Cascade Ring Expansion Reactions for Synthesis of Medium-Sized Rings and Macrocycles

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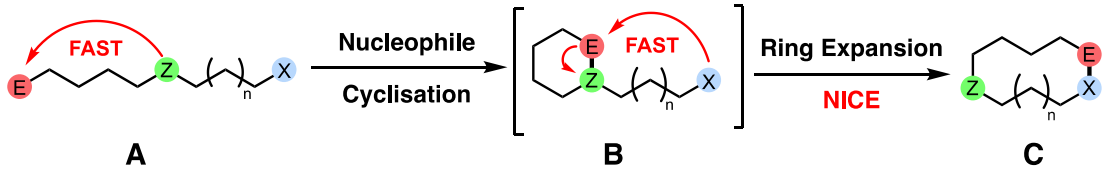
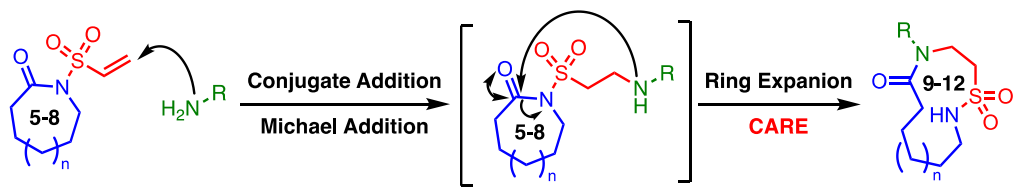
Abstract

This thesis describes research on the synthesis of medium-sized rings and macrocycles. The focus is on the development of two new synthetic concepts that make use of ring expansion reactions: nucleophile-induced cyclization/ring expansion (**NICE**) and conjugate addition ring expansion (**CARE**). Chapters 2–4 describe the development of **NICE** reactions. We explore the synthesis of linear precursors of the type **A** and their conversion into medium-sized rings and macrocycles **C** via cascade ring expansion reactions. Mechanistic studies using nuclear magnetic resonance and mass spectrometry were performed, along with control reactions to support the proposed mechanism. Additionally, there were instances where we isolated and characterised key intermediates (**B**) and by-products, especially when linear precursor components were varied. A general representation of the NICE concept is illustrated in the figure below, where E is an electrophilic component, Z is an internal nucleophile, and X is a terminal nucleophile.



This thesis also presents a new approach to creating heterocyclic-macrocyclic lactones and thioacetone through cyclizing linear precursors with multiple internal nucleophiles "Z". This is achieved through multi-internal cascade reactions of nucleophile ring expansion (double- and triple-NICE).

A new method to synthesise medium-sized ring and macrocyclic sulfonamides using **CARE** ring-expansion techniques is described in Chapter 5. These methods do not rely on traditional protecting groups, utilising amine conjugate addition instead to initiate the key ring expansion step. This approach produces various cyclic sulfonamides with excellent yields for various ring sizes and functionalisation options. The ring size dependency is consistent with computational chemistry models. CARE enables a new generation of compounds with potential antimicrobial activity to be prepared with ease.



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List of Abbreviations

Abbreviation	***Meaning***
Ac	Acetyl
AcOH	Acetic Acid
AIBN	Azobisisobutyronitrile
APCI	Atmospheric Pressure Chemical Ionization
approx.	Approximately
aq.	Aqueous
Ar	Aromatic
Bn	Benzyl
boc	*tert*-Butyloxycarbonyl
Boc_2O	Di-*tert*-butyl dicarbonate
BOP	Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
bp	Boiling Point
br	Broad
calcd.	Calculated
CARE	Conjugate Addition Ring Expansion
CCDC	Cambridge Crystallographic Data Centre
CDI	Carbonyl diimidazole
cm^{-1}	Wavenumber/Wavelength
cod	1,5-Cyclooctadiene
COSY	Correlated Spectroscopy
Cy	Tricyclohexylphosphine
Cy	Cyclohexyl
d	Doublet
D_2O	Deuterium Oxide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-Dicyclohexylcarbodiimide
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement by polarization
DIPEA	*N*,*N*-Diisopropylethylamine
DMA	Dimethylacetamide

DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
DBF	Dibenzofulvene
EDC.HCl	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
equiv.	Equivalents
ESI	Electrospray Ionisation
Et	Ethyl
Et_2O	Diethyl Ether
EtOAc	Ethyl acetate
FDA	Food and Drug Administration
Fm	9-Flurorenylmethyl
Fmoc	Fluorenylmethoxycarbonyl
g	Gram(s)
(g)	Gaseous
h	Hour(s)
HATU	Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium
HBA	Number of H-Bond Acceptors
HBD	Number of H-Bond Donors
HMBC	Heteronuclear Multiple Bond Correlation
HOAt	1-Hydroxy-7-azabenzotriazole
HOBt	1-Hydroxybenzotriazole hydrate
HRMS	High resolution Mass Spectroscopy
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
^{i}Pr	*iso*-Propyl
IR	Infra-red
IUPAC	International Union of Pure and Applied Chemistry
J	Coupling constant (Hz)
K	Kelvin
KHMDS	Potassium bis(trimethylsilyl)amide
L	Ligand
LHMDS	Lithium bis(trimethylsilyl)amide
LLAMA	Lead-Likeness and Molecular Analysis

$logP_{oct}$	Log of octanol-water partition coefficient
M	Molar
m	Multiplet
m/z	Mass to charge ratio
Me	Methyl
MeMgBr	Methylmagnesium bromide
MeOH	Methanol
Mes	Mesitylene or 1,3,5-trimethylbenzene
mg	milligram(s)
MHz	Megahertz
min	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
mol	Mole(s)
$[M]^+$	Molecular Ion
MOM	methoxymethyl
mp	melting point
Ms	Mesyl
MW	Molecular Weight
n-BuLi	*n*-Butyllithium
NaBARF	Sodium tetrakis[3,5-is(trifluoromethyl)phenyl]borate
NBS	*N*-bromosuccinimide
NGP	Neighbouring group participation
^{n}Bu	*n*-Butyl
NEt_3	Triethylamine
NICE	Nucleophile-Inducing Cyclization/ring Expansion
NRB	Number of Rotatable Bonds
Ph	Phenyl
PP2A	Protein phosphatase 2 A
4-PPY	4-Pyrrolidinylpyridine
ppm	Parts per million
PSA	Polar Surface Area
Pyr	Pyridine
Pyry-BF_4	Pyrylium-Tetrafluoroborate
q	Quartet

RCM	Ring closing metathesis
R_f	Retention Factor
ROCK	Rho-associated protein kinase
ROM	Ring-Opening Metathesis
ROS1	ROS Proto-Oncogene 1, Receptor Tyrosine Kinase
RT	Room Temperature
sat.	Saturated
sec	Second(s)
SET	Single Electron Transfer
S_NAr	Nucleophilic Aromatic Substitution
STAB	Sodium Triacetoxyborohydride
SuRE	Successive Ring Expansion
t	Triplet
T3P	Propylphosphonic anhydride
TBAF	Tetra-*n*-Butylammonium Fluoride
TBAI	Tetrabutylammonium iodide
TBS	*tert*-Butyl dimethyl silyl
TBTU	Hexafluorophosphate benzotriazole tetramethyl uronium
^{t}Bu	*tert*-Butyl
TCBC	2,4,6-Trichlorobenzoyl Chloride
TCDI	Thiocarbonyl diimidazole
td	Triplet of doublets
Tf	Triflyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyranyl ethers
TNT	Trinitrotoluene
TLC	Thin Layer Chromatography
DFT	Density Functional Theory
Trt	Trityl
UV	Ultra-Violet
XRD	X-ray diffraction
Zn–Cu	Zinc–Copper Couple
Δ	Heat
δ	Chemical Shift
µL	Microlitre(s)

µmol	Micromole(s)
ν_{max}	IR absorption maxima

Acknowledgements

The road to completing my PhD has not been easy; for this, I acknowledge the people who have helped me along the way. I begin by extending my eternal gratitude to my father, who has provided or set me on the path for every opportunity that I have been afforded. It has been through him that I owe my education, and the love and care he has fostered have been precious. Next, I thank my supervisor, Dr William Unsworth, who has provided endless guidance and inspiration, all while enduring the late-night emails and impromptu office drop-ins; his experience and knowledge have been invaluable. This support has extended past my research activities to offer encouragement during the most uncertain time in my life. During the final year of my research, the war in my home country of Ukraine began and gave me the ultimate challenge that I faced in the four years of my program. Following this, I owe great thanks to Dr Tony Wild, who funded the final year of my program through the Wild Fund scholarship. The aid provided vital stability in a time of great insecurity and removed one less burden from my situation. I want to thank my colleagues in the University of York Department of Chemistry, who ensure the exceptional functionality of laboratories and facilities. I also want express particular gratitude to Dr Adrian C. Whitwood and his world-class X-ray crystallography service.

Authors Declaration

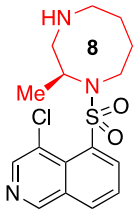
I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for a degree or other qualification at the University of York or any other university elsewhere. All sources are acknowledged as references accordingly.

Illya Zalessky

Chapter 1: Introduction

1.1.0 Applications of medium-sized rings and macrocycles

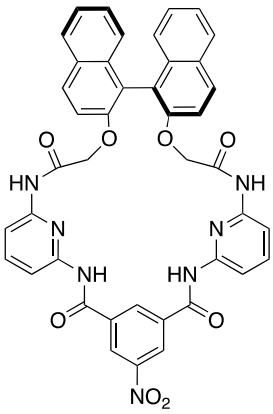
Medium-sized rings (8–11 membered)[1,2] and macrocycles (12+ membered rings)[2] are important in a wide range of physical, biological and chemical fields of science. They have found important uses in an extensive range of applications, for example, in catalysis,[3] nanoscale technology (e.g., as switchable devices)[4,5] and in mechanically interlocked molecules like rotaxanes and catenanes, that are key parts of so-called 'molecular machines".[6] Arguably, the most valuable usage of medium-sized rings and macrocycles is in medicinal chemistry [7,8,9,10] including use as marketed medicines (**Fig. 1.1.1**).[11,12]



1

Figure 1.1.1 H-0106 (**1**) drug possesses a medium-sized ring structure, is Rho-kinase (ROCK) protein inhibitor[13]

Molecules containing medium-sized rings and macrocycles are therefore in high demand and are routinely used in real-world applications (**Fig. 1.1.2**). As a result, this encourages synthetic chemists to seek novel methods to synthesize them. However, both macrocycles and medium-sized rings can be challenging synthetic targets, with the challenges associated with their described in more detail in **section 1.4.0**.



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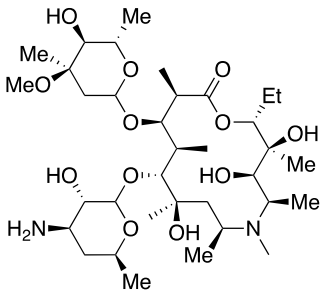
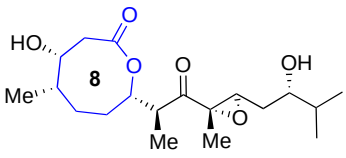


3

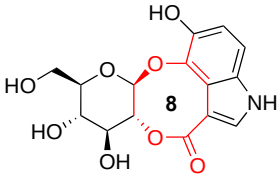
Figure 1.1.2 Shows an example of two macrocycles, the first one is **2** used as an NMR chiral shift reagent, and Azithromycin **3** is an antibiotic against bacterial infections used by the National Health Service (NHS)[14,15]

1.2.0 Medium-Sized Ring and Macrocycles in Natural Product and Medicinal Chemistry

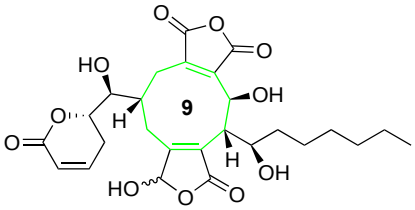
8-Membered and 9-membered ring cores are prevalent in natural products (e.g., **3** - **5 Fig. 1.2.1**),[14,16,17,18] found in plants [19,20] and marine organisms,[21] and are more common than related 10- and 11-membered ring variants.



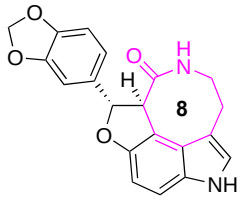
Octalactin A (**3**) – Anticancer properties against B–16–F10 murine melanoma and HCT-116 human colon tumour.[16]



(-)–Ovatolide (**4**) – Natural product used as "laxative, febrifuge and astringent".[21]



Rubratoxin A (**5**) – Protein phosphatase 2 (PP2A) an enzyme inhibitor active against primary and metastatic tumours.[20]



(+)–Decursivine (**6**) is a natural indole alkaloid used as an antimalarial drug.[23]

Figure 1.2.1 Shows structures of bioactive medium-sized rings

Macrocycles are also commonly found in natural products, with many macrocyclic natural products and/or derivatized synthetic analogues used as marketed drugs, approved by the Food and Drug Administration (FDA) (for example **7** and **8 in Fig. 1.2.2**).[22] In total, 68 macrocyclic drugs have made it to the market, with an additional 35 currently in clinical trials (**Fig. 1.2.3**).[23,24,30]

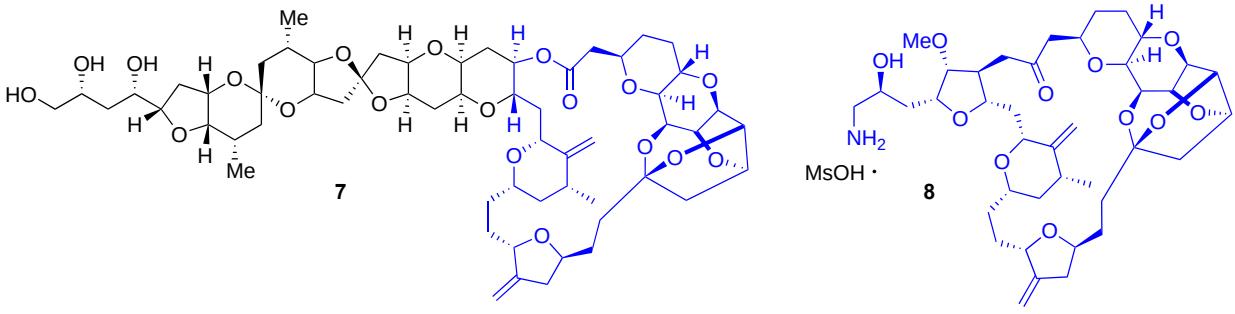
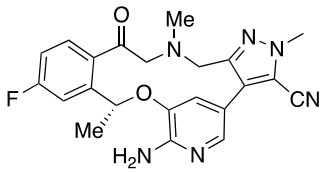


Figure 1.2.2 Halichondrin B (**7**) is a bioactive natural product (extracted from a marine sponge)[25] that shows "antitumor activity".[26] Eribulin Mesylate (**8**) is a "structurally simplified" ketone analogue of Halichondrin B (**7**), used predominately against "metastatic breast cancer".[25] Both of these macrocyclic drugs were approved in 2010 by FDA



9

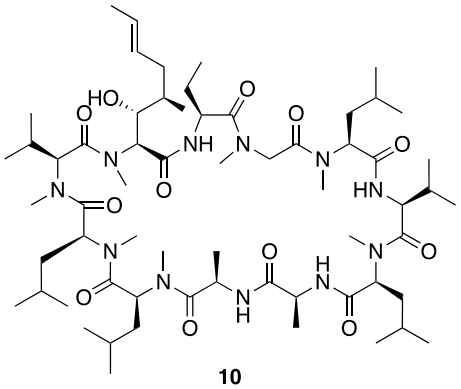
Figure 1.2.3 Structure of Larlatinib bioactive macrocycle **9**, an inhibitor for anaplsatic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1).[27] Current undergoing clinical Phase I / II trial under Pfizer Inc.[22]

Macrocyclic drugs can be divided into two major classes; peptidic and nonpeptidic.[28] The peptidic and nonpeptidic classes can be further split into the sub-classes of synthetic and natural product derived. But by far the most common class used in drug discovery programmes are peptidic macrocycles.[29] There are 30 macrocyclic drugs that are peptide-based on the market today. These peptide based macrocycles structures can mimic larger peptidic fragment (e.g., small proteins, <50 amino acids).[30,31] and are especially interesting in the context of the inhibition of protein-protein interaction (PPIs).[32,33] There is also much current focus in the pharmaceutical industry on designing and developing new therapeutic drug molecules that look like natural products, so-called “biology-oriented synthesis”.[34] It is estimated that around 40% of drugs which made it to the final stage of trials are “either natural products or a synthetic substance inspired by them” during the last 30 years.[35,36] The biology-oriented synthesis method helped to promote and boost the interest in synthesis and developing the screening libraries of medium-sized rings for medicinal applications.[37]

There are several reasons why medium-sized and macrocycles rings are attractive in medicinal chemistry compared to normal-sized rings (5–7 membered) and linear analogues. These reasons include their increased conformational diversity, greater flexibility (e.g., increasing number of rotatable bonds)[38] and greater ability to occupy diverse regions of three-dimensional (3D) chemical space [39](mimicking natural product-like physical features). As the number of conformations that cyclic molecules can adopt increases,[38] this can potentially increase the chance of achieving useful binding affinity and selectivity to the biological target.[140,38]

The conformation constraints of placing atoms in a large ring can also enhance oral bioavailability and membrane permeability.[9] But notably, the vast majority of medium-sized rings and macrocycles do not obey Lipinski’s rule of five, and therefore, may be predicted to not be unsuitable “drug-like” molecules in terms of their oral bioavailability, due to their physical

and chemical properties (e.g. high molecule weight, *log*P_{oct}, number of H bond donors/acceptors etc.) [40,41,42,43] However, some macrocycles like cyclosporin A (**10**, **Fig. 1.2.4**), which clearly don't follow the rule of five (RO5, **Table 1.2.5**).[37,38,39,40] But they still show oral absorptivity. In this case, **10** is widely used as immunosuppressant medicine during organ transplantation, where the drug is delivered orally or intravenously.[44]



10

Figure 1.2.4 Structure of bioactive macrocyclic of **10** Cyclosporin A

	MW[a] *(DA)*	*HBD*[b] *(no units)*	*HBA*[c] *(no units)*	*clog*P_{oct}[d] *(no units)*	*NRB*[e] *(no units)*	*PSA*[f] *(Å)*^{2}
*Cyclosporin A (**10**)*	1202	5	11	6.92	15	279
Lipinski's Threshold Values	< 500	≤ 5	≤ 10	≤ 5	≤ 10	≤ 140
Does it meet criteria?	No	Yes	No	No	No	No

Table 1.2.5 Showing physical parameter and experimental data for Cyclosporin A (**10**); Molecular Weight in Daltons (MW)[a 45], Number of H-bond Donors (N-H and O-H bonds / HBD)[b 45], Number of H-bond Acceptors (N and O atoms / HBA)[c], Octanol/Water Partition Coefficient (clogP_{oct})[d 46] and Number of Rotatable Bonds (NRB)[e 42,43] and Polar Surface Area (PSA)[f, 42,43] against Lipinski's rule criteria for the orally-active drug [40,41]

One rationale for the good bioavailability and greater binding affinity of cyclosporin A (**10**) (and similarly for other macrocycles) is their conformational mobility (via transannular interactions) and ability to show Janus-like behaviour.[47] In simple terms, macrocycles can reveal hydrophilic (O-H and/or N-H) or lipophilic (^{i}Pr, alkyl, alkenyl) groups by folding inside out and back to

expose them on the outside,[47,48] allowing them to adjust their externally evident physicochemical characteristics depending in which environment it is placed.[48,49] Cyclosporin A in particular, can "hide" many of its 16 hydrogen bonds donors and acceptors when introduced to a hydrophobic environment (e.g., when at cell membrane)[50] (**Fig. 1.2.5**). As the result, this causes a reduction in the total polar surface area of the macrocycle and enhances membrane permeability.[47]

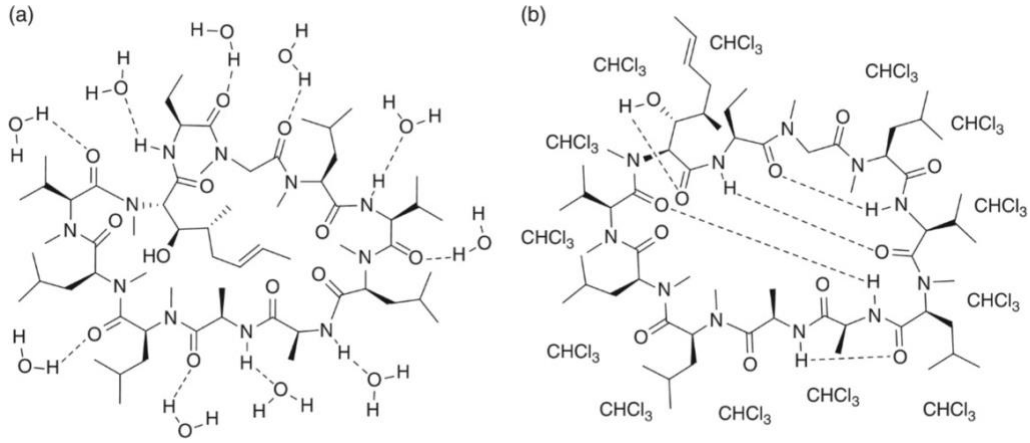


Figure 1.2.5 (a) Shows a schematic of the structural changes happening to cyclosporin A when solvated in a polar environment (i.e., water, DMSO), the dash lines indicating possible H-bond interaction with solvent molecules.[47] (b) Shows schematically conformational changes to the cyclosporine structure in a nonpolar environment (CH_2Cl_2, $CHCl_3$, *n*-hexane), highlighting how the macrocycle "hides" some of its hydrogen bond donors and acceptors thought intramolecular interactions. [47] The images were taken from Practical Medicinal Chemistry with Macrocycles Design edited by Mark L. Peterson[47,51]

Despite their advantages, macrocycles are still under-represented in most medicinal chemistry screening libraries used in bioassays.[52] One reason for this under-representation in the research and development sector is the inherent difficult of their synthesis.[53,54] Due to the pivotal role of chemical synthesis during the drug-discovery process, there is an understandable reluctance to work on macrocyclic ring systems, due to the current lack of reliable and scalable synthetic methods to make them.

1.3.0 Ring-closure approaches for the synthesis of medium-sized rings and macrocycles

The classical way to make medium-sized rings and macrocycles is via the direct end-to-end cyclization of a linear starting material (**Fig. 1.3.1**).[55] However, when the target ring is as large as eight, nine or more atoms, end-to-end cyclization is often not always efficient, with the unwanted formation of dimers, trimers, polymers etc. via intermolecular coupling often

outcompeting the desired intermolecular reaction. Common macrocyclization methods include macrolactamization and macrolactonizations.[128] However, macrocyclization by these methods is usually challenging, due to several thermodynamic factors such as the statistical improbability of the ends colliding, an overall net loss of entropy in the cyclization, and unfavorable transannular strain present in the cyclic products (and correspondingly the transition states needed to make them).[56]

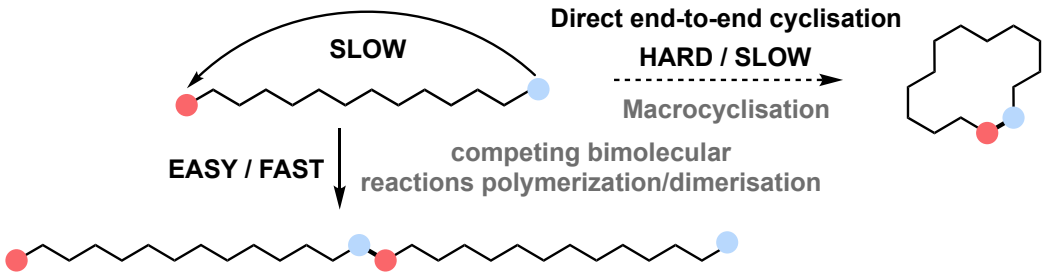
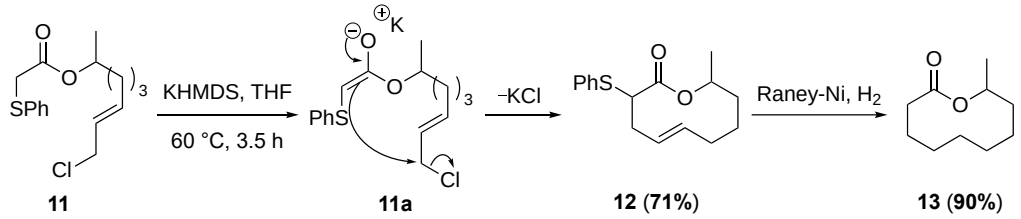


Figure 1.3.1 Graphical diagram illustrating the issues of end-to-end cyclization using long atom linear precursors to make a hypothetical macrocycle

When cyclization is relatively unfavorable, intermolecular coupling becomes a competing pathway, resulting in the unwanted formation of dimers, trimers, polymers etc. (**Fig. 1.3.1**).[57] To get around these unwanted intermolecular side reactions, various approaches have been developed. These include the use of high-dilution reactions (e.g., 0.0005 M or lower),[14] pseudo-high-dilution,[16] kinetic temptation (using metals such as K^+ or Na^+) and thermodynamic temptation.[17,18] However, these methods are often impractical on industrial and laboratory scales, or limited to narrow substrate classes.

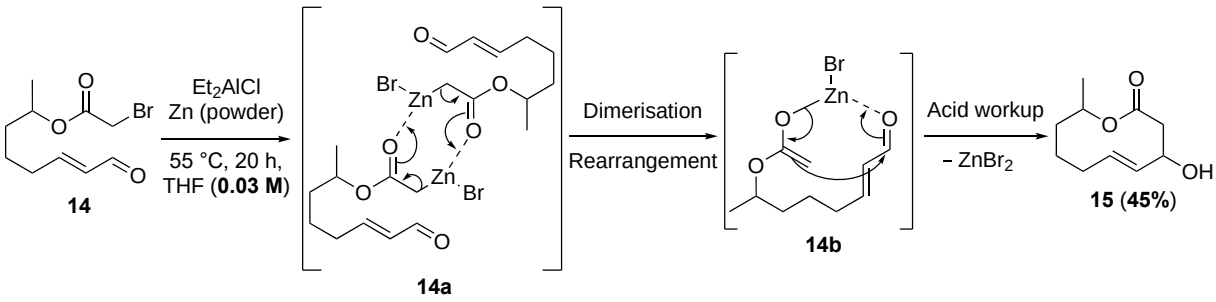
Despite the challenges, end-to-end macrocyclization approaches are still routinely used in natural product synthesis. Many different reaction approaches have been utilised (i.e., alkylation,[58] Reformatsky reactions, [59] Aldol condensation, McMurry coupling, [60] and many more) and have been used over several decades.[61] For example, cyclization via alkylation was performed by Tsuji and co-workers [62] in an elegant and simple reaction towards the total synthesis of the medium-sized ring (±)-phoracantholide. Thus, starting with alkyl chloride **11** (**Scheme 1.3.2**), its treatment with potassium hexamethyldisilazane (KHMDS, a strong non-nucleophilic base with $pK_a \approx 26$)[63] in THF, results in the formation of enolate **11a** (**Scheme 1.3.2**), which then undergoes cyclization with allyl chloride (anion stabilized) to give 10-membered lactone **12** in 71% yield (**Scheme 1.3.2**). The authors comment that cyclization is effective due to the presence of the *E*–double bond, that encourages the molecule to adopt a conformation favourable for cyclization.[62] The next steps in reduction double and

desulfurization of the SPh group using Raney nickel (Raney-Ni) to afford the natural product (±)-phoracantholide **13** in 90% yields.



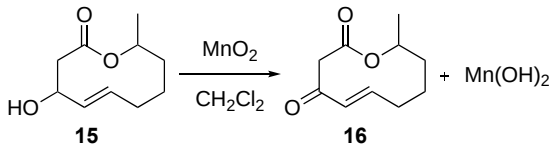
Scheme 1.3.2 Reaction scheme for forming natural product (±)–phoracantholide **13**, showing key enolate cyclization step

Similarly, Tsuji and Mandai have used the Reformatsky reaction to make (±)–diplodialide A and (±)–diplodialide B,[64] analogues to **13** shown in **Scheme 1.3.2**. After several reaction sequences, the authors arrive at the aldehyde precursor **14** and react it with Et_2AlCl and Zn-activated powder (**Scheme 1.3.3**). In this reaction, the Zn undergoes oxidative insertion into the carbon-bromide σ bond to form "Reformatsky enalote" **14a** that then undergoes dimerization/coordination and rearrangement to form *O*-zinc enolate **14b**, before reacting with aldehyde via an aldol reaction/cyclization through a Zimmerman–Traxler transition state.[65] Upon treatment with a mild acid, (±)–diplodialide B (**15**) is afforded in 45% yield; notably however, a relatively dilute **0.03 M** concentration is required to form this medium sized ring.



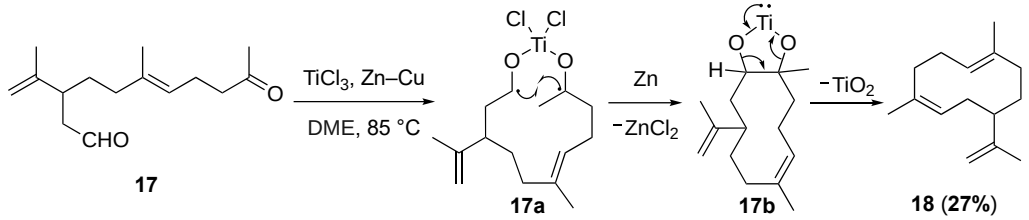
Scheme 1.3.3 Reformatsky reaction used to make natural products (±)–diplodialide B (**15**)

To arrive at (±)–diplodialide A (**16**), the authors treat (±)–diplodialide B (**15**) with MnO_2 in dichloromethane (CH_2Cl_2) to oxidize the allylic alcohol to the α,β-unsaturated ketone to finish the total synthesis.[64]



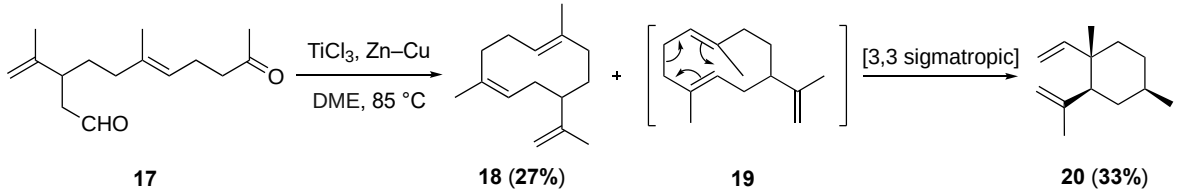
Scheme 1.3.4 Reaction for allylic oxidation using activated MnO_2 to afford the natural product (±)–diplodialide A (**16**), the yield for this oxidation was not reported

Another useful ring-closure reaction is the intramolecular coupling between dicarbonyl compounds induced by titanium/Ti(III), developed by McMurry.[66] However, as is typical for large ring forming methods, the reaction must be performed at high dilution for intramolecular cyclization rather than intermolecular polymerization to occur.[66] For example, the synthesis of (±)-helminthogermacrene uses $TiCl_3$ in combination with a zinc–copper couple (Zn–Cu) to make low valent titanium species in dimethoxyethane (DME) shown in **Scheme 1.3.5**. The reaction mechanism of the McMurry reaction starts with the formation of two ketyl radicals (**17a**) via single electron transfer (SET) into the aldehyde and ketone groups of (**17**) that $Ti(II)Cl_2$ chelates.[67] The two ketyl groups couple together to form diolate complex **17b**, [68] which will undergoes deoxygenation[69] to afford (±)-helminthogermacrene **18** in 27% yield.[70] Extrusion of TiO_2 is a driving force for this transformation.[60]



Scheme 1.3.5 McMurry reaction used in synthesising natural products (±)-helminthogermacrene (**18**), using radical coupling to make 10-membered ring alkene

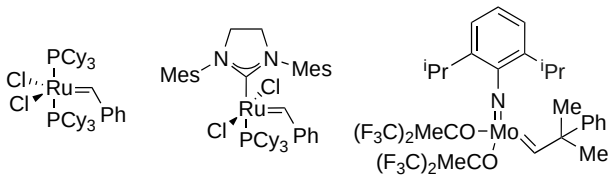
The reaction in **Scheme 1.3.5** gives a mixture of *E/Z* (45:55, 60% yield) isomers,[70] where (±)-helminthogermacrene **18** is the *E* isomer and (±)–germacrene A (**19**) is the *Z* isomer (**Scheme 1.3.6**). However, (±)–germacrene A (**19**) is unstable at room temperature and will spontaneously undergo a Cope rearrangement to yield *β*-elemene **20** in 33% yield, as shown in **Scheme 1.3.6.** In addition, to make the desired 10-membered rings **18** and **19**, the slow addition of $TiCl_3$ and Zn–Cu over 34 hours was required, which is impractical, especially if the reaction needs to be scaled up.[70] The fact that **19** rearranges to form **20** highlights another challenge in medium-ring synthesis, namely the need to avoid transannular reactions to form bicyclic or ring contracted products, after the medium-sized ring has formed.



Scheme 1.3.6 Shows the reaction condition for the formation of two natural products and demonstrates the unstable (±)–germacrene A via 3,3 sigmatropic reaction to arrive at *β*-elemene **20**, which is sesquiterpenes that are used as pheromones by insects[71]

1.4.0 Macrocyclization using Ring-Closing Metathesis (RCM)

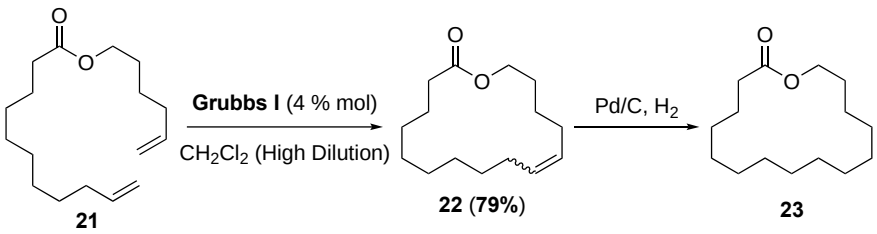
Ring-closing metathesis (RCM) is a widely used reaction, developed principally by Grubbs *et al.*[72], and Schrock *et al.*[73] for the synthesis of unsaturated ring structures where linear dienes are converted into cycloalkenes, as *E*- or *Z*-isomers.[74] The first and second generations of Grubbs catalysts (Grubbs I and II, **Fig. 1.4.1**) have been used in many areas of synthetic chemistry for RCM, including macrocycle synthesis [75] and natural product synthesis,[76] and are used far more frequently than Schrock catalysts (**Fig. 1.4.1**). The Schrock catalyst is more reactive, used in more sterically hindered demanded targets, and works for both terminals and internal alkenes with electron-deficient substituent attached.[77,78] However, the increase in reactivity comes at a cost; the Schrock catalyst is more air- and moisture-sensitive, requiring an inert (argon or nitrogen) atmosphere and dry, degassed solvents.[77] The Grubbs catalyst is more stable and can be used with a broader range of reactive functional groups.[79] In particular, Grubbs II has functional group tolerance for alcohol, aldehydes and carboxylic acids and low catalyst loading (between 2 and 5 mol% being typical).[77,80] Many methods to make macrocycles and natural products through metathesis do so through RCM,[81] using a long, linear precursor, although notably they can still encounter the same common issues seen in most macrocyclization reactions, such as competing biomolecular reactions (via cross metathesis and/or homodimerization) to form oligomers.[82]



Grubbs I **Grubbs II** **Schrock**

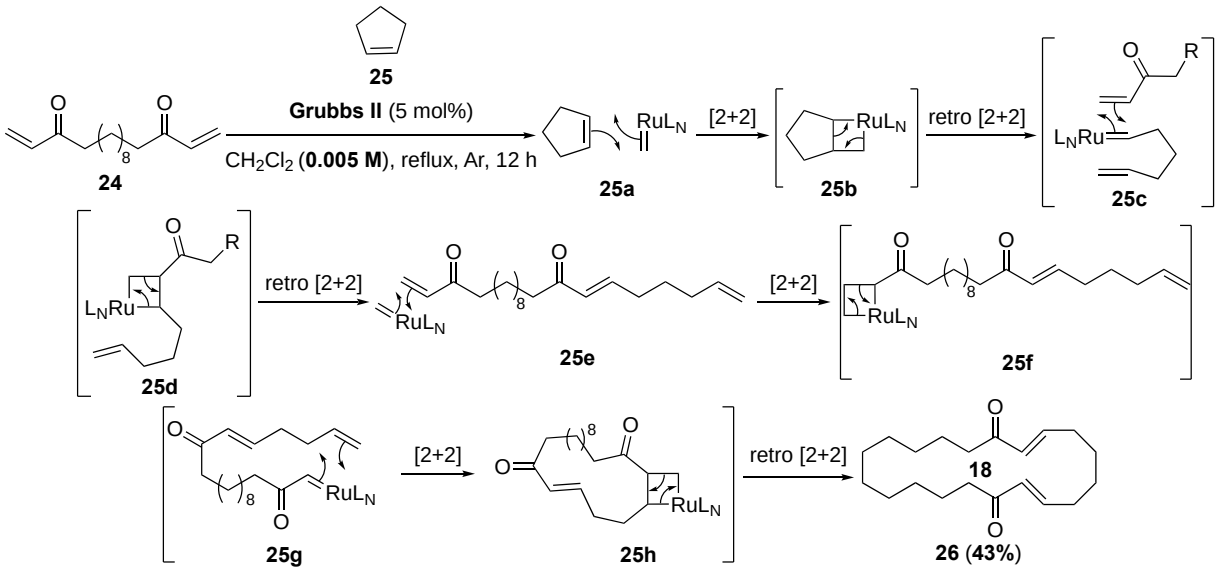
Figure 1.4.1 Chemicals structures of the most common homogeneous catalyst used for olefin metathesis: Grubbs I and II ruthenium(II)-based carbenoid complex and Schrock catalysts featuring molybdenum-(VI) center stabilized by alkoxide and imido ligands.[83] Cy = Tricyclohexylphosphine, Mes = mesitylene or 1,3,5-trimethylbenzene

RCM macrocyclization is used in the synthesis of macrocyclic musk lactones from long linear precursors like **21**, one such example being the synthesis of Exaltolide® **23** (**Scheme 1.4.1**), which is employed as a perfumed ingredient for blackberry, raspberry, or violet flower fragrance. [84,85] This demonstrates the relevance of RCM in an industrially important chemical production.[75]



Scheme 1.4.1 RCM between two terminal alkenes of lactone **21** to form ring–closing 16-remembered cycloalkene product **22** in 79% yield in a mixture of E-/Z- isomer, which was subject to hydrogenation conditions to afford Exaltolider®

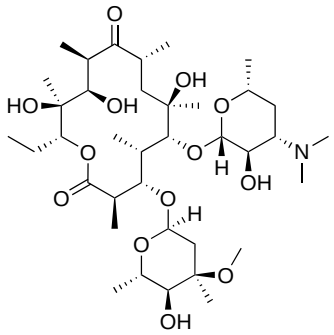
Grubbs and coworkers also developed the first tandem ring-closing metathesis via ring expansion protocol to make macrocycles.[86,87] The reaction consists of Grubbs II catalyst, cyclopentadiene **25** and symmetrical linear acyclic ketone acrylic **24**, where the reaction was heated at reflux overnight in CH_2Cl_2 at **0.005 M** (high dilution) to give macrocycle **26** in 43% yield. The reaction in **Scheme 1.4.2** proceeded by ring expansion reaction, where a 5-membered ring is enlarged to an 18-membered ring. The reaction mechanism of this transformation begins with cyclopentadiene undergoing [2+2] cycloaddition (**25a**) [88] with metal carbene (L_NRu=) to form metallacyclobutane **25b** that will do ring-opening metathesis (ROM) or retro [2+2] to form linear alkylidyne **25c** intermediate. [89, 90] The alkylidyne **25c** will react with bis vinyl ketone (**25c** → **25d**) and, after the sequence of [2+2] cycloaddition and cyclo-reversion, to arrive at desired 18-membered ring product **26**. The largest ring-sized ring reported by the authors using this method is 26-membered.[87]



Scheme 1.4.2 Formation of 18-membered macrocycle **26** with conditions and yield, through RCM via ring expansion cascade reaction

1.5.0 Macrolactonization in natural products synthesis

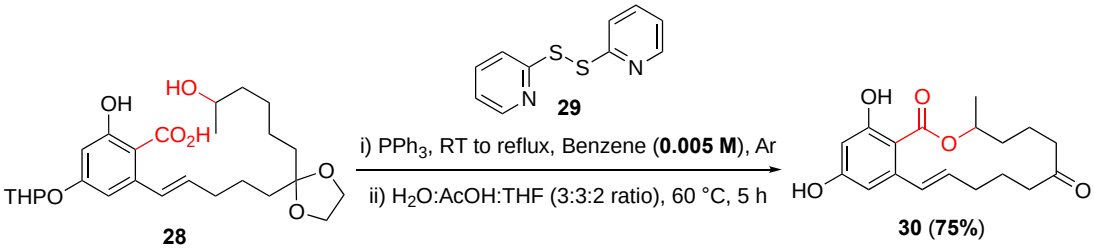
Macrolactonization is a term used to define any macrocyclization reaction that forms via lactone formation. Macrocyclic lactone is present in various bioactive natural products and pharmaceutical molecules; for example, erythromycins **27** (**Fig. 1.5.1**) are life-saving antibiotic macrolides,[91] commonly used to treat various infectious diseases.[92]



27

Figure 1.5.1 Structure of the antibiotic erythromycin **27**

There are two major classes of macrolactonization method, that make use of either carboxylic acid or alcohol activation.[61] The most widely used operates via carboxylic acid activation, and is typified by the Corey–Nicolaou macrolactonization, which uses 2,2'-dipyridyldisulfide (PyS–SPy) **29** and triphenylphosphine (PPh_3) at an elevated temperature and a high dilution (**0.005 M**).[61] Corey and Nicolaou first published this reaction in 1974, using these reaction conditions to make the natural product (±)–zearalenone in a 75% yield **30** after acid hydrolysis to remove the 1,3-dioxolanes and tetrahydropyranyl ethers (THP) protecting groups (**Scheme 1.5.2**).[93]



Scheme 1.5.2 Corey–Nicolaou macrolactonization to make 14-membered ring **30** lactone, followed by deprotecting (ii)

Other groups developed modifications and variants following the successful discovery of Corey and Nicolaou, which was well demonstrated in the complex synthesis of prostaglandin and polyether antibiotics, which works efficiently under mild conditions at high yields.[94] Some

variations of 2,2'-dipyridyldisulfide **29** are shown in **Fig. 1.5.3**, which all have different advantages in certain aspects of macrolactonization over the Corey–Nicolaou reaction.[61]

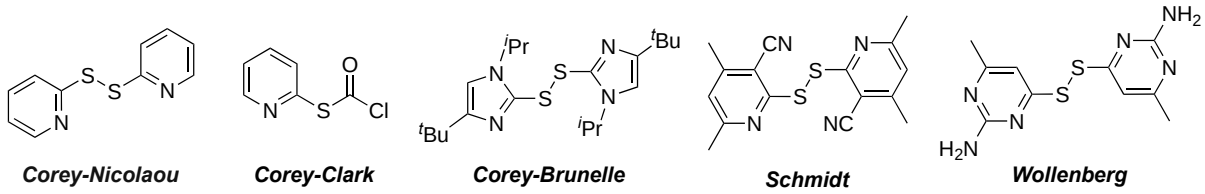
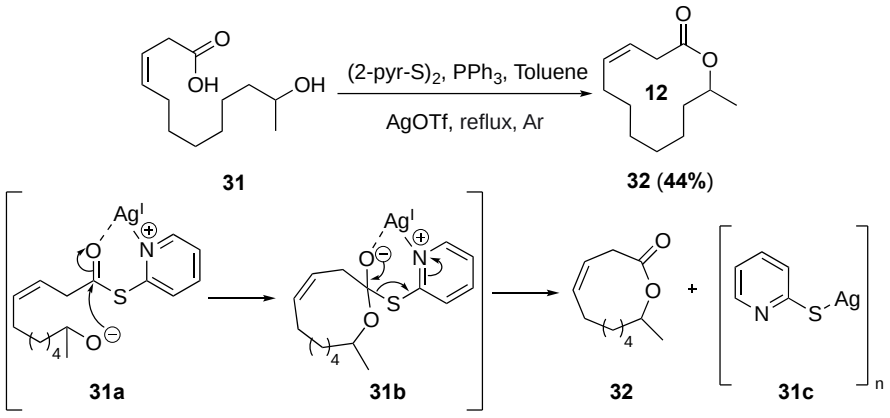


Figure 1.5.3 Molecular structures of Corey-Nicolaou reagent and variants for macrolactonization method via acid activation

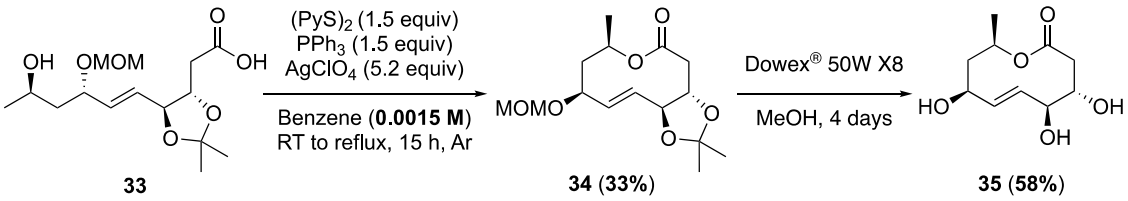
The Gerlach modification[61] demonstrates that adding Ag(I) salts (e.g., AgOTf, $AgBF_4$, and $AgClO_4$) helps catalyze macrolactonization.[95,96] This is shown in the synthesis of Furrelactone II (**32**), where the Corey–Nicolaou reagent was combined with silver salt to form a more active pyridylthioester **31a** dipolar intermediate through chelation. Next, the nucleophilic attack by alkoxide results in the formation of tetrahedral intermediate **31b**, which will collapse to give the desired lactone **32** and 2-piridinethioneaurate(I) **31c**. The driving force for macrolactonization is formation of a very stable S-Ag bond.[97]



Scheme 1.5.4 Gerlach modification for Corey-Nicolaou reagent macrolactonization used to synthesise Furrelactone II (**32**)

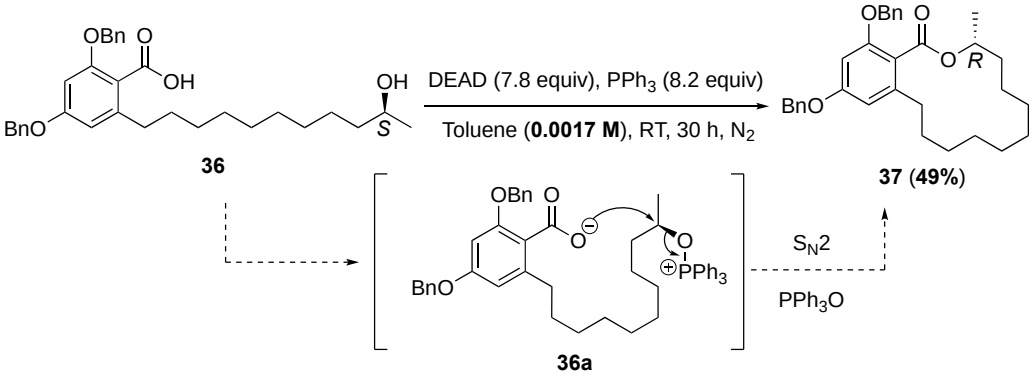
The Corey–Nicolaou reagent with the Gerlach modification is used not only used to synthesize macrocycles, but also to make medium-sized rings. One example is its use in the synthesis of (–)–decarestrictine D (aka Tuckolide, **35**) a natural product isolated from fungus and an inhibitor for cholesterol biosynthesis.[98] The penultimate step of the synthesis was macrolactonization to obtain the methoxymethyl (MOM) protecting lactone **34** in a 33% yield from linear precursor **33** (**Scheme 1.5.5**); similarly to macrolactonization, a high dilution of

0.0015 M was used. The last step to complete the total synthesis of (–)–Tuckolide was the global deprotection of MOM and the acetal group using Dowex® 50W as an acid catalyst to remove the protecting group under mild conditions to afford the product **35** in a 58% yield (**Scheme 1.5.5**).[98,99]



Scheme 1.5.5 Synthesis of (–)–decarestrictine D from linear precursor **33** using Corey–Nicolaou–Gerlach reaction conditions

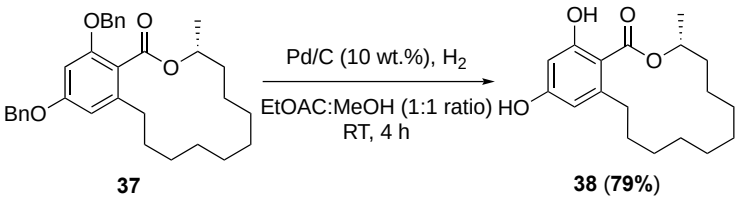
Another widely used reaction for macrolactonization is the Mitsunobu reaction, in which primary or secondary alcohol is activated towards attack by a nucleophilic carboxylate.[100] This is nicely demonstrated in macrocyclic lactone zearalane's total synthesis; interestingly, the authors synthesized both enantiomers using Mitsunobu and Corey–Nicolaou reagents (with Gerlach modification conditions) to arrive at both products in acceptable yields from the same starting material.[101]The reaction to make (*R*)–zearalane (**38**), the last reaction before the deprotecting steps, uses the classical Mitsunobu conditions: diethyl azodicarboxylate (DEAD) and PPh_3 in toluene (**0.0017 M**), as shown in **Scheme 1.5.6**; as is typical, a high dilution was needed to make the macrocycle in a good yield.[101] The Mitsunobu reaction goes through the inversion of configuration (via S_N2, **Scheme 1.5.6**) at the secondary alcohol center where substitution occurs by carboxylate **36a** nucleophile with phosphonium intermediate to afford *R*–ester **37** from *S*–alcohol of the starting material linear precursor **36**.[102]



Scheme 1.5.6 Mitsunobu reaction with the condition for macrolactonization, showing key steps of the reaction where nucleophilic attacks by alkoxide are 180° to the leaving group ($O=PPh_3$)

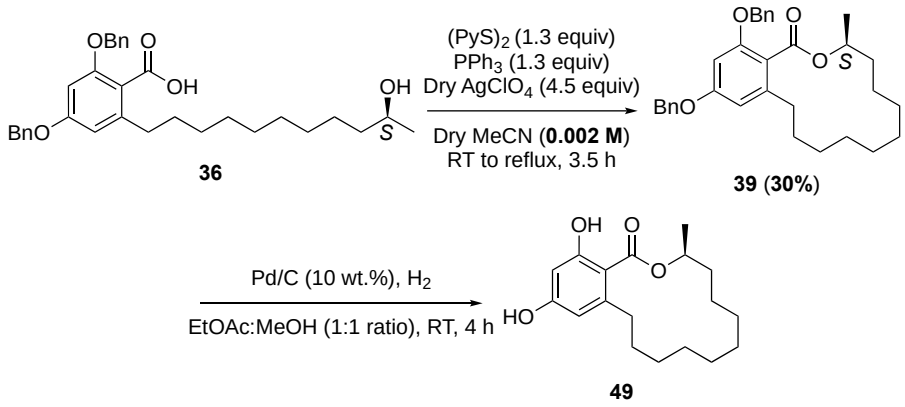
To finish the synthesis of (*R*)–zearalane (**38**), **37** was subjected to hydrogenation conditions

to remove the benzyl-protecting groups, and after simple filtration and purification via flash column chromatography, this afforded the natural product in 79% yield (**Scheme 1.5.7**).[101]



Scheme 1.5.7 Hydrogenation conditions for benzyl (Bn) deprotection to arrive at the natural product (*R*)–zearalane (**38**) with conditions and yields

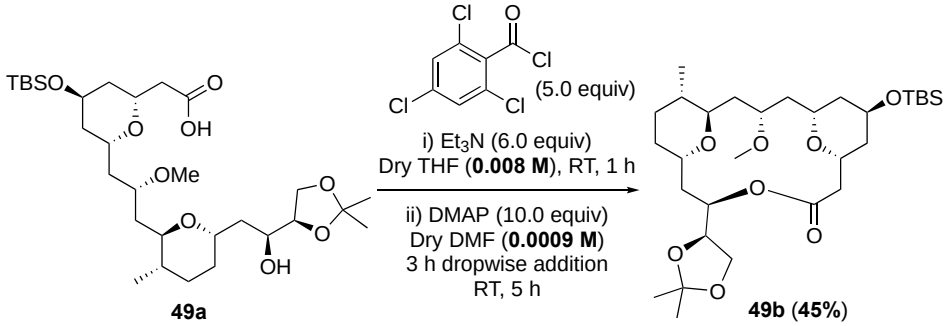
As mentioned above, the authors also isolated the other enantiomers from the same linear starting material **36** using Corey–Nicolaou–Gerlach conditions, and after benzyl deprotection using Pd/C, the authors arrived at (*S*)–zearalane **49** (**Scheme 1.5.8**).



Scheme 1.5.8 Synthesis of (*S*)–zearalane **49** natural with conditions, which is a mycotoxin that is produced by fungi belonging to the *Fusarium* genus[103]

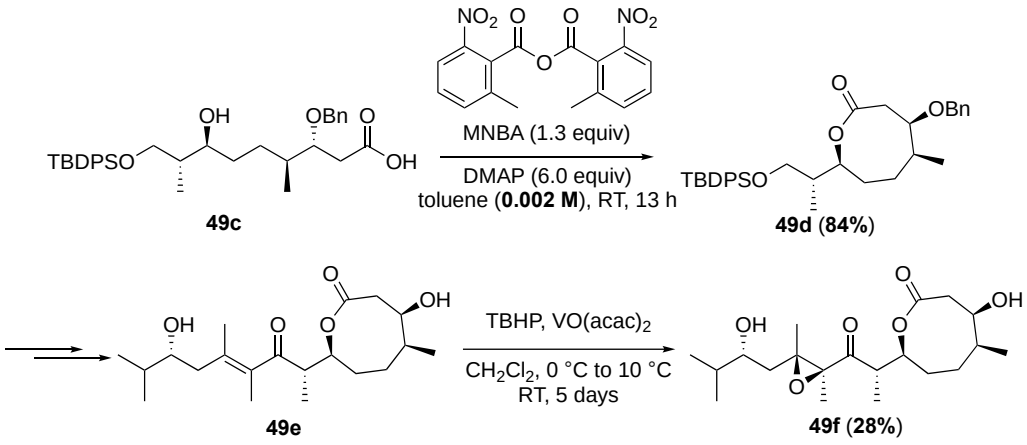
The most well-known example of a macrolactonization reaction, used extensively in natural product synthesis and taught at the undergraduate level, is the Yamaguchi and Shiina macrolactonization cyclisation developed in 1979 and 2002, respectively.[104,105] Both cyclisation approaches rely upon mixed anhydride intermediate formation in the presence of a nucleophilic catalyst.[10] Particularly, the Yamaguchi reaction is regarded as the most popular and widely used in natural product synthesis of large macrocyclic ring structures,[10] with the conditions shown **in Scheme 1.5.9**. In this example, Carreira and co-workers used the reaction in total synthesis towards the leucascandrolide natural product.[10] The seco-acid **49a** was reacted with 2,4,6-trichlorobenzoyl chloride under basic conditions to form a mixed anhydride, i.e. part i). Next, DMAP was added to the reaction mixture over 3 h via a syringe

pump, i.e. part ii), to generate a better-leaving group that enables a faster reaction with alcohol-affording lactone **49b** in 45% yield.[106] The slow addition is important in ensuring a low concentration of the activated seco acid at all times, thus favouring cyclisation over intermolecular coupling.



Scheme 1.5.9 Yamaguchi macrolactonizations reaction conditions used in natural product synthesis by Carreira *et al.*[10]

The Shiina macrolactonisation uses the same principle as the Yamaguchi esterification, but the key difference is the choice of reagent.[10] The reagent's name is 2-methyl-6-nitrobenzoic anhydride (MNBA), also known as the Shiina reagent,[107] shown in **Scheme 1.5.10**, where it is used as a dehydration condensation reagent for the formation of mixed anhydrides with a seco-acid **49c** linear precursor. The Shiina reaction was used in the synthesis for the marine-derived natural products octalactin B (**49e**) and A (**49f**), where the key reaction step involved the formation of challenge eight-membered ring core. This shows the method worked well, with the product **49d** obtained in 84% from the **49c** starting material (**Scheme 1.5.10**).[108,109]



Scheme 1.5.10 Shiina macrolactonization reaction used in total synthesis of octalactin B (**49e**) and A (**49f**) by Shiina *et. al* [109]

The above examples show that it is still common to use high or pseudo-high dilution by gradually adding the reagent for this type of reaction to increase the yield of macrocycles and medium-sized ring products. However, the success of this dilution is highly substrate-dependent and can be impractical for large-scale synthesis.

1.6.0 Radical Cascade Reaction/Ring Expansion

The synthesis of medium-sized rings and macrocycles using free radicals that undergo cascade/ring expansion reaction is well-established in the literature.[110] One example involving single radical ring expansion is the Dowd–Beckwith reaction,[111] where catalytic cycles of the reaction mechanism are shown in **Fig. 1.6.1**.[112] The first step of the cycle is activating the azobisisobutyronitrile **50** (AIBN) radical initiator by thermal decomposition (Δ) to generate two equivalents of radical **50a** with one equivalent of N_2 displaced. The 2-propyl radical **50a** free radical will abstract the proton to form tributyltin hydride (Bu_3SnH) to form tributyltin radical, which will abstract the bromide atom of starting material **51** to generate primary alkyl radical **51a**, with a displacement of $Bu_3Sn–Br$ as a by-product. The alkyl-free radical **51a** reacts with the carbonyl group via a 3–exo–trig cyclization to give bicyclic alkoxy radical **51b**. The bridging bond of the bicyclic of cyclopropane intermediate **51b** then cleaves to undergo ring expansion via fragmentation to form new cyclohexane radical **51c**, which is a more stable radical due to the electron withdrawal effect from the ester group. Finally, the cyclohexane radical **51c** abstracts hydrogen from $Bu_3Sn–H$ to afford ring expanded **52** product and regenerated tributyltin radical. This is amongst the simplest ring expansion reaction that can be performed using a free radical mechanism.

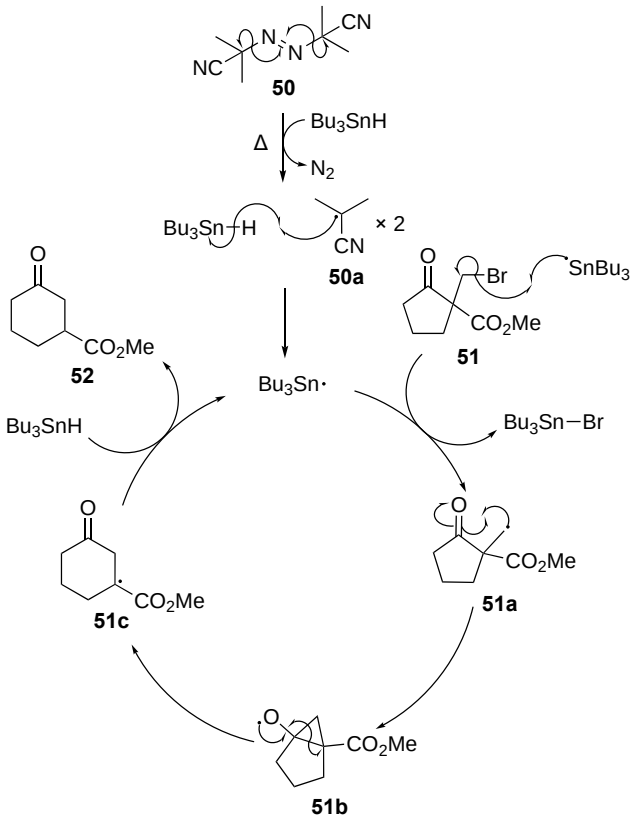
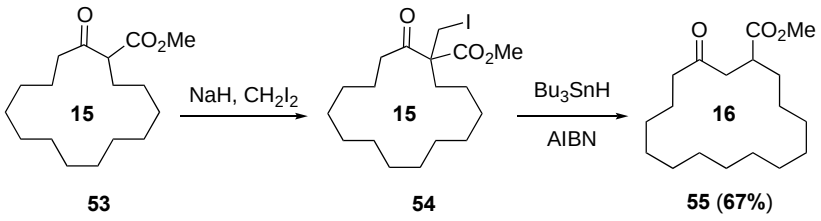


Figure 1.6.1 Proposed catalytic cycle reaction mechanism for one–carbon ring expansion of bromomethyl *β*–keto ester **51** using Dowd–Beckwith reaction conditions, where key radical intermediates are shown

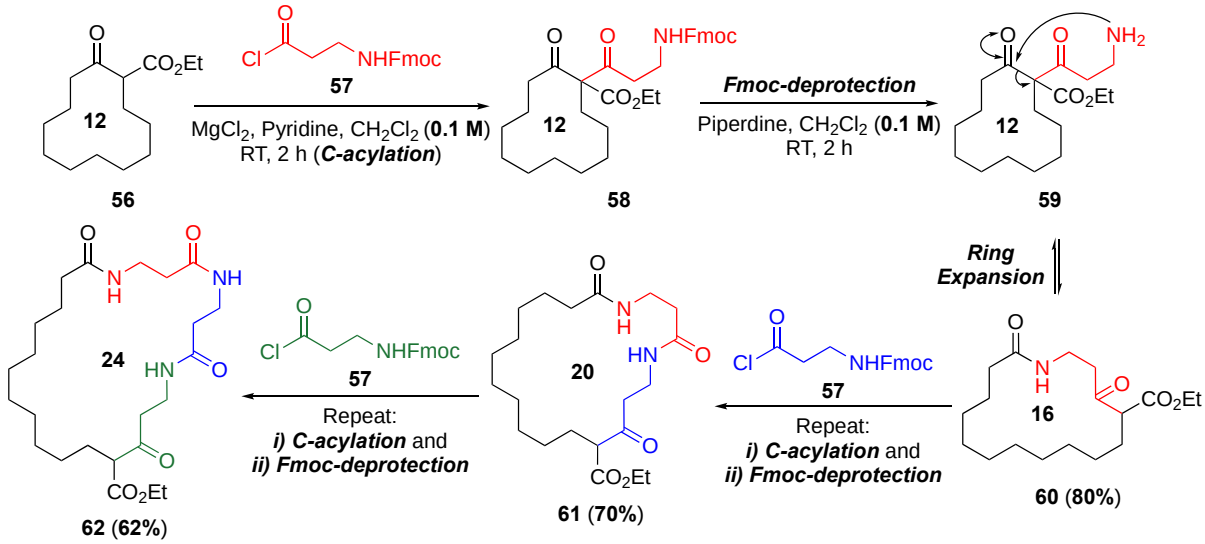
In 1991, Dowd and co-workers demonstrated that ring expansion could make a larger macrocyclic ring structure.[113] Starting with oxocyclotetradecanoate **53** that is alkylated with diiodomethane (CH_2I_2) using a strong base (sodium hydride) to afford **54**. The 15-membered ring iodide **54** was subject to standard Dowd–Beckwith conditions giving a ring expanded 16-ring *β*–keto ester **55** in 67% yield (**Scheme 1.6.2**).[113]



Scheme 1.6.2 Ring expansion strategy to access 16-membered macrocycle using free radical homologation Dowd–Beckwith reaction

1.7.0 Successive Ring Expansion (SuRE)

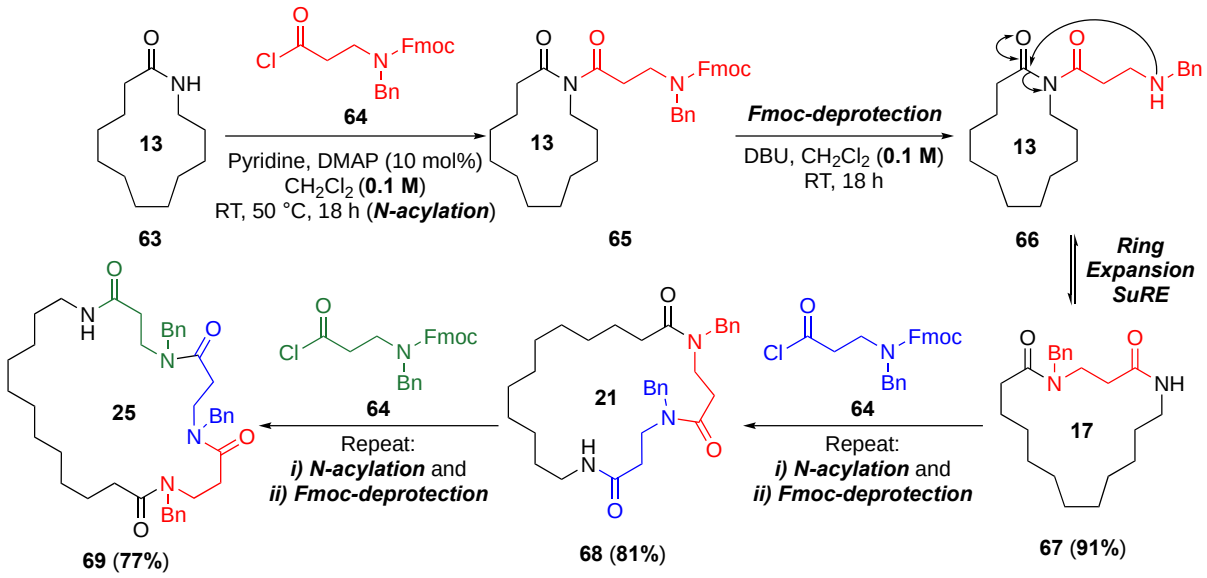
Successive Ring Expansion (SuRE) is a novel strategy for ring expansion first reported by Unsworth and coworkers in 2015 at the University of York.[114] The first SuRE reaction developed involved ring expansion via insertion of an amino acid derivative or protecting hydroxy acid into a cyclic *β*–ketoester, to form lactam or lactone products. SuRE has a unique profile that enables it to make macrocycles quickly and efficiently via iterative ring expansion reactions, performed via a short sequence of synthetic steps.[114] The first example of the SuRE reaction is illustrated in **Scheme 1.7.1**. In this method, a 12-membered **56** was acylated at the carbon of a *β*-ketoester unit (***C-acylation***) with acid chloride **57** in the presence of magnesium chloride ($MgCl_2$) and pyridine in CH_2Cl_2 at a concentration of 0.1 M. Following the ***C-acylation***, the fluorenylmethyloxycarbonyl (Fmoc) protecting group on the tethered amine on product **58** was cleaved using piperidine, revealing a primary amine *in situ* (**Scheme 1.7.1**, **58** → **59**). The unprotected amine then spontaneously undergoes cyclization, followed by spontaneous fragmentation. Proton transfer/abstraction leads to the formation of ring-expanded 16-membered lactam in an overall yield of 80% over the whole sequence. A key feature of the reaction is that it was conducted at 0.1 M concentration in both steps. Also key to the process is the fact that the final product **60** contains the same cyclic *β*-ketoester motif as that in the starting material **56**; this functional group can therefore be manipulated following the same sequence of steps and reaction conditions, i.e., ***i) C-acylation*** and ***ii) Fmoc-deprotection/ring expansion***, thus growing the 16-membered macrocycle **60** ring to form 20-membered macrocycles **61** in an overall yield of 70%. The process can be repeated to give 24-membered tri lactam **62** in an overall yield of 62%, hence referred to as "Successive Ring Expansion" or SuRE.



Scheme 1.7.1 Successive Ring Expansion with *β*–amino acid fragments

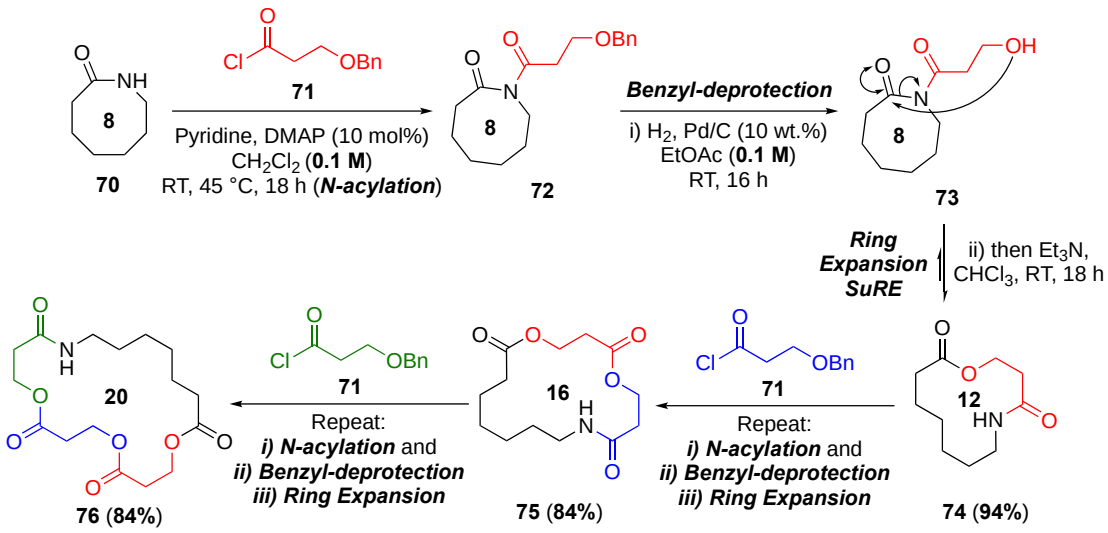
This SuRE method allows medium-sized (8–12) ring and macrocycle (12+) to be made via insertion of a range of amino acids (proteinogenic or non-proteinogenic)[115] with 3 or 4 atom ring expansion possible; these ring size changes are favoured as they proceed via cyclization via 5- or 6-membered rings respectively. Overall, the SuRE reaction is attractive for making macrocycle libraries on practical bases on a large scale. Unsworth *et al.* showed that the SuRE method could be used to generate libraries of medium-sized scaffolds for high-thought screening using computational tools like Lead-Likeness and Molecular Analysis (LLAMA) to help design the target molecules.[116] The linear amino acids used in SuRE can be pre-functionalised to construct diverse medium-sized rings and macrocycles with various degrees of freedom.

The SuRE reaction is not just for expanding *β*-ketoester medium-sized rings and macrocycles. In 2017, Unsworth group PhD student Dr Tom Stephens demonstrated for the first time that lactams could also be ring-expanded using a SuRE method to afford medium-sized ring and macrocyclic peptide mimetics.[117] The first example is illustrated in **Scheme 1.7.2**. It shows how they subjected a 13-membered ring lactam to an *N*-acylation reaction with the acid chloride **64** (generated before addition and freshly made from corresponding carboxylic acid) in the presence of a mild base, which was pyridine and nucleophilic catalyst 4-dimethylamino (DMAP) in CH_2Cl_2 (0.1 M) at reflux overnight (**Scheme 1.7.2**). After *N*-acylation, the resulting imide **65** intermediate was taken directly to the next step without further purification. Tethered amine **66** was then revealed by Fmoc deprotection using DBU.[118] However, in this case, the secondary amine, (e.g., piperidine) was found to react with the macrocyclic substrate to cleave the acyl group in an unwanted side reaction. Therefore, DBU (basic and nucleophilic) was used instead to prevent this unwanted side reaction. After revealing the benzyl-protecting secondary amine in **66** (**Scheme 1.7.2**), the amine rapidly undergoes an in-situ cyclization and fragmentation reaction sequence, i.e., ring expansion/SuRE affording 17-membered ring macrocycle **67** in 91% over two steps. The 17-ring lactam again can be *N*-acylated, and ring expanded similarly using the same procure shown in **Scheme 1.7.2** to afford 21-ring lactam **68** with an impressive 81% overall yield. Pushing the concept further, the authors showed you could expand up to 25-membered ring macrocycles **69** using the same SuRE method in an overall 77% yield.



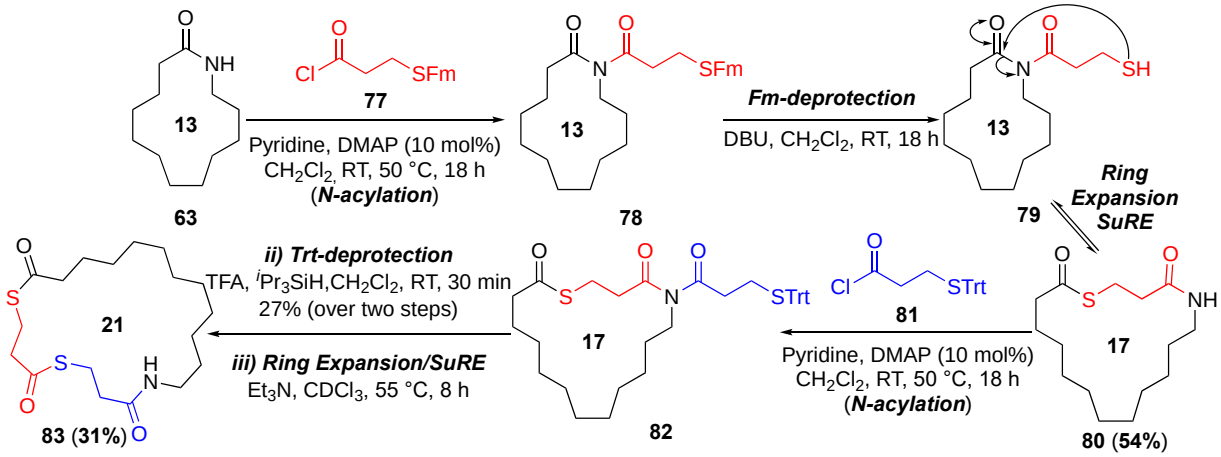
Scheme 1.7.2 Successive Ring Expansion with *β*–amino (Bn and Fmoc protecting) acid unit starting with commercially available lactam **63**

Amino acid fragments are not the only ones that can be used, with the insertion of hydroxy acid chloride also possible using the same SuRE-type method to make macrocyclic lactones.[119] The general concept is the same as seen previously, where the same *N*-acylated conditions are employed, starting with the 8-membered lactam **70** and benzyl-protected hydroxy acid **71** (**Scheme 1.7.3**). However, in this case, because we have a benzyl (Bn) protected alcohol, the deprotection was performed using hydrogenolysis conditions to afford the primary alcohol **73** (OH), with triethylamine (Et_3N) also used as a weak base to facilitate the ring expansion step. Using this SuRE reaction, 12-membered lactone **74** can be formed in an excellent yield of 94% (**Scheme 1.7.3**). The 12-membered ring 74 still has the lactam functionality, which can be acylated and ring expanded again, giving a 16-membered ring **75** an 84% yield, and the product can be expanded once more to afford the 20-membered macrocycles tri lactone **76** in 84% yield. The 8-membered ring **70** starting material has therefore been "grown" via SuRE reactions into 20-membered macrocycles **76** in an overall 44% yield from **70**. Later, Unsworth and collogues used experimental results and combined them with computation studies (DFT) to give "guidelines/rules" for which amino acid, hydroxy acid substrate is more like to be successful in undergoing SuRE reactions with various lactams and *β*-ketoester.[120]



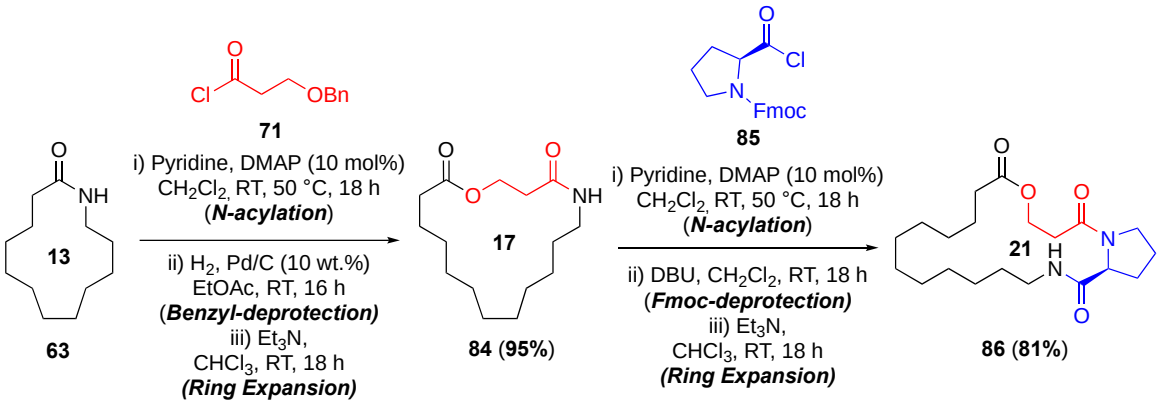
Scheme 1.7.3 Successive Ring Expansion with benzyl protected *β*–hydroxy acid fragment starting with ε-caprolactam **70**

The most recent development of the SuRE reaction involves the synthesis of thiolactone macrocycles, where amino and hydroxide acid fragments were replaced by mercaptan acids, meaning the tethered nucleophilic component is a thiol (R-SH).[121] The reaction follows the same reaction profile: it starts with *N*-acylation followed by deprotection and finishes with ring expansion to afford the thiolactone macrocycles in good yields as illustrated in **Scheme 1.7.4**. As seen previously, growing the ring by repeating the sequence can also afford the first 21-membered thiolactone **83** in an acceptable 31% yield. However, in this first instance, the 9-flurorenylmethyl (Fm)-protected mercaptan acid chloride **77** was used, while in the second case, a trityl (Trt) protected derivative **81** was used, which was smoothly removed by using trifluoroacetic acid (TFA) to reveal the R-SH group that undergoes ring expansion via a 6-membered ring cyclization (**Scheme 1.7.4**).



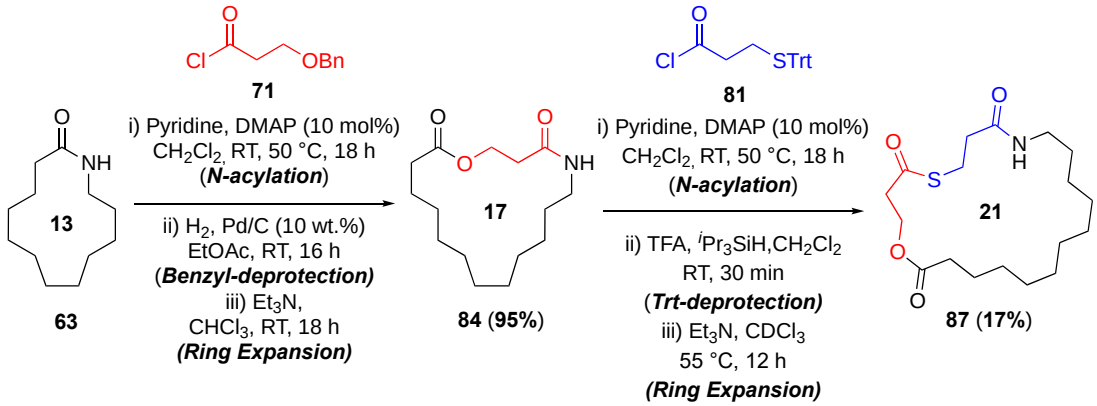
Scheme 1.7.4 Successive Ring Expansion with trityl protected *β*–thiolate acid fragment

A remarkable aspect of the SuRE reaction is the ability to use hydroxy, amino and mercaptan acid fragments (including *α* and *β*) interchangeably to make different functional macrocycles that incorporate different linear units. An example is given in **Scheme 1.7.5**, which shows that starting with the 13-membered ring **63** was *N*-acylation with *β*-hydroxy acid fragment **71** (highlighted in red), followed by hydrogenolysis and ring expansion, giving the 17-membered ring **84** in 95% yield. The 17-membered macrocycles can be further elaborated via *N*-acylation with *α*-proline acid unit **85** (highlighted in blue) to furnish the syntheses of 21-membered ring **86** in 81%, or an overall yield of 77%.[119]



Scheme 1.7.5 Successive Ring Expansion with both *β*–hydroxy and α–amino acid fragments sequentially to make 21-membered lactone and bis lactam

Another example is when the first acid chloride is *β*–hydroxy acid **71** (highlighted in red), giving the desired macrocycle a consistent 95% yield. The second insertion of mercaptan acid unit **81** (highlighted in blue) resulted in the formation of thiolactone, lactone and lactam macrocycle **87** in a respectful 17% yield (**Scheme 1.7.6**).[121] A key aspect of this reaction is that each reaction (i.e., acylation, deprotection and ring expansion) is done in CH_2Cl_2 or $CH(D)Cl_3$ at 0.1 M concentration (**Scheme 1.7.6**), so there is no need to use high dilution.



Scheme 1.7.6 Successive Ring Expansion with both *β*–hydroxy and *β* –thiolate acid fragments sequentially to make 21-membered with lactone, thiolactone and lactam functionalities

1.8.0 Nucleophile Induced Cyclization/Ring Expansion (NICE)

The ring expansion reactions summarised in this review so far all work by enlarging already-formed rings and in most cases proceed via cyclic transition states in the "normal" ring size range, i.e., 5- or 6-membered (**Fig. 1.8.1**). This is because the 5/6-membered cyclization reactions tend to be kinetically favourable.

Figure 1.8.1 Here is a visual representation of how to create a 6-membered ring by connecting the pink and light blue ends of a linear precursor in a cyclization process

Nucleophile Induced Cyclization/Ring Expansion (NICE) is a novel method whereby medium-sized rings can be accessed directly from linear precursors via cyclization/ring expansion cascade reactions. A key feature of this method is that all the individual cyclization reactions involved in the overall process proceed via kinetically favourable "normal"-sized ring cyclic transition states (specifically 5-, 6- and 7-membered). Contrastingly, medium-sized ring transition states (8 or more membered transition states) are typically higher in energy due to transannular interactions, strain and loss of entropy, which are avoided in NICE reactions. This is achieved by incorporating an internal nucleophilic (e.g., pyridine, tertiary amine derivates, green dot in **Fig**. **1.8.2**) into the linear precursor. By introducing this functionality (green dot) in the middle, the linear precursor allows the inefficient and slow direct end-to-end cyclization (highlighted by dotted lines) to be broken down into two faster and easier cyclization reactions. The process is designed so that every cyclization goes via kinetically favourable normal-sized cyclic transition states to encourage a cyclization/ring expansion cascade sequence (**Fig. 1.8.2**). This approach can be used to make medium-size rings or macrocycles, while reducing competing intermolecular reactions, even at regular dilution (e.g., 0.1–0.05 M).

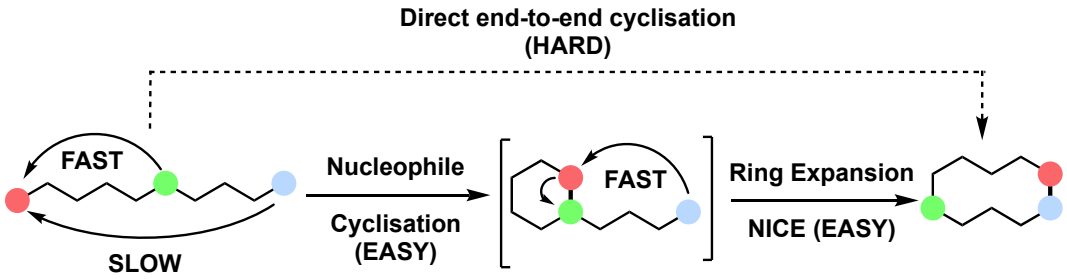
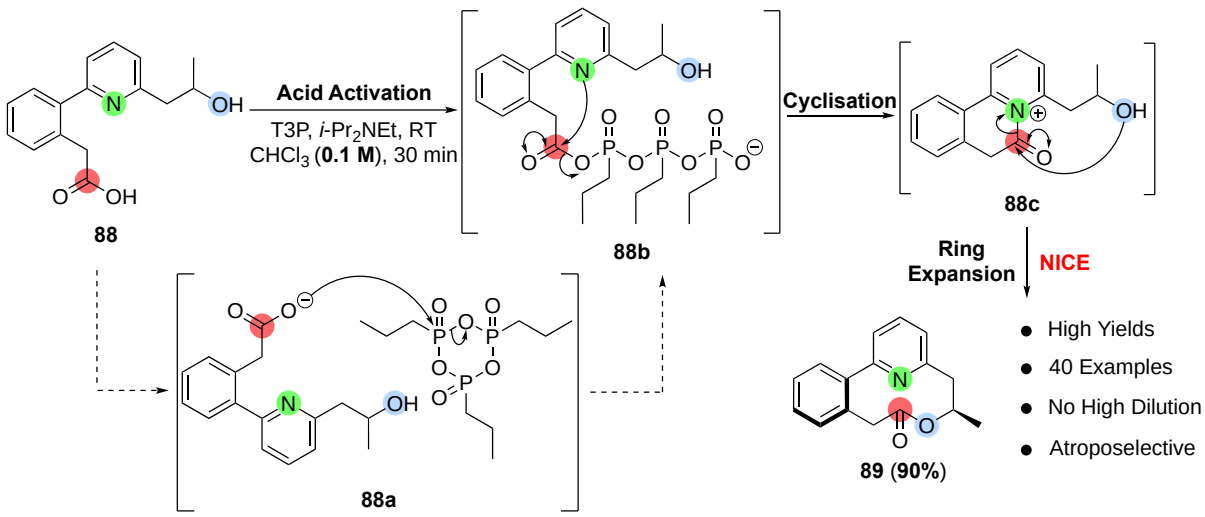


Figure 1.8.2 This illustration demonstrates how the internal nucleophilic catalyst (represented as a light green dot) facilitates cyclization in NICE reaction

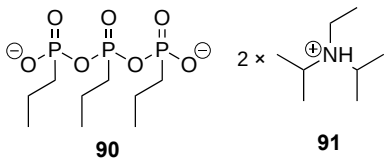
The concept of **NICE** was first published by Unsworth and co-workers in 2019.[128] This is illustrated in **Scheme 1.8.3**, starting with linear biaryl benzylic acid **88**. The carboxylic acid (the electrophilic component, highlighted in pink, RCOOH) of this linear precursor was activated using a solution of propylphosphonic anhydride (T3P) as 50 wt. % in ethyl acetate (EtOAc) to form the acyl-phosphonic acid **88b** via carboxylate attacking cyclic T3P trimer **88a** (**Scheme 1.8.3**).[122,123]

The activated ester **88b** is then attacked by the nitrogen on pyridine, which is acting as an internal nucleophile (highlighted in green, N), via a kinetically favourable six-membered ring transition state (i.e., 6-exo-trig) to form a 6-membered acyl pyridinium cation intermediate **88c** (**Scheme 1.8.3**). The alcohol (highlighted in blue, R-OH), which was part of a linear precursor, can then act as a terminal nucleophile and attack the cationic acyl ammonium **88c** intermediate via another 6-membered ring cyclization, and then fragment, affording a 10-membered ring lactone **89** in 90% yield. Crucially, the reaction was done at **0.1 M** concentration in $CHCl_3$, meaning no high dilution was required (**Scheme 1.8.3**).



Scheme 1.8.3 NICE reaction with biaryl benzylic acid linear **88** precursors, showing key intermediates formation in cyclization and ring expansion steps

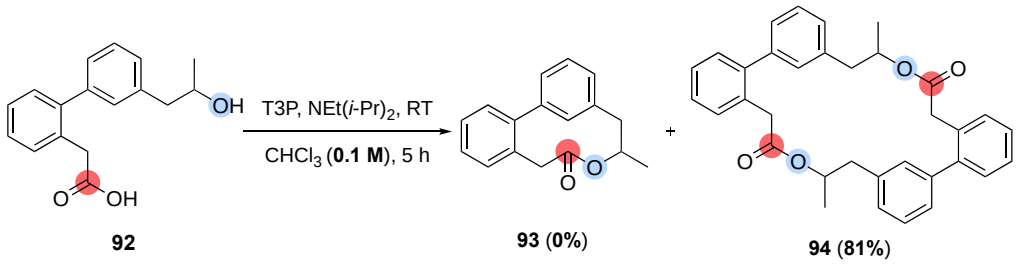
Another advantage of this reaction is the formation of water-soluble by-products from the T3P coupling reaction, such as linear trimeric propylphosphonate **90** [124] and 2 equiv. ammonium DIPEA salt **91** (*N,N*-diisopropylethylamine, *i*-Pr_2NEt), as illustrated in **Fig. 1.8.4**.



90 **91**

Figure 1.8.4 Structure of water-soluble by-products from using T3P as an acid activator in the NICE reaction

As a control, the authors also synthesized a linear precursor analogous to linear biaryl benzylic acid **88** (**Scheme 1.8.3**) but without the internal nucleophilic pyridine group (i.e., biphenyl **92**) (**Scheme 1.8.5**). This was done to help prove that the internal nucleophile in the pyridine case participated in the reaction; thus, the aryl **92** was subjected to the same reaction conditions, and the only product isolated was dimer **94** in 81% yield, with no evidence of the formation of a 10-membered lactone **93** product (**Scheme 1.8.5**). This control reaction demonstrates well the importance of having internal nucleophiles and the key role they play. Otherwise, competing biomolecular coupling (e.g., dimerization) becomes the dominant reaction pathway, as is seen here. Note that this type of control reaction will feature frequently in the chemistry described later in this thesis.



92 **93 (0%)** **94 (81%)**

Scheme 1.8.5 The control reaction for NICE indicates that the dimerization process is a significant pathway for the N-free linear precursor **92**

An important aspect of the NICE reaction is that it can be used to form biaryl containing medium-sized rings atroposelectivity. Atropisomerism is a form of chirality based on slow bond rotation, often when different functionalities are placed between two C-C sp^2-hybridized atoms with restricted rotation, like a biaryl system.[125] It is an important structural feature in drug discovery and medicinal chemistry for development due to its participation in the key role of shaping conformation.[126] Using NICE reactions, the authors were able to isolate a single atropisomer of 10-membered ring lactone. The authors rationalized the selectivity using a kinetic model and based on sterically preferer *Si* faced attack (in half-chair/boat conformation) to form acyl pyridinium intermediate, with the reaction proceeding via a 6-membered cyclic being key to the selectivity.[128]

The NICE reaction reported in 2019 had some limitations however, one being that only medium-sized ring products were synthesized (8-,9-,10- and 11-rings), and no macrocycles (12-rings +) were afforded in the published study. Secondly, only carboxylic acid was used as the electrophile component.

1.9.0 Project Objectives

Compounds containing medium-sized rings and macrocyclic heterocycles have significant biological and pharmaceutical implications, especially in medicinal chemistry and drug discovery.[127] Our goal is to enhance the NICE reaction by investigating the potential of employing alternative internal nucleophiles, including sulfur (S), and selenium (Se) rather than pyridine or tertiary amine. Additionally, we intend to broaden our substrate scope by varying the terminal nucleophiles and examining other nucleophiles, such as thiols and phenols.

In addition, a more challenging aim we set out to address was to vary the electrophilic component, to broaden the substrate scope and expand the reaction concept to entirely new reaction types. Previously, only carboxylic acids were used as the electrophile. The discovery of new electrophiles, terminal nucleophiles and internal nucleophiles was all proposed to lead to a quick and easy method for synthesizing medium-sized rings with a huge variety of functionalities under mild conditions at a standard dilution.

Arguably, the most ambitious aim of this project was to extend the cascade sequence to systems with more than one internal nucleophile. This would allow reactions to form bigger and more complex ring systems (i.e., macrocycles) to be performed. Notably, the Unsworth group had never published any examples of NICE reactions tried using two or three different heteroatoms as nucleophiles before this project. To achieve this, we developed a new approach that involves designing longer linear precursors containing multiple internal nucleophiles, as shown in **Fig. 1.9.1**. This way, we can carry out multiple cyclization and expansion processes in a single cascade sequence, resulting in the formation of larger macrocycles from a linear precursor in a single pot. We refer to this new approach as double- or triple-NICE, as shown in **Fig. 1.9.1**, depending on the number of internal nucleophiles incorporating the line precursor.

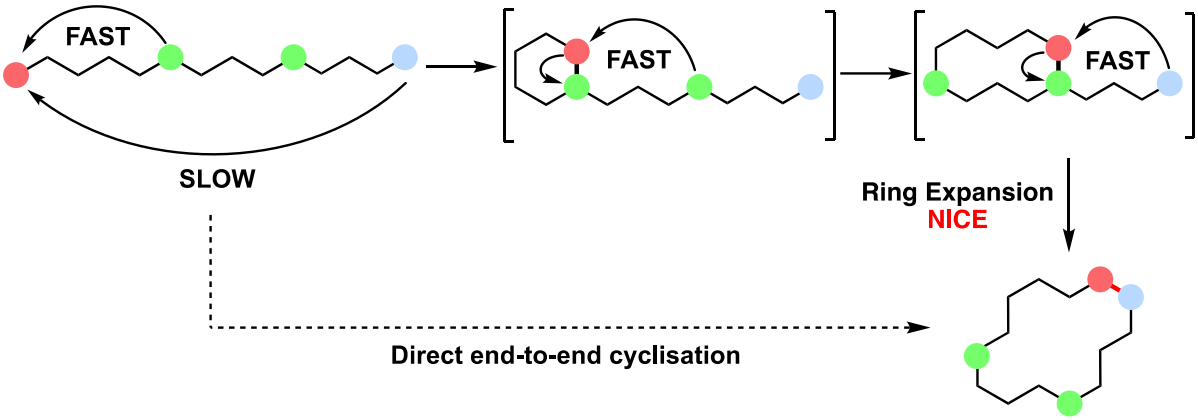
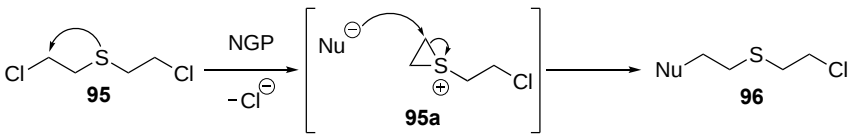


Figure 1.9.1 Graphical illustration of an internal nucleophile ring expansion reaction with two internal nucleophiles (highlighted as light green dots) in a cascade manner to form hypothetical macrocycles overcoming issues of direct end-to-end cyclization

Chapter 2: NICE Reaction for Synthesis of Medium-Sized Rings and Macrocycles

2.1.0 Synthesis of S-containing linear precursors

When arriving in York in January 2020, the general NICE (Nucleophile Induced Cyclization/Ring Expansion) method was already established by the Unsworth group, for reactions using tertiary amines and pyridines as internal nucleophiles in cyclization/ring expansion cascade reactions. These reactions proceed via acyl-ammonium ion intermediates to form nitrogen-containing medium-sized rings from simple linear precursors.[128] However, as mentioned in the project objectives, heteroatoms other than amine nucleophiles hadn't been explored (in particular, atoms in group 16 of the periodic table such as sulphur and selenium); exploring this possibility was considered to be a challenging but worthwhile goal to achieve. From the literature, sulfur is known to take part in classical neighbouring group participation (NGP) reactions,[129] famously as seen in mustard gases. Since sulfur possesses a lone pair that can undergo a simple intramolecular S_N2 (**Scheme 2.1.1**), this results in a significant increase in the electrophilicity of mustard gases like **95** with nucleophiles, compared to systems without a heteroatom.[130]

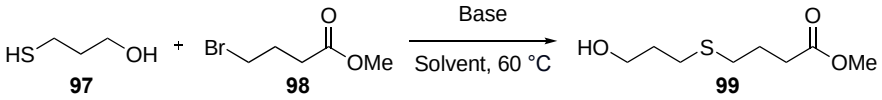


Scheme 2.1.1 Neighbouring Group Participation (NGP) reaction of bis(2-chloroethyl)sulfide **95** with a general nucleophile (donating as Nu)

As a result, it was decided to try to make aliphatic sulfur-containing medium-sized rings (8–10 membered) and macrocycles (12–15 membered). However, instead of allowing the cyclization to under via a three-membered ring sulfonium cation intermediate, as seen in mustard gases, the design of linear precursor was considered in such a way to keep the size of the cyclic transition state in the "normal" ring size range (i.e., five-, six or seven-membered rings). The initial system required there to be a pro-electrophile at one end of the chain (i.e., a carboxylic acid to be activated), as well as two nucleophiles, one terminal (OH, SH, NH) and one internal sulfide (R-S-R), which led to the substrate design that follows.

2.2.0 Synthesis of [5,6] linear precursors

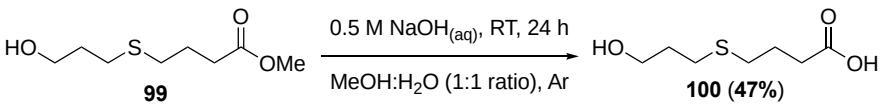
Synthesis of a suitable substrate to test whether a sulfide can act as an internal nucleophile in a NICE reaction started with the formation of sulfide **99**. The conditions used to make sulfide **99**[131,132] were based on the literature, with slight modifications, where the number of equivalents (equiv.) of bromide **98** added to the reaction mixture was increased (**Table. 2.2.1**, **entry 1–3**) from the 1.0 equiv. used in the published synthesis. It was noted that the R_f difference between thiol **97** and the desired product **99** was only 0.1; as a result, it was decided to make thiol **97** the limiting reagent to ease purification.



Entry	*Scale (mmol)*	*Solvent*	*Base*	*Nº Equiv. of Base*	*Nº Equiv. of **98***	*Concentration (M)*	*Reaction Time (h)*	Isolated Yield of ***99*** (%)
1	4.41	DMF	K_2CO_3	1.5	1.5	0.30	16	87
2	9.28	DMF	K_2CO_3	1.5	1.1	0.30	14	60
3	11.6	DMF	K_2CO_3	1.5	1.5	0.30	18	87

Table 2.2.1 Synthesise with optimisation conditions of sulphide **99**, using anhydrous solvent

The reactions were followed by TLC, and full consumption of **97** was noted by TLC after 6 h, although all the reactions were allowed to stir overnight for convenience and to ensure completion. Notably, the isolated yield was significantly better than the reported literature value, particularly in **entry 2** and **3** (**Table. 2.2.1**). The optimised condition for the S_N2 reaction to form sulphide **99** allowed for the generation of multiple grams of product with >95% purity and was sufficient to enable subsequent synthetic steps to be performed after relatively simple purifications. After a successful S_N2 reaction result, the next step was the hydrolysis of the methyl ester functional group under basic conditions.

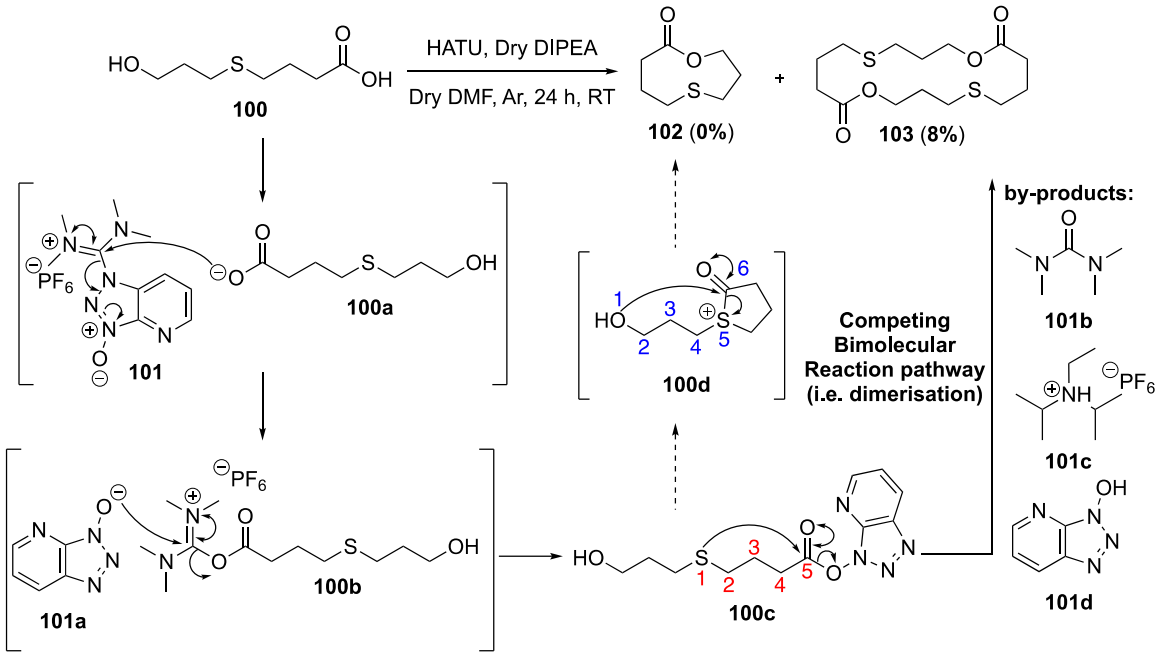


Scheme 2.2.2 Synthesis of carboxylic precursor **100**

Literature conditions reported for ester hydrolysis[133] were attempted on sulfide **99** (**Scheme 2.2.2**). The reaction mixture was monitored by TLC. After leaving the reaction mixture for 24 h at RT, the complete consumption of sulphide **99** was observed by TLC analysis. The reaction was acidified to pH ≈ 1 with 1.0 M $HCl_{(aq)}$. The crude product was obtained after liquid-liquid extraction, following the literature procedure work-up.[133] The resulting crude product was purified by column chromatography to afford carboxylic acid **100**, in an acceptable yield when considering the difficulty involved in the purification of very polar molecules.

2.3.0 Attempts to synthesise sulphur containing medium-sized ring via a [5,6] transition state with a sulfide internal nucleophile

The first ring expansion reaction attempted using sulfide **100** was done using HATU as the coupling reagent (**Scheme 2.3.1**).[134] This type of coupling agent was used based on a literature search[135] that suggested that HATU is more effective and successful in the electrophilic activation of carboxylic acid in peptide synthesis than TBTU, EDC.HCl and BOP,[135] in addition to its easier purification, handling and atom economy (i.e., no need to use explosive additives such as HOBt). The reaction mechanism as planned starts with DIPEA deprotonating the aliphatic carboxylic acid **100** (pK_a ~ 5.0),[136] and the corresponding carboxylate anion **100a** reacting with the HATU reagent **101**. The resulting OAt-activated ester intermediate **100c** (**Scheme 2.3.1**) is formed by anionic HOAt **101a** reacting with electrophilic activated carboxylic acid **100b** to yield tetramethylurea/$(Me_2N)_2CO$ **101b** and Hünig's base/hexafluorophosphate salt **101c** by-products.[137] Next, the sulfide acts as an internal nucleophile cyclizing via 5-membered ring with OAt activated ester **100c** (numbers highlighted in red, **Scheme 2.3.1**) to form a five-membered acyl sulfonium **100d** intermediate. The cation intermediate **100d** formed from the first cyclization undergoes second cyclization/ring expansion via the 6-membered ring (numbers highlighted in blue, **100d**, **Scheme 2.3.1**) with OH acting as the terminal nucleophile to afford 9-membered ring lactone **102**. The reaction was performed on 1.82 mmol scale and monitored by TLC. After 18 h the complete consumption of limiting reagent **100** was noted. However, after an acidic workup with 1.0 M $HCl_{(aq)}$ to remove excess HATU and HOAt (**101d**) and purification via column chromatography, a low yield (8%) of the dimer **103** was isolated, and none of the desired of 9-membered ring lactone **102** was formed.



Scheme 2.3.1 Attempted ring expansion reaction of carboxylic acid **100** with HATU

This result implies that the sulphur heteroatom is not nucleophilic enough (compared to nitrogen) to form a five-membered sulfonium cation intermediate **100d** and allow ring expansion to afford medium-sized lactone **102**. Instead, intermolecular coupling (i.e., dimerization) appears to be the predominant pathway, rather than intramolecular cyclization, manifesting in a low yield of dimer **103** (**Fig. 2.3.2**, with the structure of **103** confirmed by X-ray crystallography). Therefore, presumably, most of the material formed oligomers or polymers and we were unable to isolate or characterise. A single crystal of dimer **103** was obtained by a slow cooling crystallization method of a supersaturated solution using *n*-hexane as a solvent at an elevated temperature (90 °C) and gradual cooling to RT, allowing a metastable supersaturated state to be reached.

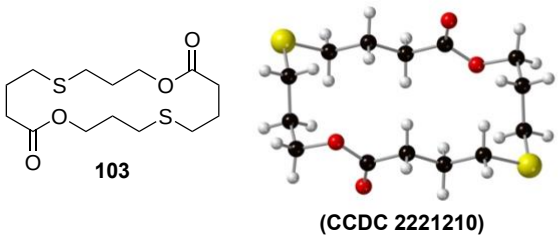
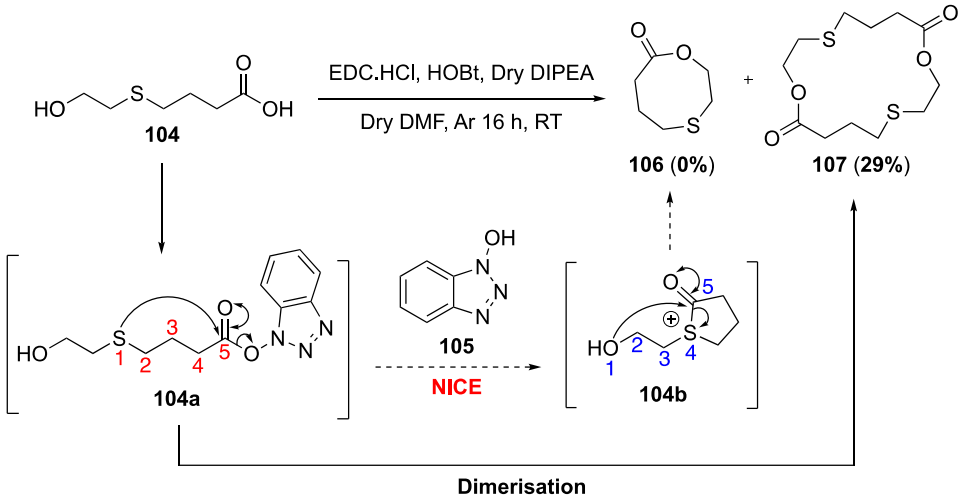


Figure 2.3.2 The **103** dimer (18-membered ring) **103** with an X-ray structure shown with Cambridge Crystallographic Data Centre (**CCDC**) deposition number

2.4.0 Attempts to synthesise sulphur-integrated medium-sized ring via a [5,5] NICE reaction connected via an aliphatic chain linker

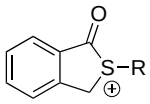
It was decided to modify the linear precursor system and try different reaction conditions for the NICE reaction. Carboxylic acid **104** (**Scheme 2.4.1**) was previously synthesised by another member of the Unsworth group, which provided a useful starting material to try another ring expansion reaction, which was performed using EDC.HCl and HOBt as an additive in anhydrous DMF.[138] The reaction was expected to operate in the same fashion as HATU, but with an OBt active ester **104a** intermediate formed instead. The first cyclization was proposed to occur in the same way as the HATU mechanism, to afford the five-membered acyl sulfonium **104b** with the displacement of HOBt **105**, whilst the second cyclization occurs via a 5-membered ring system due to the chain of the linker being one carbon shorter. However, after leaving the reaction mixture for 16 h at RT under an inert atmosphere, while consumption of the starting material was observed, the desired 8-medium-sized rings **106** was not formed; instead, macrocyclic dimer **107** was isolated in 29% yield.



Scheme 2.4.1 Attempted ring expansion cascade reaction of carboxylic acid **104** with EDC.HCl and HOBt, showing key steps mechanism

Unfortunately, the reaction described and performed above did not show any evidence of the anticipated cascade reaction taking place. It was thus decided to change the precursors by introducing aryl functionality to increase the rigidity of the system, with anticipation of an increased likelihood of the initial cyclization step taking place.[139,140] Confidence in this idea was provided by reports from 1977, in which Minato[141] and Lebedev[142] showed that aromatic thiol ester could be converted into a sulfonium cation of type **108**, which was observed and detected by ^{1}H and ^{13}C NMR spectroscopy at low temperatures. Later, in 2005, the Kozhevnikov group managed to isolate acyl sulfonium salts, where the "stability of which was

dictated by the bulky nature of aromatic groups surrounding their sulfonium cation functional" was observed.[143] Therefore, we reasoned that introducing some aromatic functionality may help to stabilize a 5-membered-ring acyl cation (**Fig. 2.4.2**, **108**).

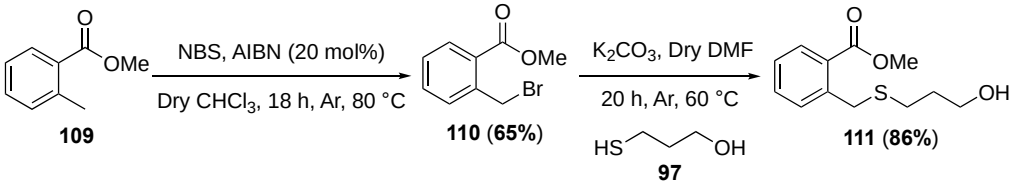


108

Figure 2.4.2 Structure of **108** five-membered-ring acyl sulfonium cation

2.5.0 Initial synthesis of aryl precursor and ring expansion via [5,6] via transition state

The synthesis of the desired precursor started with the Wohl-Ziegler bromination[144] of commercially available aryl ester **109**, which afforded bromide **110** in a good yield [145] (**Scheme 2.5.1**). Interestingly, the classical Wohl-Ziegler reaction is typically performed in solvents like benzene or CCl_4[146] however, in this case, chloroform was used due to it having fewer environmental impacts and safety considerations.[147] The next step in the synthesis was a Williamson-type sulfide formation to generate benzoate alcohol **111** (**Scheme 2.5.1**).[148] The same conditions used were applied on a 2.86 mmol scale, with the first batch of bromide **110**, and the reaction was followed by TLC. The consumption of bromide **110** was noted, where the reaction proved amenable to gram-scale synthesis and was also aided by straightforward liquid-liquid extraction and purification by column chromatography to yield **111** product in 86% yield (**Scheme 2.5.1**). The reaction to make **111** starting material was attempted five times in a scale range of 2.86 to 3.24 mmol with a mean yield of 82% and a standard deviation of 2.48, highlighting the small spread between % yields.

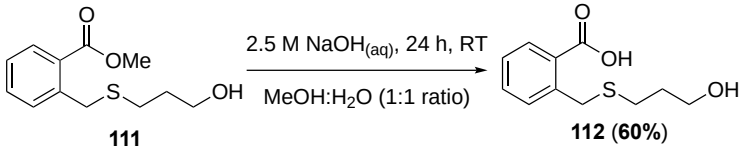


109 **110** (**65%**) **97** **111** (**86%**)

Scheme 2.5.1 Synthesis of benzoate alcohol **111** product with reaction conditions and isolated yields by a sequence of Wohl-Ziegler radical bromination and alkylation

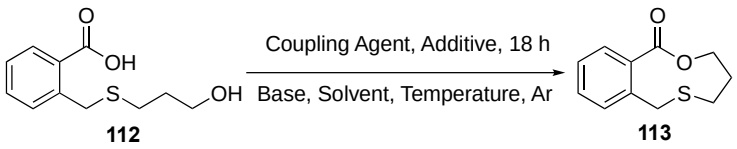
The next reaction step was ester hydrolysis under basic conditions to generate benzoic acid **112** in a good yield (**Scheme 2.5.2**). The reaction conditions were taken from the literature, [149] with slight modifications; instead of using 0.5 M of $NaOH_{(aq)}$, the concentration was increased up to 2.5 M. When complete consumption of aryl sulphide **111** was observed by

TLC, the reaction was acidified with 1.0 M $HCl_{(aq)}$, until pH = 2. The desired product was collected by simple Büchner funnel filtration without the need for further purification via flash column chromatography or recrystallisation.



Scheme 2.5.2 Reaction conditions for the synthesis of benzoic acid **112** with isolated yield

Several conditions reported for lactone formation were then tested on **112**, in the hope of promoting a NICE reaction to form lactone **113** (**Table 2.5.3**, **entry 1**–**9**). The first reaction conditions reported by Unsworth and co-workers using T3P were tried, with modification to the solvent system (DMF was used instead of $CHCl_3$) (**Table 2.5.3**, **entry 1**), where the solvent was changed since a "survey of amidation reactions using SciFinder revealed that 83% of approximately 680000 amide coupling reactions employed either CH_2Cl_2 (36%) or DMF (47%) as the reaction media".[150] But based on TLC analysis it was found that; lactone **113** was not synthesised. The reaction was repeated on a slightly larger scale (**Table 2.5.3**, **entry 2**), but this time the reaction conditions were followed exactly as reported by the Unsworth group, using chloroform as solvent.[128] The reaction was monitored by TLC and after 12 h consumption of acid **112** wasn't observed. The reaction was heated to 65 °C for 6 h to aid cyclization and, after that time, the consumption of benzoic acid **112** was noted. The reaction mixture was purified by column chromatography and the desired lactone **113** was obtained, albeit in a low 20% yield.

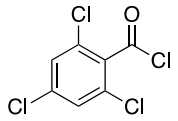


112 **113**

Entry	*Scale (mmol)*	*Coupling Agent*	*Additive*	*Base*	Solvent	Concentration (M)	Temperature (°C)	Isolated Yield of **113** (%)
1	0.513	T3P	N/A	DIPEA	DMF	0.10	RT	No reaction
2	0.898	T3P	N/A	DIPEA	$CHCl_3$	0.05	RT to 65	20
3	0.528	Yamaguchi reagent (**Fig. 2.5.4**)	DMAP	Et_3N	THF	0.10	RT	No reaction
4	0.988	EDC.HCl (**Fig. 2.5.5**)	HOBt	DIPEA	DMF	0.10	RT	86
5	0.513	EDC.HCl	HOBt	DIPEA	CH_2Cl_2	0.10	RT	45
6	0.513	HATU	N/A	DIPEA	DMF	0.10	RT	24
7	0.214	DCC	N/A	Et_3N	CH_2Cl_2	0.05	RT	No reaction
8	0.214	DCC	DMAP	Et_3N	CH_2Cl_2	0.05	RT	No reaction
9	0.214	CDI	N/A	Et_3N	CH_2Cl_2	0.05	RT	No reaction

Table 2.5.3 Synthesis of 9-membered aryl lactone **113** reaction conditions, isolated yields and result

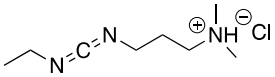
It was then decided to test a Yamaguchi etherification [151] and an EDC.HCl method (**Table 2.5.3**, **entry 3**–**5**). The Yamaguchi reaction conditions also proved to be unsuccessful, and none of the desired product was isolated. The corresponding reaction was monitored by TLC and mass spectrometry. Consumption of benzoic acid **112** was noted, and colour change to a green solution was immediately visible upon the addition of DMAP, which slowly darkened to a black/brown. But no sign of the product was observed upon analysis by NMR or by mass spectrometry.



114

Figure 2.5.4 Structure of the Yamaguchi/ 2,4,6-trichlorobenzoyl chloride/TCB reagent

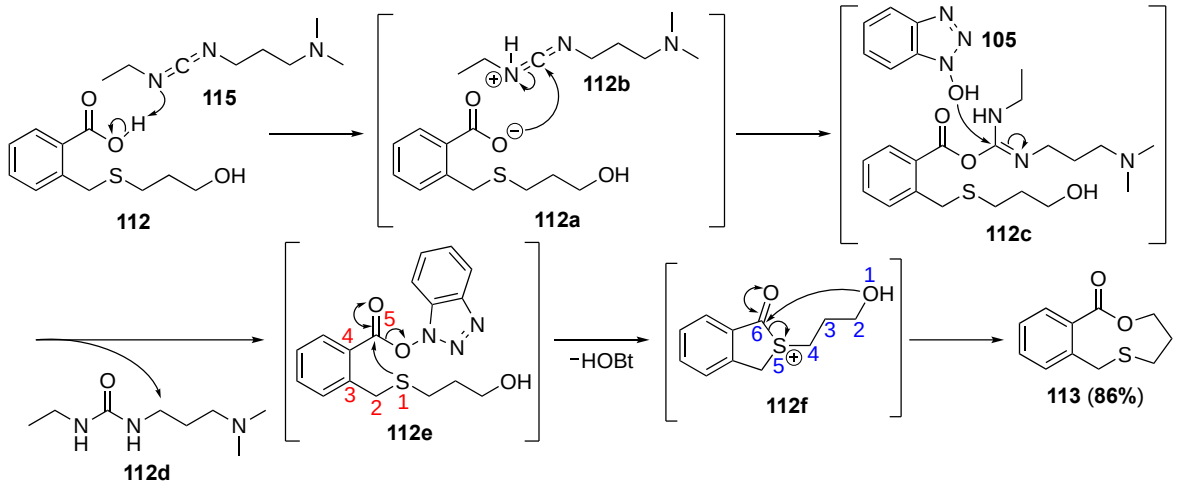
Next, it was decided to use the EDC.HCl (**Table 2.5.3**, **entry 4**) as a coupling agent with the same reaction conditions, and the results were encouraging. The reaction was monitored by TLC, and complete consumption of benzoic acid **112** was observed in 1 h, though the resulting reaction mixture was allowed to stir overnight (to aid completion). A change in the appearance of the reaction mixture was noted as the ring expansion proceeded. Benzoic acid **112** was colourless in solution, but a colour change to pale-yellow was noted in 10 min upon the addition of HOBt, and the reaction mixture slowly turned pink. We were pleased to discover that this protocol worked well, with the desired aryl lactone **113** being isolated after column chromatography in 86% yield as a white solid.



115

Figure 2.5.5 Structure of EDC.HCl (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide) **115** coupling reagent

Mechanistically, this EDC.HCl reaction likely starts with a free base of the corresponding coupling agent as EDC **115** (**Scheme 2.5.6**). The next step is the deprotonation of carboxylic acid **112** with carbodiimide **115** to afford carboxylate anion **112a** that would attack the protonated carbodiimide **112b** of EDC to afford *O*-acylisourea ester **112c** intermediate. The HOBt **105** reacts with electrophilic activated carboxylic acid/acylisoure **112c** [152] and after the urea **112d** by-product is discharged, the OBt-activated ester **112e** is formed after proton transfer.[153] Next, sulphur acts as an internal nucleophile and cyclizes via a five-membered ring with OBt-activated ester **112e** (numbers highlighted in red, **Scheme 2.5.6**) to form a five-membered acyl sulfonium **112f** intermediate.[154] The cation intermediate formed from the first cyclization undergoes second cyclization/ring expansion via the 6-membered ring (numbers highlighted in blue, **112f**, **Scheme 2.5.6**) with OH to yield a novel medium-sized ring **113** with a corresponding crystal structure. The X-ray crystal provided strong evidence that desired monomer is produced rather than a dimerised product (**Fig. 2.5.7**). A single X-ray crystal of monomer **113** was obtained by the low temperature crystallisation method of a supersaturated solution, where the purified product after column chromatography was dissolved in a minimum volume of *n*-hexane (approx. 2 mL) at RT and left overnight at –20 °C in a freezer.



Scheme 2.5.6 Reaction mechanism of EDC.HCl/HOBt for NICE reaction and structure of lactone **113** with isolated yield

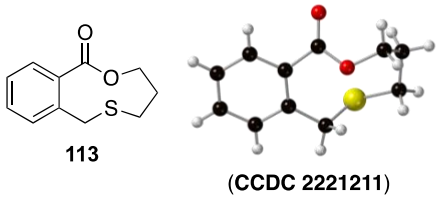


Figure 2.5.7 Structure of 9-membred ring **113** with X-ray crystal structure and **CCDC** deposit number

2.6.0 Substrate scope of ring expansion reaction

After discovering good conditions for the ring expansion cascade reaction, the next priority was to investigate the substrate scope and functional group tolerance. Initially, the aim was to boost functionalisation around the aromatic system by introducing halogens (bromide, iodide, etc.) around the ring. This will help to increase diversity and build the library of "lead-like" compounds by facilitating subsequent cross-coupling reactions (Suzuki coupling,[155] Heck reaction,[156] Stille Coupling,[157] Hiyama-Denmark Coupling[158] etc.) (**Fig. 2.6.1**).

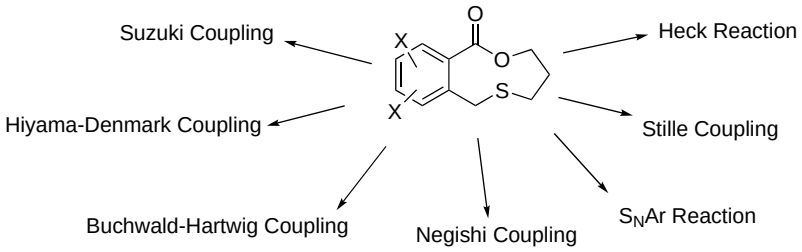
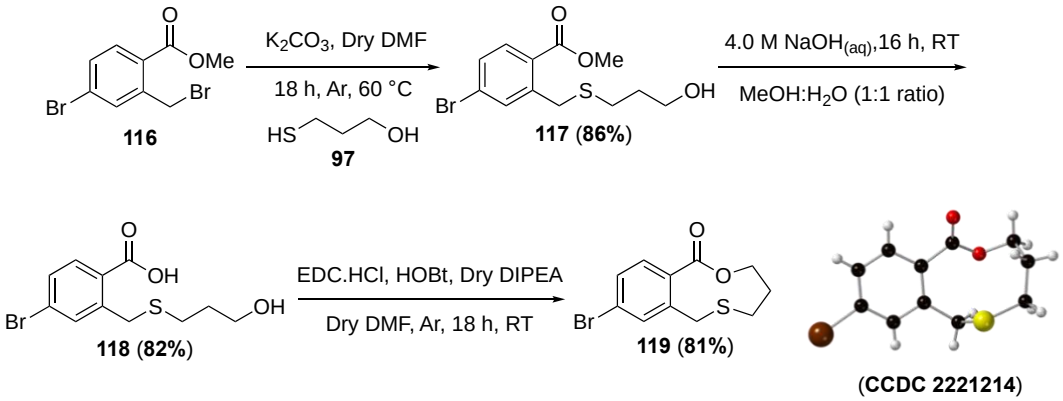


Figure 2.6.1 Possible cross-coupling reactions and another reaction with aryl halide functionality (i.e., Br, I, F etc.)

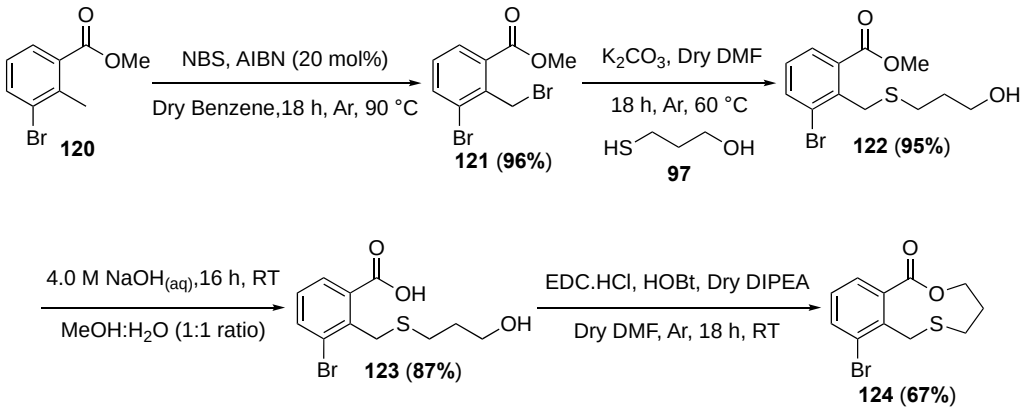
The first substrate synthesis began with bromine placed in *para*-position relative to the carboxylic acid, starting from the commercially available dibromide ester **116** (**Scheme 2.6.2**). The same reaction conditions were used as for the synthesis of unfunctionalized aryl lactone **113**. The first reaction step was a "Williamson" type reaction (**Scheme 2.6.2**, **116** → **117**) with no modifications to the initial experimental procedure, which resulted in a consistent yield of **117**. The next was the hydrolysis of the benzoate ester to form the corresponding benzoic acid **118**, which worked in excellent yield (compared with previous attempts)**.** This was achieved by increasing the concentration of $NaOH_{(aq)}$ up to 4.0 M and, after acidifying the reaction medium until pH = 2.0, the desired solid was collected by suction filtration with no further purification by column or liquid-liquid extraction. The final step of the reaction was the ring expansion with EDC.HCl and HOBt conditions. The reaction mixture was monitored by consumption of benzoic acid **118** via TLC. As expected, the result was successful, and the desired product **119** was isolated in an excellent 81% yield. A single crystal of *para*–bromide lactone **119**, shown in **Scheme 2.6.2**, was obtained by low temperature crystallisation method of a supersaturated solution, where the purified product after column chromatography was dissolved in a minimum volume of *n*-hexane (approx. 2 mL) at RT and left overnight at –20 °C.



Scheme 2.6.2 Synthesis route towards *para*–bromide lactone **119** with isolated yields and X-ray crystal structure with **CCDC** deposit number

The second substrate was chosen to facilitate the placement of the bromine in the *meta*-position relative to the carbonyl (**Scheme 2.6.3**). The first reaction in this sequence was a Wohl-Ziegler bromination (**Scheme 2.6.3**, **120** → **121**) to make the corresponding dibromide product, where modification to the solvent system was performed (here, anhydrous benzene was used instead of $CHCl_3$), which resulted in an increase in yield to 96%. The next step was using the same "Williamson" type reaction conditions previously described to yield sulfide (**Scheme 2.6.3**, **121** → **122**) in good yield. After the simple hydrolysis step of methyl ester to

form corresponding benzoic acid **123**, the ring expansion reaction with the optimized conditions was performed. The reaction mixture was monitored by consumption of benzoic acid via TLC. The reaction worked as expected, although the medium-sized ring product **124** was isolated in a slightly lower yield than for *para*-position bromide. This suggests that the bromide atom may result in some steric hindrance. The X-ray crystal structure (**Fig. 2.6.4**) showed that the distance of the bromide to hydrogen is less than the sum of the van-der-Waals radii indicating spatial interaction between two atoms on the medium-sized ring. A single crystal of *meta*–bromide lactone **124** was obtained by low-temperature crystallisation method of a supersaturated solution, where the purified product after column chromatography was dissolved in a minimum volume of *n*-hexane: EtOAc (approx. 4 mL) in a ratio of 3:1 at RT and left at –20 °C overnight in a freezer.



Scheme 2.6.3 Reaction sequence for the synthesis of *meta*–bromide lactone **124** with isolated yields and conditions

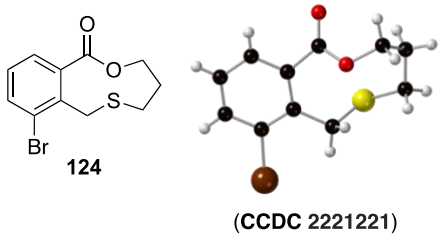
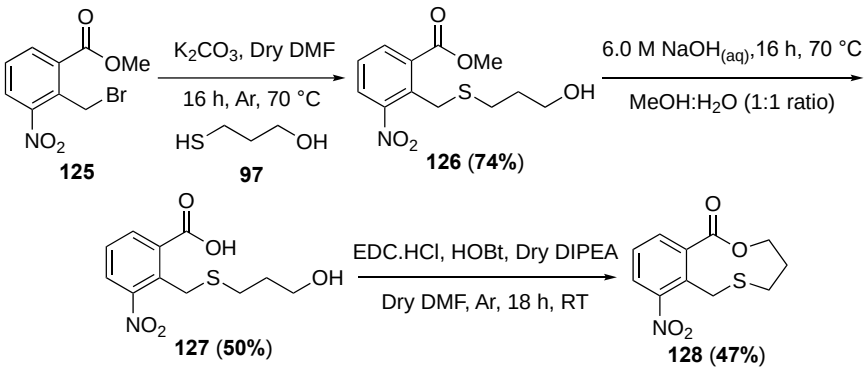


Figure 2.6.4 Structure of *meta*–bromide lactone **124** with its X-ray crystal structure and **CCDC** deposit number

Next, to investigate if the corresponding ring expansion is influenced by electronic effects, it was decided to place a strong electron-withdrawing group (-NO_2) *meta*- to the carbonyl functionality. This sequence started with the commercially available *meta*–nitro bromide ester **125** (**Scheme 2.6.5**). The "Williamson" type reaction achieved the desired product (**Scheme**

2.6.5, **125** → **126**), though a modification was needed during the hydrolysis of the aryl ester to achieve the desired benzoic acid **127** in a good yield. At RT, unreacted nitro alcohol **126** was observed by TLC, leading to a necessary modification of an increase of temperature and concentration of $NaOH_{(aq)}$ to 70 °C and 6.0 M, respectively. This result came as a surprise, with such harsh conditions being required to hydrolyse the methyl ester **126** to the corresponding carboxylic acid **127**, although this phenomenon is explained in the literature, where it has been shown that electron-withdrawing groups like $-NO_2$ can increase the activation energy for hydrolysis under base-mediated conditions.[159] The ring expansion cascade was then tested, and the result was broadly as expected; the desired product **128** **Scheme 2.6.5**, **127** → **128**) was isolated but with a lower yield compared to earlier substrates, suggesting that the strong electron-withdrawing $-NO_2$ destabilises the five-membered acyl sulfonium cation intermediate and thus lowers the yield.



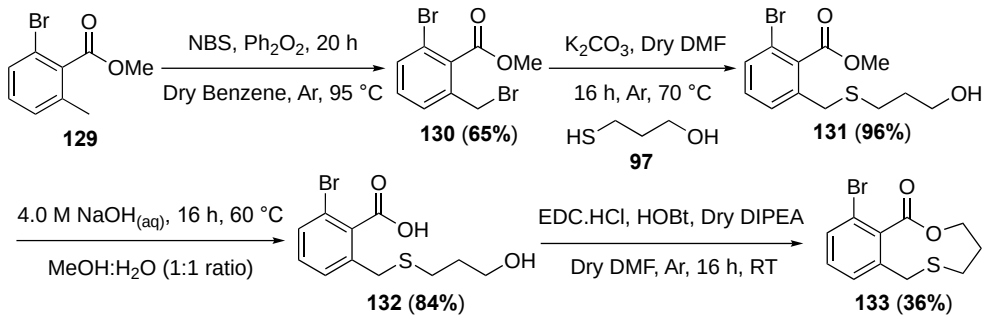
Scheme 2.6.5 Reaction sequence for affording *meta*–nitro lactone **128** with isolated yields and conditions

Many commercial explosives are composed of organic compounds with $-NO_2$ groups.[160] The most well know explosive is TNT, which is used extensively in military, industrial and mining applications.[161] Consequently, it was decided to perform calculations to assess whether nitro lactone **128** is likely to be a metastable molecule and not an explosive. This is done by using **Equation 1** (**Fig. 2.6.6**); this relates to amount of oxygen needed in the compound to fully oxidise carbon to CO or CO2, hydrogen to H_2O and sulfur to SO_2. The nitro lactone **128**, $OB\%$ number is $= -148.5\ \%$, because $OB\% = \frac{-1600}{253.2720\ gmol^{-1}} \times \left(2 \times 11 + \left(\frac{11}{2}\right) + 0 - 4\right)$. The OB% value is negative oxygen balance, indicating extra oxygen is needed for the completion formation of nitro lactone **128** molecules to CO_2, H_2O in the presence of external oxidant and its magnitude shows a lot of energy is required for denotation to take place. Hence nitro lactone **128** can be considered likely to be stable and safe.[162,163]

$$OB\% = \frac{-1600}{M_w} \times \left(2X + \left(\frac{Y}{2}\right) + M - Z\right) \textbf{ (Equation 1)}$$

Figure 2.6.6 Equation 1 for $OB\%$ – "Oxygen Balance for Thermal Hazards Assessment", M_w– molecular weight of compound, X – number of carbon atoms, Y– number of hydrogen atoms, M number of metal atoms, Z – number of oxygen atoms

Next, it was decided to place the bromide *ortho*- to the carbonyl functionality. The conditions reported for the Wohl-Ziegler were attempted on benzoate ester **129**, using Ph_2O_2 as the radical initiator instead of AIBN, to make bromide **130** (**Scheme 2.6.7**).[164] However, the modification caused a reduction in yield compared to previous attempts. The radical initiator was changed due to following the literature procedure where the same reaction has been conducted successfully; the decision was made to follow suit and use Ph_2O_2 as a reagent. Nonetheless, the moderate yield was tolerated, and the S_N2 reaction (**Scheme 2.6.7**, **130** →**131**) was performed with no modifications to the initial experimental procedure, which resulted in an excellent yield being obtained. The next step was hydrolysis of the aryl ester **131**, which worked well to form corresponding benzoic acid **132** in excellent yield. The cascade ring expansion reaction was performed using the EDC.HCl and HOBt conditions. The desired product **133** was isolated, albeit with the lowest yield of 36% (**Scheme 2.6.7**) when compared to the other substrates in this series. This observation again suggests that steric hindrance around the carbonyl and bromide could potentially result in sulfonium cation being pushed away from ideal sp^2 geometry and hence destabilizing the intermediate, resulting in a reduction in yield. This is supported by the X-ray structure, which shows that the distance of the bromide and carbonyl is less than the sum of the van-der-Waals radii, resulting in significant distortion of the C=O bond, which tilts inside the core of the medium-sized lactone **133** (compared to other X-ray structures (**Fig. 2.6.8**)). A single crystal of *ortho*-bromide lactone **133** was obtained by the hot-cold recrystallisation method, where the purified product after column chromatography was dissolved in a minimum volume of *n*-hexane (approx. 15 mL) at elevated temperature and left to cool gradually to RT overnight.



Scheme 2.6.7 Reaction sequence to make *ortho*-bromide lactone **133** with isolated yields and conditions

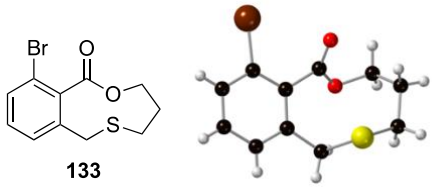
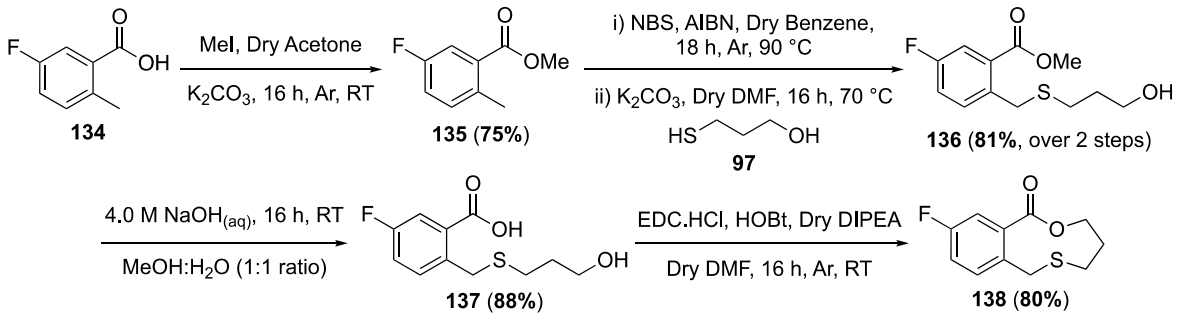


Figure 2.6.8 Structure of *ortho*-bromide lactone **133** with X-ray crystal structure and **CCDC** deposit number

To finish the functionalisation around the aromatic system with halogen atoms, a fluorine atom was placed in the 5-position relative to the carbonyl. Introducing the fluorine atom around the aromatic group allows for the use of visualising biological processes in a complex system using ^{19}F NMR technique.[165] Further, ^{19}F NMR spectroscopy has been widely applied in medicinal chemistry, driving early lead discovery efforts,[166] and the method is widely used in molecular imaging of tumour biomarkers.[167] In addition, the manipulation of this halogen via S_NAr chemistry gives a useful tool for further functionalisation reactions.[168]

This sequence began with the esterification of the commercially available fluoro-methyl benzoic acid **134** (**Scheme 2.6.9**) using the conditions reported in literature,[169] to afford methyl ester **135** (**Scheme 2.6.9**) in a good yield. The next reaction step was the Wohl-Ziegler bromination followed by S_N2 reaction to yield the desired sulfide ester (**Scheme 2.6.9**, **135** → **136**) with 81%, over two steps. The hydrolysis of the benzoate ester **136** was performed under mild conditions to form the corresponding benzoic acid **137** in excellent yield. The ring expansion cascade step was successful, with the desired product *meta*-fluoro lactone **138** isolated with an excellent 80% yield. The X-ray crystal data supported that the desired monomer **138**, rather than a dimeric product, was afforded (**Fig. 2.6.10**). A single X-ray crystal

of *meta*-fluoro **138** was crystallised from a saturated solution of purified product after column chromatography from *n*-hexane by leaving it at –20 °C overnight in a freezer.



Scheme 2.6.9 Synthesis of *meta*-fluoro lactone **138** from fluoro-methyl benzoic acid **134** with isolated yields and reaction conditions

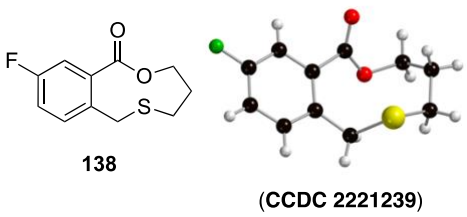


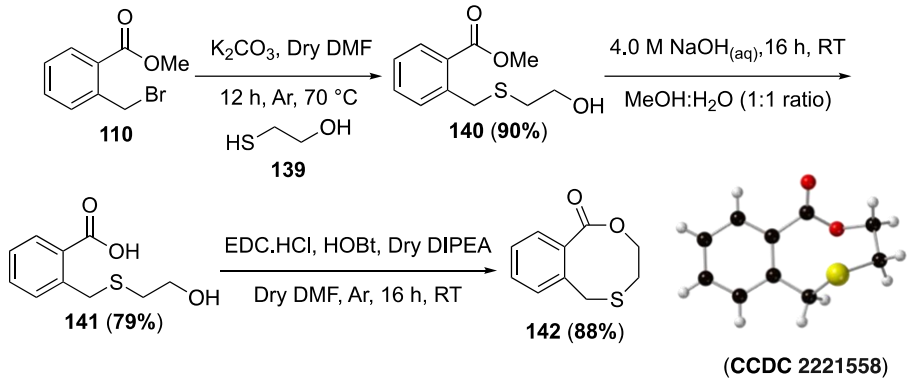
Figure 2.6.10 Molecular structure of *meta*-fluoro lactone **138** with X-ray crystal and **CCDC** deposit number

2.7.0 Further substrate scope by changing the linker and varying the terminal nucleophile

After successful results were obtained for the functionalisation of the aromatic system, it was decided to increase diversity by varying the size of the linker and the terminal nucleophile (SH, 2° alcohol, aniline and NH_2). Changing the length of the linker enables us to obtain different sized rings, in particular eight-membered rings. In general, the synthesis of eight-membered ring compounds is challenging;[170] entropic factors and transannular interactions, mean that linear precursor molecules typically employed in cyclization reactions to make eight-membered rings tend to react intermolecularly, leading to unwanted dimerization or polymerization, instead of cyclization.[171,172]

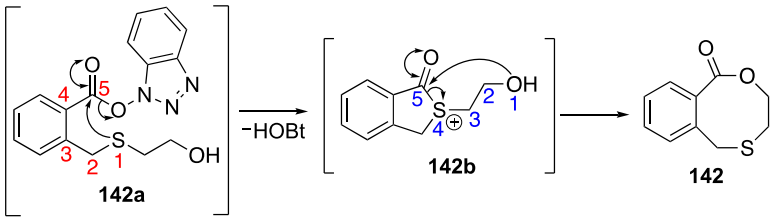
The synthesis of eight-membered lactone **142** commenced with the same reaction conditions described in the previous sections above, where the overall yield of the whole process is 50% (**Scheme 2.7.1**, over 3 steps from **110** → **142**). The results are encouraging because no side reactions were observed (i.e., formation of dimer) in the cascade ring expansion step, which

worked in an excellent yield of 88%. A single X-ray crystal, shown in **Scheme 2.7.1**, was crystallised from *n*-hexane by leaving the saturated mixture of eight-membered lactone **142** at –20 °C overnight in a freezer.



Scheme 2.7.1 Synthesis of 8-membered lactone **142** from bromide **110** with isolated yields, conditions, and X-ray crystal structure and **CCDC** deposit number

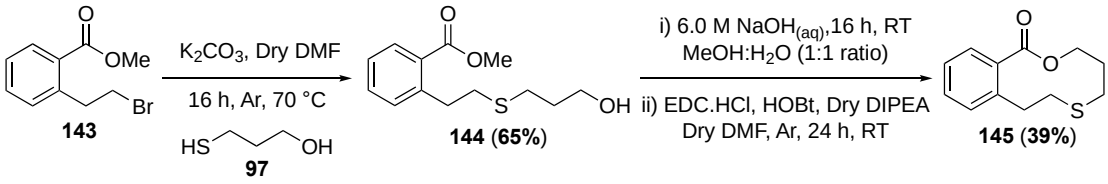
The synthesis of the 8-membered lactone **142** works in a similar fashion as before, where the OBt active ester **142a** (**Scheme 2.7.2**) is formed. Sulphur first undergoes nucleophilic cyclization via a five-membered ring (**Scheme 2.7.2**, [**142a**] → [**142b**]) to give a cationic intermediate with the elimination of HOBt, which may be referred to as a catalyst due to regeneration after completion of the reaction, which will be ring expanded by five-membered cyclization (**Scheme 2.7.2**, [**142b**] → **142**) to yield the desired medium-sized ring.



Scheme 2.7.2 Mechanism for the formation of 8-membered lactone **142** with EDC.HCl + HOBt only shows key steps and intermediates

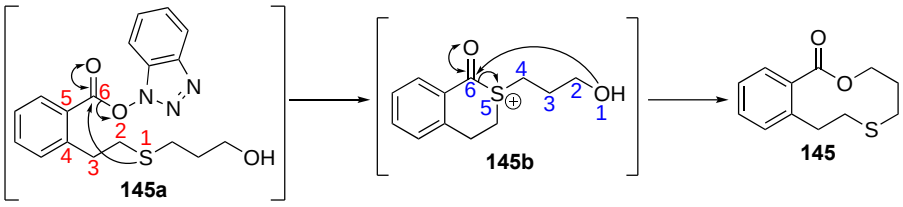
The next medium-sized ring was synthesized by varying the linker length to enable the synthesis of a ten-membered ring. The change began by adding one carbon to the benzylic position adjacent to the sulphur (**Scheme 2.7.3**, **143**). After simple reaction steps, the desired ten-member ring was isolated at a 39% yield over two steps (**Scheme 2.7.3**, **144** →**145**), which was a lower yield than those discussed previously. These results indicate that when you move

away from the ideal geometry of the planer of the 5-membered acyl sulfonium cation, the cascade is less efficient.



Scheme 2.7.3 Synthesis of 10-membered lactone **145** with isolated yields and reaction conditions

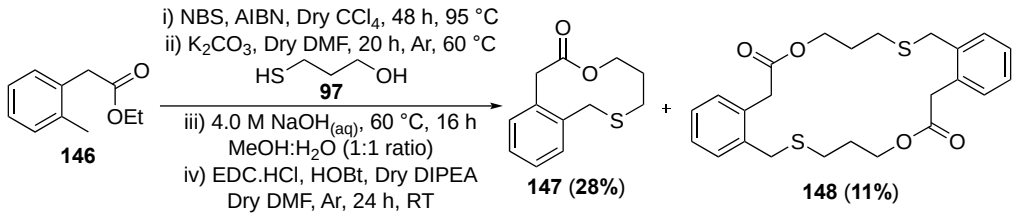
The reduction in yield could also be explained by looking at the key step of the reaction mechanism with EDC.HCl and HOBt. The OBt-activated ester **145a** (**Scheme 2.7.4**) intermediate would be under intramolecular nucleophilic cyclization from sulphur via *a* six-membered ring (**Scheme 2.7.4**, [**145a**] → [**145b**]). This first cyclization leads to the formation of a six-membered acyl sulfonium cation **145b** intermediate (**Scheme 2.7.4**), which will further ring expand via a six-membered path with OH (as terminal nucleophile) to the desired product **145**. One of the speculations is due to both cyclizations' needing to proceed through a six-membered energy pathway, compared to the reaction mechanism in **Scheme 2.5.4** (**section 2.5.0**), where cyclization occurs via the five- and six-membered system. Based on experimental values of stain energies of cyclohexane and cyclopentane (0.1 kcal mol^{-1} and 6.2 kcal mol^{-1}, respectively),[173] which indicates that six-membered acyl sulfonium cation **145b** (**Scheme 2.7.4**) is formed, the intermediate may be less likely to be ring expanded further via second cyclization. If the rate of cyclization of sulfur with an electrophilic-activated carboxylic acid is slower when it proceeds via a six-membered transition state, this will likely result in more competition from the bimolecular reaction, i.e., polymerisation, thus reducing the yield of **145**.



Scheme 2.7.4 Mechanism for the formation of 10-membered ring **145** with EDC.HCl + HOBt only shows key steps and intermediates

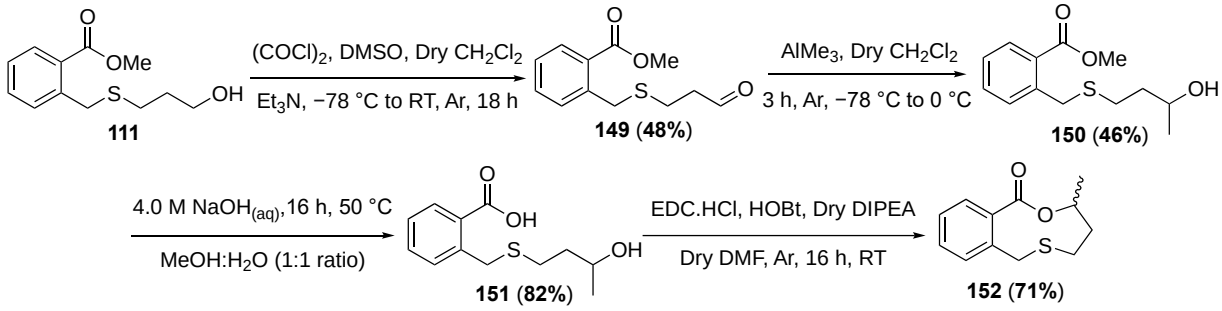
To synthesise a different ten-membered ring lactone, another substrate was chosen. The synthesis began with the commercially available **146** esters (**Scheme 2.7.5**), and after four sequence reaction steps, the desired ten-membered ring **147** (**Scheme 2.7.5**) and dimer **148** were isolated. This again shows that sulfide NICE reactions are less effective when they

proceed via six-membered cyclization compared to five-membered cyclization. Based on general cyclization chemistry literature, the general rate of formation of a five-membered ring is typically faster compared to a six-membered (even though six-membered rings tend to be more thermodynamically stable).[174,175]



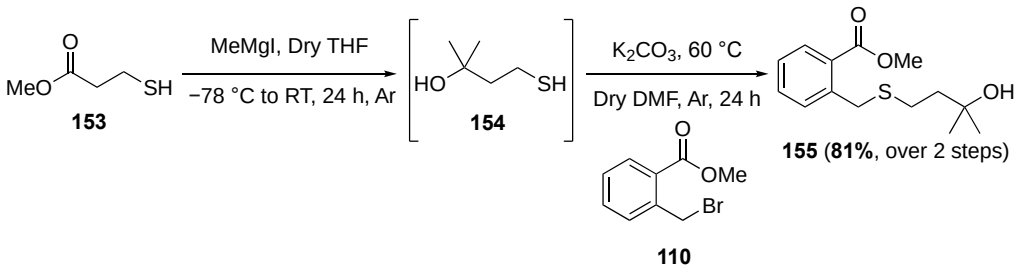
Scheme 2.7.5 Synthesis of ten-membered ring **147** and dimer **148** with isolated yields

Next, it was decided to move on and change the terminal nucleophile on the linker. Previously, the Unsworth groups have looked at 2° alcohol acting as the terminal nucleophile.[128] Therefore, this was considered to be a good starting point. Rather than following normal procedure, which would require a "Williamson" type reaction to form a sulfide with a secondary alcohol and the end of the chain, it was decided to use a primary alcohol and then perform a Swern oxidation.[176] This formed an aldehyde (**Scheme 2.7.6**, **111** → **149**) from alcohol **111** in a modest yield**.** The next step was the chemoselective methylation[177] of the aldehyde in the presence of the ester functional group to obtain the desired secondary alcohol (**Scheme 2.7.6**, **149** → **150**) in 46% yield, which was followed by hydrolysis under basic conditions at 50 °C to form carboxylic acid **151**. The reagent $AlMe_3$ was chosen as it has precedent in the literature, where an aldehyde was selectively methylated in the presence of methyl ester functionality on a similar substrate.[177] The final step of the reaction was the ring expansion with EDC.HCl and HOBt conditions and the result was successful; the desired product **152** was isolated in 71% yield, overcoming possible steric hindrance issues regarding using secondary alcohol as the terminal nucleophile.



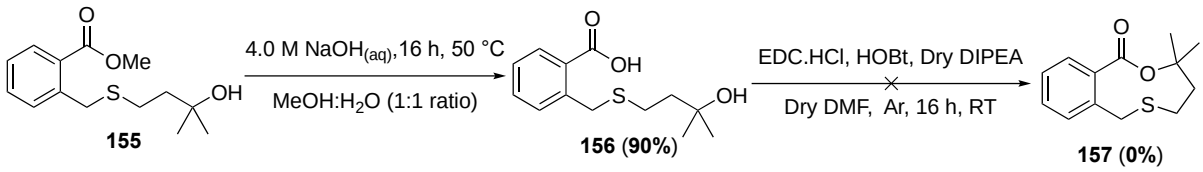
Scheme 2.7.6 Synthesis of 9-membered lactone **152** with isolated yields and conditions

As part of investigating and varying the terminal nucleophile, 3° alcohol was tested to see if the same result could be achieved as with 2° alcohol. In this instance, the reaction started with the formation of thiol alcohol **154** (**Scheme 2.7.7**), following a literature method[178] with modifications to the initial procedure. The first modification was the use of MeMgI instead of MeMgBr. The second modification was the use of dry ice and acetone to cool the reaction mixture to −78 °C and then allow the mixture to warm gradually to RT overnight, rather than adding a Grignard reagent to the reaction mixture over a period of "3.5 h and then refluxing for an additional 3 h at reflux ". This was done to avoid the generation of excess heat due to the reaction being exothermic.[178,179] The desired thiol alcohol **154** generated from ester **153** (**Scheme 2.7.7**) wasn't isolated nor characterised and, after simple liquid extraction, was taken directly to the next. After a simple S_N2 reaction with thiol alcohol **154** and benzoate bromide **110** (**Scheme 2.7.7**), the desired product **155** was isolated in good yield. It is important to note that thiols are more acidic than their corresponding alcohols (pK_a of RSH of ROH are ≈ 10.0 and 16.0, respectively).[180,181,182]



Scheme 2.7.7 Synthesis of tertiary alcohol **155** with isolated yields and conditions, starting from commercially available thiol ester **153**

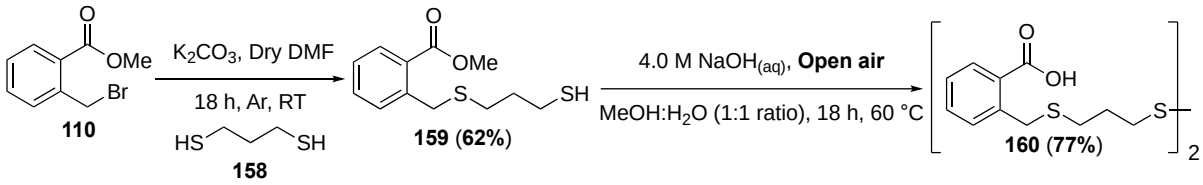
After alcohol **155** (**Scheme 2.7.7**) was synthesised, the resulting product was hydrolysed under basic conditions to give carboxylic acid **156** (**Scheme 2.7.8**) an excellent yield. Unfortunately, after several attempts to try to make the cyclisation work, with linear precursor **156** using EDC, HCl and HOBt conditions at RT and higher temperatures, the desired product **157** (**Scheme 2.7.8**, **156** → **157**) was not synthesised. This result was unexpected since the Unsworth group had already achieved similar transformations with a 3° alcohol acting as the terminal nucleophile,[128] and also a 2° alcohol has been shown above as being capable of acting as a terminal nucleophile in **Scheme 2.7.6**. A potential reason for the reaction failure may be the steric bulk of the two methyl groups of the 3° alcohol as the terminal nucleophile; the A value of a single CH_3 is 1.7 kcal mol^{-1}, and $CH(CH_3)_2$ is 2.15 kcal mol^{-1}.[183,184] However, further investigation would be required to determine the exact reason for this reaction's failure.



Scheme 2.7.8 Synthesis of linear precursor benzoic acid **156**; isolated yields, reaction conditions and failed NICE reaction with 3° alcohol as a terminal nucleophile

To further expand the substrate scope, it was decided to try using thiol (R-SH) as the terminal nucleophile instead of an alcohol (R-OH) or amine (R_2NH), which had not previously been done by the Unsworth group in any system. The reaction opens the chance to make cyclic thioesters, which are common intermediates in many biosynthetic reactions, including the formation and degradation of fatty acids and mevalonate, a precursor to steroids.[185]

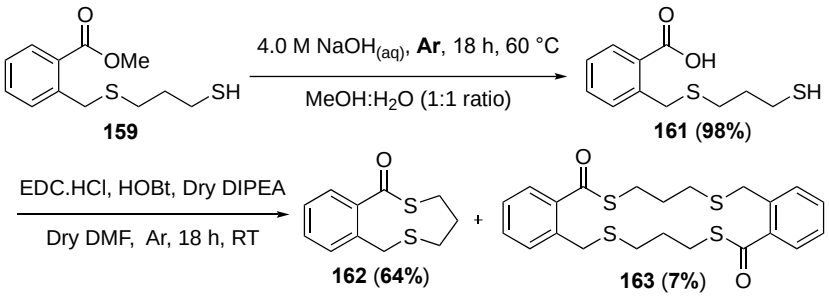
The synthesis of thioester (**Scheme 2.7.9**) commenced with a simple S_N2 reaction to afford the desired thiol **159** (**Scheme 2.7.9**, **110** + **158** → **159**) in a good yield, where the reaction proceeded at RT with no need for elevated temperature. The next step was the hydrolysis of the methyl ester **159** to obtain carboxylic acid, which caused problems. Initially, the reaction was performed under the same reaction condition as described in previous sections, with an air condenser that was open to the air. The disulfide **160** (**Scheme 2.7.9**) product was isolated in 77% yield, likely formed due to the presence of O_2 and the elevated temperature.[186] In nature, disulfide bonds (R−S−S−R), such as those in cystine, are formed via oxidation from the corresponding thiols of cysteine ($HO_2C-CH(-NH_2)-CH_2-SH$).[187,188]



Scheme 2.7.9 Synthesis of thiol ester **159** and disulfide **160** with isolated yields and reaction conditions

This indicates that oxygen-free conditions must be employed, and hence the reaction was subsequently performed under an inert atmosphere of argon (Ar), and all the solvents (MeOH) were degassed for 20 min to remove any oxygen that was dissolved; this led to a much more successful hydrolysis reaction to form carboxylic acid **161** in 98% yield. The final step of the reaction was the ring expansion, which gave an excellent result - the desired thioester **162**

(**Scheme 2.7.10**, **159** → **161** → **162** and **Fig. 2.7.11**) was isolated in high purity at 64% yield after column chromatography, with a minor dimeric side product **163** (**Scheme 2.7.10** and **Fig. 2.7.11**) obtained in much lower (7%) yield. Thiols being more nucleophilic than alcohols[189] may account for the formation of the dimer by-product; more reactive terminal nucleophiles may enable other alternative energy pathways to become available i.e., biomolecular reaction/dimerization. Furthermore, thioester and thiolactones are liable functional groups and susceptible to hydrolysis,[190] and are often described as "latent thiols".[191] Therefore, lower yield may be due to the simple fact that thioester **162** is unstable and some of the product may have hydrolysed during purification steps. A single X-ray crystal of monomer **162** and dimer **163**, shown in **Fig. 2.7.11**, were both crystallised by slow evaporation of *n*-hexane.



Scheme 2.7.10 Reaction sequence for the synthesis of thioester **162** and dimer **163** with isolated yields

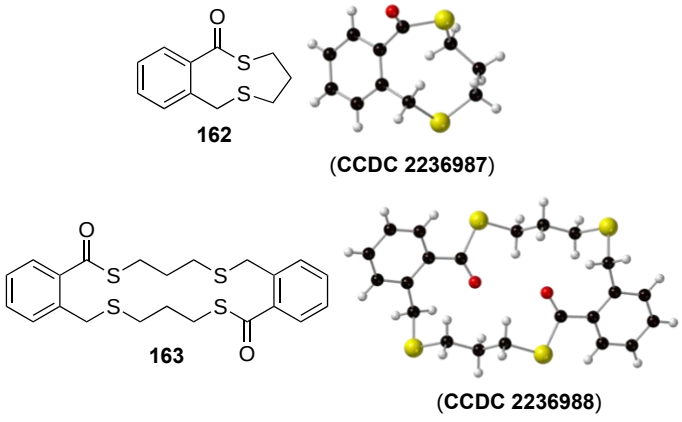
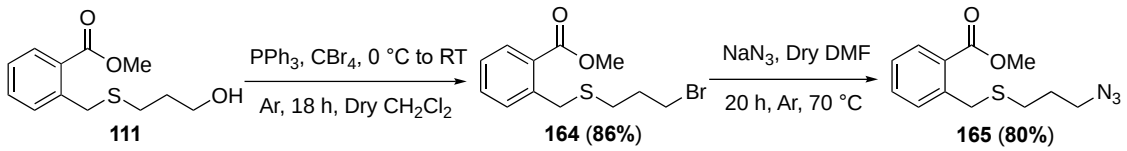


Figure 2.7.11 Shows molecular structures of monomer **162** and dimer **163** with their X-ray crystals and the corresponding **CCDC** deposit numbers associated with them

Next, it was decided to try an amine (RNH_2) as the terminal nucleophile; this is despite the fact that primary amines gave the worst result (i.e., lowest yield) when investigated by the Unsworth groups as the terminal nucleophile in the published NICE study.[128] The synthesis began with the formation of bromide **164** (**Scheme 2.7.12**) from corresponding alcohol **111**,

using Appel conditions from the literature.[192] The desired bromide **164** was achieved in excellent yield and, after S_N2 reaction with NaN_3, gave the desired product **165** in 80% yield (**Scheme 2.7.12**, **164** → **165**). The reaction vessel was covered in foil initially until it was established that the azide was not light-sensitive. The reaction to make **164** starting material was attempted four times in a scale range of 1.21 to 3.24 mmol with a mean yield of 82% and a standard deviation of 2.69. The small standard deviation highlights minimal spread between % yields, suggesting the reliability of the reaction to consistently obtain a higth yiled.



Scheme 2.7.12 Reaction sequence for bromide **164** and azide **165** synthesis with isolated yields and conditions

Before azide **165** was synthesised, safety when handling this azide was considered. Based on the equation developed by Sharpless and coworkers shown in **Fig. 2.7.13**,[193,194] organic azides are considered to be potentially explosive upon the introduction of an external energy source (heat and/or light) if the total number of carbon and oxygen atoms is less than three times the number of nitrogen atoms. Hence before the reaction was performed, the hazards associated with organoazides with low molecular weight were assessed. According to **Equation 2** (**Fig. 2.7.13**), for the target product azide, the number is $\frac{12+2}{3} = 4.67$, which is outside the threshold for potential explosivity. Therefore, we judged it to be safe for organic azide **165** to be isolated by column chromatography and stored in its pure form.

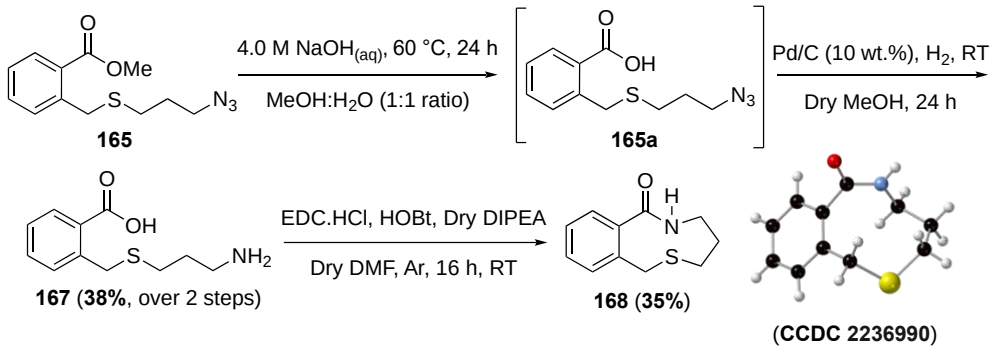
$$\frac{N_c + N_O}{N_N} \geq 3 \ (\mathbf{Equation\ 2})$$

Figure 2.7.13 Equation 2[194] takes into consideration all nitrogen's atoms in organic azide product, N_c– number of carbon atoms, N_O – number of oxygen atoms and N_N – number of nitrogen atoms

In addition, oxygen balance calculations were performed on azide **165**, using **Equation 1** (**Fig. 2.6.6**), where the number for $OB\% = -177.9\ \%$. Its negative oxygen balance and magnitude indicate that azide **165** is likely not explosive and is not easily detonated by external oxidants.

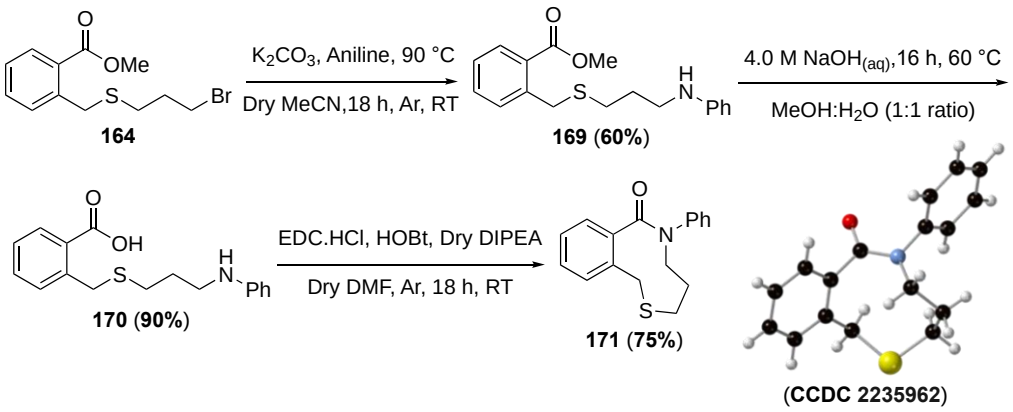
The organic azide **165** was hydrolysed, under basic conditions using 4.0 M $NaOH_{(aq)}$, to yield crude benzoic acid azide **165a** (**Scheme 2.7.14**, **165** → [**165a**]), which was taken directly to

the next reaction step without purification after liquid-liquid extraction. The resulting azide **165a** was then reduced directly via hydrogenation conditions to yield amino acid **167** (**Scheme 2.7.14**, [**165a**] → **167**) in 38% yield, over the two steps. The NICE reaction was then attempted and, afforded the expected medium-sized ring lactam **168** (**Scheme 2.7.14**, **167** → **168**), albeit in lower yield than other examples, as was expected based on the precedent. The main reason for the low yield obtained is that by changing the terminal nucleophile from -OH to RNH_2, we are making the nucleophile more reactive, resulting in increasing the rate of biomolecular processes, i.e., polymerisation and dimerization, whilst keeping the internal sulfur nucleophile constant. As a result, this leads to alternative reaction pathways being accessed and, therefore, a lower yield of the NICE product **168** is obtained. A single X-ray crystal of amide **168**, shown in **Fig. 2.7.14**, was crystallised by slow evaporation of MeOH:$CHCl_3$, at the ratio of 1:4 in approx. 5 mL of solvent.



Scheme 2.7.14 Reaction sequence for the synthesis of 9-membered amide **168**, showing isolated yield, conditions, and X-ray crystal structure with **CCDC** deposit number

After this relatively successful result, it was decided to use an aniline as a terminal nucleophile, which was shown by the Unsworth group to take part in high yielding NICE reactions (in the region of 80-100%) in previous studies. The synthesis of the aniline **170** (**Scheme 2.7.15**) began with a simple alkylation of bromide **164** to give the desired benzoate secondary aniline **169** (**Scheme 2.7.15**, **164** → **169**). The next step was the hydrolysis of the methyl ester with 4.0 M $NaOH_{(aq)}$ to yield benzoic acid **170** (**Scheme 2.7.15**) in excellent yield. Aniline-containing medium-sized lactam **171** (**Scheme 2.7.15**, **170** → **171**) was then formed in 75% yield after NICE reaction and simple purification via column chromatography. A single X-ray crystal of phenyl **171**, shown in **Fig. 2.7.15**, was crystallised by slow evaporation of *n*-hexane.



Scheme 2.7.15 Reaction sequence with the condition to afford 9-membered aniline **171**, showing isolated yields and X-ray crystal structure with **CCDC** deposit number

2.8.0 Mechanism studies

Given the challenge of forming eight-, nine- and ten-membered rings, the efficiency of the NICE reactions described was very promising, since they were performed under mild conditions and at 0.1 and 0.05 M concentrations. Nonetheless, to eliminate the possibility that they are simply unusually efficient examples of direct intramolecular cyclization, benzoic acid **172** (analogous to **112** but without the sulphur heteroatom, **Fig 2.8.1**) was synthesised as a control substrate. The idea was to see if a medium-sized ring could be generated from **172** under the same conditions used to convert **112** into lactone **113** – if so, this would shed doubt on whether the sulfur atom is really involved in the NICE cascade reaction of **112**.

