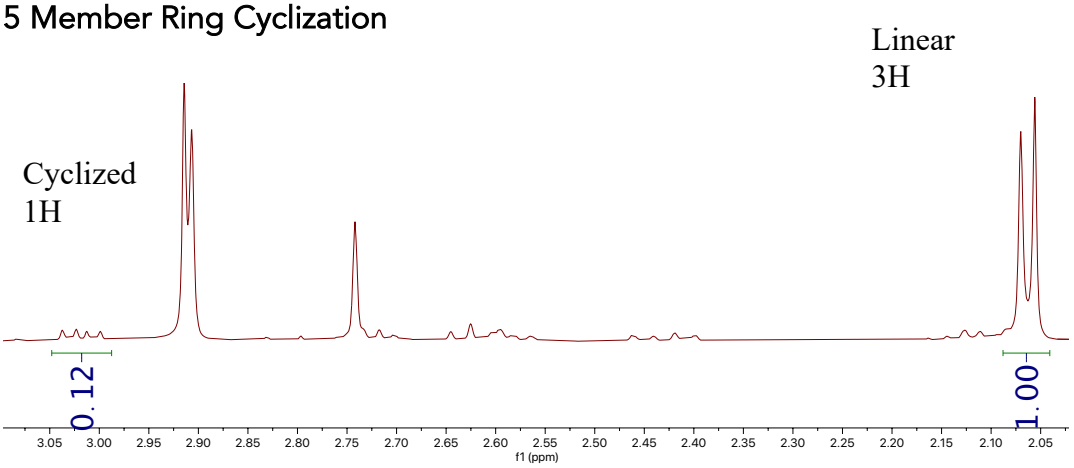
IR: (cm^{-1}) 2922, 1634, 1453, 1423, 1396, 1236, 1137, 764, 527, 432

HR-MS[M+1]: calculated 232.1695, found 232.1692

PRODUCT SELECVITITY RATIOS

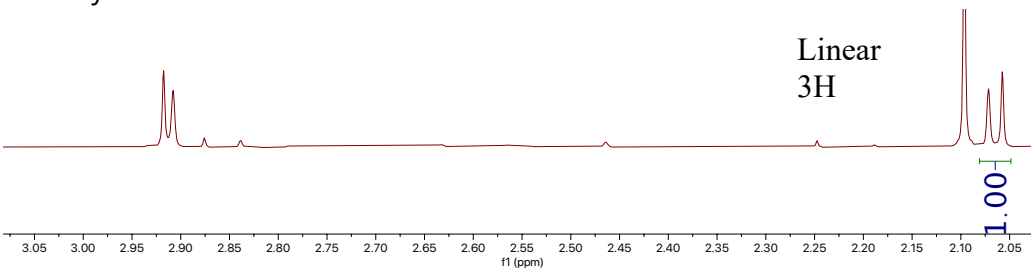
Lactam Vs Hydrodehalogenation. Crude ^{1}H-NMRS were used to determine product selectivity using diagnostic peaks determined known product standards .

