
Cracking Meldrum's Acid: Lowering the Temperature

A thesis submitted for the degree of Doctor of Philosophy of the Australian National University by

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Declaration

I declare that, to the best of my knowledge, the work presented within this thesis is the results of original work carried out by myself over the period of 2018-2023. The work detailed herein has not been submitted for previous examination for any other degree. Established methodologies and theory have been cited from the relevant original publications wherever possible.

A handwritten signature in black ink, appearing to read 'H. Bollard', with a stylized, cursive script.

Hannah Bollard

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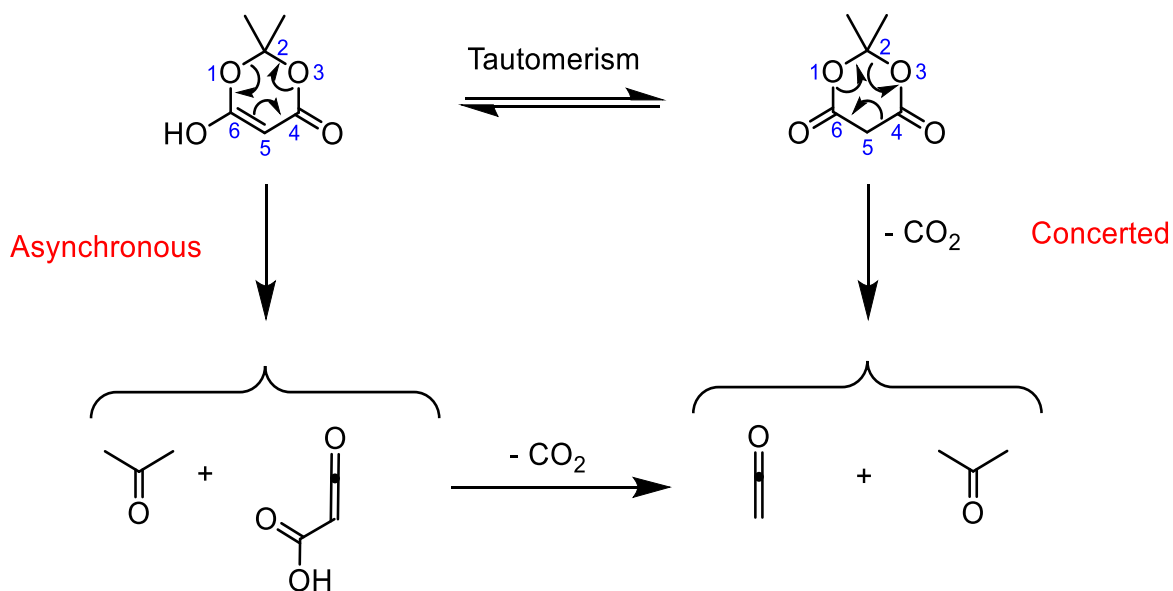
Finally, I would like to acknowledge my family. My parents Jane and Ian, as well as my twin brother and housemate Timothy, have demonstrated unconditional support for the duration of my candidature. I hope I have done them proud. I also would like to offer a thanks and apology to Tim for cooking the majority of my dinners over the years of my candidature and ensuring I was not existing on a diet comprised of frozen pizza and beans on toast. It is most definitely my turn to prepare his dinner.

Abstract

Sucrose fatty-acid mono-esters are valuable surfactants that have many industrial applications in consumer goods and medications. The current industrial syntheses are conducted through *trans*-esterification protocols, which regularly produces mixtures of sucrose fatty-acid mono-esters and other higher-order esters. The production of sucrose fatty-acid mono-esters through traditional synthetic methodologies was explored within this thesis and found to be inefficient and sometimes unreliable. A reliable and atom economical protocol for accessing esters that accounts for sucrose's own incompatibilities is required. Utilisation of ketenes as a carbonyl source may be one such protocol. Ketenes are highly reactive intermediates that can be produced and reacted under the same reaction conditions, including at a neutral pH. Ketenes present as an attractive way to produce sucrose fatty-acid mono-esters if the reaction temperature used to access the ketene intermediate can be kept lower than sucrose's caramelisation point.

Meldrum's acid, also known as 2,2-dimethyl-1,3-dioxane-4,6-dione, is a common feedstock six-membered heterocycle that can access ketenes intermediates through a single-step thermolytic pathway. The key challenge with utilising Meldrum's acid as a ketene source is identifying an analogue with a suitable thermolysis temperature for compatibility with sucrose, preferably at a temperature lower than that of Meldrum's acid itself. We sought to explore the effects of modifying the C2 and C5 residues of Meldrum's acid on the thermolysis pathway, which is currently unknown to literature. A library of 17 varying C2 substituted Meldrum's acids were prepared, where 13 of the prepared compounds were afforded as crystalline solids. The thermolytic behaviour of

these Meldrum's acids was analysed and provided insight on the effects of the C2 residue. A constraining effect for the aliphatic Meldrum's acids and an asynchronous hetero-retro-Diels-Alder thermolysis pathway operating for the acetophenone Meldrum's acids were identified.



Scheme i. Meldrum's acid thermal cycloreversion pathways via a concerted and an asynchronous reaction pathway.

A selection of the aliphatic C2 substituted Meldrum's acids was additionally derivatised at the C5 position to give a library of *gem*-dialkyl, *gem*-dialkenyl and *gem*-dialkynyl Meldrum's acids. Of these compounds, all four that were produced as crystalline solids and thus subjected to single-crystal X-ray diffraction analyses were found to adopt the chair conformation, which is unusual for Meldrum's acids to adopt. Through examination of this library of C5 disubstituted Meldrum's acids through thermogravimetric analyses, we found the thermolysis temperatures were substantially higher compared to their parent compounds. Whilst these derivatives were found to be unsuitable ketene surrogates for esterifying sucrose, they did demonstrate the effects exerted by the C5 and C2 residues on the thermolytic

pathway. The thermolysis results suggest the C5 residue takes precedence over the C2 residue on the thermolysis mechanism, and the C2 residue is the main influence when there is no substitution.

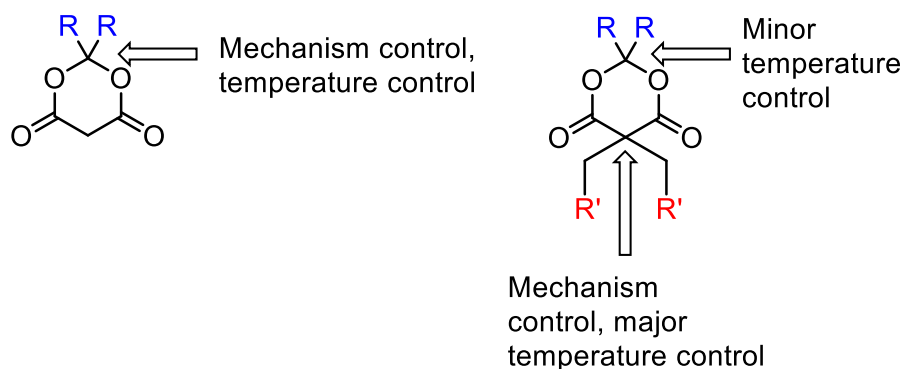


Figure i. Effects of C2 and C5 residues on Meldrum's acid thermolytic pathways
(R = alkyl, aryl; R' = alkyl, alkenyl, alkynyl).

A *gem*-dialkenyl Meldrum's acid afforded a cyclobutanone product through subjection to a thermolysis protocol, identified by some distinctive mass fragments through GC-MS analyses. It was found the same distinctive mass fragments were present in GC-MS analyses of the corresponding library of *gem*-dialkenyl Meldrum's acids, as well as the exact mass of the fragmented C2 ketone residue. Other protocols to access the cyclobutanone and different ketene products were explored.

Malonic acids were studied for their capacity to form ketenes through cyclic carbonate and cyclic thiocarbonate intermediates. The synthesised malonic acids were analysed through thermogravimetric analysis experiments. It was found that the two dialkynyl malonic acids decarboxylated readily and possessed a different thermolysis pathway compared to the other analysed malonic acid. This decarboxylation pathway was

replicated in thermolysis experiments. The same cyclobutanone product from the *gem*-dialkenyl Meldrum's acid was also prepared from a malonic acid compound. We were able to demonstrate that cyclic carbonates produced from malonic acids can also form ketene intermediates and the ketene intermediates prepared in this manner can be accessed at lower temperatures than the equivalent Meldrum's acid derivative. Thus, cyclic carbonates may be a possible ketene source for esterifying sucrose.

Publications and presentations arising from this research

Publications

Bollard, H. E.; Banwell, M. G.; Ward, J. S., (2S,3S,4R,4a'R,5R,5a'R,11a'R,12'S,12a'R)-5-(Acetoxymethyl)-2',2',10',10'-tetramethyloctahydro-3H,8'H-spiro[furan-2,7'-[1,3]dioxino[4',5':5,6]pyrano[3,2-d][1,3,6]trioxocine]-3,4,12'-triyl triacetate. *IUCrData*, **2019**, 4 (7) 1-8.

Presentations

RACI Online Symposium 3rd December 2021. Talk entitled: *Thermally-Induced Reactions of Meldrum's Acid and its Derivatives: A Tale of Two Cycloreversities*.

Abbreviations

The following abbreviations have been used throughout this thesis:

[2+2]	[2+2]-cycloaddition
(3+2)	(3+2)-cycloaddition
[4+2]	[4+2]-cycloaddition
Ac ₂ O	acetic anhydride
anhydr.	anhydrous
app	apparent (as used in ¹ H NMR reporting)
aq.	aqueous
AR	Analytical (grade) Reagent
Ar	argon
br	broad (as used in ¹ H NMR reporting)
Br	bromine
c	concentration (g/100 mL)
C	carbon
C=O	carbonyl
ca.	<i>circa</i> (approximately)
calcd.	calculated

CAN	ceric ammonium nitrate
CAPE	caffeic acid phenethyl ester
cat.	catalytic
CD ₃ OD	deuterated methanol
CDCl ₃	deuterated chloroform
CF ₃	trifluoromethyl
CH(OMe) ₃	trimethyl orthoformate
CH ₃	methyl
(CH ₃) ₂ CO	acetone
CHCl ₃	chloroform
Cl	chlorine
cm ⁻¹	wavenumbers
CN	cyano
CO	carbon monoxide
CO ₂ Me	methyl ester
conc.	concentrated
COOH	carboxylic acid
CSA	camphor sulphonic acid

d	doublet (as used in ^1H NMR reporting)
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	3,4-dihydropyran
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulphoxide
DSC	Different Scanning Calorimetry
EI	Electron impact ionisation
equiv.	equivalent
EtOH	ethanol
F	fluorine
FVP	flash vacuum pyrolysis
g	gram(s)
GC-MS	Gas-Chromatography Mass Spectra
<i>gem</i>	geminal
H	hydrogen
h	hour(s)

H ₂	molecular hydrogen
H ₂ O	water
H ₂ SO ₄	sulphuric acid
HAT	hydrogen atom transfer
HCl	hydrochloric acid
HLB	hydrophilic-lipophilic balance
HNO ₃	nitric acid
HPLC	High-Performance Liquid Chromatography
HRMS	High-Resolution Mass Spectra
<i>hν</i>	light
Hz	hertz
I	iodine
I ₂	molecular iodine
<i>i.e.</i>	<i>id est</i> (that is)
<i>in situ</i>	within the reaction flask
<i>in vitro</i>	within the glass (petri dish)
<i>in vivo</i>	within the host organism
<i>J</i>	coupling constant (as used in ¹ H NMR reporting)

K	Kelvin
K ₂ CO ₃	potassium carbonate
kJ	kilojoule
KOH	potassium hydroxide
L/h	litre per hour
lit.	literature
LRMS	Low-Resolution Mass Spectra
<i>m</i>	<i>meta</i>
m	metre
m	multiplet (as used in ¹ H NMR reporting)
M	molar (mol/L)
M	molecular weight (g/mol)
m.p.	melting point
m/z	mass to charge (ratio)
M ⁺ ·	molecular ion peak
mBar	millibar
Me	methyl
Me(CH ₂) _n CO(OCHCH ₂)	n = 4: vinyl hexanoate

	n = 6: vinyl octanoate
	n = 8: vinyl decanoate
	n = 10: vinyl laurate
(MeCO) ₂	2,3-butanedione
Me(CH ₂) _n CO ₂ Cl	n = 4: hexanoyl chloride
	n = 6: octanoyl chloride
	n = 8: decanoyl chloride
	n = 10: lauroyl chloride
Me(CH ₂) _n CO ₂	n = 4: hexanoic acid
	n = 6: octanoic acid
	n = 8: decanoic acid
	n = 10: lauric acid
MeCN	acetonitrile
MeI	iodomethane
MeMgBr	methylmagnesium bromide
mg	milligram
MHz	mega hertz
min	minute(s)

mL	millilitre
mm	millimetre
mmol	millimole
mol	mole(s)
MS	Mass Spectra
n-	normal
N	nitrogen
Na	sodium
Na ₂ SO ₄	sodium sulphate
NaBH ₄	sodium borohydride
NaH	sodium hydride
NaI	sodium iodide
NaOH	sodium hydroxide
NaOMe	sodium methoxide
n-BuLi	n-butyllithium solution
NEt ₃	triethylamine
NH ₂	amino
nm	nanometre

NMe ₂	Dimethylamino
NMR	Nuclear Magnetic Resonance
NO ₂	nitro
<i>o</i>	<i>ortho</i>
O	oxygen
O ₃	ozone
OEt	ethoxy
OH	hydroxyl
OMe	methoxy
ORTEP	Oak Ridge Thermal Ellipsoid Plot
<i>p</i>	<i>para</i>
p	pentet (as used in ¹ H NMR reporting)
Pd	palladium
Ph	phenyl
pH	logarithm of the reciprocal hydrogen concentration
Ph ₃ CCl	trityl chloride
<i>p</i> -O ₂ NC ₆ H ₄ CO ₂	<i>para</i> -nitrobenzoyl
<i>p</i> -O ₂ NC ₆ H ₄ COCl	<i>para</i> -nitrobenzoyl chloride

PPh ₃	triphenyl phosphine
ppm	parts per million (concentration)
Pt	platinum
<i>p</i> -TsOH	<i>para</i> -toluenesulphonic acid
q	quartet (as used in ¹ H NMR reporting)
R-CAD	retro-cycloaddition (cycloreversion)
<i>R_f</i>	retardation factor
<i>R_t</i>	retention time
s	singlet (as used in ¹ H NMR reporting)
S	sulphur
sat.	saturated
SMD	solvation model based on density
SME	sucrose fatty-acid mono-ester
SOCl ₂	thionyl chloride
spat.	spatula
t	triplet (as used in ¹ H NMR reporting)
T	temperature (Kelvin)
TBDMS	<i>tertiary</i> -butyl dimethylsilyl

TBDMSCl	<i>tertiary</i> -butyl dimethylsilyl chloride
<i>t</i> -BuOH	<i>tertiary</i> -butanol
TGA	Thermogravimetric analysis
Tg °C	inflection point temperature
THF	tetrahydrofuran
TLC	thin-layer chromatography
TLIM	<i>Thermomyces</i> lanuginosus immobilised lipase
™	trademarked
TOF	time of flight
Tr	trityl
TS	transition state
UV	ultra-violet radiation
<i>vide infra</i>	see below
V	volt(s)
v/v	volume to volume (ratio)
v/w	volume to mass (ratio)
Δ	heating
δ	chemical shifts (ppm)

μm	micrometre
π	pi-electron(s)
ν_{max}	infrared adsorption maxima (cm^{-1})
$^{\circ}$	degrees (angle)
$^{\circ}\text{C}$	degrees Celsius
+ve	positive mode
$\pm$	numerically above or below
$\geq$	greater than or equal to
$>$	greater than
$>>$	significantly greater than
$\leq$	less than or equal to

Table of Contents

Chapter list

Declaration.....	i
Acknowledgements.....	ii
Abstract.....	iv
Publications and presentations arising from this research	viii
Abbreviations	ix
Table of Contents	xx
Chapter One: On the Application of Meldrum's Acids and Ketene Chemistry for the Industrial Synthesis of Sucrose Fatty-Acid Mono-Esters	1
<i>1.1 Sucrose as a reagent</i>	<i>1</i>
<i>1.2 Sucrose fatty-acid mono-esters.....</i>	<i>2</i>
<i>1.2.1 Traditional industrial and modern syntheses of sucrose fatty-acid mono-esters</i>	<i>4</i>
<i>1.3 Ketenes</i>	<i>8</i>
<i>1.3.1 Ketenes as a carbonyl source</i>	<i>8</i>
<i>1.3.2 Ketene synthesis.....</i>	<i>10</i>
<i>1.4 Meldrum's acid</i>	<i>15</i>
<i>1.4.1 General information.....</i>	<i>15</i>
<i>1.4.2 Meldrum's acid derivatives with C5 modifications</i>	<i>16</i>
<i>1.4.3 The thermolytic cracking of Meldrum's acid and its analogues</i>	<i>18</i>
<i>1.4.4 Is forming the ketene intermediate in a controlled manner with Meldrum's acid or its derivatives possible?</i>	<i>23</i>

1.5 Motivations and aims of research.....	25
1.5.1 Specific aims	25
Chapter One references.....	27
Chapter Two: Attempts at Preparing Sucrose Fatty-Acid Mono-Esters Through Traditional Synthetic Methodologies (Aim 1)	40
2.1 Synthetic strategy for preparing sucrose derivatives through traditional chemistry	40
2.2 Attempts at preparing sucrose derivatives through traditional protecting group chemistry.....	40
2.2.1 Accessing sucrose mono-esters on C6'	41
2.2.2 Accessing sucrose mono-esters on C6	47
2.2.3 Accessing sucrose mono-esters on C3	48
2.2.4 Accessing sucrose mono-esters on C4	50
2.3 Rationale for a new approach	51
Chapter Two references.....	53
Chapter Three: C2 Substituted Meldrum's Acid Thermolytic Studies (Aims 2 and 3).....	55
3.1 Meldrum's acid thermolysis computational studies.....	55
3.2 Library of Meldrum's Acid targets (Aim 2)	58
3.3 X-ray crystallography studies	62
3.4 Differential scanning calorimetry Studies	71
3.5 Thermogravimetric Analysis Studies (Aim 3).....	73
Chapter Three references	81

Chapter Four: C5 Substituted Meldrum's Acid Derivatives and Thermolytic Studies (Aims 4 and 5)..... 82

<i>4.1 Library of C5 substituted Meldrum's acid derivatives (Aim 4).....</i>	<i>82</i>
<i>4.2 Crystallography studies.....</i>	<i>88</i>
<i>4.3 Thermogravimetric Analysis of derivatives (Aim 5).....</i>	<i>95</i>
<i>4.4 Effects of hydrogenated C5 groups.....</i>	<i>98</i>
<i>4.5 Thermolysis mechanism suppositions.....</i>	<i>101</i>
<i>4.6 Effects of C5 residue on the Meldrum's acid and its thermolytic pathways</i>	<i>102</i>
<i>4.7 Conclusions.....</i>	<i>103</i>
<i>4.7.1 Future studies.....</i>	<i>104</i>
<i>Chapter Four references</i>	<i>105</i>

Chapter Five: Proving the Intermediacy of Ketenes in the Thermolytic Pathway (Aim 6)..... 106

<i>5.1 Experimental observation of dialkenyl Meldrum's Acid.....</i>	<i>106</i>
<i>5.2 GC-MS studies and follow-up reactions</i>	<i>107</i>
<i>5.3 Flow reactor study for accessing ketenes</i>	<i>112</i>
<i>5.4 Accessing other kinds of ketene products.....</i>	<i>114</i>
<i>5.5 Synthesis and thermogravimetric analysis studies of malonic acid derivatives</i>	<i>116</i>
<i>5.6 Malonic acid crystallographic studies</i>	<i>119</i>
<i>5.7 Cyclic carbonates can also access ketenes (Aim 6).....</i>	<i>122</i>
<i>5.8 Conclusion</i>	<i>124</i>
<i>5.8.1 Future studies.....</i>	<i>125</i>
<i>Chapter Five references.....</i>	<i>127</i>

Chapter Six: Experimental..... 128

<i>General Experimental Procedures:</i>	128
<i>Chapter Six References</i>	198
Appendices	1
<i>Appendix 1: Crystallographic data</i>	1
<i>A1.1: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 7</i>	1
<i>A1.2: ORTEP derived from the single-crystal X-ray crystal structure analysis of Meldrum's acid</i>	2
<i>A1.3: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 16</i>	3
<i>A1.4: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 17.</i>	4
<i>A1.5: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 18</i>	5
<i>A1.6: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 19.</i>	6
<i>A1.7: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 21.</i>	7
<i>A1.8: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 29.</i>	8
<i>A1.9: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 30.</i>	9
<i>A1.10: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 31.</i>	10

A1.11: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 33 .	11
A1.12: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 34 .	12
A1.13: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 35 .	13
A1.14: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 36 .	14
A1.15: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 38 .	15
A1.16: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 41 .	16
A1.17: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 57 .	17
A1.18: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 58 .	18
A1.19: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 61 .	19
A1.20: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 70 .	20
A1.21: ORTEP derived from the single-crystal X-ray analysis of compound 73 .	21
Appendix 2: Differential scanning calorimetry analyses data	22
A2.1: Differential scanning calorimetry plot of Meldrum's acid	22
A2.2: Differential scanning calorimetry plot of compound 16 .	23
A2.3: Differential scanning calorimetry plot of compound 17 .	24

A2.4: Differential scanning calorimetry trace of compound 18	25
A2.5: Differential scanning calorimetry trace of compound 19	26
A2.6: Differential scanning calorimetry trace of compound 20	27
A2.7: Differential scanning calorimetry trace of compound 21	28
A2.8: Differential scanning calorimetry trace of compound 22	29
A2.9: Differential scanning calorimetry trace of compound 29	30
A2.10: Differential scanning calorimetry trace of compound 30	31
A2.11: Differential scanning calorimetry trace of compound 31	32
A2.12: Differential scanning calorimetry trace of compound 32	33
A2.13: Differential scanning calorimetry trace of compound 33	34
A2.14: Differential scanning calorimetry trace of compound 34	35
A2.15: Differential scanning calorimetry trace of compound 35	36
A2.16: Differential scanning calorimetry trace of compound 36	37
A2.17: Differential scanning calorimetry trace of compound 37	38
A2.18: Differential scanning calorimetry trace of compound 38	39
Appendix 3: Thermogravimetric analyses data	40
A3.1: Thermogravimetric analysis plot of Meldrum's acid	40
A3.2: Thermogravimetric analysis plot of compound 16	41
A3.3: Thermogravimetric analysis plot of compound 17	42
A3.4: Thermogravimetric analysis plot of compound 18	43
A3.5: Thermogravimetric analysis plot of compound 19	44
A3.6: Thermogravimetric analysis plot of compound 20	45
A3.7: Thermogravimetric analysis plot of compound 21	46
A3.8: Thermogravimetric analysis plot of compound 22	47
A3.9: Thermogravimetric analysis plot of compound 29	48

A3.10: Thermogravimetric analysis plot of compound 30	49
A3.11: Thermogravimetric analysis plot of compound 31	50
A3.12: Thermogravimetric analysis plot of compound 32	51
A3.13: Thermogravimetric analysis plot of compound 33	52
A3.14: Thermogravimetric analysis plot of compound 34	53
A3.15: Thermogravimetric analysis plot of compound 35	54
A3.16: Thermogravimetric analysis plot of compound 36	55
A3.17: Thermogravimetric analysis plot of compound 37	56
A3.18: Thermogravimetric analysis plot of compound 38	57
A3.19: Thermogravimetric analysis plot of compound 41	58
A3.20: Thermogravimetric analysis plot of compound 42	59
A3.21: Thermogravimetric analysis plot of compound 43	60
A3.22: Thermogravimetric analysis plot of compound 44	61
A3.23: Thermogravimetric analysis plot of compound 45	62
A3.24: Thermogravimetric analysis plot of compound 53	63
A3.25: Thermogravimetric analysis plot of compound 54	64
A3.26: Thermogravimetric analysis plot of compound 55	65
A3.27: Thermogravimetric analysis plot of compound 56	66
A3.28: Thermogravimetric analysis plot of compound 57	67
A3.29: Thermogravimetric analysis plot of compound 58	68
A3.30: Thermogravimetric analysis plot of compound 59	69
A3.31: Thermogravimetric analysis plot of compound 60	70
A3.32: Thermogravimetric analysis plot of compound 61	71
A3.33: Thermogravimetric analysis plot of compound 62	72
A3.34: Thermogravimetric analysis plot of compound 64	73

A3.35: Thermogravimetric analysis plot of compound 66	74
A3.36: Thermogravimetric analysis plot of compound 70	75
A3.37: Thermogravimetric analysis plot of compound 73	76
A3.38: Thermogravimetric analysis plot of compound 75	77
Appendix 4: GC-MS data	78
A4.1: GC-MS data of compound 71	78
A4.2: GC-MS data of compound 41	79
A4.3 GC-MS data of compound 42	81
A4.4: GC-MS data of compound 43	82
A4.5: GC-MS data of compound 44	83
A4.6: GC-MS data of compound 45	84
A4.7: GC-MS data of compound 53	86
A4.8: GC-MS data of compound 54	87
A4.10: GC-MS data of compound 56	90
A4.11: GC-MS data of compound 57	91
A4.12: GC-MS data of compound 58	92
A4.14: GC-MS data of compound 60	95
A4.15: GC-MS data of compound 61	96
A4.16: GC-MS data of compound 62	98

List of Figures and Reaction Schemes

Abstract.....	iv

Scheme i. Meldrum's acid thermal cycloreversion pathways via a concerted and an asynchronous reaction pathway.	v

Figure i. Effects of C2 and C5 residues on Meldrum's acid thermolytic pathways.	vi

Chapter One: On the Application of Meldrum's Acids and Ketene Chemistry for the Industrial Synthesis of Sucrose Fatty-Acid Mono-Esters	1

Figure 1.1.1. Structure and hydroxyl group numbering of sucrose.....	2

Figure 1.2.1. A sample sucrose fatty-acid mono-ester (SME) on the 6C free hydroxyl.	3

Scheme 1.2.1.1. A typical <i>trans</i> -esterification protocol for synthesising SMEs. ..	6

Figure 1.3.1.1. A generic ketene.	9

Figure 1.3.1.2. Sample compounds formed via ketene cycloaddition reactions..	9

Scheme 1.3.1.1. A fatty-acid associated-ketene and its trapping with a generic alcohol (ROH) leading to a fatty-acid ester.	10

Scheme 1.3.2.1. Staudinger's synthesis of diphenyl ketene.	11

Scheme 1.3.2.2. Wilsmore's synthesis of ketene from three different carbonyl sources.	11

Scheme 1.3.2.3. A sample photochemically-promoted Wolff rearrangement forming a ketene intermediate.	13

Scheme 1.3.2.4. Ketene synthesis from a general furandione precursor.....	15

Figure 1.4.1.1. Structure, relevant atom labelling and reactive sites of Meldrum's acid.	16
Figure 1.4.2.1. Types of Meldrum's acids with C5 modifications.	16
Scheme 1.4.2.1. General preparation method of C5 alkylated Meldrum's acids.	18
Scheme 1.4.3.1. Preparation of ketene intermediates from alkylidene and acyl Meldrum's acids.....	19
Scheme 1.4.3.2. Meldrum's acid thermal cycloreversion pathways via a concerted and an asynchronous reaction pathway.....	20
Scheme 1.4.3.3. Meldrum's acid thermolysis pathways <i>via</i> a charged intermediate proposed by Brown and co-workers.....	21
Scheme 1.4.3.4. Proposed formation of a sample sucrose fatty-acid mono-ester through using Meldrum's acid as a ketene source.....	22
Scheme 1.4.4.1. Results from Barrett and co-workers ¹²² where variations in the C2 residue resulted in decreased reaction rates and increased yields of the target ester.	24
Chapter Two: Attempts at Preparing Sucrose Fatty-Acid Mono-Esters Through Traditional Synthetic Methodologies (Aim 1)	40
Figure 2.2.1. Proposed sucrose intermediates 1 and 2	41
Scheme 2.2.1.1. Attempted <i>trans</i> -1,2-diol protection of sugar 3	42
.....	43
Scheme 2.2.1.2. Synthesis of compound 7 through key intermediate 1	44

Figure 2.2.1.1. ORTEP Plot derived from single-crystal X-ray crystal structure analysis of compound 7	45
Scheme 2.2.1.3. Attempted TLIM-catalysed <i>trans</i> -esterification of intermediate 1	46
Scheme 2.2.1.4. Attempted esterification of compound 1	46
Scheme 2.2.2.1. Synthetic sequence accessing compound 10	47
Scheme 2.2.2.2. Attempted TLIM <i>trans</i> -esterification of compound 10	48
Figure 2.2.3.1. ¹ H NMR of compound 11 depicting the regio-isomer drawn as the major product.....	49
Scheme 2.2.3.1. Synthesis of compound 11 and attempted further protection with silane 12	49
Scheme 2.2.4.1. Synthesis of compound 14	50
Figure 2.2.4.1. ¹ H NMR of compound 14	51
Chapter Three: C2 Substituted Meldrum's Acid Thermolytic Studies (Aims 2 and 3)	55
Figure 3.1.1. The calculated Gibbs free energy barrier to cycloreversions for <i>gem</i> -dimethylated Meldrum's acid, cyclic carbonate and cyclic thiocarbonate respectively in both the gas phase and solvated with SMD toluene. ¹	55
Figure 3.1.2. The calculated thermolytic reaction pathway profiles of acetophenone Meldrum's acids, including the transition states of each reaction pathway.	56
Scheme 3.2.1. Library of prepared aliphatic Meldrum's acids.....	59
Scheme 3.2.2. Sequence to access acetophenone 26	59

Scheme 3.2.3. Synthesis of acetophenone 28	60
Scheme 3.2.4. Library of prepared aromatic Meldrum's acids.	61
Scheme 3.2.5. Attempted reduction of compound 30 through hydrogenolysis.	62
Figure 3.3.1. a) ORTEP Plot derived from single-crystal X-ray crystal structure analysis of compound 16 . Hydrogen atoms are drawn as circles with small radii.	65
Figure 3.3.1. b) ORTEP Plot derived from single-crystal X-ray analysis of compound 30	66
Figure 3.3.2. Obtained single-crystal X-ray structure of compound 17 as a sample ellipsoid structure depicting the predicted intramolecular interaction between C5 and the carbon atom in an α -position to C2.	68
Figure 3.3.3. Obtained single-crystal X-ray structure of compound 21 , a) depicting the intramolecular interactions, b) depicting a view looking across the C5 residue to demonstrate the almost planar conformation of compound 21	68
Figure 3.4.1. Sample Differential scanning calorimetry profiles for a) compound 17 , b) compound 32 , c) compound 29	73
Figure 3.5.1. TGA traces of Meldrum's acid and its aliphatic derivatives, depicted as change in mass percent vs temperature ($^{\circ}\text{C}$).	74
Figure 3.5.2. TGA traces of Meldrum's acid and its aromatic derivatives, depicted as change in mass percent vs temperature ($^{\circ}\text{C}$).	75
Figure 3.5.3. a) Hammett plot for <i>p</i> -acetophenone Meldrum's acids, b) Hammett plot for <i>m</i> -acetophenone Meldrum's acids.	77

Figure 3.5.1. A general <i>p</i> -acetophenone Meldrum's acid depicting the bonds that change length in the transition state, as determined by our computational collaborators. ²	79
Scheme 3.5.1. The asynchronous hetero-retro-Diels-Alder pathway for acetophenone Meldrum's acids.	79

Chapter Four: C5 Substituted Meldrum's Acid Derivatives and Thermolytic Studies (Aims 4 and 5)	82
Scheme 4.1.1. Finkelstein reaction of alkene 39 to produce alkene 40	82
Scheme 4.1.2. Attempted twofold alkenylation of acetophenone Meldrum's acids.	83
Scheme 4.1.3. Twofold alkenylation products of aliphatic Meldrum's acids.	84
Figure 4.1.1. ¹ H NMR spectra of compound 41 depicting the absence of C5 protons.....	85
Scheme 4.1.4. Synthesis of electrophile 51 from alkyne 46	85
Scheme 4.1.5. Synthesis of electrophile 52 from alkyne 46	86
Scheme 4.1.6. Aliphatic <i>gem</i> -dialkynyl methyl-capped Meldrum's acids.	87
Scheme 4.1.7. Aliphatic <i>gem</i> -dialkynyl terminal Meldrum's acids.	87
Figure 4.2.1. a) ORTEP Plot derived from single-crystal X-ray crystal structure analysis of compound 41 , b) ORTEP Plot derived from single-crystal X-ray analysis of compound 58	91
Figure 4.2.3. Obtained single-crystal X-ray crystal structures of compounds 41 , 57 , 58 and 61 depicting the three-dimensional structures and bond contacts of the aliphatic C5 residues and their corresponding chemical structures.	94

Figure 4.3.1. Thermogravimetric traces for <i>gem</i> -dialkenyl compounds 41-45 , depicted as change in mass percent vs temperature (°C).	95
Figure 4.3.2. Thermogravimetric traces for <i>gem</i> -dialkynyl compounds 53-57 , depicted as change in mass percent vs temperature (°C).	96
Figure 4.3.3. Thermogravimetric profiles for <i>gem</i> -dialkynyl compounds 58-62 , depicted as change in mass percent vs temperature (°C).	97
Schemes 4.4.1. a) Synthesis of compound 64 through twofold alkylation of Meldrum's acid with compound 63 , b) Synthesis of compound 66 through twofold alkylation of Meldrum's acid with compound 65	99
Figure 4.4.1. Thermolysis traces of Meldrum's acid and its C5 alkylated/alkenylated/alkynylated derivatives, depicted as change in mass percent vs temperature (°C).....	100
Scheme 4.5.1. Concerted single-step thermolysis pathway of <i>gem</i> -dialkylated Meldrum's acids.....	102
Figure 4.6.1. Effects of C2 and C5 residues on Meldrum's acid thermolytic pathways.	103
Scheme 4.7.1.1. Proposed preferred thermolytic pathway of mono-alkylated Meldrum's acids.....	104
Chapter Five: Proving the Intermediacy of Ketenes in the Thermolytic Pathway (Aim 6)	106
Scheme 5.1.1. Conversion of compound 41 to compound 71 via a ketene intermediate.....	107
Figure 5.2.1. Low resolution GC-MS data for cyclobutanone 71	108

Figure 5.2.2. Sample low resolution GC-MS spectra of compound 45	109
Scheme 5.2.1. Proposed GC-MS fragments for cyclobutanone 71	109
Figure 5.2.3. a) Sample low resolution GC-MS spectra of compound 54 , b) sample low resolution GC-MS spectra of compound 59	111
Scheme 5.4.1. Planned reaction scheme to produce lactone 67 from compound 41	116
Scheme 5.5.1. Synthesis of compound 70 from malonate 69	117
Scheme 5.5.2. Synthesis of compounds 73 and 75 from malonate 69	117
Figure 5.5.1. Thermogravimetric traces of malonic acids 70 , 73 and 75 , depicting change in mass percent vs temperature (°C)	118
Figure 5.6.1. Obtained X-ray crystal structure of compound 73 depicting an intermolecular π -interaction.	121
Figure 5.6.2. a) Obtained single-crystal X-ray crystal structure of compound 70 depicting an intramolecular π -interaction, b) Obtained single-crystal X-ray crystal structure of compound 73 depicting an intramolecular π -interaction.	121
Scheme 5.7.1. Attempted synthesis of cyclobutanone 71 from malonic acid 70 through cyclic thionate intermediate.	122
Scheme 5.7.2. Synthesis of decarboxylation product from malonic acids 73 and 75 instead of the proposed ketene pathway.	123
Scheme 5.7.3. Synthesis of cyclobutanone 70 through malonic acid 71	124

List of Tables

Chapter Two: Attempts at Preparing Sucrose Fatty-Acid Mono-Esters Through Traditional Synthetic Methodologies (Aim 1) 40

Table 2.2.1. Comparison table of bond lengths and angles of compounds 3 and 7	43

Chapter Three: C2 Substituted Meldrum's Acid Thermolytic Studies (Aims 2 and 3)..... 55

Table 3.1.1. The relevant calculated transition state bond lengths for the screened <i>p</i> -acetophenone Meldrum's acids.	57

Table 3.3.1. Obtained dihedral angles of crystalline aliphatic C2 substituted Meldrum's acids.....	63

Table 3.3.2. Obtained dihedral angles of crystalline aromatic C2 substituted Meldrum's acids.....	64

Table 3.3.3. Comparison of the relevant transition state bond lengths, as calculated by our collaborators ² and the obtained ground state bond lengths from single-crystal X-ray diffraction analyses.	69

Chapter Four: C5 Substituted Meldrum's Acid Derivatives and Thermolytic Studies (Aims 4 and 5)..... 82

Table 4.2.2. Dihedral angles of the Meldrum's acid derivative cores.....	89

Table 4.2.1. Bond angles of the Meldrum's acid derivative cores.	89

Table 4.2.3. Bond lengths of Meldrum's acid cores and <i>gem</i> -dialkylated Meldrum's acid cores.....	92

Chapter Five: Proving the Intermediacy of Ketenes in the Thermolytic Pathway

(Aim 6) 106

Table 5.3.1. Reaction conditions for flow reactor studies. 113

List of Appendices

Appendices.....	1
<i>Appendix 1: Crystallographic data.....</i>	<i>1</i>
A1.1. ORTEP derived from the single-crystal X-ray analysis of compound 7 with labelling of all non-hydrogen atoms.	1
A1.2. ORTEP derived from the single-crystal X-ray analysis of Meldrum's acid with labelling of all non-hydrogen atoms.....	2
A1.3. ORTEP derived from the single-crystal X-ray analysis of compound 16 with labelling of all non-hydrogen atoms.....	3
A1.4. ORTEP derived from the single-crystal X-ray analysis of compound 17 with labelling of all non-hydrogen atoms.....	4
A1.5. ORTEP derived from the single-crystal X-ray analysis of compound 18 with labelling of all non-hydrogen atoms.....	5
A1.6. ORTEP derived from the single-crystal X-ray analysis of compound 19 with labelling of all non-hydrogen atoms.....	6
A1.7. ORTEP derived from the single-crystal X-ray analysis of compound 21 with labelling of all non-hydrogen atoms.....	7
A1.8. ORTEP derived from the single-crystal X-ray analysis of compound 29 with labelling of all non-hydrogen atoms.....	8
A1.9. ORTEP derived from the single-crystal X-ray analysis of compound 30 with labelling of all non-hydrogen atoms.....	9
A1.10. ORTEP derived from the single-crystal X-ray analysis of compound 31 with labelling of all non-hydrogen atoms.....	10

A1.11. ORTEP derived from the single-crystal X-ray analysis of compound 33 with labelling of all non-hydrogen atoms.....	11
A1.12. ORTEP derived from the single-crystal X-ray analysis of compound 34 with labelling of all non-hydrogen atoms.....	12
A1.13. ORTEP derived from the single-crystal X-ray analysis of compound 35 with labelling of all non-hydrogen atoms.....	13
A1.14. ORTEP derived from the single-crystal X-ray analysis of compound 36 with labelling of all non-hydrogen atoms.....	14
A1.15. ORTEP derived from the single-crystal X-ray analysis of compound 18 with labelling of all non-hydrogen atoms.....	15
A1.16. ORTEP derived from the single-crystal X-ray analysis of compound 41 with labelling of all non-hydrogen atoms.....	16
A1.17. ORTEP derived from the single-crystal X-ray analysis of compound 57 with labelling of all non-hydrogen atoms.....	17
A1.18. ORTEP derived from the single-crystal X-ray analysis of compound 58 with labelling of all non-hydrogen atoms.....	18
A1.19. ORTEP derived from the single-crystal X-ray analysis of compound 61 with labelling of all non-hydrogen atoms.....	19
A1.20. ORTEP derived from the single-crystal X-ray analysis of compound 70 with labelling of all non-hydrogen atoms.....	20
A1.21. ORTEP derived from the single-crystal X-ray analysis of compound 73 with labelling of all non-hydrogen atoms.....	21
<i>Appendix 2: Differential scanning calorimetry analyses data</i>	22

A2.1. Differential scanning calorimetry trace of Meldrum's acid.	22
A2.2. Differential scanning calorimetry trace of compound 16	23
A2.3. Differential scanning calorimetry trace of compound 17	24
A2.4. Differential scanning calorimetry trace of compound 18	25
A2.5. Differential scanning calorimetry trace of compound 19	26
A2.6. Differential scanning calorimetry trace of compound 20	27
A2.7. Differential scanning calorimetry trace of compound 21	28
A2.8. Differential scanning calorimetry trace of compound 22	29
A2.9. Differential scanning calorimetry trace of compound 29	30
A2.10. Differential scanning calorimetry trace of compound 30	31
A2.11. Differential scanning calorimetry trace of compound 31	32
A2.12. Differential scanning calorimetry trace of compound 32	33
A2.13. Differential scanning calorimetry trace of compound 33	34
A2.14. Differential scanning calorimetry trace of compound 34	35
A2.15. Differential scanning calorimetry trace of compound 35	36
A2.16. Differential scanning calorimetry trace of compound 36	37
A2.17. Differential scanning calorimetry trace of compound 37	38
A2.18. Differential scanning calorimetry trace of compound 38	39
<i>Appendix 3: Thermogravimetric analyses data</i>	40
A3.1. Thermogravimetric analytical trace of Meldrum's acid.	40
A3.2. Thermogravimetric analytical trace of compound 16	41
A3.3. Thermogravimetric analytical trace of compound 17	42

A3.4. Thermogravimetric analytical trace of compound 18	43
A3.5. Thermogravimetric analytical trace of compound 19	44
A3.6. Thermogravimetric analytical trace of compound 20	45
A3.7. Thermogravimetric analytical trace of compound 21	46
A3.8. Thermogravimetric analytical trace of compound 22	47
A3.9. Thermogravimetric analytical trace of compound 29	48
A3.10. Thermogravimetric analytical trace of compound 30	49
A3.11. Thermogravimetric analytical trace of compound 31	50
A3.12. Thermogravimetric analytical trace of compound 32	51
A3.13. Thermogravimetric analytical trace of compound 33	52
A3.14. Thermogravimetric analytical trace of compound 34	53
A3.15. Thermogravimetric analytical trace of compound 35	54
A3.16. Thermogravimetric analytical trace of compound 36	55
A3.17. Thermogravimetric analytical trace of compound 37	56
A3.18. Thermogravimetric analytical trace of compound 38	57
A3.19. Thermogravimetric analytical trace of compound 41	58
A3.20. Thermogravimetric analytical trace of compound 42	59
A3.21. Thermogravimetric analytical trace of compound 43	60
A3.22. Thermogravimetric analytical trace of compound 44	61
A3.23. Thermogravimetric analytical trace of compound 45	62
A3.24. Thermogravimetric analytical trace of compound 53	63

A3.25. Thermogravimetric analytical trace of compound 54	64
A3.26. Thermogravimetric analytical trace of compound 55	65
A3.27. Thermogravimetric analytical trace of compound 56	66
A3.28. Thermogravimetric analytical trace of compound 57	67
A3.29. Thermogravimetric analytical trace of compound 58	68
A3.30. Thermogravimetric analytical trace of compound 59	69
A3.31. Thermogravimetric analytical trace of compound 60	70
A3.32. Thermogravimetric analytical trace of compound 61	71
A3.33. Thermogravimetric analytical trace of compound 62	72
A3.34. Thermogravimetric analytical trace of compound 64	73
A3.35. Thermogravimetric analytical trace of compound 66	74
A3.36. Thermogravimetric analytical trace of compound 70	75
A3.37. Thermogravimetric analytical trace of compound 73	76
A3.38. Thermogravimetric analytical trace of compound 75	77
<i>Appendix 4: GC-MS data</i>	78
A4.1. GC-MS trace and spectra of compound 71	79
A4.2. GC-MS trace and spectra of compound 41	80
A4.3. GC-MS trace and spectra of compound 42	81
A4.4. GC-MS trace and spectra of compound 43	83
A4.5. GC-MS trace and spectra of compound 44	84
A4.6. GC-MS trace and spectra of compound 45	85
A4.7. GC-MS trace and spectra of compound 53	86

A4.8. GC-MS trace and spectra of compound 54	88
A4.9. GC-MS trace and spectra of compound 55	89
A4.10. GC-MS trace and spectra of compound 56	90
A4.11. GC-MS trace and spectra of compound 57	91
A4.12. GC-MS trace and spectra of compound 58	93
A4.13. GC-MS trace and spectra of compound 59	94
A4.14. GC-MS trace and spectra of compound 60	96
A4.15. GC-MS trace and spectra of compound 61	97
A4.16. GC-MS trace and spectra of compound 62	99

Chapter One: On the Application of Meldrum's Acids and Ketene Chemistry for the Industrial Synthesis of Sucrose Fatty-Acid Mono-Esters

1.1 Sucrose as a reagent

Sucrose (Figure 1.1.1), known as both β -D-fructofuranosyl α -D-pyranoside and as common table sugar, is a disaccharide comprised of a glucose moiety and fructose moiety and is the most commercially available low weight carbohydrate.¹⁻⁷ Sucrose is used predominantly as a foodstuff^{2, 3, 5, 8} but has found niche applications in organic syntheses by virtue of it being one of the cheapest, optically pure compounds commercially available.^{3, 8} The sucrose molecule has nine stereogenic centres and eight free hydroxyl groups of reasonably comparable reactivity,^{2, 3} which manifests as a lack of regio-selectivity under a wide variety of reaction conditions.^{5, 7, 10} In particular, functionalising a single, specific hydroxyl group is a non-trivial task. Even if selective functionalisation is achieved there are certain residues, such as the acyl moiety, that can perform an intramolecular migration from one oxygen atom to another.¹¹ Thus, sucrose has a reputation of being difficult to work with from a synthetic viewpoint.^{4, 11} Despite this, there is a wealth of chemistry around sucrose^{2, 3, 5, 6, 12, 13} and that has allowed some regio-selective reactions to be conducted. It is known that the hydroxyl group at C2 is slightly more acidic than its counterparts,^{5, 7, 14-16} whilst the free hydroxyl pair at C6 and C6' are slightly more reactive.^{3, 6, 8} Using this reactivity guide, it is possible to access a variety of sucrose derivatives through employing predominantly protecting group chemistry in a somewhat selective manner.^{6, 12, 17} Reactions of sucrose that proceed with rearrangement of the associated backbone are known and can further complicate derivatisation.^{3, 7} One type of sucrose derivative of interest both to academia and to industry are those obtained through a condensation reaction with sucrose and longer-chain (fatty) acids for their emulsifying properties.¹⁸ These

resulting esters have a wide range of applications as surfactants, where the fatty-acid esters with the broadest application are sucrose fatty-acid mono-esters.^{1, 18, 19}

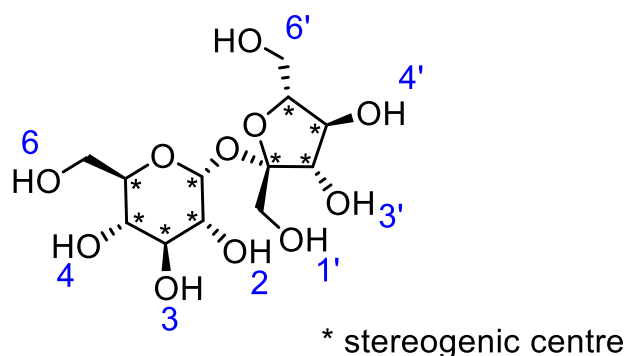


Figure 1.1.1. Structure and hydroxyl group numbering of sucrose.

1.2 Sucrose fatty-acid mono-esters

Sucrose fatty-acid mono-esters (SMEs), an example of which is depicted in Figure 1.2.1, are highly effective non-ionic surfactants that can be sourced from inexpensive, readily available feedstocks, thereby making these compounds commercially attractive.^{1, 10, 20-22} Some other appealing properties of SMEs are that they are biodegradable, non-toxic, non-irritating on skin contact, odourless and reasonably cheap to prepare.^{1, 11, 13, 23} SMEs are known to be tuneable to suit specific applications through the length of fatty-acyl side-chain used,^{1, 10, 19, 21, 22, 24} which gives rise to a wide range of possible hydrophilic-lipophilic balance (HLB) values. SMEs with HLB values in the range of 8-10 depicts a balance between hydrophobicity and lipophilicity and are used in certain food products, such as chewing gums.²⁵ Some of the most common fatty-acid mono-esters are of hexanoate-, octanoate-, decanoate-, laurate-, myristate-, palmitate-, stearate- and oleate-based esters.^{1, 26-29} Other properties of commercial relevance associated with SMEs are their foaming and antimicrobial properties, which are also strongly influenced by the nature of the associated carboxylic acid residue.

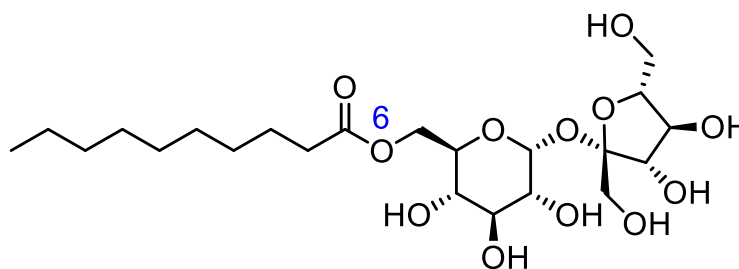


Figure 1.2.1. A sample sucrose fatty-acid mono-ester (SME) on the 6C free hydroxyl.

SMEs have found wide application in, for example food, dental and pharmaceutical industries, because of their surfactant properties^{13, 23, 30, 31} and capacity to extend the shelf-life of food products.^{2, 3, 5, 8} Evidence in the literature^{28, 29, 32, 33} suggests SMEs incorporating fatty-acid side-chains of 10-12 carbons are best for stabilising emulsions. SMEs also have utility as food additives through their anti-microbial properties, thereby reducing the rate of food spoilage.^{19, 30} The anti-microbial activity is thought to arise from the capacity of SMEs to disrupt and subsequently lyses the bacterial cell membrane.^{1, 34} This lyse mechanism has been proven to operate for sucrose mono-laurate specifically against Gram-positive bacteria³⁴ and may also apply to Gram-negative bacteria too. The anti-microbial properties of sucrose mono-laurate specifically might also be applicable to dentistry, as 6-O-lauryl sucrose has been demonstrated to completely inhibit the growth of *Streptococcus sobrinus*,³⁵ a bacterium that causes dental cavities. However, various bacterial strains express esterases that would render any applied SMEs ineffective in those instances.²⁷

There is evidence to suggest sucrose esters can act against specific types of tumours. It has been demonstrated by Kato and colleagues³⁶ that sucrose esters incorporating lauric, myristic, palmitic and linoleic acid residues exert *in vitro* cytotoxicities against

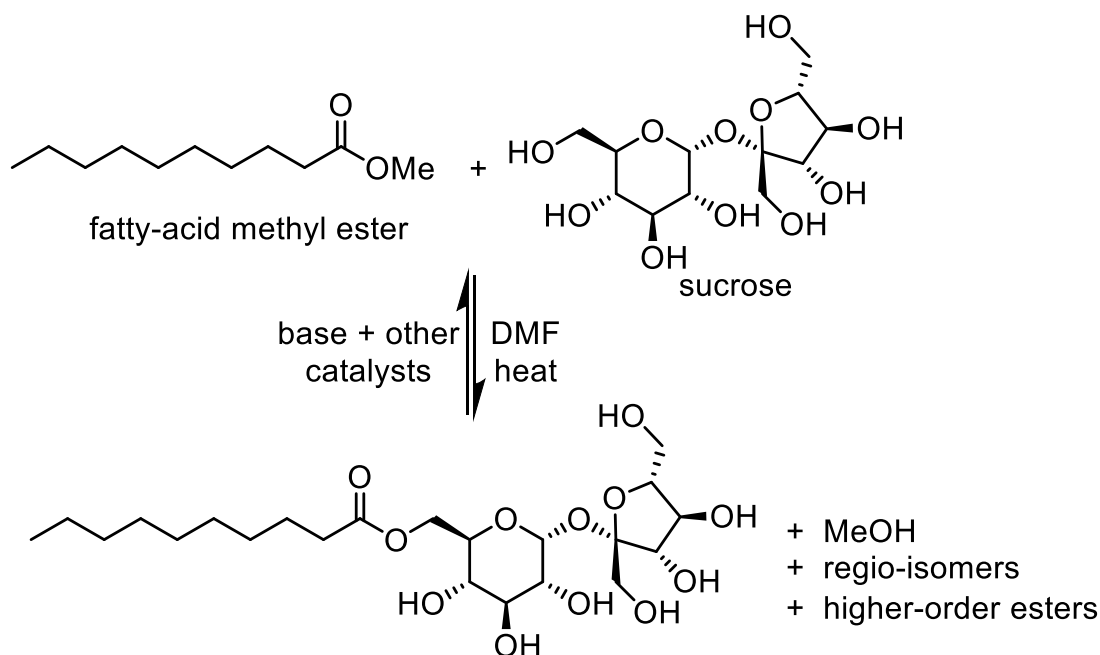
Ehrlich ascites and these same compounds have been shown to do so with mice through *in vivo* studies.^{37, 38} SMEs themselves exhibit some anti-tumour activity^{39, 40} with Petrova and colleagues⁴¹ demonstrating that some SMEs inhibit the growth of MCF7 breast and the HepG2 liver tumour cell lines. The authors determined that whilst the activities were weaker than the positive control ellipticine, the SMEs were not hepatotoxic (unlike ellipticine). Of note, Ikekawa and colleagues⁴⁰ found that the cytotoxic effects of the SMEs decreased as the HLB value increased, thereby signifying the concentration of cancerous cells decreasing as the employed surfactant becomes more hydrophilic. SMEs have also been investigated as a drug delivery system by capturing and solubilising CAPE, a potent anti-tumour drug that has noted strong activity but low water solubility.^{26, 42}

Given the aforementioned applications, it is clear SMEs have broad utility and this is reflected in the multi-million-dollar annual sales for these compounds.¹ Yet despite the high demand for them, the industrial synthesis of SMEs is still reliant on old technologies and inefficient methods that include inefficient *trans*-esterification protocols.^{1, 23}

1.2.1 Traditional industrial and modern syntheses of sucrose fatty-acid mono-esters

As indicated above, SMEs are typically prepared industrially through a *trans*-esterification protocol, whereby the sugar is reacted with a small to medium length alkyl methyl ester in the presence of base and appropriate surfactants (Scheme 1.2.1.1).^{1, 19, 24, 43, 44} Sucrose itself is a highly acid-sensitive molecule so the esterification reaction must be conducted in either neutral or basic conditions,

otherwise hydrolysis of the glycosidic bond linking the two constituent monosaccharide residues occurs.^{19, 45} Sucrose is also a polar molecule due to its eight free hydroxyl groups and requires a polar solvent to be dissolved, which creates a solubility mismatch with the employed non-polar fatty-acid methyl esters. Presently *N,N*-dimethylformamide (DMF) is the solvent used as a solubility compromise for dissolving both reactants.^{13, 19} However, it is becoming increasingly clear that DMF is unsuitable for industrial syntheses as it is an environmental pollutant and is toxic to human health, therefore it cannot be present in a final product that is to enter the food-chain.^{7, 24} Because of its polarity and high boiling point, DMF is also a challenging solvent to remove even under reduced pressures.¹ An additional problem associated with the *trans*-esterification protocol is the reaction requires heating,^{19, 24, 44} which can be expensive to achieve on an industrial scale. Heating sucrose, likewise, poses challenges as sucrose caramelises above 170 °C⁴⁶ and the subsequent products cannot be used to manufacture surfactants. Since the *trans*-esterification reaction itself produces methanol,^{1, 19} this must be constantly removed under reduced pressure to push the reaction to completion. Another complication associated with the *trans*-esterification protocol is the initially formed SMEs isomerising to other SMEs or even participating in acyl-transfer reactions that lead to complex product mixtures of so-called higher-order esters being produced,^{11, 15, 44} which tend to have inferior surface activities in comparison to SMEs.⁴⁷ The combination of the aforementioned inefficiencies with the *trans*-esterification protocol has prompted chemists to establish more economical and efficient processes for forming SMEs.^{19, 48-50}



Scheme 1.2.1.1. A typical *trans*-esterification protocol for synthesising SMEs.

Various attempts, albeit on a laboratory-scale, have been made to improve the efficiency, selectivity, and/or purification steps associated with the current industrial *trans*-esterification protocol. For example, Hang and co-workers⁴⁸ found that ultrasonication of the *trans*-esterification reaction increased the yield of sucrose mono-laurate. However, they also found that increasing the sonication frequency raised the yield of sucrose di-laurate too. These outcomes are attributed to sonication aiding in the dissolution of the sucrose and allowing for a greater number of effective collisions in the esterification reaction. Unfortunately, the HPLC analysis of the product mixtures revealed the presence of six sucrose mono-laurate regio-isomers, so their results indicated the approach did not improve selectivity under the standard *trans*-esterification conditions. While Moh and colleagues⁴⁹ were able to use HPLC to effect some degree of separation of SMEs from one another, this purification method has limited applications in industrial settings, not least because of the small scales at which the techniques can be applied in an economically effective manner. Plusquellec and

colleagues¹⁵ reported a procedure for selectively accessing 2-O-acylsucroses using basic conditions and then tried using acyl migration techniques to convert these into the more desirable 6-O-acylsucroses regio-isomers. The authors found they could access 6-O-lauroylsucrose through an irreversibly formed 3-O-lauroylsucrose intermediate.⁵⁰ In an attempt to improve upon existing processes, a solventless *trans*-esterification protocol using a melt of sucrose and the relevant fatty-acid methyl ester generated at elevated temperatures in the presence of a basic catalyst was shown to deliver the target SME. However, this is was plagued by the lack of selectivity and purification issues arose as a direct result.¹⁹ These sorts of results demonstrate that much work remains in order to find methods for the selective formation, using chemical techniques, of SMEs that addresses the listed deficiencies associated with the current *trans*-esterification protocol to access these valuable compounds.

A very efficient process for accessing SMEs involves enzymatic techniques using immobilised lipases or proteases,^{18, 24, 30, 51-55} with the two common being Novozyme 435 and TLIM.^{24, 30, 51-53, 55, 56} Such processes, which are normally conducted in an aqueous medium, are appealing because they reduce the need to use organic solvents and are thus considered to be more environmentally benign.^{1, 43, 44} However, the reaction still requires low concentrations of polar organic solvents to solubilise the fatty-acid methyl ester, such as dimethyl sulphoxide (DMSO) or DMF.^{44, 52} Nevertheless, an appealing aspect to using enzymes is that often highly regio-selective mono-esterification reactions are observed,^{18, 43, 44, 53, 57, 58} although subsequent acyl migrations can still occur. However, enzyme-catalysed reactions

must be conducted in batch-mode^{1, 59} and this is not as efficient as conducting the reaction under flow conditions.

Industrial-scale SME production remains wanting for a process that is highly selective, can be conducted at neutral pH under solvent- and catalyst-free conditions, is free from competing equilibria, does not produce by-products and proceeds in a time-economic manner. Esterification reactions require a carbonyl source that produces esters on contact with alcohols and ideally without the need for a catalyst, as well cleanly and quantitatively. There should also be no co-product arising from the reaction process. Ketenes are one such carbonyl source that do fulfil these ideal esterification reaction conditions.

1.3 Ketenes

1.3.1 Ketenes as a carbonyl source

Ketenes are highly reactive, carbonyl-containing compounds⁶⁰⁻⁶² (Figure 1.3.1.1) that readily bond with a variety of nucleophilic moieties, including with alcohols. The appeal of using ketenes is they react in the absence of solvent, catalysts, and heating,^{63, 64} which makes them potentially ideal reactants for the synthesis of SMEs. The challenges with deploying ketenes is their generation and high reactivity making them difficult to control within a reaction pathway once prepared. Therefore, an employed ketene would likely have to be prepared and reacted *in situ*,^{61, 62, 64} although some control over the reactivity can be exerted under flow conditions or at reduced temperatures.^{61, 63, 65} Ketenes engage in inter- and intra-molecular cycloaddition

reactions and such processes have been exploited in forming small to medium-sized carbocycles and heterocycles.^{63, 66, 67} The most common ketene cycloaddition reactions are through [2+2]- and [4+2]-cycloadditions, which has produced a library of interesting four-membered and six-membered carbocyclic and heterocyclic organic molecules.^{62, 63, 68-70} (3+2)-Cycloadditions reactions involving ketenes and leading to five-membered heterocycles are also known.^{70, 71} Examples of such cycloaddition processes are in Figure 1.3.1.2. Ketenes are also known to esterify alcohols in so-called trapping reactions (Scheme 1.3.1.1)^{60, 72-74} but little has been done to explore their application for esterifying carbohydrates, thereby presenting as an intriguing avenue of research.

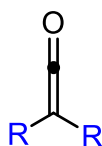


Figure 1.3.1.1. A generic ketene (R = H, alkyl, alkenyl, aryl).

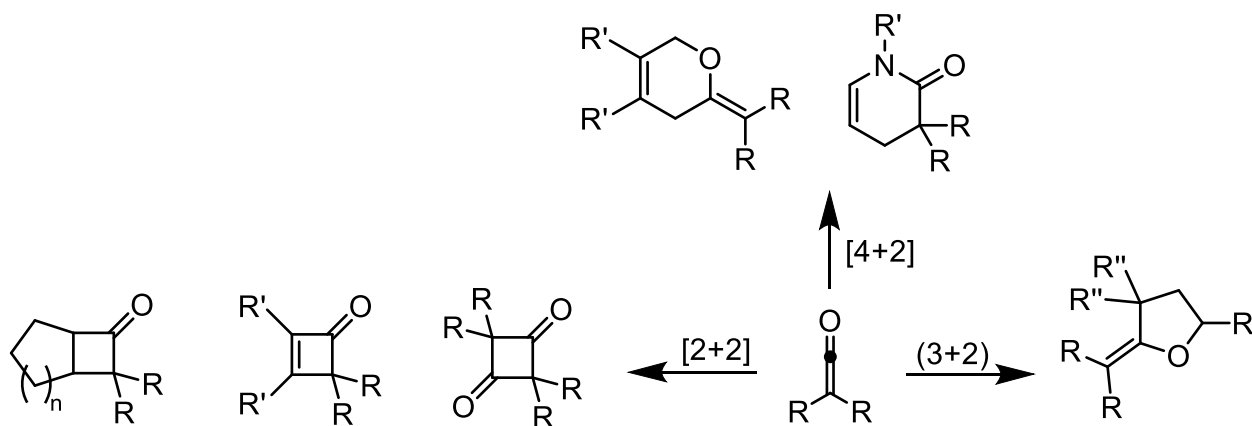
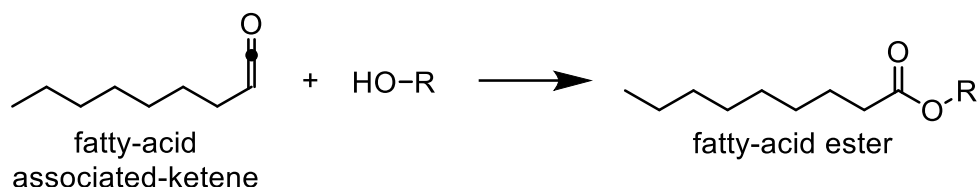


Figure 1.3.1.2. Sample compounds formed via ketene cycloaddition reactions (R = H, alkyl, alkyl, aryl).



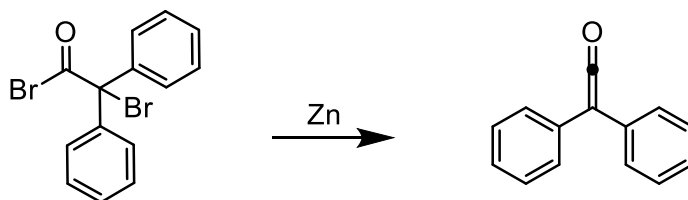
Scheme 1.3.1.1. A fatty-acid associated-ketene and its trapping with a generic alcohol (ROH) leading to

There are multiple pathways to access ketenes^{9, 63, 64, 75-77} but most of these are incompatible with sucrose as the substrate alcohol. Barrett and co-workers⁷⁸ have demonstrated that various ketenes can be used to trap geraniol and farnesol as the geranyl and farnesyl esters respectively at ca. 55 °C using toluene as solvent. The mild temperatures involved and the ability to conduct the reactions at neutral pH suggest that such conditions could be useful for forming SMEs. Therefore, the conditions used to form ketenes *in situ* would most likely be where compatibility with sucrose is required.

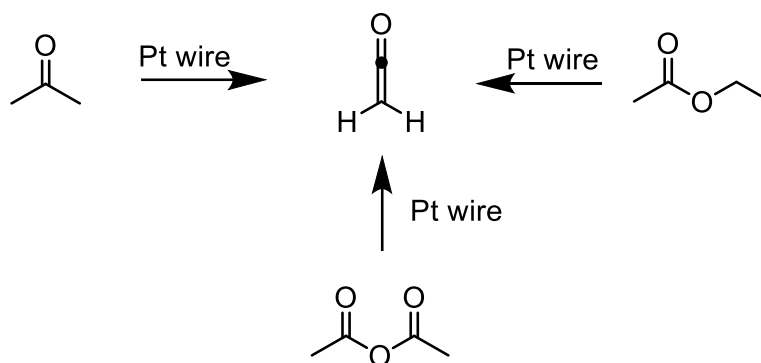
1.3.2 Ketene synthesis

There are many reaction pathways used to prepare ketenes. Staudinger reported the first synthesis of a ketene compound in 1905,⁹ by successfully isolating diphenyl ketene through reacting α -bromodiphenylacetyl bromide in the presence of zinc metal (Scheme 1.3.2.1). Wilsmore has been credited with the first preparation of the parent ketene in 1907 after discovering that immersing hot platinum wire in acetone, ethyl acetate or acetic anhydride resulted in the conversion of these liquids into a new carbonyl-containing species, diketene.^{64, 75-77} Both Staudinger's and Wilsmore's processes are examples of an elimination-type reaction,⁶⁴ which is perhaps the most common means of ketene preparation. The types of substrates that can eliminate

include esters^{79, 80}, halides⁸¹⁻⁸⁴ and even methyl ketones in the case of the Wilsmore route.^{75, 76} Typically, the substrate is a carbonyl compound with appropriate substituents at the sp^2 -carbon and the adjacent sp^3 -centre.^{61, 62, 64, 83} Elimination ketene syntheses are known to have industrial applications in the stereoselective syntheses of pharmaceutically important compounds, such as for the well-known pain relief drug S-(+)-Ibuprofen.⁶⁴ However elimination protocols rely on the use of metals, therefore are unattractive synthetic methodologies for the preparation of SMEs from an industrial perspective. Accordingly, a different means for preparing the desired fatty-acid based ketenes was required.



Scheme 1.3.2.1. Staudinger's synthesis of diphenyl ketene.⁹

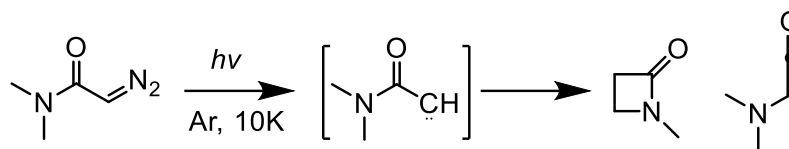


Scheme 1.3.2.2. Wilsmore's synthesis of ketene from three different carbonyl sources.⁶³

The methods used to access ketenes since the initial preparations from Staudinger and Wilsmore have evolved with the improvement in technology and gains in chemical knowledge. Modern processes to access ketenes through electrochemical protocols have been developed and involve oxidation or reduction pathways, depending on the

substrate.^{64, 85-90} Oxidation protocols typically involves oxidising an alkyne with a metal catalyst, such as rhodium or ruthenium,⁸⁸⁻⁹⁰ whereas reduction protocols tend to involve the dehydration of acids on metal surfaces to form ketenes.⁸⁵⁻⁸⁷ Neither redox pathway is ideal for producing SMEs as they both involve metal catalysts, as well as the reduction pathway employing acid which would likely hydrolyse sucrose's glycosidic bond.

Another modern process to access ketenes is through the reactions of compounds that incorporate the diazo moiety, such as through Wolff rearrangements. Wolff rearrangements are known to yield ketenes through the extrusion of nitrogen gas (Scheme 1.3.2.3)^{64, 91-95} and these reactions can be initiated photochemically,^{64, 92, 93, 95} as well as thermally.^{64, 94, 96} Another reaction type that produces ketenes through diazo compounds is carbonylation reactions. These reactions involve the introduction of carbon monoxide to a carbene to give the desired ketene, where the deployed carbene can also be derived from metallic complexes^{82, 97-100} and N-heterocyclic carbenes,^{97, 98, 101} as well as diazo moieties.¹⁰²⁻¹⁰⁴ By-product formation from carbenes derived from diazo compounds and applying Wolff rearrangement chemistry as ketene sources are known⁶⁴ and would likely necessitate a purification step if applied to an industrial-scale reaction with sucrose, due to the need to remove any metallic complexes or amines from the reaction mixture. Diazo compounds are especially undesirable for usage on an industrial scale due to their explosive propensity and high toxicity,^{95, 100, 103} therefore using compounds that incorporate diazo moieties are not ideal for applying to the esterification of sucrose on an industrial-scale.



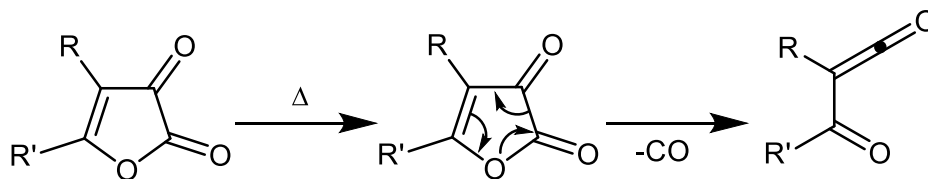
Scheme 1.3.2.3. A sample photochemically-promoted Wolff rearrangement forming a ketene intermediate.⁹⁴

A final modern protocol that can access ketenes is through cycloreversion reactions, which are the reverse reaction pathway to cycloadditions.¹⁰⁵ Cycloreversions of ketene products to ketenes has been well-researched^{63, 64, 74, 77, 106-113} and the processes that are known to crack the cyclic frameworks are potentially compatible with sucrose. The cycloreversion reaction occurs from the thermally-induced fragmentation, *i.e.*, thermolysis of a cyclic compound and yields the desired ketene with any by-products of the reaction generally being gaseous small molecules, such as carbon dioxide.^{63, 64, 74, 77, 106-113}

Ketene dimers are cyclic compounds comprised of two ketenes that have undergone a [2+2]-cycloaddition, yielding a cyclobutanone or cyclobutenone species as the dimer.^{61, 62, 77} The only products formed from the thermal cycloreversion of ketene dimers are the constituent ketenes,^{64, 77} thereby presenting as a possible ketene source. Ketene dimers also have greater stability than their ketene precursors and can be stored within a refrigerator.^{77, 114, 115} However, there are two main problems with employing ketene dimers as a ketene source. The first is ketene dimers require elevated temperatures in comparison to other cyclic molecules to undergo their thermolytic cycloreversion,¹¹⁴ which would likely cause the caramelisation of sucrose. The second problem is ketene dimers are formed directly from ketenes themselves.

Commercially available ketenes are rare so preparation of the ketene from another source would likely still be required. Therefore, thermolysis of ketene dimers is also not an ideal ketene source to produce sucrose fatty-acid mono-esters.

Thermolysis of heterocyclic compounds is a known ketene source and has been widely researched.^{63, 64, 67, 74, 106-111} Some commonly investigated compounds possess nitrogen atoms in their heterocyclic ring, such as pyrroles and pyrrolidines, and compounds incorporating the phthalimide and pyrimidinone groups.¹¹⁶⁻¹¹⁸ These compounds all produce by-products containing nitrogen along with their respective ketene after cycloreversion, which can be difficult to remove. Therefore, a heterocycle that does not contain nitrogen is potentially the best source of ketene for synthesising sucrose fatty-acid mono-esters. It is known that furan-2,3-diones can produce ketenes, through the extrusion of carbon monoxide.^{118, 119} Carbon monoxide would be an easy by-product to separate due to its gaseous state at the elevated temperatures required to enact the cycloreversion. However, these furandiones have the problem of being incapable of producing the desired fatty-acid associated-ketene (Scheme 1.3.2.4). It is known that six-membered heterocycles containing oxygen can also produce ketenes.^{78, 120-125} Barrett and co-workers^{78, 120, 122, 124} have had success employing six-membered diketodioxinone compounds as a ketene source, where the produced by-products are an easily removed ketone. Diketodioxinones are not a common feedstock molecule and produce ketenes in the same form as furan-2,3-diones, hence do not produce the desired fatty-acid associated-ketene. Fortunately, there does exist a common feedstock heterocyclic molecule that can produce fatty-acid associated-ketenes from a cycloreversion reaction.



Scheme 1.3.2.4. Ketene synthesis from a general furandione precursor (R = H, alkyl; R' = alkyl, aryl).^{118,119}

1.4 Meldrum's acid

1.4.1 General information

Meldrum's acid, also known as 2,2-dimethyl-1,3-dioxane-4,6-dione, is a six-membered heterocycle and Meldrum's acid, its derivatives and related compounds are known to access ketenes upon thermolysis.^{66, 106, 126} Meldrum's acid itself has multiple sites of reactivity, whereby a variety of derivatives can be accessed. These sites of reactivity are labelled in accordance with the respective atom of the Meldrum's acid framework (Figure 1.4.1.1). The carbonyl sites, C4 and C6, are the most susceptible atoms in the molecule for nucleophilic attack.^{60, 107, 108, 126} Malonic acids can be accessed through exploiting chemistry at these carbonyls.^{126, 127} The C2 site can undergo hydrolysis via nucleophilic attack resulting in a ring-opening, which has subsequently led to many analogues of both Meldrum's acid and other related compounds.^{107, 126} Of specific interest to us was the C5 atom. C5 is the most acidic, hence nucleophilic, site of the molecule and will preferentially undergo electrophilic substitution.^{60, 107, 128} Meldrum's acid derivatives with substitutions to the C5 residue have also been the most thoroughly investigated for accessing further derivatives.^{107, 108, 126, 129-131}

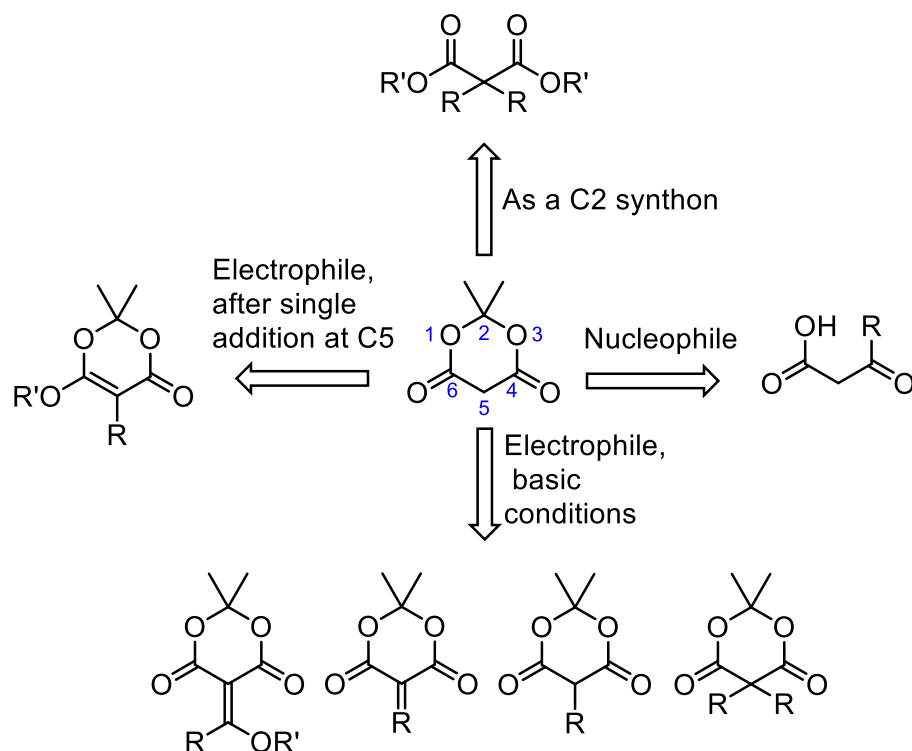


Figure 1.4.1.1. Structure, relevant atom labelling and reactive sites of Meldrum's acid ($\text{R} = \text{H}$, alkyl).

1.4.2 Meldrum's acid derivatives with C5 modifications

There are three general types of Meldrum's acids with C5 modifications: alkylidene, acylated and alkylated Meldrum's acids (Figure 1.4.2.1).¹⁰⁸ Out of these three types of derivatives, alkylidene Meldrum's acids have been the most thoroughly investigated.^{108, 117, 132-134}

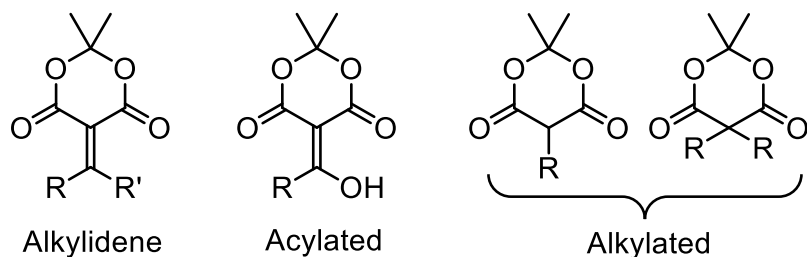
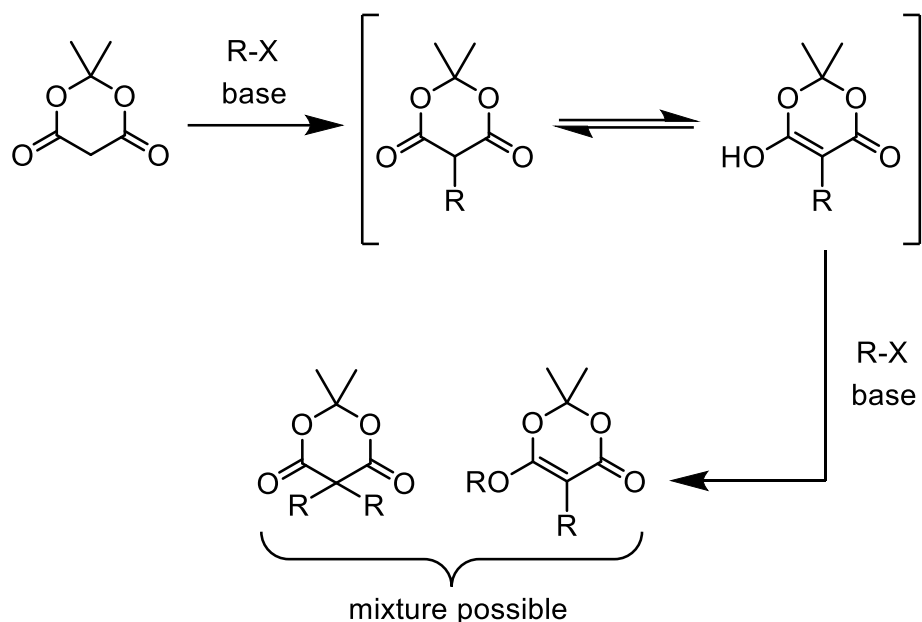


Figure 1.4.2.1. Types of Meldrum's acids with C5 modifications ($\text{R} = \text{H}$, alkyl, alkylamine, aryl; $\text{R}' = \text{alkyl}$, alkylamine, arylamine).

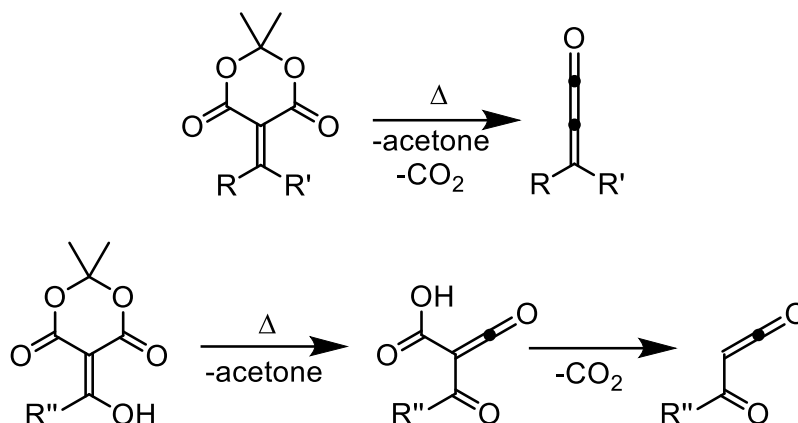
Alkylidenes and their aromatic equivalents, arylidenes, are prepared by Knoevenagel condensations with aldehydes and ketones¹³⁵ and are used to typically access lactones¹³⁶⁻¹⁴¹ and spirocyclopropanes^{107, 140-142}, but can also be used to access amides,^{143, 144} indoyls,¹⁴⁵ indanones¹⁴⁶ and cyclopentadienes.¹⁴⁷ Acyl Meldrum's acids can be synthesised from three possible pathways: through reacting Meldrum's acid with a carboxylate and a coupling reagent, Meldrum's acid with an acid chloride or a mixed anhydride and a non-nucleophilic organic base, or via an *in situ* generated acyl imidazole.¹⁰⁸ Acyl Meldrum's acids find less usage in comparison to alkylidene Meldrum's acids, which is perhaps due to acyl Meldrum's acids being prone to decomposition during flash column chromatography.^{108, 148} The final general type of C5 substituted Meldrum's acid are alkylated Meldrum's acids. The synthesis of alkylated Meldrum's acids is straightforward, whereby the predominant method is reacting Meldrum's acid with an electrophile in the presence of a base (Scheme 1.4.2.1)^{107, 149-152} and unsymmetrical C5 residues can be prepared if care is taken with the stepwise addition of two electrophiles.¹⁰⁷ Alkylated Meldrum's acids are also used as a cross-linking synthon for polymerisation,^{153, 154} as well as having been used in ring closure metathesis applications.¹⁵² Despite the differences between the C5 Meldrum's acid analogues, all are known to produce ketenes.^{123, 127, 132, 155-157}



Scheme 1.4.2.1. General preparation method of C5 alkylated Meldrum's acids
(R = alkyl; X = halogen).

1.4.3 The thermolytic cracking of Meldrum's acid and its analogues

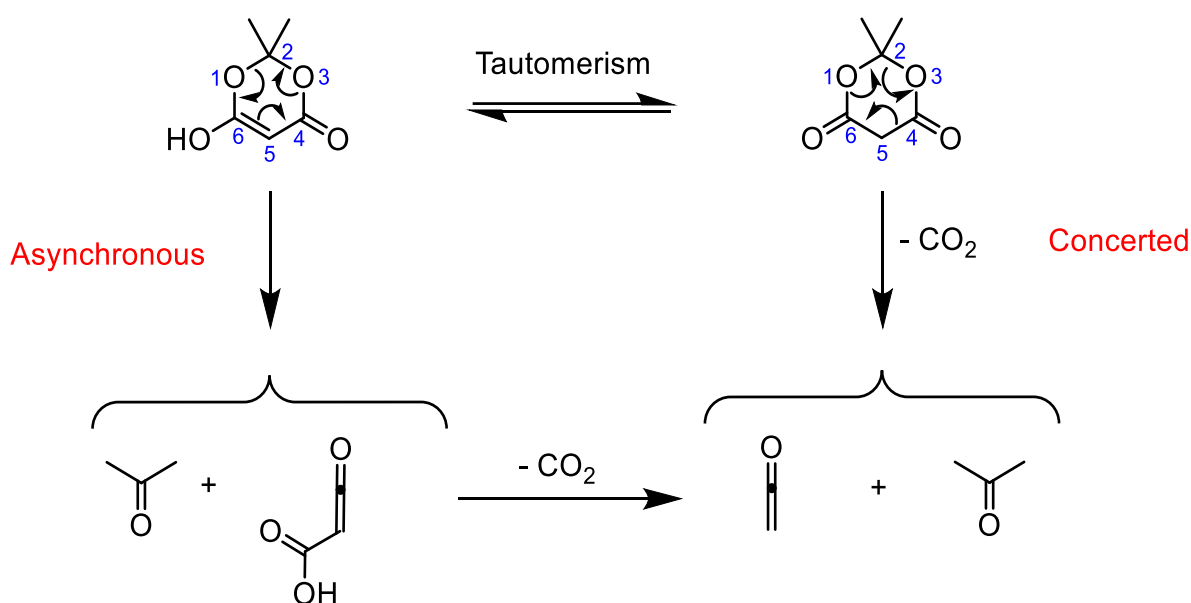
The most researched way to form ketenes via Meldrum's acid is through thermolytically cracking Meldrum's acid and its analogues,^{78, 117, 120, 122, 124, 127, 132, 155, 158} whereby flash vacuum pyrolysis (FVP) experiments provided the early evidence that ketenes could be formed in this manner.^{117, 127, 132, 155, 158} Historic FVP ketene studies involving Meldrum's acids predominantly investigated the thermolysis of alkylidene Meldrum's acids.^{132, 159-162} Acylated Meldrum's acids are also known to form ketenes (Scheme 1.4.3.1), which is thought to proceed through the same thermolysis pathway as alkylidenes.^{108, 148}



Scheme 1.4.3.1. Preparation of ketene intermediates from alkylidene and acyl Meldrum's acids (R = H, alkyl, alkylamine aryl; R' = alkyl, alkylamine, arylamine; R'' = alkyl, aryl).^{108, 117, 132, 148, 155}

Ketene research using alkylated Meldrum's acids have the smallest profile in physical organic chemistry literature to the best of the author's knowledge. As such, the application we were most interested in was investigating the capacity of alkylated Meldrum's acids to form ketenes. There are four reaction mechanisms for the production of ketene intermediates via Meldrum's acid recorded within the literature.^{106, 110, 125, 163} The first two reaction mechanisms to be discussed here are a concerted single step reaction and an asynchronous multi-step pathway (Scheme 1.4.3.1). The concerted pathway is the simplest thermolysis pathway of Meldrum's acid, whereby one molecule of ketene, ketone and carbon dioxide respectively is formed via a cycloreversion of a Meldrum's acid molecule and occurs in a single step. The asynchronous pathway involves the Meldrum's acid undergoing a hetero-retro-Diels-Alder reaction. A keto-enol tautomerism occurs in the first step, followed by the fragmentation of the heterocycle into a molecule of ketone and a ketene carboxylic acid species. The final step involves the release of carbon dioxide from the ketene carboxylic acid species, resulting in the same products as the concerted thermolysis pathway. Whilst a hydrogen atom bonded to C5 is generally required for the keto-enol

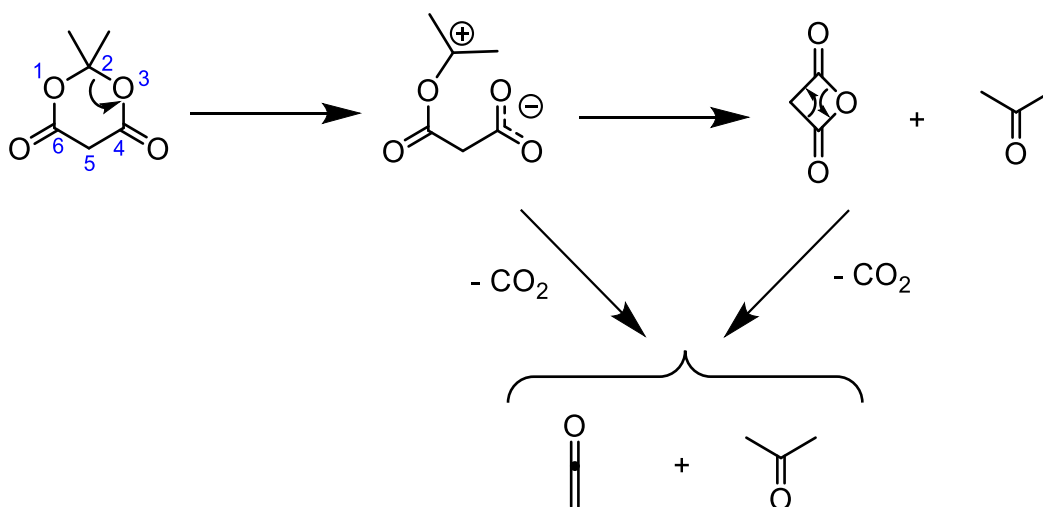
tautomerism, there is evidence some alkylidene Meldrum's acids can tautomerise into vinyl ketenes and have an asynchronous thermolytic pathway too.^{106, 132, 164} Yamamoto and co-workers¹⁴⁸ also demonstrated a hetero-retro-Diels-Alder thermolysis pathway existed in an acyl Meldrum's acid compound they were investigating. There is no experimental evidence to suggest C5 unsubstituted Meldrum's acids can proceed through a hetero-retro-Diels-Alder reaction to the best of the author's knowledge.



Scheme 1.4.3.2. Meldrum's acid thermal cycloreversion pathways via a concerted and an asynchronous reaction pathway.

The remaining two mechanisms also provide an explanation for the ketene, carbon dioxide and acetone products (Scheme 1.4.3.3). Both pathways undergo the same step of cleavage of the C2-O3 bond, resulting in an intermediate with a resonance stabilised carboxylate on C4 and a stabilised carbocation being formed at C2. The reaction pathways then diverge, whereby one pathway has the intermediate malonic acid structure collapsing to give the product ketene, carbon dioxide and acetone, and the other yields a cyclic malonic anhydride species through the release of acetone and

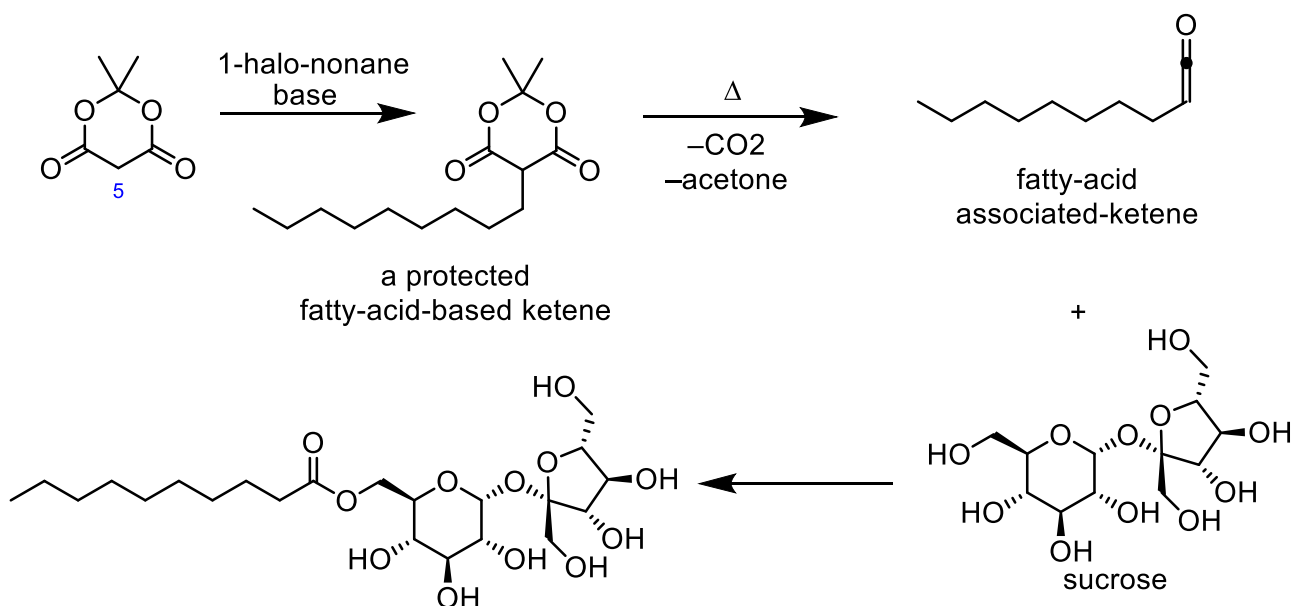
cyclisation of the malonic acid intermediate. The malonic anhydride then releases the ketene and carbon dioxide through a cycloreversion step.



Scheme 1.4.3.3. Meldrum's acid thermolysis pathways via a charged intermediate proposed by Brown and co-workers.¹¹⁰

As unlikely as the proposed charged intermediate thermolysis pathways appear, there is some limited experimental evidence to suggest Meldrum's acids can form malonic anhydrides.^{75, 164} Wentrup and colleagues¹⁶⁴ found the presence of a new compound after a FVP experiment of an alkylidene Meldrum's acid, which had a co-product of just acetone at $-196\text{ }^{\circ}\text{C}$ thus suggesting a malonic anhydride had formed. The authors surmised their studied alkylidene Meldrum's acid had undergone a keto-enol tautomerism and formed the malonic anhydride in a stepwise manner, which conflicts with the proposed mechanism by Brown and co-workers.¹¹⁰ This conflict demonstrates there is scope for investigating the mechanistic implications of the thermolytic cracking Meldrum's acid and its analogues.

Thermolytically cracking Meldrum's acid and its analogues in a manner that avoids caramelising a sucrose co-reactant is potentially possible. A fatty-acid alkyl-chain can be substituted onto the C5 position of Meldrum's acid, which can consequently be viewed as a protected fatty-acid ketene. This protected fatty-acid ketene can subsequently undergo the cycloreversion through thermolysis to produce a fatty-acid associated-ketene. The generated fatty-acid ketene may then be able to react with sucrose to form the desired SMEs (Scheme 1.4.3.4). The standard by-products of acetone and carbon dioxide are produced from this reaction, which are substantially easier to remove compared to the methanol by-product of the *trans*-esterification protocol. Therefore, the key challenge to utilising Meldrum's acid and its analogues as a ketene source to produce sucrose fatty-acid mono-esters is through controlling the temperature required for their thermolytic cracking.

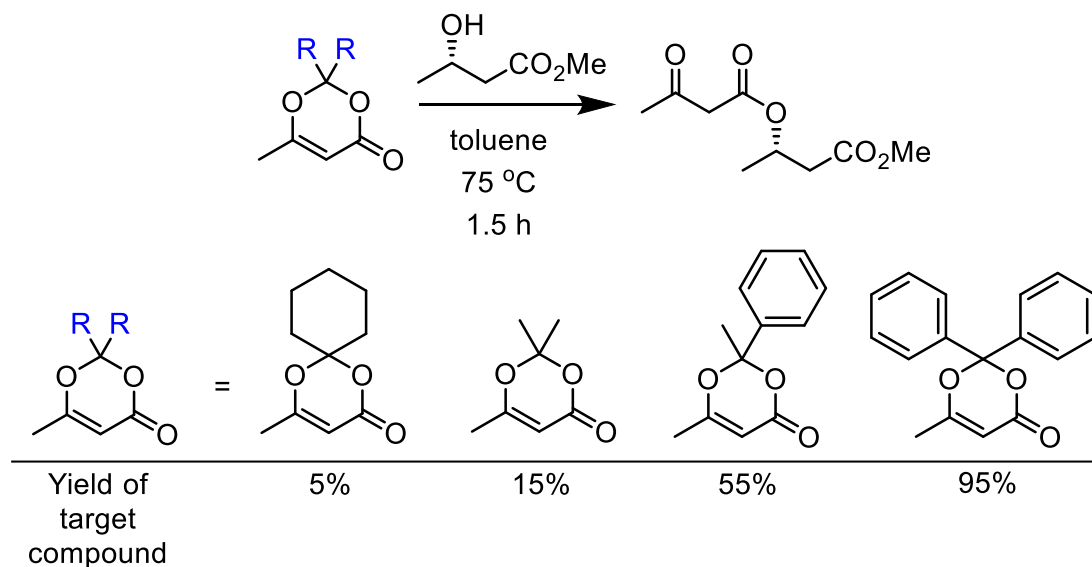


Scheme 1.4.3.4. Proposed formation of a sample sucrose fatty-acid mono-ester through using

1.4.4 Is forming the ketene intermediate in a controlled manner with Meldrum's acid or its derivatives possible?

There is limited evidence to suggest that ketene formation through thermolysis can be controlled with Meldrum's acid or its analogues. It is mechanistically supposed the C5 residue affords the desired ketene and the C2 residue produces the ketone in the cycloreversion thermolysis pathway, yet literature information on the effects of either residue on the temperature required for thermolysis is lacking. Instances of screening Meldrum's acids with various C2 residues in literature are limited in general, regardless of whether the properties or reactivities of these molecules were investigated. For example, Jiang and co-workers¹⁶⁵ synthesised Meldrum's acids with a variety of C2 residues with the aim of using them to synthesise some fullerene derivatives. The authors did not investigate whether there was a major effect of the C2 residue on the subsequent reactivity of the formed derivatives. An older study conducted by Herzog and co-workers¹⁶⁶ investigated the anti-bacterial and anti-fungal properties of Meldrum's acids with varying C2 and C5 residues. Whilst the synthesis in that work was devoted to the creation of a library of Meldrum's acids, there was no investigation on the thermolysis of those Meldrum's acids. The literature search had to be expanded to include compounds analogous to Meldrum's acids with the desired C2 residue variations. Barrett and co-workers¹²² found that the conditions required to access ketenes through thermolysis using structurally analogous diketo-1,3-dioxin-2-ones can be controlled through the choice of C2 residue. Specifically, the authors found that using sterically bulky C2 substituents accelerated the reaction rate, thereby making ketene formation more facile by reducing the prevalence of side-reactions and increasing the yields of the desired target compound (Scheme 1.4.4.1). Whilst this study did provide some evidence on the effects of the C2 residue on the thermolysis

reaction rate, it did not offer insight on any potential effect the C2 residue has on the required thermolysis temperature.



Scheme 1.4.4.1. Results from Barrett and co-workers¹²² where variations in the C2 residue resulted in decreased reaction rates and increased yields of the target ester.

There is, likewise, limited evidence for the effects of the C5 residue on the Meldrum's acid thermolytic pathway. Chen¹⁰⁷ reviewed the literature for a broad library of synthesised heterocyclic compounds, through the thermolysis of alkylidene Meldrum's acids. The author suggested the ability of the reacting partner may affect the temperature for thermolysis instead of the screened alkylidene Meldrum's acid. The relevant papers Chen reviewed had conducted FVP experiments on alkylidene Meldrum's acids that contained predominantly nitrogen and sulphur in their respective C5 residues.^{67, 112, 164, 167-169} C5 residues containing nitrogen or sulphur are irrelevant for synthesising SMEs and FVP experiments involving sucrose will likely caramelize the sugar. Therefore, an opportunity to investigate any potential controlling effects the C5 residues has on the thermolytic pathway was overlooked. We would have to

provide the initial investigations into any effects the C2 and C5 residues may exert on the temperature required for thermolytically cracking Meldrum's acid.

1.5 Motivations and aims of research

The industrial synthesis of SMEs is reliant on old and inefficient chemistry, which we reason could be improved upon by investigating reactions other than the standard *trans*-esterification or enzyme-catalysed *trans*-esterification protocol. An improved esterification protocol may also involve using ketenes as a carbonyl source, including through investigating Meldrum's acid and related compounds. The lack of research connecting the C2 and C5 residues on Meldrum's acid to any substantial effect on the thermolysis temperature of Meldrum's acids and related compounds has provided great scope to explore and lay the groundwork for future studies in this field. The research detailed herein will address the limitations in knowledge present in the current literature.

1.5.1 Specific aims

The general aim for this body of work was to develop a new method for producing SMEs using chemistry befitting the 21st Century in terms of atom economy, selectivity, mild reaction conditions and benign waste products. This is further broken down into six specific aims:

1. To assess the viability of the synthesis of a library of sucrose fatty-acid mono-esters through traditional protecting group chemistry.
2. To produce a library of Meldrum's acids with a variety of C2 residues.

3. To investigate whether the C2 residue has an effect on the temperature required for thermolytically cracking Meldrum's acid and the C2 residue.
4. To produce a library of *gem*-dialkylated Meldrum's acids with a variety of C5 residues.
5. To investigate whether C5 substitution has an effect on the temperature required for thermolytically cracking *gem*-dialkylated Meldrum's acids.
6. To extend this reactivity to enable the synthesis of some novel cyclic small molecules.

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Chapter Two: Attempts at Preparing Sucrose Fatty-Acid Mono-Esters Through Traditional Synthetic Methodologies (Aim 1)

2.1 Synthetic strategy for preparing sucrose derivatives through traditional chemistry

We started this body of work by seeking a benchmark for the production of SMEs using traditional protecting group chemistry before exploring using ketenes as a carbonyl source. Preparing a library of sucrose esters containing eight unique SME molecules per fatty-acid is a non-trivial task, therefore protecting groups that can bond to multiple hydroxyl groups were crucial for successfully achieving our aim.

2.2 Attempts at preparing sucrose derivatives through traditional protecting group chemistry

Protecting groups capable of bonding to multiple hydroxyl groups were ideal as their presence could also restrict acyl migration around the sucrose molecule. We reasoned the allylic or alkyl amine protecting groups used to connect the C6 and C6' through their free hydroxyl groups, such as in sucrose-crown molecules,¹ would possibly be too sterically hindering to allow access to other free hydroxyls or too difficult to subsequently deprotect. The smaller groups capable of multiple hydroxyl protections would be ideal, so 2,2-dimethoxypropane for a general 1,2-diol protection and 2,3-butanedione for a specific *trans*-1,2-diol protection were initially chosen as protecting groups. Both protecting groups, if successfully incorporated, would give multiple avenues of investigation through accessing up to four hydroxyl sites for esterification (Figure 2.2.1) as intermediates **1** and **2**.

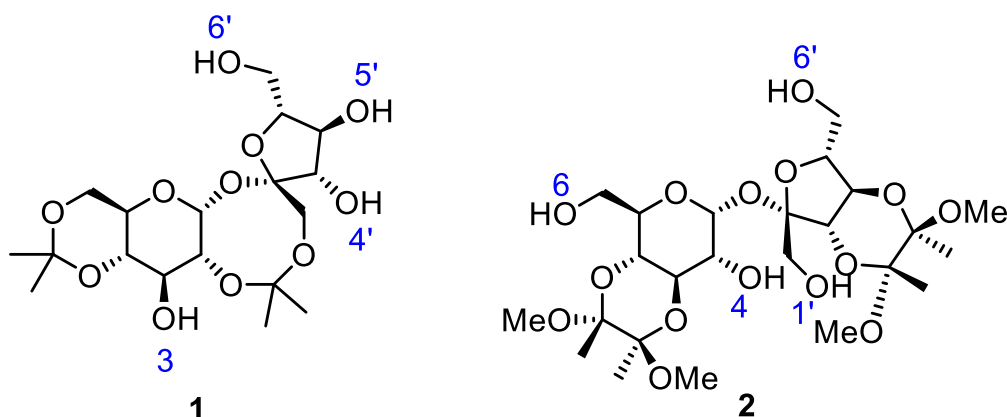
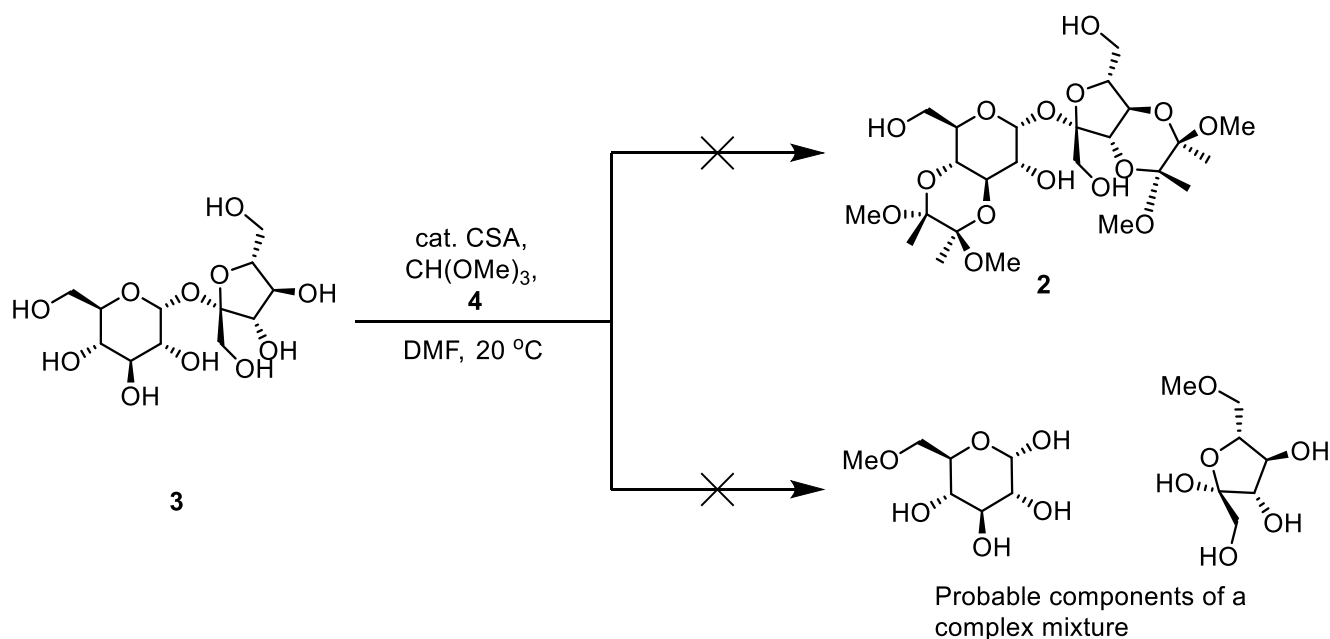


Figure 2.2.1. Proposed sucrose intermediates **1** and **2**.

2.2.1 Accessing sucrose mono-esters on C6'

The previous investigations by former members of the Banwell research group²⁻⁴ had indicated that *trans*-1,2-diols could be protected with 2,3-butanedione (**4**) in the presence of trimethyl orthoformate, thus we began by attempting to synthesise intermediate **2** from sucrose (**3**) and diketone **4** (Scheme 2.2.1.1). The choice of solvent for the protection reaction proved to be non-trivial as it was found that dissolving sugar **3** in methanol was quite challenging, leading to the use of DMF. However, the reaction conditions employed resulted in the hydrolysis of the glycosidic bond, resulting in a black tar-like mixture to be obtained containing what was likely to be methylated glucose and methylated fructose according to LRMS analysis of the crude residue. As a result, intermediate **2** was discarded as a target and attention turned to synthesising intermediate **1** instead, where the C1' and C4 positions were tethered together.



Scheme 2.2.1.1. Attempted *trans*-1,2-diol protection of sugar **3**.