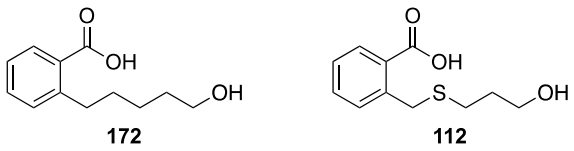
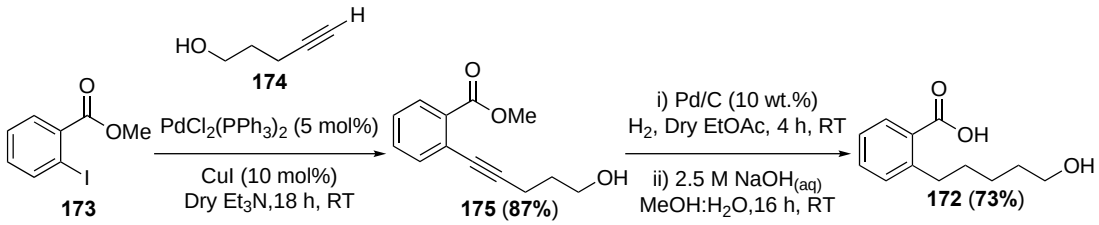


Figure 2.8.1 Molecular structures of two benzoic acids **172** and **112**

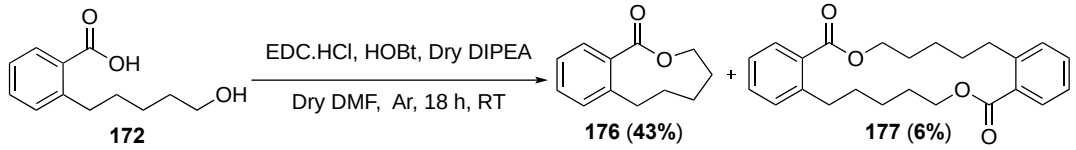
The synthesis of carboxylic acid **172** (**Scheme 2.8.2**) started with classical conditions reported by Sonogashira and co-workers.[195] This was done with commercially available iodide **173** and terminal alkyne **174** (**Scheme 2.8.2**), which afforded the desired alkyne **175** in excellent yield. The next step was the hydrogenation of the alkyne **175** according to a literature procedure.[196] The reaction was conducted in a 250 mL round-bottom flask, allowing larger headspace for hydrogen gas to occupy (2 balloons were consumed during a 4-hour period). Upon completion, the reaction mixture was filtered through Celite®, and the crude alkane product was taken directly to the next step without further purification via column chromatography. The

next step in the reaction was to hydrolyse the methyl ester **175** to the corresponding benzoic acid **172** (**Scheme 2.8.2**, **175** → **172**), which was achieved in good yield.



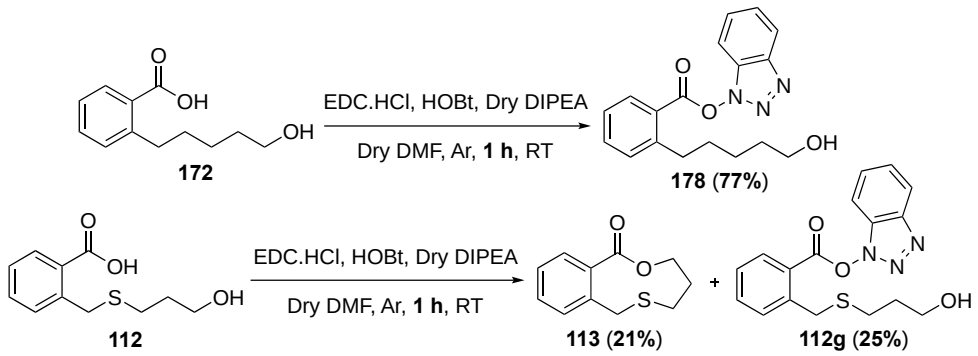
Scheme 2.8.2 Synthetic route towards the acid **172** linear precursor with isolated yields and conditions

With **172** prepared, it was then tested under our typical ring expansion cascade conditions using EDC.HCl and HOBt as coupling reagents. The result of this test showed that the formation of the medium-sized lactone **176** is possible without the internal S-nucleophile in this case, although importantly, the yield was significantly lower (43% compared to 86% for **113**, **Table 2.5.3**, **entry 4**). The reaction without sulphur was also noticeably slower (benzoic acid **172** was not fully consumed after 18 h, based on TLC analysis, **Scheme 2.8.3**). In addition, the dimeric side-product **177** (not previously observed in the sulphur-containing system) was formed and isolated in a 6% yield.



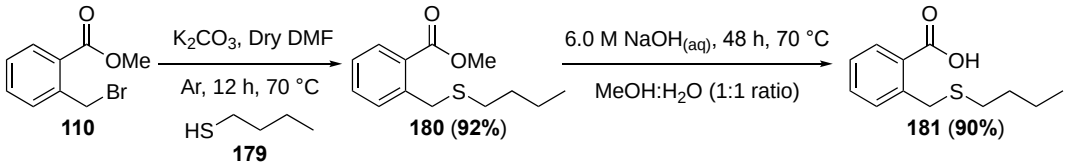
Scheme 2.8.3 Control reaction for the synthesis of monomer **176** and dimer **177**, a key cascade cyclization reaction for proving the NICE concept

To better compare the rates of the reactions for systems with and without internal S-nucleophile, acids **172** and **112** (**Scheme 2.8.4**) were each treated for 1 hour under the same reaction conditions. The products obtained from each reaction were determined, and the isolated yields measured after purification by flash column chromatography. The results clearly show that the sulfur-containing substrate **112** reacts faster, with the medium ring product (**113**) only seen in the S-containing reaction. Both reactions were incomplete, with activated HOBt esters **112g** and **178** (**Scheme 2.8.4**) also observed; note, full data was not collected for these reactive compounds as they were too unstable to isolate.[197]



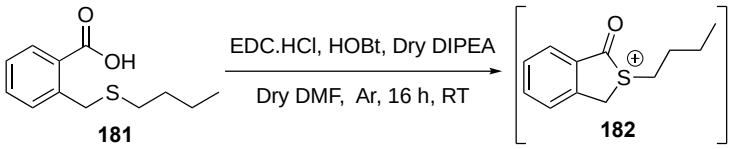
Scheme 2.8.4 Comparison of the reactions rates of two benzoic acids **172** and **112** with their corresponding isolated products/intermediates after leaving the reaction for 1 hour under the same conditions

Further mechanism studies were conducted to see if the proposed five-membered-ring acyl sulfonium cation intermediate could be detected via mass spectrometry (MS) and NMR spectroscopy. To achieve this, benzoic acid **181** was synthesized as shown in **Scheme 2.8.5**.



Scheme 2.8.5 Reaction sequence for the formation of linear precursor acid **181** and isolated yield without internal nucleophiles at the end of the chain

Carboxylic acid **181** was then subjected to the standard conditions with EDC.HCl and HOBt (**Scheme 2.8.6**) conditions, and we were pleased to find that the five-membered-ring acyl sulfonium cation **182** was observed by MS. The APCI$^+$ method of MS of the reaction mixture identified ion peak at m/z of 207.0847 which corresponds to cationic intermediate **182** $[C_{12}H_{15}OS]^+$ (**Fig. 2.8.7**). In addition to the desired intermediate detected, the by-product urea **183** (**Fig. 2.8.7**) ion peak at m/z of 174.1609 was observed, which provides supporting evidence that the NICE reactions proceed via the cascade mechanism which had been postulated. The observation of this intermediate confirms that species like **182** can be formed under the reaction conditions and therefore provides reasonable support that the ring expansion cascades of analogous sulfides also proceed via this type of intermediate (e.g., linear starting materials like **112** in **Scheme 2.5.6**, **section 2.5.0**).



Scheme 2.8.6 Reaction for the formation of 5-membered acyl cationic intermediate **182**, not showing the counter anion associated with the cationic species

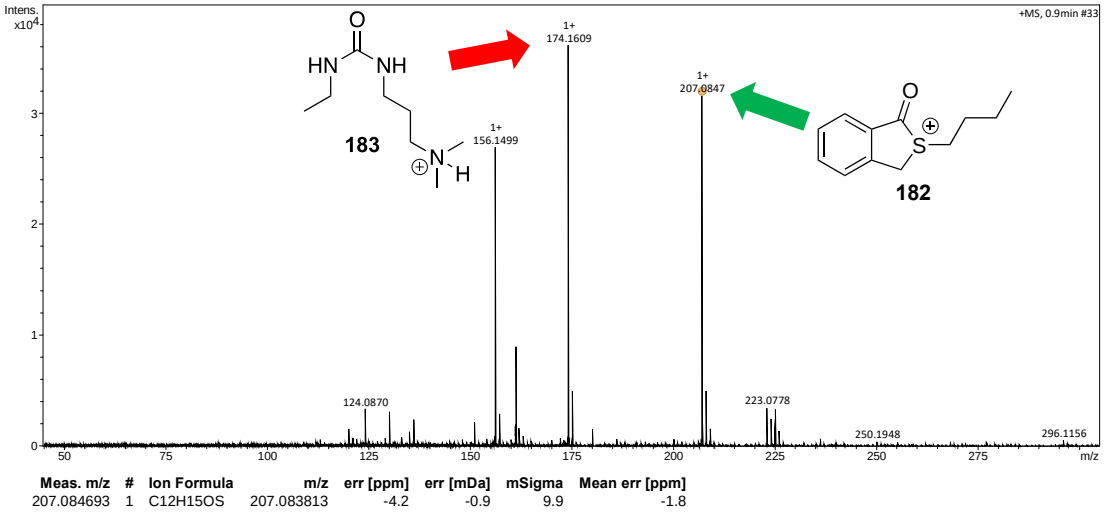


Figure 2.8.7 Atmospheric Pressure Chemical Ionisation (APCI) positive mode of ionisation spectrometry report of the reaction mixture and corresponding m/z ion peaks with the assignment of possible structures

However, while the 5-membered-ring acyl sulfonium cation **182** was observed by APCI$^+$, this could have been generated inside the mass spectrometer machine, or be a minor intermediate detected at a trace level (owing to the sensitivity of mass spectrometry).[198] To rule out the possibility that an intermediate was formed *in situ* inside the MS, a different mode of ionisation was tried. The ESI$^+$ mode of ionisation didn't show any m/z peaks for cationic intermediate **182** $[C_{12}H_{15}OS]^+$, where instead HOBt active ester **184** and urea by-product **183** (**Fig. 2.8.8**) was observed at 364.1098 and 174.1060 m/z, respectively. The major peak at m/z of 130.1591 is protonated Hünig's base **185** (**Fig. 2.8.8**), which is used as an excess reagent.

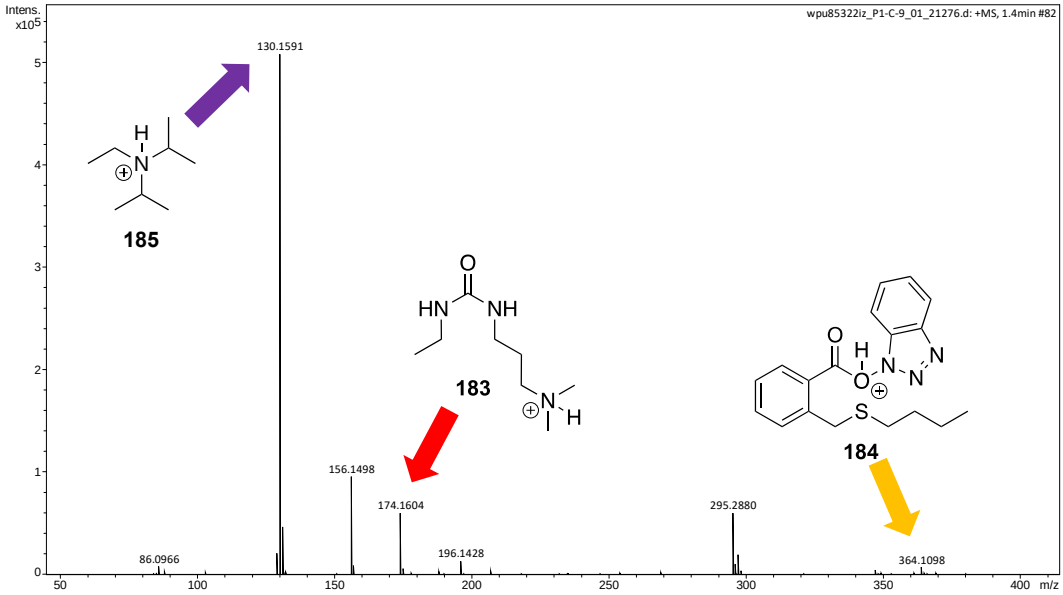
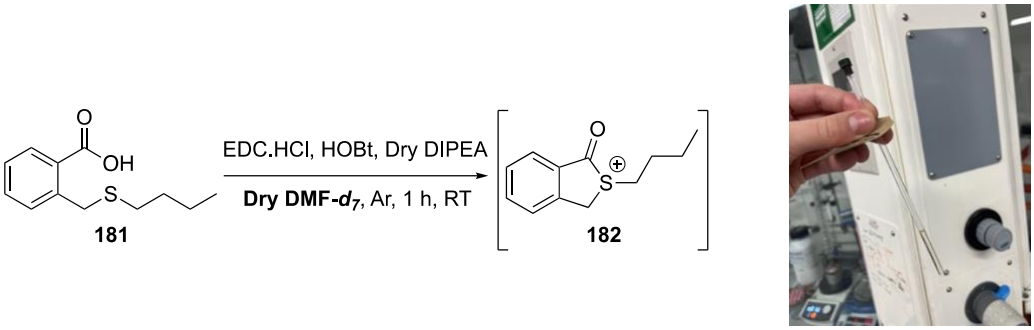


Figure 2.8.8 Electrospray Ionisation (ESI) positive mode of ionisation spectrometry report of the reaction mixture and corresponding m/z ion peaks with the assignment of possible structures of intermediates and by-products

The APCI ionisation method has less observed molecular species fragmentation than ESI. However, no further examination and experiments were conducted to investigate whether the sulfonium cation **182** (**Scheme 2.8.6**) fragment observed in the MS spectra was generated by ionisation using the instrument versus what was formed in the reaction mixture.[199,200] The mechanistic work using the MS approach was qualitative, which is a limitation.

It was also decided to try and observe **182** (**Scheme 2.8.9**) via NMR spectroscopy to see if it was possible to observe a signal of C=O of acyl sulfonium cation.[201,202] The same reaction conditions were reproduced (**Scheme 2.8.9**), but instead of normal anhydrous DMF, **DMF-*d*$_7$** (dried over activated 3 Å sieves) was used as the reaction solvent. The reaction was otherwise set up as normal and left for **1 hour**, after which time an aliquot was taken and transferred into an NMR tube.



Scheme 2.8.9 Shows the reaction to detect cationic intermediate **182** in DMF-d_7 and a picture of the NMR tube the reaction was performed in

The resulting reaction sample was analysed by ^{13}C NMR, in which we were looking at the ^{13}C signal for C=O resonance. Initially, when the first spectrum was recorded, no sign of the intermediate was observed; the only observable CO resonance was at 163.8 ppm, which was assigned to the HOBt-activated ester **184** (**Fig. 2.8.10**).

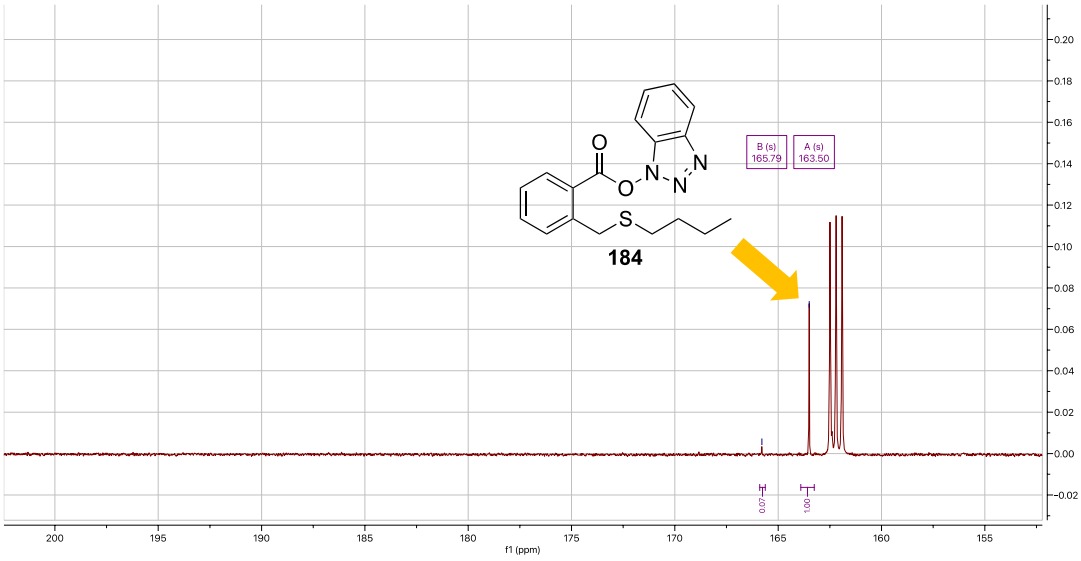


Figure 2.8.10 The ^{13}C NMR spectrum of the reaction mixture in DMF-d_7 taken after 1 hour of setting up the reaction (15th of September 2020). It also provides identification of the resonance along with the structures of HOBt **184** intermediate

In contrast, no resonance peak which corresponded to intermediate **182** was observed. Nonetheless, the reaction mixture was left in the same NMR tube for 10 days in the hope that the corresponding cation **182** would be formed. Still, after this time, no sign of the formation of intermediate was visible, and a new peak appeared at 168.8 ppm, which corresponds to benzoic acid **181** starting material (**Fig. 2.8.11**), which is presumably formed via slow hydrolysis of activated HOBt ester **184** by adventitious water in the DMF or atmosphere (the NMR tube was not purged or sealed with argon).

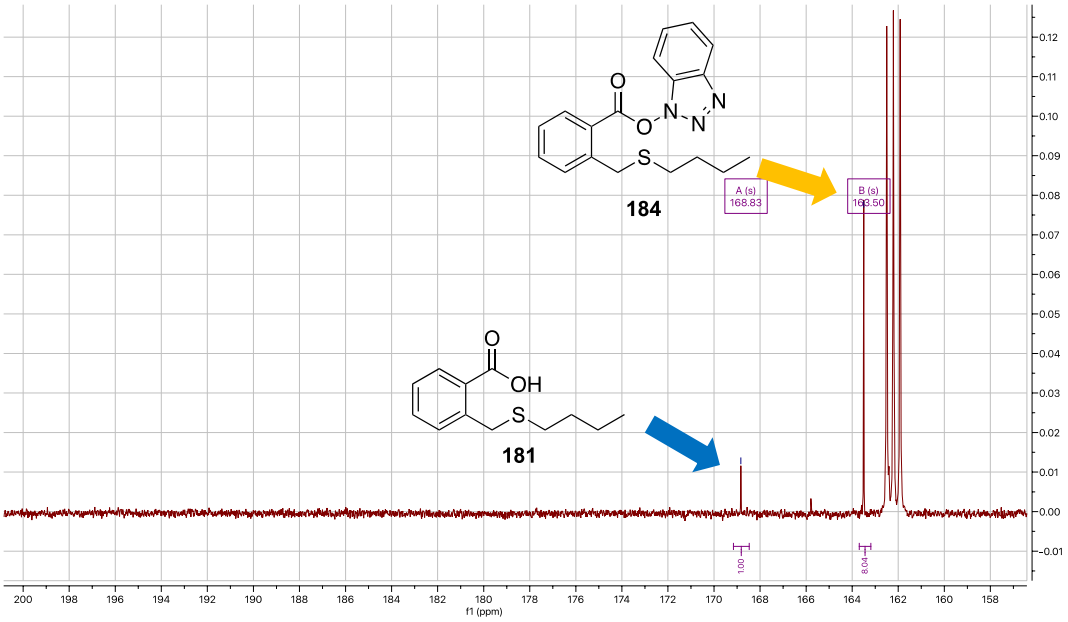


Figure 2.8.11 Shows ^{13}C NMR spectrum of the reaction mixture in DMF-d_7 after 10 days of reaction started (25th September 2020). Demonstrating identification of the resonance along with the potential structures of intermediates **185** and stating material **181**

Disappointingly, the acyl sulfonium C=O resonance was not observed. This could be a result of there being an equilibrium between HOBt adduct **184** and intermediate **182** and anionic ⁻OBt **105a**. If the equilibrium position is predominately on the left-hand side (**Fig. 2.8.12**), observing **184** in the NMR spectrum would be difficult due to its dynamic nature. In a 'real' reaction system, in which there is a terminal nucleophile, i.e., ROH, RSH or R_2NH, such an equilibrium may not be problematic, as the analogous sulfonium cation can go on to form a product; in this model system, it cannot.

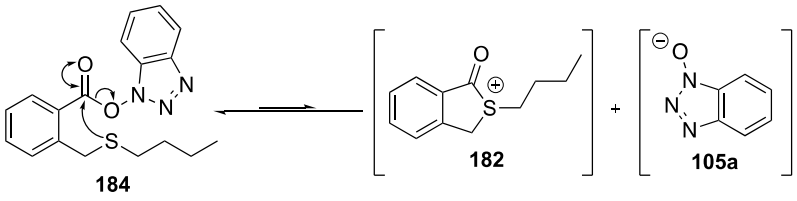


Figure 2.8.12 Shows the hypothetical dynamic equilibrium between HOBt adduct **184** and acyl sulfonium cation **182** and ⁻OBt **105a** as a counter anion, which has certain biases towards the left-hand side of the reaction

We postulated that adding something to stabilise the **182** intermediate might allow us to observe it by shifting the equilibrium. Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

(NaBARF, CAS: 79060-88-1) was chosen to do this, which is a stable, non-coordinating anion that interacts weakly with cations whilst also being soluble in organic solvents like DMF .[203 204] This was done in the hope that it would help push equilibrium in favour of the right-hand side of 5-membered-ring acyl sulfonium cation **182** (**Fig. 2.8.12**).

Pleasingly, after the addition of NaBARF **196** to the NMR tube, a new chemical peak at 172.4 ppm was observed (**Fig. 2.8.13**), which we propose corresponds to cationic intermediate **182**, presumably associated with BARF **186a** anion (**Fig. 2.8.14**). This appearance of new chemical resonance and the reduction in the intensity of peak at 163.6 ppm, which corresponded to HOBt adduct **184**, is indicative of an equilibrium shift to the 5-membered-ring acyl sulfonium cation **182** (**Fig. 2.8.14**).

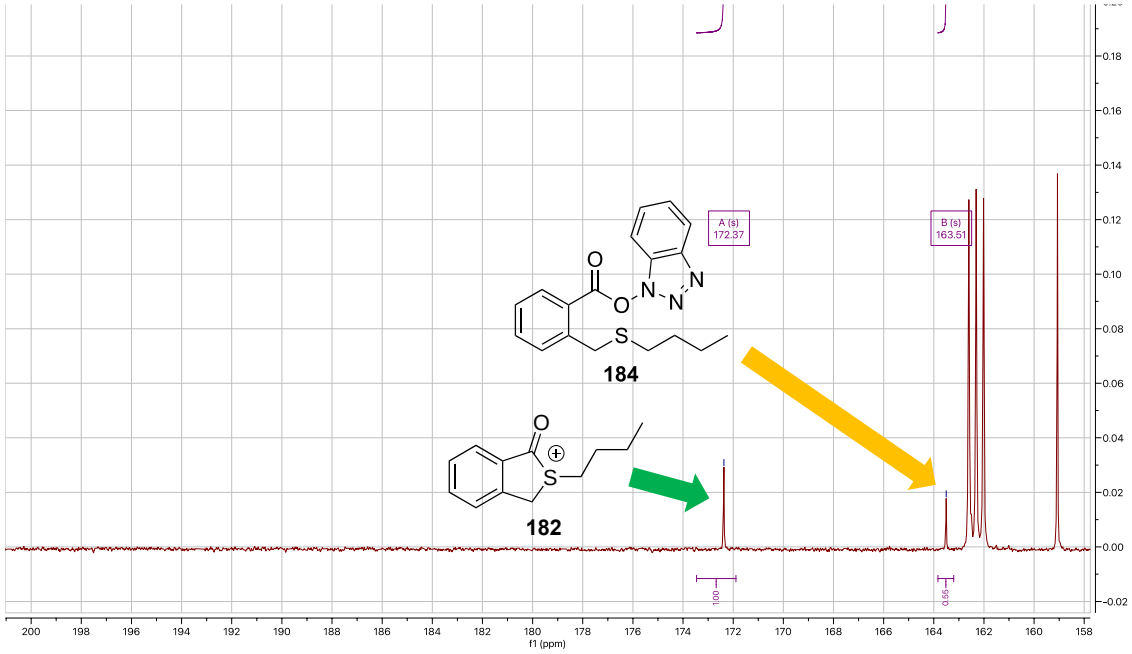


Figure 2.8.13 The 13C NMR spectrum of the reaction mixture in DMF-d_7 with NaBARF (25th September 2020) added. The NMR spectrum is recorded immediately after 130 min addition, The resonance, is assigned with potential structures of intermediates **182** and **184**

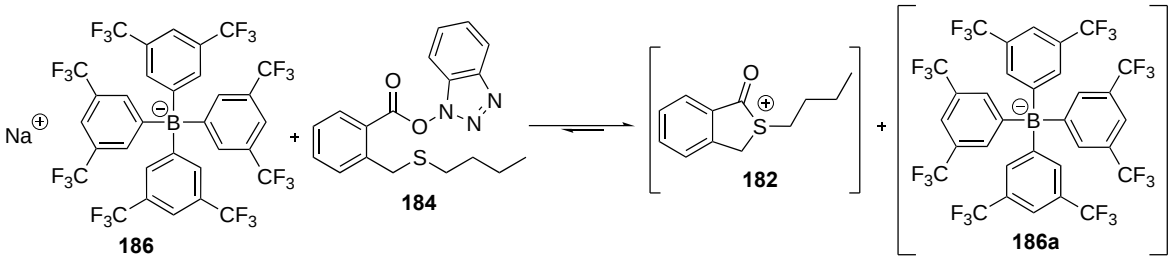


Figure 2.8.14 Change position of equilibrium between HOBt **184** adduct and acyl sulfonium cation **182** after the addition of NaBARF **186**, where a shift is observed towards the formation of cation intermediate, i.e., to the right of the reaction mixture

The resulting reaction mixture was left for additional 7 days in the NMR tube, and the sample was re-submitted to see if there were any changes. The only peak observed corresponded to acyl sulfonium C=O resonance at 173.3 ppm (**Fig. 2.8.15**), which implies that the equilibrium has shifted completely to the right-hand side. This chemical shift is in reasonably close agreement with the literature-reported value, even in $CDCl_3$,[201,202] hence provided more evidence that the reaction proceeds via this five-membered ring reactive intermediate.[167,202]

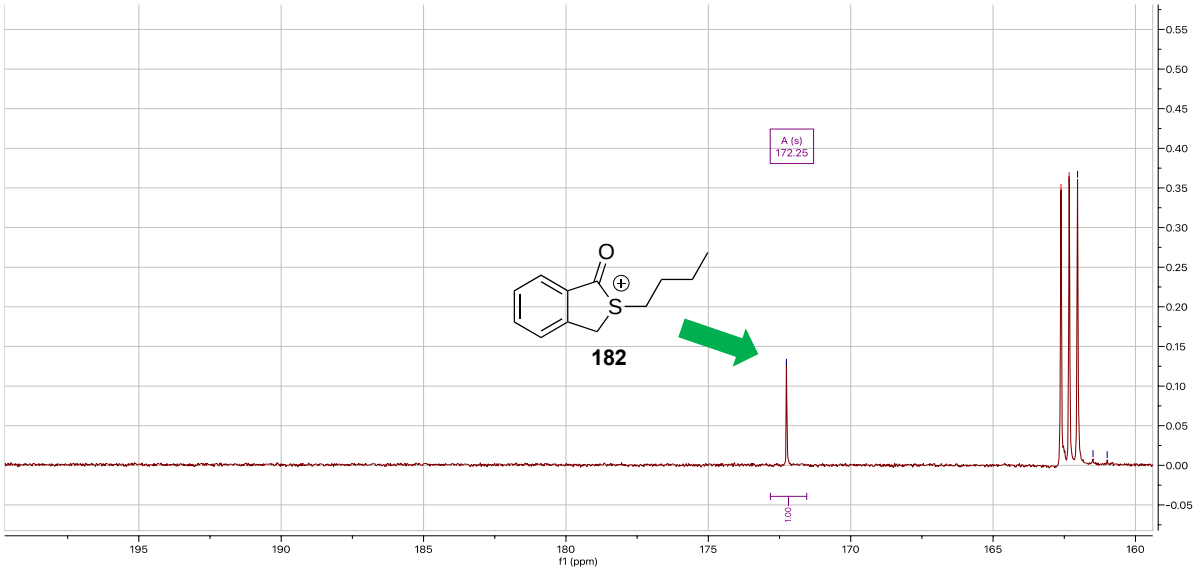
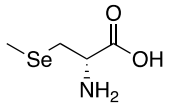


Figure 2.8.15 Shows ^{13}C NMR spectrum of the reaction mixture in DMF-d_7 + BARF (2nd of November 2020) after seven days when NaBARF, where the only resonance present in the carbonyl region corresponded to **182** intermediate C=O function group

2.9.0 Selenium as an internal nucleophile and organoselenium compounds as medicinally important compounds

Previously in the report it was demonstrated that sulphur with an aryl moiety could undergo a ring expansion reaction with optimised conditions using EDC.HCl, and HOBt can be used as an additive to achieve a variety of medium size ring products in high yield with a high functionality tolerance**.** The next goal was to extend the substrate scope to make the analogous Se containing medium-sized rings.

Selenium and organoselenium compounds were considered solely as toxins and poisons until the 1950s when Schwarz, Foltz[206],and Pinsent[205] found they play an important part in mammalian life and as micronutrients.[206,207] In later years, selenocysteine was discovered by Stadtman in the 1970s [208] and is the 21st essential proteinogenic amino acid. It was initially found at the active site of glutathione peroxidase (GPx) in mammals,[209] and hence, the interest in exploring and expanding the field of organoselenium started to increase over the decades. The methylated analogue of selenocysteine **187** (see **Fig. 2.9.1**) shows an effective antitumor activity and is used extensively as an "inhibitor for 7,12-dimethylbenz[a]anthracene (DMBA) - induced mammary tumours."[210]

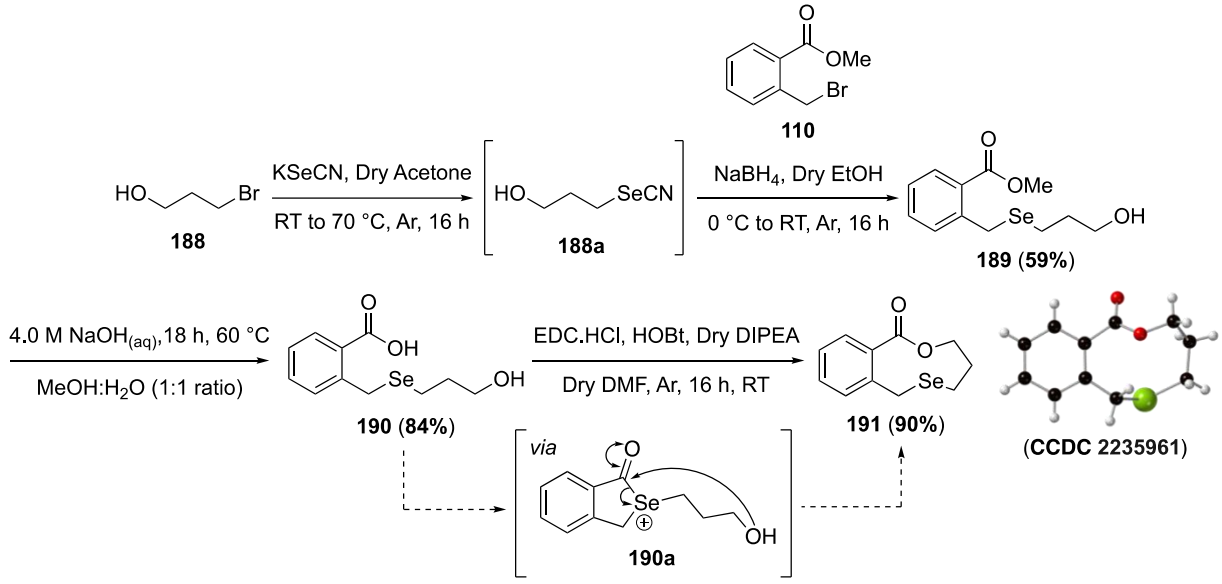


187

Figure 2.9.1 Structure of methylselenocysteine **187**

Our synthesis to make the selenium-containing medium-sized ring **191** (**Scheme 2.9.2**) began with a literature-based procedure, [211] where a "Finkelstein-type" reaction with KSeCN (NOTE: this reagent is extremely toxic and so was weighed out inside the fumehood) and alcohol bromide **188** was performed to yield selenocyanide **188a**. The crude selenocyanide **188a** product was taken directly to the next step where, after a simple filtration via a filter to remove the $KBr_{(s)}$ (not soluble in acetone), the cyanide group was reduced to RSeH under $NaBH_4$ in anhydrous EtOH conditions. After 1 h, the benzylic bromide **110** was added, which resulted *in situ* alkylation giving rise to the organoselenium ester **189** (**Scheme 2.9.2**, **188a** + **110** → **189**) in good yield. Under the same basic conditions, the methyl ester **189** was hydrolysed, for which we were able to obtain benzoic acid **190** in 84% yield after solid was collected via the Büchner funnel. Next, EDC.HCl and HOBt were used to obtain the desired medium-sized ring **191** (via five-membered acyl seleniranium intermediate **190a**, **Scheme 2.9.2**) in 90% yield, showing that Se can undergo the same NICE reaction as the sulphur systems (see previous section). Indeed, the yield achieved from the selenium system is higher compared to that of

the sulphur. This may be attributed to selenides being more nucleophilic than sulfides,[212,213] and so the rate of the first cyclization of selenium with the activated carboxylic is increased, thus enhancing the yield. A single X-ray crystal, shown in **Scheme 2.9.2**, was crystallised by leaving the saturated mixture of *n*-hexane at –20 °C in a freezer overnight.



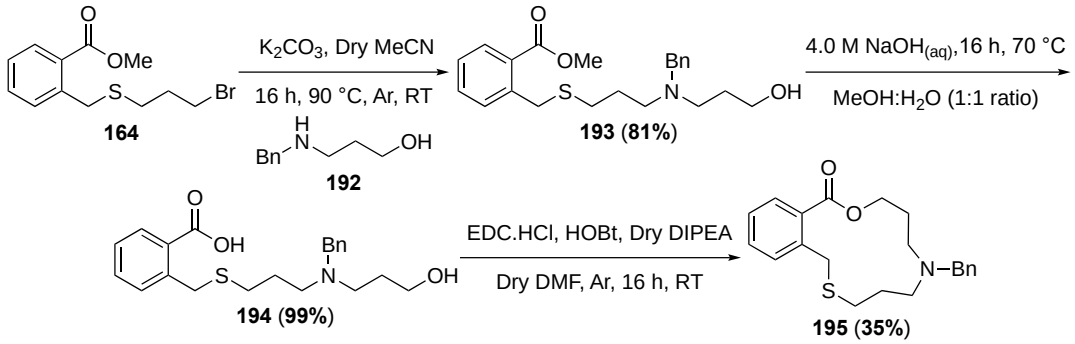
Scheme 2.9.2 Reaction sequence for synthesis of selenium 9-membered ring **191**, isolated yield and corresponding X-ray crystal structure with **CCDC** deposit number

2.10.0 Cascade ring expansion reactions with different heteroatoms

Having succeeded in obtaining a range of 8-10 medium-sized rings via the cascade ring expansion method, our attention turned to incorporating an additional heteroatom on the linker to enable a longer ring expansion cascade and obtain macrocyclic ring frameworks. The uses of 3 and 4 different heteroatoms as nucleophiles had not previously been tried in the Unsworth group.

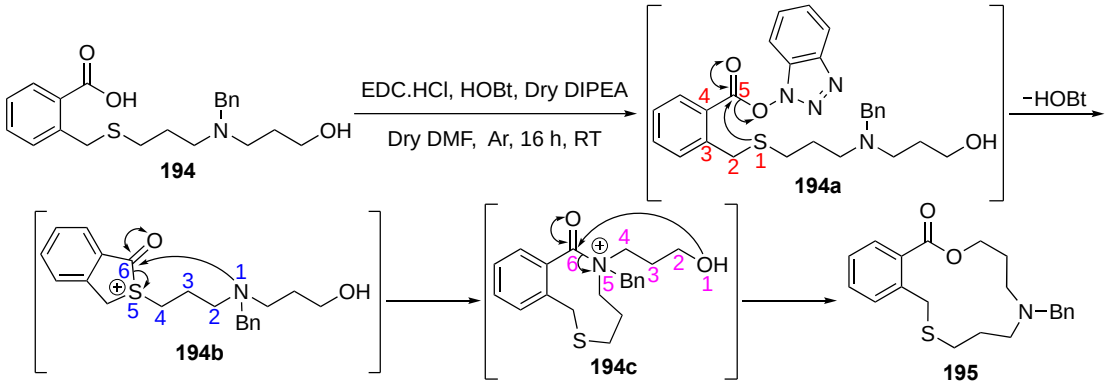
The synthesis of the first macrocycle **195** (**Scheme 2.10.1**) with a range of different heteroatoms begins with the already synthesised aliphatic bromide **164** (**Scheme 2.10.1**) that underwent an S_N2 reaction with the commercially available benzyl-protecting amine **192** to obtain desired tertiary amine alcohol **193** (**Scheme 2.10.1**) in an acceptable yield after purification via flash column chromatography. The next step was hydrolysis of the aryl ester **193** to form the corresponding benzoic acid **194** in excellent yield. Finally, the last step of the reaction was ring expansion using the EDC.HCl and HOBt conditions. The reaction mixture was monitored by consumption of the benzoic acid **194** via TLC. The desired macrocycle **195** (**Scheme 2.10.1**) was isolated in a yield of 35%, which is an exciting result considering the

cascade involved in the reaction of the 3 different heteroatoms and was done at 0.1 M concentration.



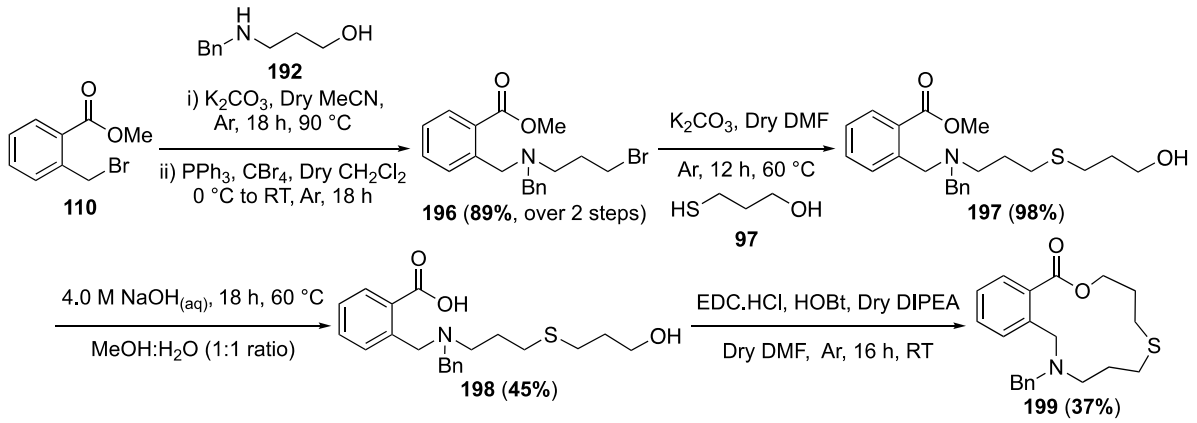
Scheme 2.10.1 Synthesis of macrocycle **195** via a "double" NICE reaction

The mechanism to make macrocycle **195** is proposed to begin with activation of benzoic acid **194** with EDC.HCl and HOBt, giving rise to the activated ester **194a** (**Scheme 2.10.2**). Next, sulphur acts as an internal nucleophile and attacks the electrophilically activated acid via 5-membered cyclization (numbers highlighted in red, **Scheme 2.10.2**) to afford an acyl sulfonium **194b** cation intermediate. The resulting cationic intermediate will be cyclized with benzyl-protected tertiary amine via a 6-membered transition state **194b** (numbers highlighted in blue, **Scheme 2.10.2**) to afford the 9-membered acyl ammonium **194c** species. The final step is ring expansion by OH (terminal nucleophile) to provide the desired result (numbers highlighted in magenta, **Scheme 2.10.2**) via a six-membered ring cyclization, to afford macrocycle **195** in a cascade manner.



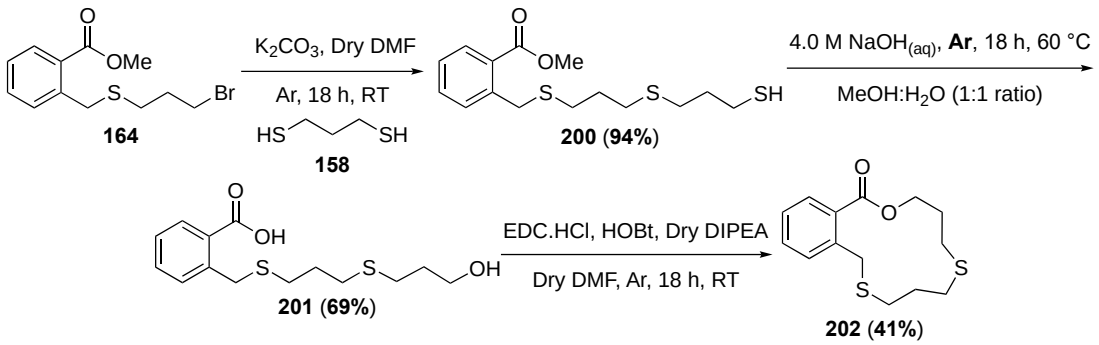
Scheme 2.10.2 Reaction mechanism for formation macrocycle **195** by cascade/tandem NICE reaction using EDC.HCl + HOBt, showing only the key steps

After successfully obtaining a macrocycle with three different heteroatoms, it was decided to see the effects of changing the order of the heteroatoms. The subsequent synthesis begins with the simple alkylation of benzylic bromide **110** with benzyl-protecting amine **192**, followed by an Appel reaction (with CBr_4) to afford the primary bromide **196** in excellent yield over two steps (**Scheme 2.10.3**, **110** → **196**). Following another high yielding S_N2 reaction with thiol **97**, we were thus able to obtain the primary alcohol **197** in 98% yield after simple purification. The hydrolysis of the methyl ester **197** under base conditions yielded benzoic acid **198** (**Scheme 2.10.3**), which was then reacted under the standard conditions with EDC.HCl and HOBt conditions, to give macrocycle **199** (**Scheme 2.10.3**) in a 37% yield. The yields of both macrocycles **195** and **199** (**Scheme 2.10.1** and **Scheme 2.10.3**, respectively) are similar, which suggests that changing the order of the heteroatoms of the linear precursors has no significant effect on the yield, in this case.



Scheme 2.10.3 Reaction sequence for the synthesis of macrocycle **199** with different arrangement of internal nucleophiles around the linear chain

It was then decided to make macrocycle **202** (**Scheme 2.10.4**), which incorporates three sulphur heteroatoms. The synthesis starts with the available primary bromide **164**, which underwent as S_N2 reaction with bis thiol **158** to afford the desired triple sulphur **200** in excellent yield (**Scheme 2.10.4**). Next, hydrolysis of the ester **200** gave benzoic acid **201** in **69%** yield, where the reaction was performed under an inert atmosphere (argon) to avoid the formation of disulphide bonds. The acid **201** was treated under EDC.HCl and HOBt conditions and afforded macrocycle **202** in a reasonable yield of 41%.



Scheme 2.10.4 Synthesis of macrocycle **202** with two sulphurs heteroatoms as internal nucleophiles

To further increase the substrate scope and diversity of macrocycles, it was decided to incorporate selenium inside the macrocycles. In the literature, there are few examples of selenium heteroatoms that are incorporated into a macrocyclic framework, particularly in medicinal chemistry, [214,215] and this niche area is yet to be explored and researched in depth. With this in mind, it was decided to synthesise macrocycles **203** and **204** (**Fig. 2.10.5**) with a different heteroatom, where one of the heteroatoms was selenium.

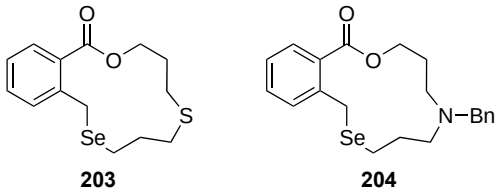
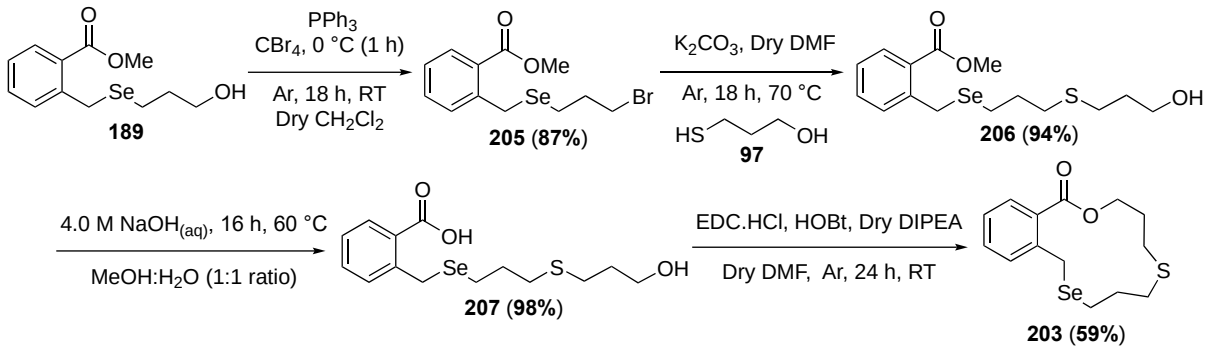


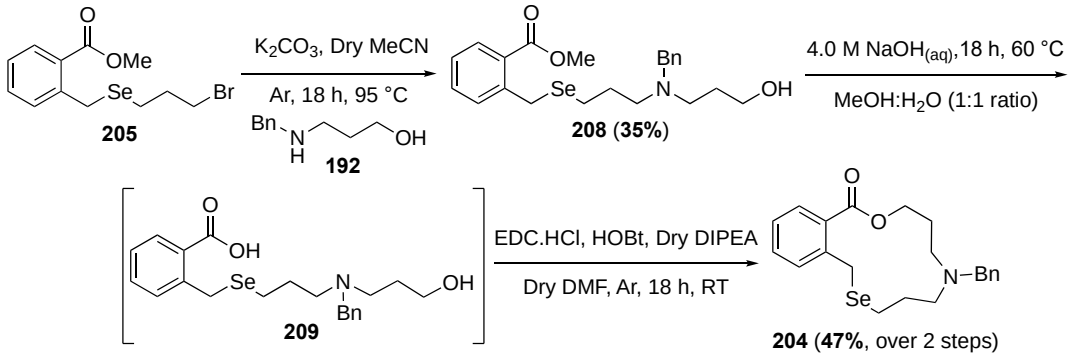
Figure 2.10.5 Structure of two macrocycles **203** and **204** with selenium acting as the first internal nucleophile in NICE reaction

The synthesis of the “Group 16” macrocycle **203** starts off with a simple Appel reaction of the corresponding organselenium **189** to afford primary bromide **205** in good yield. The S_N2 reaction with mercaptan **97** (**Scheme 2.10.6**) gives selenium sulphur ester **206** in 94% after simple purification. The resulting methyl ester was hydrolysed off using $NaOH_{(aq)}$ to give the corresponding carboxylic acid **207** in excellent yield. The acid was activated with EDC.HCl and HOBt in anhydrous DMF, affording the “Group 16” macrocycle **203** (13-membered ring, **Scheme 2.10.6**) in good yield. This is an impressive result considering metal-free conditions were employed under mild conditions, all while using only cheap available commercial reagents at 0.1 M concentration.



Scheme 2.10.6 Synthesis of "Group 16" macrocycle **203** with selenium and sulphur acting as internal nucleophiles in NICE reaction, isolated yields for each reaction step are demonstrated

We then moved on to consider the synthesis of macrocycle **204**. The synthesis begins with the primary bromide **205** (**Scheme 2.10.7**), and undergoes alkylation with benzyl-protected secondary amine **192** to afford compound **208** in relatively low yield (**Scheme 2.10.7**, **205** → **208**). The hydrolysis of methyl ester yields benzoic acid **209** did not go smoothly initially; however, significant streaking on TLC was observed compared to other acids synthesised in this project. This phenomenon may suggest that benzoic acid **209** is unstable on silica, and subsequent 2D TLC studies (**Fig. 2.10.8**) confirmed that this was the case. Hence, it was decided to take the corresponding crude product to the next reaction step directly after liquid extraction without further purification via column chromatography. The unpurified acid **209** was therefore reacted with EDC.HCl and HOBt to form macrocycle **204** (**Scheme 2.10.7**, **208** → [**209**] → **204**) in a yield of 47% over two steps.



Scheme 2.10.7 Synthesis of macrocycle **204** with selenium and tertiary amine acting as internal nucleophiles in the NICE reaction

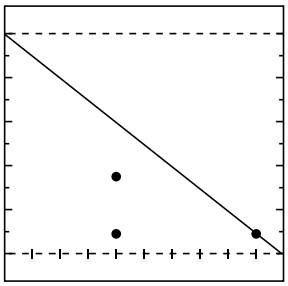
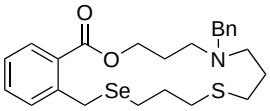


Figure 2.10.8 Representation of a 2D TLC of crude acid **209** product, eluent: 50:50, EtOAc:MeOH, visualization = UV light (short wavelength) and $KMnO_4$ dip, where the acid compound spot is below the diagonal line, indicating decomposition on silica

2.11.0 Ring Expansion with Three Different Hetero-Nucleophiles "TRIPLE NICE"

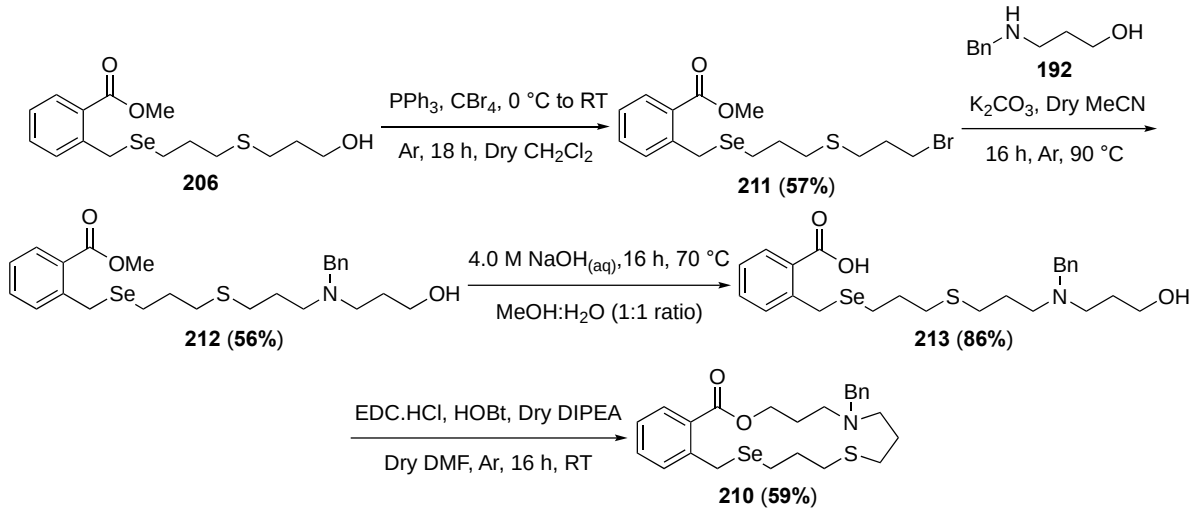
Having succeeded in obtaining a series of 13-membered rings via NICE reactions with two internal nucleophiles, attention then turned to incorporating three internal nucleophiles on the linker to enable an even longer extended ring expansion cascade reaction to obtain larger macrocyclic ring frameworks. The use of 4 different heteroatoms as nucleophiles (3 internal and 1 terminal nucleophile) had not previously been attempted in a NICE reaction in the Unsworth group (**Fig**. **2.11.1**).



210

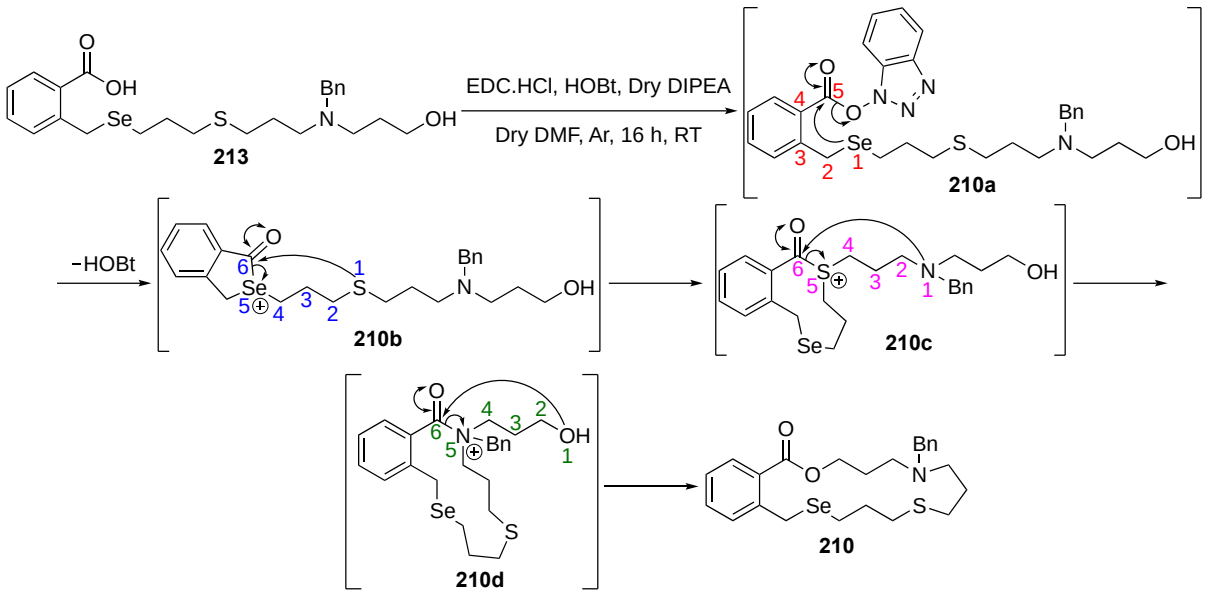
Figure 2.11.1 Structure of target macrocycle **210** with three internal nucleophiles, allowing for extended cascade NICE reaction to occur

The synthesis of macrocycle **210** began with an Appel reaction of already synthesised alcohol **206** to afford bromide **211** (**Scheme 2.11.2**) in a good yield. The next step was the S_N2 reaction of the corresponding bromide and the commercially available alcohol **192**, affording the desired product **212** in good yield (**Scheme 2.11.2**). The next step was simple hydrolysis of the methyl ester **212** to achieve the desired benzoic acid **213** in high yield after liquid-liquid extraction. The final step of the reaction was the NICE reaction with the EDC.HCl and HOBt conditions at 0.05 M concentration. The reaction mixture was monitored by consumption of benzoic acid **213** via TLC. The desired macrocycle **210** (**Scheme 2.11.2**) was isolated in 59% yield, which is an excellent result.



Scheme 2.11.2 Synthesis of 17-membered macrocycle **210** with isolated yield for each step of the reaction sequence

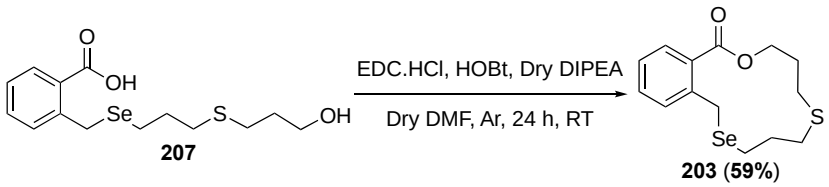
The proposed reaction mechanism to make macrocycle **210** begins with activating benzoic acid **213** with EDC.HCl and HOBt to give rise to the activated ester **210a** (**Scheme 2.11.3**). Next, selenium acts as the first internal nucleophile and attacks the electrophilically activated carboxylic acid via five-membered cyclization (numbers highlighted in red, **Scheme 2.11.3**) to afford an acyl seleniranium **210b** cation intermediate. The resulting **210b** cationic intermediate will be attacked by the second internal nucleophile, sulphur, via a six-membered transition state (numbers highlighted in blue, **Scheme 2.11.3**) to afford the nine-membered acyl sulfonium **210c** species. The **210c** cationic species will be attacked further by the third internal nucleophile, tertiary benzyl-protected amine, via six-membered cyclization (numbers highlighted in magenta, **Scheme 2.11.3**) and give rise to the 13-membered ring cationic intermediate **210d**, which will be finally expanded by OH (terminal nucleophile,) via a six-membered transition state (numbers highlighted in green, **Scheme 2.11.3**) to afford the desired macrocycle **210** in a cascade NICE manner.



Scheme 2.11.3 Proposed reaction mechanism for cascade NICE reaction with four different heteroatoms, three of which act as internal nucleophiles using EDC.HCl and HOBt conditions, showing only the key steps

2.12.0 Control reactions

Given the known challenges of forming 9, 12, and 18 membered ring lactones, the efficiency of the reactions described above, such as the synthesis of lactone **203**, was very promising, considering they were performed under mild conditions and at 0.05 M concentration (**Scheme 2.12.1**).



Scheme 2.12.1 Synthesis of macrocycle **203** with isolated yield and reaction conditions for NICE at 0.05 M concentration

To eliminate the possibility that the synthesis of **203** is simply an unusually efficient macrolactonization, benzoic acid **214** (**Fig. 2.12.2**) was synthesised.

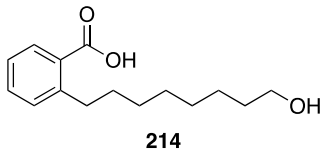
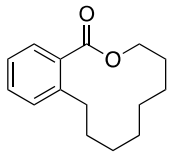


Figure 2.12.2 Molecular structure of benzoic acid **214**, without having any internal nucleophiles built in the linear chain, only OH as a terminal nucleophile

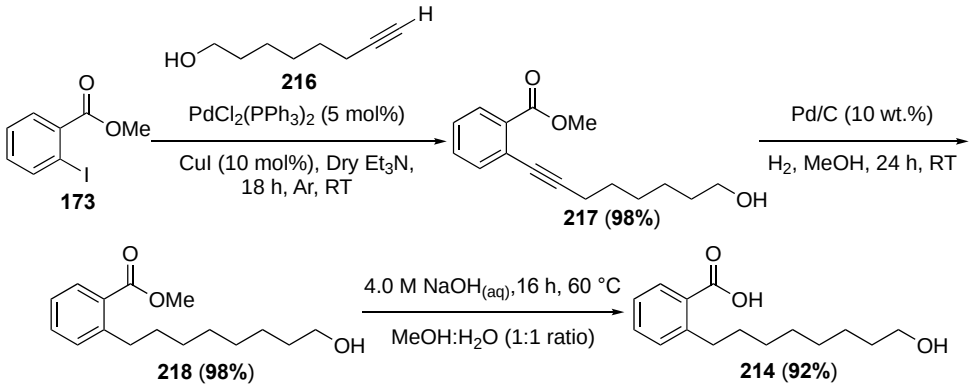
The idea was to see if the medium-sized lactone ring **215** (**Fig. 2.12.3**) could be generated from **214** under the same conditions used to form **203** as described in previous sections – if so, this would shed doubt on whether the heteroatoms are involved in the cascade.



215

Figure 2.12.3 Structure of 12-membered-sized lactone ring **215**

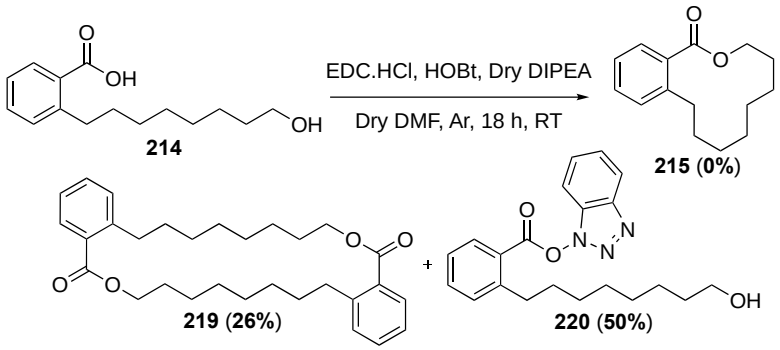
The synthesis of aryl lactone **215** started with classical conditions reported by Sonogashira and co-workers.[216] It was attempted with commercially available iodide **173** and terminal alkyne **216** (**Scheme 2.12.4**) to give the desired alkyne **217** in excellent yield. The next step was the reduction, where alkyne **217** was subjected to hydrogenation conditions taken from the literature procedure.[217] The reaction was conducted in a 250 mL round-bottom flask, allowing larger headspace for hydrogen gas to occupy (3 balloons were consumed, i.e., 3 equiv. of H_2) and allowing for the volume of MeOH required for the reaction (26 mL). Upon completion, the reaction mixture was filtered through the Celite® and then purified by column chromatography to afford alkane alcohol **218** (**Scheme 2.12.4**). The next step in the reaction was to hydrolyse ester **218** to the corresponding benzoic acid **214** (**Scheme 2.12.4**), which was achieved in good yield.



Scheme 2.12.4 Synthesis route towards starting material acid **214**, showing reaction conditions and isolated yields for each step

Benzoic acid **214** was then tested under our typical ring expansion cascade conditions using the usual EDC.HCl and HOBt coupling reagents. This test showed that the formation of the

12-membered lactone **215** does not take place without the internal heteroatom-nucleophiles. Instead, the HOBt adduct **220** (**Scheme 2.12.5**) was isolated as the major product from the reaction and the dimer **219** (**Scheme 2.12.5**) side-product was also isolated in 26% yield, with its structure confirmed by X-ray crystallography (**Fig. 2.12.6**). These control results were as expected and support our proposed cascade NICE mechanism. A single X-ray crystal of dimer **219** was crystallised by slow evaporation of *n*-hexane.



Scheme 2.12.5 Synthesis of dimer **219** and HOBt adduct **220** formations as major products, with no formation of macrocycle **215**

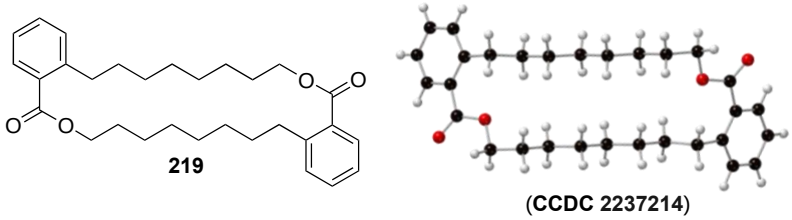


Figure 2.12.6 Molecular structure of dimer **219** with X-ray crystal structure and **CCDC** deposit number

To summarise the work in this chapter, a range of novel NICE reactions have been developed, that show that heteroatoms like S and Se are compatible as internal nucleophile. Double and triple NICE reactipon variants have also been developed for the first time. Taken together, these finding dramatically expand the scope of the NICE concept. The next chapter is focused on extending the NICE concept even further, by varying the electrophilic partner.

Chapter 3: Varying the electrophilic component

3.1.0 Unsuccessful attempts at changing the electrophilic component

After proving that activated carboxylic acids can be used as the electrophilic component (highlighted as a pink dot in **Fig. 3.1.1**, denoted as "E"), in NICE reactions our next goal was to diversify the procedure by using alternative electrophilic mediums to install different functional groups onto the medium-sized ring and macrocyclic products. Previously, activated carboxylic acids were the electrophile of choice in the NICE framework. Moving away from this was considered to be a crucial development to expand the NICE concept, and the successful realisation of this work is described in this chapter. In my opinion, this is the biggest achievement in my PhD research, due to the challenging nature of the framework and the intrinsic nature of testing never-before-performed reactions, requiring in-depth knowledge of the reaction mechanisms and optimal conditions.

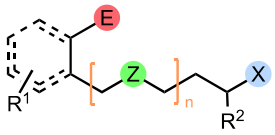


Figure 3.1.1 Illustration of general linear precursor, with 3 different components: electrophilic (E), internal n (Z) and terminal (X) nucleophiles

We begin with two scenarios. The first, when the alternative pro-electrophile is attached to the linear precursor, which will participate in the NICE reaction (**Fig. 3.1.1**, **I** → [**II**] → **III**); this is similar in concept to the previous ideas already discussed, with the difference of varying the electrophilic component.

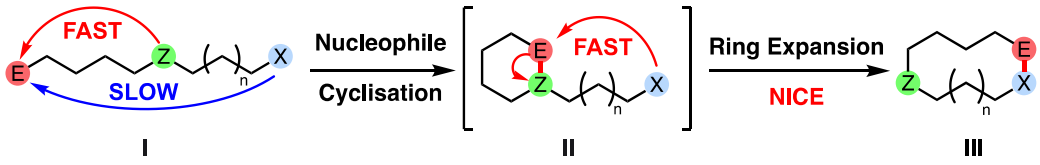


Figure 3.1.2 Showing general NICE reaction scheme where the electrophile is part of the linear precursor **I**

The second, when the electrophile (denoted as "E") is instead not bound to the linear precursor **IV** (**Fig. 3.1.3**) in a separate motif. This electrophile will then be available to react with one of the two possible terminal nucleophiles (**Fig. 3.1.3**, denoted as "X") to form the reactive electrophilic species **V** (**Fig. 3.1.3**, **IV** → [**V**]), which will go on to partake in intramolecular

cyclization via normal size “normal” ring transition state to generate intermediate **VI** (**Fig. 3.1.3**, [**V**] → [**VI**]). The resulting intermediate is set to undergo ring expansion to afford the desired medium-sized ring or macrocycle **VII** (**Fig. 3.1.3**).

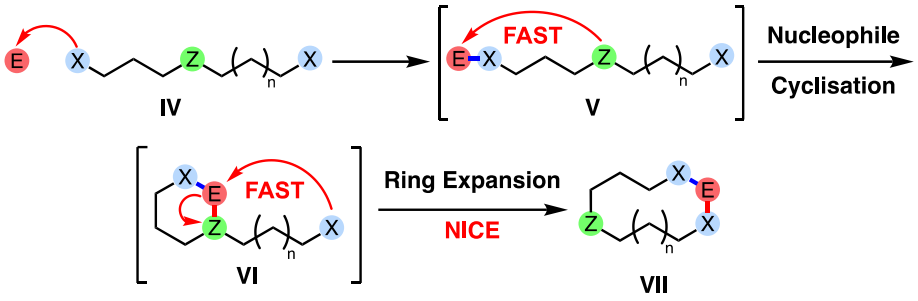
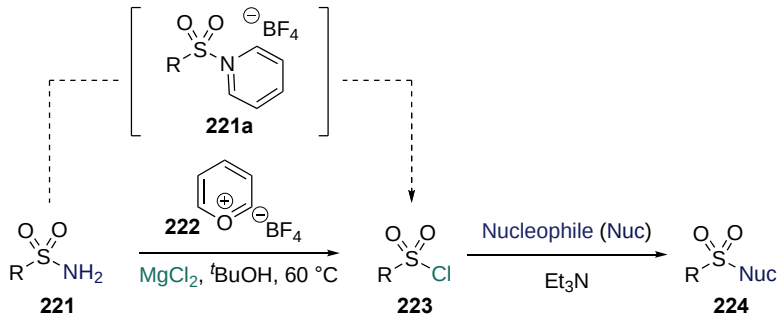


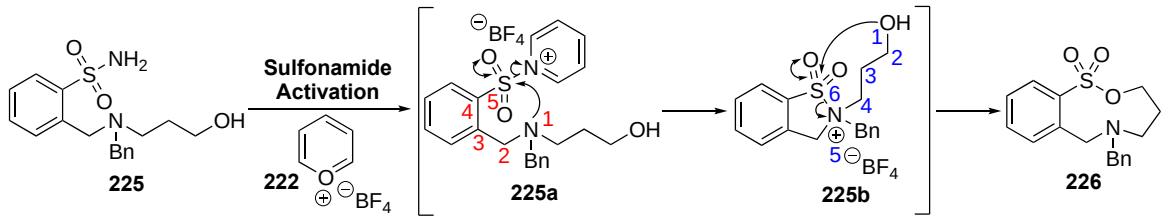
Figure 3.1.3 Showing general NICE reaction scheme where the electrophile is detached from the linear precursor **IV**

We examined both approaches, examining the scenarios in the order above. Beginning with the case when the electrophile is attached, we switched from using an activated carboxylic acid as the electrophilic precursor to a sulfonamide, with the plan to use pyrylium tetrafluoroborate **222** (Pyry-BF_4) as the activating reagent (**Scheme 3.1.4**). This idea was inspired by precedent from Cornella and co-workers, who demonstrated that primary sulfonamide **221** can be converted into sulfonyl chloride **223** using Pyry-BF_4 **222** (**Scheme 3.1.4**) via pyridinium tetrafluoroborate salt **221a**, mediated by a nucleophilic substitution, with a displacement of pyridine as a by-product. The resulting sulfonyl chloride electrophile **223** can later react in a one-pot sequence with a range of nucleophiles (i.e., amines, alcohol/, fluoride, water etc.) to afford sulfonamides, sulfonates, sulfides, sulfonyl fluorides and sulfonic acids respectively.[218,219]



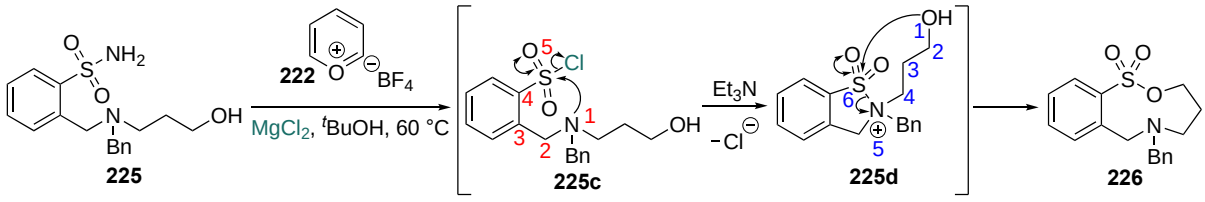
Scheme 3.1.4 Demonstrates pyridium (Pyry-BF_4 complex)-mediated activation of primary sulfonamide **221** to undergo coupling reaction with a range of nucleophiles[218]

We questioned whether similar reactivity might be applicable to NICE reactions. To test this, we synthesised a possible linear precursor **225.** The hope was that this material would undergo activation using Pyry-BF_4 **222**, to form a pyridinium tetrafluoroborate intermediate salt **225a** (**Scheme 3.1.5**), thus making the sulfonamide electrophilic. The benzyl-protected tertiary amine in the liner precursor could then act as an internal nucleophile and react with the electrophilic sulfonamide with the displacement of a leaving group in the form of pyridine. In this example, the internal nucleophile would attack the electrophilic sulphur centre via a 5-membered ring (number highlighted in red, **Scheme 3.1.5** [**225a** → **225b**]), affording a cationic sulfonamide **225b** salt intermediate. The resulting intermediate ring could then undergo ring expansion, via a 6-membered ring cyclization (numbers highlighted in blue, **Scheme 3.1.5**), to afford medium-sized ring **226**.



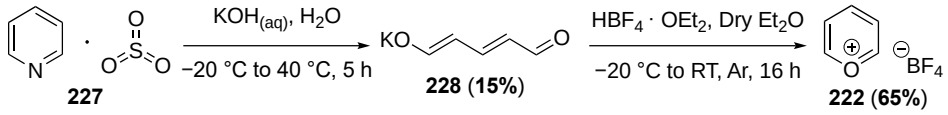
Scheme 3.1.5 Reaction mechanism for the synthesis of 9-membered sulphonate **226** ring using ring expansion/NICE reaction. The changing of the electrophilic component using pyridinium Pyry-BF_4 to activate the sulfonamide via tetrafluoroborate **225a** salt intermediate

Alternatively, the reaction could proceed with forming sulfonyl chloride **225c** first. Otherwise, the reaction would proceed similarly to that proposed above; the tertiary amine would act as an internal nucleophile, cyclizing via a 5-membered transition state (numbers highlighted in red, **Scheme 3.1.6**, [**225c** → **225d**]) with an electrophilic centre of a sulfonyl chloride displacing the chloride ion to form the same 5-membered cationic intermediate **225d**. The resulting 5-membered ring would be further ring expanded (number highlighted in blue, **Scheme 3.1.6**) to afford the product **226**.



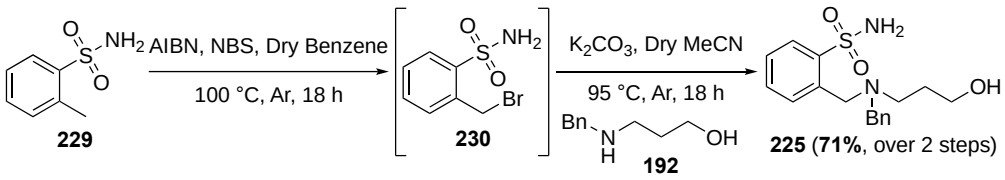
Scheme 3.1.6 Alternative mechanism for the synthesis of 9-membered sulphonate **226**, where the reaction proceeded via sulfonyl chloride **225c** intermediate

Before making the starting material primary sulfonamide **225** (**Scheme 3.1.6**), the Pyry-BF_4 **222** reagent had to be made first. The synthesis of Pyry-BF_4 **222** was followed as described in the literature procedure developed by Cornella [218] and Taylor,[220] with minor modifications to the experimental set-up and timings. The desired Pyry-BF_4 **222** was synthesised in 65% yield (**Scheme 3.1.7**), which is in very close agreement with the reported literature value.[219]

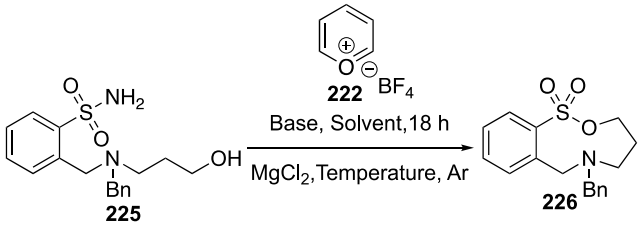


Scheme 3.1.7 Reaction sequence for the synthesis of Pyry-BF_4 **222** with isolated yields and conditions for each step

After the successful synthesis of the Pyry-BF_4 **222** reagent, the next step was to perform a Wohl–Ziegler bromination on *ortho*-toluene sulfonamide **229**, following an experimental procedure disclosed in a patent by Bristol-Myers Squibb.[221] This gave the desired crude benzyl bromide **230** (**Scheme 3.1.8**), after liquid-liquid extraction. The crude product **230** was taken directly to the next step without further purification to avoid degradation of the product; benzyl bromide **230** is unstable and is thus required to be stored under an inert atmosphere with a temperature between 2–8 °C.[222] The synthesis of sulfonamide **225** was finished with an S_N2 reaction with corresponding benzylic bromide and amine **192** to give the desired product in 71% yield, over two steps (**Scheme 3.1.8**, [**230**] → **225**).



Scheme 3.1.8 Reaction sequence towards the synthesis of linear precursor sulfonamide **225** with isolated yields and reaction conditions for each steps

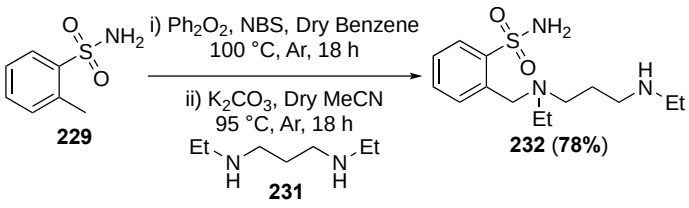


Entry	*Scale (mmol)*	*Base*	*Additive*	Solvent	Concentration (M)	Temperature (°C)	Result
1	0.529	None	None	^{t}BuOH	0.05	60	No reaction
2	0.510	None	None	^{t}BuOH	0.05	60	No reaction
3	0.345	None	None	MeCN	0.05	RT	No reaction
4	0.345	Et_3N	DMAP (10 mol%)	CH_2Cl_2	0.05	RT	No reaction
5	0.354	None	HOBt (10 mol%)	MeCN	0.05	98	No reaction
6	0.513	None	4 Å Molecular Sieves	^{t}BuOH	0.10	60	No reaction

Table 3.1.9 Reaction for the synthesis of sulphonate **225**, reaction conditions: bases, solvent, temperature, and results

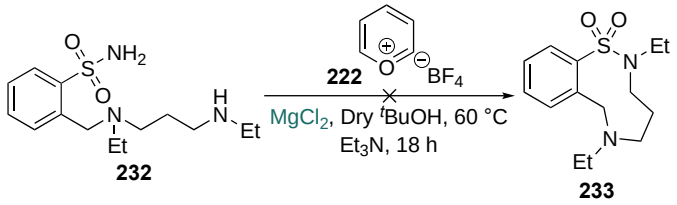
Unfortunately, the desired product **226** wasn't synthesised after several attempts (**Table 3.1.9**, **entries 1**–**6**). The starting material **225** was consumed, as observed by TLC/MS analysis, but in all cases, after aqueous workup purification, the crude NMR indicated that a complex mixture of products had formed, that we were unable to assign or characterise.

An alternative starting material was therefore made, with the internal and terminal nucleophiles both being amines, to avoid forming a tosylate product **226**, which we thought could be unstable. The first step of the synthesis started with the Wohl–Ziegler reaction to give bromide at the benzylic position, taken directly to the next step and subjected to the S_N2 reaction with diamine **231** to afford product **232** at a 78% yield (**Scheme 3.1.10**).



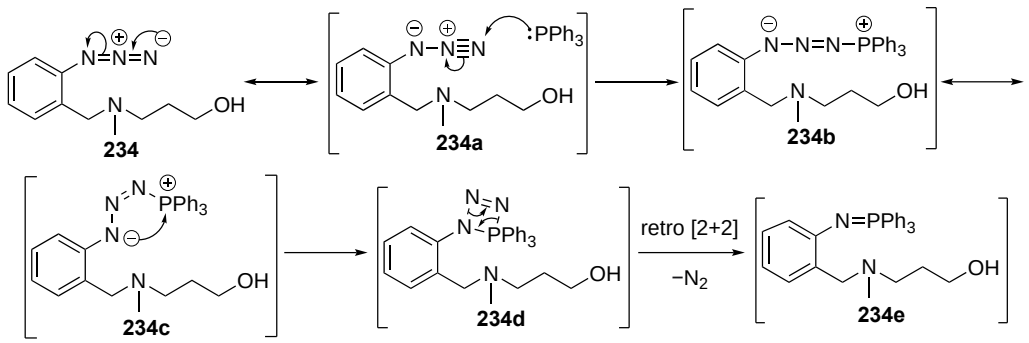
Scheme 3.1.10 Synthesis of sulfonamide diamine **232**, shows isolated yield and conditions with commercially available starting materials **229** and **231**

After the successful synthesis of the desired starting material **232**, it was subjected to the same reaction conditions using Pyry-BF_4 **222** in dry ^{t}BuOH. Unfortunately, the desired sulfonamide medium ring **233** was not synthesised, and this line of investigation was stopped at this point.



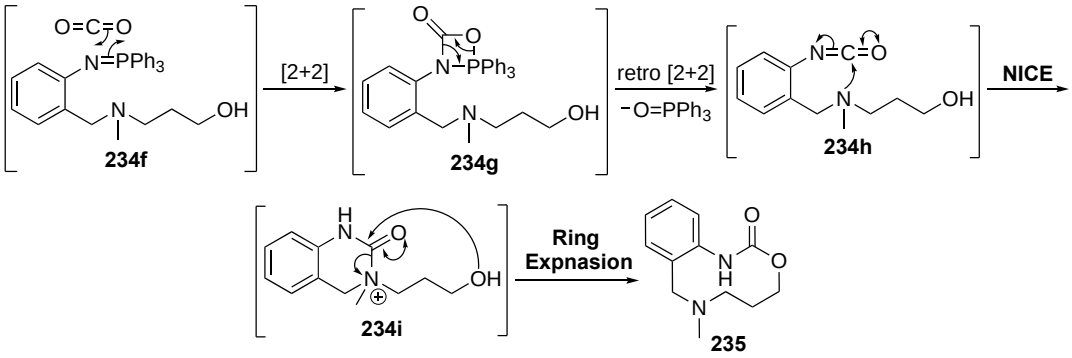
Scheme 3.1.11 Attempted reaction of 9-membered sulfonamide **233** with conditions, where no reaction has resulted

After the unsuccessful attempts and results using activated sulfonamides, alternative new electrophilic activation methods of other functional groups were considered instead. It was decided to synthesise starting material **234** (**Scheme 3.1.12**), where the azide group will be activated to form the electrophilic compound of the linear precursor. The idea was to employ an Aza-Witting type transformation where triphenylphosphine (PPh_3) reacts with azide **234a** (**Scheme 3.1.12**) to generate phosphazide **234b** ylide. The resulting intermediate could then undergo intramolecular cyclization (**Scheme 3.1.12**, [**234c**] → [**234d**], 4-exo-trig) to form four-membered phosphazenes **234d**, followed by retro [2+2] with the elimination of N_2 (**Scheme 3.1.12**, [**234d**] → [**234e**]) to yield iminophosphorane ylide **234e**.[223,224]



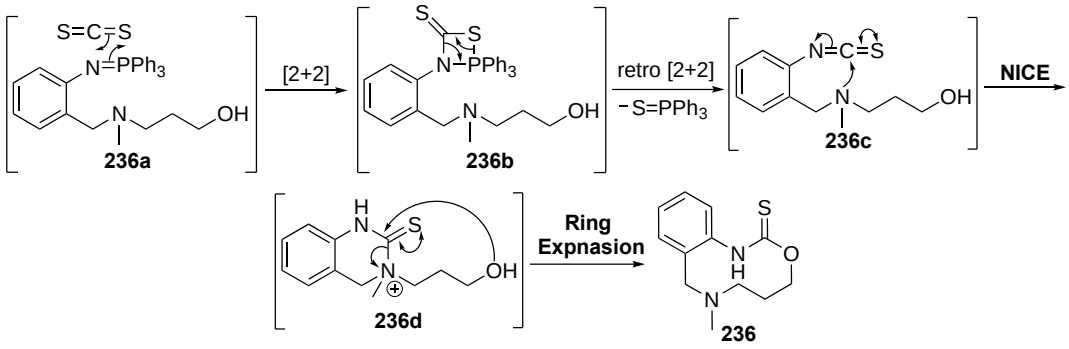
Scheme 3.1.12 Aza-Witting reaction mechanism for the formation of iminophospholane **235e** ylide intermediate before reaction with CO_2

Then, we introduce CO_2 to this intermediate by bubbling through the reaction medium (via balloon, **Figure 3.1.15**). The iminophospholane **234f** generated previously reacts with CO_2 via [2+2] cycloaddition to yield oxaphosphetane **234g** (**Scheme 3.1.13**, [**234f**] → [**234g**]). The resulting oxaphosphetane **234g** could then undergo a retro [2+2] to form an aryl isocyanate **234h** with the displacement of triphenylphosphine oxide (PPh_3O) (**Scheme 3.1.13**). The isocyanate **234h** is then set up to undergo intramolecular cyclization via a six-membered ring cyclization (i.e., NICE) to yield a six-membered cationic urea intermediate **234i** (**Scheme 3.1.13**). The urea intermediate **234i** could then finally undergo ring expansion with OH acting as a terminal nucleophile via a six-membered ring cyclization trajectory to yield a 9-membered carbamate product **235**.



Scheme 3.1.13 Reaction mechanism for the formation of the 9-membered ring carbamate **235** via isocyanate intermediate **234h** using internal nitrogen as the nucleophilic catalyst, when iminophospholane **234f** reacts CO_2 dissolved in a solvent, not showing proton transfer steps

Alternatively, carbon disulfide (CS_2) could also be used as a reagent in a similar manner, which has the advantage of being easier to use because CS_2 is a liquid rather than a gas. The mechanism of the reaction works similarly to CO_2; however, when CS_2 is employed, the thiocarbamate medium-size ring product **236** (**Scheme 3.1.14**) will be formed instead.



Scheme 3.1.14 Reaction mechanism with CS_2 to afford 9-membered ring thiocarbamate **236** product, showing only key steps

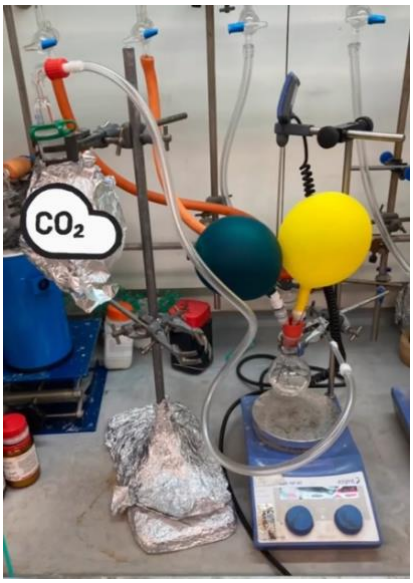
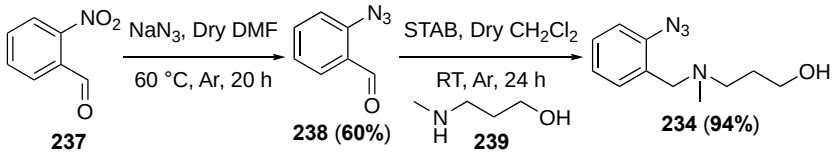


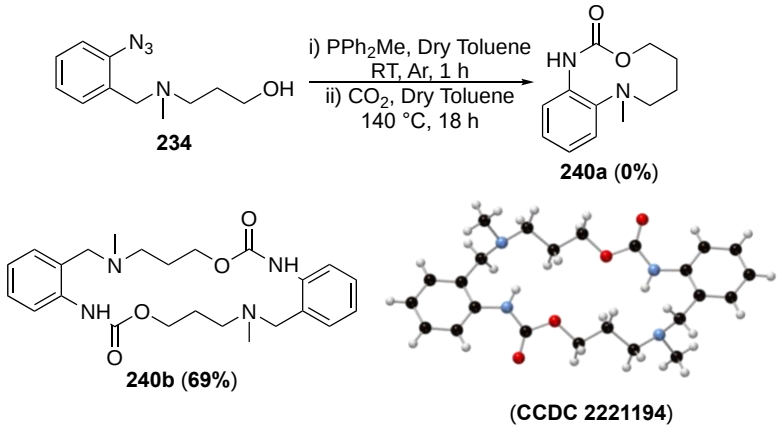
Figure 3.1.15 Recreation of reaction set-up when CO_2 was bubbled through the reaction medium for Aza-Witting type reaction for the formation of iminophospholane **234f** intermediate

The synthesis of the azide **234** starting material began with commercially available 2-nitrobenzaldehyde **237** that undergoes S_NAr with NaN_3, following a literature procedure.[225] Aryl azide aldehyde **238** was afforded in good yield**,** which was then subjected to reductive amination condition using sodium triacetoxyborohydride (STAB) and amino alcohol **239** (**Scheme 3.1.16**, **238** + **239** → **234**) to give the desired starting material **234**, in 94% yield.



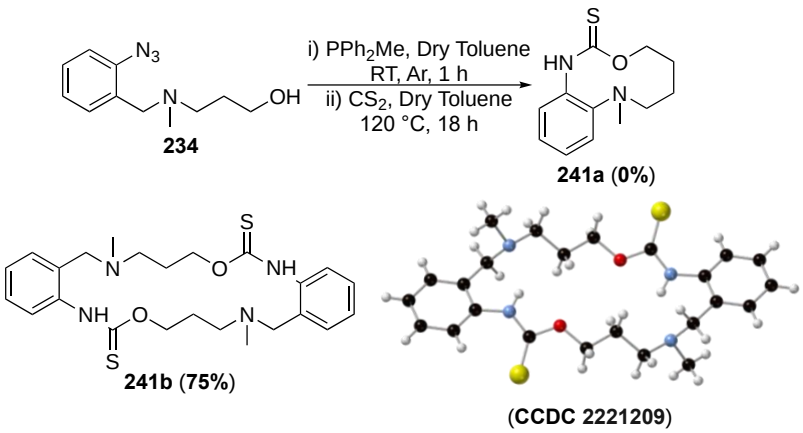
Scheme 3.1.16 Reaction sequence towards the synthesis of azide **234** starting material

Azide **234** was subjected to an aza-Witting reaction, but instead of the more common PPh_3 nucleophile, PPh_2Me was used due to its more reactive nature. This was followed by the reaction with CO_2 in toluene (**Scheme 3.1.17**), using the general approach summarised above. Unfortunately, after completion of the reaction, it was found that the desired product ten-membered ring **240a** wasn't synthesised, and instead the macrocyclic and dimeric carbamate product **240b** (**Scheme 3.1.17**) was isolated in 69% yield. This assignment was confirmed by X-ray crystal structure with its corresponding **CCDC** deposit number shown in **Scheme 3.1.17**. A single X-ray crystal of carbamate dimer **240b** was crystallised by leaving the saturated mixture of *n*-hexane:EtOAc, to the ratio of 2:1 in approx. 7 mL of solvent, at –20 °C in a freezer overnight.



Scheme 3.1.17 Synthesis of dimeric **240b** showing isolated yield and X-ray crystal structure

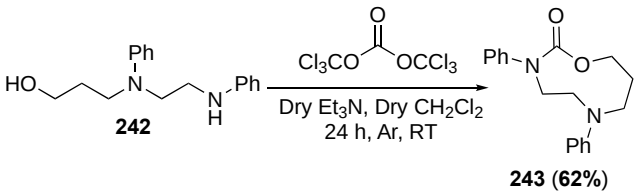
The same reaction conditions were tried, but CS_2 was used instead of CO_2. The results were the same as in **Scheme 3.1.17**, where thiocarbamate dimer **241b** was synthesised in 75% yield (**Scheme 3.1.18, 234 → 241b**) Unusually, while X-ray data for **241b** were obtained, ^1H and ^{13}C NMR data were not collected, owing to the poor solubility of the thiocarbamate dimer; DMF-d_7, DMSO-d_6, CD_2Cl_2, D_2O, THF-d_8, benzene-d_6, pyridine-d_5 and $CDCl_3$ solvents were tried, but all failed to dissolve the product and hence no ^1H or ^{13}C NMR data for **241b** were recorded. A single X-ray crystal of thiocarbamate dimer **241b**, shown in **Scheme 3.1.18**, was crystallised by slow evaporation of warm DMSO.



Scheme 3.1.18 Synthesis of the thiocarbamate dimer **241b** showing isolated yield and X-ray crystal structure with **CCDC** deposit number

3.2.0 Successfully varying the electrophilic components using bis-electrophilic reagents

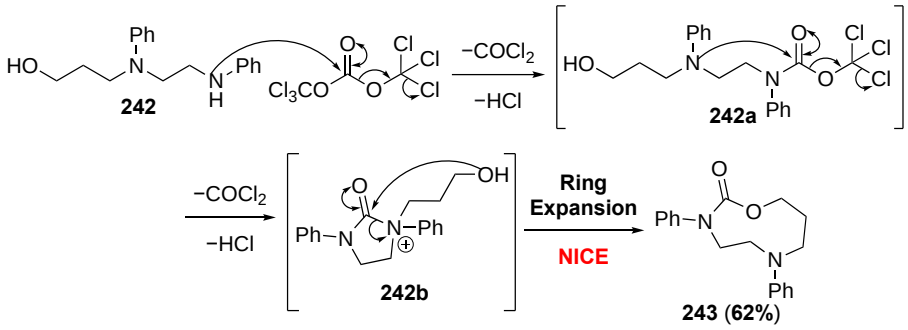
At this point, we changed focus and began exploring the use of bis-electrophilic reagents in NICE reactions with bis-nucleophilic starting materials. This is exemplified by the reaction of simple linear precursor **242** with triphosgene (**Scheme 3.2.1**). This substrate has two terminal nucleophiles at both ends of the chain (OH and aniline) and one internal (aniline) nucleophile in between. The triphosgene was chosen as a bis-electrophilic component (source of CO^{2+}) due to its ability to react with amino alcohols and convert them into carbamates. Pleasingly, the reaction went as planned, and the desired medium ring **243** (**Scheme 3.2.1**) was formed in 62% yield.



Scheme 3.2.1 First example of NICE reaction with a different electrophilic component for the synthesis of the carbamate **243** medium-sized ring with isolated yield and reaction conditions

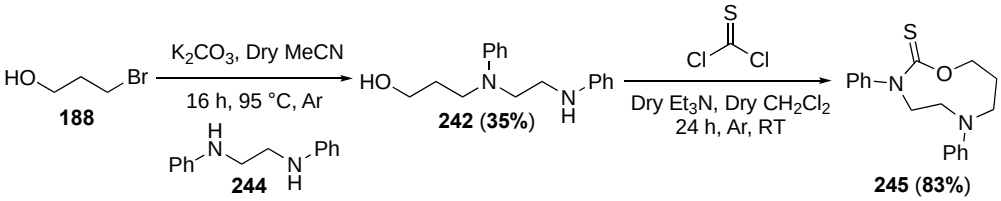
This reaction is proposed to begin at the more nucleophilic terminus, i.e., the secondary aniline, which is thought to attack the electrophilic carbonyl functional group on triphosgene, to eliminate phosgene ($COCl_2$) and HCl by-products to give intermediate **242a** (**Scheme 3.2.2**, **242** → [**242a**]). Next, the internal nucleophile (tertiary aniline), is set up to undergo an intramolecular cyclization via a five-membered ring transition state to form intermediate **242b**, displacing phosgene and HCl (**Scheme 3.2.2**, [**242a**] → [**242b**]). The resulting cationic intermediate **242b** is set to undergo ring expansion reaction (i.e., NICE) via six-membered

ring cyclization with -OH as the terminal nucleophile to afford desired product **243** in good yield (**Scheme 3.2.2**, [**242b**] → **243**). The reaction was performed at 0.05 M in CH_2Cl_2 under mild conditions.



Scheme 3.2.2 Reaction mechanism for forming 9-membered carbamate **243** product, demonstrating the participation of internal nucleophilic catalyst, only showing key steps in the reaction mechanism

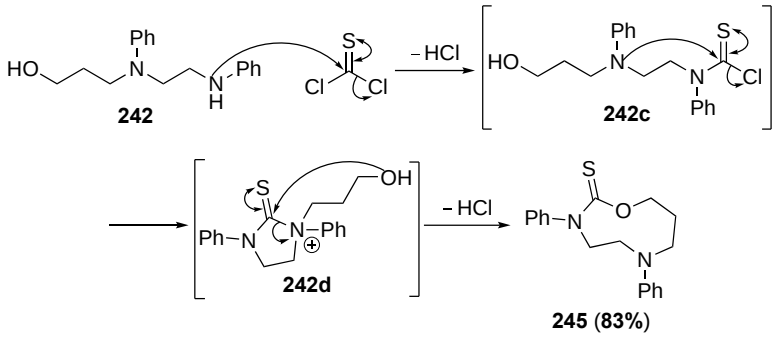
After this successful result, we decided to further extend the substrate scope and use thiophosgene ($CSCl_2$, a source of CS^{2+}). Pleasingly, the desired thiocarbamate **245** (**Scheme 3.2.3**) was formed in an excellent yield of 83% from the same linear precursor **242**. The synthesis of the desired starting material in both cases was achieved via simple alkylation of bromopropanol **188** with commercially available bis aniline **242** to give desired product **245** (**Scheme 3.2.3**).



Scheme 3.2.3 Synthesis of starting material linear precursor **243** and NICE reaction to make novel 9-membered thiocarbamate **245** using $CSCl_2$ as an electrophilic component, showing isolated yield and reaction conditions

It is likely that the reaction mechanism with thiophosgene ($CSCl_2$) works in the same way as the triphosgene system mentioned above, where the secondary aniline attacks the electrophilic carbon of the C=S bond, which gives rise to the formation of thiocarbamoyl chloride intermediate **242c** (**Scheme 3.2.4**, **242** → [**242c**]). The resulting intermediate can undergo cyclization with the internal nucleophile (tertiary aniline) via a five-membered ring transition state to give 5-membered thiourea cationic intermediate **242d** (**Scheme 3.2.4**,

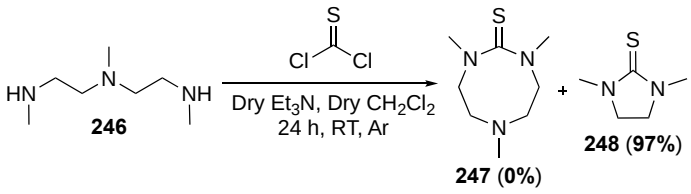
[**242c**] → [**242d**]), which is set for ring expansion via a six-membered ring transition state to afford desired medium-sized ring product **245** (**Scheme 3.2.4**, [**242d**] → **245**).



Scheme 3.2.4 Reaction mechanism for the formation of thiocarbamate **245**, showing only key aspect of the mechanism, i.e., no proton transfer steps

3.3.0 An unexpected result

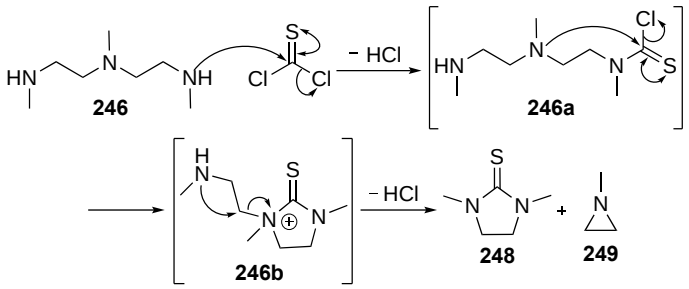
Next, it was decided to test the same reaction conditions on another linear precursor, triamine **246** (**Scheme 3.3.1**), which is a commercially available starting material. The starting material has two terminal nucleophiles, both secondary amines, and one internal nucleophile built into the linear precursor (a tertiary amine). However, when reacted with thiophosgene, the expected 8-membered ring **247** was not formed; instead five-membered ring thiourea **248** (**Scheme 3.3.1**) was isolated from the reaction.



Scheme 3.3.1 Attempt to make 8-membered thiourea **247** using the condition shown, however, 5-membered thiourea **248** side product was isolated with respective yield

This was initially surprising, but consideration of the reaction mechanism reveals a logical explanation. We propose that the first and second steps of the mechanism shown in **Scheme 3.3.2** took place as expected **246** → [**246a**] → [**246b**], but when the thiouronium **246b** intermediate is formed, it can follow two reaction pathways. One reaction pathway is the desired ring expansion to form the desired 8-membered ring **247** (**Scheme 3.3.1**), but the second is an S_N2 reaction to afford thiourea **248** (**Scheme 3.3.2**, [**246b**] → **248**). Due to several thermodynamic factors (a net loss of entropy, the transannular strain associated with forming

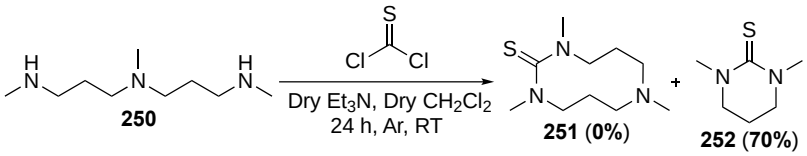
the 8-membered ring **247** (**Scheme 3.3.1**)), in this case it appears that the reaction pathway to afford thiourea **248** and aziridine **249** (**Scheme 3.3.2**) is more kinetically favourable.



Scheme 3.3.2 Proposed mechanism for the formation of 5-membered thiourea **248** and aziridine **249** side products using $CSCl_2$ as an electrophilic component

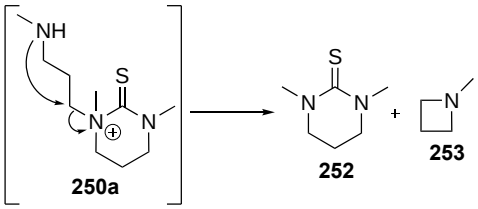
While this reaction did not deliver the expected product, it does help to reinforce an important point – that the reaction proceeds via the cation intermediate **246b** (**Scheme 3.3.2**).

The same results were obtained for the reaction that occurred when using the commercially available starting material **250** (**Scheme 3.3.3**). Triamine **250** was reacted under the same conditions, and the desired 10-membered ring **251** was not formed; instead, the six-membered thiourea **252** ring was produced in 70% yield (**Scheme 3.3.3**).



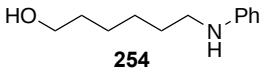
Scheme 3.3.3 An attempt to synthesise 10-membered thiourea **251**, however, 6-membered thiourea **252** side product was isolated with corresponding yield

The reaction mechanism likely proceeds through a 6-membered thiouronium **250a** intermediate (**Scheme 3.3.4**), and instead of undergoing ring expansion, thiourea **252** and the 4-membered azetidine **253** is formed.



Scheme 3.3.4 Proposed mechanism to rationalise the formation of 6-membered thiourea **252**

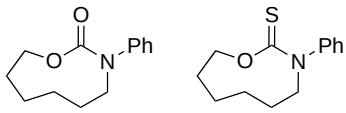
In terms of the successful reaction to make **243** and **245** (**Scheme 3.2.1** and **Scheme 3.2.4** respectively), the efficiency of both reactions was very promising, considering that it was performed at 0.05 M concentration and that nine-membered rings are difficult to make via direct cyclization. Nonetheless, to eliminate the possibility that it is an unusually efficient end-to-end cyclization, the secondary aniline **254** (**Fig. 3.3.5**) was synthesised as a control substrate.



254

Figure 3.3.5 Molecular structure of the straight chain alkane **254** without internal nucleophile in the linear precursor used later for control reaction studies

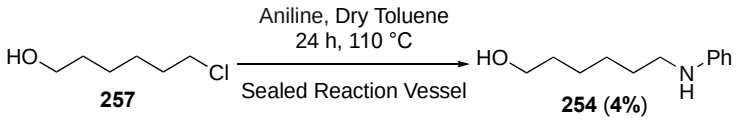
This was done to confirm that the tertiary aniline atom incorporated inside the linear precursors is acting as an internal nucleophile as proposed. The idea was to see whether the analogous medium-sized carbamate **255** and thiocarbamate **256** rings (**Fig. 3.3.6**) could be generated under the same conditions and yield as those described in the proposed NICE reactions above.



255 **256**

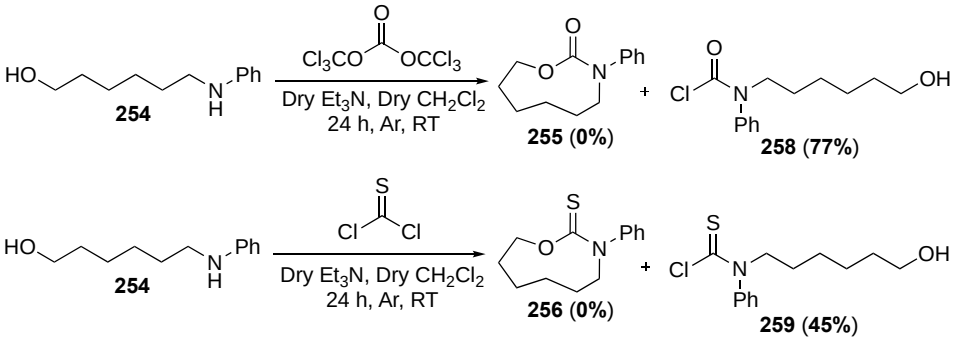
Figure 3.3.6 Molecular structures of the 9-membered-sized carbamate **255** and thiocarbamate **256**

The synthesis of the secondary aniline **254** started with a simple S_N2 reaction to displace the corresponding chloride by aniline (**Scheme 3.3.7**) to give the desired product in very low yield.



Scheme 3.3.7 Reaction conditions for the synthesis of the **254** starting material with isolated yields, a high-pressure borosilicate glass tube using used and an oil bath for heating the reaction mixture

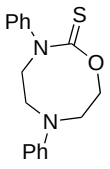
Despite the poor yield, enough of the secondary aniline **254** starting material was prepared to perform the control reactions. These tests showed that the formation of medium-sized carbamate **255** and thiocarbomate **256** (**Scheme 3.3.8**) does not take place without the internal heteroatom-nucleophiles in both cases. Instead, in both cases, the carbamoyl chloride **258** and thiocarbamoyl chloride **259** (**Scheme 3.3.8**) were isolated as the major product from the reaction in 77% and 45% yield respectively, after column chromatography, with none of the medium-sized rings **255** and **256** being formed. These results therefore supported our proposed mechanism for the NICE reactions.



Scheme 3.3.8 Control reactions leading to the formation of carbamoyl chloride **258** and thiocarbamoyl chloride **259**

3.4.0 Substrate Scope and Synthetic Applications

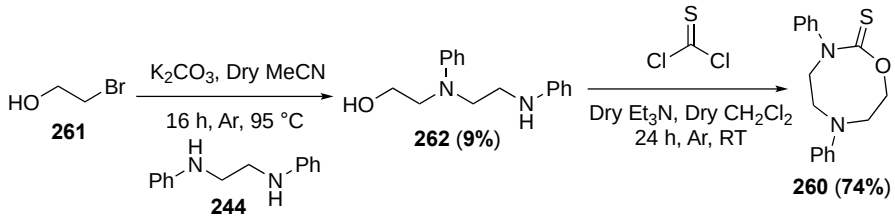
After establishing the triphosgene and thiophosgene methods work as proposed, we moved on to exploring the substrate scope and synthetic application. The first goal was to make an eight-membered thiocarbamate **260** (**Fig. 3.4.1**), a ring size which can be notoriously challenging to make.



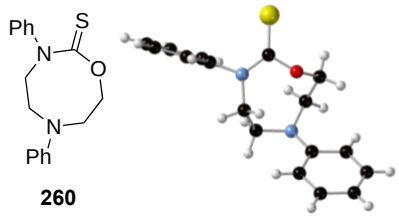
260

Figure 3.4.1 Molecular structure of the 8-membered thiocarbamate **260**

To make the desired target, the synthesis started with the formation of a linear precursor using the same reaction condition as described in **section 3.2.0**, but with bromoethanol **261** (**Scheme 3.4.2**). The desired starting material **262** was achieved in low yield, but enough product was made to attempt the following reaction. The NICE reaction with thiophosgene was set up as described in **section 3.2.0** and led to the formation of the desired 8-membered ring **260** in 74% yield at 0.05 M concentration (**Scheme 3.4.2**), with the crystal structure of the medium size ring also being afforded as shown in **Fig. 3.4.3**. A single X-ray crystal of thiocarbamate **260** was crystallised by slow evaporation of *n*-hexane:EtOAc, at the ratio of 2:1 in approx. 7 mL of solvent.



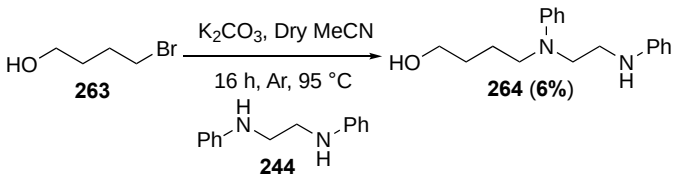
Scheme 3.4.2 Synthetic route towards the formation of the 8-membered thiocarbamate **260**



(**CCDC 2221454**)

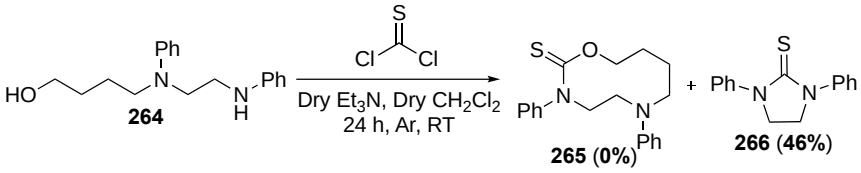
Figure 3.4.3 Structure of the 8-membered-sized thiocarbamate **260** with corresponding X-ray crystal structure and **CCDC** deposit number

Next, it was decided to test the synthesis of the 10-membered ring systems. The synthesise began by using the established reaction conditions for alkylation of bromo butanol **263** with bis aniline **244** to form **264** in low yield (**Scheme 3.4.5**). Enough material was isolated to test the NICE reaction, so no optimisation was done for this reaction.



Scheme 3.4.5 Reaction conditions for the synthesis of the extended linear precursor **264**

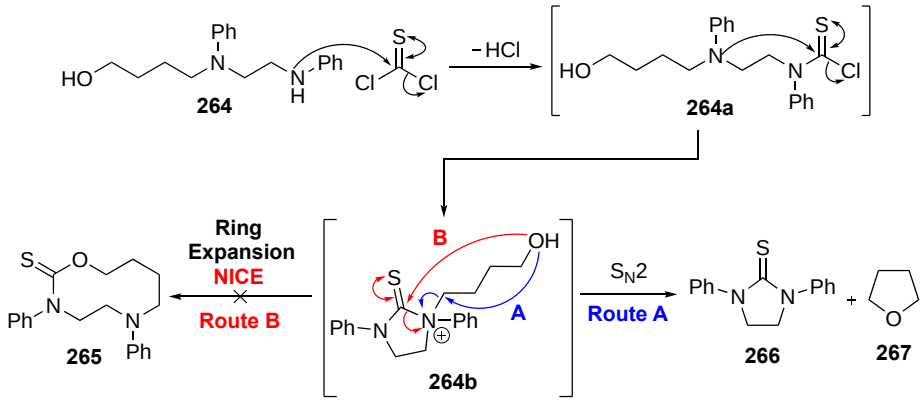
Linear product **264** was then reacted under the standard thiophosgene conditions, with another unexpected result obtained; instead of the desired 10-membered ring **265**, the five-membered diphenyl thiourea **266** was isolated as a major product in 46% yield (**Scheme 3.4.6**).



Scheme 3.4.6 An attempt to make the 10-membered thiocarbamate **265** ring using the NICE reaction method, however, instead, diphenyl 5-membered thiourea **266** was isolated as a major side product

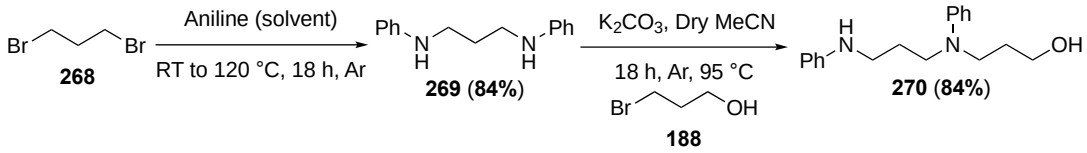
A plausible pathway for the formation of **266** is shown in **Scheme 3.4.7**. Upon the formation of intermediate **264b** in the usual way, it has two possible reaction pathways. The first is to undergo ring expansion (**Route B** in **Scheme 3.4.7**, [**264b**] → **265**) to form desired medium-sized ring **265**. But this would require a reaction to proceed via a seven-membered ring transition state, which is generally less kinetically favourable than the analogous five- or six-membered transition states.[226] As a result, the other competing reaction pathway can occur; in this case, the competing reaction pathway appears to be an intramolecular S_N2 reaction via a 5-exo-tet ring cyclization (**Route A** in **Scheme 3.4.7**, [**264b**] → **266**). This leads to the formation of diphenyl five-membered thiourea **266** and tetrahydrofuran (THF) **267**.

This again shows that if the NICE cascade reaction is not fast enough, alternative side reactions can and will compete.



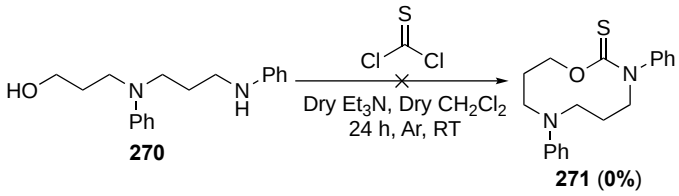
Scheme 3.4.7 Proposed mechanism for the formation of 5-membered diphenyl thiourea **266** and 10-membered thiocarbamate product **265** through the same cationic intermediate **264b**, where two possible reaction pathways are available and route A is predominant

After this unsuccessful reaction, it was decided to change the linear precursor to avoid cyclization occurring via a 7-membered ring transition state. An extra carbon was introduced in the linear precursor between the two phenyl groups to achieve this. The synthesis of the desired linear precursor begins with the bis alkylation of the dibromo **268** starting material affording dianiline **269** product in good yield, using aniline as a solvent in the reaction (**Scheme 3.4.8**). The desired product was subject to a "Williamson" type condition to yield the desired linear precursor **270** in 84% yield.



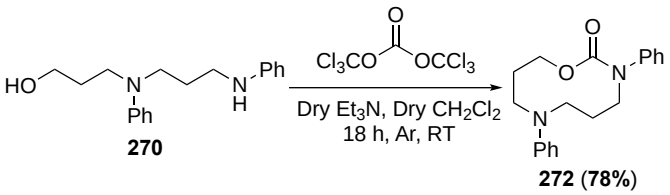
Scheme 3.4.8 Reaction sequence towards the synthesis of the linear precursor **270**, showing reaction conditions and isolated yields for each step

Initially, the linear precursor **270** was reacted under our thiophosgene conditions (**Scheme 3.4.9**), and the reaction was monitored by TLC analysis for 24 h, after which time, complete consumption of starting material **270** was observed. Next, sat. $NaHCO_{3(aq)}$ was added to the reaction vessel to quench the HCl by-product and destroy any residual thiophosgene (1.5 equiv. of reagent used). However, the crude NMR spectrum showed the formation of a very complex mixture of products, and it was concluded that the corresponding linear starting material **270** is not compatible with thiophosgene conditions (**Scheme 3.4.9**).



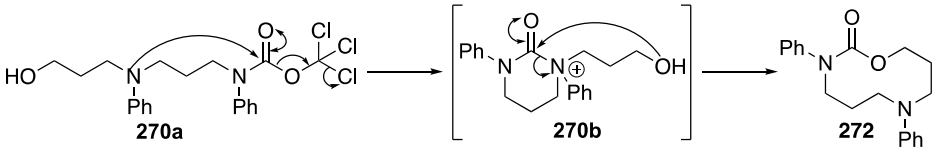
Scheme 3.4.9 Shows no reaction between linear precursor **270** and $CSCl_2$ as an electrophile component, two reagents are not compatible with each other

Nevertheless, the linear precursor starting material **270** reacted with triphosgene as the electrophilic component. The desired ten-membered carbamate **272** ring (**Scheme 3.4.10**) was successfully synthesised in 78% yield after a simple work-up procedure and purification by column chromatography.



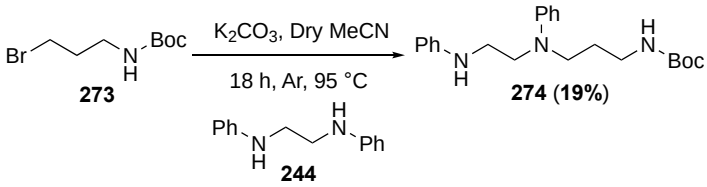
Scheme 3.4.10 Reaction conditions for the synthesis of 10-membered carbamate **272** with isolated yield, where two reagents showed competency

The reaction mechanism displayed in **Scheme 3.4.11** demonstrates only the key cyclization steps where the intermediate **270a** has aniline acting as an internal nucleophile attacking the triphosgene motif via a six-membered transition state to give urea diphenyl cationic intermediate **270b**. The resulting intermediate species **270b** will undergo ring expansion through alcohol (terminal nucleophile), cyclizing via a six-membered ring transition state to afford carbamate **272** product (**Scheme 3.4.11**).



Scheme 3.4.11 Proposed reaction mechanism for the formation of 10-membered carbamate **272** ring via NICE, showing only key cyclization steps in the reaction

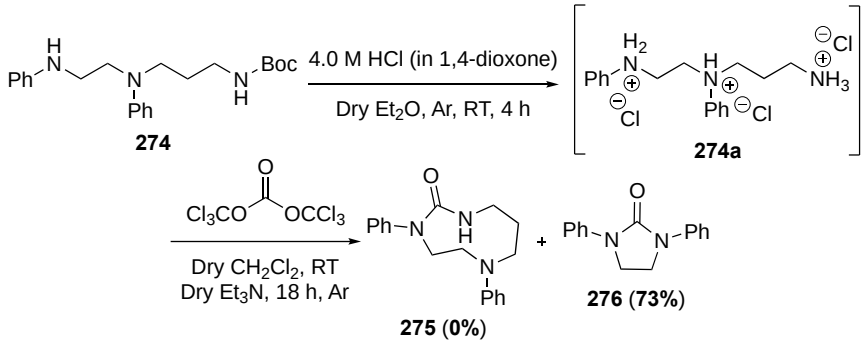
Next, we decided to vary the terminal nucleophile of the linear precursor. The linear precursor **274** was thus synthesised using standard S_N2 reaction conditions, starting from bromide **273** with diphenyl **244**, affording the desired product in an acceptable yield to carry forward (**Scheme 3.4.12**).



Scheme 3.4.12 Reaction conditions to make linear precursor **274**, showing the starting materials and isolated yield

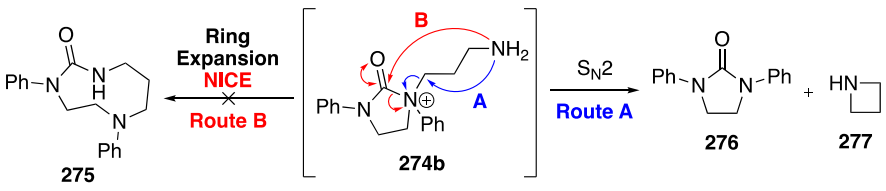
Then, the idea was to remove the Boc protective group to reveal the primary amine, which could act as a terminal nucleophile in the reaction. The classical way to remove the Boc

protecting group is with a strong acid, and therefore, the **274** starting material was reacted with HCl (in 1,4-dioxane) in Et_2O, in the ratio of 1:1, to afford crude product **274a** as an HCl salt (**Scheme 3.4.13**, **274** → [**274a**]). The reaction mixture was concentrated in *vacuo* to remove all the solvent and excess HCl, and the resulting crude product **274a** was taken directly to the next step without further purification. The crude product was reacted with triphosgene (0.4 equiv.) and an extra 3 equiv. of Et_3N added to free base the **274a** hydrochloride (**Scheme 3.4.13**). Unfortunately, instead of the desired medium-sized ring **275**, the diphenyl five-membered urea product **276** was isolated in 73% yield (**Scheme 3.4.13**).



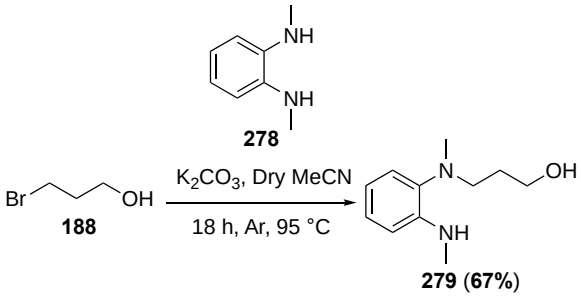
Scheme 3.4.13 Attempt reaction sequence towards the formation of 9-membered urea **275**, showing the formation of tri hydrochlorides salt intermediate **274a**, which will further be supposed to undergo NICE reaction

In this transformation, multiple pathways are possible; the lower energy profile with smaller $\Delta G^{\ddagger}$ (activation energy) will generally be the predominant one. The primary amine is significantly more nucleophilic than alcohol or aniline as the terminal nucleophile. Hence, the lowest energy pathway, S_N2 (**Route A** in **Scheme 3.4.14**), is more accessible for the amine nucleophile than the corresponding ring expansion route (**Route B** in **Scheme 3.4.14**); as a result, the five-membered ring product is formed faster.



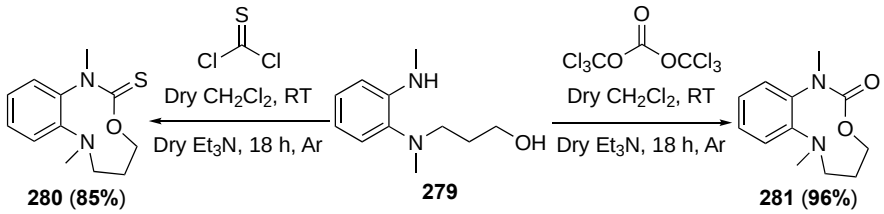
Scheme 3.4.14 Illustrates two possible reaction pathways for the 5-membered cationic intermediate **274b**: Ring Expansion/NICE (Route B, red curly arrows) to afford medium-size ring urea **275** desired product and S_N2 (Route A, blue curly arrows) to give diphenyl urea **276**

After a failed attempt in varying terminal components, it was decided to test the effects of introducing more sp^2 character into the linear precursor, i.e., to make it more rigid. The desired linear starting material **279** (**Scheme 3.4.15**) was made very quickly and with a good yield, using simple alkylation conditions used previously.



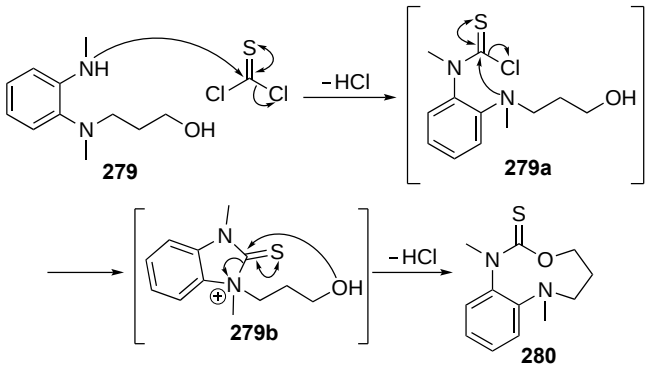
Scheme 3.4.15 Reaction to make sp^2-rich linear precursor **279**, showing the conditions and isolated yield

The synthesised linear precursor was reacted to the thiophosgene and triphosgene conditions and pleasingly afforded thiocarbamate **280** and carbamate **281** nine-membered rings in excellent yields (**Scheme 3.4.16**, **280** ← **279** → **281**). This shows how introducing an aryl functional group in the linear precursor can result in an increased yield of the reaction compared to a straight aliphatic chain.



Scheme 3.4.16 Showing reaction conditions affording 9-membered ring thiocarbamate **280** and carbamate **281** rings, with the same sp^2-rich linear precursor **279**

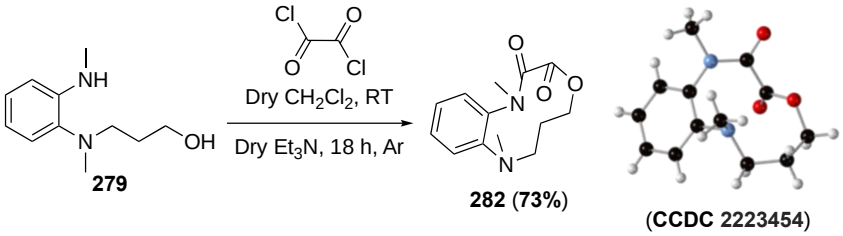
The thiophosgene reaction likely begins with the more reactive terminal nucleophile, the presumed secondary aniline that attacks the electrophilic carbon of the C=S bond, yielding the intermediate **279a** after proton transfer (**Scheme 3.4.17**, **279** → **279a**).The phenylthiocarbamoyl chloride **279a** will be further attacked by the internal nucleophile via five-membered ring cyclization affording benzimidazole thione **279b**. The cationic species **279b** will then be ring expanded by alcohol via a six-membered ring transition state to obtain the desired aryl thiocarbamate **280** medium-sized ring in excellent yield (**Scheme 3.4.17**).



Scheme 3.4.17 Illustration of a proposed reaction mechanism for the formation of the 9-membered thiocarbamate **280**, showing only key steps

This is a successful outcome and shows that increasing the sp^2 character of the linear precursor results in a significant increase in the yield of the reaction. Using the same substrate and changing the electrophilic component was then decided.

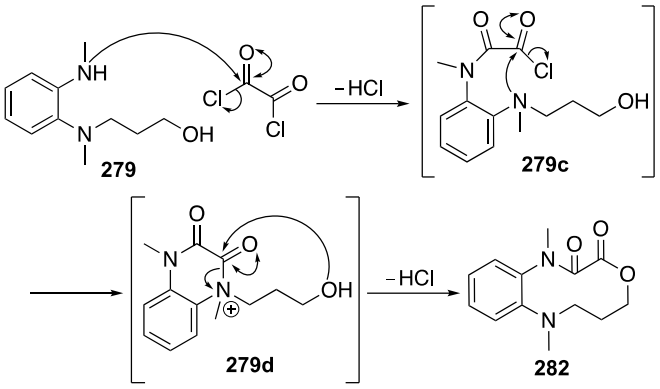
Next, we questioned whether two leaving groups needed to be attached to the same atom, as they are in the thiophosgene and triphosgene case. Consequently, oxalyl chloride was tested in a similar reaction (**Scheme 3.4.18**). Thus, amino alcohol **279** linear precursor was subjected to react with $(COCl)_2$ in CH_2Cl_2 at RT, and pleasingly, the desired 10-membered ring **282** was successfully synthesised in 73%, with an X-ray crystal structure of the medium ring product obtained (**Scheme 3.4.18**). A single X-ray crystal of 10-membered ring **282** was crystallised by slow evaporation of EtOAc:$CHCl_3$:Et_2O, at the ratio of 1:1:2 in approx. 9 mL of solvent.



Scheme 3.4.18 Reaction to make the 10-membered ring **282**, showing isolated yield and reaction conditions for transformation using $(COCl)_2$ as an electrophile, along with X-ray crystal structure

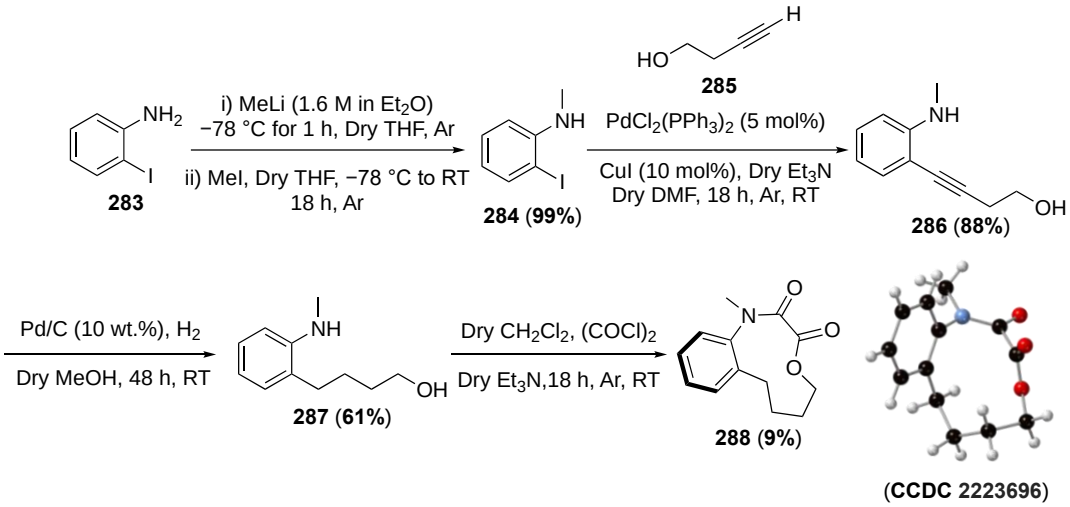
The oxalyl chloride reaction mechanism likely commences in the same fashion as seen earlier, with the secondary aniline from the liner precursor reacting with one of the acyl chlorides to make the intermediate **279c** (**Scheme 3.4.19**, **279** → **279c**). The tertiary aniline in **279c** will work as an internal nucleophile and charge towards the second acyl chlorides along a six-membered ring trajectory to produce bis amide cationic **279d** species. The charged

intermediate **279d** is set to do the ring expansion via six-membered transition state, affording the desired medium-sized ring **282** (**Scheme 3.4.19**, **279d** → **282**) in an excellent yield after a simple work-up and purification.



Scheme 3.4.19 Proposed reaction mechanism using $(COCl)_2$ as the electrophilic component and sp^2-rich linear precursor **279** yielding dicarbonyl medium-size ring product **282**

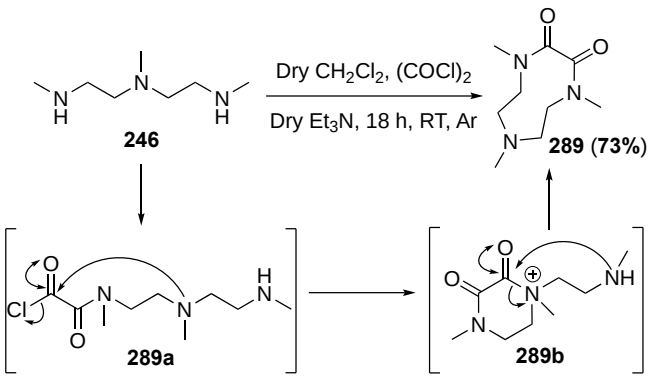
A control substrate was synthesised next, for the purpose of providing proof that *N*-heteroatoms act as nucleophilic catalysts in the new oxalyl chloride NICE reaction variant. The synthesis of the control substrate started with a literature reaction condition.[227] The synthesis of the control linear precursor substrate started with a literature-reported procedure of methylating commercially available *ortho*-iodoaniline **283** to give the desired secondary aniline **284** in excellent yield (**Scheme 3.4.20**).[227] The resulting product **284** was subject to Sonogashira coupling conditions with commercially available alkyne **285** to afford desired product **286** in 88% yield, following the literature-reported conditions.[228] Next, the alkyne **286** product was subject to hydrogenation conditions using Pd/C and H_2 (via balloon) to afford the desired straight chain alkane linear precursor **287** (**Scheme 3.4.20**), in 64% yield. Subsequently, the control reaction was performed using starting material **287**, which was reacted under the same reaction conditions previously used, and pleasingly, the medium-sized ring **288** was isolated only in 9% yield (**Scheme 3.4.20**, **287** → **288**). This demonstrates that by removing the internal nucleophile (tertiary aniline) and replacing it with carbon, the reaction works much less efficiently, with the yield reduced from 83% to 9% (**Scheme 3.4.18** and **Scheme 3.4.20**, respectively). A single X-ray crystal of 10-membered ring **288** was crystallised by slow evaporation of $CHCl_3$:Et_2O, at the ratio of 1:1 in approx. 5 mL of solvent.



Scheme 3.4.20 Shows the reaction sequence towards the formation of the linear precursor **287** with conditions and isolated yields for each step**,** and control reaction for the formation of a 9-membered ring **288**

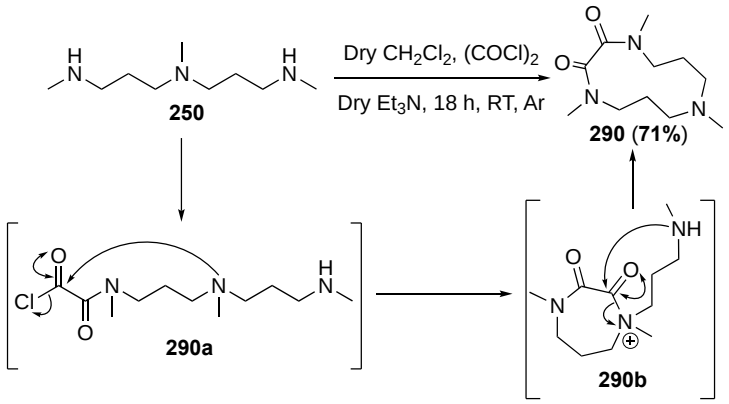
This method's advantage is the quick and easy generation of a library of medicinally important compounds from the same starting material by just varying the electrophilic component. The synthesis of the starting materials and linear precursors goes via robust and easy reaction procedures, such as S_N2, that can be easily scaled up.

After showing that $(COCl)_2$ can be used as an electrophile, it was decided to see what would happen if different lengths of starting material precursors and heteroatoms were varied. Thus, commercially available trimethyl triamine **246**, was subjected to the same reaction conditions used in **Scheme 3.4.20**, to give the desired nine-membered **289** ring in 73% yield (**Scheme 3.4.21**, **246** → **289**). The reaction mechanism presumably goes via one of the terminal nucleophiles (secondary amine), attacking the acyl chloride of $(COCl)_2$ to generate the **289a** intermediate (**Scheme 3.4.21**). The tertiary amine in the middle of the linear precursor will attack the second acyl group to form the six-membered ring cationic species **289b** (**Scheme 3.4.21**, [**289a**] → [**289b**]), which can spontaneously undergo ring expansion to achieve the target medium-sized ring **289** product (**Scheme 3.4.21**).



Scheme 3.4.21 Illustrating the reaction conditions and mechanism (showing key cyclization steps) for the formation of 9-membered bis lactam **289** product with isolated yield

Next, it was decided to make an 11-membered ring **290** by adding an extra carbon between the internal and terminal nucleophiles on each side. Helpfully, the desired substrate **250** is commercially available (**Scheme 3.4.22**) and was reacted under the standard NICE conditions with oxalyl chloride. The 11-membered ring was formed in 71% yield at 0.05 M concentration in CH_2Cl_2 (**Scheme 3.4.22**). The slight difference in this system is that the first intramolecular cyclization proceeds via seven-membered ring cyclization (7-exo-trig) to give the corresponding cationic species **290b** (**Scheme 3.4.22**, **250** → [**290a**] → [**290b**]). The intermediate will be attacked by the terminal nucleophile via a 6-membered ring transition state to end up with the 11-membered ring product **290** (**Scheme 3.4.22**, [**290b**] → **290**)

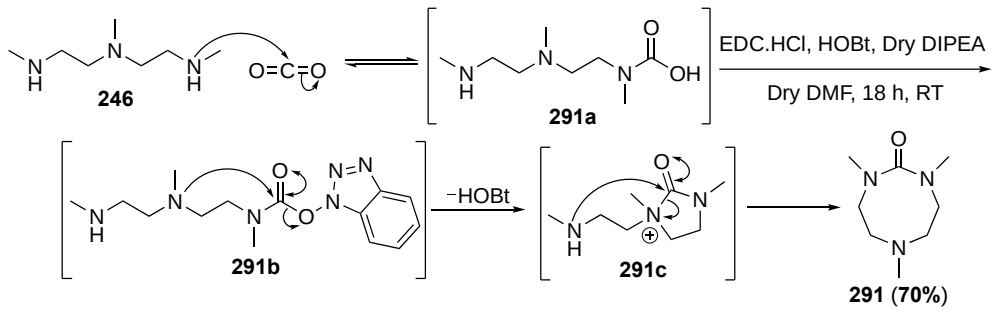


Scheme 3.4.22 Shows the reaction conditions and mechanism (demonstrating only key cyclization steps) to synthesise 11-membered **290** product using $(COCl)_2$ as an electrophilic component

After showing that thiophosgene ($CSCl_2$), triphosgene ($OC(OCCl_3)_2$) and $(COCl)_2$ can be used as electrophilic components (E^+), it was decided to seek less toxic, greener alternatives to act as the E^+ variant. We released that carbon dioxide (CO_2) could potentially be used as a source

of CO^{2+} in the reaction. The reaction set-up to test this idea differed from the standard protocol. The 250 mL round bottom flask (RBF) (large volume of headspaces required) was charged with triamine **246** in dry DMF under Ar (**Scheme 3.4.23**). The RBF was evacuated and filled with CO_2 via balloon 3 times to saturate the solvent medium. This was done to ensure enough carbon dioxide was dissolved in anhydrous DMF, and the resulting reaction was allowed to stir for 10 min before more CO_2 was bubbled through. After this was done, EDC HCl, dry Hünig's base, and finally, HOBt were added sequentially in a single portion to the reaction, and a balloon filled with CO_2 was attached to the reaction and was left to stir overnight (**Scheme 3.4.23**).

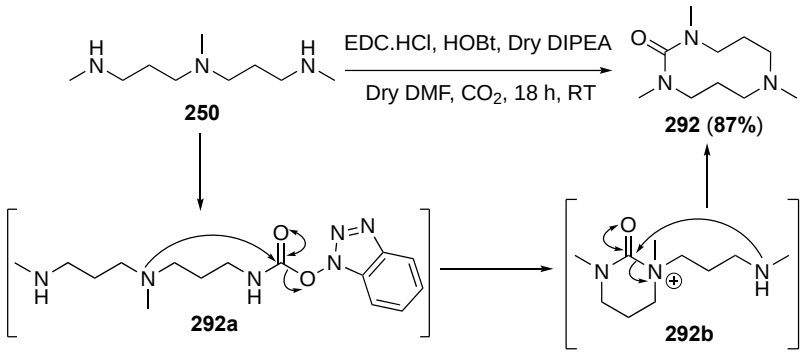
The reaction mechanism is proposed to start off with the secondary amine **246** attacking δ^+ carbon of the CO_2 to generate an unstable carbamic acid **291a**, which can revert to the starting materials (reversible step) (**Scheme 3.4.23**). However, when EDC.HCl and HOBt are added, the carbamic acid **291a** can be activated to generate reactive HOBt carbamate adduct **291b**. This HOBt-reactive adduct **291b** will be attacked by the internal nucleophile, i.e., in this case the 3° amine, via a 5-membered ring cyclization to afford cationic intermediate **291c** (**Scheme 3.4.23**, [**291b**] → [**291c**]). This intermediate can then undergo ring expansion by reacting with the 2° amine acting as a terminal nucleophile via a 5-membered ring transition state. This reaction worked remarkably well, with the desired 8-membered ring urea **291** isolated in 70% (**Scheme 3.4.23**, [**291c**] → **291**). The reaction proceeded in high yield, at 0.05 M concentration, under very mild reaction conditions, while avoiding toxic phosgene equivalents.



Scheme 3.4.23 Reaction mechanism for the formation of the 8-membered ring urea **291** product, showing only the key steps of the transformation

To extend the scope of this CO_2-based NICE variant, it was decided to try to make 10-membered urea **292** (**Scheme 3.4.24**). The synthesis was straightforward and was done using commercially available amine **250** that was subjected to the same reaction conditions as shown in **Scheme 3.4.23** to afford desired **292** product in 87% yield. The NICE reaction likely

goes via the same reaction mechanism, with the starting material **250** reacting with CO_2 to generate carbamic acid intermediate. This acid will be activated using EDC.HCl and HOBt conditions to give rise to HOBt-activated ester **292a** (**Scheme 3.4.24**, **250** → [**292a**]), which will undergo intramolecular cyclization and ring expansion via a 6-membered transition state in both instances as shown in **Scheme 3.4.24**, [**292a**] → [**292b**] → **292**.



Scheme 3.4.24 Shows synthesis of the10-membered ring urea **292** with conditions, isolated yield, and mechanism of key cyclization steps of the reaction

Both starting amines, **246** and **250** (**Scheme 3.4.23** and **Scheme 3.4.24,** respectively), have already been used with a combination of triphosgene ($OC(OCCl_3)_2$) as the electrophilic component to generate the same medium ring products, eight- and ten-membered urea. However, the five-**293**- and six-**294**-membered urea were isolated instead (**Fig. 3.4.25**), which may be attributed attacked to reactivity as $OC(OCCl_3)_2$ is more reactive than the carbamate HOBt adduct, although further mechanistic studies would be needed to better pinpoint the reason.

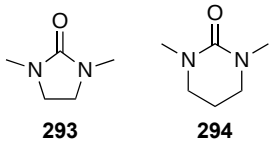
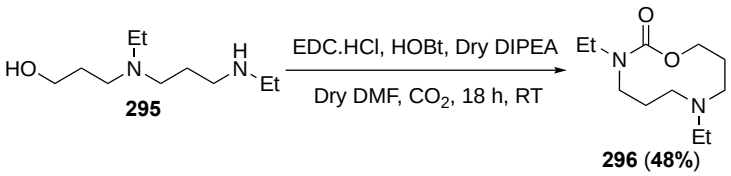


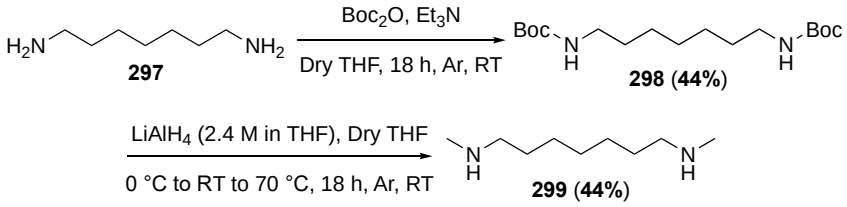
Figure 3.4.25 Molecular structure of *N*,*N*′-dimethyl **293** and *N*,*N*′-dimethylpropylene urea **294** as major side products when $OC(OCCl_3)_2$ is used as an electrophilic component

To vary the terminal nucleophile, R_2NH was swapped for R-OH, but otherwise, the reaction conditions were kept the same and, helpfully, the corresponding linear precursor **295** (**Scheme 3.4.26**) was previously synthesised by another group member. The reaction was set up as normal, and the 10-membered carbamate ring **296** was successfully synthesised in a relatively good yield of 48% using CO_2 as the electrophile (**Scheme 3.4.26**).



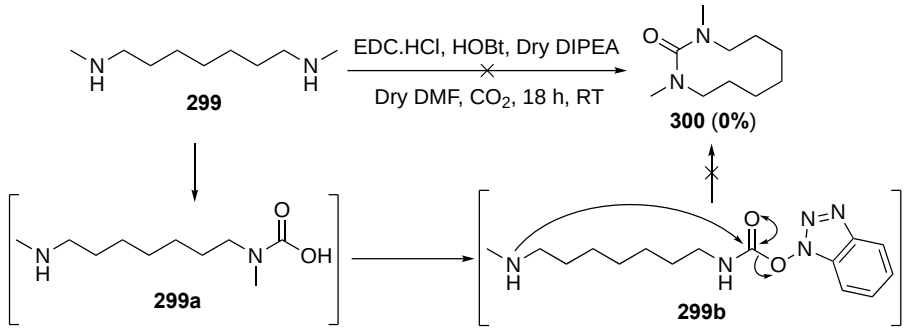
Scheme 3.4.26 Demonstrates the synthesis of the 10-membered carbamate **296** with reaction conditions and isolated yield

Given the successful nature of the reaction using CO_2 gas as E^+, another control reaction was needed. To perform the control, the linear aliphatic linear precursor **299** (**Scheme 3.4.27**) needs to be synthesised without an internal nucleophile in the middle of two terminal nucleophiles (2° amines) at each end of the chain. The reaction began with commercially available diamino heptane **297** reacting with two equivalents of di-*tert*-butyl dicarbonate (Boc_2O) to generate bis carbamate **298** (**Scheme 3.4.27**, **297** → **298**) in good yield. The resulting product was subjected to reduction with lithium aluminium hydride ($LiAlH_4$) to give desired bis methylated diamino heptane **299** in 44% yield (**Scheme 3.4.27**, **298** → **299**) after using the Fieser work-up protocol to remove excess $LiAlH_4$ and metal salts (e.g., Li and Al).[229]



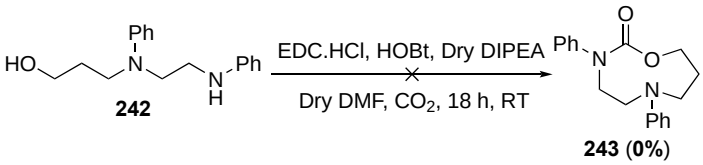
Scheme 3.4.27 Reaction sequence towards the synthesis of linear precursor **299**

The desired straight-chain aliphatic diamine **299** was subjected to reaction conditions using CO_2 as the electrophile, and the results aligned with our expectations (**Scheme 3.4.28**). The desired medium ring **300** wasn't synthesised, and instead, 40% of starting material **299** was recovered from the reaction (**Scheme 3.4.28**). Again, this serves as a very good demonstration of the importance of the internal nucleophile in mediating the cyclization.



Scheme 3.4.28 Control reaction between linear precursor **299** and CO_2

A disadvantage of this system is that a reactive aliphatic secondary amine is needed to react with the CO_2. These are "hard" nucleophiles that can react with carbon dioxide to generate the required carbamic acid intermediate. Without such a reactive amine, the reaction fails; this was shown by reacting the corresponding aniline-based starting material **242** under the same conditions using CO_2 as the E^+ (**Scheme 3.4.29**). The desired 9-membered ring carbamate **243** product wasn't synthesised, and 90% of starting material **242** was recovered from the reaction, presumably due to aniline not being nucleophilic enough to effectively trap CO_2.

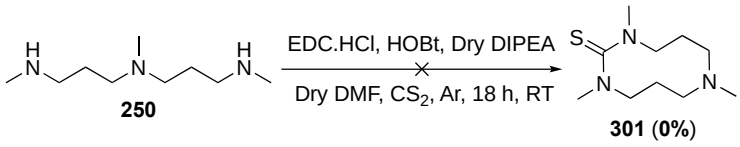


Scheme 3.4.29 An attempt to make the 9-membered carbamate **243** ring using CO_2 as electrophilic competent, but the result is no reaction

Carbon disulfide (CS_2) was also considered as an alternative reagent to be used in the same reaction as CO_2 given that they are isoelectronic. CS_2 is less electrophilic, but carbon thiocarbamic acid intermediates are more thermodynamically stable.[230]

The reaction was set as normal but with CS_2 used as the electrophile; 2.5 equiv. of liquid CS_2 were simply added to the vessel. The reaction was performed under an inert atmosphere of Ar, as shown in **Scheme 3.4.30**. The progress of the reaction was followed by TLC. The full consumption of the starting material **250** was noted after leaving the mixture to stir overnight. The resulting mixture was diluted with sat. $NaHCO_{3(aq)}$ and an aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, and after the solvent was removed via *vacuo*, the crude product was subjected to NMR analysis. Unfortunately, the crude NMR spectrum showed a complex mixture of products, and the desired thiourea **301** medium ring product

couldn't be identified. Therefore, the reaction with CS_2 and triamine **250** precursor was unsuccessful (**Scheme 3.4.30**).



Scheme 3.4.30 Shows failed reaction between triamine **250** linear precursor and CS_2, where no formation of 10-membered ring thiourea **301** was not detected

Green, less toxic and easier-to-handle alternative phosgene-like reagents were also explored; 1,1'-carbonyldiimidazole (CDI) **302** (analogues for CO_2 and triphosgene) and 1,1'-thiocarbonyldiimidazole (TCDI) **303** (equivalent to thiophosgene and CS_2) were initially tried (**Fig. 3.4.31**).

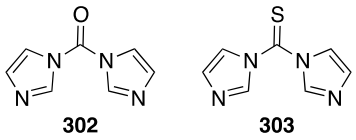
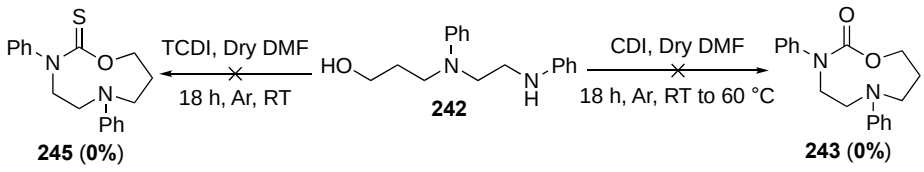


Figure 3.4.31 Shows the molecular structures of CDI **302** and TCDI **303**

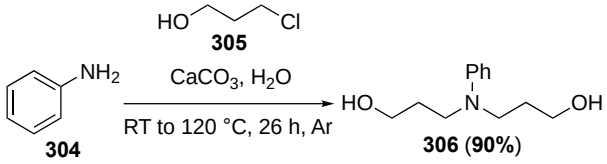
However, after trying using CDI and TCDI as alternative electrophilic components with the same diphenyl linear **242** precursor shown in **Scheme 3.4.32**, both yielded no reaction. The starting material was recovered in the reactions, even at elevated temperatures for the TCDI case, and the full consumption of the diphenyl precursor **242** was not observed by TLC analysis (**Scheme 3.4.32**).



Scheme 3.4.32 Demonstrates failed attempts to make thiocarbamate **245** and carbamate **243** medium-size ring with TCDI and CDI

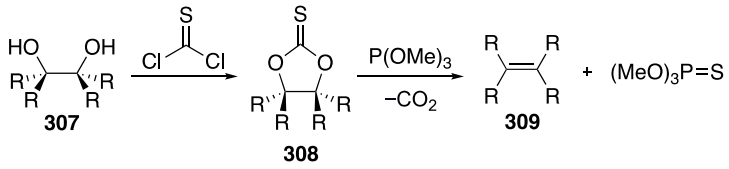
After successfully showing that CO_2, triphosgene, thiophosgene and $(COCl)_2$ can all be used as electrophiles, it was decided to explore different terminal nucleophiles by keeping the same internal nucleophilic catalyst, i.e., secondary aniline. The desired substrate was made by

reacting aniline **304** with choro propanol **305** to give diol **306** in excellent yield (**Scheme 3.4.33**).



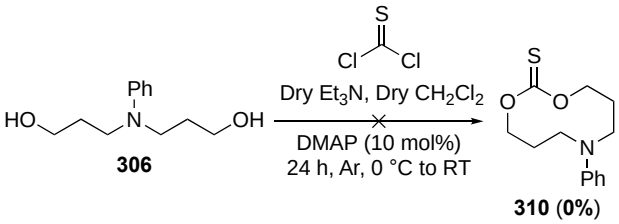
Scheme 3.4.33 Synthesis of the linear precursor **306** with two terminal nucleophiles as OH and aniline as an internal nucleophile, showing reaction conditions and isolated yield

The linear precursor **306** (**Scheme 3.4.33**) was chosen to be synthesised, partly inspired by the use of diols in the "Corey–Winter reaction" (**Scheme 3.4.34**). Here, 1,2 diol **307** reacts with thiophosgene to obtain the five-membered **308** ring upon treatment with trimethyl phosphite ($P(OMe)_3$), giving olefin **309** and by-products: CO_2, $S{=}P(OMe)_3$.[231]



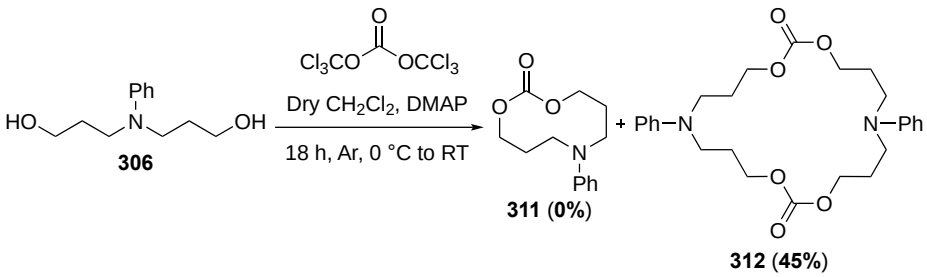
Scheme 3.4.34 Corey-Winter olefin synthesis, where the reaction goes through the 5-membered cyclic thiocarbonate **308** intermediate

Therefore, diol **306** was reacted under "Corey–Winter" conditions, as shown in **Scheme 3.4.35**. Unfortunately, the reaction gave a very complex mixture of products as judged by ^{1}H and ^{13}C NMR spectrum of the unpurified crude mixture, and no peaks which corresponded to the desired thiocarbonate medium-size ring **310** were observed. In addition, multiple spots were noted by TLC analysis, so the reaction was deemed to be unsuccessful.



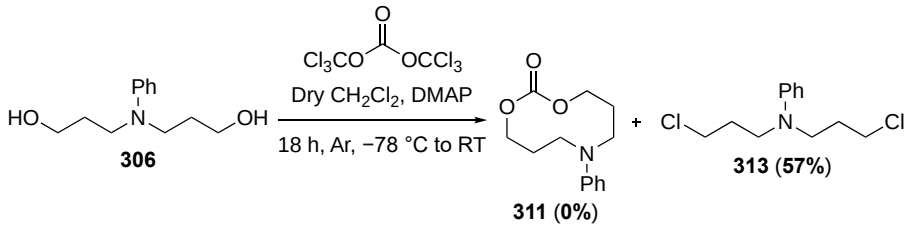
Scheme 3.4.35 An attempt to synthesise the 10-membered thiocarbonate **310** ring, using Corey–Winters conditions, where no reaction has resulted

Next, it was decided to use similar conditions to those shown in **Scheme 3.4.35** but replace the thiophosgene with triphosgene and the Et_3N with DMAP (5.0 equiv.) (**Scheme 3.4.36**). Otherwise, the reaction was set up as normal. It was found that the desired 10-membered ring **311** was not synthesised; instead, the 20-membered macrocycle **312** was isolated as a major product from the reaction in 45% yield (**Scheme 3.4.36**). The macrocycle **312** is formed by the dimerization of diol **306** with 2 equiv. of phosgene.



Scheme 3.4.36 Shows the reaction conditions with the intention of making desired monomer **311**, but the dimer **312** macrocycle was formed instead with triphosgene as an electrophile

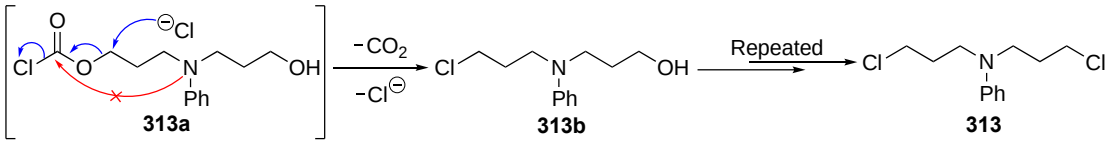
To avoid dimerization, the reaction was tried at a much lower temperature. This was motivated by work undertaken by Y.Y. Yang and co-workers,[232] who showed that eight-membered ring carbonates could be synthesised in a high yield and under standard concentration using the similar linear precursor, just one carbon short between terminal nucleophile (OH) and internal nucleophile (aniline). The reaction was performed using the literature-reported reaction conditions, with a slight modification to the initial procedure where DMAP was used as a base instead of Et_3N, as shown in **Scheme 3.4.37**. Sadly, the bis chloride **313** was isolated as a major product from the reaction instead of the 10-membered ring **311** (**Scheme 3.4.37**).



Scheme 3.4.37 Modified reaction conditions with triphosgene as the electrophile, where desired medium-size ring **311** wasn't synthesised

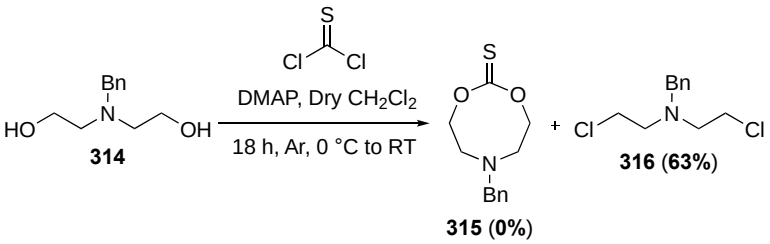
The reaction mechanism to afford bis chloride **313** is thought to start with the formation of chloroformate **313a**, but instead of undergoing 6-membered intramolecular ring cyclization (illustrated by the red curly arrow in **Scheme 3.4.38**, i.e., NICE), the in-situ chloride ion

generated from triphosgene attack the $\sigma^*_{C\text{-}O}$ in an S_N2 type manner extruding CO_2 and another chloride anion to yield mono chlorinated **313b** intermediate (illustrated by the blue curly arrows in **Scheme 3.4.38**). The second OH on the mono-chlorinated intermediate **313b** will react in the same fashion and will thus give the bis-chlorinated product **313** (**Scheme 3.4.38**). The activation of primary aliphatic alcohol using triphosgene and base (typically Et_3N) is known in the literature.[233]



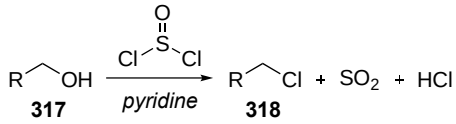
Scheme 3.4.38 Reaction mechanism for the formation of bis chloride **313**

Next, a shorter chain linear precursor was tested. Benzyl diol **314** (**Scheme 3.4.39**) is readily available, and the reaction was set using thiophosgene as the electrophile. However, the desired product 8-membered ring **315** wasn't afforded, instead bis chloride **316** product was isolated in 63% yield (**Scheme 3.4.39**). As soon as it was realised that bis chloride **316** had formed, action was taken to destroy it and avoid making it again, as it was predicted to be extremely toxic.[234] Bis chloride **316** has a very similar structure to nitrogen mustard, and so any glassware, NMR tubes, gloves, etc. that had come into contact with the bis chloride **316** were immediately soaked in ammonia dissolved in water and left in the fume hood for three days to destroy any residuals. After this incident, every next substrate was carefully selected to avoid the chance of forming "sulphur or nitrogen mustard" systems. The mustards have a specific structure, where the leaving group **X** (Cl, Br, I, etc.) and heteroatom (R-S-R or R_3N) are two carbons apart for the compound to form cyclic three-membered onium cationic species (sulfonium or ammonium) which makes it a better overall alkylating agent.[235] **Note: future researchers should note this and take similar action to avoid the same problem**.



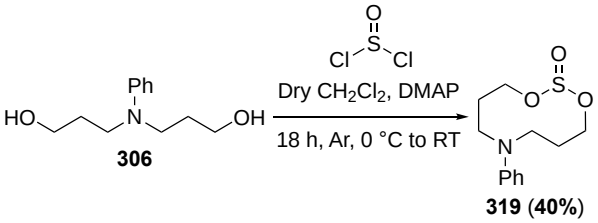
Scheme 3.4.39 Reaction conditions to make 8-membered thiocarbonate **315** using $CSCl_2$ as the electrophile, but bis chloride **316** was synthesised instead

Initially, substrate **306** (**Scheme 3.4.37**) was considered a failure, but after finding the Darzens halogenation reaction (**Scheme 3.4.40**) in the literature, [236] it gave inspiration. In this reaction the alkyl halide **318** is generated from alcohol **317**, using thionyl chloride ($SOCl_2$) in the presence of a sub-stoichiometric amount of pyridine. It is thought that pyridine acts as a nucleophile catalyst to generate chloride **318**, with SO_2 and HCl as by-products (illustrated in **Scheme 3.4.40**).[237]



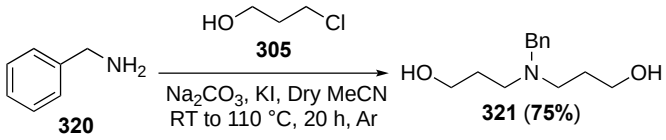
Scheme 3.4.40 General reaction for Darzens halogenation occurring via S_N2 mechanism in the presence of large excess of thionyl chloride and pyridine

A literature search found that Zhong-Xing Jiang and co-workers[238] demonstrated that a diols could be cyclised with $SOCl_2$ using *N,N*-diisopropylethylamine (DIPEA) as base and DMAP as an organic catalyst in CH_2Cl_2 at RT. The reaction was slightly modified for our procedure, whereby DMAP (5 equiv.) was used, and is thought to have a dual effect, simultaneously acting as a base and as a nucleophilic catalyst. Thus, we reacted $SOCl_2$ with diol **306** and pleasingly, the desired 10-membered ring sulfite product **319** was made in 40% yield, as shown in **Scheme 3.4.41**.



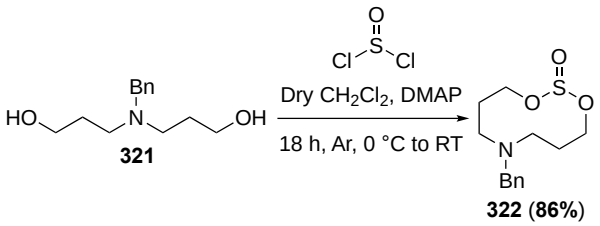
Scheme 3.4.41 Reaction conditions to make sulfites medium ring **319** with isolated yield, the first example of $SOCl_2$ acing as an electrophilic component

Next, another system of this type was tested. It was decided to swap the internal nucleophile from aniline to a tertiary amine **321** (**Scheme 3.4.42**). The synthesis of the desired benzyl-protected amine **321** starts with a simple bis alkylation of benzylamine **320** using a readily available chloro propanol reagent **305** yielding linear precursor **321** in 75% (**Scheme 3.4.42**).



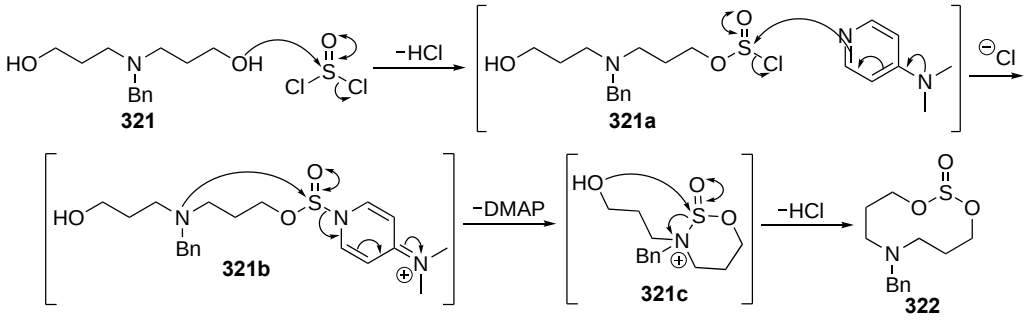
Scheme 3.4.42 Reaction conditions to make diol benzylamine **321** linear precursor with reaction conditions and isolated yield

The diol benzylamine **321** was reacted with $SOCl_2$ as the electrophile, illustrated in **Scheme 3.4.43**, and the desired 10-membered ring **322** was synthesised in excellent yield. Remarkably, no formation of the chlorinated starting material product was detected using mass spectrometry, TLC or NMR analysis, even in the crude mixture. This shows that intramolecular cyclization within the same molecule happen much faster than competing intermolecular reactions by chloride ions undergoing S_N2 attack to give chloride derivative.



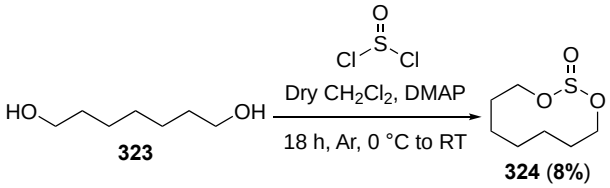
Scheme 3.4.43 Reaction conditions to make sulfites 10-membered ring **322** with isolated yield, using more nucleophilic amine as an internal catalyst

Pinpointing which intermediates the corresponding reaction mechanism generates is difficult, but a proposal is provided below. One of the alcohols on diol benzylamine **321** is thought to react with $SOCl_2$, producing chlorosulfite **321a** (**Scheme 3.4.44**). The resulting chlorosulfite **321a** reactive species can then be attacked by DMAP, generating pyridinium cation **321b** intermediate with the displacement of a chloride ion. The internal nucleophile (in this case the benzylamine) will attack the resulting intermediate **321b** via 6-membered ring cyclization to afford oxathiazolidine-oxide **321c** and will extrude DMAP as a catalyst (**Scheme 3.4.44**, [**321b**] → [**321c**]). The resulting 6-membered cation intermediate **321c** will undergo ring expansion through a 6-membered ring transition state to give the medium-sized ring **322**, with two molecules of HCl being generated as by-products (**Scheme 3.4.44**).



Scheme 3.4.44 Reaction mechanism for the formation of sulfites 10-membered ring **322**, showing only key steps, i.e., no proton transfers

The high yield for this reaction was very encouraging, but as before, a control reaction study was performed. To our luck, the desired control linear substrate diol **323** (**Scheme 3.4.45**) was commercially available. The control reaction was done using the same condition mentioned above. The result was as expected; cyclic sulfite **324** was isolated in just 8% yield after simple purification by column chromatography. The reaction yield has dropped significantly from 86% (with the internal nucleophile) to 8% (without the internal nucleophile), therefore supporting the notion that the reaction of **322** in **Scheme 3.4.44**, proceeds by a NICE mechanism, as without the internal nucleophile, the reaction of **324** in **Scheme 3.4.45**, proceeds less much efficiently and at a slower rate.



Scheme 3.4.45 Control reaction for $SOCl_2$ as an electrophile reagent, where 10-membered ring **324** was isolated in lower yields without an internal nucleophilic catalyst

Next, it was decided that an attempt would be made to see whether phenylphosphonic dichloride ($PhP(O)Cl_2$) **325** (**Fig. 3.4.46**) could react the same way due to its structural similarities to $SOCl_2$, triphosgene, and thiophosgene.