5 Member Ring Cyclization



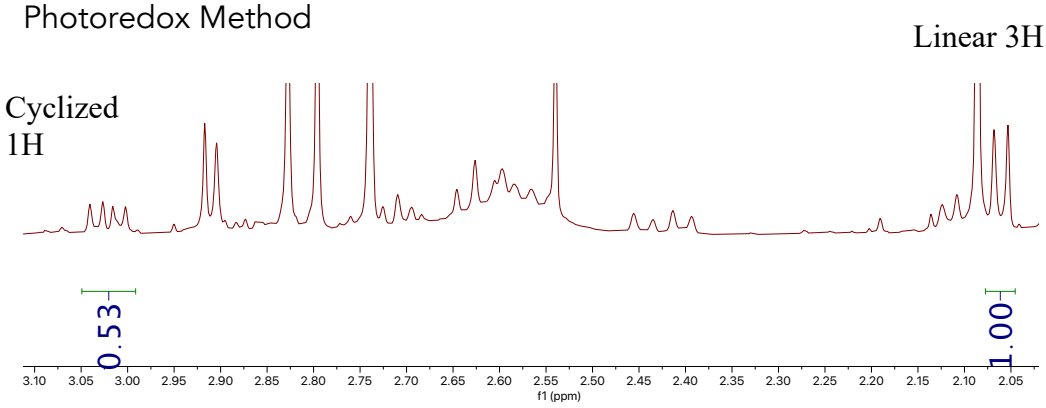
74% Linear
26% Cyclized

Iron Hydride Method



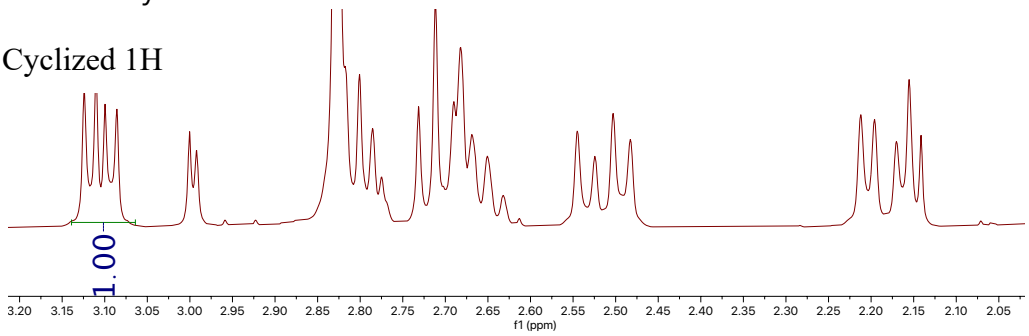
>95% Linear
<5% Cyclized

Photoredox Method



38% Linear
62% Cyclized

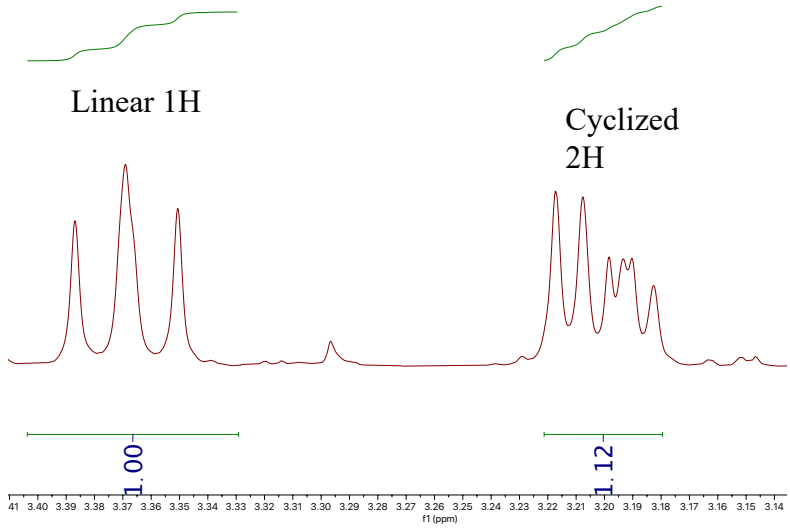
Photoenzymatic Method



<5% Linear
>95% Cyclized

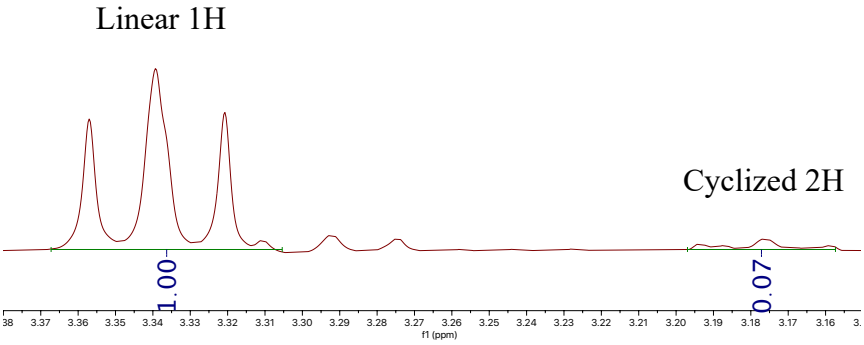
6 Member Ring Cyclization

Organotin Method



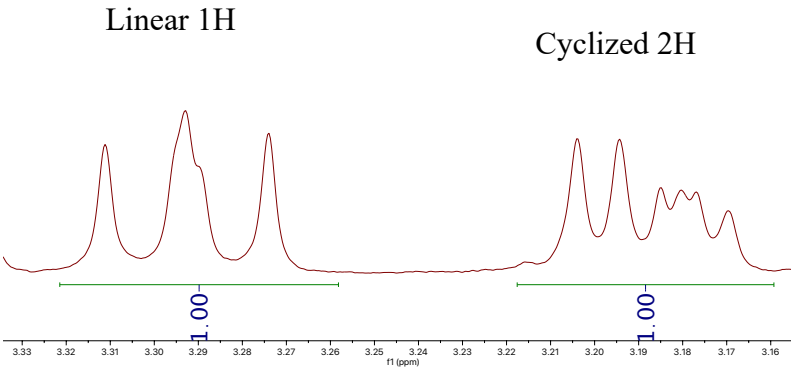
64% Linear
36% Cyclized

Iron Hydride Method



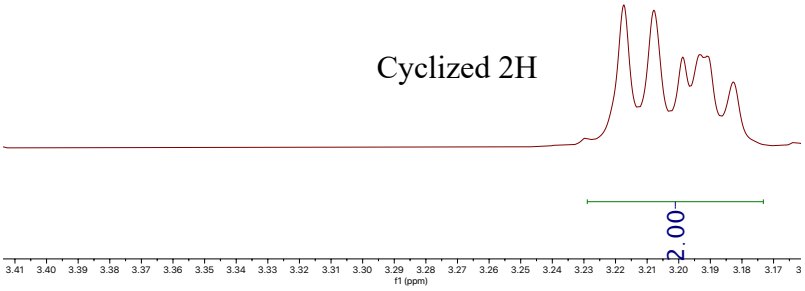
95% Linear
5% Cyclized

Photoredox Method



66% Linear
33% Cyclized

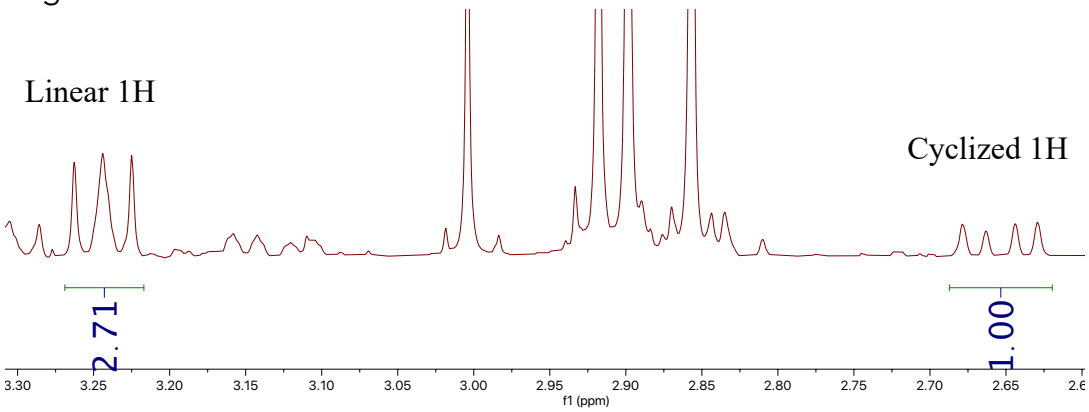
Photoenzymatic Method



<5% Linear
>95% Cyclized

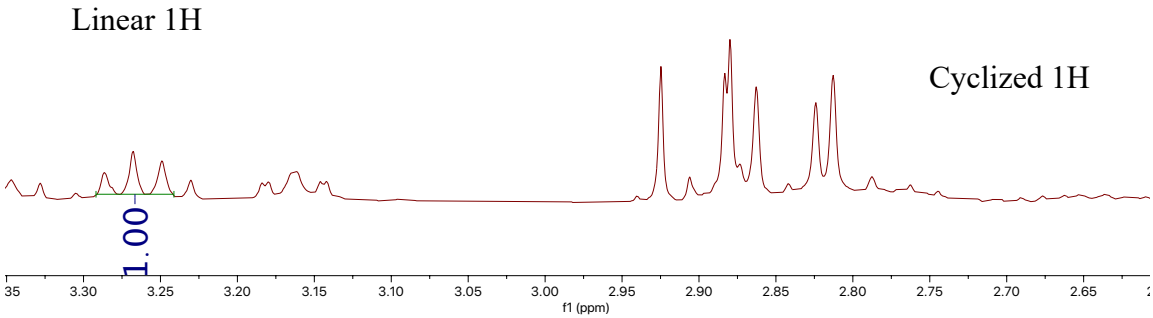
7 Member Ring Cyclization

Organotin Method



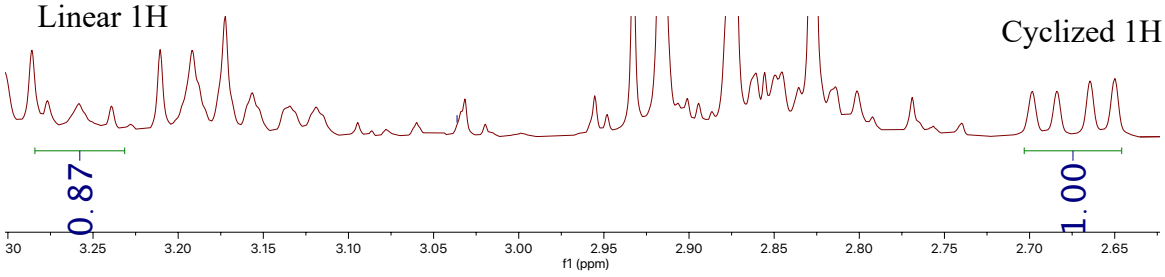
72% Linear
28% Cyclized

Iron Hydride Method



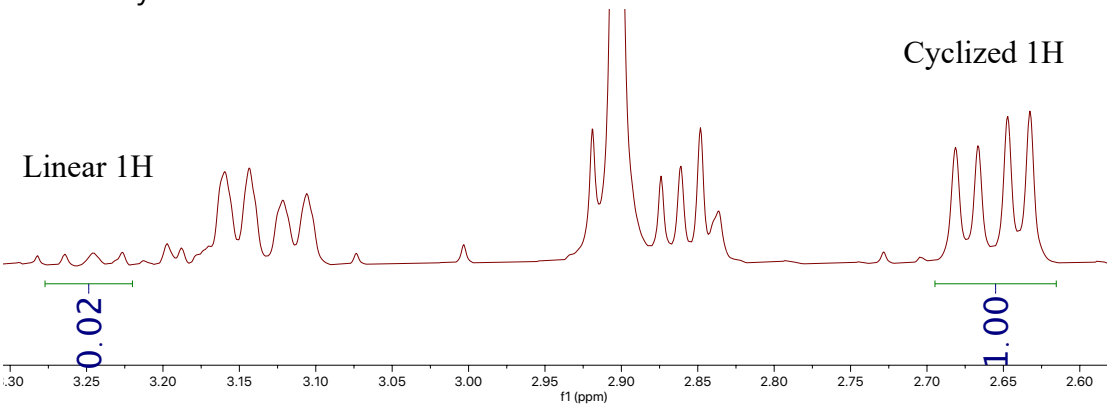
>95% Linear
<5% Cyclized

Photoredox Method



53% Linear
46% Cyclized

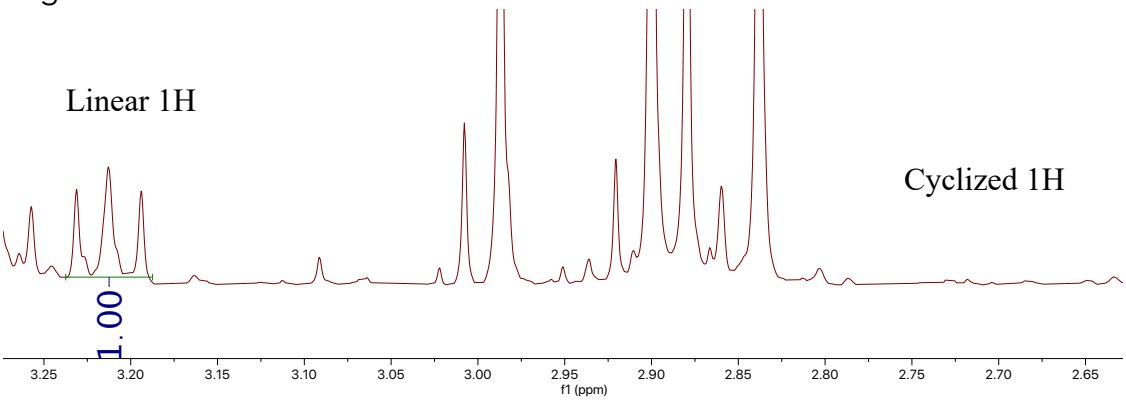
Photoenzymatic Method



<5% Linear
>95% Cyclized

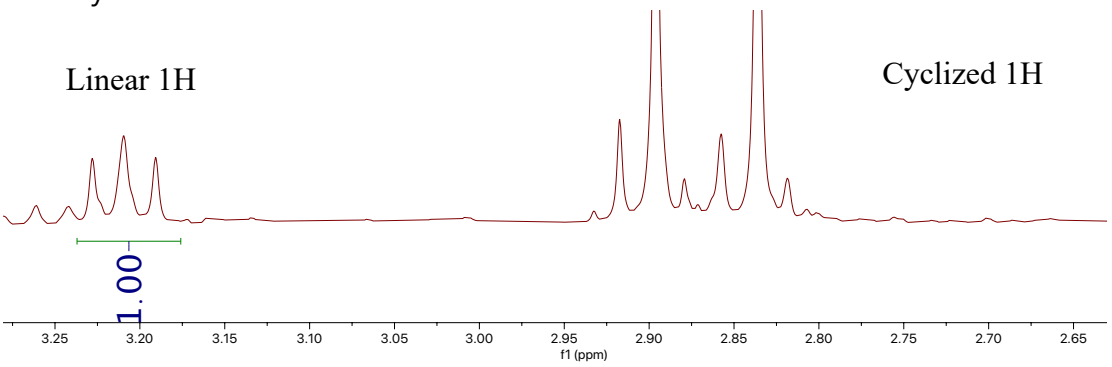
8 Member Ring Cyclization

Organotin Method



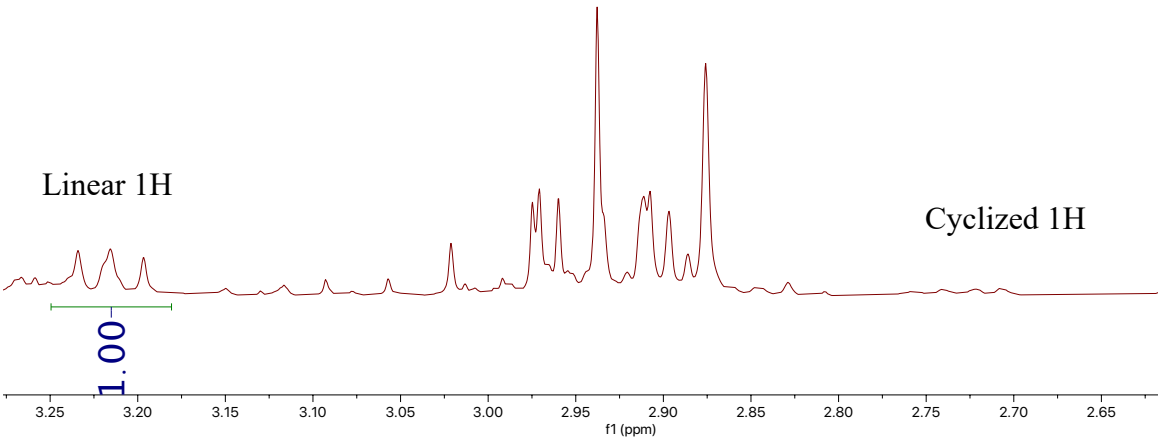
>95% Linear
<5% Cyclized

Iron Hydride



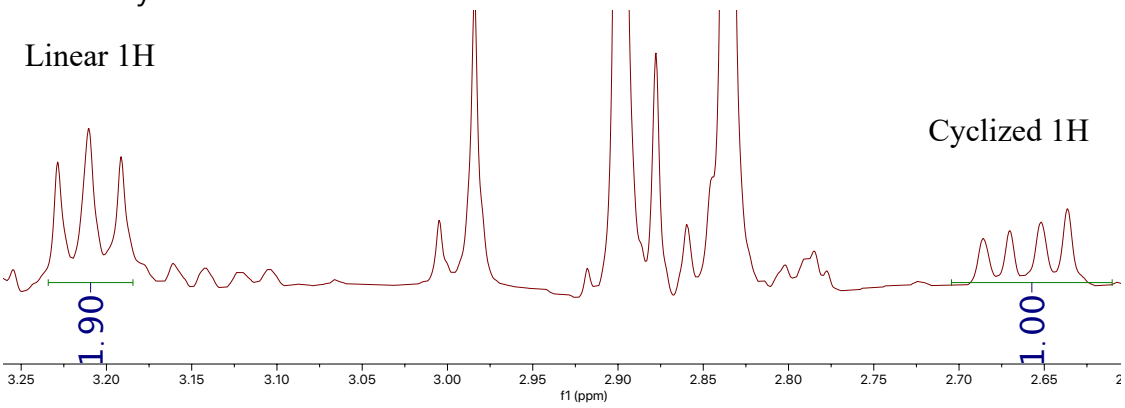
>95% Linear
<5% Cyclized

Photoredox Method



>95% Linear
<5% Cyclized

Photoenzymatic Method



66% Linear
34% Cyclized

RESULTS SUMMARY

Ring Size	Method	Yield (%)	Precent of Product HDH (%)	Precent of Product Lactam (%)
Five	Organotin	34	74	26
Five	Iron Hydride	30	95	5
Five	Photoredox	42	38	62
Five	Photoenzymatic	82	5	95
Six	Organotin	45	64	36
Six	Iron Hydride	53	83	17
Six	Photoredox	53	66	34
Six	Photoenzymatic	72	5	95
Seven	Organotin	55	72	28
Seven	Iron Hydride	79	95	5
Seven	Photoredox	31	47	53
Seven	Photoenzymatic	73	5	95
Eight	Organotin	43	95	5
Eight	Iron Hydride	70	95	5
Eight	Photoredox	34	95	5
Eight	Photoenzymatic	64	66	34