Sugar **3** was reacted with 2,2-dimethoxypropane (**5**) with a catalytic quantity of *p*-toluenesulphonic (*p*-TsOH) acid as an acid additive to furnish key intermediate **1** in DMF (Scheme 2.2.1.2). The reaction proceeded in a facile manner, although removal of the DMF was found to be a challenging task with distillation under high-vacuum proving itself the only method to satisfactorily remove the solvent. This reaction was also reliable on large scales, with the reaction proceeding when *ca.* 8 g of sugar **3** was used. It was also possible to prepare intermediate **1** using a small loading of ceric ammonium nitrate (CAN). With intermediate **1** in hand, we sought access to new derivatives in order to obtain a sense of any changes to the internal bond lengths or bond angles. As such key intermediate **1** was reacted with acetic anhydride (**6**) in the presence of 4-(*N,N*-dimethylamino)pyridine (DMAP) to produce tetra-acetylated compound **7**, which was afforded as colourless plate crystals. Compound **7** was subsequently analysed through single-crystal X-ray diffraction analysis and we published the resulting structural data in 2019 (Figure 2.2.1.1).⁵ We used the single-crystal X-ray diffraction analyses to examine whether applying an enzymatic *trans*-

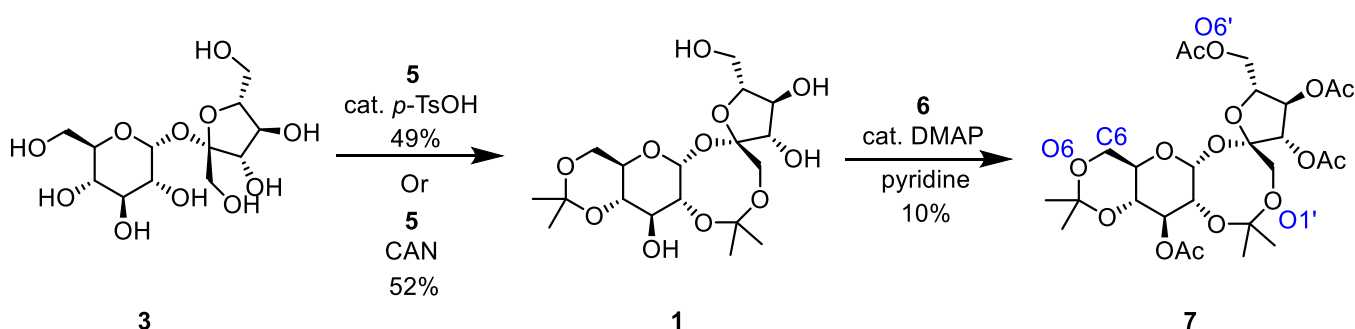
esterification protocol may be fruitful. The relevant obtained data is presented in Table 2.2.1.

Bond distance (Å)			
Compound	C6-O6	C1'-O1	C6'-O6'
3	1.417(19)	1.423(16)	1.421(19)
7	1.433(3)	1.416(3)	1.433(3)
Bond angles (°)			
Compound	C5-C6-O6	C2'-C1'-O1	C5'-C6'-O6'
3	111.52(10)	111.19(9)	113.02(9)
7	108.24(17)	113.67(17)	108.22(18)

Table 2.2.1. Comparison table of bond lengths and angles of compounds **3** and **7**. Bond lengths are given in Å and angles are given in degrees (°). Estimated standard deviations are given in parentheses.

The obtained crystals of compound **7** were found to have slightly elongated bond lengths by approximately 0.02 Å for the C6-O6 and slightly shorter C6'-O6' and C1'-O1' bonds by approximately 0.02 Å and 0.01 Å in comparison to native sugar **3**.^{6, 7} There was marked change in the bond angles of the two protected hydroxyl groups C2'-C1'-acetal and C5'-C6'-OAc by -10° and 53° respectively, most likely due to the disruption of the hydrogen-bonding in which those free hydroxyl groups engage in sugar **3**. The deviation in bond angle of the C1' moiety was of greater interest to us as

this tighter bond angle should be present in key intermediate **1** due to the acetonide protecting group. There was a -5° angle change C5-C6-acetal angle in comparison to the corresponding angle on sugar **3**, which can also be accounted to the formation of the acetonide protecting group. The remaining internal bond angles from both glucosyl and fructosyl rings deviated from sugar **3** within $\pm 5^\circ$ for compound **7**. The internal bond angle deviations indicated some puckering of both rings in comparison to sugar **3**. We hypothesised this puckering, if correct, would be present in key intermediate **1** due to the acetonide protecting groups.



Scheme 2.2.1.2. Synthesis of compound **7** through key intermediate **1**.

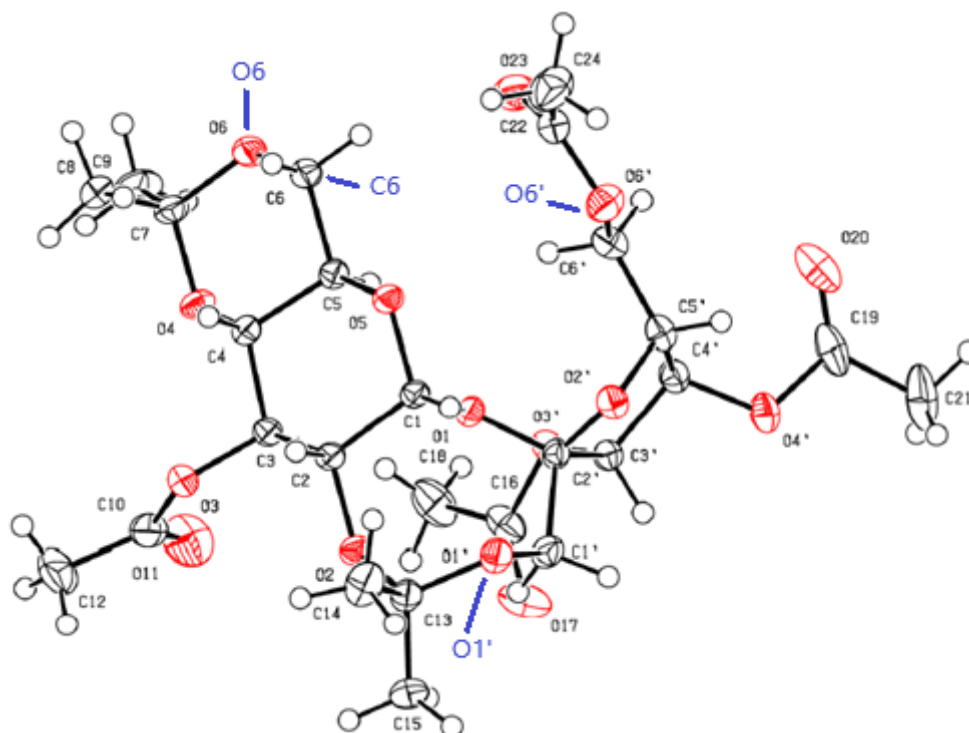
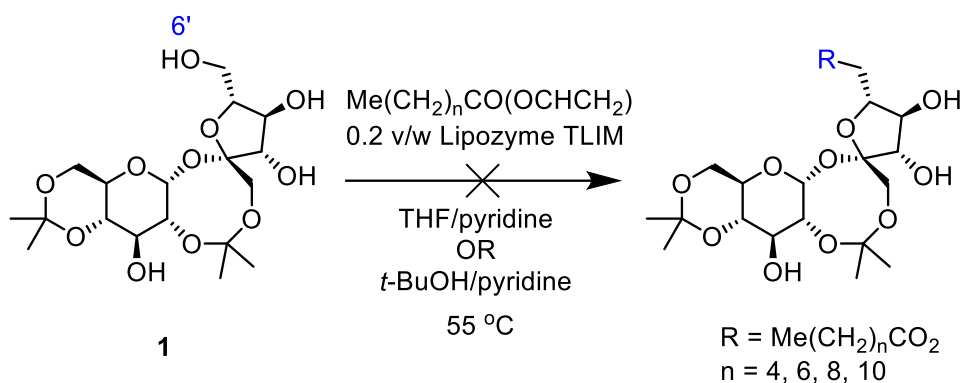


Figure 2.2.1.1. ORTEP Plot derived from single-crystal X-ray crystal structure analysis of compound **7**. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

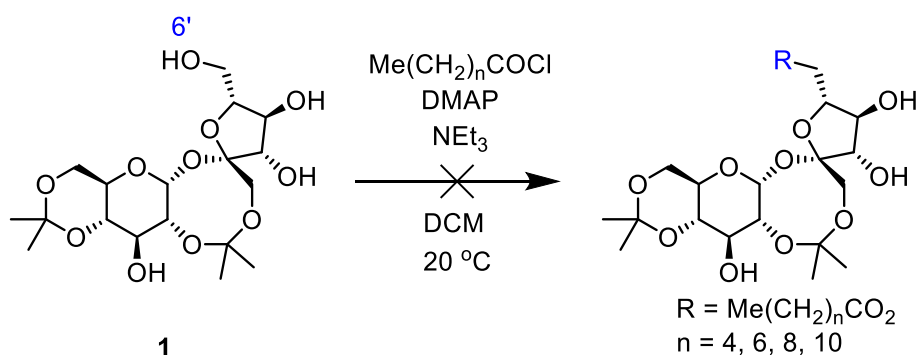
As we expected the free hydroxyl on C6' in compound **1** to have not substantially deviated from sugar **3** in respect to bond length or angle, an attempt to access a simple fatty-acid mono-ester target was conducted through reacting compound **1** in a TLIM lipase-mediated *trans*-esterification with some vinyl esters (Scheme 2.2.1.3). The reaction conditions used for the lipase-mediated *trans*-esterification are known to be successful for producing 6-*O*-fatty-acid mono-esters in the literature,⁸ albeit on lactose instead of sucrose. We hoped the reaction would proceed smoothly and with absence of any other possible fatty-acid ester regio-isomer, due to lipozyme TLIM preferring primary hydroxyl groups on sugars.⁹⁻¹³ However, no reaction occurred after a few attempts so the THF/pyridine solvent combination that was the choice of solvent in the

original literature⁸ was swapped for *t*-BuOH/pyridine to help solubilise the TLIM, but without success.



Scheme 2.2.1.3. Attempted TLIM-catalysed *trans*-esterification of intermediate **1**.

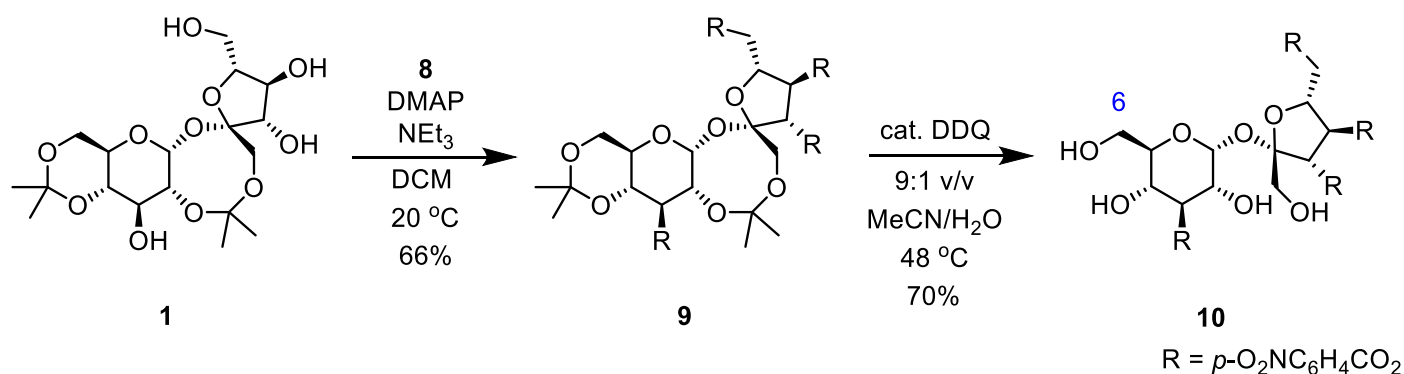
Having little success with lipase-mediated catalysis, we resorted to using a more traditional synthetic approach by using fatty-acid chlorides to esterify the free hydroxyl on C6'. We tried esterifying with a small number of acid chlorides in the presence of triethylamine and DMAP and obtained complex mixtures (Scheme 2.2.1.4), so we decided to investigate accessing other SMEs.



Scheme 2.2.1.4. Attempted esterification of compound **1**.

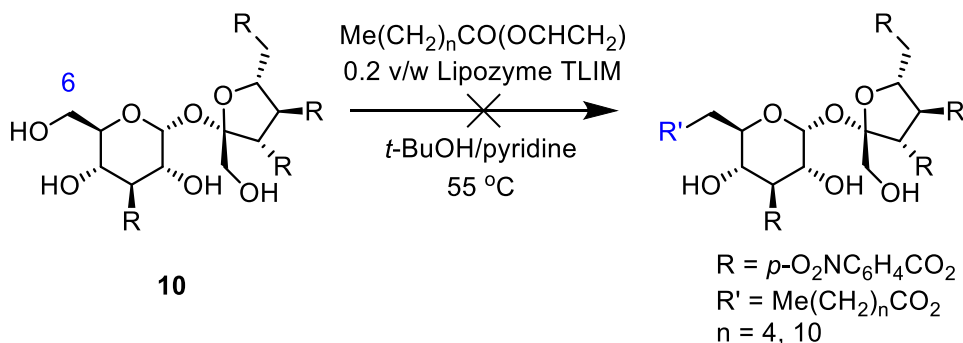
2.2.2 Accessing sucrose mono-esters on C6

The next fatty-acid mono-ester we targeted was another primary hydroxyl group on the C6 atom. Key intermediate **1** was reacted with *p*-nitrobenzoyl chloride (**8**) in the presence of triethylamine and DMAP (Scheme 2.2.2.1), furnishing intermediate **9** as a yellow powder in a good yield. Deprotection of the acetonide groups produced intermediate **10**, in a similarly good yield.



Scheme 2.2.2.1. Synthetic sequence accessing compound **10**.

Compound **10** was then reacted again with lipozyme TLIM in the same conditions as the previously attempted lipase-mediated *trans*-esterification reaction, as a more reasonable attempt at targeting the same hydroxyl group as the literature esterification.⁸ Unfortunately, the reaction once again did not proceed; we subsequently reasoned that introducing the new rings to the sucrose framework distorts the entire molecule such that the synthesised intermediate will no longer be recognised by the active site of the enzyme. We possessed large stocks of other sugar derivatives so further experimentation was carried out using these substrates.

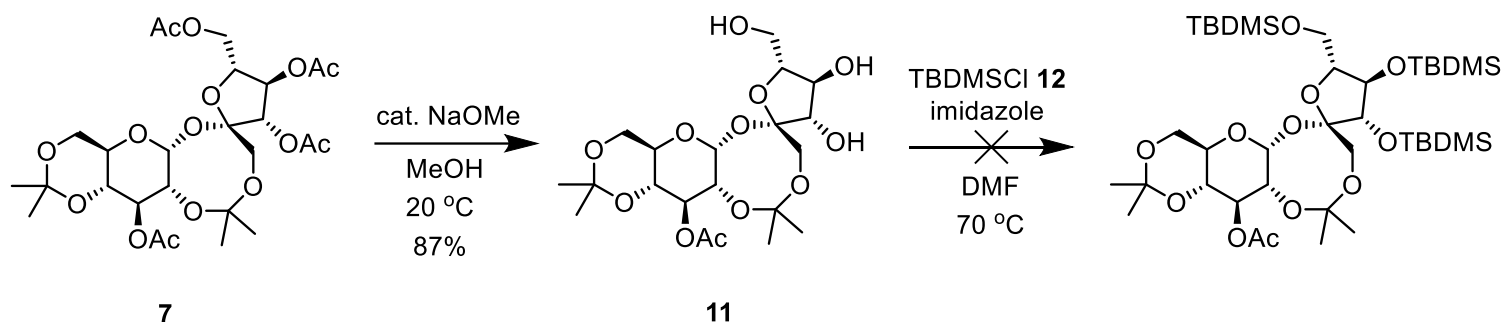


Scheme 2.2.2.2. Attempted TLIM *trans*-esterification of compound **10**.

2.2.3 Accessing sucrose mono-esters on C3

Crystalline compound **7** was prepared in a stock sufficiently large enough that we were able to use it to explore multiple reaction pathways. Under controlled basic conditions, we were able to successfully deprotect all but a single acetyl group on compound **7**, resulting in compound **11** being afforded in a good yield (Scheme 2.2.3.1). Compound **11** proved difficult to work with, as a mixture of regio-isomers was frequently obtained upon repeating the synthesis. The ^1H NMR spectra was a good match to what was recorded in literature,¹⁴ but reasonable ^{13}C NMR spectra could not be obtained due to the contamination. Acquisition of an optical rotation value was similarly hampered for this reason. An explanation of the production of the regio-isomers is that the deprotection step itself is not completely selective across the secondary hydroxyl groups, giving rise to mixtures. The ^1H NMR spectra (Figure 2.2.3.1) of compound **11** was the cleanest sample of compound **11** obtained and depicts a mono-acetylated product. The free hydroxyl groups on C6', C5' and C4' of this sample of compound **11** were subsequently attempted to be protected with a silane **12**, however this reaction did not proceed, and a complex mixture was obtained. The reaction of compound **11** with silane **12** is known to literature¹⁴ so we were surprised this reaction did not work here. We had run low on stock of compound **11**, so we attempted to synthesise more.

We obtained another mixture of regio-isomers so this reaction pathway was abandoned.



Scheme 2.2.3.1. Synthesis of compound **11** and attempted further protection with silane **12**.

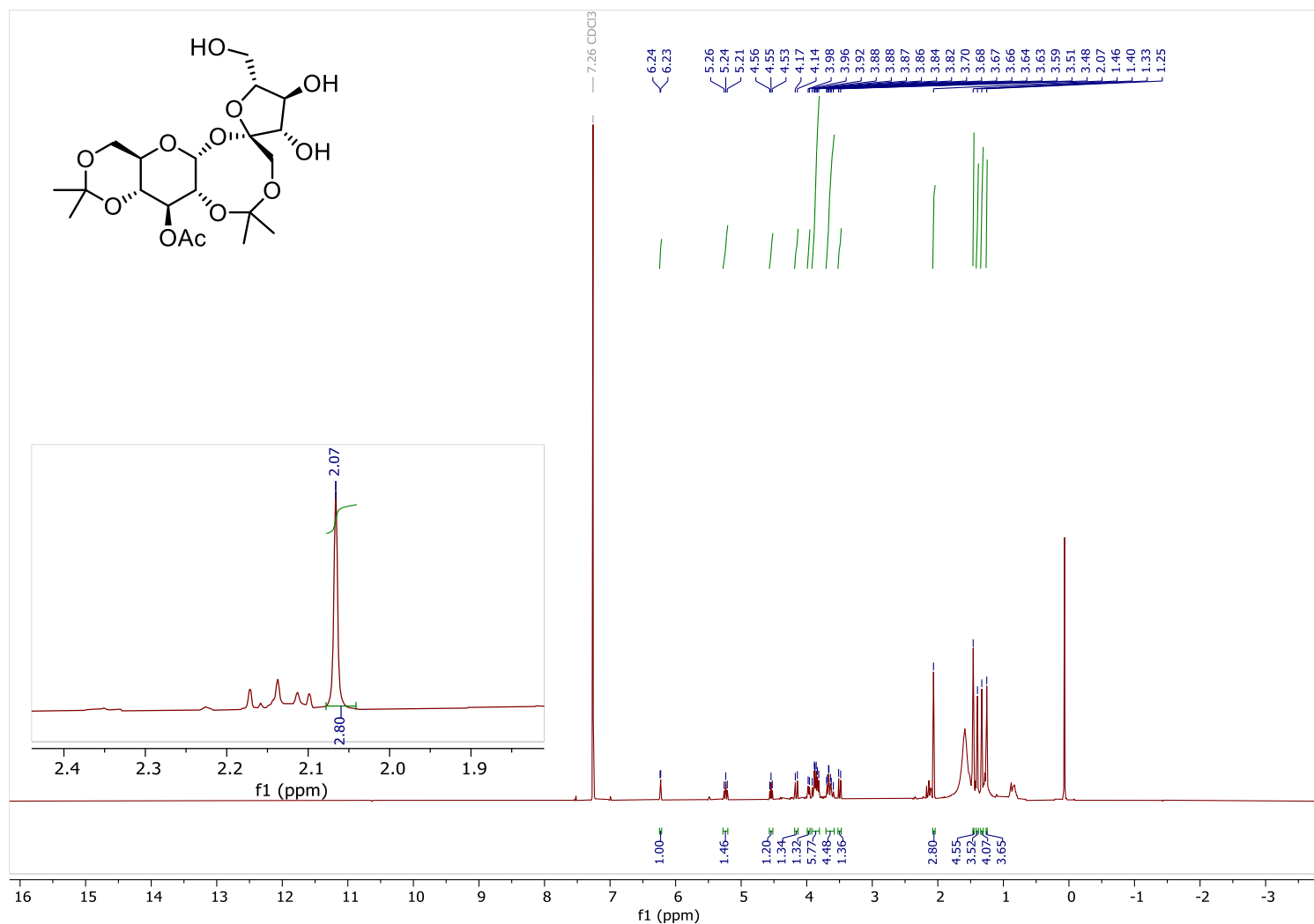
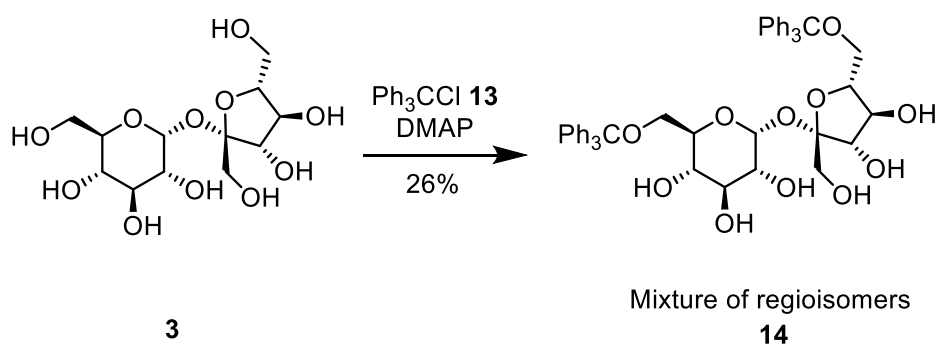


Figure 2.2.3.1. ¹H NMR of compound **11** depicting the regio-isomer drawn as the major product.

2.2.4 Accessing sucrose mono-esters on C4

The trityl-substituted compound **14** was prepared by reacting sugar **3** with chloride **13** (Scheme 2.2.4.1). The reaction proceeded and a mixture of regio-isomers was produced, whereby the 6,6'-OTr regio-isomer was the major product (Figure 2.2.4.1). Separation of the regio-isomers was attempted chromatographically but was ultimately unsuccessful.



Scheme 2.2.4.1. Synthesis of compound **14**. The major product is depicted.

Ketenes are a highly reactive species, therefore preparing them *in situ* in a manner that is compatible with sucrose is key. It is known that Meldrum's acid and related compounds can produce ketenes through thermolysis,¹⁵⁻¹⁷ and so the thermolytic pathway of Meldrum's acid and related compounds needs to be conducted with consideration of sucrose in mind, such that the thermolysis temperature cannot be too high if an effective carbonylation process is to be allowed while caramelisation of the sucrose is avoided.

Chapter Two references

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Chapter Three: C2 Substituted Meldrum's Acid Thermolytic Studies (Aims 2 and 3)

3.1 Meldrum's acid thermolysis computational studies

There are no examples in the literature that directly investigates a potential link between the C2 residue of Meldrum's acid and an effect on the temperature required for the thermolytic cleavage pathway to the best of the author's knowledge. The best starting point was determined to be to computationally screen which C2 residues would be ideal for thermolytically cracking Meldrum's acid and its analogues. We asked our computational collaborators to investigate which C2 residues would be suitable for our aims.¹ They investigated a *gem*-dimethylated Meldrum's acid, a *gem*-dimethylated cyclic carbonate and a *gem*-dimethylated cyclic thiocarbonate (Figure 3.1.1) and found the Meldrum's acid derivative had the lowest activation energy barrier to access the cycloreversion in both gas phase and solvated in toluene. Thus, research was centred on Meldrum's acid.

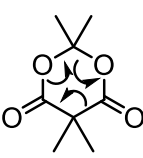
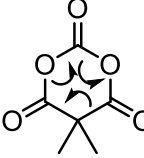
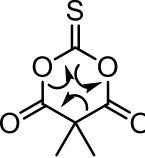
			
Barrier (kJ/mol) in Gas Phase @ M06-2X/6-311+G(d,p)	172.7	236.3	263.7
Barrier in SMD Toluene @ M06-2X/6-311+G(d,p)	149.3	198.5	266.1

Figure 3.1.1. The calculated Gibbs free energy barrier to cycloreversions for *gem*-dimethylated Meldrum's acid, cyclic carbonate and cyclic thiocarbonate respectively in both the gas phase and solvated with SMD toluene.¹

Our collaborators subsequently investigated computationally whether it was possible to lower the temperature of thermolysis via the choice of C2 residue.² They specifically

investigated *p*-substituted acetophenone derived Meldrum's acids (Figure 3.1.2) and their results suggest those molecules preferred undergoing the cycloreversion through the asynchronous hetero-retro-Diels-Alder pathway.

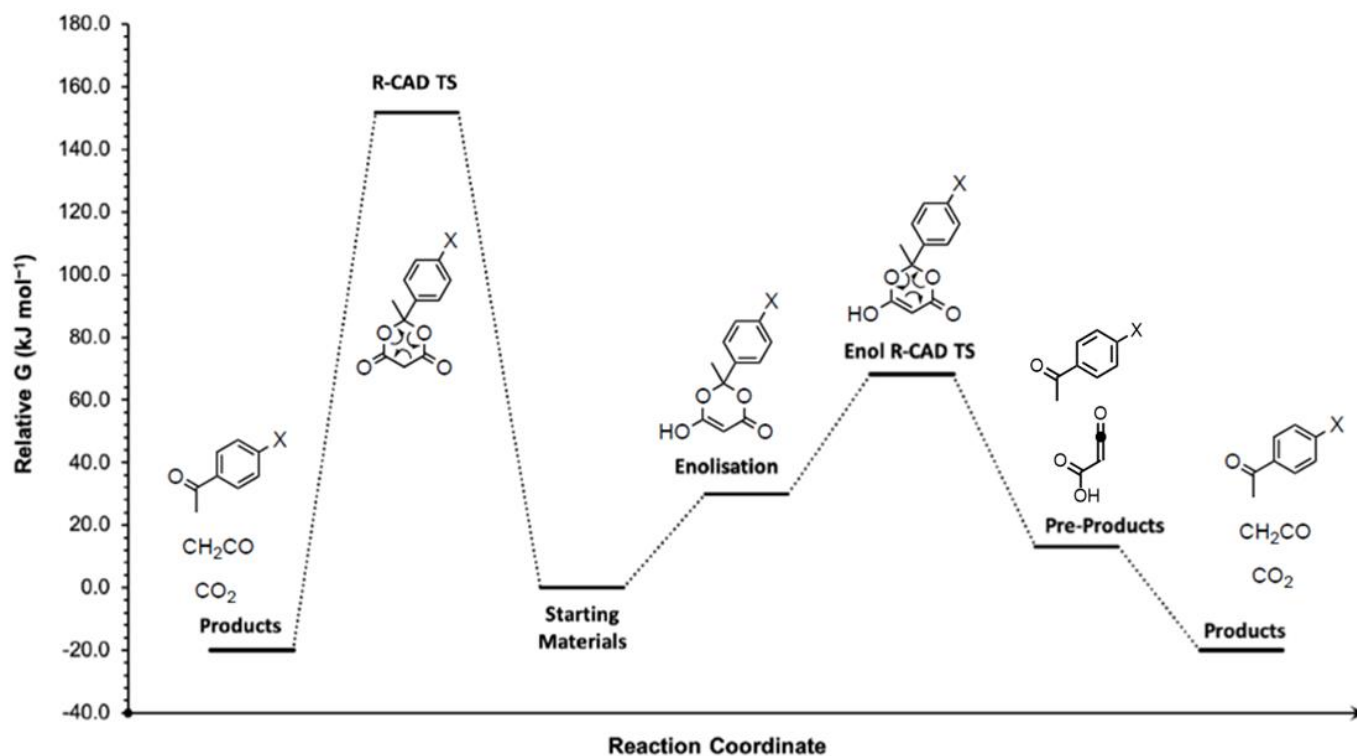


Figure 3.1.2. The calculated thermolytic reaction pathway profiles of acetophenone Meldrum's acids, including the transition states of each reaction pathway.²

Of specific interest to us, they determined the C2-O3, C4-C5 and C6-O1 bonds are the breaking bonds and are the ones most influenced by the electronic nature of the X-substituent (Table 3.1.1).

Compound	C6-O1	C2-O3	C4-C5
<i>p</i> -NMe ₂	1.607	2.739	2.081
<i>p</i> -OMe	1.703	2.76	1.982

<i>p</i> -Me	1.743	2.748	1.932
<i>p</i> -H	1.771	2.733	1.891
<i>p</i> -F	1.787	2.717	1.876
<i>p</i> -Cl	1.795	2.701	1.859
<i>p</i> -Br	1.795	2.697	1.858
<i>p</i> -COOMe	1.787	2.662	1.87
<i>p</i> -CN	1.815	2.608	1.813
<i>p</i> -CF ₃	1.866	2.579	1.727
<i>p</i> -NO ₂	1.857	2.569	1.709

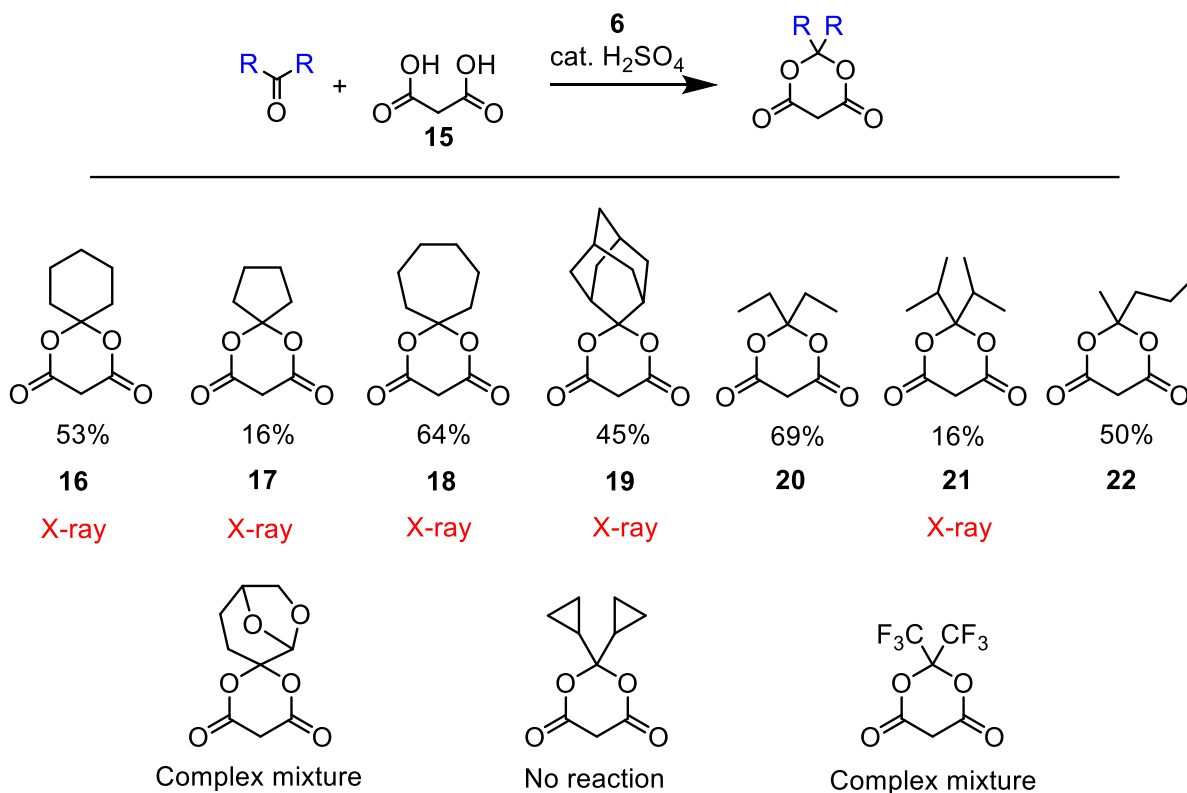
Table 3.1.1. The relevant calculated transition state bond lengths for the screened *p*-acetophenone Meldrum's acids.² All lengths are reported in Å.

Our collaborators found a general trend where the C2-O3 and C4-C5 bonds elongate whilst the C6-O1 bond contracts as the X-substituent becomes more electron-donating. They suggested the change in length of those three bonds is related to the degree of resonance stabilisation of the ketene from the X-substituent in the transition state. As a consequence, the resonance stabilisation forces the CO₂ moiety to be formed earlier in the transition state and ketene and acetophenone moieties are formed later when the X-substituent is increasingly electron-donating. Therefore, our collaborators found that the electron-donating X-substituents were even more likely to proceed through the asynchronous thermolytic reaction pathway through having a

delayed ketene-formation step. This calculation was supported by their final calculation where X-substituents with increasing electron-withdrawing strength had larger activation energy barriers to access the cycloreversion. Therefore, we became interested in producing a library of Meldrum's acid analogues with a variety of C2 residues and analysing their thermal properties as a test for their suitability as ketene surrogates. We were especially interested in the Meldrum's acid acetophenone analogues where the X-substituent was electron-donating.

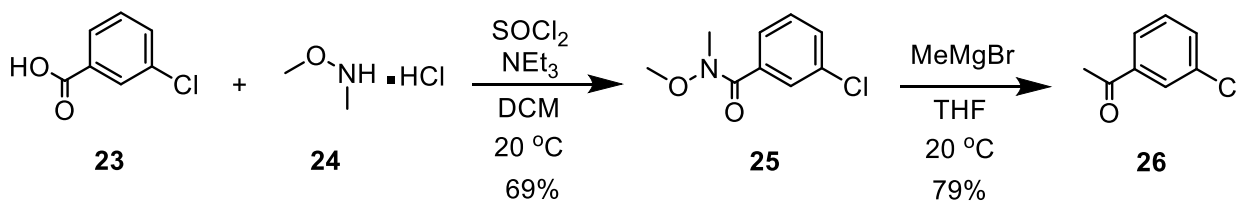
3.2 Library of Meldrum's Acid targets (Aim 2)

A library of Meldrum's acid analogues with varying C2 residues were prepared from malonic acid (**15**). A total of seven aliphatic Meldrum's acids (Scheme 3.2.1) were prepared in accordance with the procedure described by Barrett and co-workers.³ Yields across these compounds were mostly good and five out of the total seven compounds were afforded as crystalline solids. Another three compounds were attempted but could not be produced, where two of which resulted in complex mixtures and one had no reaction occur altogether. It is reasonable to expect the reaction where CyreneTM was used as the ketone to have the glucosenone moiety decompose under the acidic reaction conditions, thereby leading to the obtained complex mixture. The C2 residues that were open chains had a stronger tendency to decompose back to the precursor ketone and acid **15** compared with the cyclic C2 residues.

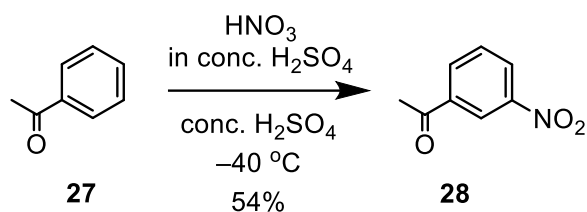


Scheme 3.2.1. Library of prepared aliphatic Meldrum's acids.

The research was expanded to include some target aromatic Meldrum's acids derived from benzophenone or acetophenones, where nine of the target acetophenone Meldrum's acids were either *p*- or *m*-substituted analogues. Eight ketones were readily commercially available, whereas another two were not and had to be synthesised. The first acetophenone prepared was *m*-chloroacetophenone (**26**) (Scheme 3.2.2) through converting benzoic acid **23** to the corresponding Weinreb amide **25**. Amide **25** was subsequently reacted to the desired acetophenone **26** by treatment with methylmagnesium bromide.

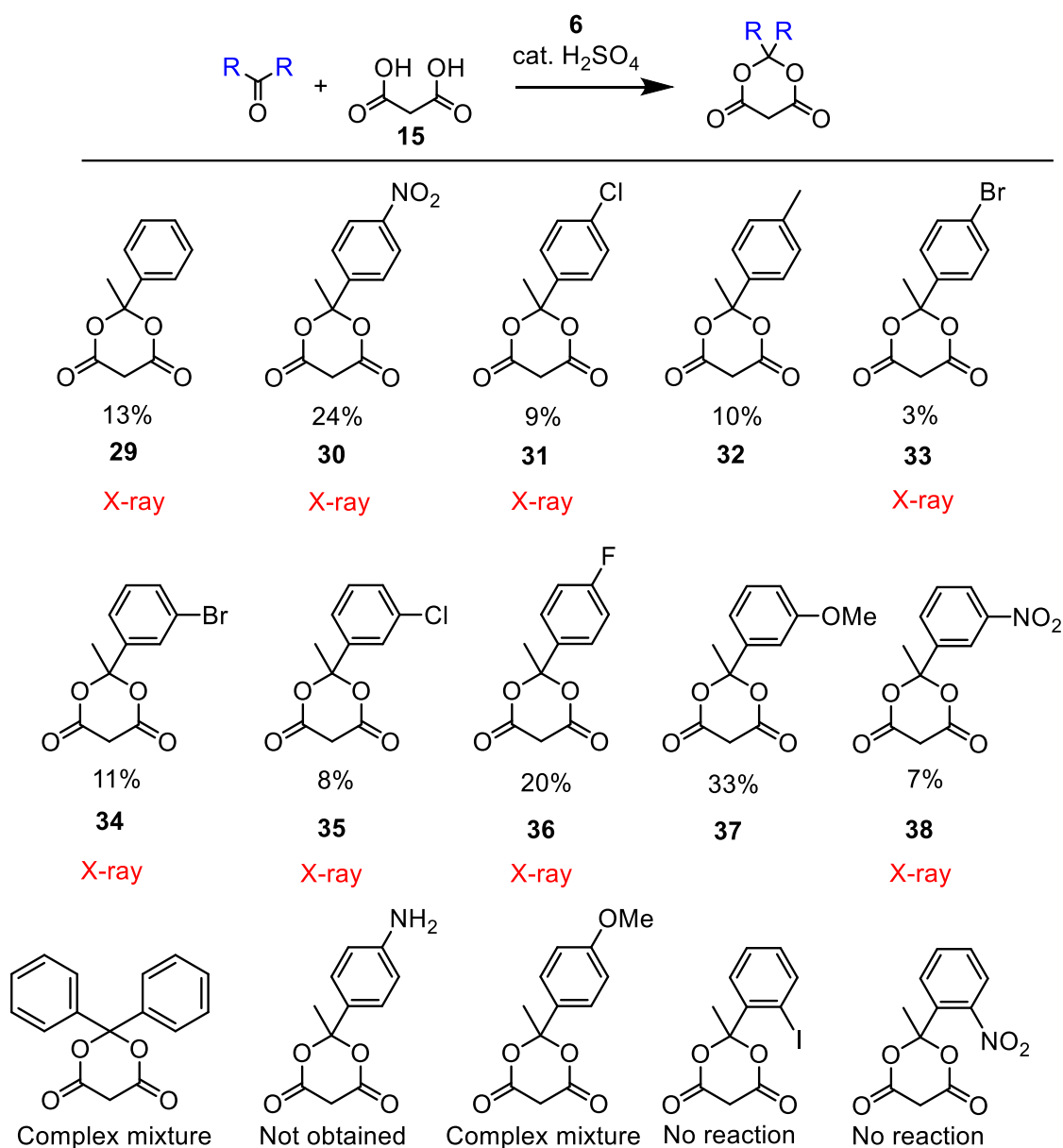
Scheme 3.2.2. Sequence to access acetophenone **26**.

The other acetophenone produced was *m*-nitroacetophenone (**28**) by treating acetophenone with a sulphuric acid/nitric acid mixture dropwise (Scheme 3.2.3). A temperature of below $-40\text{ }^{\circ}\text{C}$ was necessary to prevent runaway reactions after testing of various reaction conditions, although it was observed that the dropwise addition of the nitrating mixture at $-40\text{ }^{\circ}\text{C}$ led to the formation of two solid layers in the reaction flask, whereby one layer was acetophenone and the other was the nitrating mixture.



Scheme 3.2.3. Synthesis of acetophenone **28**.

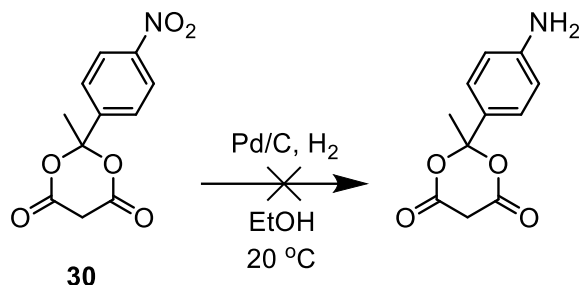
There were ten acetophenone Meldrum's acids produced in total (Scheme 3.2.4) using the same procedure as the aliphatic Meldrum's acids.³ The ten acetophenone Meldrum's acids tended to be more difficult to synthesise compared with their aliphatic analogues. Yields tended to be lower, mixtures were more readily formed and the analogues with the weaker electron-withdrawing and the electron-donating X-groups tended to decompose more readily than the stronger electron-withdrawing analogues. An interesting observation we found was the more electron-donating the X-group of the acetophenone was, the less likely the condensation reaction was to proceed. This observation could be due to the donation effect helping stabilise the acetophenone's ketone inductively. Eight of the ten synthesised acetophenone Meldrum's acids were obtained as crystalline solids and the other two were obtained as oils.



Scheme 3.2.4. Library of prepared aromatic Meldrum's acids.

The synthesis of benzophenone Meldrum's acid resulted in a complex mixture, although the most recognisable component of the obtained mixture was benzophenone in the obtained ^1H NMR spectra of the mixture. The presence of two aromatic rings possibly had a stabilising effect on the ketone, which made the ketone more impervious to the condensation reaction. Some *ortho*-substituted analogues were attempted but none were produced, possibly from the X-group sterically hindering the condensation reaction taking place. The synthesis of *p*-

aminoacetophenone Meldrum's acid was attempted by reducing compound **30** using palladium on carbon under a hydrogen atmosphere (Scheme 3.2.5). This reaction destroyed the Meldrum's acid core, whilst also reducing the *p*-nitroacetophenone.



Scheme 3.2.5. Attempted reduction of compound **30** through hydrogenolysis.

3.3 X-ray crystallography studies

There were 14 crystal structures obtained in total and the bond angles, bond lengths and ring conformations were investigated for each structure. A crystal structure for Meldrum's acid was obtained and it was a good match to the existing literature,^{4, 5} hence its data is not included in this chapter (refer to Appendix A1.2). The 13 crystal structures explored in this chapter are of the remaining C2 substituted Meldrum's acids. It is known that Meldrum's acid preferentially adopts a boat conformation,⁴⁻⁷ so we investigated the conformations of our obtained crystal structures through analysing the dihedral angles of the Meldrum's acid core. We defined the equatorial plane of the Meldrum's acid core to be the plane generated from the O1, O3, C4 and C6 atoms. We subsequently measured the dihedral angles of the C2 and C5 residues of both the aliphatic and aromatic C2 substituted Meldrum's acids (Tables 3.3.1 and 3.3.2 respectively). We defined a boat conformation to be when both the O1-C2-O3 plane (C2 residue) and C4-C5-C6 plane (C5 residue) angles were positive in magnitude *i.e.*, the C2 and C5 residues were on the same side of the defined equatorial plane. We also defined the chair conformation to be when one residue had a dihedral angle that

was positive in magnitude and one that was negative *i.e.*, the C2 and C5 residues were on opposite sides of the defined equatorial plane. Twinned structures were analysed separately to the other structures in its asymmetric unit. Compound **16** was unique in that it possessed four molecules within the asymmetric unit.

Compound	C2 residue	C5 residue
16_1	40.6	14.6
16_2	40.3	17.2
16_3	41.9	14.3
16_4	40.0	14.8
17	42.2	25.5
18	37.2	23.0
19	39.2	29.3
21	2.16	1.94

Table 3.3.1. Obtained dihedral angles of crystalline aliphatic C2 substituted Meldrum's acids. The C2 and C5 residues were analysed, and their angles are given in degrees (°).

Compound	C2 residue	C5 residue
29_1	45.6	23.7
29_2	44.9	22.6
30	42.8	21.9
31_1	45.4	22.8
31_2	41.9	30.7
33_1	45.3	23.5
33_2	42.8	30.4
34	42.6	26.8
35	42.7	26.6
36_1	42.7	31.0
36_2	44.4	28.1
38	42.1	26.0

Table 3.3.2. Obtained dihedral angles of crystalline aromatic C2 substituted Meldrum's acids. The C2 and C5 residues were analysed, and their angles are given in degrees (°).

When compound **21** was excluded (*vide infra*), the analysed Meldrum's acids had C2 residue dihedral angle ranges of 37.2-42.2° and 45.6-41.9° for the aliphatic and acetophenone Meldrum's acids respectively. The corresponding C5 residues had dihedral angle ranges of 14.3-29.3° for the aliphatic compounds and 21.9-31.0° for the acetophenone compounds respectively, thus the obtained crystal structures tended to adopt a boat conformation (refer to Appendices A1.2-A1.15 for the relevant set of crystallographic data). Sample structures for compound **16** and compound **30** are depicted in Figure 3.3.1, and clearly show the boat conformation for both, despite the difference in structure between the aliphatic and acetophenone-derived Meldrum's acids respectively.

a)

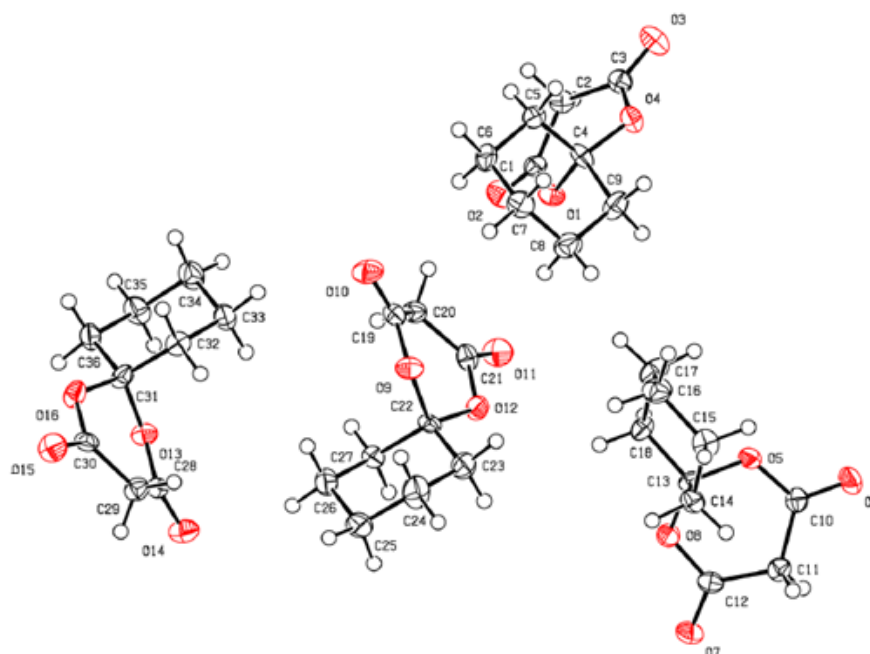


Figure 3.3.1. a) ORTEP Plot derived from single-crystal X-ray crystal structure analysis of compound **16**. Hydrogen atoms are drawn as circles with small radii.

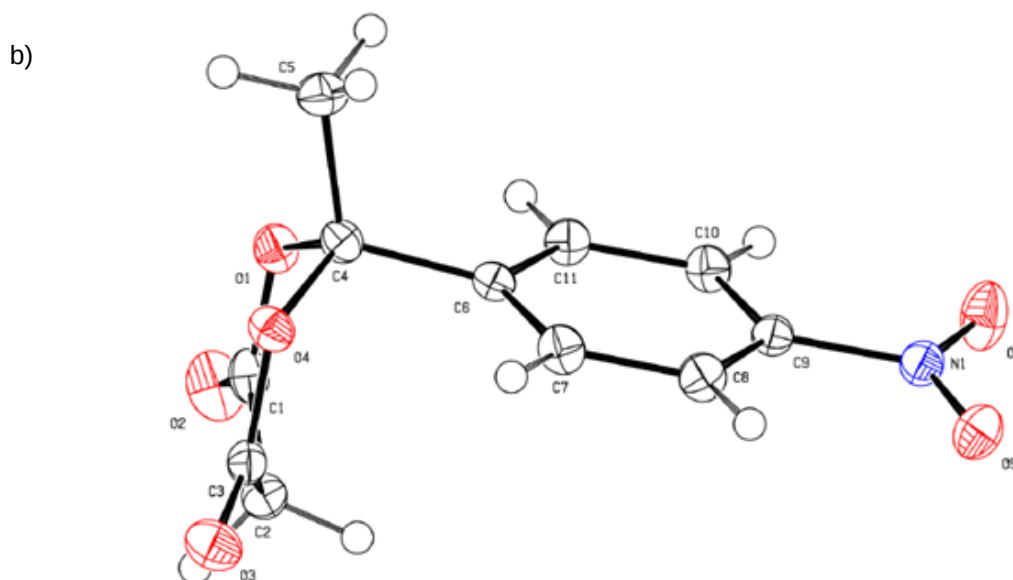


Figure 3.3.1. b) ORTEP Plot derived from single-crystal X-ray analysis of compound **30**. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

The question of why Meldrum's acids prefer the boat conformation over the chair conformation has been explored since the late 20th Century.⁵ The literature until 2009 was divided on whether this conformational preference for Meldrum's acids is influenced by electrostatic dipole moments,⁸ or hydrogen-hydrogen interactions between the axial C5 hydrogen and a hydrogen atom bonded to an adjacent carbon to C2.⁴ Wilsily and Fillion⁹ prepared a library of alkylidene Meldrum's acids and produced 16 crystal structures of C5 sp²-hybridised alkylidene derivatives. It would be expected that the lack of hydrogen-hydrogen interactions would cause the core to adopt a different conformation for these compounds without C5 hydrogen atoms if those interactions were the main contributor for adopting the boat conformation. However, the analysed crystals still had the respective Meldrum's acid cores adopting a boat conformation,⁹ giving credence to the importance of electrostatic interactions.

We analysed short contact interactions through using Mercury's¹⁰ default definition of a possible contact being less than the sum of the van der Waals radii of the atoms involved. We noted in all obtained aliphatic Meldrum's acids crystal structures, with exception of compound **21**, an intramolecular interaction between the C5 atom and a carbon atom bonded to the C2 residue at a distance range between 3.18-3.80 Å (Figure 3.3.2 as an example). There is a corresponding interaction present in the aromatic acetophenone Meldrum's acids, whereby the C5 atom interacts with the aromatic carbon bonded to C2. The C5 and aromatic carbon interaction has a distance range of 3.05-3.13 Å. Compound **21**, which we had previously excluded from our analysis, was found to be an outlier as its core adopts a planar conformation with a slight slant across the molecule, most likely due to intramolecular hydrogen-bonding from the hydrogens of the diisopropyl group of the C2 residue to the ether oxygens of the Meldrum's acid core (Figure 3.3.3). The diisopropyl group sterically hinders access for the C5 residue to interact with the adjacent carbon to C2, thus preventing the boat conformation from being adopted. Therefore, it is likely the C5 atom has some responsibility for exerting intramolecular electrostatic interactions to enforce the observed boat conformation. All obtained Meldrum's acids participated in intermolecular hydrogen-bonding between the respective carbonyls and hydrogen atoms on neighbouring C2 residues.

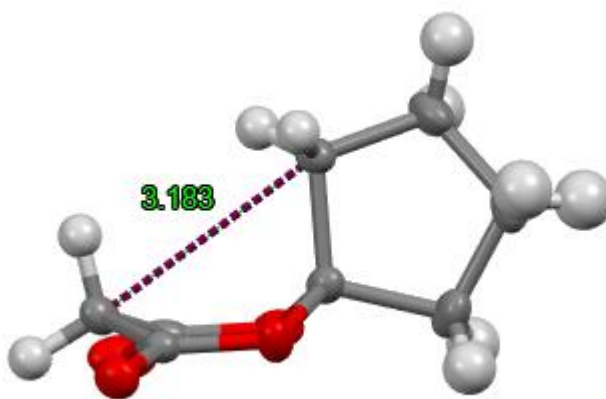


Figure 3.3.2. Obtained single-crystal X-ray structure of compound **17** as a sample ellipsoid structure depicting the predicted intramolecular interaction between C5 and the carbon atom in an α -position to C2. The distance between the two atoms is 3.183 Å.

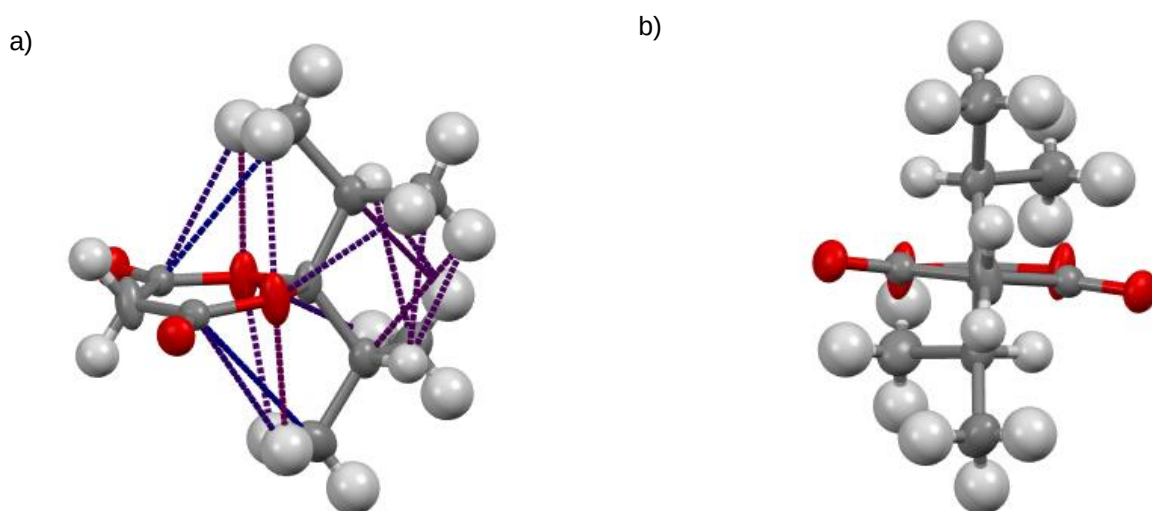


Figure 3.3.3. Obtained single-crystal X-ray structure of compound **21**, a) depicting the intramolecular interactions, b) depicting a view looking across the C5 residue to demonstrate the almost planar conformation of compound **21**.

Producing a large variety of crystalline Meldrum's acids allowed us to expand our research to investigate any possible effect the C2 residue may exert on the bond lengths or angles of the heterocyclic ring. The Structure Correlation Principle notes that any changes in bond length or structural geometry for a unimolecular reaction can be directly attributed to the electronic nature of a substituent, if the ground state and transition state geometries are similar.¹¹ We compared the relevant bond lengths for

the transition state lengths our computational collaborators obtained² with the single-crystal X-ray diffraction analyses data we obtained for the *p*-acetophenone Meldrum's acids, *i.e.*, the ground state data. The data is presented in Table 3.3.3 below.

Transition state bond lengths (Å)			
Compound	C2-O3	C4-C5	C6-O1
29	2.733	1.891	1.771
36	2.717	1.876	1.787
31	2.701	1.859	1.795
33	2.697	1.858	1.795
30	2.569	1.709	1.857
Ground state bond lengths (Å)			
Compound	C2-O3	C4-C5	C6-O1
29-1	1.442(12)	1.501(15)	1.352(14)
29-2	1.440(13)	1.504(14)	1.357(14)
36-1	1.444(12)	1.504(15)	1.358(14)
36-2	1.439(13)	1.503(15)	1.360(14)
31-1	1.436(12)	1.503(15)	1.353(12)
31-2	1.440(12)	1.505(15)	1.358(13)
33-1	1.440(2)	1.502(3)	1.357(3)
33-2	1.445(2)	1.506(3)	1.362(2)
30	1.436(12)	1.501(15)	1.358(12)

Table 3.3.3. Comparison of the relevant transition state bond lengths, as calculated by our collaborators² and the obtained ground state bond lengths from single-crystal X-ray diffraction analyses. All bond lengths are reported in Å and the obtained ground state bond lengths are given with the estimated standard deviations in parentheses.

As can be discerned from Table 3.3.3, there is substantial difference between the relevant transition and ground state bond lengths. The numerical difference varied for each data set but was at least 0.4 Å for the C6-O1 bond and 0.2 Å and 1.1 Å for the C4-C5 and C2-O3 bond length data sets respectively. The bond angles and conformations of the Meldrum's acid cores were not examined by our collaborators. Nevertheless, the drastic increases in bond lengths alone suggests there is a reasonable likelihood of the transition state adopting a different conformation to the boat conformation the ground state structures adopt. Therefore, we are confident the Structure Correlation Principle does not hold for our screened Meldrum's acids as it is likely the transition and ground state geometries are different.

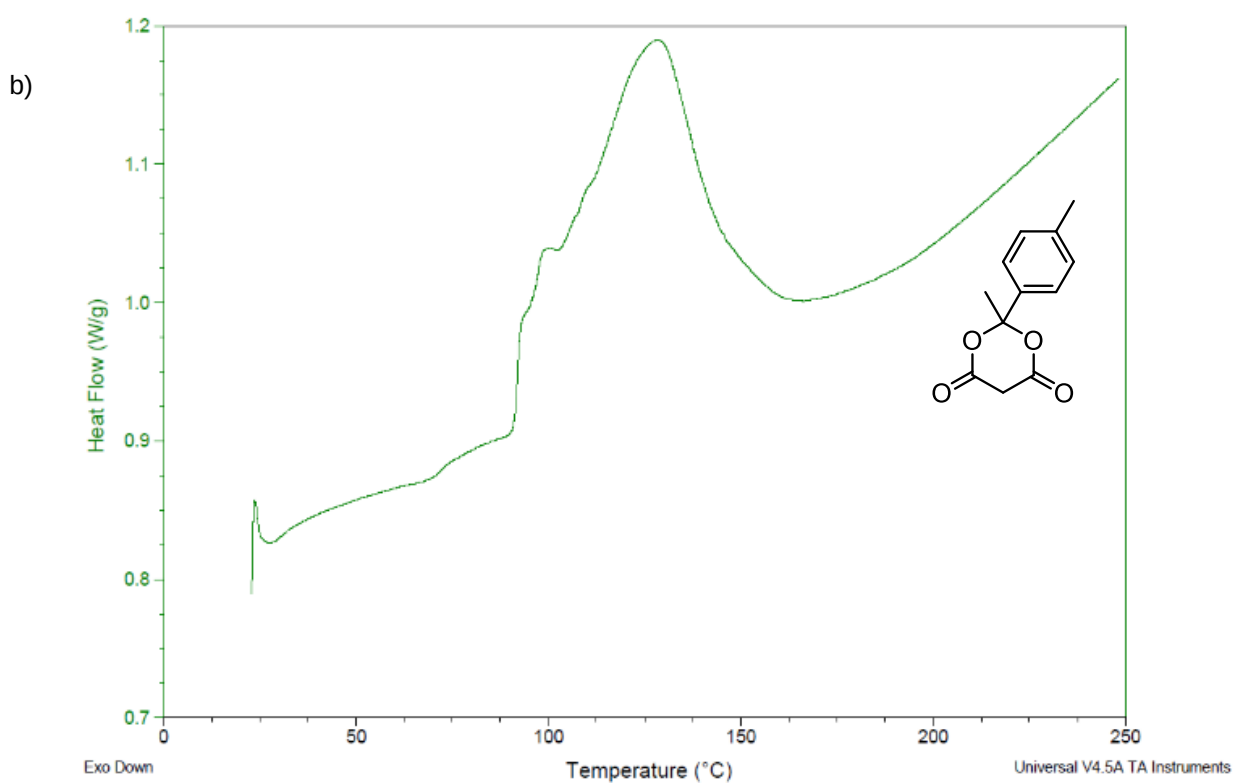
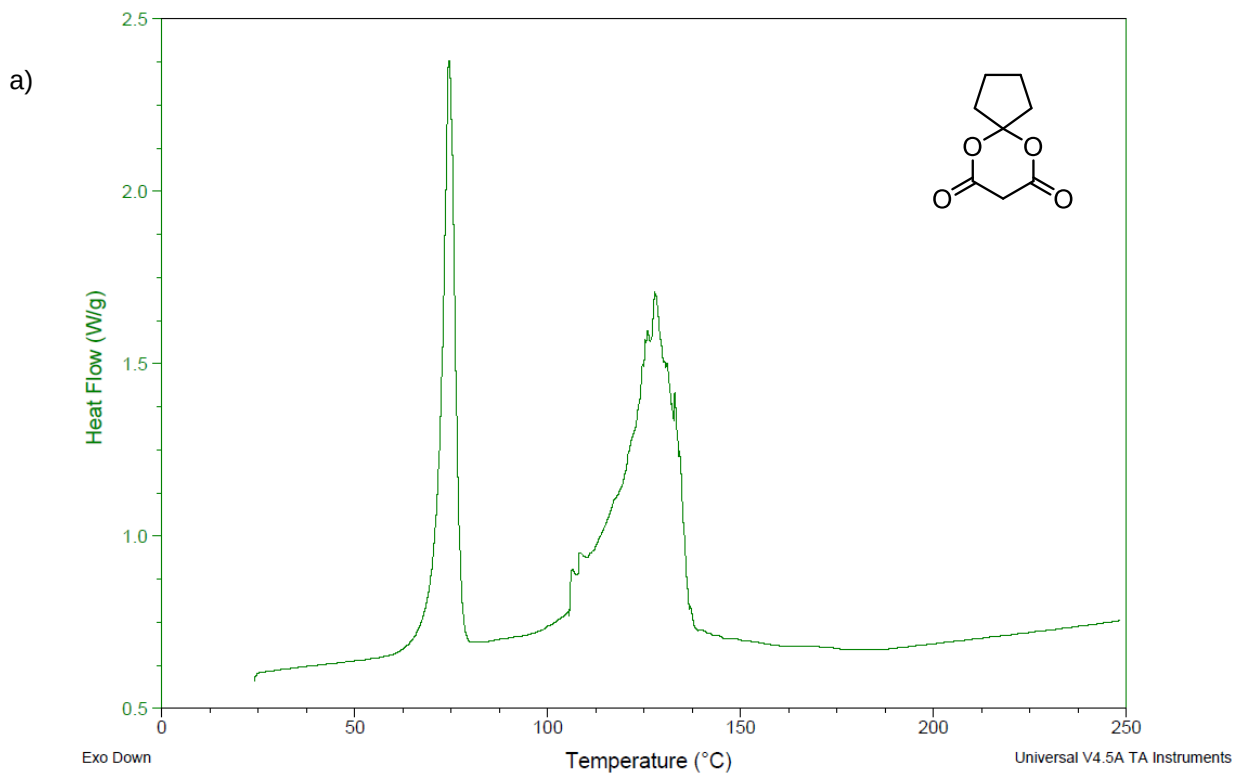
We analysed all our obtained Meldrum's acid structures based on bond lengths for the O1-C2-O3 and C4-C5-C6 moieties and found no substantial difference when comparing the acetophenone and aliphatic Meldrum's acids within their respective analogue series. We did find a range of 112.3(11)-118.3(12)° in C4-C5-C6 ring angle differences for the aliphatic Meldrum's acids and 112.0(9)-114.8(9)° for the acetophenone Meldrum's acids. The O1-C2-O3 angle for the aliphatic Meldrum's acids had a range of 107.8(5)-113.8(10)°, whilst the acetophenone Meldrum's acids had a much smaller corresponding angle range of 109.2(9)-110.2(7)°. The angle ranges for the acetophenone Meldrum's acids were within error. There was variation in O1-C2-O3 and C4-C5-C6 bond angles for the aliphatic Meldrum's acids, resulting entirely from the presence of compound **21** in the data set. It is possible the absence of the electrostatic interaction across the Meldrum's acid core in compound **21** forced the observed increase in bond angles as an electronic repulsion between neighbouring

atoms, as it had the largest bond angles of the aliphatic Meldrum's acid data set. The bond angles of the remaining aliphatic Meldrum's acids were within error.

3.4 Differential scanning calorimetry Studies

With the library of Meldrum's acids to hand, we decided to use Differential scanning calorimetry (DSC) to study their thermolytic behaviour. We noted consistency with respect to the DSC traces and the phase of the sample analysed (see Appendices A2.1-A2.18). For example, solids produced similar endotherms regardless of whether the sample was aliphatic or aromatic, where the first endotherm corresponded to the sample's melting point and the second corresponded to what we suspect is the cycloreversion (Figures 3.4.1a and 3.4.1c). All oils analysed produced a single endotherm (Figure 3.4.2b), which is most likely the point of cycloreversion for the sample. Of note, we observed compound **29** produced three endotherms for its DSC data. We suspect the second and third endotherms are both steps within the cycloreversion pathway (Figure 3.4.1c). Compound **29** was the only sample to produce three distinct endotherms. Compounds **31** and **33** produced two endotherms but had a shoulder profile on the second endotherm, which may have been obscuring a third endotherm. Compound **30** produced a single endotherm, which may correspond to a combined melting and cycloreversion point or just the melting point. The computations from our collaborators² suggested that the most electron-withdrawing substituents would require an increase in temperature to access the cycloreversion and our results with compound **30** gives some evidence that this may be the case, as compound **30** required the highest temperature to produce an endotherm. Compound **36** also produced a single endotherm, which we were not expecting as its aromatic substituent

of fluorine is between Meldrum's acids **29** and **31** in terms of electronic-withdrawing strength and therefore, we expected compound **36** to produce two or three endotherms. Overall, we found the DSC data set to not be especially informative in respect to our thermolytic studies.



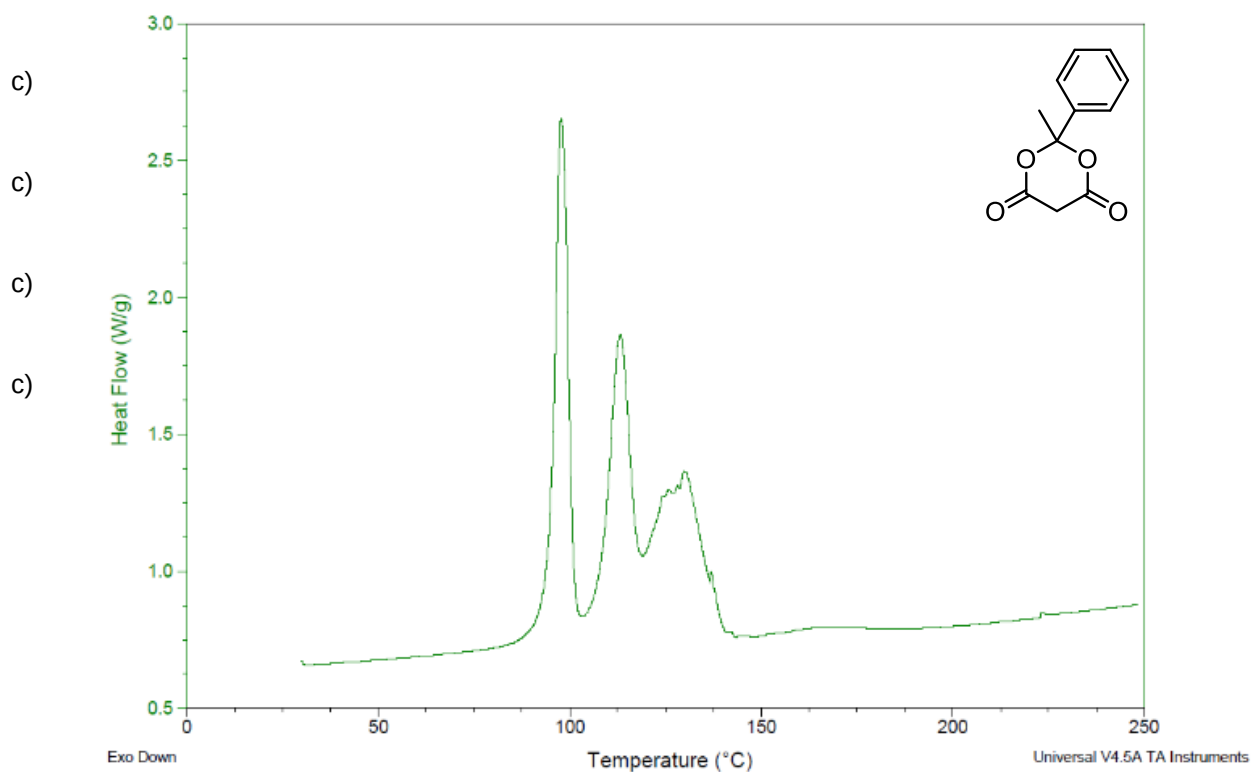


Figure 3.4.1. Sample Differential scanning calorimetry profiles for a) compound **17**, b) compound **32**, c) compound **29**.

3.5 Thermogravimetric Analysis Studies (Aim 3)

Thermogravimetric Analysis (TGA) was substantially more informative than the DSC thermolysis studies. The TGA studies provided us with the data needed to determine whether a Meldrum's acid compound was suitable to undergo thermolysis in the presence of sucrose. The point we were looking for in the data set was the inflection point, which we used as a proxy for the thermolysis temperature. The inflection point was obtained by setting an interval to analyse in the TA-500 analysis software and by calculating the average rate of change. The intersection point of the linear rate with the chart was defined as the inflection point. We also performed TGA analysis on Meldrum's acid, so we would have a comparison point between it and its synthesised aliphatic analogues (refer to Appendices A3.1-A3.18 for the individual TGA traces).

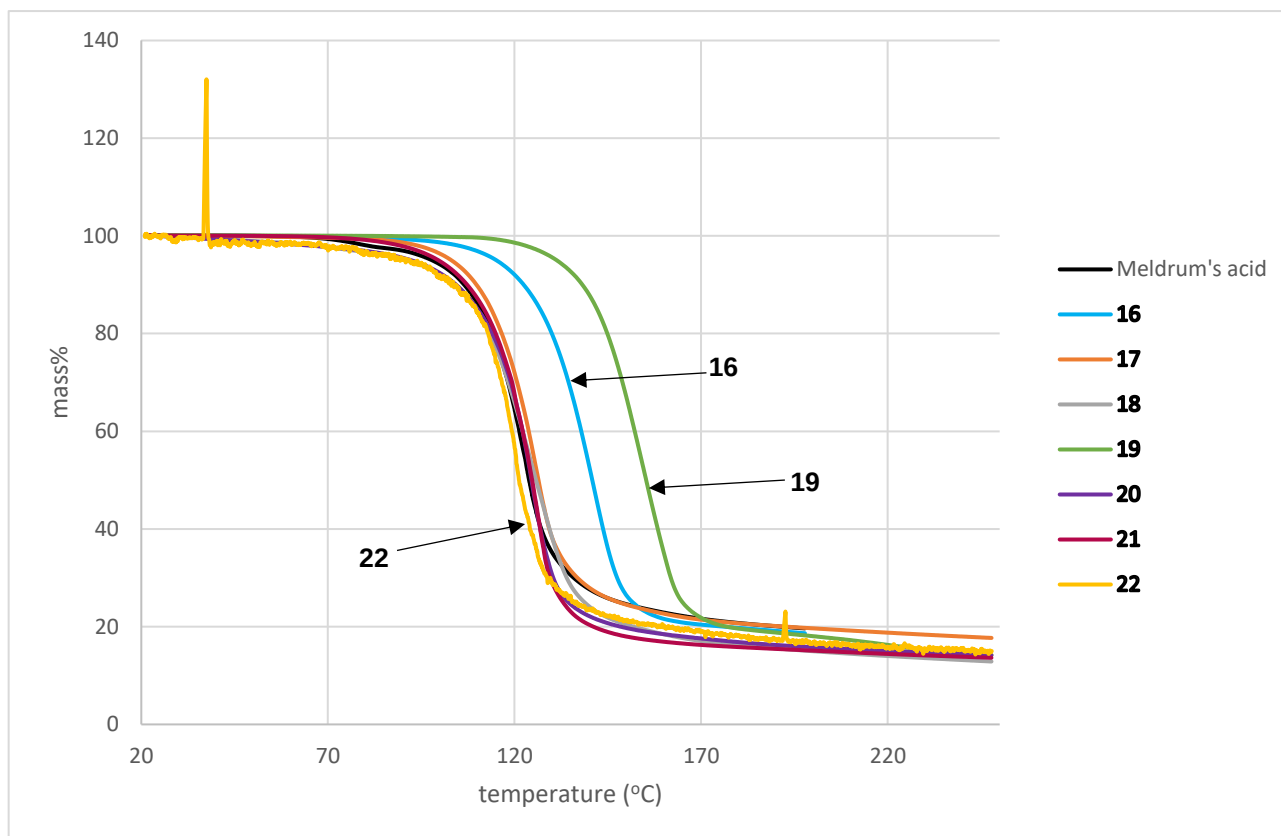


Figure 3.5.1. TGA traces of Meldrum's acid and its aliphatic derivatives, depicted as change in mass percent vs temperature (°C).

Immediately apparent from the aliphatic analogues data set is all inflection points are lower than the 170 °C required to caramelize sucrose, thus these Meldrum's acids may be suitable choices as ketene surrogates. Compound **22** had an inflection point lower than that of Meldrum's acid and the lowest overall, so it may be a particularly good ketene surrogate. Conversely, compound **19** only just finishes its thermolysis pathway by the 170 °C so this compound would be the least ideal to use as a ketene surrogate from this data set. Compound **19** also had the highest inflection point, followed by compound **16**. Overall, there was a lack of variation in inflection point temperatures within the aliphatic Meldrum's acids data set. This lack of inflection point temperature variation, when considered with the single-crystal X-ray analysis results,

suggests how defined the boat conformation the Meldrum's acid core adopts does not strongly influence the inflection point temperature. However, we suspect the respective C2 residues of compounds **16** and **19** being more conformationally rigid contributed to the observed elevated inflection point temperatures. We noted that all the compounds decomposed to approximately 15% of residual mass, with exception of compound **17**. A substantially greater spread of thermolytic data was obtained from the acetophenone Meldrum's acids series (Figure 3.5.2). As with the aliphatic analogues, Meldrum's acid was included in the data set for a comparison between the different acetophenone analogues and itself.

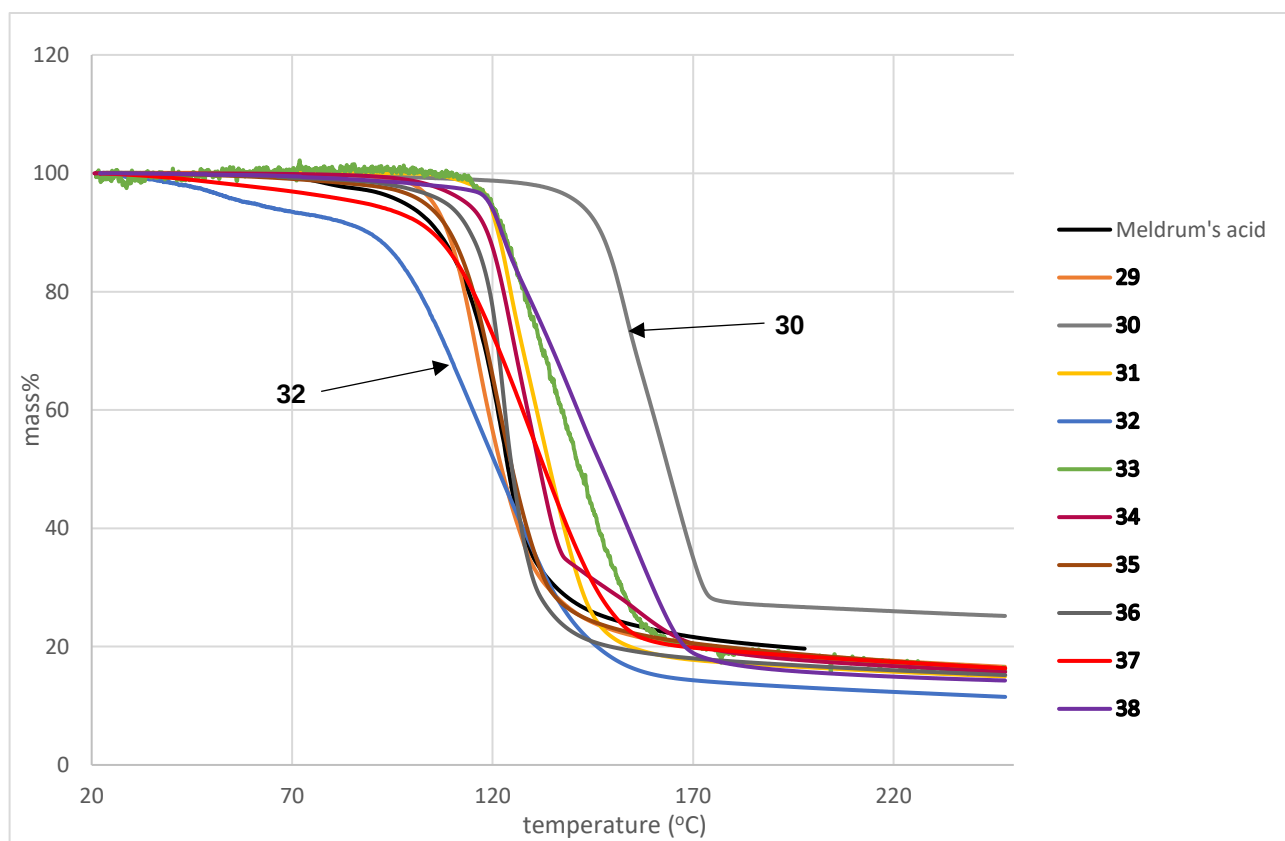


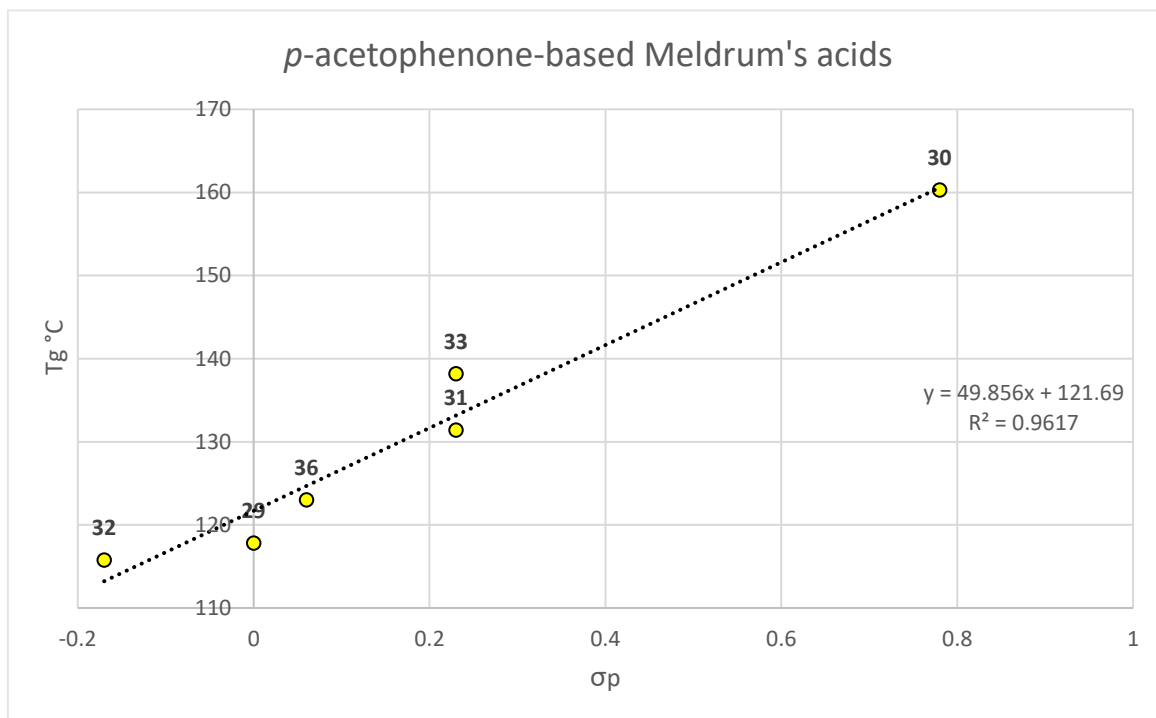
Figure 3.5.2. TGA traces of Meldrum's acid and its aromatic derivatives, depicted as change in mass percent vs temperature (°C).

The thermolytic profiles of the acetophenone Meldrum's acids depicts a much wider spread of data. Compound **30** is still undergoing thermolysis at 170 °C, so it should not be considered as a potential ketene surrogate for the purpose of esterifying sucrose. All other Meldrum's acids can be considered as potential ketene surrogates. It is notable that like compound **22**, compounds **29** and **32** had inflection points lower than that of Meldrum's acid. These two acetophenone compounds were the most electron-donating of the library of acetophenone Meldrum's acids, so their lower inflection points do lend credibility to the calculations our computational colleagues prepared for us. We found compound **32** also had the lowest residual mass% and that compound **30** had the greatest, which is more likely to be a coincidence than an electronic property trend as the next most electron-withdrawing acetophenone Meldrum's acid, compound **37**, had the second lowest residual mass%. A plausible explanation for compound **32** having the lower residual mass% is that it is the most prone out of all the library of aliphatic and aromatic Meldrum's acids for decomposition, therefore the elevated temperatures may have hastened that decomposition pathway.

There was a trend in the acetophenone Meldrum's acid TGA data set that demonstrates a reliable cause-and-effect relationship between the X-substituent on the aromatic ring and the inflection point of the acetophenone Meldrum's acid. This cause-and-effect relationship was one where the inflection point increased as the X-substituent's electron-withdrawing strength increased. This relationship suggests that the ease of thermolysis is directly affected by the electronic nature of the X-substituent. We wanted to investigate this observation further, so Hammett plots were prepared (Figure 3.5.3). Hammett plots depict the relationship between the experimentally

derived electronic property of the X-group¹² with respect to a measured property of an aromatic compound, which in this study is the inflection point temperatures from the TGA data set.

a)



b)

b)

b)

b)

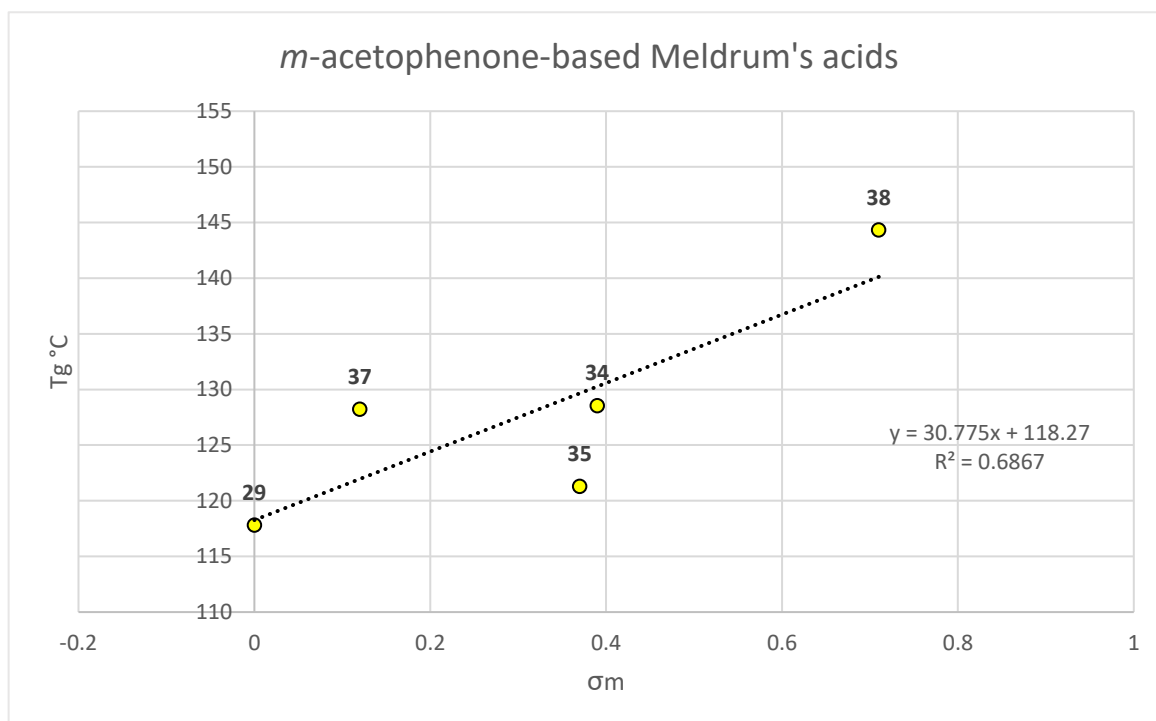


Figure 3.5.3. a) Hammett plot for *p*-acetophenone Meldrum's acids, b) Hammett plot for *m*-acetophenone Meldrum's acids.

Both sets of acetophenone Meldrum's acid data demonstrated a positive gradient trend as the X-substituent increased in electron-withdrawing strength. Compounds **33** and **35** are outliers in their respective data sets. This disruption of the trend is possibly due to the chlorine atom acting more mesomerically-donating to the aromatic ring in compound **35** and the bromine atom acting more electron-withdrawing for compound **33**. Compound **37** may also be an outlier due to the compound also being more electron-withdrawing than expected. The overall trend suggests there is a build-up of positive charge within the molecule during the cycloreversion pathway. This build-up of positive charge at the C2 site is likely caused by the greater polarisation of a C2-O bond, thereby suggesting the bonding oxygen atom is taking on a more electronegative character and shortening the bond as the electron-withdrawing strength increases. Our collaborators had determined the C2-O3 bond changing length was a defining characteristic in the transition state of the asynchronous hetero-retro-Diels-Alder thermolysis pathway, as it determined the rate of ketene formation in the fragmentation step (Figure 3.5.1).² The excellent correlation of the data for the *p*-acetophenone Meldrum's acids when considered with the build-up of positive charge at the C2 residue suggests the asynchronous hetero-retro-Diels-Alder thermolysis pathway is the preferred thermolysis pathway for those compounds. The hetero-retro-Diels-Alder thermolysis pathway may also be the preferred thermolytic pathway for the *m*-acetophenone Meldrum's acids too. Therefore, the data suggests the presence of the acetophenone C2 residue changes the preferred thermolytic pathway of Meldrum's acids from the single step pathway to the asynchronous hetero-retro-Diels-Alder pathway (Scheme 3.5.1).

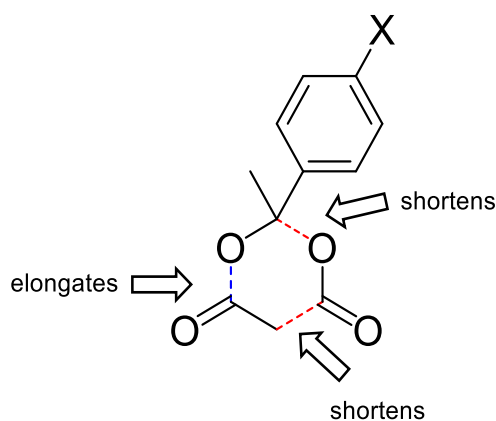
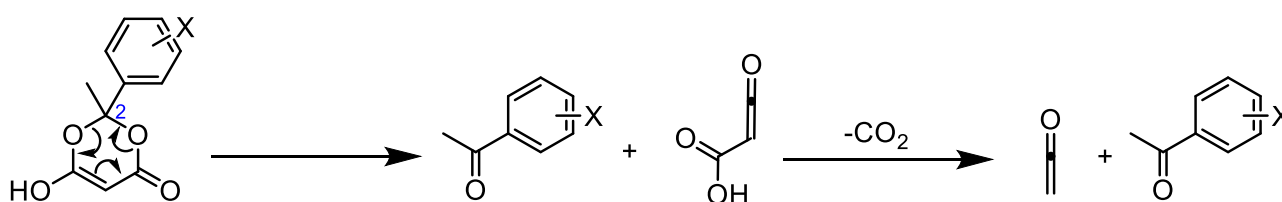


Figure 3.5.1. A general *p*-acetophenone Meldrum's acid depicting the bonds that change length in the transition state, as determined by our computational collaborators.²



Scheme 3.5.1. The asynchronous hetero-retro-Diels-Alder pathway for acetophenone Meldrum's acids.

3.6 Conclusions

We successfully prepared a library of C2 substituted Meldrum's acids in varying yields. 13 of the prepared Meldrum's acids were afforded as crystalline solids and were analysed through single-crystal X-ray diffraction. We found all analysed compounds adopted a boat conformation and there were most likely to be intramolecular electrostatic interactions enforcing the boat conformation. We also found the Structure Correlation Principle to not be applicable to these compounds. The complete library of Meldrum's acids was subjected to a TGA study for analysis of their thermolytic behaviours and we found the aliphatic Meldrum's acids with structurally rigid C2 residues may induce a constraining effect on the Meldrum's acid core. This constraining effect increased the inflection point temperature. We also noted

intramolecular electrostatic interactions did little to increase inflection point temperature regardless of the strength of the interaction. The acetophenone Meldrum's acids demonstrated that inflection point and the electron-withdrawing strength of the X-substituents are likely linked, which supports the calculations of our collaborators.² Our results suggest there is a build-up of positive charge within the acetophenone Meldrum's acids during thermolysis, implying the thermolytic fragmentation is an asynchronous step-wise process. Therefore, we propose the fragmentation proceeds through a hetero-retro-Diels-Alder thermolysis pathway. Overall, we demonstrated that the choice of C2 residue affects the temperature of thermolysis for Meldrum's acids.

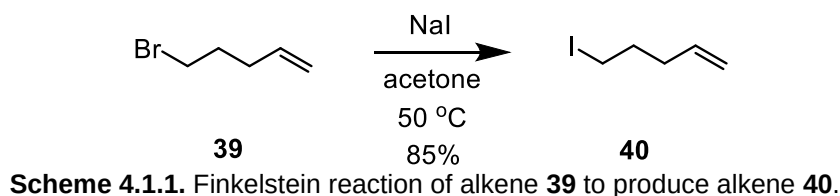
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Chapter Four: C5 Substituted Meldrum's Acid Derivatives and Thermolytic Studies (Aims 4 and 5)

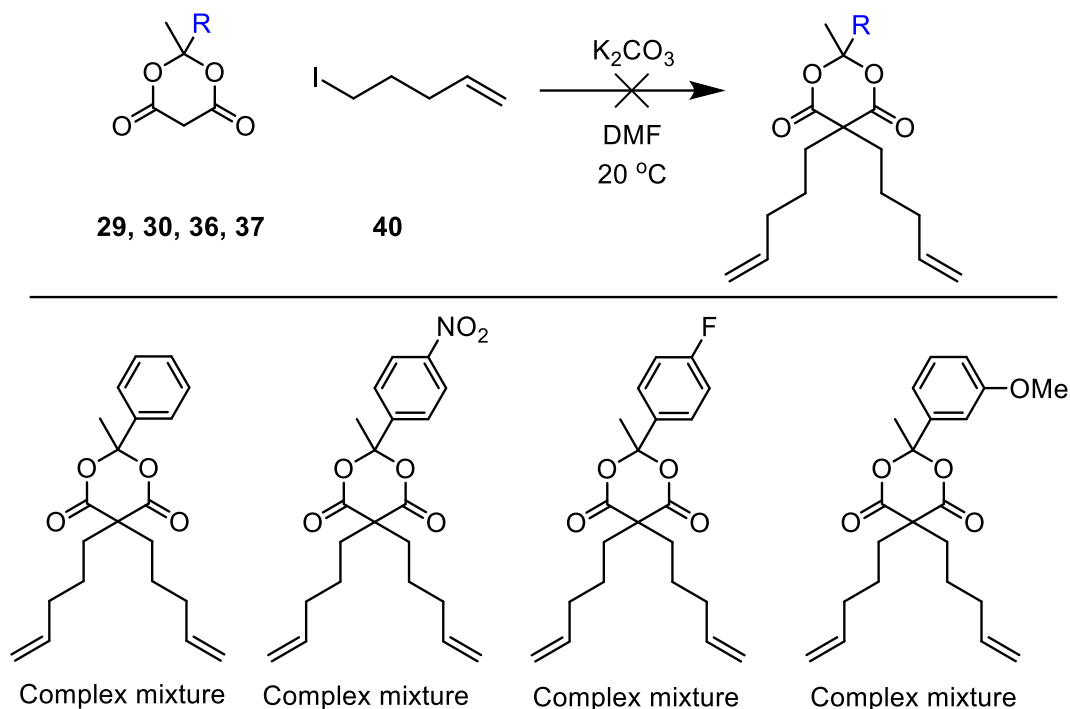
4.1 Library of C5 substituted Meldrum's acid derivatives (Aim 4)

Having demonstrated that the C2 residue affects the thermolytic behaviour of Meldrum's acids, the next step was to investigate the effects of the C5 residue on thermolysis. Preparation of a new library of derivatives from the previously screened Meldrum's acids was required. A twofold carbon-carbon bond formation via nucleophilic aliphatic substitution with an electrophile also bearing a terminal alkene (henceforth referred to as "alkenylation") was chosen as it would prevent the hetero-retro-Diels-Alder reaction taking place, and only the concerted thermolytic pathway would occur. A simple iodinated alkene **40** was chosen for the investigations and prepared through a Finkelstein reaction of the brominated analogue **39** in a high yield (Scheme 4.1.1).



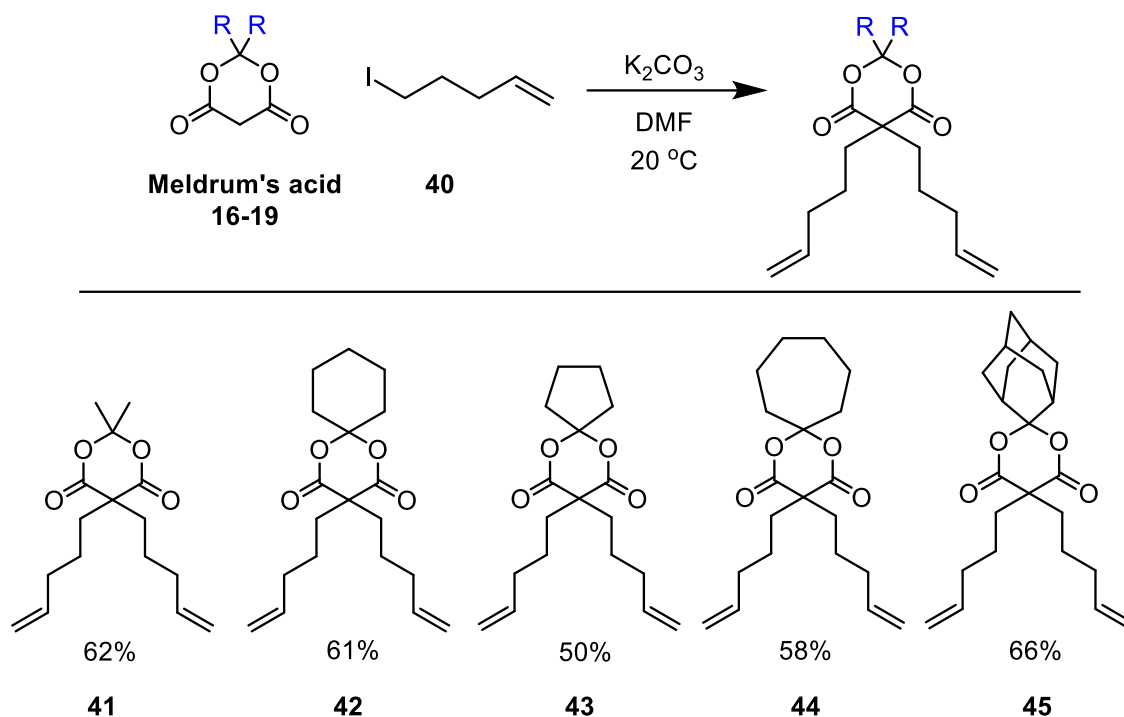
Having produced the more varied TGA results, a sample of acetophenone-derived Meldrum's acids were selected for this twofold alkenylation (Scheme 4.1.2), including substituents varying in their respective location on the aromatic ring and electron-withdrawing or electron-donating strengths. However, these reactions all produced complex mixtures instead of the target compounds. Examining the progress of these reactions by TLC analysis (1:9 v/v ethyl acetate/petroleum ether), it appeared the first alkenylation step generally proceeded with little by-product formation. The second

alkenylation step, however, was apparently responsible for the formation of multiple products. It is possible the tendency of these compounds to undergo the keto-enol tautomerism resulted in competitive alkylation of the enol form, which would produce a C-O alkenylated Meldrum's acid instead of the desired twofold C-C alkenylation product.



Scheme 4.1.2. Attempted twofold alkenylation of acetophenone Meldrum's acids.

As a result, we turned our attention to the aliphatic library of Meldrum's acids and selected a different subset of compounds to attempt the twofold C-C alkenylation (Scheme 4.1.3). A specific interest was taken in the cyclic C2 Meldrum's acids as they had demonstrated a longer shelf-life than their open chain C2 analogues, thereby presenting an opportunity to further investigate any potential effect of the C2 ring size on the inflection point temperature.



X-ray

Scheme 4.1.3. Twofold alkenylation products of aliphatic Meldrum's acids.

In contrast to the acetophenone-derived targets, all five aliphatic targets were successfully prepared in good yields. Four of the synthesised compounds were oils and one (compound **41**) was crystalline. Importantly, the ^1H NMR spectra demonstrated the absence of C5 protons (Figure 4.1.1), so we were confident the twofold carbon-carbon alkenylation reaction had taken place. To better obtain a sense of any potential thermolytic trends, more targets were added to this set requiring different C5 residues, therefore two new electrophiles were prepared from a common alkyne precursor **46** (Schemes 4.1.4 and 4.1.5). Both new alkyne electrophiles compound **51** and **52**, bearing a terminal methyl or hydrogen at the alkyne functionality, respectively, were successfully produced in reasonable quantities. The synthetic pathways could also be achieved on multi-gram scales.

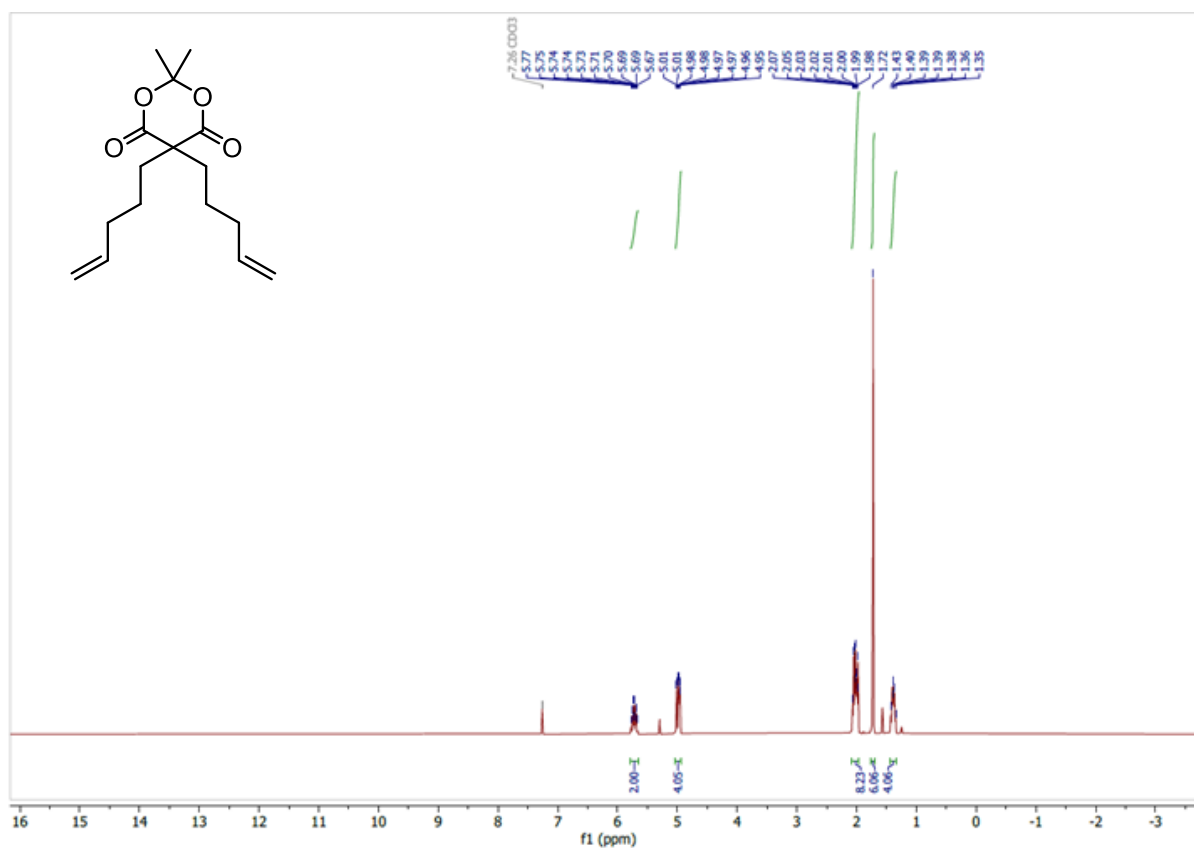
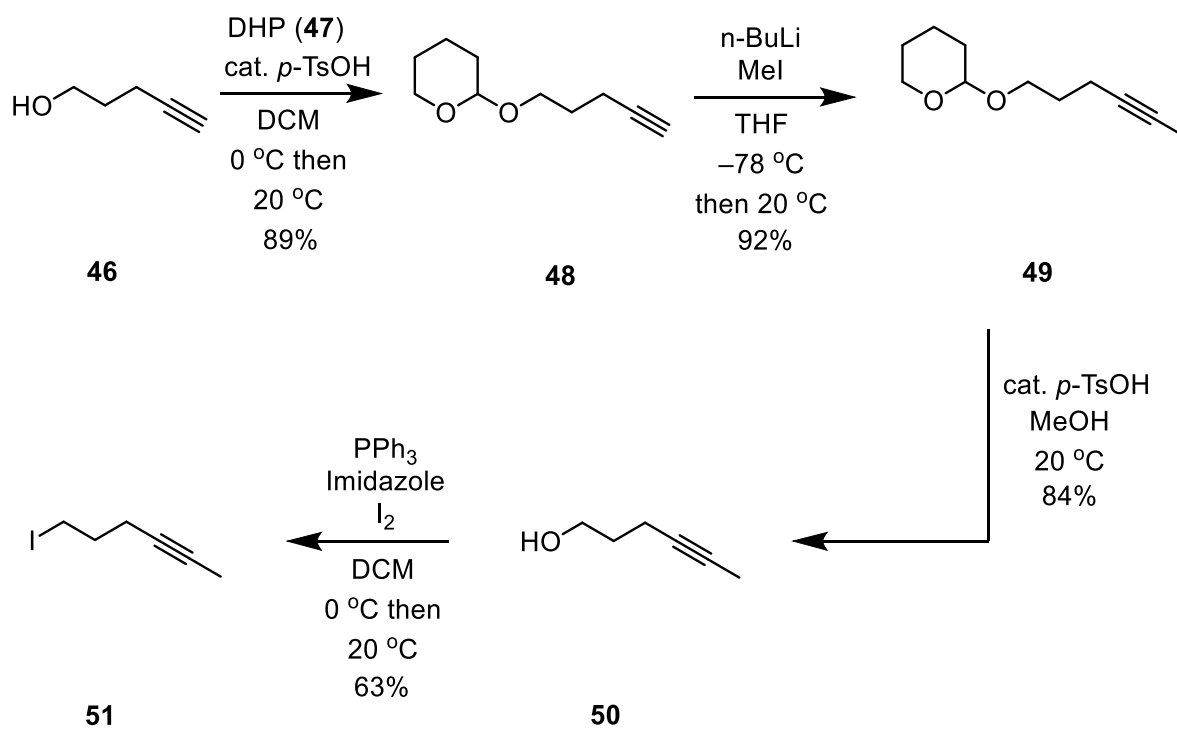
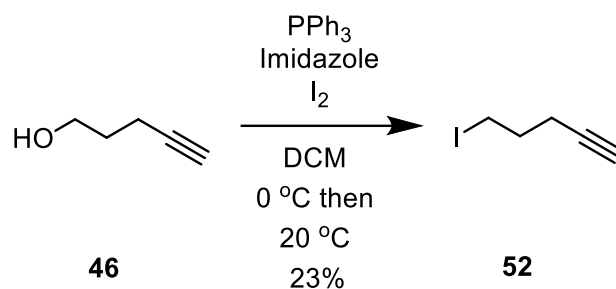


Figure 4.1.1. ^1H NMR spectra of compound **41** depicting the absence of C5 protons.

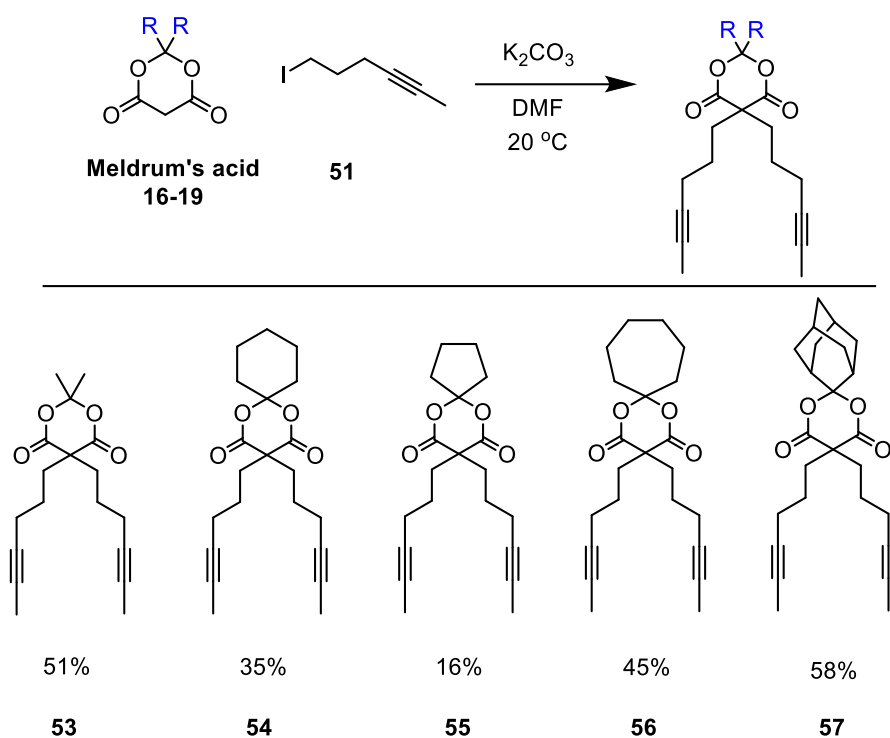


Scheme 4.1.4. Synthesis of electrophile **51** from alkyne **46**.