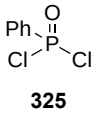
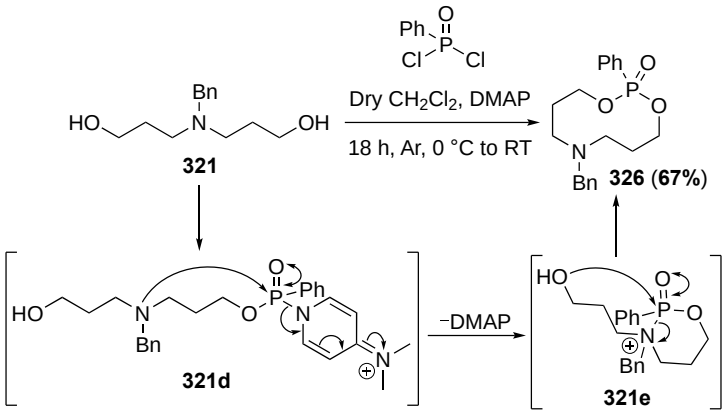


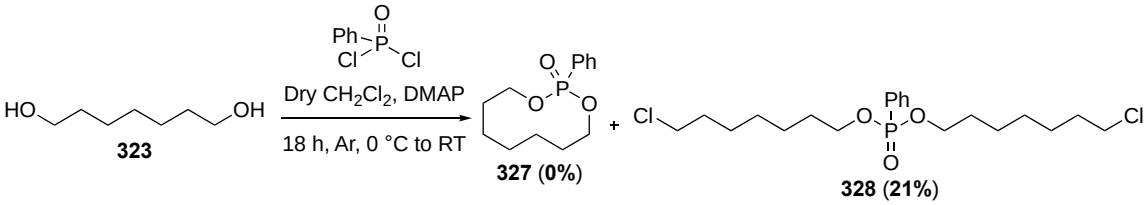
Figure 3.4.46 Molecular structure of $PhP(O)Cl_2$ **325**

The $SOCl_2$ reaction conditions were used, but the electrophilic component was changed to $PhP(O)Cl_2$ - see **Scheme 3.4.47**. In this way, ten-membered phenyl phosphonate **326** was synthesised in 67% yield from diol **321**. The reaction mechanism is thought to work the same way as in a $SOCl_2$ system. The two key cyclization steps proceed via a 6-membered ring transition step (**Scheme 3.4.47**, [**321d**] → [**321e**] → **326**).



Scheme 3.4.47 Reaction for formation of phosphorinan 10-membered ring **326**, showing key steps of the mechanism

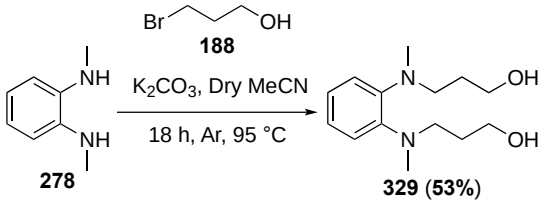
A control reaction was undertaken with diol **323** (**Scheme 3.4.48**) using $PhP(O)Cl_2$ as the electrophilic component. The result largely fell within our expectations; the desired medium-sized phosphine ring **327** wasn't synthesised, and instead bis chloride liner dimer **328** was isolated as the major product from the reaction (**Scheme 3.4.48**, **323** → **327** + **327**). This again shows how important it is to have the internal nucleophile to make the 10-membered phosphorus ring.



Scheme 3.4.48 Control reaction with diol **323** showing that 10-membered phosphorus **327** ring is not achievable without internal nucleophile incorporated in liner precursor

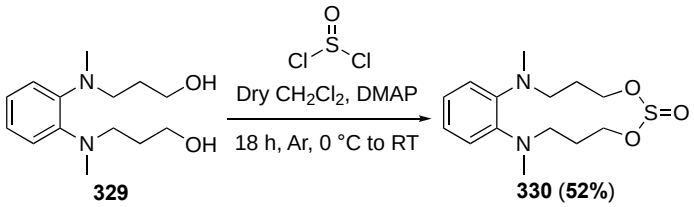
After demonstrating on numerous occasions that a single heteroatom in the linear precursor can successfully act as a nucleophilic catalyst whilst varying electrophile components, it was then decided to incorporate two internal nucleophiles (i.e., two anilines), allowing longer cascade NICE reactions to occur. The synthesis of the linear precursor with two nucleophilic

catalysts commenced in a similar fashion to those previously performed, where we start with phenyl diamine **278** (limiting reactant) undergoing bis alkylation with propanol bromide **188** yielding the desired diol **329** in 53%, as shown in **Scheme 3.4.49**.



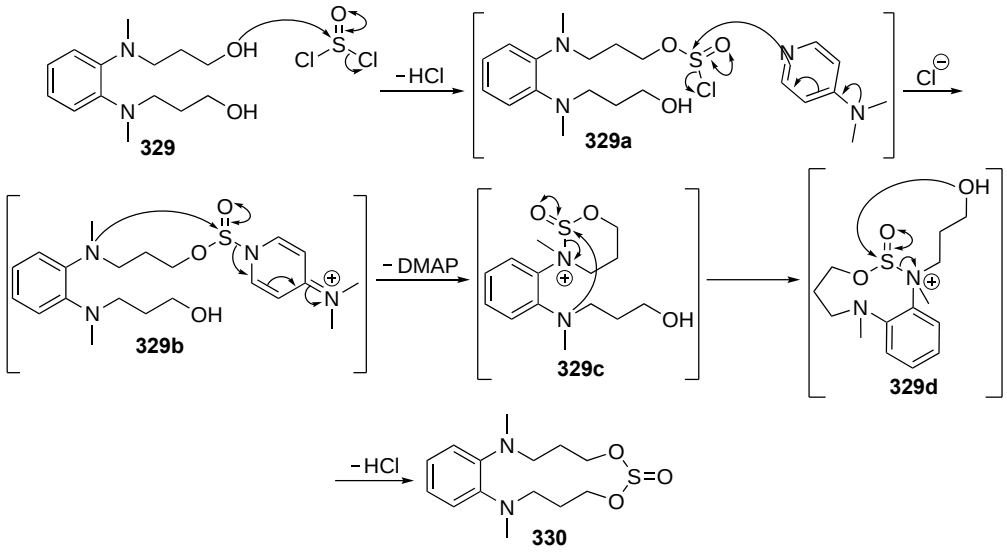
Scheme 3.4.49 Synthesis of a linear precursor **329** with two internal nucleophiles built in, showing conditions and isolated yields of product

The diol **329** was reacted with $SOCl_2$ (as an electrophile component), and the desired 13-membered ring **330** was synthesised in 52% yield, at 0.05 M concentration under relatively mild conditions (**Scheme 3.4.50**).



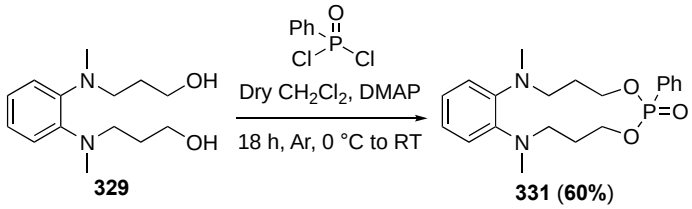
Scheme 3.4.50 Synthesis of the sulfites macrocycles **330**, with reaction conditions and isolated yield

The proposed reaction mechanism starts with one of the alcohols on diol **329** reacting with thionyl chloride, yielding chlorosulfite intermediate **329a** (**Scheme 3.4.51**). DMAP will then attack the electrophilic sulphur of **329a** intermediate to afford sulfano-pyridinium cation species **329b** (**Scheme 3.4.51**, [**329a**] → [**329b**]). The first internal nucleophile (aniline) is then proposed to attack the electrophilic sulphur of pyridinium ion **329b** affording a six-membered oxathiazan intermediate **329c** (**Scheme 3.4.51**, [**329b**] → [**329c**]), which will further undergo five-membered ring cyclization and fragmentation to give a nine-membered ring **329d** phenyl ammonium species (**Scheme 3.4.51**, [**329c**] → [**329d**]). The final step will be ring expansion of the nine-membered ring intermediate **329d** via nucleophilic attach of the primary alcohol (the terminal nucleophile) via a six-membered ring transition to title macrocycle **330** (**Scheme 3.4.51**, [**329d**] → **330**). This was the first time in the Unsworth group that a novel medium-size ring was made with two internal nucleophiles with different electrophiles that are not COOH; therefore, it was an excellent result.



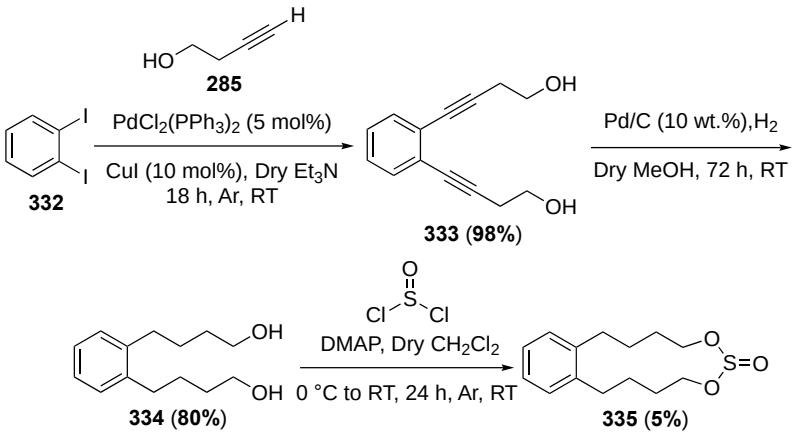
Scheme 3.4.51 Proposed reaction mechanism for the formation of 13-membered sulfite **330**

$PhP(O)Cl_2$ was tried as an electrophilic component with the same liner precursor and pleasingly, the desired phenylphosphonate macrocycle **331** was synthesised in 60% yield using the same reaction conditions as shown in **Scheme 3.4.52**.



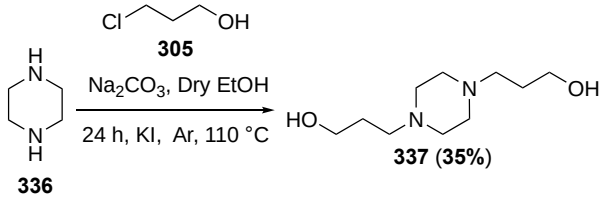
Scheme 3.4.52 Synthesis of the 13-membered ring **331** with phenylphosphonyl dichloride as an electrophile

Because it was the first time ever this reaction was performed and it was one of its kind, a control reaction was undertaken. The synthesis of the starting material linear precursor begins with a double Sonogashira coupling [239] with diiodobenzene **332** and terminal alkyne **285** (2 equiv.) to afford diol **333** in 98% yield (**Scheme 3.4.53**). The resulting product was subjected to hydrogenation conditions using Pd/C to reduce the alkyne **333** to alkane **334** (**Scheme 3.4.53**), again in excellent yield. The product was subjected to the same reaction as used to make a macrocycle with S=O functional group using $SOCl_2$ as the electrophilic component. The results were largely as expected, where a significant reduction in yield of the corresponding macrocycle **335** was observed from 52%, as seen in **Scheme 3.4.50** to 10% (**Scheme 3.4.53**).



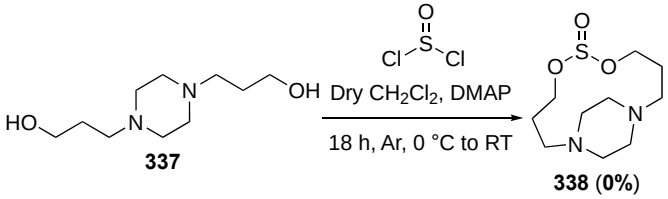
Scheme 3.4.53 Reaction sequence towards the synthesis of linear precursor **334** to undertake the control reaction, the conditions and yields for each step are shown

Following the various successful results on double NICE reaction, we next considered other substrates with similar structural characteristics. This sparked the idea of progressing to piperazine **336**, which can be doubly alkylated with chloro propanol **305** to afford the desired configuration relationship of terminal and internal nucleophiles (**Scheme 3.4.54**). To our luck, the desired compound **337** was literature-based and was formed in an acceptable yield, as shown in **Scheme 3.4.54**.[240]



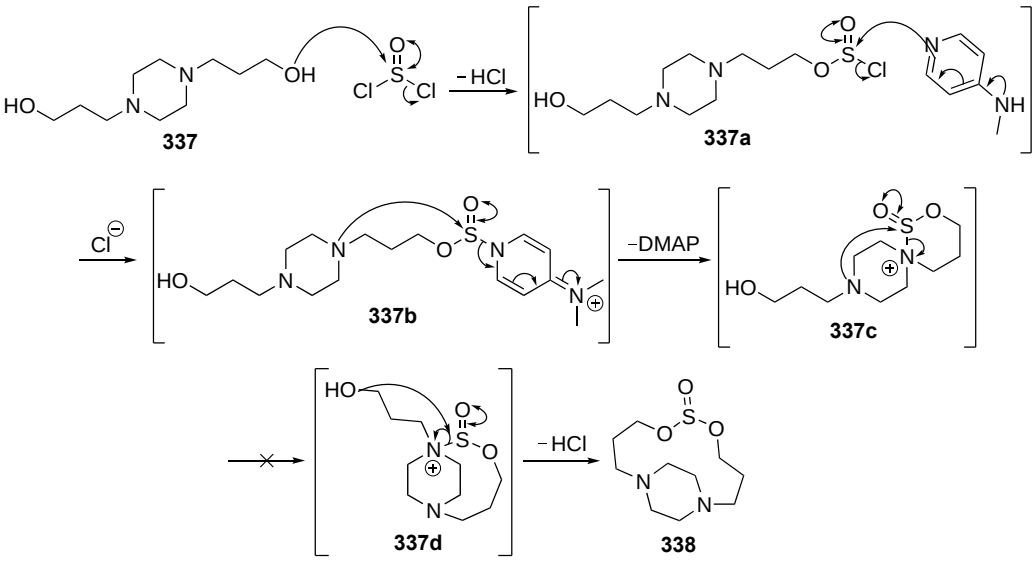
Scheme 3.4.54 Synthesis of piperazine linear substrate **337** with two internal nucleophiles

The desired piperazine diol **337** was reacted with $SOCl_2$ as the electrophilic component. Unfortunately, the reaction didn't give desired 13-membered macrocycle **338**, with the starting material piperazine diol **337** recovered in 85% yield (**Scheme 3.4.55**).



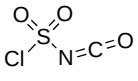
Scheme 3.4.55 Attempt reaction conditions with $SOCl_2$ as an electrophile in order to make desired macrocycles, but unfortunately, no reaction occurred and starting material **337** was recovered

Analysis of the reaction mechanism allowed the reasons for this unsuccessful result to be rationalised. The reaction mechanism likely started with a terminal OH reacting with $SOCl_2$ to eliminate HCl as a by-product and form sulfoxide chloride **337a** (**Scheme 3.4.56**, **337** → [**337a**]). DMAP then likely attacked this intermediate, to generate the charged species **337b** (**Scheme 3.4.56**, [**337a**] → [**337b**]). The first 3° nitrogen of piperazine can then undergo intramolecular cyclization with the cationic intermediate **337b** (via a 6-membered transition state) to produce a spiro ammonium compound **337c** (as shown in **Scheme 3.4.56**, [**337b**] → [**337c**]). For the NICE cascade to continue, the other 3° amine nitrogen of piperazine should then act as a second internal nucleophile and attack the spiro cationic **337c** species following a 5-membered ring trajectory, as shown in **Scheme 3.4.56**, [**337c**] → [**337c**]. However, the corresponding cyclization would need to go through a twist-boat conformation, which is likely to be high in energy, and hence may have resulted in the cyclization not occurring (**Scheme 3.4.56**, [**337c**] → [**337d**] → **338**).



Scheme 3.4.56 Proposed reaction mechanism of diol **337** reacting with $SOCl_2$ electrophile, showing only key steps, i.e., no proton transfers

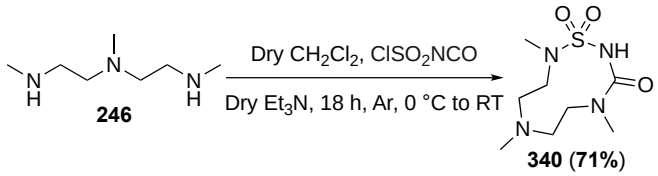
The last electrophile that was found to undergo a NICE reaction was chlorosulfonyl isocyanate **339** ($ClSO_2NCO$) (**Fig**. **3.4.57**). This component has a close resemblance to the $(COCl)_2$, by containing two reactive sites for nucleophile attack – electrophilic sulphur and isocyanate motif.



339

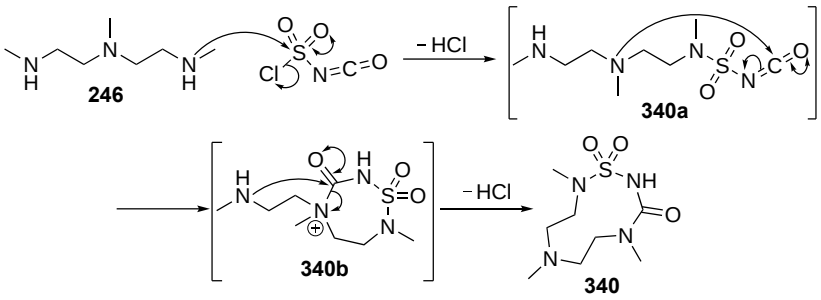
Figure 3.4.57 Shows the molecular structures of chlorosulfonyl isocyanate ($ClSO_2NCO$)

The reaction was set using $ClSO_2NCO$ as an electrophilic component with commercially available triamine **246** (**Scheme 3.4.58**), and the desired 10-membered ring **340** was synthesised in 71% yield after purification using 100% MeOH as eluent in column chromatography.



Scheme 3.4.58 Synthesis of the medium-sized sulfamoyl amide **340**, showing reaction conditions and isolated yield

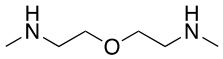
The reaction mechanism is thought to begin with one of the secondary amines reacting with electrophilic sulfur[241] to form sulfonamide intermediate **340a** (**Scheme 3.4.59**, **246** → [**340a**]). The 3° amine will undergo intramolecular cyclization (via a seven-membered ring or 7-exo-dig) with the isocyanate motif on **340a** (**Scheme 3.4.59**, [**340a**] → [**340b**]). The corresponding transformation gives rise to the 7-membered ring **340b** cationic species that is set to do ring expansion via a 5-membered transition state (**Scheme 3.4.59**, [**340b**] → **340**) yielding the desired sulfonylurea medium-size ring **340**.



Scheme 3.4.59 Proposed reaction mechanism showing only the key cyclization and intermediates and clearly showing the participation of the internal nucleophile with $ClSO_2NCO$ as the electrophile

As usual, a control reaction was undertaken to prove the participation of the internal nucleophile. Commercially available linear precursor oxapentane **341** (**Fig. 3.4.60**) was used instead of a conventional straight-chain carbon skeleton backbone substrate. **341** was ideal for the control reaction because it retained a heteroatom in the middle of the linear precursor. The bond lengths for C-O (1.41 Å) [242] and C-N (1.47 Å) [242] were similar in magnitude, in contrast to C-C (1.55 Å).[242] Although the oxygen has two lone pairs, they are unlikely to act as internal nucleophiles in the reaction due to the O heteroatom being more electronegative

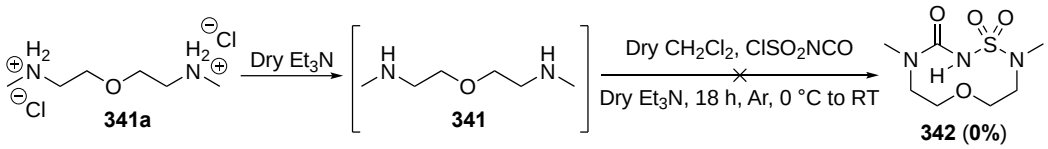
and less nucleophilic than the corresponding N (3.04 for N vs. 3.44 for O on the Pauling scale).[241,243]



341

Figure 3.4.60 Structure of 1,5-bis(methylamino)-3-oxapentane is the substrate for control reaction to prove the concept of NICE using $ClSO_2NCO$ as the electrophile

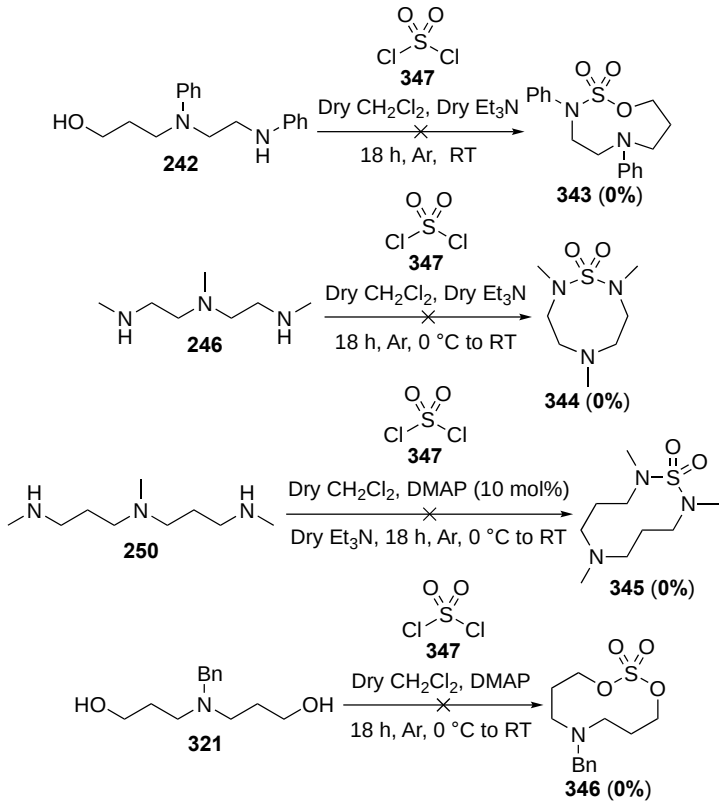
Since the resulting control substrate **341** was only commercially available as HCl salt (**Scheme 3.4.61**, **341a**), two extra equivalents of Et_3N were added to quench the hydrochloride to get the freebase amines (**Scheme 3.4.61**, **341a** → [**341**]). Otherwise, the reaction was set up as normal, and progress was followed by mass spectrometry and TLC. After the mixture was left to stir for 18 hours, complete consumption of **341** starting material was observed though no m/z peak showing the formation of desired medium-sized ring **342** was detected. The mixture was worked up and subjected to crude ^1H and ^{13}C NMR analysis. Whilst the ^1H and ^{13}C NMR spectrum showed a complex mixture of products formed, we note that none of the medium ring product **342** resonances was detected. This control reaction again indicates that without the internal nucleophile-like nitrogen, the medium-sized sulfonylurea ring **342** will not be synthesised via direct end-to-end cyclization.



341a **341** **342 (0%)**

Scheme 3.4.61 Demonstrates freebasing of the commercially available substrate **341a** to afford linear precursor **341** and the subsequent control reaction with $ClSO_2NCO$ as the electrophile

Sulfuryl dichloride **347** (SO_2Cl_2) was also tried as an electrophilic component with a variety of linear substrates, which had been synthesised earlier in the thesis or were commercially available (**Scheme 3.4.62**, **242**, **246**, **250** and **321**). However, none of the reactions shown in **Scheme 3.4.62** showed any sign that desired medium-size rings (**Scheme 3.4.62**: **343**, **344**, **345** and **346**) formed, based on analysis by TLC, mass spectrometry or NMR of the crude reaction mixture. Therefore, **347** SO_2Cl_2 was deemed as an incompatible electrophile to undergo NICE reactions with the corresponding substrate. A record of these unsuccessful attempts is included below.



Schema 3.4.62 Shows the reaction conditions for each individual reaction with their corresponding linear substrates, medium-sized rings product and **347** SO_2Cl_2 as the electrophile

Finally, a NICE reaction involving variation of both the terminal nucleophile and electrophile component was to see if the sulfonamide motif **348** (**Fig. 3.4.63**, $RSO_2\mathbf{NH_2}$) can be used as the terminal nucleophile and react in a similar fashion as R-OH, R_2NH, R-SH etc. as seen previously.

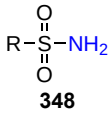
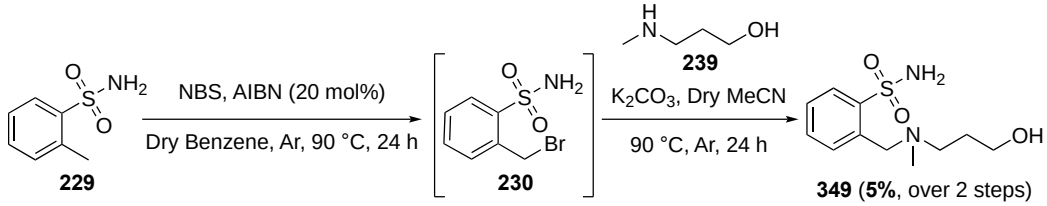


Figure 3.4.63 Shows a molecular structure of generical sulfonamide **348** functionality, where NH_2 can act as a nucleophile in a wide range of reactions [244]

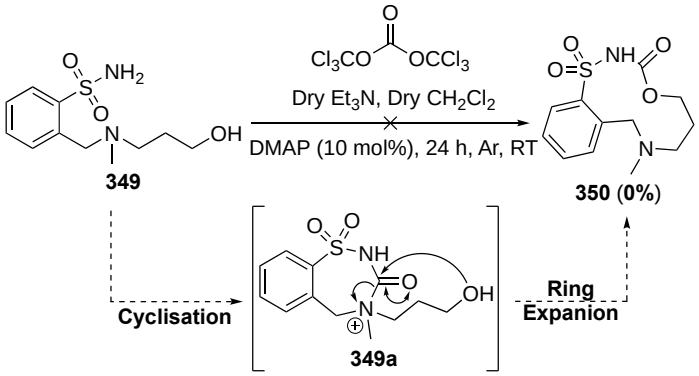
The synthesis of the desired linear precursor **349** commenced with the Wohl-Ziegler reaction[245] of *ortho*-toluene sulfonamide **229** starting material to give bromination at the benzylic position (**Scheme 3.4.64**, **229** → [**230**]). The bromide **230** was taken directly to the next reaction step without further purification and subject to alkylation conditions with amino alcohol **239** affording desired linear precursor **349** in 5% yield over two steps (**Scheme 3.4.64**).

The yield obtained from the reaction was low; however, enough material was synthesised to try reactions with triphosgene and thiophosgene as the electrophilic components.



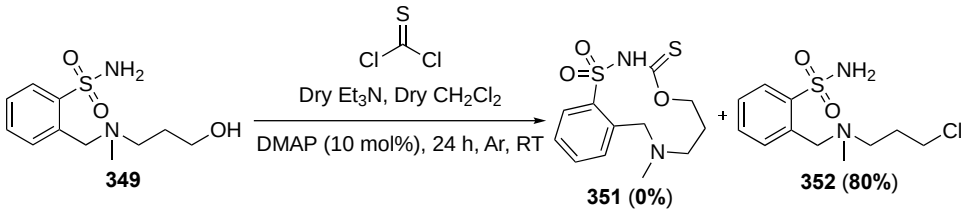
Scheme 3.4.64 Synthesis of sulfonamide linear starting material **349**, showing reaction conditions and isolated yield

Triphosgene was reacted with sulfonamide linear precursor **349** using the established conditions (**Scheme 3.4.65**, **349** → **350**) by slightly modifying the initial procedure, whereby a catalytic amount of DMAP was added. The reaction was monitored by TLC, and after leaving to stir for 24 hours, the complete consumption of starting material **349** was noted. However, after recording the crude ^{1}H and ^{13}C NMR spectrum gave a complex mixture of products with no evidence of the desired sulfonamide carbamate **350** formations.



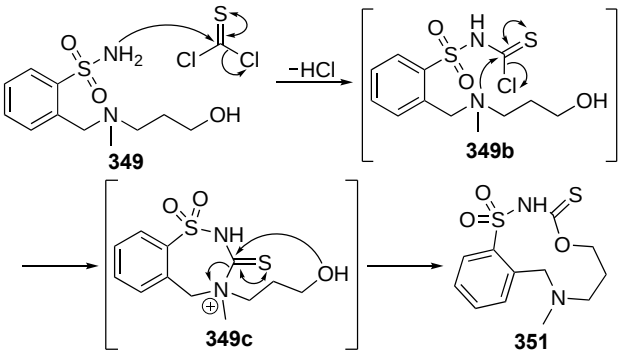
Scheme 3.4.65 An attempt to make carbamate **350** using primary sulfonamide **349** as a terminal nucleophile and with triphosgene as the electrophile

After the triphosgene reaction failed, it was decided to see if sulfonamide **349** was compatible with thiophosgene. The reaction was tested, but thiocarbamate sulfonamide **351** was not afforded (**Scheme 3.4.66**, **349** → **351**). Instead, chloride **352** was isolated as a major product after aqueous work-up and flash column chromatography purification (**Scheme 3.4.66**).



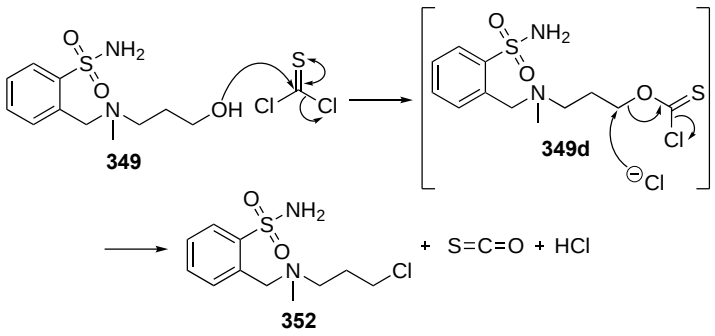
Scheme 3.4.66 Failed NICE reaction in attempting to make medium-size ring **351**

Reaction **3.4.67** was devised with the aim of showing that a primary sulfonamide may act as a terminal nucleophile with thiophosgene. This will allow for the formation of sulfonylcarbamothioyl chloride **349b** (**Scheme 3.4.67**, **349** → [**349b**]), which will be attacked by the internal nucleophile (benzylic amine) via a 7-membered ring transition state to afford the cation thiourea intermediate **349c** (**Scheme 3.4.67**, [**349b**] → [**349c**]). The resulting cation intermediate is then set to undergo ring expansion with OH (second terminal nucleophile) following a six-membered ring cyclization to achieve an eleven-membered ring (**Scheme 3.4.67**, [**349c**] → **351**).



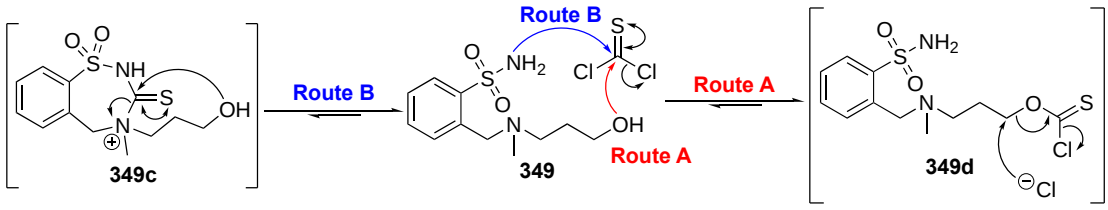
Scheme 3.4.67 Reaction mechanism for the formation of desired 11-membered ring **351** showing only key steps and intermediate, i.e., no proton transfers

However, an alternative reaction pathway is preferred, which is the formation of alkyl chloride from the corresponding primary alcohol. The R-OH reacts primarily with thiophosgene to generate chlorothionoformate **349d** (**Scheme 3.4.68**, **349** → [**349d**]) with the displacement of the chloride ion that undergoes S_N2 reaction to form the chloride **352** (**Scheme 3.4.68**, [**349d**] → **352**).



Scheme 3.4.68 Reaction mechanism for the formation of linear chloride **352**, showing only key steps of mechanism with the by-products

Moreover, to make the desired product **352**, it is pertinent to note that the reaction must proceed via an unfavourable seven-membered ring **349c** intermediate (**Scheme 3.4.69**, **349** → [**349c**]), **Route B**, highlighted as a blue curly arrow). As a result, a competing reaction pathway is preferred, which activates the primary alcohol and turns into chlorothionoformate **349d** (**Scheme 3.4.69**, **349** → [**349d**], **Route A**, highlighted as a red curly arrow).



Scheme 3.4.69 Illustrating two possible reaction pathways that primary sulfonamide **349** starting material undergoes with thiophosgene as the electrophile

It was decided to change the linear starting material to avoid cyclization via the 7-membered ring transition state. To achieve this, the CH_2 on the benzylic position would be removed, i.e., a shorter chain and the internal nucleophile attached directly to the benzene ring as an aniline motif (**Fig. 3.4.70**).

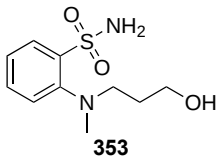
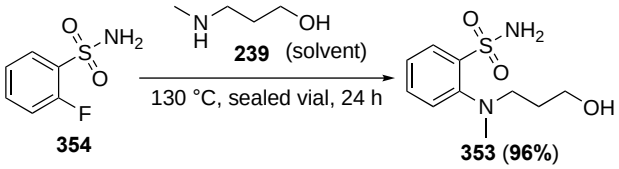


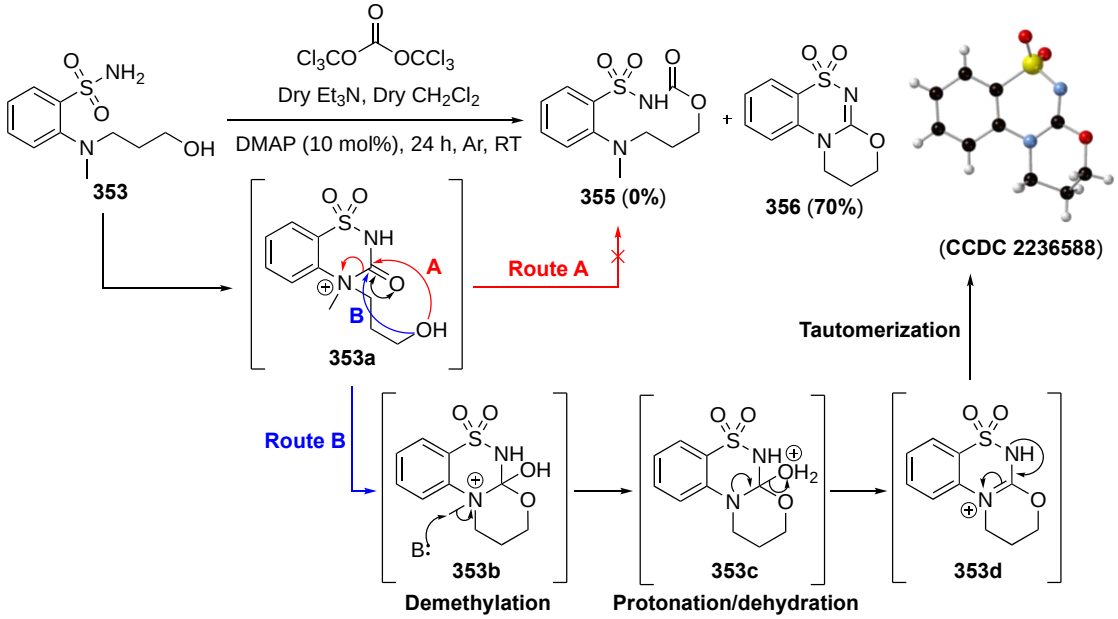
Figure 3.4.70 Molecular structure of the target starting liner precursor **353**

The liner precursor **353** was synthesised using a nucleophilic aromatic substitution (S_NAr) reaction following the literature-reported procedure with a different amino alcohol **239**. The reaction begins with fluorobenzene sulfonamide **354** in a sealed tube charged with amino alcohol **239** as the solvent (**Scheme 3.4.71**, **354** → **353**). The desired aniline sulfonamide **353** was formed in excellent yield after simple purification.



Scheme 3.4.71 Synthesis of linear precursor **353**

The aniline sulfonamide **353** was reacted with triphosgene as the electrophile, and the desired 10-membered ring was not formed (via NICE reaction, **Scheme 3.4.72**, **353** → [**353a**] → **355**), however interestingly, the benzisothiazole **356** was obtained in 70% yield (**Scheme 3.4.72**). This side product **356** is achieved by demethylation with a nucleophile (Cl^-, Et_3N, or H_2O, **Scheme 3.4.72**, [**353a**] → [**353b**]), followed by a condensation/dehydration reaction between triphosgene and R-SO_2NH_2 and R-OH (**Scheme 3.4.72**, [**353b**] → [**353c**] → [**353d**] → **356**). A single X-ray crystal of six membered sulfonamide **356** was crystallised by slow evaporation of EtOAc.



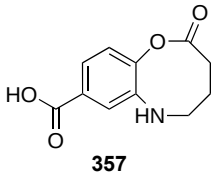
Scheme 3.4.72 Failed NICE reaction in attempting to make medium-size ring **355** with conditions, illustrating the major product **356** formed in the reaction with X-ray crystal structure and **CCDC** deposit number

In summary, the results in this chapter show that a wide range of new reaction types can be used in NICE reactions, leading to formation of a very diverse array of medium-sized ring and macrocyclic products. The next chapter is focused on the use of NICE in a target synthesis project. Additional conclusions about the results in this chapter feature in the overall conclusion section in Chapter 6.

Chapter 4: Argaminolic A natural product

4.1.0 Studies towards the total synthesis of Argaminolic A

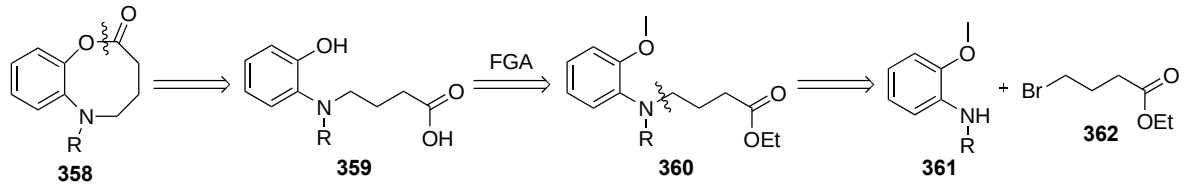
Argaminolic A was first isolated from the fruit of the argan tree (Argania spinosa)[246] located in the regions of Morocco and Algeria.[247,248] It has a fused-ring structure between the eight-membered and phenyl ring **357** (**Fig. 4.1.1**), which has been characterised by NMR and MS.[249,250]



357

Figure 4.1.1 Molecular structure of natural product Argaminolic A[251,252]

It was decided to try to make Argaminolic A using a NICE strategy, where beforehand we first try to synthesise the model substrate **358** (**Scheme 4.1.2**). Here, COOH *para*- to phenolic lactone was removed, whilst adding a protecting group to aniline. The retrosynthesis analysis of the model substrate **358** starts by breaking the lactone medium, to give linear precursor **359** (**Scheme 4.1.2**, **358** → **359**) which is subject to functional group addition (FGA) to install a methyl group on the phenol and ethyl ester (**Scheme 4.1.2**, **359** → **360**). Compound **360** can then be broken down further into two halves by disconnecting the *N*-heteroatom carbon bond to give alkyl bromide **362**, which is commercially available, and methoxy aniline **361** (where R = H).

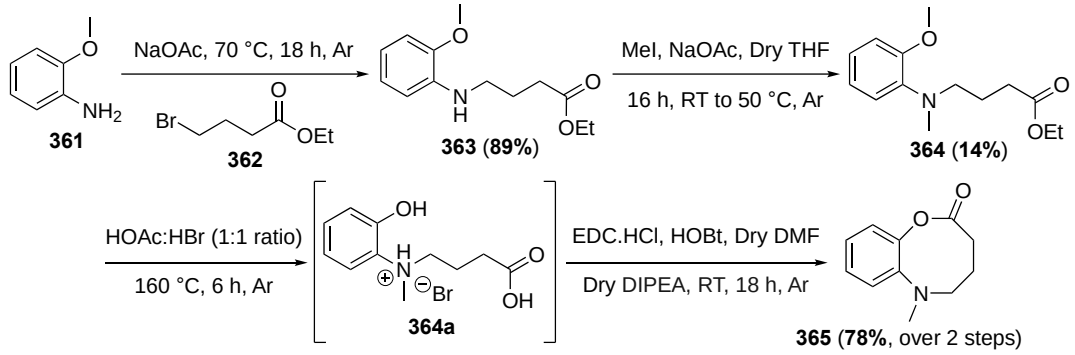


358 **359** **360** **361** **362**

Scheme 4.1.2 Retrosynthesis analysis of model substrate **358**

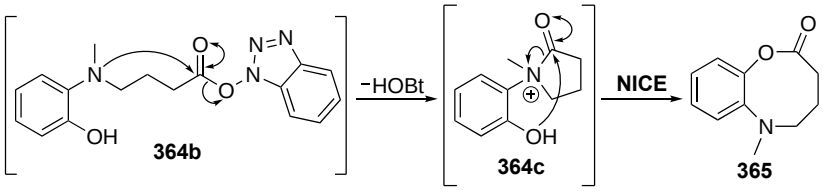
The synthesis of model compound **367** commenced with a simple alkylation reaction using conditions found in the literature [253] between ethyl 4-brombutyrate **362** and methoxy aniline **361** yielding the desired ester **363** in 89% (**Scheme 4.1.3**, **361** + **362** → **363**). The aniline would be *N*-methylated using iodomethane (MeI) to afford the compound **364** in low yield (**Scheme 4.1.3**, **363** → **364**), but the synthesis continued without further optimisation for the corresponding step. Next, methoxy phenol **364** was demethylated using hydrobromic acid (HBr, Bronsted acid) [254] in a 1:1 mixture with acetic acid (AcOH) at 160 °C, and ethyl ester was also hydrolysed under these conditions to afford carboxylic acid **364a** intermediate

(**Scheme 4.1.3**, **364** → [**364a**]). The hydrobromide salt **364a** crude product was taken directly to the next step without further purification and reacted with EDC.HCl and HOBt conditions to give desired eight-membered ring product **365** in 78% yield over two steps.



Scheme 4.1.3 Reaction sequence towards the synthesis of the model substrate **365**, showing conditions and isolated yields for each reaction step

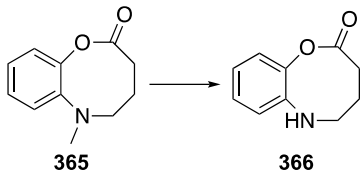
The mechanism to form eight-membered ring lactone **365** is proposed to start with the activation of the carboxylic acid group to yield HOBt-activated ester **364b**. The HOBt-activated ester is then attacked by an internal nucleophile (aniline) via 5-membered ring cyclization to give γ-lactam cationic intermediate **364c** (**Scheme 4.1.4**, [**364b**] → [**364c**]), which can then be ring expanded affording the eight-membered ring lactone lactone **365**, where phenol acting as the terminal nucleophile (**Scheme 4.1.4**, [**364c**] → **365**).



Scheme 4.1.4 Reaction mechanism for the formation of 8-membered lactone **365**, demonstrating only key cyclization steps

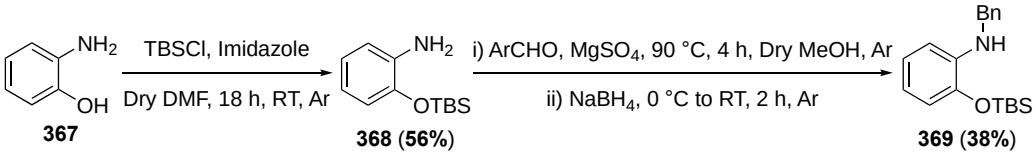
The formation of **365** in good yield was encouraging. However, it is worth noting that the methyl group on the *N*-heteroatom on **365** would need to be removed to produce secondary aniline **366**, as shown in **Scheme 4.1.5**, to make analogues of the core structure in the natural product target. This transformation is possible in theory but requires using an expensive catalyst ($RuCl_2[PPh_3]_3$,Ir[dtbbpy][ppy]$_2$[PF_6]) [255,256] and forcing oxidation conditions.[257] Consequently, it was decided to utilize the benzyl (Bn) protecting group on the aniline and change the ethyl

ester into *tert*-butyl ester (O^{t}Bu), which was considered to be a more sensible protecting group strategy.



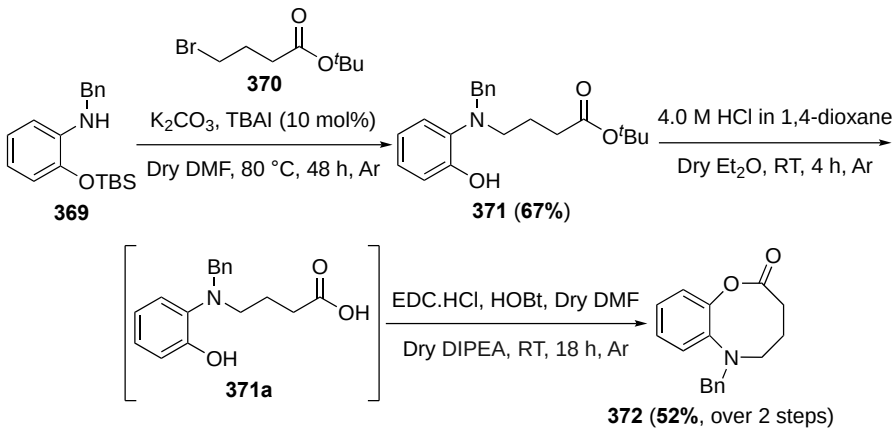
Scheme 4.1.5 Demonstrating demethylation step to afford secondary aniline **366**, which is the same functional core as in the Argaminolic A natural product

The synthesis of the model substrate with different protecting groups was set using literature reported procedures from Shu-Li You *et al.*,[258] where the first reaction is the protection of phenol with *tert*-butyldimethylsilyl ethers (TBS) group (**Scheme 4.1.6**, **367** → **368**) followed by reductive amination with benzaldehyde (ArCHO) and $NaBH_4$ (**Scheme 4.1.6**) yielding secondary aniline silyl ether **369** in 38%.



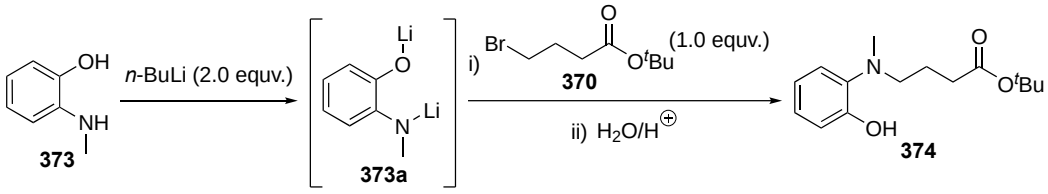
Scheme 4.1.6 Synthesis of the starting material **369** with an alternative protecting group, showing reaction conditions for each step and isolated yields

The aniline silyl ether **369** was alkylated with *tert*-butyl 4-bromobutyrate **370**, as shown in **Scheme 4.1.7**, where the TBS group was unexpectedly removed in the reaction and phenol **371** was isolated in 67% yield. Next, the *tert*-butyl ester on **371** was deprotected under acid conditions to afford acid **371a** (**Scheme 4.1.7**). The resulting acid **371a** was taken directly to the next step as a crude mixture after all the violates were removed under *vacuo*. The carboxylic acid was activated by EDC. HCl + HOBt in anhydrous DMF (0.1 M) affording the desired medium-size ring **372** in 52% yield, which was an excellent result (**Scheme 4.1.7**, [**371a**] → **372**).



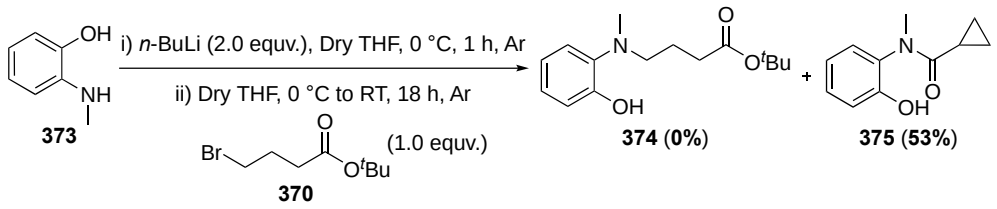
Scheme 4.1.7 Reaction sequence towards the synthesis of the model substrate **372** with benzyl protecting group, showing conditions and isolated yields for each reaction step

As part of these studies, an alternative protecting group-free strategy was also explored, with the idea to start with a commercially available methyl amino phenol **373** and use two equivalents of *n*-BuLi. This will deprotonate phenol and aniline to give di lithiated **373a** intermediate (**Scheme 4.1.8**, **373** → [**373a**]), which will be trapped further with 1.0 equivalent of bromide **370** to afford mono alkylated product **374** (**Scheme 4.1.8**, [**373a**] + **370** → **374**).



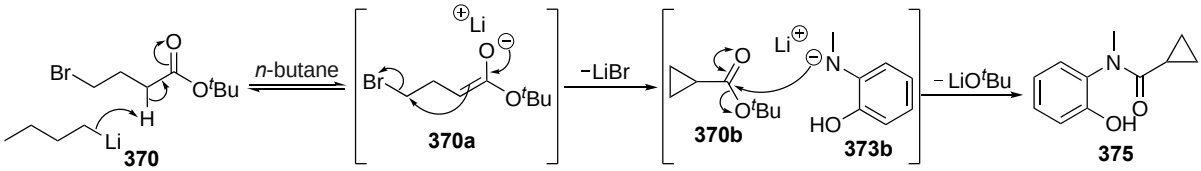
Scheme 4.1.8 Illustrates hypothetical reaction route towards the synthesis of the linear precursor **374** without using protecting groups strategies on phenol

This reaction was tested, but unfortunately, the desired product **374** was not afforded. The cyclopropane amide **375** was instead isolated unexpectedly, in a 53% yield (**Scheme 4.1.9**).



Scheme 4.1.9 An attempt reaction for the synthesis of the linear precursor **374**, where side product **375** was isolated instead

The cyclopropane amide **375** is presumably formed due to excess of the *n*-BuLi forming an enolate from tertbutyl bromide **370** (**Scheme 4.1.10**, **370** → [**370a**]). The resulting lithium enolate **370a** will undergo intramolecular 3-exo-tet cyclization to give *tert*-butylcyclopropane **370b** (**Scheme 4.1.10**, [**370a**] → [**370b**]) and deprotonated lithium *N*-methyl anilide **373b** will further attack the *tert*-butyl ester **370b** affording the amide **375** product (**Scheme 4.1.10**).



Scheme 4.1.10 Proposed reaction mechanism for the formation of cyclopropane amide **375**, showing only key steps of the transformation

To summarise all of the work on NICE reactions in Chapters 2–4, after testing the range of internal and terminal nucleophiles presented above, we have demonstrated that the NICE reaction works effectively to generate medium-sized rings and macrocycles, ranging from 8- to 25+ membered examples, all while using bench-accessible reagent amide coupling.

We have clearly shown that there is a necessity to introduce a balance in reactivity between the terminal and internal nucleophile when both are of competing reactivity, as in the case when we changed the OH terminal nucleophile to NH_2 resulting in a reduction in the yield of the medium ring formed. Using more reactive internal and terminal nucleophiles, such as when we swapped aniline in **262** (**Scheme 3.4.2** in **section 3.4.0**) to a tertiary amine **246** (**Scheme 3.3.1** in **section 3.3.0**), this resulted in the lack of formation of the desired 8-membered -sized ring **247** (**Scheme 3.3.1** in **section 3.3.0**), where instead, an alternative 5-membered thiourea **248** product (which was as expected from the reaction mechanism shown in **Scheme 3.3.2** in **section 3.3.0**) was isolated. At both ends of the spectrum, when nucleophiles are of low or high reactivity, we again see a reduction of yield highlighting that the NICE reaction is optimised when they are of tempered reactivity.

Furthermore, we have proven that an alternative route may be taken to generate medium-sized rings and macrocycles. It has been shown viable for the electrophilic component to be detached from the linear precursor to be combined and generate the desired products, all with a spectrum of functional groups including thiocarbamates, urea, thiourea, sulfonylurea and carbamates. This discovery of 7 new reactions has allowed for the incorporation of diverse functional groups, leading to the creation of a small library of medium size rings and macrocycles.

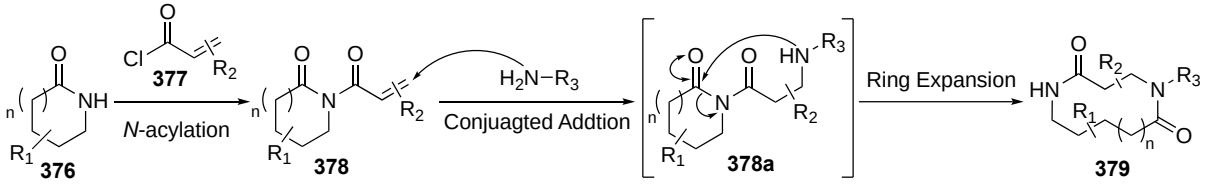
This chapter has proven that the NICE reaction can be utilised in the synthesis of the core structure of natural products and medicinally important compounds. It unmistakeably shows that the reaction is robust and leads to the creation of medium size rings and macrocycles alongside the synthesis of starting material, with ease. Details of how the total synthesis could be completed are featured in the future work chapter.

Chapter 5: Conjugate Addition and Ring Expansion (CARE)

5.1.0 Introduction to CARE and exploration of scope

The final results chapter of this thesis is focused on a different class of ring expansion, known as Conjugate Addition and Ring Expansion (CARE) reactions. CARE is a novel synthetic approach that has been used to make a range of novel medium-sized rings (8–12) and macrocyclic (14-, 16-, 18- and 21-membered) lactams from cyclic imides and primary amines, developed by Unsworth *et al.* in 2022.[259]

CARE operates via a cascade reaction, where several steps are incorporated in a single transformation without using any protecting group strategies on the primary amine. The reaction starts with a simple *N*-acylation method, in which a lactam **376** (1–5 atom rings, **Scheme 5.1.1**, **376** → **378**) is reacted with pyridine and a catalytic amount of DMAP and acryloyl chloride **377** to generate cyclic imides **378**. The vinyl group on these imides **378** is a versatile Michael acceptor, which can engage in a 1,4 addition upon treatment with primary amine nucleophiles to give intermediate **378a** (**Scheme 5.1.1**) that spontaneously undergoes ring expansion via a six-membered ring cyclization to yield cyclic amide **379** ranging from 8- to 12-membered ring atoms (**Scheme 5.1.1**).



Scheme 5.1.1 Lactam ring expansion reaction using a Conjugate Addition/Ring Expansion (CARE) method

To date, this concept has focused on the reaction of imide substrates of the **378** (**Scheme 5.1.1**) type. The synthetic approach to make medium-sized sulfonamides had not been explored and developed before this project, despite cyclic sulfonamides being important structures in medicinal chemistry.[260] Sulfanilamide drugs are used extensively as antibacterial agents and in infection treatment, [261,262] with examples shown in **Fig. 5.1.2**.[263,264]

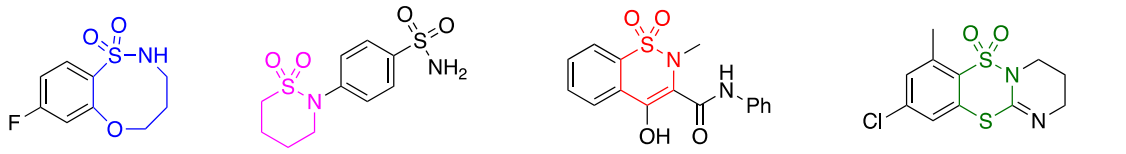
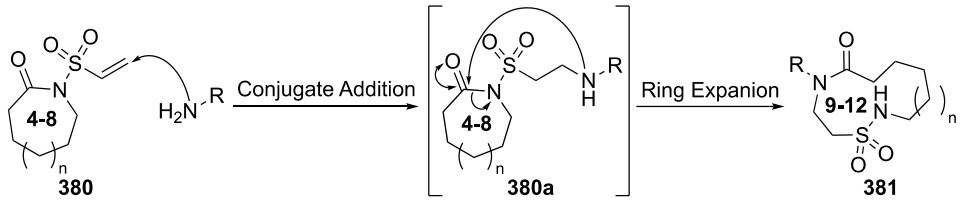


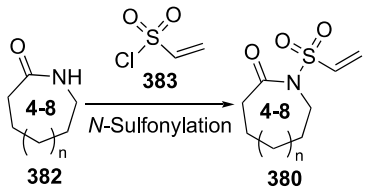
Figure 5.1.2 Structures of medically important sultams

The CARE methodology was intended to synthesis medium-sized *N*-sulfonamido lactams **381** (9–12 atom rings) containing both a lactam and a sulfonamide functionality (**Scheme 5.1.3**). The conjugate addition of an amine (primary, aniline or ammonia) with vinyl sulfonyl lactam **380** was envisaged to give a secondary amine **380a** intermediate, primed to undergo ring expansion via a six-membered (**Scheme 5.1.3**, [**380a**] → **381**) affording the medium-sized ring product. The advantage of this reaction is that the orthogonal protection of the added amine group is not required.



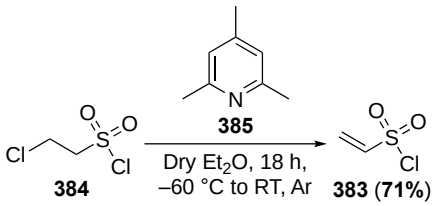
Scheme 5.1.3 Ring expansion strategies for the synthesis of the medium-sized ring **381** using CARE methodology, showing the key mechanistic steps

The synthesis of the starting material *N*-sulfonamidolactams **380** ranging from 5- to 8-membered, was the most challenging aspect of this work. To make the Michael acceptor **380** (**Scheme 5.1.4**), the *N*-sulfonylation approach with sulfonyl chloride **383** was employed, starting from the commercially available lactams **382** (4- to 8-membered as shown in **Scheme 5.1.4**).



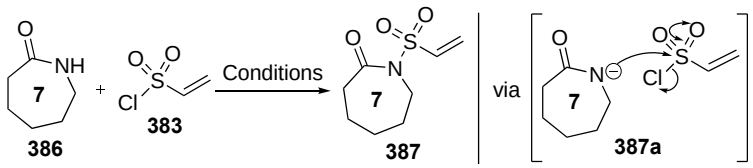
Scheme 5.1.4 Showing general reaction for the preparation of the Michael acceptor **380** via *N*-sulfonylation

The synthesis of vinyl sulfonyl chloride **383** starting material was done using a modified experimental procedure from the literature.[265] Starting with 2-chloroethane sulfonyl chloride **384** and 2,4,6-collidine **385**, these were reacted together at a low temperature, and the desired product was isolated by shorth path vacuum distillation in 71% yield (**Scheme 5.1.5**).



Scheme 5.1.5 Preparation of vinyl sulfonyl chloride **383** with reaction conditions and isolated yield

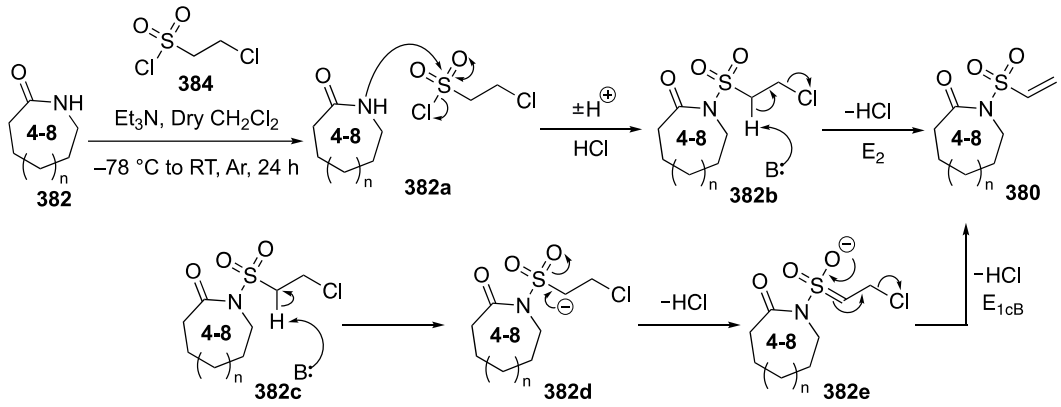
After obtaining the desired ethene-sulfonyl chloride **383**, the next task was to determine the optimal *N*-sulfonylation conditions when using caprolactam **386** as a starting material. In attempt to reach optimality, several conditions (**entries 1-6**) were tested to make **387** with the highest yield being only 25% (**entry 5**, **Table 5.1.6**). Here, we used LHMDS as a base to abstract hydrogen from lactam **386**. This generates the anion **387a** that will attack the electrophilic sulfur on **383,** with the elimination of Cl^- as a by-product (**Table 5.1.6**)..



Entry	*Conditions*	*Yield of **387** (%)*
1	Pyridine, DMAP in CH_2Cl_2, 0 °C to 60 °C, 24 h	0
2	NaH in THF, 0 °C to RT, 24 h	10
3	MeMgBr in THF, 0 °C to RT, 24 h	9 (11[a])
4	*n*-BuLi in THF, –78 °C to RT, 24 h	5
5	LHMDS in THF, –78 °C to RT, 24 h	25
6	LHMDS in THF, 0 °C to RT, 24 h	0

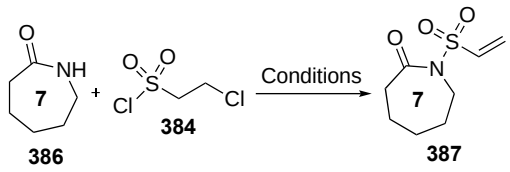
Table 5.1.6 Optimization of the *N*-sulfonylation reaction. General conditions: 1.5 eq. of bases, 1.5 eq. of ethenesulfonyl chloride **383**; [a] 3.0 eq. of ethenesulfonyl chloride **383** used

The reaction yields for the results shown in **Table 5.1.6** were not satisfactory, triggering a change of the reagent to 2-chloroethane sulfonyl chloride **384** (**Scheme 5.1.7**). A plausible mechanistic pathway in this case is that the ethene sulfonyl motif is generated initially *in situ*, following *N*-sulfonylation as is illustrated in **Scheme 5.1.7**. A general lactam (4-8 atom ring) is shown, undergoing *N*-sulfonylation to generate chloride **382b** (**Scheme 5.1.7**, **382** → **382a** → **382b** that can then undergo an elimination reaction via an E_2 or E_{1cb} mechanism. The reaction most likely operates by the E_{1cb} mechanism where anion **382d** (**Scheme 5.1.7**, **382c** → **382d**) α- to sulfonyl chloride is generated in the presence of a non-nucleophilic base (Et_3N, DMAP or 2, 4, 6-collidine), giving the highly reactive sulfene **382e**-like species (**Scheme 5.1.7**, **382d** → **382e**) that will follow the E_{1cb} pathway to give desired product **380** (**Scheme 5.1.7**, **382e** → **380**).



Scheme 5.1.7 Shows E_{1cb} and E_2 reaction mechanisms for the formation of Michael acceptor **380**

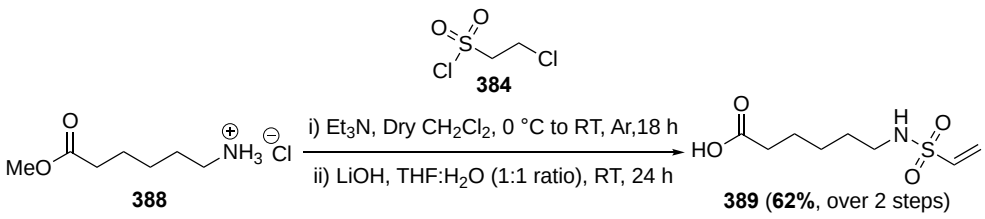
Several attempts were made to optimise the *N*-sulfonylation conditions with ethen sulfonyl chloride **384** (**Table 5.1.8**, **entries 1**–**9**). Unfortunately, the best result obtained was the formation of **387** in only a 17% yield (**Table 5.1.8**, **entry 8**) using DMAP (10 mol%) and Et_3N (5.0 eq.) in CH_2Cl_2 at a low temperature.



Entry	*Conditions*	*Yield of **387** (%)*
1	DMAP, Et_3N in CH_2Cl_2, 0 °C to Reflux, 16 h	0
2	DMAP, Et_3N in CH_2Cl_2, 0 °C to RT, 16 h	4
3	DMAP, Et_3N in CH_2Cl_2, –60 °C to RT, 16 h	10
4	DMAP, 2,4,6-collidine in CH_2Cl_2, 0 °C to RT, 16 h	0
5	NaH, 2,4,6-collidine in THF, 0 °C to RT, 16 h	0
6	DMAP, Et_3N in CH_2Cl_2, –40 °C to RT, 16 h	14
7	DMAP, Et_3N in CH_2Cl_2, –78 °C to RT, 16 h	17[a]
8	DMAP, Et_3N in CH_2Cl_2, 0 °C to RT, 16 h	0[b]
9	DMAP, Et_3N in CH_2Cl_2, –60 °C to RT, 16 h	5[c]

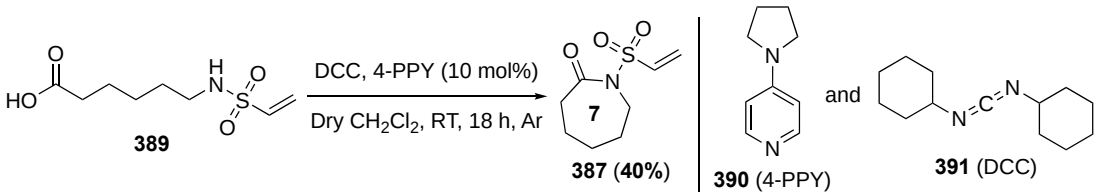
Table 5.1.8 Optimization of *N*-sulfonylation conditions using 2-chloroethanesulfonyl chloride **384**; General conditions: 3.5 eq. of bases, 2.0 eq. of ethenesulfonyl chloride **384** and 0.3 mol dm^{-3} used. [a] 5.0 eq. of ethenesulfonyl chloride **384** and 0.5 mol dm^{-3} used; [b] 5.0 eq. of ethenesulfonyl chloride **384** and 0.1 mol dm^{-3} used. [c] 0.5 mol dm^{-3} of CH_2Cl_2

In pursuit of a better result, it was decided that classical direct end-to-end cyclization would be used to make the desired seven-membered ring **387**. The reaction procedure was followed using a patent from AbbVie, a pharmaceutical company.[266] The synthesis began with a reaction between aminocaproate hydrochloride **388** and 2-chloroethanesulfonyl chloride **384** to install the vinyl sulfonamide motif (**Scheme 5.1.9**, part i)). This was followed by the hydrolysis of the methyl ester using LiOH:H_2O, yielding acid linear precursor **389** (**Scheme 5.1.9**, part ii)) in 62% over two steps.



Scheme 5.1.9 Synthesis of the carboxylic acid linear precursor **389** with conditions and yield

After the successful preparation of linear precursor **389**, the reaction to make the vinyl sulfonyl azepan **387** was set using *N,N'*-dicyclohexylcarbodimide (DCC) **391** as a coupling reagent with a catalytic amount of 4-pyrrolidinylpyridine (4-PPY) **390**. The reaction conditions were taken from the literature (**Scheme 5.1.10**)[267], and the end-to-end cyclization gave a yield of 40%. This is superior when compared to previous attempts to make **387** via lactam *N*-sulfonylation.



Scheme 5.1.10 Preparation of starting material **387** via end-to-end cyclization using high dilution concentration conditions

The major drawback of this transformation is the high dilution requirement necessary for the ring closure reaction to overcome the ring strain of the transition state associated with the 7-membered ring. To practically perform the reaction shown in **Scheme 5.1.10**, the concentration was 0.005 M (390 mL of anhydrous CH_2Cl_2 used), which is impractical in the lab setting (as shown in **Fig. 5.1.11**).

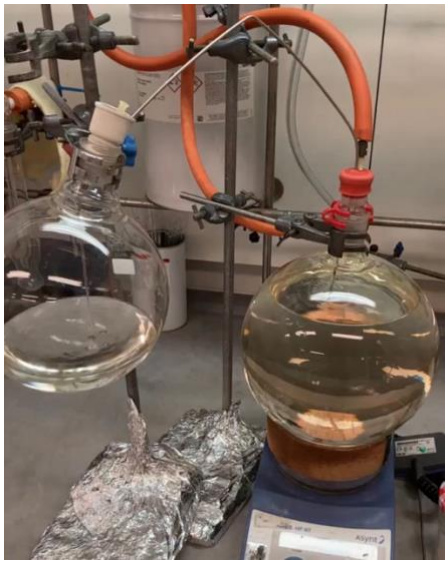
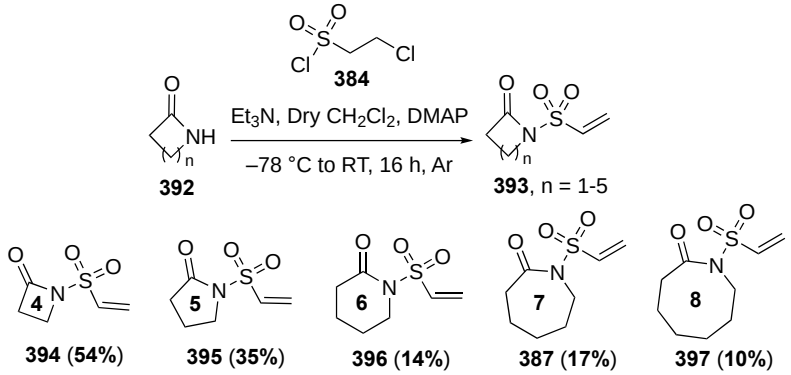


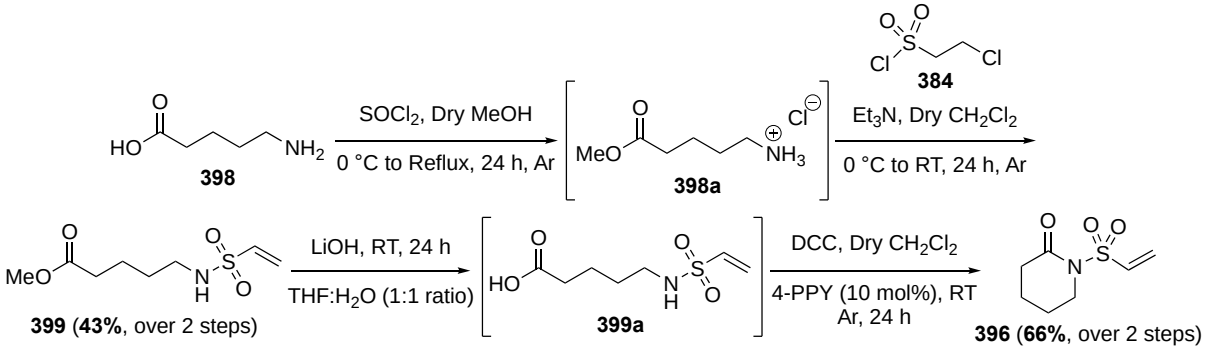
Figure 5.1.11 Reaction step-up in the round-bottom flask (500 mL), illustrating the impracticality of using a large volume of solvent

At this point, it was decided to move on and focus on the ring expansion, accepting that the starting material yields are low in some cases. The effect of ring size variation in the starting material was important, so the synthesis of the 4–8 membered starting materials was performed as shown below in **Scheme 5.1.12**. The *N*-sulfonylation reaction of lactams follows a predictable pattern, where β-lactam is easiest to install α,β-unsaturated sulfonamide functionality and *ω*-heptalactam are more challenging, as illustrated in the yields of the corresponding products **394** and **397**, respectively (**Scheme 5.1.12**).



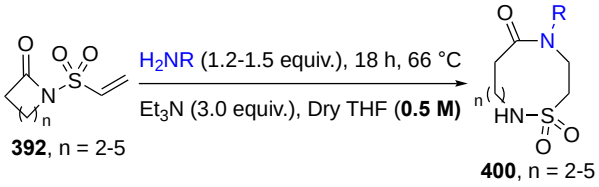
Scheme 5.1.12 Preparation of different Michael acceptors **393** (4 to 8 atom ring) using *N*-sulfonylation conditions

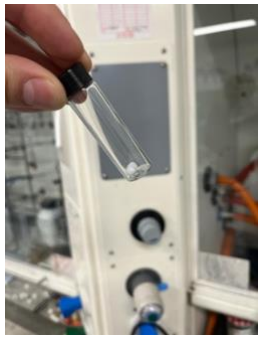
The yield of six-membered vinyl sulfonyl **396** was very low, and it was thus decided to proceed via end-to-end cyclization. Amino pentanoic acid **398** was heated in methanol in the presence of an acid catalyst (HCl), generated from thionyl chloride ($SOCl_2$), to give a methyl ester crude product (**Scheme 5.1.13**, **398** → [**398a**])[268]. This product was taken directly to *N*-sulfonylation to give the vinyl sulfonyl ester **399** in 43% yield over the two steps (**Scheme 5.1.13**, [**398a**] → **399**). Ester **399** was hydrolysed (**Scheme 5.1.13**, **399** → [**399a**]) and subjected to DCC and 4-PPY conditions in CH_2Cl_2 (**0.1 M**) (**Scheme 5.1.13**, [**399a**] → **396**), giving six-membered vinyl sulfonyl **396** in excellent yield, as expected.



Scheme 5.1.13 Reaction sequence toward the synthesis of 6-membered ring Michael acceptor **396**, with reaction conditions and yields for each of the steps

After the desired Michael acceptors with varied-sized rings had been synthesised (from 4 to 8-membered rings), they were reacted with primary amines (denoted as H_2NR in **Scheme 5.1.14**) at an elevated temperature. Notably, one of this reaction's biggest selling points is that they were done at 0.5 M concentration in THF and were successfully used to make medium-sized rings (9- to 11-atom rings) and macrocycles (12-atom rings) in high yields. This offers a practical method that we expect will be favoured in industry, due to their scalability (as they require very little solvent) and their ease to set up (see **Fig. 5.1.15**).





Scheme 5.1.14 General reaction for ring expansion method is used to synthesize medium-sized and macrocyclic sulfonamides, which is initiated through conjugate addition, and **Figure 5.1.15** Shows the reaction apparatus set-up and equipment

The reactions gave smooth conversion to 9–12-membered cyclic sulfonamides **401**–**404** from the starting material in good to excellent yield, as expected (**Fig. 5.1.16**). The lower isolated yields for the smaller ring variants was expected, following associated DFT (Density Functional Theory) calculations,[260] where the 5-membered ring starting material was calculated to have a lower driving force for ring expansion to occur, in contrast to 8-membered material, where there is a very clear thermodynamic favourability to make a 12-membered macrocycle **404**, which manifests in a higher yield (**Fig. 5.1.16**). Note, these calculations were performed by another Unsworth group member and hence are not described in detailed in this thesis but are described in the published manuscript.[260] A single X-ray of 11-membered macrocycle sulfonamide **403**, shown in **Fig. 5.1.16**, was crystallised by slow evaporation of MeCN.

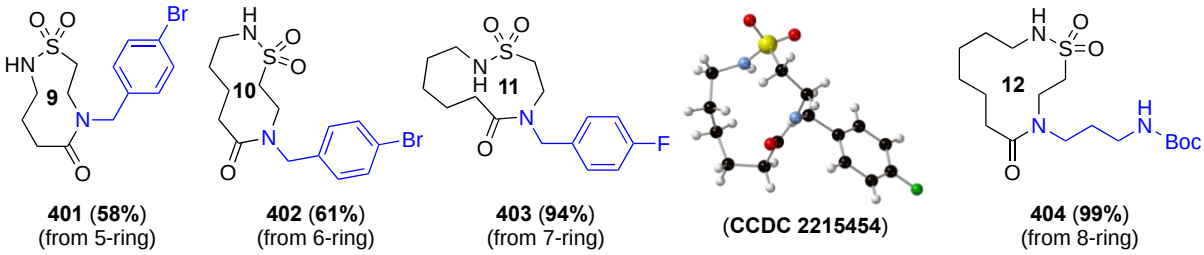
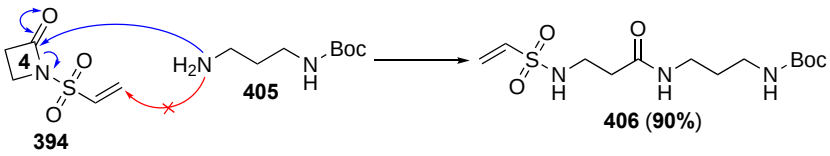


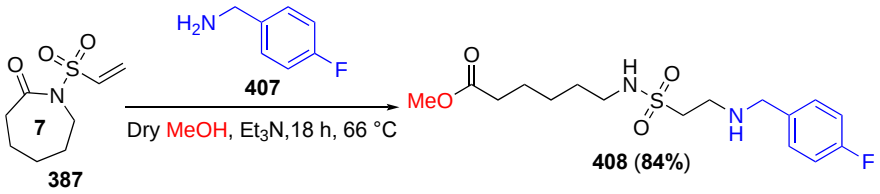
Figure 5.1.16 Shows different ring size variations and X-ray crystal structure of the 11-membered ring **403** with **CCDC** deposit number

The only substrate that didn't react as expected was the four-membered lactam **394** (**Scheme 5.1.17**), even though the DFT calculations showed the ring expansion to be highly exergonic. However, the calculation didn't consider alternative reaction pathways that are more kinetically accessible, which in this case is the ring-opening of the strained four-membered ring **394** with boc amine **405** to afford linear amide **406** in 90% yield (**Scheme 5.1.17**).



Scheme 5.1.17 The 4-membered ring opening a competing reaction pathway, highlighted with blue curly arrows, obtaining the isolated yield of **406**

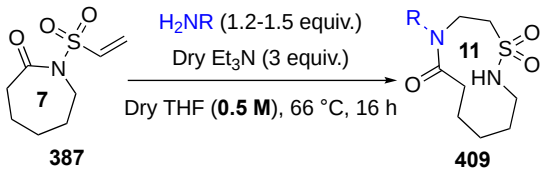
A similar reaction pathway was dominant when anhydrous MeOH was used in the reaction as the solvent (**Scheme 5.1.18**) instead of THF. Here, the linear methyl ester **408** was formed as a major product in 84% yield from the **387** and fluoro benzylamine **407** (**Scheme 5.1.18**, **387** + **407** → **408**).



Scheme 5.1.18 CARE reaction in MeOH, showing the formation of linear ester **408** as the major product with isolated yield shown

Next, we decided to explore the substrate scope of the amine component. The seven-membered ring substrate **387** was used and was reacted with various amines (H_2NR) under

the same reaction conditions to give the corresponding 11-membered rings **409** (**Scheme 5.1.19**).



Scheme 5.1.19 Showing general ring expansion conditions using **387** as starting material

The CARE reaction with Michael acceptor **387** (**Scheme 5.1.19**) was done successfully with several amines, and this led to the formation of the 16 products shown in **Fig. 5.1.20** (20 examples in total, including those in **Fig. 5.1.16**), with 16 different functionalised primary amines being used, allowing diverse chemical functionalities to be incorporated into the products. The amines (including **Fig. 5.1.16** and **Fig. 5.1.20**) were selected to challenge the CARE method with various chemical functionalities,[269] which can further react to give compound libraries for bioassay or structure–activity relationships (SAR). The first attempts were simple aliphatic amines (e.g., **401**, **403** and **411**, **Fig. 5.1.16** and **Fig. 5.1.20**); next, the ring-expanded sulfonamides were afforded in good to excellent yield-bearing terminal alkyne (**412**) that could be further fictionalised using "click chemistry", [270] fluorinated anime (**413**), a sulfide-tethered amine (**415**), electron-rich (-OMe) aniline (**423**); amines with benzyl-protected alcohol (**414**); acetal-protecting aldehydes (**416**) and Boc-protecting amines (1° and 2°, **404** and **416**, **Fig. 5.1.16** and **Fig. 5.1.20** respectively), amines attached to aza-heterocycles (e.g., γ-lactam **417**, tryptamine **424**, morpholine **419** and pyridine **420**), unprotected amino alcohol, **421** and alkyl chloride (**422**, using a chloropropylamine hydrochloride starting material with an extra equivalent of Et_3N to obtain a free base amine). The key improvement of the previously reported method is using ammonia as an amine derivative (NH_3 added to the reaction as a solution in 1,4-dioxane) to undergo a CARE reaction to generate lactam **425** in a good yield. The ability to easily introduce different functionalities into is the main benefit of the CARE reaction, using robust and straightforward reaction procedures with simple purification methods.

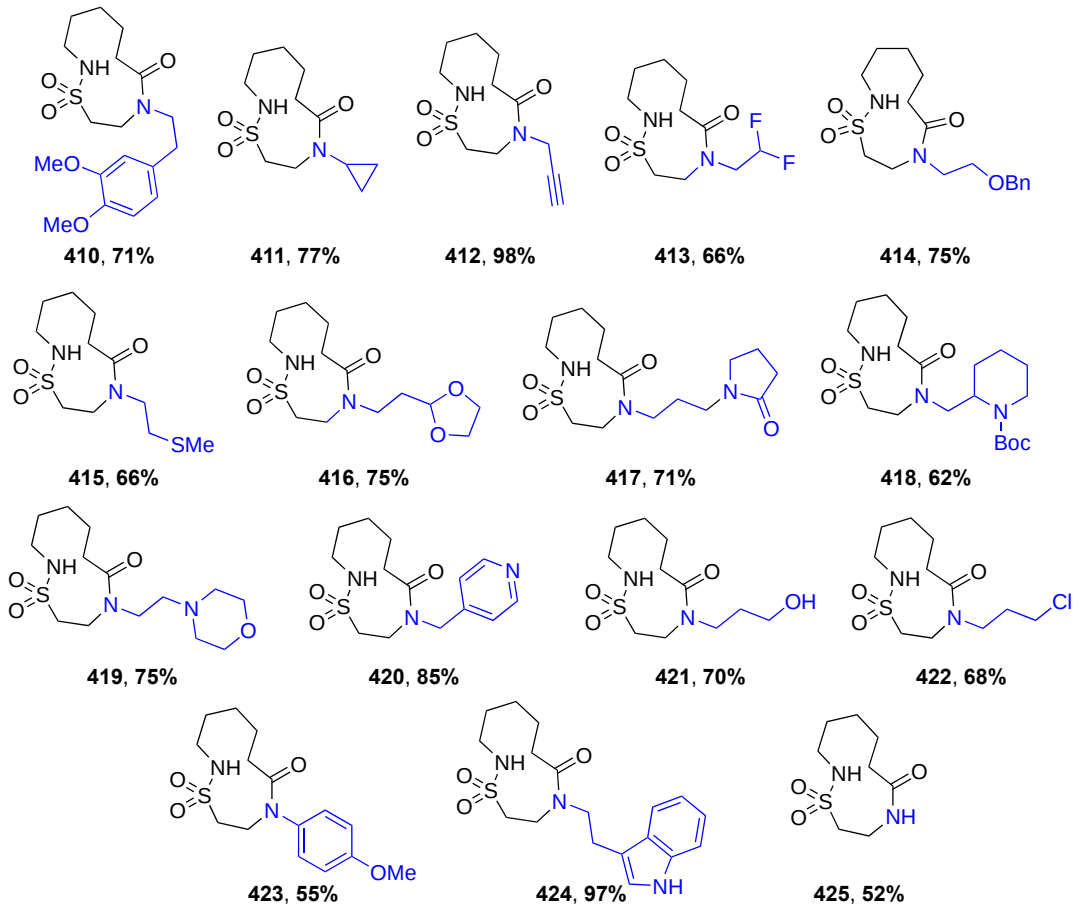
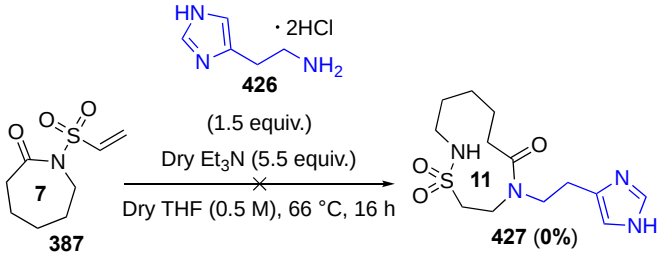


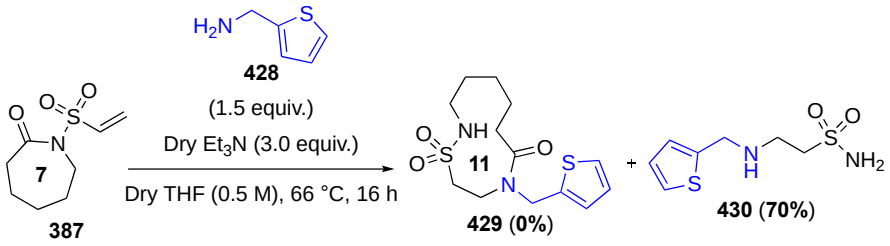
Figure 5.1.20 Illustrating diverse amine scope and yields of isolated products

However, some amine substrates did not produce the desired 11-membered sulfonamides using the CARE reaction. CARE with histamine dihydrochloride **426** (extra 2.55 equiv. of Et_3N added to obtain free base form, **Scheme 5.1.21**) as the amine produced a complex mixture of products observed via TLC and crude NMR, with no sign of the formation of the desired **427**, suggesting its incompatibility with the **387** Michael acceptor (**Scheme 5.1.21**).



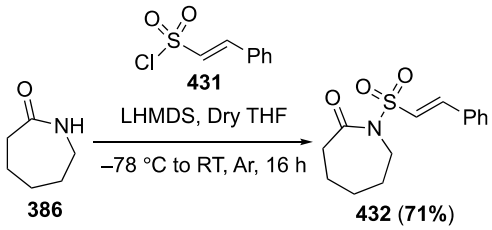
Scheme 5.1.21 CARE reaction with histamine **426**, resulting in no reaction

Another substrate that led to unsuccessful results was amino thiophene **428**. Under the standard CARE conditions, the desired 11-membered sulfonamide **429** (**Scheme 5.1.22**) was not synthesised. However, interestingly and unusually, the primary sulfonamide **430** was isolated as a major side product from the reaction in 70% yield (**Scheme 5.1.22**, **387** + **428** → **430**).



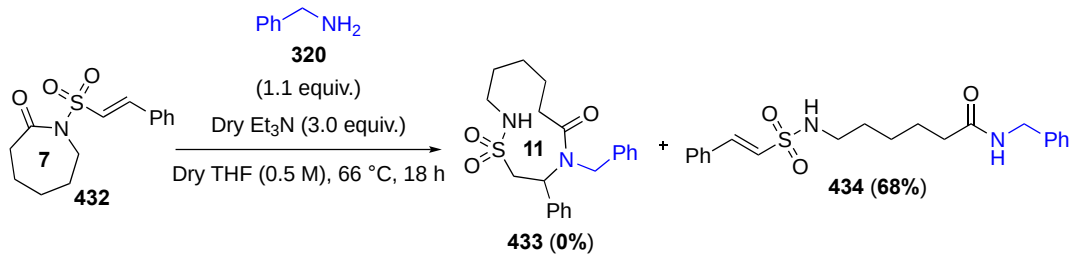
Scheme 5.1.22 CARE reaction with amino thiophene **428**, where the formation of primary sulfonamides **430** was not rationalised

The biggest drawback of this reaction was the low-yielding synthesis of the Michael acceptor starting material, and with this in mind, we explored switching to a styrene-like motif **432** (**Scheme 5.1.23**). The synthesis of styrene **432** began with optimising *N*-sulfonylation conditions using LHMDS, phenyl ethene sulfonyl chloride **431** and lactam **386,** affording Michael acceptor **432** in good yield (**Scheme 5.1.23**).



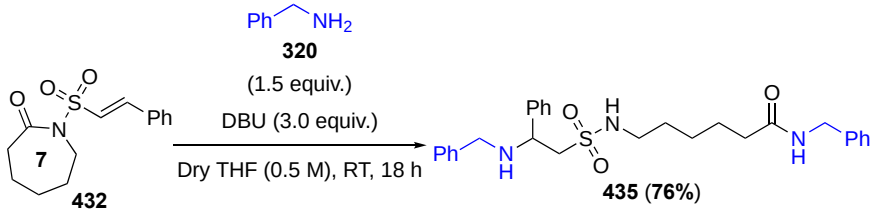
Scheme 5.1.23 *N*-sulfonylation optimised conditions with commercially available phenyl ethene sulfonyl chloride **431** and 2-piperidone **386** as starting materials

Soon after the starting material **432** (**Scheme 5.1.24**) was synthesised, it was subjected to the established reaction conditions with a slight modification to the initial procedure, whereby 1.1 equiv. of primary amine (i.e., benzylamine) was used instead of 1.5 or 1.2 equiv. (**Scheme 5.1.24**). Unfortunately, the desired medium-size ring **433** was not synthesised, and the linear amide **434** was formed in 68% yield via a competing ring-opening reaction, similar to that seen previously with methanol.



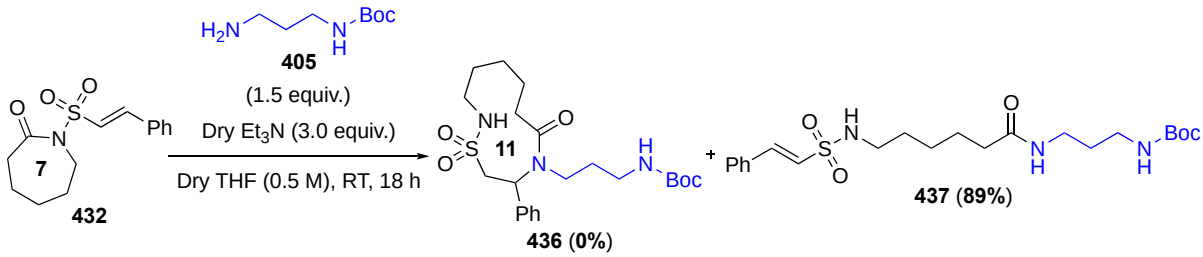
Scheme 5.1.24 Ring opening reaction with benzylamine **320**, affording linear amide **434**

This thus indicates that the CARE reaction in **Scheme 5.1.24** failed. One reason for such a failure may be attributed to the reduction in electrophilicity of the alkene/vinyl motif (i.e., the phenyl exerts an electron *-I* effect and adds steric hindrance) meaning that more kinetically favourable pathways can take over (in this case, the ring-opening reaction). To try to remedy this, it was decided to increase the nucleophilicity of the amine by using a stronger base than Et_3N (pK_a = 10.75) [271] - we proposed 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU, pK_a = 13.5).[272,273] The reaction was performed at RT with 1.5 equiv. of benzylamine **320** (pK_a = 9.34),[274] using the Michael acceptor styrene **432** (**Scheme 5.1.25**) in a sealed glass vial. Unfortunately, the linear amide **435** was isolated as a major product from the reaction following a ring-opening and 1,4-addition reaction with benzylamine **320** (**Scheme 5.1.25**, **432** + **320** → **435**).



Scheme 5.1.25 Shows the formation of linear amide **435** via ring-opening using benzylamine, which also underwent conjugation addition

After two failed attempts, it was decided to change the nucleophile and use Boc-protected linear primary amine **405** with Et_3N at RT overnight, but again, the linear amide **437** product formed in 89% yield (**Scheme 5.1.26**).



Scheme 5.1.26 CARE reaction with bulkier amine **405**, where the linear amide **437** was isolated as the major product

Chapter 6: Conclusion

A summary of the key findings from this PhD on NICE reactions is shown in **Fig. 6.1**. We have shown that sulphur and selenium can undergo a ring expansion reaction with optimised conditions using EDC. HCl and HOB, achieving a variety of medium-size ring products in high yield with a high functionality tolerance (highlighted green in **Fig. 6.2**). Alongside testing different internal nucleophiles (denoted as "Z" in **Fig. 6.1**), we examined various terminal nucleophiles (highlighted light blue in **Fig. 6.1** and **Fig. 6.2**, denoted as "X") to afford novel medium ring scaffolds ranging from 35%–75%.

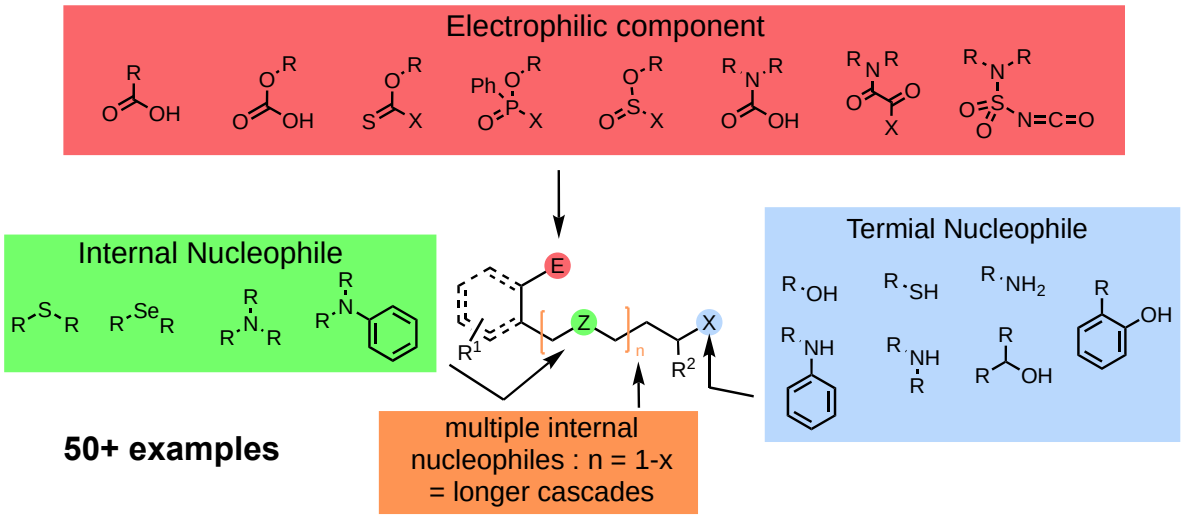


Figure 6.1 Summary of PhD work on NICE Reactions for Synthesis of Medium-Sized Rings and Macrocycles

Further, we showed that additional heteroatoms could be successfully incorporated into the linker to enable a more extended ring expansion cascade and obtain macrocyclic frameworks (n > 1, highlighted in orange in **Fig. 6.2**). We have successfully synthesized linear precursors with two, three, and four different heteroatoms as nucleophiles using EDC.HCl and HOBt conditions, with the desired compounds' macrocycles being isolated in 40%–70% yields at a standard concentration of 0.1–0.05 M. Furthermore, our development of several novel synthetic routes has made it possible to create precursors with multiple internal nucleophiles for future analogues, with several successful attempts to create a variety of precursors with slightly different structures at different stages of development.

Continuing to perhaps the most noteworthy result in this body of work, we dramatically extended substrate scope and reaction concept by varying the electrophilic component (highlighted pink in **Fig. 6.2**), involving seven new reaction classes based on different

electrophilic components. This effort in discovering new electrophiles and terminal and internal nucleophiles enables a quick and easy method for the synthesis of- and the accessibility to- a vast library of medium-sized rings.

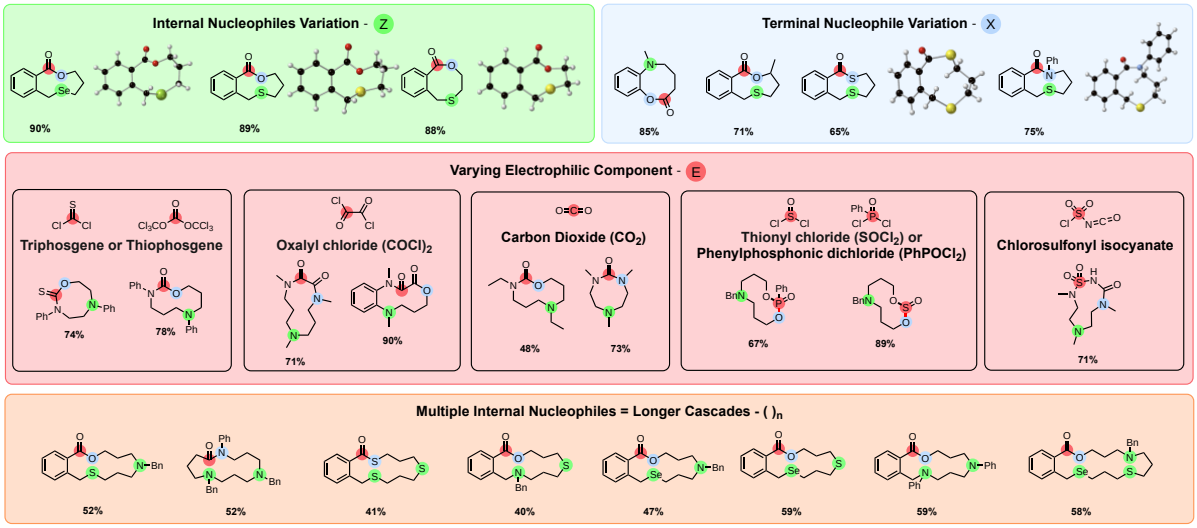
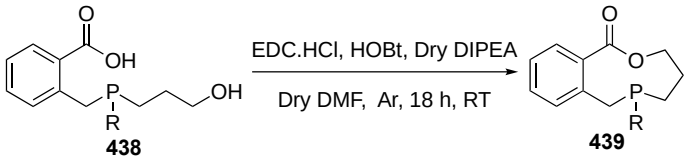


Figure 6.2 This display showcases the essential constructions of medium-sized rings (in green, light blue, and pink boxes) and macrocycles (in orange), alongside their corresponding yields

The **CARE** method described in the final chapter is a method that involves adding various functionalized primary amines to create cyclic sulfonamides of different ring sizes ranging from 9 to 12 members. The yields achieved using this method range from 52% to 99% at 0.5 M, and the conditions used are practical and robust. The synthetic series produced using this method have been found to be consistent with the predicted results obtained from DFT calculations. The production of medium-sized ring cyclic sulfonamides is not common, particularly when it involves ring expansion. The hope is that the new methods presented in this research will enable the exploration of this compound class in various fields, especially in medicinal chemistry. The research findings of this chapter were published in *Angewandte Chemie* this year.[260]

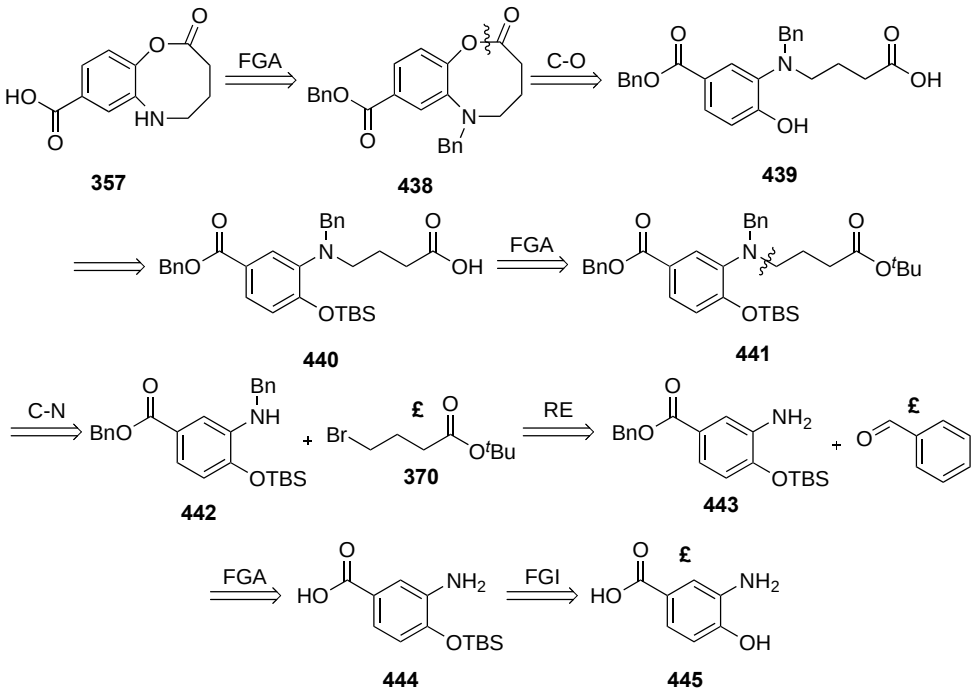
Chapter 7: Future Work

In the future, it would be interesting to test other internal heteroatoms, specifically phosphorus (P), and determining if they can undergo the same ring expansion reaction as sulphur and selenium analogue systems. To test P as an internal nucleophile, we could synthesize the benzoic acid **438** (**Scheme 7.1**) and subject it to establish the NICE condition to try to obtain a novel phosphorus nine-membered ring. The phosphorus medium-sized ring heterocycles can be ligands for asymmetrical catalysis with various metals.[275,276]



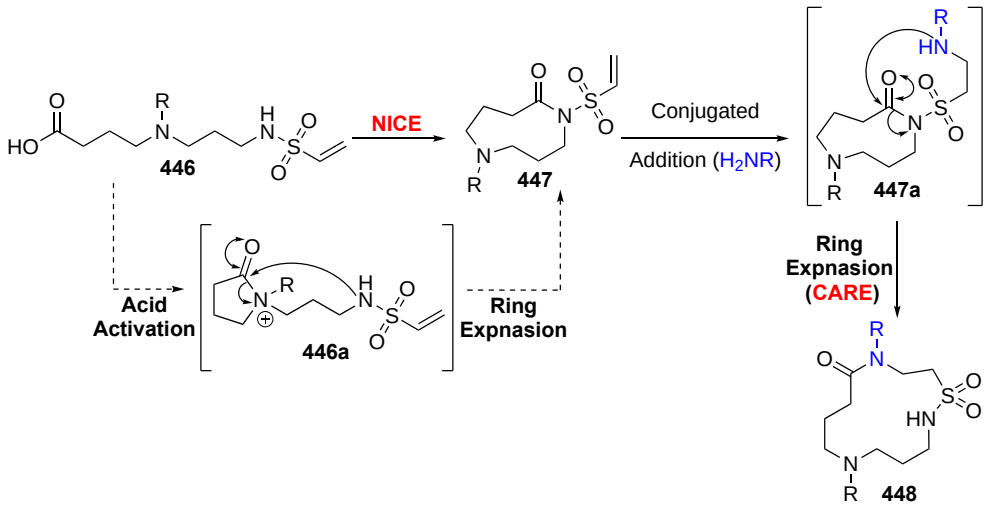
Scheme 7.1 Synthesis of novel phosphors medium size ring **439**, using established NICE reaction conditions

Our second goal is to complete the total synthesis of Argaminolic A **357** using the NICE reaction conditions tested on the model substrates. **Scheme 7.2** displays the desired molecule's retrosynthesis analysis. The analysis starts with Argaminolic A-**357**, which will undergo FGA by adding benzyl (Bn) to carboxyl acid and aniline. Next, the 8-membered ester **438** will be disconnected at C-O to afford linear precursor **439** (that will undergo NICE reaction). The phenol (terminal) nucleophile in linear precursor **439** will be TBS-protected to afford **440** (**Scheme 7.2**). The ester will be protected using *tert*-butyl ester to afford compound **441**, which can cleave using acidic conditions (i.e., orthogonal protection strategies).[277] Following the C-N disconnection, secondary aniline **442** and commercially available *tert*-butyl 4-bromobutyrate **370** will be installed using an alkylation reaction (**Scheme 7.2**). Next, a Bn-protecting group will be attached to an amine using reduction amination (RE) conditions with primary aniline **443** and benzaldehyde (ArCHO), and proceeding, FGA then adds a Bn-protecting group onto carboxylic acid **444**. The final step of retrosynthesis will be phenol protecting, as shown in **Scheme 7.2**, where the synthesis commences with 3-amino-4-hydroxybenzoic acid **445** (CAS number: 1571-72-8, £41.00 for 25 g).[278]



Scheme 7.2 Retrosynthesis analyses of the Argaminolic A

Finally, we wish to create medium-sized rings and macrocycles with sulfonamide and lactam functionality by combining NICE and CARE reactions. The process will begin with the linear precursor **446**, which will undergo the NICE reaction to form a nine-membered Michael acceptor **447** (**Scheme 7.3**). We will then subject this Michael acceptor **447** to the CARE reaction conditions with a primary amine nucleophile (H_2NR). 13-membered macrocycles **448** (**Scheme 7.4**, **477** → [**447a**] → **448**) with three reaction functional groups sites will thus be produced, which can be further manipulated. This approach to use NICE to create the Michael acceptor for the CARE reaction will address the low yield issues encountered when using *N*-sulfonylation or end-to-end cyclization (to make starting materials) and, in particular, increasing the yield for the seven- and eight-membered vinyl systems.



Scheme 7.3 Synthesis of the macrocycles **448** using NICE and CARE reactions, illustrating key steps of the mechanism

Chapter 8: Experimental

8.1 General Experimental Summary

Unless otherwise stated, all reactions were carried out at RT under an inert (N_2 or Ar) atmosphere in oven-dried glassware. Except where stated all reagents were purchased from commercial sources: Merck (Sigma Aldrich), Alfa Aesar, Acros Organics, Fisher Chemicals, VWR, TCI, Across chemicals and Fluorochem and were used without further purification. Anhydrous CH_2Cl_2, toluene, MeCN, Et_2O and DMF were obtained from an Innovative Technology Inc. PureSolv® solvent purification system. Dry THF was obtained from the SPS laboratory system and used immediately after being dispensed. Dry Et_3N and DIPEA obtained by drying with CaH_2 and then distilling and storing over KOH or 3 Å molecular sieves, 3 Å under Ar. Anhydrous MeOH, DMSO, acetone, ^{t}BuOH, benzene, CCl_4 and ^{n}BuOH was purchased from Sigma Aldrich and used as supplied.

^{1}H NMR spectra were recorded at 400 MHz on Bruker AV400 or Bruker AMX 400/JEOL ECS-400 and at 500 MHz on Bruker DRX500 MHz Ultra ShieldTM spectrometry.^{13}C NMR spectra were recorded at 101 MHz on Bruker AV 400 or Bruker AMX 400 MHz Ultra ShiledTM and 126 MHz on Bruker DRX500 MHz Ultra ShiledTM spectrometry.^{19}F NMR spectra were recorded at 376 MHz on Bruker AV400 or Bruker AMX 400/JEOL ECS-400 spectrometry. ^{31}P NMR spectra were recorded at 162 MHz on Bruker AV400 or Bruker AMX 400/JEOL ECS-400 spectrometry.

All spectral data was acquired at 295 K (25 °C) unless stated otherwise and samples were dissolved in $CDCl_3$ unless specified otherwise.Chemical shifts (δ) are reported in parts per million (ppm), with residual solvent peaks: $CDCl_3$: δ_H = 7.26, $CDCl_3$: δ_C = 77.0, $(CD_3)_2SO$: δ_H = 2.50, δ_C = 39.5, CD_3OD: δ_H = 3.31, δ_C = 49.0, C_6D_6: δ_H = 7.16, δ_C = 128.1, CD_2Cl_2: δ_H = 5.32, δ_C = 53.8, $(CD_3)_2CO$: δ_H = 2.05, δ_C = 206.3, D_2O: δ_H = 4.79, , $DCON(CD_3)_2$: δ_H = 8.03, δ_C = 163.2, being used for internal reference. The multiplicity abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; dd, doublet of doublets; dt doublet of triplets; td, triplet of doublets; tt, triplet of triplets; ddd, doublet of doublets of doublets; pd, pentet of doublets; where br indicates a broad signal, and app. indicates an apparent. ^{1}H experiments are reported as: chemical shift in ppm, quoted to the nearest 0.01 ppm, (integration, multiplicity, coupling constant and assignment (where possible)). ^{13}C experiments are reported as: chemical shift in ppm, quoted to the nearest 0.1 ppm, (carbon assignment (where possible) or multiplicity, coupling constant and assignment (where applicable)).^{19}F experiments are reported as: chemical shift in ppm, quoted to the nearest 0.1 ppm, (multiplicity, coupling constant and assignment (where possible)). ^{31}P experiments are

reported as: chemical shift in ppm, quoted to the nearest 0.1 ppm, (multiplicity, and assignment (where possible)).

Assignment of compounds was achieved through use of ^{135}DEPT, COSY, HSQC and HMBC experiments.Spectra were analysed using MestReNova 12.0.3-21384 software and values of coupling constant (*J*) are reported in Hertz (Hz) to the nearest 1 decimal place, i.e., 0.1 Hz. The term “overlapping” is used to describe resonance peak, which is behind another resonance peak, *i.e*., compound resonance behind the solvent peak or combination of two resonance peaks. The systematic chemical names were generated using the IUPAC name generator tool option is included within the ChemBioFDaw Ultra 19.1 software.

Infrared (IR) spectra were recorded on a PerkinElmer UATR 2 or Pekin Elmer Spectrum 100 spectrometer fitted with a universal Attenuated Total Reflectance (ATR) accessory; date was recorded as a thin film dispersed from either CH_2Cl_2 or $CDCl_3$, neat or solid state by ATR-FTIR. IR-recorded experiments are reported as: IR (method of recorded) v_{max} (IR absorption maxima) / unit (cm^{-1}) chemical absorption (assignment (where possible)).The intensity of each absorbance bands gives the annotated appearance, and each bond was described as w (weak), m (medium), s (strong), sh (sharp) and with the prefix v (very) and suffix br (broad).

High Resolution Mass Spectra (HRMS) were obtained by the University of York Mass Spectrometry Service, recorded on a Waters XEVO G2-XS TOF, Waters Synapt G2S TOF or Bruker Micro-TOF mass spectrometer, with HRMS mode incorporating a lock-in mass into the mobile phase (leucine enkehalin) or on a Bruker Daltonics, Micro-TOF spectrometer, using Electrospray Ionisation (ESI) or Atmospheric Pressure Chemical Ionisation (APCI), positive or negative generative modes.

Thin Layer Chromatography (TLC) was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and was visualised using UV light (λ = 254 nm, short wavelength) or UV light (λ = 366 nm, long wavelength) and stained with basic aqueous potassium permanganate ($KMnO_4$), ninhydrin or vanillin solution dip. Concentration under reduced pressure or *vacuo* was performed using a Büchi® Rotavapor® R-210 evaporator with jack and water bath, 29/32 joint, 240V rotary evaporator using a mixture of acetone and dry ice or ice/water as the coolant. Flash column chromatography was conducted using Aldrich technical grade silica gel (SiO_2), 60 Å, 230-400 mesh, 40-63 μm particle size, under a light positive pressure of air, eluting with the specified solvent system.

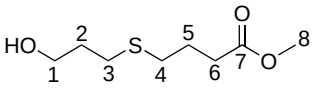
Melting points were recorded as decomposition temperature range and measured on a Stuart SMP10 or Gallenkamp apparatus using open tubes with no corrections. Before measuring the melting point, in most instances, the solids were purified by recrystallisation after purification by column chromatography, where "(from [solvent])" donating solvent systems were used, e.g. single or multiple.

X-ray crystallography data was collected, solved, and refined by Dr Adrian C. Whitwood in the School of Chemistry at the University of York. Diffraction data were collected at 100 K on an Oxford Diffraction SuperNova diffractometer with Cu-K_α radiation (λ = 1.54184 Å) using a HyPix-6000HE detector.The crystal was cooled with an Oxford Instruments Cryojet. Diffractometer control, data collection, initial unit cell determination, frame integration and unit-cell refinement were carried out with CrysAlisPro, [279] Face-indexed absorption corrections were applied using spherical harmonics, implemented in SCALE3 ABSPACK[280] scaling algorithm within CrysAlisPro. OLEX2 [281]was used for overall structure solution, refinement and preparation of computer graphics and publication data. Within OLEX2, the algorithms used for structure solution were 'Superflip charge-flipping [282] smtbx-flip charge-flipping [283]ShelXT dual-space [284] Refinement by full-matrix least-squares used the SHELXL[285] algorithm within OLEX2.[281]All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed using a riding model and included in the refinement at calculated positions. CrystalMaker® 10 software was also used to visualise the X-ray structures with their corresponding CCDC deposit number shown.

All raw data (i.e. MS, IR and NMR) for the compounds featured in this thesis are stored on the Unsworth group's storage area: wpu500 (\\storage.its.york.ac.uk\chemistry\research).

8.2 Experimental procedures

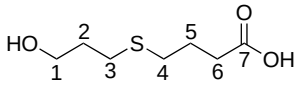
Synthesis of methyl 4-((3-hydroxypropyl)thio)butanoate – 99



K_2CO_3 (2.40 g, 17.4 mmol) was added to a solution of thiol **97** (1.05 mL, 11.6 mmol) and methyl 4-bromobutanoate **98** (1.01 mL, 17.4 mmol) in anhydrous DMF (39 mL) at RT. The resulting milky/white suspension was then heated to 60 °C. After 18 h, the reaction was deemed to have gone to completion by TLC analysis. The reaction mixture was allowed to cool to RT, before it was quenched by the addition of H_2O (30 mL). The diluted mixture was poured into a separating funnel containing Et_2O (40 mL) and the aqueous phase was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed sequentially with H_2O (3 × 20 mL) and sat. brine (1 × 40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale yellow oil (2.38 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:toluene, 30:70) to afford thiol **99** as a pale yellow oil (872 mg, 87%); R_f = 0.22 (30:70, EtOAc:toluene); IR(thin film) ν_{max}/cm^{-1}: 3416m (O–H alcohol), 2941m (C–H alkyl), 2877w (C–H alkyl), 1735s (C=O ester), 1438m, 1367w, 1316w, 1212m, 1175m, 1140w, 1054m, 885w; δ_H (400 MHz; $CDCl_3$) 3.66 (2H, t, *J* = 6.1 Hz, C(1)H_2), 3.62 (3H, s, C(8)H_3), 2.56 (2H, t, *J* = 7.2 Hz, C(3)H_2), 2.50 (2H, t, *J* = 7.2, C(4)H_2), 2.39 (2H, t, *J* = 7.2 Hz, C(6)H_2), 1.85 (2H, app. p, *J* = 7.2 Hz, C(5)H_2), 1.77 (2H, tt, *J* = 7.2, 6.1 Hz, C(2)H_2); δ_C (101 MHz; $CDCl_3$) 173.8 (C, C7), 61.4 (CH_2, C1), 51.7 (CH_3, C8), 32.7 (CH_2, C6), 32.0 (CH_2, C2), 31.2 (CH_2, C4), 28.4 (CH_2, C3), 24.5 (CH_2, C5); HRMS (ESI): *m/z* calcd. for $C_8H_{16}NaO_3S$: 215.0718, found: 215.0708 $[MNa]^+$.

Lab notebook reference: ixz_015

Synthesis of methyl 4-((3-hydroxypropyl)thio)butanzoic acid – 100

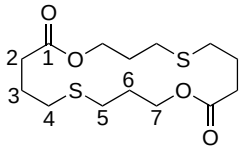


$NaOH_{(aq)}$ (0.5 M, 12 mL) was added dropwise over a period of 30 sec to a solution of methyl butanoate **99** (1.07 g, 5.59 mmol) in MeOH (6 mL). A colour change to pale yellow solution with liberation of gas was immediately noted. After a total of 24 h, the reaction mixture was deemed to have gone to completion by TLC (complete consumption of methyl butanoate **99** was noted). The reaction mixture was then acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (20 mL) and was transferred into separating funnel containing CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and organic phases were combined, before the combined organic layer was dried over $MgSO_4$, filtered and concentred under reduced pressure to yield

a pale-yellow oil (541 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: CH_2Cl_2:MeOH, 95:5) to afford carboxylic acid **100** as a pale yellow viscous oil (820 mg, 47%); R_f = 0.35 (5:95 MeOH:CH_2Cl_2); IR (thin film) ν_{max}/cm^{-1}: 3410s (O–H alcohol/carboxylic acid), 2935w (C–H alkyl),1648s (C=O carboxylic acid), 1497w, 1439w, 1389s, 1255w, 1099m, 661s; δ_H (400 MHz; $CDCl_3$) 9.08 (1H, s, OH), 3.65 (2H, t, *J* = 6.2 Hz, C(1)H_2), 2.53 (2H, t *J* = 7.3 Hz, C(3)H_2), 2.49 (2H, t *J* = 7.0 Hz, C(4)H_2), 2.39 (2H, t, *J* = 7.0 Hz, C(6)H_2), 1.83 (2H, app. p, *J* = 7.3 Hz, C(2)H_2), 1.75 (2H, app. p, *J* = 7.0 Hz, C(5)H_2); δ_C (101 MHz; $CDCl_3$) 177.8 (C, C7), 61.1 (CH_2, C1), 53.5 (CH_3, C6), 32.7 (CH_2, C5), 31.7 (CH_2, C4), 28.1 (CH_2, C2), 24.3 (CH_2, C2); HRMS (ESI): *m/z* calcd. for $C_7H_{14}NaO_3S$: 201.0556, found: 201.0555 $[MNa]^+$.

Lab notebook reference: ixz_032

Synthesis of 1,10-dioxa-5,14-dithiacyclooctadecane-9,18-dione – 103

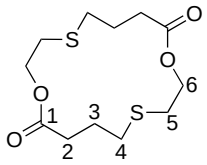


Dry DIPEA (790 µL, 4.54 mmol) was added dropwise over a period of 30 sec to a solution of butanzoic acid **100** (324 mg, 1.82 mmol) in anhydrous DMF (18 mL) at RT. A colour change to pale yellow solution was noted immediately. The resulting solution was stirred for 1 min at RT, after which time, HATU (1.03 g, 2.73 mmol) was added and a colour change to dark brown noted. After 24 h, the reaction was deemed to have gone to completion by TLC analysis, with the reaction changing to an orange/brown colour. The resulting mixture was diluted with EtOAc (30 mL), before transferred to separating funnel. The organic layer was washed sequentially with 1.0 M $HCl_{(aq)}$ (1 × 30 mL), sat. $NaHCO_{3(aq)}$ (1 × 20 mL) and sat. brine (1 × 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield a brown viscous oil (244 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: Et_2O:*n*–hexane, 40:50 to 60:40) to afford dimer **103** as a white solid (21.1 mg, 8%); R_f = 0.46 (50:50, EtAOc:*n*–hexane); melting point: 68 – 70 °C (from *n*–hexane); IR (solid state) ν_{max} / cm^{-1}: 2954w (C–H alkyl), 1725s (C=O ester), 1452w, 1271w, 1227w, 1165w, 1132w, 1033w, 968w, 898w, 781w; δ_H (400 MHz; $CDCl_3$) 4.21 (4H, t, *J* = 5.8 Hz, C(7)H_2), 2.60 (4H, t, *J* = 7.5 Hz, C(5)H_2), 2.56 (4H, t, *J* = 7.3 Hz, C(4)H_2), 2.46 (4H, t, *J* = 7.3 Hz, C(2)H_2), 1.98 – 1.88 (8 H, m, C(3+6)H_2); δ_C (101 MHz; $CDCl_3$) 173.1 (C, C1), 63.1 (CH_2, C7), 33.6 (CH_2, C2), 31.4 (CH_2, C4), 28.8 (CH_2, C6), 28.2 (CH_2, C5), 25.0 (CH_2, C3);HRMS (ESI): *m/z* calcd. for $C_{14}H_{25}O_4S_2$: 321.1189, found: 321.1187 $[MH]^+$, *m/z* calcd. for $C_{14}H_{24}NaO_4S_2$: 343.1008, found: 343.1005 $[MNa]^+$; X-ray crystallographic data for this compound can be accessed via

www.ccdc.cam.ac.uk/data_request/cif (CCDC 2221210, was crystallized by slow cooling of *n*-hexane from reflux to RT).

Lab notebook reference: ixz_035

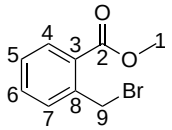
Synthesis of 1,9-dioxa-4,12-dithiacyclohexadecane-8,16-dione – 107



EDC.HCl (114 mg, 0.354 mmol) was added to solution of butanoic acid **104** (38.8 mg, 0.240 mmol), HOBt (57.1 mg, 0.288 mmol) and dry DIPEA (110 µL, 0.610 mmol) in anhydrous DMF (5 mL) at RT. A colour change to pale yellow was noted. After 16 h of stirring at RT under Ar, the reaction was deemed to have to completion by TLC analysis. The reaction was diluted with EtOAc (20 mL) and poured into separating funnel, before organic layer washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 20 mL), sat. $NaHCO_{3(aq)}$ (2 × 20 mL) and sat. brine (3 × 20 mL). The resulting organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a clear colourless oil (59.6 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 20:80) to afford title compound **107** as clear colourless oil (156 mg, 29%);R_f = 0.10 (20:80, EtOAc:*n*–hexane); IR (neat) ν_{max} /cm^{-1}: 2921w (C–H alkyl), 2857w (C–H alkyl), 1726s (C=O ester), 1452w, 1384w, 1184m, 1131m, 999w; δ_H (400 MHz; $CDCl_3$) 4.30 (4H, t, *J* 5.8, C(6)H_2), 2.80 (4H, t, *J* = 5.8 Hz, C(5)H_2), 2.7 (2H, t, *J* = 7.1 Hz, C(4)H_2), 2.47 (4H, t, *J* = 7.1 Hz, C(2)H_2), 1.97 (4H, ap. p, *J* = 7.1 Hz, C(3)H_2); δ_C (126 MHz; $CDCl_3$) 173.0 (C, C1), 64.1 (CH_2, C6), 33.1 (CH_2, C2), 32.2 (CH_2, C5), 31.6 (CH_2, C4), 25.1 (CH_2, C3); HRMS (ESI): *m/z* calcd. for $C_{12}H_{21}O_4S_2$: 293.0876, found: 293.0868 $[MH]^+$, *m/z* calcd. for $C_{12}H_{20}NaO_4S_2$: 315.0695, found: 315.0685 $[MNa]^+$.

Lab notebook reference: ixz_168

Synthesis of methyl 2-(bromomethyl)benzoate – 110

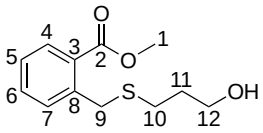


AIBN (0.105 g, 0.572 mmol) was added to a pale yellow suspension of methyl 2-methyl benzoate **109** (4.29 g, 2.86 mmol) and *N*-bromosuccinimide (5.56 g, 3.14 mmol) in anhydrous $CHCl_3$(95 mL) at RT. The resulting suspension was heated to 80 °C, whereupon a colour

changed to orange/yellow was noted. Upon further heating, the colour of the reaction changed to cherry red. After 18 h, the reaction deemed to have gone to completion by TLC. The reaction mixture was allowed to cool to RT, filtered and the filter cake was washed with cold $CHCl_3$ (30 mL). The resulting filtrate was concentrated under reduced pressure to yield a yellow oil (4.98 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane,10:90) to afford bromide **110** as a pale yellow oil (4.29 g, 65%); R_f = 0.43 (20:80, EtOAc:*n*–hexane); ^{1}H NMR data taken from J. Kim and J. Hong[286] ; δ_H (300 MHz; $CDCl_3$) 7.99 (1H, d, *J* = 7.9 Hz, C(3)H), 7.56–7.47 (2H, m, C(5)H), 7.43–7.36 (1H, m, C(6)H), 4.98 (2H, s, C(9)H), 3.97 (3H, s, C(1)H).

Lab notebook reference: ixz_021

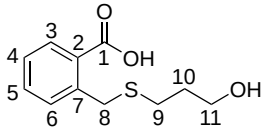
Synthesis of ethyl 2-{[(3-hydroxypropyl)sulfanyl]methyl}benzoate – **111**



K_2CO_3 (2.53 g, 18.3 mmol) was added to a pale yellow solution of 3-mercapto-1-propanol **97** (2.50 mL, 1.25 mmol) and methyl 2-bromomethylbenzoate **110** (4.29 g, 1.88 mmol) in anhydrous DMF (42 mL) at RT. The resulting milky/white suspension was then heated to 60 °C. After 20 h, the reaction was deemed to have gone to completion by TLC. The reaction mixture allowed to cool to RT, before was quenched with H_2O (30 mL). The milky/white suspension was poured into separating funnel and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed sequentially with H_2O (3 × 20 mL) and sat. brine (2 × 20 mL), before dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a yellow oil (4.21 g). The crude product was purified by flash column chromatography (SiO_2, 70 mm column, eluent: EtOAc:*n*–hexane, 60:40) to afford an alcohol **111** as a pale yellow oil (3.86 g, 86%); R_f = 0.25 (50:50, EtOAc:*n*–hexane); δ_H (400 MHz; $CDCl_3$) 7.90 (1H, dd, *J* = 7.7,1.5 Hz, C(4)H), 7.44 (2H, td, *J* = 7.7, 1.5 Hz, C(7)H), 7.40 – 7.24 (2H, m, C(6+5)H), 4.12 (2H, s, C(9)H_2), 3.90 (3H, s, C(1)H_3), 3.69 (2H, t, *J* = 6.1 Hz, C(12)H_2), 2.55 (2H, t, *J* = 7.0 Hz, C(10)H_2), 1.79 (2H, tt, *J* = 7.0, 6.1 Hz, C(11)H_2); HRMS (ESI): m/z calc. for $C_{12}H_{16}NaO_3S$: 263.0712, found: 263.0716 $[MNa]^+$.

Lab notebook reference: ixz_077

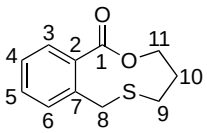
Synthesis of 2-(((3-hydroxypropyl)thio)methyl)benzoic acid – 112



2.5 M $NaOH_{(aq)}$ (16 mL) was added dropwise over a period of 2 min to solution of benzoate **111** (3.86 g, 1.61 mmol) in MeOH (16 mL). A colour change to pale yellow solution was immediately noted and the reaction mixture was stirred at RT for 24 h, at which point the reaction mixture was deemed to have gone to completion by TLC (complete consumption of benzoate **111** was noted). The reaction mixture was then acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (20 mL). The resulting white/off–white solid was collected by suction filtration and washed with H_2O (3 × 20 mL) and then air dried to yield a title compound **112** as a white solid (2.18 g, 60%, over two steps); R_f = 0.14 (10:90, MeOH:EtOAc); melting point: 110–112 °C (from CH_2Cl_2); IR (solid state) ν_{max}/cm^{-1}: 3495m (O–H alcohol), 3470m (O–H alcohol), 2950m (C–H alkyl, O–H carboxylic acid), 2643m (C–H alkyl, O–H carboxylic acid), 1674s (C=O carboxylic acid), 1597w (CC aromatic),1574s (CC aromatic), 1486m, 1435m, 1408s, 1301s (C–O), 1267s (C–O), 1197w, 1170w, 1140m, 1082m, 1055s, 1024m, 924s, 905m, 841w, 809w, 772s, 771s, 737m, 683m, 658s, 544s, 500m, 475w; δ_H (400 MHz; CD_3OD) 7.90 (1H, dd, *J* = 7.5 1.5 Hz, C(3)H), 7.45 (1H, app. td, *J* = 7.5, 1.5 Hz, C(5)H), 7.38 (1H, dd, *J* = 7.5, 1.5 Hz, C(6)H), 7.32 (1H, app. td, *J* = 7.5, 1.5 Hz, C(4)H), 4.14 (2H, s, C(8)H_2), 3.58 (2H, t, *J* = 6.3 Hz, C(11)H_2), 2.48 (2H, t, *J* = 7.4 Hz, C(9)H_2), 1.78 – 1.69 (2H, m, C(10)H_2); δ_C (101 MHz; CD_3OD) 170.9 (C, C1), 142.1 (C, C7), 132.7 (CH, C5), 132.2 (CH, C3), 132.2 (CH, C6), 131.5 (C, C2), 128.0 (CH, C4), 61.5 (CH_2, C11), 35.0 (CH_2, C8), 33.2 (CH_2, C10), 28.9 (CH_2, C9); HRMS (ESI): m/z calcd. for $C_{11}H_{14}NaO_3S$: 249.0556, found: 249.0558 $[MNa]^+$.

Lab notebook reference: ixz_080

Synthesis of 4,5-dihydro-3*H*-benzo[*g*][1,5]oxathionin-1(7*H*)-one – 113

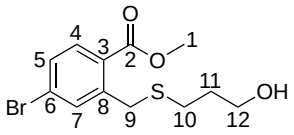


EDC.HCl (294 mg, 1.53 mmol) was added to solution of carboxylic acid **112** (223 mg, 0.988 mmol), HOBt (188 mg, 1.39 mmol) and dry DIPEA (500 µL, 5.21 mmol) in anhydrous DMF (10 mL). A colour change of the reaction mixture over 30 min from clear colorless to pale yellow. After total of 18 h of stirring at RT, the reaction deemed to have to completion by TLC. The resulting mixture was diluted with EtOAc (20 mL), before was transferred to separating funnel and the organic phase was washed sequentially with H_2O (3 × 20 mL) and sat. brine (2 × 20

mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a white solid (196 mg). The crude product was purified by flash column chromatography (SiO_2, 20 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford ester **113** as a white solid (178 mg, 86%); R_f = 0.56 (50:50, EtOAc:*n*–hexane); melting point: 163– 168 °C (from *n*–hexane); IR (solid state) ν_{max}/cm^{-1}: 2963w (C–H alkyl), 2916w (C–H alkyl), 1714s (C=O aryl ester), 1599m (CC aromatic), 1486w, 1452m, 1431m, 1423m, 1381m, 1350m, 1298s, 1268s, 1210m, 1195m, 1126s, 1088m, 1046m, 975s, 962m, 975s, 901w, 890w, 873w, 834w, 810w, 801w, 768s, 707s, 660m, 579m, 533w, 503w, 482m; δ_H (400 MHz; $CDCl_3$) 7.85 (1H, dd, *J* = 7.0, 2.0 Hz, C(3)H), 7.34 (2H, app. pd , *J* = 7.0, 2.0 Hz, C(4+5)H), 7.15 (1H, dd, *J* = 7.0, 2.0 Hz, C(6)H), 4.62 (2H, t, *J* = 5.9 Hz, C(11)H_2), 4.13 (2H, s, C(8)H_2), 2.90 – 2.86 (2H, m, C(9)H_2), 2.21 – 2.14 (2H, m, C(10)H_2); δ_C (101 MHz; $CDCl_3$) 168.2 (C, C1), 142.2 (C, C7), 131.7 (C, C2), 131.6 (CH, C5), 131.4 (CH, C3), 130.1 (CH, C6), 127.6 (CH, C4), 66.0 (CH_2, C11), 41.1 (CH_2, C8), 35.3 (CH_2, C9), 30.2 (CH_2, C10); HRMS (ESI): m/z calcd. for $C_{11}H_{13}O_2S$: 209.0631, found: 209.0631 $[MH]^+$, m/z calcd. for $C_{11}H_{12}NaO_2S$: 231.0450, found: 231.0448 $[MNa]^+$; X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2221211, was crystallised by slow cooling of *n*-hexane from RT to –20 °C).

Lab notebook reference: ixz_081

Synthesis of methyl 4-bromo-2-(((3-hydroxypropyl)thio)methyl)benzoate – 117

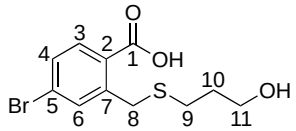


K_2CO_3 (538 mg, 3.89 mmol) was added to a solution of thiol **97** (170 µL, 2.00 mmol) and bromomethyl benzoate **116** (922 mg, 3.00 mmol) in anhydrous DMF (7 mL) at RT. The resulting pale yellow suspension was heated to 60 °C, whereupon a colour change to beige was noted. Upon further heating, the colour of the reaction suspension changed to yellow. After 18 h, the reaction was deemed to have gone to completion by TLC analysis. The reaction mixture was cooled to RT, before was quenched by addition of H_2O (10 mL). The quenched solution was poured into a separating funnel. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed sequentially with 1.0 M $HCl_{(aq)}$ (2 × 20 mL) and sat. brine (2 × 20 mL), before was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield orange oil (1.10 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 45:55) to afford an title compound **117** as pale yellow oil (812 mg, 86%); R_f = 0.33 (50:50, EtOAc:*n*–hexane); IR (thin

film) ν_{max} / cm^{-1}: 3379m (O–H alcohol), 2941m (C–H alkyl), 1716v (C=O aryl ester), 1586s (CC aromatic), 1561m (CC aromatic), 1477w (CC aromatic), 1433m, 1388w, 1260s, 1188m, 1127m, 1092s, 1073m, 963w, 867m, 836w, 809w, 781m, 753m, 723m, 693w, 593w, 560w, 489w; δ_H (400 MHz; $CDCl_3$) 7.78 (1H, d, *J* = 8.4 Hz, C(4)H), 7.53 (1H, d, *J* = 2.0 Hz, C(7)H), 7.45 (1H, dd, *J* = 8.4, 2.0 Hz, C(5)H), 4.08 (2H, s, C(9)H_2), 3.90 (3H, s, C(1)H_3), 3.72 (2H, t, *J* = 6.0 Hz, C(12)H_2), 2.57 (2H, t, *J* = 7.1 Hz, C(10)H_2), 1.81 (2H, tt, *J* = 7.1, 6.0 Hz, C(11)H_2); δ_C (101 MHz; $CDCl_3$) 167.2 (C, C2), 142.9 (C, C8), 133.9 (CH, C7), 132.7 (CH, C4), 130.3 (CH, C5), 128.3 (C, C3), 126.7 (C, C6), 61.5 (CH_2, C12), 52.4.0 (CH_3, C1), 34.3 (CH_2, C9), 31.8 (CH_2, C11), 28.6 (CH_2, C10); HRMS (ESI): m/z calcd. for $C_{12}H_{16}{}^{79}BrO_3S$: 318.9998, found: 318.9996 $[MH]^+$, m/z calcd. for $C_{12}H_{15}{}^{79}BrNaO_3S$: 340.9817, found: 340.9816 $[MNa]^+$.

Lab notebook reference: ixz_054

Synthesis of 4-bromo-2-(((3-hydroxypropyl)thio)methyl)benzoic acid – 118

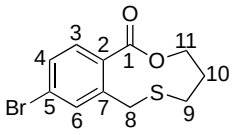


$NaOH_{(aq)}$ (4.0 M, 3.50 mL) was added dropwise over a period of 5 min to solution of alcohol **117** (666 mg, 2.08 mmol) in MeOH (3.50 mL). A colour change to pale yellow solution was noted immediately during dropwise addition. Upon further addition, the appearance of the reaction mixture changed from a cloudy pale yellow to a milky white suspension and finally to pale-yellow solution. The reaction mixture was stirred at RT for 16 h, before the reactions was deemed to have gone to completion by TLC (complete consumption of alcohol **117** was noted). The resulting pale-yellow solution was then acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (20 mL) at 0°C. The resulting white solid was collected by suction filtration and washed with cold H_2O (3 × 20 mL) and then dried under *vacuo* to yield a carboxylic acid **118** as a white solid (526 mg, 82%); R_f = 0.00 (50:50 Et_2O:*n*–hexane); melting point: 95 – 96 °C (from cyclohexane:CH_2Cl_2 + MeOH, 1:1 + 2%); IR (solid state) ν_{max} / cm^{-1}: 3368m (O–H alcohol), 2926m (C–H alkyl, O–H carboxylic acid), 2615m (C–H alkyl, O–H carboxylic acid), 2544m, 1684s (C=O aryl carboxylic acid), 1587m (CC aromatic), 1561s (CC aromatic), 1486m, 1410m, 1284m, 1272m, 1298m, 1254s, 1193m, 1139m, 1097m, 1069m, 1025m, 1010m, 917m, 894w, 871s, 847m, 837m, 785m, 769m, 676w, 551w, 474w, 461w; δ_H (400 MHz; CD_3OD) 7.81 (1H, d, *J* = 8.1 Hz, C(3)H), 7.60 (1H, d, *J* = 2.2 Hz, C(6)H), 7.50 (1H, dd, *J* = 8.1, 2.2 Hz, C(4)H), 4.12 (2H, s, C(8)H_2), 3.59 (2H, t, *J* = 6.2 Hz, C(11)H_2), 2.50 (2H, t, *J* = 7.3 Hz, C(9)H_2), 1.74 (2H, tt, *J* = 7.3, 6.2 Hz, C(10)H_2); δ_C (101 MHz; CD_3OD) 169.9 (C, C1) 144.8 (C, C7), 134.9 (CH, C6), 133.9 (CH, C3), 131.1 (CH, C4), 130.5 (CH, C6), 127.0 (C, C5), 61.5 (CH_2, C11), 34.6 (CH_2, C8) 33.3 (CH_2,

C10), 29.0 (CH_2, C9);HRMS (ESI): m/z calcd. for $C_{11}H_{14}{}^{79}BrO_3S$: 304.9842, found: 304.9831 $[MH]^+$, m/z calcd. for $C_{11}H_{13}{}^{79}BrNaO_3S$: 326.9661, found: 326.9649 $[MNa]^+$.

Lab notebook reference: ixz_060

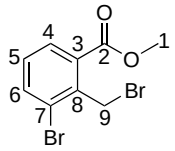
Synthesis of 9-bromo-4,5-dihydro-3*H*-benzo[*g*][1,5]oxathionin-1(7*H*)-one – 119



Dry DIPEA (280 µL, 1.61 mmol) was added dropwise over 1 min to solution of carboxylic acid **118** (196 mg, 0.642 mmol) and HOBt (108 mg, 0.799 mmol) in anhydrous DMF (6 mL). A colour change to pale yellow was noted. The resulting mixture was stirred for 5 min at RT, after which time EDC.HCl (185 mg, 0.963 mmol) was added and a colour change to pink/brown was observed. The resulting mixture was stirred at RT overnight under N_2 and progress of the reaction was monitored by TLC. After 18 h, the reaction was deemed to have gone to completion by TLC, with the reaction mixture changed to pale yellow colour. The resulting mixture was diluted with EtOAc (20 mL), before was transferred to separating funnel and organic phase was washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 20 mL), sat. $NaHCO_3$ (3 × 20 mL) and sat. brine (3 × 20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a white solid (302 mg). The crude product was purified by flash column chromatography (SiO_2, 15 mm column, eluent: EtOAc:*n*–hexane, 20:80) to afford title compound **119** as a white solid (150 mg, 81%); R_f = 0.64 (50:50 EtOAc:*n*–hexane);melting point: 129 – 130 °C (from *n*–hexane); IR (solid state)ν_{max}/cm^{-1}: 2940w (C–H alkyl), 2957w (C–H alkyl), 2915w (C–H alkyl), 1715s (C=O aryl ester), 1587s (CC aromatic), 1557m (CC aromatic),1477w (CC aromatic), 1455m, 1431w, 1423m,1393m, 1350w, 1280s, 1266s, 1213w, 1197w, 1121s, 1094s, 1038w, 977m, 900w, 888m, 868w, 843s, 814w, 792m, 776m, 717w, 695m, 682w, 639w, 594w, 559w, 517w, 499w; δ_H (400 MHz; $CDCl_3$) 7.71 (1H, d, *J* = 8.2 Hz, C(3)H), 7.47 (1H, dd, *J* = 8.2, 2.0 Hz, C(4)H), 7.33 (1H, d, *J* = 2.0 Hz, C(6)H), 4.62 (2H, br t, *J* = 6.5 Hz, C(11)H_2), 4.07 (2H, s, C(8)H_2), 2.91 – 2.84 (2H, m, C(9)H_2), 2.22 – 2.12 (2 H, m, C(10)H_2); δ_C (101 MHz; $CDCl_3$) 167.3 (C, C1) 144.2 (C, C7), 133.0 (CH, C6), 132.8 (CH, C3), 130.7 (C, C2), 130.6 (CH, C4), 126.0 (C, C5), 66.1 (CH_2, C11), 40.6 (CH_2, C8) 35.3 (CH_2, C9), 30.1 (CH_2, C10); HRMS (ESI): m/z calcd. for $C_{11}H_{12}{}^{79}BrO_2S$: 286.9736, found: 286.9729 $[MH]^+$, m/z calcd. for $C_{11}H_{11}{}^{79}BrNaO_2S$: 308.9555, found: 308.9549 $[MNa]^+$; X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2221214, was crystallized by slow cooling of *n*-hexane from RT to –20 °C).

Lab notebook reference: ixz_061

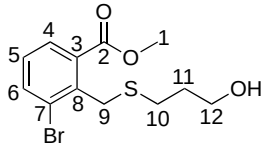
Synthesis of methyl 3-bromo-2-(bromomethyl)benzoate – 121



AIBN (78.1 mg, 0.355 mmol) was added to a yellow suspension of methyl 3-bromo-2-methylbenzoate **120** (812 mg, 3.55 mmol) and *N*-bromosuccinimide (870 mg, 4.61 mmol) in anhydrous benzene (12 mL, degasses for 15 min) at RT. The resulting suspension was heated to 90 °C, whereupon a colour changed to pale yellow was noted. After 18 h, the reaction deemed to have gone to completion by TLC. The resulting mixture was allowed to cool to RT, before concentrated under reduced pressure. The yellow solution was diluted with EtOAc (30 mL) and poured into separating funnel. The organic layer was washed sequentially with 1.0 M $HCl_{(aq)}$ (1 × 30 mL), sat. $NaHCO_3$ (1 × 30 mL), H_2O (1 × 30 mL) and sat. brine (1 × 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a pale yellow oil (1.44 g). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane,10:90) to afford title compound **121** as a pale yellow oil (1.05 g, 96%); R_f = 0.46 (20:80, EtAOc:*n*–hexane);IR (thin film)ν_{max}/cm^{-1}: 2951w (C–H alkyl), 1719s (C=O aryl ester), 1586w (CC aromatic), 1563w (CC aromatic), 1433m, 1290m, 1258s, 1221s, 1162w, 1111s, 1088m, 967m, 876m, 837w, 806m, 758s, 725m, 704m, 610s, 541w, 487w; δ_H (400 MHz; $CDCl_3$) 7.89 (1H, dd, *J* = 7.8, 1.5 Hz, C(4)H), 7.77 (1H, dd, *J* = 7.8, 1.5 Hz, C(6)H), 7.23 (1H, t, *J* = 7.8 Hz, C(5)H), 5.13 (2H, s, C(9)H_2), 3.96 (3H, s, C(1)H_3); δ_C (101 MHz; $CDCl_3$) 166.5 (C, C2), 138.0 (C, C8) 137.2 (CH, C6), 131.7 (C, C3), 130.5 (CH, C4), 129.6 (CH, C5), 127.2 (C, C7), 52.8 (CH_3, C1), 30.2 (CH_2,C9); HRMS (ESI): m/z calcd. for $C_9H_8{}^{79}Br_2NaO_2$: 328.8783, found: 328.8780 $[MNa]^+$.

Lab notebook reference: ixz_065

Synthesis of methyl 3-bromo-2-(((3-hydroxypropyl)thio)methyl)benzoate – 122

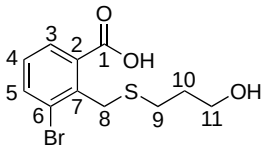


K_2CO_3 (511 mg, 3.14 mmol) was added to a pale yellow solution of thiol **97** (110 µL, 1.57 mmol) and bisbromide **121** (727 mg, 2.86 mmol) in anhydrous DMF (8 mL) at RT. The resulting suspension was then heated to 60 °C, whereupon a colour change to milky white was noted. Upon further heating, the colour of the reaction suspension changed to yellow. After 18 h, the

reaction was deemed to have gone to completion by TLC. The reaction mixture was cooled to RT, before diluted with EtOAc (30 mL). The diluted solution was poured into a separating funnel and the organic layer was washed sequentially with H_2O (1 × 20 mL), 1.0 M $HCl_{(aq)}$ (2 × 20 mL), sat. $NaHCO_{3(aq)}$ (1 × 20 mL) and sat. brine (2 × 20 mL), before dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield pale orange oil (800 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford title compound **122** as pale yellow oil (716 mg, 95%); R_f = 0.24 (60:40, EtOAc:*n*–hexane); IR (thin film) ν_{max} / cm^{-1}: 3418m (O–H alcohol), 2950w (C–H alkyl), 1720s (C=O aryl ester), 1587w (CC aromatic), 1561w (CC aromatic), 1432s, 1259s, 1224m, 1126m, 1090m, 1046m, 967m, 910m, 806w, 763m, 733s, 705s, 647w, 465w; δ_H (400 MHz; $CDCl_3$) 7.78 (1H, dd, *J* = 7.9, 1.4 Hz, C(4)H), 7.71 (1H, dd, *J* = 7.9, 1.4 Hz, C(6)H), 7.16 (1H, t, *J* = 7.9 Hz, C(5)H), 4.36 (2H, s, C(9)H_2), 3.92 (3H, s, C(1)H_3), 3.71 (2H, app. q, *J* = 6.9 Hz, C(12)H_2), 2.65 (2 H, t, *J* = 7.0 Hz, C(10)H_2), 1.88 – 1.79 (2 H, m, C(11)H_2), 1.64 (1H, br, s, OH); δ_C (101 MHz; $CDCl_3$) 167.6 (C, C2), 139.8 (C, C8), 136.5 (CH, C6), 132.3 (C, C3), 130.0 (CH, C4), 128.1 (CH, C5), 126.5 (C, C7), 61.5 (CH_2, C12), 52.7 (CH_3, C1), 33.2 (CH_2, C9), 32.1 (CH_2, C11), 29.0 (CH_2, C10); HRMS (ESI): m/z calcd. for $C_{12}H_{15}{}^{79}BrNaO_3S$: 340.9817, found: 340.9816 $[MNa]^+$.

Lab notebook reference: ixz_066

Synthesis of 3-bromo-2-(((3-hydroxypropyl)thio)methyl)benzoic acid – 123

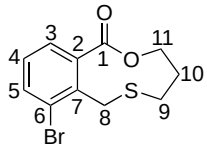


$NaOH_{(aq)}$ (4.0 M, 5.50 mL) was added dropwise over a period of 2 min to solution of alcohol **122** (344 mg, 1.08 mmol) in MeOH (5.50 mL). A colour change to milky white suspension was noted immediately during dropwise addition. Upon further addition, the appearance of the reaction mixture changed over 10 min from pale yellow to a clear colourless and finally cloudy white. The reaction mixture was stirred at RT for 16 h, after which the reaction was deemed to have gone to completion by TLC (complete consumption of alcohol **122** was noted) and was acidified to pH 2.0 by addition of 1.0 M $HCl_{(aq)}$ (20 mL). The acidified solution was poured into separating funnel and aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale-yellow viscous oil (444 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: MeOH:CH_2Cl_2, 10:90) to afford title compound **123** as a white solid (285 mg, 87%);R_f = 0.09 (5:95, MeOH:CH_2Cl_2 (10 mL) + 3

drops of AcOH);melting point: 72 – 75 °C (from MeOH:CH_2Cl_2,1:4); IR (solid state) ν_{max}/cm^{-1}: 3356m (O–H alcohol), 2958m (C–H alkyl, O–H carboxylic acid), 2925m (C–H alkyl, O–H carboxylic acid), 2881m (C–H alkyl), 2653m (C–H alkyl), 2536 (C–H alkyl), 1681s (C=O aryl carboxylic acid), 1585w (CC aromatic), 1560w (CC aromatic), 1444m, 1431m, 1403s, 1290m, 1266s, 1226m, 1186m, 1140m, 1123w, 1094w, 1069w, 1045w, 1027w, 940m, 906s, 840w, 807m, 761s, 742m, 685s, 650w, 612w, 575w, 509w, 499w, 463w; δ_H (400 MHz; $CDCl_3$) 7.90 (1H, dd, *J* = 7.9, 1.5 Hz, C(3)H), 7.75 (1H, dd, *J* = 7.9, 1.5 Hz, C(5)H), 7.17 (1H, t, *J* = 7.9 Hz, C(4)H), 6.30 (2H, br s, 2 × OH), 4.41 (2H, s, C(8)H_2), 3.77 (2H, t, *J* = 6.3 Hz, C(11)H_2), 2.68 (2H, t, *J* = 7.1 Hz, C(9)H_2), 1.89 (2H, app. Q, *J* = 6.3 Hz, C(10)H_2); δ_C (101 MHz; $CDCl_3$) 171.0 (C, C1), 140.2 (C, C7), 137.3 (CH, C5), 131.7 (CH, C2), 130.7 (CH, C3), 128.2 (CH, C4), 127.0 (C, C6), 61.7 (CH_2, C11), 33.2 (CH_2, C8), 31.9 (CH_2, C10), 29.1 (CH_2, C9); HRMS (ESI): m/z calcd. For $C_{11}H_{13}{}^{79}BrNaO_3S$: 326.9661, found: 326.9656 $[MNa]^+$.

Lab notebook reference: ixz_070

Synthesis of 8-bromo-4,5-dihydro-3*H*-benzo[*g*][*1,5*]oxathionin-1(7*H*)-one – 124

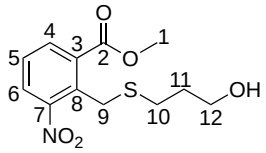


EDC.HCl (110 mg, 0.528 mmol) was added to solution of carboxylic acid **123** (108 mg, 0.352 mmol), HOBt (61.8 mg, 0.422 mmol) and anhydrous DIPEA (150 µL, 0.880 mmol) in anhydrous DMF (3.52 mL). An immediate colour change colour from pale yellow to pale pink. After total of 18 h of stirring at RT, the reaction deemed to have to completion by TLC, with colour change to dark brown noted. The resulting mixture was diluted with EtOAc (20 mL), before was transferred to separating funnel and the organic phase was washed sequentially with 1.0 M $HCl_{(aq)}$ (2 × 10 mL), sat. $NaHCO_{3(aq)}$ (3 × 20 mL), H_2O (2 × 20 mL) and sat. brine (2 × 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a white solid (129 mg). The crude product was purified by flash column chromatography (SiO_2, 20 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford title compound **124** as a white solid (67.3 mg, 67%); R_f = 0.55 (50:50, EtOAc:*n*–hexane); melting point: 80 – 82 °C (from CH_2Cl_2:$CHCl_3$, 1:1); IR (solid state) ν_{max}/cm^{-1}: 2961w (C–H alkyl), 2922w (C–H alkyl), 1713s (C=O aryl ester), 1588w (CC aromatic), 1660w (CC aromatic), 1447m, 1431m, 1383m, 1353w, 1278s, 1244m, 1212s, 1189w, 1132m, 1097m, 1077m, 1036w, 972s, 895w, 880m, 831w, 814s, 791w, 770s, 729w, 703s, 692m, 640w, 598w, 545w, 513w; δ_H (400 MHz; $CDCl_3$) 7.73 (1H, dd, *J* = 7.9, 1.5 Hz, C(3)H), 7.65 (1H, dd, *J* = 7.9, 1.5 Hz, C(5)H), 7.16 (1H, t, *J* = 7.9 Hz, C(4)H), 4.60 (2 H, t, *J* = 5.9 Hz, C(11)H_2), 4.41 (2H, s,

C(8)H_2), 2.93 – 2.86 (2 H, m, C(9)H_2), 2.23 – 2.16 (2H, m, C(10)H_2); δ_C (101 MHz; $CDCl_3$) 167.4 (C, C1), 140.7 (C, C7), 136.0 (CH, C5), 134.4 (C, C2), 130.3 (CH, C3), 128.4 (CH, C4), 125.1 (C, C6), 66.4 (CH_2, C11), 38.6 (CH_2, C8), 35.0 (CH_2, C9), 29.2 (CH_2, C10);HRMS (ESI): m/z calcd. for $C_{11}H_{12}{}^{79}BrO_2S$: 286.9736, found: 286.9734 $[MH]^+$, m/z calcd. for $C_{11}H_{11}{}^{79}BrNaO_2S$: 308.9555, found: 308.9556 $[MNa]^+$; X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2221221, was crystallised by slow cooling of *n*-hexane:EOAc from RT to –20 °C).

Lab notebook reference: ixz_074

Synthesis of methyl 2-(((3-hydroxypropyl)thio)methyl)-3-nitrobenzoate – 126

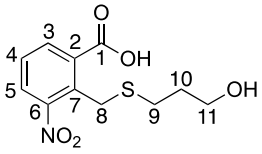


K_2CO_3 (369 mg, 2.31 mmol) was added to a pale-yellow solution of 3-mercaptopropan-1-ol **97** (90.0 µL, 1.27 mmol) and methyl 2-(bromomethyl)-3-nitrobenzoate **125** (317 mg, 1.16 mmol) in anhydrous DMF (4 mL) at RT. The resulting suspension was then heated to 70 °C, whereupon a colour change to orange/brown noted. After 16 h, the reaction was deemed to have gone to completion by TLC. The reaction mixture allowed to cool to RT and quenched by addition of H_2O (30 mL). The resulting milky white suspension was poured into separating funnel containing EtOAc (20 mL) and phases where separated. The pale yellow aqueous layer was extracted with EtOAc (3 × 20 mL), before the combined organic layers were washed sequentially with 1.0 M $HCl_{(aq)}$ (2 × 20 mL), sat. $NaHCO_{3(aq)}$ (2 × 20 mL), H_2O (2 × 20 mL) and sat. brine (2 × 20 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield brown oil (368 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford title compound **126** as pale yellow oil (246 mg, 74%); R_f = 0.26 (50:50, EtOAc:*n*–hexane); IR (thin film)ν_{max}/cm^{-1}: 3387m (O–H alcohol), 3086w (C–H alkenyl), 2952w (C–H alkyl), 2879w (C–H alkyl), 1722s (C=O aryl ester), 1604w (CC aromatic), 1575w (CC aromatic), 1529s (N–O aryl), 1434m, 1356s (N–O aryl), 1267s, 1196m, 1087w, 1047m, 981w, 904w, 863w, 823w, 801w, 770m, 722m, 704s, 590w, 525w, 487w; δ_H (400 MHz; $CDCl_3$) 7.98 (1H, dd, *J* = 8.0, 1.4 Hz, C(4)H), 7.84 (1H, dd, *J* = 8.0, 1.4 Hz, C(6)H), 7.44 (1 H, t, *J* = 8.0 Hz, C(5)H), 4.33 (2H, s, C(9)H_2), 3.95 (3H, s, C(1)H_3), 3.67 (2H, t, *J* = 6.1 Hz, C(12)H_2), 2.56 (2H, t, *J* = 7.1 Hz, C(10)H_2), 1.75 (2H, tt, *J* = 7.1, 6.1 Hz, C(11)H_2), 1.62 (1H, br s, OH); δ_C (101 MHz; $CDCl_3$) 167.1 (C, C2) 151.3 (C, C7), 135.0 (C, C8), 134.2 (CH, C4), 133.2 (C, C3),127.8 (CH, C6), 127.3 (CH, C5), 61.5 (CH_2, C12), 53.1 (CH_3, C1), 32.0 (CH_2, C11), 29.1 (CH_2, C10), 28.1 (CH_2,

C9); HRMS (ESI): m/z calcd. for $C_{12}H_{15}NNaO_5S$: 308.0563. Found: $[MNa]^+$, 308.0565 (−0.7 ppm error).

Lab notebook reference: ixz_084

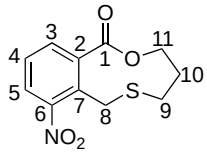
Synthesis of 2-(((3-hydroxypropyl)thio)methyl)-3-nitrobenzoic acid – 127



$NaOH_{(aq)}$ (6.0 M, 6.50 mL) was added dropwise over a period of 3 min to solution of nitro alcohol **126** (490 mg, 1.53 mmol) in MeOH (6.50 mL). A colour change to milky white suspension was noted immediately during dropwise addition. The resulting suspension stirred at RT for a total of 16 h, whereupon a colour change from pale yellow to fluorescent yellow was observed. After that time the reaction was deemed to have gone to completion by TLC analysis (complete consumption of alcohol **126** was noted). The reaction mixture was acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (20 mL). The acidified cloudy/white suspension was poured into separating funnel and aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL), before combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an orange oil (202 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: MeOH:CH_2Cl_2, 5:95) to afford carboxylic acid **127** as a white solid (88.1 mg, 50%); R_f = 0.28 (10:90, MeOH:CH_2Cl_2, (10 mL) + 3 drops of AcOH); δ_H (400 MHz; CD_3OD) 7.81–7.71 (2H, m, C(3+5)H), 7.44 – 7.35 (1H, m, C(4)H), 4.38 (2H d, J = 4.6 Hz, C(8)H_2), 3.53 (2H, t, J = 5.8 Hz, C(11)H_2), 2.54 – 2.45 (2H, m, C(9)H_2), 1.74 – 1.61 (2H, m, C(10)H_2); δ_C (101 MHz; CD_3OD) 176.1 (C, C1), 151.9 (C, C6), 143.9 (C, C2), 133.0 (CH, C3), 132.9 (C, C7), 128.4 (CH, C4), 125.7 (CH, C5), 61.6 (CH_2, C11), 33.5 (CH_2, C10), 29.6 (CH_2, C9), 29.4 (CH_2, C8); HRMS (ESI): m/z calcd. for $C_{11}H_{12}NO_5S$: 270.0442, found: 270.0441 [M−H]−, m/z calcd. for $C_{11}H_{11}NaNO_5S$: 292.0261, found: 292.0276 [MNa−2H]−.

Lab notebook reference: ixz_457

Synthesis of 8-nitro-4,5-dihydro-3*H*-benzo[*g*][1,5]oxathionin-1(7*H*)-one – 128

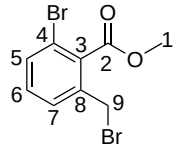


EDC.HCl (246 mg, 0.487 mmol) was added to a fluorescent green solution of carboxylic acid **127** (88.1 mg, 0.325 mmol), HOBt (63.6 mg, 0.390 mmol) and anhydrous DIPEA (140 µL,

0.813 mmol) in anhydrous DMF (3 mL) at RT. A colour change to pale yellow was noted immediately upon addition of DIPEA via syringe over a period of 30 sec. The resulting pale brown solution mixture was stirred for 18 h under Ar, after which time the reaction was deemed to have gone completion by TLC, with a colour change back to pale yellow was noted. The reaction mixture was diluted with EtOAc (20 mL) and was transferred separating funnel. The resulting organic layer was washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 20 mL), sat. $NaHCO_3$ (3 × 20 mL), H_2O (3 × 20 mL) and sat. brine (3 × 20 mL), before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale-yellow oil (183 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 30:70) to afford nitro ester **128** as a white solid (38.9 mg, 47%); R_f = 0.51 (50:50, EtOAc:*n*–hexane); melting point: 110–112 °C (from CH_2Cl_2); IR (solid state) ν_{max}/cm^{-1}: 2961w (C–H alkyl), 2917w (C–H alkyl), 1720s (C=O aryl ester), 1605w (CC aromatic), 1572w (CC aromatic), 1525s (N–O stretch), 1460m, 1432w, 1352s (N–O stretch), 1289s, 1213m, 1117s, 1082m, 1041w, 975w, 919w, 885w, 844w, 822w, 789w, 749s, 721m, 702s, 667w, 648w, 592w, 486w; δ_H (400 MHz; $CDCl_3$) 8.00 (1H, dd, *J* = 7.9, 1.5 Hz, C(3)H), 7.76 (1H, t, *J* = 7.9, 1.5 Hz, C(5)H), 7.45 (1H, dd, *J* = 7.9 Hz, C(4)H), 4.66 (2H, t, *J* = 5.9 Hz, C(11)H_2), 4.22 (2H, s, C(8)H_2), 2.95 – 2.88 (2H, m, C(9)H_2), 2.27 – 2.16 (2H, m, C(10)H_2);δ_C (101 MHz; $CDCl_3$) 166.4 (C, C1), 151.1 (C, C6), 135.7 (C, C7), 134.9 (C, C2), 134.6 (CH, C3), 128.0 (CH, C4), 126.4 (CH, C5), 66.7 (CH_2, C11), 35.2 (CH_2, C9),33.4 (CH_2, C8), 29.1 (CH_2, C10); HRMS (ESI): m/z calcd. for $C_{11}H_{12}NO_4S$: 254.0482, found: 254.0480 $[MH]^+$, m/z calcd. for $C_{11}H_{12}NNaO_4S$: 276.0301, found: 276.0299 $[MNa]^+$.

Lab notebook reference: ixz_464

Synthesis of methyl 2-bromo-6-(bromomethyl)benzoate – 130

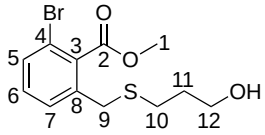


Ph_2O_2 (108 mg, 0.758 mmol) was added to a yellow suspension of *N*-bromosuccinimide (0.85 mg, 4.55 mmol) and 2-bromo-6-methyl benzoate **129** (0.869 mg, 3.79 mmol) in degassed (for 10 min) anhydrous benzene (19 mL). The resulting sunflower yellow suspension was then heated to 95 °C, whereupon a colour change to pale yellow suspension was noted. After 20 h, the reaction wasn't deemed to have gone to completion by TLC analysis (consumption of starting material wasn't observed). The reaction mixture was allowed to cool to RT, before concentrated under reduced pressure and diluted with EtOAc (30 mL). The diluted mixture was poured into a separating funnel, where organic phase was washed sequentially with 1.0

M $HCl_{(aq)}$ (3 × 20 mL), sat. $NaHCO_{3(aq)}$ (1 × 10 mL) and sat. brine (3 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale–yellow oil (1.40 g). The crude product was purified by flash column chromatography (SiO_2, 60 mm column, eluent: EtOAc:*n*–hexane, 10:90) to afford title compound **130** as colourless oil (752 mg, 65%); R_f = 0.40 (20:80 EtOAc:*n*–hexane); IR (thin film)ν_{max}/cm^{-1}: 2951w (C–H alkyl), 1728s (C=O aryl ester), 1592w (CC aromatic), 1565w (CC aromatic), 1443m (CC aromatic), 1428m, 1278s, 1214m, 1182m, 1154w, 1116m, 1102m, 1058m, 953w, 888m, 855w, 826w, 790m, 769w, 730m, 698m, 627m, 576m, 557w, 490w; δ_H (400 MHz; $CDCl_3$) 7.54 (1H, dd, *J* = 7.8, 1.1 Hz, C(5)H), 7.38 (1H, dd, *J* = 7.8, 1.1 Hz, C(7)H), 7.26 (1H, t, *J* = 7.8 Hz, C(6)H), 4.48 (2H, s, $C(9)H_2$), 4.00 (3H, s, $C(1)H_3$); δ_C (101 MHz; $CDCl_3$) 167.2 (C, C2), 137.1 (C, C4), 135.4 (C, C3), 132.9 (CH, C5), 131.1 (CH, C6), 129.1 (CH, C7), 120.1 (C, C8), 52.8 (CH_3, C1), 29.6 (CH_2, C9);HRMS (ESI): m/z calcd. for $C_9H_8{}^{79}Br_2NaO_2$: 328.8783, found: 328.8785 $[MNa]^+$.

Lab notebook reference: ixz_109

Synthesis of methyl 2-bromo-6-(((3-hydroxypropyl)thio)methyl)benzoate – 131

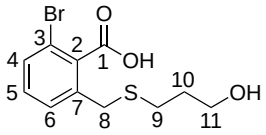


K_2CO_3 (424 mg, 2.46 mmol) was added to a pale yellow solution of thiol **97** (110 µL, 1.23 mmol) and methyl 2-bromo-6-(bromomethyl)benzoate **130** (493 mg, 1.60 mmol) in anhydrous DMF (12 mL) at RT. The resulting suspension was then heated to 70 °C, whereupon a colour change to milky/white suspension was noted. Upon further heating, the colour of the reaction suspension changed to cloudy white. After 16 h, the reaction was deemed to have gone to completion by TLC, with a colour change to sunflower yellow was observed. The mixture allowed to cool to RT and quenched by addition of H_2O (30 mL). The resulting milky white suspension was poured into separating funnel containing EtOAc (20 mL) and aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed sequentially with 1.0 M $HCl_{(aq)}$ (2 × 20 mL), sat. $NaHCO_{3(aq)}$ (2 × 20 mL), H_2O (2 × 20 mL) and sat. brine (2 × 20 mL), before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield brown oil (622 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford title compound **131** as pale yellow oil (490 mg, 96%); R_f = 0.32 (50:50, EtOAc:*n*–hexane);IR (thin film) ν_{max} /cm^{-1}: 3393m (O–H alcohol), 2949m (C–H alkyl), 2878rm (C–H alkyl) 1726s (C=O aryl ester), 1591w (CC aromatic), 1562w (CC aromatic), 1440m, 1428m, 1280s, 1184w, 1134m, 1102m, 1058s,

954w, 914w, 884w, 826w, 793w, 750w, 729m, 696w, 595w, 666w, 562w, 487w; δ_H (400 MHz; $CDCl_3$) 7.48 (1H, dd, *J* = 7.9, 1.1 Hz, C(5)H), 7.35 (1H, d, *J* = 7.9 Hz, C(7)H), 7.22 (1H, t, *J* = 7.9 Hz, C(6)H), 3.96 (3H, s, $C(1)H_3$), 3.74 (2H, s, $C(9)H_2$), 3.69 (2H, app. q, *J* = 5.5 Hz, $C(12)H_2$), 2.52 (2H, t, *J* = 7.1 Hz, $C(10)H_2$), 1.83 – 1.72 (2H, m, $C(11)H_2$); δ_C (101 MHz; $CDCl_3$) 168.1 (C, C2), 138.4 (C, C4), 135.3 (C, C8), 131.6 (CH, C5), 130.8 (CH, C6), 128.8 (CH, C7), 119.9 (C, C3), 61.4 (CH_2, C12), 52.7 (CH_3, C1), 34.0 (CH_2, C11), 28.2 (CH_2, C10); HRMS (ESI): m/z calcd. for $C_{12}H_{16}{}^{79}BrO_3S$: 318.9998, found: 318.9995 $[MH]^+$, m/z calcd. for $C_{12}H_{15}{}^{79}BrNaO_3S$: 340.9817, found: 340.9815 $[MNa]^+$.