REFRENCES

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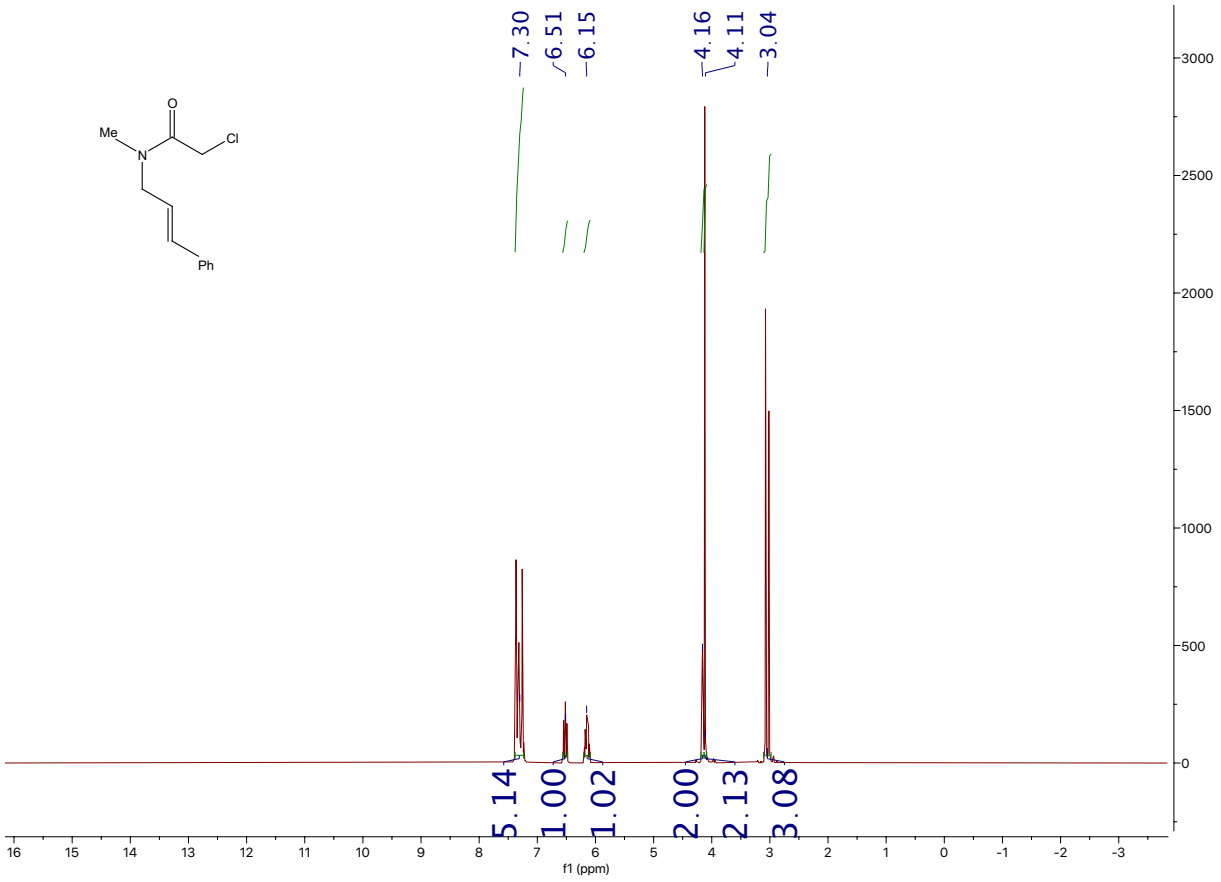
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6.15
4.16
4.11
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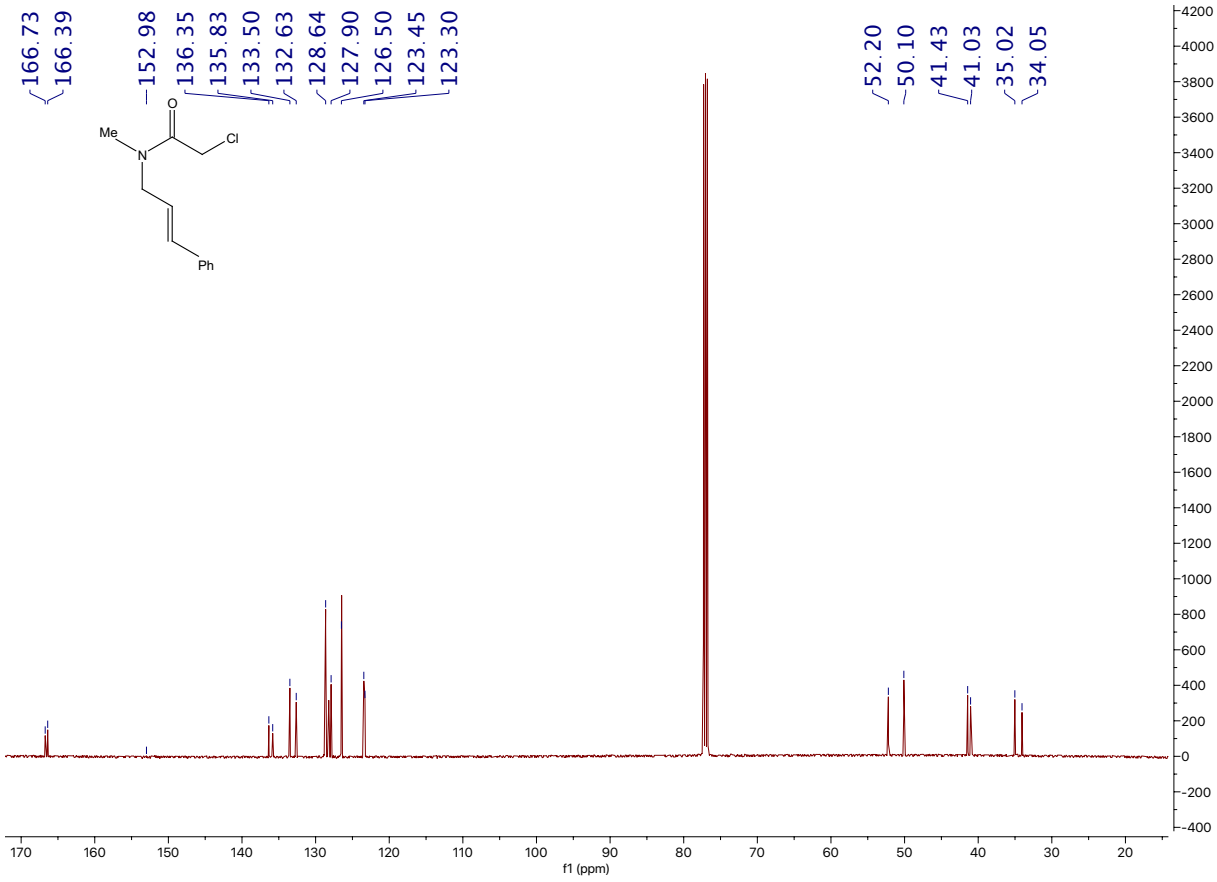
1.02
2.00
2.13
3.08
Me
N
O
Cl
Ph
f1 (ppm)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128.64
127.90
126.50
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123.30
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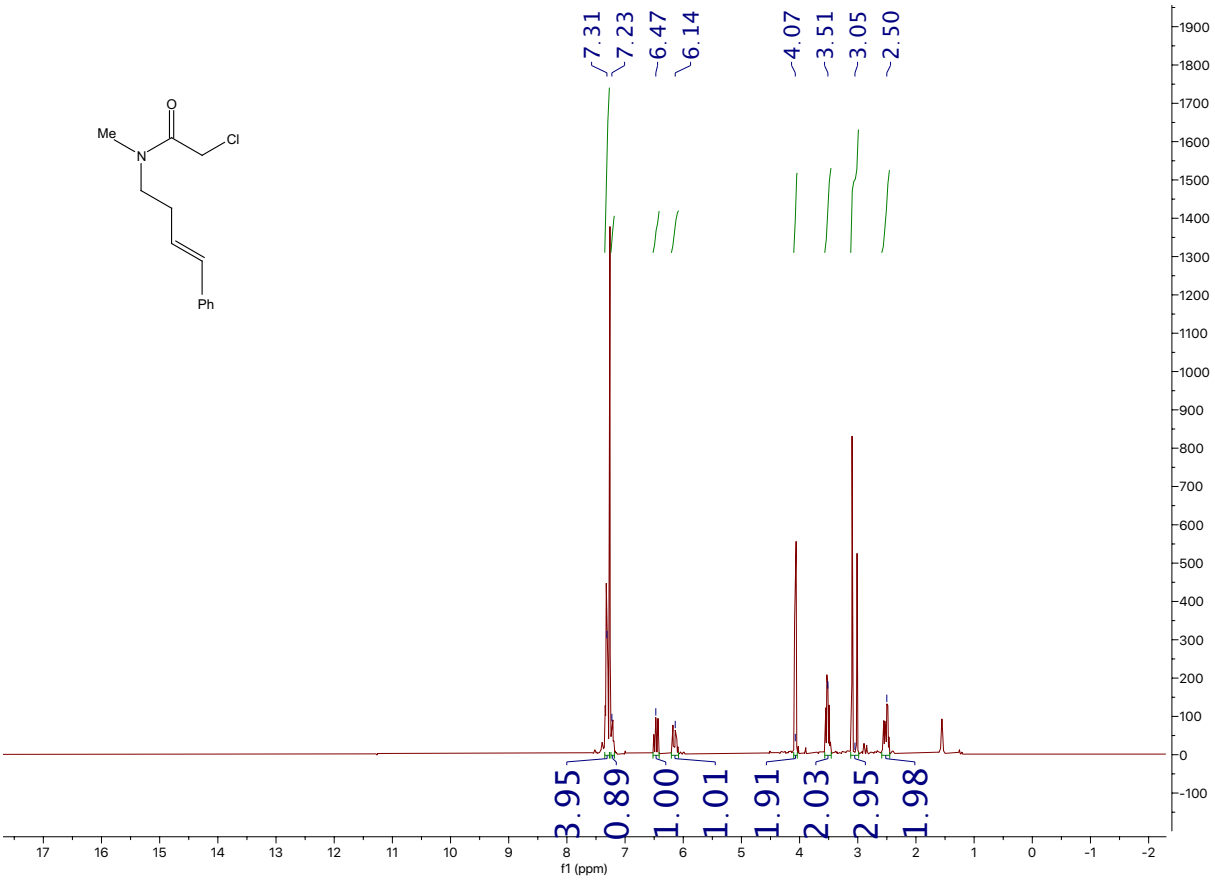
50.10
41.43
41.03
35.02
34.05
O
Me
N
Cl
Ph
f1 (ppm)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N
O
Cl
Ph
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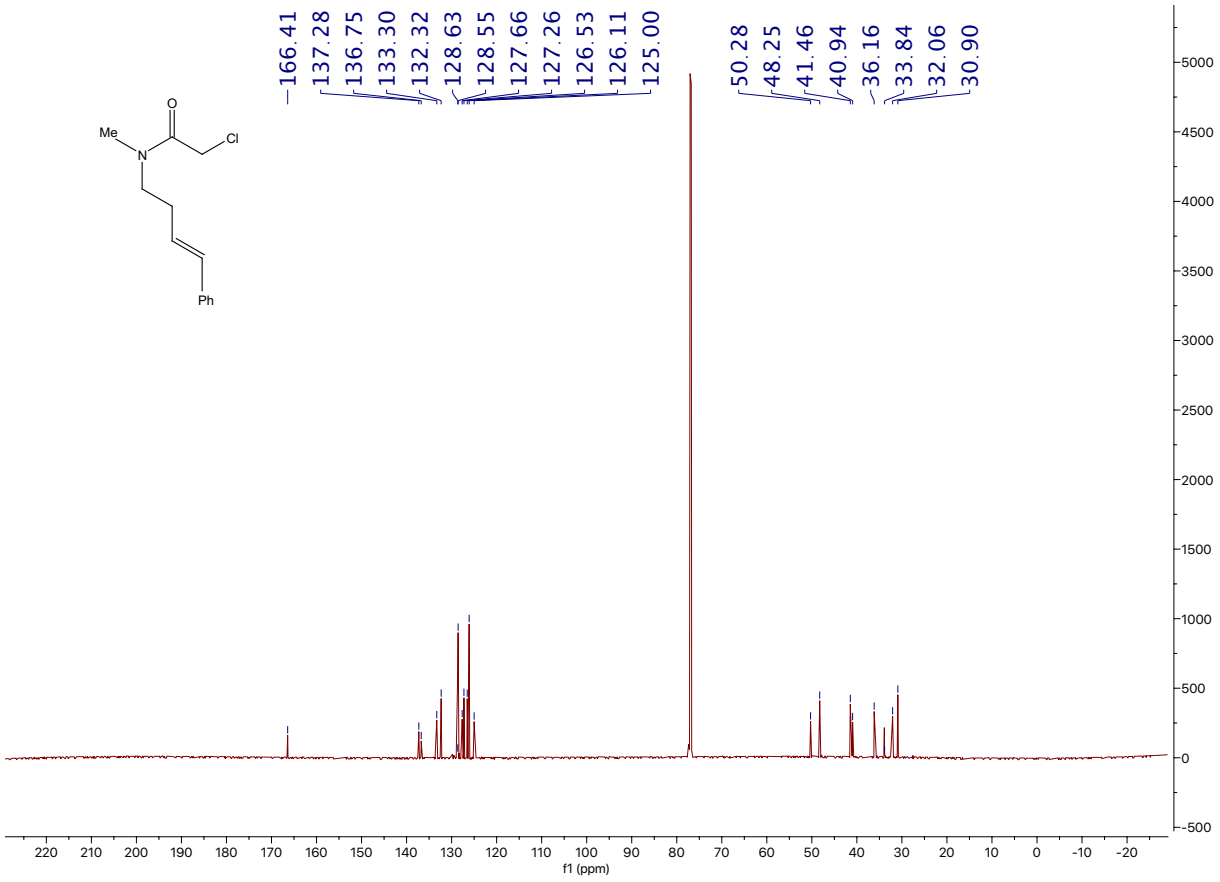
7.23
6.47
6.14
4.07
3.51
3.05
2.50
3.95
0.89
1.00
1.01
1.91
2.03
2.95
1.98
f1 (ppm)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33.84
32.06
30.90