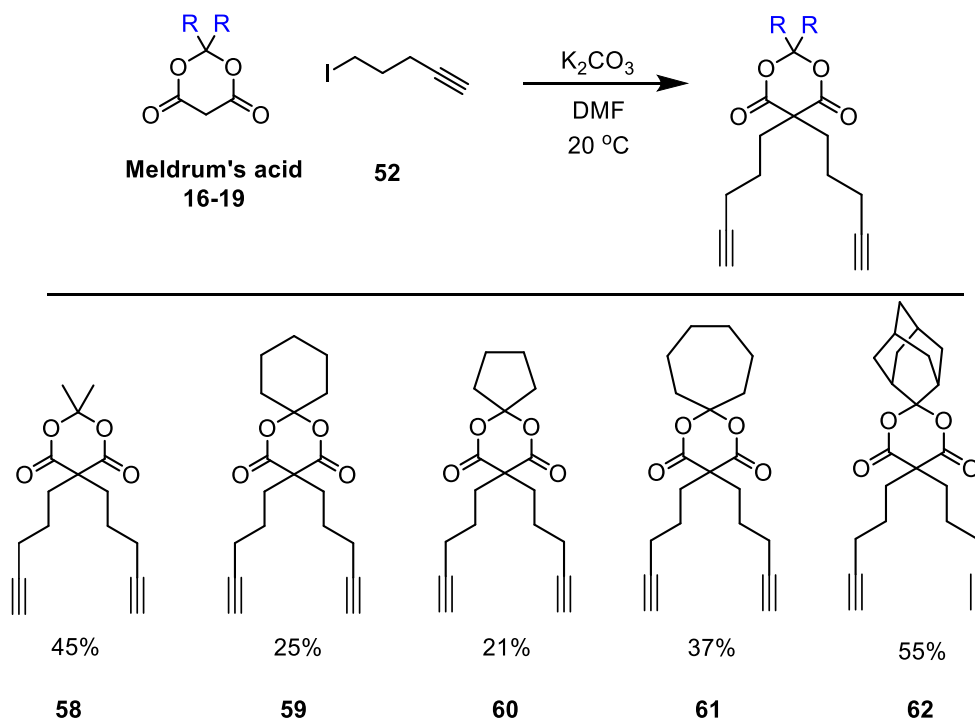
Scheme 4.1.5. Synthesis of electrophile **52** from alkyne **46**.

Having alkynes **51** and **52** to hand, the target *gem*-dialkynyl Meldrum's acids were produced using the same protocol as the *gem*-dialkenyl Meldrum's acids (Schemes 4.1.6 and 4.1.7 respectively). The yields of compounds **53-57** were generally acceptable for the purposes of this study; three of the targets were produced as solids and one of those three targets was afforded as a crystalline solid. Compounds **58-62** were produced in similar yields and three targets were also produced as solids, whereby two of those solids were successfully recrystallised. The three crystalline compounds (**57**, **58** and **61**) were analysed through single-crystal X-ray diffraction analyses, along with compound **41**.



X-ray

Scheme 4.1.6. Aliphatic *gem*-dialkynyl methyl-capped Meldrum's acids.



X-ray

X-ray

Scheme 4.1.7. Aliphatic *gem*-dialkynyl terminal Meldrum's acids.

4.2 Crystallography studies

The results of the X-ray diffraction analysis demonstrated some key differences in the Meldrum's acid core of the *gem*-dialkenyl and *gem*-dialkynyl derivatives. The obtained crystal structures were compared with the diffraction bond angles and dihedral angles data for their respective parent compounds (Tables 4.2.1 and 4.2.2). The disordered forms of compounds **41** and **61** were treated as separate molecules for ease of analysis.

Compound	O1-C2- O3	C2-O3- C4	O3-C4- C5	C4-C5- C6	C5-C6- O1	C6-O1- C2
Meldrum's acid	110.4(7)	120.1(7)	116.3(8)	113.6(8)	116.0(8)	120.2(7)
41a	111.1(1)	120.8(1)	118.5(1)	114.2(1)	117.4(1)	119.2(1)
41b_1	111.0(2)	122.2(3)	119.1(2)	114.3(1)	118.1(2)	120.1(3)
41b_2	105.4(1)	116.5(2)	116.9(1)	114.3(1)	117.5(1)	124.6(2)
58	112.4(1)	123.5(1)	119.2(1)	114.5(1)	117.8(1)	122.7(1)
19	109.5(1)	119.7(8)	116.4(9)	114.2(9)	117.1(9)	120.6(8)
57	111.5(1)	121.8(1)	118.3(1)	114.5(1)	118.1(1)	121.3(1)
18	109.9(8)	119.7(8)	116.4(9)	114.2(9)	117.1(9)	120.6(8)
61a	108.0(6)	121.1(8)	118.6(5)	114.5(2)	117.6(5)	120.8(8)

61b	109.7(1)	122.6(1)	118.0(8)	114.5(2)	118.9(8)	121.2(1)

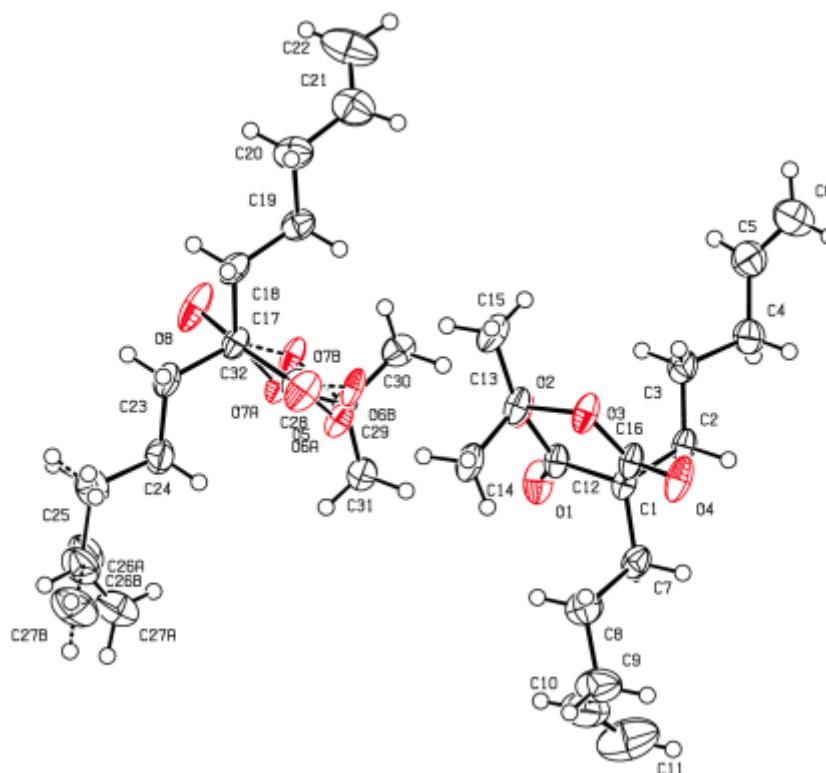
Table 4.2.1. Bond angles of the Meldrum's acid derivative cores. Angles are given in degrees (°) and estimated standard deviations are given in parentheses.

Compound	C2 residue	C5 residue
Meldrum's acid	36.0	28.1
41a	37.8	-13.8
41b_1	34.5	-8.9
41b_2	39.7	-20.7
58	25.9	-12.6
19	39.2	29.3
57	33.6	-11.3
18	37.2	23.0
61a	38.3	-12.2
61b	32.6	-15.1

Table 4.2.2. Dihedral angles of the Meldrum's acid derivative cores. Angles are given in degrees (°).

The Meldrum's acid core of all obtained crystal structures adopted a chair or chair-like conformation, rather than the boat conformation of their respective parent Meldrum's acids as evidenced by the C2 residue sitting above (positive angle) the equatorial plane of the C4, C6, O1 and O3 atoms and the C5 residue sitting below (negative angle). Structures of compounds **41** and **58** are provided as sample figures (Figure 4.2.1, refer to Appendices A1.16-A1.19 for the other relevant crystal structures). There was a dihedral angle range of -20.7° to -8.9° for the C5 residue and a corresponding angle range of 25.9 - 39.7° for the C2 residue for the obtained C5 *gem*-dialkylated crystal structures. Curiously, both the largest and smallest C5 dihedral angle belonged to a disordered form of compound **41**, depending on where the generated internal equatorial plane of the Meldrum's acid core existed. Compound **58** had the smallest dihedral C2 angle and the disordered form of compound **41b_2** had the smallest dihedral C5 angle.

a)



b)

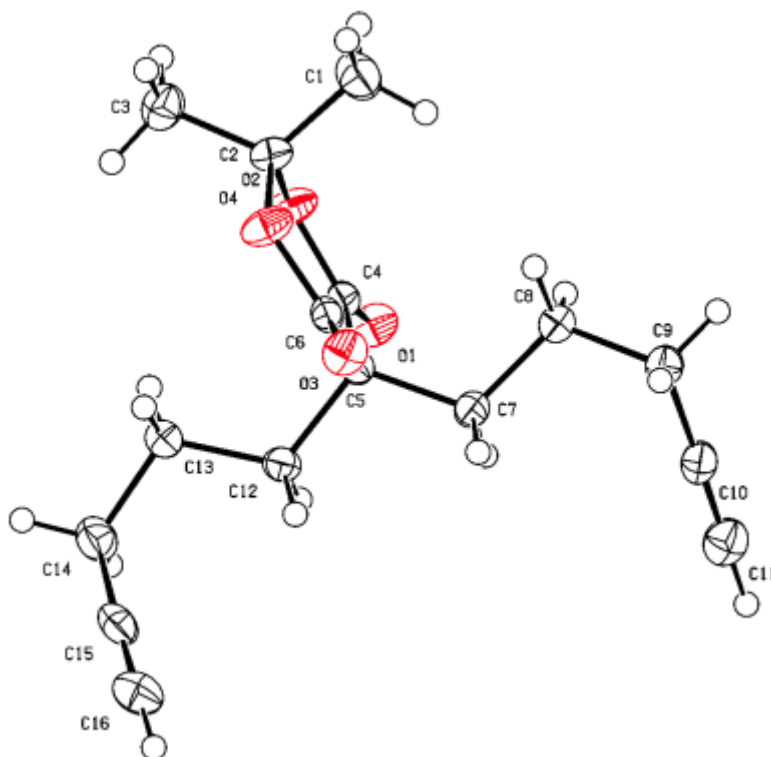


Figure 4.2.1. a) ORTEP Plot derived from single-crystal X-ray crystal structure analysis of compound **41**, b) ORTEP Plot derived from single-crystal X-ray analysis of compound **58**. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

A total of 7 molecules from the obtained 4 crystal structures were analysed for bond lengths (Table 4.2.3), where the disordered Meldrum's acid cores in compounds **41** and **68** were treated as separate molecules within the asymmetric unit for ease of analysis again.

Compound	O1-C2	C2-O3	O3-C4	C4-C5	C5-C6	C6-O1	C4=O	C6=O
Meldrum's acid	1.450(11)	1.440(11)	1.352(13)	1.500(13)	1.499(13)	1.343(12)	1.202(11)	1.196(12)
41a	1.433(18)	1.444(19)	1.352(2)	1.516(2)	1.522(2)	1.358(2)	1.197(2)	1.196(2)

41b_1	1.435(2)	1.451(3)	1.354(3)	1.517(2)	1.521(19)	1.358(3)	1.193(2)	1.193(2)
41b_2	1.570(19)	1.465(2)	1.279(15)	1.517(2)	1.521(19)	1.309(14)	1.193(2)	1.193(2)
58	1.444(2)	1.430(18)	1.344(19)	1.493(2)	1.494(2)	1.338(19)	1.200(19)	1.193(19)
19	1.441(15)	1.443(14)	1.354(16)	1.506(17)	1.500(18)	1.350(16)	1.202(16)	1.199(17)
57	1.519(2)	1.523(2)	1.350(19)	1.519(2)	1.539(2)	1.345(2)	1.198(19)	1.195(19)
18	1.361(13)	1.453(11)	1.342(19)	1.503(15)	1.502(14)	1.440(2)	1.196(13)	1.205(13)
61a	1.447(8)	1.473(6)	1.345(7)	1.513(3)	1.512(3)	1.364(8)	1.192(2)	1.191(2)
61b	1.452(7)	1.483(10)	1.348(10)	1.513(3)	1.512(3)	1.320(9)	1.192(2)	1.191(2)

Table 4.2.3. Bond lengths of Meldrum's acid cores and *gem*-dialkylated Meldrum's acid cores. All lengths are given in Å and estimated standard deviations are given in parentheses.

There was a lengthening of the C4-C5 and C5-C6 bonds in all compounds, except for compound **58**. All carbonyl bonds were shortened across the obtained crystal structures. The changes in length of the O1-C2 and C2-O3 bonds varied among the analysed molecules. The molecule of compound **41** with no disorder had elongation of the C2-O3 bond, however the first disordered form listed in Figure 4.2.2 had elongation of the O1-C2 bond. The second disordered form had elongation of both bonds. The O1-C2 and C2-O3 bonds were both shortened in compounds **57** and **58**, whilst they were lengthened in compound **61**. Curiously, the O1-C6 bond tended to be shorter when the C5 alkyl chains contained an alkyne. The second disordered form of compound **41** also had a significantly shorter O1-C6 bond length when compared to

its other forms and parent acid. Thus, there was a trend for the carbonyl bonds shortening and perhaps a trend for the C4-C5 and C5-C6 bond being lengthened and consequently weakened after the twofold C-C alkylation occurred. There was also perhaps a trend for the O1-C6 to be shortened as a consequence of the twofold C-C alkylation.

These compounds also had the direct effects of the substituted C5 residues to consider. The obtained crystal structures depicted a methylene hydrogen and the respective π -bond of the alkyl chains interacting in an intramolecular fashion in all compounds analysed with a distance range of 2.63-2.77 Å (Figure 4.2.3). Compounds **57** and **61** both had their respective alkyl chains partially eclipsing each other in their structures but this was absent in compound **58**. The difference in conformation arises from the side of the carbon the respective hydrogen atom occupies, with compounds **57** and **61** both being attracted to the hydrogen on the same side and compound **58** being attracted to the opposite hydrogen. There was also a methylene hydrogen interacting with an alkyl chain sp^2 -hybridised carbon in compound **41**. We expected to see evidence of π -stacking interactions with compound **57** but this appeared to be absent from the analysed crystal structure, however this does not rule out the existence of such interactions in solution. There were some intermolecular CH- π interactions between an alkyne carbon and a hydrogen from an adamantyl group on a neighbouring molecule. It was also found the terminal methyl group in the chain interacts with a neighbouring alkyne. The alkyne groups on compound **58** behaved closer to our expectations, as we observed an intermolecular hydrogen-bond between the terminal hydrogen and carbonyl oxygen of a neighbouring molecule. There was

also an electrostatic interaction between the terminal hydrogen of the alkyne and the π -bond of a neighbouring molecule. There was also an intermolecular electrostatic interaction between the alkyne and the alkyl chain of another neighbouring molecule.

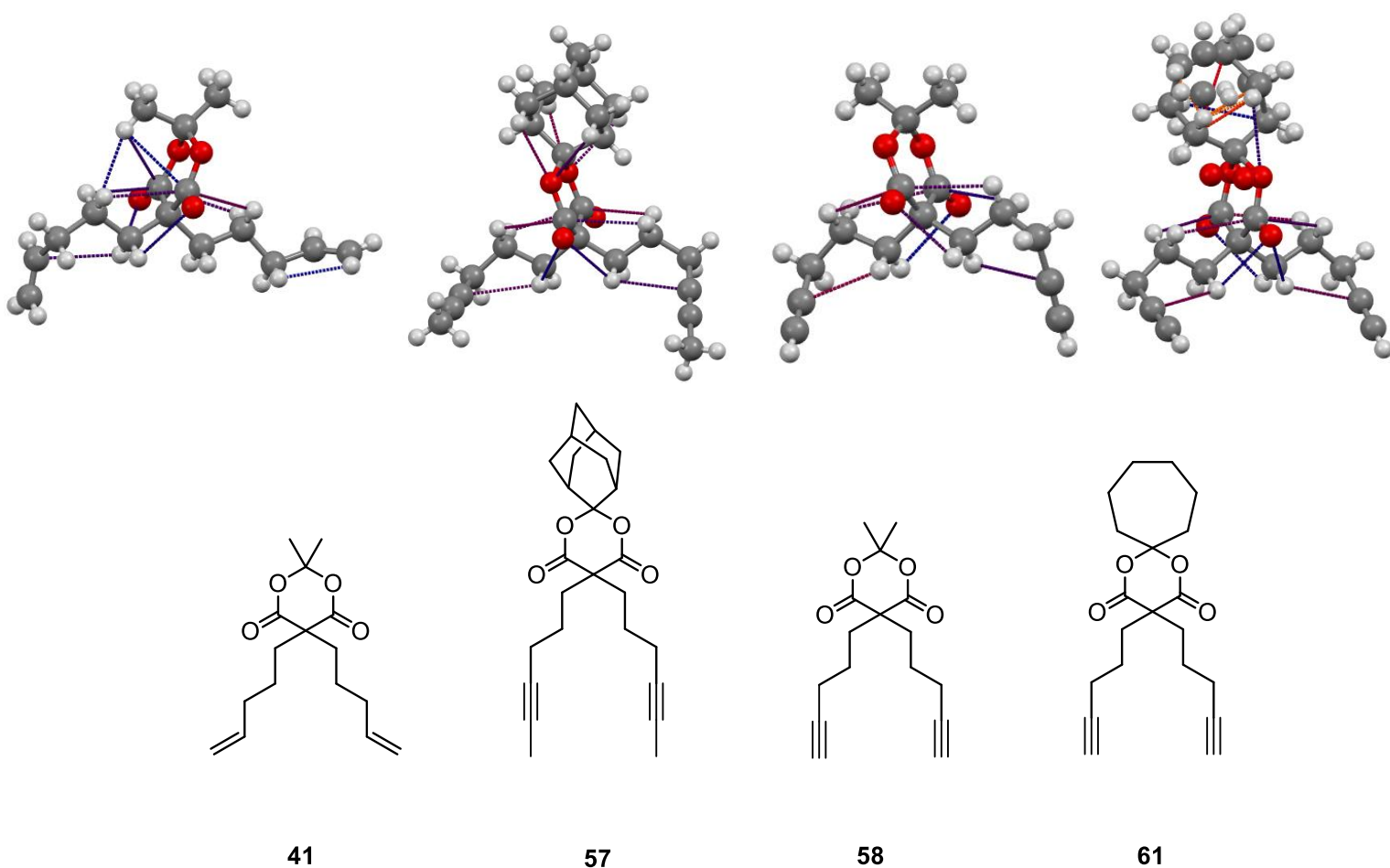


Figure 4.2.3. Obtained single-crystal X-ray crystal structures of compounds **41**, **57**, **58** and **61** depicting the three-dimensional structures and bond contacts of the aliphatic C5 residues and their corresponding chemical structures.

4.3 Thermogravimetric Analysis of derivatives (Aim 5)

With the synthesised alkylated Meldrum's acid derivatives to hand, the thermolytic behaviour of the compounds was analysed and TGA was once again the analytical instrument of choice. We postulated that the possible constraining effect we observed with the cyclohexanone and adamantanone Meldrum's acids in the parent aliphatic Meldrum's acid data set would also be observed in this data set. The TGA traces of the alkenylated Meldrum's acids **41-45** are shown in Figure 4.3.1 (refer to Appendices A3.19-A3.33 for the individual TGA traces for all synthesised C5 *gem*-dialkenylated and *gem*-dialkynylated Meldrum's acids).

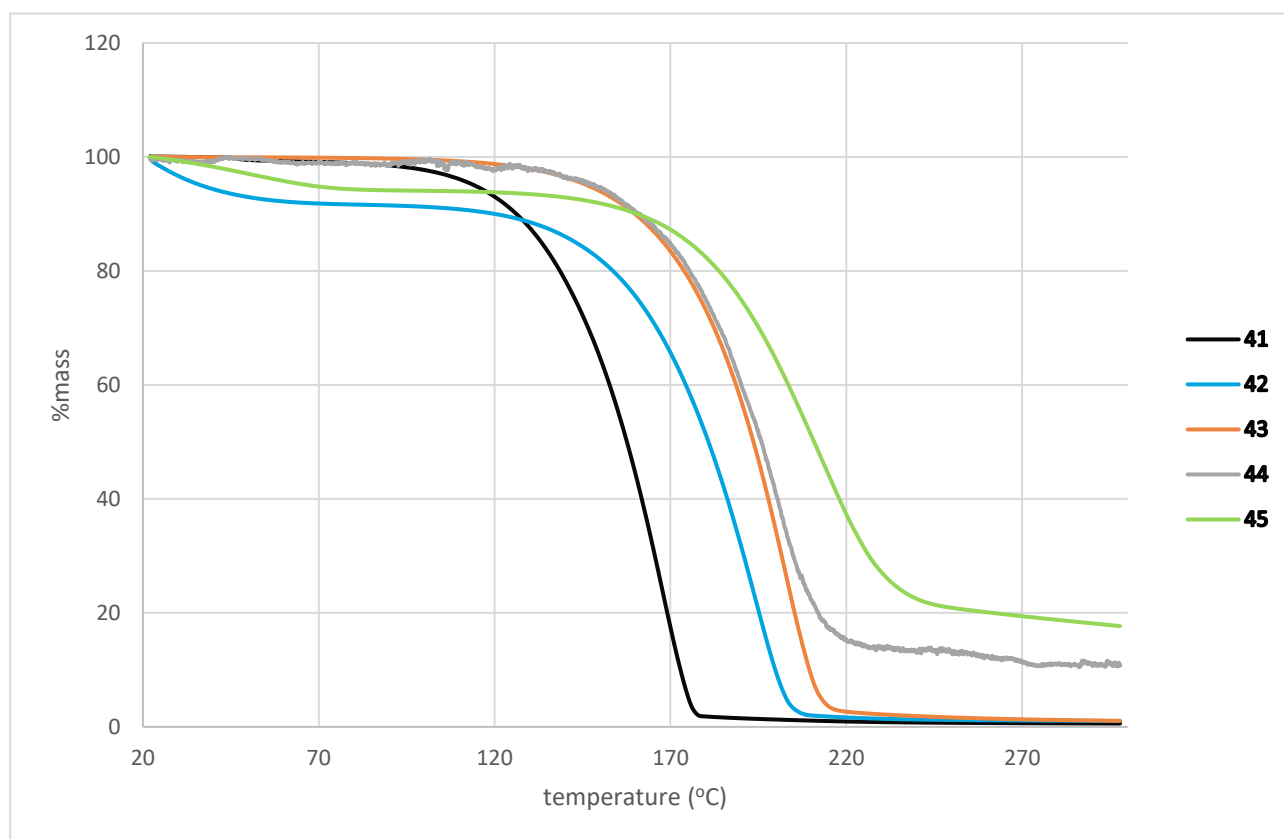


Figure 4.3.1. Thermogravimetric traces for *gem*-dialkenyl compounds **41-45**, depicted as change in mass percent vs temperature (°C).

There was found to be a reasonable spread of thermolytic profiles from the five targets analysed. The inflection point temperatures obtained with these compounds were substantially greater than that of their parent systems. Compound **41** had the lowest inflection point of approximately 158 °C and compound **45** had the highest of approximately 210 °C, which was to be expected based off the TGA results of the parent acids. Of note was compound **42**, which had the second lowest inflection point of approximately 185 °C, when its parent compound **16** had the second highest of its respective data set. This result was unexpected and suggests that any possible C2 constraining effect present in these compounds is overridden by the presence of C5 substituents. The TGA results of compounds **53-57** also demonstrated the effect the C5 substituents exert over the inflection point temperature (Figure 4.3.2).

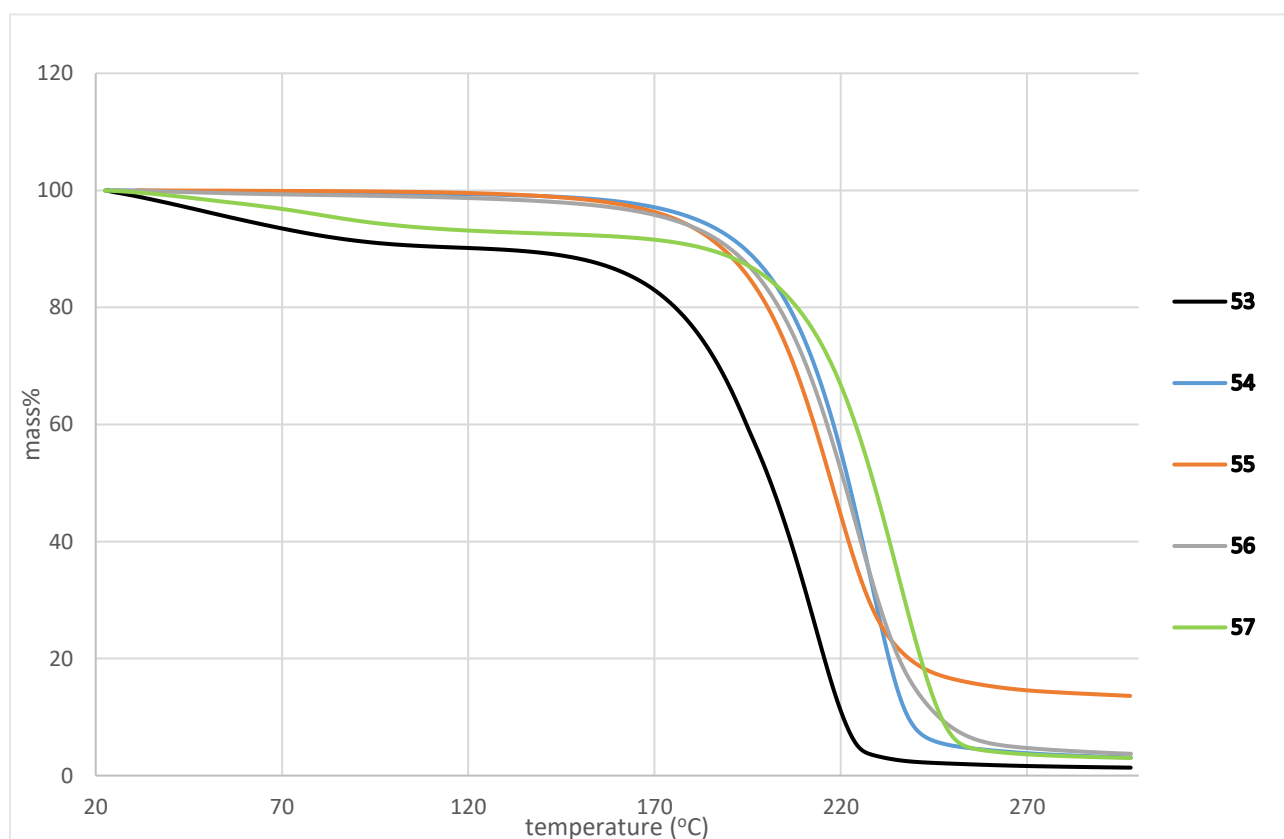


Figure 4.3.2. Thermogravimetric traces for *gem*-dialkynyl compounds **53-57**, depicted as change in mass percent vs temperature (°C).

Compounds **53-57** had the highest inflection points overall. The lowest inflection point of the data set was compound **53** with an inflection point of approximately 205 °C, which was 45 °C higher than that of its analogous compound, compound **41**. Compound **57** had the highest inflection point of approximately 233 °C and the other three inflection points of compounds **54-56** were clustered around the same value. The dramatic increase in the inflection point temperatures compared to the *gem*-dialkenyl Meldrum's acid series suggests there may be another electronic interaction operating alongside that arising from the presence of the C5 residues. This possible other effect was also evident in the TGA data set of compounds **58-62** (Figure 4.3.3).

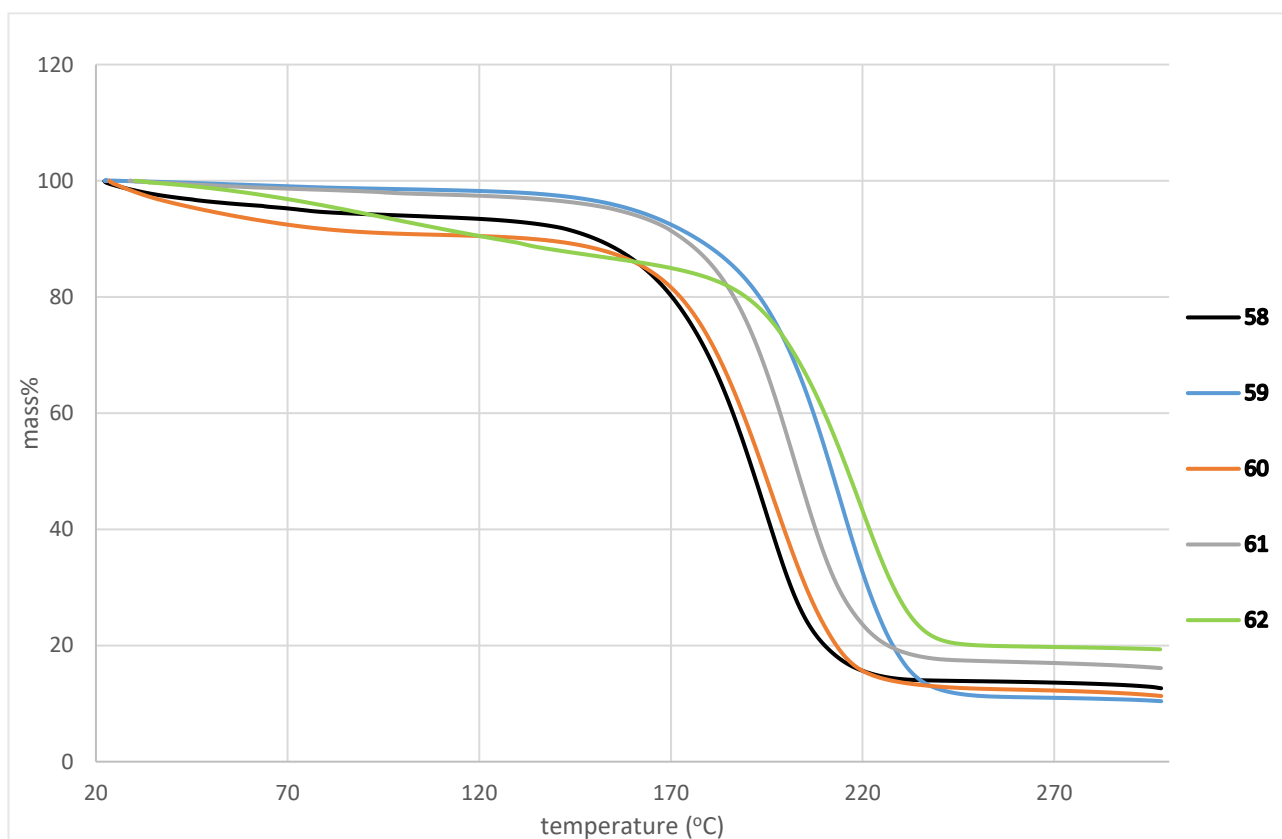


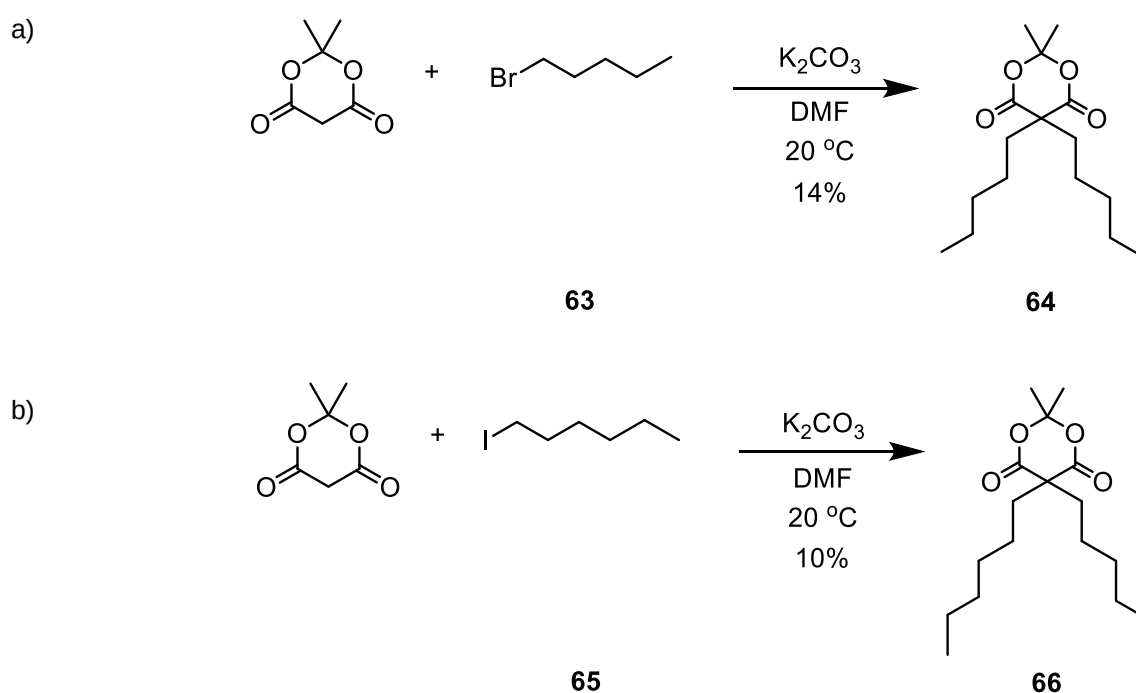
Figure 4.3.3. Thermogravimetric profiles for *gem*-dialkynyl compounds **58-62**, depicted as change in mass percent vs temperature (°C).

The results from compounds **58-62** are similar to the TGA results from compounds **53-57**, as the inflection points are much greater than the parent Meldrum's acids. Once again, compound **58** had the lowest inflection point of approximately 191 °C and compound **62** had the highest of approximately 217 °C. The spread of inflection points for the remaining three compounds were more even than with the previous samples. Overall, the most obvious result from these three TGA data sets is inflection points of the synthesised *gem*-dialkylated Meldrum's acids were above the 170 °C sucrose caramelisation¹ benchmark for all samples but one. Therefore, these *gem*-dialkylated Meldrum's acid analogues are not useful in the synthesis of SMEs. Despite the lack of success with the *gem*-dialkylated Meldrum's acids, we felt there remained a unique opportunity to further investigate the fundamental chemical reactivity of the prepared *gem*-dialkylated Meldrum's acids and related molecules. The TGA results demonstrated the effect the C5 substituents exerted on the temperatures required for thermolysis. We suspected this observed effect on the thermolysis temperature may be electronic in nature, as the obtained X-ray diffraction data suggested the presence of intramolecular π -interactions. Thus, we decided to investigate any potential inter- or intramolecular forces in the obtained Meldrum's acid derivatives through a further TGA study.

4.4 Effects of hydrogenated C5 groups

To test the presence of possible inter- and intramolecular forces in the synthesised *gem*-dialkylated Meldrum's acids, compounds **64** and **66** with saturated C5 substituents were prepared through the standard alkylation protocol used previously (Scheme 4.4.1).² The yields of both compounds were low as a result from obtaining

mixtures containing compounds **64** and **66**. Both compounds were purified through flash chromatography, although small quantities of what appeared to be C-O mono-alkylated product remained. As with the previous synthesised Meldrum's acids, the new two compounds had their thermolytic behaviour analysed by TGA and their results compared to Meldrum's acid and its other *gem*-dialkylated derivatives (Figure 4.4.1, refer to Appendices A3.34 and A3.35 for the individual TGA traces of compounds **64** and **66**).



Schemes 4.4.1. a) Synthesis of compound **64** through twofold alkylation of Meldrum's acid with compound **63**, b) Synthesis of compound **66** through twofold alkylation of Meldrum's acid with compound **65**.

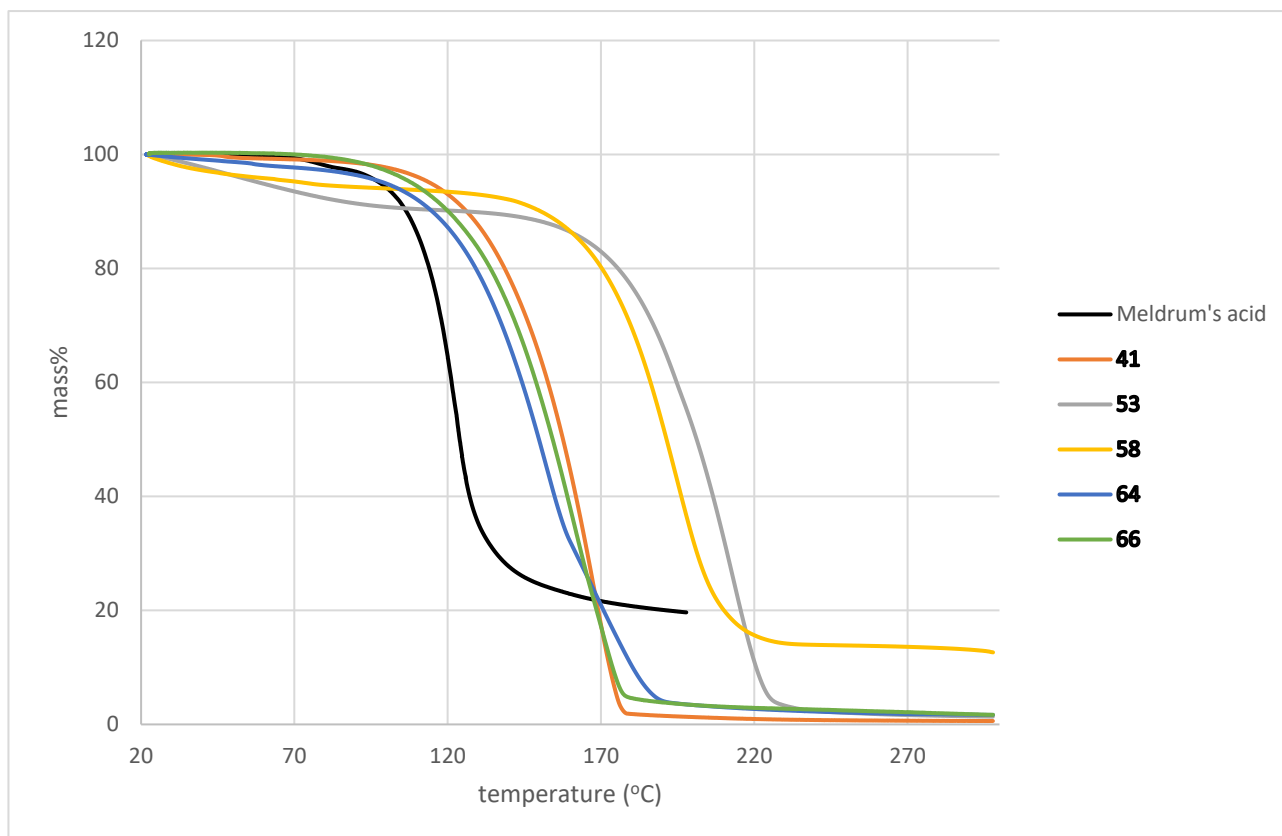


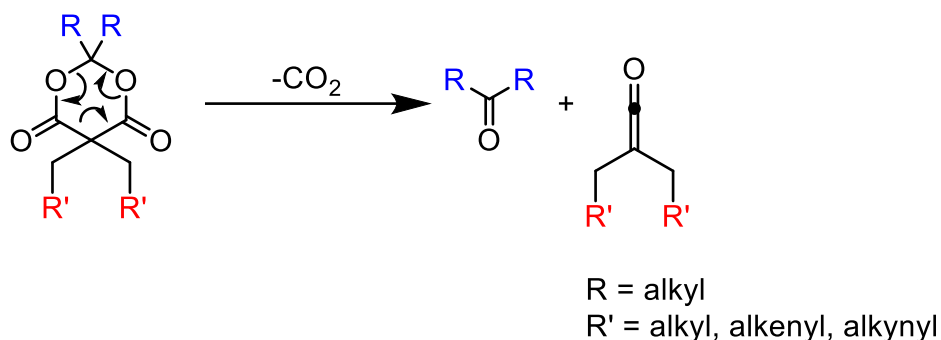
Figure 4.4.1. Thermolysis traces of Meldrum's acid and its C5 alkylated/alkenylated/alkynylated derivatives, depicted as change in mass percent vs temperature (°C).

There was less than 3 °C difference in inflection point temperatures between compounds **41**, **64** and **66**. Compounds **53** and **58** still had the two highest inflection points overall whilst having a comparable chain length to the other screened compounds, which suggests the chain length alone does not have a strong influence on inflection point temperature. The presence of the alkene also did not exert much of an effect on the inflection point in comparison to compounds **64** and **66**, which suggests the main effect in the observed TGA data for these compounds is from the presence of the alkyne directly. The observed inflection point temperature increase in compounds **53** and **58** is possibly from intermolecular π -interactions when the obtained X-ray diffraction data of compounds **41** and **58** is considered. The possible short contacts as visualised by Mercury³ suggests compound **41** only experiences

hydrogen-bonding if just the intermolecular interactions are considered, whereas compound **58** has intermolecular hydrogen-bonding and π -hydrogen interactions. Therefore, a combination of both intermolecular π -interactions and hydrogen bonding is possibly why we observed the drastic increase in inflection point temperature between the compounds **41** and **58**. A crystal of compound **53** could not be grown to verify our predictions, but we can reasonably presume there are intermolecular π -interactions of a similar nature operating for that compound too.

4.5 Thermolysis mechanism suppositions

A mechanistic rationale for the substantial difference in inflection point temperatures between the parent and the *gem*-dialkylated Meldrum's acids can be supposed from the obtained data. Having the *gem*-dialkylation means there are no C5 protons on the molecules and no way for a vinyl ketene to form, so there can be no keto-enol tautomerism pathway for compounds **41-45** and **53-62**. The remaining possible mechanisms are the concerted single-step thermolysis and the two charged intermediate fragmentation pathways.⁴ Our computational collaborators investigated whether there was the possibility of a malonic anhydride species being formed in the thermolytic reaction pathway,⁵ based on Wentrup and co-workers' successful isolation of a malonic anhydride from the thermolysis of a Meldrum's acid derivative.⁶ A rational thermolytic pathway to a malonic anhydride for our *gem*-dialkylated Meldrum's acids could not be located so we assume such a species cannot be formed. Of the last two thermolysis pathways, the concerted single-step pathway seems to be the most likely (Scheme 4.5.1).



Scheme 4.5.1. Concerted single-step thermolysis pathway of *gem*-dialkylated Meldrum's acids (R = alkyl; R' = alkyl, alkenyl, alkynyl).

4.6 Effects of C5 residue on the Meldrum's acid and its thermolytic pathways

Having no apparent change in mechanism does raise a non-trivial point with respect to the temperatures of thermolysis. The presence of the C5 residues increased the inflection point temperatures between the parent and *gem*-dialkylated Meldrum's acids and is regardless of any possible inter- or intramolecular forces. The presence of intermolecular π -interactions can then further increase the temperature of thermolysis. A main outcome from the work detailed in this thesis is we now have a profile of the effects the C2 and C5 residues exert on the thermolytic pathway of Meldrum's acid (Figure 4.6.1), where both residues affect the temperature of thermolysis. The C5 residue takes precedence and controls the mechanism of the thermolytic pathway when a group has been substituted on the residue. An absence of C5 substitution allows the C2 residue to dictate the mechanism of thermolysis.

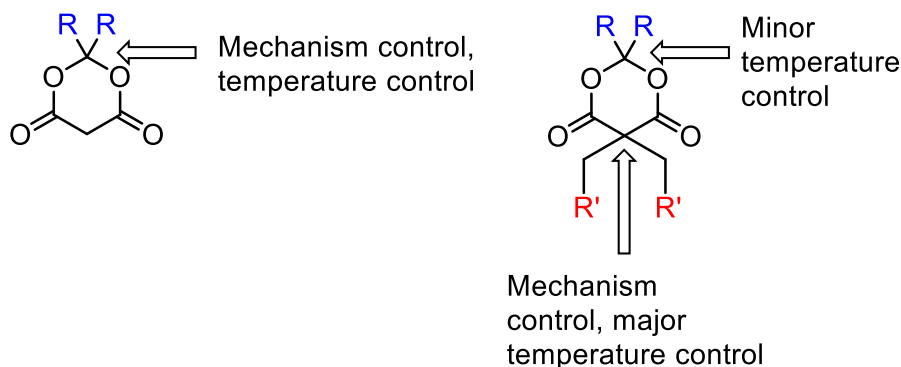


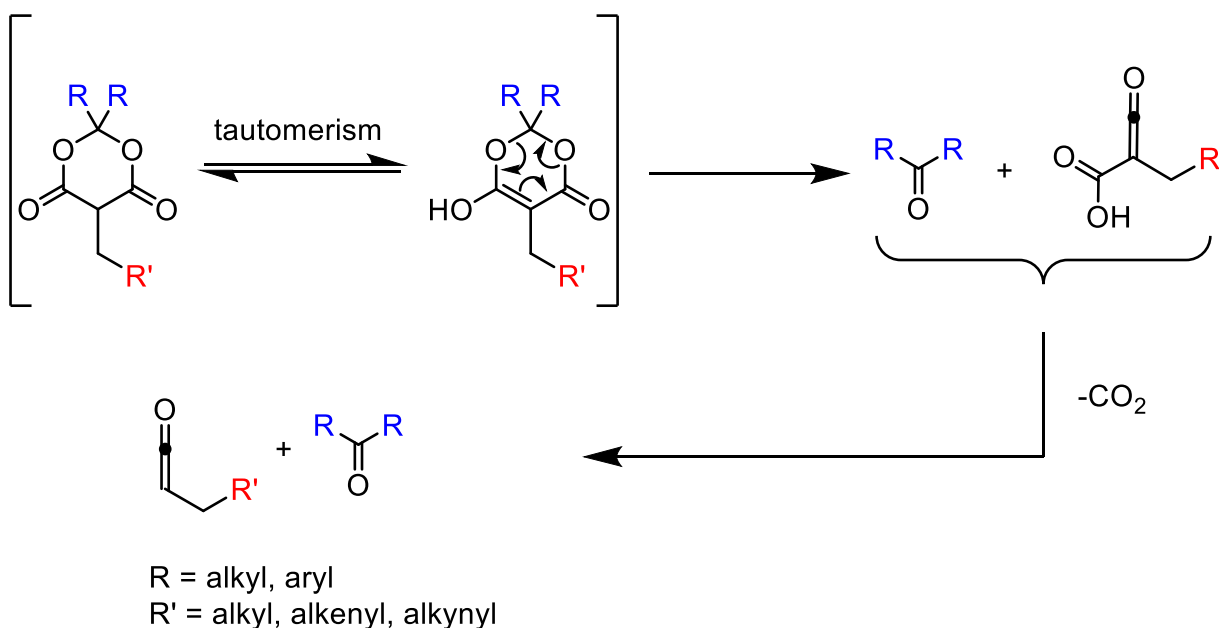
Figure 4.6.1. Effects of C2 and C5 residues on Meldrum's acid thermolytic pathways
(R = alkyl, aryl; R' = alkyl, alkenyl, alkynyl).

4.7 Conclusions

We extended our investigations of C2 substituted Meldrum's acids by *gem*-dialkylation, producing a library of dialkenyl and dialkynyl Meldrum's acids, of which four were obtained as crystalline solids. We found the presence of intermolecular π -stacking for the dialkynyl Meldrum's acids and there was a general tendency for the bond lengths of the Meldrum's acid core to be elongated around the C5 residue and shortened around the C2 residue, upon analysis of the crystallographic data. We also found all obtained crystal structures showed the Meldrum's acid core adopting a chair conformation, instead of the boat conformation of the parent compounds. The *gem*-dialkylated library of Meldrum's acids were subjected to a TGA study and we found the new series had substantially higher inflection points in comparison to their parent compounds. Thus, our results indicated that the C5 residue takes precedence for mechanism and temperature control when there is substitution at that residue. The C2 residue takes precedence when there is no C5 substitution.

4.7.1 Future studies

Whilst the *gem*-dialkylated Meldrum's acids we investigated were unsuitable for using as a ketene source for producing SMEs, it may still be possible for Meldrum's acids to be used as ketene source for esterifying sucrose. We did not investigate mono-alkylated Meldrum's acids for their thermolytic pathways but that would be a worthy future study. A mono-alkylated Meldrum's acid would have the capacity to undergo a keto-enol tautomerism, thus having the asynchronous hetero-retro-Diels Alder thermolysis as a possible pathway (Scheme 4.7.1.1). Based on our TGA results, we would expect the temperatures of thermolysis of a mono-alkylated Meldrum's acid series to be higher than the parent Meldrum's acids, although how much so remains to be investigated.



Scheme 4.7.1.1. Proposed preferred thermolytic pathway of mono-alkylated Meldrum's acids
(R = alkyl, aryl; R' = alkyl, alkenyl, alkynyl).

Chapter Four references

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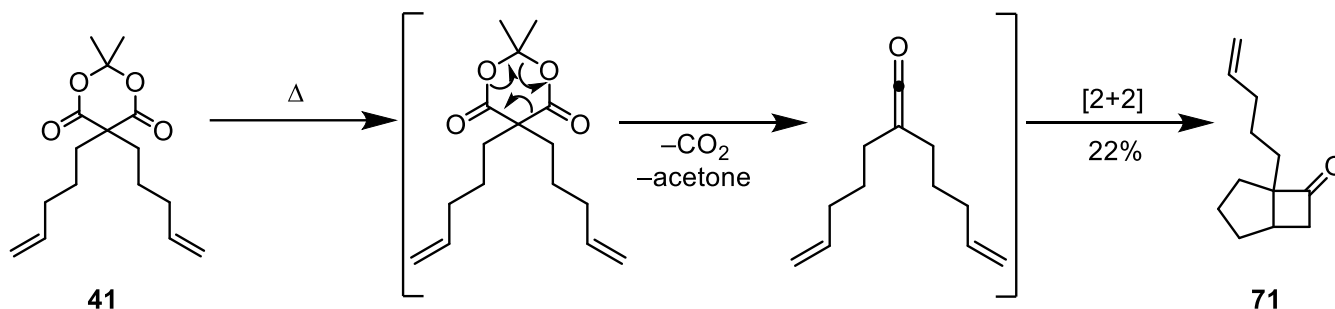
Chapter Five: Proving the Intermediacy of Ketenes in the Thermolytic Pathway

(Aim 6)

5.1 Experimental observation of dialkenyl Meldrum's Acid

Upon performing a melting point analysis on the crystalline compound **41** (see Scheme 5.1.1), bubbling in the capillary immediately was observed after melting. This bubbling was allowed to continue from the temperature slowly ramping in the melting point instrument. The melted compound was slowly cooled back to ambient temperature once the bubbling had ceased. It was observed that compound did not resolidify as it reached ambient temperature, remaining as an oil. The contents of the capillary were analysed by ^1H NMR which showed complete conversion to an entirely different compound. The obtained compound was too small in quantity to be properly characterised, so a larger quantity of compound **41** was placed into a 5 mL round-bottom flask and melted with a heat gun. The sample also began bubbling immediately after melting and was allowed to cool back to ambient temperature once the bubbling had ceased. The melting step afforded an oily mixture, so purification through flash column chromatography was undertaken. The major product was isolated as compound **71** and was found to have spectra matching that of a cyclobutanone known to literature.¹ There is realistically only one way for the cyclobutanone **71** to have been formed through the thermolysis of compound **41** and that is through a ketene intermediate (Scheme 5.1.1). The bubbling observed from melting compound **41** was most likely the release of gaseous carbon dioxide and acetone during thermolysis. Producing cyclobutanone **71** in this manner opens a new avenue of using ketenes to access small to medium-sized ring structures in a potentially smaller number of steps than they may otherwise require using existing methodology. For example, Snider and

co-workers¹ produced cyclobutanone **71** from their own synthesis in three steps whereas this work synthesised cyclobutanone **71** in two steps.



Scheme 5.1.1. Conversion of compound **41** to compound **71** via a ketene intermediate.

5.2 GC-MS studies and follow-up reactions

Cyclobutanone **71** has some distinctive fragmentation patterns when analysed through EI low-resolution GC-MS (Figure 5.2.1a). There were two main peaks in the sample trace and they eluted at a retention time of 7.5-8.0 min and 10.2-10.3 min respectively. The first peak showed a weak parent molecular ion of 178 m/z , as well as strong peaks of 136 and 121 m/z . The second peak in the trace had a very small peak of 176 m/z and two larger peaks of 154 and 136 m/z , which is likely to be an isomer of cyclobutanone **71** and the mass fragment of 176 m/z most likely arises from dehydrogenation of the sample. The peaks of 136 and 121 mass units can also be rationalised (Scheme 5.2.1). In light of the obtained retention time and mass fragment data, we decided to examine compound **41** and its analogous compounds **42-45** through GC-MS analysis for any mass fragments corresponding to cyclobutanone **71** (refer to Appendices A4.1-A4.15). It was found the same trace retention times for cyclobutanone **71** were present in the low-resolution GC-MS data for *gem*-dialkenyl Meldrum's acid compounds **41**, **43** and **45** (sample spectra as Figure 5.2.2). We also located mass peaks corresponding to the respective ketone C2 residues for compounds **42-45**, indicating thermolysis had likely occurred. Compounds **42** and **44**

had a retention time of 12.0-12.7 min where the mass peaks of 176, 154 and 136 m/z could be located. The exact mass of the Meldrum's acid derivatives could not be detected through GC-MS analyses for all the screened samples. Therefore, we had demonstrated that ketenes or ketene products can be produced through the Meldrum's acid compound being heated in the oven of the GC-MS instrument.

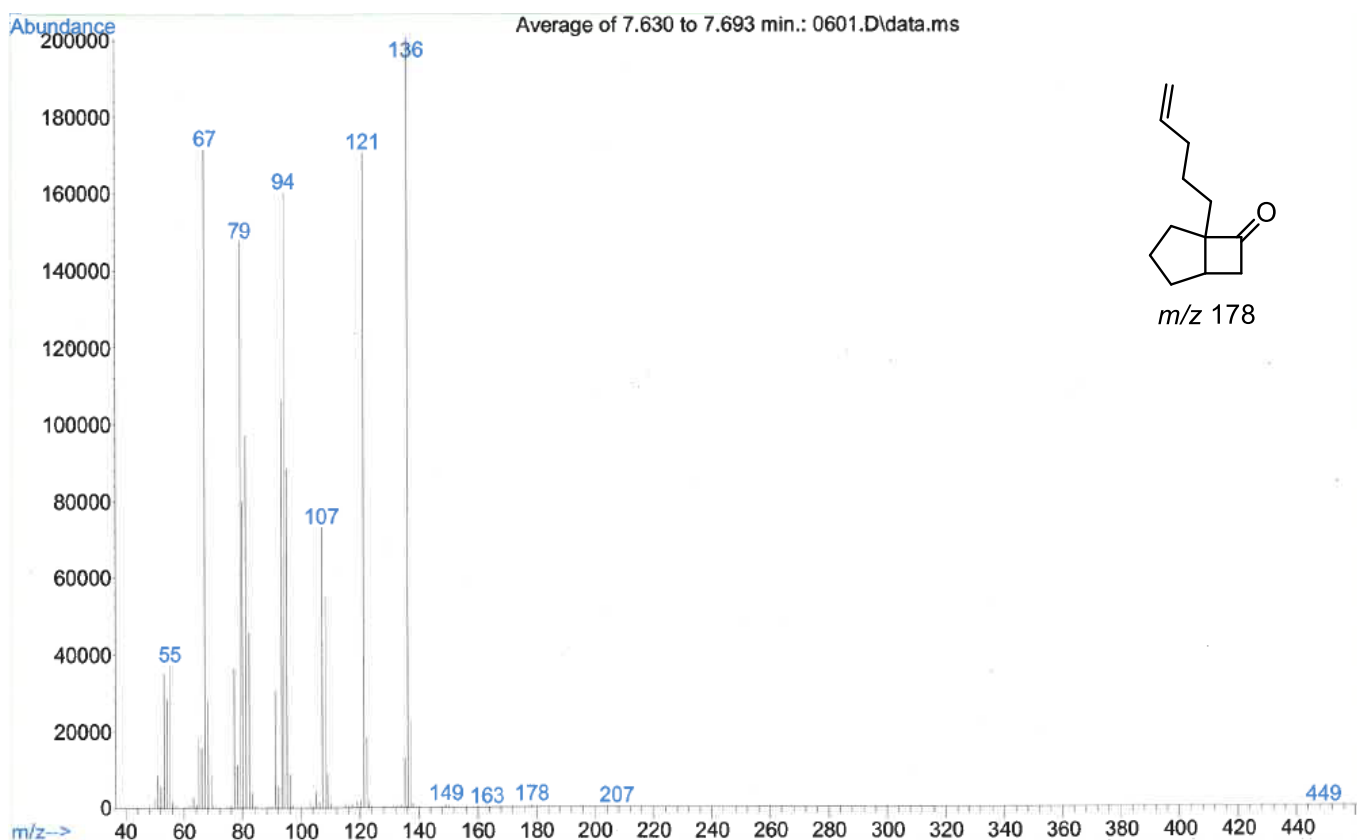
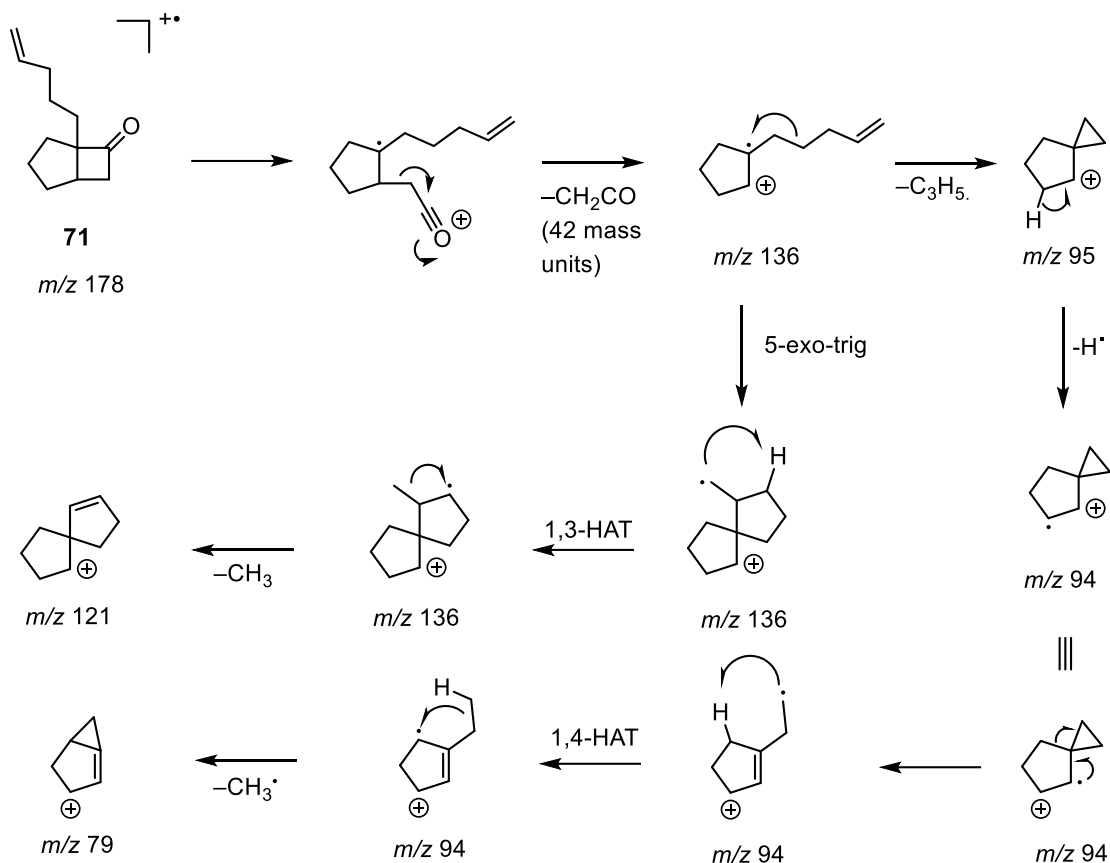
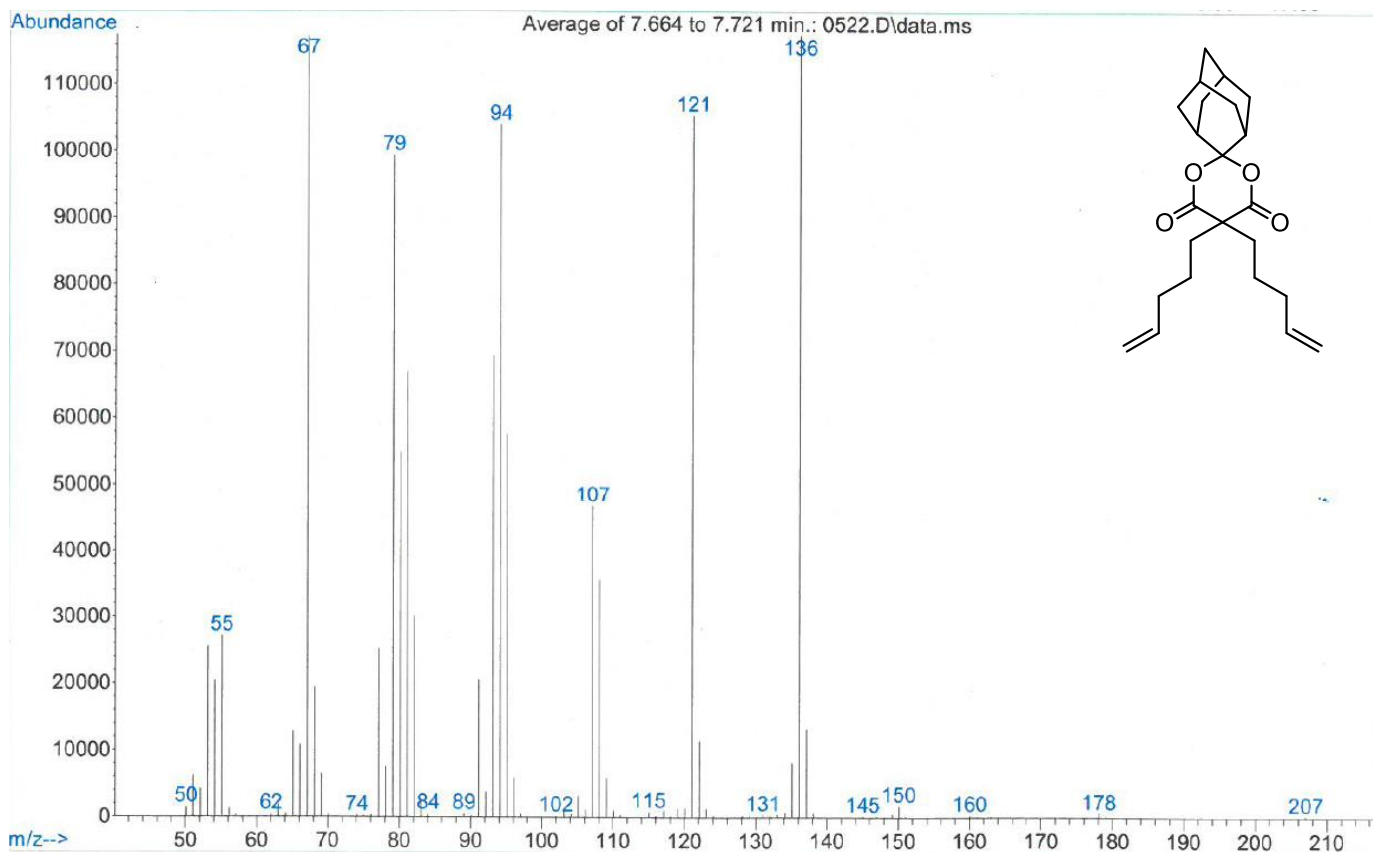


Figure 5.2.1. Low resolution GC-MS data for cyclobutanone 71.



Scheme 5.2.1. Proposed GC-MS fragments for cyclobutanone **71**.



We were intrigued by our observation of ketene products likely being formed during GC-MS analyses and decided to further investigate the remaining dialkynyl Meldrum's acids for possible common mass fragment peaks (see Figure 5.2.3 for sample spectra). Compounds **54-57** produced a group of common mass peaks, with a weak peak of 201 m/z and strong peaks of 131 and 91 m/z and a common retention time of 9.0-9.3 min. Compound **53** had mass fragment peaks of 201, 131 and 91 m/z , although those peaks were associated with a retention time of 11.8-12.3 min. The remaining compounds **58-62** had common peaks of 173, 131 and 117 m/z , although 131 m/z was not present for compound **62**. The relevant first retention time occurred regularly between 7.0-7.3 min, whilst there was a varying second retention time that occurred between 10.2-14.8 min across compounds **58-62**. We suspected the respective 201 and 173 m/z belonged to new ketene products, although access to these products in a manner which could prove their production was required. Therefore, we sought to investigate more rigorous methods of accessing cyclobutanone **71** using compound **41**, and subsequently applying the best method to access the other potential ketene products. A variety of techniques were trialled, such as heating compound **41** to reflux in toluene, mesitylene or diphenyl ether, heating in a kugelrohr apparatus and irradiation of a DCM solution of compound **41** for 1 h. None were successful. A new and reliable way to access ketenes as a usable synthetic intermediate was clearly required.

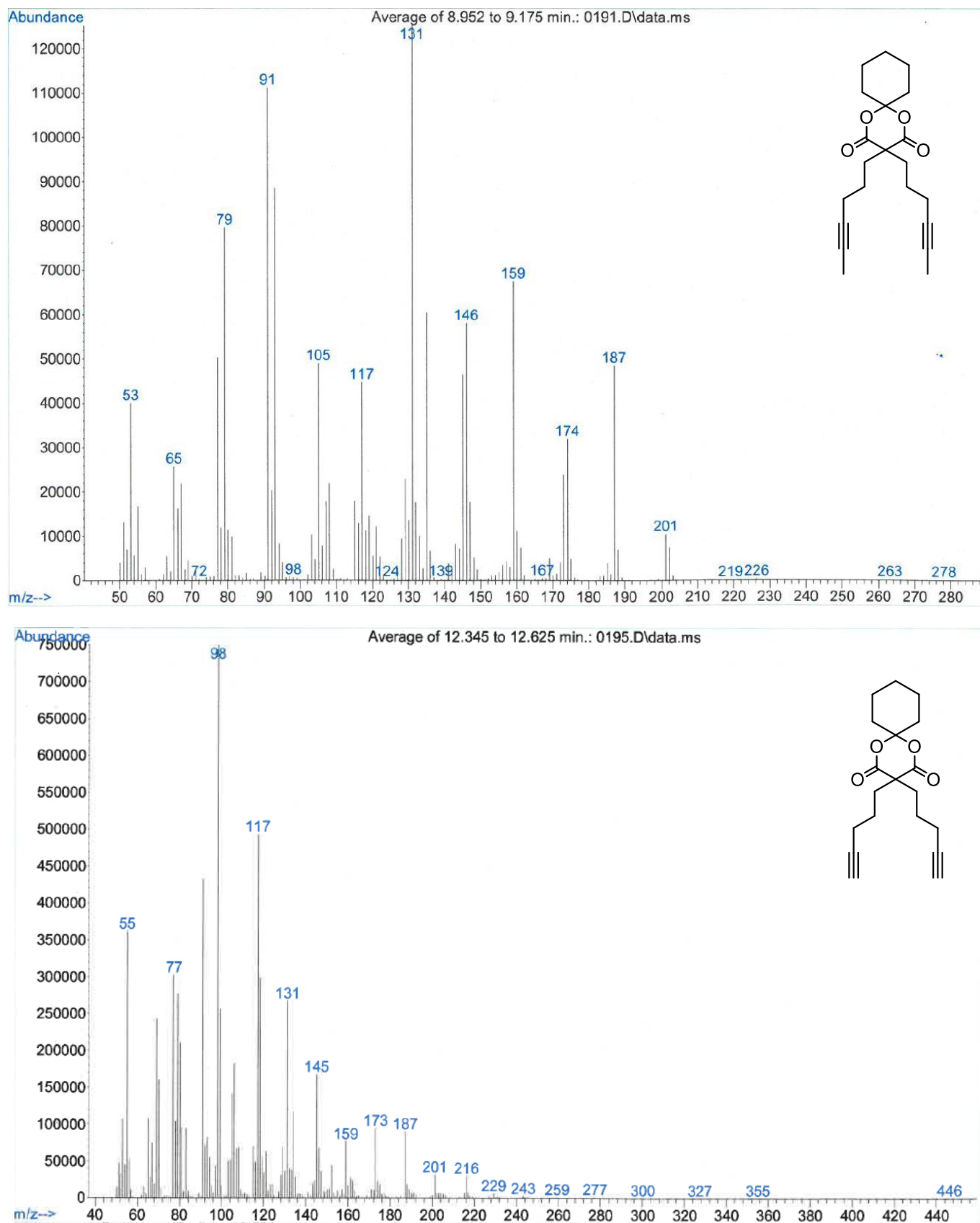


Figure 5.2.3. a) Sample low resolution GC-MS spectra of compound **54**, b) sample low resolution GC-MS spectra of compound **59**.

5.3 Flow reactor study for accessing ketenes

We tried to replicate the thermolysis of compound **41** under flow conditions. A variety of temperatures and reaction durations were screened, including up to temperatures the cycloreversion had occurred at in our TGA studies. Compound **41** was prepared as a 0.3 M solution in toluene, the obtained reaction aliquots were transferred to round bottom flasks, concentrated under reduced pressures and the residues were analysed through ^1H NMR experiments. The reaction conditions and observations of the experiments are listed in Table 5.3.1.

Solvent	Temperature (°C)	Duration (min)	Observations^a
Toluene	150	7	No change
Toluene	160	7	No change
Toluene	170	7	No change
Toluene	180	7	No change
Toluene	190	7	No change
Toluene	200	7	No change
Toluene	210	7	No change
Toluene	220	7	No change
Toluene	230	7	Loss of alkene signals at 5.71 and 5.01-4.95 ppm

Toluene	240	7	Gained signal at 6.64 ppm
Toluene	250	7	Signal to noise ratio too small to be informative
Toluene	230	10	Gained signals at 3.75 and 3.62 ppm
Toluene	230	15	Loss of signals at 3.75 and 3.62 ppm
Toluene	240	10	No change
Toluene	240	15	Signal to noise ratio too small to be informative
Toluene ^b	225	7	Many new signals across the spectral width.
n-Heptane ^b	225	7	New signals at 4.04-3.99, 3.77-3.73 and 3.62-3.57 ppm

Table 5.3.1. Reaction conditions for flow reactor studies. ^a Analysis through ¹H NMR experiments conducted on a 400 MHz instrument. ^b Concentrated aliquot obtained.

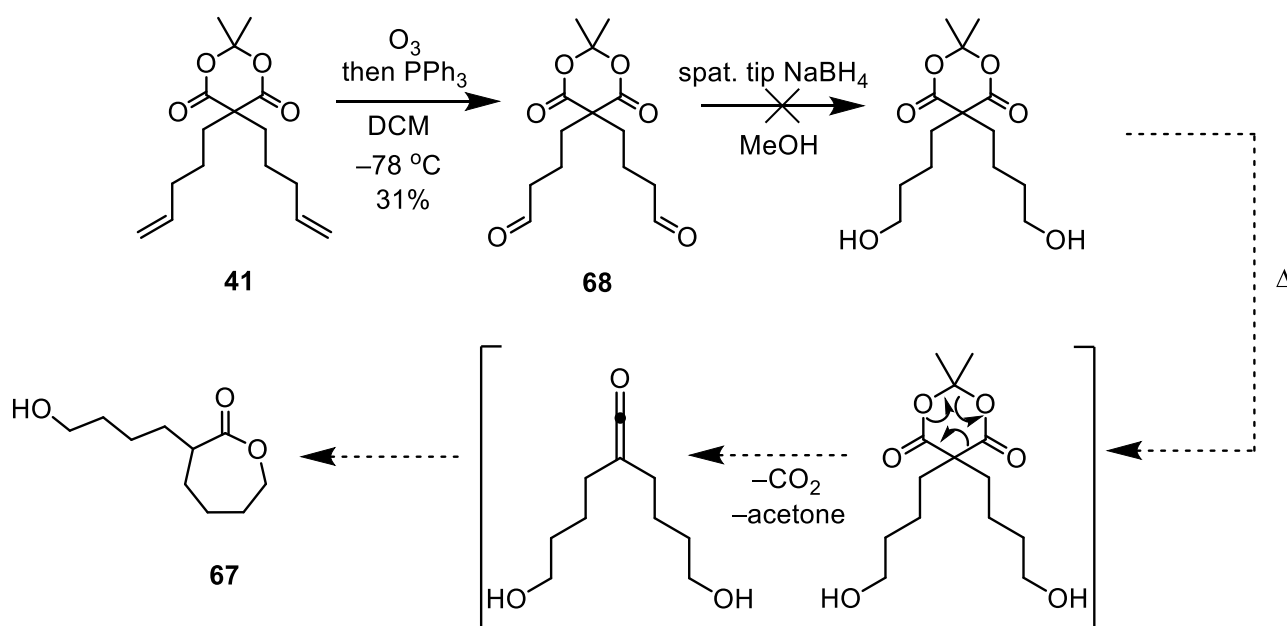
We were unable to prepare cyclobutanone **71** in this manner, even at temperatures we had previously determined the cycloreversion occurred at. We also determined that the toluene was decomposing to the tolyl radical and subsequently reacting with compound **41** when the reaction was performed on a concentrated sample at 225 °C,

as evidenced by the presence of aromatic signals that belonged to neither compound **41** nor toluene. We performed a single experiment in n-heptane as a comparison to our previous experiments and found similar signals to our other experiments, with the absence of the aromatic signals. We noted that there were consistent changes in compound **41** for the aliquots run at 225 °C or 230 °C, which is approximately the temperature range we had previously determined the cycloreversion had occurred at when melting crystalline compound **41**. We also noted some new signals consistently form at 3.75 and 3.62 ppm when we performed the thermolysis run at 230 °C and held the reaction for longer durations or when using concentrated mother solutions of compound **41**, perhaps suggesting the presence of an alkylated heteroatom or multiple alkylated heteroatoms in the obtained aliquots. We also noted the appearance of a new signal at 6.64 ppm after performing the reaction at 240 °C and using the shorter reaction duration of 7 min. This signal was not replicated under any of the other reaction conditions, so we assumed the associated product was a contaminant from a radical side-reaction. Overall, we determined that the flow reactor is perhaps not an ideal instrument to enact cycloreversions through unless the required temperature for thermolysis could be lowered.

5.4 Accessing other kinds of ketene products

We decided to investigate which other ketene products we could access from our library of Meldrum's acids and thought it may be possible to produce lactone **67** from a reaction sequence starting with compound **41** (Scheme 5.4.1). We subjected compound **41** to an ozonolysis reaction and obtained dialdehyde **68** as a clear oil in a moderate yield. Dialdehyde **68** was prone to decomposition so clean mass

spectrometry data of the compound could not be obtained, although it was sufficiently stable to have other characterisations performed on it and could be reacted further if the compound was analysed or used within 0.5 h following isolation. The subsequent step was a reduction of dialdehyde **68** to the corresponding diol compound. The previous experimentations with reduction protocols and Meldrum's acid compounds led us to be cautious with this reaction. The reduction reaction was conducted in an ice-water bath and using a less than stoichiometric amount of sodium borohydride to prevent degradation of the Meldrum's acid core. This reaction's progress could be followed by TLC analysis (1:1 v/v ethyl acetate/petroleum ether) and a single new product was detected, alongside a small portion of unreacted dialdehyde **68**. This new product could not be isolated from the flash chromatography column and most likely decomposed on the chromatography silica. Future studies using ketenes to access lactones might become synthetically viable if a way to stabilise the synthetic intermediates is determined. At this point we felt it would be prudent to explore other avenues of investigation. Thus, we decided to investigate other heterocyclic compounds that may be capable of forming ketenes.

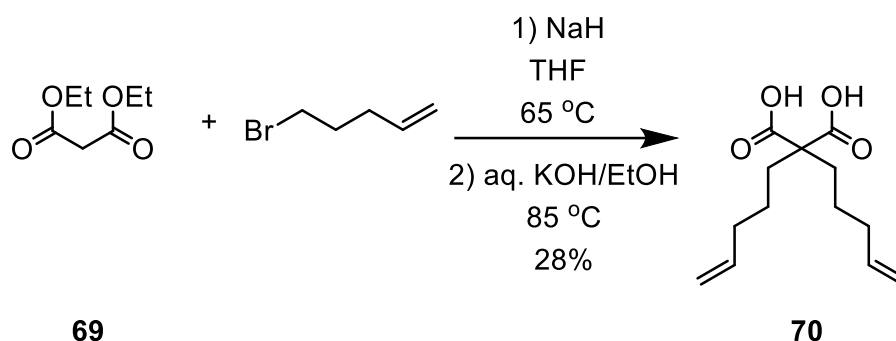


Scheme 5.4.1. Planned reaction scheme to produce lactone **67** from compound **41**.

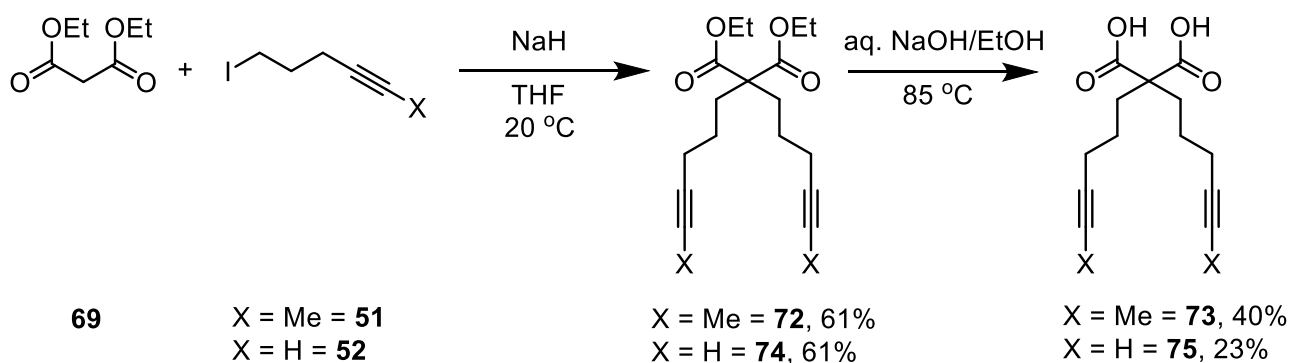
5.5 Synthesis and thermogravimetric analysis studies of malonic acid derivatives

Our computational collaborators investigated both cyclic carbonates and thiocarbonates for their ability to access ketene intermediates.² Their results suggested both could form ketenes through a cycloreversion reaction, although this would occur most readily with Meldrum's acids. Despite not being as energetically favourable for synthesising a ketene intermediate, investigating cyclic carbonates and thiocarbonates was thought to be a potentially fruitful avenue of research. Therefore, malonic acid compound **70** was prepared (Scheme 5.3.1) as it was thought compound **70** would produce the same ketene intermediate and product cyclobutanone **71** as compound **41**. The chemistry was extended further by preparing the corresponding dialkynyl malonic acid compounds **73** and **75** through an amended protocol (Scheme 5.3.2). Compounds **70** and **73** were obtained as crystalline solids. Even with the extended reaction time, an approximately 10% yield of monoalkynylated products were obtained from both reactions where alkyne compounds **51** and **52** were used as

the electrophile. The presence of the monoalkynylated products from both reactions suggests the rate of the second alkynylation step is very slow.



Scheme 5.5.1. Synthesis of compound **70** from malonate **69**.



Scheme 5.5.2. Synthesis of compounds **73** and **75** from malonate **69**.

Having the malonic acids to hand, investigating their thermolytic profiles was the next step (Figure 5.5.1). The thermolytic pathway for malonic acids cannot access ketenes; these compounds instead undergo decarboxylation.³ Therefore, we took the inflection point in the thermolytic pathway to be the point of decarboxylation (refer to Appendices A3.36-A3.38 for the individual TGA traces).

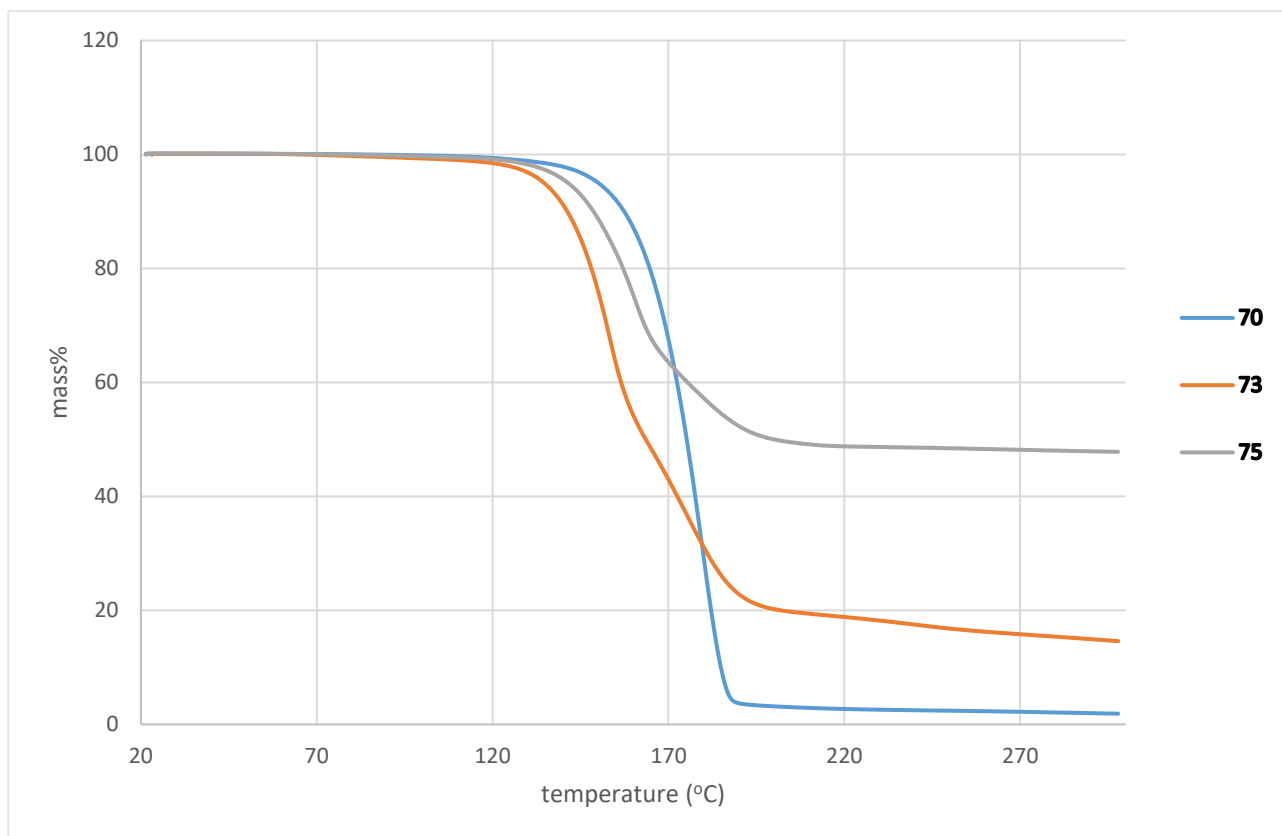


Figure 5.5.1. Thermogravimetric traces of malonic acids **70**, **73** and **75**, depicting change in mass percent vs temperature (°C)

Compound **70** had the greatest inflection point of approximately 175 °C, compound **75** had the next highest inflection point with 160 °C and was only slightly greater than compound **73** with an inflection point of 156 °C. These results are an inversion of the TGA data of the corresponding Meldrum's acid series, where compounds **41-45** had the lowest inflection points and compounds **53-57** had the highest. It is noteworthy that compounds **73** and **75** had a noticeable change in thermolysis rate after the initial decarboxylation onset. This change in rate suggests the initial decarboxylation step was rapid and then an entirely new thermolytic process occurred afterwards. We noted the residual mass% for compound **75** stabilised at 48%, which suggests a thermolytically stable product was produced during the analytical run. The next highest final residual mass% was approximately 15% with compound **73**. The respective

residues from the thermolysis of compounds **70** and **73** were dissolved in deuterated chloroform and subjected to ^1H NMR experiments so a possible structure could be elucidated. However, the signal to noise ratio for both samples was too unfavourable for the spectra to be discernible. The results from the TGA traces of compounds **73** and **75** suggests the change in rate is due to a carboxylic acid interacting with the alkyne, thereby stabilising the thermolysis products on the sample pan. Compound **70** had no change in average thermolysis rate and reached approximately 1% mass after completion of its analysis, which suggests its decarboxylation pathway's energy profile does not reach a local minimum under the TGA's temperature ramp conditions until thermolysis is complete. Thus, the results from the TGA trace suggests that compound **70** has a facile decarboxylation pathway whereas the thermolysis pathways for compounds **73** and **75** proceed down a different reaction pathway. Compounds **70** and **73** had further analyses conducted on the samples.

5.6 Malonic acid crystallographic studies

The X-ray diffraction short contact data on compounds **70** and **73** demonstrated intermolecular hydrogen-bonding between the carboxylic acid groups of neighbouring molecules in the unit cell. Dimerization through hydrogen-bonding of neighbouring carboxylic acid groups was observed for both compounds. The length of that intermolecular CO---H hydrogen-bond was 1.812 Å for both bonds of compound **70**. The intermolecular CO---C dimer interaction length was 2.631(2) Å. Compound **73** had intermolecular CO---H hydrogen-bond lengths of 1.728 Å and 1.687 Å respectively, signifying the dimers formed from these malonic acid compounds are strongly attracted. The intermolecular CO---C dimer interaction lengths were 2.659(2) Å and

2.601(2) Å respectively. Compound **70** experienced intermolecular hydrogen-bonding between hydrogen atoms bonded to an sp^2 -hybridised carbon and a carboxylate oxygen atom, with a distance of 2.695 Å between the interacting atoms. Compound **73** had a similar hydrogen-bond between the carboxylate oxygen and a hydrogen atom on the alkyl chain's terminal methyl group. The distance of this other intermolecular hydrogen-bond in compound **73** was 2.693 Å. Compound **73** also had intermolecular short contacts of 2.675 Å and 2.746 Å between a hydrogen atom on a terminal methyl group and the two sp -hybridised carbons of the alkyne (Figure 5.6.1), thereby suggesting some intermolecular π -interactions were involved. Compound **70** predominantly had intramolecular hydrogen-bonding interactions between the carboxylate oxygen atoms and multiple hydrogen atoms in the alkyl chains. There was also a likely intramolecular π -interaction between an sp^2 -hybridised and a hydrogen on the closest sp^3 -hybridised carbon to the quaternary carbon in the alkyl chain (Figure 5.6.2a), with the distance between atoms being 2.683 Å. Compound **73** also experienced intramolecular hydrogen-bonding through the carboxylate oxygens and multiple hydrogen atoms in the alkyl chains. There was also intramolecular π -interactions between a hydrogen atom bonded to an sp^3 -hybridised carbon in the alkyl chain and an sp -hybridised carbon of the alkyne (Figure 5.6.2b). This interaction appeared to occur on both sides of the molecule and the distances were 2.537 Å and 2.603 Å respectively. The interacting carbon and hydrogen atoms were in the same position of the alkyl chain as compound **70**.

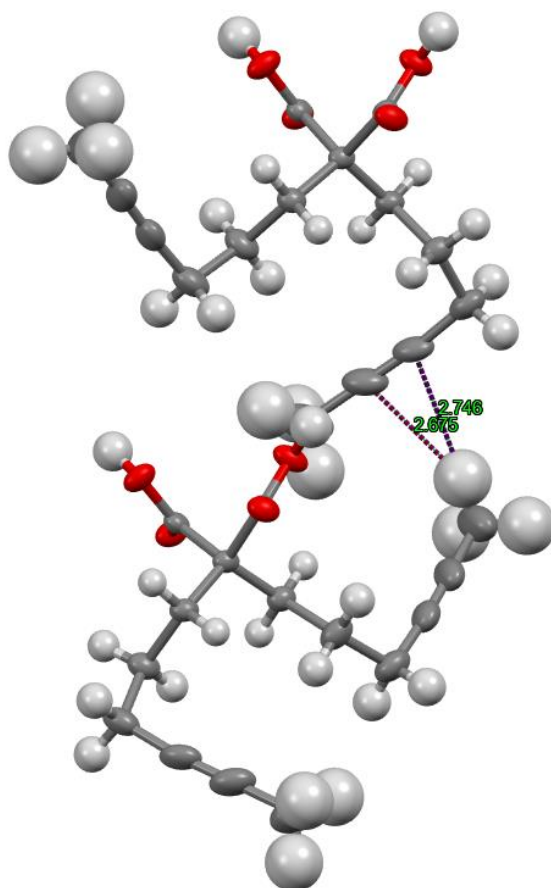
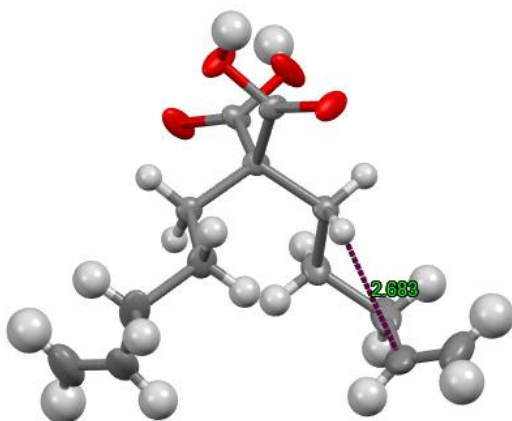


Figure 5.6.1. Obtained X-ray crystal structure of compound **73** depicting an intermolecular π -interaction.

a)



b)

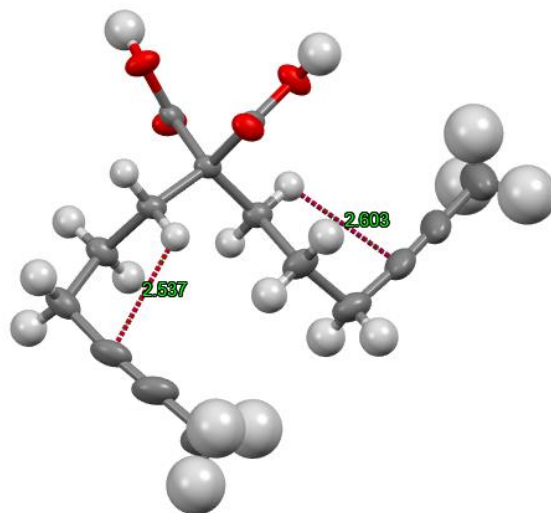
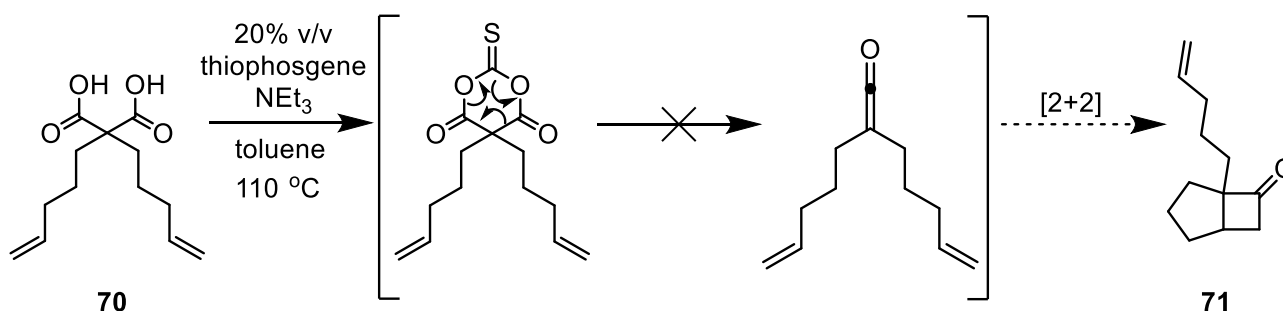


Figure 5.6.2. a) Obtained single-crystal X-ray crystal structure of compound **70** depicting an intramolecular π -interaction, b) Obtained single-crystal X-ray crystal structure of compound **73** depicting an intramolecular π -interaction.

5.7 Cyclic carbonates can also access ketenes (Aim 6)

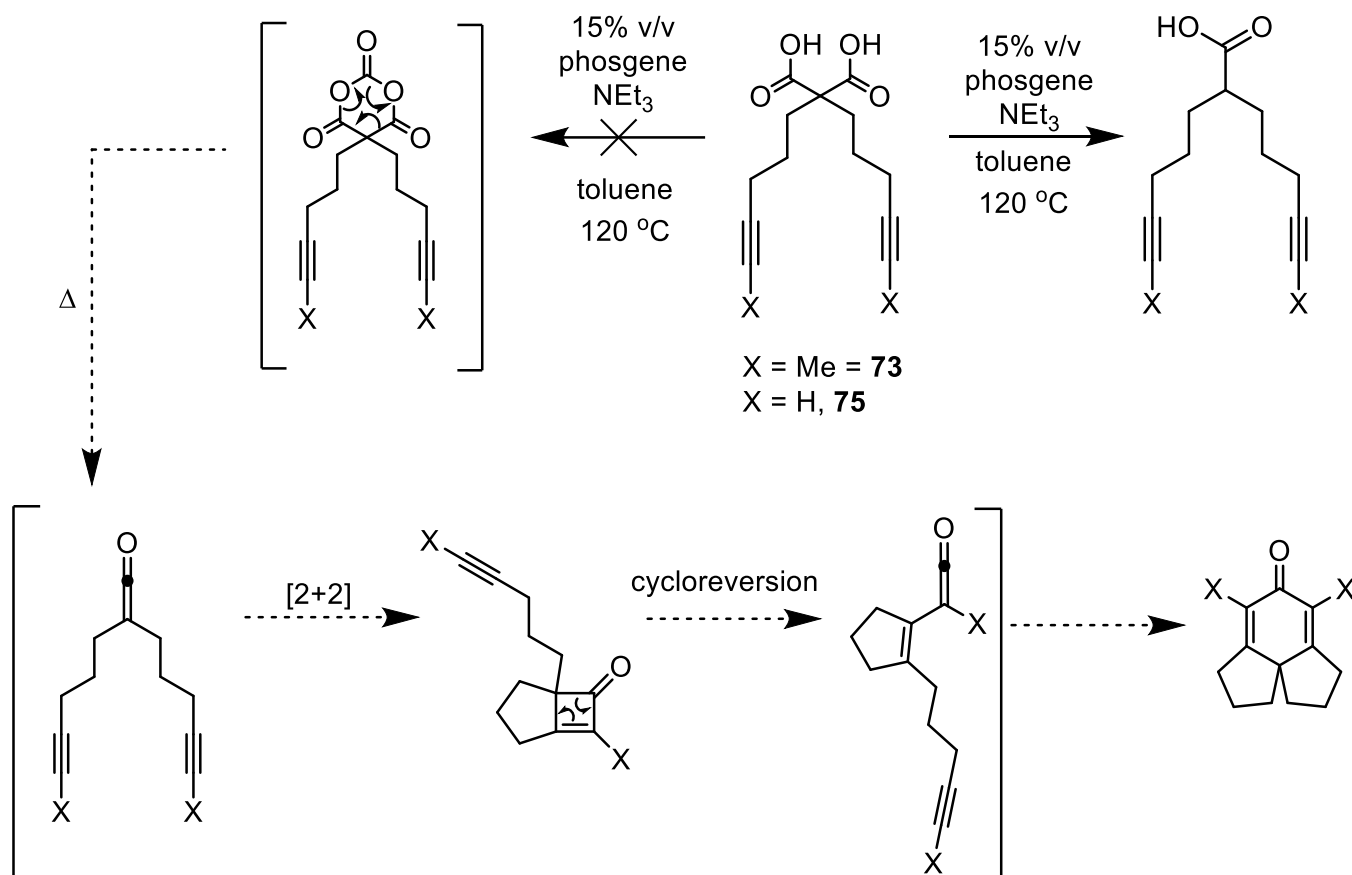
Having obtained the three malonic acids, the final aim of this research was to test their ability to form ketene intermediates. Cyclic thiocarbonates were the first derivative tested, which was conducted through reacting compound **70** with 20% v/v thiophosgene in toluene solution in the presence of triethylamine (Scheme 5.7.1). No reaction occurred and a quantitative amount of compound **70** was recovered from this process. We suspect the nucleophilic substitution step occurred but the subsequent step was a rapid hydrolysis of the formed heterocyclic ring instead of the desired thermolysis. We were unsurprised with this result, as our collaborators² had predicted that cyclic thiocarbonates had the highest activation energy barrier to overcome to access thermolysis.



Scheme 5.7.1. Attempted synthesis of cyclobutanone **71** from malonic acid **70** through cyclic thionate intermediate.

We also experimented with accessing new ketene intermediates from cyclic carbonates derived from malonic acids **73** and **75**. Thus, compounds **73** and **75** were separately reacted with 15% v/v phosgene in toluene solution (Scheme 5.7.2). In both instances we isolated a product that had the same exact mass and fragmentation patterns under GC-MS analysis as the corresponding *gem*-dialkynlyated Meldrum's acids. We conducted ¹H NMR and ¹³C NMR experiments on the major product from both reactions and it appeared to be a decarboxylation product. The TGA data did

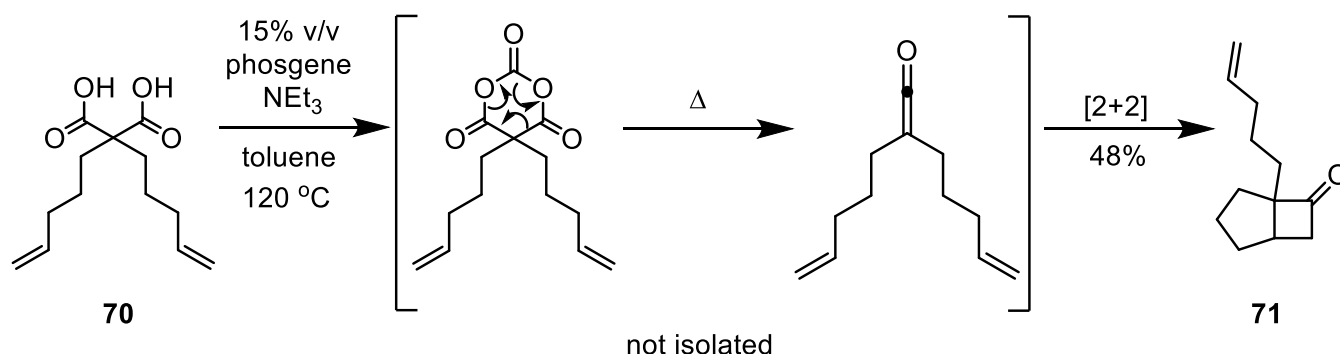
suggest that decarboxylation was more easily initiated with malonic acids **73** and **75** and the results obtained here support that observation.



Scheme 5.7.2. Synthesis of decarboxylation product from malonic acids **73** and **75** instead of the proposed ketene pathway.

We wanted to prove the existence a cyclic carbonate species intermediate for the reaction pathways with malonic acids. Therefore, we tried reacting compound **70** with the same reagents as we used for compounds **73** and **75** (Scheme 5.7.3) but without heating the reaction mixture. The presence of a new and very faint spot became noticeable on TLC after 1 h, which we thought may have been a cyclic carbonate compound. Isolating the compound corresponding to that spot was attempted but unsuccessful. We repeated the reaction using pyridine as the base and again found we could not isolate any cyclic carbonate intermediate. We hypothesised the potential

cyclic carbonate was sensitive to atmospheric moisture and decomposed in its presence so we decided to simply push the reaction ahead and see if thermolysis could occur. We also noted a large quantity of pyridinium salt being produced so we chose to revert to triethylamine as the base as it was easier to remove during work up. Thus, compound **70** was reacted with 15% phosgene solution in the presence of triethylamine. To our delight, we isolated cyclobutanone **71** in a good yield. We had successfully demonstrated that cyclobutanone **71** can be produced in a higher yield and in a more controlled manner through using compound **70** in contrast to compound **41**, thereby demonstrating that ketene intermediates can be accessed through what is assumed to be a cyclic carbonate precursor.



Scheme 5.7.3. Synthesis of cyclobutanone **70** through malonic acid **71**. It is assumed the reaction proceeded through a cyclic carbonate and then a ketene intermediate.

5.8 Conclusion

We demonstrated that the prepared *gem*-dialkenylated Meldrum's acids can access ketenes products and these ketene products can be detected through GC-MS analysis. We also demonstrated that accessing ketene products from Meldrum's acids can be difficult, even under flow conditions, if the temperatures used to enact the cycloreversion are too high. We investigated analogous compounds to Meldrum's acid and determined that accessing ketene intermediates from cyclic carbonates is

possible. Accessing ketene intermediates from cyclic carbonates was also easier than using the corresponding Meldrum's acid, and ketene products from cyclic carbonates can be accessed at lower temperatures and with higher yields when compared to the corresponding Meldrum's acids.

5.8.1 Future studies

The results from the flow reactor studies suggests the presence of solvent increases the temperature required to enact the cycloreversion of the Meldrum's acid derivatives. Therefore, utilising a solvent-free protocol to access sucrose fatty-acid mono-esters with Meldrum's acid derivatives is likely to be a more viable synthetic methodology. Sucrose melts were successfully applied for the production of SMEs⁵ and present as a possible alternative if the regio-selectivity of the process can be improved. The results from this study suggests enacting the thermolysis with either a *gem*-dialkylated or certain *gem*-dialkenylated Meldrum's acid derivative or perhaps a C5 mono-alkylated Meldrum's acid derivative might be compatible with a protocol involving the *in situ* melting of sucrose.

We have demonstrated that cyclic carbonate species can form ketene intermediates under the right conditions. There is the potential to further explore this avenue by investigating forming cyclic carbonates and subsequent ketene products without the need for phosgene. Mak and colleagues⁴ successfully demonstrated that ketenes could be formed and reacted *in situ* in a super critical CO₂ experiment with no cycloaddition product observed. Therefore, future studies could be extended to investigate whether cyclic carbonates are viable ketene sources for producing sucrose

fatty-acid mono-esters through a potential mono-alkylated malonic acid reaction with super critical CO₂ under basic conditions, whereby a subsequent mono-alkyl ketene intermediate can react with sucrose to access the desired fatty-acid mono-ester.

Chapter Five references

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Chapter Six: Experimental

General Experimental Procedures:

Unless otherwise stated, all reactions were performed in oven-dried glassware, stirred magnetically, and conducted in air. Standard Schlenk techniques were used when a nitrogen atmosphere was required. Ambient temperature was assumed to be ca. 20 °C. Temperatures higher than ambient were achieved using a thermostated oil bath or a thermostated aluminium heating mantle. To obtain temperatures below ambient, relevant cryostats [e.g. ice-water for 0 °C; dry-ice/acetone for –78 °C] were used.

Analytical TLC was performed on aluminium-backed 0.2 mm thick silica gel 60 F₂₅₄ plates as supplied by Merck. Eluted plates were visualised using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. The dips used included anisaldehyde : sulphuric acid (conc.) : ethanol (3 mL : 4.5 mL : 200 mL). An iodine vapour bath was also used on occasion. Flash chromatography was conducted using silica gel 60 (40-63 µm) as the stationary phase and the AR-grade solvents indicated.

Unless otherwise stated, all proton (¹H) and proton-decoupled carbon (¹³C{¹H}) NMR spectra were recorded in CDCl₃ or CD₃OD on a Bruker spectrometer maintained at 25 °C and operating at 400 MHz for proton nuclei and 100 MHz for carbon nuclei. The signals arising from the protio-forms of the solvent were used as internal standards for ¹H NMR spectra. ¹H NMR data sets are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral]. The multiplicities of signals recorded in the ¹H NMR data are defined as s = singlet; d = doublet; t = triplet; q =

quartet; p = pentet; m = multiplet or combinations of these. The signal due to residual CHCl_3 appearing at δ_{H} 7.26 ppm and the central resonance of the CDCl_3 “triplet” appearing at δ_{C} 77.16 ppm were used to reference ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra, respectively. The signal due to residual water and MeOH appearing at δ_{H} 4.87 ppm and δ_{H} 3.34 ppm respectively were used to reference ^1H NMR spectra. The signal due to the residual MeOH “pentet” appearing at δ_{C} 49.0 ppm was used to reference $^{13}\text{C}\{^1\text{H}\}$ NMR spectra.

Infrared spectra (ν_{max}) were recorded on a Perkin-Elmer 1800 Series FTIR Spectrometer and samples were analysed as thin films.

Low-resolution ESI mass spectra were recorded using a single-quadrupole mass spectrometer interfaced with a liquid chromatograph, while high-resolution ESI measurements were conducted on a time-of-flight instrument. Gas chromatography mass spectra (GC-MS) analyses were conducted on a single-quadrupole mass spectrometer interfaced with a gas chromatograph fitted with an Agilent 30 m x 0.250 mm, 0.25 μm column and using helium as the carrier gas. High-resolution EI measurements were recorded on a time-of-flight instrument.

Melting points were measured on a Reichert melting point apparatus and are uncorrected.

Thermogravimetric analyses were conducted on a Waters TA-Q500 instrument fitted with platinum sample pans. Analysis runs were conducted from ambient temperature up to either 200 °C, 250 °C or 300 °C with 5 °C/min ramping. Differential scanning calorimetric experiments were conducted on a Waters TA-Q20 instrument fitted with aluminium sample pans and lids. Analysis runs were conducted from ambient temperature up to either 200 °C, 250 °C or 300 °C with 5 °C/min ramping.

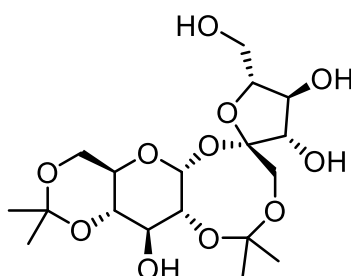
Optical rotations were recorded on a Rudolph Automatic Polarimeter using the sodium D-line and a 40T-style cell.

Starting materials and reagents were generally available from the Sigma-Aldrich, Merck, TCI, AK Scientific or Combi-Blocks companies and were used as supplied. Drying agents and other inorganic salts were purchased from the ChemSupply, Ajax, BDH or Unilab companies. THF and DMF were dried using a Glass Contour solvent purification system. Petroleum ether refers to the fraction boiling between 40 and 60 °C.

Ozonolyses were performed using a Model 500 Fischer portable ozone generator with the luteinizing power and flow rate adjusted to 80 V and 50 L/h, respectively.