Lab notebook reference: ixz_092

Synthesis of 2-bromo-6-(((3-hydroxypropyl)thio)methyl)benzoic acid – 132

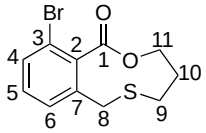


$NaOH_{(aq)}$ (4.0 M, 7.50 mL) was added dropwise over a period of 3 min to solution of alcohol **131** (490 mg, 1.53 mmol) in MeOH (7.50 mL). A colour change to milky white suspension was noted immediately during dropwise addition. The resulting suspension was then heated to 60 °C, whereupon a colour change to clear solution was noted. After 16 h, the reaction was deemed to have gone to completion by TLC analysis (complete consumption of alcohol **131** was noted). The reaction mixture was allowed to cool to RT and acidified to pH 2.0 by addition of 1.0 M $HCl_{(aq)}$ (20 mL). The acidified solution was poured into separating funnel and aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a colourless oil (666 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: MeOH:CH_2Cl_2, 10:90) to afford title compound **132** as a white solid (393 mg, 84%); R_f = 0.48 (20:80, MeOH:CH_2Cl_2, (10 mL) + 3 drops of AcOH); IR (solid state) ν_{max}/cm^{-1}: 3301m (OH alcohol, OH carboxylic acid), 2929m (OH carboxylic acid), 2618w (C–H alkyl, O–H carboxylic acid), 2496v (O–H carboxylic acid), 1695s (C=O aryl carboxylic acid), 1561s (CC aromatic), 1439s (CC aromatic), 1391m, 1274m, 1181w, 1144w, 1108w, 1040m, 911w, 751w, 678w, 597w, 575w; δ_H (400 MHz; $CDCl_3$) 7.47 (1H, dd, *J* = 7.9, 1.1 Hz, C(4)H), 7.36 (1H, dd, *J* = 7.9, 1.1 Hz, C(6)H), 7.21 (1H, t, *J* = 7.9 Hz, C(5)H), 6.70 (1H, br s, OH), 3.81 (2H, s, $C(8)H_2$), 3.74 (2H, t, *J* = 6.5 Hz, $C(11)H_2$), 2.54 (2H, t, *J* = 7.0 Hz, $C(9)H_2$), 1.81 (2H, app. q, *J* = 6.5 Hz, $C(10)H_2$); δ_C (101 MHz; $CDCl_3$) 173.3 (C, C1) 138.6 (C, C3), 137.3 (CH, C7), 131.3 (CH, C4), 129.9 (CH, C5), 129.0 (CH, C6), 118.7 (C, C2), 61.7 (CH_2, C11), 34.0 (CH_2, C8) 31.5 (CH_2,

C10), 28.6 (CH_2, C9); HRMS (ESI): m/z calcd. for $C_{11}H_{13}{}^{79}BrNaO_3S$: 326.9661, found: 326.9664 $[MNa]^+$.

Lab notebook reference: ixz_097

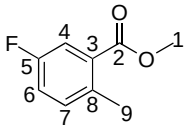
Synthesis of 11-bromo-4,5-dihydro-3*H*-benzo[*g*][1,5]oxathionin-1(7*H*)-one – 133



EDC.HCl (462 mg, 2.09 mmol) was added to solution of carboxylic acid **132** (355 mg, 1.16 mmol), HOBt (239 mg, 1.74 mmol) and anhydrous DIPEA (510 µL, 2.91 mmol) in anhydrous DMF (12 mL). An immediate colour change colour to pale yellow observed. After total of 16 h of stirring at RT, the reaction deemed to have to completion by TLC analysis with colour change to brown noted. The resulting mixture was diluted with EtOAc (30 mL). The milky white suspension was poured into separating funnel and the organic phase was washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 10 mL), sat. $NaHCO_{3(aq)}$ (3 × 20 mL), H_2O (3 × 20 mL) and sat. brine (3 × 20 mL). The resulting organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a yellow oil (594 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford ester **133** as a white solid (163 mg, 36%); R_f = 0.52 (50:50, EtOAc:*n*–hexane); IR (solid state) ν_{max}/ cm^{-1}: 2950w (C–H alkyl), 1729s (C=O aryl ester), 1588w (CC aromatic), 1453w, 1440w, 1429w, 1415w, 1284m, 1254s, 1217m, 1198w, 1178w, 1106m, 1071w, 1062m, 1045m, 967m, 867w, 831w, 787m, 770m, 724m, 698m, 637w, 500w; δ_H (400 MHz; $CDCl_3$) 7.54 (1H, dd, *J* = 7.9, 1.3 HZ, C(4)H), 7.16 (1H, t, *J* = 7.9 Hz, C(5)H), 7.10 (1H, dd, *J* = 7.9, 1.3 Hz, C(6)H), 4.59 (2H, t, *J* = 5.8 Hz, C(11)H_2), 4.00 (2H, s, C(8)H_2), 2.92 – 2.85 (2H, m, C(9)H_2), 2.23 (2H, app. p, *J* = 5.8 Hz, C(10)H_2); δ_C (101 MHz; $CDCl_3$) 166.0 (C, C1), 142.1 (C, C7), 133.4 (C, C3), 132.8 (CH, C5), 131.2 (CH, C4), 128.8 (CH, C6), 122.1 (C, C3), 66.8 (CH_2, C11), 40.7 (CH_2, C8), 35.2 (CH_2, C9), 28.7 (CH_2, C10); HRMS (ESI): m/z calcd. for $C_{11}H_{12}{}^{79}BrO_2S$: 286.9736, found: 286.9738 $[MH]^+$, m/z calcd. for $C_{11}H_{11}{}^{79}BrNaO_2S$: 308.9555, found: 308.9558 $[MNa]^+$; X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2221227).

Lab notebook reference: ixz_118

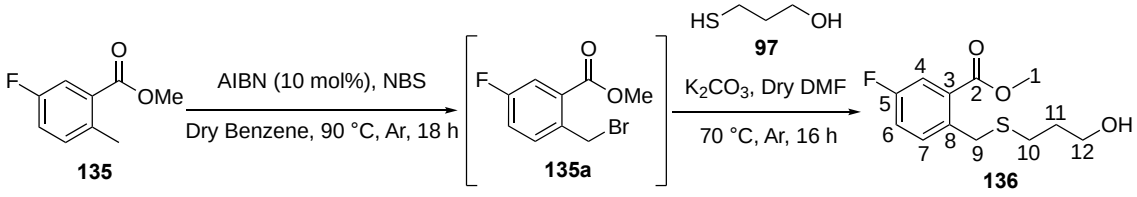
Synthesis of 5-fluoro-2-methylbenzoic acid methyl ester – 135



MeI (550 µL, 8.51 mmol) was added to a suspension of 5-fluoro-2-methylbenzoic acid **134** (1.01 g, 6.55 mmol) and K_2CO_3 (1.54 g, 9.83 mmol) in anhydrous acetone (65 mL). The resulting pale-yellow solution was stirred at RT for 16 h, after which time the reaction was deemed to have gone to completion by TLC. The reaction mixture was evaporated to dryness, before diluted with 30 mL of EtOAc and poured into separating funnel. The organic layer was washed sequentially with H_2O (3 × 30 mL), sat. $Na_2S_2O_{3(aq)}$ (3 × 30 mL) and sat. brine (1 × 30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a brown oil (1.11 g). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane, 5:95) to afford title compound **135** as clear oil (822 mg, 75%); R_f = 0.61 (20:80 EtOAc:*n*–hexane); IR (thin film) ν_{max} / cm^{-1}: 2954w (C–H alkyl), 1726s (C=O aryl ester), 1615w (CC aromatic), 1583w (CC aromatic), 1496s (CC aromatic), 1436s, 1409w, 1385w, 1301m, 1256s, 1209s, 1182s, 1134w, 1071m, 1038w, 1008w, 978w, 889w, 818m, 797m, 785m, 748m, 679w, 551w, 508w, 464w; δ_H (400 MHz; $CDCl_3$) 7.61 (1H, dd, *J* = 9.4, 2.9 Hz, C(4)H), 7.20 (1H, dd, *J* = 8.3, 5.6 Hz, C(6)H), 7.10 (1H, td, *J* = 8.3, 2.9 Hz, C(7)H), 3.90 (3H, s, C(1)H_3), 2.56 (3H, s, C(9)H_3); δ_C (101 MHz; $CDCl_3$) 166.9 (d, *J* = 2.9 Hz, C, C2), 160.6 (d, *J* = 244.0 Hz, C, C5), 136.0 (d, *J* = 3.3 Hz, C, C8), 133.2 (d, *J* = 7.2 Hz, C, C7), 130.8 (d, *J* = 7.1 Hz, CH, C3), 119.0 (d, *J* = 21 Hz, CH, C6), 117.3 (d, *J* = 23.0 Hz, CH, C4), 52.1 (CH_3, C1), 21.0 (CH_3, C9); δ_F (376 MHz; $CDCl_3$) −117.1 (td, *J* = 8.7, 5.8 Hz, C(5)F); HRMS (APCI): m/z calcd. for $C_9H_{10}FO_2$: 169.065934, found: 169.066541 $[MH]^+$.

Lab notebook reference: ixz_064

Synthesis of methyl 5-fluoro-2-(((3-hydroxypropyl)thio)methyl)benzoate – 136



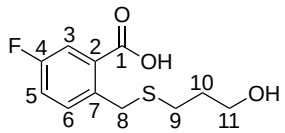
135 **135a** **136**

AIBN (46.7 mg, 0.287mmol) was added to a sunflower yellow suspension of methyl ester **135** (483 mg, 2.87 mmol) and *N*-bromosuccinimide (665 mg, 3.73 mmol) in anhydrous benzene (25 mL) at RT. The resulting suspension was heated to 90 °C, whereupon a colour changed to pale yellow was noted. After 18 h, the reaction wasn't deemed to have gone to completion by TLC analysis (consumption of stating material wasn't observed). The reaction mixture

allowed to cool to RT and evaporated to dryness, before diluted with 30 mL of EtOAc. The diluted mixture was transferred to separating funnel, where organic layer was washed sequentially with 1.0 M $HCl_{(aq)}$ (2 × 30 mL), sat. $NaHCO_{3(aq)}$ (2 × 20 mL) and sat. brine (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford bromide as orange oil (854 mg). The bromide **135a** was directly used in the next reaction step without further purification. Next, K_2CO_3 (651 mg, 3.83 mmol) was added to a yellow solution of **97** (110 µL, 1.91 mmol) and bromide **135a** (709 mg, 2.87 mmol) in anhydrous DMF (10 mL) at RT. The resulting suspension was then heated to 70 °C, whereupon a colour change to pale yellow was noted. Upon further heating, the colour of the reaction suspension changed to dark brown. After 16 h, the reaction was deemed to have gone to completion by TLC. The reaction mixture was cooled to RT, before diluted with EtOAc (30 mL). The diluted solution was poured into a separating funnel and the organic layer was washed sequentially with H_2O (1 × 30 mL), 1.0 M $HCl_{(aq)}$ (3 × 20 mL), sat. $NaHCO_{3(aq)}$ (3 × 20 mL) and sat. brine (2 × 20 mL), before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield brown oil (850 mg). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford title compound **136** as pale yellow oil (600 mg, 81%, over two steps); R_f = 0.32 (20:80, EtOAc:*n*-hexane);IR (thin film)ν_{max}/cm^{-1}:3425m(OH alcohol), 2952w (CH alkyl), 1724s (C=O aryl ester), 1611w (CC aromatic), 1583w (CC aromatic), 1495m (CC aromatic), 1436m, 1374w, 1308w, 1268s, 1241m, 1209s, 1183m, 1124w, 1066m, 1045m, 983m, 911w, 8334w, 793w, 772w, 722w, 676w, 635w, 608w, 481w; δ_H (400 MHz; $CDCl_3$) 7.61 (1H, dd, *J* = 9.4, 2.9 Hz, C(4)H), 7.33 (1H, dd, *J* = 8.3, 5.5 Hz, C(7)H), 7.15 (1H, td, *J* = 8.3, 2.9 Hz, C(6)H), 4.10 (2H, s, $C(9)H_2$), 3.91 (3H, s, $C(1)H_3$), 3.71 (2H, t, *J* = 6.2 Hz, $C(12)H_2$), 2.55 (2H, t, *J* = 7.1 Hz, $C(10)H_2$),1.84–1.77 (2H, m, $C(11)H_2$); δ_F (376 MHz; $CDCl_3$) −114.4 (q, *J* = 7.6 Hz, C(5)F); δ_C (101 MHz; $CDCl_3$) 166.7 (d, *J* = 2.7 Hz, C, C2), 161.2 (d, *J* = 247.0 Hz, C, C5), 136.5 (d, *J* = 3.7 Hz, C, C8), 132.7 (d, *J* = 7.6 Hz, CH, C7), 131.0 (d, *J* = 7.4 Hz, CH, C3), 118.8 (d, *J* = 21.1 Hz, CH, C6), 118.0 (d, *J* = 23.2 Hz, CH, C4), 61.4 (CH_2, C12), 52.4 (CH_3, C1), 33.8 (CH_2, C9), 31.80 (CH_2, C11), 28.4 (CH_2, C10); HRMS (ESI): m/z calcd. for $C_{12}H_{15}FNaO_3S$: 281.0618 found: 281.0614 $[MNa]^+$.

Lab notebook reference: ixz_072

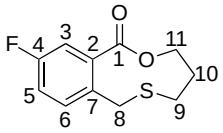
Synthesis of 5-fluoro-2-(3-hydroxypropylsulfanylmethyl)benzoic acid – 137



$NaOH_{(aq)}$ (4.0 M, 4.50 mL) was added dropwise over a period of 2 min to solution of alcohol **136** (241 mg, 1.01 mmol) in MeOH (3.50 mL). A colour change to yellow solution was noted immediately during dropwise addition. Upon further addition, the appearance of the reaction mixture changed to pale yellow. The reaction mixture was stirred at RT for 16 h, before the reactions was deemed to have gone to completion by TLC (complete consumption of alcohol **136** was noted). The resulting solution was then acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (20 mL) and transferred to separating funnel. The aqueous layer was extracted with CH_2Cl_2 (3× 30 mL), the combined organic phases were dried over $MgSO_4$, filtered and concerted under reduced pressure to yield a crude product as pale yellow oil (265 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: MeOH:CH_2Cl_2, 10:90) to afford title compound **137** as a white solid (200 mg, 88%); R_f = 0.23 (10:90, MeOH:CH_2Cl_2, (10 mL) + 3 drops of AcOH); melting point: 80–83 °C; IR (solid state) ν_{max}/cm^{-1}: 3473m (O–H alcohol), 2926m C–H alkyl, O–H carboxylic acid), 2923w (O–H carboxylic acid), 2793m (C–H alkyl, O–H carboxylic acid), 2565m (C–H alkyl, O–H carboxylic acid),1698s (C=O aryl carboxylic acid), 1603w (CC aromatic), 1584m (CC aromatic), 1494m (CC aromatic), 1429w, 1417w, 1402w, 1382w, 1335w, 1308m, 1291m, 1259s, 1215s, 1182s, 1065w, 1037m, 1007s, 938m, 890m, 877m, 813w, 799w, 782w, 752m, 721w, 689w, 666w; δ_H (400 MHz; CD_3OD) 7.58 (1H, dd, *J* = 9.4, 2.9 Hz, C(3)H), 7.41 (1H, td, *J* = 8.5, 5.5 Hz, C(5)H), 7.20 (1H, td, *J* = 8.5, 2.9 Hz, C(6)H), 4.13 (2H, s, C(8)H_2), 3.58 (2H, t, *J* = 6.3 Hz , C(11)H_2), 2.49 (2H, t, *J* = 7.3 Hz, C(9)H_2), 1.74 (2H, app. p, *J* = 6.3 Hz, C(10)H_2); δ_C (101 MHz; CD_3OD) 170.0 (C, C1), 162.6 (d, *J* = 245.2 Hz, C, C4), 138.0 (d, *J* = 3.5 Hz, C, C7), 134.0 (d, *J* = 7.7 Hz , CH, C6, C, C2, overlapping peaks), 119.1 (d, *J* = 21.4 Hz, CH, C5), 118.5 (d, *J* = 23.4 Hz, CH, C3), 61.5 (CH_2, C11), 34.2 (CH_2, C8), 33.3 (CH_2, C10), 28.9 (CH_2, C9); δ_F (376 MHz; $CDCl_3$) – 116.74 (td, *J* = 10.5, 9.3, 3.4 Hz, C(4)F); HRMS (ESI): m/z calcd. for $C_{11}H_{13}FNaO_3S$: 267.0462 found: 267.0461 $[MNa]^+$.

Lab notebook reference: ixz_470

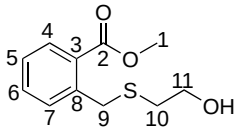
Synthesis of 10-fluoro-4,5-dihydro-3*H*-benzo[*g*][1,5]oxathionin-1(7*H*)-one – 138



Dry DIPEA (260 µL, 1.49 mmol) was added dropwise over 3 min to pale yellow solution of carboxylic acid **137** (146 mg, 0.596 mmol) and HOBt (96.5 mg, 0.715 mmol) in anhydrous DMF (6 mL). A colour change to yellow was noted immediately. The resulting mixture was stirred for 2 min at RT, after which time EDC.HCl (173 mg, 0.895 mmol) was added in equal portion and the resulting mixture stirred at RT. After 18 h, the reaction was deemed to have gone to completion by TLC. The resulting mixture was diluted with EtOAc (20 mL), before was transferred to separating funnel and organic phase was washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 20 mL), sat. $NaHCO_3$ (3 × 20 mL) and sat. brine (3 × 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale yellow solid (144 mg). The crude product was purified by flash column chromatography (SiO_2, 20 mm column, eluent: EtOAc:*n*–hexane, 30:70) to afford title compound **138** as a white solid (108 mg, 80%); R_f = 0.65 (50:50 EtOAc:*n*–hexane); melting point: 106–107 °C (from *n*–hexane);IR (solid state) ν_{max}/cm^{-1}: 2992w (C–H alkyl), 2962w (C–H alkyl), 2924w (C–H alkyl), 1710s (C=O aryl ester), 1673w (CC aromatic), 1605m (CC aromatic), 1585m (CC aromatic), 1495m (CC aromatic), 1453m, 1428s, 1380w, 1350w, 1306m, 1271s, 1232m, 1218s, 1196m, 1152w, 1134m, 1126s, 1076m, 1063m, 1045m, 965s, 932m, 886s, 879s, 835m, 817m, 797s, 777m, 762w, 717s, 693m, 672m, 637m, 579s, 525s, 504w, 477s; δ_H (400 MHz; $CDCl_3$) 7.54 (1H, dd, *J* = 8.4, 2.8 Hz, C(3)H), 7.12 (1H, dd, *J* = 8.4, 5.3 Hz, C(5)H), 7.04 (1H, td, *J* = 8.4, 2.8 Hz, C(6)H), 4.63 (2H, t, br, *J* = 5.9 Hz, C(11)H_2), 4.09 (2H, s, C(8)H_2), 2.89 – 2.85 (2H, m, C(9)H_2), 2.21 – 2.14 (2H, m, C(10)H_2); δ_C (101 MHz; $CDCl_3$) 166.7 (d, *J* = 2.8 Hz, C, C1), 161.5 (d, *J* = 247.3 Hz, C, C4), 138.0 (d, *J* = 3.4 Hz, C, C7), 133.5 (d, *J* = 7.6 Hz, C, C2), 131.5 (d, *J* = 7.6 Hz, CH, C6), 118.0 (d, *J* = 15.1 Hz, CH, C5), 117.79 (d, *J* = 12.8 Hz, CH, C3), 66.0 (CH_2,C11), 40.1 (CH_2,C8), 34.9 (CH_2,C9), 29.8 (CH_2,C10); δ_F (376 MHz; $CDCl_3$) – 114.4 (td, *J* = 8.4, 5.3 Hz, C(4)F); HRMS (ESI): m/z calcd. for $C_{11}H_{11}FNaO_2S$: 249.0356 found: 249.0359 $[MNa]^+$. X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2221239, was crystallised by slow cooling of *n*-hexane from RT to –20 °C).

Lab notebook reference: ixz_082

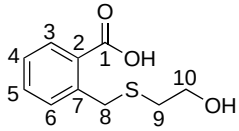
Synthesis of methyl 2-(((2-hydroxyethyl)thio)methyl)benzoate – 140



K_2CO_3 (1.26 g, 8.60 mmol) was added to pale yellow solution of thiol **139** (300 µL, 4.30 mmol) and bromide **110** (1.53 g, 6.45mmol) in anhydrous DMF (14 mL) at RT. The resulting turquoise suspension was then heated to 70 °C, whereupon a colour change to grey purple was noted. After 12 h, the reaction was deemed to have gone to completion by TLC analysis. The reaction mixture was allowed to cool to RT and quenched by addition of H_2O (30 mL). The diluted milky/white reaction mixture was transferred into separating funnel containing EtOAc (30 mL) and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 10 mL), sat. $NaHCO_{3(aq)}$ (1 × 20 mL) and sat. brine (2 × 20 mL), before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield pale yellow oil (2.80 g). The crude product was purified by flash column chromatography (SiO_2, 60 mm column, eluent: EtOAc:*n*–hexane, 40:60) to afford title compound as pale yellow oil (1.32 g, 90%); R_f = 0.29 (50:50 EtOAc:*n*–hexane); IR (thin film) ν_{max}/cm^{-1}: 3410m (O–H alcohol), 2999w (C–H alkyl), 2950w (C–H alkyl), 2876w (C–H alkyl), 1714s (C=O aryl ester), 1600w (CC aromatic), 1576w (CC aromatic), 1488w, 1434m, 1292m, 1262s, 1190w, 1164w, 1122m, 1077s, 1045s, 1011m, 963w, 891w, 840w, 801w, 767w, 714s, 663m, 580w, 470w; δ_H (400 MHz; $CDCl_3$) 7.92 (1H, dd, *J* = 7.7, 1.7 Hz, C(4)H), 7.45 (1H, td, *J* = 7.7, 1.7 Hz, C(7)H), 7.35 – 7.30 (2H, m, C(4+5)H), 4.14 (2H, s, C(9)H_2), 3.92 (3H, s, C(1)H_3), 3.70 (2H, t, *J* = 5.8 Hz, C(11)H_2), 2.67 (2H, t, *J* = 5.8 Hz, C(10)H_2); δ_C (101 MHz; $CDCl_3$) 167.9 (C, C2), 140.2 (C, C8), 132.2 (CH, C7), 131.3 (CH, C5), 131.2 (CH, C6), 129.4 (C, C3), 127.4 (CH, C4), 60.5 (CH_2, C11), 52.3 (CH_3, C1), 35.0 (CH_2, C10), 34.1 (CH_2, C9); HRMS (ESI): m/z calcd. for $C_{11}H_{14}NaO_3S$: 249.0556, found: 249.0556 $[MNa]^+$.

Lab notebook reference: ixz_085

Synthesis of 2-(((2-hydroxyethyl)thio)methyl)benzoic acid – 141

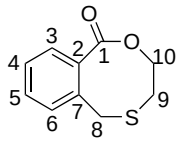


$NaOH_{(aq)}$ (4.0 M, 11 mL) was added dropwise over a period of 5 min to solution of alcohol **140** (400 mg, 2.25 mmol) in MeOH (11 mL). A colour change to pale yellow solution was noted immediately. Upon further addition, the appearance of the reaction mixture changed to a milky white suspension. The resulting clear colourless solution was stirred at RT for 16 h, after which

time the reaction was deemed to have gone to completion by TLC (complete consumption of alcohol **140** was noted). The resulting mixture was then acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (20 mL) and poured into separating funnel containing CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), before combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford title compound **141** as a white solid (377 mg, 79%); R_f = 0.27 (10:90 MeOH:CH_2Cl_2 (10 mL) + 3 drops of AcOH); melting point: 60 – 63 °C (from *n*–hexane:CH_2Cl_2 , 5:2); IR (solid state) ν_{max}/cm^{-1}: 3273m (O–H alcohol), 3064w (C–H aryl), 2954m (C–H alkyl, O–H carboxylic acid), 2919m (C–H alkyl, O–H carboxylic acid), 2815m (C–H alkyl), 2645m (C–H alkyl), 2519w, 1678s (C=O aryl carboxylic acid), 1598w (CC aromatic), 1573m (CC aromatic), 1483w, 1447w, 1407s, 1300w, 1290w, 1268s, 1201w, 1179w, 1164w, 1142w, 1077w, 1049m, 1004m, 967w, 923m, 857w, 836w, 806w, 767m, 730m, 710m, 689w, 660m, 580w, 545w, 479w; δ_H (400 MHz; CD_3OD) 7.90 (1H, dd, *J* = 7.8, 1.5 Hz, C(3)H), 7.49 – 7.42 (1H, m, C(5)H), 7.41 – 7.36 (1H, m, C(6)H), 7.36 – 7.29 (1H, m, C(4)H), 4.17 (2H, s, C(8)H_2), 4.16 (1H, s, OH), 3.60 (2H, t, *J* = 6.7 Hz, C(10)H_2), 2.55 (2H, t, *J* = 6.7 Hz, C(9)H_2); δ_C (101 MHz; CD_3OD) 170.8 (C, C1), 142.1 (C, C7), 132.8 (CH, C5),132.3 (CH, C3), 132.2 (CH, C6), 131.4 (C, C2), 128.1 (CH, C4), 62.3 (CH_2, C10), 35.0 (CH_2, C8), 34.70 (CH_2, C9); HRMS (APCI): m/z calcd. for $C_{10}H_{13}O_3S$: 213.057992, found: 213.058412 $[MH]^+$.

Lab notebook reference: ixz_089

Synthesis of 3,4-dihydrobenzo[*f*][1,4]oxathiocin-1(6*H*)-one – 142

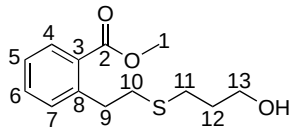


EDC.HCl (332 mg, 1.64 mmol) was added to solution of carboxylic acid **141** (194 mg, 0.912 mmol), HOBt (191 mg, 1.37 mmol) and dry DIPEA (400 µL, 2.28 mmol) in anhydrous DMF (9 mL). A colour change to pale yellow was noted immediately. After total of 16 h of stirring at RT, the reaction was deemed to have to completion by TLC analysis. The resulting mixture was diluted with EtOAc (30 mL) and poured into separating funnel, where the organic phase was washed sequentially with 1.0 M $HCl_{(aq)}$ (2 × 20 mL), sat. $NaHCO_{3(aq)}$ (1 × 20 mL) and sat. brine (2 × 20 mL). The resulting organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a clear colourless oil (289 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 20:80) to afford title compound **142** as a white crystal (156 mg, 88%); R_f = 0.77 (50:50, EtOAc:*n*–hexane); melting point: 75 – 77 °C (from *n*–hexane); IR (solid state) ν_{max}/cm^{-1}: 3072w

(C–H aryl), 3031w (C–H aryl), 2961w (C–H alkyl), 2899w (C–H alkyl), 1771m (C=O aryl ester), 1599m (CC aromatic), 1484w (CC aromatic), 1462w, 1445w, 1414w, 1404w, 1361m, 1296m, 1226m, 1203w, 1167w, 1157w, 1113m, 1102m, 1082s, 1047m, 1033m, 995w, 955w, 933w, 893w, 897w, 864w, 839w, 825w, 769m, 755s, 705m, 696m, 671w, 656m, 579w, 542w, 489m, 470w; δ_H (400 MHz; $CDCl_3$) 7.67 (1H, dd, *J* = 7.7, 1.7 Hz, C(3)H), 7.39 (1H, td, *J* = 7.7, 1.7 Hz, C(5)H), 7.33 (1H, td, *J* = 7.5, 1.4 Hz, C(4)H), 7.12 (1H, dd, *J* = 7.0, 1.0 Hz, C(6)H), 4.70 (2H, br s, C(10)H_2), 4.07 (2H, s, C(8)H_2), 3.18 (2H, s, C(9)H_2); δ_C (101 MHz; $CDCl_3$) 172.6 (C, C1), 142.1 (C, C7), 131.9 (CH, C5), 130.8 (C, C2), 130.2 (CH, C3) 129.8 (CH, C6), 127.8 (CH, C4), 67.5 (CH_2, C10), 39.7 (CH_2, C8), 39.0 (CH_2, C9); HRMS (ESI): m/z calcd. for $C_{10}H_{10}NaO_2S$: 217.0294, found: 217.0295 $[MNa]^+$; X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2221558, was crystallised by slow cooling of *n*-hexane from RT to –20 °C).

Lab notebook reference: ixz_091

Synthesis of methyl 2-(2-((3-hydroxypropyl)thio)ethyl)benzoate – 144

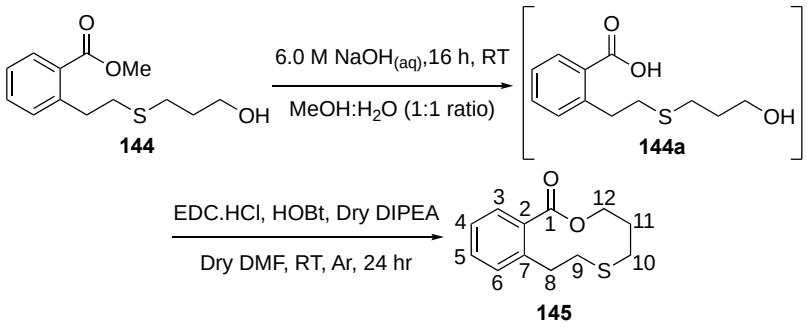


K_2CO_3 (424 mg, 2.46 mmol) was added to a clear colourless solution of 3-mercaptopropan-1-ol **97** (90.0 µL, 1.23 mmol) and methyl 2-(2-bromoethyl)benzoate **143** (250 mg, 1.03 mmol) in anhydrous DMF (10 mL) at RT under Ar . The resulting suspension was then heated to 70 °C, whereupon a colour change to pale yellow was noted. Upon further heating, the colour of the reaction suspension changed to fire orange. After 16 h, the reaction was deemed to have gone to completion by TLC and mixture allowed to cool to RT, before quenched by addition of H_2O (30 mL). The resulting milky white suspension was poured into separating funnel containing EtOAc (20 mL) and layers were separated. The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed sequentially with 1.0 M $HCl_{(aq)}$ (2 × 20 mL), sat. $NaHCO_{3(aq)}$ (2 × 20 mL), H_2O (2 × 20 mL) and sat. brine (2 × 20 mL), before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield peach orange oil (434 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:toluene, 40:60) to afford title compound **144** as clear colourless oil (171 mg, 65%); R_f = 0.23 (50:50, EtOAc:*n*–hexane); IR (thin film) ν_{max}/cm^{-1}: 3386m (O–H alcohol), 2949w (C–H alkyl), 2876w (C–H alkyl), 1717s (C=O aryl ester), 1601w (CC aromatic), 1575w (CC aromatic), 1488m (CC aromatic), 1448m, 1434m, 1293m, 1270m, 1253s, 1189w, 1164w, 1120m, 1077s, 1048m, 961w, 903w, 843w, 801w, 736m, 663w, 575w, 508w; δ_H (400 MHz;

$CDCl_3$) 7.91 (1H, dd, *J* = 7.7, 1.5 Hz, C(4)H), 7.45 (1H, dd, *J* = 7.7, 1.5 Hz, C(7)H), 7.35 – 7.20 (2H, m, C(5+6)H), 3.89 (3H, s, C(1)H_3), 3.76 (2H, t, *J* = 5.9 Hz, C(13)H_2), 3.30 – 3.20 (2H, m, C(9)H_2), 2.85 – 2.72 (2H, m, C(10)H_2), 2.71 (2H, t, *J* = 7.1 Hz, C(11)H_2), 2.55 (2H, tt, *J* = 7.1, 5.9 Hz, C(12)H_2), 1.63 (1H, br s, OH); δ_C (126 MHz; $CDCl_3$) 167.9 (C, C2), 142.5 (C, C8), 132.4 (CH, C4), 131.6 (CH, C6), 131.1 (CH, C7), 129.3 (C, C3), 126.7 (CH, C5), 62.0 (CH_2, C13), 52.2 (CH_3, C1), 35.4 (CH_2, C9), 33.4 (CH_2, C10), 32.4 (CH_2, C11), 28.6 (CH_2, C12); HRMS (ESI): calcd. for $C_{13}H_{18}NaO_3S$, 277.0869. Found: $[MNa]^+$, 277.0867 (0.5 ppm error).

Lab notebook reference: ixz_114

Synthesis of 4,5,7,8-tetrahydro-1*H*,3*H*-benzo[*h*][*1,5*]oxathiecin-1-one – 145

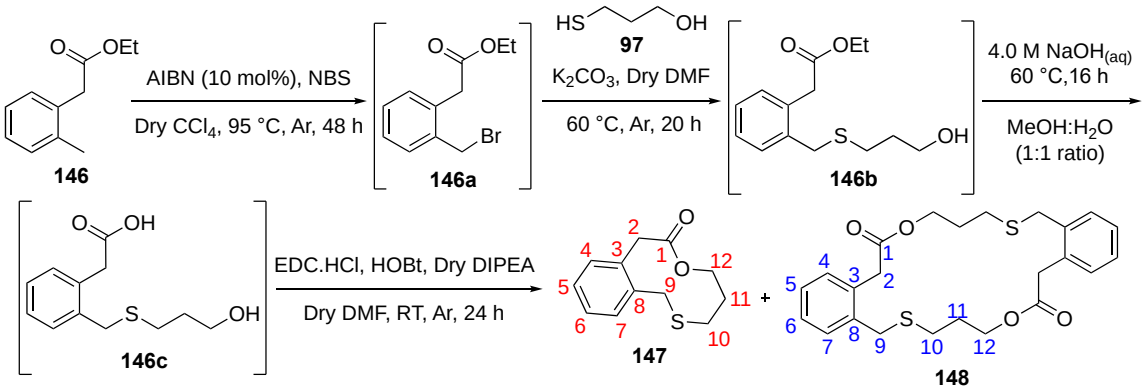


$NaOH_{(aq)}$ (6.0 M, 10.5 mL) was added dropwise over a period of 1 min to clear colourless solution of ethyl benzoate **144** (262 mg, 1.03 mmol) in MeOH (10.5 mL) at RT. A colour change to milky white suspension was noted immediately during dropwise addition. Upon further addition, the appearance of the reaction mixture changed to pale yellow. The reaction mixture was stirred at RT for 16 h, before the reactions was deemed to have gone to completion by TLC (complete consumption of ethyl benzoate **144** was noted). The resulting solution was then acidified to pH 2.0 with 3.0 M $HCl_{(aq)}$ (40 mL) and poured into to separating funnel. The aqueous layer was extracted with CH_2Cl_2 (4 × 30 mL), before the combined organic phases were dried over $MgSO_4$, filtered and concerted under reduced pressure to yield a crude product as clear colourless oil (111 mg). The crude product was taken directly to the next reaction step without further purification. Then, EDC.HCl (204 mg, 0.831 mmol) was added to a clear colourless solution of crude product **144a** (111 mg, 0.461 mmol), HOBt (93.5 mg, 0.692 mmol) and dry DIPEA (200 µL, 1.15 mmol) in anhydrous DMF (9 mL) at RT under Ar. A colour change to pale yellow was noted immediately upon the addition of DIPEA via syringe over a period of 1 min. The resulting mixture was stirred at RT for 24 h, after which time the reaction was deemed to have gone completion by TLC, with a colour change back to lemon yellow was noted. The reaction mixture was diluted with EtOAc (20 mL) and transferred into separating funnel. The resulting milky/white organic layer was washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 20 mL), sat. $NaHCO_3$ (3 × 20 mL), H_2O (3 × 20 mL) and sat. brine (3 × 20 mL), before being

dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a brown/orange oil (113 mg). The crude product was purified by flash column chromatography (SiO_2, 10 mm column, eluent: EtOAc:toluene, 20:80) to afford title compound **145** as a white solid (40.1 mg, 39%, over two steps); R_f = 0.60 (50:50, EtOAc:*n*–hexane);melting point: 90– 91 °C (from *n*–hexane); IR (solid state)ν_{max}/cm^{-1}: 2961m (C–H alkyl), 2946m (C–H alkyl), 2925m (C–H alkyl), 2853m (C–H aryl), 1696s (C=O aryl ester), 1599m (CC aromatic), 1474m, 1456m, 1449m, 1429w, 1382w, 1354w, 1335w, 1311m, 1246m, 1233m, 1291m, 1271s, 1210m, 1165w, 1147m, 1112s, 1083m, 1063m, 1048m, 965w, 861w, 802w, 772w, 763m, 738s, 702m, 586w, 515w, 468w; δ_H (400 MHz; $CDCl_3$) 7.87 (1H, dd, *J* = 7.7, 1.5 Hz, C(3)H), 7.43 (1H, td, *J* = 7.7, 1.5 Hz, C(5)H),7.32–7.26 (2H, m, C(4+6)H), 4.41 (2H, t, *J* = 7.0 Hz, C(12)H_2), 3.29 – 3.20 (2H, m, C(8)H_2), 2.80 – 2.70 (2H, m, C(9)H_2), 2.62 (2H, t, *J* = 7.0 Hz, C(10)H_2), 2.14 – 2.01 (2H, t, *J* = 7.0 Hz, C(11)H_2); δ_C (101 MHz; $CDCl_3$) 167.9 (C, C1), 141.9 (C, C7), 132.2 (CH, C3), 131.5 (CH, C5), 130.9 (CH, C6), 130.1 (C, C2), 129.7 (CH, C4), 64.1 (CH_2, C12), 35.2 (CH_2, C8), 33.7 (CH_2, C9), 29.2 (CH_2, C11), 28.3 (CH_2, C10); HRMS (ESI): m/z calcd. for $C_{12}H_{15}O_2S$: 223.0787, found: 223.0785 $[MH]^+$, m/z calcd. for $C_{12}H_{15}NaO_2S$: 245.0607, found: 245.0604 $[MNa]^+$.

Lab notebook reference: ixz_119

Synthesis of 1,4,5,8-tetrahydro-3*H*,7*H*-benzo[*g*][*1,5*]oxathiecin-7-one – 147 and 5,8,9,12,17,20,21,24-octahydro 7*H*,11*H*,19*H*,23*H*dibenzo[*g,q*][*1,11*]dioxa[*5,15*]dithiacycloicosine-11,23-dione – 148



AIBN (47.0 mg, 0.286 mmol) was added to a yellow suspension of ethyl *o*-tolyl-acetate **146** (511 mg, 2.86 mmol) and *N*-bromosuccinimide (690 mg, 3.43 mmol) in anhydrous CCl_4 (14 mL, degassed for 10 min) at RT under Ar. The resulting suspension was heated to 95 °C, whereupon a colour changed to cloudy white was noted. After 48 h, the reaction was deemed to have gone to completion by TLC, with a colour change to pale yellow suspension was observed. The reaction mixture allowed to cool to RT and evaporated to dryness, before

diluted with 30 mL of EtOAc. The diluted yellow solution was transferred to separating funnel, where organic layer was washed sequentially with 1.0 M $HCl_{(aq)}$ (2 × 30 mL), sat. $NaHCO_{3(aq)}$ (2 × 20 mL) and sat. brine (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford bromide as yellow oil (943 mg). The ethyl bromomethyl phenyl acetate **146a** was directly used in the next reaction step without further purification. Next, K_2CO_3 (441 mg, 2.81 mmol) was added to a yellow solution of 3-mercaptopropan-1-ol **97** (130 µL, 1.87 mmol) and phenyl acetate **146a** (717 mg, 2.80 mmol) in anhydrous DMF (9 mL) at RT under Ar. The resulting suspension was then heated to 60 °C, whereupon an immediate colour change pale yellow was noted. Upon further heating, the colour of the reaction suspension changed to yellow. After 20 h, the reaction was deemed to have gone to completion by TLC, with a colour change to orange was observed. The reaction mixture was then quenched by addition of H_2O (30 mL) and the resulting milky/white suspension was poured into a separating funnel containing EtOAc (30 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL), before the combined organic phases were washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 20 mL), sat. $NaHCO_{3(aq)}$ (4 × 20 mL) and sat. brine (5 × 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield crude product **146b** as pale yellow oil (485 mg). The alcohol **146b** product was directly used in the next reaction step without further purification.Next, $NaOH_{(aq)}$ (4.0 M, 9 mL) was added dropwise over a period of 1 min to clear colourless solution of crude product **146b** (485 mg, 1.81 mmol) in MeOH (9 mL). A colour change to cloudy yellow suspension was noted immediately during dropwise addition. The resulting suspension was then heated to 60 °C, whereupon a colour change to pale yellow solution was observed After 16 h, the reaction was deemed to have gone to completion by TLC analysis (complete consumption of alcohol **146b** was noted). The resulting mixture was allowed to cool to RT, before acidified to pH 2.0 by addition of 1.0 M $HCl_{(aq)}$ (30 mL). The acidified solution was poured into separating funnel and aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a crude product as pale yellow oil (257 mg). The carboxylic acid **146c** product was directly used in the next reaction step without further purification. Then, EDC.HCl (321 mg, 1.61 mmol) was added to clear colorless solution of carboxylic acid **146c** (257 mg, 1.07 mmol), HOBt (188 mg, 1.29 mmol) and dry DIPEA (470 µL, 2.68 mmol) in anhydrous DMF (11 mL) at RT. An immediate colour change to pale yellow was observed. After total of 18 h of stirring at RT under Ar, the reaction was deemed to have gone completion by TLC analysis. The reaction mixture was diluted with EtOAc (30 mL) and poured into separating funnel. The diluted solution was washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 10 mL), sat. $NaHCO_{3(aq)}$ (3 × 20 mL) and sat. brine (3 × 20 mL), before being dried over $MgSO_4$, filtered and concentrated under reduced pressure

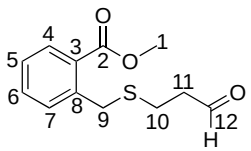
to yield a pale-yellow oil (321 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 20:80) to afford monomer **147** (67.1 mg, 28%, over four steps) and dimer **148** (54.5 mg, 11%, over four steps) both as a white solids.

Date for **147**: R_f = 0.32 (20:80 EtOAc:*n*–hexane); IR (solid state) ν_{max} / cm^{-1}: 3068w (C–H alkyl), 2921m (C–H alkyl), 2857w (C–H alkyl),1726s (C=O aryl lactone), 1604w (CC aromatic), 1586w (CC aromatic), 1489w (CC aromatic), 1452m, 1378w, 1237m, 1130m, 1008m, 938w, 874w, 764w, 716w; δ_H (400 MHz; $CDCl_3$) 7.59 (1H, dd, *J* = 7.7, 1.5 Hz, C(4)H), 7.30 (1H, td, *J* = 7.7, 1.5 Hz, C(5)H), 7.19 (1H, td, *J* = 7.7, 1.5 Hz, C(6)H), 7.15 (1H, td, *J* = 7.7, 1.5 Hz, C(7)H), 4.18 (2H, t, *J* = 5.9 Hz, C(12)H_2), 3.79 (2H, s, C(2)H_2), 3.71 (2H, s, C(9)H_2), 2.42 – 2.30 (2H, m, C(10)H_2), 2.18 – 2.08 (2H, m, C(11)H_2); δ_C (101 MHz; $CDCl_3$) 171. (C, C1), 138.0 (C, C8), 133.9 (C, C3), 131.0 (CH, C4), 130.9 (CH, C7), 128.1 (CH, C5), 127.4 (CH, C6), 63.4 (CH_2, C12), 41.4 (CH_2, C2), 31.7 (CH_2, C9), 31.4 (CH_2, C11), 25.2 (CH_2, C10): HRMS (ESI): m/z calcd. for $C_{12}H_{14}NaO_2S$: 245.0607, found: 245.0606 $[MNa]^+$.

Date for **148**;R_f = 0.08 (20:80 EtOAc:*n*–hexane); IR (solid state) ν_{max} /cm^{-1}: 2923w (C–H alkyl), 2854m (C–H alkyl), 1727s (C=O aryl lactone), 1612w (CC aromatic), 1593w (CC aromatic), 1493w (CC aromatic), 1456m, 1413m, 1380m, 1336m, 1288w, 1231m, 1186m, 1157s, 1087w, 1059m, 1010m, 961w, 933w, 887w, 779w, 754w, 702m, 612w, 570w, 481w; δ_H (400 MHz; $CDCl_3$) 7.34 – 7.18 (8H, m, C(4+5+6+7)H), 4.21 (4H, t, *J* = 6.0 Hz, C(13)H_2), 3.78 (4H, s, C(2)H_2), 3.74 (4H, s, C(10)H_2), 2.55 (4H, t, *J* = 7.4 Hz, C(11)H_2), 2.00 – 1.88 (4H, m, C(12)H_2); δ_C (101 MHz; $CDCl_3$) 171.6 (C, C1), 135.9 (C, C8), 133.2 (C, C3), 131.7 (CH, C4), 130.4 (CH, C7), 127.9 (CH, C5), 127.8 (CH, C6), 63.7 (CH_2, C13), 38.7 (CH_2, C2), 35.0 (CH_2, C10), 29.3 (CH_2, C11), 28.8 (CH_2, C12): HRMS (ESI): m/z calcd. for $C_{24}H_{29}O_4S_2$: 445.1502, found: 445.1490 $[MH]^+$, m/z calcd. for $C_{24}H_{28}NaO_4S_2$: 467.1321, found: 467.1321 $[MNa]^+$.

Lab notebook reference: ixz_156

Synthesis of methyl 2-(((3-oxopropyl)thio)methyl)benzoate – 149

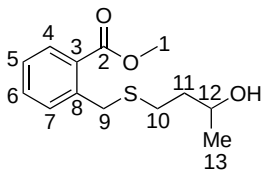


Dimethylsulfoxide (DMSO, 610 µL, 8.53 mmol) was added dropwise over 10 min (via syringe pump) to a pale-yellow solution of oxalyl chloride (340 µL, 3.91 mmol) in anhydrous CH_2Cl_2 (6 mL) at −78 °C. The resulting solution was stirred for 20 min at −78 °C, after which time, a

solution of alcohol **111** (860 mg, 3.56 mmol) in anhydrous CH_2Cl_2 (6 mL) was added dropwise over 20 min (via syringe pump). The reaction mixture was stirred at −78 °C for an additional 20 min, before dry Et_3N (1.98 mL, 0.013 mmol) was added dropwise over 10 min (via syringe pump). The resulting solution was stirred at −78 °C and gradually allowed to warm to RT. A colour change to milky/white was observed and the reaction mixture was stirred at RT for 18 h, before the reaction mixture was deemed to have gone to completion by TLC. The pale-yellow solution was then quenched with H_2O (20 mL) and poured into a separating funnel containing CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), before the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an orange viscose oil (1.24 g). The crude product was purified by flash column chromatography (SiO_2, 60 mm column, eluent: EtOAc:*n*–hexane, 10:90 to 40:60) to afford title compound **149** as a pale yellow oil (411 mg, 48%); R_f = 0.51 (EtOAc:*n*–hexane, 50:50);IR (thin film) ν_{max}/cm^{-1}: 2999w (C–H alkenyl), 2951w (C–H alkyl), 2834w (C–H alkyl), 2834w (C–H alkyl), 2729w (H–CO aldehyde), 1714s (C=O aliphatic aldehyde or/and aryl ester), 1599w (CC aromatic), 1576w (CC aromatic), 1488w (CC aromatic), 1433w, 1388w, 1332w, 1292w, 1261s, 1191m, 1164w, 1122m, 1077m, 1046w, 964w, 890w, 841w, 804w, 768w, 715s, 663w, 622w, 518w, 478w; δ_H (400 MHz; $CDCl_3$) 9.71 (1H, s, HCO), 7.92 (1H, dd, *J* = 7.7, 1.5 Hz, C(4)H), 7.45 (1H, td, *J* = 7.7, 1.5 Hz, C(7)H), 7.40 – 7.28 (2H, m, C(5+6)H), 4.15 (2H, s, C(9)H_2), 3.90 (3H, s, C(1)H_3), 2.77 – 2.62 (4H, m, C(10+11)H_2); δ_C (101 MHz; $CDCl_3$) 200.7 (C, C12), 167.9 (C, C2), 140.2 (C, C8), 131.9 (CH, C7), 131.2 (CH, C3), 131.0 (CH, C5), 129.4 (C, C3), 128.2 (CH, C6), 52.2 (CH_3, C1), 43.5 (CH_2, C11), 34.6 (CH_2, C9), 24.0 (CH_2, C10); HRMS (ESI): *m/z* calcd. for $C_{12}H_{14}NaO_3S$: 261.0556, found: 261.0559 $[MNa]^+$.

Lab notebook reference: ixz_123

Synthesis of methyl 2-(((3-hydroxybutyl)thio)methyl)benzoate – 150

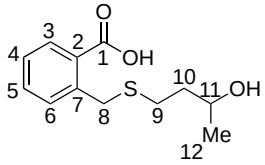


$AlMe_3$ (1.04 mL, 2.0 M in *n*–hexane, 2.07 mmol) was added dropwise over 5 min to a solution of methyl 2-(((3-oxopropyl)thio)methyl)benzoate **149** (411 mg, 1.73 mmol) in anhydrous CH_2Cl_2 (17 mL) at −78 °C. The resulting pale-yellow solution was stirred at −78 °C for 1 h, before allowed to be warmed to 0 °C for 1 h and then stirred for additional 1 h at RT. After a total of 3 h, the reaction was deemed to have gone to completion by TLC. The resulting pale-

yellow solution was quenched by addition of H_2O (20 mL), instantaneous effervescence and fizzing was noted. The quenched reaction solution was poured into separating funnel containing CH_2Cl_2 (20 mL) and aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale-yellow oil (667 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent:*n*–hexane:EtOAc, 50:50) to afford title compound **150** as a pale yellow oil (215 mg, 46%); R_f = 0.51 (EtAOc:*n*–hexane, 50:50); IR (thin film)ν_{max}/cm $^{-1}$: 3408m (O–H alcohol), 3067w (C–H alkyl), 3024w (C–H alkyl), 2964w (C–H alkyl), 2952w (C–H alkyl), 2927w (C–H alkyl), 1716s (C=O aryl ester), 1600w (CC aromatic), 1576w (CC aromatic), 1488w (CC aromatic), 1447w, 1434m, 1292w, 1262s, 1190w, 1164w, 1121m, 1077s, 1046w, 949w, 965w, 906w, 878w, 842w, 801w, 766w, 754w, 715s, 663w, 580w, 469w; δ_H (400 MHz; $CDCl_3$) 7.90 (1H, dd, *J* = 7.7, 1.5 Hz, C(4)H), 7.44 (1H, td, *J* = 7.7, 1.5 Hz, C(7)H), 7.37 – 7.28 (2H, m, C(5+6)H), 4.13 (2H, s, C(9)H_2), 3.91 (3H, s, C(1)H_3), 3.90 – 3.87 (1H, br m, C(12)H), 2.55 (2H, t, *J* = 7.2 Hz, C(10)H_2), 1.77 (1H, br, d, *J* = 4.4 Hz, OH), 1.72 – 1.64 (2H, m, C(11)H_2), 1.17 (3H, d, *J* = 6.2 Hz, C(13)H_3); δ_C (101 MHz; $CDCl_3$) 168.1 (C, C2), 140.6 (C, C8), 132.0 (CH, C4), 131.3 (CH, C6), 131.2 (CH, C7), 129.7 (C, C3), 127.3 (CH, C5), 62.8 (CH_2, C1), 52.4 (CH_3, C12), 38.2 (CH_2, C12), 34.7 (CH_2, C9), 28.5 (CH_2, C10), 23.6 (CH_3, C13); HRMS (ESI): *m/z* calcd. for $C_{13}H_{18}NaO_3S$: 277.0869, found: 277.0868 $[MNa]^+$.

Lab notebook reference: ixz_129

Synthesis of 2-(((3-hydroxybutyl)thio)methyl)benzoic acid – 151

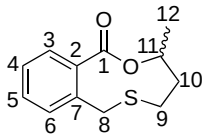


$NaOH_{(aq)}$ (4.0 M, 8 mL) was added dropwise over a period of 1 min to solution of methyl 2-(((3-hydroxybutyl)thio)methyl)benzoate **150** (215 mg, 0.802 mmol) in MeOH (8 mL). The resulting pale-yellow solution was heated to 50 °C for a total of 16 h, after which the reaction mixture was deemed to have gone to completion by TLC and was acidified to pH 2.0 by addition of 1.0 M $HCl_{(aq)}$ (20 mL). The acidified mixture was poured into separating funnel and aqueous layer was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale-yellow oil (302 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: MeOH:CH_2Cl_2, 10:90) to afford title compound **151** as pale-yellow oil (157 mg, 82%); R_f = 0.41 (10:90 MeOH:EtOAc (10 mL) + 0.35% of AcOH); IR (neat) ν_{max} / cm $^{-1}$: 3410m (O–H

alcohol), 2968m (C–H alkyl), 2928m (C–H alkyl), 2631m (O–H carboxylic acid), 2503m (O–H carboxylic acid), 1689s (C=O aryl carboxylic acid), 1600w (CC aromatic), 1576w (CC aromatic), 1490w, 1448w, 1401w, 1374m, 1295m, 12400s, 1164w, 1122m, 1073w, 1045m, 929w, 906w, 838w, 766m, 713s, 645m, 609w, 582w, 552w, 487w; δ_H (400 MHz; $CDCl_3$) 7.98 (1H, dd, *J* = 7.5 1.5 Hz, C(3)H), 7.54 (2H, br s, 2 × OH),7.43 (1H, td, *J* = 7.5, 1.5 Hz, C(5)H), 7.37 – 7.22 (2H, m, C(4+5)H), 4.22 – 4.09 (2H, m, C(8)H_2), 3.99 – 3.86 (1H, m, C(11)H), 2.55 (2H, t, *J* = 7.3 Hz, C(9)H_2), 1.83 – 1.60 (2H, m, C(10)H_2), 1.16 (3H, d, *J* = 6.2 Hz, C(12)H_3); δ_C (101 MHz; $CDCl_3$) 171.8 (C, C1), 141.2 (C, C7), 132.5 (CH, C3), 131.9 (CH, C5), 131.2 (CH, C6), 128.9 (C, C2), 127.1(CH, C4), 67.3 (CH, C11), 38.0 (CH_2, C10), 34.5 (CH_2, C8), 28.4 (CH_2, C9), 23.0 (CH_3, C12); HRMS (ESI): m/z calcd. for $C_{12}H_{16}NaO_3S$: 263.0712, found: 263.0711 $[MNa]^+$.

Lab notebook reference: ixz_550

Synthesis of 3-methyl-4,5-dihydro-3*H*-benzo[*g*][1,5]oxathionin-1(7*H*)-one – 152

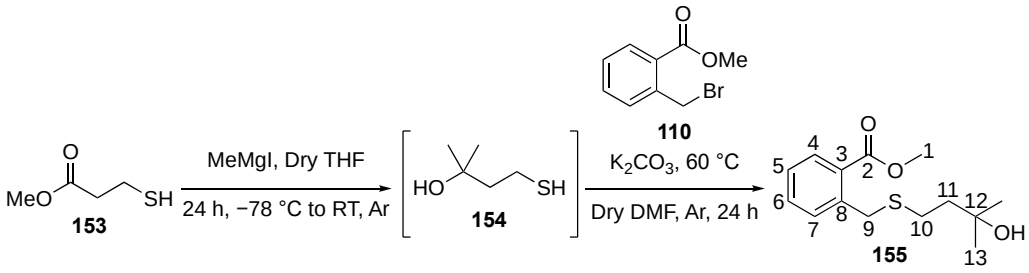


EDC.HCl (227 mg, 0.990 mmol) was added to clear colourless solution of carboxylic acid **151** (157 mg, 0.660 mmol), HOBt (174 mg, 0.787 mmol) and dry DIPEA (290 µL, 1.64 mmol) in anhydrous DMF (7 mL). A colour change to pale yellow was immediately noted and the reaction was stirred at RT for 16 h, before the reaction was deemed to have to completion by TLC. The resulting mixture was diluted with EtOAc (20 mL) and poured into separating funnel. The diluted milky/white suspension was washed sequentially with 1.0 M $HCl_{(aq)}$ (2 × 10 mL), sat. $NaHCO_{3(aq)}$ (3 × 20 mL) and sat. brine (3 × 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale-yellow oil (208 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane,20:80) to afford tittle compound **152** as a clear colourless oil (105 mg, 71%); R_f = 0.52 (50:50 EtOAc:*n*–hexane);IR (thin film) ν_{max} /cm^{-1}: 2979 (C–H alkyl), 2935w (C–H alkyl), 1712s (C=O aryl ester), 1600m (CC aromatic), 1449m (CC aromatic), 1420w, 1385w, 1348w, 1296m, 1265s, 1219w, 1117s, 1086w, 1038s, 895w, 864w, 840w, 795w, 761w, 730w, 710s, 700w, 569w, 481w; δ_H (400 MHz; $CDCl_3$) 7.81 (1H, dd, *J* = 6.9, 2.1 Hz, C(3)H), 7.39 – 7.22 (2H, m, C(4+5)H), 7.12 (1H, dd, *J* = 6.9, 2.1 Hz, C(6)H), 5.54 – 5.42 (1H, m, C(11H), 4.20 (1H d, *J* = 14.2 Hz, C(8)**H**H'), 3.95 (1H d, *J* = 14.2 Hz, C(8)H**H'**), 2.96 – 2.75 (2H, m, C(9)H_2), 2.42 – 2.29 (1H, m, C(10)**H**H'), 1.99 – 1.88 (1H, m, C(10)H**H'**), 1.38 (3H, d, *J* = 6.6 Hz, C(12)H_3); δ_C (101 MHz; $CDCl_3$) 168.1 (C, C1), 141.8 (C, C7), 131.9 (C, C2), 131.4 (t, CH,

C5), 131.0 (CH, C3), 129.9 (d, CH, C6), 127.5 (d, CH, C4), 71.3 (d, CH_2, C11), 40.0 (t, CH_2, C8), 34.5 (CH_2, C9), 30.9 (t, CH_2, C10), 18.9 (CH_3, C12); HRMS (ESI): m/z calcd. for $C_{12}H_{15}O_2S$: 223.0787, found: 223.0785 $[MH]^+$, m/z calcd. for $C_{12}H_{14}NaO_2S$: 245.0607, found: 245.0605 $[MNa]^+$.

Lab notebook reference: ixz_132

Synthesis of methyl 2-(((3-hydroxy-3-methylbutyl)thio)methyl)benzoate – 155

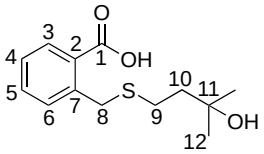


MeMgI (4.71 mL, 2.7 M in Et_2O, 16.2 mmol) was added dropwise over 3 min via syringe to a solution of thiol **153** (434 mg, 3.60 mmol) in anhydrous THF (18 mL) at −78 °C. The resulting creamy white suspension was stirred at −78 °C for 2 h, before being allowed to be warmed to 0 °C for 2 h and then stirred for additional 16 h at RT. After a total of 24 h, the reaction was deemed to have gone to completion by TLC. The resulting milky white suspension was quenched by the gradual addition of sat. $NH_4Cl_{(aq)}$ (30 mL).The quenched reaction solution was poured into separating funnel and aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a crude product thiol **154** as a colourless liquid (318 mg). The crude product was directly used in the next reaction step without further purification. Next, K_2CO_3 (264 mg, 1.91 mmol) was added to a colourless solution of thiol **154** (114 mg) and methyl bromomethyl benzoate **110** (326 mg, 1.43 mmol) in anhydrous DMF (9.50 mL) at RT under Ar. The resulting suspension was then heated to 60 °C, whereupon an immediate colour change to milky/cloudy white was observed. After 24 h, the reaction was deemed to have gone to completion by TLC, with a colour change to yellow noted. The reaction mixture was then quenched by addition of H_2O (30 mL) and the resulting yellow solution was poured into a separating funnel. The aqueous layer was extracted with EtOAc (3 × 30 mL), before the combined organic phases were washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 30 mL) and sat. brine (3 × 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield pale yellow oil (207 mg). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 40:60) to afford title compound **155** as pale yellow oil (207 mg, 81% over two steps); R_f = 0.34 (50:50 EtOAc:*n*–hexane); IR (neat)

ν_{max}/cm^{-1}: 3430w (O–H alcohol), 2967w (C–H alkyl), 1716s (C=O aryl ester), 1600w (CC aromatic), 1576w (CC aromatic), 1434m, 1374m, 1263s, 1195m, 1123m, 1077s, 1046w, 965w, 922w, 753m, 713m, 664w, 472w; δ_H (400 MHz; $CDCl_3$) 7.90 (1H, dd, *J* = 7.7, 1.5 Hz, C(4)H), 7.44 (1H, td, *J* = 7.7, 1.5 Hz, C(6)H), 7.37–7.34 (m, 1H, C(7)H), 7.31 (1H, td, *J* = 7.6, 1.4 Hz, C(5)H), 4.14 (2H, s, C(9)H_2), 3.91 (3H, s, C(1)H_3), 2.57 – 2.48 (2H, m, C(10)H_2), 1.79 – 1.69 (2H, m, C(11)H_2), 1.65 (1H, br, s, OH), 1.19 (6H, s, C(13)H_3); δ_C (101 MHz; $CDCl_3$) 167.9 (C, C2), 140.5 (C, C8), 131.9 (CH, C6), 131.1 (CH, C7), 131.1 (CH, C4), 129.5 (C, C3), 127.1 (CH, C5), 70.7 (C, C12), 52.2 (CH_3, C1), 42.8 (CH_2, C11), 34.4 (CH_2, C9), 29.2 (CH_3, C13), 26.7 (CH_2, C10); HRMS (ESI): calcd. for $C_{14}H_{21}O_3$, 269.1206. Found: $[MH]^+$, 269.1208 (−0.7 ppm error), calcd. for $C_{14}H_{20}NaO_3$, 291.1025. Found: $[MNa]^+$ 291.1025 (−0.3 ppm error).

Lab notebook reference: ixz_138

Synthesis of 2-(((3-hydroxy-3-methylbutyl)thio)methyl)benzoic acid – 156

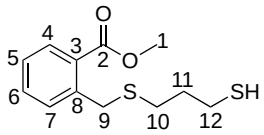


$NaOH_{(aq)}$ (4.0 M, 6.0 mL) was added dropwise over a period of 3 min via syringe to a pale yellow solution of methyl 2-(((3-hydroxy-3-methylbutyl)thio)methyl)benzoate **155** (162 mg, 0.605 mmol) in MeOH (6.06 mL) at RT. A colour change to milky white suspension was noted immediately during dropwise addition via syringe . The resulting suspension was then heated to 50 °C, whereupon a colour change to yellow solution observed. After a total of 16 h, the reaction was deemed to have gone to completion by TLC analysis (complete consumption of methyl benzoate **155** was noted). The orange solution was allowed to cool to RT and then acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (20 mL). The resulting acidified solution was poured into separating funnel. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), before combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a carboxylic acid **156** as a white solid (138 mg, 90%);R_f = 0.22 (10:90, MeOH:CH_2Cl_2 + 0.1% AcOH); melting point: 110 – 112 °C (from 9:1 CH_2Cl_2:*n*–hexane); IR (solid state)ν_{max} /cm^{-1}: 3376w (O–H alcohol/ carboxylic acid), 2971w (C–H alkyl), 2928w (C–H alkyl), 2642w, 2516w, 1690s, (C=O aryl carboxylic acid), 1601 (CC aromatic), 1576w (CC aromatic), 1490w, 1448w, 1377w, 1296m, 1212m, 1164w, 1135w, 1076w, 1047w, 919w, 902w, 838w, 751s, 711m, 666w, 648m, 583w, 551w, 488w; δ_H (400 MHz; $CDCl_3$) 8.04 (1H, dd, *J* = 7.7, 1.4 Hz, C(3)H), 7.50 (1H, td, *J* = 7.7, 1.4 Hz, C(5)H), 7.39 (1H, dd, *J* = 7.7, 1.4 Hz, C(6)H), 7.33 (1H, td, *J* = 7.7, 1.4 Hz, C(4)H), 6.37 (2H, br, s, OH), 4.20 (2H, s, C(8)H_2), 2.63 – 2.52 (2H, m,

C(9)H_2), 1.84–1.74 (2H, m, C(10)H_2), 1.21 (6H, s, C(12)H_3); δ_C (101 MHz; CD_3OD) 170.9 (C, C1), 142.3 (C, C7), 132.7 (CH, C5), 132.2 (CH, C6), 132.2 (CH, C3), 131.6 (C, C2), 128.0 (CH, C4), 71.1 (C, C11), 44.6 (CH_2, C10), 35.0 (CH_2, C8), 29.1 (CH_3, C12), 27.3 (CH_2, C9); HRMS (ESI): calcd. for $C_{13}H_{19}O_3S$, 255.1049. Found: $[MH]^+$, 255.1045 (1.7 ppm error), calcd. for $C_{13}H_{18}NaO_3S$, 277.0869. Found: $[MNa]^+$, 277.0866 (1.1 ppm error).

Lab notebook reference: ixz_141

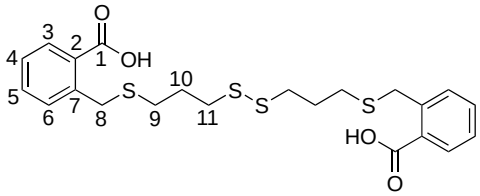
Synthesis of methyl 2-(((3-mercaptopropyl)thio)methyl)benzoate – 159



K_2CO_3 (840 mg, 6.12 mmol) was added to a pale-yellow solution of 1,3-propanedithiol **158** (615 µL, 6.12 mmol) and methyl 2-bromomethylbenzoate **110** (935 mg, 4.20 mmol) in anhydrous DMF (14 mL) at RT. The resulting milky pink suspension was stirred at RT for 18 h, after which the reaction was deemed to have gone to completion by TLC, with a colour change to milky white noted. The reaction mixture was then quenched by addition of H_2O (30 mL) and resulting solution was poured into a separating funnel. The aqueous layer was extracted with EtOAc (3 × 20 mL), before the combined organic phases were washed sequentially with 1.0 M $HCl_{(aq)}$ (2 × 20 mL) and sat. brine (3 × 20 mL). The resulting organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield pale yellow oil (1.30 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 10:90) to afford title compound **159** as pale yellow oil (667 mg, 62%); R_f = 0.34 (20:80 EtOAc:*n*–hexane); IR (thin film)ν_{max}/cm^{-1}: 2943w (C–H alkyl), 2842w (C–H alkyl), 2574w (S–H thiol), 1716s (C=O aryl ester), 1599w (CC aromatic), 1576 (CC aromatic), 1488w (CC aromatic), 1433m, 1292w, 1260s, 1189w, 1163w, 1119m, 1076m, 1046w, 964w, 889w, 839w 801w, 767m, 714s, 663w, 580w, 476w; δ_H (400 MHz; $CDCl_3$) 7.91 (1H, dd, *J* = 7.7, 1.5 Hz, C(4)H), 7.44 (1H, td, *J* = 7.7, 1.5 Hz, C(7)H), 7.35 – 7.24 (2H, m, C(5+6)H), 4.11 (2H, s, C(9)H_2), 3.91 (3H, s, C(1)H_3), 2.63 – 2.50 (4H, m, C(10+12)H_2), 1.91 – 1.77 (2H, m, C(11)H_2)1.30 (1H, t, *J* = 8.1 Hz, SH); δ_C (101 MHz; $CDCl_3$) 167.7 (C, C2) 140.5 (C, C8), 131.8 (CH, C7), 131.1 (CH, C4), 131.0 (CH, C6), 129.4 (C, C3), 127.0 (CH, C5), 52.1 (CH_3, C1), 34.4 (CH_2, C9), 33.0 (CH_2, C11), 29.9 (CH_2, C12), 23.3 (CH_2, C10); HRMS (ESI): m/z calcd. for $C_{12}H_{16}NaO_3S_2$: 279.0484, found: 279.0481 $[MNa]^+$.

Lab notebook reference: ixz_147

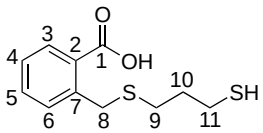
Synthesis of 2,2'-(((disulfanediylbis(propane-3,1-diyl))bis(sulfanediyl))bis(methylene))dibenzoic acid – 160



$NaOH_{(aq)}$ (4.0 M, 5.00 mL) was added dropwise over a period of 1 min to a pale-yellow solution of thiol **159** (248 mg, 0.968 mmol) in MeOH (5.00 mL) at RT and with condenser open to the air (not under Ar). A colour change to milky white suspension noted immediately during dropwise addition. The resulting suspension was then heated to 60 °C, and open to the air, whereupon a colour change to clear colourless solution observed. After a total of 18 h, the reaction was deemed to have gone to completion by TLC analysis (complete consumption of thiol **159** was noted). The colouless mixture was allowed to cool to RT and then acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (20 mL). The resulting acidified solution was poured into a separating funnel. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), before combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford to yield a colourless oil (317 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: MeOH:CH_2Cl_2 + AcOH, 10:90 + 0.1 %) to afford a disulphide **160** as a white solid (181 mg, 77%); R_f = 0.32 (MeOH:CH_2Cl_2 + AcOH, 10:90 + 0.1 %); δ_H (400 MHz; CD_3OD) 7.89 (2H, d, *J* = 7.6 Hz, 2 × C(3)H), 7.45 (2H, t, *J* = 7.6 Hz, 2 × C(5)H), 7.37 (2H, d, *J* = 7.6 Hz, 2 × C(6)H), 7.32 (2H, t, *J* = 7.6 Hz, 2 × C(4)H), 4.13 (4H, s, C(8)H), 2.67 (4H, t, *J* = 7.0 Hz, 2 × C(11)H), 2.50 (4H, t, *J* = 7.1 Hz, 2 × C(9)H), 1.92 – 1.80 (4H, m, C(10)H); HRMS (ESI): calcd. for $C_{11}H_{13}O_2S_2$, 241.0362. Found: $[M/2-H]^-$, 241.0372 (−3.9 ppm error), calcd. for $C_{22}H_{25}O_4S_4$, 481.0641. Found: $[M-H]^-$, 481.0639 (0.4 ppm error).

Lab notebook reference: ixz_108

Synthesis of 2-(((3-mercaptopropyl)thio)methyl)benzoic acid – 161

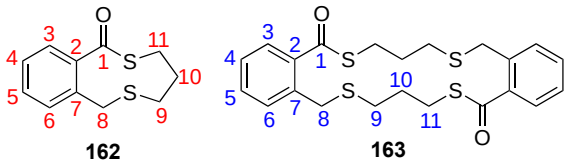


$NaOH_{(aq)}$ (4.0 M, 13.5 mL, degassed for 10 min) was added dropwise over a period of 2 min to a pale-yellow solution of methyl benzoate **159** (667 mg, 2.60 mmol) in anhydrous MeOH (13.5 mL, degassed for 15 min) at RT under Ar. A colour change to milky white suspension was noted immediately during dropwise addition. The resulting suspension was then heated to 60 °C, whereupon a colour change to clear colourless solution was observed. After a total

of 18 h, the reaction was deemed to have gone to completion by TLC analysis (complete consumption of methyl methyl benzoate **159** was noted). The resulting pale yellow mixture was allowed to cool to RT and then acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (30 mL). The resulting acidified solution was poured into separating funnel containing CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), before combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford title **161** compound as a white solid (666 mg, 98%); R_f = 0.45 (15:85, MeOH:CH_2Cl_2); melting point: 72 – 74 °C (from *n*–hexane:CH_2Cl_2, 9:1); IR (solid state) ν_{max}/cm^{-1}: 2955m (O–H alcohol, O–H carboxylic acid), 2916m (O–H carboxylic acid), 2641w (C–H alkyl, O–H carboxylic acid), 1674s (C=O aryl carboxylic acid), 1596w (CC aromatic), 1576m (CC aromatic), 1489w, 1448w, 1439w, 1425w, 1404w, 1298m, 1270s, 1198w, 1165w, 1139w, 1114w, 1080m, 1052w, 1027w, 968w, 906m, 873w, 842w, 808w, 763m, 708s, 677m, 658s, 580w, 537m, 497w; δ_H (400 MHz; $CDCl_3$) 8.08 (1H, dd, *J* = 7.7, 1.5 Hz, C(3)H), 7.51 (1H, td, *J* = 7.7, 1.5 Hz, C(6)H), 7.43 – 7.30 (2H, m, C(4+5)H), 4.18 (2H, s, C(8)H_2), 2.67 – 2.54 (4H, m, C(9+11)H_2), 1.93 – 1.81 (2H, m, C(10)H_2), 1.32 (1H, t, *J* = 8.1 Hz, SH); δ_C (101 MHz; $CDCl_3$) 173.1 (C, C1) 141.8 (C, C7), 133.0 (CH, C6), 132.4 (CH, C3), 131.4 (CH, C5), 128.2 (C, C2), 127.4 (CH, C4), 34.6 (CH_2, C8), 33.2 (CH_2, C10), 30.2 (CH_2, C11), 23.5 (CH_2, C9); HRMS (ESI): m/z calcd. for $C_{11}H_{14}NaO_2S_2$: 265.0327, found: 265.0329 $[MNa]^+$.

Lab notebook reference: ixz_149

Synthesis of 4,5-dihydro-3*H*-benzo[*g*][1,5]dithionin-1(7*H*)-one – 162 and 8,9,19,20-tetrahydro-7*H*,18*H*-dibenzo[*g,p*][1,5,10,14]tetrathiacyclooctadecine-5,16(11*H*,22*H*)-dione – 163



162 **163**

EDC.HCl (194 mg, 0.958 mmol) was added to solution of 2-(((3-mercaptopropyl)thio)methyl)benzoic acid **161** (155 mg, 0.639 mmol), HOBt (116 mg, 0.766 mmol) and anhydrous DIPEA (280 µL, 1.60 mmol) in anhydrous DMF (12 mL). An immediate colour change colour to pale yellow observed. After total of 18 h of stirring at RT, the reaction deemed to have to completion by TLC analysis with colour change to fluorescent yellow noted. The resulting mixture was diluted with EtOAc (30 mL). The milky/white suspension was transferred to separating funnel and the organic phase was washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 10 mL), sat. $NaHCO_{3(aq)}$ (3 × 20 mL), H_2O (3 × 20 mL) and sat. brine (3 × 20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure

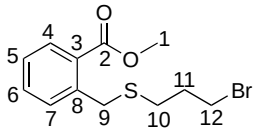
to yield a pale-yellow oil (253 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 10:90) to afford monomer **162** as clear colourless oil (91.0 mg, 64%) and dimer **163** as a white solid (20.5 mg, 7%);

Data for **162**;R_f = 0.42 (20:80, EtOAc:*n*–hexane); IR (solid state) ν_{max}/cm^{-1}: 3068w (C–H alkyl), 2921w (C–H alkyl), 2857w (C–H alkyl), 1726s (C=O aryl thioester), 1604w (CC aromatic), 1586w (CC aromatic), 1489w, 1452m, 1378w, 1237m, 1130m, 1008m, 938w, 874w, 764w, 716w; δ_H (400 MHz; $CDCl_3$) 7.44 (1H, td, *J* = 7.6, 1.4 Hz, C(3)H), 7.33 (1H, td, *J* = 7.6, 1.4 Hz, C(5)H), 7.22 (1H, dd, *J* = 7.6, 1.4 Hz, C(4)H), 7.17 (1H, dd, *J* = 7.6, 1.4 Hz, C(6)H), 3.73 (2H, s, br, $C(8)H_2$), 3.11 – 3.03 (2H, m, $C(11)H_2$), 2.92 (2H, s br, $C(9)H_2$), 1.90 – 1.80 (2H, m, $C(10)H_2$); δ_C (101 MHz; $CDCl_3$) 203.0 (C, C1) 137.6 (C, C7), 136.7 (C, C2), 131.0 (CH, C3), 129.9 (CH, C4), 127.9 (CH, C5), 125.3 (CH, C6), 37.0 (CH_2, C8) 34.2 (CH_2, C11), 33.3 (CH_2, C9), 30.7 (CH_2, C10); HRMS (ESI): m/z calcd. for $C_{11}H_{12}NaO_2S_2$: 247.0222, found: 247.0222 $[MNa]^+$; X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2236987, was crystallised by slow evaporation of *n*-hexane).

Data for **163**; R_f = 0.34 (20:80 EtOAc:*n*–hexane); IR (solid state)ν_{max} /cm^{-1}: 2923w (C–H alkyl), 2854w (C–H alkyl), 1727m (C=O aryl thioester), 1612w (CC aromatic), 1593w (CC aromatic), 1493w, 1457w, 1413w, 1380w, 1336w, 1288w, 1230w, 1186m, 1157s, 1087w, 1059w, 1010m, 961w, 933w, 887w, 779w, 754w, 702m, 613w, 570w, 481w; δ_H (400 MHz; $CDCl_3$) 7.65 (2H, dd, *J* = 7.6, 1.5 Hz, C(3)H), 7.47 (2H, dd, *J* = 7.6, 1.5 Hz, C(6)H), 7.44 (2H, td, *J* = 7.6, 1.5 Hz, C(5)H),7.30 (2H, td, *J* = 7.6, 1.5 Hz, C(4)H), 4.04 (4H, s, $C(8)H_2$), 3.10 (4H, t, *J* = 7.1 Hz, $C(11)H_2$), 2.54 (4H, t, *J* = 7.2 Hz, $C(9)H_2$), 2.06 – 1.91 (4H, m, $C(10)H_2$); δ_C (101 MHz; $CDCl_3$) 195.0 (C, C1) 138.6 (C, C7), 136.8 (C, C2), 131.8 (CH, C5), 131.5 (CH, C3), 128.1 (CH, C6), 127.2 (CH, C4), 32.4 (CH_2, C8), 31.1 (CH_2, C11) 29.2 (CH_2, C10), 29.1 (CH_2, C9); HRMS (ESI): m/z calcd. for $C_{22}H_{24}NaO_2S_4$: 471.0551, found: 471.0558 $[MNa]^+$; X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2236988, was crystallised by slow evaporation of *n*-hexane).

Lab notebook reference: ixz_150

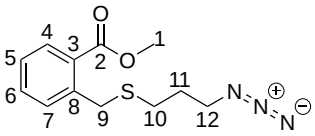
Synthesis of methyl 2-(((3-bromopropyl)thio)methyl)benzoate – 164



PPh_3 (1.48 g, 4.63 mmol) was added slowly in equal portions over a period of 1 min to a solution of alcohol **111** (618 mg, 2.57 mmol) and CBr_4 (1.72 g, 4.63 mmol) in anhydrous CH_2Cl_2 (26 mL) at 0 °C. A colour change to sunflower yellow was immediately noted. The mixture stirred for 2 h at 0 °C and then allowed to warm to RT to stir for an additional 18 h, with a colour change to orange observed. After total of 18 h, the reaction was deemed to have gone to completion by TLC. The reaction mixture was concentrated under reduced pressure to dryness to yield crude product as brown/orange oil (2.01g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 10:90) to afford title compound **164** as a clear colorless oil (108 mg 86%); R_f = 0.57 (50:50 EtOAc:*n*-hexane); IR (thin film) ν_{max}/cm^{-1}: 2949m (C–H alkyl), 1716s (C=O aryl ester), 1600w (CC aromatic), 1576w (CC aromatic), 1488m (CC aromatic), 1433w, 1292m, 1261s, 1190m, 1164w, 1120m, 1076s, 1046w, 964w, 840w, 801w, 767m, 714s, 663w, 580w, 561w; δ_H (400 MHz; $CDCl_3$) 7.91 (1H, dd, *J* = 7.7, 1.5 Hz, C(4)H), 7.45 (1H, td, *J* = 7.7, 1.5 Hz, C(7)H), 7.40 – 7.28 (2H, m, C(5+6)H), 4.13 (2H, s, C(9)H_2), 3.91 (3H, s, C(1)H_3), 3.46 (2H, t, *J* = 6.5 Hz, C(12)H_2), 2.58 (2H, t, *J* = 6.6 Hz, C(10)H_2), 2.14 – 1.98 (2H, m, C(11)H_2); δ_C (101 MHz; $CDCl_3$) 167.7 (C, C2) 140.4 (C, C8), 131.9 (CH, C7), 131.2 (CH, C4), 131.0 (CH, C6), 129.4 (C, C3), 127.1 (CH, C5), 52.2 (CH_3, C1), 34.4 (CH_2, C9) 32.3 (CH_2, C12), 32.1 (CH_2, C11), 29.9 (CH_2, C10); HRMS (ESI): m/z calcd. for $C_{12}H_{15}{}^{79}BrNaO_2S$: 324.9868, found: 324.9870 $[MNa]^+$.

Lab notebook reference: ixz_158 and ixz_172

Synthesis of methyl 2-(((3-azidopropyl)thio)methyl)benzoate – 165

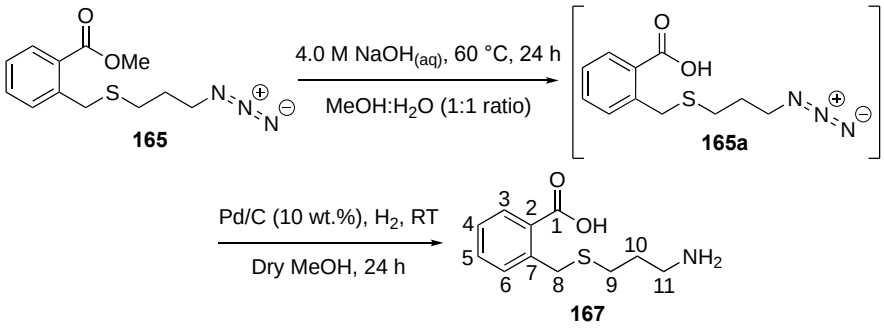


NaN_3 (342 mg, 5.30 mmol) was added to a colourless solution of methyl methyl benzoate **164** (1.06 g, 3.51 mmol) in anhydrous DMF (12 mL) at RT under Ar. The resulting suspension was then heated to 70 °C, whereupon an immediate colour change to pale yellow was noted. Upon further heating, the colour of the reaction suspension changed to milky white. After 20 h, the reaction was deemed to have gone to completion by TLC analysis, with a colour change to pale yellow creamy suspension noted. The reaction mixture was cooled to RT, before being quenched with addition of H_2O (30 mL). The resulting milky/white suspension was poured into a separating funnel containing EtOAc (30 mL). The aqueous layer was extracted with EtOAc

(3 × 20 mL), before the combined organic phases were washed with sat. brine (3 × 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield orange oil (1.09 g). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane, 10:90) to afford an azide **165** as a colourless oil (1.07 g, 80%); R_f = 0.23 (10:90 EtOAc:*n*–hexane); IR (neat) ν_{max}/cm^{-1}: 2953w (C–H alkyl), 2515w, 2094s (N=N=N azide), 1717s (C=O aryl tester), 1600w (CC aromatic), 1576w (CC aromatic), 1488w, 1447w, 1434w, 1292w, 1260s, 1190w, 1164w, 1121m, 1077s, 1046w, 966w, 893w, 801w, 765m, 715s, 663w, 580w, 556w, 467w; δ_H (400 MHz; $CDCl_3$) 7.92 (1H, dd, *J* = 7.6, 1.5 Hz, C(4)H), 7.45 (1H, td, *J* = 7.6, 1.5 Hz, C(6)H), 7.37–7.26 (2H, m, C(5+7)H), 4.12 (2H, s, C(9)H_2), 3.91 (3H, s, C(1)H_3), 3.35 (2H, t, *J* = 6.6 Hz, C(12)H_2), 2.51 (2H, t, *J* = 7.1 Hz, C(10)H_2), 1.86 – 1.72 (2H, m, C(11)H_2); δ_C (101 MHz; $CDCl_3$) 167.8 (C, C1), 140.5 (C, C8), 131.9 (CH, C6), 131.2 (CH, C4), 131.0 (CH, C7),129.5 (C, C3), 127.2 (CH, C5), 52.2 (CH_3, C1), 50.1 (CH_2, C12), 34.6 (CH_2, C9), 28.7 (CH_2, C10), 28.6 (CH_2, C11); HRMS (ESI): calcd. for $C_{12}H_{15}N_3NaO_2S$, 288.0777 Found: $[MNa]^+$, 288.0777 (–0.1 ppm error).

Lab notebook reference: ixz_177

Synthesis of 2-(((3-aminopropyl)thio)methyl)benzoic acid – 167

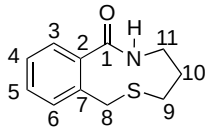


$NaOH_{(aq)}$ (4.0 M, 18.0 mL) was added dropwise over a period of 15 min to a colourless solution of methyl 2-(((3-azidopropyl)thio)methyl)benzoate **165** (1.01 g, 3.51 mmol) in MeOH (18.0 mL) at RT. A colour change to milky white suspension was noted immediately during dropwise addition. The resulting suspension was then heated to 60 °C, whereupon a colour change to a colourless solution was observed. After a total of 24 h, the reaction was deemed to have gone to completion by TLC analysis (complete consumption of methyl benzoate **165** was noted). The colourless reaction mixture was allowed to cool to RT and then acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (30 mL). The resulting acidified solution was poured into separating funnel. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), before combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a crude carboxylic acid **165a** product as a white solid. The crude product was directly used in the next reaction step without further purification. Next, crude carboxylic acid **165a** (873 mg) was

dissolved in MeOH (24.0 mL, degassed for 15 min) and placed under an Ar atmosphere. Palladium on carbon (56.0 mg, Pd 10% on carbon) was then added and the reaction vessel was evacuated and backfilled with H_2 (via balloon) three times, then stirred at RT under a slight positive pressure of H_2 (balloon) for 24 h. The reaction was then purged with Ar, filtered through Celite®, washed with MeOH (2 × 10 mL) and the solvent was removed in *vacuo* to afford the crude product as a brown solid (402 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: MeOH:EtOAc,70:30) afforded the title compound **167** as a white solid (202 mg, 38%); R_f = 0.28 (70:30, MeOH:EtOAc); melting point: 110 – 112 °C; IR (solid state) ν_{max}/cm^{-1}: 3064m (O–H alcohol/carboxylic acid/NH), 2922m (C–H alkyl), 2757m (O–H alcohol/carboxylic acid), 2214w, 1628w (C=O aryl carboxylic acid), 1600w (CC aromatic), 1579w (CC aromatic), 1524s, 1445w, 1412w, 1376s, 1331w, 1237w, 1150w, 1087w, 957w, 855w, 818w, 797w, 767w, 746w, 725s, 687w, 661m, 566w, 482w; δ_H (400 MHz; CD_3OD) 7.52 – 7.44 (1H, m, C(3)H), 7.37 – 7.31 (1H, m, C(5)H), 7.30 – 7.17 (2H, m, C(4+6)H), 4.09 – 4.03 (2H, m, C(8)H_2), 2.99 – 2.89 (2H, m, C(11)H_2), 2.53 – 2.43 (2H, m, C(9)H_2), 1.93 – 1.81 (2H, m, C(10)H_2); δ_C (126 MHz; CD_3OD) 178.0 (C, C1), 142.2 (C, C7), 137.2 (C, C2), 131.3 (CH, C5), 129.5 (CH, C3), 128.7 (CH, C6), 127.7 (CH, C4), 39.6 (CH_2, C11), 33.8 (CH_2, C8), 28.8 (CH_2, C10), 28.2 (CH_2, C9); HRMS (ESI): calcd. for $C_{11}H_{16}NO_2S$, 226.0896. Found: $[MH]^+$, 226.0896 (–0.1 ppm error), calcd. for $C_{11}H_{15}NNaO_2S$, 248.0716. Found: $[MNa]^+$, 248.0717 (–0.4 ppm error).

Lab notebook reference: ixz_185

Synthesis of 3,4,5,6-tetrahydrobenzo[*g*][1,5]thiazonin-7(1*H*)-one – 168

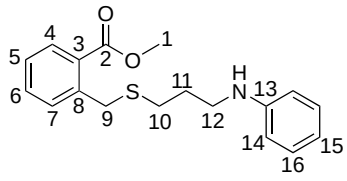


EDC.HCl (343 mg, 1.78 mmol) was added to clear colorless solution of 2-(((3-aminopropyl)thio)methyl)benzoic acid **167** (177 mg, 0.784 mmol), HOBt (127 mg, 0.941 mmol) and dry DIPEA (350 µL, 1.96 mmol) in anhydrous DMF (7.84 mL) at RT. An immediate colour change to pale yellow was observed. After total of 16 h of stirring at RT under Ar, the reaction was deemed to have gone completion by TLC analysis. The reaction mixture was diluted with EtOAc (30 mL) and poured into separating funnel. The diluted solution was washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 20 mL), sat. $NaHCO_{3(aq)}$ (3 × 20 mL) and sat. brine (4 × 20 mL), before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale yellow solid (161 mg). The crude product was purified by flash column chromatography (SiO_2, 20 mm column, eluent: EtOAc) to afford an amide **167** as a white solid

(56.4 mg, 35%). In solution in CD_2Cl_2, this compound exists as a >20:1 mixture of rotamer; R_f = 0.27 (EtOAc); melting point: 125 – 125 °C (from *n*–hexane:CH_2Cl_2); IR (solid state) ν_{max} / cm^{-1}: 3276w, 3172w (C–H alkyl), 3045w (C–H alkyl), 2921m (C–H alkyl), 2899w (C–H alkyl), 2838w, 1643s (C=O aryl amide), 1601w (CC aromatic), 1575w (CC aromatic), 1467w, 1448w, 1405s, 1348m, 1279w, 1232w, 1215w, 1148w, 1068w, 946w, 875w, 843m, 769s, 761s, 721m, 683m, 657w, 615m, 602m, 476m; NMR data for major rotamer only: δ_H (400 MHz; CD_2Cl_2) 7.37 (1H, td, *J* = 7.6, 1.5 Hz, C(3)H), 7.30 (1H, td, *J* = 7.6, 1.5 Hz, C(6)H), 7.23 (1H, dd, J = 7.6, 1.5 Hz, C(4)H), 7.16 (1H, dd, *J* = 7.6, 1.5 Hz, C(6)H), 5.90 (1H, br, s, NH), 4.07 (1H, d, *J* = 14.8 Hz, C(8)**H**H'), 3.28 (1H, d, *J* = 14.7 Hz, C(8)H**H'**), 3.21 – 3.01 (3H, m, $C(11)H_2$ + C(9)H**H'**), 2.83 – 2.71 (1H, m, C(9)**H**H'), 1.99 – 1.86 (1H, m, C(10)H**H'**), 1.49 – 1.35 (1H, m, C(10)**H**H'); δ_C (126 MHz; CD_2Cl_2) 173.4 (C, C1), 137.3 (C, C7), 135.3 (C, C2), 130.2 (CH, C3), 129.8 (CH, C4), 127.8 (CH, C5), 126.6 (CH, C6), 42.0 (CH_2, C8), 39.5 (CH_2, C11), 35.3 (CH_2, C9), 31.2 (CH_2, C10); HRMS (ESI): calcd. for $C_{11}H_{14}NOS$, 208.0791. Found: $[MH]^+$, 208.0795 (–2.2 ppm error), calcd. for $C_{11}H_{13}NNaOS$, 230.0610. Found: $[MNa]^+$, 230.0615 (–2.1 ppm error); X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2236990, was crystallised by slow evaporation of MeOH:$CHCl_3$).Characteristic NMR data for the minor rotamer can be seen at: δ_H (400 MHz; CD_2Cl_2) 6.30 (1H, s, NH), 3.88 (2H, s, $C(8)H_2$), 2.94 – 2.88 (1H, m, C(9)**H**H'); δ_C (126 MHz, CD_2Cl_2) 170.8 (C, C1), 136.8 (C, C7), 130.0 (CH, C5), 129.7 (CH, C3), 127.9 (CH, C6), 126.4 (CH, C4), 41.6 (CH_2, C11), 39.8 (CH_2, C8), 36.8 (CH_2, C10), 29.7 (CH_2, C9).

Lab notebook reference: ixz_187

Synthesis of methyl 2-(((3-(phenylamino)propyl)thio)methyl)benzoate – 169

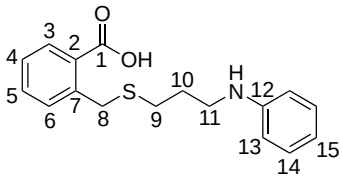


Aniline (550 µL, 5.79 mmol) was added dropwise over 1 min to a pale-yellow solution of bromide **164** (1.17 g, 3.86 mmol) in anhydrous MeCN (39 mL) at RT under Ar, along with KI (108 mg, 0.386 mmol) and K_2CO_3 (1.07 g, 7.72 mmol). The resulting beige suspension was heated at 90 °C for a total of 18 h, after which time the reaction was deemed to have gone to completion by TLC. The reaction mixture allowed to cool to RT and diluted with 40 mL of EtOAc. The diluted milky white suspension was poured into to separating funnel, where organic layer was washed with sat. brine (4 × 30 mL), before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale brown liquid (1.63 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent:

EtOAc:*n*–hexane, 20:80) to afford title compound **169** as a pale yellow oil (731 mg, 60%); R_f = 0.45 (50:50 EtOAc:*n*–hexane);IR (neat)ν_{max}/cm^{-1}: 3416w (N–H aryl secondary amine), 2945w (C–H alkyl), 1716s (C=O aryl ester), 1601s (CC aromatic), 1506s (CC aromatic), 1433m, 1297m, 1260s, 1180w, 1122m, 1077m, 1046w, 965w, 747s, 715s, 692s, 664w, 509w; δ_H (400 MHz; $CDCl_3$) 7.91 (1H, dd, *J* = 8.1 1.5 Hz, C(4)H), 7.47 – 7.37 (1H, m, C(7)H), 7.36 – 7.25 (2H, m, C(5+6)H), 7.25 – 7.11 (2H, m, C(15)H), 6.69 (1H, tt, *J* = 7.3, 1.1 Hz, C(16)H), 6.62 – 6.54 (2H, m, C(14)H), 4.12 (2H, s, C(9)H_2), 3.91 (3H, s, C(1)H_3), 3.19 (2H, t, *J* = 6.7 Hz, C(12)H_2), 2.53 (2H, t, *J* = 7.1 Hz, C(10)H_2), 1.84 (2H, app. p, *J* = 6.7 Hz, C(11)H_2); δ_C (101 MHz; $CDCl_3$) 167.9 (C, C1), 148.2 (C, C13), 140.6 (C, C8), 131.9 (CH, C7), 131.2 (CH, C6),131.0 (CH, C4), 129.6 (C, C3), 129.3 (CH, C15), 127.1 (CH, C5), 117.2 (CH, C16), 112.7 (CH, C14), 52.2 (CH_3, C1), 42.6 (CH_2, C12), 34.6 (CH_2, C9), 29.3 (CH_2, C10), 28.8 (CH_2, C11); HRMS (ESI): m/z calcd. for $C_{18}H_{22}NO_2S$: 316.1366, found: 316.1363 $[MH]^+$, m/z calcd. for $C_{18}H_{21}NNaO_2S$: 338.1185, found: 338.1184 $[MNa]^+$.

Lab notebook reference: ixz_198

Synthesis of 2-(((3-(phenylamino)propyl)thio)methyl)benzoic acid – 170

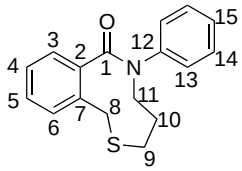


$NaOH_{(aq)}$ (4.0 M, 10.0 mL) was added dropwise over a period of 5 min to a pale-yellow solution of methyl 2-(((3-(phenylamino)propyl)thio)methyl)benzoate **169** (614 mg, 1.95 mmol) in MeOH (10 mL). A colour change to milky-white suspension was noted immediately during dropwise addition. The resulting suspension was stirred at 60 °C for 16 h, after which the reaction was deemed to have gone to completion by TLC analysis (complete consumption of methyl 2-(((3-(phenylamino)propyl)thio)methyl)benzoate **169** noted), with a colour change to pale yellow solution observed. The resulting mixture was acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (30 mL) and poured into separating funnel containing CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), before combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford title compound **170** as dark brown/green viscous oil (530 mg, 90%); R_f = 0.02 (50:50 EtOAc:*n*–hexane); IR (neat) ν_{max}/cm^{-1}: 3409w (N–H aryl secondary amine), 2925w (C–H alkyl/ O–H carboxylic acid), 2657w (O–H carboxylic acid), 1688m (C=O aryl carboxylic acid), 1601s (CC aromatic), 1575w (CC aromatic), 1505s (CC aromatic), 1374w, 1258m, 1129w, 1075w, 907m, 726s, 692s, 582m, 509w; δ_H (400 MHz; $CDCl_3$) 8.06 (1H, br, s, OH), 8.03 (1H, dd, *J* = 8.0 1.5 Hz, C(3)H), 7.47 (1H, td, *J* = 7.5 1.5 Hz,

C(6)H), 7.38 – 7.30 (2H, m, C(4+5)H), 7.25 – 7.16 (2H, m, C(14)H), 6.85 – 6.73 (3H, m, C(13+15)H), 4.17 (2H, s, C(8)H_2), 3.90 (1H, s, NH), 3.24 (2H, t, *J* = 7.1 Hz, C(11)H_2), 2.54 (2H, t, *J* = 7.1 Hz, C(9)H_2), 1.92 (2H, app. p, *J* = 7.1 Hz, C(10)H_2); δ_C (101 MHz; $CDCl_3$) 172.3 (C, C1), 145.2 (C, C12), 140.8 (C, C7), 132.3 (CH, C6), 131.8 (CH, C3), 131.1 (CH, C5), 129.4 (C, C2), 129.3 (CH, C14), 127.1 (CH, C4), 120.1 (CH, C15), 115.3 (CH, C13), 44.7 (CH_2, C11), 34.4 (CH_2, C8), 29.1 (CH_2, C9), 27.8 (CH_2, C10); HRMS (ESI): m/z calcd. for $C_{17}H_{20}NO_2S$: 302.1209, found: 302.1207 $[MH]^+$, m/z calcd. for $C_{17}H_{19}NNaO_2S$: 324.1029, found: 324.1025 $[MNa]^+$.

Lab notebook reference: ixz_200

Synthesis of 6-phenyl-3,4,5,6-tetrahydrobenzo[*g*][1,5]thiazonin-7(1*H*)-one – 171

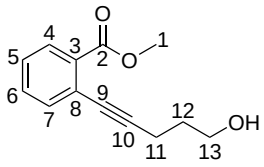


EDC.HCl (74.1 mg, 0.222 mmol) was added to a pale yellow solution of 2-(((3-(phenylamino)propyl)thio)methyl)benzoic acid **170** (44.6 mg, 0.148 mmol), HOBt (51.3 mg, 0.178 mmol) and anhydrous DIPEA (100 µL, 4.44 mmol) in anhydrous DMF (3 mL) at RT under Ar, with a colour change to orange/brown noted. The resulting mixture was stirred at RT for 24 h, after which time the reaction was deemed to have gone completion by TLC. The reaction mixture was diluted with EtOAc (30 mL) and transferred into separating funnel. The resulting milky/white organic layer was washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 20 mL), sat. $NaHCO_3$ (3 × 20 mL) and sat. brine (3 × 20 mL), before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a clear colourless oil (143 mg). The crude product was purified by flash column chromatography (SiO_2, 20 mm column, eluent: acetone:*n*–hexane, 20:80) to afford title compound **171** as a white solid (31.5 mg, 75%);R_f = 0.50 (40:60, EtOAc:*n*–hexane); IR (solid state) ν_{max}/cm^{-1}: 3064w (C–H alkyl), 3012w (C–H alkyl), 2924w (C–H alkyl), 1643s (C=O aryl lactam), 1593s (CC aromatic), 1493 (CC aromatic), 1460w, 1449w, 1398s, 1275m, 1162m, 1074w, 1011w, 752s, 707m, 664m; δ_H (400 MHz; $CDCl_3$) 7.52 – 7.28 (8H, m, C(3+4+5+6+13+14)H), 7.23 (1H, d, *J* = 7.7 Hz, C(15)H),4.20 (1H, d, *J* = 14.7 Hz, C(8)**H**H'), 3.92 – 3.80 (1H, m, C(11)**H**H'), 3.77 – 3.68 (1H, m, C(11)H**H'**), 3.54 (1H, d, *J* = 14.7 Hz, C(8)H**H'**), 3.00 – 2.90 (1H, m, C(9)**H**H'), 2.77 – 2.65 (1H, m, C(9)H**H'**), 1.92 – 1.78 (1H, m, C(10)**H**H'), 1.42 – 1.28 (1H, m, C(10)H**H'**); δ_C (126 MHz; $CDCl_3$) 171.5 (C, C1), 139.1 (C, C7), 136.62 (C, C12), 136.3 (C, C2), 130.1 (CH, C5), 129.7 (CH, C3), 129.5 (CH, C14), 127.9 (CH, C6),127.3 (CH, C4),126.7 (CH, C13),126.5 (CH, C15), 49.14 (CH_2, C11), 39.4 (CH_2, C8), 35.0 (CH_2, C9), 28.9 (CH_2, C10); HRMS (ESI): m/z calcd. for

$C_{17}H_{18}NOS$: 284.1104, found: 284.1104 $[MH]^+$, m/z calcd. for $C_{17}H_{17}NNaO_2S$: 306.0923, found: 306.0929 $[MNa]^+$; X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2235962, was crystallised by slow evaporation of *n*-hexane).

Lab notebook reference: ixz_210

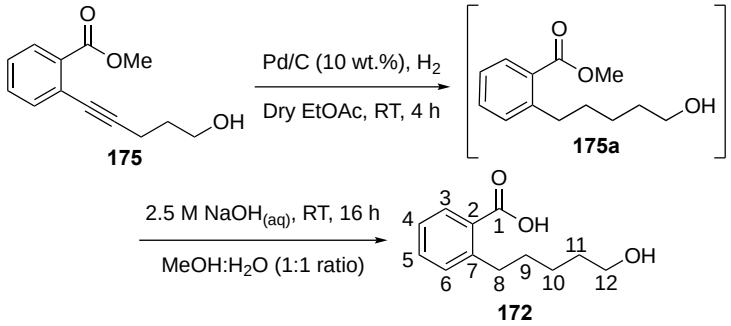
Synthesis of methyl 2-(5-hydroxypent-1-yn-1-yl) benzoate – 175



4-Pentyn-1-ol **174** (2.41 mL, 25.9 mmol) was added to solution of methyl 2-iodobenzoate **173** (2.00 mL, 13.6 mmol) in dry Et_3N (45 mL) at RT. After 5 min, CuI (256 mg, 1.36 mmol) and bis(triphenylphosphine)palladium chloride (478 mg, 68.1 µmol) was added to the pale-yellow solution. The resulting reaction mixture was stirred at RT. Upon stirring, the colour of the reaction mixture changed over 4 h from grey green (after 1 h) to dark brown (after 2 h) and finally black brown. After a total of 2 h, the reaction was deemed to have gone to completion by TLC. The dark brown reaction mixture was filtered through Celite®, washed with EtOAc (20 mL). The resulting filtrate was diluted with EtOAc (20 mL) was poured to into separating funnel and the organic layer was washes sequentially with 1.0 M $HCl_{(aq)}$ (3 × 40 mL) and sat. brine (1 × 40 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure to yield a brown/orange oil (3.11 g). The crude product was purified by flash column chromatography (SiO_2, 70 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford title compound as a yellow oil (2.58 g, 87%); R_f = 0.08 (70:30, EtOAc:*n*-hexane); IR (thin film) ν_{max}/cm^{-1}: 3403m (O–H alcohol), 3066w (C–H alkenyl), 2950m (C–H alkyl), 2878 (C–H alkyl), 2230w (CC alkynyl), 1715s (C=O aryl ester), 1597m (CC aromatic), 1556m (CC aromatic), 1485s (CC aromatic), 1447m, 1433m, 1348w, 1293s, 1276s, 1249s, 1190m, 1164w, 1130s, 1083s, 1044m, 986w, 960m, 923m, 847m, 825w, 798w, 756s, 736w, 701s, 655w, 537w, 502w; δ_H (400 MHz; $CDCl_3$) 7.83 (1H, dd, *J* = 7.8, 1.6 Hz, C(4)H), 7.45 (1H, dd, *J* = 7.5, 1.6 Hz, C(7)H), 7.36 (1H, dd, *J* = 7.7, 1.6 Hz, C(5)H), 7.25 (1H, td, *J* = 7.7, 1.6 Hz, C(6)H), 3.85 (3H, s, $C(1)H_3$), 3.79 (2H, t, *J* = 6.0 Hz, $C(13)H_2$), 3.05 (1H, s, br, OH), 2.55 (2H, t, *J* = 6.5 Hz, $C(11)H_2$), 1.81 (2H, app. p, *J* = 6.5 Hz, $C(12)H_2$); δ_C (101 MHz; $CDCl_3$) 167.9 (C, C2), 134.2 (CH, C7), 131.7 (CH, C5), 131.5 (C, C8), 130.2 (CH, C4), 127.3 (CH, C6), 124.3 (C, C3), 95.2 (C, C10), 79.7(C, C9), 61.4 (CH_2, C13), 52.2 (CH_3, C1), 31.0 (CH_2, C12), 16.5 (CH_2, C11); HRMS (ESI): m/z calcd. for $C_{13}H_{15}O_3$: 219.1021, found: 219.1016 $[MH]^+$, m/z calcd. for $C_{13}H_{14}NaO_3$: 241.0842, found: 241.0835 $[MNa]^+$.

Lab notebook reference: ixz_038

Synthesis of 2-(5-hydroxypentyl)benzoic acid – 172

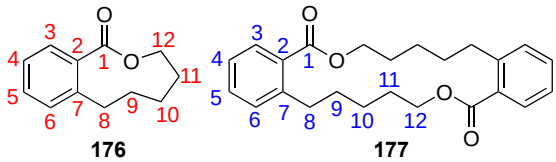


Pd/C (115 mg, Pd 10% on carbon) was added to the round bottom, previously purged under N_2 (for 10 min), containing methyl 2-(5-hydroxypent-1-yn-1-yl)benzoate **175** (1.13 g, 5.18 mmol) at RT. The alkyne was dissolved by addition of anhydrous EtOAc (26 mL, degassed for 10 min) and the reaction vessel was evacuated under *vacuo* and then backfilled with H_2 (via balloon) three times, then stirred at RT under an atmosphere of H_2 (balloon) for 4 h. The reaction was then purged with N_2 for 10 min, filtered through Celite® and washed with EtOAc (3×20 mL). The resulting filtrate was concentrated under reduced pressure to yield a crude alcohol **175a** as clear colourless oil (1.14 g). The crude product was directly used in the next reaction step without further purification. Next, $NaOH_{(aq)}$ (2.5 M, 10 mL) was added dropwise over a period of 5 min to a solution of alcohol **175a** (1.13 g, 5.10 mmol) in MeOH (10 mL). A colour change to cloudy lemon-yellow solution was immediately noted and the resulting suspension was stirred at RT. After 16 h, the reaction mixture was judged to be complete, based on TLC analysis (complete consumption of alcohol **175a** was noted). The pale-yellow solution was then acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (10 mL). The resulting white solid was collected by suction filtration and washed with H_2O (3×20 mL) and then air dried to yield title compound **172** as a white solid (760 mg, 73%); $R_f = 0.22$ (15:85, MeOH:CH_2Cl_2); melting point: 90–92 °C (from CH_2Cl_2); IR (solid state) ν_{max}/cm^{-1}: 3458s (O–H alcohol), 2943m (C–H alkyl), 2919m (C–H alkyl) 2858m (C–H alkyl), 2802 (C–H alkyl), 2627m (O–H carboxylic acid), 2560w, 2485w, 1687s (C=O carboxylic acid), 1602w (CC aromatic), 1576w (CC aromatic), 1491w (CC aromatic), 1464w, 1449w, 1418w, 1375w, 1354w, 1310s, 1287m, 1246s, 1209m, 1192m, 1167w, 1144m, 1110w, 1085m, 1062m, 1045s, 1017m, 983m, 894s, 873w, 835w, 824w, 804w, 769s, 744m, 715s, 685w, 656m, 584m, 558m, 486w; δ_H (400 MHz; CD_3OD) 7.85 (1H, dd, J = 7.7, 1.5 Hz, C(3)H), 7.41 (1H, td, J = 7.5, 1.5 Hz, C(5)H), 7.29 – 7.19 (2H, m, C(4+6)H), 3.54 (2H, t, J = 6.6 Hz, C(12)H_2), 2.97 (2H, s, C(8)H_2), 1.67 – 1.49 (4H, m, C(9+11)H_2) 1.47 – 1.35 (2H, m, C(10)H_2); δ_H (400 MHz; $CDCl_3$) 8.02 (1H, dd, J = 8.0, 1.6 Hz,

C(3)H), 7.46 (1H, td, *J* = 8.0, 1.6 Hz, C(5)H), 7.31 – 7.25 (2H, m, C(4+6)H), 6.47 (1H, s, br, OH), 3.68 (2H, t, *J* = 6.6 HZ, C(12)H_2), 3.07 – 2.98 (2H, m, C(8)H_2), 1.72 – 1.58 (4H, m, C(9+11)H_2) 1.55 – 1.40 (2H, m, C(10)H_2); δ_C (101 MHz; CD_3OD) 171.3 (C, C1), 145.5 (C, C7), 132.9 (CH, C5), 132.1 (CH, C6), 131.7 (CH, C3), 131.3 (C, C2), 126.8 (CH, C4), 62.9 (CH_2, C12), 35.4 (CH_2, C8), 33.4 (CH_2, C9), 32.9 (CH_2, C11), 27.0 (CH_2, C10); HRMS (ESI): m/z calcd. for $C_{12}H_{16}NaO_3$: 231.0992, found: 231.0997 $[MNa]^+$.

Lab notebook reference: ixz_040

Synthesis of 4,5,6,7-tetrahydrobenzo[*c*]oxonin-1(3*H*)-one – 176 and 8,9,10,11,19,20,21,22-octahydrodibenzo[*c*,*l*][1,10]dioxacyclooctadecine-5,16(7*H*,18*H*)-dione – 177



EDC.HCl (290 mg, 1.51 mmol) was added to solution of 2-(5-hydroxypentyl)benzoic acid **172** (209 mg, 1.00 mmol), HOBt (168 mg, 1.24 mmol) and dry DIPEA (440 µL, 2.50 mmol) in anhydrous DMF (10 mL). A colour change to pale yellow was noted upon after addition of DIPEA via syringe over a period of 30 sec. The resulting mixture was stirred at RT overnight under N_2 and progress of the reaction was monitored by TLC. After total of 18 h, the reaction wasn't judged to be complete, based on TLC analysis which showed carboxylic acid **172** still present. The resulting mixture was diluted with EtOAc (20 mL), before was transferred to separating funnel and the organic phase was washed sequentially with 1.0 M $HCl_{(aq)}$ (2 × 20 mL) and sat. brine (3 × 20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a white solid (303 mg). The crude product was purified by flash column chromatography (SiO_2, 20 mm column, eluent: EtOAc:*n*–hexane, 10:90) to afford monomer **176** (82.1 mg, 43%) and dimer **177** (21.4 mg, 6%) both as a white solid.

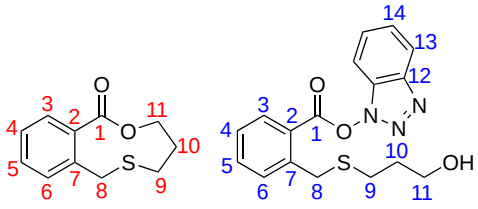
Data for **176**: R_f = 0.44 (50:50 EtOAc:*n*–hexane); IR (thin film) ν_{max}/cm^{-1}: 2930w (C–H alkyl), 1714s (C=O ester), 1604w (CC aromatic), 1451m (CC aromatic), 1287s, 1256s, 1123s, 1088w, 1044w, 979w, 777w, 748w, 704w; δ_H (400 MHz; $CDCl_3$) 7.81 (1H, dd, *J* = 7.7, 1.5 Hz, C(3)H), 7.38 (1H, td, *J* = 7.5, 1.5 Hz, C(5)H), 7.28 (1H, td, *J* = 7.5 1,5 Hz, C(4)H), 7.19 (1H, dd, *J* = 7.7, 1.5 Hz, C(6)H), 4.55 (2H, t, *J* = 5.7 Hz, C(12)H_2), 3.06 (2H, t, *J* = 6.0 Hz, C(8)H_2), 1.94 – 1.84 (2H, m, C(11)H_2), 1.76 – 1.68 (2H, m, C(9)H_2), 1.67 – 1.58 (2H, m, C(10)H_2); δ_C

(101 MHz; CD_3OD) 171.0 (C, C1), 145.6 (C, C7), 132.0 (CH, C5), 131.4 (C, C2), 131.1 (CH, C3), 130.7 (CH, C6), 126.8 (CH, C4), 67.2 (CH_2, C12), 35.1 (CH_2, C8), 31.6 (CH_2, C9), 27.8 (CH_2, C12), 26.6 (CH_2, C10); HRMS (APCI): m/z calcd. for $C_{12}H_{15}O_2$: 191.1067, found: 191.1061 $[MH]^+$;

Data for **177**; R_f = 0.35 (50:50 EtOAc:*n*–hexane); IR (thin film) ν_{max}/cm^{-1}: 2937w (C–H alkyl), 1699s (C=O ester), 1601w (CC aromatic), 1449m (CC aromatic), 1290s, 1272s, 1131s, 1110m, 1040w, 1044w, 948w, 752w, 709w; δ_H (400 MHz; $CDCl_3$) 7.85 (2H, dd, *J* = 7.7, 1.5 Hz, C(3)H), 7.42 (2H, td, *J* = 7.7, 1.5 Hz, C(5)H), 7.31 – 7.21 (4H, m, C(4+6)H), 4.36 (4H, t, *J* = 5.8 Hz, $C(12)H_2$), 2.95 (4H, t, *J* = 6.0 Hz, $C(8)H_2$), 1.90 – 1.74 (4H, m, $C(11)H_2$), 1.75 – 1.57 (8H, m, $C(10+12)H_2$); δ_C (101 MHz; CD_3OD) 169.4 (C, C1), 143.0 (C, C7), 132.0 (CH, C5), 131.2 (CH, C3), 130.8 (CH, C6), 130.6 (C, C2), 126.1 (CH, C4), 65.8 (CH_2, C12), 35.0 (CH_2, C8), 33.9 (CH_2, C9), 29.4 (CH_2, C12), 27.5 (CH_2, C10); HRMS (APCI): m/z calcd. for $C_{24}H_{29}O_4$: 381.2060, found: 381.2070 $[MH]^+$.

Lab notebook reference: ixz_041

Synthesis of 4,5-dihydro-3*H*-benzo[*g*][1,5]oxathionin-1(7*H*)-one – 113 and 1*H*-benzo[*d*][1,2,3]triazol-1-yl 2-(((3-hydroxypropyl)thio)methyl)benzoate – 112g



113 **112g**

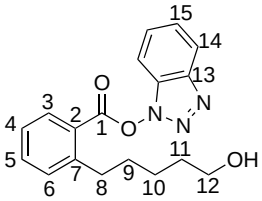
EDC.HCl (246 mg, 1.23 mmol) was added to a pale yellow solution of carboxylic acid **112** (186 mg, 0.823 mmol), HOBt (184 mg, 0.988 mmol) and anhydrous DIPEA (360 µL, 2.06 mmol) in anhydrous DMF (8 mL) at RT. A colour change to yellow was noted immediately upon addition of DIPEA via syringe over a period of 1 min. The resulting mixture was stirred at RT for a total of 1 h under Ar, after which time the reaction was diluted with EtOAc (20 mL) and poured into separating funnel. The resulting organic layer was washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 20 mL), sat. $NaHCO_3$ (3 × 20 mL), H_2O (3 × 20 mL) and sat. brine (1 × 20 mL), before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale-yellow oil (152 mg). The crude product was purified by flash column chromatography (SiO_2, 20 mm column, eluent: EtOAc:*n*–hexane, 20:80) to afford ester **113** (35.0 mg, 21%) as a white solid and HOBt **112g** adduct (35.0 mg, 21%) as milky/white viscous oil.

Data for **113**:R_f = 0.59 (50:50 EtOAc:*n*–hexane); δ_H (400 MHz; $CDCl_3$) 7.85 (1H, dd, *J* = 7.0, 2.0 Hz, C(3)H), 7.34 (2H, app. pd, *J* = 7.0, 2.0 Hz, C(4+5)H), 7.15 (1H, dd, *J* = 7.0, 2.0 Hz, C(6)H), 4.62 (2H, t, *J* = 6.0 Hz, C(11)H_2), 4.13 (2H, s, C(8)H_2), 2.92 – 2.85 (2H, m, C(9)H_2), 2.23 – 2.13 (2H, m, C(10)H_2); HRMS (ESI): m/z calcd. for $C_{11}H_{13}O_2S$: 209.0631, found: 209.0635 $[MH]^+$, m/z calcd. for $C_{11}H_{12}NaO_2S$: 231.0450, found: 231.0452 $[MNa]^+$, m/z calcd. for $C_{22}H_{24}Na_2O_4S_2$: 439.1008, found: 439.1017 $[2MNa]^+$;

Data for **112g**: R_f = 0.21 (50:50 EtOAc:*n*–hexane); δ_H (400 MHz; $CDCl_3$) 8.30 (1H, d, *J* = 8.4 Hz, C(3)H), 8.07 (1H, d, *J* = 8.4 Hz, C(6)H), 7.69 – 7.26 (6H, m, C(4+5+13+14)H), 4.11 (2H, s, C(8)H_2), 3.68 (2H, t, *J* = 6.3 Hz, C(11)H_2), 2.56 (2H, t, *J* = 6.3 Hz, C(9)H_2), 2.16 (1H, br s, OH), 1.79 (2H, app. p, *J* = 6.3 Hz, C(10)H_2); HRMS (ESI): m/z calcd. for $C_{17}H_{19}N_3NaO_3S$: 366.0883, found: 366.0878 $[MNa]^+$.

Lab notebook reference: ixz_081

Synthesis of 1*H*-benzo[*d*][1,2,3]triazol-1-yl 2-(5-hydroxypentyl)benzoate – 178

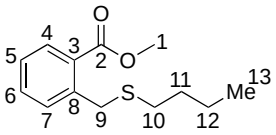


EDC.HCl (206 mg, 0.788 mmol) was added to solution of carboxylic acid **172** (106 mg, 0.525 mmol), HOBt (108 mg, 0.630 mmol) and anhydrous DIPEA (230 µL, 1.31 mmol) in anhydrous DMF (5 mL) at RT. A colour change to pale yellow was noted upon after addition of DIPEA via syringe over a period of 30 sec. The resulting mixture was stirred at RT for a total of 1 h under Ar, after which time the reaction was diluted with EtOAc (20 mL) and poured into separating funnel. The milky/white organic layer was washed sequentially with 1.0 M $HCl_{(aq)}$ (2 × 20 mL), sat. $NaHCO_3$ (2 × 20 mL), H_2O (2 × 20 mL) and sat. brine (3 × 20 mL), before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a colourless oil (187 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: *n*–hexane:Et_2O, 20:80) to afford title compound **178** HOBt adduct as a milky white viscous oil (132 mg, 77%); R_f = 0.18 (20:80, *n*–hexane:Et_2O); IR (thin film)ν_{max}/cm^{-1}: 3392m (O–H alcohol), 2933m (C–H alkyl), 2860w, (C–H alkyl), 1760m (C=O ester), 1574ww (CC aromatic), 1486m (CC aromatic), 1445w, 1376w, 1268w, 1281w, 1216s, 1155w, 1088m, 1048w, 963s, 917m, 810m, 780w, 764w, 737s, 698w, 664w, 638w, 606w, 500w; δ_H (400 MHz; $CDCl_3$) 8.30 (1H, dd, *J* = 7.7, 1.4 Hz, C(3)H), 8.08 (1H, dt, *J* = 7.7, 1.4 Hz, C(6)H), 7.62 (1H, td, *J* = 7.7, 1,4 Hz, C(5)H), 7.57 – 7.52 (1H, m, C(4)H), 7.50 – 7.37 (4H, m, C(14+15)H), 3.58 (2H, t, *J* = 6.5

Hz, C(12)H_2), 3.03 – 2.95 (2H, m, C(8)H_2), 1.87 (1H, br s, OH), 1.70 – 1.59 (2H, m, C(9)H_2), 1.59 – 1.50 (2H, m, C(11)H_2), 1.47 – 1.36 (2H, m, C(10)H_2); HRMS (ESI): m/z calcd. for $C_{18}H_{19}NaN_3O_2$: 348.1324, found: 348.1318 $[MNa]^+$.

Lab notebook reference: ixz_067

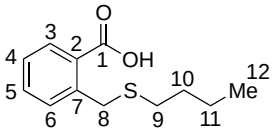
Synthesis of methyl 2-((butylthio)methyl)benzoate – 180



K_2CO_3 (1.04 g, 7.42 mmol) was added to a clear colorless solution of butane-1-thiol **179** (840 µL, 7.42 mmol) and methyl 2-(bromomethyl)benzoate **110** (880 mg, 3.71 mmol) in anhydrous DMF (12 mL) at RT. The resulting grey/purple suspension was then heated to 70 °C, whereupon a colour change to rose pink was noted. Upon further heating, the colour of the reaction suspension changed to peace orange. After 12 h, the reaction was deemed to have gone to completion by TLC. The reaction mixture was cooled to RT, before diluted with H_2O (30 mL) and poured into a separating funnel containing EtOAc (20 mL). The phases where separated and the aqueous layer was extracted with EtOAc (4 × 20 mL). The combined organic layers were washed sequentially with 1.0 M $HCl_{(aq)}$ (2 × 20 mL), 1.0 M $NaOH_{(aq)}$ (2 × 20 mL), sat. $NaHCO_{3(aq)}$ (2 × 20 mL) and sat. brine (1 × 20 mL), before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale orange oil (1.02 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 10:90) to afford title compound **180** as pale yellow oil (817 mg, 92%); R_f = 0.67 (20:80 EtOAc:*n*–hexane);IR (thin film) ν_{max}/cm^{-1}: 2954m (C–H alkyl), 2930m (C–H alkyl), 2872w (C–H alkyl), 1719s (C=O aryl ester), 1600w (CC aromatic), 1576w (CC aromatic), 1488m (CC aromatic), 1434w, 1379w, 1291w, 1260s, 1190m, 1164w, 1122m, 1077s, 1046w, 966w, 9120w, 839w, 767m, 714m, 663m, 580w, 474w; δ_H (400 MHz; $CDCl_3$) 7.90 (1H, dd, *J* = 7.7, 1.5 Hz, C(4)H), 7.43 (1H, td, *J* = 7.7, 1.5 Hz, C(6)H), 7.36 – 7.27 (2H, m, C(5+7)H), 4.11 (2H, s, C(9)H_2), 3.91 (3H, s, C(1)H_3), 2.42 (2H, t, *J* = 7.5 Hz, C(10)H_2), 1.58 – 1.46 (2H, m, C(11)H_2), 1.44 – 1.29 (2H, m, C(12)H_2), 0.87 (3H, t, *J* = 7.3 Hz, C(13)H_3); δ_C (101 MHz; $CDCl_3$) 167.9 (C, C2), 140.8 (C, C8), 131.7 (CH, C7), 132.1 (CH, C4), 130.9 (CH, C6), 129.6 (C, C3), 126.9 (CH, C5), 52.1 (CH_3, C1), 34.5 (CH_2, C9), 31.5 (CH_2, C10), 31.4 (CH_2, C11), 22.0 (CH_2, C12), 13.7 (CH_3, C13); HRMS (ESI): m/z calcd. for $C_{13}H_{18}NaO_2S$: 261.0920 found: 261.0912 $[MNa]^+$.

Lab notebook reference: ixz_104

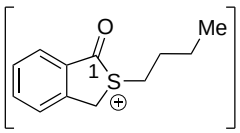
Synthesis of 2-((butylthio)methyl)benzoic acid – 181



$NaOH_{(aq)}$ (6.0 M, 17 mL) was added dropwise over a period of 3 min to solution of methyl 2-((butylthio)methyl)benzoate **180** (816 mg, 3.42 mmol) in MeOH (17 mL) at RT. A colour change to milky/white suspension was immediately noted. The resulting mixture was then heated to 70 °C, whereupon a colour change to pale yellow was noted. After 48 h, the reaction mixture was deemed to have gone to completion by TLC (complete consumption of methyl 2-((butylthio)methyl)benzoate **180** was noted). The reaction mixture was then cooled to 0 °C, before acidified to pH 2.0 with 3.0 M $HCl_{(aq)}$ (60 mL). The resulting white solid was collected by suction filtration and washed with cold H_2O (4 × 20 mL) and then air dried to yield title compound **181** as a white solid (691 mg, 90%);R_f = 0.55 (15:85 MeOH:CH_2Cl_2);melting point: 77 – 78 °C (from H_2O); IR (solid state) ν_{max}/cm^{-1}: 3496m (O–H alcohol), 2955m (C–H alkyl, O–H carboxylic acid), 2916w (C–H alkyl, O–H carboxylic acid), 2857m (C–H alkyl, O–H carboxylic acid), 2642m (C–H alkyl, O–H carboxylic acid), 1675s (C=O aryl carboxylic acid), 1597w (CC aromatic),1575s (CC aromatic), 1491w, 1466w, 1448w, 1426w, 1405m, 1300m, 1272s, 1220w, 1198w, 1168w, 1141w, 1080m, 1052w, 966w, 906m, 867w, 841w, 766m, 749m, 724w, 708s, 681w; δ_H (400 MHz; CD_3OD) 7.89 (1H, dd, *J* = 7.7, 1.5 Hz, C(3)H), 7.45 (1H, td, *J* =7.7, 1.5 Hz, C(5)H), 7.37 (1H, dd, *J* = 7.7, 1.5 Hz, C(5)H) , 7.32 (1H, td, *J* = 7.6, 1.6 Hz, C(4)H), 4.13 (2H, s, C(8)H_2), 2.40 (2H, t, *J* = 7.3 Hz, C(9)H_2), 1.55 – 1.42 (2H, m, C(10)H_2), 1.42 – 1.27 (2H, m, C(11)H_2), 0.87 (3H, t, *J* = 7.3 Hz, C(12)H_3); δ_C (101 MHz; $CDCl_3$) 173.1 (CO, C1), 142.0 (C, C7), 132.9 (CH, C6), 132.3 (CH, C5), 131.3 (CH, C3), 128.3 (C, C2), 127.2 (CH, C4), 34.7 (CH_2, C8), 31.7 (CH_2, C), 31.6 (CH_2, C), 22.1 (CH_2, C), 13.8 (CH_3, C12); HRMS (ESI): m/z calcd. for $C_{12}H_{16}NaO_2S$: 247.0763, found: 247.0767 $[MNa]^+$.

Lab notebook reference: ixz_117

Synthesis of 2-butyl-1-oxo-2,3-dihydro-1*H*-benzo[*c*]thiophen-2-ium – 182



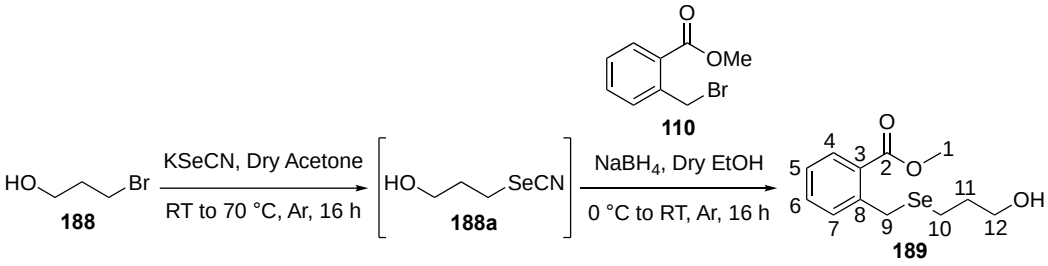
EDC.HCl (212 mg, 0.990 mmol) was added to a clear colourless solution of butyl thio methyl benzoic acid **181** (148 mg, 0.660 mmol), HOBt (139 mg, 0.792 mmol) and anhydrous DIPEA (290 µL, 1.65 mmol) in anhydrous DMF (7 mL) at RT. A colour change to pale yellow was noted immediately upon the addition of DIPEA via syringe over a period of 20 min. The

resulting mixture was stirred at RT for a total of 1 h under Ar, after which time the aliquot from reaction mixture (approximately 1 mL) was taken and subjected to analysis, the compound was not isolated; δ_C (101 MHz; $DCON(CD_3)_2$)* 173.1 (C, C1);*Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (BARF, 80.1 mg) was added to reaction mixture aliquot to shift the equilibrium towards the formation of sulfonium cation to observed the resonance for intermediate C=O on the ^{13}C NMR. HRMS (APCI): m/z calcd. for $C_{12}H_{15}OS$: 207.083813, found: 207.084693 $[M]^+$.

Lab notebook reference: ixz_120

Spectroscopic data is consistent with those previously reported in the literature.[201]

Synthesis of methyl 2-(((3-hydroxypropyl)selanyl)methyl)benzoate – 189

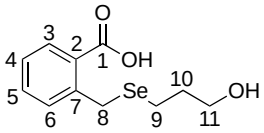


KSeCN (0.812 mg, 5.53 mmol) was added to a pale-yellow solution of 3-bromopropan-1-ol **188** (0.769 mg, 5.53 mmol) in anhydrous acetone (28 mL) at RT under Ar. The resulting pale-yellow suspension was then heated to 70 °C. A colour change to milky/white suspension was noted and a white solid (KBr) was seen to precipitate out of the reaction mixture. After a total of 16 h, the reaction was deemed to have gone to completion by TLC. The reaction mixture was cooled to RT, filtered and the filtrate cake was washed with acetone (3 × 20 mL). The reaction mixture was concentrated under reduced pressure to yield a crude 3-selenocyanatopropan-1-ol **188a** product as a pale-yellow oil (1.51 g). The crude product was directly used in the next reaction step without further purification. Next, $NaBH_4$ (0.868 g, 22.9 mmol) was added to a pale yellow solution of 3-selenocyanatopropan-1-ol **188a** (1.51 g, 9.18 mmol) and methyl 2-(bromomethyl)benzoate **110** (2.52 g, 13.8 mmol) in anhydrous EtOH (46 mL) at 0 °C. A colour change to yellow and effervescence (liberation of H_2) was observed. The resulting milky white suspension was stirred at 0 °C for 2 h, before being warmed to RT, with a colour change to clear colourless solution was noted. After a total of 16 h, the reaction was deemed to have gone to completion by TLC. The resulting reaction mixture was quenched by addition of H_2O (40 mL) and allowed to stirrer at RT for 2 min, before being concentrated under reduced pressure. The concentrated mixture was diluted with EtOAc (30 mL) and transferred into a separating funnel. The organic layer was washed with H_2O (4 × 20 mL), before being

dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale-yellow liquid (1.30 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 30:70) to afford title compound **189** as clear colourless oil (932 mg, 59%); R_f = 0.28 (40:60, EtOAc:*n*–hexane);IR (neat)ν_{max}/cm^{-1}: 3405w (O–H alcohol), 3079w (C–H aryl), 2946w (C–H alkyl), 1713s (C=O aryl ester), 1604w (CC aromatic), 1575 (CC aromatic), 1435m, 1297w, 1262s, 1189w, 1114m, 1074m, 750s, 708m, 665w; δ_H (400 MHz; $CDCl_3$) 7.92 (1H, dd, *J* = 8.1 1.5 Hz, C(4)H), 7.46 – 7.38 (1H, m, C(7)H), 7.26 (2H, dd, *J* = 8.1, 6.7, 1.5 Hz, C(5+6)H), 4.19 (2H, s, C(9)H_2), 3.91 (3H, s, C(1)H_3), 3.69 (2H, t, *J* = 6.1 Hz, C(12)H_2), 2.63 (2H, t, *J* = 7.2 Hz, C(10)H_2), 2.07 (1H, br s, OH),1.84 (2H, tt, *J* = 7.2 6.1 Hz, C(11)H_2), 1.94 – 1.80 (2H, m, C(11)H_2), 1.63 (1H, s, br, OH); δ_C (101 MHz; $CDCl_3$) 167.8 (C, C1), 142.2 (C, C8), 132.0 (CH, C7), 131.4 (CH, C4), 130.9 (CH, C6), 128.7 (C, C3), 126.9 (CH, C5), 62.3 (CH_2, C12), 52.2 (CH_3, C1), 32.8 (CH_2, C11), 25.8 (CH_2, C9), 20.7 (CH_2, C10); HRMS (ESI): m/z calcd. for $C_{12}H_{17}O_3{}^{80}Se$: 289.0337, found: 289.0339 $[MH]^+$, m/z calcd. for $C_{12}H_{16}NaO_3{}^{80}Se$: 311.0157, found: 311.0155 $[MNa]^+$.

Lab notebook reference: ixz_218

Synthesis of 2-(((3-hydroxypropyl)selanyl)methyl)benzoic acid – 190

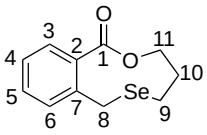


$NaOH_{(aq)}$ (4.0 M, 12 mL) was added dropwise over a period of 5 min to a clear colourless solution of methyl 2-(((3-hydroxypropyl)selanyl)methyl)benzoate **189** (672 mg, 2.44 mmol) in MeOH (12 mL) at RT. A colour change to milky/wite suspension was immediately noted and the reaction mixture was stirred at 60 °C for 18 h, at which point the reaction mixture was deemed to have gone to completion by TLC (complete consumption of methyl 2-(((3-hydroxypropyl)selanyl)methyl)benzoate **189** was noted). The reaction mixture was then acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (35 mL). The resulting white solid was collected by suction filtration and washed with H_2O (3 × 40 mL) and then air dried to yield title compound **190** as a white solid (561 mg, 84%); R_f = 0.77 (50:90, MeOH:EtOAc); melting point: 121– 123 °C (from MeOH:CH_2Cl_2,1:10); IR (solid state)ν_{max}/cm^{-1}: 3390m (O–H alcohol), 3327w (C–H aryl), 3068w (C–H alkyl, O–H carboxylic acid), 2935m (C–H alkyl, O–H carboxylic acid), 2657m (C–H alkyl), 2520w (C–H alkyl),1676s (C=O aryl carboxylic acid),1601w (CC aromatic), 1575w (CC aromatic), 1493w, 1449m, 1407m, 1267s, 1130m, 1051m, 921m, 878m, 763s, 706s, 659s, 539m; δ_H (400 MHz; CD_3OD) 7.92 (1H, dd, *J* = 7.7, 1.5 Hz, C(3)H), 7.43 (1H, td, *J* = 7.7, 1.5 Hz, C(5)H), 7.34–7.24 (2H, m, C(4+6)H), 4.21 (2H, s, C(8)H_2), 3.57 (2H, t, *J* = 6.3 Hz,

C(11)H_2), 2.57 (2H, t, *J* = 7.4 Hz, C(9)H_2), 1.87 – 1.75 (2H, m, C(10)H_2); δ_C (101 MHz; CD_3OD) 170.7 (C, C1), 144.0 (C, C7), 132.9 (CH, C5), 132.5 (CH, C3), 132.0 (CH, C6), 130.7 (C, C2), 127.7 (CH, C4), 64.4 (CH_2, C11), 34.3 (CH_2, C10), 26.1 (CH_2, C8), 20.9 (CH_2, C9); HRMS (ESI): m/z calcd. for $C_{11}H_{13}O_3{}^{80}Se$: 273.0035, found: 273.0026 [MH]−.

Lab notebook reference: ixz_220

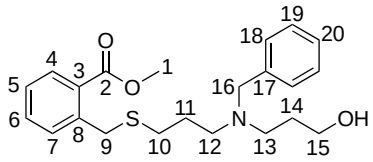
Synthesis of 4,5-dihydro-3*H*-benzo[*g*][1,5]oxaselenonin-1(7*H*)-one – 191



EDC.HCl (211 mg, 1.10 mmol) was added to a clear colourless solution of carboxylic acid **190** (174 mg, 0.735 mmol), HOBt (119 mg, 1.10 mmol) and dry DIPEA (320 µL, 1.84 mmol) in anhydrous DMF (7.50 mL). A colour change to a pale yellow was immediately noted and the reaction mixture was stirred at RT for 16 h of stirring at RT, before reaction was deemed to have to completion by TLC. The resulting mixture was diluted with EtOAc (30 mL) and transferred into separating funnel and the organic phase was washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 30 mL), sat. $NaHCO_3$ (3 × 30 mL) and sat. brine (4 × 30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a white solid (179 mg). The crude product was purified by flash column chromatography (SiO_2, 20 mm column, eluent: EtOAc:*n*–hexane, 20:80) to afford title compound **191** as a white solid (168 mg, 90%); R_f = 0.57 (40:60, EtOAc:*n*–hexane); IR (solid state)ν_{max}/cm^{-1}: 2963w (C–H alkyl), 2914w (C–H alkyl), 1712s (C=O aryl lactone), 1596w (CC aromatic), 1483w, 1451w, 1430w, 1382w, 1350w, 1263m, 1294m, 1195w, 1183w, 1142w, 1083w, 1043m, 971m, 889w, 864w, 846w, 788m, 702m, 659w, 626w, 497w, 463w; δ_H (400 MHz; $CDCl_3$) 7.89 (1H, dd, *J* = 7.5, 1.8 Hz, C(3)H), 7.35 (1H, td, *J* = 7.5, 1.8 Hz, C(5)H), 7.31 (1H, td, *J* = 7.5, 1.8 Hz, C(4)H), 7.16 (1H, dd, *J* = 7.5, 1.8 Hz, C(6)H), 4.64 (2H, t, *J* = 5.9 Hz, C(11)H_2), 4.21 (2H, s, C(8)H_2), 2.97 – 2.90 (2H, m, C(9)H_2), 2.46 – 2.33 (2H, m, C(10)H_2); δ_C (126 MHz; $CDCl_3$) 168.2 (C, C1), 143.1 (C, C7), 131.7 (CH, C5), 131.7 (CH, C3), 131.5 (C, C2), 130.0 (CH, C6), 127.4 (CH, C4), 66.1 (CH_2, C11), 31.4 (CH_2, C8), 30.7 (CH_2, C10), 25.7 (CH_2, C9); HRMS (ESI): m/z calcd. for $C_{11}H_{13}O_2{}^{80}Se$: 257.0075, found: 257.0077 $[MH]^+$, m/z calcd. for $C_{11}H_{12}NaO_2{}^{80}Se$: found: 278.9895 $[MNa]^+$; X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2235961, was crystallized by slow cooling of *n*-hexane from RT to –20 °C)

Lab notebook reference: ixz_221

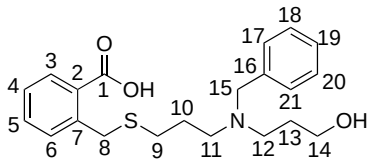
Synthesis of methyl 2-(((3-(benzyl(3-hydroxypropyl)amino)propyl)thio)methyl)benzoate – 193



K_2CO_3 (575 mg, 3.16 mmol) was added to a clear colorless solution of 3-(benzylamino)propan-1-ol **192** (530 µL, 3.15 mmol) and bromide **164** (638 mg, 2.10 mmol) in anhydrous MeCN (21 mL) at RT. The resulting suspension was then heated to 90 °C, whereupon a colour change to milky/white was noted. After 16 h, the reaction was deemed to have gone to completion by TLC (complete consumption of 3-(benzylamino)propan-1-ol **192** was noted), whereupon a colour change to cloudy pale yellow was observed . The reaction mixture was cooled to RT, before filtered through Celite® using Hirsch funnel and the filtrate residual was washed with cold MeCN (3 × 20 mL). The resulting solution was concentrated to dryness under reduced pressure to yield crude product as pale yellow oil (1.32 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 90:10) to afford an title compound **193** as pale yellow oil (657 mg, 81%); R_f = 0.26 (EtOAc); IR (thin film) ν_{max}/cm^{-1}: 3413m (O–H alcohol), 2947w (C–H alkyl), 1718s (C=O aryl ester), 1604w (CC aromatic), 1578w (CC aromatic), 1492m (CC aromatic), 14500m, 1434m, 1369w, 1292w, 1262s, 1189w, 1164w, 1122m, 1076s, 1046m, 1027m, 964w, 8401w, 801w, 733s, 715m, 698s, 663w, 591w, 580w, 515w, 471w; δ_H (500 MHz; $CDCl_3$) 7.89 (1H, dd, *J* = 7.7, 1.5 Hz, C(4)H), 7.33 (1H, td, *J* = 7.5, 1.5 Hz, C(7)H), 7.35–7.26 (7H, m, C(5+6+18+19+20)H), 4.09 (2H, s, C(9)H_2), 3.89 (3H, s, C(1)H_3), 3.70 (2H, t, *J* = 5.3 Hz, C(15)H_2), 3.57 (2H, s, C(16)H_2), 2.64 (2H, br s, C(13)H_2), 2.50 (2H, br s, C(12)H_2), 2.40 (2H, t, *J* = 7.3 Hz, C(12)H_2), 1.83 – 1.70 (4H, m, C(11+14)H_2): δ_H (126 MHz; $CDCl_3$) 167.9 (C, C2) 140.7 (C, C8), 138.3 (C, C17), 131.9 (CH, C7), 131.2 (CH, C4), 131.0 (CH, C6), 129.6 (C, C3), 129.2 (CH, C18), 128.5 (CH, C19), 127.3 (CH, C20), 127.1 (CH, C5), 64.1 (CH_2, C15), 58.9 (CH_2, C16), 54.0 (CH_2, C13), 52.9 (CH_2, C12), 52.2 (CH_3, C1), 34.8 (CH_2, C9), 29.8 (CH_2, C10), 28.2 (CH_2, C11), 26.5 (CH_2, C14); HRMS (ESI): m/z calcd. for $C_{22}H_{30}NaO_3S$: 388.1941, found: 388.1923 $[MH]^+$.

Lab notebook reference: ixz_159

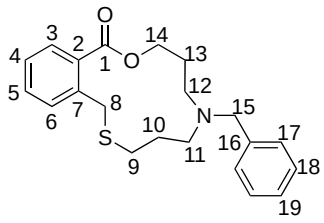
Synthesis of 2-(((3-(benzyl(3-hydroxypropyl)amino)propyl)thio)methyl)benzoic acid – 194



$NaOH_{(aq)}$ (4.0 M, 8.50 mL) was added dropwise over a period of 1 min to a clear colorless solution of methyl 2-(((3-(benzyl(3-hydroxypropyl)amino)propyl)thio)methyl)benzoate **193** (657 mg, 1.70 mmol) in MeOH (8.50 mL). A colour change to milky/white suspension was noted immediately during dropwise addition. The resulting suspension was then heated to 70 °C under Ar. After 16 h, the reaction was deemed to have gone to completion by TLC analysis (complete consumption of tertiary amine **193** noted), with a colour change to clear colourless solution observed. The reaction mixture was concentrated to dryness under reduced pressure to yield crude product as a white solid (3.32 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: MeOH:EtOAc, 50:50) to afford a title compound **194** as a white solid (632 mg, 99%); R_f = 0.48 (EtOAc); IR (solid state) ν_{max}/cm^{-1}: 3418m (O–H alcohol, O–H carboxylic), 3285m (C–H alkyl, O–H carboxylic acid), 3001w (C–H alkyl, O–H carboxylic acid), 2936m (C–H alkyl), 1706s (C=O aryl carboxylic acid), 1564w (CC aromatic), 1404s, 1287w, 1043w, 1012m, 923m, 889w, 797w, 767w, 744w, 701w, 645m, 619m, 461m; δ_H (400 MHz; CD_3OD) 7.68 – 7.60 (1H, m, C(3)H), 7.54 – 7.47 (2H, m, C(5+6)H), 7.46 – 7.37 (3H, m, C(18+19+20)H), 7.36 – 7.18 (3H, m, C(4+17+21)H), 4.19 – 4.11 (4H, m, C(8+15)H_2), 3.64 – 3.55 (2H, m, C(14)H_2), 3.09 – 2.95 (4H, m, C(11+12)H_2), 2.49 – 2.39 (2H, m, C(9)H_2), 1.95 – 1.83 (4H, m, C(10+13)H_2); δ_C (101 MHz; CD_3OD) 176.7 (CO, C1), 140.3 (C, C7), 138.2 (C, C16), 132.5 (C, C2), 131.8 (2 × CH, C17), 131.3 (CH, C3), 130.4 (CH, C5), 130.1 (2 × CH, C18), 129.9 (CH, C4/6), 129.8 (CH, C6/4), 127.7 (CH, C19), 60.3 (CH_2, C15), 58.1 (CH_2, C14), 52.6 (CH_2, C11), 51.4 (CH_2, C12), 34.6 (CH_2, C8), 29.4 (CH_2, C9), 27.6 (CH_2, C13), 24.8 (CH_2, C10); Unknow impurity: δ_C (101 MHz; CD_3OD) 179.0 (CO), 23.3 (CH_2, C10);HRMS (ESI): calcd. for $C_{21}H_{28}NO_3S$, 374.1784. Found: $[MH]^+$, 374.1777 (2.1 ppm error), calcd. for $C_{21}H_{27}NNaO_3S$, 396.1604. Found: $[MNa]^+$, 396.1591 (3.2 ppm error).

Lab notebook reference: ixz_542

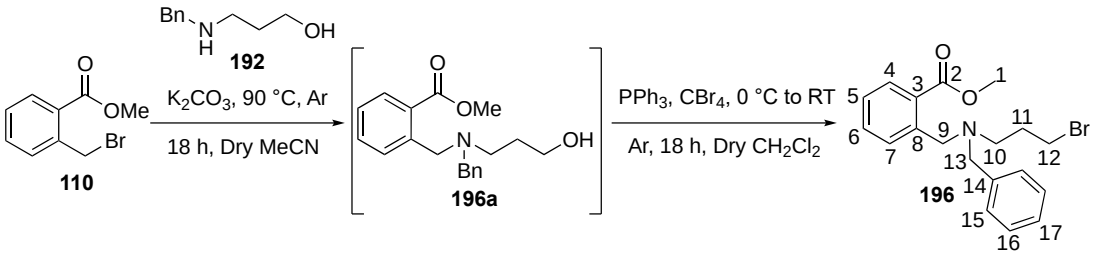
Synthesis of 6-benzyl-4,5,6,7,8,9-hexahydro-3*H*-benzo[*k*][*1*]oxa[*9*]thia[*5*]azacyclotridecin-1(11*H*)-one – 195



EDC.HCl (112 mg, 0.479 mmol) was added to clear colorless solution of carboxylic acid **194** (109 mg, 0.319 mmol), HOBt (87.1 mg, 0.383 mmol) and dry DIPEA (140 µL, 0.798 mmol) in anhydrous DMF (3.20 mL). An immediate colour change to pale yellow was observed. After total of 16 h of stirring at RT, the reaction was deemed to have gone to completion by TLC analysis. The reaction solution was diluted with EtOAc (30 mL) and poured into separating funnel. The diluted milky/white suspension was washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 10 mL), sat. $NaHCO_{3(aq)}$ (3 × 20 mL), H_2O (3 × 20 mL) and sat. brine (3 × 20 mL), before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a rose-pink oil (130 mg). The crude product was purified by flash column chromatography (SiO_2, 20 mm column, eluent: EtOAc:*n*–hexane, 20:80) to afford title compound **195** as clear colourless oil (40.1 mg, 35%); R_f = 0.74 (50:50, EtOAc:*n*–hexane); IR (thin film) ν_{max}/cm^{-1}: 3068w (C–H alkenyl), 3024w (C–H alkenyl), 2931m (C–H alkyl), 2802m (C–H alkyl),1712s (C=O aryl ester), 1600w (CC aromatic), 1493w (CC aromatic), 1450m, 1377w, 1291m, 1263s, 1122m, 1077m, 1044m, 949w, 909m, 768m, 725m, 698s, 660m, 471w; δ_H (400 MHz; $CDCl_3$) 7.74 (1H, dd, *J* = 7.8, 1.5 Hz, C(3)H), 7.45 (1H, td, *J* = 7.8, 1.5 Hz, C(5)H), 7.38 (1H, dd, *J* = 7.8, 1.5 Hz, C(6)H), 7.32 – 7.18 (6H, m, C(4+17+18+19)H), 4.55 (2H, t, *J* = 5.5 Hz, $C(14)H_2$), 4.15 (2H, s, $C(8)H_2$), 3.48 (2H, s, $C(15)H_2$), 2.59 (2H, s, br, $C(12)H_2$), 2.52–2.44 (2H, m, $C(9)H_2$), 2.35 (2H, s, br, $C(11)H_2$), 2.00 – 1.93 (2H, m, $C(10)H_2$), 1.53 – 1.49 (2H, m, $C(13)H_2$); δ_C (101 MHz; $CDCl_3$) 169.0 (C, C1), 141.1 (C, C7), 139.7 (C, C16), 131.9 (CH, C5), 131.5 (CH, C6), 131.1 (C, C2), 129.7 (CH, C3), 129.1 (CH, C17), 128.4 (CH, C18), 127.1 (CH, C4), 126.8 (CH, C19), 62.9 (CH_2, C14), 59.2 (CH_2, C8), 53.2 (CH_2, C11), 50.1 (CH_2, C12), 33.8 (CH_2, C15), 31.5 (CH_2, C9), 29.2 (CH_2, C10), 26.1 (CH_2, C13); HRMS (ESI): m/z calcd. for $C_{21}H_{26}NO_2S$: 356.1679, found: 3561676 $[MH]^+$.

Lab notebook reference: ixz_167

Synthesis of methyl 2-((benzyl(3-bromopropyl)amino)methyl)benzoate – 196

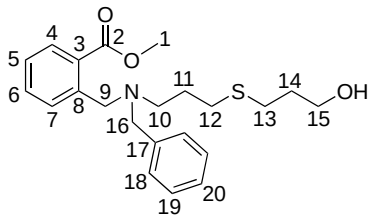


K_2CO_3 (2.30 g, 16.7 mmol) was added to a pale-yellow solution of *N*-benzyl-3-bromopropan-1-amine **192** (1.32 mL, 8.33 mmol) and methyl 2-bromomethylbenzoate **110** (2.29 g, 9.99 mmol) in anhydrous MeCN (42.0 mL) at RT under Ar. The resulting milky white suspension was stirred at 90 °C for 18 h under Ar, after which the reaction was deemed to have gone to completion by TLC, with a colour change to pale yellow suspension noted. The reaction mixture was then quenched by addition of H_2O (30 mL) and resulting solution poured into a separating funnel. The aqueous layer was extracted with EtOAc (3 × 20 mL), before the combined organic phases were washed sequentially with 1.0 M $HCl_{(aq)}$ (2 × 20 mL) and sat. brine (3 × 20 mL). The resulting organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield pale yellow liquid (2.83 g). The crude product was directly used in the next reaction step without further purification. Next, PPh_3 (2.91 g, 11.1 mmol) was added slowly in equal portions over a period of 2 min to a solution of alcohol **196a** (2.83 g) and CBr_4 (3.68 g, 11.1 mmol) in anhydrous CH_2Cl_2 (37.0 mL) at 0 °C under Ar. A colour change to sunflower yellow was immediately noted. The mixture stirred for 2 h at 0 °C and then allowed to warm to RT to stir for additional 16 h, with a colour change to wood brown observed. After total of 18 h, the reaction was deemed to have gone to completion by TLC. The reaction mixture was concentrated under reduced pressure to dryness to yield crude product as brown/orange oil (2.01g). The crude product was purified by flash column chromatography (SiO_2, 70 mm column, eluent: Et_2O:*n*–hexane, 10:90) to afford bromide **196** as a pale yellow oil (2.48 g 89%, over two steps); R_f = 0.38 (10:90, EtOAc:*n*–hexane); IR (neat) ν_{max}/cm^{-1}: 3075m (C–H alkyl), 3031w (C–H alkyl), 2950w, (C–H alkyl), 2807w (C–H alkyl), 1720s (C=O aryl ester), 1601w (CC aromatic), 1575w (CC aromatic), 1451m, 1433m, 1366w, 1266s, 1127m, 1079s, 1045w, 1028w, 967w, 910w, 806w, 733s, 698s, 649w, 560w, 467w; δ_H (400 MHz; $CDCl_3$) 7.76 (1H, dd, *J* = 7.8, 1.5 Hz, C(4)H), 7.65 (1H, d, *J* = 7.8 Hz, C(7)H), 7.46 (1H, td, *J* = 7.8, 1.5 Hz, C(6)H), 7.33 – 7.19 (6H, m, C(5+15+16+17)H), 3.93 (2H, s, $C(13)H_2$), 3.89 (3H, s, $C(1)H_3$), 3.53 (2H, s, $C(9)H_2$), 3.33 (2H, t, *J* = 6.9 Hz, $C(12)H_2$), 2.54 (2H, t, *J* = 6.8 Hz, $C(10)H_2$), 2.05 – 1.93 (2H, m, $C(11)H_2$); δ_C (101 MHz; $CDCl_3$) 168.7 (C, C2), 141.0 (C, C8), 139.3 (C, C3), 131.6 (CH, C6), 131.0 (C, C14), 130.1 (2 × CH, C4, C7, overlapping peaks), 128.9 (2 × CH, C15), 128.4 (2 × CH, C16), 127.1 (CH, C5), 126.9 (CH, C17), 58.8 (CH_2, C9), 56.7 (CH_2, C13), 52.2 (CH_2 + CH_3, C10, C1, overlapping peaks), 32.0 (CH_2,

C12), 30.5 (CH_2, C11); HRMS (ESI): calcd. for $C_{19}H_{23}{}^{79}BrO_2$, 376.0907. Found: $[MH]^+$, 376.0899 (2.0 ppm error).

Lab notebook reference: ixz_162

Synthesis of methyl 2-((benzyl(3-((3-hydroxypropyl)thio)propyl)amino)methyl)benzoate – 197

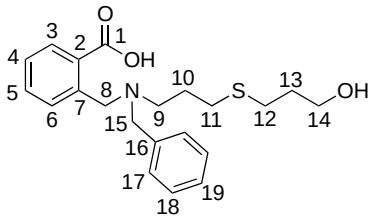


K_2CO_3 (672 mg, 4.86 mmol) was added to a colourless solution of 3-mercaptopropan-1-ol **97** (310 µL, 3.65 mmol) and methyl benzoate **196** (916 mg, 2.43 mmol) in anhydrous DMF (24 mL) at RT under Ar. The resulting suspension was then heated to 60 °C under Ar, whereupon an immediate colour change to cloudy pale yellow was noted. Upon further heating, the colour of the reaction suspension changed to cloudy yellow. After 12 h, the reaction was deemed to have gone to completion by TLC, with a colour change to blood orange observed. The reaction mixture was then quenched by addition of H_2O (30 mL) and the resulting milky/white suspension was poured into a separating funnel The aqueous layer was extracted with EtOAc (3 × 40 mL), before the combined organic phases were washed sequentially with sat. brine (3 × 40 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an orange oil (1.45 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 40:60) to afford title compound **197** as pale yellow viscous oil (1.14 g, 98%); R_f = 0.56 (50:50, EtOAc:*n*–hexane); IR (neat) ν_{max}/cm^{-1}: 3435w (O–H alcohol), 3409w (O–H alcohol), 3075w (C–H alkyl), 3031w (C–H alkyl), 2949w, (C–H alkyl), 2809w (C–H alkyl), 1719s (C=O aryl ester), 1604w (CC aromatic), 1575w (CC aromatic), 1456w, 1434m, 1268w, 1130m, 1080m, 746s, 699m, 666w; δ_H (400 MHz; $CDCl_3$) 7.75 (1H, dd, *J* = 7.8, 1.5 Hz, C(4)H), 7.66 (1H, d, *J* = 7.8, 1.1 Hz, C(7)H), 7.45 (1H, td, *J* = 7.7, 1.5 Hz, C(6)H), 7.32 – 7.21 (5H, m, C(5+18+19)H), 7.25 – 7.16 (1H, m, C(20)H), 3.92 (2H, s, C(16)H_2), 3.88 (3H, s, C(1)H_3), 3.68 (2H, t, *J* = 6.0 Hz, C(15)H_2), 3.54 (2H, s, C(9)H_2), 2.53 (2H, t, *J* = 7.1 Hz, C(10)H_2), 2.48 (2H, t, *J* = 7.1 Hz, C(13)H_2), 2.42 (2H, t, *J* = 7.3 Hz, C(12)H_2), 2.13 (1H, s, OH), 1.82 – 1.69 (4H, m, C(11+14)H_2); δ_C (101 MHz; $CDCl_3$) 168.9 (C, C2), 141.3 (C, C8), 139.5 (C, C3), 131.6 (CH, C6), 131.0 (C, C16), 130.0 (CH, C4), 130.0 (CH, C7), 128.9 (2 × CH, C18), 128.3 (2 × CH, C19), 127.0 (CH, C5), 126.8 (CH, C20), 62.0 (CH_2, C15), 58.7 (CH_2, C9), 56.8 (CH_2, C16), 52.9 (CH_2, C13),52.2

(CH_3, C1), 32.0 (CH_2, C14), 30.1 (CH_2, C13), 28.8 (CH_2, C10), 27.0 (CH_2, C11); HRMS (ESI): calcd. for $C_{22}H_{30}NO_2S$, 388.1941. Found: $[MH]^+$, 388.1939 (0.4 ppm error).

Lab notebook reference: ixz_207

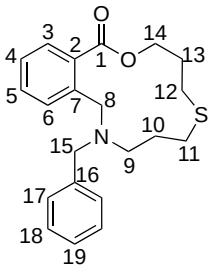
Synthesis of 2-((benzyl(3-((3-hydroxypropyl)thio)propyl)amino)methyl)benzoic acid – 198



$NaOH_{(aq)}$ (4.0 M, 12.5 mL,) was added dropwise over a period of 10 min to a pale yellow solution of alcohol **197** (1.92 g, 5.07 mmol) in MeOH (12.5 mL) at RT. A colour change to milky white suspension was noted immediately during dropwise addition. The resulting milky white suspension was then heated to 60 °C, whereupon a colour change to a cloudy beige was observed. After a total of 18 h, the reaction was deemed to have gone to completion by TLC analysis (complete consumption of alcohol **197** was noted). The colourless reaction mixture was allowed to cool to RT and then acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (25 mL). The resulting acidified solution was poured into a separating funnel. The aqueous layer was extracted with CH_2Cl_2 (4 × 30 mL), before combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford title compound **198** as am yellow viscous oil (850 mg, 45%); R_f = 0.54 (50:50, EtOAc:MeOH);IR (thin film)ν_{max}/cm^{-1}:3326w(O–H alcohol/carboxylic acid), 3063w (C–H alkyl), 2926w (C–H alkyl), 2869w (C–H alkyl), 2512w (O–H alcohol/carboxylic acid), 1699w, (C=O carboxylic acid), 1609w (CC aromatic), 1592 (CC aromatic), 1565w (CC aromatic), 1496w, 1455w, 1377m, 1294w, 1267w, 1202w, 1143w, 1053m, 961m, 910w, 811w, 748s, 699s, 656w, 615w, 511w, 491w; δ_H (400 MHz; $CDCl_3$) 8.23 – 8.14 (1H, m, C(3)H), 7.56 – 7.35 (8H, m, C(4+5+6+17+18+19)H), 4.35 (2H, s, C(15)H_2), 4.08 (2H, s, C(8)H_2), 3.69 (2H, t, J = 5.9 Hz, C(14)H_2), 3.04 – 2.96 (2H, m, C(9)H_2), 2.53 (2H, t, J = 7.3 Hz, C(12)H_2), 2.38 (2H, t, J = 6.9 Hz, C(11)H_2), 2.00 – 1.90 (2H, m, C(10)H_2), 1.81 – 1.70 (2H, m, C(13)H_2); δ_C (101 MHz; $CDCl_3$) 171.5 (C, C1), 135.4 (C, C16), 133.0 (CH, C3), 132.7 (CH, C6), 132.0 (CH, C5), 131.0 (C, C7), 130.9 (C, C2) , 130.4 (2 × CH, C17), 130.0 (CH, C4), 129.6 (C, C19), 129.4 (2 × CH, C18), 61.0 (CH_2, C14), 58.1 (CH_2, C15), 56.8 (CH_2, C8), 50.7 (CH_2, C9),32.3 (CH_2, C13), 29.0 (CH_2, C11), 28.5 (CH_2, C12), 24.1 (CH_2, C10),HRMS (ESI): calcd. for $C_{21}H_{28}NO_3S$, 374.1784. Found: $[MH]^+$, 374.1787 (–0.7 ppm error), calcd. for $C_{21}H_{27}NNaO_3S$, 396.1604. Found: $[MNa]^+$, 396.1604 (–1.0 ppm error).

Lab notebook reference: ixz_208

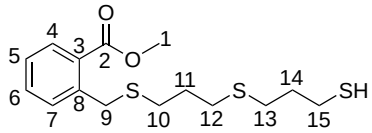
Synthesis of 10-benzyl-4,5,8,9,10,11-hexahydro-3*H*-benzo[*k*][1]oxa[5]thia[9]azacyclotridecin-1(7*H*)-one – 199



EDC.HCl (655 mg, 3.42 mmol) was added to a pale yellow solution of 2-((benzyl(3-((3-hydroxypropyl)thio)propyl)amino)methyl)benzoic acid **198** (850 mg, 2.28 mmol), HOBt (369 mg, 2.73 mmol) and dry DIPEA (991 µL, 5.69 mmol) in anhydrous DMF (22 mL) at RT under Ar. An immediate colour change to yellow was observed. After a total of 16 h of stirring at RT under Ar, the reaction was deemed to have gone completion by TLC analysis. The reaction mixture was diluted with EtOAc (30 mL) and poured into separating funnel. The diluted solution was washed sequentially with sat. $NaHCO_{3(aq)}$ (3 × 30 mL) and sat. brine (3 × 30 mL), before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an orange oil (784 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: Et_2O:*n*–hexane,10:90) to afford title compound **199** as a colourless liquid (302 mg, 37%);R_f = 0.81 (EtOAc);IR (neat) ν_{max}/cm^{-1}: 3026w (C–H alkyl), 3061w (C–H alkyl), 2941w (C–H alkyl), 2797w (C–H alkyl), 1718s (C=O aryl ester), 1602w (CC aromatic), 1495w, 1450m, 1380w, 1353w, 1270s, 1226m, 1184w, 1096s, 1060w, 1046w, 1029w, 983w, 945w, 907w, 887w, 874w, 859w, 837w, 819w, 789w, 750s, 699w, 624w, 510w, 477w; δ_H (500 MHz; CD_6D_6) 7.62 (1H, dt, *J* = 7.5, 1.1 Hz, C(3)H), 7.25 – 7.19 (2H, m, C(5+6)H), 7.16 – 7.09 (2H, m, C(17)H), 7.04 – 7.00 (3H, m, C(18+19)H), 6.98 – 6.92 (1H, m, C(4)H), 4.44 – 4.39 (2H, m, $C(14)H_2$), 3.70 (2H, s, $C(8)H_2$), 3.12 (2H, s, $C(15)H_2$), 2.51 – 2.44 (2H, m, $C(12)H_2$), 2.38 – 2.31 (2H, m, $C(11)H_2$), 2.21 – 2.15 (2H, m, $C(9)H_2$), 1.71 – 1.63 (2H, m, $C(13)H_2$), 1.63 – 1.55 (2H, m, $C(10)H_2$); δ_C (126 MHz; CD_6D_6) 170.1 (C, C1), 139.7 (C, C16), 137.9 (C, C7), 134.5 (C, C2), 132.0 (CH, C6), 130.3 (CH, C5), 130.3 (CH, C3), 129.4 (2 × CH, C17), 128.5 (2 × CH, C18),127.6 (CH, C19), 127.2 (CH, C4), 63.4 (CH_2, C14), 59.0 (CH_2, C15), 57.9 (CH_2, C8), 53.4 (CH_2, C9), 31.0 (CH_2, C13), 29.2 (CH_2, C11), 27.1 (CH_2, C10), 25.9 (CH_2, C12); HRMS (ESI): calcd. for $C_{21}H_{26}NO_2S$, 356.1679. Found: $[MNa]^+$, 356.1683 (–1.1 ppm error).

Lab notebook reference: ixz_209

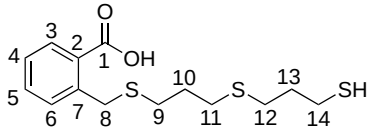
Synthesis of methyl 2-(((3-((3-mercaptopropyl)thio)propyl)thio)methyl)benzoate – 200



K_2CO_3 (415 mg, 3.01 mmol) was added to a colourless solution of 1,3-propanedithiol **158** (230 µL, 2.25 mmol) and methyl 2-(((3-bromopropyl)thio)methyl)benzoate **164** (455 mg, 1.50 mmol) in anhydrous DMF (15 mL) at RT. The resulting milky–pink suspension was stirred at RT for 18 h, after which the reaction was deemed to have gone to completion by TLC, with a colour change to milky white noted. The reaction mixture was then quenched by the addition of H_2O (30 mL) and resulting solution was poured into a separating funnel. The aqueous layer was extracted with EtOAc (4 × 30 mL), before the combined organic phases were washed sat. brine (3 × 20 mL). The resulting organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale yellow oil (1.07 g). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane, 10:90) to afford an thiol **200** as colouless oil (467 mg, 94%); R_f = 0.58 (50:50, EtOAc:*n*–hexane); IR (neat) ν_{max} / cm^{-1}: 2935w (C–H alkyl), 2557w (S–H thiol), 1717s (C=O aryl ester), 1600w (CC aromatic), 1488w (CC aromatic), 1434m, 1293w, 1263s, 1121m, 1077m, 1046, 967w, 749s, 716s, 666m, 580w; δ_H (400 MHz; $CDCl_3$) 7.91 (1H, dd, *J* = 7.7, 1.4 Hz, C(4)H), 7.44 (1H, td, *J* = 7.7, 1.4 Hz, C(6)H), 7.37 – 7.28 (2H, m, C(5+7)H), 4.11 (2H, s, C(9)H_2), 3.91 (3H, s, C(1)H_3), 2.66 – 2.50 (8H, m, C(10+12+13+15)H_2), 1.90 – 1.76 (4H, m, C(11+14)H_2), 1.36 (1H, t, *J* = 8.0 Hz, SH); δ_C (101 MHz; $CDCl_3$) 167.9 (C, C2), 140.7 (C, C8), 131.9 (CH, C7), 131.3 (CH, C4), 131.0 (CH, C6), 129.6 (C, C3), 127.2 (CH, C5), 52.3 (CH_3, C1), 34.7 (CH_2, C9), 33.4 (CH_2, C14), 30.9 (CH_2, C12), 30.7 (CH_2, C10), 30.4 (CH_2, C13), 29.2 (CH_2, C11), 23.5 (CH_2, C15),HRMS (ESI): calcd. for $C_{15}H_{23}O_2S_3$, 331.0855. Found: $[MH]^+$, 331.0852 (0.8 ppm error), calcd. for $C_{15}H_{22}NaO_2S_3$, 353.0674. Found: $[MNa]^+$, 353.0673 (0.5 ppm error).