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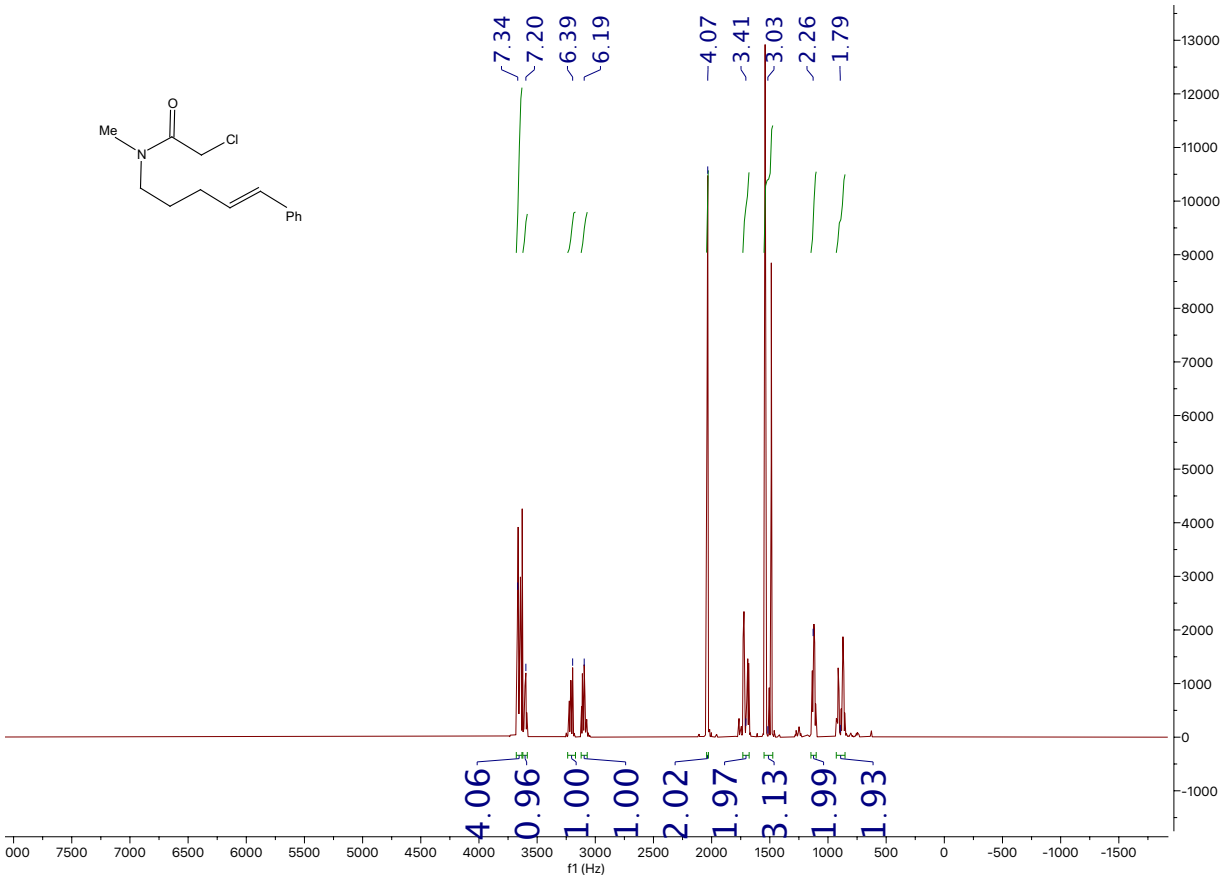
O
Cl
Ph
f1 (ppm)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6.19
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3.41
3.03
2.26
1.79
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N
O
Cl
Ph
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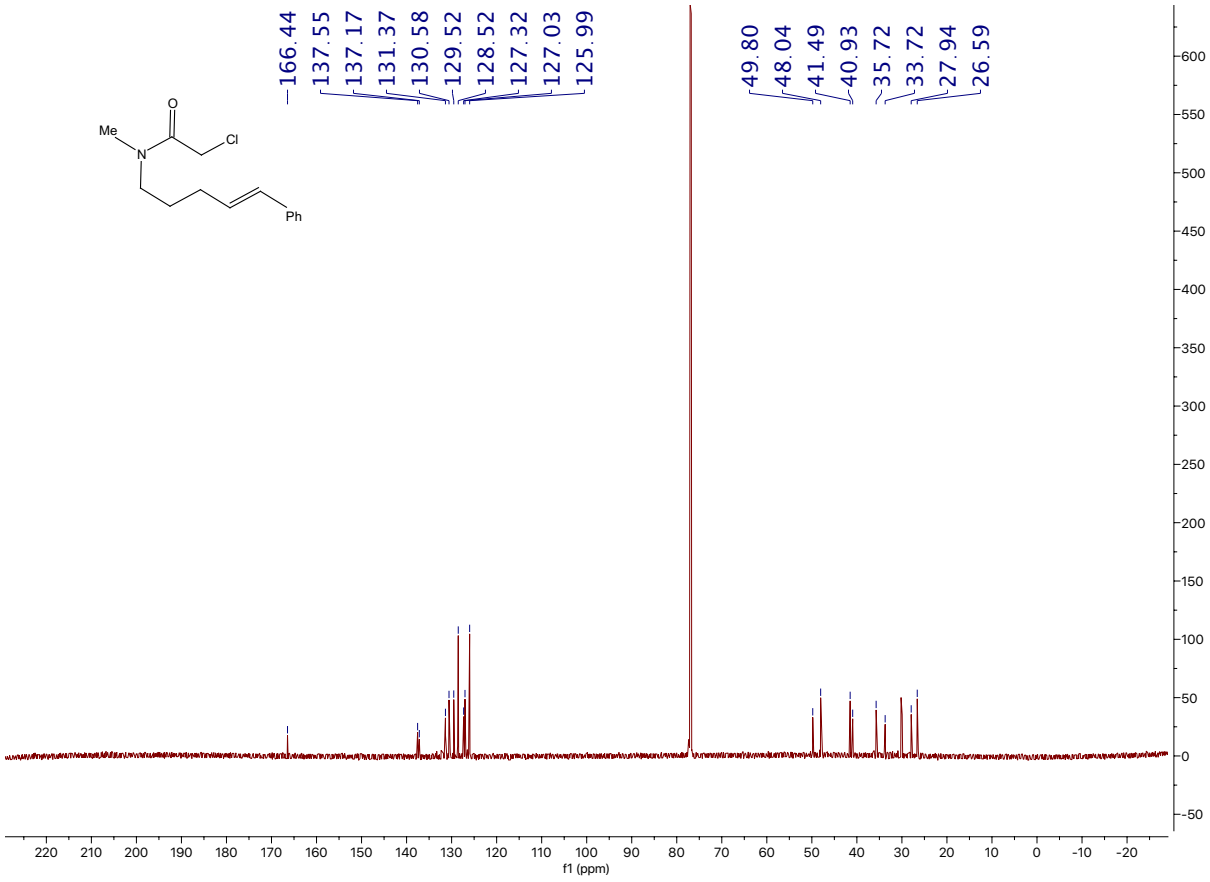
1.00
1.00
2.02
1.97
3.13
1.99
1.93
f1 (Hz)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33.72
27.94
26.59
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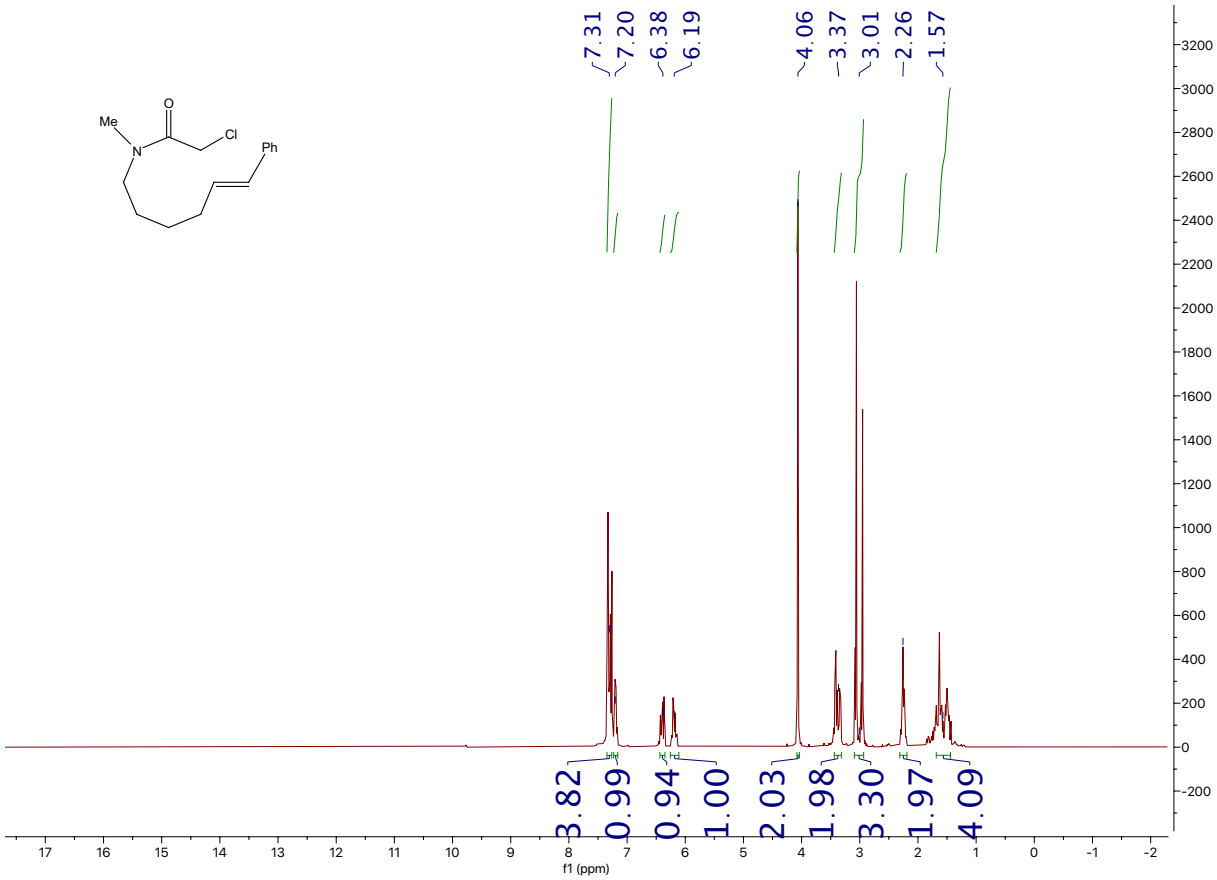
O
Cl
Ph
f1 (ppm)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O
Cl
Ph
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6.19
4.06
3.37
3.01
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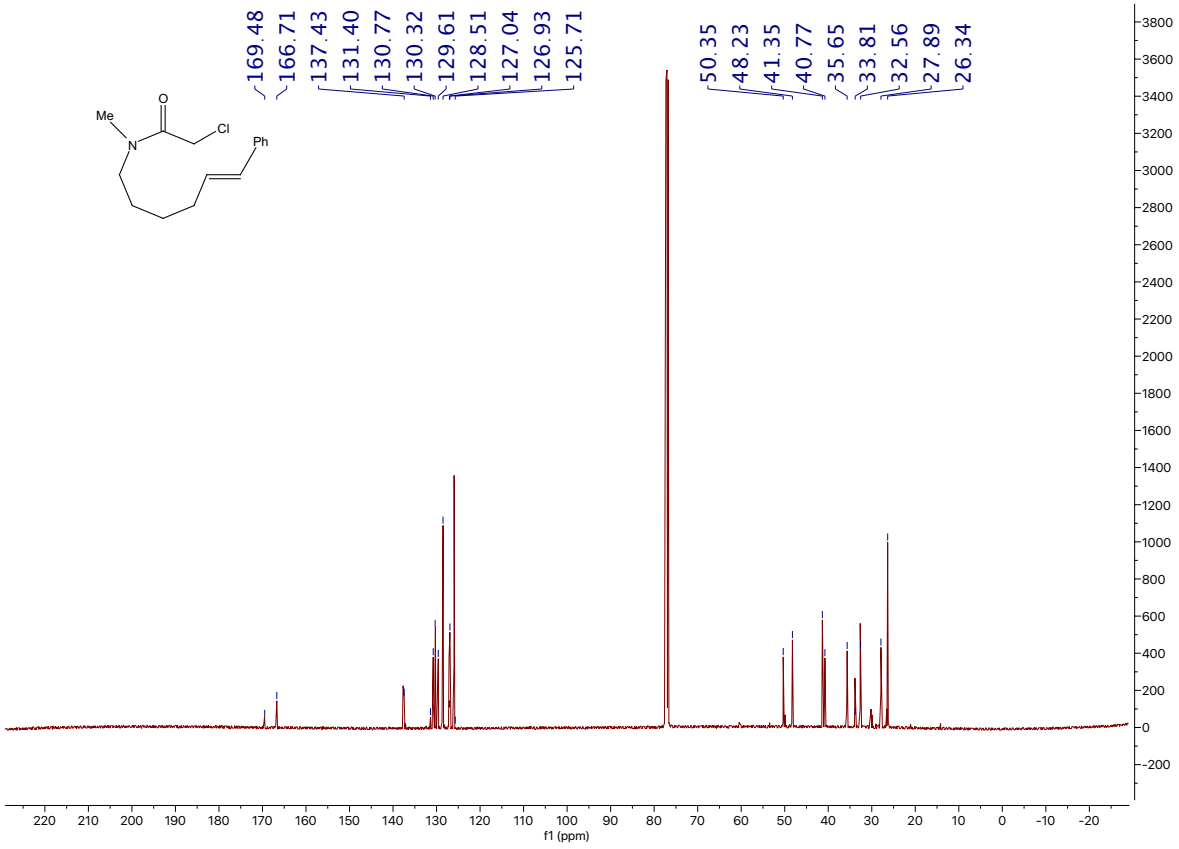
3.30
1.97
4.09
f1 (ppm)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126.93