Flow reactor experiments were conducted on a Syrris Asia Flow Chemistry System, using a Syrris Asia Automator module in conjunction with the Syrris Asia Manager software.

(2*S*,3*S*,4*S*,4*a'**R*,5*R*,5*a'**R*,11*a'**R*,12*S*,12*a'**S*)-5-(Hydroxymethyl)-2',2',10',10'-tetramethyloctahydro-3*H*,8'*H*-spiro[furan-2,7'-[1,3]dioxino[4',5':5,6]pyrano[3,2-*d*][1,3,6]trioxocine]-3,4,12'-triol (**1**)

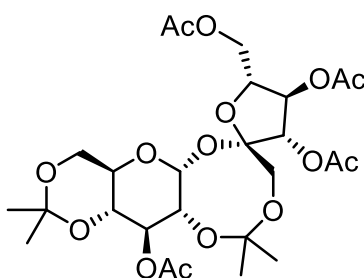


Method A: 2,2-Dimethoxypropane (**5**) (25.0 mL, 204 mmol) was added to a magnetically stirred solution of sucrose (**3**) (5.16 g, 15.1 mmol) and *p*-toluenesulphonic acid (394 mg, 2.29 mmol) in DMF (250 mL) maintained at ambient temperatures. The reaction was left to stir for 24 h then treated with sodium bicarbonate (5 mL of a sat. aq. solution). Thereafter the DMF was removed from the reaction mixture by distillation at reduced pressure (@ 50 °C, 20 mBar). The resulting yellow residue was purified by flash chromatography (silica, 5: 4.5: 0.5 to 7.5: 2: 0.5 v/v ethyl acetate /DCM /MeOH gradient elution), the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.3$ in 5:95 v/v MeOH/ethyl acetate), affording compound **1** (3.12 g, 49%) as a pale-yellow solid, m.p. = 138-139 °C; $[\alpha]_D = 12.5^\circ$ ($c = 1.0$, CHCl_3) {lit.¹ $[\alpha]_D = 15^\circ$ ($c = 1.0$, CHCl_3)}. ¹H NMR (400 MHz, CD_3OD) δ 6.07 (d, $J = 3.7$ Hz, 1H), 4.12-4.02 (complex m, 3H), 3.85-3.76 (complex m, 2H), 3.73-3.61 (complex m, 7H), 3.52 (t, $J = 9.6$ Hz, 2H), 3.38 (d, $J = 12.2$ Hz, 2H), 1.45 (d, $J = 14.3$ Hz, 7H), 1.38

(s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 104.6, 102.8, 100.9, 92.4, 84.2, 79.9, 75.7, 75.1, 74.7, 70.9, 67.1, 64.6, 64.3, 63.2, 29.5, 25.5, 24.4, 19.3; FTIR ν_{max} (thin film) 3391, 2993, 2939, 1662, 1383, 1268, 1197, 1132, 1092, 1055, 1027, 940, 855, 732 cm^{-1} ; MS (ESI, +ve) m/z 445 $[(\text{M} + \text{Na}^+, 30\%)]$, 74 $[(\text{M} - \text{C}_{15}\text{H}_{24}\text{O}_9^+, 100\%)]$; HRMS (TOF, ESI, +ve) m/z ($\text{M} + \text{Na}^+$) calcd. for $\text{C}_{18}\text{H}_{30}\text{NaO}_{11}$ 445.1686, found 445.1686.

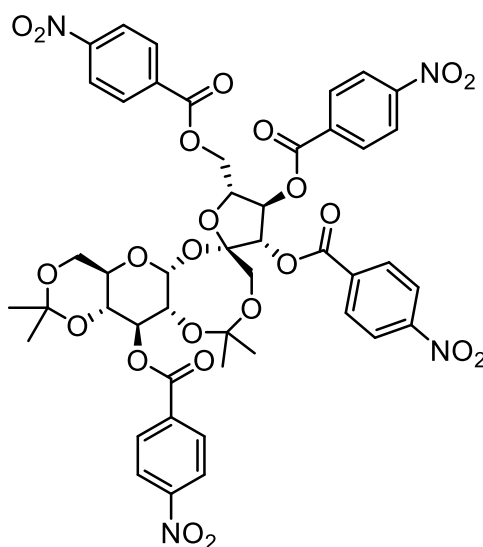
Method B: 2,2-Dimethoxypropane (**5**) (25.0 mL, 204 mmol) was added to a magnetically stirred solution of sucrose (**3**) (5.03 g, 14.7 mmol) and ceric ammonium nitrate (1.61 g, 2.94 mmol) in DMF (250 mL) maintained at ambient temperatures. The reaction mixture was stirred for 24 h then neutralised by the addition of triethylamine (4.0 mL, 28.7 mmol). The resulting mixture was subjected to distillation at reduced pressure (@ 50 °C, 20 mBar) to remove the DMF. The resulting clear, yellow residue was subjected to flash chromatography (silica, 5: 4.5: 0.5 to 7.5: 2: 0.5 v/v ethyl acetate/DCM/MeOH gradient elution), the relevant fractions were collected and concentrated under reduced pressure (R_f = 0.3 in 5:95 v/v MeOH/ethyl acetate), affording compound **1** (3.24 g, 52% yield) as a pale-yellow solid. This solid material was identical to the product obtained by Method A.

(2*S*,3*S*,4*R*,4*a'**R*,5*R*,5*a'**R*,11*a'**R*,12'*S*,12*a'**R*)-5-(Acetoxymethyl)-2',2',10',10'-tetramethyloctahydro-3*H*,8'*H*-spiro[furan-2,7'-[1,3]dioxino[4',5':5,6]pyrano[3,2-*d*][1,3,6]trioxocine]-3,4,12'-triyl triacetate (**7**)



A magnetically stirred solution of compound **1** (2.00 g, 4.73 mmol) in pyridine (10 mL) and maintained at ambient temperatures was treated with acetic anhydride (**6**) (2.3 mL, 24.3 mmol) and DMAP (30 mg, 0.25 mmol). The resulting mixture was stirred at ambient temperatures for 24 h then diluted with toluene (10 mL) before being subjected to distillation under reduced pressure (@ 50 °C, 20 mBar) to remove the pyridine. The subsequent residue was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/petroleum ether), the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.3$ in 2:3 v/v ethyl acetate/petroleum ether), providing compound **7** (878 mg, 10%) as white needles. A small portion of the obtained crystalline needles was recrystallized using vapour-vapour diffusion techniques using 1:1 v/v petroleum ether/diethyl ether, giving transparent crystalline shards, m.p. = 133-135 °C (lit.² m.p. = 136-137 °C); $[\alpha]_D = 10.3^\circ$ ($c = 1.0$, CHCl_3) {lit.¹ $[\alpha]_D = 11^\circ$ ($c = 0.9$, CHCl_3)}. ¹H NMR (400 MHz, CDCl_3) δ 6.10 (d, $J = 3.5$ Hz, 1H), 5.34-5.28 (complex m, 1H), 5.21 (t, $J = 9.5$ Hz, 1H), 5.15 (d, $J = 6.1$ Hz, 1H), 4.40 (q, $J = 9.2$ Hz, 2H), 4.31-4.21 (complex m, 2H), 4.03 (d, $J = 12.5$ Hz, 1H), 3.96 (dd, $J = 10.5$ and 5.1 Hz, 1H), 3.90-3.77 (complex m, 2H), 3.66 (dt, $J = 14.1$ and 10.1 Hz, 2H), 3.51 (d, $J = 12.5$ Hz, 1H), 2.23 (s, 3H), 2.09 (s, 3H), 2.05 (d, $J = 4.4$ Hz, 6H), 1.46 (d, $J = 5.9$ Hz, 6H), 1.40 (s, 3H), 1.26 (s, 3H); ¹³C NMR (100 MHz, CDCl_3) δ 173.0, 171.6, 171.2, 170.0, 105.2, 101.6, 92.5, 90.7, 80.2, 79.5, 78.4, 76.3, 73.6, 70.6, 69.7, 64.5, 64.3, 62.7, 25.6, 24.1, 21.3, 21.0, 20.9 (2), 20.8; FTIR ν_{max} (thin film) 2998, 2939, 1742, 1370, 1221, 1151, 1131, 1069, 1047, 1034, 1017, 945, 894, 856, 735 cm^{-1} ; MS (ESI, +ve) m/z 613 $[(M + \text{Na}^+, 100\%)]$; HRMS (TOF, ESI, +ve) m/z ($M + \text{Na}^+$) calcd. for $\text{C}_{26}\text{H}_{38}\text{NaO}_{15}$ 613.2103, found 613.2103.

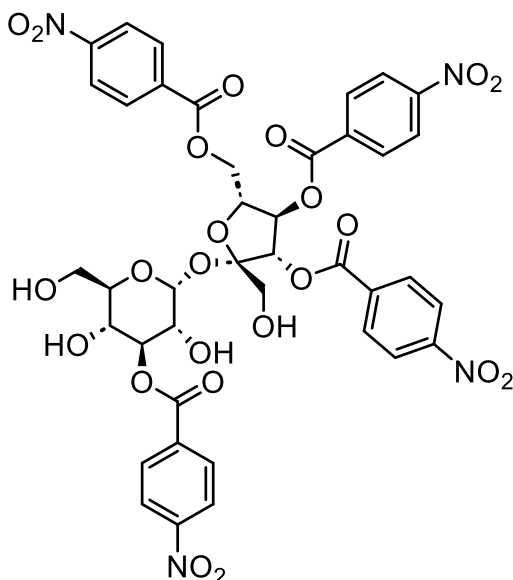
(2*S*,3*S*,4*R*,4*a'**R*,5*R*,5*a'**R*,11*a'**R*,12*S*,12*a'**R*)-2',2',10',10'-Tetramethyl-5-(((4-nitrobenzoyl)oxy)methyl)octahydro-3*H*,8'*H*-spiro[furan-2,7'-[1,3]dioxino[4',5':5,6]pyrano[3,2-*d*][1,3,6]trioxocine]-3,4,12'-triyltris(4-nitrobenzoate)
(9)



A magnetically stirred solution of compound **1** (851 mg, 20.2 mmol) in DCM (10 mL) and maintained at ambient temperatures was treated with DMAP (49 mg, 0.40 mmol), triethylamine (3.0 mL, 21.5 mmol) and *p*-nitrobenzoyl chloride **8** (2.10 g, 113 mmol). The resulting mixture was stirred for 18 h and the resulting yellow solution was washed with ammonium chloride (3 × 15 mL of a sat. aq. solution) and the organic and aq. layers were separated. The combined aq. layers were washed with ethyl acetate (3 × 15 mL) and the combined organic layers were subsequently washed with brine (2 × 20 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure, resulting in a yellow solid. A solution of the obtained yellow solid in DCM (5 mL) was treated with flash chromatography-grade silica (10 g) and the resulting mixture was subsequently concentrated under reduced pressure. The resulting fine powder was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate/petroleum ether,) the

relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.4$), affording compound **9** (1.36 g, 66%) as a pale-yellow solid, m.p. = 144-145 °C; $[\alpha]_D = 1.30^\circ$ ($c = 1.0$, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 8.34-8.15 (complex m, 16H), 6.26 (d, $J = 3.3$ Hz, 1H), 5.83 (t, $J = 9.2$ Hz, 1H), 5.56 (d, $J = 4.7$ Hz, 1H), 5.42 (t, $J = 9.3$ Hz, 1H), 4.88 (dd, $J = 10.8$ and 5.6 Hz, 1H), 4.79-4.65 (complex m, 2H), 4.28 (d, $J = 12.4$ Hz, 1H), 4.03-3.99 (complex m, 2H), 3.80-3.66 (complex m, 4H), 1.47 (s, 3H), 1.42 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.4, 164.1, 164.0, 163.9, 151.3, 151.1, 150.8, 150.7, 135.7, 135.1, 134.0, 131.5, 131.2, 131.0, 130.8, 105.4, 105.2, 102.0, 99.9, 92.1, 80.6, 79.3, 78.7, 76.1, 72.0, 71.2, 64.9, 29.0, 25.5, 24.0, 19.0; FTIR ν_{max} (thin film) 3113, 3057, 2994, 1730, 1607, 1525, 1347, 1319, 1265, 1201, 1099, 1076, 1042, 1013, 944, 869, 782, 715 cm^{-1} ; MS (ESI, +ve) m/z 1041 $[(M + \text{Na}^+, 100\%)]$, 1019 $[(M + \text{H}^+, 40\%)]$; HRMS (TOF, ESI, +ve) m/z ($M + \text{Na}^+$) calcd. $\text{C}_{46}\text{H}_{42}\text{N}_4\text{NaO}_{23}$ for 1041.2138, found 1041.2133.

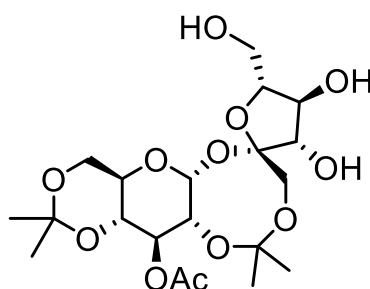
(2*S*,3*S*,4*R*,5*R*)-2-(((2*R*,3*R*,4*S*,5*R*,6*R*)-3,5-Dihydroxy-6-(hydroxymethyl)-4-((4-nitrobenzoyl)oxy)tetrahydro-2*H*-pyran-2-yl)oxy)-2-(hydroxymethyl)-5-(((4-nitrobenzoyl)oxy)methyl)tetrahydrofuran-3,4-diyl bis(4-nitrobenzoate) (**10**)



DDQ (spatula tip; CAUTION: can produce hydrogen cyanide) was added to a magnetically stirred solution of compound **9** (430 mg, 0.42 mmol) in acetonitrile/water (10 mL of a 9:1 v/v mixture) and the resulting solution was stirred at 40 °C for 18 h before being concentrated under reduced pressure. The resulting residue was subjected to flash chromatography (silica, 3:2 v/v ethyl acetate/petroleum ether). The relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.4$, 3:1 v/v ethyl acetate/petroleum ether), affording compound **10** (280 mg, 70%) as a white solid, m.p. = 125-127 °C; $[\alpha]_D = -29.6^\circ$ ($c = 1.1$, CHCl_3). ^1H NMR (400 MHz, CD_3OD) δ 8.47-8.35 (complex m, 8H), 8.29 (d, $J = 9.0$ Hz, 2H), 8.22-8.16 (complex m, 6H), 6.16 (d, $J = 7.5$ Hz, 1H), 6.06 (t, $J = 7.1$ Hz, 1H), 5.74 (t, $J = 9.7$ Hz, 1H), 5.63 (d, $J = 3.5$ Hz, 1H), 4.97 (dd, $J = 11.2$ and 5.9 Hz, 1H), 4.86-4.79 (complex m, 2H), 4.19 (ddd, $J = 9.9$, 4.2 , 2.3 Hz, 1H), 4.07 (dd, $J = 12.1$ and 2.3 Hz, 1H), 3.95-3.85 (complex m, 4H), 3.78 (d, $J = 12.7$ Hz, 1H), $4 \times \text{COH}$ not observed; ^{13}C NMR (100 MHz, CD_3OD)

δ 166.2, 165.8, 165.5, 165.4, 152.3, 152.0, 137.2, 136.2, 136.0, 135.6, 132.6, 132.1, 132.0, 131.9, 125.0, 124.6(2), 124.5, 106.1, 94.2, 79.3, 79.0, 78.9, 78.3, 75.2, 71.2, 68.9, 67.5, 63.9, 61.8; FTIR ν_{max} (thin film) 3452, 3115, 1732, 1607, 1349, 1270, 1103, 1014, 873, 718 cm^{-1} ; MS (ESI, +ve) m/z 961 [(M + Na⁺, 5%)], 79 [(M – C₃₄H₂₇N₄O₂₃⁺, 100%)]]; HRMS (TOF, ESI, +ve) m/z (M + Na⁺) calcd. C₄₀H₃₄N₄NaO₂₃ for 961.1512, found 961.1519.

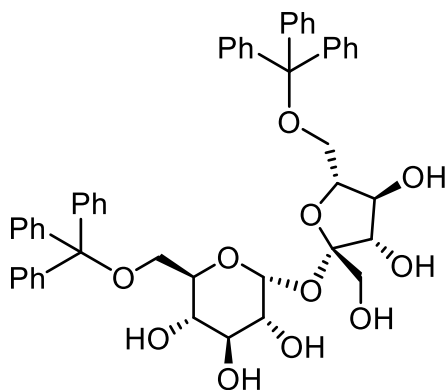
(2*S*,3*S*,4*S*,4*a'**R*,5*R*,5*a'**R*,11*a'**R*,12*S*,12*a'**R*)-3,4-Dihydroxy-5-(hydroxymethyl)-2',2',10',10'-tetramethyloctahydro-3*H*,8'*H*-spiro[furan-2,7'-[1,3]dioxino[4',5':5,6]pyrano[3,2-*d*][1,3,6]trioxocin]-12'-yl acetate (**11**)



Sodium methoxide powder (spatula tip) was added to a magnetically stirring solution of compound **7** (410 mg, 0.069 mmol) in anhydrous MeOH (5 mL) under a nitrogen atmosphere. The resulting solution was stirred at ambient temperature with close TLC monitoring (ethyl acetate) for 1.5 h. The reaction was deemed to be complete when the faint presence of compound **1** was indicated by TLC, thus Dowex-H (150 mg) was added to the reaction mixture. After 30 min of stirring, the resulting suspension was filtered over a pad of Celite with MeOH. The filtrate was concentrated under reduced pressure and purified by flash chromatography (silica, 1:1 to 1:0 v/v ethyl acetate/petroleum ether gradient elution). The relevant fractions were collected and concentrated under reduced pressure (R_f = 0.4 in ethyl acetate), providing compound

11 (286 mg, 87%) as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 6.23 (d, $J = 3.9$ Hz, 1H), 5.24 (t, $J = 9.5$ Hz, 1H), 4.54 (t, $J = 7.8$ Hz, 1H), 4.16 (d, $J = 12.4$ Hz, 1H), 3.97 (d, $J = 7.8$ Hz, 1H), 3.92-3.80 (complex m, 5H), 3.72-3.58 (complex m, 4H), 3.50 (d, $J = 12.4$ Hz, 1H), 2.07 (s, 3H), 1.46 (s, 6H), 1.40 (s, 3H), 1.33 (s, 3H), $2 \times \text{COH}$ unobserved; satisfactory ^{13}C NMR spectra could not be obtained; FTIR ν_{max} (thin film) 3392, 2992, 2938, 1728, 1371, 1235, 1200, 1175, 1132, 1049, 943, 896, 854, 734 cm^{-1} ; MS (ESI, +ve) m/z 487 [(M + Na^+ , 100%)] HRMS (TOF, ESI, +ve) m/z (M + Na^+) calcd. $\text{C}_{20}\text{H}_{32}\text{NaO}_{12}$ for 487.1791, found 487.1786.

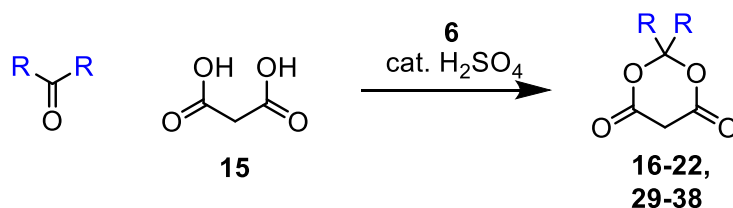
((2R,3R,4S,5S,6R)-2-(((2S,3S,4S,5R)-3,4-Dihydroxy-2-(hydroxymethyl)-5-((trityloxy)methyl)tetrahydrofuran-2-yl)oxy)-6-((trityloxy)methyl)tetrahydro-2H-pyran-3,4,5-triol (**14**))



DMAP (410 mg, 3.4 mmol) was added to a magnetically stirred suspension of sucrose (**3**) (4.00 g, 11.7 mmol) in pyridine (10 mL). Trityl chloride (**13**) (7.24 g, 26.0 mmol) was added and the resulting reaction mixture was stirred at ambient temperatures for 48 h. The reaction mixture was subsequently concentrated under reduced pressure and the resulting clear solid residue was subjected to flash chromatography (silica, 0:1 to 1:3 v/v MeOH/DCM gradient elution). The relevant fractions were collected and

concentrated under reduced pressure ($R_f = 0.2$ in 1:9 v/v MeOH/ethyl acetate), providing compound **14** (2.51 g, 26%) as a white solid. The solid was obtained as three inseparable regio-isomers with the desired 6,6'-regio-isomer being the predominant isomer in the mixture, m.p. = 136-138 °C (lit.³ m.p. = 99-102 °C); $[\alpha]_D = 43.1^\circ$ ($c = 1.2$, MeOH) {lit.¹ $[\alpha]_D = 38.0^\circ$ ($c = 1.3$, MeOH)}. ¹H NMR (400 MHz, CD₃OD) δ (regio-isomers) 7.47-7.44 (complex m, 10H), 7.25-7.15 (complex m, 20H), 5.58 (d, $J = 3.8$ Hz, 1H), 4.25 (t, $J = 8$ Hz, 1H), 4.01 (dd, $J = 10.6$ and 5.7 Hz, 1H), 3.93 (app t, $J = 4$ Hz, 1H), 3.75-3.40 (complex m, 8H), 3.37-3.27 (complex m, 8H); ¹³C NMR (100 MHz, CD₃OD) 145.5, 145.4, 145.3, 145.2, 130.0, 128.8 (2), 128.0, 105.8, 105.5, 92.9, 88.0, 87.9, 82.1, 81.6, 78.9, 78.3, 76.0, 75.1, 73.2, 73.1, 73.0, 72.2, 65.4, 65.1, 64.7; FTIR ν_{max} (thin film) 3326, 1647, 1490, 1448, 1264, 1138, 1050, 994, 898, 834, 734, 701, 632 cm⁻¹; MS (ESI, +ve) m/z 849 [(M + Na⁺, 30%)], 243 [(M - C₃₁H₃₅O₁₁⁺, 95%)], 79 [(M - C₄₄H₄₃O₁₁⁺, 100%)]; HRMS (TOF, ESI, +ve) m/z (M + Na⁺) calcd. C₅₀H₅₀NaO₁₁ for 849.3251, found 849.3231.

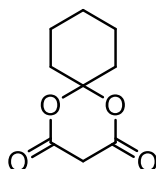
General procedure 1:



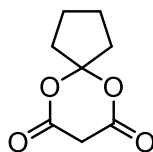
Malonic acid (**15**) (1.00 g, 9.61 mmol) was added to acetic anhydride (**6**) (3.8 mL), with magnetic stirring until the suspension became homogenous. Sulphuric acid (conc., 3 drops) was added, and the reaction mixture was left to stir at ambient temperatures for 18 h. The solution was cooled in an ice-water bath then the ketone (2 equiv.) was added dropwise/portion-wise. The resulting reaction mixture was stirred for 2 h at

ambient temperatures, unless otherwise stated. The reaction mixture was then diluted in diethyl ether (10 mL) and washed with water (3×20 mL), followed by brine (2×15 mL). The organic layer was collected, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/petroleum ether to 3:7 v/v ethyl acetate/ petroleum ether gradient elution), the relevant fractions were collected and concentrated under reduced pressure, providing the desired compound.

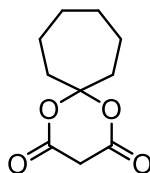
1,5-Dioxaspiro[5.5]undecane-2,4-dione (**16**)



The reaction of malonic acid (**15**) with cyclohexanone proceeded in accordance with general procedure 1 and the reaction mixture afforded an orange oil upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.3$ in 3:7 v/v ethyl acetate/petroleum ether), providing compound **16** (1.90 g, 53%) as colourless plate crystals, m.p. = 92-93 °C (lit.⁴ m.p. = 93 °C). ^1H NMR (400 MHz, CDCl_3) δ 3.61 (s, 2H), 1.97 (t, $J = 5.9$ Hz, 4H), 1.73 (p, $J = 6.5$ Hz, 4H), 1.50 (p, $J = 5.9$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.1, 107.3, 36.6 (2), 24.1, 22.3; FTIR ν_{max} (thin film) 2940, 2866, 1751, 1453, 1368, 1295, 1264, 1236, 1131, 1062, 1034, 973, 914, 897, 839 cm^{-1} ; GC-MS: $R_t = 8.5$ -8.7 min, m/z 184 [M^+ , 5%], 98 [$\text{M} - \text{C}_3\text{H}_2\text{O}_3$, 100%]; HRMS (TOF, EI) m/z ($\text{M} - \text{C}_3\text{H}_2\text{O}_3$) calcd. $\text{C}_6\text{H}_{10}\text{O}$ for 98.0726, found 98.0727.

6,10-Dioxaspiro[4.5]decane-7,9-dione (**17**)

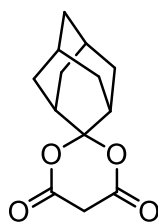
The reaction of malonic acid (**15**) with cyclopentanone proceeded in accordance with general procedure 1 and the reaction mixture afforded an orange oil upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.4$ in 3:7 v/v ethyl acetate/petroleum ether), providing compound **17** (260 mg, 16%) as colourless plate crystals, m.p. = 72-73 °C (lit.⁴ m.p. = 63 °C). ^1H NMR (400 MHz, CDCl_3) δ 3.61 (s, 2H), 2.21 (t, $J = 7.5$ Hz, 4H), 1.92-1.88 (complex m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.5, 115.6, 38.7, 37.7, 23.5; FTIR ν_{max} (thin film) 2913, 1754, 1438, 1344, 1291, 1095, 979, 842 cm^{-1} ; GC-MS: $R_t = 3.4$ -3.7 min, m/z 97 [(M – $\text{C}_{17}\text{H}_{19}\text{O}_4^+$, 70%)], 84 [(M – $\text{C}_3\text{H}_2\text{O}_3^+$, 60%)], 55 [(M – $\text{C}_4\text{H}_3\text{O}_4^+$, 100%)]; HRMS (TOF, EI) m/z calcd. 170.0579, found 170.0583; HRMS (TOF, EI) m/z (M – $\text{C}_3\text{H}_2\text{O}_3^+$) calcd. $\text{C}_5\text{H}_8\text{O}$ for 84.0575, found 84.0574.

1,5-Dioxaspiro[5.6]dodecane-2,4-dione (**18**)

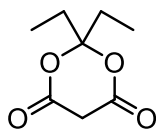
The reaction of malonic acid (**15**) with cycloheptanone proceeded in accordance with general procedure 1 and the reaction afforded a yellow oil upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and

concentrated under reduced pressure ($R_f = 0.5$ in 3:7 v/v ethyl acetate/petroleum ether), providing colourless plate-like crystals as compound **18** (1.23 g, 64%), m.p. = 51-53 °C (lit.⁵ mp = 60 °C). ^1H NMR (400 MHz, CDCl_3) δ 3.59 (s, 2H), 2.17 (d, $J = 7.7$ Hz, 2H), 1.67 (s, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.2, 111.3, 40.5, 36.6, 28.7, 21.5; FTIR ν_{max} (thin film) 2932, 2867, 1785, 1753, 1378, 1310, 1273, 1115, 1065, 1000, 971, 826 cm^{-1} ; GC-MS: $R_t = 5.0$ -5.1 min, m/z 112 [(M – $\text{C}_3\text{H}_2\text{O}_3$), 100%]; HRMS (TOF, EI) m/z (M – $\text{C}_3\text{H}_2\text{O}_3$) calcd. for $\text{C}_7\text{H}_{12}\text{O}$ 112.0883, found 112.0881.

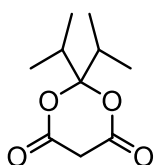
(1R,3R)-Spiro[adamantane-2,2'-[1,3]dioxane]-4',6'-dione (**19**)



The reaction of malonic acid (**15**) with adamantanone proceeded in accordance with general procedure 1 and the reaction afforded a yellow oil upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.5$ in 3:7 v/v ethyl acetate/petroleum ether), providing compound **19** (306 mg, 45%) as colourless plate crystals, m.p. = 107-109 °C. ^1H NMR (400 MHz, CDCl_3) δ 3.60 (s, 2H), 2.19-2.11 (complex m, 6H), 1.90 (s, 2H), 1.80-1.74 (complex m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.2, 109.7, 37.7, 36.8, 36.6, 33.6, 26.2; FTIR ν_{max} (thin film) 2905, 2866, 1781, 1754, 1455, 1402, 1384, 1289, 1252, 1218, 1103, 1084, 1003, 942, 887, 856, 829, 735 cm^{-1} ; GC-MS: $R_t = 11.4$ -11.7 min, m/z 150 [(M – $\text{C}_3\text{H}_2\text{O}_3$), 100%]; HRMS (TOF, EI) m/z (M – $\text{C}_3\text{H}_2\text{O}_3$) calcd. $\text{C}_{10}\text{H}_{14}\text{O}$ for 150.1039, found 150.1044.

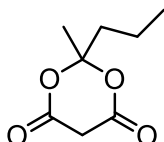
2,2-Diethyl-1,3-dioxane-4,6-dione (**20**)

General procedure 1 was followed until the addition of 3-pentanone to malonic acid (**15**), where the reaction was stirred for 4 h at ambient temperatures followed by the addition of extra 3-pentanone (1 equiv.) and another 1 h of stirring. The reaction mixture was diluted in diethyl ether (10 mL) and washed with water (3 × 20 mL), followed by brine (2 × 15 mL). The organic layer was collected, dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The subsequent crude yellow residue was subjected to flash chromatography (1:9 v/v ethyl acetate in petroleum ether to 3:7 v/v ethyl acetate in petroleum ether), the relevant fractions were collected and concentrated under reduced pressure (R_f = 0.4 in 3:7 v/v ethyl acetate/petroleum ether), affording compound **20** (1.15 g, 69%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 3.60 (s, 2H), 1.95-1.88 (complex m, 4H), 1.00-0.94 (complex m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 163.3, 110.3, 36.0, 30.9, 7.3; FTIR ν_{max} (thin film) 2988, 2949, 1750, 1469, 1364, 1309, 1280, 1157, 1060, 1044, 999, 976, 960, 884, 837 cm⁻¹; GC-MS: R_t = 7.3-7.7 min, m/z 87 [(M – C₃HO₃·, 100%]; HRMS (TOF, EI) m/z (M – C₃H₂O₃·) calcd. C₅H₁₀O for 86.0726, found 86.0727.

2,2-Diisopropyl-1,3-dioxane-4,6-dione (**21**)

The reaction of malonic acid (**15**) with 2,4-dimethylpentan-3-one proceeded in accordance with general procedure 1 and the reaction mixture afforded a yellow oil upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated ($R_f = 0.2$ in 1:9 v/v ethyl acetate/petroleum ether) under reduced pressure, providing compound **21** (320 mg, 16%) as colourless crystalline needles, m.p. = 46-49 °C. ^1H NMR (400 MHz, CDCl_3) δ 3.53 (s, 2H), 2.35 (p, $J = 6.8$ Hz, 2H), 1.02 (d, $J = 6.8$ Hz, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.9, 114.5, 35.3, 35.2, 16.0; FTIR ν_{max} (thin film) 2978, 1755, 1472, 1296, 1094, 1041, 1002, 887, 824 cm^{-1} ; GC-MS: $R_t = 12.2$ -12.7 min, m/z 157 [(M – CH_3 ·, 12%)], 114 [(M – $\text{C}_3\text{H}_2\text{O}_3$ ·, 10%)], 71 [(M – $\text{C}_5\text{H}_9\text{O}$ ·, 100%)]; HRMS (TOF, EI) m/z (M – $\text{C}_3\text{H}_2\text{O}_3$ ·) calcd. $\text{C}_7\text{H}_{14}\text{O}$ for 114.1039, found 114.104.

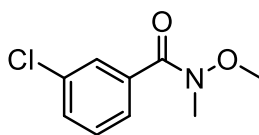
2-Methyl-2-propyl-1,3-dioxane-4,6-dione (**22**)



The reaction of malonic acid (**15**) with 2-pentanone proceeded in accordance with general procedure 1 and the reaction mixture afforded a clear oil upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.2$ in 1:9 v/v ethyl acetate/petroleum ether), providing compound **22** (840 mg, 50%) as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 3.61 (s, 2H), 1.95-1.91 (complex m, 2H), 1.73 (s, 3H), 1.59-1.49 (complex m, 2H), 0.98 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.1, 108.1, 42.7, 36.3, 25.9, 16.6, 13.9; FTIR ν_{max} (thin film) 2967, 2925, 2879, 1751, 1458, 1390, 1291, 1173,

1104, 1066, 1043, 973, 811 cm^{-1} ; GC-MS: $R_t = 7.2\text{-}7.3$ min, m/z 129 [(M – C_3H_7 , 80%)], 86 [(M – $\text{C}_3\text{H}_2\text{O}_3$, 90%)], 71 [(M – $\text{C}_4\text{H}_5\text{O}_3$, 100%)]; HRMS (TOF, EI) m/z (M – $\text{C}_3\text{H}_2\text{O}_3$) calcd. $\text{C}_5\text{H}_{10}\text{O}$ for 86.0726, found 86.0723.

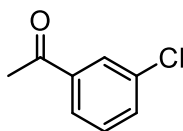
3-Chloro-N-methoxy-N-methylbenzamide (**25**)



Thionyl chloride (4.0 mL, 41.3 mmol) was added to a magnetically stirred solution of *m*-chlorobenzoic acid (**23**) (5.0 g, 40.9 mmol) in DCM (5 mL) under a nitrogen atmosphere and the resulting suspension was stirred at ambient temperatures for 7 h. Thereafter another equivalent of thionyl chloride (4.0 mL, 41.3 mmol) was added to the reaction mixture along with a drop of DMF. After stirring for a further 18 h at ambient temperatures, the reaction mixture was concentrated under reduced pressure to remove the excess thionyl chloride. The reaction mixture was diluted with more DCM (10 mL) and the reaction mixture was subsequently cooled in an ice-water bath. N,O-dimethylhydroxylamine hydrochloride (**24**) (5.6 g, 38.2 mmol) and triethylamine (7.0 mL, 64.5 mmol) were added and then the ice-water bath was removed. The reaction was stirred at ambient temperatures for 4 h. When the reaction was deemed complete by TLC (1:9 v/v ethyl acetate/petroleum ether), the solvent was removed under reduced pressure and the resulting orange residue was dissolved in ethyl acetate (10 mL) and washed with water (2 × 15 mL) then sodium bicarbonate (3 × 15 mL of a sat. aq. solution), followed by brine (2 × 15 mL). The resulting organic layer was concentrated under reduced pressure ($R_f = 0.3$ in 1:9 v/v ethyl acetate/petroleum

ether), affording amide **25** (4.40 g, 69%) as an orange oil. ^1H NMR (400 MHz, CDCl_3) δ 7.67 (t, J = 1.7 Hz, 1H), 7.56 (dt, J = 7.9 and 1.5 Hz, 1 H), 7.43 (ddd, J = 8.0, 2.1, 1.1 and 1.0 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 3.55 (s, 3H), 3.36 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.5, 135.9, 134.2, 130.8, 129.5, 128.5, 126.5, 61.3, 33.7; FTIR ν_{max} (thin film) 2936, 1645, 1568, 1419, 1375, 1211, 1082, 982, 894, 799, 763, 732, 673, 578 cm^{-1} ; GC-MS: R_t = 8.6-8.7 min, m/z 199 [$(\text{M}^+$, 5%)], 139 [$(\text{M} - \text{C}_2\text{H}_6\text{NO}^+$, 100%)]; HRMS (TOF, EI) m/z calcd. (M^+) $\text{C}_9\text{H}_{10}\text{ClNO}_2$ for 199.3095, found 199.3096.

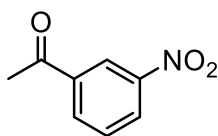
3'-Chloroacetophenone (**26**)



The synthesised amide **25** (4.4 g, 22.1 mmol) was added to a 100 mL three neck round bottom flask, charged with a magnetic stirrer bar and held under a constant nitrogen atmosphere via an inlet adaptor. The remaining two necks were plugged with rubber septa. The flask was added to an ice-water bath, whereby anhydrous THF (10 mL) was added via syringe to the flask and the resulting mixture was stirred for 15 min. Methylmagnesium bromide (9.0 mL of 3.0 M solution in anhydrous diethyl ether, 26.6 mmol) was added dropwise over 1 h, after which the reaction was left to stir in the ice-water bath for a further 15 min. The ice-water bath was removed and the reaction mixture was stirred at ambient temperatures for 18 h. The resulting reaction mixture was quenched with the addition of water (20 mL), followed by extraction with ethyl acetate (3×10 mL). The resulting combined organic layer was dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by being passed through a silica

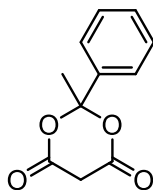
plug (silica, 1:9 v/v ethyl acetate/petroleum ether). The resulting solvent collection was concentrated under reduced pressure ($R_f = 0.5$), affording desired acetophenone **26** (2.70 g, 78%) as a pale-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.92 (s, 1H), 7.83 (d, $J = 7.8$ Hz, 1H), 7.53 (d, $J = 7.9$ Hz, 1H), 7.41 (t, $J = 7.8$ Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 196.8, 138.8, 135.1, 133.2, 130.1, 128.6, 126.6, 26.8; FTIR ν_{max} (thin film) 3068, 1685, 1571, 1471, 1422, 1355, 1104, 1073, 957, 900, 786, 682, 586, 469 cm^{-1} ; GC-MS: $R_t = 6.7$ -6.8 min, m/z 154 [(M – $\text{C}_3\text{H}_2\text{O}_3$ ·, 40%)], 139 [(M – $\text{C}_4\text{H}_5\text{O}_3$ ·, 100%)]; HRMS (TOF, EI) m/z (M – $\text{C}_3\text{H}_2\text{O}_3$) calcd. $\text{C}_8\text{H}_7\text{ClO}$ for 154.018, found 154.0186.

3'-Nitroacetophenone (**28**)

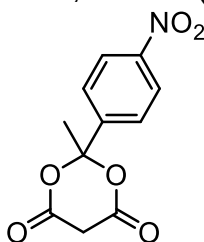


A three-necked 100 mL round bottom flask was charged with a magnetic stirrer bar and internal thermometer. The flask had sulphuric acid (conc., 10 mL) added and was subsequently immersed in an ice-water bath. Acetophenone (**27**) (4.0 mL, 34.2 mmol) was added dropwise through a pressure-equalizing dropping funnel and the reaction mixture was subsequently stirred at the temperature of the ice-water bath for 10 min. A pressure-equalizing dropping funnel containing a mixture of sulphuric acid (conc., 4.0 mL) and nitric acid (conc., 2.7 mL, 60.8 mmol) was prepared as the nitrating mixture and the ice-water bath was swapped for a dry-ice/acetone bath. The acetophenone solution was cooled until the internal thermometer read a temperature of -40 °C and then the nitrating mixture was slowly added dropwise, keeping the

internal temperature under $-40\text{ }^{\circ}\text{C}$ to prevent runaway reactions. Keeping the internal contents of the flask at $-40\text{ }^{\circ}\text{C}$ resulted in two solid layers being formed within the flask, so the dry-ice/acetone bath was swapped for an ice-water bath. The reaction mixture was warmed to the temperature of the ice-water bath, to allow the formed solid layers to melt and subsequently mix. The reaction mixture was stirred at the temperature of the ice-water bath for 10 min and was then quenched with the addition of ice-water (15 mL), diluted with DCM (10 mL) and washed with sodium bicarbonate solution ($3 \times 30\text{ mL}$ of sat. aq. solution) followed by brine ($2 \times 15\text{ mL}$). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure, providing a yellow residue. The residue was subjected to flash chromatography (silica, 10% ethyl acetate/petroleum ether to 30% ethyl acetate/petroleum ether gradient elution), affording a yellow solid after the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.4$ in 3:7 v/v ethyl acetate/petroleum ether). The solid was obtained as a mixture of *o*- and *m*-regio-isomers. The *o*-regio-isomer was separated by washing the solid residue with diethyl ether (10 mL) over a sintered funnel, thereby dissolving the *o*-regio-isomer and providing the *m*-regio-isomer compound **28** (3.04 g, 54%) as a yellow solid, m.p. = $76\text{--}77\text{ }^{\circ}\text{C}$ (lit.⁶ m.p. = $78\text{--}79\text{ }^{\circ}\text{C}$). ^1H NMR (400 MHz, CDCl_3) δ 8.77 (q, $J = 2.2\text{ Hz}$, 1H), 8.42 (dtd, $J = 8.2, 2.2$ and 1.1 Hz , 1H), 8.29 (dq, $J = 7.8$ and 1.4 Hz , 1H), 7.69 (t, $J = 8.0\text{ Hz}$, 1H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 195.8, 148.6, 138.4, 133.9, 130.0, 127.6, 123.4, 26.9; FTIR ν_{max} (thin film) 3090, 1692, 1615, 1581, 1527, 1472, 1434, 1351, 1278, 1248, 1110, 1065, 972, 912, 874, 819, 764, 741, 676, 591 cm^{-1} ; GC-MS: $R_t = 8.2\text{--}8.4\text{ min}$, m/z 165 [M^+ , 20%], 150 [$\text{M} - \text{CH}_3$, 100%]; HRMS (TOF, EI) m/z (M^+) calcd. $\text{C}_9\text{H}_{10}\text{NO}_2$ for 164.0706, found 164.0713.

2-Methyl-2-phenyl-1,3-dioxane-4,6-dione (**29**)

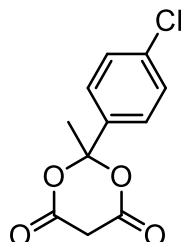
The reaction of malonic acid (**15**) with acetophenone (**27**) proceeded in accordance with general procedure 1 and the reaction mixture afforded a yellow oil upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.5$ in 3:7 v/v ethyl acetate/petroleum ether), providing compound **29** (260 mg, 13%) as another yellow oil. The oil was recrystallized through vapour-vapour diffusion techniques using 1:1 v/v *n*-pentane/diethyl ether, affording colourless needles as crystals, m.p. = 92-93 °C (lit.⁴ m.p. = 91-92 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.47-7.43 (complex m, 5H), 3.42 (d, $J = 19.6$ Hz, 1H), 2.98 (d, $J = 19.6$ Hz, 1H), 1.98 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 163.7, 139.7, 130.3, 129.7, 124.8, 106.6, 38.8, 30.3; FTIR ν_{max} (thin film) 3002, 2913, 1796, 1765, 1497, 1449, 1381, 1284, 1245, 1130, 1087, 1055, 966, 856, 766, 703, 666 cm⁻¹; GC-MS: $R_t = 5.5$ -5.6 min, m/z 120 [(M - C₃H₂O₃·, 30%)], 105 [(M - C₄H₅O₃·, 100%)]; HRMS (TOF, EI) m/z (M - C₃H₂O₃·) calcd. C₈H₈O for 120.057, found 120.057.

2-Methyl-2-(4-nitrophenyl)-1,3-dioxane-4,6-dione (**30**)

General procedure 1 was followed until after addition of the *p*-nitroacetophenone to malonic acid (**15**), whereby the reaction mixture was stirred at ambient temperatures

for 48 h. The resulting brown suspension was dissolved in DCM (20 mL) and washed with water (3×15 mL). The organic layer was collected and washed with brine solution (2×15 mL). The organic layer was collected again, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate/petroleum ether to 1:1 v/v ethyl acetate/petroleum ether) and the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.2$ in 1:1 v/v ethyl acetate/petroleum ether), affording a brown powder as compound **30** (580 mg, 24%). The brown powder was recrystallized through being redissolved in CH_3Cl and letting the solvent slowly evaporate for 5 days, yielding colourless plates as crystals, m.p. = 147-148 °C, (lit.⁷ m.p. = 160 °C). ^1H NMR (400 MHz, CDCl_3) δ 8.35-8.31 (complex m, 2H), 7.73-7.69 (complex m, 2H), 3.53 (d, $J = 19.8$ Hz, 1H), 2.98 (d, $J = 19.9$ Hz, 1H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.5, 145.9, 126.3, 125.0, 105.4, 38.4, 30.2; FTIR (thin film) ν_{max} 3079, 2901, 1794, 1765, 1661, 1519, 1354, 1289, 1247, 1166, 1061, 975, 943, 862, 841, 807, 755, 702 cm^{-1} ; GC-MS: $R_t = 8.3$ -8.4 min, m/z 165 [(M – $\text{C}_3\text{H}_2\text{O}_3$ ·, 10%)], 150 [(M – $\text{C}_4\text{H}_5\text{O}_3$ ·, 100%)]; HRMS (TOF, EI) m/z (M – $\text{C}_3\text{H}_2\text{O}_3$ ·) calcd. $\text{C}_8\text{H}_7\text{NO}_3$ for 165.042, found 165.0416.

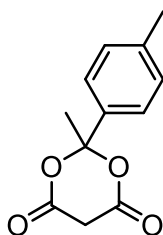
2-(4-Chlorophenyl)-2-methyl-1,3-dioxane-4,6-dione (**31**)



General procedure 1 was followed until after addition of *p*-chloroacetophenone to malonic acid (**15**), whereby the reaction mixture was stirred at ambient temperatures

for 24 h. A brown oil was obtained after the stirring period and the work-up procedure of general procedure 1 was subsequently followed. The work-up afforded a brown oil, which was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/petroleum ether to 3:7 v/v ethyl acetate/petroleum ether), the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.2$ in 3:7 v/v ethyl acetate/petroleum ether), affording compound **31** (210 mg, 9%) as an orange oil. The oil was dissolved in 1:1 v/v diethyl ether/n-pentane, the flask was transferred to a freezer thermostated at $-80\text{ }^{\circ}\text{C}$ and was cooled for 3 days. The desired product precipitated from solution and was obtained as pale-brown crystals, m.p. = $111\text{--}112\text{ }^{\circ}\text{C}$ (lit.⁷ m.p. = $108\text{--}111\text{ }^{\circ}\text{C}$). ^1H NMR (400 MHz, CDCl_3) δ 7.45-7.40 (complex m, 4H), 3.48 (d, $J = 19.7\text{ Hz}$, 1H), 3.03 (d, $J = 19.7\text{ Hz}$, 1H), 1.95 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.2, 138.2, 136.7, 130.0, 126.3, 106.0, 38.6, 30.3; FTIR ν_{max} (thin film) 2878, 1797, 1760, 1490, 1380, 1285, 1246, 1167, 1094, 1055, 963, 831, 724, 598, 506 cm^{-1} ; GC-MS: $R_t = 6.8\text{--}6.9\text{ min}$, m/z 154 $[(\text{M} - \text{C}_3\text{H}_2\text{O}_3)^+, 20\%]$, 139 $[(\text{M} - \text{C}_4\text{H}_5\text{O}_3)^+, 100\%]$; HRMS (TOF, EI) m/z ($\text{M} - \text{C}_3\text{H}_2\text{O}_3$) calcd. $\text{C}_8\text{H}_7\text{ClO}$ for 154.018, found 154.0181.

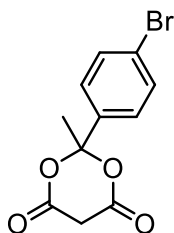
2-Methyl-2-(p-tolyl)-1,3-dioxane-4,6-dione (**32**)



The reaction of malonic acid (**15**) with *p*-methylacetophenone proceeded in accordance with general procedure 1 and the reaction mixture afforded a yellow oil upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.2$ in 3:7 v/v

ethyl acetate/petroleum ether), affording compound **32** (212 mg, 10%) as another yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.33 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 3.44 (d, J = 19.6 Hz, 1H), 3.04 (d, J = 19.6 Hz, 1H), 2.37 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.8, 140.5, 136.8, 130.3, 124.8, 106.8, 38.8, 30.3, 21.3; FTIR ν_{max} (thin film) 2996, 2915, 1797, 1765, 1679, 1607, 1381, 1291, 1257, 1160, 1086, 1054, 986, 851, 819 cm^{-1} ; GC-MS: R_t = 6.4-6.5 min, m/z 134 [(M – $\text{C}_3\text{H}_2\text{O}_3$ ·, 30%)], 119 [(M – $\text{C}_4\text{H}_5\text{O}_3$ ·, 100%)]; HRMS (TOF, EI) m/z (M – $\text{C}_3\text{H}_2\text{O}_3$ ·) calcd. $\text{C}_9\text{H}_{10}\text{O}$ for 134.0724, found 134.0726.

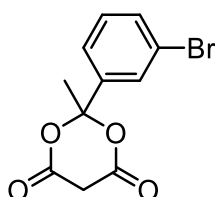
2-(4-Bromophenyl)-2-methyl-1,3-dioxane-4,6-dione (**33**)



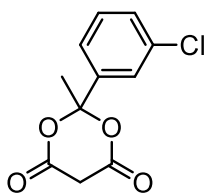
The reaction of malonic acid (**15**) with *p*-bromoacetophenone proceeded in accordance with general procedure 1 and the reaction mixture afforded a brown oil upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure (R_f = 0.1 in 3:7 v/v ethyl acetate/petroleum ether), affording a brown oil as compound **33** (70.0 mg, 3%). The oil was recrystallized using vapour-vapour diffusion techniques using 1:1 v/v diethyl ether/*n*-hexane, providing colourless block crystals, m.p. = 108-110 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.61-7.58 (complex m, 2H), 7.37-7.33 (complex m, 2H), 3.49 (d, J = 19.7 Hz, 1H), 3.04 (d, J = 19.7 Hz, 1H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.2, 138.7, 133.0, 126.6, 124.9, 106.1, 38.6, 30.3; FTIR ν_{max} (thin film) 3007, 2910, 1797, 1768, 1591, 1488, 1399, 1291, 1250, 1165, 1086, 1058, 968, 828

cm^{-1} ; GC-MS: $R_t = 7.5\text{-}7.7$ min, m/z 198 [(M – C₃H₂O₃·, 30%)], 183 [(M – C₄H₅O₃·, 100%)]]; HRMS (TOF, EI) m/z (M – C₃H₂O₃·) calcd. C₈H₇[⁷⁹Br]O for 197.9675, found 197.9674; calcd. C₈H₇[⁸¹Br]O for 199.9654, found 199.9645.

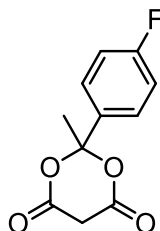
2-(3-Bromophenyl)-2-methyl-1,3-dioxane-4,6-dione (**34**)



The reaction of malonic acid (**15**) with *m*-bromoacetophenone proceeded in accordance with general procedure 1. The reaction mixture afforded a brown oil upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.1$ in 3:7 v/v ethyl acetate/petroleum ether), providing compound **34** (310 mg, 11%) as another brown oil. The oil residue was recrystallized using vapour-vapour diffusion techniques using 1:1 v/v diethyl ether/*n*-hexane to afford colourless plate crystals, m.p. = 117-119 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.65-7.56 (complex m, 2H), 7.42 (dt, $J = 7.8$ Hz, 1H), 7.33 (t, $J = 7.9$ Hz, 1H), 3.48 (d, $J = 19.6$ Hz, 1H), 3.04 (d, $J = 19.7$ Hz, 1H), 1.96 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 163.1, 141.8, 133.6, 131.3, 128.2, 124.0, 123.5, 105.6, 38.7, 30.3; FTIR ν_{max} (thin film) 3001, 2907, 1796, 1765, 1570, 1473, 1414, 1382, 1290, 1241, 1164, 1088, 1056, 969, 849, 792, 701 cm^{-1} ; GC-MS: $R_t = 7.5\text{-}7.6$ min, m/z 198 [(M – C₃H₂O₃·, 40%)], 183 [(M – C₄H₅O₃·, 100%)]]; HRMS (TOF, EI) m/z (M – C₃H₂O₃·) calcd. C₈H₇[⁷⁹Br]O for 197.9675, found 197.9683; calcd. C₈H₇[⁸¹Br]O for 199.9654, found 199.9663.

2-(3-Chlorophenyl)-2-methyl-1,3-dioxane-4,6-dione (**35**)

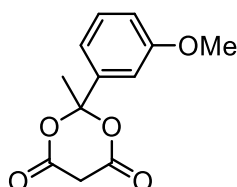
The reaction of malonic acid (**15**) with *m*-chloroacetophenone (**26**) proceeded in accordance with general procedure 1 and the reaction mixture afforded an orange oil upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.3$ in 3:7 v/v ethyl acetate/ petroleum ether), providing compound **35** (120 mg, 8%) as colourless prism crystals, m.p. = 100-101 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.47-7.35 (complex m, 4H), 3.47 (d, $J = 19.7$ Hz, 1H), 3.04 (d, $J = 19.7$ Hz, 1H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.1, 141.6, 136.0, 131.1, 130.7, 125.3, 123.0, 105.7, 38.7, 30.3; FTIR ν_{max} (thin film) 3328, 3007, 1666, 1579, 1481, 1422, 1390, 1354, 1263, 1182, 1104, 1075, 1005, 958, 819, 739, 710, 604, 590 cm^{-1} ; GC-MS: $R_t = 6.8$ -6.9 min, m/z 154 [(M - $\text{C}_3\text{H}_2\text{O}_3$), 40%], 139 [(M - $\text{C}_4\text{H}_5\text{O}_3$), 100%]; HRMS (TOF, EI) m/z (M - $\text{C}_3\text{H}_2\text{O}_3$) calcd. for 154.018, found 154.0185.

2-(4-Fluorophenyl)-2-methyl-1,3-dioxane-4,6-dione (**36**)

The reaction of malonic acid (**15**) with *p*-fluoroacetophenone proceeded in accordance with general procedure 1 and the reaction afforded a brown oil upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected

and concentrated under reduced pressure ($R_f = 0.3$ in 3:7 v/v ethyl acetate/petroleum ether), providing compound **36** (420 mg, 20%) as a brown oil. The oil was redissolved in DCM and recrystallized through using vapour-vapour diffusion techniques with 1:1 v/v diethyl ether/petroleum ether, affording colourless prism crystals, m.p. = 115-116 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.49-7.44 (complex m, 2H), 7.17-7.11 (complex m, 2H), 3.49 (d, $J = 19.7$ Hz, 1H), 3.03 (d, $J = 19.7$ Hz, 1H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.8, 163.3, 162.3, 135.7(2), 127.1, 127.0, 117.0, 116.7, 106.2, 38.6, 30.4; FTIR ν_{max} (thin film) 3006, 2924, 1765, 1603, 1510, 1381, 1289, 1235, 1160, 1088, 1054, 966, 839, 620, 516 cm^{-1} ; GC-MS: $R_t = 5.4$ -5.5 min, m/z 138 [(M – $\text{C}_3\text{H}_2\text{O}_3$ ·, 30%)], 123 [(M – $\text{C}_4\text{H}_5\text{O}_3$ ·, 100%)]; HRMS (TOF, EI) m/z (M – $\text{C}_3\text{H}_2\text{O}_3$ ·) calcd. $\text{C}_8\text{H}_7\text{FO}$ for 138.0475, found 138.0479.

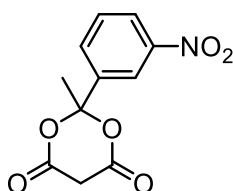
2-(3-Methoxyphenyl)-2-methyl-1,3-dioxane-4,6-dione (**37**)



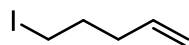
The reaction of malonic acid (**15**) with *m*-methoxyacetophenone proceeded in accordance with general procedure 1 and the reaction mixture afforded an orange oil upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.3$ in 3:7 v/v ethyl acetate/petroleum ether), providing compound **37** (750 mg, 33%) as another viscous orange oil. ^1H NMR (400 MHz, CDCl_3) δ 7.35 (t, $J = 8.5$ Hz, 1H), 7.03 (d, $J = 8.0$ Hz, 1H), 6.96-6.94 (complex m, 2H), 3.81 (s, 3H), 3.43 (d, $J = 19.5$ Hz, 1H), 3.05 (d, $J = 19.5$ Hz, 1H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.7, 160.5, 141.2,

130.9, 116.9, 115.7, 110.6, 106.4, 55.6, 38.8, 30.1; FTIR $\nu_{\max}$ (thin film) 3005, 2912, 2838, 1766, 1602, 1487, 1435, 1383, 1293, 1263, 1219, 1161, 1044, 970, 850, 787, 767, 705 cm^{-1} ; GC-MS: R_t = 6.9-7.3 min, m/z 150 [(M – C₃H₂O₃·, 70%)], 135 [(M – C₄H₅O₃·, 100%)]; HRMS (TOF, EI) m/z (M – C₃H₂O₃·) calcd. C₉H₁₀O₂ for 150.0686, found 150.0675.

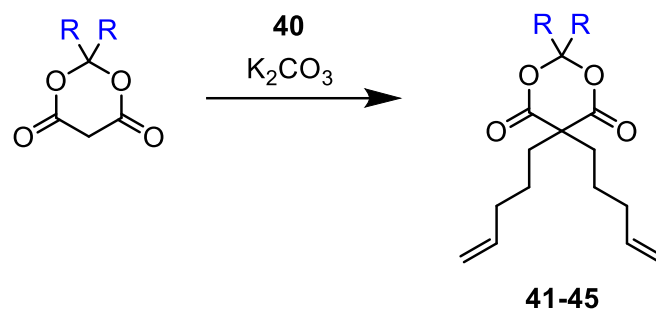
2-Methyl-2-(3-nitrophenyl)-1,3-dioxane-4,6-dione (**38**)



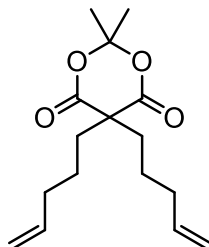
The reaction of malonic acid (**15**) with *m*-nitroacetophenone (**28**) proceeded in accordance with general procedure 1 and the reaction afforded a yellow oil upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure (R_f = 0.2 in 3:7 v/v ethyl acetate/petroleum ether), providing compound **38** (170 mg, 7%) as pale-yellow needles, m.p. = 119-121 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.37-8.31 (complex m, 3H), 7.85 (ddd, J = 7.8, 1.9 and 1.1 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 3.55 (d, J = 19.9 Hz, 1H), 3.03 (d, J = 19.9 Hz, 1H), 2.02 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 162.4, 141.8, 131.2, 130.7, 125.3, 120.3, 105.2, 38.4, 30.4; FTIR $\nu_{\max}$ (thin film) 3092, 2907, 1801, 1766, 1534, 1356, 1354, 1283, 1249, 1167, 1114, 1059, 974, 847, 813, 739, 707, 689 cm^{-1} ; GC-MS: R_t = 8.2-8.4 min, m/z 165 [(M – C₃H₂O₃·, 20%)], 150 [(M – C₄H₅O₃·, 100%)]; HRMS (TOF, EI) m/z (M – C₃H₂O₃·) calcd. C₈H₇NO₃ for 165.042, found 165.0417.

5-iodo-1-pentene (**40**)

Sodium iodide (12.8 g, 85.3 mmol) was added to a solution of 5-bromo-1-pentene **39** (5 mL, 42.0 mmol) in acetone (10 mL). The resulting reaction mixture was refluxed for 18 h and subsequently cooled to ambient temperatures. The solution was diluted in diethyl ether (20 mL), washed with water (3 × 20 mL), dried (Na₂SO₄), filtered, and the resulting organic layer was concentrated under reduced pressure (CAUTION: compound volatile; *R*_f = 0.8 in petroleum ether). Compound **40** (6.96 g, 85%) was provided as a brown oil. ¹H NMR (400 MHz, CDCl₃) δ 5.74 (ddt, *J* = 16.9, 10.1 and 6.7 Hz, 1H), 5.11-5.01 (complex m, 2H), 3.20 (t, *J* = 6.9 Hz, 2H), 2.17 (q, *J* = 7.0 Hz, 2H), 1.92 (p, *J* = 7.0 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 136.7, 116.1, 34.4, 32.6, 6.5; FTIR *ν*_{max} (thin film) 2960, 2918, 1719, 1534, 1455, 1381, 1262, 1164, 1090, 1022, 966, 797, 768 cm⁻¹; satisfactory low resolution mass spectra data could not be obtained on this compound; HRMS (TOF, EI) *m/z* calcd. C₅H₈[¹²⁷I] for 194.9671, found 194.666.

General procedure 2:

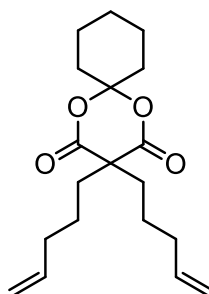
Anhydrous potassium carbonate (2.1 equiv.) and compound **40** (2.1 equiv.) were added to a magnetically stirred solution of the respective Meldrum's acid (70 mg, 1 equiv.) in anhydrous DMF (5 mL). The reaction mixture was stirred at ambient temperatures for 18 h and subsequently quenched with water (5 mL). The reaction mixture was then diluted with ethyl acetate (20 mL) and washed with water (3 × 15 mL). The collected organic layer was washed with brine (2 × 15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was purified through flash chromatography (silica, 5:95 v/v ethyl acetate/petroleum ether) and the relevant fractions were collected and concentrated under reduced pressure.

2,2-Dimethyl-5,5-di(pent-4-en-1-yl)-1,3-dioxane-4,6-dione (41**)**

General procedure 2 was followed but the quantities used were different. Meldrum's acid (50 mg, 0.3 mmol) was dissolved in anhydrous DMF (3 mL), followed by the addition of anhydrous potassium carbonate (100 mg, 0.72 mmol) and compound **40**

(150 mg, 0.75 mmol). The work-up and purification steps were as described in general procedure 2. The relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.6$ in 1:9 v/v ethyl acetate/petroleum ether), affording compound **41** (60 mg, 62%) as a white wax-like solid. The solid was recrystallized using vapour-vapour diffusion techniques using 1:9 v/v diethyl ether/n-hexane and colourless prism crystals were obtained, m.p. (non-crystalline) = 51-52 °C (lit.⁸ m.p. = 53-55 °C), m.p. (crystalline) = 227-228 °C (decomposed). ^1H NMR (400 MHz, CDCl_3) δ 5.71 (ddt, $J = 16.9, 10.2$ and 6.6 Hz, 2H), 5.01-4.95 (complex m, 4H), 2.07-1.98 (complex m, 8H), 1.73 (s, 6H), 1.43-1.35 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.5, 137.3, 115.7, 105.7, 54.7, 38.9, 33.5, 30.0, 25.0; FTIR ν_{max} (thin film) 3081, 2923, 2860, 1772, 1735, 1642, 1459, 1392, 1381, 1339, 1273, 1234, 1205, 1062, 978, 911, 749, 704, 638 cm^{-1} ; GC-MS: (i) $R_t = 7.6$ -7.7 min, m/z 178 [(M - $\text{C}_4\text{H}_6\text{O}_3^\cdot$, 1%)], 136 [(M - $\text{C}_6\text{H}_7\text{O}_4^\cdot$, 100%)], 121 [(M - $\text{C}_7\text{H}_{11}\text{O}_4^\cdot$, 90%)], 94 [(M - $\text{C}_9\text{H}_{13}\text{O}_4^\cdot$, 100%)]; (ii) $R_t = 10.2$ -10.3 min, m/z 176 [(M - $\text{C}_4\text{H}_9\text{O}_3^\cdot$, 20%)], 154 [(M - $\text{C}_6\text{H}_5\text{O}_3^\cdot$, 60%)], 136 [(M - $\text{C}_6\text{H}_7\text{O}_4^\cdot$, 70%)], 122 [(M - $\text{C}_7\text{H}_{10}\text{O}_4^\cdot$, 65%)], 67 [(M - $\text{C}_{11}\text{H}_{17}\text{O}_4^\cdot$, 100%)]; HRMS (TOF, EI) m/z (M - $\text{C}_4\text{H}_6\text{O}_3^\cdot$) calcd. $\text{C}_{12}\text{H}_{19}\text{O}$ 179.1437, found 179.143.

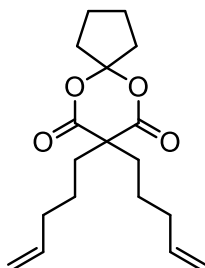
3,3-Di(pent-4-en-1-yl)-1,5-dioxaspiro[5.5]undecane-2,4-dione (**42**)



The reaction of compounds **40** and **16** proceeded in accordance with general procedure 2 and a yellow oil was afforded upon work-up. The residue was subjected

to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.2$ in 5:95 v/v ethyl acetate/petroleum ether), providing compound **42** (80 mg, 61%) as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 5.73 (ddt, $J = 16.8, 10.1$ and 6.7 , 2H), 5.04-4.94 (complex m, 4H), 2.05-1.97 (complex m, 8H), 1.89 (t, $J = 6.1$ Hz, 4H), 1.73 (p, $J = 5.9$ Hz, 4H), 1.49 (p, $J = 6.0$ Hz, 2H), 1.42-1.33 (complex m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.6, 137.4, 115.6, 106.2, 55.2, 38.9 (2), 33.5, 24.9, 24.1, 22.2; FTIR ν_{max} (thin film) 3076, 2931, 2862, 1771, 1740, 1640, 1450, 1365, 1265, 1136, 1036, 986, 912 cm^{-1} ; GC-MS: $R_t = 12.0$ -12.3 min, m/z 176 [(M - $\text{C}_7\text{H}_{12}\text{O}_3$), 20%], 98 [(M - $\text{C}_{13}\text{H}_{18}\text{O}_3$), 100%]; HRMS (TOF, EI) m/z (M - $\text{C}_{13}\text{H}_{18}\text{O}_3$) calcd. $\text{C}_6\text{H}_{11}\text{O}$ for 99.0804, found 99.0807.

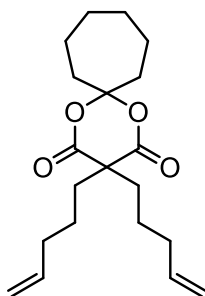
8,8-Di(pent-4-en-1-yl)-6,10-dioxaspiro[4.5]decane-7,9-dione (**43**)



General procedure 2 was followed but the quantities used were different. Compound **17** (50 mg, 0.3 mmol) was dissolved in anhydrous DMF (3 mL), whereby anhydrous potassium carbonate (80 mg, 0.6 mmol) and compound **40** (120 mg, 0.61 mmol) were subsequently added. The work-up and purification steps were as described in general procedure 2. The relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.5$ in 5:95 v/v ethyl acetate/ petroleum ether) and compound **43** (40 mg, 50%) was provided as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 5.73 (ddt, $J = 16.9, 10.2$ and 6.7 Hz, 2H), 5.01-4.95 (complex m, 4H), 2.14 (t, $J = 8$ Hz, 4H), 2.06-

1.97 (complex m, 8H), 1.89-1.86 (complex m, 4H), 1.42-1.34 (complex m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.7, 137.4, 115.6, 114.6, 55.0, 40.5, 38.2, 33.5, 24.7, 23.5; FTIR ν_{max} (thin film) 3077, 2930, 1776, 1742, 1641, 1456, 1339, 1269, 1240, 993, 912 cm^{-1} ; GC-MS: (i) R_t = 7.5-7.7 min, m/z 178 [(M – $\text{C}_6\text{H}_{10}\text{O}_3$ ·, 1%)], 136 [(M – $\text{C}_9\text{H}_{14}\text{O}_3$ ·, 100%)], 121 [(M – $\text{C}_9\text{H}_{12}\text{O}_4$ ·, 80%)], 67 [(M – $\text{C}_{13}\text{H}_{19}$ ·, 90%)] (ii) R_t = 11.4-12.0 min, m/z 84 [(M – $\text{C}_{13}\text{H}_{20}\text{O}_3$ ·, 70%)], 55 [(M – $\text{C}_{14}\text{H}_{19}\text{O}_4$ ·, 100%)] HRMS (TOF, EI) m/z (M – $\text{C}_{13}\text{H}_{20}\text{O}_3$ ·) calcd. $\text{C}_5\text{H}_8\text{O}$ for 84.057, found 84.0572; (M – $\text{C}_6\text{H}_8\text{O}_3$ ·) calcd. $\text{C}_{12}\text{H}_{18}\text{O}$ for 178.1352, found 178.1359.

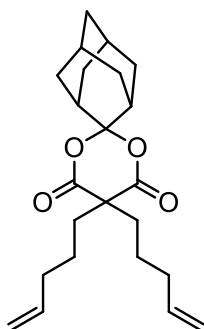
3,3-Di(pent-4-en-1-yl)-1,5-dioxaspiro[5.6]dodecane-2,4-dione (**44**)



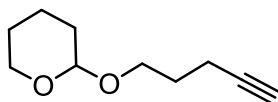
The reaction of compounds **40** and **18** proceeded in accordance with general procedure 2 and a yellow oil was afforded upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure (R_f = 0.5 in 5:95 v/v ethyl acetate/petroleum ether), providing compound **44** (70 mg, 60%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 5.72 (ddt, J = 16.9, 10.2 and 6.6 Hz, 2H), 5.01-4.95 (complex m, 4H), 2.10-1.96 (complex m, 12H), 1.65 (s, 8H), 1.37 (dtd, J = 14.7, 7.4 and 4.4 Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) 169.7, 137.4, 115.6, 110.2, 55.0, 42.9, 38.9, 33.5, 28.8, 24.9, 21.4; FTIR ν_{max} (thin film) 2926, 2863, 1774, 1740, 1640, 1460, 1376, 1339, 1267, 1127, 1003, 911 cm^{-1} ;

GC-MS: $R_t = 12.7$ min, m/z 176 [(M – C₈H₁₄O₃·, 5%)], 113 [(M – C₁₃H₁₇O₃·, 100%)]; HRMS (TOF, EI) m/z (M – C₈H₁₂O₃·) calcd. C₁₂H₁₈O for 178.1352, found 178.1357.

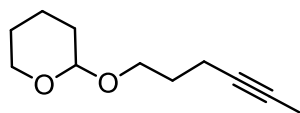
(1*r*,3*r*)-5',5'-Di(pent-4-en-1-yl)spiro[adamantane-2,2'-[1,3]dioxane]-4',6'-dione (**45**)



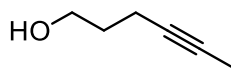
The reaction of compounds **40** and **19** proceeded in accordance with general procedure 2 and a clear oil was afforded upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.5$ in 5:95 v/v ethyl acetate/petroleum ether), providing compound **45** (70 mg, 66%) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 5.73 (ddt, $J = 16.9, 10.3$ and 6.6 Hz, 2H), 5.01-4.95 (complex m, 4H), 2.22 (d, $J = 12.8$ Hz, 4H), 2.06-1.96 (complex m, 10H), 1.90 (br s, 2H), 1.77 (d, $J = 13.9$ Hz, 6H), 1.41-1.33 (complex m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 169.7, 137.5, 115.6, 108.6, 55.1, 40.2, 38.9, 37.2, 33.6, 33.5, 26.4, 24.8; FTIR ν_{max} (thin film) 2913, 2868, 1774, 1740, 1642, 1455, 1386, 1273, 1236, 1109, 1019, 911 cm⁻¹; GC-MS: (i) $R_t = 7.7$ min m/z 178 [(M – C₁₁H₁₄O₃·, 1%)], 136 [(M – C₁₄H₂₀O₃·, 100%)], 121 [(M – C₁₅H₂₂O₃·, 90%)], 67 [(M – C₁₈H₂₅O₄·, 100%)]; (ii) $R_t = 13.9$ -14.0 min, m/z 176 [(M – C₁₁H₁₆O₃·, 1%)], 150 [(M – C₁₃H₁₈O₃·, 100%)]; HRMS (TOF, EI) m/z (M – C₁₃H₁₈O₃·) calcd. C₁₀H₁₄O for 150.1039, found 150.1047; calcd. (M – C₁₁H₁₄O₃·) C₁₂H₁₈O for 178.1352, found 178.1359.

2-(Pent-4-yn-1-yloxy)tetrahydro-2H-pyran (**48**)

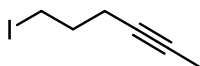
DHP (**47**) (2.20 mL, 24.1 mmol) and *p*-TsOH (spat. tip) were added to a magnetically stirred solution of pent-4-yn-1-ol (**46**) (2.0 mL, 21.5 mmol) in DCM (5 mL) in an ice-water bath. The resulting reaction mixture was stirred at ambient temperatures for 4 h. The reaction was subsequently quenched by adjusting the pH to neutrality with the addition of sodium bicarbonate (2 mL of a sat. aq. solution) and the resulting reaction mixture was left to stir for 5 min. The organic layer was separated, and the aq. layer was washed with DCM (2 × 15 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The resulting pale orange residue was subjected to flash chromatography (silica, 1:9 v/v diethyl ether/petroleum ether). The relevant fractions were collected and concentrated under reduced pressure (CAUTION: compound volatile; *R_f* = 0.4), affording compound **48** (3.23 g, 89%) as a clear oil, [α]_D = 0.3° (*c* = 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 4.60-4.56 (complex m, 1H), 3.90-3.78 (complex m, 2H), 3.53-3.41 (complex m, 2H), 2.31 (td, *J* = 7.0 and 2.4 Hz, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.81-1.50 (complex m, 4H), 1.63-1.50 (complex m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 99.0, 84.1, 68.6, 65.9, 62.4, 30.8, 28.8, 25.6, 19.7, 15.5; FTIR ν_{max} (thin film) 3295, 2941, 2871, 1441, 1353, 1322, 1261, 1200, 1136, 1119, 1032, 868, 815, 628 cm⁻¹; GC-MS: *R_t* = 3.4-3.6 min, *m/z* 115 [(*M* – C₄H₅·, 50%)], 85 [(*M* – C₅H₇O·, 100%)] 61 [(*M* – C₅H₁₅O₂·, 60%)]; HRMS (TOF, EI) *m/z* (*M*⁺) calcd. C₁₀H₁₅O₂ for 167.1067, found 167.01065.

2-(Hex-4-yn-1-yloxy)tetrahydro-2H-pyran (**49**)

Compound **48** (3.23 g, 19.2 mmol) was added to anhydrous THF (5 mL) under a nitrogen atmosphere. The solution was cooled in a dry-ice/acetone bath and *n*-BuLi (11.5 mL of a 2.0 M solution in *n*-hexanes, 22.8 mmol) was added dropwise. The resulting reaction mixture was stirred in the dry-ice/acetone bath for 15 min then iodomethane (3.6 mL, 57.8 mmol) was added dropwise. The reaction mixture was stirred in the dry-ice/acetone bath for a further 30 min, after which the bath was removed and the reaction mixture was stirred for 2 h at ambient temperatures. The reaction flask was subsequently immersed in an ice-water bath and the reaction was quenched with the slow addition of water (20 mL). Petroleum ether (2 × 15 mL) was used to extract the organic products from the aq. layer. The combined organic layers were dried (Na₂SO₄), filtered, concentrated under reduced pressure, and subjected to a silica plug (1:9 v/v ethyl acetate/petroleum ether). Concentration of the collected solution under reduced pressure (CAUTION: compound volatile; *R*_f = 0.5) afforded compound **49** (3.21 g, 92%) as a clear liquid, [α]_D = 0.7° (*c* = 1.1, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 4.60 (t, *J* = 2.8 Hz, 1H), 3.90-3.78 (complex m, 2H), 3.53-3.44 (complex m, 2H), 2.26-2.21 (complex m, 2H), 1.85-1.67 (complex m, 7H), 1.60-1.49 (complex m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 98.9, 78.7, 76.8, 75.8, 66.3, 62.3, 30.8, 29.4, 25.7, 19.7, 15.8, 3.6; FTIR ν_{max} (thin film) 2941, 2870, 1440, 1353, 1190, 1136, 1119, 1061, 1019, 1032, 988, 901, 868, 813 cm⁻¹; GC-MS: *R*_t = 7.8 min, *m/z* 181 [(*M* – H⁺, 5%)], 167 [(*M* – CH₃⁺, 20%)], 85 [(*M* – C₆H₈O⁺, 100%)]; HRMS (TOF, EI) *m/z* (*M* – H⁺) calcd. C₁₁H₁₇O₂ for 181.1223, found 181.1231.

Hex-4-yn-1-ol (**50**)

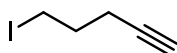
Compound **49** (3.21 g, 17.6 mmol) was magnetically stirred at ambient temperatures for 18 h in the presence of MeOH (5 mL) and *p*-TsOH (33 mg, 0.17 mmol). The resulting solution was neutralised with sodium bicarbonate (5 mL of a sat. aq. solution). The MeOH was removed under reduced pressure and the resulting solution was washed with DCM (3 × 15 mL). The organic layers were extracted, combined, dried (Na₂SO₄), filtered, and then concentrated under reduced pressure. The residue was subjected to flash chromatography (silica, 1:1 v/v diethyl ether/petroleum ether), the relevant fractions were collected and concentrated under reduced pressure (CAUTION: compound highly volatile, water bath of rotorvap at 5 °C; *R*_f = 0.3 in 3:7 v/v ethyl acetate/petroleum ether), providing compound **50** (1.45 g, 84%) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 3.75 (t, *J* = 6.1 Hz, 2H), 2.25 (tq, *J* = 6.9 and 2.4 Hz, 2H), 1.78-1.70 (complex m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 78.6, 76.4, 62.2, 31.7, 15.5, 3.6; FTIR (thin film) *ν*_{max} 3338, 2946, 2920, 2874, 1435, 1260, 1054, 1033, 930, 798 cm⁻¹; GC-MS: *R*_t = 4.4 min, (*m/z*): 97 [(*M* – H⁺, 30%)], 79 [(*M* – H₃O⁺, 100%)]; HRMS (TOF, EI) calcd. (*M*⁺) C₆H₁₀O for 98.0726, found 98.0732.

6-Iodo-hex-2-yne (**51**)

A stirred solution of triphenylphosphine (5.08 g, 19.0 mmol) and imidazole (1.38 g, 20.0 mmol) in DCM (5 mL) was cooled in an ice-water bath. Iodine crystals (5.09 g, 20.0 mmol) were added to the solution and the resulting reaction mixture was stirred

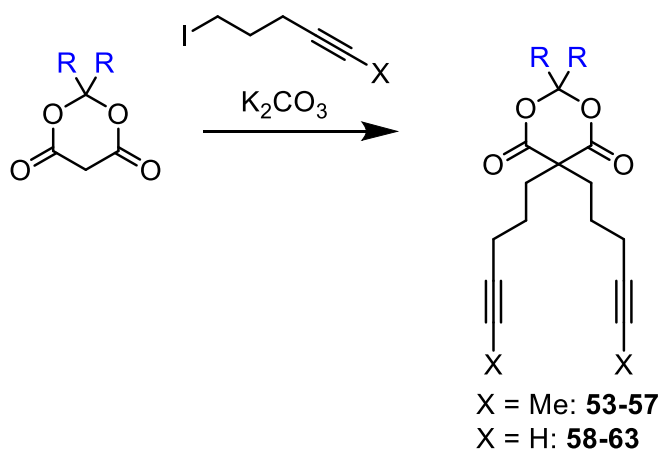
vigorously for 10 min. Compound **50** (1.45 g, 15.0 mmol) was added dropwise over 5 min, the ice-water bath was removed and then the reaction mixture was stirred at ambient temperatures for 1 h. The reaction mixture was subsequently washed with ammonium chloride (3 × 15 mL of a sat. aq. solution) and the organic layer was collected. The organic layer was dried (Na₂SO₄), filtered, immobilised on chromatography-grade silica (10 g), and concentrated under reduced pressure. The obtained fine powder was subjected to flash chromatography (petroleum ether), the relevant fractions were collected and concentrated under reduced pressure (CAUTION: compound volatile; *R*_f = 0.2), affording electrophile compound **51** (1.94 g, 63%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) 3.30 (t, *J* = 6.8 Hz, 2H), 2.28-2.24 (complex m, 2H), 1.95 (p, *J* = 6.7 Hz, 2H), 1.77 (t, *J* = 2.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 77.6, 77.0, 32.7, 20.0, 6.0, 3.7; IR *ν*_{max} (thin film) 2915, 1435, 1346, 1264, 1221, 1198, 1167, 1118, 845, 746, 720, 695, 541 cm⁻¹; GC-MS: *R*_t = 5.5-5.9 min, *m/z* 208 [(*M* + H⁺, 90%)], 81 [(*M* - I[•], 100%)]; HRMS (TOF, EI) *m/z* (*M*[•]) calcd. C₆H₉[¹²⁷I] for 207.9743, found 207.9738.

5-Iodo-pentyne (**52**)



A stirred solution of triphenylphosphine (18.7 g, 71.5 mmol) and imidazole (4.80 g, 70.5 mmol) in DCM (10 mL) was cooled in an ice-water bath. Iodine crystals (17.8 g, 70.0 mmol) was added to the solution and the resulting reaction mixture was stirred vigorously for 10 min. Compound **46** (5.0 mL, 53.7 mmol) was added dropwise over 5 min, the ice-water bath was removed and then the reaction mixture was stirred at ambient temperatures for 1 h. The resulting solution was washed with ammonium

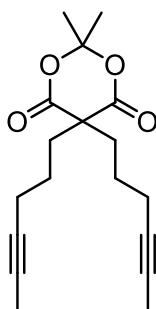
chloride (3 x 15 mL of a sat. aq. solution) and the organic layer was collected. The organic layer was dried (Na_2SO_4), filtered, immobilised on chromatography-grade silica (10 g), and concentrated under reduced pressure. The resulting fine powder was loaded subjected to flash chromatography (petroleum ether), the relevant fractions were collected and concentrated under reduced pressure (CAUTION: compound volatile; $R_f = 0.3$), affording electrophile compound **49** (2.38 g, 23%) as a pale-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 3.31 (t, $J = 6.7$ Hz, 2H), 2.34 (td, $J = 6.7$ and 2.7 Hz, 2H), 2.04-1.97 (complex m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 82.4, 69.6, 32.0, 19.6, 5.2; FTIR ν_{max} (thin film) 3295, 1434, 1223, 1192, 1118 cm^{-1} ; GC-MS: $R_t = 5.3$ -5.7 min, m/z 194 [(M + H^+ , 100%)]; HRMS (TOF, EI) m/z (M – H^+) calcd. C_5H_6 [^{127}I] for 192.9509, found 192.9507.

General procedure 3:

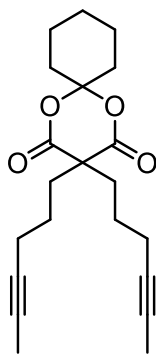
Iodinated electrophile compounds **51** or **52** (2 equiv.) was added to a solution of the respective Meldrum's acid (100 mg, 1 equiv.) and anhydrous potassium carbonate (2 equiv.) in anhydrous DMF (5 mL). The reaction was stirred at ambient temperatures for 18 h and the reaction mixture was subsequently quenched with water (5 mL). The reaction mixture was diluted in ethyl acetate (20 mL) and then washed with water (3 x

15 mL). The collected organic layer was washed with brine (2×15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was purified through flash chromatography (silica, 5:95 v/v ethyl acetate/petroleum ether) and the relevant fractions were collected and concentrated under reduced pressure.

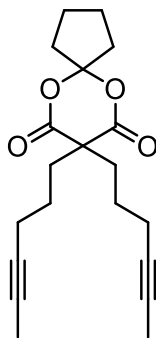
5,5-Di(hex-4-yn-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**53**)



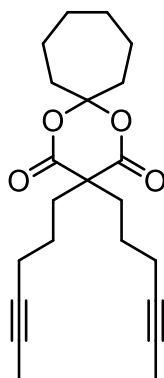
The reaction of compound **51** and Meldrum's acid proceeded in accordance with general procedure 3 and a yellow oil was afforded upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.2$ in 1:9 v/v ethyl acetate/petroleum ether), providing compound **53** (121 mg, 51%) as a white wax, m.p. = 57-58 °C. ^1H NMR (400 MHz, CDCl_3) δ 2.15-2.07 (complex m, 8H), 1.75 (t, $J = 2.4$ Hz, 6H), 1.73 (s, 6H), 1.51-1.43 (complex m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.2, 105.6, 77.6, 76.7, 54.3, 38.4, 29.9, 25.1, 18.9, 3.6; FTIR ν_{max} (film) 2921, 1776, 1743, 1455, 1393, 1380, 1273, 1203, 1115, 1058, 980 cm^{-1} ; GC-MS: $R_t = 11.8$ -12.3 min, m/z 201 [(M – $\text{C}_4\text{H}_7\text{O}_3$ ·, 30%)], 91 [(M – $\text{C}_{11}\text{H}_{17}\text{O}_4$ ·, 100%)]; HRMS (TOF, EI) m/z (M – $\text{C}_4\text{H}_7\text{O}_3$ ·) calcd. $\text{C}_{14}\text{H}_{17}\text{O}$ · for 201.1274, found 201.1271.

3,3-Di(hex-4-yn-1-yl)-1,5-dioxaspiro[5.5]undecane-2,4-dione (**54**)

The reaction of compounds **51** and **16** proceeded in accordance with general procedure 3 and a yellow oil was afforded upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.3$ in 1:9 v/v ethyl acetate/petroleum ether), providing compound **54** (36 mg, 35%) as a white wax, m.p. = 63-64 °C. ^1H NMR (400 MHz, CDCl_3) δ 2.11-2.05 (complex m, 8H), 1.88 (t, $J = 4$ Hz, 4H), 1.73 (p, $J = 4$ Hz, 4H), 1.47 (p, $J = 8$ Hz, 2H) 1.39-1.33 (complex m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.3, 106.2, 77.6, 76.6, 54.8, 38.9, 38.4, 20.1, 24.1, 22.3, 18.9, 3.6; FTIR ν_{max} (thin film) 2936, 2857, 1774, 1737, 1450, 1365, 1331, 1260, 1178, 1136, 1115, 1055, 1036, 978, 912 cm^{-1} ; GC-MS: (i) $R_t = 3.8$ -4.1 min, m/z 98 [(M – $\text{C}_{15}\text{H}_{18}\text{O}_3$ ·, 70%)], 55 [(M – $\text{C}_{17}\text{H}_{21}\text{O}_4$ ·, 100%)]]; (ii) $R_t = 9.0$ -9.2 min, m/z 201 [(M – $\text{C}_7\text{H}_{11}\text{O}_3$ ·, 10%)], 131 [(M – $\text{C}_{11}\text{H}_{17}\text{O}_4$ ·, 100%)], 91 [(M – $\text{C}_6\text{H}_{25}\text{O}_3$ ·, 90%)]; (iii) $R_t = 13.6$ -14.0 min, m/z 201 [(M – $\text{C}_7\text{H}_{11}\text{O}_3$ ·, 50%)], 131 [(M – $\text{C}_{11}\text{H}_{17}\text{O}_4$ ·, 100%)], 91 [(M – $\text{C}_6\text{H}_{25}\text{O}_3$ ·, 90%)]; HRMS (TOF, EI) m/z (M – $\text{C}_{15}\text{H}_{18}\text{O}_3$ ·) calcd. $\text{C}_6\text{H}_{10}\text{O}$ for 98.0726, found 98.0732; (M – $\text{C}_7\text{H}_{10}\text{O}_3$ ·) calcd. $\text{C}_{14}\text{H}_{18}\text{O}$ for 202.1352, found 202.1355.

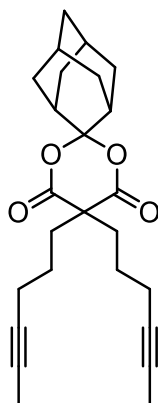
8,8-Di(hex-4-yn-1-yl)-6,10-dioxaspiro[4.5]decane-7,9-dione (**55**)

The reaction of compounds **51** and **17** proceeded in accordance with general procedure 3 and a yellow oil was afforded upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.4$ in 1:9 v/v ethyl acetate/petroleum ether), providing compound **55** (30 mg, 16%) as a pale-yellow wax, m.p. = 52-53 °C. ^1H NMR (400 MHz, CDCl_3) δ 2.17-2.07 (complex m, 12H), 1.90-1.86 (complex m, 4H), 1.76 (t, $J = 2.5$ Hz, 6H), 1.52-1.44 (complex m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.4, 114.6, 77.7, 76.7, 54.6, 40.6, 37.6, 24.9, 23.6, 18.9, 3.6; FTIR ν_{max} (thin film) 2921, 1777, 1743, 1436, 1341, 1274, 1120, 998 cm^{-1} ; GC-MS: (i) $R_t = 9.0$ -9.2 min, m/z 201 [(M – $\text{C}_6\text{H}_9\text{O}_3^{\cdot}$, 10%)], 131 [(M – $\text{C}_{10}\text{H}_{15}\text{O}_4^{\cdot}$, 100%)], 91 [(M – $\text{C}_{14}\text{H}_7\text{O}_4^{\cdot}$, 90%); (ii) $R_t = 13.2$ -13.4 min, m/z 201 [(M – $\text{C}_6\text{H}_9\text{O}_3^{\cdot}$, 20%)], 131 [(M – $\text{C}_{10}\text{H}_{15}\text{O}_4^{\cdot}$, 80%)], 91 [(M – $\text{C}_{14}\text{H}_7\text{O}_4^{\cdot}$, 75%); HRMS (TOF, EI) m/z (M – $\text{C}_{15}\text{H}_{18}\text{O}_3^{\cdot}$) calcd. $\text{C}_5\text{H}_8\text{O}$ for 84.057, found 84.0572; (M – $\text{C}_6\text{H}_8\text{O}_3^{\cdot}$) calcd. $\text{C}_{14}\text{H}_{18}\text{O}$ for 202.1352, found 202.1357.

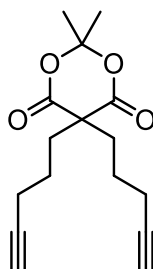
3,3-Di(hex-4-yn-1-yl)-1,5-dioxaspiro[5.6]dodecane-2,4-dione (**56**)

The reaction of compounds **51** and **18** proceeded in accordance with general procedure 3 and yellow oil was afforded upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.4$ in 0.5:9.5 v/v ethyl acetate/petroleum ether), providing compound **56** (80 mg, 45%) as a waxy yellow solid, m.p. = 49-51 °C. ^1H NMR (400 MHz, CDCl_3) δ 2.15-2.06 (complex m, 12H), 1.76 (t, $J = 2.5$ Hz, 6H), 1.65 (s, 8H), 1.50-1.43 (complex m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.4, 110.2, 77.7, 76.7, 54.7, 42.9, 38.4, 28.8, 25.1, 21.4, 18.9, 3.6; FTIR ν_{max} (thin film) 2934, 2864, 1773, 1741, 1437, 1377, 1267, 1119, 1007, 721, 696, 542 cm^{-1} ; GC-MS: (i) $R_t = 5.0$ min, m/z 112 [(M - $\text{C}_{15}\text{H}_{18}\text{O}_3$ ·, 100%)], 84 [(M - $\text{C}_{16}\text{H}_{18}\text{O}_4$ ·, 60%)], 68 [(M - $\text{C}_{17}\text{H}_{22}\text{O}_4$ ·, 90%)], 55 [(M - $\text{C}_{18}\text{H}_{23}\text{O}_4$ ·, 100%)]; (ii) $R_t = 9.1$ min, m/z 201 [(M - $\text{C}_8\text{H}_{15}\text{O}_3$ ·, 10%)], 187 [(M - $\text{C}_9\text{H}_{15}\text{O}_3$ ·, 30%)], 159 [(M - $\text{C}_{10}\text{H}_{15}\text{O}_4$ ·, 50%)], 131 [(M - $\text{C}_{12}\text{H}_{19}\text{O}_4$ ·, 100%)], 91 [(M - $\text{C}_{15}\text{H}_{23}\text{O}_4$ ·, 100%)], 77 [(M - $\text{C}_{16}\text{H}_{25}\text{O}_4$ ·, 50%)]; HRMS (TOF, EI) m/z (M - $\text{C}_8\text{H}_{14}\text{O}_3$) calcd. $\text{C}_{12}\text{H}_{18}\text{O}$ for 202.1356, found 202.1362.

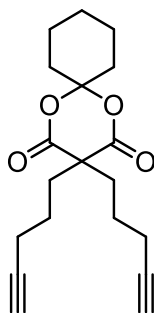
(1*r*,3*r*)-5',5'-Di(hex-4-yn-1-yl)spiro[adamantane-2,2'-[1,3]dioxane]-4',6'-dione (**57**)



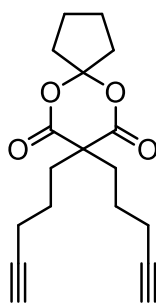
The reaction of compounds **51** and **19** proceeded in accordance with general procedure 3 and a clear oil was afforded upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.3$ in 1:9 v/v ethyl acetate/petroleum ether), providing compound **57** (100 mg, 58%) as colourless prism crystals, m.p. = 65-67 °C. ^1H NMR (400 MHz, CDCl_3) δ 2.20 (d, $J = 12.8$ Hz, 4H), 2.17-2.02 (complex m, 10H), 1.89 (br s, 2H), 1.77-1.73 (complex m, 12H), 1.50-1.42 (complex m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.4, 108.5, 77.7, 76.6, 54.6, 40.1, 38.3, 37.1, 33.6, 26.3, 25.0, 18.9, 3.60; FTIR ν_{max} (thin film) 2915, 2865, 1774, 1737, 1455, 1384, 1268, 1242, 1218, 1181, 1112, 1065, 1018, 938 cm^{-1} ; GC-MS: (i) $R_t = 7.4$ -7.6 min, m/z 150 [(M – $\text{C}_{15}\text{H}_{18}\text{O}_3$ ·, 100%)], 117 [(M – $\text{C}_{14}\text{H}_{23}\text{O}_4$ ·, 20%)], 79 [(M – $\text{C}_{18}\text{H}_{25}\text{O}_4$ ·, 50%)] (ii) $R_t = 9.0$ -9.3 min, m/z 201 [(M – $\text{C}_9\text{H}_{15}\text{O}_3$ ·, 10%)], 187 [(M – $\text{C}_{12}\text{H}_{17}\text{O}_3$ ·, 40%)], 159 [(M – $\text{C}_{14}\text{H}_{20}\text{O}_3$ ·, 60%)], 131 [(M – $\text{C}_{14}\text{H}_{21}\text{O}_4$ ·, 100%)], 91 [(M – $\text{C}_{18}\text{H}_{25}\text{O}_4$ ·, 90%)], 79 [(M – $\text{C}_{19}\text{H}_{25}\text{O}_4$ ·, 70%)] (iii) HRMS (TOF, EI) m/z (M – $\text{C}_{11}\text{H}_{14}\text{O}_3$ ·) calcd. $\text{C}_{14}\text{H}_{18}\text{O}$ for 202.1352, found 202.1357; (M – $\text{C}_{15}\text{H}_{18}\text{O}_3$ ·) calcd. $\text{C}_{10}\text{H}_{14}\text{O}$ for 150.1039, found 150.1043.

2,2-Dimethyl-5,5-di(pent-4-yn-1-yl)-1,3-dioxane-4,6-dione (**58**)

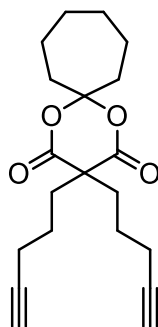
General procedure 3 was followed but the following quantities were used: Meldrum's acid (150 mg, 1.0 mmol) was dissolved in anhydrous DMF (5 mL), followed by the addition of anhydrous potassium carbonate (280 mg, 2.0 mmol) and compound **52** (430 mg, 2.2 mmol). A yellow oil was afforded upon work-up. The oil was subjected to flash chromatography using conditions as specified in general procedure 3 and the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.4$ in 1:9 v/v ethyl acetate/petroleum ether). Compound **58** (130 mg, 45%) was provided as a white solid. The solid was redissolved in DCM and left to stand at 5 °C for 3 months, affording colourless plate crystals, m.p. = 72-73 °C. ^1H NMR (400 MHz, CDCl_3) δ 2.20 (t, $J = 6.8$ Hz, 4H), 2.15-2.11 (m, 4H), 1.97 (t, $J = 2.1$ Hz, 2H), 1.74 (s, 6H), 1.54 (dt, $J = 14.8$ and 7.5 Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.1, 105.7, 82.8, 69.5, 54.2, 38.0, 29.9, 24.5, 18.5; FTIR ν_{max} (thin film) 3292, 2939, 1774, 1737, 1455, 1394, 1379, 1271, 1199, 1112, 1060, 983, 912, 641 cm^{-1} ; GC-MS: (i) $R_t = 7.1$ -7.4 min, m/z 174 [(M - $\text{C}_4\text{H}_6\text{O}_3^\cdot$, 20%)], 145 [(M - $\text{C}_5\text{H}_7\text{O}_4^\cdot$, 10%)], 131 [(M - $\text{C}_6\text{H}_9\text{O}_4^\cdot$, 20%)], 117 [(M - $\text{C}_7\text{H}_{11}\text{O}_4^\cdot$, 100%)], 91 [(M - $\text{C}_9\text{H}_{13}\text{O}_4^\cdot$, 100%)], 77 [(M - $\text{C}_{10}\text{H}_{13}\text{O}_4^\cdot$, 70%)]; (ii) $R_t = 10.2$ -10.9 min, m/z 173 [(M - $\text{C}_4\text{H}_7\text{O}_3^\cdot$, 20%)], 145 [(M - $\text{C}_5\text{H}_7\text{O}_4^\cdot$, 40%)], 131 [(M - $\text{C}_6\text{H}_9\text{O}_4^\cdot$, 40%)], 117 [(M - $\text{C}_7\text{H}_{11}\text{O}_4^\cdot$, 100%)], 91 [(M - $\text{C}_9\text{H}_{13}\text{O}_4^\cdot$, 90%)], 79 [(M - $\text{C}_{10}\text{H}_{13}\text{O}_4^\cdot$, 70%)]; HRMS (TOF, EI) m/z (M - $\text{C}_4\text{H}_6\text{O}_3^\cdot$) calcd. $\text{C}_{12}\text{H}_{13}\text{O}$ for 173.0961, found 173.0961.

3,3-Di(pent-4-yn-1-yl)-1,5-dioxaspiro[5.5]undecane-2,4-dione (**59**)

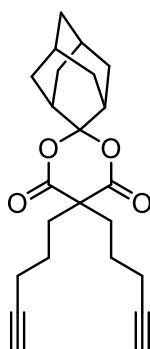
The reaction of compounds **52** and **16** proceeded in accordance with general procedure 3 and a yellow oil was afforded upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.6$ in 1:9 v/v ethyl acetate/petroleum ether), providing compound **59** (420 mg, 25%) as another yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 2.20 (dt, $J = 6.8$ and 2.0 Hz, 4H), 2.14-2.10 (complex m, 4H), 1.97 (t, $J = 2.3$ Hz, 2H), 1.89 (t, $J = 5.6$ Hz, 4H), 1.75 (appt q, $J = 11.6$ and 8.8 Hz, 4H), 1.57-1.47 (complex m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.1, 106.4, 82.8, 69.5, 54.6, 38.9, 38.1, 24.5, 24.1, 22.3, 18.5; FTIR ν_{max} (thin film) 3289, 2939, 2865, 1771, 1737, 1452, 1365, 1329, 1263, 1181, 1136, 1118, 1055, 1033, 983, 933, 638 cm^{-1} ; GC-MS: (i) $R_t = 7.0$ -7.3 min, m/z 173 [(M - $\text{C}_7\text{H}_9\text{O}_3^\cdot$, 1%)], 131 [(M - $\text{C}_9\text{H}_{13}\text{O}_4^\cdot$, 20%)], 117 [(M - $\text{C}_{11}\text{H}_{14}\text{O}_3^\cdot$, 100%)], 77 [(M - $\text{C}_{13}\text{H}_{19}\text{O}_4^\cdot$, 70%)]; (ii) $R_t = 12.3$ -12.6 min, m/z 173 [(M - $\text{C}_7\text{H}_9\text{O}_3^\cdot$, 10%)], 131 [(M - $\text{C}_9\text{H}_{13}\text{O}_4^\cdot$, 40%)], 117 [(M - $\text{C}_{11}\text{H}_{14}\text{O}_3^\cdot$, 60%)], 98 [(M - $\text{C}_{13}\text{H}_{14}\text{O}_3^\cdot$, 100%)], 77 [(M - $\text{C}_{13}\text{H}_{19}\text{O}_4^\cdot$, 40%)]; HRMS (TOF, EI) m/z (M - $\text{C}_7\text{H}_9\text{O}_3^\cdot$) calcd. $\text{C}_{12}\text{H}_{13}\text{O}$ for 173.0961, found 173.096.

8,8-Di(pent-4-yn-1-yl)-6,10-dioxaspiro[4.5]decane-7,9-dione (**60**)

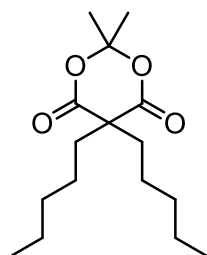
The reaction of compounds **52** and **17** proceeded in accordance with general procedure 3 and a yellow oil was afforded upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.5$ in 1:9 v/v ethyl acetate/petroleum ether), providing compound **60** (37 mg, 21%) as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 2.21-2.09 (complex m, 12H), 1.96 (t, $J = 2.3$ Hz, 2H), 1.88 (t, $J = 5.5$ Hz, 4H), 1.57-1.50 (complex m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.2, 114.7, 82.9, 69.5, 54.4, 40.5, 37.3, 24.2, 23.6, 18.5; FTIR ν_{max} (thin film) 3289, 2936, 1777, 1740, 1458, 1434, 1339, 1271, 1118, 999, 646 cm^{-1} ; GC-MS: (i) 7.0-7.3 min, m/z 173 [(M - $\text{C}_6\text{H}_9\text{O}_3^\cdot$, 1%)], 131 [(M - $\text{C}_8\text{H}_{11}\text{O}_4^\cdot$, 20%)], 117 [(M - $\text{C}_9\text{H}_{13}\text{O}_4^\cdot$, 100%)], 77 [(M - $\text{C}_{12}\text{H}_{17}\text{O}_4^\cdot$, 70%)]; (ii) $R_t = 11.8$ -12.2 min, m/z 173 [(M - $\text{C}_6\text{H}_9\text{O}_3^\cdot$, 10%)], 131 [(M - $\text{C}_8\text{H}_{11}\text{O}_4^\cdot$, 40%)], 117 [(M - $\text{C}_9\text{H}_{13}\text{O}_4^\cdot$, 80%)], 84 [(M - $\text{C}_{13}\text{H}_{14}\text{O}_3^\cdot$, 100%)]; HRMS (TOF, EI) m/z (M - $\text{C}_6\text{H}_9\text{O}_3^\cdot$) calcd. $\text{C}_{12}\text{H}_{13}\text{O}$ for 173.0961, found 173.0959.

3,3-Di(pent-4-yn-1-yl)-1,5-dioxaspiro[5.6]dodecane-2,4-dione (**61**)

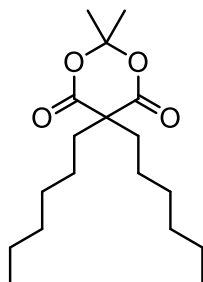
The reaction of compounds **52** and **18** proceeded in accordance with general procedure 3 and a yellow oil was afforded upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.6$ in 1:9 v/v ethyl acetate/petroleum ether), providing compound **60** (60 mg, 38%) as a gummy white solid. The compound was dissolved in DCM and left to stand at 5 °C for 3 months, giving a single colourless prism crystal, m.p. = 61-62 °C. ^1H NMR (400 MHz, CDCl_3) δ 2.18 (t, $J = 6.8$ Hz, 4H), 2.09 (dd, $J = 10.4$ and 6.5 Hz, 8H), 1.96 (appt d, $J = 2.6$ Hz, 2H), 1.64 (s, 8H), 1.51 (p, $J = 7.0$ Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.2, 110.2, 82.8, 69.5, 54.5, 42.8, 38.1, 28.7, 24.5, 21.4, 18.5; FTIR ν_{max} (thin film) 3284, 2934, 2860, 1769, 1734, 1452, 1371, 1329, 1263, 1221, 1178, 1118, 1052, 1002, 975, 915, 638 cm^{-1} ; GC-MS: (i) $R_t = 4.8$ -5.1 min, m/z 112 [(M - $\text{C}_{13}\text{H}_{14}\text{O}_3^+$, 90%)], 84 [(M - $\text{C}_{14}\text{H}_{14}\text{O}_4^+$, 60%)], 68 [(M - $\text{C}_{15}\text{H}_{18}\text{O}_4^+$, 95%)], 55 [(M - $\text{C}_{16}\text{H}_{19}\text{O}_4^+$, 100%)]]; (ii) $R_t = 7.1$ -7.2 min, m/z 173 [(M - $\text{C}_8\text{H}_{13}\text{O}_3^+$, 1%)], 131 [(M - $\text{C}_{10}\text{H}_{15}\text{O}_4^+$, 30%)], 117 [(M - $\text{C}_{11}\text{H}_{17}\text{O}_4^+$, 100%)], 91 [(M - $\text{C}_{13}\text{H}_{19}\text{O}_4^+$, 100%)], 77 [(M - $\text{C}_{14}\text{H}_{21}\text{O}_4^+$, 70%)]; (iii) $R_t = 12.5$ -13.4 min 174 [(M - $\text{C}_8\text{H}_{12}\text{O}_3^+$, 10%)], 131 [(M - $\text{C}_{10}\text{H}_{15}\text{O}_4^+$, 40%)], 117 [(M - $\text{C}_{11}\text{H}_{17}\text{O}_4^+$, 100%)], 91 [(M - $\text{C}_{13}\text{H}_{19}\text{O}_4^+$, 90%)], 77 [(M - $\text{C}_{14}\text{H}_{21}\text{O}_4^+$, 70%)]; HRMS (TOF, EI) m/z (M - $\text{C}_{13}\text{H}_{14}\text{O}_3^+$) calcd. $\text{C}_7\text{H}_{12}\text{O}$ for 112.0883, found 112.0880.