Lab notebook reference: ixz_183

Synthesis of 2-(((3-((3-mercaptopropyl)thio)propyl)thio)methyl)benzoic acid – 201

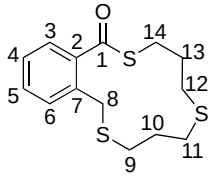


$NaOH_{(aq)}$ (4.0 M, 7.05 mL, degassed for 10 min) was added dropwise over a period of 10 min to a colourless solution of thiol **200** (466 mg, 1.41 mmol) in MeOH (7.05 mL, degassed for 15 min) at RT under Ar. A colour change to milky white suspension was noted immediately during dropwise addition. The resulting suspension was then heated to 60 °C under Ar, whereupon

a colour change to a colourless solution was observed. After a total of 18 h, the reaction was deemed to have gone to completion by TLC analysis (complete consumption of thiol **200** was noted). The colourless reaction mixture was allowed to cool to RT and then acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (30 mL). The resulting acidified solution was poured into separating funnel. The aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL), before combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a carboxylic acid **201** as a colourless oil (309 mg, 69%); R_f = 0.58 (EtOAc);IR (neat) ν_{max} / cm^{-1}: 3079w (C–H alkyl), 2917w (C–H alkyl/ O–H carboxylic acid), 2651w (C–H alkyl/ O–H carboxylic acid), 2534m (O–H carboxylic acid/ S–H thiol),1684s (C=O carboxylic acid), 1600w (CC aromatic), 1575w (CC aromatic), 1490w, 1445w, 1406w, 1296m, 1265s, 1198w, 1164w, 1132w, 1047w, 923w, 839w, 802w, 764s, 713s, 655m, 583w, 555w, 491w; δ_H (400 MHz; $CDCl_3$) 8.07 (1H, dd, *J* = 7.6, 1.5 Hz, C(3)H), 7.51 (1H, td, *J* = 7.6, 1.5 Hz, C(5)H), 7.43 – 7.30 (2H, m, C(5+7)H), 4.19 (2H, d, *J* = 6.4 Hz, C(8)H_2), 2.84–2.44 (8H, m, C(9+11+12+14)H_2), 2.04 – 1.73 (4H, m, C(10+13)H_2), 1.36 (1H, t, *J* = 8.1 Hz, SH); δ_C (101 MHz; $CDCl_3$) 173.2 (C, C1), 141.8 (C, C7), 133.0 (CH, C6), 132.3 (CH, C3), 131.4 (CH, C5), 128.3 (C, C2), 127.4 (CH, C4), 34.7 (CH_2, C8), 33.4 (CH_2, C13), 30.9 (CH_2, C9), 30.84 (CH_2, C11),30.4 (CH_2, C12), 29.2 (CH_2, C10), 23.5 (CH_2, C14); HRMS (ESI): calcd. for $C_{14}H_{20}NaO_2S_3$, 339.0518. Found: $[MNa]^+$, 339.0511 (2.1 ppm error).

Lab notebook reference: ixz_186

Synthesis of 4,5,8,9-tetrahydro-3H,7H-benzo[*k*][1,5,9]trithiacyclotridecin-1(11*H*)-one – 202

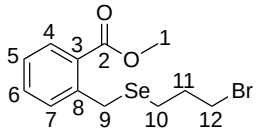


EDC.HCl (167 mg, 0.873 mmol) was added to a pale yellow solution of 2-(((3-((3-mercaptopropyl)thio)propyl)thio)methyl)benzoic acid **201** (184 mg, 0.582 mmol), HOBt (94.3 mg, 0.698 mmol) and dry DIPEA (250 µL, 1.46 mmol) in anhydrous DMF (6 mL) at RT. An immediate colour change to yellow was observed. After a total of 18 h of stirring at RT under Ar, the reaction was deemed to have gone completion by TLC analysis. The reaction mixture was diluted with EtOAc (30 mL) and poured into separating funnel. The diluted solution was washed with sat. brine (4 × 30 mL), before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a colourless oil (246 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc: *n*–hexane,10:90) to afford

an amide **202** as a pale-yellow oil (71.9 mg, 41%); R_f = 0.58 (50:50, EtOAc:*n*–hexane); IR (neat)ν_{max}/cm^{-1}: 2921m (C–H alkyl), 2853w (C–H alkyl), 1731w, 1659s (C=O aryl ester), 1597w (CC aromatic), 1571w (CC aromatic), 1480w, 1443m, 1343w, 1300w, 1207s, 1189s, 1042m, 952w, 913s, 885m, 806w, 762s, 682m, 650m, 587w, 549w, 508w; δ_H (400 MHz; CD_6D_6) 7.48 (1H, dd, *J* = 7.7, 1.4 Hz, C(3)H), 7.09 (1H, dd, *J* = 7.7, 1.4 Hz, C(6)H), 6.93 (1H, td, *J* = 7.7, 1.4 Hz, C(5)H), 6.82 (1H, td, *J* = 7.7, 1.4 Hz, C(4)H), 3.92 (2H, s, C(8)H_2), 2.85 – 2.71 (2H, m, C(14)H_2), 2.62 – 2.51 (2H, m, C(12)H_2), 2.39 – 2.32 (2H, m, C(11)H_2), 2.27 – 2.17 (2H, m, C(9)H_2), 1.87 – 1.75 (2H, m, C(13)H_2), 1.73 – 1.63 (2H, m, C(10)H_2); δ_C (126 MHz; CD_6D_6) 194.6 (C, C1), 139.7 (C, C7), 136.5 (C, C2), 131.6 (CH, C6), 131.3 (CH, C5), 127.7 (CH, C3), 127.2 (CH, C4), 32.9 (CH_2, C8), 31.9 (CH_2, C9), 31.3 (CH_2, C13), 31.0 (CH_2, C11), 30.7 (CH_2, C12), 30.7 (CH_2, C10), 29.0 (CH_2, C14); HRMS (ESI): calcd. for $C_{14}H_{18}NaOS_3$, 321.0412. Found: $[MNa]^+$, 321.0411 (0.2 ppm error).

Lab notebook reference: ixz_188

Synthesis of methyl 2-(((3-bromopropyl)selanyl)methyl)benzoate – 205

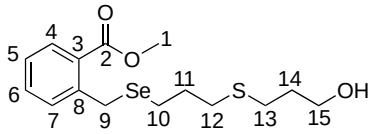


PPh_3 (3.29 g, 1.26 mmol) was added slowly in equal portions over a period of 5 min to a solution of alcohol **189** (3.01 g, 1.05 mmol) and CBr_4 (4.18 g, 1.26 mmol) in anhydrous CH_2Cl_2 (26 mL) at 0 °C. A colour change to yellow was immediately noted. The mixture stirred for 1 h at 0 °C and then allowed to warm to RT and stirred for additional 16 h, whilst a colour change to brown-orange was observed. After total of 18 h, the reaction was deemed to have gone to completion by TLC. The reaction mixture was concentrated under reduced pressure not to dryness to yield a brown/orange oil, which was diluted with EtOAc (30 mL). The resulting solid (Ph_3PO) was filtered, and the filter cake was washed with EtOAc (3 × 30 mL). The resulting filtrated was poured into separating funnel where organic layer was washed sequentially with sat. $NaHCO_3$ (3 × 20 mL) and sat. brine (3 × 30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an orange oil (8.89 g). The crude product was purified by flash column chromatography (SiO_2, 70 mm column, eluent: Et_2O:n-hexane, 10:90) to afford title compound **205** as a pale yellow oil (3.21 g 87%); R_f = 0.63 (40:60, EtOAc:*n*–hexane); IR (neat) ν_{max} / cm^{-1}: 2948w (C-H alkyl), 1714s (C=O aryl ester), 1599w (CC aromatic), 1575w (CC aromatic), 1488m (CC aromatic), 1433w, 1291m, 1260s, 1189m, 1112m, 1074m, 1045m, 965w, 839w, 751m, 707m, 664w, 614w, 558w; δ_H (400 MHz; $CDCl_3$) 7.93 (1H, dd, *J* = 7.5, 1.3 Hz, C(4)H), 7.42 (1H, td, *J* = 7.5, 1.3 Hz, C(6)H), 7.32 – 7.256 (2H,

m, C(5+7)H), 4.19 (2H, s, C(9)H_2), 3.91 (3H, s, C(1)H_3), 3.45 (2H, t, *J* = 6.5 Hz, C(12)H_2), 2.65 (2H, t, *J* = 7.1 Hz, C(10)H_2), 2.16 – 2.07 (2H, m, C(11)H_2); δ_C (126 MHz; $CDCl_3$) 167.4 (C, C2), 142.9 (C, C8), 131.9 (CH, C7), 131.2 (CH, C4), 130.8 (C, C3), 128.6 (CH, C6), 126.8 (CH, C5), 52.0 (CH_3, C1), 33.3 (CH_2, C12), 33.0 (CH_2, C11), 25.7 (CH_2, C9), 22.1 (CH_2, C10); HRMS (ESI): m/z calcd. for $C_{12}H_{16}{}^{79}BrO_2{}^{80}Se$: 350.9493, found: 350.9478 $[MH]^+$, m/z calcd. for $C_{12}H_{15}{}^{79}BrNaO_2{}^{80}Se$: 372.9313, found : 372.9290 $[MNa]^+$.

Lab notebook reference: ixz_224 and ixz_237

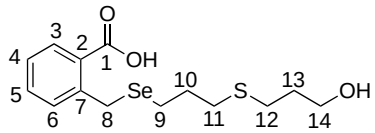
Synthesis of methyl 2-(((3-((3-hydroxypropyl)thio)propyl)selanyl)methyl)benzoate – 206



K_2CO_3 (583 mg, 4.22 mmol) was added to a pale-yellow solution of thiol **97** (221 µL, 3.17 mmol) and bromide **205** (739 mg, 2.11 mmol) in anhydrous DMF (21 mL) at RT. The resulting milky/white suspension was then heated to 70 °C. After 18 h, the reaction was deemed to have gone to completion by TLC, with a colour change to yellow suspension noted. The reaction mixture allowed to cool to RT, before it was quenched with H_2O (30 mL). The diluted milky/white suspension was poured into separating funnel and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 30 mL), sat. $NaHCO_3$ (3 × 30 mL) and sat. brine (4 × 30 mL). The resulting layer was collected and dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale yellow oil (1.15 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford title compound **206** as pale yellow liquid (719 mg, 94%); R_f = 0.43 (50:50, EtOAc:*n*–hexane); IR (neat) ν_{max} / cm^{-1}: 3428w (O–H alcohol), 3009w (C–H aryl), 2948w (C–H alkyl), 1715s (C=O aryl ester), 1601w (CC aromatic), 1578 (CC aromatic), 1493w, 1435m, 1262m, 1113m, 1074m, 750s, 708m, 665w; δ_H (500 MHz; $CDCl_3$) 7.92 (1H, dd, *J* = 7.6, 1.6 Hz, C(4)H), 7.42 (1H, td, *J* = 7.6, 1.6Hz, C(6)H), 7.33 – 7.25 (2H, m, C(5+7)H), 4.18 (2H, s, C(9)H_2), 3.91 (3H, s, C(1)H_3), 3.74 (2H, app. q, *J* = 5.9 Hz, C(15)H_2), 2.67 – 2.53 (6H, m, C(10+12+13)H_2), 1.93 – 1.77 (4H, m, C(11+12)H_2), 1.64 (1H, s, br, OH); δ_C (126 MHz; $CDCl_3$) 167.8 (C, C2), 142.2 (C, C8), 132.0 (CH, C7), 131.4 (CH, C4), 130.9 (CH, C6), 128.8 (C, C3), 126.8 (CH, C5), 61.7 (CH_2, C15), 52.2 (CH_3, C1), 32.1 (CH_2, C14), 31.9 (CH_2, C11), 30.1 (CH_2, C12), 28.8 (CH_2, C13), 25.9 (CH_2, C9), 23.2 (CH_2, C10); HRMS (ESI): m/z calcd. for $C_{15}H_{23}O_3S^{80}Se$: 363.0528, found: 363.0526 $[MH]^+$, m/z calcd. for $C_{15}H_{22}NaO_3S^{80}Se$: 385.0347, found : 385.0345 $[MNa]^+$.

Lab notebook reference: ixz_228

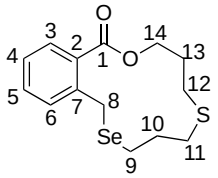
Synthesis of 2-(((3-((3-hydroxypropyl)thio)propyl)selanyl)methyl)benzoic acid – 207



$NaOH_{(aq)}$ (4.0 M, 12.5 mL) was added dropwise over a period of 1 min to a clear colourless solution of methyl 2-(((3-((3-hydroxypropyl)thio)propyl)selanyl)methyl)benzoate **206** (446 mg, 1.23 mmol) in MeOH (12.5 mL) at RT. A colour change to milky/wite suspension was immediately noted and the reaction mixture was stirred at 60 °C for 16 h, at which point the reaction mixture was deemed to have gone to completion by TLC (complete consumption of selenide **206** was noted). The transparent colourless reaction mixture was allowed to cool to RT and then acidified to pH 1.0 with 1.0 M $HCl_{(aq)}$ (30 mL). The resulting acidified solution was poured into separating funnel and aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a carboxylic acid **207** as a colourless oil (418 mg, 98%); R_f = 0.28 (15:85, MeOH:CH_2Cl_2); IR (neat) ν_{max}/cm^{-1}: 3353m (O–H alcohol/ carboxylic acid), 3068w (C–H aryl, O–H alcohol/ carboxylic acid), 2930m (C–H alkyl, O–H carboxylic acid), 2627w (C–H alkyl, O–H alcohol/ carboxylic acid), 2534w (O–H carboxylic acid) 1686s (C=O aryl carboxylic acid), 1599w (CC aromatic), 1574w (CC aromatic), 1489w (CC aromatic), 1415w, 1250s, 1044m, 953s, 757s, 707s, 649m; δ_H (500 MHz; CD_2Cl_2) 8.07 (1H, dd, *J* = 8.3, 1.5 Hz, C(3)H), 7.51 (1H, td, *J* = 7.6, 1.5 Hz, C(5)H), 7.39 – 7.33 (2H, m, C(4+6)H), 7.18 (2H, br, s, OH), 4.28 (2H, s, C(8)H_2), 3.80 (2H, t, *J* = 6.1 Hz, C(14)H_2),2.71–2.57 (6H, m, C(9+11+12)H_2), 1.99 – 1.83 (4H, m, C(10+13)H_2); δ_C (126 MHz; CD_2Cl_2) 171.7 (C, C1), 143.4 (C, C7), 133.0 (CH, C6), 132.2 (CH, C5), 131.5 (CH, C3), 128.4 (C, C2), 127.2 (CH, C4),61.9 (CH_2, C14), 32.4 (CH_2, C11), 32.1 (CH_2, C12), 30.7 (CH_2, C10), 28.8 (CH_2, C13), 25.9 (CH_2, C8), 23.5 (CH_2, C9); HRMS (ESI): calcd. for $C_{14}H_{21}O_3S^{80}Se$, 349.0371. Found: $[MH]^+$, 349.0370 (0.4 ppm error), calcd. for $C_{14}H_{20}NaO_3S^{80}Se$, 371.0191. Found: $[MNa]^+$, 371.0190 (0.0 ppm error).

Lab notebook reference: ixz_229

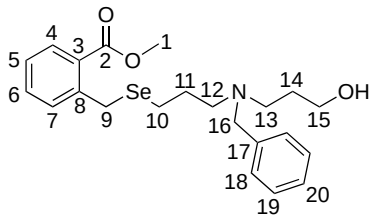
Synthesis of 4,5,8,9-tetrahydro-3H,7H-benzo[k][1]oxa[5]thia[9]selenacyclotridecin-1(11H)-one – 203



EDC.HCl (342 mg, 1.79 mmol) was added to a colouless solution of 2-(((3-((3-hydroxypropyl)thio)propyl)selanyl)methyl)benzoic acid **207** (414 mg, 1.19 mmol), HOBt (193 mg, 1.43 mmol) and dry DIPEA (520 µL, 2.98 mmol) in anhydrous DMF (24 mL) at RT under Ar, with a colour change to pale yellow noted. The resulting mixture was stirred at RT for 24 h under Ar, after which time the reaction was deemed to have gone completion by TLC. The reaction mixture was diluted with EtOAc (40 mL) and transferred into separating funnel. The resulting yellow organic layer was washed sequentially with 1.0 M $HCl_{(aq)}$ (2 × 20 mL), sat. $NaHCO_{3(aq)}$ (3 × 20 mL) and sat. brine (3 × 20 mL), before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale yellow oil (240 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: 60 EtOAc:*n*–hexane, 20:80) to afford title compound **203** as a colourless oil (230 mg, 59%); R_f = 0.64 (50:50, EtOAc:*n*–hexane); IR (thin film) ν_{max}/cm^{-1}: 2953w (C–H alkyl), 2861w (C–H alkyl), 1713s (C=O aryl lactam), 1604w (CC aromatic), 1449w, 1378w, 1293w, 1261s, 1115m, 1074w, 767w; δ_H (500 MHz; C_6D_6) 7.81 (1H, dd, *J* = 7.7, 1.4 Hz, C(3)H), 7.18 (1H, dd, *J* = 7.7, 1.4 Hz, C(6)H), 7.02 (1H, td, *J* = 7.7, 1.4 Hz, C(5)H), 6.88 (1H, td, J = 7.7, 1.4 Hz, C(4)H), 4.22 – 4.16 (2H, m, C(14)H_2), 4.13 (2H, s, C(8)H_2) 2.41 (2H, t, *J* = 7.2 Hz, C(12)H_2), 2.31 (2H, t, *J* = 6.9 Hz, C(9)H_2), 2.29 – 2.25 (2H, m, C(11)H_2), 1.73 – 1.60 (4H, m, C(10+13)H_2); δ_C (126 MHz; C_6D_6) 168.1 (C, C1), 140.8 (C, C7), 132.0 (CH, C6), 131.9 (CH, C5), 131.2 (C, C2) , 130.8 (CH, C3), 126.7 (CH,C4), 63.6 (CH, C14), 31.1 (CH_2, C11), 30.6 (CH_2, C10), 29.7 (CH_2, C13), 28.5 (CH_2, C12), 24.4 (CH_2, C8), 24.1 (CH_2, C9); HRMS (ESI): calcd. for $C_{14}H_{18}NaO_2S^{80}Se$, 353.0085. Found: $[MNa]^+$, 353.0083 (0.6 ppm error).

Lab notebook reference: ixz_230

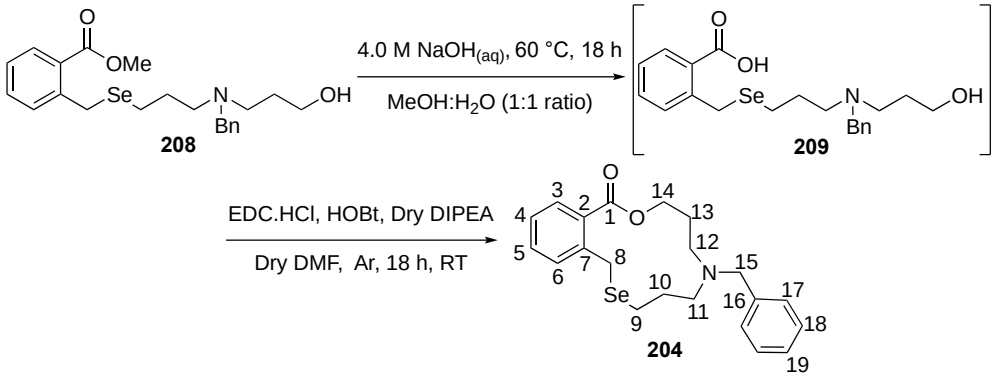
Synthesis of methyl 2-(((3-(benzyl(3-hydroxypropyl)amino)propyl)selanyl)methyl)benzoate – 208



K_2CO_3 (393 mg, 2.84 mmol) was added to a pale-yellow solution of 3-(benzylamino)propan-1-ol **192** (1.32 mL, 8.33 mmol) and methyl 2-(((3-bromopropyl)selanyl)methyl)benzoate **205** (496 mg, 1.42 mmol) in anhydrous MeCN (29.0 mL) at RT under Ar. The resulting milky white suspension was stirred at 95 °C for 18 h under Ar, after which the reaction was deemed to have gone to completion by TLC, with a colour change to pale yellow suspension noted. The reaction mixture was then quenched by addition of H_2O (30 mL) and resulting solution poured into a separating funnel. The aqueous layer was extracted with EtOAc (3 × 30 mL), before the combined organic phases were washed with sat. brine (3 × 20 mL). The resulting organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale-yellow liquid (622 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane, 50:50 to 60:50) to afford title compound **208** as a pale yellow oil (266 mg, 35%); R_f = 0.19 (50:50, EtOAc:*n*–hexane); IR (neat) ν_{max}/cm^{-1}: 3394w (O–H alcohol), 2947w (C–H alkyl), 2809w (C–H alkyl),1716s (C=O aryl ester), 1599w (CC aromatic), 1578w (CC aromatic), 1434m (CC aromatic), 1261s, 1189w, 1113s, 1073s, 756m, 699s, 665w, 616w; δ_H (500 MHz; $CDCl_3$) 7.91 (1H, dd, *J* = 7.7, 1.5 Hz, C(4)H), 7.39 (1H, td, *J* = 7.7, 1.5 Hz, C(6)H), 7.34 – 7.29 (2H, m, C(7+20)H), 7.29 – 7.25 (4H, m, C(18+19)H), 7.25 – 7.21 (1H, m, C(5)H), 4.15 (2H, s, C(9)H_2), 3.89 (3H, s, C(1)H_3) 3.70 (2H, t, *J* = 5.7, 5.3 Hz, C(15)H_2), 3.53 (2H, s, C(16)H_2), 2.61 (2H, t, *J* = 5.8 Hz, C(13)H_2), 2.52 – 2.43 (4H, m, C(10+12)H_2), 1.85 – 1.75 (2H, m, C(11)H_2), 1.74 – 1.66 (2H, m, C(14)H_2); δ_C (126 MHz; $CDCl_3$) 167.8 (C, C2), 142.4 (C, C8), 138.4 (C, C17), 132.0 (CH, C6), 131.5 (CH, C4), 131.0 (CH, C7), 129.3 (2 × CH, C(18)H), 129.0 (C, C3), 128.6 (2 × CH, C(19)H), 127.4 (CH, C20), 126.9 (CH, C5), 64.3(CH_2, C15), 59.0 (CH_2, C16), 54.2 (CH_2, C13), 53.9 (CH_2, C12), 52.2 (CH_2, C1), 28.25 (CH_2, C14), 27.5 (CH_2, C11), 26.1 (CH_2, C8), 22.0 (CH_2, C10); HRMS (ESI): calcd. for $C_{22}H_{30}NO_3{}^{80}Se$, 436.1385. Found: $[MH]^+$, 436.1372 (3.3 ppm error).

Lab notebook reference: ixz_225

Synthesis of 6-benzyl-4,5,6,7,8,9-hexahydro-3*H*-benzo[*k*][1]oxa[9]selena[5]azacyclotridecin-1(11*H*) – 204

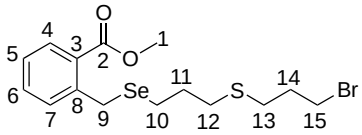


$NaOH_{(aq)}$ (4.0 M, 5.0 mL) was added dropwise over a period of 1 min via syringe to a pale yellow solution of methyl benzoate **208** (216 mg, 0.497 mmol) in MeOH (5.0 mL) at RT. A colour change to milky/wite suspension was immediately noted and the reaction mixture was stirred at 60 °C for 18 h, at which point the reaction mixture was deemed to have gone to completion by TLC (complete consumption of selenide **208** was noted). The colourless reaction mixture was allowed to cool to RT and then acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (10 mL). The acidified solution was concentrated under reduced pressure to dryness and the resulting white solid was azeotroped with toluene (3 × 20 mL, remove H_2O) to afford a crude product **209** which was directly used in the next reaction step without further purification.Next, EDC.HCl (173 mg, 0.902 mmol) was added to a pale-yellow suspension (containing NaCl) of carboxylic acid **209** (210 mg), HOBt (101 mg, 0.750 mmol) and dry DIPEA (871 µL, 5.10 mmol) in anhydrous DMF (10 mL). A colour change to a cloudy yellow was immediately noted and the reaction mixture was stirred at RT for 18 h of stirring at RT under Ar, before reaction was deemed to have to completion by TLC. The resulting mixture was diluted with EtOAc (30 mL) and transferred into separating funnel and the organic phase was washed with sat. brine (4 × 30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a colourless oil (215 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 20:80) to afford selenide **204** as colourless oil (85.7 mg, 47%, over two steps); R_f = 0.71 (50:50, EtOAc:*n*–hexane); IR (thin film) ν_{max}/cm^{-1}: 3061w (C–H alkyl), 3026w (C–H alkyl), 2942w (C–H alkyl), 2800w (C–H alkyl), 1713s (C=O aryl ester), 1600w (CC aromatic), 1574w (CC aromatic), 1493w (CC aromatic), 1449m, 1369w, 1351w, 1291w, 1262s, 1186w, 1145w, 1114m, 1084w, 1069m, 1042w, 1028w, 940w, 923w, 862w, 831w, 803w, 758m, 735m, 713m, 698s, 663w, 611w, 575w, 500w, 466w; δ_H (500 MHz; $CDCl_3$) 7.74 (1H, dd, *J* = 7.7, 1.5 Hz, C(3)H), 7.42 (1H, td, *J* = 7.7, 1.5 Hz, C(5)H), 7.34 (1H, dd, *J* = 7.7, 1.54 Hz, C(6)H), 7.32 – 7.28 (4H, m, C(17+18)H), 7.27 – 7.20 (2H, m, C(4+19)H), 4.59 – 4.53 (2H, m, $C(14)H_2$), 4.28 (2H, s, $C(8)H_2$), 3.48 (2H, s, $C(15)H_2$), 2.64 – 2.55 (4H, m, $C(9+12)H_2$), 2.36 – 2.31 (2H, m, $C(11)H_2$), 2.01 – 1.92 (2H, m,

C(10)H_2), 1.62 – 1.53 (2H, m, C(13)H_2); δ_C (126 MHz; $CDCl_3$) 169.0 (C, C1), 142.7 (C, C7), 139.7 (C, C16), 132.0 (CH, C5),131.4(CH, C3), 130.4 (C, C2), 129.9 (CH, C6), 129.0 (2 × CH, C17), 128.4 (2 × CH, C18), 127.1 (CH, C19), 126.4 (CH, C4), 62.6 (CH_2, C14), 59.2 (CH_2, C15), 54.4 (CH_2, C12), 49.6 (CH_2, C11), 30.3 (CH_2, C13), 26.1 (CH_2, C10), 24.4 (CH_2, C8), 24.0 (CH_2, C9); HRMS (ESI): calcd. for $C_{21}H_{26}NO_2{}^{80}Se$, 404.1123. Found: $[MH]^+$, 404.1121 (0.9 ppm error).

Lab notebook reference: ixz_227

Synthesis of methyl 2-(((3-((3-bromopropyl)thio)propyl)selanyl)methyl)benzoate – 211

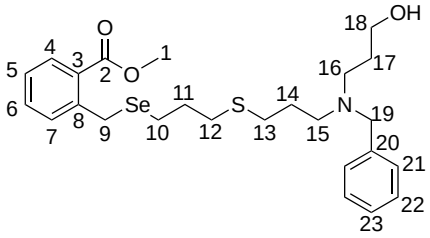


PPh_3 (1.04 g, 3.96 mmol) was added slowly in equal portions over a period of 2 min to a solution of alcohol **206** (1.19 g, 3.30 mmol) and CBr_4 (1.31 g, 3.96 mmol) in anhydrous CH_2Cl_2 (33 mL) at 0 °C. A colour change to pale yellow solution was immediately noted. The mixture stirred for 2 h at 0 °C and then allowed to warm to RT and stirred for additional 16 h. After a total of 18 h, the reaction was deemed to have gone to completion by TLC. The reaction mixture was concentrated under reduced pressure not to dryness to yield a brown/orange oil, which was diluted with Et_2O (30 mL). The resulting white solid (Ph_3PO) was filtered, and the filter cake was washed with Et_2O (3 × 20 mL). The resulting filtrate was concentrated under reduced pressure to yield a crude product as an orange oil (1.72 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: Et_2O:*n*–hexane, 10:90) to afford title compound **211** as a colourless oil (798 mg, 57%); R_f = 0.78 (50:50, EtOAc:*n*–hexane); IR (neat) ν_{max} /cm^{-1}: 2947w (C-H alkyl), 2841w (C-H alkyl), 1715s (C=O aryl ester), 1599w (CC aromatic), 1575w (CC aromatic), 1487m (CC aromatic), 1433w, 1292w, 1260s, 1189m, 1164w, 1112m, 1074s, 1045m, 964w, 840w, 791w, 758s, 707m, 664w, 616w, 562w, 512w, 462w; δ_H (400 MHz; $CDCl_3$) 7.93 (1H, dd, *J* = 7.5, 1.3 Hz, C(4)H), 7.42 (1H, td, *J* = 7.5, 1.3 Hz, C(6)H), 7.33 – 7.23 (2H, m, C(5+7)H), 4.18 (2H, s, C(9)H_2), 3.91 (3H, s, C(1)H_3), 3.50 (2H, t, *J* = 6.4 Hz, C(15)H_2), 2.66 – 2.58 (4H, m, C(10+12)H_2), 2.62 – 2.51 (2H, m, C(13)H_2), 2.14 – 2.03 (2H, m, C(14)H_2), 1.93 – 1.82 (2H, m, C(11)H_2); δ_C (126 MHz; $CDCl_3$) 167.5 (C, C2), 142.1 (C, C8), 131.8 (CH, C7), 131.2 (CH, C4), 130.7 (CH, C6), 128.7 (C, C3), 126.7 (CH, C5), 52.0 (CH_3, C1), 32.2 (CH_2, C15), 32.1 (CH_2, C14), 31.8 (CH_2, C12), 30.1 (CH_2, C13), 30.0 (CH_2, C11), 25.8 (CH_2, C9), 23.0 (CH_2, C10); HRMS (ESI): m/z calcd. for $C_{15}H_{22}{}^{79}BrO_2S^{80}Se$: 424.9684, found: 424.9679 $[MH]^+$, m/z calcd. for $C_{15}H_{21}{}^{79}BrNaO_2S^{80}Se$:

446.9503, found : 446.9501 $[MNa]^+$, m/z calcd. for $C_{15}H_{21}{}^{79}BrKO_2S^{80}Se$: 462.9242, found: 462.9257 $[MK]^+$.

Lab notebook reference: ixz_237

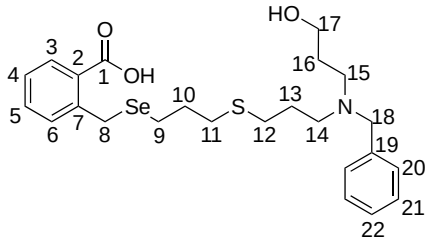
Synthesis of methyl 2-(((3-((3-(benzyl(3-hydroxypropyl)amino)propyl)thio)propyl)selanyl)methyl)benzoate – 212



K_2CO_3 (534 mg, 3.86 mmol) was added pale yellow solution of 3-(benzylamino)propan-1-ol **192** (478 mg, 2.89 mmol) and bromide **211** (818 mg, 1.93 mmol) in anhydrous MeCN (19 mL) at RT. The resulting suspension was then heated to 90 °C, whereupon a colour change to milky/white was noted. After 16 h, the reaction was deemed to have gone to completion by TLC, whereupon a colour change to cloudy yellow suspension was observed. The reaction mixture was cooled to RT, before filtered through Celite® using Hirsch funnel and the filtrate residual was washed with EtOAc (3 × 20 mL). The resulting solution was concentrated to dryness under reduced pressure to yield crude product as pale yellow oil (1.23 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 90:10 to 100:0) to afford title compound **212** as a colourless oil (554 mg, 56%); R_f = 0.22 (80:20, EtOAc:*n*–hexane); IR (neat) ν_{max}/cm^{-1}: 3420m (O–H alcohol), 2938w (C–H alkyl), 2835w (C–H alkyl), 1716s (C=O aryl ester), 1599w (CC aromatic), 1578w (CC aromatic), 1493m (CC aromatic), 1434m, 1262s, 1189m, 1112m, 1073s, 967w, 753w, 741s, 665m, 616w; δ_H (400 MHz; $CDCl_3$) 7.91 (1H, dd, *J* = 7.6, 1.6 Hz, C(4)H), 7.400 (1H, td, *J* = 7.6, 1.6 Hz, C(6)H), 7.36 – 7.23 (7H, m, C(5+7+21+22+23)H), 4.17 (2H, s, $C(9)H_2$), 3.90 (3H, s, $C(1)H_3$), 3.72 (2H, t, *J* = 6.5 Hz, $C(18)H_2$), 3.57 (2H, s, $C(19)H_2$), 2.65 (2H, t, *J* = 6.5 Hz, $C(16)H_2$), 2.59 (2H, t, *J* = 7.2 Hz, $C(15)H_2$), 2.55 – 2.48 (4H, m, $C(10+12)H_2$), 2.43 (2H, t, *J* = 7.3 Hz, $C(13)H_2$), 1.91 – 1.70 (6H, m, $C(11+14+17)H_2$); δ_C (126 MHz; $CDCl_3$) 167.8 (C, C2), 142.4 (C, C8), 138.4 (C, C20), 132.1 (CH, C7), 131.5 (CH, C4), 131.0 (CH, C6), 129.3 (CH, C21), 128.9 (C, C3), 128.6 (CH, C22), 127.4 (CH, C23), 126.9 (CH, C5), 64.3 (CH_2, C18), 59.1 (CH_2, C19), 54.3 (CH_2, C16), 53.0 (CH_2, C15), 52.2 (CH_3, C1), 32.2 (CH_2, C12), 30.2 (CH_2, C17), 30.1 (CH_2, C11), 28.2 (CH_2, C13), 26.9 (CH_2, C14), 26.0 (CH_2, C9), 23.2 (CH_2, C10); HRMS (ESI): m/z caldc. for $C_{25}H_{36}NO_3S^{80}Se$: 510.1576, found: 510.1580 $[MH]^+$.

Lab notebook reference: ixz_238

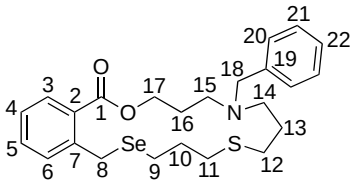
Synthesis of 2-(((3-((3-(benzyl(3-hydroxypropyl)amino)propyl)thio)propyl)selanyl)methyl)benzoic acid – 213



$NaOH_{(aq)}$ (4.0 M, 11 mL) was added dropwise over a period of 2 min to a clear colourless solution of methyl benzoate **212** (550 mg, 1.08 mmol) in MeOH (11 mL). A colour change to milky/white suspension was noted immediately during the dropwise addition. The resulting suspension was then heated to 70 °C under Ar for 16 h. After that time the reaction was deemed to have gone to completion by TLC analysis (complete consumption of methyl benzoate **212** was noted), with a colour change to colourless solution observed. The reaction mixture was acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (20 mL). The acidified cloudy/white suspension was poured into separating funnel and aqueous layer was extracted with EtOAc (3×20 mL), before combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a yellow viscous oil (458 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: MeOH: EtOAc, 10:90) to afford title compound **213** as pale yellow oil (458 mg, 86%); R_f = 0.17 (10:90, MeOH:EtOAc); IR (neat) ν_{max}/cm^{-1}: 3342m (O–H alcohol, O–H carboxylic), 3068m (C–H alkyl, O–H carboxylic acid), 2938m (C–H alkyl), 2586w (C–H alkyl), 1704s (C=O aryl carboxylic acid), 1599w (CC aromatic), 1578w, (CC aromatic) 1450w, 1374w, 1219m, 1116w, 1067m, 917w, 745s, 700s, 646m, 526w; δ_H (500 MHz; CD_3OD) 7.62 (1H, d, *J* = 7.4 Hz, C(4)H), 7.52 (2H, dd, *J* = 7.3, 2.3 Hz, C(21)H), 7.44 – 7.38 (3H, m, C(20+22)H), 7.31 (1H, dd, *J* = 7.4, 1.4 Hz, C(6)H), 7.26 (1H, t, *J* = 7.4 Hz, C(4)H), 7.18 (1H, td, *J* = 7.4, 1.4 Hz, C(5)H), 4.24 (2H, s, br, C(18)H_2), 4.19 (2H, s, C(8)H_2), 3.62 (2H, t, *J* = 5.8 Hz, C(17)H_2), 3.11 – 3.03 (4H, m, C(14+15)H_2), 2.57 (2H, t, *J* = 6.9 Hz, C(9)H_2), 2.54 – 2.48 (4H, m, C(11+12)H_2), 2.07 – 1.98 (2H, m, C(16)H_2), 1.97 – 1.88 (2H, m, C(13)H_2), 1.87 – 1.79 (2H, m, C(10)H_2); δ_C (126 MHz; $CDCl_3$) 169.8 (C, C1), 141.9 (C, C7), 132.1 (C, C19), 131.6 (CH, C6), 131.5 (CH, C20), 131.5 (CH, C3), 130.3 (CH, C5),129.8 (C, C2), 129.5 (CH, C21), 128.6 (CH, C22), 126.9 (CH, C4), 59.3 (CH_2, C17), 57.3 (CH_2, C18), 51.6 (CH_2, C14), 51.2 (CH_2, C15), 31.2 (CH_2, C11), 30.4 (CH_2, C10), 28.8 (CH_2, C13), 26.8 (CH_2, C16), 26.7 (CH_2, C12), 25.4 (CH_2, C10), 23.7 (CH_2, C8), 23.4 (CH_2, C9); HRMS (ESI): m/z calcd. for $C_{24}H_{34}NO_3S^{80}Se$: 496.1419, found: 496.1401 $[MH]^+$.

Lab notebook reference: ixz_240

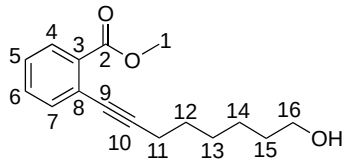
Synthesis of 6-benzyl-4,5,6,7,8,9,12,13-octahydro-3*H*,11*H*-benzo[*o*][1]oxa[9]thia[13]selena[5]azacycloheptadecin-1(15*H*)-one – 210



EDC.HCl (266 mg, 1.39 mmol) was added to solution of carboxylic acid **213** (458 mg, 0.924 mmol), HOBt (150 mg, 1.11 mmol) and dry DIPEA (805 µL, 4.62 mmol) in anhydrous DMF (18 mL). A colour change of the reaction mixture over 25 min from clear colourless to pale yellow solution. After a total of 16 h of stirring at RT, the reaction deemed to have to completion by TLC. The resulting mixture was diluted with EtOAc (30 mL), before being transferred to separating funnel and the organic phase was washed sequentially with H_2O (3 × 20 mL) and sat. brine (3 × 20 mL). The resulting organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an orange oil (441 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 30:70) to afford macrocycle **210** as colourless viscose oil (259 mg, 59%); R_f = 0.56 (50:50, EtOAc:*n*–hexane); IR (neat) ν_{max}/cm^{-1}: 3064w (C–H alkyl), 3026w (C–H alkyl), 2932w (C–H alkyl), 2803w (C–H alkyl), 1712s (C=O aryl ester), 1599m (CC aromatic), 1575w (CC aromatic), 1492w, 1150m, 1291w, 1257s, 1189w, 1148w, 1112m, 1070m, 1044w, 1028w, 964w, 926w, 758m, 733w, 699w, 665w, 618w, 468w; δ_H (500 MHz; C_6D_6) 7.85 (1H, dd, *J* = 7.0, 2.0 Hz, C(3)H), 7.28 (2H, dd, *J* = 7.3, 2.0 Hz, C(20)H), 7.21–7.15 (2H, m, C(5+6)H), 7.12 – 7.08 (1H, m, C(22)H), 7.04 – 6.96 (2H, m, C(21)H), 6.95 – 6.87 (1H, m, C(4)H), 4.27 (2H, t, *J* = 6.6 Hz, C(17)H_2), 4.26 (2H, s, C(8)H_2), 3.27 (2H, s,C(18)H_2), 2.43 (2H, t, *J* = 6.8 Hz, C(9)H_2), 2.38 – 2.33 (4H, m, C(11+14)H_2), 2.32 – 2.25 (4H, m, C(12+15)H_2), 1.73 – 1.63 (4H, m, C(13+16)H_2), 1.66 – 1.55 (2H, m, C(10)H_2); δ_C (126 MHz; C_6D_6) 167.4 (C, C1), 142.7 (C, C7), 140.3 (C, C19), 131.7 (CH, C5), 131.6 (CH, C3), 131.0 (CH, C6), 130.4 (C, C2), 129.2 (CH, C20), 128.6 (CH, C21), 127.2 (CH, C22), 126.7 (CH, C4), 63.4 (CH_2, C17), 59.6 (CH_2, C8), 53.1 (CH_2, C14), 50.3 (CH_2, C15), 31.3 (CH_2, C13), 30.7 (CH_2, C12), 29.9 (CH_2, C11), 28.2 (CH_2, C16), 27.0 (CH_2, C10), 25.7 (CH_2, C18), 23.9 (CH_2, C9); HRMS (ESI): m/z calcd. for $C_{24}H_{32}O_2S^{80}Se$: 478.1313, found: 478.1319 $[MH]^+$.

Lab notebook reference: ixz_241

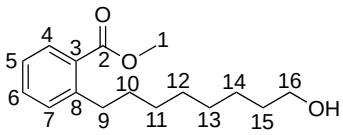
Synthesis of methyl 2-(8-hydroxyoct-1-yn-1-yl)benzoate – 217



Oct-7-yn-1-ol **216** (890 mg, 7.05 mmol) was added to solution of methyl 2-iodobenzoate **173** (1.68 g, 6.41 mmol) in dry Et_3N (21 mL) at RT. After 5 min, CuI (122 mg, 0.641 mmol) and bis(triphenylphosphine)palladium chloride (225 mg, 0.321 mmol) was added to the pale-yellow solution. The resulting reaction mixture was stirred at RT. Upon stirring, the colour of the reaction mixture changed over 4 h from grey green (after 1 h) to dark brown (after 2 h) and finally black brown. After a total of 18 h, the reaction was deemed to have gone to completion by TLC. The dark brown reaction mixture was filtered through Celite®, and washed with EtOAc (20 mL). The resulting filtrate was diluted with EtOAc (20 mL) was poured to into separating funnel and the organic layer was washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 40 mL) and sat. brine (1 × 40 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure to yield a brown/orange oil (2.74 g). The crude product was purified by flash column chromatography (SiO_2, 65 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford title compound **217** as a yellow liquid (1.79 g, 98%); R_f = 0.08 (30:70, EtOAc:*n*–hexane); IR (neat) ν_{max}/cm^{-1}: 3379m (O–H alcohol), 2933m (C–H alkyl), 2859 (C–H alkyl), 2228w (CC alkynyl), 1719s (C=O aryl ester), 1597m (CC aromatic), 1557m (CC aromatic), 1485m, 1447w, 1433m, 1293m, 1276m, 1249s, 1190w, 1163w, 1130m, 1055m, 1043m, 964w, 824w, 798w, 754s, 701m, 666w, 655w, 538w; δ_H (500 MHz; $CDCl_3$) 7.88 (1H, dd, *J* = 7.7, 1.4 Hz, C(4)H), 7.50 (1H, dd, *J* = 7.7, 1.4 Hz, C(7)H), 7.42 (1H, td, *J* = 7.7, 1.4 Hz, C(5)H), 7.30 (1H, td, *J* = 7.7, 1.4 Hz, C(6)H), 3.91 (3H, s, $C(1)H_3$), 3.68 – 3.64 (2H, m, $C(16)H_2$), 2.49 (2H, t, *J* = 7.0 Hz, $C(11)H_2$), 1.72 –1.58 (4H, m, $C(12+14)H_2$), 1.57 –1.50 (2H, m, $C(15)H_2$), 1.46 –1.38 (2H, m, $C(13)H_2$); δ_C (126 MHz; $CDCl_3$) 167.1 (C, C2), 134.4 (CH, C7), 132.0 (C, C8), 131.6 (CH, C5), 130.3 (CH, C4), 127.3 (CH, C6), 124.6 (C, C3), 96.0 (C, C10), 79.5 (C, C9), 63.0 (CH_2, C16), 52.2 (CH_3, C1), 32.8 (CH_2, C12), 28.7 (CH_2, C14), 25.4 (CH_2, C13), 19.8 (CH_2, C11); HRMS (ESI): m/z calcd. for $C_{16}H_{21}O_3$: 261.1485, found: 261.1486 $[MH]^+$, m/z calcd. for $C_{16}H_{20}NaO_3$: 283.1305, found: 283.1305 $[MNa]^+$, m/z calcd. for $C_{16}H_{20}KO_3$: 299.1044, found: 299.1044 $[MK]^+$.

Lab notebook reference: ixz_242

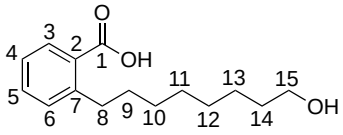
Synthesis of methyl 2-(8-hydroxyoctyl)benzoate – 218



Pd/C (68.5 mg, Pd 10% on carbon) was added to a round bottom flask, previously degassed under N_2 (for 10 min), containing alkyne **217** (1.68 g, 6.43 mmol) at RT. The alkyne **217** was dissolved by the addition of MeOH (32 mL, degassed for 10 min under N_2) and the reaction vessel was evacuated under *vacuo* and then backfilled with H_2 (via balloon) three times, then stirred at RT under an atmosphere of H_2 (balloon) for 4 h. The reaction was filtered through Celite and washed with EtOAc (3 × 20 mL). The resulting filtrate was concentrated under reduced pressure to yield a clear colourless oil (1.69 g). The crude product was purified was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 40:60) to afford title compound **218** as a clear colourless viscous oil (1.67 g, 98%); R_f = 0.26 (50:50, EtOAc:*n*–hexane); IR (thin film) ν_{max} /cm^{-1}: 3399m (O–H alcohol), 2928m (C–H alkyl), 2855m (C–H alkyl), 1722s (C=O aryl ester), 1602w (CC aromatic), 1575w (CC aromatic), 1488w (CC aromatic) 1434m, 1373w, 1291w, 1250s, 1190w, 1164w, 1132w, 1096m, 1072m, 1046m, 967w, 881w, 843w, 799w, 751m, 710m, 664w, 634w, 607w, 582w; δ_H (400 MHz; $CDCl_3$) 7.84 (1H, dd, *J* = 7.7, 1.5 Hz, C(4)H), 7.40 (1H, dd, *J* = 7.7, 1.5 Hz, C(7)H), 7.27 – 7.19 (2H, m, C(5+6)H), 3.88 (3H, s, C(1)H_3), 3.63 (2H, t, *J* = 6.6 Hz, C(16)H_2), 2.96 – 2.90 (2H, m, *J* = 7.0 Hz, C(9)H_2), 1.63 –1.51 (4H, m, C(10+15)H_2), 1.40 – 1.32 (8H, m, C(11+12+13+14)H_2); δ_C (126 MHz; $CDCl_3$) 168.4 (C, C2), 144.8 (C, C8), 131.9 (CH, C7), 131.0 (CH, C6), 130.7 (CH, C4), 129.6 (C, C3), 125.80 (CH, C5), 63.2 (CH_2, C16), 52.0 (CH_3, C1), 34.6 (CH_2, C9), 32.9 (CH_2, C14), 31.9 (CH_2, C10), 29.8 (CH_2, C13), 29.5 (CH_2, C12), 29.4 (CH_2, C11), 25.8 (CH_2, C15); HRMS (ESI): m/z calcd. for $C_{16}H_{24}NaO_3$: 287.1618, found: 287.1619 $[MNa]^+$.

Lab notebook reference: ixz_243

Synthesis of 2-(8-hydroxyoctyl)benzoic acid – 214

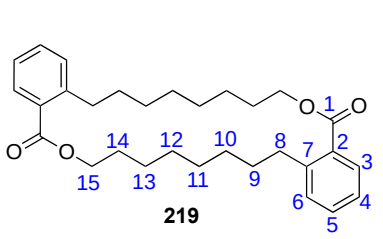


$NaOH_{(aq)}$ (4.0 M, 26 mL) was added dropwise over a period of 5 min to clear colourless solution of methyl benzoate **218** (1.39 g, 5.24 mmol) in MeOH (26 mL). A colour change to cloudy pale-yellow suspension was immediately noted, upon further addition another colour change to milky/white suspension was observed. The resulting suspension was then heated to 60 °C under Ar for 16 h. After that time the reaction was deemed to have gone to completion by TLC

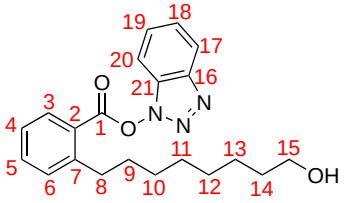
analysis (complete consumption of methyl benzoate **218** was noted), with a colour change to colourless solution. The reaction mixture was then acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (20 mL). The acidified cloudy/white suspension was poured into separating funnel and aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), before combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford title compound **214** as colourless viscous oil (1.21 g, 92%); R_f = 0.77 (50:50, MeOH:EtOAc);IR(neat)ν_{max}/cm^{-1}: 3383w (O–H alcohol), 2927w (C–H alkyl), 2855w (C–H alkyl), 2637m (O–H carboxylic acid), 1689s (C=O carboxylic acid), 1602w (CC aromatic), 1575w (CC aromatic), 1488w (CC aromatic), 1455w, 1403w, 1297m, 1263m, 1164w, 1139w, 1098w, 1070w, 1049w, 937w, 839w, 804w, 738s, 706m, 649m, 550w; δ_H (500 MHz; CD_2Cl_2) 7.98 (1H, dd, *J* = 7.7, 1.5 Hz, C(3)H), 7.69 (2H, s, br, OH), 7.45 (1H, td, *J* = 7.7, 1.5 Hz, C(5)H), 7.30 – 7.23 (2H, m, C(4+6)H), 3.65 (2H, t, *J* = 6.7 Hz, C(15)H_2), 3.04 – 2.97 (2H, m, C(8)H_2), 1.66 – 1.53 (4H, m, C(9+10)H_2) 1.44 –1.29 (8H, m, C(11+12+13+14)H_2); δ_C (126 MHz; CD_2Cl_2) 172.6 (C, C1), 146.0 (C, C7), 132.9 (CH, C5), 131.7 (CH, C3), 131.5 (CH, C6), 129.2 (C, C2), 126.2 (CH, C4), 63.1 (CH_2, C15), 34.9 (CH_2, C8), 32.9 (CH_2, C13), 32.2 (CH_2, C9), 30.0 (CH_2, C10), 29.7 (CH_2, C12), 29.6 (CH_2, C11), 26.1 (CH_2, C14); HRMS (ESI): m/z calcd. for $C_{15}H_{22}NaO_3$: 273.1461, found: 273.1466 $[MNa]^+$.

Lab notebook reference: ixz_244

Synthesis of and 7,8,9,10,11,12,13,14,21,22,23,24,25,26,27,28-hexadecahydro-5*H*,19*H*-dibenzo[*c*,*o*][1,13]dioxacyclotetracosine-5,19-dione – 219 and 1*H*-benzo[*d*][1,2,3]triazol-1-yl 2-(8-hydroxyoctyl)benzoate – 220



219



220

EDC.HCl (612 mg, 3.19 mmol) was added to colourless solution of 2-(8-hydroxyoctyl)benzoic acid **214** (532 mg, 2.13 mmol), HOBt (345 mg, 2.56 mmol) and dry DIPEA (930 µL, 5.33 mmol) in anhydrous DMF (21 mL). A colour change to pale yellow was noted after the addition of DIPEA via syringe over a period of 30 sec. The resulting mixture was stirred at RT overnight under Ar and progress of the reaction was monitored by TLC. After a total of 18 h, the reaction was judged to be complete, based on TLC analysis. The resulting mixture was diluted with EtOAc (40 mL), before being transferred to the separating funnel and the organic phase was washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 20 mL), sat. $NaHCO_{3\,(aq)}$ (3 × 20 mL) and sat. brine

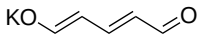
(3 × 20 mL). The resulting organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a white solid (838 mg). The crude product was purified by flash column chromatography (SiO_2, 20 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford dimer **219** as a white solid, (392 mg, 50%) and HOBt adduct **220** as colourless viscous oil (127 mg, 26%).

Data for **219**:R_f = 0.22 (50:50, EtOAc:*n*–hexane); melting point: 110 – 112 °C (from *n*–hexane); IR (solid state) ν_{max} /cm $^{-1}$: 2920w (C–H alkyl), 2848m (C–H alkyl), 1699s (C=O aryl ester), 1601w (CC aromatic), 1485m (CC aromatic), 1449m, 1463m, 1382w, 1308w, 1285m, 1269s, 1260m, 1246m, 1134m, 1100s, 1067m, 1047m, 991w, 964w, 934w, 867w, 802w, 754s, 723w, 707s, 659w, 601w, 534w, 511w; δ_H (500 MHz; $CDCl_3$) 7.78 (2H, dd, *J* = 7.7, 1.5 Hz, C(3)H), 7.38 (2H, td, *J* = 7.7, 1.5 Hz, C(5)H), 7.26–7.19 (4H, m, C(4+6)H), 4.32 (4H, t, *J* = 6.4 Hz, C(15)H_2), 2.92 – 2.85 (4H, m, C(8)H_2),1.79–1.70 (4H, m, C(14)H_2),1.60–1.51 (4H, m, C(9)H_2), 1.47 – 1.28 (16H, m, C(10+11+12+13)H_2); δ_C (126 MHz; $CDCl_3$) 169.2 (C, C1), 143.5 (C, C7), 131.6 (CH, C5), 131.0 (CH, C6), 130.9 (C, C2), 130.7 (CH, C3), 125.9 (CH, C4), 65.4 (CH_2, C15), 35.0 (CH_2, C8), 32.8 (CH_2, C9), 30.3 (CH_2, C10), 29.9 (CH_2, C11), 29.8 (CH_2, C12), 29.1 (CH_2, C14), 26.6 (CH_2, C13); HRMS (ESI): m/z calcd. for $C_{30}H_{41}O_4$: 465.2999, found: 465.2970 $[MH]^+$, m/z calcd. for $C_{30}H_{40}NaO_4$: 487.2819, found: 487.2831 $[MNa]^+$; X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2237214, was crystallised by slow evaporation of *n*-hexane).

Data for **220**: R_f = 0.67 (50:50,EtOAc:*n*–hexane); IR (neat)ν_{max}/cm^{-1}: 3381s (O–H alcohol), 2927m (C–H alkyl), 2855w, (C–H alkyl), 1797m (C=O ester), 1601w (CC aromatic), 1574w (CC aromatic), 1486m (CC aromatic), 1445w, 1375w, 1281w, 1268w, 1155w, 1217s, 1088m, 1053m, 963s, 917m, 810m, 781m, 739s, 698m, 664m, 637m, 606w, 500w; δ_H (500 MHz; $CDCl_3$) 8.29 (1H, dd, *J* = 8.1, 1.4 Hz, C(3)H), 8.08 (1H, dd, *J* = 8.1, 1.4 Hz, C(6)H), 7.61 (1H, td, *J* = 8.1, 1.4 Hz, C(5)H), 7.58 – 7.51 (1H, m, C(4)H), 7.50 – 7.36 (5H, m, C(17+18+19+20+21)H), 3.57 (2H, t, *J* = 6.7 Hz, C(15)H_2), 3.01 – 2.94 (2H, m, C(8)H_2), 1.65 – 1.56 (2H, m, C(9)H_2), 1.55 – 1.45 (2H, m, C(14)H_2), 1.38 – 1.21 (8H, m, C(10+11+12+13)H_2); δ_C (126 MHz; $CDCl_3$) 162.8 (C, C1), 147.6 (C, C7), 143.6 (C, C16), 134.7 (CH, C4), 131.7 (CH, C3), 131.5 (CH, C6), 128.9 (C, C2), 128.8 (CH, C5), 126.5 (CH, C19), 124.9 (CH, C18), 123.3 (C, C21), 120.6 (CH, C17), 108.4 (CH, C20), 62.9 (CH_2, C15), 34.6 (CH_2, C8), 32.8 (CH_2, C14), 31.6 (CH_2, C9), 29.5 (CH_2, C11), 29.3 (CH_2, C12), 29.3 (CH_2, C10), 25.7 (CH_2, C13); HRMS (ESI): m/z calcd. for $C_{21}H_{26}N_3O_3$: 368.1969, found: 368.1970 $[MH]^+$, m/z calcd. for $C_{21}H_{25}NaN_3O_3$: 390.1788, found: 390.1786 $[MNa]^+$, m/z calcd. for $C_{21}H_{25}KN_3O_3$: 406.1527, found: 406.1527 $[MK]^+$.

Lab notebook reference: ixz_245

Synthesis of potassium (1*E*,3*E*)-5-oxopenta-1,3-dien-1-olate – 228

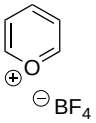


Sulfur trioxide pyridine complex **227** (25.6 g, 161 mmol) was slowly added in equal portions to a clear solution of $KOH_{(s)}$ (50.2 g, 917 mmol,) in H_2O (93 mL) at −20 °C, resulting in forming an orange suspension. The resulting reaction mixture was stirred at −20 °C for 1 h before allowed gradually raised to RT over a period 4 h. The resulting reaction suspension was heated at 40 °C for 30 mins and was cooled back down to 5 °C (ice bath) after that time. The insoluble crude product was filtered via Büchner funnel, washed with ice-cold acetone (2 × 100 mL) and methyl tert-butyl ether (MTBE) (2 × 100 mL), and dried under vacuum at RT to give a dark orange-green solid. The crude material was heated to 100 °C in MeOH (500 mL) for 30 min and the resulting insoluble solid was filtered via hot filtration. The resulting filtrated was collected and concentrated under reduced pressure not to dryness to a volume of approx. 100 mL of MeOH. The concentrated yellow suspension was filtered through Büchner funnel and resulting orange solid was collected under vacuum, washed with ice-cold acetone (3 × 30 mL) and MTBE (3 × 30 mL), and dried under vacuum to yield the desired compound as a yellow solid (2.60 g, 15%); δ_H (400 MHz; $(CD_3)_2CO$) 8.66 (2H, d, J = 9.3 Hz, CH), 7.03 (1H, t, J = 13.1 Hz, CH), 5.10 (2H, dd, J = 13.0, 9.2 Hz, CH); HRMS (ESI): calcd. for $C_5H_5O_2$, 97.0295. Found: $[MK]^-$, 97.0293 (2.2 ppm error).

Lab notebook reference: ixz_265

Spectroscopic data is consistent with those previously reported in the literature.[218]

Synthesis of pyrylium tetrafluoroborate – 222



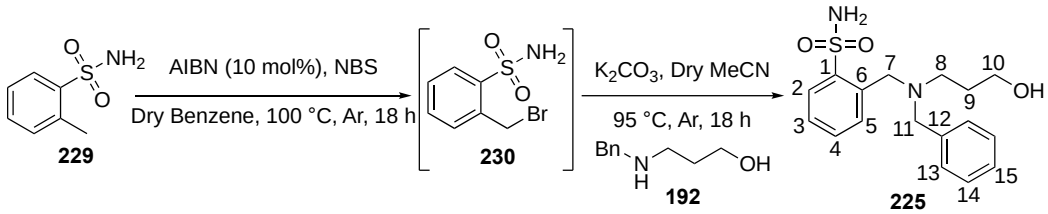
A vigorously stirred suspension of potassium (1*E*,3*E*)-5-oxopenta-1,3-dien-1-olate **228** (2.60 g, 19.1 mmol) in anhydrous Et_2O (50 mL) was cooled down to −20 °C under Ar atmosphere in the dark (reaction mixture covered in foil). To resulting mixture, precooled at −20 °C of $HBF_4{\cdot}OEt_2$ (17.6 mL, 128 mmol) was added in one portion under Ar at −20 °C. The beige suspension was stirred for 16 hours, allowing it to warm up to RT gradually. The reaction mixture was diluted with Et_2O (100 mL) and stirred for 1 additional hour at RT and the mixture was cooled to −20 °C to afford a brown slurry/suspension. The supernatant black solvent was

decanted off via cannula filtration, then the brown thick slurry was vigorously stirred with more anhydrous Et_3O (100 mL) at RT for 20 min, before reaction mixture would be cooled to −20 °C and the supernatant solvent was removed via cannula filtration. The same proceed metion above was repeated three times. Next, MeCN (120 mL) was added to the remaining crude mixture that was stirred vigorously for 10 min, and resulting suspension was filtered via Büchner funnel to obtaining a brown solution. To this filtrate solution, anhydrous Et_2O (500 mL) was added dropwise over period of 10 min via syringe pump under Ar, while gently stirring of the mixture, which resulted in appearing a fine precipitate. The suspension was allowed to stir for additional 20 minutes and the resulting solid collected under vacuum, washed with Et_2O (2 × 20 mL) and dried under *vacuo* to yield desired compound as an off-white solid (2.07 g, 65%); δ_H (500 MHz; CD_3CN) 9.58 (2H, dt, *J* = 3.5, 1.8 Hz, 2 × Ar-CH), 9.19 (1H, tt, *J* = 8.1, 1.8 Hz, Ar-CH), 8.37 (1H, ddd, *J* = 8.0, 3.6, 1.5 Hz, Ar-CH); HRMS (ESI): calcd. for C_5H_5O, 81.0335. Found: $[M-BF_4^-]^+$, 81.0336 (−1.7 ppm error).

Lab notebook reference: ixz_264

Spectroscopic data is consistent with those previously reported in the literature.[218]

Synthesis of 2-((benzyl(3-hydroxypropyl)amino)methyl)benzenesulfonamide – 225

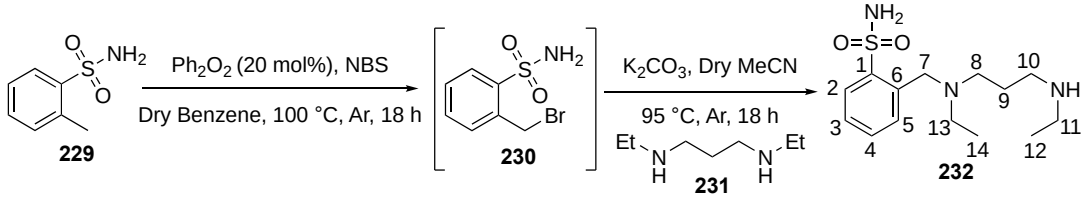


AIBN (238 mg, 1.45 mmol) was added to a yellow suspension of 2-methylbenzenesulfonamide **229** (1.24 g, 7.25 mmol) and *N*-bromosuccinimide (1.55 g, 8.70 mmol) in anhydrous benzene (24.2 mL, degasses for 20 min) at RT under Ar. The resulting suspension was heated to 100 °C, whereupon a colour changed to blood orange was noted. After 18 h, the reaction deemed to have gone to completion by TLC. The resulting mixture was allowed to cool to RT, before concentrated under reduced pressure. The concentrated orange suspension was diluted with EtOAc (30 mL) and poured into separating funnel. The organic layer was washed sequentially with sat. $NaHCO_3$ (3 × 40 mL) and sat. brine (3 × 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a crude **230** product as brown-orange oil which was directly used in the next reaction step without further purification. Next, K_2CO_3 (404 mg, 2.93 mmol) was added to a pale-yellow solution of 3-(benzylamino)propan-1-ol **192** (280 µL, 1.76 mmol) and 2-(bromomethyl)benzenesulfonamide **230** (293 mg, 1.17 mmol) in anhydrous MeCN (23 mL) at RT under Ar. The resulting milky white suspension was stirred at 95 °C for

18 h under Ar, after which the reaction was deemed to have gone to completion by TLC, with a colour change to fluorescent yellow suspension noted. The reaction mixture was then quenched by addition of H_2O (30 mL) and resulting solution was poured into a separating funnel. The aqueous layer was extracted with EtOAc (3 × 30 mL), before the combined organic phases were washed sequentially with sat. $NaHCO_{3(aq)}$ (3 × 30 mL) and sat. brine (1 × 30mL). The resulting organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale-yellow oil (365 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 80:20) to title compound **225** as a colourless viscous oil (277 mg, 71%, over two steps); R_f = 0.48 (EtAOc); IR (neat) ν_{max}/cm^{-1}: 3513w (N–H sulfonamide/O–H alcohol), 3279w (N–H sulfonamide/O–H alcohol), 2940w, 2849w, 1733s, 1572w (CC aromatic), 1496w (CC aromatic), 1446w, 1374s, 1336s, 1243s, 1198w, 1163s, 1135m, 1114w, 1044s, 916w, 828w, 763s, 746s, 701s, 634w, 588s, 551s, 513w; δ_H (500 MHz; $CDCl_3$) 8.07 (1H, dd, *J* = 7.7, 1.5 Hz, C(2)H), 7.51 (1H, td, *J* = 7.4, 1.5 Hz, C(4)H), 7.45 (1H, td, *J* = 7.6, 1.5 Hz, C(3)H), 7.38 (1H, dd, *J* = 7.3, 1.5 Hz, C(5)H), 7.34 – 7.24 (3H, m, C(14+15)H), 7.18 – 7.13 (2H, m, C(13)H), 4.11 (2H, s, $C(7)H_2$), 3.67 (2H, s, $C(11)H_2$), 3.56 (2H, t, *J* = 6.2 Hz, $C(10)H_2$), 2.63 – 2.56 (2H, m, $C(8)H_2$), 1.86 – 1.77 (2H, m, $C(9)H_2$); δ_C (126 MHz; $CDCl_3$) 142.1 (C, C1), 136.5 (C, C12), 135.4 (C, C6), 133.6 (CH, C3), 132.3 (CH, C4), 129.7 (2 × CH, C13), 128.6 (2 × CH, C14), 128.4 (CH, C5), 128.0 (CH, C2),127.7 (CH, C15), 60.9 (CH_2, C10), 58.6 (CH_2, C7), 58.2 (CH_2, C11), 49.6 (CH_2, C8), 28.4 (CH_2, C9); HRMS (ESI): calcd. for $C_{17}H_{23}N_2O_3S$, 335.1424. Found: $[MH]^+$, 335.1423 (0.4 ppm error).

Lab notebook reference: ixz_250

Synthesis of 2-((ethyl(3-(ethylamino)propyl)amino)methyl)benzenesulfonamide – 232

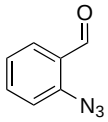


Ph_2O_2 (624 mg, 2.58 mmol) was added to a pale-yellow suspension of 2-methylbenzenesulfonamide **229** (2.21 g, 12.9 mmol) and *N*-bromosuccinimide (3.45 g, 19.4 mmol) in anhydrous benzene (43.0 mL, degasses for 15 min) at RT under Ar. The resulting suspension was heated to 100 °C, whereupon a colour changed to orange was noted. After 18 h, the reaction deemed to have gone to completion by TLC. The reaction mixture allowed to cool to RT, before was diluted with EtOAc (3 × 30 mL) and transferred into separating funnel. The organic layer was washed sequentially with sat. $NaHCO_{3(aq)}$ (3 × 40 mL) and sat. brine (3

× 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a crude product **230** as a yellow solid which was directly used in the next reaction step without further purification. Next, K_2CO_3 (314 mg, 2.93 mmol) was added to a pale-yellow solution of diethylpropane diamine **231** (300 µL, 1.89 mmol) and bromomethyl benzenesulfonamide **230** (189 mg, 0.757 mmol) in anhydrous MeCN (15 mL) at RT under Ar. The resulting milky white suspension was stirred at 95 °C for 18 h under Ar, after which the reaction was deemed to have gone to completion by TLC, with a colour change milky beige suspension noted. The reaction mixture allowed to cool to RT, before being filtered through Celite® and washed with EtOAc (3 × 30 mL). The resulting filtrate was concentrated under reduced pressure to yield an orange oil (454 mg). The crude product was purified by flash column chromatography (SiO_2, 35 mm column, eluent: MeOH:EtOAc + Et_3N, 40:60 + 5%) to afford an alcohol **232** as a pale yellow oil (177 mg, 78%); R_f = 0.43 (50:50 + 5%, MeOH:EtOAc + Et_3N); IR (neat) ν_{max}/cm^{-1}: 3302w (N–H amine), 2967w (C–H alkyl), 2827w (C–H alkyl), 1575w (CC aromatic), 1445w (CC aromatic), 1333w, 1159s, 1133w, 1066w, 751w, 666w, 587s, 552s, 509w; δ_H (500 MHz; $CDCl_3$) 8.02 (1H, dd, *J* = 7.5, 1.6 Hz, C(2)H), 7.46 (1H, td, *J* = 7.5, 1.6 Hz, C(4)H), 7.42 (1H, td, *J* = 7.5, 1.6 Hz, C(3)H), 7.30 (1H, dd, *J* = 7.5, 1.6 Hz, C(5)H), 5.01 (3H, s, NH_2 + NH), 3.99 (2H, s, C(7)H_2), 2.62 – 2.56 (4H, m, C(11+13)H_2), 2.56 – 2.49 (4H, m, C(8+10)H_2), 1.71 – 1.62 (2H, m, C(9)H_2), 1.04 (6H, t, *J* = 7.1 Hz, C(12+14)H_3); δ_C (126 MHz; $CDCl_3$) 142.5 (C, C1), 135.5 (C, C6), 133.6 (CH), 132.2 (CH), 128.4 (CH), 128.0 (CH), 58.0 (CH_2), 50.5 (CH_2), 47.9 (CH_2), 46.7 (CH_2), 44.1 (CH_2), 26.2 (CH_2), 15.2 (CH_3), 10.5 (CH_3); HRMS (ESI): calcd. for $C_{14}H_{26}N_3O_2S$, 300.1740. Found: $[MH]^+$, 300.1745 (–1.6 ppm error).

Lab notebook reference: ixz_255

Synthesis of 2-azidobenzaldehyde – 238



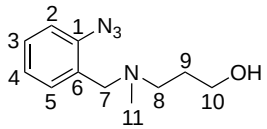
NaN_3 (2.21 g, 34.0 mmol) was added to a colourless solution of 2-nitrobenzaldehyde **237** (2.57 g, 17.0 mmol) in anhydrous DMF (56 mL) at RT under Ar. The resulting suspension was then heated to 60 °C, whereupon an immediate colour change to pale yellow was noted. Upon further heating, the colour of the reaction suspension changed to orange suspension. After 20 h, the reaction was deemed to have gone to completion by TLC analysis, with a colour change to cloudy fire orange noted. The reaction mixture was cooled to RT, before being quenched with addition of H_2O (30 mL) and poured into a separating funnel. The resulting aqueous layer was extracted with EtOAc (3 × 20 mL), before the combined organic phases were washed

with sat. brine (3 × 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an orange oil (4.78 g). The crude product was purified by flash column chromatography (SiO_2, 75 mm column, eluent: EtOAc:*n*–hexane, 10:90) to afford an azide **238** as a crystalline solid (1.50 g, 60%); R_f = 0.73 (50:50, EtOAc:*n*–hexane); δ_H (400 MHz; $CDCl_3$) 10.13 (1H, s, HCO), 7.67 (1H, dd, *J* = 7.7, 1.8 Hz, Ar-CH), 7.47 – 7.36 (1H, m, Ar-CH), 7.10 – 6.97 (2H, m, 2 × Ar-CH); δ_C (101 MHz; $CDCl_3$) 188.7 (CO), 143.0 (C), 135.5 (CH), 129.1 (CH), 127.0 (C), 125.0 (CH), 119.2 (CH).

Lab notebook reference: ixz_323

Spectroscopic data is consistent with those previously reported in the literature.[287]

Synthesis of 3-((2-azidobenzyl)(methyl)amino)propan-1-ol – 234

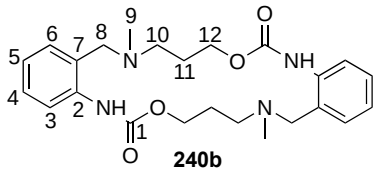


3-(methylamino)propan-1-ol **239** (1.16 mL, 12.0 mmol) was added dropwise over 30 sec. via syringe to a pale yellow solution of 2-azidobenzaldehyde **238** (411 mg, 1.73 mmol) in anhydrous CH_2Cl_2 (33 mL). The resulting yellow solution allowed to be stirred for 2 h at RT under Ar. Next, sodium triacetoxyborohydride (STAB) (5.28 g, 25.0 mmol) was added over 2 min to reaction mixture, instantaneous effervescence, fizzing (release of H_2) and colour change to milky white suspension was noted. The resulting mixture was stirred in total for 24 h at RT under Ar, at which point the reaction was deemed to have gone to completion by TLC. The cloudy white suspension was quenched by addition of sat. $NaHCO_{3(aq)}$ (30 mL), instantaneous effervescence and fizzing observed again. The diluted reaction mixture stirred for 30 min, before poured into separating funnel containing CH_2Cl_2 (30 mL) and aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an orange oil (2.54 g). The crude product was purified by flash column chromatography (SiO_2, 60 mm column, eluent: MeOH:EtOAc,20:80) to afford azide **234** as an orange oil (2.06 g, 94%); R_f = 0.23 (20:80, MeOH:EtOAc); IR (neat) ν_{max}/cm^{-1}: 3337w (O–H alcohol), 2948w (C–H alkyl), 2119s (N=N=N azide), 1737w, 1583w (CC aromatic), 1489w, 1451w, 1372w, 1285s, 1128w, 1043m, 837w, 749s; δ_H (400 MHz; $CDCl_3$) 7.23–7.13 (2H, m, C(2+4)H), 7.04 – 6.94 (2H, m, C(3+5)H), 4.87 (1H, br, s, OH), 3.60 (2H, t, *J* = 5.5 Hz, C(10)H_2), 3.35 (2H, s, C(7)H_2), 2.50 (2H, t, *J* = 6.0 Hz, C(8)H_2), 2.10 (3H, s, C(11)H_3),1.67–1.58 (2H, m, C(9)H_2); δ_C (101 MHz; $CDCl_3$) 138.5 (C, C1), 131.0 (CH), 129.1 (C, C6), 128.4 (CH), 124.3 (CH), 117.9 (CH), 63.3 (CH_2, C10), 57.1 (CH_2,

C7), 56.9 (CH_2, C8), 41.5 (CH_3, C11), 28.0 (CH_2, C9); HRMS (ESI): calcd. for $C_{11}H_{17}N_4O$, 221.1397. Found: $[MH]^+$, 221.1395 (0.9 ppm error).

Lab notebook reference: ixz_325

Synthesis of 11,23-dimethyl-5,8,9,10,11,12,17,20,21,22,23,24-dodecahydro-6*H*,18*H*-dibenzo[*d*,*n*][1,11]dioxa[3,7,13,17]tetraazacycloicosine-6,18-dione – 240b



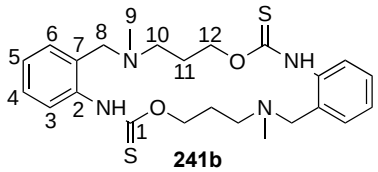
240b

PPh_2Me (256 µL, 1.38 mmol) was added dropwise over 30 sec. via syringe to an orange solution of 3-((2-azidobenzyl)(methyl)amino)propan-1-ol **234** (253 mg,1.15 mmol) in anhydrous toluene (23 mL). The resulting yellow solution allowed to be stirred for 1 h at RT under Ar. Next, reaction vessel was evacuated under *vaccuo* and backfilled with CO_2 (via balloon) 6 times, with a colour change to dark orange solution observed. The resulting mixture was stirred in total for 18 h at 140 °C under a slight positive pressure of CO_2 (balloon), at which point the reaction was deemed to have gone to completion by TLC and colour change to pale e yellow solution was noted. The reaction mixture allowed to cool to RT and then solvent was removed under reduced pressure to yield a pale-yellow solid (813 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane, 25:75 to 30:70) to afford dimer **240b** as a white solid (173 mg, 69%); R_f = 0.23 (50:50, EtOAc:*n*–hexane); melting point: 210 – 211 °C (from EtOAc); IR (solid state) ν_{max} / cm^{-1}: 3233w (N–H carbamate), 2951w (C–H alkyl), 2840w (C–H alkyl), 2793w (C–H alkyl), 2767w (C–H alkyl),1718s (C=O carbamate), 1590s (CC aromatic),1519s (CC aromatic), 1476w, 1450s, 1372w, 1320w, 1303s, 1270s, 1221s, 1195w, 1146w, 1132w, 1111w, 1070m, 1038m, 982w, 954w, 860s, 818w, 746s, 724m, 710w, 634w, 616w, 543m, 466w; δ_H (500 MHz; $CDCl_3$) 9.84 (2H, br, s, 2 × NH), 8.02 (2H, dd, *J* = 8.2, 1.2 Hz, C(3)H), 7.30 (1H, td, *J* = 7.8, 1.6 Hz, C(4)H), 7.08 (2H, dd, *J* = 7.6, 1.6 Hz, C(6)H), 6.97 (2H, td, *J* = 7.4, 1.3 Hz, C(5)H), 4.29 – 4.19 (4H, m, C(12)H_2), 3.52 (4H, s, C(8)H_2), 2.54 (4H, t, *J* = 6.7 Hz, C(10)H_2), 2.12 (6H, s, C(9)H_2), 2.00 – 1.92 (4H, m, C(11)H_2);δ_C (126 MHz; $CDCl_3$) 154.3 (2 × CO, C1), 138.9 (2 × C, C2), 129.9 (2 × CH, C6), 128.6 (2 × CH, C4), 126.4 (2 × C, C7), 122.6 (2 × CH, C5), 119.9 (2 × CH, C3), 62.8 (2 × CH_2, C8), 62.6 (2 × CH_2, C12), 54.3 (2 × CH_2, C10), 40.2 (2 × CH_3, C9), 27.5 (2 × CH_2, C11); HRMS (ESI): calcd. for $C_{24}H_{33}N_4O_4$, 441.2496. Found: $[MH]^+$, 441.2502 (–1.2 ppm error); X-ray crystallographic data for this compound can be accessed via

www.ccdc.cam.ac.uk/data_request/cif (CCDC 2221194, was crystallized by slow cooling of *n*-hexane:EtOAc from RT to –20 °C).

Lab notebook reference: ixz_334

Synthesis of 11,23-dimethyl-5,8,9,10,11,12,17,20,21,22,23,24-dodecahydro-6*H*,18*H*-dibenzo[*d*,*n*][1,11]dioxa[3,7,13,17]tetraazacycloicosine-6,18-dithione – 241b

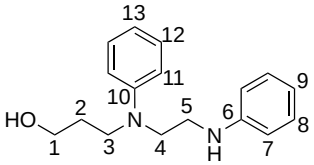


241b

PPh_2Me (257 µL, 1.38 mmol) was added dropwise over 30 sec. via syringe to an orange solution of aminopropanol **234** (304 mg, 1.38 mmol) in anhydrous toluene (28 mL). The resulting yellow solution allowed to be stirred for 1 h at RT under Ar. Next, CS_2 (141 µL, 2.35 mmol) was dropwise over 30 sec. via syringe to the resulting mixture and stirred in total for 20 h at 120 °C under Ar, at which point the reaction was deemed to have gone to completion by TLC. The reaction was allowed to cool to RT and then solvent was removed under reduced pressure to yield a paleyellow solid (855 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane, 20:80) to afford thiocarbamate dimer **241b** as a white solid (243 mg, 75%); IR (solid state)ν_{max}/cm^{-1}: 3172w (O–H thiocarbamate), 2964w (C–H alkyl), 2845w (C–H alkyl), 1588w, (C=S thiocarbamate), 1525s (CC aromatic), 1478w, 1451m, 1418w, 1371s, 1306w, 1237w, 1202s, 1192s, 1169s, 1152s, 1101m, 1083m, 1004m, 966w, 880w, 867m, 838w,751s, 734s, 707s; HRMS (APCI): calcd. for $C_{24}H_{33}N_4O_2S_2$, 473.203945. Found: $[MH]^+$, 473.205946 (–4.2 ppm error); X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2221209, was crystallised by slow evaporation of warm DMSO).

Lab notebook reference: ixz_326 and ixz_336

Synthesis of 3-(phenyl(2-(phenylamino)ethyl)amino)propan-1-ol – 242

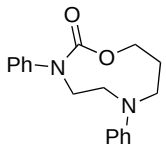


K_2CO_3 (7.64 g, 55.3 mmol) was added pale yellow solution of N^1,N^2-diphenylethane-1,2-diamine **244** (7.04 g, 33.2 mmol) and 3-bromopropan-1-ol **188** (3.07 g, 22.1 mmol) in

anhydrous MeCN (74 mL) at RT under Ar. The resulting suspension was then heated to 95 °C, with a colour change to pale pink suspension observed. After 16 h, the reaction was deemed to have gone to completion by TLC and a colour change to cloudy beige suspension was observed. The reaction mixture was cooled to RT, before filtered through Celite® using a Hirsch funnel and the filtrate residual was washed with EtOAc (3 × 60 mL). The resulting filtrate was concentrated to dryness under reduced pressure to yield crude product lilac oil (10.3 g). The crude product was purified by flash column chromatography (SiO_2, 85 mm column, eluent: EtOAc:*n*–hexane, 30:70 to 40:60) to afford title compound **242** as pale yellow oil (2.11 g, 35%); R_f = 0.55 (50:50, EtOAc:*n*–hexane); IR(neat)ν_{max}/cm^{-1}: 3550w (N–H aniline), 3378w (O–H alcohol), 3023w (N–H secondary aniline), 2940w (C–H alkyl), 2877w (C–H alkyl), 1597s (CC aromatic/aniline), 1502s (CC aromatic/aniline), 1431w, 1369w, 1320w, 1255w, 1226w, 1195w, 1178w, 1122w, 991m, 925w, 867w, 746s, 692s, 508m; δ_H (400 MHz; $CDCl_3$) 7.32 – 7.22 (2H, m, C(12)H), 7.22–7.14 (2H, m, C(8)H), 6.88 – 6.81 (2H, m, C(11)H), 6.78 (1H, tt, *J* = 7.3, 1.1 Hz, C(13)H), 6.72 (1H, tt, *J* = 7.3, 1.1 Hz, C(9)H), 6.66 – 6.59 (2H, m, C(7)H), 3.71 (2H, t, *J* = 5.9 Hz, C(1)H_2), 3.56 (2H, t, *J* = 6.4 Hz, C(4)H_2), 3.48 (2H, t, *J* = 6.9 Hz, C(3)H_2), 3.36 (2H, t, *J* = 6.4 Hz, C(5)H_2), 1.89 – 1.78 (2H, m, C(2)H_2); δ_C (101 MHz; $CDCl_3$) 147.9 (C, C10), 148.0 (C, C6), 129.6 (CH,C12), 129.5 (CH, C8), 117.8 (CH, C11), 113.9 (2× CH, C9+13), 113.1 (CH, C7), 60.7 (CH_2, C1), 51.2 (CH_2, C4), 48.8 (CH_2, C3), 41.5 (CH_2, C5), 29.9 (CH_2, C2); HRMS (ESI): m/z calcd. for $C_{17}H_{23}N_2O$: 271.1805, found: 271.1801 $[MH]^+$.

Lab notebook reference: ixz_341

Synthesis of 3,6-diphenyl-1,3,6-oxadiazecan-2-one – 243

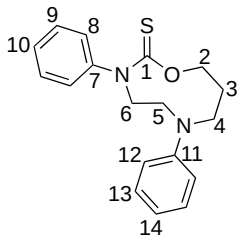


To a solution of phenylamino amino propanol **242** (75 mg, 0.277 mmol) in anhydrous CH_2Cl_2 (2.80 mL) at RT, dry Et_3N (58.0 µL, 0.416 mmol) and triphosgene (32.9 mg, 0.111 mmol) were added sequentially. The resulting mixture was stirred at RT for 24 h, quenched by the addition of H_2O (20 mL), extracted with CH_2Cl_2 (2 x 20 mL) and dried over $MgSO_4$ and concentrated under *vacuo* to yield the crude product as yellow oil (157 mg). The crude product was purified by flash column chromatography (SiO_2, 20 mm column, eluent: EtOAc:*n*–hexane, 20:80 to 30:70) to afford the title compound **243** as a colourless oil (51 mg, 62%); R_f = 0.60 (50:50, EtOAc:*n*–hexane); IR(thin film)ν_{max}/cm^{-1}: 2958w, 1705s, 1503m, 1256m, 747m, 693s; δ_H (400 MHz; $CDCl_3$) 7.30 – 7.26 (2H, m, Ar-CH), 7.21 – 7.14 (3H, m, Ar-CH), 7.08 (2H, d, *J* = 7.8 Hz, Ar-CH), 6.70 (1H, t, *J* = 7.3 Hz, Ar-CH), 6.55 (2H, d, *J* = 8.2 Hz, Ar-CH), 4.39 (2H, t, *J* = 5.7

Hz, OCH_2), 3.96 (2H, t, *J* = 5.2 Hz, NCH_2), 3.73 (2H, t, *J* = 5.5 Hz, NCH_2), 3.60 – 3.54 (2H, m, NCH_2), 2.06 – 1.98 (2H, m, CH_2); δ_C (101 MHz; $CDCl_3$) 156.3 (C=O), 147.3 (Ar-C), 142.9 (Ar-C), 129.3 (Ar-CH), 128.7 (Ar-CH), 125.8 (Ar-CH), 125.4 (Ar-CH), 116.5 (Ar-CH), 111.9 (Ar-CH), 66.1 (OCH_2), 53.5 (NCH_2), 51.8 (NCH_2), 50.6 (NCH_2), 26.4 (CH_2); HRMS (ESI): m/z calcd. for $C_{18}H_{21}N_2O_2$: 319.1417, found: 319.1418 $[MH]^+$.

Lab notebook reference: ixz_343

Synthesis of 3,6-diphenyl-1,3,6-oxadiazonane-2-thione – 245

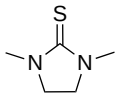


Thiophosgene (180 µL, 2.40 mmol) was added via syringe over a period of 30 sec. to a pale yellow solution of 3-(phenyl(2-(phenylamino)ethyl)amino)propan-1-ol **242** (541 mg, 2.01 mmol), dry Et_3N (976 µL, 7.01 mmol) in anhydrous CH_2Cl_2 (40 mL). An immediate colour change to black/blood red solution was noted along with liberation of fumes ($HCl_{(g)}$). The resulting mixture was stirred at RT overnight under Ar and progress of the reaction was monitored by TLC. After a total of 24 h, the reaction was judged to be complete, based on TLC analysis. The resulting mixture was quenched with sat. $NaHCO_{3(aq)}$ (40 mL), before was transferred to separating funnel. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a brown oil (1.06 g). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 20:50) to afford title compound **245** as pale yellow oil (519 mg, 83%); R_f = 0.76 (50:50, EtOAc:*n*–hexane); IR (thin film) ν_{max}/cm^{-1}: 3039w (C–H alkyl), 2951w (C–H alkyl), 2278w (C-S thiocarbonate), 1596s (CC aromatic), 1587w (CC aromatic), 1505m, 1494m, 1465m, 1412m, 1359m, 1322m, 1303m, 1261m, 1230m, 1171m, 1117m, 1037m, 987w, 973w, 926w, 860w, 837w, 812w, 745s, 692s, 617w, 570w, 544w, 500w; δ_H (500 MHz; C_6D_6) 7.24–7.16 (2H, m, C(8)H), 7.11 – 7.03 (2H, m, C(13)H), 7.01–6.94 (3H, m, C(10+12)H), 6.80 (1H, tt, *J* = 7.3, 1.1 Hz, C(14)H), 6.29 – 6.22 (2H, m, C(9)H), 4.47 (2H, t, *J* = 5.7 Hz, $C(2)H_2$), 3.44 (2H, t, *J* = 5.0 Hz, $C(6)H_2$), 3.14 (2H, t, *J* = 5.0 Hz, $C(5)H_2$), 2.98–2.93 (2H, m, $C(4)H_2$), 1.55–1.48 (2H, m, $C(3)H_2$); δ_C (101 MHz; C_6D_6) 190.7 (C, C1), 147.0 (C, C11), 146.2 (C, C7), 129.7 (CH, C8), 129.1 (CH, C13), 127.7 (CH, C12), 127.3 (CH, C10), 116.5 (CH, C14), 111.6 (CH, C9), 71.5 (CH_2, C2), 54.8 (CH_2, C5), 53.7 (CH_2, C6), 53.0 (CH_2, C4), 26.8 (CH_2, C3); HRMS (ESI): m/z calcd. for $C_{18}H_{21}N_2OS$:

311.1369, found: 313.1371 $[MH]^+$, m/z calcd. for $C_{18}H_{20}N_2NaOS$: 335.189, found: 335.188 $[MNa]^+$.

Lab notebook reference: ixz_342

Synthesis of 1,3-dimethylimidazolidine-2-thione – 248

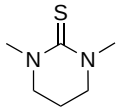


Thiophosgene (72.0 µL, 0.934 mmol) was added via syringe over a period of 40 sec to a pale orange solution of *N*,*N′*,*N″*-trimethyldiethylenetriamine **246** (113 mg, 0.779 mmol), anhydrous Et_3N (380 µL, 2.72 mmol) in anhydrous CH_2Cl_2 (16 mL). A colour change to dark brown solution was noted along with liberation of fumes ($HCl_{(g)}$). The resulting mixture was stirred at RT overnight under Ar and progress of the reaction was monitored by TLC. After total of 24 h, the reaction was judged to be complete, based on TLC analysis. The resulting mixture was quenched with sat. $NaHCO_{3(aq)}$ (20 mL), before was transferred to separating funnel and layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a brown oil (391 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 90:10) to afford title compound **248** as a white crystalline solid (98.1 mg, 97%);R_f = 0.39 (EtOAc); δ_H (400 MHz; $CDCl_3$) 3.53 (4H, s, CH_2), 3.13 (6H, s, CH_3); δ_C (101 MHz; C_6D_6) 184.7 (C), 47.6 (CH_3), 34.9 (CH_2); HRMS (ESI): m/z calcd. for $C_5H_{11}NS$: 131.0637, found: 131.0637 $[MH]^+$, m/z calcd. for $C_5H_{10}N_2NaS$: 153.0457, found: 153.0462 $[MNa]^+$.

Lab notebook reference: ixz_359

Spectroscopic data is consistent with those previously reported in the literature.[288]

Synthesis of 1,3-dimethyltetrahydropyrimidine-2(1*H*)-thione – 252



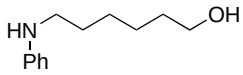
Thiophosgene (91.7 µL, 1.20 mmol) was added via syringe over a period of 30 sec to a pale brown solution of *N*,*N*-bis[3-(methylamino)propyl]methylamine **250** (200 µL, 0.997 mmol), anhydrous Et_3N (486 µL, 3.50 mmol) in anhydrous CH_2Cl_2 (20.0 mL) under Ar at RT. An immediate colour change to black solution was noted along with liberation of grey fumes ($HCl_{(g)}$). The resulting solution was stirred at RT overnight under Ar and progress of the

reaction was monitored by TLC. After total of 24 h, the reaction was judged to be complete, based on TLC analysis. The resulting mixture was quenched with sat. $NaHCO_{3(aq)}$ (30 mL), before transferred into separating funnel. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL) and combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale yellow oil (423 mg). The crude product was purified by flash column chromatography (SiO_2, 35 mm column, eluent: EtOAc, 100%) to afford thiourea **252** as a white solid (101 mg, 70%); δ_H (400 MHz; $CDCl_3$) 3.40 (6H s,), 3.38 – 3.33 (4H, m), 2.07 – 1.96 (2H, m); δ_C (101 MHz; $CDCl_3$) 179.4 (CS), 49.0 (CH_3), 43.5 (CH_2), 21.3 (CH_2); HRMS (ESI): calcd. for $C_6H_{12}N_2NaS$, 167.0613. Found: $[MH]^+$, 167.0617 (−2.2 ppm error).

Lab notebook reference: ixz_362

Spectroscopic data is consistent with those previously reported in the literature.[290]

Synthesis of 6-(phenylamino)hexan-1-ol – 254

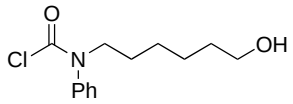


Aniline (6.78 mL, 75.1 mmol) was added to clear solution of 6-chloro-1-hexanol **257** (1.02 g, 7.05 mmol) in anhydrous toluene (38 mL) at RT. An immediate colour change to orange suspension noted, upon stirring at RT further colour change to pale red observed. The resulting mixture was stirred at 110 °C overnight under Ar and progress of the reaction was monitored by TLC. After total of 24 h, the reaction was judged to be complete, based on TLC analysis. The reaction mixture was allowed to cool to RT and concentrated under reduced to dryness to afford the crude product as a brown oil (8.01g). The crude product was purified by flash column chromatography (SiO_2, 60 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford title compound **254** as pale yellow oil (64.1 mg, 4%); R_f = 0.29 (50:50, EtOAc:*n*–hexane); δ_H (400 MHz; $CDCl_3$) 7.18 (2H, dd, *J* = 8.6, 7.3 Hz, CH), 6.78 – 6.70 (1H, m, C(H), 6.67 (2H, dd, *J* = 8.6, 7.3 Hz, CH), 3.65 (2H, t, *J* = 6.6 Hz, CH_2), 3.12 (2H, t, *J* = 7.2 Hz, CH_2), 1.70 – 1.62 (2H, m, CH_2), 1.62 – 1.54 (2H, m, CH_2), 1.47 – 1.37 (4H, m, 2 × CH_2); HRMS (ESI): m/z calcd. for $C_{12}H_{20}NO$: 194.1539, found: 194.1541 $[MH]^+$.

Lab notebook reference: ixz_345

Spectroscopic data is consistent with those previously reported in the literature.[289]

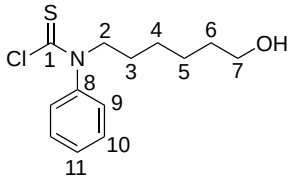
Synthesis of (6-hydroxyhexyl)(phenyl)carbamic chloride – 258



To a solution of 6-(phenylamino)hexan-1-ol **254** (56 mg, 0.290 mmol) in anhydrous CH_2Cl_2 (2.9 mL) at RT, dry Et_3N (60.6 µL, 0.435 mmol) and triphosgene (34.4 mg, 0.116 mmol) were added sequentially. The resulting mixture was stirred at RT for 24 h, quenched by the addition of H_2O (20 mL), extracted with CH_2Cl_2 (2 x 20 mL) and dried over $MgSO_4$ and concentrated under a *vacuo* to give the crude product as a pale yellow oil (189 mg). The crude product was purified by flash column chromatography (SiO_2, 20 mm column, eluent: EtOAc:*n*–hexane, 20:80 to 30:70) afforded the title compound **258** as a pale brown liquid (57 mg, 77%); R_f = 0.40 (50:50, EtOAc:*n*–hexane); IR (thin film) ν_{max}/cm^{-1} 3386br, 2935m, 1736s, 1323m, 698w; δ_H (400 MHz; $CDCl_3$) 7.45 – 7.34 (3H, m, Ar-CH), 7.21–7.16 (2H, m, Ar-CH), 3.69 (2H, br t, *J* = 6.8 Hz, OCH_2), 3.58 (2H, t, *J* = 6.6 Hz, NCH_2), 1.65 –1.47 (4H, m, 2 x CH_2), 1.38 – 1.27 (4H, m, 2 x CH_2); δ_C (101 MHz; $CDCl_3$) 149.3 (C=O), 141.9 (Ar-C), 129.6 (Ar-CH), 128.7 (Ar-CH), 128.4 (Ar-CH), 62.7 (OCH_2), 53.1 (NCH_2), 32.6 (CH_2), 27.5 (CH_2), 26.3 (CH_2), 25.4 (CH_2); HRMS (ESI): m/z calcd. for $C_{13}H_{18}{}^{35}ClNaNO_2$: 278.0918, found: 278.0925 $[MNa]^+$.

Lab notebook reference: ixz_346

Synthesis of (6-hydroxyhexyl)(phenyl)carbamothioic chloride – 259

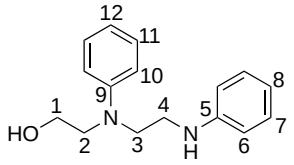


Thiophosgene (53.0 µL, 0.691 mmol) was added via syringe over a period of 35 sec to a pale brown solution of hexanol **254** (113 mg, 0.576 mmol), dry Et_3N (281 µL, 2.02 mmol) in anhydrous CH_2Cl_2 (12 mL). A colour change to dark brown solution was noted along with liberation of fumes ($HCl_{(g)}$). The resulting mixture was stirred at RT overnight under Ar and progress of the reaction was monitored by TLC. After total of 24 h, the reaction was judged to be complete, based on TLC analysis. The resulting mixture was quenched with sat. $NaHCO_{3(aq)}$ (20 mL), before was transferred to separating funnel and layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a dark brown oil (363 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 20:80 to 50:50) to afford title compound **259** as a pale yellow oil (71.1 mg, 45%); R_f = 0.32 (50:50, EtOAc:*n*–hexane); IR (thin film) ν_{max}/cm^{-1}: 3393w (H–O

alcohol), 3060w (C–H alkyl), 2932w (C–H alkyl), 2859w (C–H alkyl), 1699w (C=S carbamothioic chloride), 1673s (CC aromatic/aniline), 1594w (CC aromatic/aniline), 1491m, 1458m, 1409s, 1370w, 1244m, 1170w, 1096w, 1073w, 1055w, 1027w, 936w, 913w, 845w, 696w, 632w, 598w, 568w, 556w, 476w; δ_H (400 MHz; $(CD_3)_2CO$) 7.59 – 7.45 (3H, m, C(9+11)H), 7.41 – 7.34 (2H, m, C(10)H), 4.26 – 4.20 (2H, m, C(2)H_2), 3.49 (2H, t, *J* = 6.4 Hz, C(7)H_2), 1.81 – 1.68 (2H, m, C(6)H_2), 1.55 – 1.42 (2H, m, C(3)H_2), 1.40 – 1.26 (4H, m, C(4+5)H_2); δ_C (126 MHz; $(CD_3)_2CO$) 175.1 (C, C1), 145.7 (C, C8), 130.6 (2 × CH, C9), 129.7 (CH, C11), 127.5 (2 × CH, C10), 62.3 (CH_2, C7), 59.7 (CH_2, C2), 33.5 (CH_2, C6), 27.1 (CH_2, C3), 26.6 (CH_2, C4), 26.3 (CH_2, C5); HRMS (APCI): calcd. for $C_{13}H_{19}{}^{35}ClNOS$, 272.087039. Found: $[MH]^+$, 272.086564 (1.7 ppm error).

Lab notebook reference: ixz_349

Synthesis of 2-(phenyl(2-(phenylamino)ethyl)amino)ethan-1-ol – 262

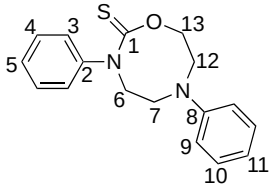


K_2CO_3 (2.44 g, 17.6 mmol) was added to a colourless solution of diamine **244** (2.25 g, 10.4 mmol) and 2-bromoethan-1-ol **261** (881 mg, 7.05 mmol) in anhydrous MeCN (35.3 mL) at RT under Ar. The resulting pale yellow suspension was then heated to 95 °C under Ar. After 16 h, the reaction was deemed to have gone to completion by TLC, with a colour change to light pink suspension noted. The reaction mixture allowed to cool to RT, before was filtered through Celite® and washed with EtOAc (3 × 30 mL). The resulting filtrate was concentrated under reduced pressure to yield a cherry red oil (3.30 g). The crude product was purified by flash column chromatography (SiO_2, 65 mm column, eluent: EtOAc:*n*–hexane, 40:60) to afford an alcohol **357** as a pale yellow oil (158 mg, 9%); R_f = 0.37 (50:50, EtOAc:*n*–hexane); IR (neat) ν_{max}/cm^{-1}: 3364w (N–H aniline/ O–H alcohol), 3023w (C–H alkyl), 2877w (C–H alkyl), 1726w, 1597s (CC aromatic), 1501s (CC aromatic), 1352w, 1322w, 1254w, 1215w, 1179w, 1123w, 1034m, 992m, 867w, 744s, 691s, 666w, 506m; δ_H (500 MHz; $CDCl_3$) 7.32 – 7.25 (2H, m, C(11)H), 7.25 – 7.17 (2H, m, C(7)H), 6.85 – 6.79 (2H, m, C(10)H), 6.82 – 6.74 (2H, m, C(8+12)H), 6.69 – 6.62 (2H, m, C(6)H), 3.77 (2H, t, *J* = 5.5 Hz, C(1)H_2), 3.61 (2H, t, *J* = 6.1 Hz, C(3)H_2), 3.52 (2H, t, *J* = 5.5 Hz, C(2)H_2), 3.39 (2H, t, *J* = 6.1 Hz, C(4)H_2), 3.20 (2H, s, OH+NH); δ_C (126 MHz; $CDCl_3$) 148.2 (C, C9), 148.0 (C, C5), 129.5 (2 × CH, C11), 129.4 (2 × CH, C7), 118.1 (CH, C8), 117.5 (CH, C12), 113.4 (2 × CH, C6), 113.3 (2 × CH, C10), 60.5 (CH_2, C1), 54.7 (CH_2, C2), 51.6 (CH_2, C3), 42.1 (CH_2, C4); HRMS (ESI): calcd. for $C_{16}H_{21}N_2O$,

257.1648. Found: $[MH]^+$, 257.1648 (−0.0 ppm error), calcd. for $C_{16}H_{20}NaN_2O$, 279.1468. Found: $[MNa]^+$, 279.1468 (−0.1 ppm error).

Lab notebook reference: ixz_357

Synthesis of 3,6-diphenyl-1,3,6-oxadiazocane-2-thione – 260

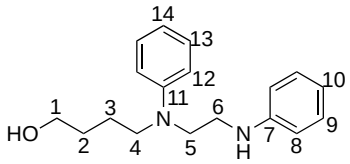


Thiophosgene (40.0 µL, 0.524 mmol) was added via syringe over a period of 20 sec to a pale yellow solution of amino ethan-1-ol **262** (112 mg, 0.437mmol), anhydrous Et_3N (213 µL, 1.53 mmol) in anhydrous CH_2Cl_2 (9.0 mL) under Ar at RT. An immediate colour change to dark purple was noted along with liberation of grey fumes ($HCl_{(g)}$). The resulting black solution was stirred at RT overnight under Ar and progress of the reaction was monitored by TLC. After a total of 24 h, the reaction was judged to be complete, based on TLC analysis. The resulting mixture was quenched with sat. $NaHCO_{3(aq)}$ (20 mL), before transferred into separating funnel. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a brown oil (360 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 20:80) to afford title compound **260** as a white solid (97.1 mg, 74%); R_f = 0.60 (50:50, EtOAc:*n*–hexane); melting point: 144 – 146 °C (from EtOAc:*n*–hexane); IR (solid state) ν_{max}/cm^{-1}: 2990w (C–H alkyl), 2948w (C–H alkyl), 1684w, 1595s (CC aromatic), 1574w (CC aromatic), 1491m, 1477s, 1452m, 1441m, 1410s, 1390w, 1369m, 1355m, 1332m, 1305s, 1268w, 1239m, 1208m, 1197m, 1183w, 1153s, 1112w, 1071m, 1057s, 1046m, 1022s, 998s, 967w, 947w, 878w, 861m, 807w, 755s, 722w, 713w, 694s, 660m, 621w, 579m, 564w, 544w, 523m, 485m, 454w; δ_H (400 MHz; $(CD_3)_2CO$) 7.47 – 7.40 (2H, m, C(3)H), 7.39 – 7.31 (3H, m, C(4+5)H), 7.27 – 7.18 (2H, m, C(10)H), 6.91 – 6.84 (2H, m, C(9)H), 6.75 – 6.67 (1H, m, C(11)H), 4.78 (2H, t, J = 5.1 Hz, C(13)H_2), 4.20 (2H, br, s, C(6 or 7)H_2) 3.87 – 3.80 (4H, m, C(6 or 7+12)H_2); δ_C (101 MHz; $(CD_3)_2CO$) 194.8 (CS, C1), 148.1 (C, C8), 146.4 (C, C2), 130.3 (2 × CH, C10), 130.1 (2 × CH, C3), 128.5 (CH, C5), 127.9 (2 × CH, C4), 118.0 (CH, C11), 113.6 (2 × CH, C9), 73.7 (CH_2, C13), 54.7 (CH_2), 52.3 (CH_2), 51.1 (CH_2); HRMS (ESI): calcd. for $C_{17}H_{19}N_2OS$,299.1213. Found: $[MH]^+$, 257.1648 (−0.1 ppm error), calcd. for $C_{17}H_{18}N_2NaOS$, 321.1032. Found: $[MNa]^+$, 321.1025 (2.2 ppm error), calcd. for $C_{17}H_{18}KN_2OS$, 337.0771. Found: $[MK]^+$, 337.0772 (−0.2 ppm error); X-ray crystallographic data for this

compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2221454, was crystallised by slow evaporation of *n*-hexane:EtOAc).

Lab notebook reference: ixz_360

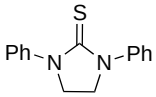
Synthesis of 4-(phenyl(2-(phenylamino)ethyl)amino)butan-1-ol – 264



K_2CO_3 (911 mg, 6.60 mmol) was added to a pale yellow solution of N^1,N^2-diphenylethane-1,2-diamine **244** (559 mg, 2.63 mmol) and 4-bromobutan-1-ol **263** (336 mg, 2.20 mmol) in anhydrous MeCN (44 mL) at RT under Ar. The resulting milky white suspension was then heated to 95 °C under Ar. After 16 h, the reaction was deemed to have gone to completion by TLC. The reaction mixture was allowed to cool to RT, before being filtered through Celite and washed with EtOAc (3 × 30 mL). The resulting filtrate was concentrated under reduced pressure to yield a beige oil (1.09 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford title compound **264** as a colourless oil (37.0 mg, 6%); R_f = 0.41 (50:50, EtOAc:*n*–hexane); IR (neat) ν_{max}/cm^{-1}: 3550w (N–H aniline), 3378w (O–H alcohol), 3023w, 2940w, 2877w; 1934w, 1727w, 1597s (CC aromatic), 1502s (CC aromatic), 1431w, 1369w, 1321w, 1255w, 1226w, 1195w, 1178w, 1122w, 1042m, 991w, 925w, 867w, 756s, 692s, 508m; δ_H (400 MHz; $CDCl_3$) 7.28 – 7.14 (4H, m, C(9+13)H), 6.81 – 6.68 (4H, m, C(10+12+14)H), 6.66 – 6.59 (2H, m, C(8)H), 3.65 (2H, t, *J* = 6.2 Hz, C(1)H_2), 3.54 (2H, t, *J* = 6.5 Hz, C(5)H_2), 3.39 – 3.30 (4H, m, C(4+6)H_2), 1.72 – 1.52 (4H, m, C(2+3)H_2); δ_C (101 MHz; $CDCl_3$) 148.3 (C, C11), 148.1 (C, C7), 129.5 (2 × CH, C13), 129.5 (2 × CH, C9), 117.8 (CH, C14), 117.1 (CH, C10), 113.3 (2 × CH, C12), 113.1 (2 × CH, C8), 62.8 (CH_2, C1), 51.5 (CH_2, C4), 50.6 (CH_2, C5), 41.5 (CH_2, C6), 30.3 (CH_2, C2), 23.7 (CH_2, C3); HRMS (ESI): calcd. for $C_{18}H_{25}N_2O$, 285.1961. Found: $[MH]^+$, 285.1964 (−1.0 ppm error).

Lab notebook reference: ixz_367

Synthesis of 1,3-diphenylimidazolidine-2-thione – 266

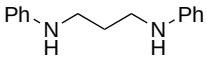


Thiophosgene (13.0 µL, 0.176 mmol) was added via syringe over a period of 30 sec to a pale brown solution of 4-(phenyl(2-(phenylamino)ethyl)amino)butan-1-ol **264** (41.6 mg, 0.146 mmol), anhydrous Et_3N (71.3 µL, 0.511 mmol) in anhydrous CH_2Cl_2 (3.0 mL) under Ar at RT. An immediate colour change to dark brown solution was noted along with liberation of grey fumes ($HCl_{(g)}$). The resulting solution was stirred at RT overnight under Ar and progress of the reaction was monitored by TLC. After total of 24 h, the reaction was judged to be complete, based on TLC analysis. The resulting mixture was concentrated under reduced pressure and purified by flash column chromatography (SiO_2, 20 mm column, eluent: EtOAc, 100%) to afford thiourea **266** as a white solid (17.1 mg, 46%); R_f = 0.41 (50:50, EtOAc:*n*–hexane); δ_H (400 MHz; $CDCl_3$) 7.64 – 7.56 (4H m, 4 × Ar-CH), 7.43 – 7.33 (4H, m, 4 × Ar-CH), 7.10 (2H td, *J* = 7.6, 7.0, 1.2 Hz, 2 × Ar-CH), 3.99 (4H, s, 2 × CH_2).

Lab notebook reference: ixz_370

Spectroscopic data is consistent with those previously reported in the literature.[290]

Synthesis of *N*^{1},*N*^{3}-diphenylpropane-1,3-diamine – 269

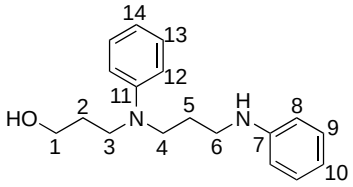


A flask charged with 1,3-dibromopropane **268** (1.00 mL, 9.85 mmol) and aniline (8.91 mL,98.5 mmol) was heated to 120 °C under Ar overnight. After 18 h, the reaction was deemed to have gone to completion by TLC analysis, with a colour change black brown slurry noted. The reaction mixture was cooled to RT, before being diluted with Et_2O (30 mL) and poured into a separating funnel. The resulting organic layer was washed with sat. $NaHCO_{3(aq)}$ (3 × 30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a dark brown liquid (8.98 g). The crude product was purified by flash column chromatography (SiO_2, 75 mm column, eluent: EtOAc:*n*–hexane, 30:70) to afford title comound **269** as a brown oil (1.88 g, 84%); R_f = 0.69 (50:50,EtOAc:*n*–hexane); δ_H (400 MHz; $CDCl_3$) 7.36 – 7.24 (4H, m, C(5)H_2), 6.86 – 6.79 (2H, m, C(6)H_2), 6.73 – 6.66 (4H, m, C(4)H_2), 3.67 (2H, br, s, 2 × NH), 3.30 (4H, t, *J* = 6.8 Hz, C(2)H_2), 2.04 – 1.91 (2H, m, C(1)H_2); δ_C (101 MHz; $CDCl_3$) 148.2 (2 × C, C3), 129.3 (2 × CH, C5), 117.5 (2 × CH, C6), 112.9 (2 × CH, C4), 42.0 (2 × CH_2, C2), 29.2 (CH_2, C1); HRMS (ESI): calcd. for $C_{15}H_{19}N_2$, 227.1543. Found: $[MH]^+$, 227.1544 (–0.5 ppm error).

Lab notebook reference: ixz_375

Spectroscopic data is consistent with those previously reported in the literature.[291]

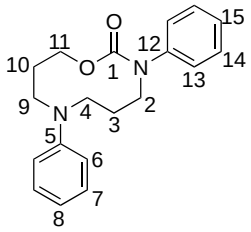
Synthesis of 3-(phenyl(3-(phenylamino)propyl)amino)propan-1-ol – 270



K_2CO_3 (2.29 g, 16.6 mmol) was added to a pale-yellow solution of *N*[1],*N*[3]-diphenylpropane-1,3-diamine **269** (1.88 g, 8.29 mmol) and 3-bromopropan-1-ol **188** (500 µL, 5.53 mmol) in anhydrous MeCN (19.0 mL) at RT under Ar. The resulting dark brown suspension was then heated to 95 °C under Ar. After 18 h, the reaction was deemed to have gone to completion by TLC. The reaction mixture allowed to cool to RT, before was quenched with H_2O (30 mL). The diluted reaction mixture was poured into separating funnel and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed sat. brine (3 × 30 mL). The resulting layer was collected and dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a brown oil (2.50 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford an alcohol **270** as pale yellow oil (1.97 g, 84%); R_f = 0.34 (50:50, EtOAc:*n*–hexane); IR (neat) ν_{max} /cm^{-1}: 3385w (O–H alcohol), 2941w (C–H alkyl), 2875w (C–H alkyl), 1729w, 1599s (CC aromatic), 1504s (CC aromatic), 1476w, 1431w, 1372w, 1318w, 1249m, 1217m, 1179w, 1042m, 990w, 917w, 867w, 745s, 692s, 683w, 608w, 509m; δ_H (400 MHz; $CDCl_3$) 7.38 – 7.33 (2H, m, C(13)H), 7.32 – 7.27 (2H, m, C(9)H), 6.89 – 6.78 (4H, m, C(8+12)H), 6.74 – 6.68 (2H, m, C(10+14)H), 3.73 (2H, t, *J* = 6.0 Hz, C(1)H_2), 3.53 – 3.43 (4H, m, C(3+4)H_2), 3.23 (2H, t, *J* = 6.8 Hz, C(6)H_2), 2.01 – 1.93 (2H, m, C(5)H_2), 1.92 – 1.85 (2H, m, C(2)H_2); δ_C (101 MHz; $CDCl_3$) 148.2 (C, C11), 148.0 (C, C7), 129.2 (2 × CH, C13), 129.3 (2 × CH, C9),117.4 (CH, C10), 116.5 (CH, C14), 113.0 (2 × CH, C12), 112.9 (2 × CH, C8), 60.5 (CH_2, C1), 49.0 (CH_2, C4), 48.2 (CH_2, C3), 41.8 (CH_2, C6), 29.8 (CH_2, C2), 26.9 (CH_2, C5); HRMS (ESI): calcd. for $C_{18}H_{25}N_2O$, 285.1961. Found: $[MH]^+$, 285.1962 (–0.1 ppm error).

Lab notebook reference: ixz_376

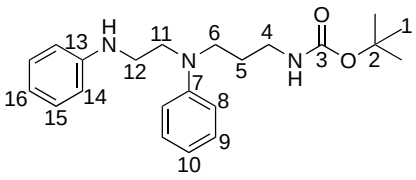
Synthesis of 3,7-diphenyl-1,3,7-oxadiazecan-2-one – 272



Triphosgene (240 mg, 0.807 mmol) was added in a single portion to a pale yellow solution of 3-(phenyl(3-(phenylamino)propyl)amino)propan-1-ol **270** (574 mg, 2.02 mmol), dry Et_3N (986 µL, 7.10 mmol) in anhydrous CH_2Cl_2 (40.0 mL) under Ar at RT. An immediate colour change to an orange solution was noted along with liberation of grey fumes ($HCl_{(g)}$). The resulting solution was stirred at RT overnight under Ar and progress of the reaction was monitored by TLC. After total of 24 h, the reaction was judged to be complete, based on TLC analysis with colour changed to pale brown solution noted. The resulting mixture was quenched with sat. $NaHCO_{3(aq)}$ (30 mL), before transferred into separating funnel. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL) and combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a yellow oil (1.37 g). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 35:65) to afford carbamate **272** as a colourless oil (487 mg, 78%); R_f = 0.53 (50:50,EtOAc:*n*–hexane); IR (neat) ν_{max}/cm^{-1}: 2957w (C–H alkyl), 2830w (C–H alkyl), 1699s (CO carbamate) 1598s (CC aromatic), 1495s, 1463m, 1452m, 1407m, 1364w, 1342w, 1331w, 1282w, 1247m, 1231m, 1208m, 1147m, 1123w 1065m, 1027w, 1005w, 991w, 870w, 764s, 709s, 694s, 665w, 650w, 618w, 595w, 541w, 521w, 4780w; δ_H (400 MHz; $CDCl_3$) 7.37 – 7.24 (4H, m, C(7+14)H), 7.24 – 7.16 (1H, m, C(15)H), 7.12 – 7.05 (2H, m, C(13)H) 6.96 – 6.85 (3H, m, C(6+8)H), 4.58 – 4.50 (2H, m, C(11)H_2), 3.93 – 3.86 (2H, m, C(2)H_2), 3.52 – 3.42 (4H, m, C(4+9)H_2), 2.20 – 2.11 (2H, m, C(10)H_2), 1.89 – 1.79 (2H, m, C(3)H_2); δ_C (101 MHz; $CDCl_3$) 156.0 (CO, C1), 150.6 (C, C5), 142.0 (C, C12), 128.9 (2 × CH, C7), 128.8 (2 × CH, C14), 126.9 (2 × CH, C13), 126.1 (CH, C15), 118.4 (CH, C8), 116.0 (2 × CH, C6), 66.3 (CH_2, C11), 58.9 (CH_2, C4), 50.2 (CH_2, C9), 49.5 (CH_2, C2), 29.0 (CH_2, C10), 26.4 (CH_2, C3); HRMS (ESI): calcd. for $C_{19}H_{23}N_2O_2$, 311.1754. Found: $[MH]^+$, 311.1758 (–1.4 ppm error), calcd. for $C_{19}H_{22}N_2NaO_2$, 333.1573. Found: $[MNa]^+$, 333.1575 (–0.5 ppm error), calcd. for $C_{19}H_{22}N_2KO_2$, 349.1313. Found: $[MK]^+$, 349.1315 (–0.7 ppm error).

Lab notebook reference: ixz_382

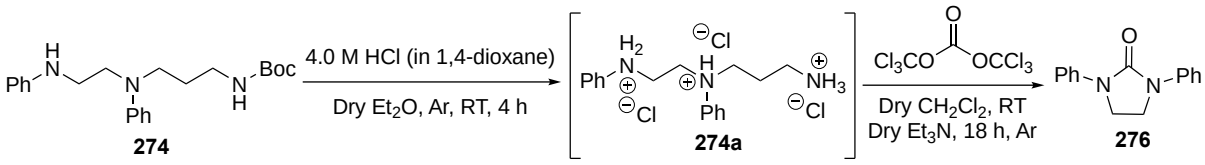
Synthesis of *tert*-butyl (3-(phenyl(2-(phenylamino)ethyl)amino)propyl)carbamate – 274



K_2CO_3 (2.44 g, 17.3 mmol) was added to a pale-yellow solution of *N*[1],*N*[2]-diphenylethane-1,2-diamine **244** (1.87 g, 8.80 mmol) and tert-butyl (3-bromopropyl)carbamate **273** (500 µL, 5.53 mmol) in anhydrous MeCN (44 mL) at RT under Ar. The resulting dark brown suspension was then heated to 95 °C under Ar. After 18 h, the reaction was deemed to have gone to completion by TLC. The reaction mixture was allowed to cool to RT and diluted with EtOAc (30 mL) and poured into a separating funnel. The diluted solution was washed with sat. $NaHCO_{3(aq)}$ (1 × 30 mL) and resulting aqueous phase was extracted with EtOAc (3 × 30 mL), before the combined organic phases were collected, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale-yellow solid (3.72 g). The crude product was purified by flash column chromatography (SiO_2, 70 mm column, eluent: EtOAc:*n*–hexane, 20:80) to afford tittle compound **274** as pale yellow oil (317 mg, 19%); R_f = 0.23 (20:80, EtOAc:*n*–hexane); IR (neat) ν_{max}/cm^{-1}: 3405w (N–H analine/carbamate), 2974w (C–H alkyl), 1693s (C=O carbamate), 1598s (CC aromatic), 1503s (CC aromatic), 1391w, 1365m,1320w, 1249m, 1210w, 1164s, 1072w, 1036w, 992w, 910w, 868m, 745s, 692s, 647w, 507m; δ_H (400 MHz; $CDCl_3$) 7.29 – 7.14 (4H, m, C(8+9)H), 6.79 –6.70 (5H, m, C(10+15+16)H), 6.67 – 6.58 (2H, m, C(14)H), 4.59 (1H, br, s, NH carbamate), 3.85 (1H, br, s, NH aniline), 3.52 (2H, t, *J* = 6.4 Hz, C(11)H_2), 3.39 – 3.30 (4H, m, C(6+12)H_2), 3.21 – 3.11 (2H, m, C(4)H_2), 1.82 – 1.70 (2H, m, C(5)H_2), 1.45 (9H, s, C(1)H_3); δ_C (101 MHz; $CDCl_3$) 156.1 (CO, C3), 148.1 (C, C7), 148.0 (C, C13), 129.5 (2 × CH, C9), 129.4 (2 × CH, C8), 117.7 (CH, C10), 117.1 (CH, C16), 113.2 (2 × CH, C15), 113.0 (2 × CH, C14), 79.4 (C, C2), 50.60 (CH_2, C11), 49.0 (CH_2, C6), 41.4 (CH_2, C12), 38.6 (CH_2, C4), 28.5 (2 × CH_3, C1), 27.8 (CH_2, C5); HRMS (ESI): calcd. for $C_{22}H_{32}N_3O_2$, 370.2489. Found: $[MH]^+$, 370.2499 (–2.7 ppm error), calcd. for $C_{22}H_{31}N_3NaO_2$, 392.2308. Found: $[MNa]^+$, 392.2319 (–2.7 ppm error), calcd. for $C_{22}H_{31}KN_3O_2$, 408.2048. Found: $[MK]^+$, 408.2060 (–3.1 ppm error).

Lab notebook reference: ixz_390

Synthesis of 1,3-diphenylimidazolidin-2-one – 276



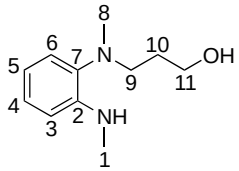
274 274a 276

Hydrogen chloride solution (4.0 M in 1,4-dioxane, 12.0 mL) was added dropwise over a period of 30 sec via syring to a solution of carbamate **274** (110 mg, 0.296 mmol) in anhydrous Et_2O (6.0 mL) at RT under Ar. A white solid was immediately noted along with a colour change to creamy white suspension and the reaction mixture was stirred at RT for 4 h under Ar, at which point the reaction mixture was deemed to have gone to completion by TLC (carbamate **274** was noted). The resulting colourless reaction with brown emission the bottom of a flask was concentrated under *vacuo* to yield brown solid **274a** crude product. Next, the crude mixture **274a** was redissolved in anhydrous CH_2Cl_2 (20 mL) to obtain a dark orange emulsion. Then Et_3N (410 µL, 2.96 mmol) was added dropwise over a period of 1 min via syringe, whereupon a liberation grey fume and colour changed to a pale yellow solution was observed. Triphosgene (87.8 mg, 0.296 mmol) was added in a single portion to a corresponding mixture, with a colour change to a pale-yellow solution was immediately noted and the reaction mixture was stirred at RT for 18 h of stirring at RT under Ar, before reaction was deemed to have to completion by TLC. The resulting mixture was concentrated under reduced pressure to yield a white solid (154 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 30:70 to 50:50) to afford urea **276** as a white solid (51.2 mg, 73%, over two steps); δ_H (400 MHz; $CDCl_3$) 7.64 – 7.54 (4H, m, 4 × Ar-CH), 7.43 – 7.32 (4H, m, 4 × Ar-CH), 7.10 (2H, tt, J = 7.5, 1.1 Hz, 2 × Ar-CH), 3.99 (4H, s, 2 × CH_2); δ_C (101 MHz; $CDCl_3$) 140.2 (CO), 129.0 (4 × CH), 123.2 (2 × CH), 122.7 (2 ×C), 118.2 (4 × CH), 42.1 (2 × CH_2).

Lab notebook reference: ixz_392

Spectroscopic data is consistent with those previously reported in the literature.[290]

Synthesis of 3-(methyl(2-(methylamino)phenyl)amino)propan-1-ol – 279

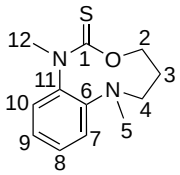


K_2CO_3 (1.30 g, 9.38 mmol) was added to a black brown suspension of N^1,N^2-diphenylethane-1,2-diamine **278** (559 mg, 2.63 mmol), 4-bromobutan-1-ol **188** (565 µL, 6.25 mmol) and KI

(2.49 g, 15.0 mmol) in anhydrous MeCN (21 mL) at RT under Ar. The resulting mixture was then heated to 95 °C under Ar. After 18 h, the reaction was deemed to have gone to completion by TLC. The reaction mixture was allowed to cool to RT, before being filtered through (via filter paper) and filter cake was washed with EtOAc (3 × 20 mL). The resulting filtrate was concentrated under reduced pressure to yield a black brown oil (1.86 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford an alcohol **279** as a brown oil (817 mg, 67%); R_f = 0.44 (50:50, EtOAc:*n*–hexane); IR (neat) ν_{max}/cm^{-1}: 3372w, (O–H alcohol/ N–H aniline), 3044w (C–H alkyl), 2936w (C–H alkyl/N–H aniline), 2868w (C–H alkyl / N–H aniline), 2808w (C–H alkyl / N–H aniline), 1734w, 1598m (CC aromatic), 1509s (CC aromatic), 1476w, 1460w, 1448w, 1425w, 1410w, 1375w, 1323w, 1272w, 1244w, 1202w, 1165m, 1119w, 1056m, 1040s, 956w, 924w, 874w, 840w, 740s, 665w, 601w, 575w, 474w; δ_H (400 MHz; $CDCl_3$) 7.11 – 7.00 (2H, m, C(4+6)H), 6.70 (1H, td, *J* = 7.8, 1.4 Hz, C(5)H), 6.63 (1H, dd, *J* = 7.8, 1.4 Hz, C(3)H), 3.72 (2H, t, *J* = 6.1 Hz, C(11)H_2), 2.97 (2H, t, *J* = 6.7 Hz, C(9)H_2), 2.86 (3H, s, C(1)H_3), 2.62 (3H, s, C(8)H_3), 1.80 – 1.69 (2H, m, C(10)H_2); δ_C (101 MHz; $CDCl_3$) 144.9 (C, C2), 139.2 (C, C7), 125.4 (CH, C4), 120.3 (CH, C6), 116.6 (CH, C5), 110.0 (CH, C3), 61.7 (CH_2, C11), 53.5 (CH_2, C9), 42.0 (CH_3, C8), 30.8 (CH_3, C1), 30.1 (CH_2, C10); HRMS (ESI): calcd. for $C_{11}H_{19}N_2O$, 195.1492. Found: $[MH]^+$, 195.1494 (−1.0 ppm error).

Lab notebook reference: ixz_404

Synthesis of 1,7-dimethyl-4,5,6,7-tetrahydrobenzo[*d*][1,3,6]oxadiazonine-2(1*H*)-thione – 280

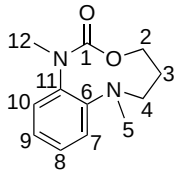


Thiophosgene (108 µL, 1.41 mmol) was added in a single portion via syringe to a pale yellow solution of 3-(methyl(2-(methylamino)phenyl)amino)propan-1-ol **279** (228 mg, 1.18 mmol), dry Et_3N (574 µL, 4.11 mmol) in anhydrous CH_2Cl_2 (24.0 mL) under Ar at RT. An immediate colour of the reaction mixture changed over 2 min from yellow to dark green and finally black brown was noted along with the liberation of grey fumes. The resulting solution was stirred at RT overnight under Ar and the progress of the reaction was monitored by TLC. After total of 18 h, the reaction was deemed to have gone to completion by TLC analysis. The resulting mixture was quenched with sat. $NaHCO_{3(aq)}$ (30 mL), before transferred into separating funnel. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and combined organic layers were

collected, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a brown oil (423 mg). The crude product was purified by flash column chromatography (SiO_2, 35 mm column, eluent: EtOAc:*n*–hexane, 40:60) to afford thiocarbamate **280** as an orange oil (238 mg, 85%); R_f = 0.61 (50:50, EtOAc:*n*–hexane); IR (thin film)ν_{max}/cm^{-1}: 3040w (C–H alkyl), 2953w (C–H alkyl), 1734w, 1598m (CC aromatic), 1596s (C=S thiocarbamate), 1571w (CC aromatic), 1505s (CC aromatic), 1495s, 1466s,1412m, 1360m, 1322m, 1303m, 1265m,1230s, 1206s, 1173s, 1117m, 1066m, 1017m, 987w, 926w, 860w, 837w, 746s, 732s, 692s, 617w, 570w, 544w, 513w, 473w; δ_H (400 MHz; $CDCl_3$) 7.42 – 7.07 (4H, m, C(7+9+10)), [5.14 – 5.04 (m), 4.69 – 4.42 (m), 4.19 – 4.09 (m), 4.07 – 3.98 (m), 3.98 – 3.89 (m), 3.86 – 3.71 (m), 3.61 (s, 3H), 3.51 – 3.40 (m), 3.27 – 3.17 (m), 3.09 – 2.97 (m), 2.56 (s, 3H), 2.28 – 2.04 (m), 1.83 – 1.70 (m), 1.64 – 1.46 (m), 1.39 – 0.97 (m)] = 12H (3 × CH_2 + 2 × CH_3). Note, due to the ^{1}H NMR spectrum suffering from severe rotameric broadening, the ^{1}H NMR signals in this region could not be confidently assigned. The ^{13}C NMR data proved to be much more informative in confirming the assigned structure; δ_C (101 MHz; $CDCl_3$) 194.2 (CS), 147.6 (C), 144.5 (C), 127.8 (CH), 126.7 (CH), 125.4 (CH), 124.9 (CH), 72.6 (CH_2), 55.6 (CH_2), 46.6 (CH_3), 42.7 (CH_3), 27.0 (CH_2); HRMS (APCI): calcd. for $C_{12}H_{17}N_2OS$, 237.105611. Found: $[MH]^+$, 237.104996 (–2.6 ppm error).

Lab notebook reference: ixz_405

Synthesis of 1,7-dimethyl-4,5,6,7-tetrahydrobenzo[*d*][1,3,6]oxadiazonin-2(1*H*)-one – 281

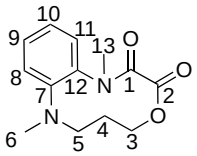


Triphosgene (227 mg, 0.766 mmol) was added in a single portion to a pale yellow solution of 3-(methyl(2-(methylamino)phenyl)amino)propan-1-ol **279** (372 mg, 1.90 mmol), dry Et_3N (795 µL, 5.70 mmol) in anhydrous CH_2Cl_2 (38 mL) under Ar at RT. An immediate colour change to yellow solution was noted along with the liberation of grey fumes. The resulting solution was stirred at RT overnight under Ar and the progress of the reaction was monitored by TLC. After total of 18 h, the reaction was deemed to have gone to completion by TLC analysis. The resulting mixture was quenched with sat. $NaHCO_{3(aq)}$ (30 mL), before transferred into separating funnel. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and combined organic layers were collected before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale-yellow oil (1.16 g). The crude product was purified by flash column chromatography (SiO_2, 20 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford

carbamate **281** as a colourless oil (400 mg, 96%); R_f = 0.43 (50:50, EtOAc:*n*–hexane); IR (thin film)ν_{max} /cm^{-1}: 3009w (C–H alkyl), 2955w (C–H alkyl), 2897w, 2843w, 2804w, 1701s (C=O carbamate), 1597m (CC aromatic), 1493s (CC aromatic) 1462w, 1421w, 1383w, 1372w, 1359m, 1338m, 1299m, 1278m, 1248m, 1216w, 1175w, 1153m, 1120w, 1080w, 1047w, 1023m, 968w, 919w, 900w, 827w, 804w, 745s, 706w, 666s, 652m, 587m, 566w, 547m, 530w, 506w, 478w; δ_H (400 MHz; $CDCl_3$) 7.27–7.20 (1H, m, C(7)H), 7.24 –7.09 (3H, m, C(8+9+10)H), 4.60 – 4.50 (1H, m, C(2)**H**H'), 3.79–3.69 (1H, m, C(2)H**H'**), 3.18 – 3.14 (1H, m, C(4)**H**H'), 3.13 (3H, s, C(12)H_3), 2.94 – 2.83 (1H, m, C(4)**H**H'), 2.50 (3H, s, C(5)H_3), 1.61 – 1.40 (2H, m, C(3)H_2); δ_C (101 MHz; $CDCl_3$) 159.6 (CO, C1), 148.2 (C, C6), 144.2 (C, C11), 126.7 (CH), 126.5 (CH), 125.4 (CH), 124.4 (CH), 66.5 (CH_2, C2), 55.3 (CH_2, C4), 47.4 (CH_3, C5), 37.5 (CH_3, C12), 27.0 (CH_2, C3); HRMS (ESI): calcd. for $C_{12}H_{17}N_2O_2$, 221.1285. Found: $[MH]^+$, 221.1291 (–2.9 ppm error), calcd. for $C_{12}H_{16}N_2NaO_2$, 243.1104. Found: $[MNa]^+$, 243.1109 (–1.9 ppm error).

Lab notebook reference: ixz_406

Synthesis of 1,8-dimethyl-5,6,7,8-tetrahydro-1*H*-benzo[*e*][1,4,7]oxadiazecine-2,3-dione – 282

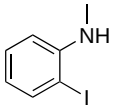


Oxalyl chloride (113 µL, 1.32 mmol) was added in a single portion via syringe to a pale yellow solution of 3-(methyl(2-(methylamino)phenyl)amino)propan-1-ol **279** (233 mg, 1.20 mmol), dry Et_3N (500 µL, 3.60 mmol) in anhydrous CH_2Cl_2 (24 mL) under Ar at RT. An immediate colour changed to dark brown solution was noted along with the liberation of grey fumes. The resulting solution was stirred at RT overnight under Ar and the progress of the reaction was monitored by TLC. After total of 18 h, the reaction was deemed to have gone to completion by TLC analysis. The resulting mixture was diluted with EtOAc (30 mL), before being filtered through Celite and washed with EtOAc (3 × 20 mL). The filtrated was concentrated under reduced pressure to yield a brown oil (371 mg). The crude product was purified by flash column chromatography (SiO_2, 20 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford title compound **282** as a white solid (217 mg, 73%); R_f = 0.36 (50:50, EtOAc:*n*–hexane); melting point: 134–136 °C (from Et_2O:EtOAc:$CHCl_3$); IR (solid state) ν_{max} /cm^{-1}: 2997w (C–H alkyl), 2955w (C–H alkyl), 2927w (C–H alkyl), 2900w, 2846m, 1718s (C=O ester), 1650s (C=O amide), 1594m (CC aromatic), 1501m (CC aromatic), 1456m (CC aromatic), 1436w, 1422w, 1390w, 1375w, 1356w, 1325w, 1302w, 1266w, 1245m, 1210m, 1178s, 1145w, 1124m, 1100s,

1071m, 1049m, 1024w, 986m, 956w, 936w, 921m, 898m, 878w, 827w, 795, 779s, 765s, 735w, 676s, 653w, 593m, 571w, 561s, 507m, 495m, 452m; δ_H (500 MHz; $CDCl_3$) 7.22 – 7.09 (3H, m, C(8+9+10)H), 6.96 (1H, dd, *J* = 7.4, 1.9 Hz, C(11)H), 4.96 (1H, br, s, C(3)**H**H'), 4.10 (1H, br, s, C(3)H**H'**), 3.41 (3H, s, C(6)H_3), 3.23 – 3.14 (2H, m, C(5)H_2), 2.49 (3H, s, C(13)H_3), 2.03 (1H, br, s, C(4)**H**H'), 1.51 (1H, br, s, C(4)H**H'**); δ_C (126 MHz; $CDCl_3$) 161.6 (NCO, C1), 160.7 (OCO, C2), 147.2 (C, C7), 138.6 (C, C12), 127.2 (CH), 125.1 (CH), 123.7 (CH), 122.7 (CH, C11), 64.6 (CH_2, C3), 53.0 (CH_2, C5), 40.9 (CH_3, C13), 35.7 (CH_3, C6), 23.8 (CH_2, C4); HRMS (ESI): calcd. for $C_{13}H_{17}N_2O_3$, 249.1234. Found: $[MH]^+$, 249.1238 (−1.7 ppm error), calcd. for $C_{13}H_{16}N_2NaO_3$, 271.1053. Found: $[MNa]^+$, 271.1055 (−0.5 ppm error); X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2223454, was crystallised by slow evaporation of EtOAc:$CHCl_3$:Et_2O).

Lab notebook reference: ixz_407

Synthesis of *N*-methyl-2-iodoaniline – 284

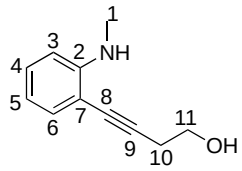


MeLi (7.25 mL, 1.6 M in Et_2O, 11.6 mmol) was added dropwise over 30 min via syringe pump to a solution of 2-Iodoaniline **283** (2.54 g, 11.6 mmol) in anhydrous THF (30 mL) at −78 °C under Ar, with a colour change to creamy pale yellow/green suspension noted. The resulting reaction mixture was stirred at −78 °C for 1 h under Ar. After that time, a solution of MeI (953 µL,15.3mmol) in anhydrous THF (10 mL) was transferred to the stirring reaction mixture dropwise over 2 min by a syringe pump. The reaction was allowed to warm to RT and stir for 18 h under Ar, after which time the reaction was deemed to have gone to completion by TLC. The resulting mixture was quenched by addition of sat. $NH_4Cl_{(aq)}$ (50 mL) and poured into the separating funnel. The aqueous layer was extracted with Et_2O (3 × 60 mL), before combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale-yellow oil (3.00 g). The crude product was purified by flash column chromatography (SiO_2, 60 mm column, eluent: EtOAc:*n*–hexane, 10:90) to afford an secondary aniline **284** as a pale yellow liquid oil (2.70 g, 99%); R_f = 0.43 (10:90, EtOAc:*n*–hexane); δ_H (400 MHz; $CDCl_3$) 7.66 (1H, dt, *J* = 8.1, 2.2 Hz, Ar-CH), 7.29 – 7.20 (1H, m, Ar-CH), 6.57 (1H, dt, *J* = 8.1, 2.2 Hz, Ar-CH), 6.51 – 6.42 (1H, m, Ar-CH) 4.25 (1H, s, NH), 2.89 (3H s, CH_3).

Lab notebook reference: ixz_410

Spectroscopic data is consistent with those previously reported in the literature.[292]

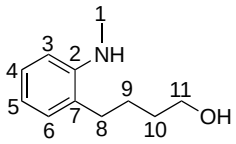
Synthesis of 4-(2-(methylamino)phenyl)but-3-yn-1-ol – 286



But-3-yn-1-ol **285** (707 µL, 9.34 mmol) was added dropwise over 20 sec via syringe to a pale-yellow solution of iodoaniline **284** (1.81 g, 7.79 mmol), dry Et_3N (3.26 mL, 23.4 mmol) in anhydrous DMF (26 mL) at RT under Ar. After 2 min, CuI (14.8 mg, 77.9 µmol) and bis(triphenylphosphine)palladium chloride (109 mg, 0.156 mmol) in a single portion. The resulting reaction mixture was stirred at RT under Ar and an immediate colour changed to yellow suspension noted. Upon stirring, the colour of the reaction mixture changed over 6 min from colourless solution (after 1 min) to pale orange (after 3 min) and finally black brown. After a total of 18 h, the reaction was deemed to have gone to completion by TLC. The resulting reaction mixture was filtered through Celite, washed with EtOAc (3 × 40 mL). The resulting filtrate was concentrated under reduced pressure to yield a dark brown oil (1.81 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 30:70) to afford alkyne **286** as a yellow oil (1.20 g, 88%); R_f = 0.11 (30:70, EtOAc:*n*-hexane);IR(neat)ν_{max}/cm^{-1}:3404w (O–H alcohol),3339w (C–H alkenyl), 2901m (C–H alkyl), 2824 (C–H alkyl), 1600s (CC aromatic), 1574s (CC aromatic), 1509s (CC aromatic), 1461s, 1425m, 1320s, 1287s, 1167s, 1036s, 744s; δ_H (400 MHz; $CDCl_3$) 7.26 (1H, dd, *J* = 8.1, 1.8 Hz, C(6)H), 7.20 (1H, td, *J* = 8.1, 1.8 Hz, C(4)H), 6.64 – 6.59 (1H, m, C(5)H), 6.58 (1H, d, *J* = 8.1 Hz, C(3)H), 3.79 (2H, t, *J* = 6.3 Hz, C(11)H_2), 2.88 (3H, s, C(1)H_3), 2.71 (2H, t, *J* = 6.3 Hz, C(10)H_2); δ_C (101 MHz; $CDCl_3$) 149.9 (C), 132.0 (CH), 129.6 (CH), 116.3 (CH), 109.1 (CH), 107.8 (C), 92.3 (C), 79.0 (C), 61.3 (CH_2, C11), 30.4 (CH_3, C1), 24.1 (CH_2, C10); HRMS (ESI): calcd. for $C_{11}H_{14}NO$, 176.1070. Found: $[MH]^+$, 176.1072 (–1.1 ppm error), calcd. for $C_{11}H_{13}NNaO$, 198.0889. Found: $[MNa]^+$, 198.0890 (–0.2 ppm error).

Lab notebook reference: ixz_412

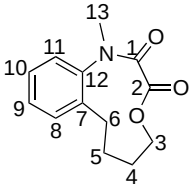
Synthesis of 4-(2-(methylamino)phenyl)butan-1-ol – 287



Pd/C (59.8 mg, Pd 10% on carbon) was added to the round bottom, previously purged under N_2 (for 10 min), containing 4-(2-(methylamino)phenyl)but-3-yn-1-ol **286** (967 mg, 5.62 mmol) at RT. The alkyne **286** was dissolved by the addition of anhydrous MeOH (26.0 mL, degassed for 10 min) and the reaction vessel was evacuated under vacuum and then backfilled with H_2 (via balloon) three times, then stirred at RT under a slight positive atmosphere of H_2 (via balloon) for 48 h. The reaction was then purged with N_2 for 20 min, filtered through Celite and washed with MeOH (3 × 20 mL). The resulting filtrate was concentrated under reduced pressure to yield crude product as pale-yellow oil (1.54 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford title compound **287** as a pale orange oil (619 mg, 61%); R_f = 0.20 (50:50, EtOAc:*n*–hexane);IR (neat) ν_{max}/cm^{-1}: 3380w (O–H alcohol/N–H aniline), 3006w, 2933w (C–H alkyl), 2864w, 2813w (C–H alkyl), 1604s (CC aromatic), 1584s (CC aromatic), 1509s (CC aromatic), 1469w, 1462w, 1426w, 1306m, 1262m, 1217w, 1168m, 11127w, 1103w, 1054m, 977w, 927w, 835w, 745s, 666w, 617w;δ_H (400 MHz; $CDCl_3$) 7.18 (1H, td, *J* = 7.7, 1.5 Hz, C(4)H), 7.06 (1H, dd, *J* = 7.7, 1.5 Hz, C(6)H), 6.71 (2H, td, *J* = 7.7, 1.5 Hz, C(5)H_2), 6.65 (1H, dd, *J* = 7.7, 1.5 Hz, C(3)H_2), 3.68 (2H, t, *J* = 6.1 Hz, C(11)H_2), 2.89 (3H, s, C(1)H_3), 2.51 (2H, t, *J* = 7.4 Hz, C(8)H_2), 1.79 – 1.56 (4H, m, C(9+10)H_2); δ_C (101 MHz; $CDCl_3$) 146.6 (C, C2), 128.8 (CH, C3), 127.1 (CH, C4), 126.1 (C, C7), 117.0 (CH, C5), 109.8 (CH, C3), 62.2 (CH_2, C11), 32.2 (CH_2, C10), 30.8 (CH_3, C1), 30.6 (CH_2, C8), 24.6 (CH_2, C9); HRMS (ESI): calcd. for $C_{11}H_{18}NO$, 180.1383. Found: $[MH]^+$, 180.1384 (–0.5 ppm error), calcd. for $C_{11}H_{17}NNaO$, 202.1202. Found: $[MNa]^+$, 202.1204 (–0.8 ppm error).

Lab notebook reference: ixz_413

Synthesis of 1-methyl-5,6,7,8-tetrahydro-1*H*-benzo[*e*][1,4]oxazecine-2,3-dione – 288

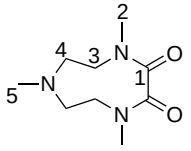


Oxalyl chloride (163 µL, 1.90 mmol) was added in a single portion via syringe to colouless solution of butan-1-ol **287** (310 mg, 1.73 mmol), dry Et_3N (724 µL, 5.19 mmol) in anhydrous CH_2Cl_2 (35 mL) under Ar at RT. An immediate colour change to pale yellow solution was noted

along with the liberation of grey fumes. The resulting solution was stirred at RT overnight under Ar and the progress of the reaction was monitored by TLC. Upon stirring, the colour of the reaction mixture changed to blood red and finally black brown solution. After total of 18 h, the reaction was deemed to have gone to completion by TLC analysis. The resulting mixture was diluted with EtOAc (30 mL), before being filtered through Celite and washed with EtOAc (3 × 20 mL). The filtrated was concentrated under reduced pressure to yield a pale yellow oil (217 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane, 40:60) to afford title compound **288** as a crystalline colourless solid (34.4 mg, 9%); R_f = 0.64 (50:50, EtOAc:*n*–hexane); melting point: 147 – 148 °C (from *n*–hexane:Et_2O); IR (solid state) ν_{max} /cm^{-1}: 2988w, 2954m (C–H alkyl), 2875w, 1737s, (C=O ester), 1657s (C=O amide), 1600w (CC aromatic), 1488m, 1463w, 1444s, 1429w, 1393s, 1374m, 1351w, 1289m, 1219s, 1211s, 1173w, 1159w, 1130w, 1104w, 1081w, 1066m, 1046m, 1035s, 1003w, 961m, 875w, 826m, 807m, 797s, 789s, 765s, 732w, 717s, 666s, 588s, 563m, 529, 511w, 459w; δ_H (400 MHz; $CDCl_3$) 7.37 – 7.30 (1H, m, C(11)H), 7.30 – 7.20 (3H, m, C(8+9+10)H), 4.82 – 4.73 (1H, m, C(3)**H**H'), 3.93 – 3.81 (1H, m, C(3)H**H'**), 3.25 (3H, s, C(13)H_3), 3.22 – 3.12 (1H, m, C(6)**H**H'), 2.78 – 2.67 (1H, m, C(6)H**H'**), 2.26 – 2.10 (1H, m, C(5)**H**H'), 2.08 – 1.94 (1H, m, C(5)H**H'**), 1.62 – 1.46 (1H, m, C(4)**H**H'), 1.36 – 1.25 (1H, m, C(4)H**H'**); δ_C (101 MHz; $CDCl_3$) 162.5 (CO, C2), 162.4 (CO, C1), 140.4 (C, C12), 137.6 (C, C7), 130.0 (CH, C8), 129.2 (CH), 129.1 (CH), 127.8 (CH, C11), 67.5 (CH_2, C3), 36.3 (CH_3, C13), 27.2 (CH_2, C6), 26.8 (CH_2, C5), 22.1 (CH_2, C4); HRMS (ESI): calcd. for $C_{13}H_{16}NO_3$, 234.1125. Found: $[MH]^+$, 234.1130 (–2.2 ppm error), calcd. for $C_{13}H_{15}NNaO_3$, 256.0944. Found: $[MNa]^+$, 256.0945 (–0.3 ppm error); X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2223696, was crystallised by slow evaporation of $CHCl_3$:Et_2O).

Lab notebook reference: ixz_415

Synthesis of 1,4,7-trimethyl-1,4,7-triazonane-2,3-dione – 289

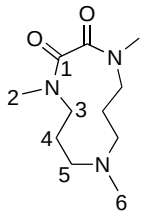


Oxalyl chloride (226 µL, 2.64 mmol) was added in a single portion via syringe to a solution of *N*[1],*N*[2]-dimethyl-*N*[1]-(2-(methylamino)ethyl)ethane-1,2-diamine **246** (400 µL, 2.40 mmol), dry Et_3N (1.17 mL, 8.40 mmol) in anhydrous CH_2Cl_2 (48 mL) under Ar at RT. The resulting solution was stirred at RT overnight under Ar, and the progress of the reaction was monitored by TLC. After total of 18 h, the reaction was deemed to have gone to completion by TLC analysis. The

resulting mixture was concentrated under *vacuo* to yield a brown oil (730 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: MeOH:EtOAc, 30:70) to afford title compound **289** as a pale yellow oil (350 mg, 73%); R_f = 0.19 (30:70, MeOH:EtOAc); IR (neat) ν_{max} /cm^{-1}: 3496w, 2941w (C–H alkyl), 2805w, 1627s (C=O amide),1511w, 1453m, 1420m, 1400m, 1359m, 1317w, 1277w, 1232m, 1203m, 1146m, 1128m, 1083w, 1067w, 1040w, 1003w, 946w, 979w, 946w, 866w, 784m, 742w, 675w, 646w, 497w; δ_H (400 MHz; $CDCl_3$) 3.56 (2H, ddd, *J* = 15.6, 9.8, 3.3 Hz, 2 × C(3)H**H'**), 3.25 – 3.13 (2H, m, 2 × C(3)**H**H'), 2.92 (6H, s, C(2)H_3), 2.70 (2H, ddd, *J* = 14.6, 9.7, 3.2 Hz, 2 × C(4)H**H'**), 2.59 (2H, dd, *J* = 14.3, 3.6 Hz, 2 × C(4)**H**H'), 2.46 (3H, s, C(5)H_3); δ_C (101 MHz; $CDCl_3$) 166.1 (CO, C1), 55.4 (CH_2, C4), 51.3 (CH_2, C3), 47.9 (CH_3, C5), 31.8 (CH_3, C2); HRMS (ESI): calcd. for $C_9H_{18}N_3O_2$, 200.1394. Found: $[MH]^+$, 200.1396 (–1.2 ppm error), calcd. for $C_9H_{17}N_3NaO_2$, 222.1213. Found: $[MNa]^+$, 222.1213 (–0.2 ppm error), calcd. for $C_9H_{17}KN_3O_2$, 238.0952. Found: $[MK]^+$, 238.0957 (–2.1 ppm error).

Lab notebook reference: ixz_434

Synthesis of 1,4,8-trimethyl-1,4,8-triazacycloundecane-2,3-dione – 290

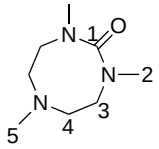


Oxalyl chloride (188 µL, 2.19 mmol) was added in a single portion via syringe to a colouless solution of *N*^{1},*N*^{3}-dimethyl-*N*^{1}-(3-(methylamino)propyl)propane-1,3-diamine **250** (400 µL, 1.99 mmol), dry Et_3N (695 µL, 4.99 mmol) in anhydrous CH_2Cl_2 (40 mL) under Ar at RT. The resulting solution was stirred at RT overnight under Ar and the progress of the reaction was monitored by TLC. After total of 18 h, the reaction was deemed to have gone to completion by TLC analysis. The resulting mixture was concentrated under *vacuo* to yield a brown oil (730 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: MeOH:EtOAc, 0:100 to 30:70) to afford title compound **290** as a white solid (321 mg, 71%); R_f = 0.08 (EtOAc); melting point: 135 – 136 °C (from *n*–hexane:Et_2O); IR (solid state) ν_{max} /cm^{-1}: 2947w, 2881w (C–H alkyl), 2803w, 2776w, 2240w, 1615s (C=O amide), 1532w, 1509w, 1452m, 1424m, 1401m, 1354m, 1314w, 1253w, 1263w, 1237m, 1218m, 1198w, 1132m, 1060m, 1031w, 1021m, 985w, 969w, 953w, 922w, 887w, 843w, 787w, 746s, 664m, 645w, 633m, 565w; δ_H (400 MHz; $CDCl_3$) 4.00 (2H, ddd, *J* = 14.6, 11.6, 2.8 Hz, 2 × C(3)H**H'**), 3.13 (2H, ddd, *J* = 14.6, 3.5, 3.5 Hz, 2 × C(3)**H**H'), 2.92 (6H, s, C(2)H_3), 2.36 (4H, dd, *J* = 6.7,

5.3 Hz, C(5)H_2), 1.94 (3H, s, C(6)H_3), 1.84 – 1.69 (2H, m, 2 × C(4)H**H'**), 1.47 – 1.34 (2H, m, 2 × C(4)**H**H'); δ_C (101 MHz; $CDCl_3$) 165.4 (CO, C1), 57.8 (CH_2, C5), 48.2 (CH_2, C3), 37.8 (CH_3, C6), 31.5 (CH_3, C2), 22.4 (CH_2, C4); HRMS (ESI): calcd. for $C_{11}H_{22}N_3O_2$, 228.1707. Found: $[MH]^+$, 228.1706 (0.1 ppm error), calcd. for $C_{11}H_{21}N_3NaO_2$, 250.1526. Found: $[MNa]^+$, 250.1525 (0.4 ppm error), calcd. for $C_{11}H_{21}KN_3O_2$, 266.1265. Found: $[MK]^+$, 266.1265 (0.0 ppm error); X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2232114).

Lab notebook reference: ixz_433

Synthesis of 1,3,6-trimethyl-1,3,6-triazocan-2-one – 291

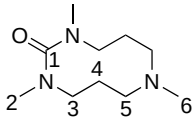


N^1,N^2-dimethyl-N^1-(2-(methylamino)ethyl)ethane-1,2-diamine **246** (900 µL, 5.99 mmol) was added reaction flask (500 mL RBF) containing anhydrous DMF (120 mL). The resulting reaction vessel was evacuated under *vacuo* and backfilled with CO_2 (via balloon) 6 times. Next, EDC.HCl (1.72 g, 8.98 mmol), HOBt (972 mg, 7.19 mmol) and dry DIPEA (3.65 mL, 21.0 mmol) were each added in single portion at RT, with a colour change to pale yellow solution noted. The resulting solution was stirred at RT overnight under a slight positive pressure of CO_2 (balloon) and the progress of the reaction was monitored via TLC. After total of 18 h, the reaction was deemed to have gone to completion by TLC analysis and colour change to pale orange solution was observed. The resulting mixture was diluted with CH_2Cl_2 (100 mL) and poured into separating funnel. The organic layer was washed sequentially with sat. $NaHCO_{3(aq)}$ (2 × 120 mL) and sat. brine (10 × 120 mL), before was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale yellow liquid (5.70 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: MeOH:EtOAc, 90:10 to 100:0) to afford title compound **291** as a colourless oil (720 mg, 70%); R_f = 0.15 (MeOH); IR (neat) ν_{max} /cm^{-1}: 3486w, 2936m (C–H alkyl), 2878m (C–H alkyl), 2850m (C–H alkyl), 2800m (C–H alkyl), 2219w, 1632s (C=O urea), 1494s, 1453s, 1428m, 1412m, 1399s, 1384s, 1329m, 1351w, 1304w, 1267w, 1221s, 1166m, 1145w, 1127m, 1107w, 1084w, 1038m, 1004w, 978w, 926w, 890w, 858w, 789w, 761w, 705w, 643w, 618w, 594m, 580w, 537w, 503w; δ_H (400 MHz; $CDCl_3$) 3.29 – 3.21 (4H, m, C(3)H_2), 2.70 (6H, s, C(2)H_3), 2.66 – 2.55 (4H, m, C(4)H_2), 2.33 (3H, s, C(5)H_3); δ_C (101 MHz; $CDCl_3$) 164.0 (CO, C1), 54.9 (2 × CH_2, C4), 54.1 (2 × CH_2, C3), 47.0 (2 × CH_3, C2), 37.1 (CH_3, C5); HRMS (ESI): calcd. for $C_8H_{18}N_3O$, 172.1444.

Found: $[MH]^+$, 172.1446 (−0.9 ppm error), calcd. for $C_8H_{17}N_3NaO$, 194.1264. Found: $[MNa]^+$, 194.1264 (0.1 ppm error).

Lab notebook reference: ixz_466

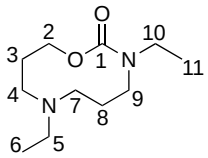
Synthesis of 1,3,7-trimethyl-1,3,7-triazecan-2-one – 292



N^1,*N*^{3}-dimethyl-*N*^{1}-(3-(methylamino)propyl)propane-1,3-diamine **250** (500 µL, 2.50 mmol) was added reaction flask (250 mL RBF) containing anhydrous DMF (50 mL). The resulting reaction vessel was evacuated under *vacuo* and backfilled with CO_2 (via balloon) 6 times. Next, EDC.HCl (719 mg, 3.75 mmol), HOBt (405 mg, 3.01 mmol) and dry DIPEA (1.52 mL, 3.14 mmol) were each added in single portion at RT, with a colour change to pale yellow solution noted. The resulting solution was stirred at RT overnight under a slight positive pressure of CO_2 (balloon) and the progress of the reaction was monitored via TLC. After total of 18 h, the reaction was deemed to have gone to completion by TLC analysis and colour change to pale orange solution was observed. The resulting mixture was diluted with CH_2Cl_2 (60 mL) and poured into separating funnel. The organic layer was washed sequentially with sat. $NaHCO_{3(aq)}$ (2×80 mL) and sat. brine (6×80 mL), before was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an orange oil (510 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: MeOH:EtOAc, 90:10) to afford title compound **292** as a colourless oil (434 mg, 87%); R_f = 0.04 (MeOH);IR (neat) ν_{max} / cm^{-1}: 3479m, 2918m (C–H alkyl), 2846m (C–H alkyl), 2784m (C–H alkyl),1626s (C=O urea), 1492s, 1466m, 1451m, 1411w, 1388s, 1354s, 1313w, 1290w, 1273m, 1249w, 1231m, 1201m, 1156s, 1121w, 1096m, 1064m, 1045w, 1004w, 982m, 953w, 908w, 869m, 855w, 829w, 812w, 775w, 746m, 708w, 590w, 534w, 493w, 452w; δ_H (400 MHz; $CDCl_3$) 3.34 – 3.27 (4H, m, C(3)H_2), 2.76 (6H, s, C(1)H_3), 2.35–2.28 (4H, m, C(5)H_2), 2.11 (3H, s, C(6)H_3), 1.62 – 1.52 (4H, m, C(4)H_3); δ_C (101 MHz; $CDCl_3$) 164.8 (CO, C1), 55.2 (CH_2, C5), 48.2 (CH_2, C3), 42.4 (CH_3, C6), 37.0 (CH_3, C2), 24.8 (CH_2, C4); HRMS (ESI): calcd. for $C_{10}H_{22}N_3O$, 200.1757. Found: $[MH]^+$, 200.1755 (1.1 ppm error), calcd. for $C_{10}H_{21}N_3NaO$, 222.1577. Found: $[MNa]^+$, 222.1576 (0.6 ppm error).

Lab notebook reference: ixz_459

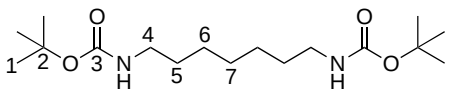
Synthesis of 3,7-diethyl-1,3,7-oxadiazecan-2-one – 296



3-(ethyl(3-(ethylamino)propyl)amino)propan-1-ol **295** (237 mg, 1.26 mmol) was added reaction flask (250 mL RBF) containing anhydrous DMF (23 mL). The resulting reaction vessel was evacuated under *vacuo* and backfilled with CO_2 (via balloon) 6 times. Next, EDC.HCl (209 mg, 1.34 mmol), HOBt (182 mg, 1.34 mmol) and dry DIPEA (546 µL, 3.14 mmol) were each added in single portion at RT, with a colour change to pale yellow solution noted. The resulting solution was stirred at RT overnight under a slight positive pressure of CO_2 (balloon) and the progress of the reaction was monitored via TLC. After total of 18 h, the reaction was deemed to have gone to completion by TLC analysis and colour change to orange solution was observed. The resulting mixture was diluted with CH_2Cl_2 (30 mL) and poured into separating funnel. The organic layer was washed with sat. brine (6 × 30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a yellow oil (154 mg). The crude product was purified by flash column chromatography (SiO_2, 20 mm column, eluent: MeOH:EtOAc,80:20) to afford title compound **296** as a colourless oil (91.7 mg, 48%); R_f = 0.20 (90:10, MeOH:EtOAc); IR (neat) ν_{max} /cm^{-1}: 2967m (C–H alkyl), 2793w (C–H alkyl), 1693s (C=O carbamate),1476m, 1455m, 1420s, 1364m, 1292m, 1244s, 1219m, 1184w, 1161m, 1141w, 1076m, 1035m, 987w, 973w, 952w, 909w, 852w, 780w, 749s, 613w, 531w; δ_H (400 MHz; $CDCl_3$) 4.32 – 4.25 (2H, m, C(2)H_2), 3.45 – 3.38 (2H, m, C(9)H_2), 3.27 (2H, q, *J* = 7.1 Hz, C(10)H_2), 2.47 – 2.38 (4H, m, C(4+7)H_2), 2.34 (2H, q, *J* = 7.2 Hz, C(5)H_2), 1.80 – 1.71 (2H, m, C(3)H_2), 1.52 – 1.43 (2H, m, C(8)H_2), 1.11 (3H, t, *J* = 7.1 Hz, C(11)H_3), 0.98 (3H, t, *J* = 7.1 Hz, C(6)H_3); δ_C (101 MHz; $CDCl_3$) 157.8 (CO, C1), 65.7 (CH_2, C2), 53.1 (CH_2, C7), 50.2 (CH_2, C4), 48.4 (CH_2, C10), 46.0 (CH_2, C9), 41.5 (CH_2, C5), 26.8 (CH_2, C3), 25.6 (CH_2, C8), 13.8 (CH_3, C11), 12.1 (CH_3, C6); HRMS (ESI): calcd. for $C_{11}H_{23}N_2O_2$, 215.1754. Found: $[MH]^+$, 215.1753 (0.6 ppm error).

Lab notebook reference: ixz_442

Synthesis of di-*tert*-butyl heptane-1,7-diyldicarbamate – 298



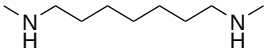
Boc_2O (7.85 g, 36.0 mmol) was added in a single portion to a solution of 1,7-diaminoheptane **297** (2.23 g, 17.1 mmol), Et_3N (9.54 mL, 68.4 mmol) in anhydrous THF (57 mL) under Ar at RT. The resulting solution was stirred at RT overnight under Ar at RT and the progress of the

reaction was monitored by TLC. After a total of 18 h, the reaction was deemed to have gone to completion by TLC analysis. The resulting mixture was quenched with sat. $NH_4Cl_{(aq)}$ (60 mL) and poured into the separating funnel. The aqueous layer was extracted Et_2O (3 × 80 mL), before combined phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a colourless oil (3.71 g). The crude product was purified by flash column chromatography (SiO_2, 70 mm column, eluent: EtOAc:*n*–hexane, 30:70) to afford title compound **298** as a white solid (2.50 g, 44%); R_f = 0.45 (30:70, EtOAc:*n*–hexane); δ_H (400 MHz; $CDCl_3$) 4.96 (2H, t, *J* = 6.1 Hz, NH), 2.90 – 2.78 (4H, m, C(4)H_2), 1.28 – 1.21 (6H, m, CH_2), 1.20 (16H, s, C(1)H_3),1.11 – 1.02 (6H, m, CH_2); δ_C (101 MHz; $CDCl_3$) 155.8 (2 × CO, C3), 78.2 (2 × C, C2), 40.1 (2 × CH_2, C4), 29.6 (2 × CH_2), 28.6 (2 × CH_2), 28.1 (2 × CH_3, C1), 26.4 (2 × CH_2); HRMS (ESI): calcd. for $C_{17}H_{34}N_2NaO_4$, 353.2411. Found: $[MNa]^+$, 353.2414 (−1.0 ppm error), calcd. for $C_{17}H_{34}KN_2O_4$, 369.2150. Found: $[MK]^+$, 369.2152 (−0.6 ppm error).

Lab notebook reference: ixz_462

Spectroscopic data is consistent with those previously reported in the literature.[293]

Synthesis of *N*^{1},*N*^{7}-dimethylheptane-1,7-diamine – 299

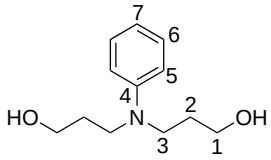


$LiAlH_4$ (2.4 M in THF, 55.0 mL, 129 mmol, 8.5 eq) was added dropwise manner via syringe pump over a period of 10 min to a solution of heptane-1,7-diyldicarbamate **298** (4.27 g, 12.9 mmol) in anhydrous THF (43 mL) under Ar at 0 °C. The clear colourless solution was stirred at 0 °C for 1 h and then gradually warmed to RT, before being allowed to be stirred overnight at 70 °C under Ar atmosphere. After a total of 18 h, the reaction was deemed to have gone to completion by TLC analysis. The resulting mixture was gradually cool to RT and then further to 0 °C under Ar. The resulting milky white suspension was quenched by the sequential addition of Et_2O (10 mL), H_2O (15 mL), 15% $NaOH_{(aq)}$ (5 mL) and H_2O (10 mL) [Note- a solid slurry formed and agitation with a spatula was needed to help mix during the quench]. The resulting slurry was then dried over $MgSO_4$ (3.60 g) and stirred at RT for 1 h. The resulting white slurry/solid was filtered through Celite®, washed with MeOH (2 × 10 ml) and the solvent was removed in *vacuo* to afford title compound **299** as a white solid (2.50 g, 44%); IR (solid state)ν_{max}/cm^{-1}:3255m (N–H, secondary amine), 1642w, 1473w, 1084w, 599w; δ_H (400 MHz; D_2O) 2.58 (4H, s, br, CH_2), 2.29 (6H, s, br, CH_2), 1.25 (4H, s, br, CH_2), 0.94 (6H, s, br, CH_2); δ_C (101 MHz; D_2O) 49.1 (CH_2), 48.9 (CH_2), 32.7 (CH_2), 27.7 (CH_2), 25.4 (CH_2); HRMS (ESI): calcd. for $C_9H_{23}N_2$, 159.1856. Found: $[MH]^+$, 159.1856 (−0.3 ppm error).