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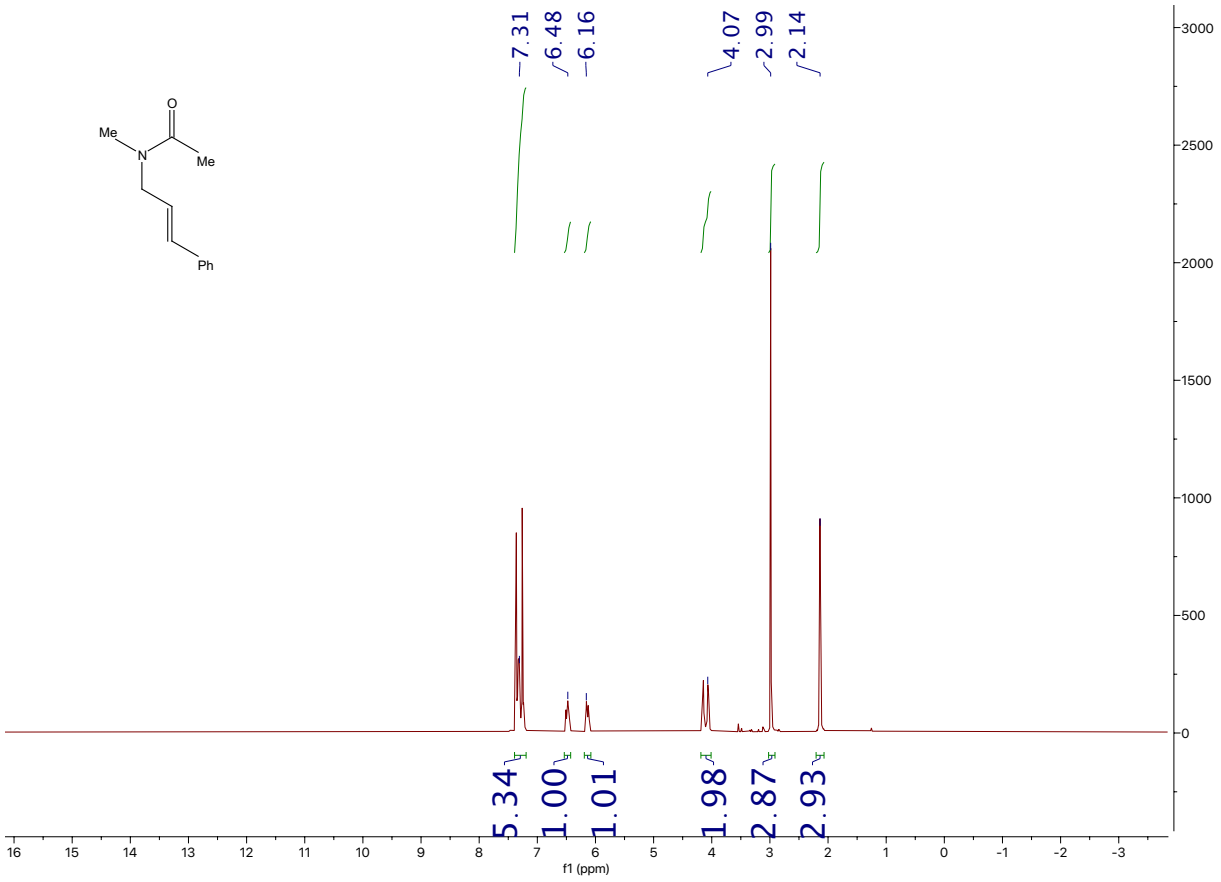
32.56
27.89
26.34
Me
N
O
Cl
Ph
f1 (ppm)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6.16
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O
Me
Ph
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1.01
1.98
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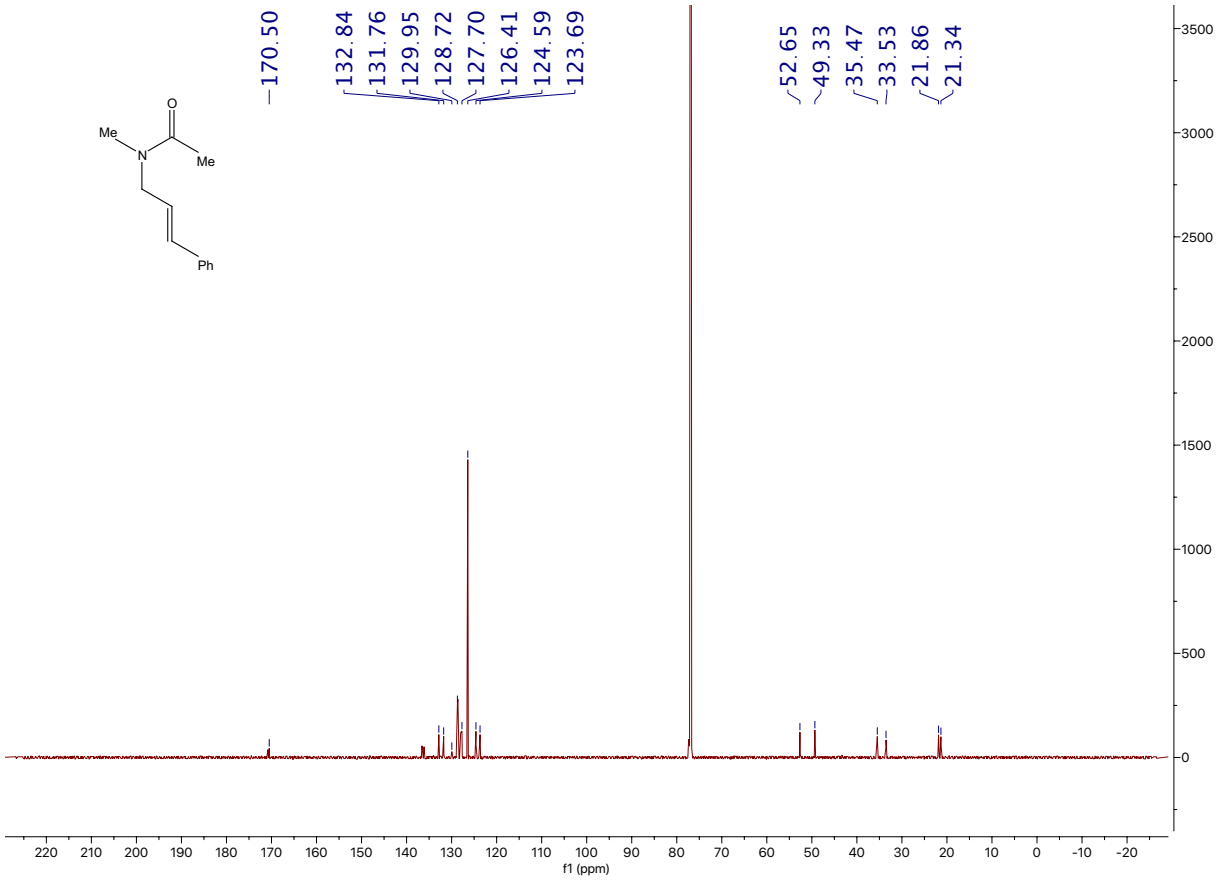
2.93
f1 (ppm)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126.41
124.59
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52.65
49.33
35.47
33.53
21.86
21.34
Me
N
O
Me
Ph
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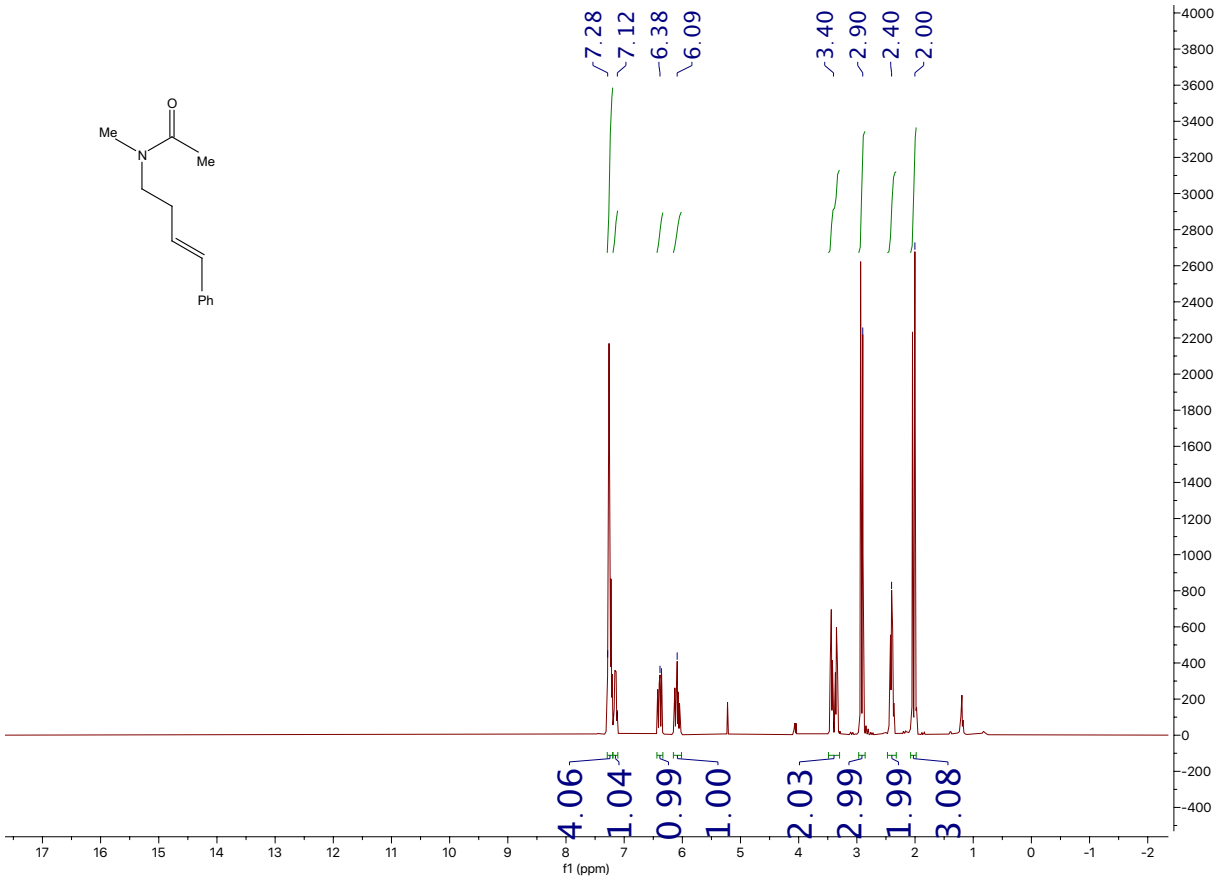
2500
2000
1500
1000
500
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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6.09
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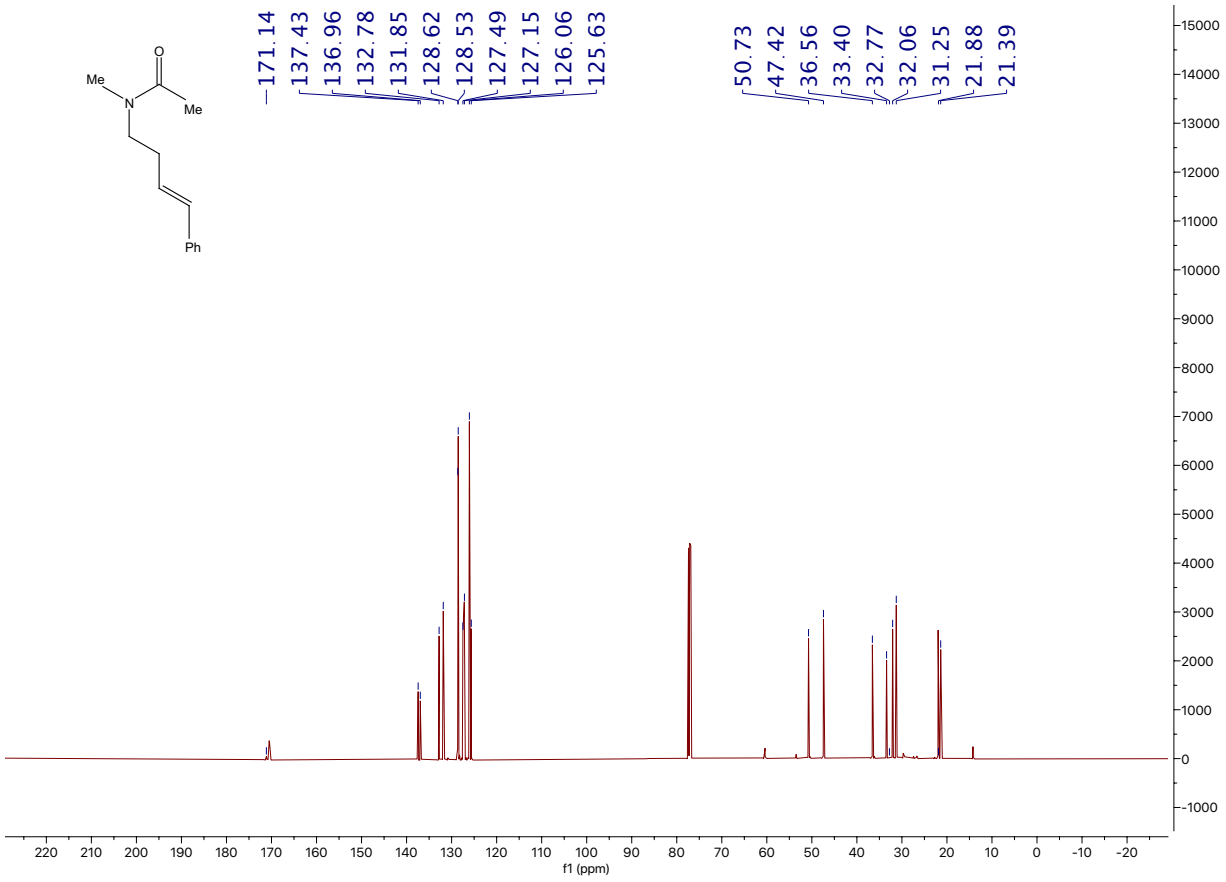
2.90
2.40
2.00