(1*r*,3*r*)-5',5'-Di(pent-4-yn-1-yl)spiro[adamantane-2,2'-[1,3]dioxane]-4',6'-dione (**62**)

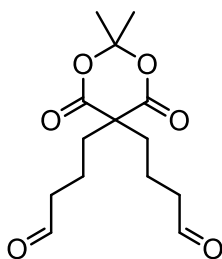
The reaction of compounds **52** and **19** proceeded in accordance with general procedure 3 and a yellow oil was afforded upon work-up. The residue was subjected to flash chromatography, the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.3$ in 0.5:9.5 v/v ethyl acetate/petroleum ether), providing compound **62** (90 mg, 55%) as a gummy white solid, m.p. = 64-67 °C. ^1H NMR (400 MHz, CDCl_3) δ 2.21-2.17 (complex m, 8H), 2.12-2.08 (complex m, 5H), 2.02 (s, 3H), 1.96 (t, $J = 2.4$ Hz, 2H), 1.90 (s, 3H), 1.76 (d, $J = 14.1$ Hz, 6H), 1.52 (dt, $J = 15.4$ and 7.0 Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.3, 108.7, 82.9, 69.4, 54.5, 40.2, 38.0, 37.1, 33.6, 26.3, 24.4, 18.5; FTIR ν_{max} (thin film) 3287, 2910, 2862, 1774, 1734, 1455, 1384, 1271, 1242, 1218, 1184, 1112, 1068, 1018, 928, 630 cm^{-1} ; GC-MS: (i) $R_t = 7.1$ -7.3 min, m/z 173 [(M - $\text{C}_{11}\text{H}_{15}\text{O}_3$ ·, 1%)], 145 [(M - $\text{C}_{12}\text{H}_{15}\text{O}_4$ ·, 10%)], 131 [(M - $\text{C}_{11}\text{H}_{15}\text{O}_3$ ·, x%)], 117 [(M - $\text{C}_{14}\text{H}_{19}\text{O}_4$ ·, 100%)], 91 [(M - $\text{C}_{16}\text{H}_{21}\text{O}_4$ ·, 100%)], 77 [(M - $\text{C}_{17}\text{H}_{23}\text{O}_4$ ·, 70%)]; (ii) $R_t = 14.3$ -14.8 min, m/z 175 [(M - $\text{C}_{11}\text{H}_{13}\text{O}_3$ ·, 1%)], 150 [(M - $\text{C}_{18}\text{H}_{16}\text{O}_3$ ·, 100%)], 117 [(M - $\text{C}_{14}\text{H}_{19}\text{O}_4$ ·, 40%)], 79 [(M - $\text{C}_{17}\text{H}_{21}\text{O}_4$ ·, 40%)]; HRMS (TOF, EI) m/z (M - $\text{C}_{11}\text{H}_{15}\text{O}_3$ ·) calcd. $\text{C}_{12}\text{H}_{13}\text{O}$ for 173.0961, found 173.0961; (M - $\text{C}_{18}\text{H}_{16}\text{O}_3$ ·) calcd. $\text{C}_{10}\text{H}_{14}\text{O}$ for 150.1039, found 150.1039.

2,2-Dimethyl-5,5-dipentyl-1,3-dioxane-4,6-dione (**64**)

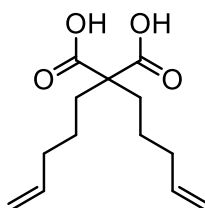
1-bromopentane (**63**) (0.12 mL, 1.0 mmol) was added to a solution of Meldrum's acid (60 mg, 0.4 mmol.) and anhydrous potassium carbonate (120 mg, 0.9 mmol)) in anhydrous DMF (5 mL). The reaction was stirred at ambient temperatures for 18 h, quenched with water (10 mL), diluted with ethyl acetate (20 mL), and washed with water (3 × 15 mL). The collected organic layer was washed with brine (2 × 10 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The resulting residue was purified through flash chromatography (silica, 1:9 v/v ethyl acetate/petroleum ether), the relevant fractions were collected and concentrated under reduced pressure (R_f = 0.4 in 0.5:9.5 v/v ethyl acetate/petroleum ether), affording compound **64** (160 mg, 14%) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 2.00-1.96 (complex m, 4H), 1.76 (s, 6H), 1.30-1.26 (complex m, 12H), 0.86 (t, J = 6.6 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 169.8, 105.6, 55.0, 39.6, 31.7, 30.0, 25.6, 22.4, 14.0; FTIR ν_{max} (thin film) 2955, 2928, 2857, 1777, 1737, 1463, 1392, 1384, 1329, 1268, 1231, 1205, 1141, 1070, 1015, 967, 896 cm⁻¹; GC-MS: R_t = 6.8-7.0 min, m/z 182 [(M – C₄H₆O₃·, 10%)], 55 [(M – C₁₂H₂₁O₄·, 100%)]; HRMS (TOF, EI) m/z (M – C₄H₆O₃) calcd. C₁₂H₂₈O₄ for 182.1665, found 182.1662; (TOF, ESI, +ve) m/z (M + Na⁺) C₁₆H₂₈NaO₄ for 307.1885, found 307.1879.

5,5-Dihexyl-2,2-dimethyl-1,3-dioxane-4,6-dione (**66**)

1-iodohexane (**65**) (0.14 mL, 0.9 mmol) was added to a solution of Meldrum's acid (60 mg, 0.4 mmol) and anhydrous potassium carbonate (120 mg, 0.9 mmol) in anhydrous DMF (5 mL). The reaction was stirred at ambient temperature for 18 h, quenched with water (10 mL), diluted with ethyl acetate (20 mL) and then washed with water (3 × 15 mL). The collected organic layer was washed with brine (2 × 10 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The resulting residue was purified through flash chromatography (silica, 1:9 v/v ethyl acetate/petroleum ether), the relevant fractions were collected and concentrated under reduced pressure (R_f = 0.4 in 0.5:9.5 v/v ethyl acetate/petroleum ether), affording compound **66** (200 mg, 15%) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 2.00-1.97 (complex m, 4H), 1.72 (s, 6H), 1.30-1.25 (complex m, 16H), 0.89-0.85 (complex m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 169.8, 105.6, 55.0, 39.7, 31.5, 30.0, 29.3, 25.9, 22.6, 14.1; FTIR ν_{max} (thin film) 2957, 2926, 2857, 1777, 1742, 1460, 1394, 1381, 1260, 1228, 1202, 1141, 1070, 975 cm⁻¹; GC-MS: R_t = 8.2-8.3 min, m/z 210 [(M – C₄H₆O₃·, 10%)], 69 [(M – C₁₃H₂₃O₄·, 100%)]; HRMS (TOF, EI) m/z (M⁺) calcd. C₁₈H₃₂O₄ for 312.2295, found 312.2287.

4,4'-(2,2-Dimethyl-4,6-dioxo-1,3-dioxane-5,5-diyl)dibutanal (**68**)

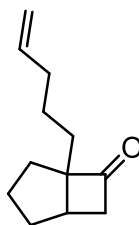
A solution of compound **41** (103 mg, 0.37 mmol) in DCM (10 mL) was prepared in a 100 mL three-neck round-bottom flask and immersed in a dry-ice/acetone bath. A line attached to an oxygen cylinder was inserted into the flask and the solution was purged with oxygen gas. After being twice-purged, the sparking tool of the oxygen outlet was engaged and ozone was bubbled through the solution at a rate of 3 L/min. The reaction was deemed complete after 20 min, when the reaction mixture took on a blue colour. The ozone outlet was switched off and a solution of triphenyl phosphine (322 mg, 1.22 mmol) in DCM (3 mL) was added dropwise to the mixture. The mixture was subsequently left to stir and reach ambient temperatures over 18 h. The resulting clear solution was subjected to a starch-iodide test for the presence of peroxides. The test indicated the absence of peroxides in the reaction mixture; thus, the reaction mixture was concentrated under reduced pressure. The resulting residue was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate/petroleum ether), the relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.2$), affording compound **68** (32 mg, 31%) as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 9.71 (s, 2H), 2.45 (t, $J = 7.1$ Hz, 4H), 2.01-1.98 (complex m, 4H), 1.75 (s, 6H), 1.62 (dt, $J = 14.5$ and 7.2 Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 200.7, 168.9, 106.0, 54.4, 43.4, 38.1, 29.9, 18.1; FTIR ν_{max} (thin film) 2939, 1770, 1732, 1708, 1456, 1394, 1381, 1269, 1201, 1119, 1061, 984, 911, 735, 701, 546 cm^{-1} ; satisfactory mass spectrometry data could not be obtained for this compound.

2,2-Di(pent-4-en-1-yl)malonic acid (**70**)

Diethylmalonate (**69**) (1.2 mL, 7.94 mmol) was added dropwise over 10 min to a magnetically stirred slurry of sodium hydride (1.1 g of a 60% dispersion in paraffin oil, 45.7 mmol) in anhydrous THF (3 mL) at ambient temperatures and under a nitrogen atmosphere. Compound **39** (2.2 mL, 10.9 mmol) in anhydrous THF (1 mL) was subsequently added dropwise over 20 min. The resulting reaction mixture was stirred at ambient temperatures for 1 h and then refluxed for 24 h. The progress of the reaction was monitored by TLC (1:3 v/v ethyl acetate/petroleum ether) and was deemed complete when diethylmalonate (**69**) had been fully consumed. The reaction was cooled in an ice-water bath and water (10 mL) was slowly added to the solution to quench the residual sodium hydride. A solution containing ethanol (5 mL) and potassium hydroxide (5 mL of a 4.0 M aq. solution) was slowly added to the reaction. The ice-water bath was removed and the reaction was vigorously refluxed for 24 h, with monitoring on TLC (1:3 v/v ethyl acetate/petroleum ether) for the disappearance of both the di-ester and generated mono-ester. When the reaction reached completion, the reaction mixture was cooled to ambient temperatures and neutralised with aq. hydrochloric acid (conc., 6 mL). The organic component of the reaction mixture was extracted with diethyl ether (2 × 20 mL) and the subsequent combined organic layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure (*R_f* = 0.1 in 1:3 v/v ethyl acetate/petroleum ether). The resulting yellow residue was recrystallized with n-pentane, affording compound **70** (540 mg, 28%) as white fibrous needles, m.p. = 129-130 °C. ¹H NMR (400 MHz, CDCl₃) δ 5.75 (dt, *J* = 16.9, 10.2 and 6.6 Hz, 2H),

5.04-4.97 (complex m, 4H), 2.10-1.94 (complex m, 8H), 1.36 (dt, $J = 15.6$ and 7.5 Hz, 4H), $2 \times \text{COOH}$ not observed; ^{13}C NMR (100 MHz, CDCl_3) δ 176.6, 137.7, 115.5, 57.6, 35.3, 33.7, 24.2; FTIR ν_{max} (thin film) 3074, 2969, 2865, 2928, 1701, 1640, 1460, 1407, 1304, 1274, 1222, 1206, 1156, 998, 915, 764, 654, 602 cm^{-1} ; MS (ESI, +ve) m/z 263 $[(\text{M} + \text{Na}^+, 100\%)]$; HRMS (TOF, ESI, +ve) m/z ($\text{M} + \text{Na}^+$) calcd. $\text{C}_{13}\text{H}_{20}\text{NaO}_4$ for 263.1259, found 263.1252.

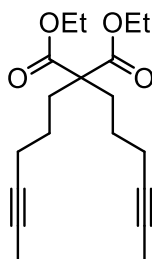
5-(Pent-4-en-1-yl)bicyclo[3.2.0]heptan-6-one (**71**)



Method A: Compound **41** (38 mg, 0.14 mmol) was heated by a heat gun in a 5 mL round-bottom flask. The solid compound melted, with bubbling observed. The contents of the flask were cooled to ambient temperatures and subjected to flash chromatography (silica, 5:95 v/v ethyl acetate/petroleum ether). The relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.5$ in 5:95 v/v ethyl acetate/petroleum ether) and compound **71** (6 mg, 22%) was afforded as a clear oil, $[\alpha]_D = 0.1^\circ$ ($c = 1.8$, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 5.77 (ddt, $J = 16.9$, 10.1 , 6.7 Hz, 1H), 4.97 (dd, $J = 18.7$ and 13.7 Hz, 2H), 3.14 (dd, $J = 18.4$ and 9.5 Hz, 1H), 2.57-2.54 (complex m, 1H), 2.46 (dd, $J = 18.4$ and 9.5 Hz, 1H), 2.07-1.98 (complex m, 3H), 1.85-1.73 (complex m, 3H), 1.71-1.49 (complex m, 4H), 1.41-1.33 (complex m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 218.3, 138.6, 114.9, 76.0, 49.4, 35.5, 34.3, 34.1, 32.9, 32.8, 25.1(2); FTIR ν_{max} (thin film) 3076, 2934, 2860, 1770, 1641, 1457, 1387, 1277, 1065, 991, 910, 419, 413 cm^{-1} ; GC-MS: (i) $R_t = 7.6$ -7.7 min, m/z 178 $[(\text{M}^+), 1\%]$, 136

[(M – C₂H₂O[•], 100%)], 121 [(M – C₂H₅O[•], 80%)], 94 [(M – C₅H₈O[•], 75%)], 67 [(M – C₇H₁₁O[•], 80%)]; (ii) *R*_t = 10.2-10.3 min, *m/z* 176 [(M – 2H⁺, 30%)], 136 [(M – C₂H₂O[•], 80%)], 122 [(M – C₂H₄O[•], 90%)], 95 [(M – C₅H₇O[•], 70%)], 67 [(M – C₇H₁₁O[•], 100%)]; HRMS (TOF, EI) *m/z* (M + H⁺) calcd. C₁₂H₁₈O for 179.1436, found 179.1439.

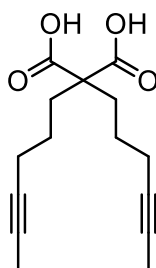
Method B: Alternatively, triethylamine (0.9 mL, 0.7 mmol) was added to a magnetically stirring solution of compound **70** (80 mg, 0.33 mmol) in anhydrous toluene (2 mL) in a screw-thread tube, followed by the addition of 15% phosgene in toluene solution (0.19 mL, 0.36 mmol). The tube's cap was tightly fastened, the resulting solution was heated to 120 °C and was maintained at that temperature for 18 h. The resulting solution was cooled to ambient temperatures, transferred to a round bottom flask, concentrated under reduced pressure, diluted in diethyl ether (5 mL) and washed with water (3 × 10 mL). The collected organic layer was washed with brine (2 × 10 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The subsequent residue was subjected to flash chromatography (silica, 5:95 v/v ethyl acetate/petroleum ether) and the relevant fractions were collected and concentrated under reduced pressure (*R*_f = 0.5), providing compound **71** (28 mg, 48%) as a clear oil. The obtained compound was identical to the one prepared through Method A.

Diethyl-2,2-di(hex-4-yn-1-yl)malonate (**72**)

A slurry of sodium hydride (57 mg of a 60% dispersion in paraffin oil, 1.4 mmol) in anhydrous THF (5 mL) was prepared under a nitrogen atmosphere and cooled in an ice-water bath. Compound **69** (0.1 mL, 0.66 mmol) was added dropwise to the slurry. The mixture was stirred in the ice-water bath for 1 h, then compound **51** (289 mg, 1.4 mmol) was added dropwise. The ice-water bath was removed, and the reaction was warmed to ambient temperatures. The reaction mixture was stirred at ambient temperatures for 2 days with TLC monitoring (1:9 v/v ethyl acetate/petroleum ether). The reaction was deemed complete when the monoalkylation product was no longer visible by TLC. The reaction mixture was cooled to ambient temperatures and then the flask was immersed in an ice-water bath. Water (5 mL) was added to the reaction mixture to quench the remaining hydride. The mixture was diluted with diethyl ether (10 mL), washed with water (3 × 10 mL), and then brine (2 × 15 mL). The resulting organic layer was dried (Na₂SO₄), filtered, concentrated under reduced pressure, and subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/petroleum ether). The relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.5$), providing compound **72** (130 mg, 61%) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 4.18 (q, $J = 7.1$ Hz, 4H), 2.12 (ddt, $J = 7.0, 4.6$ and 2.5 Hz, 4H), 1.99-1.93 (complex m, 4H), 1.76 (t, $J = 2.4$ Hz, 6H), 1.41-1.33 (complex m, 4H), 1.24 (t, $J = 7.1$ Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 171.7, 78.6, 76.1, 61.3, 57.3, 31.7, 24.0, 19.2, 14.2, 3.6; FTIR ν_{max} (thin film) 2921, 1730, 1446, 1367, 1260, 1220, 1177, 1099, 1026 cm⁻¹; MS

(ESI, +ve) m/z 663 [(2M + Na⁺, 100%)], 343 [(M + Na⁺, 55%)]; HRMS (TOF, ESI, +ve) m/z (M + Na⁺) calcd. C₁₉H₂₈NaO₄ 343.1885, found 343.1902.

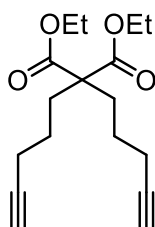
2,2-Di(hex-4-yn-1-yl)malonic acid (**73**)



Sodium hydroxide solution (5 mL of a 2.0 M aq. solution) was added to a magnetically stirred solution of compound **72** (32 mg, 0.099 mmol) in absolute ethanol (5 mL) and the resulting mixture was refluxed for 2 days. The reaction mixture was cooled to ambient temperature, quenched with aq. hydrochloric acid (conc., 5 mL) and the pH adjusted to 4. The reaction mixture was diluted with diethyl ether (15 mL), washed with water (3 × 15 mL) and the organic layer was collected. The organic layer was dried (Na₂SO₄), filtered, concentrated under reduced pressure, and subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/petroleum ether). The desired compound could not be located among the collected fractions so glacial acetic acid was added to the eluting solvent (1:1:0.01 v/v/v ethyl acetate/petroleum ether/acetic acid), allowing the desired product to elute from the silica. The relevant fractions were collected and concentrated under reduced pressure (R_f = 0.1 in 1:1 v/v ethyl acetate/petroleum ether), affording compound **73** (10 mg, 40%) as a white powder. The white powder was recrystallized using vapour-vapour diffusion techniques using 3:1 v/v DCM/petroleum ether, providing colourless plate crystals, m.p. = 125-126 °C. ¹H NMR (400 MHz, CDCl₃) δ 2.16 (ddt, J = 7.0, 4.7 and 2.6 Hz, 4H), 2.05-2.01 (complex m,

4H), 1.77 (t, $J = 2.5$ Hz, 6H), 1.52-1.44 (complex m, 4H), 2 $\times$ COOH not observed; ^{13}C NMR (100 MHz, CDCl_3) 177.5, 78.2, 76.4, 57.5, 32.8, 24.1, 19.1, 3.6; FTIR ν_{max} (thin film) 2920, 1703, 1459, 1402, 1274, 1189, 1099, 927 cm^{-1} ; MS (ESI, +ve) m/z 551 $[(2\text{M} + \text{Na}^+, 100\%)]$, 287 $[(\text{M} + \text{Na}^+, 25\%)]$, 265 $[(\text{M} + \text{H}^+, 65\%)]$; HRMS (TOF, ESI, +ve) m/z ($\text{M} + \text{Na}^+$) calcd. $\text{C}_{15}\text{H}_{20}\text{NaO}_4$ for 287.1259, found 287.1263.

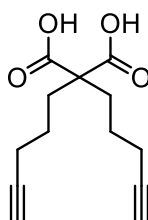
Diethyl-2,2-di(pent-4-yn-1-yl)malonate (**74**)



A magnetically stirred slurry of sodium hydride (57 mg of a 60% dispersion in paraffin oil, 1.4 mmol) in anhydrous THF (5 mL) was prepared under a nitrogen atmosphere and cooled in an ice-water bath. Compound **69** (0.1 mL, 0.66 mmol) was added dropwise to the slurry. The mixture was stirred in the ice-water bath for 1 h, then compound **52** (272 mg, 1.4 mmol) was added dropwise. The ice-water bath was removed, and the reaction was warmed to ambient temperatures. The reaction mixture was stirred at ambient temperatures for 2 days. The reaction was deemed complete when the monoalkylation product was no longer visible by TLC (1:9 v/v ethyl acetate/petroleum ether). The reaction mixture was cooled to ambient temperatures and then the flask was immersed in an ice-water bath. Water (5 mL) was added to the reaction mixture to quench the remaining hydride. The mixture was diluted with diethyl ether (10 mL), washed with water (3×10 mL) and then brine (2×15 mL). The resulting organic layer was dried (Na_2SO_4), filtered, concentrated under reduced pressure, and

subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/petroleum ether). The relevant fractions were collected and concentrated under reduced pressure ($R_f = 0.3$), affording compound **74** (172 mg, 89%) as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 4.17 (q, $J = 7.0$ Hz, 4H), 2.18 (t, $J = 5.6$ Hz, 4H), 1.98 (complex m, 6H), 1.23 (dt, $J = 13.6$ and 6.6 Hz, 4H), 1.23 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) 171.5, 83.8, 68.9, 61.4, 57.2, 31.7, 23.4, 18.8, 14.3; FTIR ν_{max} (thin film) 3290, 2961, 1728, 1462, 1370, 1299, 1257, 1217, 1180, 1091, 1025, 640 cm^{-1} ; MS (ESI, +ve) m/z 607 [(2M + Na^+ , 100%)], 315 [(M + Na^+ , 45%)]; HRMS (TOF, ESI, +ve) m/z (M + Na^+) calcd. $\text{C}_{17}\text{H}_{24}\text{NaO}_4$ for 315.1572, found 315.1579.

2,2-Di(pent-4-yn-1-yl)malonic acid (**75**)



Sodium hydroxide (5 mL of a 2 M aq. solution) was added to a magnetically stirred solution of compound **74** (700 mg, 2.4 mmol) in absolute ethanol (5 mL) and the resulting mixture was refluxed for 2 days. The reaction mixture was cooled to ambient temperatures, quenched with aq. hydrochloric acid (conc., 5 mL) and the pH adjusted to 4. The solution was diluted in diethyl ether (15 mL), washed with water (3×15 mL) and the organic layer was collected. The organic layer was dried (Na_2SO_4), filtered, concentrated under reduced pressure, and subjected to flash chromatography (silica, 1:1:0.01 v/v/v ethyl acetate/petroleum ether/acetic acid), allowing the desired product to elute from the silica. The relevant fractions were collected and concentrated ($R_f = 0.1$ in 1:1 v/v ethyl acetate/petroleum ether) under reduced pressure, yielding

compound **75** (130 mg, 23%) as a white powder, m.p. = 140-142 °C. ^1H NMR (400 MHz, CD_3OD): δ 2.17-2.13 (complex m, 6H), 1.94-1.90 (complex m, 4H), 1.40 (dt, J = 14.4 and 6.9 Hz, 4H), 2 $\times$ COOH not observed; ^{13}C NMR (100 MHz, CD_3OD): δ 175.5, 84.4, 69.9, 58.1, 33.3, 24.7, 19.3; FTIR (thin film) ν_{max} 3295, 2936, 1712, 1580, 1461, 1321, 1265, 1189, 639 cm^{-1} ; satisfactory low resolution mass spectra data could not be obtained on this compound; HRMS (TOF, ESI, +ve) m/z calcd. $\text{C}_{13}\text{H}_{16}\text{NaO}_4$ for 259.0946, found 259.0958.

Crystallographic Study. *Crystallographic Data.* Compound **7**. $\text{C}_{26}\text{H}_{38}\text{O}_{15}$, M = 590.56, T = 150.00(10) K, monoclinic, space group $P2_1$, Z = 2, a = 11.1629(2) Å, b = 8.7778(1) Å, c = 15.3748(3) Å, α = 90°, β = 101.558(2)°, γ = 90°; V = 1475.96(4) Å³, D_x = 1.329 Mg m^{-3} , from 5289 unique data ($2\theta_{\text{max}}$ = 147.4°), R = 0.037 [for 5113 reflections with $I > 2\sigma(I)$]; R_w = 0.098 (all data), S = 1.02.

Structure Determination. Data for compound **7** was collected on a SuperNova X-ray diffractometer, employing Cu $K\alpha$ radiation and a graphite monochromator (λ = 1.54184 Å). Using Olex2, the structure was solved by intrinsic phasing through using the ShelXT program and refined using least-squares minimization with the ShelXL package.

Crystallographic Data. Compound **16**. $\text{C}_9\text{H}_{12}\text{O}_4$, M = 184.19, T = 150.00(10) K, monoclinic, space group Cc , Z = 16, a = 13.2970(4) Å, b = 13.2776(3) Å, c = 20.39494(6) Å, α = 90°, β = 101.558(2)°, γ = 90°; V = 3552.99(18) Å³, D_x = 1.377 Mg m^{-3} , 10019 unique data ($2\theta_{\text{max}}$ = 142.136°), R = 0.0406 [for 8220 reflections with $I \geq 2\sigma(I)$]; R_w = 0.1094 (all data), S = 1.050.

Structure Determination. Data for compound **16** was collected on a SuperNova X-ray diffractometer, employing Cu K α radiation and a graphite monochromator ($\lambda = 1.54184$ Å). Using Olex2, the structure was solved by intrinsic phasing through using the ShelXT program and refined using least-squares minimization with the ShelXL package.

Crystallographic Data. Compound **17**. C₈H₁₀O₄, $M = 170.16$, $T = 150.00(10)$ K, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 12.4991(5)$ Å, $b = 8.6839(2)$ Å, $c = 7.3166(2)$ Å, $\alpha = 90^\circ$, $\beta = 100.543(3)^\circ$, $\gamma = 90^\circ$; $V = 3552.99(18)$ Å³, $D_x = 1.448$ Mg m⁻³, 2183 unique data ($2\theta_{\max} = 59.148^\circ$), $R = 0.0447$ [for 1953 reflections with $I \geq 2\sigma(I)$]; $R_w = 0.1192$ (all data), $S = 1044$.

Structure Determination. Data for compound **17** was collected on a SuperNova X-ray diffractometer, employing Cu K α radiation and a graphite monochromator ($\lambda = 1.54184$ Å). Using Olex2, the structure was solved by intrinsic phasing through using the ShelXT program and refined using least-squares minimization with the ShelXL package.

Crystallographic Data. Compound **18**. C₁₀H₁₄O₄, $M = 198.21$, $T = 150.00(10)$ K, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 10.7691(2)$ Å, $b = 9.9140(2)$ Å, $c = 9.2575(2)$ Å, $\alpha = 90^\circ$, $\beta = 104.660(2)^\circ$, $\gamma = 90^\circ$; $V = 956.20(3)$ Å³, $D_x = 1.377$ Mg m⁻³, 1929 unique data ($2\theta_{\max} = 147.458^\circ$), $R = 0.0310$ [for 1839 reflections with $I \geq 2\sigma(I)$]; $R_w = 0.0778$ (all data), $S = 1.057$.

Structure Determination. Data for compound **18** was collected on a SuperNova X-ray diffractometer, employing Cu K α radiation and a graphite monochromator ($\lambda = 1.54184$ Å). Using Olex2, the structure was solved by intrinsic phasing through using the

ShelXT program and refined using least-squares minimization with the ShelXL package.

Crystallographic Data. Compound **19**. $C_{13}H_{16}O_4$, $M = 236.26$, $T = 150.00(10)$ K, monoclinic, space group $C2/c$, $Z = 8$, $a = 26.6340(8)$ Å, $b = 7.5963(3)$ Å, $c = 11.2012(3)$ Å, $\alpha = 90^\circ$, $\beta = 97.301(2)^\circ$, $\gamma = 90^\circ$; $V = 2247.85(13)$ Å³, $D_x = 1.396$ Mg m⁻³, 2257 unique data ($2\theta_{\max} = 147.448^\circ$), $R = 0.0344$ [for 1886 reflections with $I \geq 2\sigma(I)$]; $R_w = 0.0862$ (all data), $S = 1.057$.

Structure Determination. Data for compound **19** was collected on a SuperNova X-ray diffractometer, employing Cu K α radiation and a graphite monochromator ($\lambda = 1.54184$ Å). Using Olex2, the structure was solved by intrinsic phasing through using the ShelXT program and refined using least-squares minimization with the ShelXL package.

Crystallographic Data. Compound **21**. $C_{10}H_{16}O_4$, $M = 200.23$, $T = 150.00(10)$ K, monoclinic, space group $C2/c$, $Z = 4$, $a = 9.5399(8)$ Å, $b = 12.7469(4)$ Å, $c = 9.5758(4)$ Å, $\alpha = 90^\circ$, $\beta = 111.032(4)^\circ$, $\gamma = 90^\circ$; $V = 1086.88(8)$ Å³, $D_x = 1.224$ Mg m⁻³, 1520 unique data ($2\theta_{\max} = 147.448^\circ$), $R = 0.0344$ [for 1337 reflections with $I \geq 2\sigma(I)$]; $R_w = 0.1129$ (all data), $S = 1.055$.

Structure Determination. Data for compound **21** was collected on a SuperNova X-ray diffractometer, employing Cu K α radiation and a graphite monochromator ($\lambda = 1.54184$ Å). Using Olex2, the structure was solved by intrinsic phasing through using the ShelXT program and refined using least-squares minimization with the ShelXL package.

Crystallographic Data. Compound **29**. $C_{11}H_{10}O_4$, $M = 206.19$, $T = 150.00(10)$ K, monoclinic, space group $P2_1/c$, $Z = 8$, $a = 7.97860(10)$ Å, $b = 16.4388(2)$ Å, $c = 15.0814(2)$ Å, $\alpha = 90^\circ$, $\beta = 92.7190(10)^\circ$, $\gamma = 90^\circ$; $V = 1975.83(4)$ Å³, $D_x = 1.386$ Mg m⁻³, 3986 unique data ($2\theta_{\max} = 147.482^\circ$), $R = 0.0318$ [for 3641 reflections with $I \geq 2\sigma(I)$]; $R_w = 0.0819$ (all data), $S = 1.030$.

Structure Determination. Data for compound **29** was collected on a SuperNova X-ray diffractometer, employing Cu K α radiation and a graphite monochromator ($\lambda = 1.54184$ Å). Using Olex2, the structure was solved by intrinsic phasing through using the ShelXT program and refined using least-squares minimization with the ShelXL package.

Crystallographic Data. Compound **30**. $C_{11}H_9NO_6$, $M = 251.19$, $T = 100$ K, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 7.2270(3)$ Å, $b = 23.4537(6)$ Å, $c = 7.2473(3)$ Å, $\alpha = 90^\circ$, $\beta = 118.571(5)^\circ$, $\gamma = 90^\circ$; $V = 1078.83(8)$ Å³, $D_x = 1.547$ Mg m⁻³, 3011 unique data ($2\theta_{\max} = 59.148^\circ$), $R = 0.0355$ [for 2715 reflections with $I \geq 2\sigma(I)$]; $R_w = 0.0912$ (all data), $S = 1.075$.

Structure Determination. Data for compound **30** was collected on a SuperNova X-ray diffractometer, employing Cu K α radiation and a graphite monochromator ($\lambda = 1.54184$ Å). Using Olex2, the structure was solved by intrinsic phasing through using the ShelXT program and refined using least-squares minimization with the ShelXL package.

Crystallographic Data. Compound **31**. $C_{11}H_9ClO_4$, $M = 240.63$, $T = 150.00(10)$ K, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 8.7351(2)$ Å, $b = 10.2527(3)$ Å, $c = 13.0113(4)$ Å, $\alpha = 69.122(3)^\circ$, $\beta = 83.154(2)^\circ$, $\gamma = 79.865(2)^\circ$; $V = 1069.75(6)$ Å³, $D_x =$

1.547 Mg m⁻³, 7036 unique data ($2\theta_{\max} = 64.944^\circ$), $R = 0.0336$ [for 6020 reflections with $I \geq 2\sigma(I)$]; $R_w = 0.0868$ (all data), $S = 1.039$.

Structure Determination. Data for compound **31** was collected on a SuperNova X-ray diffractometer, employing Cu K α radiation and a graphite monochromator ($\lambda = 1.54184$ Å). Using Olex2, the structure was solved by intrinsic phasing through using the ShelXT program and refined using least-squares minimization with the ShelXL package.

Crystallographic Data. Compound **33**. C₁₁H₉BrO₄, $M = 285.09$, $T = 149.99(10)$ K, triclinic, space group $P1$, $Z = 4$, $a = 8.7351(2)$ Å, $b = 10.2527(3)$ Å, $c = 13.0113(4)$ Å, $\alpha = 69.122(3)^\circ$, $\beta = 83.154(2)^\circ$, $\gamma = 79.865(2)^\circ$; $V = 1069.75(6)$ Å³, $D_x = 1.719$ Mg m⁻³, 6190 unique data ($2\theta_{\max} = 59.15^\circ$), $R = 0.0320$ [for 5192 reflections with $I \geq 2\sigma(I)$]; $R_w = 0.0755$ (all data), $S = 1.020$.

Structure Determination. Data for compound **33** was collected on a New Xcalibur X-ray diffractometer, employing Mo K α radiation and a graphite monochromator ($\lambda = 0.71073$ Å). Using Olex2, the structure was solved by intrinsic phasing through using the ShelXT program and refined using least-squares minimization with the ShelXL package.

Crystallographic Data. Compound **34**. C₁₁H₉BrO₄, $M = 285.09$, $T = 149.99(10)$ K, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 9.9486(3)$ Å, $b = 7.9961(2)$ Å, $c = 14.0424(3)$ Å, $\alpha = 90^\circ$, $\beta = 105.715(3)^\circ$, $\gamma = 90^\circ$; $V = 1075.32(5)$ Å³, $D_x = 1.761$ Mg m⁻³, 3013 unique data ($2\theta_{\max} = 59.136^\circ$), $R = 0.0236$ [for 2754 reflections with $I \geq 2\sigma(I)$]; $R_w = 0.0604$ (all data), $S = 1.039$.

Structure Determination. Data for compound **34** was collected on a New Xcalibur X-ray diffractometer, employing Mo K α radiation and a graphite monochromator ($\lambda = 0.71073$ Å). Using Olex2, the structure was solved by intrinsic phasing through using the ShelXT program and refined using least-squares minimization with the ShelXL package.

Crystallographic Data. Compound **35**. C₁₁H₉ClO₄, $M = 240.63$, $T = 149.99(10)$ K, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 9.9674(11)$ Å, $b = 7.9258(7)$ Å, $c = 13.9189(14)$ Å, $\alpha = 90^\circ$, $\beta = 105.043(11)^\circ$, $\gamma = 90^\circ$; $V = 1061.91(19)$ Å³, $D_x = 1.505$ Mg m⁻³, 2969 unique data ($2\theta_{\max} = 59.144^\circ$), $R = 0.0433$ [for 2414 reflections with $I \geq 2\sigma(I)$]; $R_w = 0.1173$ (all data), $S = 1.052$.

Structure Determination. Data for compound **35** was collected on a New Xcalibur X-ray diffractometer, employing Mo K α radiation and a graphite monochromator ($\lambda = 0.71073$ Å). Using Olex2, the structure was solved by intrinsic phasing through using the ShelXT program and refined using least-squares minimization with the ShelXL package.

Crystallographic Data. Compound **36**. C₁₁H₉FO₄, $M = 224.18$, $T = 150.00(10)$ K, triclinic, space group $P1$, $Z = 4$, $a = 7.4375(4)$ Å, $b = 11.7382(11)$ Å, $c = 11.7894(9)$ Å, $\alpha = 73.264^\circ$, $\beta = 80.281(5)^\circ$, $\gamma = 89.275(6)^\circ$; $V = 970.80(13)$ Å³, $D_x = 1.534$ Mg m⁻³, 3726 unique data ($2\theta_{\max} = 144.238^\circ$), $R = 0.0307$ [for 3453 reflections with $I \geq 2\sigma(I)$]; $R_w = 0.0799$ (all data), $S = 1.037$.

Structure Determination. Data for compound **36** was collected on a SuperNova X-ray diffractometer, employing Cu K α radiation and a graphite monochromator ($\lambda = 1.54184$ Å). Using Olex2, the structure was solved by intrinsic phasing through using the

ShelXT program and refined using least-squares minimization with the ShelXL package.

Crystallographic Data. Compound **38**. $C_{11}H_9NO_6$, $M = 251.19$, $T = 150.00(10)$ K, triclinic, space group $P1$, $Z = 2$, $a = 7.3964(2)$ Å, $b = 8.7612(3)$ Å, $c = 8.9763(3)$ Å, $\alpha = 79.987^\circ$, $\beta = 85.361(3)^\circ$, $\gamma = 75.810(3)^\circ$; $V = 554.89(3)$ Å³, $D_x = 1.503$ Mg m⁻³, 3677 unique data ($2\theta_{\max} = 65.078^\circ$), $R = 0.0387$ [for 3110 reflections with $I \geq 2\sigma(I)$]; $R_w = 0.1060$ (all data), $S = 1.041$.

Structure Determination. Data for compound **38** was collected on a New Xcalibur X-ray diffractometer, employing Mo $K\alpha$ radiation and a graphite monochromator ($\lambda = 0.71073$ Å). Using Olex2, the structure was solved by intrinsic phasing through using the ShelXT program and refined using least-squares minimization with the ShelXL package.

Crystallographic Data. Compound **41**. $C_{16}H_{24}O_4$, $M = 280.35$, $T = 150.00(10)$ K, monoclinic, space group $P2_1/c$, $Z = 8$, $a = 10.0743(2)$ Å, $b = 19.91991(4)$ Å, $c = 17.0687(2)$ Å, $\alpha = 90^\circ$, $\beta = 90.0160(10)^\circ$, $\gamma = 90^\circ$; $V = 3301.38(10)$ Å³, $D_x = 1.128$ Mg m⁻³, 6646 unique data ($2\theta_{\max} = 148.074^\circ$), $R = 0.0398$ [for 5962 reflections with $I > 2(I)$]; $R_w = 0.1011$ (all data), $S = 1.048$.

Structure Determination. Data for compound **41** was collected on a SuperNova X-ray diffractometer, employing Cu $K\alpha$ radiation and a graphite monochromator ($\lambda = 1.54184$ Å). Using Olex2, the structure was solved by intrinsic phasing through using the ShelXT program and refined using least-squares minimization with the ShelXL package.

Crystallographic Data. Compound **57**. $C_{25}H_{32}O_4$, $M = 369.50$, $T = 150.00(10)$ K, orthorhombic, space group $Pna2_1$, $Z = 4$, $a = 12.6413(3)$ Å, $b = 16.9383(5)$ Å, $c = 10.1650(3)$ Å, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$; $V = 2176.55(10)$ Å³, $D_x = 1.210$ Mg m⁻³, 6114 unique data ($2\theta_{\max} = 59.148^\circ$), $R = 0.0358$ [for 5686 reflections with $I \geq 2\sigma(I)$]; $R_w = 0.0950$ (all data), $S = 1.042$.

Structure Determination. Data for compound **57** was collected on a New Xcalibur X-ray diffractometer, employing Mo $K\alpha$ radiation and a graphite monochromator ($\lambda = 0.71073$ Å). Using Olex2, the structure was solved by intrinsic phasing through using the ShelXT program and refined using least-squares minimization with the ShelXL package.

Crystallographic Data. Compound **58**. $C_{16}H_{20}O_4$, $M = 276.32$, $T = 150.00(10)$ K, monoclinic, space group $P2_1/n$, $Z = 4$, $a = 10.9467(8)$ Å, $b = 10.2731(7)$ Å, $c = 14.0802(11)$ Å, $\alpha = 90^\circ$, $\beta = 105.538(8)^\circ$, $\gamma = 90^\circ$; $V = 152.5(2)$ Å³, $D_x = 1.203$ Mg m⁻³, 2779 unique data ($2\theta_{\max} = 50.696^\circ$), $R = 0.0448$ [for 2259 reflections with $I \geq 2\sigma(I)$]; $R_w = 0.0571$ (all data), $S = 1.0399$.

Structure Determination. Data for compound **58** was collected on a New Xcalibur X-ray diffractometer, employing Mo $K\alpha$ radiation and a graphite monochromator ($\lambda = 0.71073$ Å). Using Olex2, the structure was solved by intrinsic phasing through using the ShelXT program and refined using least-squares minimization with the ShelXL package.

Crystallographic Data. Compound **61**. $C_{20}H_{26}O_4$, $M = 330.41$, $T = 150.01(10)$ K, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 13.7620(6)$ Å, $b = 11.0891(6)$ Å, $c = 12.1636(5)$ Å, $\alpha = 90^\circ$, $\beta = 94.959^\circ$, $\gamma = 90^\circ$; $V = 1849.32(15)$ Å³, $D_x = 1.187$ Mg m⁻³,

3391 unique data ($2\theta_{\max} = 50.7^\circ$), $R = 0.0567$ [for 2692 reflections with $I \geq 2\sigma(I)$]; $R_w = 0.1329$ (all data), $S = 1.046$.

Structure Determination. Data for compound **61** was collected on a SuperNova X-ray diffractometer, employing Cu K α radiation and a graphite monochromator ($\lambda = 1.54184$ Å). Using Olex2, the structure was solved by intrinsic phasing through using the ShelXT program and refined using least-squares minimization with the ShelXL package.

Crystallographic Data. Compound **70**. $C_{13}H_{20}O_4$, $M = 240.29$, $T = 150.00(10)$ K, orthorhombic, space group $Pbcn$, $Z = 4$, $a = 15.8569(13)$ Å, $b = 8.1462(4)$ Å, $c = 10.6258(6)$ Å, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$; $V = 1372.57(15)$ Å³, $D_x = 1.163$ Mg m⁻³, 1275 unique data ($2\theta_{\max} = 141.296^\circ$), $R = 0.0577$ [for 974 reflections with $I > 2(I)$]; $R_w = 0.1641$ (all data), $S = 0.986$.

Structure Determination. Data for compound **70** was collected on a SuperNova X-ray diffractometer, employing Cu K α radiation and a graphite monochromator ($\lambda = 1.54184$ Å). Using Olex2, the structure was solved by intrinsic phasing through using the ShelXT program and refined using least-squares minimization with the ShelXL package.

Crystallographic Data. Compound **73**. $C_{15}H_{20}O_4$, $M = 264.31$, $T = 150.01(10)$ K, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 10.1694(9)$ Å, $b = 15.4076(10)$ Å, $c = 10.6285(8)$ Å, $\alpha = 90^\circ$, $\beta = 116.574(10)^\circ$, $\gamma = 90^\circ$; $V = 1489.4(2)$ Å³, $D_x = 1.187$ Mg m⁻³, 2721 unique data ($2\theta_{\max} = 50.7^\circ$), $R = 0.0583$ [for 2017 reflections with $I \geq 2\sigma(I)$]; $R_w = 0.1484$ (all data), $S = 1.065$.

Structure Determination. Data for compound **73** was collected on a New Xcalibur X-ray diffractometer, employing Mo K α radiation and a graphite monochromator (λ = 0.71073 Å). Using Olex2, the structure was solved by intrinsic phasing through using the ShelXT program and refined using least-squares minimization with the ShelXL package.

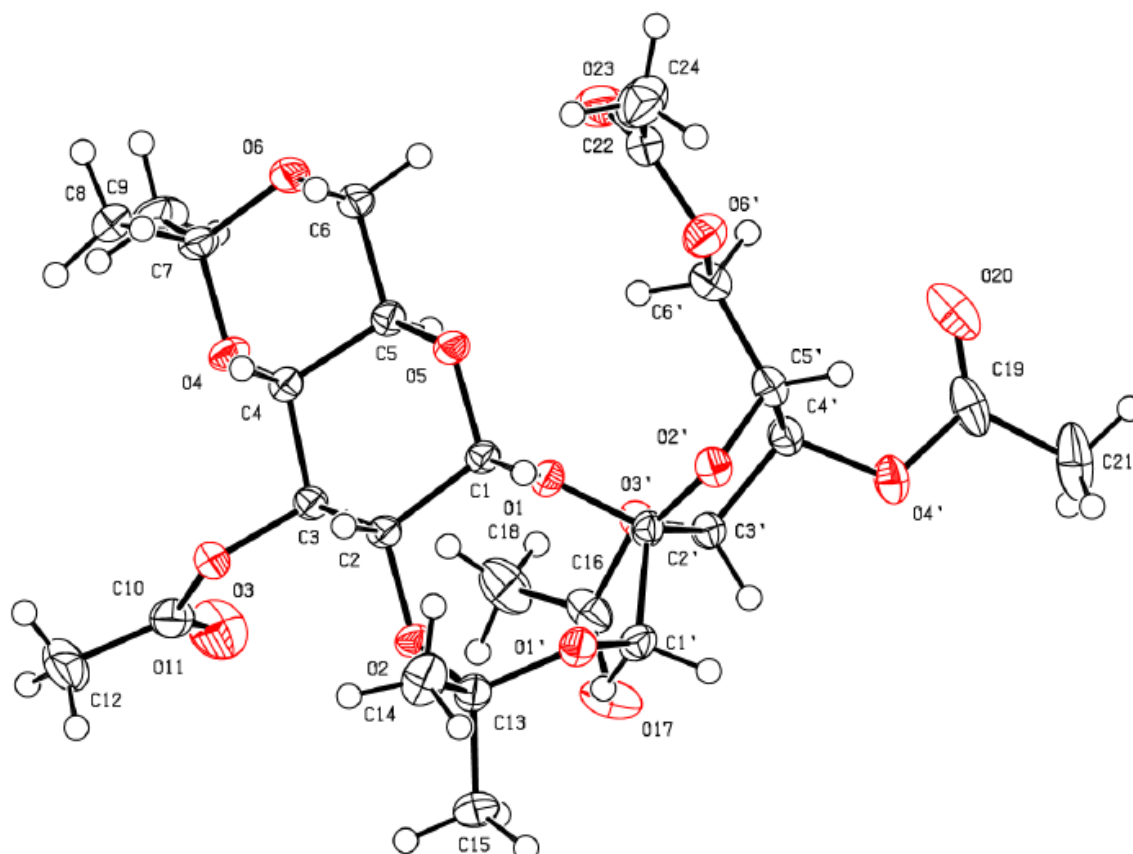
Chapter Six References

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Appendices

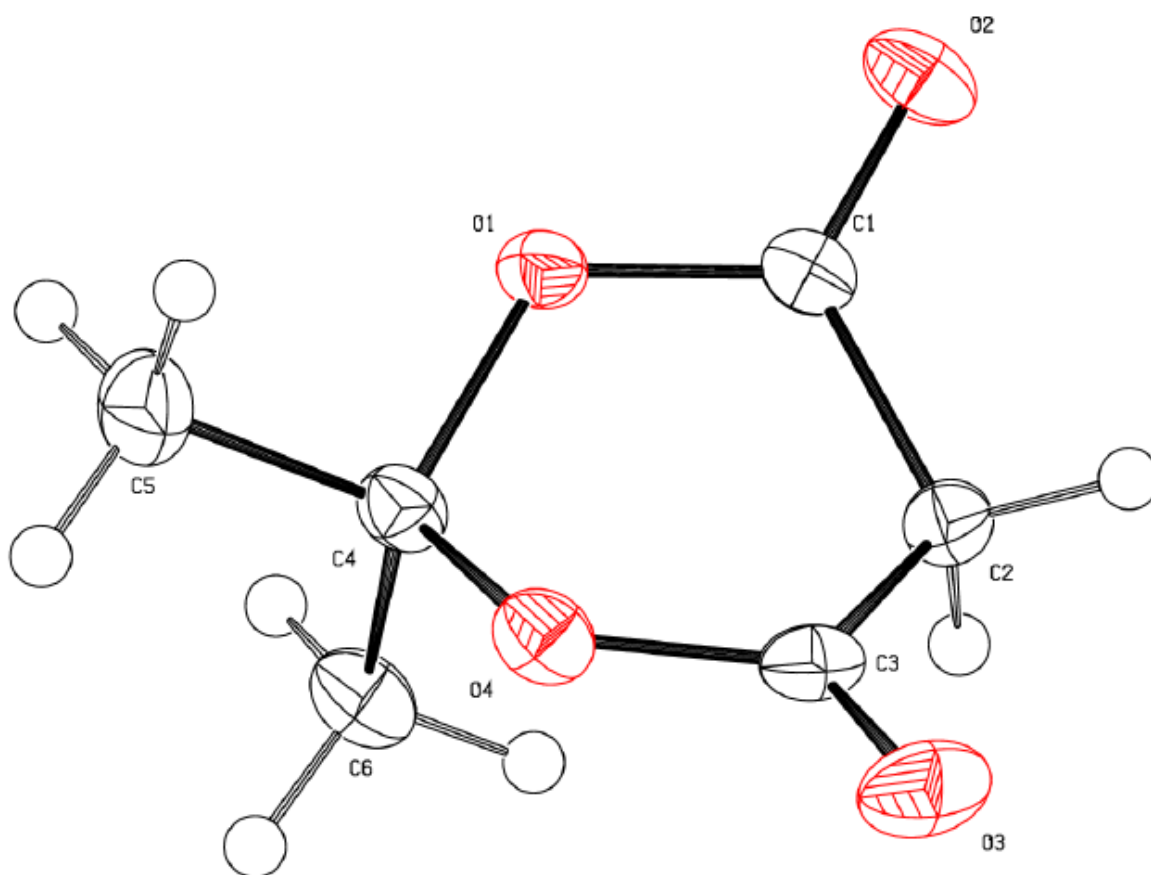
Appendix 1: Crystallographic data

A1.1: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound 7



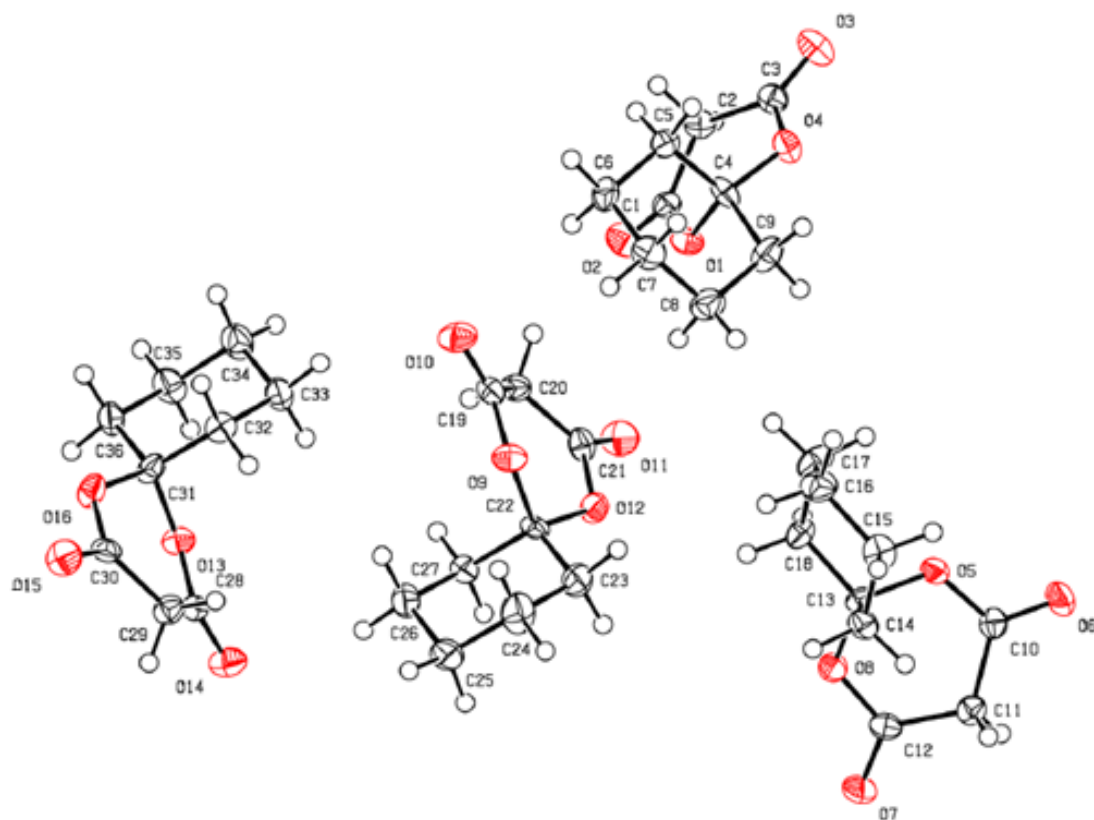
A1.1. ORTEP derived from the single-crystal X-ray analysis of compound **7** with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

A1.2: ORTEP derived from the single-crystal X-ray crystal structure analysis of Meldrum's acid



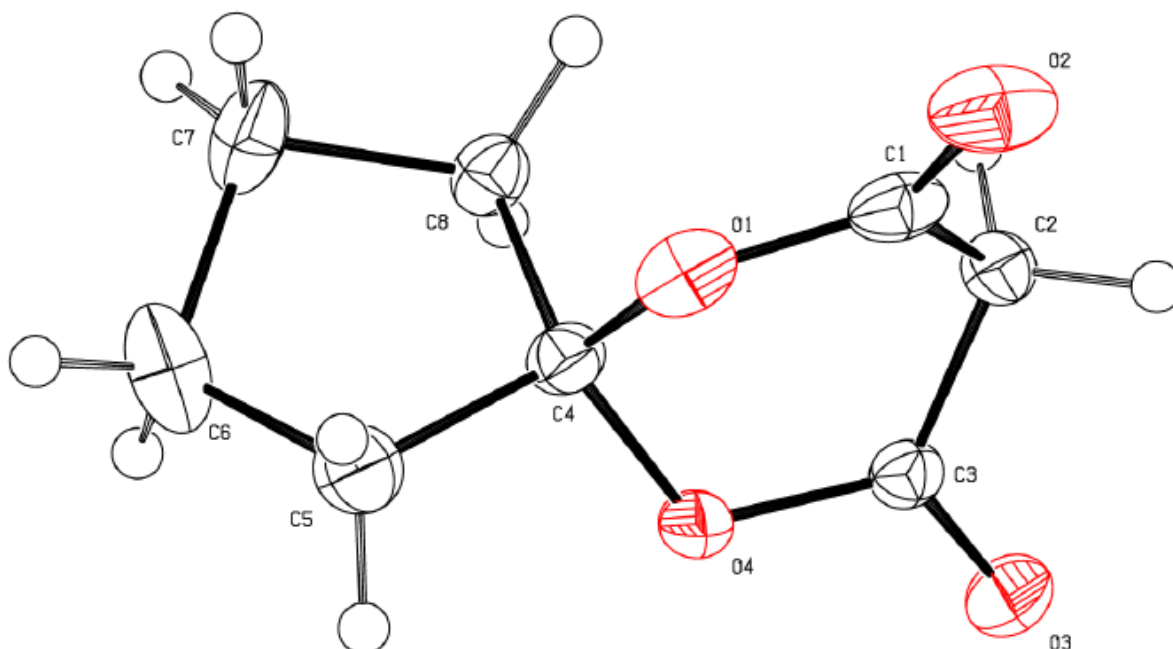
A1.2. ORTEP derived from the single-crystal X-ray analysis of Meldrum's acid with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

*A1.3: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound **16***



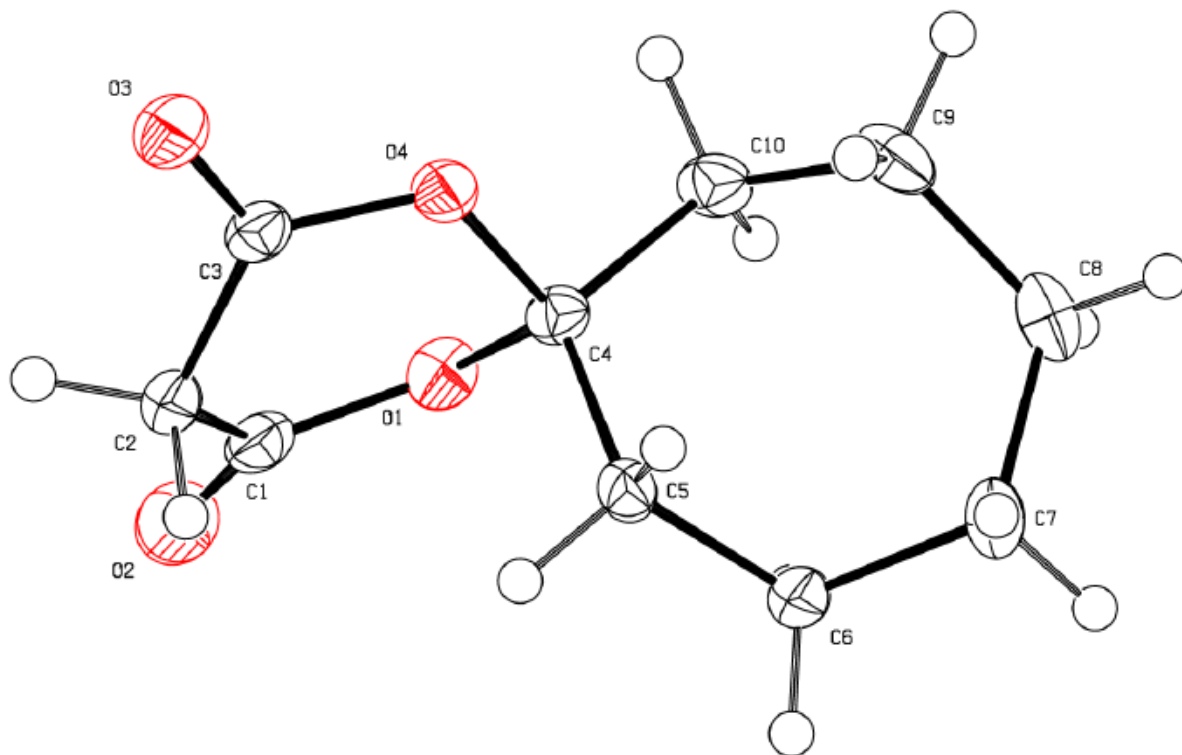
A1.3. ORTEP derived from the single-crystal X-ray analysis of compound **16** with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

*A1.4: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound **17**.*



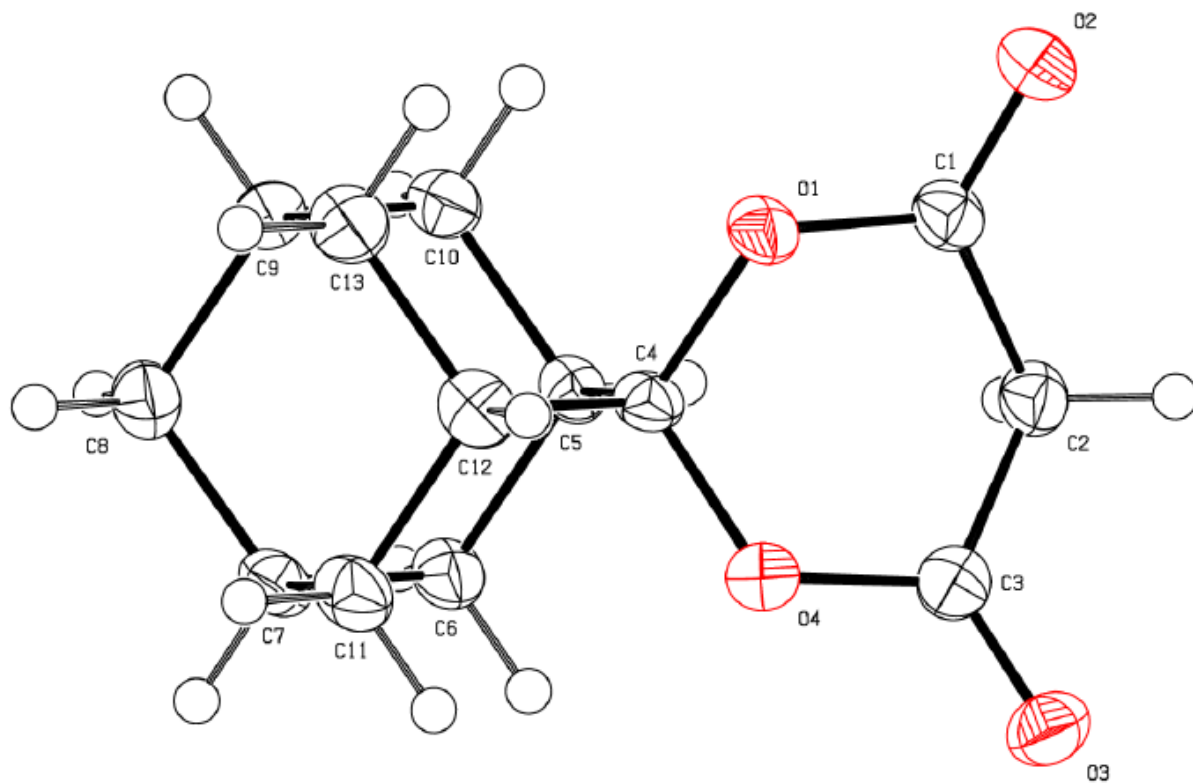
A1.4. ORTEP derived from the single-crystal X-ray analysis of compound **17** with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

*A1.5: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound **18***



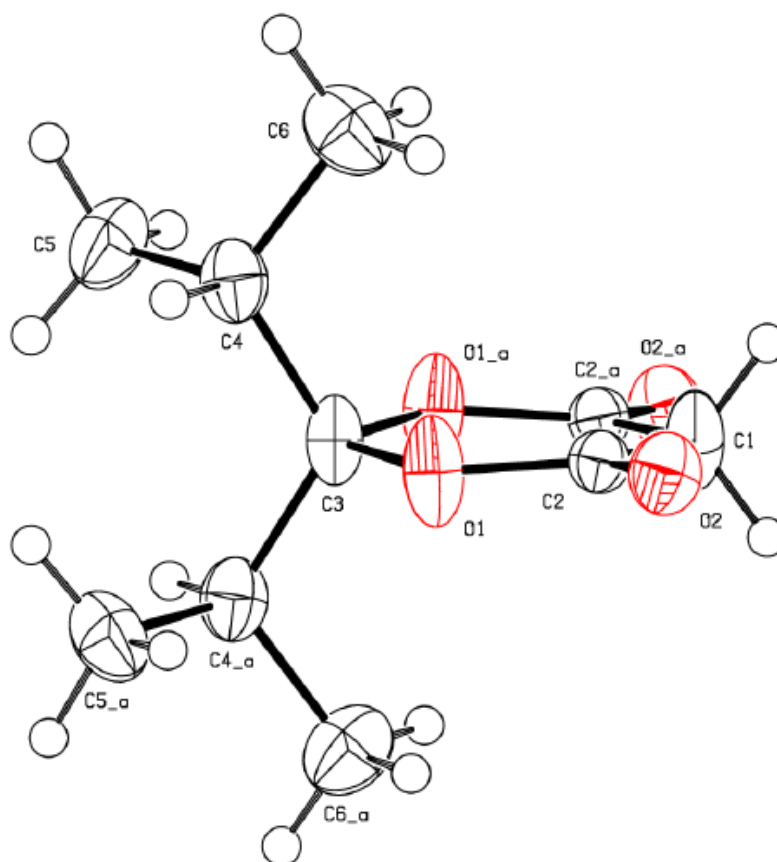
A1.5. ORTEP derived from the single-crystal X-ray analysis of compound **18** with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

A1.6: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound **19**.



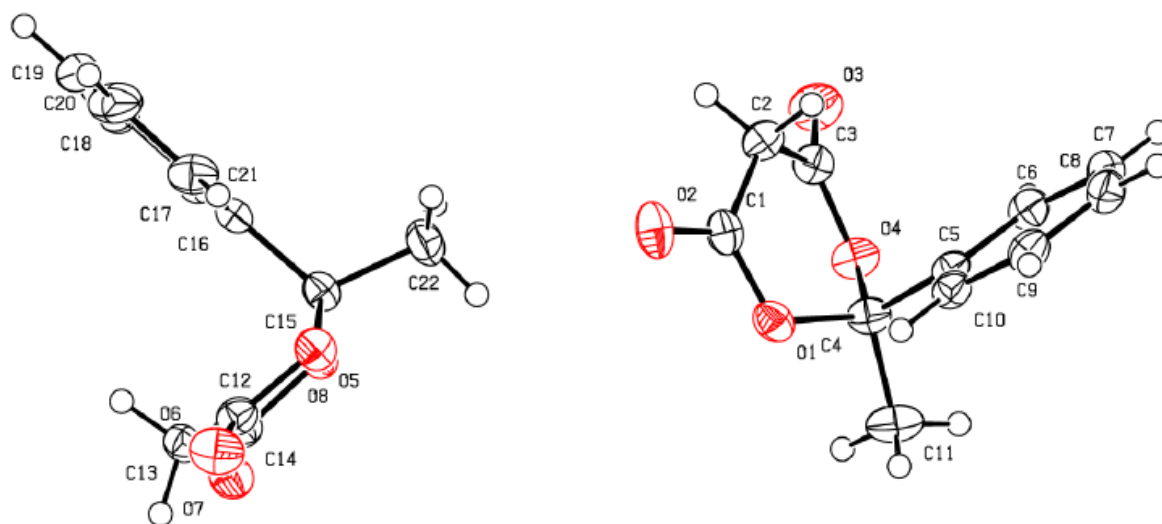
A1.6. ORTEP derived from the single-crystal X-ray analysis of compound **19** with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

*A1.7: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound **21**.*



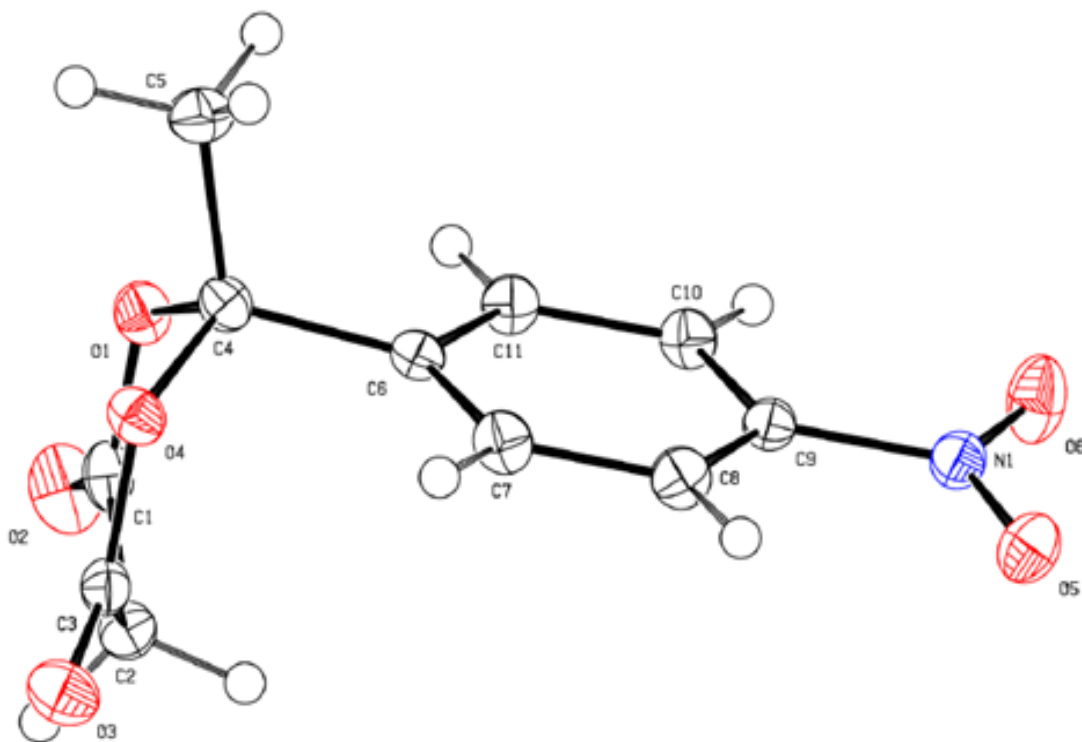
A1.7. ORTEP derived from the single-crystal X-ray analysis of compound **21** with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

*A1.8: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound **29**.*



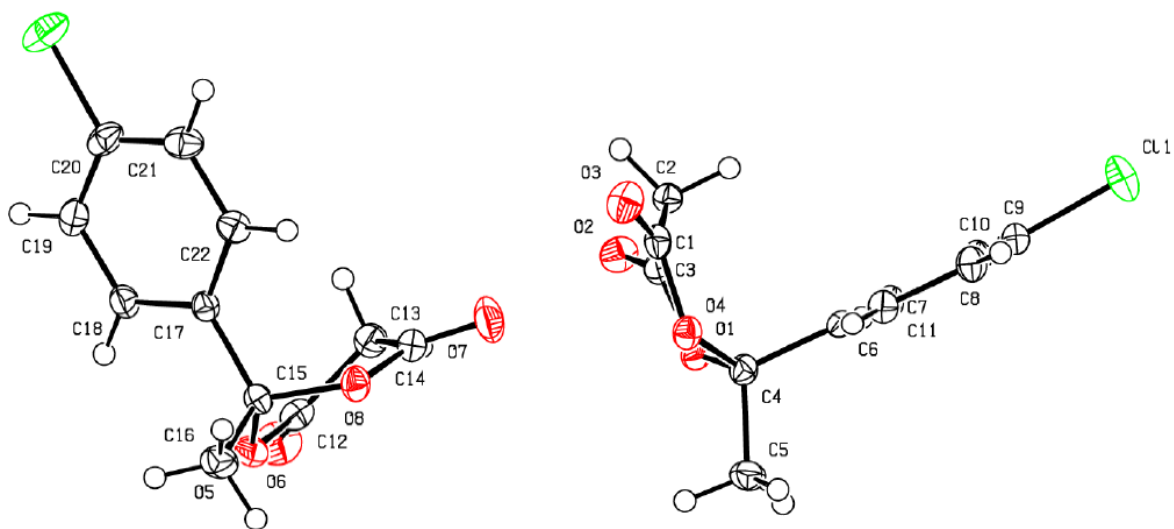
A1.8. ORTEP derived from the single-crystal X-ray analysis of compound **29** with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

A1.9: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound **30**.



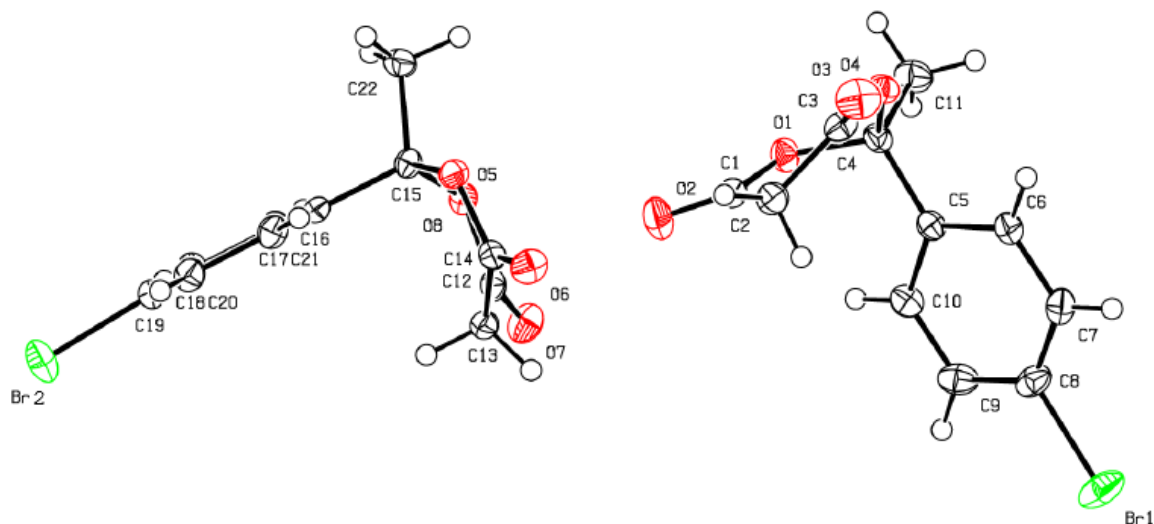
A1.9. ORTEP derived from the single-crystal X-ray analysis of compound **30** with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

A1.10: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound **31**.



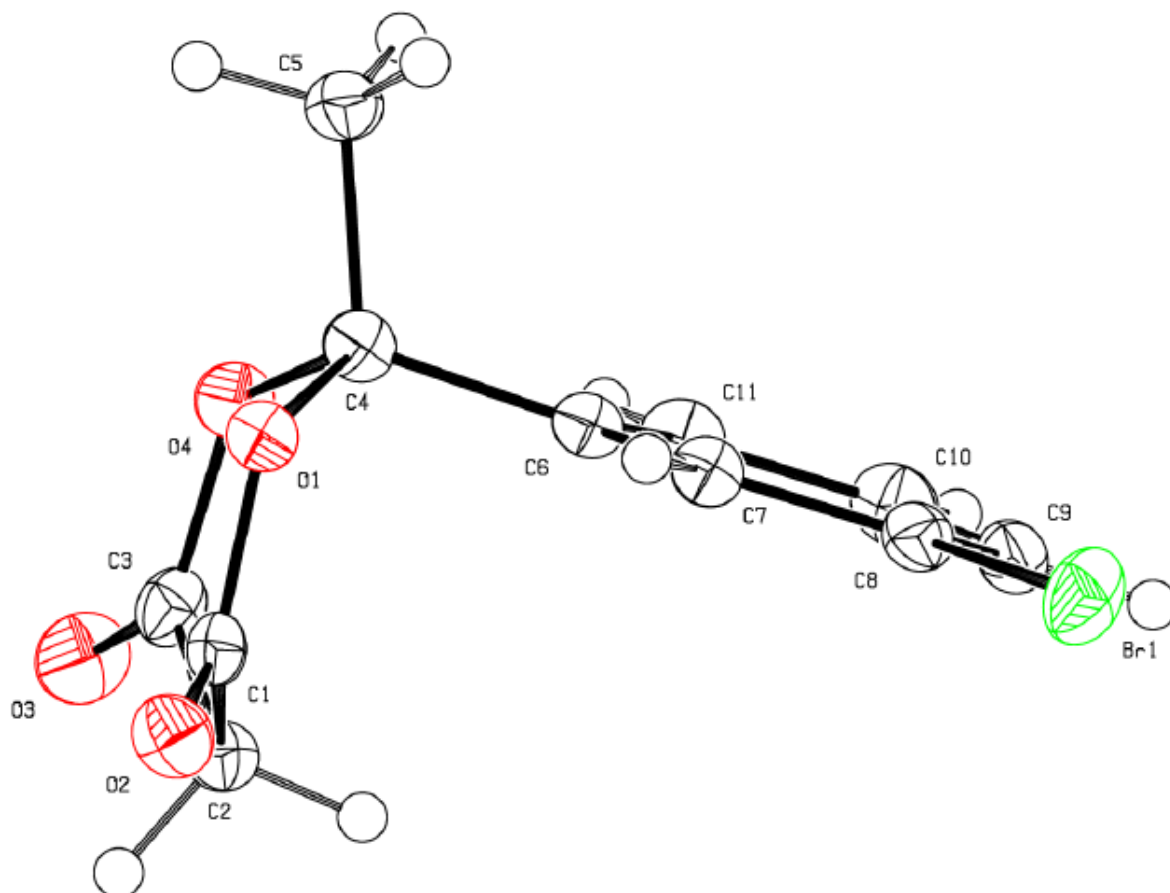
A1.10. ORTEP derived from the single-crystal X-ray analysis of compound **31** with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

A1.11: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound **33**.



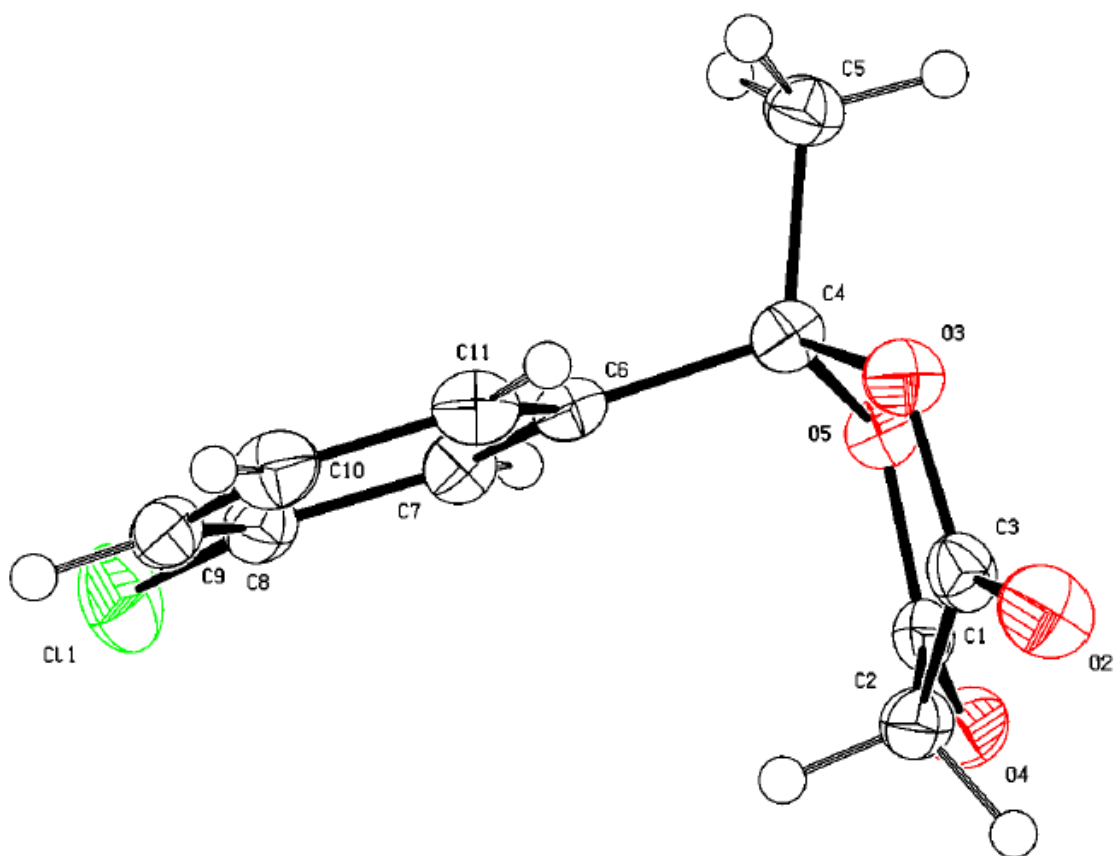
A1.11. ORTEP derived from the single-crystal X-ray analysis of compound **33** with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

A1.12: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound **34**.



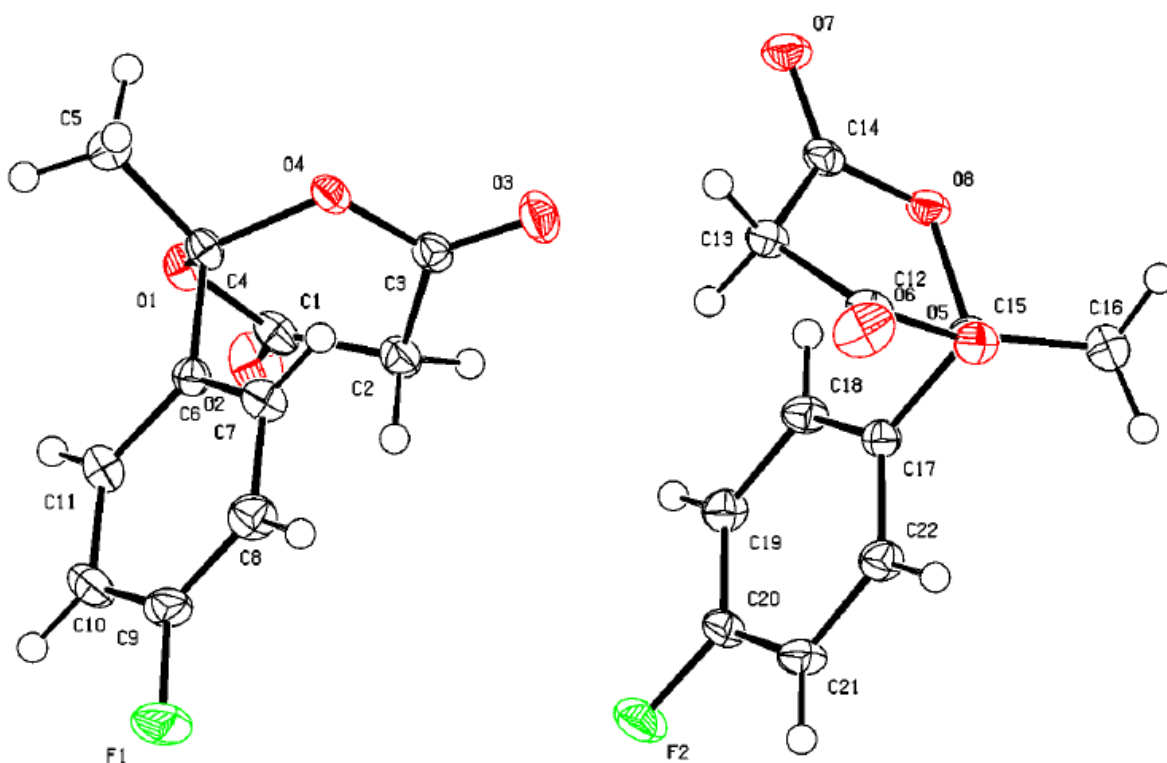
A1.12. ORTEP derived from the single-crystal X-ray analysis of compound **34** with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

A1.13: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound **35**.



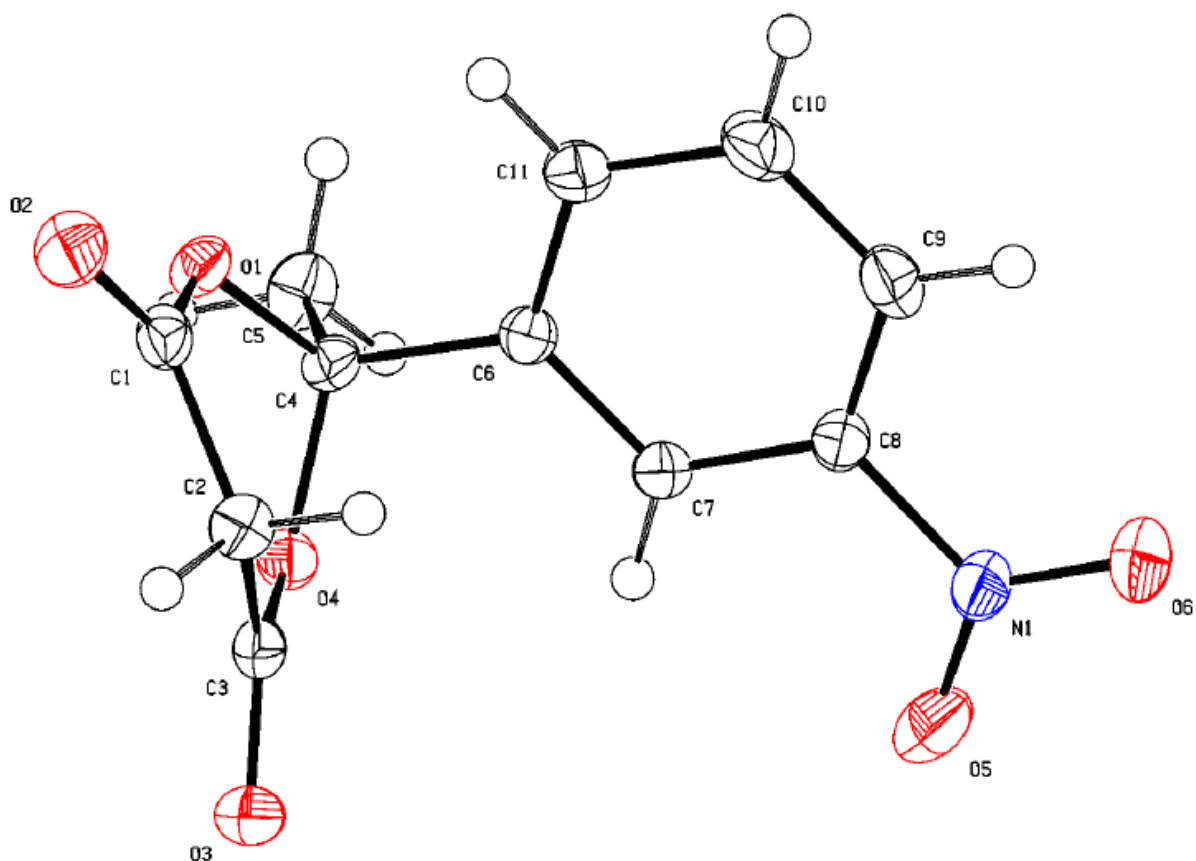
A1.13. ORTEP derived from the single-crystal X-ray analysis of compound **35** with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

A1.14: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound **36**.



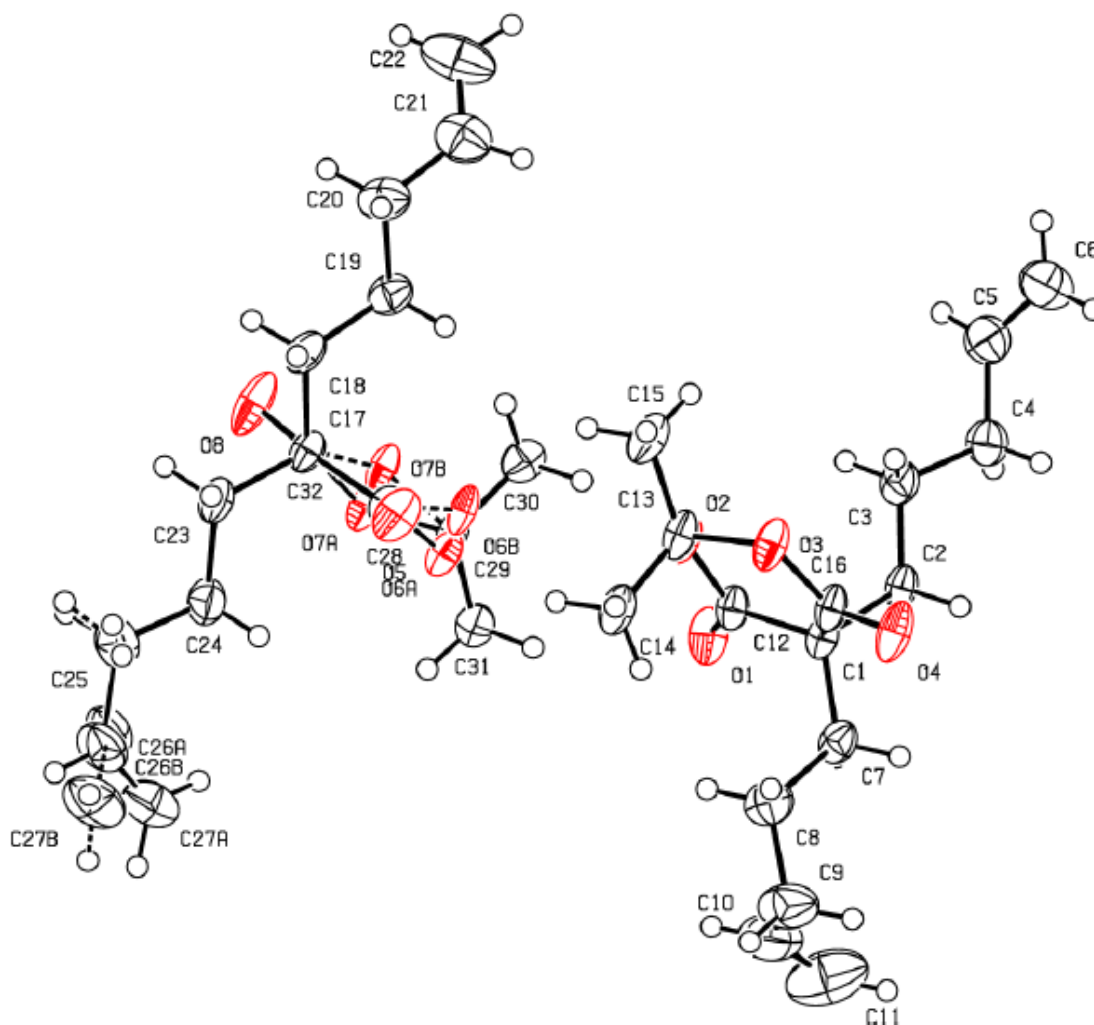
A1.14. ORTEP derived from the single-crystal X-ray analysis of compound **36** with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

A1.15: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound **38**.



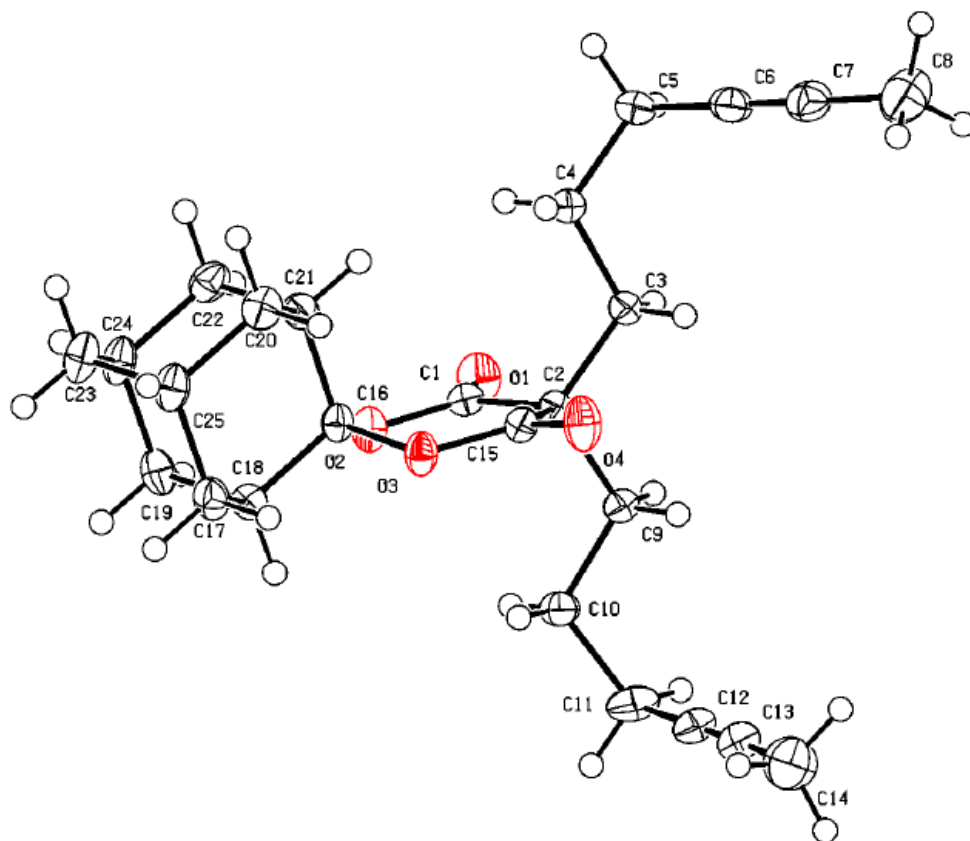
A1.15. ORTEP derived from the single-crystal X-ray analysis of compound **18** with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

A1.16: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound **41**.



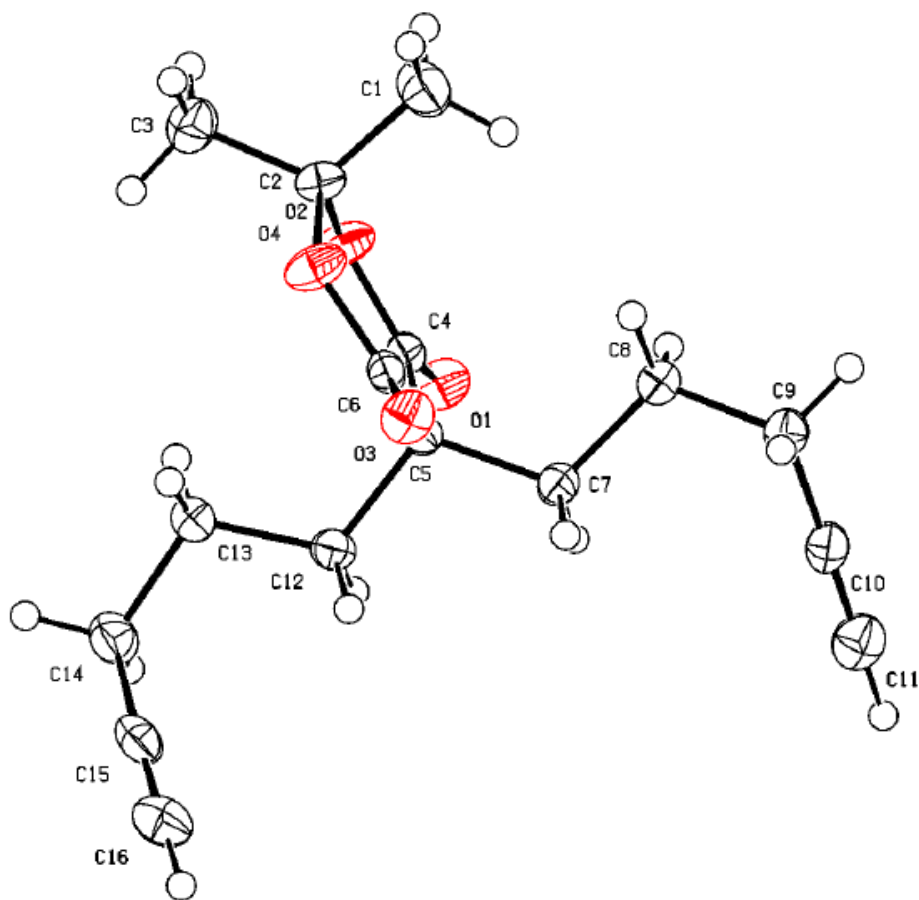
A1.16. ORTEP derived from the single-crystal X-ray analysis of compound **41** with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

A1.17: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound **57**.



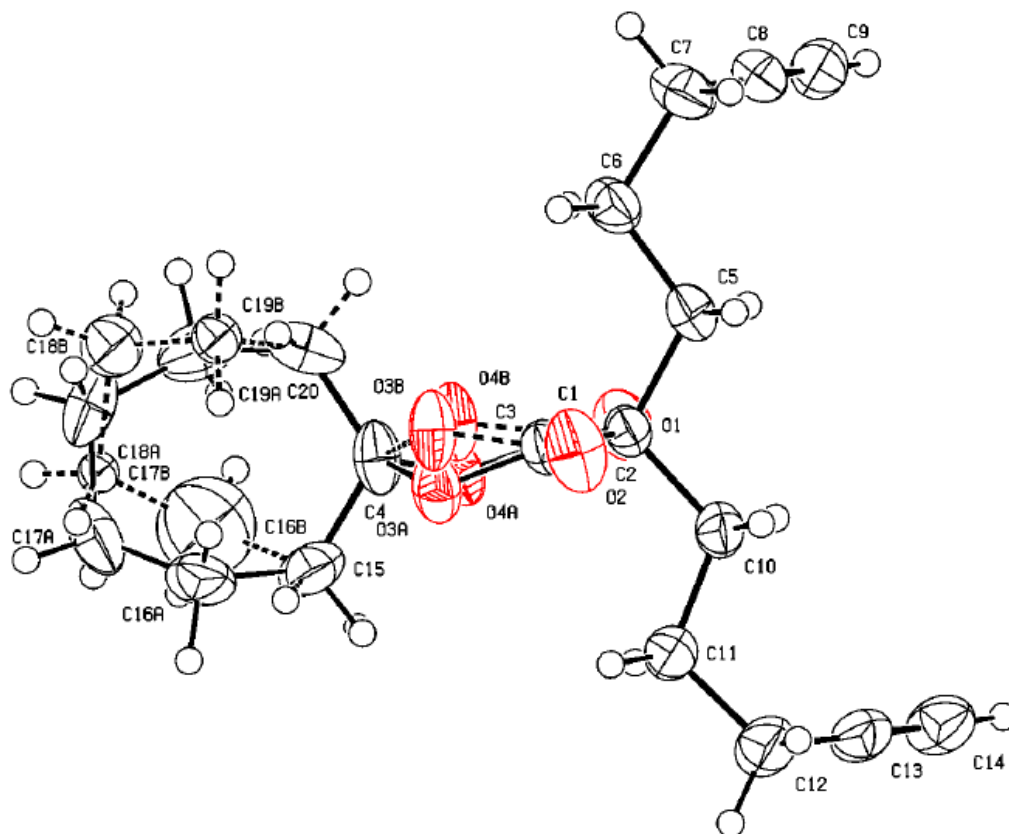
A1.17. ORTEP derived from the single-crystal X-ray analysis of compound **57** with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

A1.18: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound **58**.



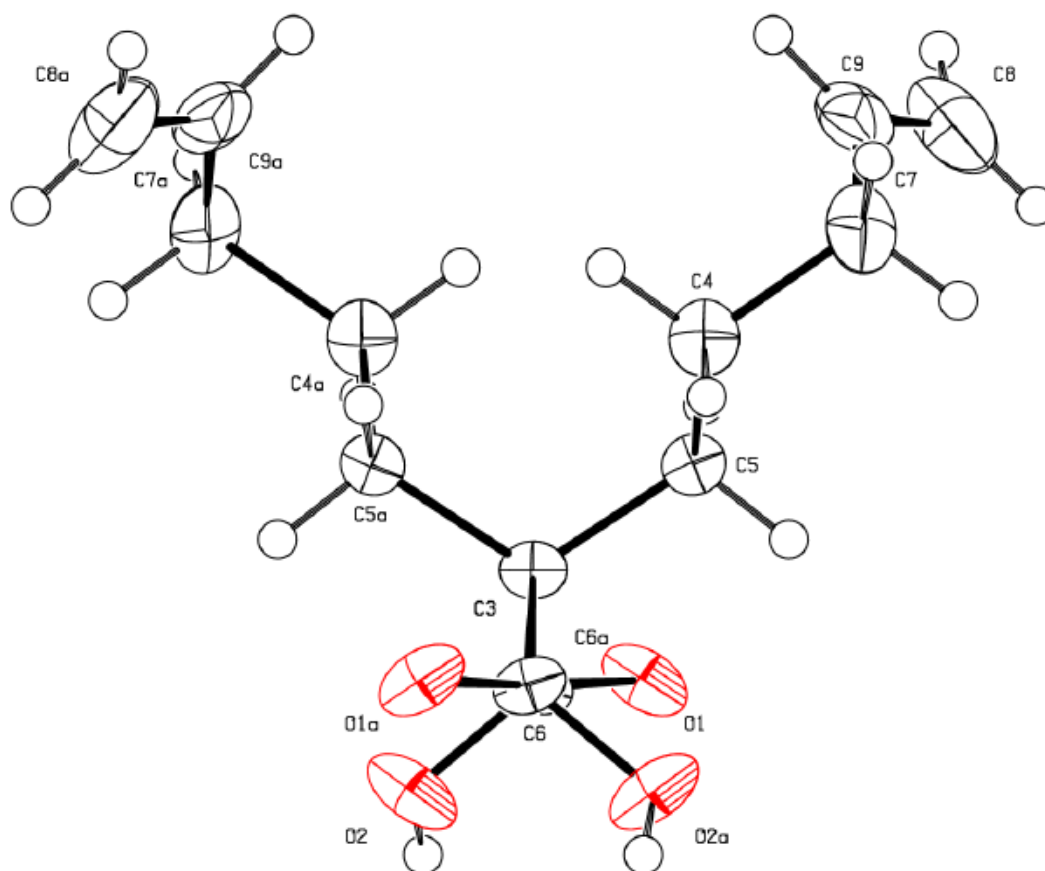
A1.18. ORTEP derived from the single-crystal X-ray analysis of compound **58** with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

A1.19: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound **61**.

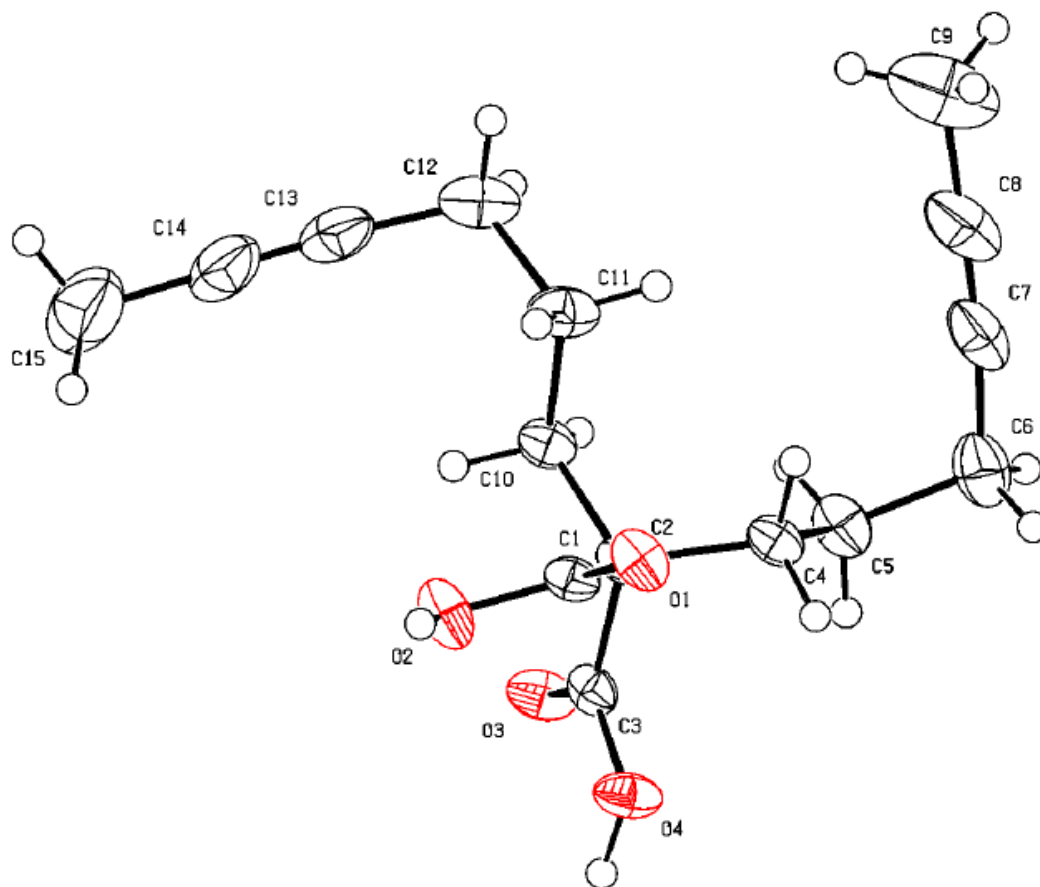


A1.19. ORTEP derived from the single-crystal X-ray analysis of compound **61** with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

*A1.20: ORTEP derived from the single-crystal X-ray crystal structure analysis of compound **70**.*



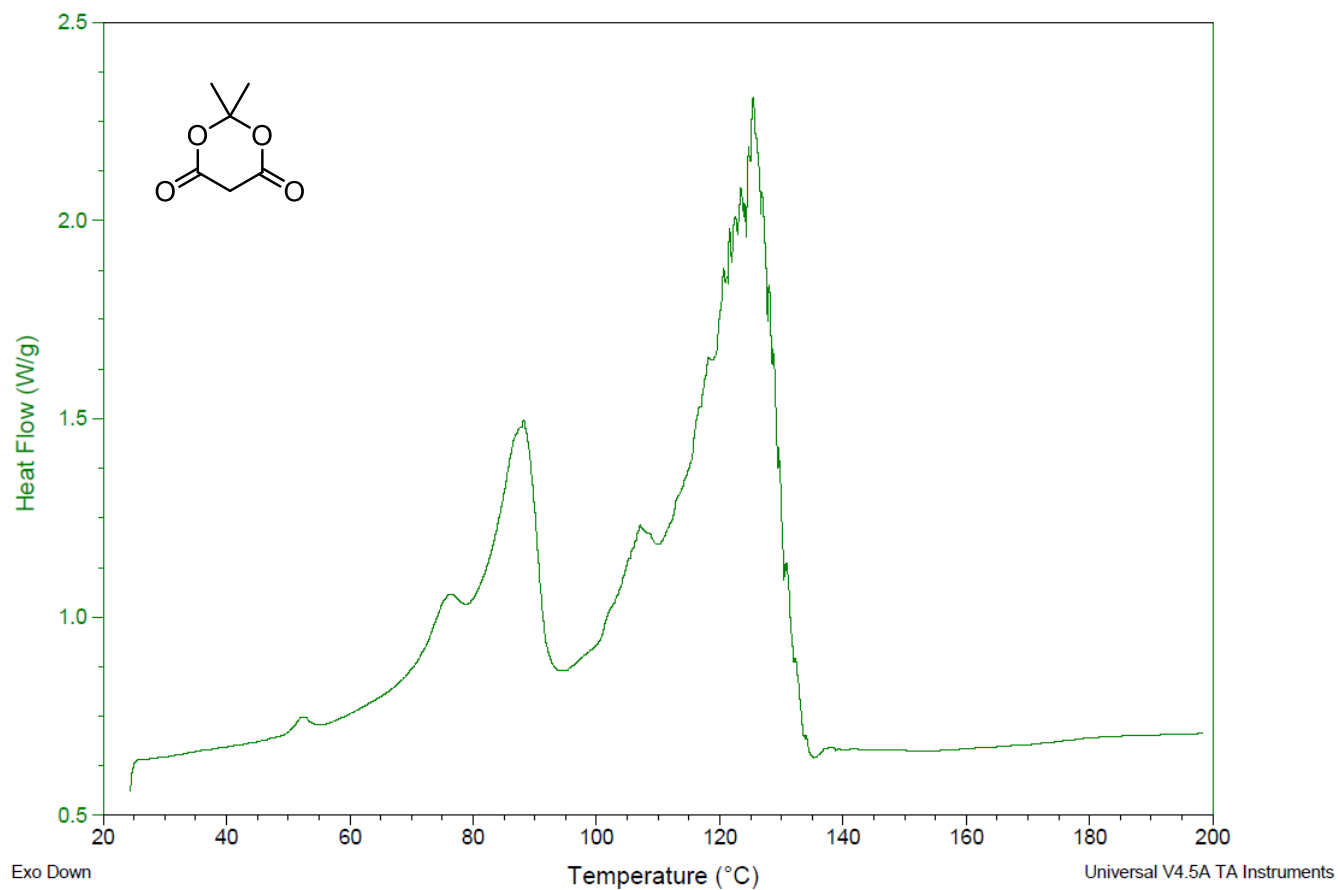
A1.20. ORTEP derived from the single-crystal X-ray analysis of compound **70** with labelling of all non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.