Lab notebook reference: ixz_463

Spectroscopic data is consistent with those previously reported in the literature.[294]

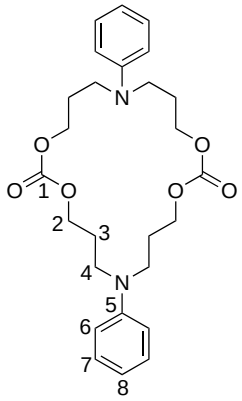
Synthesis of 3,3'-(phenylazanediyl)bis(propan-1-ol) – 306



$CaCO_3$ (6.48 g, 64.4 mmol) was added in a single portion to a brown solution of 3-chloropropan-1-ol **305** (18.3 g, 193 mmol) and aniline **304** (3.00 g, 32.2 mmol) in H_2O (108 mL) at RT. The resulting creamy pale-yellow suspension was then heated to 120 °C, after 26 h, the reaction was deemed to have gone to completion by TLC. The reaction mixture allowed to cool to RT and base was added until solution was at pH 10.0, by adding 1.0 M $NaOH_{(aq)}$ (30 mL). The basic aqueous solution poured into a separating funnel and resulting aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were collected, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a brown oil (6.10 g). The crude product was purified by flash column chromatography (SiO_2, 70 mm column, eluent: EtOAc:*n*–hexane, 80:20 to 100:0) to afford an bis alcohol **306** as colourless viscous oil (6.07 g, 90%); R_f = 0.16 (80:20, EtOAc:*n*–hexane); IR (neat)ν_{max}/cm^{-1}: 3318w (O–H alcohol), 3061w, 3006w, 2938w (C–H alkyl), 2877w (C–H alkyl), 1921w, 1597s (CC aromatic), 1571w (CC aromatic), 1504s (CC aromatic), 1476w, 1463, 1451w, 1395w, 1367m, 1285w, 1216w, 1193w, 1050s, 1038s, 990w, 980w, 909m, 863w, 744s, 693s, 666w, 511w, 461w; δ_H (500 MHz; $CDCl_3$) 7.28 – 7.20 (2H, m, C(6)H), 6.79 – 6.76 (2H, m, C(5)H), 6.75 – 6.71 (1H, m, C(7)H), 3.69 (4H, t, *J* = 6.0 Hz, C(1)H_2), 3.63 – 3.51 (2H, br, m, OH), 3.42 (4H, t, *J* = 7.1 Hz, C(3)H_2), 1.87 – 1.78 (4H, m, C(2)H_2); δ_C (126 MHz; $CDCl_3$) 148.2 (C, C4), 129.3 (2 × CH, C6), 116.7 (CH, C7), 113.3 (2 × CH, C5), 60.4 (CH_2, C1), 48.4 (CH_2, C3), 29.9 (CH_2, C2); HRMS (ESI): calcd. for $C_{12}H_{20}NO_2$, 210.1489. Found: $[MH]^+$, 210.1486 (1.3 ppm error).

Lab notebook reference: ixz_352

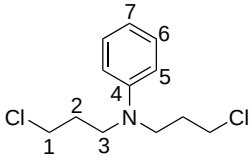
Synthesis of 7,17-diphenyl-1,3,11,13-tetraoxa-7,17-diazacycloicosane-2,12-dione – 312



Triphosgene (128 mg, 0.432 mmol) was added in a single portion to a pale yellow solution of 3,3'-(phenylazanediyl)bis(propan-1-ol) **306** (226 mg, 1.08 mmol), DMAP (858 mg, 7.02 mmol) in anhydrous CH_2Cl_2 (22.0 mL) at 0 °C under Ar. The resulting solution was allowed to warm gradually to RT overnight under Ar and the progress of the reaction was monitored by TLC. After total of 18 h, the reaction was deemed to have gone to completion by TLC analysis. The resulting mixture was quenched with sat. $NaHCO_{3(aq)}$ (30 mL), before transferred into separating funnel. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and combined organic layers were collected before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a white solid (1.71g). The crude product was purified by flash column chromatography (SiO_2, 20 mm column, eluent:EtOAc:*n*–hexane, 20:80) to afford title compound **312** as a white solid (228 mg, 45%); R_f = 0.16 (20:80, EtOAc:*n*–hexane); δ_H (400 MHz; $CDCl_3$) 7.29 – 7.20 (4H, m, C(7)H), 6.73 – 6.65 (6H, m, C(6+8)H), 4.25 – 4.18 (8H, m, C(2)H_2), 3.57 (8H, t, *J* = 6.7 Hz, C(4)H_2), 2.03 – 1.92 (8H, m, C(3)H_2); δ_C (101 MHz; $CDCl_3$) 155.3 (2 × CO, C1), 146.6 (2 × C, C5), 129.6 (4 × CH, C7), 116.0 (CH, C8), 111.8 (4 × CH, C6), 65.0 (4 × CH_2, C2), 47.6 (4 × CH_2, C4), 26.2 (4 × CH_2, C3); HRMS (ESI): calcd. for $C_{26}H_{35}N_2O_6$, 471.2490. Found: $[MH]^+$, 471.2497 (−1.6 ppm error), calcd. for $C_{26}H_{34}N_2NaO_6$, 493.2309. Found: $[MNa]^+$, 493.2312 (−0.5 ppm error), calcd. for $C_{26}H_{34}KN_2O_6$, 509.2048. Found: $[MK]^+$, 509.2056 (−1.4 ppm error).

Lab notebook reference: ixz_424

Synthesis of *N*,*N*-bis(3-chloropropyl)aniline – 313

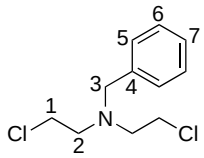


A solution of triphosgene (397 mg, 1.34 mmol) in anhydrous CH_2Cl_2 (3.0 mL) was added dropwise over period of 1 min via syringe to a pale yellow solution of 3,3'-

(phenylazanediyl)bis(propan-1-ol) **306** (226 mg, 1.08 mmol), DMAP (32.7 mg, 0.268 mmol) and dry Et_3N (2.24 mL, 16.1 mmol) in anhydrous CH_2Cl_2 (53.0 mL) at −78 °C under Ar. The resulting solution was allowed to warm gradually to RT overnight under Ar and the progress of the reaction was monitored by TLC. After a total of 18 h, the reaction was deemed to have gone to completion by TLC analysis. The resulting mixture was quenched with sat. $NaHCO_{3(aq)}$ (30 mL), before transferred into separating funnel. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and combined organic layers were collected before dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a yellow oil (685 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane, 20:80) to afford title compound **313** as a colourless oil (378 mg, 57%); R_f = 0.65 (30:70, EtOAc:*n*–hexane); δ_H (400 MHz; $CDCl_3$) 7.32 – 7.23 (2H, m, C(6)H), 6.77 (3H, dd, *J* = 7.9, 6.0 Hz, C(5+7)H), 3.64 (4H, t, *J* = 6.2 Hz, C(1)H_2), 3.54 (4H, t, *J* = 7.0 Hz, C(3)H_2), 2.15 – 2.04 (4H, m, C(2)H_2); δ_C (101 MHz; $CDCl_3$) 147.5 (C, C4), 129.5 (2 × CH, C6), 116.7 (CH, C7), 112.8 (2 × CH, C5), 48.4 (2 × CH_2, C3), 42.9 (2 × CH_2, C1), 30.0 (2 × CH_2, C2); HRMS (ESI): calcd. for $C_{12}H_{18}{}^{35}Cl_2N$, 246.0811. Found: $[MH]^+$, 246.0812 (−0.7 ppm error).

Lab notebook reference: ixz_425

Synthesis of *N*-benzyl-2-chloro-*N*-(2-chloroethyl)ethan-1-amine – 316



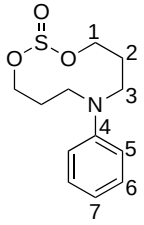
Thiophesgene (144 µL, 1.88 mmol) was added in a single portion to a solution of 2,2'-(benzylazanediyl)bis(ethan-1-ol) **314** (334 mg, 1.71 mmol), DMAP (543 mg, 4.45 mmol) in anhydrous CH_2Cl_2 (34.0 mL) at 0 °C under Ar. A colour change to yellow suspension was noted. The resulting solution was allowed to warm gradually to RT overnight under Ar and the progress of the reaction was monitored by TLC. After a total of 18 h, the reaction was deemed to have gone to completion by TLC analysis with a colour change to yellow solution observed. The resulting mixture was quenched with sat. $NaHCO_{3(aq)}$ (40 mL), before transferred into separating funnel. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL) and combined organic layers were washed with sat. brine (1 × 40 mL), before dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale-yellow orange (699 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane,10:90) to afford title compound **316** as a colourless oil (250 mg, 63%); R_f = 0.40 (20:80,EtOAc:*n*–hexane); δ_H (400 MHz; $CDCl_3$) 7.36 – 7.21 (5H, m, C(5+6+7)H), 3.73 (2H, s, C(3)H_2), 3.49 (4H, t, *J* = 7.1 Hz, C(1)H_2), 2.91 (4H, t, *J* = 7.0 Hz, C(2)H_2); δ_C (101 MHz;

$CDCl_3$) 138.9 (C, C4), 128.7 (CH, C5), 128.6 (CH, C6), 127.5 (CH, C7), 59.3 (CH_2, C3), 56.5 (CH_2, C2), 42.1 (CH_2, C1); HRMS (ESI): calcd. for $C_{11}H_{16}Cl_2N$, 232.0654. Found: $[MH]^+$, 232.0652 (−0.9 ppm error).

Lab notebook reference: ixz_419

Spectroscopic data is consistent with those previously reported in the literature.[295]

Synthesis of 7-phenyl-1,3,2,7-dioxathiazecane 2-oxide – 319

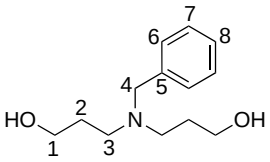


Thionyl chloride (104 µL, 1.43 mmol) was added in a single portion via syringe to colourless solution of 3,3'-(phenylazanediyl)bis(propan-1-ol) **306** (250 mg, 1.19 mmol), DMAP (509 mg, 4.17 mmol) in anhydrous CH_2Cl_2 (24.0 mL) at 0 °C under Ar. An immediate colour changed to mustard yellow suspension was noted along with the liberation of grey fumes. The resulting mixture was allowed to warm gradually to RT overnight under Ar and the progress of the reaction was monitored by TLC, with colour changed to pale orange solution. After total of 18 h, the reaction was deemed to have gone to completion by TLC analysis. The resulting mixture was quenched with sat. $NaHCO_{3(aq)}$ (30 mL) and poured into separating funnel. The aqueous solution was extracted with CH_2Cl_2 (3 × 30 mL), before combined organic layers were collected dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a yellow solid (879 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane, 20:80) to afford title compound **319** as a colourless oil (121 mg, 40%); R_f = 0.23 (20:80, EtOAc:*n*–hexane); IR (neat) ν_{max} /cm^{-1}: 3060w, 2953w, 2849w, 1599s (CC aromatic),1575w (CC aromatic), 1502s (CC aromatic), 1473w, 1459w, 1431w, 1385w, 1362w, 1326w, 1269w, 1196s (S=O), 1172s (S=O), 1124w, 1092w, 1067w, 1029w, 9892, 955w, 904s, 854w, 823w, 791w, 747m, 735m, 715w, 693, 588w, 621w, 544w, 470w; δ_H (400 MHz; $CDCl_3$) 7.29 – 7.21 (2H, m, C(6)H), 6.82 – 6.75 (3H, m, C(5+7)H), 4.48 (2H, ddd, *J* = 11.0, 7.4, 3.3 Hz, C(1)H_2), 3.94 (2H, ddd, *J* = 11.0, 7.4, 3.3 Hz, C(1)H_2), 3.54 – 3.35 (4H, m, C(3)H_2), 2.19 – 1.96 (4H, m, C(2)H_2); δ_C (101 MHz; $CDCl_3$) 149.7 (C, C4), 129.2 (2 × CH, C6), 118.3 (CH, C7), 115.0 (2 × CH, C5), 61.1 (2 × CH_2, C1), 52.1 (2 × CH_2, C3), 28.5 (2 × CH_2, C2); HRMS (ESI): calcd. for $C_{12}H_{18}NO_3S$, 256.1002. Found: $[MH]^+$, 256.1006 (−1.7 ppm

error), calcd. for $C_{12}H_{17}NNaO_3S$, 278.0821. Found: $[MNa]^+$, 278.0825 (−1.2 ppm error), calcd. for $C_{12}H_{17}KNO_3S$, 294.0561. Found: $[MK]^+$, 294.0561 (−0.2 ppm error).

Lab notebook reference: ixz_423

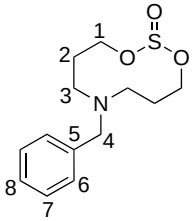
Synthesis of 3,3'-(benzylazanediyl)bis(propan-1-ol) – 321



Na_2CO_3 (4.85 g, 45.8 mmol) was added in a single portion to a solution of 3-chloropropan-1-ol **305** (3.37 mL, 40.3 mmol)**,** benzylamine **320** (2.00 mL, 18.3 mmol) and KI (3.04 g, 18.3 mmol) in anhydrous MeCN (61.0 mL) at RT under Ar. The resulting suspension was stirred at 110 °C for 20 h under Ar, after which the reaction was deemed to have gone to completion by TLC. The reaction mixture allowed to cool to RT, before was filtered through Celite and washed with EtOAc (30 mL). The resulting filtrate was concentrated under reduced pressure to yield a pale-yellow oil (4.71 g). The crude product was purified by flash column chromatography (SiO_2, 60 mm column, eluent: MeOH:CH_2Cl_2,15:85) to afford title compound **321** as a pale yellow oil (3.08 g, 75%); R_f = 0.42 (15:85, MeOH:CH_2Cl_2); IR (neat) ν_{max}/cm^{-1}: 3339w (O–H alcohol), 2943w (C–H alkyl), 2834w (C–H alkyl), 1666w (CC aromatic), 1495w, 1453m, 1371w, 1216w, 1128w, 1056s, 913w, 736m, 698s, 619w, 539w, 487w; δ_H (400 MHz; $CDCl_3$) 7.39 – 7.23 (5H, m, C(6+7+8)H), 3.69 (4H, t, J = 5.6 Hz, C(1)H_2), 3.60 (2H, s, C(4)H_2), 2.65 (4H, t, J = 6.4 Hz, C(3)H_2), 1.82 – 1.70 (4H, m, C(2)H_2); δ_C (101 MHz; $CDCl_3$) 137.9 (C, C5), 129.4 (2 × CH), 128.6 (2 × CH), 127.5 (CH, C8), 62.4 (2 × CH_2, C1), 58.9 (CH_2, C4), 52.4 (2 × CH_2, C3), 28.6 (2 × CH_2, C2); HRMS (ESI): calcd. for $C_{13}H_{22}NO_2$, 224.1645. Found: $[MH]^+$, 224.1640 (2.3 ppm error).

Lab notebook reference: ixz_427

Synthesis of 7-benzyl-1,3,2,7-dioxathiazecane 2-oxide – 322

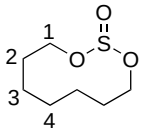


Thionyl chloride (166 µL, 2.29 mmol) was added in a single portion via syringe to a solution of 3,3'-(benzylazanediyl)bis(propan-1-ol) **321** (250 mg, 1.19 mmol), DMAP (509 mg, 4.17 mmol)

in anhydrous CH_2Cl_2 (24.0 mL) at 0 °C under Ar. An immediate colour changed to pale yellow solution was noted along with the liberation of grey fumes. The resulting mixture was allowed to warm gradually to RT overnight under Ar and the progress of the reaction was monitored *via* TLC, with a colour change to yolk yellow solution observed. After total of 18 h, the reaction was deemed to have gone to completion by TLC analysis. The resulting mixture was concentrated under reduced pressure to yield a pale-yellow oil (901 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane, 30:70) to afford title compound **322** as a colourless oil (481 mg, 86%); R_f = 0.28 (30:70, EtOAc:*n*–hexane); IR (neat)ν_{max}/cm^{-1}: 2931w, 2804w, 1702w, 1599w, 1495w, 1452m, 1372w, 1355w, 1293w, 1244w, 1197m, 1148w, 1071w, 1057w, 1044w, 1029w, 989w, 925m, 904s, 846m, 794w, 766m, 698s, 673w, 618w, 585w, 550w, 486w; δ_H (400 MHz; $CDCl_3$) 7.37 – 7.30 (2H, m, C(6)H), 7.29 – 7.20 (2H, m, C(7)H), 7.20 – 7.10 (1H, m, C(8)H), 4.44 (2H, ddd, *J* = 11.3, 7.5, 4.1 Hz, 2 × C(1)H**H'**), 3.93 (2H, ddd, *J* = 10.1, 5.7, 3.8 Hz, 2 × C(1)**H**H'), 3.45 (2H, s, C(4)H_2), 2.48 (4H, t, *J* = 5.9 Hz, C(3)H_2), 1.80 – 1.62 (4H, m, C(2)H_2); δ_C (101 MHz; $CDCl_3$) 139.6 (C, C5), 128.6 (CH, C6), 128.3 (CH, C7), 126.9 (CH, C8), 62.0 (CH_2, C1), 59.3 (CH_2, C4), 50.7 (CH_2, C3), 26.8 (CH_2, C2); HRMS (ESI): calcd. For $C_{13}H_{20}NO_3S$, 270.1158. Found: $[MH]^+$, 270.1160 (–0.4 ppm error), calcd. For $C_{13}H_{19}NnaO_3S$, 292.0978. Found: $[Mna]^+$, 292.0980 (–0.7 ppm error).

Lab notebook reference: ixz_436

Synthesis of 1,3,2-dioxathiecane 2-oxide – 324

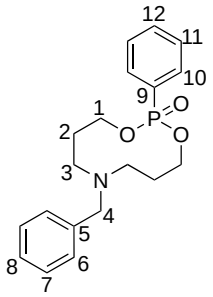


Thionyl chloride (230 µL, 3.17 mmol) was added in a single portion via syringe to a colourless solution of heptane-1,7-diol **323** (380 mg, 2.90 mmol), DMAP (1.23 g, 10.1 mmol) in anhydrous CH_2Cl_2 (58.0 mL) at 0 °C under Ar. The resulting mixture was allowed to warm gradually to RT overnight under Ar and the progress of the reaction was monitored via TLC, with a colour change to a pale-yellow solution observed. After a total of 18 h, the reaction was deemed to have gone to completion by TLC analysis and a colour change to creamy orange suspension was noted. The resulting mixture was concentrated under reduced pressure to yield a brown oil (731 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane, 10:90 to 50:50) to afford title compound **324** as a colourless oil (41.5 mg, 8%); R_f = 0.30 (10:90, EtOAc:*n*–hexane); IR (neat) ν_{max}/cm^{-1}: 2929m (C–H alkyl), 1475w, 1456w, 1381w, 1279w, 1201s (S=O sulfite), 1063w, 1003m, 950s, 922m, 887s, 871m,

859s, 840w, 816m, 781w, 696s, 665m, 579w, 518w, 471w; δ_H (400 MHz; $CDCl_3$) 4.42 (2H, ddd, *J* = 11.0, 8.6, 3.5 Hz, 2 × C(1)H**H'**), 4.01 (2H, ddd, *J* = 11.0, 6.2, 3.7 Hz, 2 × C(1)**H**H'), 1.89 – 1.67 (4H, m, C(2)H_2), 1.67 – 1.46 (6H, m, C(3+4)H_2); δ_C (101 MHz; $CDCl_3$) 63.0 (CH_2, C1), 27.0 (CH_2, C2), 24.0 (CH_2, C4), 23.3 (CH_2, C3); HRMS (ESI): calcd. For $C_7H_{14}NaO_3S$, 201.0556. Found: $[Mna]^+$, 201.0559 (−1.6 ppm error).

Lab notebook reference: ixz_435

Synthesis of 7-benzyl-2-phenyl-1,7,2,3-oxazadiphosphecane 2-oxide – 326

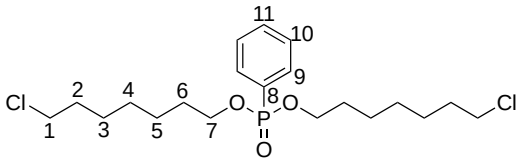


Phenylphosphonic dichloride (133 µL, 0.957 mmol) was added in a single portion via syringe to a solution of 3,3'-(benzylazanediyl)bis(propan-1-ol) **321** 178 mg, 0.797 mmol), DMAP (292 mg, 2.39 mmol) in anhydrous CH_2Cl_2 (16.0 mL) at 0 °C under Ar. The resulting mixture was allowed to warm gradually to RT overnight under Ar and the progress of the reaction was monitored via TLC. After total of 18 h, the reaction was deemed to have gone to completion by TLC analysis. The resulting mixture was concentrated under reduced pressure to yield a pale-yellow solid (304 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 70:30) to afford title compound **326** as a colourless oil (186 mg, 67%); R_f = 0.20 (30:70, EtOAc:*n*–hexane); IR (neat) ν_{max} / cm^{-1}: 3060w, 2954w (C–H alkyl), 2803w, 2731w, 1597w (CC aromatic), 1495w (CC aromatic), 1463w, 1452w, 1439w, 1374w, 1296w, 1239s, 1131m, 1088m, 1070m, 1055m, 1018m, 981s, 915w, 894w, 874w, 815m, 743s, 725s, 707s, 695s, 664w, 620w, 558s, 533w, 514m, 472w; δ_H (400 MHz; $CDCl_3$) 7.87 – 7.77 (2H, m, C(11)H), 7.56 – 7.50 (3H, m, C(6+12)H), 7.48 – 7.41 (2H, m, C(10)H), 7.40 – 7.32 (2H, m, C(7)H), 7.28 – 7.22 (1H, m, C(8)H), 4.71– 4.59 (2H, m, 2 × C(1)H**H'**), 4.14 – 4.01 (2H, m, 2 × C(1)**H**H'), 3.51 (2H, s, C(4)H_2), 2.71–2.61 (2H, m, 2 × C(3)H**H'**), 2.61 – 2.51 (2H, m, 2 × C(3)**H**H'), 1.97 – 1.81 (4H, m, C(4)H_2); δ_C (101 MHz; $CDCl_3$) 139.6 (C, C5), 132.00 (d, *J* = 3.6 Hz, CH, C12), 131.01 (d, *J* = 9.6 Hz, CH, C11), 128.9 (CH, C6), 128.6 (CH, C7), 128.1 (d, *J* = 206.3 Hz, C, C9), 127.0 (CH, C8), 64.75 (d, *J* = 6.9 Hz, CH_2, C1), 58.6 (CH_2, C4), 50.2 (CH_2, C3), 27.74 (d, *J* = 3.7 Hz, CH_2, C2); δ_P (162 MHz; $CDCl_3$) 18.2 (s, $PhPO(O)_2$); HRMS (ESI): calcd. For $C_{19}H_{25}NO_3P$, 346.1567. Found: $[MH]^+$,

346.1563 (1.1 ppm error), calcd. For $C_{19}H_{24}NnaO_3P$, 368.1386. Found: $[Mna]^+$, 368.1385 (0.4 ppm error).

Lab notebook reference: ixz_450

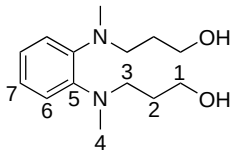
Synthesis of bis(7-chloroheptyl) phenylphosphonate – 328



Phenylphosphonic dichloride (670 µL, 4.82 mmol) was added in a single portion via syringe to a colourless solution of heptane-1,7-diol **323** (579 mg, 4.38 mmol), DMAP (1.34 g, 11.0 mmol) in anhydrous CH_2Cl_2 (88 mL) at 0 °C under Ar. The resulting mixture was allowed to warm gradually to RT overnight under Ar and the progress of the reaction was monitored *via* TLC. After a total of 18 h, the reaction was deemed to have gone to completion by TLC analysis, with a colour change to a pale yellow solution noted. The resulting mixture was concentrated under reduced pressure to yield a pale yellow oil (847 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford title compound **328** as a colourless oil (379 mg, 21%); R_f = 0.30 (50:50, EtOAc:*n*–hexane); IR (neat) ν_{max}/cm^{-1}: 3468w, 2933w (C–H alkyl), 2858w (C–H alkyl), 1735w, 1594w (CC aromatic), 1464m, 1439m, 1390w, 1249m, 1131s, 989s, 819w, 750m, 727m, 696s, 649m, 564m, 534m; δ_H (400 MHz; $CDCl_3$) 7.84 – 7.74 (2H, m, C(10)H), 7.60 – 7.51 (1H, m, C(11)H), 7.51 – 7.42 (2H, m, C(9)H), 4.12 – 3.93 (4H, m, C(7)H_2), 3.51 (4H, t, *J* = 6.7 Hz, C(1)H_2), 1.78 – 1.59 (8H, m, C(2+6)H_2), 1.46 – 1.23 (12H, m, C(3+4+5)H_2); δ_C (101 MHz; $CDCl_3$) 132.6 (d, *J* = 3.4 Hz, CH, C11), 131.9 (d, *J* = 9.6 Hz, CH, C10), 128.6 (d, *J* = 15.2 Hz, CH, C9), 128.4 (d, *J* = 187.3 Hz, C, C8), 66.1 (d, *J* = 5.8 Hz, CH_2, C7), 45.2 (CH_2, C1), 32.6 (CH_2), 30.4 (d, *J* = 6.6 Hz, CH_2, C6), 28.5 (CH_2), 26.8 (CH_2), 25.5 (CH_2); HRMS (ESI): calcd. For $C_{20}H_{34}Cl_2O_3P$, 423.1617. Found: $[MH]^+$, 423.1623 (–1.4 ppm error), calcd. For $C_{20}H_{33}Cl_2NaO_3P$, 445.1437. Found: $[Mna]^+$, 445.1440 (–0.7 ppm error).

Lab notebook reference: ixz_456

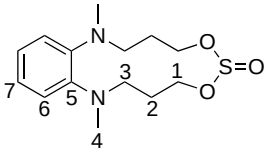
Synthesis of 3,3'-(1,2-phenylenebis(methylazanediyl))bis(propan-1-ol) – 329



K_2CO_3 (3.55 g, 25.7 mmol) was added to a black brown suspension of *N*[1],*N*[2]-diphenylethane-1,2-diamine **278** (1.01 g, 7.34 mmol), 4-bromobutan-1-ol **188** (1.99 mL, 22.1 mmol) and KI (3.05 g, 18.3 mmol) in anhydrous MeCN (25 mL) at RT under Ar. The resulting mixture was then heated to 95 °C under Ar. After 18 h, the reaction was deemed to have gone to completion by TLC. The reaction mixture was allowed to cool to RT, before being filtered through Celite® and washed with EtOAc (3 × 30 mL). The resulting filtrate was concentrated under reduced pressure to yield a dark brown oil (3.71 g). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 90:10 to 100:0) to afford title compound **329** as a pale yellow viscous oil (973 mg, 53%); R_f = 0.08 (EtOAc); IR (neat) ν_{max} / cm^{-1}: 3326w, (O–H alcohol), 2942w (C–H alkyl), 2846w (C–H alkyl), 1590w (CC aromatic), 1493s, 1453w, 1382w, 1274w, 1211w, 1173w, 1122w, 1054s, 954w, 928w, 747s, 708w, 665w, 556w, 487w; δ_H (400 MHz; $CDCl_3$) 7.12 – 7.07 (2H, m, C(7)H), 7.06 – 7.02 (2H, m, C(6)H), 4.68 (2H, s, br, OH), 3.66 (4H, t, *J* = 5.9 Hz, C(1)H_2), 3.00 (4H, t, *J* = 6.8 Hz, C(3)H_2), 2.65 (6H, s, C(4)H_3), 1.72 – 1.63 (4H, m, C(2)H_2); δ_C (101 MHz; $CDCl_3$) 147.9 (2 × C, C5), 124.4 (2 × CH, C6), 121.4 (2 × CH, C7), 60.0 (2 × CH_2, C1), 53.4 (2 × CH_2, C3), 41.5 (2 × CH_3, C4), 29.3 (2 × CH_2, C2); HRMS (ESI): calcd. For $C_{14}H_{25}N_2O_2$, 253.1911. Found: $[MH]^+$, 253.1908 (0.9 ppm error).

Lab notebook reference: ixz_476

Synthesis of 1,11-dimethyl-1,2,3,4,8,9,10,11-octahydrobenzo[*h*][1,3]dioxa[2]thia[7,10]diazacyclotridecine 6-oxide – 330

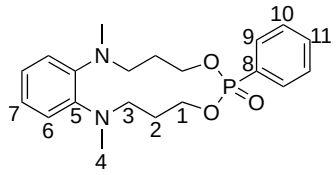


Thionyl chloride (133 µL, 1.83 mmol) was added in a single portion via syringe to a pale yellow solution of 3,3'-(1,2-phenylenebis(methylazanediyl))bis(propan-1-ol) **329** (355 mg, 1.41 mmol), DMAP (601 mg, 4.92 mmol) in anhydrous CH_2Cl_2 (28.0 mL) at 0 °C under Ar. The resulting mixture was allowed to warm gradually to RT overnight under Ar and the progress of the reaction was monitored via TLC, with a colour change to a pale brown solution observed. After a total of 18 h, the reaction was deemed to have gone to completion by TLC analysis

and a colour change to yellow was noted. The resulting mixture was concentrated under reduced pressure to yield a brown oil (412 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford title compound **330** as a colourless oil (219 mg, 52%); R_f = 0.73 (EtOAc); IR (neat)ν_{max} / cm^{-1}: 2945m (C–H alkyl), 2800w (C–H alkyl), 1591w (CC aromatic), 1494s, 1453m, 1375w, 1301w, 1267w, 1200s (S=O sulfite), 1121w, 1060m, 1016w, 922s, 900s, 835w, 813s, 734s, 701s, 605w, 583w, 509w; δ_H (400 MHz; $CDCl_3$) 6.97 (4H, s, C(6+7)H), 4.22 – 4.09 (2H, m, 2 × C(1)H**H'**), 4.07 – 3.93 (2H, m, 2 × C(1)**H**H'), 3.41 – 3.28 (2H, m, 2 × C(3)H**H'**), 3.25 – 3.14 (2H, m, 2 × C(3)**H**H'), 2.74 (6H, s, C(4)H_3), 1.98 – 1.77 (4H, m, C(2)H_2); δ_C (101 MHz; $CDCl_3$) 145.6 (2 × C, C5), 122.8 (2 × CH, C6), 120.2 (2 × CH, C7), 60.5 (2 × CH_2, C1), 50.0 (2 × CH_2, C3), 40.5 (2 × CH_3, C4), 26.1 (2 × CH_2, C2); HRMS (ESI): calcd. For $C_{14}H_{23}N_2O_3S$, 299.1424. Found: $[MH]^+$, 299.1418 (2.1 ppm error).

Lab notebook reference: ixz_478

Synthesis of 1,11-dimethyl-6-phenyl-1,2,3,4,8,9,10,11-octahydrobenzo[*h*][1,3]dioxa[7,10]diaza[2]phosphacyclotridecine 6-oxide – 331

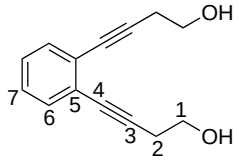


Phenylphosphonic dichloride (269 µL, 0.957 mmol) was added in a single portion via syringe to a solution of 3,3'-(1,2-phenylenebis(methylazanediyl))bis(propan-1-ol) **329** (374 mg, 1.48 mmol), DMAP (633 mg, 5.18 mmol) in anhydrous CH_2Cl_2 (30.0 mL) at 0 °C under Ar. The resulting mixture was allowed to warm gradually to RT overnight under Ar, and the progress of the reaction was monitored via TLC. After a total of 18 h, the reaction was deemed to have gone to completion by TLC analysis. The resulting mixture was concentrated under reduced pressure to yield a pale yellow solid (985 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 90:10 to 100:0) to afford title compound **331** as a colourless viscous oil (333 mg, 60%); R_f = 0.42 (EtOAc); IR (neat) ν_{max} / cm^{-1}: 2955w (C–H alkyl), 1738w, 1591w (CC aromatic), 1494m, 1450w, 1439w,1239s, 1185m, 1131s, 1086w, 1043s, 985s, 886w, 856w, 817w, 791w, 744s, 711m, 694s, 664m, 560s; δ_H (400 MHz; $CDCl_3$) 7.77 – 7.68 (2H, m, C(10)H), 7.54 – 7.44 (1H, m, C(11)H), 7.44 – 7.36 (2H, m, C(9)H), 6.95 (4H, s, C(6+7)H), 4.31 – 4.19 (2H, m, 2 × C(1)H**H'**), 4.09 – 3.97 (2H, m, 2 × C(1)**H**H'), 3.57 – 3.46 (2H, m, 2 × C(3)H**H'**), 3.33 – 3.20 (2H, m, 2 × C(3)**H**H'), 2.76 (6H, s, C(4)H_3), 2.03 – 1.91 (2H, m, 2 × C(2)H**H'**), 1.88 – 1.76 (2H, m, 2 × C(2)**H**H'); δ_C (101 MHz;

$CDCl_3$) 145.2 (2 × C, C5), 132.2 (d, *J* = 3.1 Hz, CH, C11), 131.2 (d, *J* = 9.7 Hz, CH, C10), 128.4 (d, *J* = 192.2 Hz, C, C8), 128.34 (d, *J* = 15.2 Hz, CH, C9), 122.3 (2 × CH, C6), 119.6 (2 × CH, C7), 64.1 (d, *J* = 6.5 Hz, 2 × CH_2, C1), 49.1 (2 × CH_2, C3), 39.9 (2 × CH_3, C4), 27.41 (d, *J* = 6.3 Hz, 2 × CH_2, C2); δ_P (162 MHz; $CDCl_3$) 18.3 (s, $PhPO(O)_2$); HRMS (ESI): calcd. For $C_{20}H_{28}N_2O_3P$, 375.1832. Found: $[MH]^+$, 375.1826 (1.6 ppm error).

Lab notebook reference: ixz_480

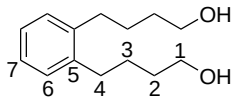
Synthesis of 4,4'-(1,2-phenylene)bis(but-3-yn-1-ol) – 333



But-3-yn-1-ol **285** (361 µL, 4.80 mmol) was added to solution of methyl 1,2-diiodobenzene **332** (250 µL, 1.91 mmol) in anhydrous Et_3N (19.0 mL, degassed for 15 min) at RT under Ar. After 10 min, CuI (10.9 mg, 0.057 mmol) and bis(triphenylphosphine)palladium chloride (67.0 mg, 0.096 mmol) were added to the pale yellow solution. The resulting reaction mixture was stirred at RT under Ar. After a total of 18 h, the reaction was deemed to have gone to completion by TLC. The dark brown reaction mixture was filtered through Celite® and washed with EtOAc (3 × 40 mL). The resulting filtrate was concentrated under *vacuo* to yield an orange oil (871 g). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane, 70:30 to 100:0) to afford title compound **333** as a pale yellow oil (403 mg, 98%); R_f = 0.22 (70:30, EtOAc:*n*–hexane); IR (neat) ν_{max}/cm^{-1}: 3341m (O–H alcohol), 3064w (C–H alkyl), 2898w (C–H alkyl), 2887w (C–H alkyl), 2238w (CC alkynyl), 1727w, 1480m, 1443w, 1265w, 1038s, 846w, 757s, 733s; δ_H (400 MHz; $CDCl_3$) 7.35 (2H, dd, *J* = 5.8, 3.4 Hz, 2 × C(6)H), 7.15 (2H, dd, *J* = 5.8, 3.4 Hz, 2 × C(7)H), 3.76 (4H, t, *J* = 6.2 Hz, C(1)H_2), 3.69 (2H, s, br, OH), 2.66 (4H, t, *J* = 6.1 Hz, C(2)H_2); δ_C (101 MHz; $CDCl_3$) 131.7 (2 × CH, C6), 127.6 (2 × CH, C7), 125.8 (2 × C, C5), 90.9 (2 × C, C3), 81.3 (2 × C, C4), 60.7 (2 × CH_2, C1), 23.8 (2 × CH_2, C2); HRMS (ESI): calcd. For $C_{14}H_{15}O_2$, 215.1067. Found: $[MH]^+$, 215.1064 (1.0 ppm error), calcd. For $C_{14}H_{14}NaO_2$, 237.0886. Found: $[Mna]^+$, 237.0883 (1.4 ppm error), calcd. For $C_{14}H_{14}KO_2$, 253.0625. Found: $[Mna]^+$, 253.0618 (3.1 ppm error).

Lab notebook reference: ixz_481

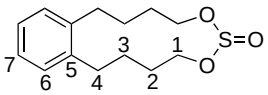
Synthesis of 4,4'-(1,2-phenylene)bis(butan-1-ol) – 334



Pd/C (22.2 mg, Pd 10% on carbon) was added to the round bottom, previously purged under Ar (for 10 min), containing 4,4'-(1,2-phenylene)bis(but-3-yn-1-ol) **333** (448 mg, 2.09 mmol) at RT. The alkyne **333** was dissolved by addition of anhydouse MeOH (21 mL, degassed for 10 min) and the reaction vessel was evacuated under vacuum and then backfilled with H_2 (via balloon) three times, then stirred at RT under slight positive atmosphere of H_2 (via balloon) for 72 h. The reaction was then purged with Ar for 10 min, filtered through Celite® and washed with MeOH (3 × 20 mL). The resulting filtrate was concentrated under reduced pressure to yield crude product as colourless oil (510 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane, 95:5 to 100:0) to afford title compound **334** as a colourless viscous oil (373 mg, 80%); R_f = 0.39 (EtOAc); IR (neat) ν_{max}/ cm^{-1}: 3338w (O–H alcohol), 2935w (C–H alkyl), 2864w (C–H alkyl),1726w, 1490w, 1451w, 1374w, 1243w, 1114w, 1045s, 980w, 934w, 749s, 666w, 608w, 464w;δ_H (400 MHz; $CDCl_3$) 7.19 – 7.09 (4H, m, C(6+7)H), 3.66 – 3.58 (4H, m, C(1)H_2), 3.37 (2H, s, OH), 2.69 – 2.60 (4H, m, C(4)H_2), 1.72 – 1.61 (8H, m, C(2+3)H_2); δ_C (101 MHz; $CDCl_3$) 140.1 (2 × C, C5), 129.2 (2 × CH, C6), 125.9 (2 × CH, C7), 62.2 (2 × CH_2, C1), 32.5 (2 × CH_2, C3), 32.3 (2 × CH_2, C4), 27.5 (2 × CH_2, C2); HRMS (ESI): calcd. For $C_{14}H_{23}O_2$, 223.1693. Found: $[MH]^+$, 223.1693 (0.0 ppm error), calcd. For $C_{14}H_{22}NaO_2$, 245.1512. Found: $[Mna]^+$, 245.1512 (–0.0 ppm error), calcd. For $C_{14}H_{22}KO_2$, 261.1251. Found: $[MK]^+$, 261.1239 (4.9 ppm error).

Lab notebook reference: ixz_482

Synthesis of 1,2,3,4,8,9,10,11-octahydrobenzo[*h*][1,3]dioxa[2]thiacyclotridecine 6-oxide – 335

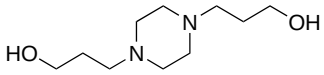


Thionyl chloride (109 µL, 1.50 mmol) was added in a single portion via syringe to a clear solution of 4,4'-(1,2-phenylene)bis(butan-1-ol) **334** (257 mg, 1.16 mmol), DMAP (496 mg, 4.06 mmol) in anhydrous CH_2Cl_2 (23 mL) at 0 °C under Ar. The resulting mixture was allowed to warm gradually to RT overnight under Ar and the progress of the reaction was monitored via TLC, with a colour change to a pale yellow solution observed. After a total of 18 h, the reaction was deemed to have gone to completion by TLC analysis and a colour change to a yellow suspension was noted. The resulting mixture was concentrated under reduced pressure to yield a yellow oil (876 mg). The crude product was purified by flash column chromatography

(SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane, 10:90 to 20:80) to afford title compound **335** as a pale yellow oil (15.5 mg, 5%); R_f = 0.27 (10:90, EtOAc:*n*–hexane); IR (neat) ν_{max} /cm $^{-1}$: 2939m (C–H alkyl), 2866w (C–H alkyl), 1489w (CC aromatic), 1463w, 1200s (S=O sulfite), 1089w, 1054w, 1029w, 924w, 886s, 865m, 851w, 826s, 774w, 738s, 702s, 613w, 584m, 500w, 472w; δ_H (400 MHz; $CDCl_3$) 7.16 (4H, s, C(6+7)H), 4.40 – 4.31 (2H, m, 2 × C(1)H**H'**), 4.14 – 4.04 (2H, m, 2 × C(1)**H**H'), 2.81 – 2.69 (2H, m, 2 × C(4)H**H'**), 2.69 – 2.56 (2H, m, 2 × C(4)**H**H') 1.95 – 1.83 (4H, m, 2 × C(2)H_2), 1.83 – 1.71 (4H, m, 2 × C(3)H_2); δ_C (101 MHz; $CDCl_3$) 140.2 (2 × C, C5), 129.9 (2 × CH, C6), 126.3 (2 × CH, C7), 61.8 (2 × CH_2, C1), 31.9 (2 × CH_2, C4), 28.2 (2 × CH_2, C2), 27.6 (2 × CH_2, C3); HRMS (ESI): calcd. For $C_{14}H_{20}NaO_3S$, 291.1025. Found: $[MH]^+$, 291.1023 (0.8 ppm error).

Lab notebook reference: ixz_482

Synthesis of 3,3'-(piperazine-1,4-diyl)bis(propan-1-ol) – 337

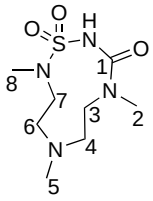


Na_2CO_3 (16.6 g, 157 mmol) was added in a single portion to a solution of 3-chloropropan-1-ol **305** (10.9 mL, 131 mmol)**,** piperazin **336** (4.51 g, 52.3 mmol) and KI (26.1 g, 157 mmol) in anhydrous EtOH (174 mL) at RT under Ar. The resulting suspension was stirred at 110 °C for 24 h under Ar, after which the reaction was deemed to have gone to completion by TLC. The reaction mixture allowed to cool to RT, before was filtered through Celite® and washed with EtOAc (3 × 30 mL). The resulting filtrate was concentrated under reduced pressure to yield a pale-orange solid (10.2 g). The crude product was purified by recrystallisation from MeOH:Et_2O (1:1, 200 mL) to afford title compound **337** as a white solid (3.71 g, 35%); melting point: 130 – 140 °C (from $CHCl_3$); IR (solid state) ν_{max} /cm^{-1}: 3405w (O–H alcohol), 3135w (O–H alcohol), 2859w (C–H alkyl), 2846w (C–H alkyl), 2828w (C–H alkyl), 2817w (C–H alkyl), 1312w, 1282w, 1271w, 1136w, 1126, 1099w, 1084w, 1068s, 1006s, 921w, 885w, 821w, 794m, 775m, 492m; δ_H (400 MHz; $CDCl_3$) 5.14 (2H, s, br, OH), 3.77 (4H, t, *J* = 5.3 Hz, CH_2), 2.59 (4H, t, *J* = 5.5 Hz, CH_2), 2.49 (9H, s, br, CH_2), 1.74 – 1.64 (4H, m, CH_2); δ_C (101 MHz; $CDCl_3$) 64.8 (CH_2), 58.8 (CH_2), 53.4 (CH_2), 27.1 (CH_2); HRMS (ESI): calcd. For $C_{10}H_{23}N_2O_2$, 203.1754. Found: $[MH]^+$, 203.1752 (1.2 ppm error), calcd. For $C_{10}H_{22}NaN_2O_2$, 225.1573. Found: $[Mna]^+$, 225.1570 (1.4 ppm error).

Lab notebook reference: ixz_469

Spectroscopic data is consistent with those previously reported in the literature.[296]

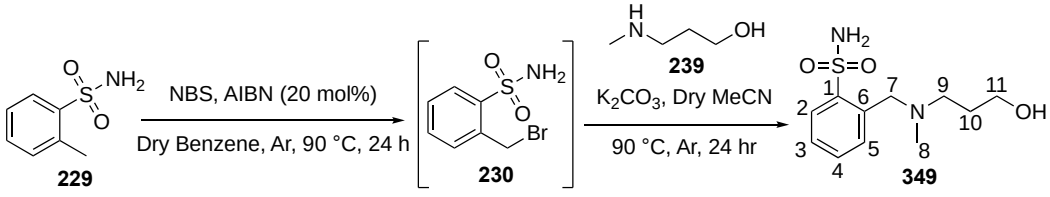
Synthesis of 4,7,10-trimethyl-1,2,4,7,10-thiatetrazecan-3-one 1,1-dioxide – 340



Chlorosulfonyl isocyanate (380 µL, 4.31 mmol) was added in a single portion via syringe to a clear solution of N^1,N^2-dimethyl-N^1-(2-(methylamino)ethyl)ethane-1,2-diamine **246** (600 µL, 3.59 mmol) and dry Et_3N (1.50 mL, 11.0 mmol) in anhydrous CH_2Cl_2 (72.0 mL) at 0 °C under Ar. The resulting mixture was allowed to warm gradually to RT overnight under Ar and the progress of the reaction was monitored via TLC, with a colour change to a pale yellow solution observed. After a total of 18 h, the reaction was deemed to have gone to completion by TLC analysis. The resulting mixture was quenched with sat. $NaHCO_{3(aq)}$ (80 mL) and poured into the separating funnel. The aqueous layer was extracted EtOAc (3 × 100 mL) and combined organic layers were washed sequentially with sat. $NH_4Cl_{(aq)}$ (3 × 80 mL) and sat. brine (3 × 80 mL), before dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an orange oil (871 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:MeOH, 90:10 to 100:0) to afford title compound **340** as a colourless oil (642 mg, 71%); R_f = 0.29 (MeOH); IR (neat) ν_{max}/cm^{-1}:3439w (N–H sulfonamide), 2940w (C–H alkyl), 2796w, 2246w, 1688w, 1574s (C=O urea), 1455m, 1392w, 1236m, 1149w, 1112m, 1067w, 1037w, 998w, 966w, 905s, 831w, 724s, 689m, 645m, 607m, 529w, 480w; δ_H (400 MHz, $CDCl_3$) 4.88 (2H, s, br, C(3)H_2), 3.48 (2H, s, br, C(7)H_2), 3.21 (2H, s, br, C(4)H_2), 2.87 (3H, s, C(8)H_3), 2.83 (3H, s, C(2)H_3), 2.71 (2H, s, br, C(6)H_2), 2.43 (3H, s, C(5)H_3); δ_C (101 MHz, $CDCl_3$, at 50 °C) 160.1 (CO, C1), 57.0 (CH_2, C6), 54.4 (CH_2, C3), 49.0 (CH_2, C4), 48.2 (CH_2, C7), 43.8 (CH_3, C5), 39.2 (CH_3, C8), 34.6 (CH_3, C8); HRMS (ESI): calcd. For $C_8H_{19}N_4O_3S$, 251.1172. Found: $[MH]^+$, 251.1166 (2.5 ppm error), calcd. For $C_8H_{18}N_4NaO_3S$, 251.1172. Found: $[Mna]^+$, 251.1166 (1.8 ppm error).

Lab notebook reference: ixz_571

Synthesis of 2-(((3-hydroxypropyl)(methyl)amino)methyl)benzenesulfonamide – 349

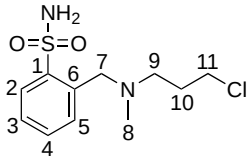


AIBN (1.17 g, 7.17 mmol) was added in a single portion to a sunflower yellow suspension of **229** (5.97 g, 35.7 mmol) and *N*-bromosuccinimide (7.44 g, 42.0 mmol) in anhydrous benzene

(40 mL) at RT. The resulting suspension was heated to 90 °C, whereupon a colour changed to pale yellow was noted. After 24 h, the reaction wasn't deemed to have gone to completion by TLC analysis (consumption of stating material wasn't observed). The reaction mixture allowed to cool to RT and solvent removed via *vacuo*, before diluted with 30 mL of EtOAc. The diluted mixture was transferred to separating funnel, where organic layer was washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 40 mL), sat. $NaHCO_{3(aq)}$ (3 × 40 mL) and sat. brine (3 × 40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude product as brown oil (576 mg). The bromide **230** was directly used in the next reaction step without further purification. Next, K_2CO_3 (955 mg, 6.91 mmol) was added to a yellow solution of **239 (**400 µL, 3.45 mmol) and **230** bromide (576 mg, 2.30 mmol) in anhydrous MeCN (23.0 mL) at RT under Ar. The resulting suspension was then heated to 90 °C, whereupon a colour change to pale yellow was noted. Upon further heating, the colour of the reaction suspension changed to dark brown. After 18 h, the reaction was deemed to have gone to completion by TLC. The reaction mixture was cooled to RT, before diluted with EtOAc (30 mL). The resulting mixture was filtered through Celite® and washed with EtOAc (3 × 40 mL). The resulting filtrate was concentrated under *vacuo* to yield an orange solid (1.10 g).The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 95:5 to 100:0) to afford title compound **349** as a colourless viscous oil (476 mg, 5%, over two steps); R_f = 0.21 (EtOAc); IR (neat) ν_{max}/cm^{-1}: 3505w (N–H sulfonamide), 3286w, 2953m, 2852w, 2807w, 1727w, 1573w, 1466w, 1445w, 1372w, 1330s, 1248w, 1199w, 1159s, 1138m, 1122w, 1064w, 924w, 889w, 835m, 751s, 691w, 667w, 621w, 588m, 551m, 504m; δ_H (400 MHz; $CDCl_3$) 7.80 (1H, dd, *J* = 7.6, 1.5 Hz, C(2)H), 7.36 (1H, td, *J* = 7.6, 1.5 Hz, C(4)H), 7.27 (1H, td, *J* = 7.6, 1.5 Hz, C(3)H), 7.20 (1H, dd, *J* = 7.6, 1.5 Hz, C(5)H), 5.82 (2H, s, br, NH_2), 3.75 (2H, s, C(7)H_2), 3.42 (2H, t, *J* = 6.3 Hz, C(11)H_2), 2.43 – 2.34 (2H, m, C(9)H_2), 2.04 (3H s, C(8)H_3), 1.67 – 1.55 (2H, m, C(10)H_2); δ_C (101 MHz; $CDCl_3$) 141.6 (C, C1), 134.8 (C, C6), 133.2 (CH, C5), 132.1 (CH, C3), 128.2 (CH, C4), 127.5 (CH, C2), 61.3 (CH_2, C7), 60.1 (CH_2, C11), 53.9 (CH_2, C9), 40.9 (CH_3, C8), 29.2 (CH_2, C10); HRMS (ESI): calcd. For $C_{11}H_{19}N_2O_3S$, 259.1111. Found: $[MH]^+$, 259.1112 (–0.5 ppm error), calcd. For $C_{11}H_{19}N_2NaO_3S$, 281.0930. Found: $[MH]^+$, 281.0935 (–1.6 ppm error).

Lab notebook reference: ixz_499

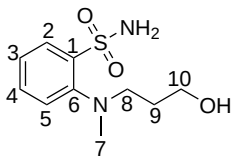
Synthesis of 2-(((3-chloropropyl)(methyl)amino)methyl)benzenesulfonamide – 352



Thiophesgene (100 µL, 1.34 mmol) was added in a single portion to a solution of 2-(((3-hydroxypropyl)(methyl)amino)methyl)benzenesulfonamide **349** (266 mg, 1.03 mmol), DMAP (440 mg, 3.61 mmol) in anhydrous CH_2Cl_2 (21 mL) at 0 °C under Ar. A colour change to yellow suspension was noted. The resulting solution was allowed to warm gradually to RT overnight under Ar and the progress of the reaction was monitored by TLC. After a total of 24 h, the reaction was deemed to have gone to completion by TLC analysis with a colour change to yellow solution observed. The resulting mixture was quenched with sat. $NaHCO_{3(aq)}$ (40 mL), before transferred into separating funnel. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL) and combined organic layers were washed with sat. brine (3 × 40 mL), before dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale-yellow orange oil (478 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane, 50:50 to 100:0) to afford title compound **352** as a colourless oil (250 mg, 88%); R_f = 0.69 (EtOAc); IR (neat) ν_{max}/cm^{-1}: 3288w (N–H sulfonamides), 3064w, 2958w, 2850w, 2810w, 1573w, 1466m, 1445m, 1333s, 1252w, 1199w, 1160s, 1137m, 1066m, 1045w, 1012w, 970w, 889w, 831m, 760s, 731m, 651w, 620w, 588s, 552m, 536w, 510w; δ_H (400 MHz; $CDCl_3$) 7.99 (1H, dd, *J* = 7.6, 1.6 Hz, C(2)H), 7.48 (1H, td, *J* = 7.6, 1.6 Hz, C(4)H), 7.42 (1H, td, *J* = 7.6, 1.6 Hz, C(3)H), 7.30 (1H, dd, *J* = 7.6, 1.6 Hz, C(5)H), 6.81 (2H, s, NH_2), 3.91 (2H, s, C(7)H_2), 3.54 (2H, t, *J* = 6.4 Hz, C(11)H_2), 2.69 – 2.54 (2H, m, C(9)H_2), 2.17 (3H, s, C(8)H_3), 2.07 – 1.96 (2H, m, C(10)H_2); δ_C (101 MHz; $CDCl_3$) 142.0 (C, C1), 134.9 (C, C6), 133.5 (CH, C5), 132.3 (CH, C3), 128.6 (CH, C4), 128.0 (CH, C2), 61.3 (CH_2, C7), 54.9 (CH_2, C9), 43.0 (CH_2, C11), 41.5 (CH_3, C8), 29.4 (CH_2, C10); HRMS (ESI): calcd. For $C_{11}H_{18}ClN_2O_2S$, 277.0772. Found: $[MH]^+$, 277.0773 (–0.3 ppm error).

Lab notebook reference: ixz_512

Synthesis of 2-((3-hydroxypropyl)(methyl)amino)benzenesulfonamide – 353

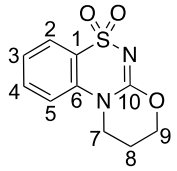


A pale yellow solution of 2-fluorobenzenesulfonamide **354** (295 mg, 1.68mmol) in 3-(methylamino)propan-1-ol **239** (1.64 mL, 16.8 mmol) was heated at 130 °C for 24 h in a closed

reaction vial (7 mL), with a colour change to brown solution was noted. The reaction mixture was directly purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 90:10 to 100:0) to afford title compound **353** as a colourless oil (395 mg, 96%); R_f = 0.40 (EtOAc); IR (neat) ν_{max}/cm^{-1}: 3479w (N–H sulfonamides), 3001w, 2958w, 2891w, 2831w, 1588w, 1574w, 1474m, 1455w, 1395w, 1364w, 1314s, 1259w, 1189w, 1169m, 1151s, 1108m, 1057m, 1039s, 999w, 889w, 799m, 777m, 752m, 588s, 544s, 513w, 496m, 461w; δ_H (400 MHz; $(CD_3)_2SO$) 7.86 (1H, dt, *J* = 7.7, 1.4 Hz, C(2)H), 7.60 (1H, tt, *J* = 7.7, 1.4 Hz, C(3)H), 7.54 (1H, dt, *J* = 7.7, 1.4 Hz, C(5)H), 7.36 – 7.27 (1H, m, C(4)H), 7.06 (2H, s, br, NH_2), 4.56 (1H, t, *J* = 5.1 Hz, OH), 3.46 (2H, t, *J* = 5.9 Hz, C(10)H_2), 2.98 (2H, t, *J* = 7.3 Hz, C(8)H_2), 2.64 (3H, s, C(7)H_3), 1.69 – 1.57 (2H, m, C(9)H_2); δ_C (101 MHz; $(CD_3)_2SO$) 151.9 ©, 139.9 (C), 133.3 (CH), 127.3 (CH), 125.0 (CH), 124.9 (CH), 58.9 (CH_2, C10), 54.0 (CH_2, C8), 44.0 (CH_3, C7), 30.3 (CH_2, C9); HRMS (ESI): calcd. for $C_{10}H_{17}N_2O_3S$, 245.0954. Found: $[MH]^+$, 245.0955 (–0.1 ppm error),calcd. for $C_{10}H_{16}N_2NaO_3S$, 267.0774. Found: $[MNa]^+$, 267.0773 (0.2 ppm error).

Lab notebook reference: ixz_508

Synthesis of 2,3-dihydro-1*H*-benzo[*e*][1,3]oxazino[2,3-c][1,2,4]thiadiazine 6,6-dioxide – 356

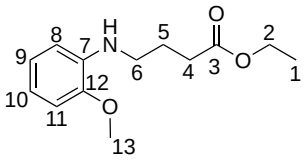


Triphosgene (139 mg, 0468 mmol) was added in a single portion to a colourless solution of 2-((3-hydroxypropyl)(methyl)amino)benzenesulfonamide **353** (286 mg, 1.17 mmol), DMAP (14.3 mg, 0.117 mmol) in anhydrous CH_2Cl_2 (23 mL) at 0 °C under Ar. The resulting solution was allowed to warm gradually to RT overnight under Ar and the progress of the reaction was monitored by TLC. After total of 18 h, the reaction was deemed to have gone to completion by TLC analysis, with a colour change to pale yellow solution was noted. The resulting mixture was diluted with H_2O (40 mL), before transferred into separating funnel. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and combined organic layers were collected. The resulting organic layer was washed sequentially with 1.0 M Citric $Acid_{(aq)}$ (1 × 40 mL), sat. $NH_4Cl_{aq)}$ (1 × 40 mL) and sat. brine (2 × 40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude product as brown oil (478 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: MeOH:EtOAc, 30:70) to afford title compound **356** as a white solid (239 mg, 70%); R_f = 0.39 (30:70, MeOH:EtOAc,); IR (solid state)ν_{max}/cm^{-1}: 3524w, 3239w, 2924w, 2853w, 2268w, 1745m (CC aromatic), 1675w

(CC aromatic), 1606m (CC aromatic), 1587w, 1545w, 1463m, 1438m, 1329m, 1291s, 1159s, 1122s, 1060m, 1009w, 994w, 958w, 910w, 889w, 841m, 764m, 730m, 707w, 647w, 593s, 572s, 547m, 524w, 515w, 498w, 462w; δ_H (500 MHz; $(CD_3)_2SO$) 7.85 (1H, dd, *J* = 7.6, 1.5 Hz, C(2)H), 7.80 – 7.74 (1H, m, C(4)H), 7.62 (1H, d, *J* = 7.6 Hz, C(5)H), 7.52 (1H, t, *J* = 7.6 Hz, C(3)H), 4.49 (2H, t, *J* = 5.2 Hz, C(9)H_2), 4.03 (2H, t, *J* = 6.2 Hz, C(7)H_2), 2.33 – 2.26 (2H, m, C(8)H_2); δ_C (101 MHz; $(CD_3)_2SO$) 152.8 (C), 136.9 (C), 133.2 (CH), 126.0 (CH), 124.7 (C), 123.4 (CH), 116.4 (CH), 67.1 (CH_2, C9), 44.8 (CH_2, C7), 20.9 (CH_2, C8); HRMS (ESI): calcd. for $C_{10}H_{10}N_2NaO_3$, 261.0304. Found: $[MNa]^+$, 261.0304 (0.0 ppm error); X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2236588, was crystallised by slow evaporation of EtOAc).

Lab notebook reference: ixz_519

Synthesis of ethyl 4-((2-methoxyphenyl)amino)butanoate – 363

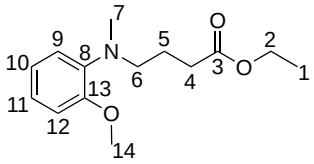


2-methoxyaniline **361** (2.05 mL, 18.2 mmol) was added via syringe over a period of 30 sec to a pale brown suspension of ethyl 4-bromobutanoate **362** (1.10 mL, 6.99 mmol) and anhydrous $NaOAc_{(s)}$ (860 mg, 10.5 mmol) in *n*–Butanol (24 mL) at RT. An immediate colour change to an orange solution was noted. The resulting solution was stirred at 70 °C overnight under Ar and progress of the reaction was monitored by TLC. After a total of 18 h, the reaction was judged to be complete, based on TLC analysis. The resulting mixture was diluted with H_2O (30 mL), before transferred into separating funnel. The aqueous phase was extracted with Et_2O (3 × 40 mL), before the combined organic phases were washed sequentially with H_2O (1 × 30 mL) and sat. brine (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a brown oil (3.92 g). The crude product was purified by flash column chromatography (SiO_2, 70 mm column, eluent: EtOAc:*n*–hexane, 30:70) to afford ester **363** as a pale yellow oil (1.47 g, 89%); R_f = 0.58 (30:70, EtOAc:*n*–hexane);IR (neat) ν_{max} / cm^{-1}: 3420w (N–H aniline), 2939w (C–H alkyl), 2835w (C–H alkyl), 1729s (C=O ester), 1602s (CC aromatic), 1513s (CC aromatic), 1456m, 1431m, 1373m, 1346w, 1301w, 1245s, 1220s, 1175s, 1125m, 1095w, 1048w, 1026s, 901w, 858w, 775w, 734s, 633w, 582w, 458w; δ_H (400 MHz; $CDCl_3$) 6.89 (1H, td, *J* = 7.8, 1.4 Hz, C(10)H), 6.78 (1H, dd, *J* = 7.8, 1.4 Hz, C(8)H), 6.70 – 6.60 (2H, m, C(9+11)H), 4.27 (1H, br, s, NH), 4.16 (2H, q, *J* = 7.2 Hz, C(2)H_2), 3.85 (3H, s, C(13)H_3), 3.21 (2H, t, *J* = 7.0 Hz, C(6)H_2), 2.45 (2H, t, *J* = 7.3 Hz, C(4)H_2), 2.05 – 1.95 (2H, m, C(5)H_2), 1.28 (2H, t, *J* = 7.2 Hz, C(1)H_3); δ_C (101

MHz; $CDCl_3$) 173.4 (C, C3), 146.8 (C, C12), 138.1 (C, C7), 121.3 (CH, C10), 116.4 (CH, C9), 109.7 (CH, C11), 109.4 (CH, C8), 60.5 (CH_2, C2), 55.4 (CH_3, C13), 43.0 (CH_2, C6), 32.0 (CH_2, C4), 24.8 (CH_2, C5), 14.3 (CH_3, C1); HRMS (ESI): calcd. for $C_{13}H_{20}NO_3$, 238.1438. Found: $[MH]^+$, 238.1441 (−1.5 ppm error), calcd. for $C_{13}H_{19}NNaO_3$, 260.1257. Found: $[MNa]^+$, 260.1262 (−2.0 ppm error).

Lab notebook reference: ixz_393

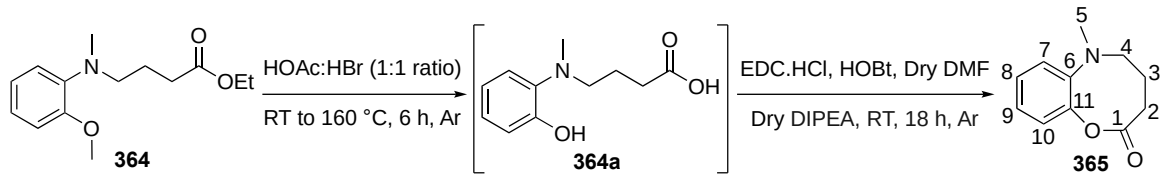
Synthesis of ethyl 4-((2-methoxyphenyl)(methyl)amino)butanoate – 364



MeI (350 µL, 5.67 mmol) was added to a pale yellow suspension of ethyl 4-((2-methoxyphenyl)amino)butanoate **363** (1.35 g, 5.67 mmol) and NaOAc (465 mg, 5.67 mmol) in anhydrous THF (19 mL) under Ar at RT. The resulting fluorescent yellow suspension was stirred at 50 °C for 16 h under Ar, after which time the reaction was deemed to have gone to completion by TLC. The reaction mixture was quenched with 30 mL of H_2O and poured into separating funnel. The resulting aqueous phase was extracted with Et_2O (3 × 30 mL), before the combined organic phases were washed sequentially with H_2O (1 × 30 mL) and sat. brine (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a yellow oil (2.11 g). The crude product was purified by flash column chromatography (SiO_2, 60 mm column, eluent: EtOAc:*n*–hexane, 20:80 to 30:70) to afford ester **364** as a pale yellow liquid (207 mg, 14%); R_f = 0.35 (30:70, EtOAc:*n*–hexane); IR (neat)ν_{max}/cm^{-1}: 2940w (C–H alkyl), 2835w (C–H alkyl), 1731s (C=O ester), 1594m (CC aromatic), 1500s (CC aromatic), 1456m, 1420m, 1372m, 1347w, 1299w 1236s, 1179s, 1162s, 1115m, 1100m, 1054m, 1027s, 958w, 915w, 856w, 803w, 742s, 596w, 527w, 486w; δ_H (400 MHz; $CDCl_3$) 7.00 – 6.80 (4H, m, C(9 +10+11+12), 4.11 (2H, q, *J* = 7.1 Hz, C(2)H_2), 3.85 (3H, s, C(14)H_3), 3.10 – 3.02 (2H, m, C(6)H_2), 2.77 (3H, s, C(7)H_3), 2.33 (2H, t, *J* = 7.5 Hz, C(4)H_2), 1.92 – 1.79 (2H, m, C(5)H_2), 1.23 (3H, t, *J* = 7.1 Hz, C(1)H_3); δ_C (101 MHz; $CDCl_3$) 173.7 (C, C3), 152.7 (C, C8), 141.5 (C, C13), 122.5 (CH, C11), 120.8 (CH, C10), 119.4 (CH, C9), 111.3 (CH, C12), 60.3 (CH_2, C2), 55.4 (CH_3, C14), 54.6 (CH_2, C6), 40.2 (CH_3, C7), 32.0 (CH_2, C4), 22.4 (CH_2, C5), 14.3 (CH_3, C1); HRMS (ESI): calcd. for $C_{14}H_{22}NO_3$, 252.1594. Found: $[MH]^+$, 252.1597 (−1.3 ppm error).

Lab notebook reference: ixz_394

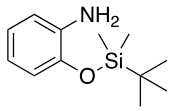
Synthesis of 6-methyl-3,4,5,6-tetrahydro-2*H*-benzo[*b*][1,4]oxazocin-2-one – 365



Hydrogen bromide solution (48% in H_2O, 3.0 mL) was added dropwise over a period of 3 min via syringe to a solution of ethyl 4-((2-methoxyphenyl)(methyl)amino)butanoate **364** (250 mg, 1.05 mmol) in AcOH (3.0 mL) at RT under Ar. A colour change to beige suspension was immediately noted along with the liberation of fumes and the reaction mixture was stirred at 160 °C for 6 h, at which point the reaction mixture was deemed to have gone to completion by TLC (4-((2-methoxyphenyl)(methyl)amino)butanoate **364** was noted). The resulting reaction mixture was allowed to cool to RT and then concentrated under rejoiced pressure to yield brown liquid. The concentrated solution was azeotroped with toluene (3 × 30 mL, remove H_2O) [water bath set to 70 °C] to afford crude product **364a** which was directly used in the next reaction step without further purification. Next, EDC.HCl (705 mg, 3.70 mmol) was added to a pale orange solution of carboxylic acid **364a**, HOBt (355 mg, 2.63 mmol) and dry DIPEA (3.75 mL, 21.2 mmol) in anhydrous DMF (21 mL). A colour change to a lilac was immediately noted and the reaction mixture was stirred at RT for 18 h of stirring at RT under Ar, before reaction was deemed to have to completion by TLC. The resulting mixture was diluted with EtOAc (30 mL) and transferred into separating funnel. The organic phase was washed sequentially with sat. $NaHCO_{3(aq)}$ (2 × 30 mL) and sat. brine (4 × 30 mL), before was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an orange oil (328 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 30:70) to afford ester **365** as colourless oil (157 mg, 78%, over two steps); R_f = 0.40 (30:70, EtOAc:*n*–hexane); IR (thin film) ν_{max}/cm^{-1}: 2945w (C–H alkyl), 2859w (C–H alkyl), 2805w (C–H alkyl), 1748s (C=O aryl ester), 1606m (CC aromatic), 1493s, 1447m, 1364w, 1341m, 1285w, 1256m, 1226m, 1197m, 1169s, 1158s, 1146s, 1104m, 1085m, 1059m, 1036w, 1007s, 982w, 914w, 881w, 832w, 799w, 746s, 706w, 649w, 560w, 541w, 513w, 465w; δ_H (400 MHz; $CDCl_3$) 7.14 – 7.03 (3H, m, C(8+9+10)H), 7.01 – 6.95 (1H, m, C(7)H), 3.20 – 3.12 (2H, m, C(4)H_2), 2.78 (3H, s, C(5)H_3), 2.51 (2H, t, *J* = 7.0, 6.4 Hz, C(2)H_2), 2.00 – 1.90 (2H, m, C(3)H_2); δ_C (101 MHz; $CDCl_3$) 174.2 (C, C1), 148.4 (C, C6), 141.8 (C, C11), 125.4 (CH), 123.5 (CH), 121.0 (CH), 119.9 (CH), 55.2 (CH_2, C4), 41.4 (CH_3, C5), 32.8 (CH_2, C2), 26.4 (CH_2, C3); HRMS (ESI): calcd. for $C_{11}H_{14}NO_2$, 192.1019. Found: $[MH]^+$, 192.1023 (−2.2 ppm error), calcd. for $C_{11}H_{13}NNaO_2$, 214.0838. Found: $[MNa]^+$, 214.0842 (−1.8 ppm error), calcd. for $C_{22}H_{26}N_2NaO_4$, 405.1785. Found: $[2MNa]^+$, 405.1789 (−1.1 ppm error).

Lab notebook reference: ixz_395

Synthesis of 2-[(tert-butyldimethylsilyl)oxy]aniline – 368

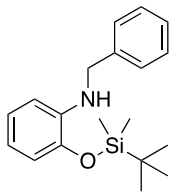


To a solution of 2-aminophenol **367** (10.9 g, 100 mmol) in anhydrous DMF (53 mL), TBSCl (16.5 g, 110 mmol) and imidazole (10.2 g, 150 mmol) was added sequentially in a single portion under RT under Ar. The mixture was stirred at RT under Ar overnight, after 18 h, the reaction was deemed to have gone to completion by TLC. The resulting reaction mixture was quenched with sat. $NH_4Cl_{(aq)}$ solution and transfer into a separating funnel. The aqueous layer was extracted with EtOAc (3 × 30 mL), before combined organic layers were collected and washed sequentially with H_2O (2 × 30 mL) and sat. brine (2 × 30 mL). The resulting organic phase was dried over Na_2SO_4, filtrated and concentrated under reduced pressure to yield the crude product as a brown oil (4.01 g). The crude product was purified by flash column chromatography (SiO_2, 60 mm column: eluent:EtOAc:*n*–hexane,10:90) to afford title compound **368** as a pale yellow oil (2.66 g, 56%); δ_H (400 MHz; $CDCl_3$) 6.84 – 6.75 (1H, m, Ar-CH), 6.74 (2H, s, Ar-CH), 6.68 – 6.59 (1H, m, Ar-CH), 3.71 (2H, br, s, NH), 1.03 (9H, s, 2 3 × CH_3), 0.25 (6H, s, 2 × CH_3); δ_C (101 MHz; $CDCl_3$) 143.0 (C), 138.3 (C), 122.0 (CH), 118.6 (CH), 118.5 (CH), 115.8 (CH), 26.0 (3 × CH_3), 18.4 (C),−4.1 (2 × CH_3); HRMS (ESI): calcd. for $C_{12}H_{22}NOSi$, 224.1465. Found: $[MH]^+$, 224.1466 (−0.6 ppm error).

Lab notebook reference: ixz_400

Spectroscopic data is consistent with those previously reported in the literature.[258]

Synthesis of N-benzyl-2-(tert-butyldimethylsilyloxy)aniline – 369



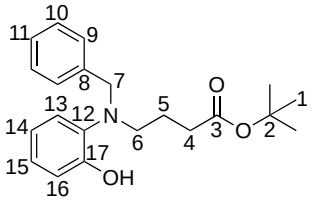
Benzaldehyde (ArCHO, 1.21 mL, 11.9 mmol) was added in a single portion via syringe to a solution of 2-[(tert-butyldimethylsilyl)oxy]aniline **368** (2.66 g, 11.9) and $MgSO_4$ (287 mg, 2.39 mmol) in in anhydrous MeOH (40.0 mL) at RT under Ar, with colour changed to bright yellow solution noted. The resulting reaction was stirred at 90 °C for 4 h under Ar, after that time mixture allowed to cool to RT. Next, $NaBH_4$ (903 mg, 23.9 mmol) was added cautiously to the resulting mixture at 0 °C, fizzing, bubbling and effervescent (liberation of H_2) was observed.

The resulting milky white suspension was stirred at RT under Ar for 2 h. The resulting mixture was quenched by the gradual addition of H_2O (50 mL) and poured into separating funnel. The aqueous layer was extracted with EtOAc (3 × 20 mL), before combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a brown oil (3.76 g). The crude product was purified by flash column chromatography (SiO_2, 60 mm column, eluent: EtOAc:*n*–hexane, 5:95) to afford title compound **369** as a pale yellow oil (1.42 g, 38%); δ_H (400 MHz; $CDCl_3$) 7.45 – 7.38 (2H, m, Ar-CH), 7.41 – 7.26 (2H, m, Ar-CH), 6.92 – 6.85 (1H, m, Ar-CH), 6.83 – 6.78 (1H, m, Ar-CH), 6.68 – 6.58 (1H, m, Ar-CH), 4.54 (1H, s, NH), 4.40 (2H, s, CH_2), 1.04 (9H, s, 3 × CH_3), 0.30 (6H, s, 2 × CH_3); δ_C (101 MHz; $CDCl_3$) 142.6, 140.3, 139.8, 128.7, 127.4, 127.2, 122.2, 117.6, 116.7, 110.9, 48.2, 26.0, 18.4, −4.1; HRMS (ESI): calcd. for $C_{19}H_{28}NOSi$, 314.1935. Found: $[MH]^+$, 314.1934 (0.1 ppm error).

Lab notebook reference: ixz_401

Spectroscopic data is consistent with those previously reported in the literature.[297]

Synthesis of *tert*-butyl 3-(benzyl(2-hydroxyphenyl)amino)propanoate – 371

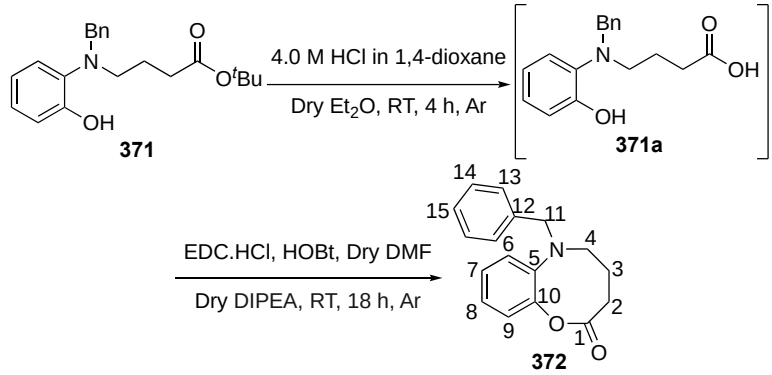


K_2CO_3 (1.29 g, 9.30 mmol) was added in a single portion to a colouless solution of *N*-benzyl-2-(tert-butyldimethylsilyloxy)aniline **369** (1.88 g, 8.29 mmol), tert-butyl 4-bromobutanoate **370** (817 µL, 4.61mmol) and TBAI (115 mg, 0.310 mmol) in anhydrous DMF (31 mL) at RT under Ar. The resulting pale green suspension was then heated to 80 °C under Ar. After 48 h, the reaction was deemed to have gone to completion by TLC. The reaction mixture allowed to cool to RT, before it was diluted with EtOAc (30 mL). The diluted reaction mixture was poured into separating funnel and organic layer was washed with sat. brine (3 × 30 mL). The resulting organic phase was collected and dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a brown oil (1.36 g). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:*n*–hexane, 20:80) to afford title compound **371** as a colourless oil (680 mg, 67%); R_f = 0.25 (20:80, EtOAc:*n*–hexane); IR (neat) ν_{max} /cm^{-1}: 3387w (O–H phenol), 2979w (C–H alkyl), 2935w (C–H alkyl), 2846w (C–H alkyl), 1755 (C=O ester), 1600m (CC aromatic), 1492s (CC aromatic), 1250m, 1149s, 910m, 730s, 698m; δ_H (400 MHz; $CDCl_3$) 7.35 – 7.24 (4H, m, Ar-CH), 7.23 – 7.19 (3H, m, Ar-CH), 7.14 (1H, dd, *J* = 7.8, 1.6 Hz, Ar-CH), 7.09 – 7.04 (1H, m, Ar-CH), 6.91 (1H, dd, *J* = 8.1, 1.5

Hz, Ar-CH), 6.87 – 6.82 (1H, m, Ar-CH), 3.95 (2H, s, CH_2), 2.96 – 2.87 (1H, m, OH), 2.14 (2H, t, J = 7.3 Hz, CH_2), 1.71 – 1.59 (2H, m, CH_2), 1.38 (9H, s, C(1)H_3); δ_C (101 MHz; $CDCl_3$) 172.6 (CO, C3), 153.0 (C), 137.5 (C), 137.5 (C), 136.7 (C), 129.3 (CH), 128.5 (CH), 127.6 (CH), 126.9 (CH), 123.5 (CH), 120.0 (CH), 114.1 (CH), 80.4 (C, C2), 60.9 (CH_2), 53.3 (CH_2), 33.1 (CH_2) 28.1 (CH_3, C1), 22.9 (CH_2); HRMS (ESI): calcd. for $C_{21}H_{28}NO_3$, 342.2064. Found: $[MH]^+$, 342.2072 (−2.3 ppm error), calcd. for $C_{21}H_{27}NNaO_3$, 364.1883. Found: $[MNa]^+$, 364.1892 (−2.5 ppm error).

Lab notebook reference: ixz_409

Synthesis of 5-benzyl-4,5-dihydrobenzo[*b*][1,4]oxazepin-2(3*H*)-one – 372

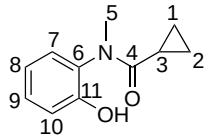


Hydrogen chloride solution (4.0 M in 1,4-dioxane, 9.0 mL) was added dropwise over a period of 1 min via syringe to a pale yellow solution of propanoate **371** (153 mg, 0.447 mmol) in anhydrous Et_2O (5.0 mL) at RT under Ar. A colour change to yellow solution was immediately noted along with the liberation of fumes and the reaction mixture was stirred at RT under Ar for 4 h, at which point the reaction mixture was deemed to have gone to completion by TLC (tert-butyl 3-(benzyl(2-hydroxyphenyl)amino)propanoate **371** was noted) with colour changed to cloudy white suspension was observed. The resulting reaction mixture was concentrated and azeotroped with toluene (3 × 30 mL) to afford crude carboxylic acid **371a** product as a pale pink emulsion which was directly used in the next reaction step without further purification. Next, EDC.HCl (214 mg, 1.12 mmol) was added to a pale-yellow solution of carboxylic acid **371a**, HOBt (90.6 mg, 0.671 mmol) and dry DIPEA (1.20 mL, 6.71 mmol) in anhydrous DMF (9 mL). A colour change to a brown solution was noted, after the reaction mixture was stirred at RT for 18 h under Ar. The resulting mixture was diluted with EtOAc (30 mL) and transferred into separating funnel. The resulting organic layer was washed sequentially with sat. $NaHCO_{3(aq)}$ (3 × 20 mL) and sat. brine (4 × 10 mL), before was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an orange oil (340 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: Et_2O:*n*–hexane, 30:70) to afford ester **372** as colourless oil (61.9 mg, 52%, over two steps); R_f = 0.59 (30:70, EtOAc:n-

hexane); IR (thin film) ν_{max}/cm^{-1}: 2931w (C–H alkyl), 1750s (C=O ester), 1723s, 1604w (CC aromatic), 1586w (CC aromatic), 1491m, 1450m, 1146s, 1062m, 968m, 748w, 698m; δ_H (400 MHz; $CDCl_3$) 7.45 – 6.98 (9H, m, C(6+7+8+9+13+14+15)H), 4.22 (2H, s, C(11)H_2), 3.09 (2H, t, *J* = 5.9 Hz, C(4)H_2), 2.51 – 2.39 (2H, m, C(2)H_2), 1.87 – 1.77 (2H, m, C(3)H_2); δ_C (101 MHz; $CDCl_3$) 173.2 (CO, C1), 149.3 (C, C10), 142.1 (C, C5), 138.2 (C, C12), 128.6 (2 × CH, C14), 128.5 (2 × CH, C13), 127.4 (CH), 125.9 (CH), 125.7 (CH), 124.5 (CH), 119.8 (CH), 59.9 (CH_2, C11), 54.0 (CH_2, C4), 32.4 (CH_2, C2), 26.9 (CH_2, C3); HRMS (ESI): calcd. for $C_{17}H_{18}NO_2$, 268.1332. Found: $[MH]^+$, 268.1331 (0.2 ppm error), calcd. for $C_{17}H_{17}NNaO_2$, 290.1151. Found: $[MNa]^+$, 290.1151 (0.1 ppm error).

Lab notebook reference: ixz_411

Synthesis of 6-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazocin-5(6*H*)-one – 375

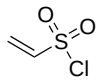


n–BuLi (4.68 mL, 2.1 M in *n*–hexane, 9.82 mmol) was added dropwise over 1 min to a blue lagoon solution of methyl amino phenol **373** (576 mg, 4.67 mmol) in anhydrous THF (47 mL) at 0 °C under Ar, with a colour changed to pale yellow solution noted. The resulting reaction mixture was stirred at 0 °C for 1 h under Ar, before allowed to be warmed to RT. After that time, tert-butyl 4-bromobutanoate **370** (826 µL, 4.67 mmol) was added in a single portion. The reaction was allowed to stir for 18 at RT under Ar after which times the reaction was deemed to have gone to completion by TLC, with colour change to orange solution noted. The resulting mixture was quenched by addition of sat. $NH_4Cl_{(aq)}$ (40 mL) and poured into separating funnel. The aqueous layer was extracted with EtOAc (3 × 20 mL), before combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale-yellow oil (758 mg). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 50:50) to afford an amide **375** as a pale yellow viscous oil (472 mg, 53%); R_f = 0.41 (50:50,EtOAc:*n*–hexane); IR (neat) ν_{max}/cm^{-1}: 3167s (O–H phenol), 1621s (C=O aryl amide), 1587s (CC aromatic), 1513s (CC aromatic), 1455s, 1398s, 1288s, 1211m, 1133m, 1099m, 937m, 909m, 869w, 829w, 730s, 637w, 580w, 510m; δ_H (400 MHz; $CDCl_3$) 8.44 (1H, br, s, OH), 7.24–7.18 (1H, m, C(8)H), 7.15 (1H, dd, *J* = 7.8, 1.5 Hz, C(10)H), 7.07 (1H, dd, *J* = 7.8, 1.5 Hz, C(7)H), 6.88 (1H, td, *J* = 7.5, 1.5 Hz, C(9)H), 3.25 (3H, s, C(5)H_3), 1.47–1.36 (1H, m, C(1 or 2)**H**H'), 1.12 – 1.05 (1H, m, C(2 or 1)H**H'**), 0.96 – 0.89 (1H, m, C(1 or 2)**H**H'), 0.67 – 0.54 (2H, m, C(2 or 1)H**H'**); δ_C (101 MHz; $CDCl_3$) 175.6 (C, C4), 153.2 (C, C11), 130.4 (C, C6), 129.6 (CH, C10), 128.9 (CH, C8), 120.4 (CH, C9),

117.5 (CH, C7), 36.7 (CH_3, C5), 12.4 (CH, C3), 8.6 (CH_2, C1 or 2), 8.2 (CH_2, C2 or 1); HRMS (ESI): calcd. for $C_{11}H_{14}NO_2$, 192.1019. Found: $[MH]^+$, 192.1025 (−3.3 ppm error), calcd. for $C_{11}H_{13}NNaO_2$, 214.0838. Found: $[MNa]^+$, 214.0843 (−2.0 ppm error), calcd. for $C_{11}H_{13}KNO_2$, 230.0578. Found: $[MK]^+$, 230.0570 (3.4 ppm error).

Lab notebook reference: ixz_397

Synthesis of ethenesulfonyl chloride – 383

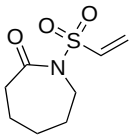


To a stirring solution of 2-chloroethane sulfonyl chloride **384** (1.90 mL, 18.2 mmol) in anhydrous Et_2O (12 mL) cooled to –60 °C, a solution of 2,4,6-trimethyl-pyridine **385** (2.89 mL, 21.8 mmol) in anhydrous Et_2O (5.0 mL) was added dropwise over a period of 30 min via syringe pump. The reaction mixture was stirred at –60 °C under argon for 45 min after the addition was completed and then allowed to warm to RT. The resulting milky white suspension was stirred for an additional 45 min at RT before it was quenched with 1% $H_2SO_{4(aq)}$ (30 mL). The diluted reaction mixture was poured into a separating funnel containing EtOAc (30 mL), and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* (water bath set at 0 °C and pressure to 30 mm/Hg) to yield the crude product as a yellow liquid (2.71 g). The crude product was purified by *vacuo* distillation [17 mm/Hg] (using a short water condenser) at 60 – 70 °C affording the title compound **383** as a colourless liquid (1.64 g, 71%); δ_H (400 MHz; $CDCl_3$) 7.01 (1H, dd, *J* = 16.2, 9.4 Hz, $SO_2C\mathbf{H}CH_2$), 6.53 (1H, dd, *J* = 16.2, 1.7 Hz, $SO_2CHC\mathbf{H}$–H'), 6.25 (1H, dd, *J* = 9.4, 1.7 Hz, SO_2CHCH–**H'**); δ_C (101 MHz, $CDCl_3$) 140.7 (CH), 130.11(CH_2).

Lab notebook reference: ixz_516

Spectroscopic data is consistent with those previously reported in the literature.[298]

Synthesis of 1-(vinylsulfonyl)azepan-2-one – 387



Compound **387** was prepared by three different methods:

Method 1: To a stirring solution of caprolactam **386** (269 mg, 2.38 mmol) in anhydrous THF (16 mL) cooled to –86 °C, LHMDS (1.0 M in THF, 4.00 mL, 3.57 mmol) was added dropwise over 30 min, with a colour change to pale yellow noted. The reaction mixture was allowed to

stir for 1 hour at –86 °C after the addition was completed. Ethenesulfonyl chloride **383** (0.240 mL, 3.00 mmol) as a solution in anhydrous THF (2.0 mL) was added dropwise over a period of 30 min and the reaction mixture was stirred for an additional 1 hour at –86 °C. The reaction was allowed to warm to RT and then stirred for additional 18 hours. After a total of 24 hours, the reaction was deemed to have gone to completion by TLC. The reaction mixture was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (30 mL) and transferred into a separating funnel. The aqueous was extracted with EtOAc (3 × 10 mL), combined with organic layers dried over $MgSO_4$, filtered and concentrated *in vacuo*, to yield crude yield a crude product as an orange oil (701 g). The crude product was purified by flash column chromatography (SiO_2, 50 mm column, eluent: EtOAc:*n*–hexane, 80:20) afforded the title compound **387** as a colourless oil (122 mg, 25%).

Lab notebook reference: ixz_525

Method 2: A stirring solution of caprolactam **386** (0.433 mg, 3.83 mmol), Et_3N (5.34 mL, 38.3 mmol) and DMAP (97.4 mg, 0.383 mmol) in anhydrous CH_2Cl_2 (23.0 mL) was cooled to –78 °C. To this was added a solution of 2-chloroethanesulfonyl chloride (2.01 mL, 19.2 mmol) in anhydrous CH_2Cl_2 (15.0 mL) dropwise over a period of 1 hour. Under an argon atmosphere this mixture was stirred at –78 °C for 1 hour, then allowed to warm to RT and stirred for additional 16 hours. The reaction mixture was then diluted with EtOAc (40 mL) and filtered through filter paper; the filtrate cake was washed with EtOAc (3 × 20 mL). The resulting filtrate was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane,70:30) affording the title compound **387** as a colourless oil (132 mg, 17%).

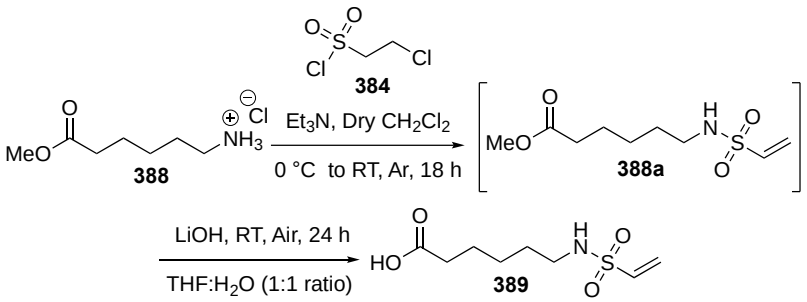
Lab notebook reference: ixz_505

Method 3: DCC **391** (863 mg, 4.18 mmol) was added to a solution of vinylsulfonamido hexanoic acid **389** (840 mg, 3.08 mmol) and 4-pyrrolidinopyridine (56.4 mg, 0.380 mmol) in anhydrous CH_2Cl_2 (390 mL). A colour change to a pale yellow was immediately noted and the reaction mixture was stirred at RT for 24 h at RT, before the reaction was deemed to have to be complete by TLC analysis, during which time a cloudy white suspension was observed. The reaction mixture was concentrated *in vacuo,* to approx. 100 mL, and the resulting white precipitate formed (dicyclohexylurea) was removed by filtration, and the filter cake was washed with CH_2Cl_2 (2 × 10 mL). The resulting filtrate was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane,70:30,) affording the title compound **387** as a colourless oil (250 mg, 40%).

Lab notebook reference: ixz_575

Data for **387**: R_f = 0.53 (EtOAc); IR(thin film) ν_{max}/cm^{-1}: 2928w, 2855m, 1651m, 1405m, 1339m, 1197m, 1144w, 1064w, 957w, 750w, 729w, 669w, 539w; δ_H (400 MHz; $CDCl_3$) 6.93 (1H, ddd, *J* = 16.7, 9.9, 0.5 Hz, $SO_2C\mathbf{H}CH_2$), 6.35 (1H, dt, *J* = 16.7, 0.6 Hz, $SO_2CHC\mathbf{H}H'$), 6.02 (1H, dt, *J* = 9.7, 0.8 Hz, $SO_2CHCH\mathbf{H'}$), 3.87–3.80 (2H, m, 2H, CH_2), 2.64 – 2.52 (m, 2H, CH_2), 1.75 – 1.67 (6H, m, 6H, 3 × CH_2); δ_C (101 MHz; $CDCl_3$) 175.9 (CO), 136.4 (SO_2CHCH_2), 128.9 (SO_2CHCH_2), 46.0 (CH_2), 38.6 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 22.9 (CH_2); HRMS (ESI): calcd. for $C_8H_{14}NO_3S$, 204.0689. Found: $[MH]^+$, 204.0691 (–1.3 ppm error), calcd. for $C_8H_{13}NNaO_3S$, 226.0508. Found: $[MNa]^+$, 226.0511 (–1.1 ppm error).

Synthesis of 6-(vinylsulfonamido)hexanoic acid – 389

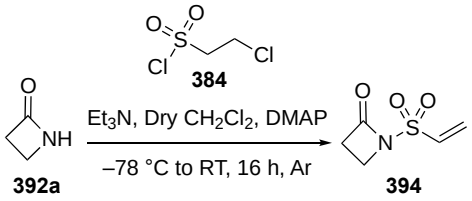


To a solution of methyl 6-aminocaproate hydrochloride **388** (14.7 g, 80.9 mmol) and Et_3N (90.3 mL, 647 mmol) in anhydrous CH_2Cl_2 (100 mL) at 0 °C, a solution of 2-chloroethanesulfonyl chloride **384** (12.7 mL, 121 mmol) in anhydrous CH_2Cl_2 (116 mL) was added dropwise over a period of 30 min. The resulting mixture was stirred at RT overnight under argon and the progress of the reaction was monitored by TLC. After a total of 18 h, the reaction was judged to be complete, based on TLC analysis. The resulting mixture was diluted with CH_2Cl_2 (100 mL), before was transferred to a separating funnel and the organic phase was washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 20 mL), sat. $NaHCO_{3\,(aq)}$ (3 × 20 mL) and sat. brine (3 × 20 mL). The resulting organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield 20.1 g of the crude product **388a** as a brown oil, which was directly used in the next reaction step without further purification. The crude product **388a** was dissolved in THF:H_2O (127 mL, 1:1 ratio) and to this mixture, LiOH (16.1 g, 382 mmol) was added at RT. The resulting pale yellow white suspension was stirred at RT overnight before being diluted with H_2O (100 mL). The diluted mixture was then acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (200 mL) and poured into a separating funnel. The resulting aqueous layer was extracted with CH_2Cl_2 (4 × 200 mL) before combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield an orange oil (19.7 g). The crude product was purified by flash

column chromatography (SiO_2, 70 mm column, eluent: EtOAc) affording the title compound **389** as a colourless viscous oil (11.1 g, 62%, over two steps); R_f = 0.17 (EtOAc); IR (neat) ν_{max}/cm^{-1}: 3274m, 2940m, 2869w, 2632w, 1706s, 1419m, 1386w, 1323w, 1253w, 1142w, 1086w, 969w, 884w, 829w, 733w, 658w, 548w, 491w; δ_H (400 MHz; $CDCl_3$) 9.09 (1H, s, O**H**), 6.56 – 6.44 (1H, m, SO_2C**H**=CH_2),6.26–6.17 (1H, m, SO_2CH=C**H**H'), 5.94 (1H, dt, *J* = 9.9, 1.1 Hz, SO_2CH=CH**H'**), 4.98 (1H, t, *J* = 6.0 Hz, N**H**), 3.04 – 2.94 (2H, m, CH_2), 2.34 (2H, t, *J* = 7.4 Hz, CH_2), 1.69 – 1.59 (2H, m, CH_2), 1.59 – 1.50 (2H, m, CH_2), 1.44 – 1.31 (m, 2H, CH_2); δ_C (101 MHz, $CDCl_3$) 179.4 (CO), 135.9 (CH_2), 126.8 (CH_2), 42.8 (CH_2), 33.8 (CH_2), 29.5 (CH_2), 25.9 (CH_2), 24.1(CH_2); HRMS (ESI): calcd. for $C_8H_{15}NNaO_4S$, 244.0614. Found: $[MNa]^+$, 244.0614 (–0.2 ppm error).

Lab notebook reference: ixz_577

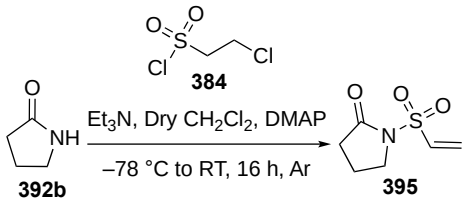
Synthesis of 1-(vinylsulfonyl)azetidin-2-one – 394



A stirring solution of 2-azetidinone **392a** (296 mg, 4.16 mmol), Et_3N (2.03 mL, 14.6 mmol) and DMAP (51.0 mg, 0.416 mmol) in anhydrous CH_2Cl_2 (25.0 mL) was cooled to –78 °C. To this was added a solution of 2-chloroethanesulfonyl chloride **384** (0.65 mL, 6.24 mmol) in anhydrous CH_2Cl_2 (17 mL) dropwise over a period of 1 hour. Under an argon atmosphere, this mixture was stirred at –40 °C for 1 h, then allowed to warm to RT and stirred for an additional 16 h. The reaction mixture was then diluted with Et_2O (40 mL) and filtered through Celite®, washing with Et_2O (3 × 20 mL). The resulting filtrate was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc) affording the title compound **394** as a colourless oil (359 mg, 54%); R_f = 0.47 (EtOAc); IR (thin film) ν_{max}/cm^{-1}: 3063w, 2983w, 1783w, 1612s, 1478m, 1467w, 1352w, 1294m, 1256w, 1207w, 1117w, 1063w, 1036w, 978w, 923m, 803m, 766m, 739m, 668w, 612w, 563w, 541w, 503w; δ_H (400 MHz, $CDCl_3$) 6.62 (1H, dd, *J* = 16.5, 9.9 Hz, SO_2C**H**CH_2), 6.33 (1H, dd, *J* = 16.5, 0.8 Hz, SO_2CHC**H**H'), 6.09 (1H, dd, *J* = 9.9, 0.8 Hz, SO_2CHCH**H'**), 3.59 (2H, t, *J* = 5.3 Hz, CH_2), 3.05 (2H, t, *J* = 5.3 Hz, CH_2); δ_C (101 MHz; $CDCl_3$) 164.1 (CO), 134.2 (CH), 130.2 (CH_2), 39.9 (CH_2), 37.0 (CH_2); HRMS (ESI): calcd. for $C_5H_7NNaO_3S$, 184.0039. Found: $[MNa]^+$, 184.0041 (–1.4 ppm error).

Lab notebook reference: ixz_528

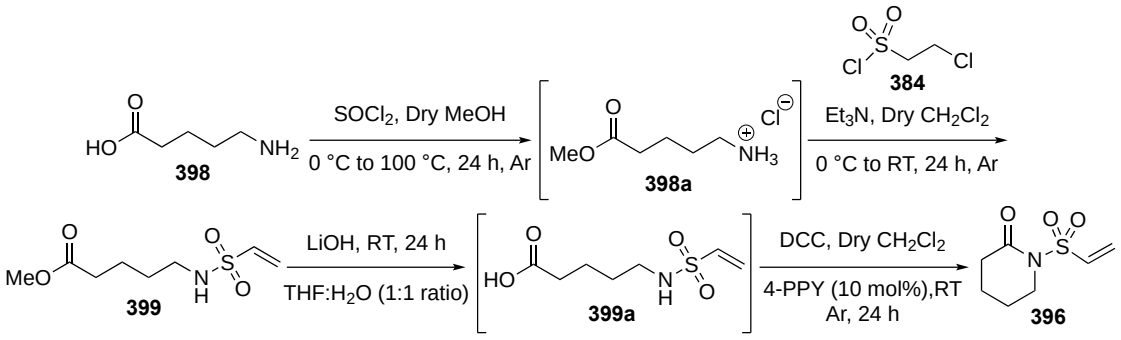
Synthesis of 1-(vinylsulfonyl)pyrrolidin-2-one – 395



A stirring solution of 2-pyrrolidinone **392b** (3.60 g, 42.3 mmol), Et_3N (59.0 mL, 423 mmol) and DMAP (517 mg, 4.23 mmol) in anhydrous CH_2Cl_2 (51.0 mL) was cooled to –78 °C. To this was added a solution of 2-chloroethanesulfonyl chloride **384** (15.0 mL, 148 mmol) in anhydrous CH_2Cl_2 (34 mL) dropwise over a period of 1 hour. Under an argon atmosphere this mixture was stirred at –78 °C for 1 hour, then allowed to warm to RT and stirred for additional 16 hours. The reaction mixture was then diluted with EtOAc (120 mL) and filtered through Celite®, washed with EtOAc (2 × 100 mL). The resulting filtrate was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc) affording the title compound **395** as a beige solid (2.59 g, 35%); R_f = 0.64 (EtOAc); melting point: 130 – 131 °C (from EtOAc:*n*–hexane); IR (solid state) ν_{max}/cm^{-1}: 3112w, 3068w, 2968w, 1720s, 1481s, 1461s, 1382w, 1346m, 1293m, 1259m, 1240m, 1212m, 1192m, 1151w, 1116w, 1077w, 1019w, 989w, 957w, 893w, 843w, 752w, 703w, 666w, 636w, 560w, 500w; δ_H (400 MHz; $CDCl_3$) 6.69 (1H, dd, *J* = 16.6, 9.9 Hz, $SO_2C\mathbf{H}{=}CH_2$), 6.32 (1H, dd, *J* = 16.6, 0.7 Hz, $SO_2CH{=}C\mathbf{H}H'$), 6.04 (1H, dd, *J* = 9.9, 0.7 Hz, $SO_2CH{=}CH\mathbf{H'}$), 3.70 (2H, t, *J* = 7.0 Hz, $CH_2C\mathbf{H_2}NSO_2$), 2.40 (2H, t, *J* = 8.0 Hz, $COC\mathbf{H_2}CH_2$), 2.01 (2H, tt, *J* = 8.0, 7.0 Hz, $COCH_2C\mathbf{H_2}$); δ_C (101 MHz; $CDCl_3$) 174.1 (CO), 133.7 (CH), 129.9 (CH_2), 46.6 (CH_2), 31.9 (CH_2), 18.0 (CH_2); HRMS (ESI): calcd. for $C_6H_{10}NO_3S$, 176.0376. Found: $[MH]^+$, 176.0376 (–0.3 ppm error), calcd. for $C_6H_9NNaO_3S$, 198.0195. Found: $[MNa]^+$, 198.0196 (–0.1 ppm error), calcd. for $C_6H_9KNO_3S$, 213.9935 Found: $[MK]^+$, 213.9936 (–0.6 ppm error).

Lab notebook reference: ixz_613

Synthesis of 1-(vinylsulfonyl)piperidin-2-one – 396



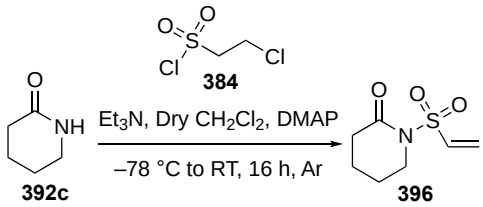
$SOCl_2$ (2.05 mL, 28.2 mL) was added dropwise over 15 min via syringe pump to a solution of methyl 5-aminopentanoic acid **398** (1.32 g, 11.3 mmol) in anhydrous MeOH (16.5 mL) at 0 °C. The pale yellow solution was stirred at 0 °C for 30 min, allowed to warm to RT and then heated at 100 °C for 24 hours. The reaction mixture was allowed to cool to RT and concentrated under reduced pressure to dryness to yield crude as off-white solid **398a** (2.51 g). The crude product was directly used in the next reaction step without further purification. 2-chloroethanesulfonyl chloride **384** (1.78 mL, 17.0 mmol) in anhydrous CH_2Cl_2 (17 mL) was added dropwise over a period of 30 min to a solution of the crude sample of **398a** (2.51 g) and Et_3N (12.6 mL, 90.4 mmol) in anhydrous CH_2Cl_2 (57 mL) at 0 °C. The resulting milky white suspension was stirred at 0 °C for 1 h, before being warmed to RT, with a colour change to a clear colourless solution noted. The resulting mixture was stirred at RT overnight under Ar and the progress of the reaction was monitored by TLC. After a total of 24 h, the reaction was judged to be complete, based on TLC analysis. The resulting mixture was diluted with CH_2Cl_2 (100 mL), before being transferred to a separating funnel and the organic phase was washed sequentially with 1.0 M $HCl_{(aq)}$ (3 × 20 mL), The resulting organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude as a yellow oil. The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 70:30) affording compound **396** (1.08 g, 43%, over two steps); R_f = 0.60 (70:30, EtOAc:*n*–hexane); IR (neat) ν_{max}/cm^{-1}: 3286w, 2953w, 2872w, 1732s, 1436s, 1385m, 1324m, 1201m, 1144m, 1081w, 1011w, 969w, 877w, 813w, 735w, 65w8, 548m, 498w; δ_H (400 MHz; $CDCl_3$) 6.38 (1H, dd, *J* = 16.5, 10.0 Hz, $SO_2C\mathbf{H}CH_2$), 6.02 (1H, d, *J* = 16.5 Hz, $SO_2CHC\mathbf{H}$–H'), 5.79 (1H, d, *J* = 10.1 Hz, SO_2CHCH–**H'**), 5.23 (1H, t, *J* = 6.0 Hz, NH), 3.48 (s, 3H, OCH_3), 2.82 (2H, app. q, *J* = 6.6 Hz, CH_2), 2.17 (2H, t, *J* = 7.3 Hz, CH_2), 1.56 – 1.46 (2H, m, CH_2), 1.46 – 1.35 (2H, m, CH_2); δ_C (101 MHz; $CDCl_3$) 173.7 (CO), 135.6 (CH), 126.2 (CH_2), 51.3 (CH_3), 42.3 (CH_2), 33.0 (CH_2), 28.8 (CH_2), 21.5 (CH_2); HRMS (ESI): calcd. for $C_8H_{15}NNaO_4S$, 244.0618. Found: $[MNa]^+$, 244.0614 (−1.8 ppm error), calcd. for $C_8H_{15}NKO_4S$, 260.0355. Found: $[MK]^+$, 260.0353 (−0.7 ppm error).

Lab notebook reference: ixz_596

LiOH (1.30 g, 29.2 mmol) was added to a solution of **399** (1.08 g) in THF:H_2O (24 mL, 1:1) at RT. The resulting pale yellow-white suspension was stirred at RT overnight before being diluted with H_2O (60 mL). The diluted mixture would then be acidified to pH 2.0 with 1.0 M $HCl_{(aq)}$ (50 mL) and poured into a separating funnel. The resulting aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) before combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield yellow viscous oil **399a**. The crude product was directly used in the next reaction step without further purification. Next, DCC (1.11 g, 5.36 mmol) was added to a solution of **399a** (854 mg) and 4-pyrrolidinopyridine (72.2 mg, 0.487 mmol) in anhydrous CH_2Cl_2 (49 mL). A colour change to a pale yellow was immediately noted and the reaction mixture was stirred at RT for 24 hours at RT before the reaction was deemed to have to complete by TLC, whilst a cloudy white suspension was observed. The reaction mixture was concentrated *in vacuo,* to approx. 15 mL and the resulting white solid (dicyclohexylurea) was filtered, and the filter cake was washed with CH_2Cl_2 (1 × 10 mL). The resulting filtrate was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 70:30) affording the title compound **399** as a pale yellow oil (605 mg, 66%); R_f = 0.50 (EtOAc); IR (thin film) ν_{max}/cm^{-1}; 2954w, 1973m, 1689s, 1481w, 1460m, 1387m, 1346m, 1284w, 1264w, 1146w, 1122w, 1075m, 971m, 923w, 889m, 830m, 744m, 701w, 675w, 646w, 55w3, 539w, 508w, 477w; δ_H (400 MHz; $CDCl_3$) 6.99 (1H, ddd, *J* = 16.8, 10.0, 0.8 Hz, $SO_2C\mathbf{H}CH_2$), 6.41 (1H, dd, *J* = 16.8, 0.8 Hz, $SO_2CHC\mathbf{H}H'$), 6.08 (1H, dd, *J* = 10.0, 0.8 Hz, $SO_2CHCH\mathbf{H'}$), 3.72 (2H, t, *J* = 5.9 Hz, CH_2), 2.50 (2H, t, *J* = 6.9 Hz, CH_2), 1.92 – 1.85 (2H, m, CH_2), 1.84 – 1.77 (2H, m, CH_2); δ_C (101 MHz; $CDCl_3$) 171.4 (CO), 136.0 (CH), 129.6 (CH_2), 46.4 (CH_2), 34.2 (CH_2), 23.3 (CH_2), 20.5 (CH_2); HRMS (ESI): calcd. for $C_7H_{12}NO_3S$, 190.0532. Found: $[MH]^+$, 190.0535 (–1.6 ppm error), calcd. for $C_7H_{11}NNaO_3S$, 212.0352. Found: $[MNa]^+$, 212.0350 (0.8 ppm error), calcd. for $C_7H_{11}KNO_3S$, 228.0091. Found: $[MK]^+$, 228.0094 (–1.3 ppm error).

Lab notebook reference: ixz_587

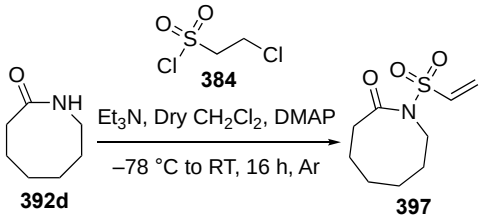
Compound **399** was also prepared by a second method via lactam *N*-sulfonylation:



Method 2: A stirring solution of piperidin-2-one **392c** (1.65 g, 13.7 mmol), Et_3N (23.0 mL, 165 mmol) and DMAP (167 mg, 1.37 mmol) in anhydrous CH_2Cl_2 (33.0 mL) was cooled to –78 °C. To this was added a solution of 2-chloroethanesulfonyl chloride **384** (6.11 mL, 58.1 mmol) in anhydrous CH_2Cl_2 (22.0 mL) dropwise over a period of 1 hour. Under an argon atmosphere this mixture was stirred at –78 °C for 1 hour, then allowed to warm to RT and stirred for additional 16 hours. The reaction mixture was then diluted with EtOAc (70 mL) and filtered through Celite®, washed with EtOAc (2 × 60 mL). The resulting filtrate was concentrated in *vacuo* and purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 70:30), affording the title compound **396** as a yellow oil (357 mg, 14%).

Lab notebook reference: ixz_602

Synthesis of 1-(vinylsulfonyl)azocan-2-one – 397

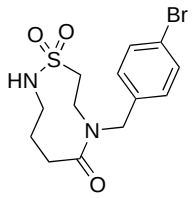


A solution of azocan-2-one **392d** (3.34 g, 26.3 mmol), Et_3N (28.0 mL, 224 mmol) and DMAP (321 mg, 2.63 mmol) in anhydrous CH_2Cl_2 (40.0 mL) was cooled to –78 °C. To this was added a solution of 2-chloroethanesulfonyl chloride **384** (9.62 mL, 92.2 mmol) in anhydrous CH_2Cl_2 (26.0 mL) dropwise over a period of 1 hour. Under an Ar atmosphere, this mixture was stirred at −78 °C for 1 h, then allowed to warm to RT and stirred for an additional 16 h. The reaction mixture was then diluted with EtOAc (80 mL) and filtered through Celite®, washed with EtOAc (3 × 60 mL). The resulting filtrate was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc) affording the title compound **397** as a colourless oil (597 mg, 10%); R_f = 0.54 (EtOAc); IR (neat) ν_{max}/cm^{-1}: 2929m, 2862m, 2257w, 1684s, 1474w, 1446w, 1376m, 1346m, 1312m, 1285w, 1241w, 1155m, 1116w, 1083m, 1028w, 994w, 965m, 914w, 892m, 877w, 837m, 814w, 711w, 741w, 668w, 648w, 612m, 574m, 546m, 498w; δ_H (400 MHz; $CDCl_3$) 7.00 (1H, ddd, *J* = 16.7, 9.9, 0.6 Hz, $SO_2C\mathbf{H}=CH_2$), 6.38 (1H, dd, *J* = 16.7, 0.6 Hz, $SO_2CH=C\mathbf{H}H'$), 6.05 (1H, dd, *J* = 9.9, 0.7 Hz, $SO_2CH=CH\mathbf{H'}$), 3.92 (2H, t, *J* = 5.8 Hz, CH_2), 2.58 – 2.50 (2H, m, CH_2), 1.87 – 1.77 (2H, m, CH_2), 1.75 – 1.67

(2H, m, CH_2), 1.59 – 1.52 (2H, m, CH_2), 1.50 – 1.42 (2H, m, CH_2); δ_C (101 MHz; $CDCl_3$) 176.2 (CO), 136.7 (CH), 129.3 (CH_2), 45.7 (CH_2), 36.2 (CH_2), 30.5 (CH_2), 28.7 (CH_2), 26.0 (CH_2), 23.6 (CH_2); HRMS (ESI): calcd. for $C_9H_{16}NO_3S$, 218.0845. Found: $[MH]^+$, 218.0849 (–1.5 ppm error), calcd. for $C_9H_{15}NNaO_3S$, 240.0665. Found: $[MNa]^+$, 240.0665 (–0.1 ppm error), calcd. for $C_9H_{15}KNO_3S$, 256.0404 Found: $[MK]^+$, 256.0405 (–0.3 ppm error).

Lab notebook reference: ixz_558

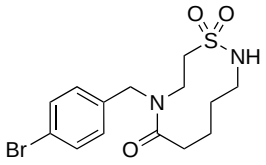
Synthesis of 7-(4-bromobenzyl)-1,2,7-thiadiazonan-6-one 1,1-dioxide – 401



To a solution of 1-(vinylsulfonyl)pyrrolidin-2-one **395** (345 mg, 1.97 mmol) and dry Et_3N (820 µL, 5.91 mmol) in anhydrous THF (3.94 mL), was added 4-bromobenzylamine (370 µL, 2.96 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at 66 °C, and then the solvent was removed in *vacuo* to yield the crude product as a pale yellow oil (456 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc) afforded the title compound **401** as a pale-yellow oil (413 mg, 58%); R_f = 0.36 (EtOAc); IR (neat) ν_{max}/cm^{-1}: 3265w, 2938w, 1619s, 1488s, 1460w, 1422s, 1403w, 1351w, 1321w, 1297m, 1243m, 1217m, 1175m, 1090m, 1046w, 1026w, 1012m, 930m, 903w, 878m, 795, 748, 724, 666, 636, 576, 536, 513, 481; δ_H (400 MHz; $CDCl_3$) 7.40 (2H, d, J = 8.4 Hz, BrC=C**H**CH), 7.06 (2H, d, J = 8.4 Hz, BrC=CHC**H**), 5.43 (1H, t, J = 6.5 Hz, SO_2NH), 4.51 (2H, s, br, 2H, CH_2), 3.75 (2H, s, br, CH_2), 3.44 – 3.35 (2H, m, CH_2), 3.19 – 3.12 (2H, m, CH_2), 2.56 – 2.48 (2H, m, CH_2), 1.99 – 1.90 (2H, m, CH_2); δ_C (101 MHz, $CDCl_3$) 175.2 (CO), 135.6 (C), 131.9 (CH), 129.8 (CH), 121.6 (C), 50.7 (CH_2), 47.3 (CH_2), 43.0 (CH_2), 42.4 (CH_2), 29.7 (CH_2), 27.5 (CH_2); HRMS (ESI): calcd. for $C_{13}H_{17}{}^{79}BrN_2NaO_3S$, 383.0035. Found: $[MNa]^+$, 383.0036 (0.0 ppm error), calcd. for $C_{13}H_{17}{}^{79}BrKN_2O_3S$, 398.9775 Found: $[MK]^+$, 398.9774 (0.2 ppm error).

Lab notebook reference: ixz_614

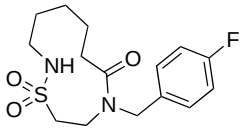
Synthesis of 8-(4-bromobenzyl)-1,2,8-thiadiazecan-7-one 1,1-dioxide 9 – 402



To a solution of 1-(vinylsulfonyl)piperidin-2-one **396** (357 mg, 1.89 mmol) and dry Et_3N (790 µL, 5.67 mmol) in anhydrous THF (3.78 mL), was added 4-bromobenzylamine (360 µL, 2.84 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at 66 °C, and then the solvent was removed in *vacuo* to afford the crude product as a brown oil (503 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 70:30) afforded the title compound **402** as a colourless oil (410 mg, 61%): In solution in $CDCl_3$, this compound exists as a roughly 2:1 mixture of rotamers based on the ^{13}C NMR data; R_f = 0.29 (70:30, EtOAc:*n*–hexane); IR (neat) ν_{max}/cm^{-1}: 3226w, 2936m, 1623s, 1488w, 1454m, 1405m, 1362m, 1320w, 1291w, 1215w, 1177m, 1150m, 1133m, 1100m, 1069m, 1010m, 963w, 925w, 909w, 890w, 818w, 796w, 747w, 666w, 647w, 573w, 550w, 522w, 482w; δ_H (400 MHz; $CDCl_3$) 7.50 – 7.37 (2H, m, BrC=C**H**CH, both rotamers), 7.12 – 6.97 (2H, m, BrC=CHC**H**, both rotamers) [5.14 – 5.00 (m), 4.99 – 4.84 (m), 4.72 – 4.46 (m), 4.41 – 4.28 (m), 4.23 – 4.04 (m), 3.97 – 3.51 (m), 3.35 – 3.26 (m), 3.22 – 3.10 (m), 3.13 – 3.01 (m), 3.01 – 2.88 (m), 2.77 – 2.61 (m), 2.36. – 2.19 (m), 2.15 – 2.01 (m), 2.00 – 1.79 (m), 1.67 – 1.46 (m) 15H (7 × CH_2 + NH). Note, due to the ^1H NMR spectrum suffering from severe rotameric broadening, the ^1H NMR signals in this region could not be confidently assigned. The ^{13}C NMR data proved to be much more informative in confirming the assigned structure]; δ_C (101 MHz; $CDCl_3$) 175.8 (CO, minor rotamer), 174.1 (CO, major rotamer), 136.2 (CCH_2NCO, major rotamer), 135.6 ($ArCCH_2NCO$, minor rotamer), 132.2 (CH, minor rotamer), 132.1 (CH, major rotamer), 129.8 (CH, major rotamer), 128.8 (CH, minor rotamer), 122.0 (C, major rotamer), 121.7 (C, major rotamer), 53.8 (CH_2, major rotamer), 51.7 (CH_2, major rotamer), 47.7 (CH_2, major rotamer), 45.1 (CH_2, minor rotamer), 43.0 (CH_2, minor rotamer), 42.2 (CH_2, major rotamer), 42.0 (CH_2, minor rotamer), 40.8 (CH_2, minor rotamer), 33.4 (CH_2, minor rotamer), 28.5 (CH_2, major rotamer), 27.4 (CH_2, minor rotamer), 25.8 (CH_2, major rotamer), 24.1 (CH_2, major rotamer), 23.5 (CH_2, minor rotamer); HRMS (ESI): calcd. for $C_{14}H_{19}{}^{79}BrN_2NaO_3S$, 397.0192. Found: $[MNa]^+$, 397.0192 (0.0 ppm error).

Lab notebook reference: ixz_603

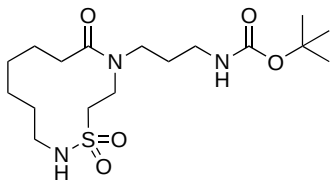
Synthesis of 9-(4-fluorobenzyl)-1-thia-2,9-diazacycloundecan-8-one 1,1-dioxide – 403



To a solution of 1-(vinylsulfonyl)azepan-2-one **387** (429 mg, 2.11 mmol) and dry Et_3N (880 µL, 6.33 mmol) in anhydrous THF (4.20 mL), was added 4-fluorobenzylamine (290 µL, 2.53 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at 66 °C and then the solvent was removed in *vacuo* to afford the crude product as brown solid (657 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc:CH_2Cl_2, 40:60) afforded the title compound **403** as a white solid (650 mg, 94%): In solution in $CDCl_3$, this compound exists as a roughly 3:2 mixture of rotamers; R_f = 0.45 (EtOAc); melting point: 180 – 181 °C (from EtOAc:*n*–hexane); IR (solid state) ν_{max}/cm^{-1}: 3238w, 2940m, 1614s, 1508w, 1323m, 1225w, 1130w, 1095m, 923w, 815w, 725w, 520w, 493w, 464w; δ_H (400 MHz; $(CD_3)_2SO$) 7.38 – 6.82 (5H, m, Ar-CH + SO_2NH, both rotamers), 5.13 – 3.98 (2H, m, Ar-CH_2N, both rotamers), 3.65 – 2.72 (6H, m, 3 × CH_2, both rotamers), 2.54 – 1.21 (8H, m, 4 × CH_2, both rotamers); δ_C (101 MHz; $(CD_3)_2SO$) for major rotamer: 174.2 (CO), 161.6 (Ar-C, d, $^1J_{CF}$ = 243.3 Hz), 133.6 (Ar-CH, d, $^4J_{CF}$ = 2.2 Hz), 128.8 (Ar-CH, d, $^3J_{CF}$ = 8.2 Hz), 115.6 (Ar-CH, d, $^2J_{CF}$ = 21.4 Hz), 52.4 (CH_2), 48.6 (CH_2), 41.9 (CH_2), 41.4 (CH_2), 33.4 (CH_2), 27.3 (CH_2), 23.4 (CH_2), 23.0 (CH_2); data for minor rotamer: 173.0 (CO), 161.4 (d, $^1J_{CF}$ = 241.5 Hz, Ar-C), 134.0 (d, $^4J_{CF}$ = 1.9 Hz, Ar-CH), 129.8 (d, $^3J_{CF}$ = 8.0 Hz, Ar-CH), 115.2 (d, $^2J_{CF}$ = 21.2 Hz, Ar-CH), 50.3 (CH_2), 46.2 (CH_2), 41.7 (CH_2), 40.1 (CH_2), 31.6 (CH_2), 25.7 (CH_2), 23.9 (CH_2), 22.7 (CH_2); δ_F (376 MHz, $(CD_3)_2SO$) –115.1 (s, Ar-F, major rotamer), –115.6 (s, Ar-F, minor rotamer); HRMS (ESI): calcd. for $C_{15}H_{21}FN_2NaO_3S$, 351.1149. Found: $[MNa]^+$, 351.1148 (0.2 ppm error), calcd. for $C_{15}H_{21}FN_2KO_3S$, 367.0888. Found: $[MK]^+$, 367.0885 (0.9 ppm error); X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2215454, was crystallised by slow evaporation of MeCN).

Lab notebook reference: ixz_500

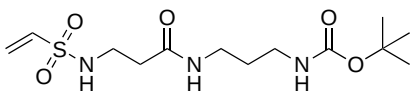
Synthesis of *tert*-Butyl (3-(1,1-dioxido-9-oxo-1-thia-2,10-diazacyclododecan-10-yl)propyl)carbamate – 404



To a solution of 1-(vinylsulfonyl)azocan-2-one **397** (83.1 mg, 0.383 mmol) and dry Et_3N (160 µL, 1.15 mmol) in anhydrous THF (0.77 mL), was added *N*-boc-1,3-diaminopropane (81.0 µL, 0.460 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at 66 °C and then the solvent was removed in *vacuo* to afford the crude product as a pale yellow oil (325 mg). The crude product was purified by flash column chromatography (SiO_2, 20 mm column, eluent: EtOAc) afforded the title compound **404**, initially as a colourless oil, but upon standing it formed a white solid) (149 mg, 99%): In solution in $(CD_3)_2SO$, this compound exists as a ≈1:1 mixture of rotamers; R_f = 0.27 (EtOAc); IR (neat) ν_{max}/cm^{-1}: 3409w, 3240w, 2935m, 1706s, 1684s, 1614s, 1512w, 1366m, 1247m, 1134m, 917w, 729w, 533w; δ_H (400 MHz; $(CD_3)_2SO$) 7.45 (1H, t, *J* = 5.6 Hz, SO_2NH, one rotamer), 6.86 (1H, t, *J* = 5.0 Hz, 1H, SO_2NH, one rotamer), 6.82 – 6.71 (2H, m, NHCOO, both rotamers), 4.13 – 3.50 (5H, m, CH_2 from both rotamers), 3.29 – 2.98 (6H, m, CH_2 from both rotamers), 2.97 – 2.78 (7H, m, CH_2 from both rotamers), 2.70 – 2.46 (4H, m, CH_2 from both rotamers), 1.97 – 1.80 (2H, m, CH_2 from both rotamers), 1.72 – 1.43 (13H, m, CH_2 from both rotamers), 1.37 (18H, s, 3 × CH_3, both rotamers), 1.35 – 1.11 (7H, m, CH_2 from both rotamers); δ_C (101 MHz, $(CD_3)_2SO$) 172.8 (CO, both rotamers), 155.7 and 155.6 (COO), 77.6 and 77.5 (C), 52.0 (CH_2, both rotamers), 48.3 (CH_2, both rotamers), 43.2 and 43.0 (CH_2), 42.4 and 41.1 (CH_2), 37.7 and 37.4 (CH_2), 29.8 and 29.2 (CH_2), 28.5 and 27.5 (CH_2), 28.3 (3 × CH_3, both rotamers), 25.9 and 25.9 (CH_2), 25.2 and 23.9 (CH_2), 23.7 and 23.3 (CH_2), 21.8 and 21.3 (CH_2); HRMS (ESI): calcd. for $C_{17}H_{33}N_3NaO_5S$, 414.2033. Found: $[MNa]^+$, 414.2044 (−2.7 ppm error),calcd. for $C_{17}H_{33}N_3KO_5S$, 430.1773. Found: $[MK]^+$, 430.1771 (0.3 ppm error).

Lab notebook reference: ixz_560

Synthesis of 3-((*tert*-butoxycarbonyl)amino)propyl 3-((vinylsulfonyl)oxy)propanoate – 406

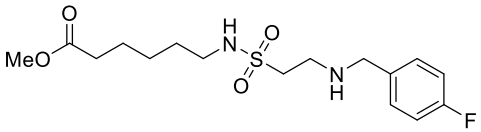


To a solution of 1-(vinylsulfonyl)azetidin-2-one **394** (192 mg, 1.19 mmol) and dry Et_3N (500 µL, 3.60 mmol) in anhydrous THF (2.38 mL), was added *N*-boc-1,3-propanediamine **405** (250 µL, 1.43 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at 66 °C

and then the solvent was removed in *vacuo* to afford crude product as yellow oil (345 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:MeOH, 90:10) afforded the title compound **406** as a pale yellow oil (358 mg, 90%). In solution in $CDCl_3$, this compound exists as a roughly 2:1 mixture of rotamers; R_f = 0.16 (EtOAc); IR (neat) ν_{max}/cm^{-1}; 3316w, 2979w, 2943w, 2888m, 2255m, 1689s, 1645m, 1516m, 1442m, 1392w, 1367w, 1326w, 1275w, 1251w, 1140w, 969w, 911m, 728m, 647m, 547w, 466m; δ_H (400 MHz; $CDCl_3$) 6.75 (1H, t, *J* = 6.0 Hz, N**H**, major rotamer), 6.51 (2H, dd, *J* = 16.6, 10.0 Hz, CH, both rotamer), 6.19 (2H, d, *J* = 16.6 Hz, SO_2CHC**H**H', both rotamer), 6.01 – 5.98 (m, 1H, N**H**, minor rotamer), 5.95 – 5.87 (2H, m, 2H, SO_2CHCH**H',** both rotamers), 5.33 (1H, t, *J* = 6.2 Hz, 1H, NH, minor rotamer), 5.06 (1H, t, *J* = 6.4 Hz, 1H, NH, major rotamer), 3.43 – 3.04 (14H, m, CH_2 and NH both rotamers), 2.45 (4H, t, *J* = 6.0 Hz, CH_2, both rotamers), 1.72 – 1.55 (4H, m, CH_2, both rotamers), 1.39 (18H, s, CH_3, both rotamers); δ_C (101 MHz; $CDCl_3$) 173.3 (CO, minor rotamer), 171.5 (CO, major rotamer), 156.8 (CO, major rotamer), 156.3 (CO, minor rotamer), 135.9 (CH, both rotamers), 126.7 (CH_2, both rotamers), 79.5 ($C(CH_3)_3$, major rotamer), 79.4 ($C(CH_3)_3$, minor rotamer), 55.0 (CH_2, one rotamer), 44.3 (CH_2, one rotamer), 43.9 (CH_2, one rotamer), 40.2 (CH_2, one rotamer), 39.4 (CH_2, one rotamer), 37.5 (CH_2, one rotamer), 37.2 (CH_2, one rotamer), 36.1 (CH_2, one rotamer), 36.1 (CH_2, one rotamer), 34.0 (CH_2, one rotamer), 29.9 (CH_2, one rotamers) 28.5 (CH_3, minor rotamer), 28.5 (CH_3, major rotamer); 28.2 (CH_2, one rotamer); HRMS (ESI): calcd. for $C_{13}H_{25}N_3NaO_5S$, 358.1407. Found: $[MNa]^+$, 358.1407 (0.0 ppm error), calcd. for $C_{13}H_{25}KN_3O_5S$, 374.1146 Found: $[MK]^+$, 374.1153 (–1.6 ppm error).

Lab notebook reference: ixz_513

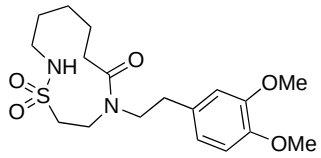
Synthesis of methyl 6-((2-((4-fluorobenzyl)amino)ethyl)sulfonamido)hexanoate – 408



To a solution of 1-(vinylsulfonyl)azepan-2-one **387** (188 mg, 0.923 mmol) and dry Et_3N (386 µL, 2.77 mmol) in anhydrous MeOH (1.85 mL), was added 4-fluorobenzylamine (339 mg, 2.75 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at 66 °C and then the solvent was removed in *vacuo* to afford the crude product as yellow oil (345 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc) afforded the title compound **408** as a pale yellow oil (279 mg, 84%); R_f = 0.13 (EtOAc); IR (neat) ν_{max}/cm^{-1}: 3295w, 2940w, 2863w, 1731s, 1603s, 1509s, 1437m, 1364w, 1319w, 1219w, 1139w, 1093m, 1015s, 981w, 823m, 756w, 636w, 581w, 549w, 501w; δ_H (400 MHz; $CDCl_3$) 7.25 – 7.18 (2H, m, Ar-CH), 7.02 – 6.87 (2H, m, 2H, Ar-CH), 5.18 (1H, s, br, SO_2NH),

3.70 (2H, s, Ar-CH_2N), 3.60 (3H, s, $COCH_3$), 3.17 – 3.09 (2H, m, CH_2), 3.05 – 2.96 (4H, m, CH_2), 2.24 (2H, t, J = 7.4 Hz, CH_2), 1.61 – 1.51 (2H, m, CH_2), 1.51 – 1.42 (2H, m, CH_2), 1.34 – 1.24 (2H, m, CH_2); δ_C (101 MHz; $CDCl_3$) 174.0 (CO), 162.0 (d, $^1J_{CF}$ = 244.9 Hz, CF), 135.2 (d, $^4J_{CF}$ = 3.2 Hz, C), 129.6 (d, $^3J_{CF}$ = 8.1 Hz, 2 × CH), 115.3 (d, $^2J_{CF}$ = 21.3 Hz, 2 × CH), 52.7 (CH_2), 51.5 (CH_2 + CH_3, overlapping peaks), 43.4 (CH_2), 42.8 (CH_2), 33.7 (CH_2), 29.8 (CH_2), 26.0 (CH_2), 24.3 (CH_2); δ_F (376 MHz, $CDCl_3$) –115.4 (s, Ar-F); HRMS (ESI): calcd. for $C_{16}H_{26}FN_2O_4S$, 361.1592 Found: $[MH]^+$, 361.1592 (−0.2 ppm error), calcd. for $C_{16}H_{25}FN_2NaO_4S$, 383.1411 Found: $[MNa]^+$, 383.1409 (0.5 ppm error), calcd. For $C_{16}H_{25}FKN_2O_4S$, 399.1151 Found: $[MK]^+$, 399.1155 (−1.2 ppm error).

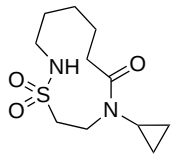
Synthesis of 9-(3,4-dimethoxyphenethyl)-1-thia-2,9-diazacycloundecan-8-one1,1-dioxide – 410



To a solution of 1-(vinylsulfonyl)azepan-2-one **387** (138 mg, 0.676 mmol) and dry Et_3N (280 µL, 2.03 mmol) in anhydrous THF (1.35 mL), was added 3,4-dimethoxyphenethylamine (147 mg, 0.811 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at 66 °C, and then the solvent was removed in *vacuo* to afford the crude product as a yellow oil (245 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane,70:30) afforded the title compound as a colourless oil (270 mg, 71%); R_f = 0.31 (EtOAc); IR (neat) ν_{max}/cm^{-1}: 3240w, 2935m, 1613s, 1515s, 1424s, 1419w, 1305m, 1261m, 1236m, 1130m, 1025m, 730w, 699w, 476w; δ_H (400 MHz; $CDCl_3$) 6.79 (1H, d, J = 8.1 Hz, Ar-CH), 6.65 (1H, dd, J = 8.1, 2.0 Hz, Ar-CH), 6.60 (1H, d, J = 2.0 Hz, Ar-CH), 4.65 (1H, dd, J = 7.6, 4.4 Hz, SO_2NH), 4.33 (1H, ddd, J = 14.4, 4.9, 2.3 Hz, C**H**$_2$), 3.85 (3H, s, **CH$_3$**), 3.84 (3H, s, C**H$_3$**), 3.75 (1H, ddd, J = 15.4, 10.3, 2.6 Hz, C**H**$_2$), 3.54 (1H, dt, J = 14.5, 6.4 Hz, C**H**$_2$), 3.21 – 3.10 (2H, m, CH_2), 3.04 (1H, ddd, J = 15.5, 5.3, 1.9 Hz, C**H**$_2$), 2.97 – 2.83 (1H, m, C**H**$_2$), 2.83 – 2.68 (2H, m, 2H, 2 × C**H**$_2$), 2.32 (1H, ddd, J = 12.9, 8.0, 3.3 Hz, C**H**$_2$), 1.88 (1H, ddd, J = 13.2, 9.3, 3.9 Hz, C**H**$_2$), 1.77 – 1.35 (7H, m, C**H**$_2$); δ_C (101 MHz; $CDCl_3$) 175.3 (CO), 149.2 (C), 148.1 (C), 130.1 (C), 121.0 (CH), 112.1 (CH), 111.6 (CH), 56.1 (CH_3), 56.0 (CH_3), 52.1 (CH_2), 48.6 (CH_2), 42.5 (CH_2), 41.9 (CH_2), 35.1 (CH_2), 33.5 (CH_2), 27.8 (CH_2), 23.6 (CH_2), 22.7 (CH_2); HRMS (ESI): calcd. for $C_{18}H_{29}N_2O_5S$, 385.1792 Found: $[MH]^+$, 385.1800 (–2.1 ppm error). calcd. for $C_{18}H_{28}N_2NaO_5S$, 407.1611. Found: $[MNa]^+$, 407.1616 (–1.1 ppm error). calcd. for $C_{18}H_{28}KN_2O_5S$, 423.1351. Found: $[MK]^+$, 423.1356 (–1.2 ppm error).

Lab notebook reference: ixz_489

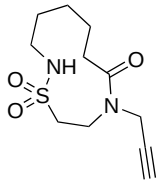
Synthesis of 9-cyclopropyl-1-thia-2,9-diazacycloundecan-8-one 1,1-dioxide – 411



To a solution of 1-(vinylsulfonyl)azepan-2-one **387** (169 mg, 0.830 mmol) and dry Et_3N (340 µL, 2.41 mmol) in anhydrous THF (1.60 mL), was added cyclopropylamine (83.0 µL, 1.20 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at 66 °C, and then the solvent was removed in *vacuo* to afford the crude product as a yellow oil (345 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc) afforded the title compound **411** as a pale-yellow oil (160 mg, 77%); R_f = 0.35 (EtOAc); melting point: 181 – 182 °C; IR (thin film) ν_{max}/cm^{-1}: 3261w, 2936w, 2877w, 2255m, 1622s, 1453w, 1416m, 1372w, 1317w, 1301w, 1245w, 1155w, 113w4, 1045w, 995w, 909w, 793w, 725w, 647m, 574m, 532m, 482m; δ_H (400 MHz, $(CD_3)_2SO$) 6.95 – 6.88 (1H, m, NH), 4.16 – 4.06 (1H, m, C**H**$_2$), 3.59 – 3.47 (1H, m, C**H**$_2$), 3.26 –3.06 (3H, m, CH_2 + NCH), 3.03 – 2.89 (2H, m, C**H$_2$**), 2.89 – 2.77 (1H, m, C**H**$_2$), 2.01 – 1.91 (1H, m, C**H**$_2$), 1.78 – 1.57 (2H, m, C**H$_2$**), 1.53 – 1.31 (3H, m, C**H**$_2$ + C**H$_2$**), 1.07 – 0.95 (1H, m, C**H**$_2$), 0.80 – 0.64 (4H, m, C**H**$_2$); δ_C (101 MHz;$(CD_3)_2SO$) 176.1 (CO), 49.2 (CH_2), 43.4 (CH_2), 42.0 (CH_2), 34.8 (CH_2), 31.6 (CH), 27.6 (CH_2), 24.3 (CH_2), 23.7(CH_2), 12.6 (CH_2), 7.8 (CH_2); HRMS (ESI):calcd. for $C_{11}H_{20}N_2NaO_3S$, 283.1087 Found: $[MNa]^+$, 283.1088 (–0.3 ppm error), calcd. for $C_{11}H_{20}KN_2O_3S$, 299.0826 Found: $[MK]^+$, 299.0824 (0.7 ppm error).

Lab notebook reference: ixz_605

Synthesis of 9-(prop-2-yn-1-yl)-1-thia-2,9-diazacycloundecan-8-one 1,1-dioxide – 412

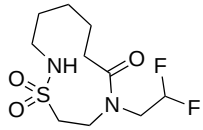


To a solution of 1-(vinylsulfonyl)azepan-2-one **387** (169 mg, 0.830 mmol) and dry Et_3N (350 µL, 2.50 mmol) in anhydrous THF (1.66 mL), was added propargylamine (63.0 µL, 0.996 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at 66 °C, and then the solvent was removed in *vacuo* to afford the crude product as a pale yellow oil (325 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:CH_2Cl_2, 40:60) afforded the title compound **412** as a colourless oil (211 mg, 98%). In solution in $(CD_3)_2SO$, this compound exists as a roughly 1:1 mixture of rotamers; R_f = 0.48 (EtOAc); IR (neat) ν_{max}/cm^{-1}: 3266w, 2939w, 2257w, 1626s, 1465s, 1421s, 1304s, 1133w,

1085m, 908w, 725w, 647w, 527,w 480w; δ_H (400 MHz; $(CD_3)_2SO$) 7.04 (1H, s, br, NH, one rotamer), 6.68 (1H, s, br, N**H**, one rotamer), 4.55 (1H, d, *J* = 18.4 Hz, C**H**$_2$, one rotamer), 4.19 – 4.09 (4H, m, both rotamers), 3.78 (2H, t, *J* = 6.2 Hz, C**H$_2$**, one rotamer), 3.51 – 3.37 (4H, m, both rotamers), 3.26 – 3.13 (3H, m, both rotamers), 3.12 (1H, s, C≡C**H**, one rotamer), 3.05 – 2.97 (2H, m, CH_2, one rotamer) 2.97 – 2.88 (2H, m,), 2.85 – 2.72 (2H, m, CH_2), 2.41 (2H, t, *J* = 6.6 Hz, CH_2, one rotamer), 2.03 – 1.88 (1H, m, C**H**$_2$, one rotamer), 1.67 – 1.57 (3H, m), 1.56 – 1.45 (2H, m, CH_2, one rotamer), 1.44 – 1.38 (5H, m); δ_C (101 MHz; $(CD_3)_2SO$) 174.0 and 172.4 (CO, both rotamers), 80.0 and 79.4 (CH, both rotamers), 75.3 and 74.0 (CH_2, both rotamers), 50.2 and 48.7 (CH_2, both rotamers), 41.8 (CH_2, both rotamers, overlapping peaks), 41.1 and 31.2 (CH_2, both rotamers), 40.1 (CH_2, both rotamers), 33.4 and 33.3 (CH_2, both rotamers), 27.1 and 25.8 (CH_2, both rotamers), 23.6 and 23.1 (CH_2, both rotamers), 22.8 and 22.7 (CH_2, both rotamers); HRMS (ESI): calcd. For $C_{11}H_{19}N_2O_3S$, 259.1111. Found: $[MH]^+$, 259.1110 (0.5 ppm error), calcd. For $C_{11}H_{18}N_2NaO_3S$, 281.0930 Found: $[Mna]^+$, 281.0931 (–0.3 ppm error), calcd. For $C_{11}H_{18}KN_2O_3S$, 297.0670 Found: $[MK]^+$, 297.0670 (–0.1 ppm error).

Lab notebook reference: ixz_504

Synthesis of 9-(2,2-difluoroethyl)-1-thia-2,9-diazacycloundecan-8-one 1,1-dioxide – 413

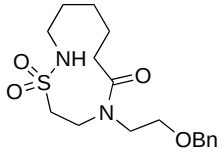


To a solution of 1-(vinylsulfonyl)azepan-2-one **387** (183 mg, 0.899 mmol) and dry Et_3N (380 µL, 2.70 mmol) in anhydrous THF (1.80 mL), was added 2,2-difluoroethylamine (90.0 µL, 1.35 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at 66 °C, and then the solvent was removed in *vacuo* to afford the crude product as a pale-yellow oil (289 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc) afforded the title compound **413** as a pale-yellow oil (170 mg, 66%); R_f = 0.35 (EtOAc); IR (neat) ν_{max}/cm^{-1}: 3346w, 2938w, 2863w, 225w6, 1733s, 1692s, 1464s, 1436w, 1350m, 1339m, 1308m, 1253m, 1183m, 1153m, 1120w, 1080w, 1045w, 959w, 911w, 880m, 841w, 769w, 728w, 648w, 629m, 554w, 509; δ_H (400 MHz; $CDCl_3$) 5.79 (1H, tt, *J* = 55.9, 4.0 Hz, NCH_2CHF_2), 3.88 – 3.82 (2H, m, C**H**$_2$), 3.67 (2H, t, *J* = 6.5, 6.0 Hz, C**H**$_2$), 3.12 (2H, t, *J* = 6.2 Hz, C**H$_2$**), 2.95 (2H, td, *J* = 15.3, 4.0 Hz, NC**H$_2$**CHF_2), 2.67 – 2.60 (2H, m, C**H$_2$**), 1.83 – 1.71 (6H, m, 3 × C**H$_2$**), 1.67 (1H, s, br, 1H, N**H**); δ_C (101 MHz; $CDCl_3$) 176.7 (**C**O), 115.8 (NCH_2**C**HF_2, $^1J_{CF}$ = 240.8 Hz), 54.2 (**C**H_2), 51.0 (N**C**H_2CHF_2, $^2J_{CF}$ = 24.2 Hz), 46.2 (**C**H_2), 43.8 (**C**H_2), 39.0 (**C**H_2), 29.5 (**C**H_2), 29.3 (**C**H_2), 23.1 (**C**H_2); δ_F (376 MHz; $CDCl_3$), –121.8 (dt, *J* = 55.9, 15.3 Hz, NCH_2CH**F**$_2$); HRMS (ESI): calcd. for $C_{10}H_{19}F_2N_2O_3S$, 285.1079 Found: $[MH]^+$, 285.1081 (–0.8 ppm error), calcd. for $C_{10}H_{18}F_2N_2NaO_3S$, 307.0898 Found: $[MNa]^+$, 307.0899

(–0.1 ppm error), calcd. for $C_{10}H_{18}F_2KN_2O_3S$, 323.0638 Found: $[MK]^+$, 323.0640 (–0.8 ppm error).

Lab notebook reference: ixz_606

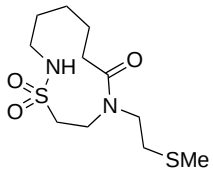
Synthesis of 9-(2-(1,3-Dioxolan-2-yl)ethyl)-1-thia-2,9-diazacycloundecan-8-one 1,1-dioxide – 414



To a solution of 1-(vinylsulfonyl)azepan-2-one **387** (136 mg, 0.670 mmol) and dry Et_3N (281 µL, 2.01 mmol) in anhydrous THF (1.34 mL), was added 2-(benzyloxy)-1-ethanamine (159 mg, 1.01 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at 66 °C, and then the solvent was removed in *vacuo* to afford the crude product as a yellow oil (356 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc) afforded the title compound **414** as a pale-yellow oil (178 mg, 75%). In solution in $CDCl_3$, this compound exists as a ≈ 15:1, mixture of rotamers, most clearly seen in the ^{13}C NMR data; R_f = 0.34 (EtOAc); IR (neat) ν_{max}/cm^{-1}: 3240w, 2934w, 2867w, 1734s, 1619s, 1455s, 1425s, 1361w, 1306w, 1266w, 1244m, 1207m, 1150m, 113m4, 1095m, 1046m, 1028m, 999m, 914m, 875w, 793m, 729m, 698m, 646w, 607w, 575w, 526w, 479w; δ_H (400 MHz; $CDCl_3$) ^1H NMR data for major rotamer only: 7.33 – 7.20 (5H, m, 5 × PhC**H**), 5.43 – 5.36 (1H, m, N**H**), 4.48 (2H, dd, *J* = 35.8, 11.4 Hz, C**H₂**), 4.23 – 4.13 (1H, m, C**H**$_2$), 3.91 – 3.82 (1H, m, C**H**$_2$), 3.82 – 3.74 (1H, m, C**H**$_2$), 3.74 – 3.62 (1H, m, C**H**$_2$), 3.55 – 3.46 (2H, m, C**H₂**), 3.25 – 3.12 (1H, m, C**H**$_2$), 3.20 – 3.00 (1H, m, C**H**$_2$), 3.00 – 2.94 (1H, m, C**H**$_2$), 2.86 – 2.66 (1H, m, C**H**$_2$), 2.12 – 2.01 (1H, m, C**H**$_2$), 1.76 – 1.53 (2H, m, C**H₂**), 1.53 – 1.36 (2H, m, C**H₂**), 1.36 – 1.18 (2H, m, C**H₂**); δ_C (101 MHz, $CDCl_3$) 176.3 (CO), 137.0 (OCH_2CPh), 128.4 (2 × PhCH), 128.2 (2 × PhCH), 128.0 (PhCH), 73.4 (CH_2), 67.3 (CH_2), 50.1 (CH_2), 48.0 (CH_2), 42.8 (CH_2), 41.9 (CH_2), 34.0 (CH_2), 27.5 (CH_2), 23.5 (CH_2), 23.0 (CH_2); HRMS (ESI): calcd. for $C_{17}H_{27}N_2O_4S$, 355.1686 Found: $[MH]^+$, 355.1694 (–2.2 ppm error), calcd. for $C_{17}H_{26}N_2NaO_4S$, 377.1505 Found: $[MNa]^+$, 377.1507 (–0.5 ppm error), calcd. for $C_{17}H_{26}KN_2O_4S$, 393.1245 Found: $[MK]^+$, 393.1246 (–0.2 ppm error).Characteristic NMR data for the minor rotamer can be seen at: δ_H (400 MHz; $CDCl_3$) 4.27 – 4.19 (1H, m, C**H**$_2$), 2.98 – 2.91 (1H, m, C**H**$_2$), 2.44 – 2.37 (1H, m, C**H**$_2$), 2.20 – 2.13 (1H, m, C**H**$_2$), 2.04 – 1.99 (1H, m, C**H**$_2$), 1.82 – 1.75 (2H, m, 2 × C**H**$_2$); δ_C (101 MHz; $CDCl_3$) 174.1 (CO), 137.6 (OCH_2CP), 128.8 (PhCH), 128.2 (PhCH), 127.9 (PhCH), 127.8 (PhCH), 125.1 (PhCH), 81.8 (CH_2), 73.2 (CH_2), 68.2 (CH_2), 51.8 (CH_2), 47.7 (CH_2), 44.7 (CH_2), 40.6 (CH_2), 31.0 (CH_2), 26.6 (CH_2), 24.1 (CH_2), 23.0 (CH_2).

Lab notebook reference: ixz_604

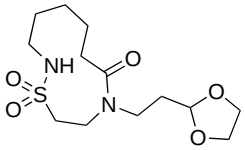
Synthesis of 9-(2-(methylthio)ethyl)-1-thia-2,9-diazacycloundecan-8-one 1,1-dioxide – 415



To a solution of 1-(vinylsulfonyl)azepan-2-one **387** (109 mg, 0.535 mmol) and dry Et_3N (225 µL, 1.61 mmol) in anhydrous THF (1.10 mL), was added 2-(methylthio)ethylamine (75.0 µL, 0.803 mmol) in a single portion. The reaction mixture was allowed to stir for 18 hours at 66 °C, and then the solvent was removed in *vacuo* to afford the crude product as a yellow solid (256 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc) afforded the title compound 415 as a white solid (104 mg, 66%). In solution in $CDCl_3$, this compound is a ≈ 11:1 mixture of rotamers; R_f = 0.32 (EtOAc); melting point: 196 – 197 °C; IR (solid state) ν_{max}/cm^{-1}: 3230w, 2926w, 2859w, 1612w, 1488m, 1458w, 1428m, 1364w, 1320w, 1305w, 1261w, 1236w, 1201m, 1187m, 1153m, 1129m, 1096m, 107m3, 1056m, 1043w, 1016w, 991w, 97w3, 931w, 880m, 861w, 786m, 733w, 685w, 584w, 536w, 474w, 461w; δ_H (400 MHz; $CDCl_3$) ^{1}H NMR data for major rotamer only: 4.86 – 4.78 (1H, m, N**H**), 4.39 – 4.29 (m, 1H, C**H**$_2$), 3.93 – 3.75 (m, 2H, C**H$_2$**), 3.60 – 3.44 (m, 1H, C**H**$_2$), 3.29 – 3.12 (m, 2H, C**H$_2$**), 3.12 – 3.01 (1H, m, C**H**$_2$), 3.01 – 2.90 (1H, m, C**H**$_2$), 2.78 – 2.66 (2H, m, C**H$_2$**), 2.66 – 2.56 (1H, m, C**H**$_2$), 2.25 – 2.15 (1H, m, C**H**$_2$), 2.14 (3H, s, SC**H$_3$**), 1.95 – 1.75 (2H, m, C**H$_2$**), 1.75 – 1.55 (2H, m, C**H$_2$**), 1.56 – 1.41 (2H, m, C**H$_2$**); δ_C (101 MHz; $CDCl_3$) ^{13}C NMR data for major rotamer only: 175.2 (CO), 49.7 (CH_2), 48.7 (CH_2), 42.7 (CH_2), 42.1 (CH_2), 34.1 (CH_2), 33.2 (CH_2), 27.8 (CH_2), 23.8 (CH_2), 23.0 (CH_2), 16.2 (CH_3); HRMS (ESI): calcd. for $C_{11}H_{22}N_2NaO_3S_2$, 317.0964 Found: $[MNa]^+$, 317.0967 (–1.1 ppm error). Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 3.42 – 3.31 (1H, m, C**H**$_2$), 2.50 (1H, t, *J* = 6.8 Hz, C**H**$_2$); δ_C (101 MHz, $CDCl_3$) 34.7 (CH_2), 34.0 (CH_2), 31.6 (CH_2), 25.0 (CH_2), 23.5 (CH_2).

Lab notebook reference: ixz_584

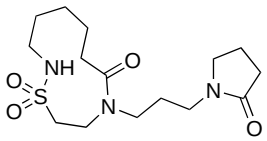
Synthesis of 9-(2-(benzyloxy)ethyl)-1-thia-2,9-diazacycloundecan-8-one 1,1-dioxide – 416



To a solution of 1-(vinylsulfonyl)azepan-2-one **387** (281 mg, 1.38 mmol) and dry Et_3N (600 µL, 4.14 mmol) in anhydrous THF (2.77 mL), was added aminoethyldioxolane (230 µL, 2.07 mmol) in a single portion. The reaction mixture was allowed to stir for 18 hours at 66 °C, and then the solvent was removed in *vacuo* to afford the crude product as a yellow solid (396 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc) afforded the title compound **416** as a white solid (332 mg, 75%). In solution in $(CD_3)_2SO$, this compound exists as a ≈ 3:1 mixture of rotamers; R_f = 0.24 (EtOAc); melting point: 173 – 174 °C; IR (solid state) ν_{max}/cm^{-1}: 3217w, 2947w, 2927m, 2869m, 1612s, 1492s, 1477s, 1462w, 1442w, 1416w, 1362w, 1326s, 1313s, 1264s, 1153w, 1128w, 1105w, 1068w, 1037m, 1009m, 990m, 968w, 946w, 934w, 895w, 886w, 861w, 796w, 754w, 737m, 754m, 708w, 693w, 627ww, 591. 540w, 524w, 470w; δ_H (400 MHz; $(CD_3)_2SO$) 7.04 (1H, t, *J* = 5.4 Hz, N**H**, minor rotamer) 6.85 – 6.78 (1H, m, N**H**, major rotamer), 4.83 – 4.75 (2H, m, C**H**, both rotamers), [4.08 – 3.97 (m), 3.96 – 3.70 (m), 3.66 (2H, t, *J* = 6.3 Hz, C**H₂**, minor rotamer), 3.60 – 3.48 (m), 3.43 – 3.23 (m), 3.15–2.90 (m), 2.71 – 2.59 (m) and 2.38 – 2.33 (m), 6 x downfield CH_2 both rotamers], [1.95 – 1.83 (m), 1.82 – 1.72 (m), 1.69 – 1.56 (m) and 1.53 – 1.31 (m) – 16H, 4 x C**H₂**, both rotamers]; δ_C (101 MHz; $(CD_3)_2SO$) 173.7 (CO, major rotamer), 172.5 (CO, minor rotamer), 102.2 (CH, minor rotamer), 101.5 (CH, major rotamer), 64.4 (CH_2, major rotamer), 64.3 (CH_2, major rotamer), 64.2 (CH_2, minor rotamer), 64.1 (CH_2, minor rotamer), 50.5 (CH_2, minor rotamer), 48.7 (CH_2, major rotamer), 45.5 (CH_2, major rotamer), 42.5 (CH_2, minor rotamer), 42.3 (CH_2, major rotamer), 41.3 (CH_2, major rotamer), 40.5 (CH_2, minor rotamer,), 39.4 (CH_2, minor rotamer), 33.1 (CH_2, major rotamer), 32.7 (CH_2, major rotamer), 31.6 (CH_2, minor rotamer), 31.2 (CH_2, minor rotamer), 25.7 (CH_2, minor rotamer), 23.8 (CH_2, minor rotamer), 27.5 (CH_2, major rotamer), 23.4 (CH_2, major rotamer), 23.0 (CH_2, major rotamer), 22.7 (CH_2, minor rotamer); HRMS (ESI): calcd. for $C_{13}H_{24}N_2NaO_5S$, 343.1298 Found: $[MNa]^+$, 343.1301 (–0.8 ppm error), calcd. for $C_{13}H_{24}KN_2O_5S$, 359.1038 Found: $[MK]^+$, 359.1044 (–1.8 ppm error).

Lab notebook reference: ixz_608

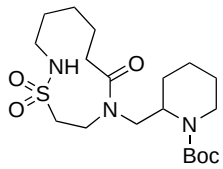
Synthesis of 9-(3-(2-oxopyrrolidin-1-yl)propyl)-1-thia-2,9-diazacycloundecan-8-one 1,1-dioxide – 417



To a solution of 1-(vinylsulfonyl)azepan-2-one **387** (139 mg, 0.686 mmol) and dry Et_3N (290 µL, 1.03 mmol) in anhydrous THF (1.37 mL), was added 1-(3-aminopropyl)-2-pyrrolidone (100 µL, 2.07 mmol) in a single portion. The reaction mixture was allowed to stir for 18 hours at 66 °C, and then the solvent was removed in *vacuo* to afford the crude product as a yellow oil (296 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:MeOH, 50:50) afforded the title compound **417** as a colourless oil (168 mg, 71%). In solution in $CDCl_3$, this compound exists as a ≈ 5:1 mixture of rotamers; R_f = 0.61 (50:50, EtOAc:MeOH); IR (neat) ν_{max}/cm^{-1}: 3227w, 2934w, 2871w, 1666s, 1619s, 1463w, 1424w, 1290w, 1131m, 915w, 724w, 644w, 479w; δ_H (400 MHz; $CDCl_3$) 6.07 (1H, t, *J* = 5.4 Hz, SO_2N**H**, minor rotamer), 5.41 (1H, dd, *J* = 7.9, 4.2 Hz, SO_2N**H**, major rotamer), 4.28 (1H, ddd, *J* = 14.4, 4.8, 2.6 Hz, C**H**$_2$, major rotamer), 3.74 – 3.63 (3H, m, C**H$_2$**, both rotamers), 3.39 – 2.84 (20H, m, 5 × C**H$_2$**, both rotamers), [2.62 – 2.50 (m), 2.38 – 2.18 (m), 2.14 – 1.92 (m) and 1.89 – 1.39 (m) 28H, 7 x C**H$_2$**, both rotamers]; δ_C (101 MHz, $CDCl_3$) data for major rotamer: 175.5 (CO), 174.7 (CO), 48.5 (CH_2), 48.0 (CH_2), 47.2 (CH_2), 42.4 (CH_2), 42.0 (CH_2), 39.9 (CH_2), 33.7 (CH_2), 30.9 (CH_2), 27.8 (CH_2), 27.0 (CH_2), 23.7 (CH_2), 22.9 (CH_2), 18.0 (CH_2); ^{13}C NMR resonances for the minor rotamer: 175.4 (CO), 174.1 (CO), 52.2 (CH_2), 47.2 (CH_2), 44.3 (CH_2), 43.8 (CH_2), 40.8 (CH_2), 40.3 (CH_2), 31.0 (CH_2), 31.0 (CH_2), 26.5 (CH_2), 26.1 (CH_2), 23.8 (CH_2), 23.2 (CH_2), 17.9 (CH_2); HRMS (ESI): calcd. for $C_{15}H_{28}N_3O_4S$, 346.1795. Found: $[MH]^+$, 368.1797 (–0.5 ppm error), calcd. for $C_{15}H_{27}N_3NaO_4S$, 368.1614. Found: $[MNa]^+$, 368.1621 (–1.8 ppm error), calcd. for $C_{15}H_{27}KN_3O_4S$, 384.1354. Found: $[MK]^+$, 384.1355 (–0.2 ppm error).

Lab notebook reference: ixz_607

Synthesis of *tert*-butyl 2-((1,1-dioxido-8-oxo-1-thia-2,9-diazacycloundecan-9-yl)methyl)piperidine-1-carboxylate – 418

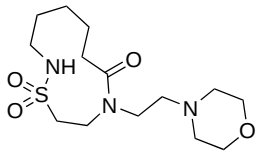


To a solution of 1-(vinylsulfonyl)azepan-2-one **387** (226 mg, 1.11 mmol) and dry Et_3N (500 µL, 3.33 mmol) in anhydrous THF (2.22 mL), was added 1-boc-2-(aminomethyl)piperidine (350 µL, 1.67 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at 66 °C,

and then the solvent was removed in *vacuo* to afford the crude product as a yellow oil (351 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc) afforded the title compound as a pale yellow oil (288 mg, 62%). In solution in $CDCl_3$, this compound exists as a ≈ 5:4 mixture of rotamers. The ^{1}H NMR spectrum suffers from sever rotmaric broadening, and some signal broadening is also seen in the ^{13}C NMR spectrum; R_f = 0.39 (EtOAc); IR (neat) ν_{max}/cm^{-1}: 2938w, 2866m, 1677s, 1626s, 1415s, 1308w, 1158w, 1134w, 906w, 724w, 646w; δ_H (400 MHz; $CDCl_3$) 4.96 (1H, dd, *J* = 7.6, 4.6 Hz, SO_2N**H**, major rotamer), 4.40 – 4.14 (3H, m, NC**H**, both rotamers + SO_2N**H**, minor rotamer), [4.11 – 3.43 (br,m) and 3.36 – 2.83 (br, m) higher field C**H$_2$**, 20H, both rotamers], [2.75 – 1.95 (br,m) and 1.78 – 1.30 (br,m) lower field CH_2 and 3 x C**H$_3$**, 46H, both rotamers]; δ_C (101 MHz; $CDCl_3$) 174.6 (CO, both rotamers), 154.7 (CO, both rotamers), 80.3 ($COOCCH_3$, major rotamer), 80.2 ($COOCCH_3$, minor rotamer), 50.0 (CH_2, minor rotamer) and 49.9 (CH_2, major rotamer), 48.6 (CH_2, both rotamers), 44.0 (CH_2, major rotamer) and 43.6 (CH_2, minor rotamer), 42.1 (CH_2, both rotamers), 40.2 (CH_2, minor rotamer, broad) and 39.1 (CH_2, major rotamer, broad), 33.6 (CH_2, major rotamer) and 33.3 (CH_2, minor rotamer), 28.4 (NCH, both rotamers), 28.4 (3 × CH_3, major rotamer) and 28.2 (3 × CH_3, minor rotamer), 27.8 (CH_2, both rotamers), 26.4 (CH_2, minor rotamer) and 26.0 (CH_2, major rotamer), 25.1 (CH_2, major rotamer) and 25.0 (CH_2, minor rotamer), 24.0 (CH_2, major rotamer) and 23.9 (CH_2, minor rotamer), 23.4 (CH_2, major rotamer) and 23.3 (CH_2, minor rotamer), 19.4 (CH_2, both rotamers); HRMS (ESI):calcd. for $C_{19}H_{36}N_3O_5S$, 418.2370. Found: $[MH]^+$, 418.2380 (–2.3 ppm error), calcd. for $C_{19}H_{35}N_3NaO_5S$, 440.2190. Found: $[MNa]^+$, 440.2200 (–2.5 ppm error), calcd. for $C_{19}H_{35}KN_3O_5S$, 456.1929. Found: $[MK]^+$, 456.1941 (–2.5 ppm error).

Lab notebook reference: ixz_609

Synthesis of 9-(2-morpholinoethyl)-1-thia-2,9-diazacycloundecan-8-one 1,1-dioxide – 419

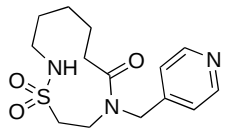


To a solution of 1-(vinylsulfonyl)azepan-2-one **387** (134 mg, 0.657 mmol) and dry Et_3N (280 µL, 1.96 mmol) in anhydrous THF (1.31 mL), was added 4-(2-aminoethyl)morpholine (130 µL, 0.986 mmol) in a single portion. The reaction mixture was allowed to stir for 18 hours at 66 °C, and then the solvent was removed in *vacuo* to afford the crude product as a yellow oil (258 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:MeOH, 50:50) afforded the title compound **419** as a pale yellow oil (164 mg,

75%): In solution in $CDCl_3$, this compound exists as a ≈ 9:1 mixture of rotamers; R_f = 0.47 (50:50, EtOAc:MeOH); IR (thin film) ν_{max}/cm^{-1}: 3558w, 3228w, 2934m, 2854m, 2825m, 1619s, 1458w, 1433w, 1361w, 1305m, 1133w, 1117w, 920w, 867w, 737w; δ_H (400 MHz; $CDCl_3$) ^{1}H NMR data for the major rotamer only: 6.38 – 6.27 (1H, m, N**H**) 4.17 – 4.07 (1H, m, C**H**$_2$), 3.85 – 3.74 (1H, m, C**H**$_2$), 3.68 – 3.57 (5H, m, C**H$_2$**), 3.38 – 3.27 (1H, m, C**H**$_2$), 3.24 – 3.07 (2H, m, C**H$_2$**), 3.05 – 2.91 (1H, m, C**H**$_2$), 2.91 – 2.77 (2H, m, C**H$_2$**), 2.60 – 2.44 (5H, m, NC**H$_2$**C**H$_2$**O + C**H**$_2$), 2.28 (1H, dt, *J* = 13.4, 4.9 Hz, C**H**$_2$), 2.15 – 2.04 (1H, m, C**H**$_2$), 1.76 – 1.52 (3H, m, C**H**$_2$ + C**H$_2$**), 1.55 – 1.37 (2H, m, C**H$_2$**), 1.40 – 1.30 (1H, m, C**H**$_2$); δ_C (101 MHz; $CDCl_3$) 175.9 (CO, major rotamer), 174.8 (CO, minor rotamer), 66.6 (CH_2, major rotamer), 66.4 (CH_2, minor rotamer), 56.7 (CH_2, major rotamer), 55.8 (CH_2, minor rotamer), 53.7 (2 × CH_2, major rotamer), 53.6 (CH_2, minor rotamer), 52.4 (CH_2, minor rotamer), 48.7 (CH_2, major rotamer), 47.0 (CH_2, major rotamer), 44.3 (CH_2, minor rotamer), 43.9 (CH_2, minor rotamer), 42.9 (CH_2, major rotamer), 42.20 (CH_2, major rotamer), 41.5 (CH_2, minor rotamer), 33.8 (CH_2, major rotamer), 31.0 (CH_2, minor rotamer), 27.9 (CH_2, major rotamer), 26.5 (CH_2, minor rotamer), 24.2 (CH_2, minor rotamer), 23.8 (CH_2, major rotamer), 23.7 (CH_2, major rotamer), 23.2 (CH_2, minor rotamer); HRMS (ESI): calcd. for $C_{14}H_{28}N_3O_4S$, 334.1795 Found: $[MH]^+$, 334.1796 (–0.2 ppm error), calcd. for $C_{14}H_{27}N_3NaO_4S$, 356.1614 Found: $[MNa]^+$, 356.1617 (–0.6 ppm error), calcd. for $C_{14}H_{27}KN_3O_4S$, 372.1354 Found: $[MK]^+$, 372.1345 (2.5 ppm error). Characteristic ^{1}H NMR data for the minor rotamer can be seen at: δ_H (400 MHz; $CDCl_3$) 6.69 (1H, t, *J* = 6.2 Hz, N**H**), 3.51 – 3.44 (2H, m, C**H$_2$**), 2.74 – 2.67 (4H, m, 2 × C**H$_2$**), 2.43 – 2.37 (2H, m, C**H$_2$**).