4.06
1.04
0.99
1.00
2.03
2.99
1.99
3.08
f1 (ppm)
Me
N
O
Me
Ph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125.63
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21.39
Me
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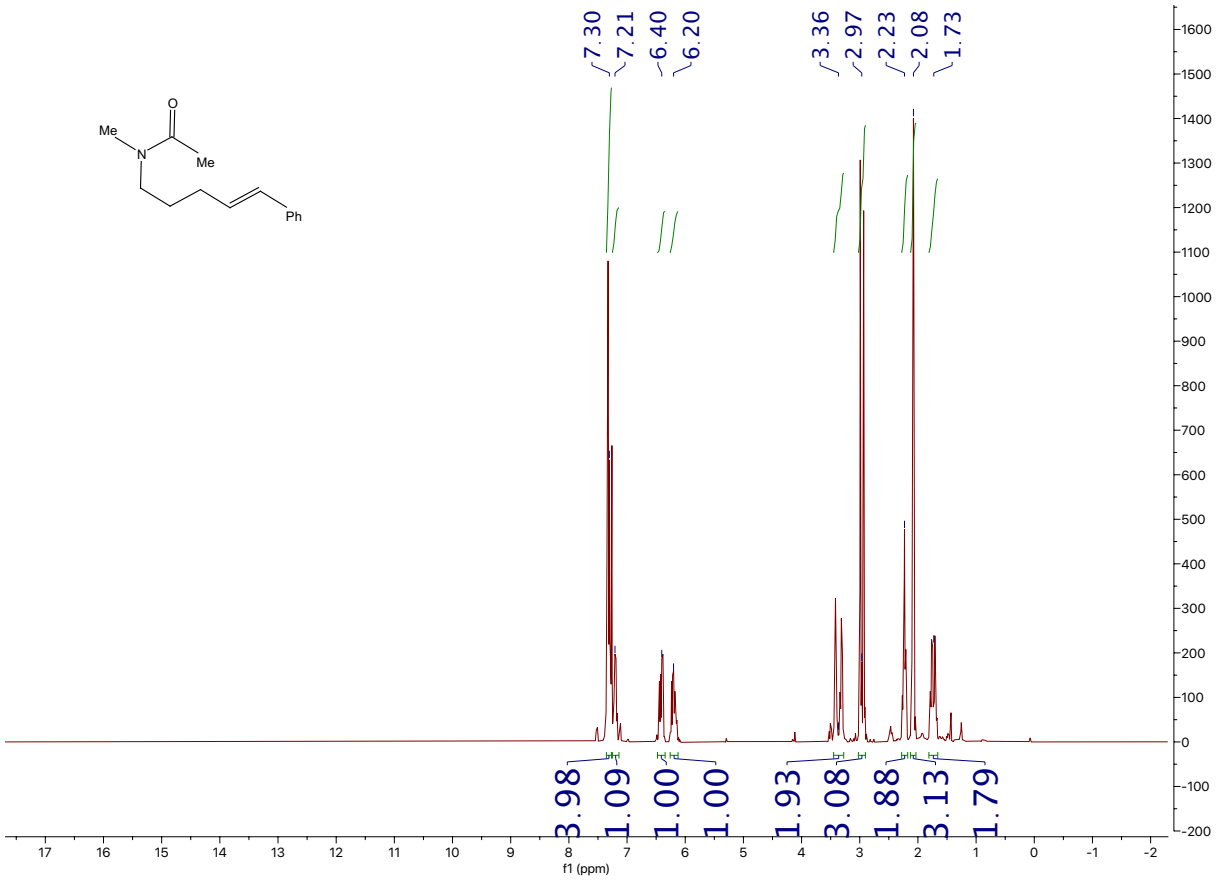
O
Me
Ph
f1 (ppm)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2.23
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1.00
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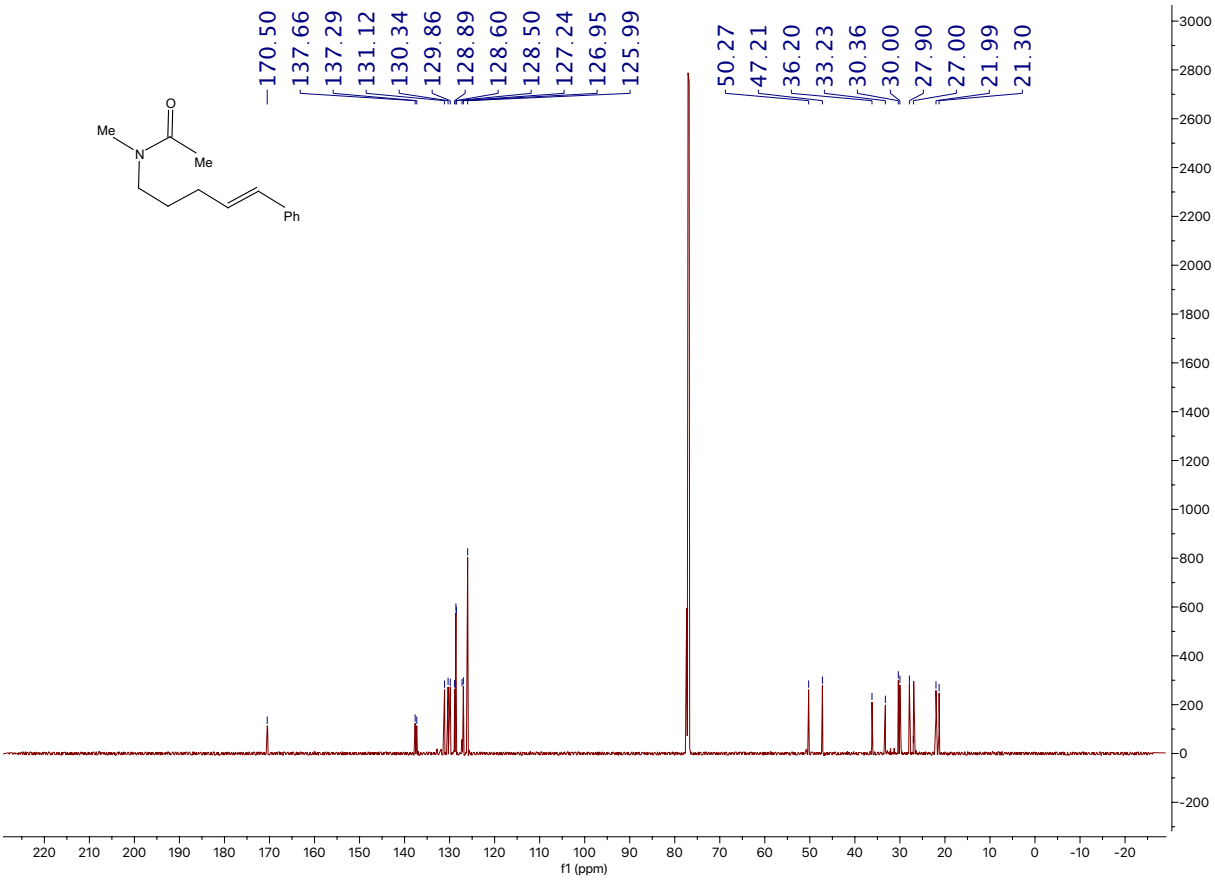
3.08
1.88
3.13
1.79
f1 (ppm)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47.21
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30.00
27.90
27.00
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21.30
Me
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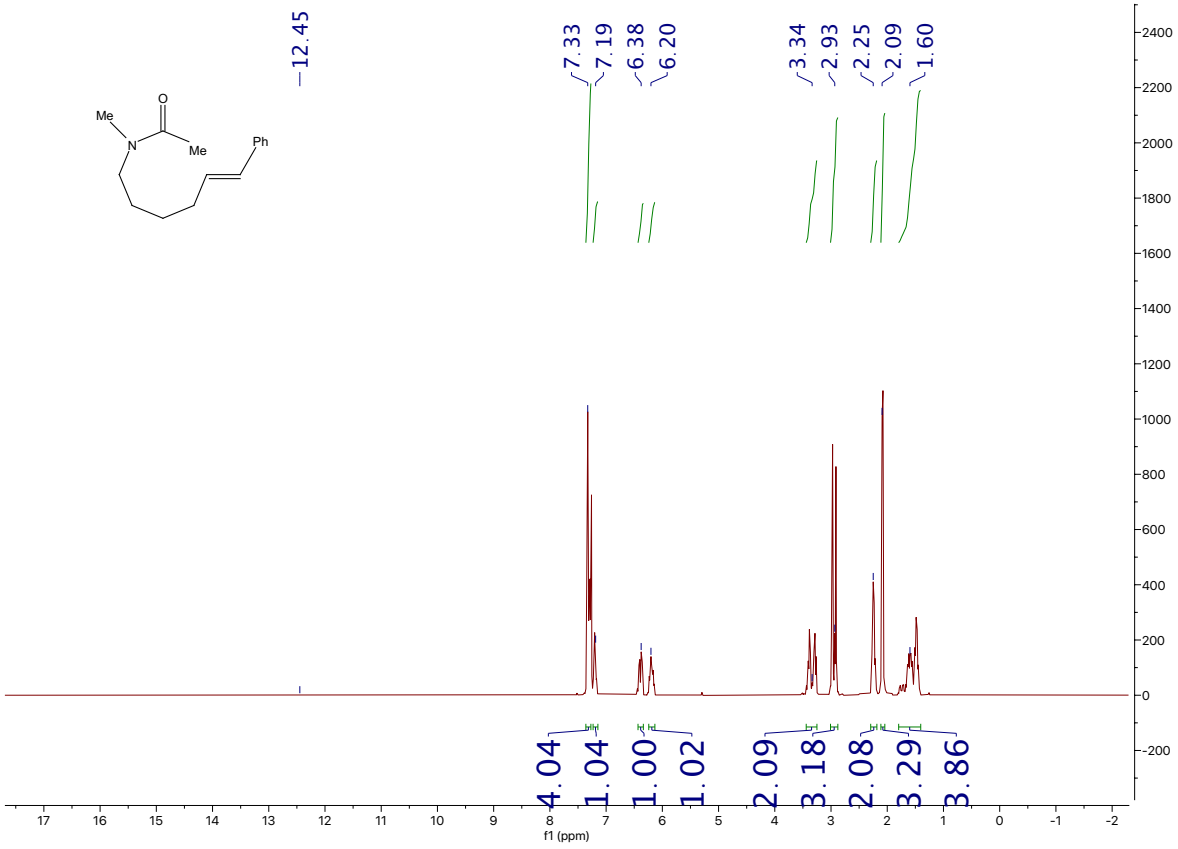
O
Me
Ph
f1 (ppm)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2.93
2.25