21

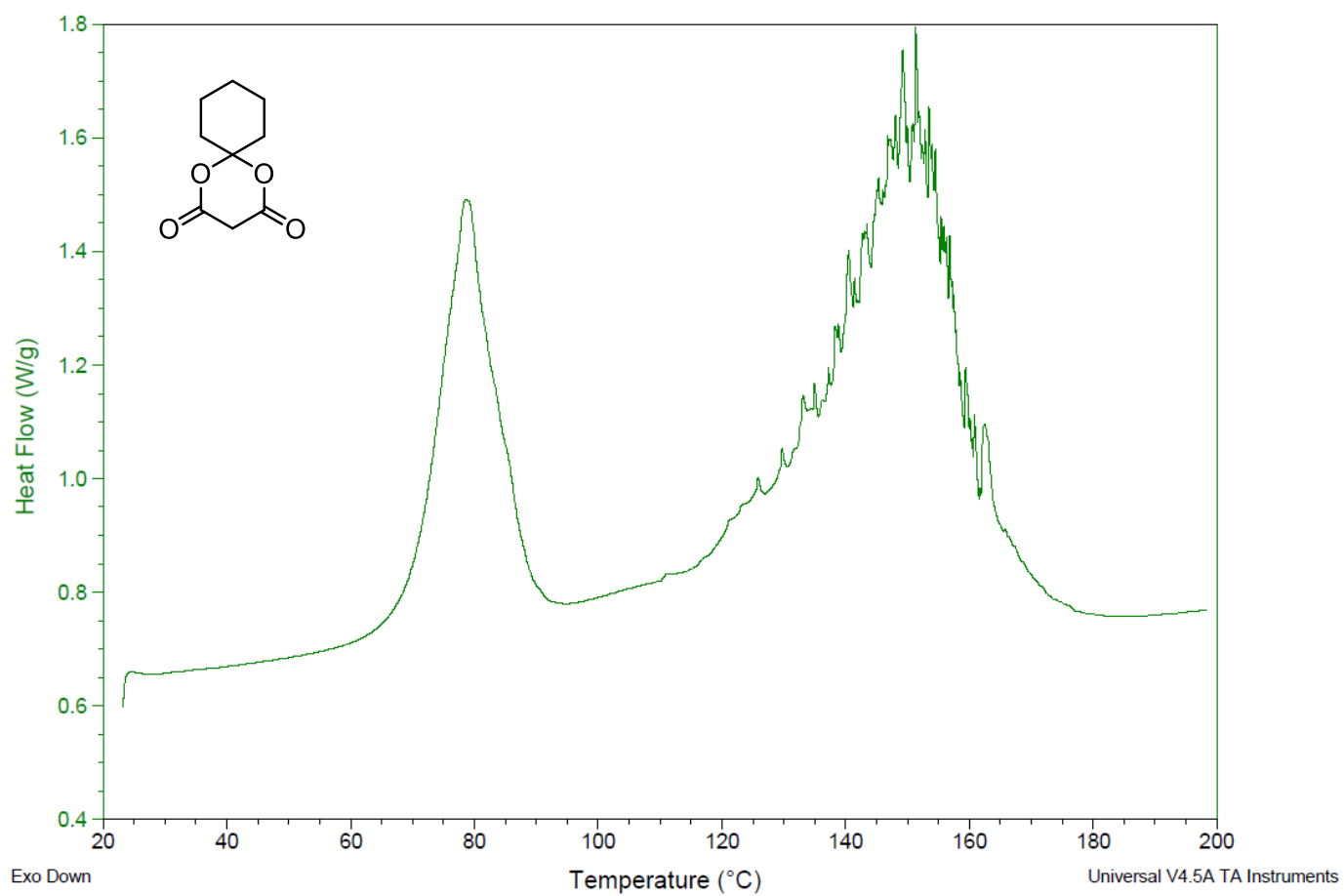
Appendix 2: Differential scanning calorimetry analyses data

A2.1: Differential scanning calorimetry plot of Meldrum's acid



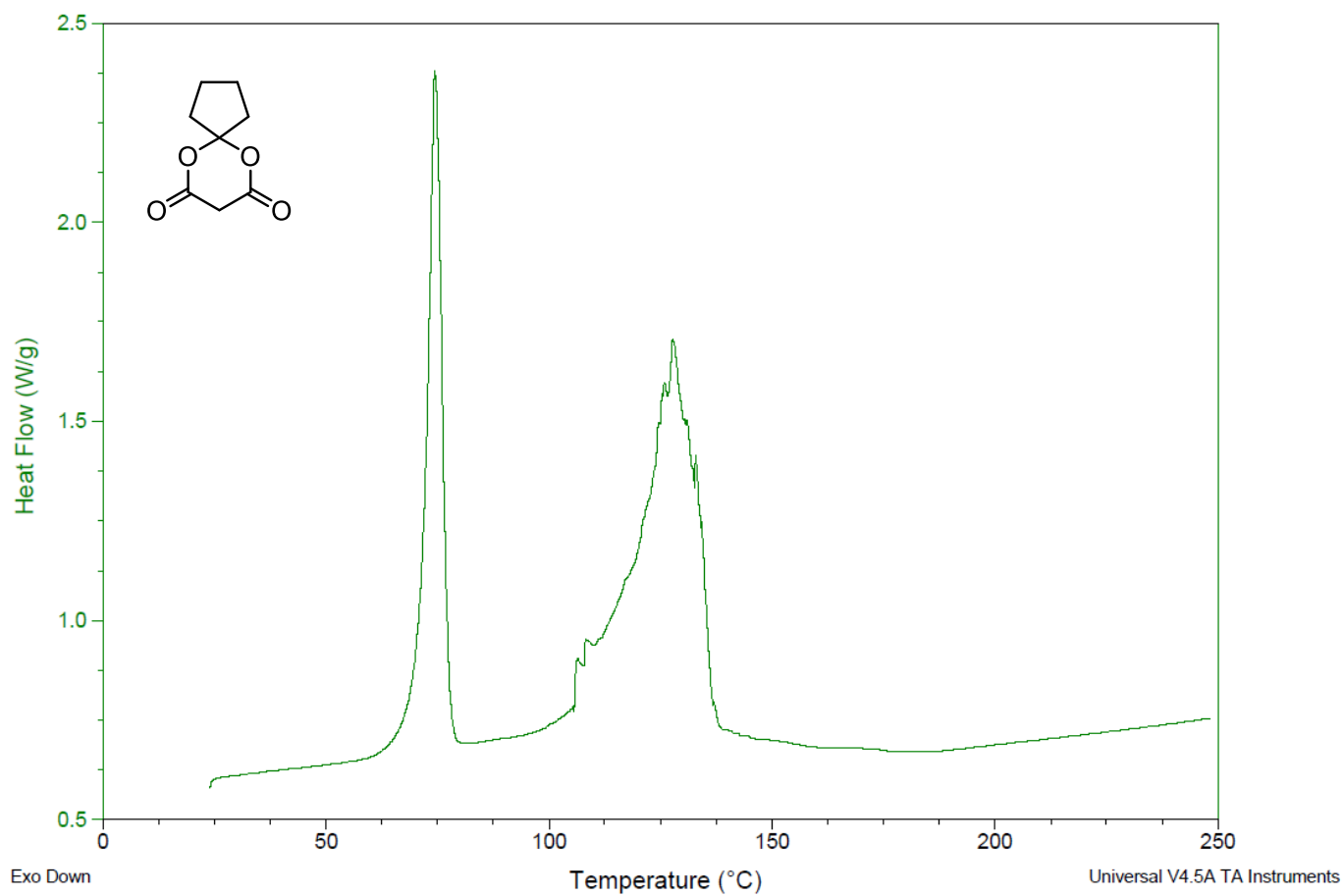
A2.1. Differential scanning calorimetry trace of Meldrum's acid. Endotherms are the peaks of the trace.

A2.2: Differential scanning calorimetry plot of compound **16**



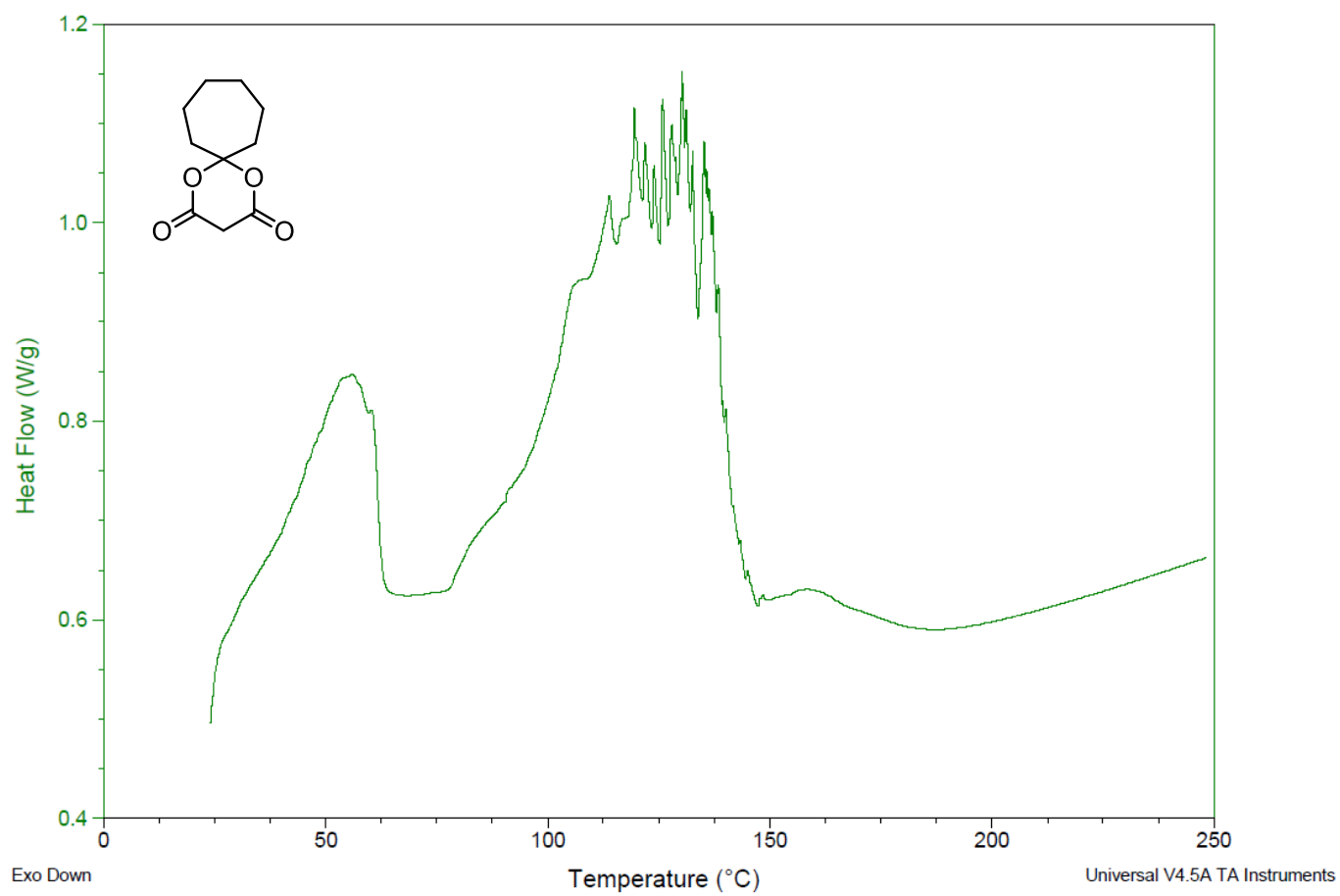
A2.2. Differential scanning calorimetry trace of compound **16**. Endotherms are the peaks of the trace.

A2.3: Differential scanning calorimetry plot of compound **17**



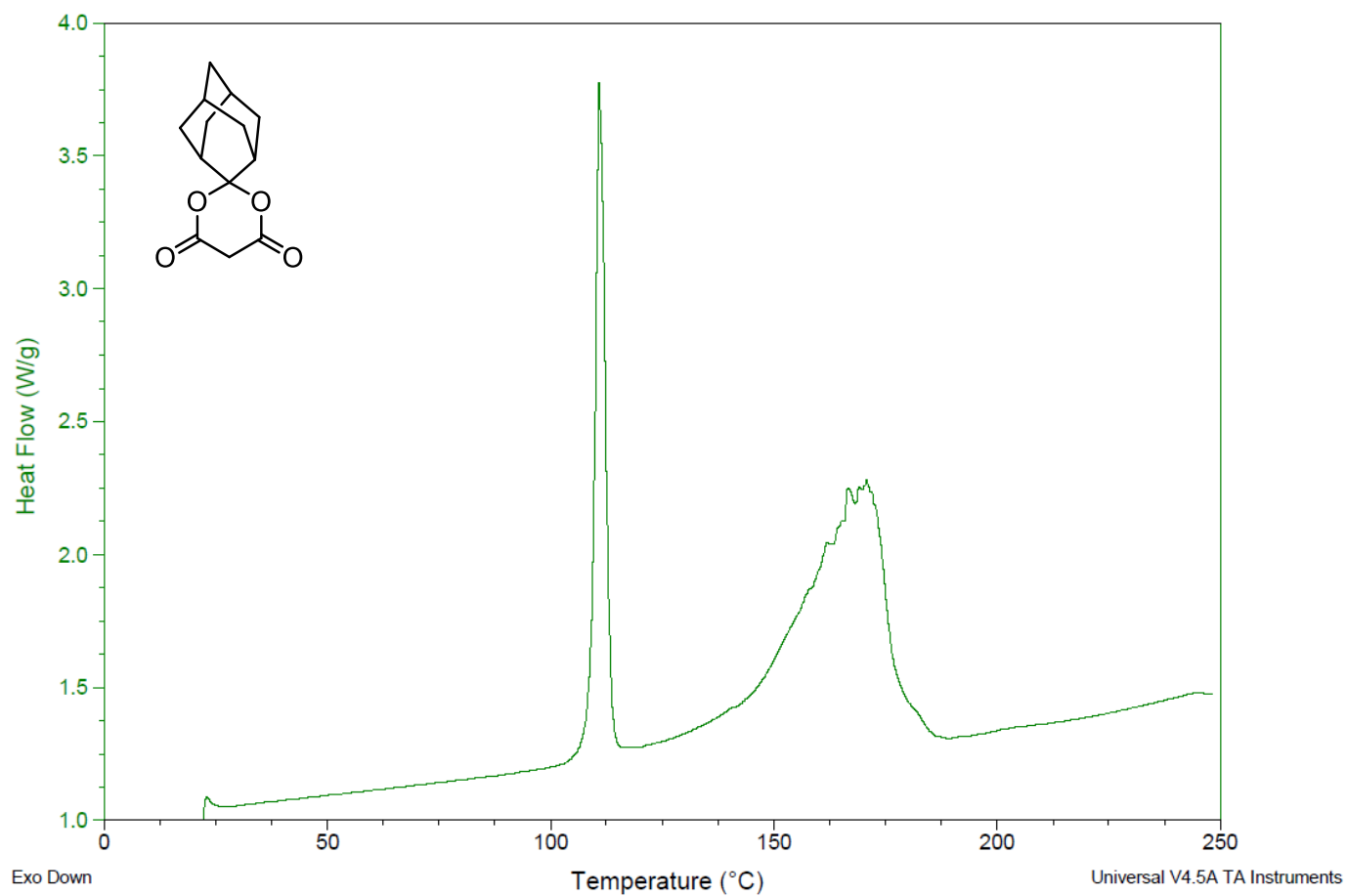
A2.3. Differential scanning calorimetry trace of compound **17**. Endotherms are the peaks of the trace.

A2.4: Differential scanning calorimetry trace of compound **18**



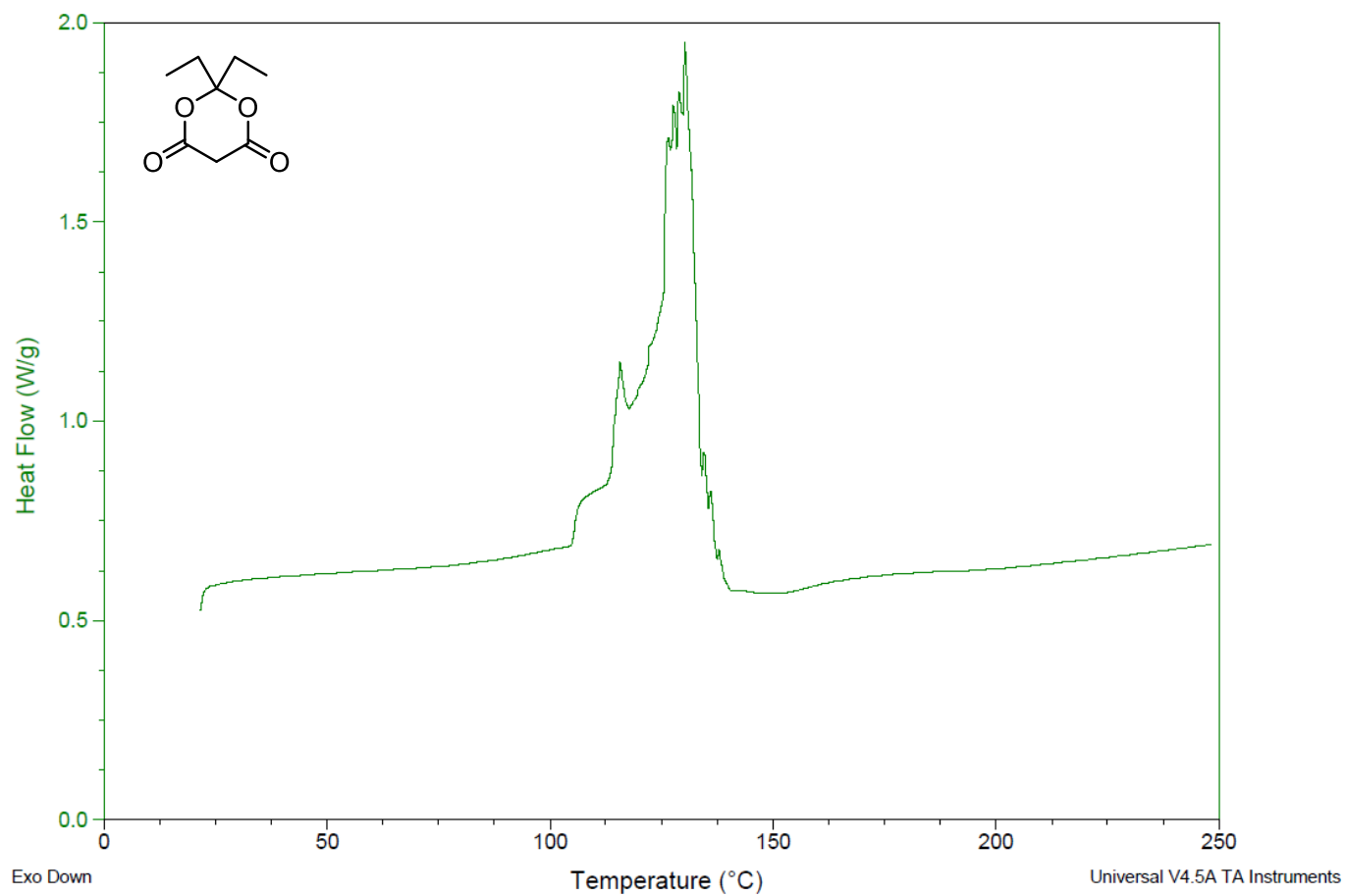
A2.4. Differential scanning calorimetry trace of compound **18**. Endotherms are the peaks of the trace.

A2.5: Differential scanning calorimetry trace of compound **19**



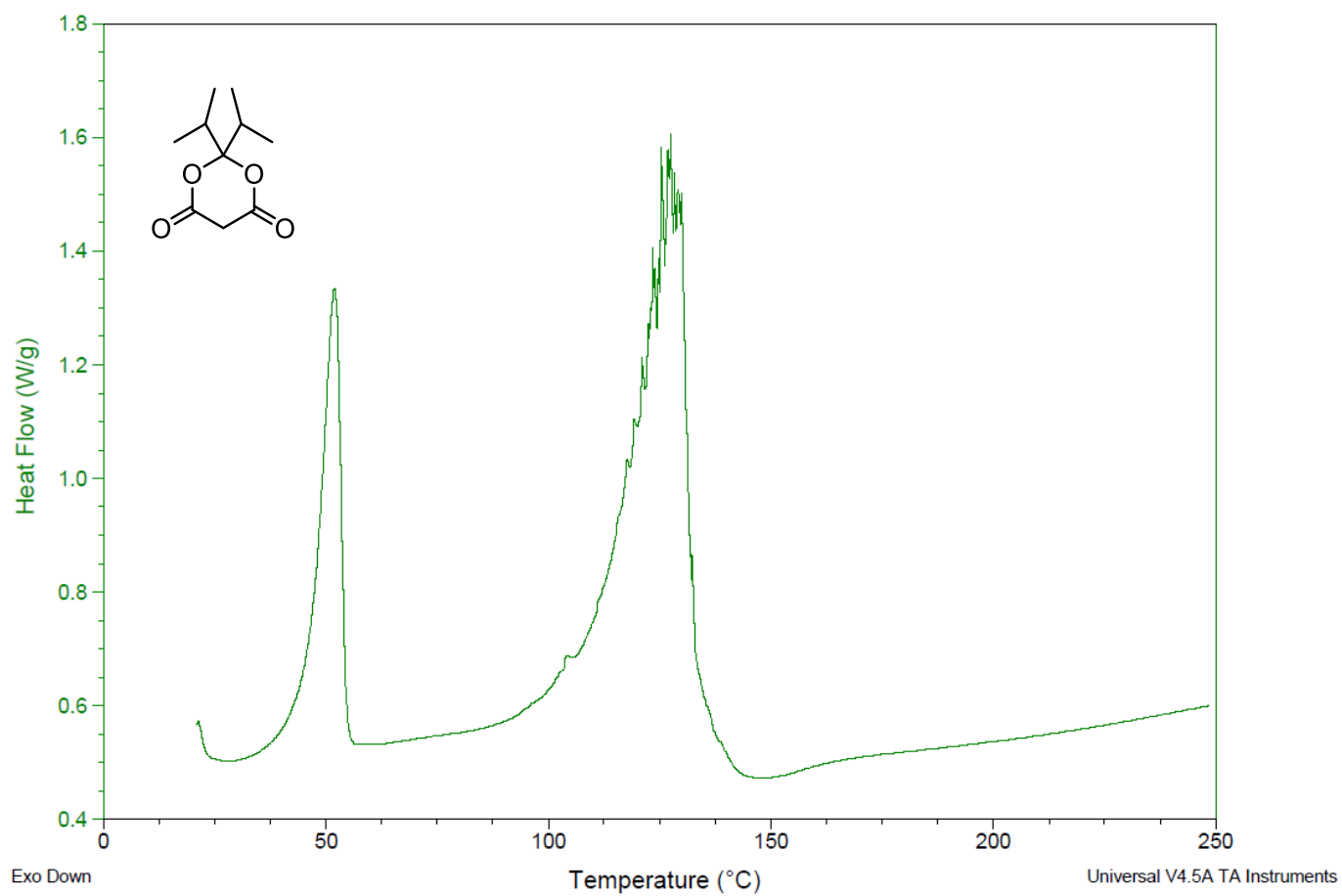
A2.5. Differential scanning calorimetry trace of compound **19**. Endotherms are the peaks of the trace.

A2.6: Differential scanning calorimetry trace of compound **20**



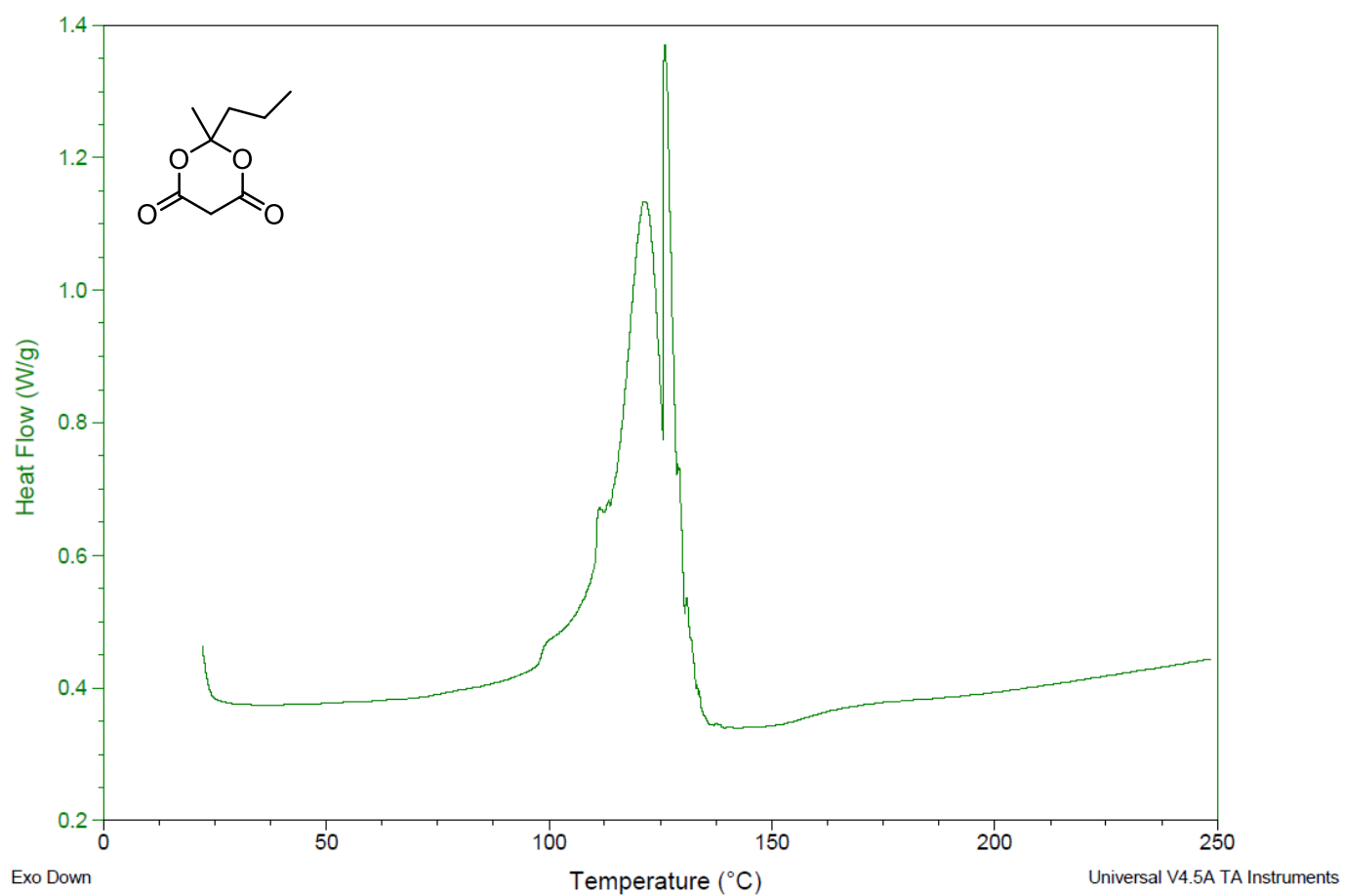
A2.6. Differential scanning calorimetry trace of compound **20**. Endotherms are the peaks of the trace.

A2.7: Differential scanning calorimetry trace of compound **21**



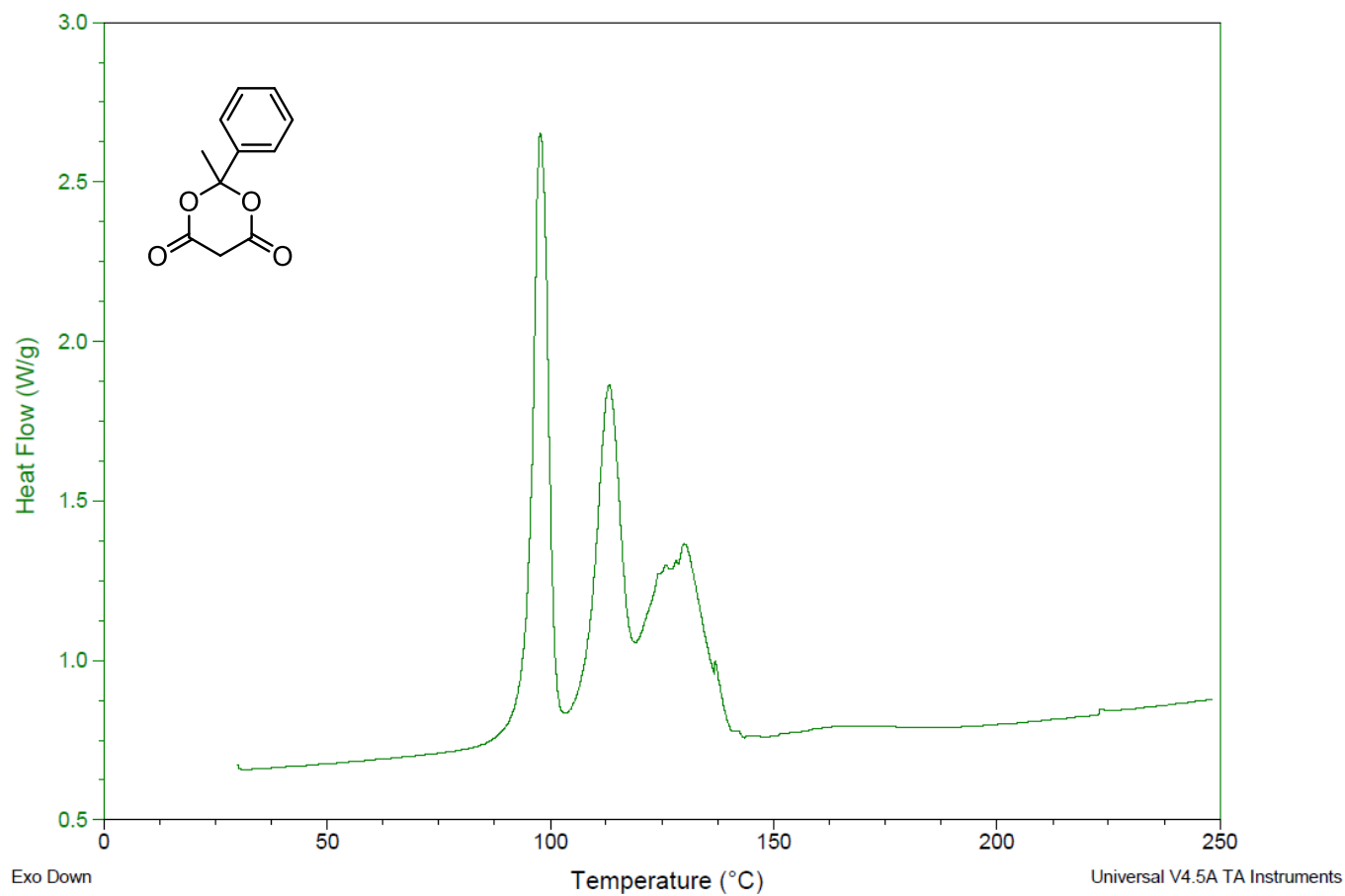
A2.7. Differential scanning calorimetry trace of compound **21**. Endotherms are the peaks of the trace.

A2.8: Differential scanning calorimetry trace of compound **22**



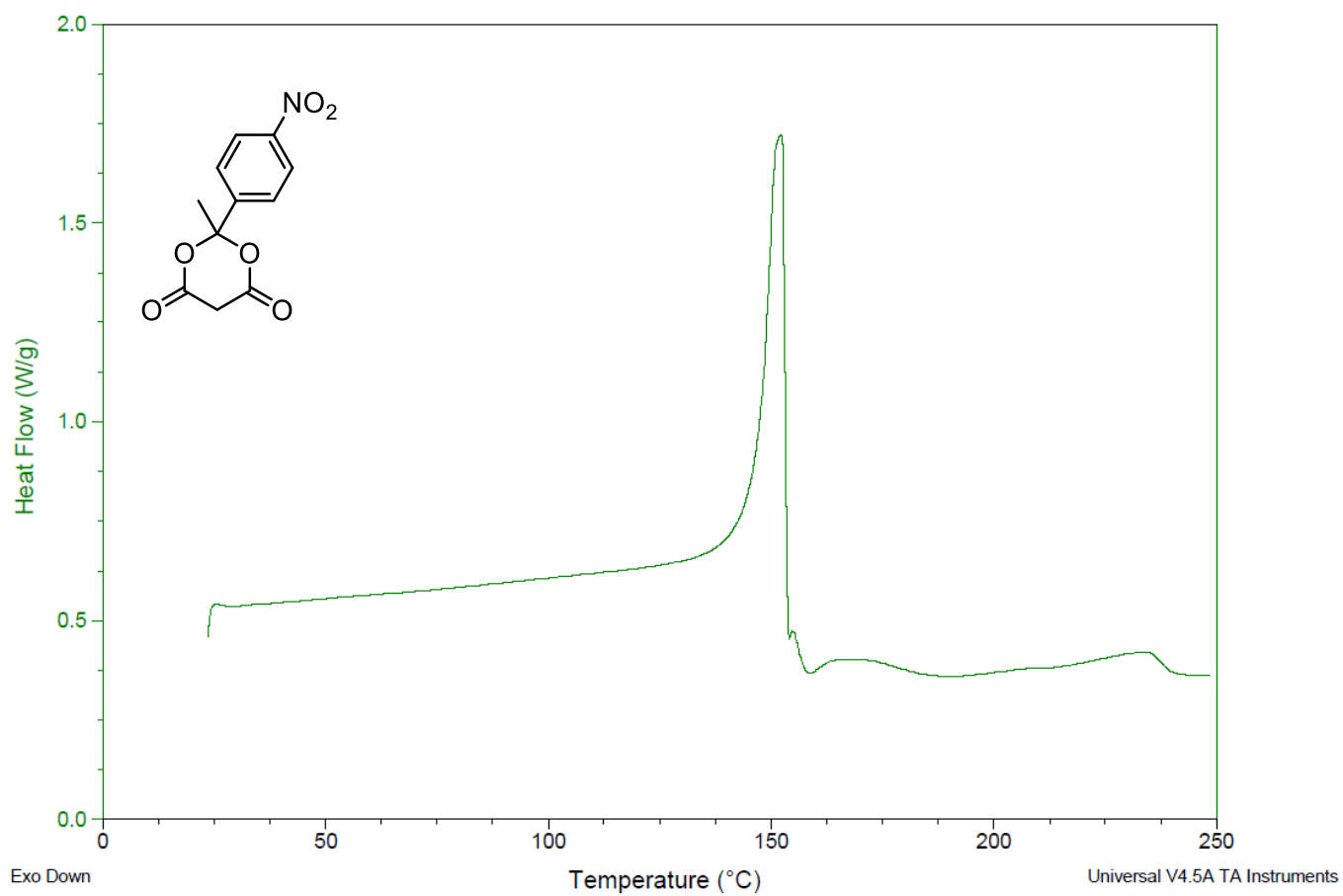
A2.8. Differential scanning calorimetry trace of compound **22**. Endotherms are the peaks of the trace.

A2.9: Differential scanning calorimetry trace of compound **29**



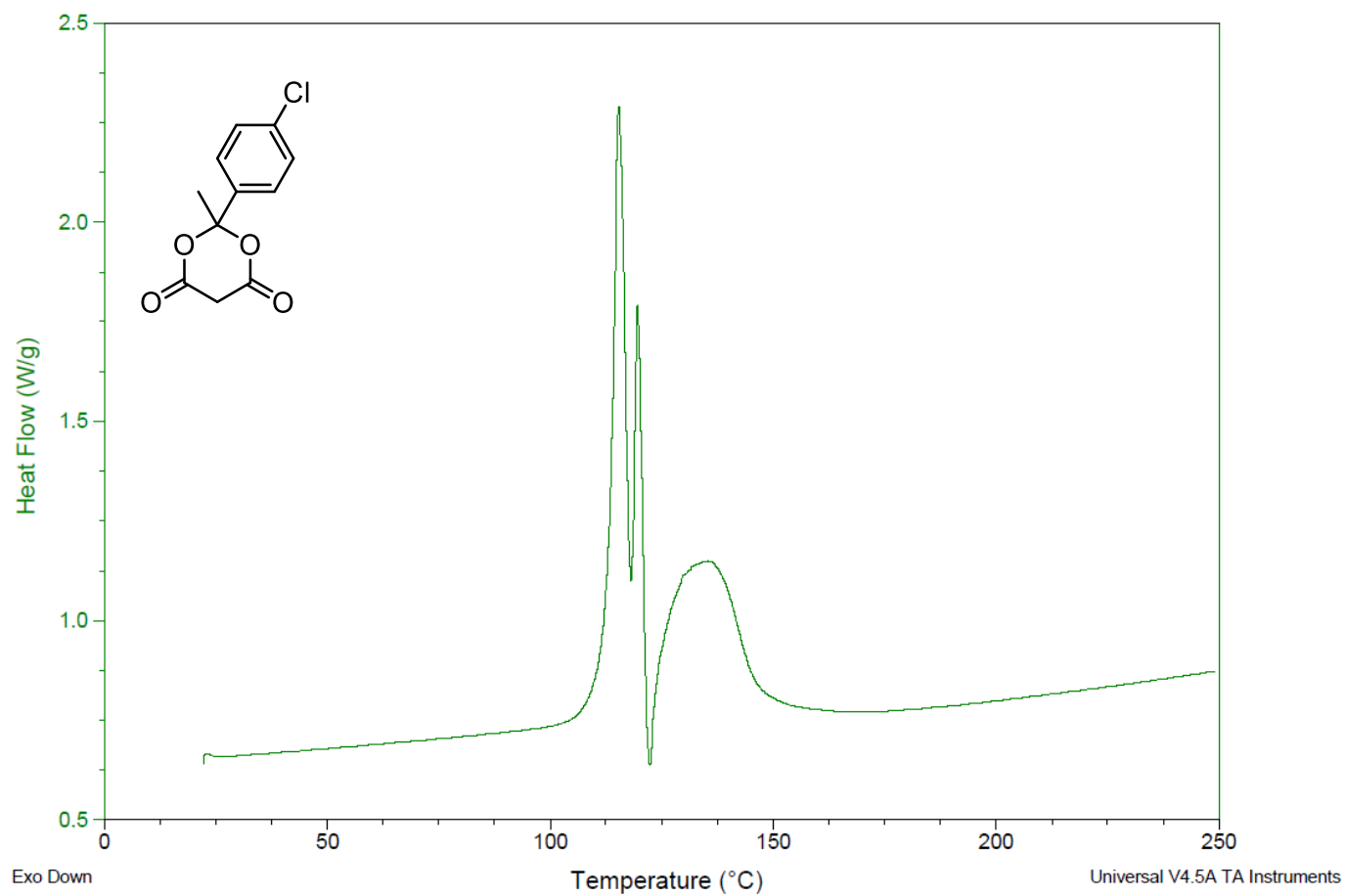
A2.9. Differential scanning calorimetry trace of compound **29**. Endotherms are the peaks of the trace.

A2.10: Differential scanning calorimetry trace of compound **30**



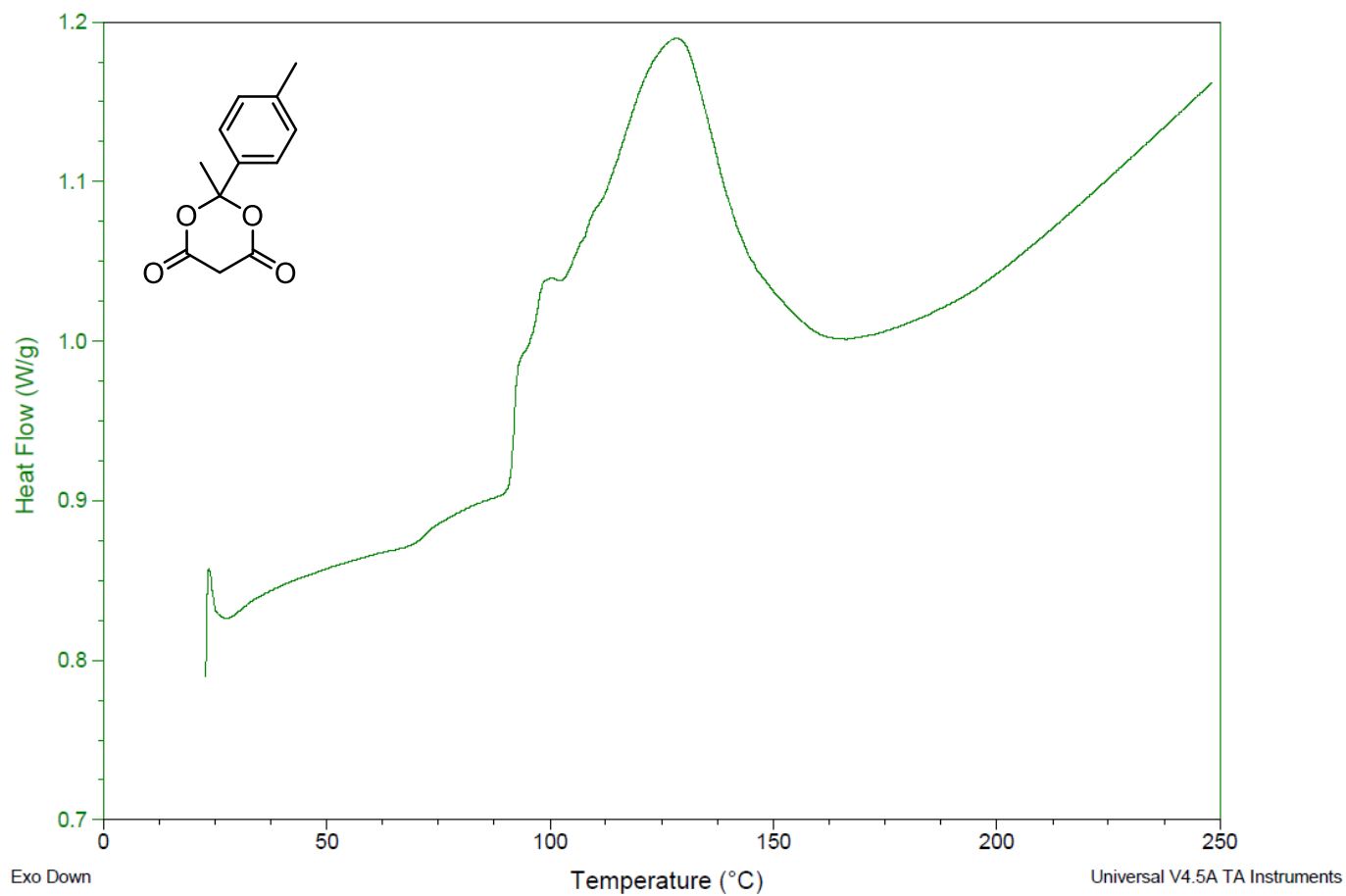
A2.10. Differential scanning calorimetry trace of compound **30**. Endotherms are the peaks of the trace.

A2.11: Differential scanning calorimetry trace of compound **31**



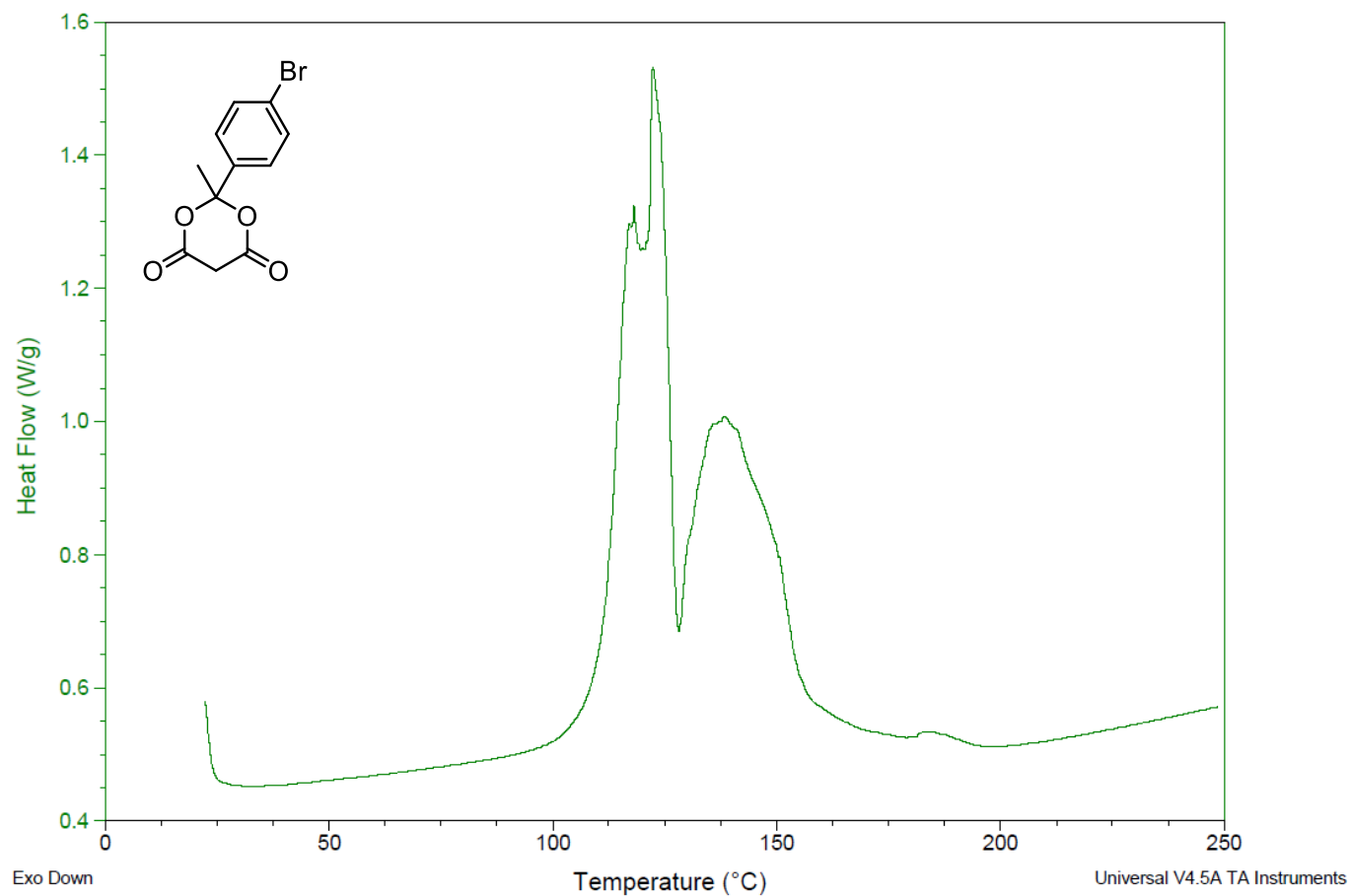
A2.11. Differential scanning calorimetry trace of compound **31**. Endotherms are the peaks of the trace.

A2.12: Differential scanning calorimetry trace of compound **32**



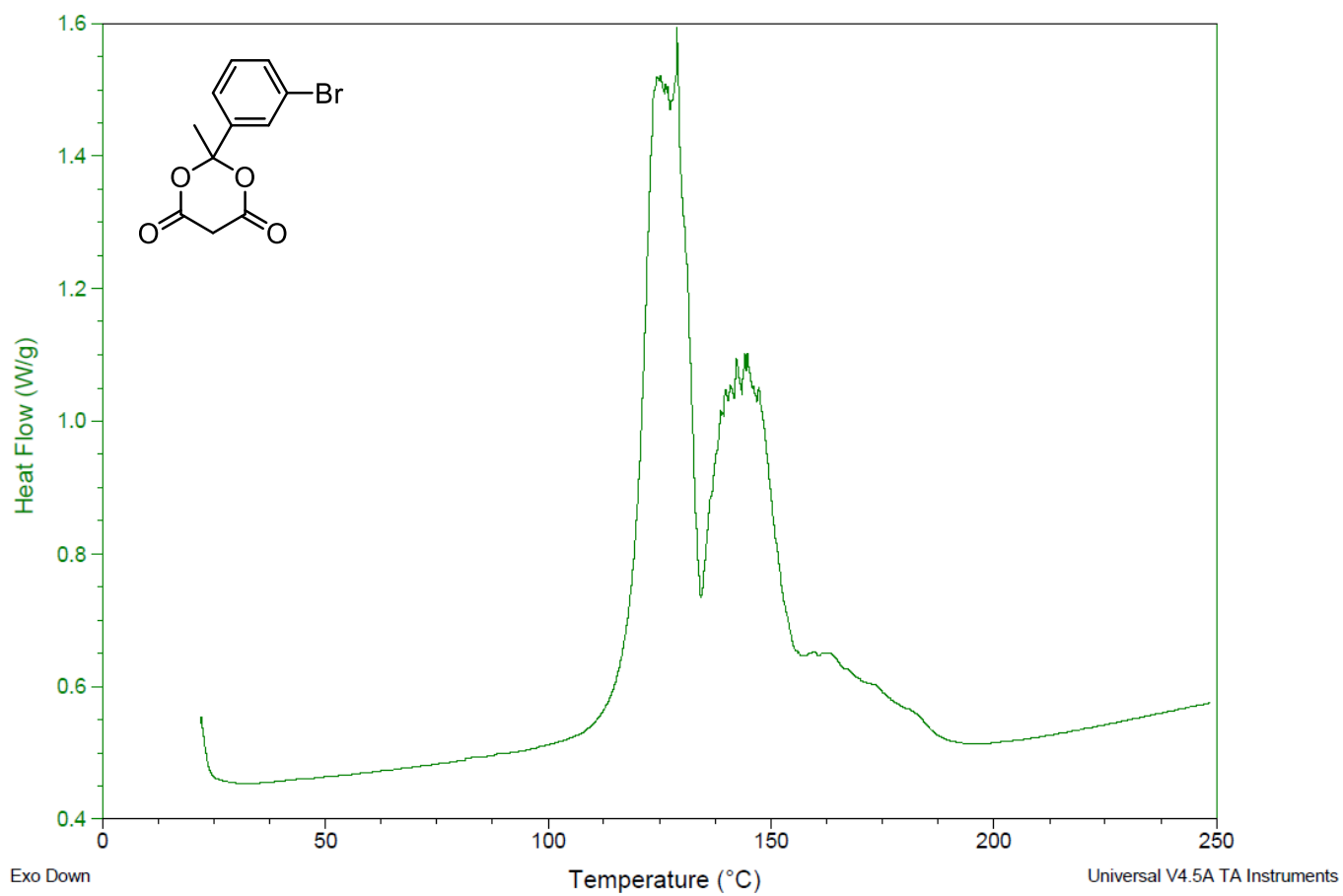
A2.12. Differential scanning calorimetry trace of compound **32**. Endotherms are the peaks of the trace.

A2.13: Differential scanning calorimetry trace of compound **33**



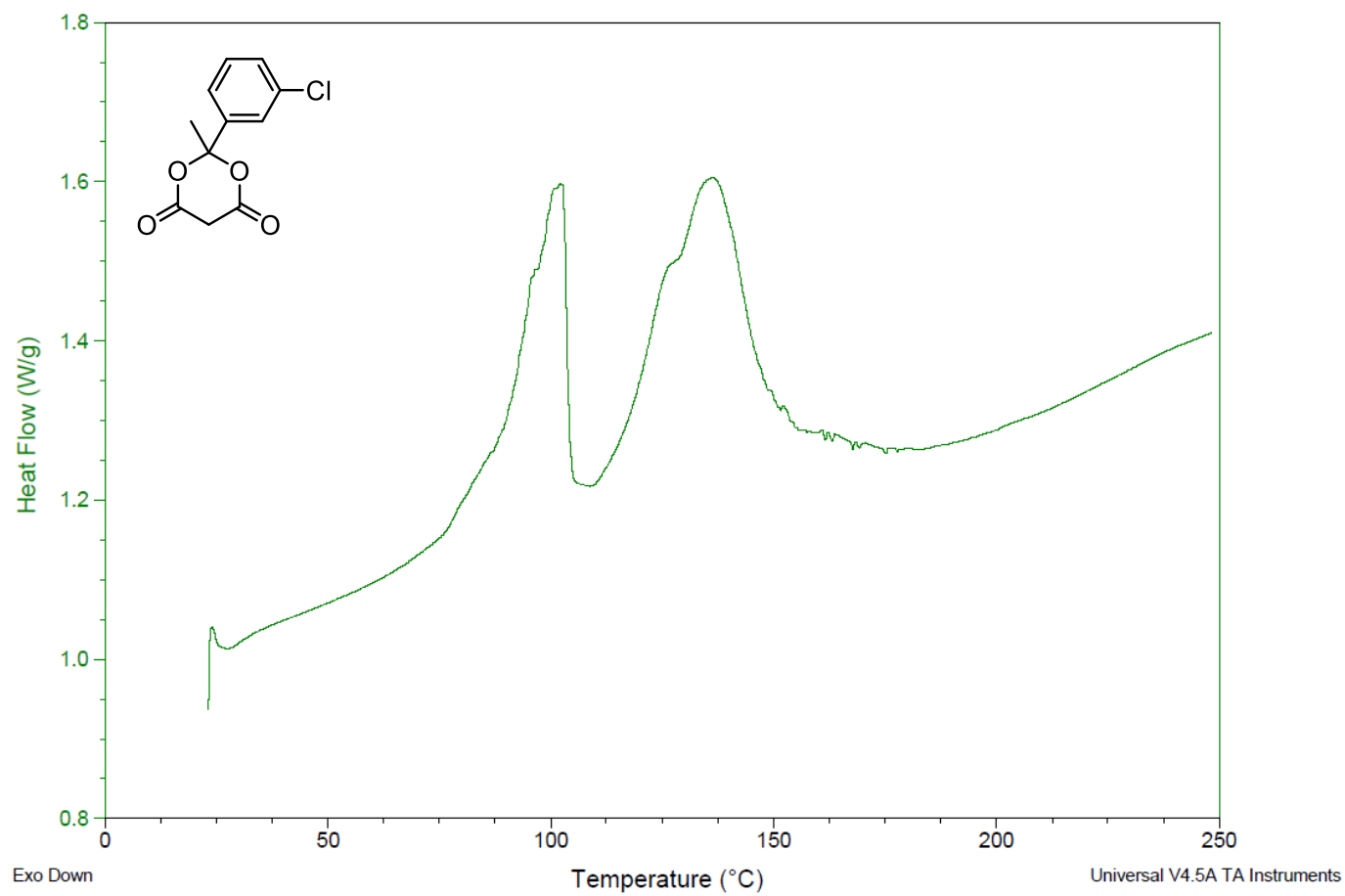
A2.13. Differential scanning calorimetry trace of compound **33**. Endotherms are the peaks of the trace.

A2.14: Differential scanning calorimetry trace of compound **34**



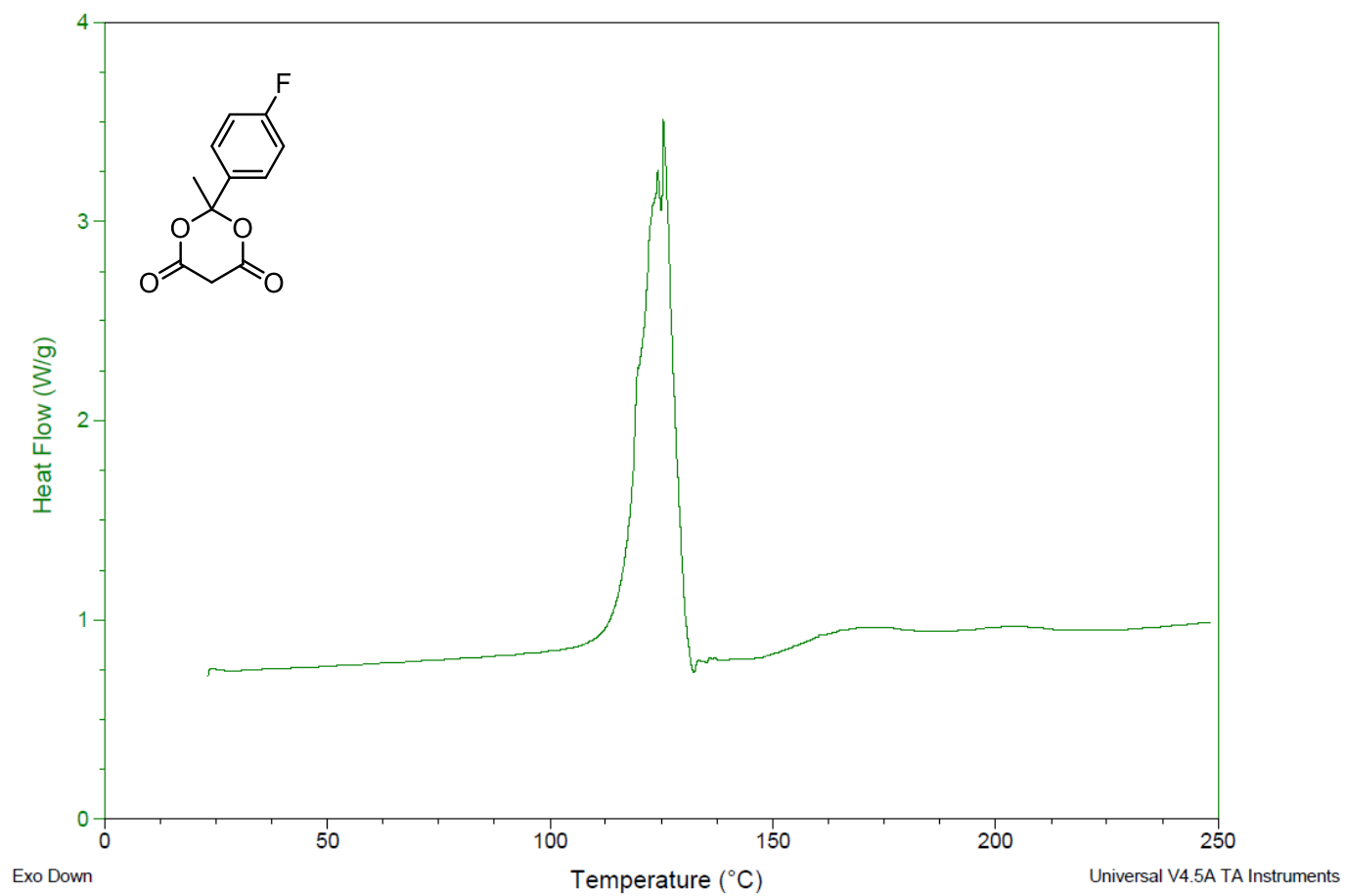
A2.14. Differential scanning calorimetry trace of compound **34**. Endotherms are the peaks of the trace.

A2.15: Differential scanning calorimetry trace of compound **35**



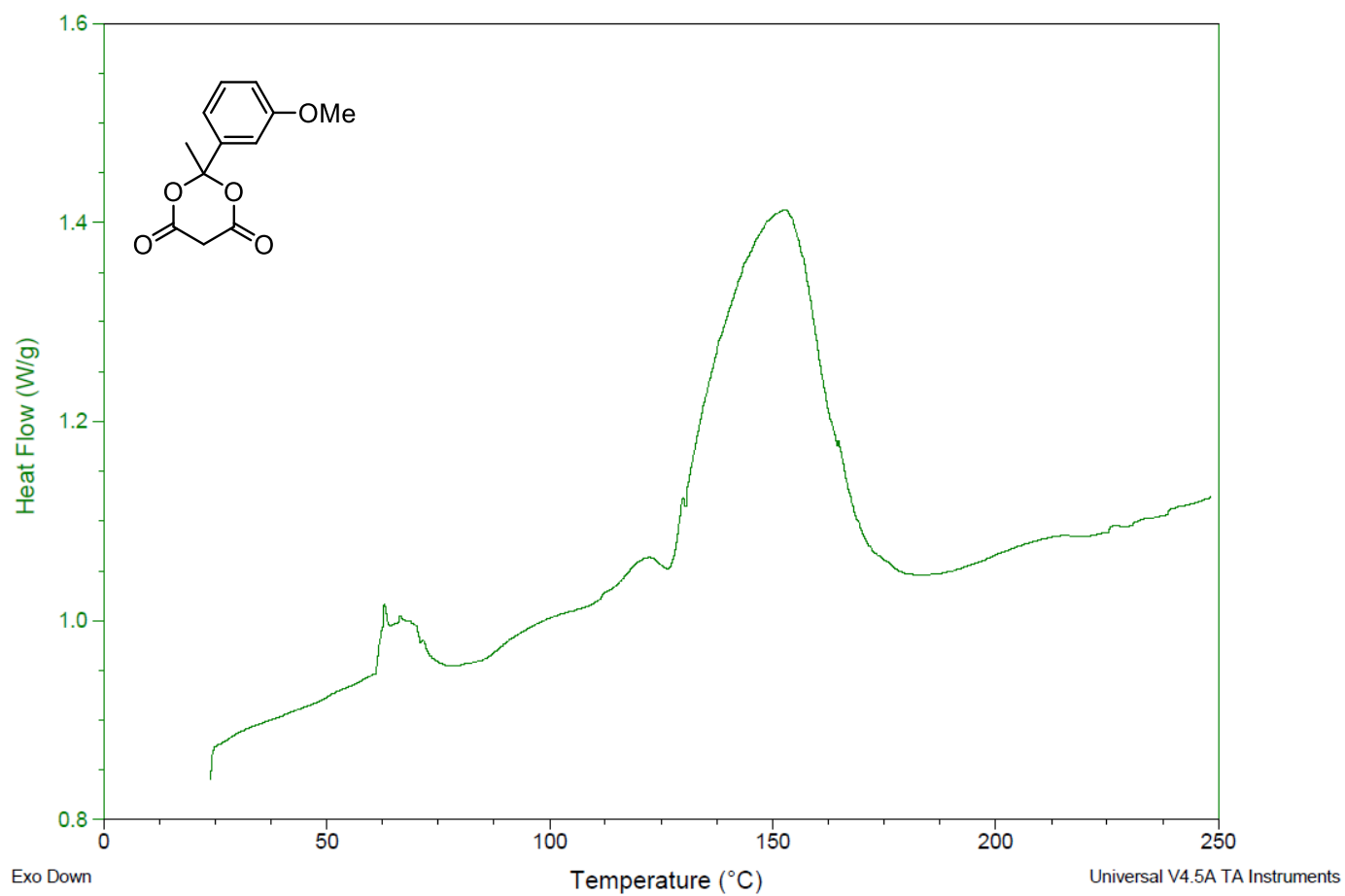
A2.15. Differential scanning calorimetry trace of compound **35**. Endotherms are the peaks of the trace.

A2.16: Differential scanning calorimetry trace of compound **36**



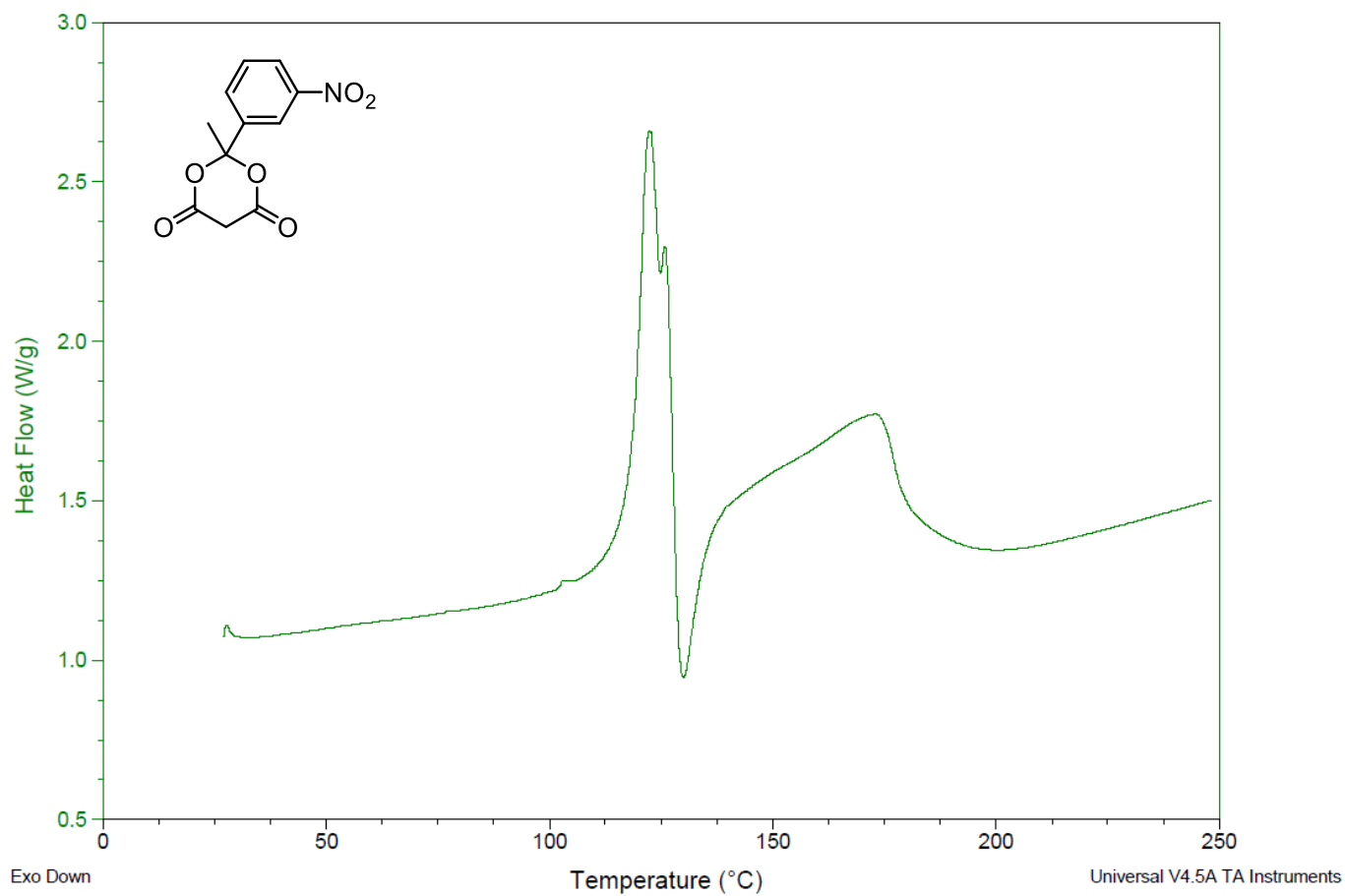
A2.16. Differential scanning calorimetry trace of compound **36**. Endotherms are the peaks of the trace.

A2.17: Differential scanning calorimetry trace of compound **37**



A2.17. Differential scanning calorimetry trace of compound **37**. Endotherms are the peaks of the trace.

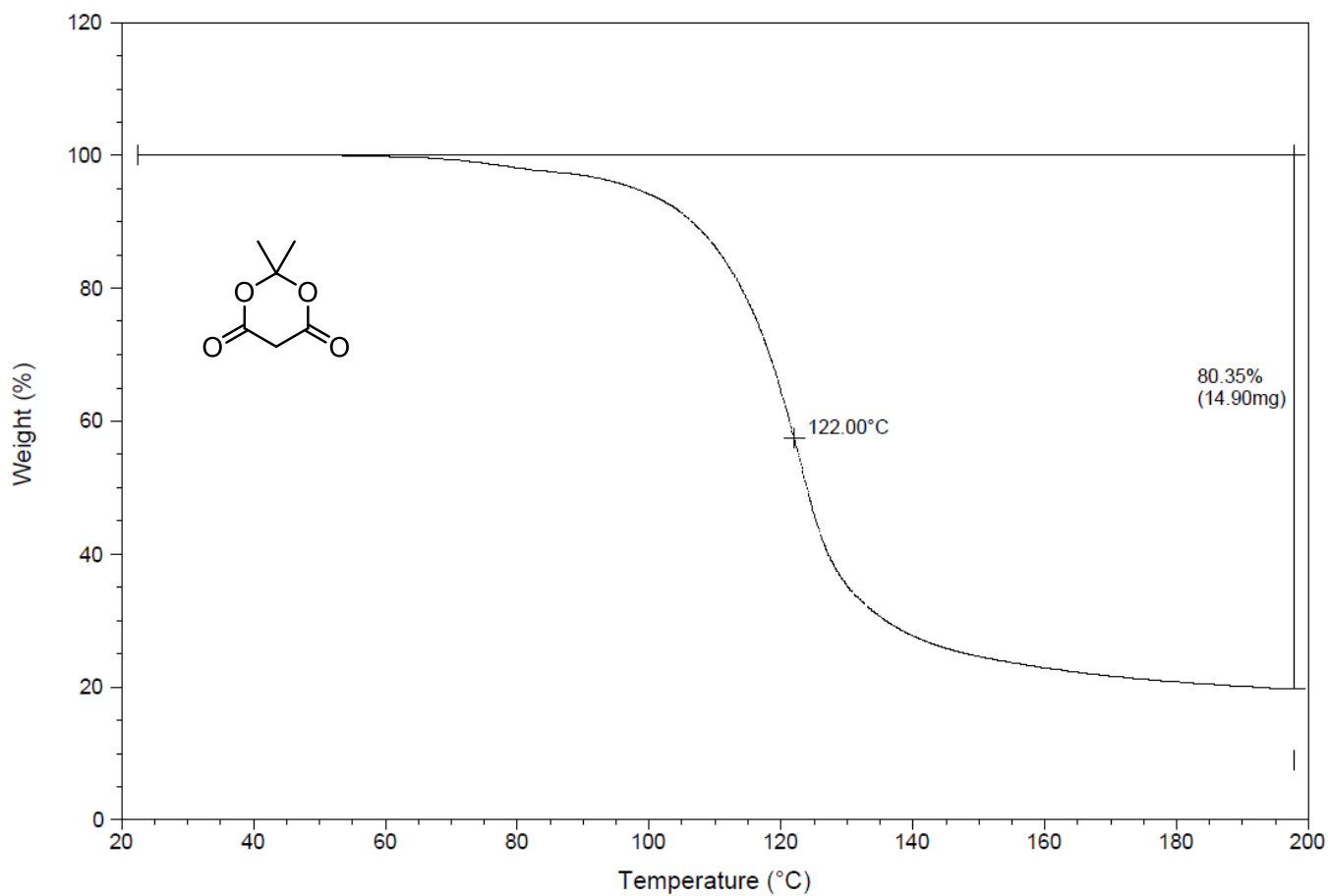
A2.18: Differential scanning calorimetry trace of compound **38**



A2.18. Differential scanning calorimetry trace of compound **38**. Endotherms are the peaks of the trace.

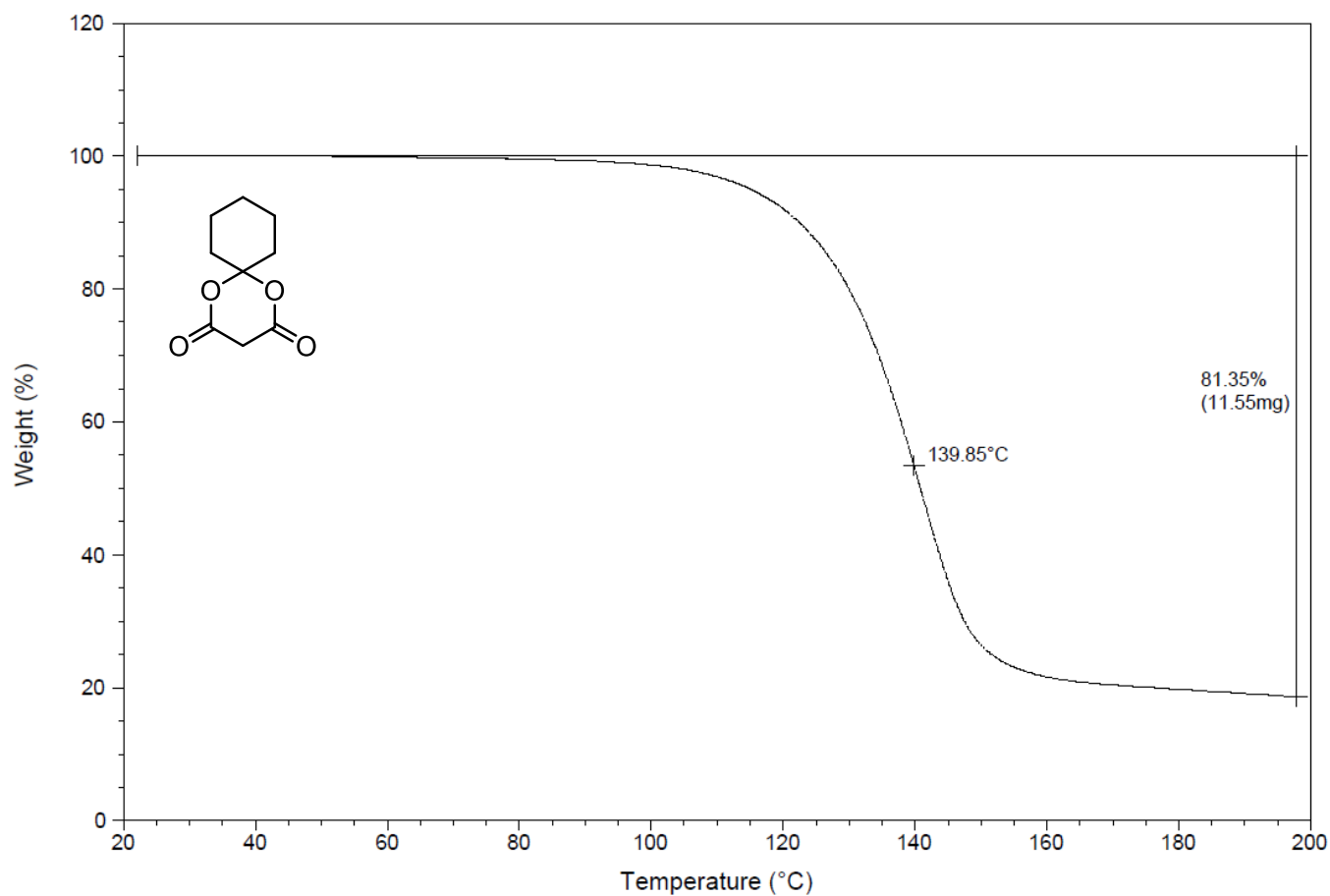
Appendix 3: Thermogravimetric analyses data

A3.1: Thermogravimetric analysis plot of Meldrum's acid



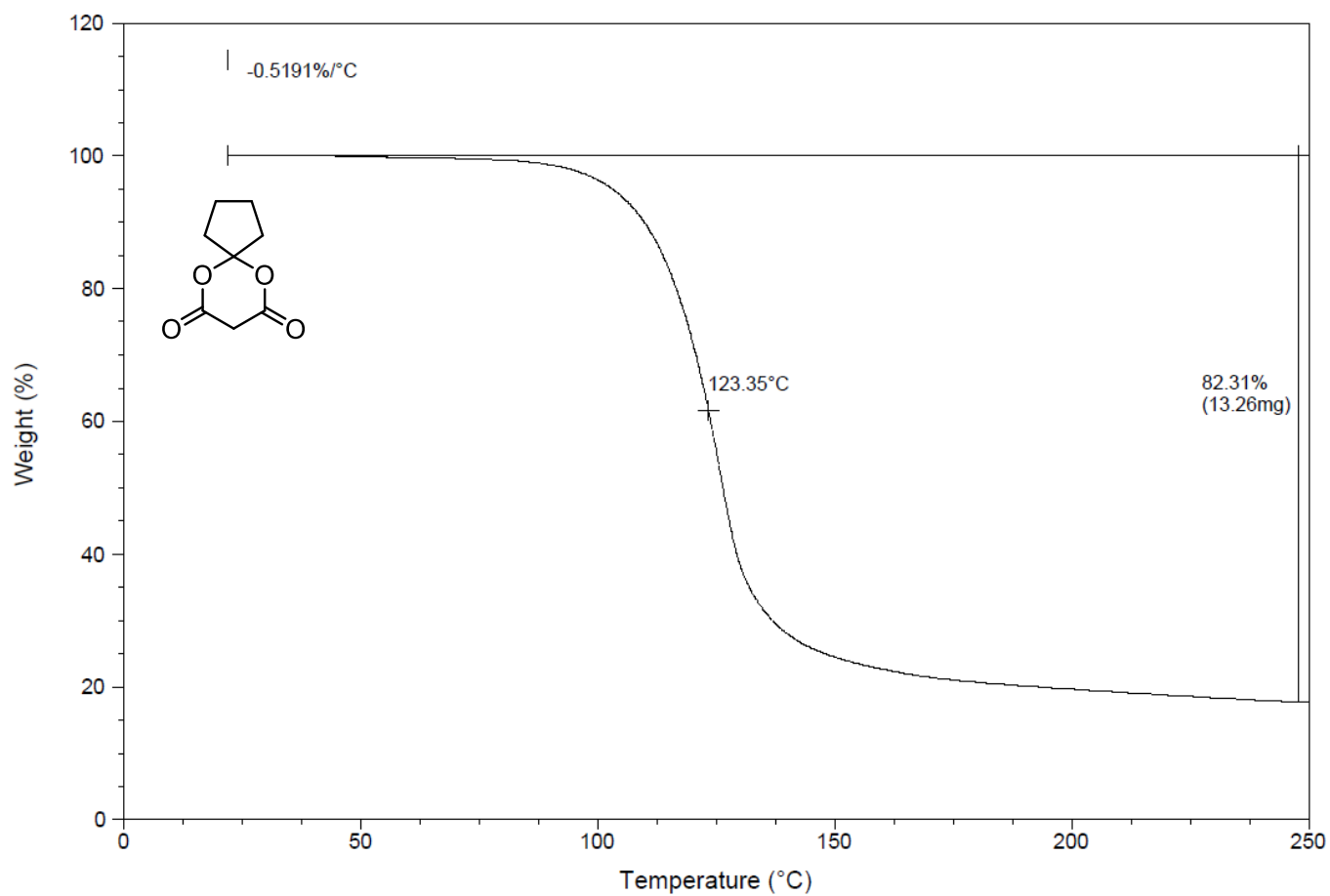
A3.1. Thermogravimetric analytical trace of Meldrum's acid. Trace was obtained from ramping 5 °C/min to 200 °C.

A3.2: Thermogravimetric analysis plot of compound **16**



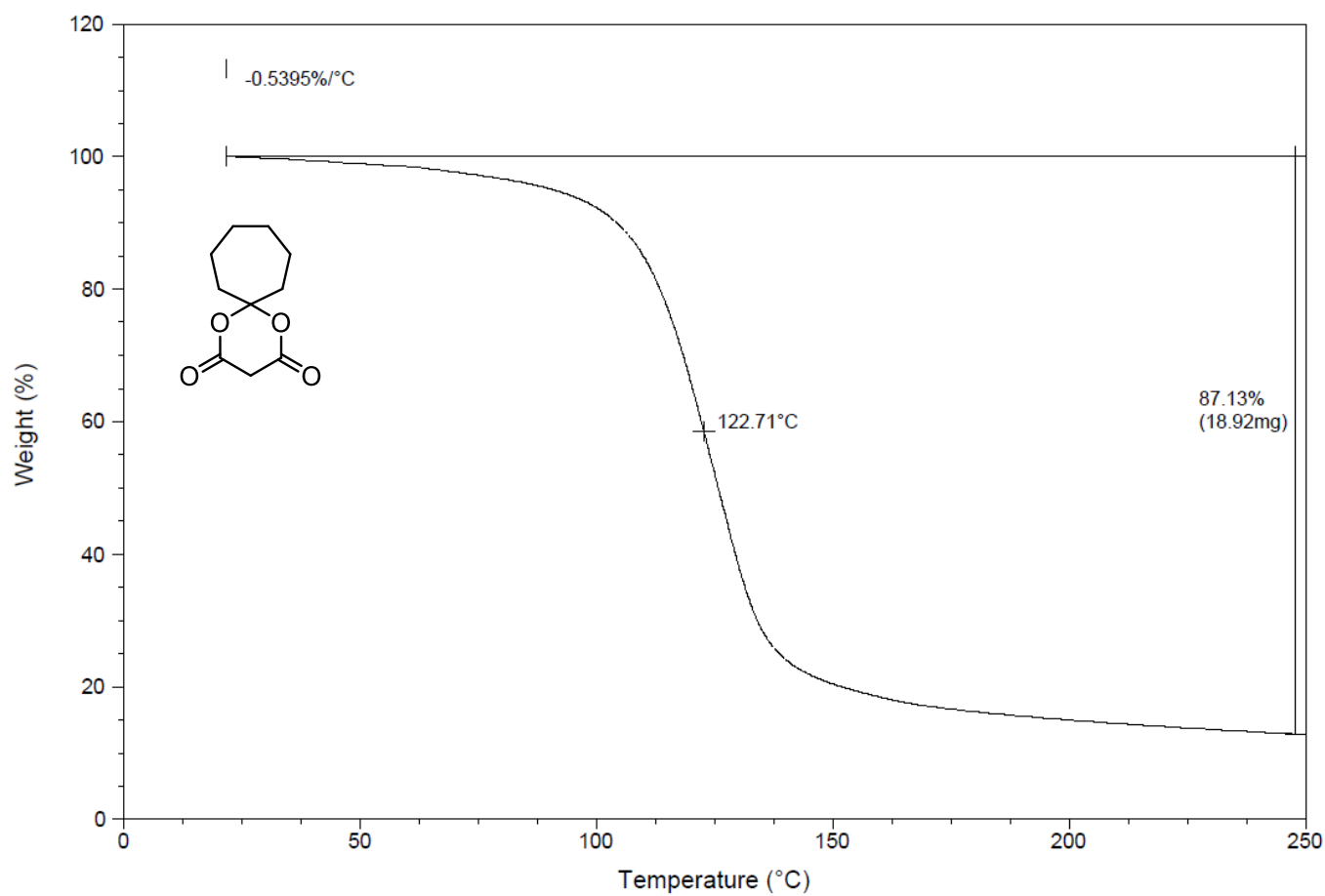
A3.2. Thermogravimetric analytical trace of compound **16**. Trace was obtained from ramping 5 °C/min to 200 °C.

A3.3: Thermogravimetric analysis plot of compound **17**



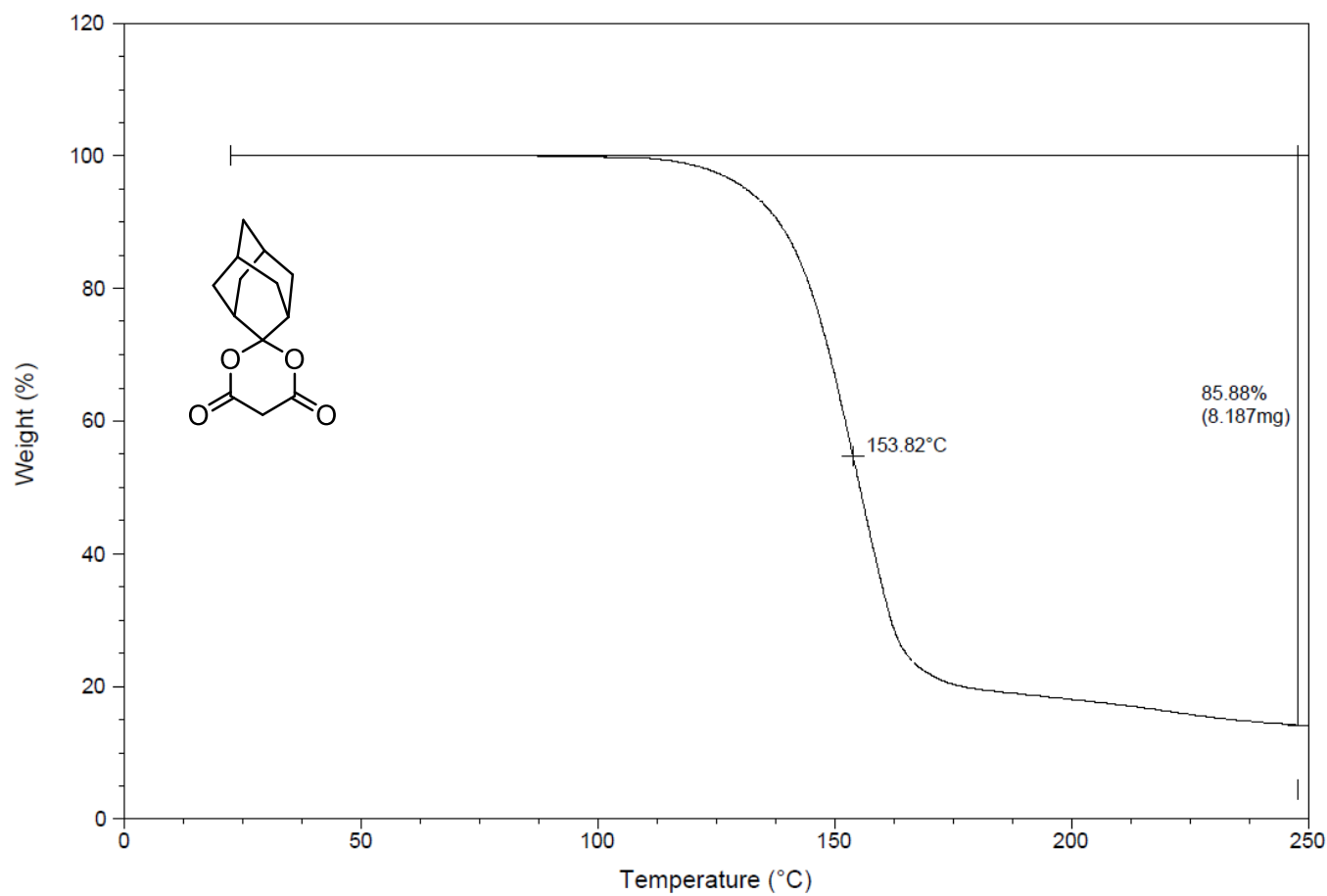
A3.3. Thermogravimetric analytical trace of compound **17**. Trace was obtained from ramping 5 °C/min to 250 °C.

A3.4: Thermogravimetric analysis plot of compound **18**



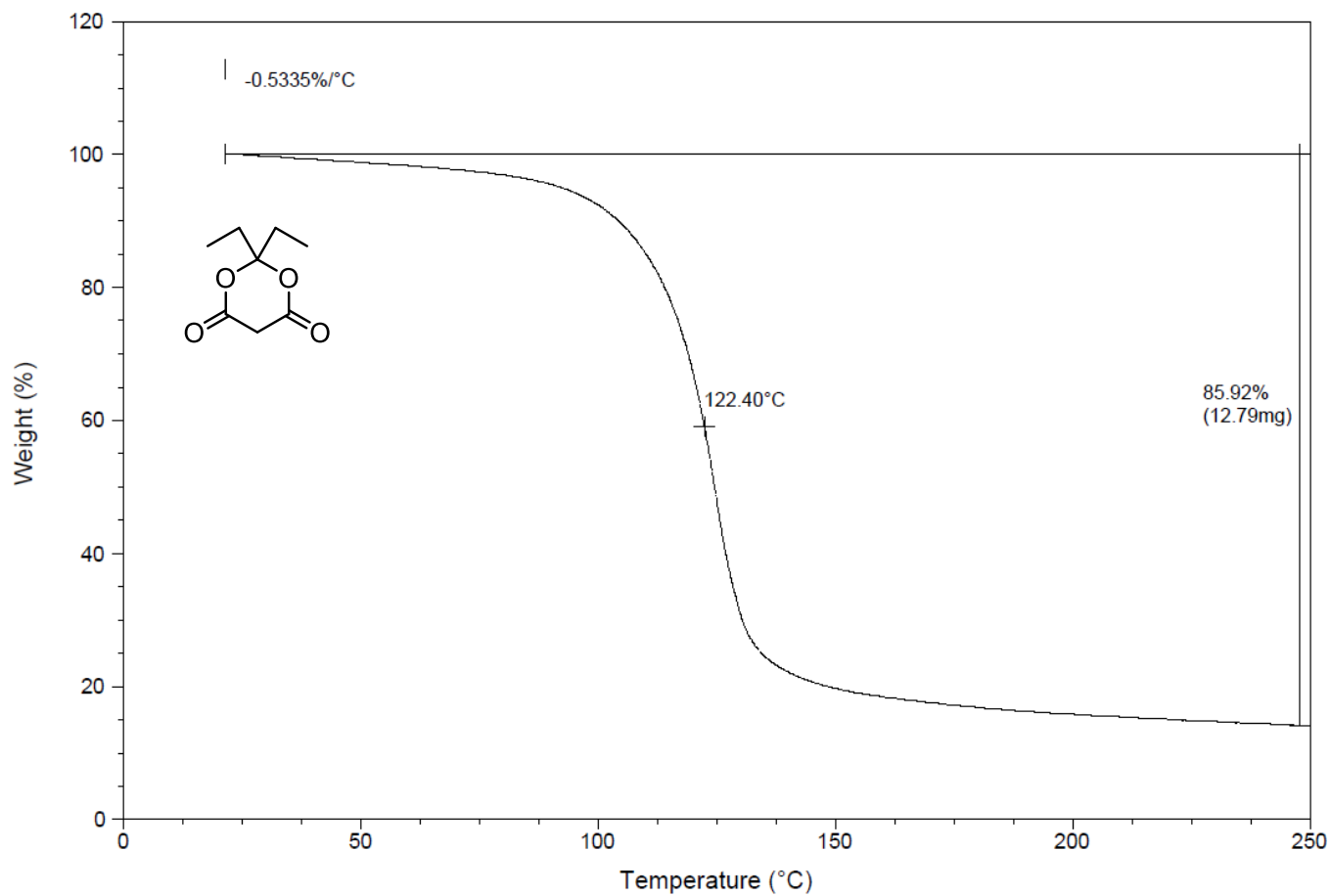
A3.4. Thermogravimetric analytical trace of compound **18**. Trace was obtained from ramping 5 °C/min to 250 °C.

A3.5: Thermogravimetric analysis plot of compound **19**



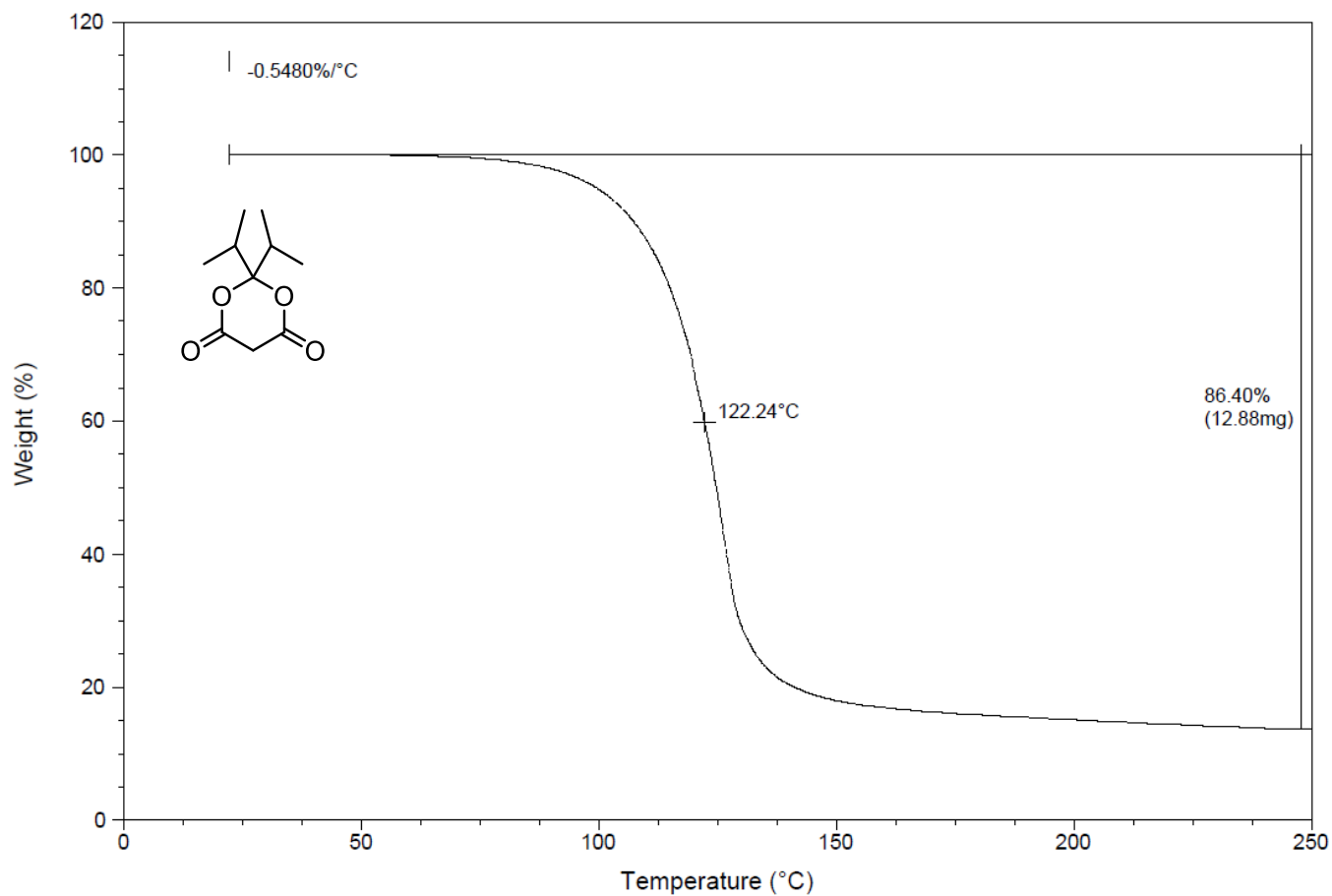
A3.5. Thermogravimetric analytical trace of compound **19**. Trace was obtained from ramping 5 °C/min to 250 °C.

A3.6: Thermogravimetric analysis plot of compound **20**



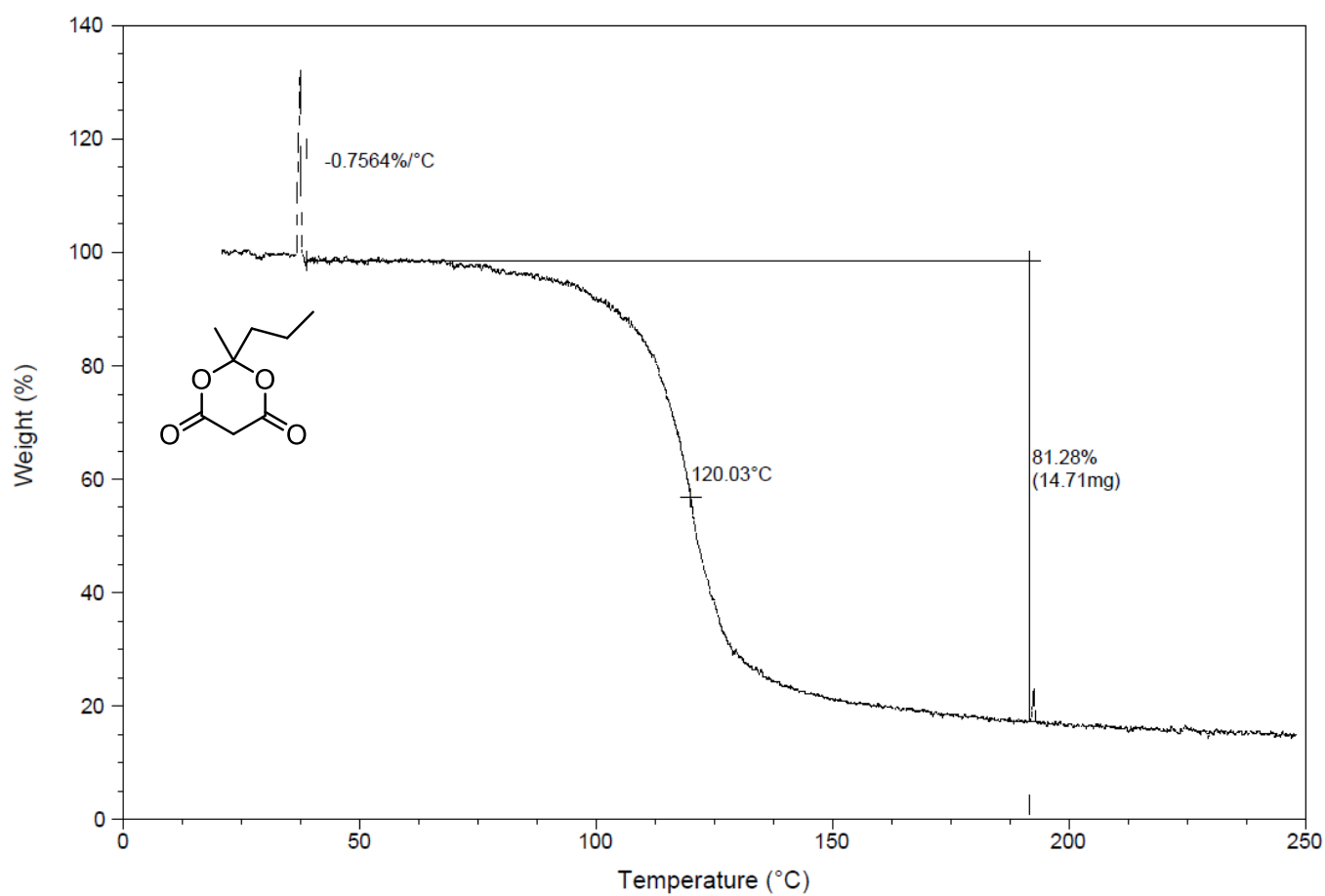
A3.6. Thermogravimetric analytical trace of compound **20**. Trace was obtained from ramping 5 °C/min to 250 °C.

A3.7: Thermogravimetric analysis plot of compound **21**



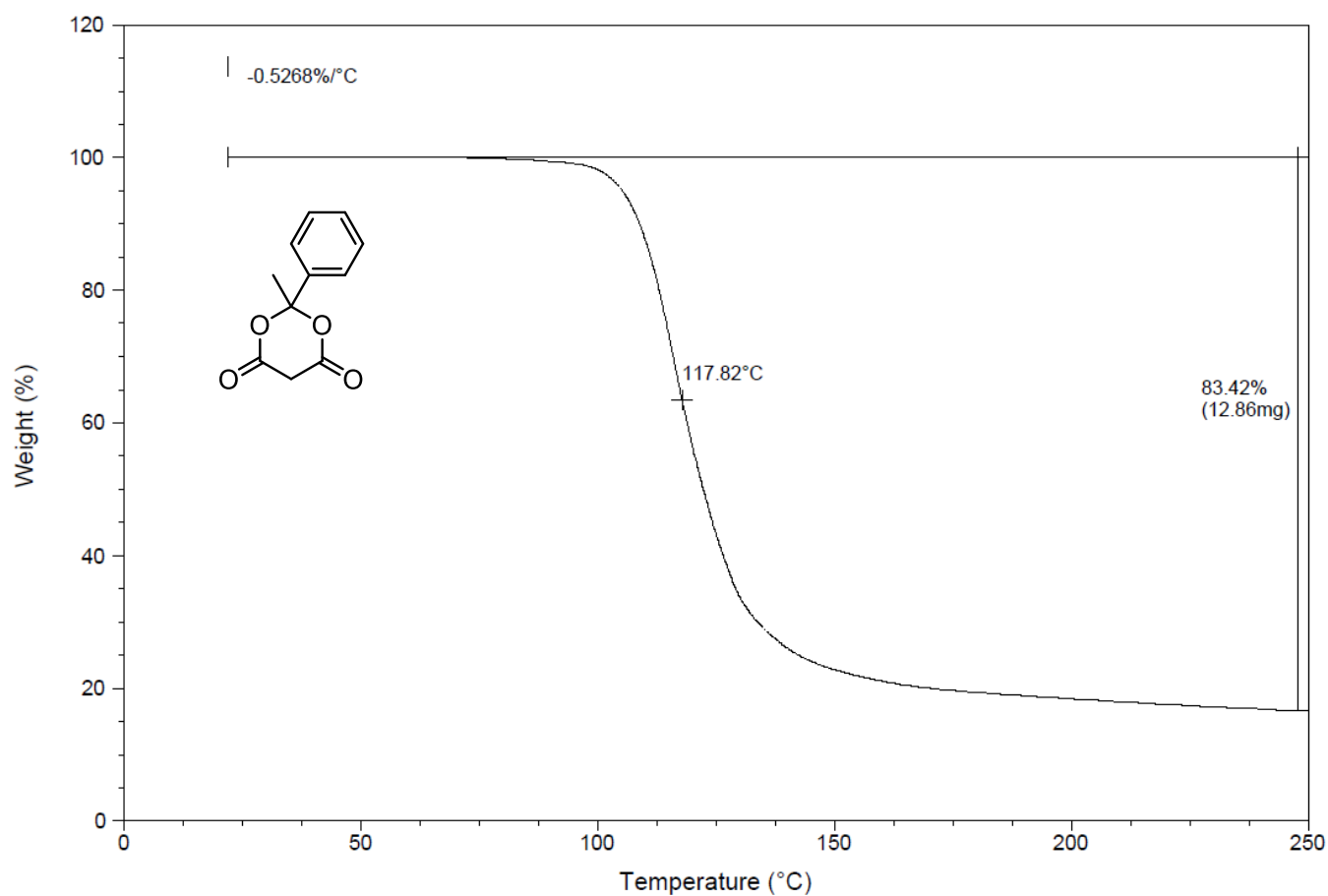
A3.7. Thermogravimetric analytical trace of compound **21**. Trace was obtained from ramping 5 °C/min to 250 °C.

A3.8: Thermogravimetric analysis plot of compound **22**



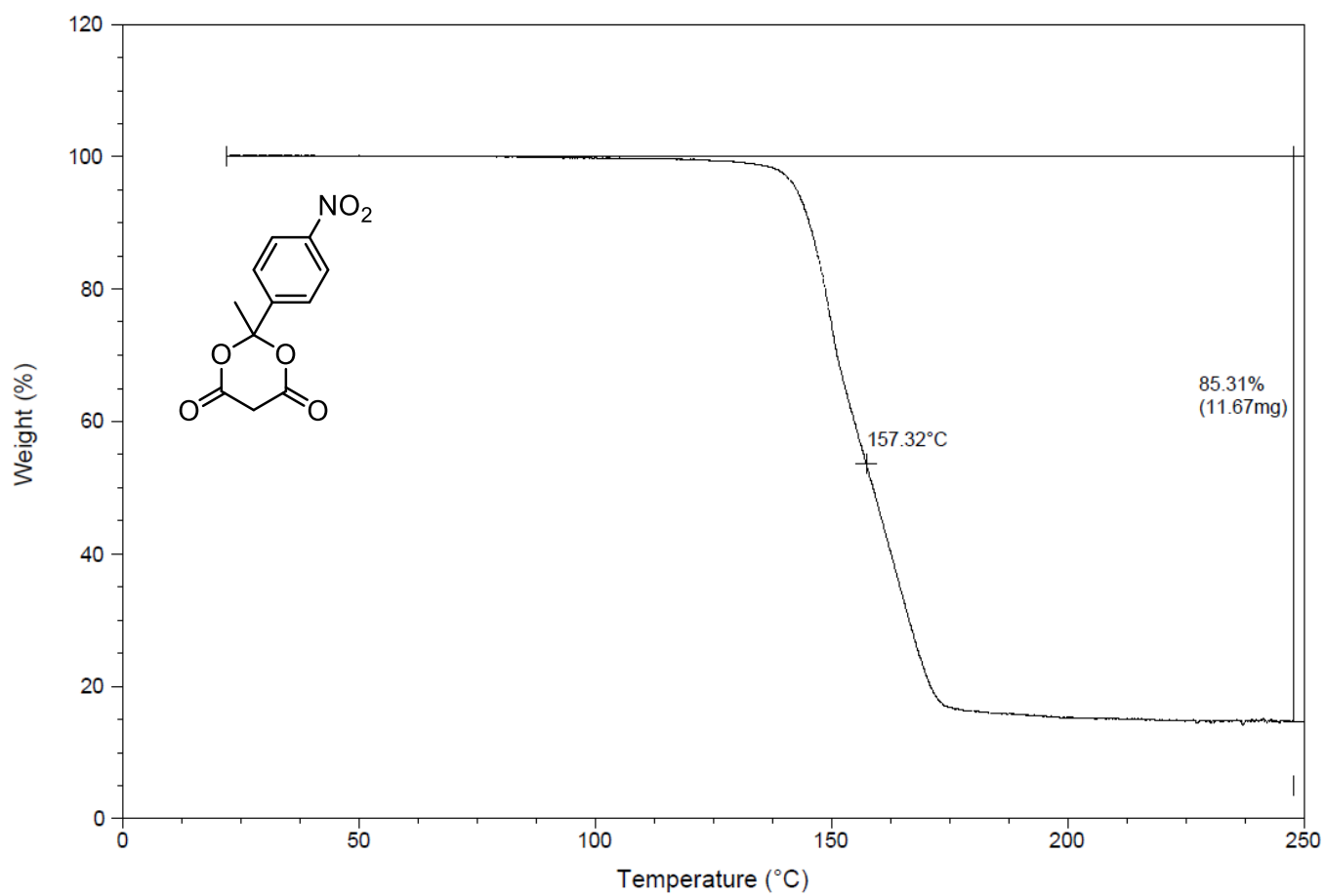
A3.8. Thermogravimetric analytical trace of compound **22**. Trace was obtained from ramping 5 °C/min to 250 °C.

A3.9: Thermogravimetric analysis plot of compound **29**



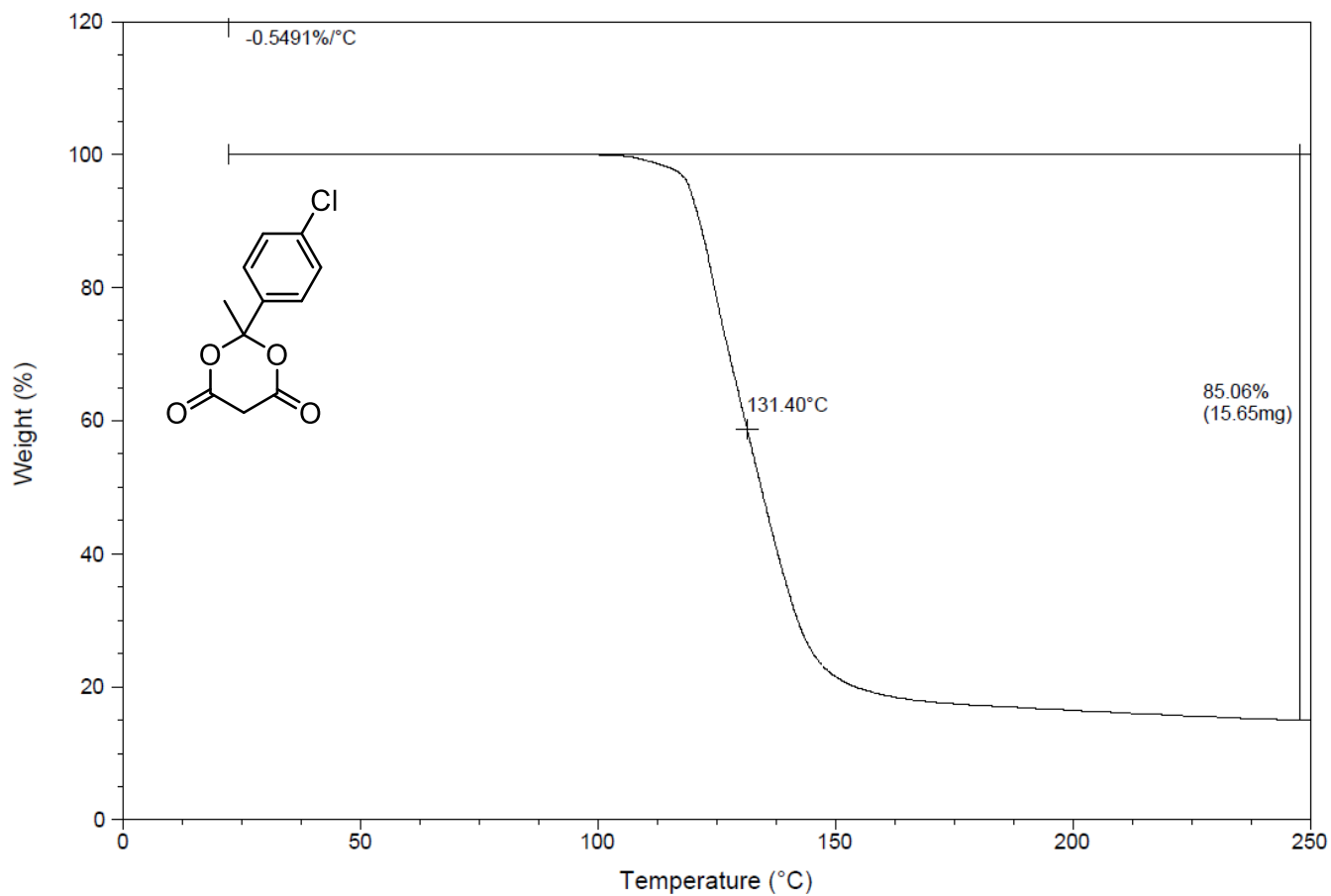
A3.9. Thermogravimetric analytical trace of compound **29**. Trace was obtained from ramping 5 °C/min to 250 °C.