Lab notebook reference: ixz_610

Synthesis of 9-(pyridin-4-ylmethyl)-1-thia-2,9-diazacycloundecan-8-one 1,1-dioxide – 420

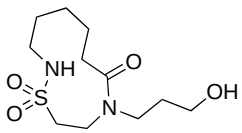


To a solution of 1-(vinylsulfonyl)azepan-2-one **387** (138 mg, 0.681 mmol) and dry Et_3N (290 µL, 2.04 mmol) in anhydrous THF (1.36 mL), was added 4-(aminomethyl)pyridine (104 µL, 0.986 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at 66 °C, and then the solvent was removed in *vacuo* to afford the crude product as a yellow solid (224 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:MeOH, 50:50) afforded the title compound **420** as a white solid (180 mg, 85%). In solution in $(CD_3)_2SO$, this compound exists as a ≈ 1:1 mixture of rotamers; R_f = 0.61 (50:50, EtOAc:MeOH); melting point: 185 – 187 °C; IR (solid state) ν_{max}/cm^{-1}: 3236w, 2934w, 2871m, 1622s, 1602s, 1563s, 1476s, 1460m, 1413m, 1362m, 1308w, 1265w, 1225w, 1207w, 1153w,

1128w, 1100m, 1085m, 1069m, 1051w, 1022w, 995w, 966w, 932w, 881w, 861m, 793w, 748w, 703w, 689w, 664w, 638w, 574w, 528w, 481w, 471w; δ_H (400 MHz; $(CD_3)_2SO$) 8.58 – 8.46 (4H, m, Ar-C**H**, both rotamers), 7.21 – 7.15 (4H, m, Ar-C**H**, both rotamers), 7.12 (1H, t, *J* = 5.1 Hz, N**H**, one rotamer), 7.01 – 6.95 (1H, m, N**H**, one rotamer), 5.12 (1H, d, *J* = 17.7 Hz, C**H**$_2$, one rotamer), 4.60 – 4.50 (3H, m, C**H$_2$** + C**H**$_2$, both rotamers), 4.22 – 4.12 (1H, m, C**H**$_2$, one rotamer), 3.66 (2H, t, *J* = 6.3 Hz, C**H$_2$**, one rotamer), 3.62 – 3.51 (1H, m, C**H**$_2$, one rotamer), 3.41 (2H, t, *J* = 6.3 Hz, C**H$_2$**, one rotamer), 3.22 – 3.12 (1H, m, C**H**$_2$, one rotamer), 3.08 – 3.00 (2H, m, C**H$_2$**, one rotamer), 3.02 – 2.82 (4H, m, C**H$_2$**, both rotamers), 2.71 – 2.60 (1H, m, C**H**$_2$, one rotamer), 1.99 – 1.88 (1H, m, C**H**$_2$, one rotamer), 1.71 – 1.39 (13H, m, both rotamers); δ_C (101 MHz;$(CD_3)_2SO$) 174.5 and 173.2 (CO, both rotamers), 150.1 and 149.6 (Ar-CH, both rotamers), 147.1 and 146.8 (Ar-C, both rotamers), 122.4 and 121.7 (Ar-CH, both rotamers), 52.5 (CH_2, one rotamer), 50.2 (CH_2, one rotamer), 48.7 (CH_2, one rotamer), 46.7 (CH_2, one rotamer), 42.7 (CH_2, one rotamer), 42.6 (CH_2, one rotamer), 41.4 (CH_2, one rotamer), 40.1 (CH_2, one rotamer), 32.3 (CH_2, one rotamer), 31.4 (CH_2, one rotamer), 27.3 (CH_2, one rotamer), 25.7 (CH_2, one rotamer), 23.7 (CH_2, one rotamer), 23.4 (CH_2, one rotamer), 23.0 (CH_2, one rotamer), 22.6 (CH_2, one rotamer); HRMS (ESI): calcd. for $C_{14}H_{22}N_3O_3S$, 312.1376 Found: $[MH]^+$, 312.1384 (–2.3 ppm error), calcd. for $C_{14}H_{21}N_3NaO_3S$, 334.1196 Found: $[MNa]^+$, 334.1205 (–2.6 ppm error).

Lab notebook reference: ixz_611

Synthesis of 9-(3-hydroxypropyl)-1-thia-2,9-diazacycloundecan-8-one 1,1-dioxide – 421

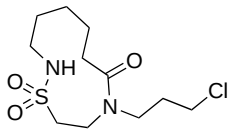


To a solution of 1-(vinylsulfonyl)azepan-2-one **387** (180 mg, 0.884 mmol) and dry Et_3N (370 µL, 2.65 mmol) in anhydrous THF (1.77 mL), was added 3-amino-1-propanol (100 µL, 1.33 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at 66 °C, and then the solvent was removed in *vacuo* to afford the crude product as a brown oil (204 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:MeOH, 90:10) afforded the title compound as a yellow oil (172 mg, 70%). In solution in $CDCl_3$, this compound exists as a ≈ 5:1 mixture of rotamers; R_f = 0.72 (50:50, EtOAc:MeOH); IR (neat) ν_{max}/cm^{-1}: 3264w, 2936w, 2874w, 2252m, 1610s, 1470s, 1425w, 1364w, 1305w, 1264m, 121m0, 1189w, 1148m, 1132s, 1081s, 1057s, 995w, 971w, 912w, 795w, 72w6, 646s, 575w, 527w, 507w, 477w; δ_H (400 MHz; $CDCl_3$) 5.45 (1H, t, N**H**, minor rotamer), 5.36 – 5.28 (1H, m, N**H**, major rotamer), 4.41 – 4.30 (1H, m, C**H**$_2$, major rotamer), 3.94 – 3.85 (1H, m, C**H**$_2$, major rotamer), 3.82–3.76 (2H, m, C**H$_2$**, minor rotamer), [3.75 – 3.55 (m), 3.51 – 3.45 (m) 3.45

– 3.30 (m), 3.20 – 3.00 (m), 2.96 – 2.45 (m) 24H in total, C**H₂** both rotamers], 2.16 – 2.04 (1H, m, C**H**$_2$, major rotamer), 1.86 – 1.39 (12H, m); δ_C (101 MHz; $CDCl_3$) ^{13}C NMR data for the major rotamer only: 175.5 (CO), 59.0 (CH_2), 48.6 (CH_2), 47.1 (CH_2) 42.0 (CH_2), 41.9 (CH_2), 33.7 (CH_2), 31.5 (CH_2), 27.8 (CH_2), 23.5 (CH_2), 22.6 (CH_2); Diagnostic ^{13}C NMR resonances for the minor rotamer: 175.4 (CO), 58.7 (CH_2) , 51.7 (CH_2), 42.9 (CH_2), 41.0 (CH_2), 31.6 (CH_2), 29.9 (CH_2), 26.4 (CH_2), 23.4 (CH_2); HRMS (ESI): calcd. for $C_{11}H_{23}N_2O_4S$, 279.1373 Found: $[MH]^+$, 279.1371 (0.8 ppm error), calcd. for $C_{11}H_{22}N_2NaO_4S$, 301.1192 Found: $[MNa]^+$, 301.1191 (0.4 ppm error).

Lab notebook reference: ixz_612

Synthesis of 9-(3-chloropropyl)-1-thia-2,9-diazacycloundecan-8-one 1,1-dioxide – 422

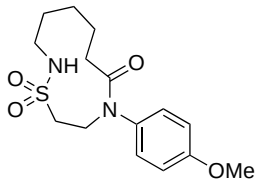


To a solution of 1-(vinylsulfonyl)azepan-2-one **387** (171 mg, 0.841 mmol) and dry Et_3N (530 µL, 3.78 mmol) in anhydrous THF (1.68 mL), was added 3-chloropropylamine hydrochloride (164 mg, 1.26 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at 66 °C, and then the solvent was removed in *vacuo* to afford the crude product as a yellow oil (341 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc) afforded the title compound **422** as a white solid (160 mg, 68%). In solution in $(CD_3)_2SO$, this compound exists as a roughly 2:1 mixture of rotamers; R_f = 0.34 (EtOAC); melting point: 173 – 174 °C; IR (solid state) ν_{max}/cm^{-1}: 3246w, 2940m, 1615s, 1495s, 1472s, 1459m, 1439m, 1374m, 1304m, 1268s, 1202s, 1185s, 1160s, 1136s, 1106m, 1079m, 1019m, 994w, 974w, 942w, 884w, 865w, 781w, 735w, 690w, 652w, 629w, 583w, 535w, 475w, 462w; δ_H (400 MHz, $(CD_3)_2SO$) 7.08 (1H, t, *J* = 5.4 Hz, N**H**, minor rotamer), 6.86 (1H, dd, *J* = 7.5, 4.4 Hz, **NH**, major rotamer), 4.14 – 3.99 (1H, m, C**H**$_2$, one rotamer), 3.93 – 3.81 (1H, m, C**H**$_2$, one rotamer), 3.71 – 3.51 (3H, m, C**H**$_2$ + C**H₂**, both rotamers), 3.43 – 3.32 (4H, m, 2 x C**H₂**, both rotamers), 3.21 – 2.63 (4H, m, 2 x C**H₂**, both rotamers), 2.37 (1H, t, *J* = 6.6 Hz, C**H**$_2$, one rotamer), 2.08 – 1.80 (2H, m, C**H₂**, both rotamers), 1.73 – 1.55 (1H, m, C**H**$_2$, one rotamer), 1.54 – 1.30 (4H, m, 2 x C**H₂**, both rotamers); δ_C (101 MHz; $(CD_3)_2SO$) 173.8 (CO, major rotamer), 172.8 (CO, minor rotamer), 50.5 (CH_2, minor rotamer), 48.7 (CH_2, major rotamer), 47.4 (CH_2, major rotamer), 43.3 (CH_2, minor rotamer), 42.7 (CH_2, major rotamer), 42.63 (CH_2, minor rotamer), 42.60 (CH_2, minor rotamer), 42.3 (CH_2, major rotamer), 41.4 (CH_2, major rotamer), 40.1 (CH_2, minor rotamer, overlapping with the solvent peak), 33.1 (CH_2, major rotamer), 31.8 (CH_2, minor rotamer), 31.6 (CH_2, major rotamer), 30.1 (CH_2, minor rotamer), 27.5 (CH_2, major rotamer), 25.7 (CH_2, minor rotamer), 23.9 (CH_2, minor rotamer), 23.5 (CH_2,

major rotamer), 23.1 (CH_2, major rotamer), 22.6 (CH_2, minor rotamer); HRMS (ESI): calcd. for $C_{11}H_{21}{}^{35}ClN_2NaO_3S$, 319.0854 Found: $[MNa]^+$, 319.0857 (–1.0 ppm error).

Lab notebook reference: ixz_621

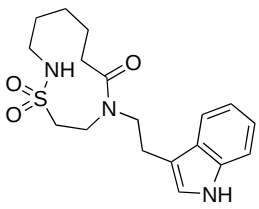
Synthesis of 9-(4-methoxyphenyl)-1-thia-2,9-diazacycloundecan-8-one 1,1-dioxide – 423



To a solution of 1-(vinylsulfonyl)azepan-2-one **387** (372 mg, 1.83 mmol) and dry Et_3N (766 µL, 5.49 mmol) in anhydrous THF (3.66 mL), was added 4-methoxy-aniline (339 mg, 2.75 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at 66 °C, and then the solvent was removed in *vacuo* to afford the crude product as a brown oil (341 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc) afforded the title compound **423** as a colourless oil (321 mg, 55%); R_f = 0.20 (50:50, EtOAc:*n*–hexane); IR (thin film) ν_{max}/cm^{-1}: 3384w, 2932m, 2865m, 1690s, 1512s, 1463s, 1338w, 1307m, 1338s, 1236s, 1180s, 1148m, 1119m, 1080w, 1034w, 959w, 911m, 879m, 822m, 767w, 732w, 716w, 65w1, 628w, 510w; δ_H (400 MHz, $CDCl_3$) 6.79 (2H, d, *J* = 8.8 Hz, Ar-C**H**), 6.59 (2H, d, *J* = 8.8 Hz, Ar-C**H**), 3.88 – 3.83 (4H, m, 2 × C**H₂**), 3.80 (2H, t, *J* = 6.2 Hz, C**H₂**), 3.75 (3H, s, OC**H₃**), 3.58 (2H, t, *J* = 6.2 Hz, C**H₂**), 2.68 – 2.58 (2H, m, C**H₂**), 1.77 – 1.72 (5H, m, 2 × C**H₂** + N**H**); δ_C (101 MHz; $CDCl_3$) 176.7 (CO), 153.0 (Ar-$COCH_3$), 140.7 (Ar-CN), 115.2 (2 × Ar-CH), 114.8 (2 × Ar-CH), 55.9 (OCH_3), 53.5 (CH_2), 46.2 (CH_2), 39.6 (CH_2), 39.0 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 23.1 (CH_2); HRMS (ESI): calcd. for $C_{15}H_{23}N_2O_4S$, 327.1373 Found: $[MH]^+$, 327.1369 (1.4 ppm error), calcd. for $C_{15}H_{22}N_2NaO_4S$, 349.1192 Found: $[MNa]^+$, 349.1194 (–0.5 ppm error), calcd. for $C_{15}H_{22}KN_2O_4S$, 365.0932 Found: $[MK]^+$, 365.0943 (–3.1 ppm error).

Lab notebook reference: ixz_585

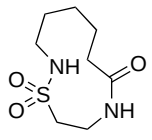
Synthesis of 9-(2-(1*H*-indol-3-yl)ethyl)-1-thia-2,9-diazacycloundecan-8-one 1,1-dioxide – 424



To a solution of 1-(vinylsulfonyl)azepan-2-one **387** (132 mg, 0.651 mmol) and dry Et_3N (400 µL, 1.95 mmol) in anhydrous THF (1.30 mL), was added tryptamine (114 mg, 0.720 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at 66 °C, and then the solvent was removed in *vacuo* to afford the crude product as a yellow oil (278 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc) afforded the title compound as a colourless oil (230 mg, 97%). In solution in $(CD_3)_2SO$, this compound exists as ≈ 4:1 mixture of rotamers; R_f = 0.54 (EtOAc); IR (thin film) ν_{max}/cm^{-1}: 3383w, 3262w, 2930m, 1609s, 145s7, 1424s, 1303w, 1131w, 909w, 728w, 541w; δ_H (400 MHz; $(CD_3)_2SO$) 10.88 (1H, s, Ar-N**H**, major rotamer), 10.81 (1H, s, Ar-N**H**, minor rotamer), 7.62 (1H, d, *J* = 7.8 Hz, Ar-C**H**, minor rotamer), 7.53 (1H, d, *J* = 7.8 Hz, Ar-C**H**, major rotamer), 7.35 (2H, d, *J* = 8.0 Hz, Ar-C**H**, both rotamers), 7.15 (2H, dd, *J* = 6.1, 2.2 Hz, Ar-C**H**, both rotamers), 7.12 – 7.04 (2H, m, Ar-C**H**, both rotamers), 7.04 – 6.94 (2H, m, Ar-C**H**, both rotamers), 6.85 – 6.75 (2H, m, SO_2N**H**, both rotamers), 4.13 – 3.87 (2H, m, C**H₂**, major rotamer), 3.66 (2H, t, *J* = 6.0 Hz, C**H₂**, minor rotamer), 3.61 – 3.44 (4H, m, C**H₂**, both rotamers) 3.25 – 3.07 (4H, m, C**H₂**, both rotamers), 3.05 – 2.81 (8H, m, 2 × C**H₂**, both rotamers), 2.80 – 2.66 (2H, m, C**H**$_2$, both rotamers), 2.50 – 2.36 (2H, m, C**H**$_2$, both rotamers), 1.83 – 1.30 (12H, m, 3 × C**H₂**, both rotamers); δ_C (101 MHz; $(CD_3)_2SO$) for major rotamer: 173.6 (CO), 136.2 (Ar-C), 127.0 (Ar-C), 123.5 (Ar-CH), 121.0 (Ar-CH), 118.5 (Ar-CH), 118.0 (Ar-CH), 111.5 (Ar-CH), 110.6 (Ar-C), 51.3 (CH_2), 48.9 (CH_2), 42.4 (CH_2), 41.3 (CH_2), 32.8 (CH_2), 27.6 (CH_2), 24.5 (CH_2), 23.4 (CH_2), 23.0 (CH_2); Diagnostic ^{13}C NMR resonances for the minor rotamer: 172.5 (CO), 127.3 (Ar-C), 122.7 (Ar-CH), 121.0 (Ar-CH), 118.3 (Ar-CH), 111.7 (Ar-CH), 111.4 (Ar-C), 50.7 (CH_2), 46.1 (CH_2), 42.7 (CH_2), 31.7 (CH_2), 25.7 (CH_2), 23.9 (CH_2), 22.9 (CH_2), 22.7 (CH_2); HRMS (ESI): calcd. for $C_{18}H_{26}N_3O_3S$, 364.1689. Found: $[MH]^+$, 364.1686 (0.9 ppm error), calcd. for $C_{18}H_{25}N_3NaO_3S$, 386.1509. Found: $[MNa]^+$, 386.1505 (1.1 ppm error), calcd. for $C_{18}H_{25}KN_3O_3S$, 402.1248. Found: $[MK]^+$, 402.1242 (1.5 ppm error).

Lab notebook reference: ixz_507

Synthesis of 1-thia-2,9-diazacycloundecan-8-one 1,1-dioxide – 425

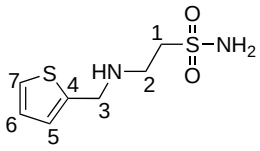


To a solution of 1-(vinylsulfonyl)azepan-2-one **387** (140 mg, 0.689 mmol) and dry Et_3N (290 µL, 2.07 mmol) in anhydrous THF (1.38 mL), was added ammonia solution (0.5 M in 1,4–dioxane, 2.07 mL, 1.03 mmol, 1.5 eq.) in a single portion. The reaction mixture was allowed to stir for 18 h at 66 °C, and then the solvent was removed in *vacuo* to afford the crude product as a yellow oil (278 mg). The crude product was purified by flash column chromatography

(SiO_2, 30 mm column, eluent: EtOAc:MeOH, 100:0 to 50:50) afforded the title compound **425** as a white solid (160 mg, 52%); R_f = 0.10 (EtOAc); melting point: 183 – 184 °C; IR (solid state) ν_{max}/cm^{-1}: 3352m, 3169m, 2940m, 2877w, 1624s, 1544s, 1474s, 1425m, 1353s, 1321m, 1308w, 1179m, 1141m, 1102mm, 1087, 1028m, 991w, 865w, 794w, 739w, 690w, 643w, 595w, 549w, 512w, 480w; δ_H (400 MHz; $(CD_3)_2SO$) 8.16 (1H, t, *J* = 6.0 Hz, $SO_2N\mathbf{H}$), 6.69 (1H, t, *J* = 6.0 Hz, CON**H**), 3.46 – 3.37 (2H, m, CONHC$\mathbf{H_2}$), 3.21 – 3.14 (2H, m, C$\mathbf{H_2}SO_2NHCH_2$), 3.00 – 2.92 (2H, m, $SO_2NHC\mathbf{H_2}$), 2.07 – 2.00 (2H, m, C$\mathbf{H_2}CONHCH_2$), 1.58 – 1.49 (2H, m, C$\mathbf{H_2}CH_2CONHCH_2$), 1.48 – 1.39 (2H, m, C$\mathbf{H_2}CH_2CH_2CONHCH_2$), 1.38 – 1.30 (2H, m, $SO_2NHCH_2C\mathbf{H_2}$); δ_C (101 MHz; $(CD_3)_2SO$) 173.0 (CO), 50.8 ($CH_2SO_2NHCH_2$), 41.6 (SO_2NHCH_2), 37.0 ($CH_2CONHCH_2$), 34.9 ($CONHCH_2$), 28.0 ($SO_2NHCH_2CH_2$), 23.9 ($CH_2CH_2CH_2CONHCH_2$), 23.4 ($CH_2CH_2CONHCH_2$); HRMS (ESI): calcd. for $C_8H_{16}N_2NaO_3S$, 243.0774 Found: $[MNa]^+$, 243.0775 (−0.3 ppm error), calcd. for $C_8H_{16}KN_2O_3S$, 259.0513 Found: $[MK]^+$, 259.0513 (−0.0 ppm error).

Lab notebook reference: ixz_622

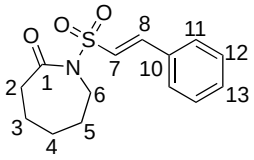
Synthesis of 2-((thiophen-2-ylmethyl)amino)ethane-1-sulfonamide – 430



To a solution of 1-(vinylsulfonyl)azepan-2-one **387** (251 mg, 1.24 mmol) and dry Et_3N (520 µL, 3.72 mmol) in anhydrous THF (2.48 mL), was added 2-aminomethylthiophene **428** (190 µL, 1.86 mmol) in a single portion. The reaction mixture was allowed to stir for 16 h at 66 °C, and then the solvent was removed in *vacuo* to afford the crude product as a yellow oil (278 mg). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc) afforded the title compound **430** as a colourless oil (275 mg, 70%); R_f = 0.43 (EtOAc); IR (neat) ν_{max}/cm^{-1}: 3306w (N–H sulfonamide), 3107w, 2929w, 2847w, 2255w, 1727w, 1556w (CC aromatic), 1461w, 1406w, 1324s, 1244w, 1183w, 1139s, 1104w, 1039w, 907m, 851w, 827w, 775w, 726s, 699s, 648m, 571m, 493m; δ_H (400 MHz; $(CD_3)_2SO$) 7.37 (1H, dd, *J* = 4.2, 1.9 Hz, C(7)H), 6.99 – 6.92 (2H, m, C(5+6)H), 6.84 (2H, s, br, SO_2NH), 3.89 (2H, s, C(3)H_2), 3.20 (1H, s, br, CH_2NH), 3.14 (2H, t, *J* = 7.1 Hz, C(1)H_2), 2.92 (2H, t, *J* = 7.1 Hz, C(2)H_2); δ_C (101 MHz; $(CD_3)_2SO$) 144.5 (C, C4), 126.7 (CH, C6), 124.8 (CH, C5), 124.7 (CH, C7), 54.3 (CH_2, C1), 47.3 (CH_2, C3), 43.1 (CH_2, C2); HRMS (ESI): calcd. for $C_7H_{13}N_2O_2S_2$, 221.0413. Found: $[MH]^+$, 221.0412 (0.3 ppm error), calcd. for $C_7H_{12}N_2NaO_2S_2$, 243.0232. Found: $[MNa]^+$, 243.0232 (0.1 ppm error).

Lab notebook reference: ixz_593

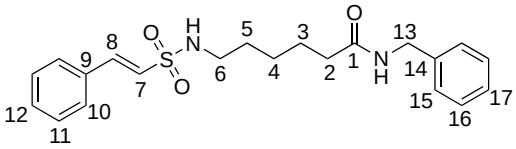
Synthesis of (*E*)-1-(styrylsulfonyl)azepan-2-one – 432



Azepan-2-one **386** (578 mg, 5.11 mmol) was dissolved in anhydrous THF (41 mL) and the temperature was lowered –78 °C (dry ice/acetone bath). LHMDS (1.0 M in THF, 8. mL, 7.67 mmol) was added dropwise via syringe over a period of 1 min and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of trans 2-phenylethenesulfonyl chloride **431** (1.60 g, 7.67 mmol) in anhydrous THF (10 mL) was transferred to the stirring reaction mixture dropwise by syringe pump over a 1 min period. The reaction was allowed to warm to room temperature overnight, with colour changed to orange solution. The resulting reaction mixture was diluted by the addition of sat. $NH_4Cl_{(aq)}$ (50 mL) and poured into the separating funnel. The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic layers dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product as a viscous yellow oil (1.71 g). The crude product was purified by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc:*n*–hexane, 30:70) to afford title compound **432** as a colourless oil (1.06 g, 71%); R_f = 0.42 (50:50, EtOAc:*n*–hexane); IR (neat) ν_{max} /cm^{-1}: 3093w (C–H alkyl), 2950w (C–H alkyl), 2862w, 1680s (C=O amide), 1608m (CC aromatic), 1574w (CC aromatic), 1497w, 1467m, 1448w, 1437w, 1378m, 1342s, 1307m, 1255w, 1238w, 1228w, 1179m, 1150s, 1116s, 1086m, 1028w, 990w, 973m, 879m, 861w, 847w, 834w, 824w, 817s, 807w, 765s, 752s, 712w, 692w, 603m, 574w, 535s, 528s, 487s; δ_H (400 MHz; $CDCl_3$) 7.52 (1H, d, *J* = 15.5 Hz, C(8)H), 7.44 – 7.38 (2H, m, C(11)H), 7.37 – 7.25 (3H, m, C(12+13)H), 3.87 – 3.80 (2H, m, C(6)H_2), 2.57 – 2.50 (2H, m, C(2)H_2), 1.72 – 1.62 (6H, m, C(6)H_2); δ_C (101 MHz; $CDCl_3$) 175.6 (C, C1), 143.3 (CH, C8), 131.9 (C, C10), 131.0 (CH, C13), 128.8 (2 × CH, C12), 128.3 (2 × CH, C11), 125.1 (CH, C7), 45.9 (CH_2, C6), 38.3 (CH_2, C2), 29.0 (CH_2, C4), 28.7 (CH_2, C5), 22.7 (CH_2, C3); HRMS (ESI): calcd. for $C_{14}H_{18}NO_3S$, 280.1002. Found: $[MH]^+$, 280.0997 (1.7 ppm error), calcd. for $C_{14}H_{17}NNaO_3S$, 302.0821. Found: $[MNa]^+$, 302.0823 (–0.5 ppm error).

Lab notebook reference: ixz_545

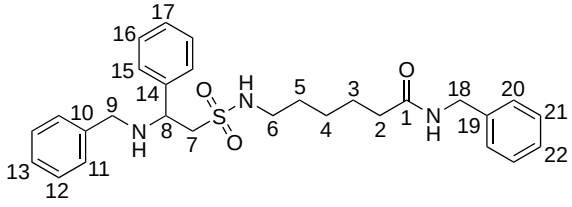
Synthesis of (*E*)-*N*-benzyl-6-((2-phenylvinyl)sulfonamido)hexanamide– 434



To a solution of (E)-1-(styrylsulfonyl)azepan-2-one **432** (336 mg, 1.14 mmol) and dry Et_3N (300 µL, 2.13 mmol) in anhydrous THF (1.42 mL), was added benzylamine (120 µL, 1.07 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at 66 °C, and then the solvent was removed in *vacuo* to afford the crude product as a yellow solid (604 mg). The crude product was purified by flash column chromatography (SiO_2, 40 mm column, eluent: EtOAc) afforded the title compound **434** as a white solid (186 mg, 68%); R_f = 0.59 (EtOAc); IR (neat) ν_{max}/cm^{-1}: 3372w (N–H sulfonamide), 3170w, 3061w, 2942w, 2863w, 1654s (C=O amide), 1541m (CC aromatic), 1495w (CC aromatic), 1479w, 1448w, 1380w, 1356w, 1314m, 1253w, 1212w, 1196w, 1138s, 1106w, 1074m, 1029w 971w, 921m, 861w, 809w, 739m, 696s, 620w, 558w, 536m, 485m, 457w; δ_H (400 MHz; $(CD_3)_2SO$) 8.31 (1H, t, *J* = 6.0 Hz, SO_2NH), 7.74 – 7.68 (2H, m, C(10)H), 7.46 – 7.14 (12H, m, C(7+8+11+12+15+16+17)H), 4.27 (2H, d, *J* = 6.0 Hz, C(13)H_2), 2.93 – 2.84 (2H, m, C(6)H_2), 2.14 (2H, t, *J* = 7.4 Hz, C(2)H_2), 1.58 – 1.42 (2H, m, C(3+5)H_2), 1.35 – 1.23 (2H, m, C(4)H_2); δ_C (101 MHz; $(CD_3)_2SO$) 172.1 (CO, C1), 139.7 (C, C14), 139.0 (CH, C8), 133.0 (C, C9), 130.4 (CH, C12), 129.0 (2 × CH), 128.4 (2 × CH), 128.3 (2 × *CH*), 127.2 (2 × CH), 127.0 (CH, C17), 126.7 (CH, C7), 42.3 (CH_2, C6), 42.0 (CH_2, C13), 35.3 (CH_2, C2), 29.2 (CH_2, C5), 25.9 (CH_2, C4), 25.0 (CH_2, C3); HRMS (ESI): calcd. for $C_{21}H_{27}N_2O_3S$, 387.1737. Found: $[MH]^+$, 387.1747 (−2.5 ppm error), calcd. for $C_{21}H_{26}N_2NaO_3S$, 409.1556. Found: $[MNa]^+$, 409.1562 (−1.4 ppm error), calcd. for $C_{21}H_{26}KN_2O3S$, 425.1296. Found: $[MK]^+$, 425.1303 (−1.6 ppm error).

Lab notebook reference: ixz_551

Synthesis of *N*-benzyl-6-((2-(benzylamino)-2-phenylethyl)sulfonamido)hexanamide – 437

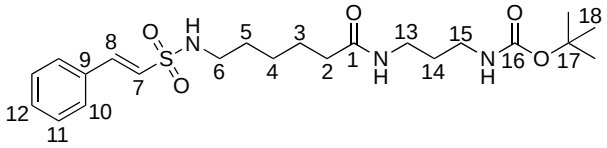


To a solution of (*E*)-1-(styrylsulfonyl)azepan-2-one **432** (336 mg, 1.14 mmol) and DBU (520 µL, 3.42 mmol) in anhydrous THF (2.28 mL), was added benzylamine (188 µL, 1.72 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at RT in reaction vial and then the solvent was removed in *vacuo* to afford the crude product as a yellow oil (543 mg).

The crude product was purified by flash column chromatography (SiO_2, 20 mm column, eluent: EtOAc) afforded the title compound **437** as a colourless oil (337 mg, 76%). In solution in $CDCl_3$, this compound exists as a roughly 5:1 mixture of rotamers; R_f = 0.47 (EtOAc); IR (neat) ν_{max}/ cm^{-1}: 3300w (N–H sulfonamide), 3064w, 3030w, 2934w, 2862w, 2248w (N–H amide), 1647s (C=O amide), 1537w (CC aromatic), 1495w (CC aromatic), 1454w, 1315m, 1240m, 1198w, 1140m, 1080w, 1028w, 974w, 908s, 727s, 697s, 647w, 619w, 600w, 555w, 535w, 496w; δ_H (400 MHz; $CDCl_3$) 7.58 – 7.21 (15H, m, C(11+12+13+15+16+17+20+21+22)H, both rotamers), 6.81 (1H, d, *J* = 15.5 Hz, one rotamer), 6.55 (1H, t, *J* = 6.1 Hz, SO_2NH, major rotamer), 5.57 (1H, t, *J* = 6.1 Hz, SO_2NH, minor rotamer), 5.33 (1H, s, br, CONH, minor rotamer), 4.43 (2H, d, *J* = 5.6 Hz, C(7)H_2, one rotamer), 4.31 (1H, dd, *J* = 9.9, 3.2 Hz, C**H**H', one rotamer), 3.72 – 3.55 (2H, m, CH_2, both rotamers), 3.42 (1H, dd, *J* = 14.3, 9.7 Hz, CH**H'**, one rotamer), 3.19 (1H, dd, *J* = 14.5, 3.2 Hz, C**H**H', one rotamer), 3.08 – 2.90 (2H, m, CH_2, both rotamers), 2.66 (1H, s, br, CONH, major rotamer), 2.26 – 2.17 (2H, m, CH_2, both rotamers), 1.75 – 1.23 (6H, m, C(3+4+5)H_2, both rotamers); δ_C (101 MHz; $CDCl_3$) 173.0 (CO, C1, minor rotamer), 173.0 (CO, C1, major rotamer), 141.1 (C, C10, minor rotamer), 141.0 (C, C10, major rotamer), 139.7 (C, C19, both rotamers), 138.4 (C, C14, both rotamer), 132.5 (CH, minor rotamer), 130.7 (CH, minor rotamer), 129.0 (CH, minor rotamer), 128.9 (CH, major rotamer), 128.5 (CH, major rotamer), 128.4 (CH, major rotamer), 128.2 (CH, minor rotamer), 128.1 (CH, major rotamer), 127.6 (CH, major rotamer), 127.3 (CH, minor rotamer), 127.0 (CH, major rotamer), 125.2 (CH, minor rotamer), 58.1 (CH_2, C7, minor rotamer), 58.0 (CH_2, C7, major rotamer), 51.0 (CH_2, both rotamers), 43.3 (CH_2, both rotamers), 42.8 (CH_2, major rotamer), 42.7 (CH_2, minor rotamer), 36.1 (CH_2, minor rotamer), 36.0 (CH_2, major rotamer), 29.6 (CH_2, major rotamer), 29.4 (CH_2, minor rotamer), 26.0 (CH_2, minor rotamer), 25.9 (CH_2, major rotamer), 25.0 (CH_2, minor rotamer), 24.9 (CH_2, major rotamer); HRMS (ESI): calcd. for $C_{28}H_{36}N_3O_3S$, 494.2472. Found: $[MH]^+$, 494.2477 (–1.0 ppm error), calcd. for $C_{28}H_{35}N_3NaO_3S$, 516.2291. Found: $[MNa]^+$, 516.2292 (–0.2 ppm error), calcd. for $C_{28}H_{35}KN_3O_3S$, 532.2031. Found: $[MK]^+$, 516.2292 (–1.0 ppm error).

Lab notebook reference: ixz_548

Synthesis of *tert*-butyl (E)-(3-(6-((2-phenylvinyl)sulfonamido)hexanamido)propyl)carbamate – 437

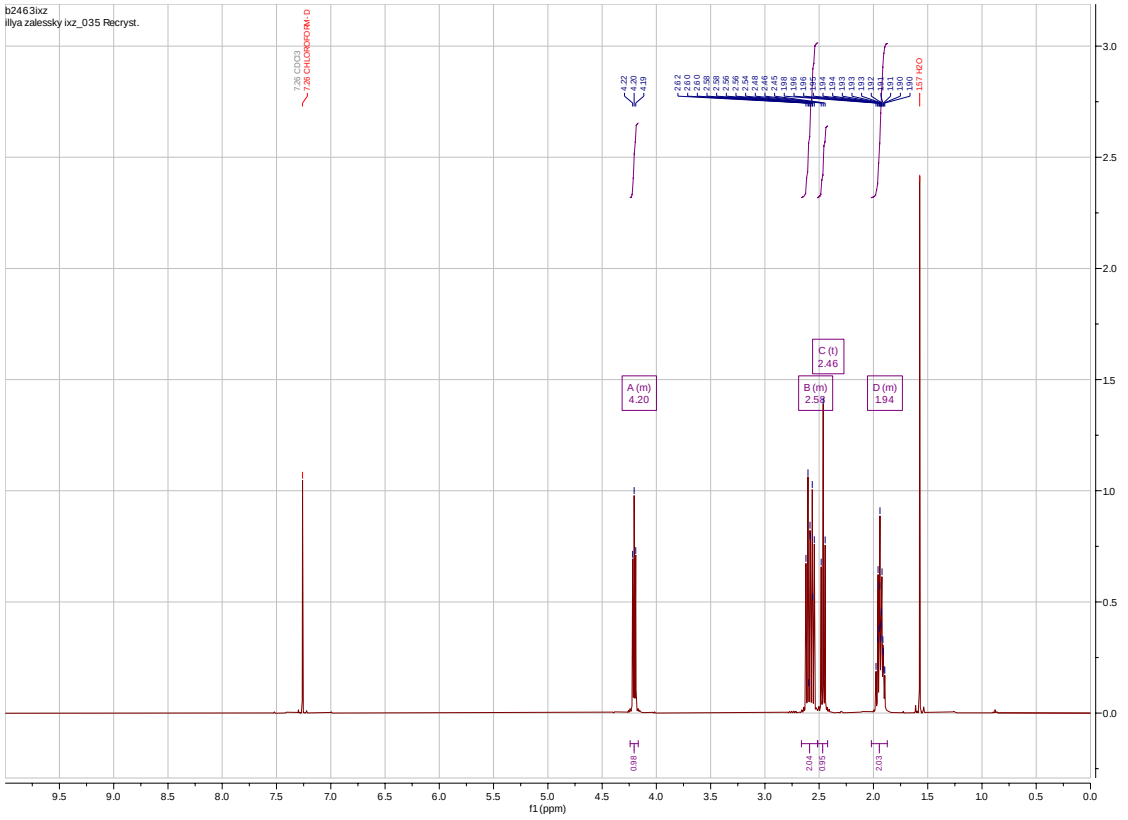


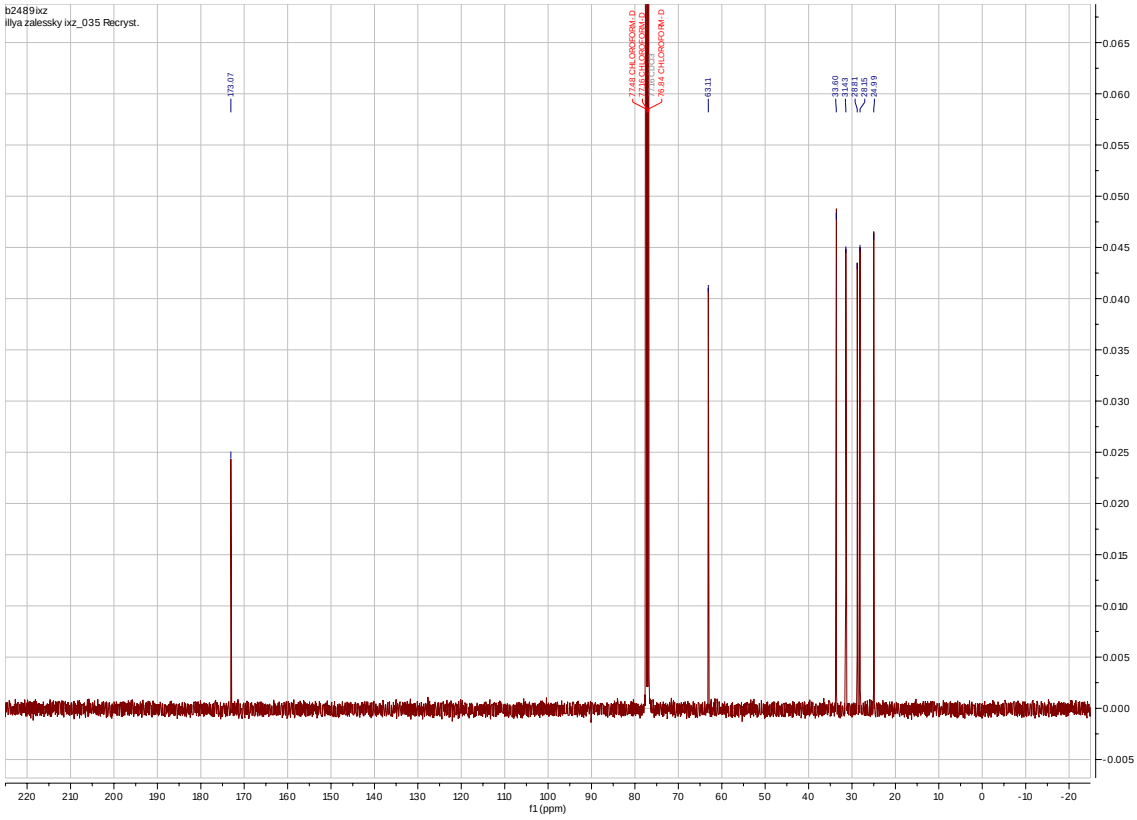
To a solution of (E)-1-(styrylsulfonyl)azepan-2-one **432** (261 mg, 0.891 mmol) and dry Et_3N (400 µL, 2.67 mmol) in anhydrous THF (1.78 mL), was added *N*-boc-1,3-diaminopropane **405** (230 µL, 1.34 mmol) in a single portion. The reaction mixture was allowed to stir for 18 h at RT at 66 °C in the reaction mixture and then the solvent was removed in *vacuo*. Purification by flash column chromatography (SiO_2, 30 mm column, eluent: EtOAc) afforded the title compound **437** as a colourless oil (359 mg, 89%); R_f = 0.28 (EtOAc); IR (neat) ν_{max}/cm^{-1}: 3301w (N–H sulfonamide), 2935w (C–H alkyl), 2866w (C–H alkyl), 2252w (N–H amide), 1691s (C=O carbamate), 1645s (C=O amide), 1515m (CC aromatic), 1449m, 1392w, 1366w, 1320w, 1274w, 1250m, 1167m, 1141s, 1089w, 972w, 910w, 862m, 816w, 729s, 690m, 646w, 616w, 534m, 488w; δ_H (400 MHz; $CDCl_3$) 7.47 – 7.32 (6H, m, C(8)H +2×C(10+11)H+C(12)H), 6.75 (1H, d, *J* = 15.4 Hz, C(7)H), 6.59 (1H, t, *J* = 6.2 Hz, SO_2NH), 5.57 (1H, t, *J* = 6.1 Hz, OCONH), 5.19 (1H, t, *J* = 6.4 Hz, CONH), 3.27 – 3.18 (2H, m, C(6)H_2), 3.14 – 3.06 (2H, m, C(13)H_2), 3.06 – 2.93 (2H, m, C(15)H_2), 2.14 (2H, t, *J* = 7.4 Hz, C(2)H_2), 1.64 – 1.48 (6H, m, C(3+5+14)H_2), 1.38 (9H, s, C(18)H_3), 1.38 – 1.28 (2H, m, C(4)H_2); δ_C (101 MHz; $CDCl_3$) 173.6 (CO, C1), 156.7 (CO, C16), 141.2 (CH, C8), 132.7 (C, C9), 130.7 (CH, C12), 129.1 (2 × CH, C11), 128.2 (2 × CH, C10), 125.2 (CH, C7), 79.2 (C, C17), 42.8 (CH_2, C15), 37.2 (CH_2, C13), 36.3 (CH_2, C2), 36.0 (CH_2, C6), 30.0 (CH_2), 29.4 (CH_2), 28.4 (CH_3, C18), 26.0 (CH_2, C4), 25.1 (CH_2);HRMS (ESI): calcd. for $C_{22}H_{36}N_3O_5S$, 454.2370. Found: $[MH]^+$, 454.2381 (−2.5 ppm error), calcd. for $C_{22}H_{35}N_3NaO_5S$, 476.2190. Found: $[MNa]^+$, 476.2193 (−0.6 ppm error), calcd. for $C_{22}H_{35}KN_3O_5S$, 492.1929. Found: $[MK]^+$, 492.1948 (−3.8 ppm error).

Lab notebook reference: ixz_552

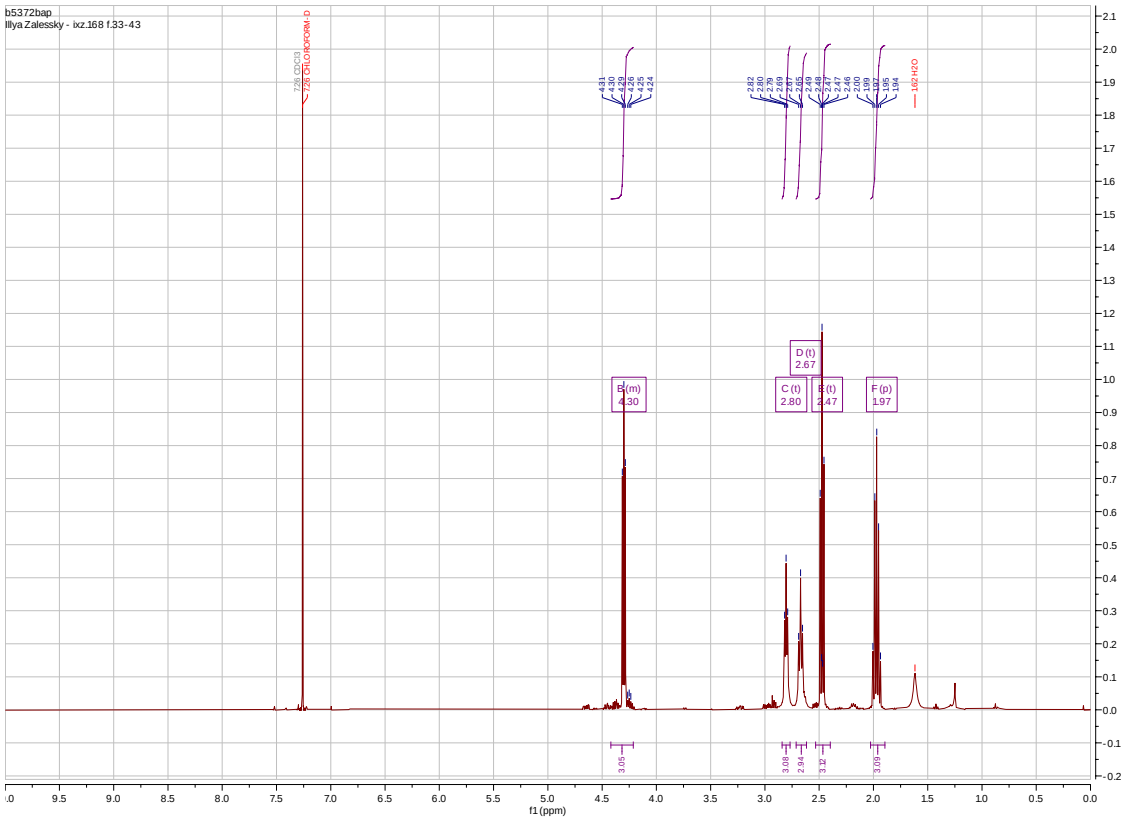
Appendix: Representative NMR spectra

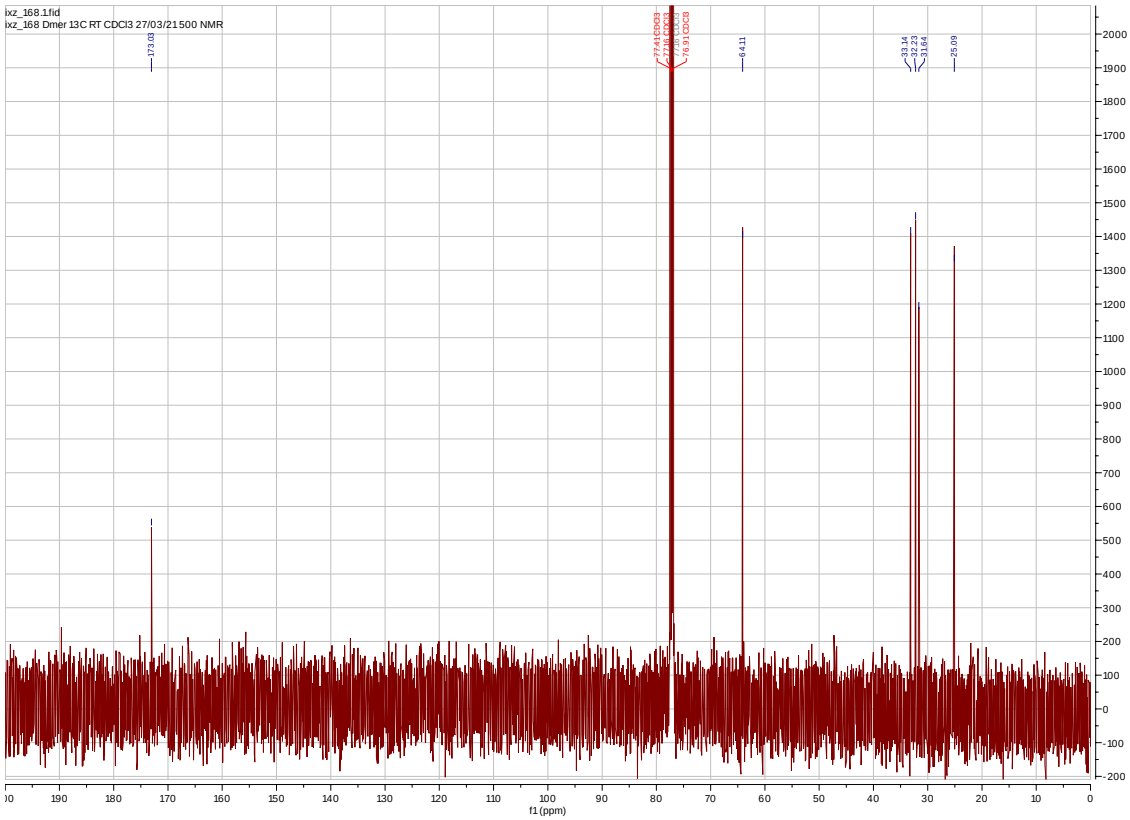
1,10-Dioxa-5,14-dithiacyclooctadecane-9,18-dione – 103



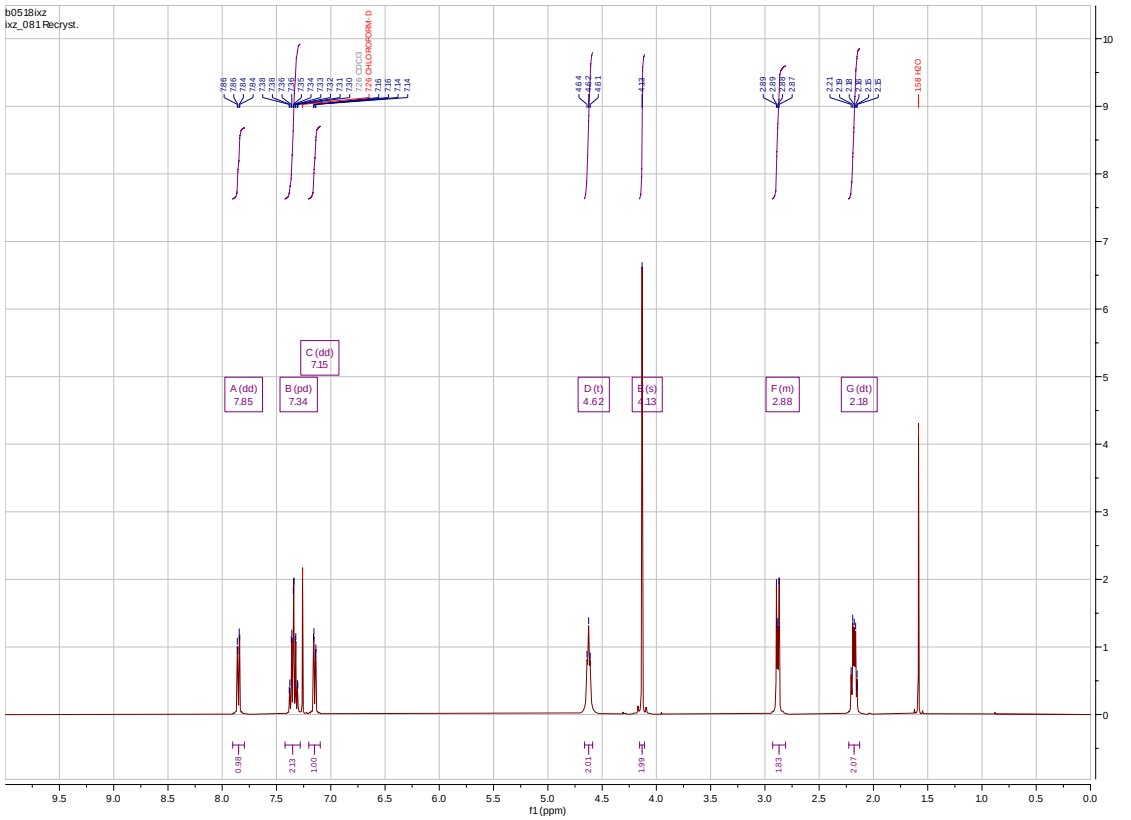


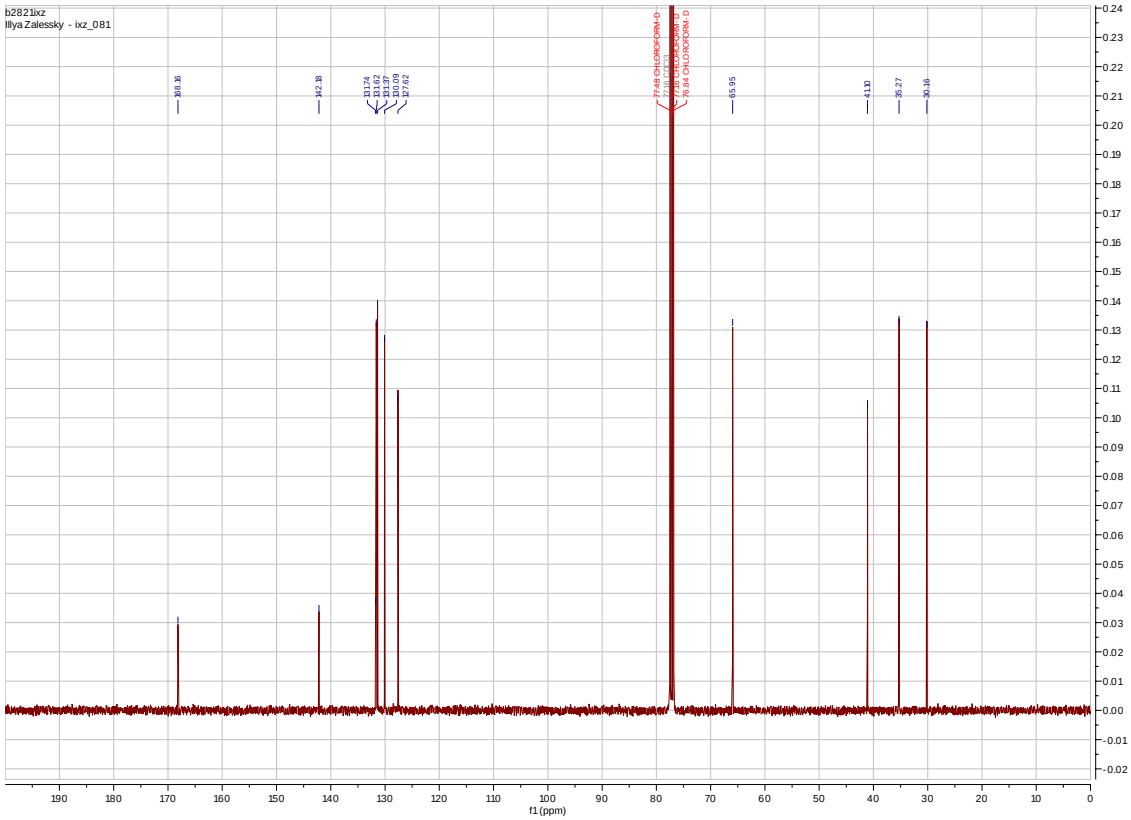
1,9-Dioxa-4,12-dithiacyclohexadecane-8,16-dione – 107



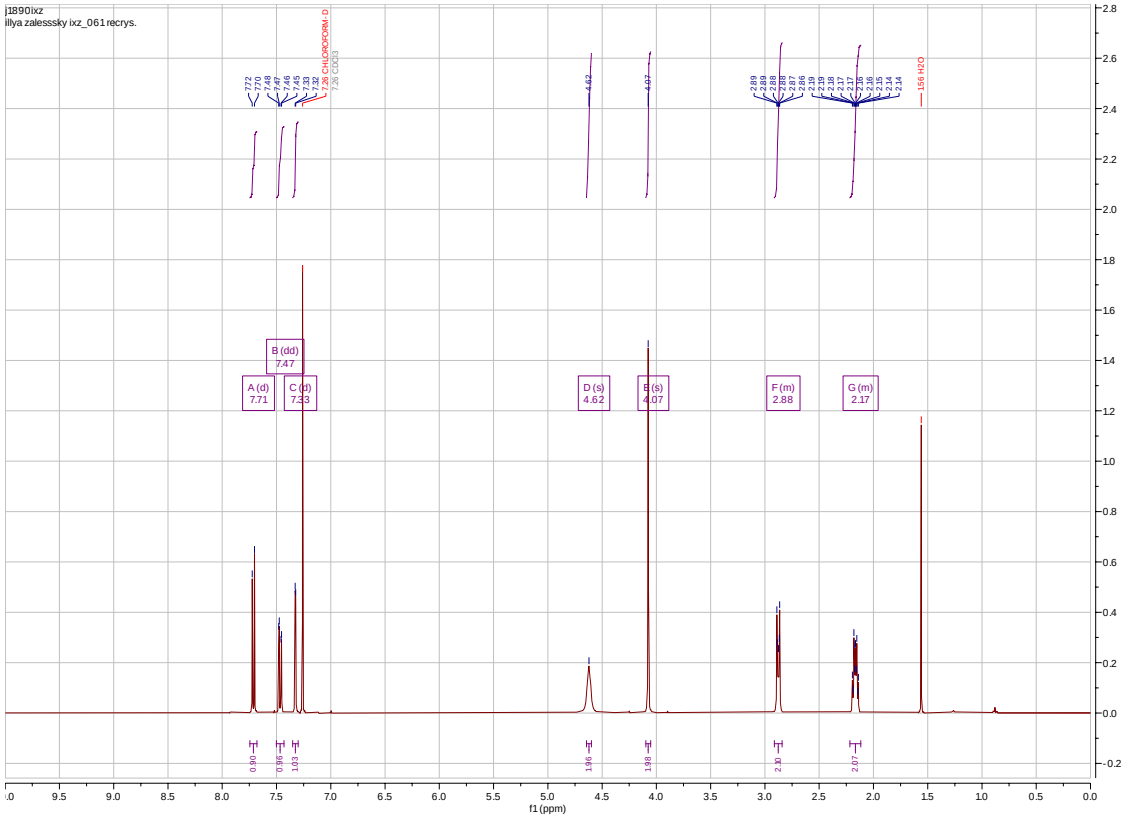


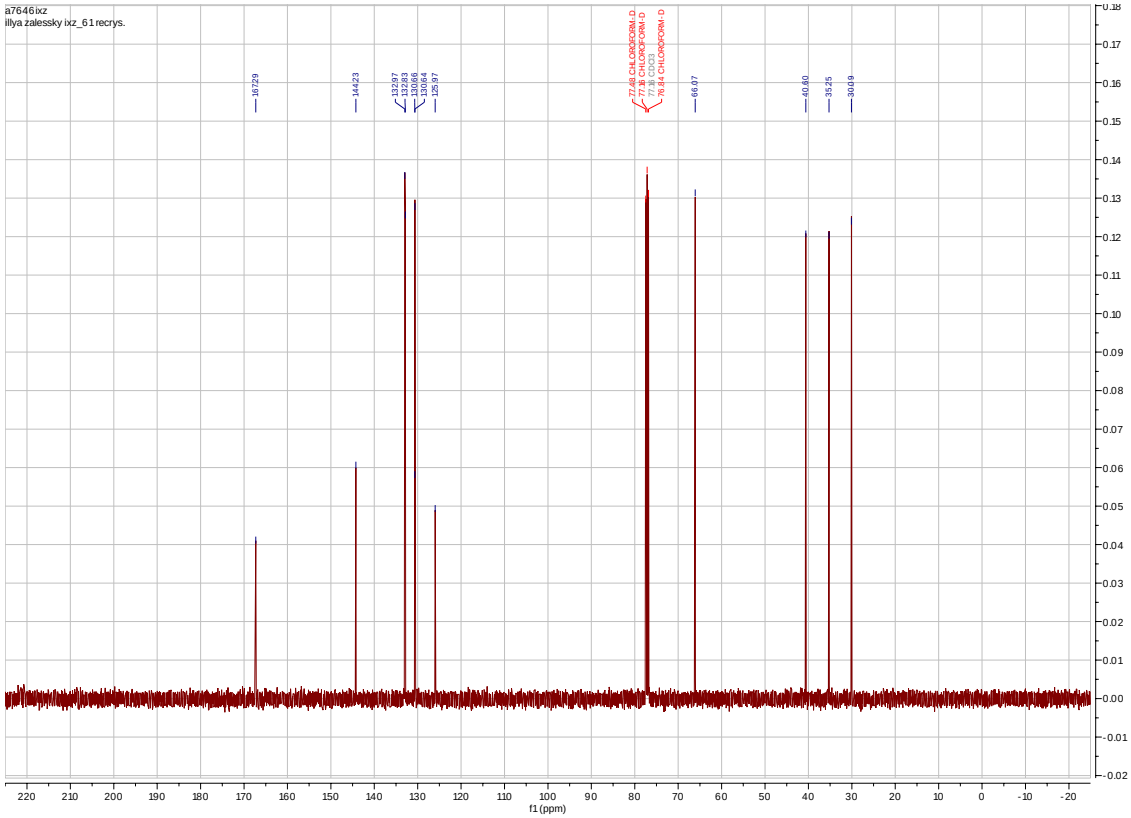
4,5-Dihydro-3H-benzo[*g*][1,5]oxathionin-1(7*H*)-one – 113



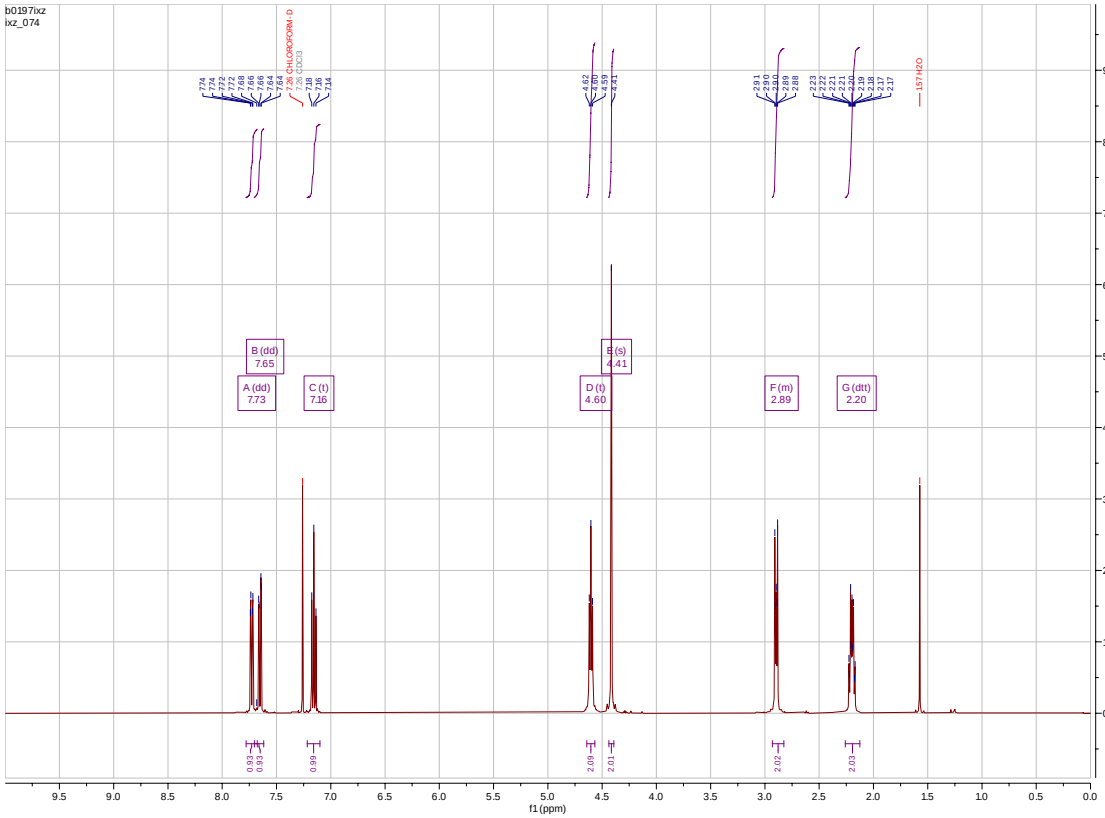


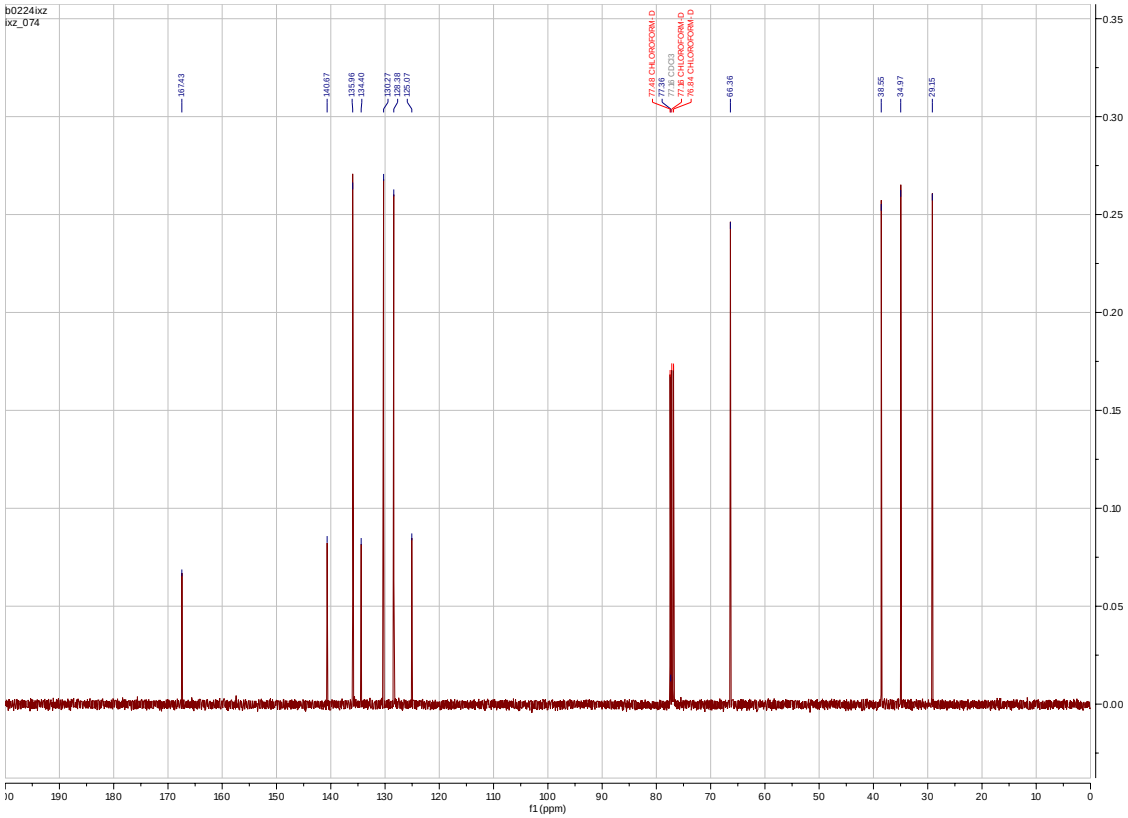
9-Bromo-4,5-dihydro-3*H*-benzo[*g*][1,5]oxathionin-1(7*H*)-one – 119



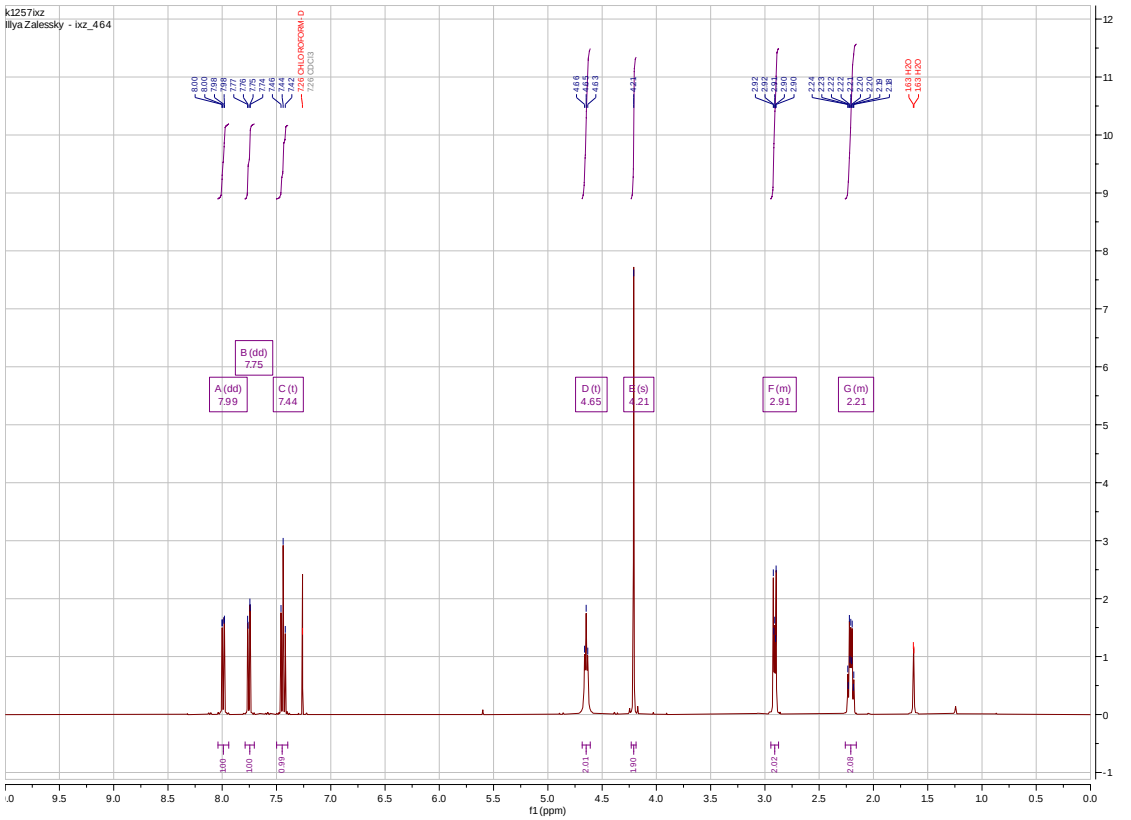


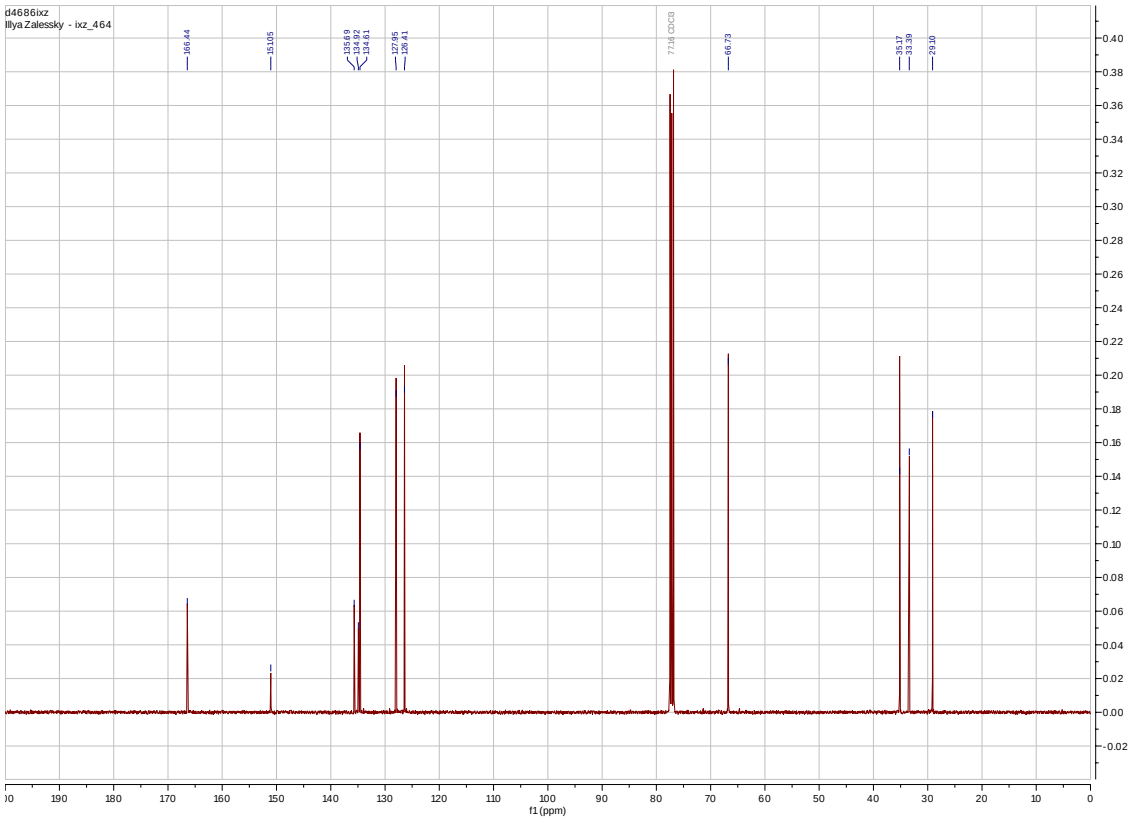
8-Bromo-4,5-dihydro-3*H*-benzo[*g*][1,5]oxathionin-1(7*H*)-one – 119



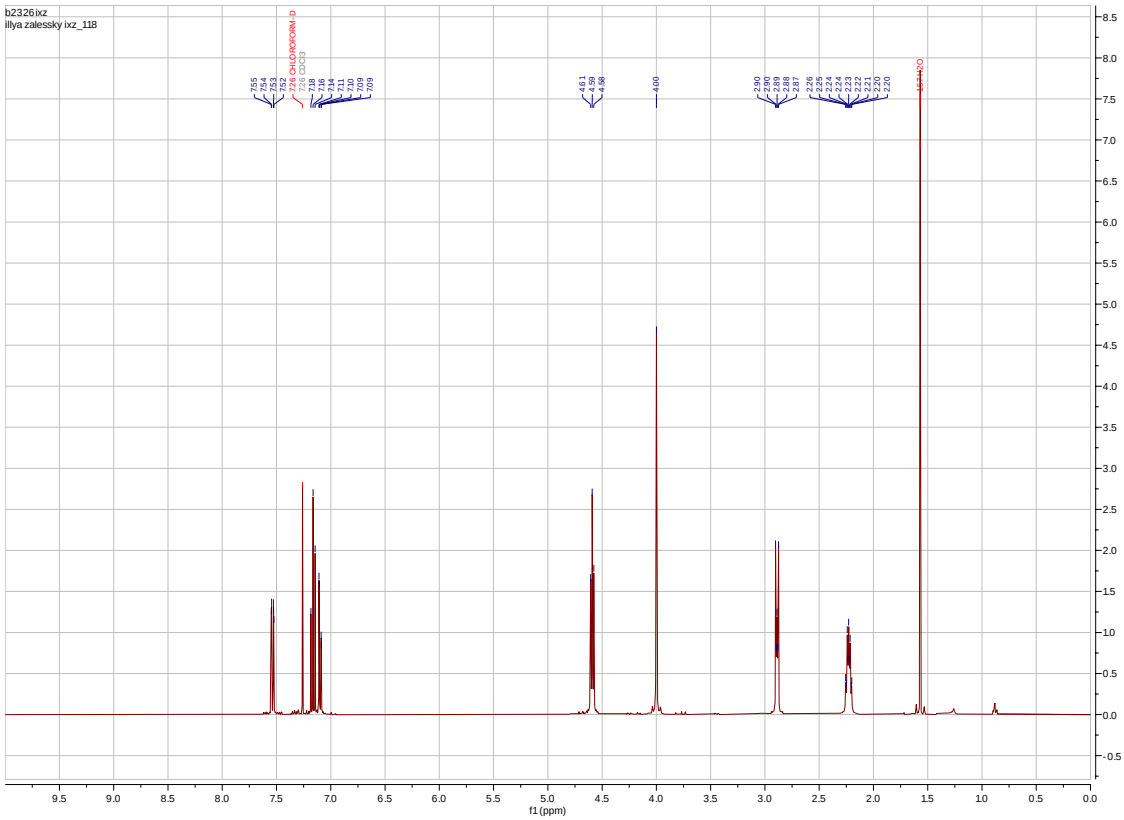


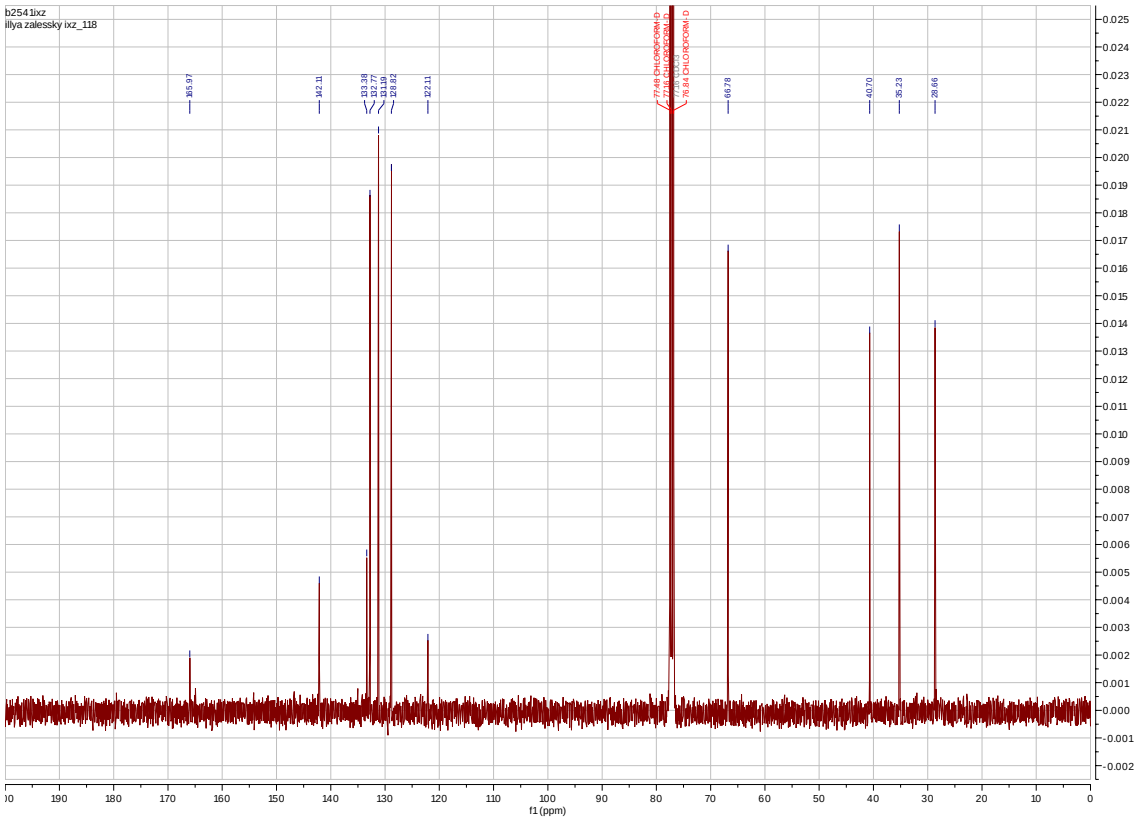
8-Nitro-4,5-dihydro-3*H*-benzo[*g*][1,5]oxathionin-1(7*H*)-one – 128



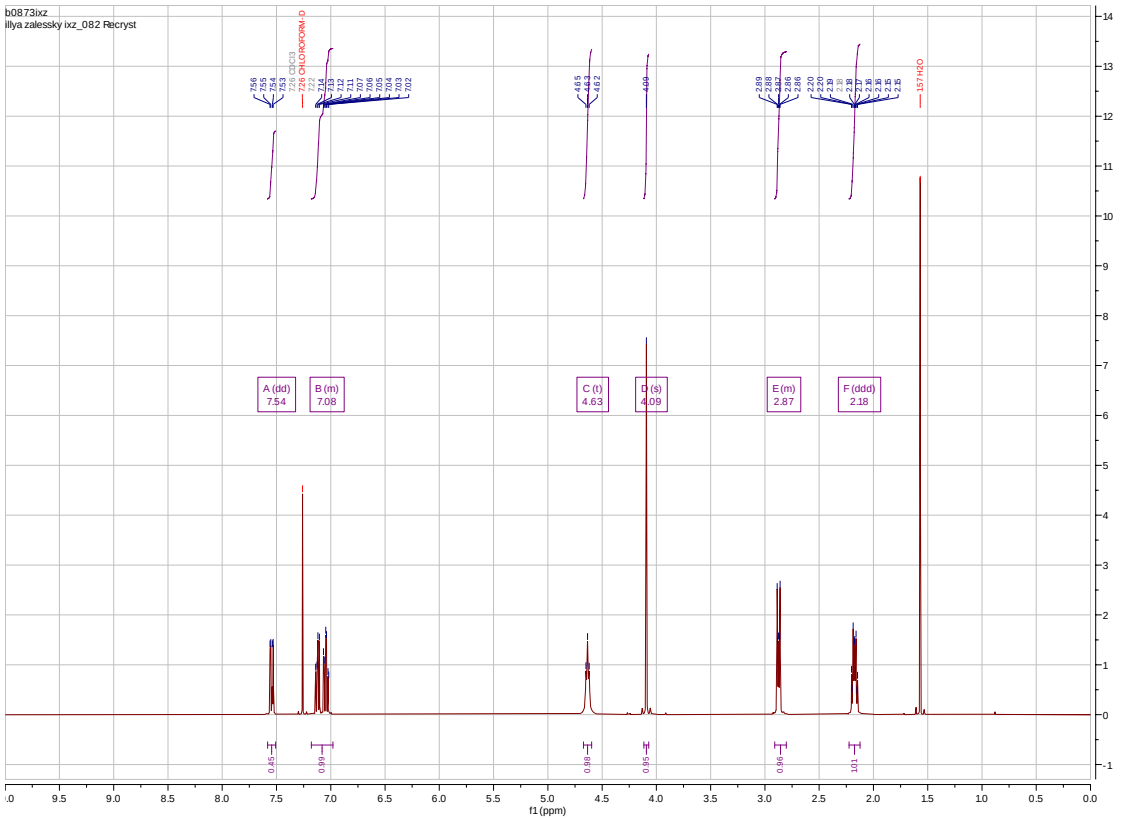


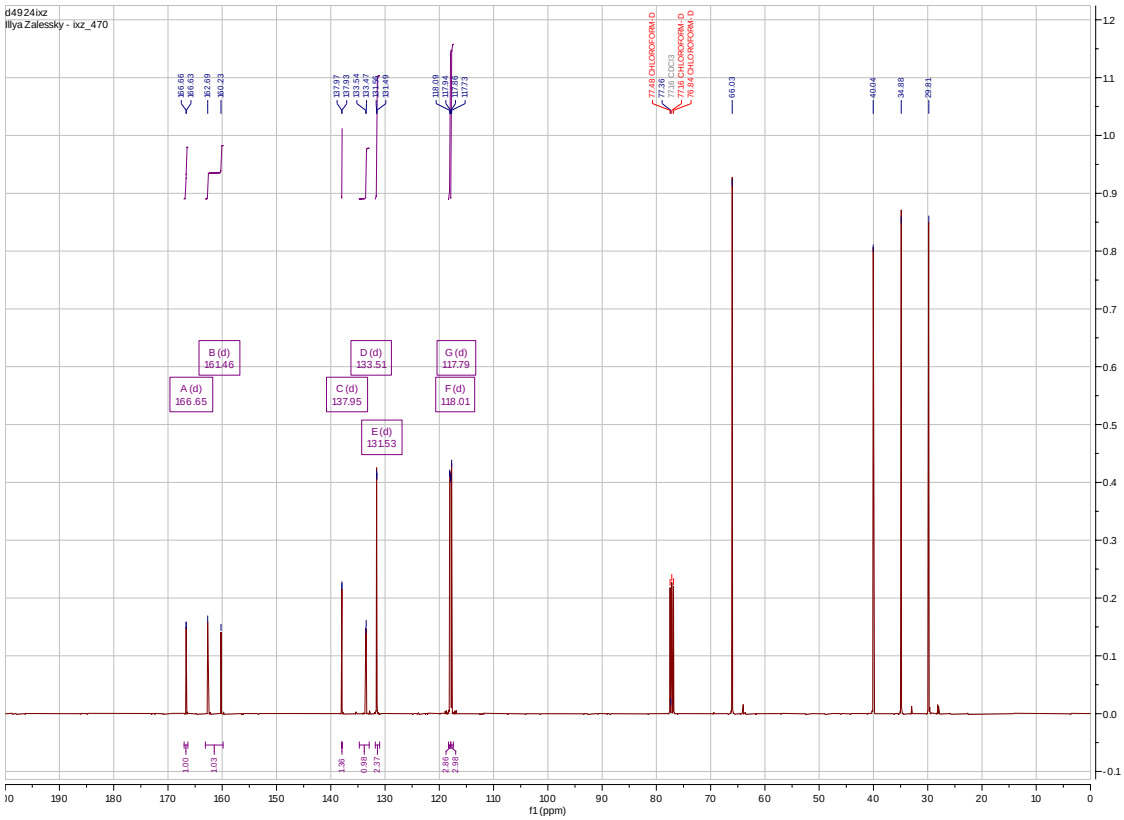
1-Bromo-4,5-dihydro-3*H*-benzo[*g*][1,5]oxathionin-1(7*H*)-one – 133

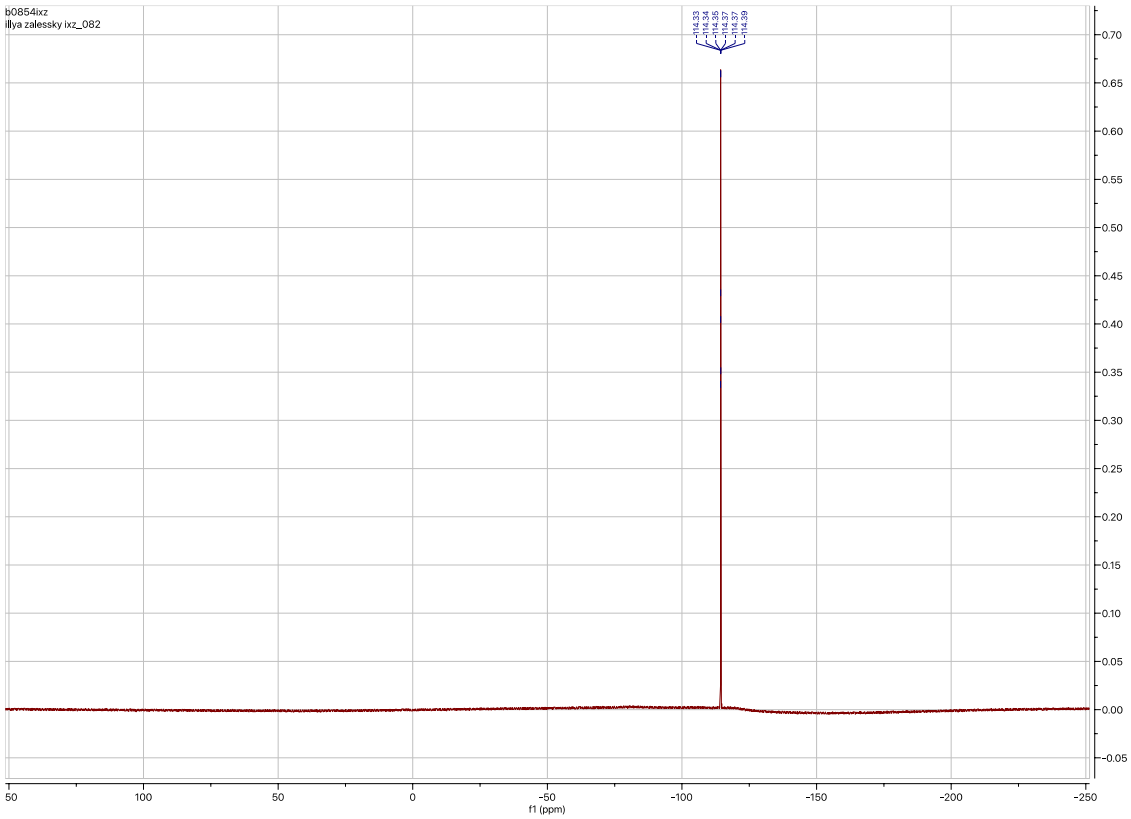




10-Fluoro-4,5-dihydro-3*H*-benzo[*g*][1,5]oxathionin-1(7*H*)-one – 138



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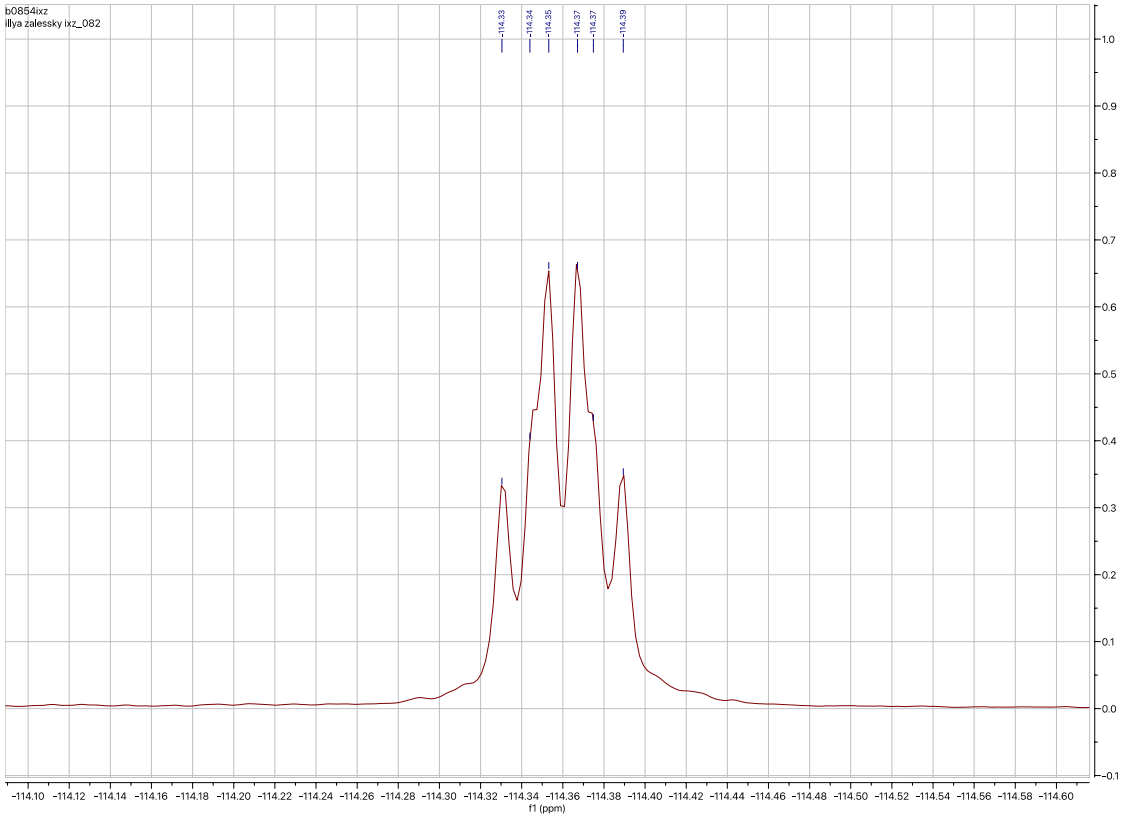
illya zalessky ixz_082
-114.33
-114.34
-114.35
-114.37
-114.37
-114.39
f1 (ppm)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illya zalessky ixz_082
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-114.34
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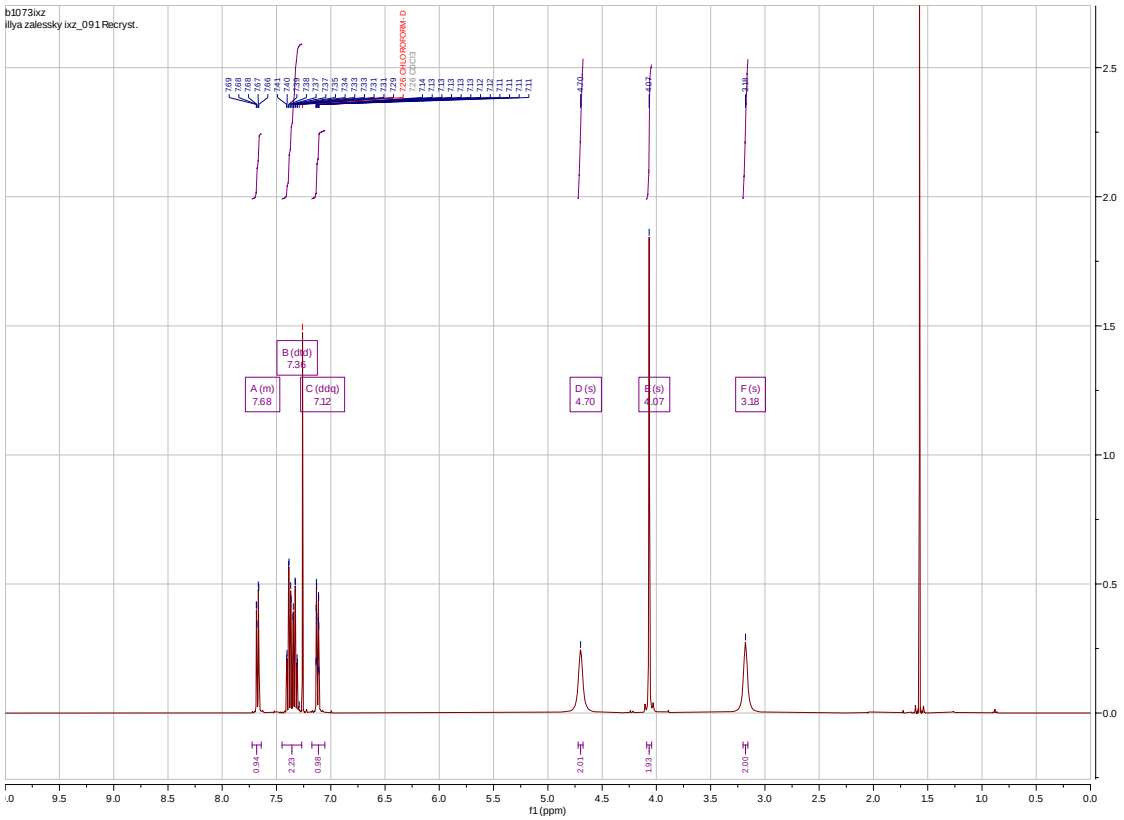
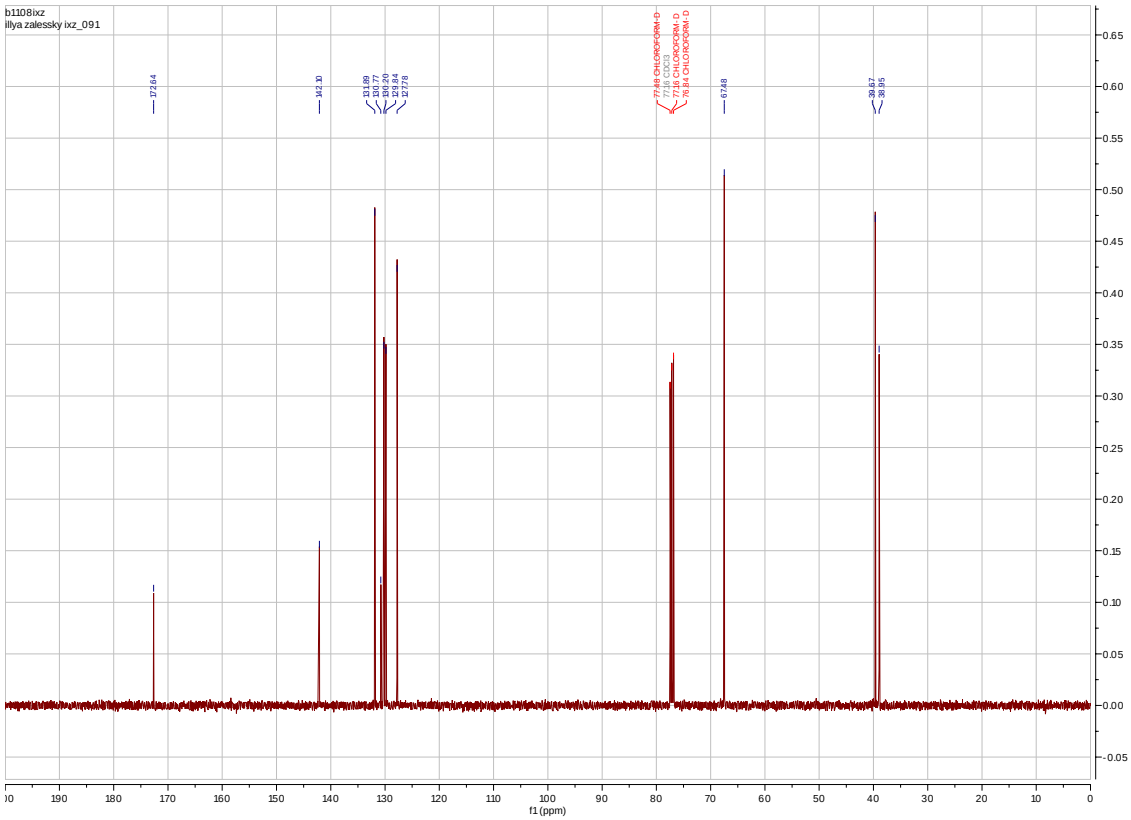
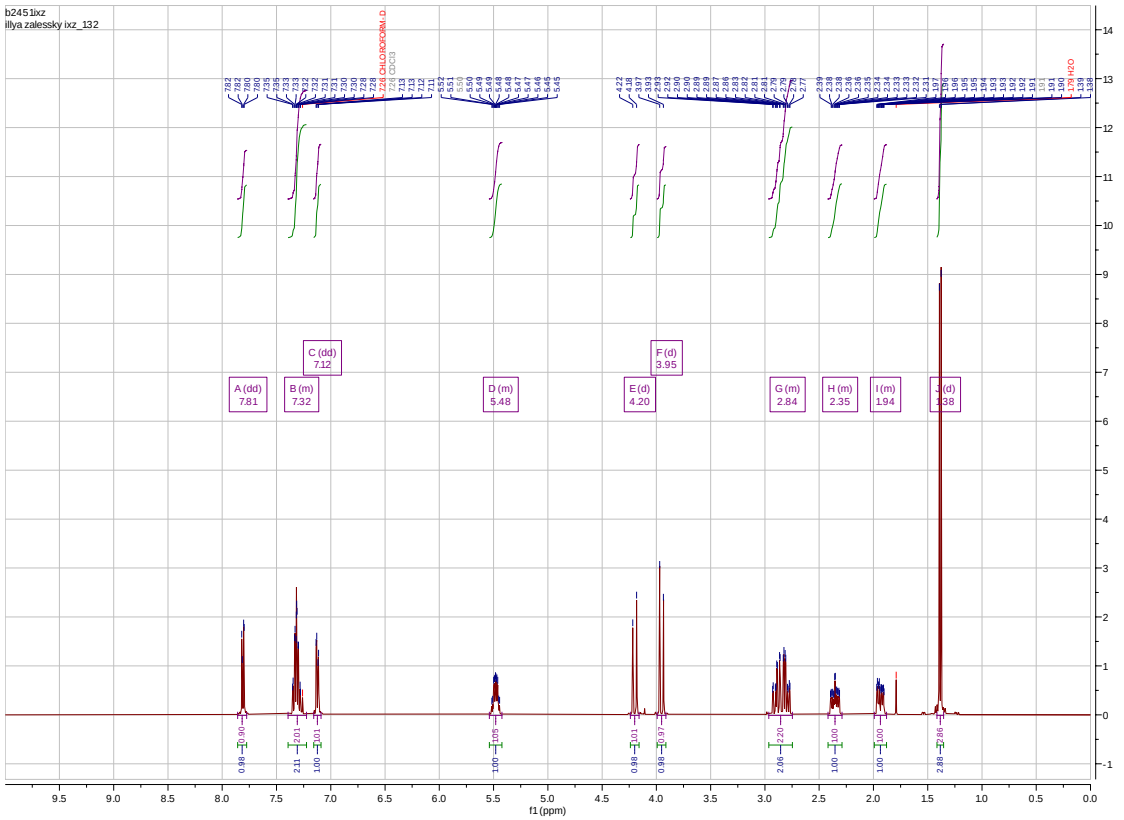
-114.37
-114.39
f1 (ppm)

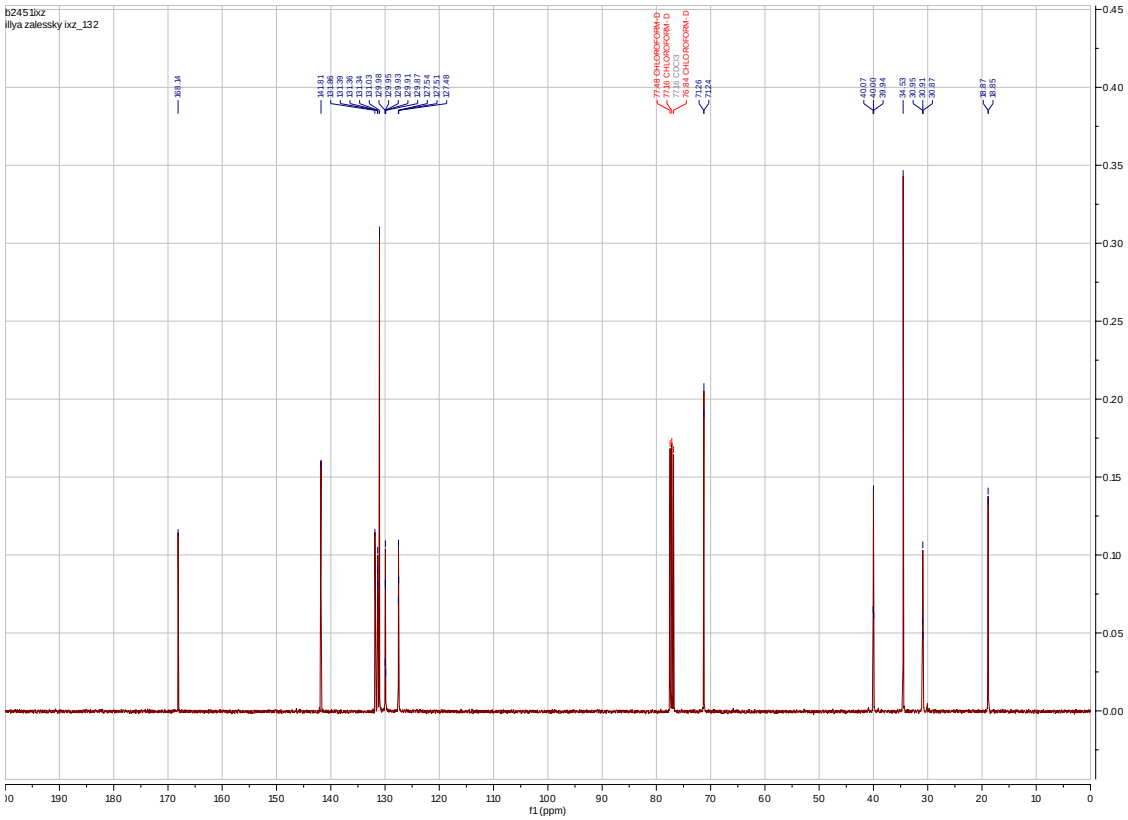
3,4-Dihydrobenzo[*f*][1,4]oxathiocin-1(6*H*)-one – 142



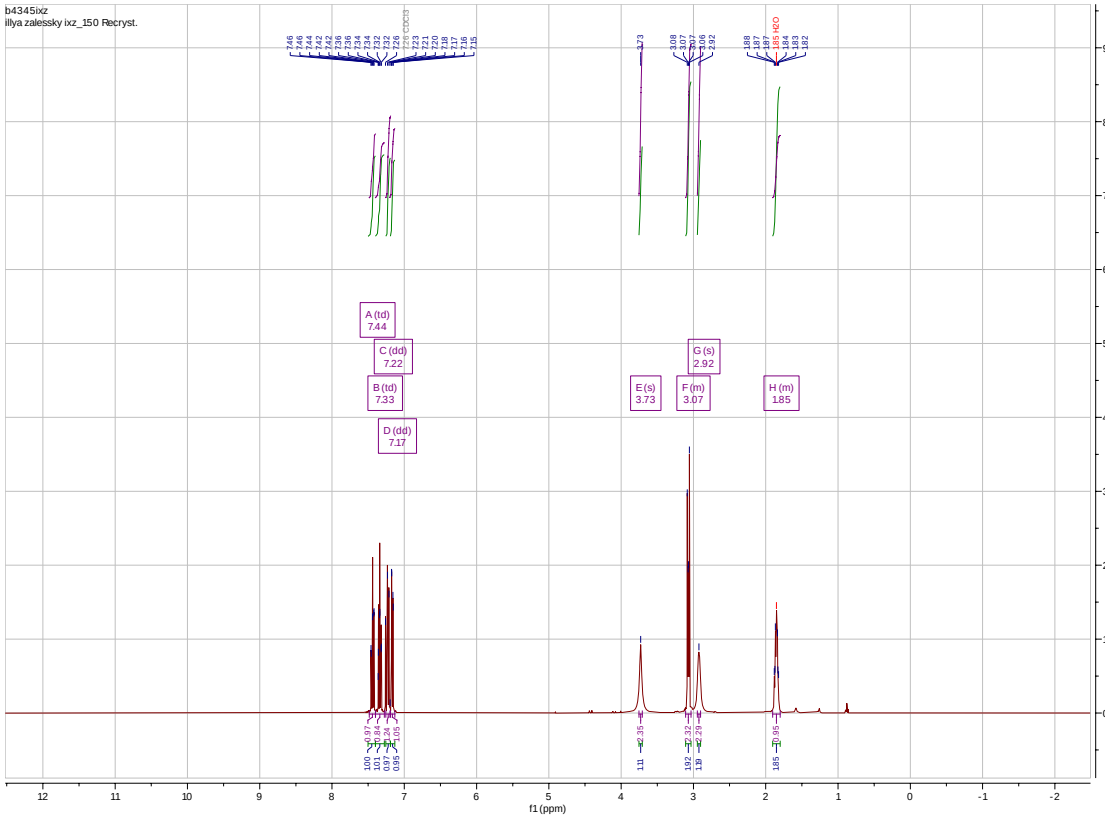


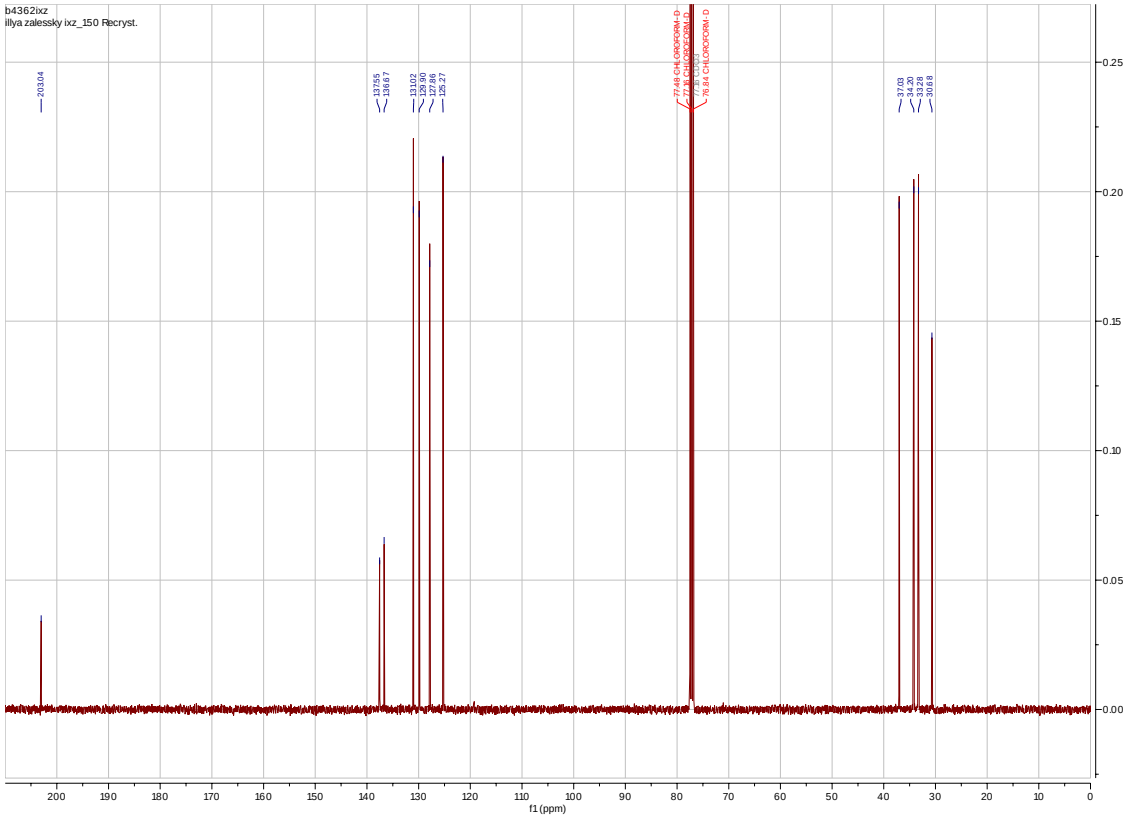
3-Methyl-4,5-dihydro-3H-benzo[*g*][1,5]oxathionin-1(7*H*)-one – 152



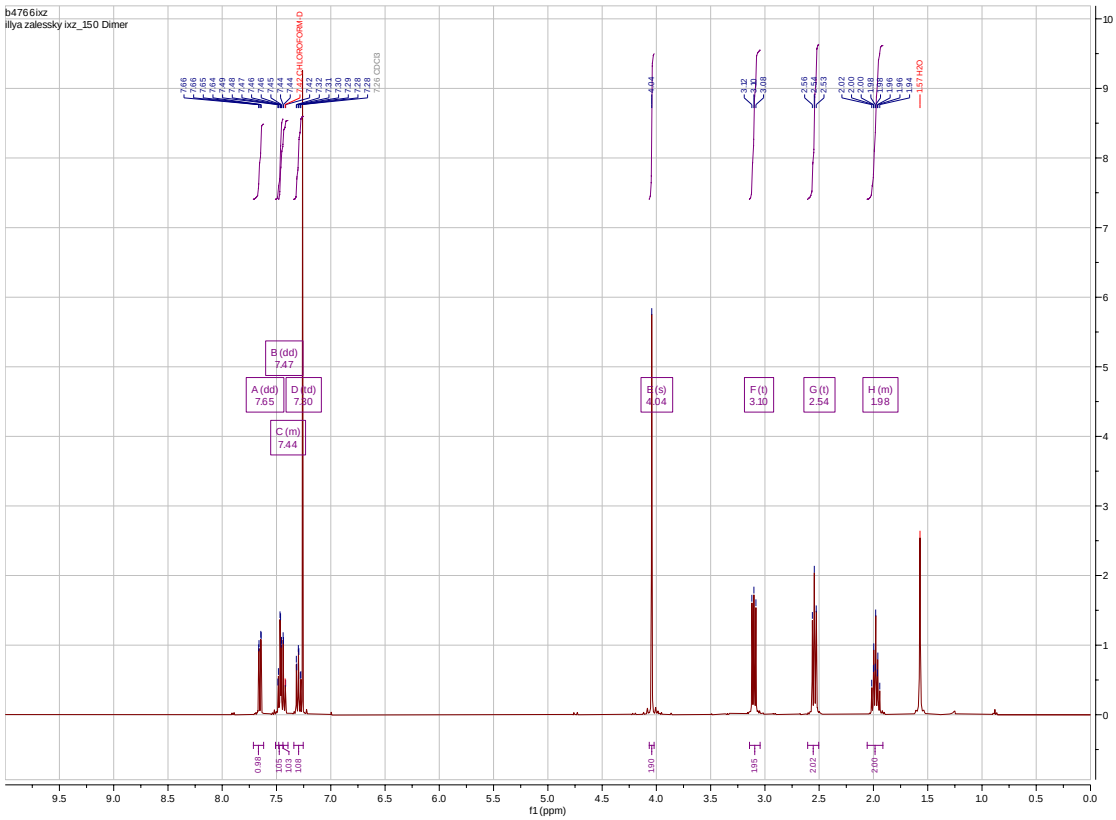


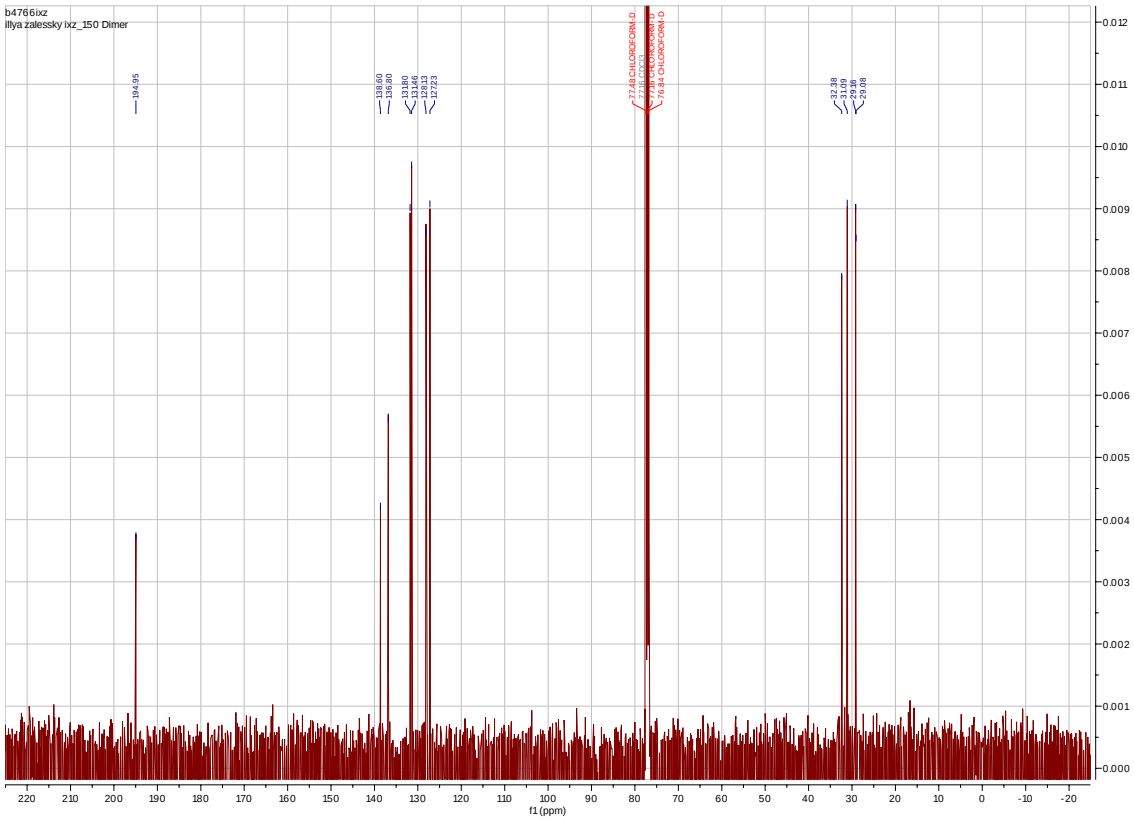
4,5-Dihydro-3*H*-benzo[*g*][1,5]dithionin-1(7*H*)-one – 162



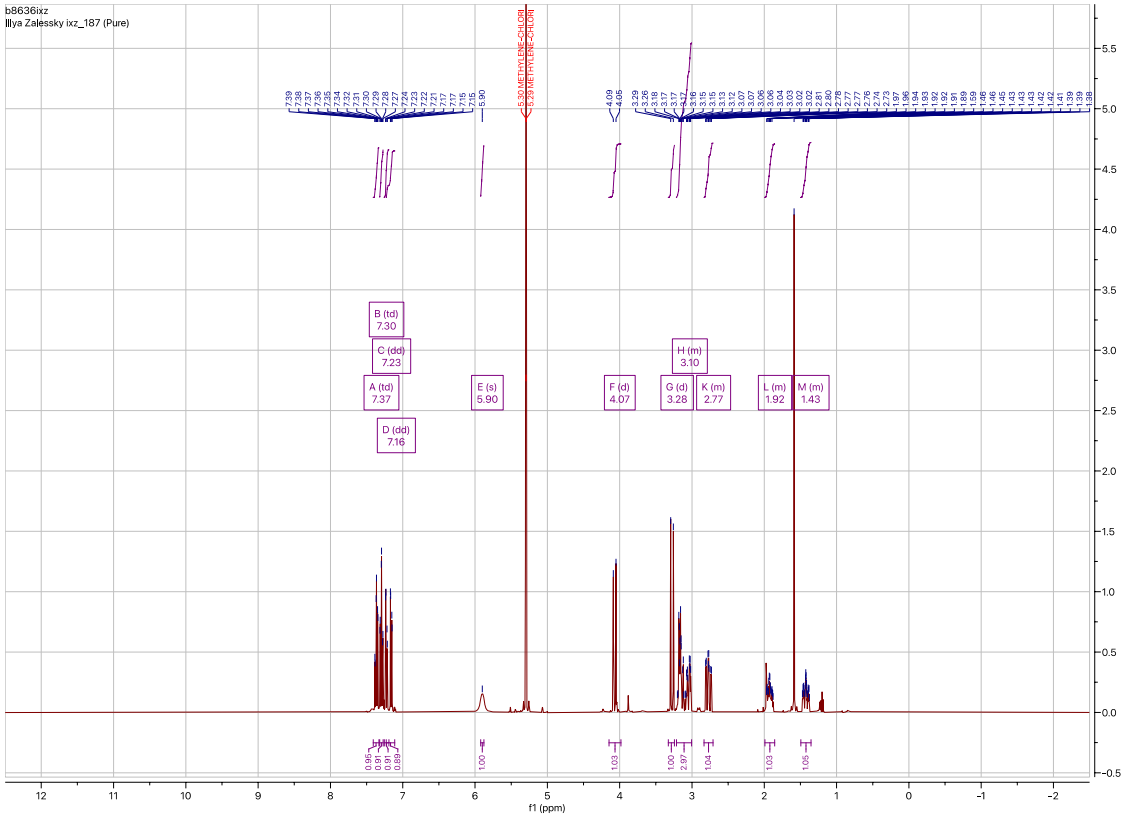


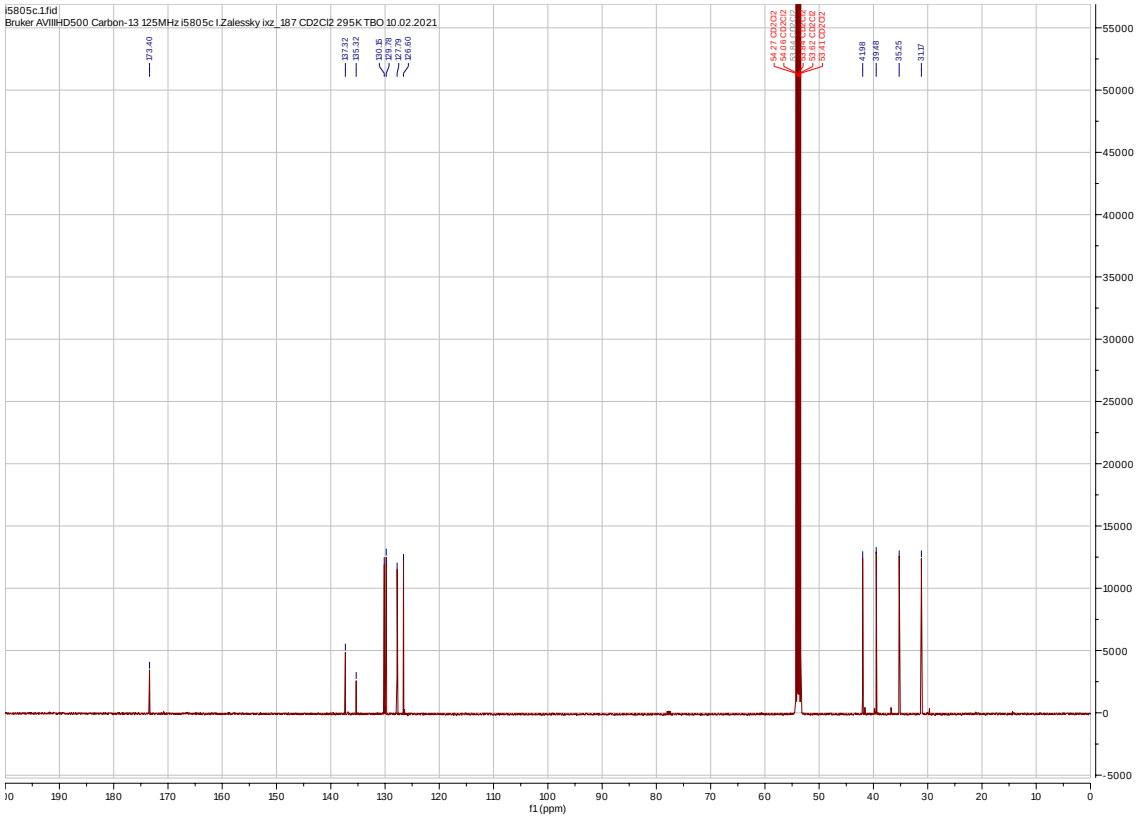
8,9,19,20-Tetrahydro-7*H*,18*H*-dibenzo[*g*,*p*][1,5,10,14]tetrathiacyclooctadecine-5,16(11*H*,22*H*)-dione – 163



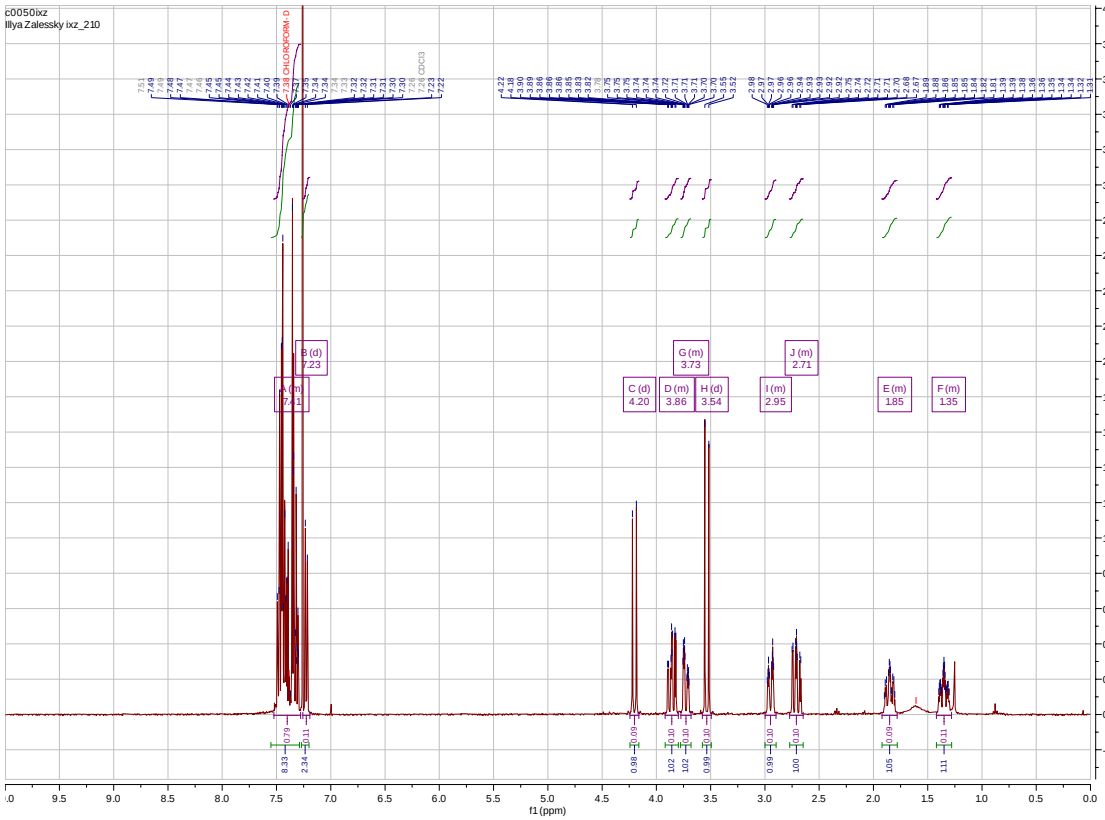


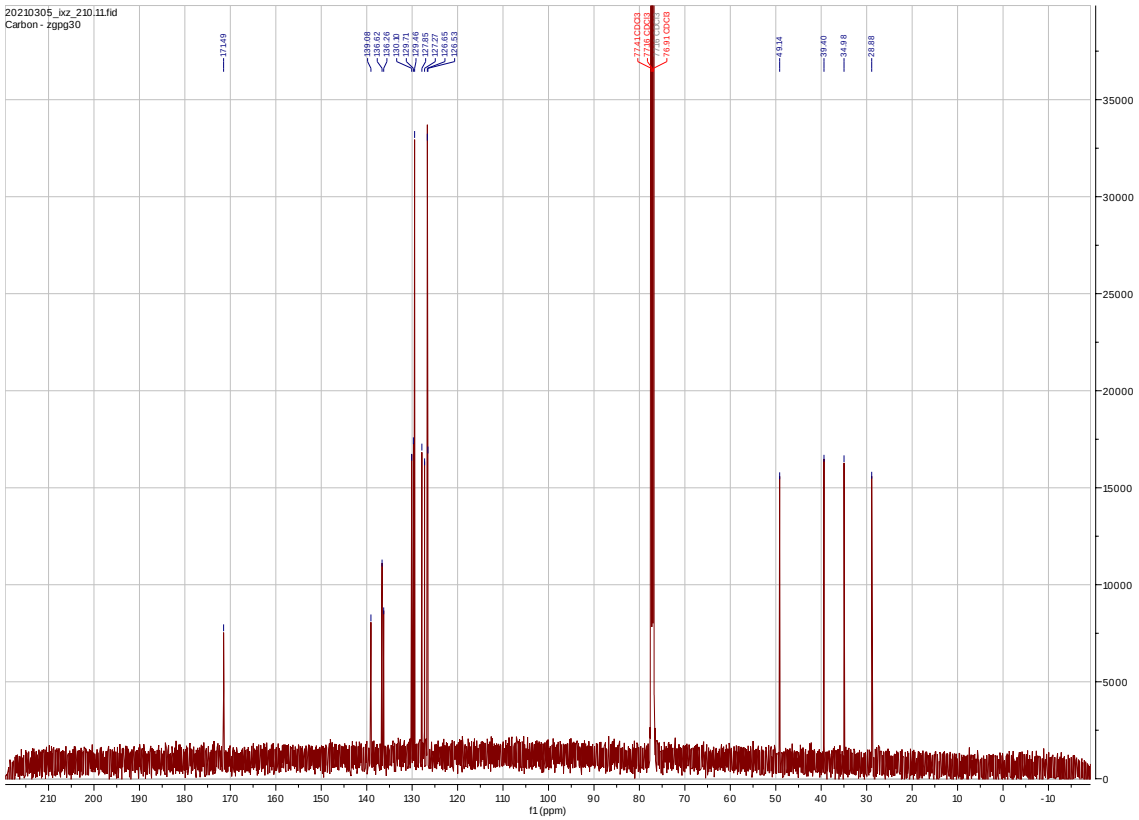
3,4,5,6-Tetrahydrobenzo[*g*][1,5]thiazonin-7(1*H*)-one – 168



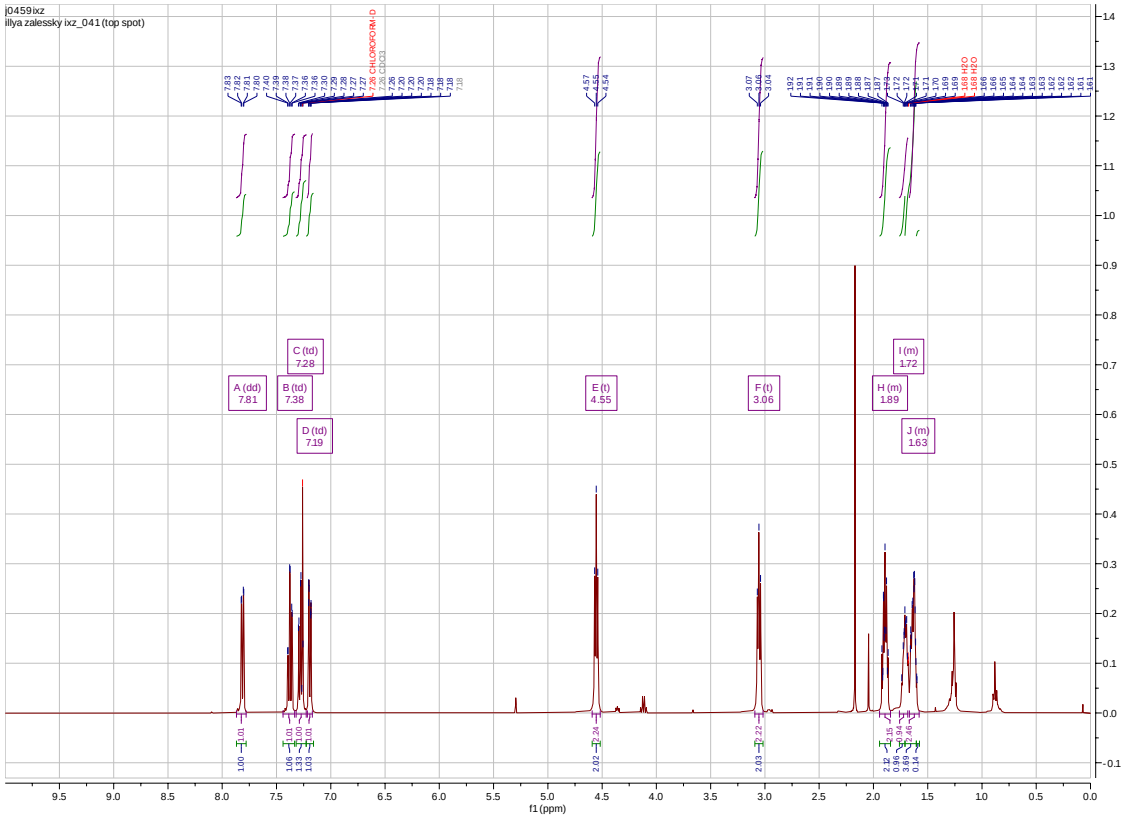


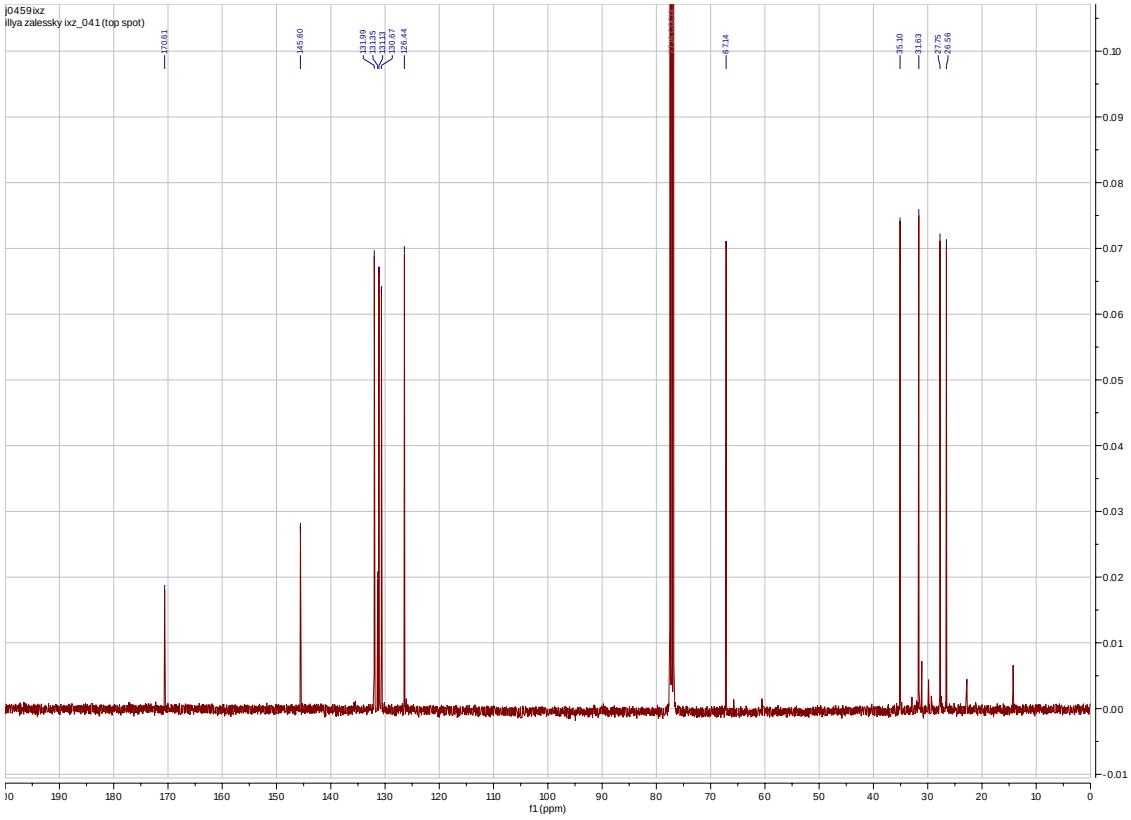
6-Phenyl-3,4,5,6-tetrahydrobenzo[*g*][1,5]thiazonin-7(1*H*)-one – 171



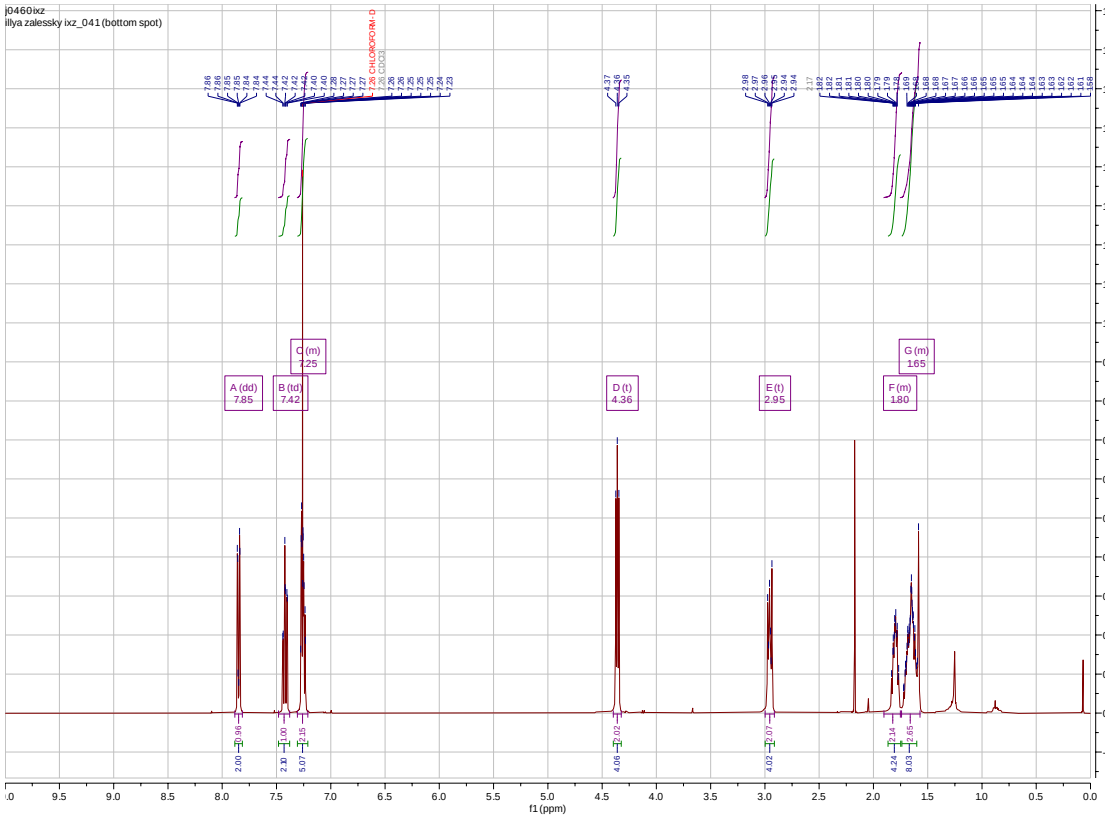


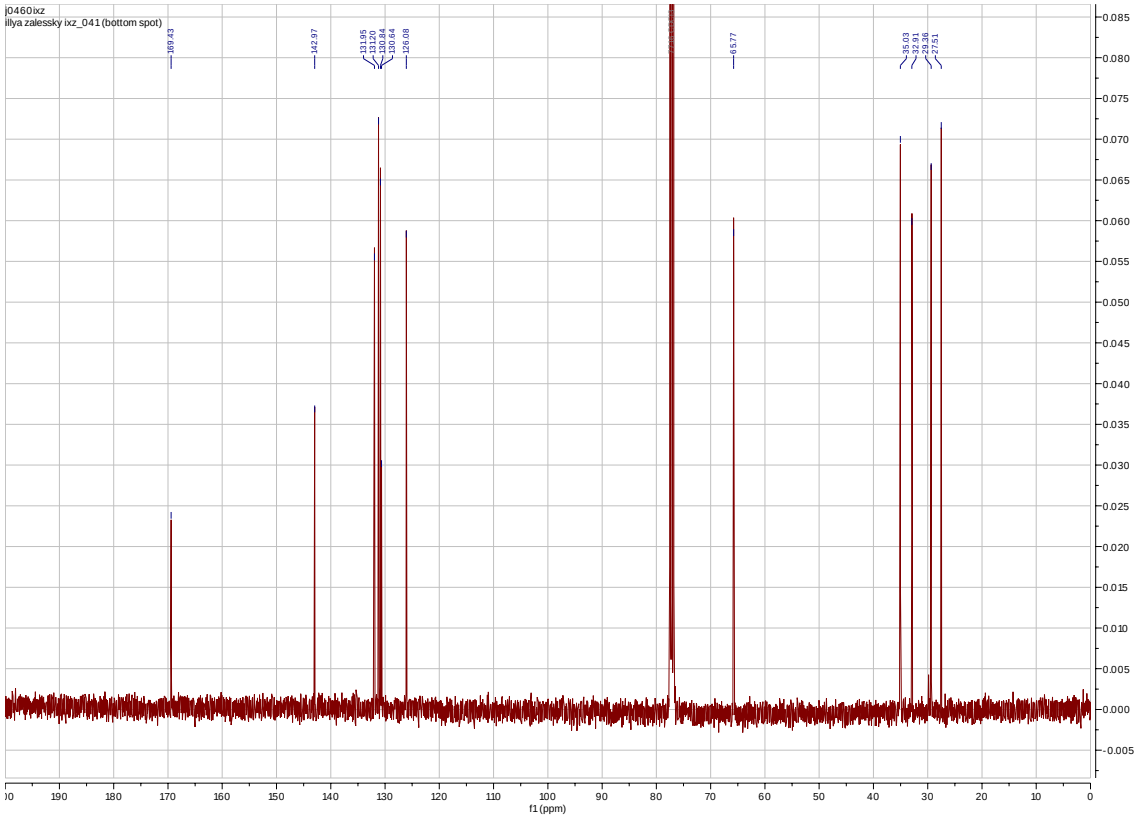
4,5,6,7-Tetrahydrobenzo[*c*]oxonin-1(3*H*)-one – 176



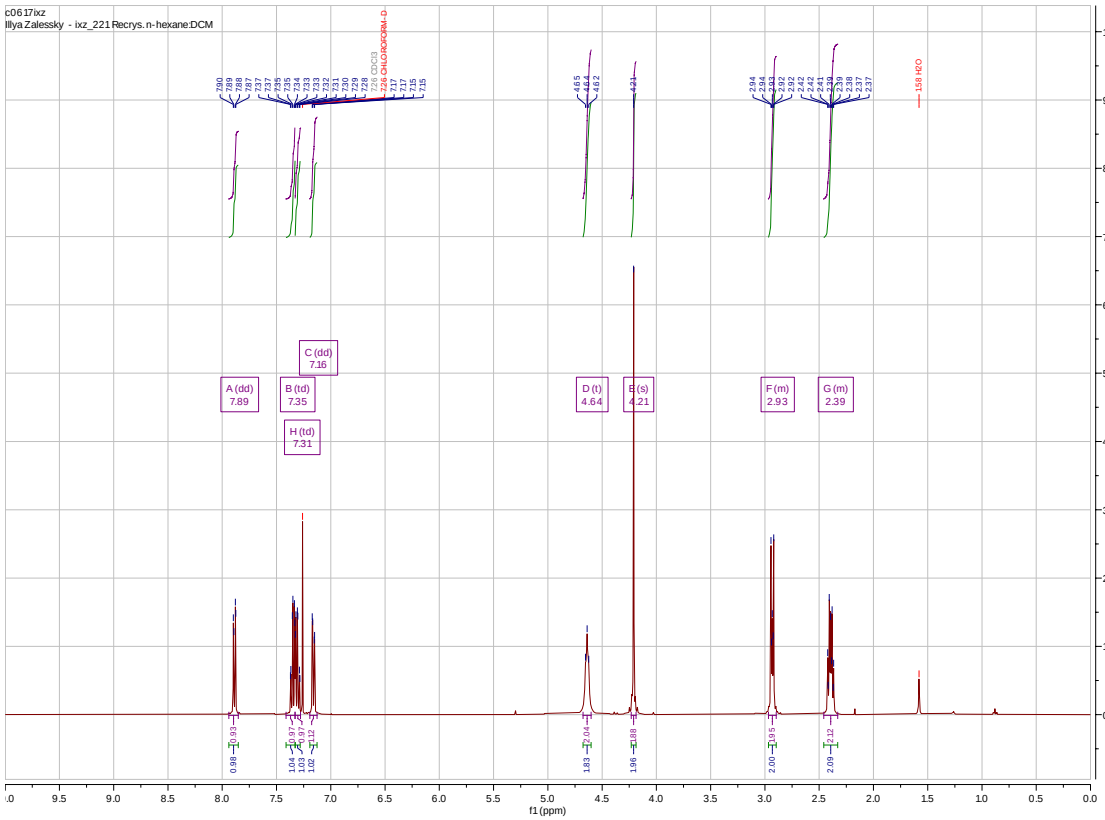


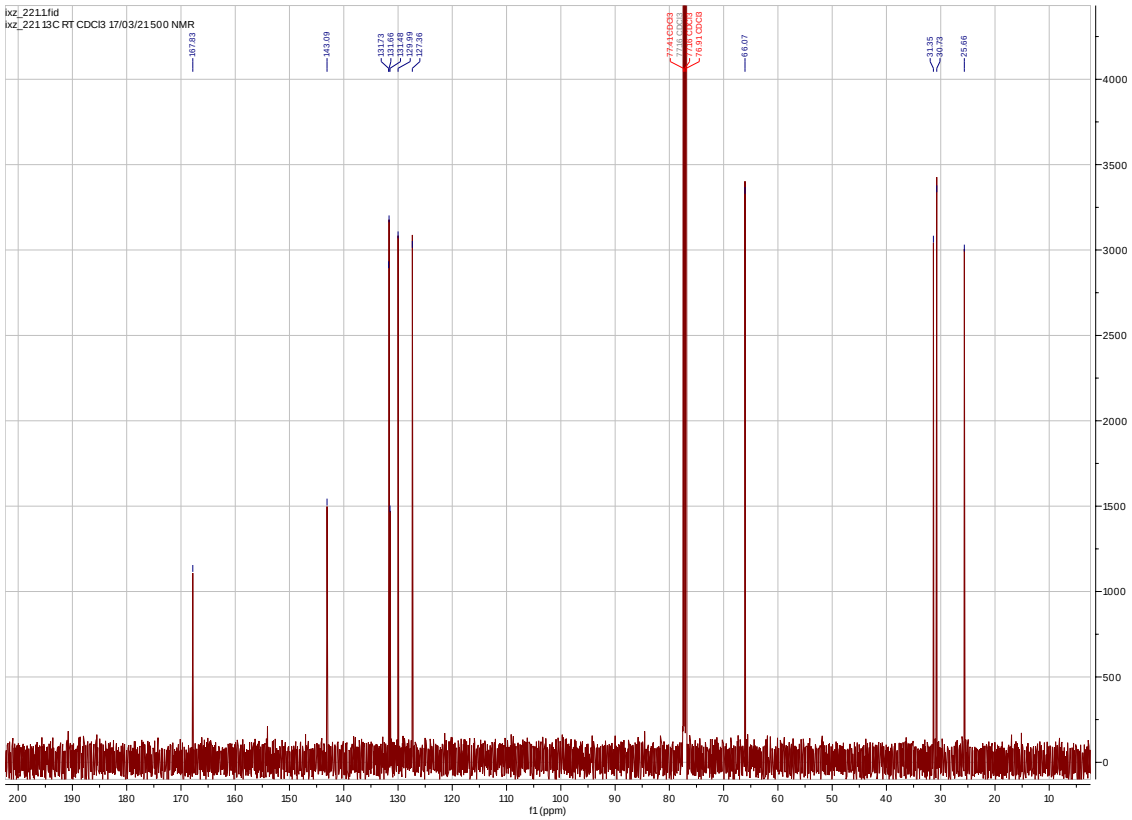
8,9,10,11,19,20,21,22-Octahydrodibenzo[*c*,*l*][1,10]dioxacyclooctadecine-5,16(7*H*,18*H*)-dione – 177



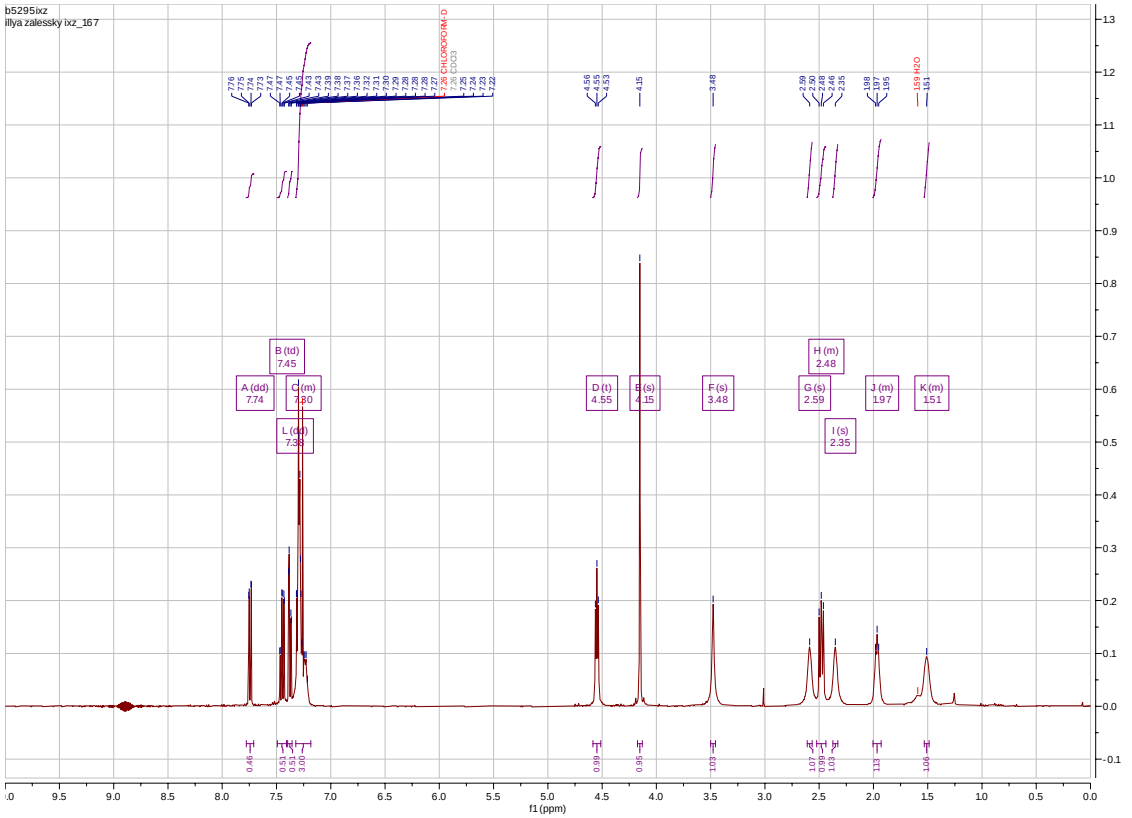


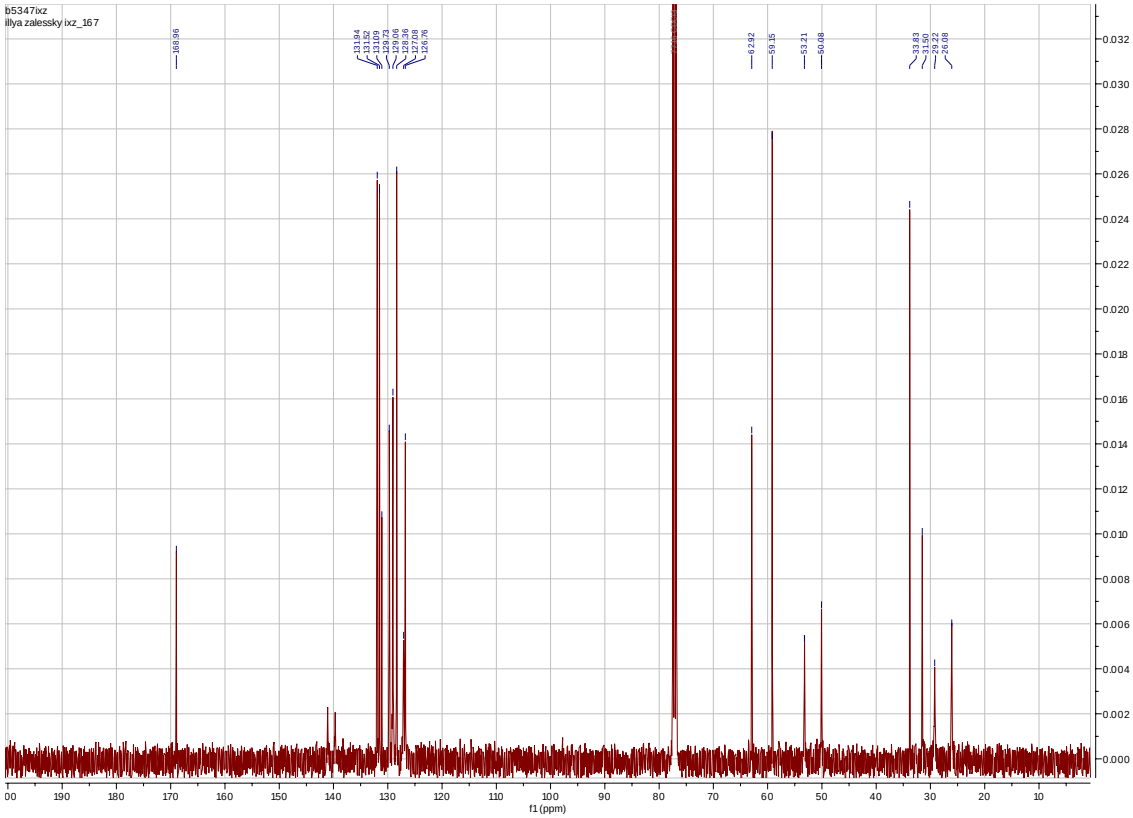
4,5-Dihydro-3*H*-benzo[g][1,5]oxaselenonin-1(7*H*)-one – 191





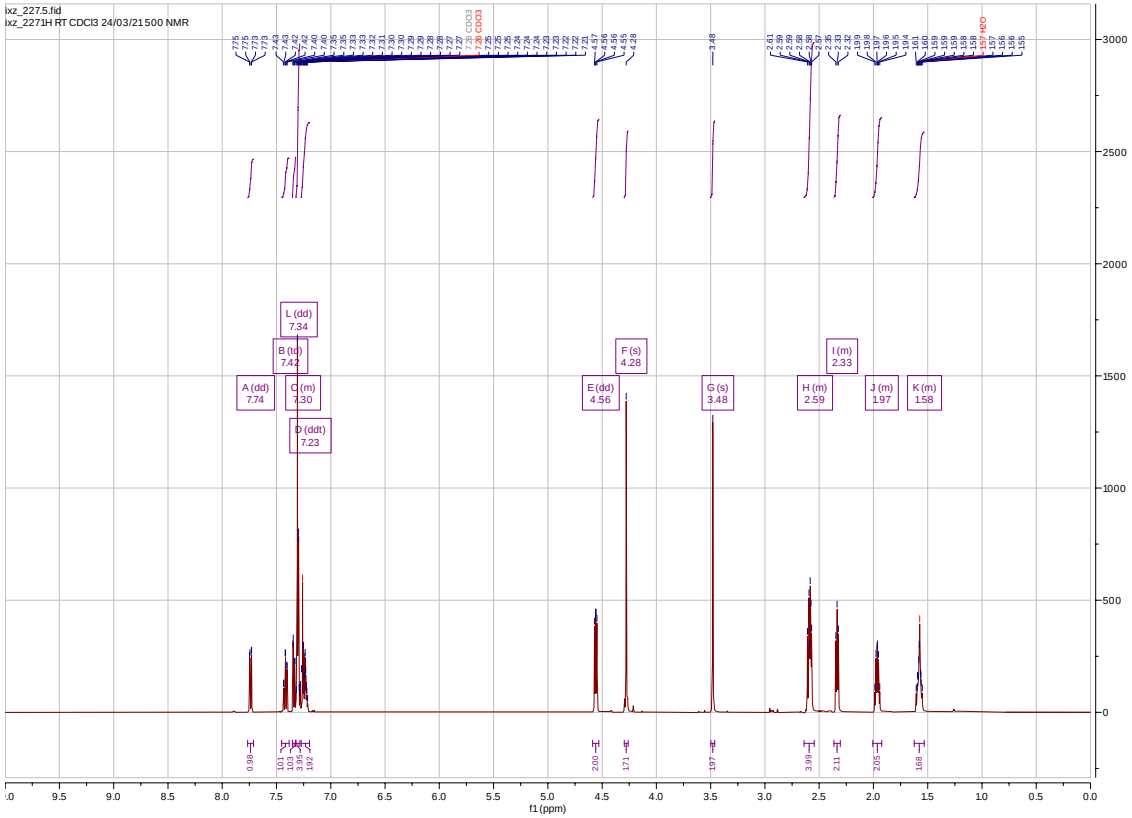
6-Benzyl-4,5,6,7,8,9-hexahydro-3H-benzo[*k*][1]oxa[9]thia[5]azacyclotridecin-1(11*H*)-one – 195

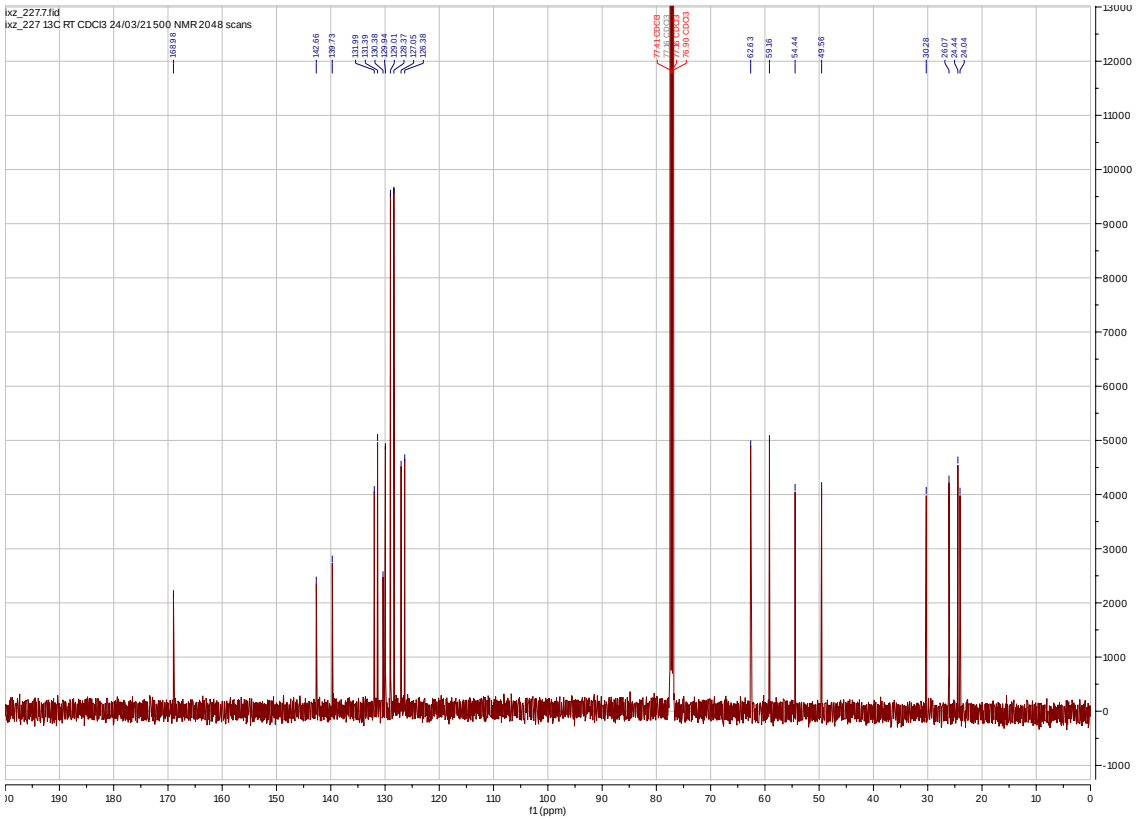




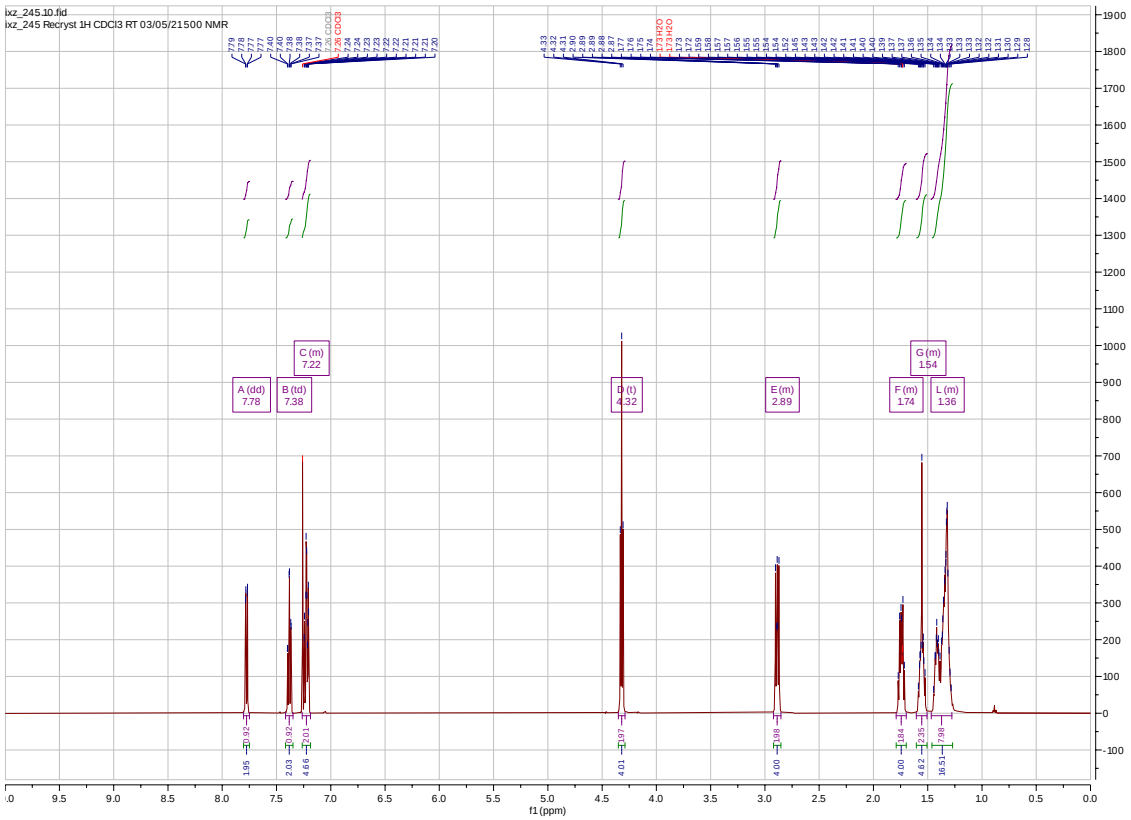
6-Benzyl-4,5,6,7,8,9-hexahydro-3*H*-benzo[*k*][1]oxa[9]selena[5]azacyclotridecin-1(11*H*)

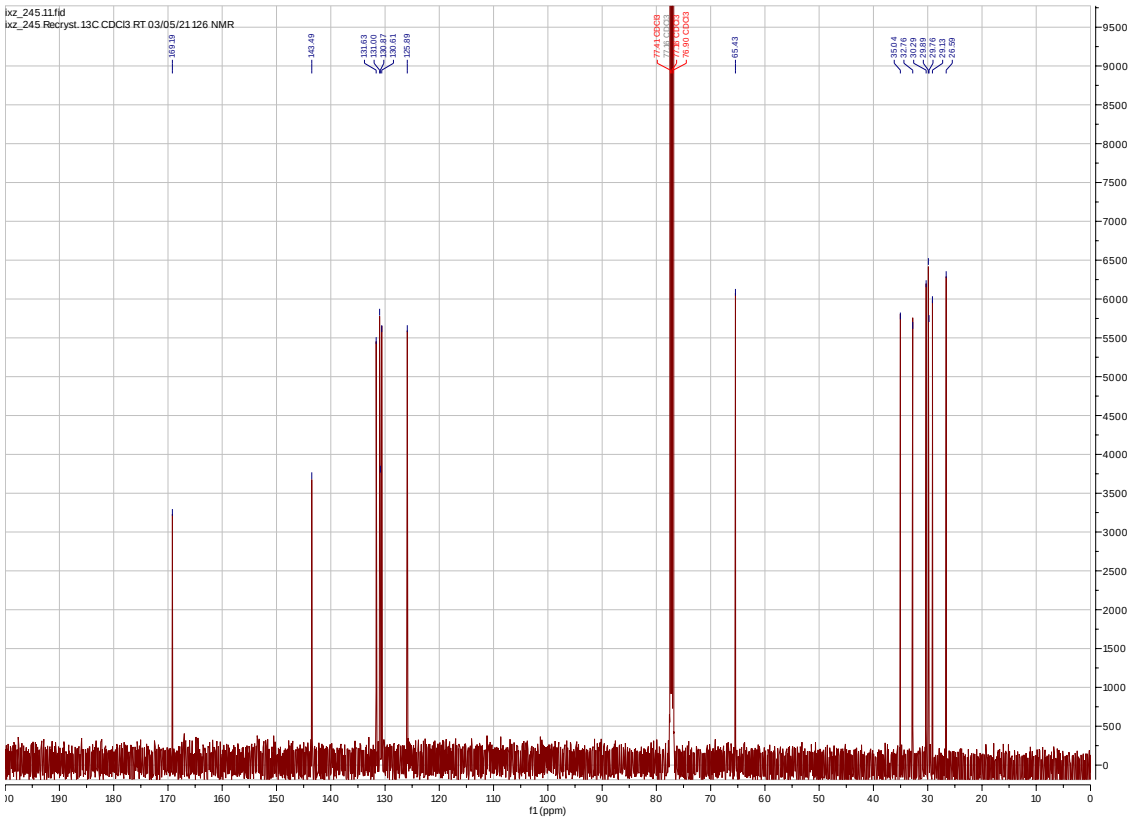
– **204**



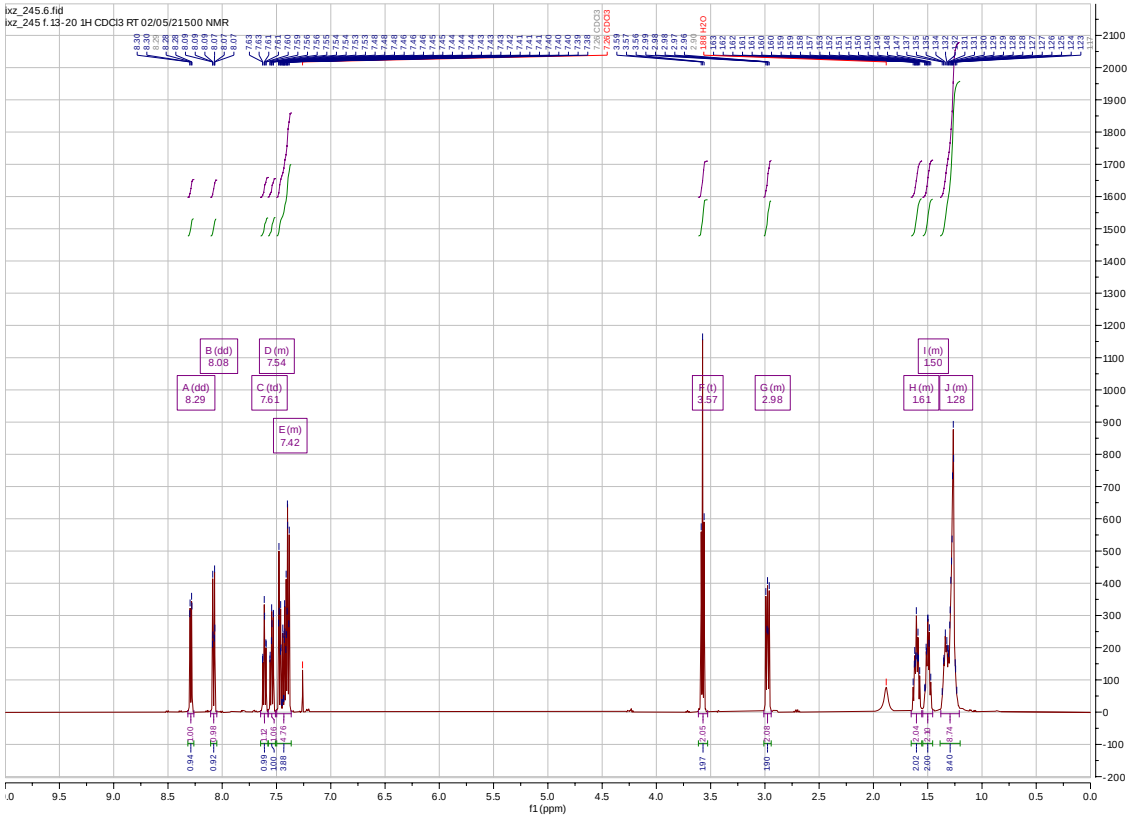


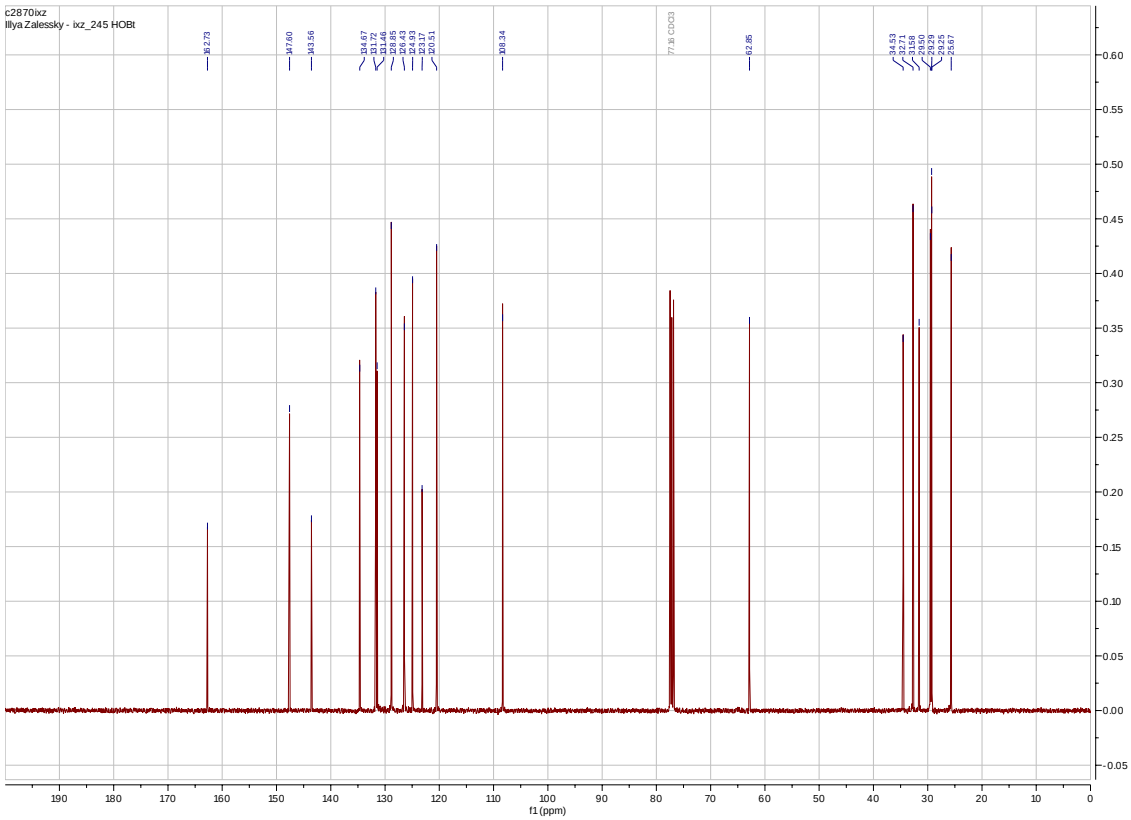
7,8,9,10,11,12,13,14,21,22,23,24,25,26,27,28-Hexadecahydro-5*H*,19*H*-dibenzo[*c*,*o*][1,13]dioxacyclotetracosine-5,19-dione – 219