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1.60
Me
N
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1.02
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2.08
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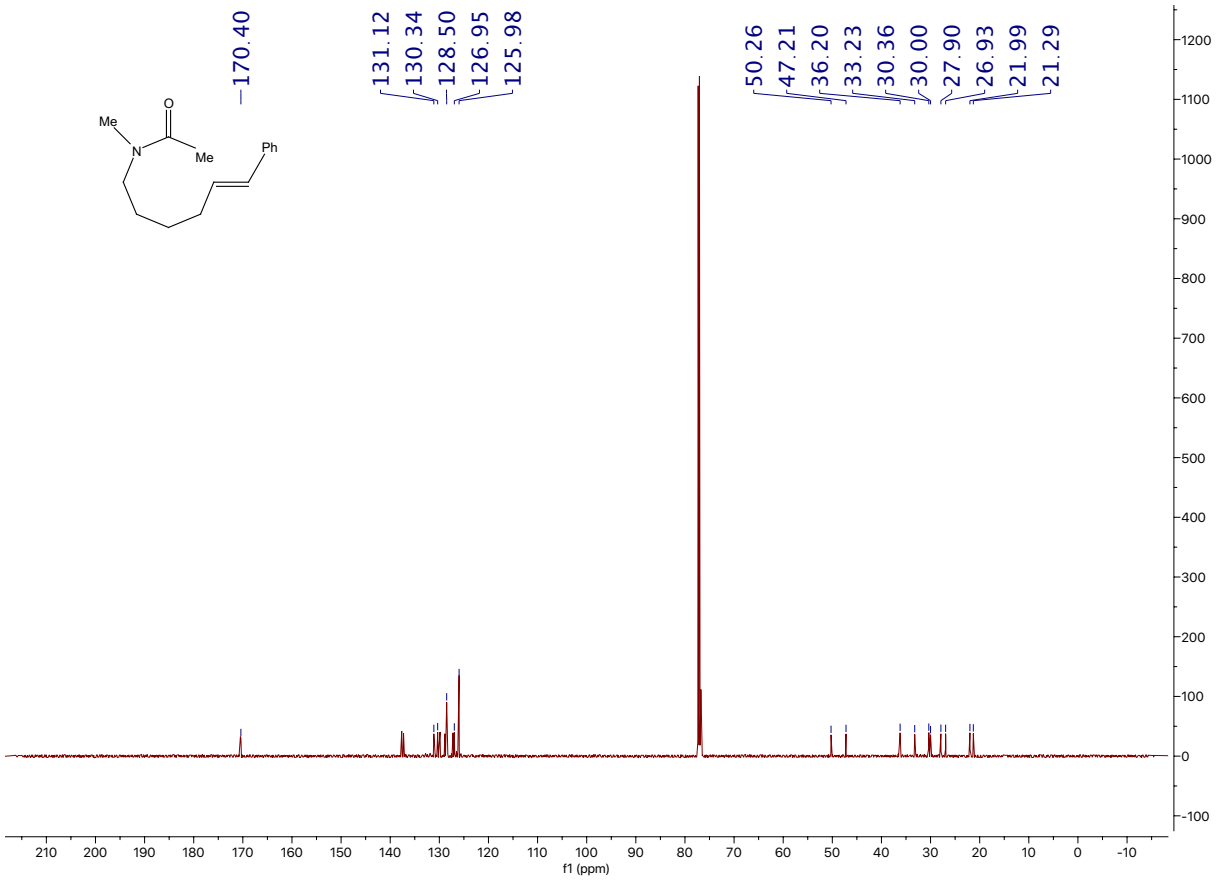
3.86
f1 (ppm)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47.21
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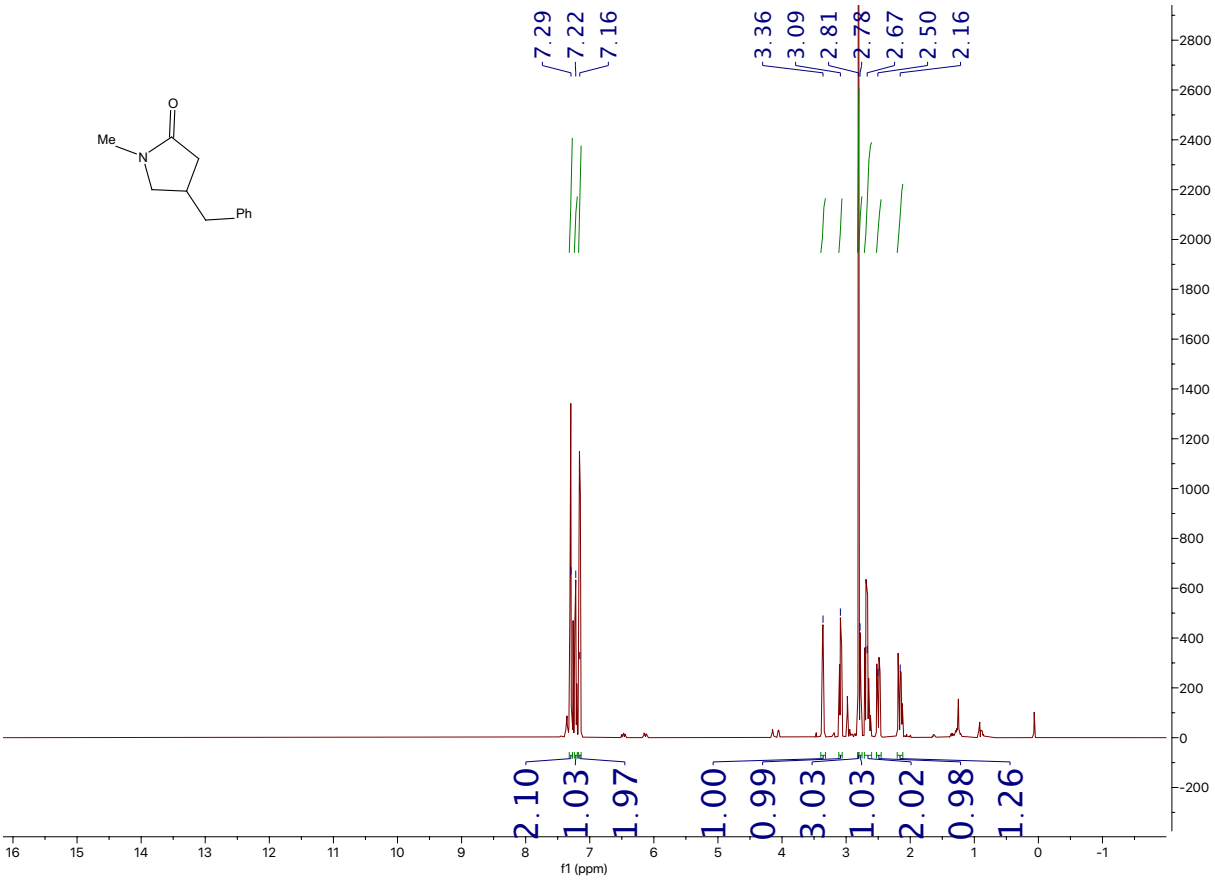
30.00
27.90
26.93
21.99
21.29
Me
N
O
Me
Ph
f1 (ppm)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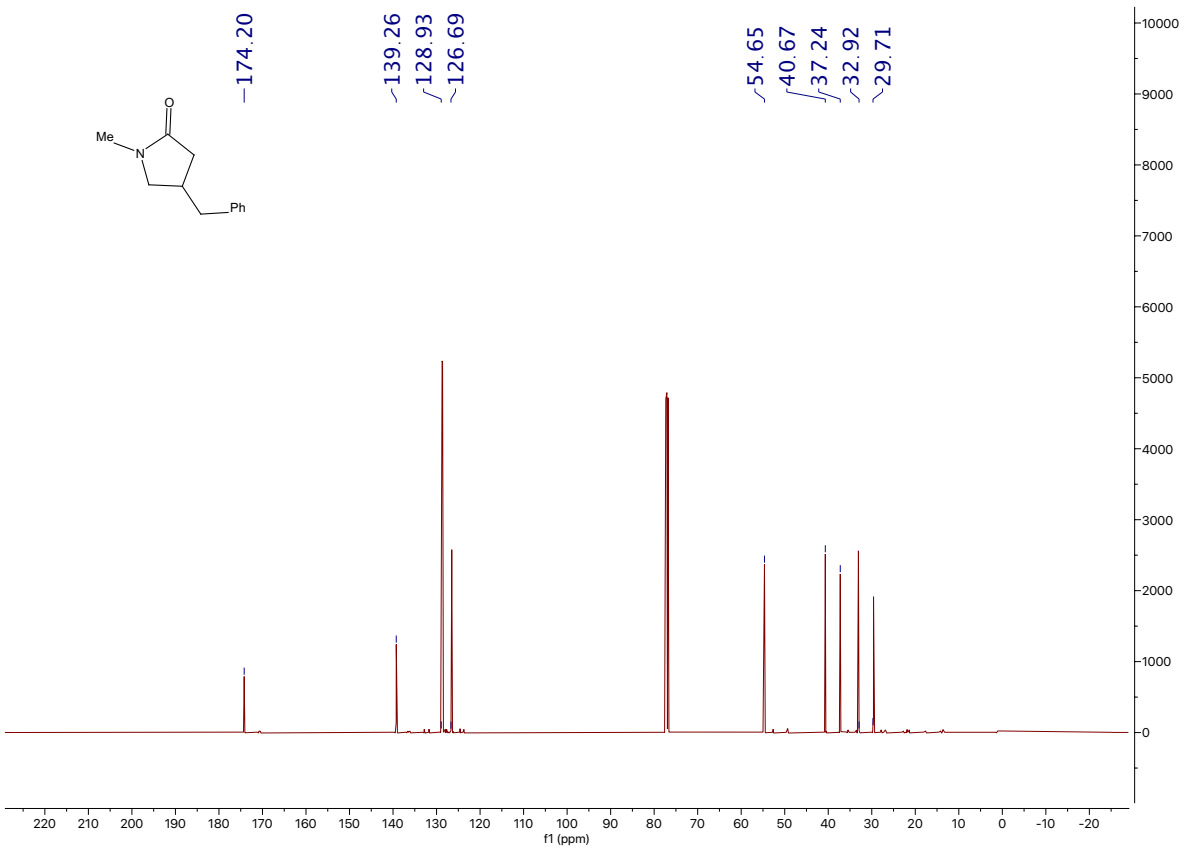
1.26
f1 (ppm)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O
Ph
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9000
8000
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3000
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1000
0
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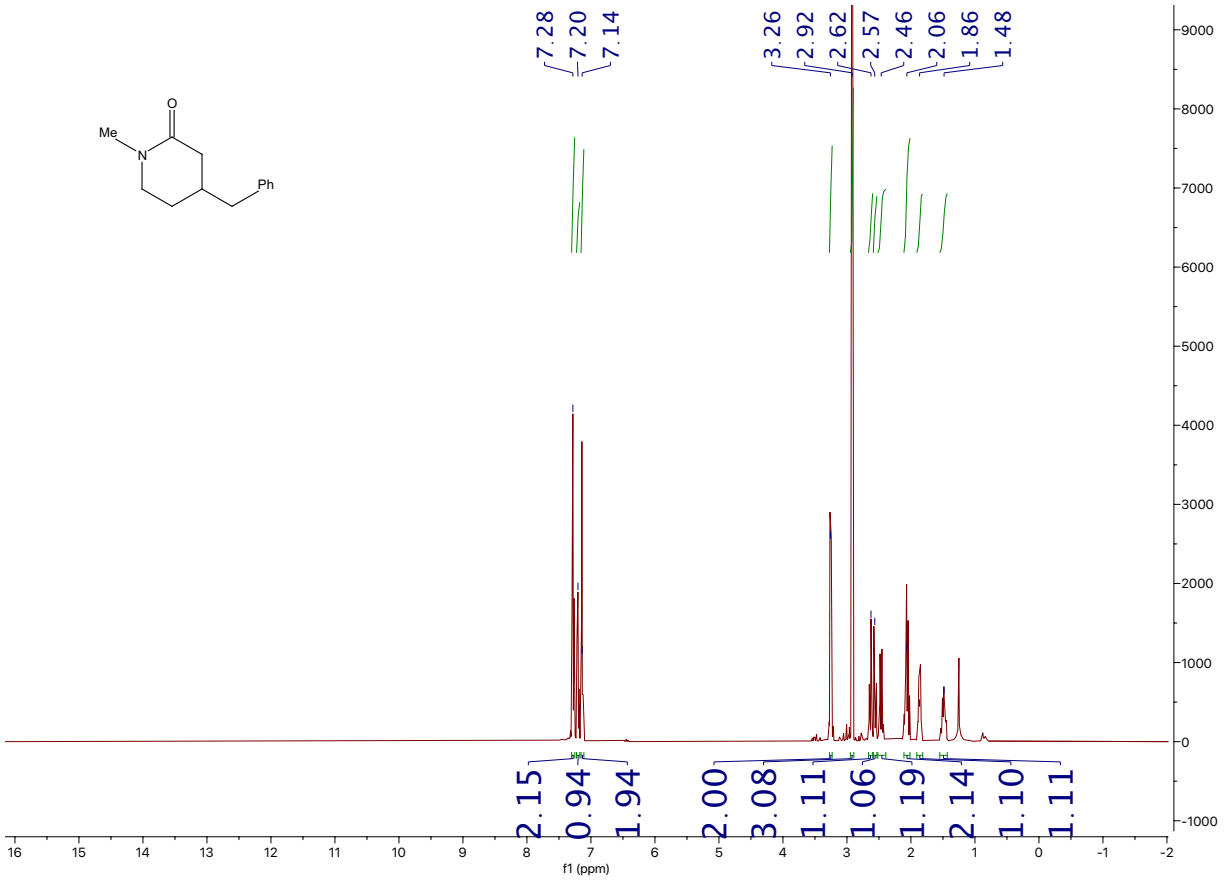