A3.10: Thermogravimetric analysis plot of compound **30**



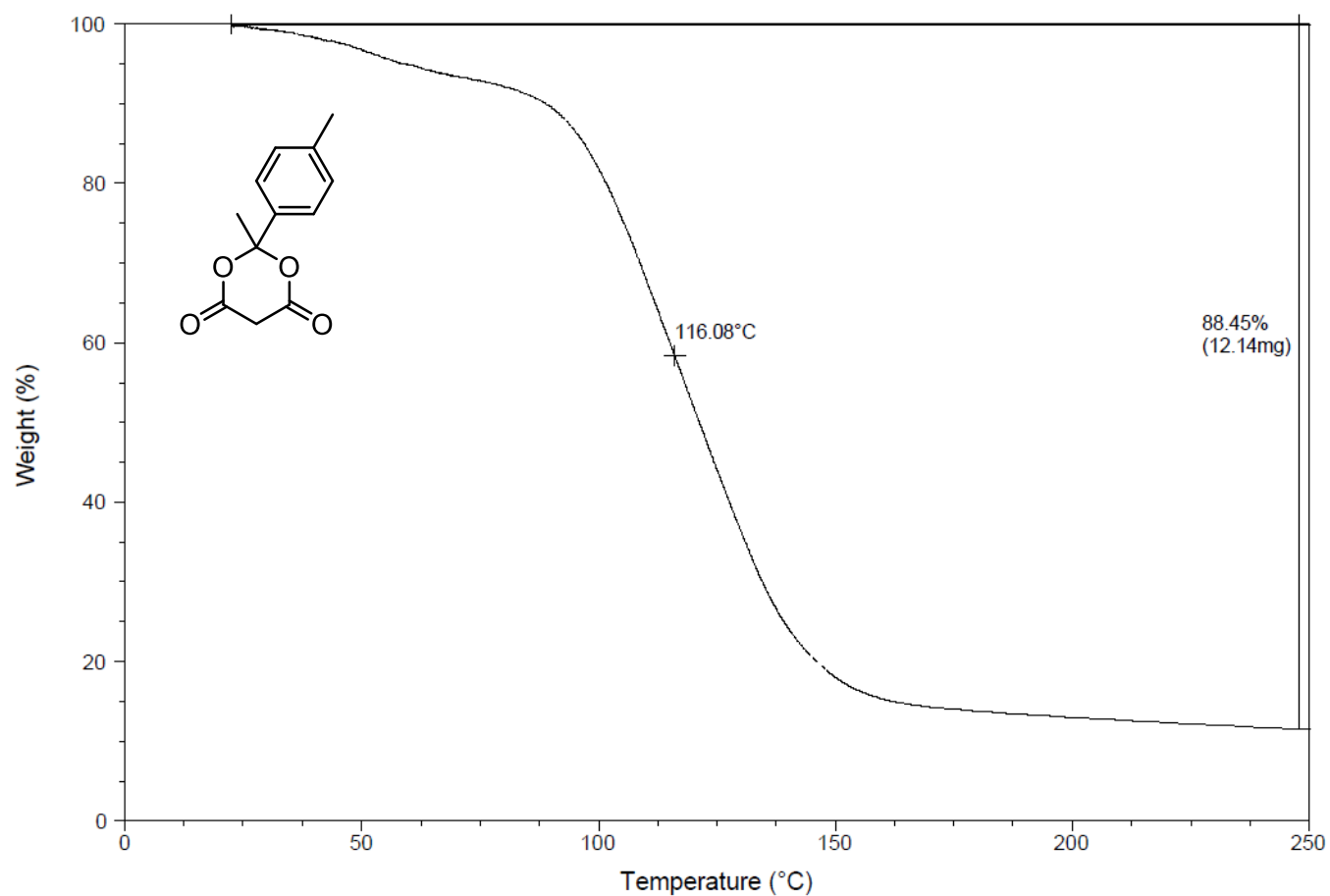
A3.10. Thermogravimetric analytical trace of compound **30**. Trace was obtained from ramping 5 °C/min to 250 °C.

A3.11: Thermogravimetric analysis plot of compound **31**



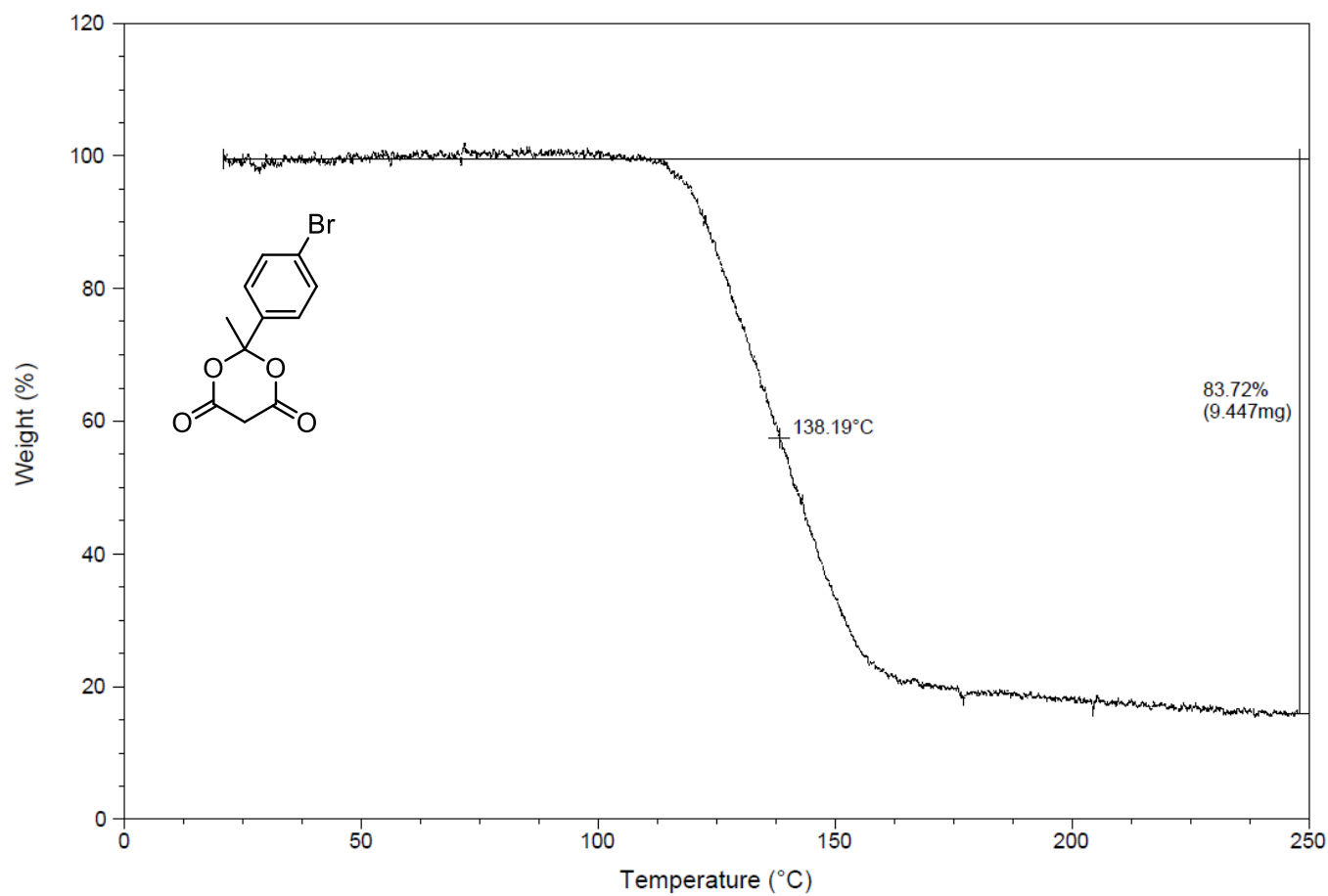
A3.11. Thermogravimetric analytical trace of compound **31**. Trace was obtained from ramping 5 °C/min to 250 °C.

A3.12: Thermogravimetric analysis plot of compound **32**



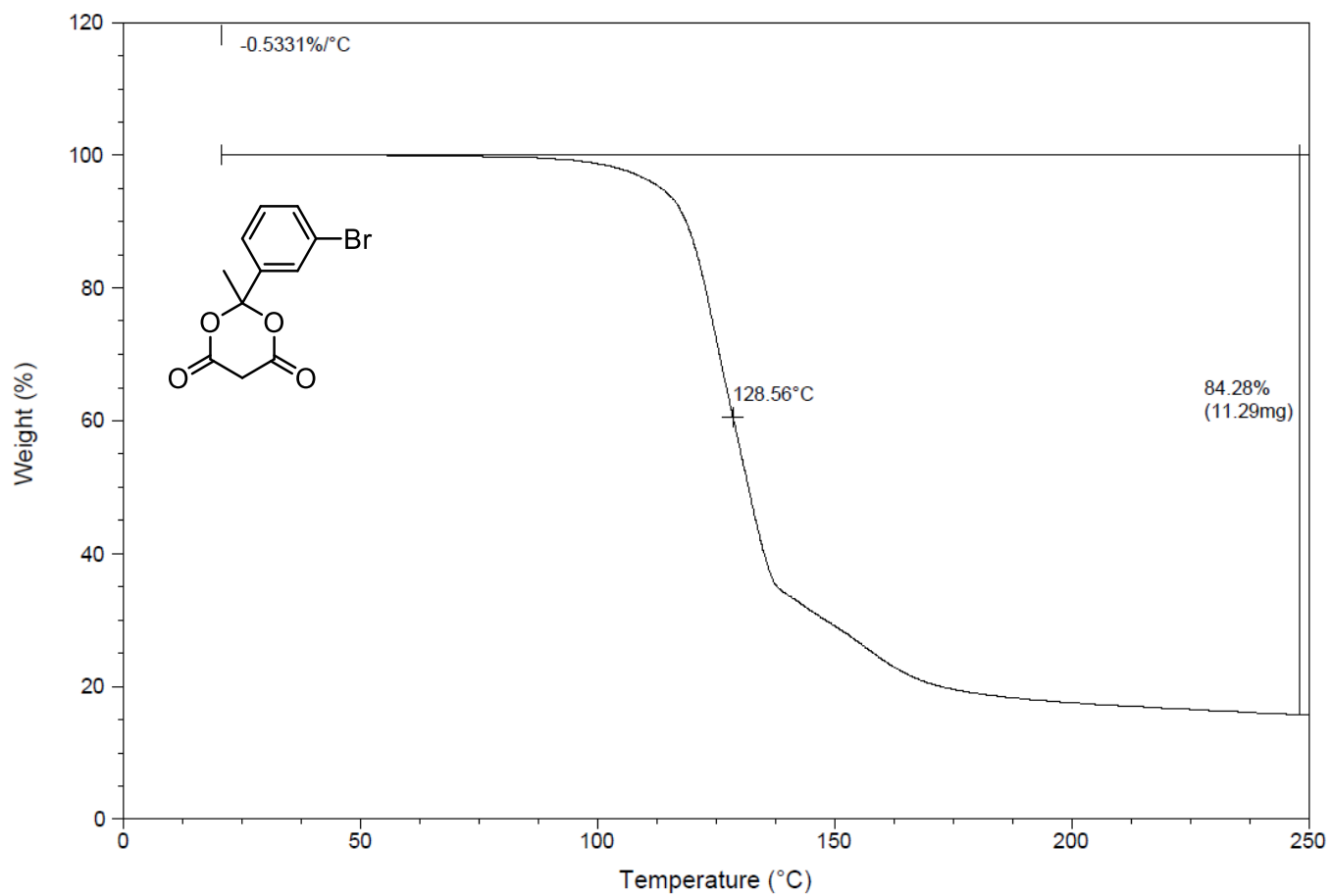
A3.12. Thermogravimetric analytical trace of compound **32**. Trace was obtained from ramping 5 °C/min to 250 °C.

A3.13: Thermogravimetric analysis plot of compound **33**



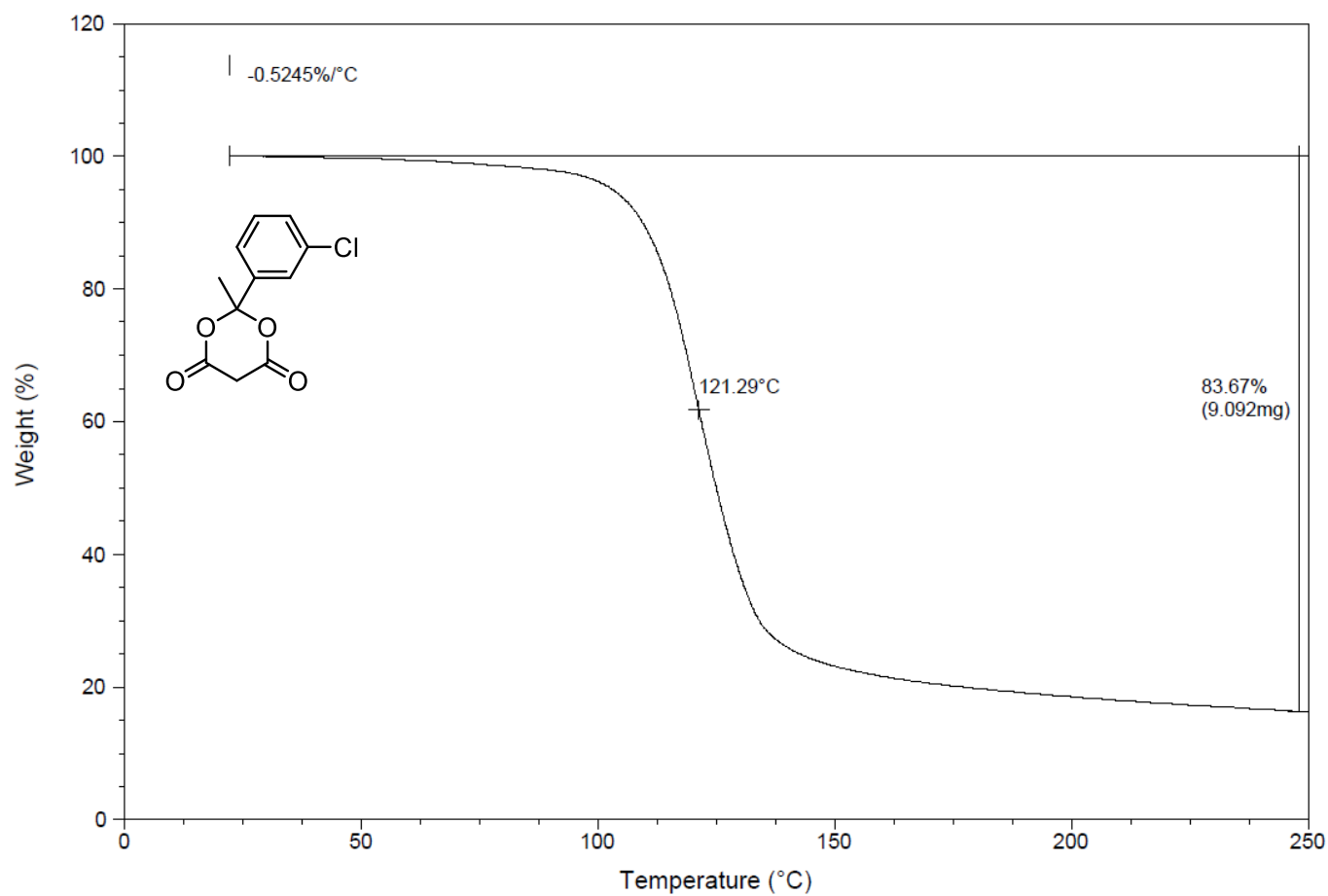
A3.13. Thermogravimetric analytical trace of compound **33**. Trace was obtained from ramping 5 °C/min to 250 °C.

A3.14: Thermogravimetric analysis plot of compound **34**



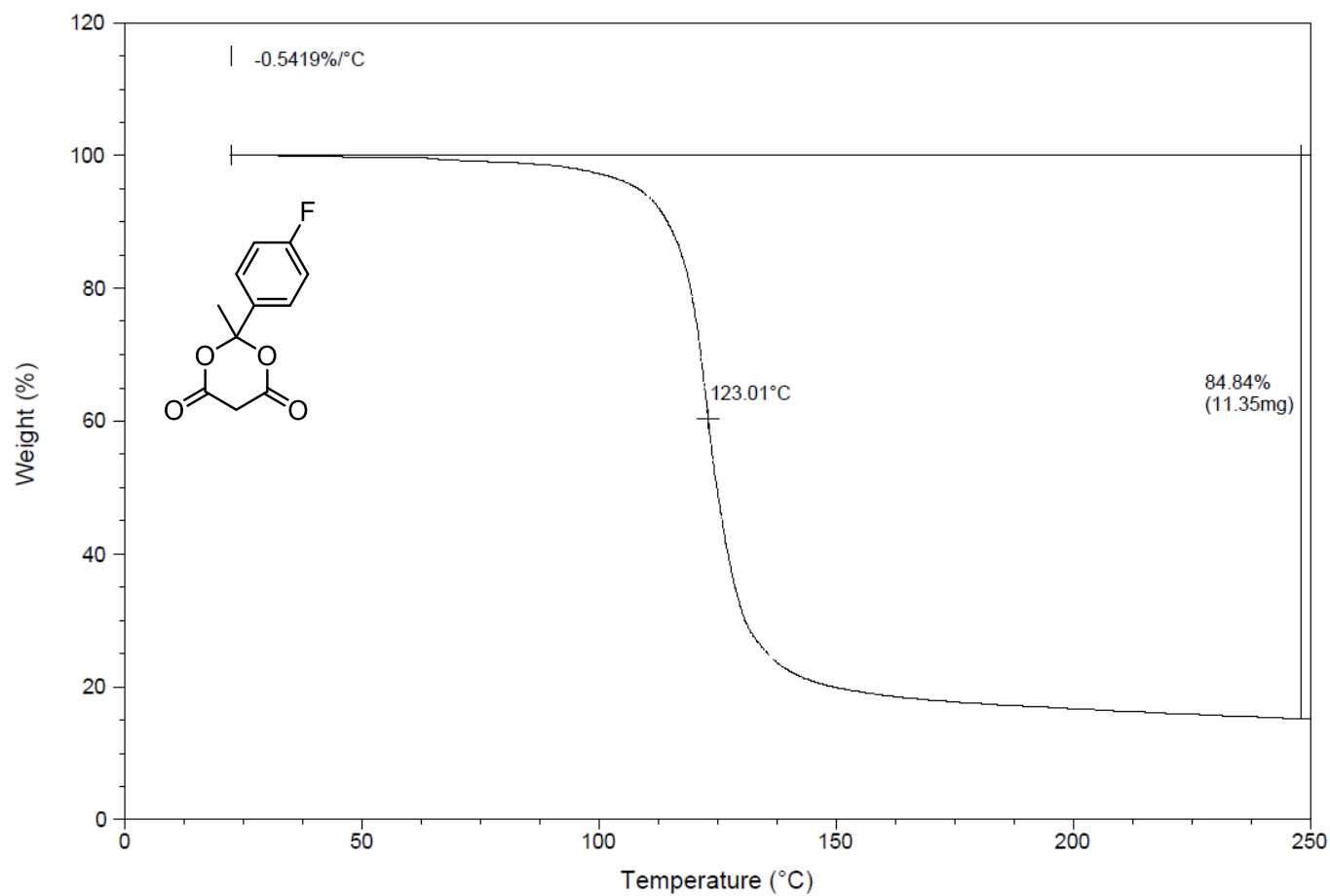
A3.14. Thermogravimetric analytical trace of compound **34**. Trace was obtained from ramping 5 °C/min to 250 °C.

A3.15: Thermogravimetric analysis plot of compound **35**



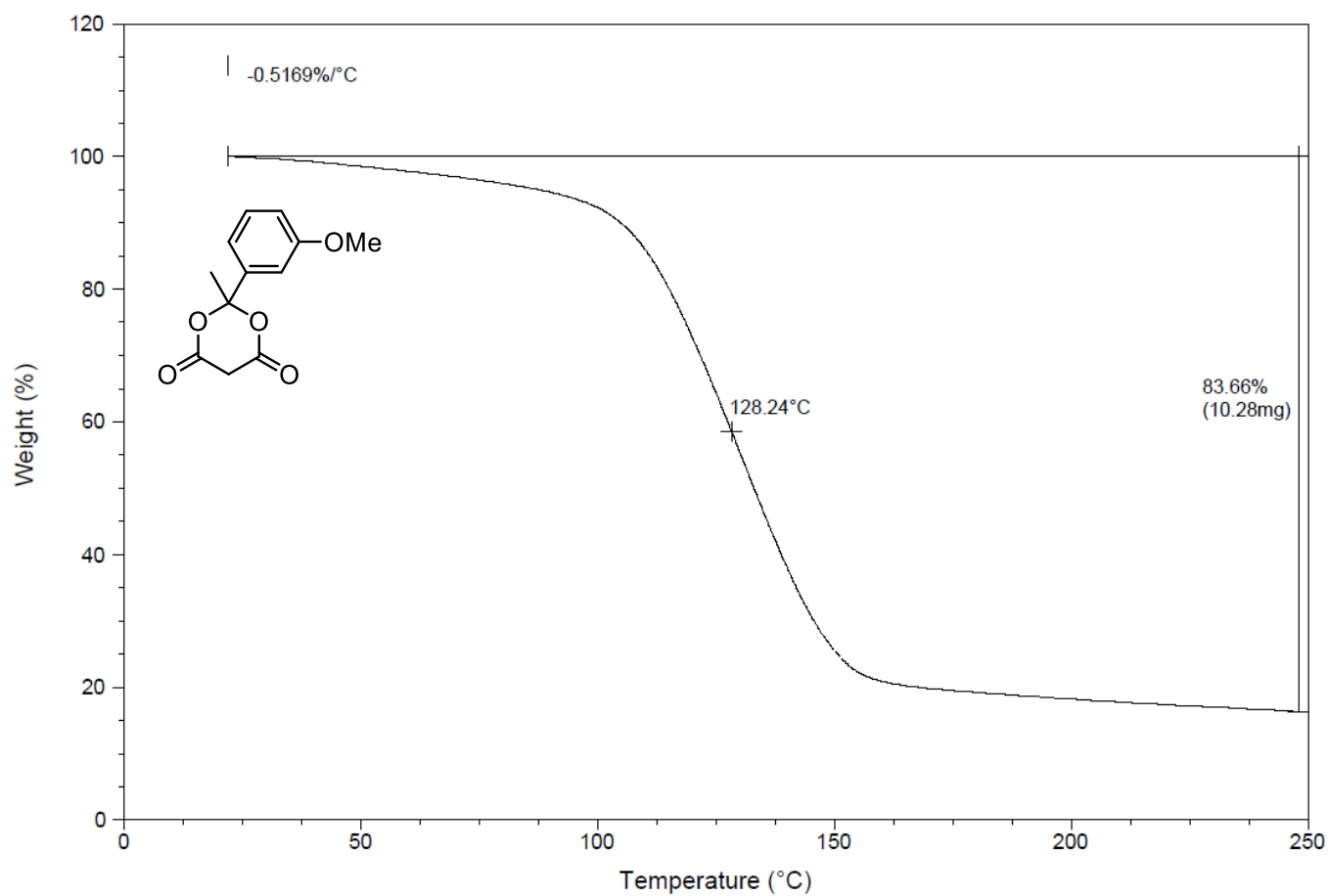
A3.15. Thermogravimetric analytical trace of compound **35**. Trace was obtained from ramping 5 °C/min to 250 °C.

A3.16: Thermogravimetric analysis plot of compound **36**



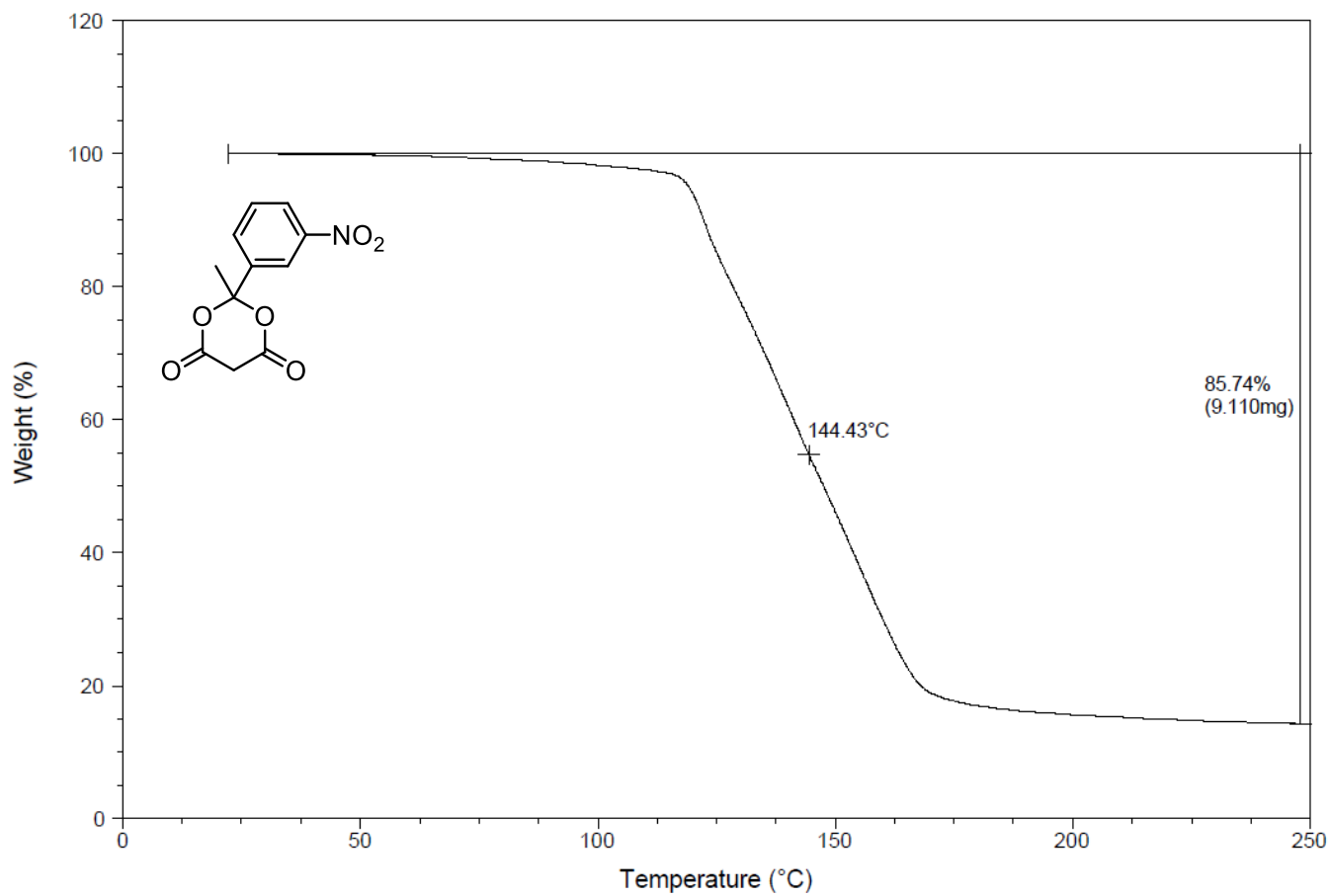
A3.16. Thermogravimetric analytical trace of compound **36**. Trace was obtained from ramping 5 °C/min to 250 °C.

A3.17: Thermogravimetric analysis plot of compound **37**



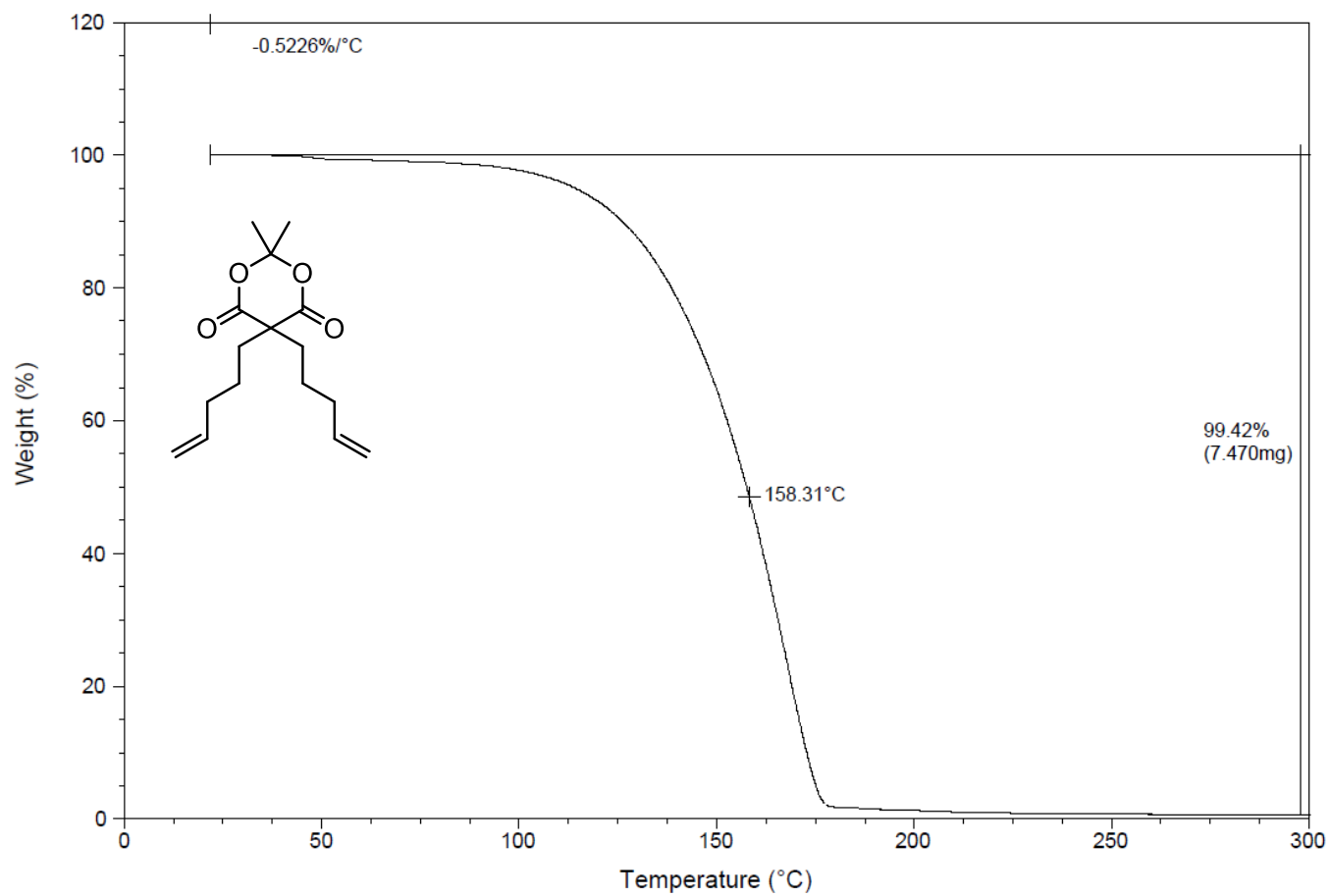
A3.17. Thermogravimetric analytical trace of compound **37**. Trace was obtained from ramping 5 °C/min to 250 °C.

A3.18: Thermogravimetric analysis plot of compound **38**



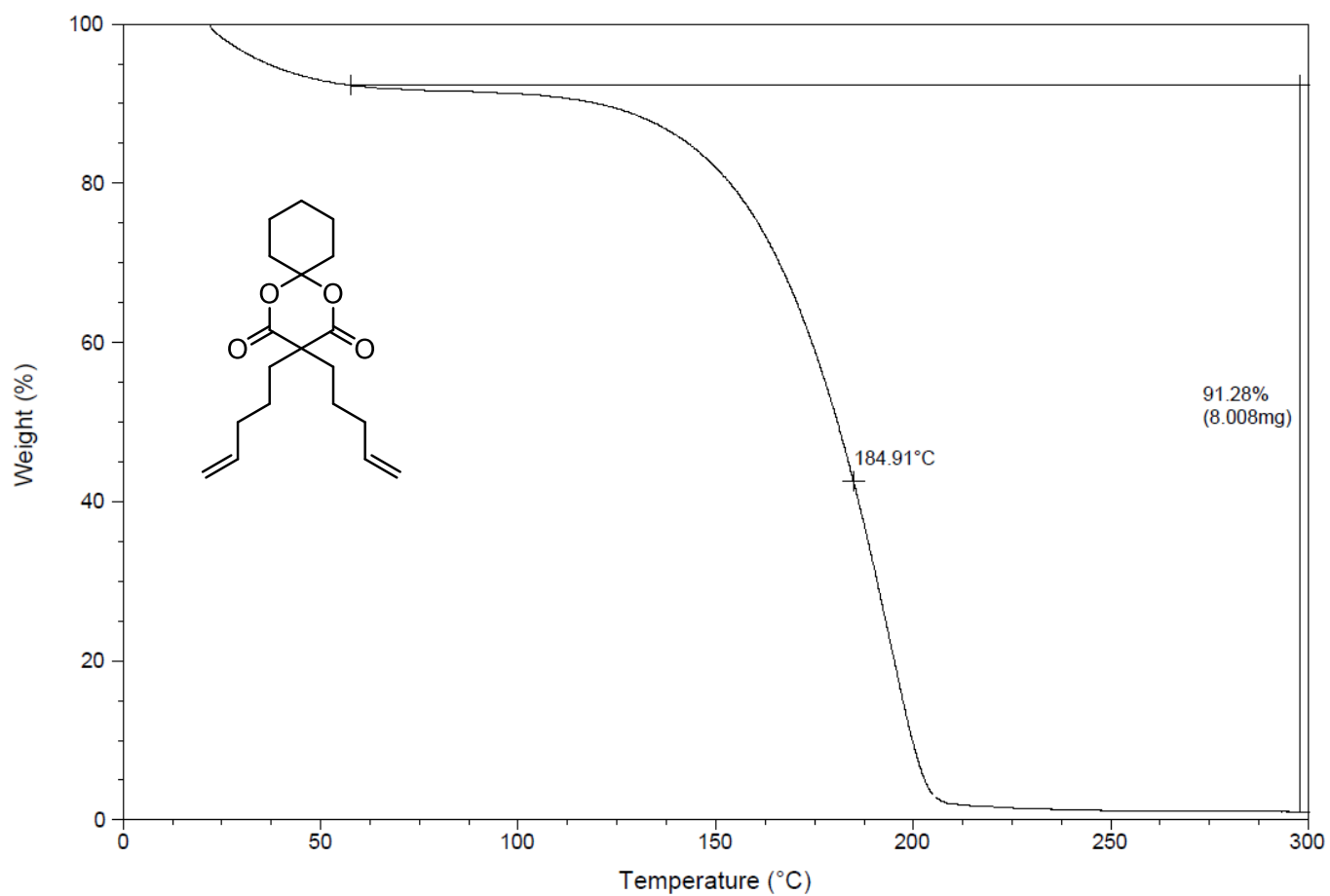
A3.18. Thermogravimetric analytical trace of compound **38**. Trace was obtained from ramping 5 °C/min to 250 °C.

A3.19: Thermogravimetric analysis plot of compound **41**



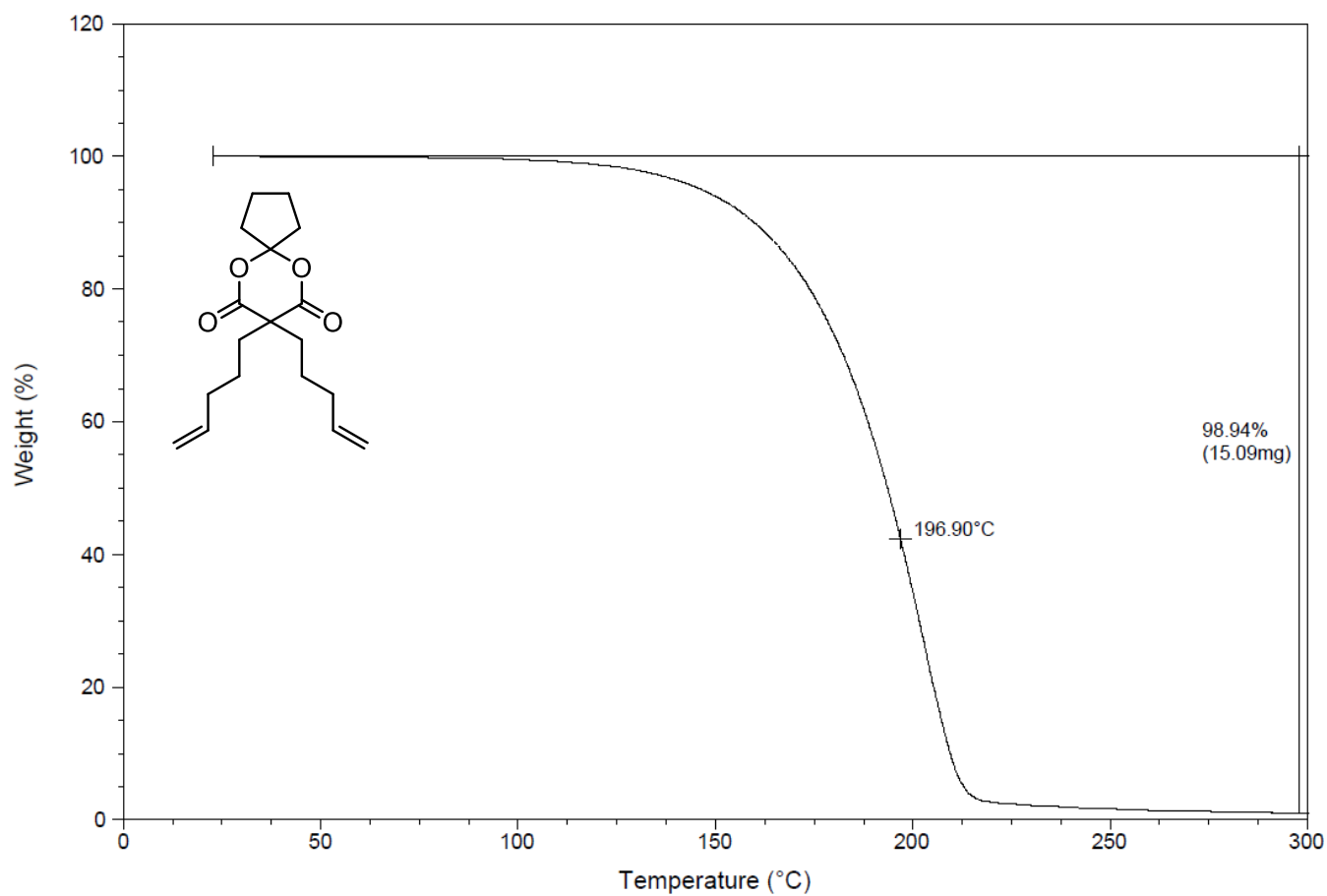
A3.19. Thermogravimetric analytical trace of compound **41**. Trace was obtained from ramping 5 °C/min to 300 °C.

A3.20: Thermogravimetric analysis plot of compound **42**



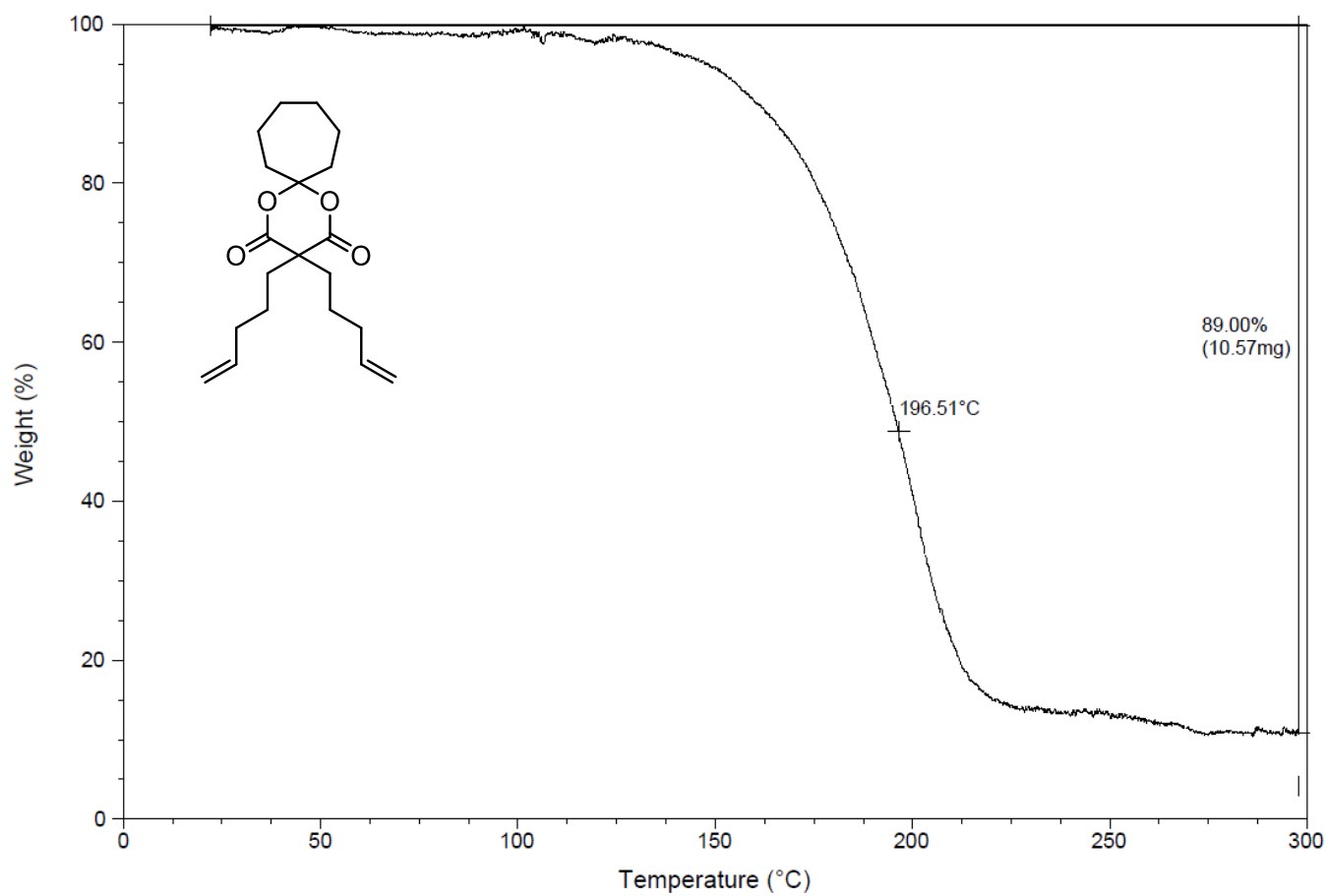
A3.20. Thermogravimetric analytical trace of compound **42**. Trace was obtained from ramping 5 °C/min to 300 °C.

A3.21: Thermogravimetric analysis plot of compound **43**



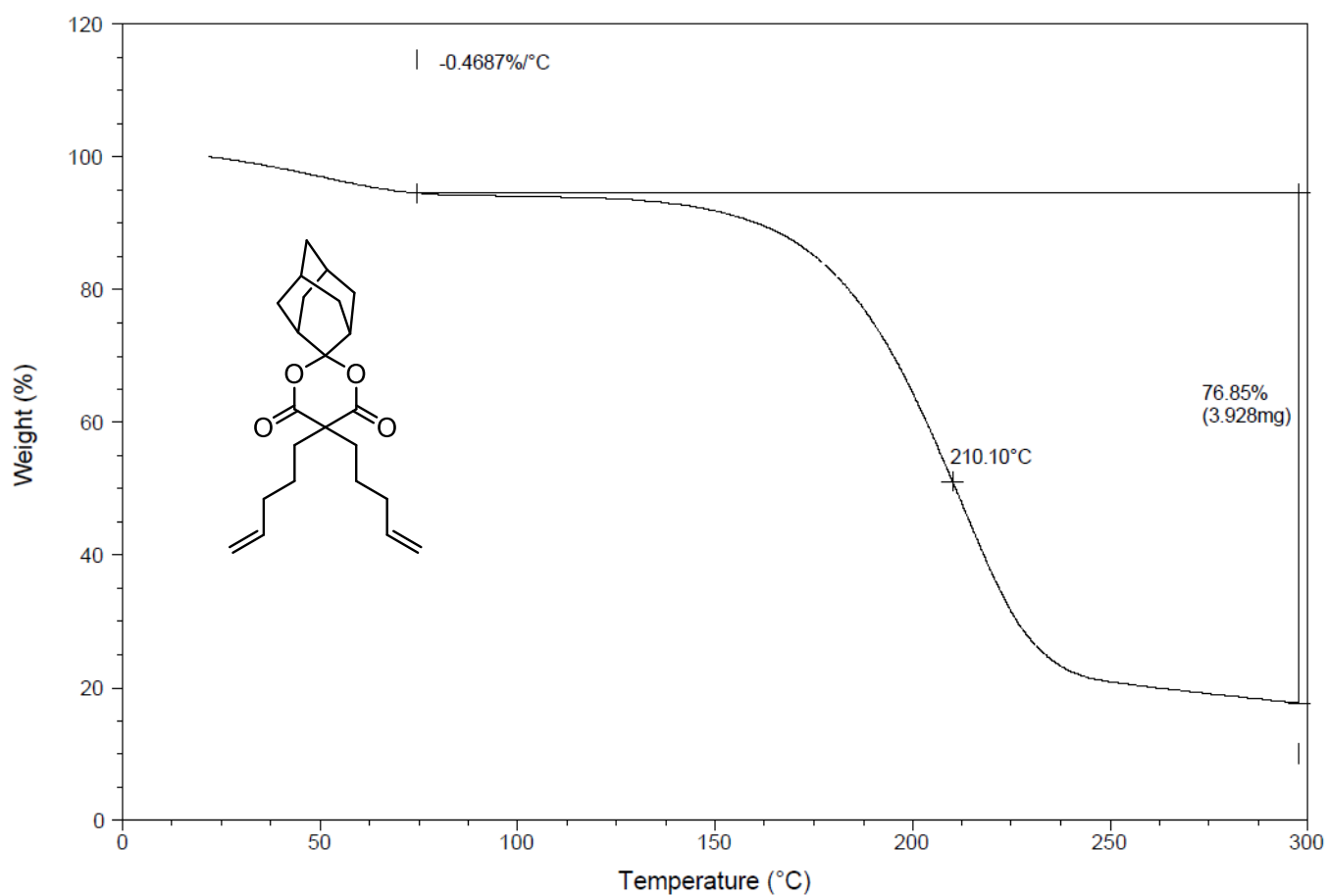
A3.21. Thermogravimetric analytical trace of compound **43**. Trace was obtained from ramping 5 °C/min to 300 °C.

A3.22: Thermogravimetric analysis plot of compound **44**



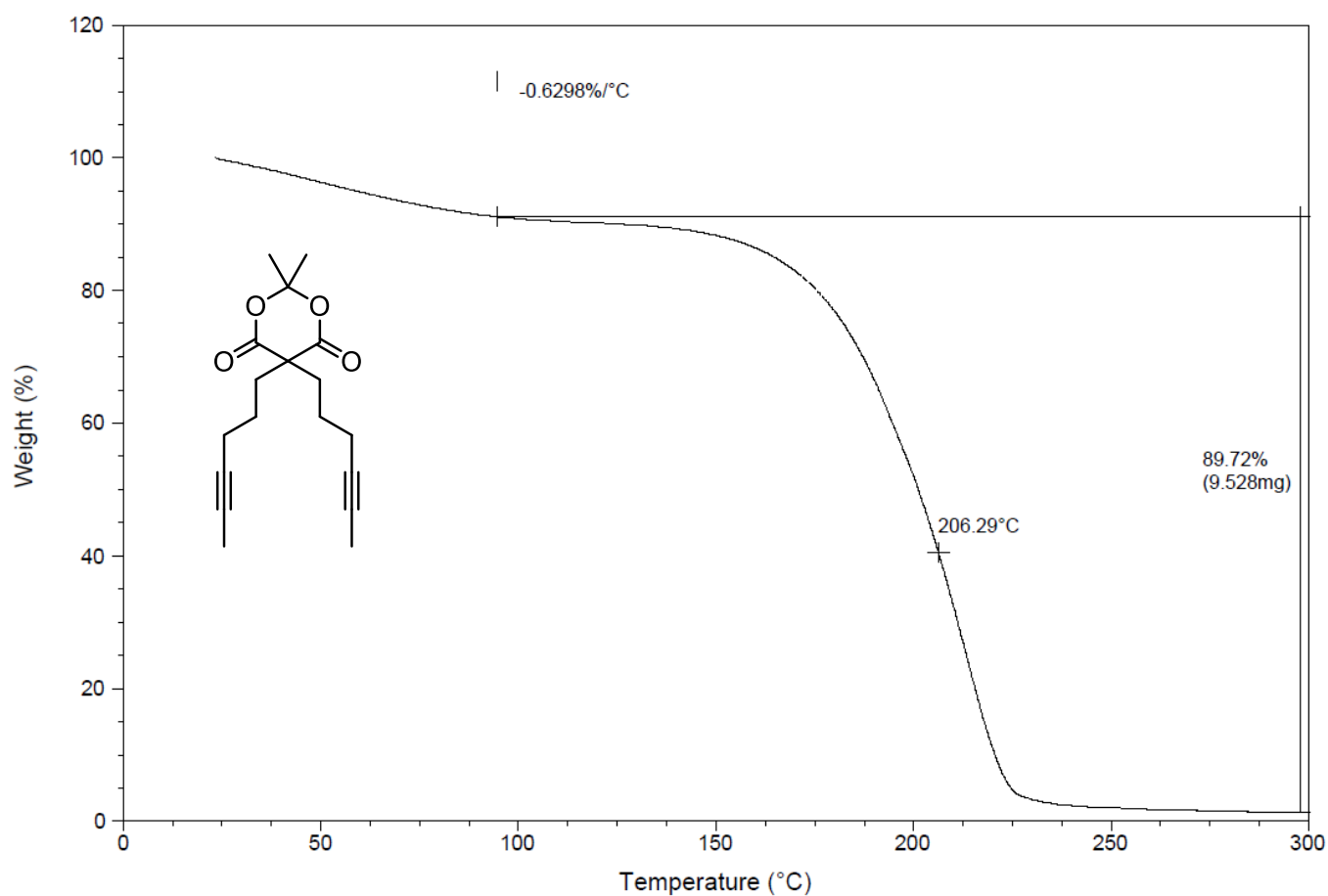
A3.22. Thermogravimetric analytical trace of compound **44**. Trace was obtained from ramping 5 °C/min to 300 °C.

A3.23: Thermogravimetric analysis plot of compound **45**



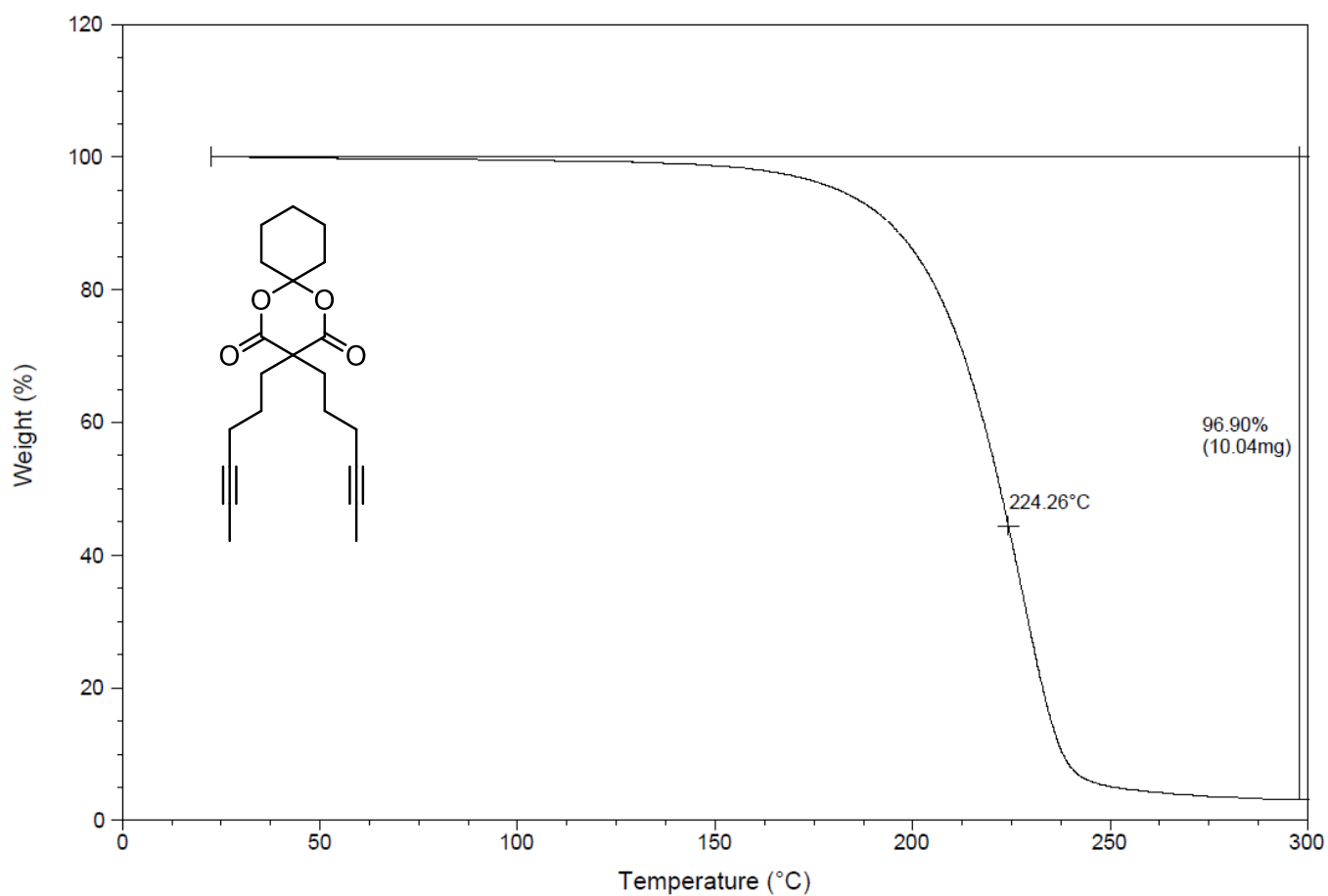
A3.23. Thermogravimetric analytical trace of compound **45**. Trace was obtained from ramping 5 °C/min to 300 °C.

A3.24: Thermogravimetric analysis plot of compound **53**



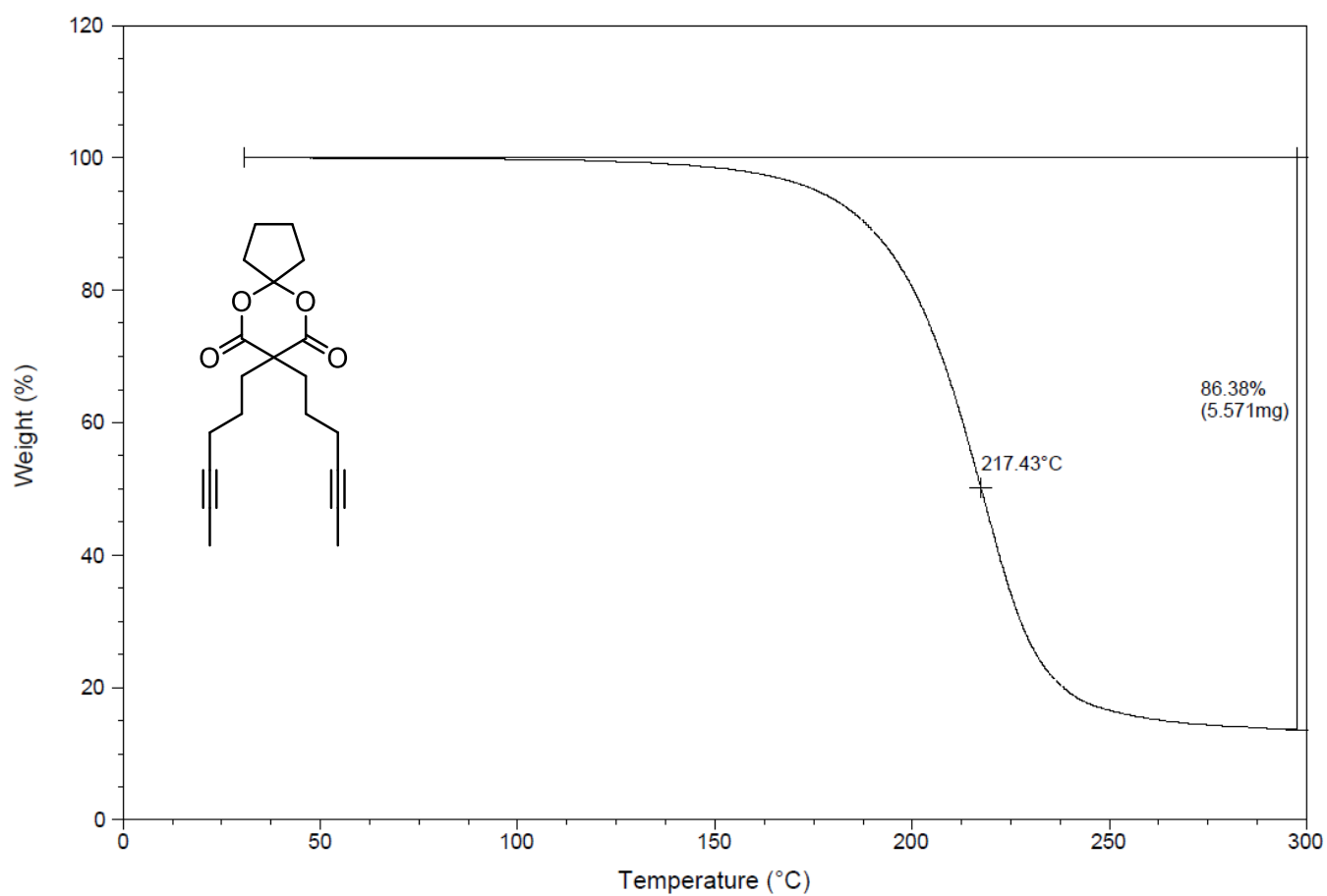
A3.24. Thermogravimetric analytical trace of compound **53**. Trace was obtained from ramping 5 °C/min to 300 °C.

A3.25: Thermogravimetric analysis plot of compound **54**



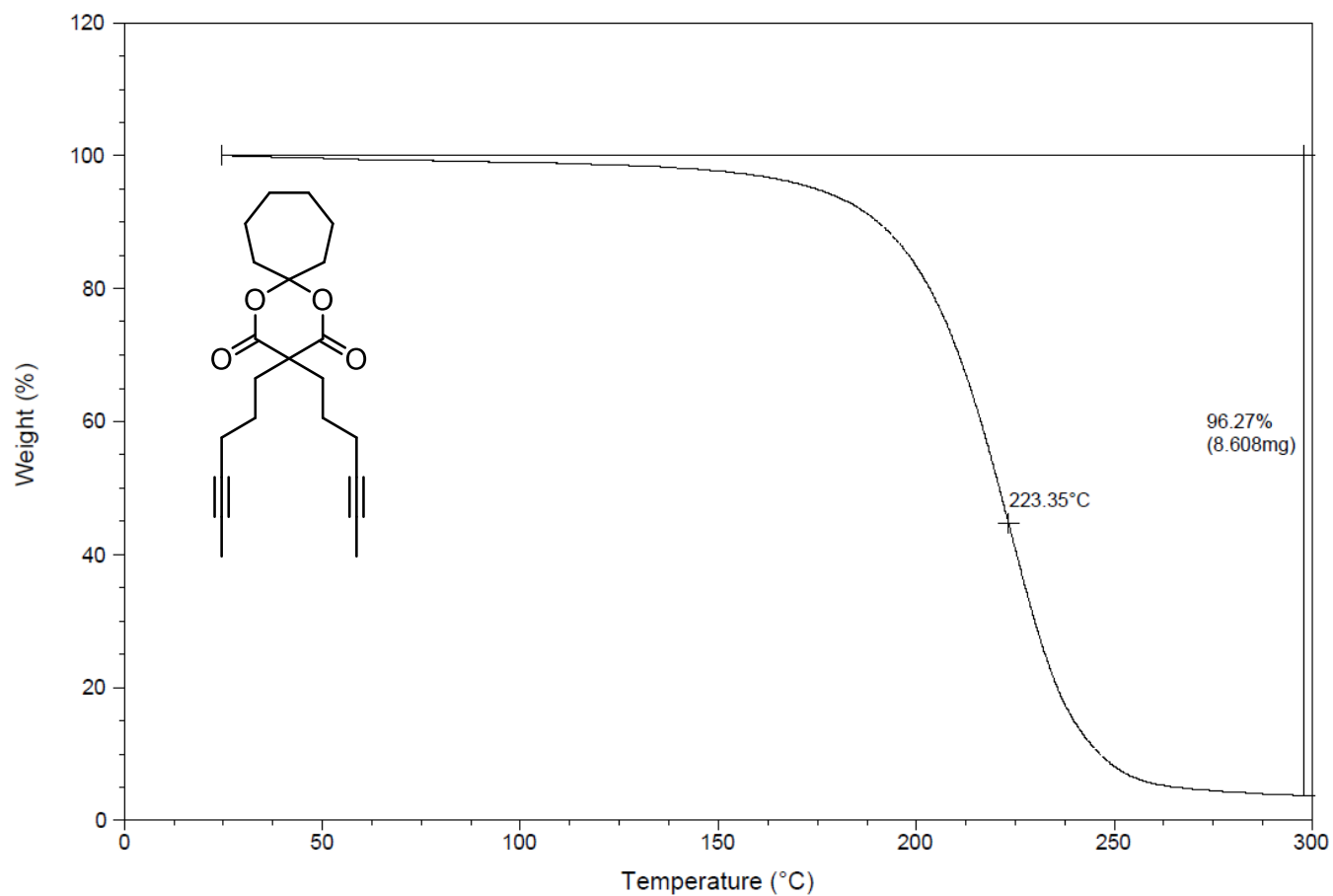
A3.25. Thermogravimetric analytical trace of compound **54**. Trace was obtained from ramping 5 °C/min to 300 °C.

A3.26: Thermogravimetric analysis plot of compound **55**



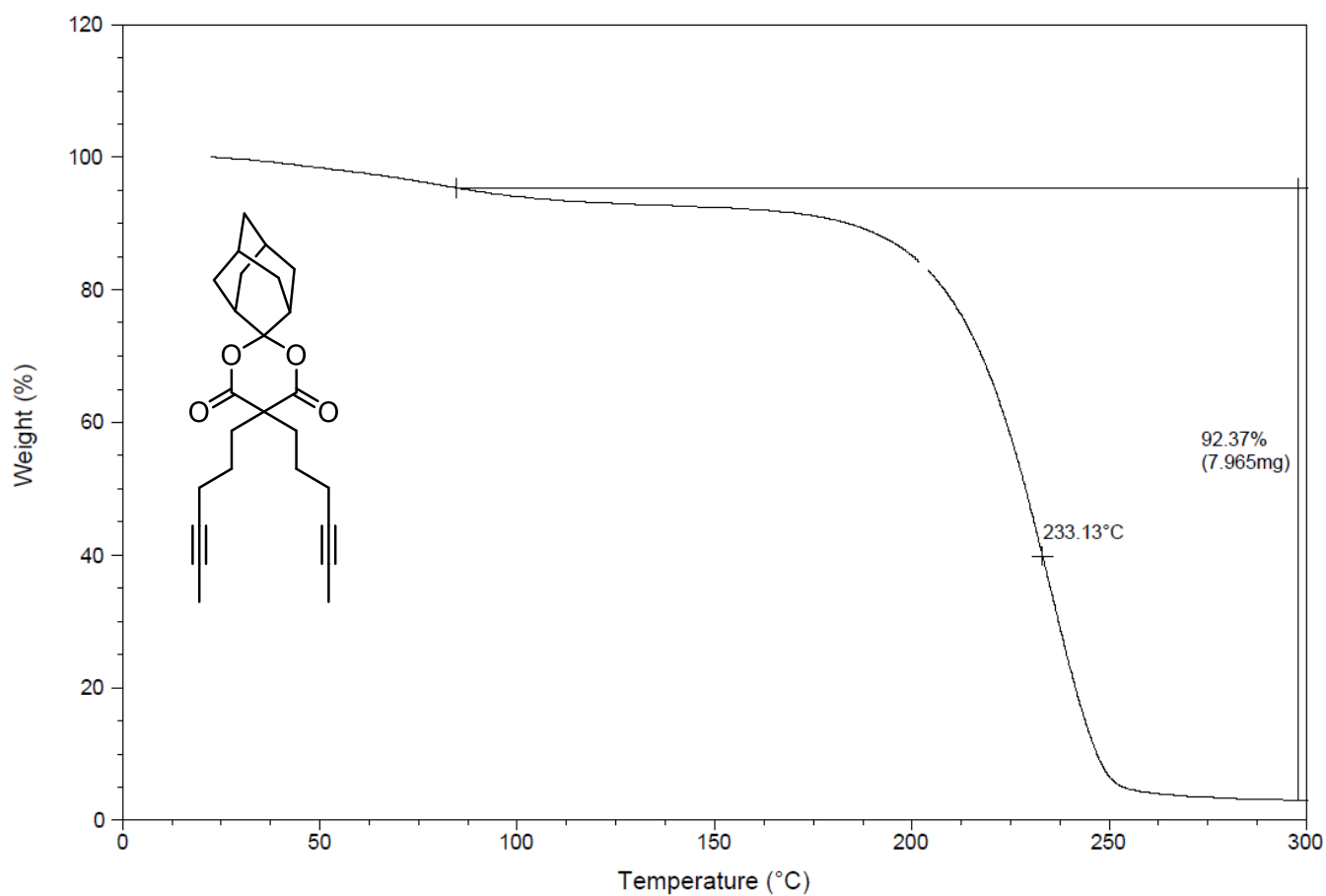
A3.26. Thermogravimetric analytical trace of compound **55**. Trace was obtained from ramping 5 °C/min to 300 °C.

A3.27: Thermogravimetric analysis plot of compound **56**



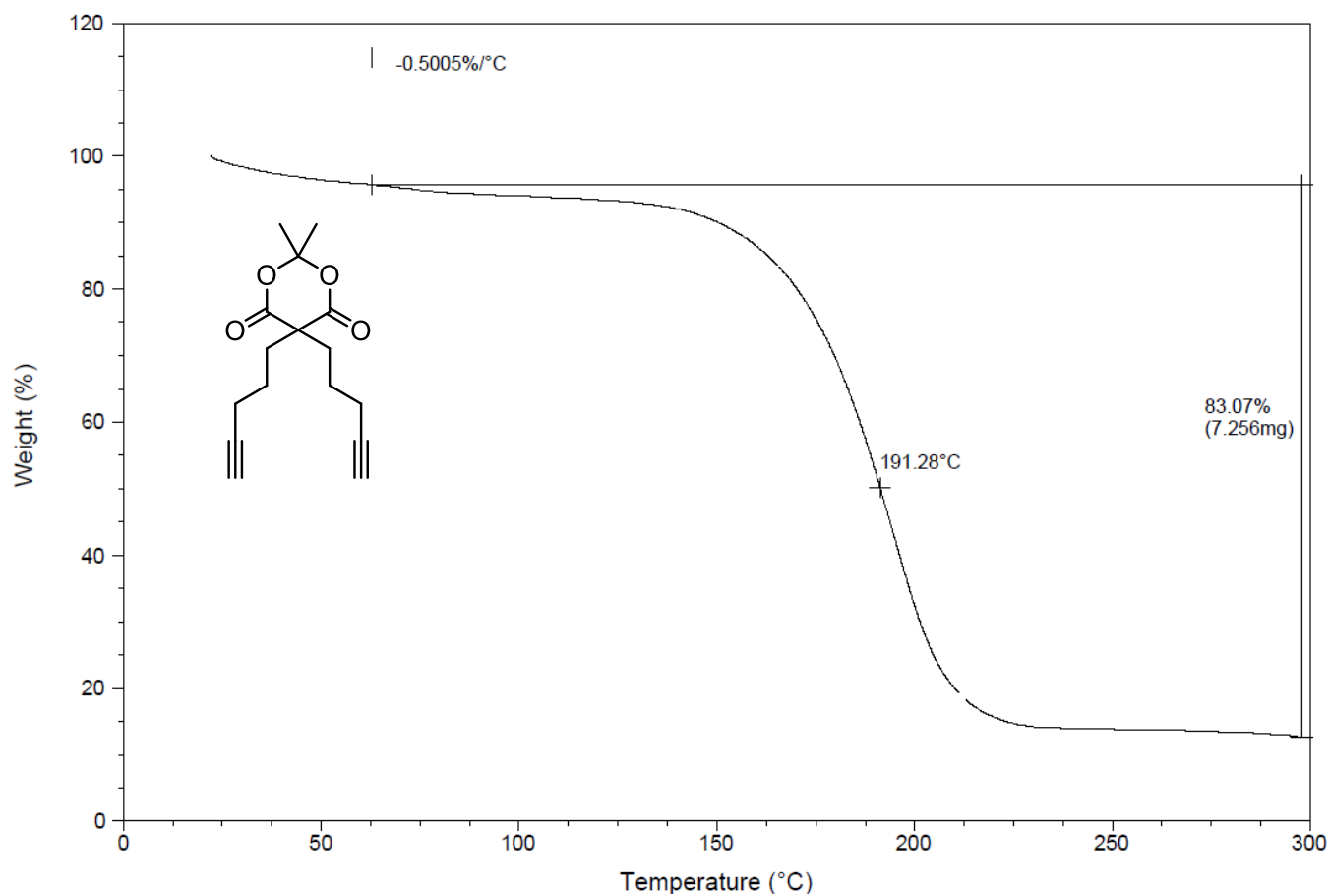
A3.27. Thermogravimetric analytical trace of compound **56**. Trace was obtained from ramping 5 °C/min to 300 °C.

A3.28: Thermogravimetric analysis plot of compound **57**



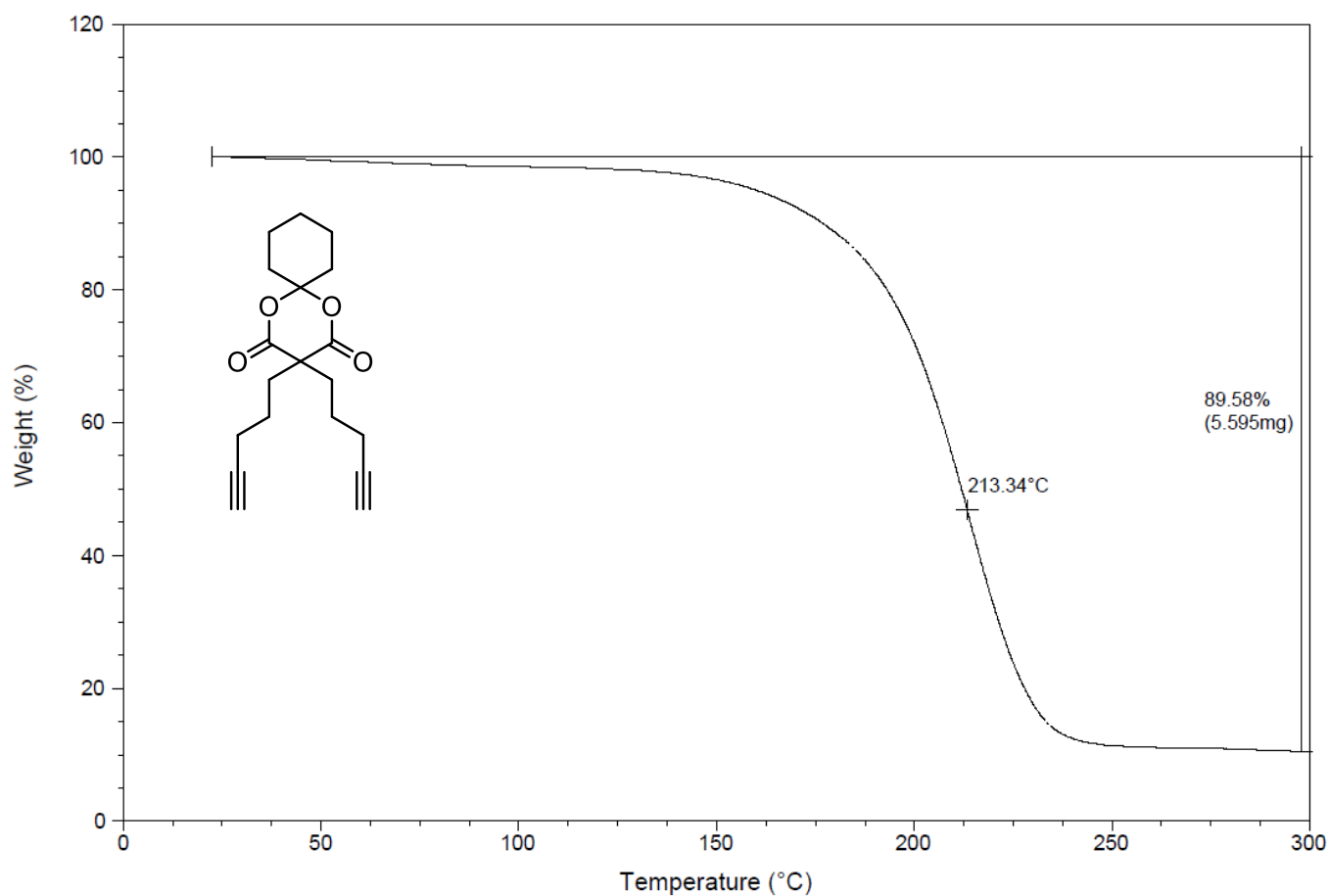
A3.28. Thermogravimetric analytical trace of compound **57**. Trace was obtained from ramping 5 °C/min to 300 °C.

A3.29: Thermogravimetric analysis plot of compound **58**



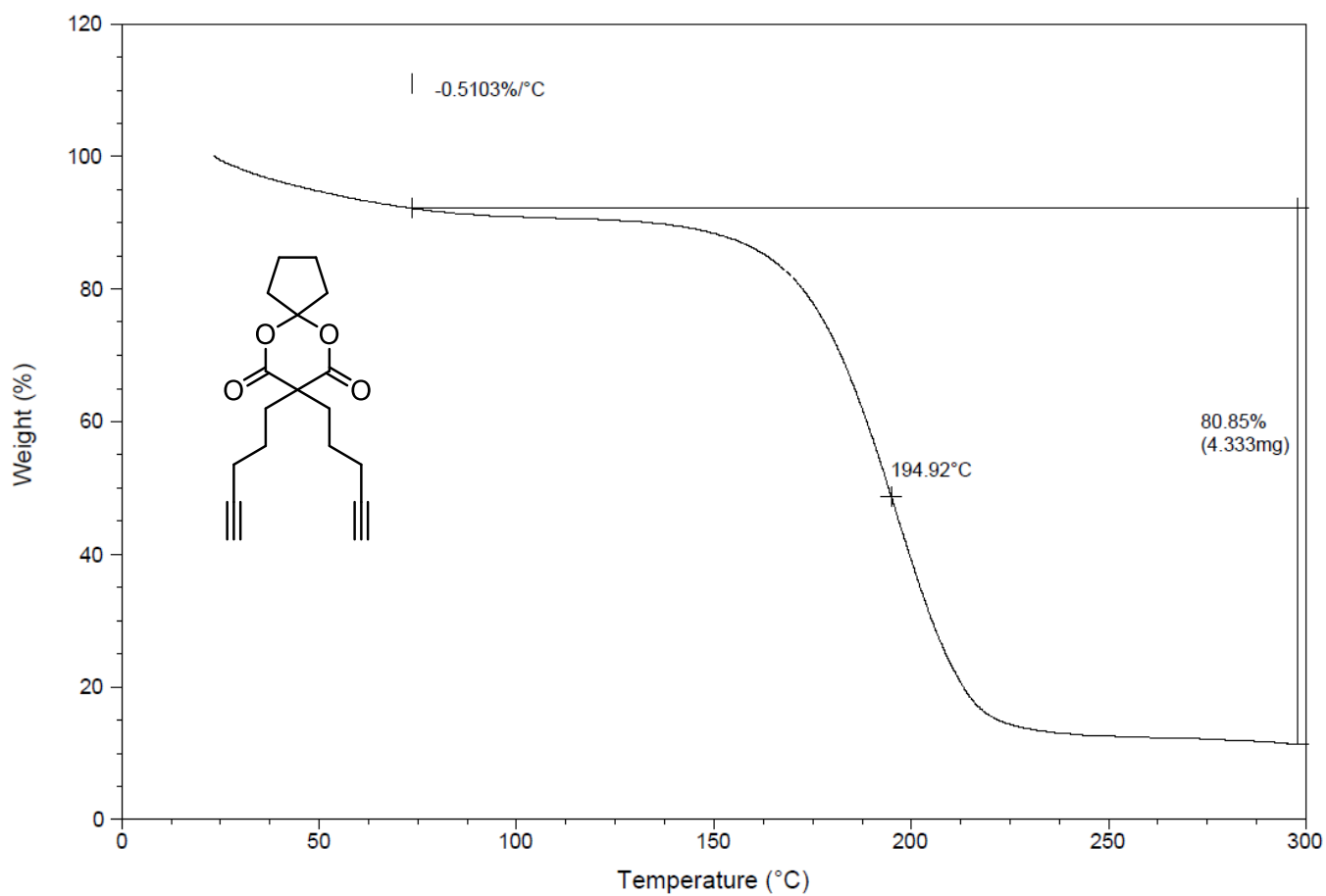
A3.29. Thermogravimetric analytical trace of compound **58**. Trace was obtained from ramping $5^{\circ}\text{C}/\text{min}$ to 300°C .

A3.30: Thermogravimetric analysis plot of compound **59**



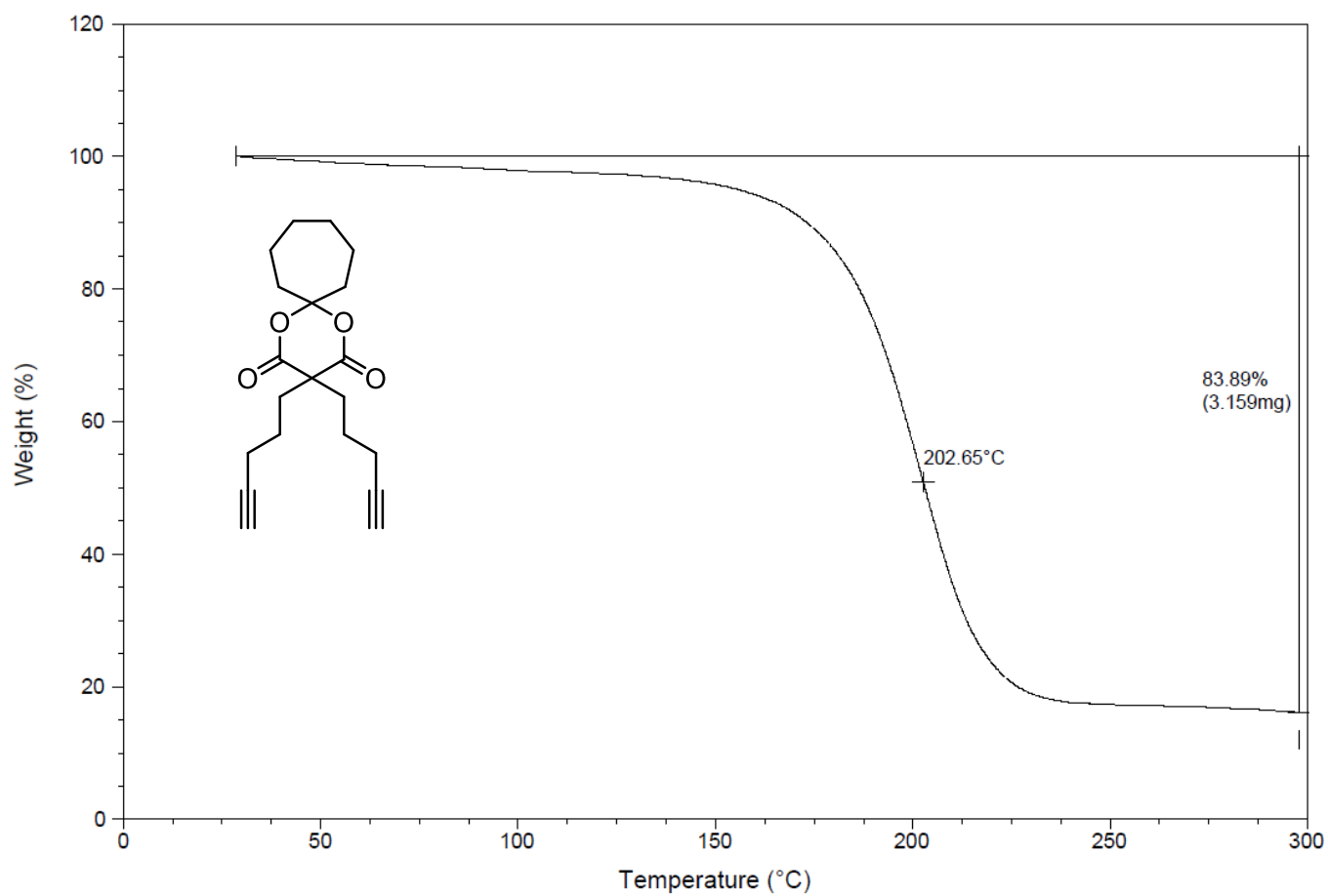
A3.30. Thermogravimetric analytical trace of compound **59**. Trace was obtained from ramping 5 °C/min to 300 °C.

A3.31: Thermogravimetric analysis plot of compound **60**



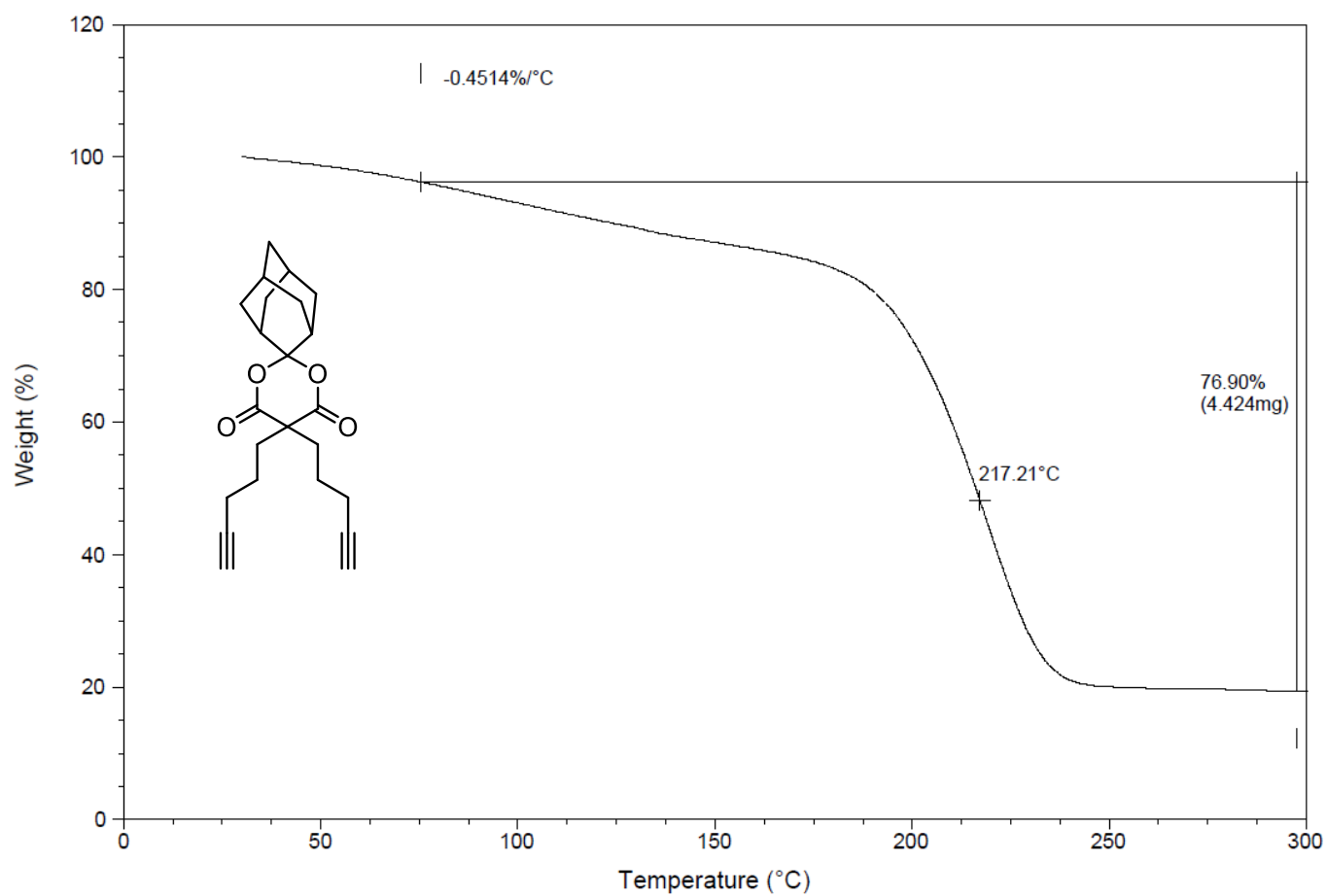
A3.31. Thermogravimetric analytical trace of compound **60**. Trace was obtained from ramping 5 °C/min to 300 °C.

A3.32: Thermogravimetric analysis plot of compound **61**



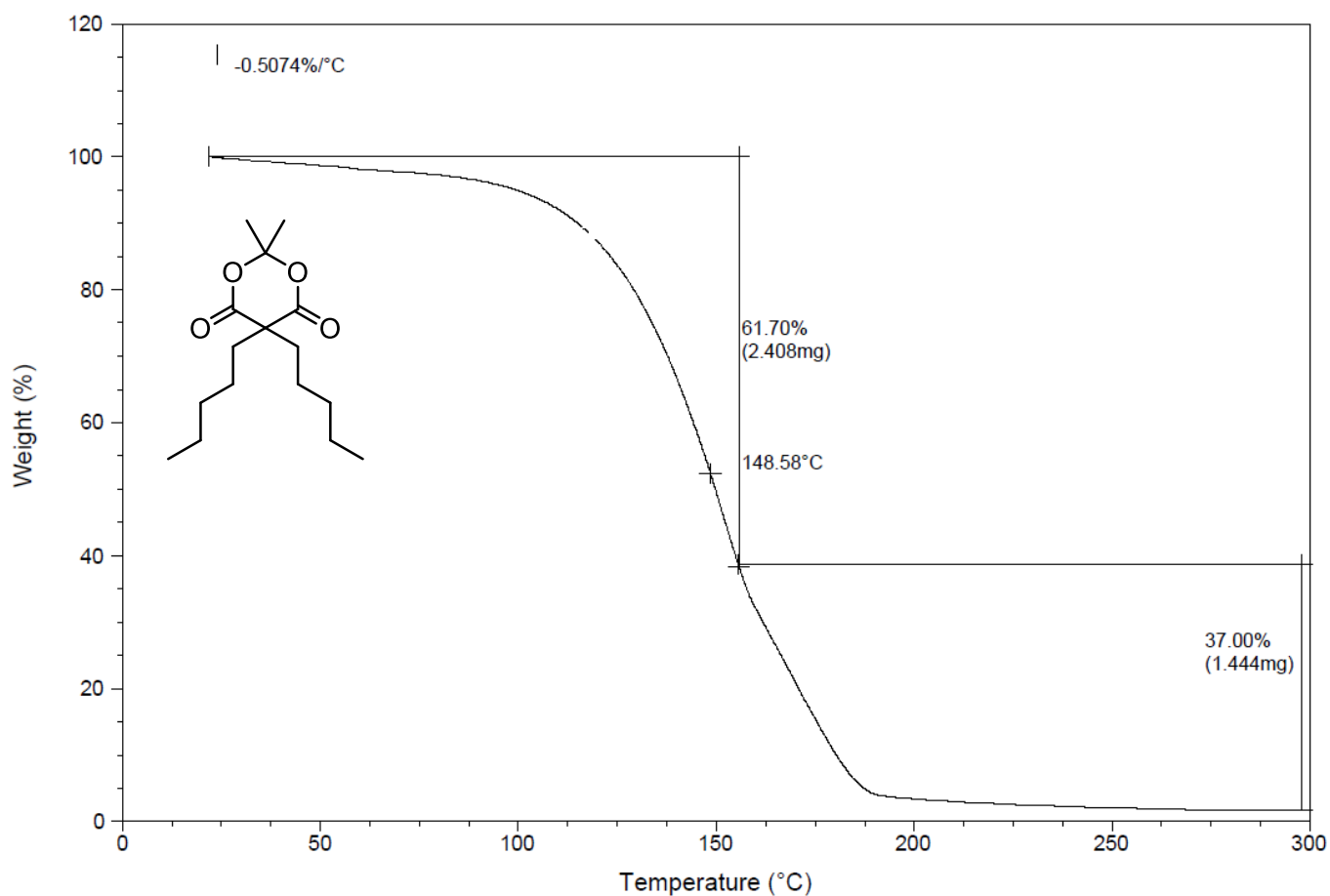
A3.32. Thermogravimetric analytical trace of compound **61**. Trace was obtained from ramping 5 °C/min to 300 °C.

A3.33: Thermogravimetric analysis plot of compound **62**



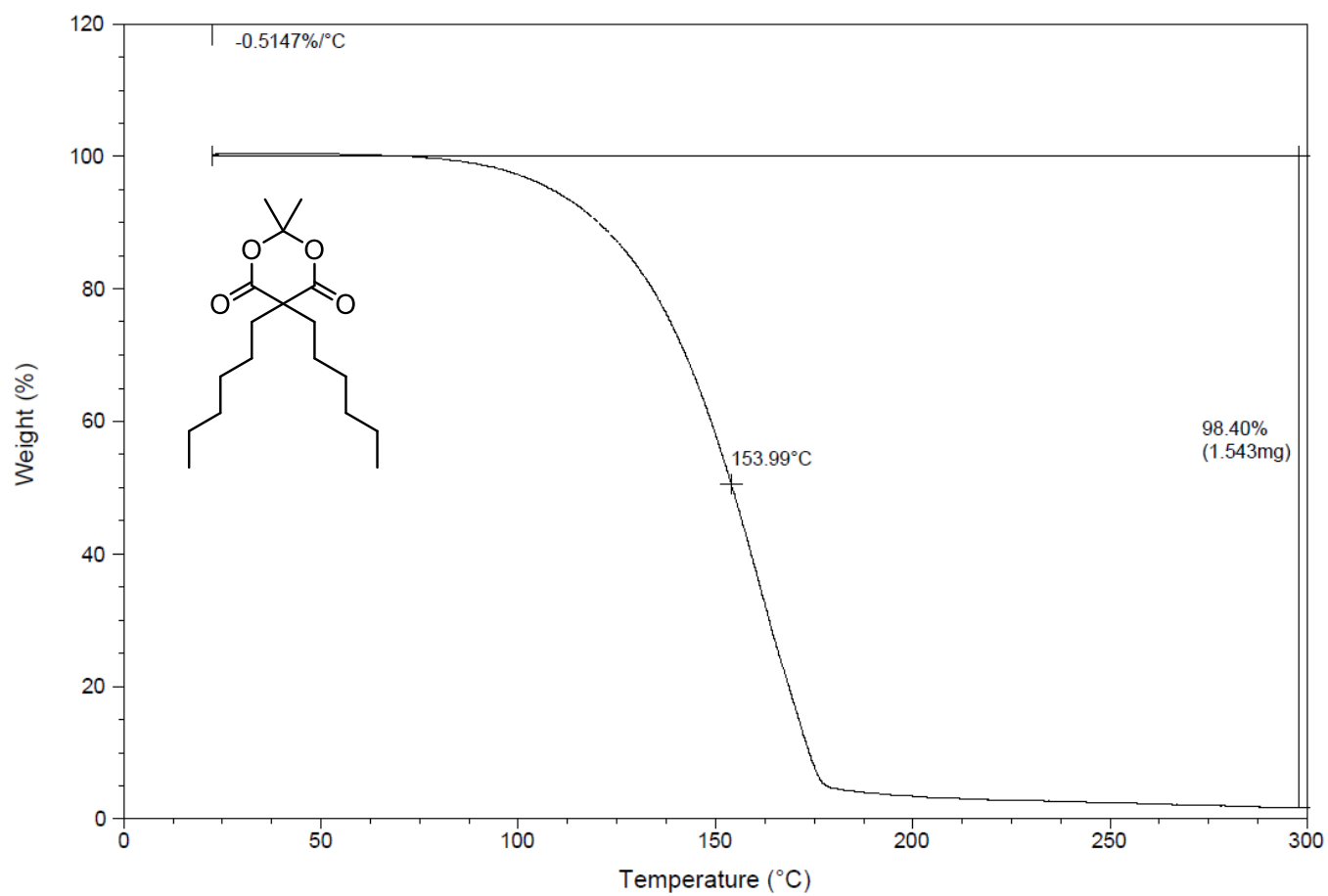
A3.33. Thermogravimetric analytical trace of compound **62**. Trace was obtained from ramping 5 °C/min to 300 °C.

A3.34: Thermogravimetric analysis plot of compound **64**



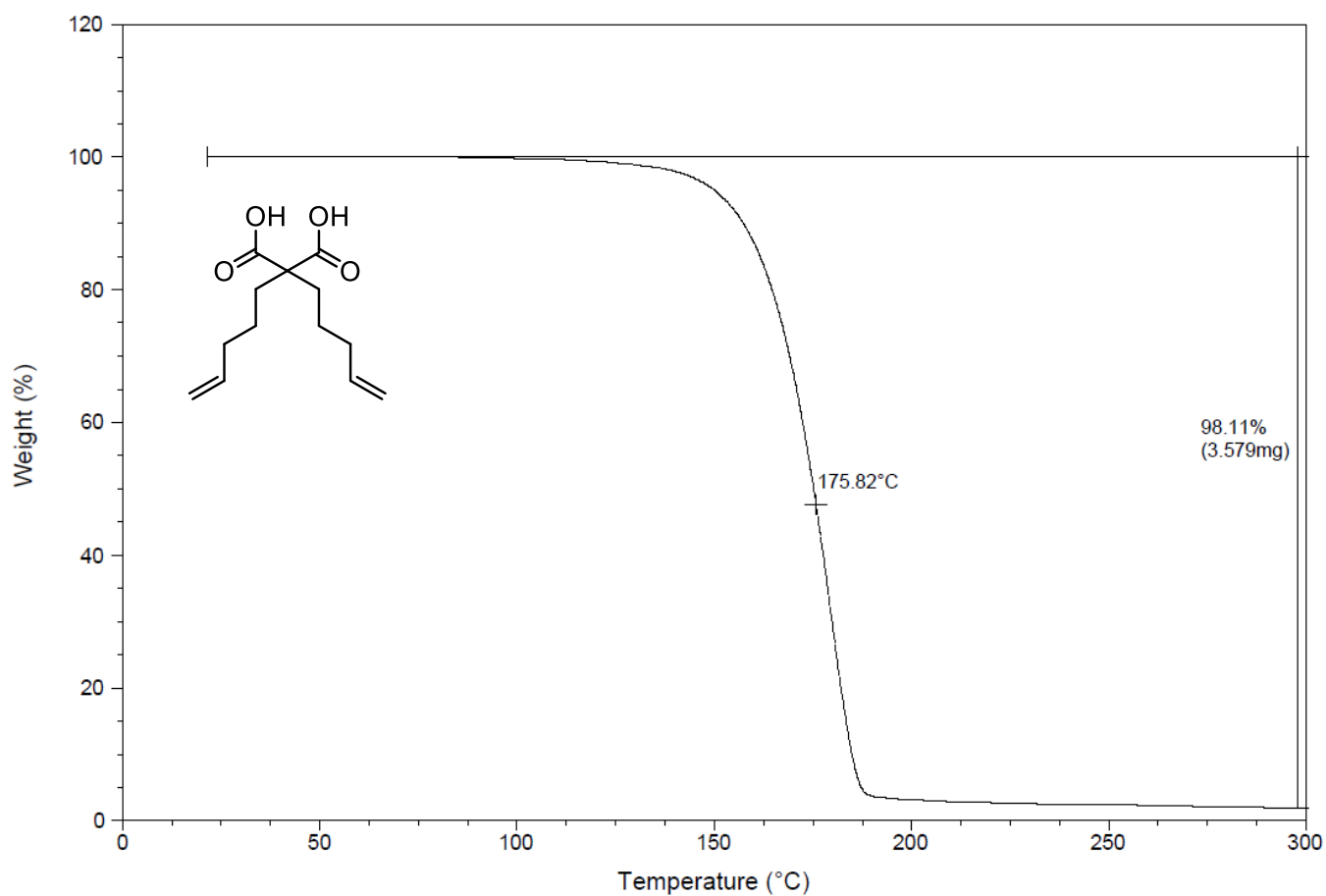
A3.34. Thermogravimetric analytical trace of compound **64**. Trace was obtained from ramping 5 °C/min to 300 °C.

A3.35: Thermogravimetric analysis plot of compound **66**



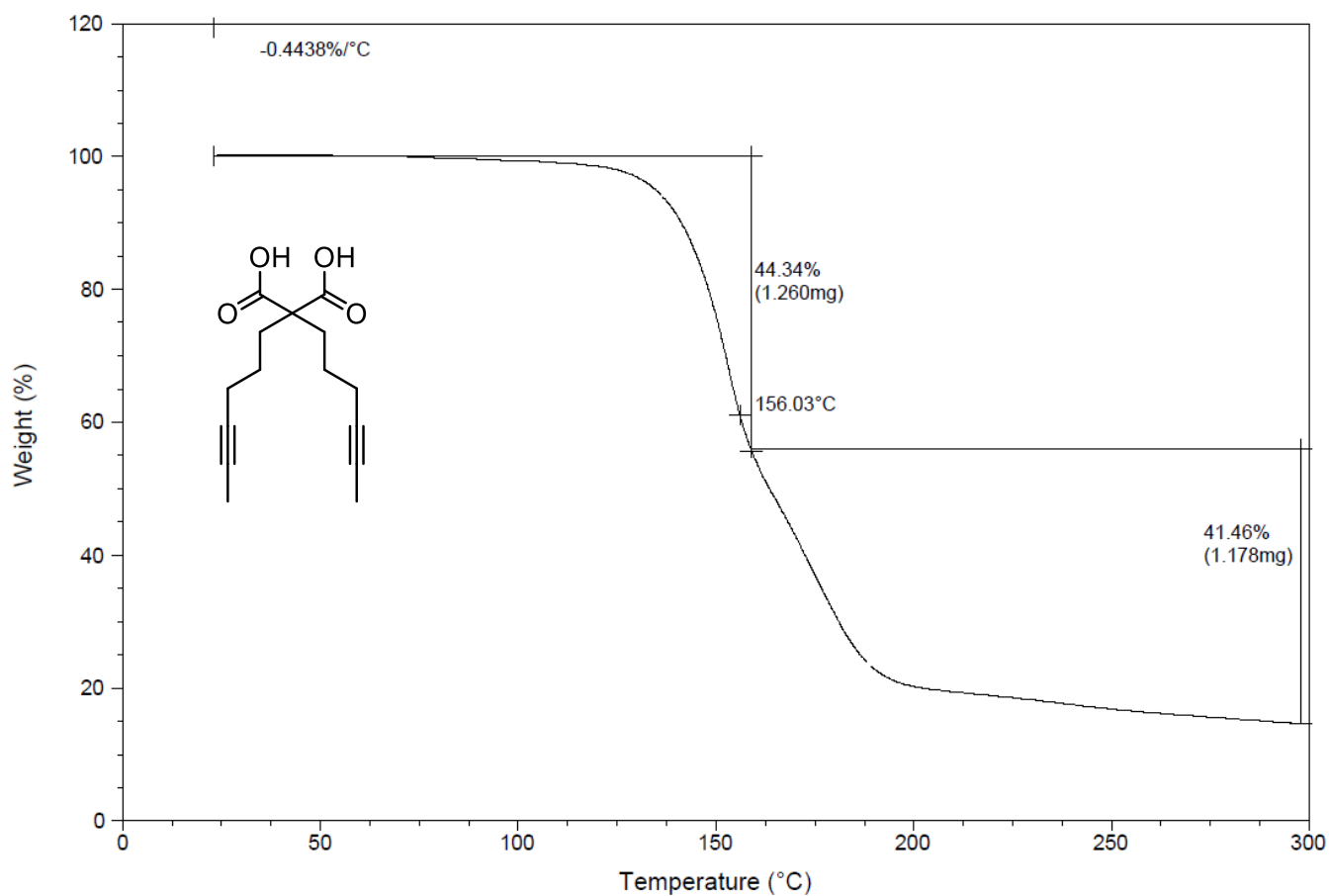
A3.35. Thermogravimetric analytical trace of compound **66**. Trace was obtained from ramping 5 °C/min to 300 °C.

A3.36: Thermogravimetric analysis plot of compound **70**



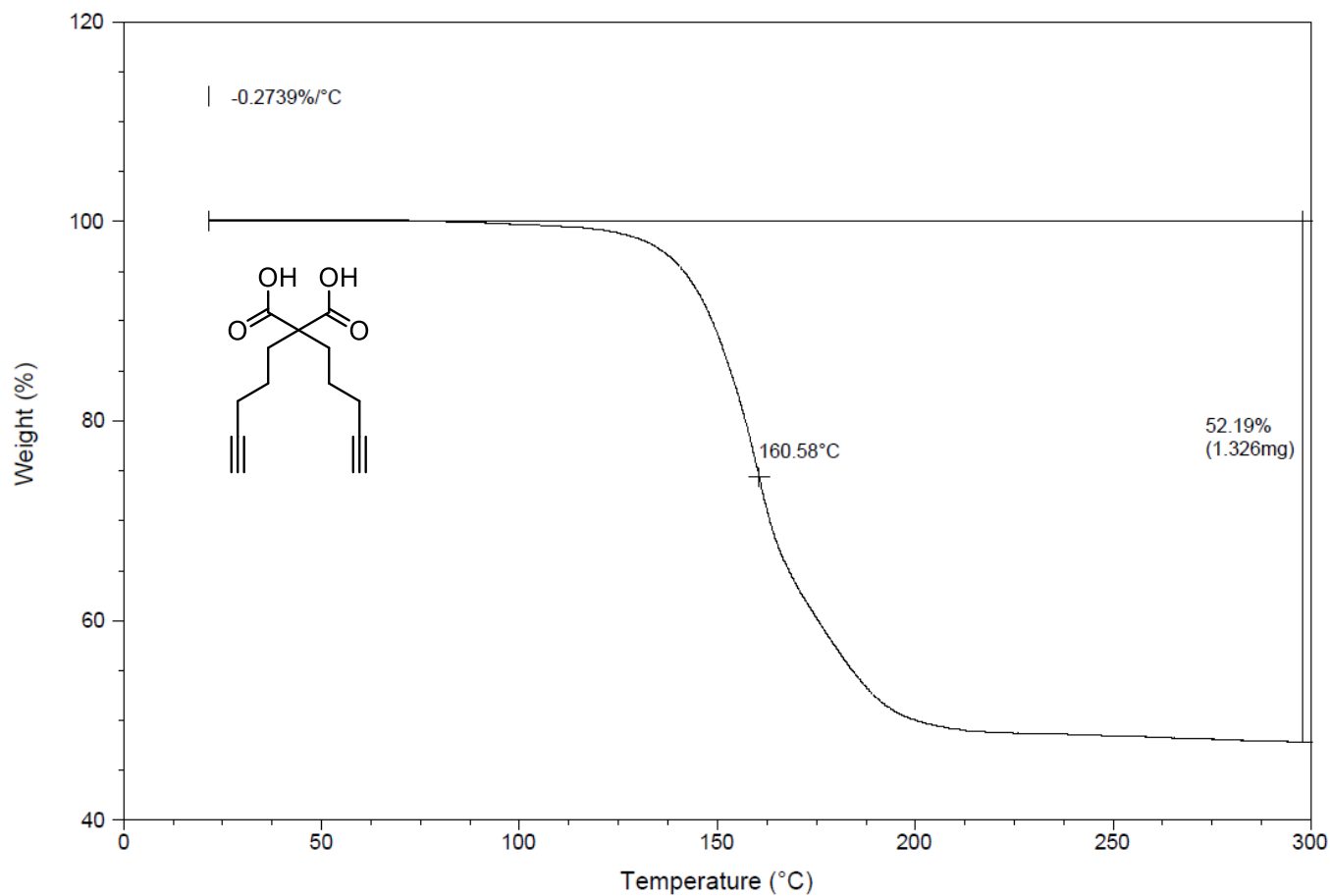
A3.36. Thermogravimetric analytical trace of compound **70**. Trace was obtained from ramping 5 °C/min to 300 °C.

A3.37: Thermogravimetric analysis plot of compound **73**



A3.37. Thermogravimetric analytical trace of compound **73**. Trace was obtained from ramping 5 °C/min to 300 °C.