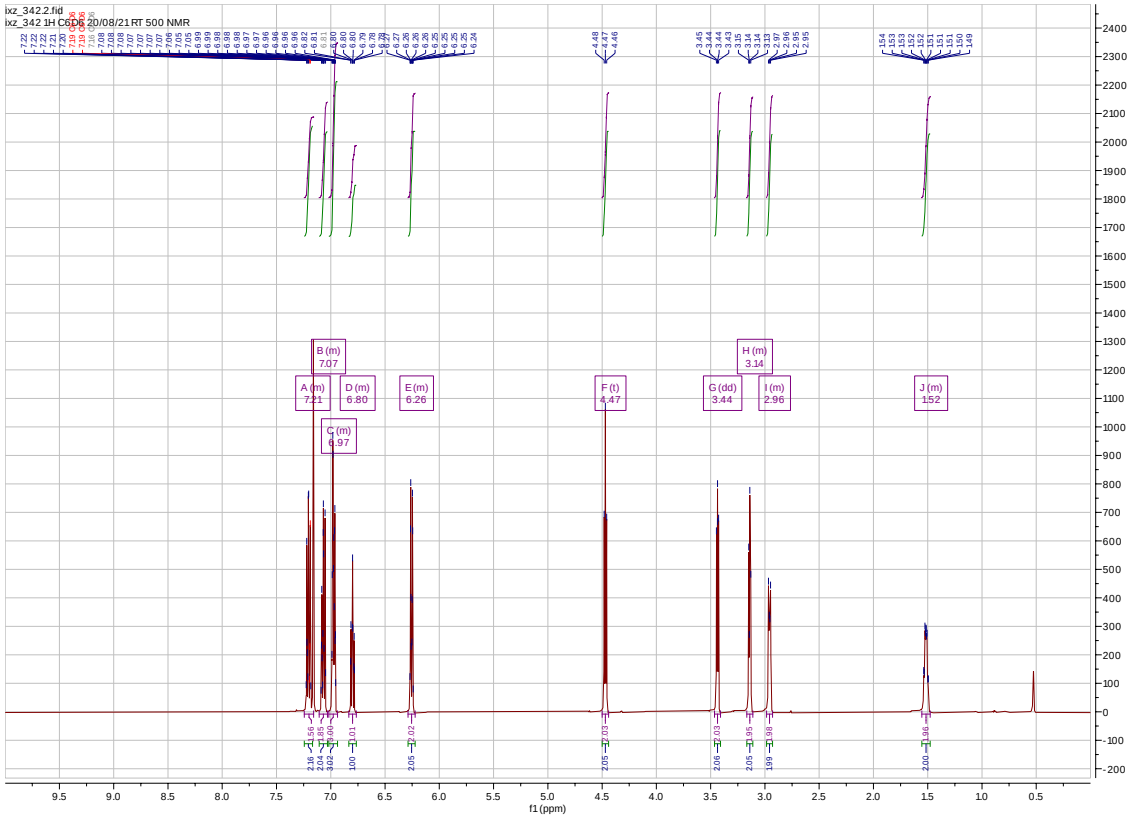


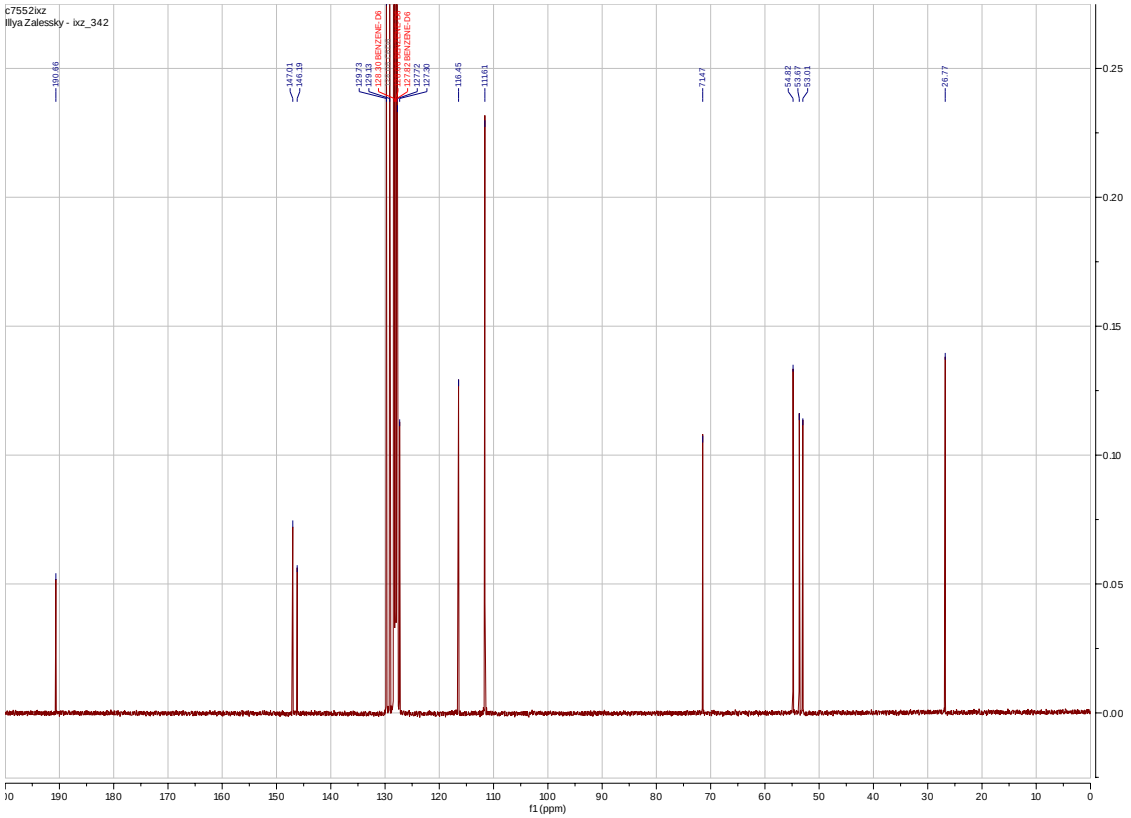
1*H*-Benzo[*d*][1,2,3]triazol-1-yl 2-(8-hydroxyoctyl)benzoate 220



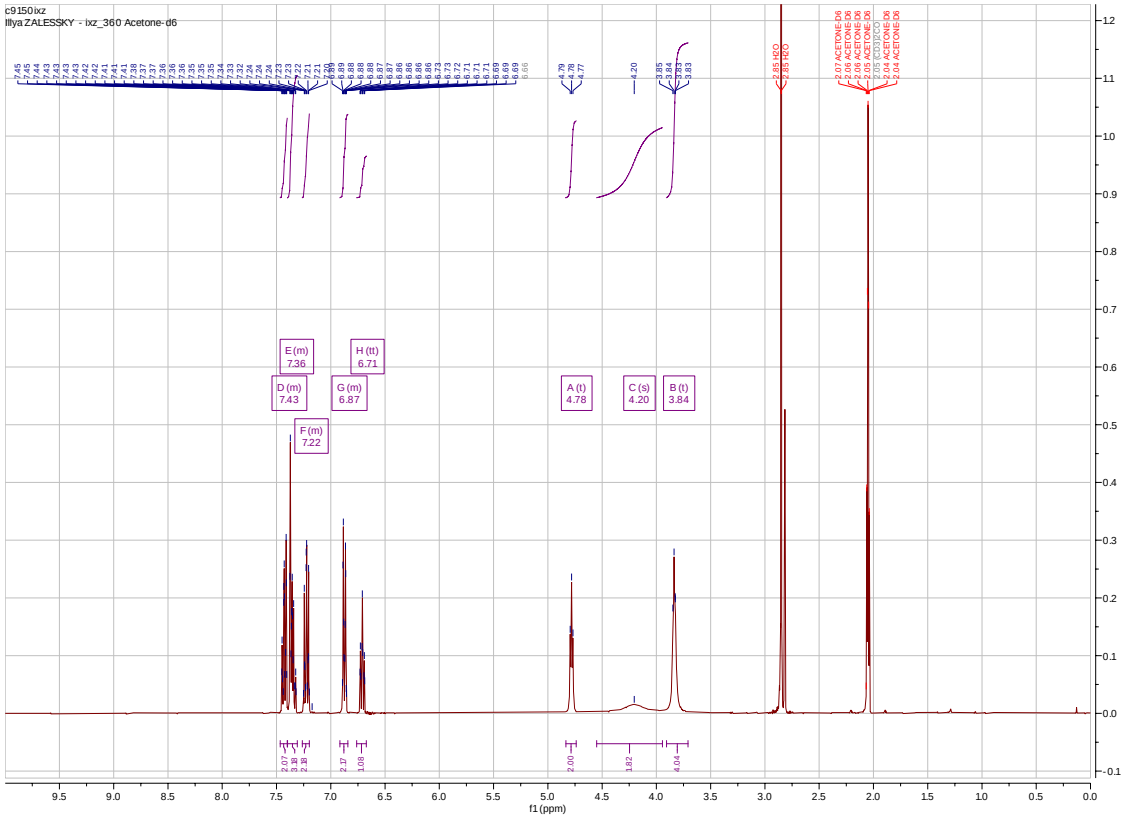


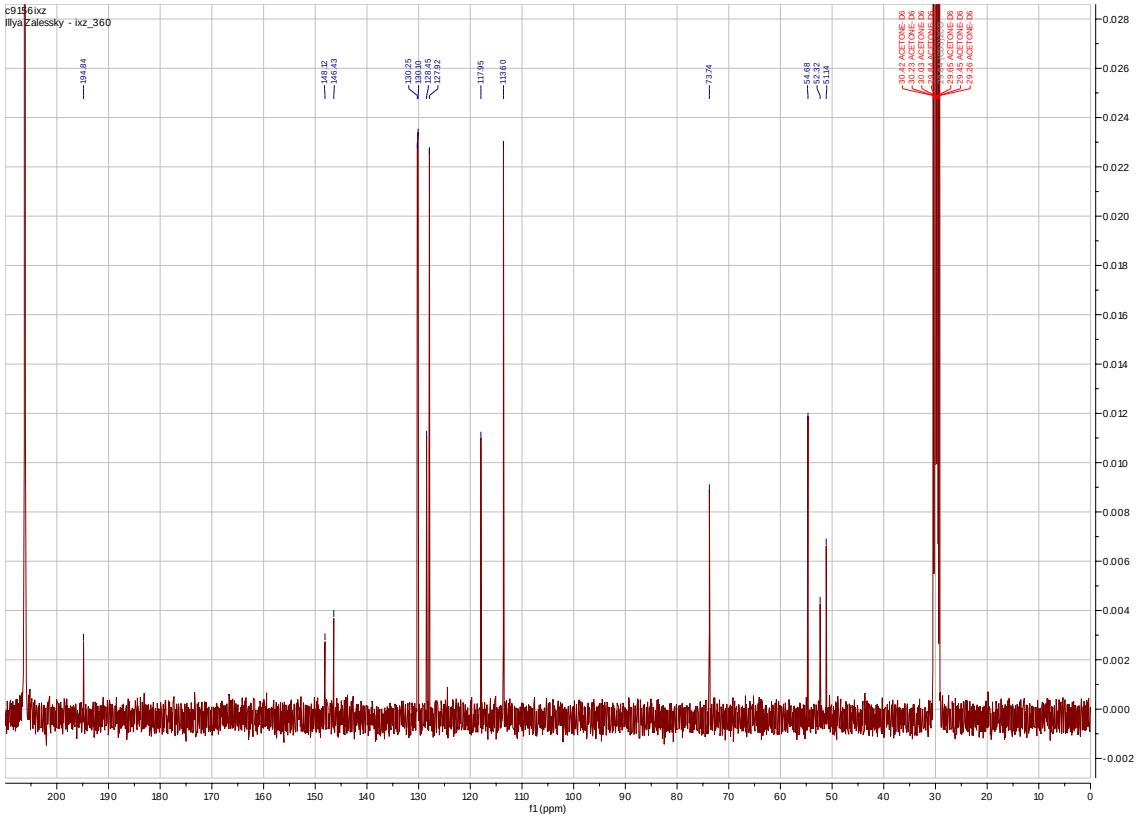
3,6-Diphenyl-1,3,6-oxadiazonane-2-thione – 245



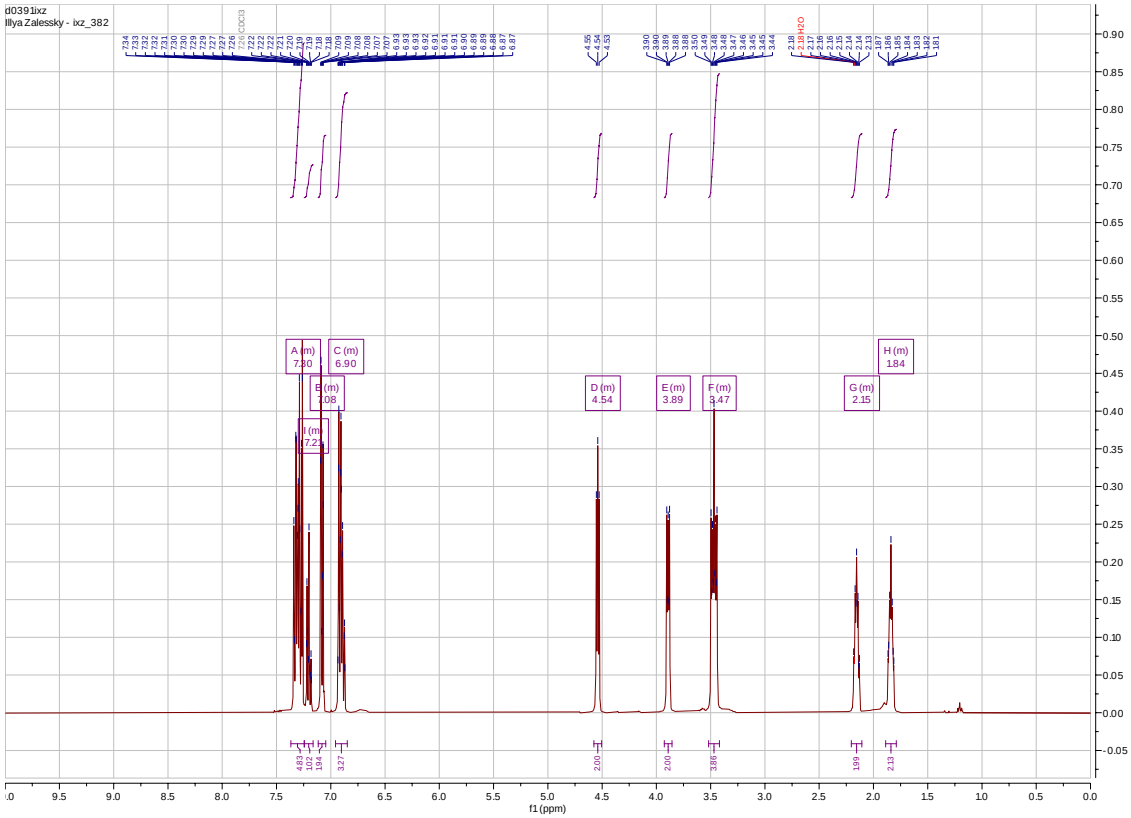


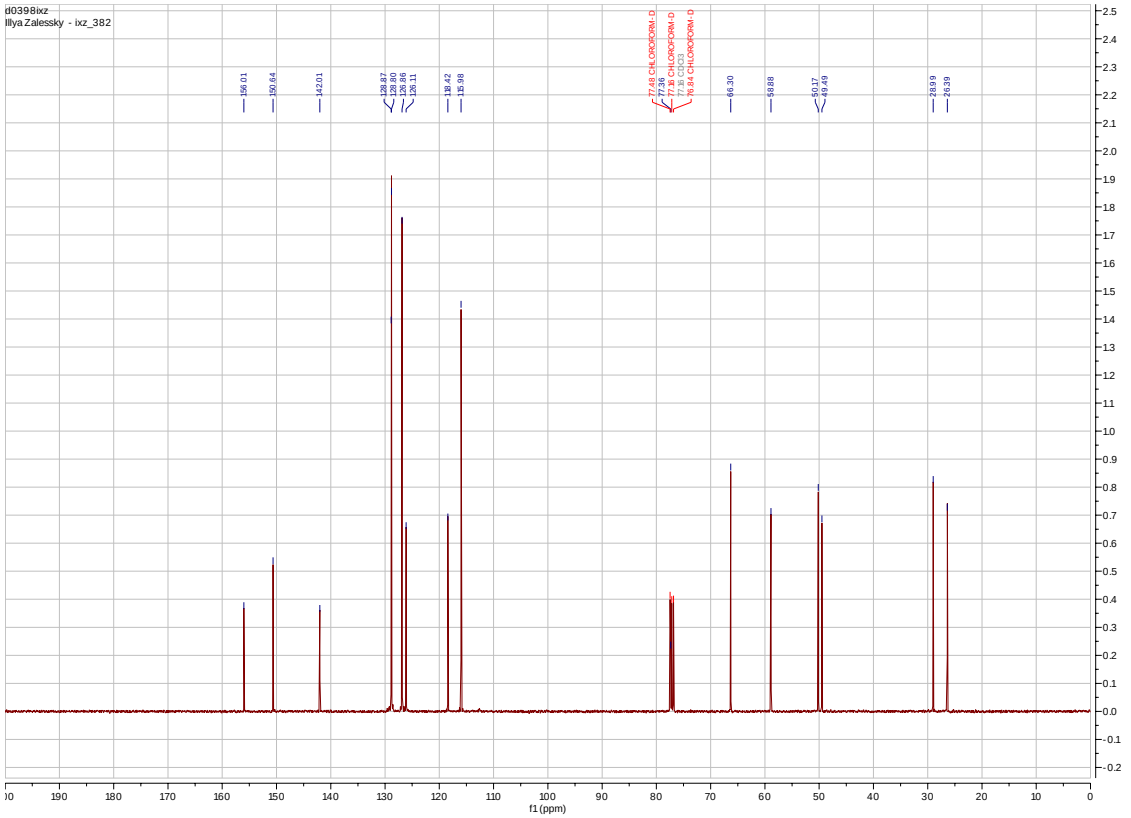
3,6-Diphenyl-1,3,6-oxadiazocane-2-thione – 260



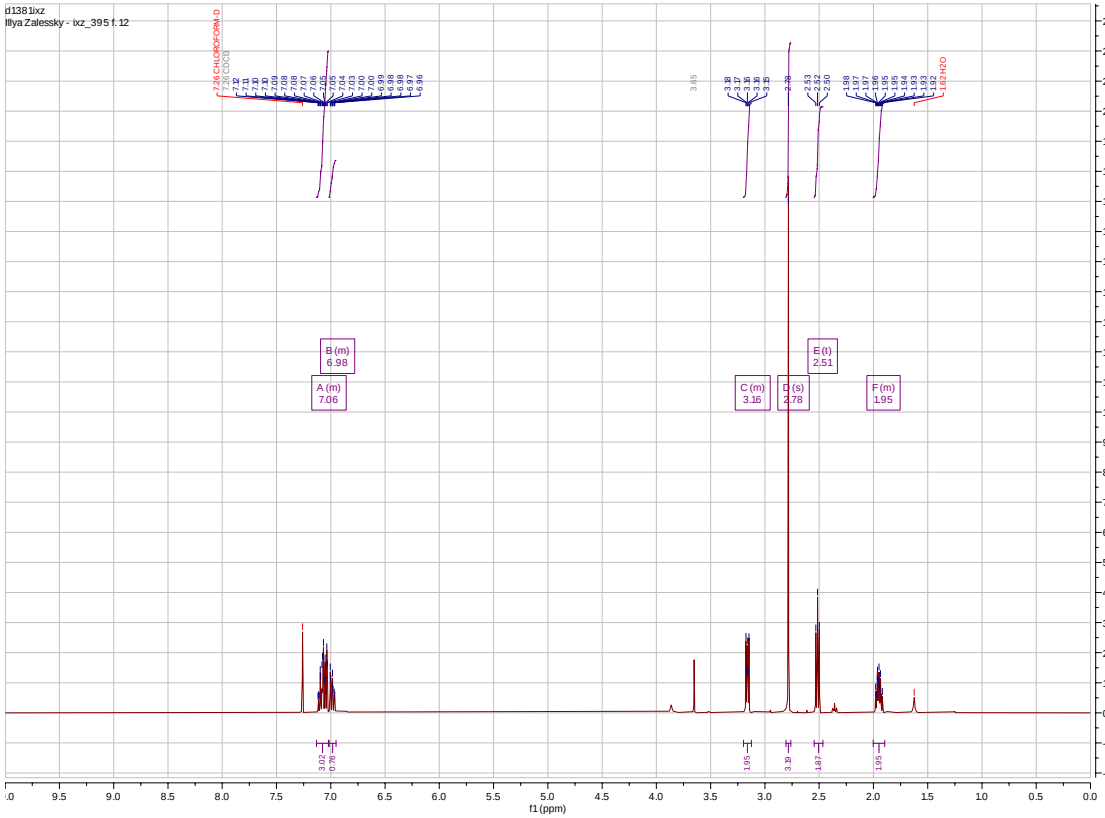


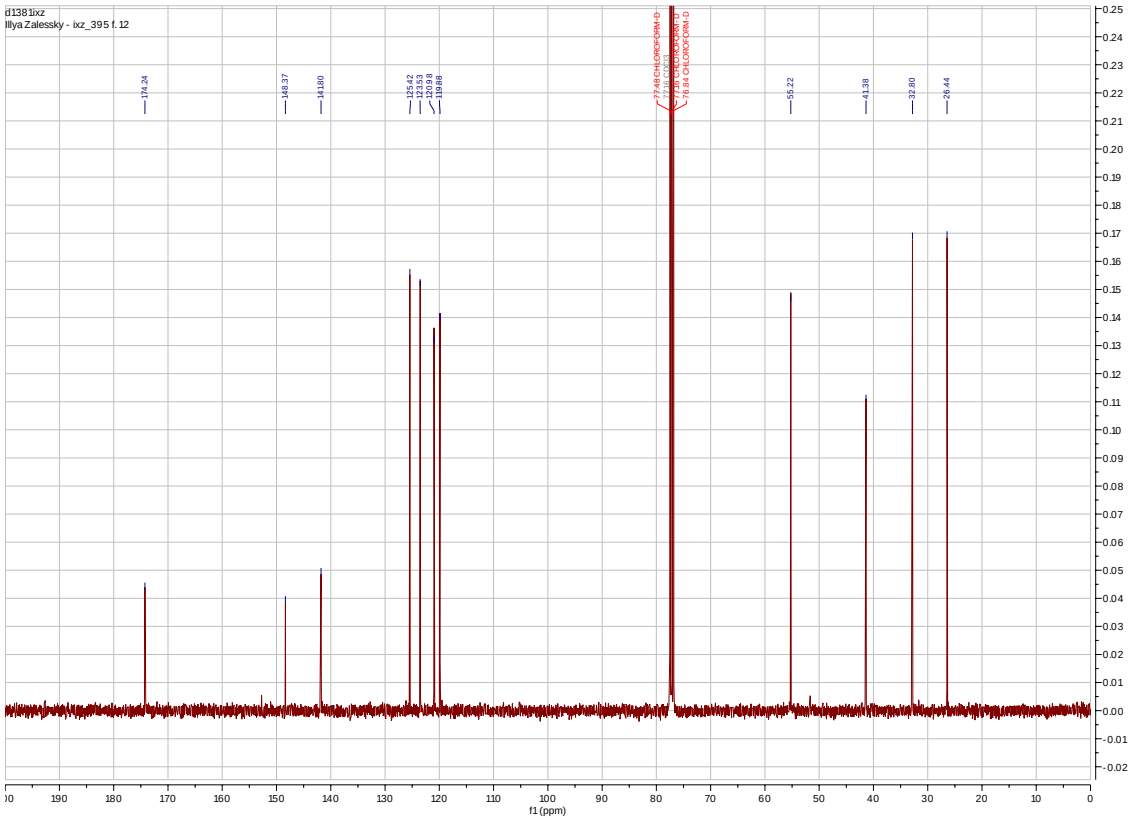
3,7-Diphenyl-1,3,7-oxadiazecan-2-one – 272



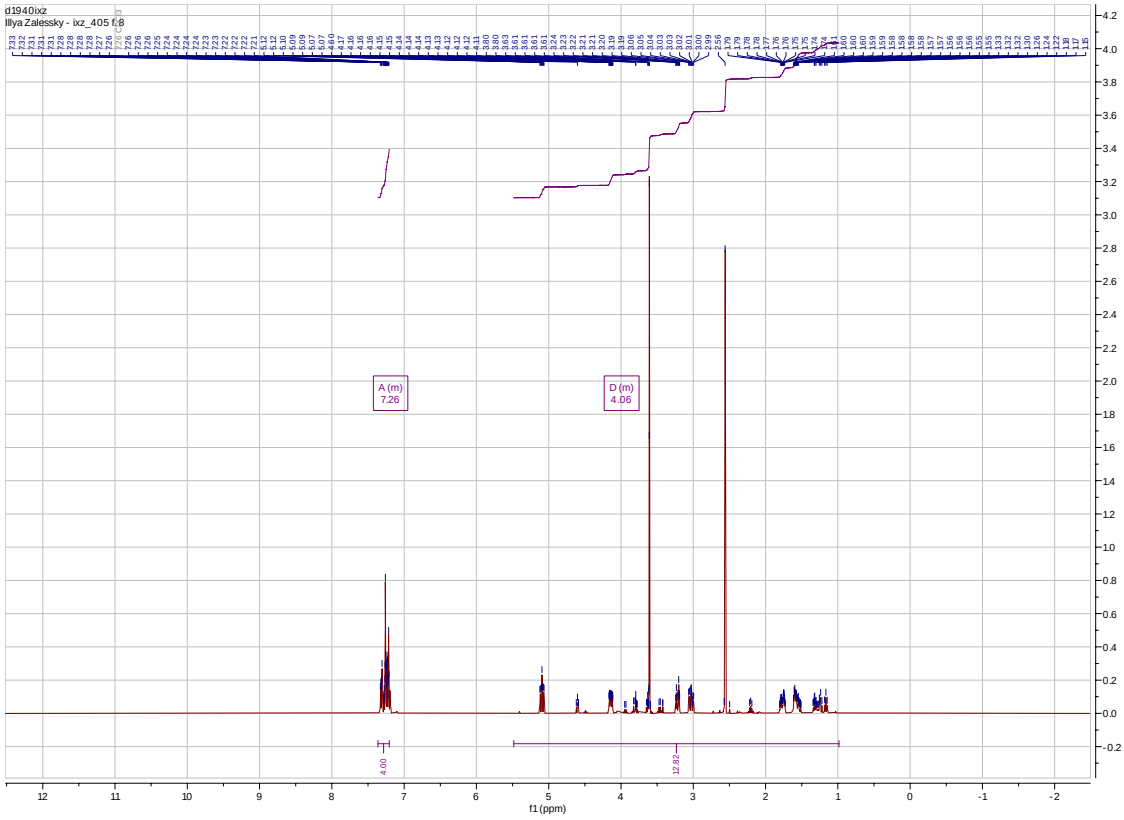


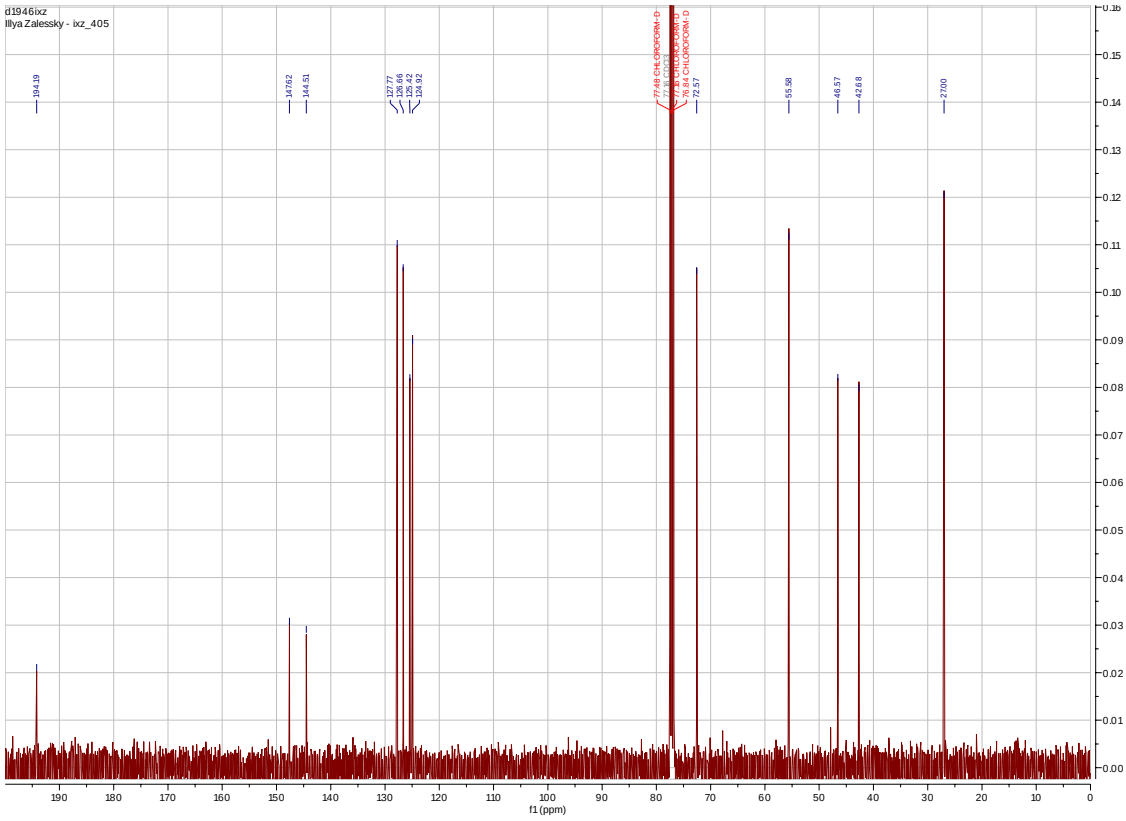
6-Methyl-3,4,5,6-tetrahydro-2H-benzo[b][1,4]oxazocin-2-one – 365



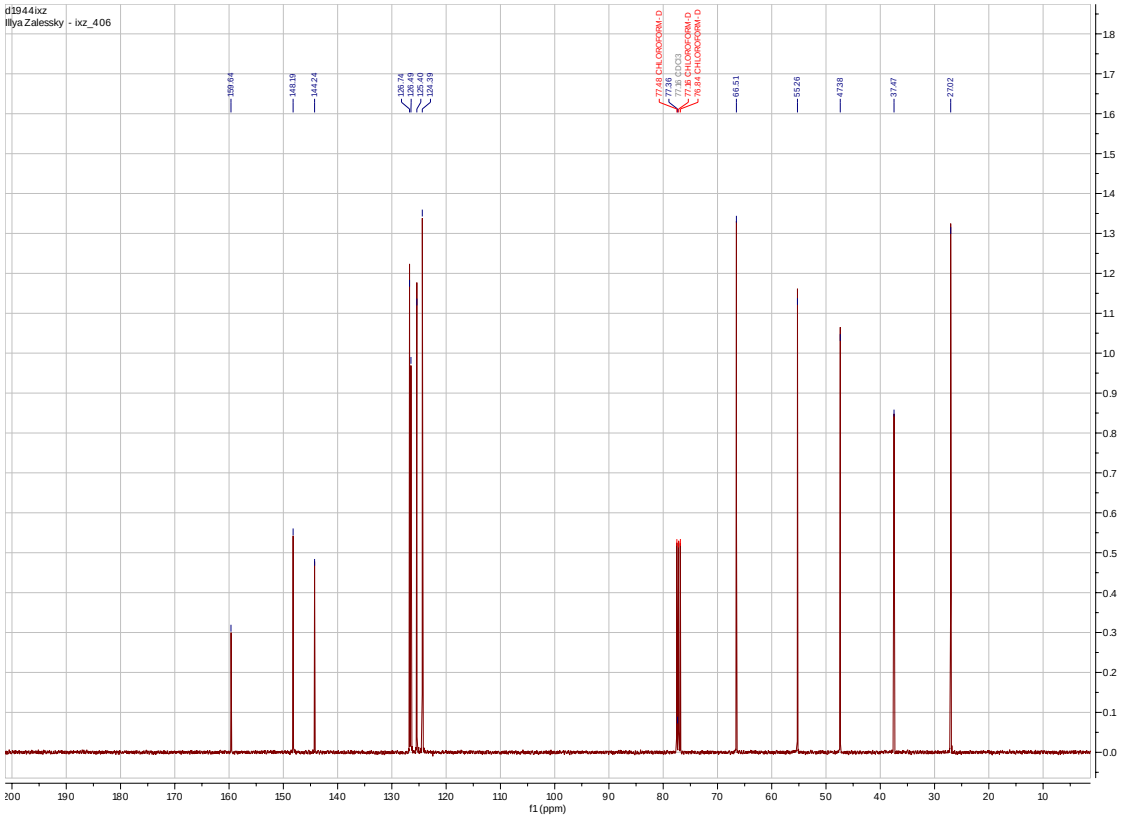


1,7-Dimethyl-4,5,6,7-tetrahydrobenzo[*d*][1,3,6]oxadiazonine-2(1*H*)-thione – 280

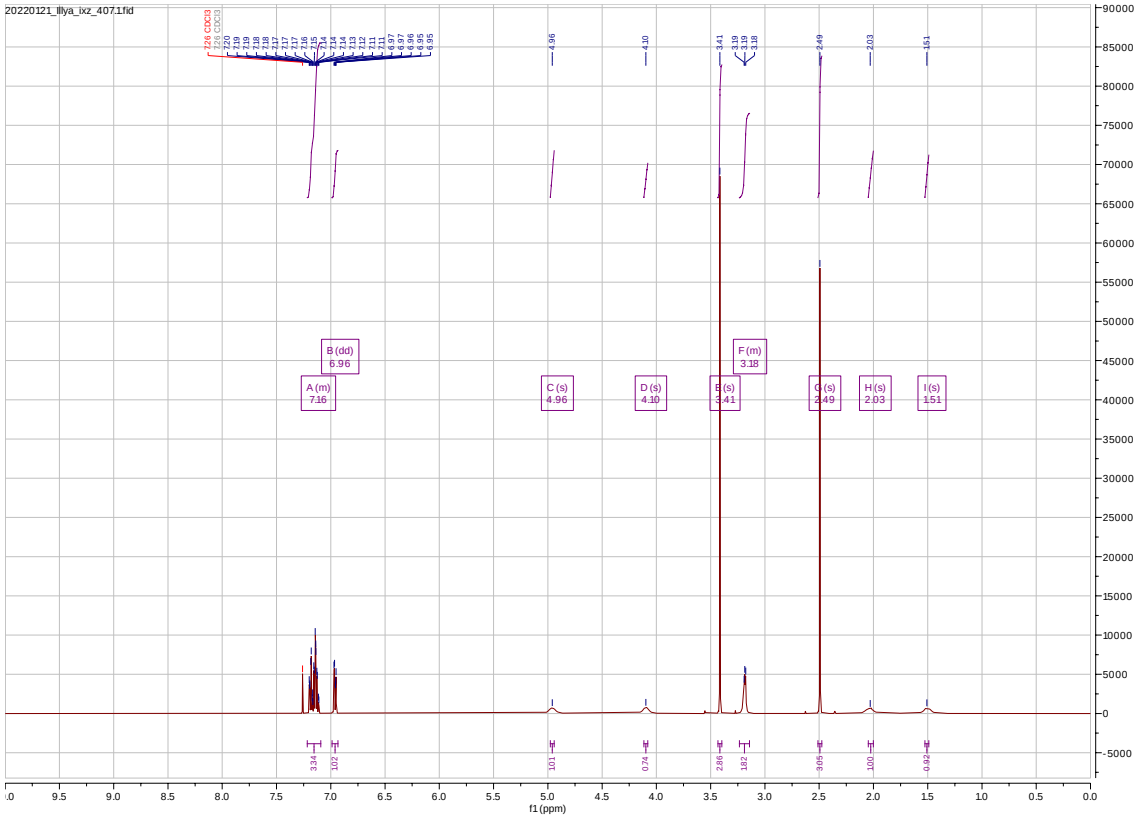


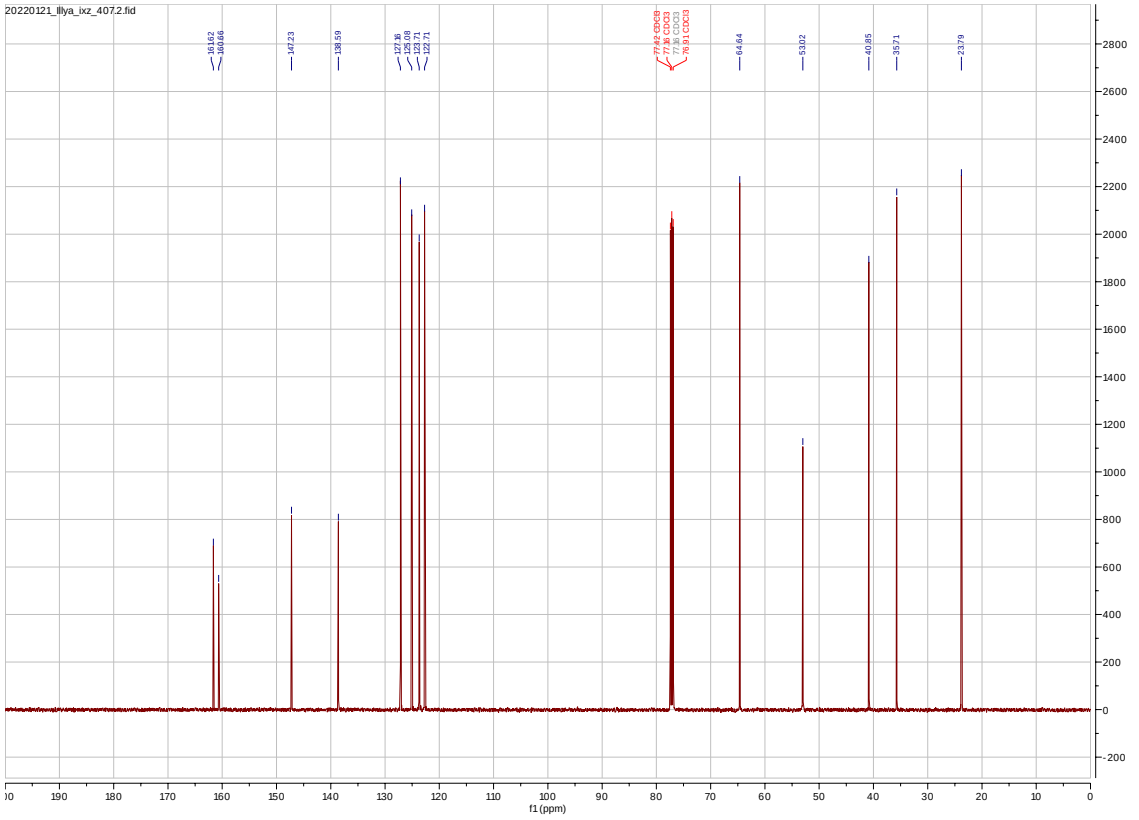


1,7-Dimethyl-4,5,6,7-tetrahydrobenzo[*d*][1,3,6]oxadiazonin-2(1*H*)-one – 281

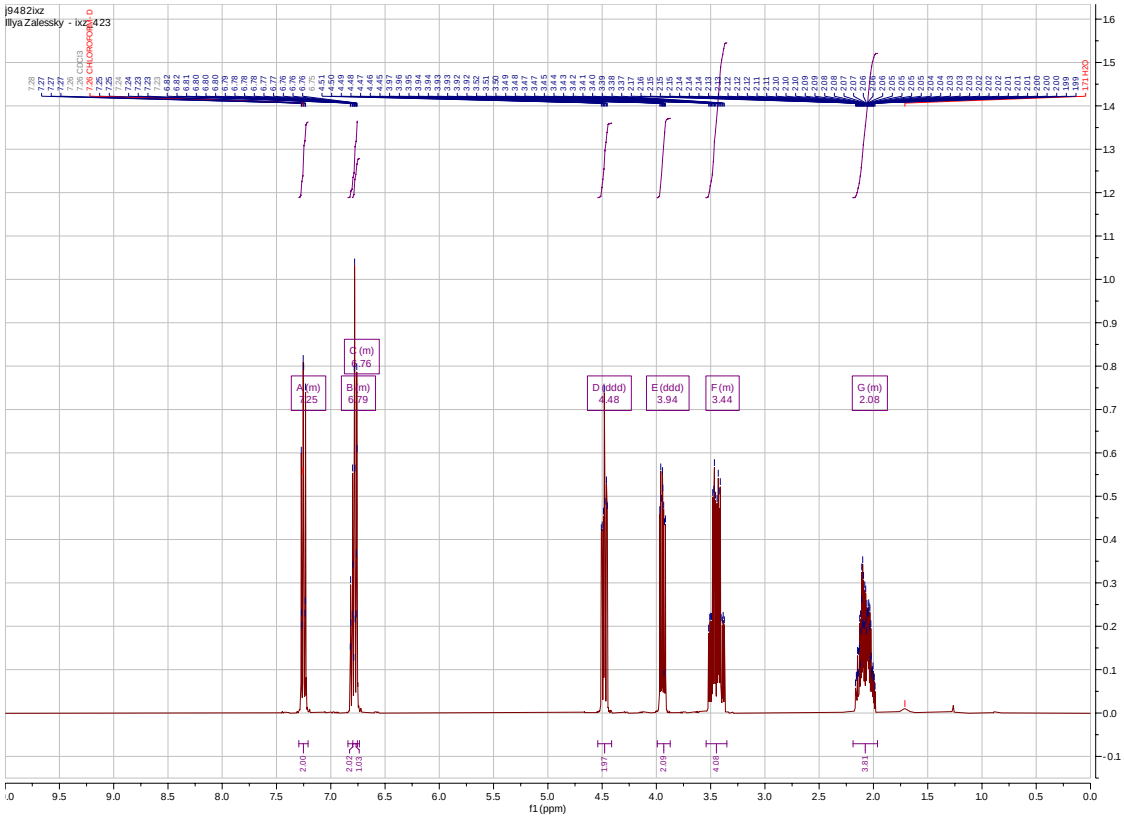


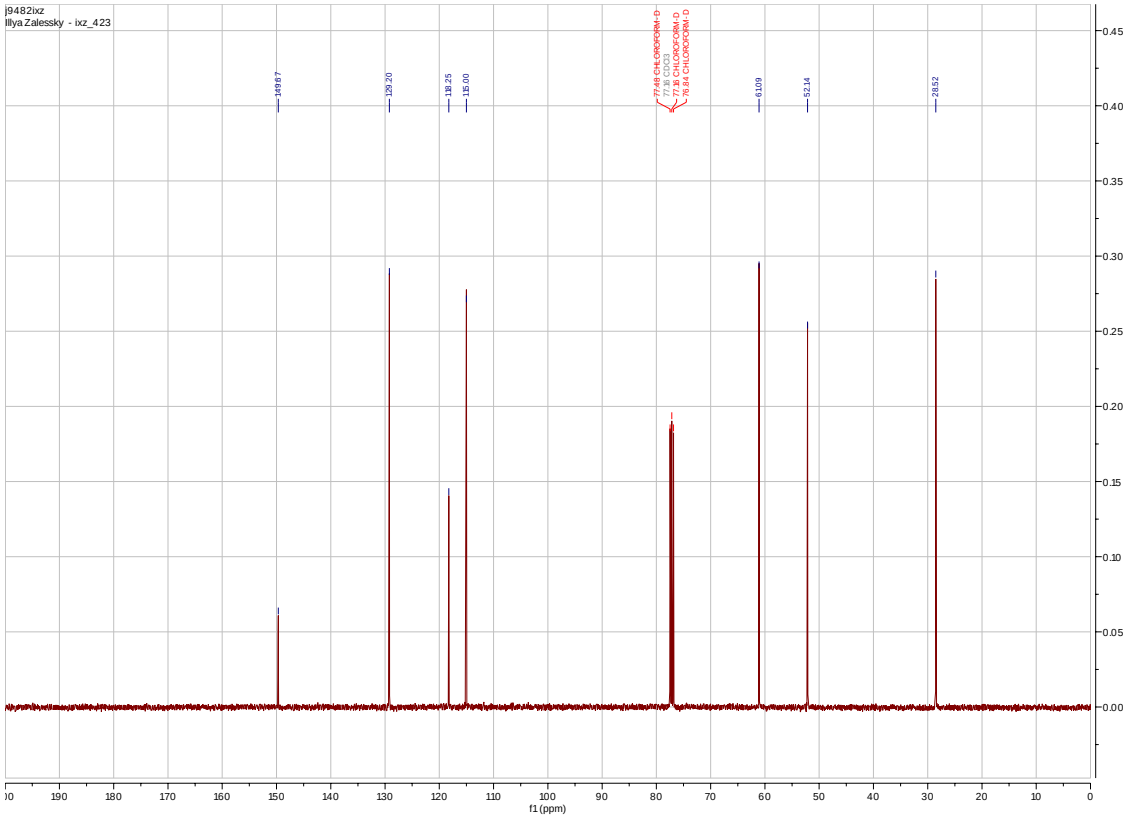
1,8-Dimethyl-5,6,7,8-tetrahydro-1H-benzo[e][1,4,7]oxadiazecine-2,3-dione – 282



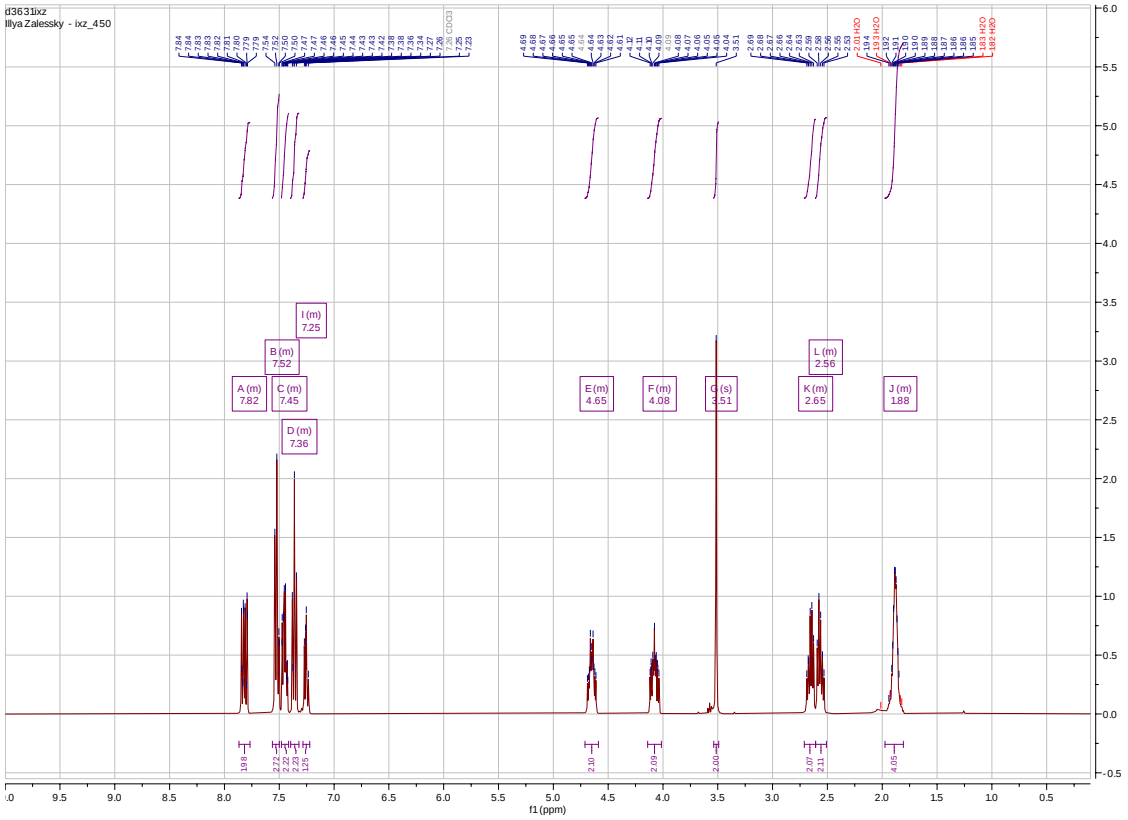


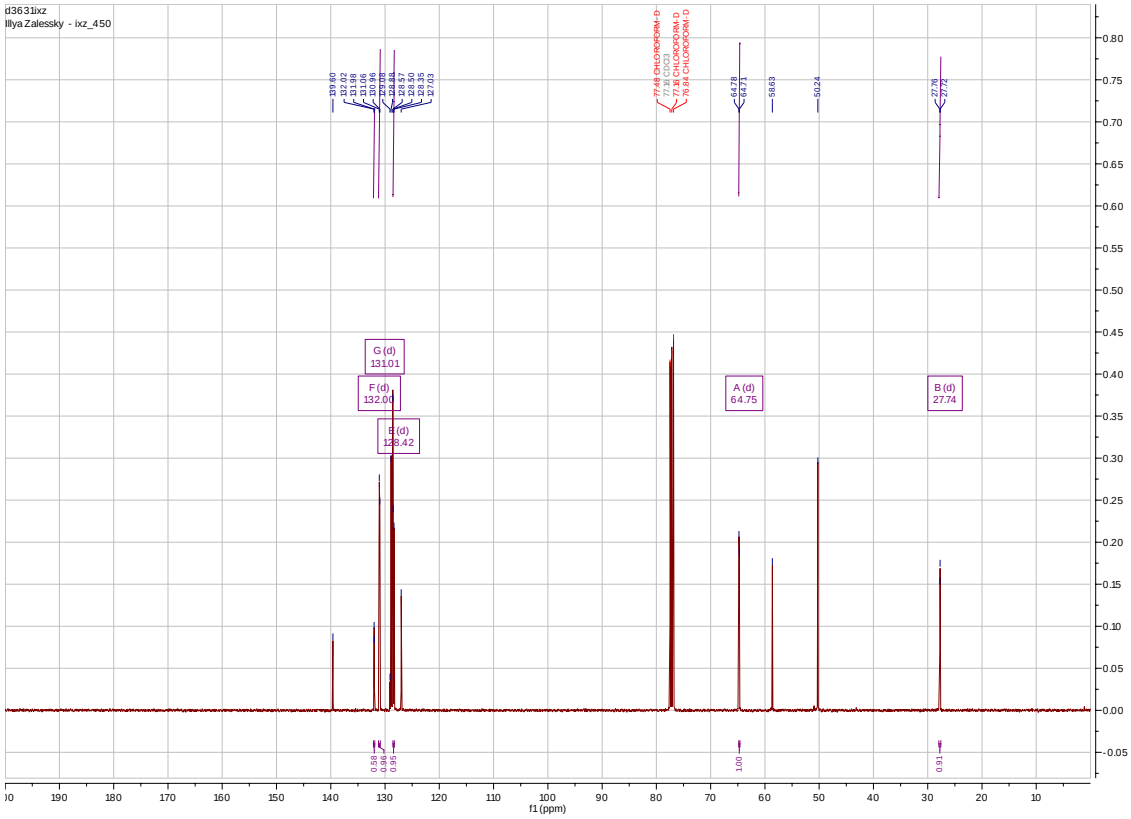
7-Phenyl-1,3,2,7-dioxathiazecane 2-oxide – 319

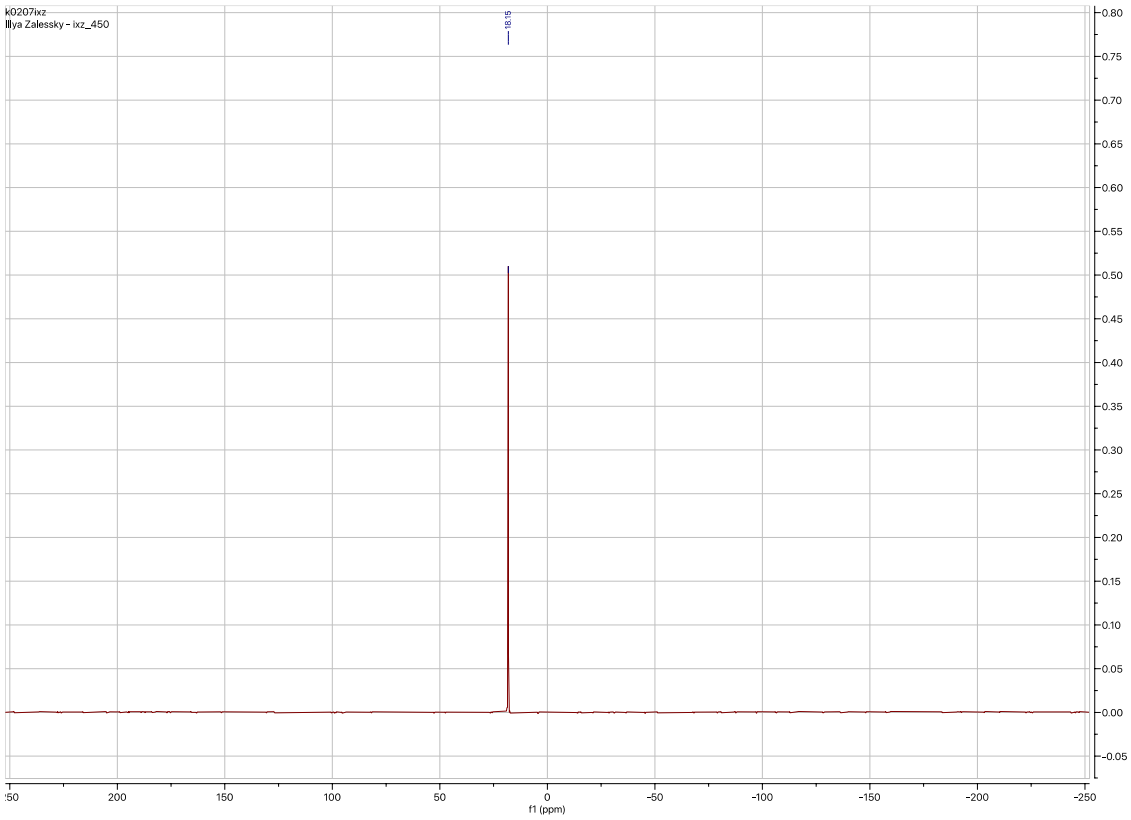




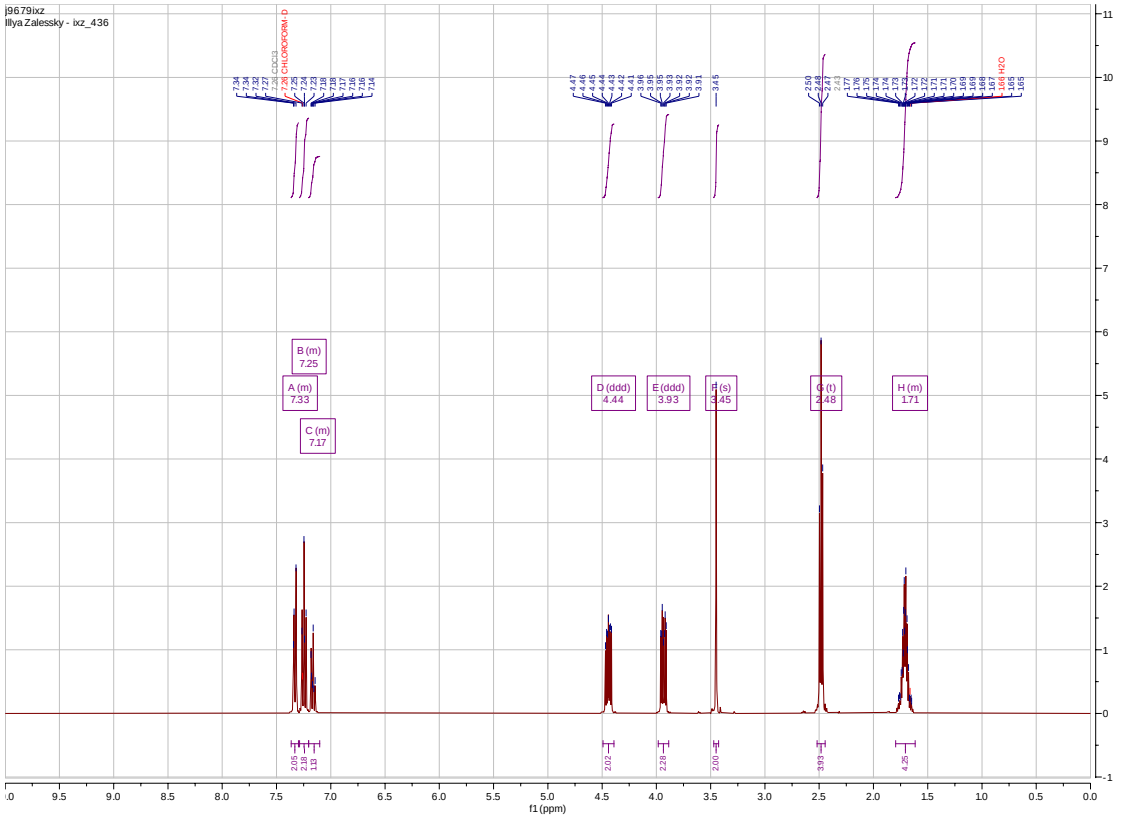
7-Benzyl-2- phenyl-1,7,2,3-oxazadiphosphecane 2-oxide – 326

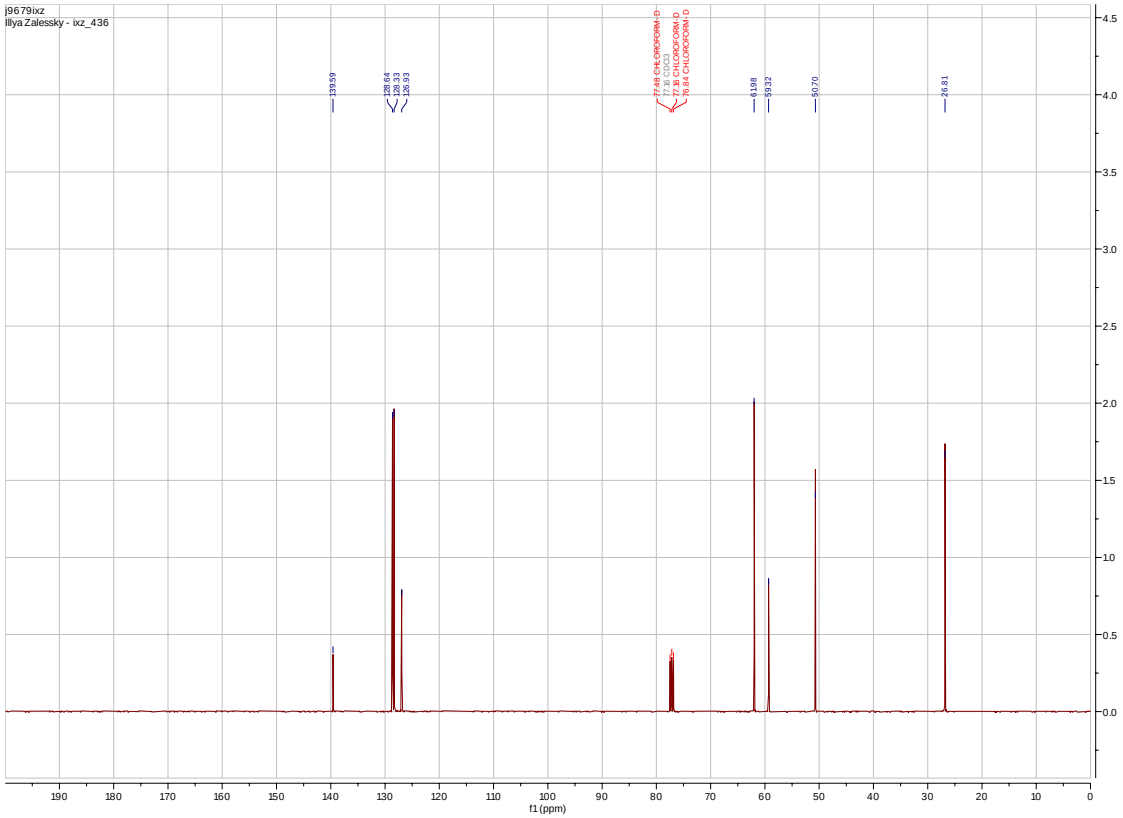




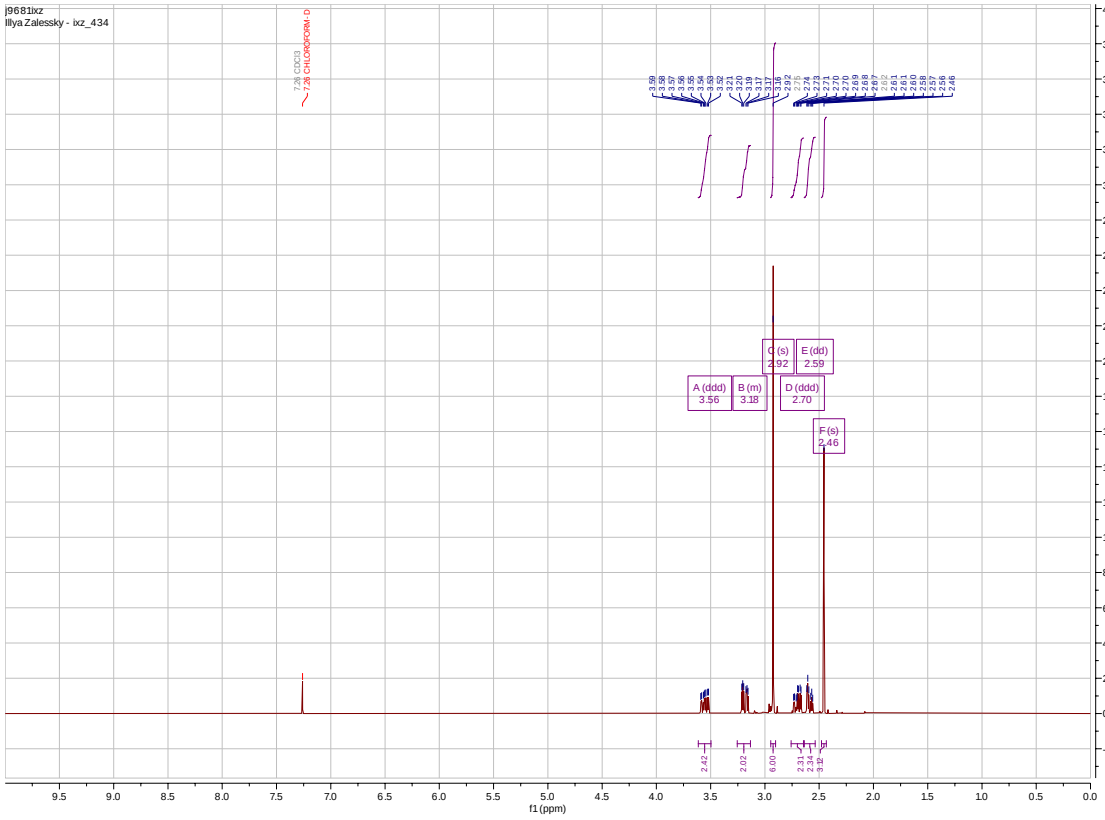

k0207ixz
Illya Zalessky - ixz_450
18.15
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
200
150
100
50
0
-50
-100
-150
-200
-250
f1 (ppm)

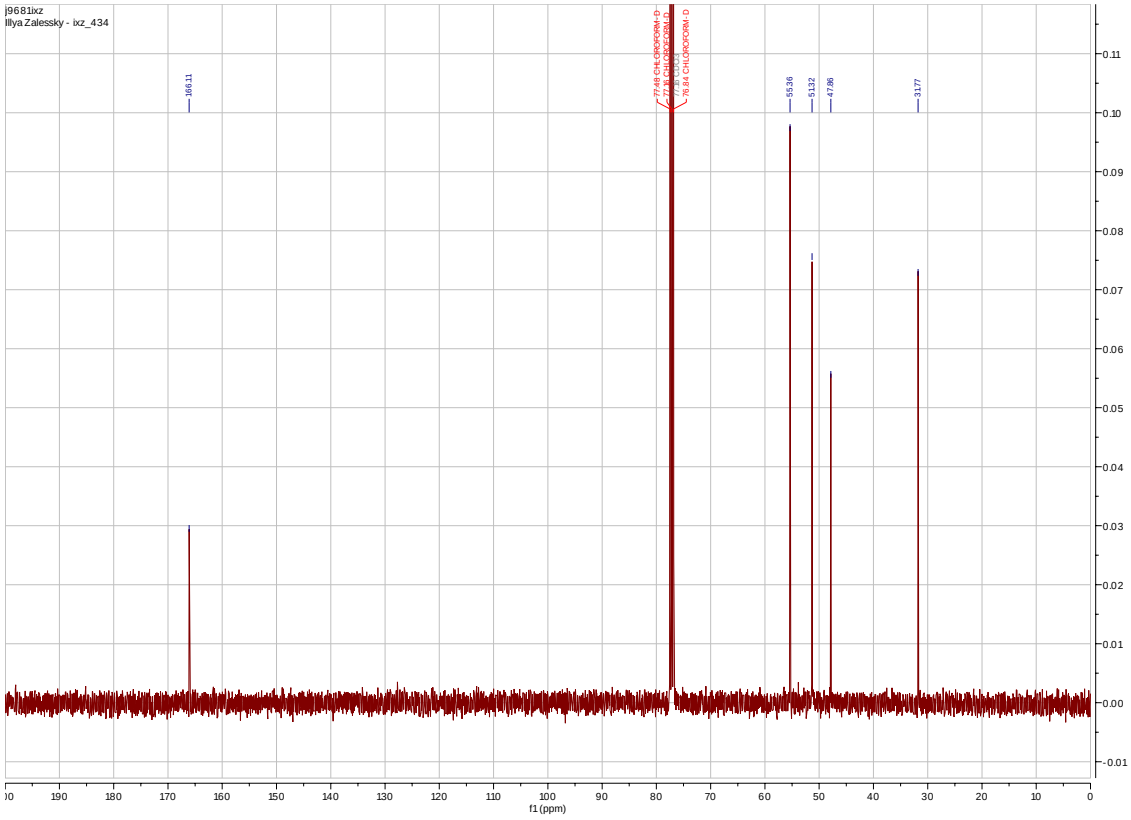
7-Benzyl-1,3,2,7-dioxathiazecane 2-oxide – 322



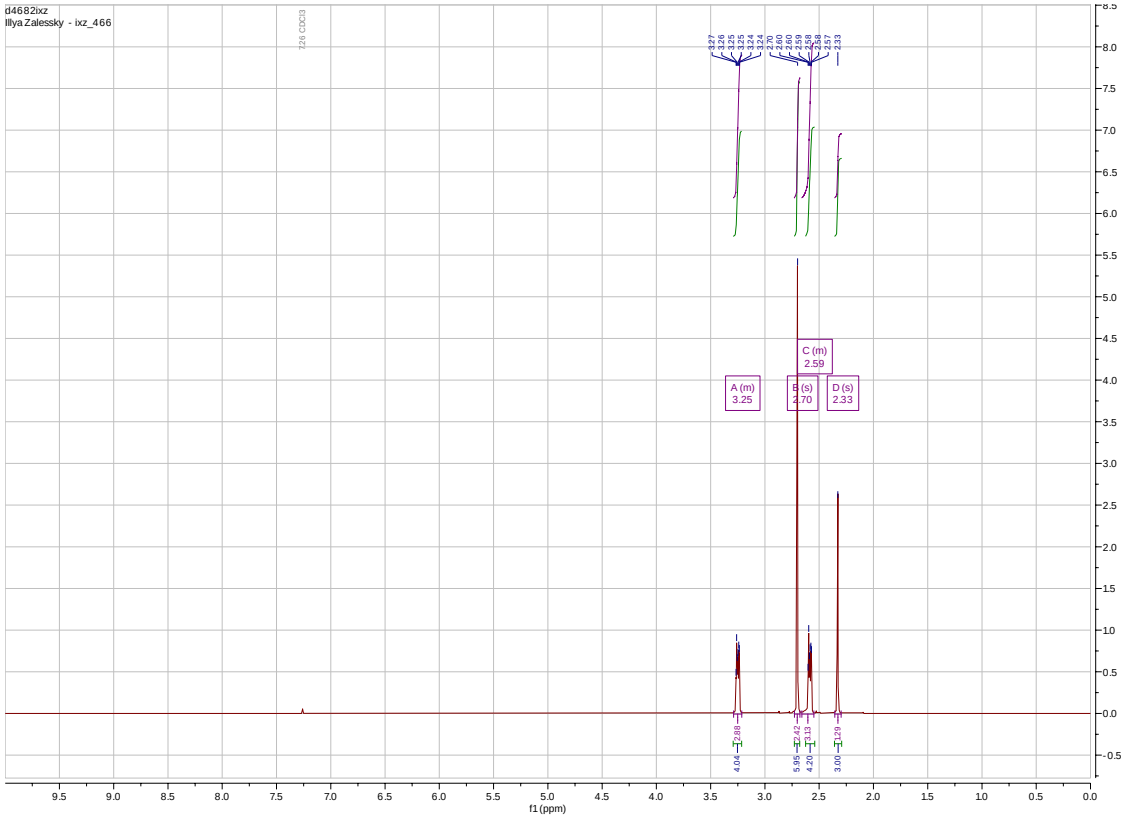


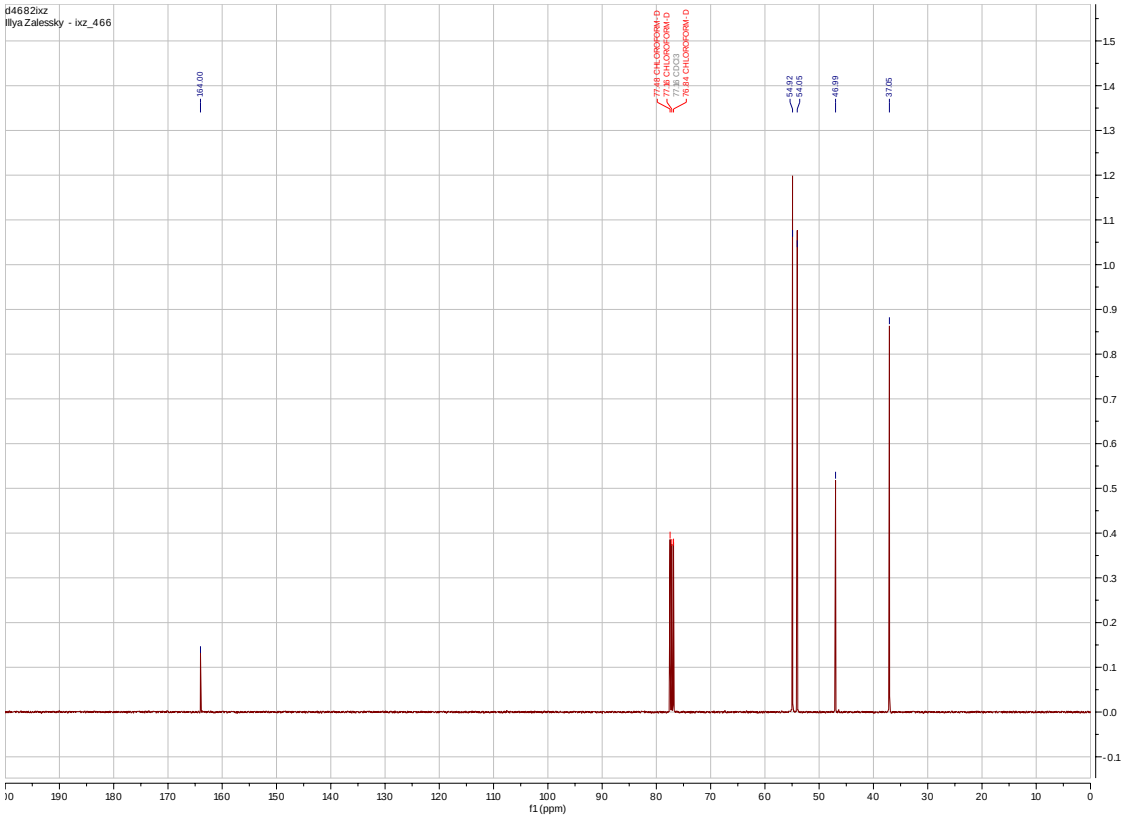
1,4,7-Trimethyl-1,4,7-triazonane-2,3-dione – 289



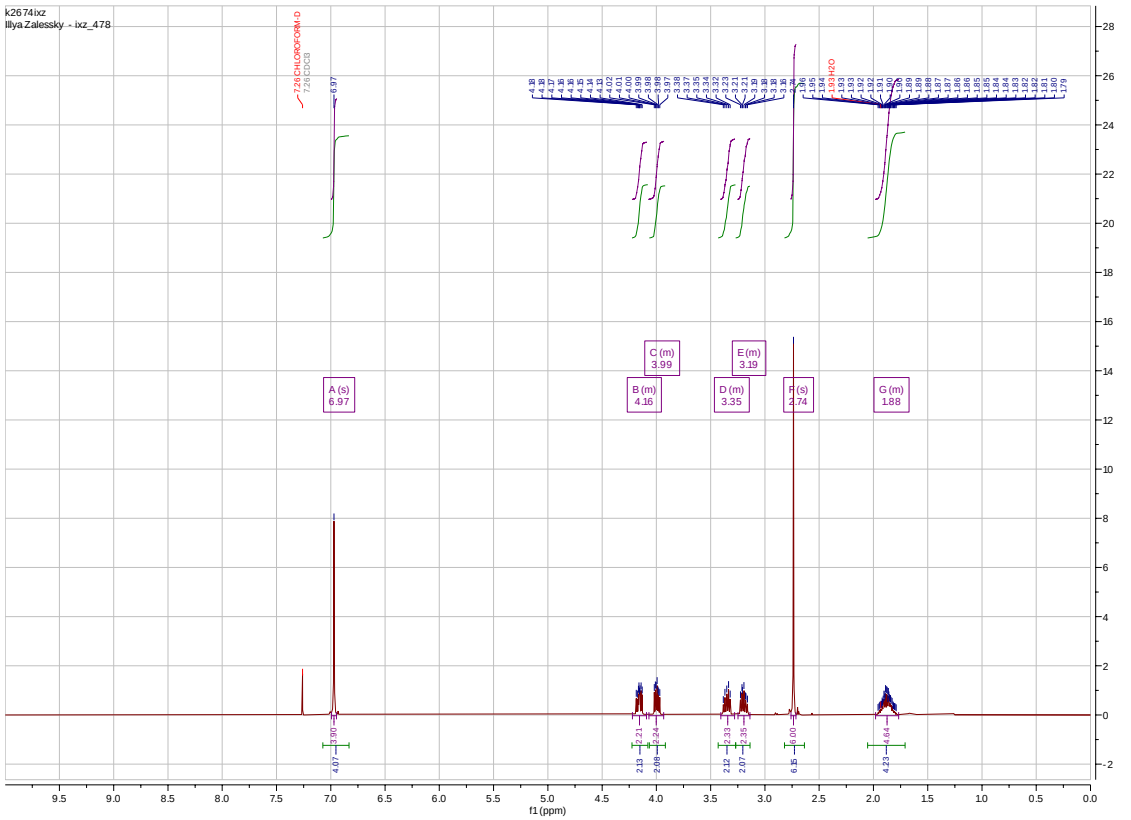


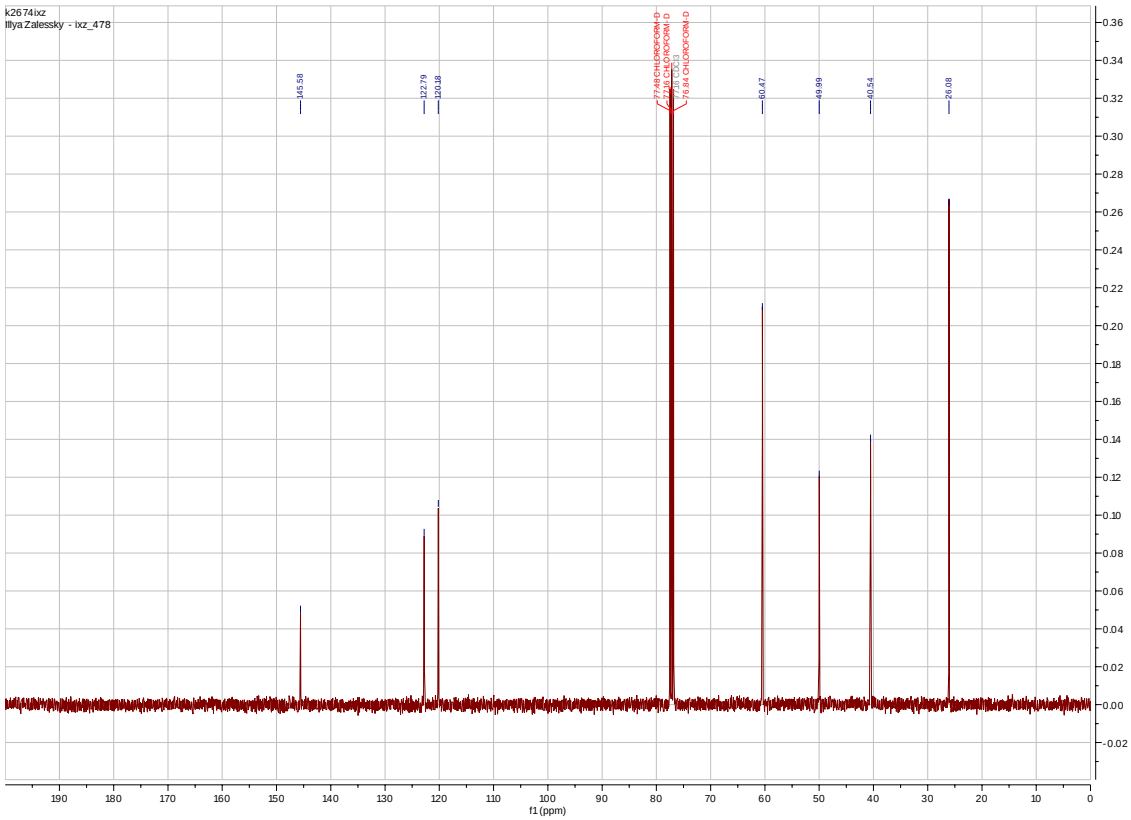
1,3,6-Trimethyl-1,3,6-triazocan-2-one – 291



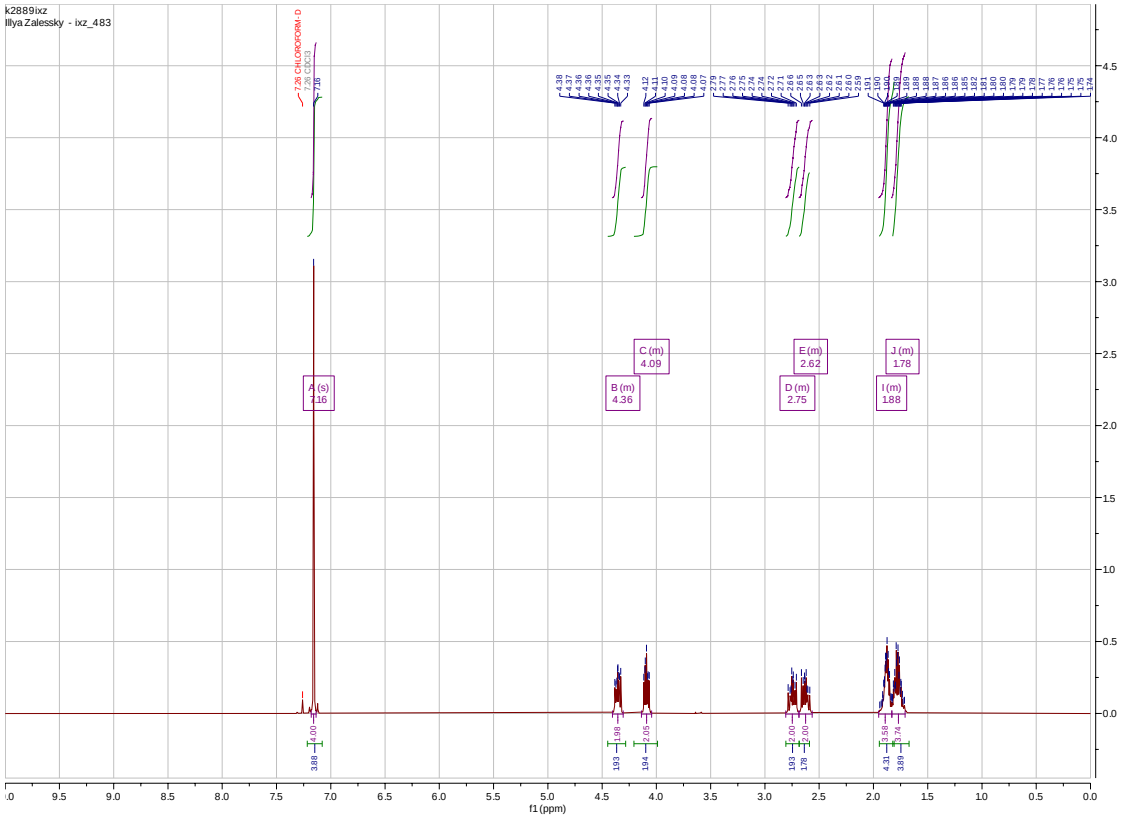


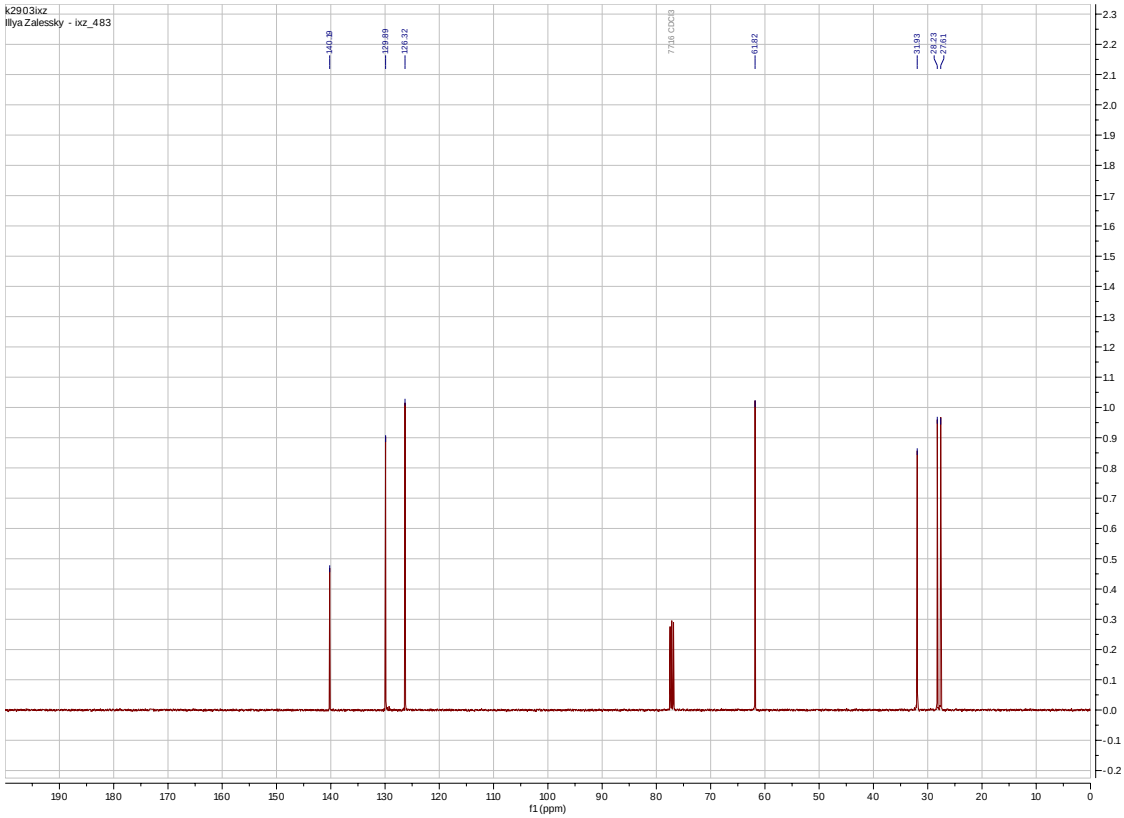
1,11-Dimethyl-1,2,3,4,8,9,10,11-octahydrobenzo[*h*][1,3]dioxa[2]thia[7,10]diazacyclotridecine 6-oxide – 330



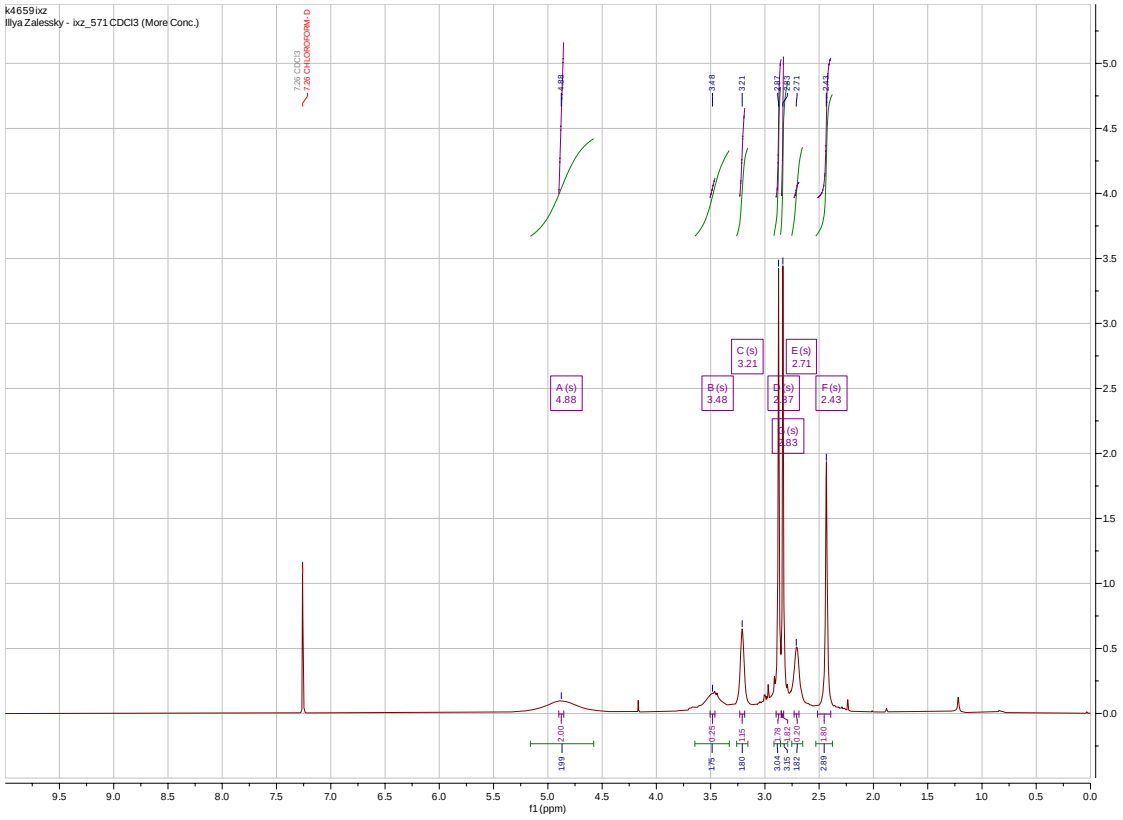


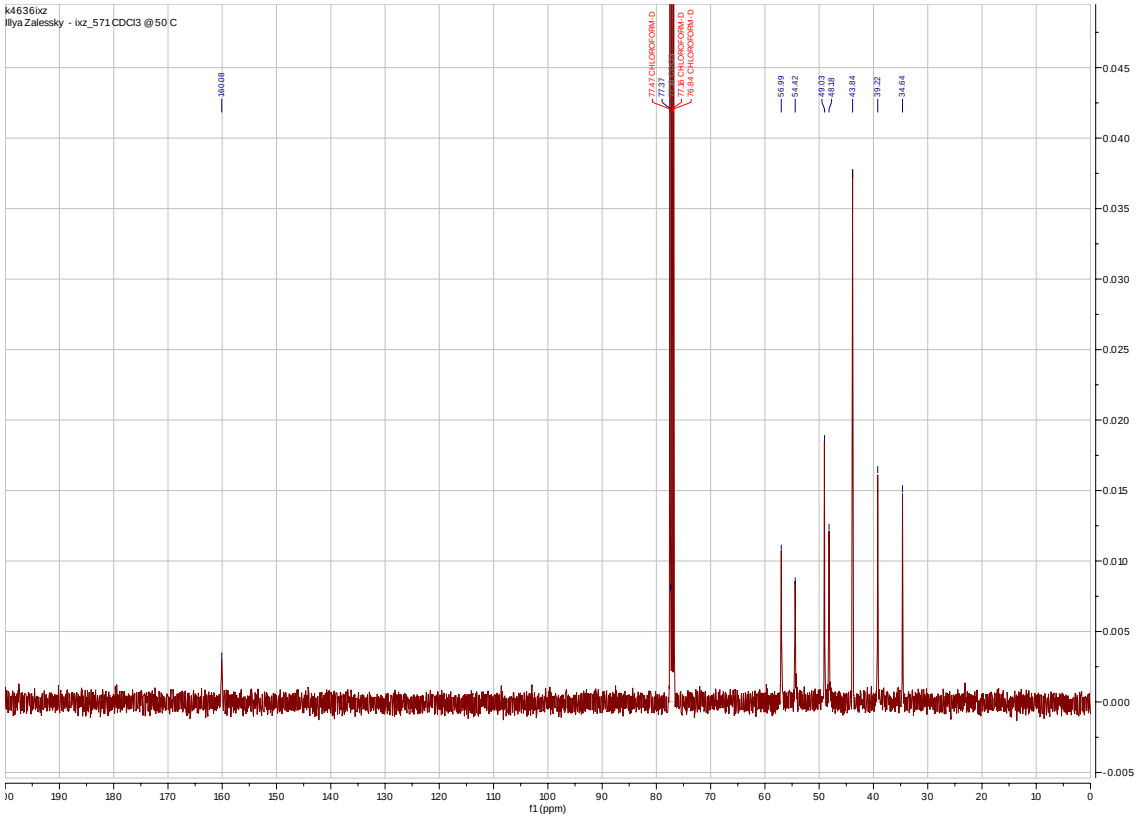
1,2,3,4,8,9,10,11-Octahydrobenzo[*h*][1,3]dioxa[*2*]thiacyclotridecine 6-oxide – 335



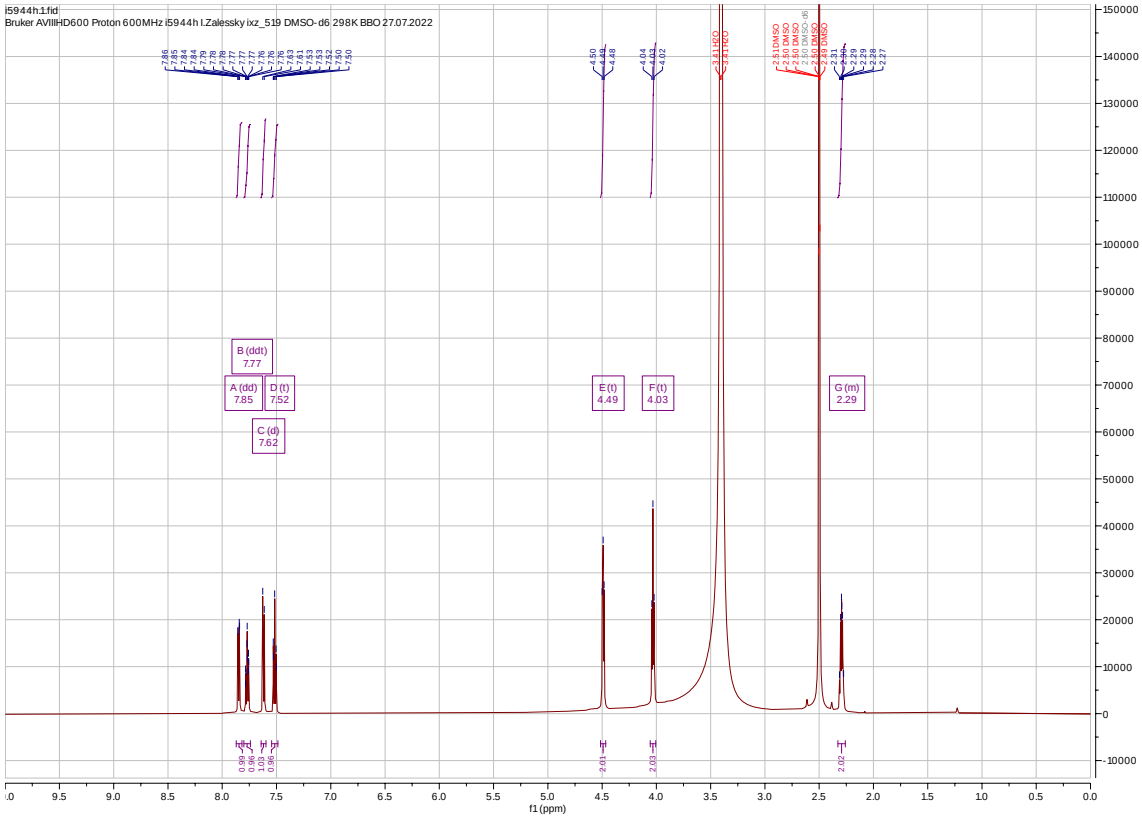


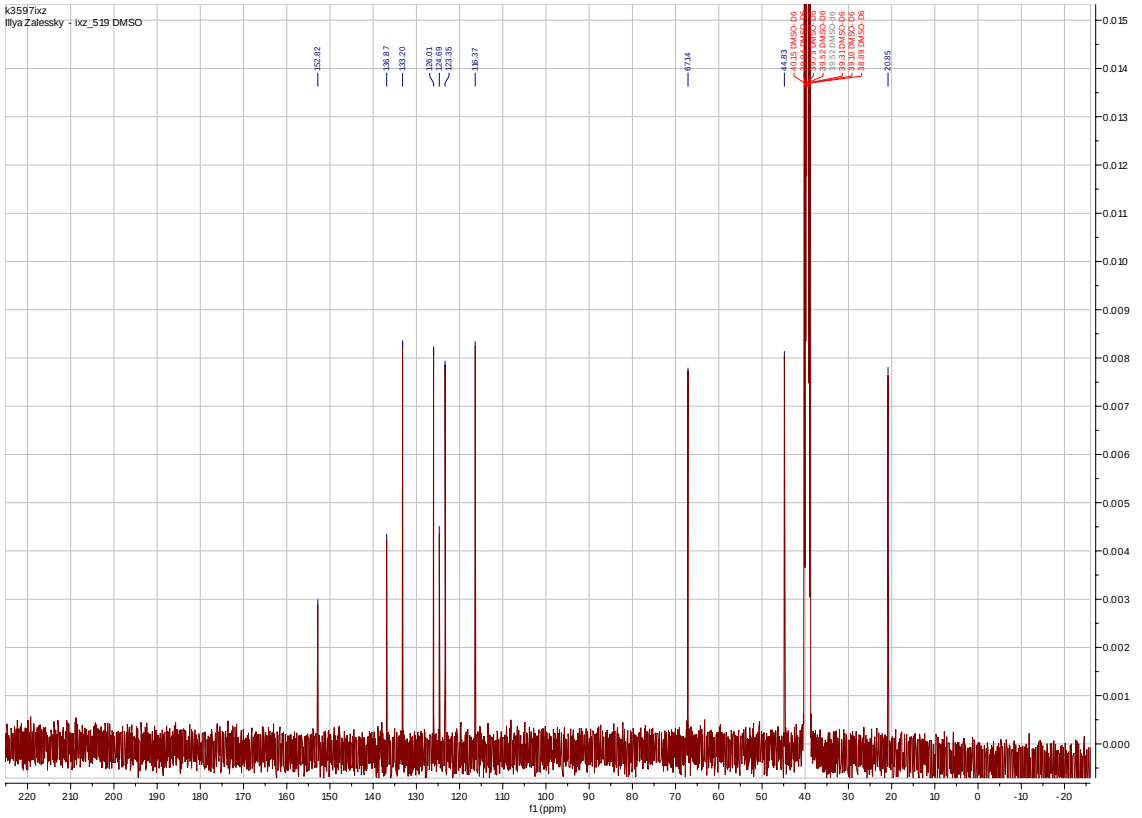
4,7,10-Trimethyl-1,2,4,7,10-thiatetrazecan-3-one 1,1-dioxide – 340



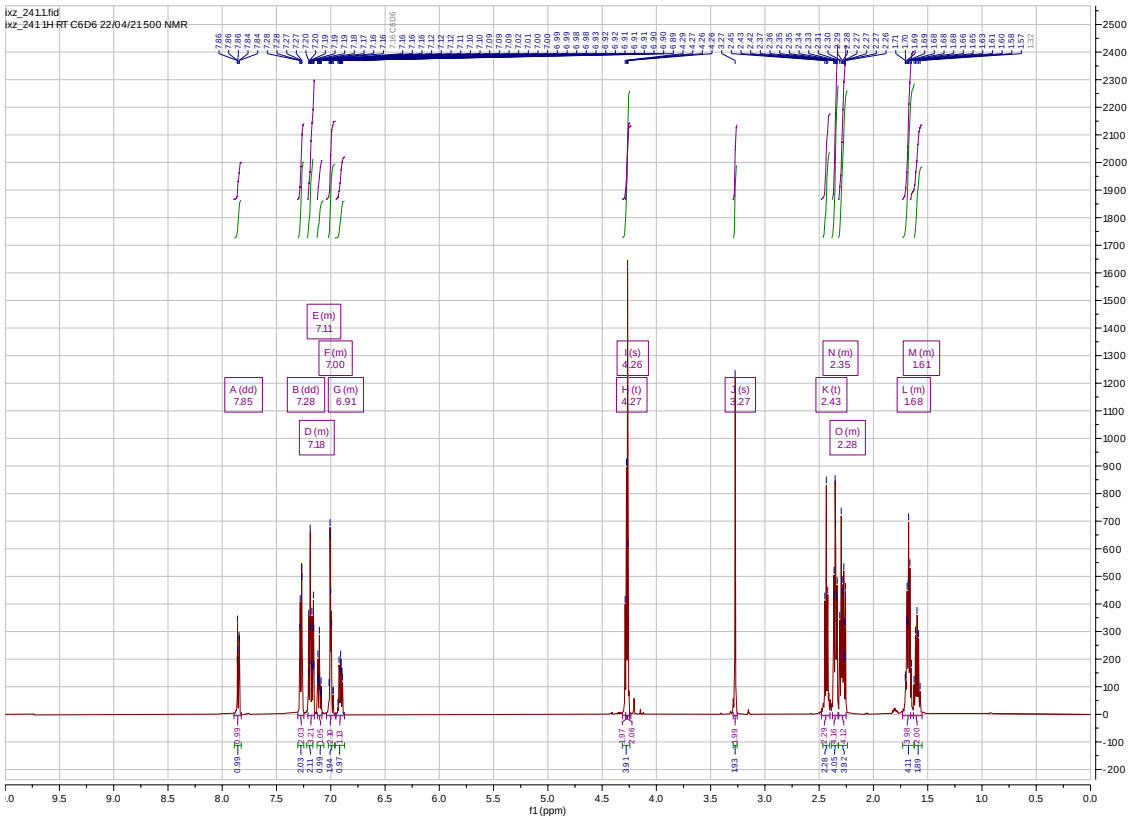


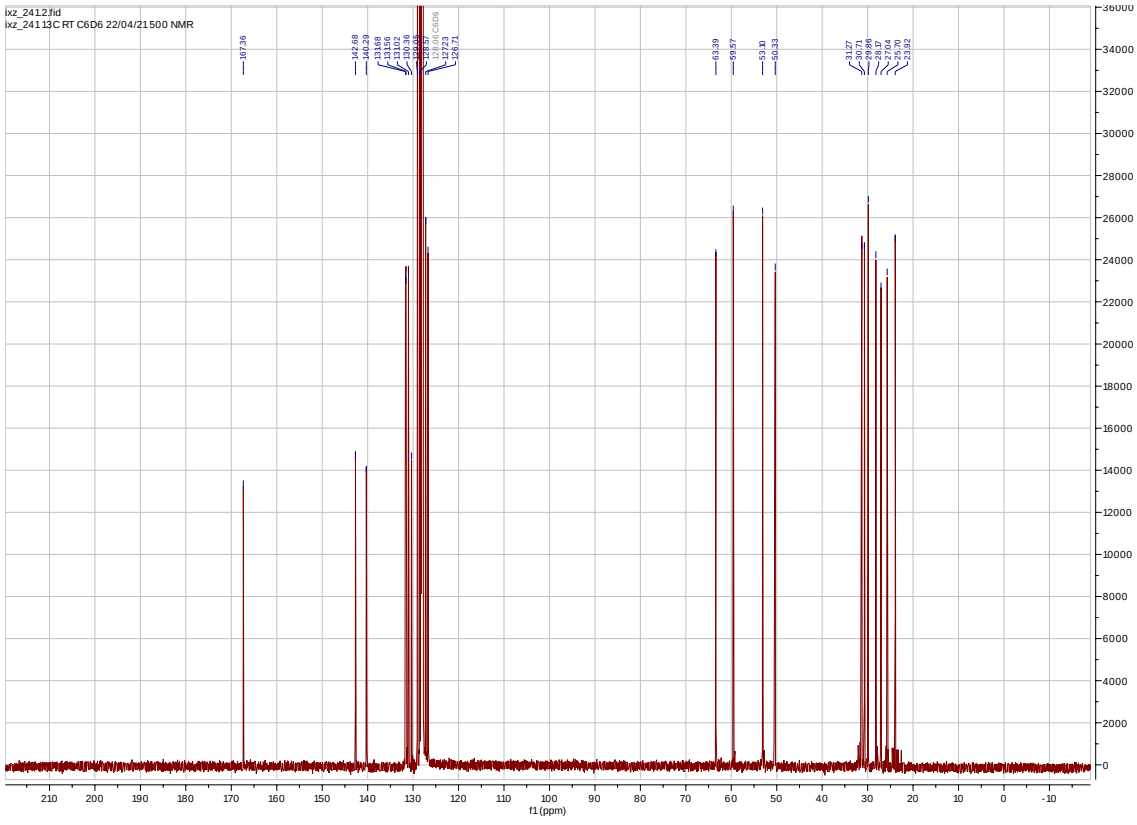
2,3-Dihydro-1H-benzo[*e*][1,3]oxazino[2,3-c][1,2,4]thiadiazine 6,6-dioxide – 356



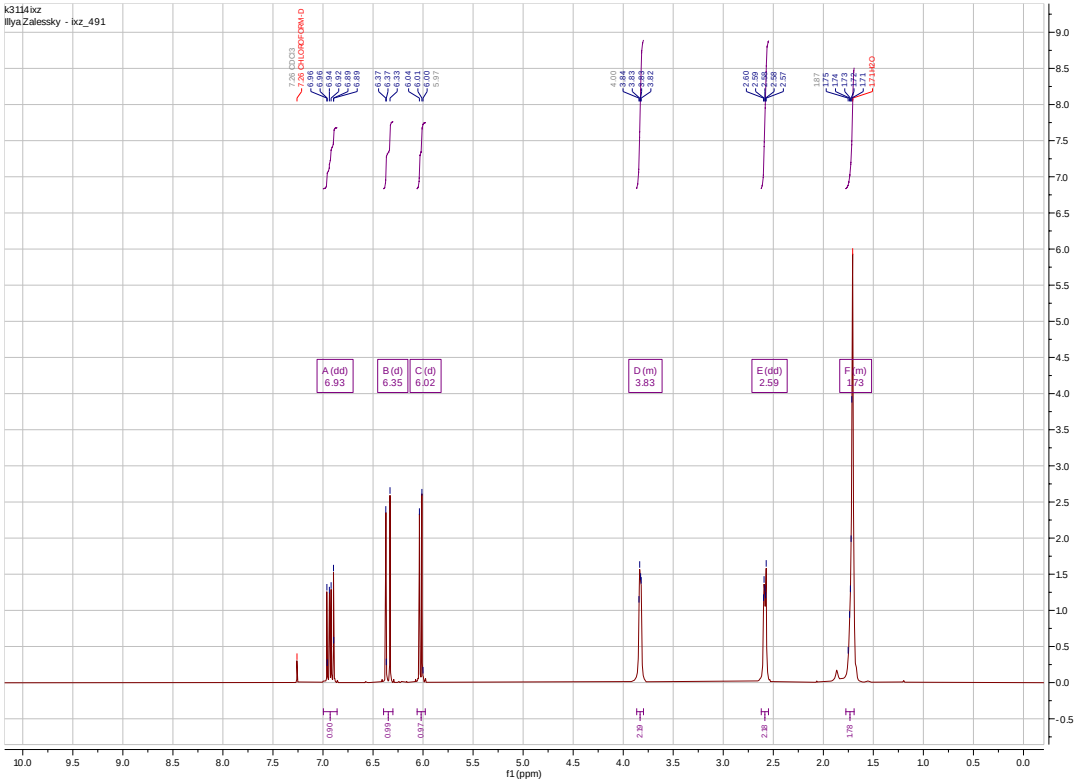


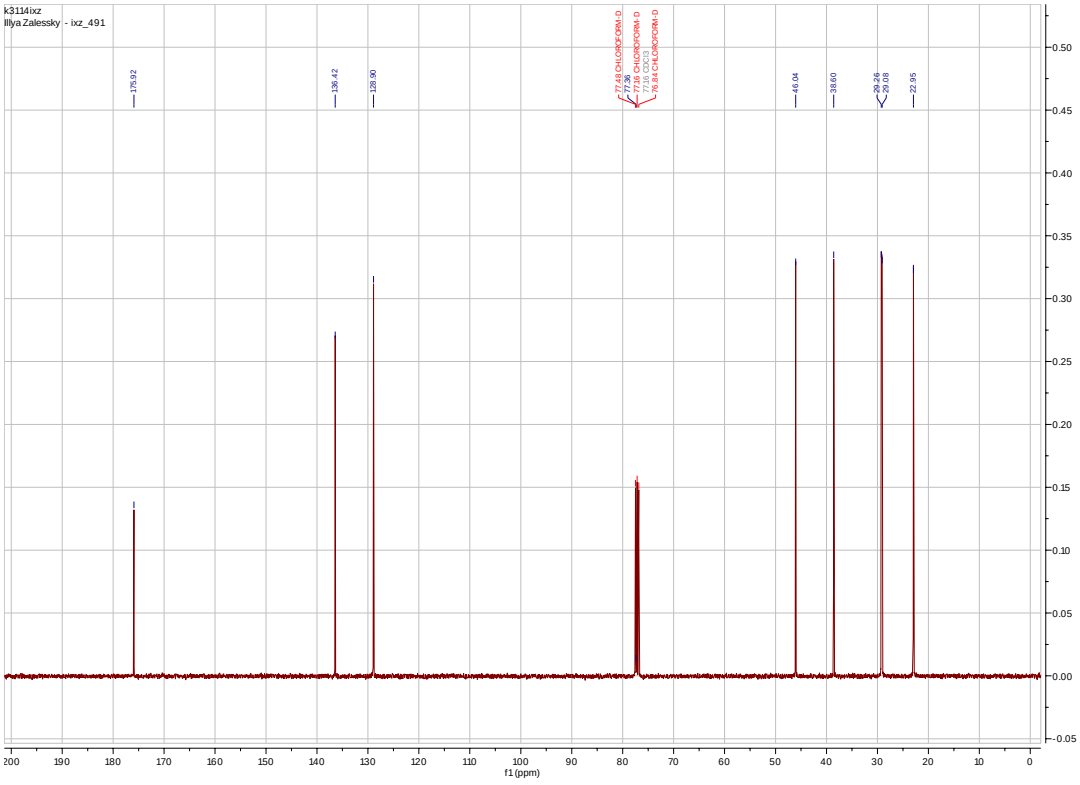
6-Benzyl-4,5,6,7,8,9,12,13-Octahydro-3H,11H-benzo[*o*][1]oxa[9]thia[13]selena[5]azacycloheptadecin-1(15H)-one – 210



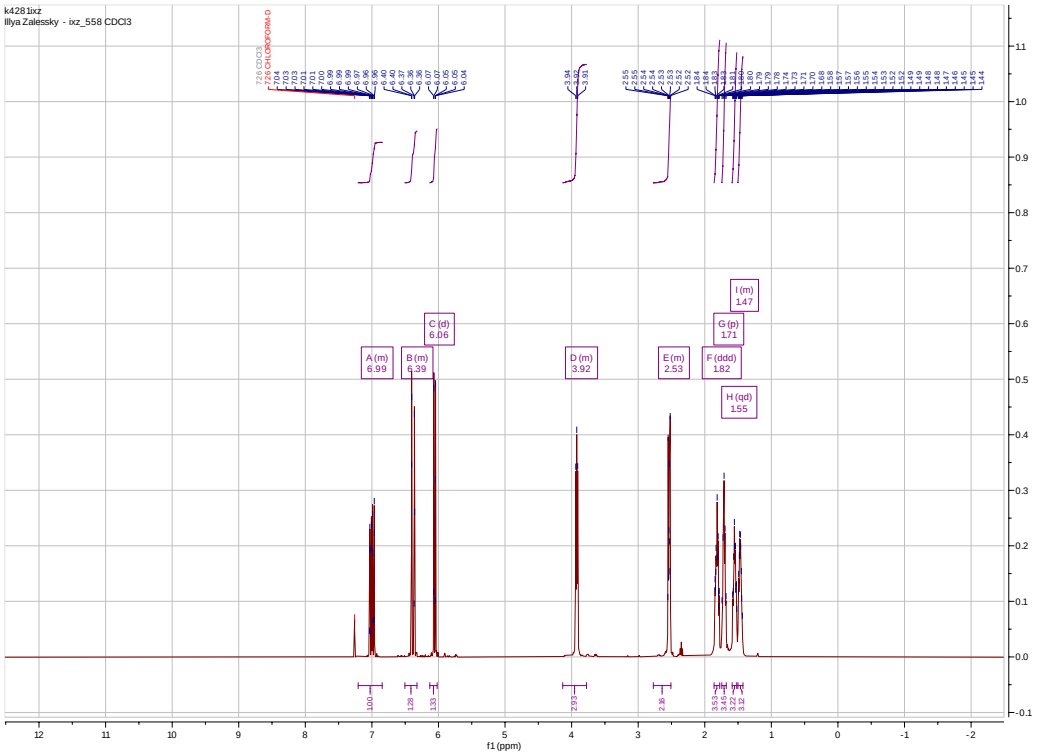


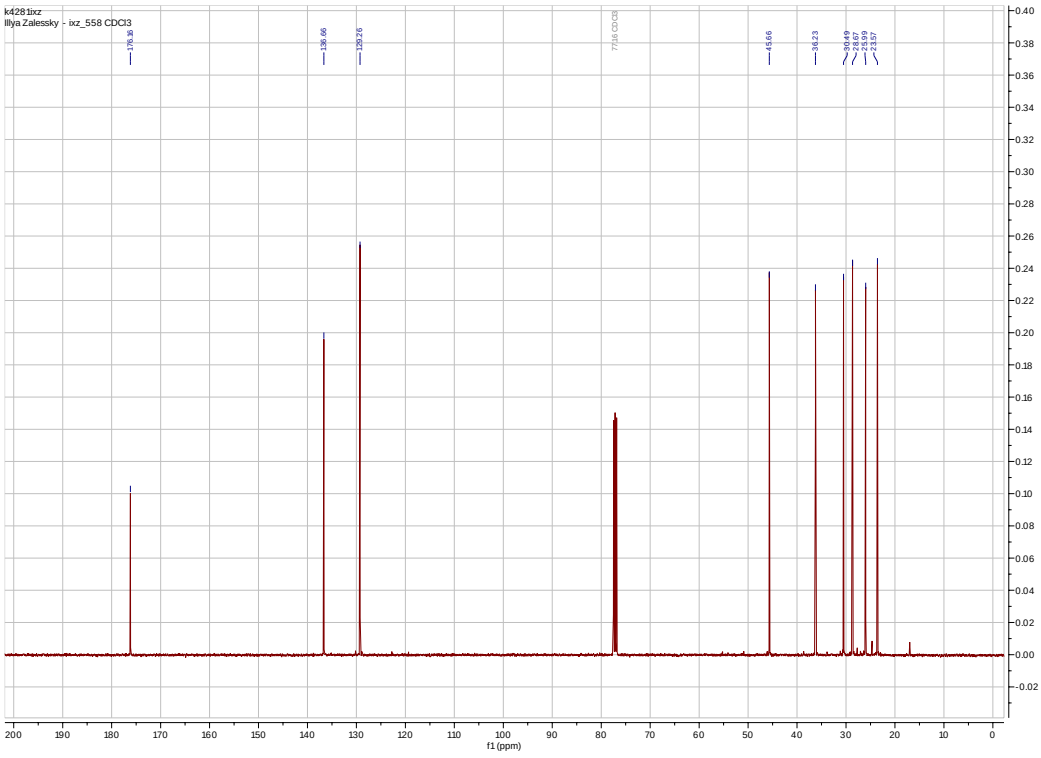
1-(Vinylsulfonyl)azepan-2-one – 387



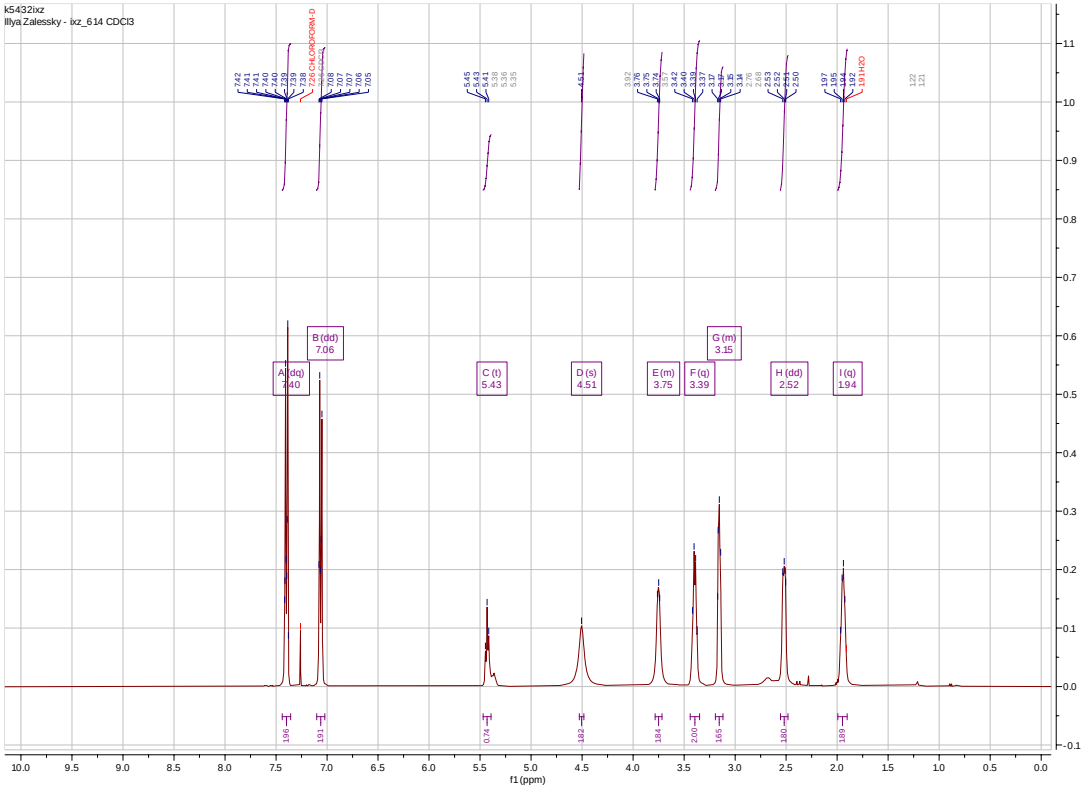


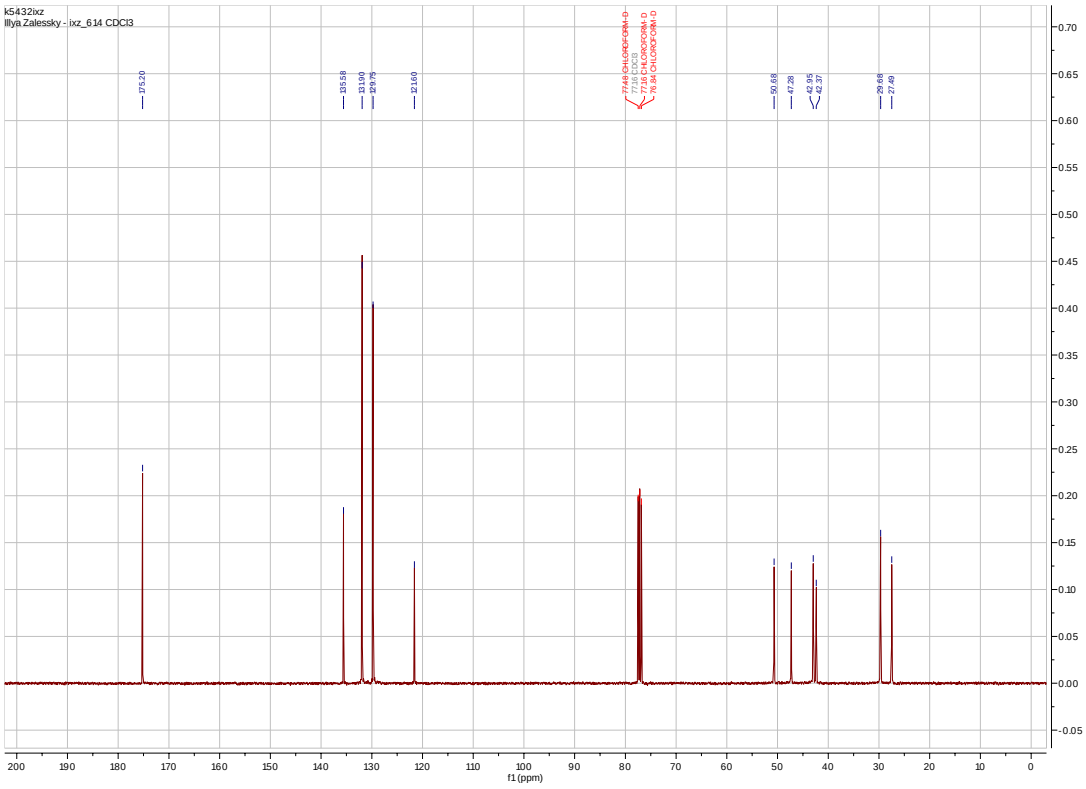
1-(Vinylsulfonyl)azocan-2-one – 397



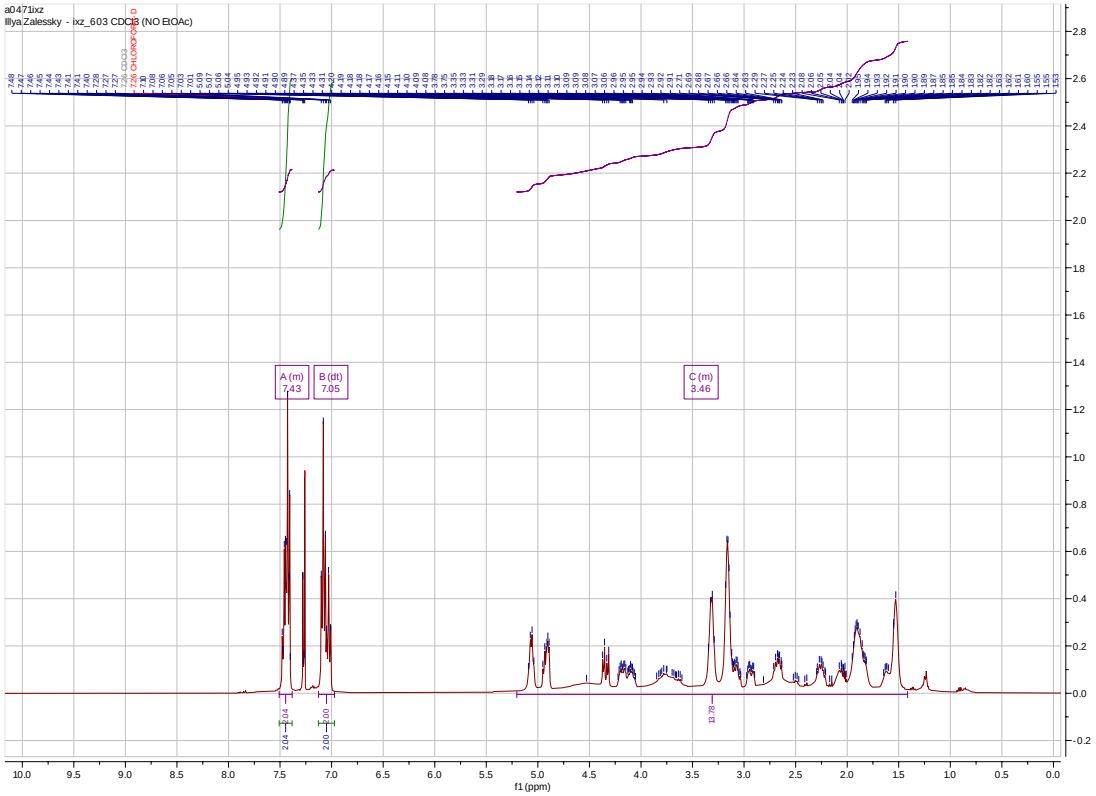


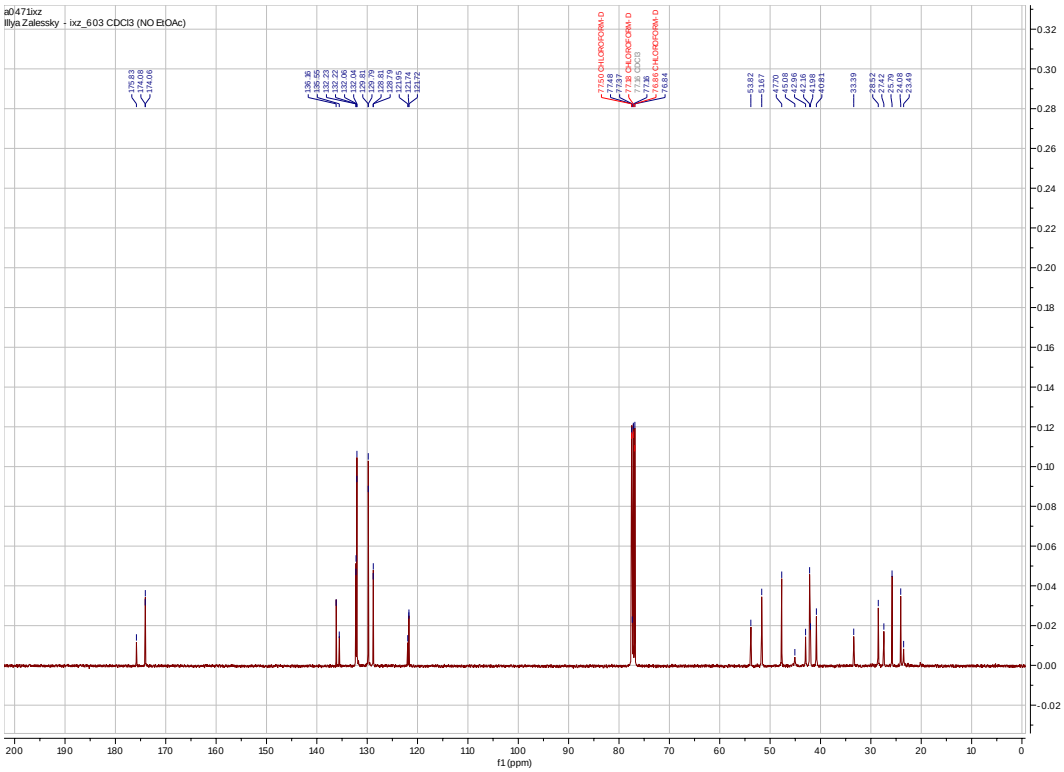
7-(4-Bromobenzyl)-1,2,7-thiadiazonan-6-one 1,1-dioxide – 401



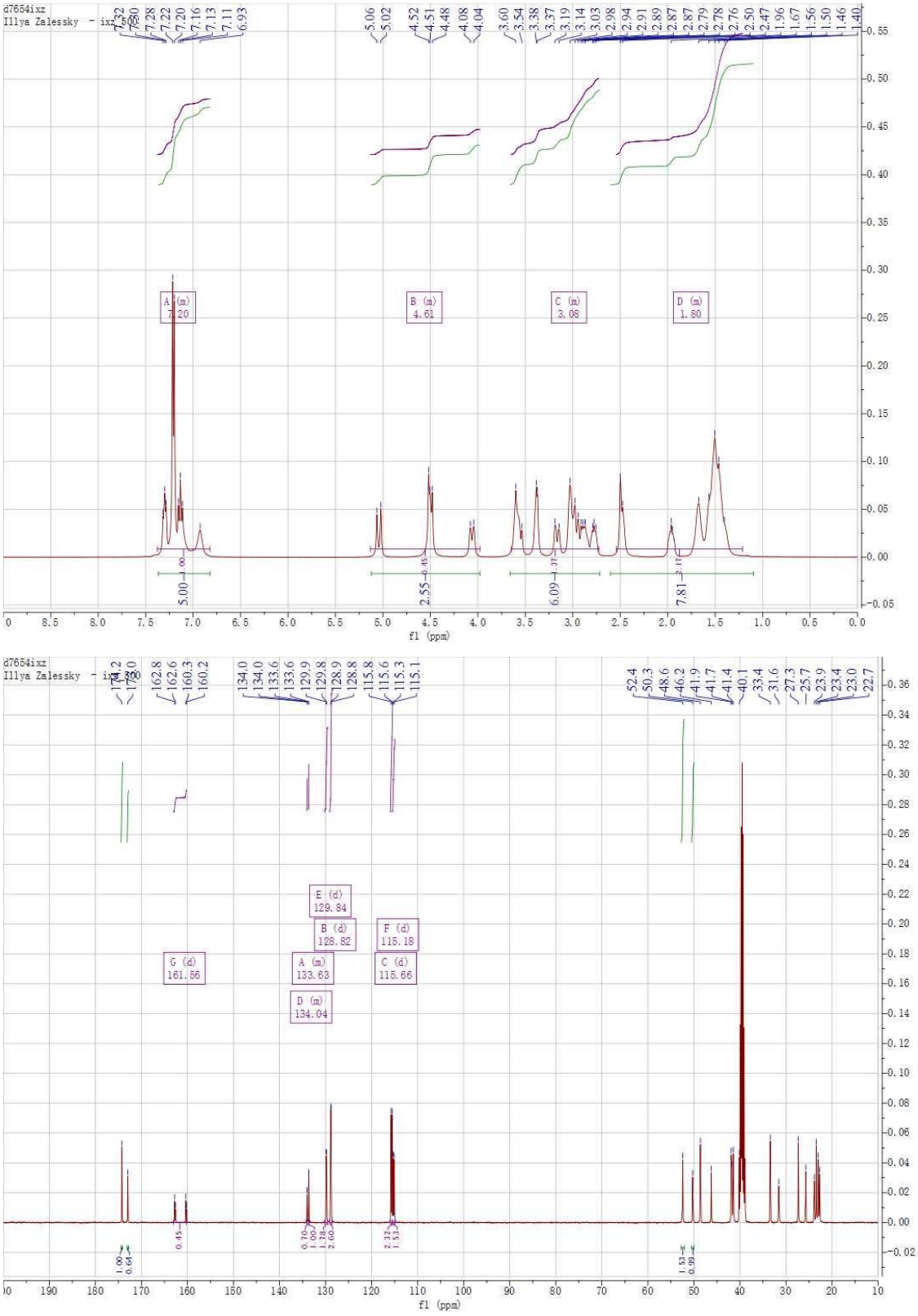


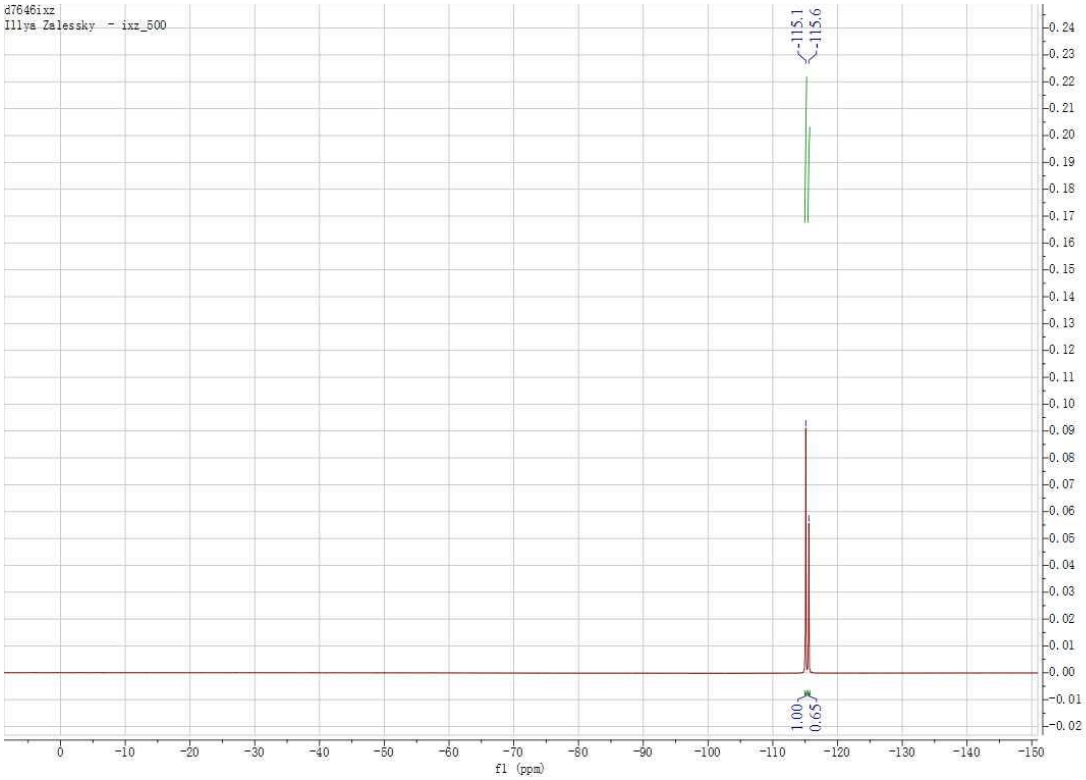
8-(4-Bromobenzyl)-1,2,8-thiadiazecan-7-one 1,1-dioxide 9 – 402



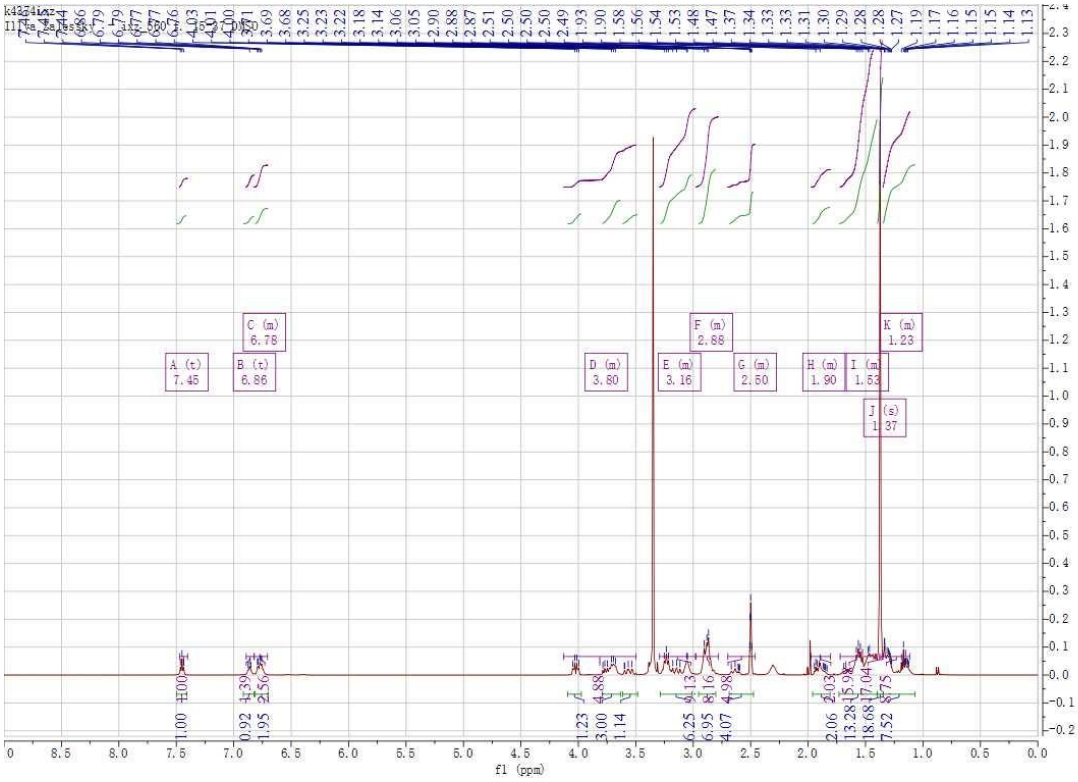


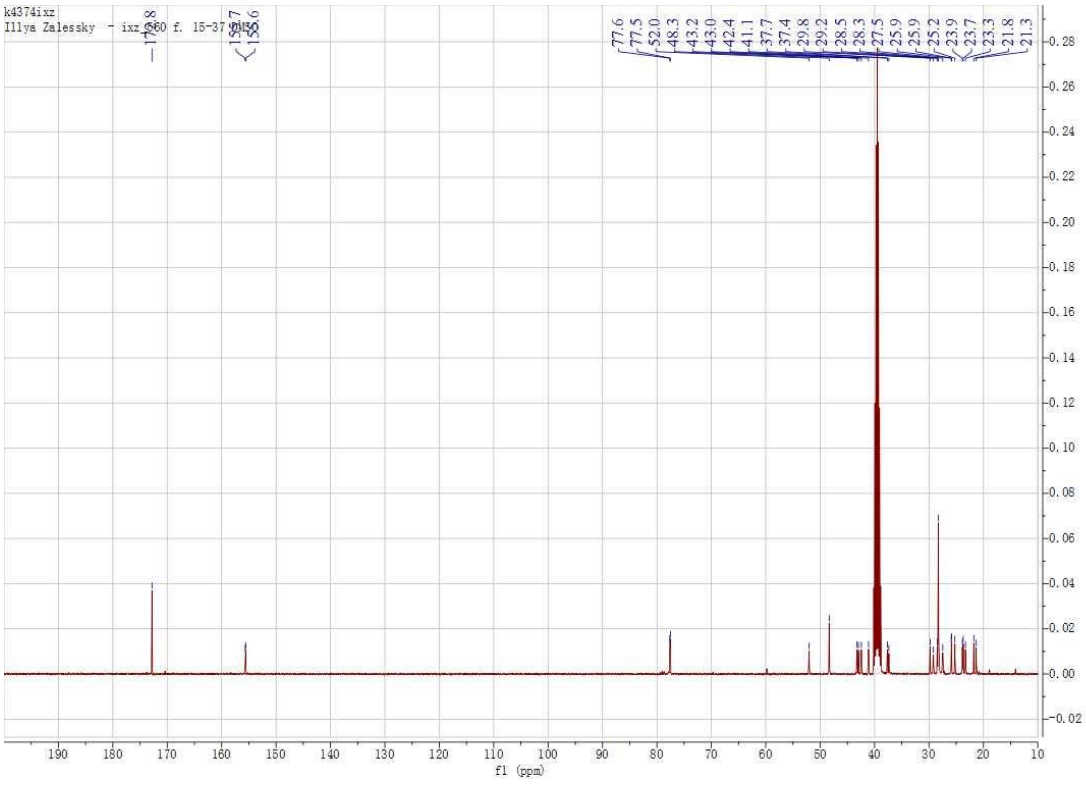
9-(4-Fluorobenzyl)-1-thia-2,9-diazacycloundecan-8-one 1,1-dioxide – 403



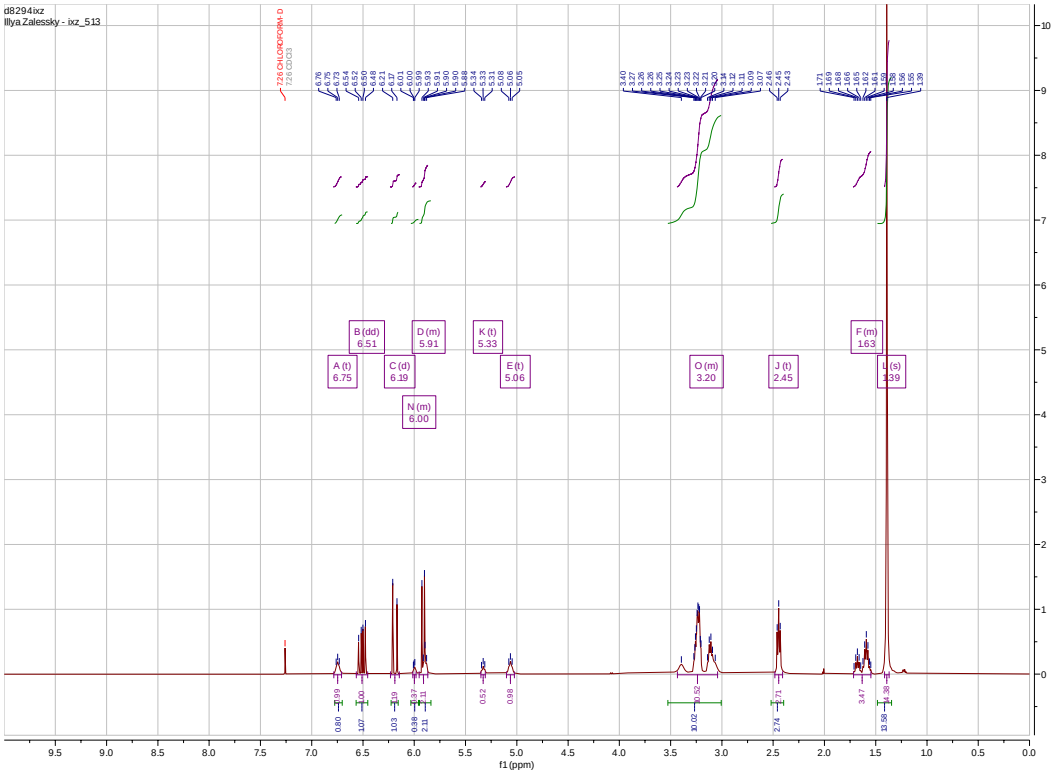

d7646ixz
Illya Zalessky - ixz_500
-115.1
-115.6
1.00
0.65
f1 (ppm)

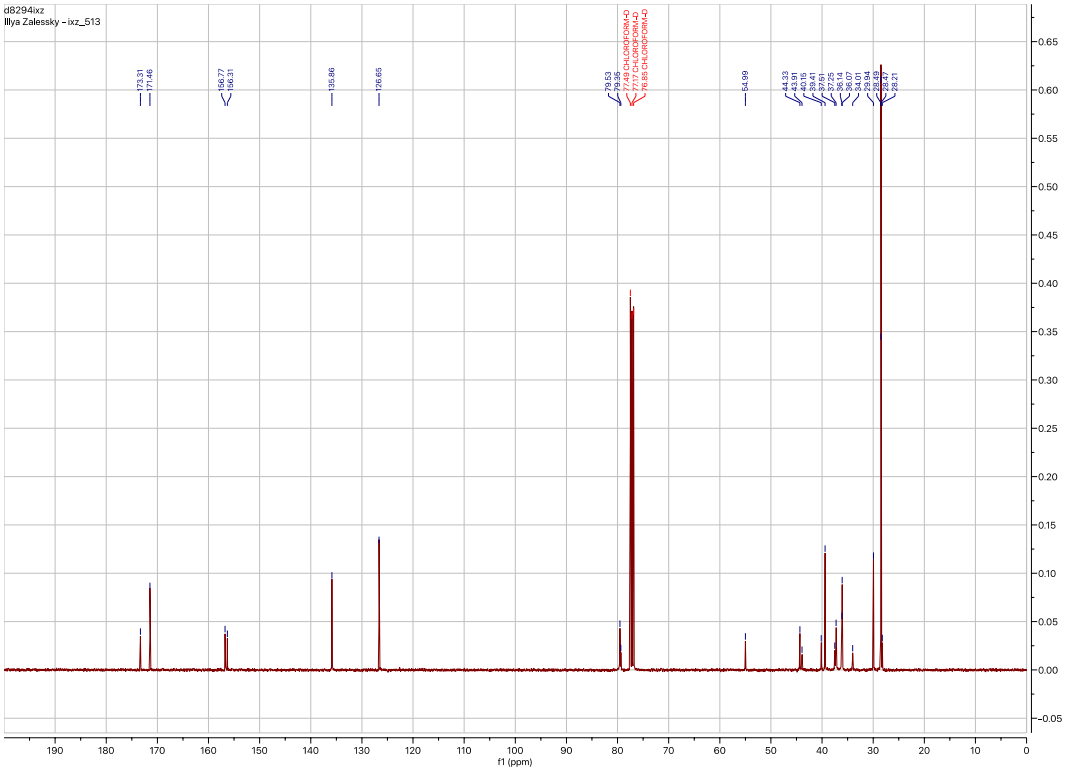
***tert*-Butyl (3-(1,1-dioxido-9-oxo-1-thia-2,10-diazacyclododecan-10-yl)propyl)carbamate – 404**



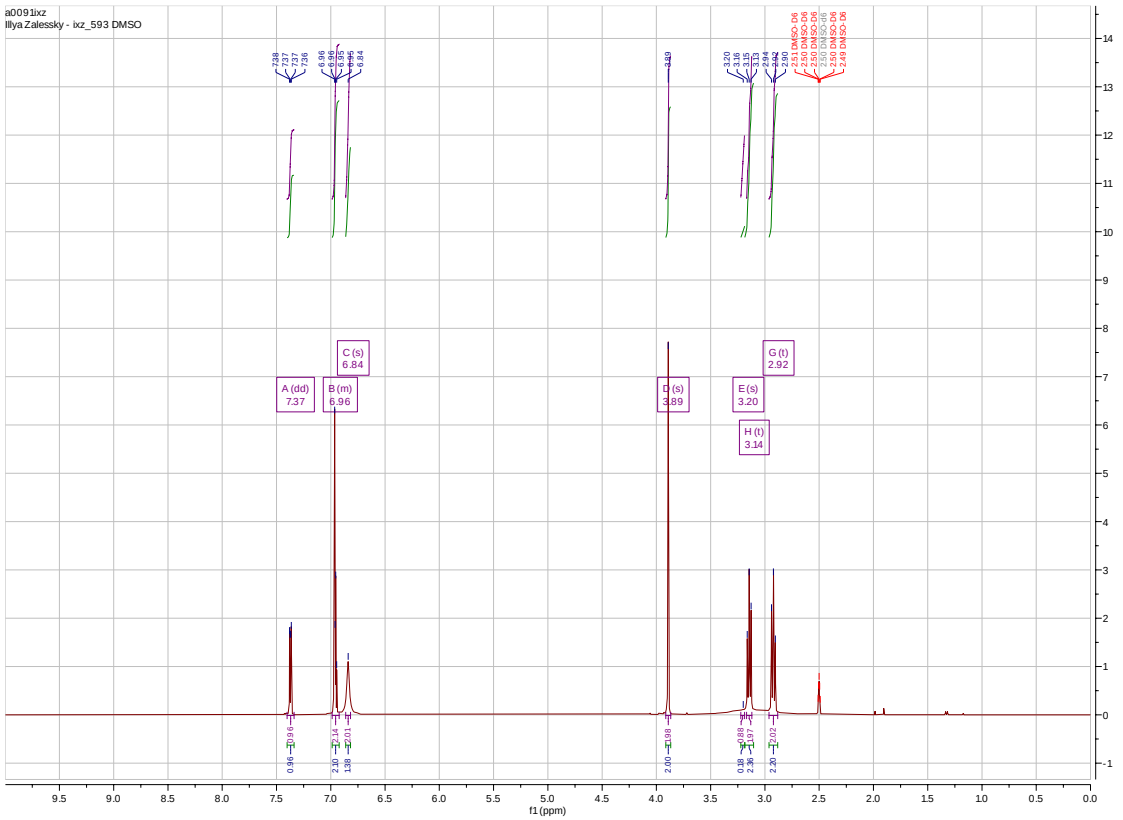


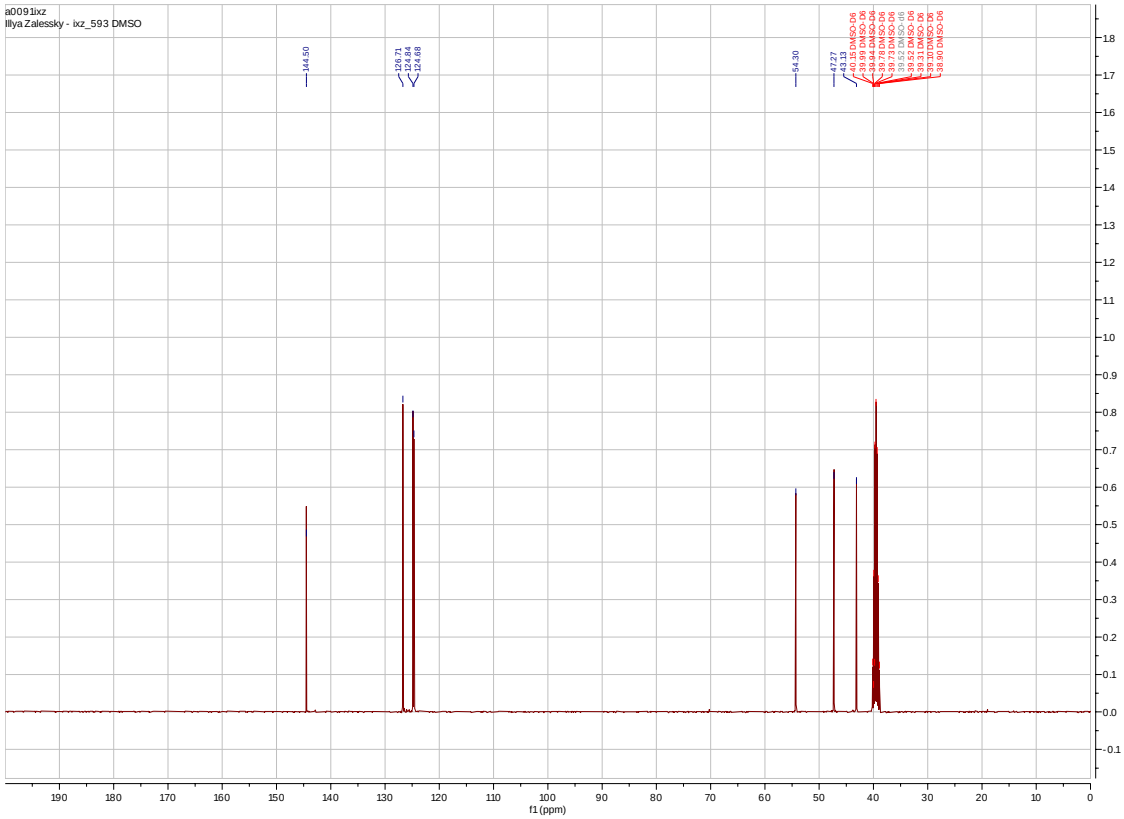
3-((*tert*-Butoxycarbonyl)amino)propyl 3-((vinylsulfonyl)oxy)propanoate – 406



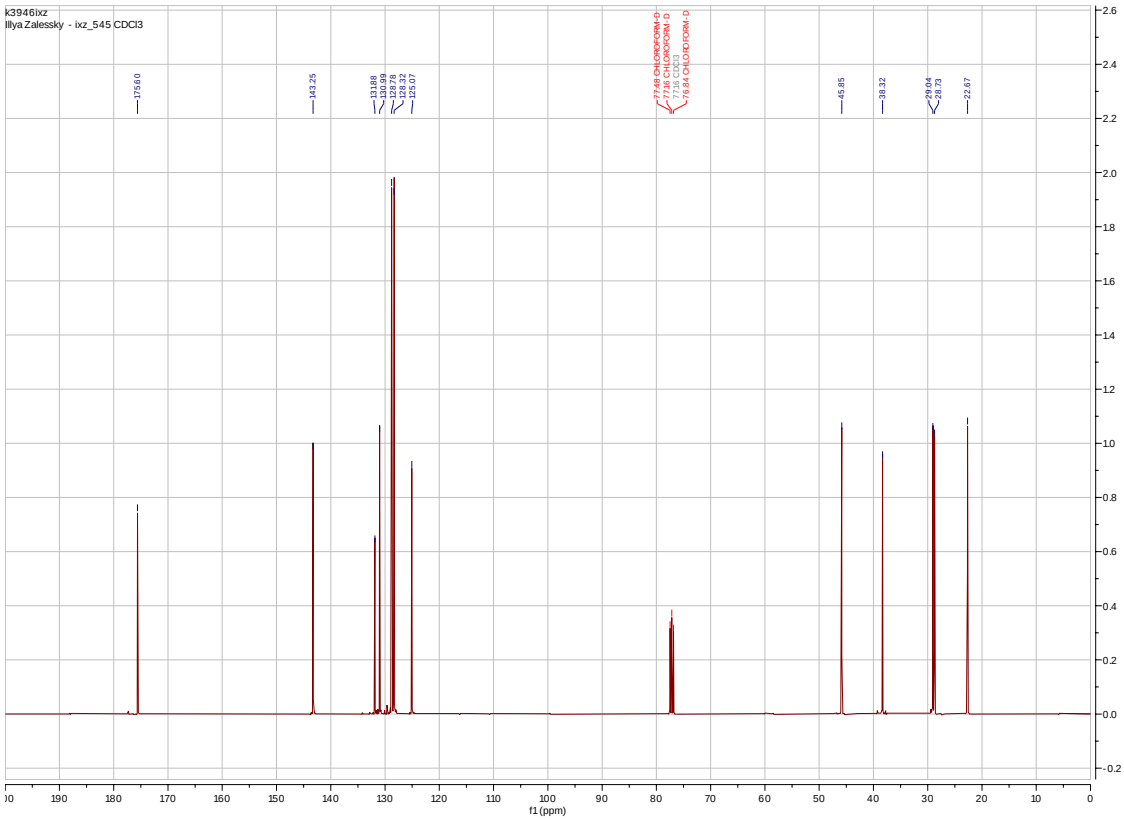


2-((Thiophen-2-ylmethyl)amino)ethane-1-sulfonamide – 430

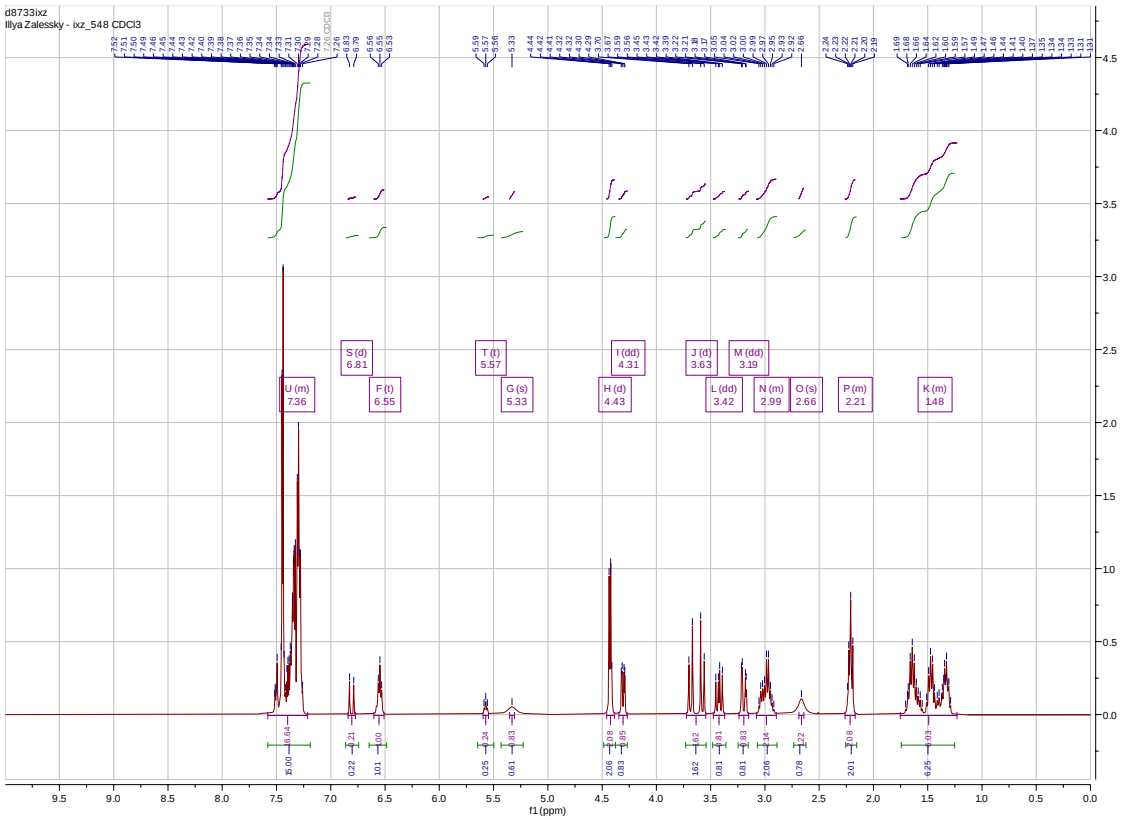


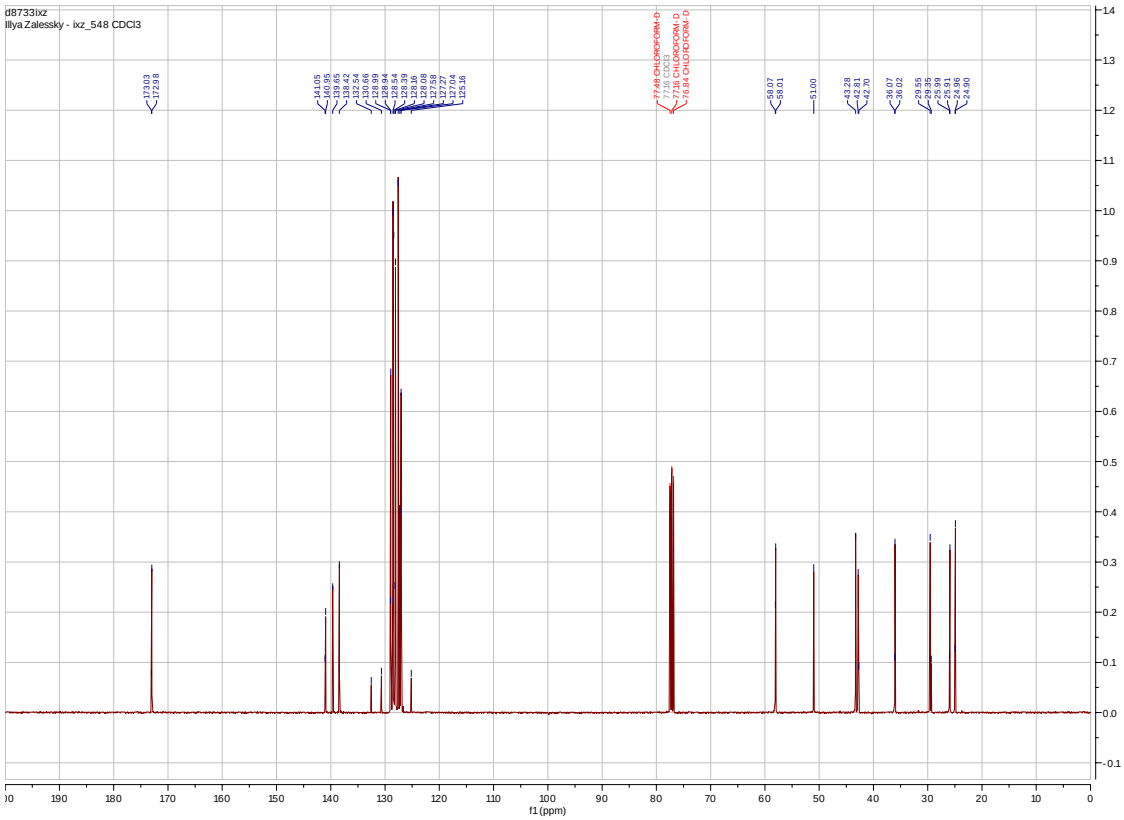


(*E*)-1-(Styrylsulfonyl)azepan-2-one – 432

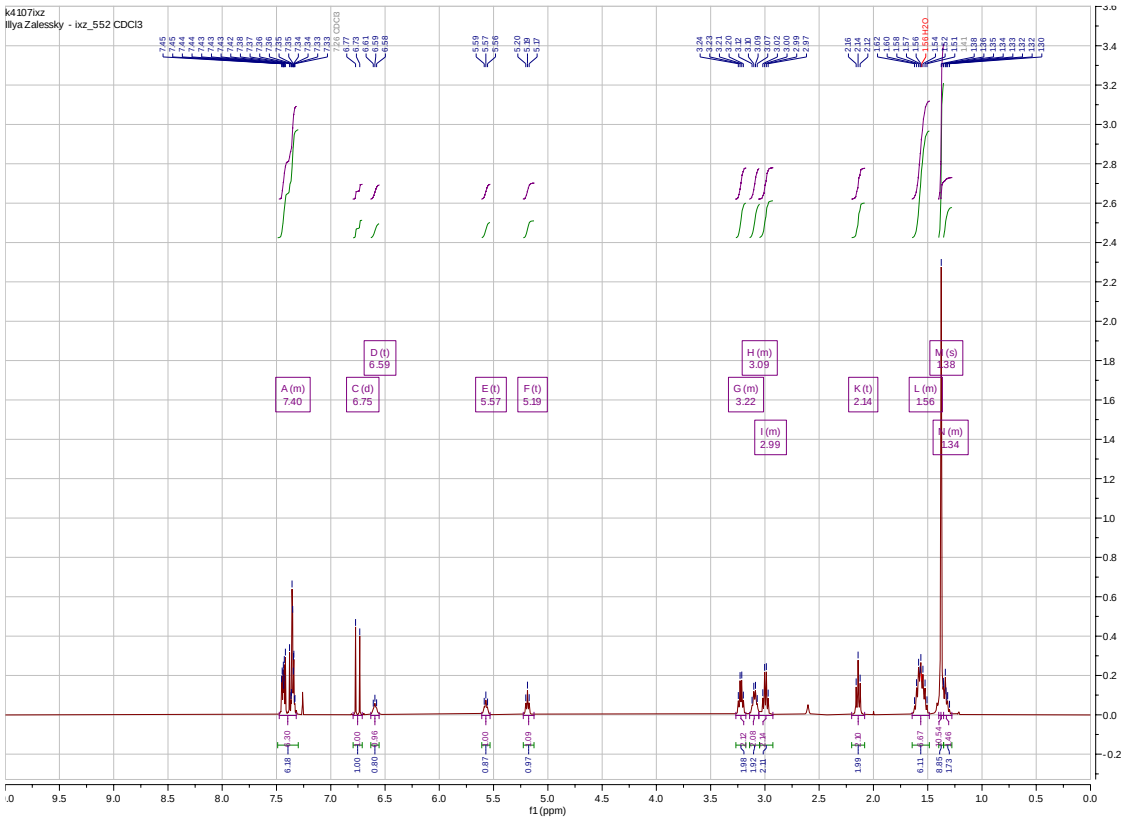


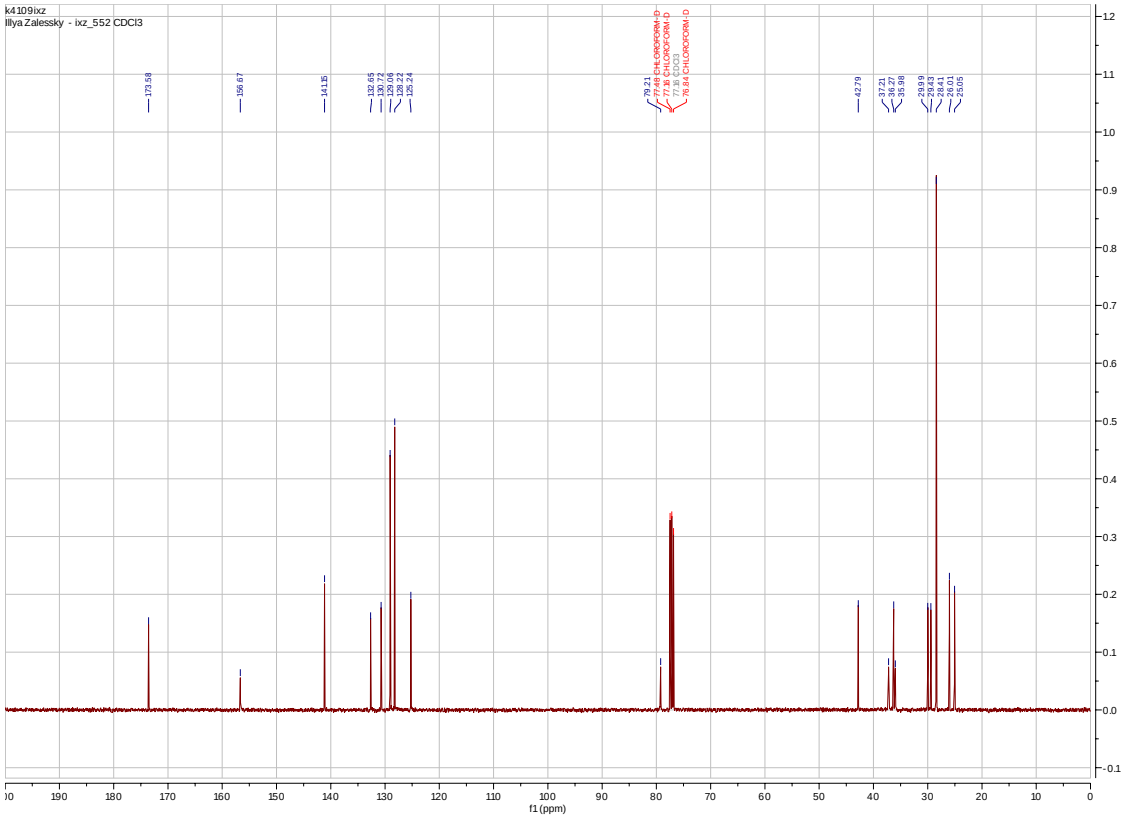
N-Benzyl-6-((2-(benzylamino)-2-phenylethyl)sulfonamido)hexanamide – 437





tert-butyl (_E_)-(3-(6-((2-Phenylvinyl)sulfonamido)hexanamido)propyl)carbamate – 437


k4107ixz
Illya Zalessky - ixz_552 CDCl3
A (m) 7.40
C (d) 6.75
D (t) 6.59
E (t) 5.57
F (t) 5.19
G (m) 3.22
H (m) 3.09
I (m) 2.99
K (t) 2.14
L (m) 1.56
M (s) 1.38
N (m) 1.34
f1 (ppm)


k4109ixz
Illya Zalessky - ixz_552 CDCl3
f1 (ppm)

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