f1 (ppm)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Me
N
O
Ph
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2.00
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1.11
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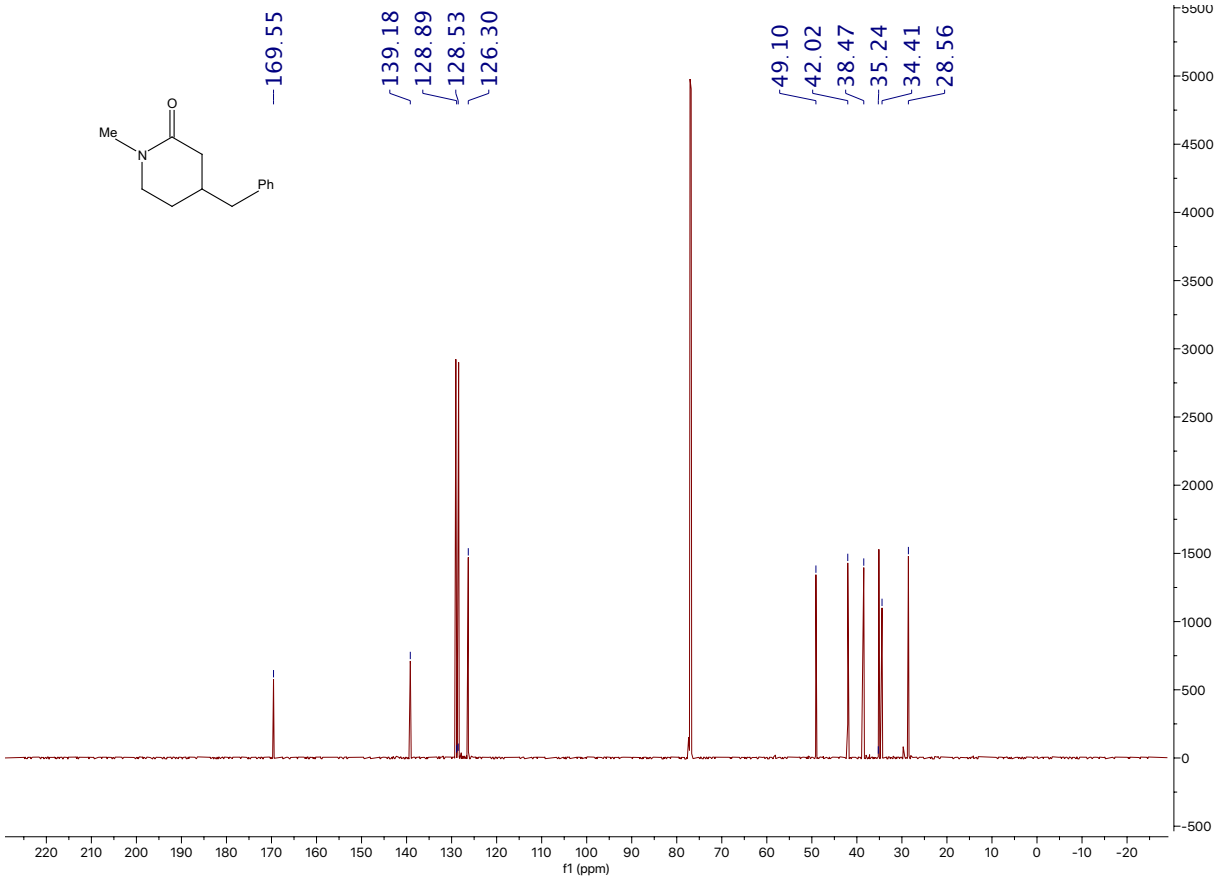
1.19
2.14
1.10
1.11
f1 (ppm)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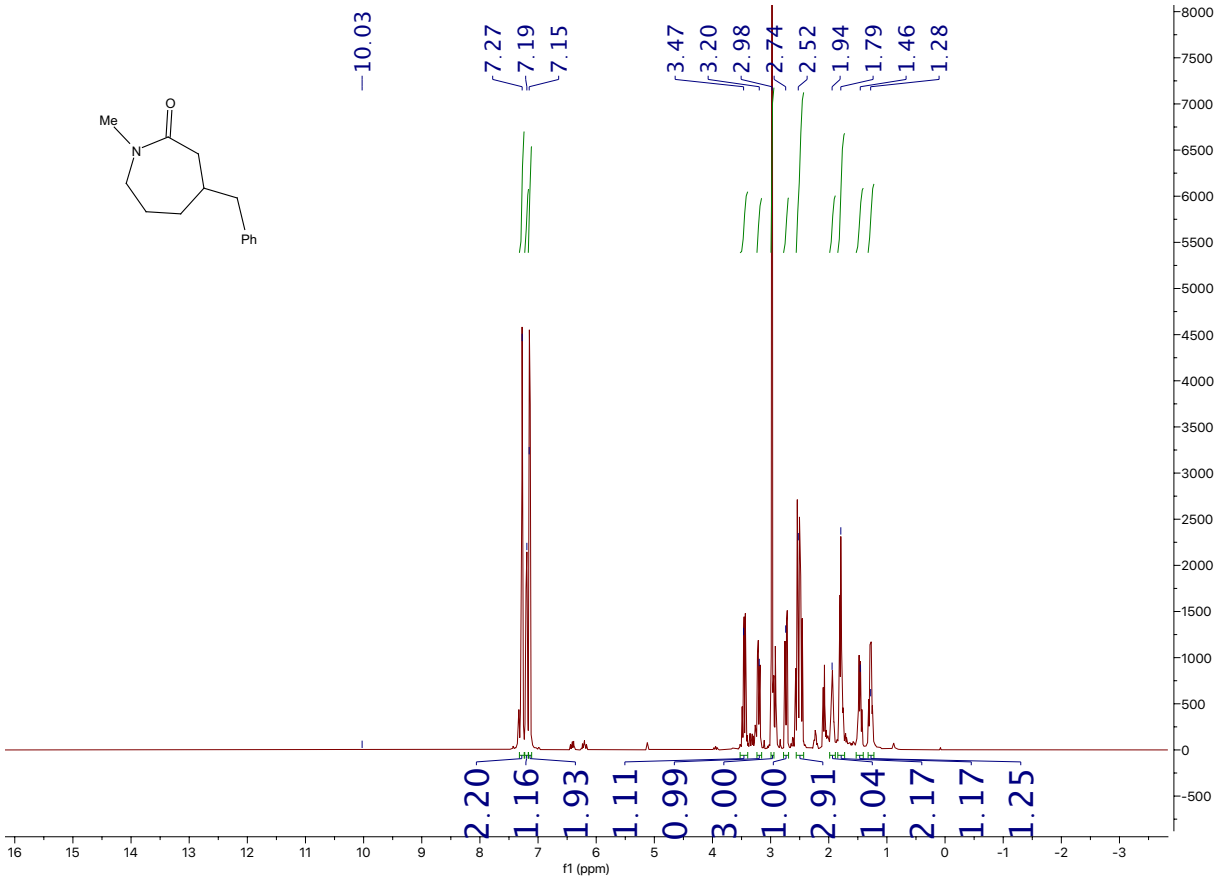
28.56
O
Me
N
Ph
f1 (ppm)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1.46
1.28
Me
N
O
Ph
2.20
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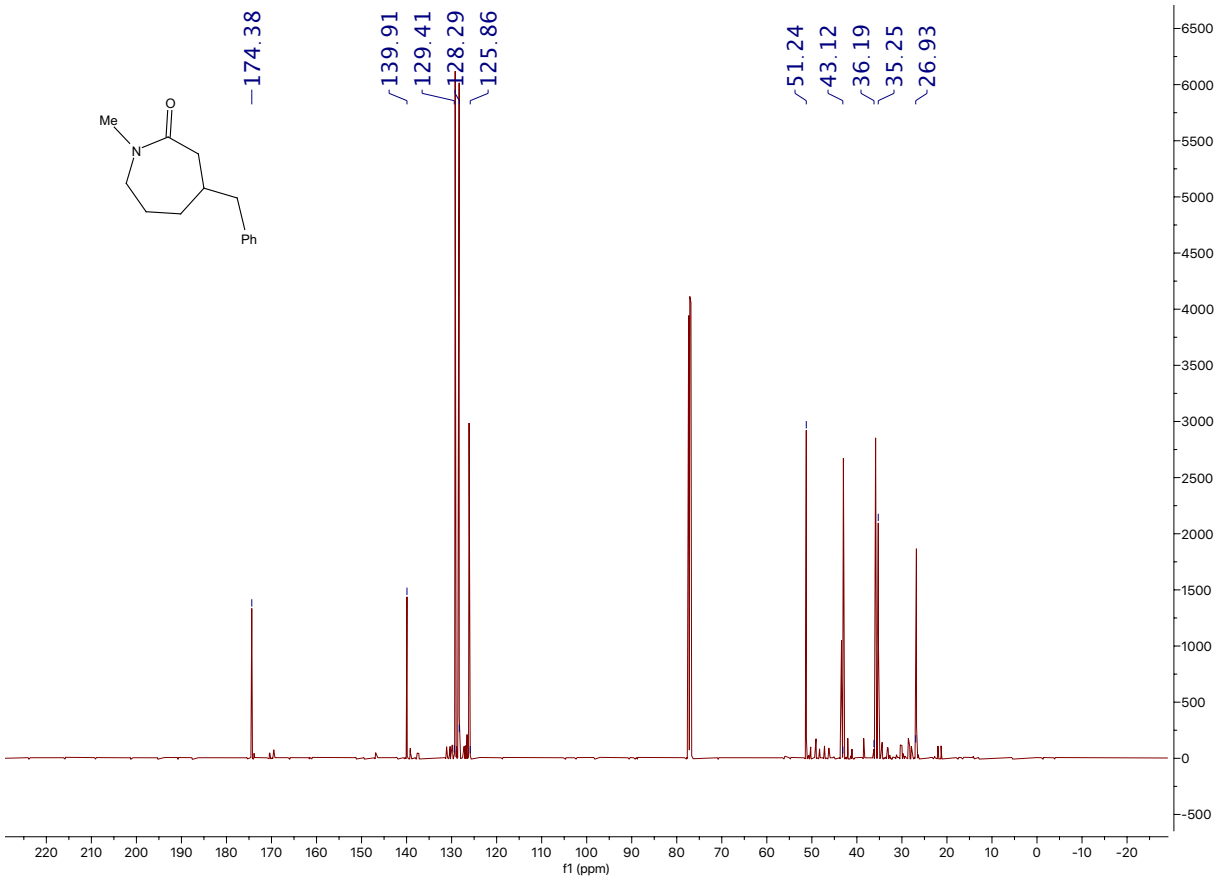
1.25
f1 (ppm)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Ph
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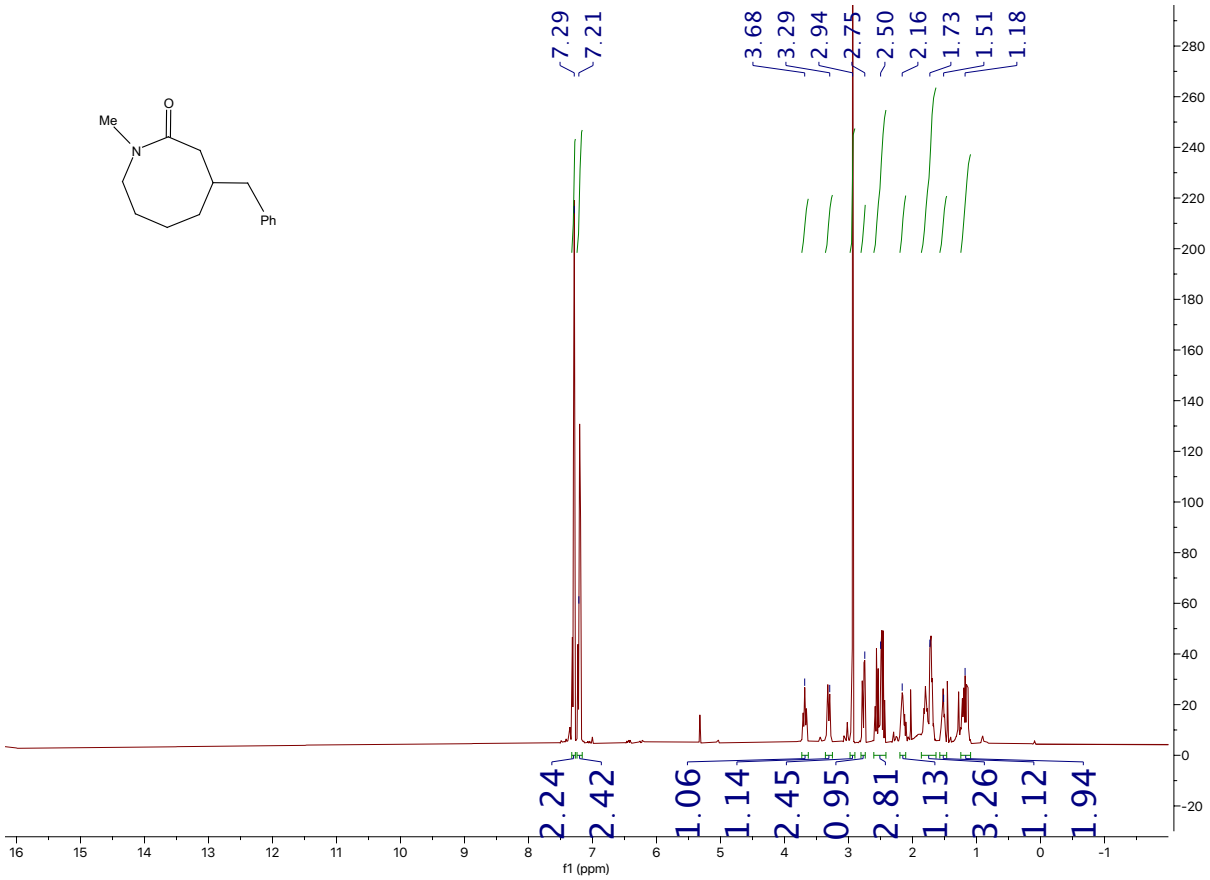
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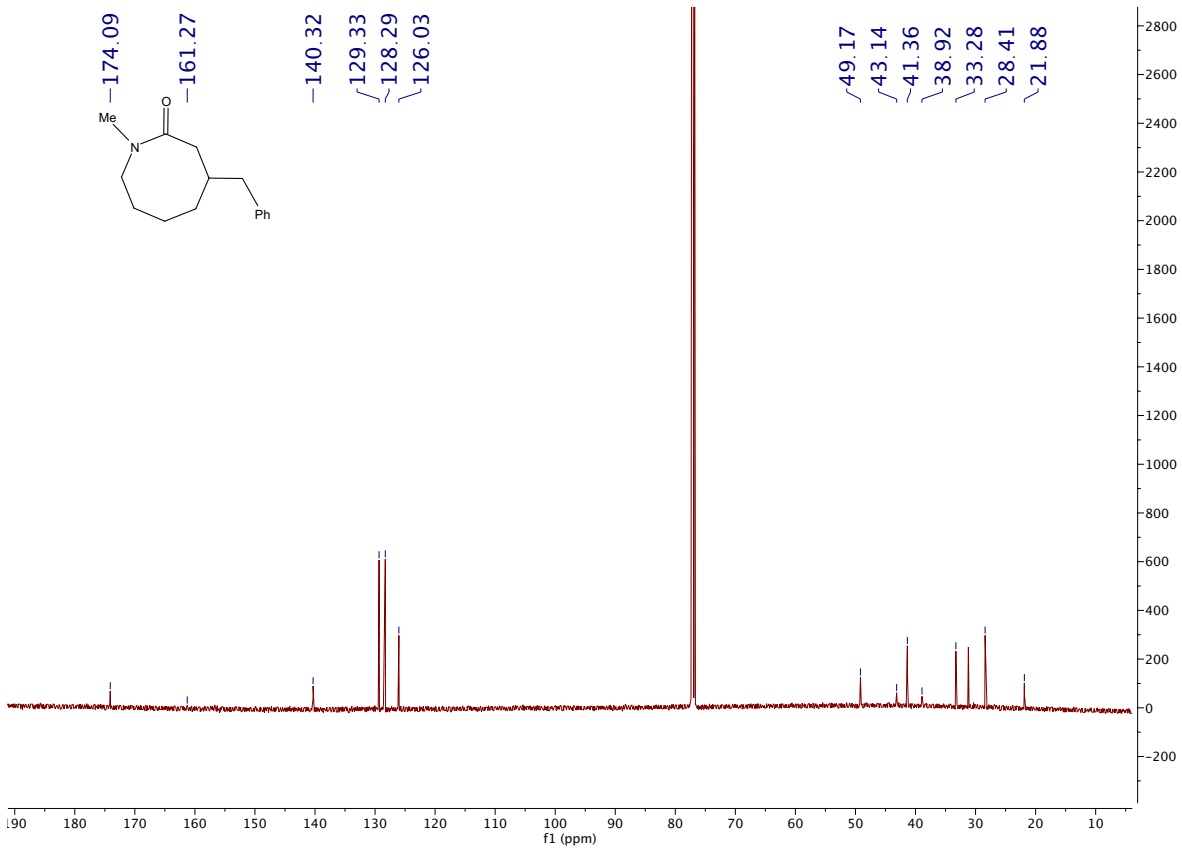
f1 (ppm)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Me
N
O
Ph
f1 (ppm)