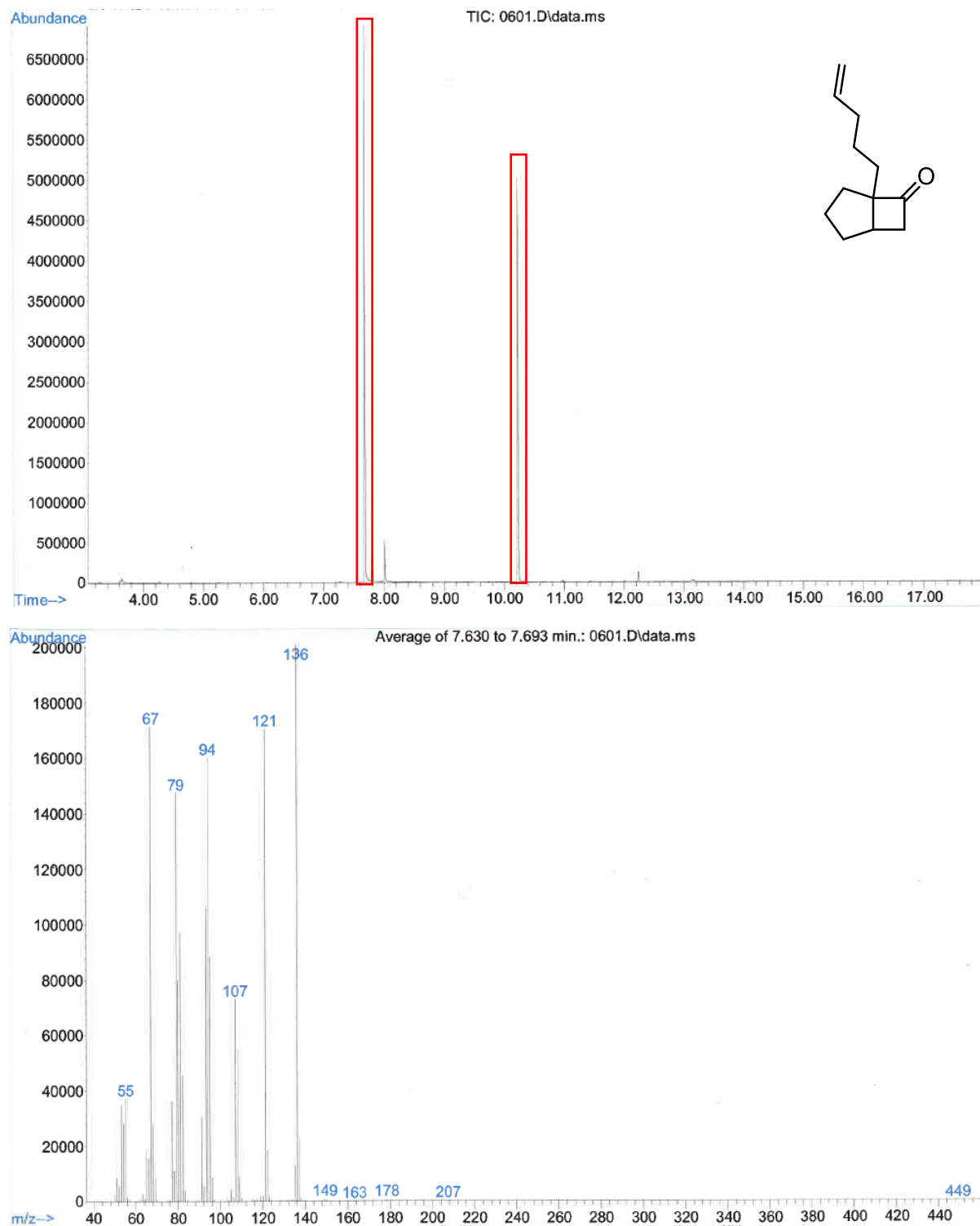
A3.38: Thermogravimetric analysis plot of compound **75**

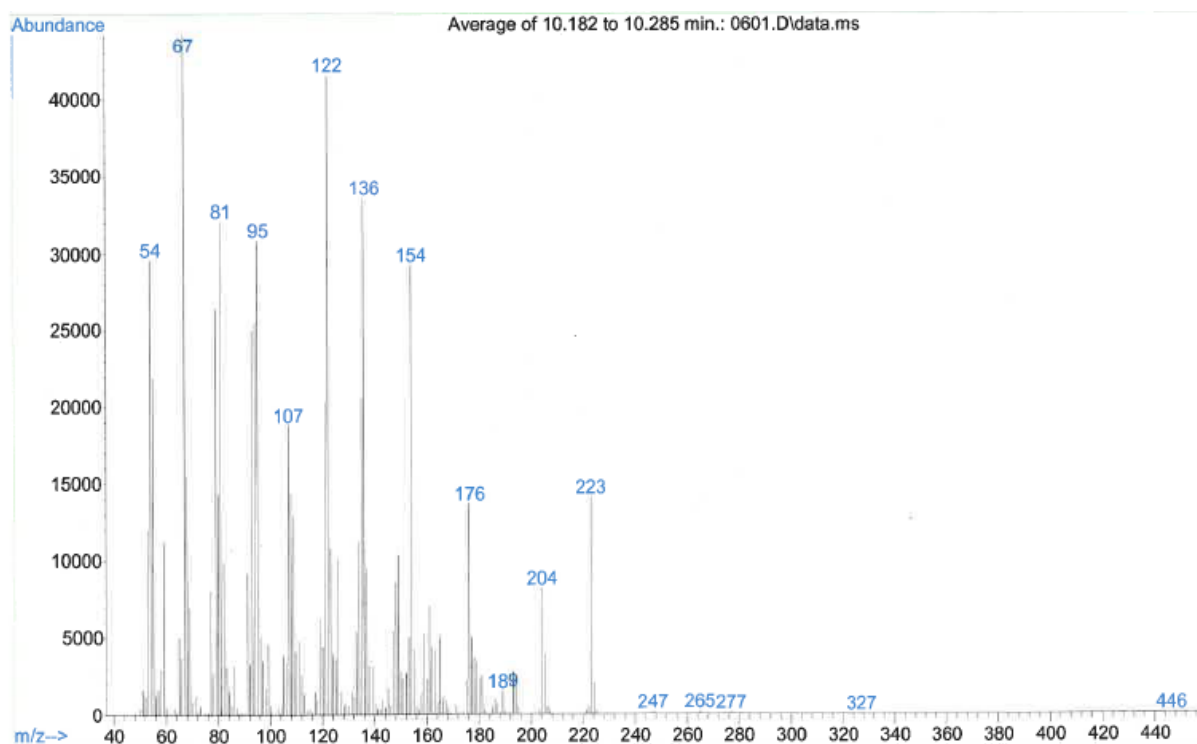


A3.38. Thermogravimetric analytical trace of compound **75**. Trace was obtained from ramping 5 °C/min to 300 °C.

Appendix 4: GC-MS data

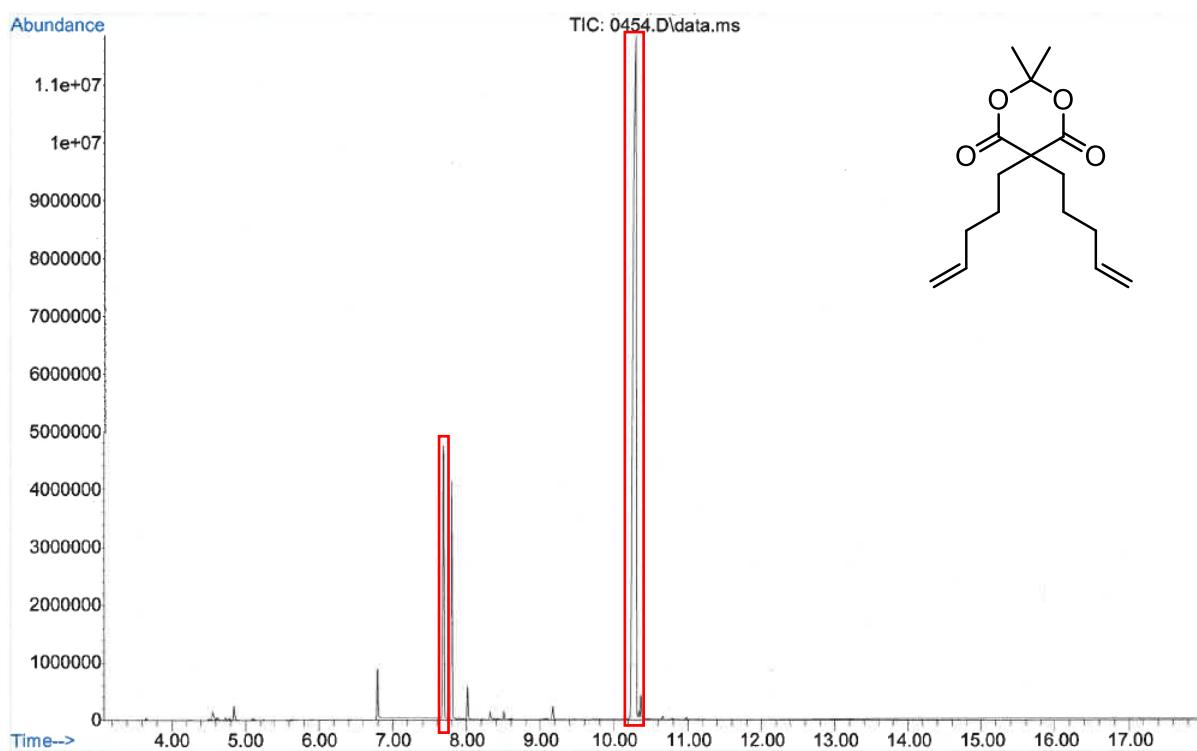
A4.1: GC-MS data of compound **71**

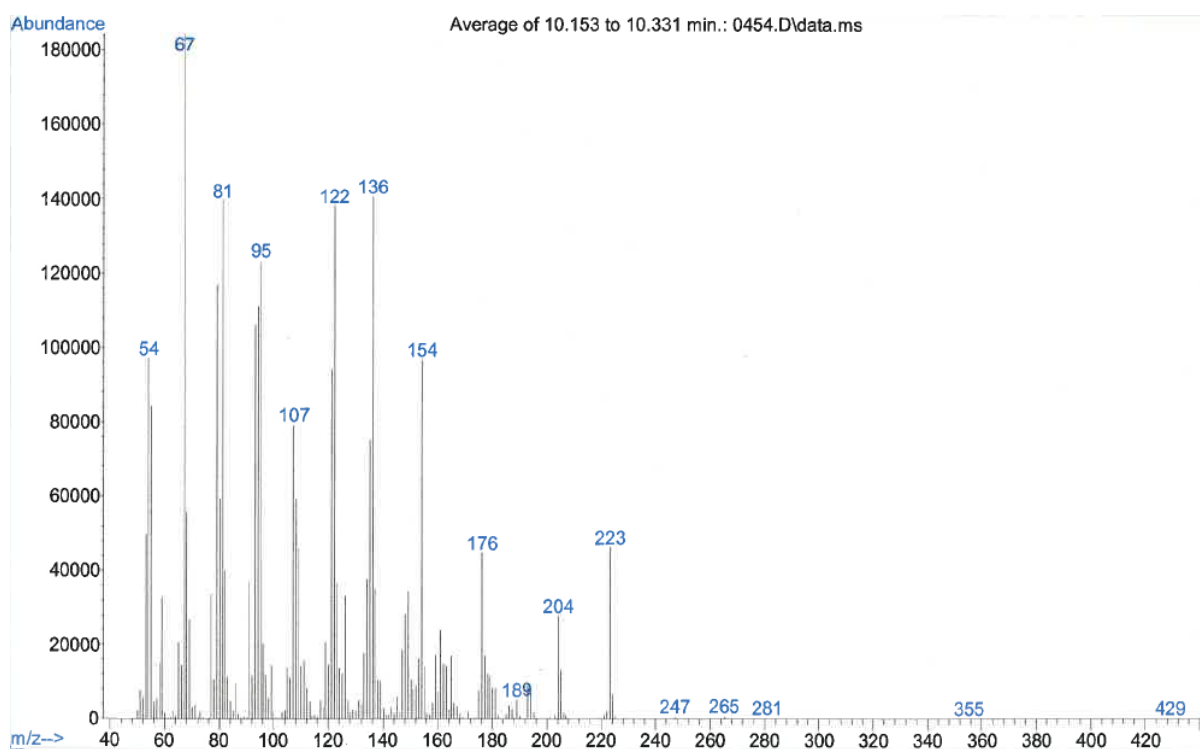
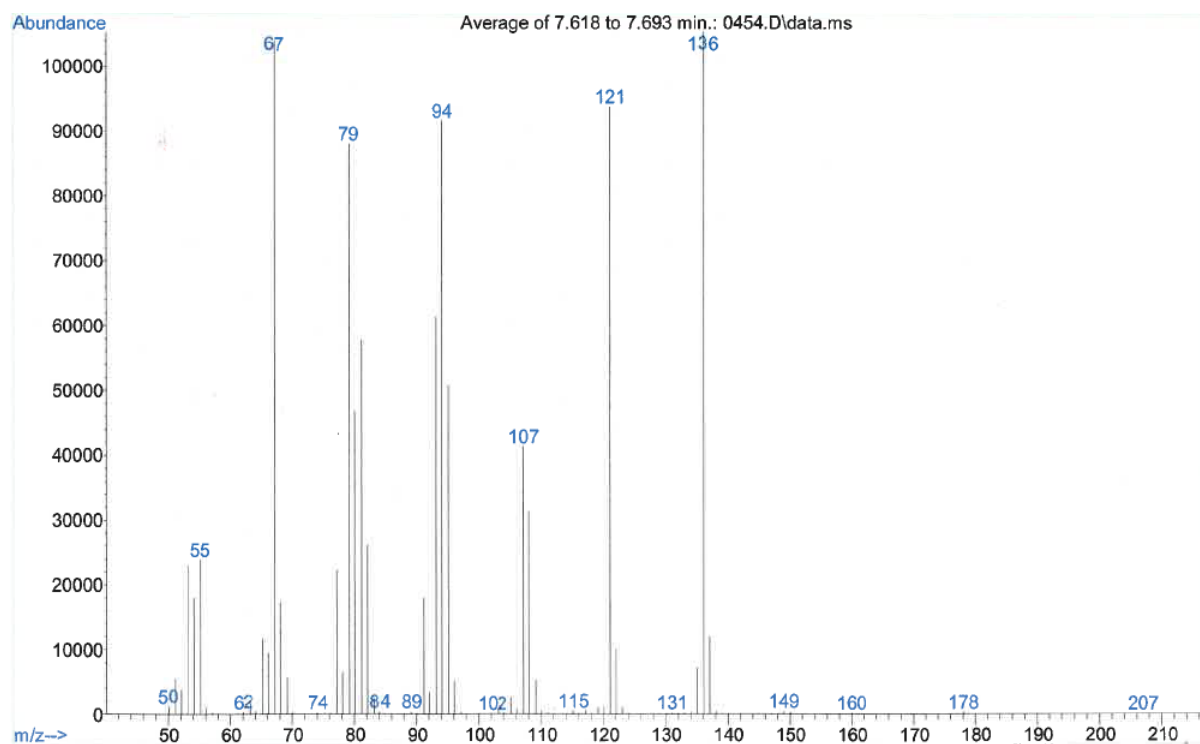




A4.1. GC-MS trace and spectra of compound **71**.

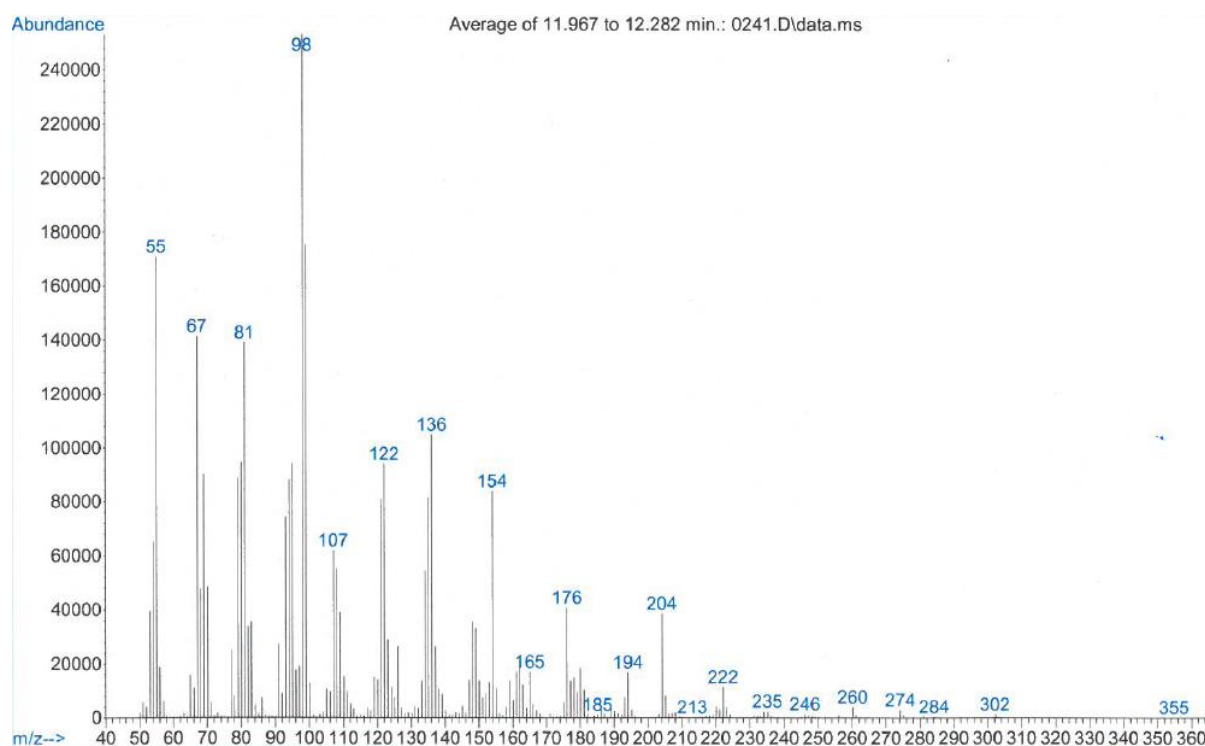
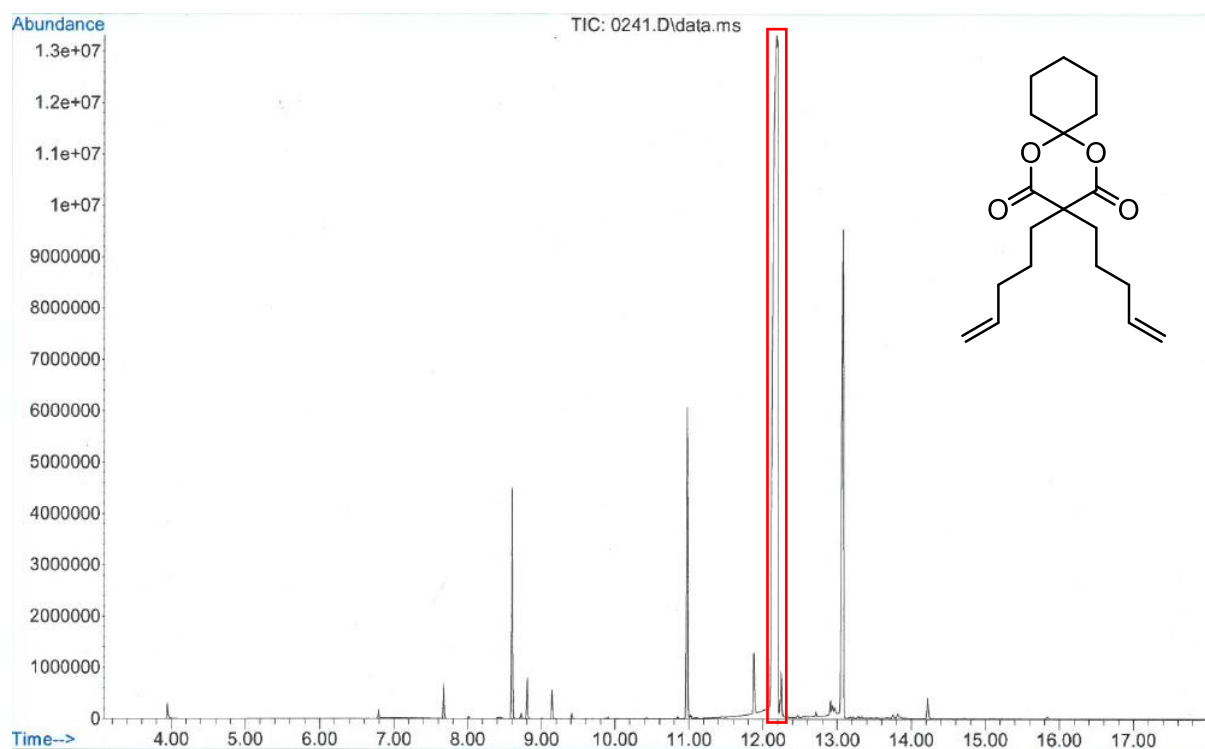
A4.2: GC-MS data of compound **41**





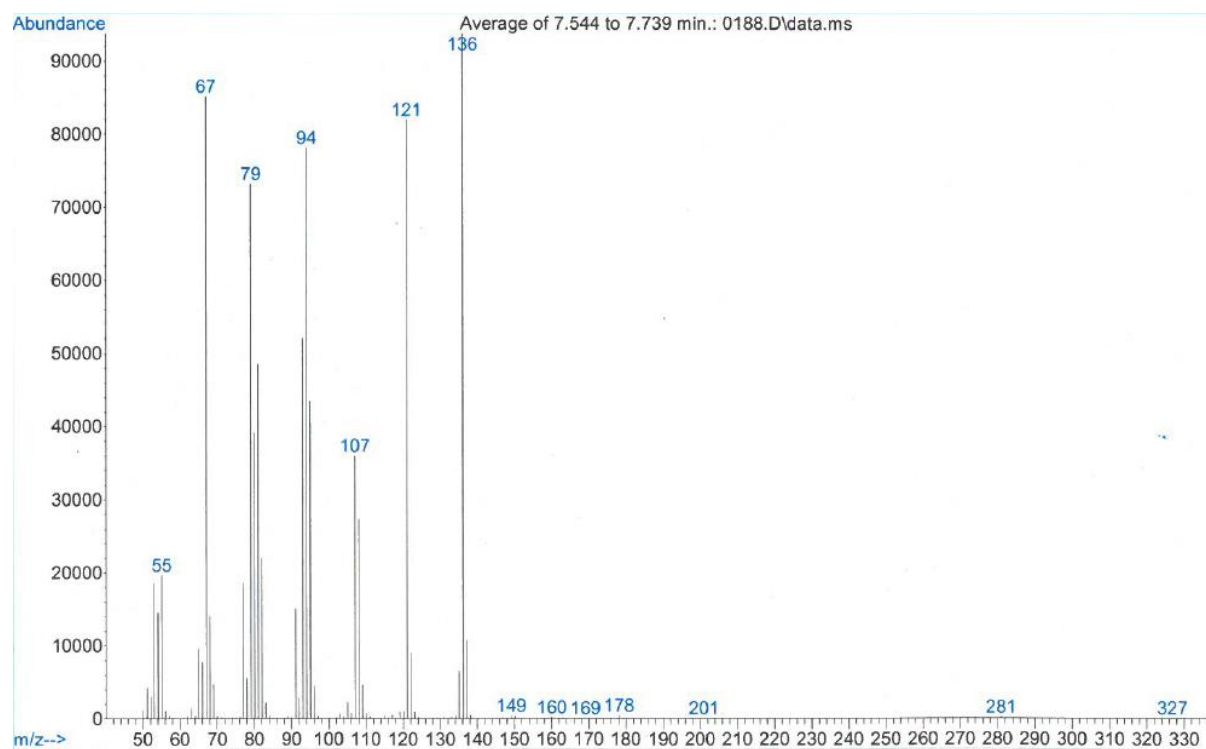
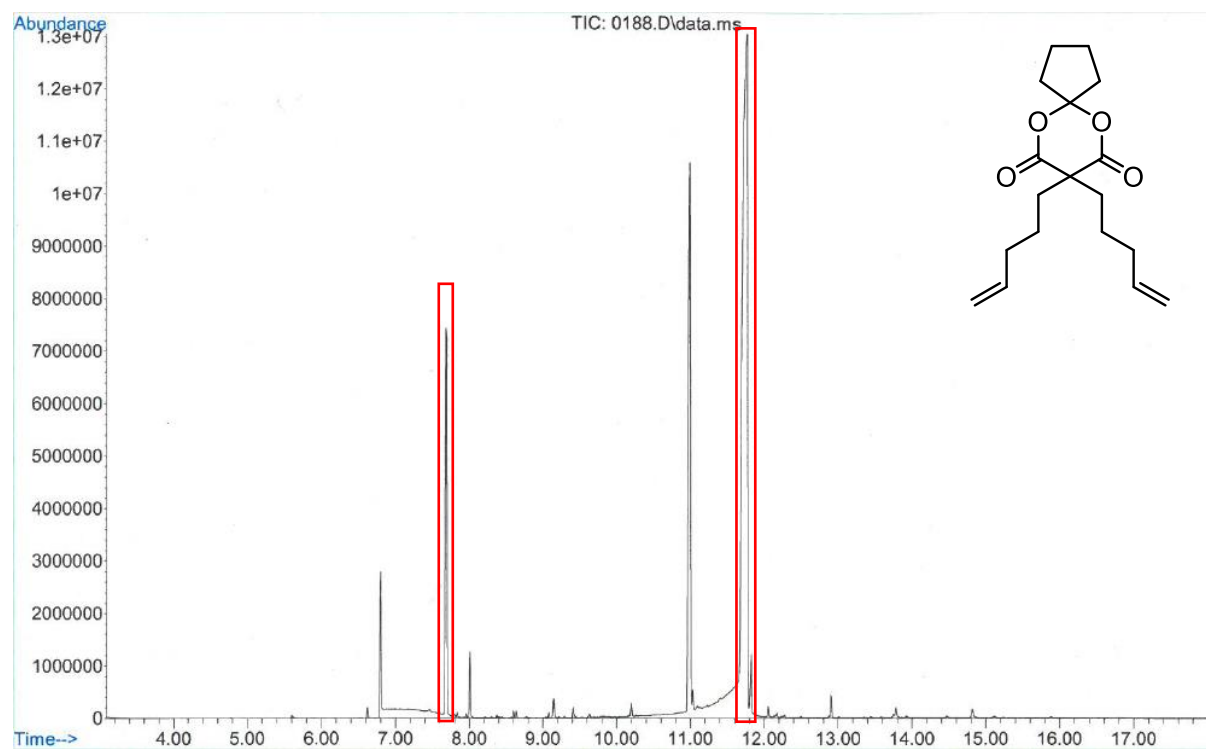
A4.2. GC-MS trace and spectra of compound 41.

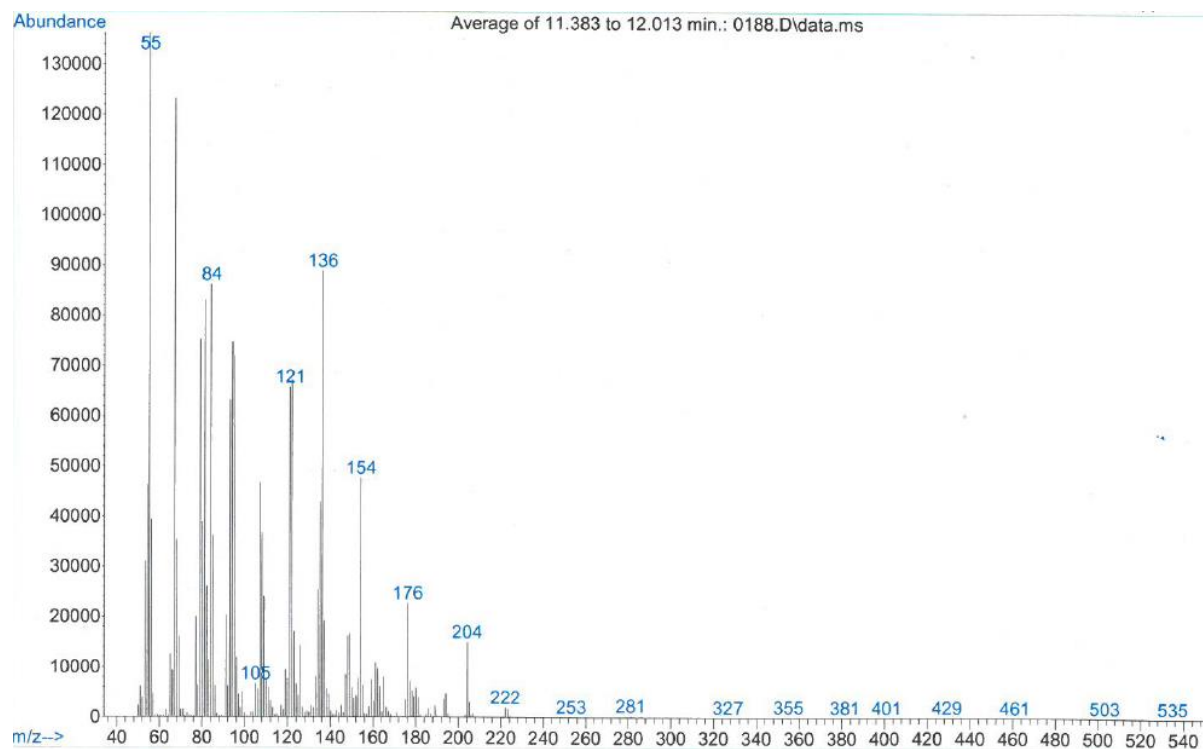
A4.3 GC-MS data of compound 42



A4.3. GC-MS trace and spectra of compound 42.

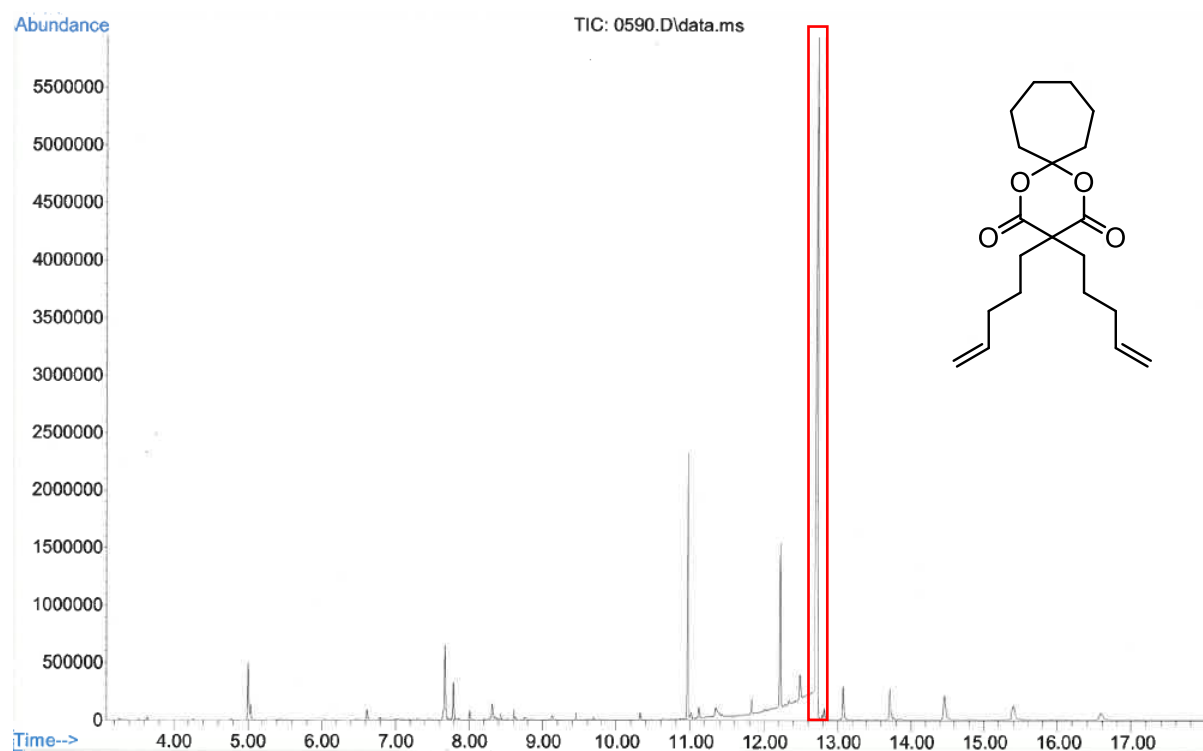
A4.4: GC-MS data of compound **43**

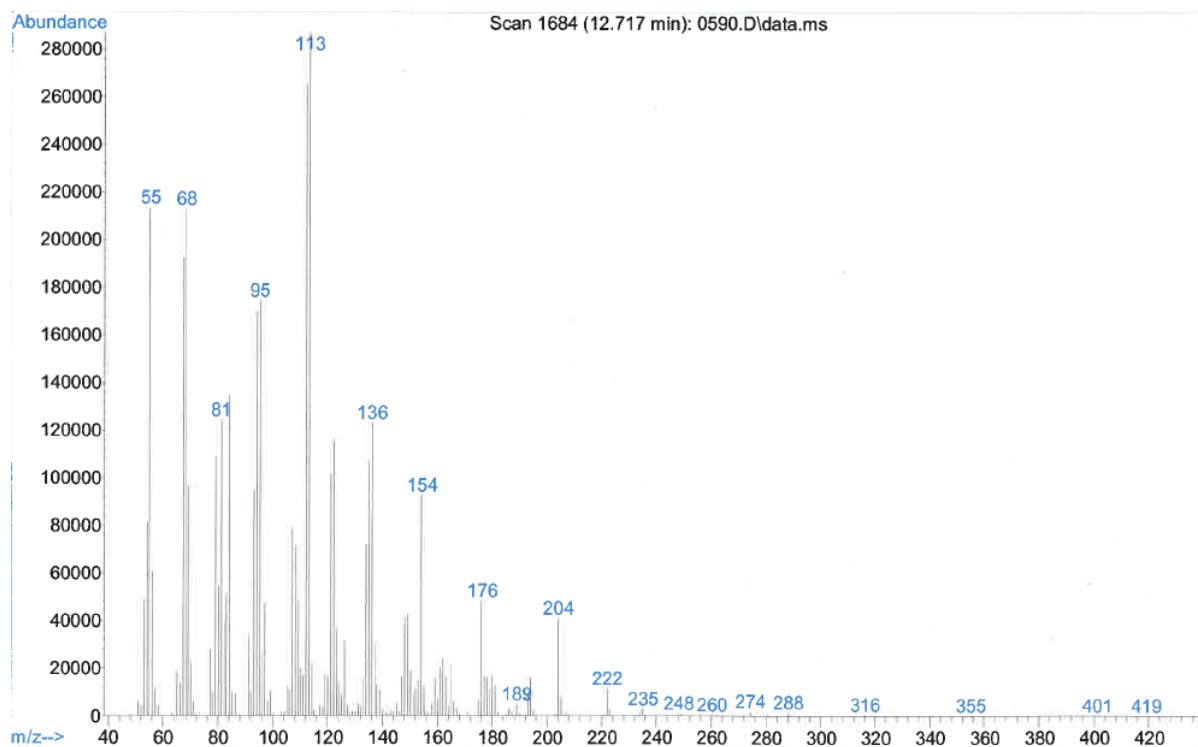




A4.4. GC-MS trace and spectra of compound **43**.

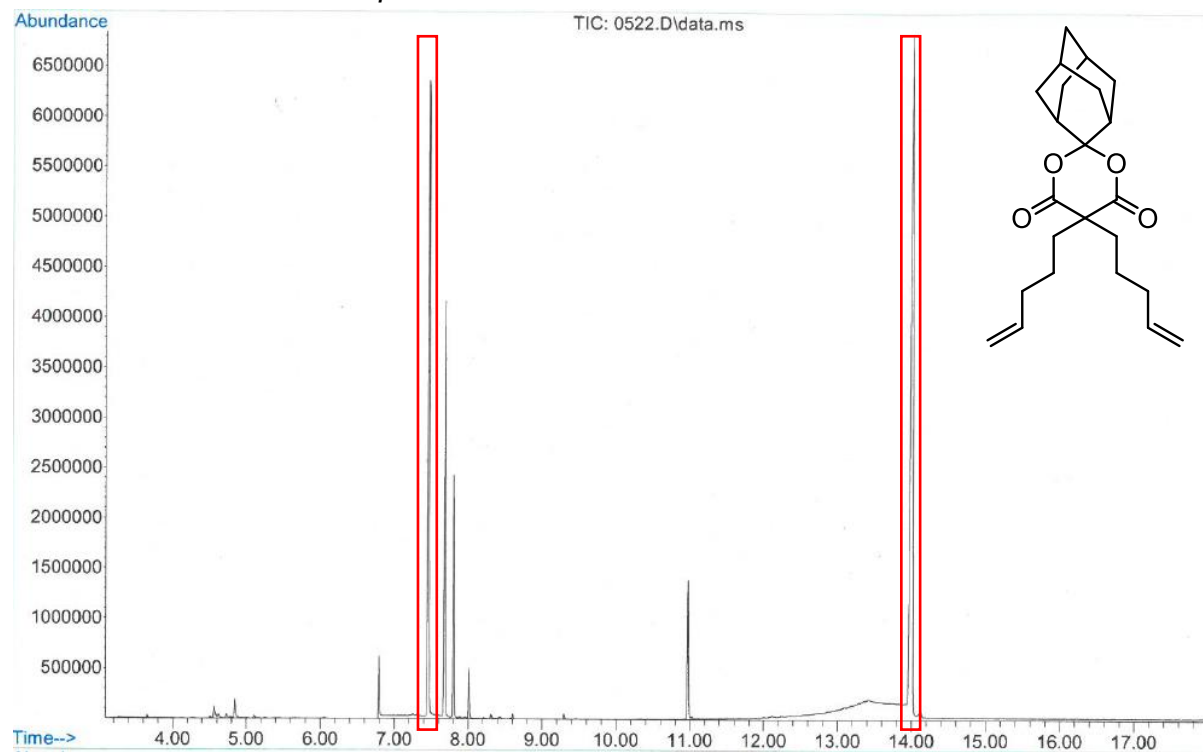
A4.5: GC-MS data of compound **44**

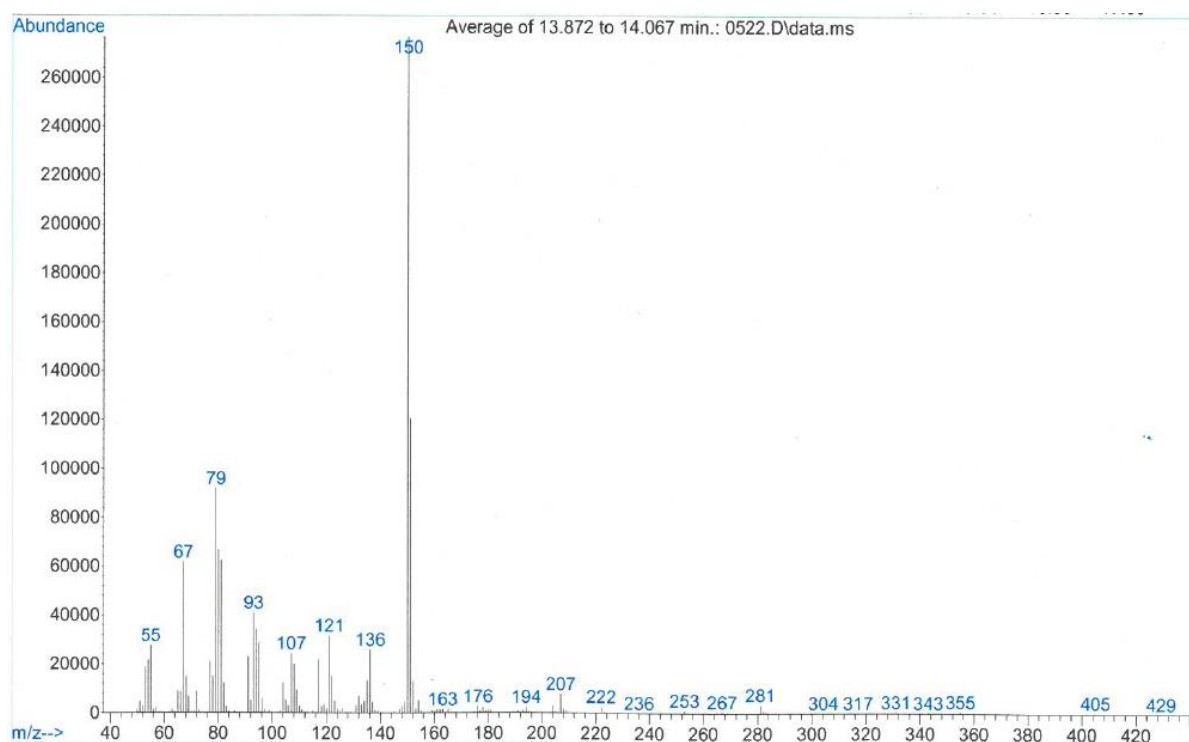
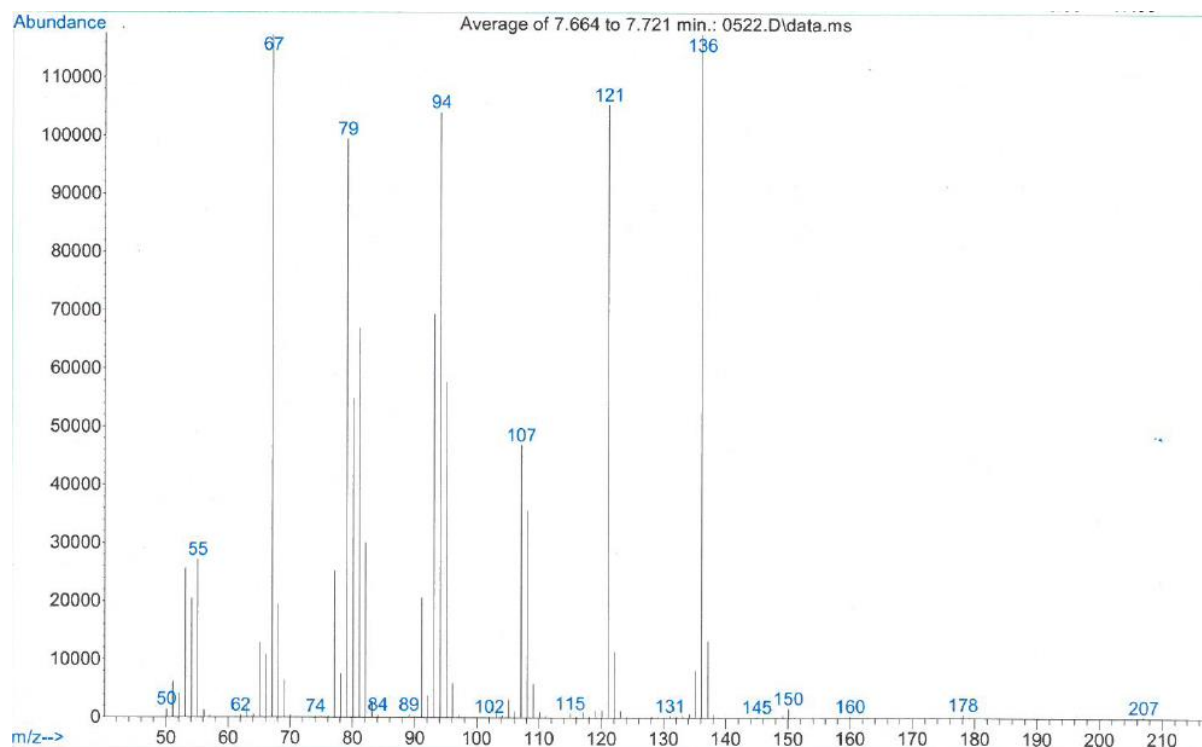




A4.5. GC-MS trace and spectra of compound **44**.

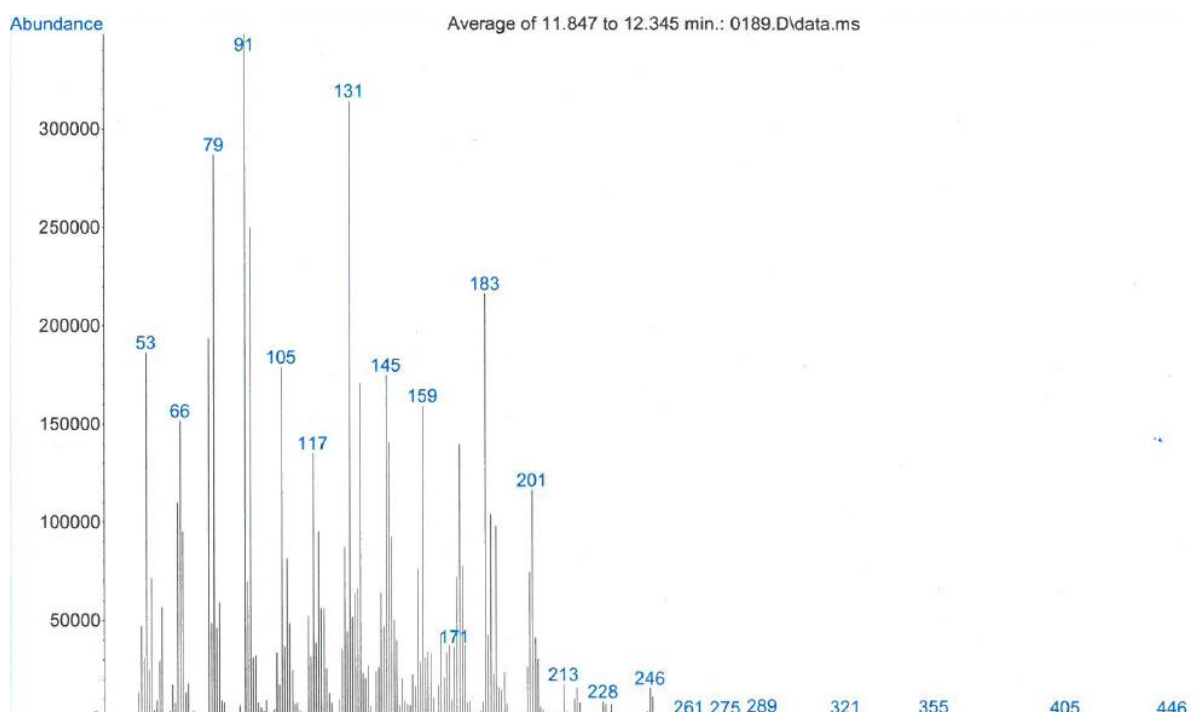
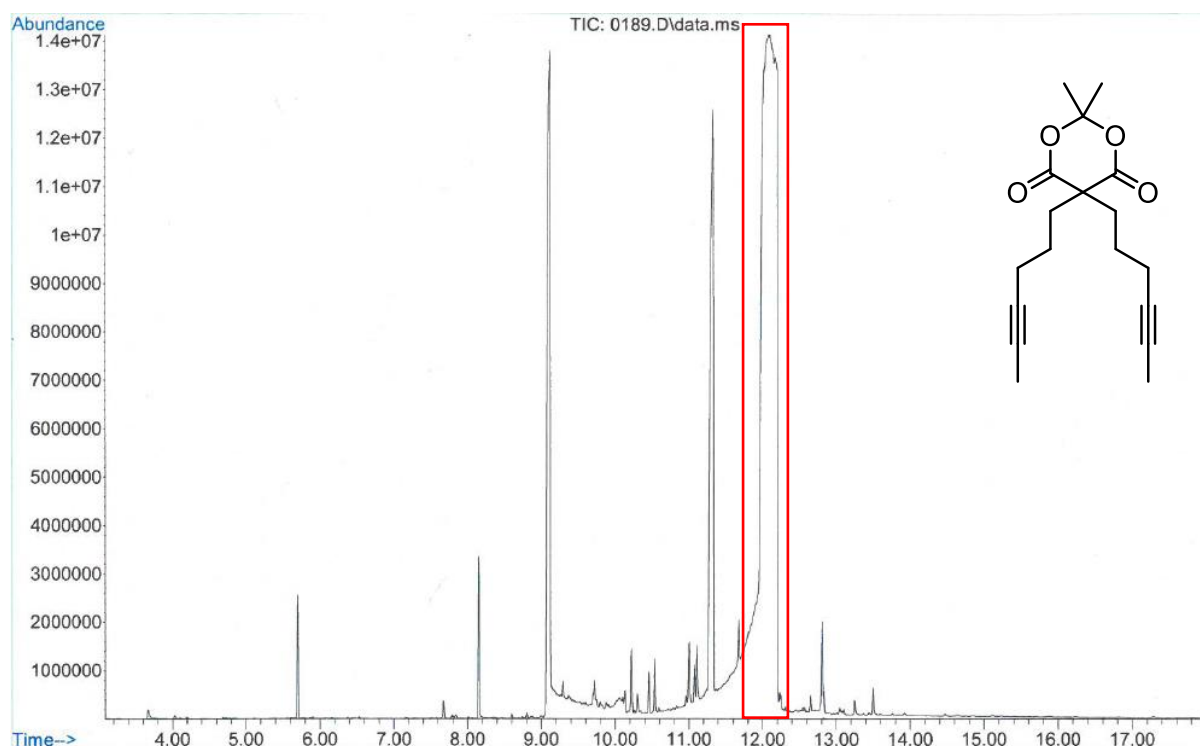
A4.6: GC-MS data of compound 45





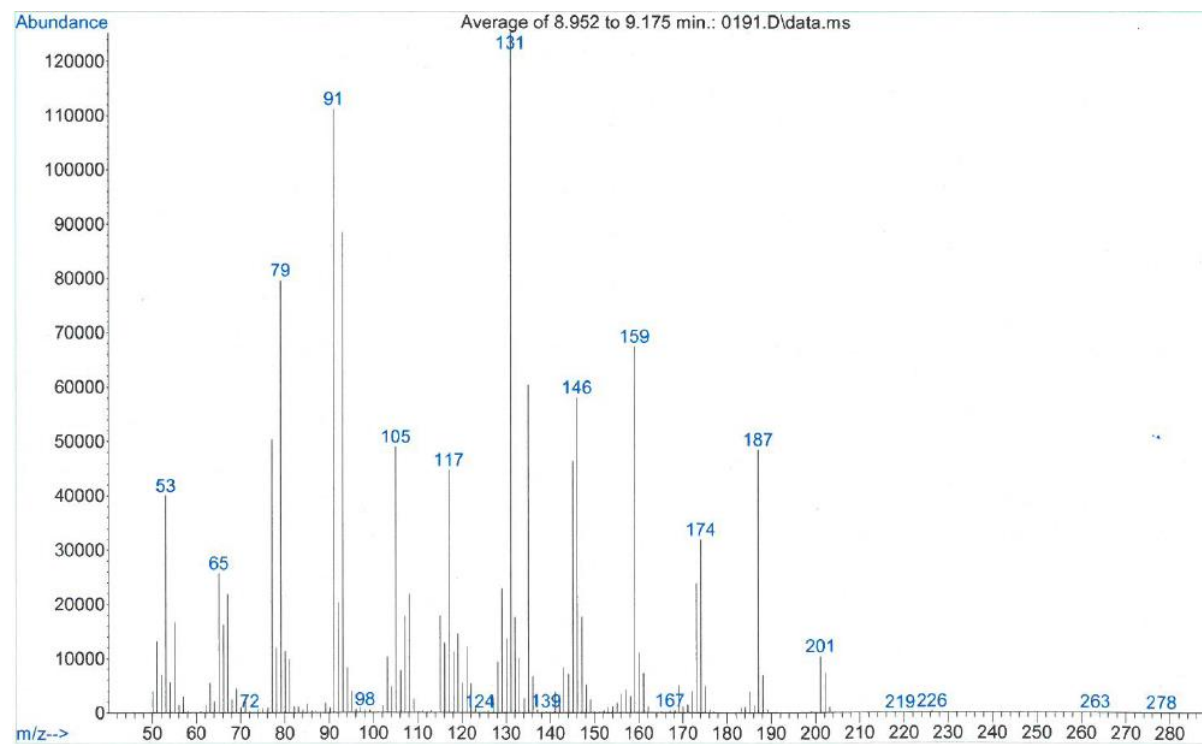
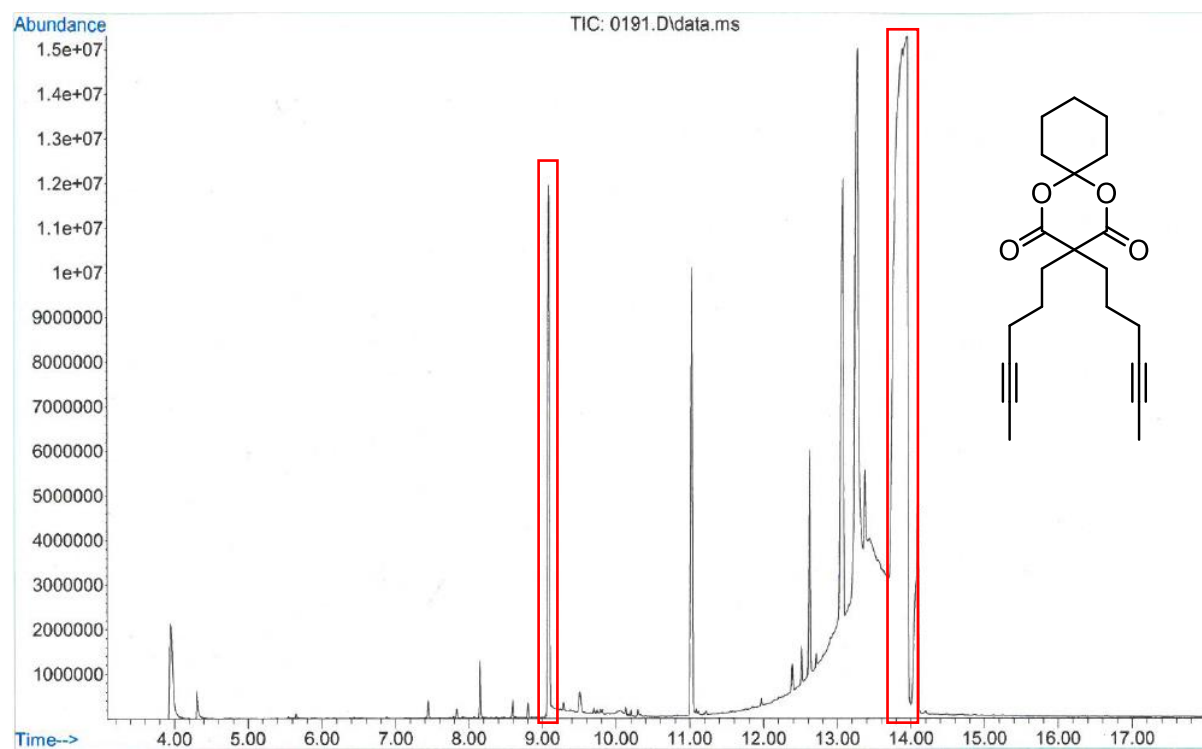
A4.6. GC-MS trace and spectra of compound **45**.

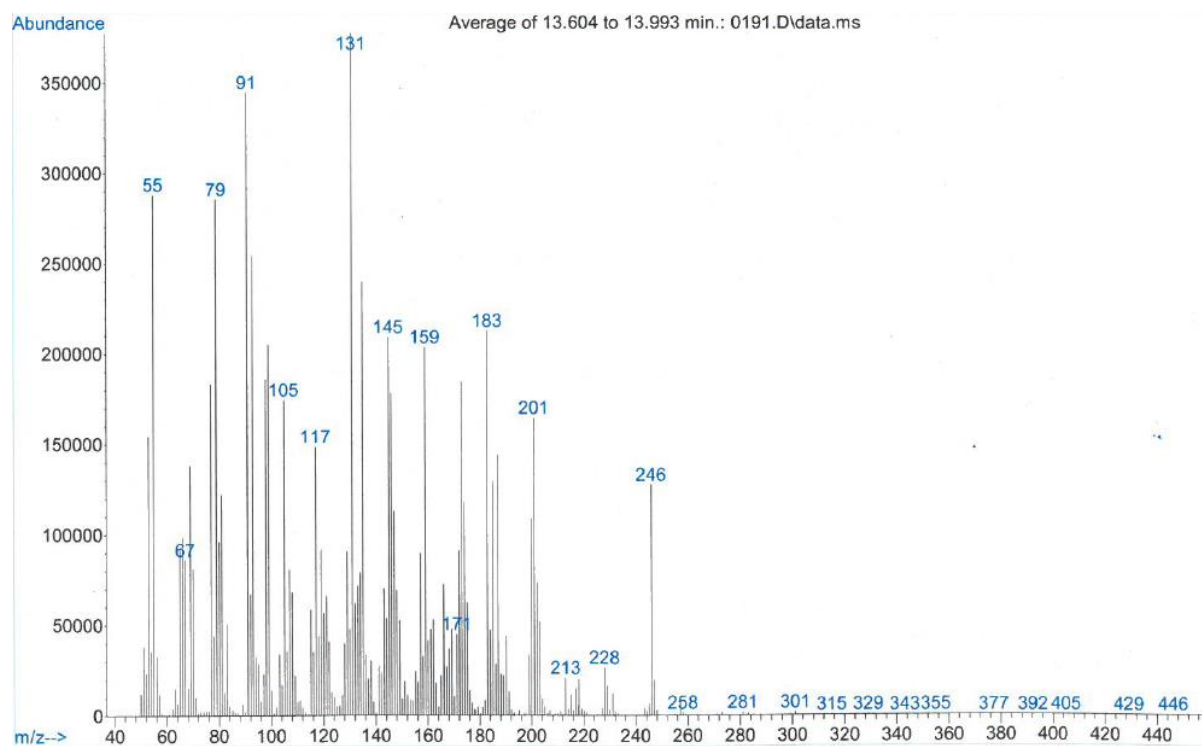
A4.7: GC-MS data of compound **53**



A4.7. GC-MS trace and spectra of compound **53**.

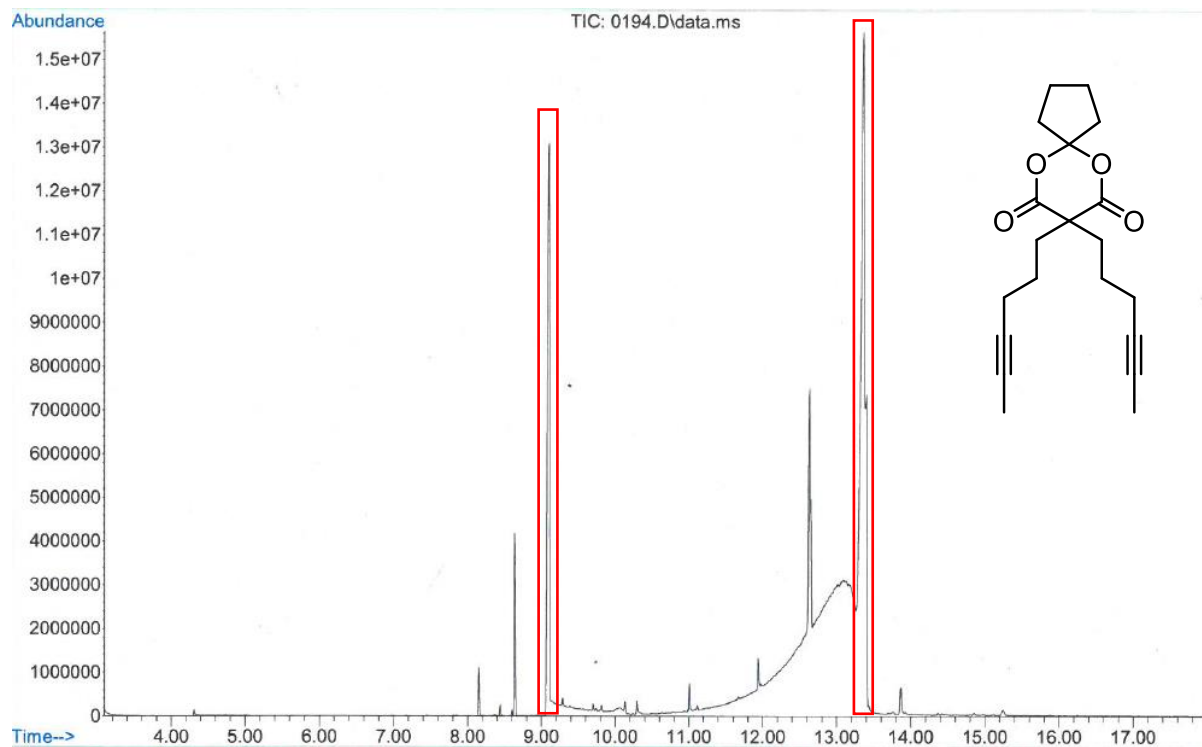
A4.8: GC-MS data of compound **54**

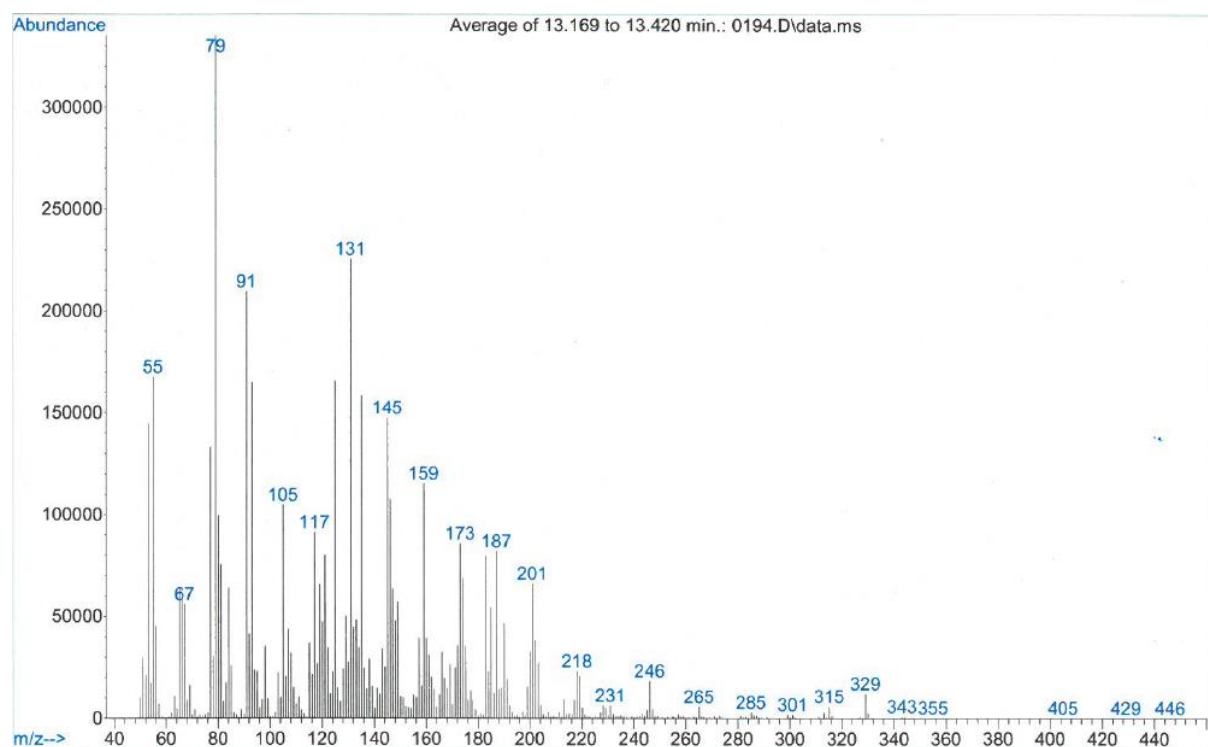
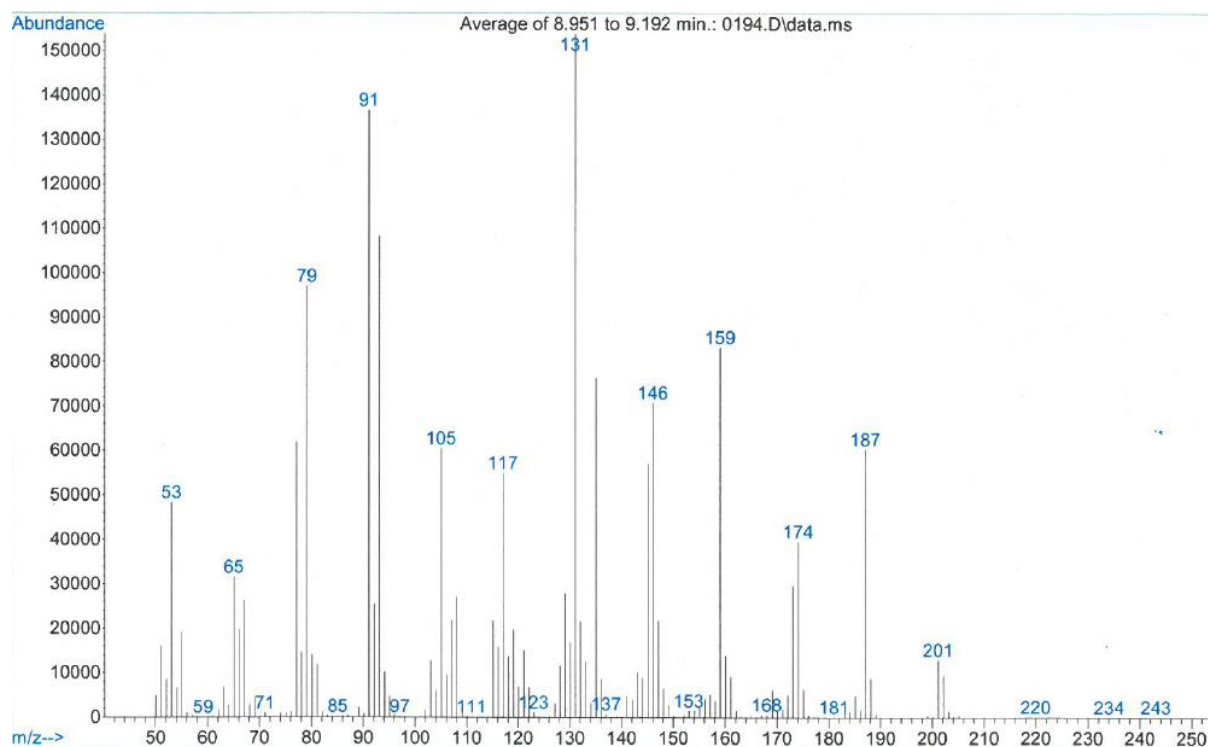




A4.8. GC-MS trace and spectra of compound **54**.

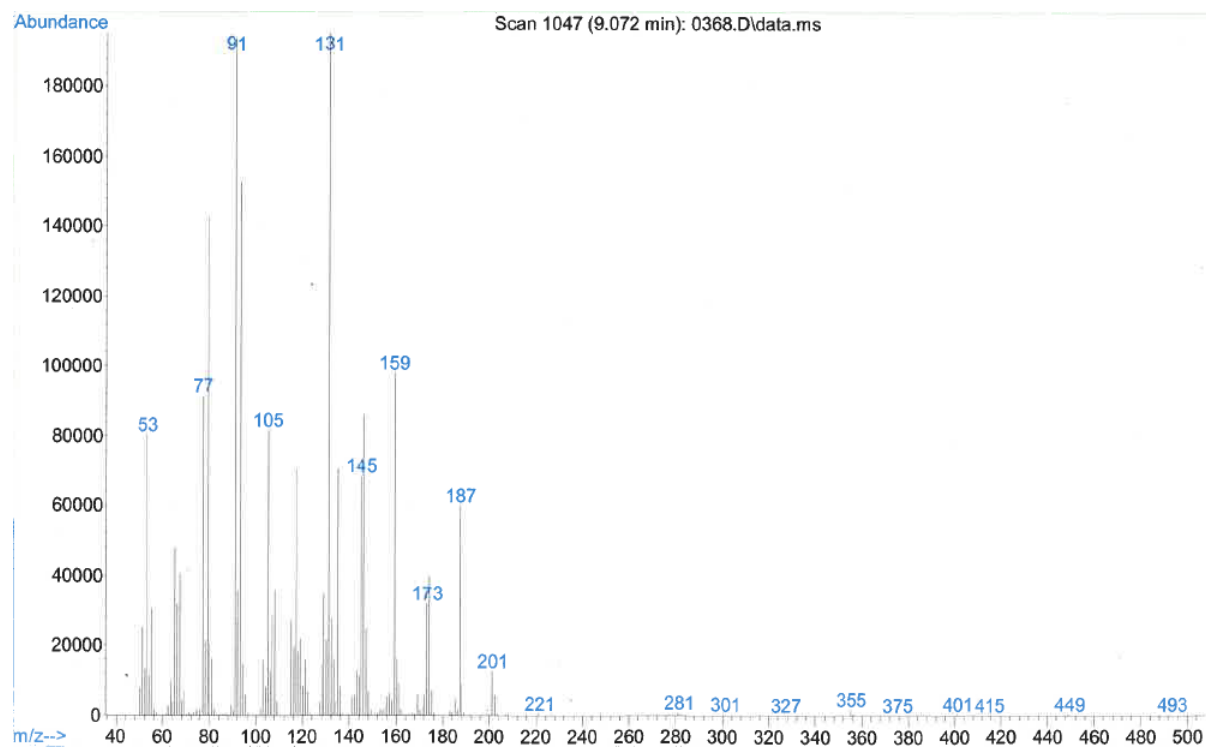
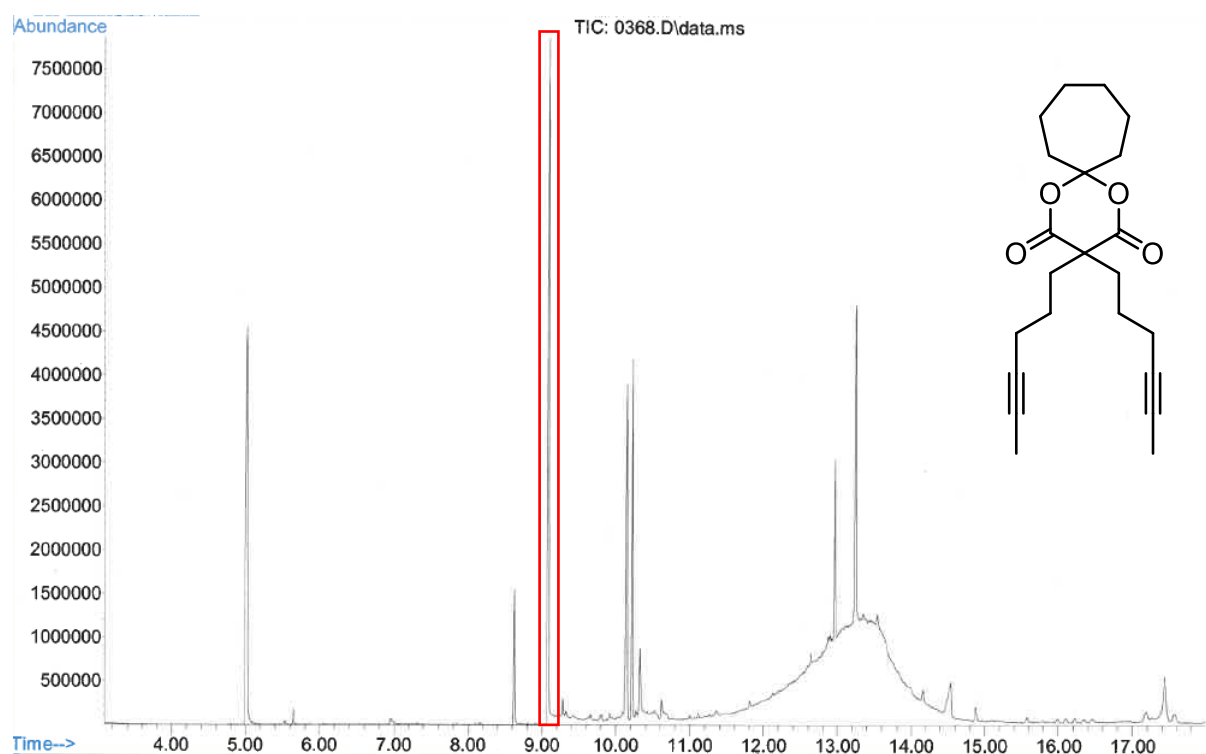
A4.9: GC-MS data of compound **55**





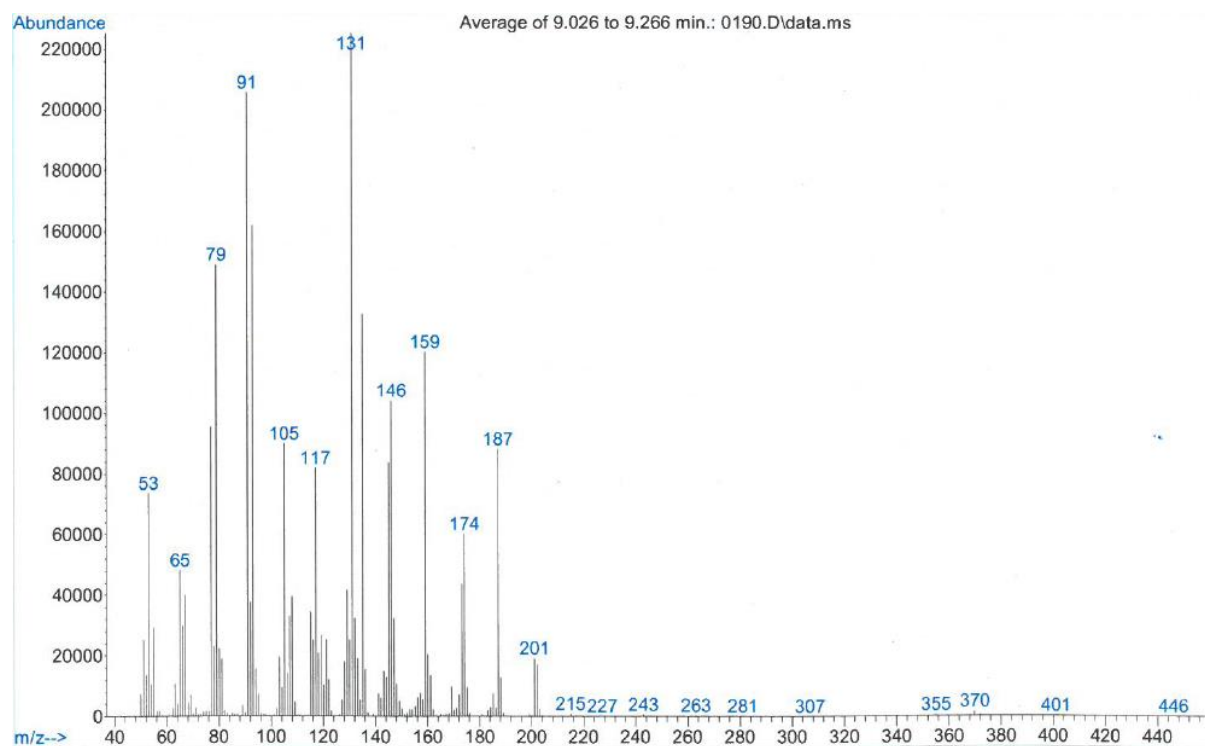
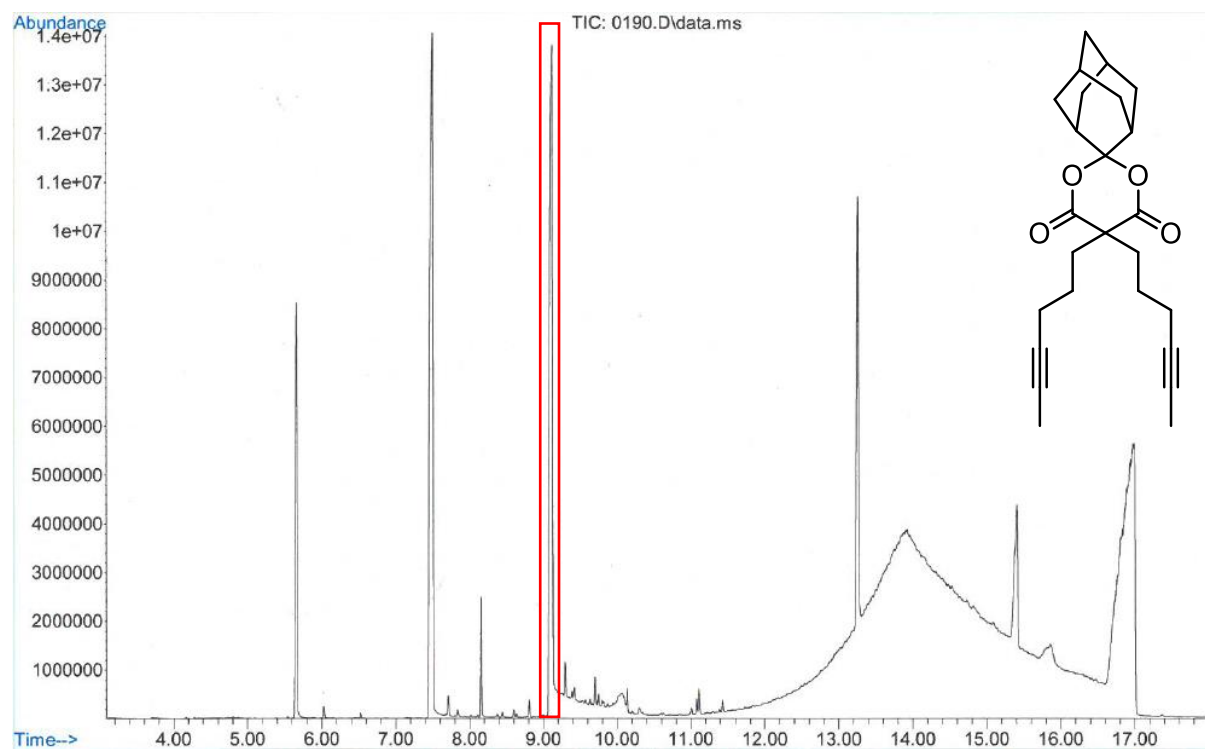
A4.9. GC-MS trace and spectra of compound 55.

A4.10: GC-MS data of compound **56**



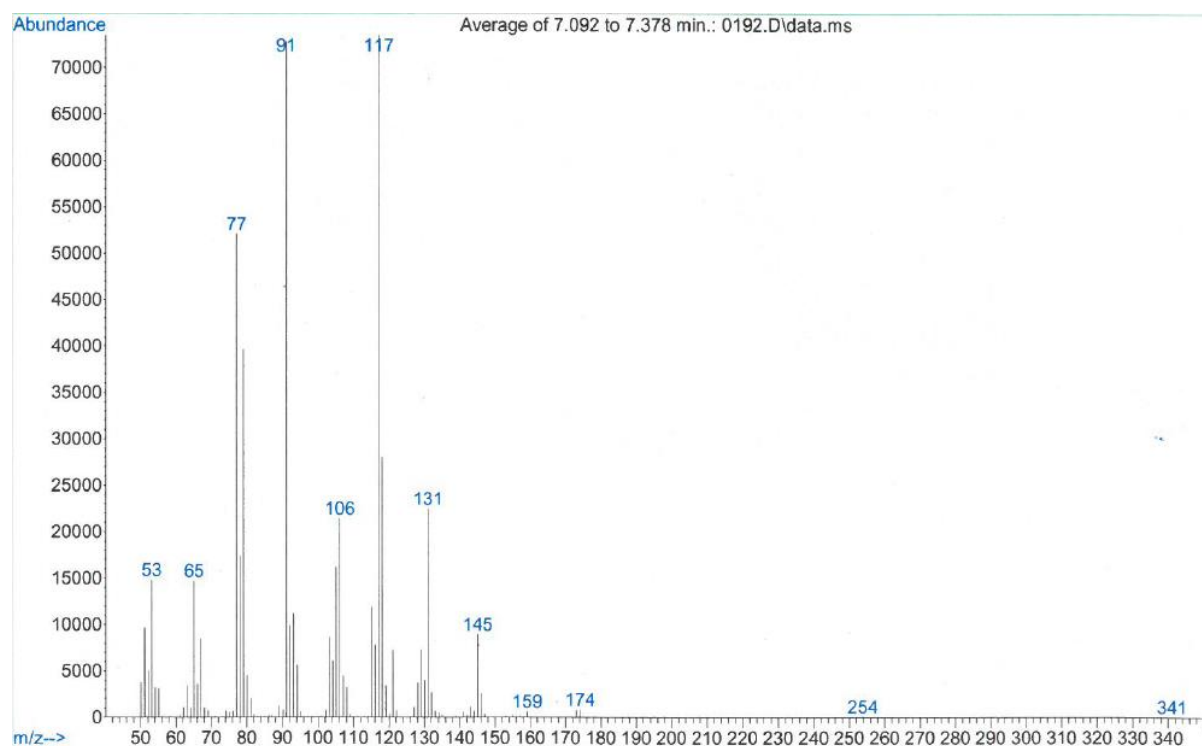
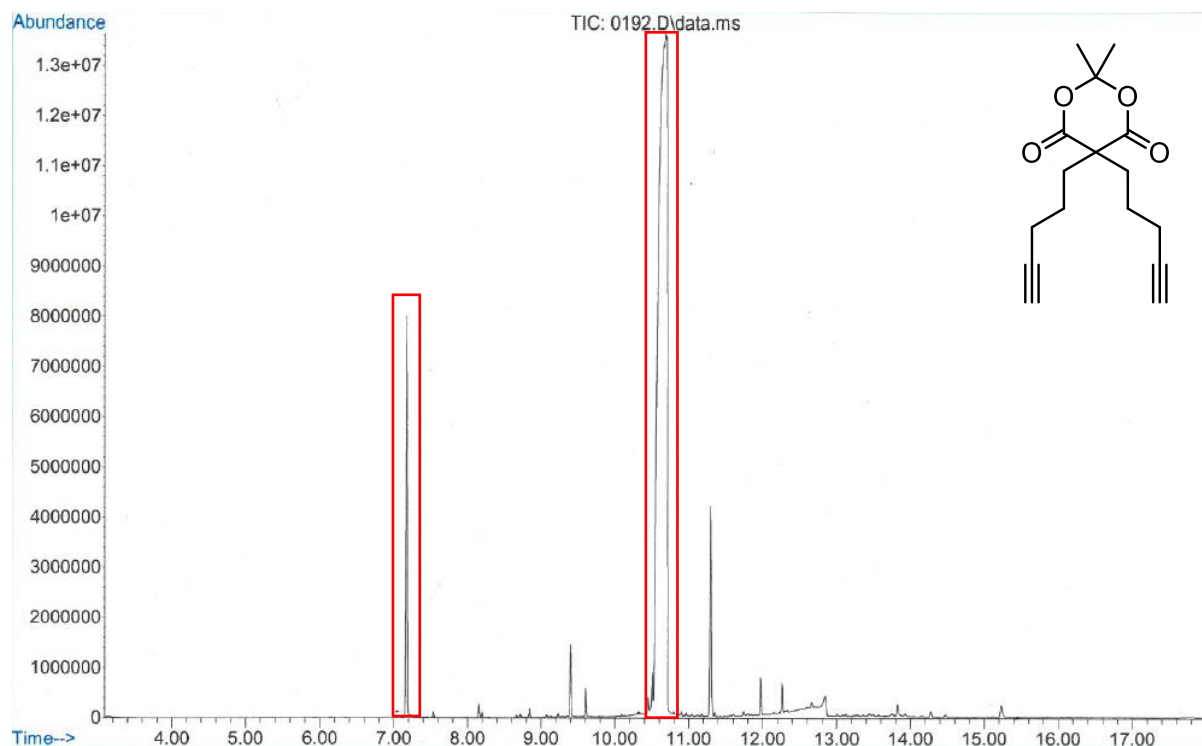
A4.10. GC-MS trace and spectra of compound **56**.

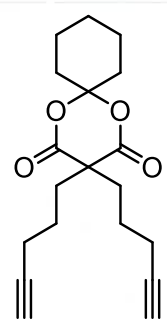
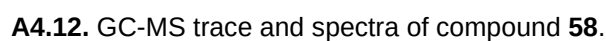
A4.11: GC-MS data of compound 57

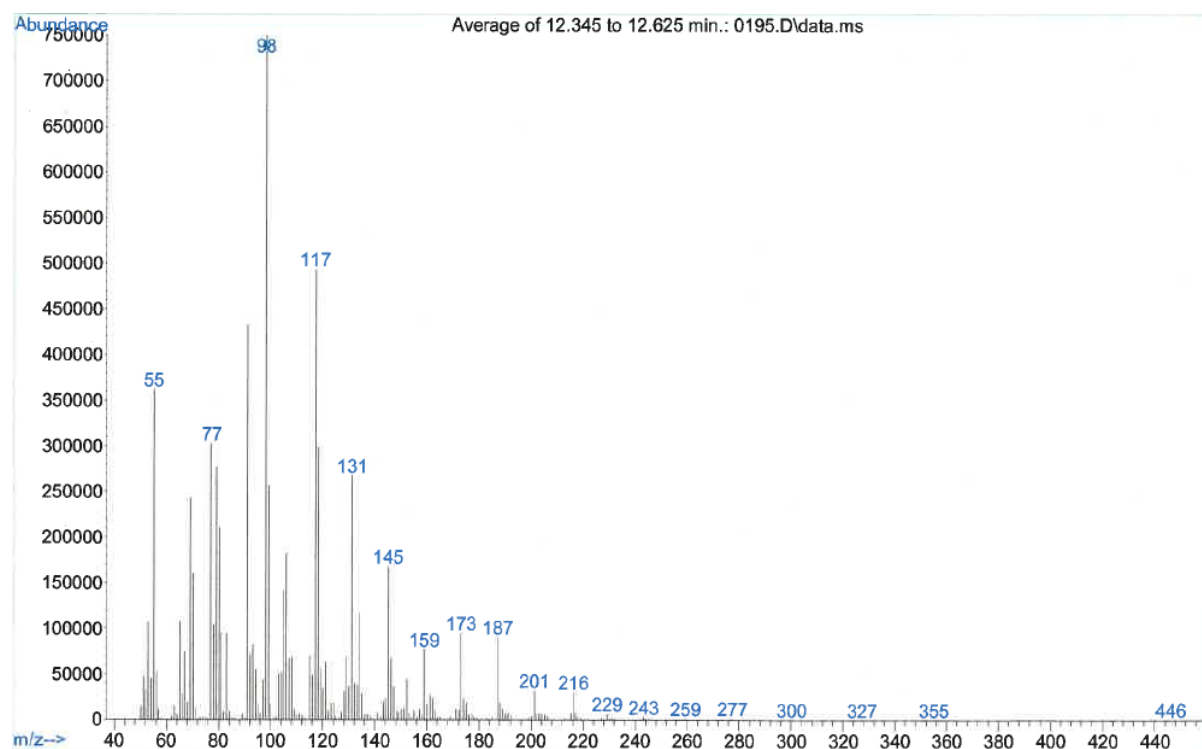
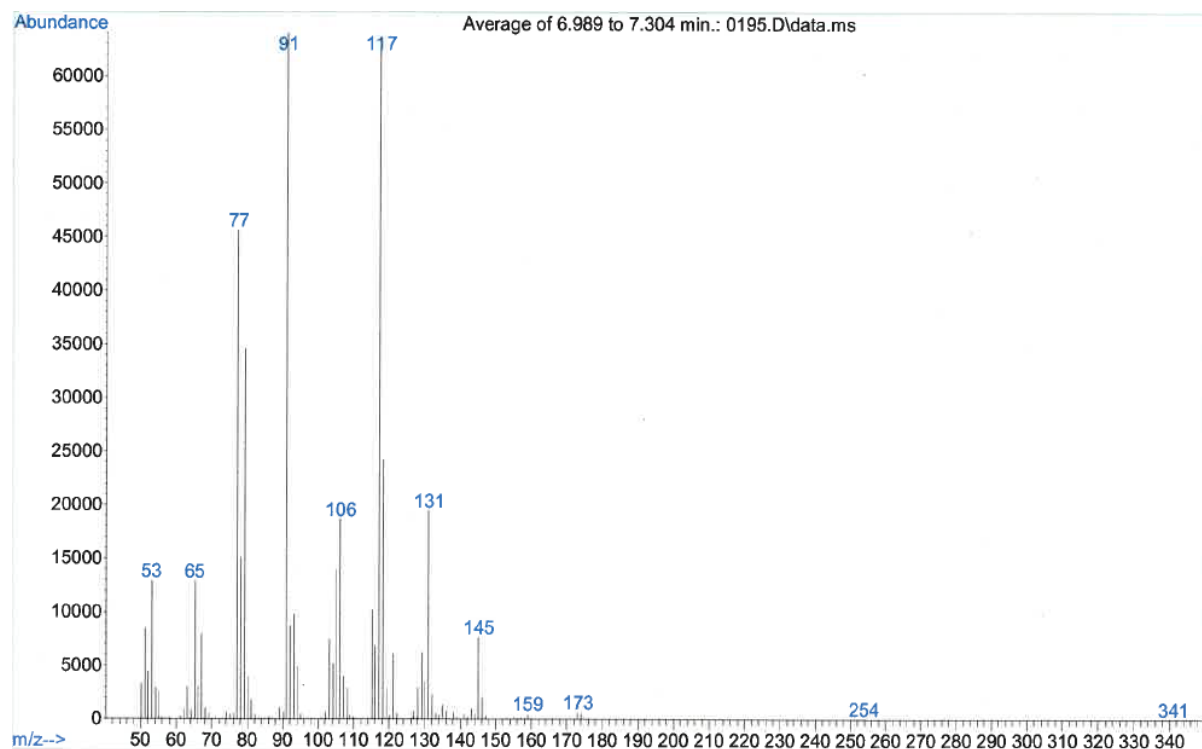


A4.11. GC-MS trace and spectra of compound 57.

A4.12: GC-MS data of compound **58**

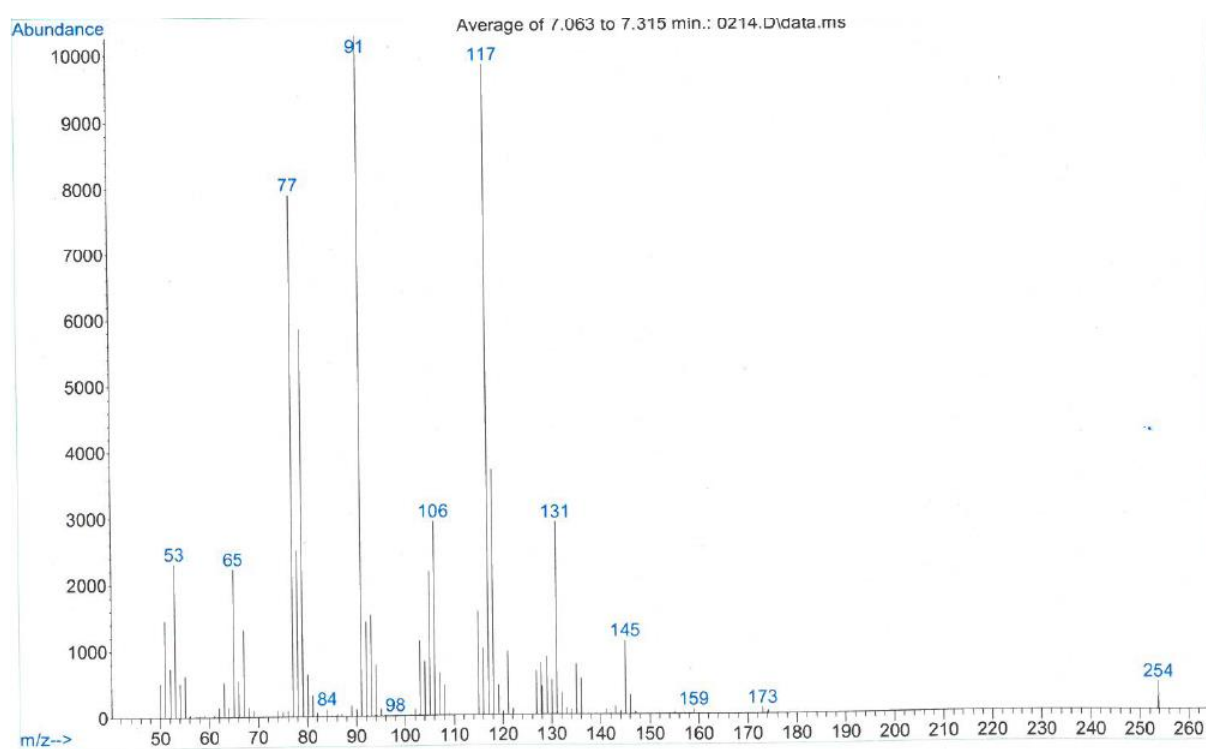
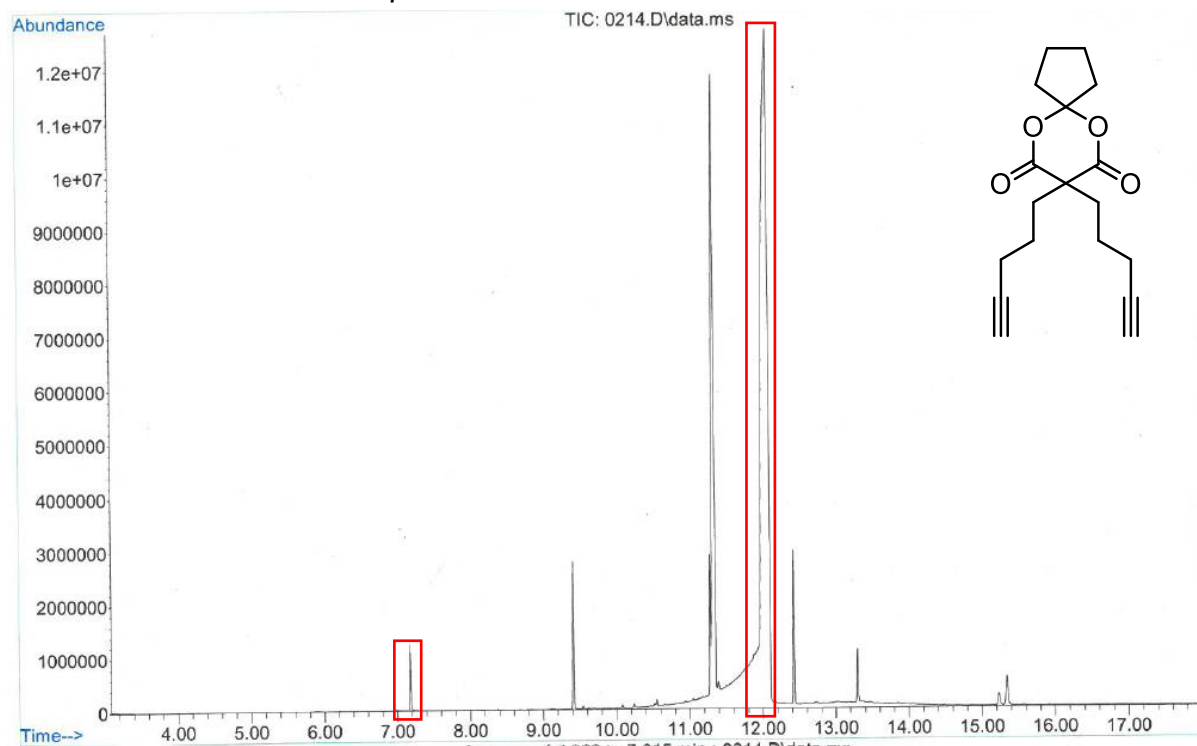


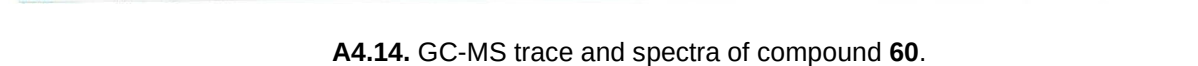




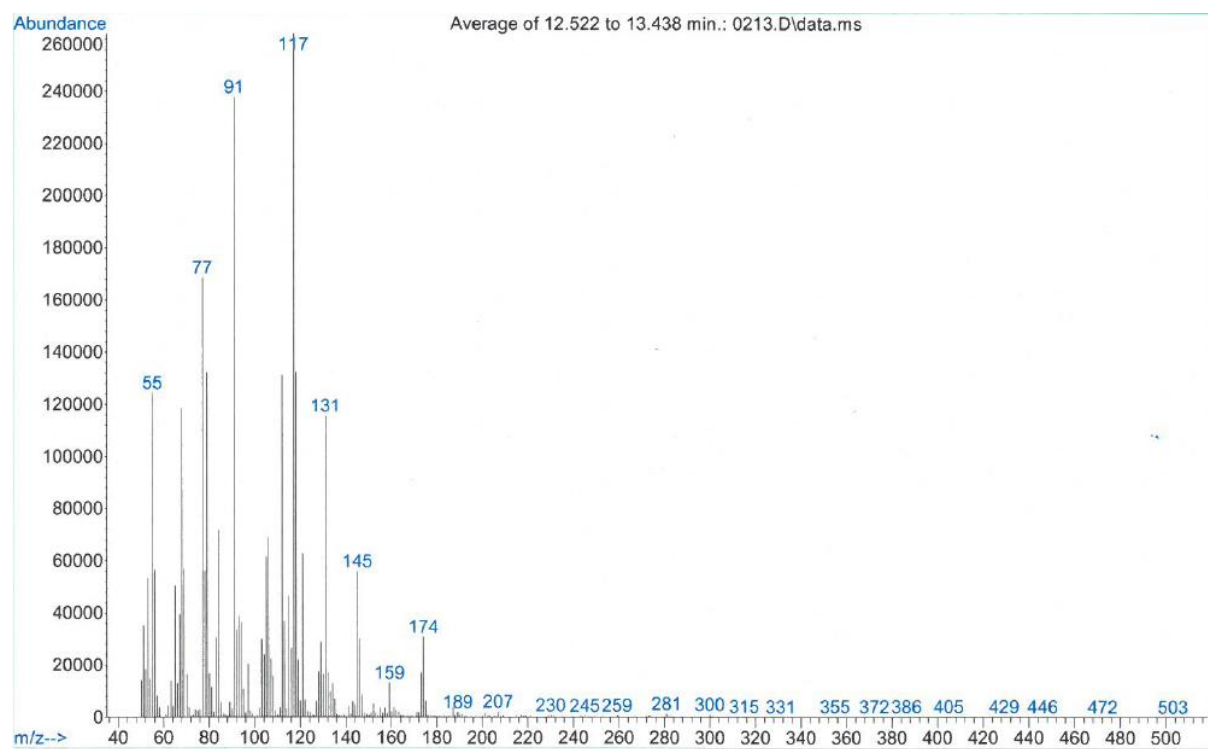
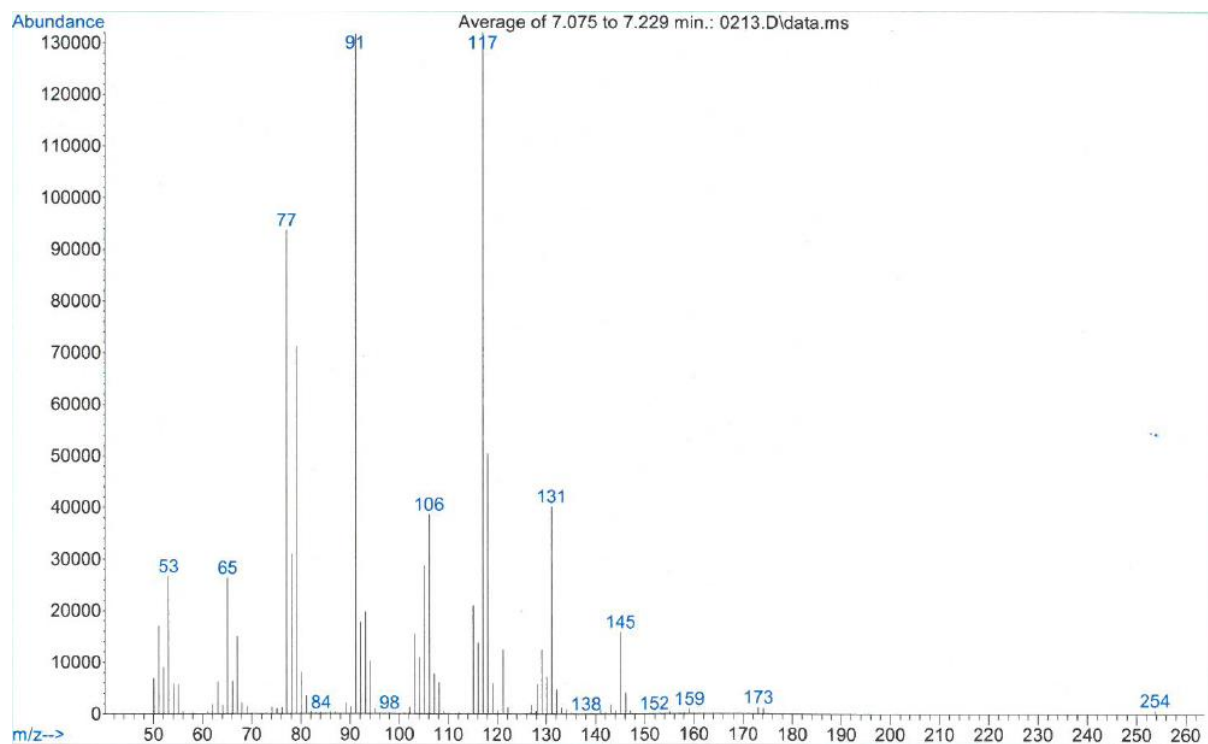
A4.13. GC-MS trace and spectra of compound **59**.

A4.14: GC-MS data of compound **60**



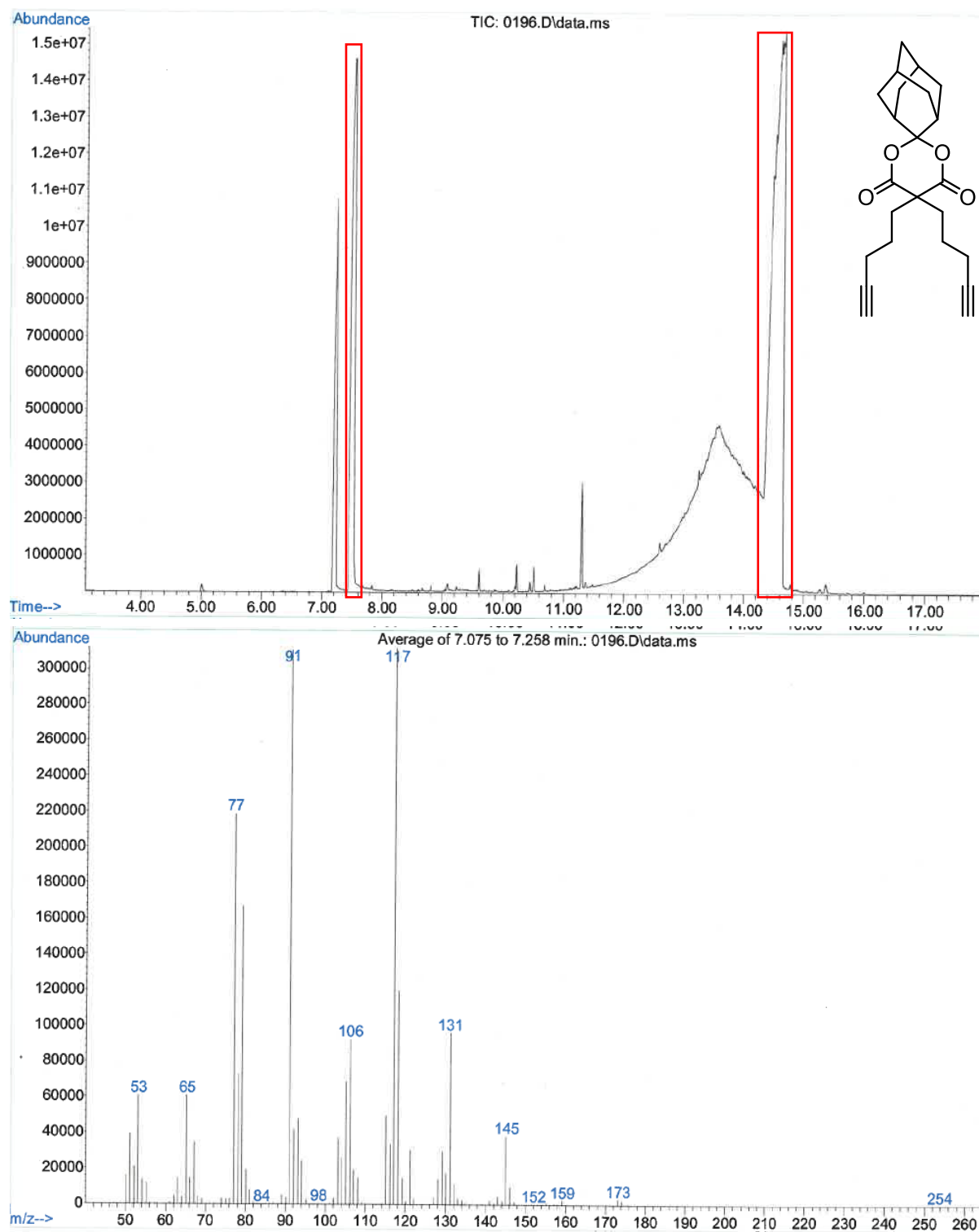


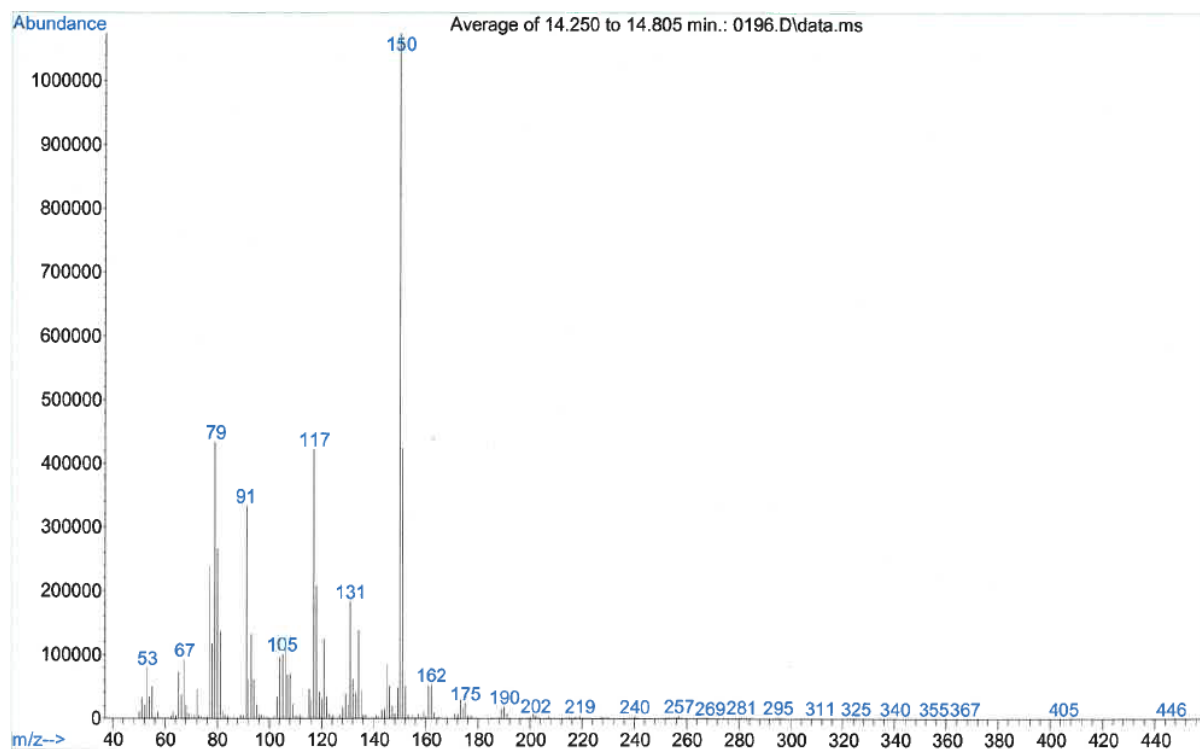
A4.14. GC-MS trace and spectra of compound 60.



A4.15. GC-MS trace and spectra of compound **61**.

A4.16: GC-MS data of compound **62**





A4.16. GC-MS trace and spectra of compound **62**.